Novel Approaches to Medium Rings, Enantiomerically Enriched Alcohols and Haloalkynes

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Declaration

I, Filippo Rota, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that it has been indicated and acknowledged.

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Abstract

Medium rings (8-12 atoms) are present in many naturally occurring molecules which in many cases have potentially useful biological activity. Unfortunately current synthetic methods to synthesise medium rings lack general applicability or require high dilution and/or tedious optimisation procedures. This thesis describes the investigation of a novel strategy in which a suitably functionalised linear precursor undergoes double cyclisation and fragmentation to afford a medium ring. The key to this proposed sequence is the generation of an intramolecular cyclic ylide which can react with a pendant electrophile generating a bicyclic intermediate that subsequently undergoes fragmentation, thus generating a medium ring. The use of sulfur ylides was initially investigated for the synthesis of the 8-membered ring natural product Cephalosporolide-D but all attempts to trigger the proposed sequence of events were unsuccessful leading only to side reactions or decomposition. Alternative metal catalysed approaches to the synthesis of sulfur ylides were also investigated with no success. Nitrogen and phosphorus cyclic ylides were also evaluated and the latter reaction gave small quantities of the target medium ring product.

This thesis also describes the discovery that high levels of diastereoselectivity could be achieved by the addition of carbon-nucleophiles to α-sulfenylaldehydes, intermediates in the synthesis of precursors to medium rings. Enantiomerically enriched secondary alcohols could be subsequently obtained from the β-hydroxysulfides after Raney-Ni reduction of the carbon-sulfur bond.

In combination with the studies on metal catalysed generation of ylides, this thesis reports a gold(I) catalysed mild procedure for the synthesis of haloalkynes from either terminal alkynes or trimethylsilylacetylenes initially discovered in our laboratories. Interestingly it was found that protic acids were able to catalyse the halogenation of trimethylsilylacetylenes but not of terminal alkynes. The reactions were successfully extended to a series of aromatic and aliphatic alkynes. Procedures were also developed for the conversions of terminal alkynes into α-iodoketones which were also used *in situ* for the synthesis of heterocycles.

Contents

Abbreviations

Ac	acetyl
acac	acetylacetonyl
aq	aqueous
9-BBN	9-borabicyclic[3.3.1]nonane
Bn	benzyl
Boc	tert-butoxycarbonyl
CAN	cerium ammonium nitrate
Cat	catalyst
***c*Hex**	cyclohexyl
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
d	days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHP	dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-N,N-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one)
DMPU	N,N -dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide
ee	enantiomeric excess
er	enantiomeric ratio
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
liq	liquid
***m*CPBA**	m-chloroperbenzoic acid
Mes	mesityl (2,4,6-trimethylphenyl)
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl

MS	molecular sieves
Ms	mesyl (methanesulfonyl)
MTPA	methoxy-(trifluoromethyl)phenylacetyl
n	normal
NMO	N-methylmorpholine N-oxide
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl (trimethylacetyl)
PMB	p-methoxybenzyl
PMP	p-methoxyphenyl
PPTS	pyridinium p-toluenesulfonate
PT	proton transfer
Py	pyridine
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
RCM	ring-closing metathesis
RT	room temperature
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat	saturated
tert	tertiary
TBAF	tetra-n-butylammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-n-propylammonium perruthenate
Ts	p-toluenesulfonyl

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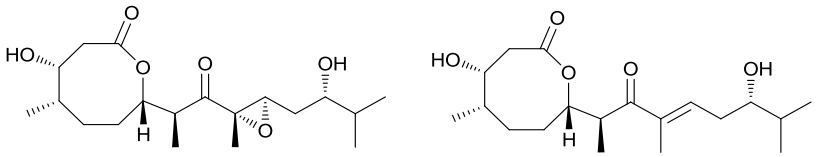
1. Introduction

1.1 Medium rings (MR) and their natural occurrence

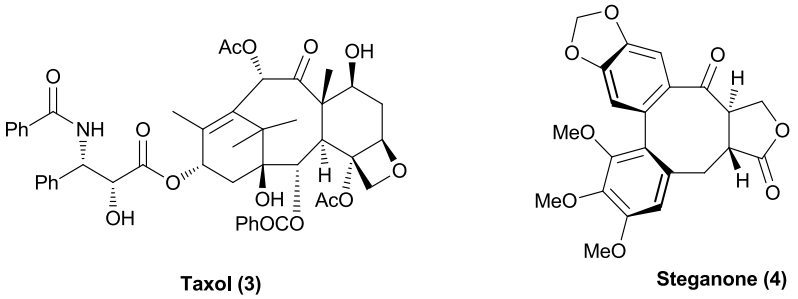
The term "medium ring" was originally introduced by Prelog[1] and Brown[2] to describe a class of carbocyclic molecules containing between 8 and 11 atoms. The term is now commonly extended to rings containing from 7 to 12 carbons and also heteroatoms, as these structures are often found in naturally occurring molecules which often show potentially useful biological activity. For example, the family of Octalactins (**1** and **2**, **Fig. 1.1**), originally isolated from the marine bacterium *Streptomyces* sp., are an interesting class of cytotoxic molecules that possess an 8-membered ring lactone in their structure. This class of compounds showed very promising cytotoxic activity against some tumour cell lines.[3]



(-)-Octalactin A (1) (-)-Octalactin B (2)

Fig. 1.1

Carbocyclic 8-membered rings also occur widely in nature, especially in two classes of natural products, terpenoids and lignans, both of which exhibit many interesting biological activities.[4] Amongst the vast terpenoid familiy, Taxol **3**, containing a carbocyclic 8-membered ring fused with two smaller rings, is possibly the best known compound as it is one of the most important mitotic inhibitors used in cancer chemotherapy (**Fig. 1.2**).[5]



Taxol (3) Steganone (4)

Fig. 1.2

Amongst the lignan family, several compounds of the Steganone class (**4**, **Fig. 1.2**) have been reported to possess significant antileukemic activity.[6] Nitrogen containing medium rings are also known to exhibit pharmacological activity, for example compound **5** (**Fig 1.3**), previously studied as an anti-hypertensive agent[7], and the alkaloid Buflavine **6**, isolated from an endemic *amaryllidaceae* alkaloid species *Boophane flava*, exhibiting interesting α-adrenolytic and anti-serotonin activities.[8]

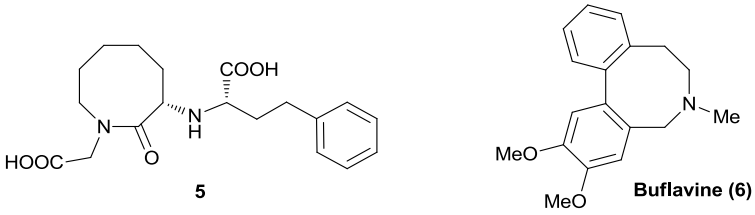


Fig. 1.3

A 9-membered unsaturated lactone ring is the moiety of the Halicholactone family, a class of fatty acid metabolites isolated from the marine sponge *Halichondria Okadai Kawta* (**7** and **8**, **Fig. 1.4**).[9]

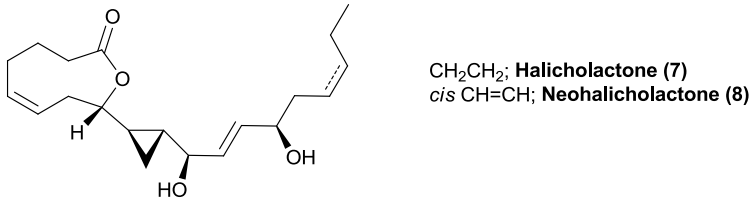


Fig.1.4

These naturally occurring molecules are able to selectively inhibit enzymes such as lipoxygenase and farnesyl protein transferase and therefore they are potentially useful in therapy.[10] The antibiotic Antimycin A_{3b} (**9**), part of the large family of secondary metabolites produced by *Streptomyces* bacteria,[11] possesses the pentasubstituted diolide 9-membered ring shown in **Fig. 1.5**.

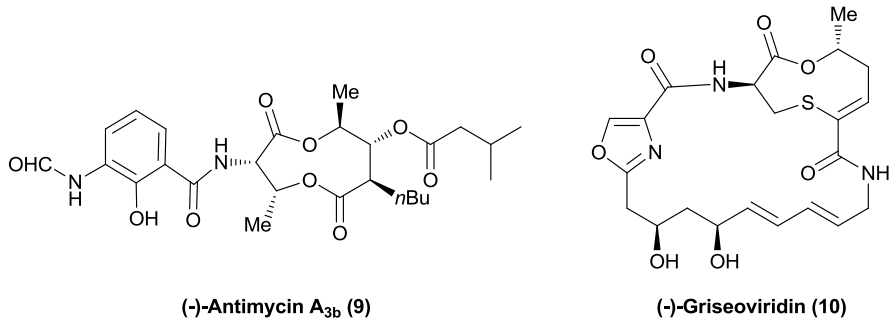


Fig. 1.5

Antymicins were found to specifically bind to cytochrome C reductase and for this property they are used as a fish poison in the catfish industry.[12] Another important broad-spectrum antibiotic containing a nine membered ring is the macrocyclic peptide Griseoviridin (**10**, **Fig**. **1.5**), isolated from *Streptomyces griseus*. Interestingly a sulfur atom is included in the medium ring subunit. The use of this potent antibiotic in therapy has been approved by the FDA, in combination with other macrolides obtained from the same bacterium, for infections caused by bacteria resistant to vancomycin.[13]

Ten and eleven membered ring lactones (**Fig**. **1.6**) are also very common structures among secondary metabolites isolated from plants (alkaloids of the Crotalanian family **19-21**, known for their high toxicity), fungi (Diplodialide family **13-15**, Cephalosporolide family **11-12** and Tuckolide **16**) and insects (Ferrulactone I (**17**) and Suspensolide (**18**)).[4]

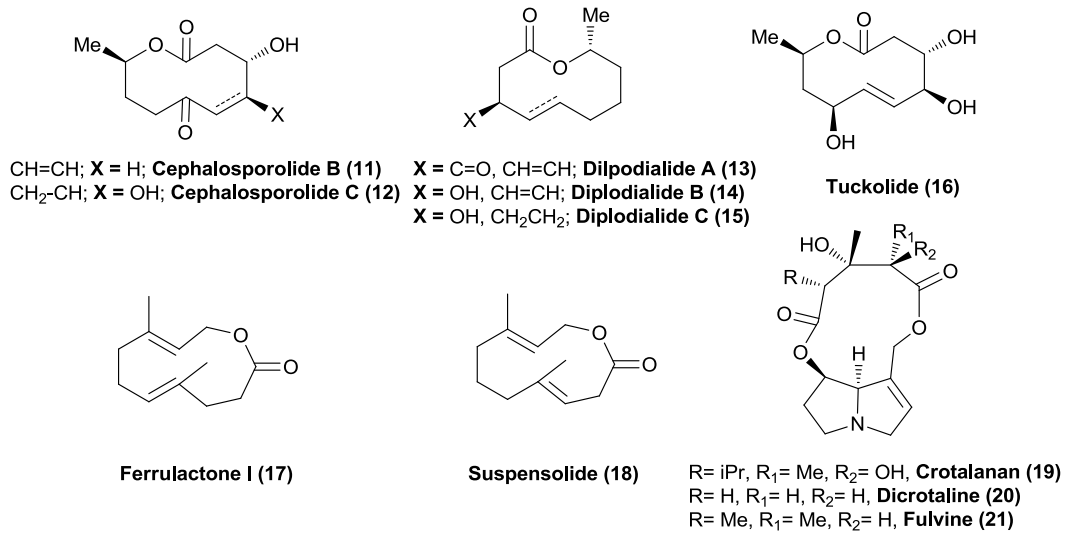


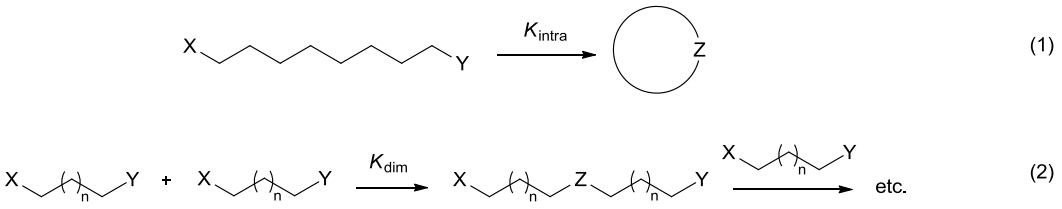
Fig. 1.6

For the aforementioned interesting biological and pharmacological properties, medium rings represent very interesting structures, especially in the light of the continuous endeavour for new classes of antibiotics and anti-cancer agents that exhibit new modes of action. From an organic chemistry perspective, the synthesis of these systems using conventional cyclisation methods has been a long standing problem because of the difficulty stemming from the high degree of ring strain involved (see **Section 1.2**). Although with a few exceptions, all the existing strategies for the synthesis of medium rings seem to be tailored to specific substrates,

therefore lacking of general applicability. The scope of the present thesis is to explore a novel approach that, if successful, could represent a more general strategy for the construction of medium rings.

1.2 Kinetic and Thermodynamic analysis of MR synthesis

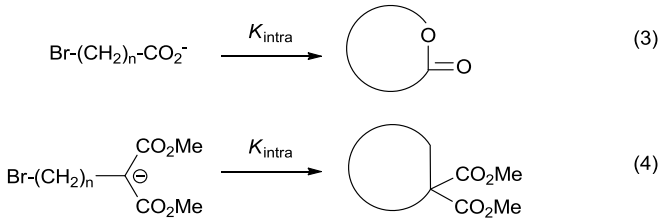
It was clear from the initial attempts by Ruzicka[14] and Ziegler[15] that the synthesis of medium rings through conventional methods that entail a "head to tail" reaction between two functional groups of an open chain precursor (**eq. 1**, **Scheme 1.1**) suffer from competing polymerisation reactions (**eq. 2**).[16]



Scheme 1.1

If the intramolecular reaction is unimolecular, and therefore first order in the reagent concentration, and the polymerisation reaction is bimolecular, at least in its initial stage, and therefore second order, high substrate concentrations should favour the latter over the former. From these kinetic observations Ruggli[17] derived the principle that cyclisation can only occur without competition from the polymerisation reaction only at very low concentration. Ziegler successfully applied this high dilution method to the synthesis of a series of medium and larger rings.[15] The synthesis of medium rings proved, however, to be extremely difficult and very low yielding even at high dilution conditions for some substrates.

In a series of experiments Mandolini *et al.* [16, 18] calculated the rate of intramolecular cyclisation as a function of the ring size for a series lactones (derived from the cyclisation of ω-bromoalkylcarboxylates, **eq. 3**, **Scheme 1.2**) and for a series of cycloalkanes (from ω-bromoalkylmalonates, **eq. 4**).



Scheme 1.2

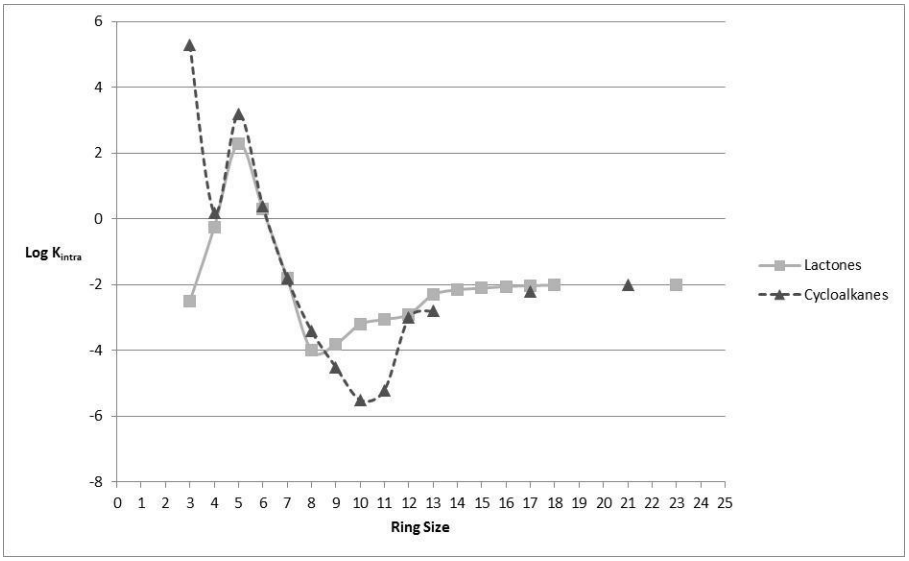


Fig. 1.7

As shown in the graph in **Fig**. **1.7**, in both cases the rate of cyclisation for rings containing from 8-12 atoms reaches a minimum. It is at this stage the rate constant for the *inter*molecular reaction becomes larger and dimerisation (and polymerisation) starts to occur.

It has been proposed that cyclisation rates depend on both the open chain initial state (entropic factor) and on the activation energy of the transition state, which reflects the structure of the cyclic product (enthalpic factor).[18] On one hand, the reactivity in the cyclisation reactions can therefore be interpreted as probability of the two chain *termini* coming to close proximity to react. The probability decreases with the increase in the number of atoms in the chain as the number of possible conformations is increased. On the other hand, experimental data showed that the strain energy of cycloalkanes is markedly dependent on the ring size,[19] and this is thought to correlate to the activation energy of the transition state. In the case of MR (8-12 atoms) the enthalpic factor outweighs the entropic factor, whereas for larger

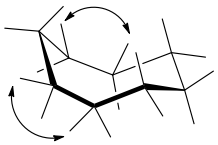
rings (>12 atoms) the entropic factors predominate as large macrocycles are virtually strain free.

The origin of the ring strain is generally a result of 3 types of forces:

1) *Baeyer* strain (due to deformation of the ring bond angles)
2) *Pitzer* strain (due to imperfect staggered conformations between adjacent atoms in the ring)
3) *transannular* strain (due to interactions between atoms across the ring).

Whereas Baeyer strains are predominant in smaller rings, Pitzer and transannular strains were found to be especially severe in medium rings when compared to both smaller and larger rings, as experimentally measured by Dunitz[20] and calculated by Allinger[21] on cycloalkanes.

The origins of these strains can be observed in cyclooctane: the conformational properties of this substrate have been extensively studied[22] and it was shown that, depending on the substitution pattern, the most stable conformation at RT is usually the ***boat-chair*** (BC) conformation shown in **Fig. 1.8**, which minimises the transannular interactions at the expense of having the unfavourable eclipsed conformation between some of the atoms in the ring.



Boat-Chair (BC)

Fig. 1.8

The presence of heteroatoms in the ring can also affect their stability and therefore their reactivity in the cyclisation reactions. For example, in medium ring lactones the ring strain decreases slightly when compared to cycloalkanes (Graph **Fig. 1.7**). This is due to the fact that lactones can exist in two forms, a *Z* (or *syn*) form usually between 2-8 kcal/mol more stable than the *E* (or *anti*) form, **Fig. 1.9**.[23]

Z (*syn*) ***E*** (*anti*)

Fig. 1.9

In 8 and 9-membered ring lactones an equilibrium exists between the two conformations, whereas for larger rings only the more stable *syn* conformation is observed.[23]

Another important factor affecting the ease of formation of medium rings is the presence of substituents on methylene units in the open chain. The presence of *gem*-dimethyl substituents is known to increase the rate of cyclisation of an open chain precursor (Thorpe-Ingold effect, **Fig**. **1.10a**). This effect is believed to be caused by the reduction of the value of the angle between the substituents (α, **Fig**. **1.10a**) caused by the presence of alkyl substituents (R= Me).[24]

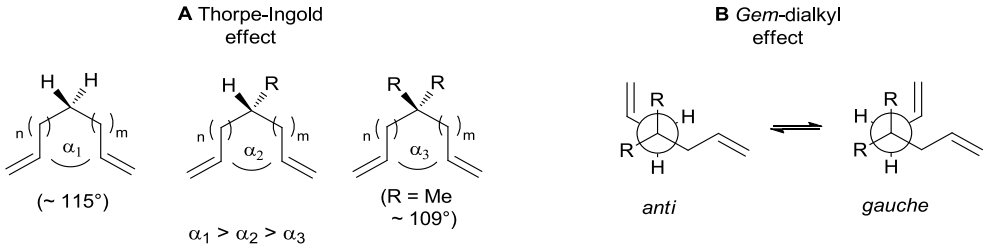
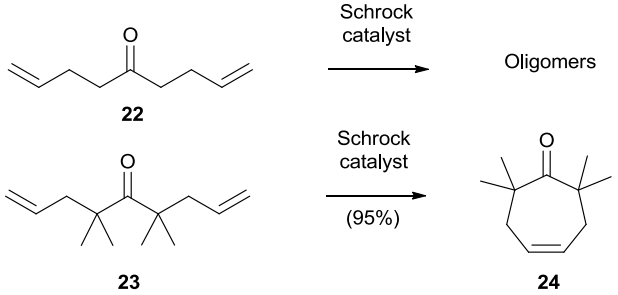


Fig. 1.10

Bruice and Pandit also showed that *gem*-disubstitution increases the probability of the rotamers to adopt the gauche conformation.[25] For unsubstituted precursor (R=H, **Fig 1.10b**) the reactive termini are predominantly in the *anti*-conformation in order to minimise the steric repulsions. Geminal disubstitution causes the *anti* and *gauche* conformations to have approximately the same energy and therefore the reactive *termini* of the open chain precursor are more likely to be closer and the rate of the ring-closing reaction is therefore increased.

This effect is exemplified by the ring closure of bis-olefin precursor **22** in **Scheme 1.3**; when no substituents are present only oligomerisation occurs. In the presence of two *gem*-dimethyl substituents instead (**23**) the *intra*molecular reaction becomes predominant and ring closed product **24** is therefore obtained.[26]



Scheme 1.3

1.3 Synthesis of Medium Rings

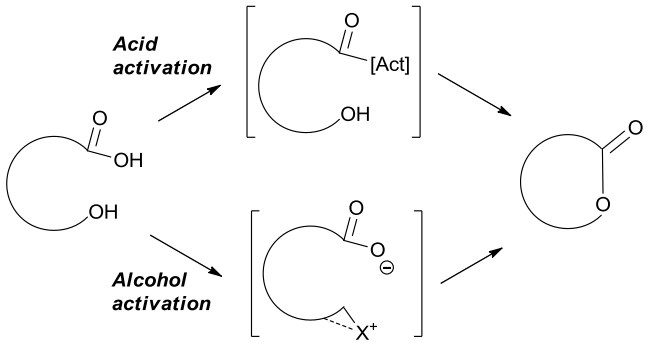
As a result of the unique structural features of medium rings, conventional synthetic methods which are effective for the synthesis of smaller or larger rings often fail when applied to MR. For this reason a plethora of diverse strategies has been reported in the literature in the past years and a brief summary of the existing methodologies will be given in this chapter.

1.3.1 Direct Cyclisation from an Open Chain Precursor

Despite the unfavourable kinetic and thermodynamic factors discussed in the previous chapter, the formation of medium sized rings via intramolecular ring closure is probably the methodology which has been mostly exploited, especially towards the synthesis of medium ring natural products.[23, 27-29] Of these synthetic targets the largest part is represented by lactones, as they are often found in natural products exhibiting therapeutic activity, therefore most of the methodologies described in the literature involve the formation of the C-O ester bond.

1.3.1.1 Macrolactonisation

The formation of medium (and large) ring lactones (macrolactones) is usually achieved via activation of either the carboxylic acid or the alcohol (**Scheme 1.4**).[28]



Scheme 1.4

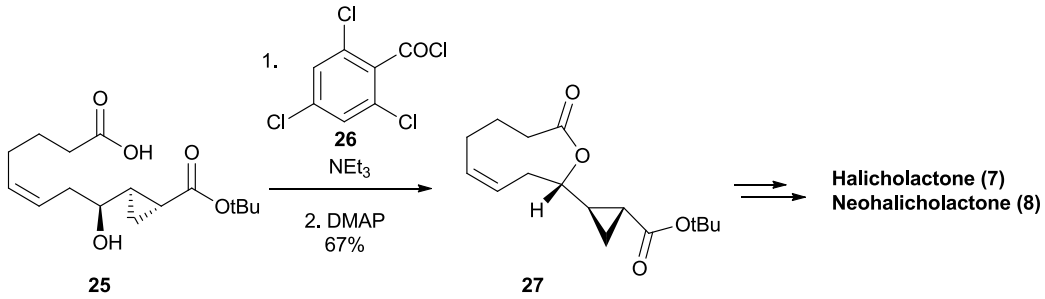
The activation of either one or another chain terminus with highly reactive functional groups is necessary in order to avoid the competing *inter*molecular reaction described in the previous chapter.

1.3.1.2 Acid activation

A series of different strategies are described for the activation of the carboxylic acid:

Yamaguchi strategy

The activation of a carboxylic acid to form mixed anhydrides with 2,4,6-trichlorobenzoyl chloride (**26**), firstly described by Yamaguchi,[30] is probably one of the most popular strategies used for the formation of medium and large ring lactones. This approach was successfully used by Critcher in the first total synthesis of the marine natural products halicholactone and neohalicholactone (**Scheme 1.5**).[31]



Scheme 1.5

Although the cyclisation of non-substituted 9-membered ring lactones is notoriously difficult and low yielding for this type of approach, in this case a smooth lactonisation was attained. A plausible explanation for this observation is the effect of the *cis* double bond of **25** which could provide the necessary enthalpic and entropic assistance to the cyclisation process, as opposed to the cyclisation of a saturated ring.[27] The authors also observed the formation of a dimeric species during the lactonisation which was subsequently minimised by the use of high dilutions and slow addition conditions.

The Yamaguchi strategy has also been successfully used for the synthesis of 8-membered rings (Datta's synthesis of Solandelactones[32] **28**, **Fig. 1.11**), and 10-membered rings (Kobayashi's synthesis of Decarestrictine D[33] **29** and Pilli's synthesis of Herbarumin I[34] **30**).

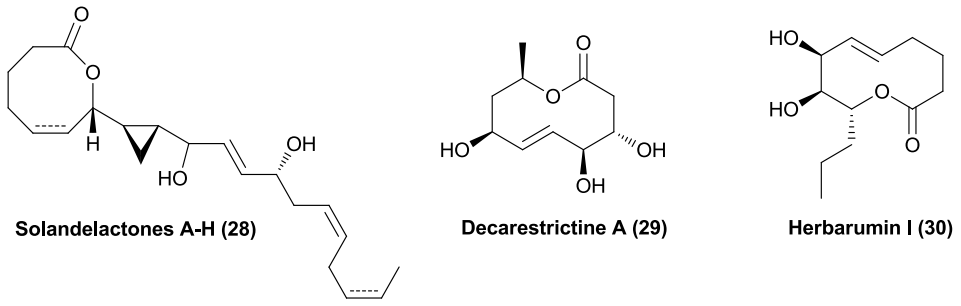
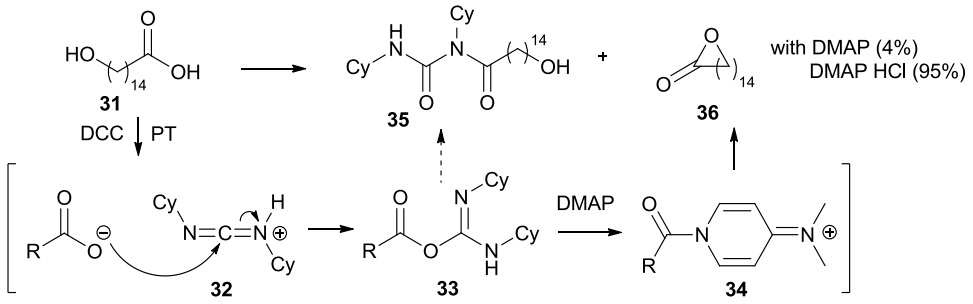


Fig. 1.11

Shiina also described the use of the more efficient 2-methyl-6-nitrobenzoic anhydride (MNBA) in the synthesis of the 8-membered ring of Octalactin A and B (**1** and **2**, **Fig. 1.1**).[35, 36]

Steglich strategy

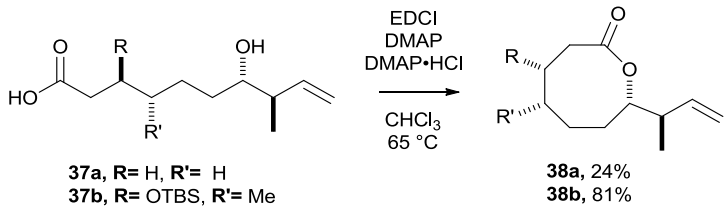
The use of dicyclohexyl carbodiimide (DCC) together with 4-*N*,*N*-dimethylamino pyridine (DMAP) was initially introduced by Steglich as a simple and high yielding procedure for esterification.[37] A common disadvantage associated with this procedure when applied to the synthesis of medium rings and macrolactones is the formation of the unreactive N-acyl urea by-product (**35**, **Scheme 1.6**).[38]



Scheme 1.6

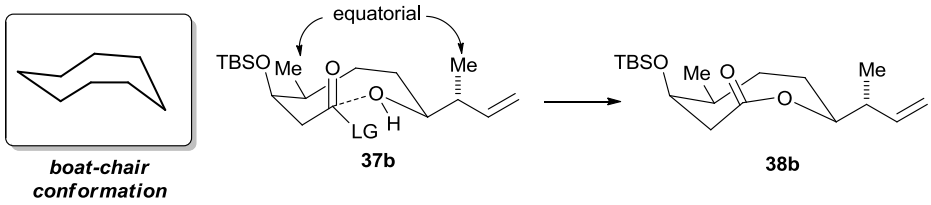
As shown in **Scheme 1.6** for the synthesis of hexadecanolide **36**, the formation of the N-acyl urea by-product **35** can be limited by the addition of small amounts of acid (i.e. TsOH or DMAP·HCl). The rationale behind this observation is that the concentration of proton sources (both alcohol and acid) for the proton transfer step is very low, therefore an external source of H^+ preserves the active ester species (*O*-acyl-uronium **33**) in solution, thus preventing it from undergoing rearrangement to give acylurea **35**.

The tedious removal of the urea by-product can be minimised by using the water soluble EDCI. This protocol has been used with different degrees of success in the synthesis of macrolactones and MR; in the following example by Andrus[39] (**Scheme 1.7**), Octalactin was obtained via ring closure of seco-acid **37b**. Interestingly, cyclisation of simple 7-hydroxyheptanoic acid via macrolactonisation had been found to be impossible or to afford very low yields under different conditions;[23, 40] in the case of Octalactin, non-substituted precursor **37a** (R=R'=H) afforded 8-membered ring lactone **38a** in very poor yield whereas substituted precursor **37b** gave 8-membered ring **38b** in excellent yield under the same reaction conditions.



Scheme 1.7

The author attributed the favourable cyclisation conditions to the presence of the two substituents that reside in a pseudo-equatorial position in the transition state, forcing the incipient ring to adopt a boat-chair conformation (**Scheme 1.8**). This has been shown to be the conformation with the lowest energy for a few 8 membered ring systems as it minimises transannular interactions and has a lower torsional strain.[22, 41]

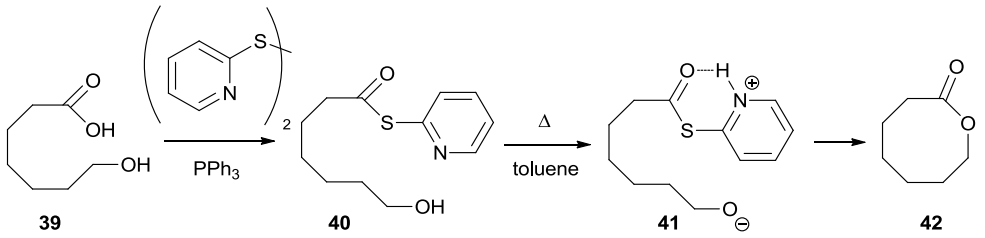


Scheme 1.8

Corey-Nicolau strategy

Corey and Nicolau first described the macrolactonisation reaction of a seco-acid via activation of the carboxylic acid as a S-Pyridyl ester.[42] The carboxy terminus is

converted to the corresponding 2-pyridyl thioester via the Mukaiyama protocol (PyS-SPy, PPh_3)[43] (**40**, **Scheme 1.9**); once formed, the substrate undergoes internal proton transfer [44, 45] to give intermediate **41** in which both chain termini are activated for ring closure ("double activation").



Scheme 1.9

Once again the reaction requires high dilution conditions in order to avoid formation of dimers, and also the removal of the by-products can be tedious. In order to avoid this disadvantage, many variants of this reaction have been developed in which the S-pyridyl moiety is substituted for more water soluble *S*-linked heterocycles which can be easily removed upon aqueous workup.[28]

A substantial increase in the rate of the cyclisation reaction has been reported with the use of stoichiometric amounts of metal salts (Ag, Hg, Cu).[28] In particular, Garlach found that some silver salts (AgOTf, $AgBF_4$, $AgClO_4$) were very effective, usually allowing the formation of macrolactones under mild conditions.[46] Three main explanations have been proposed to account for the observed increase in the reactivity. The metal could be chelated either by the basic nitrogen of the pyridine (**A**, **Fig. 1.12**) or by the sulfur (**B**) or also form a 6-membered ring chelation complex (**C**).[28]

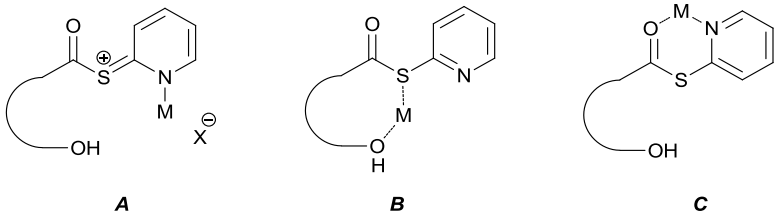
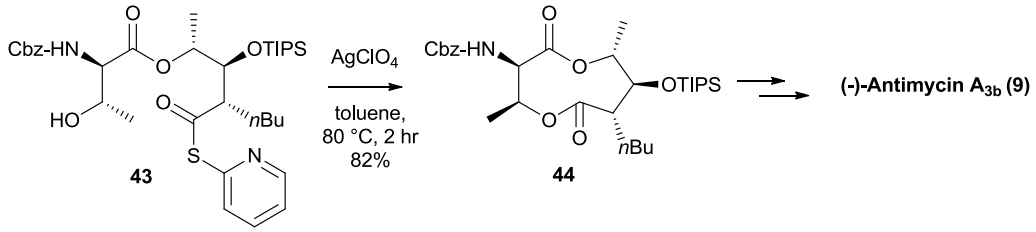


Fig. 1.12

The Garlach protocol has found widespread use in the synthesis of medium ring lactones; an excellent example is Tsunoda's synthesis of (-)-Antimycin A_{3b} (**9**,

Scheme 1.10).[47] Pyridyl thioester precursor **43** was treated with a stoichiometric amount of $AgClO_4$ in order to obtain ring closed intermediate **44** in very good yield.



Scheme 1.10

The same protocol has also been employed by Buszek in the synthesis of Cephalosporolide D[48] (**45**, **Fig. 1.13**) and Octalactin A and B[49] (**1** and **2**, **Fig. 1.1**), by Andrus in the synthesis of Tuckolide[50] (**16**, **Fig. 1.6**) and by Bartra in the synthesis of Phoracantolide I[51] (**46**, **Fig. 1.13**).

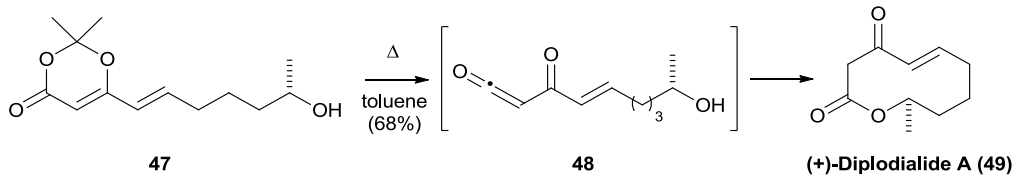
Fig. 1.13

Unfortunately, in many cases a stoichiometric or even large excess of the metal has to be used in order to achieve reasonable yields for the ring closure, rendering this technique unsuitable for large scale preparation. On the other hand this strategy is very useful because of the use of neutral conditions, therefore it can be applied when sensitive functional groups are present.

Boeckman strategy

In 1989, Boeckman described the thermolysis of dioxolenes as a strategy to generate the reactive ketene under neutral conditions. In fact, under relatively mild thermal conditions (refluxing toluene) these substrates rearrange to give the corresponding β-acylketene (**48**, **Scheme 1.11**), which subsequently reacts with the hydroxyl group to form the corresponding lactone. The author used this strategy for the synthesis of the

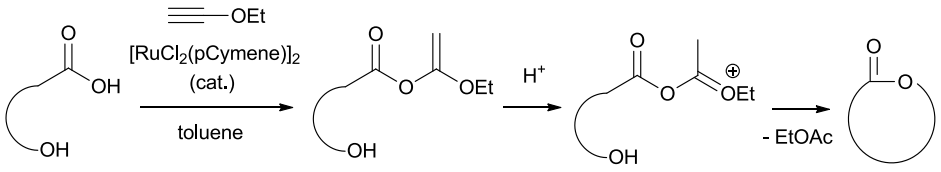
highly strained 10-membered ring (+)-Diplodialide A (**49**) bearing an endocyclic *trans* double bond.[52]



Scheme 1.11

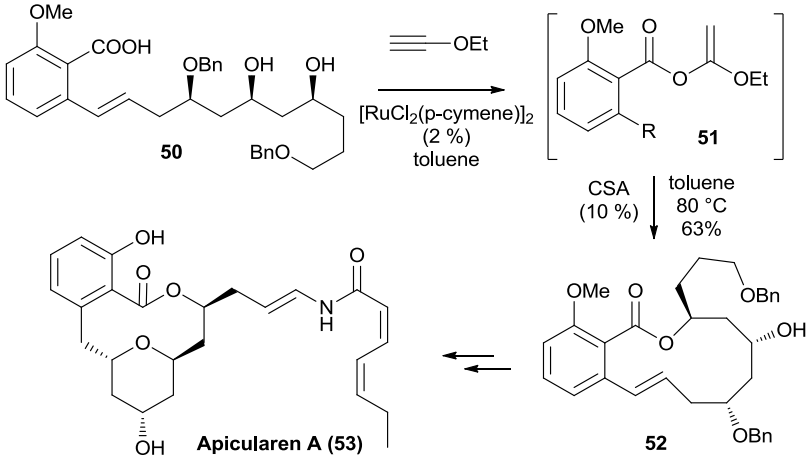
Trost vinylic ether strategy

According to the methodology firstly introduced by Kita[53] and later developed by Trost[54] for macrocyclisation, carboxylic acids can be easily converted to the ethoxyvinyl-esters via Ru catalysed addition to ethoxyacetylene. In the presence of catalytic amounts of acid the ethoxyvinyl ether is then activated towards intramolecular nucleophilic attack of the alcohol (**Scheme 1.12**).



Scheme 1.12

This methodology has been used by Maier[55] to synthesise 12-membered ring lactone **52** (**Scheme 1.13**), precursor of Apicularen A (**53**).



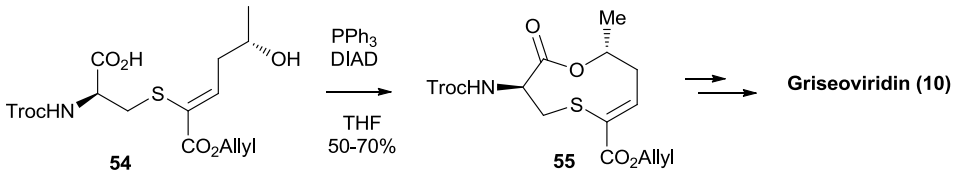
Scheme 1.13

An advantage of ethoxyvinylesters (EVEs) is that they are generally stable and can be purified by column chromatography whereas other activation methods (i.e. Yamaguchi) require anhydrous conditions. This method has recently been extensively reviewed[56] and it proved very useful for the synthesis of non-substituted 9-11 membered ring lactones which are notoriously very difficult to synthesise via other macrolactonisation techniques.

1.3.1.3 Alcohol activation

Mitsunobu strategy

The use of the Mitsunobu reaction has been successfully applied to the synthesis of macrolactones[57] although fewer examples for the synthesis of MR are reported in the literature. An excellent one is the synthesis of the sulfur containing 9-membered ring lactone moiety of the naturally occurring antibiotic Griseoviridin (**10**), initially reported by Meyer[13] (**Scheme 1.14**) and later followed by Ardisson's synthesis of *epi*-Griseoviridin.[58]

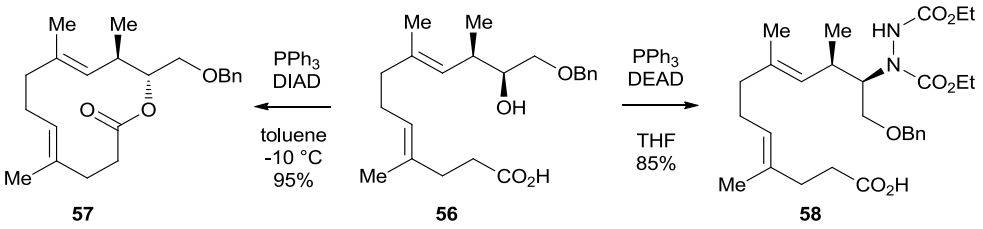


Scheme 1.14

One of the major drawbacks of the reaction is the tedious removal of the stoichiometric phosphine oxide and hydrazine dicarboxylate by-products generated. This problem can be solved by using water soluble phosphines and di-*tert*-butylazodicarboxylate (DTBAD) which gives volatile and water-soluble by-products (namely isoprene, CO_2 and hydrazine) upon a simple acidic workup, as exemplified by Marcantoni's synthesis of the medium ring moiety of Griseoviridine.[59]

Another major drawback of this protocol is the formation of hydrazide by-products (**58**, **Scheme 1.15**) resulting from the S_N2 displacement of the oxyphosphonium intermediate by the hydrazine anion. This problem was encountered by Evans in the synthesis of the 12-membered ring lactone of Lonomycin A (**Scheme 1.15**).[60] The use of more sterically encumbered azadicarboxylates (DIAD, DTBAD) together with

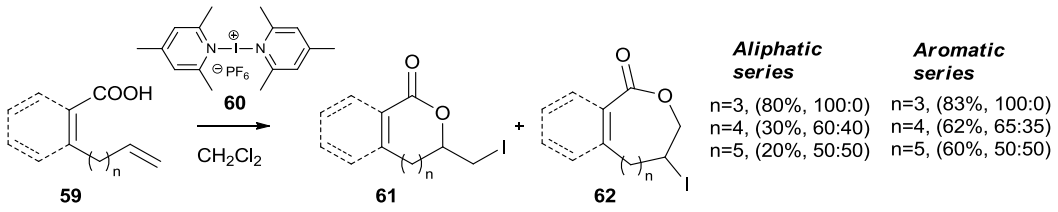
less polar solvents (i.e. benzene or toluene) usually prevents the formation of such by-products.



Scheme 1.15

Electrophilic cyclisation

Amongst other methods for macrolactonisation, electrophilic iodocyclisation has been explored by Rousseau in the synthesis of various-membered ring lactones.[61] By using bis(collidine)-iodine(I)-hexafluorophosphate (**60**, **Scheme 1.16**) as the source of electrophilic iodine, cyclisation was obtained in most of the cases in very good yields under very mild reaction conditions (RT in CH_2Cl_2).



Scheme 1.16

Interestingly, excellent yields and complete selectivities were observed for the formation of the 8-membered ring lactones (**61**, n = 3), whereas for larger rings the selectivity dropped, affording mixtures of the *exo* and *endo* products. The authors also reported that no reaction was observed when the α,β-unsaturation was not present thus indicating that some kind of conformational constraint induced by the *cis* double bond is necessary for the ring closure to occur.

1.3.2 C-C bond forming reaction

Ring Closing Metathesis (RCM)

One of the most versatile reactions employed for the synthesis of medium rings and macrocycles is Ring Closing Metathesis (RCM). This reaction has been successfully applied to the synthesis of many natural products (**Fig**. **1.14**) and it has been extensively reviewed in the literature.[29, 62-65]

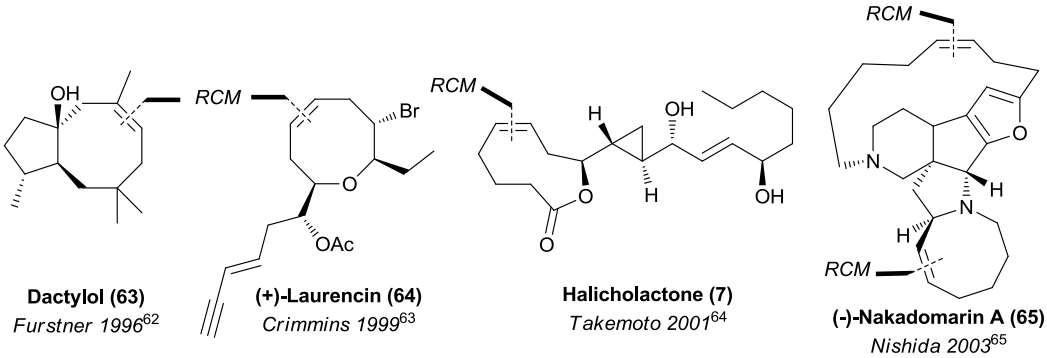


Fig. 1.14 Natural products obtained via ring closing metathesis (RCM)[62-65]

Although its origins can be traced back to the early 1970s with Chauvin's seminal work on metal carbenes,[66] it was not until the beginning of 1990s that the reaction became fully understood and surged as a powerful synthetic tool after the development of Grubbs' (**A**, **B** and **C**, **Fig 1.15**) and Schrock's (**D**) catalysts.

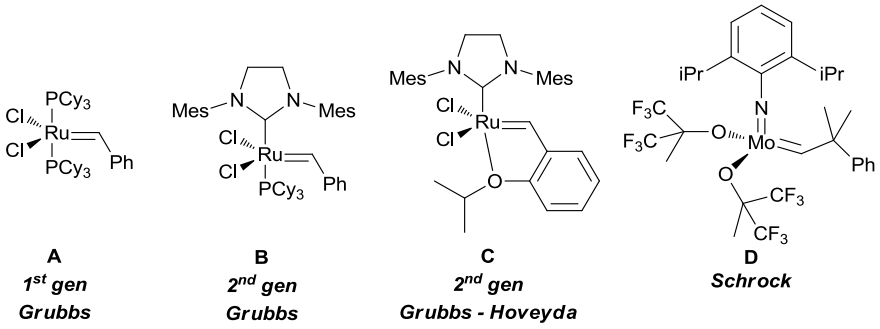
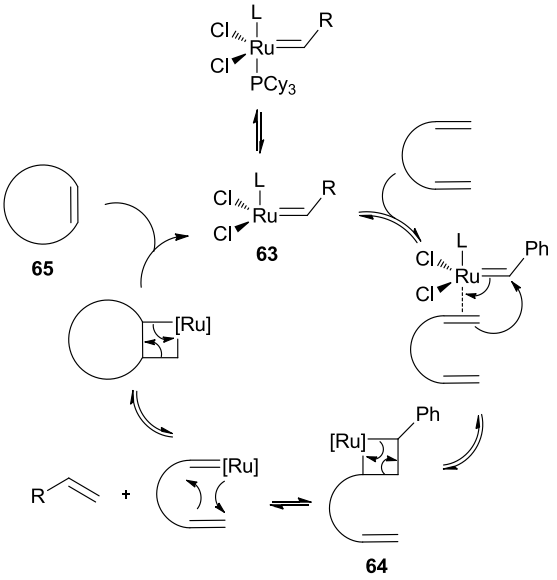


Fig 1.15 Catalysts for olefin metathesis

This reaction has many advantages over other cyclisation techniques: in the first place it is very versatile because of its high functional group tolerance.[67] In the second place the reaction usually works under neutral and mild conditions affording a double bond as a product, which can be further modified into other groups. The

mechanism for the RCM is well established (**Scheme 1.17**) and begins with the dissociation of one of the phosphine ligands to give the reactive 14 e^- complex **63**. This coordinates to the double bond of the open chain precursor and subsequently forms the metalla-cyclobutane **64** which rearranges to eventually give the ring-closed product **65** and regenerating the active catalyst.

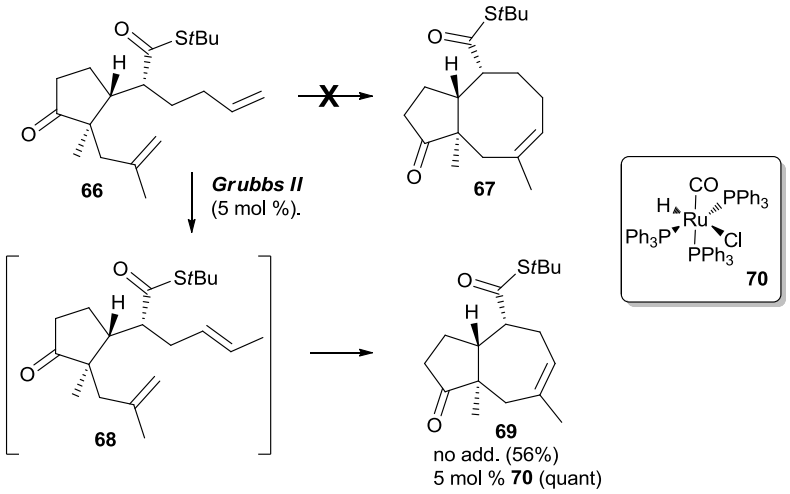


Scheme 1.17

Unfortunately the reaction sometimes requires some fine tuning before finding a suitable catalyst, catalyst loading, solvent and conditions (dilution, time, temperature).[68] Some of the issues reported with the use of this reaction in the synthesis of macrocycles are often the formation of dimers (or polymers)[69] and the migration of the double bond.[70-74]

The dimerization/polymerisation issue is often resolved by increasing the reaction dilution, thus favouring ring closing metathesis (RCM) over acyclic diene metathesis polymerisation (ADMET).[75] On the other hand, the migration of double bonds can be difficult to suppress as it can occur either prior to or during the reaction and also during the isolation procedures. This side reaction is believed to be caused by the presence of ruthenium hydride species generated after decomposition of the active metathesis catalyst.[76] While investigating the use of RCM for the synthesis of [5-8-5] tricyclic systems, Wicha reported the formation of the 7-membered ring **69** after treating precursor **66** with Grubbs II catalyst (**Scheme 1.18**).[77] The author attributes

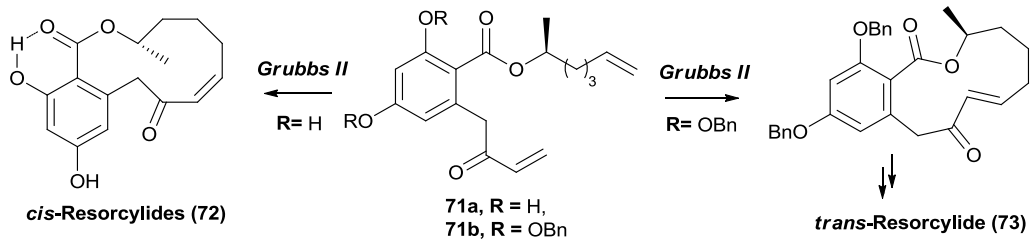
the formation of this product to the steric congestion around the double bound which caused isomerisation to occur followed by RCM and elimination of propene.



Scheme 1.18

This explanation was further supported by the fact that addition of 5 mol % of Ru-H catalyst **70** resulted in almost quantitative conversion.

Another problem of RCM is the difficulty of controlling the double bond geometry when this is part of the natural product structure. In some cases the presence of other substituents can directly influence the outcome of the reaction, as exemplified by Couladouros' synthesis of *cis* and *trans*-Resorcylide (**72** and **73**, **Scheme 1.19**).[69] The presence or lack of hydrogen bonding selectively afforded the *cis* or the *trans* isomer.



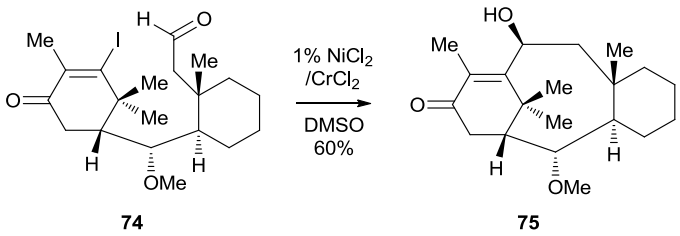
Scheme 1.19

Remote substituents across the developing ring might also have an effect on the selectivity of the reaction; clear examples of these effects have been shown by Schnier[78] and Danishefsky[79] in the syntheses of Epothilones A and B.

Despite the reaction versatility, basic nitrogen atoms are normally not tolerated by this reaction therefore the construction of medium ring alkaloids or macrolactams is often prevented or limited by the chelation of the metal catalyst by the substrate.[80] However, protection of the nitrogen with suitable electron-withdrawing groups (i.e. N-Ts or N-Boc) usually allows the reaction to proceed satisfactorily.[81]

Nozaki-Hiyama-Kishi reaction

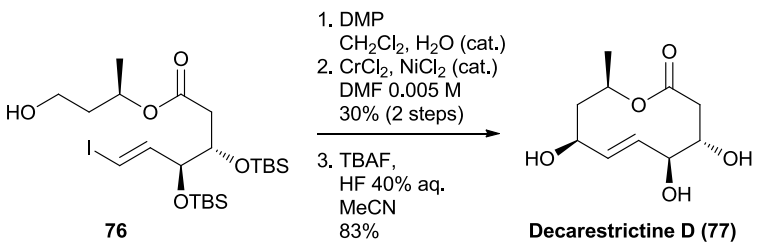
Amongst the many different metal mediated C-C coupling reactions, the Nozaki-Hiyama-Kishi (NHK) reaction has proved to be very effective in the formation of a few classes of MR. The nickel/chromium catalysed synthesis of the tricyclic taxane skeleton was described by Kishi himself (**Scheme 1.20**).[82] The reaction afforded the coupling between the vinyl iodide and the pendant aldehyde of precursor **74** to give the 8-membered ring core of **75** in good yield with excellent diastereoselectivity.



74 **75**

Scheme 1.20

Pilli *et al.* successfully used this synthetic strategy for the formation of a whole class of 10-membered ring lactones (decanolides) of the family of decarestrictines.[83] Decarestrictine D (**77**, **Scheme 1.21**), an important member of this family because of its therapeutic ability to inhibit cholesterol biosynthesis, was synthesised in very good yield and excellent diastereoselectivity (97:3).



76 **Decarestrictine D (77)**

Scheme 1.21

Interestingly the authors observed that the selectivity was controlled by the presence of different groups on the ring; substitution of the bulky OTBS groups with an isopropylidene acetal group caused total loss of stereocontrol. The same authors also reported the syntheses of 10-membered ring (-)-Aspinolide B (**78**),[84] a member of the decanolides family, using the NHK protocol (**Fig. 1.16**).

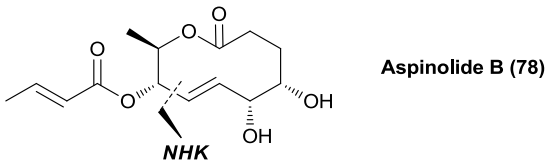
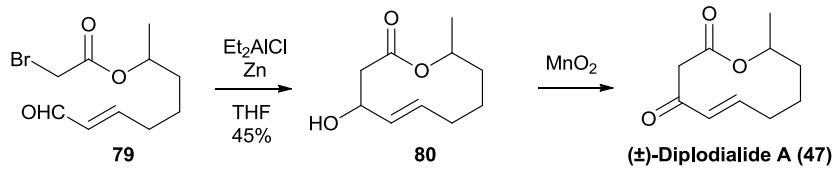


Fig. 1.16

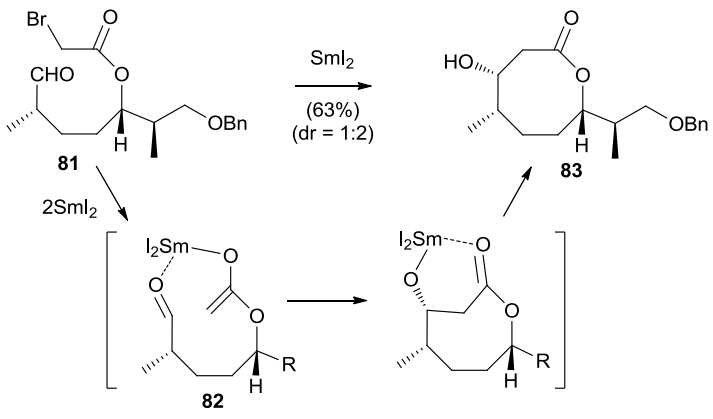
Reformatsky/Barbier type reactions

In 1978 Tsuji described the formation of the ten membered ring of Diplodialide A (**47**) via a modified intramolecular Reformatsky reaction (**Scheme 1.22**).[85]



Scheme 1.22

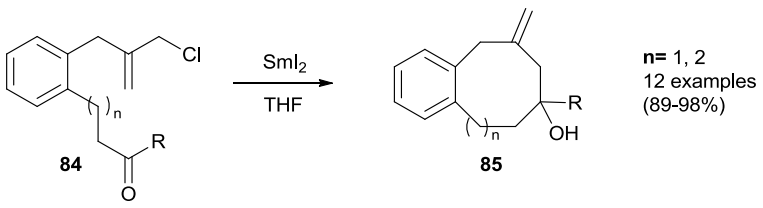
The cyclisation of **79** proceeded smoothly at 55 °C although under fairly high dilution conditions (0.025 M) to afford the 10-membered ring lactone **80** as a mixture of diastereoisomers in 45% yield. A similar approach was also used by Hatakeyama in the synthesis of the lactone moiety of Octalactins[86] (**Scheme 1.23**) using a Reformatsky-type reaction promoted by SmI_2 originally described by Inanaga[87] for a series of medium and large sized ring lactones.



Scheme 1.23

Unfortunately the reaction produced an epimeric mixture of hydroxy-lactones (**83**) in a 1:2 ratio in favour of the unwanted isomer. The undesired isomer could however be quantitatively converted into the desired one after a sequential oxidation/reduction sequence. Despite the unfavourable stereocontrol, the yields reported for this type of process are generally very good and they don't require high dilution conditions. According to the initial explanation proposed by the authors, the remarkable preference for this reaction to react intramolecularly could be ascribed to its radical mechanism[88], in which both carbon atoms to be coupled are activated at the same time by the reaction with an excess SmI_2. In a later publication the same authors propose a reaction mechanism like the one drawn in **Scheme 1.23** in which the samarium-enolate **82** is able to chelate the oxygen of the pendant aldehyde and trigger the cyclisation.[89]

More recently Matsuda reported a very efficient synthesis of 8 and 9-membered ring carbocycles using an intramolecular Barbier-type SmI_2 mediated coupling of aldehydes with allyl chlorides **84** (**Scheme 1.24**).[90]

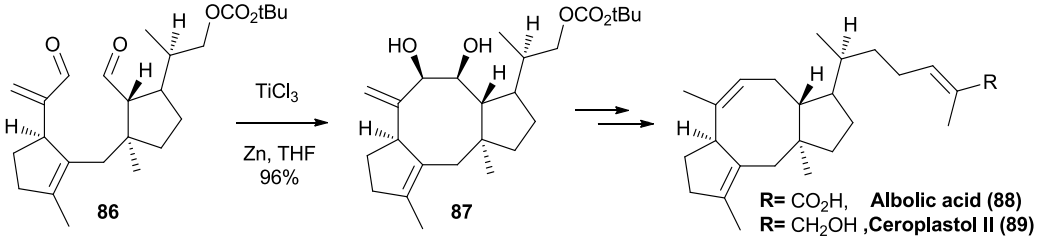


Scheme 1.24

Almost quantitative yields were reported for this reaction without the need to resort to high dilution conditions, as previously observed for the SmI_2 mediated C-C bond formation.

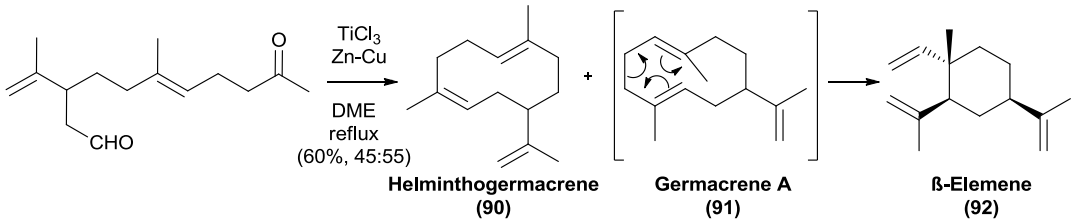
McMurry coupling

The Ti(III) induced radical coupling between two carbonyl groups of **86** was successfully used in the synthesis of medium rings natural products, as shown by Takeshita's synthesis of the 8-membered ring central core of Albolic acid and Ceroplastol II (**87**, **Scheme 1.25**).[91]



Scheme 1.25

The same strategy was also used by McMurry for the synthesis of the strained 10-membered carbocyclic ring of (±)-Helminthogermacrene (**90**) containing two trisubstituted endocyclic double bonds (**Scheme 26**).[92]



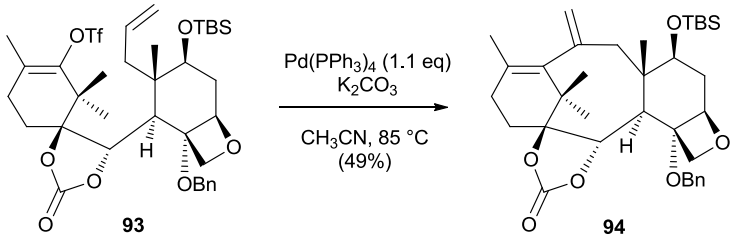
Scheme 1.26

Precedents in the literature have shown that *E*/*Z* selectivity for the newly formed double bond was negligible. In fact the authors isolated a 45:55 mixture of thermally stable medium ring product **90** (*Z*-isomer) and tetrasubstituted cyclohexane β-elemene (**92**), resulting from the Cope rearrangement of side-product Germacrene A (**91**) (*E*-isomer) that takes place at RT.

Pd mediated coupling reactions

The use of Pd catalysed reactions in the synthesis of MR natural products is well documented in the literature.[67] Danishefsky's synthesis of the 8-membered ring, tricyclic core of Taxol was accomplished via an intramolecular Pd catalysed Heck

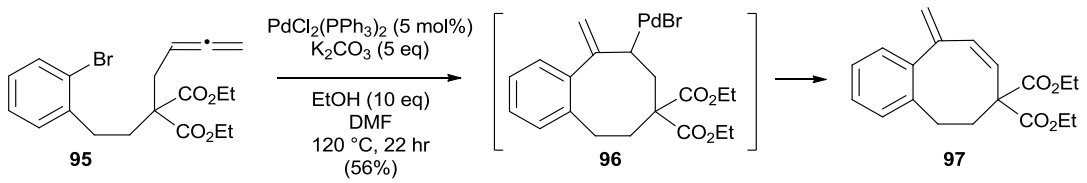
coupling between the vinyl-triflate and the allylic group of intermediate **93** (**Scheme 1.27**).[93]



Scheme 1.27

The yield of the reaction was only moderate, despite the high catalyst loading, due to the strained bridgehead olefin and the steric hindrance caused by the *gem*-dimethyl group. The Heck reaction has also been used for the synthesis of 8-membered heterocyclic rings with different degrees of success.[94]

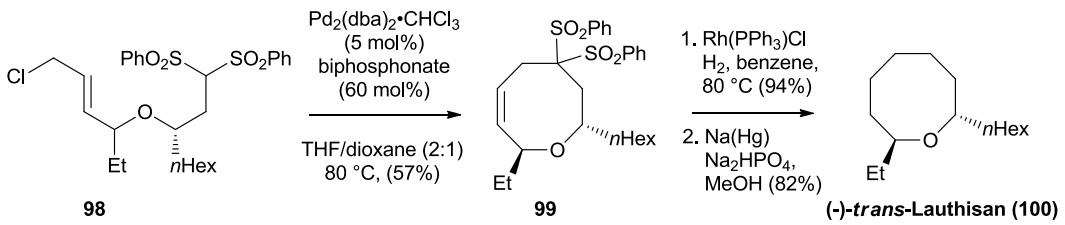
In 1994 Negishi described the first example of intramolecular carbopalladation of allenes for the synthesis of 8-membered rings.[95] In the example shown in **Scheme 1.28**, the formation of the 8-membered carbocyclic ring **97** (*endo*) takes place exclusively over the 7-membered ring (*exo*).



Scheme 1.28

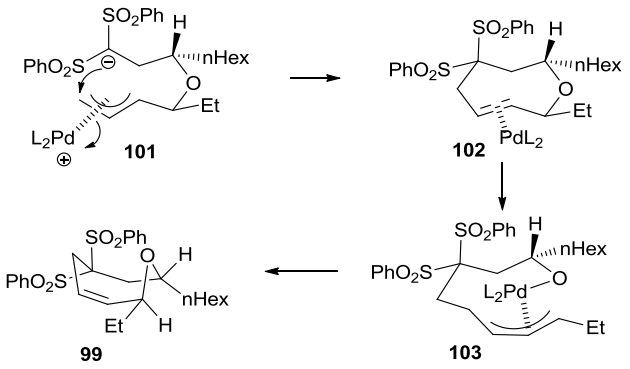
The reason for the observed regioselectivity in the carbopalladation was attributed to the formation of allylpalladium species **96**, resulting from the *endo* cyclisation, also observed as intermediates in the intermolecular carbopalladation of allenes.

In 1995 Hoffmann described a successful intramolecular Pd(0) catalysed allylic alkylation and simultaneous epimerisation at the ethyl substituted allylic centre of disulfone **98** for the stereoselective construction of (-)-*trans*-Lauthisan (**100**, **Scheme 1.29**).[96]



Scheme 1.29

The authors were able to find optimal conditions to attain kinetic control of the cyclisation reaction to afford 8-membered ring **99** as the main reaction product, alongside the thermodynamic 6-membered ring product impurity (in a 2.9:1 ratio). At the same time the reaction afforded only the less stable *trans* diastereoisomer selectively; a plausible explanation given by the author is shown in **Scheme 1.30**.



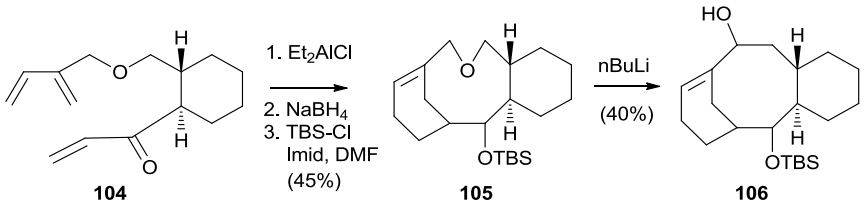
Scheme 1.30

After initial ring closure, intermediate **102** undergoes a stereoelectronically favourable carbon-oxygen bond heterolysis to afford η^3 complex **103**. In the final ring closure the Pd atom migrates such as to minimise non-bonded repulsions to give *trans*-lauthisan precursor **99**.

Miscellaneous

An interesting example of a pericyclic reaction applied to the synthesis of MR natural products was reported by Yadav (**Scheme 1.31**).[97] The strategy for the construction of the 8-membered taxane skeleton of **106** was based on an intramolecular Diels-Alder reaction between the ether-linked diene and the α,β-

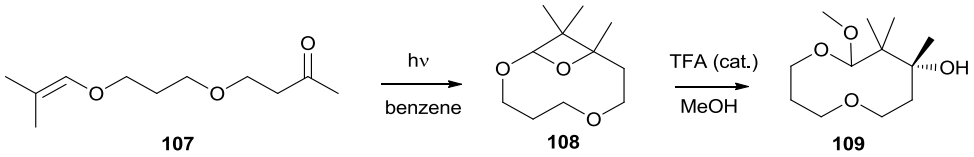
unsaturated ketone of intermediate **104** catalysed by Et_2AlCl, followed by [1,2]-Wittig ring contraction.[98]



Scheme 1.31

The carbocyclic 8-membered ring was obtained only in moderate yields but the route provided a valid alternative for the construction of the complex 6-8-6 tricyclic core of the taxane family.

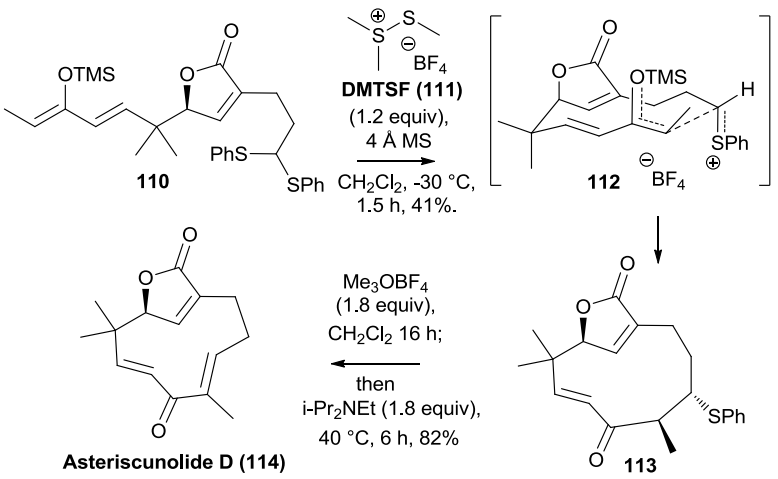
Photochemically induced [2+2] cycloadditions have been reported in the synthesis of medium ring systems. As reported by Carless[99], the Paternò-Buchi reaction between alkenes and carbonyl groups has been used to synthesise the 4-10 bicyclic adduct **108**, containing a highly reactive oxetane-acetal moiety (**Scheme 1.32**).



Scheme 1.32

Treatment of these intermediates with MeOH in the presence of acidic catalysis afforded medium ring diether **109**. The reaction was also successfully repeated for analogues with a different carbon chain spacer between the two ether functionalities to afford 8-11 membered rings.

In a recent publication by Trost[100] the strained 11-membered ring of Asteriscunolide D (**114**), a natural product important for its anticancer properties, was obtained via an unprecedented thionium ion initiated cyclisation (**112**, **Scheme 1.33**).



Scheme 1.33

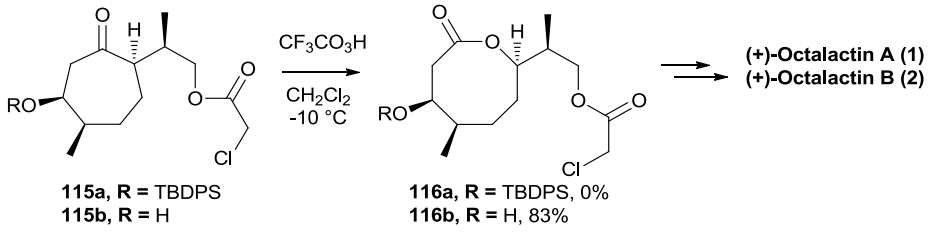
Although cyclisation proceeded in moderate yields, this method proved to be compatible with the labile butenolide functionality and the resulting sulfide substituent of intermediate **113** could be eliminated stereoselectively to afford the *trans* double bond of the natural product. Also this strategy represents a mild and irreversible alternative to an intramolecular aldol reaction, which, in the case of the formation of medium rings, would be affected by retro aldol due to the inherent strain of these systems.

1.3.3 Ring expansion

The use of ring expansion is a well-established procedure for the synthesis of MR.[101] The main advantage of this strategy relies on the more favourable formation of smaller size rings and on the mild conditions often employed to trigger the expansion sequence.

1.3.3.1 Baeyer Villiger oxidation

The B-V reaction has sometimes been successfully employed for the synthesis of medium ring lactones. An example is given by Clardy's synthesis of Octalactin A and B (**1** and **2**, **Scheme 1.34**).[102]



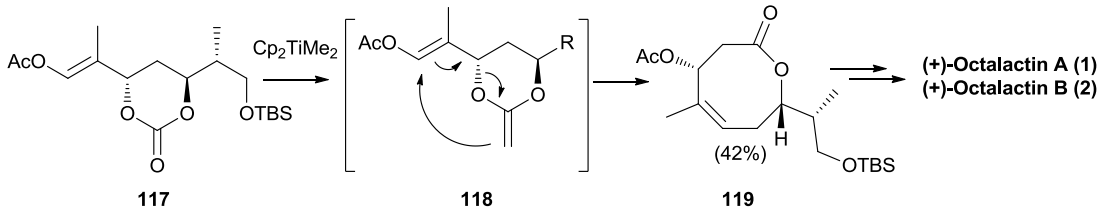
Scheme 1.34

Interestingly when the oxidation was carried out on the protected substrate **115a**, the reaction didn't afford the 8-membered ring lactone **116a** but only decomposition products. When the reaction was performed on the hydroxyketone **115b** instead, lactone **116b** was obtained smoothly in very good yield, although the temperature had to be kept at – 10 °C in order to avoid side reactions.

1.3.3.2 Pericyclic reactions

Sigmatropic Rearrangements

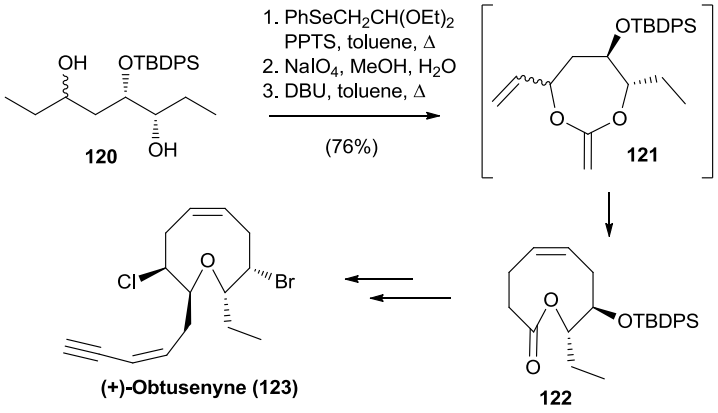
One of the most striking examples of synthesis of medium rings using unconventional methods is perhaps Holmes' strategy of an intramolecular Claisen rearrangement used in the synthesis of Octalactins[103] and Obtusenyne.[104] In the first example in **Scheme 1.35**, after Tebbe methylenation of cyclic carbonate **117**, intermediate **118** spontaneously undergoes the desired [3,3] sigmatropic rearrangement to afford an 8-membered ring lactone **119**, precursor of Octalactin A (**1**) and B (**2**).



Scheme 1.35

The expected 8-membered ring product was obtained in moderate yield and with very good diastereoselectivity (8.2:1 in favour of the desired diastereoisomer). The 9-membered ring moiety of the marine natural product Obtusenyne (**Scheme 1.36**)

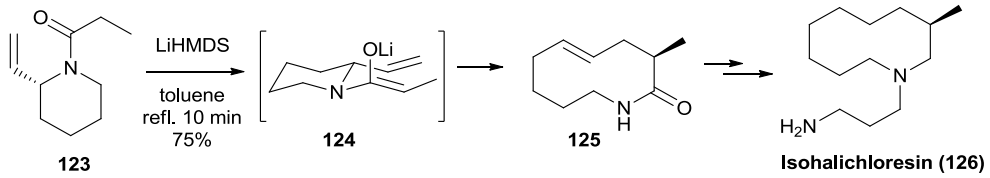
was instead obtained from diol **120** after acetal formation, oxidation of the selenide and elimination, to give intermediate **121**.



Scheme 1.36

This intermediate spontaneously undergoes Claisen rearrangement to afford the expected 9-membered ring **122** in very good yield after 3 consecutive steps.

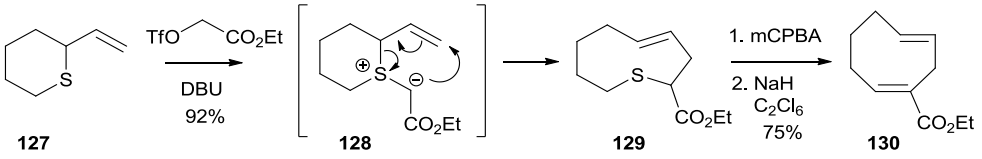
An aza-Claisen type approach was also successfully used by Huang for the synthesis of the 10-membered ring of Isohalichloresin (**126**, **Scheme 1.37**).[105]



Scheme 1.37

Ylide [2,3] sigmatropic rearrangements

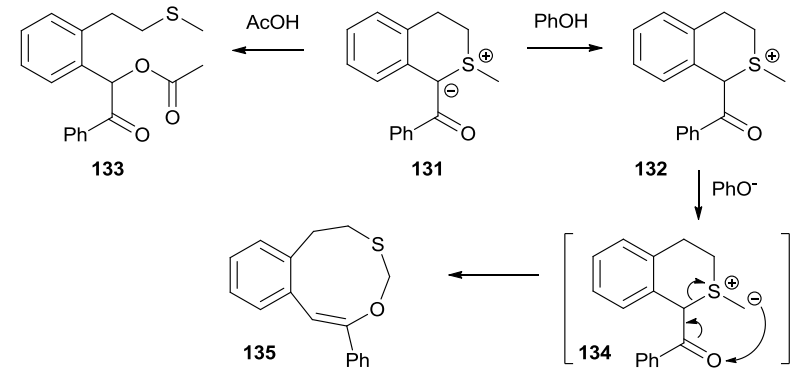
Vedejs first obtained a medium ring by exploiting the [2,3] sigmatropic rearrangement of cyclic allylic sulfonium ylide **128**, generated *in situ* from the corresponding sulfonium salt (**Scheme 1.38**).[106]



Scheme 1.38

Extrusion of the sulfur atom from medium ring **129** could also be accomplished using the Ramberg-Backlund protocol[107] to afford carbocyclic ring **130**.

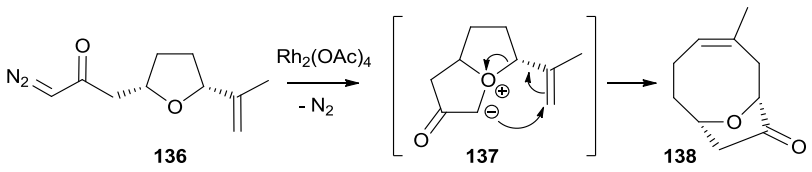
The unusual ring expansion of sulfur ylide **134** via [2,3] rearrangement shown in **Scheme 1.39** was reported by Hori.[108]



Scheme 1.39

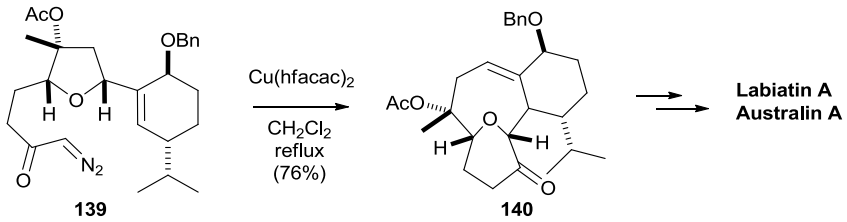
When carbonyl stabilised ylide **131** is treated with acetic acid, only ring opened product **133** is obtained. When the less acidic phenol is used instead the ylide is initially protonated and the resulting phenoxide anion abstracts the proton from the less hindered methyl group. The non-stabilised ylide **134** subsequently undergoes ring expansion via a [2-3]-rearrangement involving the carbonyl group, giving benzoxathionin **135** as the main product.

Medium ring ethers (**138**) can also be obtained from the [2,3] sigmatropic rearrangement of cyclic oxonium yildes (**137**),[109] readily obtained from the Rh catalysed intramolecular reaction between diazocompounds and the ether functionality (**Scheme 1.40**).



Scheme 1.40

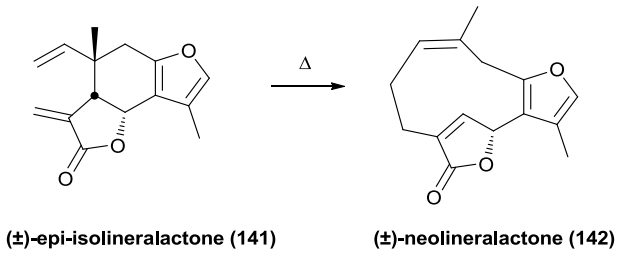
The use of copper catalysts has also been reported for this type of transformations;[110] this procedure has been used by Clark for the synthesis of the polysubstituted 8-membered ring core of the marine diterpene natural products labiatin A and australin A (**140**, **Scheme 1.41**).[111]



Scheme 1.41

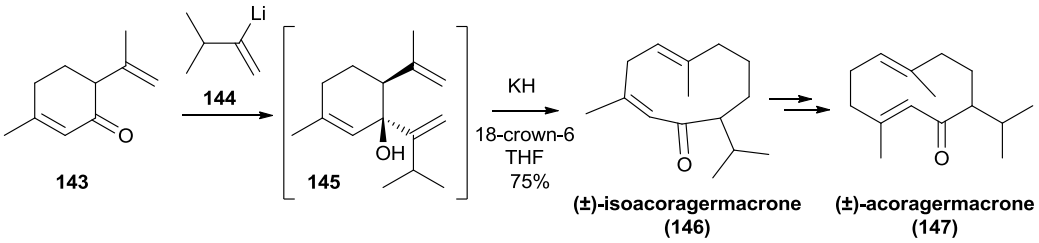
Cope rearrangement

Magnus described the thermal rearrangement of 1,5-dienes (Cope rearrangement) to synthesise some members of the lineralactone family.[112] Diene **141** underwent a facile rearrangement upon heating (160-165 °C, 20-30 min) to give the expected 10-membered ring **142** (**Scheme 1.42**).



Scheme 1.42

Reis' strategy for the synthesis of the 10-membered ring of the Germacrene family relied on an intramolecular oxy-anionic Cope rearrangement of diene **145**, readily obtained after the addition of organolithium reagent **144** to isopiperitenone **143** (**Scheme 1.43**).[113]

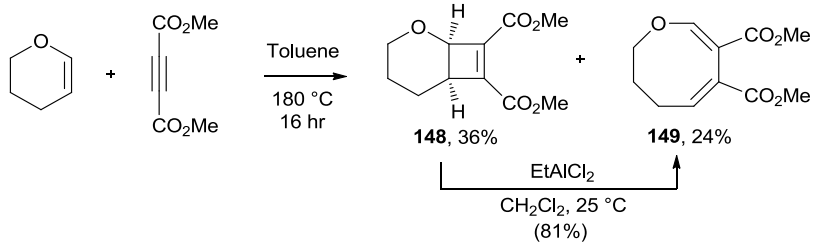


Scheme 1.43

The natural product Acoragermacrone **147** was subsequently obtained via isomerisation of the *Z* double bond of **146**.

Electrocyclic rearrangement

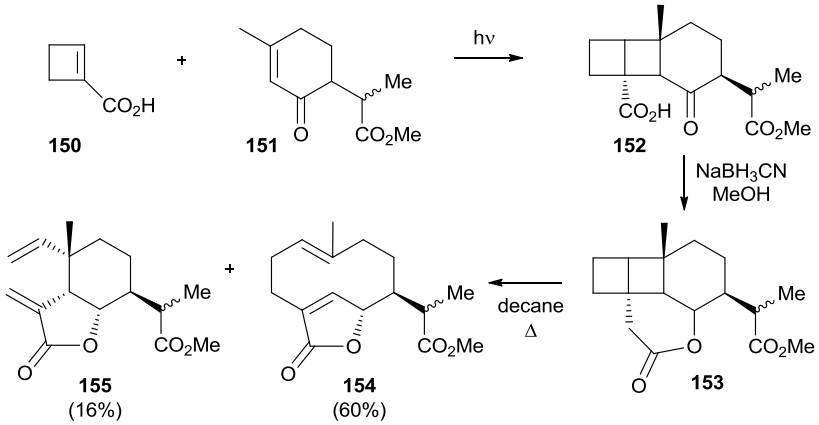
Nicolaou reported the synthesis of substituted 2-oxocins via Lewis acid catalysed rearrangement of the 6-4 fused system **148** (**Scheme 1.44**).[114] Initial [2+2]-thermal cycloaddition of dihydropyran with dimethyl acetylenedicarboxylate afforded a mixture of medium ring **149** and bicyclic intermediate **148**, which could be converted to the final product upon prolonged heating, in 60% overall yield



Scheme 1.44

It was found that $EtAlCl_2$ promoted the ring expansion very efficiently and under mild conditions.

In the same year Lange described the synthesis of the carbon skeletons of different members of the sesquiterpenoid family via an initial [2+2] photocycloaddition followed by thermolysis (**Scheme 1.45**).[115]



Scheme 1.45

Initial irradiation of cyclobutene **150** and cyclohexenone **151** at 350 nm afforded the functionalised tricyclic intermediate **152**. Reduction of the ketone and simultaneous lactonisation afforded intermediate **153** which was subsequently refluxed in decane

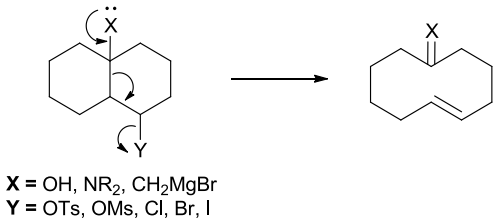
(174 °C) to give the expected product Germacranolide **154** together with a substantial amount of the Cope-rearranged product **155**. Nevertheless the readily prepared photoadduct **152** represents a very versatile intermediate for accessing the sesquiterpenoids skeleton and it was used by the authors to obtain four different members of this class of compounds in good yields.

1.3.4 Fragmentation of bicyclic systems

A very general strategy often adopted for the synthesis of medium rings relies on the formation of fused bicyclic systems and on the subsequent cleavage of the central bond. This has been achieved in many different methods, some of which will be summarised in this paragraph.

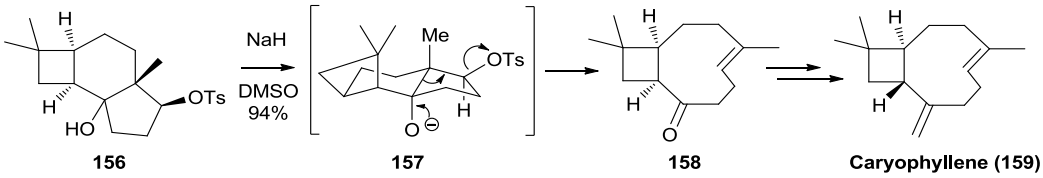
1.3.4.1 Grob Fragmentation

This type of fragmentation involves an elimination step which takes place on a 1,3-disubstituted system like the one shown in **Scheme 1.46**, where one substituent is an *electrofuge* (X) and the other one is a good leaving group (*nucleofuge*, Y).[116]



Scheme 1.46

An excellent example of the Grob fragmentation applied to the synthesis of a medium ring natural products is offered by Corey's synthesis of Caryophyllene **159** (**Scheme 1.47**).[117]

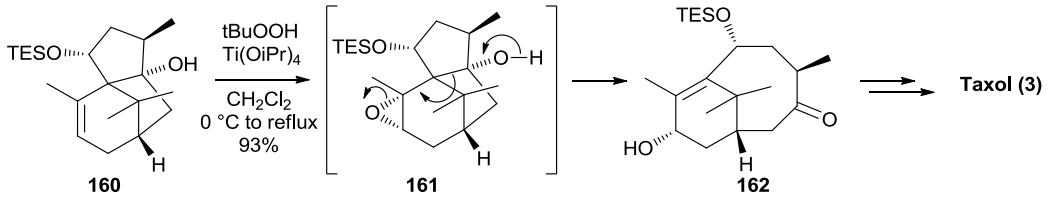


Scheme 1.47

The strained 9 membered ring containing a trisubstituted endocyclic *trans* double bond (**158**) is synthesised from tertiary alcohol **156** after deprotonation with NaH.

The fragmentation process is stereospecific; in fact the C-C bond that is broken has to be *anti*-periplanar to the leaving group (OTs) for the elimination to occur, therefore a *trans* double bond originates which reflects the *anti*-orientation of the substituents (Me and H) in the precursor.

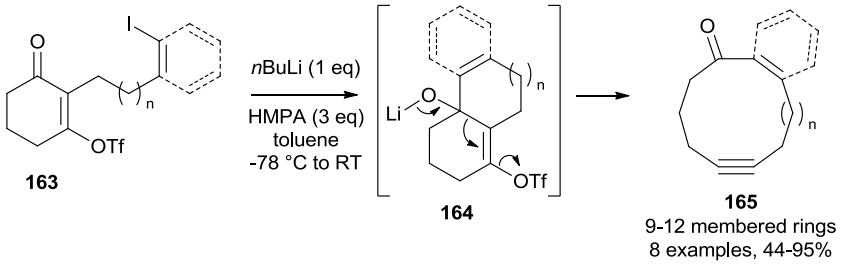
Another excellent example of fragmentation of fused bicyclic rings is offered by Holton's synthesis of Taxol (**Scheme 1.48**).[118]



Scheme 1.48

Oxidation of the double bond of **160** occurred on the least hindered face, affording unstable epoxide **161** which, upon prompt treatment with the Lewis acid $Ti(OiPr)_4$, underwent fragmentation to give the 8-membered ring Taxol core **162** in almost quantitative yields.

In a recent example by Dudley[119] the reductive cyclisation of both aryl and vinyl iodides **163** onto tethered vinylogous acyl triflates (promoted by lithium-halogen exchange) afforded intermediates **164** (**Scheme 1.49**).

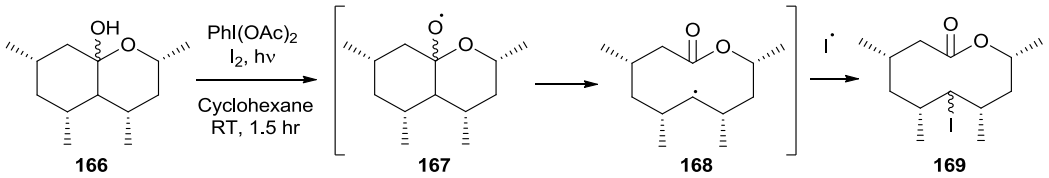


Scheme 1.49

These substrates underwent fragmentation to afford medium ring alkynylketones **165** in moderate to excellent yields. Interestingly the metal-halogen exchange was found to be effective even in the presence of the vinyl-triflate functionality.

1.3.4.2 Oxidative cleavage

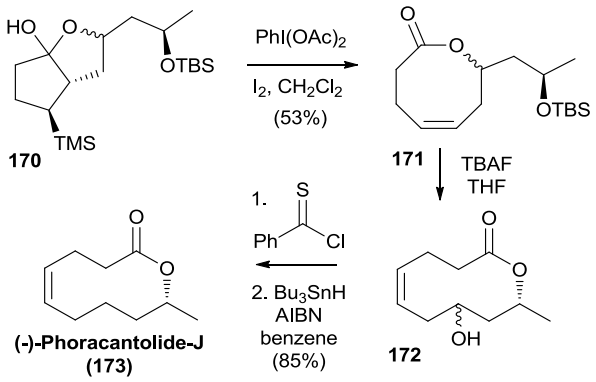
Bicyclic hemiacetals have been reported to be very good substrates for oxidative cleavage, undergoing fragmentation to afford medium rings. This process was first described by Borowitz[120] using $Pb(OAc)_4$ as the oxidant. Milder and less toxic procedures have been more recently developed using hypervalent (λ^3)-iodine ($PhI(OAc)_2$) and iodine in the presence of light (**Scheme 1.50**).[121]



Scheme 1.50

Under these conditions acetyl hypoiodite (AcOI) is formed; the latter reacts with the acetal functionality to give alkyl hypoiodite (R-OI) which generates alkoxy radical **167** upon irradiation with UV light.[122]

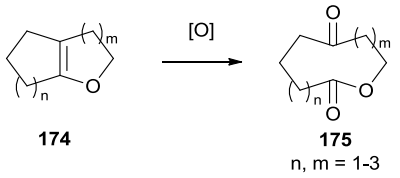
Another oxidative type cleavage has been reported for β-hydroxysilanes using mild oxidants like CAN[123, 124] and $PhI(OAc)_2/I_2$.[125] Posner used this strategy to obtain 8-12 membered rings in very good yields.[126] The author also demonstrated the synthetic usefulness of this reaction in the synthesis of the natural product (-)-Phoracantolide J (**173**, **Scheme 1.51**).[127]



Scheme 1.51

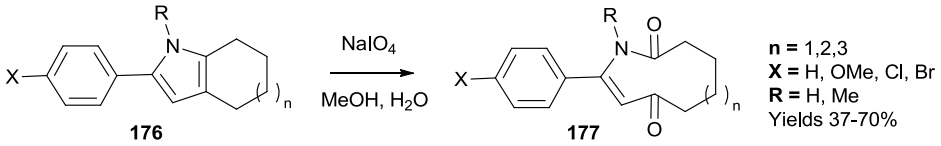
Interestingly, after hypervalent iodine mediated oxidative cleavage of **170** to afford 8-membered ring **171**, TBAF deprotection of the secondary alcohol followed by translactonisation afforded the 10-membered ring **172**, which was subsequently converted into the natural product via Barton-McCombie de-oxygenation.[128]

Another example of oxidative cleavage of bicyclic systems is the synthesis of ketolactones in **Scheme 1.52**. Oxidation of the central double bond of **174** has been achieved either with *m*CPBA,[129] ozone[130] or PCC [131] to give 8 to 12 membered rings in moderate to excellent yields.



Scheme 1.52

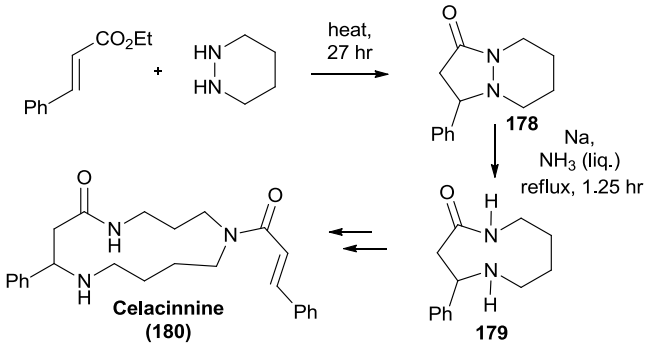
Sodium periodate has been used for the mild oxidative cleavage of enamines **176**, to give medium ring ketolactams **177** (**Scheme 1.53**)[132] via regioselective oxidation of the central double bond of the pyrrole starting material.



Scheme 1.53

1.3.4.3 Reductive Cleavage

Medium ring azalactams were obtained via reductive cleavage of the N-N bond of the cyclic hydrazone **178**, readily obtained via Michael addition and condensation between piperidazine and ethyl cinnamate (**Scheme 1.54**).[133]

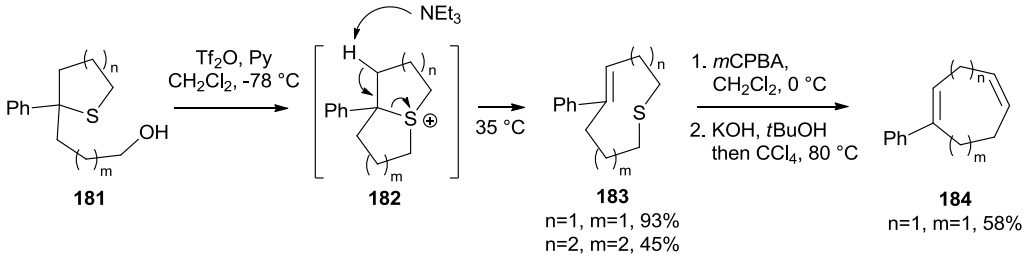


Scheme 1.54

Reduction of the central bond was achieved with sodium in liquid ammonia, to afford nine membered ring aminolactam **179**, precursor of the spermidine alkaloid Celacinnine **180**.

1.3.4.4 Miscellaneous

Zhou recently described the formation of bridged sulfonium salts **182** obtained by treatment of sulfido-alcohols **181** with triflic anhydride (**Scheme 1.55**).[134] In the presence of triethylamine it was found that elimination occurred, causing fragmentation of the C-S bond to reveal medium rings **183**.



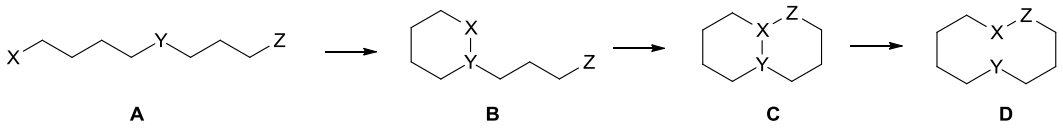
Scheme 1.55

Extrusion of the sulfur atom from the ring could also be achieved via the Ramberg-Bäcklund reaction sequence[107] to give carbocycle **184**.

2. Results and Discussion

2.1 Introduction

As discussed in the previous chapter, medium rings are synthetically challenging targets for organic chemists and new methods for their synthesis that have general applicability are constantly sought. The scope of the present thesis is to explore a new and potentially widely applicable approach using the one pot *domino* reaction sequence in **Scheme 2.1**. Starting from a linear precursor with 3 suitable functional groups (**A**), the product of the first reaction between two functional groups (small ring formation, **B**) would have the correct structure for the second step (fused rings formation, **C**) and subsequently the third step (fragmentation, **D**) to occur in a cascade fashion.



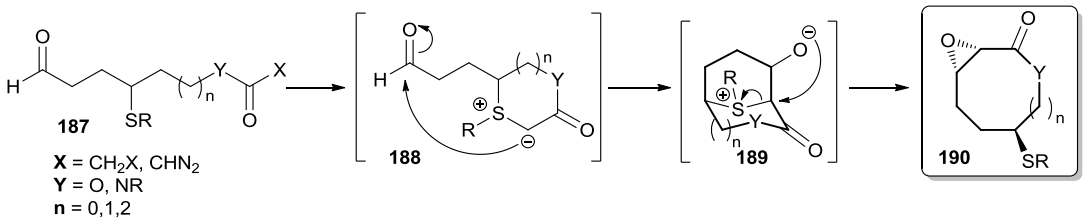
Scheme 2.1 Proposed double cyclisation-fragmentation approach to medium rings

This chain of events would eventually lead to the formation of a medium sized ring and this would still have functional groups ready for further elaboration. The ultimate goal of this strategy is to achieve the tandem double cyclisation and fragmentation in a one pot sequence. If successful this strategy could be applied to a series of natural products containing 8-12 membered rings.

This approach would have several advantages when compared to direct cyclisation techniques; in the first place the formation of two smaller rings should be thermodynamically more favourable. As described in the previous chapter, the formation of a medium ring from an acyclic bifunctional precursor is unfavourable in terms of both entropy and enthalpy because of the large number of possible conformations available to an open chain system and because of the high transannular strains involved. The construction of two smaller (5 to 7 atoms) fused rings should therefore be more favourable. In the second place the rigid bicyclic system could provide effective stereocontrol, allowing the introduction of

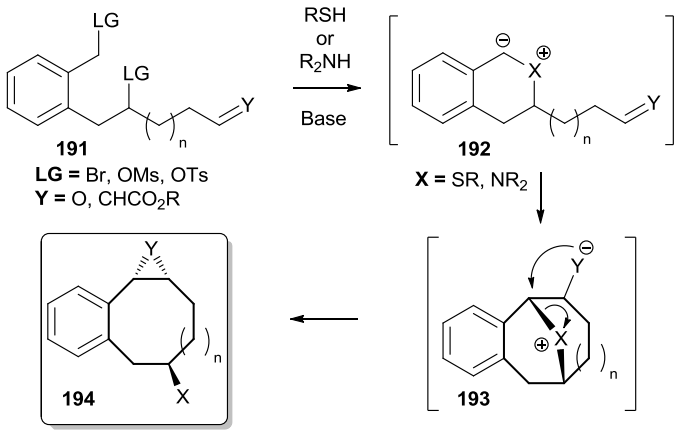
substituents in the ring with the desired configuration. We propose that suitable functional groups for the transformation described above could be ylides (X-Y group in **Scheme 2.1**) together with a suitable pendant electrophile (Z).

As exemplified in **Scheme 2.2**, once the ester/amide stabilised cyclic sulfur ylide **188** is generated *in situ*, this could react with the pendant aldehyde to give bicyclic intermediate **189**. Ring closure of the alkoxide anion onto the carbon bearing the positively charged sulfonium group would then trigger the fragmentation step required for the medium ring formation (**190**).



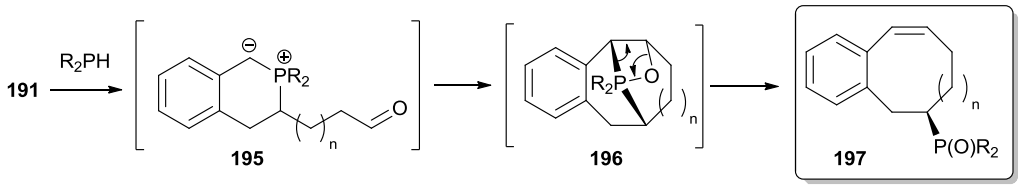
Scheme 2.2

Similarly, other types of ylides could also be employed in the same approach (**Scheme 2.3**). Benzyl stabilised sulfur and nitrogen ylides **192** could also react intramolecularly with pendant electrophiles to give bicyclic intermediates **193** and eventually rearrange into medium rings **194**.



Scheme 2.3

The same type of approach could also be extended to phosphorus ylides (**Scheme 2.4**). Cyclic phosphonium ylide **195**, obtained from precursor **191**, could react with the pendant aldehyde in an intramolecular Wittig reaction to give oxaphosphetane intermediate **196** and the latter could then rearrange into medium ring product **197**.

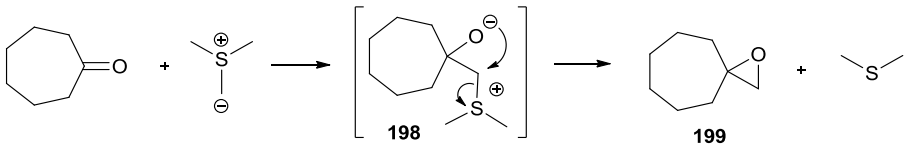


Scheme 2.4

If successful this general method could represent a useful strategy for the synthesis of medium rings containing functional groups amenable of further functionalization. A detailed description of the approaches investigated during the course of the doctorate will be given in the next paragraphs and will be divided according to the different types of ylides employed.

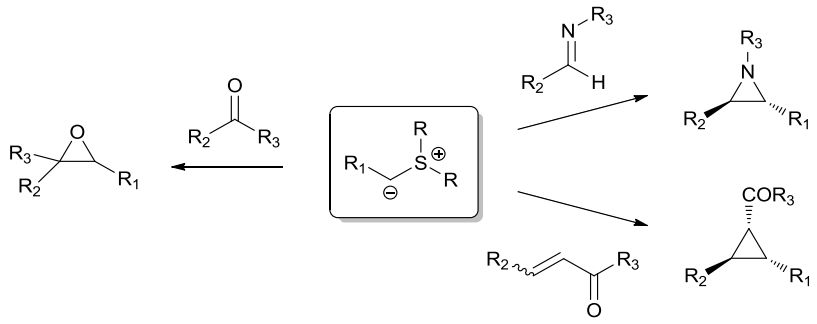
2.2 Sulfur Ylides

Sulfonium and sulfoxonium ylides were first reported to react with carbonyls and other unsaturated functionalities (imines, α,β-unsaturated carbonyls) as a methylene transfer unit to give the corresponding three membered ring (epoxides, aziridines and cyclopropanes) by E.J. Corey and M. Chaykovsky in 1965 (**Scheme 2.5,** Corey-Chaykovsky (C-C) epoxidation).[135]



Scheme 2.5 Corey Chaykovsky epoxidation

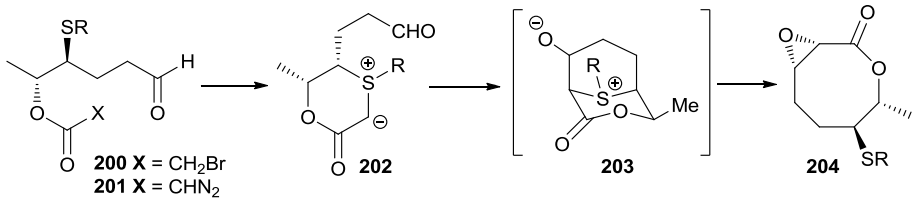
In a similar manner other sulfur ylides have been reported to react with unsaturated electrophiles (C=O, C=N and C=C) to give three membered rings (**Scheme 2.6**).[135, 136]



Scheme 2.6. Three membered ring formation from sulfur ylides

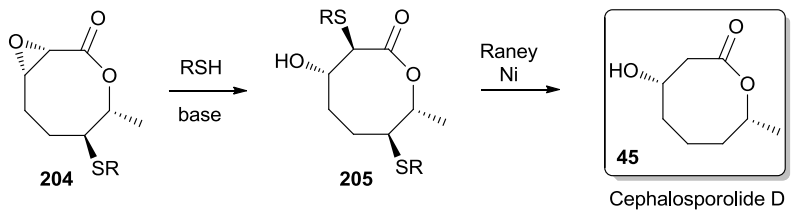
The reactivity of sulfur ylides has been widely exploited as a useful synthetic tool in the synthesis of natural molecules.[93, 136, 137]

We initially decided to investigate the use of sulfur ylides as a functional group in our proposed *domino* sequence for the synthesis of medium rings, according to the reaction sequence previously described (**Scheme 2.7**). We envisaged that cyclic ylides **202** could be obtained either from α-bromoesters **200** or from diazoesters **201**. After intramolecular attack of the negatively charged carbon of the ylide to the pendant aldehyde, bicyclic intermediate **203** would be generated. The latter could undergo ring closure of the alkoxide onto the carbon bearing the positively charged sulfur (in an intramolecular C-C epoxidation fashion) and afford medium ring **204**.



Scheme 2.7.

We also envisioned that further modifications of the 8-membered ring lactone **204** could lead to the synthesis of the natural product Cephalosporolide D **45** (**Scheme 2.8**). Although a few successful syntheses have been described for this target using macrolactonisation techniques,[27] these methods often require tedious optimisation and high dilution conditions. Our proposed approach could furnish the natural product in just two steps from intermediate **204** via epoxide opening by a sulfide followed by Raney-Ni reduction.

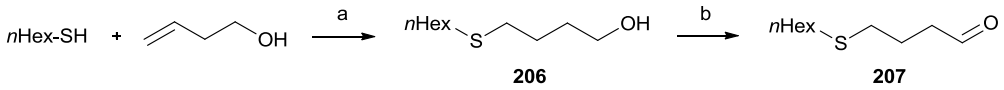


Scheme 2.8.

Unfortunately, to the best of our knowledge, there is no precedent in the literature for an intramolecular C-C epoxidation reaction. We therefore decided to investigate the viability of this approach on a simpler model substrate before moving to more complex substrates.

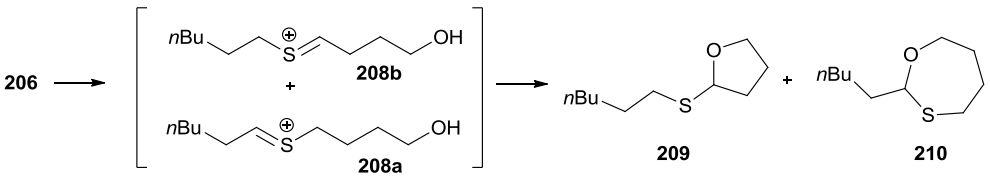
2.2.1 Investigation of intramolecular Corey-Chaykovsky epoxidation

In order to study the viability of the intramolecular reaction of a sulfur ylide with a pendant electrophile, substrate **207** was synthesised (**Scheme 2.9**). Radical addition of *n*-hexanethiol to commercially available 3-buten-1-ol afforded alcohol **206** which was oxidised to the corresponding aldehyde using the Swern protocol.



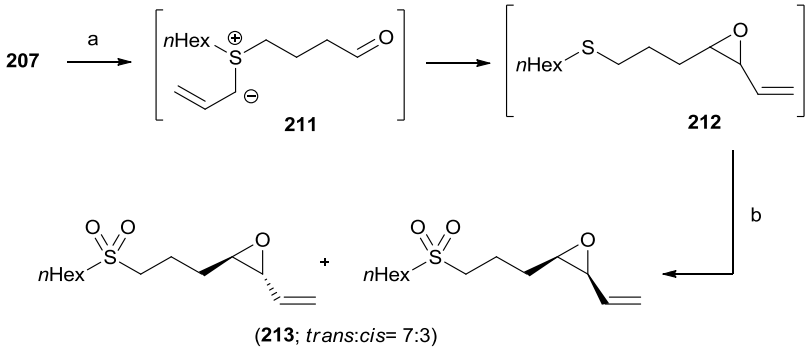
Scheme 2.9. Reagents and conditions: a) AIBN (5 mol %), MeCN, reflux, quant.; b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 36%.

Unfortunately the yield for the latter transformation was poor due to the concurrent Pummerer-type side reaction[138] (**Scheme 2.10**) which afforded thioacetals **209** and **210**. Further investigations were carried out on this substrate following these findings (See **Section 2.7.1**).



Scheme 2.10

Nevertheless aldehyde **207** was isolated in sufficient quantity to be taken onto the next step. This substrate was treated with allyl bromide in the presence of a base (KOH) under phase transfer conditions with the purpose of generating ylide **211** *in situ* (**Scheme 2.11**).

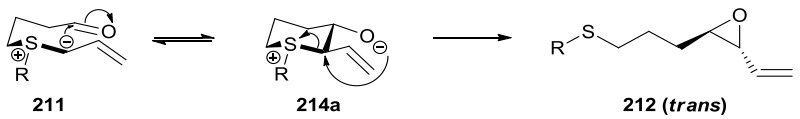


Scheme 2.11. Reagents and conditions**:** a) CH_2=$CHCH_2Br$, aq. KOH, TBAB (5 mol %), CH_2Cl_2, RT, 5 days; b) $RuCl_3 \cdot H_2O$ (2 mol%), $NaIO_4$, CCl_4, MeCN, H_2O, 16%;

The formation of epoxides **212** was observed by ^{1}H-NMR but unfortunately no material could be isolated after purification by column chromatography, probably due to decomposition on silica. Ruthenium catalysed oxidation to sulfones followed by chromatographic separation afforded epoxides **213**, albeit in low yield, as a 7:3 mixture of the two diastereoisomers. The reaction showed a diastereopreference for the *trans* isomer, as determined by the analysis of the coupling constants of the ^{1}H-NMR spectrum.

Allyl-stabilised sulfur ylides have been previously reported to preferentially afford *trans* epoxides in the reaction with carbonyl groups,[139] although with different degrees of selectivity depending on the substitution patterns.

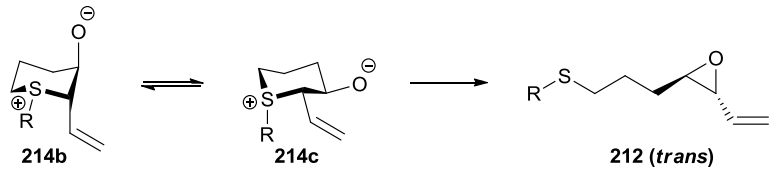
In our case the rationale for the stereochemical outcome of the intramolecular reaction can be explained by taking into account the 6-membered ring chair like intermediate betaine **214a** that originates after the reversible intramolecular nucleophilic attack of ylide **211** to the pendant aldehyde (**Scheme 2.12**).



Scheme 2.12

Intermediate **214a**, in which all substituents reside in an equatorial position, should form preferentially as the thermodynamic adduct of this reaction. At this stage the nucleophilic alkoxide anion and the sulfonium leaving group are *anti*-periplanar. Attack of the oxygen atom to the carbon bearing the sulfonium substituent affords the *trans* isomer of epoxide **212**.

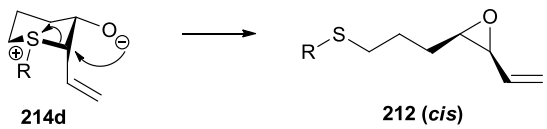
The *trans* isomer of **212** could also originate from intermediate **214c** (**Scheme 2.13**), in which the alkoxide and the sulfonium groups are still in an *anti* conformation, although the substituent on the sulfur sits in the axial position, making this conformation energetically less favourable than **214a**.



Scheme 2.13

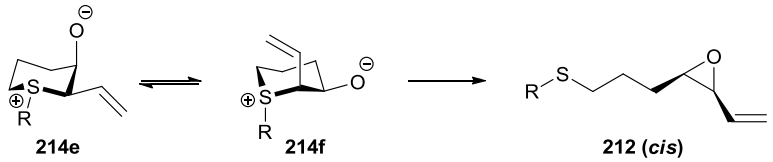
Conformation **214b** (**Scheme 2.13**) has 2 substituents in the axial orientation; in this conformation the alkoxide and sulfonium groups are orientated *gauche* to each other and can't therefore react to form the epoxide ring. Even though the energy barrier for pyramidal inversion of sulfonium salts is relatively high,[140] **214c** could also potentially be generated after ring inversion of **214b** and lead to the *trans* epoxide of **212**. In **214b** the axial orientation of the two substituents should make the conformation higher in energy than the previous two (namely **214a** and **214c**).

On the other hand, the *cis* isomer of epoxide **212** can originate from intermediate **214d** (**Scheme 2.14**). In this conformation the alkoxide and the sulfonium group are still *anti*-periplanar, but the axial orientation of the vinyl group makes this conformation less energetically favourable than **214a**.



Scheme 2.14

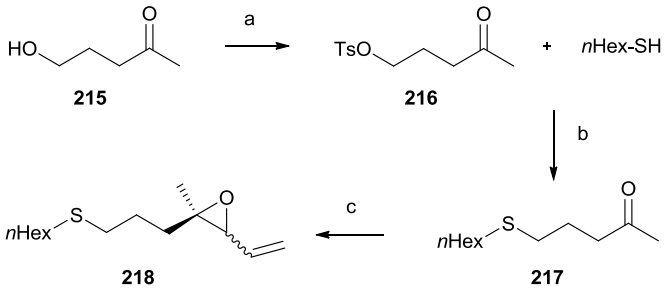
Another contribution to the *cis* isomer could come from intermediates **214e** and **214f** (**Scheme 2.15**), although the axial orientation of the two substituents in the reactive intermediate **214f** makes this conformation less energetically favourable than **214d**.



Scheme 2.15

We can assume that for the reasons discussed above, the use of substituents which are sterically more demanding than the vinyl group should lead to a greater preference for conformation **214a**, in which all substituents are in the equatorial position, and therefore a higher *trans*:*cis* ratio.

The intramolecular Corey-Chaykovsky epoxidation procedure was also extended to ketone **217** (**Scheme 2.16**). The synthetic route started from commercially available alcohol **215** which was converted to tosylate **216**.[141] Unfortunately the yields for this reaction were very low due to difficulties during the isolation of the product and also due to the decomposition of the material over time. Ketone **217** was subsequently prepared by nucleophilic displacement of the tosylate with *n*-hexanethiol. This substrate was then treated with allyl bromide and KOH under phase transfer conditions to afford a mixture of epoxides **218**.

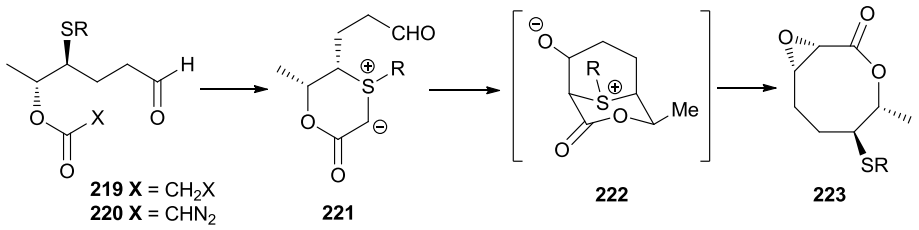


Scheme 2.16. Reagents and conditions: a) TsCl, Py, $CHCl_3$, 0 °C → RT, 23%; b) Cs_2CO_3, Acetone, 10%; c) CH_2=$CHCH_2Br$, aq. KOH, TBAB, CH_2Cl_2, 40°C, 3 days, 40%.

Epoxides **218** proved to be stable on silica gel and could therefore be isolated in moderate yields after column chromatography. A ~1:1 mixture of *trans* and *cis* isomers was obtained in this case, as confirmed by ^{1}H-NMR.

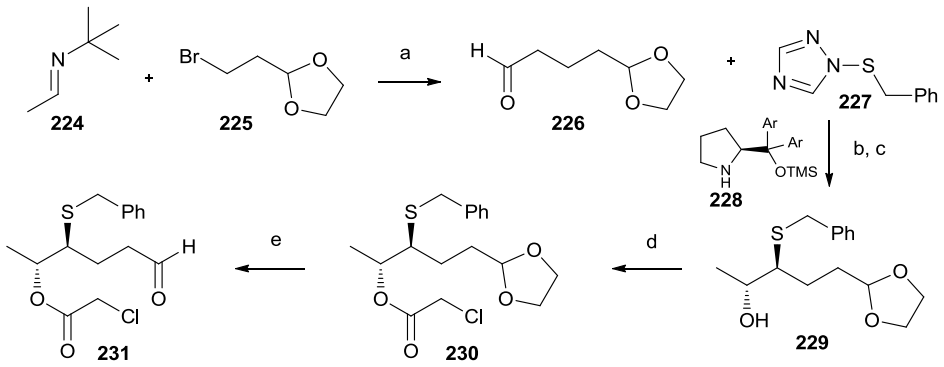
2.2.2 Octalactones via ester Stabilised S-Ylides

After the successful preliminary results of the studies on the intramolecular Corey – Chaykovsky epoxidation, the initial attempts towards the synthesis of medium rings were concentrated on the synthesis of functionalised precursors **219** and **220**, containing 3 functional groups suitable to undergo our proposed *domino* sequence (**Scheme 2.17**). As previously discussed, ylides **221** could be generated either from α-haloesters **219**, after deprotonation of the corresponding cyclic sulfonium salt with a suitable base or directly from diazoesters **220** by treatment with a suitable metal catalyst.[142] Once generated, the ylide should undergo the cascade of events that would eventually lead to the formation of medium ring **223**.



Scheme 2.17

The initial route towards α-chloroester **231** started from imine **224** which was readily synthesised using literature conditions[143] (**Scheme 2.18**). Deprotonation of the imine with LDA and alkylation of the aza-enolate with commercially available bromide **225** gave aldehyde **226** after acidic hydrolysis, although in moderate yields. The stereoselective introduction of the benzylsulfide group was achieved using sulfenyl triazole **227** as a source of electrophilic sulfur and proline based organocatalyst **228**, according to the procedure developed by Jørgensen.[144]

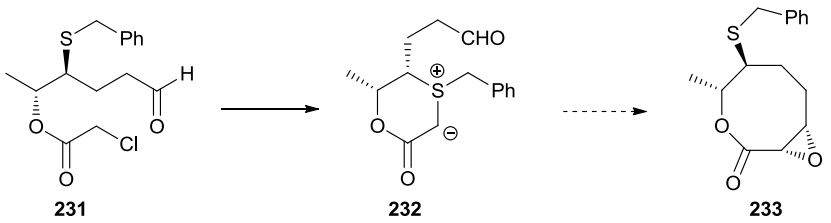


Scheme 2.18. Reagents and conditions**:** a) i. LDA, DMPU, THF, -30 °C, 4 hr; ii. 15% Tartaric acid solution, 0 °C, 2 hr, 25%; b) Cat. **228** (10% mol, Ar = 3,5-$(CF_3)_2C_6H_3$), toluene, RT, 3 hr; c) MeLi, THF, -78 °C, 1 hr, 33%; d) $ClCH_2COCl$, Py, 0 °C, 1hr, 59%; e) Amberlyst-15, Acetone/water, RT, 3days, 93%.

The product of the reaction was not isolated but treated in situ with MeLi at -78 °C to give secondary alcohol **229**. ^{1}H-NMR analysis of the crude product revealed a 90:10 ratio in favour of one diastereoisomer. It is likely that the observed facial selectivity of the nucleophilic attack to the aldehyde was favoured by the presence of the bulky sulfide substituent and the non-chelating conditions, according to the Felkin-Nguyen model. When the reaction was repeated using MeMgBr the observed diastereomeric ratio dropped to 75:25, thus suggesting a certain degree of chelation control exerted by the Mg cation.[145] The exceptional diastereoselectivity exerted during the addition of nucleophiles to α-sulfenylaldehydes was further investigated and will be discussed in Chapter 3.

Alcohol **229** was isolated in good purity after two consecutive steps albeit the yield of the process was only moderate. α-Chloroester **230** was readily synthesised from the alcohol using chloroacetyl chloride in pyridine and aldehyde **231** was subsequently obtained in almost quantitative yield after acetal deprotection catalysed by the acidic resin Amberlyst-15.

With a few milligrams of precursor **231** in hand, six reactions were attempted in order to generate ylide **232** and trigger the proposed domino reaction sequence (**Scheme 2.19**).



Scheme 2.19. Reagents and conditions summarised in **Table 2.1**

Initial attempts using K_2CO_3 in MeCN at RT (entry 1, **Table 2.1**) were not successful but after addition of KI and heating the reaction to reflux, no starting material was detected by TLC (entry 2 and 3). Analysis of crude NMR was difficult but peaks in the correct region of the spectrum for the sulfonium salt were detected. Treatment of the crude material with NaH (entry 4) gave a new spot by TLC but unfortunately no product was isolated after purification by column chromatography, suggesting possible decomposition on silica. No product was isolated after treatment of **231** with AgOTf/NEt_3 (entry 6), although salt formation was probably achieved (SM disappearance by TLC), thus suggesting that more basic conditions are required to form the ylide.

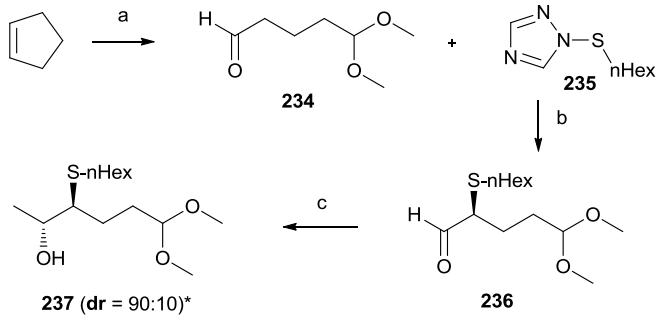
Entry	Conditions	Additive	Observations
1	K_2CO_3 (5 eq), CH_3CN, RT	-	No reaction
2	K_2CO_3 (5 eq), CH_3CN, RT	KI	Formation of alkyl iodide
3	K_2CO_3 (5 eq), CH_3CN, reflux	KI	Disappearance of SM (TLC) – NMR analysis of columned material showed traces of possible epoxide formation
4	Product of entry 3	NaH (4 eq)	New spot by TLC – degradation on column
5	Product of entry 3	KOtBu (4 eq)	No reaction
6	NEt_3/THF	AgOTf	Disappearance of SM – Interpretation of crude NMR is difficult

Table 2.1

Given the unsuccessful results of the initial attempts, a larger amount of the precursor was needed in order to test different reaction conditions. A higher yielding route was therefore sought. After a literature search, it was found that a facile route

to aldehyde **234** from cyclopentene had previously been reported via ozonolysis followed by *in situ* dimethylacetal formation (**Scheme 2.20**).[146] The advantage of this route would be the synthesis of aldehyde **234** in just one step from cheap and readily available starting materials and also the presence of the dimethyl-acetal group which could easily be removed under mildly acidic conditions.

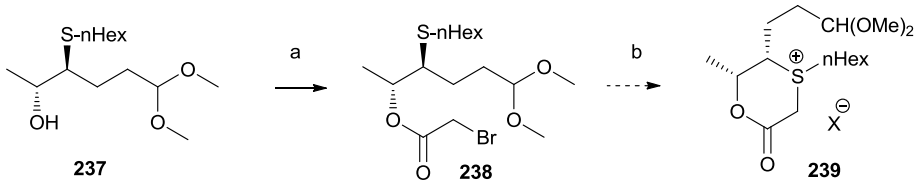
Aldehyde **234** was isolated after column chromatography albeit in low yield, but the simplicity and the scalability of this process made the route very attractive. The material was immediately used in the next step as it proved to be unstable even when stored under inert gas at low temperatures.



Scheme 2.20. Reagents and conditions: a) i. O_3, CH_2Cl_2/MeOH, -78 °C, ii. TsOH, iii. $NaHCO_3$, DMS, RT, 20%; b) Cat. **228** (10 mol %), toluene, RT, 4 hr; c) MeLi, THF, -78 °C, 79% (2 steps). (*)the configuration of the secondary alcohol was determined by Mosher's esters analyses (see Appendix)

Aldehyde **234** was therefore reacted with *n*-hexyl-sulfanyltriazole **235** in the presence of Jørgensen's organocatalyst **228** in order to introduce the sulfur substituent in a stereocontrolled fashion. It was found that better yields were obtained for the following step if the crude α-sulfenylaldehyde **236** was quickly filtered through a silica plug, in order to separate it from the triazole and sulfide impurities. Slow addition of aldehyde **236** to a MeLi solution at -78 °C gave alcohol **237**, which was also obtained in a 90:10 diastereomeric ratio, as previously observed. At this stage a different alkyl group on sulfur (*n*-hexyl) was evaluated. The *n*-hexyl group was thought to give the substrate increased stability compared to its benzyl congener and it would make the sulfonium salt less prone to Stevens-type rearrangement[147, 148] during the cyclisation step. The configuration of the newly generated stereocenter of alcohol **237** was also unambiguously assigned as (*R*) after Mosher's esters analysis (See Appendix for experimental data).

Alcohol **237** was subsequently acetylated in very good yields using bromoacetyl bromide in Py/CH_2Cl_2 allowing the isolation of ester **238** in quantitative yield and very good purity (NMR) (**Scheme 2.21**).



Scheme 2.21. Reagents and conditions: a) $BrCH_2COBr$, Py, CH_2Cl_2 -30 °C, 20 min, 98%, b) conditions (see text, **Table 2.2**)

At this stage a few conditions were tried on the acetal-protected substrate **238** in order to achieve the intramolecular cyclisation to afford sulfonium salts **239**, as summarised in **Table 2.2**.

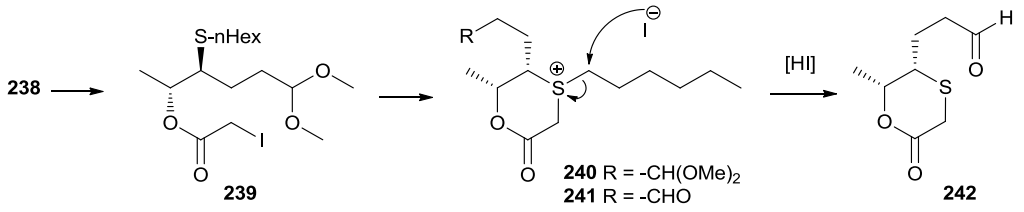
Entry	Conditions	Additive	Observations
1	MeCN, reflux	-	No reaction
2	MeCN, RT, 24 hr	$AgBF_4$	No cyclisation, acetal hydrolysis
3	MeCN, RT, 24 hr then reflux for 3 hr	AgOTf, $AgSbF_6$	Still SM present after 24 hr at RT (TLC). Complex mixtures of products (NMR) after heating. Acetal hydrolysis.
4	Product of entry 3	$AgSbF_6$, TBD	Ester hydrolysis
5	Product of entry 3	$AgSbF_6$, NaH	Decomposition
6	Product of entry 3	$AgSbF_6$, NaOtBu	Decomposition
7	MeCN, RT to reflux	KI	Cyclisation + acetal hydrolysis + dealkylation (**242**)
8	Product of entry 7	KI, Cs_2CO_3	Ester hydrolysis (**237**)
9	Product of entry 7	KI, NaH	Complex mixture, decomposition.
10	MeCN, reflux	DABCO	Ester hydrolysis

Table 2.2

Cyclisation did not occur at all when precursor **238** was refluxed in a polar solvent (MeCN, entry 1). The use of silver salts with weakly nucleophilic counterions (AgX, $X^- = SbF_6$, OTf, BF_4, entries 2 and 3) gave complex mixtures of products (NMR) and

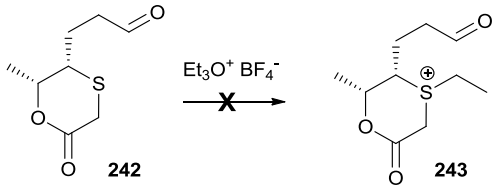
caused concomitant acetal deprotection. Treatment of the crude reaction mixtures with bases (NaH, NaOtBu, Cs_2CO_3, TBD, entries 4-6) mainly afforded decomposition products or hydrolysis of the ester functionality, as confirmed by ^{1}H-NMR.

When bromoester **238** was treated with KI in acetonitrile at RT (entry 7, **Table 2.2**), conversion to iodide **239** was quickly achieved, as confirmed by ^{1}H-NMR experiments (**Scheme 2.22**). Cyclisation occurred very slowly (6 days at RT) and afforded a mixture of salt **240**, unprotected salt **241** and de-alkylated product **242** (NMR).



Scheme 2.22. Reagents and conditions: KI, MeCN, reflux, 24 hr.

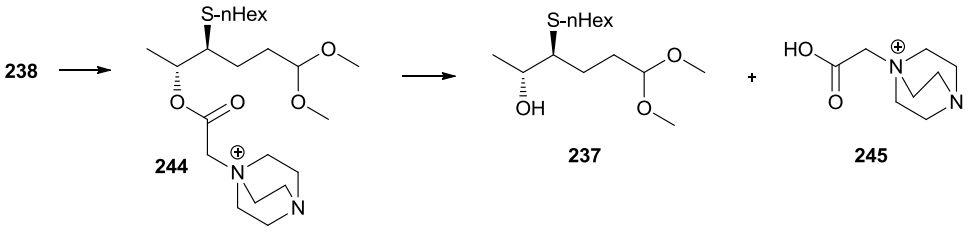
When iodide **239** was heated at reflux for 2 days, aldehyde **242** was isolated after chromatographic separation in 23% yield. The observed dealkylation is probably due to nucleophilic attack of the iodide anion at the carbon bearing the sulfonium group whereas the acetal deprotection might be caused by catalytic amounts of HI present in the reaction. Attempts to alkylate the cyclic sulfide **242** with Meerwein salt to give the corresponding sulfonium salt **243** were unfortunately unsuccessful (**Scheme 2.23**).



Scheme 2.23

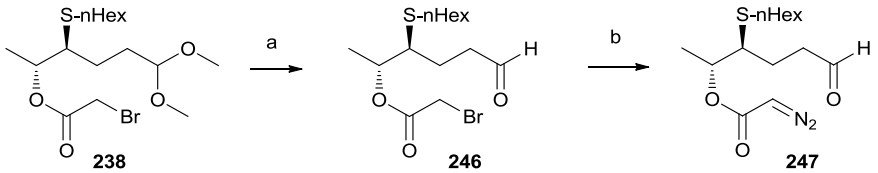
A small amount of the reaction mixture containing ~ 30% of sulfonium salt **241** (as determined by NMR) was also treated with bases (entries 8 and 9); when Cs_2CO_3 was used the main product detected was secondary alcohol **237**, probably resulting

from the hydrolysis of the unreacted iodoketone, whereas when NaH was used only decomposition occurred. In order to avoid unwanted dealkylation, the use of sterically hindered base DABCO (entry 10) was investigated (**Scheme 2.24**). Formation of quaternary ammonium salt **244** was complete (NMR) but after prolonged stirring at RT (1 week) only products of hydrolysis, namely alcohol **237** and acid **245,** were detected (NMR), probably due to residual water content in the solvent (MeCN) or in the base.



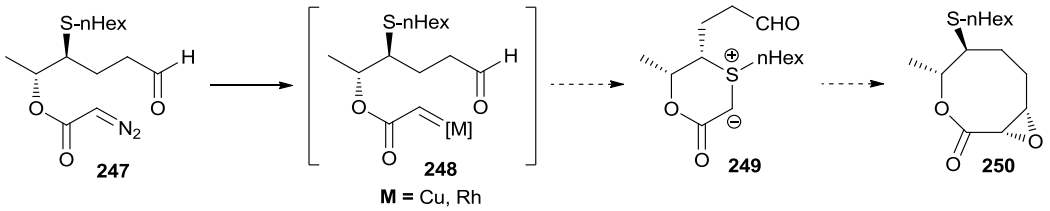
Scheme 2.24

Given the unsuccessful results from the intramolecular sulfonium salt formation, it was decided to turn our attention to alternative procedures for the synthesis of sulfur ylides. After deprotection of dimethyl-acetal **238** with Amberlyst-15, aldehyde **246** was converted to α-diazoester **247** according to Fukuyama's procedure,[149] using ditosyl-hydrazine and DBU (**Scheme 2.25**).



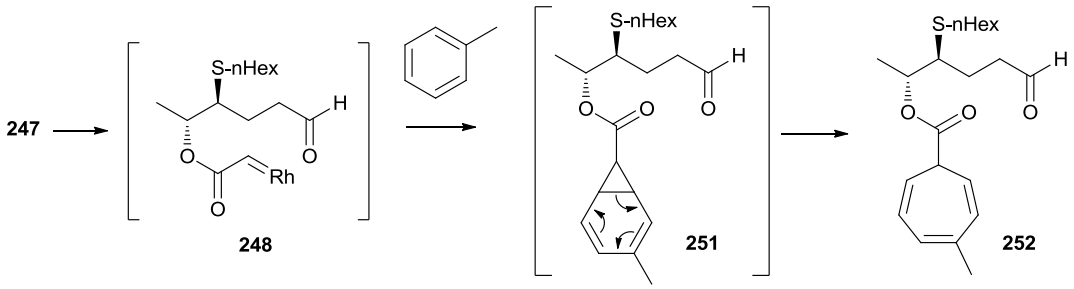
Scheme 2.25. Reagents and conditions: a) Amberlyst-15, acetone, water, 24 hr, RT, 94%; b) TsNHNHTs, DBU, THF, 0 °C, 1 hr, 93%;

The diazo compound was quickly isolated via a filtration through a silica plug and used in the next step. At this stage we were hoping that by treating α-diazoester **247** with a suitable metal catalyst this would generate metal carbenoid **248** and the latter would react with sulfur to form cyclic ylide **249** which would subsequently react with the aldehyde moiety in an intramolecular Corey-Chaykovsky epoxidation to give medium ring **250** (**Scheme 2.26**).



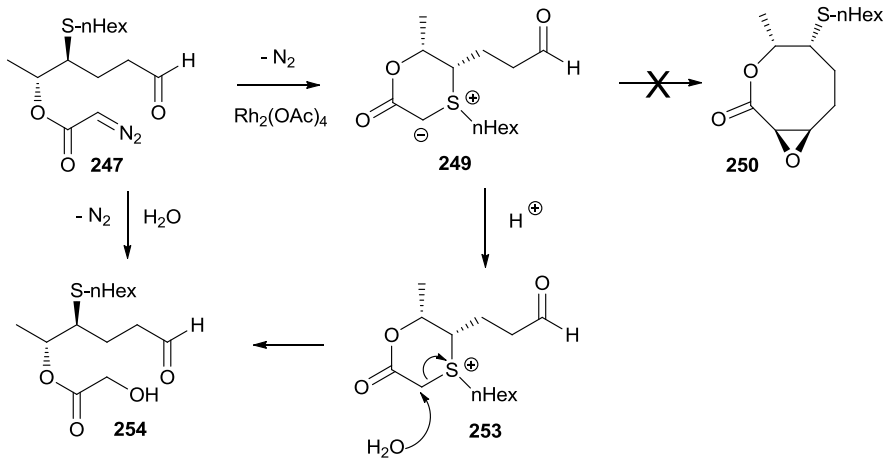
Scheme 2.26

When the reaction was first performed using $Rh_2(OAc)_4$ in toluene, the formation of **252** was observed, due to the reaction of carbenoid **248** with the solvent to give an initial cyclopropanation (**251**) followed by electrocyclic rearrangement[150] to give cycloheptatriene **252** (**Scheme 2.27**).



Scheme 2.27. Reagents and conditions: $Rh_2(OAc)_4$ (5 mol %), toluene, RT → reflux, 30 min, 21%.

The reaction was therefore repeated in a different solvent in order to avoid unwanted side reactions. After a search in the literature it was found that this type of transformation is usually carried out by slowly adding a solution of the diazocompound to a solution of the catalyst in DCE at reflux.[142] Diazoester **247** was therefore added to two different solutions of metal catalysts ($Cu(acac)_2$ and $Rh_2(OAc)_4$) in DCE at reflux over 12 hr under Ar. In the case of the Cu catalyst, only starting material and decomposition products were observed (TLC). The presence of the aldehyde peak in the ^{1}H-NMR spectrum of the crude reaction was a clear sign that the reaction hadn't been successful. In the case of the Rh catalyst the main product isolated was α-hydroxyester **254** (**Scheme 2.28**).

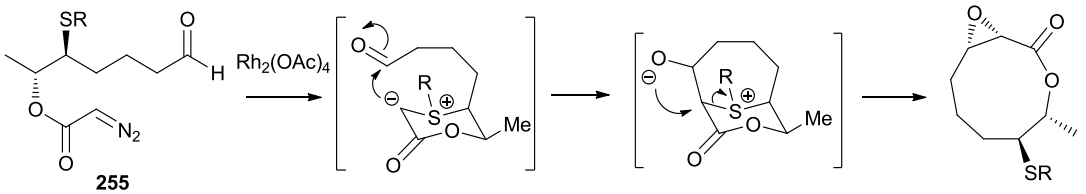


Scheme 2.28

The reaction is likely to proceed via ester stabilised ylide **249**; once formed this seems to be very stable and unable to react with the aldehyde functionality. The ylide could be protonated either via proton transfer or on silica during the isolation and the resulting sulfonium salt **253** could then be displaced by water (present in traces) to give alcohol **254**. Alcohol **254** could also derive from the carbene insertion into water which could be present in traces in the reaction mixture.

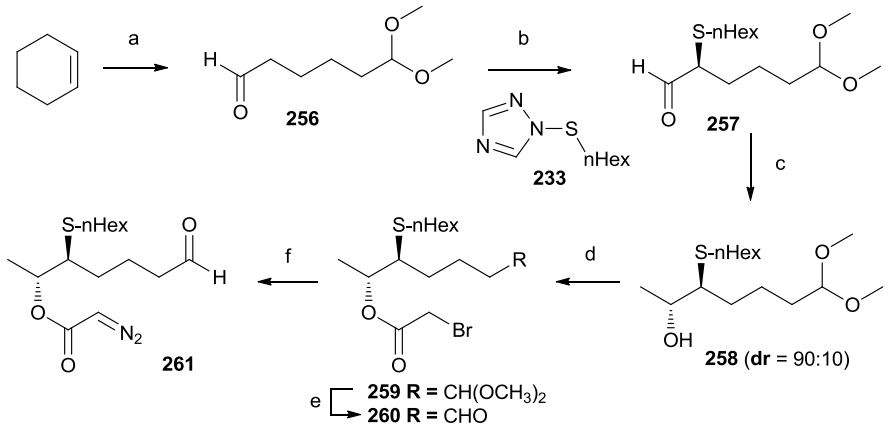
2.2.3 Nine membered lactones via ester stabilised ylides

Given the unsuccessful attempts to synthesise the 8 membered lactone ring precursor to the natural product Cephalosporolide D, it was decided to extend the tether between the aldehyde and the sulfur atom in precursor **255** by one extra carbon unit with the hope that this would give the chain some extra flexibility and therefore increase the reactivity of the substrate towards the intramolecular C-C epoxidation (**Scheme 2.29**).



Scheme 2.29

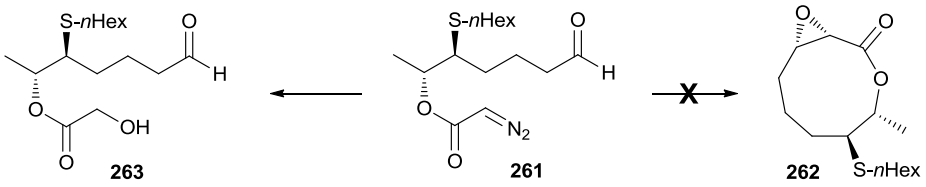
The route started from aldehyde **256** (**Scheme 2.30**) which was obtained after ozonolysis and selective acetal formation from commercially available cyclohexene.[146]



Scheme 2.30. Reagents and conditions: a) i. O_3, CH_2Cl_2/MeOH, -78 °C, ii. TsOH, iii. $NaHCO_3$, DMS, RT, 70%; b) cat. **228** (Ar = 3,5-$(CF_3)_2$-C_6H_4) (10 mol%), **233** (1.3 eq), Toluene, 87%; c) MeLi, THF, -78 °C, 60%; d) $BrCOCH_2Br$, Py, CH_2Cl_2, -30 °C, 20 min, quant.; e) Amberlyst-15, acetone/water, 24 hr, RT, 87%; f) TsNHNHTs, DBU, THF, 0°C, 67%;

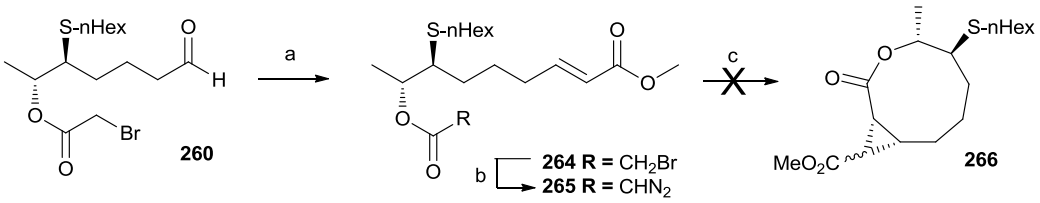
Organocatalytic stereoselective α-sulfenylation of **256** afforded aldehyde **257** which was isolated by column chromatography. Treatment of the purified aldehyde with MeLi gave alcohol **258** in excellent yield and very good diastereoselectivity (90:10, as confirmed by ^{1}H-NMR). α-Bromoester **260** was isolated in excellent yields after treatment of alcohol **258** with bromoacetyl bromide and pyridine followed by acid catalysed deprotection of the acetal. The conversion to diazoester **261** was achieved using Fukuyama's conditions (ditosylhydrazine/DBU).[149]

When substrate **261** was treated with catalytic $Rh_2(OAc)_4$, complete consumption of the starting material was observed (TLC) but unfortunately the only material isolated after chromatographic purification was alcohol **263** (**Scheme 2.31**).



Scheme 2.31. $Rh_2(OAc)_4$ (5 mol %), DCE, 60°C, 5 hr.

Aldehyde **260** was also converted to α,β-unsaturated ester **265** with the hope that the *in situ* generated cyclic ylide would react with the double bond to give cyclopropane **266**. Ester **265** was therefore synthesised from **260** in two steps via Wittig olefination followed by diazo-ester formation in good yields (**Scheme 2.32**).



Scheme 2.32. Reagents and conditions: a) $Ph_3P{=}CHCO_2Me$, Toluene, RT, 1.5 hr, 63%; b) TsNHNHTs, DBU, THF, 43%; c) $Rh_2(OAc)_4$ (5 mol %), CH_2Cl_2, RT.

The diazoester was initially treated in the presence of $Rh_2(OAc)_4$ in CD_2Cl_2 at RT and the reaction was monitored by NMR and TLC. After 24 hr complete disappearance of the starting material was observed by TLC; NMR analysis confirmed the complete disappearance of the peak for the proton α to the diazo group. A singlet peak at 4.23 ppm in the ^{1}H-NMR suggested that the formation of the cyclic ylide might have taken place, but unfortunately no peaks in the region of the cyclopropane were detected both by ^{1}H and ^{13}C-NMR. Signals for α-hydroxyester **267** were also detected (~ 20% ratio) (**Fig. 2.1**).

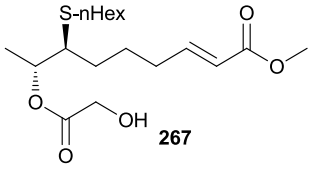


Fig. 2.1

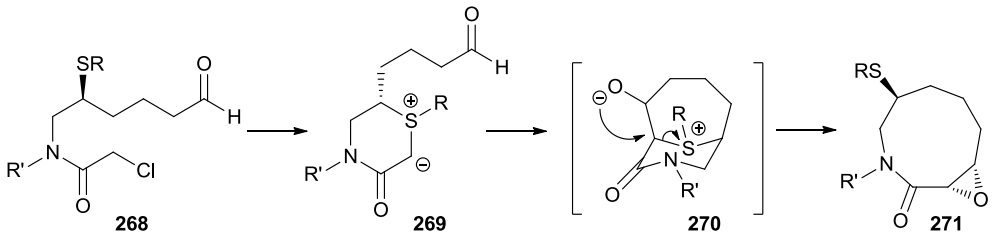
Unfortunately, even after prolonged heating and microwave irradiation no product was observed and the ratio of the formation of the α-hydroxyester **267** increased to ~50%.

These findings suggest that the formation of the cyclic ylide might take place in solution but it subsequently fails to react with the pendant aldehyde, giving only hydroxyesters **267** after purification on silica. Although a few examples of ester stabilised sulfur ylides reacting with aldehydes were reported only under specific

conditions[151, 152] reports in the literature seem to indicate that the ester group is very good at stabilising the negative charge of the ylide,[139] therefore these type of ylides are only able to react with very electrophilic aldehydes (i.e. 1,2 dicarbonyl compounds[153]). It was therefore decided to investigate the reactivity of the less stabilised, and therefore more reactive, amide sulfur ylides in the intramolecular C-C epoxidation.

2.2.4 Medium Rings via amide stabilised ylides

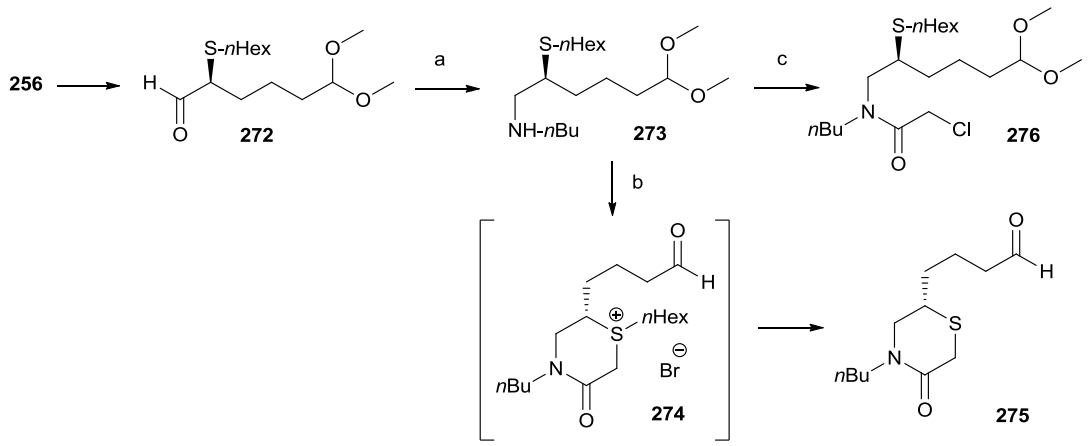
Amide stabilised sulfur ylides are well known in the literature to react with aldehydes in the C-C epoxidation to give 1,2-epoxy amides.[136, 139, 154] This strategy has been developed in recent years by Aggarwal *et al*. for the asymmetric synthesis of epoxides.[153] As discussed above, ester stabilised ylides are less reactive than the corresponding amide stabilised ylides in the epoxidation reaction. We assumed that the lack of reactivity of our ylide substrates could be ascribed to this problem; we therefore thought to introduce an amide stabilised cyclic ylide (**269**) in an attempt to increase the reactivity towards the intramolecular C-C epoxidation to give medium ring lactam **271** (**Scheme 2.33**).



Scheme 2.33

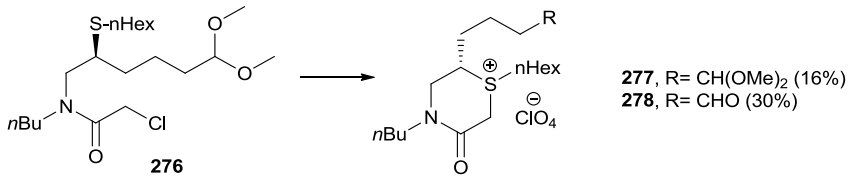
Starting from aldehyde intermediate **256**, common to the previous route (**Scheme 2.30**), reductive amination with *n*-butylamine afforded secondary amine **272** in good yields (**Scheme 2.34**). Initial attempts to form the amide bond using bromoacetylbromide at -30 °C caused simultaneous cyclisation and deprotection of the acetal group to give sulfonium salt **274**, albeit in poor yields. Unfortunately attempts to crystallise this material in order to purify it from other polar impurities

that co-eluted during the chromatographic purification resulted in dealkylation of the *n*-hexyl chain giving thiomorpholinone **275**.



Scheme 2.34. Reagents and conditions: a) i. nBuNH$_2$, NaHCO$_3$, MeOH, reflux, ii. NaBH$_4$, RT, 83%; b) BrCOCH$_2$Br, Py, CH$_2$Cl$_2$, -30 °C, 10%; c) ClCOCH$_2$Cl, NEt$_3$, CH$_2$Cl$_2$, 0 °C, quant;

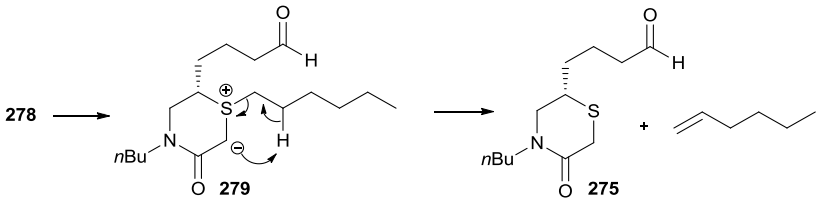
Quantitative formation of amide **276** was subsequently achieved with the use of less reactive chloroacetyl chloride. Pleasingly, crude substrate **276** underwent cyclisation after the addition of a stoichiometric amount of sodium perchlorate to afford cyclic sulfonium salt **277** (**Scheme 2.35**). Concomitant acetal deprotection was also observed (**278**), probably due to traces of perchloric acid in the acetone solution but nevertheless the two products could be easily separated by column chromatography.



Scheme 2.35. Reagents and conditions: NaClO$_4$, acetone, RT, 3 days.

At this stage sulfonium salt **278** was treated in the presence of a variety of bases under reaction conditions typically used in the C-C epoxidation.[155-157] In the presence of 3.0 M NaOH in *t*BuOH the formation of an insoluble precipitate was observed after a few minutes of stirring at RT. Unfortunately analysis of the crude NMR mixture after azeotropic removal of the solvent didn't reveal any trace of the expected product; only very weak signals in the region of terminal olefins were detected. When tBuOK was added to a solution of salt **278** in d$_6$-DMSO at RT, ^{1}H

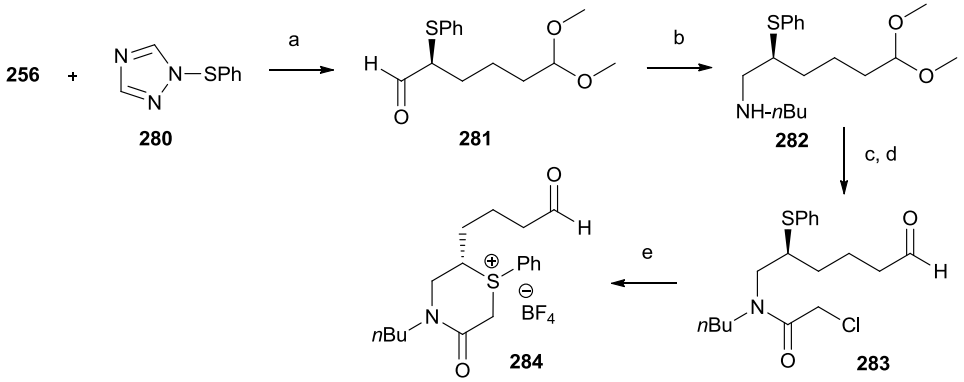
and ^{13}C NMR analysis of the reaction mixture revealed the presence of sulfide **275** and 1-hexene, probably resulting either from the intramolecular elimination reaction of ylide **279** or just simple E_2 elimination (**Scheme 2.36**).



Scheme 2.36. Reagents and conditions: NaOH, tBuOH, RT or KOtBu, d_6-DMSO

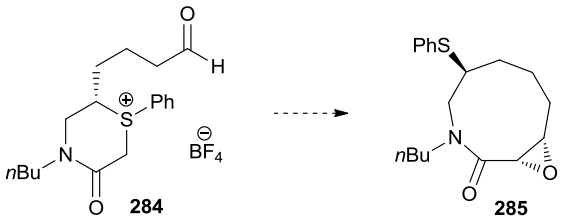
Limited by the amount of salt **278** available it was decided to test the effect of different bases on acetal protected substrate **277** in order to determine whether the formation of the corresponding ylide was possible or flawed by the [2-3]-elimination type process described in **Scheme 2.36**. Unfortunately all the bases screened (Cs_2CO_3, NaH, *t*BuOK) resulted in the formation of thiomorpholinone **275**, as determined by NMR analysis.

In order to avoid elimination, a different substrate was devised bearing a phenyl substituent on sulfur (**284**, **Scheme 2.37**). The stereoselective introduction of a thiophenol substituent has not been described in the literature before but, nevertheless, it was decided to investigate the reaction of sulfenyl-triazole **280**, synthesised following a known procedure,[158] with aldehyde **256** in the Jørgensen organocatalytic protocol. Pleasingly, the reaction proceeded smoothly, affording aldehyde **281** in very good yields after chromatographic separation.



Scheme 2.37. Reagents and conditions: a) cat **228** (10 mol %), **280** (1.3 eq), toluene, 60%; b) i. *n*$BuNH_2$, $NaHCO_3$, MeOH, reflux, 4 hr; ii. $NaBH_4$, 0 °C, 62%; c) $ClCOCH_2Cl$, NEt_3, CH_2Cl_2, 0 °C; d) Amberlyst, acetone, RT, 72% (2steps); e) $AgBF_4$, acetone, 3 days, 44%.

Amine **282** was obtained from aldehyde **281** after reductive amination with *n*-butylamine in good yield. Subsequent acetylation afforded α-chloroamide **283** quantitatively; the crude product was then deprotected by treatment over Amberlyst in acetone at RT and the resulting aldehyde was isolated in excellent yield after chromatography. The synthesis of the cyclic sulfonium salt **284** couldn't be achieved using the previously reported conditions for **278** ($NaClO_4$ in acetone), due to the fact that in this case the sulfur electron pairs are less nucleophilic because of the delocalisation onto the aromatic ring. However, when a silver salt was added ($AgBF_4$) cyclisation was achieved in good yield after a few days at RT, affording salt **284**. With a few milligrams of substrate in hand, a few different reaction conditions were attempted in order to achieve medium ring **285** formation (**Scheme 2.38**). The conditions are summarised in **Table 2.3**.



Scheme 2.38. Reagents and conditions: see **Table 3**.

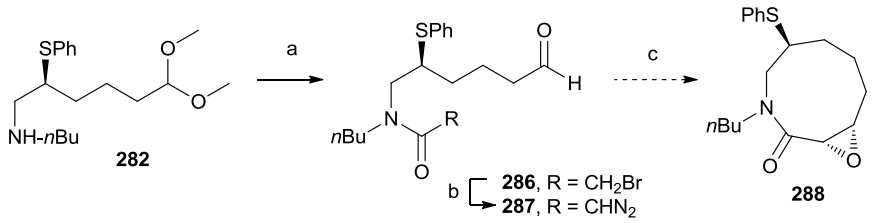
Entry	Conditions	Observations
1	KOtBu, DMSO-d_6, RT	Decomposition after workup
2	NaOH, tBuOH	Decomposition after workup
3	K_2CO_3, CD_3CN	No reaction
4	LDA, THF, -78 °C	Decomposition after workup

Table 2.3

When this substrate was treated in the presence of a KO*t*Bu in DMSO-d_6 at RT (entry 1), analysis of the ^{1}H-NMR sample showed disappearance of the peaks of the diastereotopic protons α to the carbonyl group of the amide. A new singlet peak was observed at 4.2 ppm which could possibly be attributed to the ylide. Unfortunately only decomposition products were observed after work-up of the reaction. A similar behaviour was observed when NaOH in *t*BuOH was used (entry 2). Salt **284** was also treated with the milder base K_2CO_3 in CD_3CN at RT (entry 3) but only starting material was detected by ^{1}H-NMR after 1 hour. The reaction was then heated at

reflux and monitored by ^{1}H-NMR but unfortunately no clear conversion to the product was observed, although the signals for the aldehyde and the protons α to the carbonyl could still be detected after 2.5 hr. A solution of salt **284** in anhydrous THF was also treated with LDA at -78 °C (entry 4) and slowly allowed to warm to RT but unfortunately, after evaporation of the solvent, only decomposition products could be detected by NMR.

The formation of the ylide via Rh catalysed decomposition of the α-diazoester was also investigated for these substrates (**Scheme 2.39**). Amine **282** was converted to α-bromoester **286**. During the amide formation, hydrolysis of the acetal also occurred, probably catalysed by excess HBr generated during the reaction, and aldehyde **286** could be obtained in only one step, albeit in poor yield. Diazoester **287** was synthesised according to the previously used conditions;[149] the material was quickly characterised by NMR and IR in order to avoid decomposition and then readily treated with $Rh_2(OAc)_4$ at RT.



Scheme 2.39. Reagents and conditions: a) $BrCH_2COBr$, Py, CH_2Cl_2, -40 °C, 22%; b), TsNHNHTs, DBU, THF, 0 °C,

The complete disappearance of the starting material was observed by TLC. Purification by column chromatography afforded a mixture of products which could not be identified by NMR analysis. Interestingly no signals were detected for the formation of the α-hydroxyamide **289** (**Fig. 2.2**). However the signal for the aldehyde was still present, therefore excluding the formation of the epoxide.

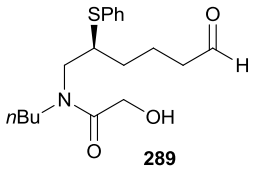
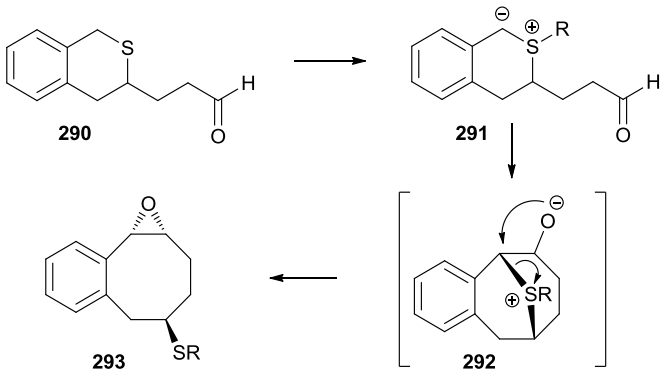


Fig. 2.2

2.2.5 Medium rings via benzyl stabilised ylides

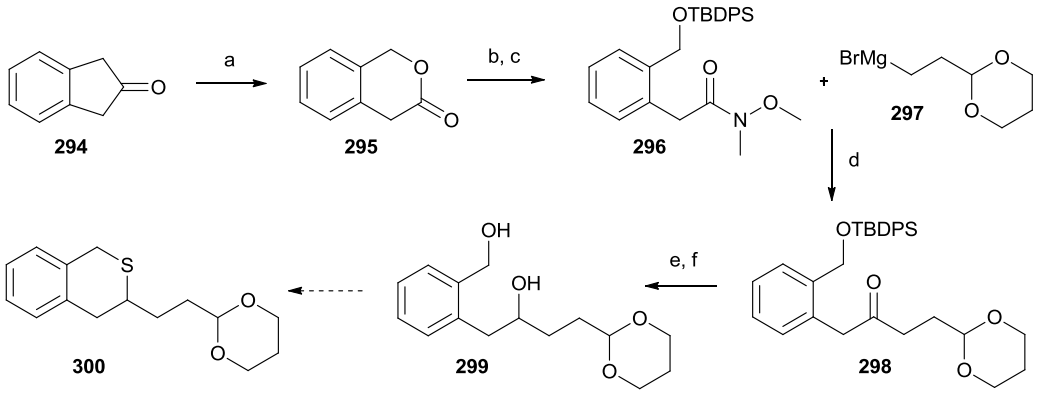
Given the unsuccessful approaches using ester and amide stabilised ylides towards an intramolecular C-C epoxidation we decided to investigate the use of the benzyl-stabilised ylides.[159, 160] As previously discussed at the beginning of this chapter (**Section 2.1**), we envisaged that epoxy-cyclooctane **293** could be obtained from sulfide precursor **290**: the intramolecular reaction of the *in situ* generated S-ylide **291** with the pendant aldehyde group (**Scheme 2.40**) would afford a substituted carbocyclic 8-membered ring.



Scheme 2.40

An advantage of this strategy is the possibility to introduce a suitable substituent on the sulfur (**291**, **R =** Me, Ph) in order to prevent Stevens type rearrangements[147] or a [2,3]-type elimination that had been previously observed for this kind of substrate.[136]

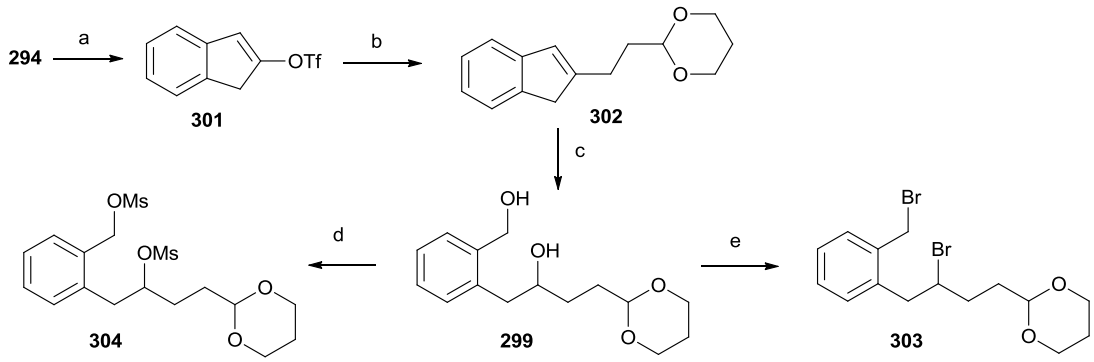
The first synthetic route towards sulfide **300** is shown in **Scheme 2.41**. Commercially available 2-indanone **294** was oxidised to lactone **295** under Baeyer-Villiger conditions. Unfortunately the yield obtained was lower than the one reported in the literature,[161] and any attempt to purify this product by column chromatography resulted in a significant loss of material, possibly due to the high reactivity of the δ-lactone.



Scheme 2.41. Reagents and conditions: a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 24 hr, RT, 27%; b) Me(OMe)NH·HCl, *i*PrMgCl, THF, 0 °C → RT, 24 hr; c) TBDPSCl, Imidazole, DMF, 0 °C → RT, 2 hr, 36% (2 steps); d) **297,** THF, 0 °C → RT, 1 hr; e) $NaBH_4$, MeOH, RT, 1 hr; f) TBAF, THF, RT, 1 hr, 45% (3steps).

Nevertheless lactone **295** was reacted with methoxymethylamine to give Weinreb amide **296**, after protection of the primary alcohol with the *tert*-butyldiphenylsilyl group. Addition of the commercially available Grignard reagent **297** to a solution of amide **296** afforded ketone **298** which was reduced by $NaBH_4$ and finally deprotected to afford diol **299**. Unfortunately the route suffered from low yields, mainly due to the instability of the early lactone intermediate, affording an overall 4% yield over 6 steps. It was clear at this point that the route was unsuitable for scaling up, given that a few grams of diol **299** were needed in order to attempt different conditions for the synthesis of sulfide **300**.

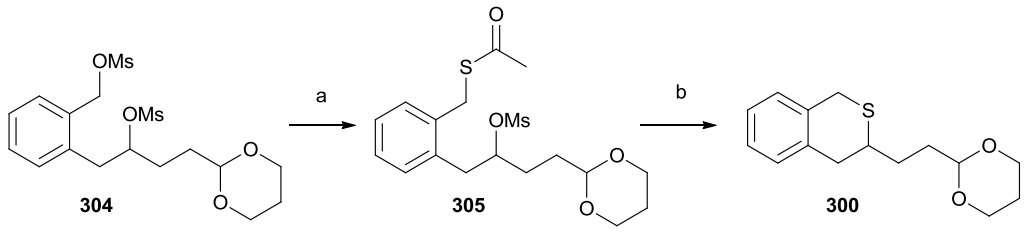
An alternative approach to the synthesis of **300** was therefore attempted (**Scheme 2.42**). This route also started from commercially available 2-indanone; this compound was converted into vinyl triflate **301** in good yields.[162] The latter was then coupled to Grignard reagent **297** in the presence of $Fe(acac)_3$ catalyst according to the procedure developed by Fürstner.[163]



Scheme 2.42. Reagents and conditions: a) LDA, $PhNTf_2$, THF, -78 °C → RT, 73%; b) **297**, $Fe(acac)_3$ (5 mol %), NMP/THF, -30 °C, 77%; c) i. O_3, MeOH, -78 °C; ii. $NaBH_4$, -78 °C → RT, 74%; d) MsCl, NEt_3, DCM, 0 °C, 83%; e) CBr_4, PPh_3, DCM, 0 °C, 1.5 hr, 33%.

This substrate underwent ozonolysis followed by *in situ* reduction with $NaBH_4$ to afford diol **299**. Pleasingly the reaction afforded the desired product in just one step and diol **299** could be easily purified from the non-polar impurities by column chromatography. Diol **299** was initially converted to bis-bromide **303** using Appel conditions (PPh_3/CBr_4) but unfortunately only in modest yields. Conversion to bis-mesylate **304** proved to be more efficient and this substrate was also stable to chromatographic purification.

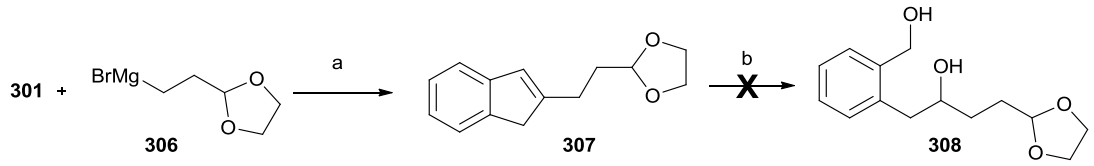
Sulfide **300** was obtained in almost quantitative yield from bis-mesylate **304** in just two steps by reaction of potassium thioacetate with the more reactive mesylate group at the benzylic position to give intermediate **305**, followed by simultaneous acetate deprotection and cyclisation (**Scheme 2.43**).



Scheme 2.43. Reagents and conditions: a) Potassium thioacetate, DMF, RT, 16 hr, 92%; b) K_2CO_3, MeOH, RT, 16 hr, 93%;

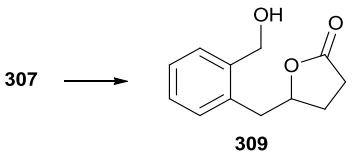
Initial attempts to deprotect the 6-membered ring acetal **300** were unsuccessful, affording only partial deprotection or decomposition. We therefore decided to synthesise diol **308** as a 5-membered ring acetal analogue with the hope that this

substrate would undergo deprotection under milder conditions and in quantitative yields (**Scheme 2.44**).



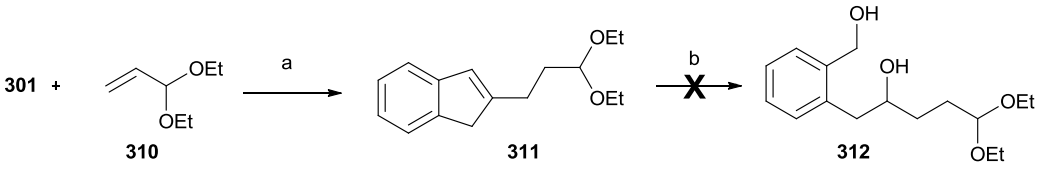
Scheme 2.44. Reagents and conditions: a) $Fe(acac)_3$ (5 mol %), NMP/THF, -30 °C, 66%; b) i. O_3, MeOH, -78 °C; ii. $NaBH_4$, -78 °C → RT, 0%;

Indene **307** was synthesised from vinyl triflate **301** via Fe catalysed coupling with Grignard reagent **306**, obtained *in situ* from the commercially available bromide (**222**). Unfortunately substrate **307** proved to be unstable to ozonolysis, affording mainly γ-lactone **309** (structure assigned by NMR analysis), probably after oxidation of the acetal (**Scheme 2.45**).



Scheme 2.45. Reagents and conditions: i. O_3, MeOH, -78 °C; ii. $NaBH_4$, -78 °C → RT.

Diethyl acetal analogue **311** was also synthesised via Pd catalysed coupling of vinyl triflate **301** with the borane derived from the addition of 9-BBN to acrolein diethyl acetal **310** (**Scheme 2.46**).[164]

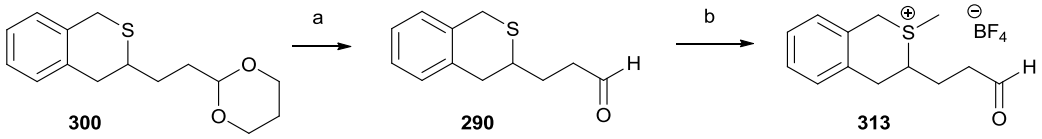


Scheme 2.46. Reagents and conditions: a) i. **310**, 9-BBN, THF 0 °C, 1.5 hr; ii. $PdCl_2$(dppf) (2.5 mol %), K_2CO_3, **301**, THF, 5 hr, reflux, 42%; b) i. O_3, MeOH, -78 °C; ii. $NaBH_4$, -78 °C → RT.

Unfortunately this substrate proved to be unstable to ozonolysis too, affording only decomposition products.

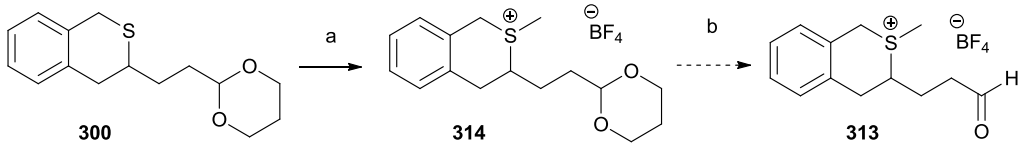
After a few more attempts to deprotect the 6-membered acetal **300**, it was discovered that treatment of this substrate with TFA/water gave almost quantitative conversion to aldehyde **290** (**Scheme 2.47**). With a sufficient amount of deprotected aldehyde **290** in hand, the synthesis of sulfonium salt **313** was attempted. Sulfide **290** was initially treated with a slight excess of MeI/$AgBF_4$ in acetone; the reaction afforded

mainly decomposition products and the formation of salt **313** could only be achieved in traces. This was probably due to self-condensation side reactions of the aldehyde or with the reaction solvent (acetone) promoted by traces of HBF_4.



Scheme 2.47. Reagents and conditions: a) TFA, water, 3 hr, RT, 40%; b) MeI, $AgBF_4$, acetone, RT, 4%.

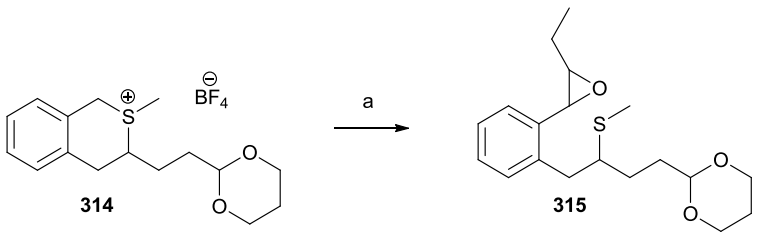
It was therefore decided to optimise the conditions for the salt formation on acetal protected substrate **300**. ^{1}H-NMR studies showed that when this substrate was treated with MeI in CD_2Cl_2, complete conversion to salt **314** couldn't be achieved, even in the presence of a large excess of electrophile, probably due to the reverse dealkylation reaction taking place, caused by nucleophilic attack of the Iodide anion. Addition of silver salts with a non-nucleophilic counterion ($AgBF_4$) allowed the isolation of sulfonium salt **314**, albeit in poor yields (**Scheme 2.48**).



Scheme 2.48. Reagents and conditions: a) MeI, $AgBF_4$, acetone, 24 hr, RT, 19%.

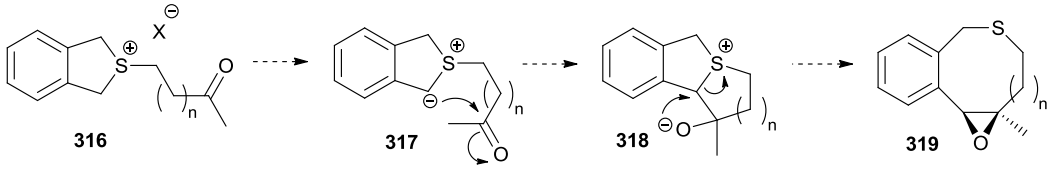
Initial attempts to deprotect the 6-membered ring acetal on sulfonium salt **314** were unsuccessful and unfortunately, due to time constraints, **313** could only be isolated in very small quantities.

In order to determine the viability of the benzyl stabilised ylide formation, sulfonium salt **314** was initially treated with 1 eq of a strong base (*n*BuLi) (**Scheme 2.49**). We hoped that quench of the ylide with propionaldehyde would afford epoxides **315**. ^{1}H and ^{13}C-NMR analysis of the crude mixture showed peaks in the correct region of the spectrum for substituted styrene oxides, alongside impurities.



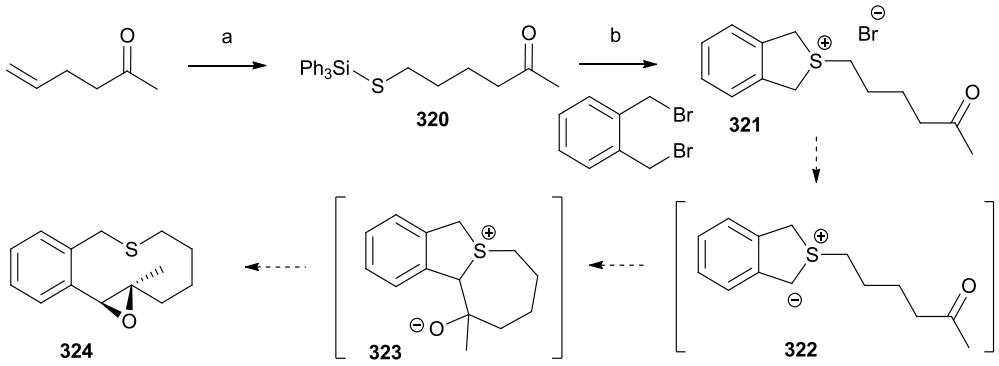
Scheme 2.49. Reagents and conditions: a) i. *n*BuLi (1 eq), - 78 °C, ii. CH_3CH_2CHO, -78 °C → RT.

In parallel with the investigation on the 6-membered ring cyclic ylide derived from **313**, we also envisaged that medium ring **319** could also be obtained from the cyclic 5 member ring sulfonium salt **316** (**Scheme 2.50**). Deprotonation of this substrate should occur at the benzylic position, giving ylide **317**. Nucleophilic attack to the pendant electrophile would then afford bicyclic intermediate **318** followed by the intramolecular C-C epoxidation to give medium ring **319**.



Scheme 2.50

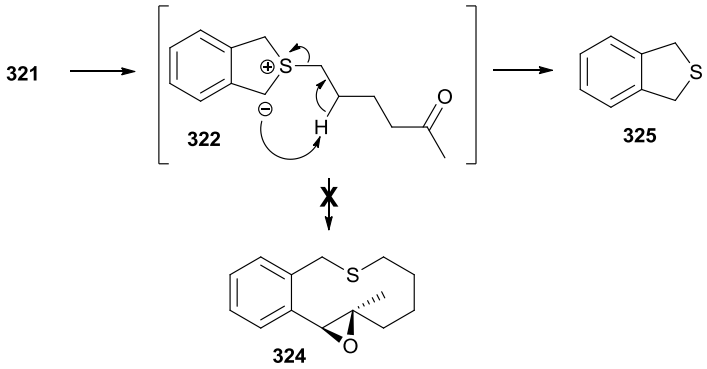
In order to study this approach we chose a precursor which could be readily obtained from commercially available materials in just a few steps. Sulfonium salt **321** was synthesised in only two steps from 5-hexen-2-one; initial radical addition of Ph_3SiH to the double bond afforded sulfide **320** in quantitative yield (**Scheme 2.51**). This intermediate was initially treated with α,α'-dibromo-*o*-xylene in the presence of KOH under phase transfer conditions with the hope to obtain the tandem sequence of desilylation/double alkylation (**321**), ylide formation (**322**) and formation of medium ring **324**.



Scheme 2.51. Reagents and conditions: a) Ph_3SiSH, AIBN (20 mol %), benzene, reflux, 3 hr, quant.; b) α,α'-dibromo-*o*-xylene, KOH, TBAB (5 mol %), DCM, water, RT, 5 days, 20%.

The only product observed after treatment of **320** under basic phase transfer conditions was cyclic salt **321**, which could be isolated in 20% yield after column chromatography.

Salt **321** was initially treated with KO*t*Bu in DMSO-d_6 at RT (**Scheme 2.52**) and the reaction was monitored by ^{1}H-NMR; unfortunately peaks for sulfide **325** were detected,[165] suggesting that the substrate mainly underwent elimination either via the [2,3] type process depicted in **Scheme 2.52** or via an E_2 type mechanism.

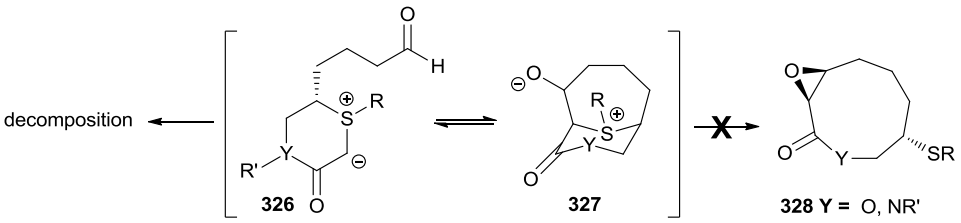


Scheme 2.52. Reagents and conditions: KOtBu (1 eq), DMSO-d_6 or NEt_3 (1 eq), DCM, reflux or LDA (1 eq), THF, -78 °C.

Alongside with the elimination product, peaks in the correct region of both ^{1}H and ^{13}C NMR spectra for an epoxide were detected, although in traces. Unfortunately the expected product could not be isolated from the many impurities generated in the reaction. Treatment of substrate **321** with milder base NEt_3 in DCM at reflux also gave cyclic sulfide **325**. The reaction was also repeated using LDA as a base at -78 °C and the mixture slowly allowed to warm up to RT. Unfortunately only decomposition was once again observed.

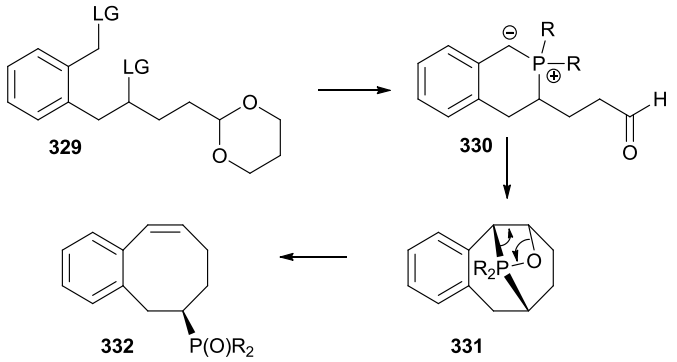
2.3 Phosphorus ylides

We reasoned that one of the potential issues connected with the use of sulfur ylides could be that, once reacted with the pendant electrophile (i.e. aldehyde or α,β-unsaturated carbonyl groups), the bicyclic betaine intermediate **327** could be in equilibrium with its precursor ylide **326** (**Scheme 2.53**). If the reaction leading to medium ring **328** is too slow, this could favour side reactions of ylide **326** eventually leading to the observed decomposition.



Scheme 2.53

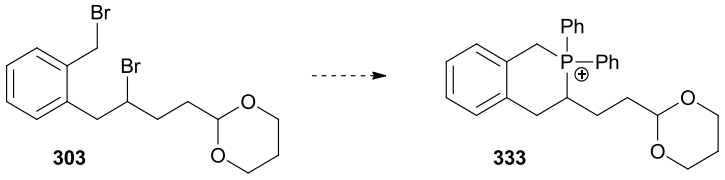
The use of phosphorus ylides in the synthesis of medium rings was therefore investigated. We envisaged that starting from phosphonium ylide **330**, which could be obtained from precursor **329**, an intramolecular Wittig reaction with the pendant aldehyde would furnish medium ring **332** (**Scheme 2.54**), as previously discussed in **Section 2.1**.



Scheme 2.54

We reasoned that once the oxygen-phosphorus bond formed, the reaction would irreversibly afford the endocyclic double bond and the dialkylphosphine oxide substituent.

The synthesis of cyclic phosphonium salt **333** was initially attempted from bis bromide **303** (**Scheme 2.55**) using various conditions summarised in **Table 2.4**.



Scheme 2.55

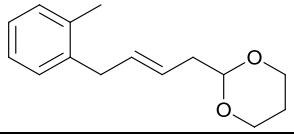
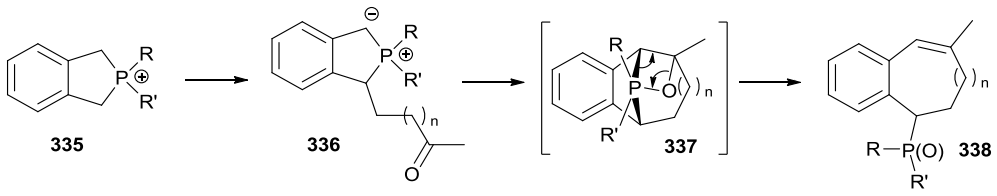
Entry	Reagents	Conditions	Observations
1	Ph_2PSiMe_3[166]	Toluene, reflux	Decomposition
2	Ph_2PH, nBuLi	THF, -78 °C	Decomposition, isolation of traces of compound **334** 
3	Ph_2PH	Neat, RT to 80 °C	Decomposition

Table 2.4.

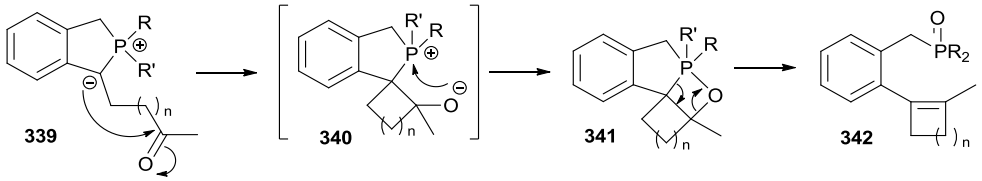
Treatment of bis-bromide **303** with Ph_2PSiMe_3 (entry 1) in refluxing toluene afforded only decomposition products. A similar behaviour was observed when bis-bromide **303** was treated with Ph_2PLi (formed *in situ* from Ph_2PH and *n*BuLi, entry 2) at -78 °C. Among the various side products generated, alkene **334** could be identified. Decomposition was also observed when substrate **303** was treated at RT in neat Ph_2PH and subsequently heated at 80 °C (entry 3).

Failing to obtain phosphonium salt **333**, a shorter route towards the synthesis of 5 membered ring cyclic salt **335** was investigated (**Scheme 2.56**). We envisaged the possibility of alkylating this substrate at the benzylic position with a side-chain bearing a pendant electrophile and subsequently deprotonate the resulting phosphonium salt with a suitable base in order to form the cyclic phosphonium ylide **336** and trigger the proposed domino sequence to give medium ring **338**.



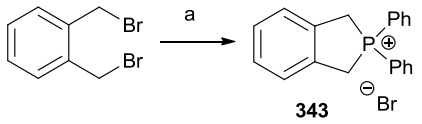
Scheme 2.56

A disadvantage of this strategy could be the concomitant deprotonation at the sterically more hindered benzylic carbon (**339**) which could afford side products **342** (**Scheme 2.57**).



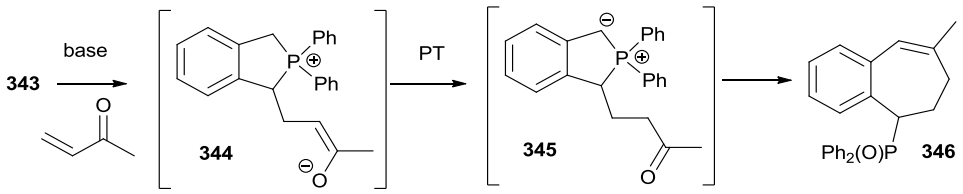
Scheme 2.57

Nevertheless we decided to investigate this route by initially synthesising cyclic diphenylphosphonium salt **343** (**Scheme 2.58**); treatment of α,α'-dibromo-*o*-xylene with Ph_2PSiMe_3 in refluxing toluene[166] afforded salt **343** in good yield.



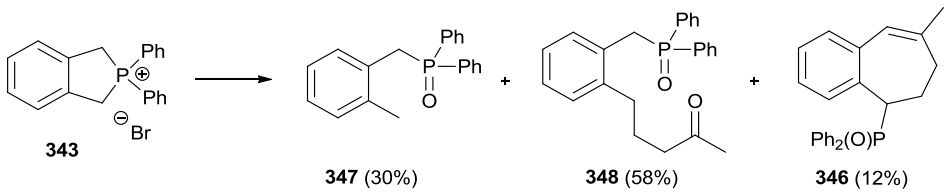
Scheme 2.58. Reagents and conditions: a) Ph_2PSiMe_3, toluene, reflux, 16 hr, 76%;

We envisaged that treatment of the ylide resulting from deprotonation of salt **343** could afford the 7 membered ring **346** via a tandem 1,4-addition of **343** to methyl-vinylketone followed by regeneration of ylide **345** via proton transfer and intramolecular Wittig reaction of the ylide with the pendant ketone (**Scheme 2.59**).



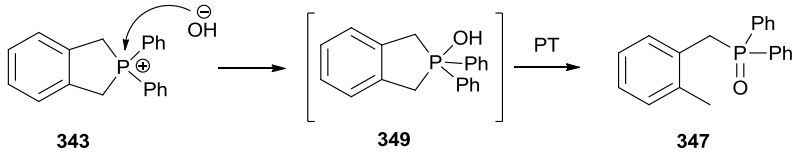
Scheme 2.59

The reaction was initially conducted at 0 °C with the use of KHMDS as a base and the reaction was slowly allowed to warm to RT (**Scheme 2.60**). The main products isolated after column chromatography were phosphine oxides **347** and **348** but, pleasingly, traces of the 7-membered ring product **346** were detected by ^{1}H-NMR (~12%) as an inseparable impurity of the main product **347**.



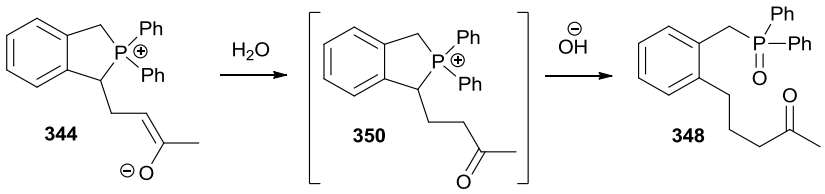
Scheme 2.60. Reagents and conditions: KHMDS (1.05 eq), MVK (1.05 eq), toluene, 0 °C → RT, 24 hr;

Phosphine oxide **347** is likely to form after the nucleophilic attack of hydroxide anions, present either in the starting material (KOH) or generated after water quench, at cyclic phosphonium salt **343** (**Scheme 2.61**).



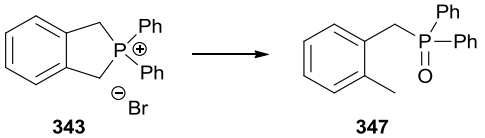
Scheme 2.61

Ketone **348** is likely to form after water quench of enolate **344** (**Scheme 2.62**).



Scheme 2.62

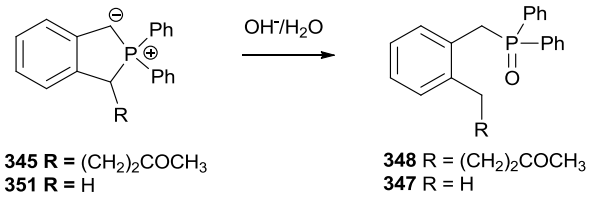
While investigating on this reaction we found that a similar reaction between unsaturated ketones and cyclic aliphatic phosphonium salts to give 7-membered rings via a tandem Michael addition/Wittig reaction had previously been described by Fujimoto.[167] When the reaction was repeated using the conditions reported by these authors (KOtBu or NaH in refluxing THF) the only product that could be isolated after chromatographic separation was phosphine oxide **347** (**Scheme 2.63**).



Scheme 2.63. Reagents and conditions: KOtBu or NaH, MVK, THF, RT → reflux

Despite all conditions attempted, the best conversion obtained for 7-membered ring **346** was only 12% and chromatographic separation of this compound from the main phosphine oxide product **347** couldn't be achieved.

The formation of unwanted phosphine oxides **347** and **348** is likely to be favoured by the stabilisation of the negative charge at the benzylic position of ylides **345** and **351** (**Scheme 2.64**), which makes these intermediates less reactive than the aliphatic phosphonium ylides described by Fujimoto.



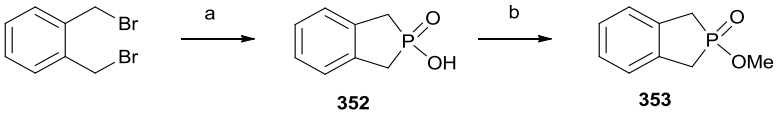
345 R = $(CH_2)_2COCH_3$
351 R = H

348 R = $(CH_2)_2COCH_3$
347 R = H

Scheme 2.64

After water quench the unreacted ylides would then ring open after hydroxide anion attack, giving the corresponding phosphine oxides as the main reaction product.

We also envisaged that a similar approach to medium rings could be carried out by using cyclic phosphonate **355** (**Scheme 2.65**).



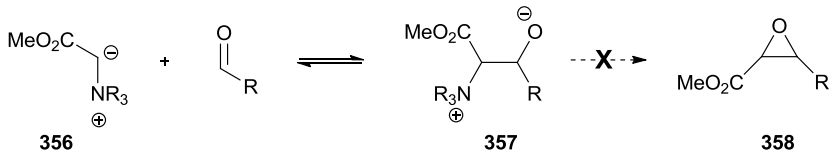
352 **353**

Scheme 2.65. Reagents and conditions: a) $(NH_4)H_2PO_2$, HMDS, Mesitylene, reflux, 16 hr, 20%; b) TsOH (5 mol %), $CH(OMe)_3$, reflux, 8 hr, 10%.

α,α'-Dibromo-*o*-xylene was initially converted into phosphonic acid **352**[168] and then converted into its methyl ester congener **353**. Unfortunately the yields for this process were very low, limiting the amount of cyclic precursor on which to test our proposed approach.

2.4 Nitrogen ylides

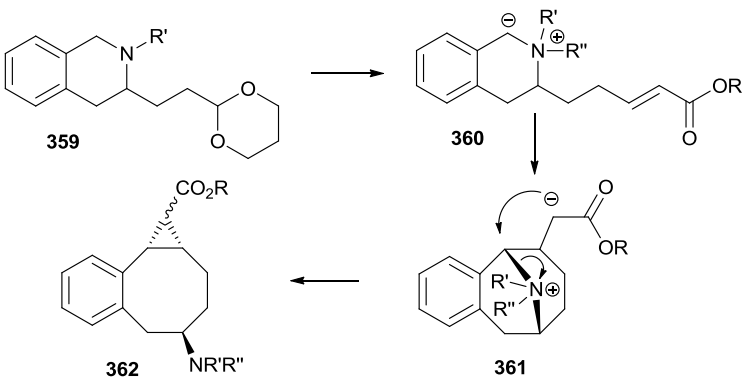
Given the low reactivity of the previously synthesised ylides towards intramolecular reaction with pendant electrophiles it was decided to investigate the use of benzyl stabilised ammonium ylides. Some ammonium ylides have been reported to react with carbonyl compounds to afford epoxides.[169] Unfortunately the scope of this reaction is only limited to benzyl or cyano substituted ammonium ylides and the yields are generally moderate. Stabilised ammonium ylides (**356**) react with carbonyl compounds to form the betaine intermediates **357** but because of the poor leaving group ability of the ammonium ion the energy barrier for the ring closure (**358**) is relatively high (**Scheme 2.66**).



Scheme 2.66

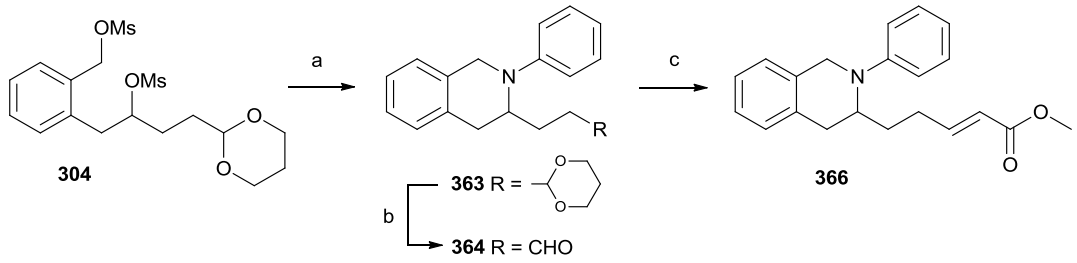
Betaines **357** are therefore very stable and in some instances can be isolated after protonation of the alkoxide anion to give β-hydroxy ammonium salts.[170] Given the reversibility of the betaine formation, side reactions are likely to occur and this accounts for the generally modest yield of the reaction.

Despite the lack of reactivity with carbonyl substrates, ammonium ylides react with α,β-unsaturated compounds to afford cyclopropanes in generally very good yields.[171] It was envisaged that ammonium ylide **360** could be obtained from tetrahydroisoquinoline precursor **359** after deprotonation of the corresponding ammonium salt at the benzylic position (**Scheme 2.67**). The ylide would then attack the pendant α,β-unsaturated ester in a 1,4-Michael type addition to generate bicyclic intermediate **361** which could then ring-close unveiling medium ring **362**.



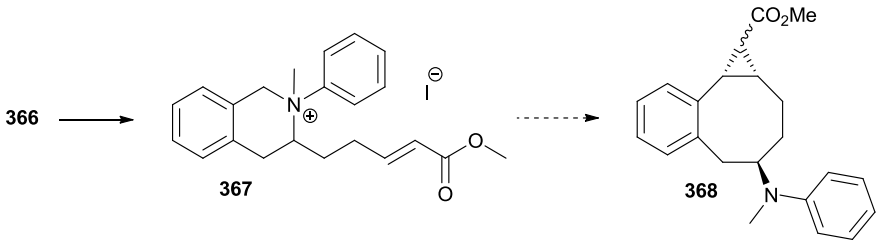
Scheme 2.67

Starting from bis-mesylate intermediate **304** common to the previous route (**Scheme 2.68**), tetrahydroisoquinoline **363** was obtained in moderate yields after treatment with excess aniline.[172] After acid catalysed deprotection of the 6-membered cyclic acetal, aldehyde **364** was treated with phosphonium ylide **365** to give α,β-unsaturated ester **366** in moderate yield.



Scheme 2.68. Reagents and conditions: a) aniline, THF, reflux, 6 hr, 20%; b) TFA, water, 24 hr, RT, 73%; c) Ph_3PCHCO_2Me (**365**), toluene, RT, 24 hr, 31%.

Ester **366** was treated with excess MeI in the presence of Cs_2CO_3 in MeCN at reflux in a sealed vessel in the hope of forming the ammonium ylide in situ. After 16 hr analysis by NMR revealed a 1:1 mixture of the ammonium salt **367** together with unreacted starting material **366** (**Scheme 2.69**). Unfortunately prolonged heating caused decomposition and also no peaks in the region of the cyclopropane were detected by both ^{1}H and ^{13}C NMR.

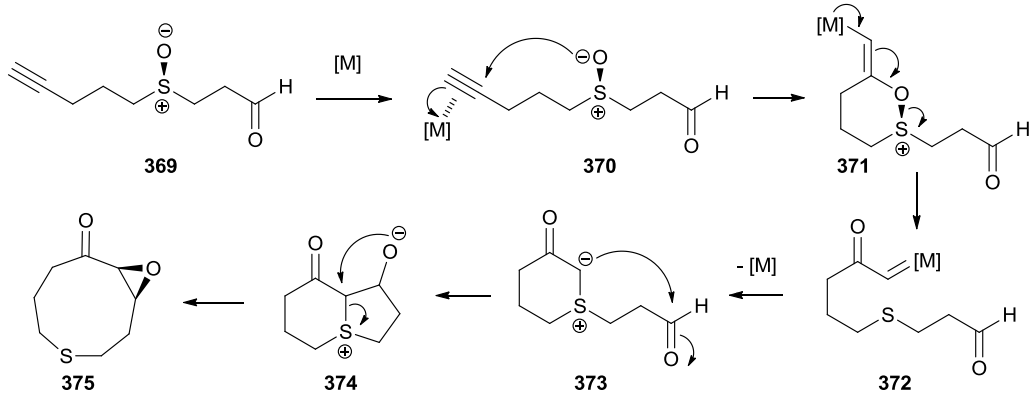


Scheme 2.69. Reagents and conditions: MeI, Cs_2CO_3, MeCN, reflux

The lack of reactivity of substrate **366** could be due to the delocalisation of the nitrogen electron pair onto the phenyl substituent which makes the substrate less reactive towards alkylation and also, once the ammonium salt is formed, the presence of the bulky phenyl substituent could create a steric barrier towards the ylide formation/intramolecular reaction. Unfortunately, due to time constraints, the influence of smaller aliphatic substituents on the nitrogen could not be investigated.

2.5 Medium rings via Au/Pt catalysed in situ ylide formation

Inspired by a recent publication regarding gold and platinum catalysed generation of ylides from bis- homopropargylic sulfoxides,[173] we thought we could apply a similar type of approach for the *in situ* generation of sulfur ylides that would eventually lead to the formation of medium rings as described in **Scheme 2.70**.

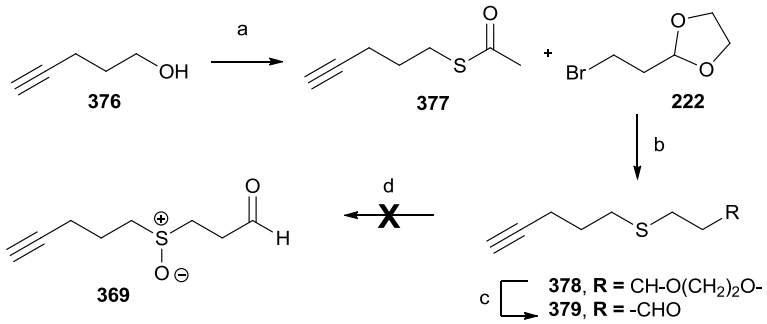


Scheme 2.70

It was proposed that the metal catalysed activation of the triple bond would trigger the initial 6-*exo*-dig attack of the sulfoxide group of **370** to give intermediate **371**,

which would rearrange into stabilised metal carbenoid **372**. The latter would then form cyclic ylide **373** and this would undergo our proposed *domino* sequence to furnish medium ring **375**.

The synthesis of precursor **369** started from commercially available 4-pentyn-1-ol **376** (**Scheme 2.71**). The alcohol was converted to the *S*-acetylated derivative **377** via Mitsunobu reaction. Simultaneous de-acetylation and alkylation with bromide **222** afforded sulfide **378** which was readily deprotected under acidic conditions to give aldehyde **379** in quantitative yields.



Scheme 2.71. Reagents and conditions: a) CH_3COSH, PPh_3, DIAD, THF, 0 °C → RT, 16 hr; b) K_2CO_3, MeOH, 3 hr, RT, 61% (2 steps); c) 2N HCl, THF, 16 hr, RT, quant.; d) MoO_2Cl_2 (1.5 mol %), H_2O_2 (1.05 eq), acetone/water, RT.

Unfortunately attempts to oxidise **379** failed,[173] affording either decomposition products or sulfone **380** (**Fig. 2.3**).

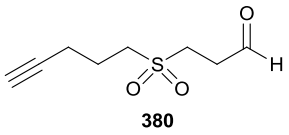
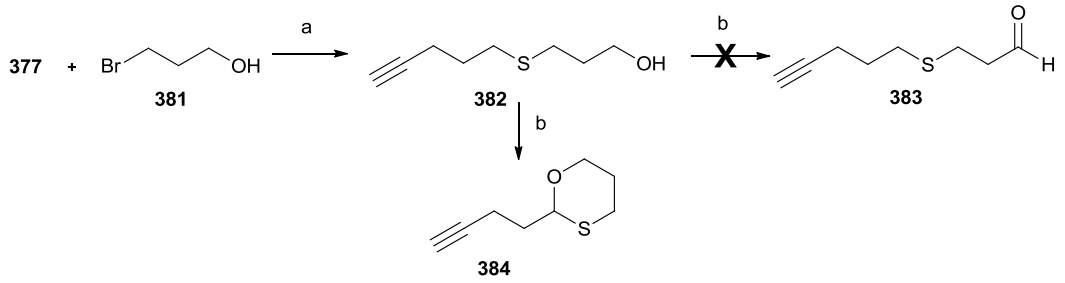


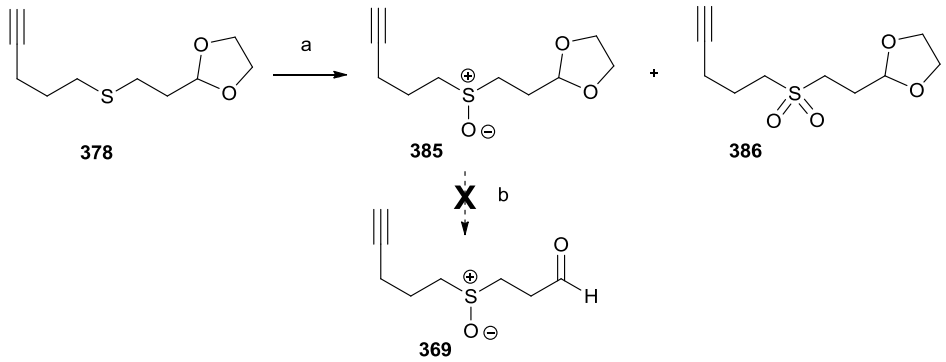
Fig. 2.3

The alternative synthetic route in **Scheme 2.72** was also investigated; alkylation of **377** with 3-bromo-1-propanol (**381**) afforded sulfide **382** in excellent yields but attempted oxidation of the primary alcohol to aldehyde **383** using Swern conditions afforded a complex mixture of products, among which oxathiolane **384**, resulting from a Pummerer type side reaction, could be identified.



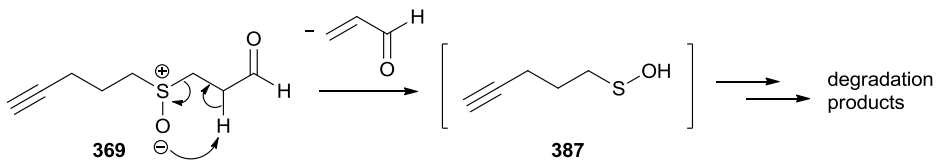
Scheme 2.72. Reagents and conditions: a) K_2CO_3, MeOH, RT, 16 hr, 89%; b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, - 78 °C.

It was therefore decided to oxidise the sulfur before attempting the deprotection step in order to avoid the oxidation of the aldehyde which could interfere in the process (**Scheme 2.78**).



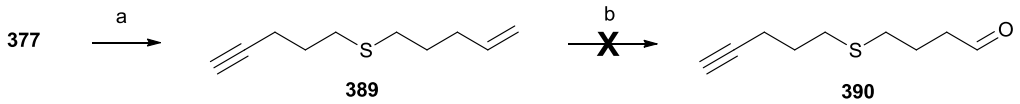
Scheme 2.78. Reagents and conditions: a) MoO_2Cl_2 (1.5 mol %), H_2O_2 (1.05 eq), acetone/water, 4 hr, RT, 46%; b) 2N HCl, THF, RT.

Sulfoxide **385** was obtained in moderate yield from sulfide **378** via Mo(VI) catalysed oxidation, although complete conversion couldn't be achieved without generating substantial amounts of the unwanted sulfone by-product **386**, which, however, could be easily removed by column chromatography. Unfortunately all the attempts to deprotect acetal **385** under acidic conditions were unsuccessful, affording only degradation products. We believe this is due to the intrinsic instability of aldehyde **369** (**Scheme 2.79**); this substrate seems to be prone to intramolecular elimination due to the acidic proton on the carbon α to the aldehyde which could be picked up by the oxygen of the sulfoxide group, generating the volatile acrolein and sulfenic acid **387**. These types of substrates are known to be not very stable and to undergo further degradation reactions.[174]



Scheme 2.79

A different precursor with one more carbon atom between the sulfur and the aldehyde was therefore devised in order to avoid the observed elimination. Starting from S-acyl intermediate **377**, sulfide **389** was obtained in quantitative yield after simultaneous deacetylation and alkylation of **377** with 5-bromopent-1-ene (**388**) (**Scheme 2.80**).

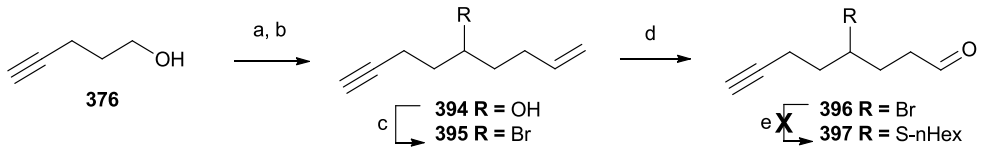


Scheme 2.80. Reagents and conditions: a) CH_2=CH$(CH_2)_3$Br (**388**), K_2CO_3, MeOH, 1.5 hr, RT, quant.; b) i. O_3, CH_2Cl_2, -78 °C, ii. PPh_3 or $K_2OsO_4 \cdot 2H_2O$ cat., $NaIO_4$, 2,6-lutidine, dioxane/water.

Unfortunately a clean oxidation of the alkene to aldehyde **390** couldn't be achieved either via ozonolysis or via Sharpless dihydroxylation followed by $NaIO_4$ oxidation without oxidising the sulfide. In fact, NMR analysis of the crude mixture revealed a mixture of oxidised products, mainly sulfones **391** and **392** (**Fig. 2.4**).

Fig. 2.4

The synthesis of branched sulfide **396** was therefore investigated (**Scheme 2.81**). The route began from commercially available 4-pentyn-1-ol **376**; Swern oxidation of the alcohol followed by addition of homoallylic magnesium bromide **393** afforded alcohol **394** in good yields.



Scheme 2.81. Reagents and conditions: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C; b) $CH_2=CH(CH_2)_2MgBr$ (**393**), THF, 2 hr, 40 °C, 79% (2 steps); c) CBr_4, PPh_3, CH_2Cl_2, 0 °C → RT, 24 hr, 66%; d) $K_2OsO_4 \cdot 2H_2O$ cat., $NaIO_4$, 2,6-lutidine, dioxane/water, 38%, e) nHex-SH, K_2CO_3, MeOH or NaH, THF

Conversion to bromide **395** was achieved under Appel conditions in good yields; this substrate was subsequently oxidised to aldehyde **396** in one step (dihydroxylation followed by $NaIO_4$ mediated oxidation/cleavage) in moderate yields. Unfortunately all the attempts to convert the bromide to sulfide **397** were unsuccessful, affording as main product a racemic mixture of cyclopropanes **398** (the structure was tentatively assigned from ^{1}H-NMR data of the crude mixture, **Fig. 2.5**).

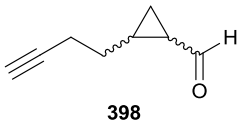
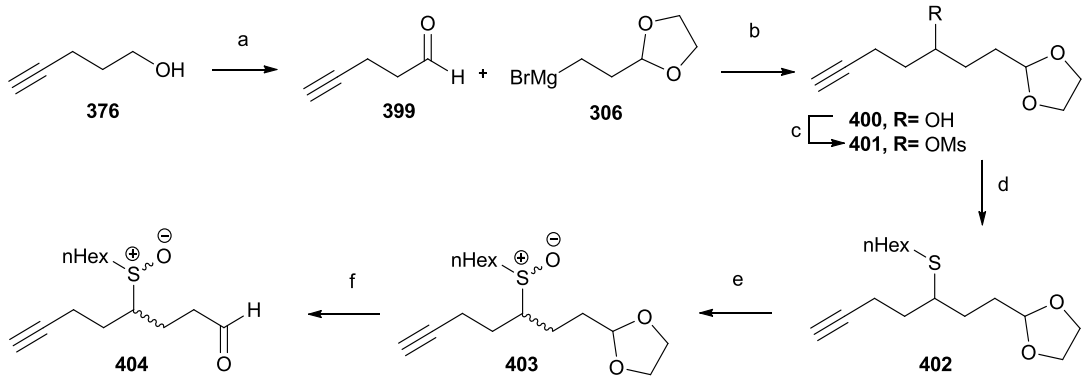


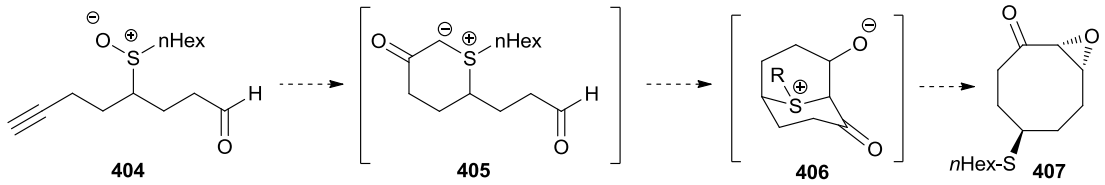
Fig. 2.5

A different approach was therefore devised (**Scheme 2.82**); secondary alcohol **400** was obtained in two steps after Swern oxidation of commercially available 4-pentyn-1-ol **376** to aldehyde **399** and addition of Grignard reagent **306**.



Scheme 2.82. Reagents and conditions: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C; b) **306**, THF, 45 °C, 2 hr, 49% (2 steps); c) MsCl, NEt_3, CH_2Cl_2, 0 °C → RT, quant; d) nHexSH, K_2CO_3, DMF, RT, 2 hr, 19%; e) MoO_2Cl_2 (1.5% mol), H_2O_2, acetone, water, RT, 2 hr, 94%; f) 2N HCl, THF, RT, 24 hr, 79%.

Conversion of alcohol **400** into mesylate **401** followed by reaction with *n*-hexanethiol under basic conditions afforded sulfide **402**, albeit in poor yields. Molybdenum catalysed oxidation gave sulfoxide **403** in almost quantitative yields. This intermediate was isolated as a ~ 1:1 mixture (^{1}H-NMR) of diastereoisomers which could be separated and fully characterised on a small scale by column chromatography. The following acid catalysed deprotection of the cyclic acetal afforded aldehyde **404** in good yields. With sufficient quantities of this intermediate in hand, our proposed tandem double cyclisation/fragmentation approach was attempted on this substrate as a precursor of 8-membered ring **407** (**Scheme 2.83**).



Scheme 2.83. Reagents and conditions: Au and Pt catalysts (see text)

When precursor **404** was stirred in DCM at RT in the presence of Gold (I) ($Ph_3PAuNTf_2$) and gold(III) catalysts (**408, Fig. 2.6**), only SM **404** could be detected by ^{1}H-NMR.

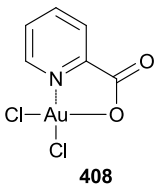
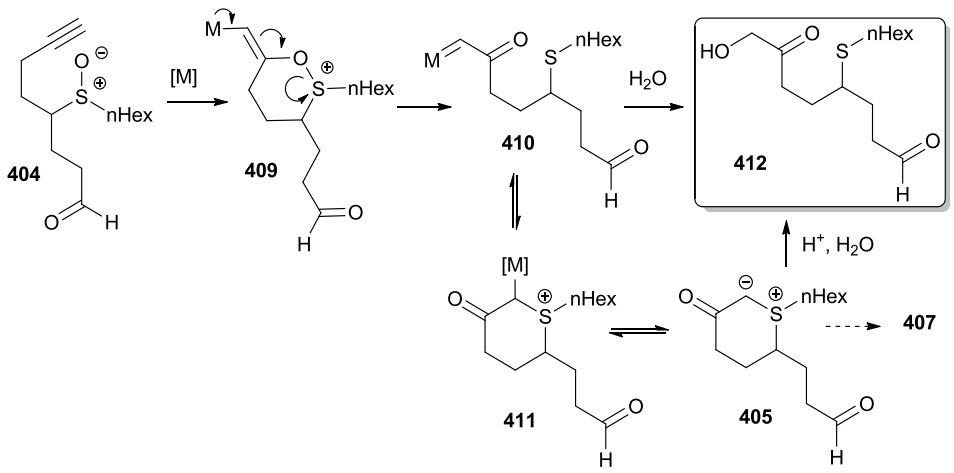


Fig. 2.6

Other attempts were carried out by heating the reaction for prolonged times at reflux and under microwave irradiation but with no success.

The use of $PtCl_2$ as a catalyst was also unsuccessful, leading only to unreacted starting material ($CDCl_3$, RT) .When substrate **404** was treated with $PtCl_4$ in DCE, complete disappearance of the starting material was observed by TLC after a stirring for a few days under inert atmosphere, initially at RT and then at reflux for 24 hr. After purification by column chromatography the only isolated material was hydroxyketone **412** (**Scheme 2.84**).

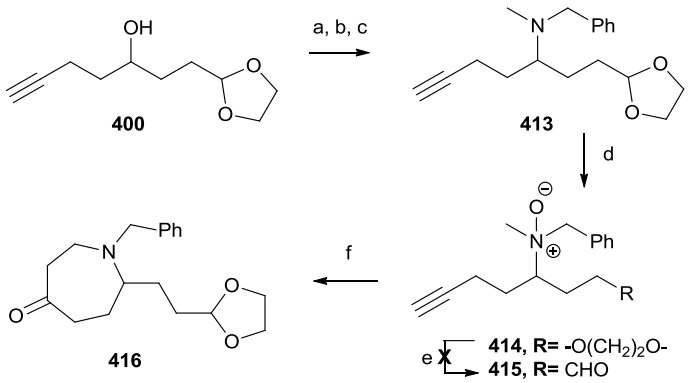


Scheme 2.84

This observation could be consistent with the above mechanism (**Scheme 2.84**): initial activation of the triple bond by the metal would lead to formation of metal carbenoid **410**. This intermediate could react with the sulfide group to generate the cyclic ylide **405**. Despite the quite harsh conditions used (24hr at reflux in DCE) the latter intermediate seemed to be unable to undergo our proposed *domino* sequence towards the formation of medium ring **407**, affording instead hydroxylketone **412** after purification on silica. Carbenoid intermediate **410** could also insert into water, which could be present in traces in the reaction solvent to give the same product.

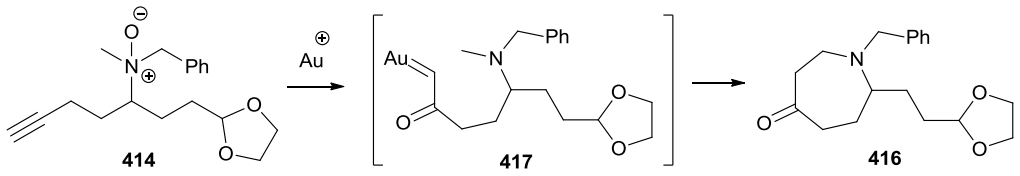
Since the sulfoxide based approach was not successful, we believed that the use of the more reactive N-ylides could trigger the proposed domino sequence. In the same way as sulfur ylides, ammonium ylides could be generated *in situ* via metal catalysed rearrangement of bis-homopropargylic N-oxides.[175]

Amine **413** was synthesised in three steps from alcohol **400** (**Scheme 2.85**) by Swern oxidation followed by reductive amination with benzylamine and alkylation of the nitrogen with MeI. Oxidation to N-oxide **414** was achieved in moderate yields using *m*CPBA. Unfortunately attempts to deprotect the cyclic acetal were unsuccessful.



Scheme 2.85. Reagents and conditions: a) a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C → RT, 16 hr; b) $BnNH_2$, $Na(OAc)_3BH$, AcOH, DCE, RT - 24hr, 55 °C - 2 hr; c) MeI, K_2CO_3, MeCN, reflux, 3 hr, 11% (3 steps); d) *m*CPBA, CH_2Cl_2, 0 °C, 20 min, 55%; e) PPTS, acetone/water; f) $Ph_3PAuNTf_2$, CH_2Cl_2, RT, 15%.

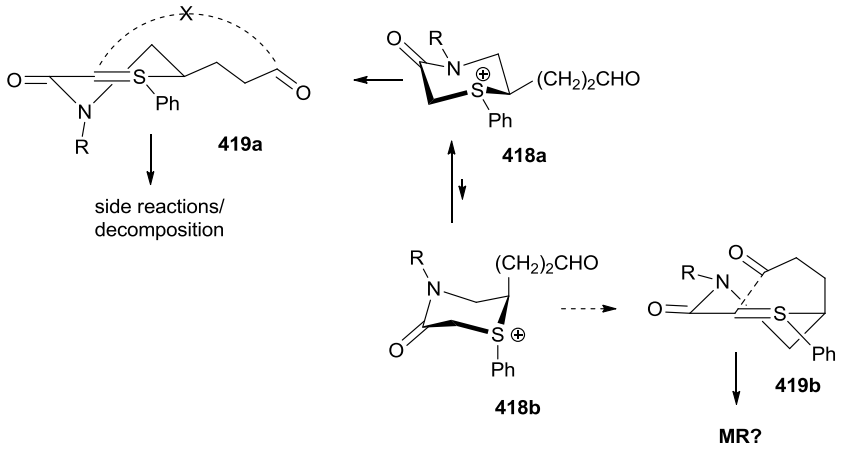
By treating intermediate **414** with gold catalyst it was reasoned that both alkyne activation towards intramolecular nucleophilic attack and acetal deprotection could be achieved, given the Lewis acidity of gold cations. To our surprise, only azepanone **416** was isolated, albeit in low yield, after insertion of the *in situ* generated gold-carbenoid **417** selectively into the methyl CH bond (**Scheme 2.86**).[175]



Scheme 2.86

2.6 Conclusions/Future work

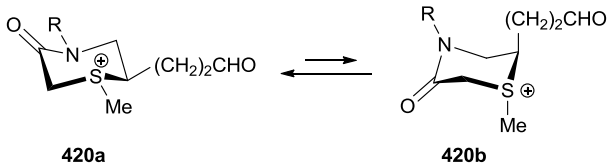
Unfortunately all the attempts of generating medium rings via sulfur and nitrogen ylides didn't afford the expected products. We believe that one of the possible explanations is shown in **Scheme 2.87**.



Scheme 2.87

When cyclic sulfonium salt is formed, between the two possible conformations the most likely to be generated is **418a** in which both substituents sit in an equatorial position. The high barrier for the pyramidal inversion of sulfonium[140] and the axial orientation of both substituents of **418b** would make this conformation less favourable. Unfortunately it's only in this conformation that the chain containing the aldehyde functionality sits in an axial orientation which seems to be necessary for the ylide reactive carbon of **419b** to be in close proximity to the electrophilic aldehyde in order to react. The observed decomposition and side reactions could originate from ylide **419a**, generated from salt **418a**, in which the reactive ylide carbon is too far from the aldehyde to react and therefore undergoes side reactions.

A possible solution worth investigating is the introduction of a methyl substituent on the sulfur (**Scheme 2.88**). The presence of a smaller substituent would lower the energy barrier between the two possible conformations **420a** and **420b**, therefore the ylide generated from this salt is more likely to be in the reactive conformation with all substituents in the axial orientation.



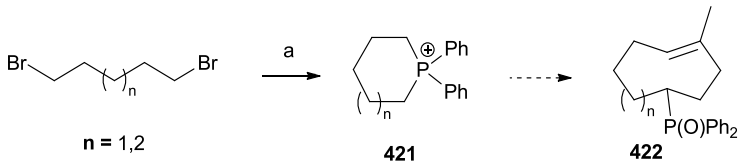
Scheme 2.88

Amongst all different types of ylides investigated in this thesis, the only approach that gave traces of a medium ring product, however, was the one based on the use of

phosphorus ylides (**Scheme 2.60**). Unfortunately due to time limitations this type of approach could not be investigated in depth, nevertheless we would like to disclose a few ideas and approaches for future work.

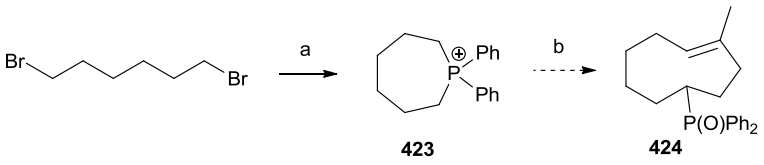
2.6.1 Phosphorus Ylides

Given the successful results obtained by Fujimoto with cyclic aliphatic phosphonium salts,[176] we believe the 8 and 9-membered cycloalkenes **422** could be obtained from cyclic aliphatic phosphonium salts **421** and methylvinylketone via tandem Michael addition/Wittig reaction (**Scheme 2.89**), as previously described in **Section 2.3**.



Scheme 2.89

Cyclic phosphonium salts **421** could be easily obtained from commercially available bis-bromides and Ph_2PSiMe_3. Preliminary studies showed that phosphonium salt **423** was easily obtained from commercially available 1,6-dibromohexane, albeit in low yield (**Scheme 2.90**).



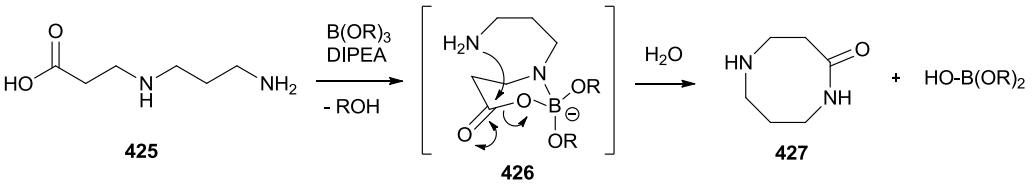
Scheme 2.90. Reagents and conditions: a) Ph_2PSiMe_3, toluene, reflux, 16 hr, 32%; b) KHMDS (1.05 eq), MVK (1.05 eq), toluene, RT→reflux

Initial attempts to treat this substrate with KHMDS and MVK under the previously reported conditions failed to give medium ring **424**. Unfortunately, due to time limitations this approach could not be further pursued.

2.6.2 Borate mediated amide formation

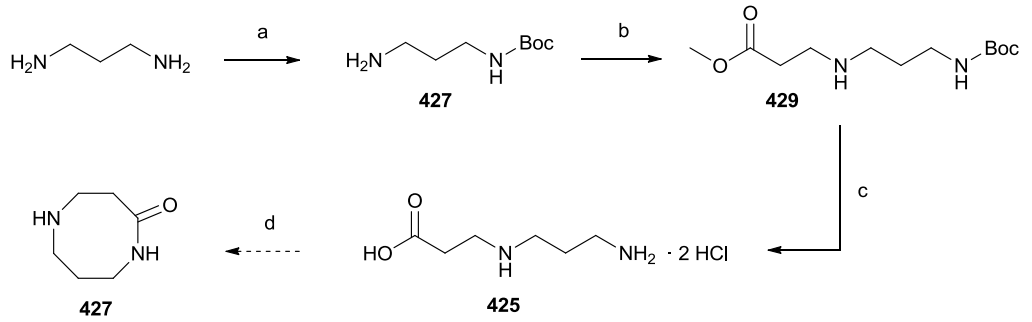
It has been recently found that boric acid or simple arylboronic acids are able to mediate the formation of amide bonds between carboxylic acids and amines.[177-181] Previous results in our research group also showed that borate esters and in particular tris(2,2,2-trifluoroethyl)-borate are able to catalyse the formation of primary amides in good yields.[182]

We thought this approach could be used for the formation of medium rings as outlined in **Scheme 2.91**; precursor **425** would react with the borate ester to give 6-membered ring cyclic borate intermediate **426**. We believe that at this stage the carboxy terminus would be activated towards the nucleophilic attack of the pendant amino group to give medium ring lactam **427**.



Scheme 2.91.

The synthesis of precursor **425** started from the *tert*-butylcarbamate protection of commercially available 1,3-diaminopropane to give monoamine **427** in good yield (**Scheme 2.92**). This substrate underwent Michael addition to methyl acrylate affording ester **429** in moderate yield. Pleasingly, Boc deprotection and ester hydrolysis could be achieved in a single step by treatment of **429** with 6 N HCl. Azeotropic removal of water followed by trituration in Et_2O allowed the isolation of the hydrochloride salt of amine **425** in excellent yield.



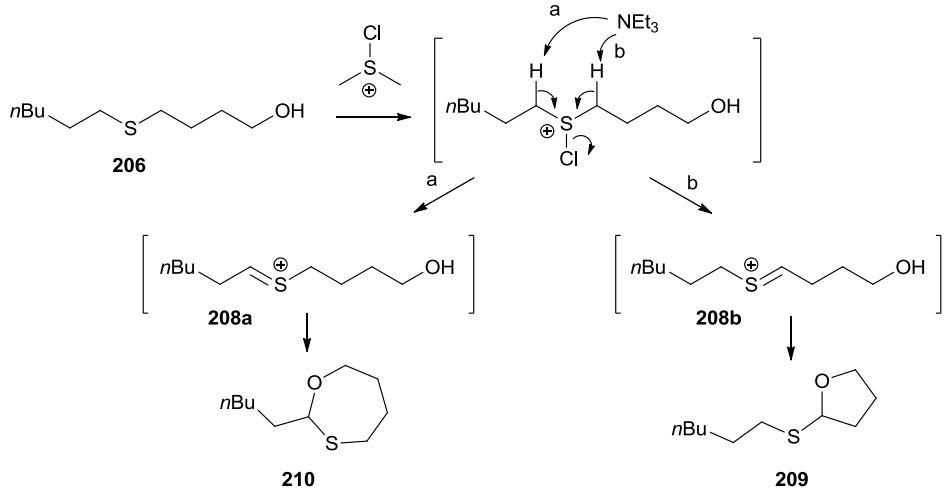
Scheme 2.92. Reagents and conditions: a) Boc_2O, dioxane, RT, 1.5 hr, 54%; b) CH_2=$CHCO_2Me$, MeCN, reflux, 24 hr, 40%; c) 6 N HCl, 80 °C, 24 hr, 90%; d) DIPEA (2 eq), $B(OCH_2CF_3)_3$ (2 eq), MeCN, reflux

Substrate **425** was initially treated with 2 eq of DIPEA to generate the free amine *in situ* and subsequently treated with $B(OCH_2CF_3)_3$ with the hope that it would undergo the proposed N-assisted, borate mediated amide bond formation. NMR analyses of the reaction showed the disappearance of the SM but the interpretation of the spectra was difficult due to the presence of broad peaks. Further studies will be required in order to determine the viability of this approach for the synthesis of MR.

2.7 Miscellaneous

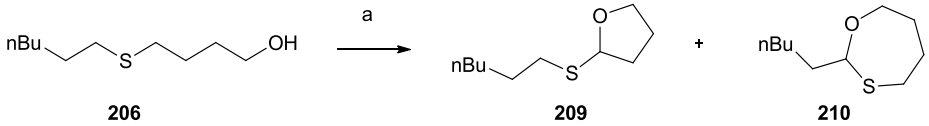
2.7.1 Studies on intramolecular Pummerer rearrangement

When alcohol **206** was oxidised under Swern conditions, the main by-products isolated after the reaction were tetrahydrofuran **209** and oxathiepan **210** (**Scheme 2.10**). These products are likely to result from the intramolecular Pummerer type rearrangement described in **Scheme 2.93**.



Scheme 2.93

In order to prove the above assumption, alcohol **206** was treated with NCS and NEt_3 (**Scheme 2.94**). After chromatographic purification tetrahydrofuran **209** and oxathiepan **210** were isolated as main products, in poor overall yield.

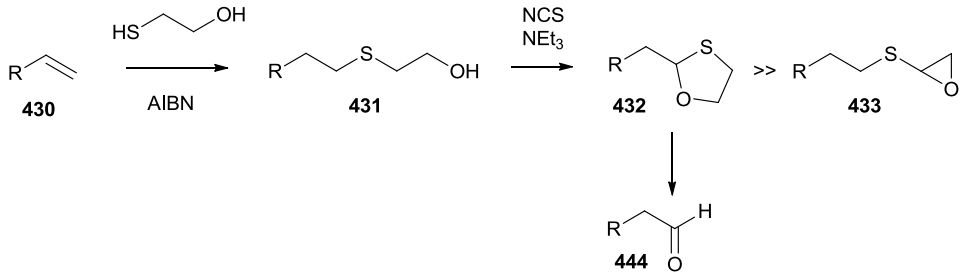


206 **209** **210**

Scheme 2.94. Reagents and conditions: a) NCS, NEt_3, toluene, RT, **209** (5%), **210** (25%); or NCS, NEt_3, CH_2Cl_2, 0 °C, **209** (41%),

When the reaction was performed in CH_2Cl_2 at 0 °C, the only product observed, apart from unreacted starting material, was the 5-membered ring acetal **209** in moderate yield.

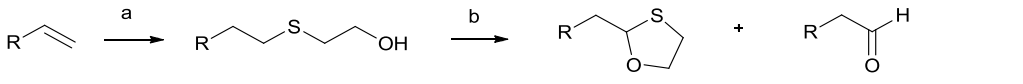
It was reasoned that this reaction could be exploited for a regioselective oxidation of terminal alkenes (**Scheme 2.95**). Mercaptoethanol was initially chosen as the thiol because it was envisaged that, after radical addition to terminal alkene **430** to give sulfide **431**, the 2-carbon spacer should preferentially lead to the formation of 5-membered rings O,S-acetals **432** over the 3 membered rings **433**. Acetals **432** could then be readily hydrolysed to give aldehydes **434**.



430 **431** **432** **433** **444**

Scheme 2.95

Commercially available alkenes **445a** (allylbenzene) and **445b** (4-allylanisole) were reacted with 2-mercaptoethanol in the presence of radical initiator AIBN to give sulfides **446a** and **446b** in quantitative yields (**Scheme 2.96**).



445a, R = Ph
445b, R = 4OMe-Ph

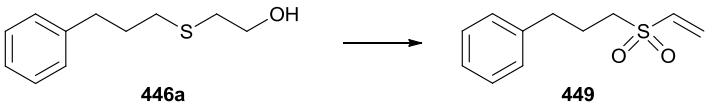
446a, R = Ph (93%)
446b, R = 4OMe-Ph (quant.)

447a, R = Ph (10%)
447b, R = 4OMe-Ph (0%)

448a, R = Ph (29%)
448b, R = 4OMe-Ph (17%)

Scheme 2.96. Reagents and conditions: a) $HS(CH_2)_2OH$, AIBN (20 mol %), MeCN, reflux, 6 hr; b) NCS, NEt_3, toluene, RT.

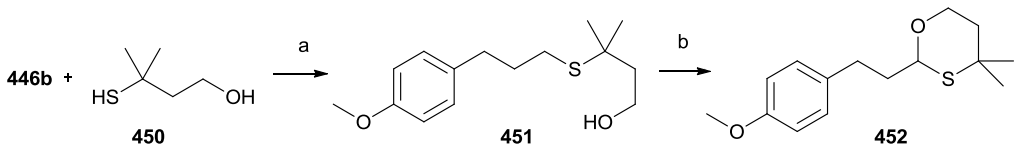
Initial experiments on sulfide **446a** using NCS and NEt_3 in toluene gave a mixture of thioacetal **447a** and its hydrolysed counterpart aldehyde **448a** in modest yields after purification by chromatography. When sulfide **446b** was treated with NCS and no base the only product isolated was aldehyde **448b** in low yields. Interestingly when the reaction was performed in CH_2Cl_2 at 0 °C using excess NCS (1.5 eq) the main product isolated was vinylsulfone **449** (**Scheme 2.97**) in moderate yield.



Scheme 2.97. Reagents and conditions: i. NCS (1.5 eq), CH_2Cl_2, 1 hr, 0 °C, ii. NEt_3, 0 °C → RT, 24 hr, 32%.

Unfortunately the yields observed for the reaction were very modest due to the generation of many unidentified side products (TLC), possibly due to the formation of the reactive 3-membered ring thioacetal **433** (**Scheme 2.95**).

It was therefore decided to attempt the same reaction on substrate **431** in which the presence of the *gem*-dimethyl substituents on one carbon next to the sulfur would prevent the formation of the smaller ring and give preferentially the 6-membered ring thioacetal **452** (**Scheme 2.98**). Unfortunately, radical addition of commercially available thiol **450** to the double bond of 4-allylanisole **446b** furnished substituted sulfide **451** in very low yields.



Scheme 2.98. Reagents and conditions: a) AIBN (20 mol %), MeCN, reflux, 16 hr, 11%; b) NCS, NEt_3; or $PhI(OAc)_2$

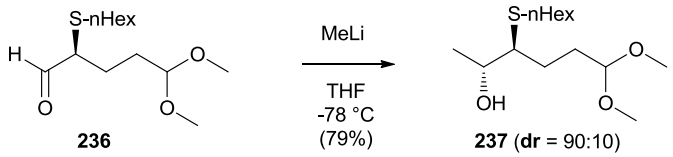
The formation of the 6-membered ring acetal **452** was followed by ^{1}H-NMR: when NCS was used no peak for an acetal was detected whereas when $PhI(OAc)_2$ was used as oxidant the acetal formation reached 27% after 1 day of stirring at 50°C and it only increased to 31% after 2 days. Unfortunately both the yields for the formation of sulfide **451** and the cyclisation to give **452** were unsatisfactory, therefore this approach was abandoned.

3. Synthesis of Enantiomerically Enriched Secondary Alcohols

3.1 Introduction

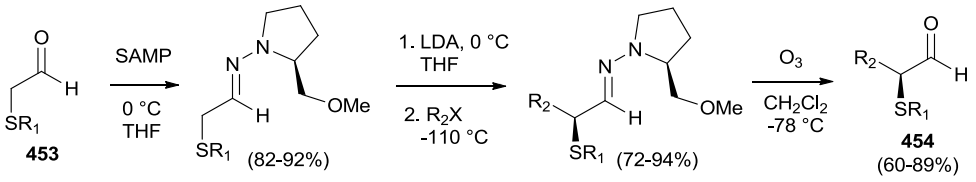
The synthesis of enantiomerically enriched/pure secondary alcohols has long been a challenging target in organic chemistry as many natural products and a large number of commercialised drugs contain hydroxyl groups in a determined configuration. Current synthetic methods entail enantioselective reduction of prochiral ketones[183, 184] and enantioselective addition of organoboron or organometallic reagents to aldehydes.[185-188]

As previously discussed in **Section 2.2.2**, during the synthesis of hydroxysulfide **237**, precursor in the synthesis of Cephalosporolide D, a good level of diastereoselectivity was achieved by the addition of MeLi to α-sulfenylaldehyde **236** to afford *anti*-hydroxysulfide **237** (**Scheme 3.1**).



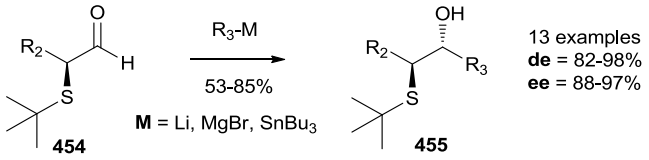
Scheme 3.1

Although previously unreported in the case of MeLi, nucleophilic additions of organometallic reagents to racemic α-sulfenylated aldehydes to give racemic vicinal thioether-alcohols with high levels of diastereoselectivity have been described in the literature.[189, 190] In a publication by Enders good levels of diastereoselectivity were also reported for the addition of carbon nucleophiles to optically active α-sulfenylaldehydes.[145] Optically active aldehydes **454** were prepared from aldehydes **453** according to the SAMP/RAMP hydrazone methodology[191] described by the same author (**Scheme 3.2**).



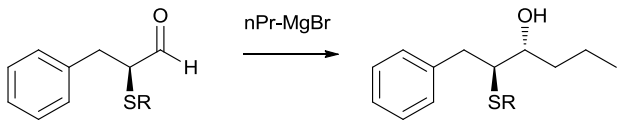
Scheme 3.2

Aldehydes **454** were subsequently treated with a range of different carbon nucleophiles to afford the vicinal hydroxysulfides **455** with generally good levels of diastereo and enantioselectivity (**Scheme 3.3**).



Scheme 3.3

The author also investigated the influence of sulfur substituent on the diastereoselectivity of the process (**Scheme 3.4**). Not surprisingly bulkier substituents (R= *t*Bu and Ph) gave the best diastereoselectivities.

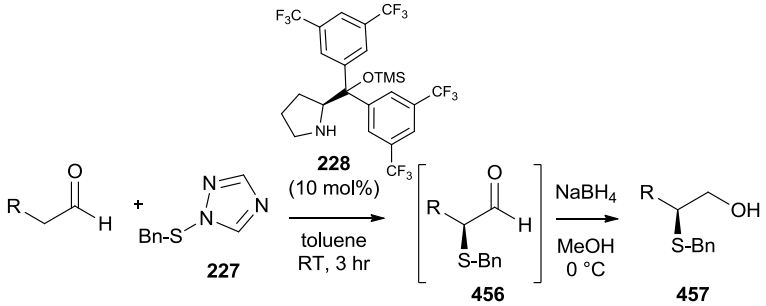


R	Yield	dr
*t*Bu	55%	98:2
*i*Pr	63%	87:13
Ph	54%	95:5
Bn	58%	91:9

Scheme 3.4

Even though this type of approach furnishes vicinal thioether-alcohols in good yields and with good level of selectivity, the whole synthetic sequence requires many steps, especially for the preparation of optically active aldehydes.

Recent advances in organocatalytic procedures for the synthesis of chiral α-sulfenylaldehydes developed by Jørgensen[144] allow the synthesis of these intermediates in only one step and with only sub-stoichiometric amounts of the proline-based chiral auxiliary **228** (**Scheme 3.5**).

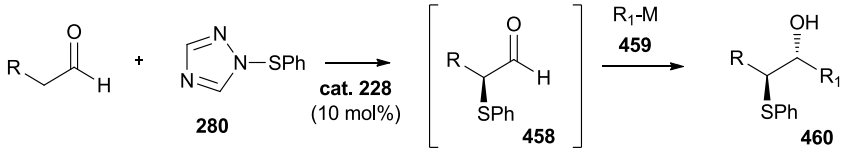


R	Yield	ee
*t*Bu	83%	97
*i*Pr	81%	98
All	64%	96
Me	60%	95
Bn	94%	97

Scheme 3.5

Although intermediate aldehydes **456** were not isolated because of racemisation problems occurring during chromatography, excellent results in terms of enantioselectivity of the corresponding alcohols **457** were achieved through this procedure.

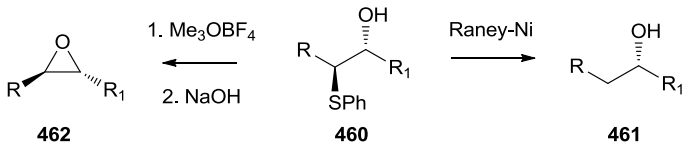
Encouraged by our promising initial results and by the previous observations reported by Enders, we thought we could exploit the exceptional diastereoselectivity exerted by α-sulfenylaldehydes **458**, readily synthesised via Jørgensen organocatalytic procedure, for the addition of carbon nucleophiles (**459**) in order to obtain sulfido-alcohols **460** with high levels of diastereoselectivity (**Scheme 3.6**).



Scheme 3.6

According to Enders, a phenyl substituent on the sulfur atom should give very good levels of diastereoselectivity during the addition step (**Scheme 3.4**). We therefore decided to investigate the sulfenylation of aldehydes using electrophilic species **280** which has never been previously reported for the enantioselective sulfenylation of aldehydes.

With a highly diastereoselective procedure in place for the synthesis of **460**, enantiomerically enriched secondary alcohols **461** could subsequently be obtained after Raney-Ni reduction (**Scheme 3.7**).



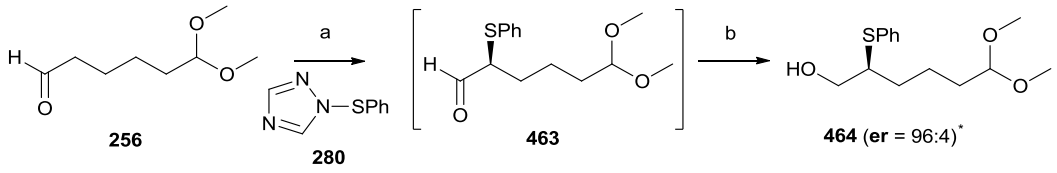
Scheme 3.7

Moreover, further manipulation of hydroxysulfides **460** could also lead to the formation of chiral epoxides **462**.[192]

3.2 Synthesis of enantiomerically enriched secondary alcohols

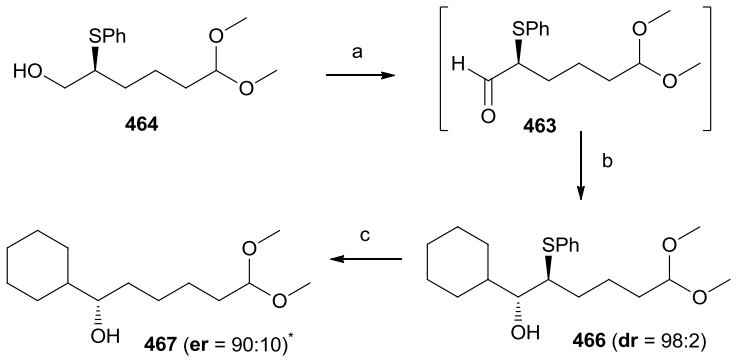
3.2.1 Proof of concept

In order to prove the viability of the aforementioned approach, phenyl substituted sulfenyl-triazole **280** was initially synthesised[158] and immediately used in the reaction with aldehyde **256** according to the Jørgensen organocatalytic procedure. The product of the reaction was not isolated but initially reduced in situ with $NaBH_4$ to give alcohol **456** (**Scheme 3.8**).



Scheme 3.8. Reagents and conditions: a) Cat. **228** (10 mol %), Toluene, RT, 12 hr; b) $NaBH_4$, MeOH/Toluene, RT, 57% ; (*) determined by Mosher's esters analysis (see Appendix)

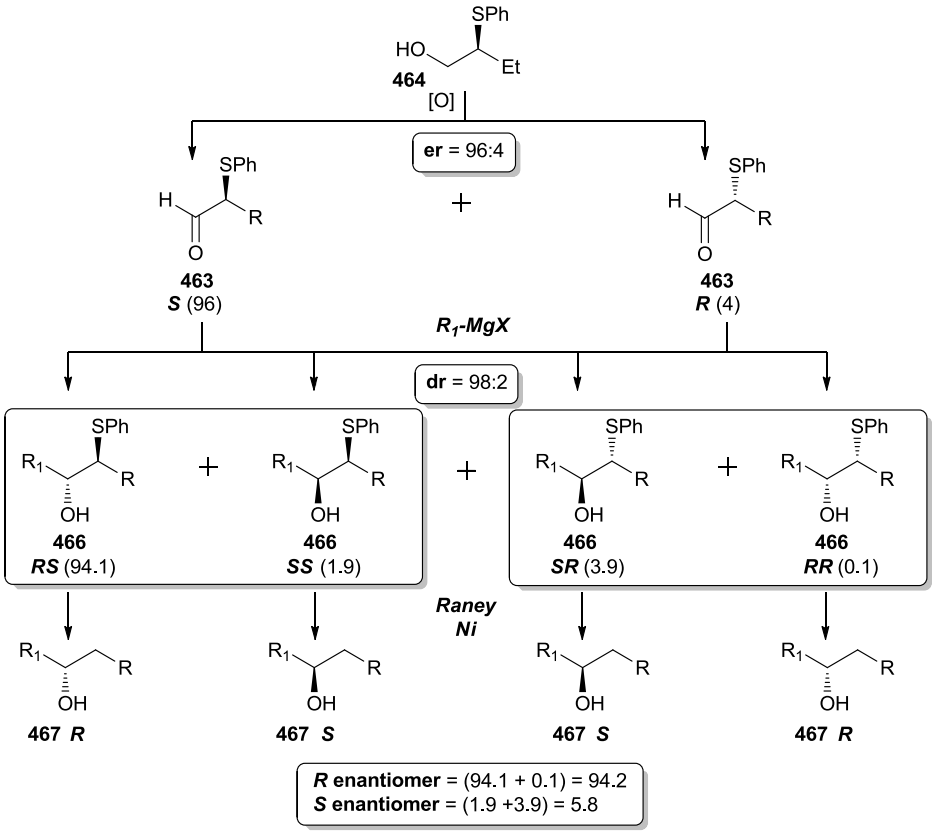
Alcohol **464** was initially isolated in order to determine the enantioselectivity of the α-sulfenylation reaction on aldehyde **463**, which had never been previously reported for this substrate. Pleasingly alcohol **464** was obtained in good yield and very good enantioselectivity. Aldehyde **463** was then synthesised *in situ* by Swern oxidation followed by addition of the Grignard reagent **465** to give sulfido-alcohol **466** (**Scheme 3.9**).



Scheme 3.9. Reagents and conditions: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 → -40 °C, 1 hr; b) *c*HexMgCl (**465**, 5 eq), THF, -78 °C → RT, 30%; c) Raney-Ni, EtOH, reflux, quant.. (*) determined by Mosher's' esters analysis

This intermediate was obtained in good yield and with excellent diastereoselectivity (dr = 98:2, determined by ^{1}H-NMR) after chromatographic purification. Pleasingly, complete reduction to alcohol **467** was observed after stirring sulfido-alcohol **466**

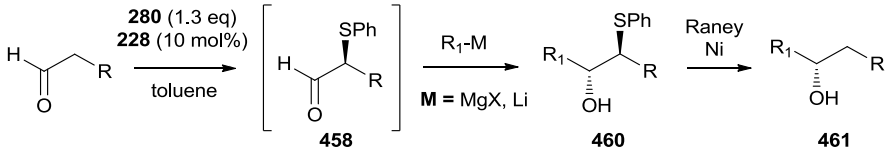
over excess Raney-Ni in refluxing EtOH over 3 hr. We were pleased to observe that the er recorded for alcohol **467** was 90:10. Assuming that no racemisation occurs during the reaction, addition of the Grignard reagent (R_1-MgX **465**, **Scheme 3.9**) to enantiomerically enriched aldehyde **463** (er = 96:4, assumed on the basis of the er of alcohol **464**) should give four stereoisomers as shown in **Scheme 3.10**, which, based on the dr (98:2) observed by ^{1}H-NMR, would be in a 94.1 : 3.9 : 1.9 : 0.1 ratio. After removal of the sulfide substituent by Raney-Ni reduction, and therefore after removal of one chiral centre, the ratio between the two enantiomers of alcohol **467** can be calculated as the ratio between the sums of the ratios of enantiomer *R* and enantiomer *S* derived from the corresponding diastereoisomers of sulfido-alcohols **466** (approximately 94:6).



Scheme 3.10

Given the observed slight loss of enantiomeric purity that we observed (90:10 against a theoretical 94:6) it is likely that modest racemisation can occur in the steps subsequent to sulfenylation. However, preliminary results in these experiments show that this could represent a rapid and efficient strategy to access enantiomerically enriched secondary alcohols which are difficult to obtain with other approaches.

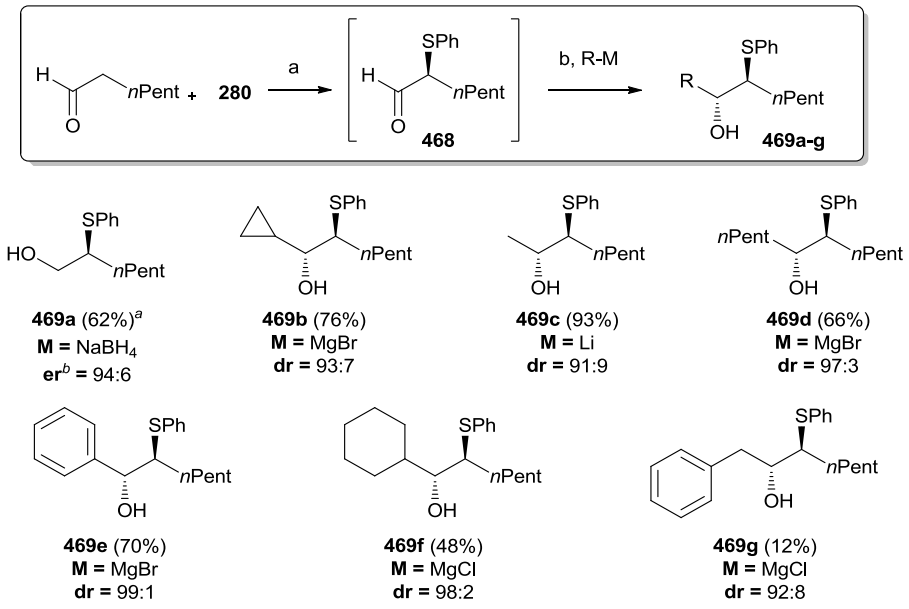
The ultimate goal of our strategy, however, is to combine the organocatalytic sulfenylation and the addition of organometallic reagents in only one step (**Scheme 3.11**) in order to obtain sulfido-alcohol **460** without isolating intermediate aldehyde **458**, thus avoiding extra steps that could affect the er of the final product **461**.



Scheme 3.11

3.2.2 Synthesis of enantiomerically enriched alcohols

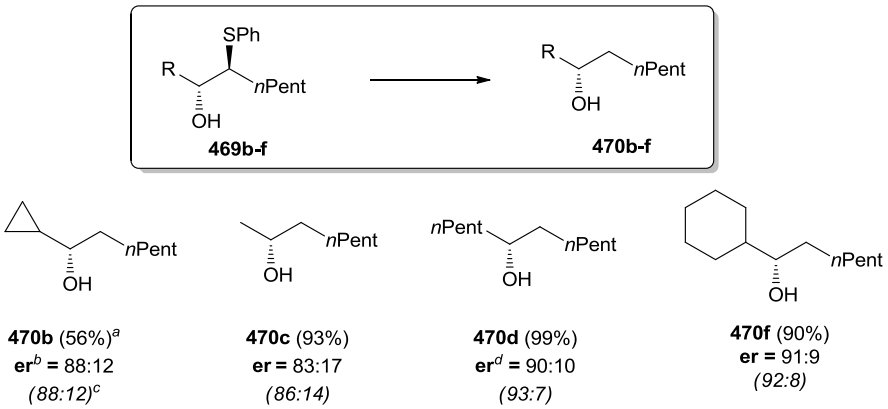
In order to determine the scope of the proposed strategy, it was initially decided to investigate the behaviour of heptanal with different commercially available nucleophiles (**Scheme 3.12**). Aldehyde **468** was therefore synthesised from heptanal and S-phenyl triazole **280** using organocatalyst **228**.



Scheme 3.12. Reagents and conditions: a) cat **228** (10 mol %), toluene, RT, 4 hr; b) R-M (3 eq), THF, -78 °C, 1 hr; c) Raney-Ni, EtOH, reflux;[(a)] isolated yield after column chromatography; [(b)] determined by Mosher's esters analysis;

The reaction mixture was quickly purified through a plug of silica and eluted with toluene. The toluene solution of aldehyde **468** was subsequently added to the ethereal solutions of organometallic reagents cooled to -78 °C and stirred at this temperature for 1 hr before being quenched. Aldehyde **468** was also reduced to primary alcohol **469a** ($NaBH_4$ in MeOH) in order to measure the er after the sulfenylation step. Unfortunately incomplete conversion to alcohols **469b-g** were observed in most cases (TLC), with the exception of the organolithium reagent (**469c**), but nevertheless the remaining starting material could be easily removed after reduction with $NaBH_4$ and chromatographic purification. Good yields and very good selectivities were generally recorded for secondary carbon nucleophiles (**469b**, **459e** and **469f**) and also for large primary nucleophiles (**469d**). The reaction of BnMgCl (**469g**) afforded the sulfido-alcohol with reasonably good diastereoselctivity but in very poor yields. As expected, the reaction with MeLi (**469c**) gave the poorest selectivity, due to the small size of the nucleophile, but the sulfido-alcohol was isolated in excellent yield.

Raney Ni reduction of sulfido-alcohols **469b-f** to the corresponding secondary alcohols **470b-f** was achieved in good to excellent yields (**Scheme 3.13**), with the exception of **469e**, due to over reduction of the substrate to heptylbenzene, and **469g**, which was not carried onto the reduction step due to the very small amount of material available.



470b (56%)[a]
er[b] **=** 88:12
(88:12)[c]

470c (93%)
er = 83:17
(86:14)

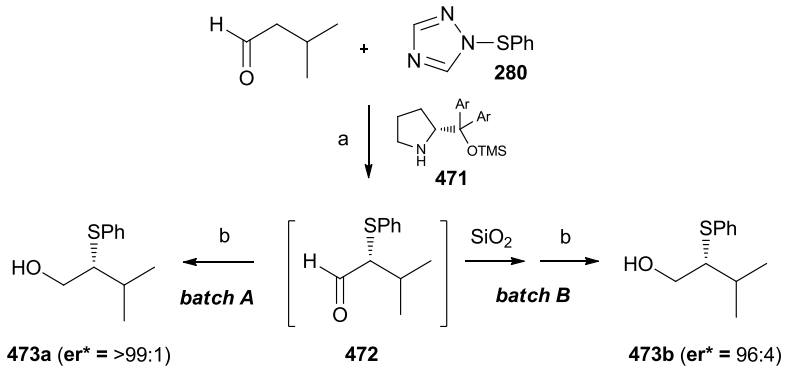
470d (99%)
er[d] **=** 90:10
(93:7)

470f (90%)
er = 91:9
(92:8)

Scheme 3.13. Reagents and conditions: Raney-Ni, EtOH, 80 °C, 2-4 hr. [(a)] Yields are calculated on the crude alcohol; [(b)] Determined using the Mosher's esters analysis; [(c)] Theoretical er (in brackets) is calculated as in **Scheme 155**, assuming the er of SM **469b-f** is (94:6), as measured for alcohol **469a**; [(d)]determination of the er was only tentative, due to the lack of distinctive signals in the ^{1}H-NMR spectrum of the corresponding Mosher's esters.

The enantioselectivities measured for isolated alcohols **470b-f** were generally good and in accordance with the ones calculated as in **Scheme 3.10** (in brackets, **Scheme 3.13**). Some racemisation was observed in the case of 2-octanol **470c**, possibly due to prolonged reaction times with Raney Ni (4 hr), whereas for the reduction of other substrates the reaction time was shorter (2 hr).

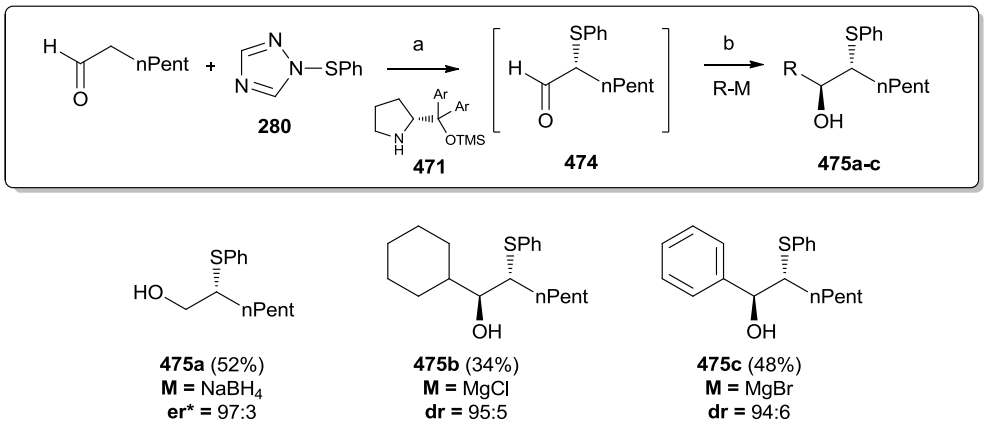
Since it has been previously reported that some racemisation can occur during the purification of intermediate aldehyde **468** (**Scheme 3.12**),[193] we decided to establish to what extent purification procedures could affect the enantiomeric purity of the final alcohol products. The experiment in **Scheme 3.14** was therefore carried out: the reaction mixture containing intermediate α-sulfenylaldehyde **472** was split into two batches of equal volumes.



Scheme 3.14. Reagents and conditions: a) Cat **467** (10 mol %, Ar = 3,5-CF_3-C_6H_3), Toluene, RT, 24 hr; b) $NaBH_4$, Toluene/MeOH, RT. $^{(*)}$ Determined using the Mosher's esters analysis

The first batch (**A**) of the crude reaction mixture was taken onto the next step ($NaBH_4$ reduction) without purification, whereas the second batch (**B**) was filtered through a plug of silica before being treated with the reducing agent under the same conditions used for batch **A**. The er measured for alcohols **473a** and **473b** clearly indicate that significant racemisation occurred during the purification of aldehyde **472** over silica gel.

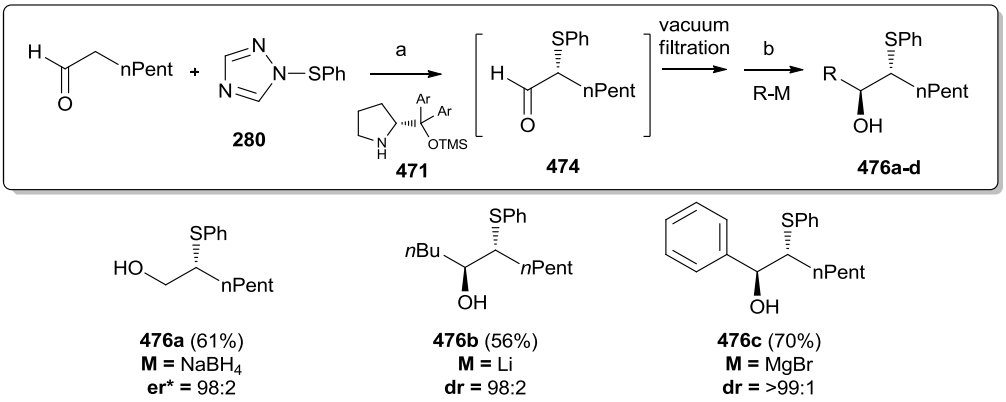
Following this observation, we decided to perform the addition of an excess organometallic reagent (4 eq) directly on the sulfenylation reaction mixture (**Scheme 3.15**) in order to avoid the racemisation observed during the purification on silica.



Scheme 3.15. Reagents and conditions: a) Cat **471** (10 mol %), Toluene, RT, 24 hr; b) R-MgX (4 eq), Et_2O (or THF), 0 °C, 1 hr. (*) determined by Mosher's' esters analysis.

The er recorded for alcohol **475a**, resulting from the $NaBH_4$ reduction of α-sulfenylaldehyde **474**, was very promising (97:3 as opposed to 94:6 previously obtained, see **Scheme 3.12**) but unfortunately the yields and the diastereoselectivities recorded for sulfido-alcohols **475b** and **475c** were lower than previously achieved. A possible explanation of the observed loss in selectivity could be either the interference of the impurities present in the reaction mixture or the increased temperature of the addition of Grignard reagents (0 °C in this case, compared to -78 °C **Scheme 3.12**), employed to allow complete conversion to alcohols **475b** and **475c** (TLC).

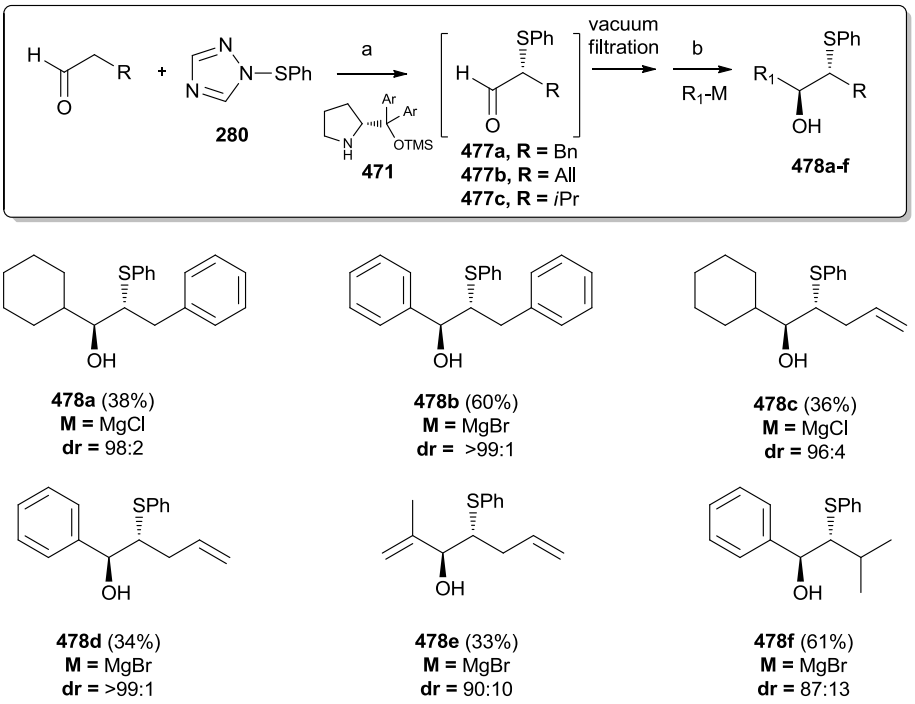
At the same time an alternative procedure of purification on silica was evaluated (**Scheme 3.16**); once reasonable levels of conversion to α-sulfenylaldehyde **474** were detected by ^{1}H-NMR (~90-95%), the reaction mixture was quickly sucked under vacuum through a very short plug of silica, thus minimising the contact time between the enolisable aldehyde and the silica.



Scheme 3.16. Reagents and conditions: a) Cat **471** (10 mol %), Toluene, RT, 24 hr; b) R-M (4 eq), Et_2O (or THF), 0 °C, 1 hr. (*) determined by Mosher's' esters analysis.

Pleasingly the er of alcohol **476a** (98:2), measured after vacuum filtration and $NaBH_4$ reduction of aldehyde **474**, was found to be similar to the one recorded for the non-purified aldehyde (97:3, **475a**, **Scheme 3.15**). In addition to that, the yields and the selectivities recorded for sulfido-alcohols **476b** and **476c** were generally better than previously observed (**475b** and **475c**, **Scheme 3.15**).

Given the successful approach of the vacuum filtration through silica, we decided to screen different aldehydes in the sulfenylation/addition sequence (**Scheme 3.17**).



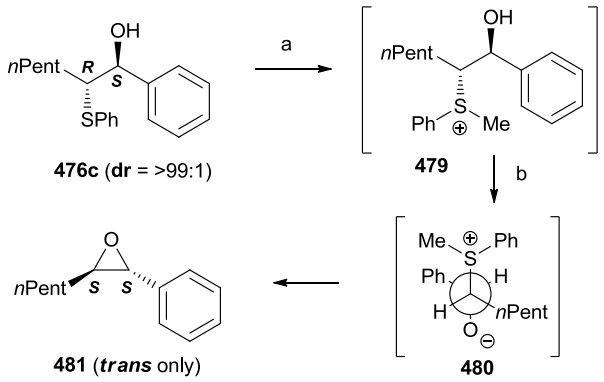
Scheme 3.17. Reagents and conditions: a) Cat **471** (10 mol %), Toluene, RT, 24 hr; b) R-M (3 eq), Et_2O (or THF), 0 °C, 1 hr.

Hydrocinnamaldehyde (R = Bn) and Isovaleraldehyde (R = iPr) gave clean and satisfactory conversions to the corresponding α-sulfenylaldehydes **477a** and **477c** (generally between 75-85% by ^{1}H-NMR) and the yields of the sulfido-alcohols, obtained after the addition of organometallic reagents, were generally good. Complex mixtures of products were instead observed by ^{1}H-NMR when 4-Pentenal (R = $-CH_2CH{=}CH_2$) was used and this translated into generally poorer yields. Nevertheless the selectivities recorded for sulfido-alcohols **478a-f**, isolated after column chromatography, were in some instances very good. The diastereoselectivity measured in the case of alcohol **478f**, derived from isovaleraldehyde, was the lowest

observed, probably due to the steric hindrance caused by the bulky *i*Pr group during the nucleophilc attack of the Grignard reagent to α-sulfenylaldehyde **477c**.

3.3 Synthesis of chiral epoxides

As described in **Section 3.1**, enantiomerically enriched vicinal thioether-alcohols can be used as a starting material in order to obtain optically active epoxides. The reaction was initially tested on sulfido-alcohol **476c** (**Scheme 3.18**), which was previously obtained in excellent diastereomeric purity. This substrate was initially treated with excess Meerwein salt (Me_3OBF_4) to give methyl-sulfonium salt **479**. The latter was subsequently treated *in situ* with NaOH in order to form alkoxide **480** and to obtain epoxide **481** via intramolecular S_N2 displacement of the sulfonium group.

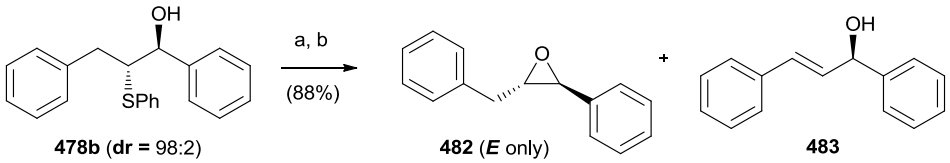


Scheme 3.18. Reagents and conditions: a) Me_3OBF_4, $MeNO_2/CH_2Cl_2$, 0 °C → RT, 30 min; b) 0.5 M NaOH, CH_2Cl_2, 0 °C →RT, 24 hr, 54%

Pleasingly, epoxide **481** was isolated in good yield as pure *trans* isomer after column chromatography. The isolation of the *trans* isomer (as determined by the analysis of the coupling constants of the epoxide protons by ^{1}H-NMR) is consistent with the *anti*-orientation of the SPh and OH groups in the starting material **476c** and consistent with inversion occurring at the carbon bearing the sulfonium leaving group during the epoxide ring closure.

Although the enantiomeric purity of the starting material **476c** could not determined by chiral HPLC, it is reasonable to assume it could be very similar to the value determined for alcohol **476a** (er = 98:2), which was obtained from the reduction of the same SM (α-sulfenylaldehyde **474, Scheme 3.16**).

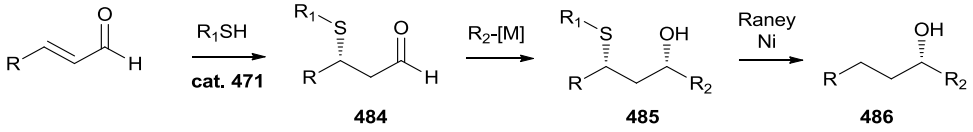
Following the same procedure sulfido-alcohol **478b** was treated under the same reaction conditions; unfortunately in this case we obtained an inseparable mixture of the expected epoxide **482** and alcohol **483**, resulting from the elimination of the methyl-sulfonium salt intermediate, albeit in very good yields (**Scheme 3.19**).



Scheme 3.19. Reagents and conditions: a) Me_3OBF_4, CH_2Cl_2, 0 °C → RT, 30 min; b) 0.5 M NaOH, CH_2Cl_2, 0 °C → RT, 24 hr.

3.4 Investigation on selectivity of the addition of nucleophiles to β-sulfenylaldehydes

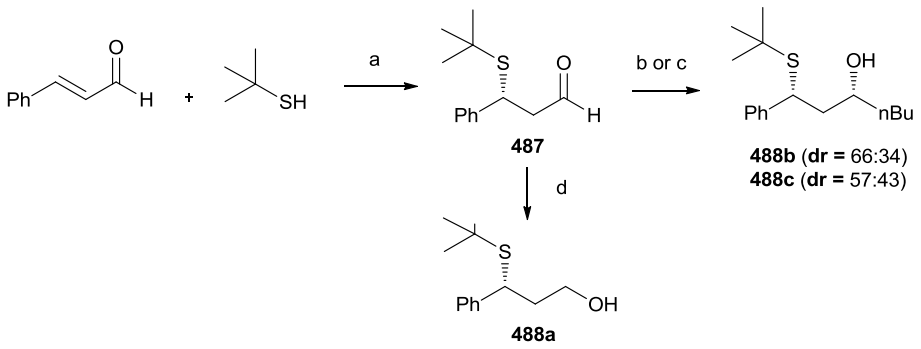
Given the easy accessibility to optically active β-sulfenylated aldehydes **484**,[194] it was decided to investigate the influence of a thioether substituent in the β position on the addition of nucleophiles to aldehyde **484** (**Scheme 3.20**).



Scheme 3.20

In analogy with the strategy previously described in **Section 3.1**, this strategy could also be exploited for the synthesis of enantiomerically enriched alcohols **486**, which could be obtained after Raney-Ni reduction of 1,3-sulfidoalcohols **485**.

Initial experiments were conducted using *trans*-cinnamaldehyde and the bulky 2-methyl-2-propanethiol as the nucleophile. β-Sulfenylaldehyde **487** was obtained via a Michael addition catalysed by proline based catalyst **471**. Crude aldehyde **487** was initially reduced to alcohol **488a**. Subsequently, crude aldehyde **487** was treated with excess *n*BuLi at -78 °C to afford alcohol **488b** in moderate yield but with very poor selectivity.



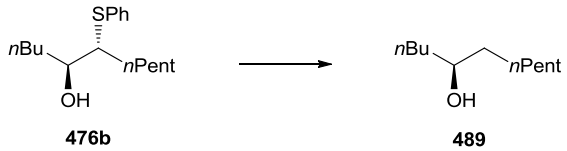
Scheme 3.21. Reagents and conditions: a) Cat **471** (10 mol %), Benzoic Acid (10 mol %), Toluene, -24 °C → RT; b) *n*BuLi, -78 °C, 30 min, 52%; c) $ZnCl_2$ (1.1 eq), *n*BuLi, -78 °C, 30 min, 80%; d) $NaBH_4$, MeOH, RT, 24%.

The same reaction was also repeated in the presence of $ZnCl_2$, with the purpose of determining whether the addition of the Lewis acid would improve the selectivity of the reaction by chelation control. Unfortunately the selectivity observed for **488c** was even worse than the one observed without the Lewis acid and this approach was not further investigated.

3.5 Future work

After the promising preliminary results of the Raney-Ni reduction of sulfido alcohols **470a-f** (**Scheme 3.13**), we plan to obtain further data on the reduction of sulfido-alcohols isolated after the optimised purification procedures that led to improved enantiomeric purity (**Scheme 3.16** and **3.17**).

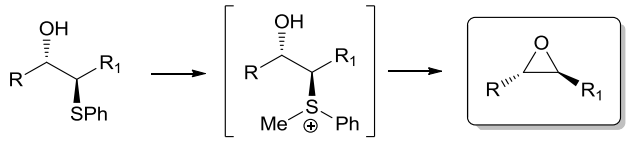
Due to time limitations, only sulfido alcohol **476b** was treated with Raney-Ni to give enantiomerically enriched alcohol **489** (**Scheme 3.23**).



Scheme 3,23. Reagents and conditions: Raney-Ni, EtOH, 40 °C, 2 hr

Unfortunately the er of alcohol **489** couldn't be assigned via Mosher's esters analysis, due to the lack of distinctive signals in both ^{1}H and ^{19}F NMR spectra.

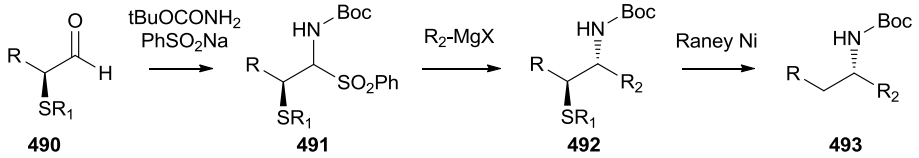
Attempts to separate the enantiomers from the racemic mixture of **489** by chiral HPLC were also unsuccessful, as also previously determined for this substrate.[195]
At the same time we plan to further investigate the formation of enantiomerically enriched *trans*-disubstituted chiral epoxides (**Scheme 3.24**), according to the procedure previously described in **Section 3.3**.



Scheme 3.24

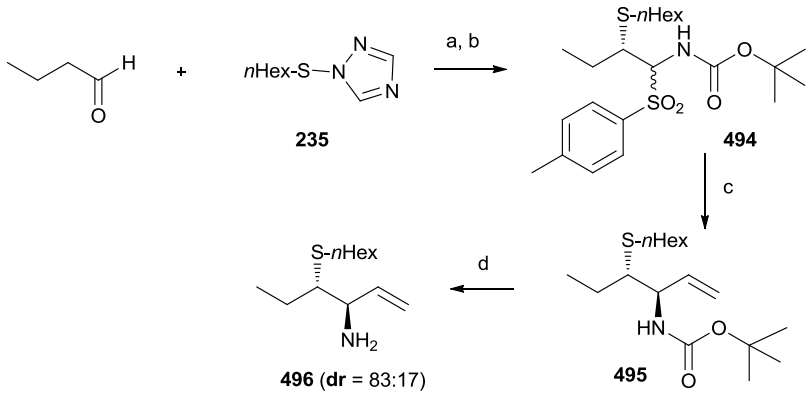
Given the initial promising results this could represent a significant advance on the synthesis of these substrates; despite a few procedures available[136, 196] optically active disubstituted *trans* epoxides are generally more difficult to synthesize when compared to *cis* epoxides.[197]

Another interesting strategy that we wish to further pursue is shown in **Scheme 3.25**. Aldehydes **490** can be converted to stable amidosulfones **491** which, upon treatment with 2 equivalents of a Grignard reagent, should furnish 1,2-sulfenylamines **492** with good selectivity.[198] Furthermore, Boc-protected enantiomerically enriched amines **493** could be obtained after Raney-Ni removal of the sulfide group.



Scheme 3.25

In order to prove the feasibility of the approach described above, amidosulfone **494** was synthesised from commercially available butanal in two steps (**Scheme 3.26**). Despite many attempts, crystallisation of **494** couldn't be achieved therefore purification by column chromatography was necessary.



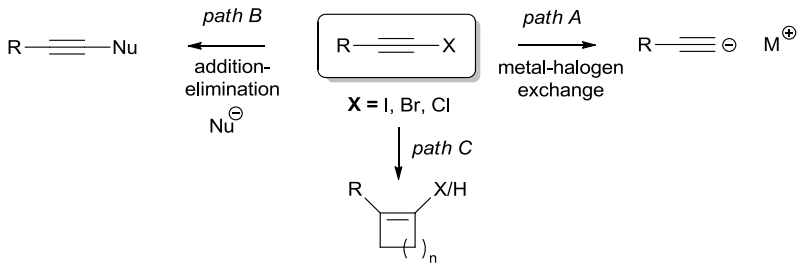
Scheme 3.26. Reagents and conditions: a) Cat. **471** (10 mol %), Toluene, RT, 3 hr; b) *tert*-Butylcarbamate (1 eq), pToluenesulfinic acid sodium salt (1 eq), HCOOH, water, THF, RT, 24 hr, 19% (over 2 steps); c) H_2C=CHMgBr (2.05 eq), THF, -20 → 0 °C; d) CH_3COCl (0.5 M), MeOH, RT, 24 hr, 30% (over 2 steps).

Addition of two equivalents of vinylmagnesium bromide to amidosulfone **494** afforded Boc-protected amine **495**. Unfortunately it was not possible to determine the diastereoselectivity of the Grignard addition at this stage as the analysis of the ^{1}H-NMR spectrum was complicated by the presence of peaks for both diastereoisomers and for rotamers of the carbamate group. The protecting group was therefore removed under acidic conditions and free amine **496** was subsequently purified after basic extraction. Good selectivity was observed (**dr** = 83:17) despite the presence of the *n*Hex substituent on the sulfur and the small size of the carbon nucleophile used (vinyl) which do not contribute to improve the facial selectivity of the addition to the *in situ* generated imine. It is therefore likely that by increasing the steric bulk of the substituent on the sulfur and by using larger nucleophiles the selectivity of the addition could be improved.

4. Gold/Brønsted acid Catalysed Formation of Haloalkynes

4.1 Haloalkynes

Haloalkynes are synthetically useful intermediates which often find application in metal catalysed reactions. From this point of view, they are often used as a source of acetylides via metal-halogen exchange (**Scheme 4.1**, path A).



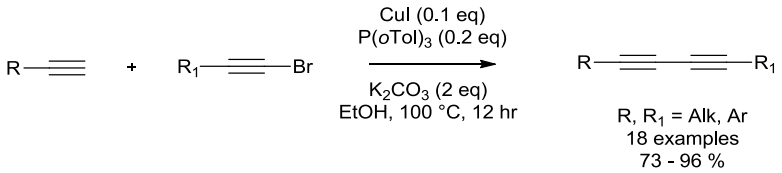
Scheme 4.1

On the other hand haloalkynes can also be used as an electrophilic source of the acetylene unit via addition of a nucleophile followed by elimination of the halide (path B). In some instances alkynylhalides have also been employed in transition metal catalysed cycloaddition reactions (Path C)

Amongst the metal-halogen exchange group of reactions haloalkynes find use in a wide variety of transition metal catalysed C-C and C-N coupling:

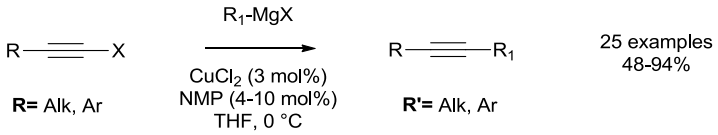
Cu catalysis

One of the first transformations described involving bromoalkynes was the Cadiot-Chodkiewicz Coupling.[199] This copper catalysed transformation is very useful for the synthesis of unsymmetrical bisacetylenes (**Scheme 4.2**).[200]



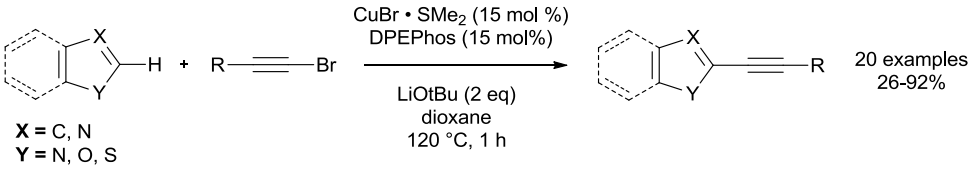
Scheme 4.2

Copper catalysis has also been successfully used in coupling reactions between haloalkynes and Grignard reagents to give unsymmetrical acetylenes under very mild reaction conditions (**Scheme 4.3**).[201]



Scheme 4.3

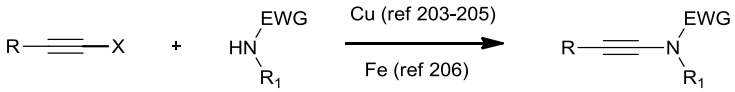
Bromoalkynes have also been used as coupling partners in the Cu catalysed alkynylation of some unfunctionalised heterocycles (**Scheme 4.4**).[202] In this case, however, more forcing conditions were required together with a higher catalyst loading.



Scheme 4.4

Although the mechanism for this reactions hasn't been fully elucidated, it has been proposed that it might proceed through a Cu(I)/Cu(III) redox cycle.

Copper catalysis has also been successfully employed for C-N coupling, in fact ynamides (**Scheme 4.5**) are usually synthesised from the corresponding haloalkyne in the presence of copper[203-205] (iron catalyst has also been used[206]).

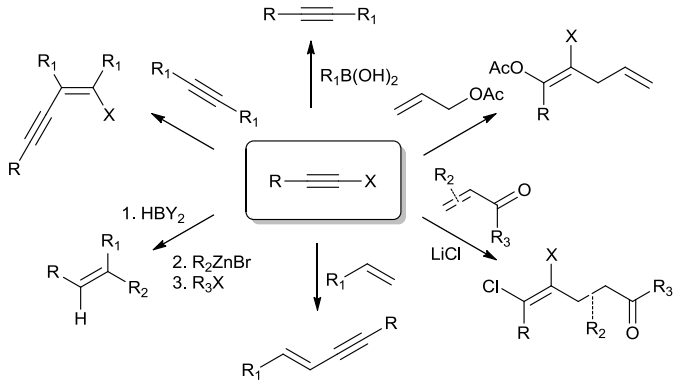


Scheme 4.5

Pd catalysis

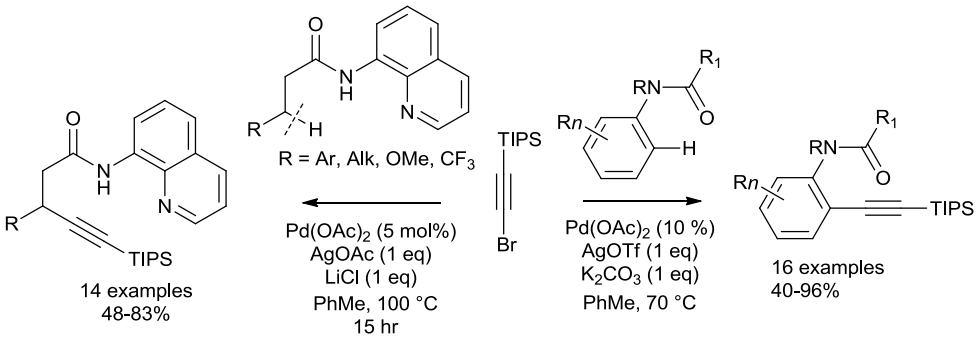
In recent years haloalkynes have also found wide application in Pd catalysed cross coupling reactions with vinyl and arylboronic acids,[207-209] α,β-unsaturated carbonyls[210], allylacetates[211], internal alkynes[212] and unactivated alkenes[213] (**Scheme 4.6**). Haloalkynes also undergo regioselective hydroboration and the resulting

vinylborate intermediates can be further functionalised via Pd mediated coupling to afford trisubstituted alkenes.[214]



Scheme 4.6 Pd catalysed cross coupling reactions of haloalkynes

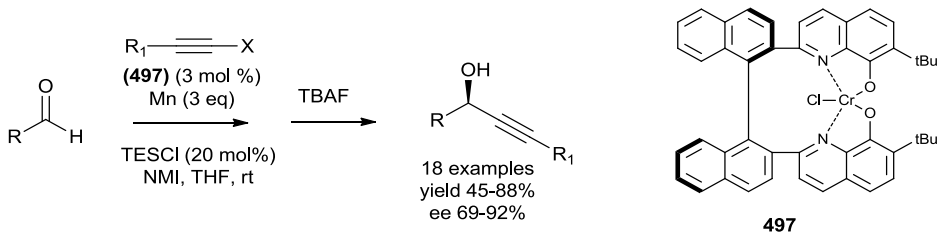
In two recent papers Chatani reported the Pd catalysed C-H activation and subsequent cross coupling of a series of aromatic and aliphatic amides with bromoalkynes (**Scheme 4.7**).[215, 216]



Scheme 4.7

Cr Catalysis

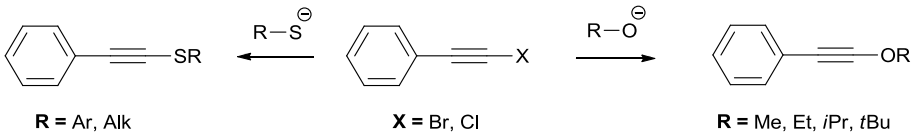
Iodoalkynes react with aldehydes and ketones in the presence of stoichiometric amounts of $CrCl_2$ to afford the corresponding propargylic alcohols under mild conditions.[217] Catalytic variants of the reactions have also been developed by Kishi[218] and Furstner[219]. In a recent paper Yamamoto achieved an enantioselective alkynylation of aldehydes using the chiral Cr based catalyst **497** (**Scheme 4.8**).[220]



Scheme 4.8

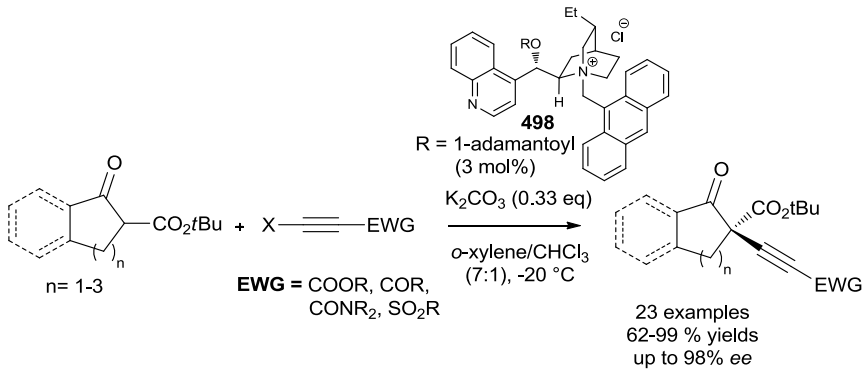
Nucleophilic substitution

Nucleophilic substitution at the acetylenic carbon (path B, **Scheme 4.1**) was originally described by Ott in 1943 using chloro and dichloroacetylenes and diethylamine as nucleophile.[221] Miller reported the synthesis of a series of acetylenic ethers[222] and thioethers[223] and from the reaction of haloalkynes with the corresponding alkoxides or thiolates (**Scheme 4.9**).



Scheme 4.9

In this perspective, haloalkynes have been recently used as substrate for the organocatalytic asymmetric alkynylation of β-ketoesters by K.A. Jørgensen (**Scheme 4.10**).[224]

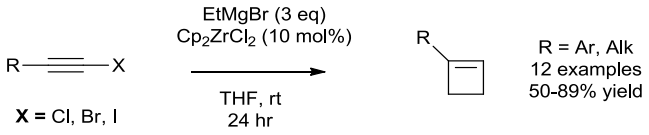


Scheme 4.10

In the presence of the Cinchona -based catalyst **498** the authors were generally able to obtain the alkynylated product in very good yields and excellent enantioselectivity.

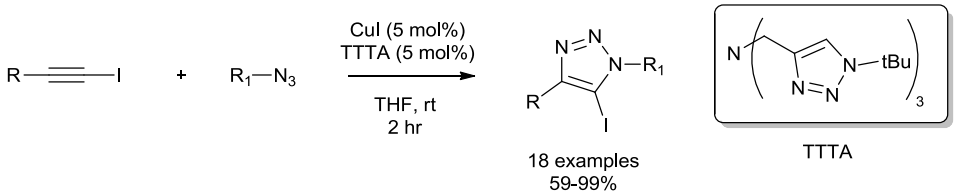
Cycloadditions

A few metal catalysed cycloadditions reactions were reported using haloalkynes (path C, **Scheme 4.1**); Takahashi first described the zirconocene catalysed formation of cyclobutenes from the reaction of haloalkynes with EtMgBr (**Scheme 4.11**).[225]



Scheme 4.11

More recently Sharpless reported the regioselective copper catalysed [3+2] cycloaddition of iodoalkynes with azides depicted in **Scheme 4.12**.[226]

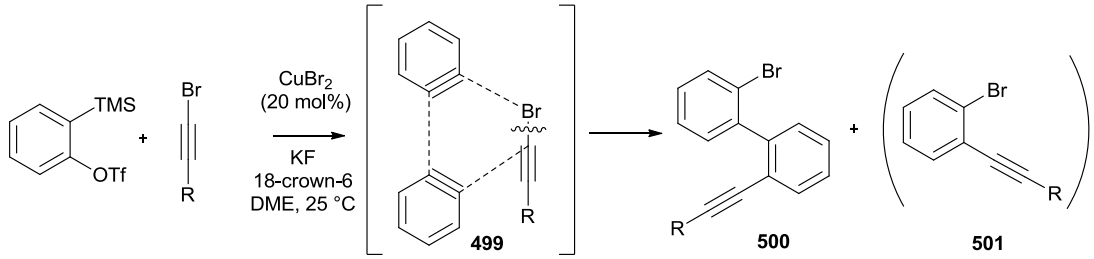


Scheme 4.12

The product of this reaction is a functionalised triazole, bearing a 5-iodo-substituent amenable to further functionalisation.

Miscellaneous

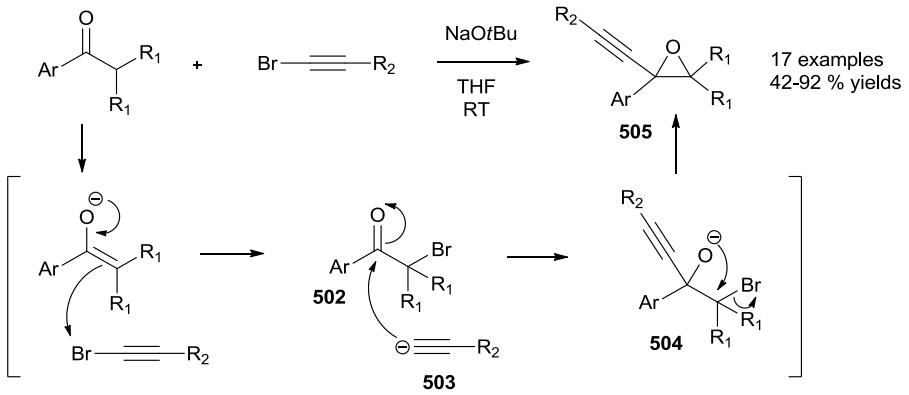
Haloalkynes have also found applications in benzyne type processes: in the example in **Scheme 4.13** by Yoshida,[227] arynes were found to insert into the C-Br bond of bromoalkynes with the aid of copper catalysis to give bis-arenes **500** as the main reaction product, originating from the insertion of the haloalkyne species in two molecules of benzyne (**499**).



Scheme 4.13

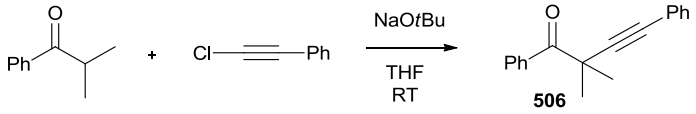
The reaction also afforded variable amounts of *o*-bromo-alkynylbenzenes **501**, which, however, were always the minor product of the reaction.

Recently Gevorgyan described the use of haloalkynes as both a source of electrophilic halogen and acetylides in the synthesis of tetrasubstituted epoxides (**Scheme 4.14**).[228]



Scheme 4.14

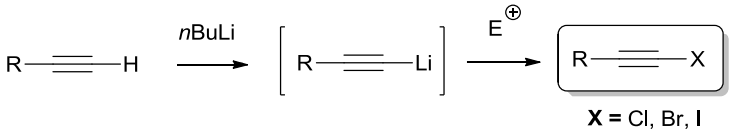
In the presence of sterically congested α,α-disubstituted ketones, the resulting enolate reacts with bromoalkynes to give α-bromoketone **502** and the resulting acetylide **503** attacks the carbonyl group. The resulting alkoxide **504** subsequently undergoes ring closure to give epoxide **505**. Interestingly when phenylchloroalkyne was used the only product of the reaction was α-alkynylated ketone **506** (**Scheme 4.15**), resulting from the nucleophilc substitution/elimination reaction pathway (path B, **Scheme 4.1**).



Scheme 4.15

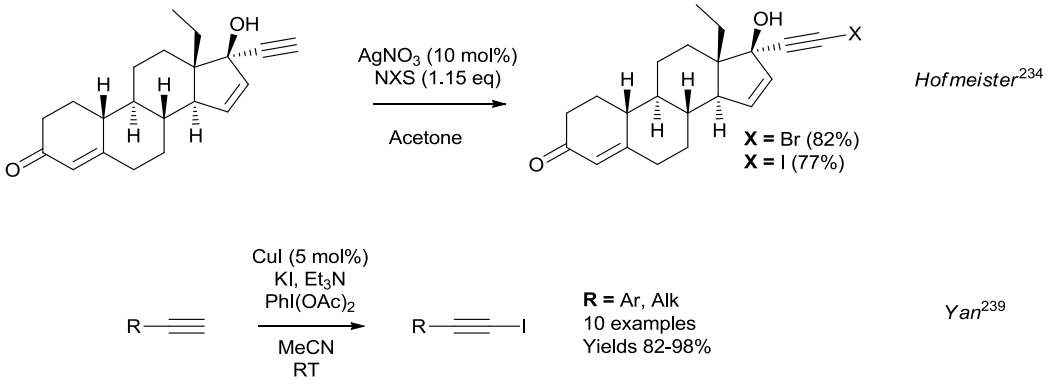
Synthesis of Haloalkynes

The synthesis of haloalkynes can be achieved via deprotonation of terminal alkynes with a base (usually *n*BuLi) at low temperatures, followed by reaction with a source of electrophilic halide (such as NCS,[229] $PhSO_2Cl$,[230] TsCl,[231] NBS,[232] Br_2,[233] I_2,[220] **Scheme 4.16**). The yields recorded for these processes are generally very good but the major drawbacks are the use of low temperatures/anhydrous conditions and also the basic conditions that might not be compatible with other functional groups present in the substrate.



Scheme 4.16

Other procedures have been developed for the synthesis of haloalkynes from terminal alkynes which employ catalytic amount of silver ($AgNO_3$,[201, 234-236] AgOAc,[237] $AgOCOCF_3$[238]) or copper (CuI[226, 239]) in the presence of electrophilic halide species (**Scheme 4.17**)

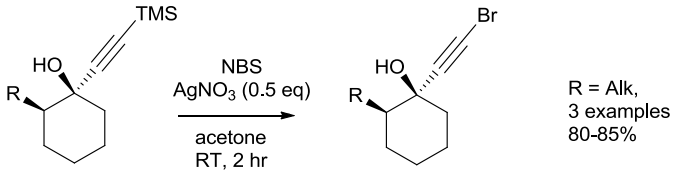


Scheme 4.17

These strategies are often preferred over deprotonation of the terminal alkyne as they normally take place under relatively mild conditions which are often compatible with other sensitive functional groups present in the molecule (**Scheme 4.17a**); moreover these reactions often don't require anhydrous conditions.

Haloalkynes can also be obtained from trimethylsilylalkynes under silver catalysis ($AgNO_3$,[240] $AgOCOCF_3$,[241] AgF[242]) in the presence of the corresponding

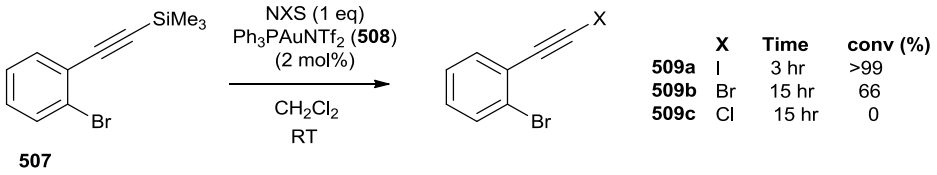
halosuccinimides. Although very efficient, this reaction sometimes requires a very high catalyst loading, unsuitable for large scale preparation (**Scheme 4.18**).[243]



Scheme 4.18

4.2 Early work

Previous research conducted in our group[244] showed that when electrophilic species N-halosuccinimides (NXS, X = I, Br, Cl) were added to trimethylsilylacetylene **507** in the presence of gold(I) catalyst **508** the formation of iodo and bromoalkynes **509** was observed, as determined by ^{1}H-NMR experiments (**Scheme 4.19**).

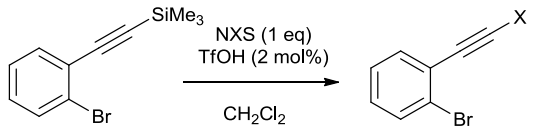


	X	Time	conv (%)
509a	I	3 hr	>99
509b	Br	15 hr	66
509c	Cl	15 hr	0

Scheme 4.19

Substrate **507** was found to be very reactive towards iodination and the reaction was complete in only 3 hr at RT. The substrate was less reactive towards bromination, giving bromoalkyne **509b** in 66% yield after 15 hr at RT and completely unreactive towards chlorination under the same reaction conditions.

In order to determine whether the reaction was effectively catalysed by the cationic gold species or by residual amounts of acid present in traces in the catalyst, the experiment in **Scheme 4.20** was carried out using triflic acid (2 mol%) as the catalyst.



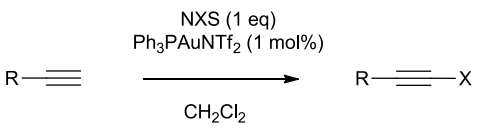
507

	X	time	conv (%)
509a	I	16 hr	>99
509b	Br	3 hr	>99
509c	Cl	1 hr	>99

Scheme 4.20. Brønsted acid catalysed formation of haloalkynes from TMS-acetylenes. *Conversions determined by ^{1}H-NMR.

Interestingly the reaction was indeed found to be catalysed by traces of acid. Initial NMR experiments seemed to show complete conversions for chloro, bromo and iodoalkynes and the order of reactivity observed was opposite to the gold(I) catalysed reaction, with the chloroalkyne being the fastest to be formed.

Direct halogenation of terminal alkynes was also found to be possible with the same gold catalyst, to give the corresponding haloalkynes in excellent yields under mild reaction conditions (**Scheme 4.21**).



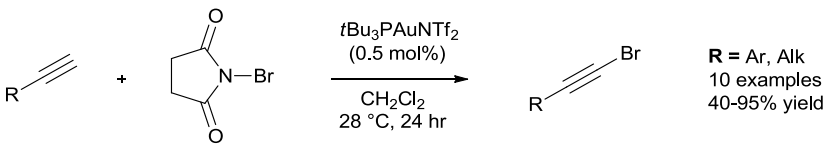
initial results

R	X	time	conv (%)[a]
Ph	Cl	15 hr	0
Ph	Br	15 hr	66
Ph	I	16 hr	>99
*n*Bu	Br	15 hr	0[b]
*n*Bu	I	15 hr	66[b]

Scheme 4.21. Gold(I) catalysed formation of haloalkynes from terminal alkynes. [a] Determined by ^{1}H-NMR, [b] Conducted at 37 °C.

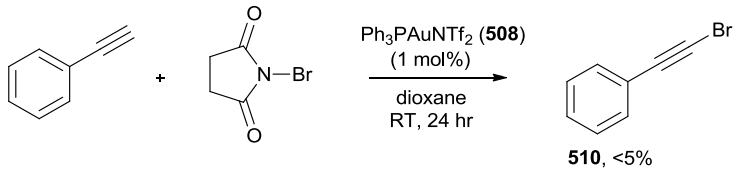
Aromatic acetylenes were found to be more reactive in the iodination and bromination reaction, affording the corresponding haloalkynes under mild reaction conditions. Chlorination couldn't be achieved even under more forcing conditions. Aliphatic alkynes proved to be less reactive than aromatic ones; iodination of 1-hexyne could be achieved after prolonged stirring at reflux.

At the same time when our research was being carried out, a publication regarding the gold(I) catalysed formation of bromoalkynes was also issued.[245] The authors found that *t*Bu$_3$AuNTf$_2$ was very effective in catalysing the bromination of terminal alkynes (**Scheme 4.22**)



Scheme 4.22

Interestingly other gold(I) catalysts were screened in the halogenation reaction and $Ph_3PAuNTf_2$ was found to afford bromoalkyne **510** in very low yield.



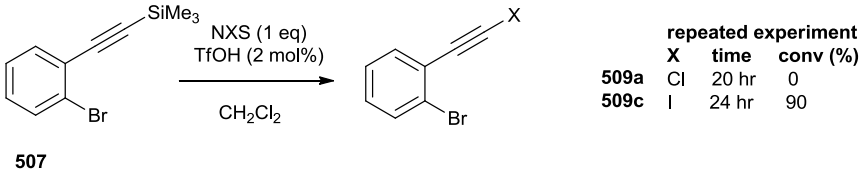
Scheme 4.23

In our hands however gold(I) catalyst **508** proved to be a very effective catalyst for the halogenation of alkynes. A plausible explanation is the use of CH_2Cl_2 as the reaction solvent instead of 1,4-dioxane, as reported by Corma. In fact, alongside the expected bromoalkyne in **Scheme 4.23**, the authors also reported bromination of the reaction solvent.

Nevertheless, encouraged by our initial findings, we thought we could investigate the scope and the limitations of the previously described halogenation reactions.

4.3 Brønsted acid catalysed halogenation of trimethylsilylalkynes

Initial experiments were aimed at reproducing the acid catalysed halogenation of trimethylsilylalkynes, previously performed by another member of our research group (**Scheme 4.24**).

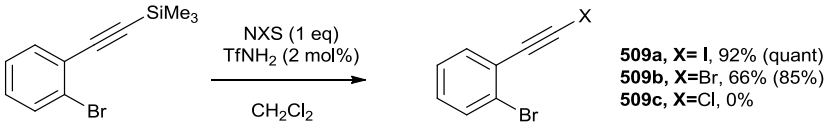


Scheme 4.24

Alkyne **507** was initially treated with NIS in the presence of TfOH (2 mol%). The formation of iodoalkyne **509c** was detected by NMR although the conversion was 90% (NMR) after stirring for 24 hr at RT (previously reported as 99%, **Scheme 4.20**). Unfortunately, when the reaction was repeated on the same substrate with recrystallized NCS no chloroalkyne **509a** was detected; the only product observed,

together with unreacted starting material, was the corresponding terminal alkyne in 20% yield after 20 hr at RT. It is likely that initial attempts using an old batch of NCS (**Scheme 4.20**), containing a substantial amount of succinimide, could have caused complete desilylation, which was erroneously assigned as chloroalkyne **509a.**

When triflimide ($TfNH_2$, 2 mol%) was used as the acid catalyst instead of TfOH, the formation of iodoalkyne **509a** was found to be faster and to reach completion within an hour (NMR, **Scheme 4.25**).

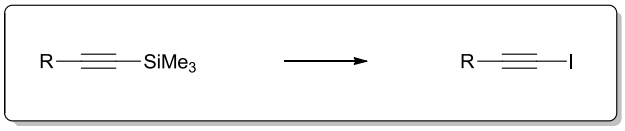


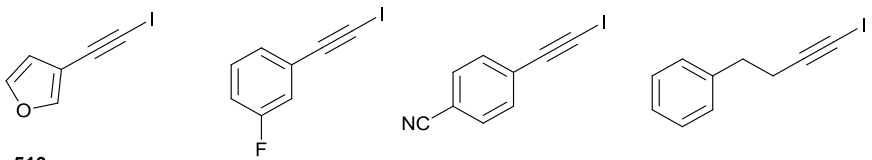
507

Scheme 4.25. Isolated yields reported for the products (^{1}H-NMR conversions in parentheses)

Formation of alkynylbromide **509b** required longer reaction times (3 hr) to achieve a reasonable conversion and afforded an inseparable mixture of starting material and product. Unfortunately treatment of alkyne **507** with NCS under the same reaction conditions didn't afford the desired alkynylchloride even after prolonged heating but only a small amount of de-silylated product probably due to traces of water either in the reaction solvent or in NCS.

Given the successful results for the synthesis of iodoalkynes, it was decided to extend the scope of the reaction to a series of aryl and heteroaryl TMS protected acetylenes (**Scheme 4.26**).





510
$HNTf_2$ 47% (96%)
TfOH 42%

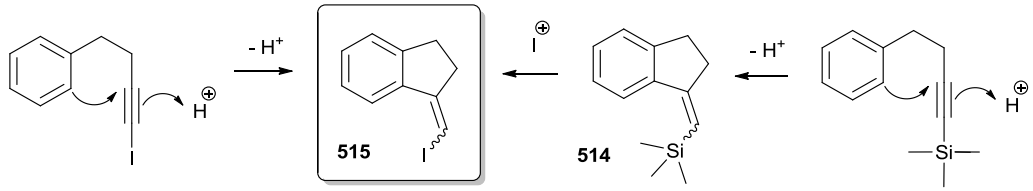
511
91%

512
90%

513
(60%)

Scheme 4.26 Reagents and conditions: NIS (1 eq), Tf_2NH (2 mol%), CH_2Cl_2 (0.1 M), RT. Isolated yields reported for the products (^{1}H-NMR conversions in parentheses)

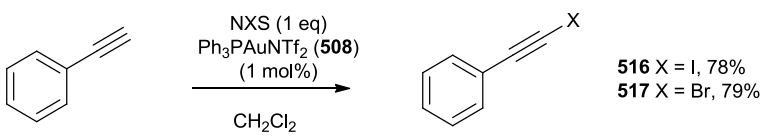
Electron rich furan substrate **510** was almost quantitatively converted to the corresponding iodoalkyne after 1 hour at RT, as observed by NMR, but unfortunately the isolated yield was only moderate, probably due to decomposition on silica during the purification step. A similar result was observed when triflic acid (2 mol %) was used, although longer reaction times were needed to achieve complete conversion (24 hr). Complete conversion to alkynes **511** and **512**, bearing electron-withdrawing substituents in the 3 and 4 position was observed: formation of the 3-fluoro derivative **511** was achieved in 4 hr at RT (TLC) whereas the formation of the 4-cyano derivative **512** required 24 hr at RT (TLC). Unfortunately the conversion observed (NMR) for the alkyl substituted acetylene **513** was only 60% even after stirring the reaction for prolonged times and at high temperatures. After purification the product was isolated in very low yields (24%) together with a mixture of starting material, and vinyliodides **515** (structures were tentatively assigned from 1 and 2D NMR data). These products are likely to result from the acid catalysed cyclisation shown in **Scheme 4.27**, either from alkynyliodide **513** or from cyclised vinylsilane **514**.



Scheme 4.27

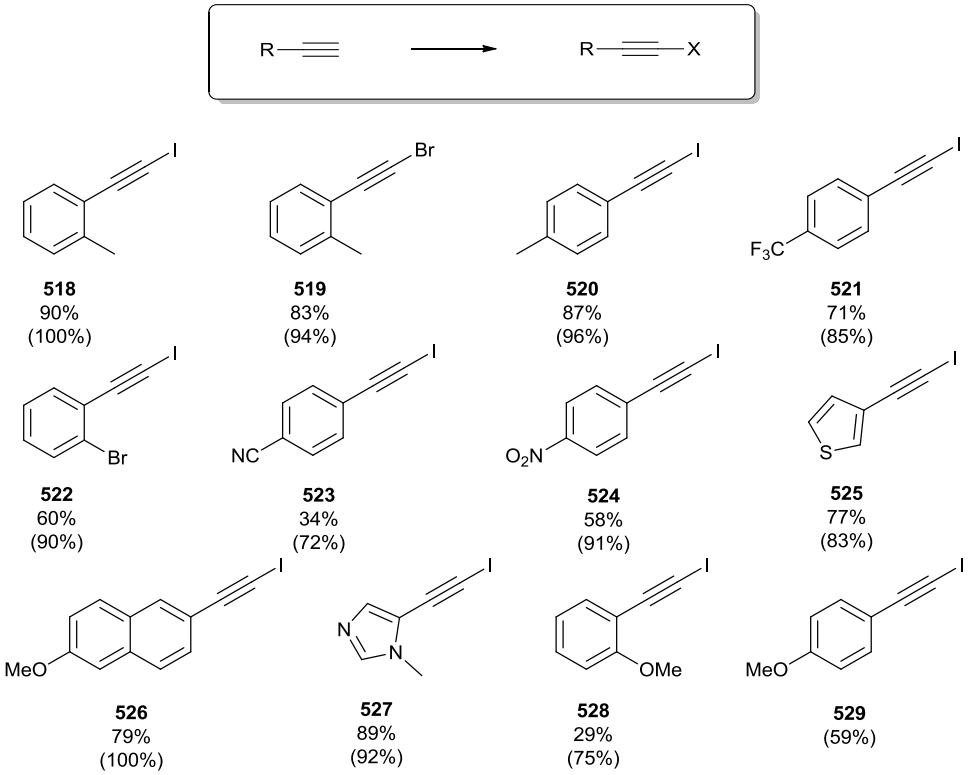
4.4 Gold catalysed halogenation of terminal alkynes

Inspired by the successful preliminary results on the halogenation of terminal alkynes catalysed by the Gagosz catalyst (**508**), the formation of iodo and bromo phenylacetylenes **516** and **517** was investigated (**Scheme 4.28**).



Scheme 4.28

Conversion to alkynyliodide **516** was complete in 1 hr at RT whereas formation of bromoalkyne **517** was found to be more sluggish and required 24 hr at reflux (NMR). Both haloalkynes could be isolated after a quick filtration through a silica plug, although minor losses of the product were observed during this purification step. Interestingly no reaction was observed when MeCN was used as the reaction solvent. The reaction was also tested on a series of aromatic and heteroaromatic terminal alkynes in order to probe the scope and the limitations of this transformation (**Scheme 4.29**).



Scheme 4.29. Reagents and conditions: $Ph_3PAuNTf_2$ (1 mol%), NXS (1 eq), DCM, RT or 40 °C. Isolated yields reported for the products (^{1}H-NMR conversions in parentheses)

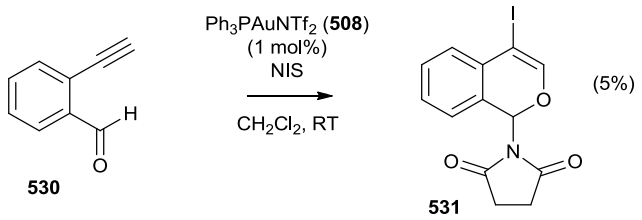
The presence of a methyl substituent in the 2 or 4 position (**518**, **519** and **520**) didn't affect the reactivity of the substrates towards halogenation. The presence of electron-withdrawing groups on the aromatic ring generally required higher temperatures (reflux) in order to achieve complete conversion. In the case of the 4-trifluoromethyl substituted compound **521** complete conversion was achieved at RT after 24 hr whereas substrate **524** bearing a 4-nitro group required heating at reflux for 24 hr in order to achieve almost complete conversion (91% by ^{1}H-NMR). The conversion observed for the *p*-cyanoaryl substituted alkyne **523** after 24 hr at RT was good (72% by ^{1}H-NMR) but unfortunately the yield dropped after purification on silica gel.

Almost quantitative conversion was observed for alkyne **522** bearing a Br substituent at the 2 position after 24 hr stirring at RT but once again chromatographic purification caused a substantial loss of product.

The presence of electron donating substituents seemed to have a detrimental effect on isolation procedures, in fact both substrates **528** and **529** bearing a methoxy group on the aromatic were isolated in low yields. In the case of 2-ethynylanisole **528** the reaction required 7 days of stirring at RT in order to achieve a reasonable conversion (77% by ^{1}H-NMR) but unfortunately product **528** could only be isolated in 29% yield after column chromatography as an inseparable mixture with the starting material. In the case of 4-ethynylanisole **529** only a moderate conversion was observed (59% by ^{1}H-NMR) after 24 hr at RT and an unidentified impurity was also detected together with the unreacted starting material. Even though iodoalkyne **529** could not be isolated from the reaction mixture it was possible to use the crude reaction mixture in subsequent transformations (see **Section 4.5**). Surprisingly the 6-methoxy naphthalene derivative afforded iodoalkyne **526** in very good yield after only 1 hr at RT.

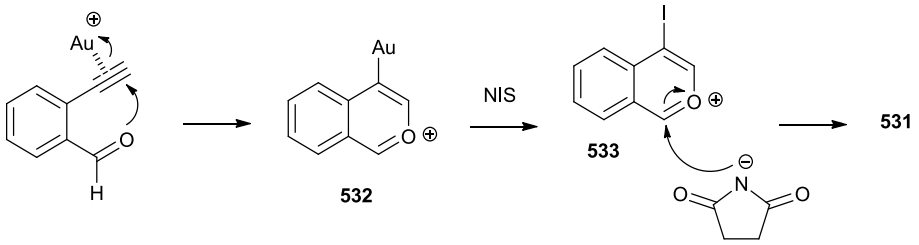
Heteroaromatic substituents **525** and **527** were very well tolerated too, affording the corresponding products in excellent yields after a few hours at RT.

Interestingly the reaction of *o*-formylphenylacetylene **530** afforded isochromene **531** as the major product after chromatographic separation, albeit in very poor yield (**Scheme 4.30**).



Scheme 4.30

Presumably, this is formed after Au catalysed 6-*endo*-dig cyclisation of the aldehyde onto the alkyne followed by iodination of the vinyl-gold intermediate **532** with NIS and trapping of the oxonium ion **533** with succinimide (**Scheme 4.31**).



Scheme 4.31.

The presence of nitrogen atoms, either in aniline **534**, pyridine **535** or amine **536**, seemed to be very detrimental to the reaction: none of the products in **Fig. 4.1** were detected by NMR.

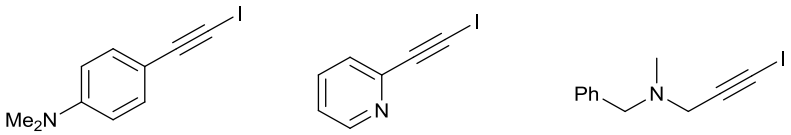
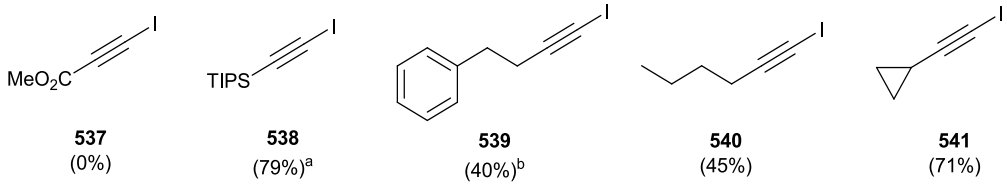


Fig. 4.1

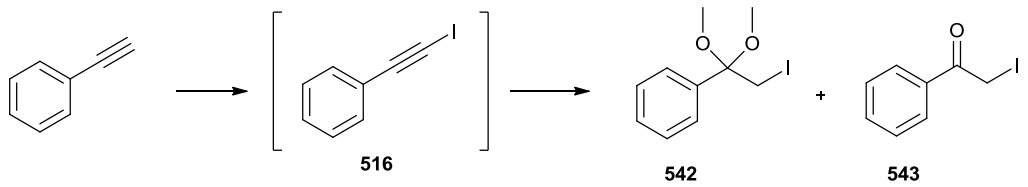
Alkyl substituted acetylenes were also tested in the reaction (**Scheme 4.32**). Methyl propiolate was not converted to the corresponding alkyne **537**. Good conversions were recorded (^{1}H-NMR) for all other substrates after 5 days at RT (**539**, **540** and **541**) or after 2 days at reflux (**538**). However, none of the iodoalkynes were isolated due to their volatility/instability to chromatographic purification.



Scheme 4.32 *(a)* Reaction carried out at reflux; *(b)* Small amounts of vinyliodides **515** were detected in the crude ^{1}H-NMR.

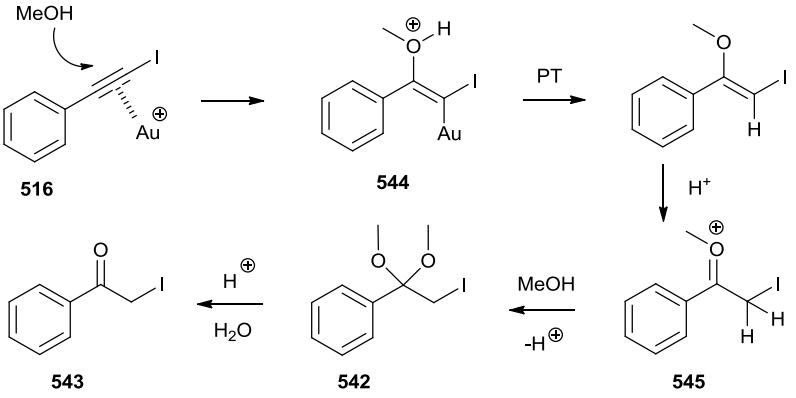
4.5 Direct synthesis of iodoketones and heterocycles from terminal alkynes

When methanol (1 eq) was added to the gold(I) catalysed reaction of terminal alkynes with N-iodosuccinimide, the formation of a mixture of dimethylacetal **542** and α-iodoketone **543** was observed by NMR (**Scheme 4.33**).



Scheme 4.33 Reagents and conditions: $Ph_3PAuNTf_2$ (1 mol%), NIS (1 eq), MeOH (1 eq), DCM, RT, 24 hr.

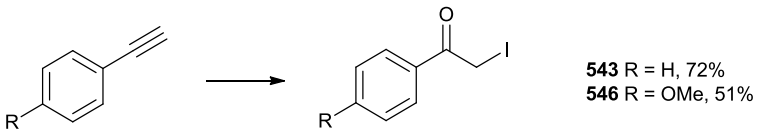
The formation of these two products is consistent with the hydration of the alkynyliodide intermediate **516**; in the presence of gold(I) alkyne **516** is activated towards nucleophilic attack of MeOH at the benzylic position.[246] Protodeauration of intermediate **544** would then furnish oxonium intermediate **545** which would still be susceptible to nucleophilic attack of another molecule of MeOH to afford ketal **542** (**Scheme 4.34**).



Scheme 4.34

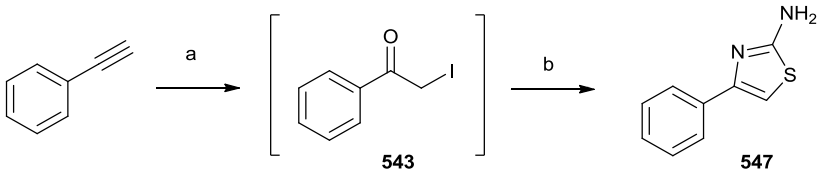
Traces of water in the reaction mixture could also explain the formation of ketone **543** after acid catalysed hydrolysis of ketal **542**.

It was also observed that a sample of the crude reaction mixture in $CDCl_3$ containing both ketal **542** and ketone **543** slowly afforded only ketone **543** when left standing at RT over 1 day. When the reaction was repeated in $CHCl_3$ as the reaction solvent, the major product isolated was α-iodoketone **543** (**Scheme 4.35**).



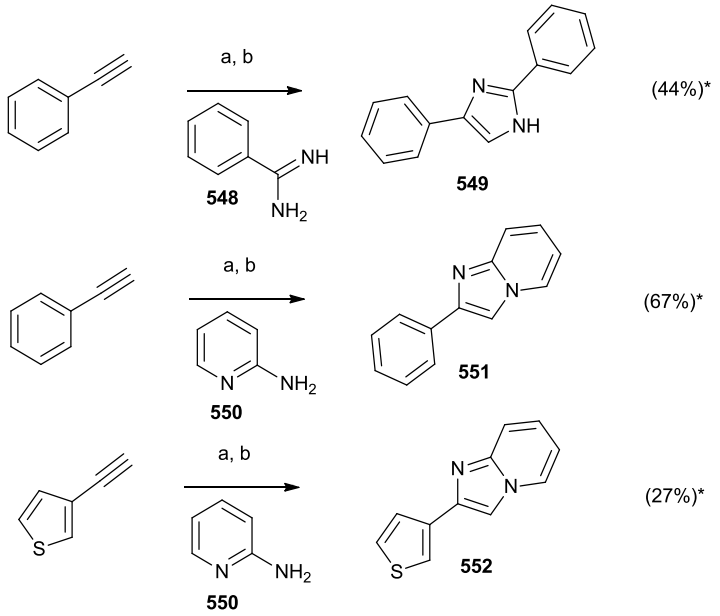
Scheme 4.35. Reagents and conditions: $Ph_3PAuNTf_2$ (1 mol%), NIS (1 eq), MeOH (1 eq), $CHCl_3$, RT, 24 hr.

Iodoacetophenone **543** was isolated from phenylacetylene in very good yield and also 4-ethynylanisole afforded the corresponding iodoketone **546** in good yield. Although these substrates proved to be sufficiently stable to be isolated by column chromatography, it was thought this reaction could be used to generate iodoketones *in situ* as intermediates for the synthesis of heterocycles (**Scheme 4.36**).[247] Iodoketone **543** was therefore synthesised from phenylacetylene and the crude reaction mixture was used in the following step in the reaction with thiourea to afford 2-aminothiazole **547** in moderate yield.



Scheme 4.36 Reagents and conditions: a) $Ph_3PAuNTf_2$ (1 mol%), NIS, MeOH, $CHCl_3$, RT, 24 hr; b) thiourea, DMF, RT, 24 hr, RT, 48% (2 steps).

Using the one-pot procedure described in **Scheme 4.36** a series of heterocycles were successfully synthesised in moderate to good yields (**Scheme 4.37**).

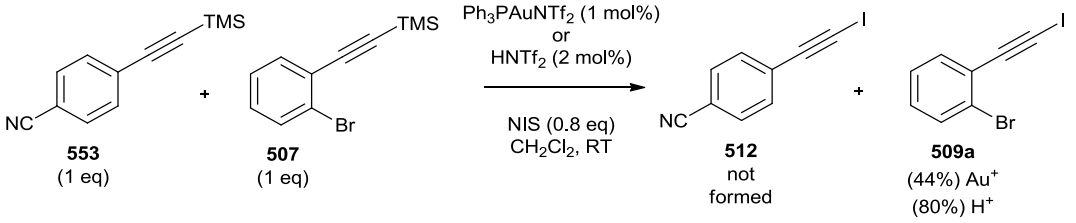


Scheme 4.37. a) $Ph_3PAuNTf_2$ (1 mol%), NIS, MeOH, $CHCl_3$, RT, 24 hr; b) **548** or **550**, DMF, RT, 24 hr, RT. $^{(*)}$yields are calculated on two consecutive steps

4.6 Mechanism of the Halogenation Reactions

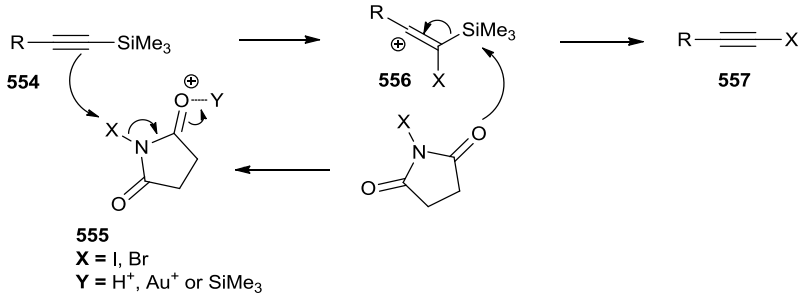
Halogenation of trimethylsilylalkynes

As previously described in **Section 4.3** and **4.4**, the formation of haloalkynes was observed from TMS-acetylenes either via gold or Brønsted acid catalysis. Interestingly, gold and acid catalysis showed similar chemoselectivity in a competition reaction between TMS-alkynes **553** and **507** (**Scheme 4.38**).



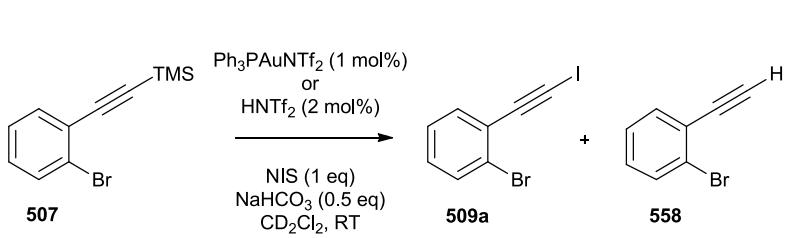
Scheme 4.38. Competition experiments for TMS-acetylenes. Conversions were recorded by ^{1}H-NMR after 1 hr at RT.

When an equimolar mixture of substrates **553** and **507** was treated with substoichiometric amounts of NIS (0.8 eq) in the presence of either gold or acid catalysis, only the more electron rich iodoacetylene **509a** was obtained in both cases. The reaction with the gold catalyst was slower than the acid catalysed one, which was essentially complete after only 1 hr at RT. These observations suggest that a similar reaction mechanism might take place in both circumstances (**Scheme 4.39**). The reaction is likely to proceed through the activation of NXS (X= I, Br) either via a Lewis acid (Y= Au or $SiMe_3$) or Brønsted acid (Y=H). The reaction of the highly electrophilic intermediate **555** with alkyne **554** could generate cation **556**, stabilised by the presence of the silicon group. This would then undergo silyl transfer onto NIS, thus affording haloalkyne **557**.



Scheme 4.39. Proposed mechanism for haloalkyne formation from TMS-acetylenes

In order to further support this hypothesis the halogenation reaction was carried out in the presence of a base ($NaHCO_3$, **Scheme 4.40**) with the intent of neutralising any trace of Brønsted acid catalyst in the reaction in both the gold and the acid catalysed reactions.



Au cat.			
time (hr)	507	509a	558
1	55	39	6
20	30	39	31

H^+ cat.			
time (hr)	507	509a	558
1	22	43	35
20	13	52	35

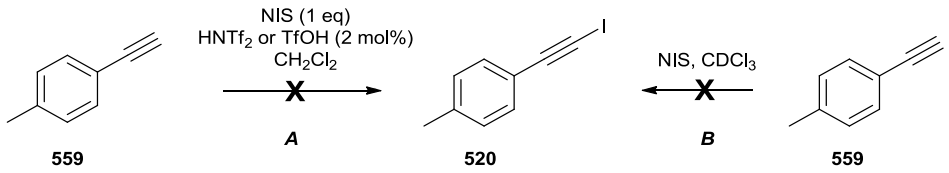
Scheme 4.40 Halogenation reaction in the presence of $NaHCO_3$. Ratios between observed products were calculated from the integration of ^{1}H-NMR peaks

In the case of the Au catalysed reaction the formation of iodoalkyne **509a** was detected by ^{1}H-NMR (~39% after 1 hr) but it was found that upon prolonged reaction times the SM was only being converted to terminal alkyne **558**. This observation could be consistent with the presence of water in the reaction mixture, either from the reagents or being generated in the neutralisation reaction, which, given the basic conditions, could cause desilylation.

Interestingly, the acid catalysed reaction afforded some halogenated product even in the presence of $NaHCO_3$, although the reaction was considerably slower than previously observed. We believe that in this case the formation of iodoalkyne **509a** could be caused by the low solubility of the inorganic base in the reaction solvent, which allows the catalysts to react with the substrate before being neutralised by the base.

Halogenation of terminal alkynes

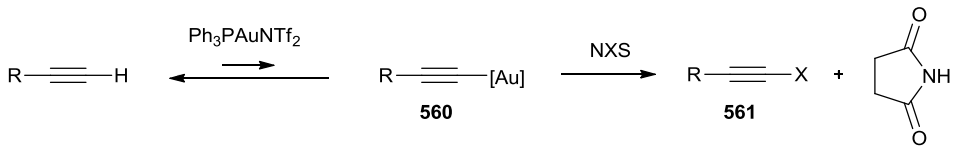
In the case of terminal alkynes no halogenation occurred when the gold catalyst was not present in the reaction. As shown by the experiments in **Scheme 4.41**, when alkyne **559** was treated with an electrophile (NIS) either under acid catalysis (**A**) or with no catalyst at all (**B**), only starting material was detected.



Scheme 4.41

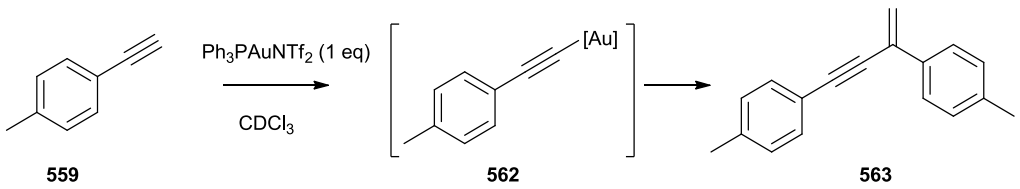
After 1 week at RT only starting material **520** could be detected by ^{1}H and ^{13}C NMR. These observations suggest that cationic gold is necessary in order to carry out the halogenation reaction from terminal alkynes.

A plausible mechanism for the gold catalysed formation of haloalkynes from terminal acetylenes is shown in **Scheme 4.42**; in the presence of the gold catalyst, small amounts of gold acetylide **560** would be formed. The organometallic species could then react with NXS to give haloalkyne **561** and succinimide.



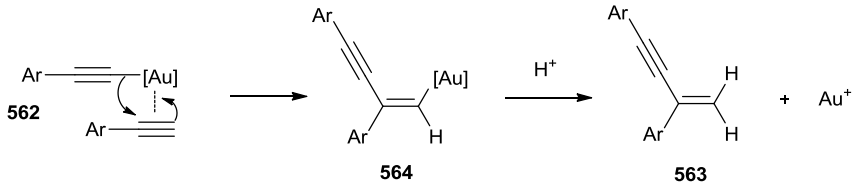
Scheme 4.42

A stoichiometric NMR experiment was also carried out with the hope to observe the formation of gold acetylide **562** (**Scheme 4.43**).[248]



Scheme 4.43

Unfortunately the concentration of gold acetylide was probably too low to be detected by NMR but, nevertheless, upon prolonged stirring at RT (3 days), the formation of dimeric species **563** was observed. A plausible mechanism for the formation of alkene **563** is shown in **Scheme 4.44**.[248]



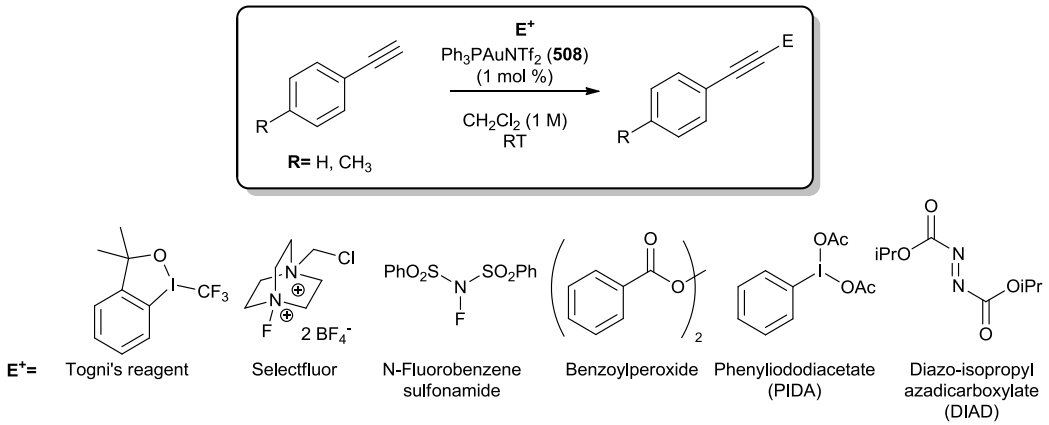
Scheme 4.44

Gold acetylide **562** could add across the triple bond giving alkenyl-gold **564**. This intermediate then undergoes protodeauration to afford terminal alkene **563**.

4.7 Miscellaneous

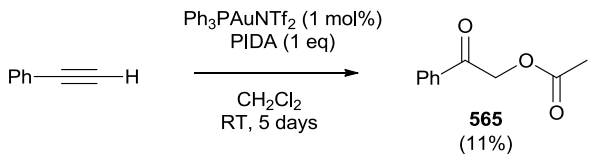
4.7.1 Reaction of terminal alkynes with electrophiles catalysed by Au(I)

A series of different electrophiles was tested in the reaction with terminal alkynes in the presence of gold catalyst $Ph_3PAuNTf_2$ (**508**) (**Scheme 4.45**).



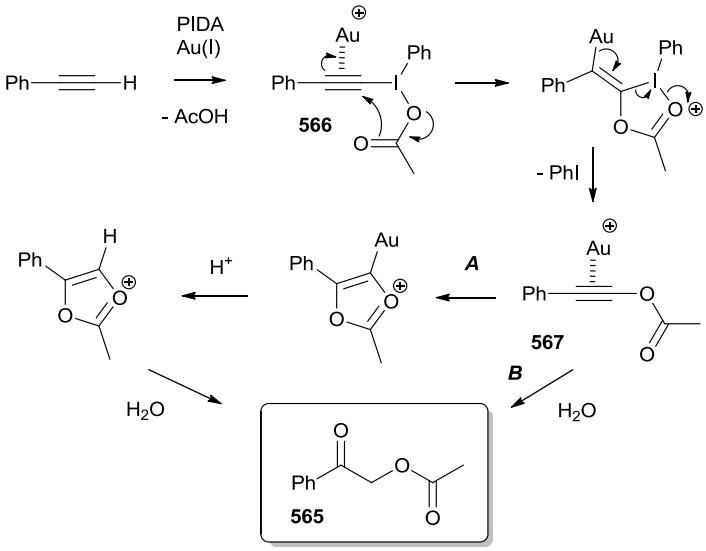
Scheme 4.45

With the exception of PIDA, all reactions showed unreacted starting material (NMR). When phenylacetylene was treated with PIDA and Gagosz catalyst **508** at RT, the slow disappearance of the SM was detected by both ^{1}H and ^{13}C NMR over the course of 5 days. After chromatographic purification the only product isolated was α-acetoxyacetophenone **565** in 11% yield (**Scheme 4.46**).



Scheme 4.46

When the reaction was monitored by NMR, the slow consumption of PIDA and the appearance of iodobenzene and acetic acid were recorded during the course of 5 days. Interestingly, new signals were also recorded by ^{13}C-NMR (at 166.5, 94.5 and 22.3 ppm) and the formation of a new spot was detected by TLC. However only a singlet peak at 2.25 ppm was recorded by ^{1}H-NMR, whereas no signal for the methylene unit of α-acetoxyacetophenone was detected (at 5.38 ppm). This observation suggests that α-acetoxyacetophenone is not formed in the reaction mixture but only after the isolation step. Although the reaction between PIDA and terminal alkynes to afford acetoxyketones has previously been described without the use of gold catalysis,[249] we believe a slightly different mechanism might take place in the case of the gold catalysed reaction (**Scheme 4.47**).



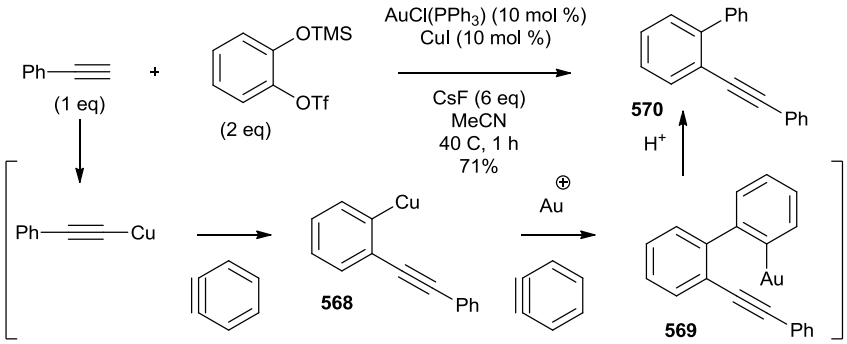
Scheme 4.47

Phenylacetylene could initially react with PIDA to form hypervalent iodine intermediate **566** which, in the presence of the gold(I) catalyst, could form ynol-acetate **567** via intramolecular nucleophilic attack of the acetate group followed deauration and reductive elimination. The formation of either intermediate **566** or **567** could be consistent with the observed NMR data. Subsequently, either gold

catalysed cyclisation followed by hydrolysis (***A***) or hydration of ynol-acetate **567** (***B***) could afford α-acetoxyacetophenone **565**.

4.7.2 Reaction of terminal alkynes with benzyne catalysed by Au(I)

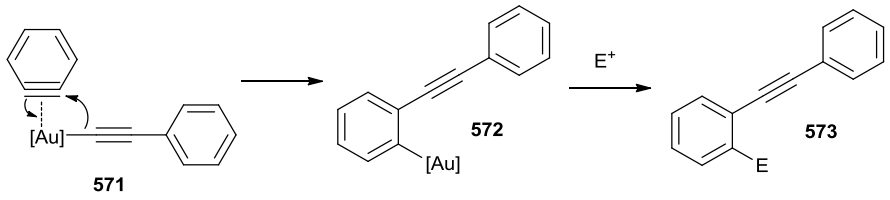
Zhang recently reported the Au/Cu catalysed reaction between terminal alkynes and arynes to give biphenyl derivatives (**Scheme 4.48**).[250]



Scheme 4.48

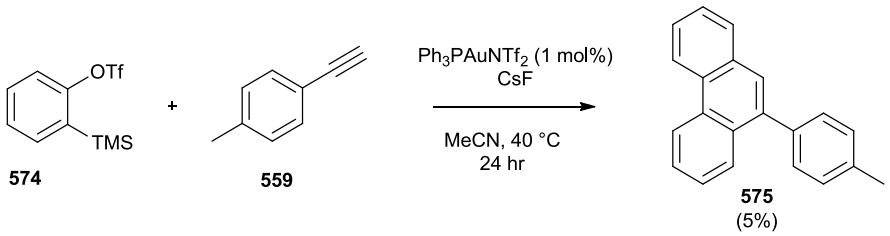
The authors propose that addition of the alkynylcopper intermediate to the *in situ* generated benzyne gives aryl-copper intermediate **568**. This reacts further with a second molecule of benzyne in the presence of the gold catalyst to give aryl-gold species **569** which affords product **570** after protodeauration. The authors reported that in the presence of $NaAuCl_4$ (10 mol%) and $AgSbF_6$ (10 mol%) product **570** was also isolated, albeit in poor yields.

Intrigued by this observation, we were interested in investigating the role of gold acetylides with the *in situ* generated benzyne. We assumed that once generated *in situ*, benzyne could react with gold acetylide **571** to give aryl-gold intermediate **572**. In the presence of an electrophile the latter would then give ortho substituted aryl **573** (**Scheme 4.49**).



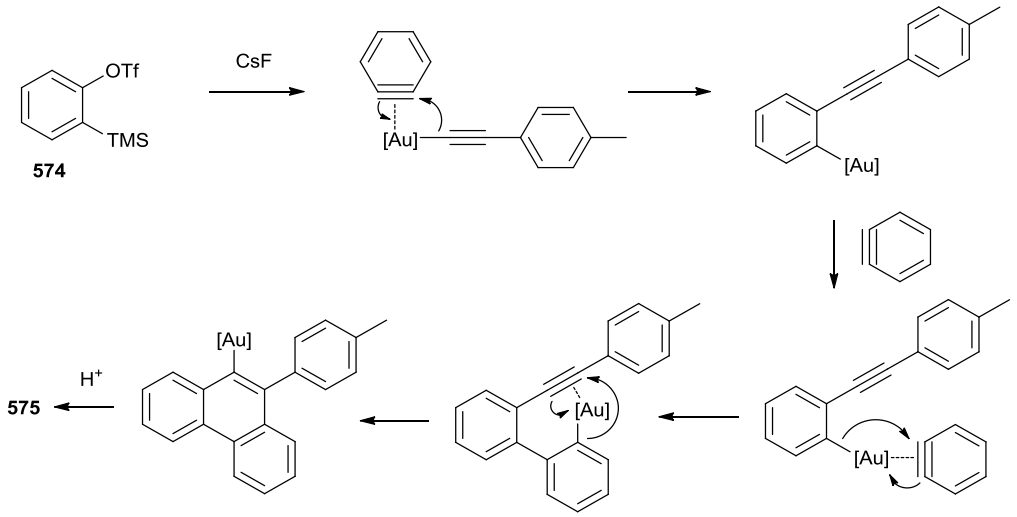
Scheme 4.49. Proposed addition of gold acetylide to benzyne followed by reaction with an electrophile

An initial experiment was carried out in the presence of benzyne precursor **574**, alkyne **559** and $Ph_3PAuNTf_2$ (1 mol %) without a source of electrophile. **(Scheme 4.50**)



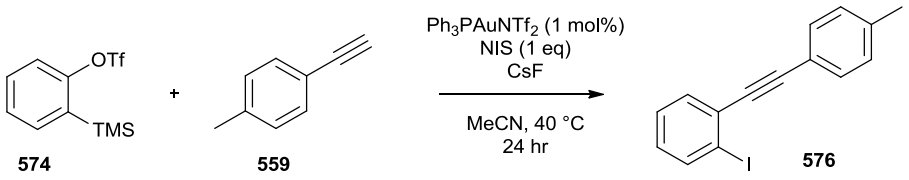
Scheme 4.50

Interestingly, 9-(*p*-tolyl)phenanthrene **575** was isolated after chromatography, albeit in a very poor yield, together with an unidentified impurity. Phenanthrene **575** is likely to generate after addition of the aryl-gold intermediate to a second molecule of benzyne, as described in **Scheme 4.51**.



Scheme 4.51

The formation of compound **575** gives further evidence that the addition of the gold acetylide to benzyne is possible, without the need of a copper co-catalyst. The reaction was subsequently repeated in the presence of the electrophile (NIS, **Scheme 4.52).** NMR analysis of the crude reaction mixture seems to show the formation of compound **576** but unfortunately the isolation of the expected product was unsuccessful.

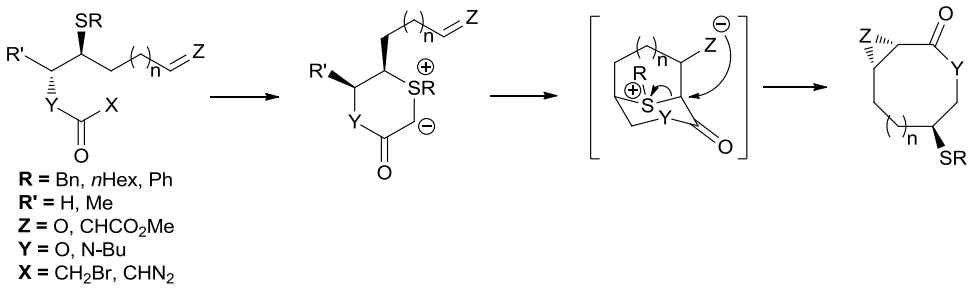


574 **559** **576**

Scheme 4.52

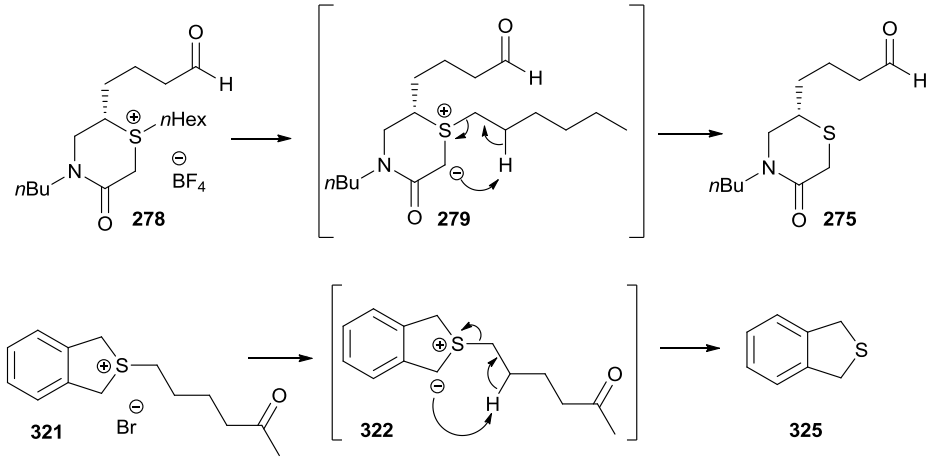
4.8 Conclusions

This thesis describes various attempts towards the formation of medium sized rings via the ylide mediated *tandem* double cyclisation/fragmentation approach described in **Scheme 4.53.**



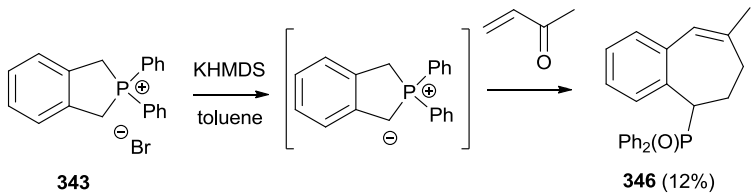
Scheme 4.53

Unfortunately all the attempts resulted either in decomposition of the starting materials or in unwanted side reactions, as observed for alkyl-substituted sulfur ylide **279** and benzyl-stabilised ylide **322** (**Scheme 4.54**).



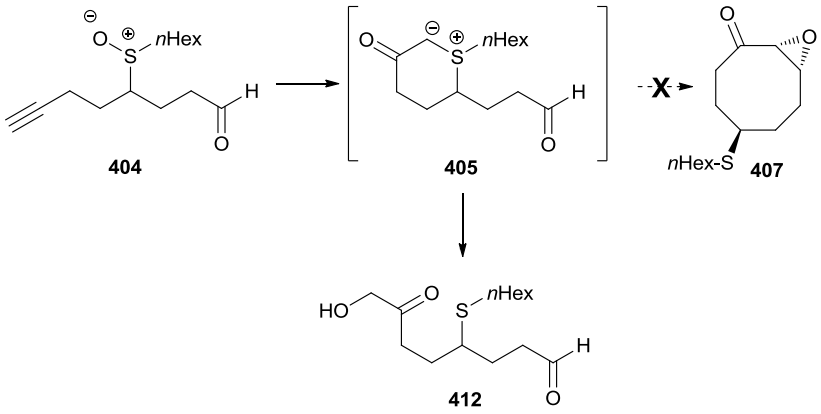
Scheme 4.54

In parallel with the investigation on sulfur ylides, nitrogen and phosphorus ylides were also studied (**Scheme 4.55**). Albeit in modest yield, medium ring product **346**, resulting from a *tandem* Michael addition/intramolecular Wittig reaction of cyclic phosphonium salt **343** with methylvinylketone, was detected by NMR but its isolation by column chromatography could not be achieved.



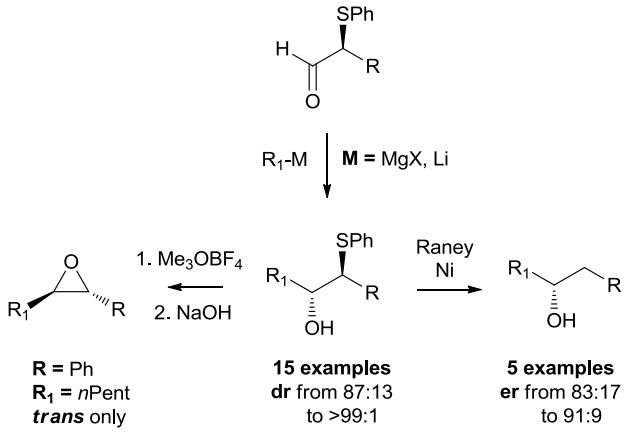
Scheme 4.55

The metal catalysed generation of ylides from bis-homopropargylic sulfoxides (**Scheme 4.56**) was also studied. Various catalysts and reaction conditions were screened but unfortunately only unwanted α-hydroxyketone **412** was isolated from the reaction mixture.



Scheme 4.56

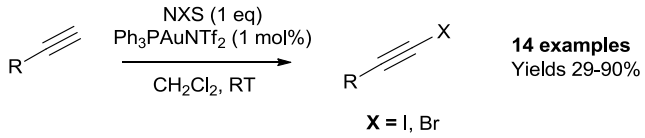
During the synthesis of vicinal sulfido-alcohols, precursors to medium rings, we discovered that high levels of diastereoselectivity were obtained after the addition of organometallic reagents to α-sulfenyladehydes (**Scheme 4.57**). Subsequently, secondary alcohols could also be obtained after Raney–Ni reduction with generally good levels of enantioselectivity.



Scheme 4.57

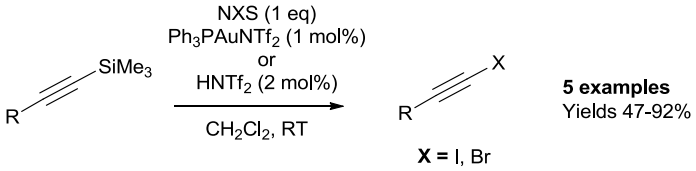
Moreover, vicinal sulfido-alcohols were also used to selectively obtain *trans* epoxides.

Alongside the studies on the gold catalysed generation of ylides, this thesis reports the use of a gold(I) catalyst ($Ph_3PAuNTf_2$) in a very mild procedure for synthesis of iodo and bromoalkynes from terminal acetylenes (**Scheme 4.58**)



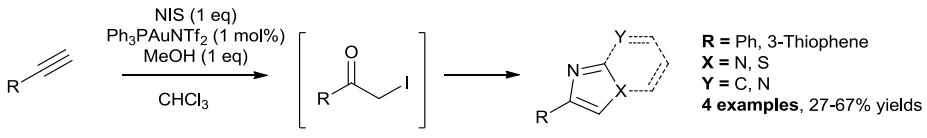
Scheme 4.58

Interestingly it was also discovered that haloalkynes could be obtained from trimethylsilylacetylenes under both gold(I) and acidic catalysis. (**Scheme 4.59**)



Scheme 4.59

Gold(I) catalysis was also successfully employed for the one-pot synthesis of heterocycles from terminal alkynes (**Scheme 4.60**).



Scheme 4.60

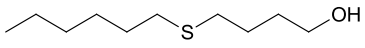
5. Experimental

5.1 General Methods

All glassware was thoroughly dried in an oven at 120°C prior to use. All reactions were carried out at atmospheric pressure, under argon, unless otherwise stated. Solvents and reagents were purchased from suppliers and used without any further purification. Normal phase silica gel (BDH) and sand (VWR) were used for flash chromatography (FC). All reactions monitored by TLC unless otherwise stated. TLC plates pre-coated with silica gel 60 F_{254} on aluminium (Merck KGaA) were used, detection was by UV (254 nm) or chemical stain ($KMnO_4$ or PMA). High resolution mass spectrometry was performed using a VG70 SE instrument operating in modes CI (chemical ionisation), EI (electron ionisation), ESI (electrospray ionisation) and FAB (fast atom bombardment). NMR spectra were recorded at 300, 400, 500 and 600 MHz for ^{1}H and at 75, 100, 125 and 150 MHz for ^{13}C on Bruker instruments (AMX-300, AMX-400, AMX-500, AMX-600 respectively) at ambient temperature, unless otherwise stated; ^{19}F and ^{31}P NMR spectra were recorded on Bruker AMX-300 at 282 MHz and 121 MHz respectively; all chemical shifts were referenced to the residual proton impurity of the deuterated solvent. The multiplicity of the signal is indicated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (double of doublets), dt (double of triplets), m (multiplet), defined as all multipeak signals where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. All peaks should be taken as sharp unless otherwise described. Coupling constants are defined as J and quoted in Hz to one decimal place. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Room temperature is defined as between 19-22ºC. *In vacuo* is used to describe solvent removal by Büchi rotary evaporation between 17ºC and 60ºC, at approx 10 mmHg unless otherwise stated. For NMR experiments, $CDCl_3$ denotes deuterated (d^1) chloroform, DMSO-d_6 denotes deuterated (d^6) dimethylsulfoxide, and CD_3OD denotes deuterated (d^4) methanol. Deuterated solvents were chosen according to the position of solvent peak in spectra and solubility of substrate.

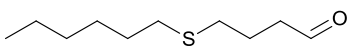
5.2 Experimental procedures

4-(Hexylsulfanyl)butan-1-ol (206)



Azobisisobutyronitrile (2.28 g, 13.9 mmol) was added in one portion to a solution of 3-butene-1-ol (5.90 ml, 69.3 mmol) and *n*-hexanethiol (19.5 ml, 139 mmol) in MeCN (200 ml) stirred at RT. The reaction mixture was heated at reflux over 1.5 hr and the solvent was then removed *in vacuo*. The crude material was purified by column chromatography (Pet/EtOAc = 70/30) to afford **206** as pale yellow oil (13.2 g, 69.3 mmol, quant.). ν_{max} (film/cm^{-1}) 3345, 2925, 2856, 1456, 1378, 1242, 1055, 924; δ_H (600 MHz, $CDCl_3$) 0.90 (3H, t, J = 6.8, CH_3), 1.30 (4H, m, 2 × CH_2), 1.39 (2H, m, 1 × CH_2), 1.59 (2H, quint, J = 7.6, 1 × CH_2), 1.69 (4H, m, 2 × CH_2), 2.52 (2H, t, J = 7.4, 1 × SCH_2), 2.56 (2H, m, 1 × SCH_2), 3.68 (2H, m, CH_2OH); δc (125 MHz, $CDCl_3$) 14.1, 21.5, 22.6, 26.0, 28.7, 29.7, 31.5, 32.0, 32.2, 62.5; Found (EI): $[M]^+$ 190.13883, $C_{10}H_{22}OS$ requires 190.13858.

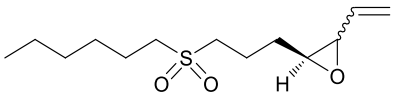
4-(Hexylsulfanyl)butanal (207)



Oxalyl chloride (2.93 ml, 34.2 mmol) was added dropwise to a solution of DMSO (4.85 ml, 68.3 mmol) in CH_2Cl_2 (200 ml) cooled to -78 °C. The solution was stirred at this temperature for 15 min after which time alcohol **206** (5.00 g, 26.3 mmol) was added. The resulting mixture was stirred for 15 min at -78 °C, then NEt_3 (18.3 ml, 131 mmol) was added and the mixture allowed to warm to RT over 1 hr. The reaction was quenched with water (100 ml) and the phases were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 90/10)

to afford **207** (1.78 g, 9.45 mmol, 36%) as a colourless oil. ν_{max} (film/cm^{-1}) 2926, 2856, 2720, 1726, 1455, 1286, 1247; δ_H (600 MHz, C_6D_6) 0.86 (3H, t, J = 7.1, CH_3), 1.11-1.27 (6H, m, $CH_3(CH_2)_3$), 1.44 (2H, quint, J = 7.3, $CH_3(CH_2)_3CH_2$), 1.57 (2H, quint, J = 7.0, CH_2CH_2CHO), 1.88 (2H, td, J = 7.0, 1.1, CH_2CHO), 2.18 (2H, t, J = 7.0, $SCH_2(CH_2)_2CHO$), 2.25 (2H, t, J = 7.3, $CH_3(CH_2)_4CH_2S$), 9.25 (1H, t, J = 1.1, CHO); δc (150 MHz, C_6D_6) 13.9, 21.7, 22.6, 28.5, 29.6, 31.1, 31.4, 31.7, 42.2, 199.6; Found (EI): $[M]^+$ 188.12248, $C_{10}H_{20}OS$ requires 188.12293.

2-(3-(Hexylsulfonyl)propyl)-3-vinyloxirane (213)

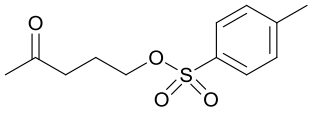


Allylbromide (0.13 ml, 1.51 mmol) was added to a solution of aldehyde **207** (190 mg, 1.01 mmol), KOH (113 mg, 2.02 mmol) and TBAB (35 mg, 0.10 mmol) in a mixture of CH_2Cl_2 (10 ml) and water (1 ml). The reaction was heated at 40 °C for 5 days, then cooled to RT and partitioned between CH_2Cl_2 (10 ml) and water (10 ml). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness.

The crude oil was dissolved in a mixture of CCl_4 (1 ml), MeCN (1 ml) and water (2 ml) and stirred at RT. A solution of ruthenium trichloride hydrate (50 µg, 0.022 µmol) in MeCN (0.2 ml) was added to the reaction mixture, followed by $NaIO_4$ (187 mg, 0.88 mmol). After 1 hr the reaction was diluted with water and extracted with Et_2O (10 ml); the phases were separated and the aqueous layer was extracted with Et_2O (10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by column chromatography (Pet/EtOAc = 80/20 → 70/30) to afford epoxide **213** (18 mg, 0.07 mmol, 16%) as a colourless oil.; ν_{max} (film/cm^{-1}) 2956, 1456, 1366, 1269, 1230, 1217, 1124, 1109; isolated as a 7:3 mixture of *trans:cis* isomers; ***trans* isomer**: δ_H (600 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.0, CH_3), 1.31 (4H, m, $CH_3CH_2CH_2$), 1.43 (2H, quint, J = 7.3, $CH_3(CH_2)_2CH_2$), 1.56-1.67 (1H, m, CH_2CHHCH), 1.82 (2H, m, $CH_3(CH_2)_3CH_2$), 1.94 (1H, m, CH_2CHHCH), 2.02 (2H,

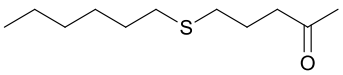
quint, J = 7.9, C*H*$_2$CH$_2$CH), 2.86 (1H, m, CH$_2$C*H*), 2.95 (2H, m, CH$_3$(CH$_2$)$_4$C*H*$_2$SO$_2$), 2.97-3.07 (2H, m, SO$_2$C*H*$_2$(CH$_2$)$_2$CH), 3.13 (1H, dd, J = 7.4, 2.0, CH$_2$=CHC*H*), 5.29 (1H, dd, J = 10.3, 1.4, CH=CH*H*$_{cis}$), 5.47 (1H, dd, J = 17.2, 1.4, CH=CH*H*$_{trans}$), 5.55 (1H, m, C*H*=CH$_2$); δc (125 MHz, CDCl$_3$) 14.1, 18.8, 22.1, 22.4, 28.3, 30.7, 31.1, 52.2, 53.1, 58.4, 59.5, 119.9, 135.2; ***cis* isomer**: δ_H (600 MHz, CDCl$_3$) 0.89 (3H, t, J = 7.0, CH$_3$), 1.31 (4H, m, CH$_3$C*H*$_2$C*H*$_2$), 1.43 (2H, quint, J = 7.3, CH$_3$(CH$_2$)$_2$C*H*$_2$), 1.56-1.67 (1H, m, CH$_2$C*H*HCH), 1.75 (1H, m, CH$_2$CH*H*CH), 1.82 (2H, m, CH$_3$(CH$_2$)$_3$C*H*$_2$), 2.02 (2H, quint, J = 7.9, C*H*$_2$CH$_2$CH), 2.95 (2H, m, CH$_3$(CH$_2$)$_4$C*H*$_2$SO$_2$), 2.97-3.07 (2H, m, SO$_2$C*H*$_2$(CH$_2$)$_2$CH), 3.06 (1H, m, CH$_2$C*H*), 3.44 (1H, dd, J = 7.0, 4.3, CH$_2$=CHC*H*), 5.37 (1H, d, J = 10.5, CH=CH*H*$_{cis}$), 5.48 (1H, d, J = 17.3, CH=CH*H*$_{trans}$), 5.69 (1H, m, C*H*=CH$_2$); δc (125 MHz, CDCl$_3$) 14.1, 19.3, 22.1, 22.4, 26.7, 28.3, 31.3, 52.2, 53.1, 57.0, 57.9, 121.2, 132.0; Found (CI): $[M+H]^+$ 261.15305, $C_{13}H_{25}O_3S$ requires 261.15243.

4-Oxopentyl-4-methylbenzenesulfonate[141] (216)



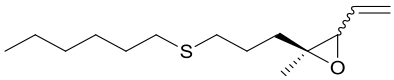
Pyridine (7.80 ml, 97.1 mmol) was added dropwise to a solution of 3-acetyl-1-propanol and *p*-toluensulfonyl chloride (11.1 g, 58.3 mmol) in CHCl$_3$ (75 ml) cooled to 0 °C and stirred at this temperature for 2 hr. The reaction was allowed to warm to RT over 18 hr then diluted with CHCl$_3$ (75 ml) and 2 N HCl (40 ml). The phases were separated and the organic layer was washed with 1 M NaHCO$_3$ (75 ml), brine (75 ml) then dried over MgSO$_4$, filtered and evaporated to dryness. The crude dark brown oil was purified by column chromatography (Pet/EtOAc = 95/5 → 50/50) to give tosylate **216** (2.82 g, 9.32 mmol, 23%) as a colourless oil. δ_H (500 MHz, CDCl$_3$) 1.90 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.10 (3H, s, COCH$_3$), 2.44 (3H, s, ArCH$_3$), 2.53 (2H, t, J = 7.0, COCH$_2$), 4.04 (2H, t, J = 6.0, CH$_2$OTs), 7.34 (2H, d, J = 8.4, 2 × ArH), 7.77 (2H, d, J = 8.4, 2 × ArH); δc (125 MHz, CDCl$_3$) 21.3, 22.5, 29.6, 38.5, 69.3, 127.6, 129.6, 132.6, 144.5, 207.0.

5-(Hexylsulfanyl)pentan-2-one (217)



n-Hexanethiol (0.92 ml, 7.80 mmol) was added dropwise to a stirred suspension of tosylate **216** (1.00 g, 3.90 mmol) and Cs_2CO_3 (5.10 g, 15.6 mmol) in acetone (30 ml). The reaction mixture was heated at reflux for 1 hr then cooled to RT. The mixture was filtered to remove the inorganic salts and the solid was washed several times with acetone. The filtrate was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 95/5) to give ketone **217** (66 mg, 0.33 mmol, 6%) as a colourless oil. ν_{max} (film/cm^{-1}) 2926, 2857, 1738, 1436, 1366, 1228, 1217; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.9, CH_2CH_3), 1.25-1.40 (6H, m, 3 × CH_2), 1.56 (2H, quint, J = 7.4, CH_2CH_2CO), 1.85 (2H, quint, J = 7.1, $CH_3(CH_2)_3CH_2$), 2.15 (3H, s, $COCH_3$), 2.48 (2H, t, J = 7.4, CH_2CO), 2.52 (2H, t, J = 7.0, 1 × SCH_2), 2.57 (2H, t, J = 7.1, 1 × SCH_2); δc (125 MHz, $CDCl_3$) 13.7, 22.2, 22.9, 28.3, 29.3, 29.7, 31.0, 31.1, 31.6, 41.8, 208.0; Found (EI): $[M]^+$ 201.13151, $C_{11}H_{22}OS$ requires 201.13130.

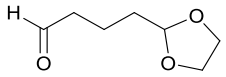
2-(3-(Hexylsulfanyl)propyl)-2-methyl-3-vinyloxirane (218)



Allylbromide (32 µl, 0.37 mmol) was added to a solution of ketone **217** (50 mg, 0.25 mmol), KOH (28 mg, 0.50 mmol) and TBAB (8 mg, 0.02 mmol) in CH_2Cl_2 (2.5 ml) and water (0.25 ml). The reaction was heated at 40 °C for 3 days, then cooled to RT and partitioned between CH_2Cl_2 (10 ml) and water (10 ml). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 80/20) to give epoxide **218** (24 mg, 0.10 mmol, 40%) as a colourless oil. ν_{max} (film/cm^{-1}) 2957, 2926, 2872, 2858, 1459, 1361; isolated as a 1:1 mixture of diastereoisomers: δ_H (600 MHz, $CDCl_3$) 0.86 (3H, t, J = 6.9, CH_2CH_3), 1.18 (1.5H, s, CCH_3), 1.19 (1.5H,

s, CCH_3), 1.23-1.34 (8H, m, 4 × CH_2), 1.47-1.65 (4H, m, 2 × CH_2), 2.44-2.49 (4H, m, 2 × CH_2S), 3.21 (0.5H, d, J = 7.4, C*H*CH=CH_2), 3.23 (0.5H, d, J = 7.4, C*H*CH=CH_2), 5.32 (1H, dd, 10.1, 1.5, CH=CHH_{cis}), 5.44 (1H, dd, J = 17.3, 1.5, CH=CHH_{trans}), 5.73-5.80 (1H, m, CH=CH_2); δc (125 MHz, $CDCl_3$) 13.9, 16.4, 16.5, 22.0, 22.1, 24.9, 27.9, 28.0, 29.1, 29.4, 30.9, 31.0, 31.1, 36.8, 36.9, 61.9, 62.0, 62.3, 63.3, 116.8, 116.9, 135.8, 136.0; Found (EI): $[M-H]^+$ 241.16212, $C_{14}H_{25}OS$ requires 241.16260.

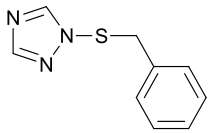
4-(1,3-Dioxolan-2-yl)butanal[251] (226)



Freshly distilled diisopropylamine (6.2 ml, 44.4 mmol) was added dropwise to a solution of *n*BuLi (2.5 M in Et_2O, 17.8 ml, 44.4 mmol) cooled to -78 °C. Anhydrous THF (16 ml) and DMPU (4.9 ml, 40.3 mmol) were added dropwise and the reaction mixture was allowed to warm to RT over 1 hr then cooled to -40 °C. A solution of imine **224** (4.0 g, 40.3 mmol) in anhydrous THF (16 ml) was slowly added dropwise by means of a syringe pump over 80 min. The resulting mixture was allowed to warm to RT over 1 hr then cooled to -40 °C. 2-(2-Bromoethyl)-1,3-dioxolane **225** (4.2 ml, 36.3 mmol) was added dropwise and the reaction mixture was stirred at RT for 3 hr. The reaction was cooled to 0 °C, quenched with 15% w/w Tartaric acid solution (15 ml) and stirred at this temperature for 2 hr. The reaction mixture was extracted with Et_2O (3 × 50 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness. Removal of unreacted alkyl bromide **225** by vacuum distillation (P = 3 Torr, Temp 85 °C) afforded aldehyde **226** as pale brown oil (1.42 g, 9.85 mmol, 25%). ν_{max} (film/cm^{-1}) 2949, 2884, 1721; δ_H (500 MHz, $CDCl_3$) 1.71 (2H, m, 1 × CH_2), 1.77 (2H, m, 1 × CH_2), 2.50 (2H, td, J = 7.0, 1.5, CH_2CHO), 3.84 (2H, m, 2 × OC*H*H), 3.96 (2H, m, 2 × OCH*H*), 4.86 (1H, t, J = 4.5, C*H*$(OR)_2$), 9.76 (1H, t, J = 1.5, CHO); δc (125 MHz, $CDCl_3$) 16.3, 33.4, 43.5, 64.7, 103.8, 201.9.

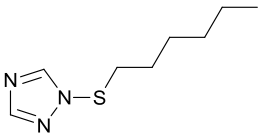
General procedure for sulfenyl-triazole formation: sulfuryl chloride (1 eq) was added dropwise to a solution of dialkyl or diaryl-disulfide (1 eq) in CH_2Cl_2 (1 M) stirred at RT. After stirring for 20 min, this solution was added to a second solution of 1,2,4-triazole (2.5 eq) and NEt_3 (2.2 eq) in CH_2Cl_2 (2.5 M). After 15 min the reaction mixture was concentrated *in vacuo*. The white solid residue was extracted with Pet and with a 7:3 mixture Pet:CH_2Cl_2. The combined extracts were evaporated to dryness and purified by column chromatography (Pet/Et_2O = 7:3 → 5:5) to afford sulfenyl-triazoles.

1-(Benzylthio)-1H-1,2,4-triazole[193] (227)



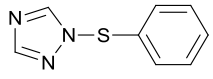
Colourless oil (3.42 g, 17.9 mmol, 45%); δ_H (500 MHz, $CDCl_3$) 4.22 (2H, s, CH_2Ph), 7.01 (2H, m, 2 × PhH), 7.27 (3H, m, 3 × PhH), 7.64 (1H, d, J = 2.7, HetH), 8.03 (1H, d, J = 2.7, HetH); δc (125 MHz, $CDCl_3$) 45.1, 128.1, 128.8, 128.9, 134.1, 151.5, 154.1.

1-Hexylsulfanyl-1,2,4-triazole[252] (235)



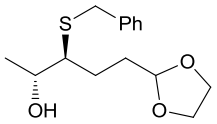
Colourless oil (4.49 g, 24.2 mmol, 61%); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.0, CH_3), 1.23-1.34 (4H, m, $(CH_2)_2CH_3$), 1.41 (2H, quint, J = 7.3, $CH_2(CH_2)_2CH_3$), 1.57 (2H, quint, J = 7.3, SCH_2CH_2), 3.05 (2H, t, J = 7.3, SCH_2), 8.06 (1H, s, HetH), 8.22 (1H, s, HetH); δc (125 MHz, $CDCl_3$) 14.0, 22.5, 27.9, 28.0, 31.3, 41.0, 151.5, 154.2; Found (EI): [M] 185.09867, $C_8H_{15}N_3S$ requires 185.09812.

1-(Phenylthio)-1H-1,2,4-triazole[158] (280)



Colourless oil (7.75 g, 4.37 mmol, 55%); δ_H (400 MHz, $CDCl_3$) 7.38-7.45 (5H, m, 5 × ArH), 8.09 (1H, s, 1 × HetH), 8.37 (1H, s, 1 × HetH), δc (125 MHz, $CDCl_3$) 129.4, 129.6, 129.8, 134.8, 151.0, 154.2, Found (CI): $[M+H]^+$ 178.04439, $C_8H_8N_3S$ requires 178.04388.

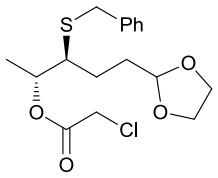
(2*R*,3*S*)-3-(Benzylthio)-5-(1,3-dioxolan-2-yl)pentan-2-ol (229)



A solution of catalyst **228** (364 mg, 0.61 mmol) in toluene (3 ml) was added to a solution of aldehyde **226** (880 mg, 6.10 mmol) in toluene (12 ml) and the reaction mixture was stirred at RT for 10 min. A solution of **227** (1.40 g, 7.32 mmol) in toluene (3 ml) was added dropwise at RT and the resulting solution was stirred for 3 hr. The reaction mixture was cooled to -78 °C and a solution of MeLi (1.6 M in Et_2O, 11.4 ml, 18.3 mmol) was added dropwise over 45 min. The reaction was quenched with 1M $KHSO_4$ (20 ml), then extracted with Et_2O (2 × 25 ml). The combined organic layers were washed with brine (25 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (Pet/EtOAc = 80/20) to give alcohol **229** (575 mg, 2.04 mmol, 33%) as a yellow oil. ν_{max} (film/cm^{-1}) 3413, 2930, 1495, 1453, 1124, 1055; isolated as a 90:10 mixture of diastereoisomers. Data for the ***major isomer***: δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, J = 6.4, CH_3), 1.49 (1H, m, C*H*HCH$(OR)_2$), 1.58 (1H, m, C*H*HCHSR), 1.71 (1H, m, CH*H*CH$(OR)_2$), 1.90 (1H, m, CH*H*CHSR), 2.64 (1H, dt, J = 9.8, 4.2, C*H*SBn), 3.76 (2H, m, SCH_2Ph), 3.82 (2H, m, 2 × OC*H*H), 3.88 (1H, m, C*H*OH), 3.93 (2H, m, 2 × OCH*H*), 4.77 (1H, t, J = 4.6, C*H*$(OR)_2$), 7.24-7.32 (5H, m, 5 × ArH); δc (125 MHz,

$CDCl_3$) 19.0, 24.7, 31.4, 36.6, 53.5, 64.9, 68.3, 104.2, 127.2, 128.6, 129.0, 149.8;. ***minor isomer***: δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, J = 6.3, CH_3), 1.49-1.92 (4H, m, 2 × CH_2), 2.48 (1H, m, CHSBn), 3.42-3.89 (7H, m, C*H*OH, SC*H*$_2$Ph,, 4 × OCH_2), 4.38 (1H, t, J = 4.6, $CH(OR)_2$), 7.24-7.32 (5H, m, 5 × ArH); ^{13}C-NMR data could not be obtained for the minor isomer; Found (CI): $[M+H]^+$, 283.13606, $C_{15}H_{23}O_3S$ requires 283.13679.

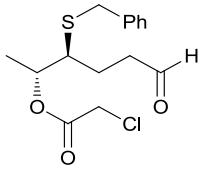
(2*R*,3*S*)-3-(Benzylthio)-5-(1,3-dioxolan-2-yl)pentan-2-yl 2-chloroacetate (230)



Chloroacetyl chloride (0.17 ml, 2.12 mmol) was added dropwise over 15 min to a solution of alcohol **229** (500 mg, 1.77 mmol) in pyridine (2.5 ml) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, then warmed to RT. The reaction was quenched with water (25 ml) and extracted with EtOAc (3 × 15 ml). The combined organic layers were washed with a 10% aq. $CuSO_4$ solution (25 ml), water (25 ml) and brine (25 ml), then dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 80/20) to give ester **230** (372 mg, 1.04 mmol, 59%) as a yellow oil; ν_{max} (film/cm^{-1}) 2953, 2886, 1753, 1453, 1287, 1185, 1134, 1029; isolated as a 90:10 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 1.32 (3H, d, J = 6.4, CH_3), 1.46-1.52 (1H, m, C*H*HCH(OR)$_2$), 1.59-1.64 (1H, m, C*H*HCHSR), 1.71-1.77 (1H, m, CH*H*CH(OR)$_2$), 1.91-1.97 (1H, m, CH*H*CHSR), 2.68 (1H, dt, J = 10.0, 4.2, C*H*SBn), 3.76 (1H, d, J = 13.4, 1 × SC*H*HPh), 3.79 (1H, d, J = 13.4, 1 × SCH*H*Ph), 3.84 (2H, m, 2 × OC*H*H), 3.95 (2H, m, 2 × OCH*H*), 3.98 (1H, d, J = 14.9, 1 x COC*H*HCl), 4.02 (1H, d, J = 14.9, 1 x COCH*H*Cl), 4.78 (1H, t, J = 4.6, $CH(OR)_2$), 5.12 (1H, qd, J = 6.4, 4.2, OCH), 7.24-7.34 (5H, m, 5 × ArH); δc (150 MHz, $CDCl_3$) 16.5, 25.0, 31.0, 36.3, 41.0, 49.0, 64.8, 64.9, 74.9, 103.9, 127.1, 128.6, 129.0, 138.1, 166.7. ; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 1.31 (3H, d, J = 6.4, CH_3), 1.46-1.52 (1H, m, C*H*HCH(OR)$_2$), 1.59-1.64 (1H, m, C*H*HCHSR), 1.71-1.77 (1H, m,

CH*H*CH(OR)$_2$), 1.91-1.97 (1H, m, CH*H*CHSR), 2.65 (1H, dt, J = 10.4, 4.0, C*H*SBn), 3.76 (1H, d, J = 13.4, 1 × SC*H*HPh), 3.79 (1H, d, J = 13.4, 1 × SCH*H*Ph), 3.84 (2H, m, 2 × OC*H*H), 3.95 (2H, m, 2 × OCH*H*), 3.98 (1H, d, J = 14.9, 1 x COC*H*HCl), 4.02 (1H, d, J = 14.9, 1 x COCH*H*Cl), 4.75 (1H, t, J = 4.6, CH(OR)$_2$), 5.17 (1H, qd, J = 6.4, 4.0, OCH), 7.24-7.34 (5H, m, 5 × ArH); δc (150 MHz, $CDCl_3$) 15.5, 25.0, 31.1, 36.2, 41.1, 48.2, 64.8, 64.9, 74.9, 104.0, 127.1, 128.5, 129.0, 138.1, 166.8; Found (CI): $[M+H]^+$ 359.10835, $C_{17}H_{24}O_4SCl$ requires 359.10838

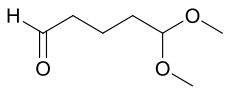
(2*R*,3*S*)-3-(benzylthio)-6-oxohexan-2-yl 2-chloroacetate (231)



Amberlyst-15®(100 mg) was added in one portion to a solution of chloroacetate **230** (100 mg, 0.28 mmol) in acetone (10 ml) and the reaction mixture was stirred for 24 hr at RT. The solvent was removed *in vacuo*. Acetone (10 ml) was added and the mixture was stirred for 1 hr at RT then concentrated *in vacuo*; the latter procedure was repeated 3 times. The mixture was then filtered through Celite and washed with acetone (20 ml). The filtrate was evaporated to dryness to afford aldehyde **231** (82 mg, 0.26 mmol, 93%) as a pale yellow oil; isolated as a 90:10 mixture of diastereoisomers; ***major isomer***: δ_H (600 MHz, $CDCl_3$) 1.35 (3H, d, J = 6.4, CH_3), 1.54-1.60 (1H, m, C*H*HCHSR), 1.93-1.98 (1H, m, CH*H*CHSR), 2.40-2.45 (1H, m, CHSR), 2.54-2.15 (2H, m, C*H*$_2$CHO), 3.71 (1H, d, J = 13.7, COC*H*HCl), 3.74 (1H, d, J = 13.7, COCH*H*Cl), 4.02 (1H, d, J = 15.0, SC*H*HPh), 4.05 (1H, d, J = 15.0, SCH*H*Ph), 5.11 (1H, qd, J = 6.5, 4.9, OCH), 7.23-7.39 (5H, m, 5 × ArH), 9.62 (1H, s, CHO); δc (600 MHz, $CDCl_3$) 16.8, 22.8, 36.3, 41.0, 41.2, 48.5, 74.9, 127.2, 128.6, 129.0, 138.2, 166.7, 201.4; ***minor isomer***: δ_H (600 MHz, $CDCl_3$) 1.33 (3H, d, J = 6.4, CH_3), 1.54-1.60 (1H, m, C*H*HCHSR), 1.93-1.98 (1H, m, CH*H*CHSR), 2.33-2.37 (1H, m, CHSR), 2.54-2.15 (2H, m, C*H*$_2$CHO), 3.75 (1H, d, J = 13.4, COC*H*HCl), 3.78 (1H, d, J = 13.4, COCH*H*Cl), 3.98 (1H, d, J = 15.0, SC*H*HPh), 4.01 (1H, d, J = 15.0, SCH*H*Ph), 5.17 (1H, qd, J = 6.5, 4.1, OCH), 7.23-7.39 (5H, m, 5 × ArH), 9.55

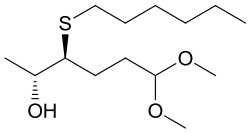
(1H, s, CHO); δc (600 MHz, $CDCl_3$) 15.2, 21.7, 36.3, 41.0, 41.2, 47.4, 74.8, 127.2, 128.6, 129.0, 138.3, 166.9, 201.4; no further data could be obtained as decomposition of the material occurred in the deuterated chloroform solution.

5,5-Dimethoxypentanal[253] (234)



A solution of cyclopentene (8.8 ml, 100 mmol) in CH_2Cl_2 (250 ml) and MeOH (50 ml) was cooled to -78 °C and ozone was bubbled through it until a blue colour was observed. Excess ozone was removed by bubbling oxygen through the reaction mixture until a clear solution was obtained. p-Toluenesulfonic acid monohydrate (1.47 g, 7.7 mmol) was added and the solution was allowed to warm to RT over 1.5 hr. Sodium bicarbonate (2.59 g, 30.8 mmol) was added and the mixture stirred for 15 minutes. The reaction was quenched with dimethylsulfide (16 ml, 200 mmol) and allowed to stir at RT for 16 hr. The solvents were removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (100 ml) and water (75 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by column chromatography (Pet/EtOAc = 80/20) to afford **234** as colourless oil (2.89 g, 19.8 mmol, 20%); δ_H (600 MHz, $CDCl_3$) 1.65 (2H, m, C*H*$_2$CH$_2$CH(OR)$_2$), 1.71 (2H, m, C*H*$_2$CH(OR)$_2$), 2.49 (2H, td, J = 7.0, 1.6, C*H*$_2$CHO), 3.33 (6H, s, 2 × OCH_3), 4.38 (1H, t, J = 5.8, C*H*(OMe)$_2$), 9.78 (1H, t, J = 1.6, CHO); δc (150 MHz, $CDCl_3$) 17.2, 31.8, 43.5, 52.7, 104.1, 202.3; Found (EI): $[M+H]^+$, 145.08521, $C_7H_{15}O_3$ requires 145.08592.

(2*R*,3*S*)-3-Hexylsulfanyl-6,6-dimethoxyhexan-2-ol (237)

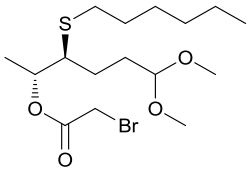


Catalyst **228** (817 mg, 1.37 mmol) was added to a solution of 5,5-dimethoxypentanal **234** (2.00 g, 13.7 mmol) in dry toluene (15 ml) and the solution was stirred at RT for 20 min. A solution of sulfenyl-triazole **235** (3.04 g, 16.4 mmol) in toluene (15 ml) was added dropwise and the reaction mixture was stirred at RT for 4 hr under Ar.

The reaction mixture was partitioned between Et_2O (50 ml) and water (50 ml) and extracted with Et_2O (2 × 50 ml). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue was filtered through a silica plug (Pet/EtOAc = 85/15). The crude aldehyde was dissolved in anhydrous THF (60 ml) and added by the means of a syringe pump to a solution of MeLi (1.6 M in THF, 21.4 ml, 34.3 mmol) cooled to – 78 °C over 2 hr. The reaction was stirred at -78 °C for 1 hr then quenched with sat. NH_4Cl (50 ml) and allowed to warm to RT. The mixture was then extracted with Et_2O (2 × 50 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography (Pet/ Et_2O = 60/40) to afford alcohol **237** as a pale yellow oil (3.01 g, 10.8 mmol, 79%); $[a]_D^{25}$ -5.4 (c 1.0, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3454, 2927, 1454, 1379, 1280, 1171, 1053; the product was isolated as a 90:10 mixture of diastereoisomers: ***major isomer*** δ_H (600 MHz, DMSO-d_6) 0.86 (3H, t, J = 6.8, CH_2CH_3), 1.13 (3H, d, J = 6.1, $CHCH_3$), 1.22-1.37 (7H, m, $(CH_2)_3CH_3$ and $SCHCHH$), 1.45-1.52 (2H, m, SCH_2CH_2), 1.54-1.59 (1H, m, $CHHCH(OR)_2$), 1.63-1.68 (1H, m, $SCHCHH$), 1.78-1.84 (1H, m, $CHHCH(OR)_2$), 2.42 (1H, ddd, J = 11.5, 5.9, 3.7, SCH), 2.46-2.55 (2H, m, SCH_2), 3.20 (3H, s, 1 × OCH_3), 3.21 (3H, s, 1 × OCH_3), 3.63 (1H, dq, J = 11.5, 6.1, $CHOH$), 4.34 (1H, t, J = 5.6, $CH(OMe)_2$), 4.62 (1H, d, J = 5.3, OH); δc (150 MHz, DMSO-d_6) 14.4, 21.1, 22.5, 26.1, 28.4, 30.0, 30.3, 31.3, 31.5, 52.5, 52.8, 53.4, 69.6, 104.2; ***minor isomer*** δ_H (600 MHz, DMSO-d_6) 0.86 (0.3H, t, J = 6.8, CH_2CH_3), 1.07 (0.3H, d, J = 6.3, $CHCH_3$), 1.22-1.37 (0.7H, m, $(CH_2)_3CH_3$ and $SCHCHH$), 1.45-1.52 (0.3H, m, SCH_2CH_2, $CHHCH(OR)_2$), 1.69-1.74 (0.1H, m, $SCHCHH$),

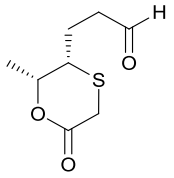
2.46-2.55 (0.2H, m, SCH_2), 2.60-2.63 (0.1H, m, SCH), 3.20 (0.3H, s, 1 × OCH_3), 3.21 (0.3H, s, 1 × OCH_3), 3.76-3.81 (0.1H, m, OCH), 4.32 (0.1H, t, J = 5.7, C*H*$(OMe)_2$), 4.63 (0.1H, d, J = 5.0, OH); δc (150 MHz, DMSO-d_6): 13.9, 20.0, 22.6, 26.2, 28.6, 30.0, 30.4, 31.0, 32.2, 51.8, 55.2, 55.8, 69.1, 104.0; Found (FAB): $[M\text{-}Na]^+$, 301.18156, $C_{14}H_{30}O_3SNa$ requires 301.18133.

(2*R*,3*S*)-3-(Hexylsulfanyl)-6,6-dimethoxyhexan-2-yl 2-bromoacetate (238)



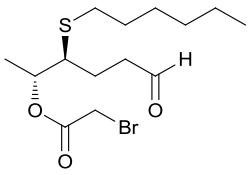
Bromoacetylbromide (0.34 ml, 3.85 mmol) was added dropwise to a solution of alcohol **237** (1.02 g, 3.66 mmol) and pyridine (0.43 ml, 5.39 mmol) in CH_2Cl_2 (20 ml) cooled to -30 °C. The reaction mixture was stirred at this temperature for 20 min then filtered through a silica pad. The pad was washed first with CH_2Cl_2 (2 × 25 ml) then with EtOAc (2 × 25 ml) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (Pet/EtOAc=95/5) to give bromoacetate **238** (1.44 g, 3.60 mmol, 98%) as a colourless oil. $[a]_D^{25}$ -4.2 (c. 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 2972, 2857, 1733; isolated as a single diastereoisomer: δ_H (600 MHz, DMSO-d_6) 0.86 (3H, t, J = 6.9, CH_2CH_3), 1.23-1.37 (10H, m, SCHC*H*H, $CHCH_3$ and $(CH_2)_3CH_3$), 1.49 (2H, m, SCH_2CH_2), 1.57-1.66 (2H, m, C*H*HCH$(OR)_2$ and SCHCH*H*), 1.80 (1H, m, CH*H*CH$(OR)_2$), 2.52-2.58 (2H, m, SCH_2), 2.77 (1H, m, CHS), 3.21 (3H, s, 1 × OCH_3), 3.22 (3H, s, 1 × OCH_3), 4.13 (2H, s, $COCH_2Br$), 4.36 (1H, t, J = 5.6, C*H*$(OMe)_2$), 4.97 (1H, m, OCH); δc (150 MHz, DMSO-d_6) 14.4, 16.9, 22.5, 25.8, 27.7, 28.3, 29.7, 30.2, 31.3, 31.6, 49.8, 52.7, 53.0, 75.0, 104.1, 167.1; Found (FAB): $[M\text{-}Na]^+$ 421.10279, $C_{16}H_{31}BrO_4SNa$ requires 421.10240.

3-((2*R*,3*S*)-2-Methyl-6-oxo-1,4-oxathian-3-yl)propanal (242)



A mixture of bromoester **238** (100 mg, 0.25 mmol) and potassium iodide (125 mg, 0.75 mmol) was stirred in MeCN (3 ml) at reflux in the dark for 48 hr. The mixture was cooled to RT, partitioned between Et_2O and water and then extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 70/30 → 60/40) to afford compound **242** (11 mg, 0.058 mmol, 23%) as a colourless oil. ν_{max} (film/cm^{-1}) 2928, 2730, 1733, 1440, 1384, 1261, 1114, 1061, 1027, 908; δ_H (600 MHz, $CDCl_3$) 1.49 (3H, d, J = 6.5, CH_3), 1.73 (1H, m, 1 × SCHC*H*H), 2.17 (1H, dtd, J = 14.2, 7.6, 3.0, 1 × SCHCH*H*), 2.61 (1H, dt, J = 18.5, 7.6, 1 × C*H*HCHO), 2.72 (1H, ddd, J = 18.5, 7.6, 5.3, 1 × CH*H*CHO), 3.19 (1H, d, J = 14.7, 1 × SC*H*HCO), 3.20-3.22 (1H, m, SCH), 3.55 (1H, d, J = 14.7, 1 × SCH*H*CO), 4.71 (1H, qd, J = 6.5, 2.6, OCH), 9.79 (1H, s, CHO); δc (150 MHz, $CDCl_3$) 18.1, 21.6, 25.7, 40.5, 42.6, 77.6, 167.9, 201.1; Found (EI): $[M]^+$ 188.05028, $C_8H_{12}O_3S$ requires 188.05017.

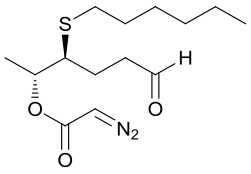
(2*R*,3*S*)-3-(Hexylsulfanyl)-6-oxohexan-2-yl 2-bromoacetate (246)



Amberlyst-15® (330 mg) was added in one portion to a solution of bromoacetate **238** (330 mg, 0.83 mmol) in acetone (10 ml) and the reaction mixture was stirred for 24 hr at RT. The solvent was removed *in vacuo*. Acetone (10 ml) was added and the mixture was stirred for 1 hr at RT then concentrated *in vacuo*; the latter procedure was repeated 3 times. The mixture was then filtered through Celite and washed with

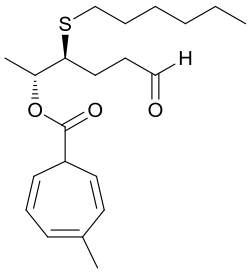
acetone (20 ml). The filtrate was evaporated to dryness to afford aldehyde **246** (275 mg, 0.78 mmol, 94%) as a pale yellow oil.; $[a]_D^{25}$ -5.3 (c. 0.25, $CHCl_3$); ν_{max} (film/cm^{-1}) 2928, 2857, 1734, 1454, 1379, 1280; isolated as a single diastereoisomer δ_H (600 MHz, C_6D_6) 0.86 (3H, t, J = 7.1, CH_2CH_3), 1.14-1.24 (6H, m, $(CH_2)_3CH_3$), 1.16 (3H, d, J = 6.4, $CHCH_3$), 1.36-1.42 (3H, m, SCH_2CH_2 and SCHCH*H*), 1.71 (1H, dtd, J = 14.6, 7.2, 3.7, SCHC*H*H), 2.06-2.22 (2H, m, CH_2CHO), 2.29 (2H, m, SCH_2), 2.43 (1H, ddd, J = 10.3, 5.2, 3.7, CHS), 3.20 (2H, s, CH_2Br), 4.98 (1H, dq, J = 10.3, 6.3, OCH), 9.30 (1H, t, J = 1.0, CHO); δc (150 MHz, C_6D_6) 13.9, 16.4, 22.6, 22.9, 25.4, 26.8, 28.5, 29.7, 29.9, 41.1, 49.7, 74.5, 166.0, 199.6; Found (CI): $[M+H]^+$, 353.07885; $C_{14}H_{25}BrO_3S$ requires 353.07859.

(2*R*,3*S*)-3-(Hexylsulfanyl)-6-oxohexan-2-yl 2-diazoacetate (247)



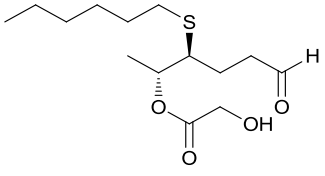
N,*N*'-Ditosylhydrazine[149] (193 mg, 0.56 mmol) was added to a solution of **246** (100 mg, 0.28 mmol) cooled to 0 °C in dry THF (4 ml) and the reaction mixture was stirred at this temperature for 10 min under Ar. DBU (0.21 ml, 1.41 mmol) was added dropwise and the reaction was stirred at 0 °C for 1 hr. The reaction mixture was quenched with sat $NaHCO_3$ (5 ml) and extracted with Et_2O (2 × 10 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give diazoacetate **247** (80 mg, 0.26 mmol, 93%) as a yellow oil. δ_H (600 MHz, C_6D_6) 0.86 (3H, t, J = 7.1, CH_2CH_3), 1.12-1.28 (9H, m, $(CH_2)_3CH_3$, $CHCH_3$), 1.36-1.42 (3H, m, SCH_2CH_2 and SCHCH*H*), 1.71 (1H, m, SCHC*H*H), 2.05-2.24 (2H, m, CH_2CHO), 2.30 (2H, m, SCH_2), 2.50 (1H, m, CHS), 3.97 (1H, br s, CHN_2), 5.15 (1H, m, OCH), 9.30 (1H, s, CHO); δc (150 MHz, $CDCl_3$) 13.9, 16.3, 21.0, 22.6, 23.1, 28.5, 29.7, 31.4, 31.7, 41.3, 50.0, 73.0, 167.8, 199.6.

(2*R*,3*S*)-3-(Hexylsulfanyl)-6-oxohexan-2-yl-4-methylcyclohepta-2,4,6-trienecarboxylate (252)



To a stirred solution of $Rh_2(OAc)_4$ (5 mg, 11 µmol) in toluene (2 ml) was added diazoacetate **247** (80 mg, 0.26 mmol) in toluene (5 ml) dropwise. The reaction mixture was stirred at RT for 1 hr and then heated to reflux for 30 min. Solvent was removed *in vacuo* and the crude residue was purified by column chromatography (Pet/EtOAc = 95/5 → 90/10) to give heptatriene **252** (20 mg, 0.054 mmol, 21%). δ_H (600 MHz, C_6D_6) 0.85 (3H, t, J = 7.1, CH_2CH_3), 1.12-1.49 (12H, m, SCHCH*H* , $(CH_2)_4CH_3$ and $CHCH_3$), 1.73-1.79 (4H, m, C=C-CH_3 and SCHC*H*H), 2.01-2.23 (2H, m, CH_2CHO), 2.30 (2H, t, J = 7.4, SCH_2), 2.51 (1H, m, CHS), 2.73 (1H, m, C*H*COOR), 5.21 (1H, m, C=CH), 5.59 (2H, m, C=CH and C*H*OCOR), 5.90 (1H, t, J = 9.9, C=CH), 6.05 (1H, m, C=CH), 6.20 (1H, m, C=CH), 9.29 (1H, s, CHO); δc (150 MHz, C_6D_6) 13.9, 16.7, 21.3, 22.6, 22.8, 23.7, 28.5, 29.7, 31.4, 31.7, 41.2, 44.0, 50.0, 72.9, 114.5, 115.4, 124.7, 125.8, 139.6, 172.0, 199.6.

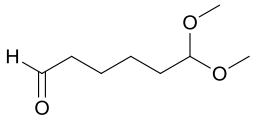
(2*R*,3*S*)-3-(Hexylsulfanyl)-6-oxohexan-2-yl 2-hydroxyacetate (254)



A solution of diazoester **247** (30 mg, 0.10 mmol) in DCE (0.75 ml) was added over 5 hr to a solution of $Rh_2(OAc)_4$ (2 mg, 0.005 mmol) in DCE (0.5 ml) stirred at 60 °C under Ar. The reaction was evaporated to dryness and purified via filtration through a silica pad (Pet/EtOAc = 80/20 → 70/30) to afford alcohol **254** (6 mg, 0.02 mmol, 21%) as a colourless oil. ν_{max} (film/cm^{-1}) 3491, 2928, 2856, 1728, 1447, 1379, 1208,

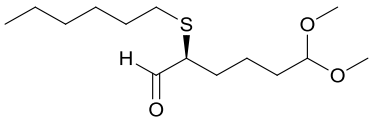
1095; δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, CH_2CH_3), 1.23-1.39 (9H, m, $(CH_2)_3CH_3$, $CHCH_3$), 1.49-1.65 (3H, m, SCH_2CH_2, 1 x SCHCHH); 2.03 (1H, dddd, J = 14.7, 7.8, 7.2, 3.6, SCHCHH), 2.36 (1H, t, J = 5.3, OH), 2.49 (2H, m, SCH_2), 2.65-2.79 (3H, m, SCH, CH_2CHO), 4.17 (2H, d, J = 5.3, CH_2OH), 5.17 (1H, qd, J = 6.4, 5.3, OCH), 9.79 (1H, t, J = 1.5, CHO); δ_C (150 MHz, $CDCl_3$) 14.1, 17.3, 22.7, 23.0, 28.7, 29.8, 31.5, 32.1, 41.7, 50.0, 60.8, 74.5, 172.9, 201.6; Found (CI): $[M+H]^+$ 291.16233, $C_{14}H_{27}O_4S$ requires 291.16300.

6,6-Dimethoxyhexanal[146] (256)



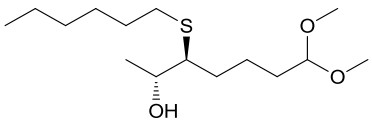
Ozone was bubbled through a solution of Cyclohexene (10.1 ml, 100 mmol) in CH_2Cl_2 (250 ml) and MeOH (50 ml) cooled to -78 °C until a blue colour was noticed. Excess ozone was removed by bubbling oxygen through the reaction mixture then *p*-toluenesulfonic acid monohydrate (1.47 g, 7.70 mmol) was added and the reaction was allowed to warm to RT over 1.5 hr. Sodium bicarbonate (2.59 g, 30.8 mmol) was added and the resulting suspension was stirred for 15 minutes before adding dimethyl sulfide (16.0 ml, 200 mmol) and stirring the reaction mixture overnight at RT. The solvents were removed under reduced pressure and the crude residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 80/20) to afford aldehyde **256** (11.2 g, 69.9 mmol, 70%) as a colourless oil. ν_{max} (film/cm^{-1}) 2947, 1708, 1459, 1389, 1127; δ_H (400 MHz, $CDCl_3$) 1.37-1.45 (2H, m, CH_2), 1.60-1.72 (4H, m, 2 × CH_2), 2.46 (2H, td, J = 7.4, 1.6, CH_2CHO), 3.34 (6H, s, 2 × OCH_3), 4.38 (1H, t, J = 5.7, $CH(OMe)_2$), 9.79 (1H, t, J = 1.6, CHO); δ_C (100 MHz, $CDCl_3$) 21.9, 24.2, 32.3, 43.8, 52.8, 104.3, 202.4; Found (EI): $[M-H]^+$ 159.10249, $C_8H_{15}O_3$ requires 159.10212.

(*S*)-2-(Hexylsulfanyl)-6,6-dimethoxyhexanal (257)



A solution of aldehyde **256** (530 mg, 3.30 mmol) and catalyst **228** (200 mg, 0.33 mmol) in toluene (3 ml) was stirred at RT for 15 min. A solution of sulfenyl-triazole **235** (734 mg, 3.96 mmol) in toluene (3 ml) was added dropwise and the resulting mixture was stirred at RT for 4 hr. The solvent was removed *in vacuo* and the crude was absorbed on silica and purified by column chromatography (Pet/EtOAc = 90/10) to give aldehyde **257** (794 mg, 2.87 mmol, 87%) as colourless oil. $[a]_D^{25}$ -7.0 (c. 0.27, $CHCl_3$); ν_{max} (film/cm^{-1}) 2929, 1714, 1458, 1129, 1054; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, J = 6.9, CH_2CH_3), 1.25-1.68 (13H, m, 6 × CH_2, SCHC*H*H), 1.77-1.86 (1H, m, SCHCH*H*), 2.38 (2H, t, J = 7.3, SCH_2), 3.10 (1H, ddd, J = 7.9, 6.7, 4.6, SCH), 3.33 (6H, s, 2 × OCH_3), 4.37 (1H, t, J = 5.6, C*H*$(OMe)_2$), 9.21 (1H, d, J = 4.6, CHO); δ_C (100 MHz, $CDCl_3$) 14.0, 22.2, 22.5, 27.6, 28.5, 29.3, 30.0, 31.3, 32.2, 52.8, 53.2, 104.1, 193.7; Found (TOF-MS): $[M-H]^-$ 275.1689, $C_{14}H_{27}O_3S$ requires 275.1681.

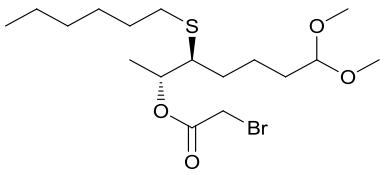
(2*R*,3*S*)-3-(Hexylsulfanyl)-7,7-dimethoxyheptan-2-ol (258)



A solution of aldehyde **257** (770 mg, 2.78 mmol) in dry THF (20 ml) was added over 20 min to a solution of MeLi (1.6M in THF, 6.95 ml, 11.1 mmol) cooled to -78 °C. The reaction was stirred at this temperature for 1 hr, quenched with sat NH_4Cl (10 ml) and extracted with Et_2O (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/Et_2O = 60/40) to afford alcohol **258** (492 mg, 1.68 mmol, 60%) as a colourless oil. $[a]_D^{25}$ -6.2 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3465, 2928, 2858, 1457, 1385, 1126, 1052; alcohol **258** was isolated as a 90:10

mixture of diastereoisomers: ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, CH_2CH_3), 1.16 (3H, d, J = 6.5, $CHCH_3$), 1.24-1.43 (8H, m, 4 × CH_2), 1.54-1.67 (6H, m, 3 × CH_2), 2.44 (1H, d, J = 6.5, OH), 2.50 (1H, dt, J = 12.4, 7.4, SC*H*H), 2.54 (1H, dt, J = 12.4, 7.4, SCH*H*), 2.64 (1H, m, SCH), 3.31 (3H, s, 1 × OCH_3), 3.32 (3H, s, 1 × OCH_3), 3.89 (1H, qd, J = 6.5, 3.8, C*H*OH), 4.37 (1H, t, J = 5.2, C*H*$(OMe)_2$); δ_C (150 MHz, $CDCl_3$) 14.2, 18.9, 22.7, 22.9, 28.7, 30.1, 30.8, 31.2, 32.5, 32.6, 52.8, 52.9, 55.0, 68.2, 104.4; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, CH_2CH_3), 1.24-1.43 (11H, m, 4 × CH_2, $CHCH_3$), 1.54-1.67 (6H, m, 3 × CH_2), 2.38 (1H, m, SCH), 2.52 (2H, m, SCH_2), 2.79 (1H, d, J = 3.2, OH), 3.31 (3H, s, 1 × OCH_3), 3.32 (3H, s, 1 × OCH_3), 3.62 (1H, qd, J = 6.5, 3.2, C*H*OH), 4.38 (1H, J = 5.3, $CH(OMe)_2$); δ_C (150 MHz, $CDCl_3$) 14.2, 20.4, 22.5, 22.9, 22.7, 28.7, 30.1, 31.3, 31.5, 32.5, 52.8, 52.9, 56.2, 69.0, 104.4; Found (TOF-MS): $[M+Na]^+$ 315.1978, $C_{15}H_{32}O_3NaS$ requires 315.1970.

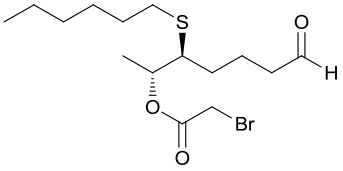
(2*R*,3*S*)-3-(Hexylsulfanyl)-7,7-dimethoxyheptan-2-yl 2-bromoacetate (259)



Bromoacetylbromide (0.15 ml, 1.67 mmol) was added dropwise to a solution of alcohol **258** (465 mg, 1.59 mmol) and pyridine (0.19 ml, 2.38 mmol) in CH_2Cl_2 (10 ml) cooled to -30 °C. The reaction mixture was stirred at this temperature for 20 min and then it was filtered through a silica pad and eluted with CH_2Cl_2 (2 × 40 ml) and EtOAc (2 × 50 ml). The filtrate was evaporated to dryness to afford bromoacetate **259** (656 mg, 1.59 mmol, quant.) as a pale yellow oil.; $[a]_D^{25}$ -5.2 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 2928, 2857, 1734, 1454, 1380, 1280, 1126; isolated as a single diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, CH_2CH_3), 1.29-1.69 (14H, m, 7 × CH_2), 1.36 (3H, d, J = 6.3, $CHCH_3$), 2.57 (2H, t, J = 7.4, SCH_2), 2.72 (1H, m, SCH), 3.34 (3H, s, 1 × OCH_3), 3.35 (3H, s, 1 × OCH_3), 3.82 (1H, d, J = 12.2, C*H*HBr), 3.86 (1H, d, J = 12.2. CH*H*Br), 4.40 (1H, t, J = 5.4, C*H*$(OMe)_2$), 5.09 (1H, dq, J = 6.3, 5.2, OCH); δ_C (150 MHz, $CDCl_3$) 14.2, 16.7, 22.5, 22.7, 26.2, 28.7,

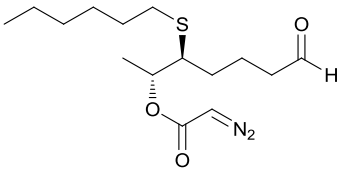
29.9, 31.1, 31.6, 32.2, 32.4, 50.4, 52.8, 52.9, 75.4, 104.4, 166.8; Found (CI): [M-OMe] 381.10911, $C_{16}H_{30}O_3SBr$ requires 381.10990.

(2*R*,3*S*)-3-(Hexylsulfanyl)-7-oxoheptan-2-yl 2-bromoacetate (260)



Amberlyst-15® (400 mg) was added to a solution of acetal **259** (400 mg, 0.97 mmol) in acetone (4 ml) and water (0.4 ml). The mixture was stirred at RT for 24 hr and then filtered through Celite®. The filtrate was evaporated to dryness to afford aldehyde **260** (309 mg, 0.84 mmol, 87%) as a pale brown oil. $[a]_D^{25}$ -6.9 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 2928, 2856, 1728, 1455, 1378, 1280, 1170; isolated as a single diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, CH_2CH_3), 1.28-1.50 (8H, m, 4 × CH_2), 1.38 (3H, d, J = 6.3, $CHCH_3$), 1.54-1.79 (5H, m, 2 × CH_2, SCHC*H*H); 1.95-2.05 (1H, m, SCHCH*H*), 2.50 (2H, td, J = 7.1, 1.5, CH_2CHO), 2.58 (2H, t, J = 7.4, SCH_2), 2.71 (1H, ddd, J = 9.5, 5.4, 4.1, SCH), 3.83 (1H, d, J = 12.2, C*H*HBr), 3.86 (1H, d = 12.2, CH*H*Br), 5.09 (1H, qd, J = 6.3, 5.4, OCH), 9.80 (1H, t, J = 1.5, CHO); δ_C (100 MHz, $CDCl_3$) 14.0, 16.8, 19.8, 22.5, 26.0, 28.6, 29.8, 30.5, 31.4, 32.2, 43.5, 50.2, 75.1, 166.7, 202.0; Found (CI): $[M+H]^+$ 367.09515, $C_{15}H_{28}O_3SBr$ requires 367.09425.

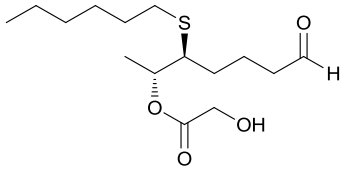
(2*R*,3*S*)-3-(Hexylsulfanyl)-7-oxoheptan-2-yl 2-diazoacetate (261)



N,*N*'-Ditosylhydrazine (371 mg, 1.09 mmol) was added in one portion to a solution of bromoacetate **260** (200 mg, 0.54 mmol) in dry THF (6 ml) at 0 °C. The mixture

was stirred at this temperature for 15 min then DBU (0.40 ml, 2.72 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 hr and then partitioned between Et_2O (20 ml) and water (10 ml). The aqueous layer was extracted with Et_2O (2 × 10 ml) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 80/20) to give diazoester **261** (115 mg, 0.37 mmol, 67%) as a colourless oil. $[a]_D^{25}$ -27.7 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 2928, 2857, 2111, 1724, 1689, 1457, 1377, 1243, 1187; isolated as a single diastereoisomer: δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, CH_2CH_3), 1.23-1.43 (6H, m, 3 × CH_2), 1.32 (3H, d, J = 6.3, $CHCH_3$), 1.50-1.76 (5H, m, 2 × CH_2, SCHC*H*H), 1.94-2.01 (1H, m, SCHCH*H*), 2.46 (2H, td, J = 5.7, 1.5, CH_2CHO), 2.52 (2H, t, J = 7.4, SCH_2), 2.70 (1H, m, SCH), 4.74 (1H, br s, CHN_2), 5.10 (1H, ddd, J = 12.7, 6.3, 4.8, OCH), 9.77 (1H, t, J = 1.5, CHO); δ_C (150 MHz, $CDCl_3$) 14.1, 17.0, 20.0, 22.7, 28.7, 29.9, 30.8, 31.5, 32.3, 43.7, 46.5 (br), 50.6, 73.6, 166.6 (br), 202.2; Found (TOF-MS): $[M+Na]^+$ 337.1561, $C_{15}H_{26}N_2O_3NaS$ requires 337.1562.

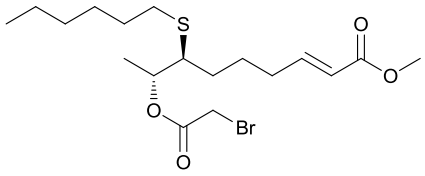
(2*R*,3*S*)-3-(Hexylsulfanyl)-7-oxoheptan-2-yl 2-hydroxyacetate (263)



A solution of diazoester **261** (80 mg, 0.25 mmol) in DCE (2 ml) was added over 5 hr to a solution of $Rh_2(OAc)_4$ (6 mg, 0.01 mmol) in DCE (1.5 ml) stirred at 60 °C under Ar. The reaction was evaporated to dryness and purified via filtration through a silica pad (Pet/EtOAc = 60/40) to afford alcohol **263** (9 mg, 0.03 mmol, 12%) as a colourless oil. ν_{max} (film/cm^{-1}) 3468, 2927, 2857, 1731, 1726, 1455, 1377, 1216, 1094; isolated as a single diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, CH_2CH_3), 1.27-1.47 (8H, m, 4 × CH_2), 1.37 (3H, d, J = 6.4, $CHCH_3$), 1.53-1.76 (5H, m, 2 × CH_2, SCHC*H*H); 1.94-2.04 (1H, m, SCHCH*H*), 2.43 (1H, t, J = 5.3, OH), 2.50 (2H, td, J = 7.1, 1.5, CH_2CHO), 2.54 (2H, t, J = 7.4, SCH_2), 2.70 (1H, ddd, J = 9.4, 5.1, 4.2, SCH), 4.17 (2H, d, J = 5.3, CH_2OH), 5.17 (1H, qd, J = 6.4, 5.3,

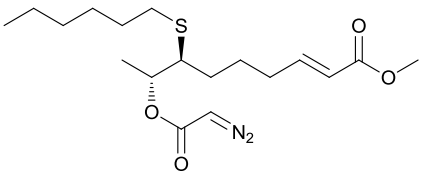
OCH), 9.79 (1H, t, J = 1.5, CHO); δ_C (100 MHz, $CDCl_3$) 14.0, 16.9, 19.8, 22.5, 28.6, 29.7, 30.5, 31.4, 32.1, 43.5, 50.3, 60.7, 74.4, 172.8, 201.9; Found (TOF-MS): $[M-H]^-$ 303.1624, $C_{15}H_{27}O_4S$ requires 303.1630.

(7*S*,8*R*,*E*)-Methyl-8-(2-bromoacetoxy)-7-(Hexylsulfanyl)non-2-enoate (264)



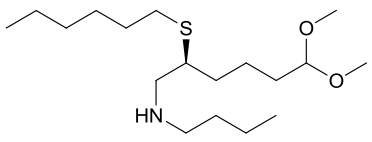
Methyl(triphenylphosphoranylidene)acetate (81 mg, 0.24 mmol) was added in one portion to a solution of aldehyde **260** (84 mg, 0.23 mmol) in toluene (1 ml) and the reaction was stirred at RT for 1 hr. The mixture was absorbed onto silica gel and then purified by column chromatography (Pet/EtOAc = 90/10) to give enoate **264** (61 mg, 0.14 mmol, 63%) as a pale yellow oil. $[a]_D^{25}$ -4.7 (c. 0.50, $CHCl_3$); ν_{max} (film/cm^{-1}) 2926, 1726, 1680, 1436, 1375, 1278; isolated as a single diastereoisomer: δ_H (600 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, CH_2CH_3), 1.27-1.47 (6H, m, 3 × CH_2), 1.36 (3H, d, J = 6.3, $CHCH_3$), 1.53-1.70 (5H, m, 2 × CH_2, SCHC*H*H), 1.78-1.87 (1H, m, SCHCH*H*), 2.25 (2H, m, CH_2CH=CH), 2.57 (2H, t, J = 7.4, SCH_2), 2.70 (1H, ddd, J = 9.5, 5.3, 4.0, SCH), 3.74 (3H, s, OCH_3), 3.82 (1H, d, J = 12.2, C*H*HBr), 3.86 (1H, d, J = 12.2, CH*H*Br), 5.07 (1H, qd, J = 6.3, 5.3, OCH), 5.86 (1H, dt, J = 15.7, 1.5, C=C*H*CO_2Me), 6.97 (1H, dt, J = 15.7, 6.9, CH_2CH=C); δ_C (150 MHz, $CDCl_3$) 14.0, 16.7, 22.5, 25.6, 26.0, 28.6, 29.8, 30.6, 31.4, 31.9, 32.2, 50.2, 51.4, 75.3, 121.4, 148.8, 166.7, 167.0; Found (TOF-ES): $[M+Na]^+$ 445.1001, $C_{18}H_{31}O_4NaSBr$ requires 445.1024.

(7*S*,8*R*,*E*)-Methyl 8-(2-diazoacetoxy)-7-(Hexylsulfanyl)non-2-enoate (265)



N,*N*'-Ditosylhydrazine (64 mg, 0.19 mmol) was added in one portion to a solution of bromoacetate **264** (40 mg, 0.10 mmol) in dry THF (1.5 ml) at 0 °C. The mixture was stirred at this temperature for 15 min then DBU (70 µl, 0.47 mmol) was added. The reaction was stirred at 0 °C for 1 hr then partitioned between Et_2O (10 ml) and 1M $NaHCO_3$ (5 ml). The aqueous layer was extracted with Et_2O (2 × 5 ml) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 85/15) to give diazoester **265** (15 mg, 0.04 mmol, 43%) as a colourless oil. $[a]_D^{25}$ -14.7 (c. 0.45, $CHCl_3$); ν_{max} (film/cm^{-1}) 2970, 2110, 1738, 1366, 1229, 1217; isolated as a single diastereoisomer: δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.1, CH_2CH_3), 1.24-1.41 (6H, m, 3 × CH_2), 1.31 (3H, d, J = 6.3, $CHCH_3$), 1.51-1.63 (5H, m, 2 × CH_2, $SCHCHH$), 1.78-1.83 (1H, m, $SCHCHH$), 2.18-2.27 (2H, m, $CH_2C{=}C$), 2.52 (2H, t, J = 7.5, SCH_2), 2.28-2.71 (1H, m, SCH), 3.73 (3H, s, OCH_3), 4.74 (1H, br s, CHN_2), 5.09 (1H, qd J = 6.3, 4.9, OCH), 5.84 (1H, dt, J = 15.6, 1.4, C=CHCO), 6.95 (1H, dt, J = 15.6, 6.9, $CH_2CH{=}C$); δ_C (150 MHz, $CDCl_3$) 14.2, 16.9, 22.7, 25.8, 28.7, 29.9, 30.9, 31.6, 32.0, 32.3, 46.5 (br), 50.6, 51.6, 53.6, 73.7, 121.4, 149.0, 167.2; Found (TOF-ES): $[M+Na]^+$ 393.1826, $C_{18}H_{30}N_2O_4NaS$ requires 393.1824.

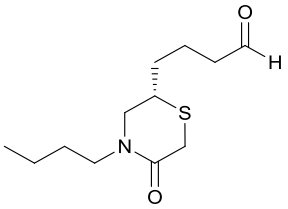
(*S*)-*N*-Butyl-2-(Hexylsulfanyl)-6,6-dimethoxyhexan-1-amine (273)



Sodium bicarbonate (149 mg, 1.78 mmol) was added to a solution of aldehyde **257** (350 mg, 1.27 mmol) and *n*-buthylamine (0.15 ml, 1.52 mmol) in MeOH (3 ml). The mixture was heated at reflux for 4 hr then cooled to 0 °C. Sodium borohydride (48

mg, 1.27 mmol) was added to the reaction mixture portionwise and the reaction was allowed to warm to RT over 18 hr. The solvent was removed *in vacuo* and the crude residue was partitioned between CH_2Cl_2 and water. After separation, the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give amine **273** (353 mg, 1.06 mmol, 83%) as a pale yellow oil. $[a]_D^{25}$ -1.8 (c. 0.25, $CHCl_3$); ν_{max} (film/cm^{-1}) 2927, 2858, 1456, 1128, 1054; δ_H (600 MHz, $CDCl_3$) 0.89-0.96 (6H, m, 2 × CH_3). 1.29-1.71 (18H, m, 9 × CH_2), 2.51 (2H, td, J = 7.3, 1.6, NHC$H_2$$CH_2$), 2.59-2.78 (5H, m, NHC$H_2CHSCH_2$), 3.34 (6H, s, 2 × OCH_3), 4.39 (1H, t, J = 5.4, C$H$$(OMe)_2$); δ_C (150 MHz, $CDCl_3$) 14.1, 20.6, 22.3, 22.7, 28.3, 28.8, 29.3, 30.2, 31.6, 32.5, 33.7, 39.3, 46.7, 49.7, 52.8, 52.9, 53.6, 104.5; Found (TOF-MS): $[M+H]^+$ 334.2784, $C_{18}H_{40}NO_2S$ requires 334.2780.

(*S*)-4-(4-Butyl-5-oxothiomorpholin-2-yl)butanal (275)

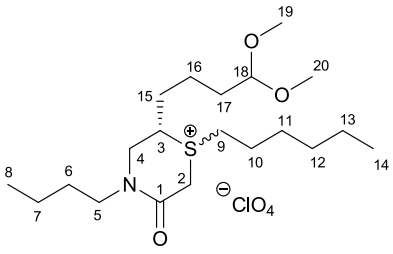


Bromoacetylbromide (40 µL, 0.46 mmol) was added dropwise to a solution of amine **273** (140 mg, 0.42 mmol) and pyridine (50 µL, 0.63 mmol) in CH_2Cl_2 (4 ml) stirred at -30 °C. The resulting mixture was stirred at -30 °C for 1.5 hr, then filtered through a silica plug and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the crude was purified by column chromatography (Pet/EtOAc = 50/50) and subsequent crystallisation from EtOAc to afford thiomorpholinone **275** (10 mg, 0.041 mmol, 10%) as a colourless oil. $[a]_D^{25}$ -2.3 (c. 0.20, $CHCl_3$); ν_{max} (film/cm^{-1}) 2924, 1649, 1457, 1261; δ_H (600 MHz, $CDCl_3$) 0.92 (3H, t, J = 7.4, CH_3), 1.31 (2H, app. sext, J = 7.4, C$H_2$$CH_3$), 1.49-1.58 (3H, m, NCH_2CH_2, SCHC$H$$HCH_2$), 1.63-1.83 (3H, m, SCHCH$H$$CH_2$, C$H_2$$CH_2$CHO), 2.51 (2H, t, J = 7.0, CH_2CHO), 3.11 (1H, dddd, J = 13.0, 8.9, 5.2, 4.0, SCH), 3.28-3.35 (3H, m, $COCH_2S$, NC$H$$HCH_2$), 3.36 (1H, dd, J = 13.5, 8.9, NCHHCH), 3.48 (1H, ddd, J = 13.5, 8.4, 6.8, NCH$H$$CH_2$), 3.54 (1H, dd, J = 13.5, 4.0, NCHHCH), 9.78 (1H, t, J = 1.2, CHO); δ_C (150 MHz,

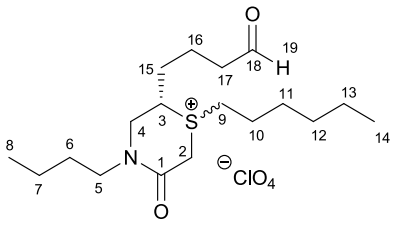
$CDCl_3$) 14.0, 19.7, 20.2, 29.6, 29.9, 33.4, 41.0, 43.5, 48.2, 54.1, 167.6, 201.8; Found (CI), $[M+H]^+$ 244.13670, $C_{12}H_{22}O_2NS$ requires 244.13712.

(2*S*)-4-Butyl-2-(4,4-dimethoxybutyl)-1-hexyl-5-oxothiomorpholin-1-ium perchlorate (277),

(2*S*)-4-Butyl-1-hexyl-5-oxo-2-(4-oxobutyl)thiomorpholin-1-ium perchlorate (278)



(277)



(278)

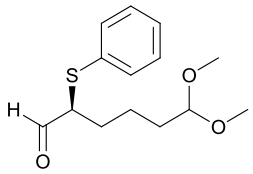
A solution of chloroacetyl chloride (0.18 ml, 2.25 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of amine **273** (500 mg, 1.49 mmol) and triethylamine (0.31 ml, 2.25 mmol) in CH_2Cl_2 (5 ml) cooled to 0 °C. The reaction mixture was stirred at this temperature for 15 min then quenched with 1M $NaHCO_3$ (5 ml). The mixture was extracted into CH_2Cl_2 and water; combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude amide (611 mg, 1.49 mmol) and sodium perchlorate (201 mg, 1.64 mmol) were stirred in acetone (1.3 ml) at RT for 3 days. The reaction was filtered and the residue washed several times with acetone. The filtrate was evaporated to dryness and the crude was purified by column chromatography (CH_2Cl_2/MeOH = 99/1 → 95/5) to afford acetal **277** (113 mg, 0.24 mmol, 16%) and aldehyde **278** (190 mg, 0.44 mmol, 30%) as colourless oils.

277: $[a]_D^{25}$ -0.6 (c. 0.50, $CHCl_3$); ν_{max} (film/cm^{-1}) 2956, 2932, 2872, 1724, 1672, 1453, 1369, 1083; δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, H-14), 0.93 (3H, t, J = 7.3, H-8), 1.29-1.35 (6H, m, H-7, H-13, H-12), 1.46-1.59 (6H, m, H-11, H-6, H-16), 1.66-1.70 (2H, m, H-17), 1.82 (2H, app. quint, J = 7.7, H-10), 1.97-2.03 (1H, m, 1 × H-15), 2.08-2.16 (1H, m, 1 × H-15), 3.3 (1H, m, H-9), 3.28-3.33 (1H, m, 1 × H-9),

3.32 (6H, s, H-19, H-20), 3.35-3.44 (2H, m, 1 × H-9, 1 × H-5), 3.56 (1H, dt, J = 14.0, 7.9, 1 × H-5), 3.78 (1H, m, H-3), 3.83-3.91 (2H, m, H-4), 3.87 (1H, d, J = 15.5, 1 × H-2), 4.36 (1H, t, J = 5.2, H-18), 4.42 (1H, d, J = 15.5, 1 × H-2); δ_C (150 MHz, $CDCl_3$) 13.8, 14.0, 20.1, 22.0, 22.3, 24.6, 28.0, 30.1, 31.0, 31.5, 32.0, 35.3, 43.4, 48.2, 49.2, 53.6, 53.7, 56.9, 104.2, 160.1; Found (TOF-MS), $[M+H]^+$ 374.2721, $C_{20}H_{40}NO_3S$ requires 374.2729.

278: $[a]_D^{25}$ -1.0 (c. 0.40, $CHCl_3$); ν_{max} (film/cm^{-1}) 2938, 2870, 1723, 1674, 1454, 1365, 1217, 1089; δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, H-14), 0.93 (3H, t, J = 7.3, H-8), 1.29-1.35 (6H, m, H-7, H-12, H-13), 1.45-1.59 (4H, m, H-6, H-11), 1.77-1.89 (4H, m, H-10, H-16), 1.98-2.04 (1H, m, 1 × H-15), 2.09-2.15 (1H, m, 1 × H-15), 2.67 (2H, t, J = 6.9, H-17), 3.27 (1H, dt, J = 13.0, 7.5, 1 × H-9), 3.40-3.45 (2H, m, 1 × H-5, 1 × H-9), 3.56-3.61 (1H, m, 1 × H-5), 3.80-3.87 (2H, m, 1 × H-3, H-4), 3.85 (1H, d, J = 15.6, 1 × H-2), 3.95 (1H, dd, J = 20.2, 9.5, 1 × H-4), 4.40 (1H, d, J = 15.6, 1 × H-2), 9.77 (1H, s, H-19); δ_C (150 MHz, $CDCl_3$) 13.8, 14.0, 19.1, 20.1, 20.4, 24.6, 28.0, 29.7, 29.8, 30.1, 31.0, 35.1, 42.9, 43.3, 48.1, 49.2, 56.5, 160.2, 202.2; Found (TOF-MS), $[M+H]^+$ 328.2301, $C_{18}H_{34}NO_2S$ requires 328.2310.

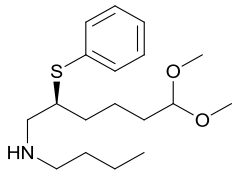
(*S*)-6,6-Dimethoxy-2-(phenylthio)hexanal (281)



Catalyst **228** (1.10 g, 1.84 mmol) was added to a solution of aldehyde **256** (2.95 g, 18.4 mmol) in toluene (15 ml) and stirred at RT for 15 min. A solution of sulfenyl triazole **280** (3.92 g, 22.1 mmol) in toluene (15 ml) was added dropwise and the resulting mixture was stirred for 24 hr under Ar. Solvent was removed *in vacuo* and the residue was purified by column chromatography (Pet/EtOAc = 90/10) to afford aldehyde **281** (2.98 g, 11.1 mmol, 60%) as a colourless oil. $[a]_D^{25}$ -1.0 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 2946, 2829, 1718, 1439, 1366, 1217, 1128. 1070; δ_H (500 MHz, $CDCl_3$) 1.44-1.71 (5H, m, C*H*$_2$C*H*$_2$CH(OCH$_3$)$_2$, SHCC*H*H), 1.78-1.88 (1H, m, SCHCH*H*), 3.31 (6H, s, 2 × OCH$_3$), 3.51 (1H, td, J = 7.3, 3.9, SCH), 4.36 (1H, t, J =

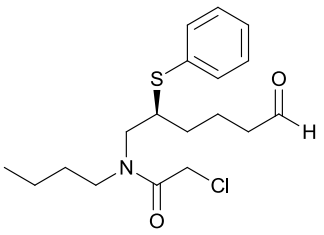
5.4, C*H*$(OCH_3)_2$), 7.27-7.40 (5H, m, ArH), 9.39 (1H, d, J = 3.9, CHO); δ_C (125 MHz, $CDCl_3$) 22.1, 27.6, 32.2, 52.9, 56.9, 104.2, 128.3, 129.2, 133.1, 136.7, 195.0; Found (EI), $[M-H]^+$ 267.10521, $C_{14}H_{19}O_3S$ requires 267.10494.

(*S*)-*N*-Butyl-6,6-dimethoxy-2-(phenylthio)hexan-1-amine (282)



A mixture of aldehyde **281** (2.80 g, 10.4 mmol), *n*-buthylamine (1.24 ml, 12.5 mmol) and $NaHCO_3$ (1.23 g, 14.6 mmol) was stirred in MeOH (28 ml) at reflux for 4 hr. The mixture was cooled to 0 °C, then $NaBH_4$ (395 mg, 10.4 mmol) was added and the reaction mixture was allowed to warm to RT overnight. The solvent was removed *in vacuo* and the crude was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (CH_2Cl_2/MeOH/NEt_3 = 100/0/0 → 95/5/0.1) to afford amine **282** (2.09 g, 6.42 mmol, 62%) as a colourless oil. $[a]_D^{25}$ -3.5 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3058, 2932, 2829, 1460, 1439, 1127, 1070; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J = 7.3, CH_3), 1.30-1.68 (10 H, m, 5 × CH_2), 2.57 (1H, ddd, J = 11.6, 7.5, 4.4, NHC*H*HCH_2), 2.61 (1H, ddd, J = 11.6, 7.5, 4.4, NHCH*H*CH_2), 2.67 (1H, dd, J = 12.4, 7.8, NHC*H*HCH), 2.77 (1H, dd, J = 12.4, 5.0, NHCH*H*CH), 3.21 (1H, m, SCH), 3.32-3.34 (6H, m, 2 × OCH_3), 4.36 (1H, t, J = 5.1, C*H*$(OCH_3)_2$), 7.25-7.33 (3H, m, 3 × ArH), 7.43-7.45 (2H, m, 2 × ArH); δ_C (100 MHz, $CDCl_3$) 14.0, 20.5, 22.1, 32.2, 32.3, 33.1, 49.5, 49.8, 52.7, 52.8, 53.3, 104.4, 127.1, 128.9, 132.6, 134.4; Found (TOF MS), $[M+H]^+$ 326.2154, $C_{18}H_{32}NO_2S$ requires 326.2154.

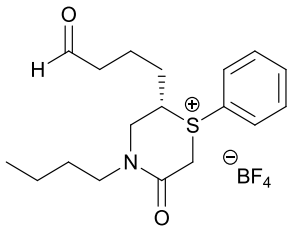
(*S*)-*N*-Butyl-2-chloro-N-(6-oxo-2-(phenylthio)hexyl)acetamide (283)



A solution of amine **282** (1.00 g, 3.07 mmol) and NEt_3 (0.64 ml, 4.61 mmol) in CH_2Cl_2 (10 ml) was cooled to 0 °C. A solution of chloroacetyl chloride (0.37 ml, 4.61 mmol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting mixture was stirred at 0 °C for 15 min. The reaction was quenched with 1M $NaHCO_3$ (20 ml) and washed with water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford the crude amide. The crude amide (200 mg, 0.50 mmol) was dissolved in acetone (5 ml) and water (0.5 ml) and stirred over Amberlyst (200 mg) for 24 hr. The reaction mixture was filtered through Celite®. The filtrate was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 80/20 → 70/30) to afford aldehyde **283** (128 mg, 0.36 mmol, 72%) as a colourless oil. $[a]_D^{25}$ -4.6 (c. 0.30, $CHCl_3$); ν_{max} (film/cm^{-1}) 3057, 2956, 2932, 2873, 2725, 1722, 1652, 1456, 1439; the product was isolated as a 77:23 mixture of rotamers; ***major rotamer:*** δ_H (600 MHz, $CDCl_3$) 0.91 (3H, t, J = 7.4, CH_3), 1.27 (2H, sext, J = 7.4, C*H*$_2$CH$_3$), 1.43-1.55 (3H, m, NCH$_2$C*H*$_2$, SCHC*H*HCH$_2$), 1.68 (1H, dddd, J = 19.2, 10.3, 8.9, 5.0, SCHCH*H*CH$_2$), 1.77-1.84 (1H, m, C*H*HCH$_2$CHO), 1.94-2.01 (1H, m, CH*H*CH$_2$CHO), 2.47 (2H, t, J = 7.2, C*H*$_2$CHO), 3.15-3.23 (1H, m, NC*H*HCH$_2$), 3.23 (1H, dd, J = 13.6, 7.3, SCHC*H*HN), 3.30-3.40 (1H, m, NCH*H*CH$_2$), 3.61-3.66 (1H, m, SCH), 3.71 (1H, dd, J = 13.6, 7.9, SCHCH*H*N), 3.82 (1H, d, J =12.7, COC*H*HCl), 3.93 (1H, d, J = 12.7, COCH*H*Cl), 7.28-7.33 (3H, m, 3 × ArH), 7.41 (2H, d, J = 7.7, 2 × ArH), 9.75 (1H, s, CHO); ***minor rotamer:*** 0.86 (0.9H, t, J = 7.4, CH_3), 1.20-1.26 (0.6H, m, C*H*$_2$CH$_3$), 1.36-1.55 (1.2H, m, SCHC*H*$_2$CH$_2$, NCH$_2$C*H*$_2$), 1.77-1.84 (0.3H, m, C*H*HCH$_2$CHO), 2.05-2.10 (0.3H, CH*H*CH$_2$CHO), 2.52 (0.6H, t, J = 7.0, C*H*$_2$CHO), 2.98 (0.3H, ddd, J = 14.7, 8.7, 6.4, NC*H*HCH$_2$), 3.15-3.23 (0.6H, m, SCH, NCH*H*CH$_2$), 3.38 (0.3H, dd, J = 15.3, 7.3, NC*H*HCH), 3.51 (0.3H, dd, J = 15.3, 7.5, NCH*H*CH), 3.97 (0.3H, d, J = 12.2, COC*H*HCl), 4.08 (0.3H, d, J = 12.2, COCH*H*Cl), 7.28-7.33 (0.9H, m, 3 × ArH), 7.41 (0.6H, d, J = 7.7, 2 × ArH), 9.79 (0.3H, s, CHO); δ_C (150 MHz, $CDCl_3$) 13.8, 13.9,

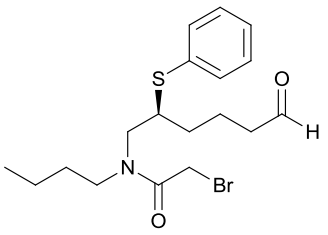
19.5, 20.1, 29.1, 31.1, 31.2, 32.0, 41.4, 41.5, 43.5, 43.6, 45.9, 46.0, 49.6, 49.9, 51.8, 52.7, 126.9, 128.2, 129.1, 129.5, 131.1, 133.2, 133.7, 135.0, 166.7, 166.9, 201.7, 202.2; Found (TOF-MS): $[M+Na]^+$ 378.1262; $C_{18}H_{26}NO_2NaSCl$ requires 378.1270.

(2*S*)-4-Butyl-5-oxo-2-(4-oxobutyl)-1-phenylthiomorpholin-1-ium tetrafluoroborate (284)



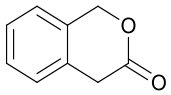
Silver tetrafluoroborate (32 mg, 0.16 mmol) was added to a solution of sulfide **283** (48 mg, 0.13 mmol) in acetone (0.3 ml) and the resulting mixture was stirred at RT for 3 days in the dark. The suspension was filtered through Celite® and the filtrate was evaporated to dryness. The crude was purified by column chromatography (CH_2Cl_2/MeOH = 100/0 → 90/10) to afford salt **284** (80 mg, 0.196 mmol, 44%) as a colourless oil. $[a]_D^{25}$ -8.0 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 2971, 1739, 1361, 1229, 1217; δ_H (600 MHz, $CDCl_3$) 0.92 (3H, t, J = 7.4, CH_3), 1.32 (2H, sext, J = 7.4, C*H*$_2$CH$_3$), 1.57 (2H, quint, J = 7.4, C*H*$_2$CH$_2$CH$_3$), 1.67-1.82 (2H, m, C*H*$_2$CH$_2$CHO), 2.06-2.12 (1H, m, C*H*HCH$_2$CH$_2$CHO), 2.18-2.25 (1H, m, CH*H*CH$_2$CH$_2$CHO), 2.52 (1H, dt, J = 18.8, 6.8, C*H*HCHO), 2.58 (1H, dt, J = 18.8, 6.8, CH*H*CHO), 3.44 (1H, dt, J = 13.5, 7.5, NC*H*HCH$_2$), 3.75 (1H, dt, J = 13.5, 7.7, NCH*H*CH$_2$), 3.91 (1H, dd, J = 15.3, 4.0, NC*H*HCH), 3.94 (1H, d, J = 15.9, SC*H*HCO), 4.04 (1H, dd, J = 15.3, 10.8, NCH*H*CH), 4.17 (1H, m, SCH), 4.76 (1H, d, J = 15.9, SCH*H*CO), 7.67 (2H, t, J = 7.8, 2 × ArH), 7.72-7.81 (3H, m, 3 × ArH), 9.67 (1H, s, CHO); δ_C (150 MHz, $CDCl_3$) 13.8, 19.3, 20.1, 29.3, 29.9, 39.6, 42.7, 48.2, 49.1, 62.2, 124.5, 130.6, 132.0, 135.4, 160.1, 201.8; δ_F (282 MHz, $CDCl_3$) -150.2; Found (TOF-MS): $[M]^+$ 320.1680, $C_{18}H_{26}NO_2S$ requires 320.1684.

(*S*)-2-Bromo-*N*-butyl-*N*-(6-oxo-2-(phenylthio)hexyl)acetamide (286)



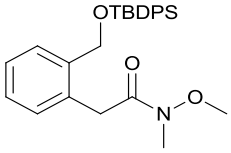
A solution of amine **282** (100 mg, 0.31 mmol) and pyridine (37 µl, 0.46 mmol) in CH_2Cl_2 (2.5 ml) was cooled to -40 °C. Bromoacetyl bromide (27 µl, 0.31 mmol) in CH_2Cl_2 (10 ml) was added and the resulting mixture was stirred at -20 °C for 15 min. The reaction was filtered through a silica plug (EtOAc).The filtrate was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 80/20) to afford aldehyde **286** (30 mg, 0.067 mmol, 22%) as a colourless oil. $[a]_D^{25}$ -7.5 (c. 0.40, $CHCl_3$); ν_{max} (film/cm^{-1}) 3032, 2955, 2930, 2732, 1721, 1655, 1456; the product was isolated as a 77:23 mixture of rotamers; ***major rotamer:*** δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J = 7.3, CH_3), 1.16-2.10 (8H, m, $(CH_2)_2CH_3$, $(CH_2)_2CH_2CHO$), 2.48 (2H, td, J = 7.2, 1.5, CH_2CHO), 3.17-3.77 (5H, m, NCH_2CH_2, NCH_2CH), 3.71 (1H, d, J = 11.1, COC*H*HBr), 3.77 (1H, d, J = 11.1, COCH*H*Br), 7.24-7.49 (5H, m, 5 × ArH), 9.76 (1H, t, J = 1.5, CHO); ***minor rotamer:*** δ_H (400 MHz, $CDCl_3$) 0.88 (0.9H, t, J = 7.3, CH_3), 1.16-2.10 (2.4H, m, $(CH_2)_2CH_3$, $(CH_2)_2CH_2CHO$), 2.54 (2H, td, J = 7.2, 1.5, CH_2CHO), 2.99 (1H, ddd, J = 14.9, 8.2 6.7, NC*H*HCH_2), 3.17-3.77 (1.2H, m, NCH*H*CH_2, NCH_2CH), 3.76 (0.3H, d, J = 11.1, COC*H*HBr), 3.92 (0.3H, d, J = 11.1, COCH*H*Br), 7.24-7.49 (1.5H, m, 5 × ArH), 9.81 (0.3H, t, J = 1.5, CHO); δ_C (100 MHz, $CDCl_3$) 13.7, 13.8, 19.3, 19.6, 19.9, 20.0, 26.2, 26.6, 31.0, 31.6, 43.4, 43.5, 46.0, 46.2, 49.5, 50.3, 51.4, 53.3, 126.9, 127.5, 128.1, 129.1, 129.4, 131.2, 133.1, 134.8, 167.4, 169.6, 201.7, 202.3; Found (EI): $[M]^+$ 399.08684, $C_{18}H_{26}NO_2SBr$ requires 399.08621.

Isochroman-3-one[161] (295)



Sodium Bicarbonate (38.0 g, 450 mmol) and *m*CPBA (70%, 17.0 g, 70 mmol) were added to a solution of 2-indanone (6.60 g, 50 mmol) in CH_2Cl_2 (50 ml). After 10 min the mixture was diluted with CH_2Cl_2 (50 ml) and stirred for 18 hr at RT. Further additions of *m*CPBA (4 × 5 g, 116 mmol) over the following 2 days were required to oxidise all the starting material (TLC). The reaction was quenched with 10% $Na_2S_2O_3$ (300 ml) and stirred until 2 clear phases were obtained. The phases were separated, and the organic layer was washed with 10% $Na_2S_2O_3$ (100 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was triturated in a 2:1 mixture Pet:Et_2O to give lactone **295** (1.97 g, 13.3 mmol, 27%) as an off white solid; ν_{max} (film/cm^{-1}) 2892, 1732, 1458, 1391, 1250, 1219, 1027; δ_H (400 MHz, $CDCl_3$) 3.74 (2H, s, CH_2CO), 5.34 (2H, s, CH_2O), 7.24-7.37 (4H, m, 4 × ArH); δc (150 MHz, $CDCl_3$) 36.3, 70.2, 124.8, 127.2, 127.5, 129.0, 131.0, 131.6, 170.9.

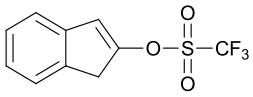
2-(2-((*tert*-Butyldiphenylsilyloxy)methyl)phenyl)-*N*-methoxy-*N*-methylacetamide (296)



A solution of *i*PrMgCl (2 M in THF, 10.2 ml, 20.4 mmol) was added dropwise to a solution of lactone **295** (500 mg, 3.38 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (985 mg, 10.1 mmol) in dry THF (15 ml) cooled to 0 °C over 1.5 hr. The reaction mixture was allowed to warm to RT over 48 hr then cooled to 0 °C, quenched with sat NH_4Cl and diluted with water. The mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was dissolved in DMF (2.5 ml) and imidazole (325 mg, 4.78 mmol) was added. A solution of *tert*-butyldiphenylchlorosilane (0.92 ml, 3.59

mmol) in DMF (2.5 ml) was added dropwise at 0 °C and the reaction mixture was allowed to warm to RT over 1.5 hr. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 90/10 → 60/40) to afford protected alcohol **296** (690 mg, 1.59 mmol, 47%) as a pale brown oil; ν_{max} (film/cm^{-1}) 2931, 2857, 1664, 1427, 1377, 1217, 1112, 1071; δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, Si^{t}Bu), 3.14 (3H, s, NCH_3), 3.45 (3H, s, OCH_3), 3.75 (2H, s, CH_2CO), 4.77 (2H, s, CH_2OSi), 7.22-7.46 (10H, m, 10 × ArH), 7.69 (4H, m, 4 × ArH); δc (150 MHz, $CDCl_3$) 19.4, 26.9, 36.3, 61.1, 64.1, 70.2, 124.8, 127.1, 127.2, 127.4, 127.5, 127.8, 128.9, 129.8, 129.9, 131.1, 132.6, 133.5, 134.9, 135.3, 135.7, 139.1, 169.8; Found (CI): $[M+H]^+$ 448.22891, $C_{27}H_{34}O_3NSi$ requires 448.23080.

1*H*-inden-2-yl trifluoromethanesulfonate[162] (301)

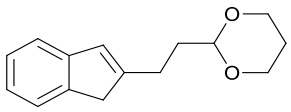


A solution of freshly distilled *i*Pr_2NH (0.87 ml, 6.24 mmol) in dry THF (7.5 ml) was cooled to -78 °C and a solution of *n*BuLi (1.6 M in THF, 3.9 ml, 6.24 mmol) was added dropwise. The reaction mixture was warmed to 0 °C and stirred under Ar at this temperature for 30 min. A solution of 2-indanone (750 mg, 5.67 mmol) in THF (7.5 ml) was added dropwise to the reaction mixture cooled at -78 °C and stirred at this temperature for 2.5 hr. *N*,*N*-bis(trifluoromethanesulfonyl)aniline (3.04 g, 8.50 mmol) was added in portions and the mixture was allowed to warm to RT over 16 hr. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (Pet) to give vinyl-triflate **301** as a colourless oil (1.09 g, 4.13 mmol, 73%); ν_{max} (film/cm^{-1}) 3081, 1619, 1427, 1245, 1237, 1140; δ_H (600 MHz, $CDCl_3$) 3.67 (2H, s, CH_2), 6.69 (1H, s, CH), 7.27 (1H, td, J = 7.5, 1.2, 1 × ArH), 7.31 (1H, t, J = 7.5, 1 × ArH), 7.37-7.40 (2H, m, 2 × ArH); δc (125 MHz, $CDCl_3$) 37.7, 117.6 (q, J = 321, CF_3), 119.6, 122.2, 123.8, 126.2, 127.3, 137.4, 140.2, 153.2; Found (EI): $[M]^+$, 264.00664, $C_{10}H_7O_3SF_3$ requires 264.00625.

General procedure for Indene formation:

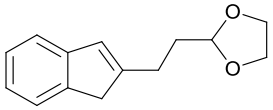
Vinyl-triflate **301** (1.2 eq) and $Fe(acac)_3$ (5 mol%) were dissolved in a 95:5 mixture of anhydrous THF:NMP (0.07 M). The resulting orange solution was cooled to -30 °C. A solution of the Grignard reagent (0.5 M in THF, 1 eq) was added dropwise and the reaction mixture was allowed to warm to RT over 18 hr. The reaction was quenched with sat. NH_4Cl and phases were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 95/5).

2-(2-(1H-Inden-2-yl)ethyl)-1,3-dioxane (302)



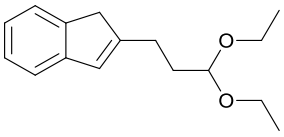
Orange oil (1.14 g, 4.95 mmol, 77%); ν_{max} (film/cm^{-1}) 3050, 2931, 1625; δ_H (400 MHz, $CDCl_3$) 1.38 (1H, dtt, J = 13.4, 2.6, 1.3, OCH_2CHH), 1.92-1.97 (2H, m, CH_2CH) 2.13 (1H, dtt, J = 13.4, 12.5, 5.0, OCH_2CHH), 2.62 (2H, t, J = 7.7, $C{=}CCH_2CH_2$), 3.34 (2H, s, $ArCH_2$), 3.79 (2H, ddd, J = 12.5, 10.6, 2.6, 2 × $OCHH$), 4.15 (2H, ddd, J = 10.6, 5.0, 1.3, 2 × $OCHH$), 4.61 (1H, t, J = 5.2, $CH(OR)_2$), 5.65 (1H, s, C=CH), 7.12 (1H, dt, J = 7.3, 1.5, 1 × ArH), 7.12 (1H, t, J = 7.3, 1 × ArH), 7.26-7.30 (1H, m, 1 × ArH) 7.40 (1H, d, J = 7.3, 1 × ArH); δc (125 MHz, $CDCl_3$) 25.6, 25.9, 34.4, 41.2, 67.0, 101.7, 120.0, 123.5, 123.7, 126.3, 126.4, 143.1, 145.6, 149.8; Found (EI): $[M]^+$, 230.12994, $C_{15}H_{18}O_2$ requires 230.1301.

2-(2-(1*H*-Inden-2-yl)ethyl)-1,3-dioxolane (307)



Pale yellow oil (598 mg, 2.76 mmol, 66%); ν_{max} (film/cm^{-1}) 3068, 2952, 2881, 1608, 1457, 1416, 1386, 1197, 1141, 1121, 1030; δ_H (600 MHz, $CDCl_3$) 1.98-2.01 (2H, m, C*H*$_2$CH), 2.63 (2H, t, J = 8.0, C=CC*H*$_2$CH$_2$), 3.33 (2H, s, ArCH$_2$), 3.85-3.91 (2H, m, 2 × OC*H*H), 3.96-4.03 (2H, m, 2 × OCH*H*), 4.94 (1H, t, J = 4.7, CH(OR)$_2$), 6.54 (1H, s, C=CH), 7.10 (1H, t, J = 7.4, 1 × ArH), 7.22 (1H, t, J = 7.4, 1 × ArH), 7.26 (1H, m , 1 ×ArH), 7.38 (1H, d, J = 7.4, 1 × ArH); δ_C (600 MHz, $CDCl_3$) 25.7, 33.2, 41.2, 65.1, 104.1, 120.1, 123.5, 123.8, 126.4, 126.5, 143.2, 145.6, 149.6; Found (EI): $[M]^+$ 216.11414, $C_{14}H_{16}O_2$ requires 216.11447.

2-(3,3-Diethoxypropyl)-1*H*-indene (311)

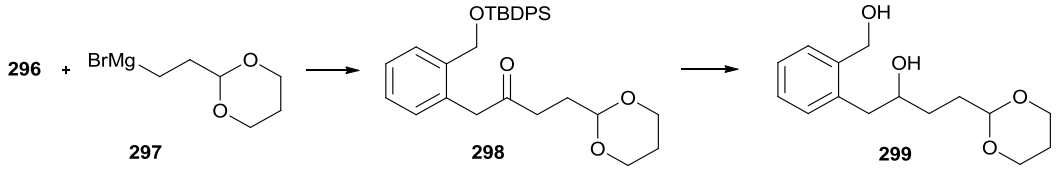


Acrolein diethyl acetal (0.25 ml, 1.66 mmol) was added dropwise to a solution of 9-BBN (0.5 M in THF, 3.33 ml, 1.66 mmol) at 0 °C and stirred under Ar for 1.5 hr. $PdCl_2$(dppf) (30 mg, 0.040 mmol) was added followed by K_2CO_3 (481 mg, 2.26 mmol) and by a solution of vinyl triflate **301** (400 mg, 1.51 mmol) in dry THF (7.5 ml). The reaction mixture was stirred at reflux for 5 hr, cooled to RT and extracted into EtOAc/water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 95/5) to afford indene **311** (157 mg, 0.637 mmol, 42%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3056, 3019, 2922, 2727, 1610, 1461,

1390, 1217; δ_H (400 MHz, $CDCl_3$) 1.26 (6H, t, J = 7.1, 2 × CH_3), 1.95-2.01 (2H, m, C*H*$_2$CH), 2.60 (2H, t, J = 7.7, C*H*$_2$CH$_2$CH), 3.35 (2H, s, ArCH$_2$), 3.52-3.60 (2H, m, 2 × OC*H*HCH$_3$), 3.68-3.77 (2H, m, 2 × OCH*H*CH$_3$), 4.59 (1H, t, J = 5.5, C*H*(OEt)$_2$), 6.56 (1H, s, C=CH), 7.12-7.48 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 15.4, 26.4, 32.9, 41.2, 61.2, 102.5, 120.0, 123.4, 123.7, 126.2, 126.3, 143.1, 145.5, 149.8; Found (EI): $[M]^+$ 246.16121, $C_{16}H_{22}O_2$ requires 246.16143

4-(1,3-Dioxan-2-yl)-1-(2-(hydroxymethyl)phenyl)butan-2-ol (299)

Procedure 1

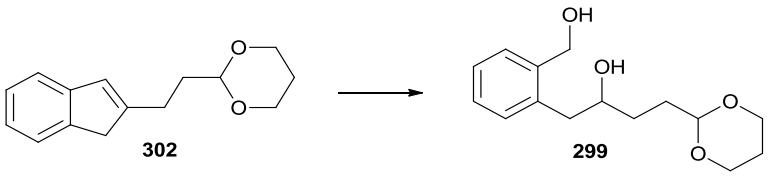


A solution of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide **297** (0.5 M in THF, 3.50 ml, 1.75 mmol) was added to solution of amide **296** (690 mg, 1.59 mmol) in dry THF (10 ml) cooled to 0 °C. The reaction mixture was allowed to warm to RT over 2 hr then cooled to 0 °C and quenched with sat. NH_4Cl solution (10 ml). The mixture was extracted with Et_2O (2 × 15 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (Pet/EtOAc = 90/10 → 80/20) to give ketone **298**.

$NaBH_4$ (42 mg, 1.12 mmol) was added to a solution of ketone **298** (530 mg, 1.05 mmol) in MeOH (5 ml) and the reaction mixture was stirred for 1 hr at RT. The solvent was removed *in vacuo* and the residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude was dissolved in THF (5 ml) and TBAF (1 M in THF, 2.0 ml, 2.04 mmol) was added to the solution dropwise. The reaction mixture was stirred for 1 hr at RT. The solvent was then removed *in vacuo* and the

crude material was purified by column chromatography (Pet/EtOAc = 50/50 → 40/60) to give diol **299** (188 mg, 0.71 mmol, 47% - 3 steps) as a colourless oil.

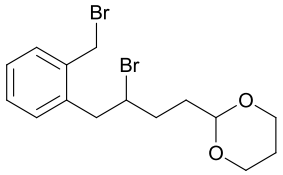
Procedure 2



Indene **302** (990 mg, 4.30 mmol) was dissolved in MeOH (50 ml) and the solution was cooled to -78 °C. Ozone was bubbled through the solution until blue colour was observed. Excess ozone was removed by flushing the solution with nitrogen. $NaBH_4$ (1.30 mg, 34.4 mmol) was added in portions and the reaction was allowed to warm to RT over 2 hr, after which time the solvent was removed *in vacuo* and the residue partitioned between EtOAc (50 ml) and sat NH_4Cl (25 ml). The aqueous layer was extracted with EtOAc (25 ml) and the combined organic layers were washed with brine (25 ml), dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 70/30) to give diol **299** as a pale yellow oil (850 mg, 3.19 mmol, 74%).

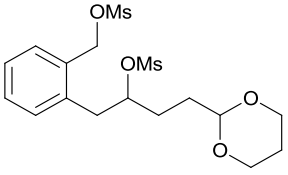
ν_{max} (film/cm^{-1}) 3371, 2970, 2856; δ_H (600 MHz, C_6D_6) 0.51 (1H, br d, J = 13.4, OCH_2CHH), 1.55-1.70 (3H, m, OCH_2CHH, $CHCH_2CH_2$), 1.77 (2H, m, $CH_2CH(OR)_2$), 2.53 (1H, dd, J = 13.8, 3.1, $CHHAr$), 2.71 (1H, dd, J = 13.8, 9.0 $CHHAr$), 3.17 (2H, m, 2 × $OCHH$), 3.59-3.66 (3H, m, $CHOH$ and 2 × $OCHH$), 4.26 (1H, t, J = 4.5, $CH(OR)_2$), 4.45 (1H, d, J = 11.6, $CHHOH$), 4.71 (1H, d, J = 11.6, $CHHOH$), 6.98 (1H, dd, J = 7.4, 1.2, 1 × ArH), 7.05 (1H, dt, J = 7.4, 1.5, 1 × ArH), 7.11 (1H, dt, J = 7.4, 1.5 1 × ArH) 7.26 (1H, dd, J = 7.4, 1.2, 1 × ArH); δc (150 MHz, C_6D_6) 25.4, 31.9, 32.0, 40.0, 63.1, 66.2, 66.3, 72.7, 101.9, 126.4, 127.8, 130.1, 130.3, 138.3, 140.5; Found (CI): $[M+H]^+$, 267.16048, $C_{15}H_{23}O_4$ requires 267.15963.

2-(3-Bromo-4-(2-(bromomethyl)phenyl)butyl)-1,3-dioxane (303)



Carbon tetrabromide (2.33 g, 7.02 mmol) and triphenylphosphine (1.76 g, 6.70 mmol) were added in portions to a solution of diol **299** (850 mg, 3.19 mmol) in CH_2Cl_2 (25 ml) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1.5 hr then quenched with MeOH (10 ml) and concentrated *in vacuo*. The crude material was purified by column chromatography (Pet/EtOAc = 100/0 → 90/10) to give bis-alkyl bromide **303** as a yellow oil (403 mg, 1.03 mmol, 33%). ν_{max} (film/cm^{-1}) 2970, 2854, 1377, 1265, 1217, 1145; δ_H (600 MHz, C_6D_6) 0.59 (1H, dtt, J = 13.2, 2.3, 1.3, OCH_2CHH), 1.74 (1H, dtt, J = 13.2, 12.6, 5.0, OCH_2CHH), 1.84-2.12 (4H, m, $CHCH_2CH_2$), 3.02 (1H, dd, J = 15.0, 5.6 $CHHAr$), 3.13 (1H, dd, J = 15.0, 8.9, $CHHAr$), 3.23-3.26 (2H, m, 2 × $OCHH$), 3.74 (2H, ddd, J = 11.2, 5.0, 1.3 2 × $OCHH$), 4.06 (1H, d, J = 10.5, $CHHBr$), 4.19 (1H, m, CHBr), 4.23 (1H, d, J = 10.5, $CHHBr$), 4.30 (1H, t, J = 4.7, $CH(OR)_2$), 6.87-6.96 (4H, m, ArH), δ_C (150 MHz, C_6D_6) 25.6, 31.3, 33.3, 41.7, 56.7, 66.3, 101.2, 126.5, 128.5, 130.6, 130.7, 136.1, 137.6; Found (CI): $[M+H]^+$, 390.98973 $C_{15}H_{21}O_2Br_2$ requires 390.99083.

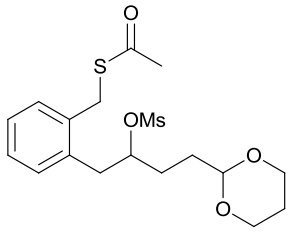
4-(1,3-Dioxan-2-yl)-1-(2-(((methylsulfonyl)oxy)methyl)phenyl)butan-2-yl methanesulfonate (304)



A solution of diol **299** (1.73 g, 6.49 mmol) and NEt_3 (2.71 ml, 19.5 mmol) in CH_2Cl_2 (35 ml) was cooled to 0 °C. Methanesulfonyl chloride (1.11 ml, 14.3 mmol) was added dropwise over 10 min. The resulting mixture was stirred at 0 °C for 20 min, then quenched with sat $NaHCO_3$ (35 ml). The phases were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness.

The crude was purified by column chromatography (Pet/EtOAc = 50/50 → 30/70) to give dimesylate **304** (2.27 g, 5.37 mmol, 83%) as a colourless oil. ν_{max} (film/cm^{-1}) 3023, 2968, 2939, 2857, 1352, 1173, 1141, 903; δ_H (600 MHz, $CDCl_3$) 1.33 (1H, br d, J = 13.5, OCH_2CHH), 1.71-2.07 (5H, m, $CHCH_2CH_2$, OCH_2CHH), 2.55 (3H, s, 1 × OSO_2CH_3), 3.00 (3H, s, 1 × OSO_2CH_3), 3.04 (1H, dd, J = 14.4, 5.4, $ArCHHCH$), 3.16 (1H, dd, J = 14.4, 8.3, $ArCHHCH$), 3.74 (2H, m, 2 × $OCHH$), 4.06-4.09 (2H, m, 2 × $OCHH$), 4.57 (1H, t, J = 4.8, $CH(OR)_2$), 4.90 (1H, ddt, J = 14.2, 8.3, 5.9, CHOMs), 5.30 (1H, d, J = 11.5, $ArCHHOMs$), 5.34 (1H, d, J = 11.5, $ArCHHOMs$), 7.29-7.33 (2H, m, 2 × ArH), 7.38 (1H, td, J = 7.5, 1.1, 1 × ArH), 7.44 (1H, d, J = 7.5, 1 × ArH); δ_C (150 MHz, $CDCl_3$) 25.8, 29.5, 30.6, 37.7, 37.9, 38.2, 66.9, 67.0, 69.1, 84.2, 101.4, 127.9, 130.1, 131.3, 131.7, 132.3, 136.7; Found (EI): [M-H] 421.09810, $C_{17}H_{25}O_8S_2$ requires 421.09854.

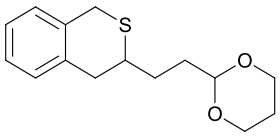
S-2-(4-(1,3-Dioxan-2-yl)-2-((methylsulfonyl)oxy)butyl)benzylethanethioate (305)



Potassium thioacetate (540 mg, 3.90 mmol) was added to a solution of bis-mesylate **304** (1.50 g, 3.55 mmol) in DMF (40 ml) and the reaction was stirred at RT for 16 hr. The mixture was diluted with water and extracted with Et_2O. The extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford S-acetate **305** (1.31 g, 3.25 mmol, 92%) as a pale brown oil. ν_{max} (film/cm^{-1}) 2970, 1689, 1351, 1171, 903; δ_H (500 MHz, $CDCl_3$) 1.33 (1H, br d, J = 13.3, OCH_2CHH), 1.71-1.83 (2H, m, $CH(OMs)CH_2CH_2$), 1.90 (2H, m, $CH(OMs)CH_2$), 2.04 (1H, dtt, J = 13.3, 7.8, 4.9, OCH_2CHH), 2.34 (3H, s, $COCH_3$), 2.43 (3H, s, OSO_2CH_3), 2.98 (1H, dd, J = 14.4, 5.5, $ArCHHCH$), 3.06 (1H, dd, J = 14.4, 8.8, $ArCHHCH$), 3.72-3.76 (2H, m, 2 × $OCHH$), 4.06-4.10 (2H, m, 2 × $OCHH$), 4.18 (2H, s, $ArCH_2S$), 4.56 (1H, t, J = 4.9, $CH(OR)_2$), 4.86 (1H, m, CHOMs), 7.17-7.36 (4H, m, 4 × ArH); δ_C (400 MHz, $CDCl_3$) 25.8, 29.8, 30.4, 30.6, 30.8, 37.7, 37.8, 66.9, 67.0, 84.4, 101.6,

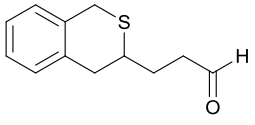
127.8, 127.9, 130.7, 131.3, 135.4, 136.2, 195.0; Found (EI): [M-H] 401.10912, $C_{18}H_{25}O_6S_2$ requires 401.10871.

2-(2-Isothiochroman-3-yl-ethyl)-[1,3]dioxane (300)



Potassium carbonate (893 mg, 6.46 mmol) was added to a solution of mesylate **305** (1.30 g, 3.23 mmol) in MeOH (33 ml). The reaction mixture was stirred at RT for 16 hr after which time the reaction was extracted with EtOAc (3 x 10 ml). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 80/20) to afford sulfide **300** (790 mg, 2.99 mmol, 93%) as a colourless oil. ν_{max} (film/cm^{-1}) 2955, 2925, 2849, 1449, 1378, 1142; δ_H (600 MHz, $CDCl_3$) 1.33 (1H, br d, J = 13.5, OCH_2CHH), 1.61-1.81 (4H, m, $SCH(CH_2)_2$), 2.07 (1H, dtt, J = 13.4, 12.6, 4.9, OCH_2CHH), 2.74 (1H, dd, J = 14.7, 8.8, $ArCHHCH$), 3.05 (1H, dd, J = 14.7, 4.3, $ArCHHCH$), 3.06-3.11 (1H, m, SCH), 3.72 (1H, d, J = 14.9, $ArCHHS$), 3.72-3.76 (2H, m, 2 × $OCHH$), 3.78 (1H, d, J = 14.9, $ArCHHS$), 4.09 (2H, m, 2 × $OCHH$), 4.53 (1H, t, J = 4.7, $CH(OR)_2$), 7.12-7.19 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 25.8, 29.5, 31.1, 32.7, 37.3, 41.0, 66.9,101.9, 126.3, 126.7, 127.1, 129.3, 135.5, 136.8; Found (EI): $[M]^+$ 264.11702, $C_{15}H_{20}O_2S$ requires 264.11785.

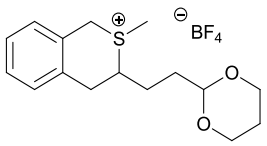
3-(Isothiochroman-3-yl)propanal (290)



Acetal **300** (200 mg, 0.756 mmol) was dissolved in TFA (4 ml) and water (0.5 ml) was slowly added to the solution. The reaction mixture was stirred at RT for 3 hr then diluted with toluene (50 ml) and evaporated to dryness. The crude was

partitioned between toluene (20 ml) and 1 M $NaHCO_3$ (20 ml). The aqueous layer was extracted with toluene (10 ml) and the combined organic layers were washed with brine (20 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 90/10) to afford aldehyde **290** (63 mg, 0.31 mmol, 40%) as a colourless oil. ν_{max} (film/cm^{-1}) 3020, 2919, 2826, 2726, 1719, 1494, 1447, 1412, 1141, 744; δ_H (600 MHz, $CDCl_3$) 1.76-1.82 (1H, m, CHC*H*HCH$_2$), 1.98-2.05 (1H, m, CHCH*H*CH$_2$), 2.59-2.70 (2H, m, C*H*$_2$CHO), 2.79 (1H, dd, J = 15.1, 8.7, ArC*H*HCH), 3.07 (1H, dd, J = 15.1, 4.4, ArCH*H*CH), 3.14 (1H, m, SCH), 3.71 (1H, d, J = 14.8, ArC*H*HS), 3.78 (1H, d, J = 14.8, ArCH*H*S), 7.12-7.20 (4H, m, ArH), 9.79 (1H, t, J = 1.2, CHO); δ_C (150 MHz, $CDCl_3$) 29.0, 29.4, 37.4, 40.6, 41.6, 126.6, 127.0, 127.3, 129.5, 135.2, 136.4, 201.7; Found (EI): $[M]^+$ 206.07651, $C_{12}H_{14}OS$ requires 206.07598.

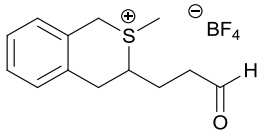
3-(2-(1,3-Dioxan-2-yl)ethyl)-2-methylisothiochroman-2-ylium tetrafluoroborate (314)



Silver tetrafluoroborate (90 mg, 0.46 mmol) was added in one portion to a solution of sulfide **300** (100 mg, 0.38 mmol) and MeI (28 µl, 0.46 mmol) in acetone (1 ml) stirred at RT. The reaction mixture was stirred for 24 hr in the dark then filtered through a silica pad (CH_2Cl_2/MeOH = 99/1 → 95/5) to give salt **314** (27 mg, 0.074 mmol, 19%) as a pale brown oil. ν_{max} (film/cm^{-1}) 2932, 2856, 1453, 1423, 1132, 1054, 762; isolated as a 80:20 mixture of diastereoisomers; ***major diastereoisomer:*** δ_H (600 MHz, acetone-d_6) 1.37 (1H, br d, J = 13.5, OCH$_2$C*H*H), 1.83-2.00 (3H, m, C*H*$_2$CH(OR)$_2$, OCH$_2$CH*H*), 2.15-2.19 (2H, m, SCHC*H*$_2$CH$_2$), 2.78 (3H, s, SCH$_3$), 3.10 (1H, dd, J = 15.3, 10.1, ArC*H*HCH), 3.57 (1H, dd, J = 15.3, 4.5, ArCH*H*CH), 3.75-3.80 (3H, m, SCH, 2 × OC*H*H), 4.05 (2H, ddd, J = 10.8, 4.9, 0.9, 2 × OCH*H*), 4.67-4.70 (3H, m, ArC*H*HS, CH(OR)$_2$), 4.86 (1H, d, J = 14.7, ArCH*H*S), 7.44-7.56 (4H, m, 4 × ArH); δ_C (150 MHz, acetone-d_6) 24.3, 26.4, 28.5, 32.5, 33.8, 38.7, 58.3,

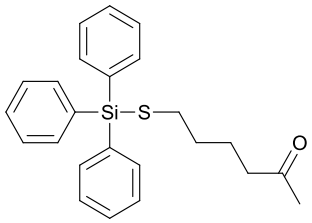
67.2, 67.3, 101.7, 127.4, 128.9, 130.2, 130.8, 130.9, 136.7; ***minor diastereoisomer:*** δ_H (600 MHz, acetone-d_6) 1.37 (1H, br d, J = 13.5, OCH_2CHH), 1.83-2.00 (3H, m, $CH_2CH(OR)_2$, OCH_2CHH), 2.15-2.19 (2H, m, $SCHCH_2CH_2$), 2.80 (3H, s, SCH_3), 3.13 (1H, dd, J = 15.5, 10.1, $ArCHHCH$), 3.60 (1H, dd, J = 15.5, 4.6, $ArCHHCH$), 3.75-3.80 (3H, m, SCH, 2 × $OCHH$), 4.05 (2H, ddd, J = 10.8, 4.9, 0.9, 2 × $OCHH$), 4.46 (1H, t, J = 5.1, $CH(OR)_2$), 4.68 (2H, d, J = 14.8, $ArCHHS$,), 4.88 (1H, d, J = 14.8, $ArCHHS$), 7.44-7.56 (4H, m, 4 × ArH) δ_C (150 MHz, acetone-d_6) 24.4, 26.5, 29.0, 32.3, 33.6, 38.8, 58.2, 67.2, 67.3, 104.9, 127.3, 128.9, 129.8, 130.8, 131.0, 136.6; Found (TOF-MS): $[M]^+$ 279.1406, $C_{16}H_{23}O_2S$ requires 279.1419.

2-Methyl-3-(3-oxopropyl)isothiochroman-2-ylium tetrafluoroborate (313)



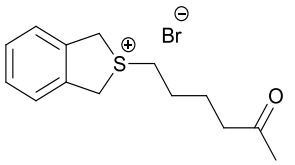
Silver tetrafluoroborate (68 mg, 0.35 mmol) was added in one portion to a solution of aldehyde **290** (60 mg) in acetone (0.6 ml) stirred at RT in the dark. The mixture was stirred for 3 hr then filtered from the insoluble salts. The filtrate was evaporated to dryness and then purified by column chromatography (CH_2Cl_2/MeOH = 95/5 → 90/10 → 85/15) to afford salt **313** (4 mg, 0.013 mmol, 4%) as a pale brown amorphous solid. ν_{max} (film/cm^{-1}) 2925, 2854, 1719, 1451, 1054, 764; δ_H (600 MHz, $CDCl_3$); 2.06-2.08 (2H, m, CH_2CH_2CHO), 2.50 (3H, s, SCH_3), 2.78 (2H, t, J = 7.1, CH_2CHO), 2.85-2.91 (1H, m, $ArCHHCH$), 3.32-3.40 (2H, m, $ArCHHCH$, SCH), 4.29 (1H, d, J = 15.1, $ArCHHS$), 4.53 (1H, d, J = 15.1, $ArCHHS$), 7.41-7.51 (4H, m, 4 × ArCH), 9.73 (1H, s, CHO); δ_C (150 MHz, $CDCl_3$) 23.2, 24.8, 31.9, 37.6, 39.5, 55.7, 127.9, 129.0, 129.6, 129.7, 129.9, 135.5, 200.7; Found (TOF-MS): $[M]^+$ 221.1003, $C_{13}H_{17}OS$ requires 221.1000.

6-((Triphenylsilyl)thio)hexan-2-one (320)



A mixture of triphenylsilanethiol (1.0 g, 3.42 mmol), 5-hexene-2-one (280 mg, 2.85 mmol) and AIBN (94 mg, 0.57 mmol) was stirred in benzene (3.5 ml) at reflux over 3 hr. The reaction mixture was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 95/5 → 90/10) to give sulfide **320** (914 mg, 2.34 mmol, 82%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3068, 3025, 2943, 1738, 1428, 1365, 1217, 1109, 698; δ_H (400 MHz, $CDCl_3$) 1.47-1.67 (4H, m, $SCH_2(CH_2)_2$), 2.08 (3H, s, CH_3), 2.28 (2H, t, J = 7.3, CH_2CO), 2.45 (2H, t, J = 7.0, SCH_2), 7.39-7.48 (15H, m, ArH); δ_C (125 MHz, $CDCl_3$) 22.7, 27.2, 29.9, 31.7, 43.0, 128.1, 130.2, 133.4, 135.7; Found (TOF-MS): $[M\text{-}Na]^+$ 413.1366, $C_{24}H_{26}ONaSSi$ requires 413.1371.

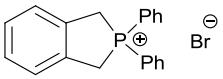
2-(5-Oxohexyl)-2,3-dihydro-1H-benzo[c]thiophen-2-ium bromide (321)



Potassium Hydroxide (229 mg, 4.08 mmol) was added to a solution of sulfide **320** (800 mg, 2.04 mmol), α,α'-dibromoxylene (810 mg, 3.07 mmol) and TBAB (40 mg, 0.12 mmol) in CH_2Cl_2 (15 ml) and water (1.5 ml) stirred at RT. The mixture was stirred for 5 days then evaporated to dryness and the residual water was removed by azeotropical distillation with toluene. The silyl by-products were removed by crystallisation from MeCN. The filtrate was evaporated to dryness and purified by column chromatography (CH_2Cl_2/MeOH = 90/10) to afford sulfonium salt **321** (130

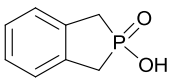
mg, 0.41 mmol, 20%) as an amorphous white solid. ν_{max} (film/cm^{-1}) 2926, 1704, 1487, 1456, 1406, 1362, 1169; δ_H (400 MHz, $CDCl_3$) 1.76-1.88 (4H, m, $SCH_2(CH_2)_2$), 2.15 (3H, s, CH_3), 2.60 (2H, t, J = 6.7, CH_2CO), 3.57 (2H, t, J = 7.3, SCH_2CH_2), 4.83 (2H, d, J = 16.2, 2 × ArC*H*HS), 5.56 (2H, d, J = 16.2, 2 × ArCH*H*S), 7.37-7.43 (4H, m, 4 × ArH); δ_C (500 MHz, $CDCl_3$) 21.9, 23.8, 30.2, 40.5, 42.1, 48.9, 126.0, 129.2, 133.6, 208.3; Found (TOF-MS): $[M]^+$ 235.1146, $C_{14}H_{19}OS$ requires 235.1157.

2,2-Diphenyl-2,3-dihydro-1H-isophosphindol-2-ium bromide[254] (343)



A solution of α,α'-dibromoxylene (1.09 g, 4.12 mmol) in toluene (5 ml) was added simultaneously with a solution of Ph_2PSiMe_3 (1.28 g, 4.95 mmol) in toluene (5 ml) to refluxing toluene (14 ml) and the resulting mixture was stirred at reflux for 16 hr. The white precipitate was filtered, washed with toluene and dried under vacuum. Phosphonium salt **343** was isolated as a white solid (1.15 g, 3.11 mmol, 76%); ν_{max} (film/cm^{-1}) 3056, 2913, 1438, 1115, 923; δ_H (300 MHz, $CDCl_3$) 4.59 (4H, d, J_{HP} = 11.7, 2 × CH_2P), 7.35-8.906 (14H, m, 14 × ArH); δ_C (150 MHz, $CDCl_3$) 31.5 (J_{CP} = 54.3), 117.8 (J_{CP} = 82.3), 127.9 (J_{CP} = 14.3), 129.7, 130.5 (J_{CP} = 13.0), 132.8 (J_{CP} = 7.2), 133.2 (J_{CP} = 10.6), 135.4 (J_{CP} = 3.1); δ_P (121 MHz, $CDCl_3$) 45.7.

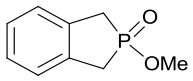
2-Hydroxy-2,3-dihydro-1H-isophosphindole 2-oxide[168] (352)



A mixture of α,α'-dibromoxylene (2.0 g, 7.6 mmol), HMDS (16.0 ml, 76 mmol) and $(NH_4)H_2PO_2$ (3.14 g, 38 mmol) was refluxed in mesitylene (75 ml) over 16 hr. The mixture was concentrated to a low volume under reduced pressure then quenched

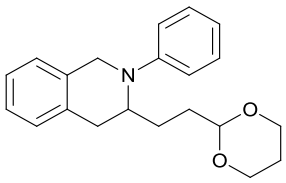
with brine (100 ml) and stirred at RT for 1 hr. The mixture was extracted in EtOAc (2 × 75 ml) and the combined organic layers were washed with 2 M NaOH (3 × 75 ml). The combined aqueous layers were acidified with 2N HCl and extracted with EtOAc (3× 75 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford cyclic phosphinate **352** (261 mg, 1.55 mmol, 20%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 3.14 (4H, d, J = 14.1, 2 × CH_2P), 7.19-7.28 (4H, m, 4 × ArH), 7.68 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 32.1 (J_{CP} = 93), 126.9, 127.4 (J_{CP} = 18), 134.6 (J_{CP} = 13); δ_P (121 MHz, $CDCl_3$) 75.1

2-Methoxy-2,3-dihydro-1H-isophosphindole 2-oxide[255] (353)



A mixture of phosphinate **352** (250 mg, 1.49 mmol) and p-toluenesulfonic acid (15 mg, 0.09 mmol) in $CH(OMe)_3$ (7.5 ml) was stirred at reflux for 8 hr. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (Pet/EtOAc = 30/70 → 0/100) to afford phosphindole **353** (28 mg, 0.15 mmol, 10%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.16 (2H, d, J = 15.0, 2 × C*H*HP), 3.17 (2H, d, J = 12.3, 2 × CH*H*P), 3.79 (3H, d, J = 11.0, OMe), 7.25 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 31.0 (J_{CP} = 90.6), 51.5 (J_{CP} = 6.7), 127.4 (J_{CP} = 17.7), 127.6 (J_{CP} = 1.4), 134.6 (J_{CP} = 12.5); δ_P (121 MHz, $CDCl_3$) 74.2; Found (EI): $[M]^+$ 182.04963, $C_9H_{11}O_2P$ requires 182.04912.

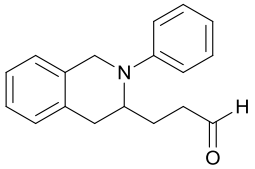
3-(2-(1,3-Dioxan-2-yl)ethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (363)



Aniline (0.42 ml, 4.60 mmol) was added to a solution of dimesylate **304** (389 mg, 0.92 mmol) and stirred in THF (4 ml) at RT for 16 hr. the mixture was then heated at reflux for 6 hr and then cooled to RT. The solvent was removed in vacuo and the

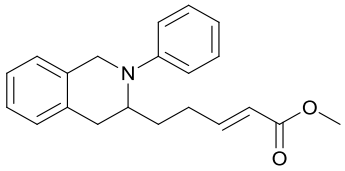
crude residue was purified by column chromatography (Pet/EtOAc = 85/15) to afford tetrahydroisoquinoline **363** (60 mg, 0.18 mmol, 20%) as pale yellow oil. ν_{max} (film/cm^{-1}) 2957, 2851, 1654, 1598, 1499, 1460, 1243, 1143, 1090, 1000; δ_H (600 MHz, $CDCl_3$) 1.27-1.32 (1H, m, OCH_2CHH), 1.38-1.44 (1H, m, $NCHCHHCH_2$), 1.58-1.61 (2H, m, $CH(OR)_2CH_2$), 1.64-1.70 (1H, m, $NCHCHHCH_2$), 2.02 (1H, dtt, J = 13.2, 7.6, 5.0, OCH_2CHH), 2.78 (1H, dd, J = 15.8, 1.7, $ArCHHCH$), 3.16 (1H, dd, J = 15.8, 5.7, $ArCHHCH$), 3.68 (2H, dtd, J = 11.8, 8.2, 2.5, 2 × $OCHH$), 4.04 (2H, m, 2 × $OCHH$), 4.21 (1H, dddd, J = 13.9, 7.9, 5.7, 1.7, NCH), 4.30 (1H, d, J = 15.7, $ArCHHN$), 4.42 (1H, t, J = 5.1, $CH(OR)_2$), 4.47 (1H, d, J = 15.7, $ArCHHN$), 6.76 (1H, t, J = 7.2, ArH), 6.92 (2H, d, J = 8.2, 2 × ArH), 7.16-7.31 (6H, m, 6 × ArH); δ_C (150 MHz, $CDCl_3$) 24.7, 25.8, 32.5, 32.6, 53.1, 66.9, 67.0, 102.3, 114.2, 117.6, 126.1, 126.4, 126.5, 129.4, 133.4, 133.9, 149.6; Found (TOF-MS): $[M]^+$ 324.1957, $C_{21}H_{26}NO_2$ requires 324.1964.

3-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)propanal (364)



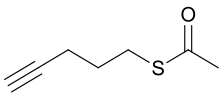
A solution of tetrahydroisoqinoline **363** (30 mg, 0.093 mmol) was stirred in TFA (0.6 ml) and water (75 µL) at RT for 16 hr. The mixture was poured into 1M $NaHCO_3$ (5 ml) and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to afford aldehyde **364** (18 mg, 0.068 mmol, 73%) as a pale brown oil. ν_{max} (film/cm^{-1}) 3025, 2927, 2835, 2724, 1720, 1598, 1501, 1459, 1391, 1241, 1036, 990; δ_H (300 MHz, $CDCl_3$) 1.68 (1H, dq, J = 14.5, 7.4, $CHHCH_2CHO$), 1.89 (1H, dq, J = 14.5, 7.4, $CHHCH_2CHO$), 2.43 (2H, td, J = 7.4, 1,4, CH_2CHO), 2.73 (1H, dd, J = 16.0, 1.9, $ArCHHCH$), 3.20 (1H, dd, J = 16.0, 5.4, $ArCHHCH$), 4.25-4.33 (2H, m, $ArCHHN$, NCH), 4.47 (1H, d, J = 16.1, $ArCHHN$), 6.79 (1H, t, J = 7.3, 1 × ArH), 6.92 (2H, d, J = 8.0, 2 × ArH), 7.13-7.30 (6H, m, 6 × ArH), 9.64 (1H, t, J = 1.4, CHO); δ_C (75 MHz, $CDCl_3$) 23.3, 32.7, 41.1, 45.9, 52.5, 114.3, 118.0, 126.2, 126.3, 126.6, 129.2, 129.4, 132.9, 133.5, 149.6, 201.8; Found (CI): $[M+H]^+$ 266.15512, $C_{18}H_{20}ON$ requires 266.15447.

(E)-Methyl 5-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)pent-2-enoate (366)



Methyl(triphenylphosphoranylidene)acetate (21 mg, 0.063 mmol) was added to a solution of aldehyde **364** (16 mg, 0.060 mmol) in toluene (0.5 ml) and stirred at RT for 24 hr. The mixture was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 90/10) to afford ester **366** (6 mg, 0.018 mmol, 31%) as a colourless oil. ν_{max} (film/cm^{-1}) 3023, 2948, 1721, 1656, 1598, 1502, 1459, 1435, 1392, 1272, 1202, 1038; δ_H (400 MHz, $CDCl_3$) 1.51 (1H, dq, J = 14.4, 7.7, NCHC*H*HCH$_2$), 1.75 (1H, dq, J = 14.4, 7.0, NCHCH*H*CH$_2$), 2.21 (2H, qd, J = 7.0, 1.4, CH$_2$CH=C), 2.77 (1H, dd, J = 16.0, 1.8, NCHC*H*HAr), 3.22 (1H, dd, J = 16.0, 5.4, NCHCH*H*Ar), 3.72 (3H, s, CO_2CH_3), 4.23 (1H, m, NCH), 4.32 (1H, d, J = 16.0, ArC*H*HN), 4.49 (1H, d, J = 16.0, ArCH*H*N), 5.74 (1H, dt, J = 15.7, 1.4, CH=C*H*CO$_2$Me), 6.80 (1H, t, J = 7.3, 1 × ArH), 6.90 (1H, dt, J = 15.7, 7.0, C*H*=CHCO$_2$Me), 6.92 (2H, d, J = 8.5, 2 × ArH), 7.15-7.31 (6H, m, 6 × ArH); δ_C (100 MHz, $CDCl_3$) 28.9, 29.5, 32.6, 46.0, 51.4, 52.9, 114.3, 117.9, 121.3, 126.1, 126.3, 126.5, 129.2, 129.3, 133.0, 133.6, 148.5, 149.5, 171.0; Found (EI): [M-H] 320.16405, $C_{21}H_{23}O_2N$ requires 320.16504.

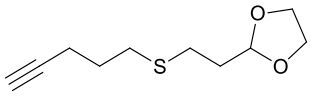
***S*-Pent-4-yn-1-yl ethanethioate[173] (377)**



Diisopropylazodicarboxylate (7.25 ml, 36.9 mmol) was added dropwise to a solution of PPh_3 (9.67 g, 36.9 mmol) in dry THF (120 ml) cooled to 0 °C. After 30 min a solution of 4-pentyn-1-ol (2.20 ml, 23.8 mmol) and thioacetic acid (2.63 ml, 36.9 mmol) in dry THF (20 ml) was added dropwise at 0 °C and the resulting mixture was allowed to warm to RT over 16 hr. The reaction was diluted with sat. NH_4Cl (100

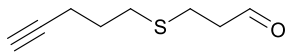
ml) and EtOAc (100 ml). The aqueous layer was extracted with EtOAc (50 ml) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 100/0 → 98/2) to give thioester **377** (3.44 g, 23.8 mmol, quant.) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3295, 2924, 1690, 1432, 1355, 1217, 1134; δ_H (600 MHz, $CDCl_3$) 1.82 (2H, quint, J = 7.2, $CH_2CH_2CH_2$), 1.99 (1H, t, J = 2.6, C≡CH), 2.29 (2H, td, J = 7.0, 2.6, $C{\equiv}CCH_2$), 2.35 (3H, s, $COCH_3$), 2.99 (2H, t, J = 7.2, CH_2S); δc (150 MHz, $CDCl_3$) 14.2, 28.0, 28.3, 30.7, 69.2, 83.0, 195.7; Found (CI): $[M+H]^+$ 143.05384, $C_7H_{11}OS$ requires 143.05306.

2-(2-(Pent-4-yn-1-ylthio)ethyl)-1,3-dioxolane (378)



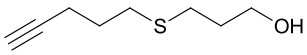
A suspension of thioester **377** (1.68 g, 8.39 mmol), bromide **225** (1.59 g, 8.81 mmol) and K_2CO_3 (2.32 g, 16.8 mmol) was stirred in MeOH (40 ml) at RT for 3 hr. The reaction was concentrated *in vacuo* to a reduced volume and then partitioned between EtOAc and 1 N HCl. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by column chromatography (Pet/EtOAc = 90/10) to afford sulfide **378** (1.09 g, 5.09 mmol, 61%) as a colourless oil. ν_{max} (film/cm^{-1}) 3288, 2880, 1406, 1280; δ_H (400 MHz, $CDCl_3$) 1.83 (2H, quint, J = 7.0, $CH_2CH_2CH_2$), 1.97 (3H, m, $CH_2CH(OR)_2$, C≡CH), 2.34 (2H, td, J = 7.0, 2.7, $C{\equiv}CCH_2$), 2.63 (2H, t, J = 7.5, 1 × SCH_2), 2.65 (2H, t, J = 7.2, 1 × SCH_2), 3.88 (2H, m, 2 × OCHH), 3.98 (2H, m, 2 × OCHH), 4.98 (1H, t, J = 4.6, $CH(OR)_2$); δc (150 MHz, $CDCl_3$) 17.6, 26.4, 28.2, 31.0, 34.1, 65.1, 69.0, 83.6, 103.3; Found (EI): $[M-H]^-$ 199.07812, $C_{10}H_{15}O_2S$ requires 199.07873.

3-(Pent-4-yn-1-ylthio)propanal (379)



A solution of acetal **378** (120 mg, 0.56 mmol) in THF (1 ml) and 2 N HCl (0.5 ml) was stirred for 16 hr at RT. The mixture was then extracted with Et_2O (2 × 5 ml). The organic layers were evaporated to dryness and then dissolved in THF (1 ml) and 2N HCl (0.5 ml) and stirred for further 16 hr. The procedure was repeated 4 times; the organic layer of the last extraction was dried over $MgSO_4$, filtered and evaporated to dryness to give aldehyde **379** (49 mg, 0.31 mmol, 56%) as a colourless oil. ν_{max} (film/cm^{-1}) 3290, 2923, 2832, 2728, 1718, 1430, 1330, 1281; δ_H (400 MHz, $CDCl_3$) 1.84 (2H, quint, J = 7.1, $CH_2CH_2CH_2$), 2.00 (1H, t, J = 2.6, C≡CH), 2.35 (2H, td, J = 6.9, 2.6, $C{\equiv}CCH_2$), 2.68 (2H, t, J = 7.1, $(CH_2)_2CH_2S$), 2.75-2.85 (4H, m, $S(CH_2)_2CHO$), 9.81 (1H, t, J = 1.2, CHO); δc (150 MHz, $CDCl_3$) 17.5, 24.4, 28.1, 31.1, 43.8, 69.2, 83.4, 200.7; Found (CI): $[M+H]^+$ 157.06923, $C_8H_{13}OS$ requires 157.06871.

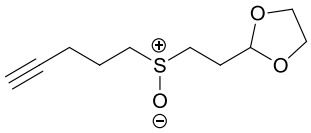
3-(Pent-4-yn-1-ylthio)propan-1-ol (382)



A mixture of thioester **377** (500 mg, 3.51 mmol), 3-bromo-1-propanol (561 mg, 4.04 mmol) and K_2CO_3 (972 mg, 7.03 mmol) in MeOH (10 ml) was stirred at RT for 16 hr. The solvent was evaporated under reduced pressure and the crude residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford alcohol **382** (550 mg, 3.51 mmol, quant.) as a pale brown oil. ν_{max} (film/cm^{-1}) 3290, 2936, 1431, 1255, 1217, 1051; δ_H (600 MHz, $CDCl_3$) 1.81 (2H, quint, J = 7.2, CH_2CH_2OH), 1.85 (2H, quint, J = 6.8, $CH_2CH_2C{\equiv}C$), 1.97 (1H, t, J = 2.7, C≡CH), 2.32 (2H, td, J = 6.8, 2.7,

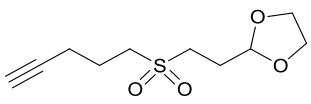
C≡CCH_2), 2.64 (4H, m, 2 × SCH_2), 3.76 (2H, br s, CH_2OH); δc (150 MHz, $CDCl_3$) 17.6, 28.3, 28.8, 30.9, 32.0, 62.0, 69.1, 83.6; Found (CI): $[M+H]^+$ 159.08455, $C_8H_{15}OS$ requires 159.08436.

2-(2-(Pent-4-yn-1-ylsulfinyl)ethyl)-1,3-dioxolane (385)



A solution of hydrogen peroxide (30% v/v, 0.11 ml, 0.98 mmol) was added dropwise to a solution of sulfide **378** (200 mg, 0.93 mmol) and MoO_2Cl_2 (3 mg, 0.014 mmol) in acetone (2 ml) and water (1 ml) stirred at RT. After 4 hr the reaction was diluted with brine (3 ml) and extracted into EtOAc (2 × 10 ml). Combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by column chromatography (Pet/EtOAc = 50/50 → 0/100) to afford sulfoxide **385** (99 mg, 0.43 mmol, 46%) as a colourless oil. ν_{max} (film/cm^{-1}) 3435, 3285, 2890, 1409, 1131, 1011; δ_H (600 MHz, $CDCl_3$) 1.99-2.40 (7H, m, C≡C$(CH_2)_2$, CHCH_2, C≡CH), 2.73-2.86 (4H, m, 2 × CH_2S(O)), 3.86 (2H, m, 2 × OC*H*H), 3.96 (2H, m, 2 × OCH*H*), 5.01 (1H, t, J = 4.1, CH$(OR)_2$); δc (150 MHz, $CDCl_3$) 17.8, 21.7, 26.9, 46.6, 51.1, 65.2, 70.0, 82.5, 102.6; Found (CI): $[M+H]^+$ 217.09078, $C_{10}H_{17}O_3S$ requires 217.08984.

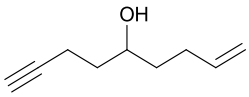
2-(2-(Pent-4-yn-1-ylsulfonyl)ethyl)-1,3-dioxolane (386)



m-Chloroperbenzoic acid (70% - 776 mg, 2.94 mmol) was added in portions to a solution of sulfide **378** (421 mg, 1.96 mmol) in CH_2Cl_2 (20 ml) cooled to 0°C. The

resulting suspension was stirred at 0 °C for 20 min then quenched with 1M $NaHCO_3$ (10 ml) and the phases were separated. The organic layer was washed with sat K_2CO_3 (2 × 10 ml), water (1 × 10 ml), brine (1 × 10 ml) then dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (Pet/EtOAc = 80/20 → 70/30) to afford sulfone **386** (84 mg, 0.36 mmol, 18%) as a colourless oil. ν_{max} (film/cm^{-1}) 3275, 2890, 1303, 1266, 1118, 1025; δ_H (600 MHz, $CDCl_3$) 2.03 (1H, t, J = 2.6, C≡CH), 2.06 (2H, m, $CH_2CH_2CH_2$), 2.21 (2H, m , $CH_2CH(OR)_2$), 2.39 (2H, td, J = 6.7, 2.6, $C{\equiv}CCH_2$), 3.11 (4H, m, 2 × CH_2SO_2), 3.88 (2H, m, 2 × OC*H*H), 3.97 (2H, m, 2 × OCH*H*), 5.03 (1H, t, J = 3.9, $CH(OR)_2$); δc (150 MHz, $CDCl_3$) 17.6, 21.0, 26.2, 47.4, 51.8, 66.3, 70.5, 81.9, 101.9; Found (CI): $[M+H]^+$ 233.08510 $C_{10}H_{17}O_4S$ requires 233.08475.

Non-1-en-8-yn-5-ol[256] (394)

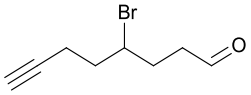


Oxalyl chloride (2.65 ml, 30.9 mmol) was added dropwise to a solution of DMSO (4.39 ml, 61.8 mmol) in dry CH_2Cl_2 cooled to -78 °C. The resulting solution was stirred at this temperature for 15 min after which time 4-pentyn-1-ol (2.00 g, 23.8 mmol) was added to the mixture dropwise. The reaction was stirred at -78 °C for 15 minutes then NEt_3 (16.56 ml, 118.8 mmol) was added and the mixture was allowed to warm to RT over 16 hr. The reaction was quenched with water (50 ml), the phases were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude aldehyde was dissolved in anhydrous THF (80 ml).

4-Bromo-1-butene (6.03 ml, 59.4 mmol) was added dropwise to a vigorously stirred suspension of Mg turnings (1.44 g, 59.4 mmol) in anhydrous THF (80 ml). The suspension was stirred under Ar at RT for 30 min, until all the Mg turnings were consumed. The solution of crude aldehyde in anhydrous THF (20 ml) was added dropwise to the Grignard solution over 20 min. When the addition was completed

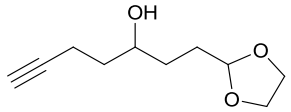
the reaction was warmed to 40 °C for 16 hr then quenched with sat. NH_4Cl (30 ml) and extracted with Et_2O (100 ml). The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford alcohol **394** (2.60 g, 18.8 mmol, 79%) as a pale brown oil. ν_{max} (film/cm^{-1}) 3302, 3077, 2924, 1641, 1433, 1069, 913; δ_H (400 MHz, $CDCl_3$) 1.56-1.77 (4H, m, 2 × C*H*$_2$CHOH), 2.00 (1H, t, J = 2.6, C≡CH), 2.20 (2H, m, C*H*$_2$CH=CH2), 2.36 (2H, td, J = 6.9, 2.6, C≡CC*H*$_2$), 3.75-3.84 (1H, m, C*H*OH), 5.01 (1H, ddt, J = 10.2, 1.9, 1.2, CH=CH*H*$_{cis}$), 5.08 (1H, dq, J = 17.1, 1.9, CH=CH*H*$_{trans}$), 5.80-5.92 (1H, m, C*H*=CH$_2$); δc (150 MHz, $CDCl_3$) 15.1, 30.1, 35.6, 36.5, 68.9, 70.5, 84.3, 115.1, 138.5.

4-Bromooct-7-ynal (395)



Alcohol **394** (500 mg, 3.62 mmol) was dissolved in CH_2Cl_2 (15 ml) and the solution was cooled to 0 °C. Carbon tetrabromide (1.80g, 5.43 mmol) was added in one portion, followed by triphenylphosphine (1.42 g, 5.43 mmol). The reaction mixture was stirred at 0 °C for 30 min then allowed to warm to RT over 16 hr. The reaction was quenched with MeOH (10 ml) and evaporated to dryness. The crude bromide (300 mg, 1.49 mmol) was dissolved in a mixture of 1,4-dioxane (10 ml) and water (3.3 ml). 2,6-Lutidine (0.35 ml, 2.98 mmol) was added followed by $K_2OsO_4 \cdot 2H_2O$ (5 mg, 0.015 mmol). The reaction mixture was cooled to 0 °C then $NaIO_4$ (1.27 g, 5.96 mmol) was slowly added in portions. After the addition was complete, the mixture was allowed to warm to RT over 2 hr then diluted with water (20 ml) and CH_2Cl_2 (40 ml). The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 (20 ml). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (Pet/CH_2Cl_2 = 50/50 → 0/100) to afford aldehyde **395** (114 mg, 0.56 mmol, 38%) as a colourless oil. ν_{max} (film/cm^{-1}) 3296, 2927, 1710, 1433, 1282, 1144; δ_H (400 MHz, $CDCl_3$) 2.01 (1H, t, J = 2.6, C≡CH), 2.04-2.12 (3H, m), 2.27 (1H, m), 2.47 (2H, m, C≡CC*H*$_2$), 2.78 (2H, m, C*H*$_2$CHO), 4.21 (1H, m, CHBr), 9.85 (1H, t, J = 0.9, CHO); δc (400 MHz, $CDCl_3$) 17.1, 31.0, 37.8, 42.1, 55.1, 69.4, 82.5, 200.7; Found (CI): $[M+H]^+$ 203.00775, $C_8H_{12}OBr$ requires 203.00715.

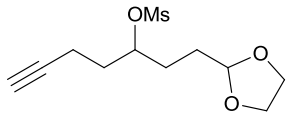
1-[1,3]Dioxolan-2-yl-hept-6-yn-3-ol (400)



Oxalyl Chloride (5.28 ml, 61.8 mmol) was added dropwise to a solution of DMSO (8.78 ml, 123.6 mmol) in CH_2Cl_2 (160 ml) cooled to -78 °C. The solution was stirred at this temperature for 15 min after which time 4-pentyn-1-ol (4.42 ml, 47.5 mmol) was added. The resulting mixture was stirred for another 15 min at -78 °C, then NEt_3 (33.1 ml, 237.7 mmol) was added and the mixture was allowed to warm to RT overnight. The reaction was quenched with water (100 ml) and the phases were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford crude pent-4-ynal as yellow oil.

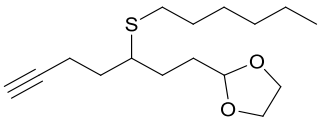
Bromide **306** (18.9 g, 104.6 mmol) was added dropwise to a suspension of Mg turnings (2.54 g, 104.6 mmol) in dry THF (160 ml) under Ar and the resulting mixture was stirred for 1 hr whilst cooling to RT. A solution of the crude pent-4-ynal in dry THF (40 ml) was added to the Grignard reagent over 15 min. When the addition was complete the reaction mixture was heated to 45 °C for 2 hr. The reaction was quenched with sat NH_4Cl (100 ml) and diluted with Et_2O (100 ml). The phases were separated and the aqueous layer was back extracted with Et_2O (50 ml). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 70/30) to afford alcohol **400** (4.27 g, 23.2 mmol, 49%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3436, 3289, 2952, 2886, 1411, 1366, 1217; δ_H (400 MHz, $CDCl_3$) 1.53-1.73 (4H, m, C*H*$_2$CH(OH)C*H*$_2$), 1.86 (2H, td, J = 7.3, 4.4, C*H*$_2$CH(OR)$_2$), 1.98 (1H, t, J = 2.7, C≡CH), 2.36 (2H, td, J = 7.2, 2.7, C≡C*CH*$_2$), 2.44 (1H, d, J = 4.3, OH), 3.79-3.81 (1H, m, C*H*OH), 3.89 (2H, m, 2 × OC*H*H), 4.01 (2H, m, 2 × OCH*H*), 4.93 (1H, t, J = 4.4, CH(OR)$_2$); δ_C (150 MHz, $CDCl_3$) 15.1, 30.1, 31.4, 35.9, 65.0, 65.1, 68.7, 70.4, 84.4, 104.5; Found (EI): [M-H] 183.10171, $C_{10}H_{15}O_3$ requires 183.10211.

1-(2-[1,3]Dioxolan-2-yl-ethyl)-pent-4-ynyl methanesulfonate (401)



Alcohol **400** (1.00 g, 5.43 mmol), was dissolved in CH_2Cl_2 (20 ml) and the solution was cooled to 0 °C. Triethylamine (1.29 ml, 9.23 mmol) was then added followed by methanesulfonyl chloride (0.59 ml, 7.60 mmol). The reaction mixture was allowed to warm to RT over 1.5 hr then it was diluted with CH_2Cl_2 (10 ml), washed with sat. $NaHCO_3$ (15 ml) and brine (15 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to afford mesylate **401** (1.40 g, 5.42 mmol, quant.) as a pale brown oil. ν_{max} (film/cm^{-1}) 3283, 2970, 1352, 1170; δ_H (600 MHz, $CDCl_3$) 1.79 (2H, m, 1 × CH_2), 1.86-1.98 (4H, m, 2 × CH_2), 2.00 (1H, t, J = 2.6, C≡CH), 2.34 (2H, m, C≡CCH_2), 3.05 (3H, s, CH_3), 3.85 (2H, m, 2 × OC*H*H), 3.97 (2H, m, 2 × OCH*H*), 4.87-4.91 (2H, m, C*H*OMs, C*H*$(OR)_2$); δ_C (150 MHz, $CDCl_3$) 14.7, 28.6, 29.0, 33.2, 38.7, 65.1, 69.7, 81.8, 82.7, 103.7; Found (EI): [M-H] 261.07904, $C_{11}H_{17}O_5S$ requires 261.07967.

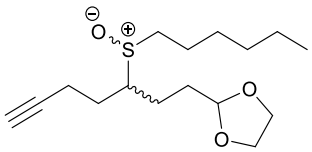
2-(3-Hexylsulfanyl-hept-6-ynyl)-[1,3]dioxolane (402)



Potassium carbonate (5.25 g, 38.0 mmol) was added to a solution of mesylate **401** (1.42 g, 5.43 mmol) and *n*-hexanethiol (3.83 ml, 27.1 mmol) in DMF (10 ml) and the suspension was stirred at RT for 2 hr. The reaction was diluted with water (40 ml) and extracted with Et_2O (2 × 30 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 100/0 → 98/2) to afford sulfide **402** (294 mg, 1.03 mmol, 19%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3310, 2925, 1454, 1377, 1217, 1140; δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.0, CH_3), 1.24-1.39 (6H, m, $(CH_2)_3CH_3$), 1.55 (2H, quint, J = 7.5, CH_2CH_2S), 1.60-1.73 (3H, m,

C*H*HCH$_2$C≡C, C*H*$_2$CH$_2$CH(OR)$_2$), 1.76-1.81 (2H, m, C*H*HCH(OR)$_2$, CH*H*CH$_2$C≡C), 1.86-1.92 (1H, m, CH*H*CH(OR)$_2$), 1.95 (1H, t, J = 2.6, C≡CH), 2.33-2.44 (2H, m, C≡CCH$_2$), 2.48 (2H, t, J = 7.5, SCH$_2$), 2.72 (1H, m, SCH), 3.85 (2H, m, 2 × OC*H*H), 3.97 (2H, m, 2 × OCH*H*), 4.88 (1H, t, J = 4.6, CH(OR)$_2$); δ_C (150 MHz, CDCl$_3$) 14.2, 16.3, 22.7, 28.8, 29.2, 30.0, 30.4, 31.2, 31.6, 33.9, 44.7, 65.0, 68.8, 84.2, 104.4; (CI): $[M-H]^+$ 285.18908, $C_{16}H_{29}O_2S$ requires 285.18882

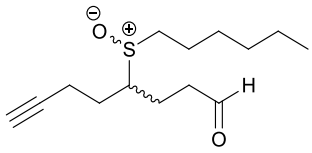
2-[3-(Hexane-1-sulfinyl)-hept-6-ynyl]-[1,3]dioxolane (403)



Sulfide **402** (25 mg, 0.88 mmol) was dissolved in acetone (2.5 ml) and water (1.25 ml). A catalytic amount of MoO_2Cl_2 (2.6 mg, 0.013 mmol) was added followed by H_2O_2 (30% wt, 103 µL, 0.92 mmol) and the resulting mixture was stirred at RT for 2 hr. The reaction was diluted with brine (5 ml) and extracted with EtOAc (2 × 15 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give sulfoxide **403** (235 mg, 0.83 mmol, 94%) as a colourless oil. Sulfoxide **403** was isolated as a mixture of diastereoisomers. A small amount of the diastereoisomeric mixture (20 mg) was purified by column chromatography (Pet/EtOAc = 1/1) in order to separate the two isomers. ν_{max} (film/cm^{-1}) 3287, 2927, 1456, 1139, 1031; ***diastereoisomer A***: δ_H (600 MHz, CDCl$_3$) 0.89 (3H, t, J = 7.0, CH$_2$C*H*$_3$), 1.30-1.33 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.38-1.52 (2H, m, S(O)CH$_2$CH$_2$C*H*$_2$), 1.70-1.93 (7H, m, S(O)CHC*H*$_2$CH$_2$CH(OR)$_2$, S(O)CH$_2$C*H*$_2$, C*H*$_2$CH(OR)$_2$, S(O)CHC*H*HCH$_2$C≡C), 1.99 (1H, t, J = 2.6, C≡CH), 2.02-2.09 (1H, m, S(O)CHCH*H*CH$_2$C≡C), 2.35 (1H, dddd, J = 17.0, 8.5, 6.6, 2.6, C*H*HC≡C), 2.47 (1H, dtd, J = 17.0, 6.6, 2.6, CH*H*C≡C), 2.60 (1H, ddd, J = 12.8, 9.5, 6.8, S(O)C*H*H), 2.70 (1H, ddd, J = 12.8, 9.5, 5.2, S(O)CH*H*), 2.75 (1H, m, S(O)CH), 3.82-3.88 (2H, m, 2 × OC*H*H), 3.93-3.98 (2H, m, 2 × OCH*H*), 4.89 (1H, t, J = 4.3, C*H*(OR)$_2$); δ_C (150 MHz, CDCl$_3$) 14.1, 16.3, 21.2, 22.5, 23.1, 23.7, 25.7, 28.7, 30.7, 31.5, 49.5, 57.6, 65.1, 69.8, 83.0, 103.8; ***diastereoisomer B***: δ_H (600 MHz, CDCl$_3$) 0.88 (3H, t, J = 7.0, CH$_2$C*H*$_3$), 1.30-1.33 (4H, m, (C*H*$_2$)$_2$CH$_3$), 1.39-1.50 (2H, m,

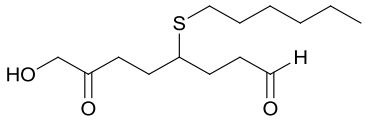
S(O)$CH_2CH_2CH_2$), 1.70-2.01 (8H, m, S(O)CH$CH_2CH_2CH(OR)_2$, S(O)CH_2CH_2, $CH_2CH(OR)_2$, S(O)CHCH_2CH_2C≡C), 1.99 (1H, t, J = 2.5, C≡CH), 2.39 (1H, ddd, J = 16.9, 10.1, 2.7, C*H*HC≡C), 2.42 (1H, ddd, J = 16.9, 9.6, 2.7, CH*H*C≡C), 2.57 (1H, ddd, J = 12.8, 9.6, 6.8, S(O)C*H*H), 2.68-2.77 (2H, m, S(O)CH*H*, S(O)CH), 3.83-3.86 (2H, m, 2 × OC*H*H), 3.95-3.98 (2H, m, 2 × OCH*H*), 4.89 (1H, t, J = 3.7, C*H*$(OR)_2$); δ_C (150 MHz, $CDCl_3$) 14.3, 16.3, 22.5, 23.2, 23.9, 25.7, 26.9, 28.7, 30.7, 31.5, 48.8, 57.3, 65.1, 69.9, 82.8, 103.9; Found (CI): $[M+H]^+$ 301.18397, $C_{16}H_{29}O_3S$ requires 301.18374.

4-(Hexane-1-sulfinyl)-oct-7-ynal (404)



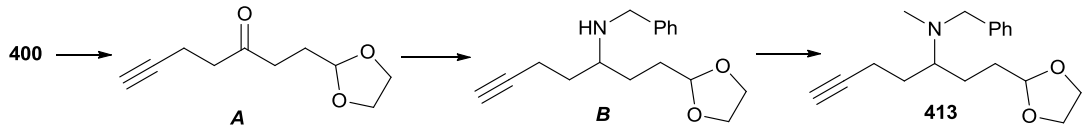
Sulfoxide **403** (235 mg, 0.83 mmol) was stirred in a mixture of 2 N HCl (0.5 ml) and THF (5 ml). After 24 hr the mixture was extracted with Et_2O and evaporated to dryness. The crude residue was dissolved in a mixture of 2 N HCl (0.5 ml) and THF (5 ml) and stirred for another 24 hr. This procedure was repeated for 4 times, until no starting material was detected by ^{1}H-NMR. The mixture was then extracted with Et_2O, dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (Pet/EtOAc = 30/70) to give aldehyde **404** (167 mg, 0.65 mmol, 79%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3283, 2929, 1724, 1455, 1366, 1217, 1029; isolated as a 1:1 mixture of diastereoisomers: δ_H (600 MHz, $CDCl_3$) 0.88-0.90 (3H, m, CH_3), 1.30-1.34 (4H, m, $(CH_2)_2CH_3$), 1.40-1.51 (2H, m, S(O)$CH_2CH_2CH_2$), 1.71-2.17 (7H, m, S(O)CH_2CH_2, C*H*2CH2CHO, CH_2CH_2C≡C, C≡CH), 2.35-2.50 (2H, m, CH_2C≡C), 2.57-2.63 (1H, m, 1 × S(O)C*H*H), 2.68-2.78 (4H, m, 1 × S(O)CH*H*, CH_2CHO, S(O)CH), 9.80 (1H, s, CHO); δ_C (600 MHz, $CDCl_3$) 14.1, 14.3, 16.2, 16.3, 19.1, 20.8, 21.2, 22.5, 23.1, 23.2, 25.3, 27.1, 28.7, 31.4, 31.5, 40.7, 40.8, 49.4, 49.5, 56.6, 60.5, 65.1, 70.1, 70.2, 82.5, 82.8, 200.7, 201.0; Found (CI): $[M]^+$ 257.15812, $C_{14}H_{24}O_2S$ requires 257.15752.

4-(Hexylsulfanyl)-8-hydroxy-7-oxooctanal (412)



Platinum (IV) chloride (3 mg, 0.0086 mmol) was added to a solution of sulfoxide **404** (22 mg, 0.086 mmol) in DCE (0.2 ml). The reaction mixture was initially stirred at RT for 24 hr then heated at reflux for 24 hr. The solvent was evaporated to dryness and the residue was purified by column chromatography (Pet/EtOAc = 80/20 → 50/50) to give hydroxyketone **412** (2 mg, 0.006 mmol, 8%) as a colourless oil. δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.9, CH_3), 1.21-1.41 (6H, m, $(CH_2)_3CH_3$), 1.51 (2H, quint, J = 7.6, SCH_2CH_2), 1.75-1.82 (2H, m, 1 × CH_2CH), 1.88-1.96 (2H, m, 1 × CH_2CH), 2.40 (2H, t, J = 7.5, SCH_2), 2.57 (1H, tt, 8.6, 4.9, SCH), 2.67 (2H, td, J = 7.1, 0.7, CH_2CHO), 2.80 (2H, t, J = 7.2, CH_2COCH_2OH), 4.13 (2H, s, CH_2OH), 9.82 (1H, t, J = 0.7, CHO); δ_C (150 MHz, $CDCl_3$) 14.2, 22.7, 27.2, 28.4, 28.8, 29.7, 29.8, 31.5, 37.0, 41.5, 44.8, 48.5, 201.8, 202.4; Found (TOF-MS): $[M+H]^-$ 303.1624, $C_{15}H_{27}O_4S$ requires 303.1630.

Benzyl-[1-(2-[1,3]dioxolan-2-yl-ethyl)-pent-4-ynyl]-methyl-amine (413)

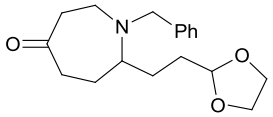


Oxalyl Chloride (0.15 ml, 3.53 mmol) was added dropwise to a solution of DMSO (0.50 ml, 7.05 mmol) in CH_2Cl_2 (20 ml) cooled to -78 °C. The solution was stirred at this temperature for 15 min after which time **400** (500 mg, 2.71 mmol) was added. The resulting mixture was stirred for another 15 min at -78 °C, then NEt_3 (1.88 ml, 13.5 mmol) was added and the mixture was allowed to warm to RT over 1 hr. The reaction was quenched with water (10 ml) and the phases were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give intermediate ketone ***A*** as pale brown oil.

A solution of crude ketone ***A*** (450 mg, 2.47 mmol) and benzylamine (0.30 ml, 2.72 mmol) in DCE (25 ml) was cooled to 0 °C. Sodium triacetoxyborohydride (1.05 g, 4.94 mmol) was added to the reaction mixture, followed by acetic acid (1.25 ml). The mixture was allowed to warm to RT over 24 hr. The reaction was quenched with 1M NaOH (20 ml) and extracted with CH_2Cl_2 (2 × 20 ml). Combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness.

Crude amine ***B*** was dissolved in MeCN (50 ml), K_2CO_3 (1.36 g, 9.88 mmol) was added and the resulting suspension was stirred at RT. Iodomethane (0.18 ml, 2.96 mmol) was added dropwise and the mixture was heated at reflux for 3 hr. The reaction was cooled to RT, diluted with CH_2Cl_2 (40 ml) and the solids were removed by filtration. The filtrate was washed with 2N NaOH, brine, then dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc/NEt_3 = 80/20/0.2) to afford amine **413** (78 mg, 0.27 mmol, 11%) as colourless oil. ν_{max} (film/cm^{-1}) 3404, 2885, 1650, 1440, 1282, 1119, 1076; δ_H (500 MHz, $CDCl_3$) 1.40 (1H, m, C*H*HCH$_2$CH(OR)$_2$), 1.56 (1H, m, C*H*HCH$_2$C≡C), 1.65-1.84 (4H, m, CH*H*C*H*$_2$CH(OR)$_2$, CH*H*CH$_2$C≡C), 1.93 (1H, t, J = 2.6, C≡CH), 2.12 (3H, s, CH_3), 2.30 (2H, m, C≡CCH_2), 2.65 (1H, m, NCH), 3.56 (1H, d, J = 13.6, NC*H*HPh), 3.60 (1H, d, J = 13.6, NCH*H*Ph), 3.86 (2H, m, 2 × OC*H*H), 3.98 (2H, m, 2 × OCH*H*), 4.87 (1H, t, J = 4.5, CH(OR)$_2$), 7.21 (1H, m, ArH), 7.27-7.34 (4H, m, ArH); δ_C (500 MHz, $CDCl_3$) 16.2, 23.4, 29.3, 31.5, 35.8, 58.3, 61.6, 65.0, 68.3, 84.9, 104.7, 126.7, 128.2, 128.6, 140.4; Found (TOF-MS): $[M+H]^+$ 288.1961, $C_{18}H_{26}NO_2$ requires 288.1964.

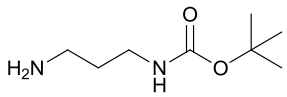
7-(2-(1,3-Dioxolan-2-yl)ethyl)-1-benzylazepan-4-one (416)



Amine **413** (75 mg, 0.26 mmol) was dissolved in CH_2Cl_2 (5 ml) and the solution was cooled to 0° C. *m*CPBA (45 mg, 0.26 mmol) was added and the reaction mixture was stirred at this temperature for 20 minutes. A catalytic amount of [Bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)Gold(I) (2:1) toluene adduct (4 mg, 0.003 mmol) was added and the reaction mixture was allowed to warm

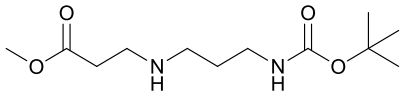
to RT over 1 hr. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography (Pet/EtOAc/NEt_3 = 70/30/0.2) to afford **416** (12 mg, 0.04 mmol, 15%) as a colourless oil. ν_{max} (film/cm^{-1}) 2925, 2604, 1710, 1575, 1430, 1381, 1284, 1251, 1140; δ_H (600 MHz, $CDCl_3$) 1.50-1.55 (1H, m, NCHC*H*HCH$_2$CH(OR)$_2$), 1.65-1.73 (2H, m, COCH$_2$C*H*HCH, C*H*HCH(OR)$_2$), 1.76-1.86 (2H, m, CH*H*CH(OR)$_2$, NCHCH*H*CH$_2$CH(OR)$_2$), 1.99-2.05 (1H, m, COCH$_2$CH*H*CH), 2.47-2.67 (4H, m, C*H*$_2$COC*H*$_2$), 2.80 (1H, ddd, J = 14.8, 7.2, 4.8, NC*H*HCH$_2$), 2.95 (1H, ddd, J = 8.2, 7.2, 3.4, NCH), 3.06 (1H, ddd, J = 14.8, 7.7, 4.1, NCH*H*CH$_2$), 3.70 (1H, d, J = 13.8, C*H*HPh), 3.80 (1H, d, J = 13.8, CH*H*Ph), 3.83-3.87 (2H, m, 2 × OC*H*H), 3.93-3.98 (2H, m, 2 × OCH*H*), 4.86 (1H, t, J = 4.6, CH(OR)$_2$); δ_C (500 MHz, $CDCl_3$) 24.3, 25.3, 31.0, 40.0, 41.6, 43.2, 65.0, 104.4, 127.3, 128.5, 128.7, 129.9, 130.3, 133.6, 213.5; Found (TOF-MS): $[M+H]^+$ 304.1909, $C_{18}H_{26}NO_3$ requires 304.1913.

tert-Butyl (3-aminopropyl)carbamate[257] (427)



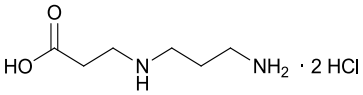
A solution of di-*tert*-butyl carbonate (7.70 g, 35.3 mmol) in dioxane (100 ml) was added to a solution of 1,3-diaminopropane (23.5 ml, 279 mmol) in dioxane (100 ml) stirred at RT. The mixture was stirred for 3 days then concentrated *in vacuo*. Water (100 ml) was added and the insoluble residues were filtered. The filtrate was extracted with CH_2Cl_2 (4 × 50 ml) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness to give amine **427** (3.31 g, 19.0 mmol, 54%) as a colourless oil. ν_{max} (film/cm^{-1}) 3356, 2973, 2931, 1691, 1521, 1365, 1252, 1166, 1120; δ_H (600 MHz, $CDCl_3$) 1.35 (2H, br s, NH_2), 1.40 (9H, s, C(CH$_3$)$_3$), 1.58 (2H, quint, J = 6.6, CH$_2$C*H*$_2$CH$_2$), 2.73 (2H, t, J = 6.6, C*H*$_2$NH$_2$), 3.12-3.18 (2H, br m, C*H*$_2$NH), 4.98 (1H, br s, NH); δ_C (150 MHz, $CDCl_3$) 28.5, 33.5, 38.5, 39.8, 79.1, 156.3; Found (CI): $[M+H]^+$ 175.14437, $C_8H_{19}N_2O_2$ requires 175.14465.

Methyl 3-((3-((*tert*-butoxycarbonyl)amino)propyl)amino)propanoate (428)



A solution of amine **427** (1.50 g, 8.61 mmol) and methylacrilate (0.77 ml, 8.61 mmol) in MeCN (15 ml) was stirred at reflux for 24 hr. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/MeOH = 95/5) to give ester **428** (904 mg, 3.47 mmol, 40%) as a colourless oil. ν_{max} (film/cm^{-1}) 3343, 2934, 1732, 1693, 1516, 1437, 1364, 1249, 1168; δ_H (600 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.65 (2H, quint, J = 6.5, $CH_2CH_2CH_2$), 1.81 (1H, br s, CH_2NHCH_2), 2.52 (2H, t, J = 6.5, $NHCH_2(CH_2)_2$), 2.67 (2H, t, J = 6.4, CH_2CO_2Me), 2.87 (2H, t, J = 6.5, CH_2NHCO_2tBu), 3.19 (2H, app. q, J = 6.4, $CH_2CH_2CO_2Me$), 3.68 (3H, s, CO_2CH_3), 4.82 (1H, br s, $NHCO_2tBu$); δ_C (150 MHz, $CDCl_3$) 28.5, 29.8, 34.5, 39.2, 45.1, 47.5, 51.8, 79.2, 156.3, 173.3; Found (CI): $[M+H]^+$ 261.18087, $C_{12}H_{25}N_2O_4$ requires 261.18142.

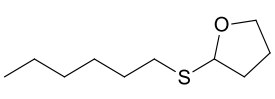
***N*^{1}-(2-carboxyethyl)propane-1,3-diaminium dichloride (425)**



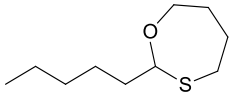
A solution of ester **429** (750 mg, 2.88 mmol) in 6 N HCl (15 ml) was heated at 80 °C for 24 hr. The mixture was cooled to RT and extracted with Et_2O to remove the unreacted starting material. The aqueous layer was evaporated to dryness and the residual water was removed by azeotropical distillation with toluene. The crude residue was triturated in Et_2O (5 ml), then filtered and washed several times with Et_2O. Aminoacid **425** (571 mg, 2.61 mmol, 90%) was isolated as white crystalline solid. ν_{max} (film/cm^{-1}) 3392, 2944, 2909, 2800, 1726, 1617, 1489, 1402, 1205, 1163, 1145, 847; isolated as bis-hydrochloride salt: δ_H (600 MHz, $CDCl_3$) 1.97 (2H, quint, J = 7.5, $CH_2CH_2CH_2$), 2.50 (2H, t, J = 7.4, CH_2CO_2H), 2.89 (2H, br s, 1 × CH_2), 2.99 (2H, br s, 1 × CH_2), 3.06 (2H, br s, 1 × CH_2), 8.17 (3H, br s, $^+NH_3$), 9.26 (2H, br s,

$^{+}NH_2$), 12.70 (1H, br s, CO_2H); δ_C (150 MHz, $CDCl_3$) 23.6, 30.2, 36.1, 42.4, 43.8, 171.6; Found (CI): $[M+H]^+$ 147.11298, $C_6H_{15}N_2O_2$ requires 147.11335

2-Hexylsulfanyl-tetrahydrofuran (209), 2-Pentyl-[1,3]oxathiepane (210)



209



210

Procedure 1

N-Chlorosuccinimide (140 mg, 1.05 mmol) was added in one portion to a solution of alcohol **206** (200 mg, 1.05 mmol) in toluene (4 ml) then stirred at RT. After 15 min NEt_3 (0.15 ml, 1.05 mmol) was added dropwise and the reaction mixture stirred for 1 hr at RT and monitored by TLC. After this time *N*-chlorosuccinimide (70 mg, 0.52 mmol) was added followed by NEt_3 (0.07 ml, 0.52 mmol) and the reaction stirred for another 15 min. The reaction mixture was quenched with water (10 ml) and extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography to give **209** (10 mg, 0.05 mmol, 5%) and **210** (49 mg, 0.29 mmol, 25%) as colourless oils.

Procedure 2

A solution of sulfide **206** (200 mg, 1.05 mmol) in CH_2Cl_2 (2.5 ml) was added dropwise to a suspension of *N*-chlorosuccinimide (168 mg, 1.26 mmol) stirred in CH_2Cl_2 (2.5 ml) at 0 °C. The resulting mixture was stirred at this temperature for 1.5 hr then NEt_3 (0.18 ml, 1.26 mmol) was slowly added dropwise and the mixture was allowed to warm to RT over 2 hr. The solvent was removed in vacuo and the crude was purified by column chromatography (Pet/EtOAc = 95/5) to afford thioacetal **209** (82 mg, 0.43 mmol, 41%) as a colourless oil.

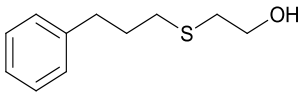
209: ν_{max} (film/cm^{-1}) 2927, 2856, 1458, 1278, 1098; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, J = 6.8, CH_3), 1.29-1.34 (4H, m, 2 × CH_2), 1.40-1.49 (2H, m, 1 × CH_2), 1.65-1.87 (4H, m, 2 × CH_2), 1.95 (2H, quint, J = 5.9, OCH_2CH_2), 2.68 (1H, dt, J = 14.3, 6.2, C*H*HS), 2.82 (1H, dt, J = 14.3, 5.4, CH*H*S), 3.75 (1H, ddd, J = 12.1, 8.2, 2.4, OC*H*H), 4.05 (1H, ddd, J = 12.1, 6.6, 2.8, OCH*H*), 4.78 (1H, dd, J = 6.7, 5.7, C*H*(OR)(SR)); δc (150 MHz, $CDCl_3$), 14.2, 22.7, 25.9, 30.0, 30.2, 30.8, 31.7, 37.4, 68.3, 85.7; Found (CI): $[M-H]^+$ 189.13111, $C_{10}H_{21}OS$ requires 189.13130.

210: ν_{max} (film/cm^{-1}) 2929, 2859, 1381, 1349, 1171; δ_H (600 MHz, $CDCl_3$) 0.85 (3H, t, J = 6.8, CH_3), 1.17-1.35 (6H, m, 3 × CH_2), 1.57-1.69 (4H, m, 2 × CH_2), 2.00 (1H, m, C*H*HCH), 2.09 (1H, m, CH*H*CH), 2.50 (1H, m SC*H*H), 2.59 (1H, m, SCH*H*), 3.61 (2H, t, J = 6.2, OCH_2), 5.06 (1H, dd, J = 8.7, 7.2, CH(OR)(SR)); δc (150 MHz, $CDCl_3$) 14.1, 22.5, 26.0, 26.8, 31.1, 31.7, 32.0, 32.4, 56.2, 62.1; Found (CI): $[M-H]^+$ 189.13085, $C_{10}H_{21}OS$ requires 189.13130.

General procedure for radical addition of mercaptoethanol to terminal alkenes.

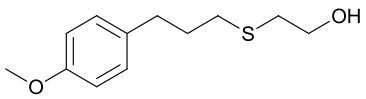
A solution of alkene (1 eq), mercaptoethanol (2 eq) and AIBN (20 mol %) in MeCN (0.4 M) was heated at reflux for 6 hr. The reaction mixture was cooled to RT and then partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness.

2-((3-Phenylpropyl)thio)ethanol (446a)



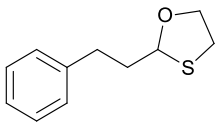
Pale yellow oil (3.10 g, 15.8 mmol, 93%). ν_{max} (film/cm^{-1}) 3376, 3026, 2923, 2859, 1496, 1454, 1044; δ_H (600 MHz, $CDCl_3$) 1.92 (2H, quint, J = 7.4, $CH_2CH_2CH_2$), 2.53 (2H, t, J = 7.4, $PhCH_2$), 2.72 (4H, m, 2 × CH_2S), 3.69 (2H, app. q, J = 6.1, CH_2OH), 7.19 (3H, m, 3 × ArH), 7.29 (2H, m, 2 × ArH); δc (150 MHz, $CDCl_3$) 31.0, 31.3, 34.8, 35.3, 60.2, 126.1, 128.5, 128.6, 141.4; Found (EI): $[M]^+$ 196.09245 ,$C_{11}H_{16}OS$ requires 196.09163.

2-((3-(4-Methoxyphenyl)propyl)thio)ethanol (446b)

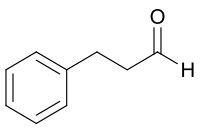


Pale yellow oil (15.2 g, 67.3 mmol, quant.). ν_{max} (film/cm^{-1}) 3414, 2929, 1611, 1510, 1463, 1442, 1241, 1176, 1033; δ_H (400 MHz, $CDCl_3$) 1.90 (2H, quint, J = 7.4, $CH_2CH_2CH_2$), 2.54 (2H, t, J = 7.4, $ArCH_2$), 2.69 (2H, t, J = 7.4, $CH_2CH_2CH_2S$), 2.75 (2H, t, J = 5.9, SCH_2CH_2O), 3.72 (2H, t, J = 5.9, CH_2OH), 3.81 (3H, s OCH_3), 6.85 (2H, d, J = 8.7, 2 × ArH), 7.12 (2H, d, J = 8.7, 2 × ArH); δ_C (125 MHz, $CDCl_3$) 30.9, 31.5, 33.9, 35.3, 55.3, 60.3, 113.9, 129.4, 133.4, 158.0; Found (EI): $[M]^+$ 226.10253, $C_{12}H_{18}O_2S$ requires 226.10219.

2-Phenethyl-1,3-oxathiolane[258] (447a) and 3-Phenylpropanal[259] (448a)



447a



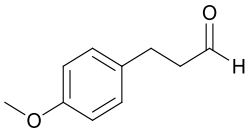
448a

N-Chlorosuccinimide (408 mg, 3.06 mmol) was added in one portion to a solution of alcohol **446a** (500 mg, 2.55 mmol) in toluene (10 ml) and the mixture was stirred at RT for 15 min. After this time NEt_3 was added dropwise (0.43 ml, 3.06 mmol) and the mixture was stirred at RT for 1 hr. *N*-Chlorosuccinimide (204 mg, 1.58 mmol) followed by NEt_3 (0.21 ml, 1.58 mmol) were added to the reaction mixture to obtain complete conversion of the starting material (TLC). The mixture was quenched with sat $NaHCO_3$ then extracted into EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by column chromatography (Pet/EtOAc = 100/0 → 85/15) to afford 1,3-oxathiolane **447a** (48 mg, 0.24 mmol, 10%) and aldehyde **448a** (100 mg, 0.74 mmol, 29%) both as colourless oils.

447a: δ_H (400 MHz, $CDCl_3$) 2.05-2.15 (1H, m, C*H*HCH), 2.22-2.37 (1H, m, CH*H*CH), 2.79 (2H, m, $PhCH_2$), 3.07 (2H, dt, J = 7.7, 4.6, SCH_2), 3.89 (1H, m, OC*H*H), 4.38 (1H, m, PhCH*H*), 5.07 (1H, t, J = 6.0, CH), 7.19-7.33 (5H, m, PhH); δc (150 MHz, $CDCl_3$) 30.7, 34.5, 38.2, 71.4, 86.2, 126.1, 128.5, 128.6, 141.4;

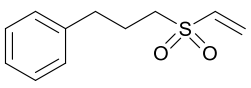
448a: δ_H (600 MHz, $CDCl_3$) 2.79 (2H, td, J = 7.6, 1.4, CH_2CHO), 2.96 (2H, t, J = 7.6, $PhCH_2$), 7.19-7.22 (3H, m, 3 × PhH), 7.28-7.32 (2H, m, 2 × PhH), 9.83 (1H, t, J = 1.4, CHO); δc (150 MHz, $CDCl_3$) 28.2, 45.4, 126.4, 128.4,128.7, 140.4, 201.7;

3-(4-Methoxyphenyl)propanal[260] (448b)



N-Chlorosuccinimide (59 mg, 0.44 mmol) was added in one portion to a solution of alcohol **446b** (100 mg, 0.44 mmol) in toluene (2 ml) cooled to 0 °C. The reaction mixture was allowed to warm to RT over 48 hr. The reaction was diluted with CH_2Cl_2, adsorbed on silica gel and purified by column chromatography (Pet/EtOAc = 97/3) to afford aldehyde **448b** (12 mg, 0.073 mmol, 17%) as a colourless oil. δ_H (600 MHz, $CDCl_3$) 2.74 (2H, dt, J = 7.5, 1.4, CH_2CHO), 2.90 (2H, t, J = 7.5, $ArCH_2$), 3.78 (3H, s, OCH_3), 6.83 (2H, d, J = 8.6, 2 × ArH), 7.11 (2H, d, J = 8.6, 2 × ArH), 9.81 (1H, t, J = 1.4, CHO); δ_C (600 MHz, $CDCl_3$) 27.4, 45.7, 55.4, 114.1, 129.4, 132.4, 158.0, 202.0.

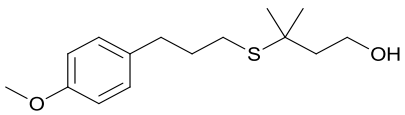
(3-(Vinylsulfonyl)propyl)benzene (449)



A solution of alcohol **446a** (200 mg, 1.05 mmol) in CH_2Cl_2 (2.5 ml) was slowly added to a suspension of *N*-chlorosuccinimide (204 mg, 1.53 mmol) in CH_2Cl_2 (2.5 ml) cooled to 0 °C. The reaction mixture was stirred at this temperature for 2 hr. Triethylamine (0.21 ml, 1.53 mmol) was added dropwise at 0 °C and the mixture

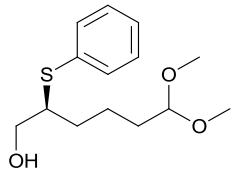
was allowed to warm to RT over 24 hr. The solvent was removed under reduced pressure and the crude was purified by column chromatography (Pet/EtOAc = 80/20) to give vinylsulfone **449** (64 mg, 0.33 mmol, 32%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3060, 3027, 2926, 2864, 1497, 1454, 1307, 1135, 1120, 978; δ_H (400 MHz, $CDCl_3$) 2.14 (2H, m, $CH_2CH_2CH_2$), 2.79 (2H, t, J = 7.4, $PhCH_2$), 2.99 (2H, m, CH_2SO_2), 6.17 (1H, d, J = 9.8, $CH=CH_{cis}$), 6.44 (1H, d, J = 16.6, $CH=CH_{trans}$), 6.61 (1H, dd, J = 9.8, 16.6, $CH=CH_2$), 7.18-7.35 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 23.9, 34.2, 53.4, 126.5, 128.4, 128.7, 130.6, 136.1, 139.8; Found (CI): $[M+H]^+$ 211.07886, $C_{11}H_{15}OS$ requires 211.07927.

3-((3-(4-Methoxyphenyl)propyl)thio)-3-methylbutan-1-ol (451)



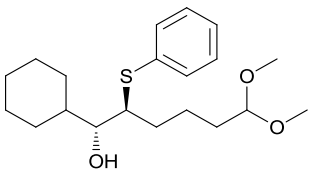
AIBN (111 mg, 0.67 mmol) was added to a solution of 4-allylanisole (500 mg, 3.37 mmol) and thiol **450** (811 mg, 6.75 mmol) in MeCN (10 ml). The reaction mixture was heated at reflux for 16 hr then concentrated *in vacuo* and partitioned between EtOAc and 2N NaOH; the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude material was purified by column chromatography (Pet/EtOAc = 80/20) to give alcohol **451** (104 mg, 0.39 mmol, 11%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3434, 2933, 1514, 1245; δ_H (400 MHz, $CDCl_3$) 1.33 (6H, s, 2 × CH_3), 1.82 (2H, t, J = 6.3, $(CH_3)_2CCH_2$), 1.88 (2H, quint, J = 7.3, $CH_2CH_2CH_2$), 2.56 (2H, t, J = 7.3, $ArCH_2$), 2.68 (2H, t, J = 7.3, CH_2S), 3.81 (3H, s, OCH_3), 3.84 (2H, t, J = 6.3, CH_2OH), 6.85 (2H, d, J = 8.6, 2 × ArH), 7.12 (2H, d, J = 8.6, 2 × ArH); δc (150 MHz, $CDCl_3$) 27.4, 29.5, 31.5, 34.3, 43.4, 44.1, 55.4, 60.3, 113.9, 129.4, 133.6, 157.9; Found (EI): [M], 268.14942 , $C_{15}H_{24}O_2S$ requires 268.14915.

(*S*)-6,6-Dimethoxy-2-(phenylthio)hexan-1-ol (464)



A solution of sulfenyl triazole **280** (1.32 g, 7.49 mmol) in toluene (5 ml) was added to a solution of aldehyde **256** (1.00 g, 6.24 mmol) in toluene (5 ml) stirred at RT. The reaction mixture was stirred at RT for 16 hr then diluted with MeOH (40 ml). Sodium borohydride (284 mg, 7.49 mmol) was added in portions and the mixture was stirred at RT for 20 min. The solvents were removed under reduced pressure and the crude was purified by column chromatography (Pet/EtOAc = 70/30) to afford alcohol **464** (954 mg, 3.53 mmol, 57%) as a colourless oil. $[\alpha]_D^{25}$ -6.0 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3425, 3058, 2943, 2830, 1584, 1474, 1438, 1386, 1125, 1047; spectra recorded at 60 °C: δ_H (400 MHz, $CDCl_3$) 1.59-1.73 (6H, m, 3 × CH_2), 2.07 (1H, br s, OH), 3.17 (1H, dtd, J = 12.5, 6.1, 4.6, SCH), 3.33 (3H, s, 1 × CH(O*Me*)$_2$), 3.34 (3H, s, 1 × CH(O*Me*)$_2$), 3.58 (1H, dd, J = 11.1, 6.1, C*H*HOH), 3.67 (1H, dd, J = 11.1, 4.6, CH*H*OH), 4.36 (1H, t, J = 5.2, C*H*(OMe)$_2$), 7.27-7.33 (3H, m, 3 × ArH), 7.46 (2H, m, 2 × ArH); δ_C (100 MHz, $CDCl_3$) 22.1, 31.3, 32.4, 52.6, 52.7, 52.8, 64.1, 104.6, 127.3, 128.9, 132.7, 133.9; Found (EI): $[M]^+$ 270.12867, $C_{14}H_{22}O_3S$ requires 270.12841.

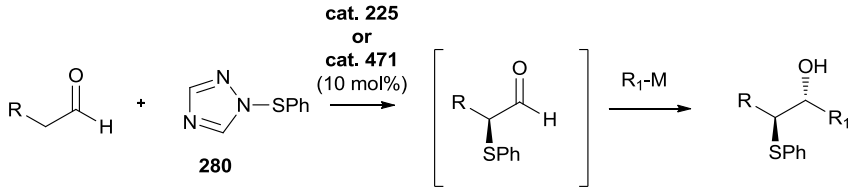
(1*R*,2*S*)-1-Cyclohexyl-6,6-dimethoxy-2-(phenylthio)hexan-1-ol (466)



Dimethylsulfoxide (62 µl, 0.88 mmol) was added dropwise to a solution of oxalyl chloride (38 µl, 0.44 mmol) in CH_2Cl_2 (2 ml) cooled to -78 °C. The resulting solution was stirred at -78 °C for 5 minutes. A solution of alcohol **464** (100 mg, 0.37 mmol) in CH_2Cl_2 (0.2.ml) was added dropwise to the reaction mixture and then stirred at -40 °C for 40 min. The reaction was subsequently cooled to -78 °C and

added via syringe pump to a solution of Cyclohexylmagnesiumchloride (2.0 M in Et_2O, 1.3 ml, 2.59 mmol) cooled to -78 °C. The resulting mixture was stirred at -78 °C for 30 min and then quenched with sat NH_4Cl (10 ml) and partitioned between CH_2Cl_2 and water. The phases were separated and the organic layer was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (Pet/EtOAc = 95/5) to give **466** as a colourless oil (39 mg, 0.11 mmol, 30%). $[a]_D^{25}$ -40 (c. 0.10, $CHCl_3$); ν_{max} (film/cm^{-1}) 3471, 2925, 2852, 1583, 1479, 1449,1386, 1126, 1068, 1049; isolated as a 98:2 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.78-0.90 (2H, 2 × *c*Hex), 1.04-1.25 (2H, m $CH_2CH_2CH_2$), 1.48-1.81 (11H, m, 7 × *c*Hex, $SCHCH_2$, $CH_2CH(OMe)_2$), 2.00 (1H, m, 1 × *c*Hex), 2.45 (1H, d, J = 2.7, OH), 3.22-3.25 (1H, m, C*H*OH), 3.29-3.34 (7H, m, SCH, 2 × OMe), 4.38 (1H, t, J = 5.6, $CH(OMe)_2$), 7.22-7.39 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 22.9, 25.9, 26.0, 26.4, 26.9, 28.8, 30.1, 32.5, 39.6, 53.0, 53.8, 76.0, 104.6, 127.2, 129.2, 132.0, 134.6; Found (TOF-MS): $[M+Na]^+$ 375.1964, $C_{20}H_{32}O_3NaS$ requires 375.1970.

General procedure for the synthesis of 1,2-sulfidoalcohols:



A solution of aldehyde (1 eq) and catalyst **228** (or **471**) (0.1 eq) was stirred in toluene (1.3 M) for 15 min. A solution of sulfenyl-triazole **280** (1.3 eq) in toluene (1.6 M) was added dropwise and the resulting mixture was stirred under Ar at RT for 24 hr. The reaction mixture was subsequently treated according to the following 3 different procedures:

Procedure A

The reaction mixture was quickly filtered through a short pad of silica gel eluting with toluene. The fractions containing the product were combined and used in the following step. The concentration of α-sulfenylaldehyde in the toluene solution was determined each time by ^{1}H-NMR.

Procedure B

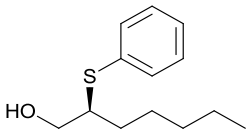
The reaction mixture was quickly sucked under vacuum through a pre-wet (toluene) pad of silica (~1.5g per 100 mg of SM) and washed with toluene (10 ml per 100 mg of SM). The toluene solution of α-sulfenylaldehyde was used in the following step.

Procedure C

The crude reaction mixture was taken onto the following step without further purification.

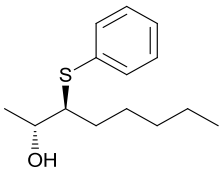
The toluene solution of the intermediate α-sulfenylaldehyde obtained via one of the 3 procedures described above was added dropwise to a solution of the organometallic reagent (3-4 eq) cooled to -78 °C (for Li reagents) or -10 °C (for Grignard reagents). The reactions were monitored by TLC and stirred until all the intermediate α-sulfenylaldehyde was consumed. The reactions were quenched with sat NH_4Cl, partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude sulfido-alcohols were purified by column chromatography (Pet/Et_2O).

(*S*)-2-(Phenylthio)heptan-1-ol (469a)



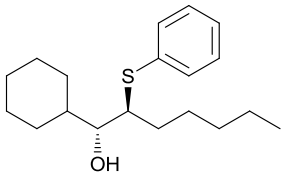
Obtained via purification procedure **A**; colourless oil (91 mg, 0.41 mmol, 62%). $[a]_D^{25}$ -8.3 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3368, 3059, 2954, 2928, 2857, 1584, 1466, 1438, 1279, 1024; δ_H (600 MHz, $CDCl_3$) 0.89 (3H, t. J = 7.0, CH_3), 1.26-1.33 (4H, m, $(CH_2)_2CH_3$), 1.42-1.65 (4H, m, $CH(CH_2)_2$), 1.99 (1H, br s, OH), 3.13-3.17 (1H. m, SCH), 3.50 (1H, dd, J = 11.4, 6.4, 1 × C*H*HOH), 3.62 (1H, dd, J = 11.4, 4.6, 1 × CH*H*OH), 7.26-7.31 (3H, m, 3 × ArH), 7.43-7.45 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.6, 26.9, 31.3, 31.7, 52.9, 63.7, 127.6, 129.1, 133.0, 133.5; Found (EI): $[M]^+$ 224.12321, $C_{13}H_{20}OS$ requires 224.12294.

(*2R*,3*S*)-3-(Phenylthio)octan-2-ol (469c)

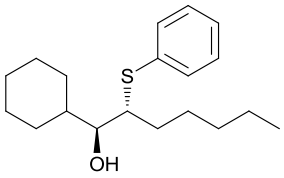


Obtained via purification procedure **A**; colourless oil (180 mg, 0.75 mmol, 94%). $[a]_D^{25}$ -4.2 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3414, 3060, 2959, 2929, 2858, 1584, 1466, 1439, 1279, 1139; Isolated as a 91:9 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.8, CH_2CH_3), 1.19 (3H, d, J = 6.4, $CHCH_3$), 1.27-1.71 (8H, m, 4 × CH_2), 2.33 (1H, br s, OH), 3.16 (1H, ddd, J = 9.4, 5.8, 3.2, SCH), 3.89 (1H, qd, J = 6.4, 3.2, C*H*OH), 7.22-7.30 (3H, m, 3 × ArH), 7.44 (2H, d, J = 7.7, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 19.1, 22.6, 27.5, 30.1, 31.8, 58.7, 68.3, 127.1, 129.2, 132.0, 135.5; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.8, CH_2CH_3), 1.25 (3H, d, J = 6.1, $CHCH_3$), 1.27-1.71 (8H, m, 4 × CH_2), 2.91 (1H, ddd, J = 9.6, 6.5, 3.2, SCH), 3.72 (1H, dq, J = 6.5, 6.1, C*H*OH), 7.22-7.30 (3H, m, 3 × ArH), 7.44 (2H, d, J = 7.7, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 20.2, 22.7, 27.0, 30.1, 31.1, 59.3, 68.3, 127.3, 129.1, 132.5, 135.5, Found (EI): $[M]^+$ 238.13884, $C_{14}H_{22}OS$ requires 238.13859.

1-Cyclohexyl-2-(phenylthio)heptan-1-ol (469f) (475b)



469f
(1R,2S)

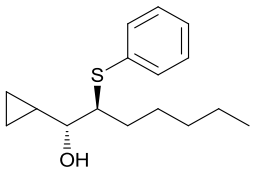


475b
(1S,2R)

469f Obtained via purification procedure **A**; colourless oil (64 mg, 0.21 mmol, 48%); **475b** Obtained via purification procedure **C**; colourless oil (104 mg, 0.34 mmol, 34%); **469f** $[a]_D^{25}$ -13.2 (c. 0.33, $CHCl_3$); **475b** $[a]_D^{25}$ +12.8 (c. 1.0, $CHCl_3$); ν_{max}

(film/cm^{-1}) 3471, 3057, 2925, 2853, 1584, 1449, 1439, 1279, 1139; **469f** was isolated as a 98:2 mixture of diastereoisomers, **475b** was isolated as a 95:5 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.78-0.90 (2H, m, 2 × *c*Hex), 0.90 (3H, t, J = 7.1, CH_3), 1.04-1.73 (17H, m, 9 × *c*Hex, 4 × CH_2), 2.01 (1H, br d, J = 12.9, 1 × *c*Hex), 2.45 (1H, d, J = 2.6, OH), 3.23 (1H, dt, J = 8.4, 2.4, SCH), 3.30-3.33 (1H, m, OCH), 7.21-7.40 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.7, 25.9, 26.0, 26.4, 27.1, 27.6, 28.8, 30.1, 31.8, 39.6, 54.0, 76.0, 127.1, 129.2, 131.9, 134.8; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.78-0.90 (2H, m, 2 × *c*Hex), 0.90 (3H, t, J = 7.1, CH_3), 1.04-1.73 (17H, m, 9 × *c*Hex, 4 × CH_2), 1.83 (1H, br d, J = 13.2, 1 × *c*Hex), 2.45 (1H, d, J = 2.6, OH), 3.17-3.20 (1H, m, SCH), 3.27-3.29 (1H, m, OCH), 7.21-7.40 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.8, 26.2, 26.3, 26.5, 27.1, 27.3, 30.4, 31.7, 32.4, 40.7, 55.3, 75.9, 127.3, 129.0, 132.8, 137.1; Found (EI): $[M]^+$ 306.20106, $C_{19}H_{30}OS$ requires 306.20119.

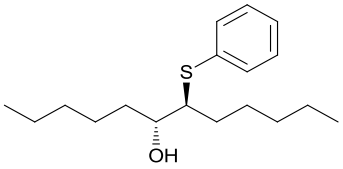
(1*R*,2*S*)-1-Cyclopropyl-2-(phenylthio)heptan-1-ol (469b)



Obtained via purification procedure **A**; colourless oil (161 mg, 0.61 mmol, 76%). $[a]_D^{25}$ -1.5 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3437, 3004, 2955, 2928, 2858, 1584, 1479, 1466, 1438, 1279, 1025; Isolated as a 93:7 mixture of diastereoisomers, ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.09-0.14 (1H, m, 1 × *c*Pr), 0.32 (1H, app sext, J = 4.9, 1 × *c*Pr), 0.47-0.57 (2H, m, 2 × *c*Pr), 0.88 (3H, t, J = 6.8, CH_3), 0.99 (1H, qt, J = 8.2, 4.9, *c*Pr*H*-CHOH), 1.26-1.90 (8H, m, 4 × CH_2), 2.37 (1H, br s, OH), 2.93-2.95 (1H, m, SCH), 3.31 (1H, m, OCH), 7.19-7.43 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 2.8, 3.2, 13.9, 14.2, 22.6, 27.6, 29.8, 31.8, 57.3, 76.9, 127.0, 129.1, 131.7, 135.6; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.23-0.27 (1H, m, 1 × *c*Pr), 0.35-0.38 (1H, m, 1 × *c*Pr), 0.45-0.55 (2H, m, 2 × *c*Pr), 0.88 (3H, t, J = 6.8, CH_3), 1.01 (1H, qt, J = 8.2, 4.9, *c*Pr*H*-CHOH), 1.26-1.90 (8H, m, 4 × CH_2), 2.54 (1H, br s, OH), 2.85-2.87 (1H,

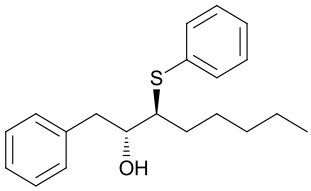
m, SCH), 3.16 (1H, m, OCH), 7.19-7.45 (5H, m, 5 × ArH); δ_C (600 MHz, $CDCl_3$) 2.9, 3.7, 14.2, 15.8, 22.7, 27.2, 31.7, 31.9, 57.9, 77.8, 127.1, 129.0, 132.1, 135.0; Found (EI): $[M]^+$ 264.15388, $C_{16}H_{24}OS$ requires 264.15424

(6*R*,7*S*)-7-(Phenylthio)dodecan-6-ol (469d)



Obtained via purification procedure **A**; colourless oil (155 mg, 0.53 mmol, 66%); $[a]_D^{25}$ -1.2 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3446, 3060, 2955, 2929, 2858, 1468, 1439, 1374, 1277, 1175, 1137; isolated as a 97:3 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.86 (3H, t, J = 7.0, 1 × CH_3), 0.88 (3H, t, J = 6.9, 1 × CH_3), 1.21-1.73 (16H, m, 8 × CH_2), 3.18 (1H, dt, J = 9.8, 3.3, SCH), 3.62-3.65 (1H, m, OCH), 7.22-7.45 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.6, 22.7, 26.0, 27.5, 29.2, 31.8, 31.9, 33.1, 57.4, 72.2, 127.1, 129.1, 132.0, 135.3; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.86-0.92 (6H, m, 2 × CH_3), 1.21-1.73 (16H, m, 8 × CH_2), 2.98-3.02 (1H, m, SCH), 3.53-3.56 (1H, m, OCH), 7.22-7.45 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.6, 22.7, 25.7, 27.1, 29.3, 31.6, 31.9, 34.3, 57.9, 73.2, 127.2, 129.0, 132.4, 135.0; Found (EI): $[M]^+$ 294.20131, $C_{18}H_{30}OS$ requires 294.20119.

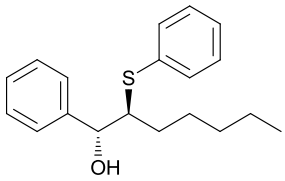
(2*R*,3*S*)-1-Phenyl-3-(phenylthio)octan-2-ol (469g)



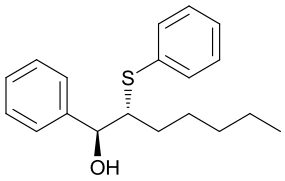
Obtained via purification procedure **A**; colourless oil (30 mg, 0.095 mmol, 12%). $[a]_D^{25}$ -6.1 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3442, 3061, 3027, 2954, 2926, 2857, 1584, 1466, 1454, 1438, 1279, 1025; ***major isomer*** δ_H (400 MHz, $CDCl_3$) 0.93 (3H,

t, J = 6.8, CH_3), 1.28-1.93 (8H, m, 4 × CH_2), 2.27-2.29 (1H, br m, OH), 2.85 (1H, dd, J = 13.8, 7.9, PhC*H*H), 2.89 (1H, dd, J = 13.8, 5.7, PhCH*H*), 3.20 (1H, dt, J = 9.7, 3.6, SCH), 3.93-3.99 (1H, m, OCH), 7.18-7.48 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 27.3, 28.9, 31.7, 39.9, 55.3, 73.5, 126.5, 126.8, 128.5, 129.0, 129.2, 131.4, 135.2, 138.4; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.81 (3H, t, J = 7.3, CH3), 1.26-1.89 (8H, m, 4 × CH_2), 2.30-2.32 (1H, br m, OH), 2.77 (1H, dd, J = 13.6, 8.5, PhC*H*H), 3.02 (1H, dd, J = 13.6, 4.1, PhCH*H*), 3.17-3.22 (1H, m, SCH), 3.79-3.84 (1H, m, OCH), 7.18-7.48 (10H, m, 10 × ArH); δ_C (150 MHz, $CDCl_3$)14.1, 22.5, 27.1, 31.8, 40.5, 59.9, 71.8, 126.4, 126.8, 128.6, 129.1, 129.5, 132.2, 135.7, 139.5; Found (EI): $[M]^+$ 314.17021, $C_{20}H_{26}OS$ requires 314.16989.

1-Phenyl-2-(phenylthio)heptan-1-ol (469e) (475c)



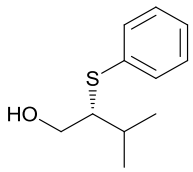
469e
(1*R*,2*S*)



475c
(1*S*,2*R*)

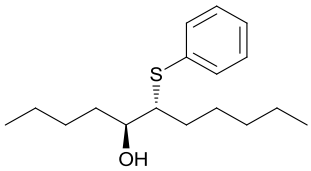
469e Obtained via purification procedure **A**; colourless oil (168 mg, 0.56 mmol, 70%); **475c** Obtained via purification procedure **B**; colourless oil (119 mg, 0.40 mmol, 70%); **469e** $[a]_D^{25}$ +39.3 (c. 1.0, $CHCl_3$); **475c** $[a]_D^{25}$ -43.7 (c.1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3450, 3061, 3029, 2955, 2928, 2858, 1584, 1452, 1439, 1279, 1179, 1139; both enantiomers were isolated as a 99:1 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.83 (3H, t, J = 7.1, CH_3), 1.10-1.63 (8H, 4 × CH_2), 2.81 (1H, br s, OH), 3.38 (1H, dt, J = 10.1, 3.2, SCH), 4.78 (1H, d, J = 3.2, OCH), 7.23-7.49 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.1, 22.5, 27.4, 27.5, 31.6, 58.2, 73.5, 126.1, 127.4, 127.5, 128.3, 129.3, 132.4, 134.8, 140.9; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.81 (3H, t, J = 7.1, CH_3), 1.10-1.63 (8H, 4 × CH_2), 2.74 (1H, br s, OH), 3.14 (1H, ddd, J = 9.8, 8.5, 3.4, SCH), 4.42 (1H, d, J = 8.5, OCH), 7.20-7.47 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.1, 22.6, 26.8, 30.9, 31.5, 59.9, 75.8, 127.2, 127.8, 128.1, 128.5, 129.1, 133.1, 133.5, 141.3; Found (EI): $[M]^+$ 300.15449, $C_{19}H_{24}OS$ requires 300.15424.

(*R*)-3-Methyl-2-(phenylthio)butan-1-ol[261] (473)



Obtained via purification procedure **A** or **C**; colourless oil (141 mg, 0.72 mmol, 62%); ν_{max} (film/cm^{-1}) 3378, 3059, 2960, 2930, 2873, 1584, 1478, 1438, 1386, 1367, 1385, 1367, 1063, 1025; δ_H (600 MHz, $CDCl_3$) 1.06 (3H, d, J = 6.8, 1 × CH_3), 1.08 (3H, d, J = 6.8, 1 × CH_3), 1.90 (1H, br s, OH), 2.01 (1H, septd, J = 6.8, 6.3, C*H*(CH_3)$_2$), 3.06 (1H, ddd, J = 7.2, 6.3, 5.1, SCH), 3.61 (1H, dd, J = 11.6, 7.2, C*H*HOH), 3.74 (1H, dd, J = 11.6, 5.1, CH*H*OH), 7.22-7.30 (3H, m, 3 × ArH), 7.44-7.46 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 20.0, 20.5, 29.9, 60.9, 62.6, 127.2, 129.1, 132.2, 135.2; Found (EI): $[M]^+$ 196.09200, $C_{11}H_{16}OS$ requires 196.09164.

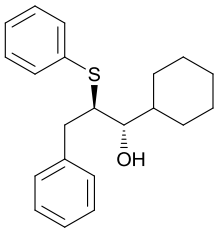
(5*S*,6*R*)-6-(Phenylthio)undecan-5-ol (476b)



Obtained via purification procedure **B**; colourless oil (89 mg, 0.32 mmol, 56%); $[a]_D^{25}$ -2.7 (c. 0.30, $CHCl_3$); ν_{max} (film/cm^{-1}) 3443, 3061, 2955, 2930, 2858, 1584, 1466, 1439, 1279, 1025; isolated as a 98:2 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.87-0.90 (6H, m, 2 × CH_3), 1.22-1.73 (14H, m, 7 × CH_2), 2.08 (1H, br s, OH), 3.18 (1H, ddd, J = 9.7, 3.7, 3.2, SCH), 3.62-3.65 (1H, m, OCH), 7.22-7.30 (3H, m, 3 × ArH), 7.41-7.43 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$); 14.1, 14.2, 22.6, 22.8, 27.5, 28.5, 29.2, 31.8, 32.9, 57.4, 72.2, 127.1, 129.1, 132.0, 135.3; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.85-0.90 (6H, m, 2 × CH_3), 1.22-1.73 (14H, m, 7 × CH_2), 2.99-3.03 (1H, m, SCH), 3.55 (1H, ddd, J = 9.1, 5.8, 3.7, OCH), 7.22-7.43 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.1, 14.2, 22.7, 22.8,

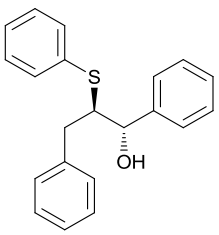
27.1, 28.2, 29.2, 31.6, 34.1, 57.9, 73.2, 127.2, 129.0, 132.4, 135.0; Found (CI): $[M+H]^+$ 280.18589, $C_{17}H_{28}OS$ requires 280.18554.

(1*S*,2*R*)-1-Cyclohexyl-3-phenyl-2-(phenylthio)propan-1-ol (478a)



Obtained via purification procedure **B**; colourless oil (124 mg, 0.38 mmol, 38%); $[a]_D^{25}$ -65.7 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3467, 3062, 3027, 2924, 2852, 1583, 1496, 1479, 1451, 1439, 1026; isolated as a 98:2 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.85-1.27 (5H, m, 5 × *c*Hex), 1.62-1.72 (5H, m, 5 × *c*Hex), 2.05 (1H, br d, J = 12.8, 1 × *c*Hex), 2.70 (1H, dd, J = 14.8, 10.8, PhC*H*H), 3.14 (1H, dd, J = 14.8, 3.5, PhCH*H*), 3.43 (1H, dd, J = 8.5, 2.7, OCH), 3.59 (1H, ddd, J = 10.8, 3.5, 2.7, SCH), 7.20-7.33 (10H, m, 10 × ArH); δ_C (150 MHz, $CDCl_3$) 25.9, 26.0, 26.4, 28.9, 30.1, 33.8, 39.7, 55.7, 76.1, 126.5, 127.2, 128.5, 129.1, 129.3, 132.0, 134.5, 139.7; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.85-1.27 (5H, m, 5 × *c*Hex), 1.62-1.72 (5H, m, 5 × *c*Hex), 1.96 (1H, br d, J = 12.7, 1 × *c*Hex), 2.96 (1H, dd, J = 14.0, 10.8, PhC*H*H), 3.07 (1H, dd, J = 14.0, 8.1, PhCH*H*), 3.27 (1H, dd, J = 8.0, 3.3, OCH), 3.49 (1H, ddd, J = 8.1, 7.2, 3.3, SCH), 7.20-7.33 (10H, m, 10 × ArH); δ_C (150 MHz, $CDCl_3$) 25.9, 26.0, 26.2, 28.7, 29.8, 34.3, 41.2, 55.9, 76.6, 126.5, 127.3, 128.4, 129.1, 129.4, 132.7, 135.0, 139.4, Found (EI): $[M]^+$ 326.16966, $C_{21}H_{26}OS$ requires 326.16989

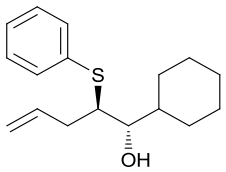
(1*S*,2*R*)-1,3-diphenyl-2-(phenylthio)propan-1-ol (478b)



Obtained via purification procedure **B**; colourless oil (191 mg, 0.60 mmol, 60%); $[a]_D^{25}$ -127.4 (c. 0.50, $CHCl_3$); ν_{max} (film/cm^{-1}) 3431, 3062, 3028, 2923, 1603, 1583,

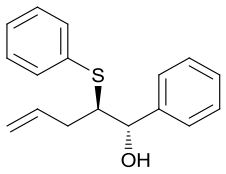
1495, 1475, 1453, 1439, 1219, 1026; isolated as a single diastereoisomer: δ_H (600 MHz, $CDCl_3$) 2.64 (1H, dd, J = 14.7, 10.6, PhC*H*H), 2.93 (1H, dd, J = 14.7, 3.3, PhCH*H*), 3.61 (1H, dt, J = 10.6, 3.3, SCH), 4.87 (1H, d, J = 3.3, OCH), 7.22-7.35 (15H, m, 15 × ArH); δ_C (150 MHz, $CDCl_3$) 34.0, 60.2, 73.4, 126.1, 126.5, 127.6, 127.7, 128.4, 129.2, 129.3, 129.8, 132.5, 134.4, 139.4, 140.7; Found (EI): $[M]^+$ 320.16947, $C_{21}H_{20}OS$ requires 320.16989.

(1*S*,2*R*)-1-Cyclohexyl-2-(phenylthio)pent-4-en-1-ol (478c)



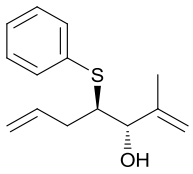
Obtained via purification procedure **B**; pale yellow oil (120 mg, 0.44 mmol, 36%); $[a]_D^{25}$ -8.9 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3466, 3074, 2924, 2851, 1640, 1583, 1449, 1439, 1025; isolated as a 96:4 mixture of diastereoisomers: ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.84-1.27 (5H, m, 5 × *c*Hex), 1.54-1.70 (5H, m, 5 × *c*Hex), 1.98-2.01 (1H, m, 1 × *c*Hex), 2.26-2.32 (1H, m, 1 × C*H*HCH=CH_2), 2.49-2.54 (1H, m, 1 × CH*H*CH=CH_2), 3.28 (1H, dd, J = 8.0, 3.2, OCH), 3.39 (1H, dt, J = 9.8, 3.2, SCH), 5.11 (1H, d, J = 10.1, CH=CHH_{cis}), 5.16 (1H, dq, J = 17.0. 1.6, CH=CHH_{trans}), 6.00 (1H, ddt, J = 17.0, 10.1, 7.0, C*H*=CH_2), 7.23-7.40 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 25.9, 26.1, 26.4, 28.9, 29.8, 32.1, 39.8, 53.1, 75.9, 117.1, 127.3, 129.2, 132.0, 134.5, 136.3; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.84-1.27 (5H, m, 5 × *c*Hex), 1.54-1.70 (5H, m, 5 × *c*Hex), 1.89-1.91 (1H, m, 1 × *c*Hex), 2.36-2.41 (1H, m, 1 × C*H*HCH=CH_2), 2.49-2.54 (1H, m, 1 × CH*H*CH=CH_2), 3.35 (1H, dd, J = 7.0, 4.7, OCH), 3.40-3.44 (1H, m, SCH), 5.10-5.34 (2H, m, CH=CH_2), 5.91 (1H, ddt, J = 17.1, 10.1, 7.0, C*H*=CH_2), 7.23-7.40 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 26.1, 26.2, 26.4, 27.9, 30.0, 37.2, 40.7, 54.0, 76.8, 117.5, 127.4, 129.1, 132.8, 135.8, 137.0; Found (EI): $[M]^+$ 276.15465, $C_{17}H_{24}OS$ requires 276.15424.

(1*S*,2*R*)-1-Phenyl-2-(phenylthio)pent-4-en-1-ol (478d)



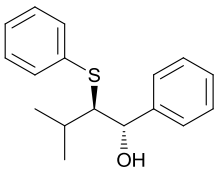
Obtained via purification procedure **B**; pale yellow oil (109 mg, 0.40 mmol, 34%); $[a]_D^{25}$ -55.3 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3448, 3062, 3029, 2978, 2921, 1640, 1583, 1494, 1478, 1452, 1438, 1025; isolated as a single diastereoisomer: δ_H (600 MHz, $CDCl_3$) 2.22-2.36 (2H, m, CH_2), 3.46 (1H, dt, J = 9.5, 3.8, SCH), 4.80 (1H, d, J = 3.8, OCH), 5.00-5.06 (2H, m, CH=C*H*$_2$), 5.84 (1H, dddd, J = 17.1, 9.8, 7.3, 6.5, C*H*=CH_2), 7.24-7.48 (10H, m, 10 × ArH); δ_C (150 MHz, $CDCl_3$) 32.3, 57.5, 73.3, 117.3, 126.2, 127.6, 128.4, 128.9, 129.3, 132.5, 134.3, 135.8, 140.7; Found (EI): $[M]^+$ 270.10694, $C_{17}H_{18}OS$ requires 270.10729.

(3*S*,4*R*)-2-Methyl-4-(phenylthio)hepta-1,6-dien-3-ol (478e)



Obtained via purification procedure **B**; colourless oil (91 mg, 0.39 mmol, 33%); $[a]_D^{25}$ +3.5 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3447, 3074, 2924, 1639, 1583, 1478, 1439, 1279; isolated as a 90:10 mixture of diastereoisomers: ***major isomer*** δ_H (400 MHz, $CDCl_3$) 1.68 (3H, s, CH_3), 2.24-2.31 (1H, m, SCHC*H*H), 2.46-2.53 (1H, m, SCHCH*H*), 3.37 (1H, dt, J = 9.4, 3.7, SCH), 4.11 (1H, d, J = 3.7, OCH), 5.00-5.17 (4H, m, 2 × CH=C*H*$_2$), 6.00 (1H, dddd, J = 17.0, 13.9, 10.2, 7.0, C*H*=CH_2), 7.26-7.52 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 19.4, 32.2, 53.4, 74.4, 112.7, 117.2, 127.6, 129.2, 132.5, 134.2, 136.1, 143.2; ***minor isomer*** δ_H (400 MHz, $CDCl_3$) 1.74 (3H, s, CH_3), 2.14-2.21 (1H, m, SCHC*H*H), 2.37-2.44 (1H, m, SCHCH*H*), 3.14 (1H, ddd, J = 8.6, 8.0, 4.9, SCH), 3.95 (1H, d, J = 8.0, OCH), 5.00-5.17 (4H, m, 2 × CH=C*H*$_2$), 5.91-6.00 (1H, m, C*H*=CH_2), 7.26-7.52 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 17.3, 35.8, 55.0, 76.5, 115.1, 117.6, 128.0, 129.1, 133.9, 134.2, 135.4, 143.9; Found (EI): $[M]^+$ 234.10761, $C_{14}H_{18}OS$ requires 234.10729.

(1*S*,2*R*)-3-Methyl-1-phenyl-2-(phenylthio)butan-1-ol (478f)

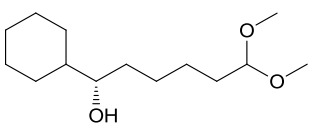


Obtained via purification procedure **B**; colourless oil (193 mg, 0.71 mmol, 61%); $[a]_D^{25}$ -6.4 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3431, 3061, 3031, 2960, 2927, 2871, 1583, 1478, 1454, 1439, 1383, 1026; isolated as a 87:13 mixture of diastereoisomers: ***major isomer*** δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, J = 6.8, 1 × CH_3), 1.14 (3H, d, J = 6.8, 1 × CH_3), 2.23 (1H, septd, J = 6.8, 3.2, C*H*$(CH_3)_2$), 2.64 (1H, br s, OH), 3.29 (1H, dd, J = 6.4, 3.2, SCH), 4.84 (1H, d, 6.4, OCH), 7.19-7.37 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 18.2, 22.5, 27.9, 65.7, 75.0, 126.7, 126.9, 127.5, 128.1, 128.8, 132.3, 135.7, 141.8; ***minor isomer*** δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, J = 6.7, 1 × CH_3), 1.03 (3H, d, J = 6.7, 1 × CH_3), 1.80 (1H, septd, J = 6.7, 3.2, C*H*$(CH_3)_2$), 3.28 (1H, dd, J = 8.6, 3.2, SCH), 4.72 (1H, d, 8.6, OCH), 7.24-7.50 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 17.4, 21.4, 29.8, 69.1, 75.3, 126.7, 126.8, 128.0, 129.0, 131.3, 135.5, 143.1; Found (EI): $[M]^+$ 272.40544, $C_{17}H_{20}OS$ requires 272.40510.

General procedure for the synthesis of secondary alcohols:

A solution of hydroxysulfide (1 mmol) and Raney-Ni (2 g) in EtOH (0.05 M) was stirred at reflux for 2-4 hr. The mixture was cooled to RT and filtered through a pad of Celite®. The filtrate was evaporated to dryness to afford crude alcohols.

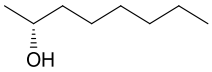
(*S*)-1-Cyclohexyl-6,6-dimethoxyhexan-1-ol (467)



$[a]_D^{25}$ -12.5 (c. 0.15, $CHCl_3$); ν_{max} (film/cm^{-1}) 3346, 2965, 2930, 1584, 1462, 1438, 1373, 1279, 1177, 1125; δ_H (600 MHz, $CDCl_3$) 0.96-1.81 (15H, m, 11 × *c*Hex,4 ×

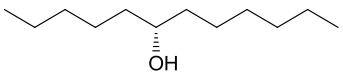
CH_2), 3.31 (6H, s, 2 × CH_3), 3.33-3.36 (1H, m, OCH), 4.36 (1H, t, J = 5.8, C*H*(OCH_3)$_2$); δ_C (150 MHz, $CDCl_3$) 24.8, 25.9, 26.3, 26.5, 26.7, 27.8, 29.4, 32.6, 34.1, 43.7, 52.7, 52.8, 76.2, 104.5. Accurate mass could not be obtained for this compound.

(*R*)-Octan-2-ol[262] (470c)



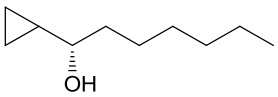
$[a]_D^{25}$ -5.4 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3339, 2960, 2927, 2857, 1462, 1373, 1279, 1177, 1141, 1115; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, CH_2CH_3), 1.21 (3H, d, J = 6.1, $CHCH_3$), 1.27-1.51 (10 H, m, 5 × CH_2), 3.81 (1H, m, C*H*OH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 23.5, 25.7, 29.3, 31.8, 39.4, 68.2.

(*R*)-Dodecan-6-ol (470d)



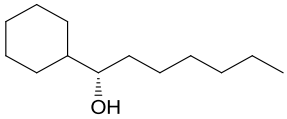
$[a]_D^{25}$ -6.5 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3320, 2956, 2923, 2853, 1467, 1377, 1351, 1137, 1071; δ_H (400 MHz, $CDCl_3$) 0.89-0.93 (6H, m, 2 × CH_3), 1.27-1.50 (18H, 9 × CH_2), 3.58-3.64 (1H, m, OCH); δ_C (100 MHz, $CDCl_3$) 14.0, 14.1, 22.6, 22.7, 25.3, 25.6, 29.4, 31.8, 31.9, 37.4, 37.5, 72.0; Accurate mass could not be obtained for this compound.

(*S*)-1-Cyclopropylheptan-1-ol (470b)



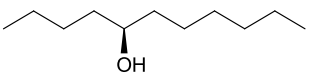
$[a]_D^{25}$ -5.5 (c. 0.30, $CHCl_3$); ν_{max} (film/cm^{-1}) 3360, 2957, 2927, 2857, 1461, 1372, 1279, 1177, 1141; δ_H (600 MHz, $CDCl_3$) 0.18-0.27 (2H, m, 2 × *c*Pr), 0.45-0.54 (2H, m, 2 × *c*Pr), 0.88 (3H, t, J = 7.1, CH_3), 1.24-1.61 (11H, m, 5 × CH_2, 1 × *c*Pr), 2.84 (1H, app q, J = 7.0, OCH); δ_C (150 MHz, $CDCl_3$) 2.5, 2.9, 14.2, 18.1, 22.8, 25.8, 29.5, 32.0, 37.4; Accurate mass could not be obtained for this compound.

(*S*)-1-Cyclohexylheptan-1-ol (470f)



$[a]_D^{25}$ -10.5 (c. 0.20, $CHCl_3$); ν_{max} (film/cm^{-1}) 3370, 2926, 2854, 1450, 1373, 1279, 1141; δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.9, CH_3), 0.96-1.81 (21H, 11 × *c*Hex, 5 × CH_2), 3.33-3.35 (1H, m, OCH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.8, 26.0, 26.3, 26.5, 26.7, 27.8, 29.4, 29.6, 32.0, 34.3, 43.7, 76.4; Found (EI): $[M\text{-}H]^+$ 197.19097, $C_{13}H_{25}O$ requires 197.19054.

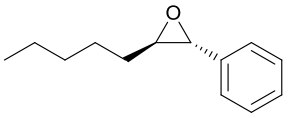
(*S*)-Undecan-5-ol[195] (489)



Colourless oil (25 mg, 0.15 mmol, 74%), ν_{max} (film/cm^{-1}) 3319, 2954, 2921, 1466, 1377, 1350, 1137; δ_H (600 MHz, $CDCl_3$) 0.87-0.91 (6H, m, 2 × CH_3), 1.24-1.49

(16H, m, 8 × CH_2), 1.60 (1H, br s, OH), 3.56-3.60 (1H, m, OCH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.7, 22.9, 25.7, 28.0, 29.5, 32.0, 37.3, 37.6, 72.1; Found (CI): $[M\text{-}OH]^+$ 155.17900, $C_{11}H_{23}$ requires 155.17943.

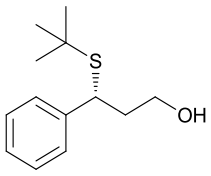
(2*S*,3*S*)-2-Pentyl-3-phenyloxirane[263] (481)



A solution of sulfido-alcohol **476c** (100 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (1 ml) and the solution was cooled to 0 °C. Trimethyloxonium tetrafluoroborate (488 mg, 3.30 mmol) was added and the mixture was allowed to warm to RT over 1 hr. The mixture was subsequently cooled to 0 °C and 0.5 M NaOH (4 ml) was added. The reaction was allowed to warm to RT over 24 hr then partitioned between water and Et_2O. The aqueous layer was extracted multiple times with Et_2O and the combined organic layers were then dried over $MgSO_4$, filtered and evaporated to dryness. The crude oil was purified by column chromatography (Pet/EtOAc = 100/0 → 99/1) to give epoxide **481** as a colourless oil (34 mg, 0.18 mmol, 54%).

$[a]_D^{25}$ -13.6 (c. 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J = 7.0, CH_3), 1.33-1.74 (8H, m, 4 × CH_2), 2.97 (1H, td, J = 5.6, 2.0, C*H*CH_2), 3.63 (1H, d, J = 2.0, PhCH), 7.27-7.39 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 25.6, 31.6, 32.3, 58.7, 63.3, 125.5, 128.0, 128.4, 137.9; Found (CI): $[M+H]^+$ 191.14319, $C_{13}H_{19}O$ requires 191.14359.

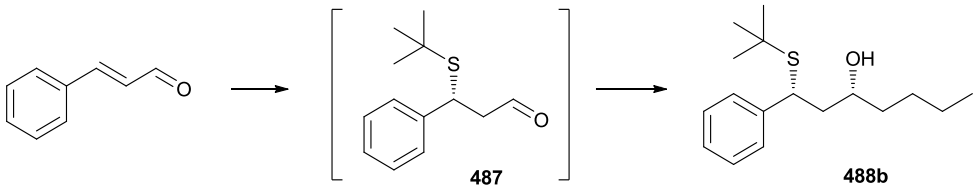
(*R*)-3-(*tert*-Butylthio)-3-phenylpropan-1-ol[194] (488a)



A mixture of *trans*-cinnamaldehyde (0.21 ml, 1.67 mmol), catalyst **471** (67 mg, 0.11 mmol) and benzoic acid (14 mg, 0.11 mmol) was stirred in toluene (2 ml) at -25 °C. 2-Methyl-2-propanethiol (0.13 ml, 1.11 mmol) was added and the resulting mixture

was allowed to slowly warm to RT over 24 hr. The mixture was diluted with MeOH (2 ml), cooled to 0 °C and $NaBH_4$ was added (126 mg, 3.3 mmol),. The mixture was allowed to warm to RT over 2 hr. The mixture was evaporated to dryness and purified by column chromatography (Pet/EtOAc = 90/10) to give alcohol **488a** as a colourless oil (61 mg, 0.27 mmol, 24%); $[a]_D^{25}$ +15.4 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3360, 3061, 3027, 2959, 2941, 2924, 2898, 2862, 1492, 1453, 1364, 1279, 1162, 1036; δ_H (600 MHz, $CDCl_3$) 1.21 (9H, s, *t*Bu), 1.69 (1H, br s, OH), 1.96-2.01 (1H, m, SCHC*H*H), 2.05-2.11 (1H, m, SCHCH*H*), 3.54-3.58 (1H, m, C*H*HOH), 3.70-3.73 (1H, app quint, J = 5.4, CH*H*OH), 4.05 (1H, t, J = 7.7, SCH), 7.19-7.37 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 31.5, 41.4, 44.2, 44.9, 61.0, 126.9, 127.7, 128.6, 145.2; Found (EI): $[M]^+$ 224.12337, $C_{13}H_{20}OS$ requires 224.12294.

(1*R*,3*R*)-1-(*tert*-Butylthio)-1-phenylheptan-3-ol (488b)

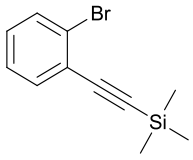


A mixture of *trans*-cinnamaldehyde (0.21 ml, 1.67 mmol), catalyst **471** (67 mg, 0.11 mmol) and benzoic acid (14 mg, 0.11 mmol) was stirred in toluene (2 ml) at -25 °C. 2-Methyl-2-propanethiol (0.13 ml, 1.11 mmol) was added and the resulting mixture was allowed to slowly warm to RT over 24 hr. The mixture was evaporated to dryness and filtered through a silica plug (Pet/EtOAc = 100/0 → 95/5) to give aldehyde **487**. Aldehyde **487** (80 mg, 0.36 mmol) was dissolved in toluene (0.5 ml) and slowly added to a solution of *n*BuLi (1.6 M in hexanes, 0.67 ml , 1.07 mmol) cooled to -78 °C. The resulting mixture was stirred at -78 °C for 30 min then quenched with sat NH_4Cl and partitioned between water and Et_2O. Combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness to give crude alcohol **488b** as a pale yellow oil (53 mg, 0.19 mmol, 52%); $[a]_D^{25}$ +3.2 (c. 0.48, $CHCl_3$); isolated as a 66:34 mixture of diastereoisomers: ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.85 (3H, t, J = 7.0, CH_2CH_3), 1.18-1.46 (6H, m, $(CH_2)_3CH_3$), 1.22 (9H, s, *t*Bu), 1.85-1.95 (2H, m, $CHCH_2CH$), 3.35-3.40 (1H, m OCH), 4.10 (1H, dd, J

= 9.1, 6.8, SCH), 7.19-7.38 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.1, 22.8, 27.7, 31.5, 37.8, 44.4, 45.3, 46.1, 70.4, 126.8, 127.8, 128.6,145.1; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.2, CH_2CH_3), 1.18-1.46 (6H, m, $(CH_2)_3CH_3$), 1.19 (9H, s, tBu), 1.79 (1H, ddd, J = 14.4, 9.0, 5.5, CHC*H*HCH), 1.86 (1H, ddd, J = 14.4, 9.9, 3.3, CHCH*H*CH), 3.86-3.91 (1H, m, OCH), 4.08-4.10 (1H, m, SCH), 7.19-7.38 (5H, m, 5 × ArH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.8, 27.9, 31.6, 37.3, 44.0, 44.8, 46.4, 69.6, 126.7, 127.6, 128.6, 146.2; Found (EI): $[M]^+$ 280.18601, $C_{17}H_{28}OS$ requires 280.18554.

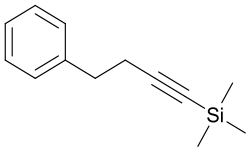
See Appendix for the determination of the enantiomeric ratios obtained with the Mosher's esters analysis

((2-Bromophenyl)ethynyl)trimethylsilane[264] (507)



2-Bromoiodobenzene (5.0 g, 17.7 mmol) was dissolved in Et_2NH (55 ml), followed by $Pd(PPh_3)Cl_2$ (248 mg, 0.35 mmol) and CuI (67 mg, 0.35 mmol). The reaction mixture was stirred for 10 min. After this time a solution of TMS-acetylene (3.67 ml, 25.5 mmol) in Et_2NH (5 ml) was added dropwise over 12 hr at RT under Ar. The reaction was quenched with sat NH_4Cl and extracted with Pet. The combined organic layers were dried over $MgSO_4$, filtered and evaporated top dryness. The crude was purified by column chromatography (Pet) to give acetylene **507** (3.67g, 14.5 mmol, 82%) as a pale yellow oil. ν_{max} (film/cm^{-1}) 3066, 2960, 2899, 2163, 1465, 1249, 1046, 1027, 860; δ_H (600 MHz, $CDCl_3$) 0.27 (9H, s, $Si(CH_3)_3$), 7.15 (1H, td, J = 7.7, 1.7, ArH), 7.24 (1H, td, J = 7.7, 1.0, ArH), 7.48 (1H, dd, J = 7.7, 1.7, ArH), 7.56 (1H, dd, J = 7.7, 1.0, ArH); δ_C (150 MHz, $CDCl_3$) 0.0, 99.7, 103.1, 125.3, 125.9, 127.0, 129.7, 132.5, 133.7; Found (EI): $[M]^+$ 202. 11750, $C_{13}H_{18}Si$ requires 212.11722.

Trimethyl(4-phenylbut-1-yn-1-yl)silane[265] (507b)



A solution of 4-Phenyl-1-butyne (500 mg, 3.84 mmol) in anhydrous THF (5 ml) was cooled to -78 °C and a solution of *n*-BuLi (2.5M in hexanes, 1.69 ml, 4.22 mmol) was slowly added dropwise. The reaction mixture was stirred at -78 °C for 1 hr then TMSCl (0.54 ml, 4.22 mmol) was added and the reaction was allowed to warm to RT over 16 hr. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford acetylene **507b** (756 mg, 3.84 mmol, quant.) as a pale brown oil. ν_{max} (film/cm^{-1}) 3029, 2958, 2175, 1603, 1496, 1454, 1249, 1041, 836; δ_H (600 MHz, $CDCl_3$) 0.14 (9H, s, $Si(CH_3)_3$), 2.50 (2H, t, J = 7.7, $CH_2C{\equiv}C$), 2.84 (2H, t, J = 7.7, $PhCH_2$), 7.21-7.30 (5H, m, ArH); δ_C (150 MHz, $CDCl_3$) 0.2, 22.3, 35.2, 85.4, 106.8, 126.4, 128.4, 128.6, 140.7; Found (EI): $[M]^+$ 202.11750, $C_{13}H_{18}Si$ requires 220.11722

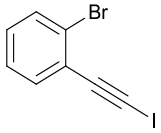
General Procedure for the Bronsted acid catalysed halogenation of trimethylsilyl alkynes

Brønsted acid catalyst (TfOH or Tf_2NH, 2 mol%) was added to a solution of alkyne or trimethylsilyl alkyne (1 eq) and NIS/NBS (1 eq) in CH_2Cl_2 (0.1 M). The reaction mixture was stirred at room temperature and monitored by NMR or TLC. Upon completion, the solvent was evaporated to dryness and the crude material was purified by filtration through a silica pad eluting with mixtures of Petrol:EtOAc.

General Procedure for the gold-catalysed halogenation of terminal or trimethylsilyl alkynes

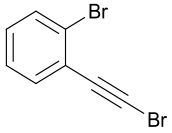
$[Ph_3PAuNTf]_2$·PhMe (0.5 mol%) was added to a solution of alkyne or trimethylsilyl alkyne (1 eq) and NIS/NBS (1 eq) in CH_2Cl_2 (0.1 M). The reaction mixture was stirred at room temperature and monitored by NMR or TLC. Upon completion, the solvent was evaporated to dryness and the crude material was purified by filtration through a silica pad eluting with mixtures of Petrol:EtOAc.

1-Bromo-2-(iodoethynyl)benzene[266] (509a)



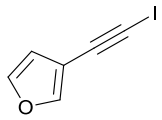
1 hr reaction time with Tf_2NH; yellow oil (284 mg, 0.91 mmol, 92%); ν_{max} (film/cm^{-1}) 3063, 2172, 1583, 1157, 1466, 1433, 1045, 1027; δ_H (600 MHz, $CDCl_3$) 7.15 (1H, t, J = 7.7, ArH), 7.25 (1H, t, J = 7.7, ArH), 7.47 (1H, d, J = 7.7, ArH), 7.°(1H, d, J =7.7, ArH); δ_C (150 MHz, $CDCl_3$) 12.0, 92.7, 125.5, 126.1, 127.0, 130.0, 132.4, 134.4; Found (EI): $[M]^+$ 305.85303, C_8H_4IBr requires 305.85356.

1-Bromo-2-(bromoethynyl)benzene[267] (509b)



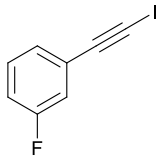
3 hr reaction time with $HNTf_2$; yellow oil (197 mg, 0.65 mmol, 66%); δ_H (600 MHz, $CDCl_3$) 7.18 (1H, td, J = 7.7, 1.7, ArH), 7.25 (1H, td, J = 7.7, 1.0, ArH), 7.47 (1H, dd, J = 7.7, 1.7, ArH), 7.57 (1H, dd, J = 7.7, 1.0, ArH); δ_C (150 MHz, $CDCl_3$) 55.0, 78.8, 124.9, 125.8, 127.1, 130.0, 132.6, 134.0; Found (EI): $[M]^+$ 257.86710, $C_8H_4Br_2$ requires 257.86742

3-(Iodoethynyl)furan (510)



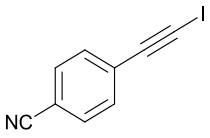
1 hr reaction time with Tf_2NH; pale yellow oil (100 mg, 0.46 mmol, 47%); ν_{max} (film/cm^{-1}) 3016, 2970, 2947, 2123, 1435, 1366, 1216, 1228; δ_H (600 MHz, $CDCl_3$) 6.44 (1H, d, J = 1.6, H-5), 7.35 (1H, t, J = 1.6, H-4), 7.64 (1H, s, H-2); δ_C (150 MHz, $CDCl_3$) 7.4, 85.0, 108.2, 112.7, 142.7, 147.1; Found (EI): $[M]^+$ 217.92260, C_6H_3OI requires 217.92231.

1-Fluoro-3-(iodoethynyl)benzene (511)



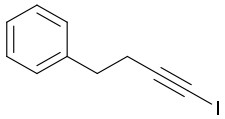
4 hr reaction time with Tf_2NH; pale yellow oil (220 mg, 0.89 mmol, 91%); ν_{max} (film/cm^{-1}) 3071, 2959, 2159, 1610, 1579, 1483, 1433, 1271, 1262, 1250, 1139, 1075, 944; δ_H (600 MHz, $CDCl_3$) 7.03 (1H, dd, J = 8.4, 6.0, H6), 7.12 (1H, m, H2), 7.21 (1H, d, J = 7.8, H4), 7.27 (1H, td, J = 7.8, 6.0, H5); δ_C (150 MHz, $CDCl_3$) 8.2, 92.9 (d, J_{CF} = 3.4), 116.4 (d, J_{CF} = 21.1), 119.3 (d, J_{CF} = 23.0), 125.2 (d, J_{CF} = 9.5), 128.3 (d, J_{CF} = 3.0), 129.9 (d, J_{CF} = 8.6), 162.2 (d, J_{CF} = 247.0); Found (EI): $[M]^+$ 245.93390, C_8H_4IF requires 245.93362.

4-(Iodoethynyl)benzonitrile (512)



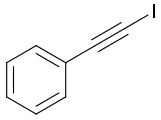
24 hr reaction time with Tf_2NH; pale yellow solid (223mg, 0.88 mmol, 90%); m.p. 165-167 °C, ν_{max} (film/cm^{-1}) 3084, 2233, 2166, 1921, 1598, 1496, 1404, 1387, 1272, 1387, 1272, 1224, 1172, 1103; δ_H (600 MHz, $CDCl_3$) 7.51 (2H, d, J = 8.5, 2 × ArH), 7.60 (2H, d, J = 8.5, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 13.1, 92.7, 112.2, 118.4, 128.2, 132.1, 133.0; Found (EI): $[M]^+$ 252.93854, C_9H_4NI requires 252.93829.

(4-Iodobut-3-yn-1-yl)benzene[268] (513)



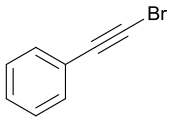
5 days reaction time with PPh_3AuNTf_2; 32% conversion; pale brown oil; ν_{max} (film/cm^{-1}) 3061, 3026, 2945, 2828, 2172, 1577, 1546, 1475, 1449, 1248, 1222, 1045, 840; δ_H (600 MHz, $CDCl_3$) 2.65 (2H, t, J = 7.6, $CH_2C{\equiv}C$), 2.84 (2H, t, J = 7.6, $ArCH_2$), 7.16-7.24 (3H, m, 3 × ArH), 7.28-7.32 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) -5.8, 23.2, 35.0, 94.0, 126.5, 128.6, 128.7, 140.4; Found (EI): $[M]^+$ 255.97460, $C_{10}H_9I$ requires 255.97434

(Iodoethynyl)benzene[220] (516)



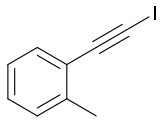
3 hr reaction time with PPh_3AuNTf_2; pale brown oil (176 mg, 0.77 mmol, 78%); ν_{max} (film/cm^{-1}) 3056, 3031, 2171, 1597, 1573, 1488, 1442, 754; δ_H (600 MHz, $CDCl_3$) 7.28-7.34 (3H, m, ArH), 7.42-7.45 (2H, m, ArH); δ_C (600 MHz, $CDCl_3$) 6.3, 94.2, 123.5, 128.4, 128.9, 132.4; Found (EI): $[M]^+$ 227.94288, C_8H_5I requires 227.94304

(Bromoethynyl)benzene[220] (517)



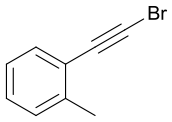
24 hr reaction time with PPh_3AuNTf_2; yellow oil (141 mg, 0.78 mmol, 79%); ν_{max} (film/cm^{-1}) 3060, 2201, 1596, 1574, 1485, 1442, 1223, 1069, 1026, 914; δ_H (600 MHz, $CDCl_3$) 7.29 (3H, m, 3 × ArH), 7.44-7.46 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 49.8, 80.1, 122.8, 128.4, 128.8, 132.1; Found (EI): $[M]^+$ 179.95718, C_8H_5Br requires 179.95691.

1-(Iodoethynyl)-2-methylbenzene (518)



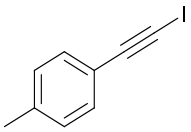
1 hr reaction time with PPh_3AuNTf_2; pale yellow oil (214 mg, 0.88 mmol, 90%); ν_{max} (film/cm^{-1}) 3061, 3030, 2857, 2166, 1598, 1482, 1454, 1378, 1109, 1042; δ_H (600 MHz, $CDCl_3$) 2.44 (3H, s, CH_3), 7.13 (1H, t, J = 7.5, ArH), 7.19-7.23 (2H,m, 2 × ArH), 7.40 (1H, d, J = 7.5, ArH); δ_C (150 MHz, $CDCl_3$) 9.0, 20.7, 93.3, 123.3, 125.6, 128.9, 129.5, 132.8, 141.3; Found (EI): $[M]^+$ 241.95839, C_9H_7I requires 241.95869.

1-(Bromoethynyl)-2-methylbenzene[269] (519)



24 hr reaction time with PPh_3AuNTf_2; yellow oil (158 mg, 0.81 mmol, 83%); ν_{max} (film/cm^{-1}) 3062, 3023, 2950, 2195, 1486, 1455, 1379, 1219, 1110, 1043; δ_H (600 MHz, $CDCl_3$) 2.43 (3H, s, CH_3), 7.13 (1H, td, J = 7.5, 0.8, ArH), 7.19 (1H, dt, J = 7.6, 0.8, ArH), 7.23 (1H, td, J = 7.5, 1.2, ArH), 7.41 (1H, dd, J = 7.6, 1.2, ArH); δ_C (150 MHz, $CDCl_3$) 20.6, 52.9, 79.2, 122.6 125.6, 128.7, 129.6, 132.4, 140.9; Found (EI): $[M]^+$ 193.97204, C_9H_7Br requires 193.97256.

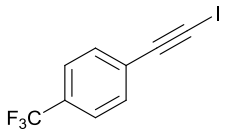
1-(Iodoethynyl)-4-methylbenzene[226] (520)



1.5 hr reaction time with PPh_3AuNTf_2; pale yellow oil (207 mg, 0.86 mmol, 87%); ν_{max} (film/cm^{-1}) 3027, 2918. 2154, 1905, 1604, 1507, 1439, 1178, 1019, 812; δ_H (500 MHz, $CDCl_3$) 2.35 (3H, s, CH_3), 7.11 (2H, d, J = 8.0), 7.32 (2H, d, J = 8.0); δ_C (125

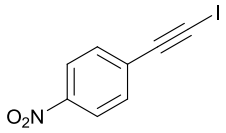
MHz, $CDCl_3$) 4.9, 21.6, 94.3, 120.4, 129.0, 132.3, 139.1; Found (EI): $[M]^+$ 241.95852, C_9H_7I requires 241.95870.

1-(Iodoethynyl)-4-(trifluoromethyl)benzene (521)



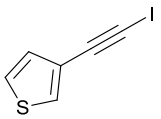
24 hr reaction time with PPh_3AuNTf_2; pale yellow solid (205 mg, 0.69 mmol, 71%); ν_{max} (film/cm^{-1}) 3061, 2175, 1615, 1318, 1123, 1064; δ_H (400 MHz, $CDCl_3$) 7.56 (2H, d, J = 8.5, 2 × ArH), 7.°(2H, d, J = 8.5, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 10.3, 92.9, 123.9 (q, J_{CF} = 272, CF_3), 125.3 (q, J_{CF} = 3.7, *C*HC-CF_3), 129.0, 130.6 (q, J_{CF} = 33.0, *C*CF_3), 132.7; Found (EI): $[M]^+$ 295.93077, $C_9H_4F_3I$ requires 295.93044.

1-(Iodoethynyl)-4-nitrobenzene (524)



24 hr reaction time with PPh_3AuNTf_2; yellow solid (155 mg, 0.57 mmol, 58%); m.p. 168-169 °C; ν_{max} (film/cm^{-1}) 3104, 2927, 2829, 2166, 1587, 1496, 1337, 1309, 1285, 1105, 849; δ_H (600 MHz, $CDCl_3$) 7.57 (2H, d, J = 8.9, 2 × ArH), 8.19 (2H, d, J = 8.9, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 14.3, 92.5, 123.7, 130.1, 133.3, 147.4; Found (EI): $[M]^+$ 272.92774, $C_8H_4O_2NI$ requires 272.92812.

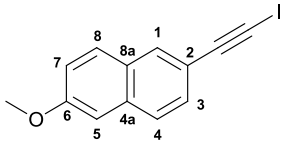
3-(Iodoethynyl)thiophene[226] (525)



24 hr reaction time with PPh_3AuNTf_2; yellow oil (168 mg, 0.72 mmol, 77%); ν_{max} (film/cm^{-1}) 3105, 2160, 1567, 1356, 1218, 1159, 1077, 945, 870, 778; δ_H (600 MHz,

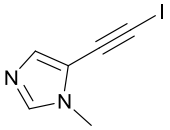
$CDCl_3$) 7.11 (1H, dd, J = 5.0, 1.1, H5), 7.24-7.26 (1H, dd, J = 5.0, 3.0, H4), 7.47 (1H, dd, J = 3.0, 1.1, H2); δ_C (150 MHz, $CDCl_3$) 5.9, 89.2, 122.6, 125.3, 130.1, 130.4; Found (EI): $[M]^+$ 233.89989, C_6H_3SI requires 233.89947.

2-(Iodoethynyl)-6-methoxynaphthalene (526)



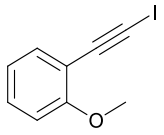
1 hr reaction time with PPh_3AuNTf_2; yellow solid (237 mg, 0.77 mmol, 79%); m.p. 103-104 °C; ν_{max} (film/cm^{-1}) 3052, 3002, 2941, 2843, 2165, 1626, 1598, 1480, 1388, 1228, 1172, 1161, 1026; δ_H (400 MHz, $CDCl_3$) 3.94 (3H, s, OCH_3), 7.11 (1H, d, J = 2.3, H5), 7.17 (1H, dd, J = 8.9, 2.3, H7), 7.46 (1H, dd, J = 8.5, 1.4, H3), 7.68 (1H, d, J = 8.5, H4), 7.70 (1H, d, J = 8.9, H8), 7.91 (1H, s, H1); δ_C (150 MHz, $CDCl_3$) 5.4, 55.5, 94.7, 105.8, 118.4, 119.6, 126.9, 128.3, 129.4, 129.5, 132.5, 134.5, 158.6; Found (EI): $[M]^+$ 307.96940, $C_{13}H_9OI$ requires 307.96926.

5-(Iodoethynyl)-1-methyl-1H-imidazole (527)



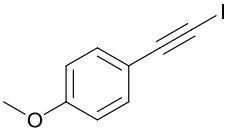
8 hr reaction time with PPh_3AuNTf_2; pale yellow solid (203 mg, 0.87 mmol, 89%); ν_{max} (film/cm^{-1}) 3217, 3082, 2123, 1564, 1357, 1155, 1116; δ_H (600 MHz, $CDCl_3$) 3.66 (3H, s, NCH_3), 7.24 (1H, s, ArH), 7.40 (1H, s, ArH); δ_C (150 MHz, $CDCl_3$) 15.0, 32.3, 82.0, 117.0, 135.4, 138.2; Found (EI): $[M]^+$ 231.94941, $C_6H_2N_2I$ requires 231.94920.

1-(Iodoethynyl)-2-methoxybenzene[270] (528)



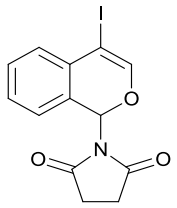
5 days reaction time with PPh_3AuNTf_2; isolated as an inseparable mixture of starting alkyne and product **528** (33:67), (92 mg, 0.26 mmol, 29%) ν_{max} (film/cm^{-1}) 3075, 2835, 2024, 1595, 1490, 1462, 1433, 1254, 1114, 1047, 1023, 751; δ_H (600 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 6.86-6.91 (2H, m, 2 × ArH), 7.29 (1H, t, J = 7.6, ArH), 7.40 (1H, d, J = 7.6, ArH); δ_C (150 MHz, $CDCl_3$) 9.5, 55.9, 90.4, 110.6, 112.6, 120.4, 130.4, 134.5, 161.1; Found (EI): $[M]^+$ 257.95391, C_9H_7OI requires 257.95361.

1-(Iodoethynyl)-4-methoxybenzene[239] (529)



The iodoalkyne could not be separated from the starting alkyne or an unidentified by-product. 56% conversion after 24 hr reaction time with PPh_3AuNTf_2; ν_{max} (film/cm^{-1}) 2961, 2837, 2162, 1604, 1508, 1461, 1440, 1292, 1250, 1172, 1030, 831; δ_H (500 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.83 (2H, d, J = 8.8, 2 ArH), 7.37 (2H, d, J = 8.8, 2 ArH); δ_C (150 MHz, $CDCl_3$) 3.8, 55.4, 94.0, 113.7, 115.6, 133.9, 160.0; Found (EI): $[M]^+$ 257.95380, C_9H_7OI requires 257.95361.

1-(4-iodo-1H-isochromen-1-yl)pyrrolidine-2,5-dione (531)

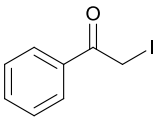


Pale brown oil (16 mg, 0.05 mmol, 5%), ν_{max} (film/cm^{-1}) 2944, 1711, 1377, 1347, 1175; δ_H (600 MHz, $CDCl_3$) 2.72 (2H, d, J = 5.7, 2 × C*H*H), 2.73 (2H, d, J = 5.7, 2 × CH*H*), 6.87 (1H, d, J = 7.6, ArH), 6.90 (1H, s, C=CH), 7.17 (1H, s, N-CH-O), 7.21 (1H, td, J = 7.6, 1.0, ArH), 7.30 (1H, d, J = 7.6, ArH), 7.35 (1H, t, J = 7.6, ArH); δ_C (100 MHz, $CDCl_3$) 28.1, 72.4, 76.2, 124.3, 124.9, 128.2, 128.3, 129.9, 130.7, 146.8, 175.3; Found (EI): $[M]^+$ 354.97033, $C_{13}H_{10}O_3NI$ requires 354.96999

General procedure for the synthesis of α-iodoketones

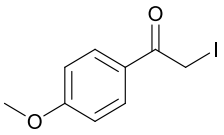
Terminal alkyne (1 eq) and NIS (1 eq) were dissolved in $CHCl_3$ (1 M). Methanol (1 eq) was added followed by $[Ph_3PAuNTf_2]_2$·PhMe (0.5 mol%). The reaction mixture was stirred at RT for 24 hr. The mixture was taken up in acetone and evaporated to dryness three times; the crude was then purified by column chromatography (Pet/EtOAc)

2-Iodo-1-phenylethanone[271] (543)



Pale brown oil (174 mg, 0.71 mmol, 72%); ν_{max} (film/cm^{-1}) 3027, 2970, 2942, 1670, 1597, 1579, 1447, 1365, 1245, 1002; δ_H (600 MHz, $CDCl_3$) 4.37 (2H, s, CH_2I), 7.45-7.50 (2H, m, 2 × ArH), 7.56-7.61 (1H, m, ArH), 7.98-8.00 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 1.8, 129.0, 129.2, 133.5, 134.0, 193.0; Found (EI): $[M]^+$ 245.95397, C_8H_7OI requires 245.95361.

2-Iodo-1-(4-methoxyphenyl)ethanone[272] (546)

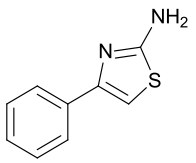


Pale brown oil (138 mg, 0.50 mmol, 51%), ν_{max} (film/cm^{-1}) 2935, 2838, 1661, 1594, 1509, 1250, 1169, 1025, 836; δ_H (600 MHz, $CDCl_3$) 3.09 (3H, s, CH_3), 4.31 (2H, s, CH_2), 6.94 (2H, d, J = 8.8, 2 × ArH), 7.97 (2H, d, J = 8.8, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 1.8, 55.7, 114.2, 126.5, 131.6, 164.1, 191.7; Found (EI): $[M]^+$ 275.96368, $C_9H_9O_2I$ requires 275.96418.

General procedure for Heterocycle formation

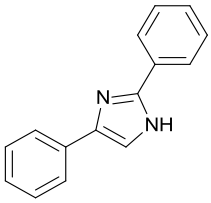
Terminal alkyne (1 eq) and NIS (1 eq) were dissolved in $CHCl_3$ (1 M). Methanol (1 eq) was added followed by $[Ph_3PAuNTf_2]_2$·PhMe (0.5 mol%) and the resulting mixture was stirred at RT for 24 hr. The mixture was diluted with $CHCl_3$ (0.1 M) and the nucleophile (3 eq) was added followed by DMF (0.2 M). The solution was concentrated under reduced pressure to remove the excess $CHCl_3$ and stirred for further 16 hr. The reaction was then diluted with water and extracted multiple times with Et_2O. The combined organic extracts were washed with sat LiCl solution and dried over $MsSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (Pet/EtOAc).

4-Phenylthiazol-2-amine[247] (547)



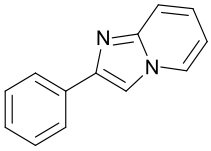
Off-white solid (105 mg, 0.60 mmol, 61%); ν_{max} (film/cm^{-1}) 3262, 3155, 2920, 1599, 1516, 1403, 1330, 1075; δ_H (600 MHz, $CDCl_3$) 5.07 (2H, br s, NH_2), 6.73 (1H, s, SCH), 7.29 (1H, t, J = 7.5, 3 × ArH),7.38 (2H, t, J = 7.5, 2 × ArH), 7.78 (2H, d, J = 7.5, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 103.0, 126.1, 127.9, 128.7, 134.8, 151.5, 167.3; Found (EI): $[M]^+$ 176.04060, $C_9H_8N_2S$ requires 176.04027

2,4-diphenyl-1H-imidazole[273] (549)



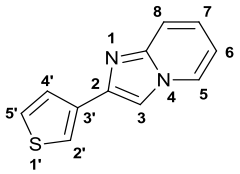
Pale yellow solid (94 mg, 0.43 mmol, 44%); ν_{max} (film/cm^{-1}) 3063, 1606, 1587, 1488, 1459, 906; δ_H (600 MHz, $CDCl_3$) 7.23-7.36 (7H, m, 7 × ArH), 7.72 (2H, d, J = 7.5, 2 × ArH), 7.84 (2H, dd, J = 7.9, 1.5, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 117.9, 125.1, 125.6, 127.2, 128.8, 128.9, 129.0, 130.2, 132.7, 147.6; Found (EI): $[M]^+$ 220.10013, $C_{15}H_{12}N_2$ requires 220.09950

2-Phenylimidazo[1,2-a]pyridine (551)



White solid (127 mg, 0.65 mmol, 67%); ν_{max} (film/cm^{-1}) 3132, 3072, 1633, 1504, 1474, 1445, 1370, 1352, 1270, 1143, 1080, 916; δ_H (600 MHz, $CDCl_3$) 6.78 (1H, t, J = 6.7, H6), 7.17 (1H, ddd, J = 9.1, 6.7, 1.0, H7), 7.33 (1H, t, J = 7.4, ArH), 7.44 (2H, t, J = 7.7, 2 × ArH), 7.63 (1H, d, J = 9.1, H8), 7.87 (1H, s, H3), 7.96 (2H, d, J = 7.4, 2 × ArH), 8.12 (1H, d, J = 6.7, H5); δ_C (150 MHz, $CDCl_3$) 108.2, 112.6, 117.7, 124.8, 125.7, 126.2, 128.1, 128.8, 133.9, 145.8, 145.9; Found (EI): $[M]^+$ 194.08411, $C_{13}H_{10}N_2$ requires 194.08385

2-(Thiophen-3-yl)imidazo[1,2-a]pyridine (552)



Off-white solid (52 mg, 0.26 mmol, 27%); ν_{max} (film/cm^{-1}) 3124, 3085, 1631, 1507, 1493, 1475, 1339, 1306, 1270, 1240, 855; δ_H (300 MHz, $CDCl_3$) 6.78 (1H, td, J = 6.8, 1.1, H6), 7.17, (1H, ddd, J = 9.1, 6.8, 1.2, H7), 7.39 (1H, dd, J = 5.0, 3.0, H4'), 7.52 (1H, dd, J = 5.0, 1.3, H5'), 7.61 (1H, d, J = 9.1, H8), 7.75 (1H, s, H3), 7.81 (1H, dd, J = 3.0, 1.3, H2'), 8.10 (1H, dt, J = 6.8, 1.2, H5); δ_C (150 MHz, $CDCl_3$) 108.2, 112.6, 117.4, 121.6, 125.0, 125.7, 126.0, 126.3, 135.5, 142.0, 145.5; Found (EI): $[M]^+$ 200.04062, $C_{11}H_8N_2S$ requires 200.04027

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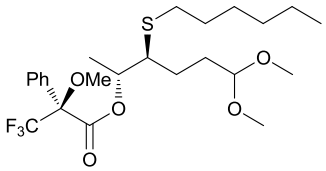
Appendix

General procedure for Mosher's esters preparation

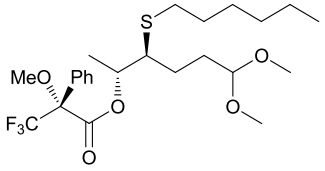
A solution of alcohol (1 eq) and (*S*) or (*R*)–MTPA (3 eq) in DCM (0.2 M) was stirred at RT. EDCI·HCl (3 eq) was added, followed by DMAP (3.3 eq) and the resulting solution was stirred at RT for 24 hr. The mixture was partitioned between water and DCM; the phases were separated and the organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (Pet/EtOAc).

(*S*)-(2*R*,3*S*)-3-(Hexylsulfanyl)-6,6-dimethoxyhexan-2-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (237m1)



ν_{max} (film/cm^{-1}) 2932, 2856, 1744, 1599, 1521, 1451, 1379, 1257, 1181, 1123; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, J = 7.0, CH_2CH_3), 1.24-1.38 (8H, m, $(CH_2)_3CH_3$, $SCHCH_2$), 1.47 (3H, d, J = 6.3, $CHCH_3$), 1.55-1.67 (3H, m, $CHHCH(OMe)_2$, SCH_2CH_2), 1.88-1.97 (1H, m, $CHHCH(OMe)_2$), 2.36 (1H, dt, J = 12.1, 7.4, $SCHH$), 2.43 (1H, dt, J = 12.1, 7.4, $SCHH$), 2.61 (1H, ddd, J = 3.5, 5.3, 9.6, SCH), 3.30 (3H, s, 3 × $CH(OMe)_2$), 3.31 (3H, s, 3 × $CH(OMe)_2$), 3.60 (3H, s, COMe), 4.29 (3H, t, J = 5.5, $CH(OMe)_2$), 5.25 (1H, dq, J = 11.9, 6.1, OCH), 7.40-7.43 (3H, m, 3 × ArH), 7.56-7.58 (2H, m, 2 × ArH); δ_C (125 MHz, $CDCl_3$) 14.1, 17.1, 22.6, 25.9, 28.6, 29.7, 30.1, 31.4, 32.0, 50.4, 52.6, 53.0, 55.6, 76.1, 84.4 (q, J_{CF} = 28), 104.3, 123.5 (q, J_{CF} = 290), 127.3, 128.4, 129.6, 132.5, 166.0; Found (TOF-MS): $[M\text{-}OMe]^+$ 463.2111, $C_{23}H_{34}O_4F_3S$ requires 463.2130.

(*R*)-(2*R*,3*S*)-3-(Hexylsulfanyl)-6,6-dimethoxyhexan-2-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (237m2)



ν_{max} (film/cm^{-1}) 2931, 2860, 1744, 1599, 1521, 1451, 1379, 1256, 1181, 1123; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, J = 7.0, CH_2CH_3), 1.25-1.43 (8H, m, $(CH_2)_3CH_3$, $SCHCH_2$), 1.37 (3H, d, J = 6.3, $CHCH_3$), 1.52 (1H, m, $CHHCH(OMe)_2$), 1.65-1.75 (2H, m, $SCHCH_2$), 1.94-1.98 (1H, m, $CHHCH(OMe)_2$), 2.51 (2H, t, J = 7.4, SCH_2), 2.67-2.72 (1H, m, SCH), 3.32 (3H, s, 3 × $CH(OMe)_2$), 3.33 (3H, s, 3 × $CH(OMe)_2$), 3.58 (3H, br s, COMe), 4.35 (1H, t, J = 5.4, $CH(OMe)_2$), 5.28 (1H, qd, J = 6.3, 4.7, OCH), 7.39-7.44 (3H, m, 3 × ArH), 7.58-7.60 (2H, m, 2 × ArH); δ_C (150 MHz, $CDCl_3$) 14.1, 17.3, 22.7, 25.6, 28.6, 29.7, 30.2, 31.4, 31.9, 41.4, 49.7, 51.0, 52.6, 55.6, 75.5, 80.9, 84.8 (q, J_{CF} = 27), 104.3, 123.5 (q, J_{CF} = 291), 127.6, 128.5, 128.7, 132.2, 166.2; Found (TOF-MS): $[M\text{-}OMe]^+$ 463.2145, $C_{23}H_{34}O_4F_3S$ requires 463.2130.

Determination of the configuration of the secondary alcohol 237

The Mosher's esters analysis is based on the differences in chemical shifts of the following signals for the two diastereoisomers:

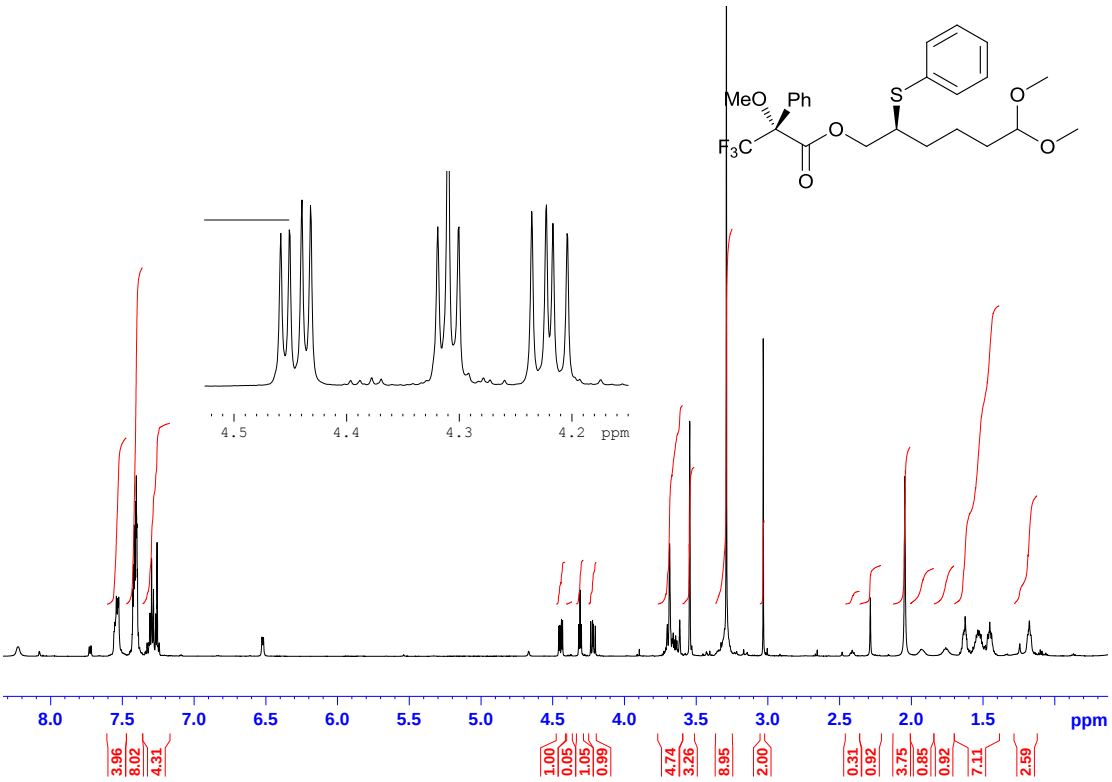
Proton	δ_S (**237m1**)	δ_R (**237m2**)	$\Delta_{(S-R)}$	Freq (400 MHz)
1	1.47	1.37	0.1	+ 40
2	5.25	5.28	-0.03	-12
3	2.61	2.69	-0.08	-32
S-CH$_2$	2.40	2.51	-0.09	-36
6	4.29	4.35	-0.06	-24

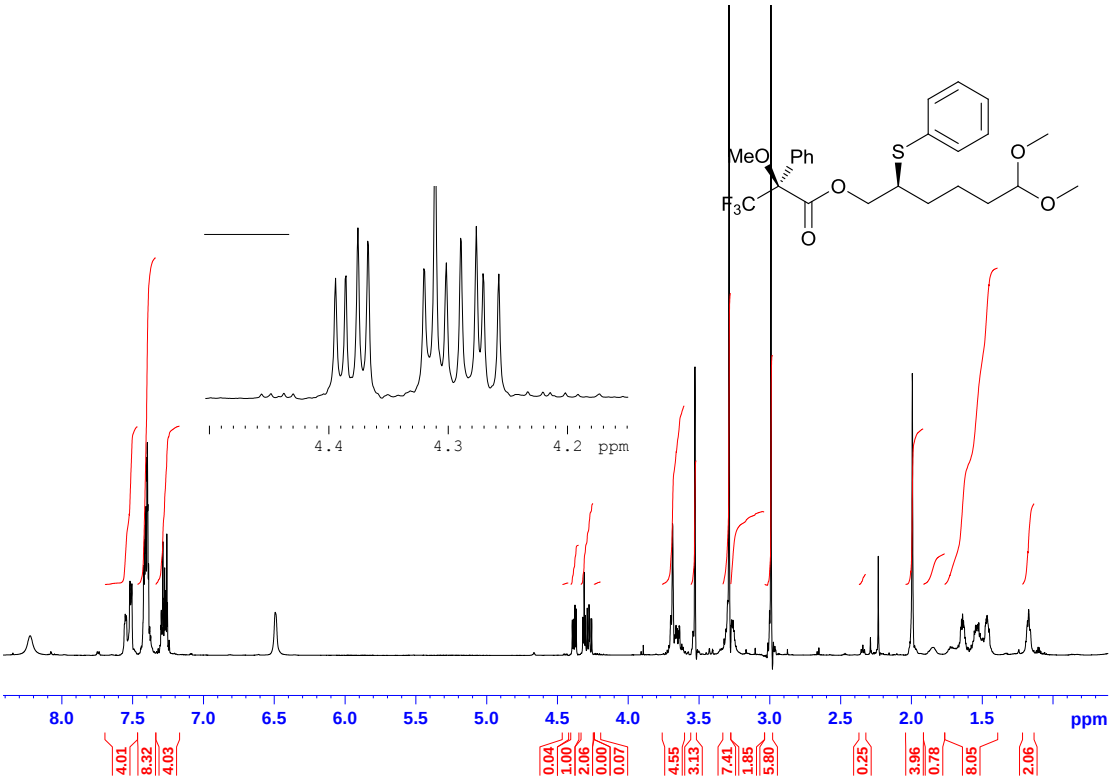
From the difference in the frequencies observed above, the configuration of the secondary alcohol can be assigned as (*R*).

Determination of the enantiomeric ratios of alcohols obtained with the Mosher's esters analysis.

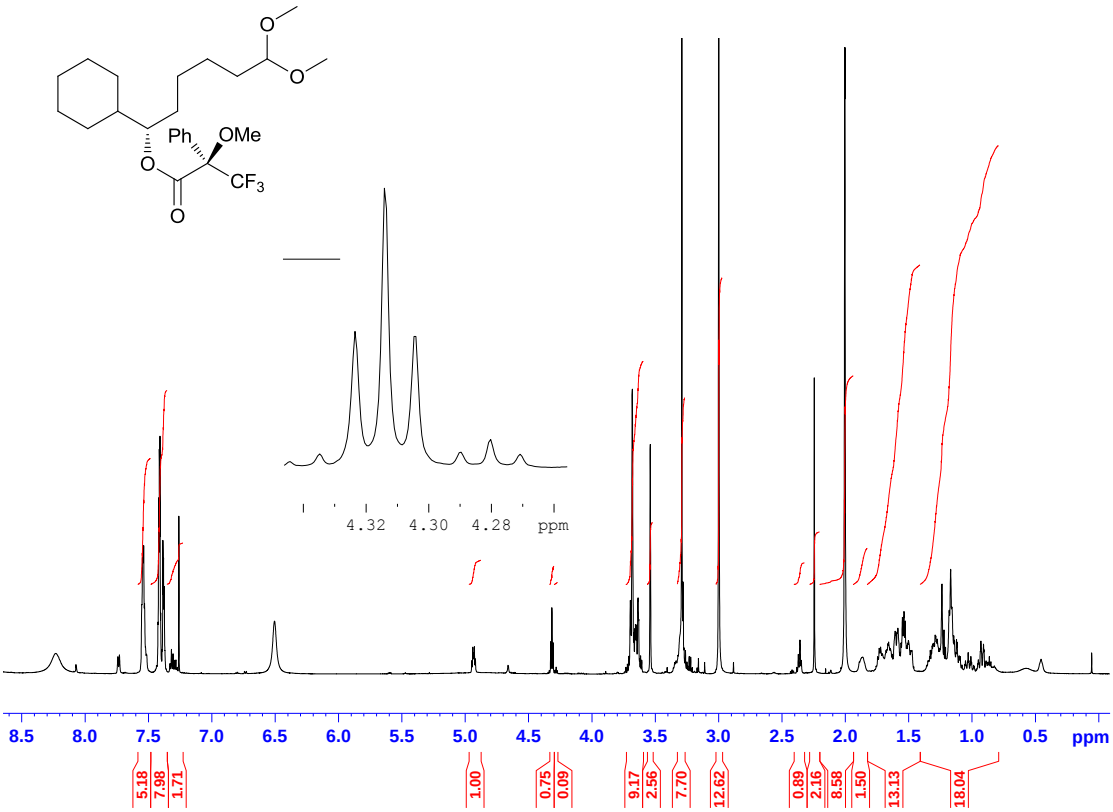
Esters were prepared according to the general procedure. After extraction, the crudes was analysed either by ^{1}H or ^{19}F-NMR. The enantiomeric ratio was determined from the integration of the peaks of the two diastereoisomers (peaks expanded in the NMR spectra).

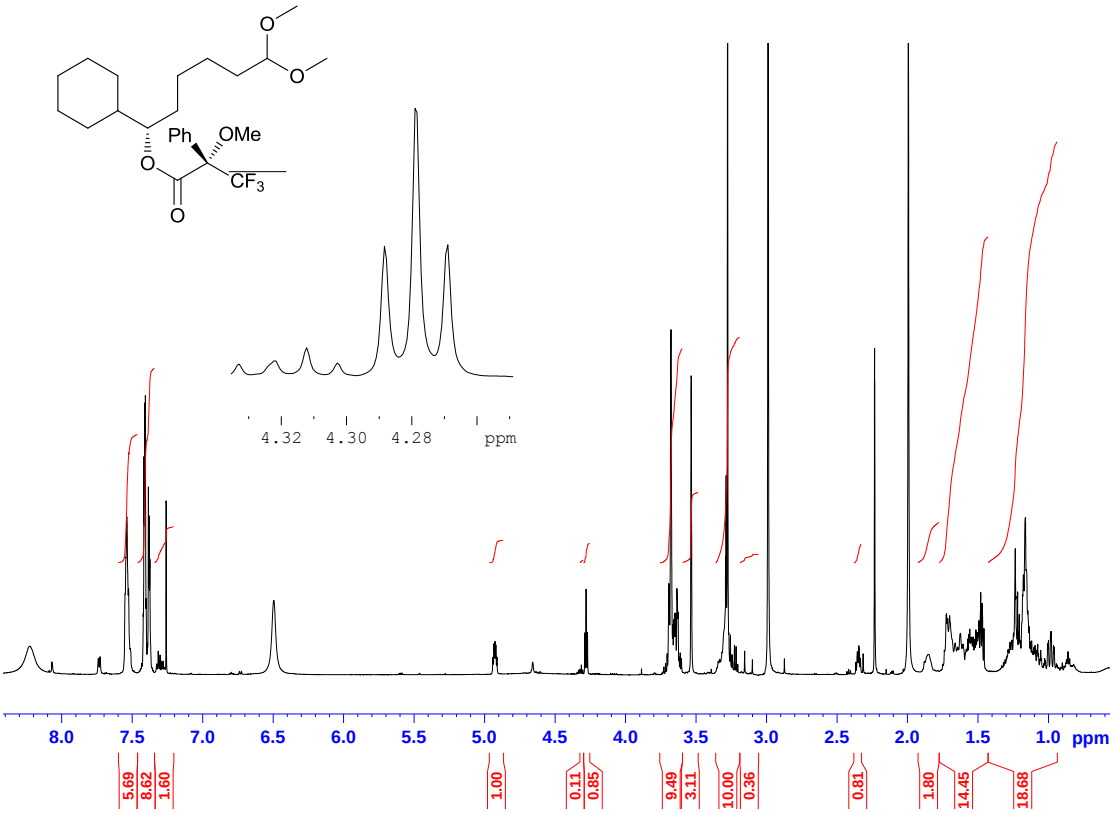
Determination of the er of alcohol 464



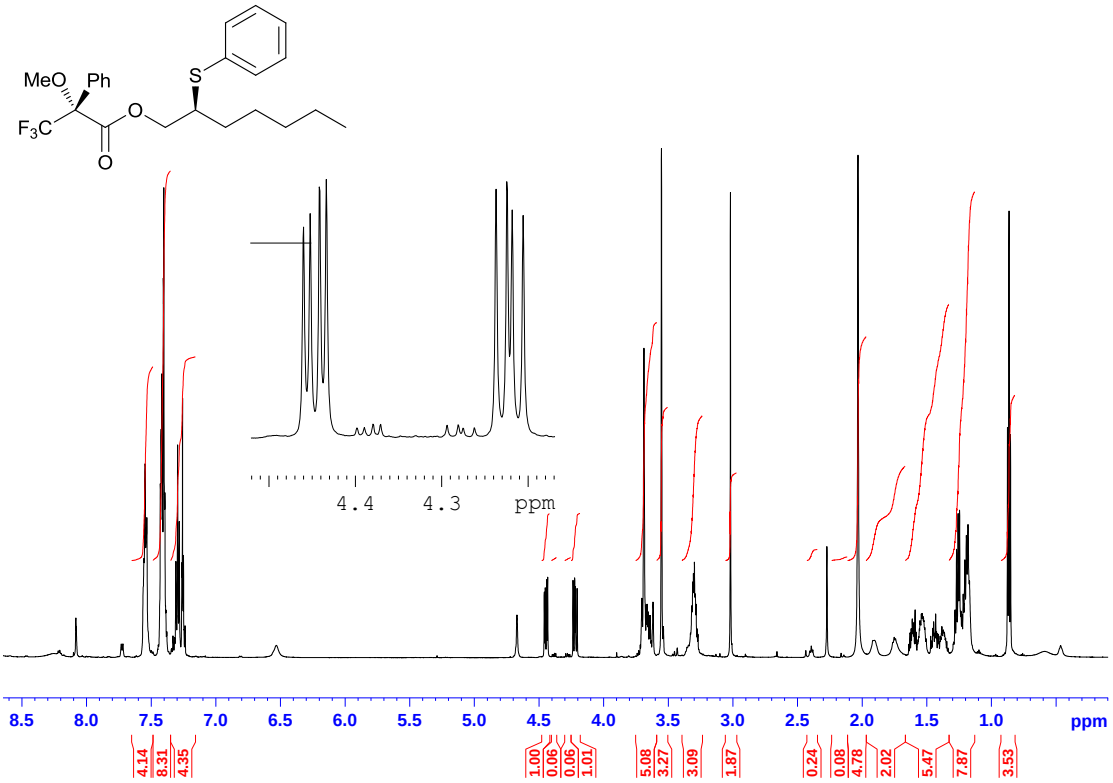


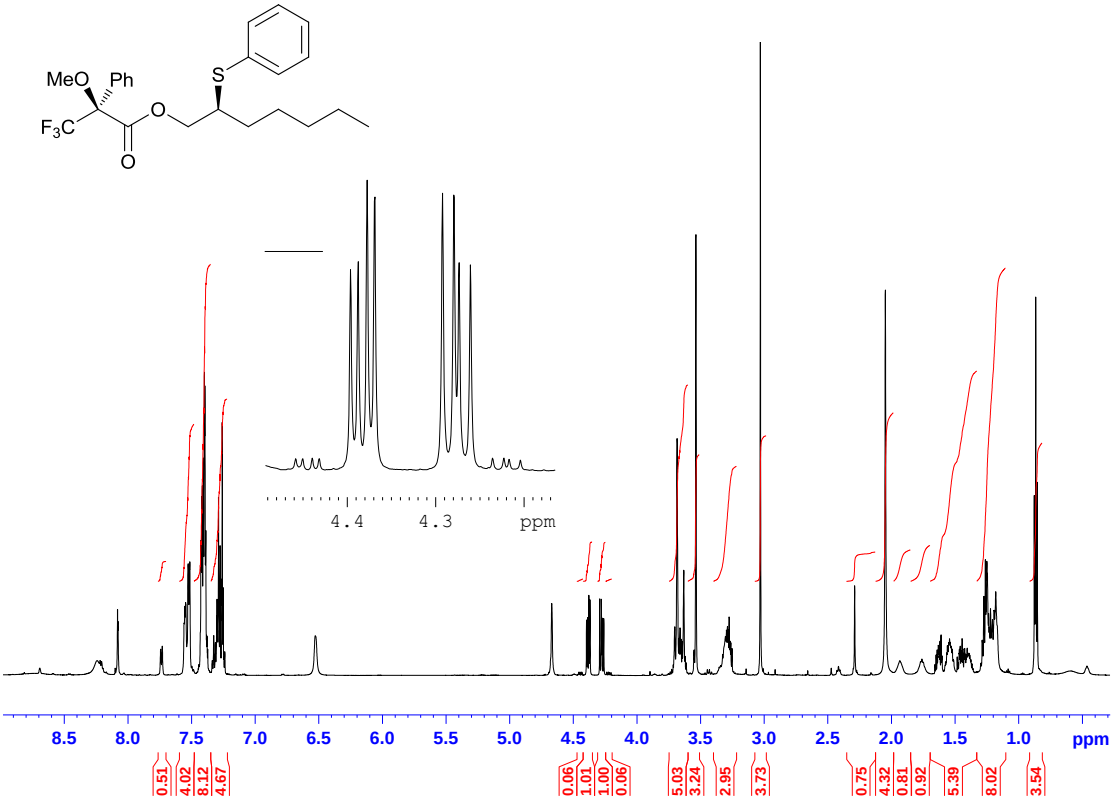
Determination of the er of alcohol 467



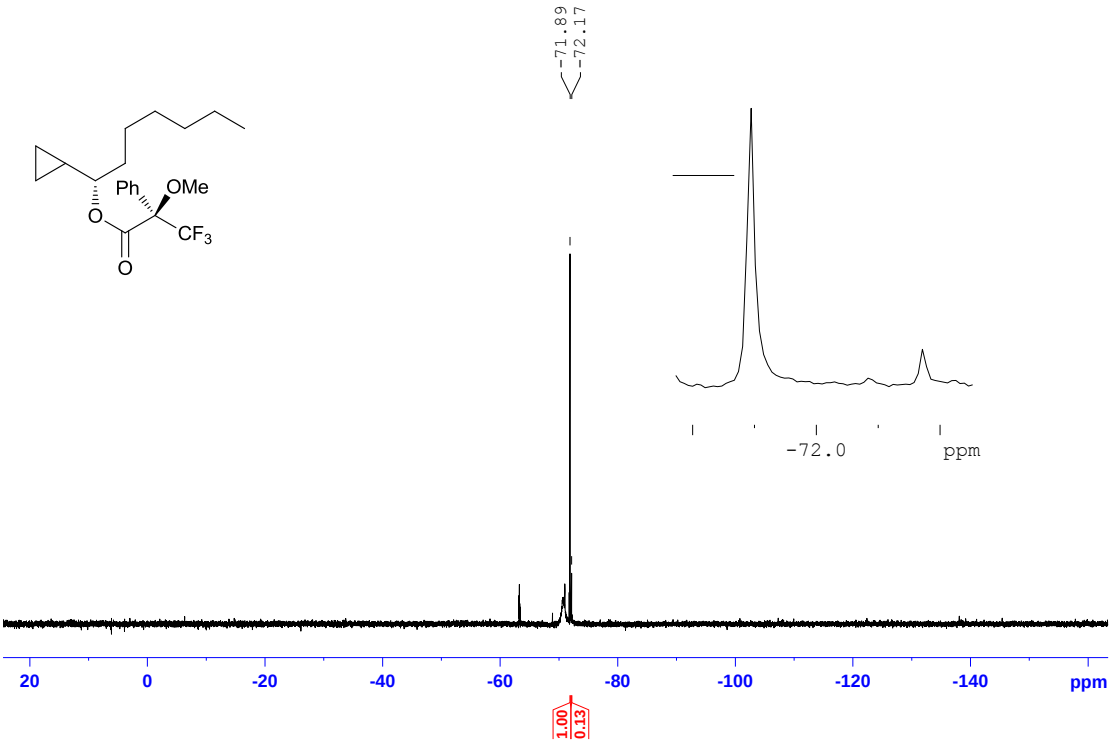


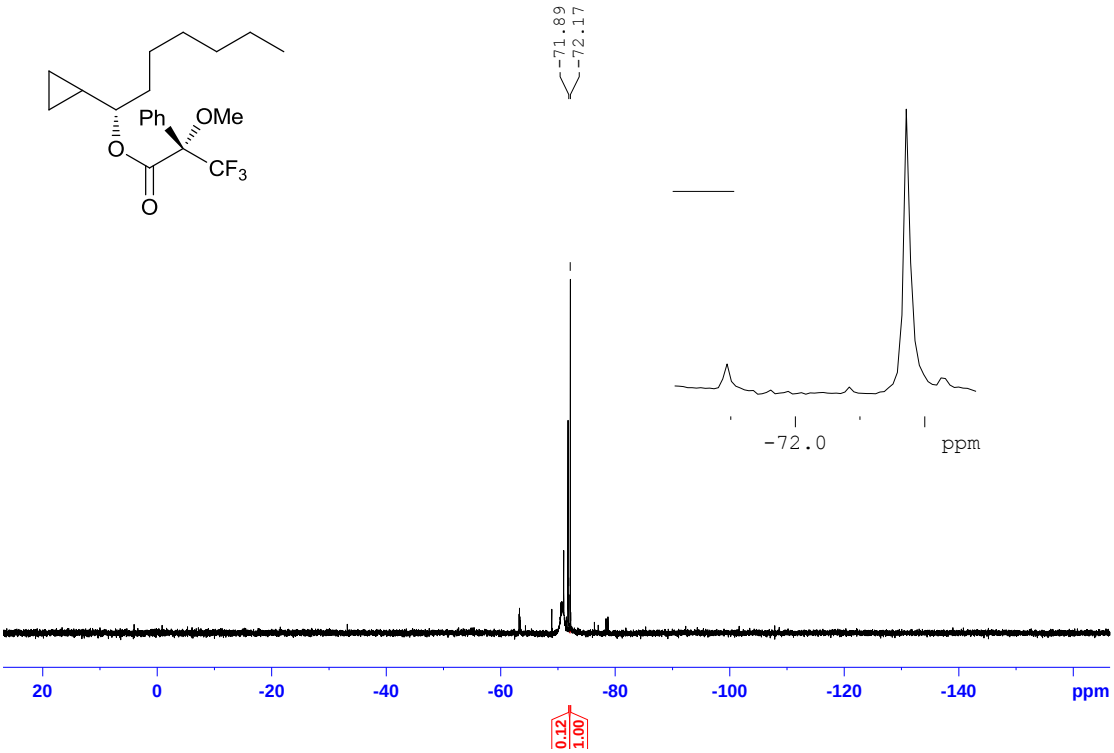
Determination of the er of alcohol 469a



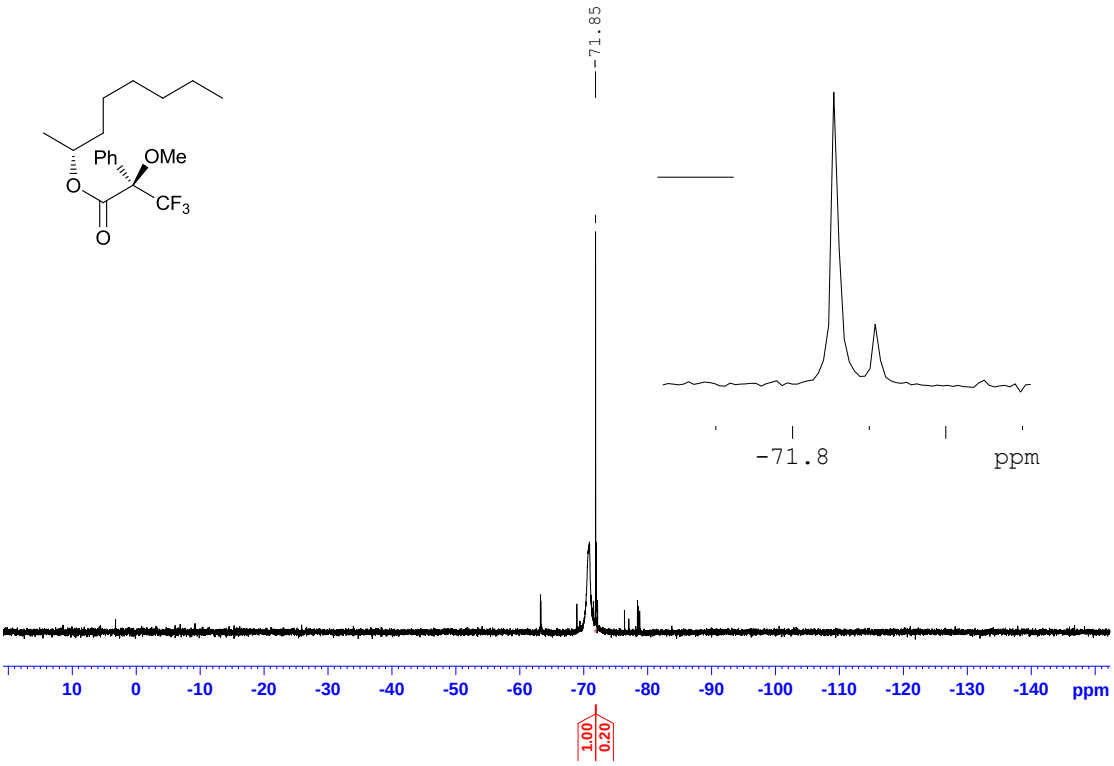


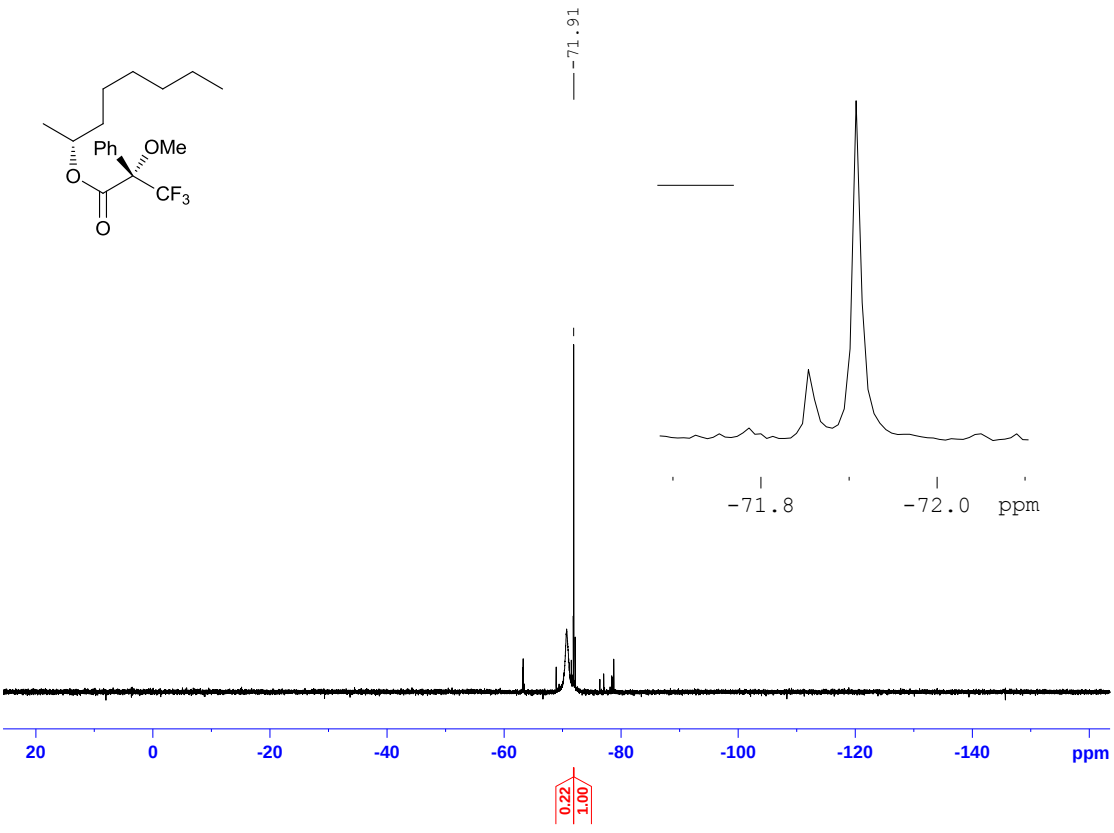
Determination of the er of alcohol 470b



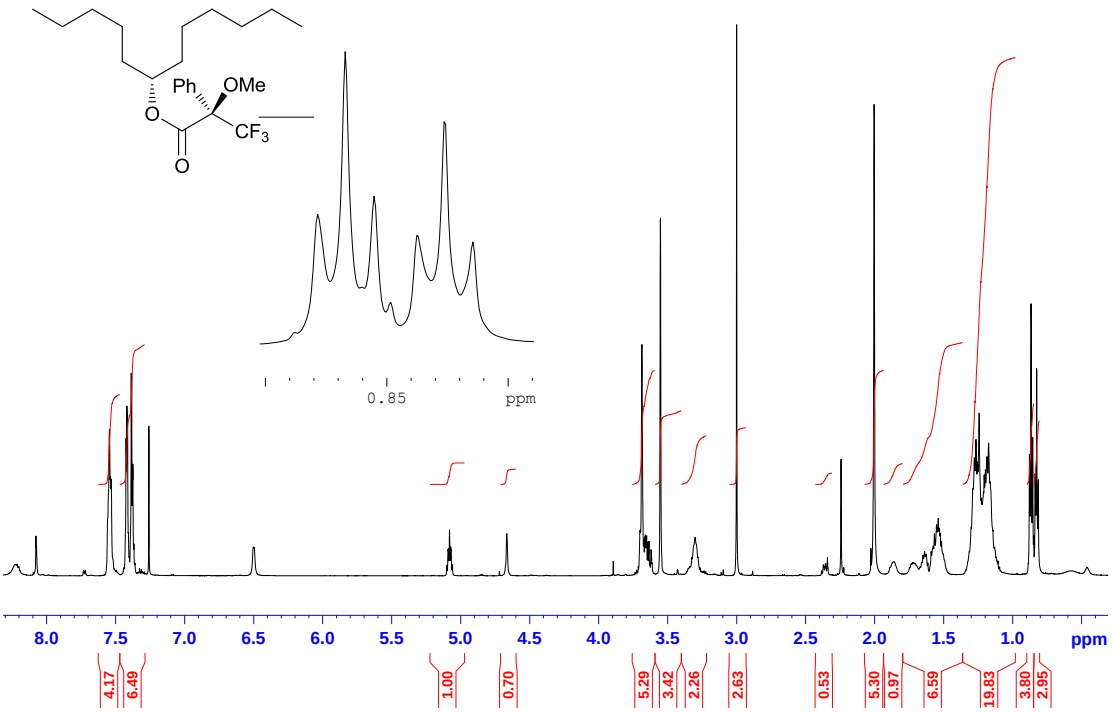


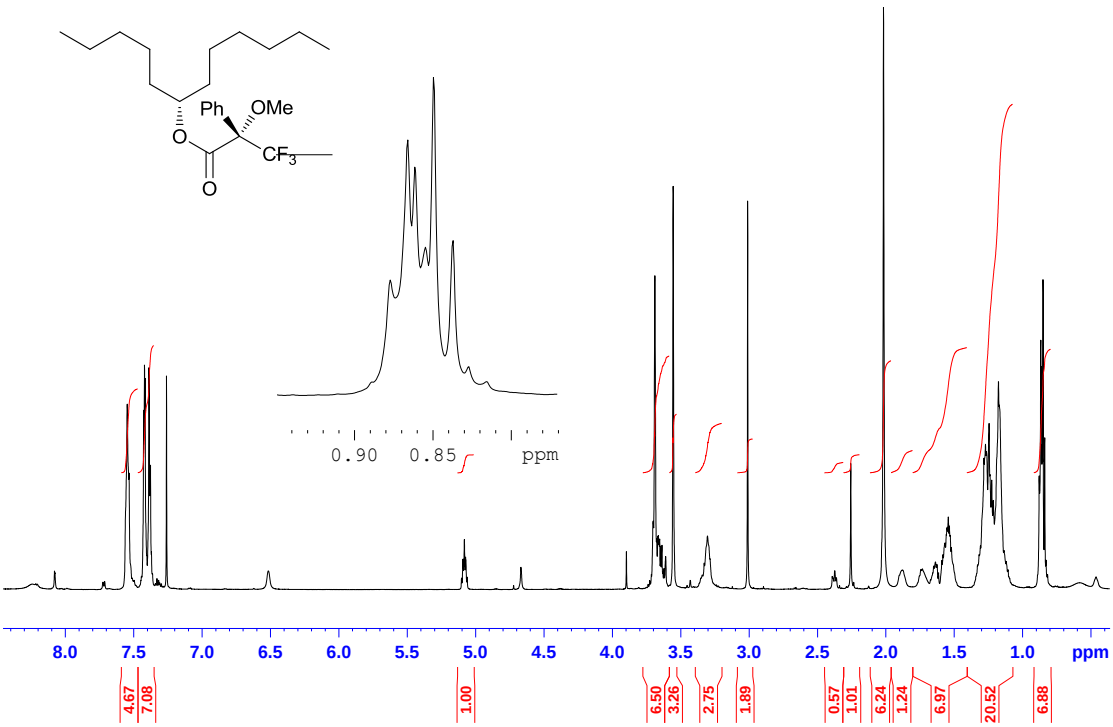
Determination of the er of alcohol 470c



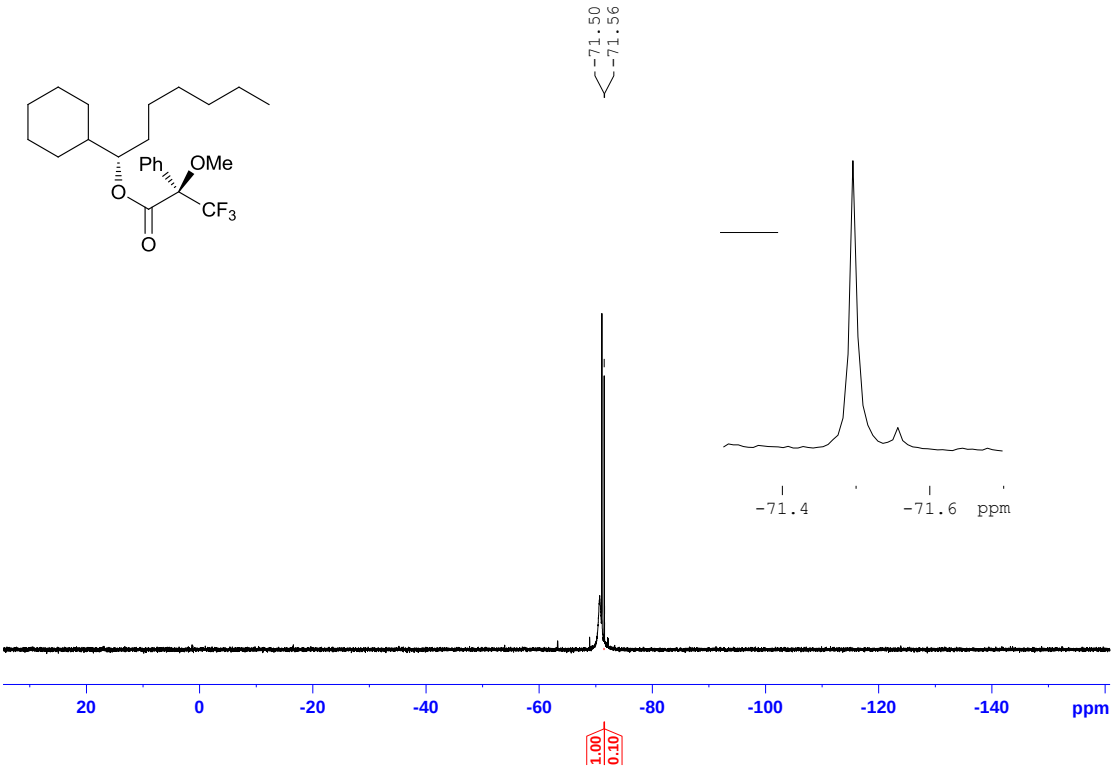


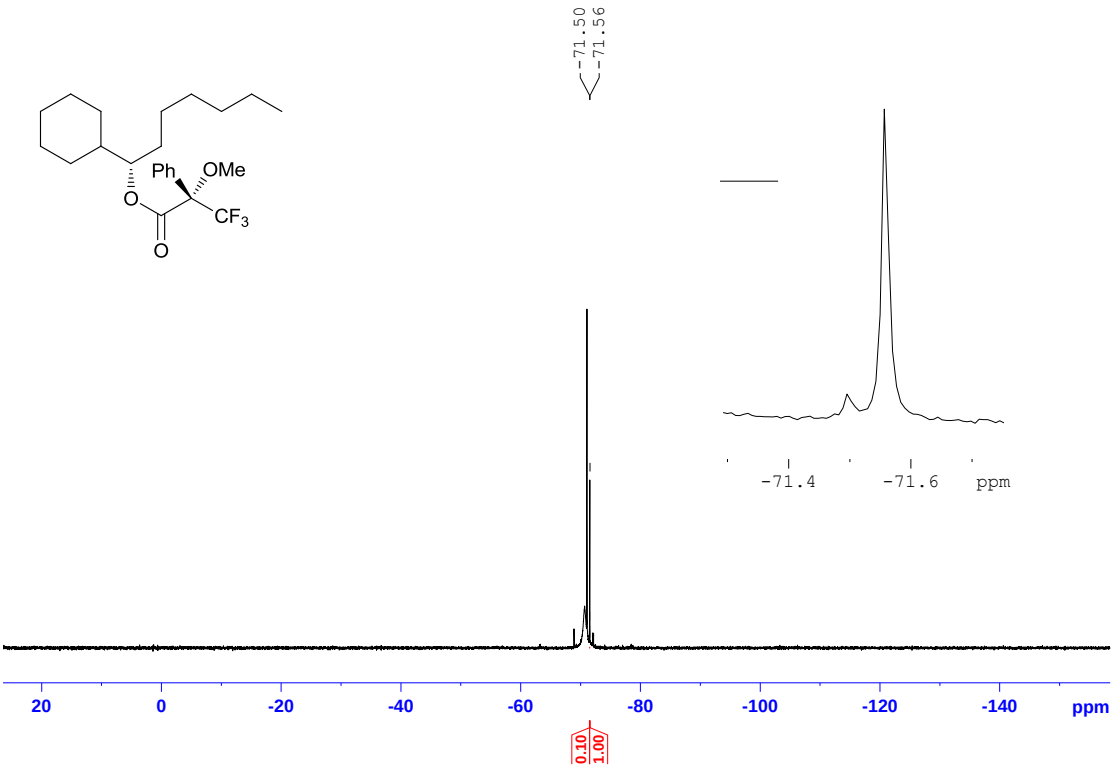
Determination of the er of alcohol 470d



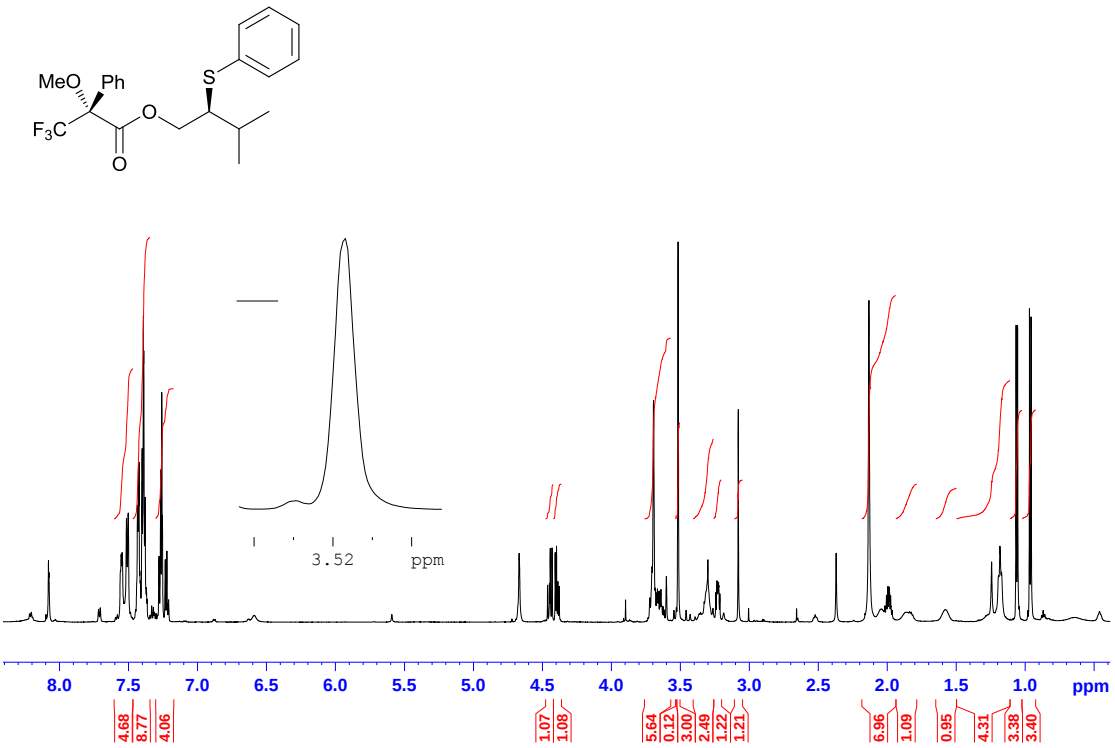


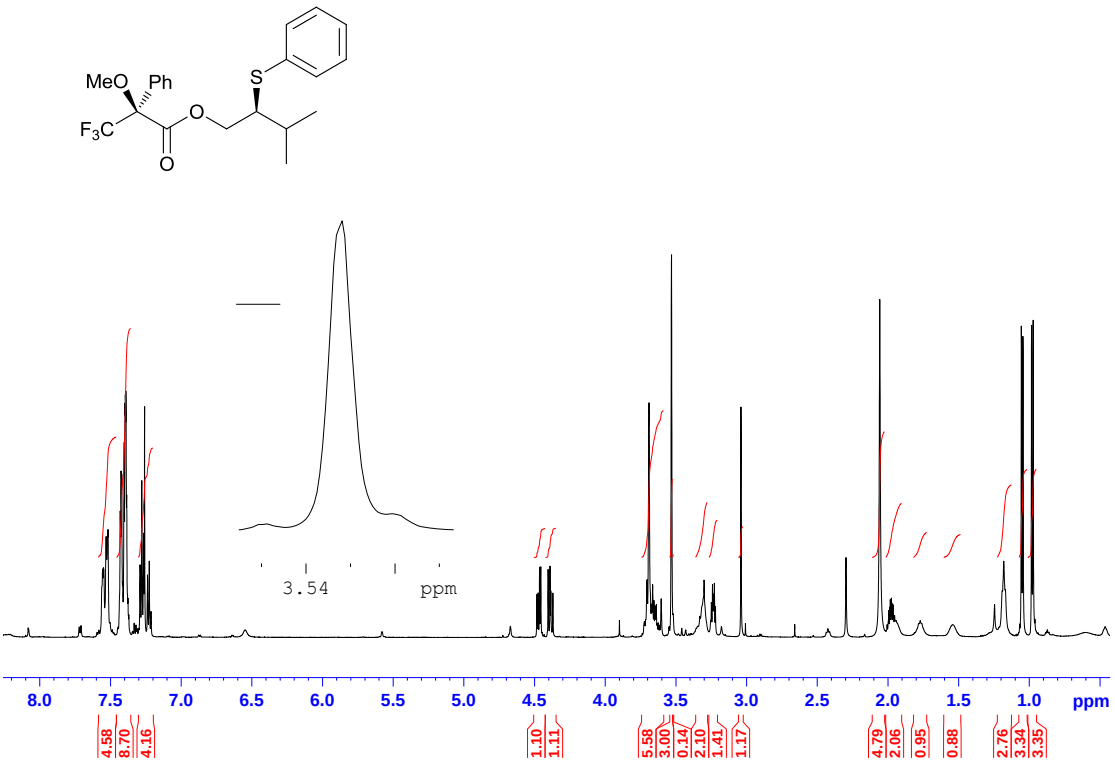
Determination of the er of alcohol 470f



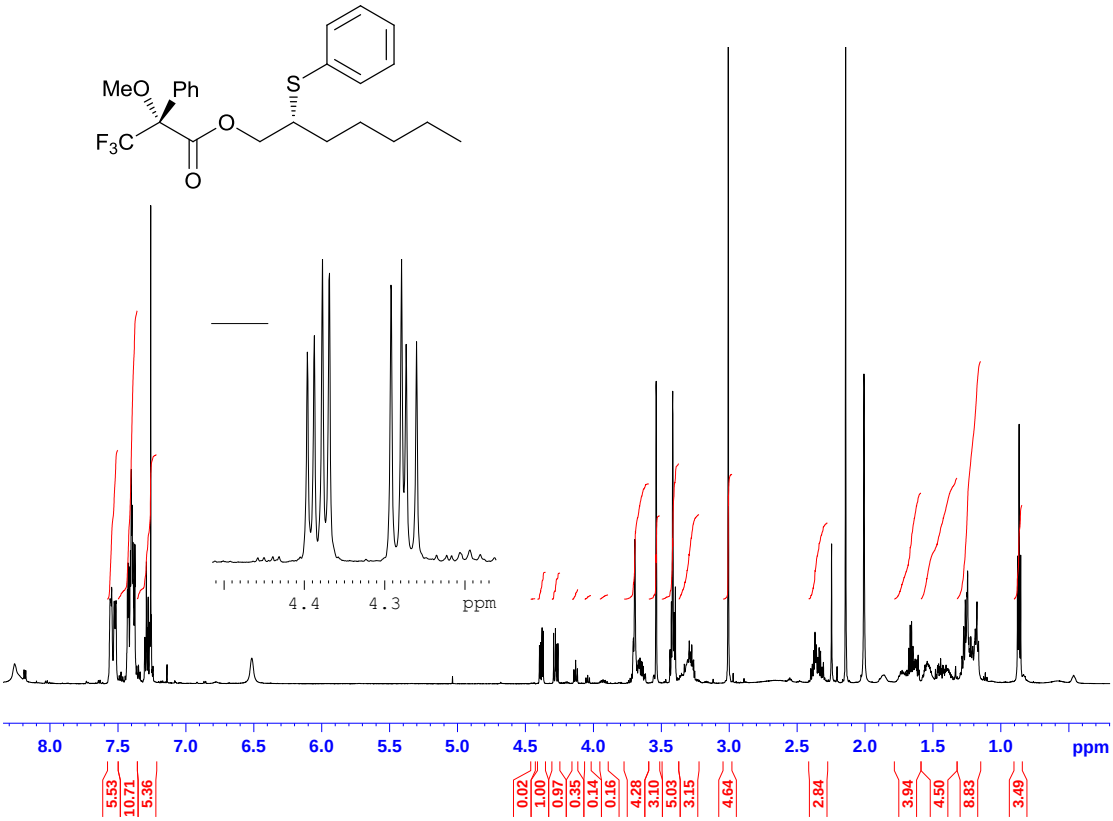


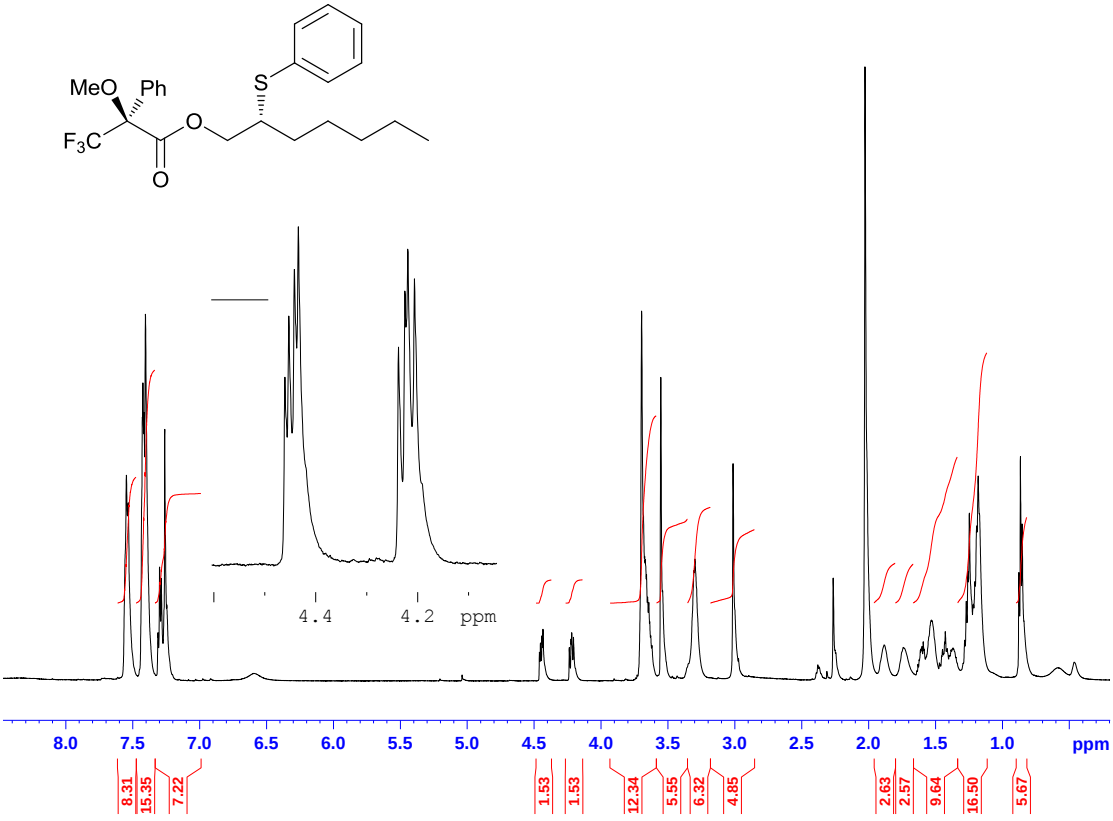
Determination of the er of alcohol 473





Determination of the er of alcohol 475a





Determination of the er of alcohol 476a