Applications for the Activation of Hydroxyl Groups to Nucleophilic Attack

A thesis submitted in partial fulfilment of the

requirements for the degree of Doctor of Philosophy.

By

Ismail M. Awheda

School of Science and Technology
Nottingham Trent University
Clifton Lane
Nottingham
NG11 8NS
United Kingdom

2012

Declaration.

I hereby certify that the work embodied in this thesis is the result of my own investigations except where reference has been made to published literature.

Abstract.

This thesis investigates the applications of the activation of hydroxyl groups to nucleophilic attack within three key areas:

Cyclic five-membered thionocarbamates bearing a N-Boc group undergo ring opening reactions at the 5-C with soft nucleophiles such as thiophenolate, pyridine-2-thiolate and potassium thioacetate. Hard nucleophiles react at the thiocarbonyl group followed by a variety of successive reactions involving breakage of C-N (e. g. with n-BuLi) or C-O bond (e. g. with PhLi). Treatment with iodide under microwave conditions led to a rearrangement to a thiazolidin-2-one.

Two approaches to the synthesis of *vic*-dithiols were investigated. The more successful approach involves reaction of the trithiocarbonate dianion with cyclic sulphate esters of *vic*-diols to yield a protected version of the *vic*-dithiols. In a second approach, rearrangement of thionocarbonates with bromide gave the oxathiolan-2-one. Under thionation conditions with (e. g. Lawesson's reagent and HMDO) it was possible to replace both oxygens, while with Lawesson's reagent and HMDO in dry xylene only the carbonyl group was replaced. It was not possible to rearrange this material again with bromide or iodide.

New chiral organosulphur donors related to TTF and bearing multiple hydroxyl groups (from two to eight) were prepared starting from reaction of [(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl trifluoromethanesulphonate with 2-thioxo-1,3-dithiole-4,5-dithiolate and several further steps. A triiodide complex of a tetrahydroxy substituted donor was prepared and structurally characterized.

Acknowledgements.

First and foremost I would like to thank my supervisor Professor John D. Wallis for all his help and support throughout my studies, as well as for providing me with the opportunity to undertake research into this most interesting field of organic chemistry. His encouragement, enthusiasm and advice have inspired me throughout the past few years.

Thank you also to Dr Christopher Garner, Dr Gareth Cave, Dr Ray Leslie and to Dr Muriel Funck for their help and support throughout my studies over the past few years, and Dr Lee Martin for his help with measurements. I also want to thank Dr Songjie Yang and Dr Sara Krivikas for their advice and help over my first year.

A big thank you to all the people in the lab: Fathi Smida, Vicky Mundell, Daniel Guest and Metteo Zecchini for the experiences shared over the past few years, and to the many other students who have made the labs enjoyable places in which to conduct research. I would like to thank Ms Barbara Stevenson and Mark Sleden for assistance with training on equipment and providing valuable technical support.

Thanks to the EPSRC National Mass Spectrometry Service for the mass spectrometry data, and Mr Stephen Boyer (London Metropolitan University) for providing the elemental analysis data.

A special thank you to all staff members of the School of Science and Technology in Nottingham Trent University from whom I learnt a lot during meetings, workshops, seminars and conferences.

I am most grateful to the Libyan Ministry of Higher Education for offering me the scholarship to pursue my PhD study.

Many thanks go to Fathi, Omer, wesam, Salem, addukali, Emad and Adel and all my friends for being great friends, and helping me to leave work at work when I needed to relax.

I sincerely wish to give my deepest gratitude to my wife and children for their patience and support. My completion of this thesis would not have been possible without their presence with me in the U.K during the full period of my study.

Lastly, my biggest thanks go to Mum, Dad, my brothers, my sisters, and every other member of the family in the UK and Libya who have in one way or another helped me achieve this thesis. Without all of your support, this couldn't have been done.

Dedication

To my father

To my beloved mother

To my wife and children

To all my brothers, sisters and dearest friends

without whom this thesis could never have been complete.

List of acronyms, abbreviations and symbols.

Ka	Acidity constant
Å	Angstrom
Ac	Acetyl
aq.	Aqueous
Ar	Aryl / heteroaryl
BEDT-TTF	Bis(ethylenedithio)tetrathiafulvalene
BINOL	1,1'-Bi-2-naphthol
Boc	Di tert-butyloxycarbonyl
br	Broad
CHN	Chemical analysis
COSY	Correlation spectroscopy
CSEs	Cyclic Sulphate Esters
d	Doublet
d.	Day
DCM	Dichloromethane
dd	Doublet of doublets
DMAP	4-dimethylaminopyridine
DMF	N, N-dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electron impact
eq.	Equivalents
ES	Electrospray
ESI	Electrospray ionosation
ET	Bis(ethylenedithio)tetrathiafulvalene
Et	Ethyl
eV	Electron Volts
Fig.	Figure
GC-MS	Gas chromatography–mass spectrometry
h.	Hour
HMDO	Hexa Methyl Di Siloxane

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High performance
HRMS	High Resolution Mass Spectrum
iPr	Iso-propyl
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
LG	Leaving Group
LR	Lawesson's reagent
m	Meta
m	Multiplet
m. /min.	Minutes
MDT-TTF	Methylenedithiotetrathiafulvalene
Me	Methyl
mol	Mole
Mp	Melting Point
MS	Mass spectrometry
Ms	Mesylate
MW	Microwave
NEt3	Triethylamine
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
o	Ortho
p	Para
Ph	Phenyl
pka	−log10 Ka
ppm	Parts per million
py	Pyridine
q	Quintet
Rf	Retention Factor
S	Chemical shift (ppm)
s	SingleT

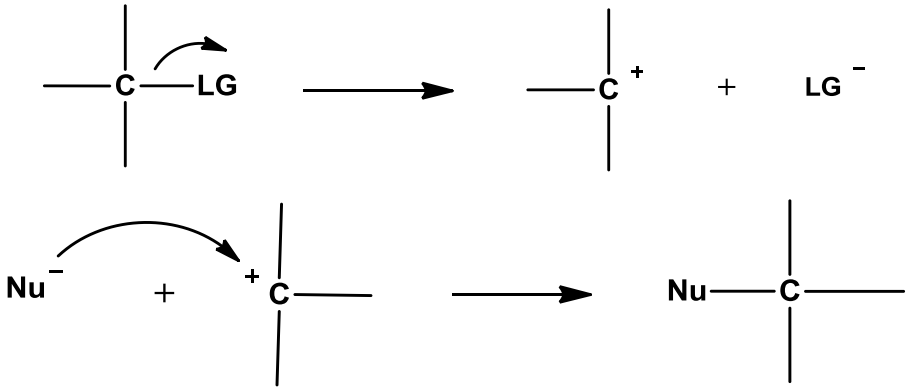
t	Triplet
tBu	Tert-butyl
Tc	Superconducting Transition Temperature
TCNQ	Tetracyanoquinodimethane
TEMPO	Tetramethylpiperidine-N-oxide
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMTSF	Tetramethyltetraselenafulvalene
TMTTF	Tetramethyltetrathiafulvalene
tosylate	p-toluenesulfonic acid
TTF	Tetrathiafulvalene
UV	Ultra-violet
vic	Vicinal
α	Alpha
β	Beta

Contents.

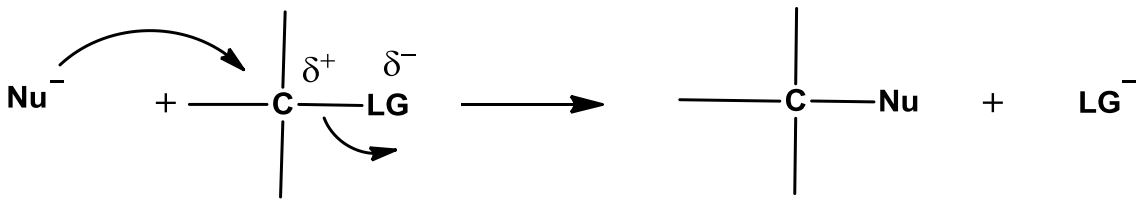
1. Chapter 1: Introduction: Leaving Groups.

1.1: General considerations.

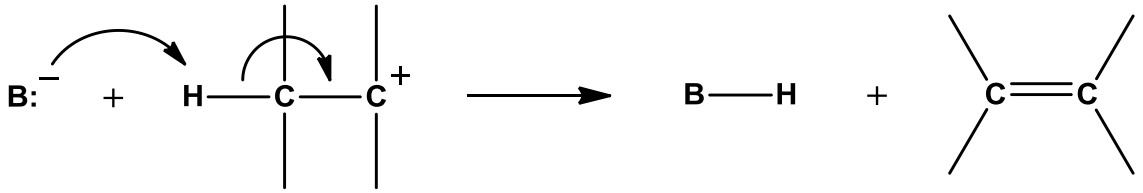
The definition given by IUPAC states that a leaving group is a molecular fragment which may or may not be charged that becomes detached from the main part of a molecule in a given reaction.[1] Most commonly a leaving group is a fragment of a molecule that leaves with an electron pair in heterolytic bond cleavage.[2] They can be anionic or neutral. There are also examples where an electrophile can displace another electrophile. Although the role of a leaving group was understood much earlier it entered chemical literature in the early of 1950s,[3] for example a paper 1951 studying nucleophilic displacement reactions expressed the concept by naming the actual departing group in each example under consideration.[4] By the late 1960s the term leaving group had been used in the titles of over 25 papers.[5] When a leaving group carries away an electron pair it can also be called a nucleofuge.[6] Leaving groups are important in organic chemistry playing a key role in a range of reactions from aliphatic or aromatic nucleophilic substitution to electrophilic substitution and elimination reactions. It is thought they play a key role in up to 25% of all organic reactions.[7] In regards to leaving groups it is important to appreciate the mechanism of a substitution reaction and how it differs from an elimination reaction based on basicity which is shown by the following diagram as outlined in Schemes 1.1, 1.2, 1.3 and 1.4.[7,8]



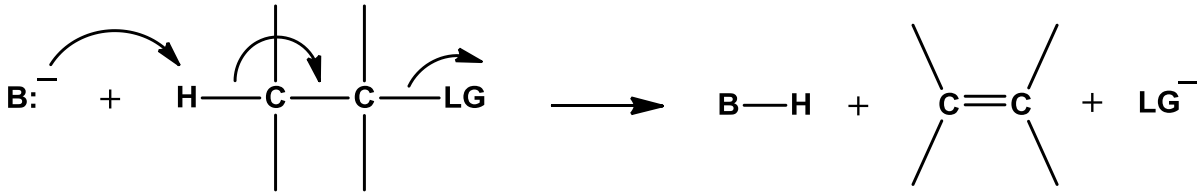
Scheme 1.1: SN1: Nucleophilic Substitution: Unimolecular Reaction.



Scheme 1.2: SN2: Nucleophilic Substitution: Bimolecular Reaction.

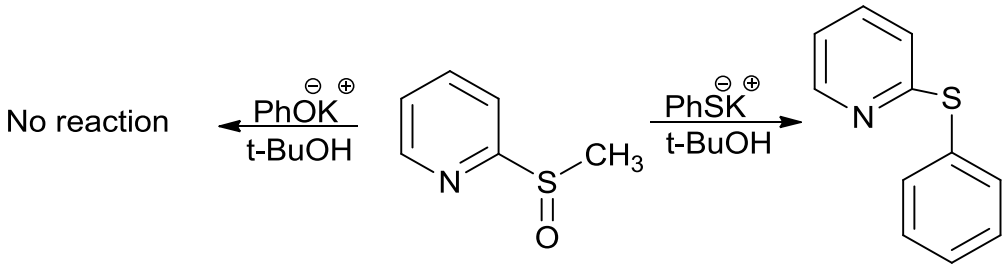


Scheme 1.3: E1: Elimination: Unimolecular Reaction.

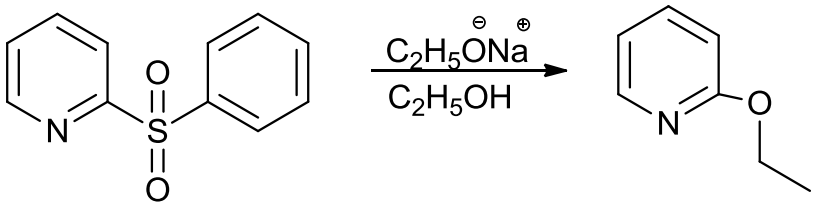


Scheme 1.4: E2: Elimination: Bimolecular Reaction.

The halides and sulfonates are common leaving groups in aliphatic and aromatic nucleophilic substitution reactions. Another point of interest is that the following groups: NO_2, OR, OAr, SO_2R, SOR and SR, when attached to an aromatic system can be leaving groups but, in contrast, these groups are difficult to displace in aliphatic systems. A key point to note is that this does depend on the nature of the nucleophile, as is shown by the reactions below (Scheme 1.5 and 1.6).[9-12]



Scheme 1.5: Substitution reaction of 2-methylsulfinylpyridine.[11] 47%

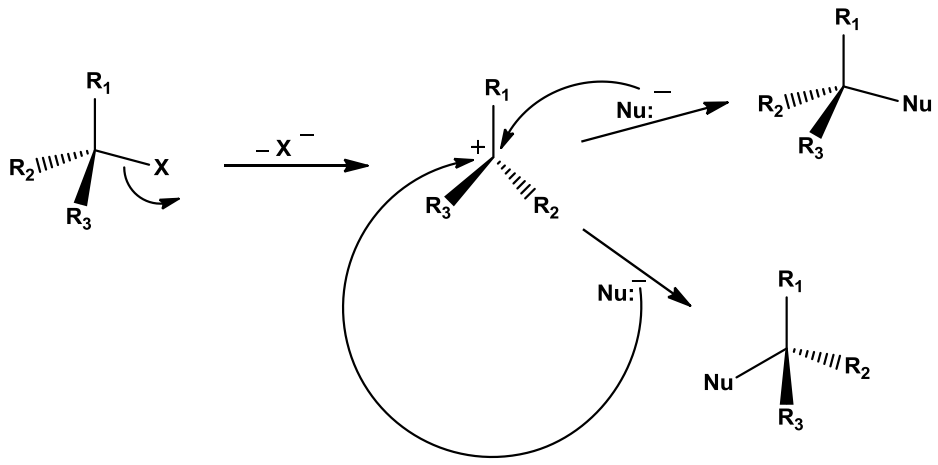


87 %

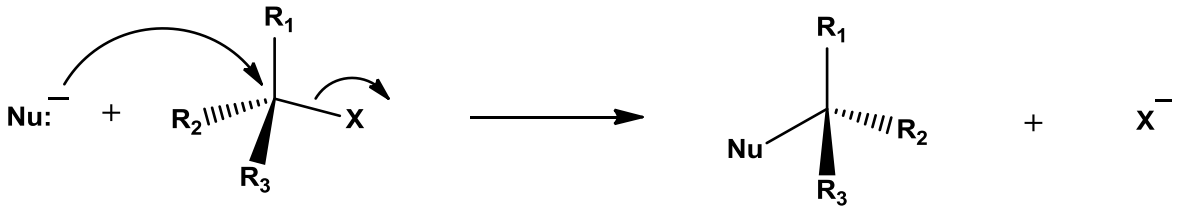
Scheme 1.6: Substitution reaction of 2-phenylsulfonylpyridine.[12]

In regards to the ease with which a leaving group breaks away from the residual, it is generally dependent on how stable the molecule will be as a free entity. This stability of the free entity can be calculated on the basis of its basicity as the relationship between basicity and stability is thought to be one that is inverse. Therefore to determine whether a leaving group will make a good or poor leaving group, the strength of the bond between the residual and leaving group and the pK_a of the conjugate acid of the leaving group need to be taken into account. For example, if fluoride is considered as a potential leaving group we can use this relationship to determine, due to its high basicity (high pK_a of HF), that it would be a poor leaving group, whilst its fellow halide iodide would be a good leaving group due to its weak basicity (Low pK_a of HI). This is found to be true as iodide is the best leaving group whilst fluoride is the poorest among the halides in S_N2 reactions where bond breaking of the C-Hal bond is involved in the rate-determining step. This means that strong bases such as hydroxyl (OH^-) are poor leaving groups, whilst most of the halides are better leaving groups due to the fact they are weaker bases (low pK_a of HX). In regards to the hydroxyl group, this does not break away from ordinary alcohols, but when protonated where the R-OH is converted to ROH^+ it leaves more willingly. This is due to the fact that (X^-) is more basic than (XH) it thus follows that nucleophilic substitution will be easier at a substrate RXH^+ than at (RX). This type of reaction in which protonation is required is

called S_N1cA or S_N2cA (sometimes named A1 and A2). The designation given to the reaction will depend on the conditions of the reaction. The cA in the designation correlates with the conjugate acid as the substitution part of the reaction will take place on the substrate's conjugate acid. Such reactions of course need acidic conditions which limit the nucleophiles which can be used. Protonation of the nucleophile can change its reactivity. For example $^{-}OCH_3$ in acid becomes CH_3OH. S_N2 reactions are dependent on powerful nucleophiles which themselves tend to be strong bases and so reactions must be carried out in neutral or basic conditions. In regards to the steps of the mechanism, in the S_N1 reaction the first step is the formation of a planar carbenium ion which will then go on to react with the nucleophile. This allows the nucleophile to attack from both sides therefore this mechanism is associated with racemization. The S_N2 mechanism requires both species to be in the transition state where the departure of the leaving group occurs simultaneously with a backside attack by the nucleophile.[10] S_N2 reactions thus lead to a predictable configuration of the stereocentre which involves the reversal of the configuration. Below are diagrams showing both mechanisms (See Scheme 1.7 and 1.8).[7]



Scheme 1.7: Mechansium of nucleophilic substitution (S_N1).



Scheme 1.8: Mechansium of nucleophilic substitution (S_N2).

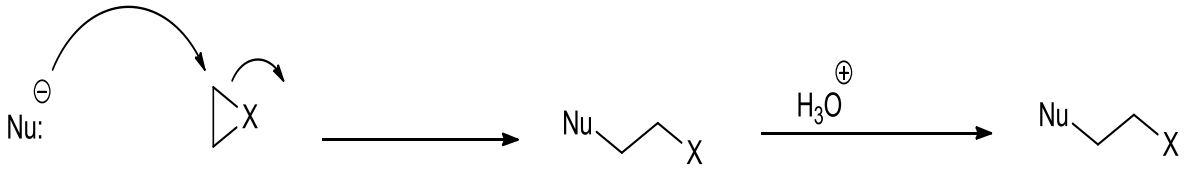
Substitution at aliphatic carbon is the main consideration in this thesis. However, nucleophilic substitution at aromatic centers (S_NAr) is well known, and usually goes by a stepwise mechanism. For example, if the first step of the mechanism is the rate determining step then fluoro and nitro groups are found to be good leaving groups. This is the common case. This is thought to be due to the fact what the first step is promoted by groups with strong negative ionic electronic withdrawing is a better expression effects. However, if the second step of the mechanism is rate determining then fluoro is the poorest leaving group amongst the halogens, because it makes the strongest bond to carbon.[13]

Table 1.1: Commonly used leaving groups in approximate order of decreasing ability to leave. Reactivity is quite similar for S_N1 and S_N2 reactions at sp^3 carbon centres.[10]

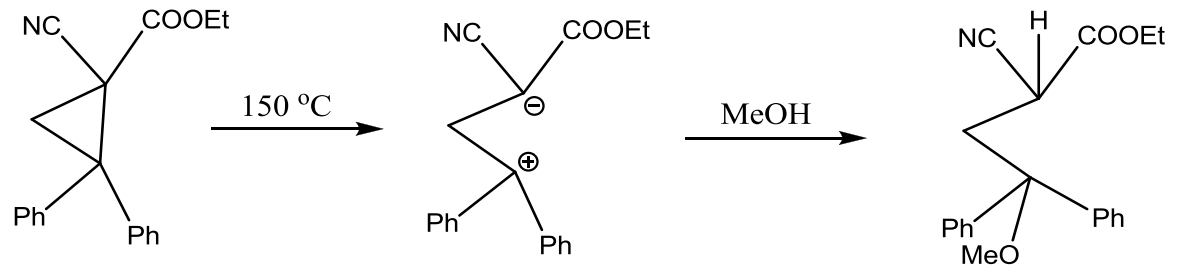
Substrate		Common leaving groups at saturated carbon
$R\text{-}N_2^+$	Diazonium salts	√
$R\text{-}OSO_2CF_3$	Triflates	√
R-OTs, R-OMs, etc.	Tosylates, mesylates, and similar	√
R-I	Iodides	√
R-Br	Bromides	√
$R\text{-}OH_2^+$	Conjugate acid of an alcohol	√
R-Cl	Chlorides and acyl chloride	√
$R\text{-}OHR'^+$	Conjugate acid ot an ether	√
$R\text{-}NR'_3^+$	Tetraalkylammonium salts	√
R-OCOR	Anhydrides	√

Another factor which increases the power of a leaving group is the ring strain; epoxides, aziridines and episulfides are easier to cleave than an unstrained system, for example acyclic ethers cleave only under strenuous conditions (Scheme 1.9). Also, the

cyclopropane ring can be cleaved, however this depends on whether there are any groups which can stabilize the resultant negative and positive charges after which the carbocation can react with a nucleophile, as shown in Scheme 1.10.[10]



Scheme 1.9: Epoxides, aziridines and episulfides are cleaved. X = O, NH, S

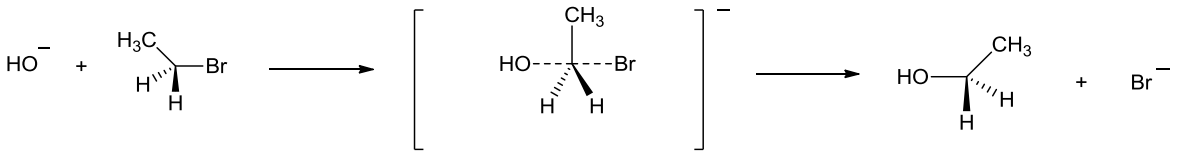


Scheme 1.10: Ring cleavge of a suitably substituted cyclopropane. [14]

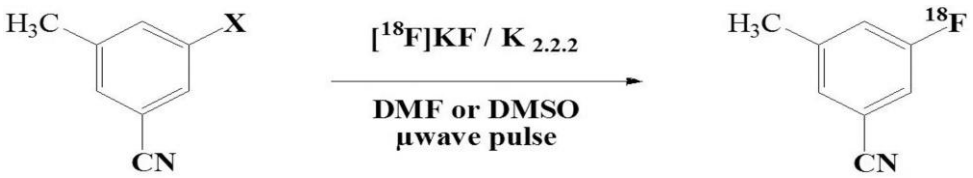
1.2: Halide leaving groups.

Halides in the order $I^- > Br^- > Cl^- > F^-$ are common anionic leaving groups in aliphatic systems. It was found that fluoride is actually the worst leaving group,[15] see Table 1.2.[16,17,18] The latter order was found when the cleavage of the C-halide bond is rate determining.[9] In contrast the reactivity of halogens as leaving groups in aromatic systems is F > Cl > Br > I,[17] however there are cases where bromide appears slightly more effective than chloride.[9] Electron withdrawing groups *ortho* and *para* to the leaving group activate the substitution. However, it has recently been found in a synthesis of isotopically labled material, that a *meta* activating group (-CN) is also effective under microwave conditions (Scheme 1.12).[18] Factors that need to be taken into account include the strength of C-halide bond, the polarity of C- halide bond due to the halogens being more electronegative than

carbon and the stability of halide ions as these all affect the ability of halides as leaving groups. It was found during the S_N2 reactions that the C-halide bond breaks during the rate-determining step (see Scheme 1.9). The leaving groups need to be electronegative, however it was found that iodide is a better leaving group than fluoride because it has a weaker C-I bond and also, the iodide ion is more stable.[7] (see Table 1.2).



Scheme 1.11: Nucleophilic aliphatic substitution reaction (S_N2).



Labelling yields: X = F 64%, X = Br 13%, X = Cl 9%

Scheme 1.12: [18F] Fluorine labelling reaction.[18]

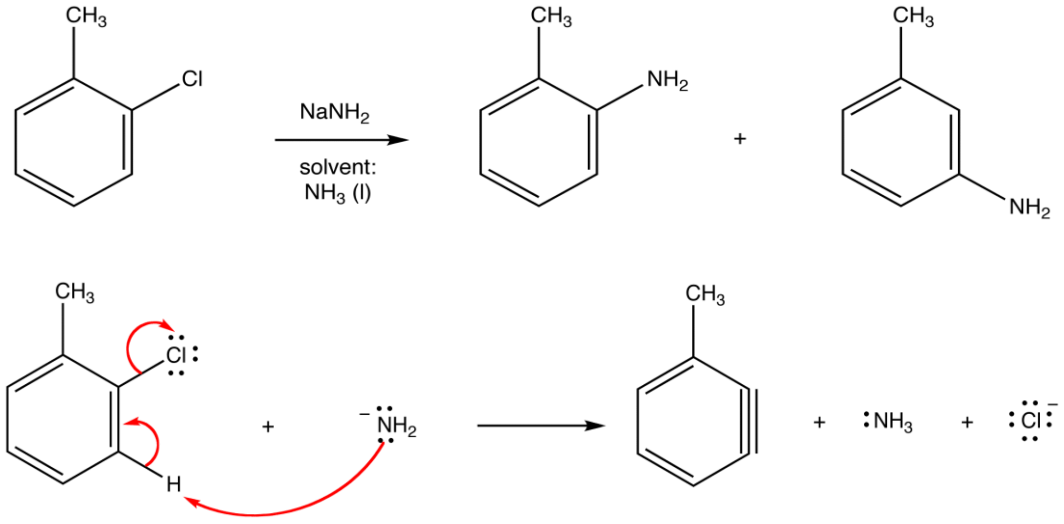
Table 1.2: Comparative data for breakage of C-Hal Bonds.

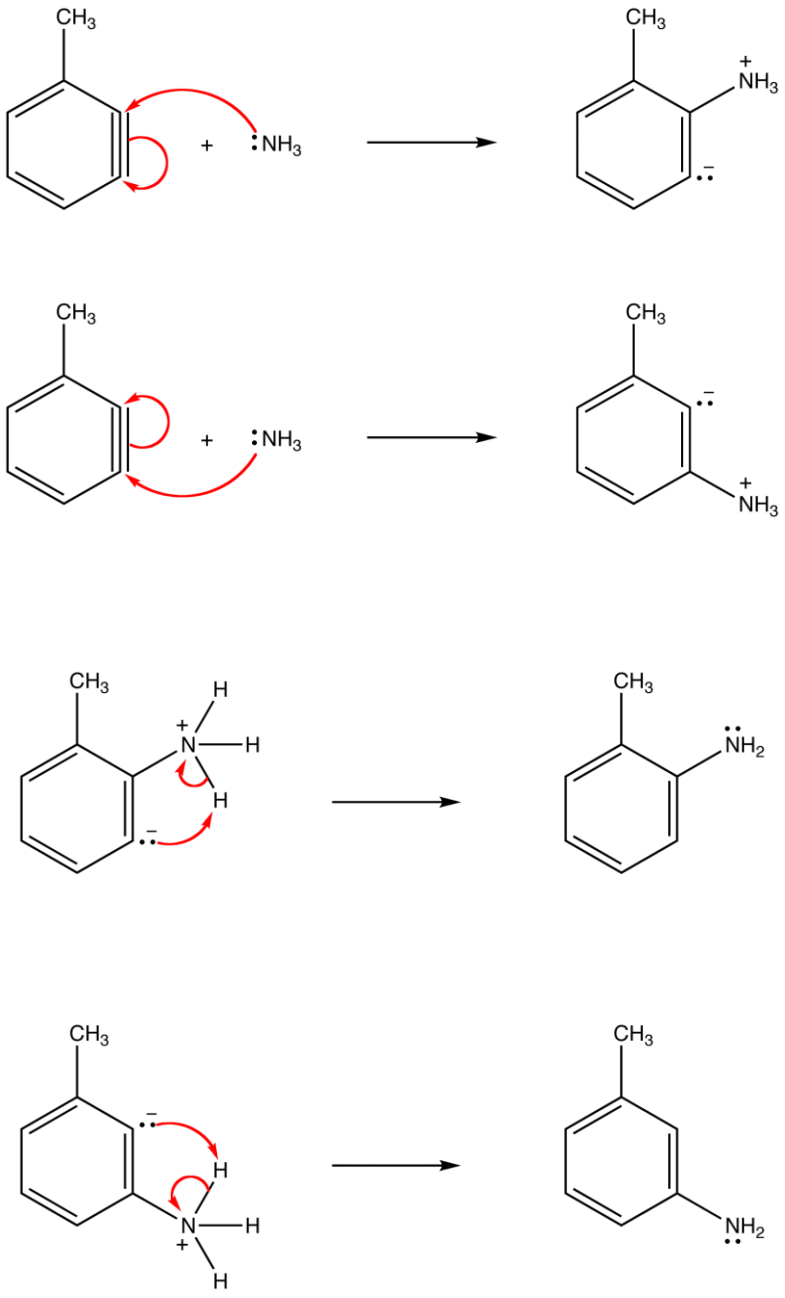
Halogen X	Bond length (Å) in CH_3-halogen	Bond strength kcal mol^{-1}	p*Ka* = - log K_a of H-Halogen	Electronegativity of X
C-F	1.38	110	3.18	3.98
C-Cl	1.77	85	-6.50	3.16
C-Br	1.94	70	-8.50	2.96
C-I	2.13	57	-9.00	2.66

1.2.1: The Benzyne Mechanism

It is very difficult to eliminate HX from aryl halides because the resulting intermediate is very unstable. In the benzyne mechanism (Elimination Addition Mechanism) under difficult conditions, unactivated halobenzenes can react with very strong bases such as

$NaNH_2$ or n-BuLi to generate the highly reactive benzyne intermediate. For example, o-chlorotoluene reacts with sodium amide as a strong base to give a 50:50 mixture of *meta* and *para* substituted compounds. The base abstracts the proton adjacent to the leaving group. The product is a carbanion with a non bonding pair of electrons localized in the sp^2 orbital that once formed the C-H bond. The carbanion can expel the chloride ion to become a neutral species. As chloride leaves with its bonding electrons, an empty sp^2 orbital remains. This orbital overlaps with the filled orbital adjacent to it, giving additional bonding between these two carbon atoms. This reactive intermediate is called a benzyne (a type of highly strained alkyne), therefore approximately symbolized by drawing a triple bond between these two carbon atoms. The benzyne reactive intermediate is highly susceptible to nucleophilic addition and is very reactive. In this example, the strong nucleophile is the ammonia which attacks the triple bond to generate a carbanion, which then gets protonated to give an almost equal amount of products resulting from attack by ammonia at the *ortho* and *meta* carbons.[4,19]



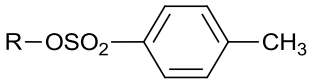


Scheme 1.13: Benzyne Mechanism

1.3: O centered leaving groups: sulfonate.

1.3.1: Sulfonate leaving groups (-OSO_2X).

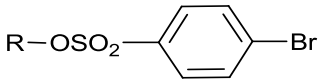
The sulfonic ester groups with the general formula $R^1SO_2OR^2$ *p*-toluenesulfonates (*tosylates*), *p*-bromobenzenesulfonates (*brosylates*), *p*-nitrobenzenesulfonates (*nosylates*), methanesulfonates (*mesylates*), nonafluorobutanesulfonates (nonaflates), 2,2,2-trifluoroethanesulfonates (*tresylates*) and trifluoromethanesulfonates (*triflates*) (see Figour.2), are found to be very good leaving groups which are better than halides. They have found widespread use as leaving group in S_N1, S_N2, E1 and E2 reactions.[7]



ROTs

p-Toluenesulfonates

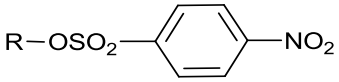
Tosylates



ROBs

p-Bromobenzenesulfonates

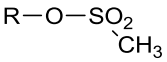
Brosylates



RONs

p-Nitrobenzenesulfonates

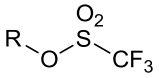
Nosylates



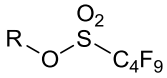
ROMs

Methanesulfonates

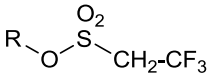
Mesylates



Triflates



Nonaflates



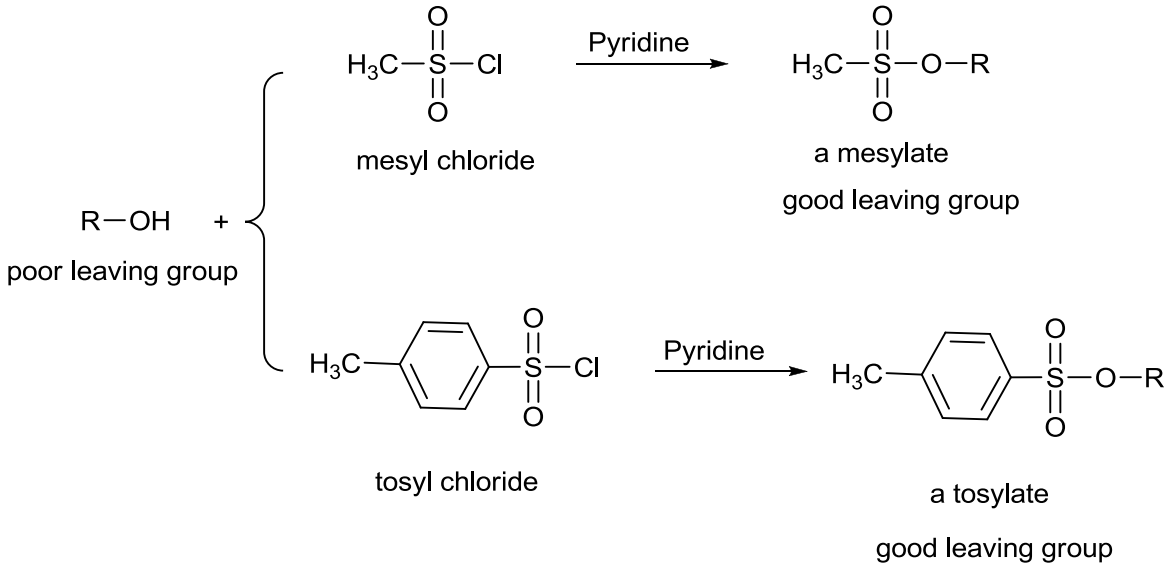
Tresylates

Figure 1.2: Structure of sulfonic esters groups.

Alcohols can be converted into sulfonic ester groups by using sulfonyl chlorides such as *p*-toluenesulfonyl chloride (*tosyl chloride*) and methanesulfonyl chloride (*mesyl chloride*) in the presence of a base often an amine base such as pyridine or triethylamine (Scheme 1.14).[20,21]

The direct esterification of hydroxy compounds with the sulfonyl chloride seems to be limited to polyhalogenated alcohols[22,23] while normal alkyl alcohols are unreactive.[24] An alternative general strategy for the synthesis of sulfonates from alcohols is the preparation of sulfur(II) or sulfur(IV) intermediates (sulfenates, sulfinates), followed by their oxidation to the sulfur(VI) compounds.[23]

For the preparation of sulfonate esters there are many other methods known.[25,26]



Scheme 1.14: Preparation of a mesylate and a tosylate.

Mesylates are considered excellent leaving groups in nucleophilic substitution reactions and are often employed, while fluorosubstituted groups like triflate and nonaflate are even better.[20]

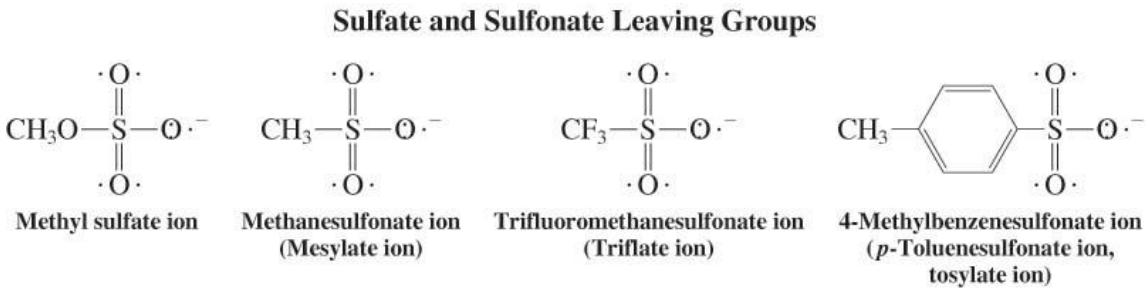
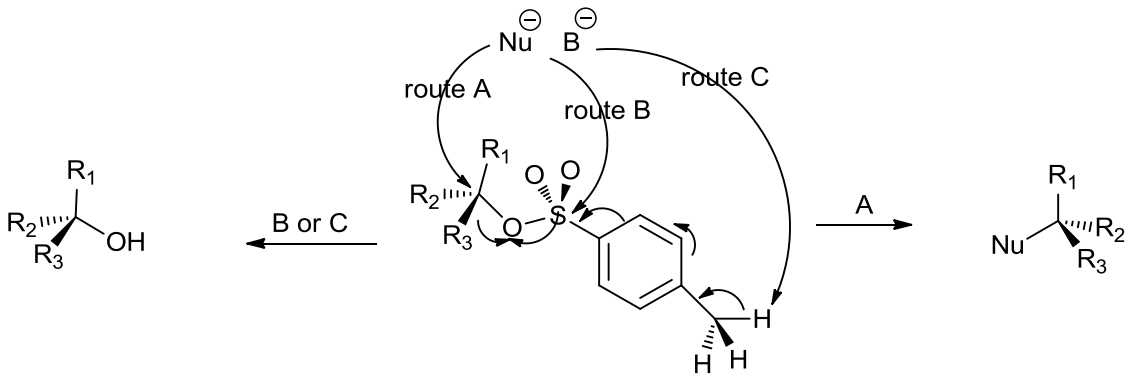


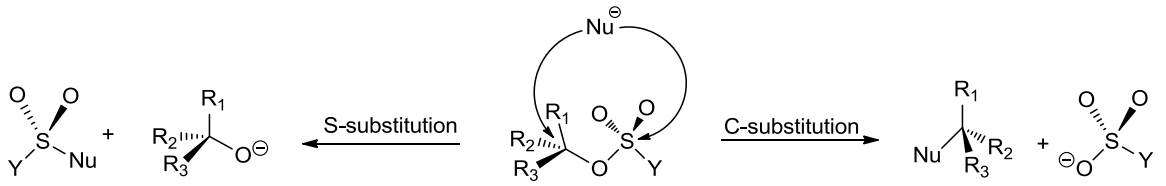
Figure 1.3: Sulfate and Sulfonate Leaving Groups

However, when applying known standard sulfonic esters like mesylates and tosylates serious problems can arise from unwanted side reactions. The proper choice of reagents and conditions for nucleophilic substitution reactions requires careful attention to the steric and electronic requirements of both the attacking nucleophile and the electrophile that will be used. For example if alkyl sulfonates are to be used, a key problem that is often encountered is the unwanted breaking of the sulfur-oxygen bond. A typical example of this would be the S_N2 reaction by Nu^- at the saturated carbon atom of an alkyl *p*-toluenesulfonates **1** (Scheme 1.15, route A)[23] which has to compete with attack on the sulfur atom (route B) or sulfene formation if the nucleophile behaves as a strong base B^- (route C), resulting in the formation of alcohol **3** besides the desired product **2**. Due to the demanding nature of some S_N2 substitution reactions, research has been directed at the use of more stable sulfonyl functionalities. Two key aspects in this regard to be considered are 1) S-substitution this should be retarded effectively by steric shielding, and 2) nucleofugality which should be reasonably high, i.e. the reactivity of the esters should be in the range between trifluoroethanesulfonates (tresylates **8**) (Scheme 1.16),[25,27] and perfluoroalkylsulfonates (triflates **9**, nonaflates **14**).[26]



3 **1** **2**

Scheme 1.15: S_N2 reaction by Nu^- at the saturated carbon atom of alkyl *p*-toluenesulfonates.[23]

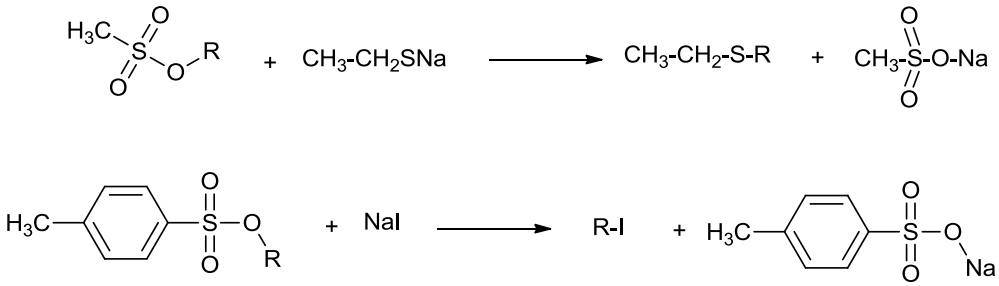


4 - 14

	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Y	CH_3	$C_6H_4CH_3$-(4)	$C(CH_3)_3$	$C(C_6H_5)_2CF_3$	CH_2CF_3	CF_3	CCl_3	$CHCl_2$	F	Cl	C_4F_9

Scheme 1.16: Substitution reaction of esters of alkyl and aryl sulfonic acids. [23]

The better the leaving group the shorter the shelf life of the material in atmospheric conditions. The tosyl group is a strongly electron-withdrawing group which makes it an excellent leaving group. Toluenesulfonate esters undergo nucleophilic attack or elimination as outlined in Scheme 1.17.



Scheme 1.17: Reaction of mesylate and tosylate via S_N2 reaction.

A group similar to the tosyl group is the brosyl, Bs or brosylate (*p*-bromobenzenesulfonyl) group wherein the methyl group has been replaced with a bromine atom. Nosyl groups in nosylates, Ns, are 4-nitrobenzenesulfonyl groups with a nitro group in the para position. Another related example is Nps which stands for 2-nitrobenzenesulfonyl.

Triflates **9**, are also seen as an excellent alternative leaving groups which can be used in certain organic reactions such as nucleophilic substitution. Triflates are more formally known as trifluoromethanesulfonates, the functional group has the formula CF_3SO_3-. The

triflate group is often represented by -OTf. For example, the *n*-butyl triflate, $CH_3CH_2CH_2CH_2OTf$.

The triflate anion, $CF_3SO_3^-$ is an extremely stable polyatomic ion, this is due to it being the conjugate base of triflic acid (CF_3SO_3H), one of the strongest acids known. It is defined as a superacid, because it is more acidic than pure sulfuric acid. Triflates are extremely reactive in S_N2 reactions, they must be stored in conditions free of any nucleophiles (such as water). The anion owes its stability to resonance stabilization where the negative charge is spread over the three oxygen atoms and the sulfur atom. An additional stabilization is achieved by the trifluoromethyl group acting as a strong electron-withdrawing group.[28] Due to the instability of the commonly used triflates **9**, problems often arise resulting in storage or purification difficulties of the highly reactive triflates. This high reactivity of the intermediates also means that simple processes such as analysis require special attention.[29] Thus on occasion it can often be a demanding task simply preparing triflates. One such example of this is seen when carrying out the esterification of sterically congested alcohols with triflic anhydride, where the formation of sulfur(IV) esters (sulfinates) has been noticed, this side reaction is dependent on the base used and conditions applied.[30] Another such example is if pyridine is used as a standard base and solvent, pyridinium salts may be formed by reaction with the newly formed triflate.[23] High reactivity nonafluorobutane sulfonates, $CF_3CF_2CF_2CF_2SO_3^-$ (nonaflates), are the salts or esters of perfluorobutanesulfonic acid, and uses are similar to those of triflates.[15,17]

Sulfonate esters are particularly useful for transforming polyfluorinated side chains by nucleophilic attack. They are usually more reactive than the corresponding halides.[26] The structure of perfluorobutyl p-tolyl sulfide is shown in Figure 1.4.

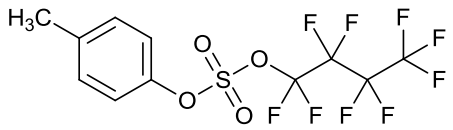


Figure 1.4: Perfluorobutyl p-tolyl sulfate.

Thus, the general formula of polyfluoroalkyl sulfonate esters is $R_F(CH_2)_nOSO_2G$, when G is CH_3, p-tolyl, CF_3 or C_4F_9 (these are termed Group G).

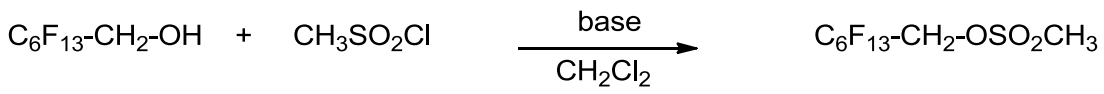
A key point of consideration is the reactivity of the sulfonate esters which itself depends on two key factors. One is the electronic properties of the Group G, and the number of methylene units in the polyfluoroalkyl chain $(CH_2)_nRF$. These both have a strong influence on the leaving ability of the sulfonate group $G\text{-}SO_2O^-$.[25,32,33] The second factor that influences reactivity of the sulfonic ester is the electron-withdrawing effect of the perfluorinated chain which is acting against the forces of the group G. The lower the electron withdrawing ability of the perfluroalkyl chain the easier it will be to obtain formation of a sulfonate anion, and overall it results in greater reactivity of the sulfonate as a whole. The influence shown by the perfluorinated chain largely depends upon the length of the spacer between the sulfonate group and the chain itself. This is shown by the fact that if you use two identical sulfonic groups $–SO_2G$, with spacers with varying length, the one with the longer spacer will have the lower electron withdrawing ability. So for a low reactivity sulfonate a shorter spacer is needed. In terms of spacer length the order of reactivity is the following: methylene < ethylene < propylene.

As previously mentioned the polyfluoroalkyl and arenesulfonates are predominant due to their high reactivity and are irreplaceable in many synthetic processes: for example they are widely used for the preparation of various types of structures.

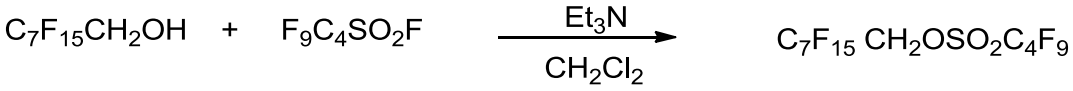
On the other hand mesylates have two advantages when compared with the tosylates. One is their greater stability against hydrolysis and reduced steric hindrance for a nucleophilic attack. However triflates are the most interesting group of activated polyfluoroalcohol derivatives due to their high reactivity.[34] Triflates are powerful fluoroalkylating agents (around 10,000 times more reactive than the corresponding tosylates)[35] whilst nonaflates can be designated as the most reactive sulfonates.

Several methods for the preparation of polyfluoroalkyl sulfonate esters can be used.

For polyfluoroalkyl mesylates (see Scheme 1.18) or tosylates, chlorides of the corresponding acids are most frequently used. For the preparation of nonaflates, the fluoride of nonafluorobutanesulfonic acid was used (See Scheme 1.19). All the reactions are carried out most frequently in dry dichloromethane or chloroform. Triethylamine, pyridine or aqueous sodium hydroxide are used as bases. The temperature range, in which components are added, varies from -40 to 20 ^{o}C.[34]



Scheme 1.18: Preparation of polyfluoroalkyl methanesulfonates (mesylates)

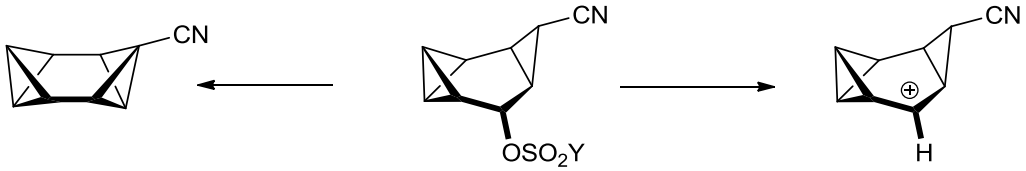


Scheme 1.19: Preparation of polyfluoroalkyl nonaflates.

1.3.2: <u>tert-Butylsulfonates.</u>

tert-Butylsulfonates **6** are synthesized by treatment of alcohols with tert-butylsulfinyl chloride in presence of a base (triethylamine) to obtain sulfinates. Subsequent oxidation with peracids converts these to sulfonates **6**. Di-tert-butyl disulfide is used to prepare tert-butylsulfinyl chloride by peracid oxidation and subsequent chlorinolysis.[26,36] tert-

Butylsulfonates are well crystallizing compounds, and have better solubility in weak polarity or non polar organic solvents than corresponding tosylates.[37] On the reactivity level of sulfonate esters **6** in S_N2 substitution reactions, they have been found to be weak nucleofuges when compared to methanesulfonates, which is advantageous when used in the synthesis of the highly strained cyano-octabisvalene **18** (Scheme 1.20),[26] Preparation of sulfonate derivatives **19** led instead to cation **20** (which undergoes further reactions) when mesylate **19a**, benzenesulfonate **19b**, and tosylate **19c** were used. On the other hand this does not happen when tert-butylsulfonate **19d** is used, and when this product is treated with potassium bis(trimethylsilyl)amide, the highly strained system **18** could be prepared, a octabisvalene derivative **18**.[37]



18 **19a - d** **20**

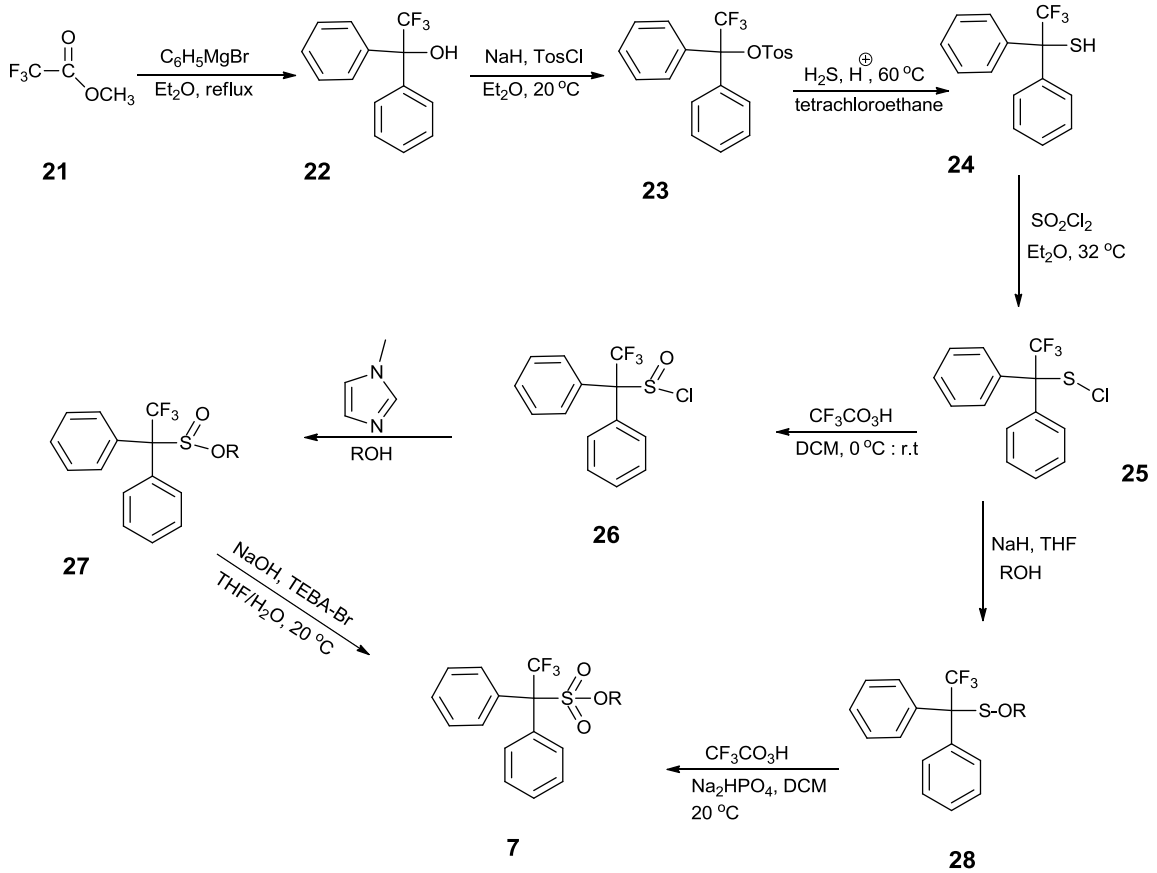
	19a	**19b**	**19c**	**19d**
Y	CH_3	C_6H_5	$C_6H_4CH_2$-CF_3	$C(CH_3)_3$

Scheme 1.20: Synthesis of the highly strained cyano-octabisvalene 18 and solvolysis of esters 19a-d to the stabilized cation 20.[37]

1.3.3: 2,2,2-Trifluoro-1,1-diphenylethanesulfonates (TDE-sulfonates).

For the preparation of 2,2,2-trifluoro-1,1-diphenylethanesulfonates **7**, the starting compound used was methyl trifluoroacetate **21**, by reaction with 2 equivalents of PhMgBr gave alcohol **22**, which was converted to a tosylate to give **23**, thus was then treated with hydrogen sulfide and followed by sulfuryl chloride to produce crystalline TDE-sulfenyl chloride **25**. Partial oxidation using trifluoroperacetic acid gave the thermally labile sulfinyl

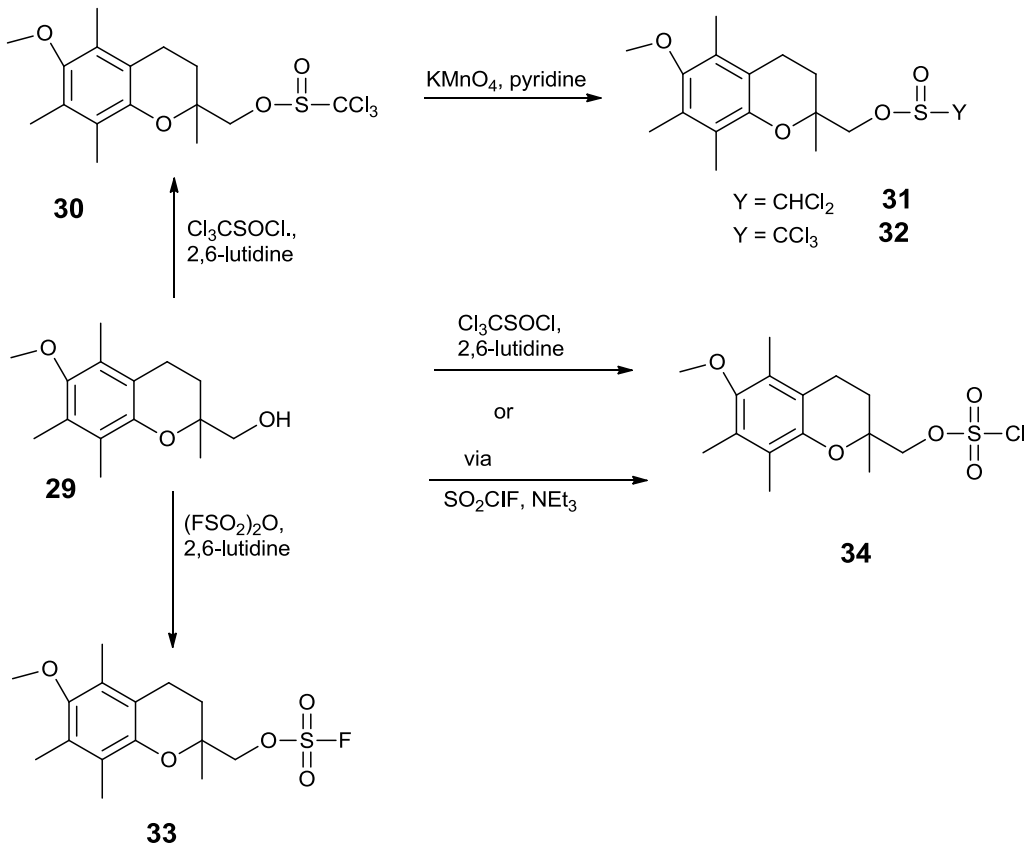
chloride **26**.[26] TDE-sulfonates **7** are obtained from the corresponding alcohol by treatment with **25** or **26** in the presence of bases and oxidation of sulfinyl esters **27** or sulfenyl esters **28** (Scheme 1.21).[36] In comparison to the tosylate group there is much more steric hindrance caused by the competing of the S-O cleavage by the bulky TDE- group, as well as considerably higher nucleofugality due to the TDE-sulfonate anion. Evidence of this is provided by the production of polyfunctionalized, or sterically demanding substrate when using different nucleophiles.[26]



Scheme 1.21: Preparation of TDE-sulfonates 7 via oxidation of corresponding sulfenyl or sulfinyl esters.

1.3.4: Halogenated sulfonic esters.

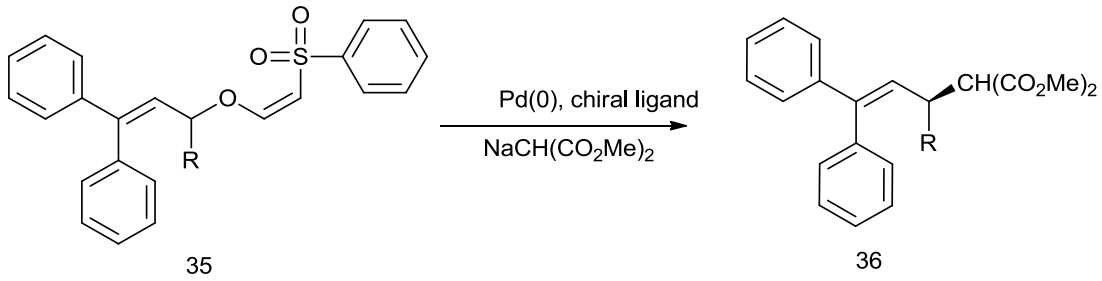
To create a broader range of sulfonic esters suitable for S_N2 substitution reactions, endeavours have been made to develop additional alternatives or enhanced sulfonyl moieties which have both the advantageous electronic and steric features. Example of possible leads are the esters of halogenated sulfonic acids, e.g. trichloromethanesulfonates **10** which it was thought would be strongly activated due to their strong electron withdrawing abilities and also possess the advantage of being a similar size to the tert-butyl group, leading potentially to a "sterically hindered triflate" leaving group. For the preparation and the properties of halogenated sulfonic esters, the oxa-neopentyl alcohol **29** was used as starting material (Scheme 1.22). The sulfonate **30** was easily produced in high yield from **29** by treatment of the alcohol with the sulfinyl chloride in the presence of 2,6-lutidine as a base, which is then oxidized by using potassium permanganate delivering a mixture of trichloromethanesulfonates **32** and dichloromethanesulfonates **31**.[23] Also, treatment of the alcohol with sulfuryl chloride fluoride and triethylamine as base delivered a chlorosulfonate **34** in high yield; on the other hand the direct esterification of **29** with the sulfonyl chloride failed and led to the unexpected chlorosulfonate **34**. The fluorosulfonate **33** was prepared from oxa-neopentyl alcohol **29** by adding fluorosulfonic anhydride (toxic reagent) in the presence of triethylamine as a base.[23,26] In substitution and rearrangement reactions the monochloromethanesulfonate group was found to be an effective leaving group.[38,39]



Scheme 1.22: Preparative accessibility and properties of halogenated sulfonic esters.[23]

1.3.5: <u>Vinylogous sulfonates.</u>

A variety of palladium-catalyzed allylic substitution reactions has used vinylogous sulfonates as good leaving groups.[40] For example, alkyl-substituted β-phenylcinnamyl substrate **35** can be converted into chiral molecules **36** using Pd(0) with a chiral phosphino-1,3-oxazine legend (Scheme 1.23). This allylation reaction has a high enantioselectivity (ee 95%) and increased turnover rate of the catalyst relative to more traditional acetate leaving group. This, however, has only been demonstrated with β-phenylcinnamyl alcohol derivatives **35** with straight chain substituents at the carbinol position.[41]



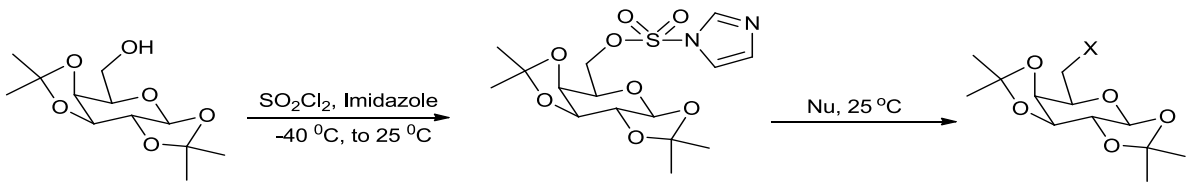
35 36

R = methyl, *n*-propyl, $BnOCH_2$, $TBSO(CH_2)_3$

Scheme 1.23: Vinylogous sulfonate leaving groups for asymmetric allylic alkylation.

1.3.6: Imidazole -1-sulfonates.

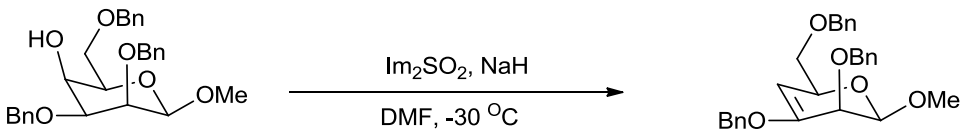
For preparation of imidazole-1-sulfonates, the alcohol is reacted with sulfuryl chloride to provide a chlorosulfate ester, after which thus is reacted with imidazole, or the alcohol is reacted with N,N'-sulfuryldiimidazole.[42] The imidazylates have been used successfully in S_N2 reactions as leaving groups in the synthesis of mono- and oligosaccharides. For example, the derivative imidazyl **38** was made from diisopropylidene galactopyranose **37** via addition of an imidazyl group at the 6-position to give **38**. The imidazyl **38** was converted to the corresponding 6-fluoro, iodo, and azido products **39** in good yields (Scheme 1.24). Recently the enopyranoside **41** was obtained in a very good yield (95%) from the pyranose **40** via a highly regioselective elimination reaction (Scheme 1.25). Formation of the imidazylate occurs with loss of the imidazole anion, which reacts as a base for the *in situ* elimination to give the alkene.[41]



37 **38** **39**

Nu = Bu_4NF, Bu_4NI, Bu_4NN_3 and MeI; X = F, I, N_3

Scheme 1.24: Galactopyranose derivatization via imidazylates.

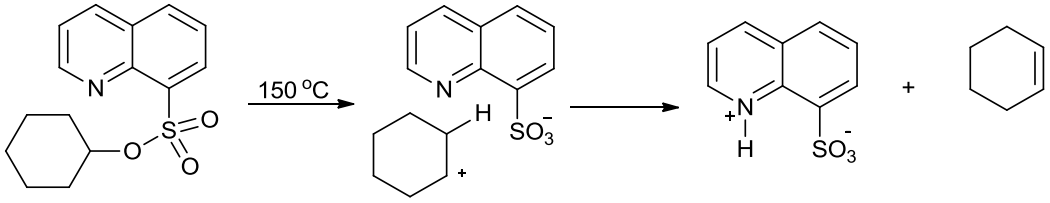


40 **41**

Scheme 1.25: Highly regioselective imidazylate elimination to give an enopyranoside.

1.3.7: Pyridine and quinoline sulfonate.

8-Quinoline sulfonate has been used as a leaving group in the pyrolysis via an E_2 reaction of **42** to cyclohexene.[41] The 2-pyridine sulfonate derivative was also easily converted to the alkene (Scheme 1.26).[43]

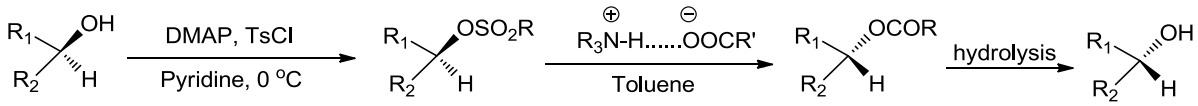


42

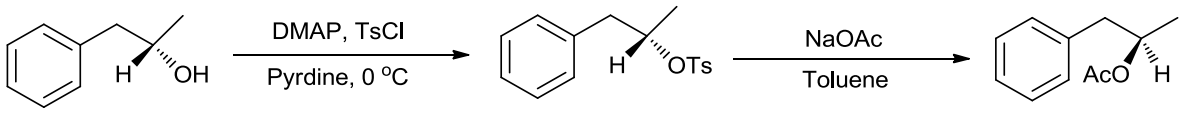
Scheme 1.26: Pyrolysis of 8-quinoline sulfonate 42 to give cyclohexene.

1.3.8: Chiral sulfonates.

A method has been devised for the inversion of chiral secondary alcohols involving formation of a chiral sulfonate leaving group which is then substituted by S_N2 reactions by oxygen nucleophiles using $R_3NR'COOH$. This conversion of various chiral sulfonates to inverted carboxylates in the low polarity solvent toluene proceeds in good yield and without observable racemisation (Scheme 1.27). For example, S-1-phenylpropan-2-yl p-toluenesulfonate was prepared from S-1-phenylpropan-2-ol in the presence of 4-dimethylaminopyridine and p-toluenesulfonyl chloride in pyridine at 0 ^oC. The chiral toluenesulfonate was treated with various acetate salts [MOAc (M = Na, K and Cs)] to obtain (R)-1-phenylpropan-2-yl acetate (Scheme 1.28).[44]



Scheme 1.27: Inversion of secondary chiral alcohols in toluene with the tunable complex of R_3N-R'COOH

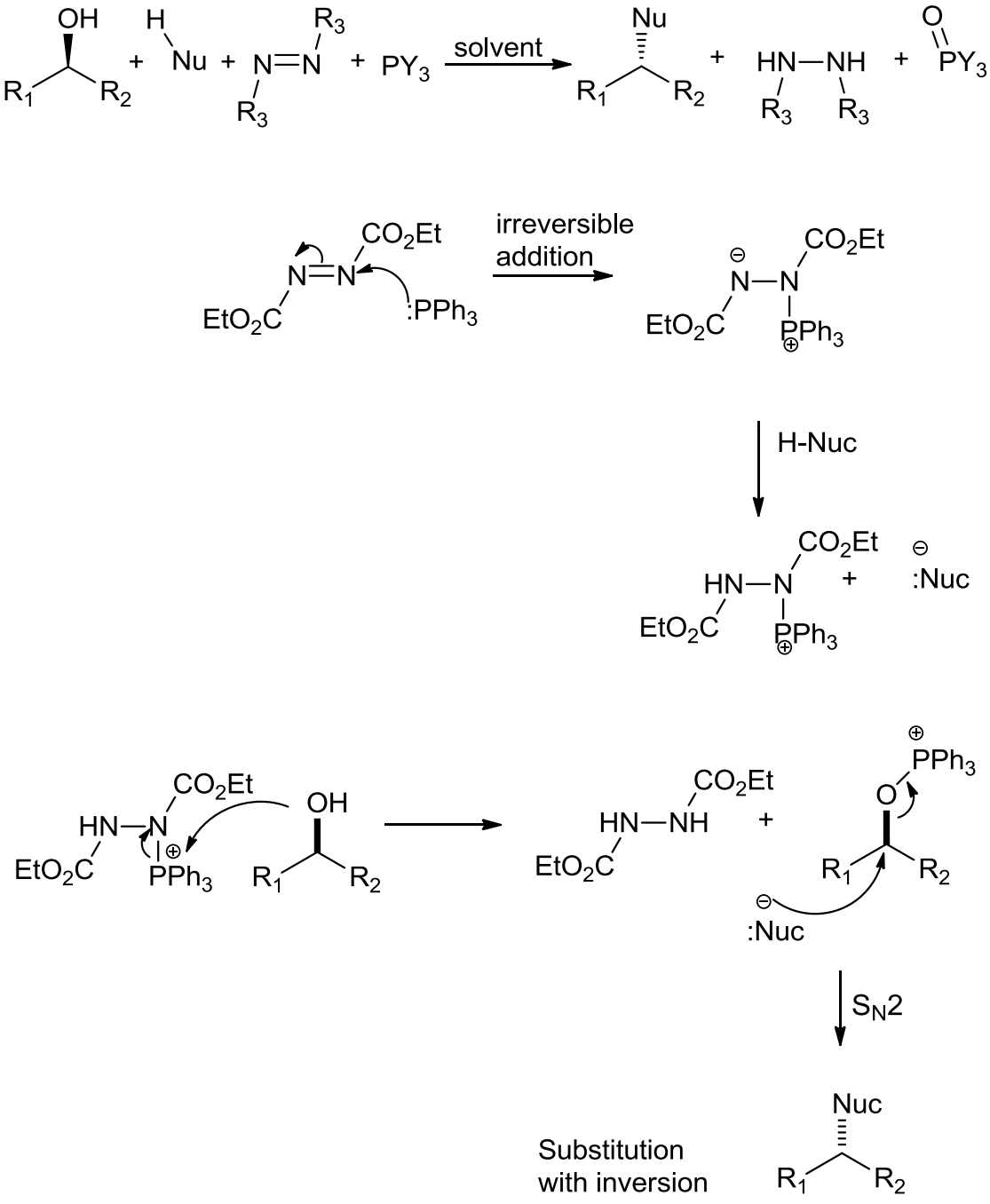


Scheme 1.28: Preparation of (R)-1-phenylpropan-2-yl acetate.

1.4: Further O-centered leaving groups.

1.4.1: Mitsunobu reactions

In 1967 Mitsunobo described a reaction which overall results in the substitution of a hydroxyl group in primary or secondary alcohols. The reaction requires an acidic pro.nucleophile (NuH) in the presence of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP). The hydroxyl group is converted into a good leaving group which deprotonates the pro-nucleophile which then displaces the leaving group, and the mechanism of this reaction is shown in the Scheme 1.29.[45-47]



Scheme 1.29: Mitsunobu mechanism

1.4.1.1: <u>The general features of the reactants and conditions.</u>[46,47]

i) The best substrates are primary and secondary alcohols,

ii) The nucleophile employed should be acidic ($pK_a \leq 15$). Suitable nitrogen nucleophiles make the corresponding amines accessible, oxygen nucleophiles

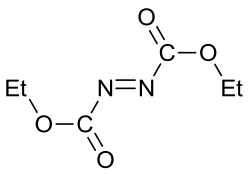
alcohols and phenols give ethers, carboxylic acids afford esters, and the use of active methylene compounds such as β–diketones or β–keto esters as nucleophiles leads to formation of C-C bonds, whilst when acyl/alkyl halides or zinc/lithium halides are used with DEAD/PPh_3, alcohols are converted to halides (Scheme 1.30).

iii) This reaction has found widespread use in organic synthesis and medicinal chemistry because it is a highly reliabile, extensively versatile and a highly stereoselective process occurring in mild conditions. Also, it is a most efficient tool for the inversion of configuration in secondary chiral alcohols.

iv) Common solvents that are used in this reaction are THF, DCM, dioxane, toluene, and benzene; common phosphines for the reaction are PPh_3 or P(*n*-Bu)$_3$, and common azodicarboxylate reagents are DEAD and DIAD.

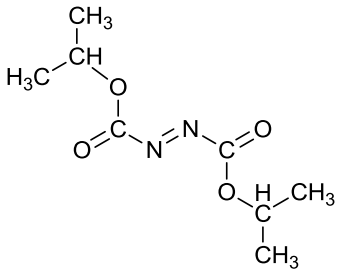
v) This reaction offers compounds in high yield containing newly formed C-O, C-S, C-N or C-C bonds (see Scheme 1.30). The OEt group in DEAD has been replaced with bulky groups such as NR_2 (see Figure 1.5).[45,46]

vi) Usually the mixture of the phosphine, alcohol, and the nucleophile are dissolved and the solution of the azodicarboxylate is added dropwise at temperatures between 0˚C and 25 ˚C.



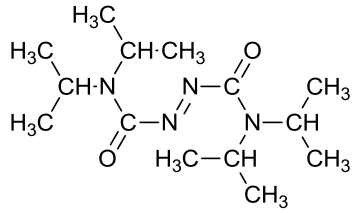
Diethyl azodicarboxylate

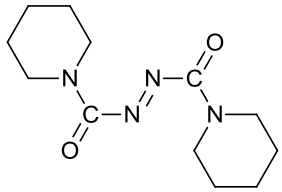
DEAD



Diisopropyl azodicarboxylate

DIAD





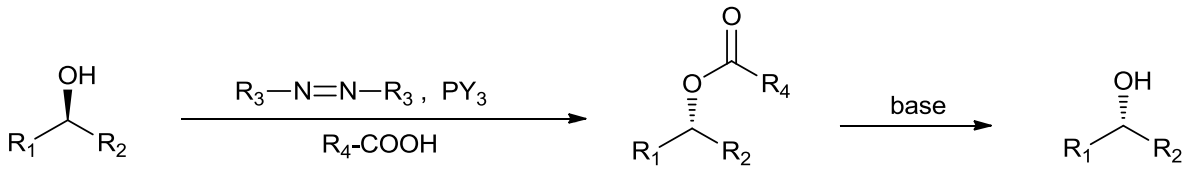
Tetraisopropyl azodicarboxamide

Azodicarbonyl dipiperidine

TIPA

ADDP

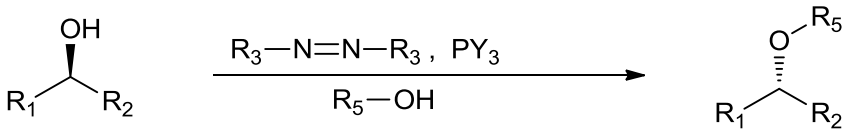
Figure 1.5: Mitsunobu reagents.



1^0 or 2^0 alcohol

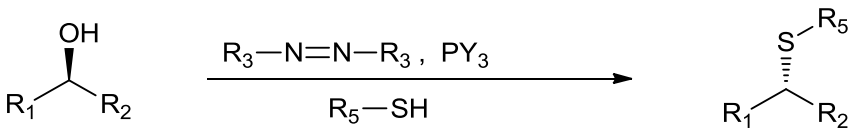
ester

inverted alcohol



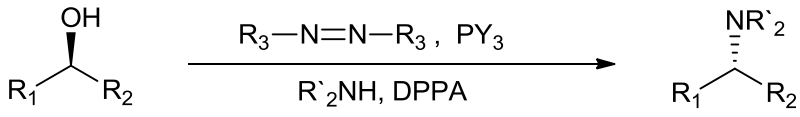
1^o or 2^o alcohol

ether



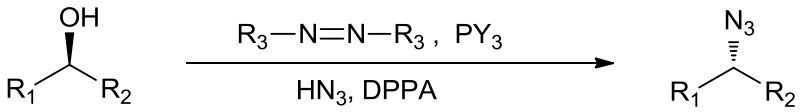
1^o or 2^o alcohol

sulfide

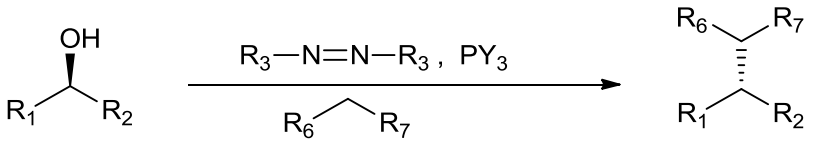


1^o or 2^o alcohol

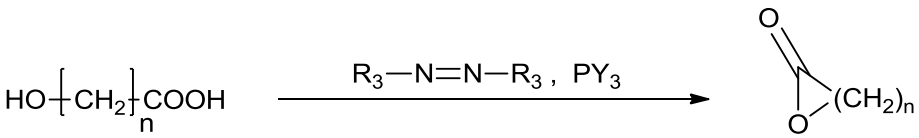
alkyl amine



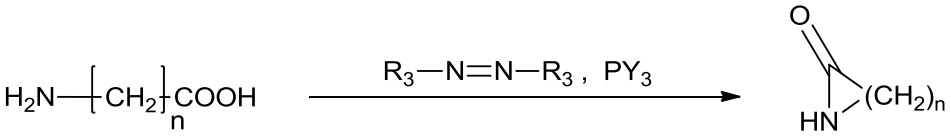
1^o or 2^o alcohol alkyl azide



1^o or 2^o alcohol



Lactone



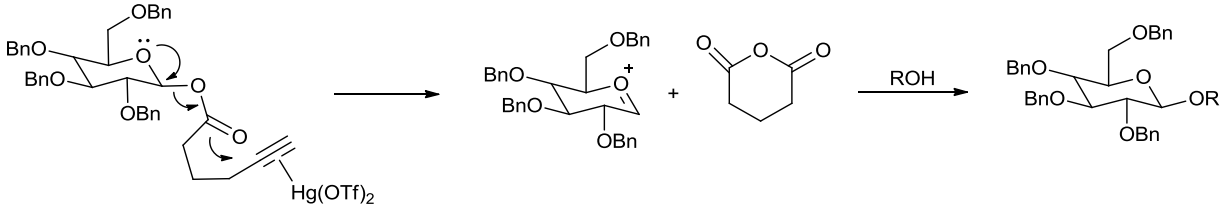
Lactam

R_1 and R_2 = alkyl, aryl, heteroaryl, alkenyl; H-Nu = *O*-, *S*-, *N*-, and C- nucleophiles; R_3 = CO_2Et (DEAD), CO_2*i*-Pr (DIAD), $CON(CH_2)_5$ (ADDP), $CONMe_2$ (TMAD); Y = alkyl, aryl, heteroaryl, O-alkyl; solvent: THF, dioxane, DCM, chloroform, DMF, toluene, benzene, HMPA; R_4 = H, alkyl, aryl; R_5 = alkyl, aryl, heteroaryl; R_6 and R_7 = CO-alkyl, CO-aryl, CO_2-alkyl, CO_2-aryl, CN.

Scheme 1.30: The most significant type of transformations under the Mitsubonu protocol.45-47

1.4.2: Carboxylate leaving groups.

A carboxylate group, RCO_2^-, can also react as a leaving group in certain occasions. For example, a novel glycosylation procedure catalysed by $Hg(OTf)_2$ has been developed using alkynoic acid residues as the leaving groups.[48] The procedure itself requires mild reaction conditions and has an efficient catalytic turnover. The acidic residue leaving group is remotely activated by the presence of Hg (II) which complexes with the alkyne moiety as shown in **43** (Scheme 1.31). The intermediate **43** undergoes cyclization with the complex resulting in the oxonium cation **44** and methylene lactone **45**. Further addition of alcohols to the intermediate **44** give glycosyl products **46**. Although it is a novel procedure it is particularly efficient for the glycolysation of hindered alcohols such as menthol.[41]



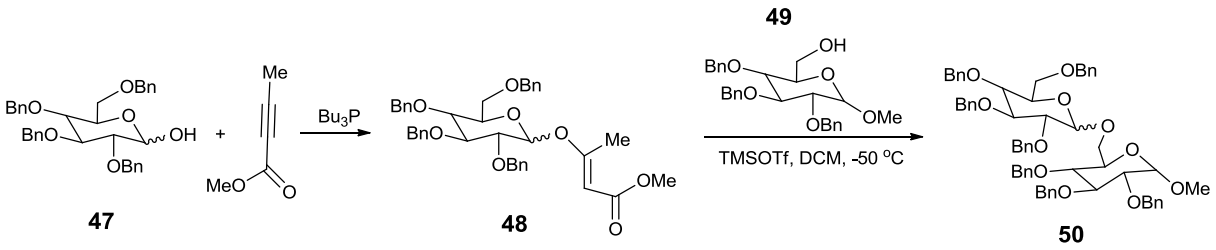
43 **44** **45** **46**

Scheme 1.31: Alkynoate leaving group for glycosylation.

1.4.3: Vinylogous carboxylates and carbonates.

Glycosyl donors are carbohydrate mono- or oligosaccharides which will react with a suitable glycosyl acceptor to form a new glycosidic bond. In this case either vinylogous carboxylates or carbonates (enol ethers) are the leaving groups.[49] These were easily prepared by the addition of the tetra-O-benzyl glucopyranose **47** to twice the amount of methyl 2-butynoate in the presence of a catalytic amount of tri-*n*-butylphosphine to give corresponding glycosyl donors **48** in the E-configuration by reason of the steric bulk imposed by the pyranose moiety during the reaction forming the enol ether (Scheme1.32).[41]

The disaccharide **50** was prepared in highest yield 82% (α/β = 9:2) by the reaction of donor **48** with alcohol **49** when the large excess of TMSOTf (9-12 equiv) was used at low temperature in dichloromethane as a solvent. The reaction conditions such as the solvent, the temperature and the amount of reagents significantly affected the yield and anomeric configuration.[41]

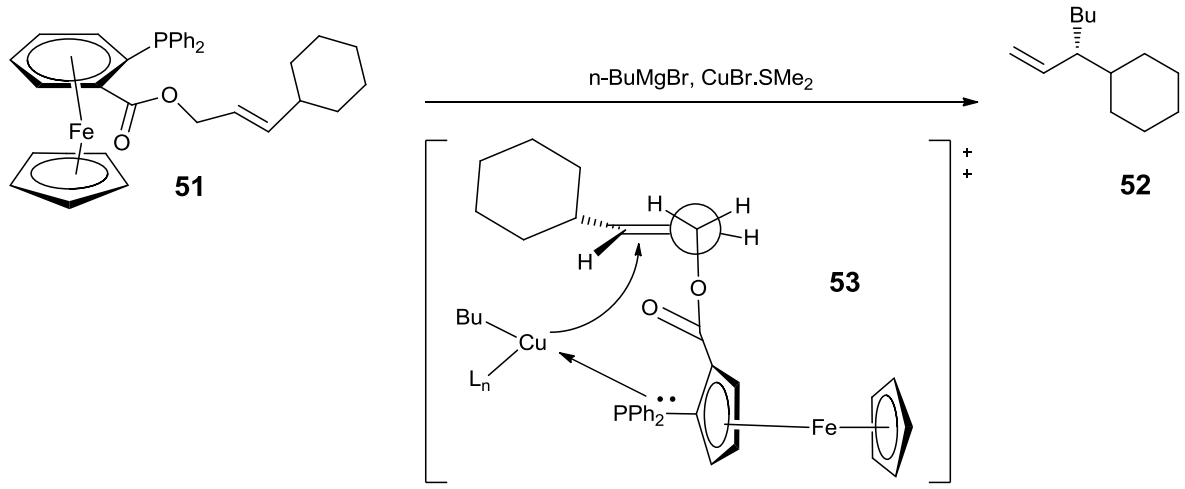


Scheme 1.32: Synthesis of disaccharide 50 using a vinylogous carbonate leaving group.

1.4.4: Chiral carboxylates.

An area that is also currently being investigated is the use of chiral carbamates as leaving groups in allylic substitution. Allylic substitution is a powerful carbon-carbon or carbon-heteroatom bond forming reaction, in which an electrophile containing an allylic leaving group reacts with a nucleophile.[50] However, analogous reactions using chiral carboxylates have not been sufficiently explored and therefore may be a point of possible interest. Enantioselective copper-mediated S_N2' substitution reactions involving *ortho*-diphenylphosphanylferrocene carboxylate (*o*-DPPF) as a chiral leaving group have been recently reported (Scheme 1.33).[51] DPPF, which is conveniently prepared, was initially developed as a catalyst-directing group in rhodium-based hydroformglation reactions.[52] The high enantioselectivity in the production of compound **52** (ee 95%) observed in the copper catalyzed addition of a butyl group to **51** was thought to be due to the presence of a strong phosphine–copper liganding interaction in transition state **53** (Scheme 33).[51]

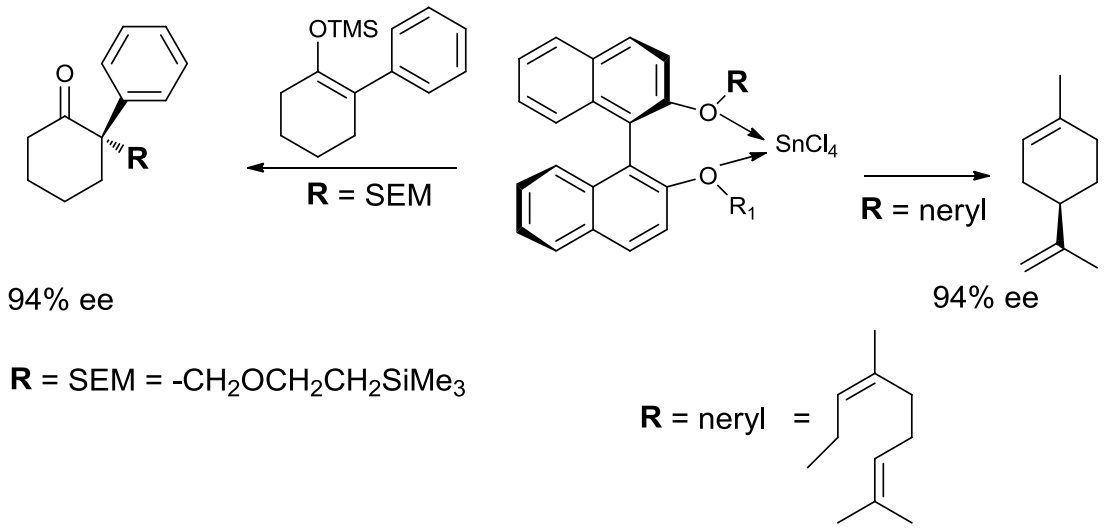
Interestingly, the use of a chiral ferrocene thiol as a copper ligand gave product **52** at only 64% ee when reacted with the precursor allylic acetate. In this case a nearly stoichiometric amount of the ferrocene thiol ligand was required to achieve a reasonable enantioselectivity.[41]



Scheme 1.33: Enantio- and regioselective addition of *n*-BuMgBr to *o*-DPPF ester 51.

1.4.5: BINOL derivatives.

A new strategy using a BINOL derivative as a chiral leaving group and a Lewis acid has been developed for enantioselective alkylation of prochiral olefins. (*R*)-2,2'-Bis[2-(trimethylsilyl)ethoxymethyl]-1,1'-binaphthol is demonstrated to be an effective reagent for enantioselective hydroxymethylation of silyl enol ethers and trisubstituted alkenes. Electrophilic addition to prochiral olefins is accompanied by cleavage of an acetal that is dual activated by $SnCl_4$ and the δ-effect of silicon through the S_N2 substitution process (Scheme 1.34). Enantioselective synthesis of cyclic terpenes is also described using this strategy.[53]

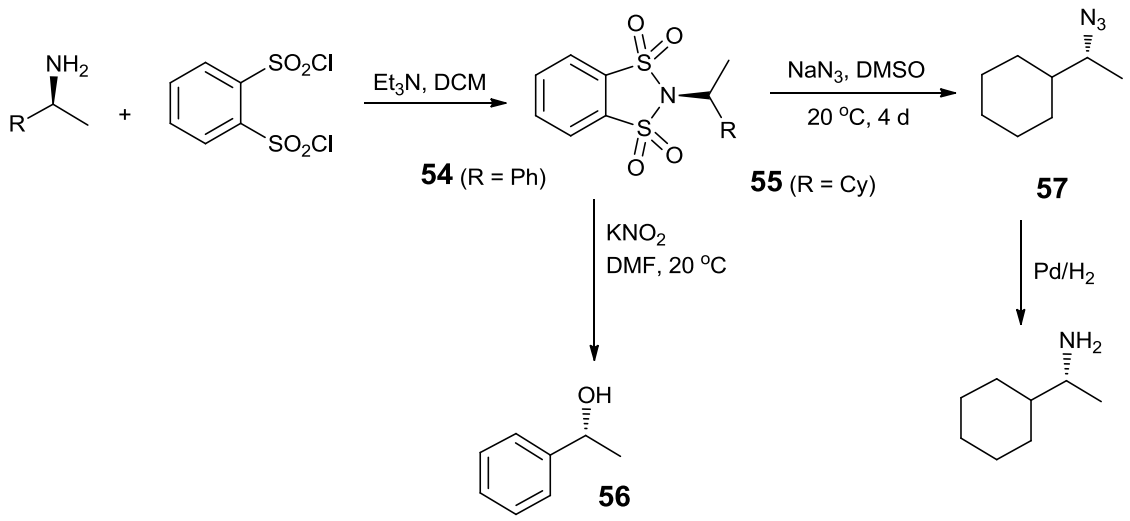


Scheme 1.34: Enantioselective electrophilic addition to prochiral olefins.

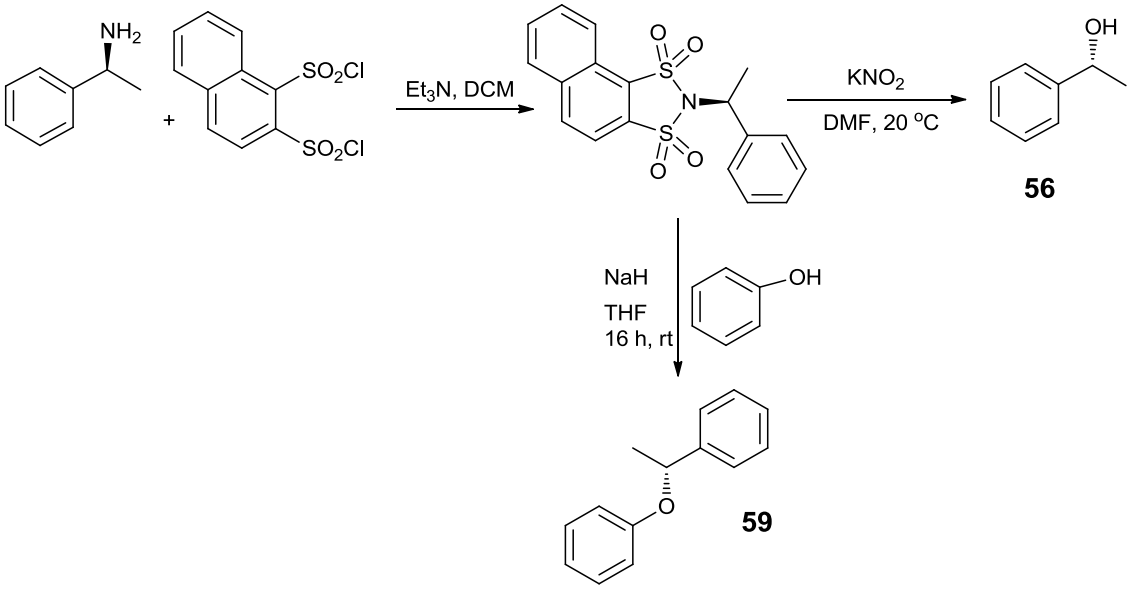
1.5: N-centered leaving groups.

1.5.1: Benzenedisulfonylimides.

Amides, $-NR_2$, are very poor leaving groups, and need to be deactivated considerably to make a more stable leaving group. One way is to use a trialkylammonium group as a leaving group. However another is to attach two sulfonyl groups. For example, an amino group can be converted to a better leaving group and converted to an alcohol or azide.[54] Treatment of primary amines e.g. 1-phenyl- or 1-cyclohexyl-ethylamine with benzene-1,2-disulfonyl chloride under basic conditions gives the corresponding benzenedisulfonylimide intermediates **54, 55** having a suitable leaving group. Secondly, reacting **54** with KNO_2 gives alcohol **56** whilst on the other hand reacting **55** with NaN_3 gives azide **57** (see Scheme 1.35).[41,55] A similar leaving group has been produced from naphthalene-1,2-disulfonylchloride to give **58**, which has been converted to an ether by substitution. The second sulfonyl group in naphthyl disulfonylimide **58** provides a suitable leaving group[56] and by use of this technique amines have been converted to ethers e.g. **59**, as summarized in Scheme 1.36.



Scheme 1.35: Conversion of primary amine to azides.

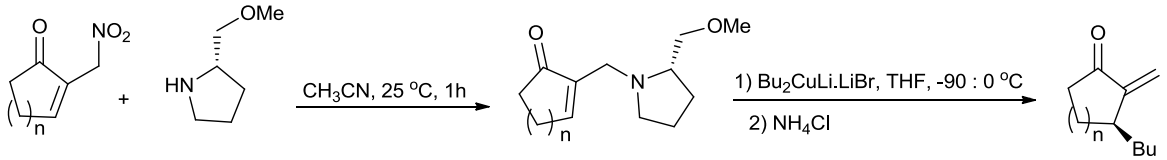


Scheme 1.36: Conversion of a primary amine to an alcohol or an aryl ether via disulfonylimide intermediates[45].

1.5.2: Chiral amines.

Chiral amines have become functional nucleophilic catalysts, having been largely overlooked until recently. Chiral amines are leaving groups that are derived from prolines and have been used to direct cuprate additions to cycloalkanones **62**. Treatment of this **62** with *n*-$Bu_2CuLi{\cdot}LiBr$ and added salts (LiBr or $ZnBr_2$) can lead to a non-racemic 3-substituted 2-*exo*-methylenecycloalkanone **63**. In most cases such reactions provide very

good yields of 80-90%. They also tend to show good enantioselectivities (Scheme 1.37).[57] Enones **62** can be conveniently prepared from the substitution reaction between α-(nitromethyl) enones **60** with (S)-(+)-(methoxymethyl)pyrrolidine **61** in acetonitrile (Scheme 1.37).[58] The chiral amine substituent controls the enantioselective addition of a butyl cuprate to the enone, and is subsequently lost in an elimination reaction. It has also been noted that the use of $ZnBr_2$ as an additive can lead to lower enantioselectivities particularly in the case of cyclopentanone.[41]

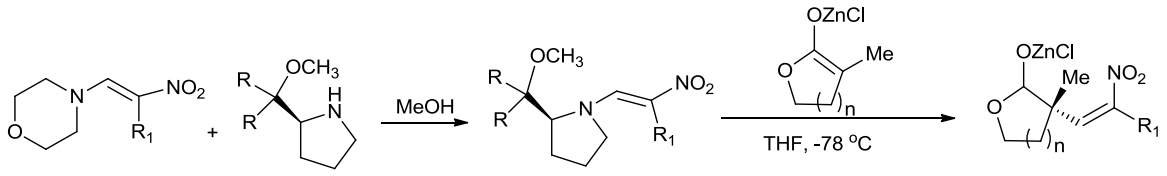


60 **61** **62** **63**

Scheme 1.37: Synthesis of non-racemic 3-butyl-2-*exo*-methylenealkanones.

Efforts to explain the enantioselectivity for the selective Bu_2CuLi additions include a transition state model. The theory states that the chiral enone **62** initially forms a weak tridentate chelating complex with Bu_2CuLi through the coordination of three heteroatoms to the lithium. This is then followed by the additional d–π* complex formation between the copper atom and a conjugated enone moiety. This chelation d–π* complexation occurs at the ***Si*** face, this is because the ***Re*** face is shielded by an extruding pyrrolidine ring. Added $ZnBr_2$ gives the complex, which leads to lower enantioselectivities by impeding the Li^+-directed chelation π-complexation between Bu_2CuLi and **62** leading to fast 1,4-addition via a kinetic or non-chelated d–π* complex due to the strong Lewis acidity of $ZnBr_2$.[41] Another example of using a chiral amine is the reaction between morpholino enamines **64** with amines **65** to give chiral enamines **66** in high yield which are reacted with zinc enolates of alpha- methyl substituted lactones **67** to give adducts **68** in high yield and enantioselectivity

(Scheme 1.38).[59] Leaving groups that have been derived from L-Proline have also been used to induce asymmetry in both addition and elimination reactions of chiral nitroenamines and the enantioselectivitiy increases with the bulk of the group R in the chiral nitroenamines and the order was Ph > Et > Me (See Scheme 1.38). For high enantioselectivities 4 equiv of zinc enolate were used.[60]

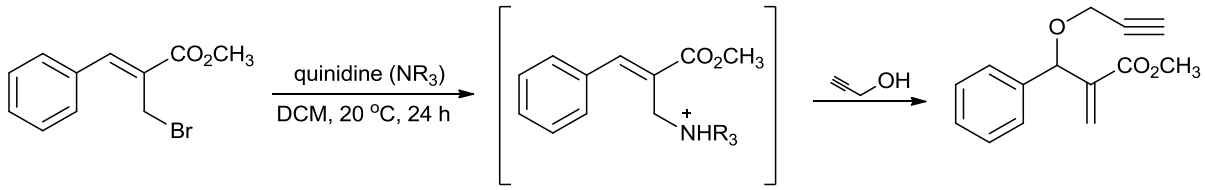


64 **65** **66** **67** **68**

n = 1 or 2; R = Me, Et, Ph; R_1 = H, Me

Scheme 1.38: Synthesis of chiral nitroenamines 66 and asymmetric addition of α-methyl substituted lactone enolates 67.

A recent development is the Bayliss-Hillman type reaction which has been developed to give propargyl ethers **71** by using stoichiometric amounts of (+) or (-) quinidine as a chiral leaving group (Scheme 1.39). Propargyl alcohol was added to bromomethyl enoates **69** via quinidinium intermediates **70** to give adducts **71** in modest enantioselectivities (25–40% ee) and provides modest yields (32–47%).[56]

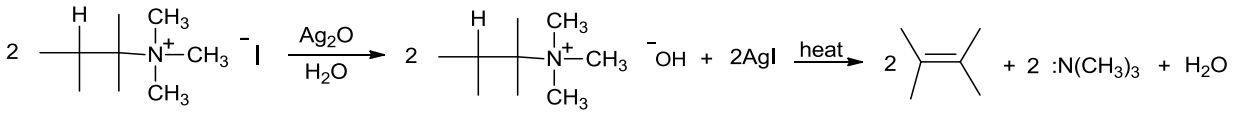


69 **70** **71**

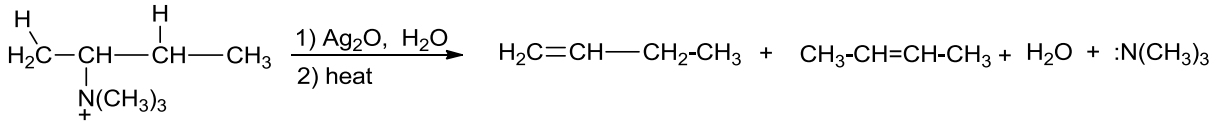
Scheme 1.39: Enantioselective synthesis of propargyl ethers 71 using quinidine as a chiral amine leaving group.

1.5.3: Ammonium as leaving group.

The quaternary ammonium salt is a very good leaving group. It produces a neutral tertiary amine via the E2 mechanism (the Hofmann elimination), and usually requires a strong base. Typically the tetraalkylammonium iodide salt is converted to the corresponding hydroxide salt by reaction with silver oxide in water and then the quaternary ammonium hydroxide is heated to obtain the alkene (Scheme 1.40). For example, 2-butanamine is converted into a mixture of 1-butene (major) and 2-butene (minor) (Scheme 1.41).

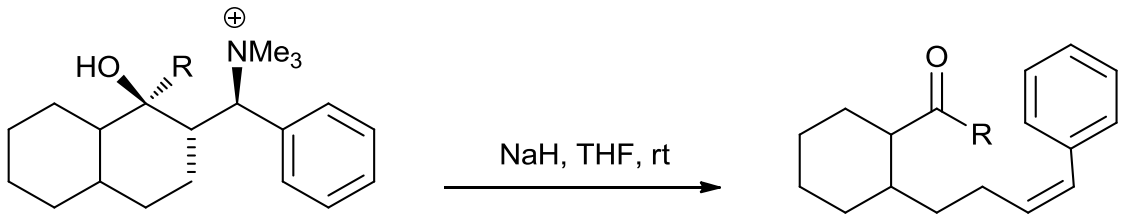


Scheme 1.40



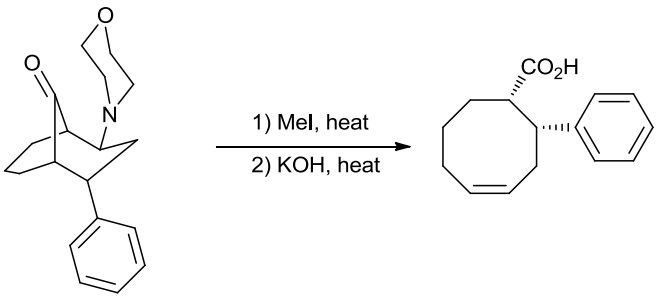
Scheme 1.41: Ammonium as leaving group

The Grob-type fragmentation of quaternary γ-aminoalcohols has evolved into an outstanding piece of chemistry with utility in the construction of functionalised aldehydes and ketones with (Z)-double bonds (Scheme 1.42)



Scheme 1.42: γ-Ammonium alcohols as fragmentation substrates

A related case is application of the Wharton fragmentation. In an approach to eight-membered cycloolefins, morpholino-ketone **72** was treated with methyl iodide to generate the quaternary amine as leaving group. Addition of hydroxide to the carbonyl group induces the Wharton fragmentation to give **73** (Scheme 1.43).[62]

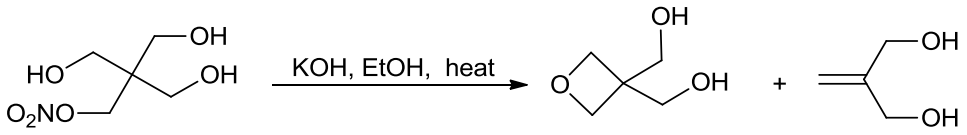


72 **73**

Scheme 1.43: Morpholine as leaving group.

1.5.4: Nitrate as leaving group.

An example of a nitrate as a leaving group occurs (Scheme 1.44), when pentaerythritol mononitrate **74** is treated with potassium hydroxide in refluxing ethanol. Two different reactions take place, an intramolecular substitution to give **75**, and fragmentation to give main product **76**. However, substitution to give **75** was the minor reaction.[63]



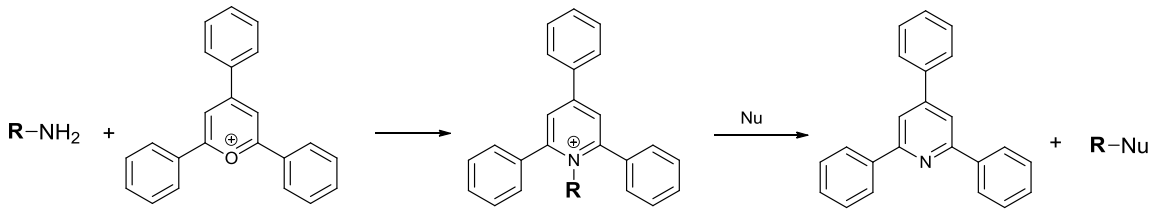
74 **75** **76**

Scheme 1.44: Nitrate as Leaving Group

1.5.5: Pyridine as leaving group.

In this case the primary amine is converted to the corresponding pyridinium derivative in high yields by reaction with a pyrylium salt (2,4,6-triphenylpyrylium) at 20 ˚C in DCM,

and then a nucleophilic substitution reaction at 50-100˚C displaces the N-substituent as a pyridine nitrogen atom, and replaces it with the nucleophile. The nucleophiles which have been successfully used are I^- , Br^- , Cl^-, F^-, OAc^-, N_3^-, NHR_2 and H^- (see Scheme 1.45).[7,64]

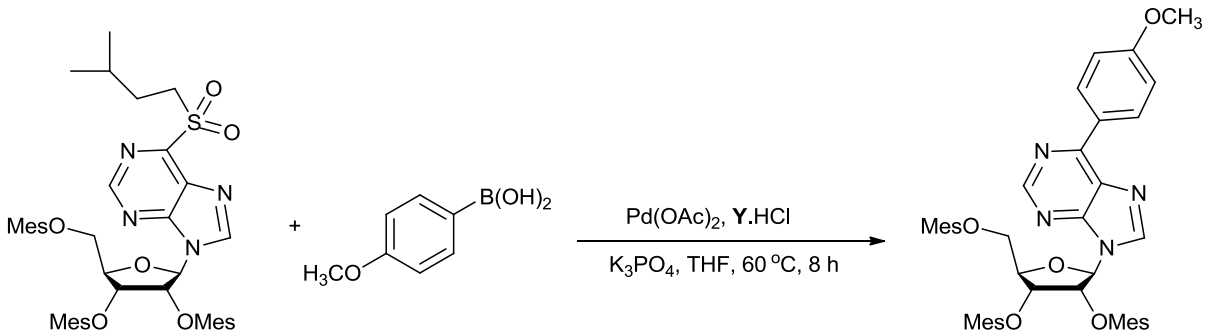


Scheme 1.45: Converting NH_2 into a good leaving group.

1.6: S-centered leaving groups.

1.6.1: Alkyl sulfonyls.

In the following methods a new avenue for modification of purines at the C6 position has been opened. Via a Suzuki reaction (Scheme 1.46) the sulfonyl purine nucleoside **77** was coupled to a *p*-methoxyphenyl group to produce product **78** in a good yield by using 1,3-(2,6-diisopropyl)imidazolin-2-ylidene **Y** as a palladium ligand. Using S_NAr displacement of a halopurine precursor followed by an oxidation gave the sulfonyl purine derivative.[41]



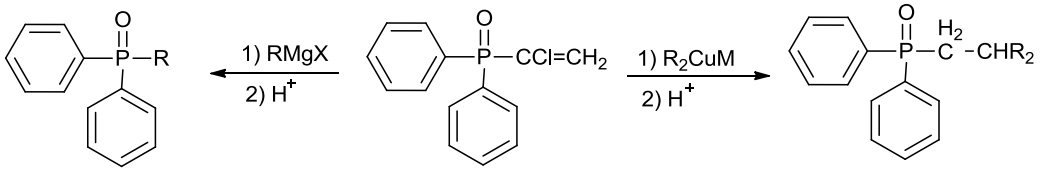
77 **78**

Y = 1,3-(2,6-diisopropyl)imidazolin-2-ylidene

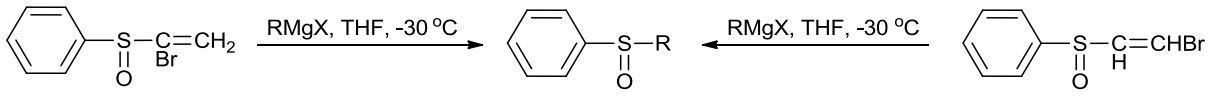
Scheme 1.46: An alkyl sulfonyl leaving group in a Suzuki coupling reaction to give a substituted nucleoside.

1.7: Carbon based leaving groups.

Recently, Cardellicchio and his group have reported some synthetic, mechanistic and stereochemical features regarding the use of carbon leaving groups in the reactions of organometallic reagents with sulfoxides and phosphine oxides (Scheme 1.47). It was confirmed that the halovinyl group (Scheme 1.48) could be successfully and stereospecifically displaced in the reaction between Grignard reagents and sulfoxides or phosphine oxides bearing these groups.[65-68]



Scheme 1.47: Grignard reagents with phosphine oxides



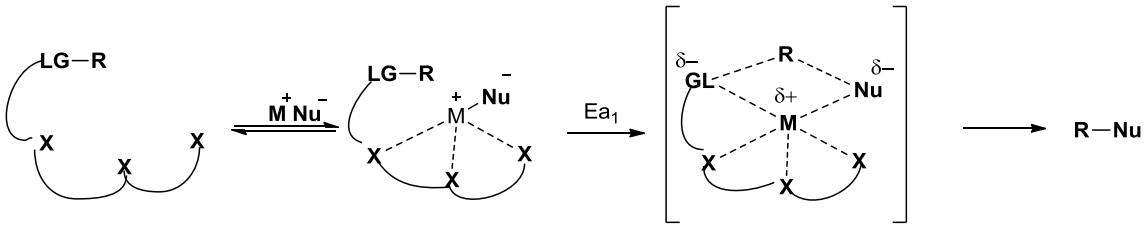
Scheme 1.48: Grignard reagents with sulfoxides

In contrast, it was have found that treatment of diphenyl(methoxymethyl)-phosphine oxide as a starting material with Grignard reagents or organolithium compounds elicits a completely different behaviour from the substrate, leading to a facile nucleophilic substitution, with the methoxymethyl anion acting as a leaving group.[66]

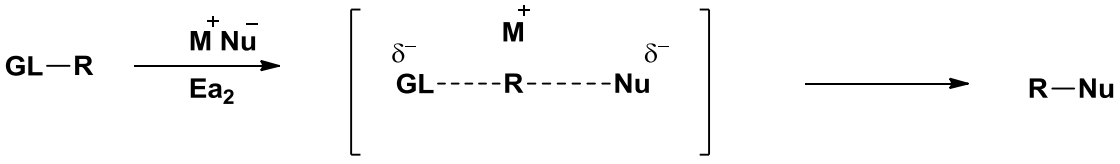
1.8: Nucleophile assisting leaving groups (NALGs).

Nucleophile assisting leaving groups (NALGs) can be defined as leaving groups that contain a chelating group that can provide stability for the transition state of a nucleophilic reaction. Although they provide a rate enhancement this is not generally down to an

increase in the nucleofugacity of the leaving group upon cationic chelation. It is thought to instead be due to an interaction between the NALG and the nucleophiles resulting in the lowering of the transition stage energy required of the rate limiting step. For example, in the case of substrate **79**, it is expected that the negative charge imparted to the leaving group moiety (LG) by the incoming nucleophile (Nu) in transition state **81** results in a more favourable chelation complex compared to its precursor ligand **80** (Scheme 1.49). Depending on the nucleophilic mechanism of reaction used the cationic chelation should reduce the energy of activation required for the transition state compared to reactions which use substrates that have more traditional leaving groups. It is also thought that without the added stabilizing effect of nucleophilic salt chelation with the nearby multidentate ligand, the energy of activation (Ea2) for reactions involving traditional leaving groups (leading to a transition state such as **82**) is expected to be higher (Ea2 > Ea1). Differential metal ion stabilization of transition states relative to reactants in acetyl transfer reactions has been observed in numerous systems.



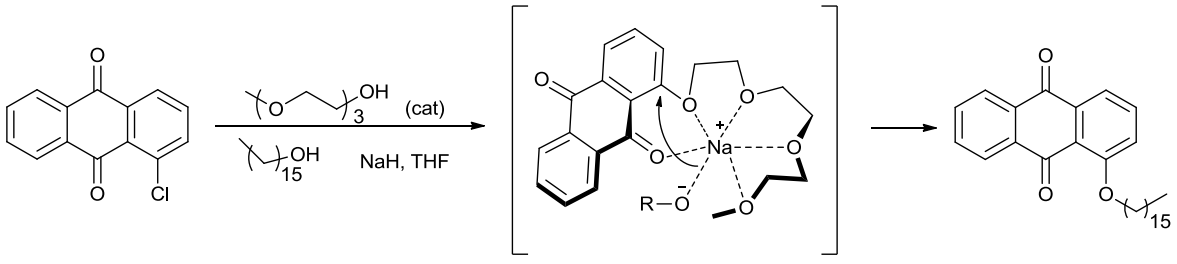
79 **80** **81** [transition state]



82 [transition state]

Scheme 1.49: Rationale for rate enhancement observed with nucleophile assisting leaving groups (NALGs).

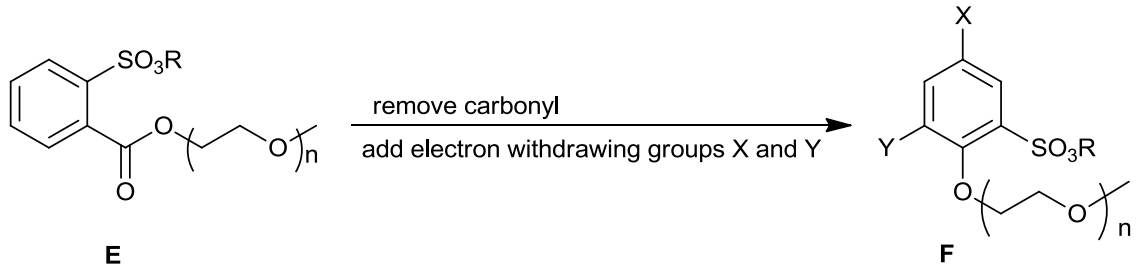
It was noted that the reaction of 1-chloroanthraquinone **83** with a variety of alkanols and NaH failed to give the desired nucleophilic aromatic substitution product in refluxing THF. But when the addition of catalytic amounts of oligo-ethylene glycols was made it led to successful alkanol substitution. In the case of n-hexadecanol, the substitution product formed, **84,** was obtained in 80% yield using a catalytic amount (24%) of triethylene glycol (Scheme 1.50). Initially acting as a nucleophile, triethylene glycol was added to chloro compound **83** resulting in intermediate **85**. This is thought to have been achieved through the coordination of the sodium cation by the glycol.[67] Evidence for this is X-ray crystal structure data obtained. This cation-complexed intermediate most likely plays a key role in both coordination of the stoichiometric alkoxide nucleophile (RO^-) as well as stabilization of the negative charge forming on the oxygen of the leaving group. In this chloroanthraquinone study, metal chelated oligo-glycol oxides were found to be the superior nucleophilic agents in relation to straight chain alkanoxide anions. However, a separate group demonstrated that phenolate anions containing oligoether units in the ortho position exhibited no improved nucleophilic properties when compared to their non-chelating analogues.[68]



83 **85** **84**

Scheme 1.50: Podand-catalyzed nucleophilic aromatic substitution reaction of 1-chloroanthraquinone.67

Crown ether-based phenolate and carboxylate nucleophile assisting leaving groups exhibited enhanced nucleofugacity in methylation and acylation reactions.[69,71] The arylsulfonate NALG design E consisted of an oligoether (also macrocyclic) unit connected to the aryl ring *ortho* to the sulfonate via an ester linking unit (Scheme 1.51). NALGs E was proved to be a useful leaving group in a number of reactions.[72-75] The chelated conformation is not ideal, further nucleophilic reaction rate gains might be realized with NALG systems devoid of the ester carbonyl. Also, the aryl ether linker in F should possess broader chemical stability than a carboxyl ester for applications as a leaving group in complex synthesis.



Scheme 1.51: Design strategy

In addition, it was found in some cases of NALGs with electron-withdrawing fluorines on the aryl ring that they were more reactive toward LiBr than other systems which suggested that future variation of the linker element may provide additional rate enhancements. The NALGs were then evaluated for their effectiveness in 18F-fluorination, an application requiring fast and high yield reactions. Under microwave irradiation, several NALGs, especially those with three ethylene oxide units in the chelating arm, exhibited useful reactivity toward K18F.[76]

1.9: References.

1. P. Muller, *Pure Appl. Chem*. **1994**, *66*, 1077.
2. M. B. Smith,; *March, J. Advanced Organic Chemistry*, 5th ed.; John Wiley: New York, NY, **2001**; 275.
3. Based on a CAS database search using SciFinder Scholar **2006** searching the term 'leaving group' with the two words closely associated.
4. F. G. Bordwell, B. M.Pitt, M. Knell, *J. Am. Chem. Soc.* **1951**, *73*, 5004.
5. Including the popular undergraduate text by Morrison, R. T.; Boyd, R. N. Organic Chemistry, 2nd ed.; Allyn and Bacon: Boston, MA, **1966.**
6. J. Mathieu, A. Allais, *J. Valls, Angew. Chem*. **1960**, *72*, 71.
7. M. J. Jones, Organic Chemistry, 2nd ed, W.W. Norton, New. York, **2000**, Chapter 6, 207.
8. CJM. Stirling, Acc. Chem. Res., **1979**, *12*, 198.
9. N. Furukawa, S. Ogawa, T. Kawai and S. Oae, *J. Chem. Soc.,Perkin Trans. 1*, **1984**, 1839.
10. M. B. Smith and J. March, March's Advanced Organic Chemistry : Reactions, Mechanisms and Structure, Wiley, New York ; Chichester, **2001**. Chapter 10, 310.
11. N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, *Tetrahedron Lett*., **1983**, *24*, 3243.
12. N. Furukawa, S. Ogawa, T. Kawai and S. Oae, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1839.
13. J. F. Bunnett, *Acc Chem. Res*., **1978**, *11*, 413.

14. E. W. Yankee, F. D. Badea, N. E. Howe and D. J. Cram. *J. Am. Chem. Soc*., **1973**, *95*., 4210,

15. Y. Ren and H. Zhu, *J. Am. Soc. Mass Spectrom*., **2004**, *15*, 673.

16. S. J. Blanksby and G. B. Ellison. *Acc*. *Chem*. *Res*. **2003**, *36*, 255.

17. K. J. Stanger, J. J. Lee and B. D. Smith, *J. Org. Chem*., **2007**, *72*, 9663.

18. N. Guo, D. Alagille, G. Tamagnan, R. R. Price and R. M. Baldwin, Appl. Radiat. Isot.,. **2008**, *66*, 1396.

19. C. L. Perrin, B. L. Rodgers and J. M. O'Connor, *J. Am. Chem. Soc*., **2007**, *129*, 4795.

20. T. N. Sorrell, *Organic Chemistry*, **2006**.

21. R. L. Danheiser, Y.-M. Tsai and David M. Fink., *Org. Synth. Coll*., **1993**, *8*, 471.

22. J. W. Czerkawski and G. Breckenridge, *Br J Nutr*., **1975**, *34*, 429.

23. T. Netscher, *Molecules*, **2002**, *7*, 601.

24. F.A. Drahowzal, *Organic Sulfur Compounds*, **1961**, *1*, 371.

25. P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, **1982**, *2*, 85.

26. T. Netscher, *Organic Chem*., **2005**, *36*.

27. R. K. Crossland, W. E. Wells and V. J. Shiner Jr., *Ant. Chem. Soc*. **1971**, *93*, 4217.

28. N. E. Dixon, G. A. Lawrance, P. A. Lay, A. M. Sargeson and H. Taube, *Inorg. Synth.* **1990**, *28*, 70.

29. W. Walther and T. Netscher, *J. Chromatog. Sci*. **1994,** *32*, 418.

30. T. Netscher and P. Bohrer, *Tetrahedron Lett.*, **1996**, *37*, 8359.

31. D. S. Noyce and J. A. Virgilio, *J. Org. Chem*., **1972,** *37*, 2643.

32. D. D. Roberts, *J. Org. Chem*., **1972**, *37*, 1510.

33. D. Prescher, T. Thiele and R. Ruhmann, *J. Fluorine Chem*., **1996**, *79*, 145.

34. T. Bříza, V. Král, P. Martásek and R. Kaplánek, *J. Fluorine Chem*., **2008**, *129*.

35. R.L. Hansen, *J. Org. Chem*., **1965**, *30*, 4322.

36. T. Netscher and H. Prinzbach, *Synthesis*, **1987**, 683.

37. T. Netscher, R. Schwesinger, B. Trupp and H. Prinzbach, *Tetrahedron Lett*., **1987**, *28*, 2115.

38. Y. Sakamoto, K. Tamegai and T. Nakata, *Org. Lett*., **2002**, *4*, 675.

39. N. Hori, K. Nagasawa, T. Shimizu and T. Nakata, *Tetrahedron Lett*., **1999**, *40*, 2145.

40. P. Andrew Evans and Thomas A. Brandt., *Org. Lett.*, **1999**, *1*, 1563.

41. S. D. Lepore and D. Mondal, *Tetrahedron*, **2007**, *63*, 5103.

42. J. Vatèle and S. Hanessian, *Tetrahedron*, **1996**, *52*, 10557.

43. E. J. Corey, Gary H. Posner, Richard F. Atkinson, Astrid K. Wingard, Daniel J. Halloran, Donna M. Radzik, John J. Nash, *J. Org. Chem*., **1989**, *54*, 389.

44. X. Shi, C. Shen, J. Yao, L. Nie and N. Quan, *Tetrahedron: Asymmetry*, **2010**, *21*, 277.

45. E. A. Véliz, and P. A. Beal, *Tetrahedron Lett*., **2006**, *47*, 3153.

46. B. C. Laszlo Kurti, *Strategic Applications of Named Reactions in Organic Synthesis*., **2005**.

47. K.C. Kumara Swamy, N. N. Bhuvan Kumar, E. Balaraman, and K. V. P. Pavan Kumar, *Chem. Rev*., **2009**, *109*, 2551.

48. H. Imagawa, A. Kinoshita, T. Fukuyama, H. Yamamoto and M. Nishizawa, *Tetrahedron Lett.*, **2006**, *47*, 4729.

49. Y. Osa, K. Takeda, T. Sato, E. Kaji, Y. Mizuno and H. Takayanagi, *Tetrahedron Lett*., **1999**, *40*, 1531.

50. A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola, *International Journal for Chemistry*, **2006**, *60*, 124.

51. D. B. B. Breit , *Synthesis*, **2005**, *1*, 147.

52. D. B. B. Breit, *Synthesis*, **2005**, *16*, 2782.

53. K. Ishihara, H. Nakamura, and H. Yamamoto, *J. Am. Chem. Soc*., **1999**, *121*, 7720.

54. K. Sørbye, C. Tautermann, P. Carlsen and A. Fiksdahl, *Tetrahedron: Asymmetry*, **1998**, *9*, 681.

55. L. R. Heggvik and A. Fiksdahl, *Tetrahedron: Asymmetry*, **1997**, *8*, 2189.

56. S. A. Said and A. Fiksdahl, *Tetrahedron: Asymmetry*, **1999**, *10*, 2627.

57. C. Cardellicchio, V. Fiandanese, F. Naso and A. Scilimati, *Tetrahedron Lett*., **1992**, *33*, 5121.

58. R. Tamura, H. Katayama, K. Watabe and H. Suzuki, *Tetrahedron*, **1990**, *46*, 7557.

59. X. Yang and R. Wang, *Tetrahedron: Asymmetry*, **1997**, *8*, 3275.

60. C. Forzato, P. Nitti, G. Pitacco, E. Valentin, S. Morganti, E. Rizzato, D. Spinelli, C. Dell'Erba, G. Petrillo and C. Tavani, *Tetrahedron*, **2004**, *60*, 11011.

61. D. Basavaiah, N. Kumaragurubaran, D. S. Sharada and R. M. Reddy, *Tetrahedron*, **2001**, *57*, 8167.

62. D. Díez,. M. Parra, S. G. San Feliciano, I. S. Marcos, N. M. Garrido, P. Basabe, A. Jiménez, H. B. Broughton, J. G. Urones, *Synth. Commun*., **2002**, *32*, 1829.

63. A. M. Korolev, L. T. Eremenko, L. V. Meshikhina, *Russian Chemical Bulletin*, **2002**, *51*, 2306.

64. Alan R. Katritzky and Giuseppe Musumarra, *Chem. Soc. Rev*., **1984**, *13*, 47.

65. C. Cardellicchio, G. Fracchiolla, F. Naso and P. Tortorella, *Tetrahedron*, **1999**, *55*, 525.

66. C. Cardellicchio, G. Fracchiolla, F. Naso, P. Tortorella, W. Holody and K. M. Pietrusiewicz, *Tetrahedron Lett*., **1999**, *40*, 5773.

67. T. Lu, H. K. Yoo, H. Zhang,. S. Bott, J. L. Atwood, L. Echegoyen and G. W. Gokel, J. Org. Chem., **1990**, *55*, 2269.

68. G. Illuminati, L. Mandolini, B. Masci, *J. Am. Chem. Soc*. **1983**, *105*, 555.

69. C. Cardellicchio, V. Fiandanese, F. Naso, K. M. Pietrusiewicz and W. Wisniewski, *Tetrahedron Lett*., **1993**, *34*, 3135.

70. C. Cardellicchio, A. Iacuone, F. Naso and P. Tortorella, *Tetrahedron Lett*., **1996**, *37*, 6017.

71. R. Cacciapaglia and L. Mandolini, *Pure Appl. Chem*., **1993**, *65*, 533.

72. S. D. Lepore, A. K. Bhunia and P. C. Cohn, *J. Org. Chem*., **2005**, *70*, 8117.

73. S. D. Lepore, A. K. Bhunia, D. Mondal, P. C. Cohn and C. Lefkowitz, *J. Org. Chem.*, **2006**, *71*, 3285.

74. S. D. Lepore, D. Mondal, S. Y. Li and A. K. Bhunia, Angew. *Chem. , Int. Ed*., **2008**, *47*, 7511.

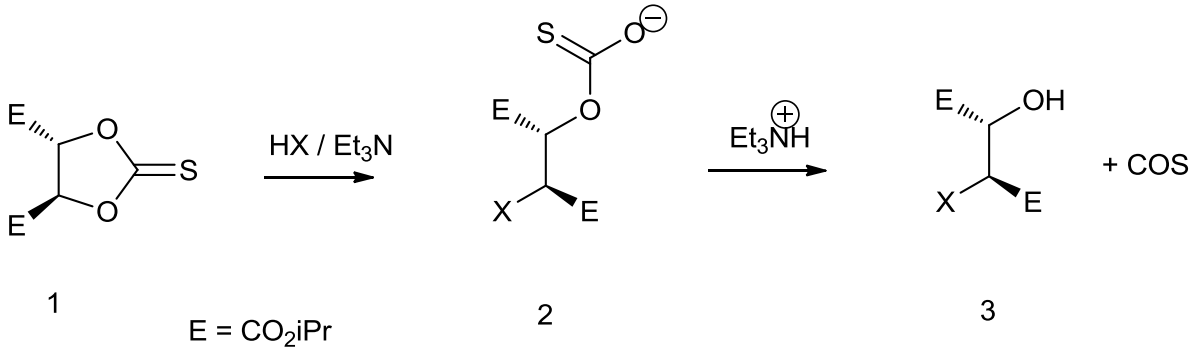
75. D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond and A. J. P. White, *Chem. Commun*., **2009**, 1082.

76. S. Lu, S. D. Lepore, S. Y. Li, D. Mondal, P. C. Cohn, A. K. Bhunia, and V. W. Pike, *J. Org. Chem*. **2009**, *74*, 5290.

2. Chapter 2: Reactions of Cyclic Thionocarbamates.

2.1: Background

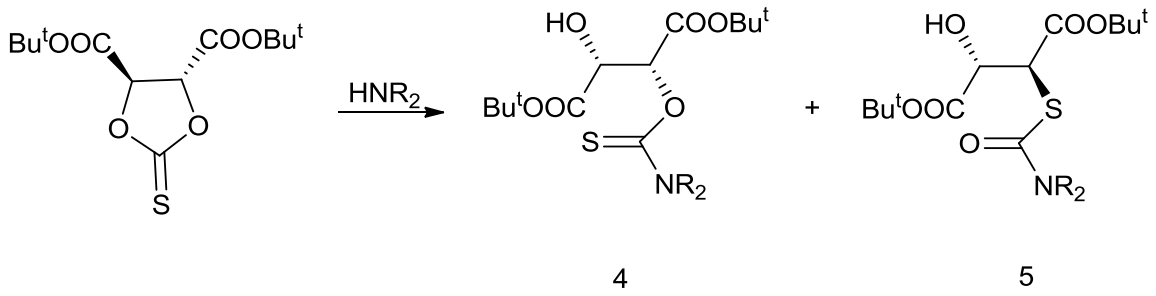
Ko has introduced the cyclic thionocarbonate derivative of a *vic*-diol, e.g. **1**, which undergoes nucleophilic substitution to give the substituted alcohol **3** directly without an acidic hydrolysis step since the intermediate thionocarbonate salt **2** loses COS *in situ* or during aqueous work up.[1] In all the cyclic thionocarbonates reported, a carboxylic ester or a phenyl group is present at the point of nucleophilic attack. Nucleophiles used in the work were NaN_3, PhSH, PhCOOH, PhCOSH and Bu_4NBr (Scheme 2.1). Cyclic thionocarbonates of tartrate esters have been converted to the corresponding malate esters with magnesium / iodine, hypophosphorous acid/AIBN and with tributyltin hydride.[2-4]

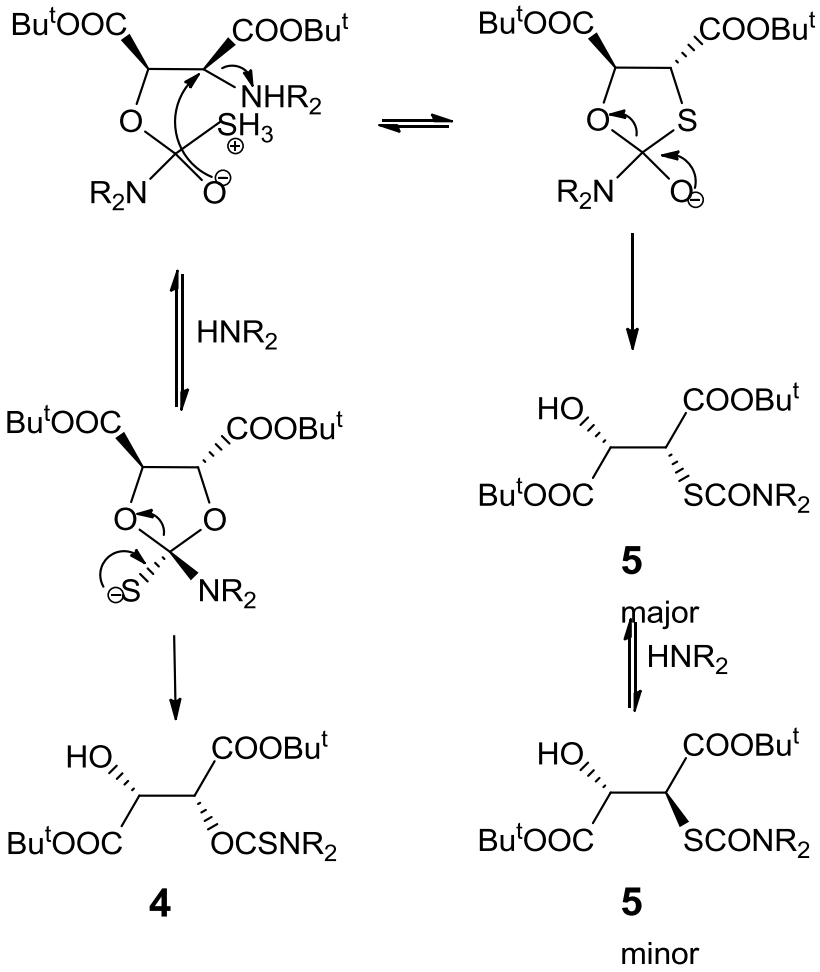


Scheme 2.1:

Secondary amines have been reported to react with cyclic thionocarbonates of tartrate esters (*t*-butyl and isopropyl) by addition at the thione carbon followed by cleavage of the ring O-C bond to give acyclic thionourethanes in enantiopure form e.g. **4**. More hindered amines give the thiolcarbamate as a mixture of diastereomers e.g. **5** (Scheme 2.2). A mechanism for formation of the latter involving attack of the amine at both the thiocarbonyl group and then at the ring C atom was proposed, however it may be possible to rationalise the formation of these products by an initial deprotonation step followed by ring opening to an

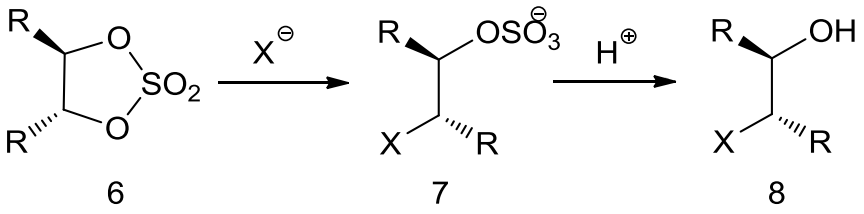
alkene, ring closure by attack of sulfur on the alkene and only then attack by amine on the ring carbonyl group.[5]





Scheme 2.2

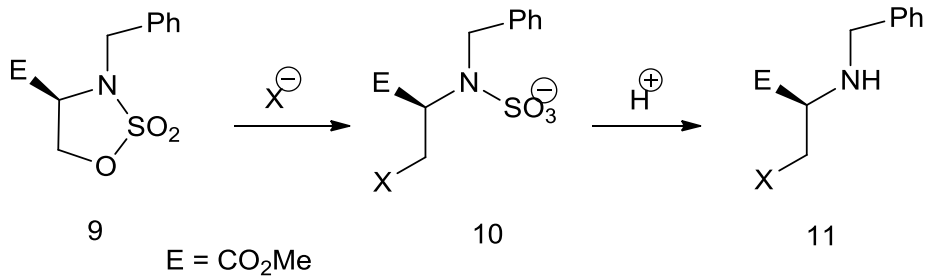
Cyclic sulfate esters show similar chemistry but require acid hydrolysis of the intermediate formed by ring opening. Thus, cyclic sulfate esters such as **6** prepared from *vic*-diols in two steps via cyclic sulfite ester formation and subsequent oxidation, undergo ring opening with a variety of nucleophiles to give hemisulfates **7** which can be hydrolysed to the substituted alcohols **8** (Scheme 2.3).[6] In some cases two nucleophilic substitutions lead to complete displacement of sulfate.[7-10] Cyclic sulfate ester chemistry has been widely exploited in synthetic chemistry, but cyclic thionocarbonate chemistry has not.



Scheme 2.3

Similarly, *vic*-aminoalcohols can be converted into cyclic sulfamidates e.g. **9** which also undergo nucleophilic substitution with breaking of the C-O(SO_2) bond to produce sulfamate salts **10** which, after hydrolysis with concentrated sulfuric acid, yield substituted amines **11** (Scheme 2.4).[7,11,12] However, the corresponding chemistry with cyclic thionocarbamates has not been reported. Some initial studies have been carried out in the group. Cyclic thionocarbamates have been used synthetically in other ways, primarily as chiral auxiliaries,[13] but also as intermediates in the synthesis of enantiopure protected aryl-β-hydroxyl-α-amino acids[14] and 1-(Boc)-amino-1-alkenylphosphonate esters,[15] as a derivative for kinetic resolutions,[16] as pseudo-C-nucleosides,[17] in radical reactions,[18] and as precursors for other oxazolidines.[19] Carbon disulfide,[20] thiophosgene[17,21] or bis(imidazolyl)thione[18,19] have been used to prepare them from the corresponding

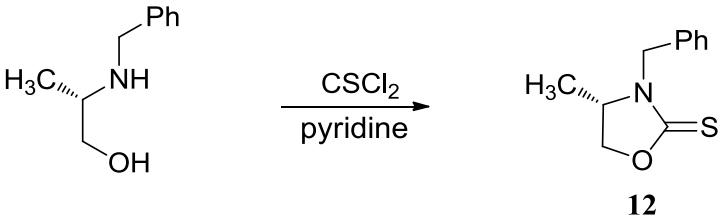
aminoalcohols, as well as hydroxide addition to isothiocyanates[17] and cycloaddition of aldehydes to anions of substituted methyl isothiocyanates.[14,15]



Scheme 2.4

In earlier work S-N-benzylalaninol was converted to its cyclic thionocarbamate **12** in 56% yield (Scheme 2.5). This cyclic thionocarbamate with a N-benzyl group **12** did not react at the 5-C atom with a variety of nucleophiles e.g. potassium phthalimide and potassium thioacetate under a range of conditions.[22] In the crystal structure of **12** (Figure 2.1) at 120 K the five-membered ring adopts a shallow half chair conformation; the torsion angles around the ring are all less than 13^{o} with the two sp^{3} carbon atoms deviating most from the best ring plane (by 0.073 and -0.074 Å). The bonding geometry at nitrogen in **12** is planar. The most notable aspect of the structure of **12** is the difference in the ring bond lengths to the thiocarbonyl carbon atom; that from the nitrogen atom (1.3319 (18) Å) is 0.025 Å shorter than that from the oxygen atom (1.3574(17) Å) in contrast to the usual trend of bond lengths from these heteroatoms to carbon. The structures of five N-unsubstituted five-membered cyclic thionocarbamates (carrying methyl or phenyl substituents at one or more of the ring sp^{3} carbon atoms) also show a similar trend in the bond lengths of the heterocyclic system: averaged values N-C: 1.315 (4), O-C: 1.347 (8) Å.23 This strongly suggests that there is substantial electron donation from the nitrogen atom into the thiocarbonyl group. This proposal is supported by the long thiocarbonyl bond in **12**

(1.6558(14) Å) and in the other cyclic thionocarbamates (average value 1.662 (7) Å). As a consequence of the strong conjugation between the thiocarbonyl group and the nitrogen atom, the electron donation from the oxygen atom into the thiocarbonyl group in **12** is considerably reduced. Thus, the lack of reactivity of **12** to nucleophilic attack can be explained by the reduced electron donation from oxygen into the thiocarbonyl group which makes the oxygen atom a poorer leaving group if the attached ring sp^3 carbon atom is attacked by a nucleophile.



12

Scheme 2.5

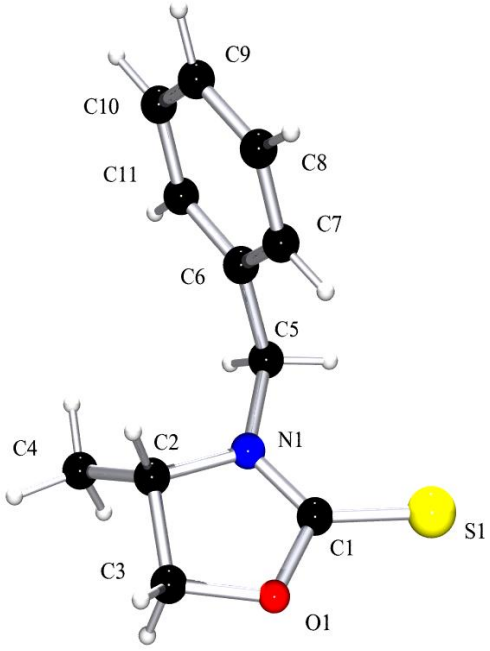


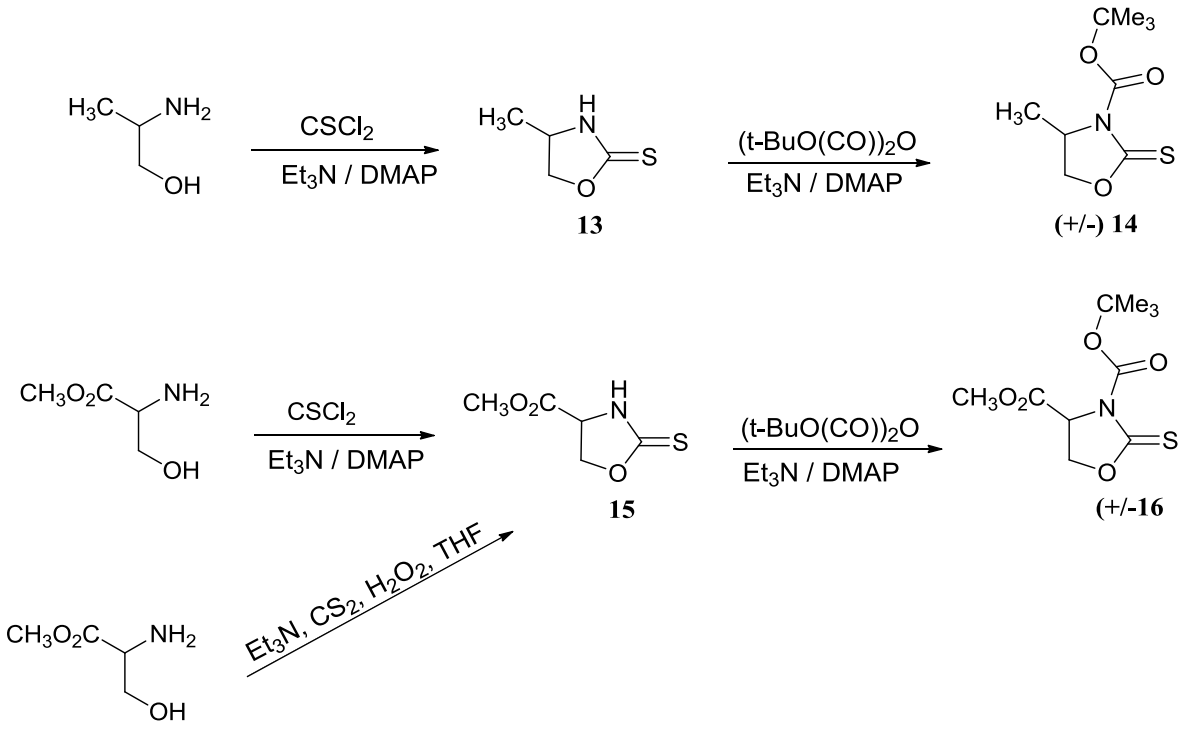
Figure 2.1: View of molecule 12

A logical step is to replace the benzyl group with a group which would attract the nitrogen atom lone pair away from the thiocarbonyl group. Attachment of a group with an electron-withdrawing mesomeric effect to the nitrogen atom of a cyclic thionocarbamate would be expected to reduce the delocalisation of charge into the thione, which would increase charge delocalisation from the ring oxygen atom, and thus increase the potential for substitution reactions at the attached sp^3 carbon atom. Indeed it has recently been shown in the group that a thionocarbamate of *vic*-aminoalcohol derivatised with a Boc group **16** is susceptible to nucleophilic attack by thiolate at 5-C.[2] There are clear potential advantages to using the thiono derivatives rather than the cyclic sulfate esters[3,4] and sulfamidates:[4] (a) the product of initial nucleophilic substitution decomposes directly to the corresponding alcohol or amine and does not require a hydrolysis step in strong acid, and (b) the ring system of the thionocarbonates and thiocarbamates are made in one step, not two. So in this new work reactions using **14** and **16**, the racemic N-Boc analogue of **12** and the N-Boc derivative of the cyclic thionocarbamate of *DL*-serine methyl ester, with a range of nucleophiles have been investigated. The overall aim is to develop new chemistry for reacting diols and amino alcohols with nucleophiles, to provide novel amines and amino acids which are useful building blocks in pharmaceutical chemistry.

2.2: Results and discussion.

The preparation of cyclic thionocarbamates **14** and **16** was carried out following the methods developed in the Wallis group. 4-Methyloxazolidine-2-thione **13** was made from *DL*-alaninol via ring formation with thiophosgene and triethylamine in dichloromethane, at 0 ^{o}C, giving the product as a yellow solid in 36% yield. In similar way *DL*-serine methyl ester was converted to methyl S-2-thioxooxazolidine-4-carboxylate **15** in 66% yield,

however, a higher yielding procedure for this transformation was also used. In this case *DL*-serine methyl ester was reacted with carbon disulfide, Et_3N (2 eq) and H_2O_2 in dry THF to give a much cleaner product **15** in 83% yield.



Scheme 2.6: Synthesis of cyclic thiocarbamates 14 &16[24]

Installation of the Boc group by reaction with di-t-butyl dicarbonate, triethylamine and 4-dimethylaminopyridine in dichloromethane, at 0 ^oC gave the desired final products **14** and **16** in yields of 44 and 78% (Scheme 2.6).

The structures of **14** and **16** were confirmed by X-ray crystallography (Figures 2.2 & 2.3). However, now with these structures in hand it can be noted that the C=S infrared stretches are at 1157 and 1143 cm^{-1}, and the ^{13}C resonances are at δ_C: 184.4 O-C(=S)-N and δ_C: 183.5 (O-C(=S)-N), the methylene C resonances at δ_C: 72.9 and δ_C: 68.8 and the methine carbon resonances at δ_C: 55.4 and δ_C: 59.9 respectively. Those structures were also confirmed by spectral data and CHN chemical analysis.

The x-ray crystal structure of **14** had already been measured. Cyclic thionocarbamate **14** adopts an approximate half chair conformation for the heterocyclic ring, significantly more puckered than in **12**, with the ring sp^3 carbon atoms deviating most from the ring best plane. The bonding at the nitrogen atom is planar. In complete contrast to **12** the ring bond from nitrogen to the thiocarbonyl group is longer than the ring bond from oxygen to the thiocarbonyl group. There is clear evidence of less electron delocalization from the ring nitrogen atom into the thione bond than in the N-benzyl derivative **12** from the longer N-C(=S) bond (by 0.040 Å) and the shorter thiocarbonyl bond (by 0.019 Å). There is a small contraction in the O-C(=S) bond (by 0.014 Å), signifying an increase in the electron delocalization from oxygen into the thiocarbonyl group, and there is a marginal lengthening of the sp^3 C-O bond (by 0.009 Å). However, the fact that the thiocarbonyl group in **14** is still receiving some electron delocalization from the nitrogen atom is shown by a consideration of the length of the bond from the nitrogen to the Boc group (1.4069 (14) Å) which is notably longer (by 0.055 Å) than the corresponding (t-BuOOC-N) bonds involving a nitrogens devoid of a further electron pulling group observed in the literature. In fact, for the N-Boc thionocarbamate **14** the nitrogen atom still makes a shorter bond to the thiocarbonyl group than to the carbonyl group,

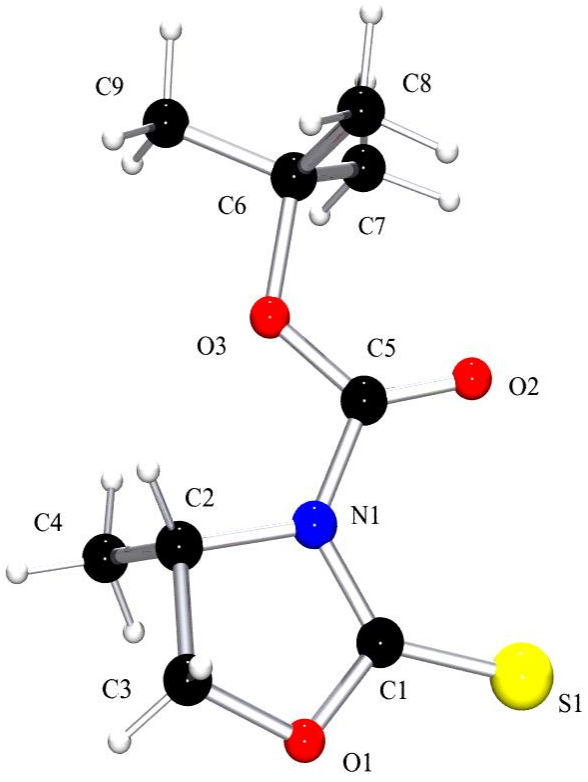


Figure 2.2: View of one enantiomer from the crystal structure of racemic 14.

The structure of **16**, the cyclic thionocarbamate of N-Boc *L*-serine methyl ester, also shows evidence of reduced electron delocalization into the thione group, with a N-C(=S) bond length of 1.376(2) Å and a C=S bond length of 1.6318(17) Å which are respectively longer and shorter than the corresponding data from the structure of **12**, but very similar to those observed for the N-Boc derivative **14**. In addition, the N-C(=S) bond is shorter than the N-C(=O) bond to the Boc group (by 0.033 Å) as in **14**. The Boc group is oriented well for conjugation with the nitrogen atom. The O-C(=S) bond to the thiocarbonyl group is slightly shorter (by 0.021 Å) than in **12**, as observed for **14**, indicative of slightly more conjugation between the oxygen and the thiocarbonyl. The sp^3 C-O bond is very slightly shorter than in **12** (by 0.007 Å), while for **14** this bond was slightly longer (0.009 Å) than in

12, there is thus no evidence for a significant change in the bond length from the ring oxygen to the ring sp^3 carbon atom. The heterocyclic ring is close to planar with a rms deviation of the five ring atoms from their best plane of only 0.030 Å. The Boc group makes contacts to the thione sulfur atom (O2---S1: 3.0689(12) Å) and the ester group (O3---C4: 2.7267(14) Å) however there is no pyramidalisation at the carbonyl carbon of the ester group. Although crystals were obtained of racemic **16** prepared in this work, no very satisfactory solution could be obtained, possibly because of difficulties in measuring data due to a long cell axis (50 Å).

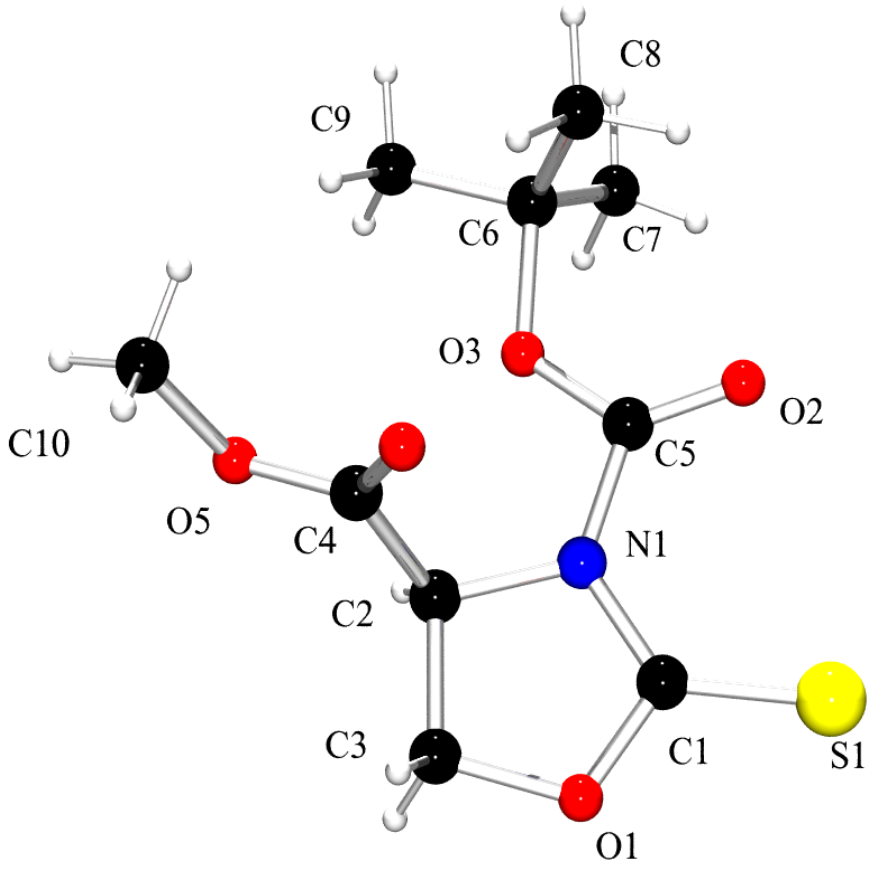


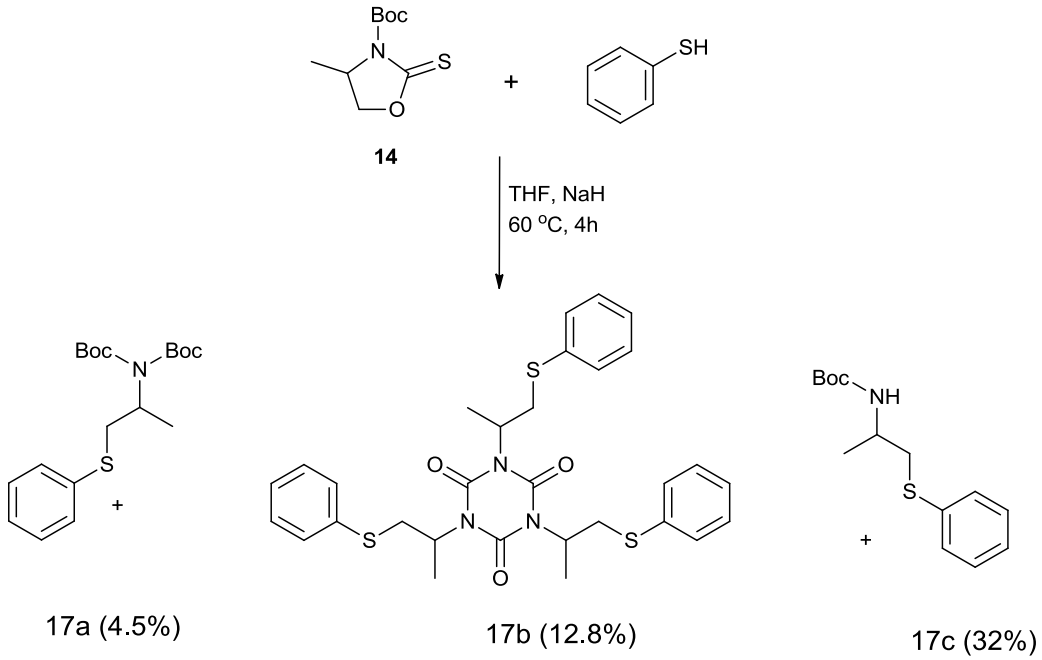
Figure 2.3: View of 16 in the crystal structure of *S*-16.

2.2.1: Reactions of 14 with sulfur and iodide nucleophiles.

From measurements of the structures of **14** and **16** it appears that acylation of the nitrogen atom has had the desired effect of increasing the interaction of the thiocarbonyl group with the ring oxygen atom, and thus improving the leaving group characteristic of this oxygen at 5-C of the ring system. Thus, some preliminary investigations of the reactions of cyclic thionocarbamates **14** and **16** with nucleophiles have been made, and indicate some successful ring openings by breaking of the ring sp^3 C-O bond at carbon.

2.2.1.1: with phenylthiolate

Compound **14** was reacted with the sodium salt of thiophenol in dry THF and stirred at 60 ^oC for 4 hours. Some drops of water were added and the mixture was extracted with dichloromethane. The organic layer was evaporated, and the residue was purified by flash chromatography to give three compounds (Scheme 2.7):



Boc : -C(=O)O*t*-Bu

Scheme 2.7: Synthesis of 17a, 17b and 17c

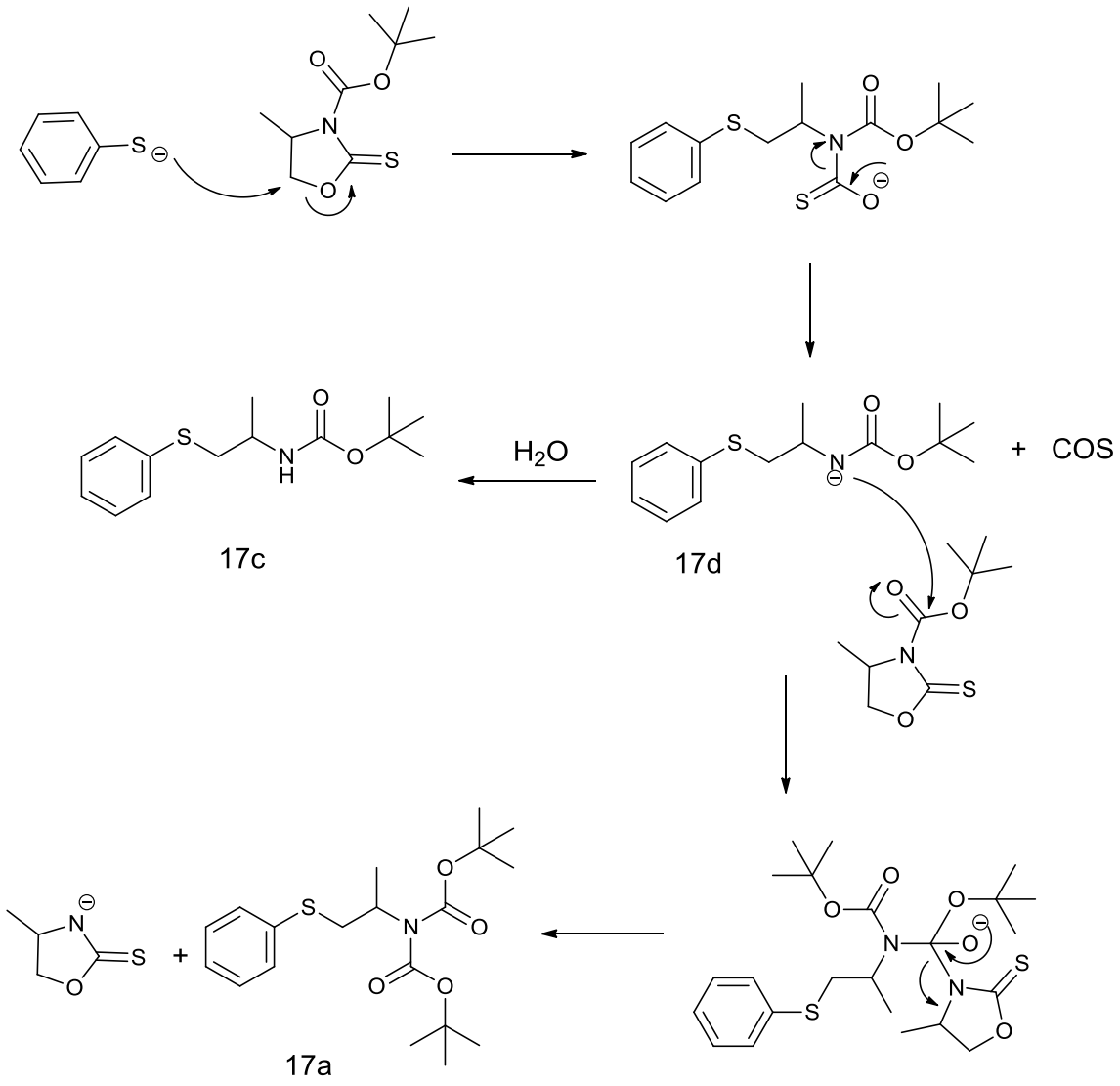
17a as a clear colourless liquid in 4.5% yield; NMR analysis indicated that the nucleophile has opened the ring and another Boc group has been installed on the N atom. Evidence was given by the ^{1}H NMR spectrum. A singlet was observed for six methyl groups of the two Boc groups at δ_H: 1.39, and the side chain methyl group gave a signal at δ_H: 1.30. The ^{13}C NMR confirmed the presence of Boc groups, the chemical shift noted at δ_C: 82.2 (2 x $C(CH_3)_3$) & 152.8 (2 x N-C=O). Furthermore, there is no signal than can be assigned as N-H in the ^{1}H NMR spectrum or infrared spectrum. The resonance of the 5-C atom in the starting material has been changed from 72.9 (5-C-O) to 38.6 (1-C-S) in **17a,** indicating the replacement of oxygen with sulfur.

Interestingly the former reaction also led to production of a tris-N-substituted cyanuric acid derivative **17b** as a clear colorless liquid in 12.8% yield. Evidence for **17b** was given by the ^{1}H NMR spectrum. Aromatic protons were observed as a doublet at δ_H: 7.35 and two triplets at δ_H: 7.33 and 7.25. ^{1}H NMR indicates the methyl, methylene and methine protons at δ_H: 1.44, 3.56 – 3.18 and 4.92 respectively. ^{13}C NMR showed the three carbonyl groups with a shift at δ_C: 159.4 and the aryl carbons present in the range δ_C: 135.3 - 126.8. The methylene carbon appears at δ_C: 37.7. Infrared spectroscopy showed the carbonyl absorption at 1683 cm^{-1}, and the N*H* absorption has disappeared. Mass spectrometry confirms the molecular mass of 579 g mol-1 and the largest peak corresponds to the [$PhSC_3H_5$-] fragment, which is an important feature of the molecule.

17c as a white solid in 32% yield, and is the main goal of the reaction. In the ^{1}H NMR spectrum, aromatic protons were observed as a doublet at δ_H: 7.37 and two triplets at δ_H: 7.27 and 7.15. ^{1}H NMR indicates the Boc. and the amide protons at δ_H: 1.41 and δ_H: 4.86 respectively, and the infrared spectrum confirms that, with an N*H* absorption at 3368 cm^{-1} and the carbonyl absorption at 1681 cm^{-1}. After opening the ring with breaking of the C-O

bond the 5-C is attached to the PhS- group and the ^{13}C NMR indicated the resonance of this carbon at δ_C: 40.8.

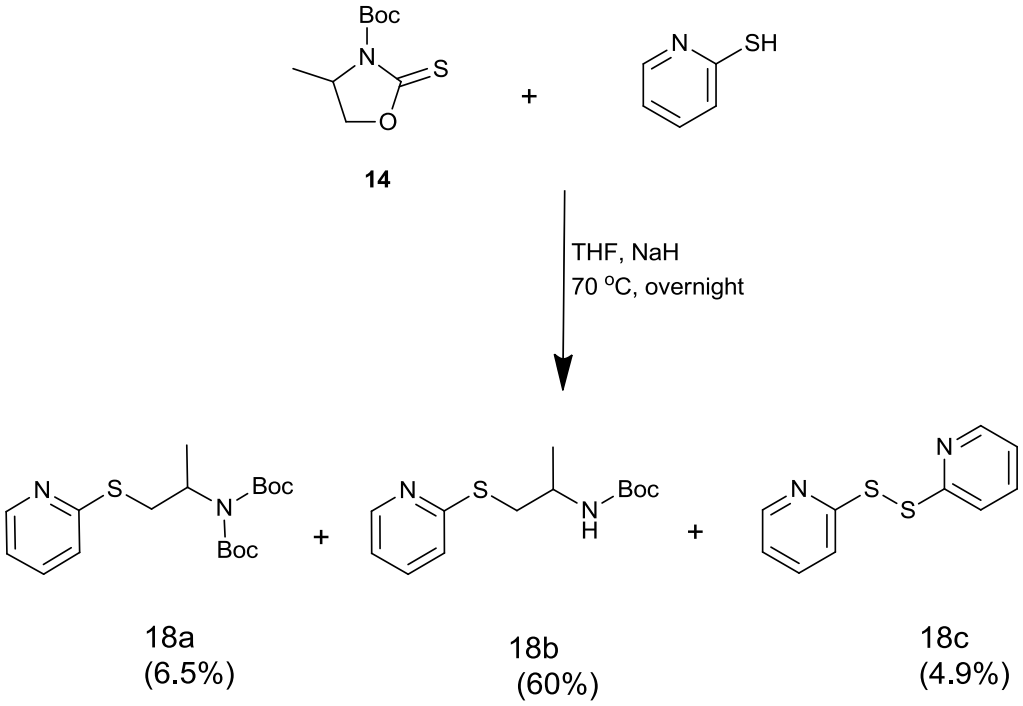
The mechanism for formation of **17c** and the di-Boc compound **17a** is shown in Scheme 8. The latter is thought to be formed by attack of the initial intermediate **17d** on the Boc group of starting material. The formation of the trimeric product may be due to successive attacks of intermediate **17d** on its protonated form, or may involve **17d** losing t-butoxide to give an isocyanide. This is the only case where a trimeric compound was isolated.



Scheme 2.8: proposed mechanisms for the formation of 17a, 17b and 17c.

2.2.1.2: with pyridine-2-thiolate.

A solution of the sodium salt of 2-mercaptopyridine in dry THF was added to the thionocarbamate **14** and was stirred at 70 ºC overnight. Some drops of water were added and the mixture extracted with dichloromethane. The organic layer was evaporated and purified by chromatography to give three compounds (Scheme 2.9).



Boc : -C(=O)O*t*-Bu

Scheme 2.9: Synthetic route to 18a, 18b and 18c.

18a as pale yellow solid obtained in 6.5% yield. NMR analysis indicated that ring opening had taken place and another Boc group had been installed on the N atom. Evidence was given by the ^{1}H NMR spectrum. A singlet was observed for six methyl groups of two Boc groups at δ_H: 1.39, and the methyl group shift is at δ_H: 1.43. The ^{13}C NMR spectrum confirmed the presence of the Boc groups, the shift noted at δ_C: 82.0 (2 x C $(CH_3)_3$) &

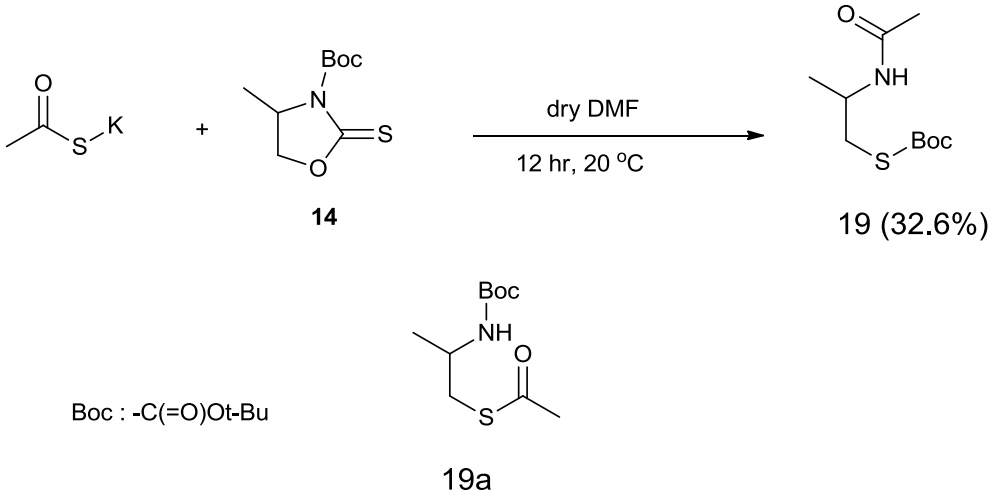
157.1 (2 x N-C=O). There is no signal assigned as N*H* in the ^{1}H NMR spectrum or the infrared spectrum. The 5-C in the starting material has been changed from 72.9 (5-C-O) to 34.6 (1-C-S) in **18a**, consistent with substitution by sulfur. Infrared spectroscopy showed the carbonyl (2 x N-C=O) absorption at 1699 cm^{-1}.

18b, the desired product as a pale yellow solid in 60.0% yield. The ^{1}H NMR showed the aromatic protons between δ_H: 8.40 and 6.85 and the Boc group and the amide protons at δ_H: 1.39 and 5.49 respectively. ^{13}C NMR indicated the position of methyl, methylene and methine carbon atoms at δ_C: 20.3 36.0 and 47.1 respectively. Infrared spectroscopy showed an N*H* absorption at 3359 cm^{-1} and the carbonyl absorption at 1678 cm^{-1}.

18c, a small amount of di (2-pyridyl)disulfide, from oxidation of the thiolate.

2.2.1.3: <u>with potassium thioacetate</u>

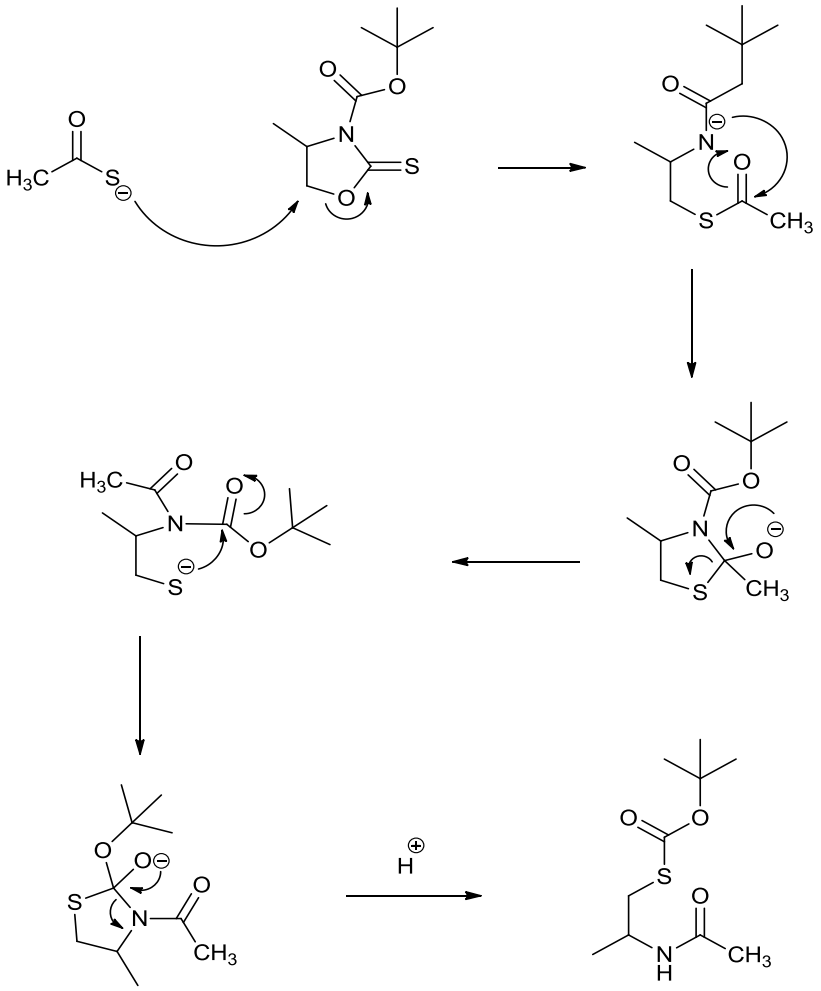
Compound **19** was obtained by reaction of thionocarbamate **14** with potassium thioacetate in stirred dry DMF at room temperature for 12 h. The mixture was neutralized and purified by column chromatography to give **19** as a yellow liquid in 32.6% yield. This material is the expected ring opened structure, but with the –Boc and acetyl groups interchanged between nitrogen and sulfur atoms (Scheme 2.10).



Scheme 2.10: Synthesis of 19.

Evidence was given by the ^{1}H NMR spectrum. Three singlets were observed corresponding to N*H*, (O=C)C*H*$_3$ and Boc protons at δ_H: 5.76, 1.86 and 1.43 respectively. The methyl protons were observed as a doublet at δ_H: 1.14. ^{13}C NMR shows eight peaks including two carbonyl groups observed at δ_C: 169.8 (S-*C*=O) and δ_C: 169.5 (N-*C*=O). Infrared spectroscopy showed an N*H* absorption at 3278 cm^{-1} and the two carbonyl absorptions at 1702 cm^{-1} and 1645 cm^{-1}. Compound **19** is clearly distinguished from the expected compound **19a** by the infrared and ^{13}C NMR signals. For **19a** the two ^{13}C signals are expected at ca δ_C: 195 (S-*C*=O) and δ_C: 155 (N-Boc), while for **19** they are expected at ca δ_C: 170. Furthermore, the infrared absorption at 1645 cm^{-1} is only compatible with an amide and not with a –Boc group (expected ca 1680 cm^{-1}).

The possible mechanism for the formation of **19** is given below (Scheme 2.11). The driving force for the exchange of groups between nitrogen and sulfur atoms is the strength of the amide bond.

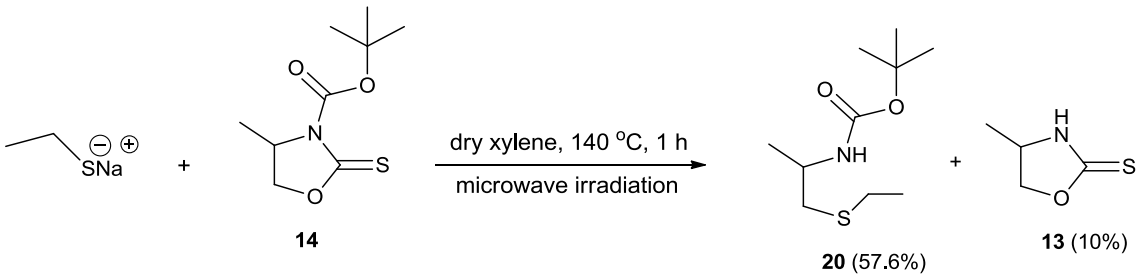


Scheme 2.11: Proposed mechanism for formation of 19.

2.2.1.4: <u>with ethanethiolate.</u>

Cyclic thionocarbamate **14** and sodium ethanthiolate (4 eq) were dissolved in dry xylene and the mixture was stirred and irradiated in a microwave oven at 145 ^{o}C for 1 h. The mixture was cooled to room temperature, dissolved in dichloromethane and then washed with distilled water. The organic layer was purified by column chromatography furnishing **20** as a pale yellow oil in 57.6% yield. The sodium ethanethiolate reacts more readily with the substrate **14** under microwave conditions than under standard conditions of reflux in THF overnight. The microwave conditions gave a yield of the ring opened compound **20** of

57.6% (Scheme 2.12) compared with a very small amount of **20** (<10%) along with **13**, which is the main product under the non-microwave conditions. Compound **13** is derived from starting material by loss of the Boc group, presumably by attack of ethanethiolate.

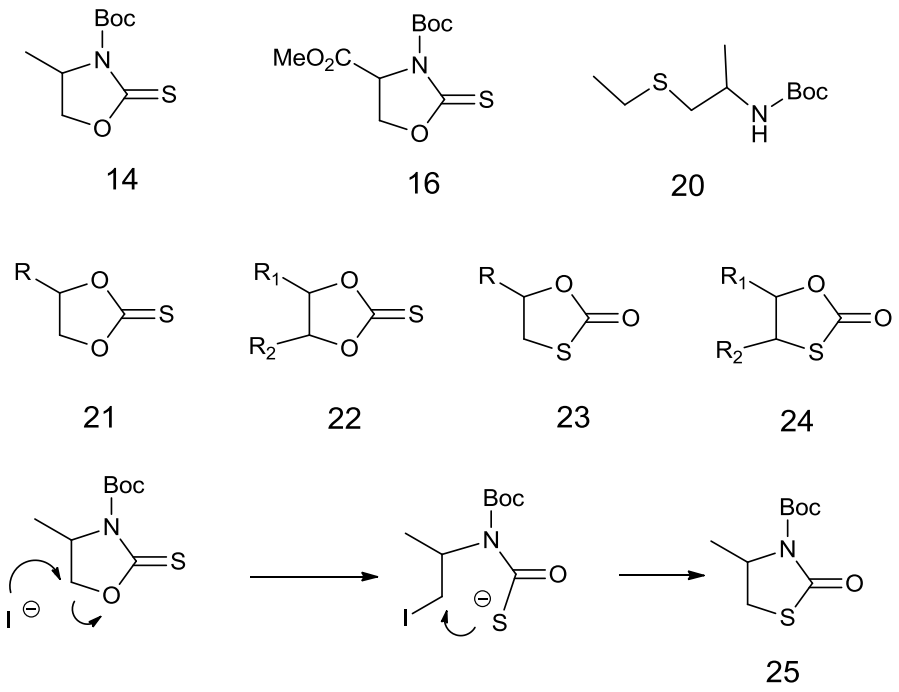


Scheme 2.12: Synthesis of 20.

Analysis of the ^{1}H NMR spectrum of **20** showed two singlets corresponding to N*H* and Boc protons at δ_H: 4.59 and δ_H: 1.37 respectively, a multiplet at δ_H: 3.76 corresponding to C*H*, and two double doublets at δ_H: 2.63 and 2.84 corresponding to 1-H_α & 1-H_β. The S-ethyl group shows the expected quartet and triplet at δ_H: 2.50 and at δ_H: 1.20, and the methyl protons were observed as a doublet at δ_H: 1.14. Infrared spectroscopy showed an N*H* absorption at 3332 cm^{-1} and the carbonyl absorption at 1689 cm^{-1}.

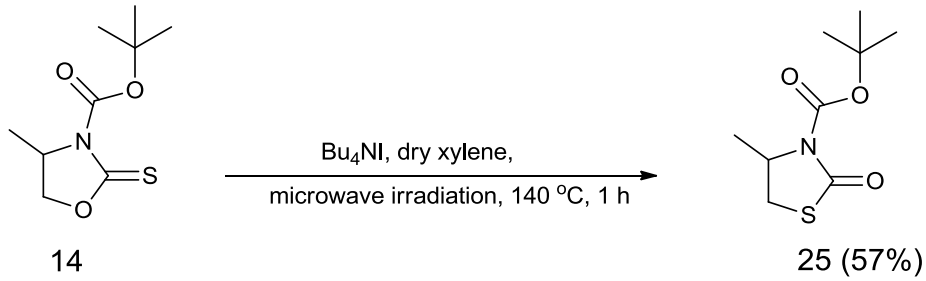
2.2.1.5: <u>with iodide.</u>

It was interesting to see if iodide would react in a similar way, since by analogy with the cyclic thionocarbonates **21** and **22** it could be expected that ring opening of the C-O bond could be followed by ring closure by attack of sulfur on the formed C-I bond, which for **21** and **22** give the corresponding thioxolanes **23** and **24** (Scheme 2.13).



Scheme 2.13: cyclic thionocarbonates 21, 22 and corresponding thioxolanes 23, 24

Reaction of **14** with tetrabutylammonium iodide under refluxing conditions was unsuccessful, but transferring the reaction to microwave conditions using dry xylene as solvent at 145 ^{o}C for 1 hour. gave a 57.0% yield of the thiazolidin-2-one **25** (Scheme 2.14).



Scheme 2.14: Rearrangement reaction of 14.

The structure of the latter was supported by the ring carbon resonances at δc: 169.6 (2-C), 54.6 (4-C) and 31.6 (5-C) and the Boc group carbon resonances at δ_C: 148.5 (N-*C*=O), 83.3 (*C*$(CH_3)_3$) and 27.7 (3 x *C*H_3). Crystals of **25** were grown from ethyl acetate and its x-ray

crystal structure was measured at 120K. The result confirmed that the rearrangement had taken place. (Figure 2.4). Hydrolysis of the S-C=O-N link would give access to a useful ligand.

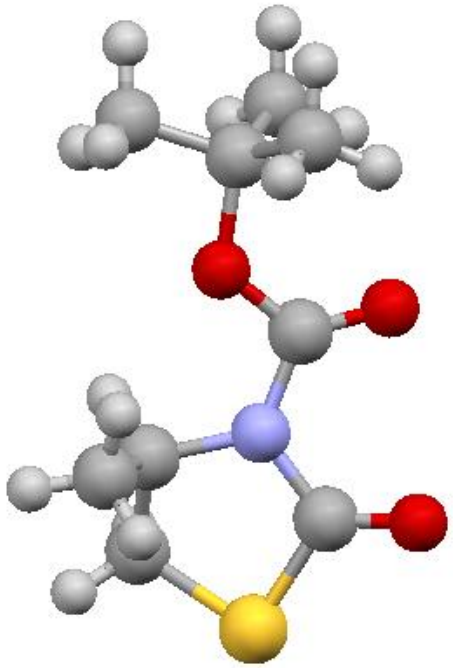
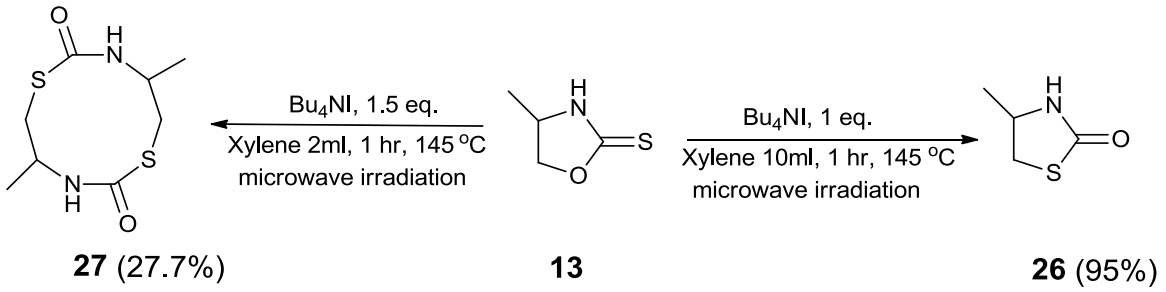


Figure 2.4: Molecular structure of 25

The molecular structure of **25** shows that the ring carbonyl group competes more effectively than the urethane carbonyl group for the N lone pair electrons so that the endocyclic C(=O)-N bond (1.389Å) is shorter than the exocyclic C(=O)-N (1.407Å). Of the two endocyclic C-S bonds, the one to the carbonyl group is significantly shorter (1.769Å) than the one to the methylene group (1.813Å). There is an unusual feature in the structure of the t-butyl group. Two of three methyl groups disordered, as shown by "banana-like" thermal ellipoids but the third one is near spherical.

Due to the interest in synthesis under microwave conditions, this reaction was also conducted on compound **13**, which is closely related to **14** but does not carry the Boc group thought to be necessary for activation to nucleophilic attack. The product obtained from the rearrangement of *rac* 4-methyloxazolidine-2-thione **13** using tetrabutylammonium iodide as the nucleophile was dependent on the precise conditions used. The use of dry xylene (10 ml of xylene per 2.0 mmol of **13**) and a lengthy reaction time under microwave irradiation gave the pure *rac* 4-methyl-1,3-thiazolidine-2-one **26** as a yellow oil in high yield (95%) (Scheme 2.15). Evidence was given by ^{13}C NMR which confirmed the carbonyl group (*C*=O) δ_C: 175.4 and the methylene at δ_C: 36.4 and infrared spectroscopy showed a C=O absorption at 1654 cm^{-1}. Mass spectrometry confirms the molecular mass of 117 g mol^{-1}.



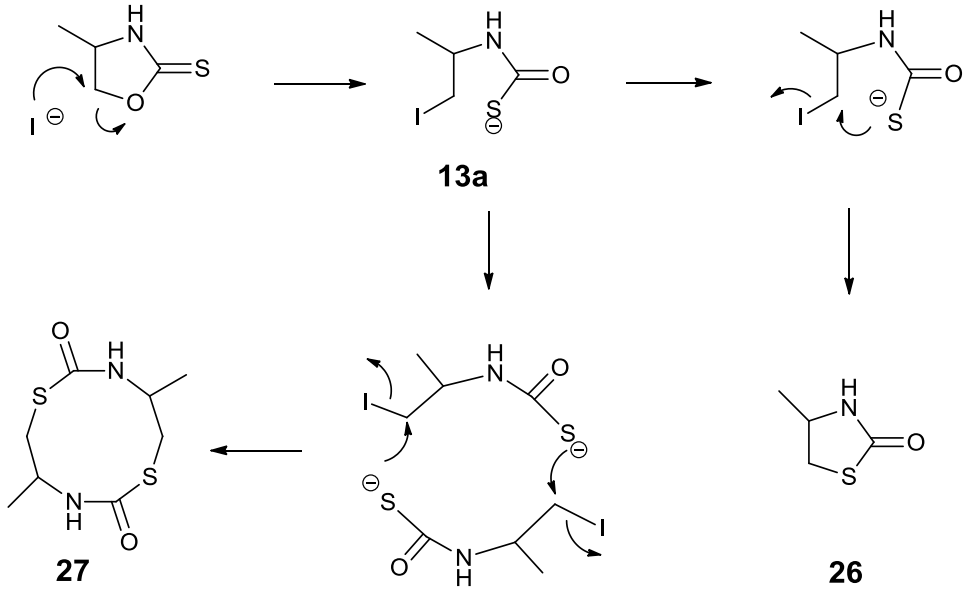
27 (27.7%) **13** **26** (95%)

Scheme 2.15: Rearrangements of 13.

On the other hand in the same microwave conditions but using very little solvent (2 ml of xylene per 6.0 mmol of **13**) the reaction resulted in a dimeric product containing a ten membered ring **27** as pale brown oil in 27% yield. ^{13}C NMR of **27** indicated the two carbonyl groups and the two methylene carbons at δ_C: 176.2 and 41.6 distinctly different from those for **26**. Infrared spectroscopy indicated the N-H absorptions at 3231 cm^{-1} and

the carbonyl group (C=O) absorptions at 1661 cm^{-1}. Mass spectrometry confirms the molecular mass of 234 g mol^{-1}.

The difference is due to two molecules of the ring-opened intermediate **13a** reacting together under the more concentrated reaction conditions to give **27** faster than the intramolecular reaction to give **26** (Scheme 2.16).



Scheme 2.16: Proposed mechanism for the rearrangements of 13

In summary the construction of the N-Boc-1,3-oxothiazolidine-2-thione is a useful way of activating the hydroxyl group of β-aminoalcohols to nucleophilic substitution. The inclusion of the N-acyl group is sufficient to reduce the delocalisation of pi electron density from nitrogen into the thione, and permit the thione to activate the ring oxygen atom to displacement.

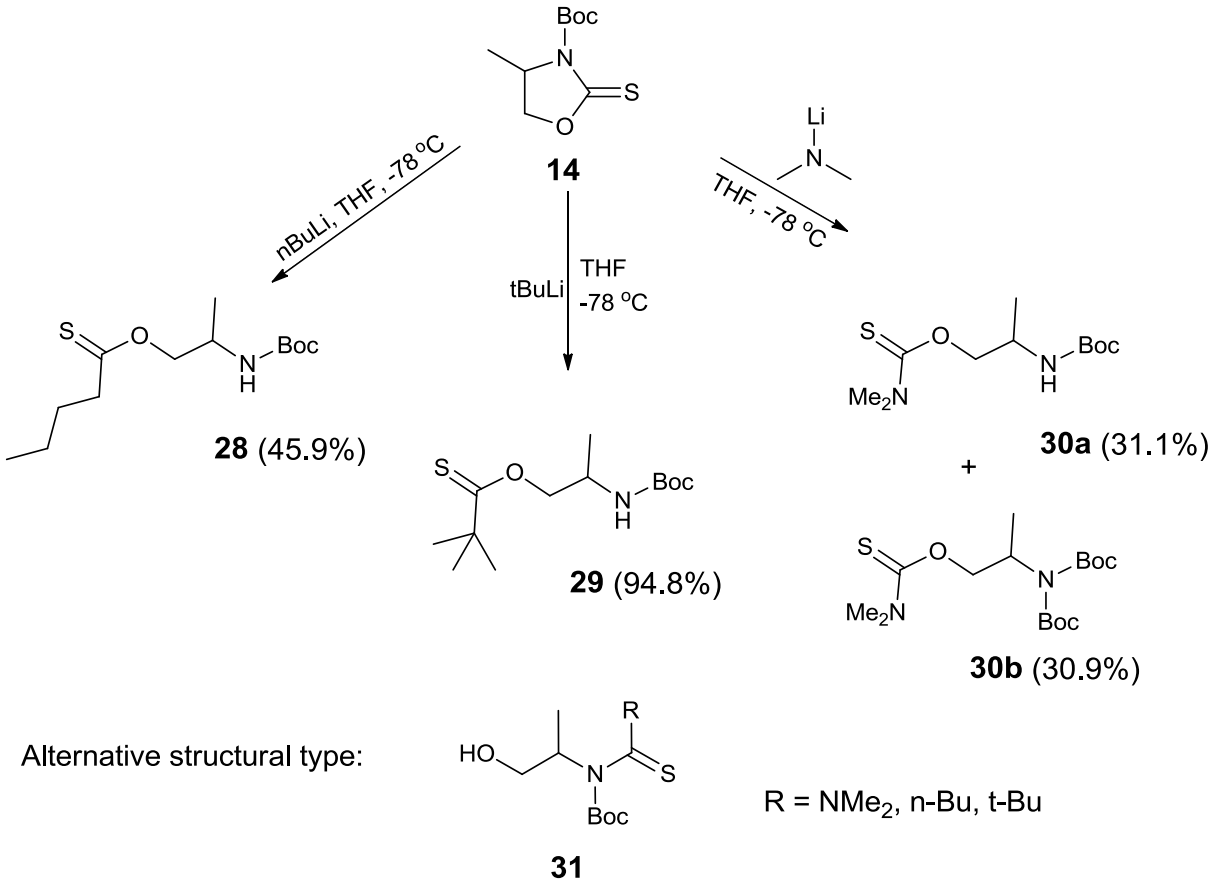
Initial examples were reported with sulfur nucleophiles such as phenylthiolate and 2-pyridine-thiolate and potassium thioacetate on the substrates **14** and **16** and are supported by spectral data and CHN chemical analysis. The use of microwave conditions was beneficial to the rearrangement reaction with iodide and for the substitution reaction with

thionocarbamate. The observation that microwave conditions overcame the need for an N-activating group in the reaction of **13** with iodide, open up a new avenue for further work.

Given the presence of thione and urethane funtionalities in these molecules we were interested to see how different nucleophiles selected between attack at these groups and attack at the ring carbon with breaking of the C-O bond. Thus, the range of nucleophiles was extended from the "soft" nucleophiles such as thiolate and iodide through to the "harder" organlithium and organomagnesium nucleophiles. This has unveiled a rather selective and interesting chemistry, leading to unusual products in some cases depending on which organometallic reagent is used.

2.2.1.6: <u>Reaction of 14 with organometallic reagents.</u>

The reaction with "harder" organolithium and organomagnesium nucleophiles presented a different picture. Their reactions start by attack of the organometallic on the thione group, but the precise product formed depends on the subsequent reactions of this addition product. Thus, n-butyl lithium, t-butyl lithium and lithium dimethylamide were reacted with thione **14** in dry THF, stirring under anhydrous conditions at -78 ^{o}C. The solution was allowed to warm to room temperature, drops of water carefully added, and the product purified by chromatography. Analysis of the products showed that the organometallic adds to the thione group, the tetrahedral intermediate collapses with breakage of the ring C-N bond to give **28**, **29** and (**30a** + **30b**) as main products in yields of 45.9, 94.8 and (31.1 + 30.9%) see Scheme 2.17.



Scheme 2.17: Synthetic of 28, 29, 30a, 30b and 31.

It was important to exclude the isomeric structural assignments i.e. alcohols of type **31** which would be formed by breaking the ring C-O bond rather than the ring C-N bond. Examination of the literature suggested that there was no clearly unambiguous spectroscopic method for this based on literature values for the infrared stretch of the C=S thiocarbonyl or the ^{13}C shift of the thione C atom, so the structures of **29**, **30a** and **30b** were confirmed by X-ray crystallography. However, now with these structures in hand it can be noted that the C=S infrared stretches are at 1163, 1123 and 1123 cm^{-1}, and the ^{13}C resonances are at δ_C: 231.14 (O-*C*(=S)-C), δ_C: 189.59 and δ_C: 187.59 (O-*C*(=S)-N) and the methylene C resonances at δ_C: 74.85, δ_C: 76.67 and δ_C: 72.18 respectively. The product **25**

from n-butyllithium was a liquid, so structural assignment has to rely on spectroscopy. The C=S thiocarbonyl is at δ_C: 224.18 and the methylene carbon at δ_C: 74.3 and infrared spectroscopy showed an C=S absorption at 1174 cm^{-1}, all of which are similar to those in **26**, the product from t-butyllithium whose structure is clear from X-ray crystallography.

Product **30a** was accompanied by a yield of the diBoc compound **30b**, whose structure was also confirmed by X-ray crystallography. This material has probably arisen by the anion formed on ring cleavage removing a Boc group from starting material.

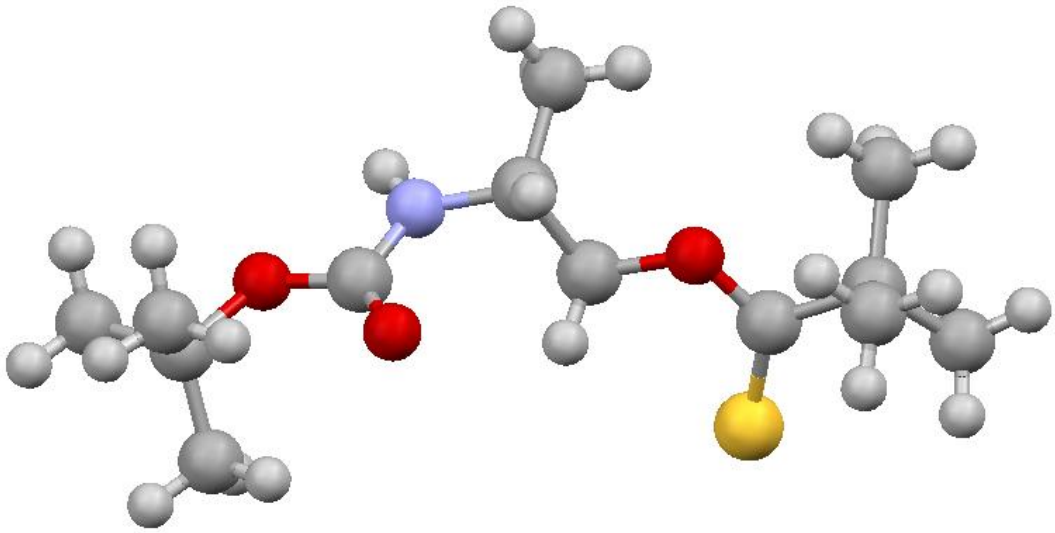


Figure 2.5: Molecular structure of 29 determined by X-ray diffraction.

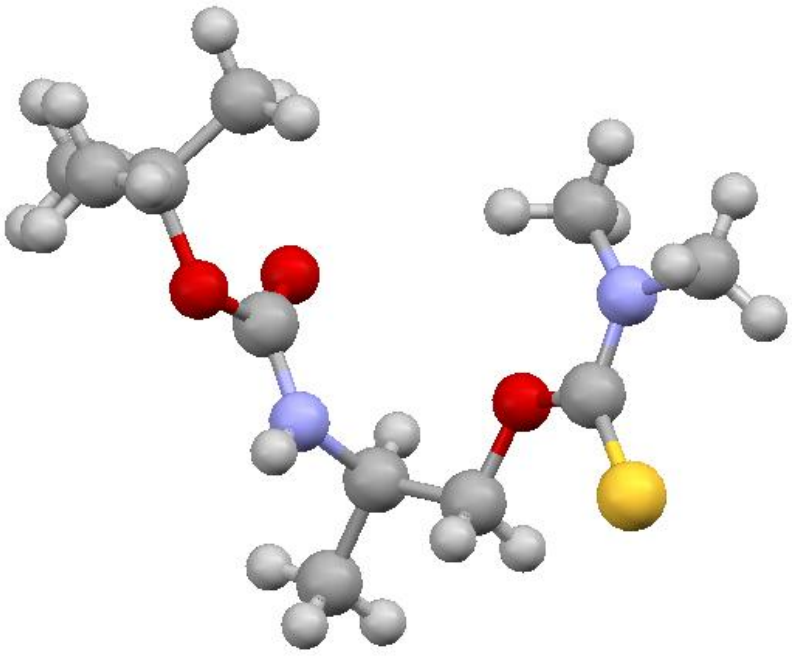


Figure 2.6: Molecular structure of 30a determined by X-ray diffraction.

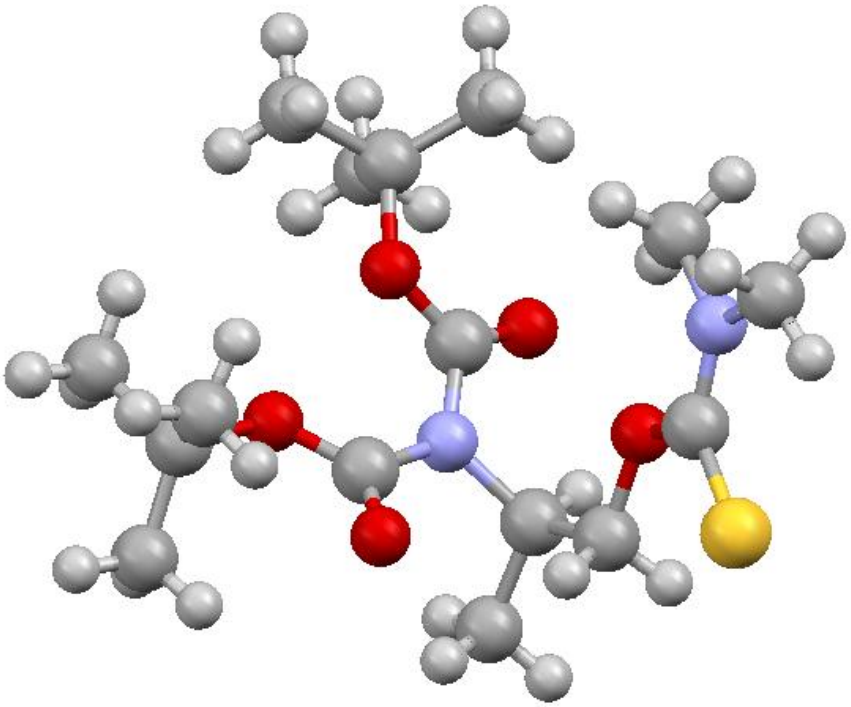
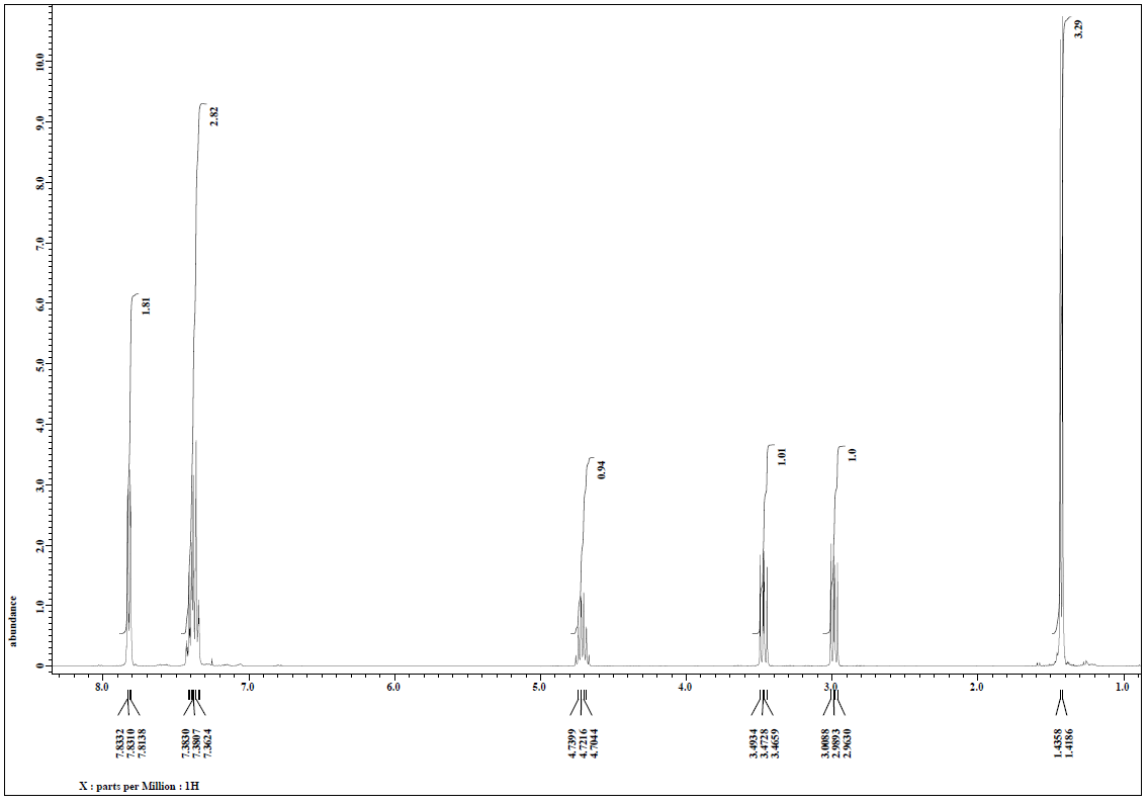


Figure 2.7: Molecular structure of 30b determined by X-ray diffraction, showing the arrangement of the two Boc groups on the nitrogen atom.

The structures **29**-**30b** all show a planar arrangement involving the thiocarbonyl group and the attached O and C or N atoms. For the two thionourethanes in **30a** + **30b** the thiocarbonyl group is much longer (1.6710(15) and 1.6788(15) Å) than for the thionoester in **29** (average of two molecules: 1.616Å). It is also noteworthy that in the case of the thionoester the O-C(=S) bond (average value 1.321Å) is significantly shorter than in the thionourethanes (1.3408(17) and 1.3415(17) Å) since in the latter the strong donation of pi electron density from N to the thiocarbonyl over-rides the donation of pi electron density from O. In the compound **30b** which has two Boc groups attached to the nitrogen atom, the two carbonyl groups are directed away from each other but there is a short 1,5 contact between the butoxy O atoms of just 2.545(2) Å. The bond geometry at the nitrogen and the two carbonyl carbons remains planar, but the two Boc groups have twisted apart to maximise the O---O separation with the two C-O(butoxy) bonds making torsions of 168.5^{o} and 153^{o} with the N-CH_3 bond, and a torsion of 35.3^{o} between the two C-O (butyl) bonds.

Interestingly, the reaction of **14** with phenyl lithium or phenyl magnesium Grignard in the same conditions gave a different type of product. Thus the reaction was carried out in dry THF stirring under anhydrous conditions at -78 ^{o}C, after which the solution was allowed to warm to room temperature and a small amount of water was added. Chromatography led to isolation of the thiazoline **32** (95.0 % from phenyllithium, 38.6 % from phenyl magnesium bromide), with complete loss of the atoms of the Boc group. The structural assignment is supported by the very similar ^{13}C resonance of the 4-C and 5-C shown at δ_C: 72.7 and 39.6 with a series of thiazolines reported in the literature. More information about the ^{1}H and ^{13}C NMR spectra for compound **32** is given in Figure 2.8.



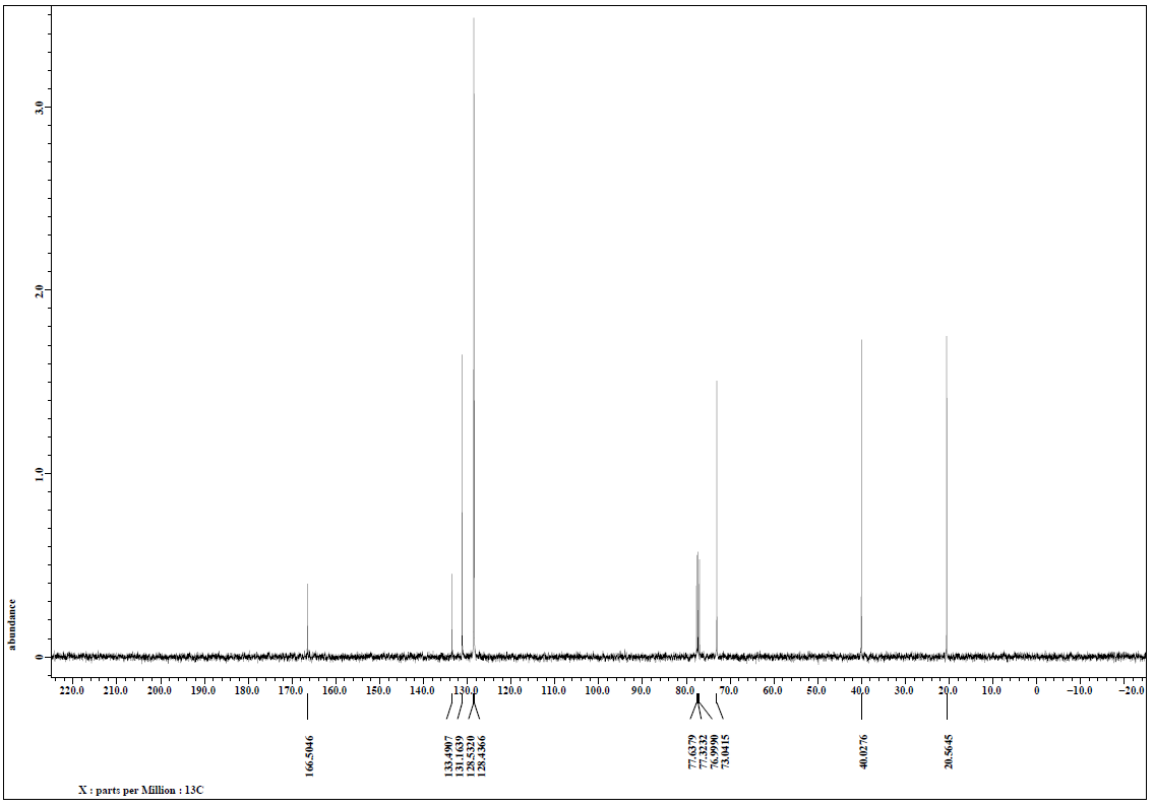
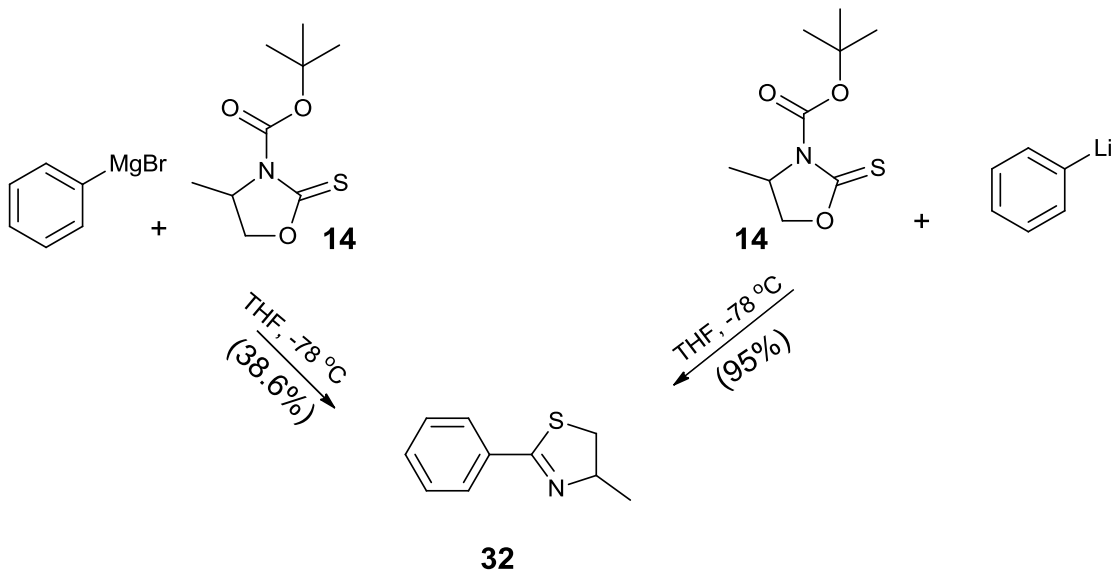
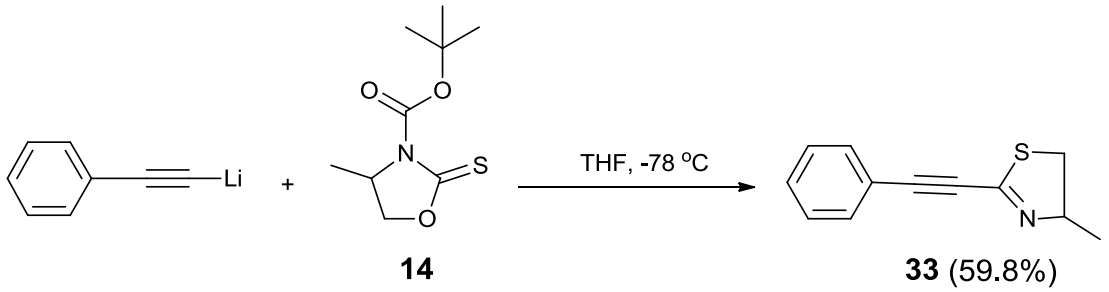


Figure 2.8: ^{1}H and ^{13}C NMR spectra for compound 32



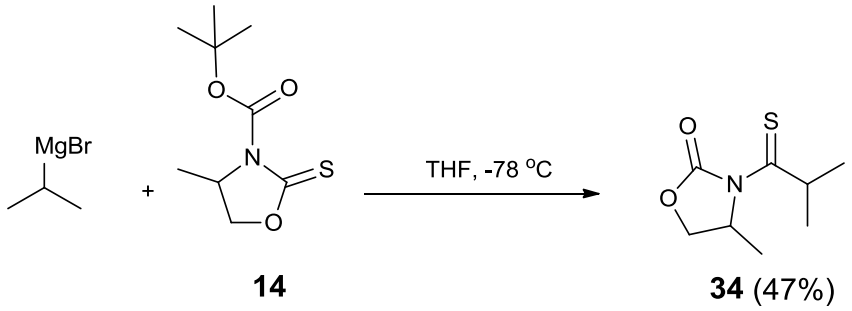
Scheme 2.18: Synthetic routs to 32.

Reaction of thionocarbamate **14** with lithium phenylacetylide in dry THF under similar conditions afforded the thiazoline **33** as yellow oil in 59.5% yield (Scheme 2.19). The structural assignment is supported by ^{13}C resonance of the two acetylene carbons at δ_C: 93.0 and 81.9 and the position of methyl, methylene and methine carbon atoms at δ_C: 20.0, 40.6 and 72.5 respectively.



Scheme 19

In contrast, reaction of thionocarbamate **14** with isopropyl magnesium bromide in the same conditions used above gave the oxazolidinone **34** as yellow oil in 47.0 % yield (Scheme 2.20).



Scheme 2.20: Synthesis of oxazolidinone 34.

The structure of **34** was supported by the carbon resonances at δ_C: 219.53 (*C*=S), 150.38 (*C*=O), 68.40 (5-*C*), 55.82 (4-*C*), 38.38 (S=*C*-CH), 24.00 (-*C*H_3), 23.45 (- *C*H_3), 17.65 (4-*C*H_3). The chemical shifts of sp^3 ring carbon atoms are very similar to those in the starting material (thionocarbamate **14**), supportive of the five ring structure. The results of the HMQC NMR experiment are shown in Figure 2.9. They show two H atoms (δ_H: 4.37 and 3.99) attached to the carbon with shift δ_C: 68.4, and one hydrogen (δ_H: 5.13) attached to the ring carbon with δ_C: 55.8. The infrared spectrum shows the thione group (C=S) stretch at 1161 cm^{-1} and the carbonyl group (C=O) stretch at 1777 cm^{-1}. In this case the carbonyl group at the Boc is included in the structure, but the t-butoxide group has gone.

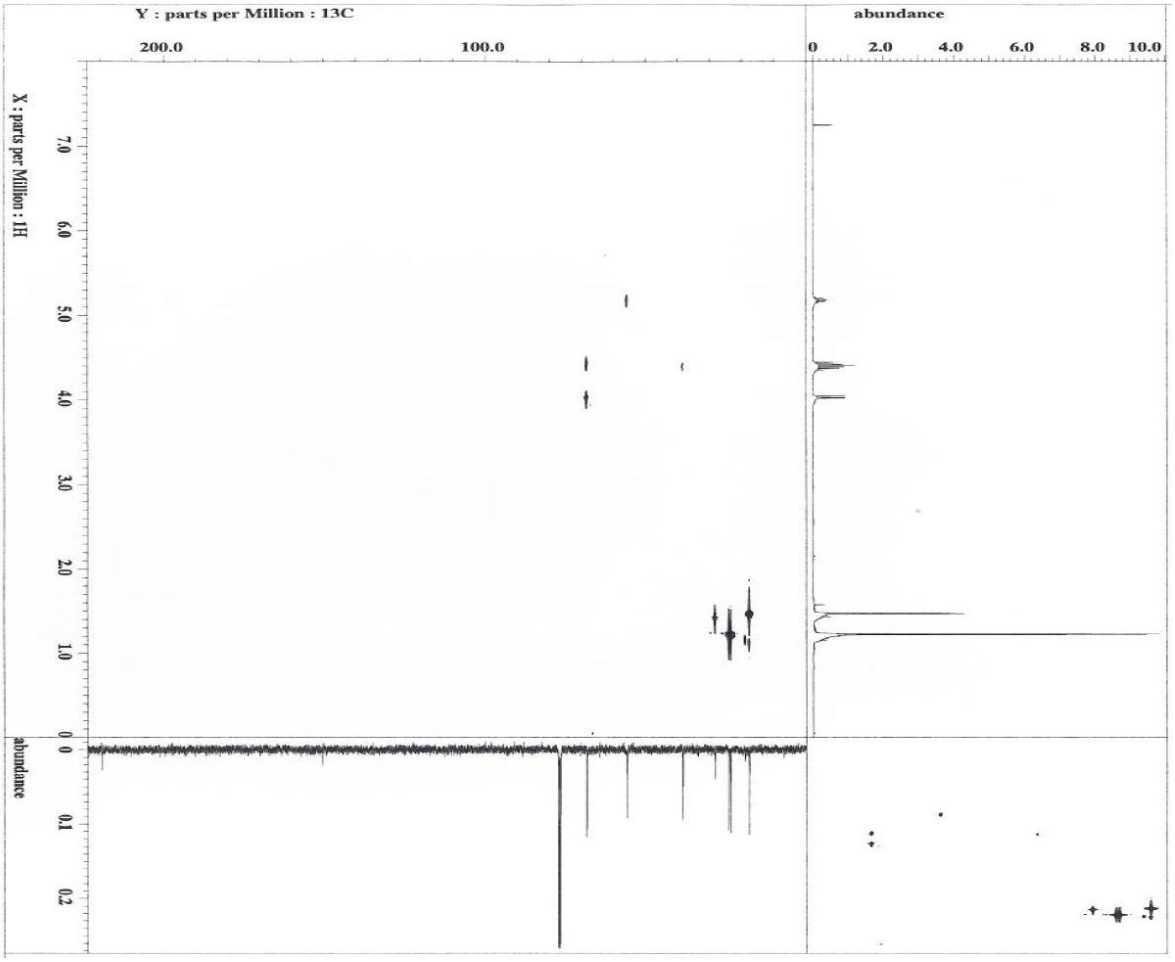
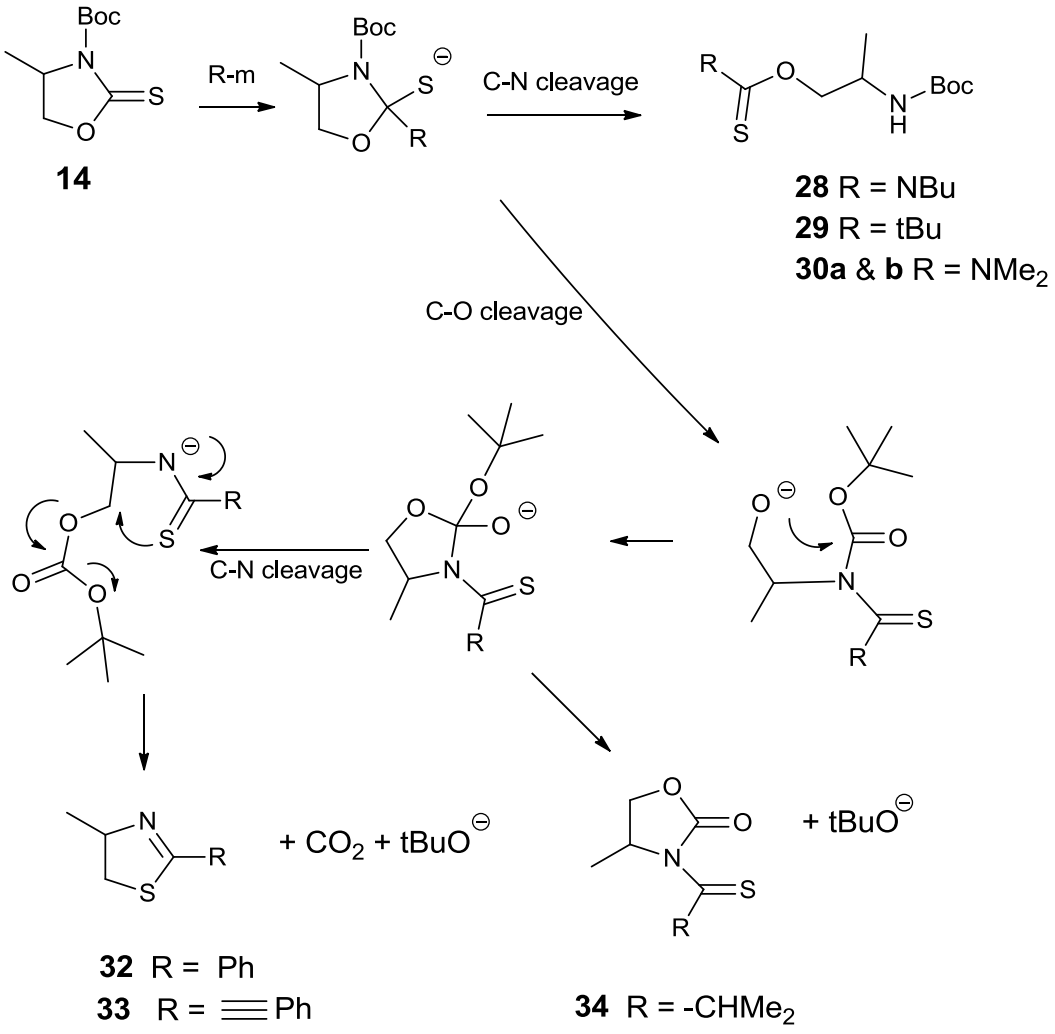


Figure 2.9: HMQC NMR spectra for compound 34

It is proposed that these thiazolines and oxazolidinones arise also from initial addition to the thione and subsequent ring opening by ring O-C bond cleavage, followed by attack of the oxyanion on the Boc carbonyl group. In the case of the thiazolines, the Boc group is transferred to oxygen making the latter a good leaving group which is displaced by the thioamide anion to form the ring system. In the case of the oxazolidones the attack of the oxyanion on the Boc group is followed by expulsion of the butoxide ion. All processes following the attack on the thiocarbonyl group may well be reversible, with the exception of the loss of $tBuO_2C$ to give the thiazolines, which may be favoured by groups which

conjugate with the thioamide anion. The structures proposed are supported by CHN chemical analysis and their spectral data.

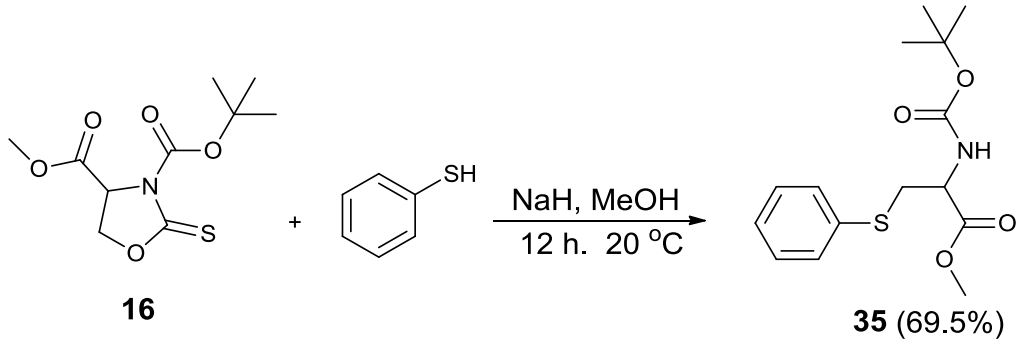


Scheme 2.21: Proposed mechanism for oxazolidinone 34.

2.2.2: <u>Reactions of Thionocarbamate 16.</u>

Several reactions of the thionocarbamate **16** carrying an ester group at the 4-C position were investigated. Reaction with sulfur nucleophiles such as phenylthiolate and 2-pyridinethiolate gave the products **35** and **36** arising from attack at the 5-C, in 69.5 and 56.7%. The desired product **35** colourless oil, was synthesized by reaction of thionocarbamate **16** with thiophenol in presence of sodium hydride in dry methanol and the

mixture stirred at room temperature for 30 min. The mixture was then neutralized and extracted with diethyl ether, and concentrated in *vacuo*. Final purification was achieved by flash column chromatography to obtain **35** (Scheme 2.22).

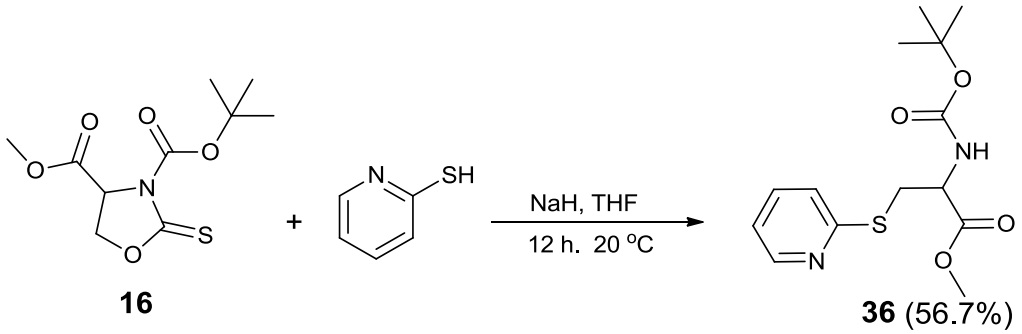


Scheme 2.22: Synthesis of 35.

The ^{1}H NMR showed the aromatic protons between δ_H: 7.39-7.15 the Boc group, methoxy and the amide protons at δ_H: 1.43, 3.45 and 5.32 respectively. ^{13}C NMR indicated the position of methoxy, methylene and methine carbon atoms at δ_C: 52.1, 37.0 and 53.7 respectively. Infrared spectroscopy showed an NH absorption at 3373 cm^{-1} and the two carbonyl absorptions at 1746 and 1712 cm^{-1}.

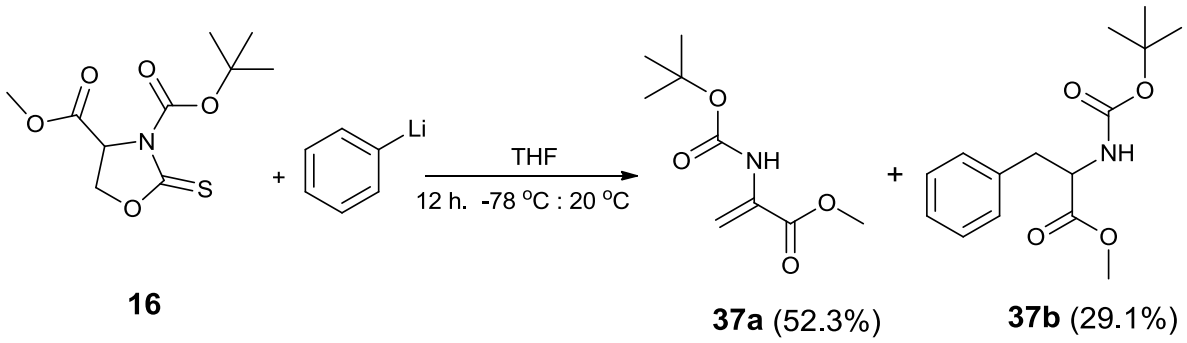
Compound **36** was obtained by reaction of thionocarbamate **16** with 2-mercaptopyridine in the presence of sodium hydride in dry THF and the mixture was stirred at room temperature overnight. The mixture was neutralized by adding drops of acetic acid and purified by flash column chromatography to obtain **36** (Scheme 2.23).

The ^{1}H NMR showed the aromatic protons between δ_H: 8.34 – 6.90, the Boc group, methoxy and the amide protons at δ_H: 1.30, 3.61 and 6.32 respectively. ^{13}C NMR indicated the position of methoxy, methylene and methine carbon atoms at δ_C: 52.2, 31.9 and 54.4 respectively. Infrared spectroscopy showed an N*H* absorption at 3352 cm^{-1} and the two carbonyl absorptions at 1744 and 1711 cm^{-1}.



Scheme 23

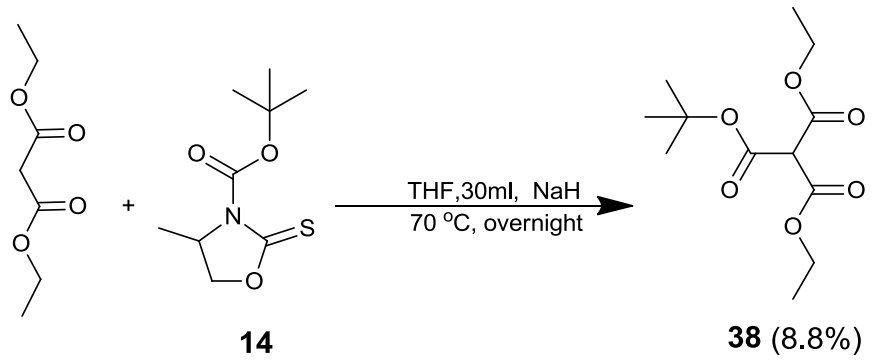
However reaction of thionocarbamate **16** with phenyllithium, which is a strong base, in dry THF, stirring under anhydrous conditions at -78 °C for 2 hours led to the alkene **37a** as an yellow oil in 52.3% yield. Thus arises from deprotonation at 4-C followed by loss of COS. There is also some of the phenyl substituted material **37b** produced as a pale yellow solid in 29.1% yield (Scheme 2.24), which may arise by Michael addition to the alkene **37a**, rather than direct substitution of thionocarbamate **16**. This is consistent with a greater yield of **37b** being produced with a longer reaction time. The structures proposed are supported by CHN chemical analysis and their spectral data.



Scheme 2.24: Snthesis of 37a and 37b.

2.2.3: Further investigations with thionocarbamate 14.

In addition, different nucleophiles such as nitrogen, oxygen and carbon nucleophiles should be used for the reaction. It is of great interest as a way towards new results. These nucleophiles are known to be less reactive and sometimes lead to different selectivity than sulfur nucleophiles. However, it was found that the reactions that ring opened with breaking of the C-O bond or attack of the (C=S) thiocarbonyl group by using a N-nucleophile such as phthalimide or carbazole or O-nucleophiles such as phenolate did not take place and did not proceed in the conditions which were used before with sulfur nucleophiles. C-nucleophiles, for example diethyl malonate, reacted with thionocarbamate **14** in the presence of sodium hydride in dry THF. The mixture was stirred and heated to 70 ^{o}C for 12 hours, the solution became a clear pale red oil and was left to cool to room temperature, some drops of water were added, and the mixture was left to stir for 30 min. The residue was extracted and the organic layer was evaporated *in vacuo*. The crude product was purified by column chromatography to give **38** as yellow oil in 8.8% yield (Scheme 2.25). In this case what happened was just the carbon-centred nucleophile taking the Boc group from starting material **14**. The structure of **38** was confirmed by ^{1}H NMR, ^{13}C NMR, IR and spectral data.



Scheme 2.25: Synthesis of 38.

2.3: Experimental

2.3.1: General

All the glassware for the experiments was dried in an oven (100 ^{o}C or higher) overnight and allowed to cool completely to room temperature under a flow of nitrogen before any reagents were introduced. All metal needles used were acetone washed and oven dried for a minimum of 3 hours. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Organic solutions were concentrated under reduced pressure by rotary evaporation and vacuum pump.

2.3.2: Reagents and solvents

2.3.2.1: Reagents

In our experiments, all the reagents were analytical grade and used without further purification. All chemicals were purchased from Sigma Aldrich and used without further purification, unless otherwise stated.

2.3.2.2: Solvents

The solvents used in reactions were dried, distilled and stored under nitrogen prior to use. Methanol, dichloromethane and triethylamine were dried by distillation from CaH_2. THF and toluene were dried by distillation from sodium with benzophenone as indicator. Some dry solvents were commercially available [N,N-dimethylformamide (DMF) and xylene] and were used as such. The solvents ethyl acetate, hexane and cyclohexane (Reagent grade) which were used for chromatography and some others were purchased from Fisher Scientific Ltd.

2.3.3: Reaction conditions

For all reactions where dry conditions were required, glassware was oven dried and reactions were carried out under a nitrogen atmosphere with magnetic stirring. Reaction

temperatures of -78 °C were obtained using solid CO_2 \ acetone bath. For those reactions at 0 °C an ice bath was employed, and where heat was required a thermostatted aluminium dish on an adjustable dual-purpose laboratory electric heater and magnetic stirrer was used. Reactions were monitored by thin layer chromatography (TLC).

2.3.4: Purification techniques

2.3.4.1: Thin-layer chromatography TLC

Thin-layer chromatography (TLC) was carried out using foil backed alumina or silica plates, UV-active, and substances were detected in UV light with wavelength λ = 254 nm, or by dipping into iodine vapours or solutions of potassium permanganate or vanillin.

2.3.4.2: Column chromatography

Flash column chromatography was performed using silica gel (Fluorochem, 60A, 40 ± 63 micron). The samples were either applied in solution directly to the top of the silica / solvent column or applied absorbed onto a dry silica gel slurry. Pressure was applied at the column head via hand bellows or an electric pressure pump.

2.3.5: Nuclear Magnetic Resonance Spectroscopy (NMR)

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were measured on a JEOL ECLIPSE 400 spectrometer at 400 MHz and 100 MHz respectively. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale and coupling constants (J) are given in Hertz (Hz). The solvent peaks were used as reference values. For $CDCl_3$ ^{1}H NMR: = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.00 ppm; for CD_3OD, the internal reference was designated at 3.31ppm (^{1}H) and 49.0ppm (^{13}C), for $(CD_3)_2SO$ the internal reference was designated at 2.50ppm (^{1}H) and 39.5ppm (^{13}C). The abbreviations for the multiplicity for proton data were as follows: s = singlet, d = doublet, dd = doublet of

doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, t = triplet, tt = triplet of triplets, q = quintet, m = multiplet, p = pentet, br = broad.

2.3.6: Mass spectrometry

High and low resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service Centre, School of Medicine, Swansea University.

2.3.7: Elemental analyses

Chemical analysis data were obtained from Mr Stephen Boyer, London Metropolitan University.

2.3.9: IR

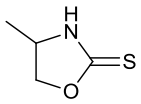
Infrared (IR) absorption spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR Spectrometer using an ATR attachment, and are reported in cm^{-1}.

2.3.10: Melting Point.

Melting points were determined on a Stuart melting point apparatus SMP30.

2.3.11: Procedures.

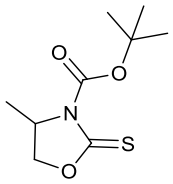
Procedure A for preparation of *rac* 4-methyloxazolidine-2-thione 13.



A solution of *rac*-2-amino-1-propanol (3.86g, 4.0ml, 51.2mmol) and triethylamine (13.2g, 18ml, 128.8mmol) in anhydrous dichloromethane (100ml) was stirred for 30 min at 0˚C (ice bath), whilst a solution of thiophosgene (4.0ml, 51.1mmol) in dichloromethane (7.0 ml) was added dropwise. The mixture was allowed to warm to room temperature, and was stirred for a further 3 h. The reaction was quenched with 10% HCl (50ml) and the mixture was washed with water (80 ml) and extracted with dichloromethane (2 x 70 ml). The layers were separated and the organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude material was purified by column chromatography using ethyl acetate

/ cyclohexane (1:1) as eluent to provide *4-methyloxazolidine-2-thione* **13** as a yellow solid (2.18g, 36%), m.p. = 71 ºC. Anal. calcd for C_4H_7NOS: C, 41.00; H, 6.02; N, 11.95%; found: C, 41.05; H, 6.13; N, 11.81%; δ_H : 8.21 (1H, br-s, N*H*), 4.70 (1H, m, 4-C*H*), 4.17 (2H, m, 5-CH_2), 1.30 (3H, d, J = 5.8, CH_3); δ_C: 189.0 (2-*C*), 76.8 (5-*C*), 52.5 (4-*C*), 19.9 (*C*H_3); ν_{max}: 3346, 2974, 1529, 1513, 1463, 1374, 1142, 1026, 935, 823, 619, 524, 440 cm^{-1}; *m/z* (EI): 117 (M^+, 100%), 102, 86, 42; *m/z* HRMS (EI) calcd for C_4H_7NOSH $[M+H]^+$:118.0321; Found: 118.0320.

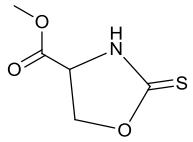
Procedure B for preparation of *rac* 3-t-butyloxycarbonyl-4-methyl–oxazolidine-2-thione 14.



Triethylamine (5.20g, 7.20ml, 50.60mmol) and di-tert-butyl dicarbonate (11.64g, 51.6mmol) were added to a solution of *rac* 4-methyloxazolidine-2-thione 13 (6.00g, 51.6mmol) in dry dichloromethane (120ml) under nitrogen and the mixture stirred. A solution of 4-(dimethylamine)pyridine (6.36g, 51.6mmol) in dichloromethane (18ml) was added dropwise at 0˚C. The solution was stirred for 7h at room temperature. The volatiles were removed and the crude residue was purified by column chromatography using ethyl acetate / cyclohexane (1:2) as eluent to give *rac 3-t-butyloxycarbonyl-4-methyl–oxazolidine-2-thione* **14** as a yellow solid (4.80g, 44%), m. p. = 98 ºC. Anal. calcd for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N: 6.40%; Found: C, 49.87; H, 7.01; N: 6.39%; δ_H (400 MHz): 4.58 (2H, m, 5-H_2), 4.15 (1H, dd, J = 8.4 & 3.0, 4-*H*), 1.58 (9H, s, 3 x CH_3), 1.46 (3H, d, J = 6.2, 4-CH_3); δ_C (100 MHz): 184.4 (*C*=S), 149.3 (N-*C*=O), 84.8 (*C*$(CH_3)_3$), 72.9

(5-*C*), 55.4 (4-*C*), 28.0 (3 x *C*H_3), 19.3 (4-C*H*$_3$); $\nu_{max.}$ 2986, 2930, 1759, 1157 cm^{-1}; *m/z* (EI): 217 (M^+),162 (100%), 144, 118, 102, 84, 57, 41.

Preparation of methyl 2-thioxooxazolidine-4-carboxylate 15



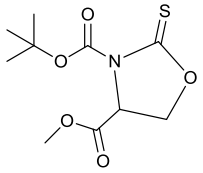
Prepared following procedure **A**. Triethylamine (10.4g, 14.4ml, 98.4 mmol) was added to a stirring solution of *DL*-serine methyl ester hydrochloride (5.00g, 32.8 mmol) in dichloromethane (50 ml) under nitrogen at 0 °C. Thiophosgene (2.6 ml, 32.8 mmol) in dichloromethane (15 ml) was added dropwise and the resulting mixture was allowed to stir at 0 °C for 3 hours, and gradually warming to room temperature overnight. Water was added to the mixture and the two layers separated. The organic layer was washed with 1M hydrochloric acid (2 × 30 ml) and then brine (50 ml) before the organic layer was dried over sodium sulfate and the solvent removed under reduced pressure. Final purification was achieved by flash column chromatography with ethyl acetate / dichloromethane (1:5) as eluent to give *methyl 2-thioxooxazolidine-4-carboxylate* **15** (3.50 g, 66%) in the fourth fraction as a colourless oil. δ_H (400 MHz): 8.68 (1H, br s, N-*H*), 4.89 (3H, m, 4-*H* and 5-H_2), 3.85 (3H, s, -OCH_3); δ_C (100 MHz): 189.7 (*C*=S), 169.4 (*C*=O), 72.4 (5-*C*), 57.4 (4-*C*), 53.5 (-O*C*H_3); *m/z* (ESI) found: 162 $C_5H_7O_3NS$+H $[M+H]^+$; *m/z* HRMS (ESI) calcd for $C_5H_7NO_3S$+H $[M + H]^+$ 162.0212; Found: 162.0213.

Another procedure to prepare methyl 2-thioxooxazolidine-4-carboxylate 15

However, a higher yielding procedure for this transformation was also used[24]. Triethylamine (6.7 g, 9.2 ml, 66.2 mmol) was slowly added to a suspension of *DL*-serine

methyl ester hydrochloride (5.20 g, 33.4 mmol) in THF (35 ml) at 0 °C under nitrogen. A solution of carbon disulfide (3.80 g, 50.0 mmol) in THF (4 ml) at 0 °C was then added. The mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h. After that, hydrogen peroxide (30 %, 6.7 ml) was slowly added to the resulting mixture at room temperature, and the mixture was concentrated by a rotary evaporator. Ethyl acetate (170 ml) was added to the residual mass. The organic phase was dried over $MgSO_4$ and volatile products were evaporated. Final purification was achieved by flash column chromatography with chloroform / acetone (20: 1) as eluent to give a much cleaner product **15** (4.41 g, 83%).

Preparation of methyl 3-t-butyloxycarbonyl-2-thioxooxazolidine-4-carboxylate 16



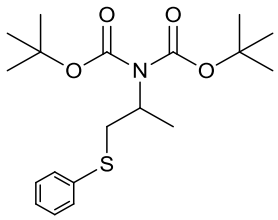
Prepared following procedure **B**. Triethylamine (6.00 ml, 42.6 mmol), di-t-butyl dicarbonate (18.77 g, 85.2 mmol) and 4-dimethylaminopyridine (4.80 g, 42.8 mmol) were added to a stirred solution of **15** (6.86 g, 42.6 mmol) in dichloromethane (80 ml) under nitrogen at 20 ^{o}C and the mixture stirred for 7 hours. The mixture was evaporated, and the residue purified by chromatography on silica using chloroform / acetone (95:5) followed by crystallization from ethanol to give *methyl 3-t-butyloxycarbonyl-2-thioxooxazolidine-4-carboxylate* **16** (8.70 g, 78%) as a white solid. m. p. = 101 - 103 ºC. Anal. calcd for $C_{10}H_{15}NSO_5$: C: 46.0, H: 5.8, N: 5.4%; Found C: 46.3, H: 5.9, N: 5.3%; δ_H (400 MHz, DMSO-d_6): 5.09 (1H, dd, J = 9.6, 4.2 Hz, 4-*H*), 4.74 (1H, t, J = 9.6 Hz, 5-H_α), 4.52 (1H, dd, J = 9.6, 4.2 Hz, 5-H_β), 3.84 (3H, s, -OCH_3), 1.52 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, DMSO-d_6): 183.5 (*C*=S), 168.8 (*C*O_2Me), 148.4 (N-*C*=O), 85.4 (*C*Me_3), 68.8 (5-*C*), 59.9

(4-*C*), 53.3 (-O*C*H_3), 27.7 (C(*C*H_3)$_3$); ν_{max}: 2976, 2954, 1764, 1743, 1364, 1316, 1249, 1204, 1143, 1060, 977, 851, 755 and 512 cm^{-1}; *m/z* (ESI) found: 262 $C_{10}H_{15}NSO_5$+H [M +H]$^+$, 162 [(M+H) – Boc]$^+$; *m/z* HRMS (ESI) calcd for $C_5H_7NO_3S$+H [M + H]$^+$ 262.0736; Found: 262.0737.

Procedure C for preparation of 17a, 17b and 17c

To a solution of the sodium salt of thiophenol in dry THF (15ml), formed from thiophenol (101.4 mg, 0.108ml, 0.92mmol) and sodium hydride (60% dispersion in mineral oil, 74mg, 1.84mmol), was added to a solution of **14** (200 mg, 0.92mmol), dissolved in dry THF (10ml). The mixture was stirred and heated to 60 ºC for 4 hours. After adding some drops of water, the mixture was left stirring for 30 min. The solution became clear, and was quenched with water (30ml) and then extracted with dichloromethane (2 x 20 ml). The organic layer was evaporated, and the crude product was absorbed onto silica and purified by column chromatography eluting with ethyl acetate / cyclohexane (1:10). The separation gave three compounds (**17a, 17b, 17c**). Representative physical data and microanalyses follow:

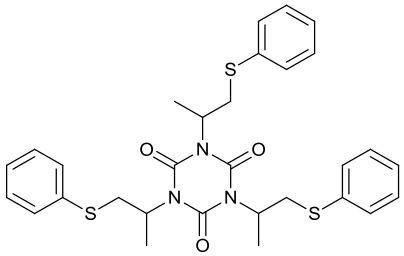
rac -N,N-Bis (t-butoxycarbonyl)-1-(phenylthio)propyl-2-amine **17a**



Clear colourless liquid (15 mg, 4.45%). Anal. calcd for $C_{19}H_{29}NO_4S$: C, 62.12; H, 7.90; N, 3.81%; Found: C, 62.14; H, 7.83; N, 3.96%; δ_H (400 MHz): 7.29 (2H, d, J = 7.8, *ortho* Ar*H*$_2$), 7.19 (2H, t , J = 7.8, *meta* Ar*H*$_2$), 7.10 (1H, t, J = 7.2, *para* Ar*H*), 4.33 (1H, m, 2-*H*), 3.35 (1H, dd, J = 8.0 & 13.6, 1-H_α), 3.06 (1H, dd, J= 7.2 & 13.6, 1-H_β), 1.39 (18H, s, 6

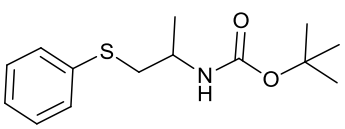
x CH_3), 1.30 (3H, d, J = 6.8, 3-H_3); δ_C (100 MHz): 152.8 (2 x N-*C*=O), 135.8, 129.5, 128.8 & 126.1, (Ar-C_6), 82.2 (2 x *C*(CH_3)$_3$), 52.2 (2-*C*), 38.6 (1-*C*), 27.9 (6 x *C*H_3), 17.6 (*C*H_3); ν_{max}: 2978, 1736, 1699, 1367, 1345, 1273, 1142, 740, 691 cm^{-1}; *m/z* (ESI) found: 390 (M + Na), other peaks at 757 $[2M+NH_4]^+$, 268, $[M - Boc]^+$, 151 $[M - 2N(Boc)_2]^+$; *m/z* HRMS (ESI) calcd for $C_{19}H_{29}NO_4S$+H $[M + H]^+$ 368.1890; Found: 368.1890.

rac-R,R,R & R,R,S-1,3,5-Tris(1`-(phenylthio)propan-2`-yl)hexahydro-1,3,5 triazine-2,4,6-trione **17b**



Clear colourless liquid (68 mg, 12.8%). δ_H (400 MHz): 7.35 (6H, d, J = 7.8, 3 x *ortho* ArH_2), 7.33 (6H, t, J = 7.8, 3 x *meta* ArH_2), 7.25 (3H, t, J = 7.2, 3 x *para* Ar*H*), 4.92 (3H, m, 3 x 2`-*H*), 3.56 (3H, m, 3 x 1`-H_α), 3.18 (3H, m, 3 x 1`-$H_\beta$), 1.44 (9H, d, J = 6.8, 3 x 3`-H_3); δ_C (100 MHz): 159.4 (3 x N_2-*C*=O), (135.3, 130.4, 130.2, & 126.8, 3 x Ar-C_6), 51.1 (3 x 2`-*C*), 37.1 (3 x 1`-*C*), 17.3 (3 x 3`-*C*); ν_{max}: 2975, 1683, 1425, 1369, 1024, 762, 734, 689, 421 cm^{-1}; *m/z* (EI): Found: 579 (M+, 15), 151 (PhS-CH_2-CH-CH_3, 35), 150 (PhS-CH=CH-CH_3, 100); *m/z* HRMS (ESI) calcd for $[M + H]^+$, $C_{30}H_{33}N_3O_3S_3$+H: 580.1749 $[M + H]^+$ found: 580.1749.

rac. N-1-t-Butoxycarbonyl-1-phenylthiopropyl-2-amine **17c**.

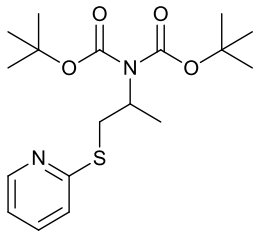


White solid (78 mg, 32%), m.p. = 63 ºC. Anal. calcd for $C_{14}H_{21}NO_2S$: C, 62.92; H, 7.86; N, 5.24%; Found: C, 63.00; H, 7.96; N, 5.21%; δ_H (400MHz, CD_3OD): 7.37 (2H, d, J = 8.0, *ortho* ArH_2), 7.27 (2H, t , J = 8.0, *meta* ArH_2), 7.15 (1H, t, J = 7.2, *para* ArH), 4.86 (1H, s, NH), 3.71 (1H, m, 2-H), 3.09 (1H, br. dd, J = 6.0 & 13.0, 1-H_α), 2.88 (1H, dd, J= 7.2 & 13.0, 1-H_β), 1.41 (9H, s, 3 x CH_3), 1.18 (3H, d, J = 6.8, 3-H_3); δ_C (100 MHz): 157.6 (N-C=O), 137.8, 130.3, 129.9 & 127.0, (Ar-C_6), 79.9 (C-$(CH_3)_3$), 48.6 (2-C), 40.8 (1-C), 28.8 (3 x CH$_3$), 20.0 (3-C); ν_{max}: 3368, 2976, 1681, 1518, 1244, 1153, 1026, 737, 610, 468 cm^{-1}; *m/z* (EI) Found: 290 $[M + Na]^+$, 212 $[M+H - C_4H_8]^+$, 151 $[M - NHBoc]^+$; *m/z* HRMS (EI) calcd for $[M + Na]^+$, $C_{14}H_{21}NO_2S$ + Na: 290.1185; found: 290.1189, other peaks at 557.2473 $[2M+Na]^+$.

Preparation of 18a, 18b and 18c

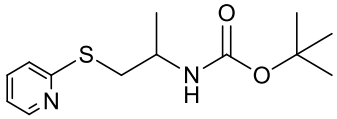
Prepared following procedure **C** using 2-mercaptopyridine. A solution of the sodium salt of 2-mercaptopyridine in dry THF (15ml), formed from 2-mercaptopyridine (101.4 mg, 0.108 ml, 0.92 mmol) and sodium hydride (60% dispersion in mineral oil, 74 mg, 1.84 mmol), was added to a solution of **14** (200 mg, 0.92mmol), dissolved in dry THF (10 ml). The mixture was stirred and heated to 70 ºC overnight. The solution became pale red in colour and was left to cool to room temperature, several drops of water were added, and the mixture left to stir for 30 min. The solvent was evaporated, and the residue was extracted with dichloromethane (2 x 20ml) and the extract was washed with water (30 ml). The combined organic layers were evaporated and the crude product was absorbed on silica and purified by column chromatography using ethyl acetate / cyclohexane (1:1), which was increased to 4:1. The separation gave three compounds (**18a, 18b, 18c**). Representative physical data and microanalysis are follows.

rac. N,N-Di(t-butoxycarbonyl)-1-(pyrid-2`-ylthio)propyl-2-amine **18a**



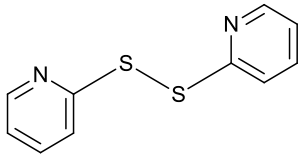
Pale yellow solid (22 mg, 6.5%). δ_H (400 MHz): 8.38 (1H, dd, J= 4.0, 6`-*H*), 7.44 (1H, m, Ar*H*), 7.14 (1H, m, Ar*H*), 6.99 (1H, m, Ar*H*), 4.53 (1H, m, 2-*H*), 3.52 (2H, m, 1-H_2), 1.43 (18H, s, 6 x CH_3), 1.39 (3H, d, J = 7.2, 3-H_3); δ_C (100 MHz): 157.1 (2 x N-*C*=O), 159.1, 149.1, 135.7, 122.3 & 119.5 (Ar-C_5), 82.0 (2 x *C*$(CH_3)_3$), 52.2 (2-*C*), 34.6 (1-*C*), 27.9 (6 x *C*H_3), 17.9 (3-*C*); ν_{max}: 3049, 2978, 1942, 1699, 1577, 1553, 1454, 1337, 1212, 1142, 1121, 1039, 985, 752 & 395 cm^{-1}; *m/z* (ESI) found: 369 $[M + H]^+$ other peaks at 759 [2M + Na], 269 [M – Boc]+, 213, 152 $[M – N(Boc)2]^+$; *m/z* HRMS (ESI) calcd for $[M + H]^+$, $C_{18}H_{28}N_2O_4S + H^+$ 369.1843; found: 369.1838.

rac. N-tert-butoxycarbonyl-1-(pyridin-2`-ylthio)prop-2-ylamine **18b**



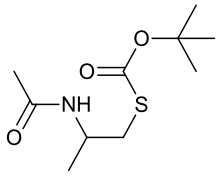
Pale yellow solid (148 mg, 60.0%); m.p. = 56 ºC. Anal. calcd for $C_{13}H_{20}N_2O_2S$: C, 58.20; H, 7.46; N, 10.44%; Found: C, 58.33; H, 7.41; N, 10.36%; δ_H (400 MHz): 8.40 (1H, d, J = 4.0, 6'-*H*), 7.46 (1H, m, ArH_1), 7.23 (1H, d, J = 8.0, ArH_1), 6.85 (1H, m, ArH_1), 5.49 (1H, s, N*H*), 3.95 (1H, m, 2-*H*), 3.30 (2H, m, 1-H_2), 1.39 (9H, s, 3 x CH_3), 1.25 (3H, d, J = 6.8, 3-H_3); δ_C (100 MHz): 155.4 (N-*C*=O), 158.7, 149.1, 135.9, 122.3 & 119.5, (Ar-C_5), 78.8 (*C*-$(CH_3)_3$), 47.1 (2-*C*), 36.0 (1-*C*), 28.3 (3 x *C*H_3), 20.3 (3-*C*); ν_{max}: 3359, 2973, 1678, 1581, 1519, 1415, 1167, 1154, 1125, 1059, 1053, 752, 578, 399 cm^{-1}; *m/z* (ESI) found: 269 $[M + H]^+$, $C_{13}H_{20}N_2O_2SH$, other peaks at 559 [2M+Na], 213, 152 ([M – NHBoc]+; *m/z* HRMS (ESI) calcd for $[M + H]^+$, $C_{13}H_{20}N_2O_2 + H^+$: 269.1318; Found: 269.1324.

Di(2-pyridyl)disulfide **18c**



liquid (10 mg, 4.9%). $C_{10}H_8N_2S_2$; δ_H (400 MHz): 8.45 (1H, d, J= 4.0, 2 x 6-*H*), 7.45 (1H, m, 2 x 4-*H*), 7.17 (1H, d, J = 8.4, 2 x 3-*H*), 6.97 (1H, m, 2 x 5-*H*); δ_C (100 MHz): 157.57, 149.63, 136.32, 122.23 & 120.24 (Ar-*C*5); *m/z* (EI) found: 220 $[M]^+$, 187, 156, 142, 110, 78.

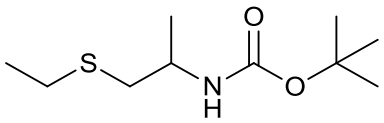
Preparation of N-acetyl-S-*t*-butoxycarbonyl-1-mercaptopropyl-2-amine 19.



Potassium thioacetate (116 mg, 1.01 mmol) was added to a solution of rac-3-t-butoxycarbonyl-4-methyloxazolidin-2-thione **14** (200 mg, 0.92 mmol) dissolved in dry DMF (20 ml) under anhydrous conditions. The mixture was stirred at 20 ºC for 12 h. After adding some drops of water, and stirring for 30 min, the mixture was concentrated in vacuo. The crude material was absorbed on to silica and purified by column chromatography (ethyl acetate /cyclohexane 1:4) to give N-acetyl-S-t-butoxycarbonyl-1-mercaptopropyl-2-amine **19** as a yellow liquid (70 mg, 32.6%), Anal. calcd. for $C_{10}H_{19}NO_3S$: C, 51.48; H, 8.21; N, 6.00%; Found: C, 51.33; H, 7.92; N, 5.92%; δ_H (400 MHz): 5.76 (1H, s, N*H*), 4.10 (1H, m, 2-*H*), 2.88 (2H, m, 1-H_2), 1.86 (3H, s, COCH_3), 1.43 (9H, s, 3 x CH_3), 1.14 (3H, d, J = 6.4, 3-H_3); δ_C (100 MHz): 169.84 (S-*C*=O), 169.54 (N-*C*=O), 85.31 (*C*-$(CH_3)_3$), 45.96 (2-*C*), 36.28 (1-*C*), 28.09 (3 x *C*H_3), 23.33 ((O=C)*C*H_3), 19.90 (-*C*H_3); ν_{max}: 3278, 2979, 1702, 1645, 1547, 1369, 1200, 1123, 838, 732 cm^{-1}; *m/z* (ESI) found: 234 $[M + H]^+$, other

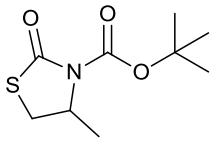
peaks at 200, 178 ([M + H]+ - C4H8), 156; *m/z* HRMS (ESI) calcd for $[M + H]^+$, $C_{10}H_{19}NO_3S$: 234.1158, Found: 234.1159.

Preparation of *rac* N-t-butoxycarbonyl-1-(ethylthio)propyl-2-amine 20



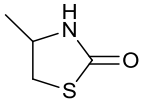
Compound **14** (200 mg, 0.92 mmol) and sodium ethanthiolate (336 mg, 4.0 mmol) were mixed in dry xylene (10 ml) and the mixture was stirred and irradiated in a microwave oven at 145 ^oC for 1 hours. After cooling to room temperature the reaction mixture was dissolved in dichloromethane (15 ml) and was washed with distilled water (2 x 10 ml). The organic layer was dried over sodium sulfate, and solvent removed in *vacuo*. The crude residue was purified by column chromatography using ethyl acetate / cyclohexane (1:2) as eluent to give *rac N-t-butoxycarbonyl-1-(ethylthio)propyl-2-amine* **20** as a pale yellow oil (116 mg, 57.6%). Anal. calcd for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.39%; found: C, 54.82; H, 9.49; N, 6.27%; δ_H (400 MHz): 4.59 (1H, s, N*H*), 3.76 (1H, m, 2-*H*), 2.84 (1H, dd, J = 7.4 & 14.2, 1-H_α), 2.63 (1H, dd, J = 7.2 & 14.2, 1-H_β), 2.50 (2H, m, CH_2), 1.37 (9H, s, 3 x CH_3), 1.20 (3H, t, J = 7.3, CH_3), 1.14 (3H, d, J = 6.8, 3-H_3); δ_C (100 MHz): 155.1 (N-*C*=O), 79.2 (*C*-$(CH_3)_3$), 45.9 (2-*C*), 38.4 (1-*C*), 28.3 (3 x *C*H_3), 26.7 (S-*C*H_2), 19.8 (3-*C*), 14.8 (*C*H_3); ν_{max}: 3332, 2972, 2928, 1689, 1506, 1365, 1246, 1166, 1048, 1025 cm^{-1}; *m/z* (ESI): 220 $[M +H]^+$, other peaks at 164 [M+H – C_4H_8], 146; *m/z* HRMS (ESI) calcd for $[M + H]^+$ $C_{10}H_{21}NO_2S$ + H: 220.1366; found: 220.1368.

Procedure D for preparation of 25



rac-3-t-Butoxycarbonyl-4-methyl-oxazolidin-2-thione **14** (200 mg, 0.92 mmol) and tetrabutylammonium iodide (339 mg, 0.92mmol) were dissolved in dry xylene (10 ml) and the mixture was stirred and irradiated in a microwave oven at 145 ^{o}C for 1 h. After cooling to room temperature the reaction mixture was dissolved in dichloromethane (15 ml) and was washed with distilled water (2 x 10 ml). The organic layer was dried over sodium sulfate, and solvent removed in *vacuo*. The crude residue was purified by column chromatography using ethyl acetate / cyclohexane (1:2) as eluent to give *N-t-butoxycarbonyl-4-methyl-1,3-thiazolidin-2-one* **25** as a white solid (114 mg, 57.0%), which was crystallized from ethyl acetate. m.p. = 77 - 78 ºC; anal. calcd for $C_9H_{15}NO_3S$: C, 49.7; H, 7.0; N, 6.4%; found: C, 49.7; H, 7.0; N, 6.3 %; δ_H: 4.53 (1H, m, 4-*H*), 3.51 (1H, m, 5-H_α), 2.73 (1H, m, 5-H_β), 1.45 (9H, s, 3 x CH_3), 1.35 (3H, d, J=6.2, 4-CH_3); δ_C (100 MHz): 169.6 (2-*C*), 148.5 (N-*C*=O), 83.3 (*C*$(CH_3)_3$), 54.6 (4-*C*), 31.6 (5-*C*), 27.7 (3 x *C*H_3), 18.7 4-CH_3; ν_{max}: 2977, 1755, 1672, 1369, 1354, 1326, 1278, 1245, 1169, 1147, 942, 859, 768, 672, 548 cm^{-1}; *m/z* (ESI) found: 235 (35%) $[M + NH_4]^+$, 218 (15%) $[M + H]^+$, 162 (100%) $[M+NH_4 - C_4H_9O]$, 144; *m/z* HRMS (ESI) calcd for $[M + NH_4]^+$, $C_9H_{15}NO_3S + NH_4$: 235.1111; found: 235.1114.

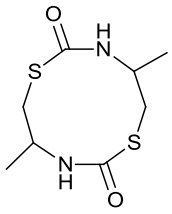
Rearrangement of 13 with tetrabutylammonium iodide



Prepared following procedure **D**. Bu_4NI (550 mg, 1.7 mmol) was added to a solution of rac 4-methyl-1,3-oxazolidine-2-thione **13** (200 mg, 1.7 mmol) dissolved in dry xylene (10ml).

The mixture reaction was stirred for 30 min. The glass tube was placed in an alumina bath inside the microwave oven (CEM Discover SP), and irradiated so that the internal temperature reached 145 °C for 1 h. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered, the solvent was evaporated and the crude compound was adsorbed on silica gel and purified by column chromatography using a mixture of cyclohexane and ethyl acetate (3 : 1) which afforded the pure *rac 4-methyl-1,3-thiazolidine-2-one* **26** as a yellow oil (190 mg, 95%). Anal. calcd for C_4H_7NOS: C, 41.00; H, 6.02; N, 11.95%; found: C, 41.02; H, 6.03; N, 11.89%; δ_H (400 MHz, $CDCl_3$): 7.07 (1H, br-s, N*H*), 3.95 (1H, hex, J = 7.2, 4-*H*), 3.42 (1H, dd, J = 7.0, 10.8, 5-Hα), 2.96 (1H, dd, J =7.2, 10.8, 5-H_β), 1.28 (3H, d, J = 6.3, -CH_3); δ_C (100 MHz, $CDCl_3$): 175.4 (2-*C*), 51.2 (4-*C*), 36.4 (5-*C*), 20.3 (*C*H_3); ν_{max}: 3230, 2971, 1654, 1355, 1217 and 684 cm^{-1}; *m/z* (GC-EIP) C_4H_7NOS $[M]^+$ found: 117 other peaks at 102 $[M - CH_3]^+$, 74 [M – NHCO]+, 59 $[M +1 – CH_2NHCO]^+$, 47, 45, 41; *m/z* HRMS (GC-EIP) calcd for C_4H_7NOS $[M]^+$: 117.0243; Found: 117.0241.

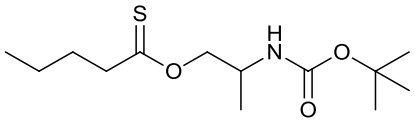
Rearrangement 13 with tetrabutylammonium iodide



Using procedure **D**, but using a much smaller amount of dry xylene (2 ml) and 1.5 eq. Bu_4NI to obtain *rac 4,9-dimethyl-1,6,3,8-dithiadiazocyclodecane-2,7-dione* **27** as a pale brown oil (110 mg, 27.7%). Anal. calcd for $C_8H_{14}N_2O_2S_2$: C, 41.00; H, 6.02; N, 11.95%; found: C, 41.14; H, 6.03; N, 11.89%; δ_H (400 MHz $CDCl_3$): 6.72 (2H, br-s, 2 x N*H*), 3.87 (2H, m, 4-, 9-*H*), 3.64 (2H, dd, J = 7.0, 5-,10-H_α), 3.17 (2H, dd, J =6.4, 5-,10-H_β), 1.28 (2 x 3H, d, J = 6.7, 2 x CH_3); δ_C (100 MHz, $CDCl_3$): 176.2 (2 x *C*=O), 50.6 (4-,9-*C*), 41.6 (5-

,10-*C*), 20.8 (2 x *C*H_3); ν_{max}: 3231, 2966, 1869, 1661, 1215, 1060, 681 and 615 cm^{-1}; *m/z* (ESI) $C_8H_{14}N_2O_2S_2H$ $[M + H]^+$ found: 235 other peaks at 201, 158, 140. *m/z* HRMS (ESI) calcd for $C_8H_{14}N_2O_2S_2H$ $[M + H]^+$ 235.0569, Found: $[M + H]^+$ 235.0571.

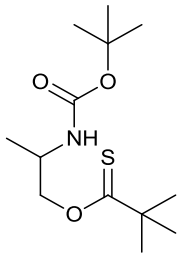
Procedure E for preparation of 28.



n-Butyllithium (2.5 M in hexane, 0.37 ml, 0.92 mmol) was added to a stirred solution of rac-3-t-butoxycarbonyl-4-methyloxazolidin-2-thione **14** (200 mg, 0.92mmol) in anhydrous tetrahydrofuran (20 ml), under a nitrogen atmosphere at -78 ºC, and the solution was stirred under anhydrous conditions. The solution was allowed to warm to 20 ºC and was stirred overnight and became yellow. After adding some drops of a mixture of THF and water, and stirring for 30 min, the solvent was evaporated, the residue was extracted with dichloromethane (2 x 20 ml) and the extract was washed with water (30ml). The organic layer was evaporated and the resulting residue was chromatographed on silica using ethyl acetate / cyclohexane (1:2) to give the product *O-2`-(tert-butoxycarbonylamino)propyl pentanethioate* **28** (116 mg, 45.9%) as a yellow liquid. Anal. calcd for $C_{13}H_{25}NO_3S$: C, 56.72; H, 9.09; N, 5.09%; found: C, 56.68; H, 9.15; N, 5.05%; δ_H (400 MHz, CD_3OD): 4.85 (1H, s, N*H*), 4.36 (1H, m, 1-H_α), 4.25 (1H, m, 1-H_β), 4.00 (1H, m, 2-*H*), 2.72 (2H, m, 2`-C$H_2$), 1.70 (4H, m, 3`-,4`-C$H_2$), 1.41 (9H, s, 3 x C$H_3$), 1.16 (3H, d, J = 6.8, 3-$H_3$), 0.90 (3H, t, J = 6.8, 5`-H_3); δ_C (100 MHz CD_3OD): 224.18 (*C*=S), 157.29 (N-*C*=O), 78.7 (*C*$(CH_3)_3$), 74.3 (1`-*C*), 46.78 (2`-*C*), 45.38 (2-*C*), 31.74 (3-*C*), 27.48 (3 x *C*H_3), 21.61 (4-*C*), 16.31 (3`-*C*), 12.85 (5-*C*), ν_{max}: 3328, 2961, 2933, 1683, 1409, 1366, 1248, 1175, 1077, 982, 778 cm^{-1}; *m/z* (EI) found: 276 $[M + H]^+$ $C_{13}H_{25}NO_3SH$, other peaks at 260, 220, 204,

186, 180, 160; *m/z* HRMS (EI) calcd for $[M + H]^+$ $C_{13}H_{25}NO_3S + H^+$: 276.1629; found: 276.1631.

Preparation of 29

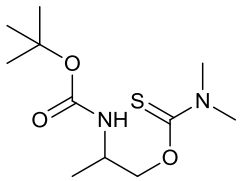


Prepared following procedure **E**, but using tert-butyllithium (1.6 M in pentane, 0.7ml, 1.1 mmol). The product was isolated by flash column chromatography on silica gel using cyclohexane : ethyl acetate (80 : 20) to give *(N-t-butoxycarbonyl)-2`-aminopropyl 2,2-dimethylthionopropionate* **29** ( 240 mg, 94.8%) as a yellow solid, m.p. = 67-68 ºC. Anal. calcd for $C_{13}H_{25}NO_3S$: C, 56.69; H, 9.15; N, 5.09%; found: C, 57.0; H, 9.21; N, 4.96%. $\delta_H$ (400 MHz): 4.47 (1H, s, N*H*), 4.27 (1H, m, 2`-*H*), 3.98 (1H, m, CH_αO), 3.91 (1H, m, CH_βO), 1.37 (9H, s, 3 x CH_3), 1.23 (9H, s, 3 x CH_3), 1.14 (3H, d, J = 6.8, -3`-$H_3$); $\delta_C$ (100 MHz): 231.14 (*C*=S), 154.98 (N-*C*=O), 81.50 (O-*C*$(CH_3)_3$), 74.85 (1`-*C*), 67.01 (*C*$(CH_3)_3$), 47.34 (2`-*C*), 29.66 (O-C-(*C*$H_3)_3$), 28.34 (C-$(CH_3)_3$), 17.95 (*C*H_3); ν_{max}: 3314, 2975, 1681, 1539, 1368, 1255, 1211, 1163, 1114, 1059, 658 cm^{-1}; *m/z* (ESI) found: 276 $[M + H]^+$; *m/z* HRMS (ESI) calcd for $[M + H]^+$, $C_{13}H_{26}NO_3S$: 276.1628 $[M + H]^+$ found 276.1629.

Preparation of 30

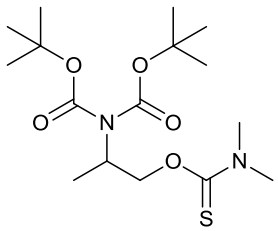
Prepared following procedure **E**, but using lithium dimethylamide (1.0 ml, 5 wt. % in hexane, 0.92 mmol). The product was isolated by flash column chromatography on silica gel using cyclohexane : ethyl acetate (4 : 1) The separation gave two compounds [**30a** and **30b**].

N-t-Butoxycarbonyl-O-(dimethyl aminothiocarbonyl)-2-aminopropanol **30a**



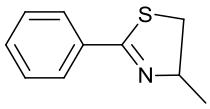
(75 mg, 31.1%) as a yellow solid, m.p. = 87 ºC. δ_H (400 MHz): 4.55 (1H, br-s, N*H*), 4.29 (1H, m, 2-*H*), 4.02 (2H, m, 1-H_2), 3.29 (3H, s, N-CH_3), 3.06 (3H, s, N-CH_3), 1.36 (9H, s, 3 x CH_3), 1.13 (3H, d, J = 6.8, -CH_3); δ_C (100 MHz): 189.59 (*C*=S), 155.10 (N-*C*=O), 79.19 (*C*$(CH_3)_3$), 76.67 (1-*C*), 45.98 (2-*C*), 42.72 (N-*C*H_3), 37.75 (N-*C*H_3), 28.30 (C(*C*$H_3)_3$), 17.71 (3-C); ν_{max}: 3357, 2977, 1684, 1526, 1366, 1271, 1163, 1025, 634, 549 cm^{-1}; *m/z* HRMS (ESI) calcd for $[M + H]^+$ $C_{11}H_{23}N_2O_3S$: 263.1424, found 263.1420, other peaks at 207.0793 (50%) [M+H – C_4H_8], 525.2757 (75%) [2M + H].

N,N-Di(t-Butoxycarbonyl)-O-(dimethyl aminothiocarbonyl)-2-aminopropanol **30b**



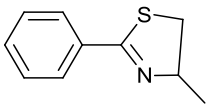
(103 mg, 30.9%) as a yellow solid, m.p. = 100 - 102 ºC. Anal. Calcd. for $C_{16}H_{30}N_2O_5S$: C, 53.01; H, 8.34; N, 7.73%; found: C, 53.28; H, 8.47; N, 7.60%; δ_H (400 MHz): 4.55 (1H, m, 2-C), 4.52 (2H, m, 1-H_2), 3.27 (3H, s, N-CH_3), 3.01 (3H, s, N-CH_3), 1.42 (18H, s, 6 x CH_3), 1.24 (3H, d, J = 6.8, -CH_3); δ_C (100 MHz): 187.59 (*C*=S), 152.79 (2 x N-*C*=O), 82.19 (2 x *C*$(CH_3)_3$), 72.18 (1-*C*), 50.99 (2-*C*), 42.54 (N-*C*H_3), 37.62 (N-*C*H_3), 27.89 (2 x C(*C*$H_3)_3$), 15.16 (3-*C*); ν_{max}: 2977, 1743, 1690, 1366, 1352, 1276, 1200, 1123, 1020, 766, 457, 430 cm^{-1}; *m/z* HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{31}N_2O_5S$: 363.1948; found: 363.1940, other peaks at 307.1316 (50%) [M + H – C_4H_9], 263.1419 (100%) [M + H – Boc], 207.0791 (90%) [M + H – (C_4H_8-Boc)], 146.0440 (20%).

Preparation of 13



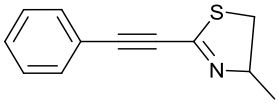
Prepared following procedure E, but using phenyl lithium (1.8 M in diethyl ether, 0.52 ml, 0.92mmol). The product was isolated by flash column chromatography on silica gel using cyclohexane : ethyl acetate (2 : 1) to give *4-methyl-2-phenylthiazoline* **32** (155 mg, 95.0%) as a yellow oil. δ_H (400 MHz): 7.83 – 7.81 (2H, m, 2`-,6`-H), 7.39 – 7.36 (3H, m, 3`-, 4`-, 5`-*H*), 4.72 (1H, m, 4-*H*), 3.46 (1H, dd, J= 6.8 & 8.4, 5-H_α) 2.98 (1H, dd, J = 7.2 & 8.4, 5-H_β), 1.43 (3H, d, J = 6.2, 4-CH_3); δ_C (100 MHz): 166.1 (2-*C*), 133.1, 130.8, 128.2 and 128.1 (Ar-C_6), 72.7 (4-*C*), 39.6 (5-*C*), 20.2 (4-*C*H_3); v_{max}: 2967, 1605, 1446, 1300, 1249, 1107, 948, 765, 690, 612, 396 cm^{-1}; *m/z* (ESI): 178 $[M + H]^+$, other peaks at 177 (80%) $[M]^+$, 162 (40%) [M – CH_3], 131(30%) [M – C_3H_6N], 77 (30%) [M – C_6H_5], 74 (100%); *m/z* HRMS (ESI) calcd for [M + H]+ $C_{10}H_{12}NS$: 178.0683 found: 178.0679.

Preparation of 32



Prepared following procedure E, but using phenylmagnesium bromide (3.0 M in diethyl ether, 0.31ml, 0.92 mmol). The product was isolated by flash column chromatography on silica gel using cyclohexane : ethylacetate (100 : 50) to give *4-methyl-2-phenylthiazoline* **32** (63 mg, 38.6%) as a yellow oil.

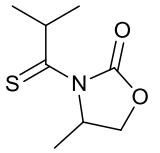
Preparation of 33



Prepared following procedure E, but using lithium phenylacetylide (1.0 M in THF, 1.0 ml, 0.92 mmol). The product was purified by flash column chromatography using cyclohexane/ethyl acetate (2:1) to yield the *rac 4-methyl-2-(phenylethynyl) thiazoline* **33** as

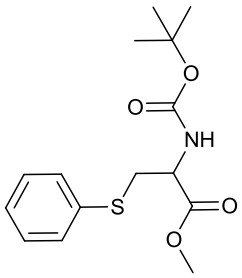
a yellow oil (110 mg, 59.5%), δ_H (400 MHz): 7.44 (2H, d, J= 7.8, ortho Ar*H*$_2$), 7.27 (2H, t , J = 7.8, meta Ar*H*$_2$), 7.25 (1H, t, J = 7.2, para Ar*H*), 4.57 (1H, m, 4-C*H*), 3.44 (1H, dd, J= 7.0 & 8.3, C*H*$_\alpha$), 2.96 (1H, dd, J = 6.8 & 8.3, 5-C*H*$_\beta$), 1.43 (3H, d, J= 6.2, 4-C*H*$_3$); δ_C (100 MHz): 163.5 (2-*C*), 132.1, 129.8, 128.3 and 122.7 (Ar-*C*$_6$), 93.0 (sp *C*), 81.9 (sp *C*) 72.5 (4-*C*), 40.6 (5-*C*), 20.0 (4-*C*H$_3$); ν_{max}: 2980, 2210, 1704, 1369, 1299, 1205, 1149, 756, 689 cm^{-1}; *m/z*: GC-MC found: 201 $[M]^+$ other peaks at 186 (25%) [M – CH_3], 155 (40%) [M – SCH_2], 127 (70%) [M – C_3H_6S], 100 (20%) [M – C_8H_5], 74 (100%) [M – C_9H_5N]; HRMS: *m/z* (ESI) calcd for $[M + H]^+$ $C_{12}H_{11}NSH$: 202.0692 found: 202.0685.

.**Preparation of 34**



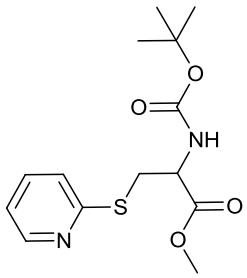
Prepared following procedure **E**, but using isopropylmagnesium chloride (2.0 M in THF, 0.50 ml, 0.92 mmol). The product was purified by column chromatography cyclohexane : ethyl acetate (2:1) to give *3-(2`-methylpropanethioyl)-4-methyl-1,3-oxazolidin-2-one* **34** (80 mg, 47 %) as a yellow oil, $\delta_H$ (400 MHz): 5.13 (1H, m, 4-*H*), 4.35 (1H, m, 2`-*H*), 4.37 (1H, m, 5-*H*$_\alpha$), 3.99 (1H, dd, J = 1.8 & 8.6, 5-*H*$_\beta$), 1.42 (3H, d, J = 6.3, 4-C*H*$_3$), 1.16 (6H, d, J = 6.4, 2 x -C*H*$_3$); δ_C (100 MHz): 219.53 (*C*=S), 150.38 (2-*C*), 68.40 (5-*C*), 55.82 (4-*C*), 38.38 (S=C-*C*H), 24.00 (-*C*H$_3$), 23.45 (-*C*H$_3$), 17.65 (4-*C*H$_3$); ν_{max}: 2973, 1777, 1371, 1312, 1242, 1161, 1120, 1046, 914, 761, 698 cm^{-1}; *m/z* (EI) found: 187 $[M]^+$, other peaks at 110 (40%) [M – C_3H_9S], 86 (100 %) [(M+H) - $C_4H_6NO_2$], 41(50%) [(M+H) - $C_5H_6NO_2S$]; *m/z* HRMS (EI) calcd for $[M]^+$ $C_8H_{13}NO_2S$: 187.0662; found: 187.0663.

The Synthesis of methyl -2-N-t-Butoxycarbonylamino-3-(phenylthio)propanoate 35



Sodium hydride (60% dispersion in mineral oil, 71mg, 1.78 mmol) was added to anhydrous methanol (10 ml) and the mixture stirred at room temperature for 30 min. Dry thiophenol (0.28ml, 2.67mmol) was added and the mixture was stirred for a further 30 min after which time thionocarbamate **16** (261 mg, 1.0 mmol) was added. After stirring at room temperature overnight a white slurry was obtained which was filtered then washed with diethyl ether and dried. The filtrate was then neutralized water was added, the whole was extracted with diethyl ether, concentrated in *vacuo*. Final purification was achieved by flash column chromatography with ethyl acetate as eluent to give the desired product in the second fraction as a clear oil, *rac methyl 2-((tert-butoxycarbonyl)amino)-3-(phenylthio)propanoate* **35** (216 mg, 69.5%). Anal. calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%; found: C, 57.85; H, 6.81; N, 4.41%; δ_H (400 MHz): 7.39 – 7.15 (Ar-H_5), 5.32 (1H, s, N*H*), 4.48 (1H, m, -C*H*), 3.66 (1H, dd, J = 4.7 , 7.4, 2-*H*), 3.50 (3H, s, -OCH_3), 3.34 (2H, m, 3-H_2), 1.43 (9H, s, 3 x CH_3); δ_C (100 MHz): 170.8 (1-*C*), 154.8 (N-*C*=O), 134.81 (ipso-*C*), 130.51 (2 x meta-*C*), 129.00 (2 x ortho-*C*), 126.79 (para-*C*), 79.94 (*C*-$(CH_3)_3$), 53.73 (2-*C*), 52.14 (-O*C*H_3), 37.0 (3-*C*), 28.2 (3 x *C*H_3); ν_{max}: 3373, 2977, 1746, 1712, 1499, 1438, 1366, 1161, 1053, 1011, 742 and 691 cm^{-1}; *m/z* (EI) found: 311 $[M]^+$ $C_{15}H_{21}NO_4S$, other peaks at 193, 122, 56; *m/z* HRMS (EI) calcd for $[M]^+$ $C_{15}H_{21}NO_4S$: 311.1186, found: 311.1183.

Preparation of methyl N-t-butoxycarbonyl-2-amino-3-(pyridin-2-ylthio)propanoate 36

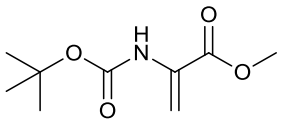


A solution of the sodium salt of 2-mercaptopyridine in dry THF (15ml), formed from 2-mercaptopyridine (122 mg, 1.1 mmol) and sodium hydride (60% dispersion in mineral oil, 71 mg, 1.78 mmol), was added to a solution of thionocarbamate **16** (261 mg, 1.0 mmol). After stirring at room temperature overnight, drops of 20% acetic acid were added, and the mixture left to stir for 30 min. The solvent was evaporated, and the residue was extracted with dichloromethane (2 x 20 ml) and the extract was washed with water (30 ml). The combined organic layers were evaporated and the crude product was absorbed on silica and purified by column chromatography using ethyl acetate / cyclohexane (2:1), to furnish the final product as a yellow oil, *rac methyl 2-((tert-butoxycarbonyl)amino)-3-(pyridin-2-ylthio)propanoate* **36** (177 mg, 56.7%). Anal. calcd for $C_{14}H_{20}N_2O_4S$: C, 53.62; H, 6.45; N, 8.97%, found: C, 53.62; H, 6.47; N, 8.88%. δ_H (400 MHz): 8.32 (1H, d, J = 4.0, 6`-*H*), 7.41 (1H, m, 4`-*H*), 7.14 (1H, d, J = 8.0, 3`-*H*), 6.94 (1H, m, 5`-*H*), 6.26 (1H, s, N*H*), 4.50 (1H, m, 2-*H*), 3.63 (3H, s, -OCH_3), 3.55 (2H, m, 3-H_2), 1.33 (9H, s, 3 x CH_3); δ_C (400 MHz): 171.4 (1-*C*), 158.8 (N-*C*=O), 149.7 (ipso-*C*), 137.1 (2 x meta-*C*), 121.9 (2 x ortho-*C*), 119.5 (para-*C*), 79.94 (*C*-$(CH_3)_3$), 54.4 (2-*C*), 52.2 (-O*C*H_3), 31.9 (3-*C*), 28.2 (3 x *C*H_3); ν_{max}: 3352, 2961, 1744, 1711, 1578, 1454, 1416, 1365, 1258, 1164, 1017, 797, 761 and 401 cm^{-1}; *m/z* (EI) found: 312 $[M]^+$ $C_{15}H_{21}N_2O_4S$, other peaks at 239, 219, 196, 156, 135, 123, 110, 83, 56, and 48; *m/z* HRMS (EI) calcd for $[M]^+$ $C_{15}H_{21}NO_4S$: 312.1138, found: 312.1136.

Preparation of 37a and 37b

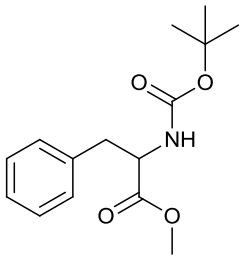
Phenyllithium (84mg, 0.56 ml, 1.1 mmol) was added to a stirred solution of thionocarbamate **16** (261 mg, 1.0 mmol) in anhydrous tetrahydrofuran (15 ml), under a nitrogen atmosphere at -78 ºC, and the solution was stirred under anhydrous conditions. The solution was allowed to warm to 20 ºC and was stirred overnight and became yellow. After adding some drops of a mixture of THF and water, and stirring for 30 min, the solvent was evaporated, the residue was extracted with dichloromethane (2 x 20 ml) and the extract was washed with water (30 ml). The organic layer was evaporated and the resulting residue was chromatographed on silica using ethyl acetate / cyclohexane (1:2) to give the products **37a** and **37b**.

2-tert-Butoxycarbonylamino-acrylic acid methyl ester **37a**



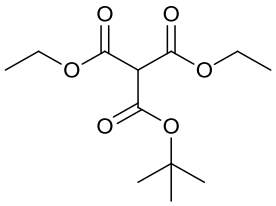
Yellow oil (105 mg, 52.3%). Anal. calcd for $C_9H_{15}NO_4$: δ_H (400 MHz): 6.96 (1H, s, N*H*), 6.10 (1H, br s, 3-H_α), 5.65 (1H, d, J= 1.5, 3-H_β), 3.74 (3H, s, -OCH_3), 1.31 (9H, s, 3 x CH_3), δ_C (100 MHz): 164.4 (1-*C*), 152.4 (N-*C*=O), 131.2 (2-*C*), 105.1 (3-*C*), 80.6 (C-$(CH_3)_3$), 52.7 (-O*C*H_3), 28.2 (3 x *C*H_3); ν_{max}: 3356, 2973, 1741, 1700, 1510, 1366, 1222, 1151, 1055, 1018, 751, 699, 498 and 382 cm^{-1}.

Methyl 2-((tert-butoxycarbonyl)amino)-3-phenylpropanoate **37b**



Pale yellow solid (81 mg, 29.1%), m.p. = 89 - 91 ºC. Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.00%; found: C, 64.42; H, 7.63; N, 4.95%; δ_H (400 MHz): 7.11 – 7.28 (Ar-H_5), 5.14 (1H, s, N*H*), 4.58 (1H, m, 2-*H*), 3.69 (3H, s, OCH_3), 3.16 (2H, m, 3-H2), 1.39 (9H, s, 3 x CH_3) δ_C (100 MHz): 172.0 (1-C), 155.1 (N-*C*=O), 135.9 (ipso-*C*), 129.2 (2 x meta-*C*), 128.5 (2 x ortho-*C*), 126.9 (para-*C*), 79.9 (*C*-$(CH_3)_3$), 54.3 (2-*C*), 52.2 (O*C*H_3), 38.3 (3-*C*), 28.2 (3 x *C*H_3); ν_{max}: 3356, 2973, 1741, 1700, 1510, 1366, 1222, 1151, 1055, 1018, 751, 699, 498 and 382 cm^{-1}; *m/z* (ESI) found: 302 $[M + Na]^+$ $C_{15}H_{21}NO_4Na$, other peaks at 180 and 149.

Preparation of 38.



Prepared following general procedure **A**. A solution of the sodium salt of diethyl malonate in dry THF (15ml), formed from diethyl malonate (148 mg, 0.14 ml, 0.92 mmol) and sodium hydride (60% in oil, 74mg, 1.84 mmol), was added to a solution of thionocarbamate **14** (200 mg, 0.92 mmol), in dry THF (10 ml). The mixture was stirred and heated to 70 ºC for 12 hours. The solution became a clear pale red liquid and was left to cool to room temperature, and some drops of water were added, and the mixture left to stir for 30 min. The solvent was removed in *vacuo* at room temperature. The residue was extracted with dichloromethane (2 x 20 ml) and the extract was washed with water. The organic layer was evaporated in *vacuo*. The crude product was absorbed on silica and purified by column chromatography using ethyl acetate / cyclohexane (2:1). The separation gave *t-butyl diethyl methanetricarboxylate* **38**, as a yellow oil (21 mg, 8.8%). Anal. calcd

for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69%; found: C, 55.37; H, 7.71%; δ_H (400 MHz): 4.24 (1H, s, C*H*), 4.18 (4H, q , J = 7.0, 2 x CH_2), 1.42 (9H, s, 3 x CH3), 1.23 (6H, t, J = 7.0, 2 x CH_3); δ_C (100 MHz): 164.3 (2 x *C*=O), 162.6 (*C*(=O)OtBu), 83.4 (*C*-$(CH_3)_3$), 62.2 (2 x *C*H_2), 60.0 (*C*H), 27.7 (3 x *C*H_3), 13.9 (2 x *C*H_3); *m/z* GC-CIP(NH_3) found: 278 [M + $NH_4]^+$, $C_{12}H_{20}O_6$ + NH_4^+, other peaks at 220 [M – $C_4H_9CH_2$ + NH_3, 100], 205 [M – $CO_2C_2H_5$ + NH_4, 10], 178 [M-Boc + NH_4+, 45], 161.

X-ray Crystallography.

Data was collected with MoKα radiation at 120-150 K on a Bruker Nonius diffractometer equipped with a rotating anode source, and a 95 mm CCD camera by the EPSRC National X-ray Crystallography Service at Southampton University for **11** and **14** or on an Agilent Xcalibur diffractometer equipped with a Sapphire detector at Nottingham Trent University for **17**, **31** and **35-37**. Structures were solved and refined with SHELXS and SHELXL suite of programs[25] using the XSEED[26] interface, and molecular illustrations are prepared with Mecury[27] and POV-RAY.[28] Cif files will be deposited at the CCDC when the work is published.

Crystal data for **12**: $C_{11}H_{13}NSO$, M_r = 207.3, orthorhombic, *a* = 19.5407(9), *b* = 8.0050(4), *c* = 6.7851(3) Å, *V* = 1061.35(9) Å^3, $P2_12_12$, *Z* = 4, $D_{calc.}$ = 1.297 g cm^{-3}, T = 120 K, μ = 0.271 mm^{-1}, F(000) = 440, 2439 unique reflections, 2242 with I > 2σ(I), max. (sin θ)/λ = 0.65 Å^{-1}, final R = 0.027, wR = 0.069. Crystals from dichloromethane.

Crystal data for **14**: $C_9H_{15}NSO_3$, M_r = 217.2, monoclinic, *a* = 7.4816(2), *b* = 15.2728(4), *c* = 9.6621(3) Å, β = 97.115(2)°, *V* = 1095.54(5) Å^3, $P2_1/a$, *Z* = 4, $D_{calc.}$ = 1.317 g cm^{-3}, T = 120 K, μ = 0.278 mm^{-1}, F(000) = 464, 2506 unique reflections, 2183 with I > 2σ(I), max. (sin θ)/λ = 0.65 Å^{-1}, final R = 0.029, wR = 0.070. Crystals from ethyl acetate.

thiazoline

Crystal data for **26**: $C_9H_{15}NO_3S$, M_r = 217.3, monoclinic, a = 9.6972 (6), b = 6.7661 (3), c = 17.4884(10) Å, β = 100.177 (3)°, V = 1129.40(11) Å^3, $P2_1/n$, Z = 4, $D_{calc.}$ = 1.28 g cm^{-3}, T = 120 K, μ = 0.270 mm^{-1}, *F(000)* = 464, 2390 unique reflections, 1996 with I > 2σ(I), final R = 0.052, wR = 0.119. Crystals from ethyl acetate.

Tbutyl compound

Crystal data for **29**: $C_{13}H_{25}NO_3S$, M_r = 275.4, monoclinic, a = 11.4804(3), b = 9.9540(3), c = 28.7919(8) Å, β = 90.00(3)°, V = 3290.22(16) Å^3, $P2_1/c$, Z = 8, $D_{calc.}$ = 1.11 g cm^{-3}, T = 150 K, μ = 0.198 mm^{-1}, F(000) = 1200, 7791 unique reflections, 5508 with I > 2σ(I), final R = 0.064, wR = 0.15. Twinned crystal, twin law 1 0 0 0 -1 0 0 0 -1, with 0.41:0.59 distribution. Crystals from ethyl acetate.

N-Boc amide

Crystal data for **30a**: $C_{11}H_2N_2O_3S$, M_r = 262.37, monoclinic, a = 13.1321(4), b = 11.0452(3), c = 10.1525(3) Å, β = 100.532(3)°, V = 1447.78(7)Å^3, $P2_1/c$, Z = 4, $D_{calc.}$ = 1.20 g cm^{-3}, T = 150 K, μ = 0.223 mm^{-1}, *F(000)* = 568, 3569 unique reflections, 2818 with I > 2σ(*I*), final R = 0.039, wR = 0.11. Crystals from ethyl acetate.

N-diBocamide

Crystal data for **30b**: $C_{16}H_{30}N_2O_5S$, M_r = 362.48, monoclinic, a = 5.9611(2, b = 19.2487(6), c = 17.6222(5) Å, β = 94.909(3)°, V = 2014.61(11)) Å^3, $P2_1/n$, Z = 4, $D_{calc.}$ = 1.19 g cm^{-3}, T = 150 K, μ = 0.186 mm^{-1}, *F(000)* = 784, 4614 unique reflections, 3514 with I > 2σ(*I*), final R = 0.040, wR = 0.010. Crystals from ethyl acetate.

2.4: Future Work

The chemistry of thionocarbamates has already been investigated in this PhD project, in particular their reaction with nucleophiles. The aim now is to build on the chemistry of the related thionocarbonates, and to investigate the synthesis of vic-dithiols, a rare group of materials, via a combination of thionocarbonate chemistry and thionations. This chemistry is designed to take advantage of the increasing availability of vic-diols by asymmetric dihydroxylation, as well as from the chiral pool. Apart from the initial work discovered in first year, this area has hardly been explored. There are very few enantiopure vic-dithiols readily available, yet they are important building blocks for chiral heterocyclic chemistry, for preparing chiral thiocrown ethers and will be useful resolution agents for chiral aldehehydes and ketones. One of the simplest chiral dithiols, ent-butane-2,3-dithiol, requires a four step synthesis with harsh reagents from the corresponding chiral diol though it has been made via the corresponding bis tosylate and trithiocarbonate in 3 steps.

Further work will involve functionalisations of compounds with more than two hydroxyl groups, e.g. four or six hydroxyl groups.

2.5: References

1. S. Y. Ko, *J. Org. Chem.*, **1995**, *60*, 6250.
2. M. Alpegiani and S. Hanessian, *J. Org. Chem*., **1987**, *52*, 278
3. H. S. Rho, *Synth. Commun*., **1998**, *28*, 843.
4. G. Y. Cho and S. Y. Ko. *J. Org. Chem.*, **1999**, *64*, 8745.
5. L. Faissat, C. Chavis, J-L. Montéro and M. Lucas. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1253.
6. Y. Gao and K. B. Sharpless, *J. Amer. Chem. Soc.*, **1988**, *110*, 7538-7539; B.B. Lohray, *Synthesis*, **1992**, 1035.
7. M.K. Pound, D.L. Davies, M. Pilkington, M.M. de Pina Vaz Sousa and J.D. Wallis, *Tetrahedron Lett*., **2002**, 43, 1915.
8. J. D. Wallis, A. Karrer and J. D.Dunitz, *Helv. Chim. Acta*, **1986**, *69*, 69.
9. R. Oi and K. B. Sharpless, *Tetrahedron Lett.*, ***1991***, *32*, 999.
10. B. B. Lohray, Y. Gao and K. B. Sharpless, *Tetrahedron Lett*., **1989**, *30*, 2623.
11. M. Pilkington and J. D. Wallis, *J. Chem. Soc. Chem. Commun.*, **1993**, 1857.
12. J. E. Baldwin, A. C. Spivey and C. J. Schofield, *Tetrahedron Asymmetry*, **1990**, *1*, 881.
13. M.T. Crimmins, B. W. King and E.A. Tabet, *J. Amer. Chem. Soc*, **1997**, *119*, 7883.; E. Fujita and Y. Nagao, *Adv. Het. Chem*., **1989**, *45*, 1-36; M. El Sous, D. Ganame, P.A. Tregloan and M.A. Rizzacasa, *Org. Lett.*, **2004**, *6*, 3001.
14. M.C. Willis, G.A. Cutting, V. J.-D, Piccio, M.J. Durbin and M.P. John, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1543.
15. K. Blazewska and T. Gajda, *Tetrahedron*, **2004**, *60*, 11701.
16. G. T. Notte, T. Sammakia and P.J. Steel, *J. Amer. Chem. Soc.*, **2005**, *127*, 13502.

17. J. M. Garcia Fernandez, C.O. Mellet and J. Fuentes, *J. Org. Chem*., **1993**, *58*, 5192.

18. D. E. Ward and B.F. Kaller, *J. Org. Chem*., **1994**, *59*, 4230.

19. B. K. Goering and B. Ganem, *Tetrahedron Lett*., **1994**, *35*, 6997.

20. Y. Wu, Y.-Q. Yang and Q. Hu, *J. Org. Chem*., **2004;** *69*, 3990.

21. M. T. Crimmins, B. W. King, E.A. Tabet and K. Chaudhary, *J. Org. Chem*., **2001**, *66*, 894.

22. D. L. Davies and J. D. Wallis, unpublished work.

23. S. Kitoh, K.-K. Kunimoto, N. Funaki, H. Senda, A. Kuwae and K. Hanai, *J. Chem. Cryst*., **2002**, *32*, 547.; T. Gray, C.E. Laplaza and R.J. Staples, *Z. Krist. – New. Cryst. Struct.*, **1999**, *214*, 230 & 410; S. Kitoh, H. Senda and K. Kunimoto, *X-Ray Struct. Anal. Online*, **2003**, *19*, x15-x16.

24. A. Nagai, T. Miyagawa, H. Kudo and T. Endo, *Macromolecules,* **2003**, *36*, 933.

25. G.M. Sheldrick, *Acta Crystallogr*. *Sect. A*, **2008**, *64*, 112.

26. L. J. Barbour, "X-Seed - A software tool for supramolecular crystallography", *J. Supramol. Chem.*, **2001**, *1*, 189.

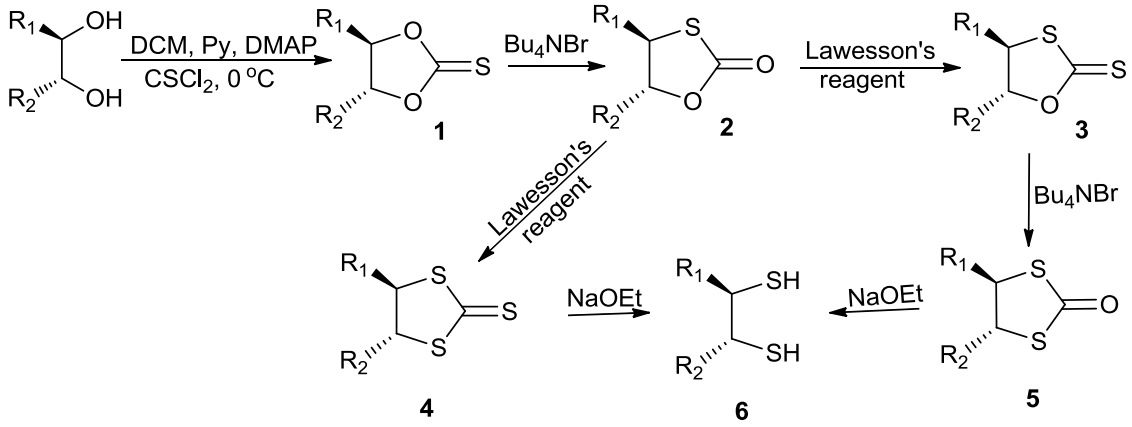
27. C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, *J. Appl. Crystallogr*., **2006**, *39*, 453.

28. Persistence of Vision Pty. Ltd. (2004). Persistence of Vision (TM) Raytrac Persistence of Vision Pty. Ltd., Williamstown, Victoria, Australia, http://www.povray.org

3. Chapter 3: Synthesis of *vic*-dithiols.

3.1: Background of *vic*-dithiols.

There are very few enantiopure *vic*-dithiols readily available, yet they are important building blocks for synthesis of chiral heterocyclic compounds, for preparing chiral thiocrown ethers and as useful resolution agents for chiral aldehydes and ketones and can be used to prepare chiral organosulphur compounds of high enantiomeric purities. One of the simplest chiral dithiols, *ent*-butane-2,3-dithiol, requires a four step synthesis with harsh reagents e.g. P/HI from the corresponding chiral diol,[1] though racemic *vic*-dithiols have been prepared by $LiAlH_4$ reduction of the corresponding trithiocarbonate.[2]



Scheme 3.1

It was thus of interest to look for alternative procedures to prepare these chiral molecules. To do this two approaches were investigated: (a) via a combination of thionocarbonate chemistry and thionation reactions and (b) ring opening of cyclic sulphate esters.

3.2: Background to thionocarbonate chemistry and thionations.

The chemistry of thionocarbamates has already been investigated in this PhD project, in particular their reaction with nucleophiles. The aim now is to build on the chemistry of the

related thionocarbonates. This chemistry is designed to take advantage of the increasing availability of *vic*-diols by asymmetric dihydroxylation and as well as from the chiral pool. Apart from initial work by Ko, this area has hardly been explored. Ko showed that the thionocarbonates of *vic*-diols such as **1** were susceptible to nucleophilic substitution e.g. with azide or thiophenolate to give alcohol derivatives.[3] The Wallis group have recently shown that thionocarbamates of *vic*-aminoalcohols e.g. **7** are susceptible to nucleophilic attack by thiolate at 5-C, providing the N atom was derivatised with an electron-attracting group such as Boc.[4] For both cases there are clear potential advantages to using the thiono derivatives rather than the cyclic sulphate esters[5-7] and sulphamidates.[6,7]

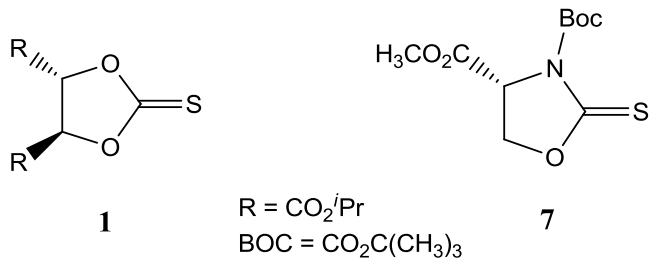
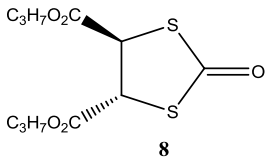


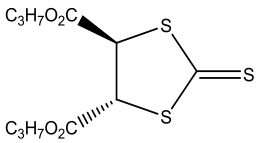
Figure 3.1

The new approach is a combination of thionocarbonate chemistry and thionation reactions which can provide access to *vic*-dithiols. Thus, it is known[1,8] that ring opening of thionocarbonate **1** with bromide and *in situ* recyclisation via the thiono S atom yields the oxathiazolidine **2**. The novel steps to be introduced are converting the carbonyl group to a thiocarbonyl by thionation with Lawesson's reagent to give **3** (Scheme 3.1), and then to repeat the reaction with bromide on **3** so that the second ring oxygen is replaced by sulphur. This has the added advantage of furnishing the product as a cyclic dithiocarbonate **5**. In this work a reaction for replacement of two O atoms of **2** with S atoms to give the 1,3-dithiolan-2-thione **4** was also discovered. The compounds **4** or **5** can be purified and then converted

in situ to the dithiol for immediate reaction, thus avoiding the need to handle the dithiol **6** itself. Initial studies used racemic material to establish reaction conditions. This was then extended to enantiopure starting materials and the results assessed by chiral HPLC on the protected dithiols **4** or **5** by comparison with racemic materials already prepared. Further development of this chemistry to enantiopure tartaric esters to furnish **8** and **9** was attempted, since **8** and **9** are useful building blocks for chiral sulphur heterocycles, and the latter is useful for preparing nucleoside analogues.[1,8,9]



8



9

Figure 3.2

Thionation, the conversation of a carbonyl group into a thiocarbonyl group, has been an important organic transformation for the preparation organosulphur compounds for many years.[10] For their synthetic importance, the thio-compounds are highly versatile intermediates, which find many applications in synthetic organic chemistry [11-16] and occur in biologically active molecules developed in pharmaceutical industries.[17] In recent years many routes and protocols have been developed. Phosphorus pentasulphide (P_4S_{10})[18-20] and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide, known as Lawesson's reagent (LR)[21-24] are the most widely used, powerful and versatile reagents for thionation chemistry[25,26]. Lawesson's reagent is commonly used in the thionation of amides because it gives higher yields with only small amounts of side reactions[27]. In reaction with the esters LR and P_4S_{10} have their advantages and disadvantages: long reaction time and

high temperature are required for reaction and there are side reactions. P_4S_{10} has the advantage that the side reaction products can be removed using aqueous workup.[28]

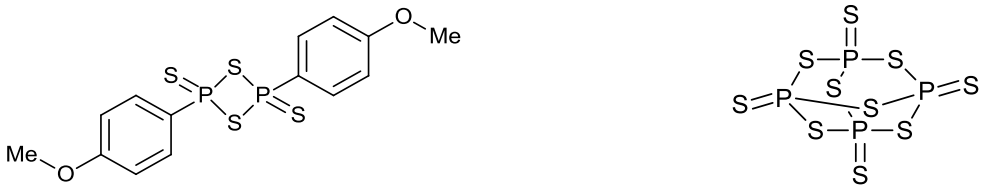
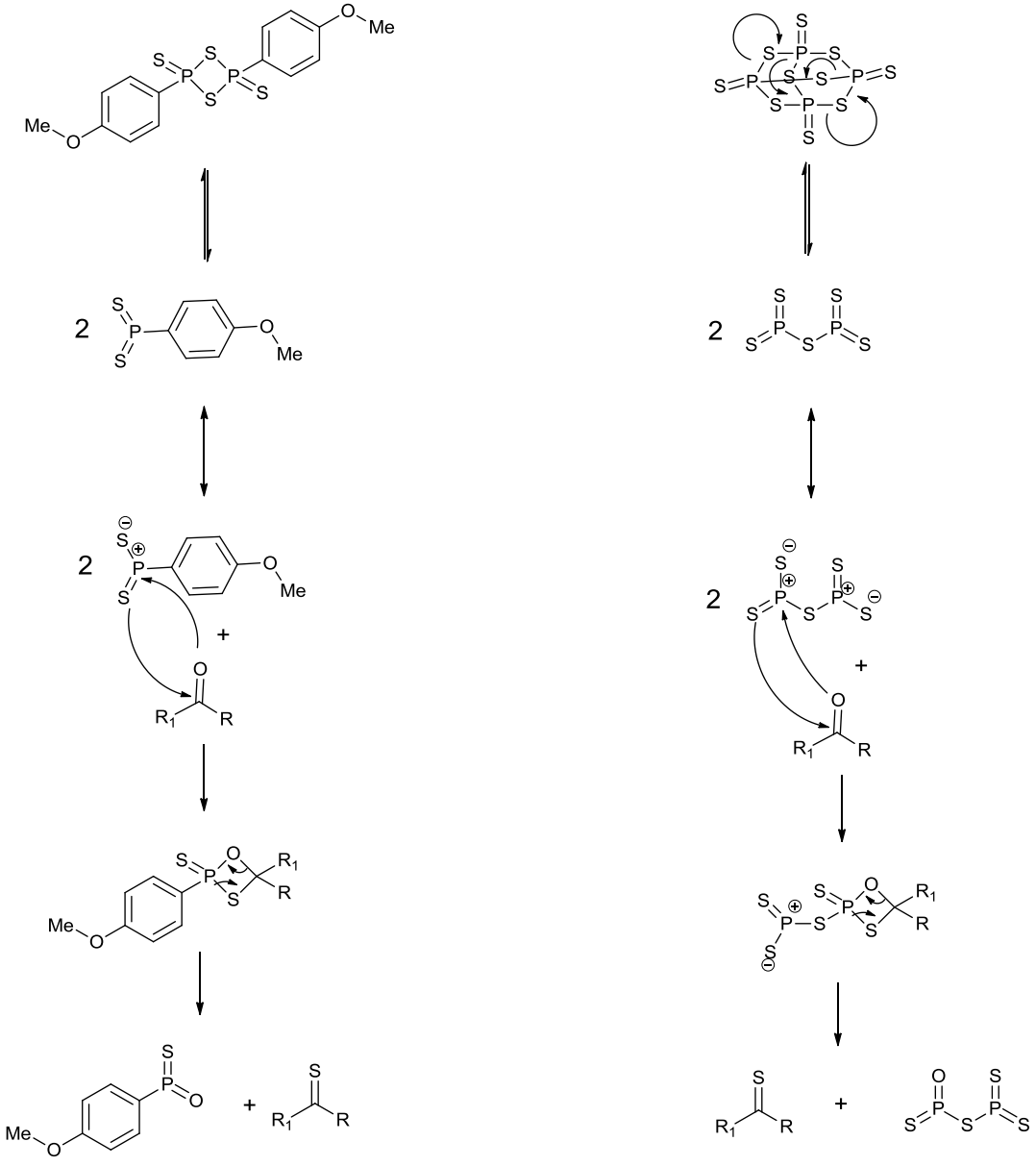


Figure 3.3: Lawesson's reagent (LR) and phosphorus pentasulfide (P_4S_{10}).



Scheme 3.2: Suggested mechanism of reaction for P_4S_{10} and LR.

Both of these reagents have a similar reactivity profile and have highly electrophilic phosphorus species which is why reactions with either reagent require very dry conditions. The thionation reactions using these reagents are determined by the electron density at the carbonyl oxygen. Normally the thionation is performed in refluxing toluene or xylene. The suggested mechanisms of both of them involve dissociation equilibria, and the dissociation products react with carbonyl functional groups to make a four membered ring, which decomposes to the corresponding thioproducts (Scheme 3.2).[12,29,30]

With the development of microwave heating technology,[31] Polshettiwar[32] reported a milder microwave assisted thionation method using phosphorous pentasulfide and hexamethyldisiloxane (HMDO)[23,25]. Curphey,[25] has shown that the addition of HMDO to P_4S_{10} increased the selectivity for the formation of thionolactones. Moreover, Varma and Kumar[33] reported a solvent-free method using Lawesson's reagent[34] under microwave irradiation.

3.3: Results and Discussion of synthesis of *vic*-dithiols from dithionocarbonates.

3.3.1: *rac*-Propane-1,2-dithiol (see Scheme 3.3).

Cyclic thionocarbonates are widely used as synthetic intermediates in the transformation of *vic*-diols into the deoxygenated products, alkenes, which is a convenient way to build a carbon–carbon double bonds. Synthesis of thionocarbonates has been achieved via different routes, either by using thiocarbonyldiimidazole,[9,25,27] thiophosgene,[35-37] or carbon disulphide and methyl iodide[26,38] with various bases. Phase transfer catalysis has also been used.[39] *rac*-4-Methyl-1,3-dioxolan-2-thione **10** was made from 1,2-propanediol in one step in 77% yield, via ring formation by reaction with thiophosgene, DMAP and pyridine in dichloromethane at 0 ºC following a procedure from Stansbury,[40] with minor modifications. The C=S infrared stretch is at 1176 cm^{-1}, and the ^{13}C NMR resonance at δ_C: 191.5 (O-C=S),

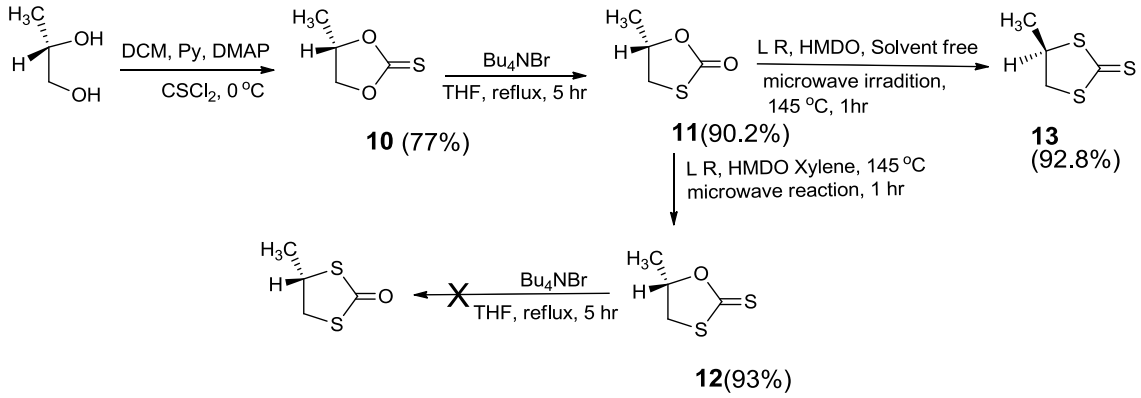
the methyl group C resonance at δ_C: 18.3 (4-CH_3), the methylene C resonance at δ_C : 74.3 (4-C), and the methine carbon resonance at δ_C : 78.8 (5-C).

For the regioselective rearrangement reaction,[3] the *rac*-4-methyl-1,3-dioxolan-2-thione **10** was reacted with Bu_4NBr as the nucleophile, in refluxing THF to obtain *rac*-4-methyl-1,3-oxathiolane-2-one **11** in 90% yield. The bromide ion substituted the oxygen atom at the primary position 5, and the thiocarbonate group released then substituted the bromide again via the sulphur atom. The NMR data for the product was in agreement with the literature. The carbon resonances were at δ_C: 172.6 (S-C=O), 77.7 (4-C), 37.7 (5-C) and 19.3 (4-CH_3) and the ^{1}H NMR spectrum showed the methyl group hydrogen resonance at δ_H : 1.46 ppm, as a doublet with coupling constant of 6.3 Hz, the methylene group at δ_H : 3.20 – 3.50 and the methine group at δ_H : 4.78. The infrared spectrum showed a C=O absorption at 1721 cm^{-1}.

The next reaction involved an oxygen-sulphur exchange from the corresponding carbonyl compound, and is a widely used synthetic transformation for the preparation of organosulphur compounds.

In this case it was found that a high yield (96%) of ***rac*-12** was obtained as a pale yellow oil when ***rac*-11** was thionated using HMDO and LR. It required the use of dry xylene and a lengthy reaction time under microwave irradiation (Scheme 3.3). Evidence was given by ^{13}C NMR which confirmed the thione group δ_C: 212.1 (-C=S), and the rest of the carbon resonances at δ_C: 87.9 (4-C), 40.7 (5-C) and 19.2 4-CH_3, and infrared spectroscopy showed a C=S absorption at 1039 cm^{-1}. Mass spectrometry confirmed the molecular mass of 134 g mol^{-1}. On the other hand under the same conditions but without solvent this reaction resulted in the *rac*-dithiolanethione **13** in high yield as a very thick yellow oil (96% yield) (Scheme 3.3). Evidence was given by ^{13}C NMR which confirmed the ring carbon

resonances at δ_C: 228.1 (S-C=S), 55.2 (4-C), 50.1 (5-C) and 18.8 (4-CH_3), and infrared spectroscopy showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirmed the molecular mass of 150 g mol^{-1} with high resolution mass spectrometry confirming the molecular composition.



Scheme 3.3: Synthetic route for thione 12 and thione 13.

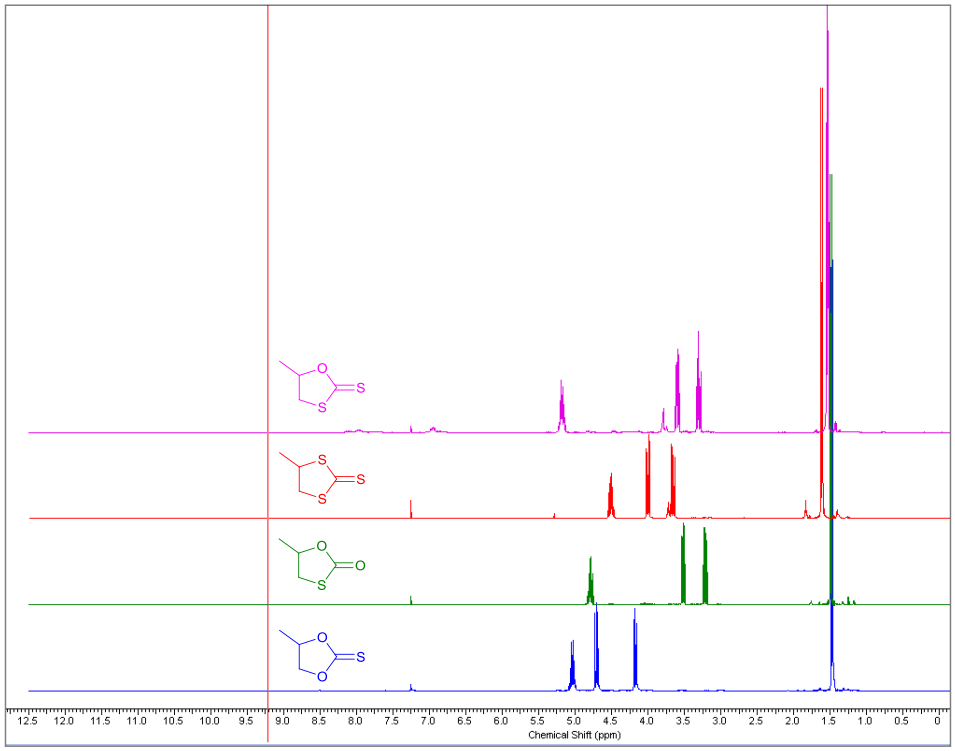


Figure 3.4: ^{1}H NMR spectra for compounds 10, 11, 12 and 13.

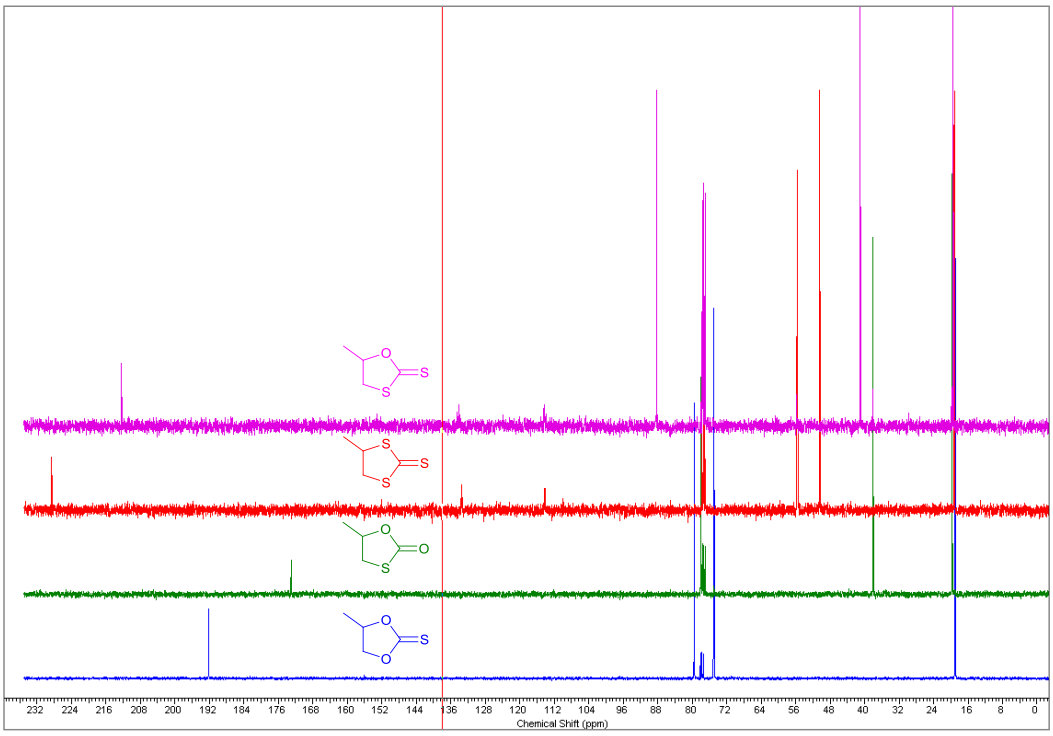
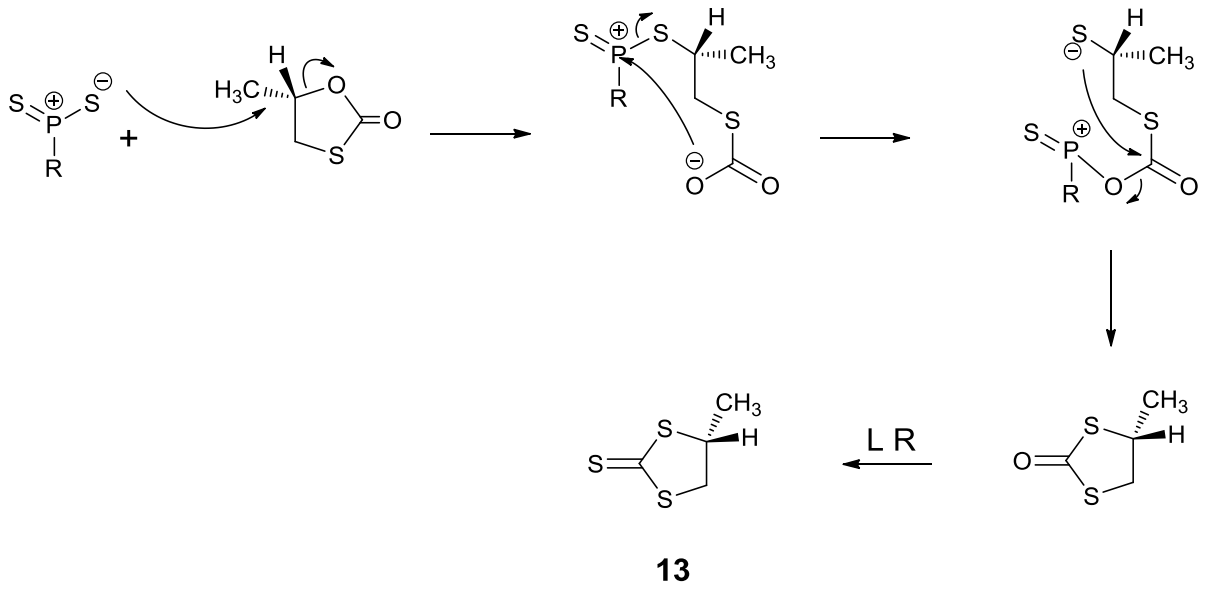


Figure 3.5: ^{13}C NMR spectra for compounds 10, 11, 12 and 13.

This chemistry was repeated successfully starting from enantiopure *S*-propane-1,2-diol, to give single enantiomers of **12** and **13**. The integrity of these materials was established by chiral HPLC using a CHIRALPAK® IC (250 mm L x 4.6MM ID) column (Figures 3.7 and 3.9), and comparing the results with the two results obtained using racemic **12** and **13** (Figures 3.6 and 3.8). The specific optical rotation of **13** is a similar as that from the product obtained from the cyclic sulphate of (+112^{o}) propane-1,2-diol and trithiocarbonate (see later), which suggests that there has been inversion of configuration at 4-C. If the thionation reagent had substituted at 4-C and then the dithiocarbonate residue had re-substituted via *R* at 4-C, then there would be retention of configuration. A possible mechanism using $ArPS_2$ as nucleophile is proposed (see Scheme 3.4 below).



Scheme 3.4: Proposed mechanism using $ArPS_2$ as nucleophile.

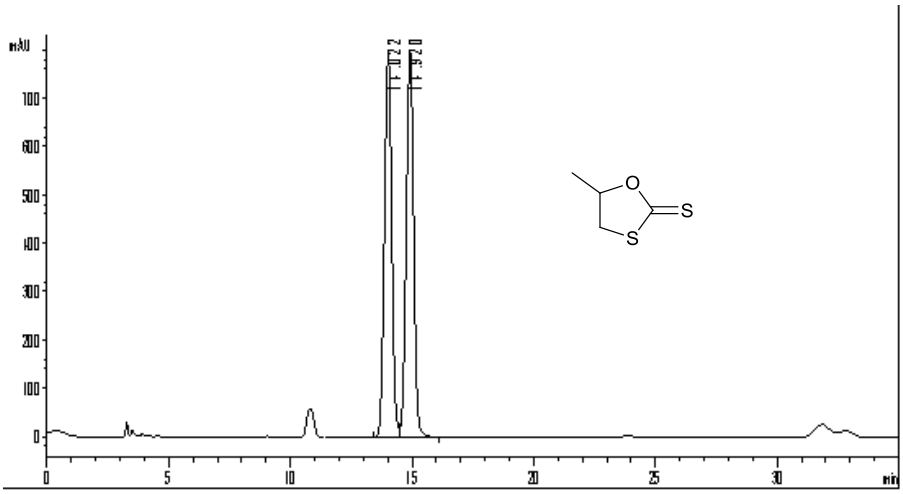


Figure 3.6: Separation of enantiomers of *rac*-12 using HPLC on a chiral phase.

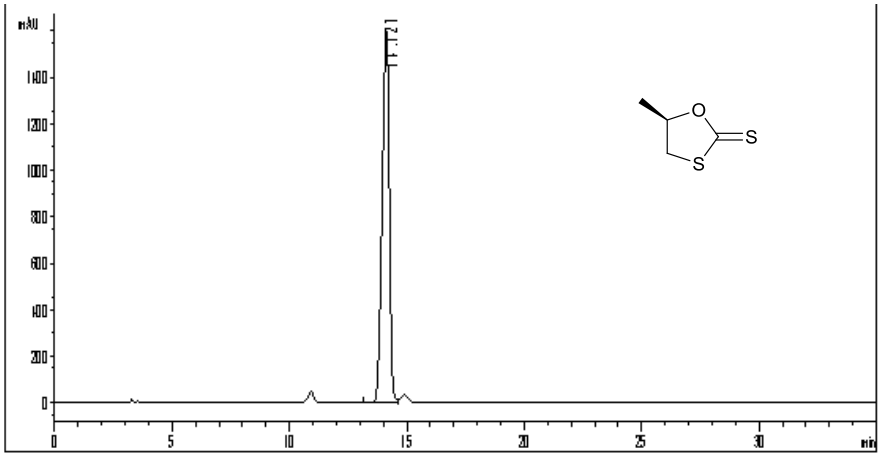


Figure 3.7: HPLC results for *R*-12.

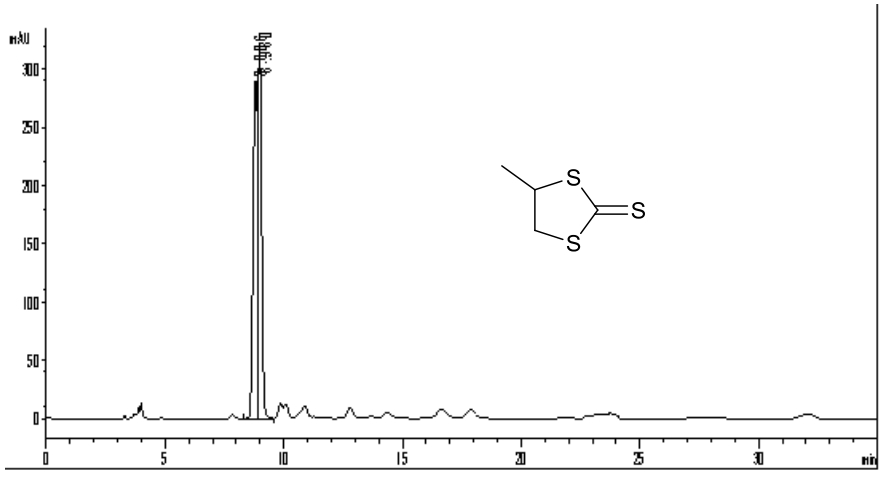


Figure 3.8: Separation of enantiomers of *rac*-13 using HPLC on a chiral phase.

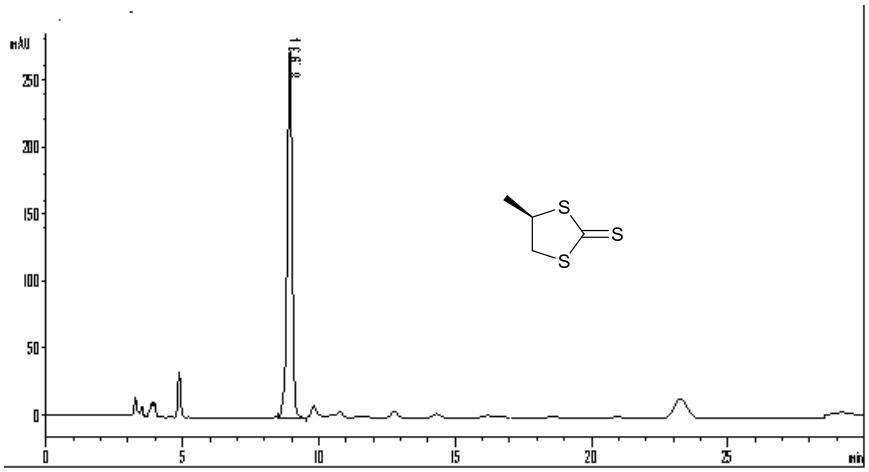


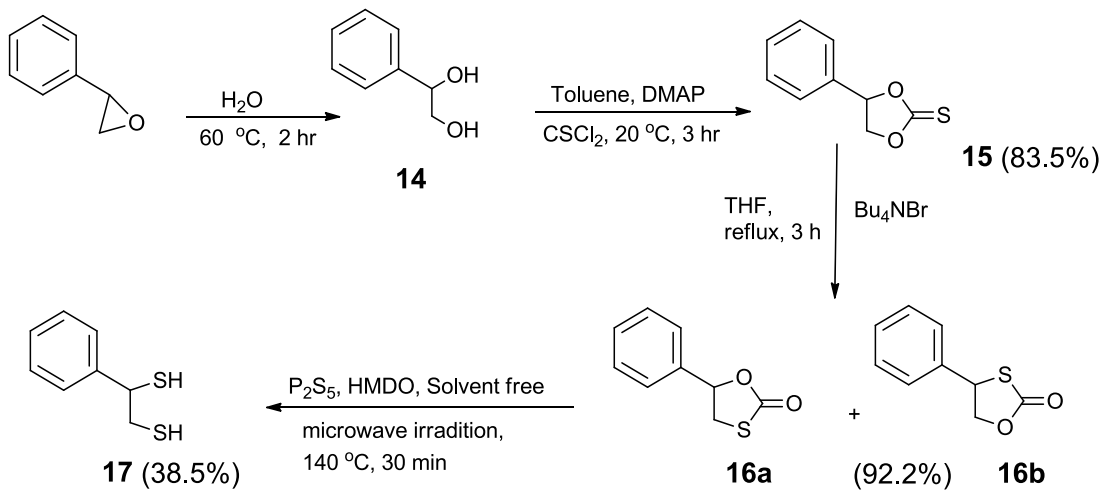
Figure 3.9: HPLC results for *R*-13.

It is interesting to note that in 2010 North's group have reported some chemistry which converts an epoxide into the corresponding dithiocarbonate and trithiocarbonate catalysed by a bimetallic aluminium salen complex and tetrabutylammonium bromide.[41,42] Their studies suggest that the formation of the dithiocarbonate involves inversion at the less hindered carbon of the epoxide by a sulfur centered nucleophile. Furthermore, they suggest that the trithiocarbonate is formed in a subsequent step via attack on the thione by a nucleophilic species leading to formation of a thiirane by a substitution at the more hindered carbon atom. The latter is then opened by a sulphur-centred nucleophile at the less substituted carbon atom. So overall, from epoxide to trithiocarbonate, the only stereochemical change is an inversion at the more substituted carbon atom.

The reaction of the cyclic sulfate ester of *S*-propan-1,2-diol with trithiocarbonate dianion would be expected to yield the product with *R*-configuration, **33**, for which we measured a specific optical rotation of +112 o (c = 0.25, $CHCl_3$). North is very careful in his report, and does not claim to have proved the stereochemical outcome, since he could not find a HPLC system to characterise his products, nor is the specific optical rotation reported in the literature for **33**. (Indeed the literature is rather confused). What he does report is that the reaction of *R* propylene oxide yields a sample of the trithiocarbonate with specific optical rotation of - 35.9 (c = 2.5, $CHCl_3$). From the measurement made in this laboratory, it would appear that North's sample is a 1:2 mixture of *R* and *S* enantiomers. The configuration of the main product is thus consistent with their mechanism, but the reaction is not highly stereospecific. A crystal structure of a material derived from the oil **33**, is the next step in this work.

3.3.2: <u>1-Phenylethane-1,2-dithiol. (see Scheme 3.5)</u>

Racemic phenylethane-1,2-diol **14** was prepared by ring opening of commercially available styrene oxide. The diol was converted to the thionocarbonate **15** in good yield (83%) by treatment with thiophosgene in the presence of 4-dimethylaminopyridine (DMAP) in toluene as solvent at room temperature. The rearrangement with Bu_4NBr gave a mixture of 1,3-oxathiolan-2-ones **16a** and **16b** in a ratio of approximately 30 : 70, as a pale yellow oil in 92% yield. The compounds were identified by analytical and spectroscopic methods. The ^{1}H and ^{13}C NMR data showed a mixture of **16a** and **16b** in a ratio of approximately 30 : 70. This is due to a greater amount of nucleophilic attack adjacent to the phenyl group. The phenyl ring can activate S_N2 substitution at 4-C.



Scheme 3.5: Synthetic route to dithiol 17.

The minor isomer: 4-phenyl-1,3-oxathiolan-2-one 16a

The ^{1}H NMR spectrum showed the the aromatic hydrogen resonances between δ_H: 7.27-7.40, the methine hydrogen resonance at δ_H: 5.63 as a double doublet with coupling constants of 6.5 and 9.4 Hz and the methylene hydrogens at δ_H: 3.73 and 3.55 as a double doublets. The ^{13}C NMR spectrum showed a carbonyl at δ_C: 172.4 (S-C=O), and sp^3 C atoms at 81.1, adjacent to O and phenyl, and 38.4 (adjacent to S).

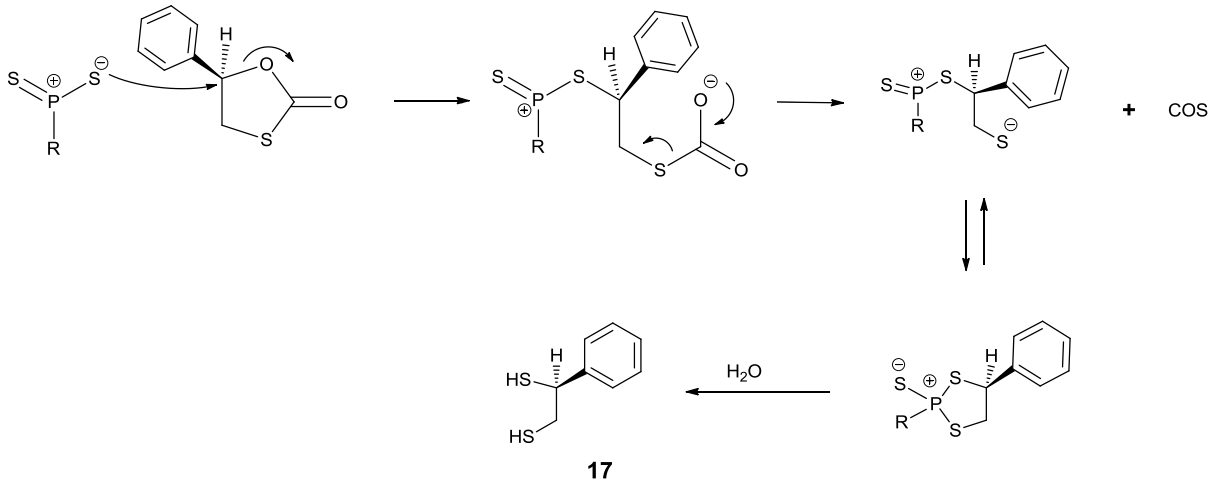
The major isomer: 5-phenyl-1,3-thioalan-2-one 16b

The ^{1}H NMR spectrum showed the the aromatic hydrogen resonance between δ_H: 7.27-7.40, the methine hydrogen resonance at δ_H: 5.13 and the methylene at δ_H: 4.38 and 4.70 as a double doublets and 4.70. The ^{13}C NMR spectrum showed peaks at δ_C: 172.6 (S-C=O), and sp^3 carbons at 74.4 (adjacent to S and phenyl) and 52.0 (adjacent to O).

Surprisingly, 1-phenylethane-1,2-dithiol **17** was obtained directly by treatment of the mixture **16a** and **16b** with P_4S_{10} and HMDO under microwave irradiation at 140 ^{o}C without solvent in (38%) yield as a very pungent yellow oil. TLC showed a variety of further products. The dithiol **17** showed spectral data consistent with literature values. The ^{1}H NMR spectrum showed the aromatic hydrogen resonance between at δ_H: 7.19 - 7.26, the

methine hydrogen resonance at δ_H: 4.04, the two methylene hydrogens at δ_H: 3.03 and 2.90 as a multiplets and the two thiol groups at δ_H: 2.23 as a double doublet with coupling constant 5.6 Hz and at 1.41 as a triplet with coupling constant 7.4 Hz. The ^{13}C NMR spectrum showed sp^3 C atoms at 47.0 (CH) and 34.0 (CH_2). The high resolution mass spectrometry confirmed the molecular composition.

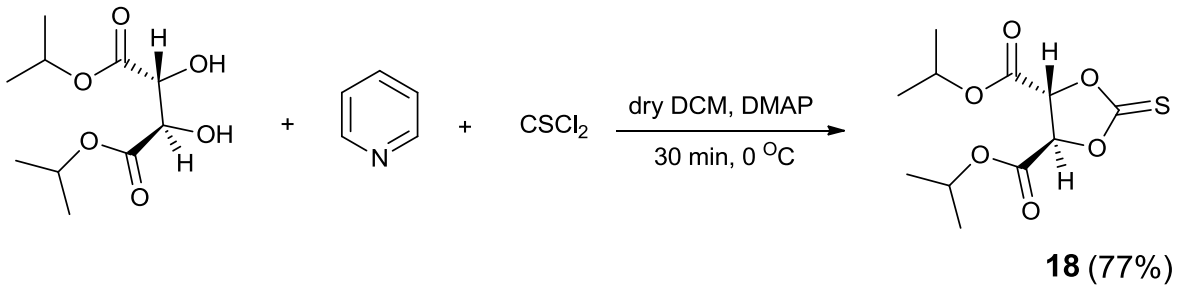
This chemistry was repeated successfully starting from enantiopure R-1-phenyl-1,2-ethanediol, to give single enantiopure of **17**. It would be expected that **17** rotation ***S*** configuration since no reaction takes place at 4-C. For **17**, the situation is not so clear, if the thionation reagent had substituted at 4-C and then the dithiocarbonate residue had re-substituted via S at 4-C, then there would be inversion of configuration. This will be considered further in this discussion. A possible mechanism is shown below (Scheme 3.6). This would mean inversion of configuration at 4-C for one enantiomer (**16a**) but not for the other (**16b**), but we have not had time to follow this up.



Scheme 3.6: Proposed mechanism for formation dithiol 17.

3.3.3: Diisopropyl tartrate as starting material.

The thione **18** (Scheme 3.7) was prepared from diisopropyl *L*-tartrate and thiophosgene in one step in 77% yield as for thionocarbonate **10**. The crude material was purified by flash column chromatography and identified by analytical and spectroscopic methods. In the ^{13}C NMR spectrum the thione resonance is at δ_C: 188.2 (O-C=S), the resonance of the ester carbonyl groups are at δ_C: 164.6, and the isopropyl resonances at δ_C: 79.2 and 21.4. Infrared spectroscopy indicated the carbonyl groups in the esters stretch at 1752 cm^{-1}, and the thione group stretches at 1075 cm^{-1}.

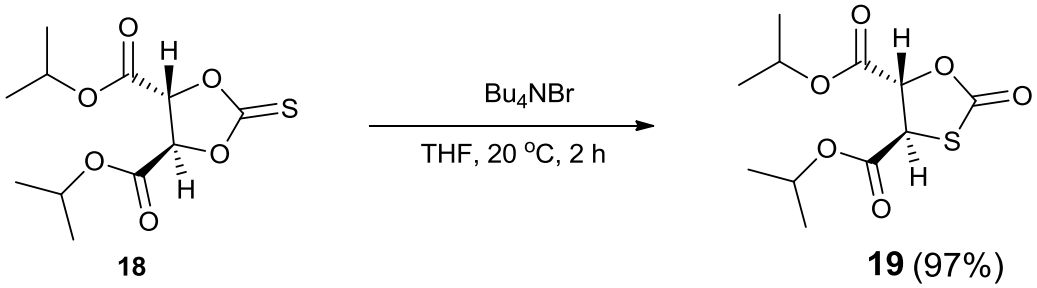


18 (77%)

Scheme 3.7: Synthesis of thione 18.

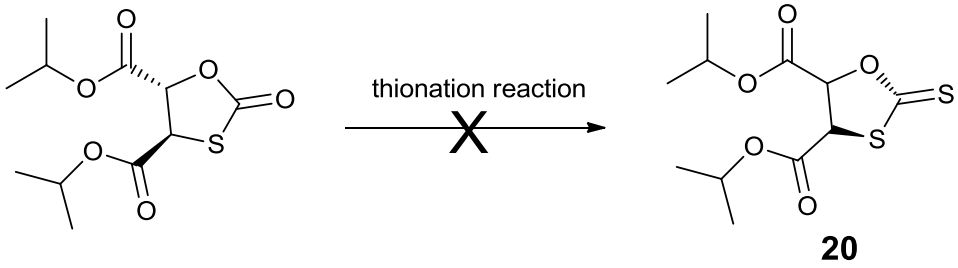
The known[3] rearrangement reaction of **18** with Bu_4NBr in THF at 20 ºC gave a single product, diisopropyl-*trans*-2-oxo-1,3-oxathiolane-4,5-dicarboxylate **19**, in 97% yield (Scheme 3.8). The bromide ion substituted the oxygen atom at position 5, and the thiocarbonate group released then substituted the bromine again via the sulphur atom. So overall retention of configuration is expected. The NMR data for the product was in agreement with the literature.[3] Evidence was given by the ^{13}C NMR spectrum which confirmed the cyclic carbonyl group resonance at δ_C: 169.2 (S-C=O), the ring carbon resonances at δ_C 71.1 (O-CH) and 50.1 (S-CH), and ester carbonyl resonances at 167.1 and 166.3. The ^1H NMR spectrum showed the ring methine protons at δ_H : 5.40 and 4.58 and

the diisopropyl methine protons at δ_H : 5.11. The infrared spectroscopy shows the cyclic carbonyl group absorption at 1758 cm^{-1} and the ester carbonyl absorption at 1732 cm^{-1}.



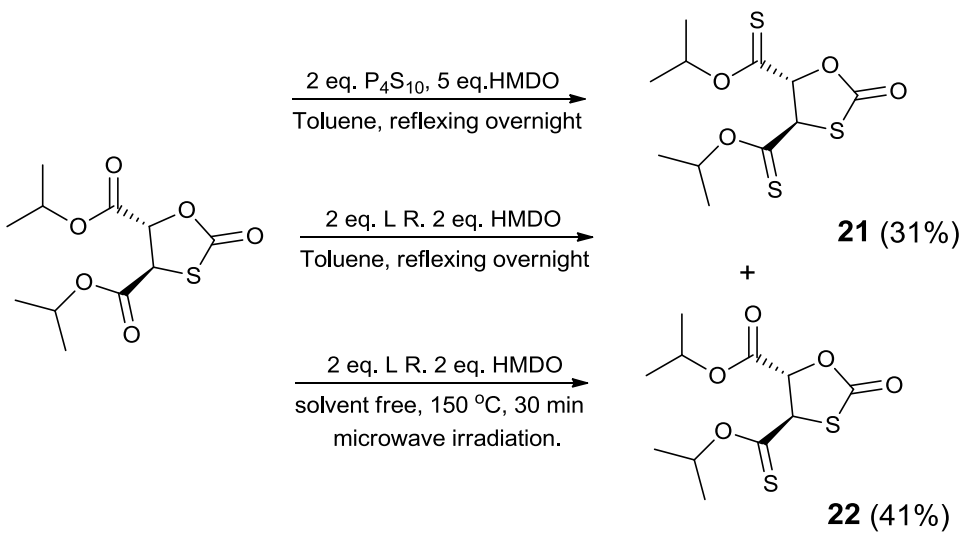
Scheme 3.7: Rearrangement of thione 18.

The next reaction involved an oxygen-sulphur exchange on compound **19**. Usually this transformation proceeds by thermal processes using either Lawesson's reagent (LR) or phosphorus pentasulfide (P_4S_{10}), which have a similar reactivity profile.[25,26,38] In this case it was desired that there would be thionation of the ring carbonyl group (S-C=O) to give compound **20**, (shown in Scheme 3.9), but hopefully not the ester carbonyl groups.



Scheme 3.9: expected thionation reaction of 19.

However, surprising results showed that one or both of carbonyl groups in the esters have been thionated depending on the reaction conditions, but not the ring carbonyl group. A variety of conditions were used from mild up to harsh (see Scheme 3.10).



Scheme 3.10: Different routes to prepare 21 and 22.

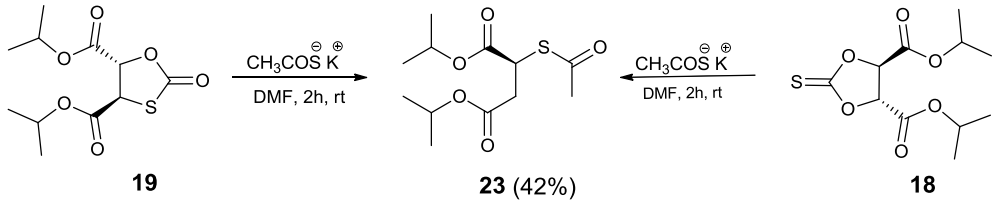
The highest yields were found when using microwave irradiation and no solvent, to give two compounds separated by chromatography. The first fraction is the compound **21** in 31% yield, which has both ester carbonyls thionated (see Scheme 3.10). Structural assignment were based on NMR spectra which confirmed the two thione group resonances at δ_C: 212.0 and 210.6 respectively, the ring carbonyl carbon resonances at δ_C: 170.2 (S-C=O), the isopropyl methine carbon resonance at δ_C: 85.1, the ring methine carbon resonance next to the O atom at δ_C: 77.9, the ring methine carbon resonance next to the S atom at δ_C: 61.8 and infrared spectroscopy showed a C=S absorption at 1090 cm^{-1}. The molecular ion was observed using mass spectrometry (+ve EI), at 308 g mol^{-1}. The second fraction is the compound **22** in 41% yield, which has one ester carbonyl group thionated (see Scheme 3.10). Structural assignment was based on NMR spectra which confirmed the thione group resonance at δ_C: 211.8, the ring carbonyl carbon resonance at δ_C: 169.7 (S-

C=O), the carbonyl ester resonance at δ_C: 166.6 and the methine carbon resonance at δ_C: 59.4. The infrared spectroscopy showed a thioester C=S group absorption at 1090 cm^{-1}, and the two carbonyl groups, in ring and in ester, absorb at 1758 cm^{-1} and 1728 cm^{-1} respectively. Mass spectrometry confirms the molecular mass of $[M + NH_4]^+$: 310 g mol^{-1}. HRMS (*m/z*) Found: 310.0782 Da $[M + NH_4]+$ $C_{11}H_{16}O_5S_2 + NH_4$ requires: 310.0777 Da. An ester group is thus thionated more readily than a thiocarbonate group, despite the presence of two electron donating atoms attached to it.

3.3.4: <u>Alternative procedures using tartrate as starting material.</u>

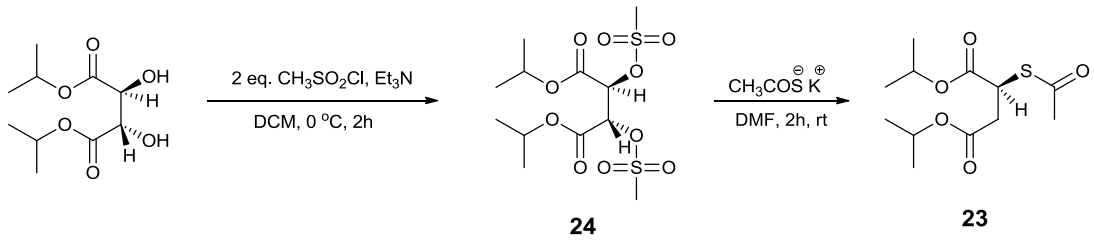
After the difficulties in the thionation reaction for diester **19**, it was decided to react **19** with two equivalents of potassium thioacetate as nucleophile by stirring in DMF at room temperature for 2 h to produce doubly substituted material. This reaction caused many problems, and many differing methods were tried. After work-up including neutralization by addition of drops of HCl (2M) and partition between ethyl acetate and water, the organic layer was washed with aq. $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The crude material was purified by flash column chromatography to afforded compound **23** in (42%) yield where one substituent has been lost. The ring was opened by the sulphur nucleophile, but surprisingly, the second substitution did not take place and the remaining C-O bond was reduced to C-H to give a mono-thioacetate (Scheme 3.11). ^{13}C NMR confirmed no sign of a thione group and showed the carbonyl group in thioacetate (S-C=O) at δ_C: 193.0 and the acetyl methyl group at δ_C: 29.9. The methine carbon next to sulphur atom is at δ_C: 41.5 and the methylene carbon at δ_C: 36.9. The two ester carbonyl groups resonate at δ_C: 169.4 and 169.6 respectively. The two methine carbons in isopropyl groups are at δ_C: 68.4 and 69.4. The ^1H NMR spectrum showed the methylene protons at δ_H: 2.81 and 2.76 as a double doublets. The methine proton next to the S atom is at δ_H : 4.40 as a multiplet and the

diisopropyl methine protons appear at δ_H : 4.95. The infrared spectroscopy showed a thioacetate C=O group absorption at 1703 cm^{-1}, and the two ester carbonyl groups at 1728 cm^{-1}. Mass spectrometry confirms the molecular mass of $[M + H]^+$: 277 g mol^{-1} and high resolution mass spectrometry confirmed the molecular composition (Found: 277.1106 Da $[M + H]^+$ $C_{12}H_{20}O_5S$ + H requires: 277.1104 Da).

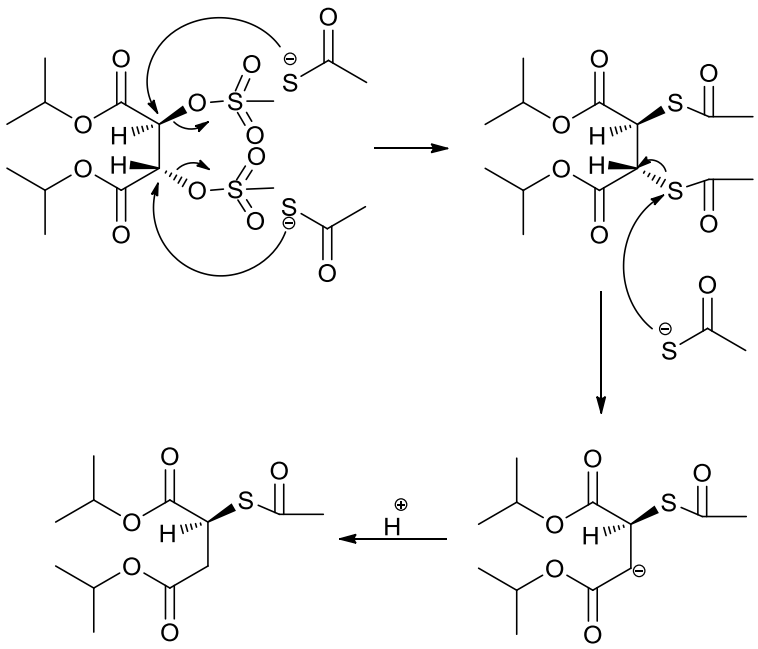


Scheme 3.11: Synthetic route to 23.

To explore further routes to a *vic*-dithiol, diisopropyl *L*-tartrate was treated with methanesulphonyl chloride in the presence of triethylamine as base at 0 ^oC to give, after usual work-up, the *bis*(methanesulphonate) **24** in (98%) yield (Scheme 3.12). However, reaction with thioacetate also gave the product **23**. A suggested mechanism is shown in Scheme 3.13, in which substitution of both mesyl groups is followed by thioacetate attack on S to break a C-S bond leaving a carbanion adjacent to an ester. The weakness of a (ester) C-S bond has been noted before.[43]



Scheme 3.12: Synthesis of 24.

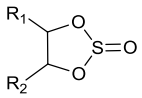


Scheme 3.13: Proposed mechanism for formation 23.

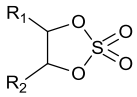
To overcome the failed attempts of double substitution of thionocarbonates and thionation reactions, it was decided to investigate reactions of cyclic sulphate esters with *bis*-nucleophiles containing two thiolate groups.

3.4: Background of Cyclic Sulphate Esters (CSEs).

Cyclic sulphate esters (CSEs) have been known[44] since 1932 and the lack of efficient methods for preparing them limited their applications until recent years. The importance of cyclic sulphates in organic synthesis originates from several points. Sharpless in 1992 developed a route to catalytic asymmetric dihydroxylation of alkenes,[45] so that chiral *vic*-diols became available in high enantioselectivity. The cyclic sulphate esters can be synthesised in two steps from the corresponding diols. The first step is to produce the cyclic sulphite ester **25** using thionyl chloride in the presence of base. The second step is the oxidation of sulphite to sulphate **26**.



25



26

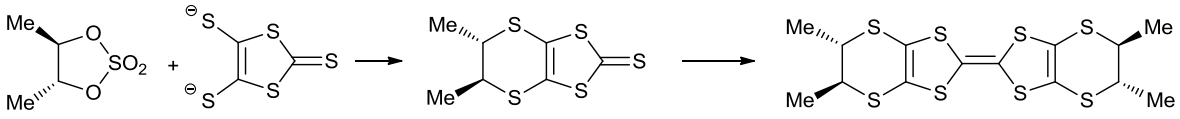
Figure 3.6

Moreover, the significant feature is that the carbon atoms in the cyclic sulphate moiety are highly reactive toward various nucleophiles and more reactive than in epoxides,[46] CSEs can be reacted under acidic, basic and neutral conditions without the use of a catalyst.[47] The enhanced reactivity relative to an acyclic sulphate may originate from ring strain and partial double bond character between the ring oxygen atoms and sulphur atom.[48] The cyclic sulphate esters undergo single substitution reactions at carbon by ring opening by nitrogen, oxygen and sulphur-centred nucleophiles to give the substituted alcohol after hydrolysis of the resulting hemi-sulphate. For example, reactions with nucleophiles such as azide and benzoates give products which can be successfully hydrolyzed by using a catalytic amount of sulphuric acid and 0.5 : 1.0 eq. of water in THF.[49] Since the intermediate of nucleophilic substitution is generally the salt of a monosulphate ester, separation of the product from the

non-salt byproducts is typically a facile process. Thus, CSEs can activate nucleophilic attack at one position while serving as a protecting group at a second position. Under more vigorous conditions they can serve as an activator for two sequential reactions and provide materials to give two contiguous stereocentres. Cyclic sulphamidites and cyclic sulphamidates of corresponding *vic*-amino alcohols share similar properties to cyclic sulphite esters and cyclic sulphate esters.[50]

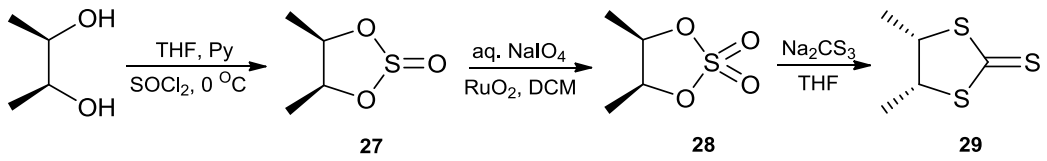
In recent years the addition of nucleophiles to cyclic sulphates has had applications in the synthesis of natural products,[51,52] biologically active materials[53,54] and heterocyclic systems[55-57] and also in cascade reactions.[58] Several monosubstitution reactions with a variety of carbon-centred nucleophiles have been reported, for example with cyanide, a Grignard reagent with copper catalysis[57] and lithiated alkynes and 1,3-dithiane derivatives.[60,61]

Several double substitution reactions with *bis*-nucleophiles leading to the loss of sulphate are known e.g. with a dithiolate to afford dihydro(1,4)dithiins which is of use in the synthesis of chiral organosulphur donors (see Scheme 3.14 below),[62,63] with sulphide to afford episulphides[64] and with amidines to afford diamines.[65] The disubstitution reaction with malonate and related species has found considerable application in the preparation of cyclopropane derivatives, and double substitution reactions with lithium dianions of β-ketoesters and their enamines were successful.[66]



Scheme 3.14

Here we are exploring the double substitution reactions of the cyclic sulphate esters of *vic*-diols with the trithiocarbonate dianion to give the protected *vic*-dithiols (Scheme 3.15).



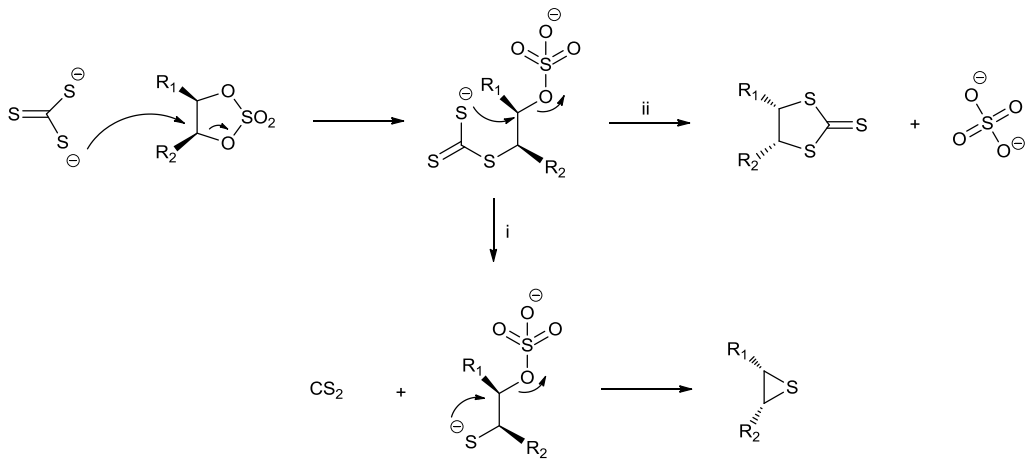
27 28 29

Scheme 3.15

3.5: Results and Discussion.

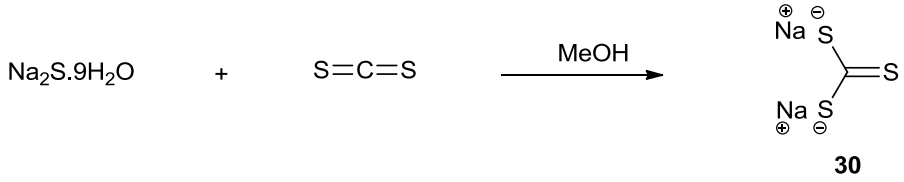
3.5.1: Synthesis of *vic*-Dithiols via cyclic sulphate esters (CSEs).

The long term aim of this part of the research was the development of new synthetic approaches to the convenient preparation of protected enantiomerically pure *vic*-dithiols. In Scheme 3.16 is shown the expected mechanism of the reaction of a CSE with the two sulphur atoms of the sodium trithiocarbonate. There are two possible products i) double substitution reactions give the protected *vic*-dithiol and ii) mono substitution, loss of CS_2, followed by the second substitution to give thiiranes. The former reaction is successful for both singly and doubly substituted *vic*-diols, surprisingly in very high yield (Scheme 3.16).



Scheme 3.16: Proposed mechanisms of single + double substitution of CSEs.

3.5.2: <u>Synthesis of sodium trithiocarbonate 30.</u>

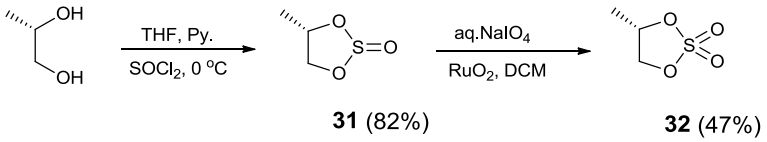


30

Scheme 3.17: Synthesis of sodium trithiocarbonate.

The starting point was the production of sodium trithiocarbonate salt (Schame 3.17). There are many procedures to prepare trithiocarbonate salts, however in this study a new method to obtain sodium trithiocarbonate was used. Sodium sulphide was dissolved in methanol and carbon disulphide was added. The mixture reaction was left stirring under nitrogen atmosphere till the solution became an orange-red colour. The solvents (methanol, the extra carbon disulphide and water) were removed under vacuum to give dry sodium trithiocarbonate **30** as an orange solid.

3.5.3: Synthesis of *rac*-4-Methyl-1,3,2-dioxathiolane-2,2-dioxide, *rac*-32.



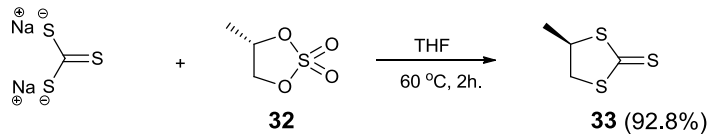
Scheme 3.18: Synthesis of CSE 32.

The cyclic sulphite ester of racemic propane-1,2-diol was prepared via the reaction of the *rac*-diol and thionyl chloride in the presence of pyridine. The pyridine was used to scavenge the HCl produced during the reaction. It is a quick and easy reaction. After work-up including washing of the organic layer with water to remove the pyridinium hydrochloride and washing with 0.5 M HCl to remove extra pyridine, the corresponding cyclic sulphite ester ***rac*-31** was obtained in high yield (Scheme 3.18). The compound ***rac*-31** showed a bright yellow spot on the TLC plate when treated with permanganate solution. The compound has been identified by analytical and spectroscopic methods. The ^{1}H and ^{13}C NMR data for the cyclic sulphite ester showed a mixture of two isomers in a ratio of approximately 40:60. This is due to the two relative orientations available for the S=O group.

The cyclic sulphite ester was oxidized to the corresponding sulphate following the improved procedure of Gao and Sharpless in high yield (Scheme 3.18). In this method a catalytic amount of RuO_2 and aqueous sodium periodate with dichloromethane as a two phase system was used. The reaction mixture was stirred vigorously, the colour became green-grey and the reaction was monitored by TLC. If the unreacted cyclic sulphite ester appeared as a bright yellow spot when treated with permanganate solution, the reaction was carried on and tested later by TLC. A pale yellow spot was seen on developing the plate with permanganate solution, which became brighter with addition of heat to the plate,

confirming the production of the CSE ***rac*-32**. The reaction mixture was then worked up, which included adding some drops of propan-2-ol to the organic layer, to reduce RuO_4 back to ruthenium (IV) oxide, which is precipitated, then the solution was dried over magnesium sulphate, filtered and evaporated. The CSE ***rac*-32** was a yellow oil, and the NMR data for the product was in agreement with the literature. For the CSE ***rac*-32** the ^{1}H NMR spectrum showed the ring methyl group at δ_H: 1.60 ppm, as a doublet with coupling constant of 6.4 Hz. The resonance for one of the hydrogens on 5-C was at δ_H: 4.33 ppm as a multiplet. The resonance for the other hydrogen on the 5-C was seen at δ_H: 4.75 ppm as a double doublet with coupling constant of 8.8 and 5.8 Hz. The resonance for hydrogen atom on 4-C was shown at δ_H: 5.14 ppm as a multiplet. The ^{13}C NMR spectrum showed peaks at δ_C: 79.7 (4-C), δ_C: 74.3 (5-C) and δ_C: 17.1 (Me).

3.5.4: Synthesis of *rac*-4-methyl-1,3-dithiolane-2-thione *rac*-33.



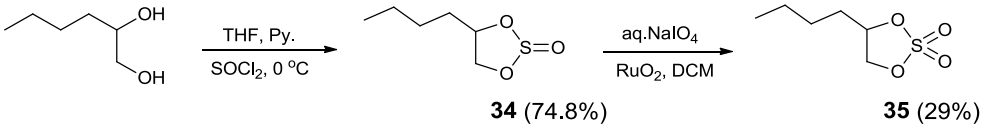
Scheme 3.19: Synthesis of thione 33.

A successful reaction of CSE ***rac*-32** with sodium trithiocarbonate **30** was achieved. Sodium trithiocarbonate in dry THF was stirred for 1 h and a solution of CSE ***rac*-32** in THF was added. This solution was stirred at 60 ^{o}C for 2 h. The work-up involved the reaction mixture being filtered and partitioned between an organic and an aqueous phase. The organic layers were combined and dried over magnesium sulphate. The filtrate was evaporated which afforded the pure 4-methyl-1,3-dithiolane-2-thione ***rac*-33** as a deep yellow oil in high yield (93% yield) (Scheme 3.19). The data was the same as a similar

sample from the thionocarbonate / thionation experiment (compound **13**). The ^{13}C NMR confirmed the ring carbon resonances at δ_C: 228.1 (S-C=S), δ_C: 55.2 (4-C), δ_C: 50.1 (5-C) and δ_C: 18.8 (4-CH_3), and infrared spectroscopy showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirms the molecular mass of 150 g mol^{-1} and high resolution mass spectrometry confirmed the molecular compostion. (HRMS (*m/z*) Found: 149.9623 $[M]^+$ $C_4H_6S_3$ requires: 149.9626 Da).

This chemistry was repeated starting from the enantiopure diol to give chiral thione ***R*-33** which is expected to have the *R*-configuration at 4-C.

3.5.5: Synthesis of *rac*-4-butyl-1,3,2-dioxathiolane-2,2-dioxide, *rac*-35.



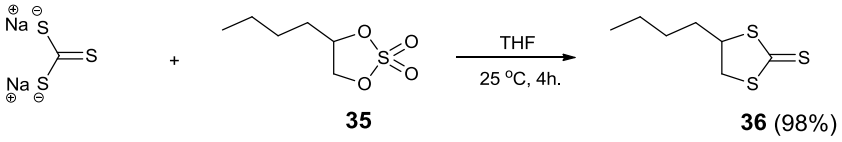
Scheme 3.20: Synthesis of CSE 35.

CSE ***rac*-35** was prepared in a similar way to **32**. The cyclic sulphite ester of racemic hexane-1,2-diol was prepared via the reaction of the *rac*-diol and thionyl chloride in presence of pyridine. After usual work up, the corresponding cyclic sulphite ester ***rac*-34** was obtained in high yield (Scheme 3.20). The ^1H and ^{13}C NMR data for the cyclic sulphite ester showed the ring methine group at δ_H: 4.90, the ring methylene group at δ_H: 4.61 and 3.85, the methylene chain at δ_H: 1.31 – 1.82 ppm and the terminal methyl group at δ_H: 0.85 ppm.

The cyclic sulphite ester ***rac*-34** was oxidized to the corresponding sulphate ***rac*-35** following the improved procedure of Gao and Sharpless in high yield (Scheme 3.20). After usual work up, the corresponding cyclic sulphate ester ***rac*-35** was a orange/yellow oil.[67]

The ^{1}H NMR spectrum showed the ring methyl group at δ_H: 0.91 ppm as a triplet with coupling constant of 6.7 Hz. The resonance for one of the ring methylene hydrogens was at δ_H: 4.31 ppm as a double doublet with coupling constants of 8.8 and 11.9 Hz. The resonance for the other methylene hydrogen was seen at δ_H: 4.68 ppm as a double doublet with coupling constants of 11.9 and 5.4 Hz. The resonance for the methine hydrogen atom appeared at δ_H: 4.95 ppm as a multiplet. The ^{13}C NMR confirmed the ring carbon resonances at δ_C: 82.9 (4-C) and δ_C: 72.8 (5-C), and the methylene chain carbon resonances at δ_C: 31.9, 26.6, 22.1 and 13.7 (4-CH_3) respectively, and infrared spectroscopy showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirmed the molecular mass of [M + H] 193 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition.

3.5.6: <u>Synthesis of *rac*-4-butyl-1,3-dithiolane-2-thione, *rac*-36.</u>

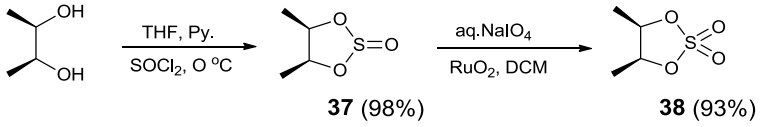


Scheme 3.21: Synthesis of thione 36.

This is another successful example of the reaction of CSE ***rac*-35** with the sulphur *bis*-nucleophile **30**. Following the procedure used for **33**, sodium trithiocarbonate **30** was obtained *in situ*, stirred in dry THF, and the CSE ***rac*-35** was added to the solution which was left stirring at room temperature for 12 h. The work up involved the reaction mixture being filtered and partitioned between an organic and an aqueous phase. The organic layers were combined and dried over magnesium sulphate. The filtrate was evaporated which afforded the pure 4-butyl-1,3-dithiolane-2-thione ***rac*-36** as a deep yellow oil in high yield (95%) (Scheme 3.21). The data were in agreement with literature for this compound which

was made in low yield by reaction of butyloxirane with CS_2.[41] The ^{13}C NMR confirmed the ring carbon resonances at δ_C: 227.9 (S-C=S), 60.9 (4-C), 48.2 (5-C), and the methylene chain carbon resonances at δ_C: 33.2, 30.3, 22.3 and 13.8 (4-CH_3) respectively, and infrared spectroscopy showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirmed the molecular mass of [M + H] 193 g mol^{-1}. HRMS (*m/z*) Found: 193.0171 $[M + H]^+$ $C_7H_{12}S_3H$ requires: 193.0174 Da.

3.5.7: Synthesis of *R,S*-4,5-Dimethyl-1,3,2-dioxathiolane-2,2-dioxide, *meso*--38.

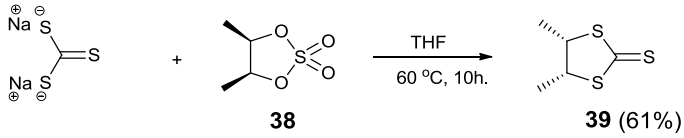


Scheme 3.22: Synthesis of CSE 38.

To produce the di-substituted CSE ***meso*-38** the same method was followed as for the mono-substituted CSE **32**. The *vic*-diol was converted to cyclic sulphate ***meso*-38** in two high yielding steps. The *meso*-2,3-butandiol was reacted with thionyl chloride in the presence of pyridine to give ***meso*-37** (Scheme 3.22). The compound has been identified by analytical and spectroscopical methods; the ^1H and ^{13}C NMR data for the cyclic sulphite ester showed a mixture of two isomers in a ratio of approximately 50 : 50. For the CSE ***meso*-37** there are two structures for this substance, in one the methyl groups are both *cis* to the S=O group, and in the other the methyl groups are both trans to the S=O bond. So there will be two methine signals, one from each isomer, but they need not be the same size. The methyl signals will be in the same ratio. This is due to the relative orientations available for the S=O group. The next step was to oxidize it the CSE ***meso*-38**. This step took a longer time than that necessary for the oxidation to the CSE ***meso*-37**. The reaction was carried out until the TLC showed no evidence of starting material left. The addition of the second O

atom means that the methyl groups become equivalent, as do the ring carbons had become equivalent upon production of the CSE ***meso*-38**. Therefore in the ^{1}H NMR spectrum only two resonances were seen δ_H: 1.50 ppm as a doublet with a coupling constant of 6.4 Hz, and at δ_H: 5.10 ppm as a multiplet. This data was in agreement with the literature for this compound[68]. The ^{13}C NMR spectrum showed peaks at δ_C: 83.0 ppm for the methine carbon and at δ_C: 14.1 ppm for the ring methyl groups.

3.5.8: Synthesis of *R,S*-4,5-Dimethyl -1,3-dithiolane-2-thione, *meso*-39.

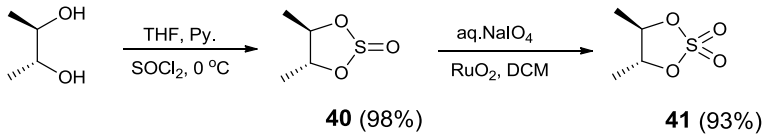


38 **39** (61%)

Scheme 3.23: Synthesis of thione 39.

Following the established procedure the CSE ***meso*-38** was added to a solution of sodium trithiocarbonate in dry THF. This solution was stirred at 60 °C overnight. The work up involved the reaction mixture being filtered and partitioned between an organic and an aqueous phase. The organic layers were combined and dried over magnesium sulphate. The filtrate was evaporated which afforded the pure ***meso*-39** as a deep yellow oil in 60% yield (Scheme 3.23). The ^{13}C NMR spectrum showed the carbon resonances at δ_C: 226.3 (S-C=S), 61.3 (methine carbon) and 18.3 (methyl). The ^{1}H NMR spectrum showed the methyl group resonance at δ_H: 1.53 ppm as a doublet with coupling constant of 5.2 Hz, and the methine group at δ_H: 4.04 ppm as a multiplet. The infrared spectrum showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirmed the molecular mass of [M + H] 164 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition. (HRMS (*m/z*) Found: 164.9858 $[M + H]^+$ $C_5H_8S_3H$ requires: 164.9861 Da).

3.5.9: Synthesis of *R,R*-4,5-Dimethyl-1,3,2-dioxathiolane-2,2-dioxide, *R,R*-41.

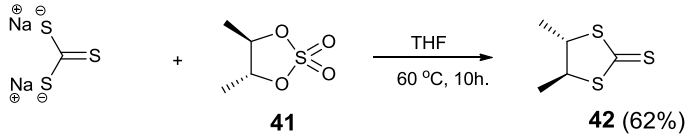


40 (98%) **41** (93%)

Scheme 3.24: Synthesis of CSE 41.

To produce the enantiopure dimethyl-substituted CSE ***R,R*-41** the same method was followed as for mono-substituted CSE **32**.[69] The *R,R*-2,3-butanediol was converted to the cyclic sulphite ester ***R,R*-40** in good yield (80%) as yellow oil (Scheme 3.24). Resonances for the hydrogens of the ring methyl groups were found at δ_H: 1.25 and 1.27 ppm as doublets with a coupling constant of 1.84 Hz. A resonance for the ring hydrogens on the ring carbons was observed at δ_H: 5.00 ppm as a multiplet. For ***R,R*-41** (single enantiomer) there is just one structure for this substance, but the two methine H atoms are not equivalent, since one is *cis* and one is *trans* to the S=O group, so it will show two methine signals in the ratio 1:1, also two methyl signals in a 1:1 ratio. The oxidation into the CSE ***R,R*-41** proceeded in high yield (98%) (Scheme 3.24) to give ***R,R*-41** as a deep yellow oil. A resonance for the methyl groups hydrogen was found at δ_H: 1.48 ppm as a doublet with a coupling constant of 6.3 Hz. A resonance for the methine hydrogens was observed at δ_H: 4.62 ppm as a multiplet. This data was in agreement with literature for this compound.[68] The ^{13}C NMR spectrum showed peaks at δ_C: 85.2 ppm for the methine carbon and at δ_C: 16.3 ppm for the methyl groups.

3.5.10: Synthesis of *S,S*-4,5-Dimethyl -1,3-dithiolane-2-thione, 42.

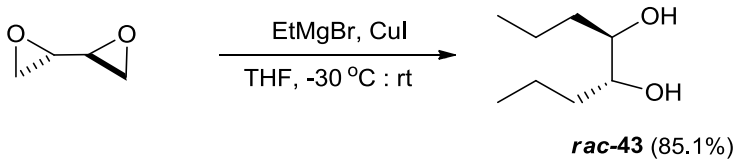


41 **42** (62%)

Scheme 3.25: Synthesis of thione 42.

CSE ***R,R*-41** was successfully reacted with sodium trithiocarbonate **30** to give thione **42** following the procedure used to prepare **39**, which afforded the pure **42** as a deep yellow oil in 60% yield (Scheme 3.25). The ^{13}C NMR spectrum confirmed the structure showing the thione resonance at δ_C: 227.6, the methine groups at δ_C: 58.3 and the methyl group at δ_C: 14.3, and the ^{1}H NMR spectrum showed the methyl group resonance at δ_H: 1.45 ppm as a doublet with coupling constant of 5.3 Hz, and the methine group at δ_H: 4.39 ppm as a multiplet. The infrared spectrum showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirms the molecular mass of [M + H] 164 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition. (HRMS (*m/z*) Found: 164.9858 $[M + H]^+$ $C_5H_8S_3H$ requires: 164.9861 Da).

3.5.11: Synthesis of *rac*-Octane-4,5-diol, *rac*-43.

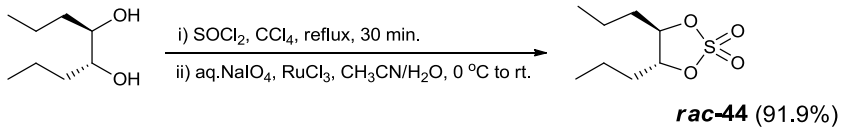


Scheme 3.26: Synthesis of octane-4,5-diol.

Using the method described by Devin and et al.[70] ethylmagnesium bromide was added to a solution of copper iodide in dry THF at -30 ºC. The solution was stirred for 10 min and the diepoxide was added. The reaction mixture was warmed to 0 ºC and stirred for 2 h. A the usual aqueous work-up, the crude product was passed through a short silica gel column to gave *rac*-octane-4,5-diol **43** in 85% yield as a pale yellow oil (Scheme 3.26). The NMR data for the product were in agreement with the literature.[71] The ^{1}H NMR spectrum showed the methyl groups at δ_H: 1.60 ppm as a triplet with coupling constant of 7.0 Hz. The resonance for the side chain methylenes were shown at δ_H: 1.60 – 1.36 ppm as a multiplet.

The resonance for the hydroxyl group was seen at δ_H: 2.85 ppm as a singlet. The resonance for the methine hydrogens was shown at δ_H: 3.39 ppm as a multiplet. The ^{13}C NMR spectrum showed peaks at δ_C: 74.0 (4,5-C), 35.5 (3,6-C), 18.7 (2,7-C) and 14.0 (2 x Me).

3.5.12: <u>Synthesis of *rac*-4,5-Dipropyl-1,3,2-dioxathiolane-2,2-dioxide, *rac*-44.</u>

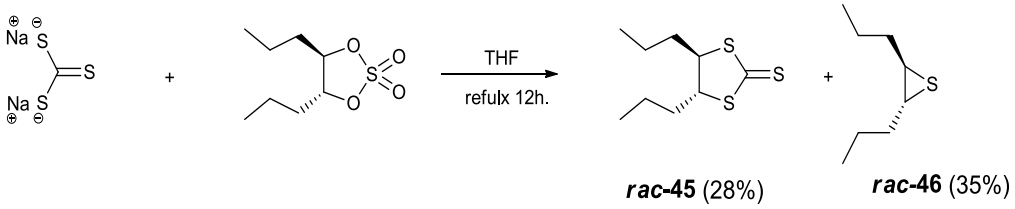


***rac*-44** (91.9%)

Scheme 3.27: Synthesis of CSE 44.

To prepare the disubstituted CSE **44**, a modified one-pot procedure was used.[72] Thionyl chloride was added to a solution of *rac*-4,5-octanediol in carbon tetrachloride, and the suspension was refluxed for 2 h. The solution was cooled and diluted with acetonitrile and water. Ruthenium(III) chloride and sodium periodate were added, and the mixture reaction was stirred at room temperature until the reaction was complete. The reaction mixture was then worked up, which included dilution with dichloromethane, washing with water, aq. Na_2CO_3 and brine. The organic phase was dried over magnesium sulphate, filtered and passed through a short silica gel column to remove black material and evaporated to afford CSE **44** as a colorless oil in 92% yield (Scheme 3.27). The ^{13}C NMR confirmed the methine group at δ_C: 87.3, the methylene groups at δ_C: 33.7 and 18.5 and the methyl group at δ_C: 13.4. The ^{1}H NMR spectrum showed the methyl group resonance at δ_H: 0.95, methine groups at δ_H: 4.54 ppm as a multiplet and the methylene groups between 1.40 - 1.83 ppm. Mass spectrometry confirmed the molecular mass of [M + H] 209 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition. (HRMS (*m/z*) Found: 209.0841 $[M + H]^+$ $C_8H_{16}O_4S_1H$ requires: 209.0842 Da).

3.5.13: Synthesis of *rac*-4,5-Dipropyl-1,3-dithiolane-2-thione, *rac*-45 and *rac*-46.



Scheme 3.28: Synthesis of thione 45 and 2,3-dipropylthiirane 46

Following the established procedure *rac*-4,5-dipropyl-1,3,2-dioxathiolane-2,2-dioxide CSE **44** was added to a solution of sodium trithiocarbonate in dry THF. This solution was stirred at 70 ^{o}C overnight. The work-up involved the reaction mixture being filtered and partitioned between an organic and an aqueous phase. The organic layers were combined and dried over magnesium sulphate. The filtrate was evaporated, the crude compound was purified by chromatographic separation over silica which afforded two products: the first compound was *trans*-2,3-dipropylthiirane **46** as a yellow oil in 35% yield (Scheme 3.28). The ^{13}C NMR confirmed the carbon methine group at δ_C: 43.8, the carbon methylene groups at δ_C: 38.3 and 22.3 respectively and the methyl group at δ_C: 13.7. The ^{1}H NMR spectrum showed the methyl group resonance at δ_H: 0.88, methine groups at δ_H: 2.55 ppm as a multiplet and the methylene groups between 1.75–1.33 ppm. Mass spectrometry confirmed the molecular mass of $[M + H]^+$ 145 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition. (HRMS (*m/z*) Found: 145.1042 $[M + H]^+$ $C_8H_{16}S_1H$ requires: 145.1045 Da).

The second fraction was the desired compound **45** as a yellow oil in 28% yield (Scheme 3.28). The ^{13}C NMR spectrum confirmed the thione resonances at δ_C: 227.4, the methine groups at δ_C: 63.5, the chain methylene groups at δ_C: 30.5 and 21.3 and the methyl groups at δ_C: 13.6 and the ^{1}H NMR spectrum showed the resonance of the methyl groups

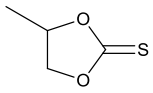
resonance at δ_H: 0.91, the methine groups at δ_H: 4.28 ppm as a multiplet and the methylene groups between 1.33-1.83 ppm. The infrared spectrum showed a C=S absorption at 1078 cm^{-1}. Mass spectrometry confirmed the molecular mass of [M + H] 221 g mol^{-1}. High resolution mass spectrometry confirmed the molecular composition. (HRMS (*m/z*) Found: 221.0487 $[M + H]^+$ $C_9H_{16}S_3H$ requires: 221.0487 Da).

3.6: Experimental Section

For all reactions where dry conditions were required, glassware was oven dried and reactions were carried out under a nitrogen atmosphere with magnetic stirring. All the reagents were analytical grade and used without further purification. All chemicals were purchased from Sigma Aldrich and used without further purification Organic solutions were concentrated under reduced pressure by rotary evaporation and vacuum pump. The solvents used in reactions were dried, distilled and stored under nitrogen prior to use. Dichloromethane was dried by distillation from CaH_2, THF was dried by distillation from sodium with benzophenone as indicator. Dry xylene was commercially available. The solvents ethyl acetate, hexane and cyclohexane (analytical grade) which were used for chromatography were purchased from Sigma Aldrich. For those reactions at 0 °C an ice bath was employed, and where heat was required a thermostatted aluminium dish on an adjustable dual-purpose laboratory electric heater and magnetic stirrer was used. Reactions were monitored by TLC.

3.6.1: Thionocarbonate chemistry and thionations.

Procedure A for Preparation of *rac*-10.

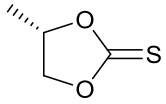


1,2-Propanediol (2 ml, 1.93 g, 25.4 mmol) was dissolved in dry DCM (50 ml), DMAP (a catalytic amount (5%)) and pyridine (5.1 ml, 63.5 mmol) were added, and the mixture was cooled in ice bath. A solution of thiophosgene (2.5 ml, 33.0 mmol) in dichloromethane (4.0 ml) was added dropwise. The mixture was allowed to warm to room temperature, and was stirred for a further 2 h. The reaction was quenched with 10% aq. citric acid (50 ml). The organic layer was separated and washed successively with aq. $NaHCO_3$ (50 ml) and

brine (50 ml), and dried over anhydrous $MgSO_4$. The crude material was purified by column chromatography using hexane / EtOAc (5:1) as eluent to provide *4-methyl-1,3-dioxolan-2-thione* ***rac*-10** as a red oil (2.20 g, 77%). δ_H (400 MHz, $CDCl_3$): 4.95 (1H, hex*, J = 6.5, 4-CH), 4.61 (1H, dd, J = 8.8, 7.9, 5-CH_α), 4.07 (1H, dd, J = 8.7, 7.9, 5-CH_β), 1.52 (3H, d, J = 6.2, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 191.5 (O-C=S), 78.8 (4-C), 74.3 (5-C), 18.3 (4-CH_3); ν_{max}: 2981, 1715, 1385, 1348, 1277, 1176, 978, 895, 837 and 539 cm^{-1}.

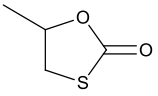
* a further small coupling was observed.

Preparation of *S*-10.



The enantiopure product ***S*-10** was prepared by a procedure identical to that described above for ***rac*-10**, in 77% yield; $[\alpha]_D$ = - 50 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.04 in THF).

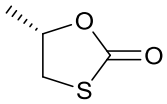
Rearrangement of *rac*-10 with tetrabutylammonium bromide.[3]



Bu_4NBr (64 mg, 0.20 mmol) was added under anhydrous conditions to a solution of *rac*-4-methyl-1,3-dioxolan-2-thione ***rac*-10** (236 mg, 2.0 mmol) dissolved in dry THF (15 ml). The mixture was stirred and refluxed for 12 h. The solvent was removed, and the residue was partitioned between EtOAc and 10% aq. citric acid (20 ml : 20 ml). The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column chromatography using cyclohexane / EtOAc (2:1) as eluent to provide *4-methyl-1,3-oxathiolane-2-one* ***rac*-11** as a pale yellow oil (213 mg, 90.2%). δ_H (400 MHz, $CDCl_3$): 4.78 (1H, hex*, J = 6.8, 4-CH), 3.50 (1H, dd, J = 6.3, 10.9, 5-CH_α), 3.20 (1H, dd, J = 8.3, 10.9, 5-CH_β), 1.46 (3H, d, J = 6.3, 4-CH_3); δ_C (100 MHz, $CDCl_3$):

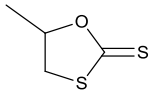
172.6 (S-C=O), 77.7 (4-C), 37.7 (5-C), 19.3 (4-CH_3); ν_{max}: 2922, 1721, 1442, 1384, 1331, 1153, 1071, 1023, 945, 876, 685, 658 and 424; HRMS (EI) (*m/z*) Found: 118.0082 $[M]^+$, $C_4H_6O_2S$ requires: 118.0083; other peaks at 103 [M- CH_3], 74 [M – C=S], 45 [M – C_3H_5-O_2].

Preparation of *S*-11.



The enantiopur product ***S*-11** was prepared by a procedure identical to that described above for ***rac*-11**; yield 90% ; $[\alpha]_D$ = - 40 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.05 in THF).

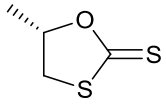
Preparation of *rac*-12.



A mixture of 4-methyl-1,3-oxathiolane-2-one ***rac*-11** (236 mg, 2 mmol), Lawesson's reagent (808 mg, 2.0 mmol) and hexamethyldisiloxane (324 mg, 0.42 ml, 2 mmol) in dry xylene (7 ml) was stirred for 30 min. The glass tube placed in an aluminium bath inside the microwave oven (CEM Discover SP) and irradiated so that the internal temperature reached 145 °C for 1 h. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered. The filtrate was evaporated and the crude compound was adsorbed on silica gel and purified by column chromatography using a mixture of cyclohexane and ethyl acetate (5 : 1) which afforded pure *4-methyl-1,3-oxathiolane-2-thione* ***rac*-12** as a yellow oil (221 mg, 93.6%). δ_H (400 MHz, $CDCl_3$): 5.20 (1H, m, 4-CH), 3.59 (1H, dd, J = 6.5 , 11.0, 5-CH_α), 3.32 (1H, dd, J = 7.8, 11.0, 5-CH_β), 1.59 (3H, d, J = 6.2 Hz, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 212.1 (S-C=S), 87.9 (4-C), 40.7 (5-C), 19.2 (4-CH_3); ν_{max}: 2928, 1727, 1595, 1438, 1341, 1241, 1186, 1039, 915, 831, 645 and 433; HRMS (EI)

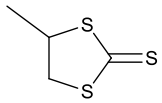
(*m/z*) Found: 133.9853 $[M]^+$, $C_4H_6O_1S_2$ requires: 133.9855; other peaks at 103 [M- CH_3], 74 [M – C=S], 44 [M – C_3H_4-S], 41 [M – $C_2H_5S_2$].

Preparation of *S*-12.



The enantiomeric product ***S*-12** was prepared by a procedure identical to that described above for ***rac*-12**, yield 93%, $[\alpha]_D$ = - 150 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.04 in THF). The enantiopurity was measured by HPLC using a chiral column; ChiralPAK® IC (250 mm L x 4.6 mm ID) using a mobile phase: Hept / EtOH 99:1, at 1 ml/min and 25 ºC, detection at 240 nm): Retention time 14.09 min., of 14.03 and 14.93 for the racemate.

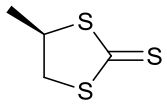
Preparation of *rac*-13.



A mixture of ***rac*-11** (236 mg, 2.0 mmol), Lawesson's Reagent (808 mg, 2 mmol) and hexamethyldisiloxane (324 mg, 0.42 ml, 2.0 mmol) was taken in a special glass tube, and the reaction mixture was stirred for 30 min. The glass tube was placed in an aluminium bath inside a microwave oven (CEM Discover SP), and irradiated so that the internal temperature reached 145 °C for 1 h. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered. The solvent was evaporated and the crude compound was adsorbed on silica gel and purified by column chromatography using a mixture of cyclohexane and ethyl acetate (10 : 1) which afforded the pure *4-methyl-1,3-dithiolane-2-thione* ***rac*-13** as a deep yellow oil (219 mg, 92.8%). δ_H (400 MHz, $CDCl_3$): 4.44 (1H, hex*, J = 6.6, 4-CH), 3.94 (1H, dd, J = 5.4, 11.9, 5-CH_α), 3.60 (1H, dd, J = 7.4 , 11.9, 5-CH_β), 1.53 (3H, d, J = 6.2, 5-CH_3); δ_C (100 MHz, $CDCl_3$): 228.1 (S-C=S), 55.2 (4-

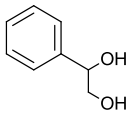
C), 50.1 (5-C), 18.8 4-CH_3; ν_{max}: 2921, 1590, 1495, 1447, 1253, 1078, 1052, 1034, 866, 685, 626, 537 and 505; HRMS (EI) (*m/z*) Found: 149.9623 $[M]^+$, $C_4H_6S_3$ requires: 149.9626, other peaks at 107 [(M+1) – CS], 75 [(M+1) – CS_2], [(M+1) – CS_3].

Preparation of *R*-13.



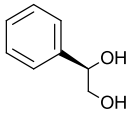
The enantiopure product ***R*-13** was prepared by a procedure identical to that described above for ***rac*-13**, in 93% yield; $[\alpha]_D$ = + 80° $g^{-1}ml^{-1}dm^{-1}$ (c = 0.025 in THF). The enantiopurity was measured by HPLC using a chiral column; ChiralPAK® IC (250 mm L x 4.6 mm ID) mobile phase: Hept / EtOH 99:1, 1 ml/min at 25 ºC detection at 240 nm): Retention time 8.9 min., of 8.80 and 8.98 for racemate.

Preparation of 1-Phenylethane-1,2-diol, *rac*-14.



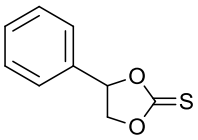
Styrene oxide (1.20 g, 10 mmol) in distilled water (70 ml) was stirred at 60 ºC for 2 h. The reaction mixture was extracted with ethyl acetate (2 x 50 ml). The organic layer was separated and successively washed with brine (50 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude material was purified by column chromatography using hexane / EtOAc (5:1) as eluent to provide 1-phenyl-1,2-ethanediol ***rac*-14** as a white solid (1.15 g, 95.8%). δ_H (400 MHz, $CDCl_3$): 7.31-7.37 (5H, m, Ar-H_5), 4.83 (1H, dd, J = 3.2 , 8.0, 1-H), 3.76 (1H, dd, J = 3.0 , 11.4, 2-H_α), 3.66 (dd, J = 8.2 , 11.1, 2-H_β), 2.69 (1H, br s, O-H), 2.27 (1H, br s, O-H); δ_C (100 MHz, $CDCl_3$): 140.3, 128.4, 127.8, 126.0 (Ar-C_6), 74.6 (1-C), 67.8 (2-C).

1-Phenylethane-1,2-diol, *R*-14.



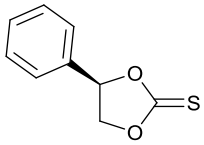
The enantiopure product ***R*-14** was commercially available.

Preparation of *rac*-15.[73]



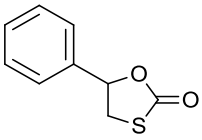
To a solution of diol ***rac*-14** (2.00 g, 14.5 mmol) and DMAP (3.25 g, 26.6 mmol) in toluene (100 ml) was added a solution of thiophosgene (1.40 g, 12.1 mmol) in toluene (11 ml) dropwise. After stirring for 3 h at 20 ºC, the reaction mixture, containing a lot of yellow solid, and was diluted with toluene (50 ml) and filtered through a sintered glass frit containing a small pad of silica gel. The reaction solution was washed successively with 0.1 % HCl aqueous solution (30 ml), water (3 × 50 ml) and brine (50 ml), and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude material was purified by flash column chromatography using cyclohexane / ethyl acetate (2:1) as eluent to provide *4-phenyl-1,3-dioxolane-2-thione* ***rac*-15** as a white solid (2.21 g, 83.5%). δ_H (400 MHz, $CDCl_3$): 7.21-7.34 (5H, m, Ar-H_5), 5.85 (1H, t, J = 8.2, 4-CH), 4.89 (1H, t, J = 8.2, 5-CH_α), 4.45 (1H, t, J = 7.8, 5-CH_β); δ_C (100 MHz, $CDCl_3$): 191.3 (C=S), 134.3, 129.7, 129.0, 126.0 (Ar-C_6), 82.9 (4-C), 74.7 (5-C).

Preparation of *R*-15.

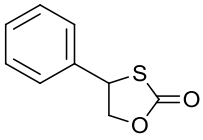


The enantiopure product ***R*-15** was prepared by a procedure identical to that described above for ***rac*-15**, in 84% yield.

Rearrangement of *rac*-15 with tetrabutylammonium bromide.



16a



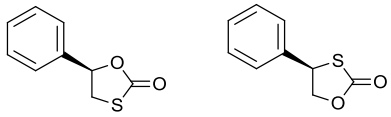
16b

Bu_4NBr (1.60 g, 5.0 mmol) was added under anhydrous conditions to a solution of *rac*-4-phenyl-1,3-dioxolan-2-thione **14** (1.80 g, 10.0 mmol) in dry THF (50 ml). The mixture was stirred and refluxed for 3 h. The solvent was removed and the residue was partitioned between ethyl acetate and 10% aq. citric acid (40 ml : 40 ml). The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column chromatography using hexane / ethyl acetate (2:1) as eluent to provide a mixture of *4-phenyl-1,3-oxathiolan-2-one* **16a** and *5-phenyl-1,3-oxathiolane-2-one* **16b** in a ratio of approximately 30 : 70, as a pale yellow oil (1.66 g, 92.2%).

16a δ_H (400 MHz, $CDCl_3$): 7.27-7.40 (m, Ar-H_5), 5.63 (1H, dd, J = 6.5 , 9.4, 4-CH), 3.73 (1H, dd, J = 6.5 , 11.2, 5-CH_α), 3.55 (1H, dd, J = 9.5 , 11.2, 5-CH_β); δ_C (100 MHz, $CDCl_3$): 172.4 (S-C=O), 136.1, 129.1, 127.2, 125.5 (Ar-C_6), 81.8 (4-C), 38.4 (5-C).

16b δ_H (400 MHz, $CDCl_3$): 7.27-7.40 (5H, m, Ar-H_5), 5.13 (1H, t, J = 7.2, 4-CH), 4.70 (1H, dd, J = 6.9 , 9.6, 5-CH_α), 4.38 (1H, dd, J = 7.5 , 9.6, 5-CH_β); δ_C (100 MHz, $CDCl_3$): 172.6 (S-C=O), 136.0, 129.1, 127.2, 125.5 (Ar-C_6), 74.4 (4-C), 52.0 (5-C).

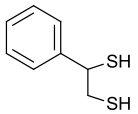
Preparation of *S*-16a and *S*-16b.



16a **16b**

The enantiopure products ***S*-16a** and ***S*-16b** were prepared by a procedure identical to that described above for ***rac*-16a** and ***rac*-16b** in a ratio of approximately 30 : 70, yield 93%; $[\alpha]_D$ = + 57.1 $g^{-1}ml^{-1}dm^{-1}$ (c = 0.035 in THF).

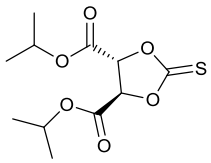
Preparation of Dithiol 17.



A mixture of ***rac*-16a** and ***rac*-16b** from the previous preparation (360 mg, 2 mmol), phosphorus pentasulphide (P_4S_{10}) (888 mg, 2.0 mmol) and hexamethyldisiloxane (1.54 g, 2.0 ml, 10.0 mmol) was put in glass tube and the reaction mixture was stirred for 30 min. The glass tube was placed in an aluminium bath inside a microwave oven (CEM Discover SP), and irradiated so that the internal temperature reached 140 °C for 30 min. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered. The filtrate was evaporated and the crude compound was adsorbed on silica gel and purified by column chromatography using a mixture of cyclohexane and ethyl acetate (4 : 1) which afforded pure *4-phenylethane-1,2-dithiol* ***rac*-17** as a very pungent yellow oil (131 mg, 38.5%). δ_H (400 MHz, $CDCl_3$): 7.19 - 7.26 (m, Ar-H_5), 3.03 (1H, m, 2-H_β), 4.01 (1H, m, 1-H), 2.90 (1H, m, 2-H_α), 2.23 (1H, d, J = 5.6, methine-SH), 1.41 (1H, t, J = 7.4,

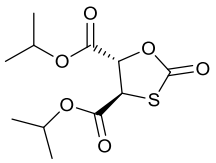
methylene-SH); δ_C (100 MHz, $CDCl_3$): 141.5, 129.0, 128.5, 127.1 (Ar-C_6), 47.0 (1-C), 34.0 (2-C); HRMS (EI) (*m/z*) Found: 170.0217 $[M]^+$, $C_8H_{10}S_2$ requires: 170.0217 $[M]^+$, other peaks at 137 [M – SH], 123 [M – CH_2SH], 104 [M – 2SH], 77 [(M +1) –$C_2H_5S_2$], 51, 45.

Preparation of cyclic thionocarbonate, *R,R*-18.



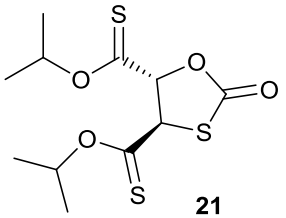
The cyclic thionocarbonate ***R,R*-18** was synthesized according to Ko[3] and spectroscopic data correspond to the literature values. A solution of diisopropyl *L*-tartrate (2.34 g, 10.0 mmol) and pyridine (2.0 ml, 25.0 mmol) in anhydrous dichloromethane (50 ml) and DMAP (less than 5.0%) was stirred for 10 min at 0 ºC. A solution of thiophosgene (1.0 ml, 13 mmol) in dichloromethane (7.0 ml) was added dropwise. The mixture was allowed to stir in the cold bath for 30 min. The reaction mixture was partitioned between dichloromethane (50 ml) and 10% aq. citric acid (50ml), the organic layer was separated, and firstly washed with water (80 ml) and secondly with aq. $NaHCO_3$ solution and brine. The layers were separated and the organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude material was purified by column chromatography using hexane / ethyl acetate (5:1) as eluent to provide ***R,R*-18** as a pale orange solid (2.11 g, 77.0%). m. p. 57-60 ^oC, δ_H (400 MHz, $CDCl_3$): 5.21 (2H, s, 4,5-H), 5.10 (2H, sep, J = 6.3, 2 x isopr.C-H), 1.27 (12H, d, J = 6.3, 4 x isopr.–CH_3); δ_C (100 MHz, $CDCl_3$): 188.2 (C=S), 164.6 (2 x C=O), 79.2 (2 x isopr.CH), 71.9 (4,5–C), 21.4 (4 x isopr.CH_3); ν_{max}: 2990, 1752, 1380, 1264 cm^{-1}.

Rearrangement of *R,R*-18 with Bu_4NBr.[3]

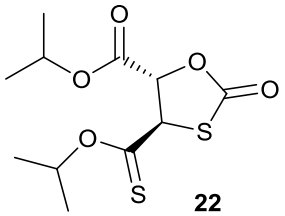


The cyclic thionocarbonate ***R,R*-18** (1.1 g, 4 mmol) was dissolved in dry tetrahydrofuran (50 ml) and tetrabutylammonium bromide (128 mg, 0.4 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and 10% aq. citric acid and the organic layer was separated and washed with brine. The organic layer was dried over $MgSO_4$, the solvent evaporated and the crude compound adsorbed on silica gel and purified by column chromatography using hexane and ethyl acetate (3 : 1) which afforded the pure ***R,R*-19** as a pale orange oil (1.07 g, 97%), δ_H (400 MHz, $CDCl_3$): 5.40 (1H, d, J = 2.8, 4-H), 5.11 (2H, m, 2 x isopr.C-H), 4.58 (H, d, J = 2.8, 5-H), 1.25 (12H, d, J = 2.9, 4 x isopr.–CH_3); δ_c (100 MHz, $CDCl_3$): 169.2 (S-C=O), 167.1 (C=O), 166.3 (C=O), 76.5 (2 x isopr.CH), 71.1 (4–C), 50.1 (5-C), 21.3 (4 x isopr.CH_3); ν_{max}: 2984, 1758, 1732, 1376, 1279, 1092, 1059 cm^{-1}.

Preparation of *R,R*-21 and *R,R*-22.



21



22

A mixture of ***R,R*-19** (554 mg, 2.0 mmol), Lawesson's reagent (808 mg, 2 mmol) and hexamethyldisiloxane (324 mg, 0.42 ml, 2.0 mmol) was taken in a special glass tube, and the reaction mixture was stirred for 30 min. The glass tube placed in an aluminium bath

inside a microwave oven (CEM Discover SP), and irradiated so that the internal temperature reached 150 °C for 30 min. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered. The solvent was evaporated and the crude product showed five spots (TLC, cyclohexane and ethyl acetate 9:1). Separation of compounds by column chromatography using a mixture of cyclohexane and ethyl acetate (10 : 1) afforded two compounds:

***R,R*-21,** deep yellow oil (191 mg, 31%). δ_H (400 MHz, $CDCl_3$): 5.79 (1H, d, J = 2.8, 4-H), 5.65 (2H, m, 2 x isopr.C-H), 4.95 (H, d, J = 2.8, 5-H), 1.38 (12H, d, J = 2.9, 4 x isopr.–CH_3); δ_C (100 MHz, $CDCl_3$): 210.7 (C=S), 85.1 (2 x isopr.CH), 170.2 (S-C=O), 212.1 (C=S), 77.9 (O–CH), 61.8 (S-CH), 20.8 (4 x isopr.CH_3); ν_{max}: 2980, 1758, 1372, 1277, 1190, 1090, 917 cm^{-1}; EI (+ve): 308 $[M]^+$, HRMS (EI) (*m/z*) Found: 309.0282 $[M + H]^+$, $C_{11}H_{16}O_4S_3H$ requires: 309.0288.

***R,R*-22** as a deep yellow oil (243 mg, 41%). δ_H (400 MHz, $CDCl_3$): 5.66 (H, d, J = 2.8, 4-H), 5.59 (1H, m, isopr.C-H), 5.12 (1H, m, isopr.C-H), 4.86 (H, d, J = 2.8, 5-H), 1.38 (6H, d, J = 2.9, 2 x isopr.–CH_3), 1.28 (6H, d, J = 2.9, 2 x isopr.–CH_3); δ_C (100 MHz, $CDCl_3$): 211.7 (C=S), 170.2 (C=O), 166.6 (S-C=O), 78.5 and 77.9 (2 x isopr.CH), 71.3 (O–CH), 59.5 (S-CH), 21.5 (2 x isopr.CH_3), 20.6 (2 x isopr.CH_3); ν_{max}: 2982, 1758, 1732, 1374, 1286, 1248, 1090, 1059, 961, 914 cm^{-1}; *m/z*: (EI) 310 $[M + NH_4]^+$; HRMS (EI) (*m/z*) found: 310.0782 $[M + NH_4]^+$ $C_{11}H_{16}O_5S_2 + NH_4$ requires: 310.0777.

Alternative procedures:

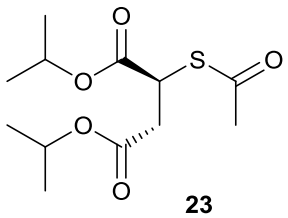
First procedure: To a solution of ***R,R*-19** (277 mg, 1.0 mmol) in dry toluene (10 ml), Lawesson's reagent (808 mg, 2 mmol) and hexamethyldisiloxane (324 mg, 0.42 ml, 2.0 mmol) were added at room temperature under a nitrogen atmosphere, and the resulting solution was refluxed for 4 h. After cooling to room temperature, the reaction mixture was

dissolved in dichloromethane and filtered. The solvent was evaporated and the crude product showed five spots (TLC, cyclohexane and ethyl acetate 9:1). Separation of compounds by column chromatography using a mixture of cyclohexane and ethyl acetate (10 : 1) afforded mainly two compounds: ***R,R*-21 and *R,R*-22.**

Second procedure: To a solution of ***R,R*-19** (277 mg, 1.0 mmol) in dry toluene (5 ml), Lawesson's reagent (808 mg, 2 mmol) and hexamethyldisiloxane (324 mg, 0.42 ml, 2.0 mmol) were taken in a special glass tube, and the reaction mixture was stirred for 30 min. The glass tube placed in an aluminium bath inside a microwave oven (CEM Discover SP), and irradiated so that the internal temperature reached 115 °C for 30 min. After cooling to room temperature, the reaction mixture was dissolved in dichloromethane and filtered. The solvent was evaporated and the crude product showed five spots (TLC, cyclohexane and ethyl acetate 9:1). Separation of compounds by column chromatography using a mixture of cyclohexane and ethyl acetate (10 : 1) afforded mainly two substances: ***R,R*-21 and *R,R*-22.**

Third procedure: using the same conditions as the second procedure but with P_4S_{10} as a reagent instead of Lawesson's reagent, which afforded mainly two compounds: ***R,R*-21 and *R,R*-22.**

Preparation of *R,R*-23.



23

***R,R*-19** (277 mg, 1.0 mmol) was dissolved in dry DMF (10 ml) and the solution was stirred at room temperature. Potassium thioacetate (125 mg, 1.1 mmol) was added and the mixture stirred 2 h. at room temperature. The mixture became a black solution. Drops of HCl (2M)

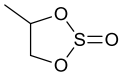
were added until the pH fell to ≤ 4. Aqueous work-up (ethyl acetate-water) was followed by flash chromatography (cyclohexane : EtOAc 4:1), to afford ***R,R*-23** as a yellow oil (116 mg, 42%), δ_H (400 MHz, $CDCl_3$): 5.94 (2H, m, 2 x isopr.C-H), 4.40 (1H, m, 2-H), 2.81 (2H, m, 3-H_2), 2.28 (1H, s, (CO)-CH_3), 1.17 (12H, d, J = 2.9, 4 x isopr.–CH_3); δ_C (100 MHz, $CDCl_3$): 193.0 (CH_3-C=O), 169.6 (-C=O), 169.4 (C=O), 69.4 and 69.6 (2 x isopr.CH), 41.5 (3–C), 36.9 (2-C), 29.9 ((CO)-CH_3), 21.4 (4 x isopr.CH_3); ν_{max}: 2981, 1728, 1712, 1374, 1114, 955, 733, 623 cm^{-1}; (*m/z*) EI (+ve) found: 277 $[M + H]^+$, (*m/z*) HRMS (EI) found: 277.1106 $[M + H]^+$, $C_{12}H_{20}O_5S_1H$ requires: 277.1104 Da.

3.6.2: Cyclic Sulphate Ester Chemistry.

Synthesis of sodium trithiocarbonate (Na_2CS_3) 30.

A solution of sodium sulphide $Na_2S.9H_2O$ (0.48 mg, 2.0 mmol) in methanol (5 ml) was stirred for 30 min. and then carbon disulphide (2.4 ml, 4.0 mmol) was added. The mixture was left stirring under nitrogen at room temperature. The reaction mixture became an orange colour, as the trithiocarbonate salt **30** formed. The solvent and the excess CS_2 were evaporated carefully at room temperature. Sodium trithiocarbonate, Na_2CS_3, **30** (308 mg) was obtained as an orange solid which was used directly in the reaction with a cyclic sulphate ester.

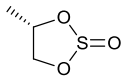
Synthesis of *rac*-4-methyl-1,3,2-dioxathiolane-2-oxide, procedure G.



To a stirred solution of *rac*-1,2-propandiol (5.18 g, 68.0 mmol) and pyridine (12.52 g, 158.5 mmol) in dry THF (20 ml) at 0˚C under a nitrogen atmosphere, thiony1 chloride (9.42, 79.2 mmol) was added dropwise. The mixture was stirred at room temperature for approximately 12 h. The precipitate was filtered off and the solvent evaporated under reduced pressure. The residue was partitioned between dichloromethane and water, the organic layer separated and the aqueous layer was further extracted by dichloromethane (2 x 20 ml). The organic layers were combined and washed with 0.5M hydrochloric acid and water, then dried over sodium sulphate. The solvent was evaporated under reduced pressure giving the cyclic sulphite ester **8** as a yellow oil (6.7g, 82%), containing two diastereoisomers in the ratio 2:1. The major isomer had δ_H (400 MHz $CDCl_3$): 4.65 (1H, m, 4-H), 4.55 (1H, m, 5-H_α), 3.98 (1H, dd J 8.2, 6.9 Hz, 5-H_β), 1.53 (3H, d, J = 5.9 Hz, 4-CH_3); δ_C (100 MHz $CDCl_3$): 75.9 (4-C), 66.9 (5-C), 14.3 (CH_3). The minor isomer had δ_H

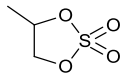
(400 MHz $CDCl_3$): 5.04 (1H, m, 4-H), 4.60 (1H, dd, J = 8.5, 5.9 Hz, 5-H_α), 4.20 (1H, dd, J = 9.3, 8.6 Hz, 5-H_β), 1.35 (3H, d, J = 6.3 Hz, 4-CH_3); δ_C (100 MHz $CDCl_3$): 72.9 (4-C), 68.4 (5-C), 13.2 (CH_3).

Synthesis of *S*-4-methyl-1,3,2-dioxathiolane-2-oxide, *S*-31.



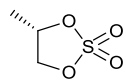
The enantiopure product ***S*-31** was prepared by a procedure identical to that described above for ***rac*-31** but using S-1,2-propanediol in 82% yield.

Synthesis of *rac*-4-methyl-1,3,2-dioxathiolane-2,2-dioxide *rac*-32, procedure H.



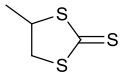
A solution of cyclic sulphite ester **31** (1.0 g, 8.2 mmol) in dichloromethane (60 ml) was stirred vigorously with aqueous sodium periodate (3.5 g, 16.4 mmol) and ruthenium(IV) oxide (5 mg, catalytic). After approximately 10 min the brown mixture turned green, which upon further stirring produced a grey-green coloured solution. Reaction was monitored by TLC. The organic layer was separated, stirred with a few drops of propan-2-ol for 15 min, dried over sodium sulphate and filtered through high flo cel. The solvent was evaporated to give ***rac*-32** as a yellow oil (0.53 g, 47%). δ_H (400 MHz $CDCl_3$): 5.19 (1H, m, 4-H), 4.68 (1H, dd, J = 8.8 and 5.8 Hz, 5-H_α), 4.25 (1H, m, 5-H_β), 1.60 (3H, d, J = 6.4 Hz, CH_3); δ_C (100 MHz $CDCl_3$): 79.5 (4-C), 74.0 (5-C), 17.6 (CH_3); (*m/z*) HRMS (EI) (*m/z*) found: 139.0057 $[M + H]^+$, $C_3H_6O_4S$ + H requires: 139.0060.

Synthesis of *S*-4-methyl-1,3,2-dioxathiolane-2,2-dioxide *S*-32.



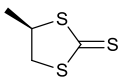
The enantiopure product ***S*-32** was prepared by a procedure identical to that described above for ***rac*-32** but using ***S*-31** in 48% yield; $[\alpha]_D$ = + 66.6 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.03 in THF).

Synthesis of *rac*-4-methyl-1,3-dithiolane-2-thione *rac*-33, procedure I.



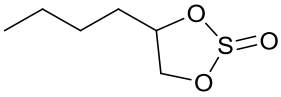
To sodium trithiocarbonate (616 mg, 4.0 mmol) in dry THF (10 ml), the cyclic sulphate ester ***rac*-32** (276 mg, 2.0 mmol) was added and the mixture was stirred and heated to 60 ºC for 2 h. The mixture was cooled to room temperature and left stirring for 30 min. The reaction mixture was filtered, the solvent was removed and the crude product was quenched with water (30 ml) and then extracted with dichloromethane (2 x 20 ml). The organic layer was dried over magnesium sulphate ($MgSO_4$) and filtered. The filtrate was evaporated which afforded the pure *rac*-4-methyl-1,3-dithiolane-2-thione ***rac*-33** as a deep yellow oil (219 mg, 92.8%), δ_H (400 MHz, $CDCl_3$): 4.47 (1H, t, J = 6.5 Hz, 13.6 Hz, 4-H), 3.94 (1H, t, J = 8.0 Hz, 5-H_α), 3.62 (1H, t, J = 7.8 Hz, 5-H_β), 1.56 (3H, d, J = 6.2 Hz, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 228.1 (S-C=S), 55.2 (4-C), 50.1 (5-C), 18.9 (4-CH_3); ν_{max}: 2921, 1590, 1495, 1447, 1253, 1078, 1052, 1034, 866, 685, 626, 537 and 505; (*m/z*) HRMS (EI) found: 150.9702 $[M + H]^+$, C4H6S3+H requires: 150.9704.

Synthesis of *S*-4-methyl-1,3-dithiolane-2-thione, *R*-33.



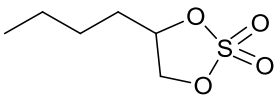
The enantiopure product ***R*-33** was prepared by a procedure identical to that described above for ***rac*-33** but using ***S*-32** in 93% yield; $[\alpha]_D$ = + 112 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.25 in $CHCl_3$).

Synthesis of *rac*-4-butyl-1,3,2-dioxathiolane-2-oxide, *rac*-34.



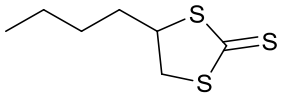
Following procedure **G**, a solution of *rac*-hexane-1,2-diol (5.0 g, 5.2 ml, 42.37mmol) in similar way and usual work-up to give *rac*-4-butyl-1,3,2-dioxathiolane-2-oxide ***rac*-34** as a pale yellow oil (5.2 g, 74.8 %), as two diastereoisomers in the ratio 2:1. The major isomer δ_H (400 MHz $CDCl_3$): 4.90 (1H, m, 4-H), 4.62 (1H, dd, J = 11.8, 5.4 Hz, 5-H_α), 3.85 (1H, dd, J = 11.8, 7.8 Hz, 5-H_β), 1.78 (2H, m, CH_2), 1.59 (2H, m, CH_2), 1.27 (2H, m, CH_2), 0.85 (3H, t, J = 6.6 Hz, $–CH_3$); δ_C (100 MHz, $CDCl_3$): 80.2 (4-C), 71.5 (5-C), 31.8 ($-CH_2$), 26.6 ($-CH_2$), 22.3 ($-CH_2$), 13.7 ($-CH_3$). The minor isomer had δ_H (400 MHz, $CDCl_3$): 4.48 (1H, m, 4-H), 4.38 (1H, dd, J = 11.8, 5.4 Hz, 5-H_α), 4.25 (1H, dd, J = 11.8, 7.8 5-H_β), 1.89 (2H, m, $-CH_2$), 1.44 (2H, m, $-CH_2$), 1.30 (2H, m, $-CH_2$), 0.85 (3H, t, J = 6.6 Hz, $–CH_3$); δ_C (100 MHz, $CDCl_3$): 84.1 (4-C), 70.1 (5-C), 32.9 ($-CH_2$), 27.9 ($-CH_2$), 22.3 ($-CH_2$), 13.7 ($-CH_3$).

Synthesis of *rac*-4-butyl-1,3,2-dioxathiolane-2,2-dioxide, *rac*-35.



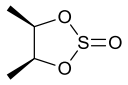
Following procedure **H**, *rac*-4-buty1-1,3,2-dioxathiolane-2-oxide ***rac*-34** (4.75 g, 28.96 mmol) was oxidized to gave *rac*-4-buthyl-1,3,2-dioxathiolane-2,2-dioxide ***rac*-35** as a light yellow oil (86.9%). δ_H (400 MHz, $CDCl_3$): 4.95 (1H, m, 4-H), 4.78 (1H, dd, J = 11.8, 5.4 Hz, 5-H_α), 4.34 (1H, dd, J = 11.8, 7.8 Hz, 5-H_β), 1.97 (2H, m, $-CH_2$), 1.76 (2H, m, $-CH_2$), 1.37 (2H, m, $-CH_2$), 0.92 (3H, t, J = 6.6 Hz, $–CH_3$); δ_C (100 MHz, $CDCl_3$): 82.9 (4-C), 72.8 (5-C), 31.8 ($-CH_2$), 26.6 ($-CH_2$), 22.1 ($-CH_2$), 13.7 ($-CH_3$).

Synthesis of *rac*-4-butyl-1,3-dithiolane-2-thione *rac*-36.



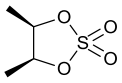
Sodium trithiocarbonate **30** (616 mg, 4.0 mmol), prepared by procedure F, was dissolved in dry THF (10ml), and a solution of *rac*-4-butyl-1,3,2-dioxathiolane-2,2-dioxide ***rac*-35** (360 mg, 2.0 mmol) was added, following procedure **I**, except that the reaction time was 4 h. to give a yellow very pungent oil *rac*-4-butyl-1,3-dithiolane-2-thione ***rac*-36** (377 mg, 98%),[41] δ_H (400 MHz, $CDCl_3$): 4.41 (1H, m, 4-H), 3.9 (1H, dd, J = 11.8, 5.4 Hz, 5-H_α), 3.69 (1H, dd, J = 8.0, 5.4 Hz, 5-H_β), 1.90 (2H, m, -CH_2), 1.35 (4H, m, 2 x –CH_2), 0.90 (3H, t, J = 6.6 Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 227.8 (C=S), 61.0 (4-C), 48.2 (5-C), 33.2 (-CH_2), 30.3(-CH_2), 22.3 (-CH_2), 13.8 (-CH_3); (*m/z*) HRMS (EI) Found: 193.0171 $[M + H]^+$, $C_7H_{12}S_3H$ requires: 193.0174.

Synthesis of *R,S*-4,5-dimethyl-1,3,2-dioxathiolane-2-oxide, *meso*-37.



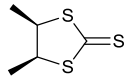
Following procedure **G**, *meso*-2,3-butanediol (5.13 g, 56.85 mmol) gave cyclic sulfite ester ***meso*-37** as a yellow oil (7.55 g, 98%) containing two diastereoisomers in the ratio 4:1. The major isomer δ_H (400 MHz, $CDCl_3$): 4.90 (2H, m, 4-,5-H), 1.21 (6H, d, J = 6.2 Hz, 2 x CH_3); δ_C (100 MHz, $CDCl_3$): 78.3 (4-,5-C), 14.0 (4-,5-CH_3). The minor isomer had δ_H (400 MHz, $CDCl_3$): 4.59 (1H, m, 4,5-H), 1.40 (6H, d, J = 6.2 Hz, 2 x CH_3); δ_C (100 MHz, $CDCl_3$): 80.9 (4-,5-C), 15.8 (4-,5-CH_3).

Synthesis of *R,S*-4,5-dimethyl-1,3,2-dioxathiolane-2,2-dioxide, *meso*-38.



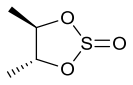
This material was prepared from *R,S*-4,5-dimethy1-1,3,2-dioxathiolane 2-oxide (7.55 g, 55.5 mmol) following procedure **H** to give **CSE *meso*-38** as a pale brown solid (7.85g, 93%), mp 49- 50˚C (lit[74] mp 48-49. 5˚C). δ_H: 5.02 (2H, m, 4-,5-H), 1.44 (6H, d, J = 6.4 Hz, 4-,5-CH_3); δ_C (100 MHz, $CDCl_3$): 82.3 (4-,5-C), 14.2 (4-,5-CH_3).

Synthesis of *R,S*-4,5-dimethyl-1,3-dithiolane-2-thione *meso*-39.



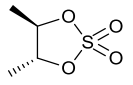
Cyclic sulphate ester ***meso*-38** (304 mg, 2.0 mmol) and sodium trithiocarbonate **30** (616 mg, 4.0 mmol, prepared by procedure **F**) were reacted according to procedure **I**, to afford pure *R,S-4,5-dimethyl-1,3-dithiolane-2-thione* ***meso*-39** as a deep yellow oil (187 mg, 61%), δ_H (400 MHz, $CDCl_3$): 4.04 (2H, m, 4-,5-H), 1.53 (6H, d, J = 6.2 Hz, 5-CH_3); δ_C (100 MHz, $CDCl_3$): 226.3 (-C=S), 61.2 (4-,5-C), 18.4 (4-,5-CH_3); ν_{max}: 2921, 1590, 1495, 1447, 1253, 1078, 1052, 1034, 866, 685, 626, 537 and 505; (*m/z*) HRMS (EI) Found: 164.9858 [M]+, $C_5H_8S_3H$ requires: 164.9861.

Synthesis of *R,R*-4,5-dimethyl-1,3,2-dioxathiolane-2-oxide, *R,R*-40.



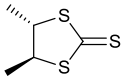
Following procedure **G**, *R,R*-2,3-butanediol (5.13g, 56.85mmol), gave cyclic sulphite ester product ***R,R*-40** as yellow oil (7.55g, 98%). δ_H (400 MHz, $CDCl_3$): 4.57 (2H, m, 5-H), 4.04 (2H, m, 4-H), 1.48 (3H, d, J = 6.2 Hz, -CH_3), 1.40 (3H, d, J = 6.2 Hz, -CH_3); δ_C (100 MHz, $CDCl_3$): 85.3 (5-C), 80.2 (4-C), 17.7 (5-CH_3), 15.8 (4-CH_3).

Synthesis of *R,R*-4,5-dimethyl-1,3,2-dioxathiolane-2,2-dioxide, *R,R*-41.



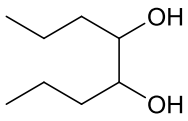
Following procedure **H**, gave the CSE ***R,R*-41** as a pale brown oil (15.68g, 93%) δ_H (400 MHz, $CDCl_3$): 4.62 (2H, m, 4-,5-H), 1.48 (6H, d, J = 6.4 Hz, 4-,5-CH_3); δ_C (100 MHz, $CDCl_3$): 85.3 (4-,5-C), 16.2 (4-,5-CH_3) $[\alpha]_D$ = + 29.6 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.135 in THF).

Synthesis of *S,S*-4,5-dimethyl-1,3-dithiolane-2-thione, *S,S*-42.



Cyclic sulphate ester ***R,R*-41** (304 mg, 2.0 mmol) and sodium trithiocarbonate **30** (616 mg, 4.0 mmol, prepared by procedure F) were reacted according to procedure I, to afford pure *R,R-4,5-dimethyl-1,3-dithiolane-2-thione* ***R,R*-42** as a deep yellow oil (190 mg, 62%), δ_H (400 MHz, $CDCl_3$): 4.04 (2H, m, 4-,5-H), 1.53 (6H, d, J = 6.2 Hz, 5-CH_3); δ_C (100 MHz, $CDCl_3$): 226.3 (-C=S), 61.2 (4-,5-C), 18.4 (4-,5-CH_3); ν_{max}: 2921, 1590, 1495, 1447, 1253, 1078, 1052, 1034, 866, 685, 626, 537 and 505; (*m/z*) HRMS (EI) Found: 164.9858 [M]+, $C_5H_8S_3H$ requires: 164.9861; $[\alpha]_D$ = + 325 $g^{-1}mL^{-1}dm^{-1}$ (c = 0.016 in THF).

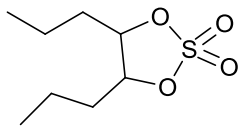
Synthesis of *rac*-octane-4,5-diol, *rac*-43.[65]



A suspension of CuI (665 mg, 3.73 mmol) in dry THF (10 ml) was cooled to -30 ºC (o-xylene / liquid nitrogen) and ethylmagnesium bromide (11.67 ml, 3.0 M in Et_2O, 35.0 mmol) was added dropwise. The solution was stirred for 10 min and *rac*-1,3-butanediene diepoxide (1.04 ml, 11.6 mmol) was added. The mixture reaction was warmed to 0 ºC using an ice bath, and aqueous saturated NH_4Cl solution (50 ml) was slowly added. After 30 min. the layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with brine, water, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product was passed through a short silica gel column using cyclohexane / ethylacetate (4:1) to give *rac*-octane-4,5-diol ***rac*-43** (1.430 g, 85.1 %) as a pale yellow oil.[75] δ_H (400 MHz, $CDCl_3$): 3.66 (2H, m, 4-,5-H), 2.86 (2H, m, 2 x -OH), 1.51

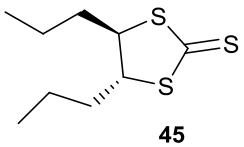
– 1.28 (8H, m, 2-, 3-, 6-, 7-H_2), 0.88 (6H, t, J = 7.1 and 2.0, 2 x CH_3); δ_C (100 MHz, $CDCl_3$): 73.9 (4-,5-C), 35.5 (3-,6-C), 18.7 (2-,7-C), 14.0 (2 x CH_3).

Synthesis of *rac*-4,5-dipropyl-1,3,2-dioxathiolane-2,2-dioxide, *rac*-44.[72]

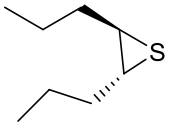


Thionyl chloride (1.5 ml, 21 mmol) was added to a solution of *rac*-4,5-octanediol (2.40 g, 16.4 mmol) in carbon tetrachloride (15 ml) and the suspension was refluxed for 2 h. The solution was cooled with an ice bath and diluted with acetonitrile (15 ml) and water (25 ml). Ruthenium chloride (0.16 mmol) and sodium periodate (5.18 g, 24.0 mmol) were added, and the reaction mixture was stirred at room temperature until the reaction was complete (the reaction was monitored by TLC). The reaction mixture was diluted with dichloromethane (50 ml) and the layers were separated. The organic layer was washed with water, aq. Na_2CO_3 and brine and dried over magnesium sulphate. The solution was filtered and concentrated under a vacuum, and the crude compound was passed through a short silica gel column to remove black material. Evaporation of the solvent afforded *rac*-4,5-dipropyl-1,3,2-dioxathiolane-2,2-dioxide ***rac*-44** as a colourless oil (4.10 g, 91.9%). δ_H (100 MHz, $CDCl_3$): 4.55 (2H, m, 4-,5-H), 1.82 – 1.40 (8H, m, 2 x -CH_2-CH_2-), 0.96 (6H, t, J = 7.4, 2 x -CH_3); δ_C (100 MHz, $CDCl_3$): 87.2 (4-,5-C), 33.7 (3-,6-C), 18.5 (2-,7-C), 13.4 (2 x -CH_3). *m/z* [M + H] 209. HRMS (EI) (*m/z*) found: 209.0841 $[M + H]^+$ $C_8H_{16}O_4S_1H$ requires: 209.0842.

Synthesis of *rac*-4,5-dipropyl-1,3-dithiolane-2-thione, *rac*-45 and 2,3-dipropyl thiirane, *rac*-46.



45



46

Cyclic sulphate ester ***rac*-44** (500 mg, 2.4 mmol) and sodium trithiocarbonate **30** (740 mg, 4.8 mmol, prepared by procedure **F**) were reacted according to procedure **I**, except the crude compound was purified by chromatographic separation over silica using cyclohexane / ethyl acetate (20 :1) which afforded two products: the first compound to be checked was desired substance *R,R-4,5-dipropyl-1,3-dithiolane-2*-thione, ***rac*-45** as a yellow oil (148 mg, 28%). δ_H (400 MHz, $CDCl_3$): 4.50 (2H, m, 4-,5-H), 1.83 – 1.33 (8H, m, 2 x -CH_2-CH_2-)) 0.93 (6H, t, J = 7.4 Hz, 2 x -CH_3)); δ_C (100 MHz, $CDCl_3$): 227.4 (-C=S), 63.6 (4-,5-C), 30.5 (2 x -CH_2), 21.2 (2 x -CH_2), 13.7 (2 x -CH_3). *m/z* (EI) [M + H] 221; HRMS (EI) found: 221.0487 $[M + H]^+$, $C_9H_{16}S_3H$ requires: 221.0487.

The second fraction gave *trans*-4,5-dipropylthiirane ***rac*-46** as a yellow oil (122 mg, 35%). δ_H (400 MHz, $CDCl_3$): 2.55 (2H, m, 2-,3-H), 1.75 – 1.33 (8H, m, 2 x -CH_2-CH_2-), 0.88 (6H, m, 2 x -CH_3); δ_C (100 MHz, $CDCl_3$): 43.8 (2-,3-H), 38.3 (2 x -CH_2), 22.3 (2 x -CH_2), 13.7 (2 x -CH_3). *m/z* $[M + H]^+$ 145; HRMS (EI) found: 145.1042 $[M + H]^+$, $C_8H_{16}SH$ requires: 145.1045.

3.7: <u>References.</u>

1. E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc*., **1962**, *84*, 2938.
2. S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, **1960**, 1030.
3. S.Y. Ko, *J. Org. Chem*., **1995**, *60*, 6250.
4. D.L. Davies, N. Saygili and J.D. Wallis, unpublished work.
5. B. B. Lohray, *Synthesis*, **1992**, 1035.
6. M. K. Pound, D. L. Davies, M. Pilkington, M. M. Pina Vaz Sousa and J. D. Wallis, *Tetrahedron Lett.* **2002**, *43*, 1915.
7. J. O'Leary, C. Colli and J. D. Wallis, *SynLett.*, **2003**, *5*, 675.
8. H. Buding, B. Deppisch, H. Musso and G. Snatzke, *Angew. Chem*., **1985**, *97*, 503.
9. B. Classon and B. J. Samuelsson, *J. Org. Chem.*, **1996**, *61*, 3611.
10. U. Pathak, L. K. Pandey and R. Tank, *J. Org. Chem*., **2008**, *73*, 2890.
11. E. Campaigne, *Chem. Rev*., **1946**, *39*, 1.
12. M. P. Cava and M. I. Levinson, *Tetrahedron*, **1985**, *41*, 5061.
13. R. A. Cherkasov, G. A. Kutyrex and A. N. Pudovik, *Tetrahedron*, **1985**, *41*, 2567.
14. J. Nagaoka, *J. Synth. Org. Chem. Jpn*., **1995**, *53*, 1138.
15. D. Brillon, *Sulfur Rep*., **1992**, *12*, 297.
16. M. Jesberger, T.P. Davis and L. Barner, *Synthesis*, **2003**, *13*, 1929.
17. D. Cho, J. Ahn, K. A. De Castro, H. Ahn and H. Rhee, *Tetrahedron*, **2010**, *66*, 5583.
18. L. Henry, *Ann. Chem. Pharm*., **1869**, *148*, 152.
19. J. Wislicenus, *Z. Chem*., **1869**, *12*, 324.
20. V. Polshettiwar, *Synlett*., **2004**, *12*, 2245.
21. S. Scheibye, B. S. Pedersen and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, **1978**, *87*,

229.

22. B.S. Pedersen, S. Scheibye, N.H. Nilsson and S.O. Lawesson, *Bull. Soc. Chim. Belg.*, **1978**, *87*, 223.
23. S. Scheibye, B. S. Pedersen and S. O. Lawesson, *Bull. Soc. Chim. Belg*., **1978**, *87*, 299.
24. B. S. Pedersen, S. Scheibye, K. Clausen and S. O. Lawesson, *Bull. Soc. Chim. Belg*., **1978**, *87*, 293
25. T. J. Curphey, *Tetrahedron Lett.*, **2002**, *43*, 371.
26. A. Sudalai , S. Kanagasabapathy and B. C. Benicewicz, *Org. Lett.*, **2000**, *2*, 3213.
27. M. P. Cava and M. I. Levinson, *Tetrahedron*, **1985**, *41*, 5061.
28. T. J. Curphey, *J. Org. Chem*., **2002**, *67*, 6461.
29. H.Z. Lecher, R.A. Greenwood, K.C. Whitehouse and T.H. Chao, *J. Am. Chem. Soc*., **1956**, *78*, 5018.
30. S. O. Lawesson, J. Perregaad, S. Scheibye, H. J. Meyer and I. Thomsen, *Bull. Soc. Chim. Belg.*, **1977**, *86*, 679.
31. C.O. Kappe and D. Dallinger, *Nat. Rev. Drug. Discov*., **2006**, *5*, 51.
32. V. Polshettiwar, M. Nivsarkar, D. Paradashani and M.R. Kaushik, *J. Chem. Res., Synop.*, **2004**, 474.
33. R. S. Varma and D. Kumar, *Org. Lett*., **1999**, *1*, 697.
34. M. Jesberger, T. P. Davis and L. Barner, *Synthesis*, **2003**, *13*, 1929.
35. D.Trimnell, B.S.Shasha and W.M.Doane, *Methods Carbohydr. Chem*., **1980**, *8*, 277.
36. E. J. Corey and P. B. Hopkins, *Tetrahedron Lett*. **1982**, *23*, 1979.
37. R. H. Mitchell, T. Fyles and L. M. Ralph, *Canad. J. Chem.*, **1977**, *55*, 1480.

38. B.S. Pedersen, S. Scheibye, N.H. Nilsson and S.O. Lawesson, *Bull. Soc. Chim. Belg*., **1978**, *87*, 223.

39. P. di Cesare and B Gross, *Synthesis*, **1980**, 714.

40. J. W. Stansbury, Ph.D. Dissertation, The University of Maryland, **1988**, *17*.

41. W. Clegg, R.W. Harrington, M. North and P. Villuendas, *J. Org. Chem*., **2010**, *75*, 6201.

42. M. North and P. Villuendas, *SynLett*, **2010,** 623.

43. T. Ozturk, D. C. Povey and J. D. Wallis, *Tetrahedron*, **1994**, *50*, 11205.

44. W. Baker and F. B. Field, *J. Chem. Soc.*, **1932**, *86*.

45. K. B. Sharpless, et al., *J. Org. Chem*., **1992**, *57*, 2768.

46. B. B. Lohray, *Synthesis*, **1992**, 1035.

47. J. G. Tillett, *Phosp. Sulf.*, **1976** , 1341.

48. E. T. Kaiser, M. Panar and F. H. Westheimer, *J. Am. Chem. Soc.*, **1963**, *85*, 602.

49. B. M. Kim and K. B. Sharpless, *Tetrahedron Lett*., **1989**, *30*, 655.

50. H. S. Byun, L. He and R. Bittman, *Tetrahedron*, **2000**, 56, 7051.

51. R. Hirsenkorn, *Tetrahedron Lett*., **1991**, *32*, 1775.

52. H. Yuasa, J. Takada and H. Hashimoto, *Tetrahedron Lett*., **2000**, *41*, 5515.

53. K.E.B. Parkes, D.J. Bushnell, P.H. Crackett, S.J. Dunsdon, A.C. Freeman, M.P. Gunn, R.A. Hopkins, R.W. Lambert, J.A. Martin, J.H. Merrett, S. Redshaw, W.C. Spurden and G.J. Thomas, *J. Org. Chem*., **1994**, *59*, 3656.

54. T. Yokomatsu, K. Suemune and S. Shibuya, *Heterocycles.* **1993**, *35*, 577.

55. V. Glacon, M. Benazza, D. Beaupere and G. Demailly, *Tetrahedron Lett*. **2000**, *41*, 5053.

56. B. J. Littler, T. Gallagher, I. K. Boddy and P. D. Riordan, *Synlett.*, **1997**, *22*.

57. F. E. McDonald, P. Vadapally, *Tetrahedron Lett*. **1999**, *40*, 2235.

58. T. J. Beauchamp, J. P. Powers and S. D. Rychnovsky, *J. Am. Chem. Soc*., **1995**, *117*, 12873.

59. B. B. Lohray and V. Bhushan, *Adv. Heterocycl. Chem*., **1997**, *68*, 89.

60. P. A. M. van der Klein, G. J. P. H. Boons, G. H. Veeneman, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett*., **1989**, *30*, 5477.

61. M.J. Ford, J.G. Knight, S.V. Ley and S. Vile, *Synlett.*, **1990**, 331.

62. J. D. Wallis, A. Karrer and J. D. Dunitz, *Helv. Chim. Acta*, **1986**, *69*, 69.

63. F. Leurquin, T. Ozturk, M. Pilkington and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, **1997** , *21*, 3173.

64. F. G. Calvo-Flores, P. Garcia-Mendoza, F. Hernandez-Mateo, J. lsac-Garcia and F. Santoyo Gonzalez, *J. Org. Chem.,* **1997**, *62*, 3944.

65. R. Oi and K. B. Sharpless, *Tetrahedron Lett*., **1991**, *32*, 999.

66. M. K. Pound, D. L. Davies, M. Pilkington, M. M. de Pena Vaz Sousa and J. D. Wallis, *Tetrahedron. Lett*., **2002**, *43*, 1915.

67. N. S. Zefirov, V. V. Zhdankin, Yu. V. Dan'kov, V. D. Sorokin, V. N. Semerikov, A. S. Kozmin, R Caple and B. A. Berglund. *Tetrahedron Lett*., **1986**, *27*, 3971.

68. G. V. Shustov, A. V. Kachanov, V. A. Korneev, R. G. Kostyanovsky and A. Rauk, *J. Am. Chem. Soc.,* **1993**, *115*, 10267.

69. T. Ozturk, C. R. Rice and J. D. Wallis, *J. Mater. Chem*., **1995**, *5*, 1553.

70. P. N. Devine and T. Oh, *Tetrahedron Lett.,* **1991**, *32*, 883.

71. A. Nelson and S. Warren, *J. Chem. Soc., Perkin Trans. I*, **1999**, 3425.

72. H. Nakagawa,Y. Sei, K. Yamaguchi et al., *J. Mol. Cat. A: Chem.*, **2004** , *219*, 221.

73. C. Kim, M. Park, B. Song and K. Park, *Bull. Korean Chem. Soc*., **2003**, *24*,1371.

74. J. Lichtenberger and J. Hinckley, *Bull. Soc. Chim. Fr.*, **1961**, 1495.

75. A. Nelson and S. Warren, *J. Chem. Soc., Perkin Trans. I*, **1999**, 3425.

4. Chapter 4: Chiral Organosulphur donors.

4.1: Background.

The first organic metal prepared was the charge transfer salt, tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ),[1] and these two molecules became important for the field of organic conductors.[2] (TTF-TCNQ) is the prototype of charge-transfer organic crystals. X-ray diffraction studies showed that its crystal structure exhibits segregated columns of donor TTF and acceptor TCNQ molecules, between which there has been partial charge transfer.[2,3] Wudl *et al*. and Ferraris et al. showed that the charge-transfer salt TTF-TCNQ had high metallic conductivity, rising to 10^4 Ω^{-1} cm^{-1} around 60 K, at which point a metal-insulator transition occurred.[1,4] This "segregated stack" motif was unexpected and is responsible for the distinctive electrical properties, i.e. high and anisotropic electrical conductivity.[5]

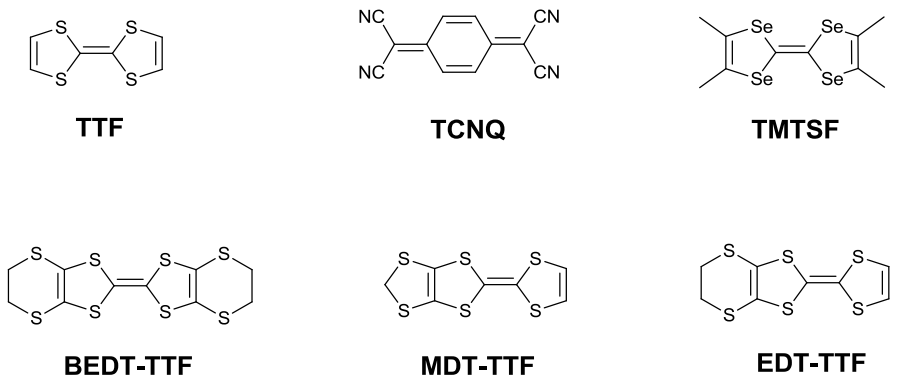


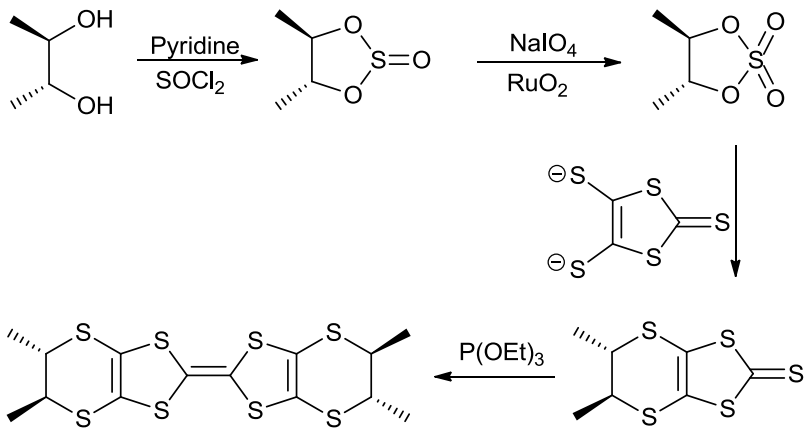
Figure 4.1: donors and acceptor.

In 1974 the tetramethyltetraselenafulvalene donor (TMTSF) was reported by Bechgaard.[6] In 1979, he prepared the first selenium-based salt by electrocrystallisation with a tetramethylammonium salt, i. e. $(TMTSF)_2X$ where X is a monovalent anion such as PF_6^-, AsF_6^-, TaF_6^-, NbF_6^-, SbF_6^-, ClO_4^-, ReO_4^-, BF_4^-, BrO_4^-, IO_4^-, NO_3^-, FSO_3^-, $CF_3SO_3^-$, and TeF_5^-. These salts are known as Bechgaad salts and the materials with the anions PF_6^-, AsF_6^-,

NbF_6^-, SbF_6^-, ReO_4^- and $TeF6^-$ were found to be superconducting (Tc = 1-2 K) under applied pressure of approximately 5-12 kbar.[7] In 1981, Bechgaard prepared the first ambient pressure organic superconductor $(TMTSF)_2ClO_4$ with a Tc of 1.4 K.[8] This discovery has led to a continuation of production of electroactive salts based on symmetrical and unsymmetrical TTF-type donors such as EDT-TTF and MDT-TTF.[9,10,11,12]

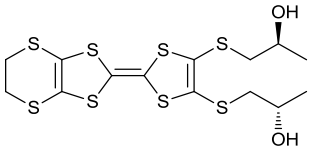
In 1978, Mizuno prepared the molecule bis(ethylenedithio)tetrathiafulvalene (ET or BEDT-TTF). It shows two reversible oxidations at 0.50 and 0.91 V relative to the Ag/AgCl electrode, ca. 0.15 V more positive than those for TTF.[13] A wide range of radical cation salts, was prepared by electrocrystallisation including the first ambient pressure BEDT-TTF superconductor with inorganic anions such as I_3^-, IBr_2^-, AuI_2^-, [14,15,16,17] and also the highest temperature superconductor $(BEDT\text{-}TTF)_2[Cu(N(CN)_2)Cl]$ with Tc = 12.8 K.[18] Many derivatives of TTF, EDT, ET have been reported, and TTF especially has found application in sensors and molecular switches, and more recently in the preparation of conducting fibres. BEDT-TTF has been functionalised with one, two or four side chains e.g. – CH_2NH_2,[19] $CH_2CO_2CH_3$.[20]

There is current interest in chiral metals. Rikken *et al*. have demonstrated magnetochiral anisotropy in carbon nanotubes with a chiral surface when the magnetic field is coaxial with the nanotube,[21] i.e. the resistance is partly dependent on the chirality. Hence the chirality should affect the electrical properties of an enantiopure radical cation salt, and so the installation of chirality into the donor molecules has attracted attention, e.g. the organosulphur donor S,S,S,S,S-TMET which was first prepared by Dunitz and Wallis (see Scheme 4.1).[22] A considerable number of enantiopure donors based on BEDT-TTF have been reported including those with a stereogenic centre at a ring C or even at an S atom,[23,24] or external to the donor system.[25,26,27]

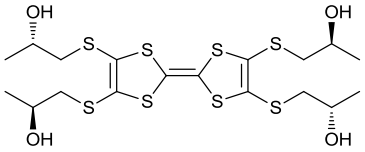


Scheme 4.1: synthetic route of preparation of S,S,S,S-TMET.

A large number of TTF derivatives with chiral side chains have been also reported.[28,29] Kato used the formation of hydrogen bonding between amino acid derivatives having TTF moieties in liquid crystals to provide fibrous conducting materials.[30] It is interesting that the hydrogen bonding with the anion in a salt, or between donors can offer new organisations in the crystalline state.[31,32] A few enantiopure donors with hydrogen bonding functionality have been reported e.g. BEDT-TTF derivatives, with a peptide or sugar unit attached.[33,34,35,36] Most recently in the Wallis group the donors **1** and **2** were prepared which are both enantiopure and have two or four hydroxyl groups. Treatment with iodine has produced a range of phases including a 6 : 6 semiconductor from **1**.



1



2

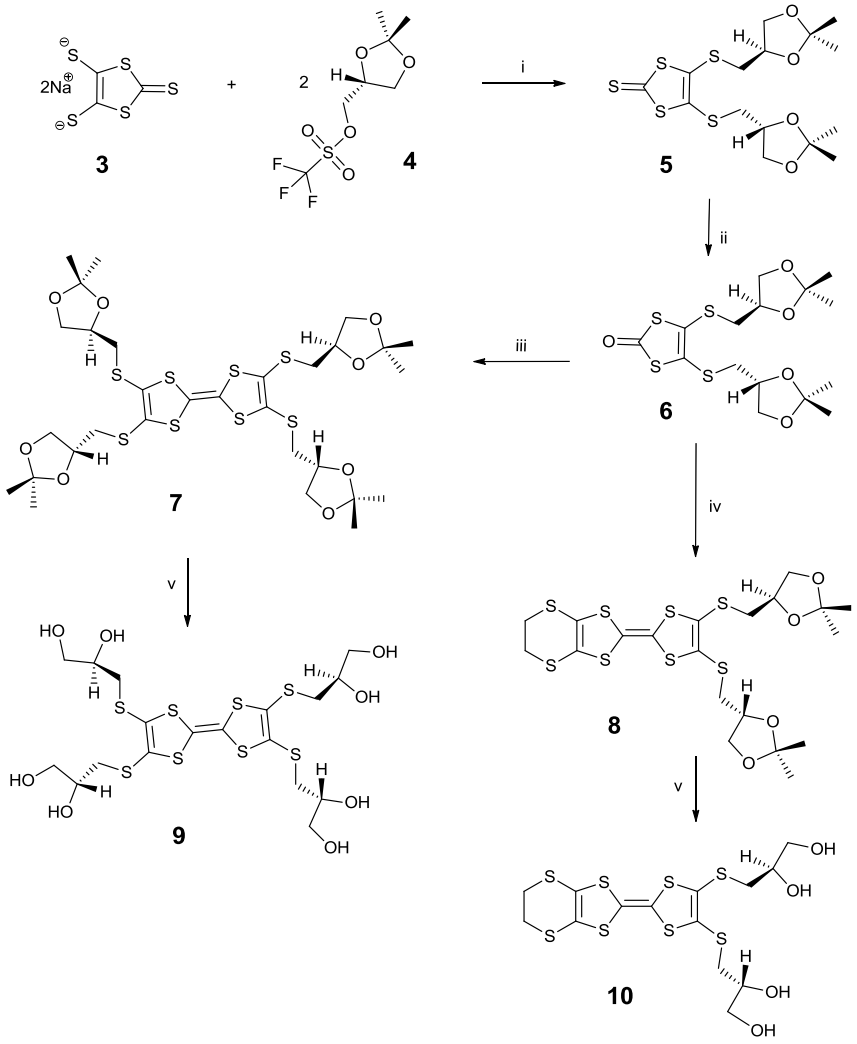
Figure 4.2: structure of 1 and 2.

The preparation of new chiral donors which are enantiopure and have hydrogen bond donating groups will now be described.

4.2: Results and discussion.

4.2.1: Synthesis of Chiral organosulphur donors octol 9 and tetrol 10.

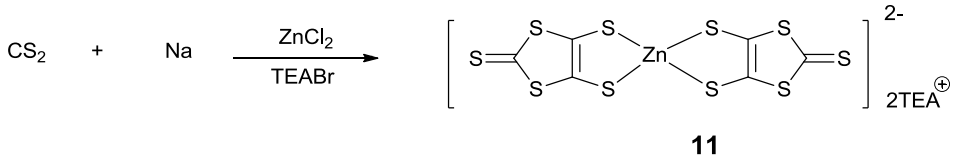
Building on the success of this work, it was decided to prepare chirally pure hydroxyl-bearing electron donors having two or four side chains each carrying two hydroxyl groups. This approach afforded the electron donor species **9** and **10** bearing eight or four hydroxyl groups, with controlled stereochemistry at each carbon atom. The synthetic route to target materials **9** and **10** proceeded as in Scheme 4.2.



Reaction conditions: (i) dry MeOH, rt; (ii) $CHCl_3$, $Hg(OAc)_2$, rt, 2 h; (iii) $P(OEt)_3$, 90 ^oC, 2 h; (iv) 1.5 eq.of **6**, $P(OEt)_3$, 90 ^oC, 2 h; (v) HCl(aq), THF.

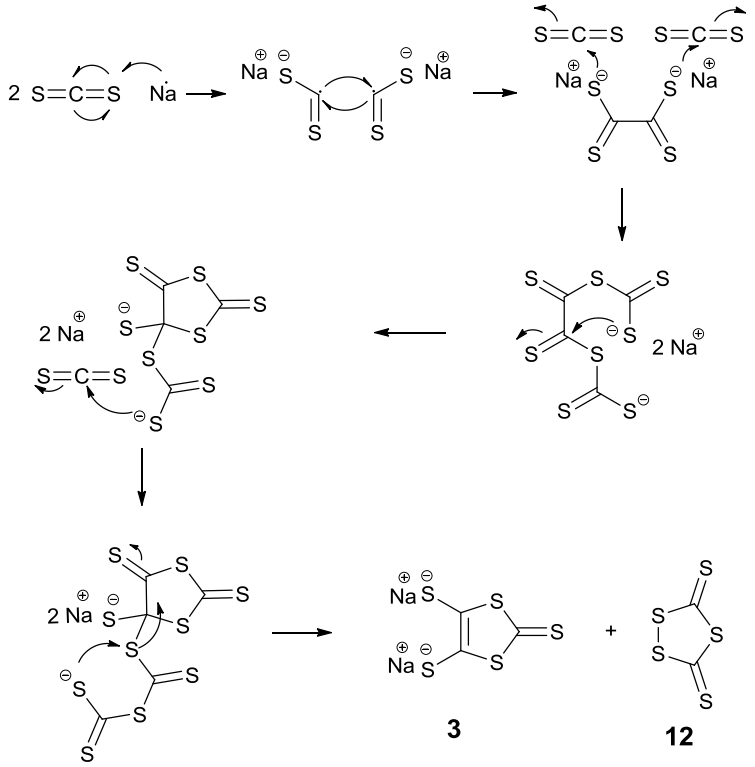
Scheme 4.2: synthesis route to the final hydroxylated donors 9 and 10.

The starting step of the synthesis of donors is the single electron reduction of carbon disulphide with sodium metal in dimethylformamide to produce the basic sulphur network (see Scheme 4.3). See scheme 4.4 below for a mechanism for the reduction leading to the disodium salt of dithiolate **3**[37] and the sulphur heterocycle **12** which has been proposed by Bryce.[38] The 1,3-dithiole-4,5-dithiolate is isolated as zinc complex **11**.



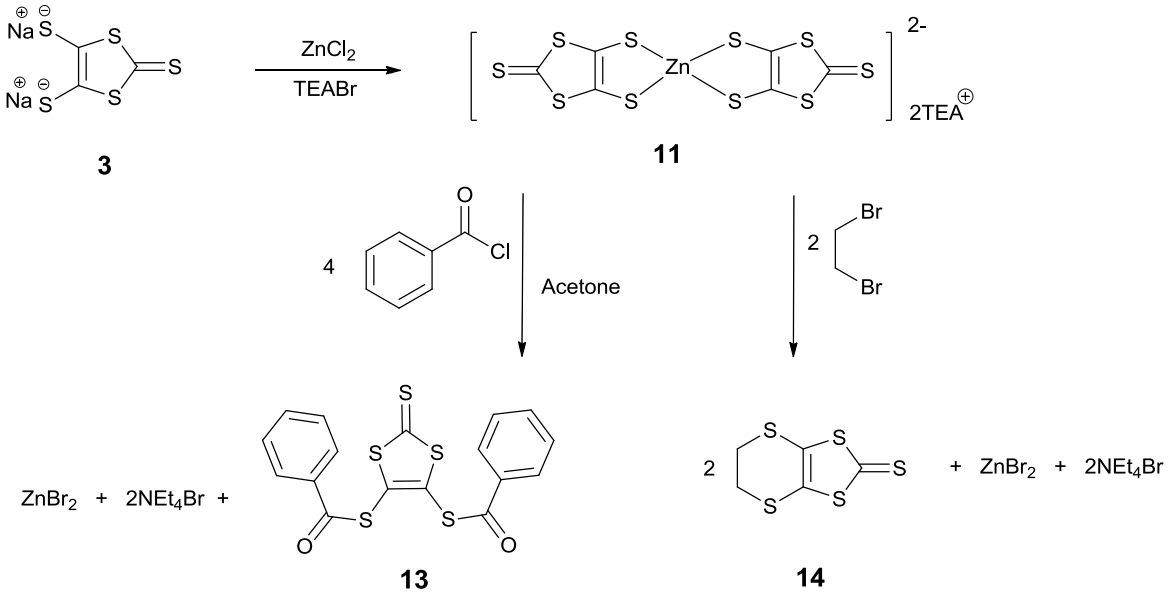
11

Scheme 4.3: Synthesis of Zn complex 3.

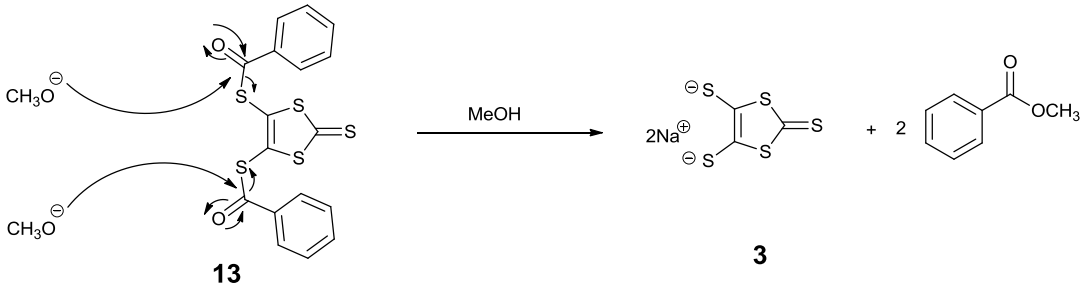


Scheme 4.4: Mechanism of synthesis of dithiolate 3 and sulphur heterocycle 12.

The unsubstituted thione **14** is an important unit used for EDT + ET derivative synthesis. It can be prepared by reacting zinc complex **11** with an electrophilic agent such as 1,2-dibromoethane, with the sulphur atoms acting as nucleophiles allowing formation of a six-membered ring in **14**. For subsequent chemistry the zinc salt was first converted to its sodium salt **3**. The zinc salt is easily converted to the dibenzoyl derivative **13** as a yellow solution in 87% yield, by treatment with benzoyl chloride, and the dithiolate salt **3** generated *in situ* by treatment of *4,5-bis(benzylthio)-1,3-dithiole-2-thione* **13** with sodium methoxide in methanol.

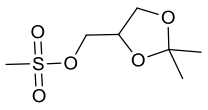


Scheme 4.5: Synthesis of thione ET 14 and 4,5-bis(benzoylthio)-1,3-dithiole-2-thione 13.

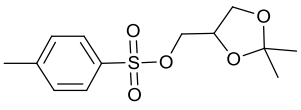


Scheme 4.6: Mechanism for synthesis of dithiolate 3.

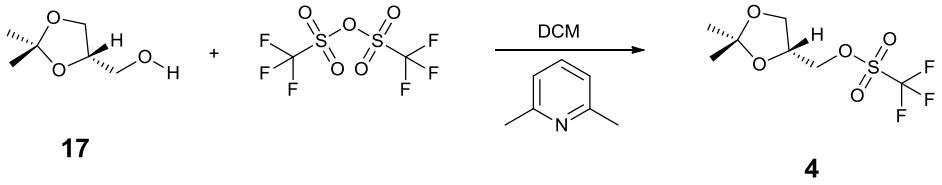
It was decided to introduce the side chain with *vic*-hydroxyl groups protected as a dimethyl ketal. Initial studies were made with racemic solketal to determine what leaving group was optimal. It was converted to both O-mesyl and O-tosyl derivatives **15**[39] and **16**, but neither reacted with dithiolate **3**. Therefore, solketal was converted to its more reactive triflate derivative **4.** This was achieved using trifluoromethane sulphonic anhydride to give **4** in 88% yield, and the highly reactive product was used directly for next step, but it can also be stored at -20 °C.[40]



15



16

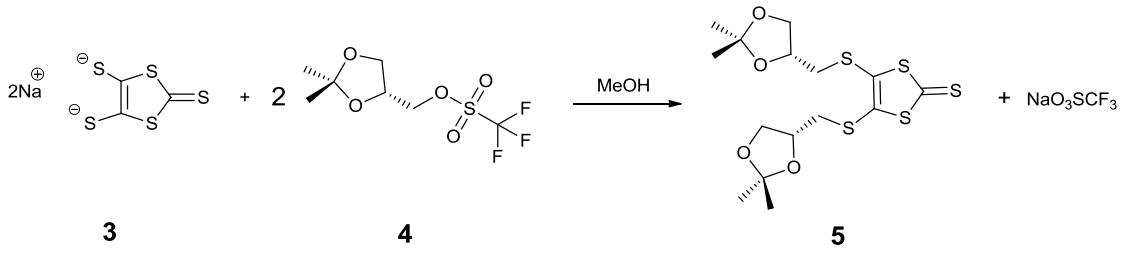


17 **4**

Scheme 4.7: Synthesis of protected ketal 4.

4,5-bis(Benzylthio)-1,3-dithiole-2-thione **13** was dissolved in dry and degassed methanol in presence of sodium methoxide as a nucleophile to give dithiolate salt **3**, and the triflate **4** added. (Scheme 4.8). An orange precipitate formed after some minutes and the compound **5** was isolated via a simple work-up in 90 % yield, as a yellow solid. The reaction was then reported using enantiopure triflate **4** to give the thiocarbonyl **5** since the stereo-center is not involved in the reaction. The required stereoisomer **5** was characterised by its ^{1}H NMR

spectrum displaying two singlet resonances due to the hydrogen atoms of the four methyl groups at δ 1.36 and 1.28 ppm. The single hydrogen atoms adjoining the heterocyclic ring resonated as a quintet at δ 4.26 ppm, and showed coupling to the adjacent hydrogens on the cyclic ketal ring and side chain with a coupling constant of J = 6.0 Hz. The ^{13}C NMR spectrum indicated the presence of a thiocarbonyl fragment at δ 210.0 ppm, and the methylene group originally joined to oxygen and new bond to the sulphur giving a signal at δ 39.6 ppm. The infrared spectrum confirmed the presence of the thiocarbonyl with a strong stretching band at 1051 cm^{-1}, and the [M + Na]$^+$ ion was observed in the electrospray mass spectrum at 449.0008 Da.

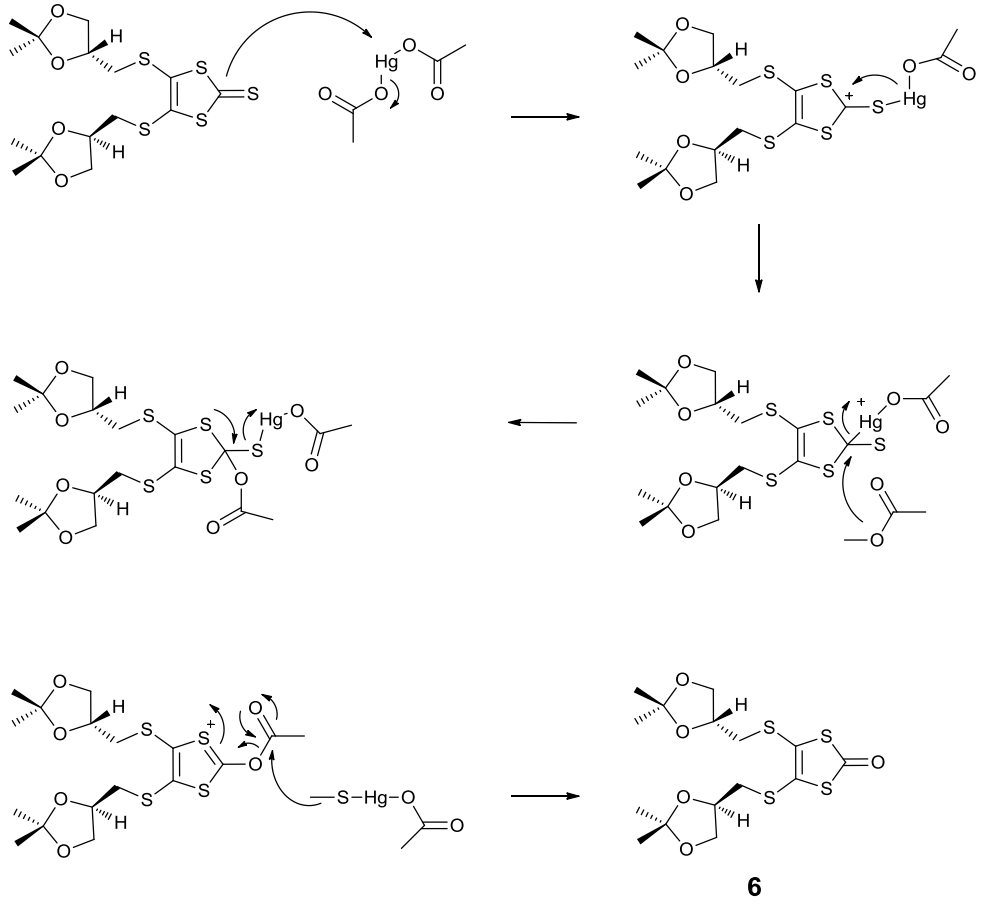


3 **4** **5**

Scheme 4.8: formation of 11.

The thiocarbonyl compound **5** was converted to its oxo compound **6** with mercuric acetate mediated sulphur-oxygen exchange in chloroform solution in very high yield (93%); the structure is supported by the signal in the ^{13}C NMR spectrum at δ 188.6 ppm indicating the presence of the carbonyl species. Further evidence of the transformation is observable by a shift in the resonance signals for the ring sp^2 carbon atoms from δ 136.1 ppm in **7** to δ 127.1 ppm in **6**. The stretching frequency of the carbonyl fragment is identifiable in the infrared spectrum as a strong vibration at ν = 1668 cm^{-1}, and the molecular ion is observed in the high resolution electron impact mass spectrum at 428.0686 Da. The carbonyl compounds

have been shown to be more reactive than their thiocarbonyl analogues during the next coupling step.

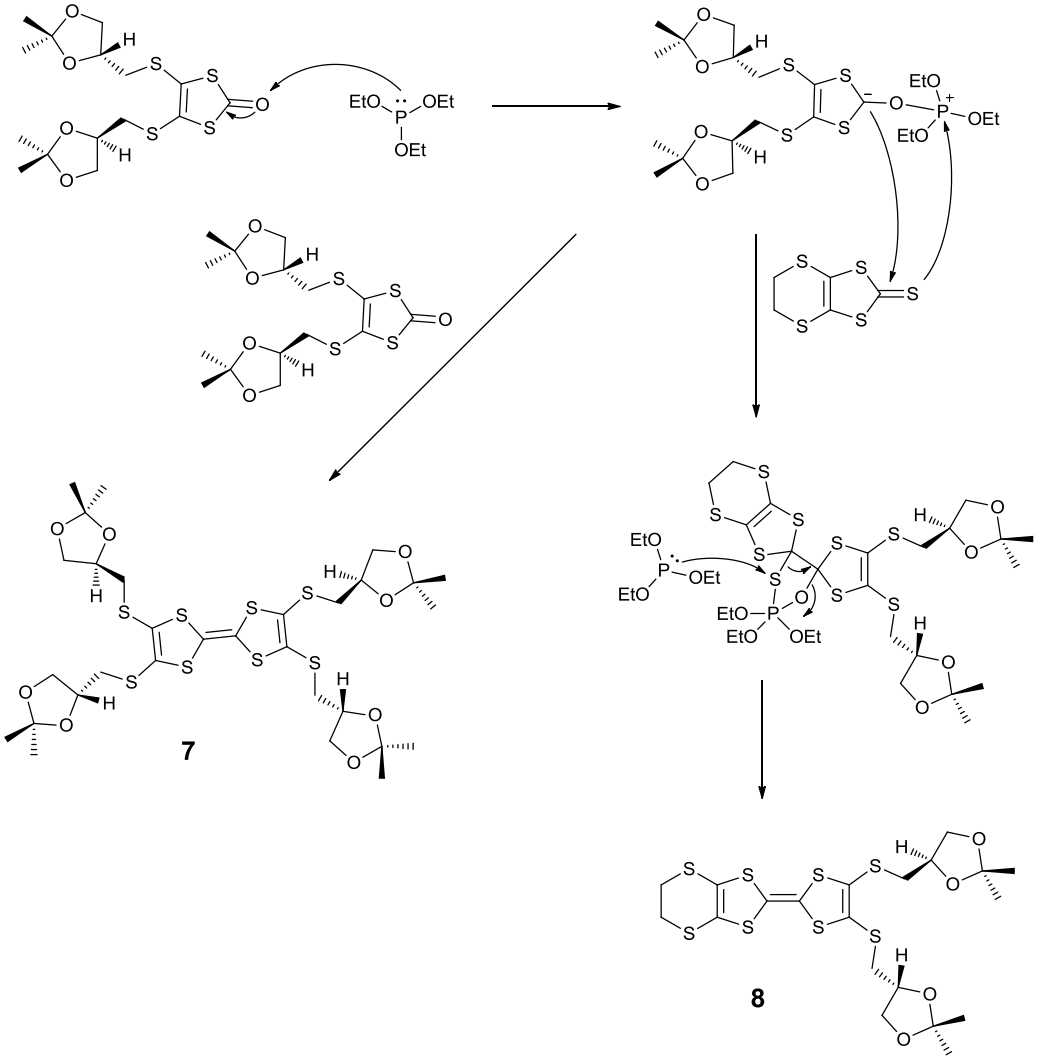


6

Scheme 4.9: Exchange reaction of thione sulphur to oxygen

The triethyl phosphite-mediated coupling of oxo compound **6** either with itself, or with thione **14** gave the protected donors, (the chirally pure tetraketal **7** and diketal **8** compounds) in 51% and 60% yield, respectively (Scheme 4.10). The homo-coupling reaction of carbonyl compound **6** to afford the chiral tetraketal donor **7** proceeded without complication in moderate yield. The orange needles isolated after filtration were identified by their ^{1}H NMR spectrum showing resonances attributable to the hydrogen atoms of eight methyl groups as two singlets at δ 1.41 and 1.32 ppm. The ^{13}C NMR spectrum indicated

the symmetry of the species as signals at δ 109.9 ppm were observed for the C=C network throughout the core of the electron donor and the sp^2 hybridised carbon signal at δ 127.7 ppm. High resolution electron impact mass spectrometry confirmed the molecular ion as 806.1142 Da.



Schema 4.10: The homo-coupling reaction of compound 6 to give 7 and cross coupling reaction of 6 with half ET 14 to give 8.

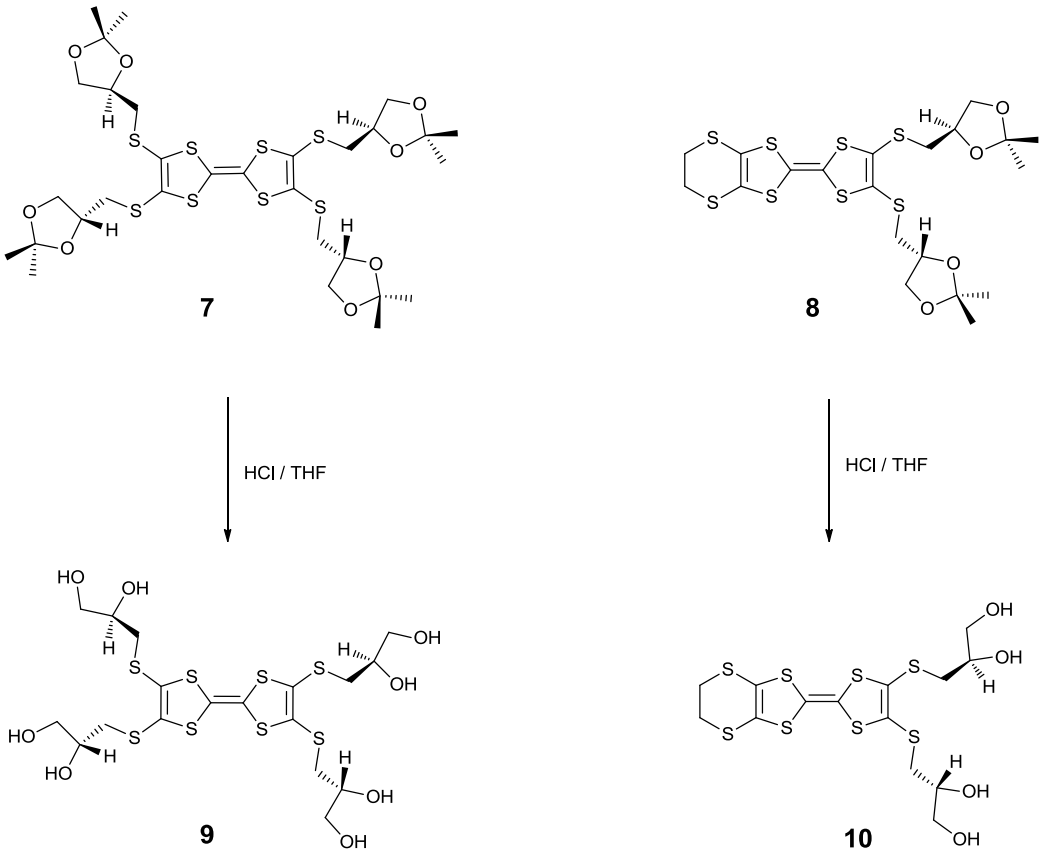
To isolate the cross-coupled electron donor, excess triethyl phosphite and by-products were removed by Kugelrohr distillation and the residue was subjected to flash chromatography

and product **8** was characterised. The ^{1}H NMR spectrum of **8** indicates the presence of the four methyl groups, whose hydrogen atoms resonate as two singlets at δ 1.35 and 1.29 ppm due to their orientations, and the ethylene function at the opposite end of the chalcogenic species as a singlet at δ 3.20 ppm. The absence of peaks in the ^{13}C NMR due to carbonyl and thiocarbonyl confirm that the isolated orange solid is not a composite mixture of both of the reactants. The formation of the central C=C bond is observed as an additional resonance in the sp^2 region of the ^{13}C NMR, with the resonances occurring at δ 113.8, 112.2 and 109.8 ppm for the cross-coupled donor **8**. High resolution electrospray mass spectrometry confirmed the presence of the $[M+H]^+$ ion at 586.9675 Da.

The deprotection of diketal **8** in tetrahydrofuran solution was achieved readily using 2M hydrochloric acid under an atmosphere of nitrogen to give the tetrol **10** as a brown solid. The identity of **10** was determined from the infrared spectrum, which displayed stretching frequencies attributable to the presence of hydroxyl functions at 3244 cm^{-1}. The ^{1}H NMR spectrum showed the absence of resonances due to the hydrogen atoms of the methyl groups, and the presence of a signal at δ 4.80 ppm that was partly due to the hydroxyl protons. The ^{13}C NMR indicated a significant shift for the carbon atoms bearing the hydroxyl functions from δ_C 74.4 and 68.3 ppm in the protected donor **8** to δ_C 70.5 and 64.2 ppm in the free hydroxyl donor **10**. High resolution electron impact mass spectrometry identified the molecular ion at 504.8889 Da.

The deprotection of tetraketal **7** proved to be much more difficult. The octol species **9** was found to be very sensitive to air and moisture, rapidly turning dark brown in colour and giving a highly insoluble material which did not allow characterisation of the compound. The concentration of acid used in the deprotection was also shown to have an effect and after significant optimisation freshly prepared and thoroughly degassed (by bubbling

nitrogen gas through for 30 min) ratio 1 : 15 HCl conc : THF was determined to be most successful. Monitoring the reaction by TLC, eluting with cyclohexane / ethyl acetate (10:1) and increasing amounts of methanol, allowed the intermediary products to be observed in which some but not all of the ketal fragments had been removed. Careful evaporation under high vacuum at room temperature afforded the octol **9** as a dark brown solid m.p. = 166 ^{o}C, The infrared spectrum indicated the presence of the hydroxyl groups at ν = 3243 cm^{-1}. The ^{1}H NMR spectrum was not as informative as expected, showing only a multiplet at δ_H 3.31-3.70 ppm for all hydrogen resonances. The ^{13}C NMR spectrum indicated the presence of free hydroxyl groups as the carbons bearing the O-functions were shifted to δ_C 70.5 and 64.2 ppm as observed in the deprotection of diketal **9**. High resolution electrospray showed the [M -H] ion at 626.9468 Da.



Scheme 4.11: Synthetic route to the final hydroxylated donors 9 and 10.

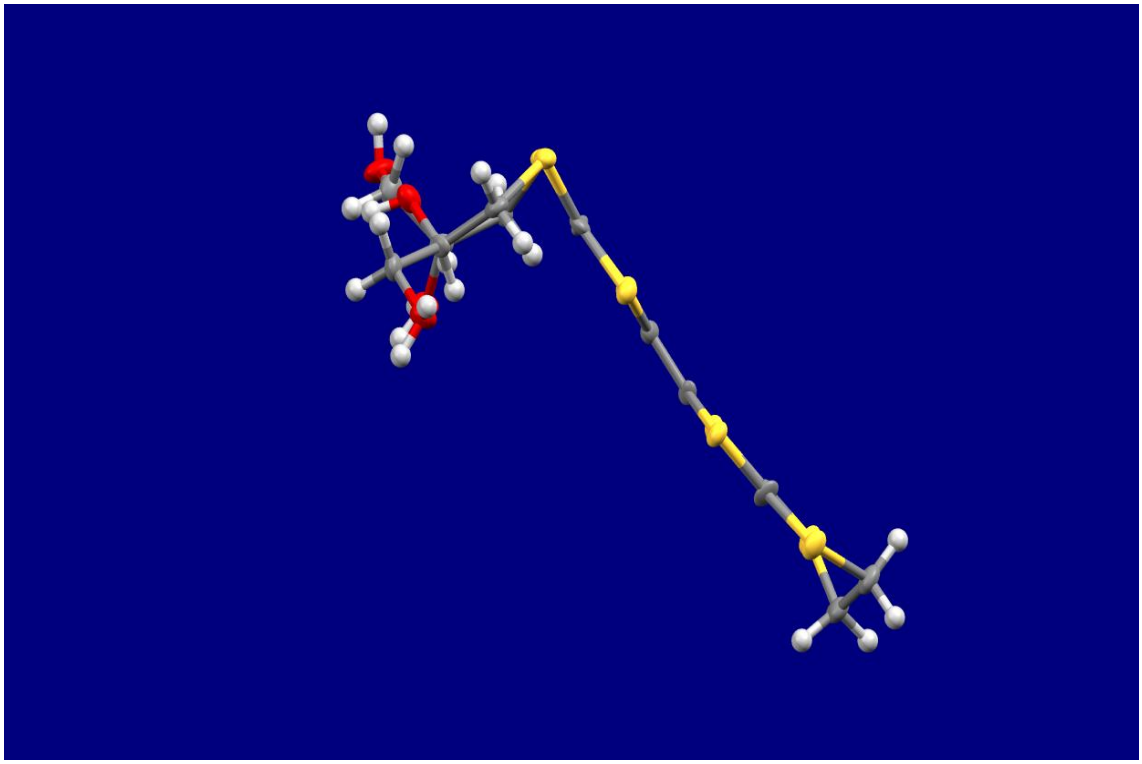


Figure 4.3: Molecular structure of 10.

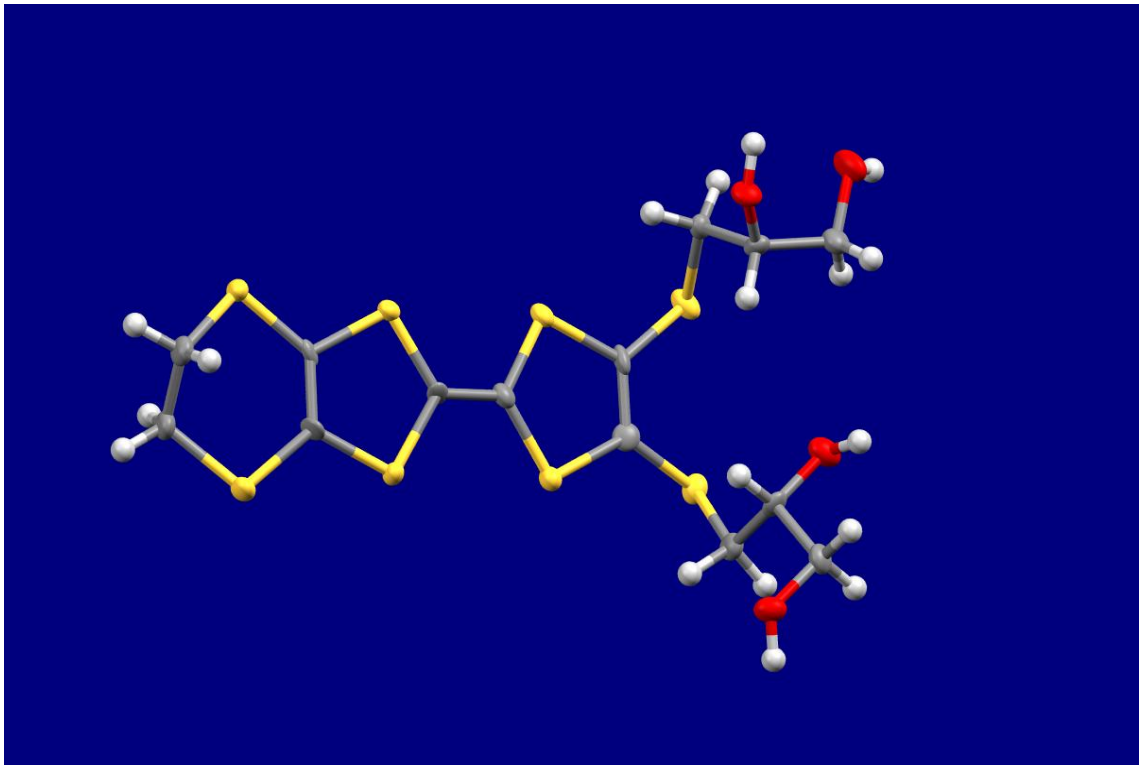


Figure 4.4: Molecular structure of 10.

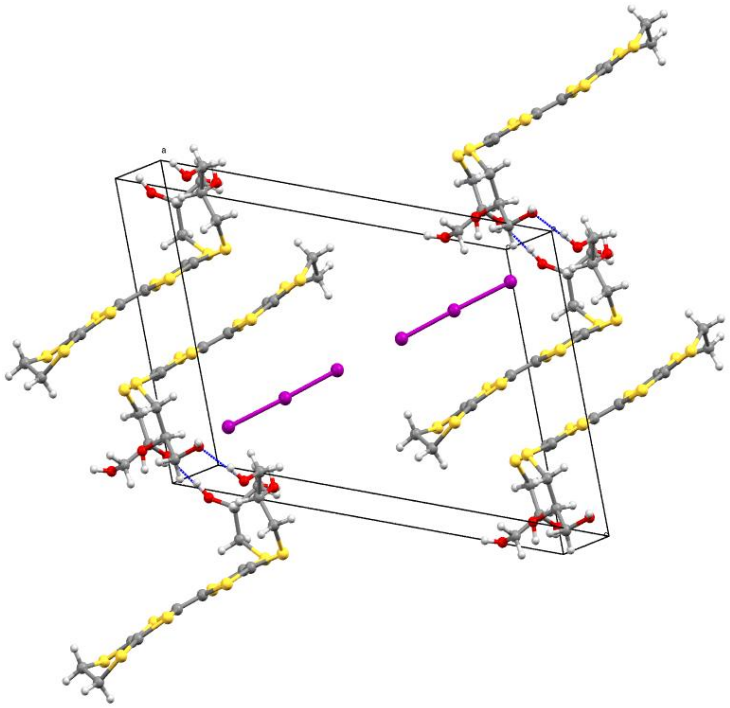


Figure 4.5: Crystal packing of 10.

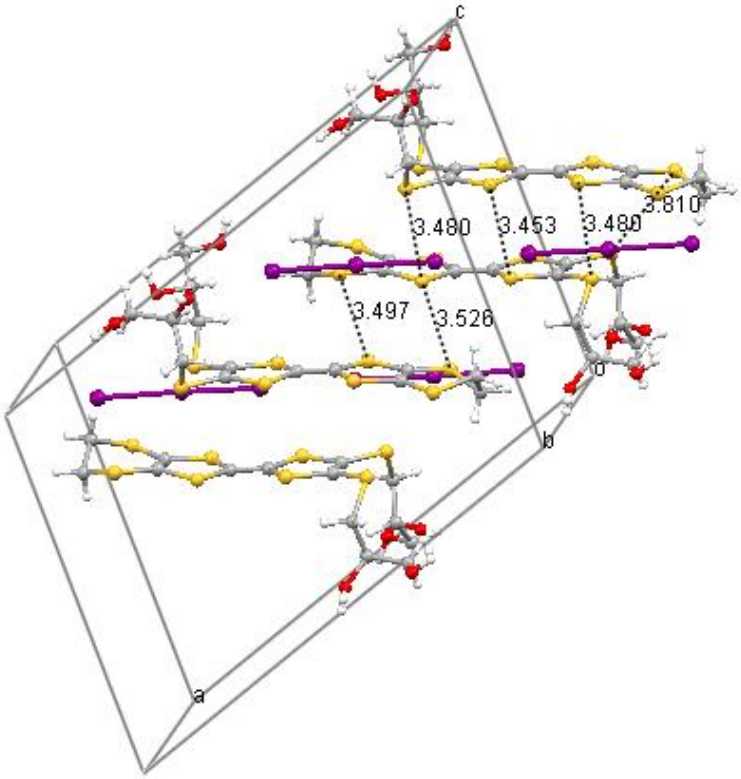


Figure 4.6: Crystal packing of 10.

Diffusion of a solution of **10** in DCM with a solution of iodine in THF gave black crystals after five days. The X-ray crystal structure of this material (Figure 4.5) showed it to be the 1:1 salt with I_3^-. The donors are packed in face to face pairs and the triiodides are in "end to end" pairs with a short I---I contact distance (3.442 Å) which is one of the shortest I_3---I_3 contacts reported. These pairs are surrounded at the each side chains see Figure 4.5. There are short S----S contacts whtenin a pair, and also between pairs (Figure 4.6).

4.2.2: Synthesis of Chiral organosulphur donor diol 22 (Scheme 4.12).

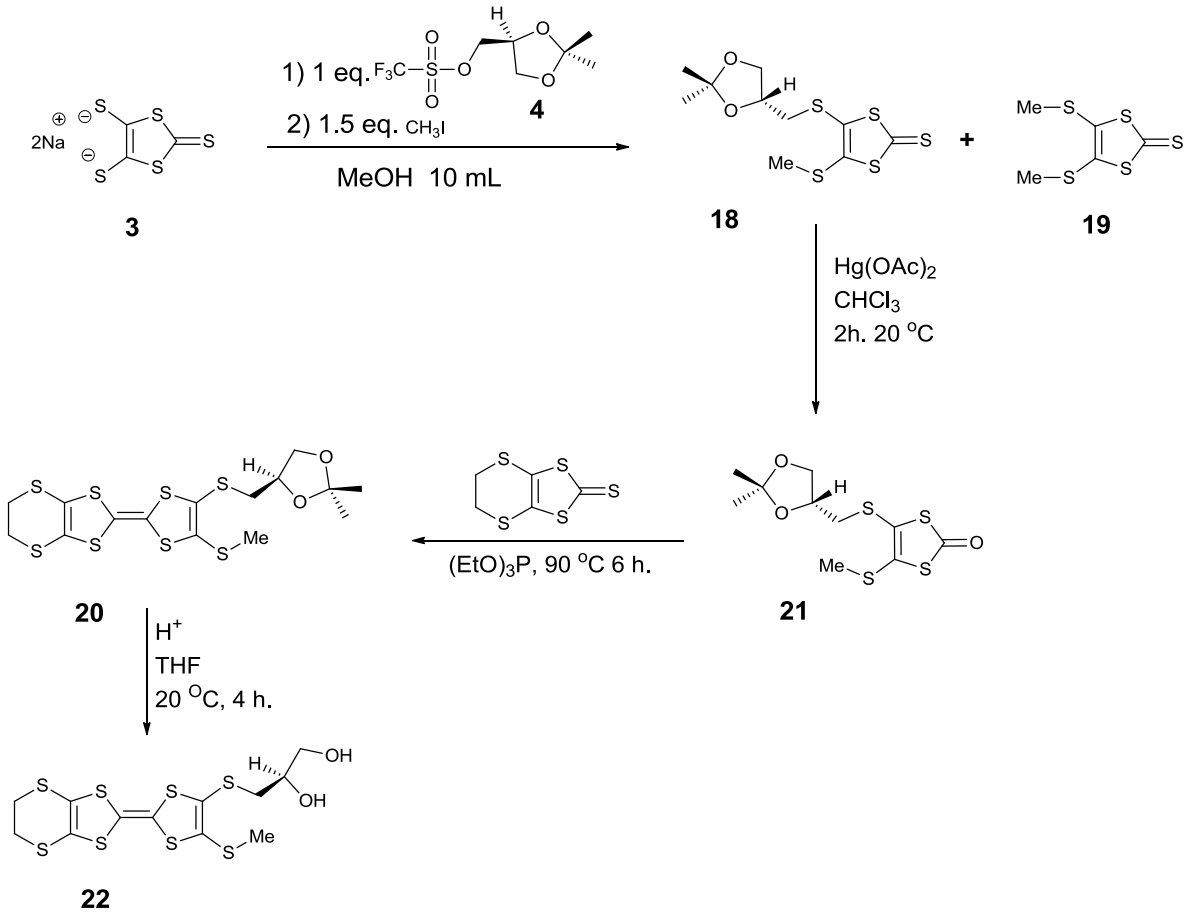
To prepare a donor with just one chiral hydrogen bonding side chain, a modified approach was taken. Reaction of dithiolate **3** with just one equivalent of the triflate of *(S)-1,2-isopropylidene-glycerol* **4** followed by reaction with iodomethane in dry methanol under nitrogen at -20 ^oC, gave the unsymmetrically substituted thione *4,5-bis(methylsulphanyl)-1,3-dithiole-2-thione* **19** in a reasonable yield of 42% after separation from the dimethylated material **18** which is known compound (Scheme 4.12). The ^1H NMR spectrum of **19** indicates the presence of the methyl group next to sulphur atom, whose hydrogen atoms resonate as singlet at δ_H 2.46 ppm, and for two methyl groups on the ketal ring, whose hydrogen atoms resonate as two singlets at δ_H 1.36 and 1.29 ppm due to their orientations. The ^{13}C NMR spectrum indicated the presence of a thiocarbonyl fragment at δ_C 210.0 ppm, and the loss of the methylene group originally joined to oxygen and new bound to sulphur giving a signal at δ_C 39.4 ppm and three methyl groups at δ_C 26.7, 25.2 and 18.9 respectively. The infrared spectrum confirmed the thiocarbonyl presence with a strong stretching band at 1058 cm^{-1}, and the $[M + H]^+$ ion was observed in the electrospray mass spectrum at 326.9670 Da.

The thiocarbonyl compound **19** was converted to its oxo compound **21** with mercuric acetate mediated sulphur-oxygen exchange in chloroform solution in very high yield (96%); the structure is supported by the shift in the ^{13}C NMR spectrum at δ_C 189.1 ppm indicating the presence of the carbonyl species. Further evidence of the transformation is observable by a shift in the resonance signals for the ring sp^2 carbon atoms from δ_C 132.7 ppm in **19** to δ_C 124.5 ppm in **21**. The stretching frequency of the carbonyl fragment is identifiable in the infrared spectrum as a strong vibration at ν = 1720 cm^{-1}, and the molecular ion is observed in the high resolution electron impact mass spectrum at 428.0686 Da.

This material, the oxo compound **21**, was then cross coupled on the usual way with the unsubstituted thione **14** to give donor **20** in 65% yield. The cross-coupled electron donor **20** was isolated, after removal of triethyl phsphite by Kugelrohr distillation and flash chromatography and characterised. The ^1H NMR spectrum of **20** indicates the presence of the three methyl groups, whose two of hydrogen atoms resonate as two singlets due to their orientations at δ_H 1.40 and 1.32 ppm, and the methyl group next to sulphur as a singlet at δ_H 3.26 ppm. The ethylene function at the opposite end of the chalcogenic species gives rise to a singlet at δ_H 2.40 ppm. The absence of peaks in the ^{13}C NMR due to carbonyl and thiocarbonyl confirm that the obtained red oil is not a composite mixture of both of the reactants. High resolution electrospray mass spectrometry confirmed the presence of the $[M+H]^+$ ion at 486.9141Da.

The following step is quantitative deprotection of the hydroxyl groups with HCl in THF to give cross-coupled donor **22** as a brown solid, with just one chiral side chain. The deprotection of ketal **20** proved to be much more difficult. The diol donor **22** was found to be very sensitive to air and moisture, rapidly turning dark brown in colour and giving a

highly insoluble material which did not allow characterisation of the compound. The concentration of acid used in the deprotection was also shown to have an effect and after significant optimisation freshly prepared and thoroughly degassed (by bubbling nitrogen gas through for 30 min) 2 M HCl was determined to be most successful. Monitoring the reaction by TLC, eluting with cyclohexane / ethyl acetate (10:1) and increasing amounts of methanol, allowed the intermediary products to be observed in which some but not all of the ketal fragments had been removed. Careful evaporation under high vacuum at room temperature afforded the diol donor **22** as a brown solid, The infrared spectrum indicated the presence of the hydroxyl groups at n = 3319 cm^{-1}. The ^{1}H NMR spectrum using d_6-DMSO indicates the presence of the two hydroxyl groups, whose hydrogen atoms resonate as broad singlets at δ_H 3.47 and 4.47 ppm, and the methyl protons were observed as a singlet at δ_H 3.27 ppm. The ^{13}C NMR spectrum indicated the presence of free hydroxyl groups as the carbons bearing the functions shifted to δ_C 70.5 and 64.2 ppm as observed in the deprotection of the other donors e.g. octol species **9** and tetrol **10**. High resolution electrospray showed the [M +H] ion at 446.8832 Da.



Scheme 4.12: Synthetic route to the final hydroxylated donor 22.

4.2.3: <u>Synthesis of Chiral organosulphur donor hexol 28 (Scheme 4.13).</u>

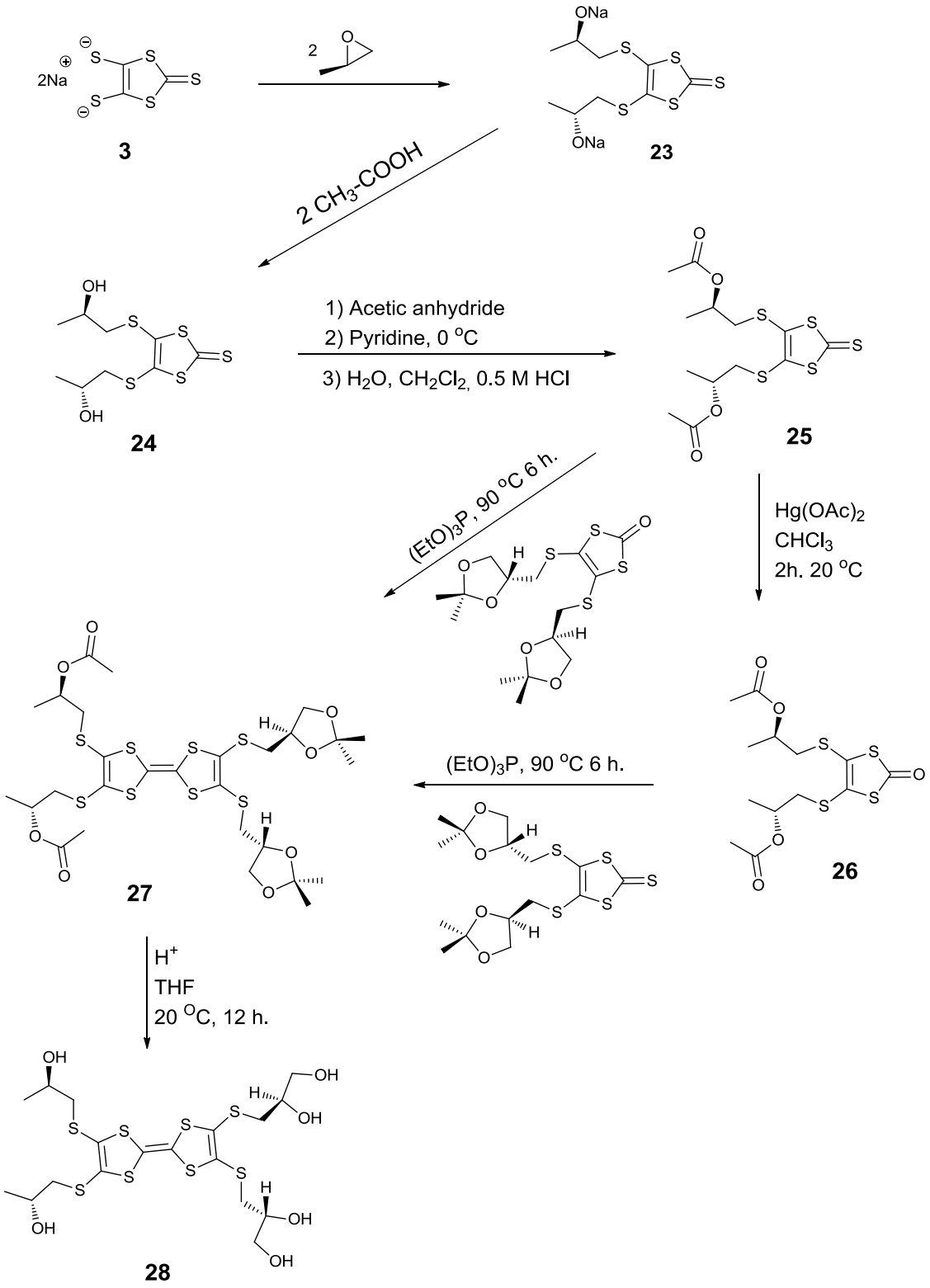
To provide a donor with different chirally disposed hydrogen bonding functionality at either end the donor **28** was prepared which at one end had two (R)-2-hydroxypropylthio side chains and at the other side two (R)-2,3-dihydroxypropylthio side chains. This was achieved by reacting the R-enantiomer of bis(acetoxy) thione **25** with the bis ketal-protected oxo compound **6** in triethyl phosphite to give the O-protected hexol **27** in 30% yield after removal of triethyl phsphite by Kugelrohr distillation and chromatography to separate from homo-coupled species. The ^{1}H NMR spectrum of **27** indicates the presence of the methyl groups, whose four of hydrogen atoms resonate as two singlets due to their

orientations at δ_H 1.42 and 1.35 ppm, the methyl group next to methine groups as doublet at δ_H 1.33 ppm and the methyl groups in the acetate groups as a singlet at δ_H 2.05 ppm. The ^{13}C NMR spectrum indicated the symmetry of the species as signals at δ_C 109.9 ppm were observed for the C=C bond at the core of the electron donor and the sp^2 hybridised carbon at the ring fusions at δ_C 128.0 ppm and the carbonyl group at δ_C 170.3 ppm. High resolution electron impact mass spectrometry confirmed the molecular ion as 778.0827 Da.

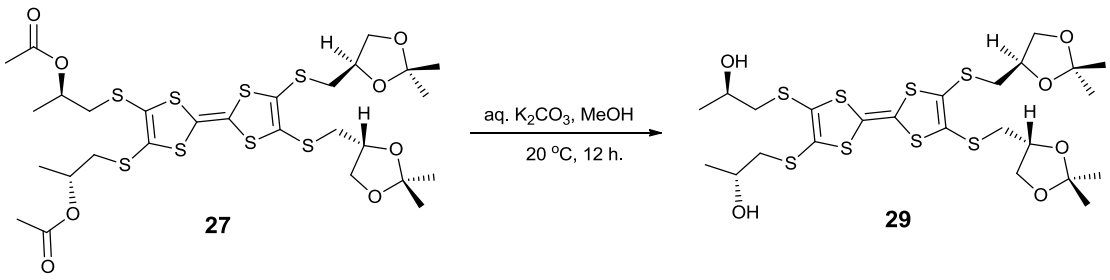
Removal of the ketal and acetyl protecting groups was achieved using HCl in THF to yield the unsymmetrical chiral hexol donor with two different pairs of stereogenic centres **28**, but the proudoct was not a very clean compound (see Scheme 4.13). After the difficulties in purification of donor **28**, it was decided to use an alternative procedure in two steps. The first step was to deprotect the acetate groups using aqueous potassium carbonate in methanol and tetrahydrofuran stirred over night. Careful evaporation under high vacuum at room temperature to remove organic solvents only and filtration afforded the diol donor **29** as a light orange solid in high yield and purity (see Scheme 4.14). The infrared spectrum indicated the presence of the hydroxyl groups at n = 0000 cm^{-1}. The ^1H NMR spectrum using CD_3OD indicates the presence of the two hydroxyl groups, whose hydrogen atoms resonate as a broad singlet at δ_H 4.87 ppm. The methyl group appears as a doublet at δ_H 1.25 and the methyl protons of ketal were observed as a singlet at δ_H 1.39 and 1.31 ppm The ^{13}C NMR spectrum indicated the presence of free hydroxyl groups as the carbons bearing these functions shifted to δ_C 67.4 ppm, and there was an absence of carbonyl and methyl groups from the acetate group. High resolution electron impact mass spectrometry confirmed the molecular ion as 778.0827 Da.

The second step was to deprotect the ketal groups by using 5% HCl in methanol and tetrahydrofuran at room temperature overnight (see Scheme 4.14). After removing the

solvents carefully, the reaction mixture was filtered to afford a deep orange solid **28** in high yield and purity. The identity of **28** was determined from the infrared spectrum, which displayed stretching frequencies attributable to the presence of hydroxyl functions at 3244 cm^{-1}. The ^{1}H NMR spectrum showed the absence of resonances due to the hydrogen atoms of the ketal methyl groups. The methyl group appears as a doublet at δ_H 1.26 and the presence of a signal at δ 4.88 ppm that was partly due to the hydroxyl protons. The ^{13}C NMR indicated a significant shift for the carbon atoms bearing the hydroxyl functions from δ_C 76.4, 69.5 and 67.8 ppm in the protected donor **27** to δ_C 72.3, 67.8 and 65.7 ppm in the free hydroxyl donor **28**.

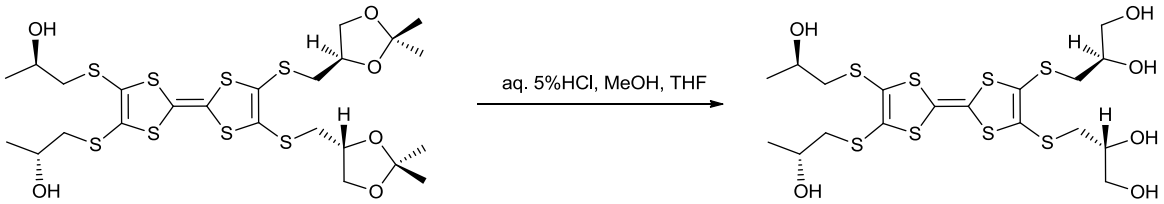


Scheme 4.13: Synthetic route to the final hydroxylated donor 28.



27 **29**

Scheme 4.14: Synthetic route to the final hydroxylated donor 29.

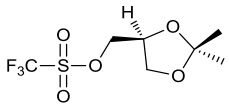


29 **28**

Scheme 4.15: Synthetic route to the final hydroxylated donor 28.

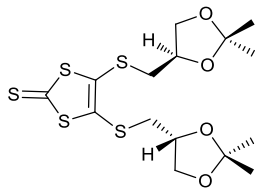
4.3: <u>Experimental.</u>

Preparation of [(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl trifluoromethanesulfonate 4.[40]



In a dried flask (S)-(-)-2,2-dimethyl-1,3-dioxolane-4-methanol (2.88 g, 2.5 ml, 20 mmol) was dissolved in anhydrous DCM (10 ml). The reaction mixture was cooled down to - 40 ºC, and 2,6-lutidine (2.54 ml, 22 mmol) was added; after 5 min. trifluoromethanesulphonic anhydride (5.92 g, 3.52 ml, 21 mmol) was added dropwise. The reaction mixture was stirred 2 h at - 40 ºC and then diluted with DCM and washed with citric acid/sodium hydroxide buffer solution (pH = 4). The organic layers were combined and washed twice with brine and dried over magnesium sulphate. The crude product was used directly for the next reaction. δ_H (400 MHz; $CDCl_3$): 4.42 (2H, m, 4-CH_2-O), 4.30 (1H, m, 4-H), 4.05 (1H, dd, J = 6.2, 8.8 Hz, 5-H_α), 3.77 (1H, dd, J = 5.0, 8.8 Hz, 5-H_β), 1.36 (3H, s, -CH_3), 1.29 (3H, s, -CH_3); δ_C (100 MHz, $CDCl_3$): 118.5 (q, $J_{C,F}$ = 317.5 Hz, -CF_3), 110.6 (2-C), 75.3 (CH_2-O), 72.6 (4-C), 65.3 (5-C), 26.3 (-CH_3), 24.8 (-CH_3).

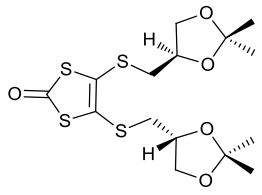
Preparation of 4,5-bis(((4`R)-2`,2`-dimethyl-1`,3`-dioxolan-4-yl)methylthio)-1,3-dithiole-2-thione 5.



Sodium methoxide (0.48 ml, 25%wt solution, 2.0 mmol) was added to a solution of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione (410 mg, 1.0 mmol) in dry and degassed methanol (7 ml) under nitrogen at room temperature, and the mixture stirred for 30 min. as the purple

dithiolate **3** formed. The reaction mixture was treated with **4** (528 mg, 2.0 mmol) at room temperature. After 5 min. an orange precipitate formed, which was collected, washed with methanol and dried to yield **5** as a yellow solid (390 mg, 90%), R_f (cyclohexane:ethyl acetate 5:1) 0.31; m. p. = 124 ºC; δ_H (400 MHz; $CDCl_3$): 4.26 (2H, quin, J = 6.0 Hz, 4`-H), 4.11 (2H, dd, J = 6.2, 8.4 Hz, 5´-H_α), 3.74 (2H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 3.09 (2H, dd, J = 5.8, 13.4 Hz, 4´-CH_α-S), 2.92 (2H, dd, J = 6.6, 13.4 Hz, 4´-CH_β-S), 1.40 (3H, s, -CH_3), 1.32 (3H, s, -CH_3); δ_C (100 MHz, $CDCl_3$) 210.0 (2-C), 136.1 (4-, 5- C), 110.1 (2 x 2´-C), 74.5 (2 x 4´-C), 68.4 (2 x 5´-C) 39.6 (2 x 4´-CH_2-S), 26.9 (2 x -CH_3), 25.3 (2 x -CH_3); ν_{max}: 2990, 2876, 1370, 1214, 1051, 1036, 894, 864, 816, 421 cm^{-1}; *m/z* (ESI) found: 449 $[M + Na]^+$ $C_{15}H_{22}O_4S_5Na$, other peaks at 413, 301; HRMS *m/z* (ESI) calcd for $[M + Na]^+$ $C_{15}H_{22}O_4S_5$ + Na : 449.0014 $[M + Na]^+$; found: 449.0008; 0.32; $[\alpha]^{19}_D$ = - 41.6 g^{-1} ml^{-1} dm^{-1} (c = 0.24 in THF).

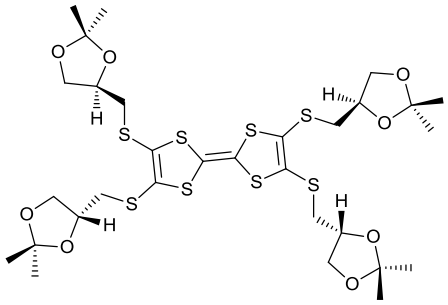
Preparation of 4,5-bis(((4´R)-2´,2´-dimethyl-1´,´3-dioxolan-4´-yl)methylthio)-1,3-dithiol-2-one 6.



To a solution of the thione **5** (390 mg, 9.1 mmol) in chloroform (10 ml) was added mercuric (II) acetate (435 mg, 1.4 mmol). The reaction mixture was stirred for 2h before being filtered and the solid residue washed with chloroform. The filtrate was collected, mixed with water (10 ml), and the solution was neutralised with solid sodium bicarbonate. The organic layer was separated, dried over magnesium sulphate and concentrated by evaporation to give **6** (348 mg, 93%) as a yellow oil; R_f (cyclohexane:ethyl acetate 5:1) 0.42; (Found C, 45.77; H, 5.48. $C_{15}H_{22}O_5S_4$ requires C, 43.88; H, 5.40%); δ_H (400 MHz;

$CDCl_3$) 4.22 (2 H, quin, J = 6.0 Hz, 4´-H), 4.07 (2H, dd, J = 6.2, 8.4 Hz, 5´-H_α), 3.72 (2H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 3.02 (2H, dd, J = 5.8, 13.4 Hz, 4´-CH_α-S), 2.87 (2H, dd, J = 6.6, 13.4 Hz, 4´-CH_β-S), 1.36 (6 H, s, 2 x -CH_3), 1.28 (6 H, s, 2 x -CH_3); δ_C (100 MHz, $CDCl_3$) 188.6 (2-C), 127.1 (4-, 5- C), 109.8 (2 x 2´-C), 74.4 (2 x 4´-C), 68.3 (2 x 5´-C) 39.3 (2 x 4´-CH2-S), 26.8 (2 x -CH3), 25.2 (2 x - CH_3); ν_{max}: 2985, 1668, 1370, 1213, 1149, 1057, 884, 755 cm^{-1}; *m/z* (ESI) found: 428 $[M + NH_4]^+$ $C_{15}H_{22}O_5S_4NH_4$, other peaks at 386, 353, 294, 217, 186; HRMS *m/z* (ESI) calcd. for $[M + NH_4]^+$ $C_{15}H_{22}O_5S_4 + NH_4$: 428.0688 $[M + NH_4]^+$; found: 428.0686; $[\alpha]^{19}_D$ = + 28.5 ^{o} g^{-1} ml^{-1} dm^{-1} (c = 0.28 in THF).

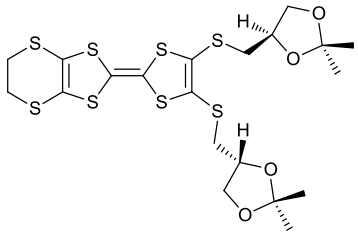
Preparation of *Tetrakis* ((4´´(R))-2´´,2´´-dimethyl-1´´,3´´-dioxan-4-methylethio) TTF 7.



A suspension of compound **6** (348 mg, 8.5mmol) in freshly distilled triethyl phosphite (7 ml) was heated to 90 ^{o}C under nitrogen for 6 h. The resulting orange precipitate was filtered off, washed with n-hexane and dried to afford **7** as an orange solid. The trimethyl phosphite was removed from the filtrate by Kugelrohr distillation, and the residue was washed with hexane, filtered and dried to yield further donor **7** as an orange solid , (total yield 169 mg. 51%); R_f (cyclohexane:ethyl acetate 5:1) 0.22; m. p. = 147 ºC; (Found C, 45.77; H, 5.53. $C_{30}H_{44}O_8S_8$ requires C, 45.66; H, 5.62%); δ_H (400 MHz, $CDCl_3$) 4.28 (4 H, quin, J = 6.0 Hz, 4 x 4``-H), 4.12 (4H, dd, J = 6.2, 8.4 Hz, 4 x 5´´-H_α), 3.77 (4H, dd, J = 5.4, 8.4 Hz, 4 x 5´´-H_β), 3.06 (4H, dd, J = 5.8, 13.4 Hz, 4 x 4´´-CH_α-S), 2.87 (4H, dd, J = 6.6, 13.4 Hz, 4 x

4´´-CH_β-S), 1.41 (12 H, s, 4 x CH_3), 1.32 (12 H, s, 4 x CH_3); δ_C (100 MHz, $CDCl_3$) 127.7 (4-, 5-, 4´-, 5´-C), 110.2 (2 x sp^2-C (central)), 109.9 (2- 2`-C), 74.8 (4 x 4´´-C), 68.5 (2 x 5´´-C) 39.1 (4 x 4´´-CH_2-S), 26.9 (4 x -CH_3), 25.4 (4 x -CH_3); ν_{max}: 2985, 2938, 2883, 1369, 1224, 1202, 1150, 1052, 1020, 864, 841, 820, 770, 511, 408 cm^{-1}; *m/z* (ESI) found: 806 $[M + NH_4]^+$ $C_{30}H_{44}O_8S_8NH_4$, other peaks at 613, 437, 351, 312, 219, 197; HRMS *m/z* (ESI) calcd for $[M + NH4]^+$ $C_{30}H_{44}O_8S_8 + NH_4$: 806.1140 $[M + NH_4]^+$; found: 806.1142; $[\alpha]^{21}_D$ = + 77.5° g^{-1} ml^{-1} dm^{-1} (c = 0.40 in THF).

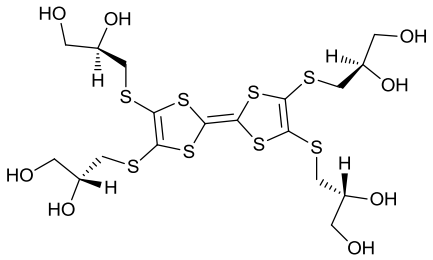
Preparation of bis(4´´(R)-2´´,2´´-dimethyl-1´´,3´´-dioxan-4´´-methylenethio) (ethylenedithio) TTF 8.



A suspension of oxo compound **6** (348 mg, 0.85 mmol) and unsubstituted thione **14** (285 mg, 1.27 mmole) in freshly distilled triethyl phosphite (7 ml) was heated to 90 ºC under nitrogen for 6 h. The mixture was allowed to cool before triethyl phosphite was removed by Kugelrohr distillation. The residue was purified by flash chromatography (SiO_2, eluting with cyclohexane:ethyl acetate 5:1) to yield the protected donor **8** (301 mg. 60%) as a red-orange solid; R_f (cyclohexane:ethyl acetate 5:1) 0.38; m. p. = 71 ºC; (Found C, 41.03; H, 4.54. $C_{15}H_{26}O_4S_8$ requires C, 40.93; H, 4.46%); δ_H (400 MHz, $CDCl_3$) 4.22 (2 H, quin, J = 6.0 Hz, 4`-H), 4.07 (2H, dd, J = 6.2, 8.4 Hz, 2 x 5´-H_α), 3.72 (2H, dd, J = 5.4, 8.4 Hz, 2 x 5´-H_β), 3.20 (4H, s, 5´-, 6´-H_2), 2.99 (2H, dd, J = 5.8, 13.4 Hz, 2 x 4´-CH_α-S), 2.81 (2H, dd, J = 6.6, 13.4 Hz, 2 x 4´-CH_β-S), 1.35 (6 H, s, 2 x CH_3), 1.29 (6 H, s, 2 x CH_3); δC (100 MHz, $CDCl_3$) 127.6 (4-, 5-C), 113.8 (3a´-, 7a´-C), 112.2 & 110.1 (2 x sp^2-C (central)),

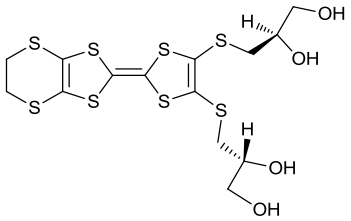
109.8 (2- & 2´-C), 74.4 (2 x 4´´-C), 68.3 (2 x 5´´-C) 39.3 (2 x 4´´-CH_2-S), 30.1 (5´-, 6´-C), 26.8 (2 x -CH_3), 25.2 (2 x - CH_3); ν_{max}: 2982, 2925, 2873, 1369, 1256, 1212, 1149, 1057, 842, 772 cm^{-1}; *m/z* (ESI) found: 586 [M] $C_{15}H_{26}O_4S_8$, other peaks at 536, 502, 462, 391, 279, 217, 186; HRMS *m/z* (ESI) calcd for $[M + H]^+$ $C_{15}H_{26}O_4S_8$ + H : 586.9670 $[M + H]^+$; found: 586.9675; $[\alpha]^{21}_D$ = + 28º g^{-1} ml^{-1} dm^{-1} (c = 0.25 in THF).

Preparation of *Tetrakis* ((2R)-2,-3-dihydroxy propyl-1-thio) TTF 9.



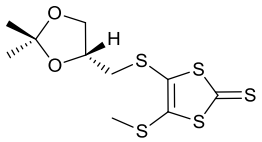
Tetra-ketal **7** (158 mg, 0.2 mmol) was stirred in a mixture of HCl (10 M, 0.9 ml) and tetrahydrofuran (15 ml) under nitrogen for 4 h. Evaporation and drying in vacuo at room temperature afforded the octol **9** (122 mg, 97 %) as a brown solid; m. p. = 166 ºC; (Found C, 34.30; H, 4.39 $C_{18}H_{28}O_8S_8$ requires C, 34.37; H, 4.49%); δ_H (400 MHz, d_6-DMSO) 4.35 (8H, br, 8 x O*H*), 3.63 (4H, m, 4 x C*H*(OH)), 3.52 (8H, m, 4 x CH_2OH), 3.12 (4H, br, 4 x CH_αS), 2.86 (4H, br, 4 x CH_βS); δ_C (100 MHz, d_6-DMSO) 126.9 (4-, 4´-, 5-, 5´-C), 109.4 (2-, 2´-C), 70.5 (4 x –CH(OH)), 64.2 (4 x –CH_2OH), 39.7 (4 x -CH_2S); ν_{max}: 3243 br, 2916, 1395, 1229, 1063, 1018, 878, 770 cm^{-1}; *m/z* (ESI) found: 627 [M - H] $C_{18}H_{28}O_8S_8$; HRMS *m/z* (ESI) calcd for [M - H] $C_{18}H_{28}O_8S_8$ - H : 626.9468 [M - H]; found: 626.9467; Found C, 34.30; H, 4.39 % $C_{18}H_{28}O_8S_8$ requires C, 34.37; H, 4.49 %; $[\alpha]^{21}_D$ = - 116.6 º g^{-1} ml^{-1} dm^{-1} (c = 0.24 in THF).

Preparation of bis ((R)-2,-3-dihydroxy propyl-1-thio)(ethylenedithio) TTF 10.



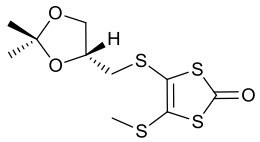
A solution of **8** (140 mg, 0.24 mmol) in a mixture of HCl (10 M, 0.9 ml) and tetrahydrofuran (15 ml) under nitrogen for 4 h. was stirred under nitrogen. Evaporation and drying in vacuo afforded the tetrol **10** (114 mg, 95 %) as a brown solid; m. p. = 94 ºC; (Found C, 33.16; H, 3.54 $C_{14}H_{18}O_4S_8$ requires C, 33.18; H, 3.58%); δ_H (400 MHz, d_6-DMSO) 4.80 (4 H, br 2 x -OH), 3.50 (2 H, m , 2 x CH-OH), 3.30 (4 H, m, 2 x $CH_\alpha CH_\beta OH$), 2.91 (2H, dd, J = 6.2, 8.4 Hz, 5´-H_α), 2.75 (2H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 2.41 (4 H, s, 5´, 6´-H_2); δ_C (100 MHz, d_6-DMSO) 127.0 (4-, 5-C), 112.9 (3a´-, 7a´-C), 113.2 & 110.1 (2 x sp^2-C (central)), 70.5 (4 x –CH(OH)), 64.2 (4 x –CH_2OH), 39.7 (2 x –CH_2S), 29.5 (5`, 6`-C); ν_{max}: 3244 br, 2919, 1395, 1290, 1259, 1182, 1109, 1061, 1016, 877, 767 cm^{-1}; *m/z* (ESI) found: 505 [M - H] $C_{14}H_{18}O_4S_8$, other peaks at 503, 501, 491, 455, 364; HRMS *m/z* (ESI) calcd for $[M - H]^+$ $C_{14}H_{18}O_4S_8$: 504.8889 $[M - H]^+$; found: 504.8898; $[\alpha]^{25}_D$ = - 390º g^{-1} ml^{-1} dm^{-1} (c = 0.40 in MeOH). *Crystal data* for $C_{14}H_{18}O_4S_8.I_3$, M_r = 887.46, monoclinic, *a* = 19.1095(7) , *b* = 10.1013(3), *c* = 13.8161(6) Å, β = 110.103(4)º, *V* = 2504.45(16)Å ^{3}, *Z* = 4, *C2*, D_c = 2.35 g cm^{-3}, μ = 4.43 mm^{-1}, *T* = 150 K, 3845 unique reflections (R_{int} = 0.0249), 3282 with $F^2 > 2\sigma$, $R(F, F^2>2\sigma)$ = 0.038, $R_w(F^2$, all data) = 0.084.

4-(((R)-2´,2´-Dimethyl-1´,3´-dioxolan-4´-yl)methyl)thio)-5-methylthio-1,3-dithiolane-2-thione 13B.



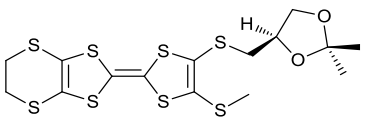
Sodium methoxide (0.96 ml, 25%wt solution, 4.0 mmol) was added to a solution of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione **3** (820 mg, 2.0 mmol) in dry and degassed methanol (10 ml) under nitrogen at room temperature, and the mixture stirred for 30 min. as the purple dithiolate **3** formed The reaction mixture was treated with **4** (528 mg, 2.0 mmol) at -20 $^{\circ}$C, stirred for 1 h, methyl iodide (426 mg, 0.42 ml, 3.0 mmol) added and the reaction mixture was left to warm to room temperature. An orange precipitate of 4,5-bis(methylsulphanyl)-2H-1,3-dithiole-2-thione **18** (87 mg, 19 %) was filtered off. The filtrate was collected, concentrated and purified by flash chromatography (SiO_2, eluting with cyclohexane:ethyl acetate 4:1) to yield the desired compound **19** as a brown oil (280 mg, 42 %), R_f (cyclohexane : ethyl acetate 4:1) 0.34; δ_H (400 MHz; $CDCl_3$) 4.25 (1 H, quin, J = 6.0 Hz, 4`-H), 4.08 (1H, dd, J = 6.2, 8.4 Hz, 5´-H_α), 3.72 (1H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 3.03 (1H, dd, J = 5.8, 13.4 Hz, 4´-CH_α-S), 2.87 (1H, dd, J = 6.6, 13.4 Hz, 4´-CH_β-S), 2.46 (3H, s, S-CH_3), 1.36 (3H, s, -CH_3), 1.29 (3H, s, -CH_3); δ_C (100 MHz, $CDCl_3$) 210.0 (2-C), 132.7 (4-,5- C), 109.7 (2´-C), 74.5 (4´-C), 68.2 (5´-C) 39.4 (4´-CH_2-S), 26.7 (-CH_3), 25.2 (-CH_3), 18.9 (S-CH_3); ν_{max}: 2982, 2159, 1971, 1720, 1369, 1211, 1058, 887, 713, 515 cm^{-1}; *m/z* (ESI) found: 325 $[M - H]^+$ $C_{10}H_{14}O_2S_5$ - H, other peaks at 314, 297, 256, 228, 199, 179; HRMS *m/z* (ESI) calcd for $[M + H]^+$ $C_{10}H_{14}O_2S_5$ +H: 326.9670, found: 326.9676; $[\alpha]^{22}_D$ = + 28.9º g^{-1} ml^{-1} dm^{-1} (c = 0.276 in THF).

4-(((R)-2´,2´-Dimethyl-1´,3´-dioxolan-4`-yl)methyl)thio)-5-(methylthio)-1,3-dithiolan-2-one 21.



To a solution of the thione **19** (280 mg, 0.86 mmol) in chloroform (10 ml) was added mercuric (II) acetate (400 mg, 1.29 mmol). The reaction mixture was stirred for 2h before being filtered and the solid residue washed with chloroform. The filtrate was collected, mixed with water (10 ml), and the solution was neutralised with solid sodium bicarbonate. The organic layer was separated, dried over magnesium sulphate and concentrated by evaporation to give **21** as a brown oil (255 mg, 96 %), R_f (cyclohexane : ethyl acetate 4:1) 0.35; δ_H (400 MHz; $CDCl_3$) 4.25 (1 H, quin, J = 6.0 Hz, 4`-H), 4.08 (1H, dd, J = 6.2, 8.4 Hz, 5`-H_α), 3.72 (1H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 3.03 (1H, dd, J = 5.8, 13.4 Hz, 4´-CH_α-S), 2.87 (1H, dd, J = 6.6, 13.4 Hz, 4´-CH_β-S), 2.46 (3H, s, S-CH_3), 1.36 (3H, s, -CH_3), 1.29 (3H, s, -CH_3); δ_C (100 MHz, $CDCl_3$) 189.1 (2-C), 124.5 (4-, 5- C), 109.7 (2´-C), 74.5 (4´-C), 68.3 (5´-C) 39.2 (4´-CH_2-S), 26.7 (-CH_3), 25.2 (-CH_3), 19.0 (S-CH_3); ν_{max}: 2986, 2918, 1668, 1615, 1370, 1213, 1058, 885 cm-1; *m/z* (EI) found: 310 $[M]^+$ $C_{10}H_{14}O_3S_4^+$; *m/z* HRMS calcd for $[M]^+$ $C_{10}H_{14}O_3S_4$: 309.9820, found: 309.9818; $[\alpha]^{23}_D$ = + 11.4 ^{o} g^{-1} ml^{-1} dm^{-1} (c = 0.35 in THF).

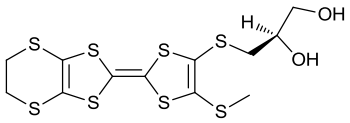
(R)-4-(((2-(5,6-dihydro-[1,3]dithiolo[4,5-b][1,4]dithiin-2-ylidene)-5-(methylthio)-1,3-dithiol-4-yl)thio)methyl)-2,2-dimethyl-1,3-dioxolane 20.



A suspension of oxo compound **21** (280 mg, 0.86 mmol) and unsubstituted thione **14** (285 mg, 1.27 mmole) in freshly distilled triethyl phosphite (7 ml) was heated to 90 ^oC under nitrogen for 6 h. The mixture was allowed to cool before triethyl phosphite was removed by

Kugelrohr distillation. The residue was purified by flash chromatography (SiO_2, eluting with cyclohexane:ethyl acetate 5:1) to yield the protected donor **20** as a red oil (265 mg. 65%); R_f (cyclohexane:ethyl acetate 5:1) 0.39; (Found: C, 40.46; H, 3.62% $C_{15}H_{18}O_2S_8$ requires C, 37.01; H, 3.73%); δ_H (400 MHz, $CDCl_3$) 4.23 (1 H, m, 4´-H), 4.11 (1H, m, 5´-H_α), 3.77 (1H, m, 5´-H_β), 3.26 (3H, s, S-CH_3), 3.06 (1H, m, 4´-CH_α-S), 2.81 (1H, m, 4´-CH_β-S), 2.40 (4 H, s, 5´, 6`-H_2), 1.40 (3H, s, CH_3), 1.32 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 127.6 (4-, 5-C), 113.8 & 113.2 (3a´-, 7a´-C), 109.8 (2-C), 74.8 (4-C), 68.6 (5-C) 38.9 (4-CH_2-S), 30.1 (5´-, 6´-C), 26.8 (-CH_3), 25.4 (- CH_3), 15.9 (S-CH_3); ν_{max}: 2980, 2919, 1419, 1369, 1223, 1149, 1058, 886, 772, 512 cm^{-1}; *m/z* (ESI) found: 487 $[M + H]^+$ $C_{15}H_{18}O_2S_8$ + H, other peaks at 419, 371, 327, 304, 199, 179, 149; *m/z* HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{18}O_2S_8$ + H : 486.9145, found: 486.9141; $[\alpha]^{21}_D$ = + 33.3 ^{o} g^{-1} ml^{-1} dm^{-1} (c = 0.30 in THF).

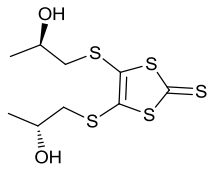
(R)-3-((2-(5,6-dihydro-[1,3]dithiolo[4,5-b][1,4]dithiin-2-ylidene)-5-(methylthio)-1,3-dithiol-4-yl)thio)propane-1,2-diol 22.



A solution of **20** (50 mg, 0.10 mmol) in a mixture of HCl (10 M, 0.2 ml) and tetrahydrofuran (10 ml) under nitrogen was stirred for 4 h. under nitrogen. Evaporation and drying in vacuo afforded the diol **16** (44 mg, 96 %) as a brown solid; (Found C, 45.02; H, 4.57% $C_{12}H_{14}O_2S_8$ requires C, 32.26; H, 3.16%); δ_H (400 MHz, d_6-DMSO) 4.47 (2 H, br 2 x -OH), 3.47 (1H, m , CH-OH), 3.27 (3H, s, S-CH_3), 3.23 (2 H, m, $CH_\alpha CH_\beta OH$), 2.89 (1H, dd, J = 6.2, 8.4 Hz, 5´-H_α), 2.72 (1H, dd, J = 5.4, 8.4 Hz, 5´-H_β), 2.38 (4 H, s, 5´, 6´-H2); δ_C (100 MHz, d_6-DMSO) 128.3 (4-,5-C), 113.1 & 112.8 (2-, 2´-C), 70.5 (4 x –

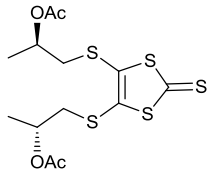
CH(OH)), 64.2 (4 x $-CH_2OH$), 39.7 (2 x $-CH_2S$), 29.6 (5´, 6´-C), 18.6 (S-CH_3); ν_{max}: 3319 br, 2919, 2332, 1725, 1418, 1286, 1067, 1030, 886, 772 cm^{-1}; *m/z* (ESI) found: 447 [M + H] $C_{12}H_{14}O_2S_8$ + H, other peaks at: 910 (2M +H_2O), 419, 371, 327, 304, 149; HRMS *m/z* (ESI) calcd for $[M + H]^+$ $C_{12}H_{14}O_2S_8$ + H: 446.8832, found: 446.8832; $[\alpha]^{15}_D$ = - 35 ^{o} g^{-1} ml^{-1} dm^{-1} (c = 0.20, in MeOH).

Bis(2R-2-hydroxylpropylthio)-1,3-dithiole-2-thione 24.



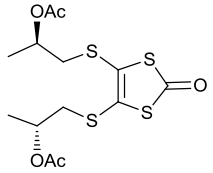
A solution of dithiolate **3** (5.90 g, 14.5 mmol) in dry methanol under a nitrogen atmosphere was then treated with (R)-(+)-propylene oxide (1.68 g, 2.02ml, 28.9 mmol) at room temperature. The deep purple solution turned orange–red over several minutes, and the mixture was stirred at room temperature for 3h. Acetic acid (4 ml) was added. After stirring for 1 h, the reaction mixture was concentrated in vacuo, the methyl benzoate was removed by Kugelrohr distillation and the residue was purified by flash chromatography (SiO_2, eluting with cyclohexane : ethyl acetate (1:1) to yield **24** as a red brown oil (3.75g, 82.2%); R_f (cyclohexane:ethyl acetate 1:1) 0.44; δ_H (400 MHz, $CDCl_3$): 3.90 (2H, m, 2×CHOH), 3.23 (2H, br, 2×OH), 2.99 (2H, dd, J = 3.6, 13.6 Hz, 2×$CH_\alpha S$), 2.78 (2H, dd, J = 8.4, 13.7 Hz, 2×$CH_\beta S$), 1.24 (6H, d, J = 6.2 Hz, 2 × CH_3); δ_C ($CDCl_3$): 208.9 (C=S), 136.6 (4-,5-C), 66.1 (2 × CHOH), 45.4 (2 × CH_2S), 22.0 (2 × CH_3); ν_{max}: 3342, 2968, 2920, 1724, 1455, 1400, 1372, 1240, 1189, 1124, 1058, 1034, 932, 890, 820, 515, 452 cm^{-1}.

R-bis(*2`*-acetoxypropylthio)-1,3-dithiole-2-thione 25.



Acetic anhydride (2.5 ml, 26.5 mmol) was added to a solution of thione **24** (3.25 g, 10.3 mmol) in pyridine (35 ml) at 0 ^{o}C and then stirred overnight at room temperature. Water (150 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 50 ml). The organic solution was washed consecutively with 0.5 M HCl solution (3 × 50 ml) and H_2O (50 ml), dried with $MgSO_4$ and evaporated. The rest of the pyridine was removed by stirred with toluene and evaporation three times. The residue was purified by flash chromatography (SiO_2, eluting with cyclohexane : ethyl acetate (3:1)) to yield the thione **25** as an orange brown oil (3.51g, 88 %); R_f (cyclohexane:ethyl acetate 3:1) 0.34; δ_H (400 MHz, $CDCl_3$): 5.05 (2H, m, 2 × CHOAc), 3.02 (4H, d, J = 5.8 Hz, 2 × CH_2S), 2.03 (6H, s, 2 × CH_3CO), 1.33 (6H, d, J = 6.4 Hz, 2 × -CH_3); δ_C ($CDCl_3$): 209.8 (C=S), 170.1 (2 × C=O), 136.5 (4-,5-C), 69.2 (2 × CHOAc), 41.6 (2 × CH_2S), 21.1 (2 × CH_3CO), 19.1 (2 × -CH_3); ν_{max}: 2980, 2932, 1733, 1456, 1371, 1228, 1128, 1060, 1035, 956, 889, 632, 604, 515, 451 410 cm-1.

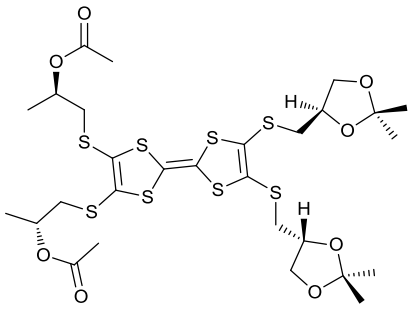
R-Bis(*2´*-acetoxypropylthio)-1,3-dithiole-2-one 26.



To a solution of the thione **25** (3.98 g, 10.0 mmol) in chloroform (80 ml) was added mercuric acetate (4.83 g, 15.1 mmol). After stirring for 2 h, the reaction mixture was filtered and the solid residue washed with chloroform. The combined filtrates were concentrated by evaporation to give **26** as a yellow oil (3.55 g, 97%); R_f (cyclohexane:ethyl acetate 4:1) 0.00; δ_H (400 MHz, $CDCl_3$) 5.03 (2H, m, 2 × CHOAc), 2.98 (4H, d, J = 5.8 Hz,

2 × CH_2S), 2.02 (6H, s, 2 × CH_3CO), 1.32 (6H, d, J = 6.3 Hz, 2 × -CH_3); δ_C ($CDCl_3$): 189.1 (C=O), 170.1 (2×$COCH_3$), 127.5 (4-,5-C), 69.3 (2 × CHOAc), 41.4 (2 × CH_2S), 21.1 (2 × CH_3CO), 19.1 (2 × -CH_3) ; ν_{max}: 2980, 2929, 1734, 1666, 1612, 1445, 1372, 1230, 1129, 1094, 1034, 952, 880, 741, 632, 607, 515, 452 cm^{-1}.

***vic*-Bis(((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-*vic*-bis((2´R)-2´-acetoxy)propylthio)TTF 27.**

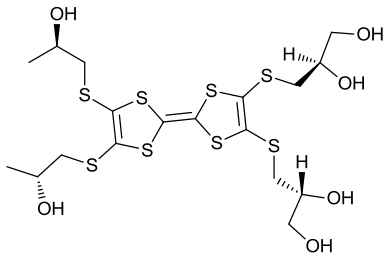


A mixture of oxo compound **26** (1.1g, 3.0 mmol), **5** (1.28 g, 3.0 mmole) and freshly distilled triethyl phosphite (10 ml) was heated at 90 ^oC overnight. The resulting orange precipitate of homo-coupled side product **7** was filtered off, washed with hexane, the triethyl phosphite removed by Kugelrohr distillation and the residue subjected to flash chromatography (SiO_2, eluting with cyclohexane : ethyl acetate (3:1)) to yield the donor **27** as brown oil (686 mg, 30 %); R_f (cyclohexane:ethyl acetate 3:1) 0.44; (Found C, 43.18; H, 5.30% $C_{28}H_{40}O_8S_8$ requires C, 44.18; H, 5.30%); δ_H (400 MHz, $CDCl_3$) 4.97 (2H, m, 2 × 2´-H), 4.23 (2 H, quin, J = 6.0 Hz, 4-H), 4.10 (2H, dd, J = 6.2, 8.4 Hz, 2 x 5-H_α), 3.72 (2H, dd, J = 5.4, 8.4 Hz, 2 x 5-H_β), 3.15 (2H, dd, J = 5.8, 13.4 Hz, 2 x 4´-CH_α-S), 2.93 (4H, d, J = 5.8 Hz, 2 × 1´-H_2), 2.80 (2H, dd, J = 6.6, 13.4 Hz, 2 x 4-CH_β-S), 1.98 (6H, s, 2 × CH_3CO), 1.35 (6 H, s, 2 x -CH_3), 1.29 (6 H, s, 2 x -CH_3), 1.28 (6H, d, J = 6.4Hz, 2 x $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 170.0 (2 x C=O), 127.9 (2 x sp^2-C), 127.6 (2 x sp^2-C), 110.9 & 110.5 (2 x sp^2-C(central)), 109.8 (2 x 2-C), 74.4 (2 x 4-C), 69.3 (2 x 2´-C), 68.3 (2 x 5-C), 40.9 (2 x 1´-C), 38.9 (2 x 4-CH_2-S), 26.8 (2 x 2-CH_3), 25.4 (2 x 2-CH_3) 21.0 (2

x CH_3CO), 19.0 (2 x 3´-CH_3); ν_{max}: 3324, 2927, 2850, 1737, 1625, 1517, 1370, 1310, 1229, 1088, 1055, 892, 642, 393cm-1; *m/z* (ESI) found: 778 $[M + NH_4]^+$ $C_{28}H_{40}O_8S_8$ + NH_4; HRMS *m/z* (ESI) calcd for $[M + NH4]^+$ $C_{28}H_{40}O_8S_8$ + NH_4: 778.0827, found: 778.0827; $[\alpha]^{20}_D$ = + 11.6 ^{o} g^{-1} ml^{-1} dm^{-1} (c = 0.345 in THF).

However, another procedure for this coupling was also used. In this case, a suspension of oxo compound **6** (580 mg, 1.40 mmol) and unsubstituted thione **25** (562 mg, 1.40 mmole) in freshly distilled triethyl phosphite (7 ml) was heated to 90 ^{o}C under nitrogen for 6 h. The resulting orange precipitate of the homo-coupled side product of **7** was filtered off, washed with hexane, the triethyl phosphite removed from the filtrate by Kugelrohr distillation and the residue subjected to flash chromatography (SiO_2, eluting with cyclohexane : ethyl acetate (3:1)) to yield the donor **27** as a brown oil.

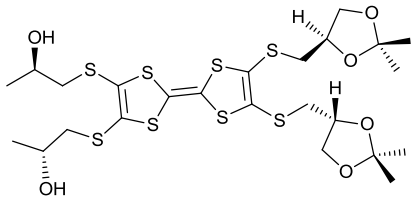
***vic*-Bis((2R)-2,3-hydroxypropylthio)-*vic*-bis((2´R)-2´-hydroxypropylthio)TTF 28.**



A solution of **27** (100 mg, 0.13 mmol) in a mixture of HCl (10 M, 0.9 ml) and tetrahydrofuran (15 ml) was stirred under nitrogen for 4 h under nitrogen. Evaporation and drying in vacuo afforded the tetrol **28** (75 mg, 97 %) as a brown solid; (Found C, 36.22; H, 5.07% $C_{18}H_{28}O_6S_8$ requires C, 36.22; H, 4.73); δ_H ($CDCl_3$): 3.57 (2H, m, 2 × CHOH), 2.50 (4H, s, 5´-,6´-H_2), 2.97 (4H, dd, J = 3.3, 13.8 Hz, 4 × $CH_\alpha S$), 2.84 (2H, br, s, 2×OH), 2.62 (2H, dd, J = 9.0, 13.8 Hz, 2 × $CH_\beta S$), 1.20 (6H, d, J = 6.3 Hz, 2 × -CH_3); long δ_C ($CDCl_3$):

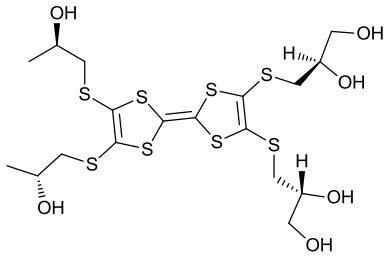
131.0 (4-,5-C), 113.8 (3a´-,7a´-C), 112.3 & 109.7 (2-,2´-C), 62.2 (2 × CHOH), 45.7 (2 × CH_2S), 30.7 (5`-,6`-C), 30.2 (2 × -CH_3); ν_{max}: 3361, 2927, 2324, 1722, 1375, 1275, 1173, 1124, 1032, 931, 813, 743 cm^{-1}; $[\alpha]^{23}{}_D$ = - 40^o g^{-1} ml^{-1} dm^{-1} (c = 0.20 in THF).

***vic*-Bis(((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-*vic*-bis((2´R)-2´-hydroxypropylthio)TTF 29.**



An aqueous solution (2.5 ml) of potassium carbonate (142 mg, 1.0 mmol) was added to a solution of **27** (100 mg, 0.13 mmol) in methanol (10 ml) and tetrahydrofuran (1.5 ml) which was stirred under nitrogen for 12 h. Methanol and tetrahydrofuran were evaporated under vecuom, and the orange solid was collected and washed with water to yield the chiral diol **29** as a light orange (84 mg, 95%); m.p. 92 – 93 ^oC; (Found 42.49; H, 5.36%.. $C_{24}H_{36}O_6S_8$ requires C, 42.57; H, 5.36 %); δ_H (400 MHz, CD_3OD): 4.87 (2H, br, 2 × CHO*H*), 4.26 (2 H, quin, J = 6.0 Hz, 4-H), 4.14 (2H, dd, J = 6.2, 8.4 Hz, 2 x 5-H_α), 3.88 (2H, dd, J = 5.4, 8.4 Hz, 2 x 5-H_β), 3.76 (2H, dd, J = 5.8, 13.4 Hz, 2 x 4´-CH_α-S), 3.05 (4H, d, J = 5.8 Hz, 2 × 1´-H_2), 2.95 (2H, dd, J = 6.6, 13.4 Hz, 2 x 4-CH_β-S), 1.39 (6 H, s, 2 x -CH_3), 1.31 (6 H, s, 2 x -CH_3), 1.25 (6H, d, J = 6.4Hz, 2 x $CHCH_3$); δ_C (100 MHz, CD_3OD): 129.3 (4 x sp^2-C), 110.9 (2 x sp^2-C(central)), 109.8 (2 x 2-C), 76.4 (2 x 4-C), 69.5 (2 x 2´-C), 67.8 (2 x 5-C), 45.3 (2 x 1´-C), 40.1 (2 x 4-CH_2-S), 27.2 (2 x 2-CH_3), 25.7 (2 x 2-CH_3), 22.3 (2 x 3´-CH_3); ν_{max}: 3355, 2984, 1370, 1243, 1226, 1203, 1053, 864, 770 cm^{-1}; $[\alpha]^{23}{}_D$ =+ 266 g^{-1} ml^{-1} dm^{-1} (c = 0.015 in Methanol).

Alternative procedure to prepare *vic*-Bis((2R)-2,3-hydroxypropylthio)-*vic*-bis((2´R)-2´-hydroxypropylthio)TTF 28.



An aqueous solution of 5% HCl (5 ml) was added to a solution of **29** (100 mg, 0.14 mmol) in methanol (7 ml) and tetrahydrofuran (2 ml) which was stirred under nitrogen for 12 h. Methanol and tetrahydrofuran were evaporated under vecuom, and the orange solid was collected and washed with water to yield the chiral hexol **28** as a deep orange solid (85 mg, 96%); (Found C, 36.13; H, 4.68%. $C_{18}H_{28}O_6S_8$ requires C, 36.22; H, 4.73%); δ_H (CD_3OD): 4.88 (6H, br, s, 6×OH), 3.87 (2H, m, 2 × C*H*OH), 3.33(4H, s, 5´-,6´-H_2), 3.73 (4H, dd, J = 3.3, 13.8 Hz, 4 × $CH_\alpha S$), 3.59 (2H, dd, J = 9.0, 13.8 Hz, 2 × $CH_\beta S$), 3.02 (4H, d, J = 5.8 Hz, 2 × 1´-H_2), 2.86 (2H, dd, J = 6.6, 13.4 Hz, 2 x 4-CH_β-S), 1.26 (6H, d, J = 6.3 Hz, 2 × -CH_3); δ_C (CD_3OD): 129.5 (4-,5-C), 111.8 (3a´-,7a´-C), 110.3 & 109.7 (2-,2´-C), 72.3 (2 × CHOH), 67.8 (2 x 2´-C), 65.8 (2 x 5-C), 44.3 (2 x 1´-C), 40.1 (2 x 4-CH_2-S), 22.3 (2 x 3´-CH_3); ν_{max}: 3293, 2966, 2918, 1395, 1372, 1066, 1033, 885, 771 cm^{-1}; $[\alpha]^{23}{}_D$ = - 40^o g^{-1} ml^{-1} dm^{-1} (c = 0.20 in THF).

Charge transfer salt (10)I_3.

Donor **10** (15 mg) dissolved in DCM (5ml) was placed in a test tube and a layer of THF (5ml) was added very slowly. A solution of iodine (50mg) in THF (5ml) was added as a further layer very slowly and the tube was left at room temperature for five days. Some crystals formed by diffusion[41,42] and were collected.

X-ray Crystallography.

Data was collected with MoKα radiation at 150 K on an Agilent Xcalibur diffractometer equipped with a Sapphire detector at Nottingham Trent University for 10. The structure was solved and refined with SHELXS and SHELXL suite of programs[43] using the XSEED[44] interface, and molecular illustrations are prepared with Mecury[45] and POV-RAY.[46] Cif files will be deposited at the CCDC when the work is published.

Crystal data for **10.I_3:** $C_{14}H_{18}O_4S_8.I_3$, M_r = 887.46, monoclinic, a = 19.1095(7), b = 10.1013(3), c = 13.8161(6) Å, β = 110.103(4)°, V = 2504.45(16)Å ^{3}, Z = 4, *C2*, D_c = 2.35 g cm^{-3}, μ = 4.43 mm^{-1}, T = 150 K, 3845 unique reflections (R_{int} = 0.0249), 3282 with $F^2 > 2\sigma$, $R(F, F^2>2\sigma)$ = 0.038, $R_w(F^2$, all data) = 0.084.

4.5: <u>Future work.</u>

The new chiral donors will be converted into radical cation salts by electrocrystallisation e.g. with BF_4^-, Cl^- and oxalate complexes, or diffusion with an acceptor such as I_2, TCNQ-F_4, C_{60}. Furthermore, a new approach to vic-dithiols has been developed and will be applied to the preparation of new chiral donors.

4.6: References.

1. J. Ferraris, D. O. Cowan, V. Walatka Jr. and J. H. Perlstein, *J. Am. Chem. Soc.*, **1973**, *95*, 948.
2. T. J. Kistenmacher, T. E. Phillips and D. O. Cowan, *Acta Cryst*., **1974**, Sect. B30, 763.
3. J. Ferraris, D. O. Cowan, V. V. Walatka and J. H. Perlstein, *J. Am. Chem. Soc.*,**1972**, *94*, 3372.
4. F. Wudl, G. M. Smith and E. J. Hufnagel, *Chem. Commun*., **1970**, *8*, 1453.
5. J. Larsen, C. Lenoir, M. Carson and D. L. Coffen, Organic *Syntheses*, *Coll.*,**1998**, *9*, 72.
6. K. Bechgaard, D. O. Cowan and A. N. Bloch, *J. Chem. Soc. Chem. Commun*., **1974**, *22*, 937.
7. D. Jerome, A. Mazaud, M. Ribault and K. Bechgaard, *J. Phys. (Paris) Lett*., **1980**, *41*, L95–L98.
8. K. Bechgaard, K. Carneiro, F. B. Rasmussen, M. Olsen, G. Rindorf, C. S. Jacobsen, H. J. Pedersen and J. C. Scott, *J. Am. Chem. Soc*., **1981**, *103*, 2440.
9. M. R. Bryce, *J. Mater. Chem*., **1995**, *5*, 1481.
10. T. Ishiguro, K. Yamaji and G. Saito, Organic Superconductors, 2nd ed., **1998**, 88.
11. J. M. Williams, Organic superconductors **1992**.
12. J. M. Fabre, *J. Phys. IV France*, **2000**, *10*, 3.
13. M. Mizuno, A. F. Garito and M. P. Cava, *J. Chem. Soc., Chem. Commun.*, **1978**, *1*. 18.
14. E. B. Yagubskii, I. F. Schegolev, V. N. Laukhin, P. A. Kononovich, M. V. Kartsovnik, A. V. Zarykina and L. I. Buravov, *JETP Lett*., **1984**, *39*, 12.

15. H. H. Wang, M. A. Beno, U. Geiser, M. A. Firestone, K. S. Webb, L. Nunez, G. W. Crabtree, K. D. Carlson, J. M. Williams, L. J. Azevedo, J. F. Kwak and J. E. Schirber, *Inorg. Chem.*, **1985**, *24*, 2465.
16. J. M. Williams, T. J. Emge, H. H. Wang, M. A. Beno. P. T. Copps, L. N. Hall, K. D. Carlson, and G. W. Crabtree, *Inorg. Chem.*, **1984**, *23*, 2558.
17. J. M. Williams, H. H. Wang, M. A. Beno, T. J. Emge, L. M. Sowa, P. T. Copps, F. Behroozi, L. N. Hall, K. D. Carlson and G. W. Crabtree, *Inorg. Chem.*, **1984**, *23*, 3839.
18. J. M. Williams, A. M. Kini, H. H. Wang, et al., *Inorg. Chem.*, **1990**, *29*, 3272.
19. J.-P. Griffiths, A. A. Arnal, G. Appleby and J. D. Wallis, *Tetrahedron Lett.*, **2004**, *45*, 2813.
20. J.-P. Griffiths, H. Nie, R. J. Brown, P. Day and J. D. Wallis, *Org. Biomol. Chem.*, **2005**, *3*, 2155.
21. V. Krstic and G. L. J. A. Rikken, *Chem. Phys. Lett.*, **2002**, *364*, 51.
22. J. D. Wallis, A. D. Karrer, and J. D. Dunitz, *Helv. Chim. Ada*, **1986**, *69*, 69.
23. S. J. Krivickas, A. Ichikawa, K. Takahashi, H. Tajima, J. D. Wallis and H. Mori, *Synth. Met.* , **2011**, *161*, 1563.
24. J. R. Galán-Mascarós, E. Coronado, P. A. Goddard, J. Singleton, A. I. Coldea, J. D. Wallis, S. J. Coles and A. Alberola, *J. Am. Chem. Soc.*, **2010**, *132*, 9271.
25. C. Réthoré, A. Madalan, M. Fourmigué, E. Canadell, E. B. Lopes, M. Almeida, R. Clérac and N. Avarvari, *New. J. Chem.*, **2007**, *31*, 1468.
26. C. Réthoré, N. Avarvari, E. Canadell, P. Auban-Senzier, M. Fourmigué, *J. Am. Chem. Soc.* **2005**, *127*, 5748.

27. S. Yang, A. C. Brooks, L. Martin, P. Day, H. Li, L. Male, P. Horton and J. D. Wallis, *Cryst. Eng. Comm*, **2009**, *11*, 993.

28. E. Gomar-Nadal, C. Rovira and D. B. Amabilino, *Tetrahedron*, **2006**, *62*, 3370.

29. Y. Zhou, D. Zhang, L. Zhu, Z. Shuai and D. Zhu, *J. Org. Chem.* **2006**, *71*, 2123.

30. T. Kitamura, S. Nakaso, N. Mizoshita, Y. Tochigi, T. Shimomura, M. Moriyama, K. Ito and T. Kato, *J. Am. Chem. Soc.*, **2005**, *127*, 14769.

31. N. Avarvari and J. D. Wallis, *J. Mater. Chem.*, **2009**, *19*, 4061.

32. E. Coronado and J. R. Galán-Mascarós, *J. Mater. Chem.*, **2005**, *15*, 66.

33. F. Leurquin, T. Ozturk, M. Pilkington and J.D. Wallis, *J. Chem. Soc., Perkin Trans 1*, **1997**, *21*, 3173.

34. R. J. Brown,. A. C. Brooks, J.-P. Griffiths, B. Vital, P. Day and J. D. Wallis, *Org. Biomol. Chem.*, **2007**, *5*, 3172.

35. S. Booth, E. N. K. Wallace, K. Singhal, P.N. Bartlett and J. D Kilburn, *J. Chem. Soc, Perkin Trans.1*, **1998**, 1467.

36. G. V. Alea, G. C. Janairo and J. D. Kilburn, Philipp, *J. Sci.*, **2007**, *136*, 33.

37. N. Svenstrup and J. Becher, *Synthesis* **1995,** *215*, 235.

38. C. S. Wang, A.S. Batsanov, M.R. Bryce and J. A. K. Howard, *Synthesis*, **1998**, *11*, 1615.

39. H. S. Kim, D. Barak, T.K. Harden, J. L. Boyer and K. A. Jacobson. *J. Med. Chem.*, **2001**, *44*, 3092.

40. E. Aktoudianakis et al., US Patent application, PCT/US2009/051741, **2009**.

41. H. Anazi, *J. Cryst. Growth*, **1976**, *1*, 33.

42. J. S. Miller, M. Drillon, Magnetism: *Molecules to Materials II*, **2001**.

43. G.M. Sheldrick, *Acta Crystallogr. Sect. A*, **2008**, *64*, 112.

44. L. J. Barbour, "X-Seed - A software tool for supramolecular crystallography", *J. Supramol. Chem.*, **2001**, *1*, 189.

45. C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, *J. Appl. Crystallogr*., **2006**, *39*, 453.

46. Persistence of Vision Pty. Ltd. (**2004**). Persistence of Vision (TM) Raytrac Persistence of Vision Pty. Ltd., Williamstown, Victoria, Australia, http://www.povray.org.