

STUDIES IN HOST-GUEST CHEMISTRY

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in the Faculty of Engineering and Physical Sciences**

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SCHOOL OF CHEMISTRY

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Abstract

Previous work in our group has been directed towards the synthesis of crown-ethers for use in the selective complexation of metal ions and as chiral ligands for use in asymmetric catalysis. The development of a modular approach to macrocycle assembly has enabled the synthesis of a library of pyridine-based macrocycles possessing multiple donor sites where chirality was readily introduced from simple amino acids.

The nucleophilic ring opening of aziridines **181**, **193** or **194**, allowed the highly selective synthesis of thioether-based spacers and macrocycles. Extension of this basic approach to the synthesis of seleno-crown ethers was also investigated. The use of chiral-pool starting materials derived from D- or L-alanine, provided access to optically pure macrocycles.

The use of the Sharpless-Huisgen “click” reactions allowed the attachment of a carbohydrate residue directly to a macrocycle *via* a triazole unit. We hope to attach a macrocycle, carbohydrate residue and azo dye together, to be able to examine further diseases such as Alzheimer’s. We have so far succeeded in attaching a macrocycle and sugar to a central scaffold by performing a one-pot double “click” reaction. The distance between the points of attachment of the chromophore to the macrocycle metal binding site is probably, in this first generation sensor, too great to enable a metal-macrocycle binding event to be reported.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Never-ending thanks are also extended, of course, to James. For his support throughout my PhD, I will never be able to fully convey my thanks. I hope I can repay him whenever he needs it.

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Family are an integral part of my life, despite always saying "are you still not finished yet?" when I explain how my work is still not finished yet. None of this would have been possible without my parents and sister Meera.

I would also not be in the position I am in today without the help and support of all the technical and administrative staff from the Chemistry Department. Especially, Val, Rehanna and Gareth from the mass spectrometry team who were always willing to rush samples through and give helpful advice where needed.

List of abbreviations

AAC	Azide-alkyne cyclisation
AD	Alzheimer's Disease
ATR	Attenuated total reflectance
BBB	Blood-brain barrier
BPP[34]-crown-10	bis-Paraphenylene-34-crown-10
br.s	Broad singlet
CHQ	5-Chloro-8-hydroxyquinoline
<i>m</i> CPBA	3-Chloroperoxybenzoic acid
CuAAC	Copper mediated azide-alkyne cyclisation
d	doublet
DCM	Dichloromethane
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethylformamide
DPPA	Diphenylphosphoryl azide
EPR	Electron paramagnetic resonance
EtOAc	Ethyl acetate
GLUT	Glucose transporters
HBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HD	Huntington's Disease
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
ITC	Isothermal titration calorimetry
m	multiplet
MeOH	Methanol
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
NRO	Nucleophilic ring opening

PCP	Phosphorous-carbon-phosphorous
PD	Parkinson's Disease
PTC	Phase-transfer catalysis
q	quartet
quin.	quintet
RuAAC	Ruthenium mediated azide-alkyne cyclisation
s	singlet
SCS	Sulfur-carbon-sulfur
t	triplet
TEA	Triethylamine
TEG	Triethyleneglycol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TON	Turnover number
TsCl	Tosyl chloride

INTRODUCTION

1 Introduction

1.1 Supramolecular Chemistry

Supramolecular chemistry was defined in 2002 by Jean-Marie Lehn as “chemistry involving two or more molecules held together by non-covalent interactions”.¹ This chemistry and its potential uses are therefore dependent on both the molecules involved and the forces holding them together. These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π - π interactions and electrostatic effects.² These non-covalent, intermolecular interactions provide the basis for highly specific biological processes, such as the formation of protein complexes and substrate binding by enzymes or receptors.³

Supramolecular chemistry is a large and highly active field with several overlapping research areas. Of particular importance to this project is work pertaining to host-guest chemistry and self-assembly.

1.1.1 Host-Guest Chemistry

Host-guest chemistry is a branch of supramolecular chemistry that is concerned with the formation of aggregate structures and their properties. The complex is held by one or a combination of forces including: hydrogen bonding, ion-dipole, ion-ion, π - π , van der Waals and hydrophobic interactions.⁴⁻¹¹ The host generally possesses binding sites, which converge in the complex. Guests can be ionic or neutral, and can include metal ions, ammonium ions, carboxylic acids, amino acid derivatives, and many others.¹²⁻¹⁵

There are many different types of “host-guest” interaction with various network topologies, such as metal-organic frameworks or zeolites with small molecules, or synthetic cyclic compounds containing a cavity. Two examples of typical host-guest complexes are shown (Figure 1-1) where the non-covalent bonds are represented by broken lines.

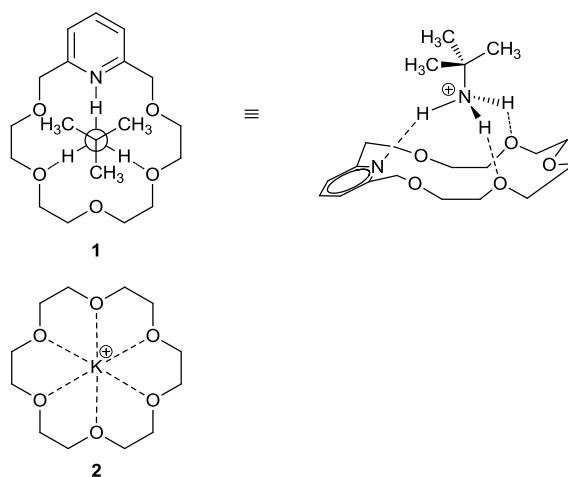
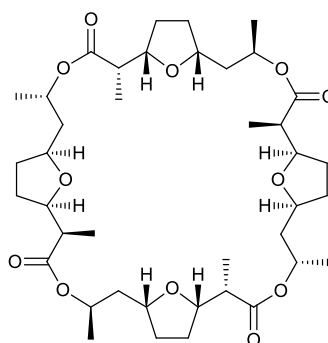


Figure 1-1: Two examples of typical host-guest complexes

Probably the earliest and most common examples of “host-guest” chemistry are enzyme-substrate interactions where the substrate fits into the enzyme’s active site with complete specificity. In 1894, Emil Fischer proposed the now ubiquitous ‘Lock and Key’ principle for the active site and the substrate,¹⁶ where the ‘lock’ represents the host and the ‘key’ the guest.

Macrocyclic Antibiotics

One example of an application for host-guest chemistry is the use of nonactin **3** for ion transfer. Nonactin is a naturally occurring cyclic ionophore consisting of a 48-membered ring, which has four tetrahydrofuran rings and four ester groups embedded into the core structure.¹⁷ Nonactin is a member of a family of ionophores known as macrotetralide antibiotics.¹⁸ It has high specificity for potassium and sodium ions.¹⁹



3

When nonactin complexes to a K⁺ ion, the ion is ligated by four carbonyl oxygen atoms and the four oxygen atoms of the furan rings, such that the complex adopts a near cubic

coordination geometry. The structure of the complex, as reported by Dobler *et al.*,^{19,20} shows the carbonyl groups directed inwards towards the metal ion with the non-polar residues coating the periphery. This arrangement generates a lipophilic assembly, which is able to diffuse across cell membranes. The non-polar groups are on the outside of the complex making the outside lipophilic. Nonactin therefore enables ion flow through pores in bacterial membranes, disrupting the membrane potential and resulting in the death of the organism.

1.1.1.1 Phase-Transfer Systems

Phase-transfer catalysis (PTC) involves the transport of guest molecules from one phase to another.²¹ The phases involved are two immiscible liquids. A suitable lipophilic organic host promotes the solubility of the guest salts (*e.g.* metal picrates) in the nonpolar solvent. The use of PTC can achieve faster reaction times, higher yields, and fewer unwanted products.²²⁻²⁵ Also, it is possible to carry out “green chemistry” as in some cases organic solvents are not required.^{26,27}

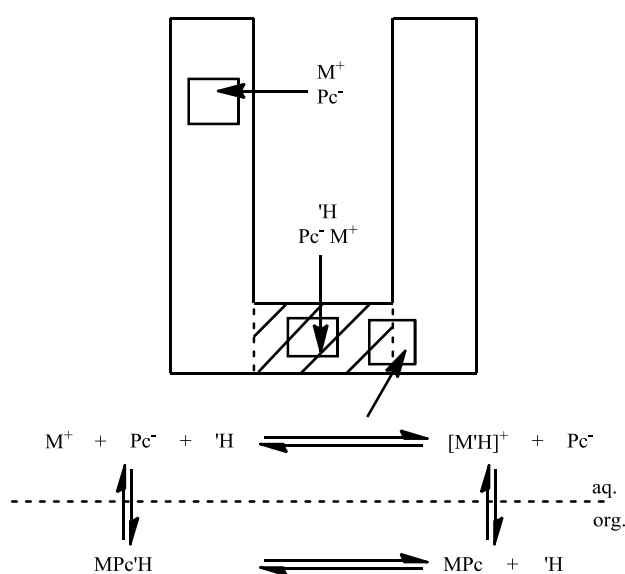
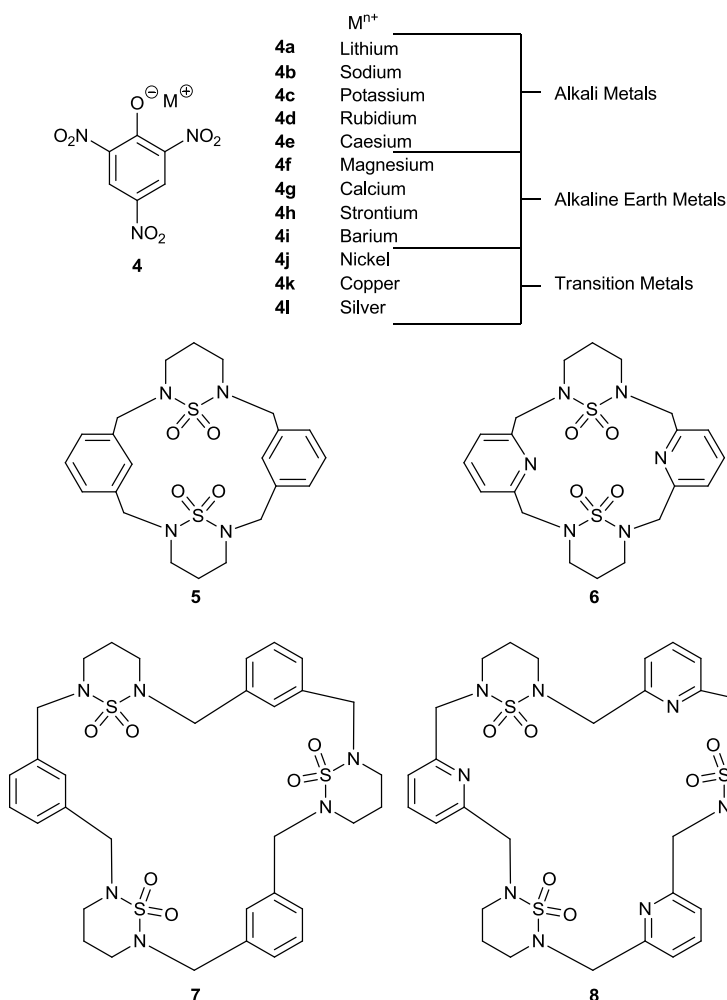


Figure 1-2: Illustration of the reactions and phase migrations that occur during phase transfer catalysis (PTC)

Previous work in the Bailey group by Anupama Sethi can be used to illustrate the role of macrocycles in PTC (Figure 1-2).^{28,29} A variety of metal picrates (**4a-1**, M⁺Pc⁻) were chosen for phase-transfer experiments with host macrocycles (**5-8**, 'H). The host macrocycles were only soluble in an organic solvent and the metal picrates were only

soluble in the aqueous phase. The complexation of a variety of cations by the hosts was expected to produce cationic metal-macrocycle complexes that were readily soluble in nonpolar solvents.



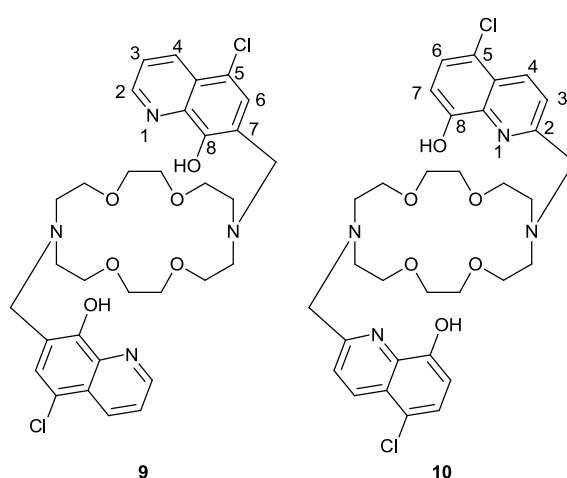
In an immiscible two-phase liquid system, the picrate anion was pulled into the organic phase as the cationic complex crossed the phase boundary. The presence of the picrate anion was detected using UV-Visible spectrometry and binding constants were calculated using a series of key equations.

The Bailey group observed the high affinity of both trimers (**7** and **8**) for rubidium over the other alkali metals in chloroform. A binding constant of 664 M^{-1} was seen for the benzyl trimer (**7**) with rubidium compared to 12.1 M^{-1} for potassium. For the pyridyl trimer (**8**) the binding constant was 530 M^{-1} with rubidium, compared to 18.4 M^{-1} for potassium. On the contrary, dimer **5** showed the highest affinity for barium in

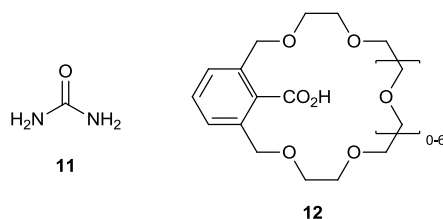
chloroform over the other alkaline earth metals. The pyridyl trimer **8** showed high selectivity for both barium and silver.

1.1.2 Crown Ethers

The synthesis of crown ethers was first reported in 1967 by Pedersen,³⁰ who synthesised thirty-three different ethers from vicinal diols and formed cavity dependent complexes using a variety of cations. After carrying out a vast amount of work on the ethers,^{31,32} Pedersen went on to win the Nobel Prize in 1988.³³



Cavity size of the crown ether is a major determining factor when examining to which ligands they can effectively bind. The size of the cavity affects which cation can bind to the ligand as cavities significantly vary in size and shape. In 1996, Bordunov *et al.* published examples of this phenomenon.³⁴ These workers showed that when the 5-chloro-8-hydroxyquinoline (CHQ) group was attached to the main ring *via* position 7 (**9**), the complex was selective for Mg^{2+} over the other alkali and alkaline earth metals. However, if the CHQ was attached *via* the 2 position (**10**), the complex became selective for K^+ over other alkali metals, and Ba^{2+} over the other metal ions they studied.



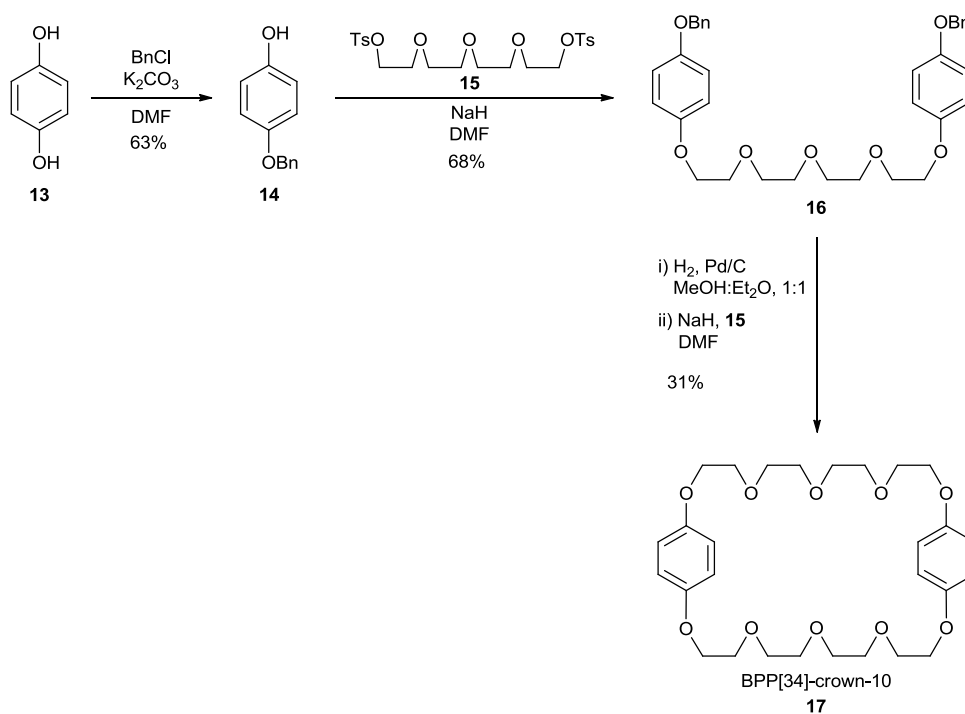
Reinhoudt *et al.*, used a variety of crown ethers (especially 18-crown-6 derivatives **12**) to complex a range of charged and neutral molecules such as urea **11**.³⁵⁻⁴⁰ Reinhoudt showed that complexes between neutral molecules and the crown ether derivatives exist

not only in the solid state, but also in solution.^{38,41} Formation of the complexes was evaluated by measuring the acidities of the *intraannular* acidic group. The acidic group protonates the urea molecule which is a very weak base. Reinhoudt *et al.* realised the acidity of the carboxylic group in the crown ethers **12** was dependent on the size of the crown ether.³⁵ Further experimentation led to the observation that the urea complex exists by coordination of the proton from the carboxylic group to the urea oxygen atom. In certain cases, upon addition of lithium perchlorate, the Li⁺ acted as a vital bridging species in the complexation of the urea.

1.1.2.1 Synthesis of Crown Ethers

Macrocyclic polyethers are normally prepared by the Williamson ether synthesis⁴² which involves the S_N2 displacement of an alkyl halide by an alkoxide. Generally, a diol is reacted with a dihalide in the presence of a base. Methods have also been reported in which the leaving group was changed from a halide to the generally more reactive tosylate or mesylate.⁴³⁻⁴⁵

In many cases, a base such as sodium hydride or potassium *tert*-butoxide is used in the reaction in conjunction with strongly co-ordinating dipolar aprotic solvents, such as *N,N*-dimethylformamide (DMF) or THF, which facilitates the S_N2 reaction mechanism.



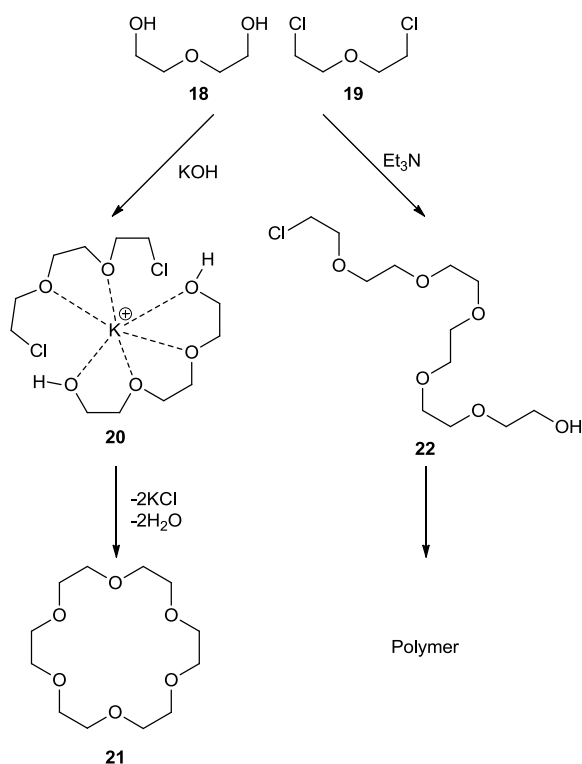
Scheme 1-1

Scheme 1-1 shows the synthesis of bisparaphenylene-34-crown-10 (BPP[34]-crown-10 **17**).⁴⁶ The commercially available hydroquinone **13** was monoprotected using benzyl chloride to form **14**. Two equivalents of **14** were then reacted with the ditosylate **15** using sodium hydride as the base giving the dibenzyl ether derivative **16**. Catalytic hydrogenolysis removed the protecting groups, and then subsequent reaction with another equivalent of ditosylate **15** afforded crown **17** in 31% yield.

1.1.2.2 Templating

During the synthesis of crown ethers, it is possible that unwanted side reactions, such as oligomerisation, can compete with cyclisation. The possible outcomes are shown in Scheme 1-2 with [18]crown-6 used for illustration.⁴⁷

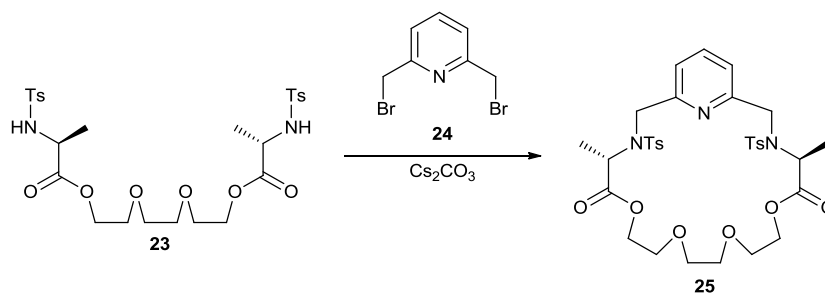
Using triethylamine (Et₃N) or potassium hydroxide as the base in this reaction leads to the formation of either the polymeric product **22** or the crown ether **21**. The difference in pathway is due to the presence of the K⁺ ion, which enables the reactants to arrange themselves giving a reaction intermediate (similar to **20**) that is preorganised to form the cyclic product. The close proximity of the –OH and –Cl groups enables cyclisation. The potassium ion is therefore thought of as a template for the reaction and the synthesis of macrocyclic compounds in this manner is called the ‘template effect’.^{48,49}



Scheme 1-2

In the absence of potassium ions, the cyclisation reaction is entropically disfavoured and so polymerisation is the dominant outcome when Et_3N is used as a base. The choice of base is therefore crucial to the successful synthesis of crown ethers.

In the case of [18]crown-6, K^+ is unique in its ability to promote cyclisation to the macrocycle. Subsequently, it has been observed that other cationic species can behave as templating agents, such as alkali metals, alkaline earth, transition metals and the lanthanides.⁵⁰⁻⁵⁴ For example, Bailey has used the templating effect of Cs^+ (as Cs_2CO_3) in the synthesis of macrocycle **25**. The crown ether-based structure **25** was ring-closed using ester **23** templated around a caesium ion. This prevented any dimerisation to form a [2]catenane, or even polymerisation.



Scheme 1-3

1.1.2.3 The Caesium effect

In 1955, Stetter carried out a macrocyclisation reaction forming a C-N bond between a sulfonamide and an alkane using sodium or potassium carbonate in DMF. Dilute conditions were required to avoid polymerisation.⁵⁵ In 1984, Kellogg experimented with this procedure, carrying out a C-O bond forming reaction with a variety of carbonate salts (Figure 1-3).⁵⁶ He found caesium to be a more effective ion and since then much work has been carried out into the full extent of this principle. This modification, now termed the “caesium effect”, defines caesium as the best templating ion for macrocyclisations and allows the reaction to be carried out under non-dilute conditions and generally with a higher yield.

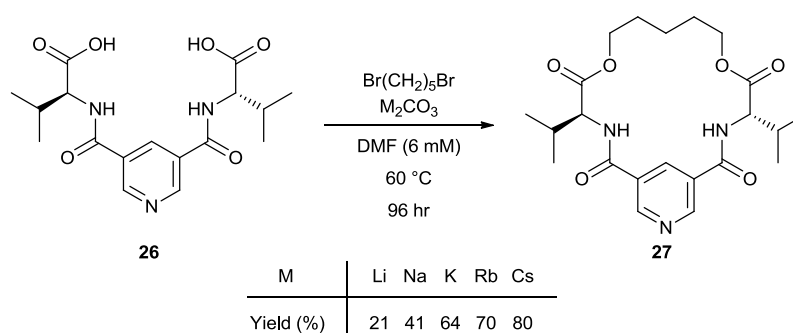


Figure 1-3: Differences in a macrocyclisation reaction when using various carbonate salts

The “caesium effect” is not wholly understood, but some have tried to explain it in an exemplary fashion.⁵⁷ A variety of caesium compounds have been used in macrocyclisation reactions as basic reagents.⁵⁸⁻⁶⁰ Caesium fluoride is less desirable compared to the carbonate or hydroxide analogues due to its low solubility. Caesium carbonate is preferred over caesium hydroxide as it is less hygroscopic and therefore easier to handle.

1.2 Mixed-Donor Macrocycles

As discussed in the previous section, crown ethers are well known for their ability to bind alkali and alkaline-earth metal ions. They are, however, limited in their ability to bind transition metal ions.

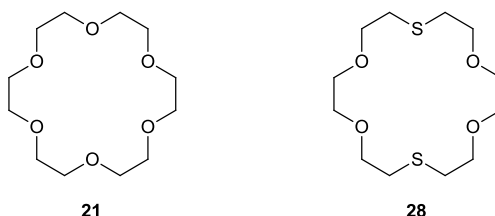
Transition metals are both vital to life (iron, copper, zinc) and also toxic (cadmium, mercury). They are known to play a role in certain neurological diseases such as Alzheimer's. The ability to selectively detect, and ideally remove, such ions has the

potential for widespread applications in water-treatment, environmental monitoring, animal and human health.⁶¹⁻⁶³

Mixed-donor macrocycles have been developed to extend the chemistry of crown ethers. They have the advantage over their simpler single-donor counterparts in being able to offer the coordination of both hard σ -donor N-ligands and soft σ -donor and potential π -acceptor S-ligands. It was Busch who was the first to show that thioether-based ligands could coordinate metals,⁶⁴⁻⁶⁶ and since then a wide range of complexes have been made.^{67,68}

Mixed-donor macrocycles have been used for molecular recognition, catalysis, and chromatographic separation of metal cations.⁶⁹⁻⁷¹ Many researchers have exploited the variety of binding abilities offered by the ligands, and the geometry of the complexes they form.⁷²

An example of the effect of changing one or more of the donor atoms in a crown ether was reported by Bradshaw *et al.*,⁷¹ who showed that 1,10-dithia-18-crown-6 **28** formed higher affinity complexes with Hg^{2+} and Ag^+ than 18-crown-6 **21**. In contrast, **28** showed a low affinity for alkali metal cations compared to 18-crown-6.



The first use of a crown ether as a transport mimic was described by Vögtle *et al.* in 1977.⁷³ They synthesised a variety of open chain crowns in an effort to replicate ion carriers across biological membranes in molecules.

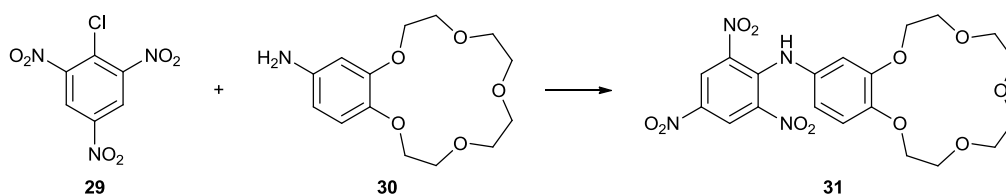
1.3 Synthesis and application of coordinating dye molecules

1.3.1 Introduction

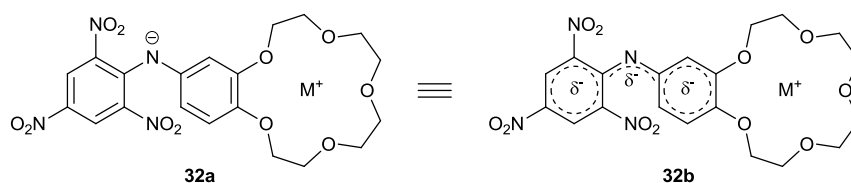
The first reagents reported for the colourimetric determination of alkali metal cations were based on crown ethers and were developed in the late 1970s by both Takagi *et al.*,⁷⁴ and Dix *et al.*⁷⁵ Takagi developed a series of crown ether derivatives designed for the purpose of liquid-liquid extraction of alkali and alkaline earth metal ions.

1.3.2 Use of Crown Ethers

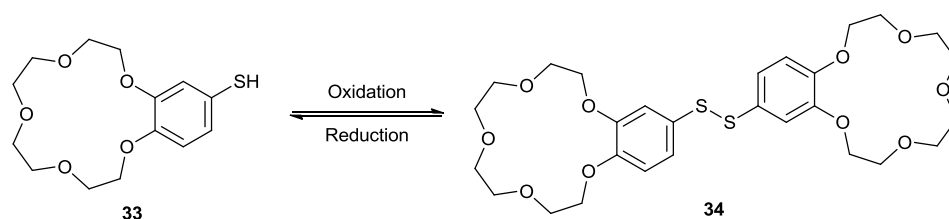
In 1977, Takagi *et al.* prepared a new type of complex in order to further explore an area of chemistry concerned with the selective extraction of alkali metals.^{74,76} Very few colourimetric reagents had been discovered for alkali metal ions due to their low affinity for anions or dipolar ligands. Takagi's first colourimetric molecule **31** simply placed the binding site close to a monobasic acid chromophore, allowing its dissociation on complexation. The molecule successfully complexed K^+ and also Rb^+ in a biphasic solution, changing the colour of the solution from orange to blood red in the presence of these ions.



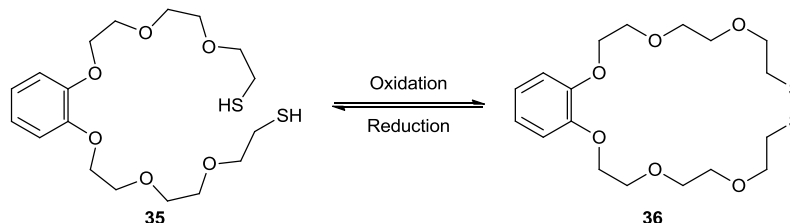
Takagi carried out further experiments on a series of colourimetric crowns⁷⁷ and came to the conclusion that the most important factors when designing a colourimetric sensor are: an extensive delocalisation of anionic charge and also a small distance between the positive and negative charges on the resultant complex (Figure 1-4).



In 1985, Shinkai *et al.* published research on redox-switched crown ethers.^{78,79} Scheme 1-5 and Scheme 1-6 illustrate the two pairs of oxidised and reduced crowns that he discovered, which he showed to have distinctly different binding abilities. The increase in order and organisation in the bridged structures intensifies their affinity for cations.

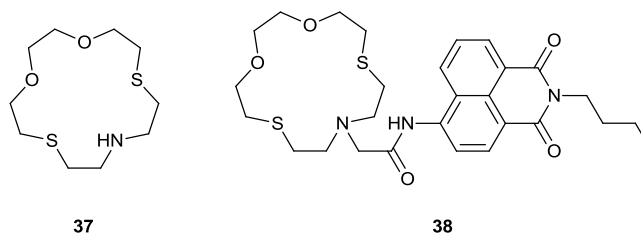


Scheme 1-5



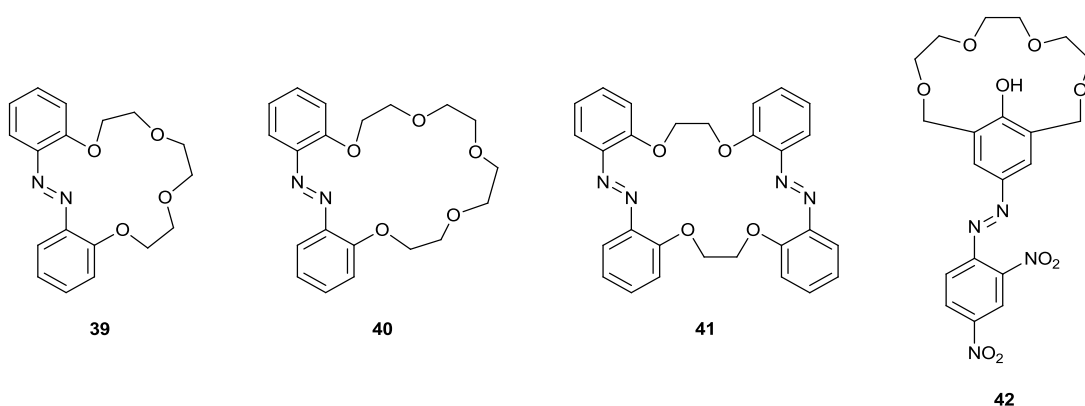
Scheme 1-6

In 2010, Spring *et al.* published details of a crown-based molecule which was Ag⁺ selective.⁸⁰ They examined both the simple crown derivative **37** and the crown derivative **38**, which possessed a fluorophore. Both prove to be highly selective receptors for Ag⁺. The fluorophore enables an observer to see when a molecule has complexed an ion or molecule, either by sight or by spectrometry.



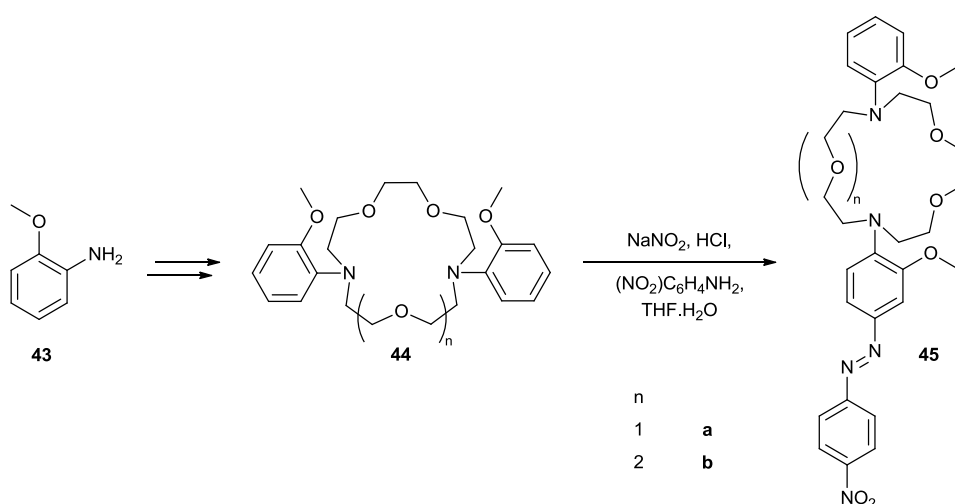
1.3.3 Azo Dyes

Takagi was the first to incorporate the azo-functional group within the framework of a crown ether in 1980.⁸¹ Unfortunately his first attempts to use azo dyes **39-41** to selectively bind sodium or potassium were less successful than simple 18-crown-6, most probably due to the ring strain introduced by the azo group, affecting the cavity size. Upon further investigation it was found that including the azo-moiety within the crown ether ring structure was not favourable and led to poor binding affinities.⁸²



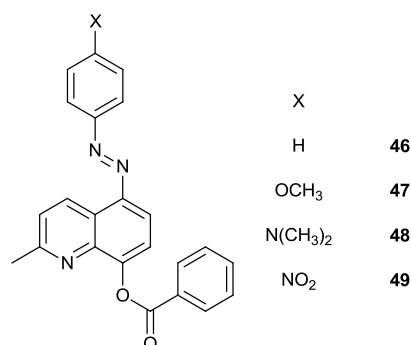
Subsequently, Nakashima *et al.*⁸³ reported the synthesis of the azo dye **42** which they discovered could be used to selectively bind Rb^+ and Cs^+ . Rather than trying to incorporate the azo dye into the ring, they simply placed it pendant. This neatly avoided the problem of ring-strain, and allowed for greatly improved functionality of the compounds.

In 2002, Gunnlaugsson and Leonard synthesised **44**,⁸⁴ which had the ability to selectively bind Na^+ or K^+ . Extending this research,⁸⁵ they went on to discover that the attachment of an azo dye moiety enabled a visual observation of the presence of Na^+ or K^+ . Crown **45a** displayed large changes in the absorption spectra upon complexation with Na^+ , and similarly **45b** showed a strong shift in its spectral band position to a shorter wavelength (higher frequency) as well as a decrease in its absorbance upon titration with K^+ . Binding of both ions resulted in a colour change from red to yellow.

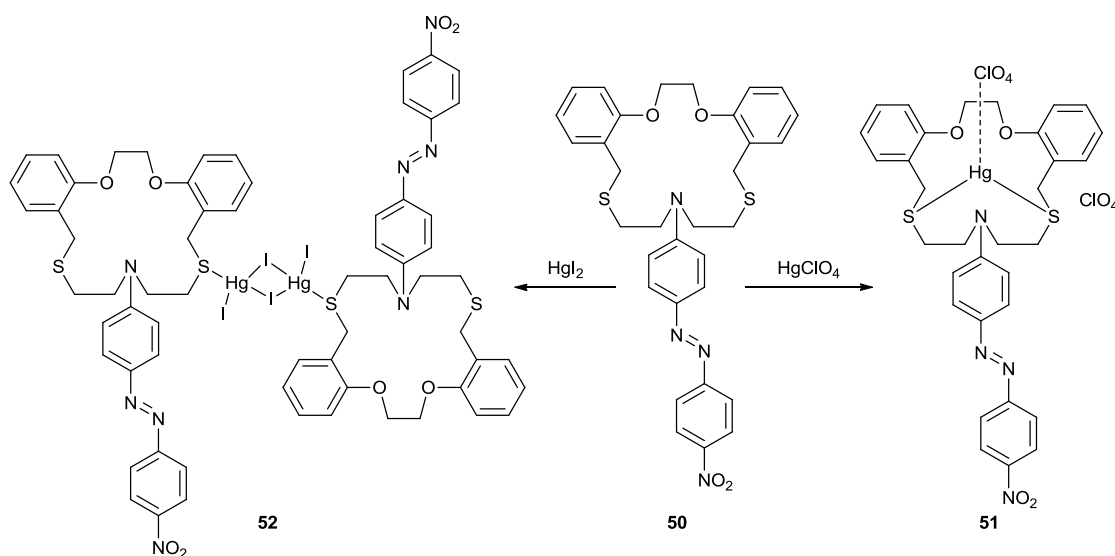


Scheme 1-7

In 2008 Huang *et al.*⁸⁶ synthesised a range of 8-hydroxyquinoline benzoates from the corresponding arylamines and 2-methyl-8-hydroxyquinoline **46-49**. On testing their affinity for sensing metal ions, he discovered all four products had good selectivity for Hg^{2+} . In particular, he found that **48** showed an obvious colour change from yellow to red on binding of the Hg^{2+} .



A new type of chromoionophore was created in 2006 by Shim Sung Lee *et al.*, which also showed selectivity for Hg^{2+} .⁸⁷ He discovered that the solid state structure of the complex depended on the counter ion of the Hg^{2+} . When the counterion was iodide, the structure formed red crystals in dimeric form, using a Hg-I₂-Hg bridge **51**, whereas perchlorate formed yellow crystals in a 1:1 manner **52**.

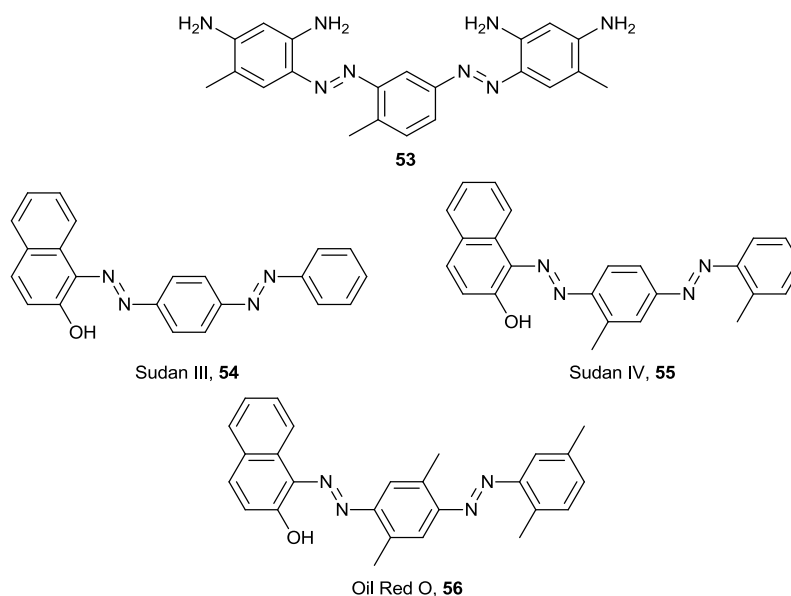


Scheme 1-8

1.3.4 Biological Applications

Since their introduction, the technical application of dyes in science has expanded enormously. One area where they have had significance is their use as biological stains.

As one of the first azo dyes to be synthesised, Bismarck brown **53** has been developed as a stain for tissues, acid mucins, cartilage and also DNA in the Feulgen stain.⁸⁸⁻⁹¹



Expanding on the idea of Sudan III, Michaelson proposed Sudan IV as a biological stain in 1901.⁹² He suggested that Sudan IV carried out the same function, but with a deeper, more orange colour. In the same respect, introduction of another methyl group on the phenolic rings to form Oil Red O **56** intensifies the colour again. This is preferred as a biological stain with its deep scarlet colouring.⁹³

Oil Red O, like its simpler counterparts **54** and **55**, has been used as a fat-soluble dye, staining lipids and triglycerides. More recently it has been proposed as a stain to reveal otherwise invisible fingerprints in certain forensic situations.⁹⁴

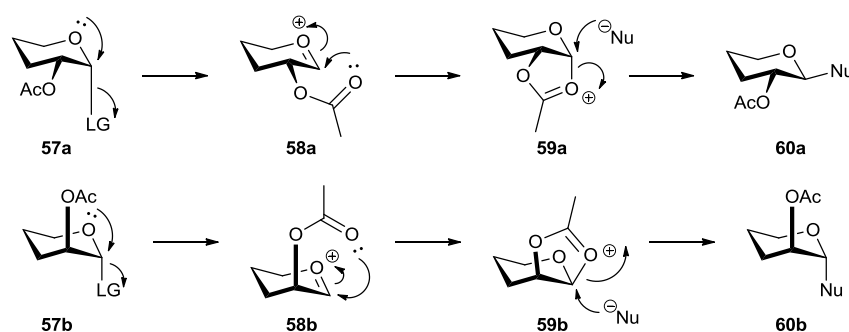
1.4 Use of Sugars as Transporters

1.4.1 Properties of Sugars

Carbohydrate is the term for a large family of compounds possessing the empirical formula $C_n(H_2O)_n$. As a family, they are an essential part of life, involved in a multitude of biological processes, acting as sources of energy, taking part in biological signalling and forming the basic building blocks of life. These structures vary greatly, and exist in nature in many different forms including various open and closed chain structures. Within the carbohydrate family are four chemical groups: monosaccharides, disaccharides, oligosaccharides and polysaccharides. The monosaccharides are the

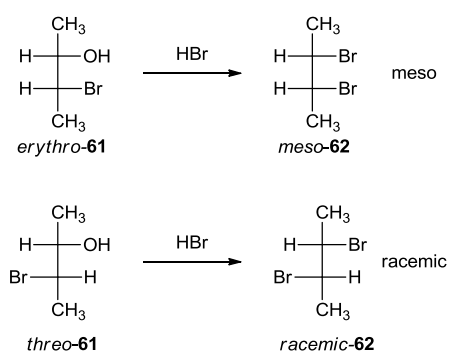
smallest (generally C₃₊) and normally referred to as ‘sugars’. The chemistry of these monosaccharides is vast, and one of the most important factors when manipulating them for specific syntheses is stereochemistry.

There are many strategies for controlling the stereochemistry resulting from a nucleophilic substitution reaction at the anomeric centre in carbohydrates. One method is by the neighbouring group participation of an ester protecting group such as an acetate (Scheme 1-9). The involvement of the neighbouring group becomes significant only when the reaction rate with its participation is faster than without it.



Scheme 1-9

In 1939, Weinstein and Lucas^{95,96} first recognised the presence of neighbouring group participation when treating **61** with fuming hydrogen bromide. They observed formation of a *meso* mixture of **62** when reacting *erythro*-**61**, but a racemic mixture when treating *threo*-3-bromo-2-butanol (*threo*-**61**).



Scheme 1-10

It was J. T. Edward who first stated that unpaired pairs of electrons play a role in the conformational preferences of glycosyl halides. This statement was then extended by experimentation to carbohydrates and their derivatives, observing that heteroatomic groups adjacent to the oxygen prefer the axial position.⁹⁷

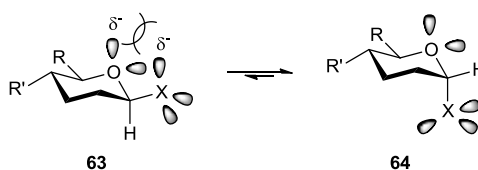


Figure 1-5: Illustration of the origins of the anomeric effect⁹⁸

There have been many explanations given to account for the origins of the anomeric effect or Edward-Lemieux effect. More recently, evidence has supported two theories contributing to the effect: i) unfavourable dipole-dipole interactions and ii) a favourable interaction between the ring heteroatom lone pair, and the antibonding σ^* -orbital of the C-X bond (Figure 1-6).^{99,100}

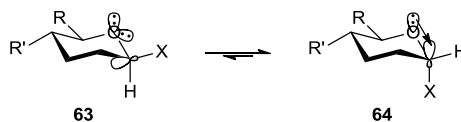
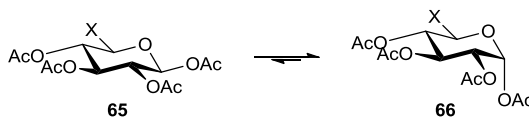


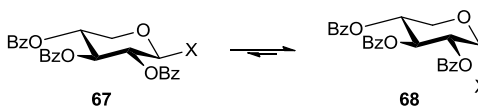
Figure 1-6: Illustration of the stabilising effect observed due to the partial transfer of a lone pair

The extent of the anomeric effect in determining the reactivity of carbohydrates is dependent upon a number of factors: the functionality attached to the ring (Figure 1-7),¹⁰¹ the group at the anomeric position,¹⁰² or the solvent which is used for example polar solvents favour the more polar, equatorial product.¹⁰³



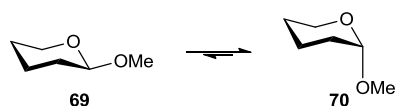
	X	Axial anomer (%)
a	CH ₂ I	84
b	CH ₂ Cl	86
c	CH ₂ OAc	86
d	CH ₂ OTs	91

Figure 1-7: Effect of other ring substituents¹⁰¹



	X	Axial anomer (%)
a	H	19
b	OMe	26
c	OAc	47
d	OBz	50
e	F	90-100
f	Cl	98
g	Br	90-100

Figure 1-8: Effect of the group at the anomeric centre¹⁰²



Solvent	Dielectric constant (ϵ)	Axial anomer (%)
CCl ₄	2.2	83
Benzene	2.3	82
CS ₂	2.6	80
CHCl ₃	4.7	71
Acetone	20.7	72
Methanol	32.6	69
Acetonitrile	37.5	68
water	78.5	52

Figure 1-9: Effect of the solvent on the anomeric equilibrium¹⁰³

1.4.2 Transport across the blood-brain barrier

The blood-brain barrier (BBB) facilitates the separation and filtration of objects or molecules entering or leaving the blood supply within the brain.¹⁰⁴ The barrier exists along capillaries which are lined with endothelial cells. It is these cells that restrict the flow of certain molecules out of the bloodstream by packing tightly together, whilst still allowing the diffusion of smaller molecules such as oxygen.

Glucose is essential to the mammalian brain as it is the primary source of metabolic energy and a constant supply of the molecule is vital to normal cerebral function.¹⁰⁵ The molecule is not able to pass through the membrane without assistance due to its hydrophilicity.

Glucose transporters (GLUT) are proteins which transport glucose and other hexoses across the various membranes in the body, with GLUT1 being present in high levels in the endothelial cells at the BBB.^{106,107}

1.4.3 Transportation of therapeutic agents to specific locations

Although many therapeutic agents are synthesised and brought to clinical trials every year, their limitation is realised when they fail to reach the site at which they need to perform the role for which they are intended.

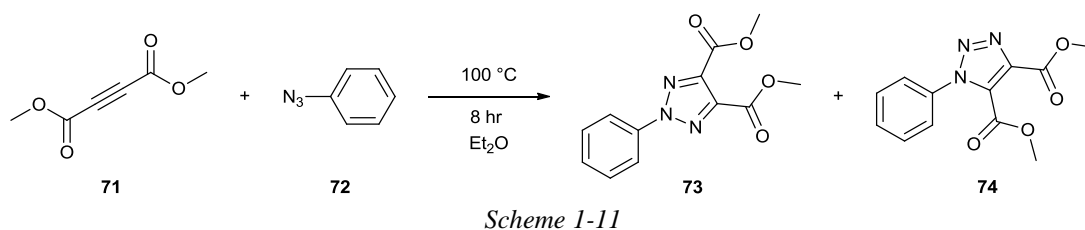
In 1971, John Rogers *et al.* first reported an example of “carrier mediated” targeting, by targeting protein receptors in the liver using carbohydrate ligands.¹⁰⁸ In some more recent cases, the attachment of a carbohydrate to a drug or therapeutic agent can increase their ability to transport across the BBB due to active transport.¹⁰⁹⁻¹¹¹

1.5 'Click' Chemistry

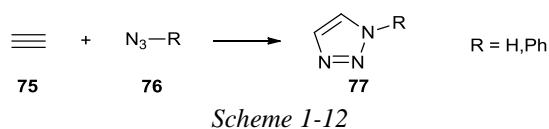
1.5.1 Introduction

In 1954, Boyer and Canter published a review on azides and their chemistry.¹¹² On discussing the thermal reaction of alkynes and azides to form triazoles, they said, "the reaction has not been extensively investigated but appears to be quite general". At that time, Boyer and Canter were unaware of the scope and depth that this type of clean, simple reaction would have.

Arthur Michael reported the first example of an uncatalysed cycloaddition reaction of the type shown in Scheme 1-11.¹¹³ The results of this investigation were published in 1893 and required high temperatures as is shown in Scheme 1-11.



Dimroth and Fester followed Michael in 1910 with their reaction between alkyne **75** and azide **76** to form a triazole.¹¹⁴ They combined acetylene with hydrogen azide and phenyl azide to form triazole and 1-phenyl-triazole (Scheme 1-12).



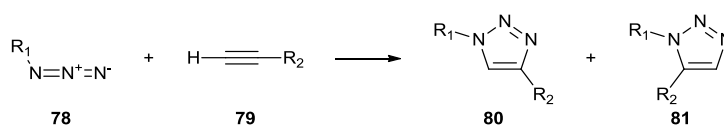
It was not until 2001, when Barry Sharpless published work on what he termed "click" chemistry, that this reaction was used as a simple way of forming complicated structures. The term "click" chemistry refers to a whole series of reactions where complex structures are created from simple starting materials with minimal side products that can be removed simply.¹¹⁵

1.5.2 Huisgen Cyclisations

The Huisgen cyclisation is a type of 1,3-dipolar cyclisation between a 1,3-dipole and a dipolarophile. Rolf Huisgen was one of the first people to research the full scope of this

type of reaction including cyclisations between nitrile ylides, nitrilimines, nitrile oxides, diazoalkanes, azides and nitrous oxide.¹¹⁶

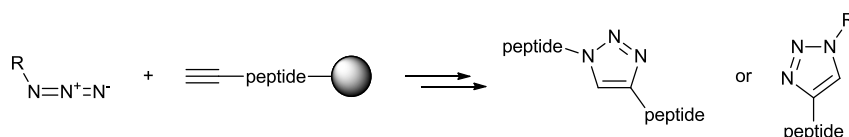
When carrying out the cycloaddition reaction between an azide and an alkyne, there are two possible products as the 1,3-cycloaddition is non-regiospecific (Scheme 1-13). To get the reaction to proceed in reasonable yields, high temperatures are needed. There is still the problem of regioisomers, unless an electron withdrawing group is attached to the acetylene, in which case, higher ratios of the 1,4 product **80** are obtained.



Scheme 1-13

Copper mediated azide-alkyne cyclisation (CuAAC)

In 2002, Meldal *et al.* published the first example of a copper catalysed, fully regioselective cyclisation reaction.¹¹⁷ His work involved the synthesis of solid-supported histidine analogues and investigations towards peptidotriazoles (Scheme 1-14).



Scheme 1-14

The use of a copper catalyst in his reaction affords the 1,4-isomer as the sole adduct, and allows mild conditions, making the reaction ideal on a practical basis. Although the reaction can be carried out using Cu^I directly, from compounds such as copper bromide, the reaction is improved by forming the Cu^I in situ, using Cu^{II} and a reducing agent such as sodium ascorbate.

The CuAAC reaction is limited in that only terminal alkynes can be used.

Ruthenium mediated azide-alkyne cyclisation (RuAAC)

By comparison, replacing copper with ruthenium in this reaction can result in a dramatic change in the regiochemistry of the reaction resulting in the formation of the 1,5-regioisomer.^{118,119} In addition, both terminal alkynes and internal alkynes can be

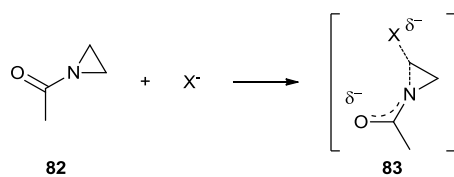
employed in this reaction.¹¹⁹ The reactions between aryl azides and alkynes can meet with problems, where low yields and side-products are often recovered. This can be rectified by the modification of the type of ruthenium catalyst.¹²⁰

1.6 Aziridine Chemistry

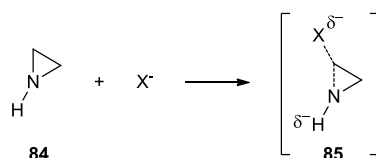
The chemistry of aziridines has become of great interest in recent decades, with their application in synthetic chemistry becoming more widespread.¹²¹⁻¹²³ Their flexibility arises from their ability to ring open regioselectively and stereoselectively using a variety of nucleophiles in a 1,2-relationship to nitrogen.¹²⁴⁻¹²⁸ The adaptability of aziridines has allowed them to be used as intermediates of several natural products,¹²⁹⁻¹³¹ and aziridine units are present in a small number of natural products.¹³²⁻¹³⁴

Aziridines can be described as activated and non-activated, terms coined by Ham in 1964.¹³⁵ He described activated aziridines as those that were able to stabilise a negative charge on the nitrogen in the reaction transition state (Scheme 1-15), and non-activated systems as those generally with either no substituent at the nitrogen or a basic substituent.

Ham described how the ability to conjugate a partial negative charge on the aziridine reduces the activation energy required to form the transition state compared to that of a non-substituted or base-substituted aziridine (Scheme 1-16).



Scheme 1-15

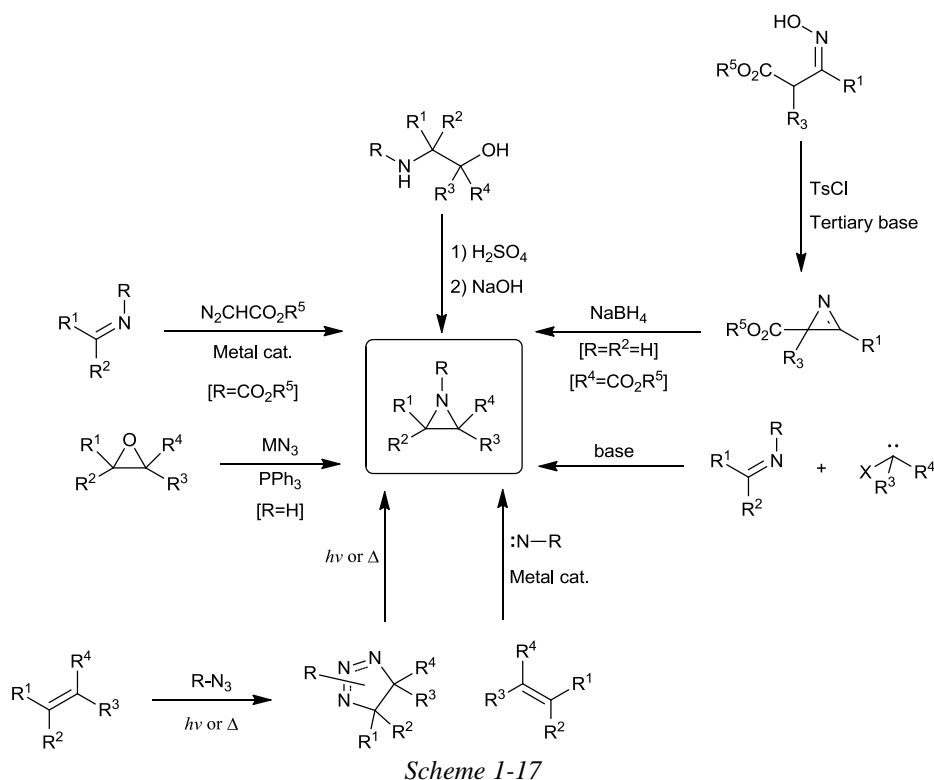


Scheme 1-16

1.6.1 Synthesis of aziridines

Though the methods to form aziridines are dwarfed by those described for the analogous epoxides, there is an assortment of preferred routes to the three-membered ring, illustrated in Scheme 1-17.¹³⁶ Aziridines are generally synthesised from cheap,

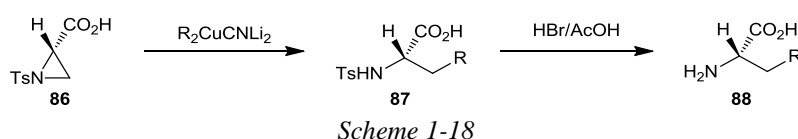
chiral starting materials, as the introduction of specific stereocentres has been found to be difficult, leading to the formation of multiple regioisomers.¹³⁷



1.6.2 Nucleophilic Ring-Opening Reactions

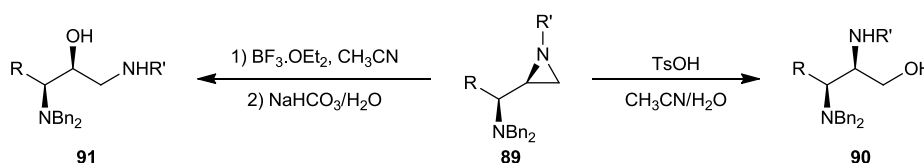
When examining ring opening reactions which have been performed on aziridines, often observed are those which employ Lewis acid catalysts or alternatively, activation of the ring by substitution on the nitrogen. The responsiveness of aziridines to nucleophilic ring opening stems from the strained ring structure.

The ring opening reaction can be facilitated by a variety of nucleophiles, including carbon-based nucleophiles. In 1995, Church and Young managed to synthesise a variety of α -amino acids by the nucleophilic ring-opening (NRO) of aziridines with carbon-based nucleophiles (Scheme 1-18).¹³⁸



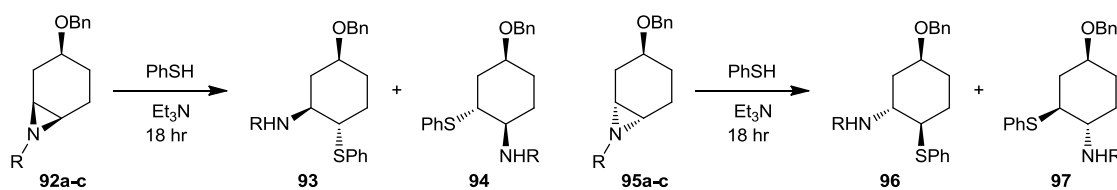
Examples of the regioselective NRO of aziridines using oxygen nucleophiles have also been performed. Concellón and Riego illustrated a reagent-dependant NRO, where the

use of a protic acid leads to attack at the C-3 position and use of boron trifluoride etherate leads to ring opening at C-2 (Scheme 1-19).¹³⁹



Scheme 1-19

Regioselectivity has also been observed when ring opening aziridines with sulfur-based nucleophiles. The NRO can be carried out on both activated and non-activated aziridines, and generally, attack at the less hindered position is observed to provide 2-amino sulfide products.^{140,141} In 1995, Crotti *et al.* carried out the ring opening on a variety of aziridines using thiophenol and triethylamine (Et₃N).¹⁴² Scheme 1-20 shows the results he obtained when performing the NRO using mild conditions. He suggested a reaction intermediate by way of a chelate structure where the coordination leads to regioselectivity.



92	R	% 93	% 94	95	R	% 96	% 97
a	H	59	41	a	H	>99	<1
b	CO ₂ Et	<1	>99	b	CO ₂ Et	>99	<1
c	Ts	<1	>99	c	Ts	>99	<1

Scheme 1-20

1.7 Macrocycles as sensors

1.7.1 Neurodegenerative disorders

1.7.1.1 Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease (HD) and Parkinson's disease (PD) arise due to the loss of function of neurons. A contributory factor to this disease is a genetic mutation, in which a CAG nucleotide triplet is repeated.¹⁴³⁻¹⁴⁵ The CAG nucleotide triplet is responsible for encoding the glutamine amino acid. The protein that results from this mutation therefore contains a

large string of glutamine residues leading to what is known commonly as polyglutamine-repeat diseases. Despite the fact that these polyglutamine proteins are toxic to cells, these proteins are not enough to cause neurodegenerative diseases in isolation.¹⁴⁶

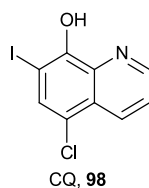
Oxidative stress has also been linked to the development of diseases such as AD, HD and PD.¹⁴⁷ Although vital to life, the reactivity of oxygen must be tightly controlled. Oxidative stress is what occurs when the production of reactive oxygen species (ROS) *e.g.* oxygen ions, peroxides, and oxygen radicals, as well as the body's ability to remove or repair damage due to the ROS, become imbalanced.^{148,149}

1.7.1.2 Alzheimer's Disease

Alzheimer's Disease is thought to occur due to a build-up of plaques of a derivative of β -amyloid ($A\beta$) within the brain tissue, although hypotheses are continuously being modified.¹⁵⁰ $A\beta$ is cleaved from the membrane-bound amyloid precursor protein (APP), whose function is as yet unknown. The plaques have been described as metal sinks as they readily coordinate high concentrations of copper, zinc and iron.¹⁵¹⁻¹⁵³ In areas of the brain which are more susceptible to AD neurodegeneration, the metals in question are found in high concentration, often 3 – 5 times higher than usual levels.^{152,154} Recent theories have linked the production of ROS to the presence of Fe, Cu and Zn.¹⁵²

Treatment

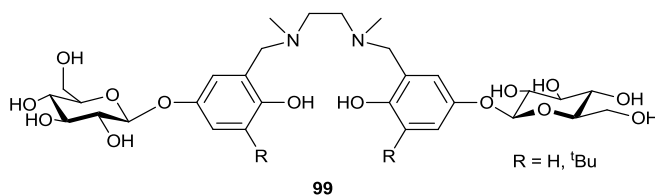
Clioquinol (CQ, **98**) originally developed as an antifungal drug, is commonly used to treat a variety of infections. Its use against protozoal infections was halted in some countries after a number of people developed a disease of the nervous system in Japan, which led to paralysis, blindness and occasionally death. CQ was therefore withdrawn from use despite this result not being seen in other countries around the world.¹⁵⁵⁻¹⁵⁷ CQ was later proposed as an early treatment of AD, and taken to phase 2 clinical trials.¹⁵⁸ The trial proved the concept in humans that drugs targeting metal- $A\beta$ interactions have a large effect on the amyloid's metabolism. Unfortunately, it also showed that CQ had minimal effect on patients, except those that were more severely affected.



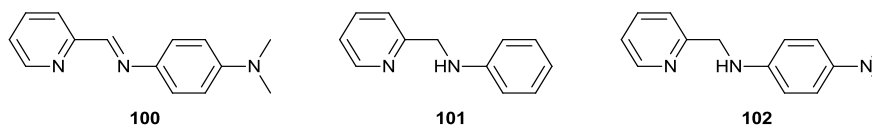
On tests against Huntington's Disease, treatment with CQ promoted cell survival *in vitro* and decreased associated symptoms in model animals. Massa *et al.* thought that the mechanism of action might be due to the coordination of metals. Despite the fact that CQ is a relatively weak chelator and will not interact with tightly bound metals, under some conditions, the metals can be released or loosened allowing low-affinity chelators to have an effect.¹⁵⁹

Investigations

In 2003, Orvig *et al.* first suggested the use of carbohydrate-functionalised ligands **99** as potential complexants for copper or iron to disrupt the formation of ROS under the assumption that the metals played a large role in the manifestation of AD.¹⁶⁰



On investigating the potential use of this compound, they discovered that it had moderate potential for binding Cu and Zn and reduced aggregation of A β due to this binding, demonstrating its possible use as an AD therapeutic.



Lim *et al.* have also investigated bifunctional molecules **100-102**, able to coordinate the metals and also interact with A β , which was characterised by their ability to modulate aggregation *in vitro* and in living cells.¹⁶¹

1.8 Macrocycles as catalysts

1.8.1 Previous studies by the Bailey group

Previous work within the Bailey group has explored a group of novel peptidic, pyridine-derived macrocycles, with the aim of creating a new type of enantioselective catalyst or enzyme mimic.¹⁶² The chiral centres in the structures **103a-d** are provided by the incorporation of alanine, with the hope of influencing the approach of any incoming nucleophile, but also allowing sufficient room for reactions to take place on the pyridyl nitrogen. The macrocycles are all C₂-symmetric along their principle axis ensuring the chiral environments on either side of the structure are identical.

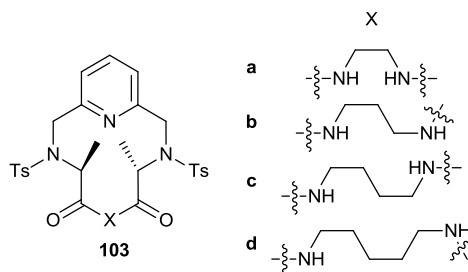
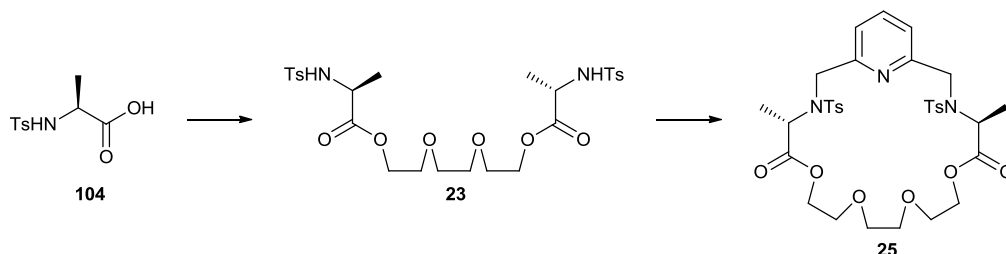


Figure 1-10: Series of peptidic, pyridine derived macrocycles synthesised by Bailey *et al.*

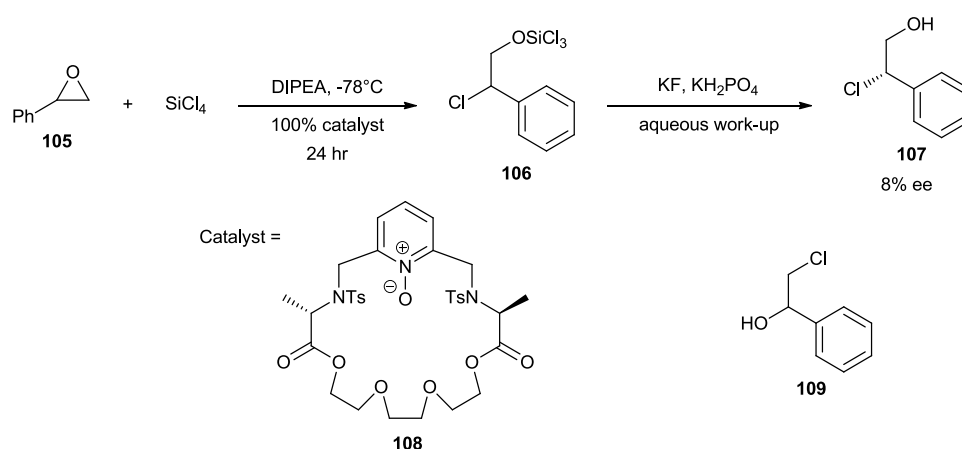
In 2006, Sethi carried out research on a slightly different range of these macrocycles, examining their potential for binding a range of organic guests such as glycine amide, acetyl L-alanine, L-alanine amide and acetyl glycine.²⁸ In particular, Bailey and Sethi examined the triethylene glycol-based macrocycle **25** synthesised from the simple amino acid L-alanine **104**, observing that binding to the host was entropically driven. The most stable binding was observed with acetyl L-alanine, and the least stable with L-alanine amide.



The chiral crown ether macrocycles prepared by the Bailey group comply with requirements observed by Fu *et al.*, and therefore are potential asymmetric catalysts

(section 1.8.3.2). He realised that the high selectivity of the catalyst he employed, was dependent on the presence of an electron rich donor group and also steric hindrance.

The pyridine *N*-oxide macrocycle **108** has been synthesised and used by the Bailey group in the ring-opening of styrene epoxides (Scheme 1-21, for more explanation see section 1.8.3.2). The product 2-chloro-2-phenylethanol **107** was synthesised in 95% yield, and there was no evidence for formation of 2-chloro-1-phenylethanol **109**. The C_2 -symmetry of the macrocycle enabled the epoxides to approach from either side ensuring the reaction was not hindered in any way.

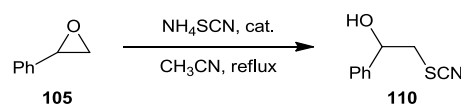


Scheme 1-21

A series of control reactions were also carried out to show that the regioselective ring-opening was due to the catalyst **108** and not the presence of the by-product HCl, by stirring the epoxides with HCl. This resulted in the formation of equal amounts of chloroalcohols **107** and **109**. In addition, carrying out the procedure as in Scheme 1-21, but without the catalyst showed no reaction at all, so the base was not strong enough to open the ring by itself.

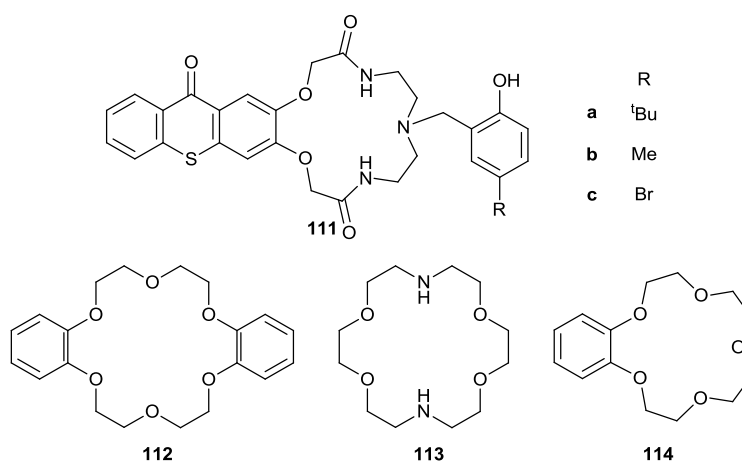
1.8.2 The application of mixed-donor crown ethers to catalysis

Many types of crown ether have been used in the past as catalysts. Most popular is their application to the regioselective ring opening of epoxides.¹⁶³



Scheme 1-22

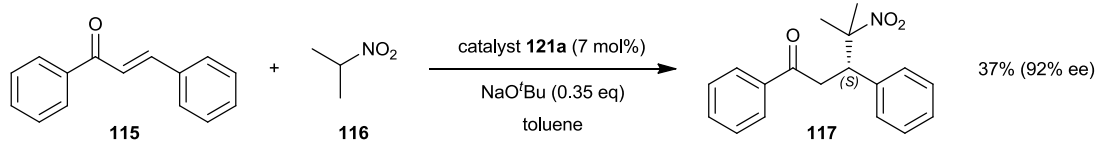
In 2007, Sharghi *et al.*¹⁶⁴ published a body of work investigating the use of various crown-ether derivatives as catalysts for the ring opening of epoxides with ammonium thiocyanate in the aprotic solvent acetonitrile (Scheme 1-22). The β -hydroxy thiocyanate **110** was formed under mild conditions using 0.01 mol% of a variety of catalysts (**111a-c**) synthesised by the group, and also, known ethers **112–114** for comparison.



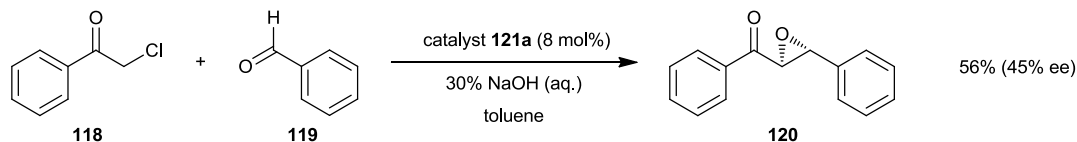
The reactions were successful and gave over 90% regioselectivity. For crown ethers **112-114**, reactions times ranged from 60 to 90 minutes, with the yield varying from 55 – 70%. For reactions where the modified catalysts **111a-c** were present, conditions ranged from 25 minutes with a 90% yield for **111a** to 90 minutes with a 55% yield for **111c**. Having discovered the superiority of **111a**, further epoxide ring opening reactions were performed to test the generality of their conditions. They obtained regioselective thiocyanate products with yields over 75% for 10 different epoxides.

Although first synthesised by Bakó *et al.* in 1995,¹⁶⁵ it was not until 2001 that varieties of azocrown ether **121** were applied as phase-transfer catalysts (PTC) in reactions like the Michael reaction or Darzens reaction (Figure 1-11).¹⁶⁶⁻¹⁶⁸ Bakó *et al.* discovered the catalysts' ability to induce asymmetrically a reaction as a PTC. Early in 2011, Bakó *et al.* published results originating from the use of crown ether catalysts containing the α -D-glucopyranoside unit **121**. They observed a greater extent of asymmetric induction than for the mannose-based **122** when carrying out the Darzens reaction and epoxidation on furan-, thiophene-, or pyrrole-based molecules.

Michael Addition:



Darzens condensation:



Asymmetric epoxidation:

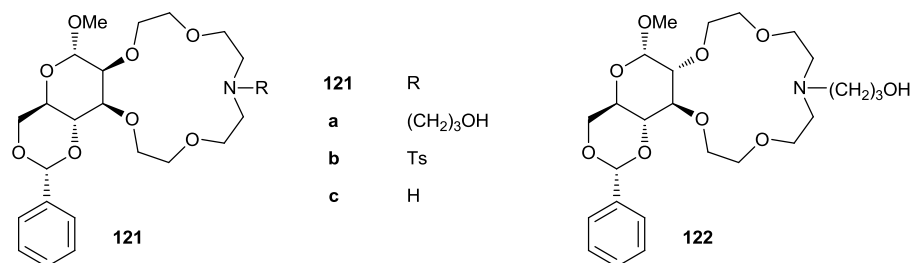
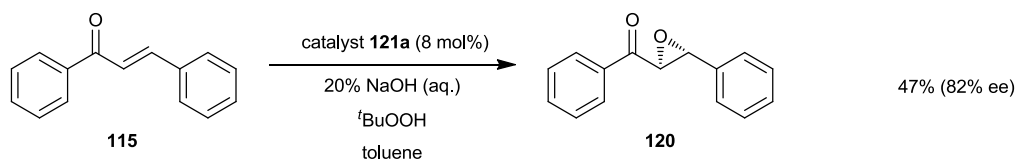
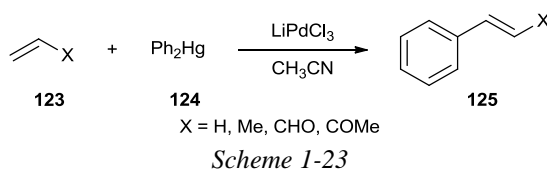


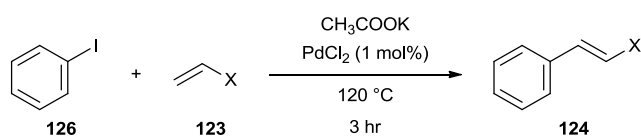
Figure 1-11: Use of crown ether-based catalysts in various bond forming reactions

1.8.3 The use of macrocycles as catalysts

1.8.3.1 The Heck Reaction

The palladium catalysed coupling of either a haloarene or haloalkene with an alkene was first discovered by Richard Heck in 1968 (Scheme 1-23^{169,170}) and has now come to be known as the Heck or Mizoroki-Heck reaction. In the early 1970s, Mizoroki published his findings on the potential of the Heck reaction, using iodophenol to replace the mercuric materials initially used by Heck (Scheme 1-24).¹⁷¹ Soon after, Heck *et al.*, published the same, independent findings using palladium acetate.^{172,173}





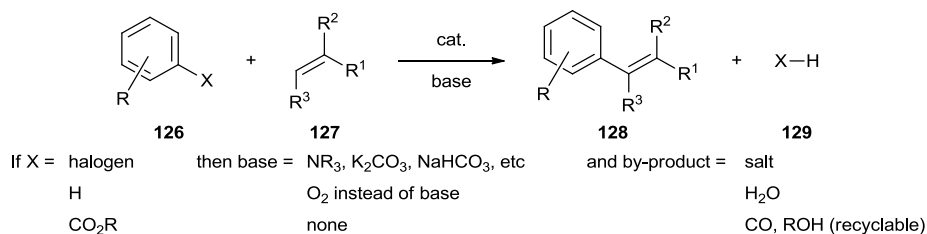
X = H, Ph, Me, CO₂Me

Scheme 1-24

Since then, the scope of this type of C-C bond forming reaction has been greatly explored. It is commonly used in natural product synthesis as a simple way of regioselectively creating a C-C bond.¹⁷⁴⁻¹⁷⁶

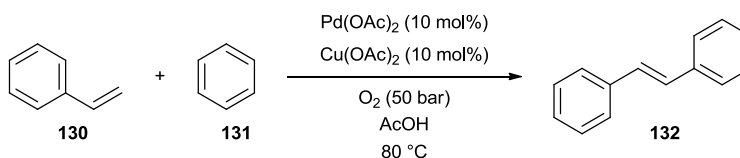
Limitations of the Heck reaction

Unfortunately, although a very useful method, the Heck reaction creates waste material originating from the halide leaving group, which results in the formation of strong acids. Normally these strong acids are trapped by the addition of base which then results in the formation of salts. Even worse, some of the best yields in the Heck reaction have been obtained when using polar aprotic solvents like DMF which in itself are environmentally harmful. To become a truly useful reaction, the formation of waste which in a laboratory environment is disposed of as aqueous waste, must be eliminated or at least limited, otherwise the industrial use of the Heck reaction is restricted.



Scheme 1-25

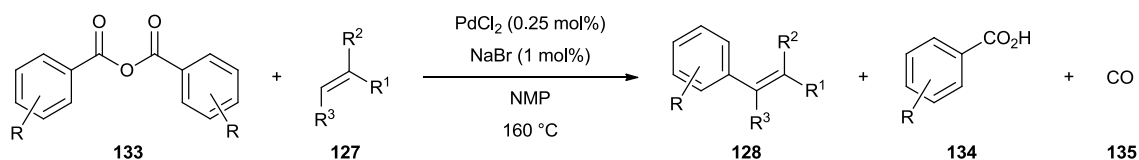
Replacement of the halide with a proton eliminates the formation of salt, and instead results in water as a sideproduct. The first example of an oxidation Heck reaction was published by Fujiwara *et al.*, who carried out a number of C-C bond forming reactions using palladium acetate (Scheme 1-26).¹⁷⁷



Scheme 1-26

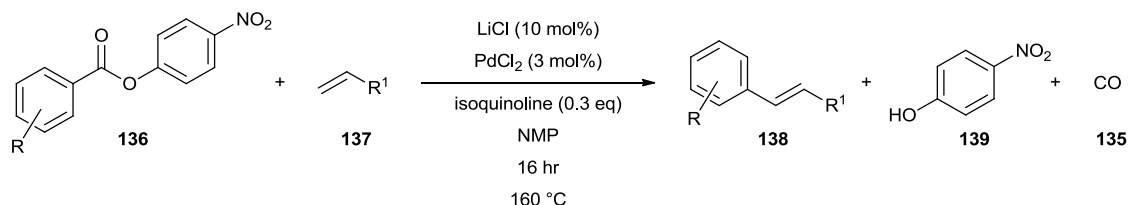
Of course, the drawback of this approach is obvious. As with many electrophilic aromatic substitution reactions, a mixture of regioisomers may be obtained as an often inseparable mixture when carrying out the reaction on substituted starting materials.

The possibility to maintain the “green” nature of the reaction, and yet still have an attached leaving group to direct the position of bond formation has been shown. It was de Vries *et al.* who discovered that aromatic anhydrides when added to palladium catalysts, decarbonylate to result in the formation of the substituted olefin, a benzoic acid derivative, and carbon monoxide (Scheme 1-27).¹⁷⁸ In this example, the benzoic acid derivative formed can be recycled into its anhydride, and the carbon monoxide simply burnt to carbon dioxide.

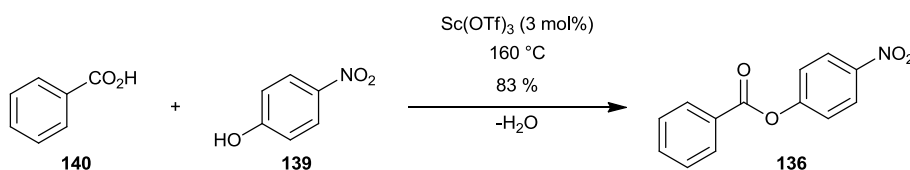


Scheme 1-27

Four years later, in 2002, Gooßen and Paetzold published their advancements on de Vries’ use of carboxylic anhydrides, by the use of esters (Scheme 1-28).¹⁷⁹ This body of work furthered the environmental viability of the reaction by forming an alcohol instead of a carboxylic acid. The alcohol could be easily recycled by reaction with the desired carboxylic acid and Sc(OTf)₃ so that overall, the only waste products from the Heck reaction were carbon monoxide and water. Despite having only two by-products, the reaction still requires a high temperature and two reactions to ensure there are minimal side products.



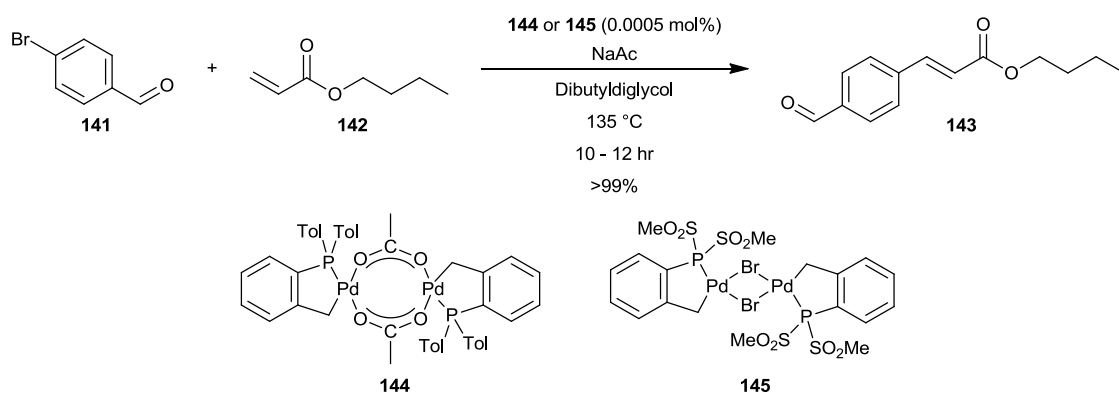
Scheme 1-28



Scheme 1-29

A major problem with the Heck reaction is that the catalyst is often lost at the end of the reaction as it is overly soluble in the polar solvents that are most commonly used. This problem has been shown to be overcome by the use of ionic liquids as solvents by Carmichael *et al.*,¹⁸⁰ who, in 1999, carried out Heck reactions on a variety of substrates in low melting point *N,N*-dialkylimidazolium or *N*-alkylpyridinium ionic liquids. The modification of solvent makes no substantial difference in the overall reaction, as ionic compounds are often added to increase yields of Heck reactions in polar solvents. Carmichael *et al.* also observed the ease at which the product can be isolated from the reaction mixture, by a simple solvent extraction, leaving the catalyst and ionic liquid to be recycled.

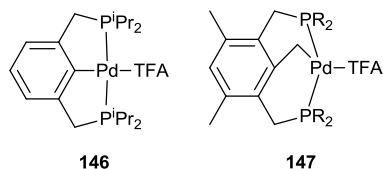
Problems with variable yield and overall environmental sustainability of the Heck reaction then arise because of the type of catalyst being used in individual reactions. Palladium (II) chloride, although relatively cheap by comparison to other Pd(II) compounds, is insoluble in aqueous solutions leading to problems with homogeneous reactions. Work has therefore been carried out into the modification of these catalysts to try to make them more manageable. Key in the modification of the catalyst is what is known as the turnover number (TON), which is a measure of the ratio of moles of product to catalyst.



Scheme 1-30

In 1995, Herrmann *et al.* published work on a new type of palladacycle (for example **144** and **145**) which afford exceptional TONs of up to 2×10^5 (Scheme 1-30).¹⁸¹ From this piece of work, many other research groups began to look into different types of high TON catalysts.^{182,183} These include pincer complexes and half pincer complexes which have shown great promise in C-C bond forming reactions of all types. These types of

catalyst possess several other advantages, such as their air stability and the ease of handing over catalysts formed *in situ* from palladium acetate and phosphines.

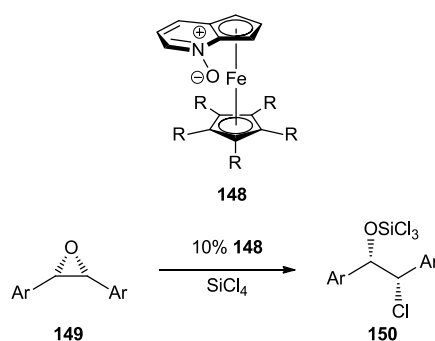


Soon after Hermann published his work on the palladacycles, Milstein *et al.* reported a new type of palladium catalyst for the Heck reaction, which was thermally stable up to 180 °C and insensitive to oxygen.¹⁸⁴ These PCP catalysts (**146** and **147**) showed very high catalytic activity, with TONs of up to 5.3×10^5 in the Heck coupling of aryl iodides and bromides.

Other palladacycles containing not just phosphorous, but also nitrogen and sulfur, are among the most active catalysts for the promotion of the Heck reaction to date, and are still frequently being researched.^{182,185,186}

1.8.3.2 Enantioselective opening of *meso*-epoxides

A large amount of work has been carried out on the regio- and enantioselective nucleophilic ring opening (NRO) of epoxides. Germane to our work is the observation by Fu *et al.*, where “planar chiral” pyridine *N*-oxides **148** were employed in the desymmetrisation of *meso*-epoxides.¹⁸⁷ To date there is no single catalyst that opens a wide range of epoxides with good enantioselectivity.



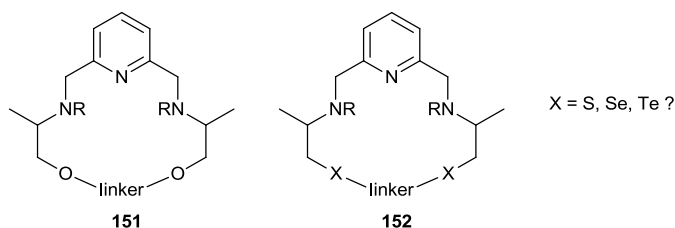
Scheme 1-31

Denmark *et al.* first looked into the desymmetrisation of *meso*-epoxides, to give optically active chlorohydrins.^{188,189} Fu *et al.* then went on to study this reaction and use the *N*-oxide **148** to catalyse the reaction.¹⁸⁷ It was noticed that when R = Me in the catalyst **148**, the ring opening of *cis*-stilbene **149** progressed with just an 11% e.e.

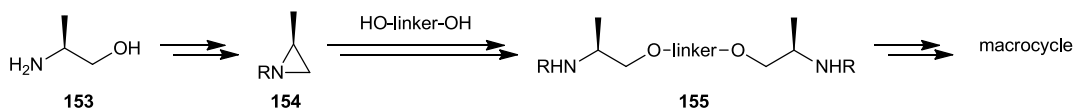
(enantiomeric excess). Use of a more sterically hindered group on the catalyst, R = Ph, provides higher selectivity (25% e.e.) at room temperature which is further enhanced by decreasing the temperature to -78 °C (60% e.e.).

1.9 Project Aims

Upon reviewing the literature, it is evident that macrocycles already reported in the Bailey group may have potential applications in a variety of areas, including the development of selective metal ion complexants or chiral ligands for use in asymmetric catalysis. What is also clear from these earlier studies is the fact that the presence of ester-based linkages within the backbone of the macrocycle may limit their general utility because of their lack of chemical stability. Further investigations into the nature of the spacer units embedded within the macrocycle with a view to enhancing their overall stability is therefore required. For example, the incorporation of ether linkages (**151**) or “softer” chalconides (**152**) in the basic motif may engender either chemical robustness or selectivity in complexation with specific (“softer”) metal ions

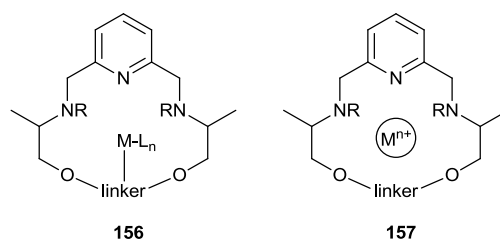


Synthesis of the ether-based macrocycles will rely upon the ring opening of an aziridine **154**, which is based on research carried out previously within the Bailey group,¹⁹⁰ where the chirality originates from the chiral pool. In this potentially modular approach it was envisaged that nucleophilic ring opening of the aziridines such as **154** could be achieved using a range of diols, generating “spacers” **155**, which could then be utilised in the desired macrocyclisation reactions. Extension of this approach using dithiols or diselenols in the aziridine ring-opening reaction would ultimately enable a library of macrocycles to be prepared, whose chemistry could then be investigated.



Scheme 1-32

The binding efficiency of these novel macrocycles – which possess combinations of mixed hard/soft donor sites - could then be probed in order to optimise their binding to specific metal ions. The synthesis of macrocycles of this type is currently of interest because of their potential to bind to heavy metals such as Cu and Hg.



Having optimised the specificity in the binding of macrocycles **156/157** to metal ions (*e.g.* Cu) their incorporation into sensors for use in biological assays will be developed (Figure 1-12). One current hypothesis concerning the aetiology of Alzheimer's Disease suggests that the build-up of plaque within brain tissue is associated with the presence of metal ions such as Zn^{2+} and Cu^{2+} . The development of a probe capable of mapping the distribution of metal ions in brain tissue in comparison to location sites of plaque generation may have some diagnostic value.

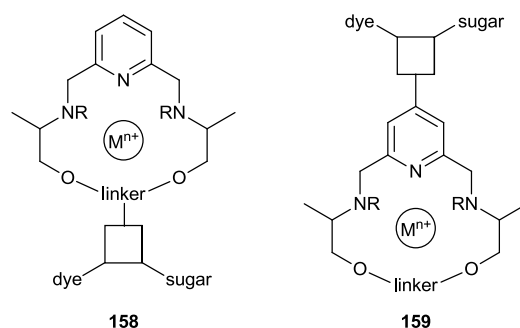


Figure 1-12: Potential targets for use in biological assays

Naïvely, it was considered that attachment of a carbohydrate to the macrocycle would aid the transport of the sensing macrocycles across the blood-brain barrier. Ligation of a dye or fluorescing agent to the macrocycle would also facilitate the determination of the bio-distribution of the macrocycle. The ultimate aim of this project is therefore to identify a selective metal-ion sensor which will be transportable across the BBB and will be able to report (*via* fluorescence *etc.*) the detection of specific metal ions in brain tissue.

RESULTS AND DISCUSSION

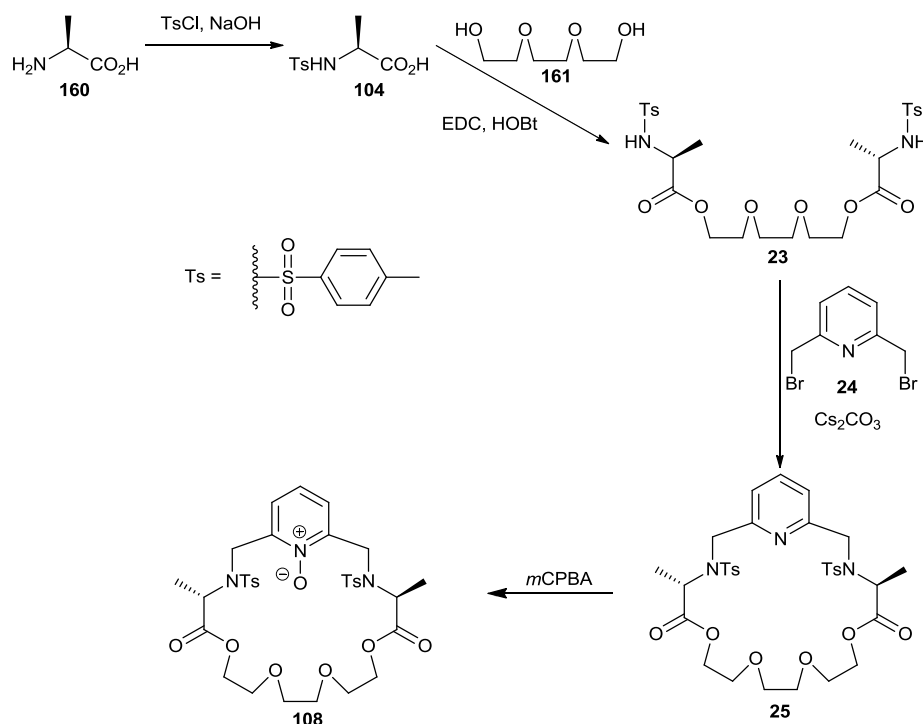
2 Results and Discussion

2.1 Chiral Peptidic Macrocycles

2.1.1 Introduction

Previous work in the Bailey group²⁸ has been based on synthesising novel pyridine-based crown ether macrocycles. The main use of these macrocycles was to explore their catalytic enantioselective properties in the Heck reaction and their host-guest properties with respect to the binding of small molecules and ions (see section 1.1).

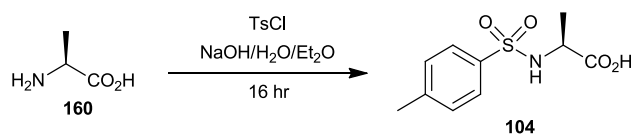
First, the synthesis of a macrocycle **108** previously prepared by the group²⁸ was repeated. An overview of the synthesis is shown in Scheme 2-1. The chirality is provided by the incorporation of L-alanine.



Scheme 2-1

2.1.2 N-Tosyl Alanine

The first step in the synthesis was the tosylation of L-alanine. The amino acid was dissolved in 1.5 M aqueous NaOH, and tosyl chloride in diethyl ether was added (Scheme 2-2). The reaction was stirred overnight at room temperature and after acidic work-up produced N-tosyl alanine in 74% yield as a colourless crystalline solid.¹⁹¹



Scheme 2-2

The *N*-tosyl alanine was chosen as the building block for two reasons. The tosyl group makes the anion formed after deprotonation more acidic, due to stability by resonance, allowing the key cyclisation reaction to proceed smoothly (Figure 2-1). The sulfonamide is also UV active and so subsequent reactions can be monitored by TLC analysis.

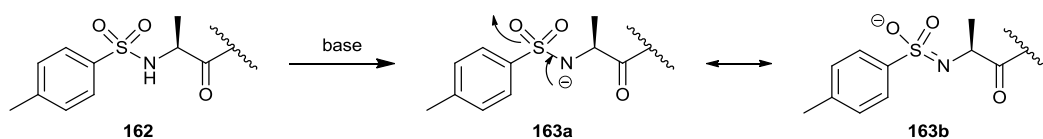
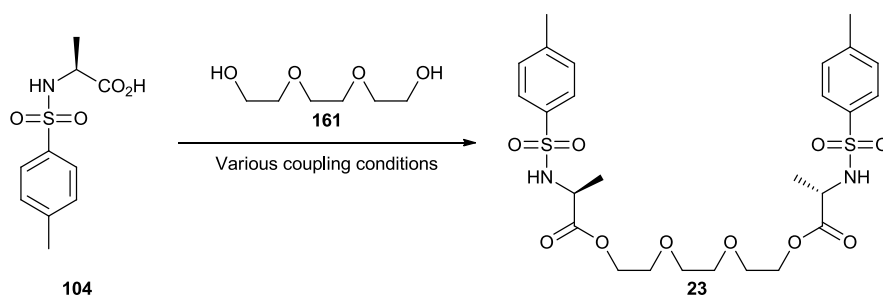


Figure 2-1: Illustration of the stabilisation of anionic charge after deprotonation of a tosyl protected amine

2.1.3 The Spacer Unit

When deciding upon the structural properties of the macrocycle, the spacer unit is an important aspect. Both Sauvage^{192,193} and Stoddart¹⁹⁴ have shown that, in general, it is easier to make large supramolecular structures that incorporate glycol rather than alkyl spacers. This is because glycols provide more flexibility and rotational freedom.



Scheme 2-3

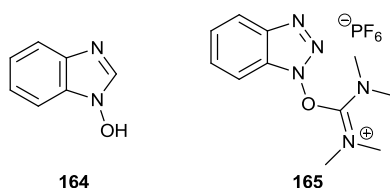
Initially, we wished to improve upon the original Bailey group synthesis by avoiding the need to use *N*-hydroxybenzotriazole (HOBt) in the esterification reaction (Scheme 2-3), due to its potentially explosive nature. However, when alternative coupling reagents and conditions were investigated, all suffered from significantly reduced yields.

Entry	Reaction Conditions				Reaction Time (hr)	Outcome	
	Reagents (Equivalents)		Temperature (°C)	Solvent			
	TsAlaOH (104)						
1	2.0	HBTU (2.2)		0 → rt	DMF	40	104 (60%)
2	2.1	HBTU (2.4)		0 → rt	THF	24	Unidentifiable
3	2.0	HBTU (2.2)	DIPEA (2.0)	0 → rt	DMF	48	Unidentifiable
4	2.0	HOSu (2.0)	EDC (2.0)	0 → rt	THF	24	104 (100%)
5	2.0	HOBt (2.0)	EDC (2.0)	0 → rt	THF	24	23 (15%)
6	2.0	DCC (2.0)	DMAP (0.2)	0 → rt	DMF	16	Unidentifiable
7	2.0	EDC (2.2)	DMAP (0.2)	0 → rt	DCM	24	Unidentifiable
8	2.2	HOBt (2.2)	EDC (2.2)	0 → rt	DMF	24	23 (5%)
9	2.2	HOBt (2.2)	EDC (2.2)	0 → rt	THF	48	23 (11%)
10	4.0	HOBt (5.0)	EDC (5.0)	DIPEA (5.2)	THF	24	23 (12%)
11	2.0	Ph ₃ P (2.2)	DIAD (2.2)	rt	THF	15 min sonication	104 (35%)
12	2.0	HOBt (2.0)	EDC (2.0)	rt	THF	96	23 (8%)
13	2.2	HOBt (2.2)	HBTU (2.2)	DIPEA (5.0)	THF	161	23 (22%)
14	2.2	HOBt (2.2)	HBTU (2.2)	DIPEA (5.0)	THF	24	104 (20%)
15	2.2	HOBt (2.2)	HBTU (2.2)	DIPEA (5.0)	DMF	40	104 (90%)

Table 2-1: Summary of explored conditions for di-ester syntheses. (Equivalents are in relation to TEG.)

Table 2-1 outlines the various attempts to synthesise the di-ester **23**. The same method was followed in each case, in which the acid was stirred first with the coupling reagent(s) in the presence of base where applicable. The glycol was added and the reactions monitored by TLC analysis and NMR spectroscopy before work-up after stirring at the stated temperature and for the stated time. Analysis by NMR spectroscopy focussed on the shift difference between the sulfonamide NH of the acid **104** (5.18 ppm) and the di-ester **23** (5.53 ppm).

We had hoped *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate **165** (HBTU) in particular would provide an efficient alternative as it contains both the functionality of HOBt **164** and also a carbodiimide. HBTU is commonly employed in peptide coupling reactions for this reason.¹⁹⁵ Despite repeated and various attempts at optimisation (entries 1-3) no evidence of di-ester formation was seen.



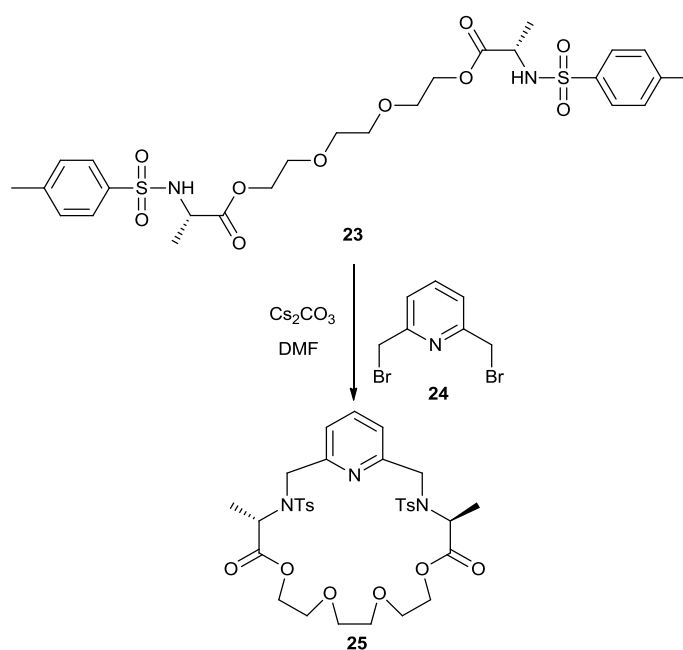
Surveying methods that the Bailey group have followed in previous years for this di-ester formation, it was known that the standard method of HOBt and EDC (entry 5, Table 2-1) was used for the synthesis of amides.¹⁹⁶ Entry 13 (using the method of Jou *et al.*¹⁹⁷) was the most successful despite a yield of 22%.

We thought that warming the reaction gently would accelerate the progress of the reaction, so the procedure was repeated at 40 °C (entry 14, Table 2-1). After 24 hours, analysis by NMR spectroscopy indicated that the ratio of product to starting material was 1:1. After 48 hours, the product ratio had increased to 3:2. When the rest of the reaction was worked-up, yield of the crude material was 50%, and the ratio was still around 3:2 in favour of the di-ester. However, due to the presence of a large amount of unreacted glycol, flash column chromatography was problematic, and gave a yield of 6%.

The next step was to investigate solvent effects. As many amino acid coupling reactions take place in DMF, not THF, the reaction was repeated (entry 15, Table 2-1), in this solvent. Unfortunately, after purification, only starting material was recovered.

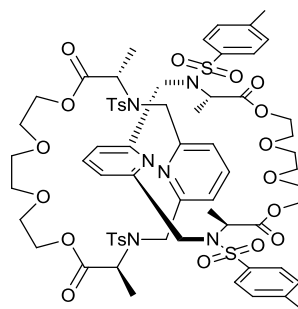
2.1.4 Cyclisation of the *N*-tosyl alanine spacer unit

Although the experimentation in di-ester synthesis was incomplete, the product was taken through to the next step, to form the macrocycle **25** by reaction of the di-ester with 2,6-bis(bromomethyl)pyridine **24** as the cross-linking unit (Scheme 2-4).



Scheme 2-4

Stabilisation of the di-ester anion spacer (**23**) by the tosyl groups (Figure 2-1) made it possible to use a mild base which incorporated templating features (as discussed in section 1.1.2.2). Alternative protecting groups may not have afforded this ability.



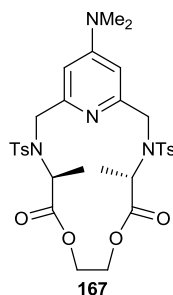
166

It was thought that the reaction potentially could give a [2]-catenane **166**, where the macrocycles form through one another. To prevent this, the reaction was carried out under high dilution (3 mM). High dilution also prevented polymerisation, which could have been possible due to the flexibility of the glycol chain within the spacer unit.

Equimolar amounts of the di-ester **23** and 2,6-bis(bromomethyl)pyridine **24** were stirred in dry DMF with 5 equivalents of caesium carbonate at room temperature. Once the reaction was complete as judged by TLC analysis, it was worked-up to give the desired macrocycle **25** in quantitative yield.

2.1.5 Synthesis of the Macrocylic *N*-Oxides

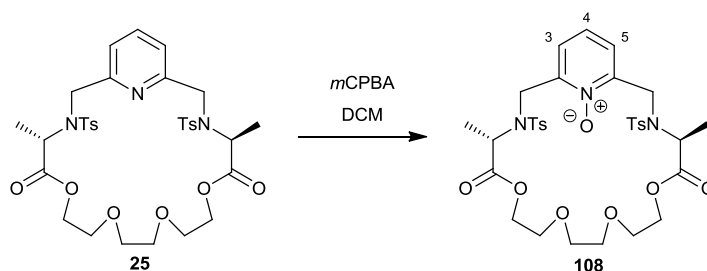
Previous work carried out by the Bailey group on these macrocyclic derivatives had experimented with the use of 4-dimethylaminopyridine (DMAP) derivatives (for example **167**) in acyl-transfer catalysis instead of the unfunctionalised pyridine ring. The 4-dimethylamino group however, made the ring susceptible to intramolecular cleavage, possibly by attack of the pyridyl nitrogen at the ester carbonyl.²⁸



167

It is also possible to oxidise the pyridine to form the electron rich *N*-oxide, which could act as a ligation site. It was Fu and his coworkers¹⁸⁷ who were the first to investigate this modification (see section 1.8.3.2).

Oxidation of the macrocycle was carried out using *m*CPBA in DCM (Scheme 2-5) at room temperature for 48 hours. Upon work-up, analysis by TLC showed the presence of some unreacted starting material, which explained why the yield after column was a moderate 58%.

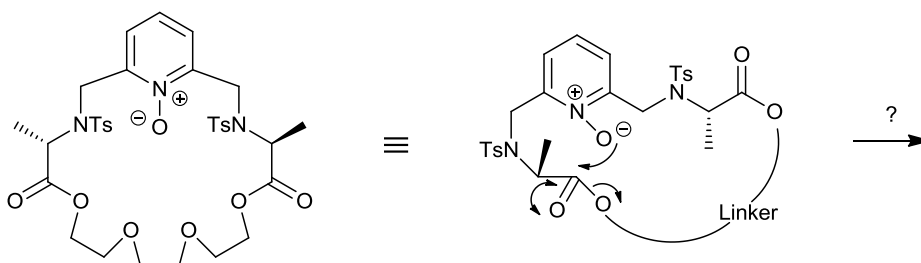


Scheme 2-5

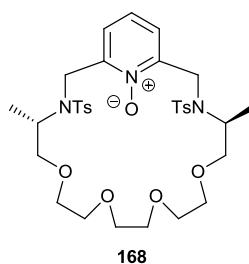
The transformation of di-ester **25** into *N*-oxide **108** was accompanied by a number of changes in the ^1H NMR spectrum concerned. The signal for the 3- and 5- protons, a doublet, shifted downfield from δ 7.44 ppm to δ 7.63 ppm after oxidation, and the 4-proton signal, a triplet, had shifted upfield from δ 7.63 ppm to δ 7.26 ppm. Mass spectrometry also confirmed the successful formation of the *N*-oxide, with a peak at 719.9 $[\text{M}+\text{H}]^+$ compared to its precursor 704.3 $[\text{M}+\text{H}]^+$.

2.1.6 Variation of the Spacer Unit

Previous theories within the Bailey group²⁸ suggested that the macrocycle **108** suffers decomposition *via* intramolecular acylation reaction pathways (Scheme 2-6). If the esters were replaced by ether linkages, this mechanism of cleavage could not occur. The synthesis of macrocycle **168** was therefore targeted.

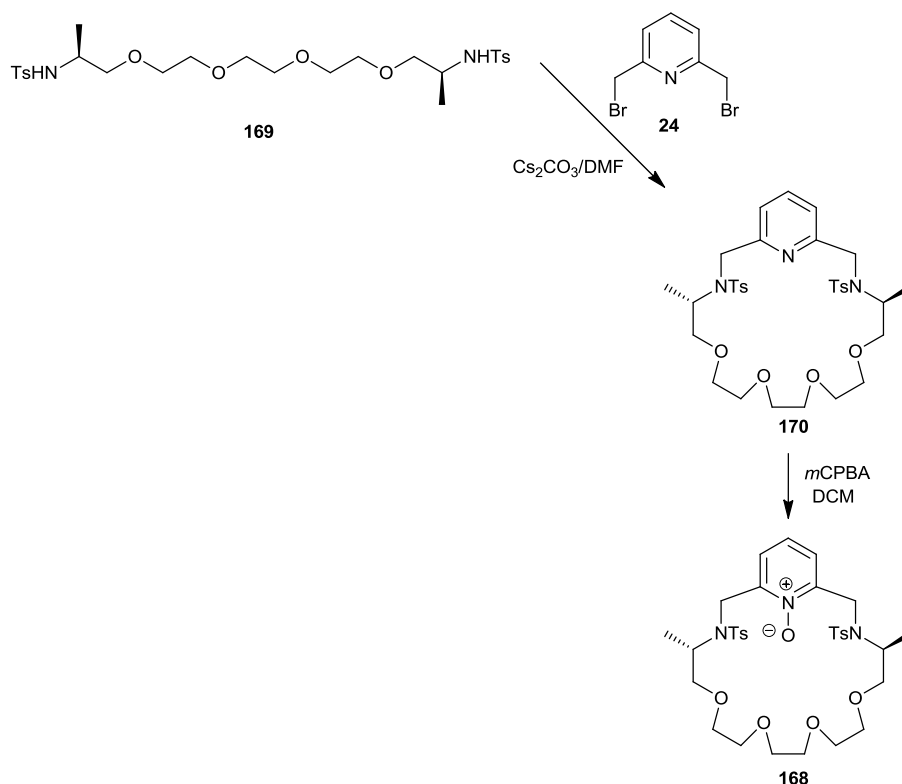


Scheme 2-6



2.1.6.1 A retrosynthesis of macrocycles containing ether linkages

It was envisioned that if the key intermediate **168** containing diether linkages could be synthesised, the desired macrocycle could be made readily using the conditions optimised for the di-ester synthesis (Scheme 2-7). Several potential routes to this compound were considered and attempted. To date, successful isolation of the desired ether has proven elusive, but we have gained valuable understanding of the factors and complications involved in its synthesis.

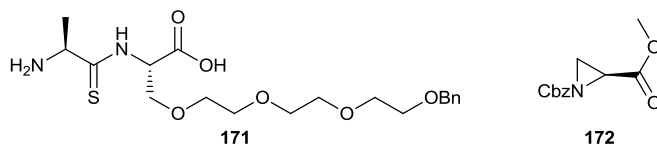


Scheme 2-7

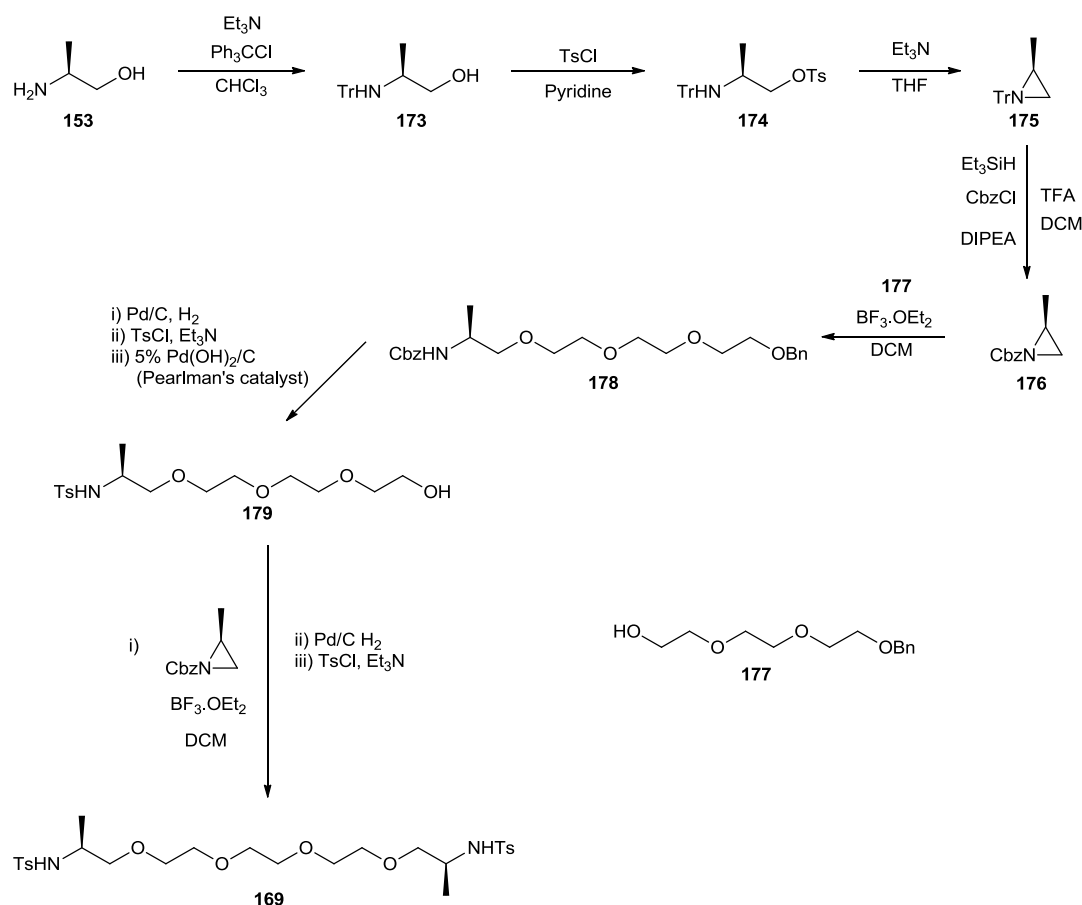
Synthesis of β -alkoxyamines via aziridine ring-opening

Our initial approach to this spacer centred on the ring opening reactions of aziridines using a synthetic glycol as a nucleophile. Work of this type has been carried out by Ho

et al.,¹⁹⁸ who managed to synthesise an ethylene glycol cross-linked amino acid using the Lewis acid boron trifluoride diethyl etherate. This methodology has been successfully employed within the Bailey group in the synthesis of serine ethers (*e.g.* acid **171**) by way of aziridine **172**.¹⁹⁰



The proposed synthesis (Scheme 2-8) would start from the alcohol derivative of L-alanine **104**, L-alaninol **153**. L-Alaninol ((*S*)-2-aminopropan-1-ol) would have its amine protected with a trityl group,¹⁹⁹ and then the alcohol would be turned into a leaving group by tosylation. Using Et₃N, the alaninol derivative would ring close, and the trityl group would be replaced with a Cbz group. Reaction with the mono-protected glycol **177** would give carbamate **178**. The Cbz group would be replaced with the desired tosyl group, and then the benzyl group removed. Reaction with another equivalent of the aziridine **176** then replacement of the trityl group with a tosyl group would give the desired product **169**.



Scheme 2-8

The tritylation reaction¹⁹⁹ of L-alanine proceeded in good yield (94%), but the tosylation, under the reported conditions did not.²⁰⁰ ^1H NMR spectroscopy and mass spectrometry of the crude product showed no evidence of the desired product **174**.



Scheme 2-9

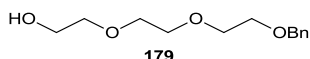
Due to the unexpected failure of this route, chosen because of experience within the group, an alternative route to the desired aziridine (Scheme 2-9) was investigated which had been reported by Pei *et al.*²⁰¹ Here, L-alanine was protected first with tosyl chloride, followed by *O*-mesylation and cyclisation to the aziridine **181**. This route had the advantage of employing tosyl protection of the amine at an early stage, thus avoiding extra deprotection-reprotection steps.

The methylaziridine **181** was therefore prepared in a one-pot procedure by sequential addition of 1.2 equivalents of tosyl chloride and 4 equivalents of triethylamine to L-alaninol in dry dichloromethane. This was followed by the addition of 1.05 equivalents of methanesulfonyl chloride after four hours. After an aqueous work-up and purification, the aziridine was obtained in 72% yield. In some cases, unreacted intermediate **180** was also recovered. This was stirred with 1.05 equivalents of Et₃N in dry dichloromethane to drive the reaction to completion and give an overall yield of 27% of the aziridine.

Formation of aziridine **181** was confirmed by an examination of its ¹H NMR spectrum. Specifically, signals from the tosyl residues were clearly in evidence, as was the methyl group in the form of a doublet at δ 1.24 ppm, while the diastereotopic methylene protons of the aziridine ring appeared as two doublets at δ 2.60 and 2.02 ppm. The αCH proton appeared as a doublet of doublet of quartets (ddq) at δ 2.82 ppm as expected from coupling to the methyl group and the adjacent CH₂ protons. Mass spectrometry confirmed that the product had the desired mass for the final aziridine.

Opening of the Aziridine

It was decided to perform the ring opening using a mono-protected triethylene glycol **179**,²⁰² as a simple model (no dimerisation possible) to investigate if the synthesis was viable.



The first method was to see if the conditions previously employed by the Bailey group would be successful with our aziridine (Scheme 2-8). The reaction was carried out using 1 equivalent of the Lewis acid boron trifluoride diethyl etherate (BF₃.OEt₂) and 1.5 equivalents of the glycol, in dry DCM at -10 °C then warmed to room temperature. The reaction was worked-up and purified by column chromatography to give the product in 82% yield (Entry 1, Table 2-2).

The proton NMR spectrum showed the presence of two different amine environments in the ratio of 5:2. Initially it was thought that purification was not thorough enough, but evaluation by TLC analysis showed the presence of only spot. We examined the COSY spectrum (Figure 2-3), focussing our attention on the coupling of the two amine environments. The major NH peak coupled to two multiplets which integrated as 1

proton each and so it was deduced that these two multiplets was a CH₂ group. The CH₂ coupled to a clear signal within the glycol region thought to be the αCH which in turn coupled to the doublet from the methyl group.

The minor amine peak coupled to a distinct peak in the glycol region, thought to be the αCH, which in turn coupled to another methyl doublet with a slightly different chemical shift.

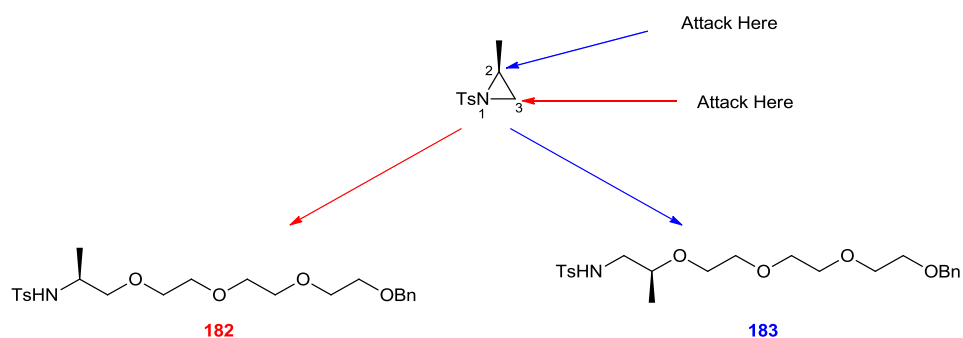


Figure 2-2: Products formed after nucleophilic attack at the C-2 or C-3 position

Therefore, it was concluded that the larger of the two amide peaks was in fact the result of the aziridine ring opening resulting from attack at C2 affording the undesired isomer **183**. Instead of attacking at the least substituted C3 position, to give the desired product **182**, the more substituted position was attacked, giving **183** in higher ratio than **182** (Figure 2-2). This implies the mechanism is predominantly S_N1-like, forming a more stable carbocation.

After purification, efforts were made to separate the two isomers by reverse-phase HPLC. Despite investigating several solvent systems, it proved impossible to resolve the two products.

Entry	Reactants (equivalents)		Lewis Acid	Temp (°C)	Yield (%)	Ratio 183:182
	Aziridine	Protected glycol				
1	1	1.5	BF ₃ .OEt ₂	-10 → rt	44	2.2:1
2	1	5	Cu(OTf) ₂	rt	46	4.1:1
3	1	1.5	BF ₃ .OEt ₂	-40	65	2.8:1
4	1	1.5	BF ₃ .OEt ₂	-10 → 40	-	-

Table 2-2: Modification of ring opening conditions

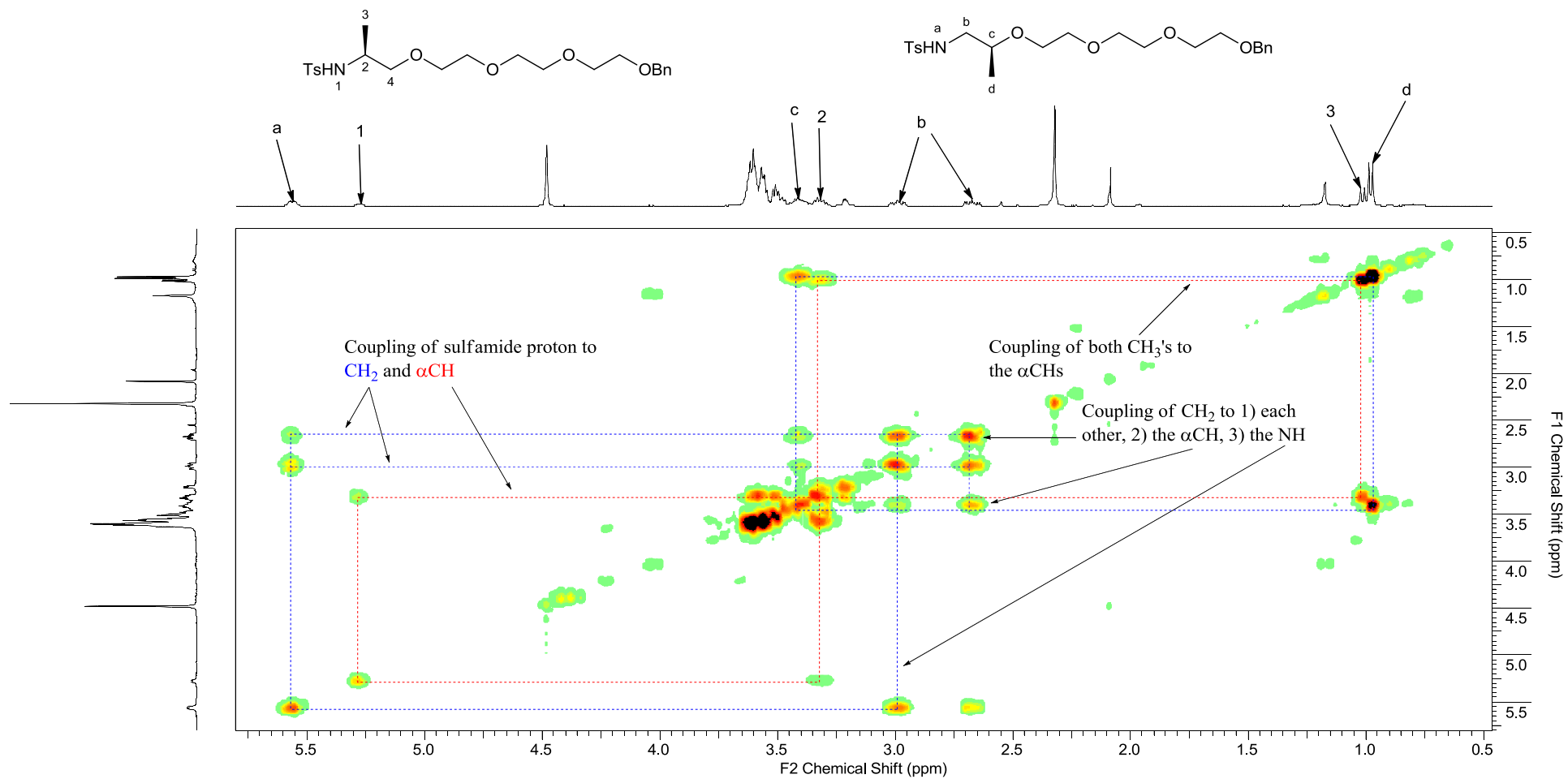


Figure 2-3: COSY spectrum of the mix of **182** and **183**, from the aziridine ring opening with $\text{BF}_3 \cdot \text{OEt}_2$

As well as carrying out the reaction in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, the Lewis acid was also modified to attempt to improve the selectivity of ring-opening, and increase the amount of sulfonamide **182**. Following methods reported by Ghorai *et al.*,²⁰³ copper triflate ($\text{Cu}(\text{OTf})_2$) was employed as a Lewis acid in the ring opening of the aziridine ring (Entry 2, Table 2-2). Although the yield was similar, the ratio favoured the product formed from opening at the more substituted position, which was not desirable.

Having found that overall $\text{BF}_3 \cdot \text{OEt}_2$ promoted formation of the desired product **182**, further experimentation was carried out (Entries 3 and 4, Table 2-2). It was thought that thermodynamic or kinetic conditions may affect the ratio of formation, so two reactions were carried out, one at 40 °C, and the other at -40 °C. The reaction carried out at 40 °C was unsuccessful. Despite there being evidence of **183** in the crude reaction, there was not enough material for it to have been an overall success. The reaction at -40 °C had almost the same ratio as if it had been carried out at room temperature. The only benefit was a yield increase from 44% to 65%.

Having seen no improvement in regioselectivity with changing temperature, it was decided to carry out one experiment which used boron trifluoride at room temperature, but instead of the mono-protected glycol **179**, triethylene glycol was used. Analysis of the reaction mixture by mass spectrometry showed the presence of both the monomers and dimers (**178**, **184** and **69**, **185** and **186**) although distinction between them was not possible. After purification, a yield of 63% was isolated which comprised primarily of the dimers, with a small amount of the monomers. These results were promising but conditions needed to be sought that allowed for improved regiocontrol.

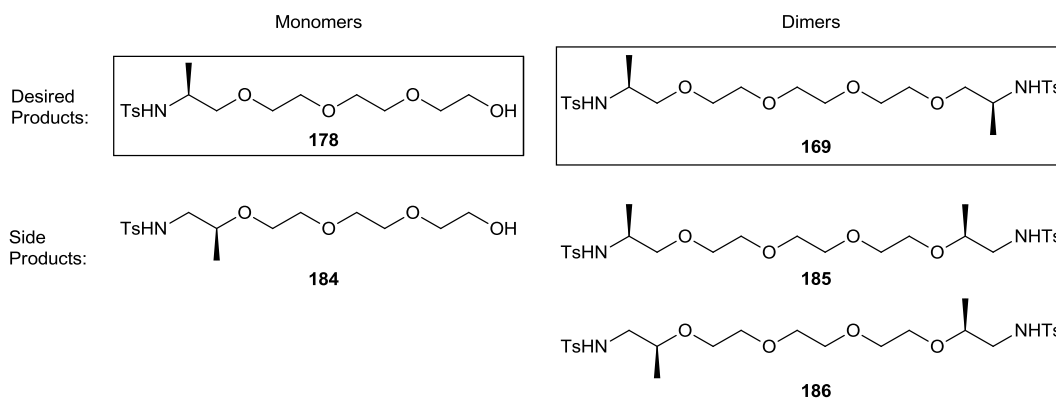
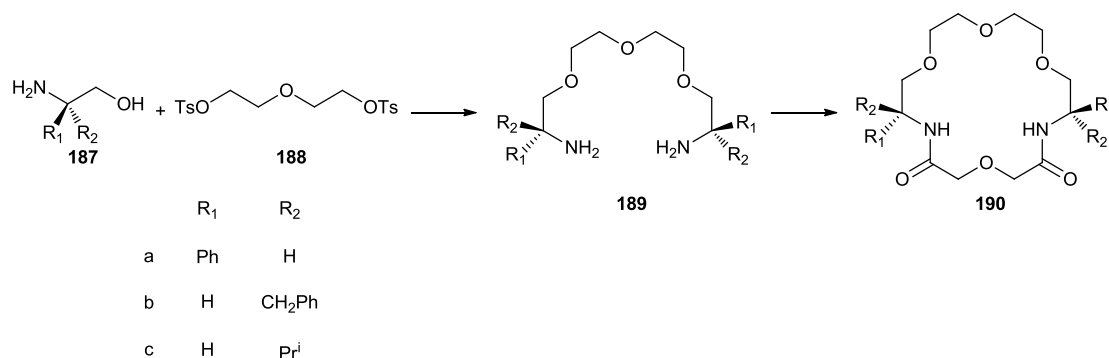


Figure 2-4: Compounds isolated from the reaction of triethylene glycol and aziridine **181**

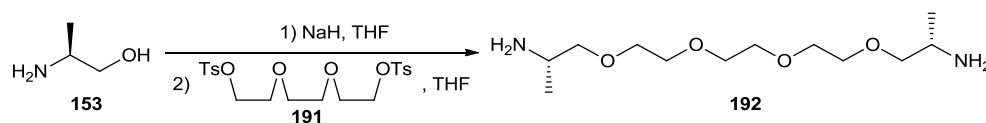
2.1.6.2 Alternative Routes

Another route to form the macrocycles containing diether linkages was considered that would employ the method of Chadwick *et al.*²⁰⁴ who used ditosyl diethylene glycol **188** and a variety of amino alcohols to form cyclic amides **190a-c** (Scheme 2-10).



Scheme 2-10

It was planned to modify their conditions to suit our needs using tri- instead of diethylene glycol and using L-alaninol as the amino alcohol (Scheme 2-11).



Scheme 2-11

The alaninol was deprotonated using sodium hydride in dry THF, and then glycol **191** was added slowly, where the O-tosyl leaving groups are substituted, theoretically forming the desired product. Unfortunately, the reaction was not a success, and only gave a 4% yield, the majority of which seemed to be composed of the glycol starting material **191**.

2.2 Chiral Thioether Macrocycles

2.2.1 Initial Strategies

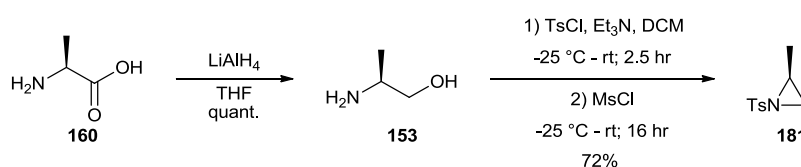
2.2.1.1 Introduction

Following on from the difficulties observed in controlling aziridine ring-opening with oxygen nucleophiles, our focus switched to the use of “softer” sulfur nucleophiles in these reactions. Evidence has shown that this type of NRO proves highly beneficial, leading more often than not, to a single regioisomer.^{205,206}

As with any NRO, regioselectivity in this reaction is controlled by a number of factors (see section 1.6 for more examples).

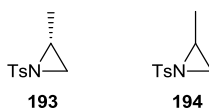
2.2.1.2 Synthesis of an aziridine

We decided to keep the tosyl-protecting group analogous to the ester macrocycle and also the methyl group due to the effects they both have on the reactive properties of the ring. Having the knowledge that the target was aziridine **181**, we found a method beginning from L-alanine (Scheme 2-12), reducing it to L-alaninol followed by the formation of the aziridine as previously prepared in section 2.1.6.1. This resulted in the desired product **181** in a 72% overall yield.



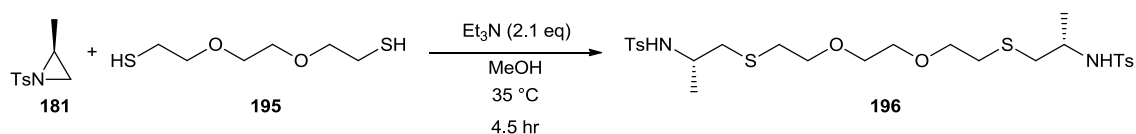
Scheme 2-12

In order to explore future reactions, where epimerisation may be an issue, we elected to synthesise both the chiral and racemic analogues of the aziridine. When the reaction to form the (*R*)-2-methyl-1-tosylaziridine **193** was accomplished from D-alaninol, the product was obtained in 71% yield, and similarly, the racemic version **194** was isolated in 78% from DL-alaninol.



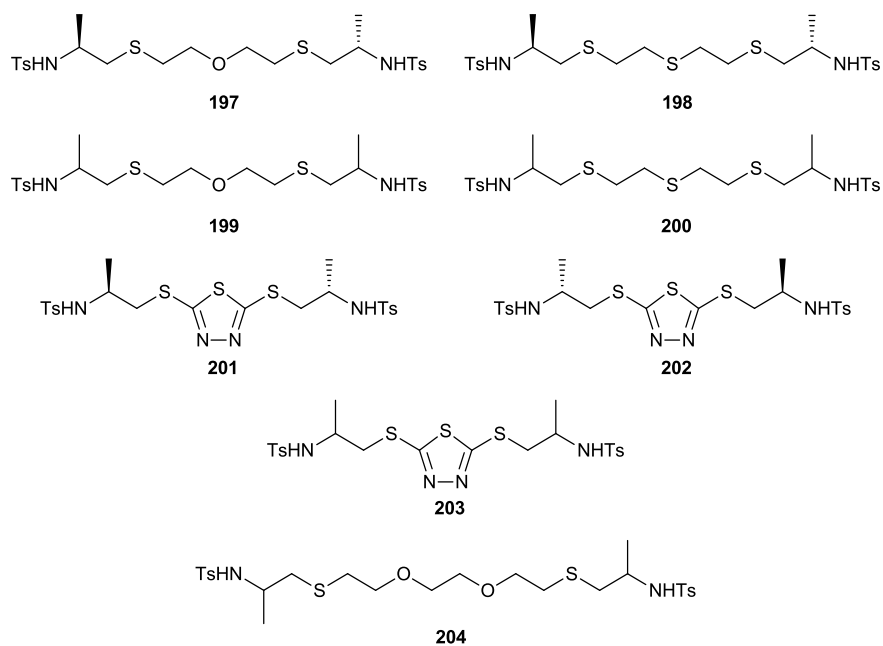
2.2.1.3 Ring-opening of aziridines with sulfur nucleophiles

After briefly experimenting with microwave conditions for the NRO, we eventually employed a modified method by Maligres²⁰⁷ and Crotti¹⁴² who regioselectively ring opened a range of activated aziridines with thiols. In order to compare directly the ether and ester analogues of the macrocycles we decided to attempt first the ring opening with dithiol **195**. In these reactions exposure of the thiol to just over two equivalents of the aziridine **181** and triethylamine in dry methanol yielded 86% of the desired product as a single regioisomer **196** (Scheme 2-13).

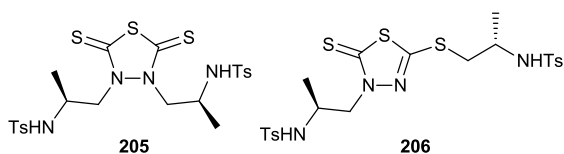


Scheme 2-13

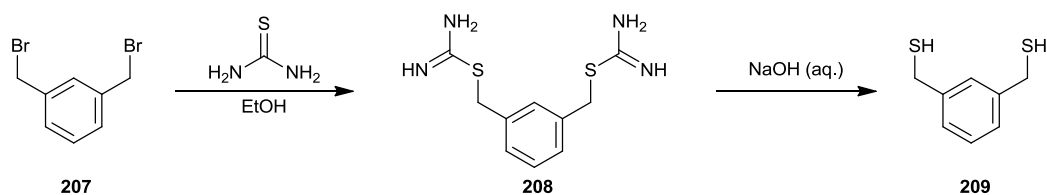
To test whether this reaction could be used for a range of dithiols, we carried out a similar reaction to form **197**, which resulted in a 79% yield. In both cases, after a simple aqueous work-up, the only purification necessary was straightforward column chromatography.



The library of compounds was expanded using commercially available thiols, synthesising each tosyl-protected spacer **198-204** in moderate to good yields of 51 – 90%. The synthesis of thiadiazole spacer **201** and not its regioisomer **205** or unsymmetrical isomer **206** was confirmed by ^{13}C NMR spectroscopy.

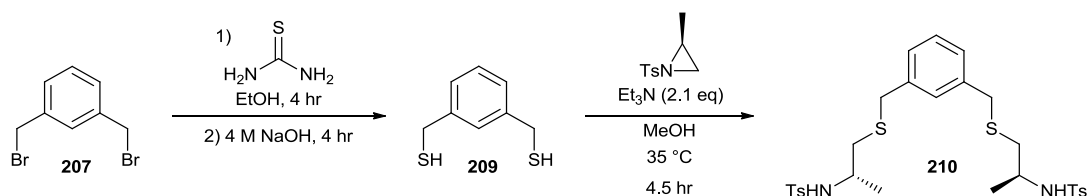


Next, we decided to synthesise a range of non-commercially available dithiols. A simple preparation of thiols takes the bromide and forms the thiouronium species by reaction with thiourea in degassed ethanol, then isolating the thiol upon reaction with aqueous sodium hydroxide.²⁰⁸

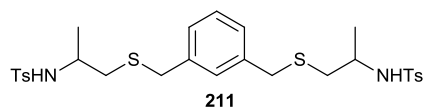


Scheme 2-14

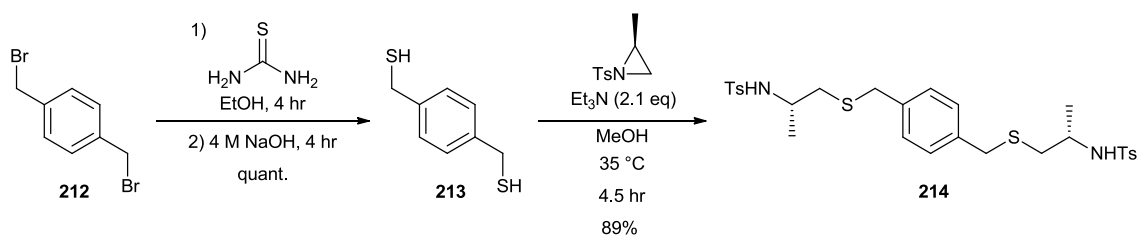
Our initial efforts used 1,3-bis(bromomethyl)benzene **207** and 2 equivalents of thiourea and yielded the desired thiol **209** in a quantitative yield (Scheme 2-15). By this time, the selective ring opening of the aziridine was a well-established method and **210** was obtained in a 61% yield. Using the same strategies, we also synthesised the racemic spacer **211** in 51% yield.



Scheme 2-15



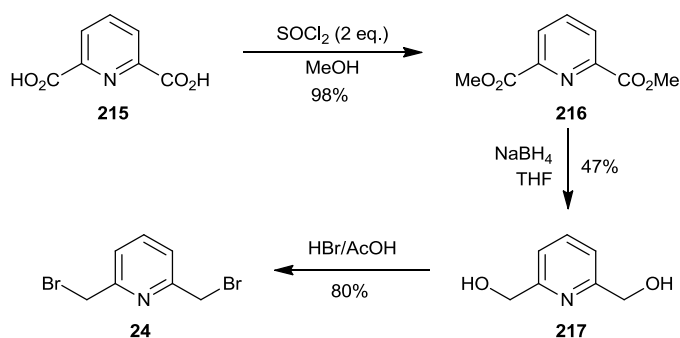
These reactions were also applied to the 1,4-bis(bromomethyl)benzene **212**, resulting in an 89% yield over the two steps from **212** to product **214**.



Scheme 2-16

2.2.2 Broadening the Spectrum

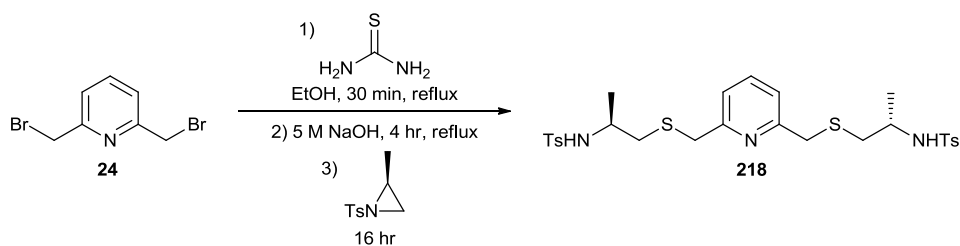
Having exhausted the supply of readily available dithiols, we set about synthesising a range of spacers from more readily available starting materials: this would enable us to determine the effect of substituents on the effectiveness of the cyclisation reaction itself and provide a broad range of mixed heteroatom-donor ligands for future complexation studies. This required the synthesis of bromide **24** prior to cyclisation.



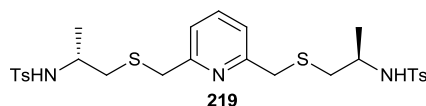
Scheme 2-17

Using standard techniques, dipicolinic acid **215** was transformed into di-ester **216** in near quantitative yield. The di-ester was then reduced using sodium borohydride to diol **217** and brominated by refluxing in an acetic acid and hydrogen bromide solution resulting in 2,6-bis(bromomethyl)pyridine **24** in 37% yield over 3 steps.

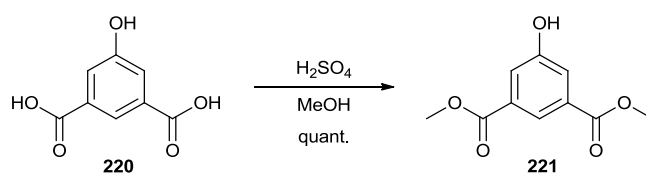
Having discovered our ability to transform the bromide into the thiol and subsequently using the thiol to ring open the aziridine, we wondered whether it was possible to combine these two steps as the thiols were very unpleasant to handle. Therefore, we decided to attempt to amalgamate the steps into a novel, simple, one-pot reaction (Scheme 2-18).



Scheme 2-18

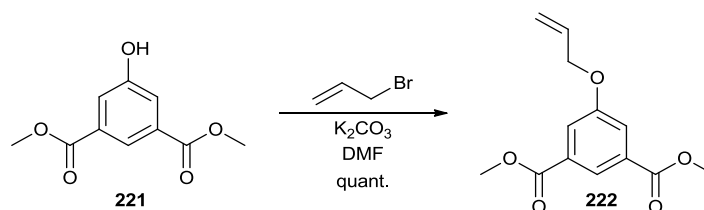


The reaction to form the thiol was performed as before, except it was refluxed for 30 minutes instead of stirring at room temperature for 4 hours. Then sodium hydroxide was added and the reaction refluxed for 4 hours followed by the addition of the aziridine straight into the reaction mixture. Purification and isolation of the product **218** resulted in an 89% yield. This method was repeated using (*R*)-2-methyl-1-tosylaziridine **193** resulting in **219** in an 80% yield.



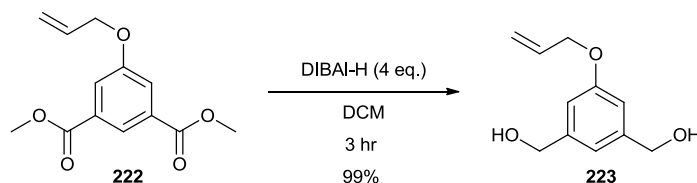
Scheme 2-19

To test both the scope of the reaction and to incorporate an additional functional group for diversification of the spacers, 5-hydroxyisophthalic acid **220** was used as a starting material. The diacid was converted into the diester under standard conditions in quantitative yield (Scheme 2-19). From di-ester **221** was formed the allylated di-ester **222** in quantitative yield (Scheme 2-20). This was formed using the method of Xin *et al.*²⁰⁹

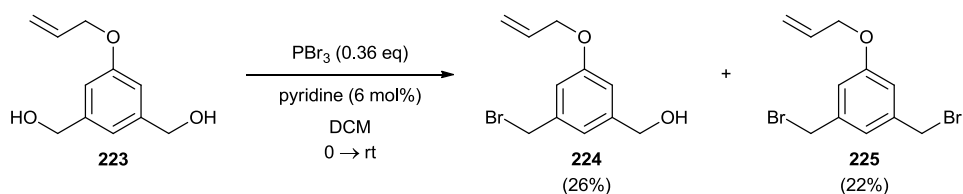


Scheme 2-20

Allyl ester **222** was reduced to its diol counterpart using DIBAL-H in dry DCM leading to (5-(allyloxy)-1,3-phenylene)dimethanol **223** in 99% yield (Scheme 2-21).



Scheme 2-21

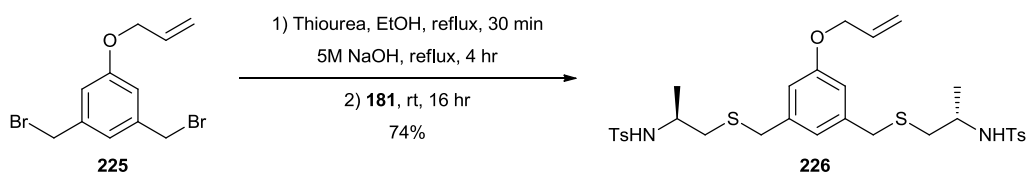


Scheme 2-22

The next step was the conversion of the diol to the dibromide. Allyl diol **223** was brominated following the method reported by Toshi Nagata,²¹⁰ who used phosphorous tribromide with catalytic pyridine. Unfortunately, when carrying out this reaction, as well as forming the desired product **225** in 15% yield, the bromoalcohol product **224**

was also formed in 26% yield. This occurrence did not change when increasing the scale of this reaction, but the dibromide was obtained in a slightly higher yield (22%).

Fortunately, reaction of the dibromide **225** with the aziridine proceeded smoothly, affording the allyl spacer **226** in 74% yield. Allyl spacer **226** was isolated following the established one-pot method directly from the dibromide, reacting the thiuronium salt with aziridine **181** *in situ*.



Scheme 2-23

X-ray Crystal Structure of thioether spacer **198**

It was important to show unambiguously that the ring opening of aziridines under these conditions was regioselective, and this was confirmed by single crystal X-ray diffraction analysis of a sample of **198** as shown in Figure 2-5. The S(2)-C(10)-C(11)-S(3), and S(3)-C(12)-C(12)-S(4) units have an anti-conformation, with torsional angles of $+179.5^\circ$ and $+176.6^\circ$ respectively which concur with other linear and macrocyclic polythioethers which have been characterised crystallographically before.²¹¹⁻²¹³ It is also interesting to mention not only the SC-CS torsional angles, but also those for the CS-CC bond. Previous studies into these torsional angles have described how in both linear and macrocyclic structures, these bonds tend to adopt gauche torsional angles. We have observed the C(9)-S(2)-C(10)-C(11), S(2)-C(10)-C(11)-S(3) and C(10)-C(11)-S(3)-C(12) bonds adopting gauche⁺, anti, and gauche⁻ torsion angles respectively and also the C(11)-S(3)-C(12)-C(13), S(3)-C(12)-C(13)-S(4) and C(12)-C(13)-S(4)-C(14) bonds preferring gauche⁻, anti, and gauche⁺ torsion angles respectively (Table 2-3).

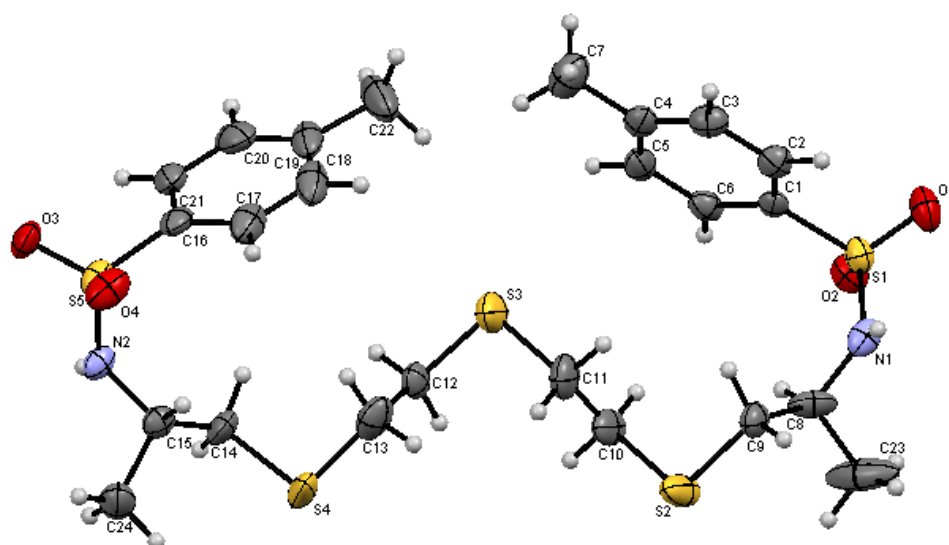


Figure 2-5: An ORTEP view of the X-ray crystal structure of thioether spacer **198**

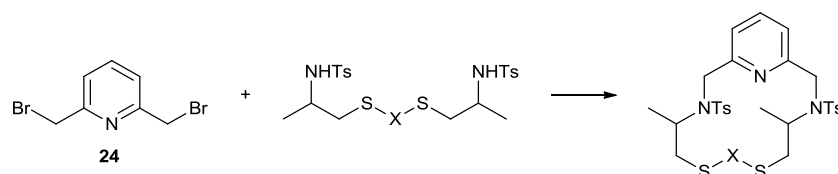
C(9)-S(2)-C(10)-C(11)	73.1 °
S(2)-C(10)-C(11)-S(3)	179.5 °
C(10)-C(11)-S(3)-C(12)	-72.7 °
C(11)-S(3)-C(12)-C(13)	-68.3 °
S(3)-C(12)-C(13)-S(4)	176.6 °
C(12)-C(13)-S(4)-C(14)	76.9 °

Table 2-3: Torsion angles of **198**

2.3 Assembly of the pyridine-based macrocycles

2.3.1 Initial macrocyclisation studies

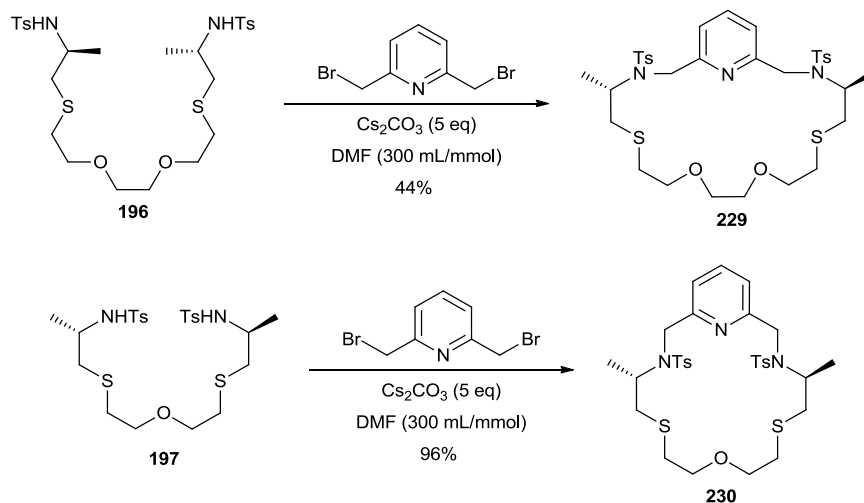
Having successfully synthesised a diverse and novel library of different spacers, the next task was to react them with the pyridine derivative **24**, which would complete the macrocycles of the type shown in Scheme 2-24.



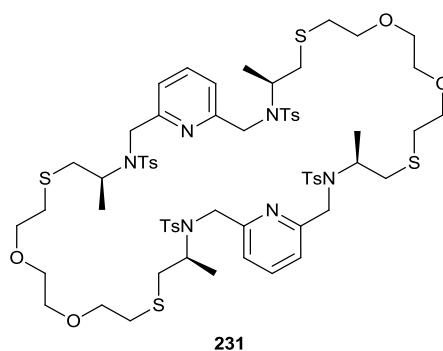
Scheme 2-24

Using the conditions reported by Bailey and discussed in sections 1.1.2.2 and 1.8.1, we isolated novel macrocycles **229-230** from ether-type spacers **196** and **197**. The spacers were dissolved in DMF with an equimolar quantity of pyridine derivative **24** and 5 equivalents of Cs₂CO₃. The reaction was carried out under dilute conditions, 3 mM, to prevent larger macrocycles from being formed. 18-membered ring system **230** was

formed in excellent yield, 96%, but the larger, more flexible 21-membered macrocycle **229** was formed in a 44% yield.



Scheme 2-25



Despite using high-dilution conditions, the “dimeric” product **231** was isolated in 4% yield after careful column chromatography. The high-field ¹H NMR spectra of these two compounds were remarkably similar. The only discernible difference was the signals which could be assigned to the methylene protons next to the pyridine ring. For macrocycle **229**, the signal appeared as a broad singlet at around 4.41 ppm; however, for the dimeric product **231** the signal appears as an AB system (Figure 2-6).

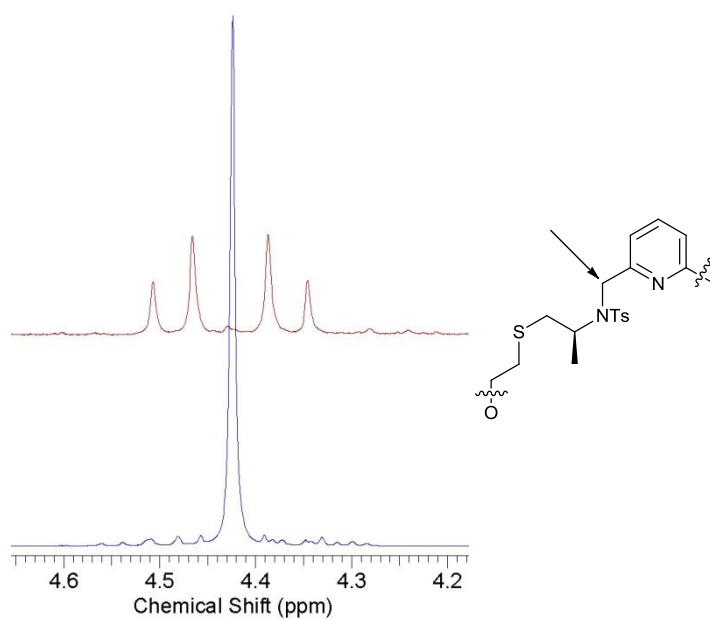
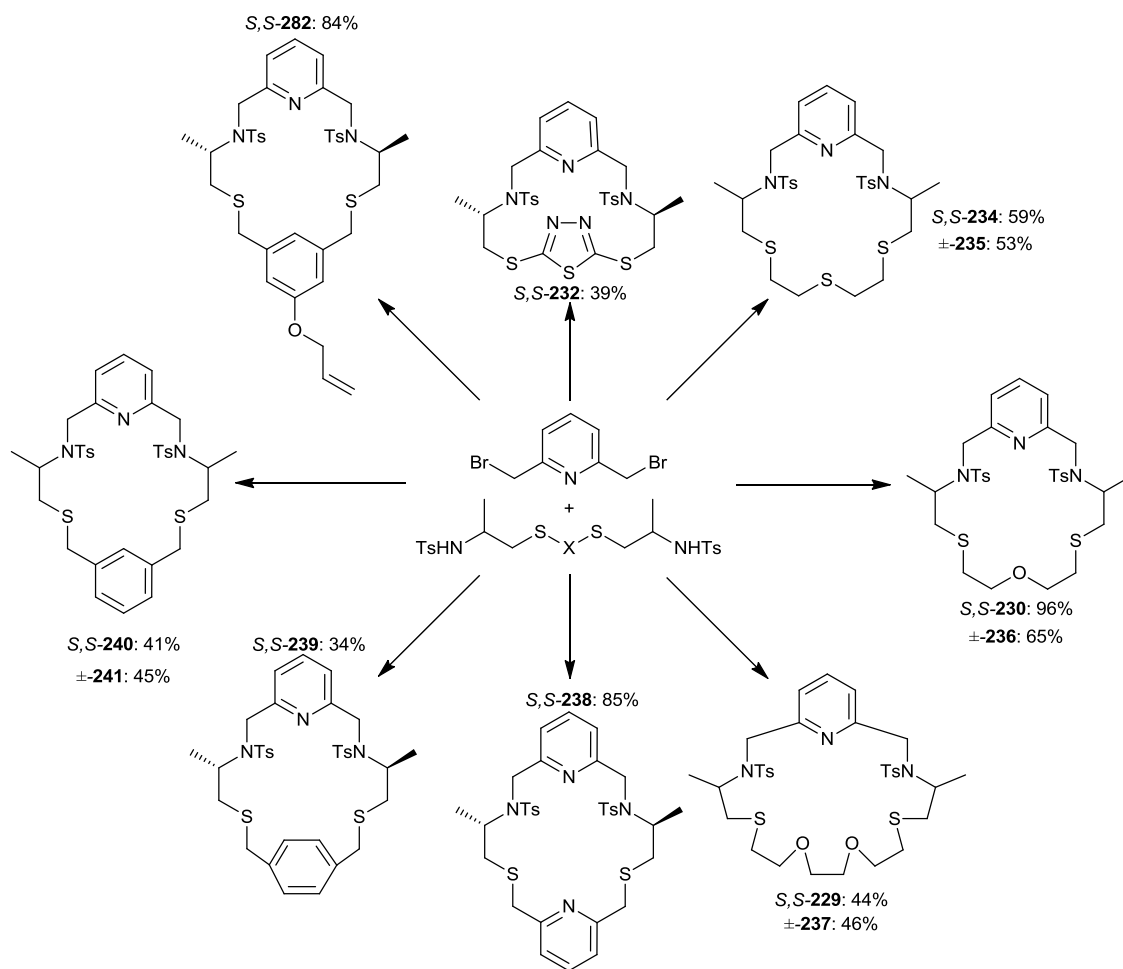


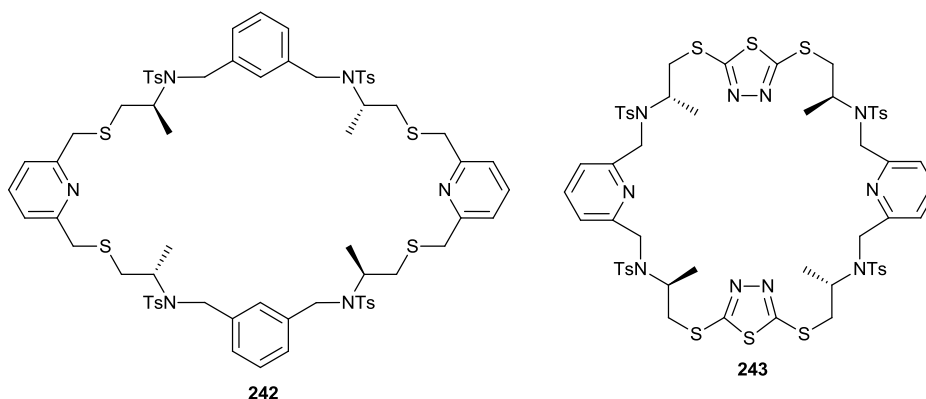
Figure 2-6: ^1H NMR spectrum of macrocycle **229** (blue) compared to its “dimer” **231** (red) in CDCl_3

2.3.2 Advancing the library



Scheme 2-26

On proving the scope of this approach to *S,N*-macrocycles, the same process was applied to the full spectrum of spacers synthesised previously (Scheme 2-26). Yields ranged from as low as 34% for the synthesis of **239** to 96% for **230**. Formation of the “dimeric-type” structures did not occur for every cyclisation. In fact, as well as the formation of **231** previously mentioned, thiadiazole-based product **243** was isolated in 3% yield and 1,3-benzyl-based product **242** was isolated in 8% yield.



Solid state structures

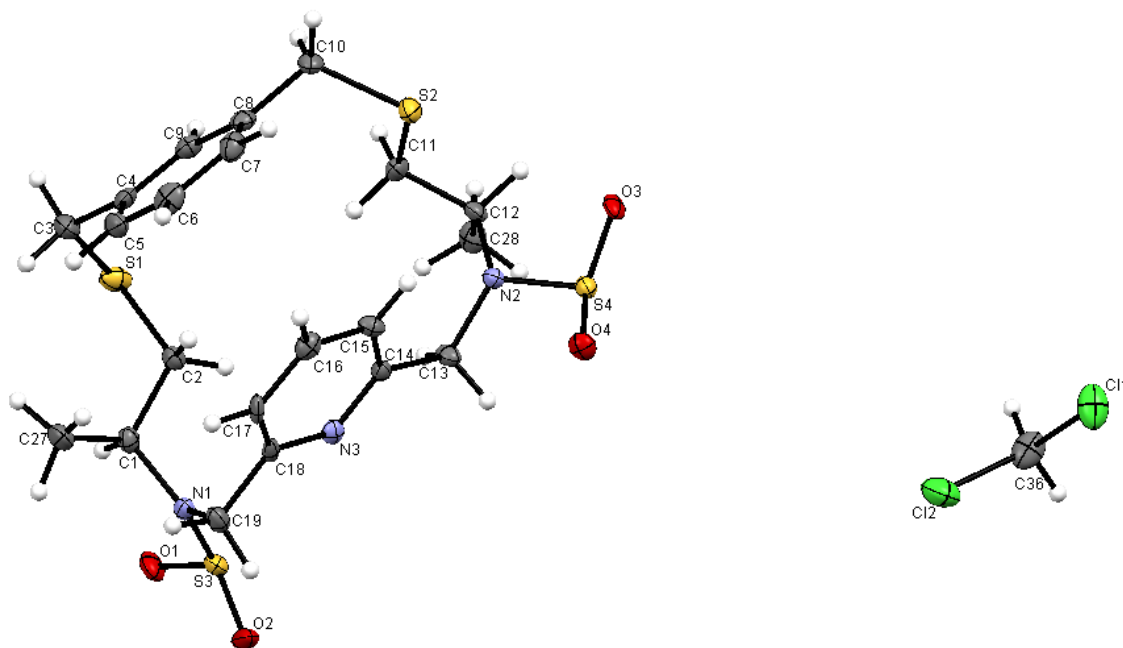


Figure 2-7: An ORTEP view of the X-ray crystal structure of macrocycle **240**.CH₂Cl₂

Single crystals suitable for X-ray diffraction were successfully isolated for two of the macrocycles, **240** and **282**. The rest varied from thick oils to glasses to solid foams. One of the structures contained the simple benzylic macrocycle **240**, and was isolated with a

molecule of dichloromethane, the recrystallisation solvent used. Figure 2-7 shows the solid state nature of the structure with the toluenes from the tosyl groups removed for clarity. It can be seen that the two aromatic rings almost lie parallel to each other, were it not for a slight twist which can be observed by measuring the distances between the two rings (Figure 2-8). The aromatic rings are close enough to suggest π - π stacking as the distance between the closest part of the ring is 3.342 Å.

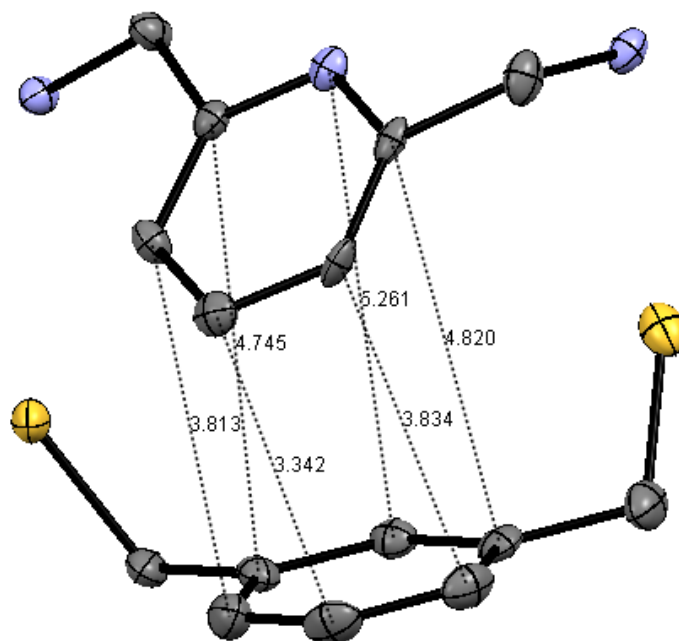


Figure 2-8: Illustration of the distances between atoms (Å) on the pyridine and benzylic and rings system in **240**.CH₂Cl₂

Also obtained was the solid state X-ray crystal structure of the allylic analogue of **240**, **282** (Figure 2-9). Again, the distances between the atoms in each of the rings are shown in Figure 2-10. The differences were subtle, but close examination revealed that the rings appear only slightly further apart in the allylic macrocycle **282**, but the rings showed a more definite twist.

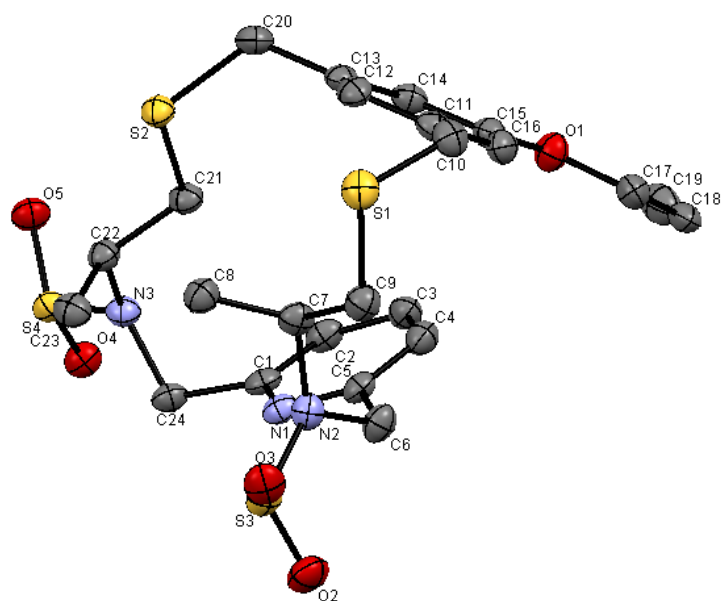


Figure 2-9: An ORTEP view of the X-ray crystal structure of macrocycle **282**.

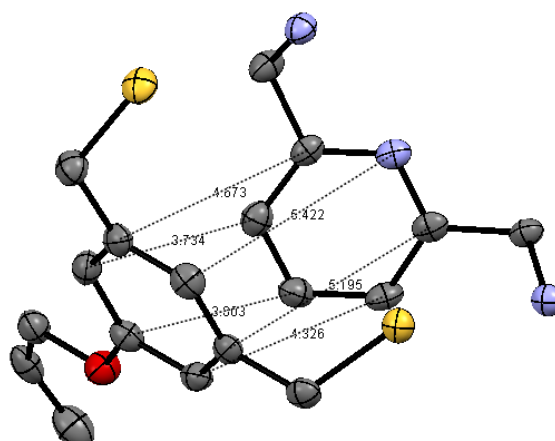


Figure 2-10: Illustration of the distances between atoms (Å) on the pyridine and benzylic and rings system in **282**

The single-crystal X-ray structure of macrocycle **282** proved to be of some interest as the macrocycle was found to adopt three discrete, yet subtly different conformations in the solid state (Figure 2-12). This occurrence was also noted by some other workers during the synthesis of related “NS₄” ligand systems. In the case of macrocycle **282**, this was further complicated by the appearance of a highly disordered allyl group (Figure 2-11).²¹⁴

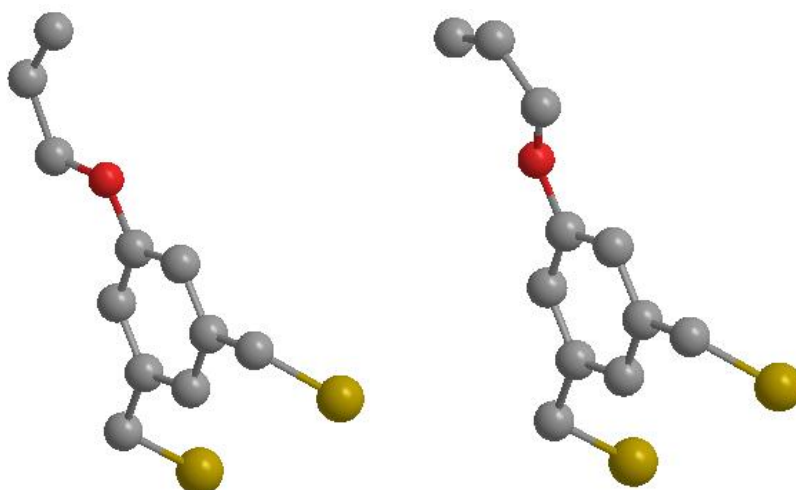


Figure 2-11: Observed differences in the solid state structures found within in allylic group for macrocycle **282**

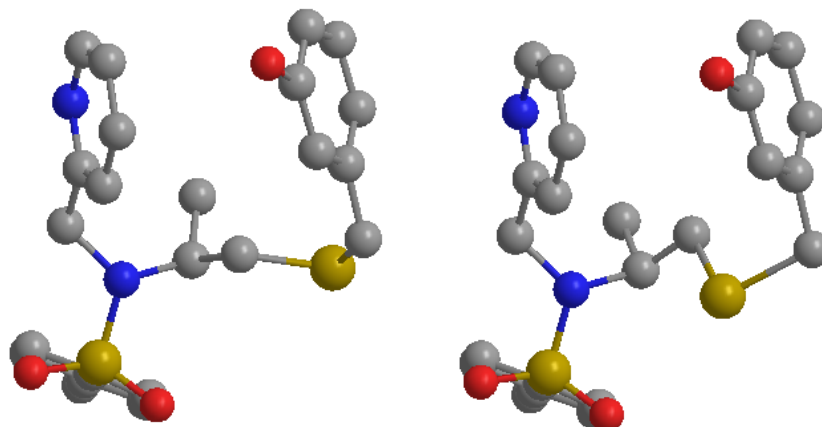


Figure 2-12: Observed differences in the solid state structures found between the aromatic rings in the macrocycle **282**

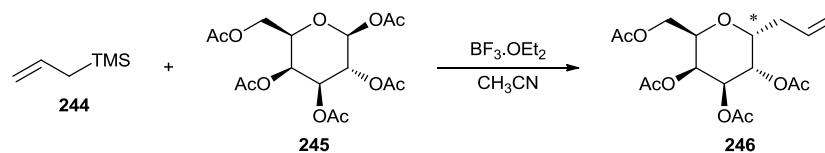
2.4 Development towards a multifunctional compound – the macromolecule

2.4.1 Formation of the multifunctional products

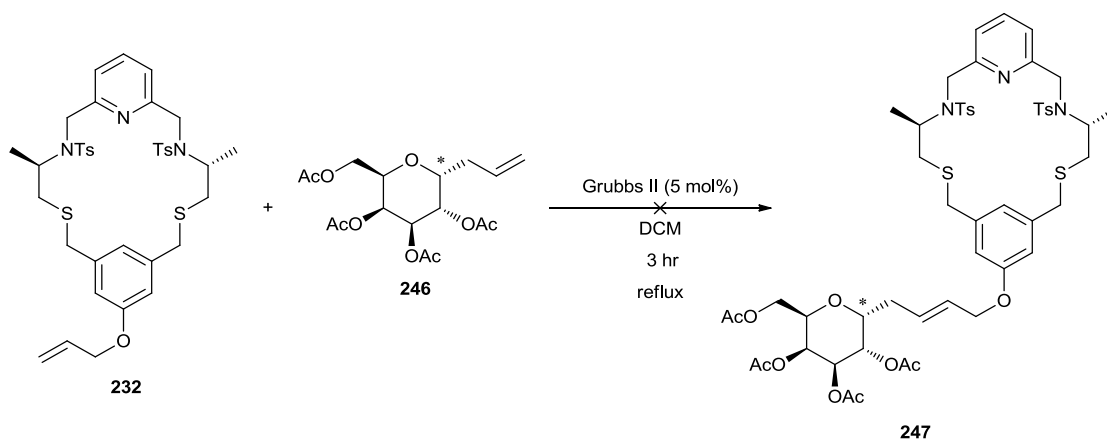
2.4.1.1 Initial Attempts

We first envisioned that attachment of the macrocycle and sugar moiety could be achieved *via* Grubbs' metathesis (Scheme 2-28). The allylic sugar **246** was synthesised from β -D-galactose pentaacetate **245** which was readily available, in 28% yield. By examination of the ^1H NMR spectrum, the product was a mixture of anomers in a 6:1 ratio. As we were only testing the potential of the metathesis reaction we continued with the isomeric mixture, reacting 3 equivalents of the allylic macrocycle **282** with 1 equivalent of the sugar **246**. Grubbs II catalyst was used, refluxing in dry

dichloromethane. Unfortunately, the reaction was unsuccessful. After purification, a mixture of starting materials was recovered in the same ratio added into the reaction, with no evidence of any reaction having taken place.

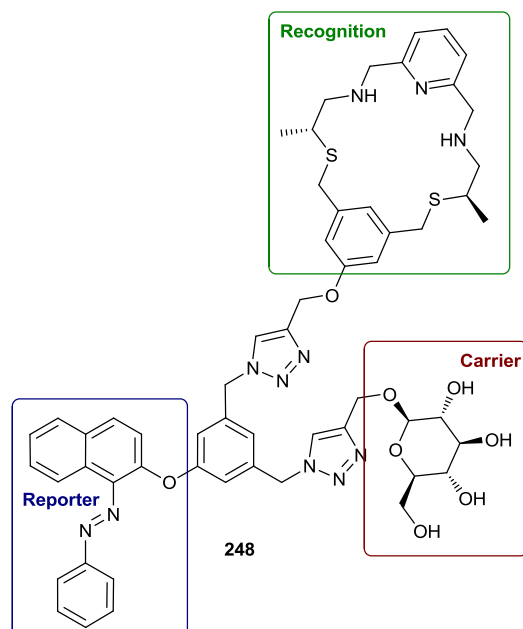


Scheme 2-27



Scheme 2-28

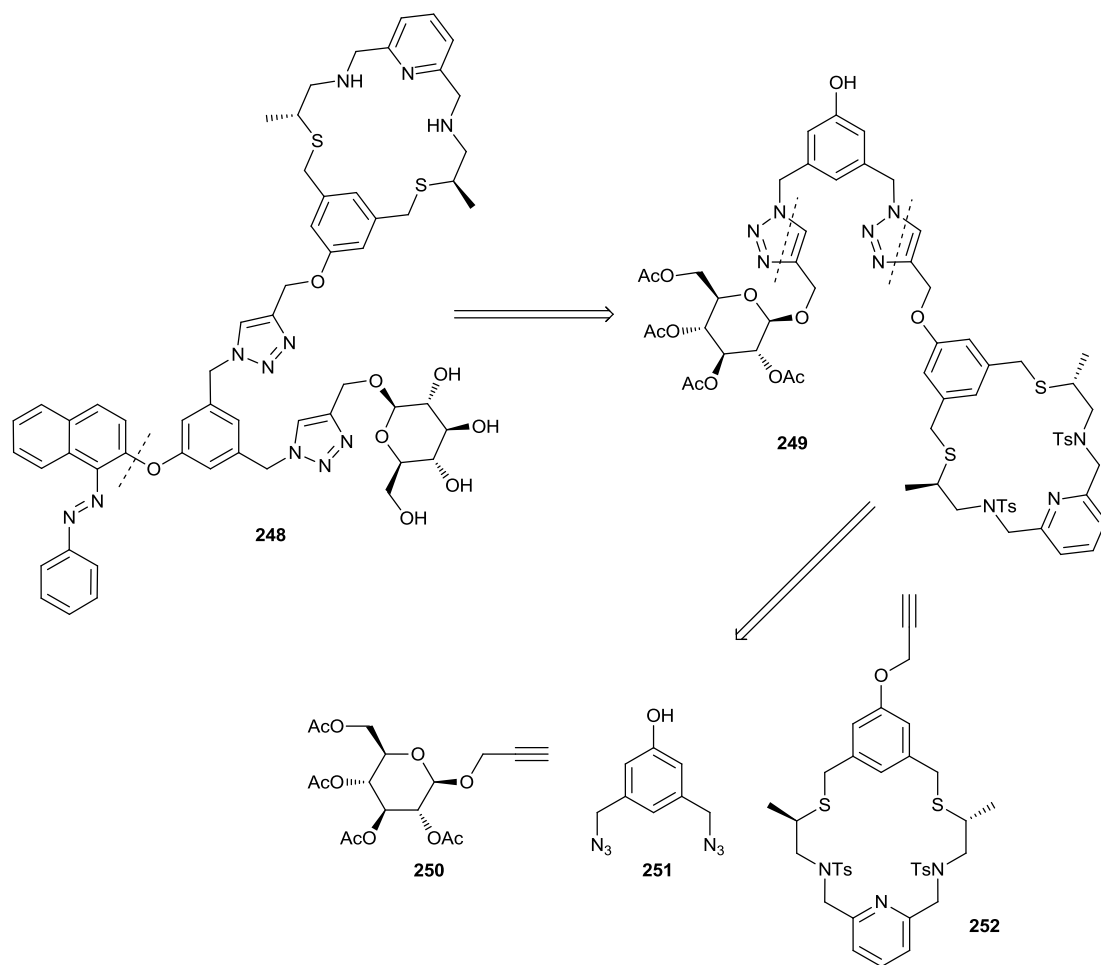
2.4.1.2 Towards a sensor



We envisaged a multifunctional macromolecule, which possessed three different functional areas: a reporter, an area for recognition and an organic carrier. These three

areas would come in the form of an azo dye, the macrocycle, and the glucose sugar, respectively.

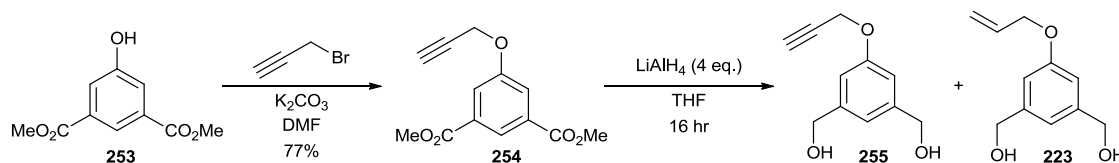
By modification of our target molecule, we would be able to employ chemistry we had already developed on structures that were relatively easy to synthesise and isolate (Scheme 2-29).



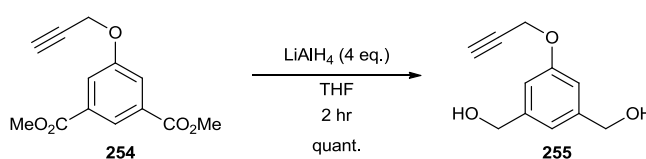
Scheme 2-29

Having developed a potential route to the multifunctional compound, we began by synthesising the macrocycle in the tried and tested manner. Firstly, we needed to form the spacer, following methods similar to those used to synthesise the allyl-analogue **282**. The propargyl ester **254** was formed in 77% yield, followed by its attempted reduction to the diol using DIBAL-H, which was unsuccessful. We attempted the same reaction, but instead using lithium aluminium hydride (LiAlH_4), which initially gave results that were more promising. Unfortunately, when carrying out the reaction on a larger scale,

the alkyne bond reduced also suffered reduction to an alkene, resulting in the isolation of a mixture of **255** and **223** (15:1). Instead of refluxing for 16 hours, the reaction was monitored by TLC analysis showing the consumption of the starting material after just 2 hours at reflux (Scheme 2-31).

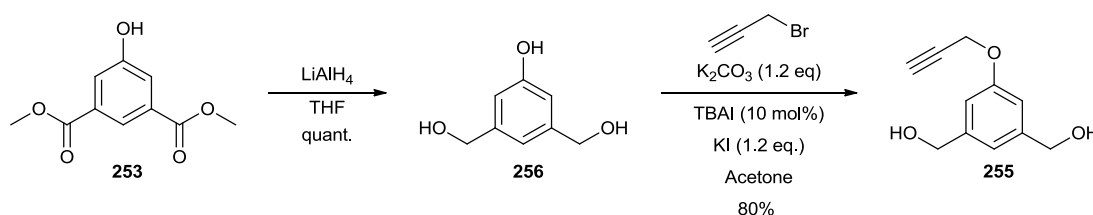


Scheme 2-30

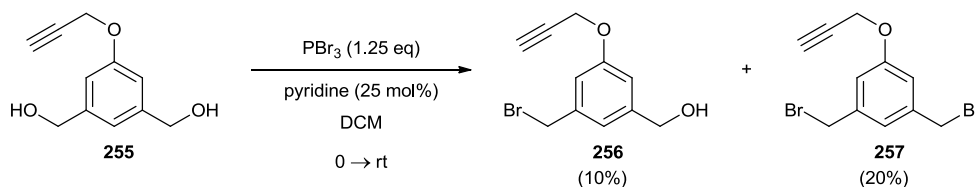


Scheme 2-31

During the course of these experiments, an alternative route to diol **255** was developed which involved the ester reduction prior to propargylation. The di-ester **254** was reduced to diol **255** in quantitative yield using LiAlH_4 in dry THF. The resulting 3,5-bis(hydroxymethyl)phenol **256** was reacted with propargyl bromide, potassium carbonate, potassium iodide and *tetra-n*-butyl ammonium iodide in dry acetone, a modification of a procedure reported by Azagarsamy.²¹⁵ Following purification, the product **255** was obtained in an 80% yield.



Scheme 2-32



Scheme 2-33

Once again, the same effect was observed when attempting to convert the diol **255** to the bromide **257**. Both the dibromide **257** and the bromoalcohol **256** were obtained,

with the low yield of 20% and 10% respectively. This product was confirmed by X-ray crystal analysis (Figure 2-13).

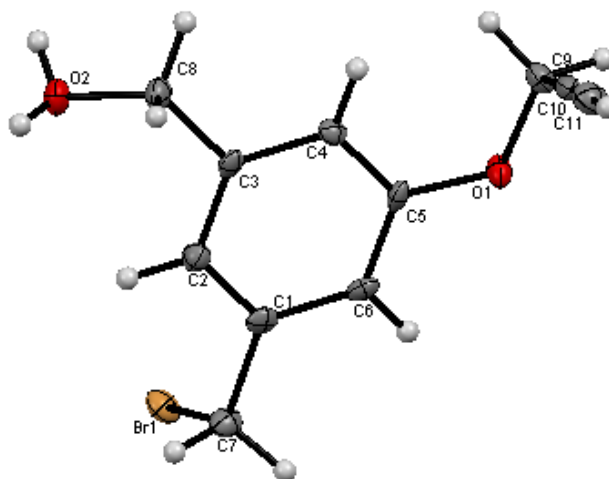
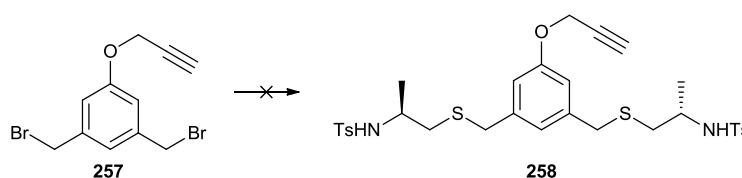
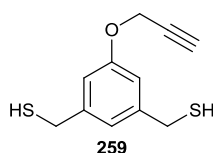


Figure 2-13: An ORTEP view of the X-ray structure of bromoalcohol **256**

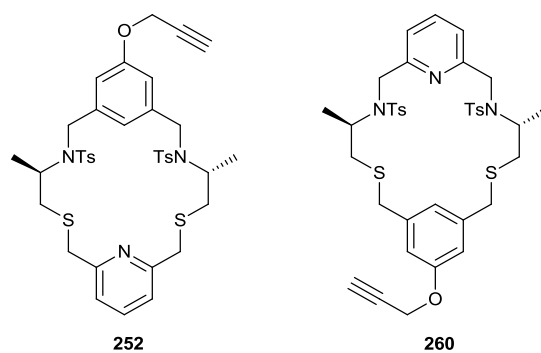


Scheme 2-34

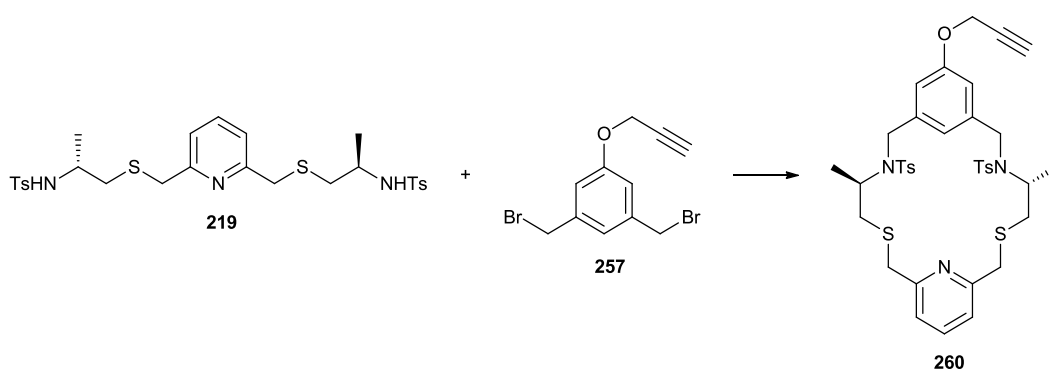
When our novel one-pot reaction was attempted with the propargyl dibromide, the reaction was unsuccessful. Therefore, we attempted a variety of experiments including the formation and isolation of dithiol **259**, which was also a failure as it led to a product that was potentially polymeric, and insoluble in solvent. We also tried to isolate the thiouronium species, but this was deemed unsuccessful, as on analysis, it seemed that the alkyne proton was not present in the ^1H NMR spectrum. Recovered was a mixture of tosyl-protected alanine derivatives, with no evidence for the presence of the central ring system.



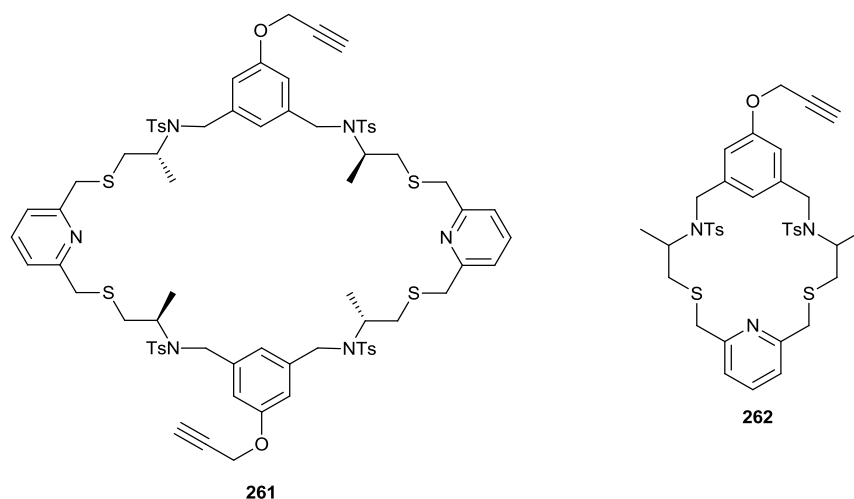
At this point, we had to rethink the proposed structure. We decided to attempt the macrocyclisation reaction using the pyridine-based spacer **219**, and propargyl “cap” **257**, to form macrocycle **260** instead of **252**.



The desired macrocycle was successfully synthesised using caesium carbonate, under dilute conditions. Macrocycle **260** was isolated in 84% yield, together with minor quantities of the dimeric species **261** in 5% yield. This reaction was also tested on the racemic form of the spacer, resulting in a 57% yield of macrocycle **262** as a mixture of diastereoisomers (Scheme 2-35).



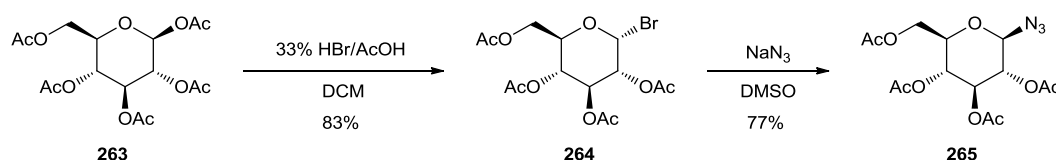
Scheme 2-35



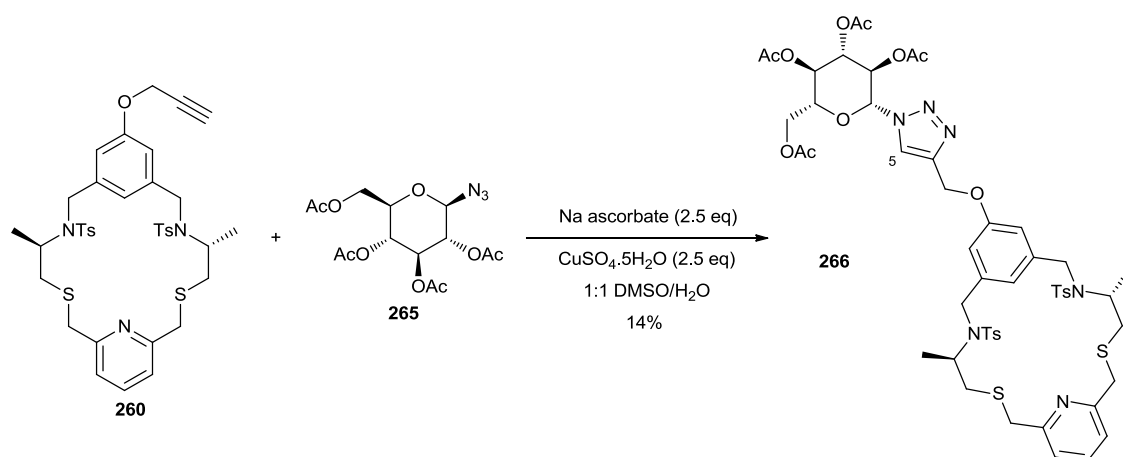
2.4.1.3 Joining of the 2 parties

In order to provide proof of principle for the “click” chemistry, the direct union of the macrocycle and with the sugar unit was attempted. As it was easier to form the azido-

sugar than the azido-macrocycle, we formed the bromide from β -D-glucose pentaacetate. The bromide was synthesised in 83% yield using HBr in acetic acid. Stirring of bromide **264** with sodium azide in DMSO, resulted in the desired product in 77% yield. The azide **265** was isolated as its β -anomer, its spectroscopic data and optical rotation -28° (compared to the literature value of -29° ²¹⁶) being in accord with that in the literature.



Scheme 2-36



Scheme 2-37

After some experimentation, we eventually adopted the conditions which had been developed by Kumar *et al.*,²¹⁷ for the synthesis of glycosyl 1,2,3-triazole conjugates. We performed the click reaction using 2.5 equivalents of sodium ascorbate and copper sulfate in DMSO/water as the solvent and the desired product **266** was isolated in 14% yield. The proton attached onto the 1,2,3-triazole, in position 5, appeared at 8.05 ppm in the ¹H NMR spectrum. NOe interactions were observed between the anomeric proton in the sugar and the triazole proton, as shown in Figure 2-14. This shows the reaction's preference for forming the 1,4-triazole over the 1,5-triazole.

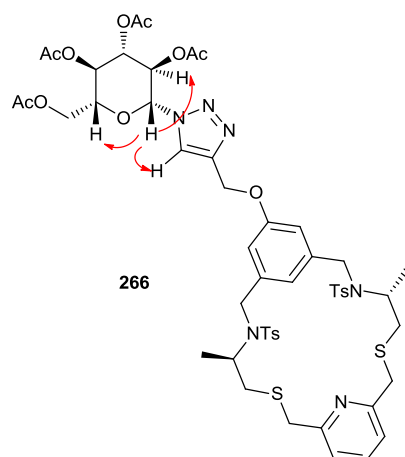
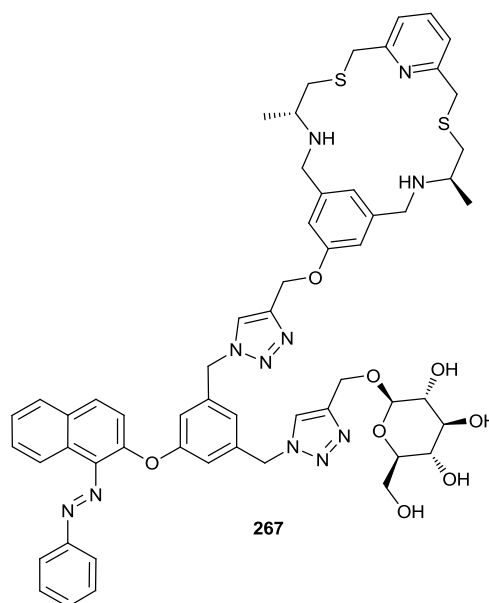


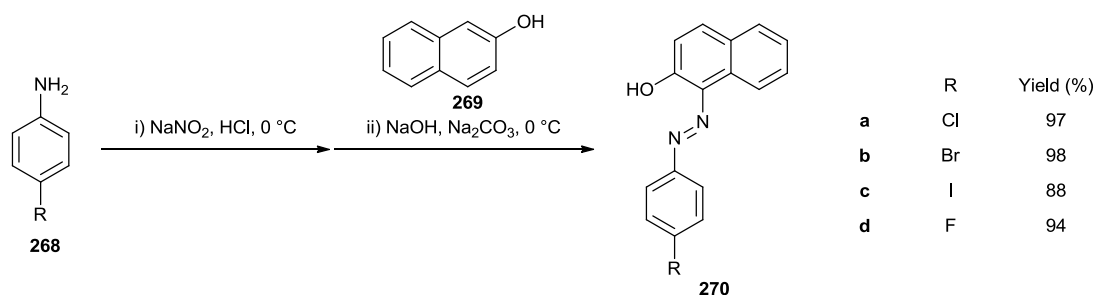
Figure 2-14: NOe interactions observed around the triazole ring

2.4.1.4 Attachment of a dye

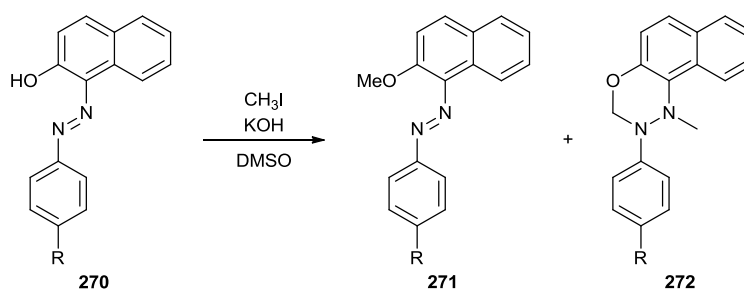
Once the click reaction had been shown to be viable with such large structures, it was necessary to begin thinking how a dye unit was to be attached.



Previous work within the Quayle group by Omer Rasheed has explored the synthesis of azo dyes, in order to develop a robust method for the attachment of the dye, macrocycle and organic transport to the central scaffold unit forming macromolecule **267**.²¹⁸ The work was aimed at producing methodology that was suitably general enough to generate a series of sensors, which could be evaluated in biological systems.



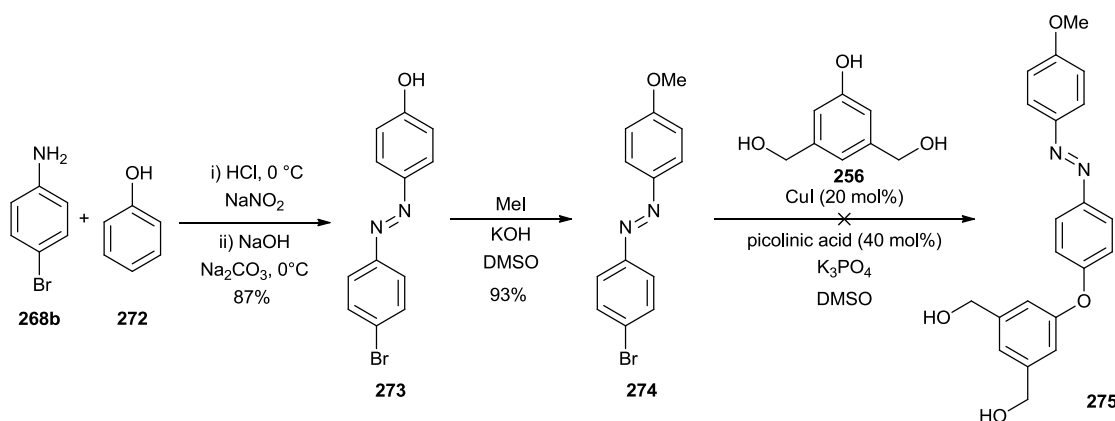
Scheme 2-38



R	Yield of 271 (%)	Yield of 272 (%)
a	69	29
b	64	33
c	62	32
d	69	26
e	70	27

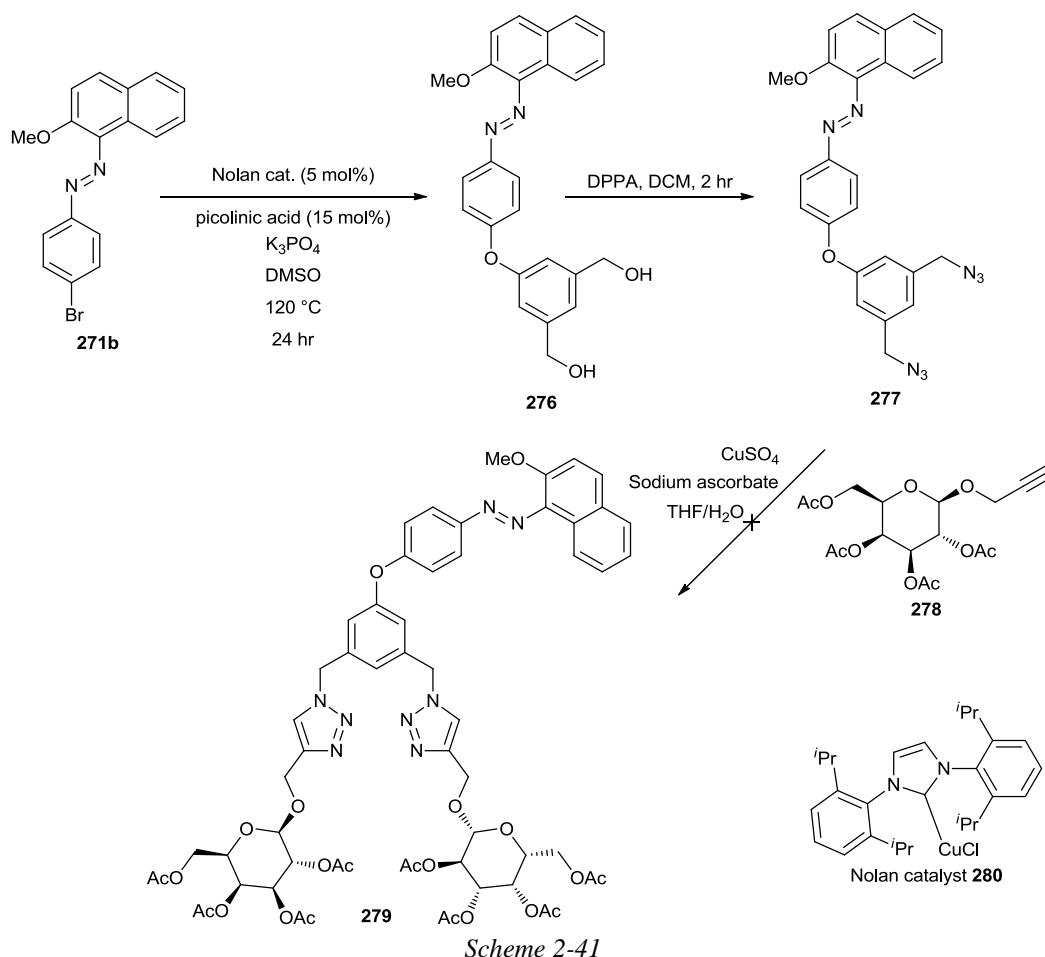
Scheme 2-39

Initially work was carried out by Rasheed to synthesise the series of naphthol-based azo dyes **271a-e**, however when methylating the free hydroxyl a side product **272a-e** was formed (Scheme 2-38 and Scheme 2-39). The strategy was therefore modified to the simple phenolic-type azo dye **273** which would eliminate the cyclisation problem (Scheme 2-40). Although the issues associated with the protection of the alcohol were eliminated, an Ullmann coupling using the aromatic diol **256** was unsuccessful.



Scheme 2-40

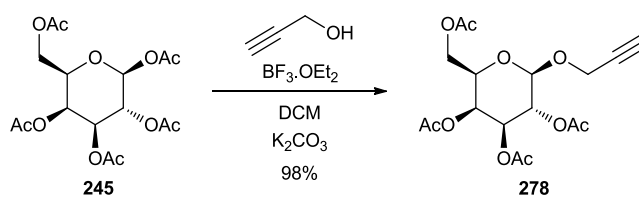
Focus reverted back to the naphthol system, upon which numerous methodical reactions were undertaken by Omer Rasheed to improve the yield of the Ullmann reaction to 50% (Scheme 2-41).²¹⁸ Once attached to the central scaffold unit, conversion of the diol to the diazide **277** could be attempted to synthesise the macromolecule **279**.



Initial attempts to perform a click reaction on the diazide **277** were unsuccessful, so we decided to leave the attachment of the dye *via* Ullmann reaction as the final convergent step.

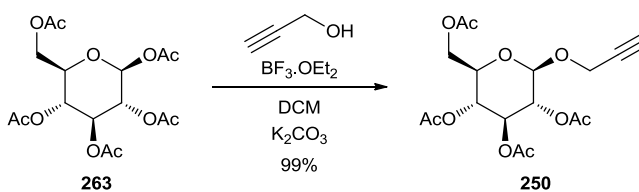
2.4.1.5 Development of an organic carrier

To be able to attach a sugar moiety onto a central frame using click chemistry, we needed to synthesise a sugar which possessed a propargyl group. Using a preparation by Mereyala and Gurralla,²¹⁹ we synthesised the desired product **278** from β -D-galactose pentaacetate (Scheme 2-42).



Scheme 2-42

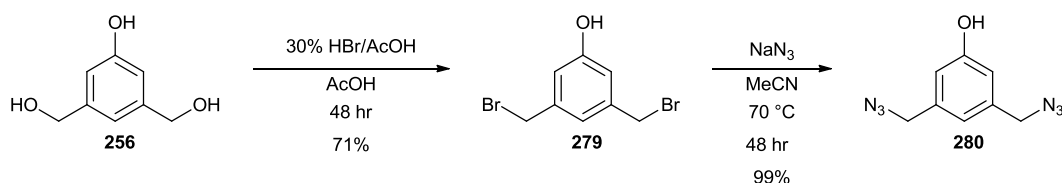
Despite the reaction proceeding in excellent yield, the product obtained was a sticky glass, and not easy to handle. We therefore decided to change the sugar-type to the glucose variety, forming the sugar **250** in 99% yield as a colourless crystalline powder.



Scheme 2-43

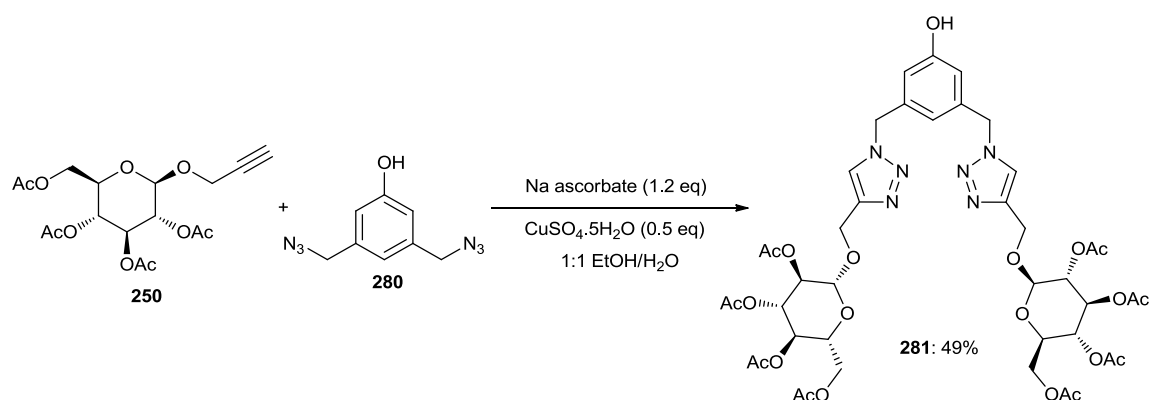
2.4.1.6 A convergent synthesis

In order to attach the sugar and the macrocycle onto the central aromatic unit, it was necessary to form diazide **280**. This was simply made from dibromide **279**, using sodium azide, resulting in the desired product, bisazide **280** in 99% yield.



Scheme 2-44

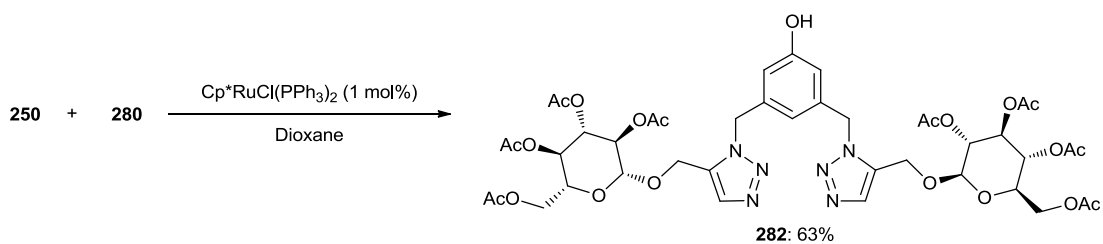
To ensure the chemistry was viable, we first tested the copper mediated azide-alkyne cyclisation (CuAAC) reaction on the azide with 2 equivalents of the propargyl sugar **250**, to form the macromolecule **281** (Scheme 2-45).



Scheme 2-45

The initial reaction attempted was a success, and resulted in a 49% yield of **281** after column purification. There were some problems with the reaction however. Initially the sodium and copper salts were added with the sugar and azide as solids, so when the solvent mixture was added, the reaction was not homogenous. Additional solvent was added after 3 hours and the reaction turned homogenous. On carrying out analysis of the reaction mixture by TLC, it was discovered that starting material was present, so further amount of the catalysts were added.

Since the completion of this body of work, further research has been carried out by Omer Rasheed into the reaction shown in Scheme 2-45 but with the replacement of the copper catalyst by a ruthenium complex. It has now been shown that the use of such a catalyst results in the formation of the 1,5-regioisomer as determined by nOe experiments.



Scheme 2-46

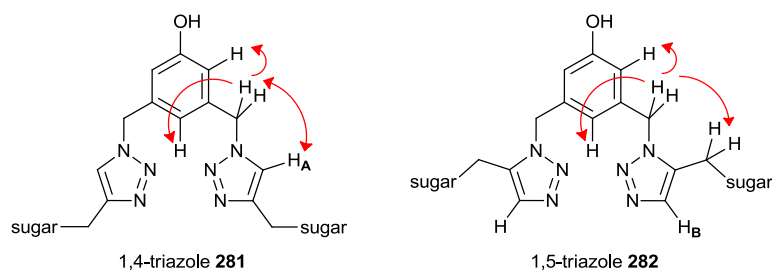


Figure 2-15: Indication of nOe interactions for both the sugar-based 1,4 and 1,5-triazolzes

In the case of **281**, on examination of the nOe spectra the 1,4-triazole proton, H_A, showed an interaction with the benzylic proton which in turn coupled to the aromatic protons. In contrast, the 1,5-triazole proton, H_B, showed no nOe interaction with any proton, whereas the benzylic protons interacted with the allylic CH₂. Figure 2-16 shows the difference in the ¹H NMR spectra between the 1,4-macromolecule **281** (green) and the 1,5- version **282** (blue). The main differences are seen with the two CH₂ groups either side of the triazole ring. The benzylic CH₂ differs slightly between an almost collapsed AB system for **281** and slightly broadened singlet for **282**. The allylic CH₂ shows greater differences. For the 1,4-triazole, the signals centre on 4.80 and 4.91 ppm compared to the 1,5 analogue which were present at 4.52 and 4.85 ppm.

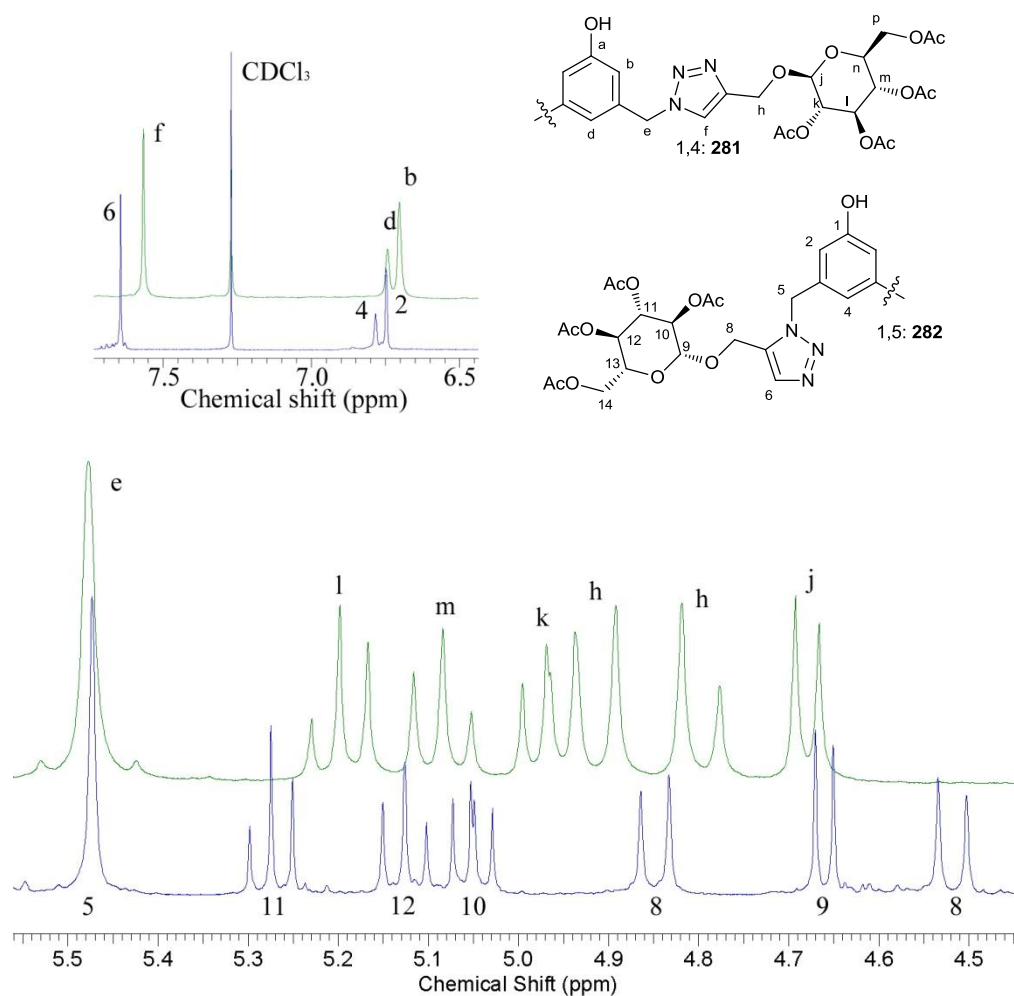
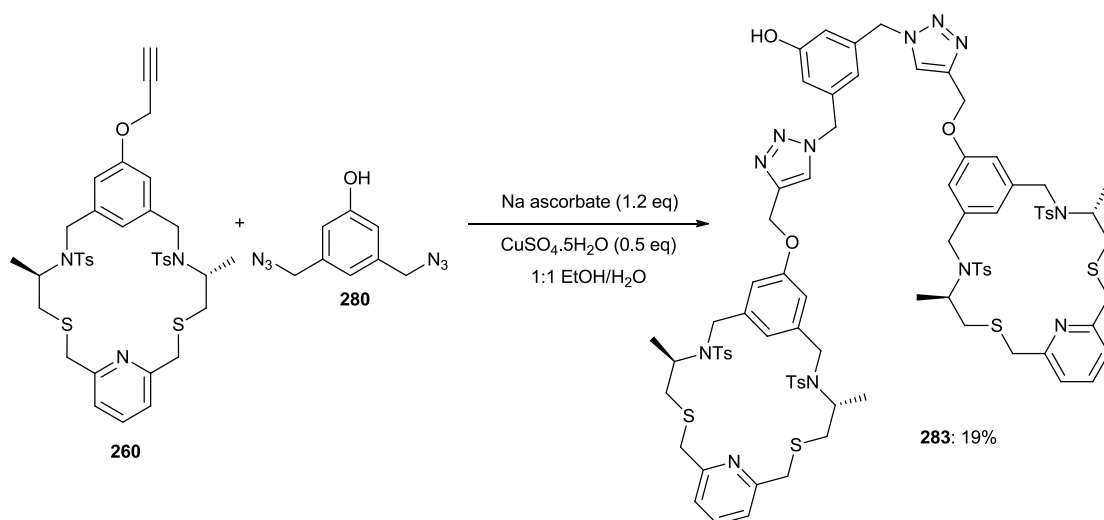


Figure 2-16: Illustration of the difference in ¹H NMR spectra of the 1,4- (green) and 1,5-triazoles (**281** and **282**) in CDCl₃

Synthesis of the bis-macrocylic analogue **283** was carried out in parallel with the bis-sugar moiety **281**, so the reaction met with the same problems, and again required further portions of the sodium and copper salts to be added during the reaction. This reaction was carried out on a much smaller scale, 0.4 moles compared to 1 mole, and a lower yield was obtained presumably due to the problems with the heterogeneous nature of the reaction mixture.



Scheme 2-47

¹H NMR spectroscopy of both the sugar-based and macrocyclic macromolecules **281** and **283** clearly demonstrated that the click reaction had worked. The signature proton on the triazole rings appeared as singlets at 7.57 ppm for the sugar macromolecule **281** (Figure 2-17) and 7.89 ppm for the macrocyclic analogue **283** (Figure 2-18).

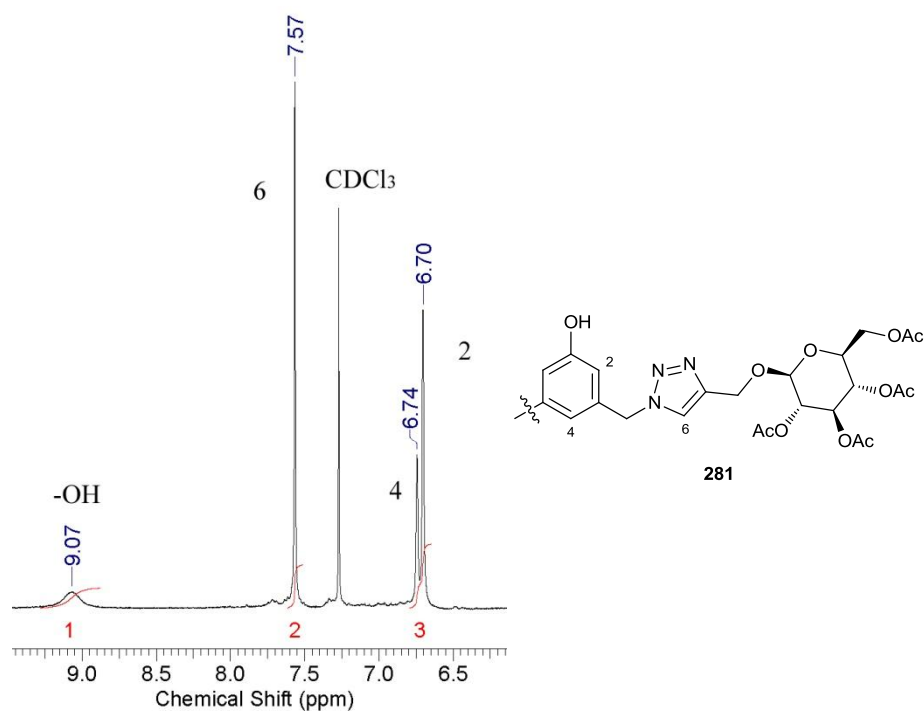


Figure 2-17: ¹H NMR spectrum of macrocyclic molecule **281** in CDCl₃

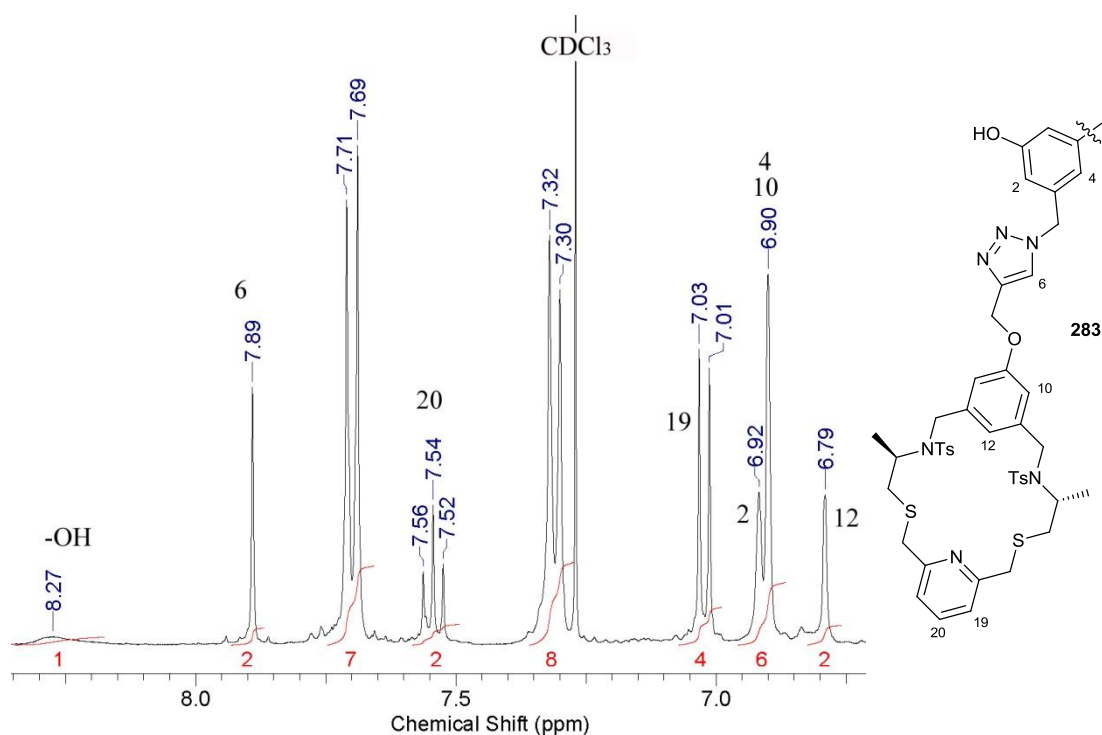


Figure 2-18: ^1H NMR spectrum of macromolecule **283** in CDCl_3

On examination of the nOe data for both the symmetrical macromolecules **281** and **283**, interactions were observed between the CH_2 site, H_a , and the proton attached to the triazole ring, H_b , (Figure 2-19). By comparison with what has been seen previously in the nOe data for the 1,5-triazole **282**, this proves the stereoselectivity of the click reaction, which formed the 1,4-triazole over the 1,5 product. Unfortunately, both the products isolated were glasses in their pure form so a solid-state X-ray crystal structure was not possible to obtain.

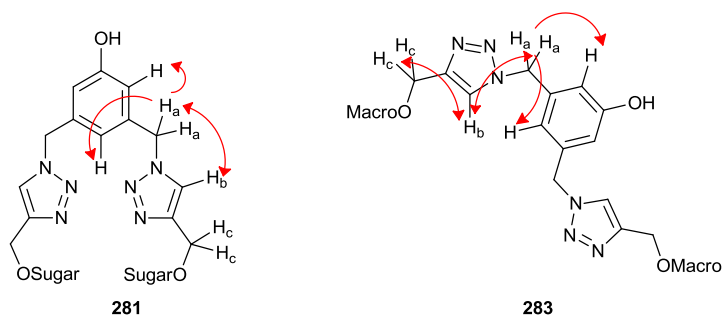
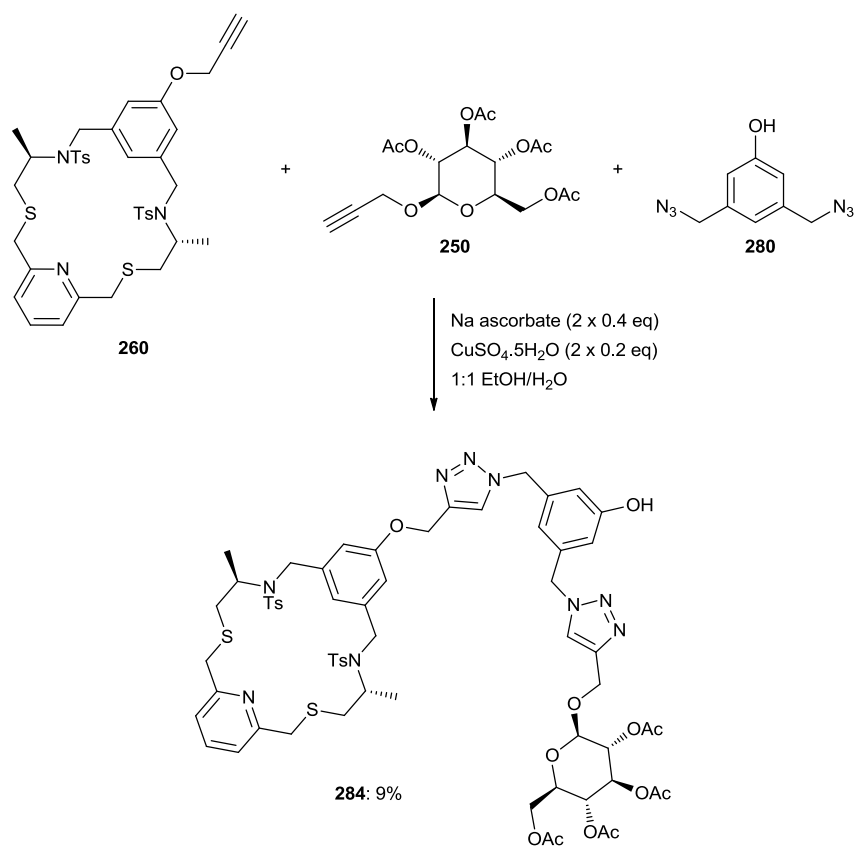


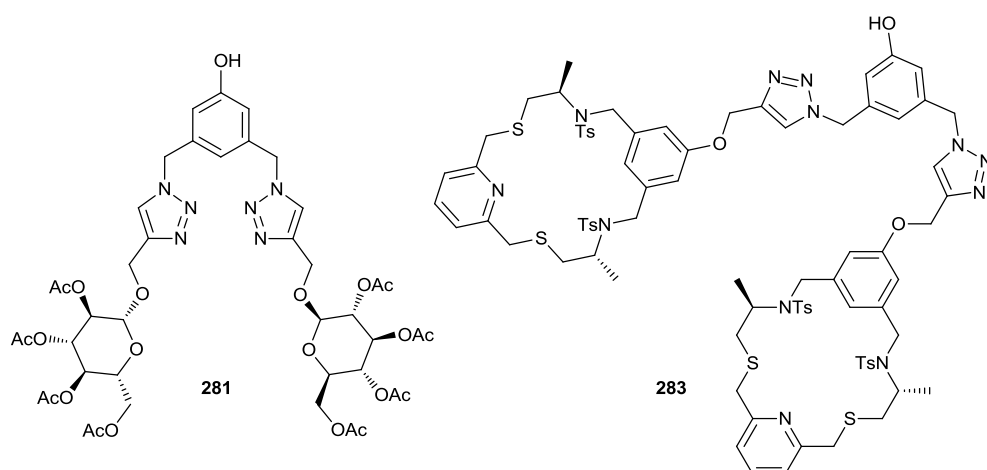
Figure 2-19: A comparison of nOe interactions observed around the triazole ring

Having validated the chemistry on both the sugar and macrocyclic substrates, we next decided to attempt to synthesise the desired product by carrying out a one-pot, two-stage synthesis.

Learning from our previous observations, the reaction was conducted by adding an equivalent of macrocycle **260** as a concentrated solution in a minimal amount of acetonitrile, to a slight excess of diazide **280** in ethanol. Copper sulfate and sodium ascorbate were added as 0.1 M aqueous solutions followed by additional water to make the solvent mixture to 1:1 ethanol/water. After 24 hours, the sugar **250** was added as a solution followed by further aliquots of the copper and sodium salts. After 24 hours, allowing sufficient time for the reaction to complete, the reaction was worked-up and purified by column chromatography.



Scheme 2-48



This reaction resulted in the formation of the desired sugar-macrocycle product **284** in 9% yield. Also recovered were the two alternative macromolecules, bis-sugar **281** (11%) and bis-macrocycle **283** (5%) and remaining starting materials.

Complete purification of the product by column chromatography proved difficult, as all three products had very similar retention times in a variety of solvent systems.

In an attempt to reduce the amount of by-products, the reaction was repeated, adding the sugar first, followed by the macrocycle later. The reaction, once complete, was reduced to dryness, passed through a plug of silica to remove the inorganic salts, and purified by preparative HPLC eluting with ethyl acetate.

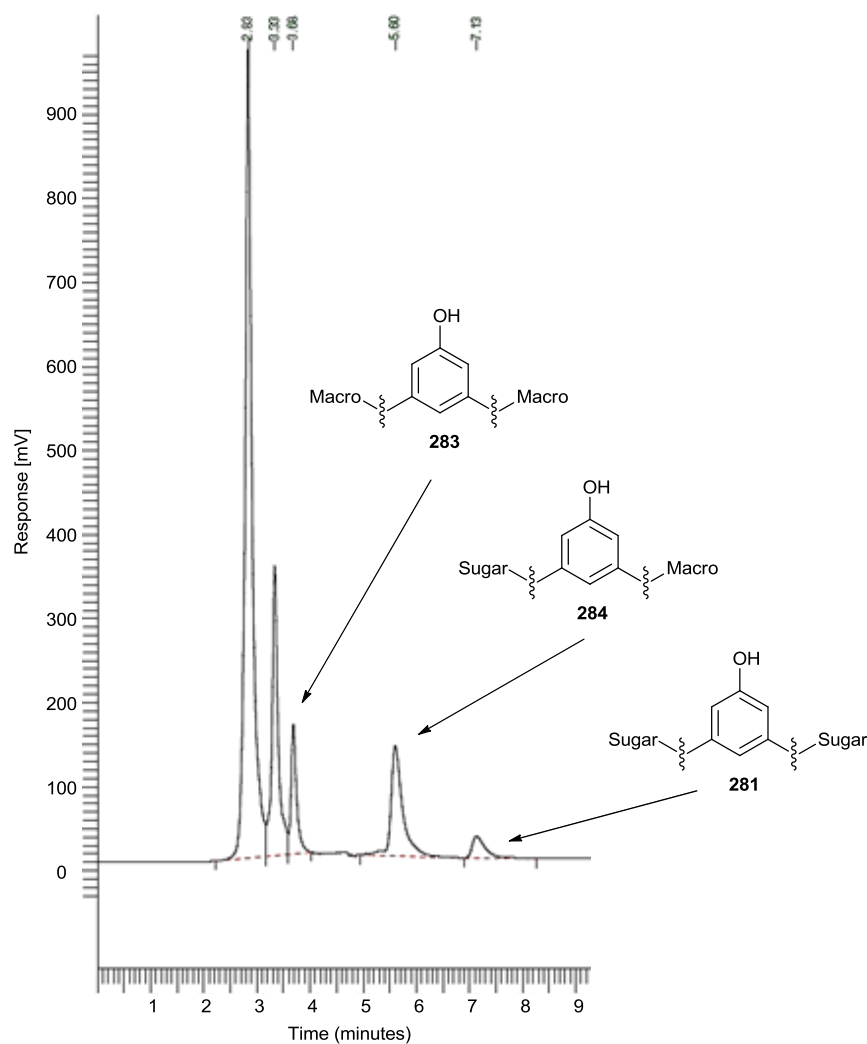


Figure 2-20: HPLC trace for the reaction mixture on purification of the macromolecule **284** eluting with EtOAc

The HPLC trace is shown in Figure 2-20. Initially it was thought that the desired product **284** was the eluting after 7 minutes but on isolation this was found to be the less polar by-product **281** which was recovered in 13% yield. At this point it was realised the product eluted between 5 and 6 minutes, and this product was isolated in 10% yield, far purer than after the purification of the reaction by flash column chromatography. The other side-product **283** eluted at around 3.5 minutes, with starting material eluting before then.

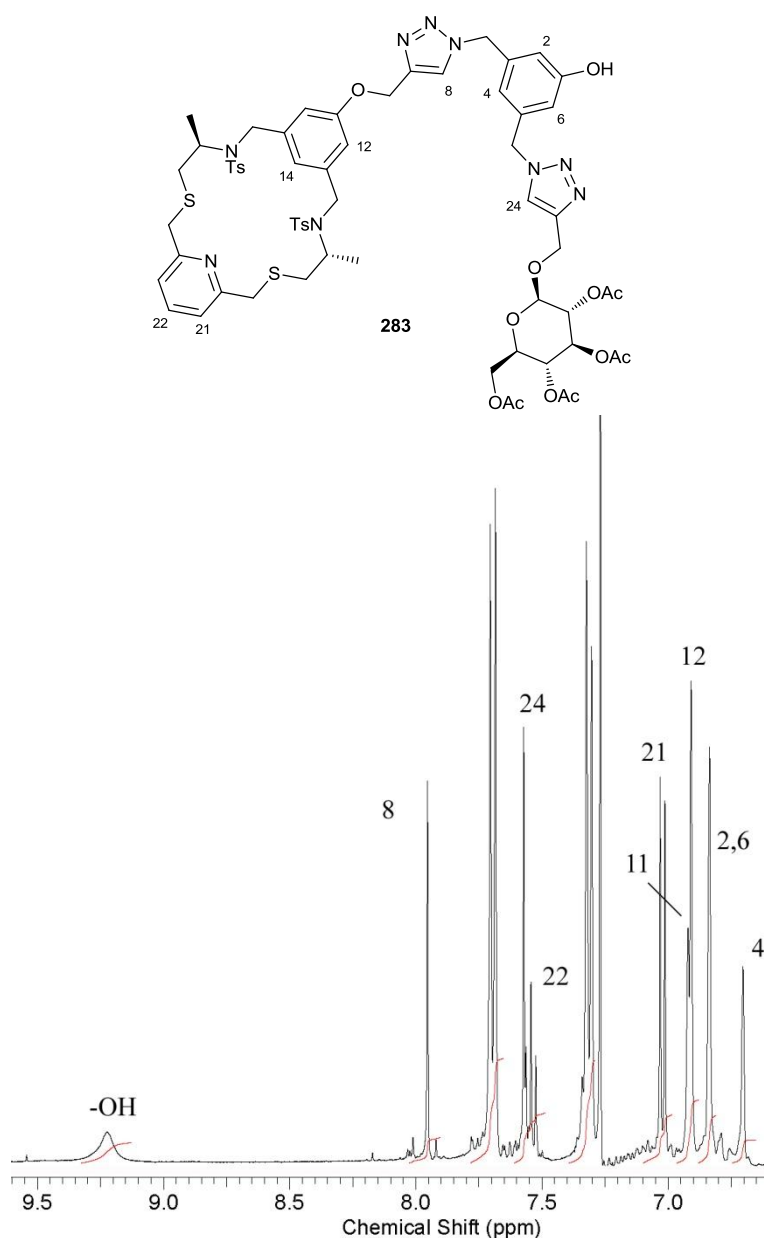


Figure 2-21: ^1H NMR spectrum of macromolecule **284** in CDCl_3

A ^1H NMR spectrum of the purified product is shown in Figure 2-21 and its comparison to the symmetrical macromolecules is shown in Figure 2-22. It is worth noting that the triazole protons have similar shift between the symmetric macromolecules **283** and **281** and the non-symmetric product **284**. This is illustrated by the triazole proton at 7.89 ppm for **283** and 7.95 ppm for **284**, and the other triazole proton appearing at 7.57 ppm for both **281** and **284**.

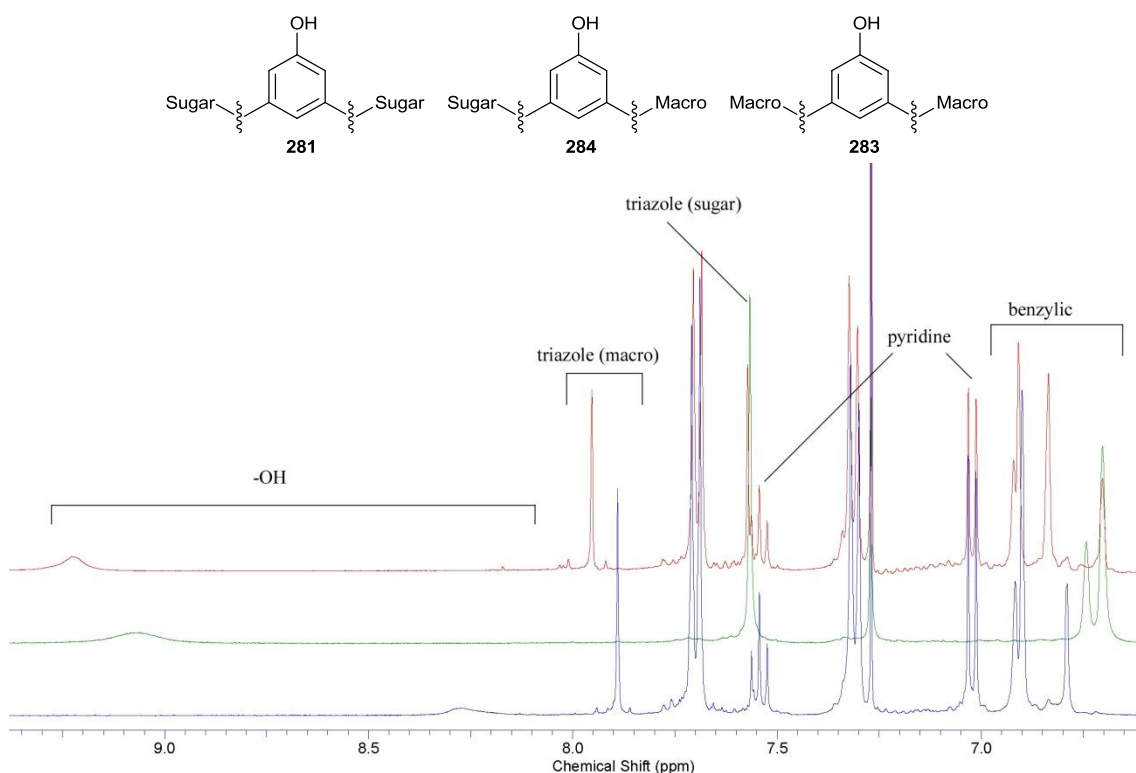


Figure 2-22: Comparison of the ^1H NMR spectrum of the three difference macromolecules: **283** (blue), **281** (green), **284** (red) in CDCl_3

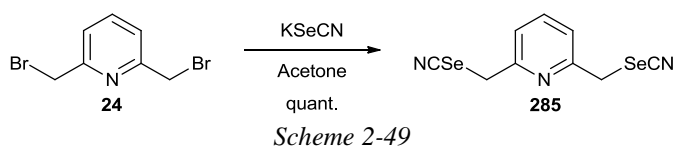
2.5 Alternative Strategies

2.5.1 Softer Nucleophile – Increased Reactivity?

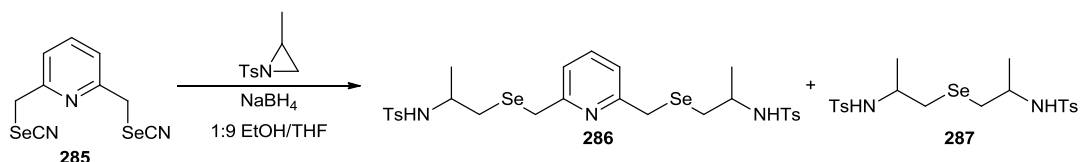
The ring opening of aziridines using selenium nucleophiles has become of interest in recent years due to the presence of selenium in a large number of biological compounds.²²⁰⁻²²²

Having observed the increased nucleophilicity of sulfur over oxygen when carrying out the nucleophilic ring opening (NRO) we wondered if this trend would continue on to selenium.^{223,224}

Initially we attempted to form selenocyanate **285** from 2,6-bis(bromomethyl)pyridine **24** which we had used for previous chemistry. We adopted a procedure published by Muralidharan *et al.*,²²⁵ and formed the product by displacement from potassium selenocyanate in quantitative yield (Scheme 2-49).

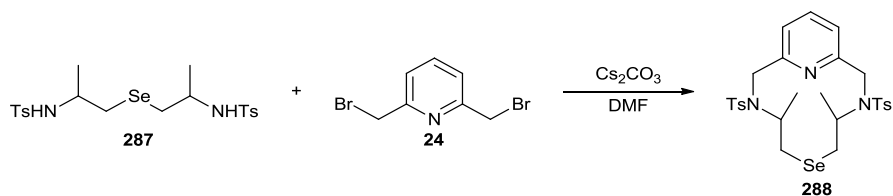


The diselenocyanate **285** was reacted with racemic aziridine **194** and sodium borohydride with the aim to form spacer diselenide **286**. We managed to form this spacer in 46% yield, and evidence for this came from the presence of the characteristic ^1H NMR spectroscopy peaks usually expected for the spacers such as the NH and αCH_2 . Curiously, the seleno ether **287** was also isolated from the reaction in 17% yield.



Scheme 2-50

This selenide side product **287** was successfully cyclised in the usual manner to form the 12-membered macrocycle **288**. However due to problems with the purification process, and the instability of the products, full data for the pure racemic mixture was not collected. Even so, it is clear from the ^1H NMR spectrum of the crude material that the cyclisation took place. Figure 2-23 highlights the diastereotopic CH_2 protons neighbouring the pyridine ring for both (S^*,S^*)- and (S^*,R^*)-macrocycles **288**.



Scheme 2-51

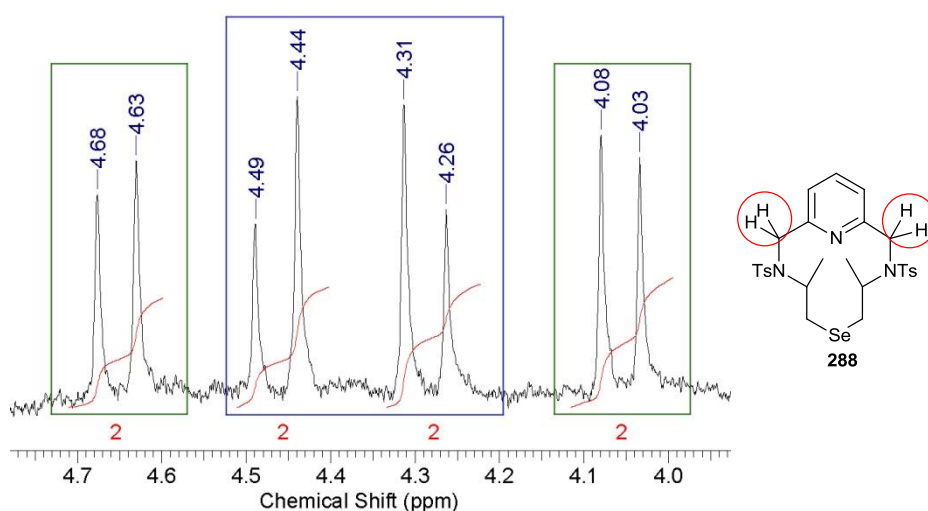
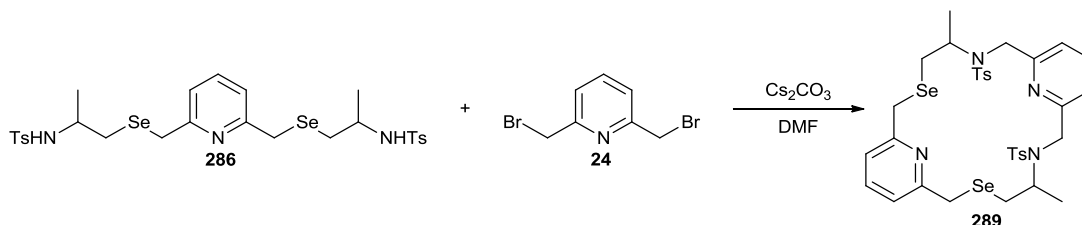
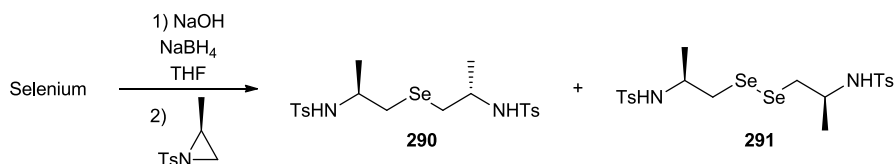


Figure 2-23: Part of ^1H NMR spectrum of the crude material isolated from the synthesis of racemic macrocycle **288** in CDCl_3

Also taken through to the macrocyclic stage was racemic spacer **286** which was reacted with dibromide **24** to form the macrocycle in an excellent yield of 100% (crude). Also recorded was a mass spectrum of the mixture of macrocyclic products, proving the isolation of the macrocycle mixture **289**.



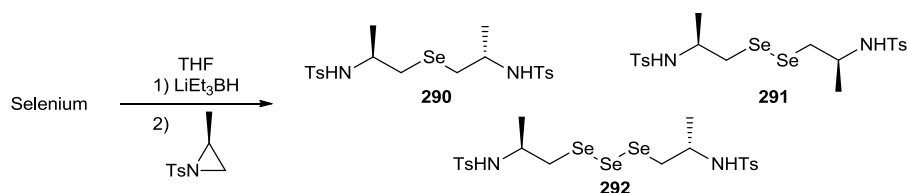
Scheme 2-52



Scheme 2-53

In a similar manner, we attempted to synthesise chiral selenide **290** using *S*-aziridine **181**, by the reaction of elemental selenium, with sodium hydroxide and sodium borohydride, forming Na_2Se *in situ*. To the reaction mixture, we added the chiral aziridine **181**, forming selenide **290**. Evidence for the formation of a small amount of the diselenide **291** was observed in the ^1H NMR spectrum, but was not isolated.

A modification of this reaction replaced sodium borohydride with lithium triethylborohydride. We anticipated this change would result in diselenide **291** as the major product. However, upon purification and isolation of what was thought to be one pure product, we discovered a mixture of 3 different, but similar compounds. Upon analysis, and comparison with previously prepared sulfides and selenides, these were discovered to be triselenide **292**, diselenide **291**, and selenide **290**, in a ratio of 1:2.8:3.4 respectively.



Scheme 2-54

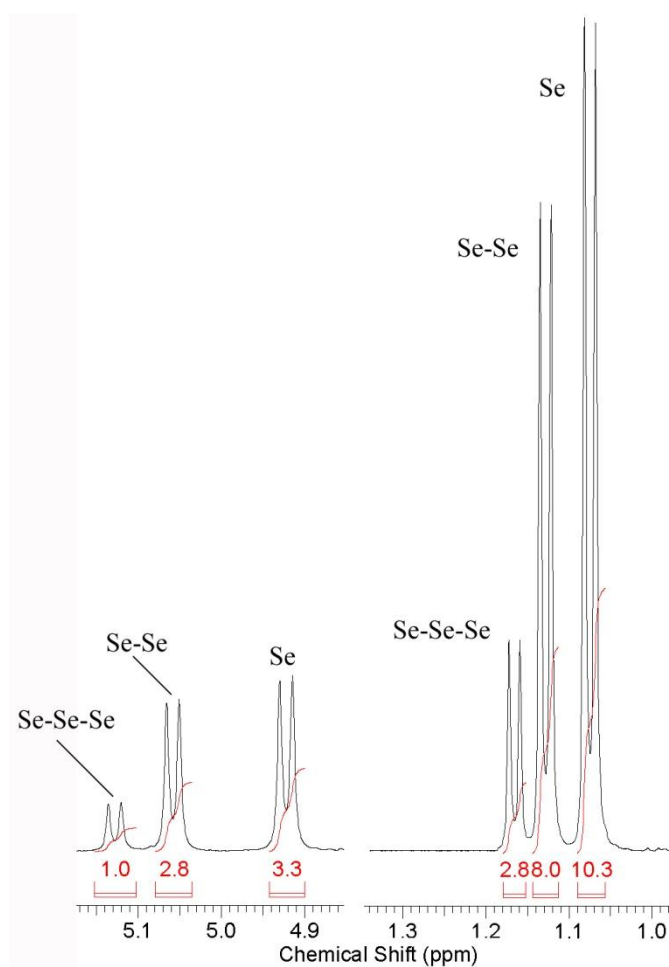
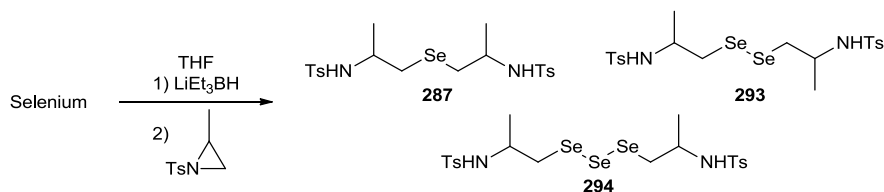


Figure 2-24: View of the NH peaks (left) and αCH_3 peaks (right) obtained in CDCl_3 when carrying out the reaction in Scheme 2-54 showing the ratio of products.

Similar phenomena were observed when the same reaction was repeated with racemic aziridine **194** (Scheme 2-55). Although the ^1H NMR spectrum was more complicated (Figure 2-25) the ratios can be calculated as a 1:3.4:3 mixture of triselenide **294**, diselenide **293** and selenide **287**.



Scheme 2-55

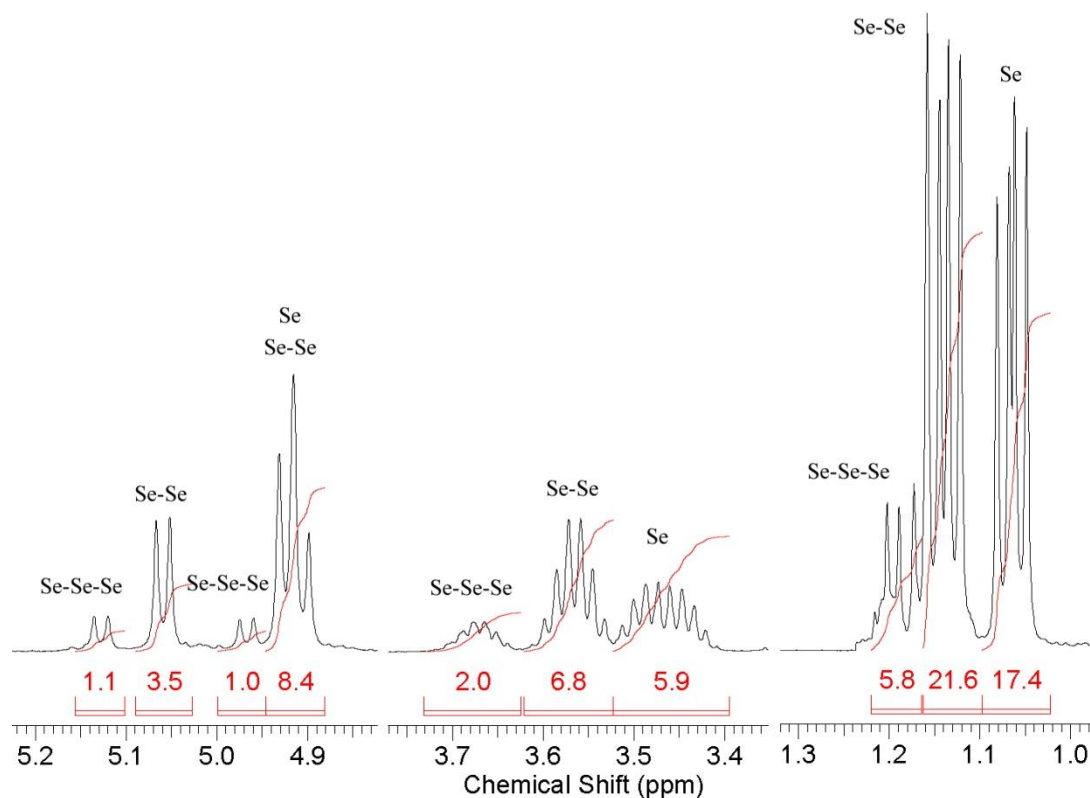
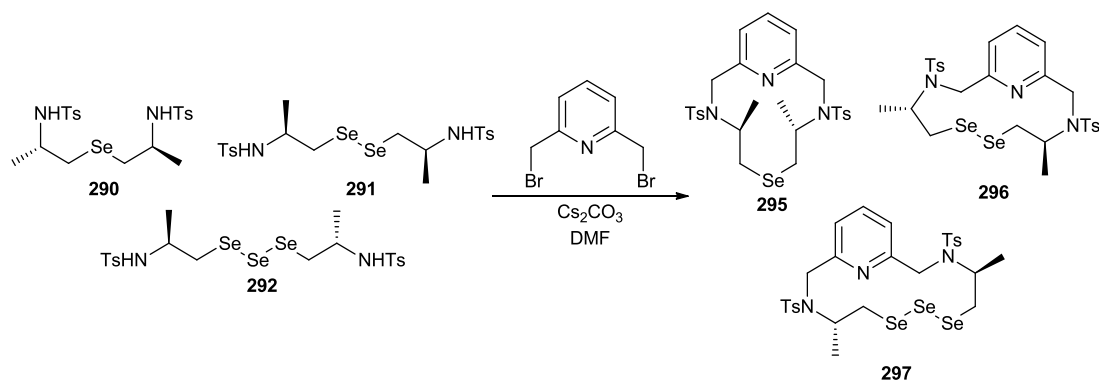


Figure 2-25 View of the NH peaks (left), αCH peaks (centre) and αCH₃ peaks (right) obtained in CDCl₃ when carrying out the reaction in Scheme 2-55 showing the ratio of products.

Despite not being able to separate the mixtures of chiral selenides **290-292**, we decided to take the mixture and cyclise the products with 2,6-bis(bromomethyl)pyridine **24**. The reaction was a success with a crude yield of 91%, where spectra of the crude material showed evidence of the formation of all three macrocycles **295-297**. However, on purification, the material recovered showed little evidence of triselenide **297**, which perhaps was lost during the process. It is clear selenide **295** and diselenide **296** were formed from the ¹H NMR spectra and mass spectrometry data showed peaks of both macrocycles [M+Na]⁺.

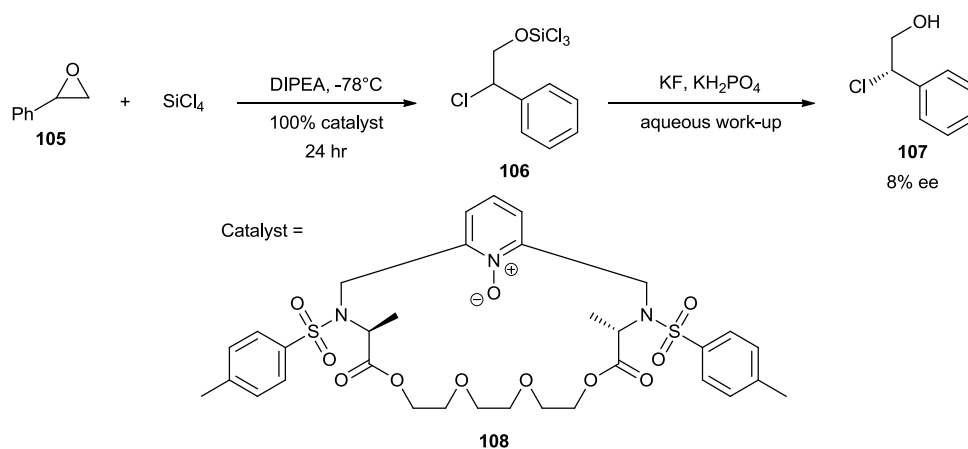


Scheme 2-56

This preliminary work represents the first successful synthesis and partial purification of a variety of novel seleno-macrocycles. The inability to control the reactivity of the selenium nucleophile during the aziridine ring-opening step, is a major complication with this chemistry. In every nucleophilic ring opening reaction attempted, this has led to a mixture of selenide, diselenide triselenides and potentially even more complicated compounds. To date, complete purification of these diverse compounds has proven difficult, perhaps in part due to the instability of the products.

2.5.2 Trials with the macrocycles

Previous work carried out within the Bailey research group explored the use of C2 symmetric macrocycles as stereoselective catalysts.²⁸ This included the use of ester-based macrocycle **108** as a “catalyst” in the epoxide opening shown in Scheme 2-57. Despite having to use 1 equivalent of the macrocycle, the ring opening showed promise; an 8% enantiomeric excess was obtained.



Scheme 2-57

2.5.2.1 Attempts with a metal centre – Pincer complexes

Pincer complexes have been of much interest in recent years as catalysts in synthesis and in particular C-C bond formation reactions. The first Pincer complex was first reported in 1976 by Bernard Shaw and Christopher Moulton who were examining a variety of different types of carbon-metal bonds.²²⁶ Pincer complexes are desirable targets due their straightforward synthesis and easy customisation. Their properties are modified by donor groups, counterion, and various attachments (Figure 2-26).^{183,227}

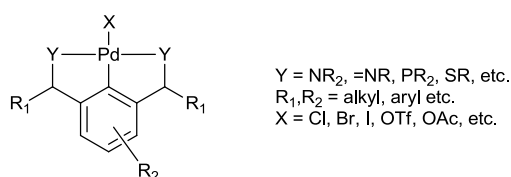
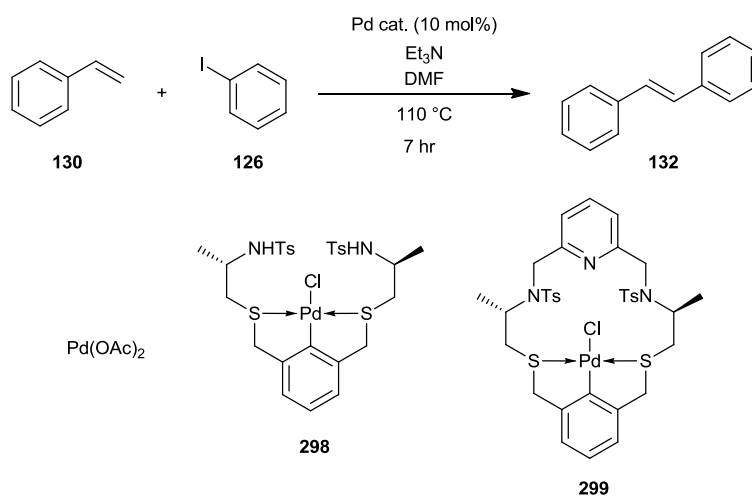


Figure 2-26

Using macrocycles synthesised during this research, we decided to target palladium-based sulfur-carbon-sulfur (SCS) pincer complexes, with the aim of performing a simple, yet reliable Heck reaction (Scheme 2-58).¹⁸³ The SCS palladacycles **298** and **299** were synthesised by refluxing the spacer **210** or macrocycle **240** with palladium(II) chloride diacetonitrile complex in acetonitrile for 24 hours. Once the solvent was removed the resulting complex was analysed by ¹H NMR spectroscopy, which showed the disappearance of the proton attached to the aromatic ring due to the formation of the Pd-C bond. ¹³C NMR spectroscopy showed the broadening of the carbon signals. Mass spectral data was obtained and reinforced the evidence for the production of the Pd-C bond.



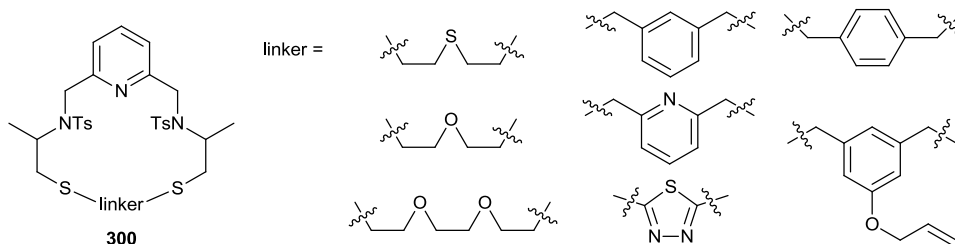
Scheme 2-58

We chose palladium acetate as the control catalyst for our studies. The Heck reaction was performed by heating to 110 °C a mixture of the catalyst (10 mol%), iodobenzene, styrene and triethylamine in DMF. This allowed the synthesis of *trans*-stilbene. The control reaction afforded the product in 91% compared to the SCS pincer complexes **298** and **299**, which both afforded *trans*-stilbene **132** in 11% yield showing the complexes are not particularly efficient for the Heck reaction, but have potential as catalysts.

Although the isolated yield of *trans*-stilbene was only 11%, NMR analysis showed the macrocyclic complex **299** was more effective as a catalyst. The ratio of styrene: product was 1:12 for the macrocyclic complex **299** but 1:5 for the spacer complex **298**.

3 Conclusions

A modular approach to the synthesis of a library of pyridine-based macrocycles (**300**) has been developed. Preliminary studies on the use of the macrocycles in asymmetric synthesis and palladium mediated cross-coupling reactions are also reported.



The nucleophilic, regioselective ring opening of an aziridine, derived from alaninol, allowed the synthesis of a diverse array of thio-ether spacer units in good to excellent yields. Pyridine analogues **300** were then synthesised in good yields using a pyridyl cross-linker. The use of readily available chiral pool starting materials derived from either D- or L-alanine, provided access to optically pure macrocycles.

The conjugation of functionalised macrocycles such as **282** using Heck chemistry was unsuccessful, however adopting the Sharpless-Huisgen “click” protocol on ether **260** provided access to macrocycles decorated with carbohydrate residues (**266**). We hoped to be able to functionalise further the macrocycle by attaching it to an azo dye and sugar unit.

Conjugation of macrocycle **260** or sugar **250** using a “click” approach provided the macromolecules **283** and **281**, albeit in low yield. Attachment of both a carbohydrate and macrocycle onto a central scaffold, which now has the potential for further chemical elaboration, was also successful (**284**). Optimisation of this reaction sequence is now underway, with a view to attaching a dye or fluorescing agent to the central scaffold.²²⁸

The use of **210** or **240** as ligands in Pd-mediated reactions has been briefly explored. Formation of the Pd-complexes **298** and **299** was successful, as shown by ¹H NMR spectroscopy, but the complexes were only slightly efficient as catalysts, yielding *trans*-stilbene in 11%.

The synthesis of selenium-containing macrocycles using the chemistry outlined above, while viable, is hampered by the concomitant formation of di- and tri-selenide by-

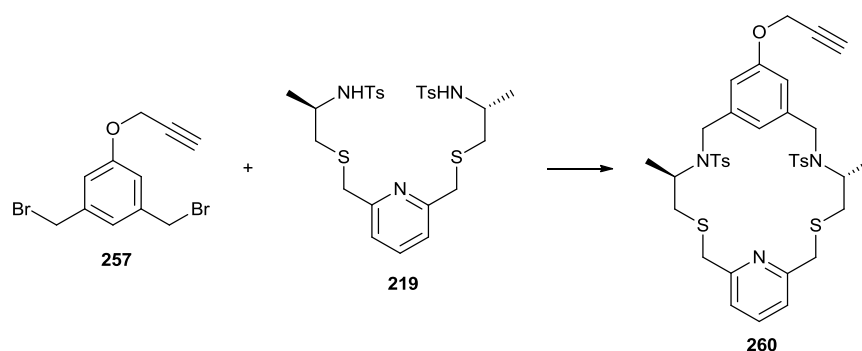
products. Efforts are also underway to develop a cleaner synthesis of this under-represented class of crown-selenospacers.

3.1 Future Work

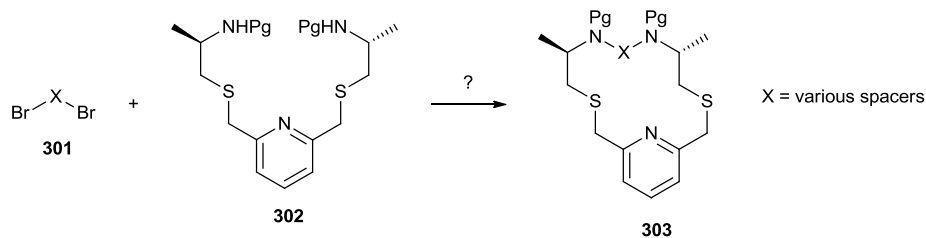
The project has now progressed to the stage where the Quayle group have synthesised a library of macrocycles, and succeeded in the ligation of the central core with carbohydrates. The group has begun to investigate different applications for the novel chiral pyridine-derived thioether macrocycles, but further investigations need to be carried out.

(a) The binding ability of the macrocycles themselves need to be analysed, perhaps by isothermal titration calorimetry (ITC) in the case of small molecules or electron paramagnetic resonance (EPR) or phase-transfer catalysis (PTC) in the case of ions or metals. PTC in particular would be the most useful as it would evaluate the ability of the macrocycles to go into lipophilic solvents, almost directly comparable to blood or soft tissue.

(b) The optimisation of macrocycle assembly requires investigation. The propargylic macrocycle **260** was synthesised using a different route, with a spacer, which already possessed the pyridyl unit (Scheme 3-1).



It might be easier to synthesise a wide variety of macrocycles, by forming a large amount of the pyridyl spacer **219**, and then simply ring closing the macrocycle with various dibromides, leading to more easily attainable macrocycles (Scheme 3-2).



Scheme 3-2

(c) It is also important at this stage to highlight the importance of the protecting/activating group on the aziridine during the ring-opening and macrocyclisation steps. The tosyl group is chemically robust – hence its incorporation into our basic scheme for the proof of principle investigations. However, the mere fact that this group is stable almost certainly means that its removal, post-macrocyclisation, will be difficult to achieve and alternatives will have to be sought. Commonly used amine protecting groups such as the 2-(trimethylsilyl)ethylsulfonamide (SES) or the nosyl group (Figure 3-1) will therefore be screened in the optimisation of the synthesis of the macrocycle.

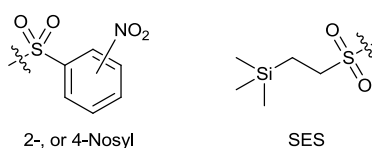
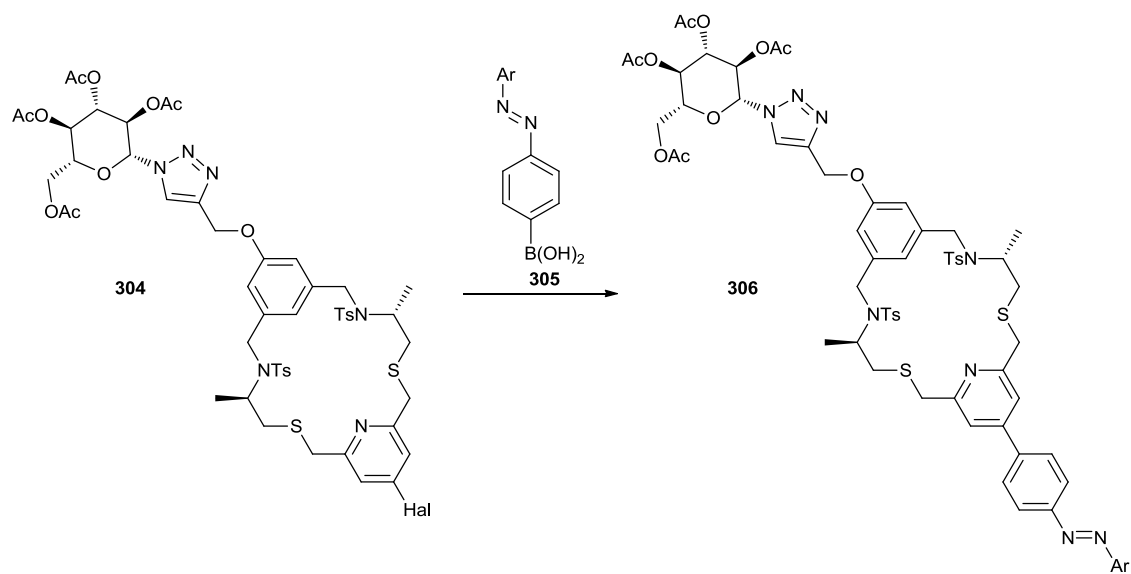


Figure 3-1

(d) The addition of a dye-unit onto the central, pre-formed, macrocyclic scaffold must also be explored. Stability issues and ease of synthesis have already been explored previously in the Quayle group by O. Rasheed and have examined phenyl- and naphthyl-derivatives **273** and **270**.²¹⁸ Alternatively, the synthesis of the halogenated macromolecule **304** would enable the synthesis of **306** using well-established Suzuki-type coupling (Scheme 3-3). This transformation would place the chromophore in direct conjugation with the pyridine metal binding site (Figure 3-2), and facilitate the detection and reporting of a metal binding event.



Scheme 3-3

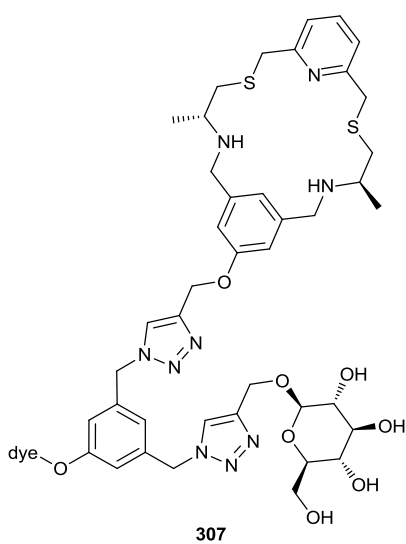


Figure 3-2

EXPERIMENTAL

4 Experimental

4.1 General Experimental	112
4.2 Cyclic Crown Ether (Ester Version)	113
<i>N</i> -Tosyl (<i>S</i>)-alanine 104	113
1,8-bis-(<i>N</i> -Tosyl-(<i>S</i>)-alanyloxy) triethylene glycol 23	114
<i>N,N</i> -(2,6-Dimethylenylpyridine)-1,8-(<i>N</i> -tosyl-(<i>S</i>)-alanyloxy) triethylene glycol 25	115
<i>N,N'</i> -(2,6-Dimethylenylpyridine- <i>N</i> -oxide) 1,8-(<i>N</i> -tosyl-(<i>S</i>)-alanyloxy) triethylene glycol 108	116
4.3 Cyclic Crown Ethers (Ether Version)	117
4.3.1 Spacer Premolecules	117
2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol 179 ^{190,202}	117
(<i>S</i>)-4-methyl- <i>N</i> -(1-phenyl-2,5,8,11- <i>tetraoxatetradecan</i> -13-yl)benzenesulfonamide 182 & (<i>S</i>)-4-methyl- <i>N</i> -(12-methyl-1-phenyl-2,5,8,11- <i>tetraoxatetradecan</i> -13-yl)benzenesulfonamide 183	117
2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) 191 ²²⁹	119
4.3.2 Aziridines and Premolecules	120
(<i>S</i>)-2-(Tritylamino)propan-1-ol 173	120
(<i>S</i>)-2-methyl-1-tosylaziridine 181 ^{201,230,231}	120
(<i>R</i>)-2-methyl-1-tosylaziridine 193	122
(±)-2-Methyl-1-tosylaziridine 194 ²⁰¹	122
4.4 Thioether Spacers [CARE: Malodourous]	123
4.4.1 Spacer pre-molecules	123
1,3-phenylenedimethanethiol 209 ²³⁵	123
1,4-phenylenedimethanethiol 213 ²³⁶	123
Dimethyl pyridine-2,6-dicarboxylate 216 ²³⁷	124
Pyridine-2,6-diyl dimethanol 217 ²⁴⁰	124
2,6-bis(Bromomethyl)pyridine 24 ²⁴⁰	125
Dimethyl 5-hydroxyisophthalate 221 ²⁴²	126
Dimethyl 5-(prop-2-yn-1-yloxy)isophthalate 254 ²⁴⁴	126
Dimethyl 5-(allyloxy)isophthalate 222 ²⁴⁶	127
(5-Hydroxy-1,3-phenylene)dimethanol 256 ²⁴⁷	128
(5-(prop-2-yn-1-yloxy)-1,3-phenylene)dimethanol 255 ²⁴⁴	129
(5-(Allyloxy)-1,3-phenylene)dimethanol 223 ²⁴⁹	130
1,3-bis(bromomethyl)-5-(prop-2-yn-1-yloxy)benzene 257	130
	108

1-(Allyloxy)-3,5-bis(bromomethyl)benzene	225 ²¹⁰	132
4.4.2 Dithiol Spacers		133
General method for the formation of the dithiol spacer unit from the dithiol	^{141,250}	133
<i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(2,2'-thiobis(ethane-2,1-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	198	133
(<i>S</i> *, <i>S</i> *),(<i>R</i> *, <i>S</i> *)- <i>N,N'</i> -1,1'-(2,2'-thiobis(ethane-2,1-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	200	134
<i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(2,2'-oxybis(ethane-2,1-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	197	135
(<i>S</i> *, <i>S</i> *),(<i>R</i> *, <i>S</i> *)- <i>N,N'</i> -1,1'-(2,2'-oxybis(ethane-2,1-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	199	135
<i>N,N'</i> -((2 <i>S</i> ,15 <i>S</i>)-7,10-dioxa-4,13-dithiahexadecane-2,15-diyl)bis(4-methylbenzenesulfonamide)	196	136
(<i>S</i> *, <i>S</i> *),(<i>R</i> *, <i>S</i> *)- <i>N,N'</i> -(7,10-dioxa-4,13-dithiahexadecane-2,15-diyl)bis(4-methylbenzenesulfonamide)	204	137
<i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	201	138
<i>N,N'</i> -(2 <i>R</i> ,2' <i>R</i>)-1,1'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	202	138
(<i>S</i> *, <i>S</i> *),(<i>R</i> *, <i>S</i> *)- <i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	203	139
<i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(1,3-phenylenebis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	210	140
(<i>S</i> *, <i>S</i> *),(<i>R</i> *, <i>S</i> *)- <i>N,N'</i> -(1,1'-(1,3-phenylenebis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	211	141
<i>N,N'</i> -(2 <i>S</i> ,2' <i>S</i>)-1,1'-(1,4-phenylenebis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	214	141
<i>N,N'</i> -((2 <i>S</i> ,2' <i>S</i>)-((5-(allyloxy)-1,3-phenylene)bis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	226	142
<i>N,N'</i> -((2 <i>S</i> ,2' <i>S</i>)-((pyridine-2,6-diylbis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	218	143
<i>N,N'</i> -((2 <i>R</i> ,2' <i>R</i>)-((pyridine-2,6-diylbis(methylene))bis(sulfanediy))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide)	219	144
4.5 The Macrocycles		145
4.5.1 General Method for the synthesis of the macrocycles		145
(4 <i>S</i> ,14 <i>S</i>)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-6,9,12-trithia-3,15,21-triaza-bicyclo[15.3.1]hencosa-1(20),17(21),18-triene	234	146
		109

(<i>S*,S*</i>),(<i>R*,S*</i>)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-6,9,12-trithia-3,15,21-triaza-bicyclo[15.3.1]hencosa-1(20),17(21),18-triene	235	147
(<i>4S,14S</i>)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-9-oxa-6,12-dithia-3,15,21-triaza-bicyclo[15.3.1]hencosa-1(20),17(21),18-triene	230	148
(<i>S*,S*</i>),(<i>R*,S*</i>)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-9-oxa-6,12-dithia-3,15,21-triaza-bicyclo[15.3.1]hencosa-1(20),17(21),18-triene	236	149
(<i>4S,17S</i>)-4,17-Dimethyl-3,18-bis-(toluene-4-sulfonyl)-9,12-dioxa-6,15-dithia-3,18,24-triaza-bicyclo[18.3.1]tetracosa-1(23),20(24),21-triene	229	150
(<i>S*,S*</i>),(<i>R*,S*</i>)-4,17-Dimethyl-3,18-bis-(toluene-4-sulfonyl)-9,12-dioxa-6,15-dithia-3,18,24-triaza-bicyclo[18.3.1]tetracosa-1(23),20(24),21-triene	237	151
(<i>4S,13S</i>)-4,13-Dimethyl-3,14-bis-(toluene-4-sulfonyl)-6,11,21-trithia-3,8,9,14,20-pentaaza-tricyclo[14.3.1.1 ^{7,10}]hencosa-1(19),7,9,16(20),17-pentaene	233	152
(<i>4S,16S</i>)-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene	240	154
(<i>S*,S*</i>),(<i>R*,S*</i>)-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene	241	155
(<i>4S,16S</i>)-10-allyloxy-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene	282	157
(<i>5S,15S</i>)-5,15-Dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,24-triaza-tricyclo[17.2.2.1 ^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene	239	158
(<i>5S,15S</i>)-5,15-Dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23,24-tetraaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene	238	159
(<i>5R,15R</i>)-10-But-3-ynyl-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene	260	160
(<i>S*,S*</i>),(<i>R*,S*</i>)-10-But-3-ynyl-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene	262	162

4.6 The Macromolecules 163

4.6.1 Metathesis Attempt 163

Allyl 2,3,4,6- <i>tetra</i> -O-acetyl- α -D-galactopyranoside	246 ²⁵¹	163
----------------------------------------------------------------------	---------------------------	-----

4.6.2 Click Chemistry Precursors 164

2-Propynyl 2,3,4,6- <i>tetra</i> -O-acetyl- β -D-galactopyranoside	278 ²¹⁹	164
1- <i>O</i> -propargyl 2,3,4,6- <i>tetra</i> -O-acetyl- β -D-glucose	250 ²¹⁹	165
2,3,4,6- <i>tetra</i> -O-Acetyl- α -D-glucopyranosyl bromide	264 ²⁵⁴	166
2,3,4,6- <i>tetra</i> -O-Acetyl- β -D-glucopyranosyl azide	265 ²¹⁷	167
3,5-bis(Bromomethyl)phenol	279 ²⁵⁶	167
3,5-bis(Azidomethyl)phenol	280 ²⁵⁶	168

4.6.3	The Click Products	169
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	3,5-bis{4-(2',3',4',6'- <i>tetra-O</i> -acetyl- β -D-glucopyranosyloxymethyl)-1 <i>H</i> -[1,2,3]-triazol-1-methyl}phenol 281	170
	3,5-bis-[4-((5 <i>R</i> ,15 <i>R</i>)-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1 ^{8,12}]tetracos-1(23),8,10,12(24),19,21-hexaen-10-yloxymethyl)-1,2,3-triazol-1-ylmethyl]-phenol 283	171
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4.1 General Experimental

Anhydrous solvents and reagents were obtained as follows: DMF was dried three times over molecular sieves (3 Å), DMSO was left over molecular sieves (4 Å), THF was distilled from sodium wire and benzophenone, DCM was distilled from calcium hydride, methanol was dried over molecular sieves (4 Å). Dried Et₂O, THF and DCM were alternatively obtained from the PureSolv MD Solvent Purification System. Petrol or pet. ether refers to light petroleum which distils between 40 °C and 60 °C. All reactions were conducted in dry glassware under a nitrogen atmosphere, unless otherwise stated. All chemicals were used directly from the suppliers' vessel without further purification, unless otherwise stated.

¹H NMR spectra were recorded at 300, 400 or 500 MHz and ¹³C NMR spectra at 75, 100 or 125 MHz on a Bruker AC300, AC400 or AC500 spectrometer. ⁷⁷Se NMR spectra were recorded at 76 MHz on a Bruker AC400 spectrometer. All NMR experiments were carried out at 25 °C. The splitting patterns for NMR spectra are designated as follows: s (singlet), br.s (broad singlet), d (doublet), t (triplet), q (quadruplet), quin (quintet), sext (sextet), sept. (septet), m (multiplet), or combinations thereof. Chemical shifts are denoted in ppm (δ) relative to internal solvent standard. Coupling constants (*J*) are designated in Hz and rounded to the nearest 0.5 Hz. Assignments were made with the aid of DEPT135, COSY, HMBC and HMQC experiments.

Mass spectra were recorded on one of the following: Waters QTOF (ES, HRMS), Thermo Finnigan MAT95XP (GC/MS, EI, HRMS) or a Hewlett Packard 5971 MSD (GC/MS).

HPLC was carried out using a Gibson-Abimed Preparative HPLC Model 305 with a detection wavelength of 260 nm.

Infrared spectra were recorded on a Bruker Alpha FT-IR.

Analytical TLC was performed on Merck silica gel 60 F₂₅₄ aluminium backed plates or Macherey-Nagel silica gel 60 UV₂₅₄ polyester backed plates. The plates were visualised under UV fluorescence (254 nm) or developed using acidified potassium permanganate

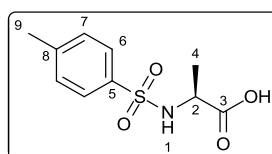
solution and charring. R_f values are reported to the nearest 0.01. Mixed solvent system compositions are quoted as volumetric ratios.

Optical rotations were measured using an Optical Activity Ltd. AA-100 automatic polarimeter.

Elemental analyses were recorded by Mr Martin Jennings on the ThermoScientific Flash 2000 (CHN), Carlo Erba EA1108 (S), Fisons Horizon ICPOES (metals) or Metrohm 686 Titroprocessor (halides).

4.2 Cyclic Crown Ether (Ester Version)

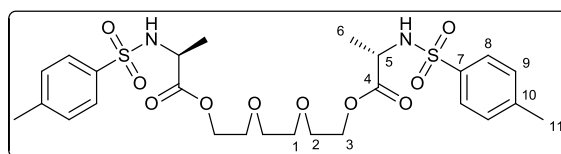
N-Tosyl (*S*)-alanine **104**



104

Preparation was analogous to that of Li and Zhao:¹⁹¹ Tosyl chloride (12.9 g, 67.9 mmol) in diethyl ether (56 mL) was added slowly to a stirring solution of (*S*)-alanine (5.01 g, 56.2 mmol) in 1.5 M NaOH (5.67 g in 95 mL H₂O) and left overnight. 11.5 M HCl was added dropwise in order to adjust the pH of the aqueous phase to pH 2. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over Na₂SO₄, and the excess solvent removed *in vacuo* to give the *title compound* as a colourless crystalline product in an essentially pure state (10.1 g, 74%), $R_f = 0.4$ (5% methanol in ethyl acetate), (found [ES⁺] M⁺ + H, 244.0632. C₁₀H₁₄O₄NS requires *M*, 244.0638); ν_{\max} (film) 3434, 1713, 1652, 1423, 1342 and 1150 cm⁻¹; δ_{H} (CDCl₃, 500 MHz) 1.44 (3H, d, $J = 7.0$ Hz, CH₃, H-4), 2.43 (3H, s, CH₃, H-9), 4.03 (1H, app. quin., $J = 7.5$ Hz, CH, H-2), 5.18 (1H, d, $J = 7.5$ Hz, NH, H-1), 7.31 (2H, d, $J = 8.0$ Hz, Ar-H, H-7) and 7.75 (2H, d, $J = 8.0$ Hz, Ar-H, H-6); δ_{C} (CDCl₃, 75 MHz) 19.64 (CH₃, C-4), 21.54 (CH₃, C-9), 51.03 (CH, C-2), 127.17 (CH, C-6), 129.77 (CH, C-7), 136.67 (C, C-6), 143.93 (C, C-8) and 175.95 (C, C-3); m/z (ES⁺) 244.0 (M⁺ + H), 261.1 (M⁺ + NH₃) and 266.0 (M⁺ + Na).

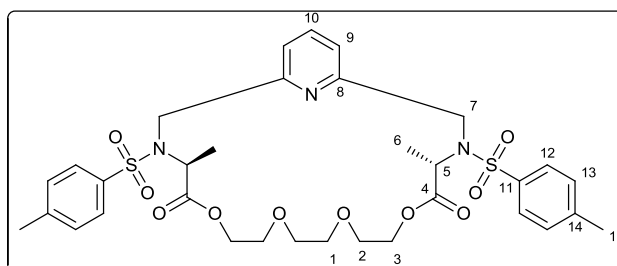
1,8-bis-(*N*-Tosyl-(*S*)-alanyloxy) triethylene glycol **23**



23

N-Tosyl (*S*)-alanine **104** (488 mg, 2.0 mmol) was dissolved in dry THF (50 mL) and stirred under nitrogen for 20 minutes at room temperature. HOBT (307 mg, 2.0 mmol) was added in one portion and the mixture was stirred for 20 minutes then cooled to 0 °C. EDC (383 mg, 2.0 mmol) was added in one portion and then the mixture was stirred at 0 °C for 1 hour. Triethylene glycol (140 μL, 1.1 mmol) was added and the mixture was stirred at 0 °C for 1 hour and then at room temperature for 24 hours. The THF was then removed *in vacuo* and the resultant oil was dissolved in ethyl acetate (30 mL) which was then washed with 4 M HCl (2 x 30 mL), saturated aqueous sodium hydrogen carbonate (2 x 30 mL), brine (2 x 30 mL) and dried with magnesium sulfate. The solution was filtered and concentrated *in vacuo* to yield the crude product (446 mg). Purification of the crude product by column chromatography (1% methanol in DCM) afforded the *title compound* as a colourless oil (131 mg, 22%), $R_f = 0.2$ (1% methanol in DCM), (found $[\text{ES}^+] \text{M}^+ + \text{NH}_4$, 618.2141. $\text{C}_{26}\text{H}_{40}\text{O}_{10}\text{N}_3\text{S}_2$ requires M , 618.2150); ν_{max} (film) 3507, 3279, 2943, 1738, 1653, 1452, 1338 and 1164 cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.36 (6H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.41 (6H, s, CH_3 , H-11), 3.59 (8H, t, $J = 5.0$ Hz, CH_2 , H-1,2), 4.00 (2H, dq, $J = 8.5, 7.0$ Hz, CH , H-5), 4.07 (2H, dt, $J = 12.0, 5.0$ Hz, CH_2 , H-3), 4.14 (2H, dt, $J = 12.0, 5.0$ Hz, CH_2 , H-3), 5.53 (2H, d, $J = 8.5$ Hz, NH), 7.29 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-9) and 7.74 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-8); δ_{C} (CDCl_3 , 75 MHz) 19.57 (CH_3 , C-6), 21.48 (CH_3 , C-11), 51.53 (CH , C-5), 64.52 (CH_2 , C-3), 68.57, 70.54 (CH_2 , C-1,2), 127.18 (CH , C-8), 129.64 (CH , C-9), 137.01 (C , C-7), 143.54 (C , C-10) and 172.12 (C , C-4); m/z (ES^+) 618.3 ($\text{M}^+ + \text{NH}_4$), 623.3 ($\text{M}^+ + \text{Na}$).

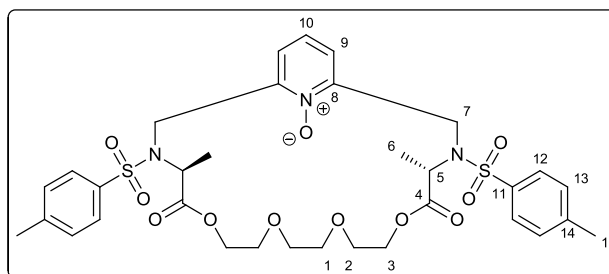
N,N-(2,6-Dimethylenylpyridine)-1,8-(*N*-tosyl-(*S*)-alanyloxy) triethylene glycol **25**



25

Commercially available 2,6-bis(bromomethyl)pyridine **24** (46.1 mg, 170 μmol) followed by caesium carbonate (250 mg, 770 μmol , ~ 5 eq.) were added to a stirring solution of the di-ester **23** (103 mg, 170 μmol) in dry DMF (60 mL) under nitrogen. The resulting suspension was then left to stir for 48 hours. The DMF was removed *in vacuo* and the crude product, an oil, was dissolved into DCM (40 mL) and filtered. The filtrate was washed with H_2O (4 x 30 mL), dried over MgSO_4 , filtered and concentrated to afford the *title compound* **25** as a viscous oil in an essentially pure state (120 mg, 99%), $R_f = 0.48$ (2% methanol in DCM); δ_{H} (CDCl_3 , 500 MHz) 1.28 (6 H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.40 (6H, s, CH_3 , H-15), 3.41 (2H, ddd, $J = 12.0, 6.5, 3.0$ Hz, CH_2 , H-2), 3.49 - 3.59 (6H, m, CH_2 , H-1,2), 3.87 (2H, ddd, $J = 12.0, 6.5, 3.0$ Hz, CH_2 , H-3), 4.04 (2H, ddd, $J = 12.0, 6.5, 3.0$ Hz, CH_2 , H-3), 4.38 (2H, d, $J = 16.0$ Hz, CH_2 , H-7), 4.61 (2H, d, $J = 16.0$ Hz, CH_2 , H-7), 4.69 (2H, q, $J = 7.0$ Hz, CH , H-5), 7.27 (4H, d, $J = 8.0$ Hz, CH , H-13), 7.45 (2H, d, $J = 8.0$ Hz, CH , H-9), 7.63 (1H, t, $J = 8.0$ Hz, CH , H-10) and 7.72 (4H, d, $J = 8.0$ Hz, CH , H-12); δ_{C} (CDCl_3 , 125 MHz) 16.82 (CH_3 , C-6), 21.39 (CH_3 , C-15), 51.01 (CH_2 , C-7), 55.87 (CH , C-5), 64.02 (CH_2 , C-3), 68.59 (CH_2 , C-2), 70.54 (CH_2 , C-1), 121.67 (CH , C-9), 127.46 (CH , C-12), 129.38 (CH , C-13), 136.92 (CH , C-11), 137.24 (CH , C-10), 143.34 (CH , C-14), 156.77 (CH , C-8) and 170.50 (CH , C-4); m/z (ES^+) 704.3 ($\text{M}^+ + \text{H}$), 726.6 ($\text{M}^+ + \text{Na}$).

108



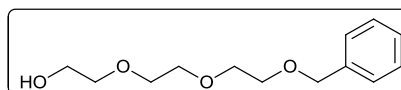
108

*m*CPBA (121 mg, 0.7 mmol, 5 eq.) was added to a stirring solution of triethylene glycol derivative **25** (98.1 mg, 140 μ mol) in dry DCM (7 mL) at room temperature. The reaction was left to stir at room temperature for 48 hours. The reaction was quenched by the addition of 0.1 M NaOH (2 x 20 mL) and the organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography (1% \rightarrow 4% methanol in DCM) to give **108** as a pale yellow oil (54.3 mg, 58%), $R_f = 0.31$ (2% methanol in DCM) (found [ES⁺] M⁺ + Na 742.2068. C₃₃H₄₁O₁₁N₃S₂Na requires *M*, 742.2075); δ_H (CDCl₃, 400 MHz) 1.34 (6H, d, $J = 7.5$ Hz, CH₃, H-6), 2.36 (6H, s, CH₃, H-15), 3.3 (2H, ddd, $J = 11.0, 6.5, 3.5$ Hz, CH₂, H-2), 3.43 (2H, ddd, $J = 11.0, 5.5, 3.5$ Hz, CH₂, H-2), 3.48 (4H, s, CH₂, H-1), 3.76 (2H, ddd, $J = 11.5, 5.5, 3.5$ Hz, CH₂, H-3), 3.99 (2H, ddd, $J = 11.5, 7.0, 3.5$ Hz, CH₂, H-3), 4.50 (2H, d, $J = 18.0$ Hz, CH₂, H-7), 4.72 (2H, d, $J = 18.0$ Hz, CH₂, H-7), 4.73 (2H, q, $J = 7.5$ Hz, CH, H-5), 7.21 – 7.28 (5H, m, Ar-H, H-10,13), 7.62 (2H, d, $J = 8.0$ Hz, Ar-H, H-9) and 7.66 (4H, d, $J = 8.0$ Hz, Ar-H, H-12); δ_C (CDCl₃, 100 MHz) 15.82 (CH₃, C-6), 21.46 (CH₃, C-15), 43.37 (CH₂, C-7), 56.09 (CH, C-5), 63.74 (CH₂, C-3), 68.33 (CH₂, C-2), 70.56 (CH₂, C-1), 124.58 (CH, C-9), 125.13 (CH, C-10), 127.31 (CH, C-12), 129.59 (CH, C-13), 136.45 (C, C-14), 143.70 (C, C-11), 148.39 (C, C-8) and 170.17 (C, C-4); m/z (ES⁺) 719.9, (M⁺ + H), 742.7 (M⁺ + Na).

4.3 Cyclic Crown Ethers (Ether Version)

4.3.1 Spacer Premolecules

2-(2-(2-(benzyloxy)ethoxy)ethoxy)ethanol **179**^{190,202}



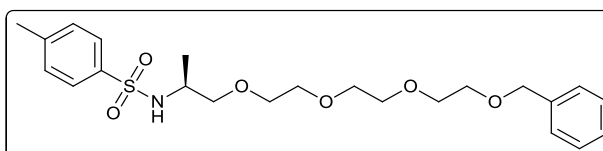
179

Triethylene glycol (800 μL , 6.0 mmol) was added to a suspension of silver(I) oxide (2.09 g, 9.0 mmol) in dry DCM (20 mL) under N_2 at room temperature and then stirred for 30 minutes. Benzyl bromide (860 μL , 7.2 mmol) was added dropwise, and the reaction vessel was surrounded in foil to keep it in darkness. The reaction was stirred for 44 hours at room temperature, filtered through Celite[®] and concentrated *in vacuo*. The crude product, a viscous oil was purified by flash chromatography (0% \rightarrow 50% EtOAc in hexane) to afford the *title compound* as a colourless oil (1.03 g, 72%), $R_f = 0.42$ (EtOAc) (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 263.1253. $\text{C}_{13}\text{H}_{20}\text{O}_4\text{Na}$ requires M , 263.1254); ν_{max} (film) 3430, 2872, 1647, 1453, 1350, 1249 and 1096 cm^{-1} ; δ_{H} (CDCl_3 , 400 MHz) 2.61 (1H, br.s., OH), 3.59 – 3.71 (12H, m, CH_2 , $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_3-$), 4.56 (2H, s, CH_2 , benzyl) and 7.26 – 7.36 (5H, m, Ar-H); δ_{C} (CDCl_3 , 100 MHz) 61.86 (CH_2 , CH_2OH), 69.48, 70.50, 70.73, 70.78, 72.60 (CH_2 , CH_2O), 73.37 (CH_2 , CH_2Ph , benzyl), 127.73, 127.87, 128.47 (CH, Ar) and 138.25 (C, Ar); m/z (ES^+) 452.3 ($\text{M}^+ + \text{H}$), 469.4 ($\text{M}^+ + \text{NH}_4$), 474.4 ($\text{M}^+ + \text{Na}$).

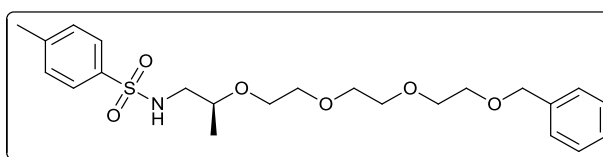
(S)-4-methyl-N-(1-phenyl-2,5,8,11-tetraoxatetradecan-13-yl)benzenesulfonamide **182**

& (S)-4-methyl-N-(12-methyl-1-phenyl-2,5,8,11-tetraoxatridecan-13-

yl)benzenesulfonamide **183**



182



183

Entry 1, Table 2-2: **181** (48.7 mg, 0.2 mmol) and **179** (80.5 mg, 0.3 mmol) was dissolved in dry DCM (1 mL) under N₂. The reaction was cooled to -10 °C for 20 minutes and BF₃.OEt₂ (25 μL, 0.2 mmol) was added. The reaction was allowed to warm to room temperature and was stirred overnight. The crude oil was purified by column chromatography (30% → 40% EtOAc in hexane) to afford **182** and **183** as an inseparable mixture (39.4 mg, 44%, 2.2:1 **183:182**).

Entry 2, Table 2-2: Anhydrous Cu(OTf)₂ (75.7 mg, 0.2 mmol) and **179** (237 mg, 1.0 mmol) were dissolved in dry DCM (0.3 mL) under N₂. **181** (43.1 mg, 0.2 mmol) was added in dry DCM (0.7 mL). The reaction was stirred overnight at room temperature and then quenched with saturated NaHCO₃ (10 mL). The aqueous layer was washed with DCM (4 x 5 mL), and the combined organic extracts were then dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% → 50% EtOAc in hexane) to afford **182** and **183** as an inseparable mixture (41.1 mg, 46%, 4.1:1 **183:182**).

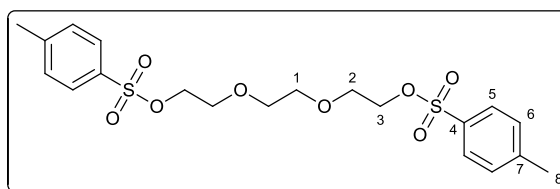
Entry 3, Table 2-2: (As for Entry 1) **181** (42.9 mg, 0.2 mmol), **179** (70.5 mg, 0.3 mmol) in dry DCM (1 mL) at -40 °C. BF₃.OEt₂ (25 μL, 0.2 mmol) added and kept at -40 °C. After purification, an inseparable mixture was isolated (58.9 mg, 65%, 2.8:1 **183:182**).

Entry 4, Table 2-2: (As for Entry 1) **181** (43.1 mg, 0.2 mmol), **179** (70.9 mg, 0.3 mmol) in dry DCM (1 mL) at -15 °C. BF₃.OEt₂ (25 μL, 0.2 mmol) added and warmed to 40 °C. Attempted purification afforded none of the desired product.

R_f = 0.37 (50% EtOAc in Hexane); δ_H (CDCl₃, 400 MHz) 1.02 (3H, d, *J* = 6.0 Hz, αCH₃, **183**), 1.06 (3H, d, *J* = 7.0 Hz, αCH₃, **182**), 2.37 (6H, s, CH₃, tosyl, **182** + **183**), 2.71 (1H, dddd, *J* = 13.0, 12.0, 9.0, 4.0 Hz, NHCH₂, **183**), 3.04 (1H, dddd, *J* = 13.0, 12.0, 8.0, 3.0 Hz, NHCH₂, **183**), 3.24 – 3.70 (28H, m, [24H, -OCH₂(CH₂OCH₂)₂CH₂O-, **182** + **183**], [2H, CH₂CH, **182** + **183**], [2H, αCH₂, **182**]), 4.52 (4H, s, CH₂Ph, **182** + **183**), 5.32 (1H, d, *J* = 6.0 Hz, N-H, **182**), 5.61 (1H, dd, *J* = 5.0, 3.0 Hz, N-H, **183**), 7 (14H, m, [10H,

Ar-H, benzyl, **182** + **183**], [4H, Ar-H_m, tosyl, **182** + **183**]) and 7.72 (4H, m, Ar-H_o, tosyl, **182** + **183**); δ_C (CDCl₃, 100 MHz) 17.42 (CH₃, α CH₃, **183**), 18.28 (CH₃, α CH₃, **182**), 21.41 (CH₃, tosyl, **182** + **183**), 48.18 (CH₂, NHCH₂, **183**), 49.37 (CH, α CH, **182**), 67.99 (CH₂, CH₂OCH₂Ph, **182** + **183**), 69.34, 70.36, 70.49, 70.53 (CH₂, -OCH₂(CH₂OCH₂)₂CH₂O-, **182** + **183**), 73.09 (CH₂, CH₂Ph, **182** + **183**), 73.98 (CH₂, -OCH₂(CH₂OCH₂)₂CH₂O-, **182** + **183**), 74.31 (CH, α CH, **183**), 126.99, 127.05, 127.49, 127.67, 128.26, 129.47, 129.53 (CH, Ar-H, tosyl + benzyl, **182** + **183**), 137.16 (C, C-CH₃, tosyl, **182** + **183**), 138.15, 138.18 (C, CH₂-C, benzyl, **182** + **183**), 142.98 and 143.01 (C, N-S-C, Tosyl, **182** + **183**).

2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) **191**²²⁹

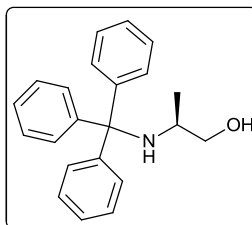


191

Triethylene glycol (670 μ L, 5.0 mmol) in THF (3 mL) was added dropwise to a solution of 2.7 M NaOH (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 minutes and then a solution of tosyl chloride (2.92 g, 15.3 mmol) in THF (10 mL) was added dropwise. The reaction was heated to 40 °C and left to stir for 48 hours. The organic layer was removed *in vacuo* and the remaining aqueous layer was washed with DCM (5 x 10 mL). The combined organic layers were concentrated *in vacuo* to give a liquid, which was dissolved in acetone (30 mL) and chilled in the freezer overnight to afford the *title compound* as a crystalline solid (1.62 g, 71%), $R_f = 0.42$ (50% EtOAc in Hexane), m.p. 79 – 81 °C [Ref: 82 – 83 °C²²⁹] (found [ES⁺] M⁺ + NH₄, 476.1402. C₂₀H₃₀O₈NS₂ requires *M*, 476.1407); ν_{\max} (film) 3453, 1653, 1350 and 1172 cm⁻¹; δ_H (CDCl₃, 500 MHz) 2.44 (6H, s, CH₃, H-9), 3.53 (4H, s, CH₂, CH₂, H-1), 3.63 (4H, t, *J* = 5.0 Hz, CH₂, CH₂, H-2), 4.14 (4H, t, *J* = 5.0 Hz, CH₂, H-3), 7.34 (4H, d, *J* = 8.0 Hz, Ar-H, H-6) and 7.79 (4H, d, *J* = 8.0 Hz, Ar-H, H-5); *m/z* (ES⁺) 476.3 (M⁺ + NH₄), 481.2 (M⁺ + Na).

4.3.2 Aziridines and Premolecules

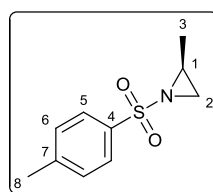
(S)-2-(Tritylamino)propan-1-ol **173**



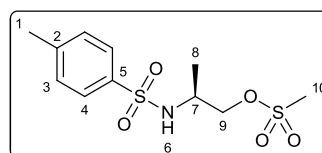
173

Preparation was analogous to that of Occhiato:¹⁹⁹ Trityl chloride (4.18 g, 15.0 mmol) in CHCl_3 (10 mL) was added dropwise to a stirring solution of (*S*)-alaninol (1.17 mL, 15.0 mmol) and Et_3N (4.20 mL, 30.1 mmol) in CHCl_3 (10 mL) at $-10\text{ }^\circ\text{C}$. The reaction was left to warm to room temperature overnight. The reaction was washed with 0.6 M citric acid (2 x 20 mL), H_2O (1 x 20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo* to leave an oil. The oil was purified by column chromatography (20% \rightarrow 25% EtOAc in hexane) to afford the *title compound* **173** as an off colourless crystalline solid (3.79 g, 80%), $R_f = 0.71$ (50% EtOAc in hexane) (found $[\text{ES}^+]$ $\text{M}^+ + \text{Na}$, 340.1682. $\text{C}_{22}\text{H}_{23}\text{ONNa}$ requires M , 340.1672); ν_{max} (film) 3411, 3056, 2962, 2868, 1489, 1447 and 1265 cm^{-1} ; δ_{H} (CDCl_3 , 400 MHz) 0.68 (3H, d, $J = 6.5\text{ Hz}$, αCH_3), 2.08 (2H, br.s., OH [1H] + NH [1H]), 2.75 – 2.81 (1H, m, αCH), 3.08 (1H, dd, $J = 11.0, 5.0\text{ Hz}$, CH_2), 3.19 (1H, dd, $J = 11.0, 4.0\text{ Hz}$, CH_2), 7.21 (3H, t, $J = 7.5\text{ Hz}$, Ar- H_p , Trityl), 7.29 (6H, t, $J = 7.5\text{ Hz}$, Ar- H_m , Trityl) and 7.56 (6H, d, $J = 7.5\text{ Hz}$, Ar- H_o , Trityl); m/z (ES^+) 318.2 ($\text{M}^+ + \text{H}$), 340.2 ($\text{M}^+ + \text{Na}$).

(S)-2-methyl-1-tosylaziridine **181**^{201,230,231}



181



180

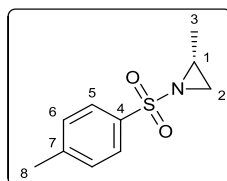
To a solution of (*S*)-alaninol (1.95 mL, 25 mmol) and tosyl chloride (5.72 g, 30 mmol) in dry DCM (200 mL) at $-25\text{ }^\circ\text{C}$ was added Et_3N (13.9 mL, 100 mmol). The reaction was stirred at $-25\text{ }^\circ\text{C}$ for 45 minutes, and then at room temperature for 3 hours. The

reaction was again cooled to $-25\text{ }^{\circ}\text{C}$, and mesyl chloride (2 mL, 26.3 mmol) was added dropwise over 10 minutes. The reaction was allowed to warm up to room temperature over 22 hours. The orange solution was washed with 0.5 M NaOH (2 x 20 mL), sat. NaHCO_3 (2 x 20 mL), dried over MgSO_4 and concentrated *in vacuo*. This left a brown oil (7.07 g) as a crude product which was purified by column chromatography (15% \rightarrow 20% EtOAc in petrol) to afford the *title compound* **181** as a colourless waxy solid (3.80 g, 72%).

N-Tosyl *O*-mesyl (*S*)-alaninol **180** (854 mg, 2.8 mmol) and Et_3N (408 μL , 2.9 mmol) were stirred in dry DCM under N_2 at room temperature for 90 minutes. The reaction was then warmed to $40\text{ }^{\circ}\text{C}$ and left for 22 hours at this temperature. Work-up and purification as above, afforded the *title compound* **181** as a waxy solid (158 mg, 27%), $R_f = 0.78$ (50% EtOAc in hexane), $[\alpha]_{\text{D}}^{30} = +30$ ($c = 1.48$, CHCl_3) [Ref:²³¹ $[\alpha]_{\text{D}} = +30.3$ ($c = 1.02$, CHCl_3)], m.p. $54 - 56\text{ }^{\circ}\text{C}$ [Ref: $58 - 59\text{ }^{\circ}\text{C}^{230}$] (found C, 56.19; H, 6.14; N, 6.36%. $\text{C}_{10}\text{H}_{13}\text{O}_2\text{NS}$ requires C, 56.85; H, 6.20; N, 6.63%. Found $[\text{ES}^+] \text{M}^+ + \text{H}$, 212.0730. $\text{C}_{10}\text{H}_{14}\text{O}_2\text{NS}$ requires M , 212.0740); δ_{H} (CDCl_3 , 400 MHz) 1.24 (3H, d, $J = 6.0$ Hz, CH_3 , H-3), 2.02 (1H, d, $J = 5.0$ Hz, CH_2 , H-2), 2.44 (3H, s, CH_3 , H-8), 2.60 (1H, d, $J = 7.0$ Hz, CH_2 , H-2), 2.82 (1H, dqd, $J = 7.0, 6.0, 5.0$ Hz, CH , H-1), 7.33 (2H d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.81 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-5); δ_{C} (CDCl_3 , 100 MHz) 17.05 (CH_3 , C-3), 21.90 (CH_3 , C-8), 35.00 (CH_2 , C-2), 36.13 (CH , C-1), 128.05 (CH , C-5), 129.95 (CH , C-6), 135.56 (C, C-4) and 144.67 (C, C-7); m/z (ES^+) 212.0 ($\text{M}^+ + \text{H}$), 234.3 ($\text{M}^+ + \text{Na}$).

On further elution of the crude compound during the synthesis of the *title compound* **181**, was sometimes isolated the aziridine precursor *N*-tosyl *O*-mesyl (*S*)-alaninol **180** as a thick yellow oil (39%),²³² $R_f = 0.49$ (50 % EtOAc in hexane), $[\alpha]_{\text{D}}^{32} = -43$ ($c = 2.14$, CHCl_3); δ_{H} (CDCl_3 , 400 MHz) 1.11 (3H, d, $J = 7.0$ Hz, CH_3 , H-8), 2.42 (3H, s, CH_3 , H-1), 3.00 (3H, s, CH_3 , H-10), 3.56 – 3.65 (1H, m, CH , H-7), 4.11 (1H, dd, $J = 10.0, 5.0$ Hz, CH_2 , H-9), 4.14 (1H, dd, $J = 10.0, 5.0$ Hz, CH_2 , H-9), 5.19 (1H, d, $J = 8.0$ Hz, NH , H-6), 7.32 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-3) and 7.76 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-4); m/z (ES^+) 241.2 ($\text{M}^+ + \text{H}$), 258.2 ($\text{M}^+ + \text{NH}_4$), 263.1 ($\text{M}^+ + \text{Na}$).

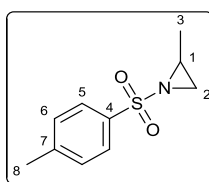
(R)-2-methyl-1-tosylaziridine **193**



193

Preparation was analogous to **181**, using (*R*)-Alaninol (2.50 mL, 32.1 mmol), tosyl chloride (7.30 g, 38.3 mmol), Et₃N (19.8 mL, 142 mmol), and mesyl chloride (2.6 mL, 33.6 mmol), resulting in **193** as a colourless solid (4.77 g, 71%), *R_f* = 0.82 (50% EtOAc in hexane), $[\alpha]_D^{31} = 31$ (*c* = 1.52, CHCl₃), m.p. 55 – 56 °C [Ref: 57 – 58 °C²³³], (found [ES⁺] M⁺ + H 212.0737. C₁₀H₁₄O₂NS requires *M*, 212.0740); ν_{\max} (ATR) 2998 (w), 2972 (w), 2967 (w), 1596 (m), 1451 (m), 1316 (m), 1307 (m), 1151 (s) and 1036 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.25 (3H, d, *J* = 6.0 Hz, CH₃, H-3), 2.02 (1 H, d, *J* = 5.0 Hz, CH₂, H-2), 2.44 (3 H, s, CH₃, H-8), 2.60 (1H, d, *J* = 7.0 Hz, CH₂, H-2), 2.82 (1H, dqd, *J* = 7.0, 6.0, 5.0 Hz, CH, H-1), 7.33 (2H, d, *J* = 8.0 Hz, ArH, H-6) and 7.82 (2H, d, *J* = 8.0 Hz, ArH, H-5); δ_C (CDCl₃, 125 MHz) 16.69 (CH₃, C-3), 21.57 (CH₃, C-8), 34.68 (CH₂, C-2), 35.80 (CH, C-1), 127.70 (CH, C-5), 129.61 (CH, C-6), 135.18 (C, C-4) and 144.35 (C, C-7); *m/z* (ES⁺) 234 (M⁺ + Na), 266 (M⁺ + Na, MeOH).

(±)-2-Methyl-1-tosylaziridine **194**²⁰¹



194

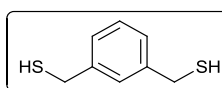
Preparation was analogous to **181**, using (±)-alaninol (4.87 mL, 64.8 mmol), tosyl chloride (14.3 g, 75.0 mmol), Et₃N (35 mL, 251.1 mmol), and mesyl chloride (5 mL, 45.8 mmol), resulting in **194** as a colourless solid (10.7 g, 78%), *R_f* = 0.70 (50% EtOAc in petrol); $[\alpha]_D^{29} = 0$ (*c* = 1.75, CHCl₃), m.p. 59 – 61 °C [Ref: 60 – 61 °C²³⁴], (found [ES⁺] M⁺ + H, 212.0750. C₁₀H₁₄O₂NS requires *M*, 212.0740); ν_{\max} (ATR,): 3255 (w), 3003 (w), 2980 (w), 1596 (w), 1315 (m), 1148 (s), 1031 (m) and 844 (s) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.26 (3H, d, *J* = 6.0 Hz, αCH₃), 2.03 (1H, d, *J* = 5.0 Hz, CH₂), 2.45

(3H, s, CH₃, Tosyl), 2.62 (1H, d, *J* = 7.0 Hz, CH₂), 2.80 – 2.87 (1H, m, αCH), 7.35 (2H, d, *J* = 8.0 Hz, Ar-H_m) and 7.83 (2H, d, *J* = 8.0 Hz, Ar-H_o); δ_C (CDCl₃, 125 MHz) 16.76 (CH₃, CH₃, Ala), 21.60 (CH₃, CH₃, Tosyl), 34.71 (CH₂, CH₂), 35.83 (CH, αCH), 127.77 (CH, CH_o, Tosyl), 129.66 (CH, CH_m, Tosyl), 135.31 (C, C-S, Tosyl) and 144.38 (C, C-CH₃, Tosyl); *m/z* (ES⁺) 212.0 (M⁺ + H), 234.0 (M⁺ + Na).

4.4 Thioether Spacers [CARE: Malodourous]

4.4.1 Spacer pre-molecules

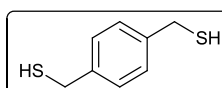
1,3-phenylenedimethanethiol 209²³⁵



209

1,3-bis(bromomethyl)benzene (3.03 g, 11.5 mmol) and thiourea (1.75 g, 23.0 mmol) were dissolved in degassed, dry EtOH (30 mL) and stirred for 4 hours. The solvent was removed *in vacuo*, and the residual thiuronium salt was dissolved in degassed H₂O (30 mL). NaOH (1.83 g, 45.8 mmol) was added and the reaction stirred for 4 hours. The solution was cooled on an ice bath and 4 M HCl was added until the aqueous layer was acidic (pH 2). The solution was extracted with CHCl₃ (5 x 30 mL) and the combined organic extracts were dried over MgSO₄, and concentrated *in vacuo* to give **209** as a yellow oil (2.53 g, quant.), δ_H (CDCl₃, 300 MHz) 1.78 (2H, t, *J* = 7.5 Hz, SH), 3.75 (4H, d, *J* = 7.5 Hz, CH₂SH) and 7.18 – 7.32 (4H, m, Ar-H).

1,4-phenylenedimethanethiol 213²³⁶

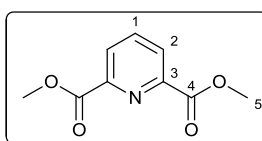


213

Synthesis was analogous to 1,3-bis(bromomethyl)benzene **209**: 1,4-bis(bromomethyl)benzene (1.01 g, 3.8 mmol) and thiourea (582 mg, 7.6 mmol) were dissolved in degassed, dry EtOH (10 mL) and stirred for 4 hours. The solvent was removed *in vacuo* to afford the crude thiuronium salt as near-colourless crystals. To this solid was added 5 M NaOH (degassed aq., 3 mL) and the reaction was refluxed for

30 minutes. The solution was cooled on an ice bath and 4 M HCl was added until acidic (pH 2). The solution was extracted with CHCl₃ (5 x 10 mL), the combined organic extracts were dried over MgSO₄, and then concentrated *in vacuo* to give **213** as a thick yellow oil (650 mg, quant.), (found [EI] M, 170.0215. C₈H₁₀S₂ requires M, 170.0218); δ_{H} (CDCl₃, 400 MHz) 1.70 (2H, t, $J = 7.0$ Hz, CH₂SH), 3.67 (4H, d, $J = 7.0$ Hz, CH₂SH) and 7.22 (4H, s, Ar-H); δ_{C} (CDCl₃, 100 MHz) 28.58 (CH₂, CH₂SH), 128.31 (CH, CH, aryl) and 139.92 (C, C, aryl); m/z (EI) 170, 171 (M), 137(M – HS⁻), 104 (M – 2HS⁻).

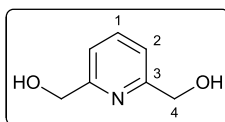
Dimethyl pyridine-2,6-dicarboxylate **216**²³⁷



216

Preparation taken from Jew *et al.*:²³⁸ To methanol (300 mL) at 0 °C was added dropwise thionyl chloride (9.6 mL, 131.6 mmol) followed by pyridine 2,6-dicarboxylic acid (10 g, 59.8 mmol). The reaction was refluxed for 5 hours, after which the solid was dried by azeotropic removal of the solvent using toluene (3 x 200 mL), to give the *title compound* as a colourless powder (11.4 g, 98%), $R_f = 0.65$ (30% EtOAc in petrol), m.p. 117 – 120 °C [Ref: 120 – 122 °C²³⁹], (found [ES⁺] M⁺ + Na, 218.0421. C₉H₉O₄NNa requires M, 218.0424); ν_{max} (ATR,) 3063 (w), 2850 (w), 1740 (s), 1571 (m), 1449 (m), 1290 (m), 1245 (s) and 1163 (m) cm⁻¹; δ_{H} (CDCl₃, 500 MHz) 4.02 (6H, s, CH₃, H-5), 8.03 (1H, t, $J = 8.0$ Hz, CH, H-1) and 8.31 (2H, d, $J = 8.0$ Hz, CH, H-2); δ_{C} (CDCl₃, 125 MHz) 53.17 (CH₃, C-5), 128.00 (CH, C-2), 138.34 (CH, C-1), 148.18 (C, C-3) and 165.02 (C, C-4); m/z (ES⁺) 196.0 (M⁺ + H), 218.0 (M⁺ + Na).

Pyridine-2,6-diylldimethanol **217**²⁴⁰

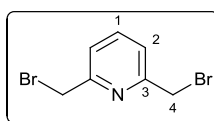


217

NaBH₄ (9.49 g, 251 mmol) added in portions to a solution of ester **216** (11.4 g, 58.3 mmol) in dry THF (100 mL) at room temperature ensuring the reaction does not get too hot. The reaction was left for 16 hours at room temperature. Saturated aqueous Na₂CO₃

solution (200 mL) was added dropwise, and the reaction was heated to 60 °C for 2 hours. On cooling to ambient temperature, the reaction mixture was taken to dryness *in vacuo*, azeotroping with MeOH. The fine colourless solid was extracted by Soxhlet extraction with chloroform for 16 hours. The solvent was removed *in vacuo*, resulting in a fine colourless crystalline product (3.85 g, 47%), $R_f = 0.60$ (EtOAc), m.p. 105 – 108 °C [Ref: 111 – 113 °C²⁴⁰] (found [ES⁺] M⁺ + Na, 162.0519. C₇H₉O₂NNa requires *M*, 162.0525); ν_{\max} (ATR): 3349 (m), 3097 (w), 2967 (w), 2895 (w), 1599 (m), 1469 (w), 1444 (m), 1220 (w), 1159 (m) and 1082 (s) cm⁻¹; δ_H (CDCl₃, 300 MHz) 4.79 (4H, s, CH₂, H-4), 7.20 (2H, d, *J* = 8.0 Hz, CH, H-2) and 7.71 (1H, t, *J* = 8.0 Hz, CH, H-1); δ_C (CDCl₃, 75 MHz) 64.38 (CH₂, C-4), 119.16 (CH, C-2), 137.44 (CH, C-1) and 158.40 (C, C-3); *m/z* (ES⁺) 140 (M⁺ + H), 162 (M⁺ + Na), 178 (M⁺ + K), 317 (2M⁺ + K); *m/z* (ES⁻) 265 (M⁻ + I).

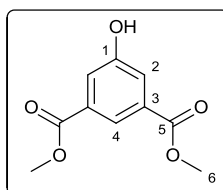
2,6-bis(Bromomethyl)pyridine **24**²⁴⁰



24

Diol **217** (1.82 g, 13.1 mmol) and 33% HBr in acetic acid (26 mL, 2 mL/mmol) were heated at 100 °C for 90 minutes. The reaction was poured straight onto some ice, and neutralised with 1 M NaOH to pH 9. The precipitated product was collected as a pale brown solid (2.75 g, 80%), $R_f = 0.32$ (20% EtOAc in petrol), m.p. 81 – 83 °C [Ref: 80 – 82 °C²⁴¹], found [ES⁺] M⁺ + H 263.9019. C₇H₈N⁷⁹Br₂ requires *M*, 263.9018); ν_{\max} (ATR) 3063 (w), 3020 (w), 2967 (w), 1570 (m), 1449 (m), 1203 (m), 817 (m) and 585 (s) cm⁻¹; δ_H (CDCl₃, 400 MHz) 4.54 (4H, s, CH₂, H-4), 7.38 (2H, d, *J* = 8.0 Hz, CH, H-2) and 7.71 (1H, t, *J* = 8.0 Hz, CH, H-1); δ_C (CDCl₃, 125 MHz) 33.37 (CH₂, C-4), 122.72 (CH, C-2), 138.04 (CH, C-1) and 156.55 (C, C-3); *m/z* (ES⁺) 264 (M⁺ + H).

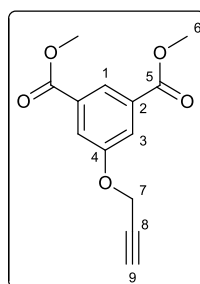
Dimethyl 5-hydroxyisophthalate **221**²⁴²



221

5-Hydroxyisophthalic acid (10 g, 54.9 mmol) was dissolved in methanol (55 mL) to which was then added 98% H₂SO₄ (6.5 mL, 12.1 mmol, 0.22 eq.). The reaction was refluxed for 5 hours, allowed to cool, and concentrated to dryness *in vacuo*. EtOAc (150 mL) was added, and the organic extract washed (5% NaHCO₃; 2 x 80 mL; brine; 80 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The *title compound* was isolated as colourless crystalline solid in an essentially pure state (11.5 g, quant.), $R_f = 0.57$ (50% EtOAc in petrol), m.p. 158 – 159 °C [Ref: 160 – 161 °C²⁴³], (found [ES⁻] M⁻ 209.0449. C₁₀H₉O₅ requires M , 209.0455); ν_{\max} (ATR) 3354 (m), 2962 (w), 1698 (s), 1597 (m), 1428 (s), 1353 (s), 1299 (m), 1241 (s) and 1096 (m) cm⁻¹; δ_H (CD₃OD, 500 MHz) 3.91 (6H, s, CH₃, H-6), 7.59 (2H, d, $J = 1.0$ Hz, ArH, H-2) and 8.06 (1H, t, $J = 1.0$ Hz, ArH, H-2); δ_C (CD₃OD, 125 MHz) 52.99 (CH₃, C-6), 121.58 (CH, C-2), 122.51 (CH, C-4), 133.12 (C, C-3), 159.35 (C, C-1) and 167.71 (C, C-5); m/z (ES⁺) 233 (M⁺ + Na); m/z (ES⁻) 209 (M⁻).

Dimethyl 5-(prop-2-yn-1-yloxy)isophthalate **254**²⁴⁴

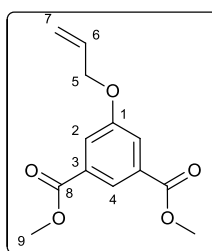


254

Preparation as for Rajakumar *et al.*:²⁴⁵ K₂CO₃ (5.20 g, 40.5 mmol) was added to a solution of ester **221** (5.28 g, 25.1 mmol) in dry DMF (50 mL). After 2 hours at room temperature, propargyl bromide (3.4 mL, 80% wt. soln. 30.5 mmol) was added and the reaction heated to 90 °C overnight. The reaction mixture was concentrated to dryness *in*

vacuo and water (30 mL) added. The aqueous solution was extracted with DCM (8 x 50 mL), the organic extracts combined, dried over MgSO₄, filtered and reduced *in vacuo*, giving ester **254** as a colourless solid (4.97 g, 77%) in an essentially pure state, $R_f = 0.31$ (70% EtOAc in petrol), m.p. 110 – 112 °C, (found [ES⁺] M⁺ + H, 249.0769. C₁₃H₁₃O₅ requires *M*, 249.0757); ν_{\max} (ATR): 3272 (m), 3079 (w), 3014 (w), 2960 (w), 2131 (w), 1719 (s), 1592 (m), 1456 (w), 1431 (m) and 1244 (s) cm⁻¹; δ_{H} (CDCl₃, 400 MHz) 2.56 (1H, t, $J = 2.5$ Hz, CH, H-9), 3.95 (6H, s, CH₃, H-6), 4.79 (2H, d, $J = 2.5$ Hz, CH₂, H-7), 7.84 (2H, d, $J^d = 2.0$ Hz, Ar-H, H-3) and 8.34 (1H, t, $J^d = 2.0$ Hz, Ar-H, H-1); δ_{C} (CDCl₃, 125 MHz) 52.45 (CH₃, C-6), 56.21 (CH₂, C-7), 76.28 (CH, C-9), 77.56 (C, C-8), 120.27 (CH, C-3), 123.80 (CH, C-1), 131.85 (C, C-2), 157.51 (C, C-4) and 165.93 (C, C-5); m/z (ES⁺) 249 (M⁺ + H), 271 (M⁺ + Na).

Dimethyl 5-(allyloxy)isophthalate **222**²⁴⁶

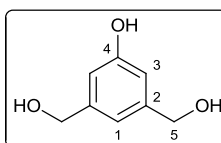


222

Synthesis analogous to dimethyl 5-(prop-2-yn-1-yloxy)isophthalate **254**: K₂CO₃ (10.3 g, 80.3 mmol) was added to a solution of ester **221** (10.5 g, 49.6 mmol) in dry DMF (100 mL) at room temperature. After 2 hours, allyl bromide (4.25 mL, 50.2 mmol) was added and the reaction was warmed to 90 °C for 9 hours. On cooling to ambient temperature, the solvent was removed *in vacuo*, water (300 mL) was added and extracted with DCM (4 x 200 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo* to give **222** as a colourless crystalline solid (12.4 g, quant.) in an essentially pure state, $R_f = 0.50$ (20% EtOAc in petrol), m.p. 59 – 60 °C [Ref: 68 – 69 °C²⁴⁶], (found [ES⁺] M⁺ + Na, 273.0742. C₁₃H₁₄O₅Na requires *M*, 273.0733); ν_{\max} (ATR) 3089 (w), 2954 (w), 1732 (s), 1721 (s), 1593 (m), 1453 (m), 1433 (m), 1336 (s), 1237 (s), 1189 (m) cm⁻¹; δ_{H} (CDCl₃, 300 MHz) 3.95 (6H, s, CH₃, H-9), 4.63 (2H, d, $J = 5.0$ Hz, CH₂, H-5), 5.33 (1H, dd, $J = 10.5, 1.0$ Hz CH₂, H-7), 5.45 (1 H, dd, $J = 17.0, 1.0$ Hz, CH₂, H-7), 6.06 (1 H, ddt, $J = 17.0, 10.5, 5.0$ Hz, CH, H-6), 7.77 (2H, d, $J = 1.0$

Hz, ArH,H-2) and 8.29 (1H, t, $J = 1$ Hz, ArH, H-4); δ_C (CDCl₃, 75 MHz) 52.40 (CH₃, C-9), 69.23 (CH, C-5), 118.18 (CH, C-7), 120.10 (CH, C-2), 123.11 (CH, C-4), 131.78 (CH, C-6), 132.40 (C, C-3), 158.65 (C, C-1) and 166.12 (C, C-8); m/z (ES⁺) 251 (M⁺ + H), 273 (M⁺ + Na).

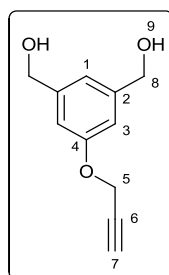
(5-Hydroxy-1,3-phenylene)dimethanol **256**²⁴⁷



256

A solution of di-ester **253** (5.25 g, 25 mmol) in dry THF (50 mL) was added dropwise to a slurry of LiAlH₄ (1.71 g, 45 mmol) in dry THF (75 mL) at room temperature. The reaction was brought to reflux for 3 hours, left to cool to ambient temperature and then cautiously quenched with the addition of 10% aq. H₂SO₄ (35 mL) [**CARE**]. The solvent was removed *in vacuo* and the residue azeotroped with methanol (4 x 200 mL). The residue was triturated with EtOAc (6 x 50 mL) and the combined extracts concentrated *in vacuo*. The crude oil was purified by flash column chromatography (10% methanol in DCM) to give the *title compound* **256** as a colourless solid (3.84 g, quant.) in an essentially pure state, $R_f = 0.27$ (12% methanol in DCM), m.p. 69 – 70 °C [Ref: 71 – 73 °C²⁴⁸], found [ES⁻] M⁻, 153.0557. C₈H₉O₃ requires M , 153.0557); ν_{\max} (ATR): 3359 (w), 3048 (br., m), 2830 (w), 1599 (m), 1451 (m), 1300 (s), 1161 (m) and 1025 (s) cm⁻¹; δ_H (CD₃OD, 300 MHz) 4.49 (4H, br.s., CH₂, H-5), 6.70 (2H, br.s., CH, H-3) and 6.78 (1H, br.s., CH, H-1); δ_C (CD₃OD, 75 MHz) 65.16 (CH₂, C-5), 113.81 (CH, C-3), 117.83 (CH, C-1), 144.25 (C, C-2) and 158.51 (C, C-4); m/z (ES⁺) 177 (M⁺ + Na), 331 (2M⁺ + Na); m/z (ES⁻) 153 (M⁻), 307 (2M⁻).

(5-(prop-2-yn-1-yloxy)-1,3-phenylene)dimethanol **255**²⁴⁴



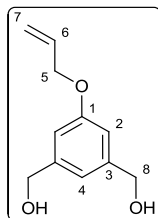
255

From ester **254**:²⁴⁴ A solution of ester **254** (5.00 g, 20.1 mmol) in THF (60 mL) was added dropwise to a slurry of LiAlH₄ (3.06 g, 80.6 mmol) in THF (200 mL) at 0 °C. The reaction was refluxed and monitored by TLC analysis. After 2 hours, the reaction was allowed to cool and quenched by the slow addition of H₂O. The reaction mixture was filtered and concentrated *in vacuo* to give **255** as a near-colourless solid (3.86 g, quant.) as an essentially pure product. [Caution: refluxing the reaction for longer than is needed, has resulted in the reduction of some of the alkyne to the alkene **223**.]

From diol **256**: Propargyl bromide (0.9 mL, 7.8 mmol, 1.2 eq.) was added to a solution of diol **256** (1 g, 6.5 mmol) in dry acetone (33 mL). To this solution was added K₂CO₃ (1 g, 7.8 mmol, 1.2 eq.), KI (1.3 g, 7.8 mmol, 1.2 eq.) and TBAI (240 mg, 0.7 mmol, 10 mol%). The reaction was refluxed for 20 hours, the left to cooled and concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH: DCM) resulting in the desired product as a near-colourless solid (1.03 g, 80%) as an essentially pure compound, R_f = 0.32 (80% EtOAc in petrol), m.p. 76.5 – 77.5 °C [Ref: 81 °C²⁴⁴], (found [ES⁺] M⁺ + Na, 215.0681. C₁₁H₁₂O₃Na requires M, 215.0679); ν_{max} (ATR): 3276 (sharp, m), 3259 (broad, m), 2922 (w), 2873 (w), 1448 (m), 1293 (m), 1166 (m) and 1022 (s) cm⁻¹; δ_H (CDCl₃, 300 MHz) 2.43 (1H, t, *J* = 2.0 Hz, CH, H-7), 3.92 (2H, br.s., OH), 4.45 (4H, s, CH₂, H-8), 4.54 (2H, d, *J* = 2.0 Hz, CH₂, H-5), 6.73 (2H, br.s., Ar-H, H-3) and 6.82 (1H, br.s., Ar-H, H-1); δ_H (DMSO-*d*₆, 500 MHz) 3.54 (1H, t, *J* = 3.0 Hz, CH, H-7), 4.45 (4H, d, *J* = 5.0 Hz, CH₂, H-8), 4.75 (2H, d, *J* = 3.0 Hz, CH₂, H-5), 5.19 (2H, t, *J* = 5.0 Hz, OH), 6.79 (2H, s, Ar-H, H-3) and 6.88 (1H, s, Ar-H, H-1); δ_C (DMSO-*d*₆, 125 MHz) 55.27 (CH₂, C-7), 62.79 (CH₂, C-8), 78.04 (CH, C-9), 79.49 (C,

C-8), 110.98 (CH, C-3), 117.28 (CH, C-1), 143.97 (C, C-2) and 157.22 (C, C-4); m/z (ES^+) 215 ($M^+ + Na$).

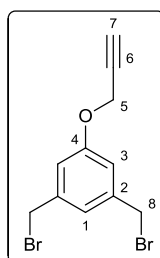
(5-(Allyloxy)-1,3-phenylene)dimethanol **223**²⁴⁹



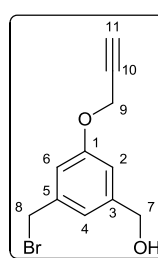
223

1 M Dibal-H in Et₂O (160 mL, 160 mmol) was added dropwise to a solution of ester **222** (10.0 g, 34.0 mmol) in dry DCM (140 mL) at -78 °C. The reaction was stirred for 3 hours at -78 °C after which EtOAc (50 mL) was added and the reaction was allowed to warm to ambient temperature. Excess Dibal-H was quenched with water. The whole reaction mixture was filtered, dried over MgSO₄, filtered again and concentrated *in vacuo* giving **223** as a near-colourless solid (7.70 g, 99%), $R_f = 0.17$ (50% EtOAc in petrol), m.p. 50 – 52 °C [Ref: 54 – 55 °C²⁴⁹], (found [ES^+] $M^+ + Na$, 217.0841. C₁₁H₁₄O₃Na requires M , 217.0835); ν_{max} (ATR): 3393 (m), 2927 (m), 1593 (m), 1421 (m), 1289 (m), 1151 (s), 1044 (s) and 987 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 3.46 (2H, br. s, OH), 4.46 (2H, d, $J = 5.5, 1.5$ Hz, CH₂, H-5), 4.49 (4H, s, CH₂, H-8), 5.26 (1H, dd, $J = 10.5, 1.0$ Hz, CH₂, H-7), 5.38 (1H, dd, $J = 17.0, 1.0$ Hz, CH₂, H-7), 6.01 (1H, ddt, $J = 17.0, 10.5, 5.5$ Hz, CH, H-6), 6.73 (2H, s, ArH, H-2) and 6.82 (1H, s, ArH, H-4); δ_C (CDCl₃, 125 MHz) 64.58 (CH₂, C-8), 68.72 (CH₂, C-5), 112.14 (CH, C-2), 117.62 (CH, C-4 + CH₂, C-7), 133.08 (CH, C-6), 142.67 (C, C-3) and 158.71 (C, C-1); m/z (ES^+) 217 ($M^+ + Na$).

1,3-bis(bromomethyl)-5-(prop-2-yn-1-yloxy)benzene **257**



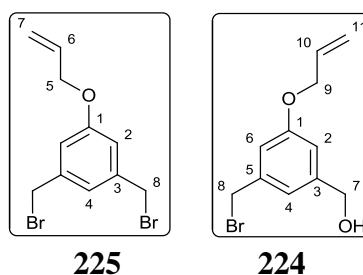
257



256

The preparation is analogous to that used by Hosokawa *et al.*:²¹⁰ Dry pyridine (210 μL , 2.6 mmol) was added to a stirring solution of diol **255** (3.5 g, 18.2 mmol) in dry DCM (50 mL) at 0 °C under nitrogen. The nitrogen line was replaced by a CaCl_2 drying tube and PBr_3 (1.2 mL, 12.8 mmol) was added dropwise. The reaction was allowed to warm up to room temperature, and stirred for 5 hour. Water (50 mL) was added and the mixture extracted with DCM (6 x 50 mL). The organic layers were combined, dried over MgSO_4 , filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (5 \rightarrow 20% EtOAc:Pet. Ether) to afford two products. The less polar material ($R_f = 0.52$) was collected as colourless crystals (1.16 g, 20%), and identified as the *title compound* **257**, $R_f = 0.52$ (30% EtOAc in petrol), m.p. 66 – 68 °C, (found $[\text{EI}^+]$ M, 315.9096. $\text{C}_{11}\text{H}_{10}\text{O}^{79}\text{Br}_2$ requires M, 315.9093); ν_{max} (ATR) 3278 (m), 3040 (w), 3035 (w), 2926 (w), 2113 (w), 1594 (m), 1370 (m), 1206 (m), 686 (s) and 639 (s) cm^{-1} ; δ_{H} (CDCl_3 , 300 MHz) 2.56 (1H, t, $J = 2.0$ Hz, $-\text{CH}_2\text{C}\equiv\text{CH}$), 4.44 (4H, s, $-\text{CH}_2\text{OBr}$), 4.72 (2H, d, $J = 2.0$ Hz, $-\text{CH}_2\text{C}\equiv\text{CH}$), 6.95 (2H, d, $J = 2.0$ Hz, Ar- H_3) and 7.06 (1H, t, $J = 2.0$ Hz, Ar- H_1); δ_{C} (CDCl_3 , 75 MHz) 32.61 (CH, $-\text{CH}_2\text{Br}$), 55.95 (CH_2 , $-\text{C}_5\text{H}_2\text{C}\equiv\text{CH}$), 76.01 (CH, $-\text{CH}_2\text{C}\equiv\text{C}_7\text{H}$), 78.01 (C, $-\text{CH}_2\text{C}_6\equiv\text{CH}$), 115.61 (Ar-H, $\text{C}_3\text{-H}$), 122.68 (Ar-H, $\text{C}_1\text{-H}$), 139.69 (C, $\text{C}_2\text{-CH}_2\text{Br}$) and 157.87 (C, $\text{C}_4\text{-OCH}_2\text{C}\equiv\text{CH}$); m/z (GC-MS) 318 ($\text{M}^+ + \text{H}$), 237 ($\text{M}^+ - \text{Br}$), 157 ($\text{M}^+ - 2\text{Br}$). Further elution afforded a second fraction, (3-(bromomethyl)-5-(prop-2-yn-1-yloxy)phenyl)methanol **256**, as a near-colourless solid (487 mg, 10%), $R_f = 0.45$ (40% EtOAc in petrol), m.p. 96 – 98 °C, (found C, 51.75; H, 4.20; Br, 32.47%, $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Br}$ requires C, 51.79; H, 4.35; Br, 31.32%); ν_{max} (ATR): 3265 (m), 3214 (m, br), 2915 (w), 2863 (w), 2116 (w), 1596 (m), 1454 (m), 1291 (s) and 1154 (s) cm^{-1} ; δ_{H} (CD_3OD , 500 MHz) 2.94 (1H, t, $J = 2.0$ Hz, CH , H-11), 4.53 (2H, s, CH_2 , H-8), 4.57 (2H, s, CH_2 , H-7), 4.73 (2H, d, $J = 2.0$ Hz, CH_2 , H-9), 6.94 (2H, s, CH , H-2,8) and 7.03 (1H, s, CH , H-4); δ_{C} (CDCl_3 , 125 MHz) 33.11 (CH_2 , C-8), 55.86 (CH_2 , C-9), 64.73 (CH_2 , C-7), 75.79 (CH , C-11), 78.21 (C, C-10), 113.24 (CH , C-2), 114.71 (CH , C-6), 120.43 (CH , C-4), 139.41 (C, C-5), 143.17 (C, C-3) and 157.91 (C, C-1); m/z (ES^+) 175.0 ($\text{M}^+ - \text{Br}$), 276.9 ($\text{M}^+ + \text{Na}$).

1-(Allyloxy)-3,5-bis(bromomethyl)benzene **225**²¹⁰



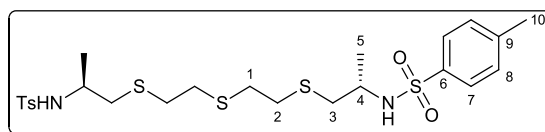
Dry pyridine (100 μ L, 1.2 mmol) added to a solution of diol **223** (4.00 g, 20.6 mmol) in dry DCM (22 mL) at room temperature under N_2 before cooling to 0 $^{\circ}$ C. N_2 was replaced by a $CaCl_2$ tube and PBr_3 (704 μ L, 7.5 mmol) was added dropwise. The reaction was allowed to warm up to room temperature and stirred for 24 hours. After quenching with water, the reaction was extracted with DCM (5 x 70 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (DCM) to afford two products. The less polar material ($R_f = 0.80$) was collected as dark crystals (1.48 g, 22%), and identified as the *title compound* **225**, $R_f = 0.80$ (DCM), m.p. 38 – 40 $^{\circ}$ C [Ref: 38 – 39 $^{\circ}$ C²¹⁰], (found [EI] M , 317.9251. $C_{11}H_{12}O^+Br_2$ requires M , 317.9249); δ_H ($CDCl_3$, 500 MHz) 4.44 (4H, s, CH_2 , H-8), 4.55 (2H, d, $J = 5.0$ Hz, CH_2 , H-5), 5.32 (1H, dd, $J = 10.5, 1.0$ Hz, CH_2 , H-7), 5.44 (1H, dd, $J = 17.0, 1.0$ Hz, CH_2 , H-7), 6.06 (1H, ddt, $J = 17.0, 10.5, 5.0$ Hz, CH , H-6), 6.89 (2H, d, $J = 1.0$ Hz, ArH, H-2) and 7.01 (1H, t, $J = 1.0$ Hz, ArH, H-4); δ_C ($CDCl_3$, 125 MHz) 32.82 (CH_2 , C-8), 68.85 (CH_2 , C-5), 115.37 (CH , C-2), 117.90 (CH_2 , C-7), 121.89 (CH , C-4), 132.68 (CH , C-6), 139.51 (C, C-3) and 158.87 (C, C-1); m/z (GC-MS): 320 ($M^+ + H$), 239 ($M^+ - Br$), 159 ($M^+ - 2Br$). Further elution afforded a second fraction, (3-(allyloxy)-5-(bromomethyl)phenyl)methanol **224**, as a colourless solid (202 mg, 26%), $R_f = 0.18$ (DCM); δ_H ($CDCl_3$, 500 MHz) 1.86 (1H, br. s., OH), 4.45 (2H, s, CH_2 , H-8), 4.55 (2H, dt, $J = 5.0, 1.5$ Hz, CH_2 , H-9), 4.65 (2H, s, CH_2 , H-7), 5.30 (1H, dq, $J = 10.5, 1.5$ Hz, CH_2 , H-11), 5.43 (1H, dq, $J = 17.0, 1.5$ Hz, CH_2 , H-11), 6.05 (1H, ddt, $J = 17.0, 10.5, 5.0$ Hz, CH , H-10), 6.87 (2H, s, Ar-H, H-2,6) and 6.98 (1H, s, Ar-H, H-4); δ_C ($CDCl_3$, 125 MHz) 33.31 (CH_2 , C-8), 64.81 (CH_2 , C-7), 68.84 (CH_2 , C-9), 113.12 (CH , C-2), 114.54 (CH , C-6), 117.81 (CH_2 , C-11), 119.71 (CH , C-4), 132.90 (CH , C-10), 139.30 (C, C-5), 143.05 (C, C-3) and 158.99 (C, C-1)

4.4.2 Dithiol Spacers

General method for the formation of the dithiol spacer unit from the dithiol^{141,250}

Et₃N (2.1 eq.) was added slowly to the dithiol (1 eq.) in dry methanol (10 mL per mmol of thiol) at room temperature under nitrogen. After 10 minutes, 2-methyl-1-tosylaziridine (2.1 eq.) was added, the reaction stirred for 30 minutes, warmed to 35 °C and then stirred for 4.5 hours at this temperature. On cooling to room temperature, 0.1 M NaOH was added and the solvent removed *in vacuo* to about 1 mL. EtOAc was added and then washed with H₂O, 0.1 M NaOH and brine. The combined organic layers were dried over MgSO₄ and filtered to give the crude product which was purified by flash column chromatography (EtOAc:Pet. Ether) to give the desired product.

N,N'-(2*S*,2'*S*)-1,1'-(2,2'-thiobis(ethane-2,1-diyl)bis(sulfanediyl))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **198**

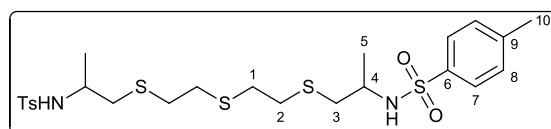


198

Spacer **198** was prepared using the method described above starting from 2,2'-thiodiethanethiol (391 μ L, 3.0 mmol), Et₃N (880 μ L, 6.3 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (1.34 mg, 6.3 mmol) in dry methanol (30 mL). **198** (1.55 g, 90%) was isolated as fluffy colourless solid after column chromatography (20% EtOAc in petrol), $R_f = 0.48$ (40% EtOAc in petrol), $[\alpha]_D^{27} = -30$ ($c = 1.4$, CHCl₃), m.p. 63.5 – 64.5 °C, (found C, 50.34; H, 6.45; N, 4.79%. C₂₄H₃₆N₂O₄S₅ requires C, 49.97; H, 6.29; N, 4.86%. Found [ES⁺] M⁺ + Na, 599.1178. C₂₄H₃₆N₂NaO₄S₅ requires M , 599.1171); ν_{\max} (ATR) 3237 (m), 1708 (w), 1457 (w), 1327 (s), 1154 (s), 1076 (s) and 985 (s) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.11 (6H, d, $J = 7.0$ Hz, CH₃, H-5), 2.43 (6H, s, CH₃, H-10), 2.61 – 2.70 (12H, m, CH₂, H-1,2,3) 3.43 (2H, app. sept, $J = 6.0$ Hz, CH, H-4), 5.21 (2H, d, $J = 7.0$ Hz, NH), 7.31 (4H, d, $J = 8.0$ Hz, ArH, H-8) and 7.78 (4H, d, $J = 8.0$ Hz, ArH, H-7); δ_C (CDCl₃, 125 MHz) 20.41 (CH₃, C-5), 21.53 (CH₃, C-10), 32.03 (CH₂, C-1), 32.83 (CH₂, C-2), 39.34 (CH₂, C-3), 49.24 (CH, C-4), 127.04 (CH, C-7), 129.72 (CH, C-8), 137.52

(C, C-6) and 143.49 (C, C-9); m/z (ES^+) 576.9 ($M^+ + H$), 593.8 ($M^+ + NH_4$), 599.1 ($M^+ + Na$).

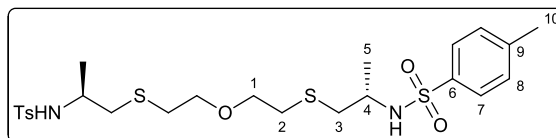
(S,S*), (R*,S*)-N,N'-1,1'-(2,2'-thiobis(ethane-2,1-diyl)bis(sulfanediyl))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) 200*



200

Spacer **200** was prepared using the method described above starting from 2,2'-thiodiethanethiol (652 μ L, 5.0 mmol), Et_3N (1.5 mL, 10.8 mmol), and (\pm)-2-methyl-1-tosylaziridine **194** (2.22 mg, 10.5 mmol) in dry methanol (50 mL). **200** (2.11 g, 73%) was isolated as a fluffy colourless solid after column chromatography (20% EtOAc in petrol), $R_f = 0.46$ (40% EtOAc in petrol), $[\alpha]_D^{24} = 0$ ($c = 1.37$, $CHCl_3$), (found $[ES^+]$ $M^+ + Na$, 599.1178. $C_{24}H_{36}O_4N_2NaS_5$ requires M , 599.1171); ν_{max} (ATR): 3269 (w), 2922 (w), 1598 (w), 1421 (m), 1324 (m), 1156 (s) and 1091 (m) cm^{-1} ; δ_H ($CDCl_3$, 300 MHz) 1.11 (6H, d, $J = 6.0$ Hz, CH_3 , H-5 (S^*,R^*)), 1.12 (6H, d, $J = 7.0$ Hz, CH_3 , H-5, (S^*,S^*)), 2.43 (12H, s, CH_3 , H-10, (S^*,S^*) + (S^*,R^*)), 2.55 – 2.73 (24H, m, CH_2 , H-1,2,3, (S^*,S^*) + (S^*,R^*)), 3.43 (4H, m, CH, H-4 (S^*,S^*) + (S^*,R^*)), 5.08 (2H, d, $J = 7.0$ Hz, NH, (S^*,R^*)), 5.21 (2H, d, $J = 7.0$ Hz, NH, (S^*,S^*)), 7.31 (8H, d, $J = 8.0$ Hz, C-H, H-8, (S^*,S^*) + (S^*,R^*)) and 7.75 – 7.81 (8H, m, C-H, H-7, (S^*,S^*) + (S^*,R^*)); δ_C ($CDCl_3$, 100 MHz) 20.23 (CH_3 , C-5, (S^*,S^*)), 20.28 (CH_3 , C-5 (S^*,R^*)), 21.42 (CH_3 , C-10, (S^*,S^*) + (S^*,R^*)), 31.86 (CH_2 , C-1 (S^*,S^*) + (S^*,R^*)), 32.48, 32.59 (CH_2 , C-2 (S^*,S^*) + (S^*,R^*)), 39.07, 39.10 (CH_2 , C-2, (S^*,S^*) + (S^*,R^*)), 49.11, 49.19 (CH, C-4, (S^*,S^*) + (S^*,R^*)), 126.92 (CH, C-7, (S^*,S^*) + (S^*,R^*)), 129.62 (CH, C-8 (S^*,S^*) + (S^*,R^*)), 137.36 (C, C-6, (S^*,S^*) + (S^*,R^*)) and 143.38 (C, C-9, (S^*,S^*) + (S^*,R^*)); m/z (ES^+) 599.3 ($M^+ + Na$).

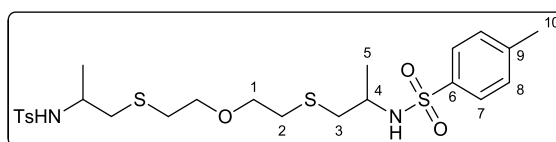
N,N'-(2*S*,2'*S*)-1,1'-(2,2'-oxybis(ethane-2,1-diyl)bis(sulfanediyl))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **197**



197

Spacer **197** was prepared using the method described above starting from 2,2'-oxydiethanethiol (375 μ L, 3.0 mmol), Et₃N (880 μ L, 6.3 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (1.31 g, 6.2 mmol) in dry methanol (30 mL). **197** (1.33 g, 79%) was isolated as viscous pale yellow oil after column chromatography (30% EtOAc in petrol), $R_f = 0.43$ (50% EtOAc in petrol); $[\alpha]_D^{32} = -24$ ($c = 1.43$, CHCl₃), (found C, 51.06; H, 6.57; N, 4.79%. C₂₄H₃₆N₂O₅S₄ requires C, 51.40; H, 6.47; N, 5.00%. Found [ES⁺] M⁺ + Na, 583.1389. C₂₄H₃₆O₅N₂S₄Na requires *M*, 583.1399); ν_{\max} (ATR): 3270 (m), 2970 (w), 2921 (w), 2866 (w), 1453 (m), 1324 (m), 1155 (s), 1091 (s), 982 (m) and 900 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.12 (6H, d, $J = 6.5$ Hz, CH₃, H-5), 2.42 (6H, s, CH₃, H-10), 2.53-2.69 (4H, m, CH₂, H-2), 2.64 (4H, d, $J = 6.0$ Hz, CH₂, H-3), 3.44 (2H, app. sept, $J = 6.5$ Hz, CH, H-4), 3.57 (4H, t, $J = 6.5$ Hz, CH₂, H-1), 5.34 (2H, d, $J = 7.0$ Hz, NH), 7.30 (4H, d, $J = 8.0$ Hz, CH, H-8) and 7.77 (4H, d, $J = 8.0$ Hz, CH, H-7); δ_C (CDCl₃, 125 MHz) 20.49 (CH₃, C-5), 21.47 (CH₃, C-10), 32.30 (CH₂, C-3), 39.77 (CH₂, C-2), 49.25 (CH, C-4), 70.49 (CH₂, C-1), 127.04 (CH, C-7), 129.61 (CH, C-8), 137.64 (C, C-6) and 143.29 (C, C-9); m/z (ES⁺) 561.1 (M⁺ + H), 578.0 (M⁺ + NH₄), 583.0 (M⁺ + Na).

(S,S*), (R*,S*)-N,N'*-1,1'-(2,2'-oxybis(ethane-2,1-diyl)bis(sulfanediyl))bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **199**

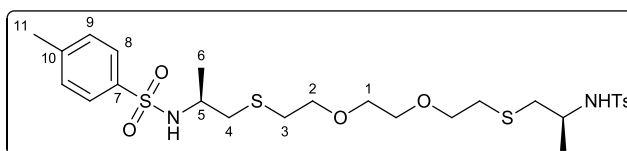


199

Spacer **199** was prepared using the method described above starting from 2,2'-oxydiethanethiol (619 μ L, 5.0 mmol), Et₃N (1.5 mL, 10.8 mmol), and (\pm)-2-methyl-1-tosylaziridine **194** (2.27 g, 10.7 mmol) in dry methanol (50 mL). **199** (2.22 g, 79%) was

isolated as viscous pale yellow oil after column chromatography (30% EtOAc in petrol), $R_f = 0.40$ (50% EtOAc in petrol), $[\alpha]_D^{28} = 0$ ($c = 1.52$, CHCl_3), (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 583.1396. $\text{C}_{24}\text{H}_{36}\text{O}_5\text{N}_3\text{NaS}_5$ requires M , 583.1399); ν_{max} (ATR): 3270 (w), 2922 (w), 2860 (w), 1598 (w), 1421 (m), 1325 (m), 1302 (m), 1156 (s) and 1092 (s) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.12 (6H, d, $J = 7.0$ Hz, CH_3 , H-5, (S^*, S^*)), 1.13 (6H, d, $J = 6.0$ Hz, CH_3 , H-5, (S^*, R^*)), 2.42 (12H, s, CH_3 , H-10, (S^*, S^*) + (S^*, R^*)), 2.55-2.67 (8H, m, CH_2 , H-2, (S^*, S^*) + (S^*, R^*)), 3.39 – 3.50 (4H, m, CH , H-4, (S^*, S^*) + (S^*, R^*)), 3.54 – 3.63 (8H, m, CH_2 , H-1, (S^*, S^*) + (S^*, R^*)), 5.27 (2H, d, $J = 7.0$ Hz, NH , (S^*, R^*)), 5.30 (2H, d, $J = 7.0$ Hz, NH , (S^*, S^*)), 7.30 (8H, d, $J = 8.0$ Hz, CH , H-8, (S^*, S^*) + (S^*, R^*)) and 7.77 (8H, d, $J = 8.0$ Hz, C-H , H-7, (S^*, S^*) + (S^*, R^*)); δ_{C} (CDCl_3 , 125 MHz) 20.54, 20.59 (CH_3 , C-5), 21.50 (CH_3 , C-10), 32.38 (CH_2 , C-3), 39.86 (CH_2 , C-2), 49.25, 49.57 (CH , C-4), 70.53, 70.56 (CH_2 , C-1), 127.08 (CH , C-7), 129.64 (CH , C-8), 137.70, 137.72 (C, C-6) and 143.32 (C, C-9); m/z (ES^+) 578.4 ($\text{M}^+ + \text{NH}_4$), 583.5 ($\text{M}^+ + \text{Na}$), 599.5 ($\text{M}^+ + \text{K}$).

N,N'-((2*S*,15*S*)-7,10-dioxa-4,13-dithiahexadecane-2,15-diyl)bis(4-methylbenzenesulfonamide) **196**

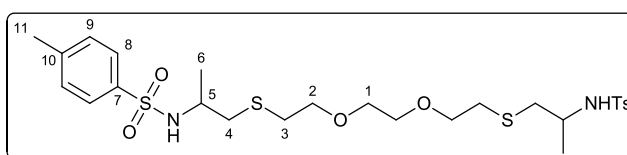


196

Spacer **196** was prepared using the method described above starting from 2,2'-(ethane-1,2-diylbis(oxy))diethanethiol (488 μL , 3.0 mmol), Et_3N (880 μL , 6.3 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (1.30 g, 6.2 mmol) in dry methanol (30 mL). **196** (1.56 g, 86%) was isolated as a viscous pale yellow oil after column chromatography (20% EtOAc in petrol), $R_f = 0.35$ (50% EtOAc in petrol), $[\alpha]_D^{27} = -20$ ($c = 5.62$, CHCl_3), (found C, 51.83; H, 6.88; N, 4.51%. $\text{C}_{26}\text{H}_{40}\text{O}_6\text{N}_2\text{S}_4$ requires C, 51.63; H, 6.67; N, 4.63%. Found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 627.1652. $\text{C}_{26}\text{H}_{40}\text{O}_6\text{N}_2\text{NaS}_4$ requires M , 627.1661); ν_{max} (ATR): 3267 (w), 2920 (w), 2866 (w), 1494 (w), 1324 (m), 1156 (s), 1092 (s), 662 (s) and 551 (s) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.11 (6H, d, $J = 6.5$ Hz, CH_3 , H-6), 2.41 (6H, s, CH_3 , H-11), 2.51 – 2.72 (8H, m, CH_2 , H-3,4), 3.41 (2H, app. sept, $J = 6.5$ Hz, CH , H-5), 3.59

(4H, t, $J = 6.0$ Hz, CH_2 , H-2), 3.62 (4H, s, CH_2 , H-1), 5.43 (2H, d, $J = 7.0$, NH), 7.29 (4H, d, $J = 8.0$ Hz, CH , H-9) and 7.76 (4H, d, $J = 8.0$ Hz, CH , H-8); δ_{C} (CDCl_3 , 125 MHz) 20.51 (CH_3 , C-6), 21.45 (CH_3 , C-11), 32.26 (CH_2 , C-4), 39.68 (CH_2 , C-3), 49.28 (CH , C-5), 70.17 (CH_2 , C-1), 70.88 (CH_2 , C-2), 127.02 (CH , C-8), 129.59 (CH , C-9), 137.66 (C , C-7) and 143.25 (C , C-10); m/z (ES^+) 605.1 ($\text{M}^+ + \text{H}$), 621.9 ($\text{M}^+ + \text{NH}_4$), 627.0 ($\text{M}^+ + \text{Na}$). On shaking with D_2O and NaOH : δ_{H} (CDCl_3 , 400 MHz) 1.11 (6H, d, $J = 6.5$ Hz, CH_3 , H-6), 2.40 (6H, s, CH_3 , H-11), 2.52 – 2.68 (8H, m, CH_2 , H-3,4), 3.40 (2H, app. sext, $J = 6.5$ Hz, CH , H-5), 3.59 (4H, t, $J = 6.5$ Hz, CH_2 , H-2), 3.61 (4H, s, CH_2 , H-1), 4.91 (2H, br. s, HDO), 7.28 (4H, d, $J = 8.0$ Hz, CH , H-9) and 7.76 (4H, d, $J = 8.0$ Hz, CH , H-8).

(S^,S^*), (R^*,S^*)-N,N'-(7,10-dioxa-4,13-dithiahexadecane-2,15-diyl)bis(4-methylbenzenesulfonamide)* **204**

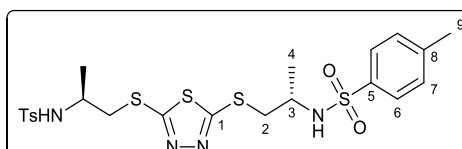


204

Spacer **204** was prepared using the method described above from 2,2'-(ethane-1,2-diylbis(oxy))diethanethiol (288 μL , 1.8 mmol), Et_3N (462 μL , 3.3 mmol), and (\pm)-2-methyl-1-tosylaziridine **194** (705 mg, 3.3 mmol) in dry methanol (15 mL). **204** (540 mg, 54%) was isolated as a viscous pale yellow oil after column chromatography (30% EtOAc in petrol), $R_f = 0.46$ (50% EtOAc in petrol), $[\alpha]_D^{26} = 0$ ($c = 1.42$, CHCl_3), (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 627.1654. $\text{C}_{26}\text{H}_{40}\text{O}_6\text{N}_2\text{NaS}_4$ requires M , 627.1661); ν_{max} (ATR): 3269 (w), 2927 (w), 2867 (w), 1597 (w), 1423 (m), 1325 (m), 132 (m), 1156 (s) and 1091 (s) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.13 (6H, d, $J = 6.0$ Hz, CH_3 , H-6, (S^*,S^*)), 1.15 (6H, d, $J = 6.0$ Hz, CH_3 , H-6, (S^*,R^*)), 2.43 (12H, s, CH_3 , H-11, (S^*,S^*) + (S^*,R^*)), 2.54 – 2.69 (16H, m, CH_2 , H-3,4, (S^*,S^*) + (S^*,R^*)), 3.45 (4H, m, CH , H-5, (S^*,S^*) + (S^*,R^*)), 3.62 (8H, m, CH_2 , (S^*,S^*) + (S^*,R^*)), 5.24 (2H, d, $J = 7.0$ Hz, NH , (S^*,R^*)), 5.34 (2H, d, $J = 7.0$ Hz, NH , (S^*,S^*)), 7.31 (8H, d, $J = 8.0$ Hz, CH , H-9, (S^*,S^*) + (S^*,R^*)) and 7.78 (8H, m, CH , H-8, (S^*,S^*) + (S^*,R^*)); δ_{C} (CDCl_3 , 125 MHz) 20.66, 20.75 (CH_3 , C-6), 21.55 (CH_3 , C-11), 32.44 (CH_2 , C-4), 39.84, 39.87 (CH_2 , C-3), 49.29, 49.36 (CH ,

C-5), 70.29, 70.31 (CH₂, C-1), 70.98, 71.03 (CH₂, C-2), 127.14 (CH, C-8), 129.69 (CH, C-9), 137.79 (C, C-10) and 143.36 (C, C-7); *m/z* (ES⁺) 622.6 (M⁺ + NH₄), 627.4 (M⁺ + Na).

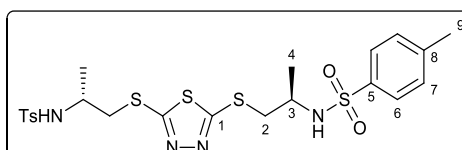
N,N'-(2*S*,2'*S*)-1,1'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **201**



201

Spacer **201** was prepared using the method described above starting from 1,3,4-thiadiazole-2,5-dithiol (452 mg, 3.0 mmol), Et₃N (880 μL, 6.3 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (1.34 g, 6.3 mmol) in dry methanol (30 mL). **201** (1.40 g, 82%) was isolated as a colourless crystalline solid after column chromatography (30% EtOAc in petrol), *R_f* = 0.52 (60% EtOAc in petrol), [*α*]_D³⁰ = -10 (c = 0.91, CH₂Cl₂), m.p. 76.5 – 77.5 °C, (found C, 45.51; H, 4.92; N, 9.00; S, 26.28%. C₃₁H₄₁O₄N₃S₅ requires C, 46.13; H, 4.93; N, 9.78; S, 27.99%. Found [ES⁺] M⁺ + Na, 595.0602. C₂₂H₂₈O₄N₄NaS₅ requires *M*, 595.0606); *ν*_{max} (ATR): 3283 (m), 1738 (w), 1596 (w), 1378 (m), 1330 (m), 1151 (s) and 1045 (s) cm⁻¹; *δ*_H (CD₂Cl₂, 500 MHz) 1.21 (6H, d, *J* = 7.0 Hz, CH₃, H-4), 2.40 (6H, s, CH₃, H-9), 3.32 (4H, d, *J* = 6.0 Hz, CH₂, H-2), 3.70 (2H, app. sept, *J* = 7.0 Hz, CH, H-3), 5.49 (2H, d, *J* = 7 Hz, NH), 7.28 (4H, d, *J* = 8.0 Hz, CH, H-7) and 7.69 (4H, d, *J* = 8.0 Hz, CH, H-6); *δ*_C (CDCl₃, 125 MHz) 21.67 (CH₃, C-4), 21.77 (CH₃, C-9), 40.75 (CH₂, C-2), 50.62 (CH, C-3), 127.58 (CH, C-6), 130.19 (CH, C-7), 138.10 (C, C-8), 144.18 (C, C-5) and 166.29 (C, C-1); *m/z* (ES⁺) 573.3 (M⁺ + H), 595.5 (M⁺ + Na).

N,N'-(2*R*,2'*R*)-1,1'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **202**

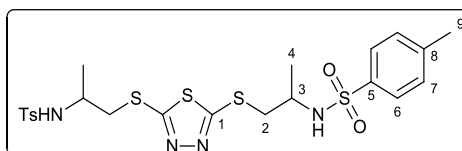


202

Spacer **202** was made following the standard method described above, starting from 1,3,4-thiadiazole-2,5-dithiol (360 mg, 2.4 mmol), Et₃N (700 μL, 5.0 mmol), and (*R*)-2-methyl-1-tosylaziridine **193** (1.07 g, 5.1 mmol) in dry methanol (22 mL). **202** (839 mg, 61%) was isolated as a colourless powder after column chromatography (30% EtOAc in petrol), R_f = 0.71 (70% EtOAc in petrol), (found [ES⁺] M⁺ + Na, 595.0602. C₂₂H₂₈O₄N₄NaS₅ requires *M*, 595.0606); δ_H (CDCl₃, 500 MHz) 1.24 (6H, d, *J* = 6.5 Hz, CH₃, H-4), 2.41 (6H, s, CH₃, H-9), 3.31 (2H, dd, *J* = 14.5, 7.5 Hz, CH₂, H-2), 3.37 (2H, dd, *J* = 14.5, 4.5 Hz, CH₂, H-2), 3.75 (2 H, tqd, *J* = 7.5, 6.5, 4.5 Hz, CH, H-3), 5.42 (2H, d, *J* = 7.5 Hz, NH), 7.27 (4H, d, *J* = 8.0 Hz, CH, H-7) and 7.73 (4H, d, *J* = 8.0 Hz, CH, H-6); δ_C (CDCl₃, 75 MHz) 21.31 (CH₃, C-4), 21.53 (CH₃, C-9), 40.24 (CH₂, C-2), 49.99 (CH, C-3), 127.09 (CH, C-6), 129.66 (CH, C-7), 137.65 (C, C-8), 143.42 (C, C-5) and 165.59 (C, C-1); *m/z* (ES⁺) 595.3 (M⁺ + Na), 1167.6 (2M⁺ + Na), 1739.9 (3M⁺ + Na).

(*S**,*S**),(*R**,*S**)-*N,N'*-(2*S*,2'*S*)-1,1'-(1,3,4-thiadiazole-2,5-

diyl)bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **203**

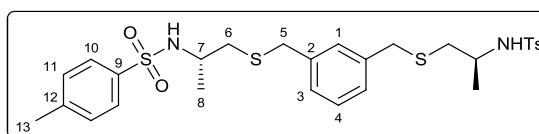


203

Spacer **203** was prepared using the method described above starting from 1,3,4-thiadiazole-2,5-dithiol (760 mg, 5.1 mmol), Et₃N (1.5 mL, 10.8 mmol), and (±)-2-methyl-1-tosylaziridine **194** (2.24 mg, 10.6 mmol) in dry methanol (50 mL). **203** (2.48 g, 86%) was isolated as a solid colourless foam after column chromatography (30% EtOAc in petrol), R_f = 0.40 (50% EtOAc in petrol), [α]_D²⁷ = 0 (c = 1.65, CHCl₃), m.p. 72 – 75 °C, (found [ES⁺] M⁺ + Na, 595.0601. C₂₂H₂₈O₄N₄NaS₅ requires *M*, 595.0606); ν_{max} (ATR): 3270 (m), 15.97 (w), 1376 (m), 1312 (m), 1153 (s), 1039 (s) cm⁻¹; δ_H (CDCl₃, 400 MHz) 1.15 – 1.32 (12H, m, CH₃, H-4, (*S**,*S**) + (*S**,*R**)), 2.41 (12H, s, CH₃, H-9, (*S**,*S**) + (*S**,*R**)), 3.22 – 3.44 (8H, m, CH₂, H-2, (*S**,*S**) + (*S**,*R**)), 3.65 – 3.83 (4H, m, CH, H-3, (*S**,*S**) + (*S**,*R**)), 5.54 – 5.64 (4H, m, NH, (*S**,*S**) + (*S**,*R**)), 7.26 (8H, d, *J* = 8.0 Hz, CH, H-7, (*S**,*S**) + (*S**,*R**)) and 7.73 (8H, d, *J* = 8.0 Hz, CH, H-6, (*S**,*S**)

+ (*S*,R**); δ_C (CDCl₃, 100 MHz) 21.17, 21.23 (CH₃, C-4), 21.51 (CH₃, C-9), 40.03, 40.12 (CH₂, C-2), 49.82 (CH, C-3), 127.02 (CH, C-7), 129.60 (CH, C-6), 137.47 (C, C-5), 143.39 (C, C-8), 165.48 and 165.52 (C, C-1); m/z (ES⁺) 573.4 (M⁺ + H), 595.3 (M⁺ + Na), 611.4 (M⁺ + K).

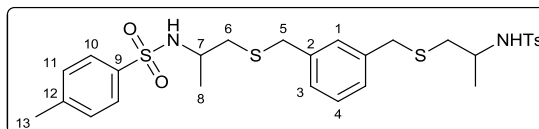
N,N'-(2*S*,2'*S*)-1,1'-(1,3-phenylenebis(methylene))bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **210**



210

Spacer **210** was prepared using the method described above starting from 1,3-phenylenedimethanethiol **209** (1.38 g, 8.1 mmol), Et₃N (2.4 mL, 17.2 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (3.59 g, 17.0 mmol) in dry methanol (80 mL). **210** (1.40 g, 61%) was isolated as a pale oil after column chromatography (40% EtOAc in petrol), R_f = 0.48 (40% EtOAc in petrol), $[\alpha]_D^{25}$ = - 22 (c = 1.425, CHCl₃), m.p. 77 – 78 °C, (found C, 55.54; H, 6.20; N, 4.51; S, 20.78%. C₂₈H₃₆N₂O₄S₄·½H₂O requires C, 55.88; H, 6.20; N, 4.65; S, 21.31%. Found [ES⁺] M⁺ + Na, 615.1446. C₂₈H₃₆N₂NaO₄S₄ requires *M*, 615.1450); ν_{\max} (ATR): 3270 (m), 2972 (w), 2920 (w), 1598 (m), 1494 (w), 1421 (m), 1324 (s), 1155 (s), 1091 (s) and 982 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.10 (6H, d, *J* = 7.0 Hz, CH₃, H-8), 2.42 (6H, s, CH₃, H-13), 2.43 (2H, dd, *J* = 13.5, 6.5 Hz, CH₂, H-6), 2.52 (2H, dd, *J* = 13.5, 5.5 Hz, CH₂, H-6), 3.41 (2H, m, CH, H-7), 3.52 (2H, d, *J* = 14.0 Hz, CH₂, H-5), 3.58 (2H, d, *J* = 14.0 Hz, CH₂, H-5), 5.29 (2H, d, *J* = 7.0 Hz, NH), 7.12 (2H, dd, *J* = 8.0, 1.0 Hz, CH, H-3), 7.18 (1H, br.t, *J* = 1.0 Hz, CH, H-1), 7.24 (1H, t, *J* = 8.0 Hz, CH, H-4), 7.30 (4H, d, *J* = 8.0 Hz, CH, H-11) and 7.78 (4H, d, *J* = 8.0 Hz, CH, H-11); δ_C (CDCl₃, 125 MHz) 20.62 (CH₃, C-8), 21.52 (CH₃, C-13), 36.24 (CH₂, C-6), 38.25 (CH₂, C-5), 48.87 (CH, C-7), 127.04 (CH, C-10), 127.69 (CH, C-3), 128.91 (CH, C-4), 129.49 (CH, C-1), 129.68 (CH, C-11), 137.70 (C, C-9), 138.19 (C, C-2) and 143.38 (C, C-12); m/z (ES⁺) 610.8 (M⁺ + NH₄), 615.4 (M⁺ + Na).

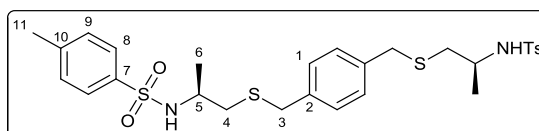
(*S*,S**),(*R*,S**)-*N,N'*-(1,1'-(1,3-phenylenebis(methylene))bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **211**



211

Spacer **211** was prepared using the method described above starting from 1,3-phenylenedimethanethiol **209** (326 mg, 2.1 mmol), Et₃N (600 μL, 4.3 mmol), and (±)-2-methyl-1-tosylaziridine **194** (879 mg, 4.2 mmol) in dry methanol (20 mL). **211** (631 mg, 51%) was isolated as a pale oil after column chromatography (30% EtOAc in petrol), R_f = 0.50 (40% EtOAc in petrol), $[\alpha]_D^{25} = 0$ (c = 0.98, CHCl₃), δ_H (CDCl₃, 400 MHz) 1.09 (6H, d, *J* = 7.0 Hz, CH₃, H-8, (*S*,R**)) 1.10 (6H, d, *J* = 7.0 Hz, CH₃, H-8, (*S*,S**)), 2.41 - 2.48 (6H, m, CH₂, H-6, (*S*,S**) + (*S*,R**)) 2.43 (12H, s, CH₃, H-13, (*S*,S**) + (*S*,R**)), 2.53 (2H, dd, *J* = 13.0, 6.0 Hz, CH₂, H-6, (*S*,S**)), 3.38 - 3.47 (4H, m, CH, H-7, (*S*,S**) + (*S*,R**)), 3.51 (2H, d, *J* = 13.0 Hz, CH₂, H-5, (*S*,R**)), 3.53 (2H, d, *J* = 14.0 Hz, CH₂, H-5, (*S*,S**)), 3.57 (2H, d, *J* = 14.0 Hz, CH₂, H-5, (*S*,R**)), 3.60 (2H, d, *J* = 13.0 Hz, CH₂, H-5, (*S*,S**)), 4.83 (2H, d, *J* = 7.0 Hz, NH, (*S*,R**)), 5.02 (2H, d, *J* = 7.0 Hz, NH, (*S*,S**)), 7.10 - 7.15 (4H, m, CH, H-3, (*S*,S**) + (*S*,R**)), 7.17 (1H, s, CH, H-1, (*S*,R**)), 7.19 (1H, s, CH, H-1, (*S*,S**)), 7.23 - 7.27 (2H, m, CH, H-4, (*S*,S**) + (*S*,R**)), 7.31 (8H, d, *J* = 8.0 Hz, CH, H-11, (*S*,S**) + (*S*,R**)) and 7.76 (8H, d, *J* = 8.0 Hz, CH, H-10, (*S*,S**) + (*S*,R**)).

N,N'-(2*S*,2'*S*)-1,1'-(1,4-phenylenebis(methylene))bis(sulfanediyl)bis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **214**



214

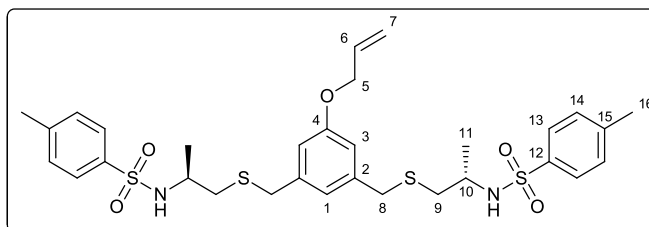
Spacer **214** was prepared using the method described above starting from 1,4-phenylenedimethanethiol **213** (450 mg, 2.6 mmol), Et₃N (859 μL, 6.2 mmol), and (*S*)-2-methyl-1-tosylaziridine **181** (1.31 g, 6.2 mmol) in dry methanol (30 mL). **214** (1.39 g,

89%) was isolated as a pale yellow oil after column chromatography (30% EtOAc in petrol), $R_f = 0.63$ (50% EtOAc in petrol), $[\alpha]_D^{31} = 15$ ($c = 1.82$, CHCl_3), (found $[\text{ES}^+ \text{M}^+ + \text{Na}]$, 615.1462. $\text{C}_{28}\text{H}_{36}\text{O}_4\text{N}_2\text{NaS}_4$ requires M , 615.1450); ν_{max} (ATR): 3264 (w), 2920 (w), 1597 (w), 1422 (m), 1324 (m), 1154 (s) and 1091 (s) cm^{-1} ; δ_{H} (CDCl_3 , 400 MHz) 1.09 (6H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.39 (2H, dd, $J = 13.5$, 6.5 Hz, CH_2 , H-4), 2.43 (6H, s, CH_3 , H-11), 2.47 (2H, dd, $J = 13.5$, 6.0 Hz, CH_2 , H-4), 3.31 – 3.44 (2H, m, CH , H-5), 3.47 (2H, d, $J = 13.0$ Hz, CH_2 , H-3), 3.54 (2H, d, $J = 13.0$ Hz, CH_2 , H-3), 5.11 (2H, d, $J = 7.0$ Hz, NH), 7.15 (4H, s, CH , H-1), 7.31 (4H, d, $J = 8.0$ Hz, CH , H-9) and 7.77 (4H, d, $J = 8.0$ Hz, CH , H-8); δ_{C} (CDCl_3 , 100 MHz) 20.61 (CH_3 , C-6), 21.46 (CH_3 , C-11), 35.97 (CH_2 , C-4), 38.12 (CH_2 , C-3), 48.73 (CH , C-5), 127.01 (CH , C-8), 128.96 (CH , C-1), 129.61 (CH , C-9), 136.61 (C , C-2), 137.50 (C , C-7) and 143.33 (C , C-10); m/z (ES^+) 593.0 ($\text{M}^+ + \text{H}$), 615.4 ($\text{M}^+ + \text{Na}$), 631.3 ($\text{M}^+ + \text{K}$).

N,N'-((2*S*,2'*S*)-((5-(allyloxy)-1,3-

phenylene)bis(methylene))bis(sulfanediyl))bis(propane-2,1-diyl))bis(4-

methylbenzenesulfonamide) **226**

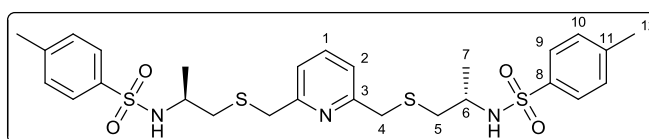


226

A solution of the dibromoether **225** (1.48 g, 4.6 mmol) and thiourea (714 mg, 9.4 mmol) in degassed ethanol (13 mL) were brought to reflux under N_2 . After 30 minutes, the reaction was allowed to cool to room temperature and 5 M NaOH (degassed, 3.75 mL, 18.6 mmol) was added. The reaction mixture was then brought to reflux for 4 hours and cooled to room temperature. Once cool, aziridine **181** (1.97 g, 9.3 mmol) was added and the reaction left to stir overnight. Aqueous 0.1 M NaOH was added until the reaction turned opaque, and the mixture reduced to dryness *in vacuo*. The residue was taken up in EtOAc (50 mL), and the organic extract was washed with H_2O (2 x 40 mL), 0.1 M NaOH (1 x 40 mL) and brine (1 x 40 mL). The organic extract was dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography (20% EtOAc in petrol) affording the *title compound* **226** as a viscous yellow oil (2.22 g, 74%), $R_f = 0.65$ (50% EtOAc in petrol), $[\alpha]_D^{32} = -24$ ($c = 2.02$, CHCl_3), (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 671.1718. $\text{C}_{31}\text{H}_{40}\text{O}_5\text{N}_2\text{NaS}_4$ requires M , 671.1712); ν_{max} (ATR): 3267 (m, br), 2972 (w), 2922 (w), 2869 (w), 1593 (m), 1450 (m), 1422 (m), 1322 (m), 1298 (m) and 1153 (s) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.08 (6H, d, $J = 6.0$ Hz, CH_3 , H-11), 2.42 (6H, s, CH_3 , H-16), 2.43 (2H, dd, $J = 14.0, 7.0$ Hz, CH_2 , H-9), 2.52 (2H, dd, $J = 14.0, 5.5$ Hz, CH_2 , H-9), 3.41 (2H, dqd, $J = 7.0, 6.0, 5.5$ Hz, CH, H-10), 3.47 (2H, d, $J = 14.0$ Hz, CH_2 , H-8), 3.54 (2H, d, $J = 14.0$ Hz, CH_2 , H-8), 4.54 (2H, d, $J = 5.0$ Hz, CH_2 , H-5), 4.72 (2H, br. s., NH), 5.29 (1H, d, $J = 10.0$ Hz, CH_2 , H-7), 5.42 (1H, d, $J = 17.0$ Hz, CH_2 , H-7), 6.05 (1H, ddt, $J = 17.0, 11.0, 5.0$ Hz, CH, H-6), 6.71 (2H, s, CH, H-3), 6.76 (1H, s, CH, H-1), 7.29 (4H, d, $J = 8.0$ Hz, CH, H-14) and 7.75 (4H, d, $J = 8.0$ Hz, CH, H-13); δ_{C} (CDCl_3 , 125 MHz) 20.57 (CH_3 , C-11), 21.47 (CH_3 , C-16), 36.31 (CH_2 , C-8), 38.26 (CH_2 , C-9), 48.90 (CH, C-10), 68.73 (CH_2 , C-5), 113.96 (CH, C-3), 117.68 (CH_2 , C-7), 122.07 (CH, C-1), 127.01 (CH, C-13), 129.64 (CH, C-14), 133.06 (CH, C-6), 137.73 (C, C-12), 139.57 (C, C-2), 143.32 (C, C-15) and 158.96 (C, C-4); m/z (ES^+) 649 ($\text{M}^+ + \text{H}$), 671 ($\text{M}^+ + \text{Na}$), 687 ($\text{M}^+ + \text{K}$), 1319 ($2\text{M}^+ + \text{Na}$).

N,N'-((2*S*,2'*S*)-((pyridine-2,6-diylbis(methylene))bis(sulfanediyl))bis(propane-2,1-diyl))bis(4-methylbenzenesulfonamide) **218**

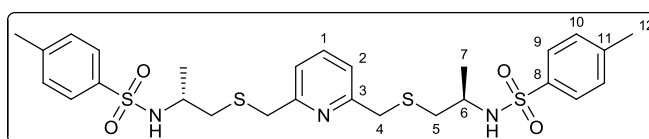


218

A solution of the dibromoether **24** (791 mg, 3.0 mmol) and thiourea (462 mg, 6.1 mmol) in degassed ethanol (7.5 mL) were brought to reflux under N_2 . After 30 minutes, the reaction was allowed to cool to room temperature and 5 M NaOH (degassed, 2.4 mL, 12 mmol) was added. The reaction mixture was then brought to reflux for 4 hours and cooled to room temperature. Once cool, aziridine **181** (1.28 g, 6.1 mmol) was added and the reaction left to stir overnight at room temperature. Aqueous 0.1 M NaOH was added until the reaction turned opaque, and the mixture reduced to dryness *in vacuo*. The residue was taken up in EtOAc (25 mL), and the organic extract was washed with H_2O

(2 x 20 mL), 0.1 M NaOH (1 x 20 mL) and brine (1 x 20 mL). The organic extract was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc in petrol) affording the *title compound* **218** as a near-colourless crystalline solid (1.41 g, 89%), $R_f = 0.67$ (40% EtOAc in petrol), $[\alpha]_D^{32} = -65$ (c = 2.14, CHCl₃), m.p. 88 – 90 °C, (found [ES⁺] M⁺ + Na, 616.1399. C₂₇H₃₅O₄N₃NaS₄ requires *M*, 616.1403); ν_{\max} (ATR): 3246 (m), 3030 (w), 2989 (w), 2968 (w), 2926 (w), 2854 (w), 2773 (w), 2735 (w), 1594 (m), 1573 (m), 1431 (m), 1321 (s), 1156 (s) and 1140 (s) cm⁻¹; δ_H (CDCl₃, 300 MHz) 1.11 (6H, d, *J* = 6.5 Hz, CH₃, H-7), 2.41 (6H, s, CH₃, H-12), 2.60 (4H, app. d, *J* = 6.0 Hz, CH₂, H-5), 3.53 (2H, dqt, *J* = 7.0, 6.5, 6.0 Hz, CH, H-6), 3.71 (2H, d, *J* = 13.0 Hz, CH₂, H-4), 3.76 (2H, d, *J* = 13.0 Hz, CH₂, H-4), 6.12 (2H, d, *J* = 7.0 Hz, NH), 7.15 (2H, d, *J* = 7.0 Hz, CH, H-2), 7.28 (4H, d, *J* = 8.0 Hz, CH, H-10), 7.62 (1H, t, *J* = 7.0 Hz, CH, H-1) and 7.76 (4H, d, *J* = 8.0 Hz, CH, H-9); δ_C (CDCl₃, 125 MHz) 20.69 (CH₃, C-7), 21.46, 21.49 (CH₃, C-12), 37.88 (CH₂, C-4), 38.80 (CH₂, C-5), 49.58, 49.59 (CH, C-6), 121.58 (CH, C-2), 126.98 (CH, C-9), 129.59 (CH, C-10), 137.99 (C, C-8), 138.04 (CH, C-1), 143.14 (C, C-11) and 158.11 (C, C-3); *m/z* (ES⁺) 593.8 (M⁺ + H), 615.9 (M⁺ + Na), 1187.7 (2M⁺ + H), 1209.2 (2M⁺ + Na), 1803.0 (3M⁺ + Na).

N,N'-((2*R*,2'*R*)-((pyridine-2,6-diylbis(methylene))bis(sulfaneyl))bis(propane-2,1-diyl))bis(4-methylbenzenesulfonamide) **219**



219

A solution of dibromoether species **181** (932 mg, 3.5 mmol) and thiourea (543 mg, 7.1 mmol) in degassed ethanol (10 mL) were brought to reflux under a nitrogen atmosphere. After 30 minutes, the reaction was allowed to cool to room temperature. 5 M NaOH (degassed, 2.85 mL, 14.2 mmol) was added, and the reaction refluxed for 4 hours. On cooling to room temperature, aziridine **193** (1.48 g, 7.0 mmol) was added and the reaction left to stir overnight. 0.1 M NaOH was added until the reaction turned opaque, and the mixture reduced to dryness *in vacuo*. The residue was taken up in EtOAc (25 mL), and the organic extract was washed with H₂O (2 x 20 mL), 0.1 M NaOH (1 x 20

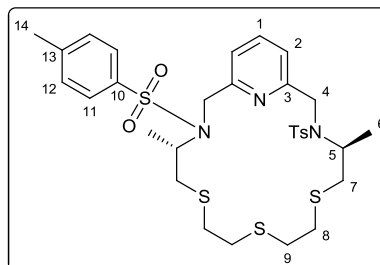
mL) and brine (1 x 20 mL). The organic extract was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc in petrol) giving the *title compound 219* as a near-colourless solid (1.67 g, 80%), R_f = 0.70 (60% EtOAc in petrol), $[\alpha]_D^{26} = -63$ (c = 1.85, CHCl₃), m.p. 89 – 92 °C, (found [ES⁺] M⁺ + Na, 594.1581. C₂₇H₃₅O₄N₃NaS₄ requires M, 594.1584); ν_{\max} (ATR): 3270 (br., w), 3026 (w), 2972 (w), 2856 (w), 1593 (m), 1573 (m), 1452 (m), 1429 (m), 1327 (m), 1314 (m), 1157 (s) and 1093 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.12 (6H, d, *J* = 6.5 Hz, CH₃, H-7), 2.41 (6H, s, CH₃, H-12), 2.60 (4H, app. d, *J* = 5.5 Hz, CH₂, H-5), 3.49 - 3.58 (2H, m, CH, H-6), 3.71 (2H, d, *J* = 13.5 Hz, CH₂, H-4), 3.76 (2H, d, *J* = 13.5 Hz, CH₂, H-4), 6.08 (2H, d, *J* = 7.0 Hz, NH), 7.15 (2H, d, *J* = 7.5 Hz, CH, H-2), 7.28 (4H, d, *J* = 8.0 Hz, CH, H-10), 7.62 (1H, t, *J* = 7.5 Hz, CH, H-1) and 7.76 (4H, d, *J* = 8.0 Hz, CH, H-9); δ_C (CDCl₃, 125 MHz) 20.66, 20.70 (CH₃, C-7), 21.43, 21.48 (CH₃, C-12), 37.86 (CH₂, C-4), 38.80 (CH₂, C-5), 49.56, 49.60 (CH, C-6), 121.54 (CH, C-2), 126.96 (CH, C-9), 129.58 (CH, C-10), 137.96 (C, C-8), 138.05 (CH, C-1), 143.12 (C, C-11) and 158.09 (C, C-3); *m/z* (ES⁻) 628 (M⁻ + Cl), 1221 (2M⁻ + Cl).

4.5 The Macrocycles

4.5.1 General Method for the synthesis of the macrocycles

The ditosamide (1 eq.) was dissolved in dry DMF (300 mL/mmol dithiol) under N₂. After 10 minutes of stirring, 2,6-bis(bromomethyl)pyridine **24** (1 eq.) and Cs₂CO₃ (5 eq.) were added and the reaction was left to stir for 48 hours at room temperature. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane which was washed with H₂O (6 times). The combined organic extracts were dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (EtOAc: Pet. Ether) to yield the desired product.

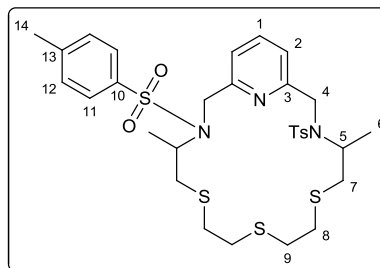
(4*S*,14*S*)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-6,9,12-trithia-3,15,21-triaza-
bicyclo[15.3.1]hencosa-1(20),17(21),18-triene **234**



234

Using the general method described above, starting from ditosamide **198** (111 mg, 193 μmol), 2,6-bis(bromomethyl)pyridine (56.4 mg, 213 μmol), and Cs_2CO_3 (315 mg, 969 μmol), **234** was isolated as a near-colourless glass (77.7 mg, 59%) after column chromatography (20% EtOAc in petrol), $R_f = 0.63$ (60% EtOAc in petrol), (found C, 55.15; H, 6.23; N, 6.06%. $\text{C}_{31}\text{H}_{41}\text{O}_4\text{N}_3\text{S}_5$ requires C, 54.75; H, 6.08; N, 6.18%. Found $[\text{ES}^+] \text{M}^+ + \text{H}$, 680.1764. $\text{C}_{31}\text{H}_{42}\text{O}_4\text{N}_3\text{S}_5$ requires M , 680.1773); ν_{max} (ATR): 2921 (w), 1594 (w), 1576 (w), 1331 (m), 1150 (s), 1089 (m), 867 (m) and 813 (m) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.05 (6H, d, $J = 6.0$ Hz, CH_3 , H-6), 2.43 (6H, s, CH_3 , H-14), 2.53 (2H, dd, $J = 13.0, 9.0$ Hz, CH_2 , H-7), 2.57 – 2.70 (8H, m, CH_2 , H-8,9), 2.86 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7), 3.93 (2H, app. sext., $J = 7.0$ Hz, CH , H-5), 4.46 (4H, br.s., CH_2 , H-4), 7.29 (4H, d, $J = 8.0$ Hz, CH , H-12), 7.49 (2H, d, $J = 8.0$ Hz, CH , H-2), 7.69 (1H, t, $J = 8.0$ Hz, CH , H-1) and 7.72 (4H, d, $J = 8.0$ Hz, CH , H-11); δ_{C} (CDCl_3 , 125 MHz) 18.28 (CH_3 , C-6), 21.49 (CH_3 , C-14), 32.03 (CH_2 , C-9), 33.28 (CH_2 , C-8), 37.67 (CH_2 , C-7), 49.45 (CH_2 , C-4), 54.85 (CH , C-5), 121.89 (CH , C-2), 127.12 (CH , C-11), 129.64 (CH , C-12), 137.32 (CH , C-1), 137.70 (C, C-10), 143.31 (C, C-13) and 157.43 (C, C-3); m/z (ES^+) 680.4 ($\text{M}^+ + \text{H}$), 701.9 ($\text{M}^+ + \text{Na}$).

(*S**,*S**),(*R**,*S**)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-6,9,12-trithia-3,15,21-triaza-bicyclo[15.3.1]henicosa-1(20),17(21),18-triene **235**

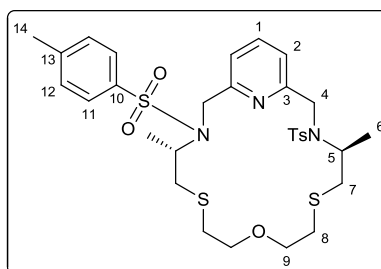


235

Using the general method described above, starting from ditosamide **200** (992 mg, 1.7 mmol), 2,6-bis(bromomethyl)pyridine (459 mg, 1.7 mmol), and Cs₂CO₃ (2.86 g, 8.8 mmol), **235** was isolated as a thick yellow oil (621 mg, 53%) after purification by column chromatography (20% EtOAc in petrol), R_f = 0.70 (50% EtOAc in petrol), [α]_D²⁴ = 0 (c = 1.24, CHCl₃), (found [ES⁺] M⁺ + Na, 702.1594. C₃₁H₄₁O₄N₃NaS₅ requires M, 702.1593); ν_{max} (ATR): 2975 (m), 1651 (w), 1455 (w), 1335 (m), 1260 (m), 1155 (m), 1089 (s), 1044 (s) and 800 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.00 (6H, d, J = 7.0 Hz, CH₃, H-6, (*S**,*S**)), 1.04 (6H, d, J = 7.0 Hz, CH₃, H-6, (*S**,*R**)), 2.29 (2H, dd, J = 12.0, 8.0 Hz, CH₂, H-7, (*S**,*R**)), 2.41 (6H, s, CH₃, H-14, (*S**,*R**)), 2.42 (6H, s, CH₃, H-14, (*S**,*S**)), 2.45 – 2.69 (20H, m, CH₂, H-7,8,9, (*S**,*S**) + (*S**,*R**)), 2.84 (2H, dd, J = 13.0, 6.0 Hz, CH₂, H-7, (*S**,*S**)), 3.92 (2H, m, CH, H-5, (*S**,*S**)), 4.05 (2H, m, CH, H-5, (*S**,*R**)), 4.23 (2H, d, J = 17.0 Hz, CH₂, H-4, (*S**,*R**)), 4.43 (2H, d, J = 17.0 Hz, CH₂, H-4, (*S**,*S**)), 4.46 (2H, d, J = 17.0 Hz, CH₂, H-4, (*S**,*S**)), 4.69 (2H, d, J = 16.0 Hz, CH₂, H-4, (*S**,*R**)), 7.28 (4H, d, J = 8.0 Hz, CH, H-12, (*S**,*S**)), 7.30 (4H, d, J = 8.0 Hz, CH, H-12, (*S**,*R**)), 7.49 (2H, d, J = 8.0 Hz, CH, H-2, (*S**,*S**)), 7.65 – 7.69 (4H, m, CH, H-1 (*S**,*S**) + (*S**,*R**) + 2H, m, CH, H-2 (*S**,*R**) and 7.71 (8H, d, J = 8.0 Hz, CH, H-11, (*S**,*S**) + (*S**,*R**)); δ_C (CDCl₃, 125 MHz) 17.40, 17.44 (CH₃, C-6, (*S**,*R**)), 18.20, 18.24 (CH₃, C-6, (*S**,*S**)), 21.44, 21.50 (CH₃, C-14, (*S**,*S**) + (*S**,*R**)), 31.90, 31.97 (CH₂, C-9, (*S**,*S**) + (*S**,*R**)), 33.23, 33.42 (CH₂, C-8, (*S**,*S**) + (*S**,*R**)), 37.62 (CH₂, C-7, (*S**,*S**)), 38.13 (CH₂, C-7, (*S**,*R**)), 48.77, 48.83 (CH₂, C-4, (*S**,*R**)), 49.38 (CH₂, C-4, (*S**,*S**)), 53.98, 54.10 (CH, C-5, (*S**,*R**)), 54.74, 54.86 (CH, C-5, (*S**,*S**)), 121.84, 121.99 (CH, C-2, (*S**,*S**) + (*S**,*R**)), 127.04 (CH, C-11, (*S**,*S**) + (*S**,*R**)), 129.60, 129.70 (CH, C-12, (*S**,*S**) + (*S**,*R**)), 137.39 (CH, C-1, (*S**,*S**) + (*S**,*R**)), 137.62 (C,

C-10, (S^*,S^*) + (S^*,R^*)), 143.28, 143.43 (C, C-13, tosyl, (S^*,S^*) + (S^*,R^*)), 157.38 and 157.50 (C, C-3, (S^*,S^*) + (S^*,R^*)); m/z (ES^+) 680.5 (M^+ + H), 702.6 (M^+ + Na), 718.9 (M^+ + K).

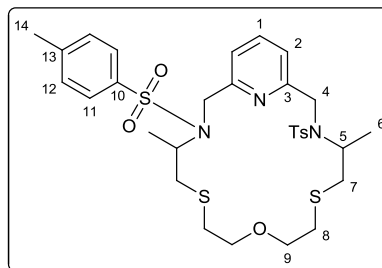
(4*S*,14*S*)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-9-oxa-6,12-dithia-3,15,21-triaza-bicyclo[15.3.1]heneicosane-1(20),17(21),18-triene **230**



230

Using the general method described above, starting from ditosamide **197** (107 mg, 190 μmol), 2,6-bis(bromomethyl)pyridine (51.3 mg, 194 μmol), and Cs_2CO_3 (3078 mg, 942 μmol) **236** was isolated as a pale yellow oil (121 mg, 96%) after purification by column chromatography (40% EtOAc in petrol), $R_f = 0.54$ (60% EtOAc in petrol), $[\alpha]_D^{29} = +75$ ($c = 1.15$, CHCl_3), (found C, 56.32; H, 6.53; N, 6.05%. $\text{C}_{31}\text{H}_{41}\text{O}_4\text{N}_3\text{S}_5$ requires C, 56.08; H, 6.22; N, 6.33%. Found $[ES^+]$ M^+ + H, 664.1998. $\text{C}_{31}\text{H}_{42}\text{N}_3\text{O}_5\text{S}_4$ requires M , 664.2002); ν_{max} (ATR): 3971, 3921, 2854, 1594, 1333, 1152, 1090 and 870 cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.13 (6H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.36 – 2.48 (4H, m, CH_2 , H-8), 2.42 (6H, s, CH_3 , H-14), 2.67 (2H, dd, $J = 13.0, 8.0$ Hz, CH_2 , H-7), 2.84 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7), 3.45 (4H, t, $J = 6.0$ Hz, CH_2 , H-9), 3.93 (2H, app. sext., $J = 7.0$ Hz, CH , H-5), 4.40 (2H, d, $J = 16.0$ Hz, CH_2 , H-4), 4.47 (2H, d, $J = 16.0$ Hz, CH_2 , H-4), 7.26 (4H, d, $J = 7.0$ Hz, CH , H-12), 7.52 (2H, d, $J = 8.0$ Hz, CH , H-2), 7.68 (1H, t, $J = 8.0$ Hz, CH , H-1) and 7.70 (4H, d, $J = 8.0$ Hz, CH , H-11); δ_{C} (CDCl_3 , 125 MHz) 18.15 (CH_3 , C-6), 21.49 (CH_3 , C-14), 32.03 (CH_2 , C-8), 38.19 (CH_2 , C-7), 49.74 (CH_2 , C-4), 55.04 (CH , C-5), 71.68 (CH_2 , C-9), 121.75 (CH , C-2), 127.26 (CH , C-11), 129.57 (CH , C-12), 137.15 (CH , C-1), 137.82 (C, C-10), 143.24 (C, C-13) and 157.31 (C, C-3); m/z (ES^+) 664.3 (M^+ + H), 686.2 (M^+ + Na), 772.2 (M^+ + K).

(*S**,*S**),(*R**,*S**)-4,14-Dimethyl-3,15-bis-(toluene-4-sulfonyl)-9-oxa-6,12-dithia-3,15,21-triaza-bicyclo[15.3.1]henicosa-1(20),17(21),18-triene **236**

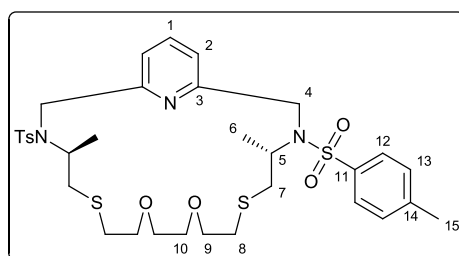


236

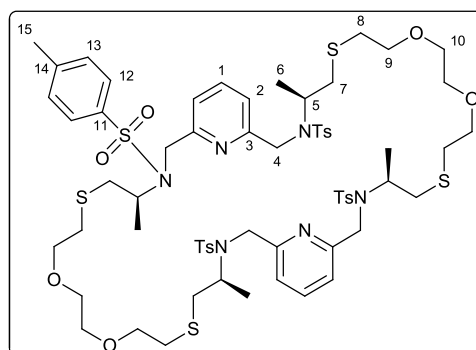
Using the general method described above, starting from ditosamide **199** (1.03 g, 1.8 mmol), 2,6-bis(bromomethyl)pyridine (492 mg, 1.9 mmol), and Cs₂CO₃ (3.04 g, 9.3 mmol), **236** was isolated as a thick pale yellow oil (791 mg, 65%) after purification by column chromatography (30% EtOAc in petrol), R_f = 0.74 (60% EtOAc in petrol); 0.60 (50% EtOAc in petrol), [α]_D²⁷ = 0 (c = 1.12, CHCl₃), (found [ES⁺] M⁺ + H, 664.2011. C₃₁H₄₂O₅N₃S₄ requires M, 664.2002); ν_{max} (ATR): 2918 (w)m 2850 (w), 1594 (m), 1456 (m), 1332 (s), 1152 (s), 1090 (s) and 1016 (w) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.02 (6H, d, J = 7.0 Hz, CH₃, H-6, (*S**,*R**)), 1.13 (6H, d, J = 7.0 Hz, CH₃, H-6, (*S**,*S**)), 2.35 – 2.48 (8H, m, CH₂, H-8, (*S**,*S**) + (*S**,*R**) + 2H, m, CH₂, H-7, (*S**,*R**)), 2.41 (6H, s, CH₃, H-14, (*S**,*S**)), 2.43 (6H, s, CH₃, H-14, (*S**,*R**)), 2.55 (2H, dd, J = 13.0, 7.0 Hz, CH₂, H-7, (*S**,*R**)), 2.66 (2H, dd, J = 13.0, 8.0, Hz, CH₂, H-7, (*S**,*S**)), 2.84 (2H, dd, J = 13.0, 6.0 Hz, CH₂, H-7, (*S**,*S**)), 3.39 – 3.51 (8H, m, CH₂, H-9, (*S**,*S**) + (*S**,*R**)), 3.84 – 3.93 (2H, m, CH, H-5, (*S**,*S**)), 3.99 – 4.08 (2H, m, CH, H-5, (*S**,*R**)), 4.21 (2H, d, J = 16.0 Hz, CH₂, H-4, (*S**,*R**)), 4.40 (2H, d, J = 16Hz, CH₂, H-4, (*S**,*S**)), 4.46 (2H, d, J = 16.0 Hz, CH₂, H-4, (*S**,*S**)), 4.71 (2H, d, J = 16.0 Hz, CH₂, H-4, (*S**,*R**)), 7.26 (4H, d, J = 8.0 Hz, CH, H-12, (*S**,*S**)), 7.30 (4H, d, J = 8.0 Hz, CH, H-12, (*S**,*R**)), 7.52 (2H, d, J = 8.0 Hz, CH, H-2, (*S**,*S**)), 7.66 – 7.71 (4H, m, CH, H-11, (*S**,*S**), + 2H, CH, H-2, (*S**,*R**), + 2H, CH, H-1, (*S**,*S**) + (*S**,*R**)) and 7.73 (4H, d, J = 8.0 Hz, CH, H-11, (*S**,*R**)); δ_C (CDCl₃, 125 MHz) 17.14, 17.18 (CH₃, C-6, (*S**,*R**)), 18.08, 18.13 (CH₃, CH₃, C-6, (*S**,*S**)), 21.45, 21.46 (CH₃, C-14, (*S**,*R**)), 21.50, 21.53 (CH₃, C-14, (*S**,*S**)), 31.99 (CH₂, C-8, (*S**,*S**)), 32.48 (CH₂, C-8, (*S**,*R**)), 38.14 (CH₂, C-7, (*S**,*S**)), 38.69 (CH₂, C-7, (*S**,*R**)), 49.01, 49.06 (CH₂, C-4, (*S**,*R**)), 49.68 (CH₂, C-4, (*S**,*S**)), 54.50, 54.63 (CH, C-5, (*S**,*R**)), 54.94, 55.07 (CH, C-5, (*S**,*S**)), 71.55 (CH₂,

C-9, (S^*,R^*), 71.64 (CH_2 , C-9, (S^*,S^*)), 121.71 (CH , C-2, (S^*,S^*)), 122.20 (CH , C-2, (S^*,R^*)), 127.09 (CH , C-11, (S^*,R^*)), 127.21 (CH , C-11, (S^*,S^*)), 129.56 (CH , C-12, (S^*,S^*)), 129.69 (CH , C-12, (S^*,R^*)), 137.15 (CH , C-1, (S^*,S^*)), 137.38 (CH , C-1, (S^*,R^*)), 137.57 (C , C-10, (S^*,R^*)), 137.75 (C , C-10, (S^*,S^*)), 143.34, 143.35 (C , C-13, (S^*,S^*) + (S^*,R^*)), 157.27 and 157.38 (C , C-3, (S^*,S^*) + (S^*,R^*)); m/z (ES^+) 664.6 ($\text{M}^+ + \text{H}$), 686.6 ($\text{M}^+ + \text{Na}$), 722.6 ($\text{M}^+ + \text{K}$).

(4*S*,17*S*)-4,17-Dimethyl-3,18-bis-(toluene-4-sulfonyl)-9,12-dioxa-6,15-dithia-3,18,24-triaza-bicyclo[18.3.1]tetracos-1(23),20(24),21-triene **229**



229

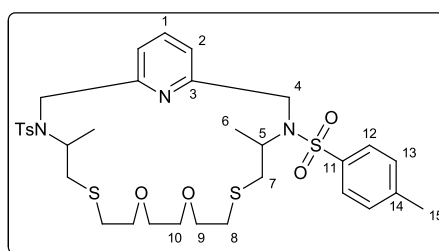


231

Using the general method described above, starting from ditosamide **196** (106 mg, 176 μmol), 2,6-bis(bromomethyl)pyridine (49.6 mg, 187 μmol), and Cs_2CO_3 (301 mg, 924 μmol) were isolated two products. The less polar product **229** ($R_f = 0.43$) was isolated as a near-colourless solid foam (55.1 mg, 44%) after purification by column chromatography (30% EtOAc in petrol), $R_f = 0.43$ (40% EtOAc in petrol), m.p. 45 – 47 $^\circ\text{C}$, (found [ES^+] $\text{M}^+ + \text{H}$, 708.2279. $\text{C}_{33}\text{H}_{46}\text{O}_6\text{N}_3\text{S}_4$ requires M , 708.2264); ν_{max} (ATR): 2922 (w), 2872 (w), 1596 (w), 1455 (m), 1334 (m), 1158 (s) and 1091 (s) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 1.11 (6H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.43 (6H, s, CH_3 , H-15), 3.44 – 2.54 (4H, m, CH_2 , H-8), 2.60 (2H, dd, $J = 13.0, 8.0$ Hz, CH_2 , H-7), 2.73 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7), 3.51 (4H, s, CH_2 , H-10), 3.52 – 3.59 (4H, m, CH_2 , H-9), 3.96 (2H, app. sext. $J = 7.0$ Hz, CH , H-5), 4.42 (4H, s, CH_2 , H-4), 7.29 (4H, d, $J = 8.0$ Hz, CH , H-13, tosyl), 7.53 (2H, d, $J = 8.0$ Hz, CH , H-2), 7.69 (1H, t, $J = 8.0$ Hz, CH , H-1), 7.73 (4H, d, $J = 8.0$ Hz, CH , H-12); δ_{C} (CDCl_3 , 125 MHz) 18.47 (CH_3 , C-6), 21.53 (CH_3 , C-15), 31.86 (CH_2 , C-8), 37.59 (CH_2 , C-7), 49.52 (CH_2 , CH_2 , C-4), 54.70 (CH , C-5), 70.44 (CH_2 , C-10), 71.37 (CH_2 , C-9), 122.00 (CH , C-2), 127.23 (CH , C-12),

129.59 (CH, C-13), 137.39 (CH, C-1), 137.69 (C, C-11), 143.26 (C, C-14), 157.36 (C, C-3); m/z (ES^+) 708.0 ($M^+ + H$), 730.3 ($M^+ + Na$), 746.1 ($M^+ + K$). Further elution afforded a second fraction, analysed as dimer product **231** as a pale yellow oil (4.9 mg, 4%), $R_f = 0.22$ (40% EtOAc in petrol), δ_H ($CDCl_3$, 400 MHz) 1.04 (12H, d, $J = 7.0$ Hz, CH_3 , H-6), 2.34 (4H, dd, $J = 13.0, 9.0$ Hz, CH_2 , H-7), 2.43 (12H, s, CH_3 , H-15), 2.51 – 2.60 (12H, m, CH_2 , H-7 + CH_2 , H-8), 3.48 – 3.57 (16H, CH_2 , H-10 + CH_2 , H-9), 3.99 – 4.10 (4H, m, CH , H-5), 4.37 (4H, d, $J = 16.0$ Hz, CH_2 , H-4), 4.49 (4H, d, $J = 16.0$ Hz, CH_2 , H-4), 7.30 (8H, d, $J = 8.0$ Hz, CH , H-13, tosyl), 7.54 (4H, d, $J = 8.0$ Hz, CH , H-2), 7.69 (2H, t, $J = 8.0$ Hz, CH , H-1) and 7.72 (8H, d, $J = 8.0$ Hz, CH , H-12); m/z (ES^+) 1415.3 ($M^+ + H$), 1437.2 ($M^+ + Na$), 1453.2 ($M^+ + K$).

(S^*,S^*),(R^*,S^*)-4,17-Dimethyl-3,18-bis-(toluene-4-sulfonyl)-9,12-dioxa-6,15-dithia-3,18,24-triaza-bicyclo[18.3.1]tetracos-1(23),20(24),21-triene **237**

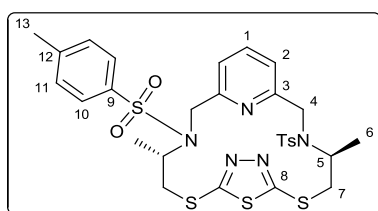


237

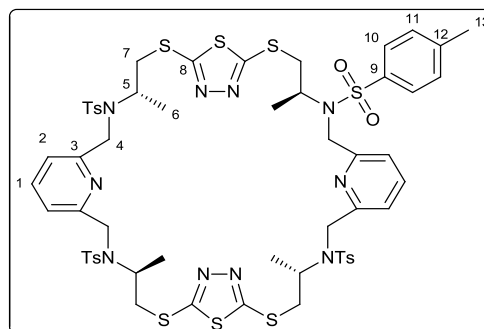
Using the general method described above, starting from ditosamide **204** (1.19 g, 2.0 mmol), 2,6-bis(bromomethyl)pyridine (553 mg, 2.1 mmol), and Cs_2CO_3 (3.28 g, 10.1 mmol), **237** was isolated the *title compound* as a colourless foam (643 mg, 46%) after purification by column chromatography (40% EtOAc in petrol), $R_f = 0.43$ (50% EtOAc in petrol), $[\alpha]_D^{27} = 0$ ($c = 1.22$, $CHCl_3$), m.p. 43 – 47 °C, (found [ES^+] $M^+ + Na$, 730.2092. $C_{33}H_{45}O_6N_3NaS_4$ requires M , 730.2083); ν_{max} (ATR): 2919 (w), 2862 (w), 1595 (w), 1455 (m), 1331 (m), 1151 (s), 1089 (s), 923 (m) and 867 (m) cm^{-1} ; δ_H ($CDCl_3$, 500 MHz) 1.03 (6H, d, $J = 7.0$ Hz, CH_3 , H-6, (S^*,R^*)), 1.10 (6H, d, $J = 7.0$ Hz, CH_3 , H-6, (S^*,S^*)), 2.41 (6H, s, CH_3 , H-15, (S^*,R^*)), 2.42 (6H, s, CH_3 , H-15, (S^*,S^*)), 2.43 – 2.55 (4H, m, CH_2 , H-7, (S^*,R^*) + 8H, CH_2 , H-8, (S^*,S^*) + (S^*,R^*)), 2.59 (2H, dd, $J = 13.0, 8.0$ Hz, CH_2 , H-7, (S^*,S^*)), 2.72 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7, (S^*,S^*)), 3.43 – 3.59 (16H, m, CH_2 , H-9,10, (S^*,S^*) + (S^*,R^*)), 3.90 – 3.99 (2H, m, CH , H-5, (S^*,S^*)), 4.00 – 4.11 (2H, m, CH , H-5, (S^*,R^*)), 4.24 (2H, d, $J = 16.0$ Hz, CH_2 , H-

4, (S^*,R^*)), 4.42 (4H, s, CH_2 , H-4, (S^*,S^*)), 4.61 (2H, d, $J = 16.0$ Hz, CH_2 , H-4, (S^*,R^*)), 7.28 (4H, d, $J = 8.0$ Hz, CH , H-13, (S^*,R^*)), 7.29 (4H, d, $J = 8.0$ Hz, CH , H-13, (S^*,S^*)), 7.51 (2H, d, $J = 8.0$ Hz, CH , H-2, (S^*,S^*)), 7.62 (2H, d, $J = 8$ Hz, CH , H-2, (S^*,R^*)), 7.67 (1H, t, $J = 8.0$ Hz, CH , H-1, (S^*,S^*)), 7.70 – 7.72 (1H, m, CH , H-1, (S^*,R^*)) and 7.71 (8H, d, $J = 8.0$ Hz, CH , H-12, (S^*,S^*) + (S^*,R^*)); δ_{C} (CDCl_3 , 125 MHz) 17.39, 17.44 (CH_3 , C-6 (S^*,R^*)), 18.35, 18.41 (CH_3 , C-6, (S^*,S^*)), 21.40, 21.46 (CH_3 , C-15, (S^*,S^*) + (S^*,R^*)), 31.78, 31.93 (CH_2 , C-8, (S^*,S^*) + (S^*,R^*)), 37.50 (CH_2 , C-7, (S^*,S^*)), 38.03 (CH_2 , C-7, (S^*,R^*)), 48.78, 48.80, 48.88 (CH_2 , CH_2 , C-4, (S^*,R^*)), 49.41 (CH_2 , C-4, (S^*,S^*)), 54.11, 54.25 (CH , C-5, (S^*,R^*)), 54.57, 54.72 (CH , C-5, (S^*,S^*)), 70.29, 70.33 (CH_2 , C-10, (S^*,S^*) + (S^*,R^*)), 71.05, 71.28 (CH_2 , C-9, (S^*,S^*) + (S^*,R^*)), 121.91 (CH , C-2, (S^*,S^*)), 122.13 (CH , C-2, (S^*,R^*)), 127.01, 127.06, 127.12, 127.16 (CH , C-12, (S^*,S^*) + (S^*,R^*)), 129.52, 129.61 (CH , C-13, (S^*,S^*) + (S^*,R^*)), 137.32 (CH , C-1, (S^*,S^*) + (S^*,R^*)), 137.46, 137.60 (C , C-11, (S^*,S^*) + (S^*,R^*)), 143.19, 143.26 (C , C-14, (S^*,S^*) + (S^*,R^*)), 157.28 and 157.29 (C , C-3, (S^*,S^*) + (S^*,R^*)); m/z (ES^+) 730.6 (M^+ + Na), 746.6 (M^+ + K).

(4S,13S)-4,13-Dimethyl-3,14-bis-(toluene-4-sulfonyl)-6,11,21-trithia-3,8,9,14,20-pentaaza-tricyclo[14.3.1.1^{7,10}]henicosa-1(19),7,9,16(20),17-pentaene **233**



233

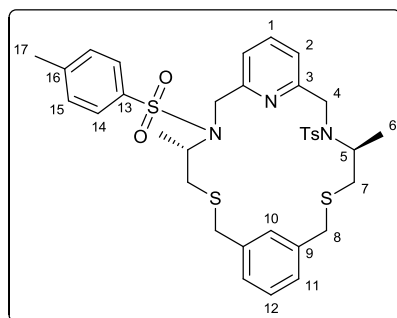


243

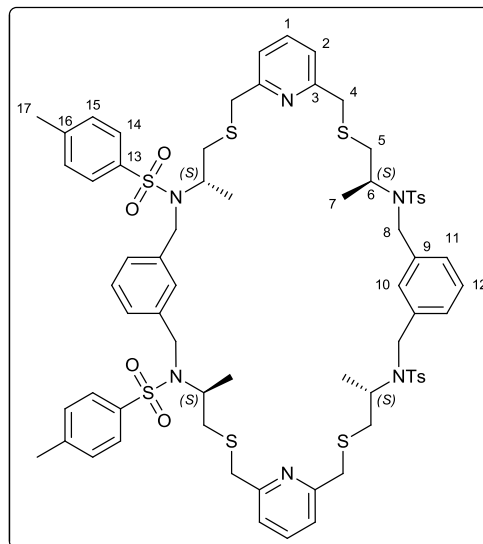
Using the general method described above, starting from ditosamide **201** (703 mg, 1.2 mmol), 2,6-bis(bromomethyl)pyridine (324 mg, 1.2 mmol), and Cs_2CO_3 (2.01 g, 6.2 mmol) were isolated two products. The less polar product **233** ($R_f = 0.57$) was isolated as a solid colourless foam (322 mg, 39%) after purification by column chromatography (40% EtOAc in petrol), $R_f = 0.57$ (50% EtOAc in petrol), 0.26 (40% EtOAc in petrol), $[\alpha]_D^{29} = +78$ ($c = 3.06$, CHCl_3), m.p. 87.0 – 89.0 °C, (found C, 51.98; H, 5.07; N, 9.81;

S, 22.76%. $C_{29}H_{33}N_5O_4S_5$ requires C, 51.53; H, 4.92; N, 10.36; S, 23.72%. Found [ES⁺] $M^+ + H$, 676.1215. $C_{29}H_{34}O_4N_5S_5$ requires M , 676.1209); ν_{\max} (ATR): 2927 (w), 1595 (m), 1575 (w), 1456 (m), 1334 (s), 1151 (s), 1089 (m), 924 (w) and 873 (m) cm^{-1} ; δ_H (CDCl₃, 400 MHz) 1.28 (6H, d, $J = 7.0$ Hz, **CH**₃, H-6), 2.46 (6H, s, **CH**₃, H-13), 3.36 (2H, dd, $J = 14.0, 8.0$ Hz, **CH**₂, H-7), 3.54 (2H, dd, $J = 14.0, 7.0$ Hz, **CH**₂, H-7), (2H, app. sext. $J = 7.0$ Hz, **CH**, H-5), 4.36 (4H, s, **CH**₂, H-4), 7.33 (4H, d, $J = 8.0$ Hz, **CH**, H-11), 7.35 (2H, d, $J = 8.0$ Hz, **CH**, H-2), 7.59 (1H, t, $J = 8.0$ Hz, **CH**, H-1) and 7.77 (4H, d, $J = 8.0$ Hz, **CH**, H-10); δ_C (CDCl₃, 125 MHz) 16.86, 16.98 (**CH**₃, C-6), 21.47, 21.57 (**CH**₃, C-13), 40.40 (**CH**₂, C-7), 53.09 (**CH**₂, C-4), 54.82, 54.98 (**CH**, C-5), 121.68 (**CH**, C-2), 127.22, 127.33 (**CH**, C-10), 129.44, 129.82 (**CH**, C-11), 137.47 (**CH**, C-1), 138.02 (**C**, C-9), 143.73 (**C**, C-12), 156.26 (**C**, C-3) and 165.15 (**C**, C-8); m/z (ES⁺) 698.5 ($M^+ + Na$), 714.4 ($M^+ + K$). Further elution afforded a second fraction, the dimer product **243** as a pale yellow solid foam (28.2 mg, 3%), $R_f = 0.18$ (40% EtOAc in petrol), m.p. 118 – 122 °C (decomp.), δ_H (CDCl₃, 400 MHz) 1.19 (12H, d, $J = 7.0$ Hz, **CH**₃, H-6), 2.38 (12H, s, **CH**₃, H-13), 3.30 (4H, dd, $J = 14.0, 10.0$ Hz, **CH**₂, H-7), 3.53 (4H, dd, $J = 14.0, 5.0$ Hz, **CH**₂, H-7), 4.17 – 4.24 (4H, m, **CH**, H-5), 4.27 (4H, d, $J = 16.0$ Hz, **CH**₂, H-4), 4.51 (4H, d, $J = 16.0$ Hz, **CH**₂, H-4), 7.18 (8H, d, $J = 8.0$ Hz, **CH**, H-11), 7.42 (4H, d, $J = 8.0$ Hz, **CH**, H-2), 7.58 (8H, d, $J = 8.0$ Hz, **CH**, H-10) and 7.64 (2H, t, $J = 8.0$ Hz, **CH**, H-1); δ_C (CDCl₃, MHz) 18.70 (**CH**₃, C-6), 21.53 (**CH**₃, C-13), 38.11 (**CH**₂, C-7), 50.27 (**CH**₂, C-4), 54.86 (**CH**, C-5), 122.61 (**CH**, C-2), 127.30 (**CH**, C-10), 129.46 (**CH**, C-11), 137.47 (**CH**, C-1 + **C**, C-9), 143.41 (**C**, C-12), 156.74 (**C**, C-3) and 164.56 (**C**, C-8); m/z (ES⁺) 1368.9 ($M^+ + NH_4$), 1373.8 ($M^+ + Na$).

(4*S*,16*S*)-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triaza-
tricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **240**



240

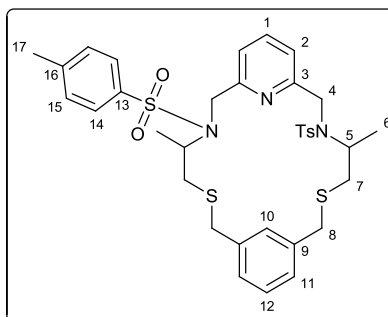


242

Using the general method described above, starting from ditosamide **210** (856 mg, 1.4 mmol), 2,6-bis(bromomethyl)pyridine (379 mg, 1.4 mmol), and Cs₂CO₃ (2.41 g, 7.4 mmol) were isolated two products. The less polar compound **240** (R_f = 0.54) was the *title compound* isolated as a colourless foam (377 mg, 41%) after purification by column chromatography (40% EtOAc in petrol), R_f = 0.54 (60% EtOAc in petrol). $[\alpha]_D^{29} = -9$ (c = 1.78, CHCl₃), m.p. 141 – 143 °C, (found C, 57.69; H, 5.69; N, 5.54; S, 17.25%. C₃₅H₄₁N₃O₄S₄·½CH₂Cl₂ requires C, 57.74; H, 5.73; Cl, 4.80; N, 5.69; S, 17.37%. Found [ES⁺] M⁺ + Na, 718.1868. C₃₅H₄₁O₄N₃NaS₄ requires M, 718.1872); ν_{max} (ATR): 2975 (w), 1594 (w), 1465 (w), 1333 (m), 1148 (s), 1088 (m), 1015 (w) and 815 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.00 (6H, d, J = 7.0 Hz, CH₃, H-6), 2.21 (2H, dd, J = 13.0, 9.0 Hz, CH₂, H-7), 2.42 (6H, s, CH₃, H-17), 2.51 (2H, dd, J = 10.0, 6.0 Hz, CH₂, H-7), 3.54 (2H, d, J = 14.0 Hz, CH₂, H-8), 3.58 (2H, d, J = 14.0 Hz, CH₂, H-8), 3.96 (2H, m, CH, H-5), 4.21 (2H, d, J = 16.0 Hz, CH₂, H-4), 4.35 (2H, d, J = 16.0 Hz, CH₂, H-4), 7.06 (2H, d, J = 8.0 Hz, CH, H-11), 7.17 (1H, s, CH, H-10), 7.18 (1H, t, J = 7.0 Hz, CH, H-12), 7.26 (4H, d, J = 8.0 Hz, CH, H-15), 7.34 (2H, d, J = 8.0 Hz, CH, H-2), 7.55 (1H, t, J = 8.0 Hz, CH, H-1) and 7.67 (4H, d, J = 8.0 Hz, CH, H-14); δ_C (CDCl₃, 125 MHz) 18.32 (CH₃, C-6), 21.51 (CH₃, C-17), 35.62 (CH₂, C-7), 36.25 (CH₂, C-8),

48.93 (CH₂, C-4), 54.53 (CH, C-5), 121.64 (CH, C-2), 127.15 (CH, C-14), 127.65 (CH, C-11), 128.73 (CH, C-12), 129.17 (CH, C-10), 129.55 (CH, C-15), 137.05 (CH, C-1), 137.96 (C, C-13), 138.43 (C, C-9), 143.12 (C, C-16) and 157.09 (C, C-3); m/z (ES⁺) 718.5 (M⁺ + Na), 734.7 (M⁺ + K). Further elution afforded a second fraction, dimer-type product **242**, isolated as a near-colourless foam (154 mg, 8%), R_f = 0.32 (60% EtOAc in petrol), $[\alpha]_D^{32}$ = -18 (c = 2.61, CHCl₃), m.p. 162 – 167 °C, ν_{max} (ATR): 3025 (w), 2976 (w), 2921 (w), 1593 (m), 1493 (w), 1454 (m), 1332 (m), 1215 (w), 1150 (s) and 1089 (s) cm⁻¹; δ_H (CDCl₃, 500 MHz) 1.00 (12H, d, J = 7.0 Hz, CH₃, H-6), 2.21 (4H, dd, J = 13.0, 9.0 Hz, CH₂, H-7), 2.42 (12H, s, CH₃, H-17), 2.52 (4H, dd, J = 13.0, 6.0 Hz, CH₂, H-7), 3.54 (4H, d, J = 14.0 Hz, CH₂, H-8), 3.58 (4H, d, J = 14.0 Hz, CH₂, H-8), 3.96 (4H, app. sext, J = 7.0 Hz, CH, H-5), 4.22 (4H, d, J = 16.0 Hz, CH₂, H-4), 4.35 (4H, d, J = 16.0 Hz, CH₂, H-4), 7.07 (2H, d, J = 7.5 Hz, CH, H-11), 7.17 (1H, br. s., CH, H-10), 7.18 (2H, t, J = 7.5 Hz, CH, H-12), 7.26 (8H, d, J = 8.5 Hz, CH, H-15), 7.34 (4H, d, J = 7.5 Hz, CH, H-2), 7.55 (2H, t, J = 7.5 Hz, CH, H-1) and 7.67 (8H, d, J = 8.5 Hz, CH, H-14); δ_C (CDCl₃, 125 MHz) 18.32 (CH₃, C-6), 21.51 (CH₃, C-17), 35.62 (CH₂, C-7), 36.26 (CH₂, C-8), 48.93 (CH₂, C-4), 54.53 (CH, C-5), 121.64 (CH, C-2), 127.15 (CH, C-14), 127.65 (CH, C-11), 128.73 (CH, C-12), 129.17 (CH, C-10), 129.55 (CH, C-15), 137.04 (CH, C-1), 137.97 (C, C-13), 138.43 (C, C-9), 143.11 (C, C-16) and 157.09 (C, C-3); m/z (ES⁺) 1391 (M⁺ + H), 1413 (M⁺ + Na); m/z (ES⁻) 1425 (M⁻ + Cl).

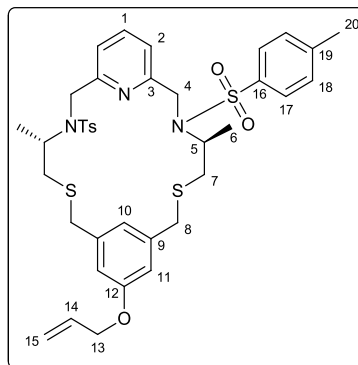
(S*,S*), (R*,S*)-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triazatricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **241**



241

Using the general method described above, starting from ditosamide **211** (397 mg, 669 μmol), 2,6-bis(bromomethyl)pyridine (176 mg, 669 μmol), and Cs_2CO_3 (1.10 g, 3.4 mmol) **241** was isolated as a solid colourless foam (193 mg, 45%) after purification by column chromatography (40% EtOAc in petrol), $R_f = 0.54$ (60% EtOAc in petrol), $[\alpha]_D^{26} = 0$ ($c = 1.52$, CHCl_3), m.p. 114.5 – 116.0 $^\circ\text{C}$, (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 718.1866. $\text{C}_{35}\text{H}_{41}\text{O}_4\text{N}_3\text{NaS}_4$ requires M , 718.1872); ν_{max} (ATR): 2927 (w), 1592 (w), 1456 (m), 1331 (s), 1148 (s), 1090 (s), 1014 (m) and 862 (m) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 0.88 (6H, d, $J = 7.0$ Hz, CH_3 , H-6, (S^*,R^*)), 1.00 (6H, d, $J = 7.0$ Hz, CH_3 , H-6, (S^*,S^*)), 1.90 (2H, dd, $J = 12.0, 9.0$ Hz, CH_2 , H-7, (S^*,R^*)), 2.08 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7, (S^*,R^*)), 2.21 (2H, dd, $J = 13.0, 9.0$ Hz, CH_2 , H-7, (S^*,S^*)), 2.42 (6H, s, CH_3 , H-17, (S^*,S^*)), 2.45 (6H, s, CH_3 , H-17, (S^*,R^*)), 2.51 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-7, (S^*,S^*)), 3.51 – 3.62 (8H, m, CH_2 , H-8, (S^*,S^*) + (S^*,R^*)), 3.96 (2H, m, CH, H-5, (S^*,S^*)), 4.09 (2H, d, $J = 16.0$ Hz, CH_2 , H-4, (S^*,R^*)), 4.11 – 4.19 (2H, m, CH, H-5, (S^*,R^*)), 4.21 (2H, d, $J = 16.0$ Hz, CH_2 , H-4, (S^*,S^*)), 4.34 (2H, d, $J = 16.0$ Hz, CH_2 , H-4, (S^*,S^*)), 4.49 (2H, d, $J = 16.0$ Hz, CH_2 , H-4, (S^*,R^*)), 7.06 (2H, d, $J = 8.0$ Hz, CH, H-11, (S^*,S^*)), 7.08 (1H, s, CH, H-10, (S^*,R^*)), 7.10 (2H, d, $J = 8.0$ Hz, CH, H-11, (S^*,R^*)), 7.16 (1H, s, CH, H-10, (S^*,S^*)), 7.18 (1H, t, $J = 7.0$ Hz, CH, H-12, (S^*,S^*)), 7.22 (1H, t, $J = 7.0$ Hz, CH, H-12, (S^*,R^*)), 7.26 (4H, d, $J = 9.0$ Hz, CH, H-15, (S^*,S^*)), 7.31 (4H, d, $J = 8.0$ Hz, CH, H-15, (S^*,R^*)), 7.34 (2H, d, $J = 8.0$ Hz, CH, H-2, (S^*,S^*)), 7.49 – 7.58 (2H, m, CH, H-1 (S^*,S^*) + (S^*,R^*) + 2H, CH, H-2, (S^*,R^*)), 7.67 (4H, d, $J = 8.0$ Hz, CH, H-14, (S^*,S^*)) and 7.71 (4H, d, $J = 8.0$ Hz, CH, H-14, (S^*,R^*)); δ_{C} (CDCl_3 , 100 MHz) 17.63 (CH_3 , C-6, (S^*,R^*)), 18.19 (CH_3 , C-6, (S^*,S^*)), 21.44, 21.47 (CH_3 , C-17, (S^*,S^*) + (S^*,R^*)), 35.50 (CH_2 , C-7, (S^*,S^*)), 36.10 (CH_2 , C-7, (S^*,R^*)), 36.14, 36.17 (CH_2 , C-8, (S^*,S^*) + (S^*,R^*)), 48.57 (CH_2 , C-4, (S^*,R^*)), 48.79 (CH_2 , C-4, (S^*,S^*)), 53.69 (CH, C-5, (S^*,R^*)), 54.43 (CH, C-5, (S^*,S^*)), 121.53, 121.82 (CH, C-2, (S^*,S^*) + (S^*,R^*)), 126.98, 127.15 (CH, C-14, (S^*,S^*) + (S^*,R^*)), 127.56, 127.84 (CH, phenyl, (S^*,S^*) + (S^*,R^*)), 128.49, 128.63, 128.71, 129.08 (CH, CH, phenyl, (S^*,S^*) + (S^*,R^*)), 129.48, 129.63 (CH, C-15, (S^*,S^*) + (S^*,R^*)), 136.96, 137.23 (CH, C-1, (S^*,S^*) + (S^*,R^*)), 137.45, 137.81 (C, C-13, (S^*,S^*) + (S^*,R^*)), 138.07, 138.31 (C, C-9, (S^*,S^*) + (S^*,R^*)), 143.05, 143.28 (C, C-16, (S^*,S^*) + (S^*,R^*)), 156.97 and 157.09 (C, C-3, (S^*,S^*) + (S^*,R^*)); m/z (ES^+) 696.8 ($\text{M}^+ + \text{H}$), 718.6 ($\text{M}^+ + \text{Na}$).

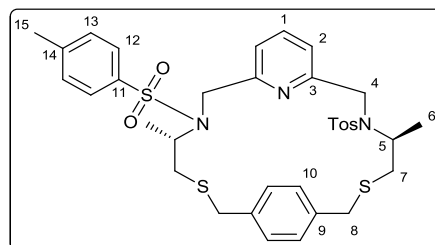
(4*S*,16*S*)-10-allyloxy-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-dithia-3,17,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **282**



282

Using the general method described above, starting from ditosamide **226** (2.19 g, 3.4 mmol), 2,6-bis(bromomethyl)pyridine (890 mg, 3.4 mmol), and Cs₂CO₃ (5.53 g, 17.0 mmol) **282** was isolated as a near-colourless foam (2.13 g, 84%) after purification by column chromatography (20% EtOAc in petrol), R_f = 0.56 (50% EtOAc in petrol), [α]_D³² = -5.3 (c = 2.17, CHCl₃), m.p. 139 – 143 °C, (found [ES⁺] M⁺ + H, 752.2307. C₃₈H₄₆O₅N₃S₄ requires M, 752.2315); ν_{max} (ATR): 2977 (w), 2921 (w), 1591 (m), 1453 (m), 1331 (m), 1145 (s), 1089 (m), 864 (m) cm⁻¹; δ_H (CDCl₃, 400 MHz) 1.01 (6H, d, J = 6.5 Hz, CH₃, H-6), 2.21 (2H, dd, J = 12.5, 9.0 Hz, CH₂, H-7), 2.42 (6H, s, CH₃, H-20), 2.53 (2H, dd, J = 12.5, 6.0 Hz, CH₂, H-7), 3.50 (2H, d, J = 14.0 Hz, CH₂, H-8), 3.55 (2H, d, J = 14.0 Hz, CH₂, H-8), 3.96 (2 H, app. sext, J = 7.0 Hz, CH, H-5), 4.22 (2H, d, J = 16.0 Hz, CH₂, H-4), 4.38 (2H, d, J = 16.0 Hz, CH₂, H-4), 4.49 (2H, d, J = 4.5 Hz, CH₂, H-13), 5.29 (1H, d, J = 10.0 Hz, CH₂, H-15), 5.42 (1H, d, J = 17.0 Hz, CH₂, H-15), 6.05 (1H, ddt, J = 17.0, 10.0, 4.5 Hz, CH, H-14), 6.67 (2H, s, CH, H-11), 6.76 (1H, s, CH, H-10), 7.27 (4H, d, J = 8.0 Hz, CH, H-18), 7.34 (2H, d, J = 7.5 Hz, CH, H-2), 7.55 (1H, t, J = 7.5 Hz, CH, H-1) and 7.68 (4H, d, J = 8.0 Hz, CH, H-17); δ_C (CDCl₃, 125 MHz) 18.26 (CH₃, C-6), 21.44, 21.47 (CH₃, C-20), 35.72 (CH₂, C-7), 36.37 (CH₂, C-8), 49.01 (CH₂, C-4), 54.59 (CH, C-5), 68.63 (CH₂, C-13), 113.93 (CH, C-11), 117.68 (CH₂, C-15), 121.57 (CH, C-10), 121.79 (CH, C-2), 127.07 (CH, C-17), 129.51 (CH, C-18), 132.97 (CH, C-14), 136.95 (CH, C-1), 137.93 (C, C-16), 139.84 (C, C-9), 143.09 (C, C-19), 157.02 (C, C-3) and 158.73 (C, C-12); m/z (ES⁺) 752 (M⁺ + H), 774 (M⁺ + Na), 790 (M⁺ + K).

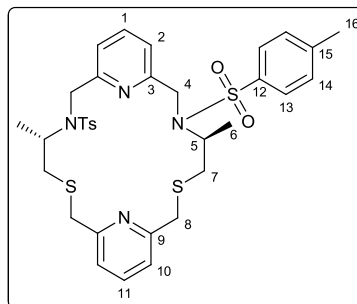
(5*S*,15*S*)-5,15-Dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,24-triaza-
tricyclo[17.2.2.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **239**



239

Using the general method described above, starting from ditosamide **214** (672 mg, 1.1 mmol), 2,6-bis(bromomethyl)pyridine (366 mg, 1.4 mmol), and Cs₂CO₃ (1.51 g, 4.6 mmol) was isolated the *title compound* (269 mg, 34%) as a pale yellow oil after purification by column chromatography (30% EtOAc in petrol), R_f = 0.69 (50% EtOAc in petrol), [α]_D³⁰ = + 6 (c = 1.46, CHCl₃), (found [ES⁺] M⁺ + H, 696.2064. C₃₅H₄₂O₄N₃S₄ requires *M*, 696.2053. Found [ES⁺] M⁺ + Na, 718.1872. C₃₅H₄₁O₄N₃NaS₄ requires *M*, 718.1872); ν_{\max} (ATR): 2921 (w), 2951 (w), 1594 (m), 1575 (w), 1455 (m), 1330 (s), 1151 (s) and 1090 (s) cm⁻¹; δ_{H} (CDCl₃, 500 MHz) 0.80 (6H, d, *J* = 6.5 Hz, CH₃, H-6), 2.17 (2H, dd, *J* = 12.5, 7.0 Hz, CH₂, H-7), 2.45 (6H, s, CH₃, H-15), 2.52 (2H, dd, *J* = 12.5, 8.5 Hz, CH₂, H-7), 3.47 (2H, d, *J* = 14.0 Hz, CH₂, H-8), 3.55 (2H, d, *J* = 14.0 Hz, CH₂, H-8), 3.94 (2H, ddq, *J* = 8.5, 7.0, 6.5, CH, H-5), 3.99 (2H, d, *J* = 16.0 Hz, CH₂, H-4), 4.49 (2H, d, *J* = 16.0 Hz, CH₂, H-4), 7.11 (4H, s, CH, H-10), 7.31 (4H, d, *J* = 8.0 Hz, CH, H-13), 7.50 (2H, d, *J* = 7.5 Hz, CH, H-2), 7.62 (1H, t, *J* = 7.5 Hz, CH, H-1) and 7.73 (4H, d, *J* = 8.0 Hz, CH, H-12); δ_{C} (CDCl₃, 125 MHz) 20.25 (CH₃, C-6), 21.50, 21.54 (CH₃, C-15), 34.51 (CH₂, C-5), 36.09 (CH₂, C-8), 48.80 (CH₂, C-4), 53.52, 53.58 (CH, C-5), 122.10 (CH, C-2), 127.23 (CH, C-12), 128.96 (CH, C-10), 129.45 (CH, C-13), 136.85 (C, C-9), 137.11 (CH, C-1), 137.71 (C, C-11), 143.11 (C, C-14) and 157.42 (C, C-3); *m/z* (ES⁺) 696.6 (M⁺ + H), 718.6 (M⁺ + Na), 734.6 (M⁺ + K), 1414.1 (2M⁺ + Na).

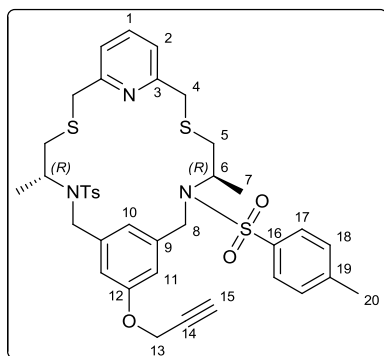
(5*S*,15*S*)-5,15-Dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23,24-tetraaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **238**



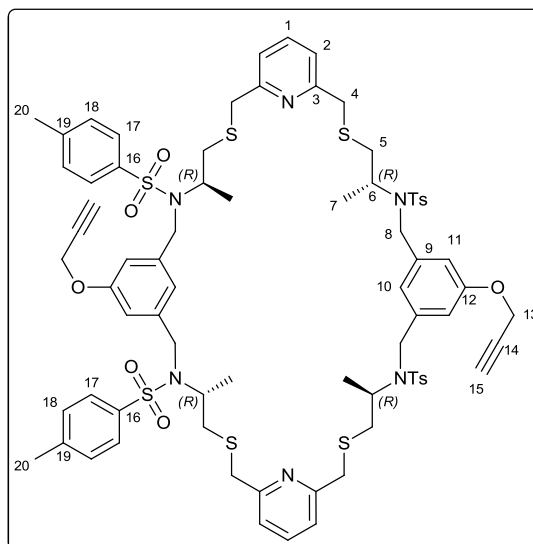
238

Using the general method described above, starting from ditosamide **218** (478 mg, 806 μmol), 2,6-bis(bromomethyl)pyridine (213 mg, 810 μmol), and Cs_2CO_3 (1.34 g, 4.1 mmol) **238** was isolated as a viscous, colourless oil (477 mg, 85%) after purification by column chromatography (50% EtOAc in petrol), $R_f = 0.72$ (80% EtOAc in petrol), $[\alpha]_D^{28} = 62^\circ$ ($c = 2$, CHCl_3), (found $[\text{ES}^+] M^+ + \text{Na}$, 719.1825. $\text{C}_{34}\text{H}_{40}\text{O}_4\text{N}_4\text{NaS}_4$ requires M , 719.1825), ν_{max} (ATR): 2972 (w), 2924 (w), 1591 (m), 1573 (m), 1493 (w), 1453 (m), 1332 (s), 1152 (s), 1089 (s), 993 (m) cm^{-1} ; δ_{H} (CDCl_3 , 400 MHz) 1.01 (6H, d, $J = 6.5$ Hz, CH_3 , H-6), 2.37 (6H, s, CH_3 , H-16), 2.58 (2H, dd, $J = 13.0, 8.0$ Hz, CH_2 , H-7), 2.70 (2H, dd, $J = 13.0, 6.5$ Hz, CH_2 , H-7), 3.54 (2H, d, $J = 13.5$ Hz, CH_2 , H-8), 3.64 (2H, d, $J = 13.5$ Hz, CH_2 , H-8), 4.00 (2H, dqin, $J = 8.0, 6.5$ Hz, CH , H-5), 4.32 (2H, d, $J = 16.5$ Hz, CH_2 , H-4), 4.45 (2H, d, $J = 16.5$ Hz, CH_2 , H-4), 7.06 (2H, d, $J = 8.0$ Hz, CH , H-10), 7.21 (2H, d, $J = 8.0$ Hz, CH , H-2), 7.41 (4H, d, $J = 8.0$ Hz, CH , H-14), 7.54 (1H, t, $J = 8.0$ Hz, CH , H-11), 7.58 (1H, t, $J = 8.0$ Hz, CH , H-1) and 7.65 (4H, d, $J = 8.0$ Hz, CH , H-13); δ_{C} (CDCl_3 , 100 MHz) 18.61 (CH_3 , C-6), 21.46 (CH_3 , C-16), 35.99 (CH_2 , C-7), 37.95 (CH_2 , C-8), 49.22 (CH_2 , C-4), 54.53 (CH , C-5), 121.02 (CH , C-10), 121.75 (CH , C-2), 127.16 (CH , C-13), 129.50 (CH , C-14), 137.07 (CH , C-1), 137.50 (CH , C-11), 137.79 (C, C-12), 143.12 (C, C-15), 157.09 (C, C-3) and 157.88 (C, C-9); m/z (ES^+) 697 ($M^+ + \text{H}$), 719 ($M^+ + \text{Na}$); m/z (ES^-) 731 ($M^- + \text{Cl}$).

(5*R*,15*R*)-10-But-3-ynyl-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(23),8,10,12(24),19,21-hexaene **260**



260

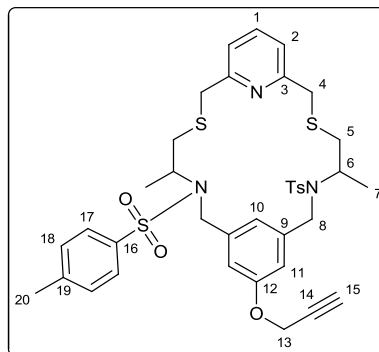


261

Dibromide species **287** (780 mg, 2.5 mmol), and Cs₂CO₃ (3.92 g, 12.0 mmol) were added to a solution of tosyl protected spacer **219** (1.45 g, 2.4 mmol) in dry DMF (700 mL). After stirring for 2 days at room temperature, the solvent was removed *in vacuo* and azeotroping to dryness using toluene. Column chromatography (40% EtOAc in petrol) of the residue afforded 2 distinct products. The less polar product (*R_f* = 0.39) was the *title compound* **260** (1.54 g, 84%) isolated as a colourless solid foam, *R_f* = 0.39 (50% EtOAc in petrol), $[\alpha]_D^{24} = -11$ (*c* = 2.54, CHCl₃), m.p. 89 – 91 °C, (found C, 59.51; H, 5.85; N, 5.38; S, 15.53%. C₃₈H₄₃N₃O₅S₄·H₂O requires C, 59.42; H, 5.91; N, 5.47; S, 16.70%. Found [ES⁺] M⁺ + H, 750.2151. C₃₈H₄₄O₅N₃S₄ requires *M*, 750.2159); ν_{\max} (ATR): 3281 (w), 3268 (w), 2972 (w), 2919 (w), 1865 (w), 1593 (m), 451 (m), 328 (m), 1288 (m), 1150 (s), 1089 (s) and 1053 (m) cm⁻¹; δ_H (CDCl₃, 400 MHz) 1.02 (6H, d, *J* = 7.0 Hz, CH₃, H-7), 2.08 (2H, dd, *J* = 13.0, 8.0 Hz, CH₂, H-5), 2.38 (2H, dd, *J* = 13.0, 6.5 Hz, CH₂, H-5), 2.42 (6H, s, CH₃, H-20), 2.57 (1H, t, *J* = 2.0 Hz, CH, H-15), 3.55 (2H, d, *J* = 14.0 Hz, CH₂, H-4), 3.60 (2H, d, *J* = 14.0 Hz, CH₂, H-4), 3.86 (2H, d, *J* = 16.0 Hz, CH₂, H-8), 4.00 (2H, dqd, *J* = 8.0, 7.0, 6.5 Hz, CH, H-6), 4.65 (2H, dd, *J* = 15.0, 2.0 Hz, CH₂, H-13), 4.66 (1H, d, *J* = 16.0 Hz, CH₂, H-8), 4.73 (2H, dd, *J* = 15.0, 2.0 Hz, CH₂, H-13), 6.84 (2H, s, CH, H-11), 6.94 (1H, s, CH, H-10), 7.06 (2H, d, *J* =

7.5 Hz, **CH**, H-2), 7.30 (4H, d, $J = 8.0$ Hz, **CH**, H-18), 7.58 (1H, t, $J = 7.5$ Hz, **CH**, H-1) and 7.71 (4H, d, $J = 8.0$ Hz, **CH**, H-17); δ_C (CDCl₃, 100 MHz) 16.92 (**CH**₃, C-7), 21.46 (**CH**₃, C-20), 37.16 (**CH**₂, C-5), 37.96 (**CH**₂, C-4), 47.72 (**CH**₂, C-8), 54.73 (**CH**, C-6), 55.77 (**CH**₂, C-13), 75.67 (**CH**, C-15), 78.27 (**C**, C-14), 113.47 (**CH**, C-11), 120.53 (**CH**, C-10), 121.01 (**CH**, C-2), 126.95 (**CH**, C-17), 129.73 (**CH**, C-18), 137.52 (**C**, C-16), 137.58 (**C**, C-1), 139.61 (**C**, C-9), 143.31 (**C**, C-19), 157.48 (**C**, C-12) and 158.02 (**C**, C-3); m/z (ES⁺) 750 (M⁺ + H), 772 (M⁺ + Na), 1521 (2M⁺ + Na); m/z (ES⁻) 784 (M⁻ + Cl), 1533 (2M⁻ + Cl). Further elution afforded a second product **261** as a colourless solid foam (78.7 mg, 5%), $R_f = 0.34$ (50% EtOAc in petrol), (found C, 60.49; H, 6.09; N, 5.72%. requires C, 60.85; H, 5.78; N, 5.60%); ν_{\max} (ATR): 3281 (w), 3269 (w), 2976 (w), 2954 (w), 2872 (w), 1671 (w), 1594 (m), 1451 (m), 1330 (m), 1151 (s) and 1089 (m) cm⁻¹; δ_H (CDCl₃, 400 MHz) 0.97 (12H, d, $J = 7.0$ Hz, **CH**₃, H-7), 2.16 (4H, dd, $J = 13.5, 8.0$ Hz, **CH**₂, H-5), 2.41 (4H, dd, $J = 13.5, 6.5$ Hz, **CH**₂, H-5), 2.43 (12H, s, **CH**₃, H-20), 2.54 (2 H, t, $J = 2.0$ Hz, **CH**, H-15), 3.61 (8H, app.t, $J = 14.0$ Hz, **CH**₂, H-4), 3.98 - 4.08 (4H, m, **CH**, H-6), 4.03 (4H, d, $J = 15.5$ Hz, **CH**₂, H-8), 4.48 (4H, d, $J = 15.5$ Hz, **CH**₂, H-8), 4.60 (4H, d, $J = 2.0$ Hz, **CH**₂, H-13), 6.84 (4H, s, **CH**, H-11), 6.98 (2H, s, **CH**, H-10), 7.08 (4H, d, $J = 8.0$ Hz, **CH**, H-2), 7.30 (8H, d, $J = 8.0$ Hz, **CH**, H-18), 7.54 (2H, t, $J = 8.0$ Hz, **CH**, H-1) and 7.69 (8H, d, $J = 8.0$ Hz, **CH**, H-17); δ_C (CDCl₃, 100 MHz) 17.28 (**CH**₃, C-7), 21.52 (**CH**₃, C-20), 37.35 (**CH**₂, C-5), 37.85 (**CH**₂, C-4), 47.26 (**CH**₂, C-8), 53.89 (**CH**, C-6), 55.82 (**CH**₂, C-13), 75.84 (**CH**, C-15), 78.39 (**C**, C-14), 113.76 (**CH**, C-11), 120.78 (**CH**, H-10), 121.21 (**CH**, C-2), 127.06 (**CH**, C-17), 129.74 (**CH**, C-18), 137.28 (**CH**, C-1), 137.71 (**C**, C-19), 139.97 (**C**, C-9), 143.30 (**C**, C-16), 157.67 (**C**, C-12) and 157.94 (**C**, C-3); m/z (ES⁻) 1533 (M⁻ + Cl).

(S*,S*), (R*,S*)-10-But-3-ynyl-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(23),8,10,12(24),19,21-hexaene **262**



262

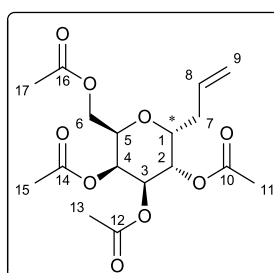
Dibromide species **287** (155 mg, 0.5 mmol), and Cs₂CO₃ (799 mg, 2.5 mmol) were added to a solution of tosyl protected spacer **219** (290 mg, 0.5 mmol) in dry DMF (150 mL) After stirring for 2 days at room temperature, the solvent was removed *in vacuo* and azeotroping to dryness using toluene. The residue was purified by column chromatography (40% EtOAc in petrol) to result in the *title compound* **262** (210 mg, 57%) as a colourless solid foam, R_f = 0.22 (40% EtOAc in petrol), m.p. 89 – 94 °C, (found [ES⁺] M⁺ + H, 750.2144. C₃₈H₄₄O₅N₃S₄ requires M, 750.2159); ν_{max} (ATR): 3272 (w), 2972 (w), 2921 (w), 2871 (w), 1593 (m), 1451 (m), 1330 (m), 1288 (m), 1151 (s) and 1090 (m) cm⁻¹; δ_H (CDCl₃, 400 MHz) 0.94 (6H, d, J = 7.0 Hz, CH₃, H-7), 1.02 (6H, d, J = 7.0 Hz, CH₃, H-7), 2.04 - 2.18 (4H, m, CH₂, H-5), 2.39 (4H, m, CH₂, H-5), 2.43 (6H, s, CH₃, H-20), 2.44 (6H, s, CH₃, H-20), 2.54 (1H, t, J = 2.5 Hz, CH, H-15), 2.57 (1H, t, J = 2.5 Hz, CH, H-15), 3.55 (2H, d, J = 14.0 Hz, CH₂, H-4), 3.56 (2H, d, J = 13.5 Hz, CH₂, H-4), 3.61 (2H, d, J = 13.5 Hz, CH₂, H-4), 3.69 (2H, d, J = 14.0 Hz, CH₂, H-4), 3.86 (2H, d, J = 16.0 Hz, CH₂, H-8), 3.96 - 4.05 (2H, m, CH, H-6), 4.05 - 4.13 (2H, m, CH, H-6), 4.17 (2H, d, J = 16.0 Hz, CH₂, H-8), 4.32 (2H, d, J = 16.0 Hz, CH₂, H-8), 4.63 - 4.77 (2H, s, CH₂, H-8), 4.65 (2H, d, J = 2.5 Hz, CH₂, H-13), 6.60 (1H, s, CH, H-10), 6.85 (2H, s, CH, H-11), 6.94 (s, 2H, CH, H-11 + 1H, CH, H-10), 7.06 (2H, d, J = 8.0 Hz, CH, H-2), 7.18 (2H, d, J = 8.0 Hz, CH, H-2), 7.32 (4H, d, J = 8.0 Hz, CH, H-17), 7.31 (4H, d, J = 8.0 Hz, CH, H-17), 7.59 (1H, t, J = 8.0 Hz, CH, H-1), 7.64 (1H, t, J = 8.0 Hz, CH, H-1), 7.71 (4H, d, J = 8.0 Hz, CH, H-18) and 7.74 (4H, d, J = 8.0 Hz, CH, H-18); δ_C (CDCl₃, 100 MHz) 16.94, 18.50 (CH₃, C-7), 21.48, 21.50

(CH₃, C-7), 36.64, 37.19 (CH₂, C-5), 37.57, 37.98 (CH₂, C-4), 47.19, 47.75 (CH₂, C-8), 53.68, 54.75 (CH, C-6), 55.77 (CH₂, C-13), 75.68 (CH, C-15), 78.27, 78.28 (C, C-14), 113.50, 114.00 (CH, C-11), 120.49, 120.55 (CH, C-10), 121.03, 121.47 (CH, C-2), 126.97, 127.11 (CH, C-17), 129.67, 129.74 (CH, C-18), 137.55 (C, C-16), 137.59 (CH, C-1), 139.63, 139.77 (C, C-8), 143.27, 143.33 (C, C-19), 157.51, 157.89 (C, C-12), 157.98 and 158.03 (C, C-3); m/z (ES⁺) 750 (M⁺ + H), 772 (M⁺ + Na), 1521 (2M⁺ + Na); m/z (ES⁻) 748 (M⁻).

4.6 The Macromolecules

4.6.1 Metathesis Attempt

Allyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside 246²⁵¹



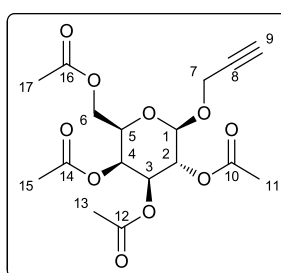
246

Preparation taken from Giannis and Sandhoff:²⁵² β -D-Galactose pentaacetate (1.05 g, 2.7 mmol) was dissolved in dry acetonitrile (13 mL) at 0 °C. Allyltrimethylsilane (1.25 mL, 7.9 mmol) was added followed by BF₃·OEt₂ (700 μ L, 5.7 mmol). The reaction was left to stir for 5 hours and the poured onto sat. NaHCO₃ (20 mL). The resulting solution was extracted with DCM (3 x 20 mL). The organic phases were combined, dried over MgSO₄, filtered and reduced *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in petrol) resulting in the *title compound* as a pale yellow oil (280 mg, 28%, 6:1 α : β), R_f = 0.45 (40% EtOAc in petrol), (found [ES⁺] M⁺ + Na, 395.1317. C₁₇H₂₄O₉Na requires *M*, 395.1313); ν_{\max} (ATR): 3077 (w), 2976 (w), 2963 (w), 1739 (s), 1434 (w), 1368 (m), 1213 (s) and 1041 (m) cm⁻¹; δ_{H} (CDCl₃, 500 MHz) 2.03 (3H, s, CH₃), 2.04 (3H, s, CH₃), 2.07 (3H, s, CH₃), 2.12 (3H, s, CH₃), 2.24 - 2.34 (1H, m, CH₂, H-7), 2.42 - 2.52 (1H, m, CH₂, H-7), 4.07 - 4.11 (2H, m, CH, H-5 + CH₂, H-6), 4.16 - 4.24 (1H, m, CH₂, H-6), 4.30 (1H, dt, *J* = 10.0, 5.0 Hz, CH, H-1), 5.09 - 5.16 (2H, m, CH₂, H-9), 5.22 (1H, dd, *J* = 9.0, 2.5 Hz CH, H-3), 5.27 (1H, dd, *J*

= 10.0, 5.5 Hz, **CH**, H-2), 5.42 (1H, br. s., **CH**, H-4) and 5.71 - 5.81 (1H, m, **CH**, H-8); δ_C (CDCl₃, 125 MHz) 20.64, 20.70, 20.76 (**CH**₃, C-11,13,15,17), 30.87 (**CH**₂, C-7), 61.43 (**CH**₂, C-6), 67.55 (**CH**, C-4), 67.87 (**CH**, C-3), 68.20 (**CH**, C-2,5), 71.40 (**CH**, C-1), 117.65 (**CH**₂, C-9), 133.28 (**CH**, C-8), 169.81, 169.93, 170.08 and 170.55 (**C**, C-10,12,14,16) m/z (ES⁺) 395 (M⁺ + Na).

4.6.2 Click Chemistry Precursors

2-Propynyl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranoside **278**²¹⁹

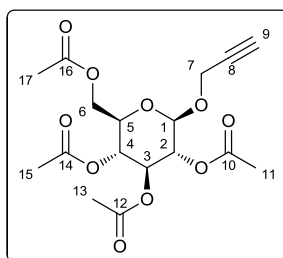


278

BF₃.OEt₂ (1.46 mL, 11.5 mmol) and propargyl alcohol (660 μ L, 11.3 mmol) were added to a solution of β -D-galactose pentaacetate (3.06 g, 7.8 mmol) in DCM (80 mL) at room temperature. After stirring at room temperature for 24 hours, K₂CO₃ (1.50 g, 10.9 mmol) was added to quench the reaction and left to stir for 1 hour. The reaction mixture was filtered, and the residue washed with DCM (100 mL). The combined organic extracts were washed with water (3 x 120 mL), brine (60 mL), dried over MgSO₄ filtered and concentrated *in vacuo*, affording the *title compound* **278** as a viscous glass (2.96 g, 98%), R_f = 0.67 (60% EtOAc in petrol), $[\alpha]_D^{33} = -33$ (c = 2.32, CHCl₃), (found [ES⁺] M⁺ + Na, 409.1122. C₁₇H₂₂O₁₀Na requires M, 409.1105); ν_{\max} (ATR): 3272 (w), 2979 (w), 2984 (w), 1739 (s), 1432 (w), 1367 (m), 1211 (s), 1073 (s) and 1043 (s) cm⁻¹; δ_H (CDCl₃, 400 MHz) 1.98 (3H, s, **CH**₃, H-13), 2.04 (3H, s, **CH**₃, H-17), 2.06 (3H, s, **CH**₃, H-11), 2.14 (3H, s, **CH**₃, H-15), 2.47 (1H, t, $J = 2.5$ Hz, **CH**, H-9), 3.93 (1H, ddd, $J = 7.0, 6.5, 1.0$ Hz, **CH**, H-5), 4.12 (1H, dd, $J = 11.0, 7.0$ Hz, **CH**₂, H-6), 4.17 (1H, dd, $J = 11.0, 6.5$ Hz, **CH**₂, H-6), 4.37 (2H, d, $J = 2.5$ Hz, **CH**₂, H-7), 4.73 (1H, d, $J = 8.0$ Hz, **CH**, H-1), 5.04 (1H, dd, $J = 10.5, 3.5$ Hz, **CH**, H-3), 5.20 (1H, dd, $J = 10.5, 8.0$ Hz, **CH**, H-2) and 5.39 (1H, dd, $J = 3.5, 1.0$ Hz, **CH**, H-4); δ_C (CDCl₃, 125 MHz) 20.28 (**CH**₃, C-13), 20.36 (**CH**₃, C-17), 20.38 (**CH**₃, C-15), 20.50 (**CH**₃, C-11), 55.62 (**CH**₂, C-7), 60.95

(CH₂, C-6), 66.74 (CH, C-4), 68.22 (CH, C-2), 70.51 (CH, C-5), 70.56 (CH, C-3), 75.26, 75.29 (CH, C-9), 78.00 (C, C-8), 98.36 (CH, C-1), 169.25 (C, C-10), 169.80 (C, C-12), 169.96 (C, C-14) and 170.08 (C, C-16); *m/z* (ES⁺) 404 (M⁺ + NH₄), 409 (M⁺ + Na), 425 (M⁺ + K); *m/z* (ES⁻) 385 (M⁻ - H).

1-*O*-propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucose **250**²¹⁹

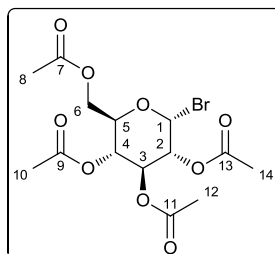


250

BF₃.OEt₂ (3.48 mL, 27.5 mmol) and propargyl alcohol (1.6 μL, 27.6 mmol) were added to a solution of β-D-glucose pentaacetate (7.16 g, 18.4 mmol) in DCM (180 mL at room temperature). After stirring at room temperature for 24 hours, K₂CO₃ (3.56 g, 25.8 mmol) was added to quench the reaction and left to stir for 1 hour. The reaction mixture was filtered, and the residue washed with DCM (200 mL). The combined organic extracts were washed with water (3 x 200 mL), brine (100 mL), dried over MgSO₄ filtered and concentrated *in vacuo*, affording the *title compound* **250** as a near-colourless solid (7.02 g, 99%), R_f = 0.70 (60% EtOAc in petrol), [α]_D²⁵ = -39 (c = 2.24, CHCl₃) [Ref: -43.4 (c = 0.9, CHCl₃)²⁵³], m.p. 116 – 118 °C [Ref: 116 – 117 °C²⁵³], (found [ES⁺] M⁺ + Na, 409.1119. C₁₇H₂₂O₁₀Na requires *M*, 409.1106); ν_{max} (ATR): 3273 (m), 2980 (w), 2957 (w), 2120 (w), 1751 (s), 1731 (s), 1460 (m), 1231 (s) and 1206 (s) cm⁻¹; δ_H (CDCl₃, 500 MHz) 2.01 (3H, s, CH₃, H-13), 2.02, 2.06 (3H, s, CH₃, H-11,15), 2.09 (3H, s, CH₃, H-17), 2.48 (1H, t, *J* = 2.0 Hz, CH, H-9), 3.73 (1H, ddd, *J* = 10.0, 4.5, 2.0 Hz, CH, H-5), 4.14 (1H, dd, *J* = 12.0, 2.0 Hz, CH₂, H-6), 4.27 (1H, dd, *J* = 12.0, 4.5 Hz, CH₂, H-6), 4.37 (2H, d, *J* = 2.0 Hz, CH₃, H-7), 4.78 (1H, d, *J* = 8.0 Hz, CH, H-1), 5.01 (1H, dd, *J* = 9.5, 8.0 Hz, CH₃, H-2), 5.10 (1H, t, *J* = 10.0 Hz, CH, H-4) and 5.24 (1H, t, *J* = 9.5 Hz, CH₃, H-3); δ_C (CDCl₃, 125 MHz) 20.56, 20.58, 20.66, 20.70 (CH₃, C-11,13,15,17), 55.90 (CH₂ C-7), 61.67 (CH₂ C-6), 68.18 (CH, C-4), 70.86 (CH, C-2), 71.84 (CH, C-5), 72.67 (CH, C-3), 75.48 (CH, C-9), 78.03 (C, C-8), 98.04 (CH, C-1), 169.38 (C, C-

14), 169.42 (C, C-10), 170.23 (C, C-12) and 170.65 (C, C-16); m/z (ES^+) 409 ($M^+ + Na$).

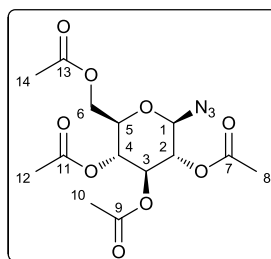
2,3,4,6-tetra-O-Acetyl- α -D-glucofuranosyl bromide **264**²⁵⁴



264

33% HBr in acetic acid (15 mL, 82.8 mmol) was added dropwise to a solution of β -D-Glucose pentaacetate (2.01 g, 5.1 mmol) in dry DCM (20 mL). The reaction was left to stir for 3 hours at room temperature. Ice-water was added and the reaction left to stir for 10 minutes. The organic layer was separated and the aqueous extracted with further portions of DCM (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ until pH 8 was reached, then brine. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was recrystallised (EtOAc/Pet Ether) to leave the *title compound* **264** as a colourless crystalline solid (1.76 g, 83%), $R_f = 0.48$ (30% EtOAc in petrol); δ_H ($CDCl_3$, 300 MHz) 2.02 (3H, s, CH_3 , H-10), 2.04 (3H, s, CH_3 , H-12), 2.09 (3H, s, CH_3 , H-8), 2.09 (3H, s, CH_3 , H-14), 4.11 (1H, dd, $J = 12.0, 2.0$ Hz, CH_2 , H-6), 4.28 (1 H, ddd, $J = 10.0, 4.0, 2.0$ Hz, CH , H-5), 4.32 (1H, dd, $J = 12.0, 4.0$ Hz, CH_2 , H-6), 4.83 (1H, dd, $J = 10.0, 4.0$ Hz, CH , H-2), 5.15 (1H, t, $J = 10.0$ Hz, CH , H-3), 5.54 (1H, t, $J = 9.5$ Hz, CH , H-4) and 6.60 (1H, d, $J = 4.0$ Hz, CH , H-1); δ_C ($CDCl_3$, 75 MHz) 20.48, 20.54, 20.57, 20.58 (CH_3 , C-8,10,12,14), 60.89 (CH_2 , C-6), 67.12 (CH , C-3), 70.11 (CH , C-2), 70.54 (CH , C-4), 72.09 (CH , C-1), 86.52 (CH , C-5), 169.39 (C, C-7), 169.71, 169.77 (C, C-9,13) and 170.42 (C, C-11).

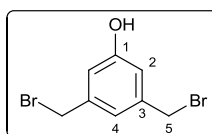
2,3,4,6-tetra-O-Acetyl- β -D-glucopyranosyl azide **265**²¹⁷



265

A solution of bromide **264** (411 mg, 1.0 mmol) and sodium azide (79.1 mg, 1.2 mmol) in dry DMSO (5 mL) was stirred for 24 hours. Water (25 mL) was then added and the reaction mixture extracted with EtOAc (3 x 20 mL). The organic extracts were dried over MgSO₄ and concentrated *in vacuo* to afford the crude product which was then recrystallised from DCM/Pet. ether to afford the *title compound* **265** as colourless crystals (287 mg, 77%), R_f = 0.64 (60% EtOAc in petrol), [α]_D³² = - 28 (c = 2.33, CHCl₃) [Ref: -29 (c = 2.0, CHCl₃)²¹⁶], m.p. 120 – 121 °C [Ref: 123 – 124 °C²⁵⁵], (found [ES⁺] M⁺ + Na, 396.1001. C₁₄H₁₉O₉N₃Na requires M, 396.1014); ν_{\max} (ATR): 2968 (w), 2908 (w), 2116 (m), 1745 (s), 1730 (s), 1367 (m), 1230 (s), 1033 (s) and 906 (m) cm⁻¹; δ_{H} (CDCl₃, 300 MHz) 1.98 (3H, s, CH₃, H-10), 2.00 (3H, s, CH₃, H-12), 2.05 (3H, s, CH₃, H-8), 2.07 (3H, s, CH₃, H-14), 3.78 (1H, ddd, *J* = 10.0, 4.5, 2.0 Hz, CH, H-5), 4.14 (1H, dd, *J* = 12.5, 2.0 Hz, CH₂, H-6), 4.25 (1H, dd, *J* = 12.5, 4.5 Hz, CH₂, H-6), 4.64 (1H, d, *J* = 9.0 Hz, CH, H-1), 4.93 (1H, app.t, *J* = 9.0 Hz, CH, H-2), 5.08 (1H, app.t, *J* = 10.0 Hz, CH, H-4) and 5.20 (1H, app.t, *J* = 9.5 Hz, CH, H-3); δ_{C} (CDCl₃, 75 MHz) 20.43 (CH₃, C-8,10,12), 20.58 (CH₃, C-14), 61.58 (CH₂, C-6), 67.82 (CH, C-4), 70.56 (CH, C-2), 72.51 (CH, C-3), 73.91 (CH, C-5), 87.79 (CH, C-1), 169.12 (C, C-7), 169.22 (C, C-11), 170.02 (C, C-9) and 170.51 (C, C-13); *m/z* (ES⁺) 396 (M⁺ + Na); *m/z* (ES⁻) 408 (M⁻ + Cl).

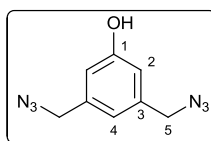
3,5-bis(Bromomethyl)phenol **279**²⁵⁶



279

To a solution of diol **256** (1.08 g, 7.0 mmol) in acetic acid (7 mL) was added HBr (4.6 mL of 30% soln. in AcOH, 23.1 mmol) at room temperature. After 48 hours, water (40 mL) was added and the reaction stirred for 10 minutes. The reaction mixture was extracted with diethyl ether (4 x 25 mL) and the organic extracts washed with water (25 mL), sat NaHCO₃ (25 mL), brine (20 mL), then dried over MgSO₄ and reduced *in vacuo*. This afforded the product as a near-colourless powder (1.39 g, 71%) in an essentially pure state, R_f = 0.85 (8% methanol in DCM), m.p. 81 – 82 °C [Ref: 82 – 84 °C²⁵⁶], (found [ES⁻] M⁻, 276.8863. C₈H₇O⁷⁹Br₂ requires M, 276.8869); ν_{max} (ATR): 3213 (broad, w), 1595 (m), 1452 (m), 1309 (s), 1207 (m), 1151 (w), 1002 (w) and 862 (m) cm⁻¹; δ_H (CDCl₃, 500 MHz) 4.41 (4H, s, CH₂, H-5), 5.35 (1H, br. s., OH), 6.82 (2H, s, CH, H-2) and 6.99 (1H, s, CH, H-4); δ_C (CDCl₃, 125 MHz) 32.56 (CH₂, C-5), 116.11 (CH, C-2), 121.96 (CH, C-4), 139.86 (C, C-3) and 155.87 (C, C-1); m/z (ES⁺) 197 (M⁺ - Br); m/z (ES⁻) 315 (M⁻ + Cl).

3,5-bis(Azidomethyl)phenol **280**²⁵⁶

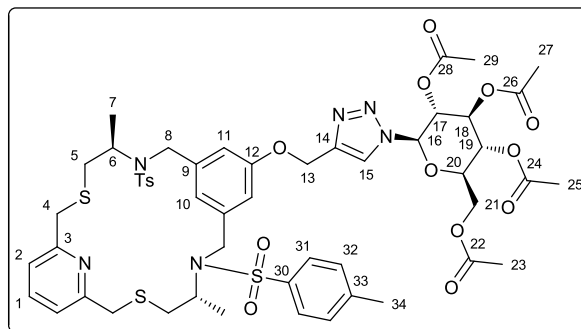


280

A solution of 3,5-bis(bromomethyl)phenol **279** (1.00 g, 2.1 mmol) and sodium azide (0.539 g, 8.3 mmol) in CH₃CN (10 mL) was heated to 70 °C for 48 hours. The reaction was allowed to cool to ambient temperature and then water (5 mL) was added. The reaction mixture was extracted with EtOAc (5 x 5 mL); the organic extracts combined, dried over MgSO₄, and reduced *in vacuo* resulting in the title product as a pale yellow oil (419 mg, 99%) in an essentially pure state, R_f = 0.76 (40% EtOAc in petrol), (found [ES⁻] M⁻, 203.0679. C₈H₇ON₆ requires M, 203.0686); ν_{max} (ATR): 3329 (br., m), 2957 (w), 2931 (w), 3873 (w), 2090 (s), 1598 (m), 1598 (m), 1455 (m), 1251 (br., m) cm⁻¹; δ_H (CDCl₃, 400 MHz) 4.32 (4H, s, CH₂, H-5), 5.28 (1H, br. s., OH), 6.78 (2H, d, J = 1.0 Hz, CH, H-2) and 6.84 (1H, t, J = 1.0 Hz, CH, H-4); δ_C (CDCl₃, 100 MHz) 54.24 (CH₂, C-5), 114.83 (CH, C-2), 120.00 (CH, C-4), 137.83 (C, C-3) and 156.24 (C, C-1); m/z (ES⁻) 203 (M⁻), 239 (M⁻ + Cl), 407 (2M⁻).

4.6.3 The Click Products

(4*S*,16*S*)-4,16-Dimethyl-10-[1-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-6,14-dithia-3,17,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **266**

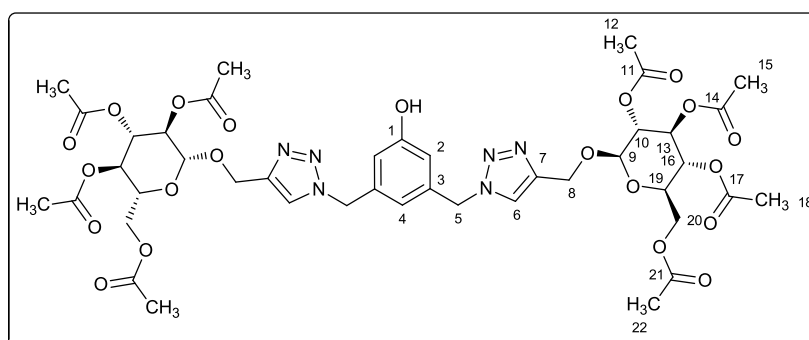


266

To a solution of azide **265** (129 mg, 340 μ mol) in dry DMSO (1.7 mL) was added the macrocycle **260** (202 mg, 270 μ mol) followed by sodium L-ascorbate (670 μ L, 1 M aq. soln.) and copper sulfate (670 μ L, 1 M aq. soln.). The reaction was left at room temperature and monitored by TLC analysis. After 4 hours, water (5 mL) was added and the solution was with DCM (5 x 5 mL). The combined extracts were dried over MgSO₄, filtered and reduced *in vacuo* to give the crude product. Purification by flash column chromatography (60 \rightarrow 80% EtOAc in petrol) afforded the *title compound* as a pale yellow glass (41.0 mg, 14%), $R_f = 0.65$ (80% EtOAc in petrol), m.p. 120 – 124 $^{\circ}$ C, ν_{\max} (ATR): 2960 (w), 2925 (w), 2852 (w), 1749 (s), 1595 (m), 1494 (m), 1367 (m), 1213 (s), 1152 (s), 1035 (s) cm^{-1} ; δ_{H} (CDCl₃, 500 MHz) 1.00 (6H, d, $J = 7.0$ Hz, CH₃, H-7), 1.87 (3H, s, CH₃, H-29), 2.00 – 2.09 (2H, m, CH₂, H-5), 2.02 (3H, s, CH₃, H-23,25,27), 2.06 (6H, br. s, CH₃, H-23,25,27), 2.36 (2H, dd, $J = 13.0, 6.5$ Hz, CH₂, H-5), 2.42 (6H, s, CH₃, tosyl), 3.55 (2H, d, $J = 14.0$ Hz, CH₂, H-4), 3.61 (2H, d, $J = 14.0$ Hz, CH₂, H-4), 3.85 (2H, d, $J = 15.5$ Hz, CH₂, H-8), 3.96 - 4.06 (2H, m, CH, H-6), 4.00 – 4.05 (1H, m, CH, H-20), 4.17 (1H, dd, $J = 12.5, 2.0$ Hz, CH₂, H-21), 4.31 (1H, dd, $J = 12.5, 5.0$ Hz, CH₂, H-21), 4.66 (2H, d, $J = 15.5$ Hz, CH₂, H-8), 5.14 (1H, d, $J = 12.0$ Hz, CH₂, H-13), 5.23 (1H, d, $J = 12.0$ Hz, CH₂, H-13), 5.27 (2H, app. dd, $J = 11.5, 9.5$ Hz, CH, H-19), 5.43 (1H, app. t, $J = 9.5$ Hz, CH, H-18), 5.53 (1H, app. t, $J = 9.5$ Hz, CH, H-17), 5.91 (1H, d, $J = 9.5$ Hz, CH, H-16), 6.90 (2H, s, CH, H-11), 6.92 (1H, s, CH, H-10), 7.05

(2H, d, $J = 7.5$ Hz, CH, H-2), 7.31 (4H, d, $J = 8.0$ Hz, CH, H-32), 7.56 (1H, t, $J = 7.5$ Hz, CH, H-1), 7.71 (4H, d, $J = 8.0$ Hz, CH, H-31) and 8.05 (1H, s, CH, H-15); δ_C (CDCl₃, 125 MHz) 16.97, 17.00 (CH₃, C-7), 20.08, 20.12, 20.46, 20.62 (CH₃, C-23,25,27,29), 21.41, 21.46 (CH₃, tosyl), 37.18 (CH₂, C-5), 37.96 (CH₂, C-4), 47.58, 47.67 (CH₂, C-8), 54.70, 54.81 (CH, C-6), 61.21 (CH₂, C-13), 61.51 (CH₂, C-21), 67.63 (CH, C-19), 70.26 (CH, C-17), 72.66 (CH, C-18), 75.01, 75.10 (CH, C-20), 85.63 (CH, C-16), 113.28, 113.31, 113.33 (CH, C-11), 120.02, 120.06 (CH, C-10), 121.13 (CH, C-2), 122.18, 122.22 (CH, C-15), 126.91 (CH, C-31), 129.76 (CH, C-32), 137.62 (CH, C-1, + C, C-31), 139.71 (CH, C-9), 143.34 (C, C-33), 144.02 (C, C-14), 157.98 (C, C-3), 158.05 (C, C-12), 168.74 (C, C-28), 169.25 (C, C-24), 169.89 (C, C-26) and 170.46 (C, C-22); m/z (ES⁺) 1123 (M⁺ + H), 1145 (M⁺ + Na); m/z (ES⁻) 1157 (M⁻ + Cl).

3,5-bis{4-(2',3',4',6'-tetra-*O*-acetyl- β -D-glucopyranosyloxymethyl)-1*H*-[1,2,3]-triazol-1-methyl}phenol **281**

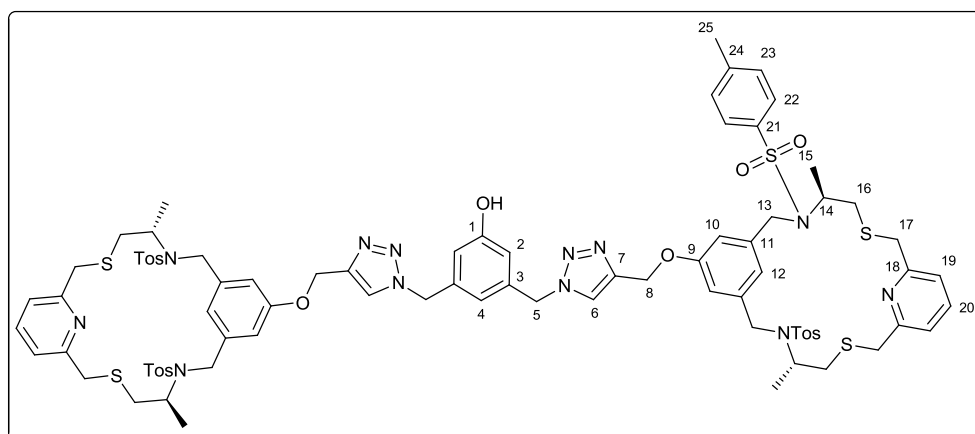


281

Diazide **259** (221 mg, 1.1 mmol), propargyl sugar **250** (777 mg, 2.0 mmol), copper sulfate (51.5 mg, 0.2 mmol) and sodium ascorbate 126 mg, 0.6 mmol) were dissolved in 1:1 EtOH/H₂O (16 mL) under an atmosphere of N₂ at room temperature. After 24 hours, water (5 mL) was added and the reaction mixture extracted with EtOAc (5 x 10 mL). The organic extracts were combined, dried over MgSO₄ filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography (EtOAc) to afford the *title compound* as a transparent, slightly yellow glass (479 mg, 49%), $R_f = 0.34$ (EtOAc), $[\alpha]_D^{32} = -35$ ($c = 2.16$, CHCl₃), m.p. 85 – 87 °C, (found C, 50.62; H, 5.47; N, 8.45%. C₄₂H₅₂N₆O₂₁·H₂O requires C, 50.62; H, 5.21; N, 8.20%); ν_{\max} (ATR): 2951

(w), 1739 (s), 1602 (m), 1432 (m), 1211 (s), 1165 (w), 1032 (s), 833 (m) cm^{-1} ; δ_{H} (CDCl_3 , 400 MHz) 1.92 (6H, s, CH_3 , H-22), 2.00 (6H, s, CH_3 , H-20), 2.03 (6H, s, CH_3 , H-18), 2.08 (6H, s, CH_3 , H-16), 3.73 (2H, ddd, $J = 9.5, 4.5, 2.5$ Hz, CH , H-19), 4.13 (2H, dd, $J = 12.5, 2.5$ Hz, CH_2 , H-20), 4.24 (2H, dd, $J = 12.5, 4.5$ Hz, CH_2 , H-20), 4.68 (2H, d, $J = 8.0$ Hz, CH , H-9), 4.80 (2 H, d, $J = 12.5$ Hz, CH_2 , H-8), 4.91 (2 H, d, $J = 12.5$ Hz, CH_2 , H-8), 4.97 (2H, dd, $J = 9.5, 8.0$ Hz, CH , H-10), 5.09 (2H, app. t, $J = 9.5$ Hz, CH , H-16), 5.20 (2H, app. t, $J = 9.5$ Hz, CH , H-13), 5.46 (2H, d, $J = 15.5$ Hz, CH , H-5), 5.50 (2H, d, $J = 15.5$ Hz, CH , H-5), 6.71 (2H, s, ArH, H-2), 6.74 (1H, s, ArH, H-4), 7.57 (2H, s, CH , H-6) and 9.12 (1H, br. s., ArOH); δ_{C} (CDCl_3 , MHz) 20.57 (CH_3 , C-12,15, 18), 20.74 (CH_3 , C-22), 53.72 (CH_2 , C-5), 61.79 (CH_2 , C-20), 62.92 (CH_2 , C-8), 68.26 (CH , C-16), 71.33 (CH , C-10), 71.84 (CH , C-19), 72.62 (CH , C-13), 100.06 (CH , C-9), 115.12 (CH , C-2), 118.20 (CH , C-4), 123.29 (CH , C-6), 137.09 (C, C-3), 144.60 (C, C-7), 158.48 (C, C-1), 169.42 (C, C-17), 169.66 (C, C-11), 170.18 (C, C-14) and 170.79 (C, C-21); m/z (ES^+) 994 ($\text{M}^+ + \text{NH}_4$), 999 ($\text{M}^+ + \text{Na}$); m/z (ES^-) 1011 ($\text{M} + \text{Cl}$).

3,5-bis-[4-((5*R*,15*R*)-5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(23),8,10,12(24),19,21-hexaen-10-yloxymethyl)-1,2,3-triazol-1-ylmethyl]-phenol **283**

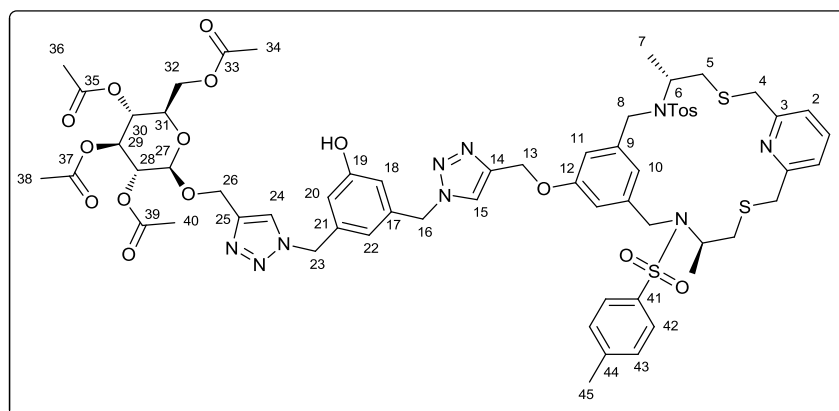


283

Diazide **259** (43.1 mg, 0.2 mmol), propargyl macrocycle **260** (287 mg, 0.4 mmol), copper sulfate (10 mg, 40 μmol) and sodium ascorbate (22.8 mg, 0.1 mmol) were dissolved in 1:1 EtOH/ H_2O (8 mL) in a nitrogen atmosphere. After 24 hours at room

temperature, water (5 mL) was added and the reaction mixture extracted with EtOAc (5 x 10 mL). The organic extracts were combined, dried over MgSO₄ filtered and reduced *in vacuo*. The crude material was then purified by column chromatography (80% EtOAc in petrol) to afford the *title compound* as a slightly yellow glass (61.7 mg, 19%), R_f = 0.58 (EtOAc), $[\alpha]_D^{34} = -27$ (c = 1.32, CHCl₃), m.p. 145 – 150 °C, δ_H (CDCl₃, MHz) 0.98 (12H, d, *J* = 7.0 Hz, CH₃, H-15), 2.06 (4H, dd, *J* = 12.5, 8.0 Hz, CH₂, H-16), 2.35 (4H, dd, *J* = 12.5, 6.5 Hz, CH₂, H-16), 2.42 (12H, s, CH₃, H-25), 3.47 (4H, d, *J* = 14.0 Hz, CH₂, H-17), 3.56 (4H, d, *J* = 14.0 Hz, CH₂, H-17), 3.84 (4H, d, *J* = 16.0 Hz, CH₂, H-13), 4.01 (4H, app. dqd, *J* = 8.0, 7.0, 6.5 Hz, CH, H-14), 4.65 (4H, d, *J* = 16.0 Hz, CH₂, H-13), 5.16 (2H, d, *J* = 13.0 Hz, CH₂, H-8), 5.19 (2H, d, *J* = 13.0 Hz, CH₂, H-8), 5.47 (4H, s, CH₂, H-5), 6.79 (2H, s, CH, H-2), 6.90 (5H, s, CH, H-4, 10), 6.92 (2H, s, CH, H-12), 7.02 (4H, d, *J* = 7.5 Hz, CH, H-19), 7.31 (8H, d, *J* = 8.0 Hz, CH, H-23), 7.54 (2H, t, *J* = 7.5 Hz, CH, H-20), 7.70 (8H, d, *J* = 8.0 Hz, CH, H-22), 7.89 (2H, s, CH, H-6) and 8.28 (1H, br. s., -OH); δ_C (CDCl₃, 100 MHz) 16.93 (CH₃, C-15), 21.51 (CH₃, C-25), 37.27 (CH₂, C-16), 38.05 (CH₂, C-17), 47.54 (CH₂, C-13), 53.76 (CH₂, C-5), 54.77 (CH, C-14), 61.33 (CH₂, C-8), 113.51 (CH, C-10), 115.58 (CH, C-2), 119.32 (CH, C-4), 119.85 (CH, C-12), 121.14 (CH, C-19), 124.00 (CH, C-6), 126.95 (CH, C-22), 129.86 (CH, C-23), 136.92 (C, C-3), 137.55 (C, C-21), 137.66 (CH, C-20), 139.69 (C, C-11), 143.47 (C, C-24), 143.75 (C, C-7), 158.02 (C, C-18) and 158.18 (C, C-1,9); *m/z* (ES⁺) 1726, 1728 (M⁺ + Na).

3-[4-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxymethyl)-1H-[1,2,3]-triazol-1-methyl]-5-[4-((5R,15R)--5,15-dimethyl-6,14-bis-(toluene-4-sulfonyl)-3,17-dithia-6,14,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(23),8,10,12(24),19,21-hexaen-10-yloxymethyl)-1,2,3-triazol-1-ylmethyl]-phenol **284**



284

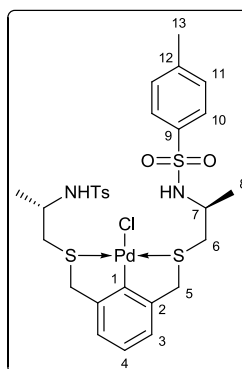
A solution of propargylic sugar **250** (103 mg, 270 μmol) in dry acetonitrile was added to a stirring solution of diazide **259** (68.2 mg, 330 μmol) in EtOH (5 mL). 0.1 M aq. CuSO₄ (0.55 mL, 55 μmol) and 0.1 M aq. sodium ascorbate (1.1 mL, 110 μmol) were added followed by H₂O (3.5 mL), and the reaction was left to stir for 30 minutes. Propargylic macrocycle **260** (188 mg, 250 μmol) in dry acetonitrile was added, and the transparent-colourless reaction turned opaque-yellow. Further portions of 0.1 M aq. CuSO₄ (0.55 mL, 55 μmol) and 0.1 M aq. sodium ascorbate (1.1 mL, 110 μmol) were added and the reaction left to stir for 24 hours. The solvent was removed *in vacuo* and the residue filtered through a plug of silica (EtOAc). The crude material (215 mg) was purified by preparative HPLC, eluting with EtOAc, to give two products. The less polar material (*R*_f = 0.44) was the *title compound* **284**, isolated as a near-colourless glass (31.7 mg, 9%), *R*_f = 0.44 (EtOAc), [*α*]_D²⁸ = 41.7 (c = 1.27, CHCl₃), m.p. 102 – 107 °C; *ν*_{max} (ATR): 2979 (w), 2960 (w), 2922 (w), 1742 (s), 1597 (m), 1454 (m), 1217 (s), 1153 (s), 1036 (s) cm⁻¹; δ_H (CDCl₃, 400 MHz) 0.97 (6H, d, *J* = 7.0 Hz, CH₃, H-7), 1.87 (3H, s, CH₃, H-40), 1.98 (3H, s, CH₃, H-38), 2.01 (3H, s, CH₃, H-36), 2.01 - 2.06 (2H, m, CH₂, H-5), 2.06 (3H, s, CH₃, H-34), 2.32 (2H, dd, *J* = 13.0, 7.0 Hz, CH₂, H-5), 2.43 (6H, s, CH₃, H-45), 3.46 (2H, d, *J* = 14.0 Hz, CH₂, H-4), 3.55 (2H, d, *J* = 14.0 Hz, CH₂,

H-4), 3.72 (1 H, ddd, $J = 9.5, 4.5, 2.0$ Hz, **CH**, H-31), 3.83 (2H, d, $J = 16.0$ Hz, **CH₂**, H-8), 4.01 (2H, app. dq, $J = 14.0, 7.0$ Hz), 4.12 (1H, dd, $J = 12.0, 2.0$ Hz, **CH₂**, H-32), 4.23 (1H, dd, $J = 12.0, 4.5$ Hz, **CH₂**, H-32), 4.65 (2H, d, $J = 16.0$ Hz, **CH₂**, H-8), 4.67 (1H, d, $J = 8.0$ Hz, **CH**, H-27), 4.77 (1H, d, $J = 12.5$ Hz, **CH₂**, H-26), 4.87 (1H, d, $J = 12.5$ Hz, **CH₂**, H-26), 4.95 (1H, dd, $J = 9.5, 8.0$ Hz, **CH**, H-28), 5.07 (1H, t, $J = 9.5$ Hz, **CH**, H-30), 5.18 (1H, t, $J = 9.5$ Hz, **CH**, H-29), 5.19 (2H, s, **CH₂**, H-13), 5.45 (2H, s, **CH₂**, H-23), 5.49 (2H, s, **CH₂**, H-16), 6.70 (1H, s, Ar-**H**, H-22), 6.84 (2H, s, Ar-**H**, H-18,20), 6.91 (2H, s, Ar-**H**, H-11), 6.92 (1H, br. s., Ar-**H**, H-10), 7.02 (2H, d, $J = 7.5$ Hz, Ar-**H**, H-2), 7.31 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-43), 7.54 (1H, t, $J = 7.5$ Hz, Ar-**H**, H-1), 7.57 (1H, s, **CH**, H-24), 7.69 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-42), 7.95 (1H, s, **CH**, H-15) and 9.22 (1H, br. s., -**OH**); δ_C (CDCl₃, 125 MHz) 16.88 (**CH₃**, C-7), 20.51 (**CH₃**, C-40), 20.57 (**CH₃**, C-36,38), 20.74 (**CH₃**, C-34), 21.50 (**CH₃**, C-45), 37.22 (**CH₂**, C-5), 38.01 (**CH₂**, C-4), 47.40 (**CH₂**, C-8), 53.75 (**CH₂**, C-16,23), 54.73 (**CH**, C-6), 61.12 (**CH₂**, C-13), 61.72 (**CH₂**, C-32), 62.65 (**CH₂**, C-26), 68.17 (**CH**, C-30), 71.20 (**CH**, C-28), 71.73 (**CH**, C-29), 72.62 (**CH**, C-31), 99.81 (**CH**, C-27), 113.35 (**CH**, C-11), 115.20 (**CH**, C-22), 115.61 (**CH**, C-20), 118.72 (**CH**, C-18), 119.73 (**CH**, C-10), 121.11 (**CH**, C-2), 123.37 (**CH**, C-24), 124.22 (**CH**, C-15), 126.88 (**CH**, C-42), 129.87 (**CH**, C-43), 136.89, 136.98 (**C**, C-17,21), 137.46 (**C**, C-41), 137.65 (**CH**, C-1), 139.70 (**C**, C-9), 143.50 (**C**, C-44), 143.66 (**C**, C-14), 144.34 (**C**, C-25), 157.97 (**C**, C-3), 158.08 (**C**, C-12), 158.45 (**C**, C-19), 169.44 (**C**, C-35), 169.60 (**C**, C-39), 170.18 (**C**, C-37) and 170.79 (**C**, C-33); m/z (ES⁺) 994 (M⁺ + NH₄), 999 (M⁺ + Na); m/z (ES⁻) 1011 (M⁻ + Cl). Further elution afforded a second fraction, bis-sugar analogue **281** (17.3 mg, 13%).

4.7 Applications of the Macrocycles

4.7.1 Heck Reactions

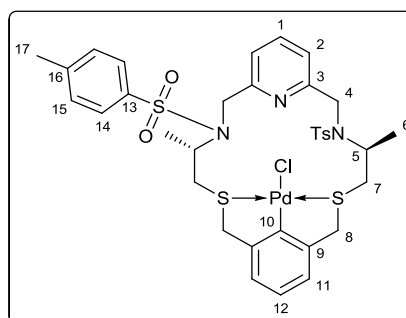
Palladium complexed spacer **298**



298

A solution of the spacer **210** (103 mg, 173 μmol) and $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (45.5 mg, 175 μmol) in dry CH_3CN (70 mL) was brought to reflux for 24 hours. After an additional period at room temperature for 24 hours, the solvent was removed *in vacuo* to leave the desired product **298** (121 mg, 95%) as a yellow powder; δ_{H} (CDCl_3 , 500 MHz) 1.17 (6H, d, $J = 6.0$ Hz, CH_3 , H-8), 2.36 (6H, s, CH_3 , H-13), 3.46 (2H, br.s, CH_2 , H-6 + 2H, CH , H-7), 3.73 (2H, br.s, CH_2 , H-6), 4.13 (2H, br.s, CH_2 , H-5), 4.31 (2H, br.s, CH_2 , H-5), 6.80 – 6.94 (3H, m, CH , H-3,4), 7.24 (4H, d, $J = 7.0$ Hz, CH , H-11) and 7.77 (4H, d, $J = 6.0$ Hz, CH , H-10); δ_{C} (CDCl_3 , 75 MHz) 20.59 (CH_3 , C-7), 21.40 (CH_3 , C-13), 46.25 (CH_2 , C-6), 48.39 (CH_2 , C-5), 48.47 (CH , C-7), 122.54 (CH , C-3), 124.81 (CH , C-4), 126.91 (CH , C-10), 129.61 (CH , C-11), 137.92 (C, C-9), 143.23 (C, C-12), 148.13 (C, C-2) and 158.99 (C, C-1); m/z (ES^+) 695.1, 696.1, 697.1, 698.1, 699.1, 700.1, 701.0, 702.1 ($\text{M}^+ - \text{Cl}$).

Palladium complexed macrocycle **299**



299

A solution of the macrocycle **240** (102 mg, 160 μmol) and $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (41.2 mg, 159 μmol) in dry CH_3CN (40 mL) was brought to reflux for 24 hours. The solvent was removed *in vacuo* to leave the *title compound* **299** (122 mg, quant.) as a dark yellow powder; (found C, 46.75; H, 4.78; N, 4.62; Cl, 7.39; S, 13.83; Pd, 12.94%. $\text{C}_{35}\text{H}_{40}\text{ClN}_3\text{O}_4\text{PdS}_4 \cdot \text{HCl}$ requires C, 48.14; H, 4.73; N, 4.81; Cl, 8.12; S, 14.69; Pd, 12.19%. Found $[\text{ES}^+] \text{M}^+ - \text{Cl}$, 800.0928. $\text{C}_{35}\text{H}_{40}\text{O}_4\text{N}_3\text{PdS}_4$ requires M , 800.0931); δ_{H} (CDCl_3 , 500 MHz) Spectrum showed formation of the *title compound*, key peaks reported as follows 1.11 (6H, d, $J = 7.0$ Hz, CH_3 , H-6), 1.52 (6H, d, $J = 6.5$ Hz, CH_3 , H-6), 2.44 (6H, s, CH_3 , H-17), 2.45 (6H, s, CH_3 , H-17), 2.92 (2H, dd, $J = 14.5, 6.5$ Hz, CH_2 , H-7), 3.46 (2H, dd, $J = 14.5, 6.0$ Hz, CH_2 , H-7), 3.83 (2H, d, $J = 16.0$ Hz, CH_2), 4.10 (2H, d, $J = 15.5$ Hz, CH_2), 4.21 (2H, d, $J = 16.5$ Hz, CH_2), 4.31 (2H, d, $J = 16.5$ Hz, CH_2), 4.40 (2H, d, $J = 15.5$ Hz, CH_2), 4.51 (2H, d, $J = 16.0$ Hz, CH_2); m/z (ES^+) 798.4 799.4, 800.2, 802.6, 803.8, 804.6, 805.4 ($\text{M}^+ - \text{Cl}$).

Control: Palladium Acetate catalysed synthesis of stilbene

Palladium Acetate (8.7 mg, 38.8 μmol), iodobenzene (43 μL , 384 μmol), styrene (67 μL , 588 μmol), and Et_3N (81 μL , 581 μmol) were dissolved in DMF (300 μL) and heated at 110 $^\circ\text{C}$ for 7 hours. On cooling to room temperature, the reaction was poured onto diethyl ether (10 mL), filtered, the residue washed with further portions of diethyl ether (4 x 10 mL). The organic portions were combined and the solvent removed *in vacuo*. The crude material showed a 1:30 ratio of styrene: product. *Trans*-stilbene was isolated after purification by column chromatography (57 mg, 91%).

Benzyl spacer catalysed stilbene synthesis

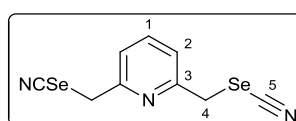
298 (27.5 mg, 37.5 μmol), iodobenzene (42 μL , 375 μmol), styrene (65 μL , 588 μmol), and Et_3N (79 μL , 567 μmol) were dissolved in DMF (300 μL) and heated at 110 $^\circ\text{C}$ for 7 hours. On cooling to room temperature, the reaction was poured onto diethyl ether (10 mL), filtered, the residue washed with further portions of diethyl ether (4 x 10 mL). The organic portions were combined and the solvent removed *in vacuo*. The crude material showed a 1:5 ratio of styrene: product. Purification by flash chromatography (Pet. Ether) gave exclusively *trans*-stilbene (7.2 mg, 11%).

Benzyl macro catalysed stilbene synthesis

299 (31.5 mg, 37.6 μmol), iodobenzene (42 μL , 375 μmol), styrene (65 μL , 567 μmol), and Et_3N (81 μL , 567 μmol) were dissolved in DMF (300 μL) and heated at 110 $^\circ\text{C}$ for 7 hours. On cooling to room temperature, the reaction was poured onto diethyl ether (10 mL), filtered, the residue washed with further portions of diethyl ether (4 x 10 mL). The organic portions were combined and the solvent removed *in vacuo*. The crude material showed a 1:12 ratio of styrene: product. Purification by flash chromatography (Pet. Ether) gave exclusively *trans*-stilbene (7.3 mg, 11%).

4.8 Organoselenium Trials [CARE: malodourous]

2,6-bis(selenocyanatomethyl)pyridine **285**²²⁵

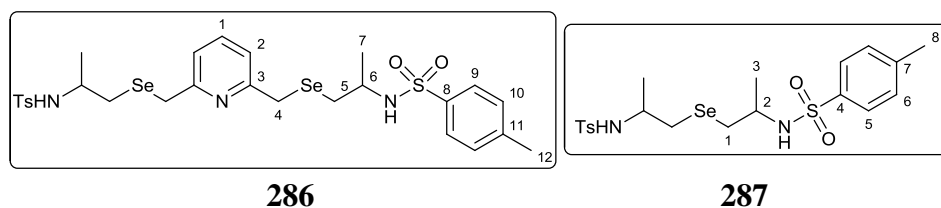


285

KSeCN (724 mg, 5.0 mmol) in degassed acetone (20 mL) was added dropwise to a solution of 2,6-bis(bromomethyl)pyridine (524 mg, 2.0 mmol) in degassed acetone (15 mL). The reaction which was left to stir at room temperature for 5 hours after which it was filtered and concentrated *in vacuo* resulting in the *title product* **285** as a pale yellow solid (621 mg, 99%), (found $[\text{ES}^+] \text{M}^+ + \text{Na}$, 339.8870. $\text{C}_9\text{H}_7\text{N}_3\text{Na}^{80}\text{Se}_2$ requires M , 339.8863); ν_{max} (ATR): 3418 (br, m), 2950 (w), 2923 (w), 2149 (m), 2069 (s), 1697 (m), 1591 (m), 1567 (m), 1455 (s), 1154 (m) cm^{-1} ; δ_{H} (CDCl_3 , 500 MHz) 4.49 (4H, s, CH_2 , H-4), 7.31 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-2), 7.76 (1H, t, $J = 8.0$ Hz, Ar-**H**, H-1); δ_{C}

(CDCl₃, 125 MHz) 33.69 (CH₂, CH₂Se, C-4), 102.32 (C, SeCN, C-5), 121.67 (CH, C-2), 138.12 (CH, C-1), 154.75 (C, C-3); ⁷⁷Se NMR: (CDCl₃, 76 MHz) 231.74 (2Se, t, *J*_{SeH} = 10.0 Hz, CH₂SeCN); *m/z* (ES⁺) 311.9, 313.9, 315.8, 317.2 (M⁺ + H), 339.9 (M⁺ + Na), 353.9, 355.9 (M⁺ + K).

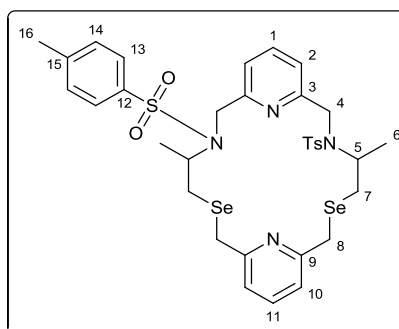
(*S**,*S**),(*R**,*S**)-*N,N'*-1,1'-(pyridine-2,6-diylbis(methylene))bis(selanediy)bis(propane-2,1-diyl)bis(toluene-4-sulfonamide) **286**



NaBH₄ (120 mg, 3.2 mmol) in 1:9 EtOH/THF (13 mL) was added dropwise at room temperature to a solution of selenocyanate **285** (332 mg, 1.1 mmol) and racemic aziridine **194** (447 mg, 2.1 mmol) in degassed 1:9 EtOH/THF (12 mL). After 2 hours at room temperature, the solvent was removed *in vacuo* to dryness. EtOAc (20 mL) was added, and washed with H₂O (2 x 10 mL), 0.1 M NaOH (10 mL), and brine (10 mL), before being dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material (645 mg) was purified by column chromatography (30 → 40% EtOAc in petrol) to afford two compounds. The less polar compound (*R*_f = 0.76) was isolated as (*S**,*S**),(*R**,*S**)-*N,N'*-(1,1'-selenobis(propane-2,1-diyl))bis(toluene-4-sulfonamide) **287** (92.8 mg, 17%), *R*_f = 0.76 (60% EtOAc in petrol), (found [ES⁺] M⁺ + Na, 527.0540. C₂₀H₂₈O₄N₂NaS₂⁸⁰Se requires *M*, 527.0548); δ_H (CDCl₃, 400 MHz) 1.05 (6H, d, *J* = 6.5 Hz, CH₃, H-3), 1.07 (6H, d, *J* = 6.5 Hz, CH₃, H-3), 2.43 (12H, s, CH₃, H-8), 2.53 (2H, dd, *J* = 12.5, 6.0 Hz, CH₂, H-1), 2.54 (4H, d, *J* = 6.0 Hz, CH₂, H-1), 2.59 (2H, dd, *J* = 12.5, 5.5 Hz, CH₂, H-1), 3.39 - 3.51 (4H, m, CH, H-2), 5.04 (2H, d, *J* = 7.5 Hz, NH), 5.05 (2H, d, *J* = 7.5 Hz, NH), 7.31 (8H, d, *J* = 8.0 Hz, Ar-H, H-6), 7.77 (4H, d, *J* = 8.0 Hz, Ar-H, H-5) and 7.78 (4H, d, *J* = 8.0 Hz, Ar-H, H-5); δ_C (CDCl₃, 125 MHz) 21.09, 21.19 (CH₃, C-3), 21.47, 21.50 (CH₃, C-8), 33.04, 33.31 (CH₂, C-1), 49.46, 49.51 (CH, C-2), 127.01, 127.03 (CH, C-5), 129.70, 129.72 (CH, C-6), 137.72 (C, C-4) and 143.45 (C, C-7); ⁷⁷Se NMR: (CDCl₃, 76 MHz) 65.76 (1Se, br. m, CH₂SeCH₂) and 68.42 (1Se, br. m, CH₂SeCH₂); *m/z* (ES⁺) 522.8, 523.5, 525.2, 527.3, 529.4 (M⁺ + Na). Further

elution afforded the *title compound* **286** as a near-colourless foam (331 mg, 45%), $R_f = 0.56$ (60% EtOAc in petrol), (found $[ES^+]$ $M^+ + Na$, 712.0282. $C_{27}H_{35}O_4N_3NaS_5^{80}Se_2$ requires M , 712.0292); δ_H ($CDCl_3$, 400 MHz) 1.13 (6H, d, $J = 6.5$ Hz, CH_3 , H-7), 1.14 (6H, d, $J = 6.5$ Hz, CH_3 , H-7), 2.42 (12H, s, CH_3 , H-12), 2.67 (4H, ddd, $J = 13.0, 7.0, 5.5$ Hz, CH_2 , H-5), 2.75 (4H, ddd, $J = 13.0, 5.0, 2.0$ Hz, CH_2 , H-5), 3.58 - 3.67 (4H, m, CH , H-6), 3.79 (4H, dd, $J = 12.0, 4.0$ Hz, CH_2 , H-4), 3.85 (4H, d, $J = 12.0$ Hz, CH_2 , H-4), 6.29 (2 H, d, $J = 7.5$ Hz, NH), 6.34 (2H, d, $J = 7.5$ Hz, NH), 7.07 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-2), 7.08 (2H, d, $J = 8.0$ Hz, Ar-**H**, H-2), 7.29 (8H, d, $J = 8.0$ Hz, Ar-**H**, H-10), 7.57 (1H, t, $J = 8.0$ Hz, Ar-**H**, H-1), 7.57 (1H, t, $J = 8.0$ Hz, Ar-**H**, H-1), 7.77 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-9) and 7.77 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-9); δ_C ($CDCl_3$, 125 MHz) 21.47 (CH_3 , C-12), 21.60, 21.67 (CH_3 , C-7), 28.80 (CH_2 , C-4), 32.08, 32.11 (CH_2 , C-5), 49.99, 50.08 (CH , C-6), 121.08 (CH , C-2), 126.98 (CH , C-9), 129.60 (CH , C-10), 137.97, 137.99 (CH , C-1), 138.34 (C, C-8), 143.10 (C, C-11), 159.21 and 159.23 (C, C-3); ^{77}Se NMR: ($CDCl_3$, 76 MHz) 205.09 - 206.05 (2Se, br. m, CH_2SeCH_2) and 206.55 - 207.62 (2Se, br. m, CH_2SeCH_2); m/z (ES^+) 686.8, 690.5 ($M^+ + H$), 706.5, 708.5, 710.4, 712.4, 714.4 ($M^+ + Na$).

(S^,S^*), (R^*,S^*)*-4,16-Dimethyl-3,17-bis-(toluene-4-sulfonyl)-6,14-diseleno-3,17,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracos-1(22),8,10,12(24),19(23),20-hexaene **289**

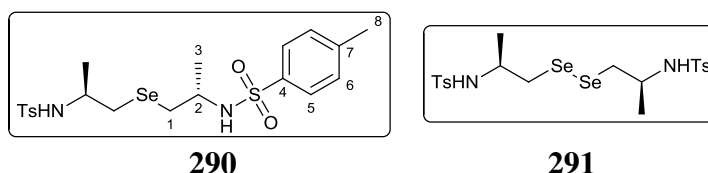


289

Caesium carbonate (751 mg, 2.3 mmol) was added to a solution of selenospacer **286** (312 mg, 0.5 mmol) and 2,6-bis(bromomethyl)pyridine **24** (121 mg, 0.5 mmol) in dry DMF (150 mL). After stirring for 2 days at room temperature, the solvent was removed *in vacuo*. The residue dissolved in dichloromethane (100 mL) which was washed with H_2O (6 x 50 mL). The organics layer was dried over $MgSO_4$, filtered and the solvent

removed *in vacuo* leaving crude material (356 mg, 100%) which was not stable on silica, $R_f = 0.33$ (40% EtOAc in petrol); δ_H (CDCl₃, 400 MHz) 0.94 (6H, d, $J = 6.5$ Hz, CH₃, H-6, **A**), 1.08 (6H, d, $J = 6.5$ Hz, CH₃, H-6, **B**), 2.09 (2H, dd, $J = 12.0, 6.5$ Hz, CH₂, H-7, **A**), 2.30 (2H, dd, $J = 12.0, 8.0$ Hz, CH₂, H-7, **A**), 2.37 (6H, s, CH₃, H-16, **B**), 2.44 (6H, s, CH₃, H-16, **A**), 2.64 (2H, dd, $J = 12.5, 8.0$ Hz, CH₂, H-7, **B**), 2.72 (2H, dd, $J = 12.5, 6.5$ Hz, CH₂, H-7, **B**), 3.60 (2H, d, $J = 12.0$ Hz, CH₂, H-8, **B**), 3.61 (2H, d, $J = 12.0$ Hz, CH₂, H-8, **A**), 3.69 (2H, d, $J = 12.0$ Hz, CH₂, H-8, **A**), 3.71 (2H, d, $J = 12.0$ Hz, CH₂, H-8, **B**), 4.13 (2H, d, $J = 16.0$ Hz, CH₂, H-4, **A**), 4.03 - 4.21 (4H, m, CH, H-5), 4.34 (2H, d, $J = 16.0$ Hz, CH₂, H-4, **B**), 4.54 (2H, d, $J = 16.0$ Hz, CH₂, H-4, **B**), 4.69 (2H, d, $J = 16.0$ Hz, CH₂, H-4, **A**), 7.01 (2H, d, $J = 7.5$ Hz, CH, H-10, **B**), 7.04 (2H, d, $J = 7.5$ Hz, CH, H-10, **A**), 7.22 (4H, d, $J = 8.0$ Hz, CH, H-14, **B**), 7.31 (4H, d, $J = 8.0$ Hz, CH, H-14, **A**), 7.45 (2H, d, $J = 7.5$ Hz, CH, H-2, **B**), 7.50 (2H, t, $J = 7.5$ Hz, CH, H-1,11, **B**), 7.65 (2H, d, $J = 7.5$ Hz, CH, H-2, **A**), 7.62 (1H, t, $J = 8.0$ Hz, CH, H-1,11, **A**), 7.63 (1H, t, $J = 8.0$ Hz, CH, H-1,11, **A**), 7.66 (4H, d, $J = 8.0$ Hz, CH, H-13, **B**), 7.72 (4H, d, $J = 8.0$ Hz, CH, H-13, **A**)

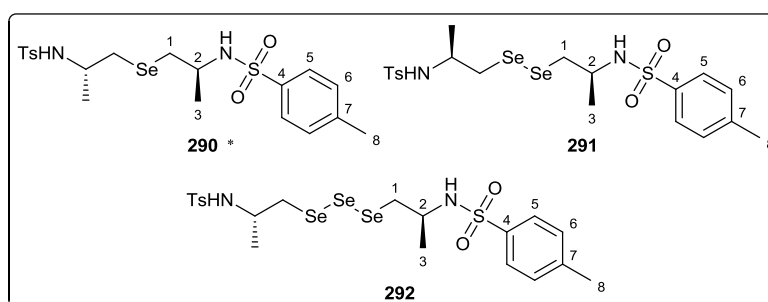
N,N'-(2*S*,2'*S*)-1,1'-selenobis(propane-2,1-diyl)bis(4-methylbenzenesulfonamide) **290**²⁵⁷



Selenium powder (−100 mesh, 85.3 mg, 1.1 mmol), sodium hydroxide (97.9 mg, 2.5 mmol) and NaBH₄ (89.8 mg, 2.4 mmol) were dissolved in aqueous THF (20 mL, 1% H₂O) at 0 °C under N₂. The reaction was left for stir at 0 °C for 30 minutes, then allowed to warm to room temperature and left to stir for 30 minutes. Aziridine **181** (465 mg, 2.2 mmol) was added and the reaction was left to stir at 35 °C for 2 hours. 0.1 M NaOH was added and the solution was dried *in vacuo*. The residues were taken up in EtOAc (30 mL), washed with H₂O (2 x 15 mL), 0.1 M NaOH (15 mL x 1), brine (15 mL x 1), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30% EtOAc in petrol) to give **290** as a thick yellow oil (338 mg, 62%). Product contained a small amount **291** which was inseparable from **290** by chromatography, $R_f = 0.52$ (50% EtOAc in petrol), (found [ES⁺]

$M^+ + Na$, 527.0550. $C_{20}H_{28}O_4N_2NaS_2^{80}Se$ requires M , 527.0548); δ_H ($CDCl_3$, 400 MHz) 1.07 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.43 (6H, s, CH_3 , H-8), 2.54 (4H, d, $J = 6.0$ Hz, CH_2 , H-1), 3.43 (2H, dqt, $J = 7.5, 6.5, 6.0$ Hz, CH , H-2), 5.08 (2H, d, $J = 7.5$ Hz, NH), 7.31 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.77 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-5); ^{77}Se NMR: ($CDCl_3$, 76 MHz) 66.93 - 68.12 (1Se, br. m, CH_2SeCH_2) and 290.84 - 291.86 (2Se, br. m, $CH_2SeSeCH_2$); m/z (ES^+) 522.0, 524.3, 525.2, 527.3, 529.4 ($M^+ + Na$), 543.2 ($M^+ + K$).

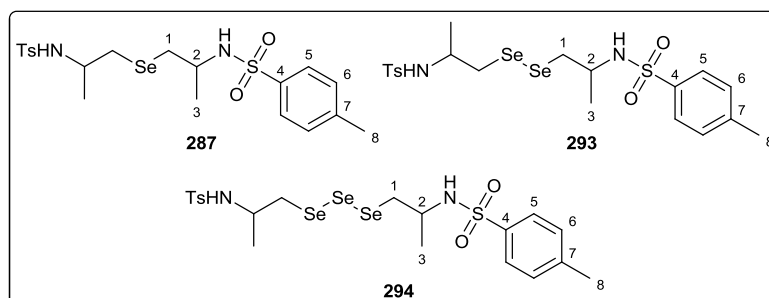
Formation of chiral selenide spacers via Se_2^{2-} dianion (**290-292**)



Selenium powder (−100 mesh, 239 mg, 3.0 mmol) and 1 M lithium triethylborohydride in THF (2.85 mL, 1.2 eq.) were stirred together in dry THF (24 mL) for 30 minutes. S-aziridine **181** (534 mg, 2.5 mmol) in dry THF (5 mL) was added dropwise and the reaction stirred for 16 hours which was then quenched with NH_4Cl and extracted with DCM. The crude product (912 mg) was purified by flash column chromatography (30 → 100% EtOAc in petrol) resulting in a mixture of inseparable products **290-292** (514 mg, 35%). Products **290:291:292** isolated in ratio 3.4:2.8:1, $R_f = 0.58$ (50% EtOAc in petrol); δ_H ($CDCl_3$, 500 MHz) **290** 1.07 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.44 (6H, s, CH_3 , H-8), 2.54 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-1), 2.57 (2H, dd, $J = 13.0, 5.5$ Hz, CH_2 , H-1), 3.40 - 3.49 (2H, m, CH , H-2), 4.92 (2H, d, $J = 7.5$ Hz, NH), 7.32 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.77 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-5); **291** 1.13 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.44 (6H, s, CH_3 , H-8), 2.97 (2H, dd, $J = 13.0, 6.0$ Hz, CH_2 , H-1), 3.14 (2H, dd, $J = 13.0, 5.5$ Hz, CH_2 , H-1), 3.57 (2H, app. sept, $J = 6.5$ Hz, CH , H-2), 5.06 (2H, d, $J = 7.5$ Hz, NH), 7.32 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.79 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-5); **292** 1.17 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.44 (6H, s, CH_3 , H-8), 3.19 (2H, dd, $J = 13.0, 5.5$ Hz, CH_2 , H-1), 3.28 (2H, dd, $J = 13.0, 5.5$ Hz, CH_2 , H-1), 3.63 - 3.73 (2H, m, CH , H-2), 5.13 (2H, d, $J = 7.5$ Hz, NH), 7.32 (4H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.77

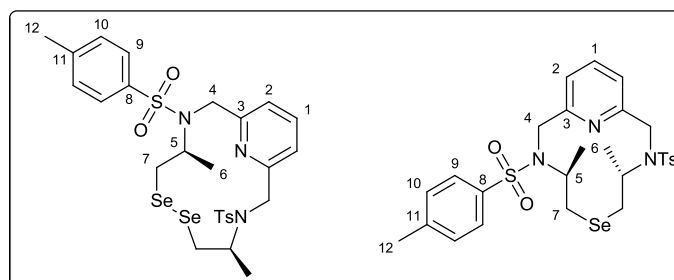
(4H, d, $J = 8.0$ Hz, Ar-**H**, H-5); m/z (ES^+) 522.4, 527.3 ($M_{290}^+ + Na$), 600.4, 602.4, 605.0, 607.1, 608.9, 610.1 ($M_{291}^+ + Na$), 682.4, 687.1 ($M_{292}^+ + Na$).

Formation of racemic selenide spacers via Se_2^{2-} dianion (**287**, **293**, **294**)



Selenium powder (–100 mesh, 230 mg, 2.9 mmol) and 1 M lithium triethylborohydride in THF (2.90 mL, 1.2 eq.) were stirred together in dry THF (25 mL) for 30 minutes. S-aziridine **194** (508 mg, 2.4 mmol) in dry THF (5 mL) was added dropwise and the reaction stirred for 16 hours which was then quenched with NH_4Cl and extracted with DCM. The crude product was purified by flash column chromatography (30 → 100% EtOAc in petrol) resulting in a mixture of inseparable products (511 mg, 36%). Products **287:293:294** isolated in ratio 3:3.4:1, $R_f = 0.58$ (50% EtOAc in petrol), (found [ES^+] $M_{293}^+ + H$, 584.9887. $C_{20}H_{29}O_4N_2S_2^{80}Se_2$ requires M , 584.9894), δ_H ($CDCl_3$, 500 MHz) **287** 1.07 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 1.05 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.44 (12H, s, CH_3 , H-8), 2.51 - 2.62 (8H, m, CH_2 , H-1), 3.41 - 3.52 (4H, m, $J = 7.0$ Hz, CH , H-2), 4.89 - 4.94 (4H, m, NH), 7.32 (8H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.75 - 7.81 (8H, m, Ar-**H**, H-5); **293** 1.13 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 1.15 (6H, d, $J = 7.0$ Hz, CH_3 , H-3), 2.44 (12H, s, CH_3 , H-8), 2.93 - 3.16 (8H, m, CH_2 , H-1), 3.52 - 3.62 (4H, m, $J = 7.0$ Hz, CH , H-2), 4.92 (2H, d, $J = 7.5$ Hz, NH), 5.06 (2H, d, $J = 7.5$ Hz, NH), 7.32 (8H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.75 - 7.81 (8H, m, Ar-**H**, H-5); **294** 1.16 (6H, d, $J = 7.0$ Hz, CH_3 , H-3), 1.20 (6H, d, $J = 6.5$ Hz, CH_3 , H-3), 2.44 (12H, s, CH_3 , H-8), 3.15 - 3.33 (8H, m, CH_2 , H-1), 3.62 - 3.73 (4H, m, $J = 7.0$ Hz, CH , H-2), 4.97 (2H, d, $J = 7.5$ Hz, NH), 5.13 (2H, d, $J = 7.5$ Hz, NH), 7.32 (8H, d, $J = 8.0$ Hz, Ar-**H**, H-6) and 7.75 - 7.81 (8H, m, Ar-**H**, H-5); m/z (ES^+) 521.5, 523.5, 524.5, 525.4, 527.3, 529.4 ($M_{287}^+ + Na$), 602.0, 603.2, 605.3, 607.2, 609.2, 610.2 ($M_{293}^+ + Na$), 685.5 ($M_{294}^+ + Na$).

Cyclisation of mixture of seleno-spacers



296 and 295

Cs₂CO₃ (938 mg, 2.9 mmol) and 2,6-bis(bromomethyl)pyridine (150 mg, 0.6 mmol) were added to a solution of the mixture of selenide **290**, diselenide **291**, and triselenide **292** (333 mg, 0.6 mmol) in DMF (150 mL). After stirring at room temperature for 2 days, the reaction was reduced to dryness. DCM (100 mL) was added and extracted with water (5 x 30 mL). The organic extract was dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude material (358 mg, 91%, approx. 1:2.5:3). The material was purified by flash column chromatography (30% EtOAc in petrol), affording approximately a 1:1 mixture of selenide **295** and diselenide **296** (255 mg, 65%), R_f = 0.48 (40% EtOAc in petrol), δ_{H} (CDCl₃, 500 MHz) 1.20 (6H, d, J = 6.5 Hz, CH₃, H-6, **A**), 1.37 (6H, d, J = 7.0 Hz, CH₃, H-6, **B**), 2.41 (6H, s, CH₃, H-12), 2.37 - 2.43 (2H, m, CH₂, H-7, **B**), 2.45 (6H, s, CH₃, H-12), 3.06 - 3.15 (4H, m, CH₂, H-7, **A**), 3.10 - 3.19 (2H, m, CH₂, H-7, **B**), 3.66 - 3.76 (2H, m, CH₂, H-5, **A**), 3.81 - 3.89 (2H, m, CH₂, H-5, **B**), 4.28 (2H, d, J = 15.0 Hz, CH₂, H-4, **B**), 4.37 (4H, dd, J = 17.5, 15.0 Hz, CH₂, H-4, **A**), 4.45 (2H, d, J = 15.0 Hz, CH₂, H-4, **B**), 7.24 - 7.27 (2H, m, CH, H-2, **B**), 7.25 (4H, d, J = 8.0 Hz, CH, H-10), 7.33 (4H, d, J = 8.0 Hz, CH, H-10), 7.62 (1H, t, J = 7.5 Hz, CH, H-1, **B**), 7.64 (2H, d, J = 7.0 Hz, CH, H-2, **A**), 7.67 (4H, d, J = 8.0 Hz, CH, H-9), 7.70 (1H, t, J = 7.5 Hz, CH, H-1, **A**) and 7.77 (4H, d, J = 8.0 Hz, CH, H-9); δ_{C} (CDCl₃, 125 MHz) 16.04 (CH₃, C-6, **A**), 17.61 (CH₃, C-6, **B**), 21.46, 21.47, 21.51, 21.53 (CH₃, C-12), 28.11 (CH₂, C-7, **B**), 39.10 (CH₂, C-7, **A**), 51.35 (CH₂, C-4, **A**), 52.68 (CH₂, C-4, **B**), 56.88 (CH, C-5, **A**), 58.84 (CH, C-5, **B**), 122.88 (CH, C-2, **B**), 124.27 (CH, C-2, **A**), 127.18, 127.34 (CH, C-9), 129.49, 129.77 (CH, C-10), 137.56 (CH, C-1, **B**), 137.79 (CH, C-1, **A**), 137.90, 138.45 (C, C-8), 143.11, 143.55 (C, C-11), 156.49 (C, C-3, **A**) and 156.55 (C, C-3, **B**); m/z (ES⁺) 621.0, 622.3, 628.5, 630.2, 631.0, 632.7 (M₂₉₅⁺ + H), 705.5, 706.5, 707.6, 709.7, 710.8, 711.7 (M₂₉₆⁺ + Na); m/z (ES⁻)

638.3, 640.2, 642.1, 642.8, 644.4, 645.7 ($M_{295}^- + Cl$), 716.1, 717.9, 718.7, 719.9,
721.9, 724.3, 725.7 ($M_{296}^- + Cl$).

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Appendix

Table 1. Crystal data and structure refinement for s3119m **198**

Identification code	s3119m
Empirical formula	C ₂₄ H ₃₆ N ₂ O ₄ S ₅
Formula weight	576.85
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.9470(5) Å alpha = 90 deg. b = 17.8499(16) Å beta = 90 deg. c = 27.203(3) Å gamma = 90 deg.
Volume	2887.7(4) Å ³
Z, Calculated density	4, 1.327 Mg/m ³
Absorption coefficient	0.433 mm ⁻¹
F(000)	1224
Crystal size	0.30 x 0.20 x 0.10 mm
Theta range for data collection	1.36 to 28.28 deg.
Limiting indices	-7<=h<=7, -23<=k<=23, -35<=l<=35
Reflections collected / unique	25072 / 6868 [R(int) = 0.0805]
Completeness to theta = 25.00	100.0%
Absorption correction	None
Max. and min. transmission	0.9580 and 0.8810
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6868 / 0 / 328
Goodness-of-fit on F ²	0.879
Final R indices [I>2sigma(I)]	R1 = 0.0585, wR2 = 0.1153
R indices (all data)	R1 = 0.1157, wR2 = 0.1452
Absolute structure parameter	-0.07(11)

Largest diff. peak and hole 0.422 and -0.425 e.A⁻³

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (A² x 10³) for s3119m. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	9936(8)	5624(2)	11025(2)	28(1)
C(2)	8316(8)	5981(2)	11298(2)	35(1)
C(3)	6701(9)	6414(3)	11065(2)	39(1)
C(4)	6702(8)	6494(2)	10560(2)	36(1)
C(5)	8319(9)	6129(3)	10294(2)	39(1)
C(6)	9962(8)	5692(2)	10517(2)	34(1)
C(7)	4941(9)	6974(3)	10312(2)	57(2)
C(8)	10618(10)	3697(3)	11073(2)	45(2)
C(9)	8131(9)	3564(3)	10988(2)	36(1)
C(10)	7604(11)	3670(3)	9976(2)	47(2)
C(11)	5528(10)	4153(3)	9981(2)	50(2)
C(12)	4849(8)	4290(3)	8972(2)	36(1)
C(13)	2571(9)	3936(3)	8963(2)	50(2)
C(14)	1752(10)	4019(3)	7944(2)	47(1)
C(15)	-706(8)	4099(2)	7827(2)	31(1)
C(16)	-33(9)	5985(3)	8006(2)	38(1)
C(17)	125(10)	5876(3)	8514(2)	50(2)
C(18)	1822(11)	6216(3)	8776(2)	58(2)
C(19)	3389(11)	6668(3)	8546(2)	51(2)
C(20)	3214(10)	6778(3)	8043(2)	55(2)
C(21)	1537(9)	6431(3)	7769(2)	42(1)
C(22)	5327(11)	7011(4)	8836(2)	82(2)
C(23)	11856(10)	2998(3)	11217(3)	95(3)
C(24)	-1642(10)	3381(3)	7598(2)	50(2)
N(1)	10945(7)	4267(2)	11459(1)	35(1)
N(2)	-1057(7)	4722(2)	7478(1)	31(1)
O(1)	12403(6)	5438(2)	11795(1)	47(1)
O(2)	13795(5)	4959(2)	10989(1)	39(1)
O(3)	-2497(5)	5943(2)	7230(1)	40(1)
O(4)	-3884(6)	5340(2)	7997(1)	48(1)
S(1)	11980(2)	5073(1)	11330(1)	33(1)
S(2)	7591(4)	2979(1)	10463(1)	68(1)
S(3)	5402(3)	4851(1)	9504(1)	64(1)
S(4)	2225(4)	3336(1)	8429(1)	85(1)
S(5)	-2077(2)	5509(1)	7665(1)	33(1)

Table 3. Bond lengths [A] and angles [deg] for s3119m.

C(1)-C(2)	1.373(6)
C(1)-C(6)	1.387(6)
C(1)-S(1)	1.770(5)
C(2)-C(3)	1.386(7)
C(2)-H(2)	0.9500

C (3) -C (4)	1.383 (7)
C (3) -H (3)	0.9500
C (4) -C (5)	1.368 (7)
C (4) -C (7)	1.510 (7)
C (5) -C (6)	1.390 (6)
C (5) -H (5)	0.9500
C (6) -H (6)	0.9500
C (7) -H (7A)	0.9800
C (7) -H (7B)	0.9800
C (7) -H (7C)	0.9800
C (8) -N (1)	1.475 (7)
C (8) -C (23)	1.500 (7)
C (8) -C (9)	1.516 (7)
C (8) -H (8)	1.0000
C (9) -S (2)	1.799 (5)
C (9) -H (9A)	0.9900
C (9) -H (9B)	0.9900
C (10) -C (11)	1.506 (7)
C (10) -S (2)	1.810 (4)
C (10) -H (10A)	0.9900
C (10) -H (10B)	0.9900
C (11) -S (3)	1.801 (5)
C (11) -H (11A)	0.9900
C (11) -H (11B)	0.9900
C (12) -C (13)	1.495 (7)
C (12) -S (3)	1.791 (5)
C (12) -H (12A)	0.9900
C (12) -H (12B)	0.9900
C (13) -S (4)	1.818 (6)
C (13) -H (13A)	0.9900
C (13) -H (13B)	0.9900
C (14) -C (15)	1.503 (7)
C (14) -S (4)	1.818 (5)
C (14) -H (14A)	0.9900
C (14) -H (14B)	0.9900
C (15) -N (2)	1.478 (5)
C (15) -C (24)	1.530 (6)
C (15) -H (15)	1.0000
C (16) -C (21)	1.385 (7)
C (16) -C (17)	1.398 (6)
C (16) -S (5)	1.750 (5)
C (17) -C (18)	1.378 (8)
C (17) -H (17)	0.9500
C (18) -C (19)	1.381 (8)
C (18) -H (18)	0.9500
C (19) -C (20)	1.387 (7)
C (19) -C (22)	1.524 (8)
C (20) -C (21)	1.390 (7)
C (20) -H (20)	0.9500
C (21) -H (21)	0.9500
C (22) -H (22A)	0.9800
C (22) -H (22B)	0.9800
C (22) -H (22C)	0.9800
C (23) -H (23A)	0.9800
C (23) -H (23B)	0.9800

C (23) -H (23C)	0.9800
C (24) -H (24A)	0.9800
C (24) -H (24B)	0.9800
C (24) -H (24C)	0.9800
N (1) -S (1)	1.604 (4)
N (1) -H (1N)	0.8308
N (2) -S (5)	1.612 (4)
N (2) -H (2N)	0.86 (5)
O (1) -S (1)	1.442 (3)
O (2) -S (1)	1.438 (3)
O (3) -S (5)	1.435 (3)
O (4) -S (5)	1.438 (3)
C (2) -C (1) -C (6)	120.4 (5)
C (2) -C (1) -S (1)	119.1 (4)
C (6) -C (1) -S (1)	120.6 (4)
C (1) -C (2) -C (3)	119.9 (5)
C (1) -C (2) -H (2)	120.1
C (3) -C (2) -H (2)	120.1
C (4) -C (3) -C (2)	120.8 (5)
C (4) -C (3) -H (3)	119.6
C (2) -C (3) -H (3)	119.6
C (5) -C (4) -C (3)	118.4 (5)
C (5) -C (4) -C (7)	121.5 (5)
C (3) -C (4) -C (7)	120.1 (5)
C (4) -C (5) -C (6)	122.0 (5)
C (4) -C (5) -H (5)	119.0
C (6) -C (5) -H (5)	119.0
C (1) -C (6) -C (5)	118.5 (5)
C (1) -C (6) -H (6)	120.8
C (5) -C (6) -H (6)	120.8
C (4) -C (7) -H (7A)	109.5
C (4) -C (7) -H (7B)	109.5
H (7A) -C (7) -H (7B)	109.5
C (4) -C (7) -H (7C)	109.5
H (7A) -C (7) -H (7C)	109.5
H (7B) -C (7) -H (7C)	109.5
N (1) -C (8) -C (23)	108.9 (5)
N (1) -C (8) -C (9)	110.2 (4)
C (23) -C (8) -C (9)	112.9 (4)
N (1) -C (8) -H (8)	108.2
C (23) -C (8) -H (8)	108.2
C (9) -C (8) -H (8)	108.2
C (8) -C (9) -S (2)	112.7 (4)
C (8) -C (9) -H (9A)	109.0
S (2) -C (9) -H (9A)	109.0
C (8) -C (9) -H (9B)	109.0
S (2) -C (9) -H (9B)	109.0
H (9A) -C (9) -H (9B)	107.8
C (11) -C (10) -S (2)	112.3 (4)
C (11) -C (10) -H (10A)	109.1
S (2) -C (10) -H (10A)	109.1
C (11) -C (10) -H (10B)	109.1
S (2) -C (10) -H (10B)	109.1
H (10A) -C (10) -H (10B)	107.9

C(10)-C(11)-S(3)	115.0(4)
C(10)-C(11)-H(11A)	108.5
S(3)-C(11)-H(11A)	108.5
C(10)-C(11)-H(11B)	108.5
S(3)-C(11)-H(11B)	108.5
H(11A)-C(11)-H(11B)	107.5
C(13)-C(12)-S(3)	114.5(4)
C(13)-C(12)-H(12A)	108.6
S(3)-C(12)-H(12A)	108.6
C(13)-C(12)-H(12B)	108.6
S(3)-C(12)-H(12B)	108.6
H(12A)-C(12)-H(12B)	107.6
C(12)-C(13)-S(4)	111.3(4)
C(12)-C(13)-H(13A)	109.4
S(4)-C(13)-H(13A)	109.4
C(12)-C(13)-H(13B)	109.4
S(4)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0
C(15)-C(14)-S(4)	111.6(4)
C(15)-C(14)-H(14A)	109.3
S(4)-C(14)-H(14A)	109.3
C(15)-C(14)-H(14B)	109.3
S(4)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	108.0
N(2)-C(15)-C(14)	110.2(4)
N(2)-C(15)-C(24)	108.5(4)
C(14)-C(15)-C(24)	111.1(4)
N(2)-C(15)-H(15)	109.0
C(14)-C(15)-H(15)	109.0
C(24)-C(15)-H(15)	109.0
C(21)-C(16)-C(17)	119.6(5)
C(21)-C(16)-S(5)	120.0(4)
C(17)-C(16)-S(5)	120.2(5)
C(18)-C(17)-C(16)	119.9(6)
C(18)-C(17)-H(17)	120.0
C(16)-C(17)-H(17)	120.0
C(17)-C(18)-C(19)	121.2(5)
C(17)-C(18)-H(18)	119.4
C(19)-C(18)-H(18)	119.4
C(18)-C(19)-C(20)	118.6(6)
C(18)-C(19)-C(22)	120.8(6)
C(20)-C(19)-C(22)	120.6(7)
C(21)-C(20)-C(19)	121.3(6)
C(21)-C(20)-H(20)	119.4
C(19)-C(20)-H(20)	119.4
C(16)-C(21)-C(20)	119.4(5)
C(16)-C(21)-H(21)	120.3
C(20)-C(21)-H(21)	120.3
C(19)-C(22)-H(22A)	109.5
C(19)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(19)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(8)-C(23)-H(23A)	109.5

C (8) -C (23) -H (23B)	109.5
H (23A) -C (23) -H (23B)	109.5
C (8) -C (23) -H (23C)	109.5
H (23A) -C (23) -H (23C)	109.5
H (23B) -C (23) -H (23C)	109.5
C (15) -C (24) -H (24A)	109.5
C (15) -C (24) -H (24B)	109.5
H (24A) -C (24) -H (24B)	109.5
C (15) -C (24) -H (24C)	109.5
H (24A) -C (24) -H (24C)	109.5
H (24B) -C (24) -H (24C)	109.5
C (8) -N (1) -S (1)	121.0 (3)
C (8) -N (1) -H (1N)	120.8
S (1) -N (1) -H (1N)	109.8
C (15) -N (2) -S (5)	120.5 (3)
C (15) -N (2) -H (2N)	115 (3)
S (5) -N (2) -H (2N)	118 (3)
O (2) -S (1) -O (1)	119.9 (2)
O (2) -S (1) -N (1)	107.5 (2)
O (1) -S (1) -N (1)	106.3 (2)
O (2) -S (1) -C (1)	106.9 (2)
O (1) -S (1) -C (1)	106.3 (2)
N (1) -S (1) -C (1)	109.7 (2)
C (9) -S (2) -C (10)	100.7 (2)
C (12) -S (3) -C (11)	101.8 (2)
C (14) -S (4) -C (13)	101.7 (2)
O (3) -S (5) -O (4)	120.1 (2)
O (3) -S (5) -N (2)	106.1 (2)
O (4) -S (5) -N (2)	107.2 (2)
O (3) -S (5) -C (16)	107.2 (2)
O (4) -S (5) -C (16)	106.7 (2)
N (2) -S (5) -C (16)	109.2 (2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for s3119m.

The anisotropic displacement factor exponent takes the form: $-\pi^2 [h^2 a^2 U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
C (1)	28 (3)	22 (2)	33 (3)	4 (2)	-4 (2)	-10 (2)
C (2)	37 (3)	34 (3)	32 (3)	3 (2)	5 (2)	-6 (3)
C (3)	37 (3)	35 (3)	46 (3)	0 (2)	6 (3)	-2 (3)
C (4)	32 (3)	30 (3)	45 (3)	6 (2)	-6 (3)	-11 (2)
C (5)	52 (4)	34 (3)	31 (3)	8 (2)	-7 (3)	-13 (3)
C (6)	43 (3)	30 (3)	29 (3)	-1 (2)	4 (2)	-9 (2)
C (7)	48 (4)	57 (4)	66 (4)	22 (3)	-5 (3)	-3 (3)
C (8)	52 (4)	23 (3)	59 (4)	2 (3)	18 (3)	-4 (3)
C (9)	49 (3)	38 (3)	22 (2)	3 (2)	-2 (3)	4 (3)

C(10)	82(5)	41(3)	17(2)	1(2)	1(3)	1(3)
C(11)	60(4)	63(4)	26(3)	7(3)	-8(3)	1(3)
C(12)	45(3)	40(3)	23(2)	5(2)	-4(2)	-5(3)
C(13)	49(4)	53(3)	49(3)	26(3)	-3(3)	-6(3)
C(14)	54(4)	34(3)	52(3)	15(2)	-20(3)	6(3)
C(15)	35(3)	32(3)	27(3)	6(2)	4(2)	-1(2)
C(16)	51(4)	26(3)	36(3)	0(2)	-3(3)	17(3)
C(17)	66(4)	53(4)	30(3)	-3(3)	2(3)	25(3)
C(18)	69(5)	67(4)	39(3)	-18(3)	-16(4)	36(4)
C(19)	59(4)	48(3)	46(4)	-19(3)	-21(3)	33(3)
C(20)	54(4)	31(3)	80(4)	-2(3)	-19(4)	14(3)
C(21)	50(4)	32(3)	44(3)	-2(2)	-14(3)	12(3)
C(22)	75(6)	80(5)	90(5)	-43(4)	-48(4)	28(4)
C(23)	31(4)	32(3)	223(9)	-6(5)	6(5)	2(3)
C(24)	57(4)	40(3)	52(3)	9(3)	-14(3)	-13(3)
N(1)	32(3)	43(3)	29(2)	7(2)	9(2)	10(2)
N(2)	35(2)	34(2)	24(2)	7(2)	6(2)	6(2)
O(1)	36(2)	67(2)	37(2)	-10(2)	-10(2)	3(2)
O(2)	28(2)	46(2)	44(2)	-2(2)	5(2)	-5(2)
O(3)	41(2)	40(2)	39(2)	13(2)	-10(2)	5(2)
O(4)	47(2)	50(2)	47(2)	11(2)	18(2)	14(2)
S(1)	27(1)	41(1)	32(1)	-2(1)	-4(1)	-3(1)
S(2)	145(2)	32(1)	28(1)	-1(1)	-13(1)	-5(1)
S(3)	105(1)	50(1)	36(1)	-1(1)	-25(1)	3(1)
S(4)	129(2)	36(1)	88(1)	22(1)	-77(1)	-10(1)
S(5)	34(1)	36(1)	30(1)	8(1)	3(1)	11(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for s3119m.

	x	y	z	U(eq)
H(2)	8301	5931	11646	41
H(3)	5580	6659	11255	47
H(5)	8318	6175	9946	47
H(6)	11077	5446	10326	41
H(7A)	5507	7487	10279	85
H(7B)	3569	6976	10512	85
H(7C)	4606	6769	9986	85
H(8)	11288	3890	10761	54
H(9A)	7373	4052	10940	43
H(9B)	7476	3326	11284	43
H(10A)	8948	3992	10011	56
H(10B)	7708	3411	9654	56
H(11A)	5438	4408	10304	60
H(11B)	4193	3824	9952	60
H(12A)	5013	4608	8676	43
H(12B)	5998	3890	8952	43
H(13A)	1407	4332	8959	60
H(13B)	2360	3635	9266	60
H(14A)	2359	4510	8048	56

H (14B)	2569	3861	7644	56
H (15)	-1546	4207	8138	38
H (17)	-938	5567	8678	60
H (18)	1917	6139	9121	70
H (20)	4260	7097	7882	66
H (21)	1469	6499	7423	50
H (22A)	6139	6615	9011	123
H (22B)	4734	7374	9073	123
H (22C)	6356	7265	8609	123
H (23A)	13467	3106	11242	143
H (23B)	11611	2610	10967	143
H (23C)	11298	2820	11535	143
H (24A)	-3266	3434	7549	75
H (24B)	-1348	2957	7817	75
H (24C)	-910	3293	7280	75
H (1N)	10042	4306	11691	17 (12)
H (2N)	-150 (80)	4730 (30)	7230 (18)	50 (17)

Table 6. Torsion angles [deg] for s3119m.

C (6) -C (1) -C (2) -C (3)	-0.3 (7)
S (1) -C (1) -C (2) -C (3)	-180.0 (3)
C (1) -C (2) -C (3) -C (4)	-0.2 (7)
C (2) -C (3) -C (4) -C (5)	0.7 (7)
C (2) -C (3) -C (4) -C (7)	-179.5 (4)
C (3) -C (4) -C (5) -C (6)	-0.9 (7)
C (7) -C (4) -C (5) -C (6)	179.3 (4)
C (2) -C (1) -C (6) -C (5)	0.1 (7)
S (1) -C (1) -C (6) -C (5)	179.8 (3)
C (4) -C (5) -C (6) -C (1)	0.5 (7)
N (1) -C (8) -C (9) -S (2)	171.5 (3)
C (23) -C (8) -C (9) -S (2)	-66.5 (6)
S (2) -C (10) -C (11) -S (3)	-179.5 (3)
S (3) -C (12) -C (13) -S (4)	-176.6 (2)
S (4) -C (14) -C (15) -N (2)	172.9 (3)
S (4) -C (14) -C (15) -C (24)	-66.8 (5)
C (21) -C (16) -C (17) -C (18)	0.7 (7)
S (5) -C (16) -C (17) -C (18)	176.0 (4)
C (16) -C (17) -C (18) -C (19)	-0.1 (8)
C (17) -C (18) -C (19) -C (20)	0.5 (8)
C (17) -C (18) -C (19) -C (22)	-177.0 (5)
C (18) -C (19) -C (20) -C (21)	-1.5 (8)
C (22) -C (19) -C (20) -C (21)	176.0 (5)
C (17) -C (16) -C (21) -C (20)	-1.6 (7)
S (5) -C (16) -C (21) -C (20)	-177.0 (4)
C (19) -C (20) -C (21) -C (16)	2.1 (8)
C (23) -C (8) -N (1) -S (1)	123.5 (4)
C (9) -C (8) -N (1) -S (1)	-112.2 (4)
C (14) -C (15) -N (2) -S (5)	-104.9 (4)
C (24) -C (15) -N (2) -S (5)	133.3 (4)
C (8) -N (1) -S (1) -O (2)	-41.4 (4)
C (8) -N (1) -S (1) -O (1)	-170.9 (4)
C (8) -N (1) -S (1) -C (1)	74.6 (4)

C(2)-C(1)-S(1)-O(2)	-163.1(3)
C(6)-C(1)-S(1)-O(2)	17.2(4)
C(2)-C(1)-S(1)-O(1)	-34.0(4)
C(6)-C(1)-S(1)-O(1)	146.3(4)
C(2)-C(1)-S(1)-N(1)	80.6(4)
C(6)-C(1)-S(1)-N(1)	-99.1(4)
C(8)-C(9)-S(2)-C(10)	-85.6(4)
C(11)-C(10)-S(2)-C(9)	-73.1(4)
C(13)-C(12)-S(3)-C(11)	68.3(4)
C(10)-C(11)-S(3)-C(12)	72.7(4)
C(15)-C(14)-S(4)-C(13)	-99.4(4)
C(12)-C(13)-S(4)-C(14)	-76.9(4)
C(15)-N(2)-S(5)-O(3)	-171.9(3)
C(15)-N(2)-S(5)-O(4)	-42.4(4)
C(15)-N(2)-S(5)-C(16)	72.8(4)
C(21)-C(16)-S(5)-O(3)	-29.0(4)
C(17)-C(16)-S(5)-O(3)	155.6(4)
C(21)-C(16)-S(5)-O(4)	-158.9(4)
C(17)-C(16)-S(5)-O(4)	25.7(5)
C(21)-C(16)-S(5)-N(2)	85.5(4)
C(17)-C(16)-S(5)-N(2)	-89.8(4)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for s3119m [A and deg.].

D-H...A <(DHA)	d(D-H)	d(H...A)	d(D...A)
N(1)-H(1N)...O(3)#1 162.4	0.83	2.15	2.957(5)
N(2)-H(2N)...O(1)#2 162(5)	0.86(5)	2.04(5)	2.875(5)

Symmetry transformations used to generate equivalent atoms:

#1 $-x+1/2, -y+1, z+1/2$ #2 $-x+3/2, -y+1, z-1/2$

Table 1. Crystal data and structure refinement for s3433 - **256**

Identification code	s3433abs	
Empirical formula	C11 H11 Br O2	
Formula weight	255.11	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 4.4316(11) Å	alpha = 90 deg.
	b = 14.731(4) Å	beta = 96.215(5) deg.
	c = 15.879(4) Å	gamma = 90 deg.
Volume	1030.6(4) Å ³	
Z, Calculated density	4, 1.644 Mg/m ³	
Absorption coefficient	3.958 mm ⁻¹	
F(000)	512	
Crystal size	0.25 x 0.20 x 0.10 mm	
Theta range for data collection	1.89 to 26.39 deg.	
Limiting indices	-5<=h<=5, -14<=k<=18, -19<=l<=15	
Reflections collected / unique	5750 / 2111 [R(int) = 0.0555]	
Completeness to theta = 26.39	99.8%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.599	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2111 / 2 / 133	
Goodness-of-fit on F ²	1.142	
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1018	
R indices (all data)	R1 = 0.0659, wR2 = 0.1070	
Largest diff. peak and hole	0.648 and -0.607 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s3433abs. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
Br(1)	4894(1)	1625(1)	-2239(1)	20(1)
O(1)	10595(7)	689(2)	1094(2)	17(1)
O(2)	7512(7)	4523(2)	59(2)	19(1)
C(1)	5158(10)	1806(3)	-434(3)	14(1)
C(2)	5411(10)	2709(3)	-179(3)	16(1)
C(3)	7420(9)	2951(3)	510(3)	13(1)
C(4)	9172(10)	2296(3)	973(3)	13(1)
C(5)	8931(10)	1393(3)	705(3)	14(1)
C(6)	6938(9)	1153(3)	5(3)	14(1)
C(7)	2971(10)	1536(3)	-1180(3)	18(1)
C(8)	7717(11)	3938(3)	787(3)	19(1)
C(9)	12607(10)	890(3)	1833(3)	16(1)
C(10)	10978(10)	997(3)	2594(3)	17(1)
C(11)	9619(11)	1067(3)	3181(3)	22(1)

Table 3. Bond lengths [\AA] and angles [deg] for s3433abs.

Br(1)-C(7)	1.971(5)
O(1)-C(5)	1.378(5)
O(1)-C(9)	1.426(5)
O(2)-C(8)	1.437(5)
O(2)-H(20)	0.81(2)
O(2)-H(30)	0.81(2)
C(1)-C(6)	1.383(6)
C(1)-C(2)	1.391(6)
C(1)-C(7)	1.501(6)
C(2)-C(3)	1.381(6)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.398(6)
C(3)-C(8)	1.520(6)
C(4)-C(5)	1.398(6)
C(4)-H(4)	0.9500
C(5)-C(6)	1.388(6)
C(6)-H(6)	0.9500
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.482(7)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.168(7)
C(11)-H(11)	0.9500

C(5)-O(1)-C(9)	118.0(3)
C(8)-O(2)-H(20)	113(8)
C(8)-O(2)-H(30)	107(8)
H(20)-O(2)-H(30)	117(10)
C(6)-C(1)-C(2)	119.6(4)
C(6)-C(1)-C(7)	119.9(4)
C(2)-C(1)-C(7)	120.5(4)
C(3)-C(2)-C(1)	120.2(4)
C(3)-C(2)-H(2A)	119.9
C(1)-C(2)-H(2A)	119.9
C(2)-C(3)-C(4)	120.8(4)
C(2)-C(3)-C(8)	120.3(4)
C(4)-C(3)-C(8)	118.8(4)
C(5)-C(4)-C(3)	118.5(4)
C(5)-C(4)-H(4)	120.7
C(3)-C(4)-H(4)	120.7
O(1)-C(5)-C(6)	115.5(4)
O(1)-C(5)-C(4)	124.0(4)
C(6)-C(5)-C(4)	120.5(4)
C(1)-C(6)-C(5)	120.4(4)
C(1)-C(6)-H(6)	119.8
C(5)-C(6)-H(6)	119.8
C(1)-C(7)-Br(1)	110.7(3)
C(1)-C(7)-H(7A)	109.5
Br(1)-C(7)-H(7A)	109.5
C(1)-C(7)-H(7B)	109.5
Br(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	108.1
O(2)-C(8)-C(3)	110.1(4)
O(2)-C(8)-H(8A)	109.6
C(3)-C(8)-H(8A)	109.6
O(2)-C(8)-H(8B)	109.6
C(3)-C(8)-H(8B)	109.6
H(8A)-C(8)-H(8B)	108.1
O(1)-C(9)-C(10)	112.2(4)
O(1)-C(9)-H(9A)	109.2
C(10)-C(9)-H(9A)	109.2
O(1)-C(9)-H(9B)	109.2
C(10)-C(9)-H(9B)	109.2
H(9A)-C(9)-H(9B)	107.9
C(11)-C(10)-C(9)	177.9(5)
C(10)-C(11)-H(11)	180.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Hydrogen bonds for s3433abs [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(30)...O(2)#1	0.81(2)	1.81(2)	2.623(6)	174(12)
O(2)-H(20)...O(2)#2	0.81(2)	1.83(2)	2.639(6)	179(12)

Symmetry transformations used to generate equivalent atoms:
#1 $-x+1, -y+1, -z$ #2 $-x+2, -y+1, -z$

Table 1. Crystal data and structure refinement for s3313m - **240**

Identification code	s3313m
Empirical formula	C36 H43 Cl2 N3 O4 S4
Formula weight	780.87
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 10.9439(14) Å alpha = 90 deg. b = 17.302(2) Å beta = 90 deg. c = 19.969(3) Å gamma = 90 deg.
Volume	3781.2(8) Å ³
Z, Calculated density	4, 1.372 Mg/m ³
Absorption coefficient	0.435 mm ⁻¹
F(000)	1640
Crystal size	0.50 x 0.40 x 0.25 mm
Theta range for data collection	2.04 to 28.27 deg.
Limiting indices	-14<=h<=14, -22<=k<=22, -26<=l<=15
Reflections collected / unique	23961 / 8896 [R(int) = 0.0802]
Completeness to theta = 25.00	100.0%
Absorption correction	None
Max. and min. transmission	0.8990 and 0.8118
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8896 / 0 / 446
Goodness-of-fit on F ²	0.743
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.0636
R indices (all data)	R1 = 0.0756, wR2 = 0.0694
Absolute structure parameter	-0.07(5)
Largest diff. peak and hole	0.522 and -0.350 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s3313m. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	8516(3)	11192(2)	9843(2)	17(1)
C(2)	7114(3)	11265(2)	9805(2)	17(1)
C(3)	6435(3)	12652(2)	9133(2)	25(1)
C(4)	5691(3)	12172(2)	8652(2)	18(1)
C(5)	6209(3)	11902(2)	8054(2)	23(1)
C(6)	5520(3)	11466(2)	7606(2)	25(1)
C(7)	4317(3)	11288(2)	7756(2)	23(1)
C(8)	3786(3)	11540(2)	8346(2)	18(1)
C(9)	4486(3)	11981(2)	8782(2)	18(1)
C(10)	2471(3)	11357(2)	8509(2)	20(1)
C(11)	2917(3)	10420(2)	9604(1)	20(1)
C(12)	2742(3)	9667(2)	9988(2)	17(1)
C(13)	4823(3)	9045(2)	9854(2)	18(1)
C(14)	5667(3)	9330(2)	9305(2)	14(1)
C(15)	5305(3)	9442(2)	8647(2)	16(1)
C(16)	6157(3)	9700(2)	8188(2)	19(1)
C(17)	7337(3)	9845(2)	8411(2)	17(1)
C(18)	7624(3)	9716(2)	9071(2)	15(1)
C(19)	8891(3)	9854(2)	9346(2)	21(1)
C(20)	7887(3)	9755(2)	11079(2)	16(1)
C(21)	7178(3)	10289(2)	11408(2)	22(1)
C(22)	6142(3)	10045(2)	11743(2)	22(1)
C(23)	5822(3)	9272(2)	11774(2)	24(1)
C(24)	6541(3)	8741(2)	11434(2)	21(1)
C(25)	7572(3)	8978(2)	11079(2)	18(1)
C(26)	4728(3)	9009(2)	12176(2)	31(1)
C(27)	9145(3)	11567(2)	9242(2)	27(1)
C(28)	2959(3)	9792(2)	10741(2)	25(1)
C(29)	2766(3)	7747(2)	10349(2)	15(1)
C(30)	1703(3)	7831(2)	10723(2)	16(1)
C(31)	1654(3)	7545(2)	11367(2)	18(1)
C(32)	2663(3)	7184(2)	11655(2)	17(1)
C(33)	3709(3)	7094(2)	11268(2)	17(1)
C(34)	3769(3)	7363(2)	10616(2)	17(1)
C(35)	2628(3)	6919(2)	12377(1)	24(1)
C(36)	2601(3)	1433(2)	2743(2)	31(1)
Cl(1)	1626(1)	958(1)	2174(1)	36(1)
Cl(2)	3928(1)	1785(1)	2339(1)	39(1)
N(1)	8924(2)	10379(1)	9928(1)	16(1)
N(2)	3503(2)	9050(1)	9692(1)	15(1)
N(3)	6804(2)	9458(1)	9522(1)	15(1)
O(1)	9714(2)	10690(1)	11048(1)	25(1)
O(2)	9966(2)	9371(1)	10580(1)	28(1)
O(3)	1678(2)	8331(1)	9304(1)	19(1)
O(4)	3741(2)	7768(1)	9161(1)	20(1)
S(1)	6552(1)	12233(1)	9966(1)	24(1)
S(2)	2207(1)	10372(1)	8789(1)	20(1)

S (3)	9242 (1)	10051 (1)	10665 (1)	19 (1)
S (4)	2885 (1)	8198 (1)	9561 (1)	16 (1)

Table 3. Bond lengths [Å] and angles [deg] for s3313m.

C (1) -N (1)	1.485 (4)
C (1) -C (27)	1.527 (4)
C (1) -C (2)	1.541 (4)
C (1) -H (1)	1.0000
C (2) -S (1)	1.812 (3)
C (2) -H (2A)	0.9900
C (2) -H (2B)	0.9900
C (3) -C (4)	1.509 (4)
C (3) -S (1)	1.819 (3)
C (3) -H (3A)	0.9900
C (3) -H (3B)	0.9900
C (4) -C (9)	1.384 (4)
C (4) -C (5)	1.402 (4)
C (5) -C (6)	1.392 (4)
C (5) -H (5)	0.9500
C (6) -C (7)	1.384 (4)
C (6) -H (6)	0.9500
C (7) -C (8)	1.385 (4)
C (7) -H (7)	0.9500
C (8) -C (9)	1.389 (4)
C (8) -C (10)	1.509 (4)
C (9) -H (9)	0.9500
C (10) -S (2)	1.815 (3)
C (10) -H (10A)	0.9900
C (10) -H (10B)	0.9900
C (11) -C (12)	1.525 (4)
C (11) -S (2)	1.806 (3)
C (11) -H (11A)	0.9900
C (11) -H (11B)	0.9900
C (12) -N (2)	1.478 (4)
C (12) -C (28)	1.538 (4)
C (12) -H (12)	1.0000
C (13) -N (2)	1.481 (4)
C (13) -C (14)	1.516 (4)
C (13) -H (13A)	0.9900
C (13) -H (13B)	0.9900
C (14) -N (3)	1.337 (4)
C (14) -C (15)	1.386 (4)
C (15) -C (16)	1.381 (4)
C (15) -H (15)	0.9500
C (16) -C (17)	1.388 (4)
C (16) -H (16)	0.9500
C (17) -C (18)	1.374 (4)
C (17) -H (17)	0.9500
C (18) -N (3)	1.347 (4)
C (18) -C (19)	1.510 (4)
C (19) -N (1)	1.476 (4)
C (19) -H (19A)	0.9900
C (19) -H (19B)	0.9900

C (20) -C (21)	1.375 (4)
C (20) -C (25)	1.387 (4)
C (20) -S (3)	1.773 (3)
C (21) -C (22)	1.383 (4)
C (21) -H (21)	0.9500
C (22) -C (23)	1.383 (4)
C (22) -H (22)	0.9500
C (23) -C (24)	1.387 (4)
C (23) -C (26)	1.512 (4)
C (24) -C (25)	1.394 (4)
C (24) -H (24)	0.9500
C (25) -H (25)	0.9500
C (26) -H (26A)	0.9800
C (26) -H (26B)	0.9800
C (26) -H (26C)	0.9800
C (27) -H (27A)	0.9800
C (27) -H (27B)	0.9800
C (27) -H (27C)	0.9800
C (28) -H (28A)	0.9800
C (28) -H (28B)	0.9800
C (28) -H (28C)	0.9800
C (29) -C (34)	1.389 (4)
C (29) -C (30)	1.390 (4)
C (29) -S (4)	1.761 (3)
C (30) -C (31)	1.379 (4)
C (30) -H (30)	0.9500
C (31) -C (32)	1.392 (4)
C (31) -H (31)	0.9500
C (32) -C (33)	1.390 (4)
C (32) -C (35)	1.513 (4)
C (33) -C (34)	1.384 (4)
C (33) -H (33)	0.9500
C (34) -H (34)	0.9500
C (35) -H (35A)	0.9800
C (35) -H (35B)	0.9800
C (35) -H (35C)	0.9800
C (36) -C1 (1)	1.762 (3)
C (36) -C1 (2)	1.768 (4)
C (36) -H (36A)	0.9900
C (36) -H (36B)	0.9900
N (1) -S (3)	1.616 (3)
N (2) -S (4)	1.641 (2)
O (1) -S (3)	1.440 (2)
O (2) -S (3)	1.427 (2)
O (3) -S (4)	1.437 (2)
O (4) -S (4)	1.439 (2)
N (1) -C (1) -C (27)	110.8 (3)
N (1) -C (1) -C (2)	112.5 (3)
C (27) -C (1) -C (2)	112.1 (3)
N (1) -C (1) -H (1)	107.0
C (27) -C (1) -H (1)	107.0
C (2) -C (1) -H (1)	107.0
C (1) -C (2) -S (1)	113.9 (2)
C (1) -C (2) -H (2A)	108.8

S (1) -C (2) -H (2A)	108.8
C (1) -C (2) -H (2B)	108.8
S (1) -C (2) -H (2B)	108.8
H (2A) -C (2) -H (2B)	107.7
C (4) -C (3) -S (1)	113.6 (2)
C (4) -C (3) -H (3A)	108.9
S (1) -C (3) -H (3A)	108.9
C (4) -C (3) -H (3B)	108.9
S (1) -C (3) -H (3B)	108.9
H (3A) -C (3) -H (3B)	107.7
C (9) -C (4) -C (5)	117.7 (3)
C (9) -C (4) -C (3)	121.8 (3)
C (5) -C (4) -C (3)	120.5 (3)
C (6) -C (5) -C (4)	120.6 (3)
C (6) -C (5) -H (5)	119.7
C (4) -C (5) -H (5)	119.7
C (7) -C (6) -C (5)	119.8 (3)
C (7) -C (6) -H (6)	120.1
C (5) -C (6) -H (6)	120.1
C (6) -C (7) -C (8)	120.8 (3)
C (6) -C (7) -H (7)	119.6
C (8) -C (7) -H (7)	119.6
C (7) -C (8) -C (9)	118.4 (3)
C (7) -C (8) -C (10)	121.2 (3)
C (9) -C (8) -C (10)	120.4 (3)
C (4) -C (9) -C (8)	122.6 (3)
C (4) -C (9) -H (9)	118.7
C (8) -C (9) -H (9)	118.7
C (8) -C (10) -S (2)	114.5 (2)
C (8) -C (10) -H (10A)	108.6
S (2) -C (10) -H (10A)	108.6
C (8) -C (10) -H (10B)	108.6
S (2) -C (10) -H (10B)	108.6
H (10A) -C (10) -H (10B)	107.6
C (12) -C (11) -S (2)	111.1 (2)
C (12) -C (11) -H (11A)	109.4
S (2) -C (11) -H (11A)	109.4
C (12) -C (11) -H (11B)	109.4
S (2) -C (11) -H (11B)	109.4
H (11A) -C (11) -H (11B)	108.0
N (2) -C (12) -C (11)	110.2 (2)
N (2) -C (12) -C (28)	113.9 (3)
C (11) -C (12) -C (28)	110.6 (2)
N (2) -C (12) -H (12)	107.2
C (11) -C (12) -H (12)	107.2
C (28) -C (12) -H (12)	107.2
N (2) -C (13) -C (14)	115.8 (3)
N (2) -C (13) -H (13A)	108.3
C (14) -C (13) -H (13A)	108.3
N (2) -C (13) -H (13B)	108.3
C (14) -C (13) -H (13B)	108.3
H (13A) -C (13) -H (13B)	107.4
N (3) -C (14) -C (15)	123.4 (3)
N (3) -C (14) -C (13)	112.7 (3)
C (15) -C (14) -C (13)	123.9 (3)

C (16) -C (15) -C (14)	118.7 (3)
C (16) -C (15) -H (15)	120.6
C (14) -C (15) -H (15)	120.6
C (15) -C (16) -C (17)	118.4 (3)
C (15) -C (16) -H (16)	120.8
C (17) -C (16) -H (16)	120.8
C (18) -C (17) -C (16)	119.3 (3)
C (18) -C (17) -H (17)	120.3
C (16) -C (17) -H (17)	120.3
N (3) -C (18) -C (17)	122.9 (3)
N (3) -C (18) -C (19)	114.9 (3)
C (17) -C (18) -C (19)	122.2 (3)
N (1) -C (19) -C (18)	113.9 (2)
N (1) -C (19) -H (19A)	108.8
C (18) -C (19) -H (19A)	108.8
N (1) -C (19) -H (19B)	108.8
C (18) -C (19) -H (19B)	108.8
H (19A) -C (19) -H (19B)	107.7
C (21) -C (20) -C (25)	120.8 (3)
C (21) -C (20) -S (3)	120.0 (2)
C (25) -C (20) -S (3)	119.2 (2)
C (20) -C (21) -C (22)	119.3 (3)
C (20) -C (21) -H (21)	120.4
C (22) -C (21) -H (21)	120.4
C (21) -C (22) -C (23)	121.6 (3)
C (21) -C (22) -H (22)	119.2
C (23) -C (22) -H (22)	119.2
C (22) -C (23) -C (24)	118.4 (3)
C (22) -C (23) -C (26)	121.0 (3)
C (24) -C (23) -C (26)	120.6 (3)
C (23) -C (24) -C (25)	120.9 (3)
C (23) -C (24) -H (24)	119.6
C (25) -C (24) -H (24)	119.6
C (20) -C (25) -C (24)	119.1 (3)
C (20) -C (25) -H (25)	120.5
C (24) -C (25) -H (25)	120.5
C (23) -C (26) -H (26A)	109.5
C (23) -C (26) -H (26B)	109.5
H (26A) -C (26) -H (26B)	109.5
C (23) -C (26) -H (26C)	109.5
H (26A) -C (26) -H (26C)	109.5
H (26B) -C (26) -H (26C)	109.5
C (1) -C (27) -H (27A)	109.5
C (1) -C (27) -H (27B)	109.5
H (27A) -C (27) -H (27B)	109.5
C (1) -C (27) -H (27C)	109.5
H (27A) -C (27) -H (27C)	109.5
H (27B) -C (27) -H (27C)	109.5
C (12) -C (28) -H (28A)	109.5
C (12) -C (28) -H (28B)	109.5
H (28A) -C (28) -H (28B)	109.5
C (12) -C (28) -H (28C)	109.5
H (28A) -C (28) -H (28C)	109.5
H (28B) -C (28) -H (28C)	109.5
C (34) -C (29) -C (30)	120.3 (3)

C (34) -C (29) -S (4)	119.8 (3)
C (30) -C (29) -S (4)	119.7 (2)
C (31) -C (30) -C (29)	119.7 (3)
C (31) -C (30) -H (30)	120.1
C (29) -C (30) -H (30)	120.1
C (30) -C (31) -C (32)	121.0 (3)
C (30) -C (31) -H (31)	119.5
C (32) -C (31) -H (31)	119.5
C (33) -C (32) -C (31)	118.3 (3)
C (33) -C (32) -C (35)	121.1 (3)
C (31) -C (32) -C (35)	120.6 (3)
C (34) -C (33) -C (32)	121.6 (3)
C (34) -C (33) -H (33)	119.2
C (32) -C (33) -H (33)	119.2
C (33) -C (34) -C (29)	119.0 (3)
C (33) -C (34) -H (34)	120.5
C (29) -C (34) -H (34)	120.5
C (32) -C (35) -H (35A)	109.5
C (32) -C (35) -H (35B)	109.5
H (35A) -C (35) -H (35B)	109.5
C (32) -C (35) -H (35C)	109.5
H (35A) -C (35) -H (35C)	109.5
H (35B) -C (35) -H (35C)	109.5
Cl (1) -C (36) -Cl (2)	111.40 (18)
Cl (1) -C (36) -H (36A)	109.3
Cl (2) -C (36) -H (36A)	109.3
Cl (1) -C (36) -H (36B)	109.3
Cl (2) -C (36) -H (36B)	109.3
H (36A) -C (36) -H (36B)	108.0
C (19) -N (1) -C (1)	119.1 (2)
C (19) -N (1) -S (3)	120.4 (2)
C (1) -N (1) -S (3)	120.1 (2)
C (12) -N (2) -C (13)	117.8 (2)
C (12) -N (2) -S (4)	118.7 (2)
C (13) -N (2) -S (4)	115.6 (2)
C (14) -N (3) -C (18)	117.3 (3)
C (2) -S (1) -C (3)	103.33 (15)
C (11) -S (2) -C (10)	99.55 (14)
O (2) -S (3) -O (1)	119.76 (14)
O (2) -S (3) -N (1)	107.47 (14)
O (1) -S (3) -N (1)	106.88 (14)
O (2) -S (3) -C (20)	106.38 (14)
O (1) -S (3) -C (20)	105.95 (14)
N (1) -S (3) -C (20)	110.26 (14)
O (3) -S (4) -O (4)	118.84 (13)
O (3) -S (4) -N (2)	106.99 (13)
O (4) -S (4) -N (2)	106.55 (13)
O (3) -S (4) -C (29)	108.85 (15)
O (4) -S (4) -C (29)	108.30 (14)
N (2) -S (4) -C (29)	106.67 (13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for s3313m. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
C (1)	17 (2)	15 (2)	18 (2)	-3 (2)	1 (2)	-3 (2)
C (2)	14 (2)	18 (2)	19 (2)	1 (2)	2 (2)	-1 (2)
C (3)	15 (2)	23 (2)	35 (2)	4 (2)	-4 (2)	-2 (2)
C (4)	20 (2)	10 (2)	23 (2)	3 (2)	1 (2)	3 (2)
C (5)	16 (2)	23 (2)	30 (2)	8 (2)	6 (2)	1 (2)
C (6)	34 (2)	25 (2)	15 (2)	2 (2)	6 (2)	2 (2)
C (7)	28 (2)	20 (2)	22 (2)	1 (2)	-3 (2)	-3 (2)
C (8)	18 (2)	16 (2)	19 (2)	1 (2)	-5 (2)	3 (2)
C (9)	22 (2)	14 (2)	19 (2)	0 (2)	0 (2)	4 (2)
C (10)	16 (2)	20 (2)	23 (2)	4 (2)	-6 (2)	0 (1)
C (11)	19 (2)	13 (2)	27 (2)	0 (2)	-1 (2)	1 (2)
C (12)	10 (2)	21 (2)	21 (2)	-1 (2)	-2 (2)	-1 (2)
C (13)	13 (2)	23 (2)	17 (2)	4 (2)	-2 (2)	1 (2)
C (14)	13 (2)	11 (2)	18 (2)	0 (2)	2 (2)	0 (1)
C (15)	13 (2)	20 (2)	15 (2)	-4 (2)	-2 (2)	3 (1)
C (16)	25 (2)	16 (2)	16 (2)	-3 (2)	1 (2)	1 (2)
C (17)	18 (2)	12 (2)	22 (2)	-1 (2)	8 (2)	-7 (1)
C (18)	14 (2)	8 (2)	23 (2)	-3 (2)	6 (2)	-1 (1)
C (19)	14 (2)	20 (2)	28 (2)	-4 (2)	4 (2)	-2 (1)
C (20)	15 (2)	16 (2)	16 (2)	4 (1)	1 (2)	1 (2)
C (21)	25 (2)	21 (2)	19 (2)	0 (2)	-3 (2)	-4 (2)
C (22)	20 (2)	29 (2)	19 (2)	-9 (2)	2 (2)	6 (2)
C (23)	17 (2)	37 (2)	17 (2)	1 (2)	-2 (2)	-5 (2)
C (24)	22 (2)	19 (2)	24 (2)	2 (2)	-2 (2)	-5 (2)
C (25)	17 (2)	19 (2)	19 (2)	-3 (2)	-1 (2)	5 (1)
C (26)	26 (2)	48 (2)	19 (2)	7 (2)	4 (2)	-2 (2)
C (27)	14 (2)	26 (2)	41 (2)	6 (2)	3 (2)	-1 (2)
C (28)	26 (2)	26 (2)	22 (2)	1 (2)	6 (2)	-2 (2)
C (29)	15 (2)	14 (2)	17 (2)	4 (2)	0 (2)	-4 (2)
C (30)	15 (2)	13 (2)	21 (2)	0 (2)	-4 (2)	1 (1)
C (31)	18 (2)	18 (2)	19 (2)	-1 (2)	6 (2)	-4 (2)
C (32)	27 (2)	6 (2)	18 (2)	-1 (1)	0 (2)	-3 (2)
C (33)	20 (2)	11 (2)	20 (2)	3 (2)	-3 (2)	1 (1)
C (34)	12 (2)	14 (2)	24 (2)	-2 (2)	5 (2)	-1 (1)
C (35)	32 (2)	17 (2)	23 (2)	0 (2)	1 (2)	4 (2)
C (36)	48 (3)	27 (2)	18 (2)	-1 (2)	-4 (2)	-2 (2)
Cl (1)	49 (1)	38 (1)	22 (1)	-2 (1)	0 (1)	-16 (1)
Cl (2)	24 (1)	47 (1)	45 (1)	-2 (1)	-6 (1)	5 (1)
N (1)	13 (2)	13 (1)	23 (2)	0 (1)	4 (1)	0 (1)
N (2)	11 (2)	15 (1)	18 (2)	2 (1)	1 (1)	1 (1)
N (3)	17 (2)	12 (1)	17 (2)	-3 (1)	3 (1)	0 (1)
O (1)	18 (1)	28 (1)	29 (2)	2 (1)	-8 (1)	-9 (1)
O (2)	16 (1)	23 (1)	46 (2)	14 (1)	4 (1)	6 (1)
O (3)	14 (1)	22 (1)	20 (1)	3 (1)	-7 (1)	-7 (1)
O (4)	19 (1)	23 (1)	18 (1)	-2 (1)	5 (1)	1 (1)
S (1)	21 (1)	23 (1)	28 (1)	-8 (1)	-4 (1)	6 (1)
S (2)	18 (1)	18 (1)	24 (1)	2 (1)	-4 (1)	-3 (1)

S (3)	11 (1)	20 (1)	28 (1)	4 (1)	-2 (1)	0 (1)
S (4)	14 (1)	17 (1)	17 (1)	2 (1)	0 (1)	-2 (1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s3313m.

	x	y	z	U(eq)
H(1)	8786	11482	10250	20
H(2A)	6746	10907	10135	20
H(2B)	6840	11102	9354	20
H(3A)	6060	13171	9170	29
H(3B)	7268	12719	8948	29
H(5)	7037	12018	7954	28
H(6)	5874	11291	7199	30
H(7)	3850	10989	7449	28
H(9)	4123	12158	9186	22
H(10A)	1968	11453	8106	23
H(10B)	2189	11716	8863	23
H(11A)	3801	10524	9551	24
H(11B)	2556	10852	9862	24
H(12)	1869	9509	9932	21
H(13A)	5062	8510	9971	21
H(13B)	4954	9369	10256	21
H(15)	4486	9343	8514	19
H(16)	5941	9777	7732	23
H(17)	7941	10031	8109	21
H(19A)	9249	9351	9477	25
H(19B)	9408	10073	8986	25
H(21)	7397	10821	11405	26
H(22)	5638	10417	11958	27
H(24)	6329	8209	11444	26
H(25)	8052	8613	10840	22
H(26A)	4999	8832	12618	47
H(26B)	4320	8584	11942	47
H(26C)	4157	9441	12230	47
H(27A)	10019	11447	9253	41
H(27B)	9031	12128	9261	41
H(27C)	8787	11366	8828	41
H(28A)	2982	9290	10969	37
H(28B)	2294	10105	10927	37
H(28C)	3738	10060	10808	37
H(30)	1013	8084	10535	20
H(31)	921	7595	11618	22
H(33)	4400	6842	11456	20
H(34)	4484	7285	10355	20
H(35A)	3032	6416	12415	36
H(35B)	1777	6873	12523	36
H(35C)	3053	7297	12658	36
H(36A)	2841	1070	3102	37
H(36B)	2159	1870	2952	37

Table 6. Torsion angles [deg] for s3313m.

N(1)-C(1)-C(2)-S(1)	161.6(2)
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C (27) -C (1) -C (2) -S (1)	-72.7 (3)
S (1) -C (3) -C (4) -C (9)	58.2 (4)
S (1) -C (3) -C (4) -C (5)	-121.7 (3)
C (9) -C (4) -C (5) -C (6)	0.8 (5)
C (3) -C (4) -C (5) -C (6)	-179.3 (3)
C (4) -C (5) -C (6) -C (7)	-0.8 (5)
C (5) -C (6) -C (7) -C (8)	0.1 (5)
C (6) -C (7) -C (8) -C (9)	0.6 (5)
C (6) -C (7) -C (8) -C (10)	179.3 (3)
C (5) -C (4) -C (9) -C (8)	-0.1 (5)
C (3) -C (4) -C (9) -C (8)	180.0 (3)
C (7) -C (8) -C (9) -C (4)	-0.5 (5)
C (10) -C (8) -C (9) -C (4)	-179.2 (3)
C (7) -C (8) -C (10) -S (2)	76.5 (3)
C (9) -C (8) -C (10) -S (2)	-104.8 (3)
S (2) -C (11) -C (12) -N (2)	71.6 (3)
S (2) -C (11) -C (12) -C (28)	-161.4 (2)
N (2) -C (13) -C (14) -N (3)	167.5 (3)
N (2) -C (13) -C (14) -C (15)	-13.0 (4)
N (3) -C (14) -C (15) -C (16)	-0.2 (5)
C (13) -C (14) -C (15) -C (16)	-179.6 (3)
C (14) -C (15) -C (16) -C (17)	-0.7 (4)
C (15) -C (16) -C (17) -C (18)	1.0 (4)
C (16) -C (17) -C (18) -N (3)	-0.4 (5)
C (16) -C (17) -C (18) -C (19)	179.4 (3)
N (3) -C (18) -C (19) -N (1)	-55.0 (4)
C (17) -C (18) -C (19) -N (1)	125.2 (3)
C (25) -C (20) -C (21) -C (22)	0.2 (5)
S (3) -C (20) -C (21) -C (22)	-178.2 (2)
C (20) -C (21) -C (22) -C (23)	2.1 (5)
C (21) -C (22) -C (23) -C (24)	-2.6 (5)
C (21) -C (22) -C (23) -C (26)	176.4 (3)
C (22) -C (23) -C (24) -C (25)	0.9 (5)
C (26) -C (23) -C (24) -C (25)	-178.1 (3)
C (21) -C (20) -C (25) -C (24)	-1.8 (5)
S (3) -C (20) -C (25) -C (24)	176.6 (2)
C (23) -C (24) -C (25) -C (20)	1.2 (5)
C (34) -C (29) -C (30) -C (31)	1.3 (4)
S (4) -C (29) -C (30) -C (31)	-173.4 (2)
C (29) -C (30) -C (31) -C (32)	1.2 (4)
C (30) -C (31) -C (32) -C (33)	-2.3 (4)
C (30) -C (31) -C (32) -C (35)	176.0 (3)
C (31) -C (32) -C (33) -C (34)	0.9 (5)
C (35) -C (32) -C (33) -C (34)	-177.3 (3)
C (32) -C (33) -C (34) -C (29)	1.5 (5)
C (30) -C (29) -C (34) -C (33)	-2.6 (4)
S (4) -C (29) -C (34) -C (33)	172.1 (2)
C (18) -C (19) -N (1) -C (1)	-62.8 (4)
C (18) -C (19) -N (1) -S (3)	109.8 (3)
C (27) -C (1) -N (1) -C (19)	-50.6 (4)
C (2) -C (1) -N (1) -C (19)	75.8 (3)
C (27) -C (1) -N (1) -S (3)	136.8 (2)
C (2) -C (1) -N (1) -S (3)	-96.8 (3)
C (11) -C (12) -N (2) -C (13)	78.2 (3)
C (28) -C (12) -N (2) -C (13)	-46.8 (3)

C (11) -C (12) -N (2) -S (4)	-134.1 (2)
C (28) -C (12) -N (2) -S (4)	100.8 (3)
C (14) -C (13) -N (2) -C (12)	-104.2 (3)
C (14) -C (13) -N (2) -S (4)	107.2 (3)
C (15) -C (14) -N (3) -C (18)	0.8 (4)
C (13) -C (14) -N (3) -C (18)	-179.7 (2)
C (17) -C (18) -N (3) -C (14)	-0.5 (4)
C (19) -C (18) -N (3) -C (14)	179.7 (3)
C (1) -C (2) -S (1) -C (3)	93.5 (2)
C (4) -C (3) -S (1) -C (2)	53.5 (3)
C (12) -C (11) -S (2) -C (10)	175.5 (2)
C (8) -C (10) -S (2) -C (11)	70.9 (3)
C (19) -N (1) -S (3) -O (2)	26.0 (2)
C (1) -N (1) -S (3) -O (2)	-161.4 (2)
C (19) -N (1) -S (3) -O (1)	155.8 (2)
C (1) -N (1) -S (3) -O (1)	-31.7 (3)
C (19) -N (1) -S (3) -C (20)	-89.5 (2)
C (1) -N (1) -S (3) -C (20)	83.0 (2)
C (21) -C (20) -S (3) -O (2)	160.5 (3)
C (25) -C (20) -S (3) -O (2)	-17.9 (3)
C (21) -C (20) -S (3) -O (1)	32.1 (3)
C (25) -C (20) -S (3) -O (1)	-146.4 (3)
C (21) -C (20) -S (3) -N (1)	-83.2 (3)
C (25) -C (20) -S (3) -N (1)	98.3 (3)
C (12) -N (2) -S (4) -O (3)	41.3 (2)
C (13) -N (2) -S (4) -O (3)	-170.4 (2)
C (12) -N (2) -S (4) -O (4)	169.4 (2)
C (13) -N (2) -S (4) -O (4)	-42.3 (2)
C (12) -N (2) -S (4) -C (29)	-75.1 (2)
C (13) -N (2) -S (4) -C (29)	73.3 (2)
C (34) -C (29) -S (4) -O (3)	161.7 (2)
C (30) -C (29) -S (4) -O (3)	-23.6 (3)
C (34) -C (29) -S (4) -O (4)	31.2 (3)
C (30) -C (29) -S (4) -O (4)	-154.1 (2)
C (34) -C (29) -S (4) -N (2)	-83.1 (3)
C (30) -C (29) -S (4) -N (2)	91.6 (3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for s3313m [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
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Table 1. Crystal data and structure refinement for s3334bm - **282**

Identification code	s3334bm
Empirical formula	C38 H45 N3 O5 S4
Formula weight	752.01
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 16.764(3) Å alpha = 90 deg. b = 23.931(4) Å beta = 90 deg. c = 27.815(5) Å gamma = 90 deg.
Volume	11159(3) Å ³
Z, Calculated density	12, 1.343 Mg/m ³
Absorption coefficient	0.303 mm ⁻¹
F(000)	4776
Crystal size	0.50 x 0.50 x 0.40 mm
Theta range for data collection	1.42 to 25.03 deg.
Limiting indices 33<=l<=33	-19<=h<=19, -28<=k<=28, -
Reflections collected / unique	80756 / 19696 [R(int) = 0.0461]
Completeness to theta = 25.03	99.9%
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	19696 / 199 / 1420
Goodness-of-fit on F ²	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0362, wR2 = 0.0755
R indices (all data)	R1 = 0.0400, wR2 = 0.0770
Absolute structure parameter	-0.02(3)
Largest diff. peak and hole	0.517 and -0.236 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for s3334bm. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S (1)	1956 (1)	2893 (1)	6477 (1)	31 (1)
S (2)	-1054 (1)	3378 (1)	7180 (1)	26 (1)
S (3)	2535 (1)	3455 (1)	8213 (1)	29 (1)
S (4)	-2115 (1)	3599 (1)	8907 (1)	23 (1)
O (1)	-146 (1)	942 (1)	7369 (1)	31 (1)
O (2)	2825 (1)	3178 (1)	8631 (1)	40 (1)
O (3)	3089 (1)	3643 (1)	7856 (1)	37 (1)
O (4)	-2216 (1)	3288 (1)	9343 (1)	28 (1)
O (5)	-2750 (1)	3608 (1)	8563 (1)	31 (1)
N (1)	524 (1)	2779 (1)	8565 (1)	24 (1)
N (2)	1897 (1)	3030 (1)	7961 (1)	26 (1)
N (3)	-1328 (1)	3344 (1)	8635 (1)	25 (1)
C (1)	-223 (2)	2680 (1)	8712 (1)	25 (1)
C (2)	-612 (2)	2175 (1)	8637 (1)	27 (1)
C (3)	-236 (2)	1765 (1)	8375 (1)	29 (1)
C (4)	526 (2)	1873 (1)	8202 (1)	28 (1)
C (5)	890 (2)	2375 (1)	8314 (1)	23 (1)
C (6)	1750 (2)	2480 (1)	8172 (1)	30 (1)
C (7)	1622 (2)	3103 (1)	7452 (1)	28 (1)
C (8)	1373 (2)	3693 (1)	7331 (1)	30 (1)
C (9)	2256 (2)	2870 (1)	7106 (1)	31 (1)
C (10)	1551 (2)	2196 (1)	6392 (1)	31 (1)
C (11)	783 (2)	2071 (1)	6656 (1)	26 (1)
C (12)	149 (2)	2440 (1)	6651 (1)	27 (1)
C (13)	-564 (2)	2312 (1)	6883 (1)	24 (1)
C (14)	-639 (2)	1802 (1)	7115 (1)	25 (1)
C (15)	-6 (2)	1429 (1)	7120 (1)	27 (1)
C (16)	706 (2)	1558 (1)	6892 (1)	28 (1)
C (17)	485 (2)	549 (1)	7411 (1)	30 (1)
C (18)	237 (2)	96 (1)	7746 (1)	33 (1)
C (19)	-453 (2)	48 (1)	7959 (1)	42 (1)
C (20)	-1248 (2)	2721 (1)	6871 (1)	27 (1)
C (21)	-1048 (2)	3109 (1)	7792 (1)	26 (1)
C (22)	-1144 (2)	3586 (1)	8152 (1)	25 (1)
C (23)	-434 (2)	3981 (1)	8164 (1)	30 (1)
C (24)	-653 (2)	3165 (1)	8943 (1)	25 (1)
C (25)	2003 (2)	4054 (1)	8411 (1)	28 (1)
C (26)	1517 (2)	4015 (1)	8812 (1)	29 (1)
C (27)	1094 (2)	4481 (1)	8955 (1)	31 (1)
C (28)	1134 (2)	4980 (1)	8706 (1)	30 (1)
C (29)	1645 (2)	5012 (1)	8309 (1)	35 (1)
C (30)	2087 (2)	4555 (1)	8164 (1)	34 (1)
C (31)	625 (2)	5472 (1)	8846 (1)	39 (1)
C (32)	-1890 (2)	4297 (1)	9061 (1)	26 (1)
C (33)	-2190 (2)	4732 (1)	8792 (1)	33 (1)

C (34)	-1983 (2)	5274 (1)	8906 (1)	40 (1)
C (35)	-1470 (2)	5388 (1)	9290 (1)	38 (1)
C (36)	-1174 (2)	4942 (1)	9551 (1)	35 (1)
C (37)	-1379 (2)	4399 (1)	9445 (1)	29 (1)
C (38)	-1254 (2)	5982 (1)	9417 (1)	50 (1)
S (5)	3734 (1)	1421 (1)	9382 (1)	44 (1)
S (6)	6934 (1)	1738 (1)	9977 (1)	34 (1)
S (7)	2805 (1)	1039 (1)	7680 (1)	26 (1)
S (8)	7521 (1)	1158 (1)	8232 (1)	27 (1)
O (6)	5040 (1)	3781 (1)	9095 (1)	46 (1)
O (7)	2761 (1)	1257 (1)	7203 (1)	32 (1)
O (8)	2161 (1)	1140 (1)	8006 (1)	32 (1)
O (9)	8118 (1)	984 (1)	8571 (1)	34 (1)
O (10)	7764 (1)	1423 (1)	7795 (1)	35 (1)
N (4)	5503 (1)	1828 (1)	7947 (1)	24 (1)
N (5)	3609 (1)	1301 (1)	7929 (1)	28 (1)
N (6)	6902 (1)	1589 (1)	8497 (1)	28 (1)
C (39)	5896 (2)	2250 (1)	8155 (1)	23 (1)
C (40)	5561 (2)	2770 (1)	8231 (1)	29 (1)
C (41)	4792 (2)	2869 (1)	8068 (1)	34 (1)
C (42)	4386 (2)	2437 (1)	7849 (1)	31 (1)
C (43)	4749 (2)	1925 (1)	7806 (1)	26 (1)
C (44)	4299 (2)	1419 (1)	7616 (1)	30 (1)
C (45)	3763 (2)	1118 (1)	8436 (1)	31 (1)
C (46)	4481 (2)	741 (1)	8473 (1)	39 (1)
C (47)	3821 (2)	1634 (1)	8757 (1)	32 (1)
C (48)	3660 (2)	2109 (2)	9646 (1)	44 (1)
C (49)	4408 (2)	2456 (1)	9614 (1)	32 (1)
C (50)	5116 (2)	2277 (1)	9831 (1)	32 (1)
C (51)	5801 (2)	2605 (1)	9803 (1)	28 (1)
C (52)	5775 (2)	3107 (1)	9554 (1)	29 (1)
C (53)	5070 (2)	3284 (1)	9339 (1)	32 (1)
C (54)	4390 (2)	2956 (1)	9367 (1)	34 (1)
C (55)	5601 (3)	4149 (2)	9110 (2)	39 (1)
C (56)	5329 (4)	4667 (3)	8858 (2)	45 (2)
C (57)	4628 (7)	4733 (6)	8670 (7)	52 (3)
C (55B)	4390 (4)	4050 (3)	8906 (2)	34 (2)
C (56B)	4510 (8)	4621 (6)	8697 (8)	39 (2)
C (57B)	5204 (6)	4864 (4)	8658 (3)	43 (2)
C (58)	6558 (2)	2441 (1)	10062 (1)	30 (1)
C (59)	7250 (2)	1755 (1)	9350 (1)	31 (1)
C (60)	6628 (2)	1509 (1)	9004 (1)	30 (1)
C (61)	6417 (2)	907 (1)	9131 (1)	33 (1)
C (62)	6761 (2)	2144 (1)	8290 (1)	29 (1)
C (63)	2934 (2)	306 (1)	7651 (1)	25 (1)
C (64)	3403 (2)	73 (1)	7293 (1)	28 (1)
C (65)	3520 (2)	-496 (1)	7288 (1)	29 (1)
C (66)	3172 (2)	-842 (1)	7635 (1)	26 (1)
C (67)	2707 (2)	-599 (1)	7989 (1)	28 (1)
C (68)	2586 (2)	-26 (1)	8001 (1)	28 (1)
C (69)	3297 (2)	-1464 (1)	7622 (1)	35 (1)
C (70)	6971 (2)	551 (1)	8076 (1)	26 (1)
C (71)	7132 (2)	47 (1)	8299 (1)	31 (1)
C (72)	6679 (2)	-416 (1)	8193 (1)	33 (1)
C (73)	6052 (2)	-388 (1)	7864 (1)	28 (1)

C (74)	5929 (2)	115 (1)	7631 (1)	30 (1)
C (75)	6371 (2)	586 (1)	7733 (1)	29 (1)
C (76)	5519 (2)	-880 (1)	7765 (1)	36 (1)
S (9)	1815 (1)	3855 (1)	3590 (1)	30 (1)
S (10)	-1322 (1)	3576 (1)	3869 (1)	33 (1)
S (10B)	-1423 (1)	3187 (1)	4280 (1)	28 (1)
S (11)	3138 (1)	4007 (1)	5258 (1)	31 (1)
S (12)	-1666 (1)	3849 (1)	5569 (1)	27 (1)
O (11)	757 (1)	1438 (1)	3921 (1)	36 (1)
O (12)	3212 (1)	3786 (1)	5734 (1)	38 (1)
O (13)	3830 (1)	4228 (1)	5022 (1)	41 (1)
O (14)	-1626 (1)	3592 (1)	6031 (1)	37 (1)
O (15)	-2316 (1)	3723 (1)	5254 (1)	36 (1)
N (7)	1180 (1)	3255 (1)	5316 (1)	25 (1)
N (8)	2771 (1)	3512 (1)	4925 (1)	31 (1)
N (9)	-845 (1)	3691 (1)	5279 (1)	26 (1)
C (77)	397 (2)	3142 (1)	5354 (1)	26 (1)
C (78)	68 (2)	2634 (1)	5227 (1)	32 (1)
C (79)	560 (2)	2229 (1)	5041 (1)	33 (1)
C (80)	1366 (2)	2336 (1)	4993 (1)	32 (1)
C (81)	1652 (2)	2850 (1)	5139 (1)	26 (1)
C (82)	2538 (2)	2974 (1)	5131 (1)	32 (1)
C (83)	2759 (2)	3602 (1)	4396 (1)	28 (1)
C (84)	3265 (2)	3170 (1)	4136 (1)	37 (1)
C (85)	1897 (2)	3634 (1)	4215 (1)	28 (1)
C (86)	1735 (2)	3187 (1)	3281 (1)	31 (1)
C (87)	1049 (2)	2831 (1)	3448 (1)	26 (1)
C (88)	268 (2)	3033 (1)	3434 (1)	29 (1)
C (89)	-361 (2)	2709 (1)	3593 (1)	29 (1)
C (90)	-224 (2)	2168 (1)	3757 (1)	28 (1)
C (91)	553 (2)	1961 (1)	3772 (1)	30 (1)
C (92)	1184 (2)	2299 (1)	3621 (1)	28 (1)
C (93)	125 (2)	1084 (1)	4076 (1)	33 (1)
C (94)	463 (2)	528 (1)	4200 (1)	36 (1)
C (95)	1213 (2)	385 (1)	4167 (1)	40 (1)
C (96)	-1195 (2)	2944 (1)	3608 (1)	41 (1)
C (97)	-950 (4)	3358 (3)	4456 (2)	35 (1)
C (99)	-66 (4)	4194 (3)	4652 (2)	44 (1)
C (97B)	-582 (4)	3651 (3)	4391 (2)	30 (1)
C (99B)	-108 (5)	4458 (3)	4845 (3)	37 (2)
C (98)	-786 (2)	3937 (2)	4793 (1)	45 (1)
C (100)	-109 (2)	3607 (1)	5560 (1)	28 (1)
C (101)	2430 (2)	4552 (1)	5269 (1)	30 (1)
C (102)	2476 (2)	4986 (1)	4942 (1)	37 (1)
C (103)	1930 (2)	5419 (1)	4964 (1)	42 (1)
C (104)	1335 (2)	5429 (1)	5311 (1)	36 (1)
C (105)	1298 (2)	4988 (1)	5636 (1)	32 (1)
C (106)	1829 (2)	4548 (1)	5615 (1)	31 (1)
C (107)	749 (2)	5905 (1)	5345 (1)	46 (1)
C (108)	-1633 (2)	4581 (1)	5643 (1)	25 (1)
C (109)	-2022 (2)	4924 (1)	5313 (1)	28 (1)
C (110)	-1957 (2)	5494 (1)	5354 (1)	29 (1)
C (111)	-1511 (2)	5738 (1)	5721 (1)	27 (1)
C (112)	-1118 (2)	5385 (1)	6046 (1)	29 (1)
C (113)	-1179 (2)	4809 (1)	6009 (1)	26 (1)

C (114)	-1459 (2)	6357 (1)	5770 (1)	39 (1)
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Table 3. Bond lengths [Å] and angles [deg] for s3334bm.

S(1)-C(10)	1.815(3)
S(1)-C(9)	1.819(3)
S(2)-C(21)	1.819(3)
S(2)-C(20)	1.822(3)
S(3)-O(2)	1.425(2)
S(3)-O(3)	1.431(2)
S(3)-N(2)	1.634(2)
S(3)-C(25)	1.775(3)
S(4)-O(5)	1.4305(18)
S(4)-O(4)	1.4325(18)
S(4)-N(3)	1.638(2)
S(4)-C(32)	1.768(3)
O(1)-C(15)	1.376(3)
O(1)-C(17)	1.420(3)
N(1)-C(1)	1.340(3)
N(1)-C(5)	1.341(3)
N(2)-C(6)	1.461(3)
N(2)-C(7)	1.499(3)
N(3)-C(24)	1.483(3)
N(3)-C(22)	1.493(3)
C(1)-C(2)	1.388(4)
C(1)-C(24)	1.509(4)
C(2)-C(3)	1.376(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.389(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.382(4)
C(4)-H(4)	0.9500
C(5)-C(6)	1.517(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.512(4)
C(7)-C(9)	1.539(4)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.512(4)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.383(4)
C(11)-C(16)	1.398(4)
C(12)-C(13)	1.392(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.387(4)
C(13)-C(20)	1.508(4)
C(14)-C(15)	1.387(4)
C(14)-H(14)	0.9500
C(15)-C(16)	1.387(4)
C(16)-H(16)	0.9500

C(17)-C(18)	1.490(4)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.304(4)
C(18)-H(18)	0.9500
C(19)-H(19A)	0.9500
C(19)-H(19B)	0.9500
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.527(3)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(23)	1.521(4)
C(22)-H(22)	1.0000
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(25)-C(26)	1.386(4)
C(25)-C(30)	1.388(4)
C(26)-C(27)	1.380(4)
C(26)-H(26)	0.9500
C(27)-C(28)	1.382(4)
C(27)-H(27)	0.9500
C(28)-C(29)	1.400(4)
C(28)-C(31)	1.506(4)
C(29)-C(30)	1.382(4)
C(29)-H(29)	0.9500
C(30)-H(30)	0.9500
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800
C(32)-C(33)	1.377(4)
C(32)-C(37)	1.389(4)
C(33)-C(34)	1.381(4)
C(33)-H(33)	0.9500
C(34)-C(35)	1.397(4)
C(34)-H(34)	0.9500
C(35)-C(36)	1.384(4)
C(35)-C(38)	1.508(4)
C(36)-C(37)	1.376(4)
C(36)-H(36)	0.9500
C(37)-H(37)	0.9500
C(38)-H(38A)	0.9800
C(38)-H(38B)	0.9800
C(38)-H(38C)	0.9800
S(5)-C(48)	1.808(4)
S(5)-C(47)	1.818(3)
S(6)-C(58)	1.811(3)
S(6)-C(59)	1.825(3)
S(7)-O(8)	1.4297(19)
S(7)-O(7)	1.4298(19)
S(7)-N(5)	1.641(2)
S(7)-C(63)	1.767(3)

S (8) -O (9)	1.4359 (19)
S (8) -O (10)	1.432 (2)
S (8) -N (6)	1.637 (2)
S (8) -C (70)	1.775 (3)
O (6) -C (55)	1.290 (6)
O (6) -C (53)	1.369 (3)
O (6) -C (55B)	1.371 (6)
N (4) -C (39)	1.339 (3)
N (4) -C (43)	1.345 (3)
N (5) -C (44)	1.474 (3)
N (5) -C (45)	1.500 (3)
N (6) -C (62)	1.467 (3)
N (6) -C (60)	1.496 (3)
C (39) -C (40)	1.380 (4)
C (39) -C (62)	1.518 (4)
C (40) -C (41)	1.388 (4)
C (40) -H (40)	0.9500
C (41) -C (42)	1.379 (4)
C (41) -H (41)	0.9500
C (42) -C (43)	1.375 (4)
C (42) -H (42)	0.9500
C (43) -C (44)	1.520 (4)
C (44) -H (44A)	0.9900
C (44) -H (44B)	0.9900
C (45) -C (46)	1.506 (4)
C (45) -C (47)	1.526 (4)
C (45) -H (45)	1.0000
C (46) -H (46A)	0.9800
C (46) -H (46B)	0.9800
C (46) -H (46C)	0.9800
C (47) -H (47A)	0.9900
C (47) -H (47B)	0.9900
C (48) -C (49)	1.507 (4)
C (48) -H (48A)	0.9900
C (48) -H (48B)	0.9900
C (49) -C (54)	1.378 (4)
C (49) -C (50)	1.400 (4)
C (50) -C (51)	1.393 (4)
C (50) -H (50)	0.9500
C (51) -C (52)	1.387 (4)
C (51) -C (58)	1.511 (4)
C (52) -C (53)	1.390 (4)
C (52) -H (52)	0.9500
C (53) -C (54)	1.386 (4)
C (54) -H (54)	0.9500
C (55) -C (56)	1.496 (8)
C (55) -H (55A)	0.9900
C (55) -H (55B)	0.9900
C (56) -C (57)	1.296 (11)
C (56) -H (56)	0.9500
C (57) -H (57A)	0.9500
C (57) -H (57B)	0.9500
C (55B) -C (56B)	1.498 (12)
C (55B) -H (55C)	0.9900
C (55B) -H (55D)	0.9900

C (56B) -C (57B)	1.305 (12)
C (56B) -H (56B)	0.9500
C (57B) -H (57C)	0.9500
C (57B) -H (57D)	0.9500
C (58) -H (58A)	0.9900
C (58) -H (58B)	0.9900
C (59) -C (60)	1.536 (4)
C (59) -H (59A)	0.9900
C (59) -H (59B)	0.9900
C (60) -C (61)	1.525 (4)
C (60) -H (60)	1.0000
C (61) -H (61A)	0.9800
C (61) -H (61B)	0.9800
C (61) -H (61C)	0.9800
C (62) -H (62A)	0.9900
C (62) -H (62B)	0.9900
C (63) -C (64)	1.386 (4)
C (63) -C (68)	1.386 (4)
C (64) -C (65)	1.377 (4)
C (64) -H (64)	0.9500
C (65) -C (66)	1.399 (4)
C (65) -H (65)	0.9500
C (66) -C (67)	1.384 (4)
C (66) -C (69)	1.503 (4)
C (67) -C (68)	1.385 (4)
C (67) -H (67)	0.9500
C (68) -H (68)	0.9500
C (69) -H (69A)	0.9800
C (69) -H (69B)	0.9800
C (69) -H (69C)	0.9800
C (70) -C (71)	1.382 (4)
C (70) -C (75)	1.390 (4)
C (71) -C (72)	1.376 (4)
C (71) -H (71)	0.9500
C (72) -C (73)	1.395 (4)
C (72) -H (72)	0.9500
C (73) -C (74)	1.383 (4)
C (73) -C (76)	1.504 (4)
C (74) -C (75)	1.379 (4)
C (74) -H (74)	0.9500
C (75) -H (75)	0.9500
C (76) -H (76A)	0.9800
C (76) -H (76B)	0.9800
C (76) -H (76C)	0.9800
S (9) -C (86)	1.819 (3)
S (9) -C (85)	1.822 (3)
S (10) -C (96)	1.690 (3)
S (10) -C (97)	1.824 (5)
S (10B) -C (97B)	1.820 (7)
S (10B) -C (96)	1.993 (4)
S (11) -O (12)	1.430 (2)
S (11) -O (13)	1.434 (2)
S (11) -N (8)	1.624 (2)
S (11) -C (101)	1.763 (3)
S (12) -O (14)	1.425 (2)

S(12)-O(15)	1.430(2)
S(12)-N(9)	1.640(2)
S(12)-C(108)	1.764(3)
O(11)-C(91)	1.363(3)
O(11)-C(93)	1.425(3)
N(7)-C(77)	1.344(3)
N(7)-C(81)	1.344(3)
N(8)-C(82)	1.462(3)
N(8)-C(83)	1.487(3)
N(9)-C(100)	1.475(3)
N(9)-C(98)	1.479(4)
C(77)-C(78)	1.381(4)
C(77)-C(100)	1.511(4)
C(78)-C(79)	1.374(4)
C(78)-H(78)	0.9500
C(79)-C(80)	1.381(4)
C(79)-H(79)	0.9500
C(80)-C(81)	1.381(4)
C(80)-H(80)	0.9500
C(81)-C(82)	1.514(4)
C(82)-H(82A)	0.9900
C(82)-H(82B)	0.9900
C(83)-C(84)	1.519(4)
C(83)-C(85)	1.532(4)
C(83)-H(83)	1.0000
C(84)-H(84A)	0.9800
C(84)-H(84B)	0.9800
C(84)-H(84C)	0.9800
C(85)-H(85A)	0.9900
C(85)-H(85B)	0.9900
C(86)-C(87)	1.504(4)
C(86)-H(86A)	0.9900
C(86)-H(86B)	0.9900
C(87)-C(92)	1.380(4)
C(87)-C(88)	1.396(4)
C(88)-C(89)	1.381(4)
C(88)-H(88)	0.9500
C(89)-C(90)	1.391(4)
C(89)-C(96)	1.508(4)
C(90)-C(91)	1.393(4)
C(90)-H(90)	0.9500
C(91)-C(92)	1.396(4)
C(92)-H(92)	0.9500
C(93)-C(94)	1.486(4)
C(93)-H(93A)	0.9900
C(93)-H(93B)	0.9900
C(94)-C(95)	1.305(4)
C(94)-H(94)	0.9500
C(95)-H(95A)	0.9500
C(95)-H(95B)	0.9500
C(96)-H(96A)	0.9900
C(96)-H(96B)	0.9900
C(97)-C(98)	1.694(7)
C(97)-H(97A)	0.9900
C(97)-H(97B)	0.9900

C(99)-C(98)	1.410(6)
C(99)-H(99A)	0.9800
C(99)-H(99B)	0.9800
C(99)-H(99C)	0.9800
C(97B)-C(98)	1.355(7)
C(97B)-H(97C)	0.9900
C(97B)-H(97D)	0.9900
C(99B)-C(98)	1.693(8)
C(99B)-H(99D)	0.9800
C(99B)-H(99E)	0.9800
C(99B)-H(99F)	0.9800
C(98)-H(98)	1.0000
C(100)-H(10C)	0.9900
C(100)-H(10D)	0.9900
C(101)-C(102)	1.382(4)
C(101)-C(106)	1.392(4)
C(102)-C(103)	1.386(4)
C(102)-H(102)	0.9500
C(103)-C(104)	1.387(4)
C(103)-H(103)	0.9500
C(104)-C(105)	1.393(4)
C(104)-C(107)	1.507(4)
C(105)-C(106)	1.379(4)
C(105)-H(105)	0.9500
C(106)-H(106)	0.9500
C(107)-H(10E)	0.9800
C(107)-H(10F)	0.9800
C(107)-H(10G)	0.9800
C(108)-C(113)	1.383(4)
C(108)-C(109)	1.392(4)
C(109)-C(110)	1.375(4)
C(109)-H(109)	0.9500
C(110)-C(111)	1.394(4)
C(110)-H(110)	0.9500
C(111)-C(112)	1.400(4)
C(111)-C(114)	1.491(4)
C(112)-C(113)	1.387(4)
C(112)-H(112)	0.9500
C(113)-H(113)	0.9500
C(114)-H(11A)	0.9800
C(114)-H(11B)	0.9800
C(114)-H(11C)	0.9800
C(10)-S(1)-C(9)	101.60(13)
C(21)-S(2)-C(20)	97.84(12)
O(2)-S(3)-O(3)	119.39(12)
O(2)-S(3)-N(2)	106.46(12)
O(3)-S(3)-N(2)	108.84(12)
O(2)-S(3)-C(25)	107.13(12)
O(3)-S(3)-C(25)	106.68(12)
N(2)-S(3)-C(25)	107.87(11)
O(5)-S(4)-O(4)	118.98(11)
O(5)-S(4)-N(3)	107.24(11)
O(4)-S(4)-N(3)	107.07(11)
O(5)-S(4)-C(32)	107.88(12)

O(4)-S(4)-C(32)	108.09(11)
N(3)-S(4)-C(32)	107.02(11)
C(15)-O(1)-C(17)	118.4(2)
C(1)-N(1)-C(5)	117.3(2)
C(6)-N(2)-C(7)	115.6(2)
C(6)-N(2)-S(3)	119.96(18)
C(7)-N(2)-S(3)	122.18(17)
C(24)-N(3)-C(22)	118.3(2)
C(24)-N(3)-S(4)	117.05(16)
C(22)-N(3)-S(4)	115.89(16)
N(1)-C(1)-C(2)	123.2(2)
N(1)-C(1)-C(24)	116.1(2)
C(2)-C(1)-C(24)	120.6(2)
C(3)-C(2)-C(1)	119.1(2)
C(3)-C(2)-H(2)	120.5
C(1)-C(2)-H(2)	120.5
C(2)-C(3)-C(4)	118.1(3)
C(2)-C(3)-H(3)	120.9
C(4)-C(3)-H(3)	120.9
C(5)-C(4)-C(3)	119.3(3)
C(5)-C(4)-H(4)	120.3
C(3)-C(4)-H(4)	120.3
N(1)-C(5)-C(4)	122.9(2)
N(1)-C(5)-C(6)	116.8(2)
C(4)-C(5)-C(6)	120.3(2)
N(2)-C(6)-C(5)	114.5(2)
N(2)-C(6)-H(6A)	108.6
C(5)-C(6)-H(6A)	108.6
N(2)-C(6)-H(6B)	108.6
C(5)-C(6)-H(6B)	108.6
H(6A)-C(6)-H(6B)	107.6
N(2)-C(7)-C(8)	114.0(2)
N(2)-C(7)-C(9)	109.7(2)
C(8)-C(7)-C(9)	112.9(2)
N(2)-C(7)-H(7)	106.6
C(8)-C(7)-H(7)	106.6
C(9)-C(7)-H(7)	106.6
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-S(1)	113.65(19)
C(7)-C(9)-H(9A)	108.8
S(1)-C(9)-H(9A)	108.8
C(7)-C(9)-H(9B)	108.8
S(1)-C(9)-H(9B)	108.8
H(9A)-C(9)-H(9B)	107.7
C(11)-C(10)-S(1)	115.97(19)
C(11)-C(10)-H(10A)	108.3
S(1)-C(10)-H(10A)	108.3
C(11)-C(10)-H(10B)	108.3
S(1)-C(10)-H(10B)	108.3
H(10A)-C(10)-H(10B)	107.4

C(12)-C(11)-C(16)	119.7(2)
C(12)-C(11)-C(10)	121.5(2)
C(16)-C(11)-C(10)	118.8(2)
C(11)-C(12)-C(13)	120.9(2)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(14)-C(13)-C(12)	119.2(2)
C(14)-C(13)-C(20)	120.7(2)
C(12)-C(13)-C(20)	120.0(2)
C(13)-C(14)-C(15)	120.1(2)
C(13)-C(14)-H(14)	119.9
C(15)-C(14)-H(14)	119.9
O(1)-C(15)-C(16)	124.4(2)
O(1)-C(15)-C(14)	114.9(2)
C(16)-C(15)-C(14)	120.7(2)
C(15)-C(16)-C(11)	119.3(2)
C(15)-C(16)-H(16)	120.4
C(11)-C(16)-H(16)	120.4
O(1)-C(17)-C(18)	109.0(2)
O(1)-C(17)-H(17A)	109.9
C(18)-C(17)-H(17A)	109.9
O(1)-C(17)-H(17B)	109.9
C(18)-C(17)-H(17B)	109.9
H(17A)-C(17)-H(17B)	108.3
C(19)-C(18)-C(17)	126.5(3)
C(19)-C(18)-H(18)	116.8
C(17)-C(18)-H(18)	116.8
C(18)-C(19)-H(19A)	120.0
C(18)-C(19)-H(19B)	120.0
H(19A)-C(19)-H(19B)	120.0
C(13)-C(20)-S(2)	114.45(18)
C(13)-C(20)-H(20A)	108.6
S(2)-C(20)-H(20A)	108.6
C(13)-C(20)-H(20B)	108.6
S(2)-C(20)-H(20B)	108.6
H(20A)-C(20)-H(20B)	107.6
C(22)-C(21)-S(2)	110.45(17)
C(22)-C(21)-H(21A)	109.6
S(2)-C(21)-H(21A)	109.6
C(22)-C(21)-H(21B)	109.6
S(2)-C(21)-H(21B)	109.6
H(21A)-C(21)-H(21B)	108.1
N(3)-C(22)-C(23)	112.6(2)
N(3)-C(22)-C(21)	108.8(2)
C(23)-C(22)-C(21)	113.3(2)
N(3)-C(22)-H(22)	107.3
C(23)-C(22)-H(22)	107.3
C(21)-C(22)-H(22)	107.3
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
N(3)-C(24)-C(1)	109.9(2)

N (3) -C (24) -H (24A)	109.7
C (1) -C (24) -H (24A)	109.7
N (3) -C (24) -H (24B)	109.7
C (1) -C (24) -H (24B)	109.7
H (24A) -C (24) -H (24B)	108.2
C (26) -C (25) -C (30)	121.0 (3)
C (26) -C (25) -S (3)	119.4 (2)
C (30) -C (25) -S (3)	119.6 (2)
C (27) -C (26) -C (25)	118.8 (3)
C (27) -C (26) -H (26)	120.6
C (25) -C (26) -H (26)	120.6
C (28) -C (27) -C (26)	121.9 (3)
C (28) -C (27) -H (27)	119.1
C (26) -C (27) -H (27)	119.1
C (27) -C (28) -C (29)	118.2 (3)
C (27) -C (28) -C (31)	121.3 (3)
C (29) -C (28) -C (31)	120.5 (3)
C (30) -C (29) -C (28)	121.0 (3)
C (30) -C (29) -H (29)	119.5
C (28) -C (29) -H (29)	119.5
C (29) -C (30) -C (25)	119.0 (3)
C (29) -C (30) -H (30)	120.5
C (25) -C (30) -H (30)	120.5
C (28) -C (31) -H (31A)	109.5
C (28) -C (31) -H (31B)	109.5
H (31A) -C (31) -H (31B)	109.5
C (28) -C (31) -H (31C)	109.5
H (31A) -C (31) -H (31C)	109.5
H (31B) -C (31) -H (31C)	109.5
C (33) -C (32) -C (37)	120.7 (2)
C (33) -C (32) -S (4)	120.2 (2)
C (37) -C (32) -S (4)	119.0 (2)
C (32) -C (33) -C (34)	119.5 (3)
C (32) -C (33) -H (33)	120.3
C (34) -C (33) -H (33)	120.3
C (33) -C (34) -C (35)	120.9 (3)
C (33) -C (34) -H (34)	119.5
C (35) -C (34) -H (34)	119.5
C (36) -C (35) -C (34)	118.2 (3)
C (36) -C (35) -C (38)	121.1 (3)
C (34) -C (35) -C (38)	120.8 (3)
C (35) -C (36) -C (37)	121.7 (3)
C (35) -C (36) -H (36)	119.2
C (37) -C (36) -H (36)	119.2
C (36) -C (37) -C (32)	119.0 (3)
C (36) -C (37) -H (37)	120.5
C (32) -C (37) -H (37)	120.5
C (35) -C (38) -H (38A)	109.5
C (35) -C (38) -H (38B)	109.5
H (38A) -C (38) -H (38B)	109.5
C (35) -C (38) -H (38C)	109.5
H (38A) -C (38) -H (38C)	109.5
H (38B) -C (38) -H (38C)	109.5
C (48) -S (5) -C (47)	97.97 (14)
C (58) -S (6) -C (59)	101.82 (13)

O(8)-S(7)-O(7)	119.22(11)
O(8)-S(7)-N(5)	106.74(11)
O(7)-S(7)-N(5)	107.08(11)
O(8)-S(7)-C(63)	106.85(12)
O(7)-S(7)-C(63)	109.02(12)
N(5)-S(7)-C(63)	107.38(12)
O(9)-S(8)-O(10)	119.23(11)
O(9)-S(8)-N(6)	109.19(11)
O(10)-S(8)-N(6)	106.42(11)
O(9)-S(8)-C(70)	106.57(12)
O(10)-S(8)-C(70)	107.63(12)
N(6)-S(8)-C(70)	107.26(12)
C(55)-O(6)-C(53)	123.4(3)
C(55)-O(6)-C(55B)	105.7(4)
C(53)-O(6)-C(55B)	128.9(3)
C(39)-N(4)-C(43)	117.3(2)
C(44)-N(5)-C(45)	118.4(2)
C(44)-N(5)-S(7)	117.94(17)
C(45)-N(5)-S(7)	115.21(17)
C(62)-N(6)-C(60)	115.8(2)
C(62)-N(6)-S(8)	119.78(18)
C(60)-N(6)-S(8)	122.55(18)
N(4)-C(39)-C(40)	123.1(2)
N(4)-C(39)-C(62)	116.7(2)
C(40)-C(39)-C(62)	120.1(2)
C(39)-C(40)-C(41)	118.9(3)
C(39)-C(40)-H(40)	120.6
C(41)-C(40)-H(40)	120.6
C(42)-C(41)-C(40)	118.4(3)
C(42)-C(41)-H(41)	120.8
C(40)-C(41)-H(41)	120.8
C(43)-C(42)-C(41)	119.2(3)
C(43)-C(42)-H(42)	120.4
C(41)-C(42)-H(42)	120.4
N(4)-C(43)-C(42)	123.0(2)
N(4)-C(43)-C(44)	115.5(2)
C(42)-C(43)-C(44)	121.4(2)
N(5)-C(44)-C(43)	109.6(2)
N(5)-C(44)-H(44A)	109.7
C(43)-C(44)-H(44A)	109.7
N(5)-C(44)-H(44B)	109.7
C(43)-C(44)-H(44B)	109.7
H(44A)-C(44)-H(44B)	108.2
N(5)-C(45)-C(46)	112.1(2)
N(5)-C(45)-C(47)	108.9(2)
C(46)-C(45)-C(47)	113.2(2)
N(5)-C(45)-H(45)	107.5
C(46)-C(45)-H(45)	107.5
C(47)-C(45)-H(45)	107.5
C(45)-C(46)-H(46A)	109.5
C(45)-C(46)-H(46B)	109.5
H(46A)-C(46)-H(46B)	109.5
C(45)-C(46)-H(46C)	109.5
H(46A)-C(46)-H(46C)	109.5
H(46B)-C(46)-H(46C)	109.5

C (45) -C (47) -S (5)	109.10 (18)
C (45) -C (47) -H (47A)	109.9
S (5) -C (47) -H (47A)	109.9
C (45) -C (47) -H (47B)	109.9
S (5) -C (47) -H (47B)	109.9
H (47A) -C (47) -H (47B)	108.3
C (49) -C (48) -S (5)	114.9 (2)
C (49) -C (48) -H (48A)	108.5
S (5) -C (48) -H (48A)	108.5
C (49) -C (48) -H (48B)	108.5
S (5) -C (48) -H (48B)	108.5
H (48A) -C (48) -H (48B)	107.5
C (54) -C (49) -C (50)	119.9 (3)
C (54) -C (49) -C (48)	119.3 (3)
C (50) -C (49) -C (48)	120.7 (3)
C (51) -C (50) -C (49)	120.1 (3)
C (51) -C (50) -H (50)	119.9
C (49) -C (50) -H (50)	119.9
C (52) -C (51) -C (50)	119.4 (3)
C (52) -C (51) -C (58)	119.3 (2)
C (50) -C (51) -C (58)	121.2 (3)
C (51) -C (52) -C (53)	120.3 (3)
C (51) -C (52) -H (52)	119.9
C (53) -C (52) -H (52)	119.9
O (6) -C (53) -C (54)	119.3 (3)
O (6) -C (53) -C (52)	120.5 (3)
C (54) -C (53) -C (52)	120.1 (3)
C (49) -C (54) -C (53)	120.1 (3)
C (49) -C (54) -H (54)	119.9
C (53) -C (54) -H (54)	119.9
O (6) -C (55) -C (56)	109.1 (5)
O (6) -C (55) -H (55A)	109.9
C (56) -C (55) -H (55A)	109.9
O (6) -C (55) -H (55B)	109.9
C (56) -C (55) -H (55B)	109.9
H (55A) -C (55) -H (55B)	108.3
C (57) -C (56) -C (55)	124.6 (8)
C (57) -C (56) -H (56)	117.7
C (55) -C (56) -H (56)	117.7
C (56) -C (57) -H (57A)	120.0
C (56) -C (57) -H (57B)	120.0
H (57A) -C (57) -H (57B)	120.0
O (6) -C (55B) -C (56B)	118.1 (7)
O (6) -C (55B) -H (55C)	107.8
C (56B) -C (55B) -H (55C)	107.8
O (6) -C (55B) -H (55D)	107.8
C (56B) -C (55B) -H (55D)	107.8
H (55C) -C (55B) -H (55D)	107.1
C (57B) -C (56B) -C (55B)	123.9 (11)
C (57B) -C (56B) -H (56B)	118.1
C (55B) -C (56B) -H (56B)	118.1
C (56B) -C (57B) -H (57C)	120.0
C (56B) -C (57B) -H (57D)	120.0
H (57C) -C (57B) -H (57D)	120.0
C (51) -C (58) -S (6)	118.16 (19)

C (51) -C (58) -H (58A)	107.8
S (6) -C (58) -H (58A)	107.8
C (51) -C (58) -H (58B)	107.8
S (6) -C (58) -H (58B)	107.8
H (58A) -C (58) -H (58B)	107.1
C (60) -C (59) -S (6)	113.14 (19)
C (60) -C (59) -H (59A)	109.0
S (6) -C (59) -H (59A)	109.0
C (60) -C (59) -H (59B)	109.0
S (6) -C (59) -H (59B)	109.0
H (59A) -C (59) -H (59B)	107.8
N (6) -C (60) -C (61)	114.2 (2)
N (6) -C (60) -C (59)	109.5 (2)
C (61) -C (60) -C (59)	112.0 (2)
N (6) -C (60) -H (60)	106.9
C (61) -C (60) -H (60)	106.9
C (59) -C (60) -H (60)	106.9
C (60) -C (61) -H (61A)	109.5
C (60) -C (61) -H (61B)	109.5
H (61A) -C (61) -H (61B)	109.5
C (60) -C (61) -H (61C)	109.5
H (61A) -C (61) -H (61C)	109.5
H (61B) -C (61) -H (61C)	109.5
N (6) -C (62) -C (39)	113.7 (2)
N (6) -C (62) -H (62A)	108.8
C (39) -C (62) -H (62A)	108.8
N (6) -C (62) -H (62B)	108.8
C (39) -C (62) -H (62B)	108.8
H (62A) -C (62) -H (62B)	107.7
C (64) -C (63) -C (68)	120.8 (2)
C (64) -C (63) -S (7)	120.1 (2)
C (68) -C (63) -S (7)	119.1 (2)
C (65) -C (64) -C (63)	119.2 (2)
C (65) -C (64) -H (64)	120.4
C (63) -C (64) -H (64)	120.4
C (64) -C (65) -C (66)	121.2 (3)
C (64) -C (65) -H (65)	119.4
C (66) -C (65) -H (65)	119.4
C (67) -C (66) -C (65)	118.5 (2)
C (67) -C (66) -C (69)	120.8 (2)
C (65) -C (66) -C (69)	120.7 (2)
C (66) -C (67) -C (68)	121.1 (2)
C (66) -C (67) -H (67)	119.5
C (68) -C (67) -H (67)	119.5
C (67) -C (68) -C (63)	119.3 (2)
C (67) -C (68) -H (68)	120.4
C (63) -C (68) -H (68)	120.4
C (66) -C (69) -H (69A)	109.5
C (66) -C (69) -H (69B)	109.5
H (69A) -C (69) -H (69B)	109.5
C (66) -C (69) -H (69C)	109.5
H (69A) -C (69) -H (69C)	109.5
H (69B) -C (69) -H (69C)	109.5
C (71) -C (70) -C (75)	120.2 (2)
C (71) -C (70) -S (8)	120.2 (2)

C (75) -C (70) -S (8)	119.6 (2)
C (72) -C (71) -C (70)	120.0 (3)
C (72) -C (71) -H (71)	120.0
C (70) -C (71) -H (71)	120.0
C (71) -C (72) -C (73)	121.1 (3)
C (71) -C (72) -H (72)	119.4
C (73) -C (72) -H (72)	119.4
C (74) -C (73) -C (72)	117.6 (2)
C (74) -C (73) -C (76)	120.5 (2)
C (72) -C (73) -C (76)	122.0 (3)
C (73) -C (74) -C (75)	122.3 (3)
C (73) -C (74) -H (74)	118.8
C (75) -C (74) -H (74)	118.8
C (74) -C (75) -C (70)	118.7 (3)
C (74) -C (75) -H (75)	120.7
C (70) -C (75) -H (75)	120.7
C (73) -C (76) -H (76A)	109.5
C (73) -C (76) -H (76B)	109.5
H (76A) -C (76) -H (76B)	109.5
C (73) -C (76) -H (76C)	109.5
H (76A) -C (76) -H (76C)	109.5
H (76B) -C (76) -H (76C)	109.5
C (86) -S (9) -C (85)	101.55 (13)
C (96) -S (10) -C (97)	94.9 (2)
C (97B) -S (10B) -C (96)	100.8 (2)
O (12) -S (11) -O (13)	119.27 (12)
O (12) -S (11) -N (8)	107.00 (12)
O (13) -S (11) -N (8)	108.26 (12)
O (12) -S (11) -C (101)	108.39 (12)
O (13) -S (11) -C (101)	106.24 (13)
N (8) -S (11) -C (101)	107.13 (12)
O (14) -S (12) -O (15)	119.83 (12)
O (14) -S (12) -N (9)	107.67 (11)
O (15) -S (12) -N (9)	106.75 (11)
O (14) -S (12) -C (108)	108.84 (12)
O (15) -S (12) -C (108)	107.78 (12)
N (9) -S (12) -C (108)	105.01 (12)
C (91) -O (11) -C (93)	116.9 (2)
C (77) -N (7) -C (81)	117.3 (2)
C (82) -N (8) -C (83)	120.7 (2)
C (82) -N (8) -S (11)	121.27 (18)
C (83) -N (8) -S (11)	117.70 (18)
C (100) -N (9) -C (98)	118.8 (2)
C (100) -N (9) -S (12)	118.25 (17)
C (98) -N (9) -S (12)	114.53 (18)
N (7) -C (77) -C (78)	123.1 (2)
N (7) -C (77) -C (100)	115.5 (2)
C (78) -C (77) -C (100)	121.4 (2)
C (79) -C (78) -C (77)	118.6 (3)
C (79) -C (78) -H (78)	120.7
C (77) -C (78) -H (78)	120.7
C (78) -C (79) -C (80)	119.5 (3)
C (78) -C (79) -H (79)	120.3
C (80) -C (79) -H (79)	120.3
C (79) -C (80) -C (81)	118.5 (3)

C (79) -C (80) -H (80)	120.7
C (81) -C (80) -H (80)	120.7
N (7) -C (81) -C (80)	123.0 (3)
N (7) -C (81) -C (82)	116.2 (2)
C (80) -C (81) -C (82)	120.7 (2)
N (8) -C (82) -C (81)	116.1 (2)
N (8) -C (82) -H (82A)	108.3
C (81) -C (82) -H (82A)	108.3
N (8) -C (82) -H (82B)	108.3
C (81) -C (82) -H (82B)	108.3
H (82A) -C (82) -H (82B)	107.4
N (8) -C (83) -C (84)	111.4 (2)
N (8) -C (83) -C (85)	110.2 (2)
C (84) -C (83) -C (85)	113.9 (2)
N (8) -C (83) -H (83)	107.0
C (84) -C (83) -H (83)	107.0
C (85) -C (83) -H (83)	107.0
C (83) -C (84) -H (84A)	109.5
C (83) -C (84) -H (84B)	109.5
H (84A) -C (84) -H (84B)	109.5
C (83) -C (84) -H (84C)	109.5
H (84A) -C (84) -H (84C)	109.5
H (84B) -C (84) -H (84C)	109.5
C (83) -C (85) -S (9)	113.53 (18)
C (83) -C (85) -H (85A)	108.9
S (9) -C (85) -H (85A)	108.9
C (83) -C (85) -H (85B)	108.9
S (9) -C (85) -H (85B)	108.9
H (85A) -C (85) -H (85B)	107.7
C (87) -C (86) -S (9)	114.12 (18)
C (87) -C (86) -H (86A)	108.7
S (9) -C (86) -H (86A)	108.7
C (87) -C (86) -H (86B)	108.7
S (9) -C (86) -H (86B)	108.7
H (86A) -C (86) -H (86B)	107.6
C (92) -C (87) -C (88)	118.8 (2)
C (92) -C (87) -C (86)	120.4 (2)
C (88) -C (87) -C (86)	120.9 (2)
C (89) -C (88) -C (87)	120.9 (3)
C (89) -C (88) -H (88)	119.5
C (87) -C (88) -H (88)	119.5
C (88) -C (89) -C (90)	120.0 (3)
C (88) -C (89) -C (96)	120.5 (3)
C (90) -C (89) -C (96)	119.4 (2)
C (91) -C (90) -C (89)	119.7 (3)
C (91) -C (90) -H (90)	120.2
C (89) -C (90) -H (90)	120.2
O (11) -C (91) -C (90)	124.8 (2)
O (11) -C (91) -C (92)	115.6 (2)
C (90) -C (91) -C (92)	119.6 (3)
C (87) -C (92) -C (91)	121.0 (3)
C (87) -C (92) -H (92)	119.5
C (91) -C (92) -H (92)	119.5
O (11) -C (93) -C (94)	108.6 (2)
O (11) -C (93) -H (93A)	110.0

C (94) -C (93) -H (93A)	110.0
O (11) -C (93) -H (93B)	110.0
C (94) -C (93) -H (93B)	110.0
H (93A) -C (93) -H (93B)	108.4
C (95) -C (94) -C (93)	125.9 (3)
C (95) -C (94) -H (94)	117.1
C (93) -C (94) -H (94)	117.1
C (94) -C (95) -H (95A)	120.0
C (94) -C (95) -H (95B)	120.0
H (95A) -C (95) -H (95B)	120.0
C (89) -C (96) -S (10)	117.6 (2)
C (89) -C (96) -S (10B)	108.3 (2)
S (10) -C (96) -S (10B)	46.57 (10)
C (89) -C (96) -H (96A)	107.9
S (10) -C (96) -H (96A)	107.9
S (10B) -C (96) -H (96A)	68.3
C (89) -C (96) -H (96B)	107.9
S (10) -C (96) -H (96B)	107.9
S (10B) -C (96) -H (96B)	143.0
H (96A) -C (96) -H (96B)	107.2
C (98) -C (97) -S (10)	108.4 (3)
C (98) -C (97) -H (97A)	110.0
S (10) -C (97) -H (97A)	110.0
C (98) -C (97) -H (97B)	110.0
S (10) -C (97) -H (97B)	110.0
H (97A) -C (97) -H (97B)	108.4
C (98) -C (99) -H (99A)	109.5
C (98) -C (99) -H (99B)	109.5
C (98) -C (99) -H (99C)	109.5
C (98) -C (97B) -S (10B)	104.6 (4)
C (98) -C (97B) -H (97C)	110.8
S (10B) -C (97B) -H (97C)	110.8
C (98) -C (97B) -H (97D)	110.8
S (10B) -C (97B) -H (97D)	110.8
H (97C) -C (97B) -H (97D)	108.9
C (98) -C (99B) -H (99D)	109.5
C (98) -C (99B) -H (99E)	109.5
H (99D) -C (99B) -H (99E)	109.5
C (98) -C (99B) -H (99F)	109.5
H (99D) -C (99B) -H (99F)	109.5
H (99E) -C (99B) -H (99F)	109.5
C (97B) -C (98) -C (99)	77.0 (4)
C (97B) -C (98) -N (9)	124.8 (4)
C (99) -C (98) -N (9)	119.0 (3)
C (97B) -C (98) -C (99B)	105.9 (4)
C (99) -C (98) -C (99B)	29.4 (3)
N (9) -C (98) -C (99B)	105.0 (3)
C (97B) -C (98) -C (97)	34.1 (3)
C (99) -C (98) -C (97)	110.1 (4)
N (9) -C (98) -C (97)	99.7 (3)
C (99B) -C (98) -C (97)	139.4 (4)
C (97B) -C (98) -H (98)	113.8
C (99) -C (98) -H (98)	109.2
N (9) -C (98) -H (98)	109.2
C (99B) -C (98) -H (98)	92.6

C(97)-C(98)-H(98)	109.2
N(9)-C(100)-C(77)	111.7(2)
N(9)-C(100)-H(10C)	109.3
C(77)-C(100)-H(10C)	109.3
N(9)-C(100)-H(10D)	109.3
C(77)-C(100)-H(10D)	109.3
H(10C)-C(100)-H(10D)	107.9
C(102)-C(101)-C(106)	120.0(3)
C(102)-C(101)-S(11)	120.4(2)
C(106)-C(101)-S(11)	119.6(2)
C(101)-C(102)-C(103)	119.8(3)
C(101)-C(102)-H(102)	120.1
C(103)-C(102)-H(102)	120.1
C(104)-C(103)-C(102)	121.2(3)
C(104)-C(103)-H(103)	119.4
C(102)-C(103)-H(103)	119.4
C(103)-C(104)-C(105)	118.0(3)
C(103)-C(104)-C(107)	121.7(3)
C(105)-C(104)-C(107)	120.2(3)
C(106)-C(105)-C(104)	121.5(3)
C(106)-C(105)-H(105)	119.3
C(104)-C(105)-H(105)	119.3
C(105)-C(106)-C(101)	119.5(3)
C(105)-C(106)-H(106)	120.3
C(101)-C(106)-H(106)	120.3
C(104)-C(107)-H(10E)	109.5
C(104)-C(107)-H(10F)	109.5
H(10E)-C(107)-H(10F)	109.5
C(104)-C(107)-H(10G)	109.5
H(10E)-C(107)-H(10G)	109.5
H(10F)-C(107)-H(10G)	109.5
C(113)-C(108)-C(109)	120.7(2)
C(113)-C(108)-S(12)	119.6(2)
C(109)-C(108)-S(12)	119.6(2)
C(110)-C(109)-C(108)	119.6(2)
C(110)-C(109)-H(109)	120.2
C(108)-C(109)-H(109)	120.2
C(109)-C(110)-C(111)	121.2(2)
C(109)-C(110)-H(110)	119.4
C(111)-C(110)-H(110)	119.4
C(110)-C(111)-C(112)	118.2(2)
C(110)-C(111)-C(114)	120.8(3)
C(112)-C(111)-C(114)	120.9(2)
C(113)-C(112)-C(111)	121.2(2)
C(113)-C(112)-H(112)	119.4
C(111)-C(112)-H(112)	119.4
C(108)-C(113)-C(112)	119.1(2)
C(108)-C(113)-H(113)	120.4
C(112)-C(113)-H(113)	120.4
C(111)-C(114)-H(11A)	109.5
C(111)-C(114)-H(11B)	109.5
H(11A)-C(114)-H(11B)	109.5
C(111)-C(114)-H(11C)	109.5
H(11A)-C(114)-H(11C)	109.5
H(11B)-C(114)-H(11C)	109.5

Symmetry transformations used to generate equivalent atoms: