Studies towards the first synthesis of tetronothiodin

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Studies towards the first synthesis of tetronothiodin

by

David Foley

A doctoral thesis

Submitted in partial fulfilment of the requirements

For the award of

Doctor of Philosophy of Loughborough University

22nd April 2009

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Abstract

Studies Towards The First Synthesis of Tetronothiodin

David Foley

Key Words. Tetronothiodin, Cholecystokinin, Tetrahydrothiophene, 1,3-Dipolar Cycloaddition, Thiocarbonyl Ylide.

Cholecystokinin (CCK) is a 33 amino acid peptide which acts as a digestive hormone in peripheral tissues and functions as a neurotransmitter, widely distributed throughout the brain and central nervous system. Two types of CCK receptors exist, those primarily located in peripheral tissues, CCK1 receptors, and those primarily located in the brain and central nervous system, CCK2 receptors.

Tetronothiodin 1 is a recently discovered potent CCK2 receptor antagonist isolated from the culture Streptomyces sp NR0489. It consists of an oxaspirobicyclic unit and a functionalized tetrahydrothiophene moiety, linked by a macrocyclic framework.

This thesis details the first studies towards the synthesis of the substituted tetrahydrothiophene moiety of tetronothiodin. Four different approaches were attempted; a route in which the key step proceeded via a nitro-aldol reaction, a dicarboxylic acid cyclisation route, cyclisations of substituted butadienes, and finally 1,3-dipolar cycloaddition reactions of novel thiocarbonyl ylides and dipolarophiles.
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Chapter 1

Introduction
1.1 Cholecystokinin

Cholecystokinin (CCK) 1 is a major intestinal peptide hormone, which acts as a regulator in peripheral tissues, where it affects factors such as gut motility and gallbladder contraction, by stimulating the release of digestive enzymes from the pancreas and bile from the gallbladder. It is also a neuropeptide, widely distributed throughout central tissues such as the brain and central nervous system, where it is proposed to play a role as a neurotransmitter or neuromodulator.

Cholecystokinin is a linear 33 amino acid peptide containing a carboxyl-terminal pentapeptide amino acid sequence, similar in structure to gastrin. It was first discovered in the 1920’s and finally isolated and purified from brain tissue in 1975 by Vanderhaeghen et al.

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1

The 33 amino acid peptide Cholecystokinin

1.1.2 CCK peptide fragments

CCK also exists in truncated peptide fragments, units of CCK-5 and CCK-4 occur, the 4 amino acid residue being the smallest peptide to exhibit a high binding affinity for CCK receptors. CCK-4 is also identical in structure to tetragastrin (G-4) 2, as both cholecystokinin and gastrin share a common terminal amino acid sequence.
The 4 amino acid residue CCK-4 and tetragastrin

However, the most abundant naturally occurring forms of the CCK peptide are CCK-58 and the sulfated octapeptide CCK-8S. These residues are derived from the 115-amino acid peptide preprocholecystokinin.

These 8 amino acid residues in both the sulfated (CCK-8S) and non-sulfated (CCK-8NS) forms are responsible for the majority of the CCK-induced gastrin-like activity in the brain. Other less common molecular forms of CCK have also been identified, including CCK-5, CCK-12 and CCK-21, all of which share the same C-terminal pentapeptide sequence, which is essential for activity.

1.1.3 CCK as a peripheral hormone

CCK is a hormone secreted by the endocrine cells of the anterior pituitary gland and is regulated by hypothalamic hormones. CCK is released into the bloodstream by these cells in response to stimuli such as food intake, and is
transported to the duodenum, where it exerts its effects by binding selectively to specific protein molecules known as CCK receptors.

CCK was originally named cholecystokinin-pancreozymin as it was identified in porcine intestine extracts. It is the main hormonal regulator of pancreatic enzyme secretion, and stimulates the delivery of digestive enzymes from the pancreas into the duodenum. These pancreatic enzymes are large proteins that are essential for digestion and include proteases such as carboxypeptidase, which break down peptide fragments into individual amino acids, pancreatic amylase which degrades starch and glycogen, pancreatic lipase which breaks down triglyceride into free fatty acids, as well as several nucleases and elastases. The release of these enzymes allows food to be broken down and converted into the necessary components to be absorbed by the body, such as amino acids, monosaccharides and fatty acids.

The release of cholecystokinin into the gastrointestinal tract also stimulates the contraction of the gallbladder, in fact the name cholecystokinin is derived from the Greek “gallbladder movement”. This contraction leads to the delivery of bile into the duodenal area of the small intestine. Bile contains bile acids that are critical for digestion and absorption of fats and fat-soluble vitamins. CCK is also responsible for the secretion of gastric acid into the stomach to further aid digestion.

The minimum sequence necessary for high affinity binding in peripheral tissues, retaining full biological activity such as gallbladder contraction, gut motility and pancreas secretion, is the sulfated octapeptide (CCK-8). This is due to the sensitivity of the peripheral receptors to the presence and exact position of the sulfated tyrosine residue. The release of CCK from the neuroendocrine cells is stimulated by feeding induced changes such as pH level, fat content and the presence of certain individual amino acids. Pancreatic enzymes and bile flow lead to digestion and absorption of the molecules that stimulate cholecystokinin.
When absorption is completed, cholecystokinin secretion ceases, halting the release of bile and pancreatic enzymes.

1.1.4 CCK as a neurotransmitter or neuromodulator

Like many substances used as peripheral hormones, Cholecystokinin is also produced by neurons and has been shown to exist in both the central and peripheral nervous systems. It is synthesised within the presynaptic neuron and released into the synapse, causing CCK to diffuse across the synaptic cleft and bind to the receptor located on the adjacent neuron, so acting as a neurotransmitter.

The concentration of CCK in the brain exceeds that of all other neurotransmitters, and it is located in several regions, including all layers of all regions of the cerebral cortex, the hippocampus, piriform, anterior cingulate and prefrontal cortices, the olfactory and subicular cortices and the basal ganglia spinal cord. CCK coexists in large regions of the brain with other neurotransmitters, most notably dopamine. CCK also acts as a neuromodulator, regulating the pathways of other hormones and neurotransmitters such as glutamate, dopamine, serotonin (5-HT), endogenous opioid, and γ-aminobutyric acid (GABA).

CCK in the brain exists as a variety of analogues, the most common being the sulfated CCK-8, which is responsible for approximately 75% of the CCK-induced activity. However, in contrast to the peripheral tissues, smaller fragments such as the tetrapeptide CCK-4 as well as the non-sulfated CCK-8NS are sufficient for binding, albeit less potently than CCK-8.
1.2 CCK receptor subtypes

The existence of two distinct CCK receptor subtypes was suggested by Innis and Snyder in a study into the binding affinities of differing CCK fragments to rat pancreatic and guinea pig brain tissue.\(^8\) They reported that both gastrin and pentagastrin exhibited a nanomolar binding affinity towards brain tissue, while the two peptides are inactive towards pancreatic tissue. However both tissues responded in the same manner to the CCK-8 and CCK-8NS peptides, with both receptors showing far greater sensitivity to the sulfated octapeptide, suggesting some similarities between the receptors.

The presence of these two distinct CCK receptors was later confirmed by the determination of their molecular masses\(^20\) and detailed radio-ligand binding studies,\(^4,21,22\) which demonstrated the relative binding affinity of the two receptors to a variety of CCK peptide fragments. These radio-ligand binding studies were undertaken using radiolabelled CCK peptide fragments of differing lengths, typically \(^{[125]}\text{I}\text{CCK-33}\) or \(^{[3]}\text{H}\text{CCK-8}\). These radio-ligands were then used in competitive binding studies with a range of unlabelled ligands, and used to calculate the IC\(_{50}\), or half maximal inhibitory concentration, of the unlabelled ligand. The IC\(_{50}\) concentration is that concentration of the unlabelled ligand that blocks 50% of the specific binding of the radiolabelled ligand, and is a measure of the binding affinity or potency of a ligand. The receptors isolated from pancreatic and brain tissue were found to have markedly differing binding affinities for the CCK-8, CCK-8NS and CCK-4 subunits, further confirming the presence of two distinct subtypes.

The two receptor subtypes were originally classified as CCK\(_A\) for receptors found in the alimentary canal, and CCK\(_B\) for brain receptors\(^23\) Peripherally circulating CCK is rapidly metabolized and is unable to cross the blood-brain barrier, resulting in two distinct functional CCK pools in the periphery and central nervous system serving the two receptor types\(^24\) However, the classification of CCK\(_A\) and CCK\(_B\) was an oversimplification Radio-ligand
binding studies can also give accurate information about the location of receptors through autoradiography, and this technique revealed the presence of two CCK receptor types within the brain. One was relatively non-specific in its binding affinity for varying CCK fragments, while the other exhibited the same degree of specificity as the receptors found in peripheral tissue. This also raised the possibility of peripherally circulating CCK reaching receptors located within the central nervous system. CCKB receptors have also been identified within the pancreas and digestive tract, and together these findings led to the reclassification of the receptor subtypes to better reflect their distribution.

In keeping with guidelines set by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification, the receptors were renamed with a numerical subscript corresponding to the chronological order of the formal demonstration of their existence by cloning and sequencing. As the CCKA receptor was the first to be cloned, it was renamed CCK1, with CCKB receptors becoming CCK2. Little information is known on the structures of the receptors, with only their amino acid sequences known. Elucidation of the secondary and tertiary structures by X-ray or NMR techniques has yet to be successfully completed, due to insufficient quantities of sufficiently pure samples.

1.2.1 CCK1 receptors

CCK1 receptors are the predominant receptors in the peripheral tissues, most notably the pancreatic acinar cells, gallbladder and gastric smooth muscle cells and the vagus nerve. They are responsible for mediating the secretion of pancreatic enzymes, gallbladder contraction, gastric emptying and intestinal motility as described above. CCK1 receptors are also found in the brain, although with limited distribution, and tend to be found in regions where the blood-brain barrier is relatively porous, allowing access to peripherally circulating CCK. These regions include the posterior hypothalamic nucleus,
the interpeduncular nucleus (IPN); the nucleus tractus solitarius (NTS), and the anterior pituitary (AP), which is responsible for the release of several major hormones. The precise distribution of the receptors is species-dependent however, with a much higher prevalence and broader distribution of CCK$_{1}$ receptors in primates and humans than in rodents.

CCK$_{1}$ receptors are also expressed in several tumours, including pancreatic adenocarcinomas and meningiomas, pancreatic carcinomas and lung cancer cell lines. They have also been discovered in oesophageal, gastric and colon cancers.

CCK$_{1}$ receptors exhibit binding specificity for the terminal heptapeptide of CCK, enabling differentiation between CCK, smaller CCK peptide fragments and gastrin. In addition, CCK$_{1}$ receptors show a high degree of selectivity for the sulfated octapeptide CCK-$8$ over the non-sulfated CCK-$8$NS.

1.2.2 CCK$_{2}$ receptors

CCK$_{2}$ receptors are the predominant receptor type present throughout the central nervous system and brain. They are widely distributed throughout the brain, most notably in the cerebral cortex, olfactory bulbs, hippocampus and nucleus accumbens, where their role differs according to their location. CCK$_{2}$ receptors within these non-porous regions of the brain and CNS are isolated from the circulating CCK and gastrin in the peripheral tissues by the blood-brain barrier, and therefore are responsive only to neuropeptide CCK. Within peripheral tissues, CCK$_{2}$ receptors are mainly located in smooth muscle cells throughout the gastrointestinal tract, pancreatic acinar cells, T lymphocytes and chief cells of the gastric mucosa.
CCK2 receptors have also been identified within tumours, including medullary thyroid, gastric, colon, ovarian and small cell lung carcinomas, as well as certain pancreatic and lung cancer cell lines.35

In contrast to CCK1 receptors, CCK2 receptors are relatively non-specific. They exhibit binding towards various CCK peptide fragments, including both the sulfated and non-sulfated CCK-8 residues as well as CCK-4, the smallest active CCK peptide, and gastrin.21 This difference between the receptors provides a useful tool in determining both the location and individual role of the receptor subtypes.

1.3 Receptor agonists and antagonists

Receptors are small protein molecules, usually located within the cell membrane, that bind with substances such as hormones, antigens, drugs, or neurotransmitters. They are usually specific to a certain compound or class of compounds. Molecules which bind to these receptors and initiate a standard change in the cell function are called agonists. The potency of a receptor agonist is determined by two factors: the binding affinity, that is the tendency of the agonist to bind to the receptor, and the efficacy of the agonist, the measure of the agonist’s ability to initiate a response from the receptor once bound.

A substance that inhibits the normal physiological function of the receptor is called an antagonist. There are two main ways in which a receptor antagonist can act, either by direct competition with an agonist for a receptor binding site, or by indirect interference with the natural action of the receptor. Antagonists that compete with an agonist for a receptor are called competitive antagonists. They bind to the receptor in the same manner as an agonist but do not activate them. Those that antagonize by other means are non-competitive antagonists.
Initially, agonists and antagonists are attracted to the receptor by relatively weak long range electrostatic forces. Once bound, their affinity for the receptor will depend on how closely the two structures interact and on the non-covalent bonds that form between the two, such as Van der Waals attractions and hydrogen bonding.

Receptor antagonists play a vital role in determining the location and effects of particular receptor functions. Antagonists can be designed specifically to target receptors of interest and block the natural cell function in order to investigate the individual role of the receptor. It has been demonstrated that some known CCK receptor antagonists have caused an increase in food intake and reduced anxiety, and have displayed an analgesic effect in studies undertaken on rats. These findings suggest possible clinical applications of CCK receptor antagonists, but the precise physiological role of some CCK receptors is not fully understood, due in part to the shortage of potent and highly selective receptor antagonists.

1.4 Therapeutic applications of CCK receptor antagonists

In line with its wide distribution throughout the brain, CNS and peripheral tissues, CCK is involved in a number of essential functions. Numerous clinical and experimental studies have shown that CCK₁ and CCK₂ receptors play a role in the neurobiology of depression, anxiety, nociception, psychosis and cognition. In peripheral tissues they are responsible for the release of the digestive enzyme pancreatic amylase, the contraction of the gallbladder and the transmission of sensory information from the gut to the brain. Further studies remain ongoing, investigating the possible clinical applications of CCK receptor antagonists.

Problems related to CCK can be caused by either excessive or deficient levels of secretion. In humans, CCK deficiency has been described as part of an
autimmune polyglandular syndrome, which is manifested as a malabsorption syndrome clinically similar to pancreatic exocrine insufficiency.\textsuperscript{36} However, the majority of problems are due to excessive production of CCK or excessive assimilation by the receptors within the human brain. This increase in CCK levels in the brain is thought to play a significant role in several types of pathogenesis such as certain panic attacks and anxiety,\textsuperscript{3} schizophrenia,\textsuperscript{37} nociception\textsuperscript{38} and aberrations in feeding behaviour.\textsuperscript{39}

1.4.1 Role of CCK in panic attacks and anxiety

The implication of CCK in anxiety originated in experiments by Bradwejn and de Montigny,\textsuperscript{40} which demonstrated that benzodiazepine receptor agonists could reduce the CCK-induced excitation of neurons in rat hippocampus. Subsequent studies demonstrated that injections of the CCK\textsubscript{2} receptor agonist CCK-4 or pentagastrin provoked panic attacks in patients with panic disorders.\textsuperscript{41} The induced symptoms were comparable to those produced by a standard panic producing agent such as CO\textsubscript{2}, and could be reduced by pharmacological antipanic agents such as antidepressants. Similar panic-inducing effects were observed with the injection of CCK-4 into healthy subjects, though sensitivity to the peptide is markedly increased in patients with a panic disorder, suggesting that the CCK system is altered in panic disorders. The effects of CCK-4 are not limited to panic disorder; patients with other anxiety disorders such as social phobia, obsessive compulsive disorder and premenstrual dysphoric disorder also exhibit a marked behavioural response to the agonist, although the sensitivity to these agents is significantly higher in panic disorder than others in which anxiety is a major factor.\textsuperscript{42} These behavioural effects of CCK administration are accompanied by marked biological alterations, including a significant increase in heart rate, blood pressure and ventilation, along with elevated blood levels of dopamine, adrenalin and noradrenalin.\textsuperscript{43}
Recent research into single-strand conformational polymorphism analysis has indicated a significant association between panic disorder and polymorphism of the CCK₂ receptor gene. A repeat polymorphism in the promoter region of the gene is different in patients compared to control subjects, suggesting that CCK₂ receptor gene variations may be a factor in the neurobiology of panic disorder.

1.4.1.1 Application of CCK receptor antagonists in panic disorders

Studies into the neurobiological mechanisms by which CCK-4 and other agonists provoke panic have indicated that selective stimulation of CCK₂ receptors occurs. The anxiolytic effect of CCK₂ receptor antagonists has been investigated in several animal studies such as the ‘elevated plus maze’ test, in which rats treated with the CCK₂ antagonists L-365,260 and PD-134,308 were placed in an elevated four-arm maze, with two of the arms open and exposed and two arms covered. The number of times the rats enter the open or enclosed arms is recorded, along with the time spent in each arm. Subjects treated with the CCK₂ antagonists spent significantly increased periods of time in the open arms of the maze, whilst L-365,031, a selective CCK₁ receptor antagonist, exhibited no behavioural effects.

CCK₂ specific receptor antagonists have also been investigated for potential therapeutic applications. The selective CCK₂ receptor antagonist L-365,260 was shown to block both CCK-4 induced panic attacks in patients suffering from panic disorder, and pentagastrin-induced symptoms in healthy volunteers. However, the therapeutic potential of CCK₂ receptor antagonists in treating panic disorder patients remains a matter for debate, as the two compounds available for clinical trials, L-365,260 and CI-988, both have unfavourable pharmacokinetic properties.
1.4.2 Role of CCK in schizophrenia and other disorders

Current research into the physiological mechanisms of schizophrenia suggests that a key component is a change in the functioning of the dopamine system, and dopamine receptor blockers are currently used in the treatment of this disorder. The links and interactions between the dopamine and CCK systems have been well established by behavioural, physiological and neurochemical studies, and dopamine and CCK have been shown to coexist in a number of regions of the brain. Studies have shown that the interaction between dopamine and CCK is complex and bidirectional, with CCK modulating the release of dopamine, and dopaminergic agents modulating the release of CCK, though the effects can vary, with CCK differentially potentiating and inhibiting the action of dopamine depending on the region of the brain examined.

The precise role of CCK in schizophrenia remains inconclusive, although post-mortem findings of schizophrenic patients have discovered both a reduction of CCK levels in certain regions of the brain including the frontal and cerebral cortices and the subiculum, and an increase in CCK levels in other regions such as the ventral tegmental area and substantia nigra. In addition, significant reductions in CCK immunoreactivity has been reported in several regions of the brain in patients suffering from schizophrenia, along with a lower density of CCK receptor binding sites in the hippocampus and frontal cortex. These findings together suggest that elevated CCK synthesis in regions high in dopamine may be associated with schizophrenia, along with reduced CCK activity in particular regions of the brain, resulting from either a reduction in the synaptic level of CCK, a decrease in the processing of CCK, or degeneration of CCK related neurons.

Dopaminergic pathways in the brain are also thought to be altered in patients suffering from depression. One study undertaken on mice is the ‘conditioned motility suppression test’ used to study antidepressant drugs, in which mice are placed in a transparent cage and subjected to electric shocks. On the following
day they are placed in the same cage without being shocked and their level of movement is recorded. Previously shocked mice exhibit a marked suppression of movement when compared to a control group who were not exposed to electric shocks. CCK$_2$ receptor agonists potentiate the effects of the conditioned motility suppression test and this may be reversed by administering CCK$_2$ receptor antagonists,$^5_1$ suggesting that CCK$_2$ receptor antagonists have antidepressant-like properties in mice.

Low levels of dopamine in the brain can also cause symptoms of Parkinson’s disease. Due to the modulatory interaction between CCK and dopamine in many regions of the brain, it has been suggested that CCK has an inhibitory role in dopamine-dependent locomotory functions in conditions such as CCK-induced catalepsy. The ability of CCK receptor antagonists to potentiate the effects of dopamine replacement therapy has been investigated, with the CCK$_2$ receptor antagonist L-365,260 able to potentiate up to 50-60% of the effects of existing therapy. No positive reaction was observed after administration of Devazepide, a selective CCK$_1$ antagonist,$^5_2$ suggesting that CCK$_2$ receptor antagonists may prove useful adjuncts to existing dopamine replacement therapy in the treatment of Parkinson’s disease.

1.4.3 Role of CCK in nociception

Studies have shown that the distribution of CCK receptors parallels that of opioid receptors in pain processing regions of the brain and spinal cord,$^4_5$ leading to suggestions that CCK may play a role in nociception, the measurable physiological response to a painful stimulus. Small doses of CCK, just sufficient to cause a physiological response, have been proven to reduce the analgesic effects of morphine and endogenous opioids, leading to suggestions that CCK acts as an endogenous opiate antagonist.
Possible clinical applications of CCK receptor antagonists lie in the management of chronic pain. Peripherally administered CCK antagonists have been shown to potentiate between 200 and 800% of the antinociceptive effects of endogenous opioids in rodents. Related studies have also shown that CCK antagonists potentiate the analgesic effects of some externally administered opiates such as morphine. The CCK₁ receptor antagonists L-365,031 and Devazepide and the CCK₂ antagonist L-365,260 were administered to rats in conjunction with morphine. The potency of the antagonists in enhancing morphine analgesia is much higher for L-365,260, suggesting that CCK/opiate interactions are mediated by CCK₂ receptors. This may lead to potential therapeutic applications of CCK₂ receptor antagonists as adjuvants to morphine, enabling lower doses of opiates to be administered and reducing the possible onset of opiate dependence. In addition, this increase in the analgesic effect does not also cause an increase in side effects such as respiratory problems.

Throughout their testing, the CCK receptor antagonists produced no signs of dependence, or of withdrawal anxiety. In addition, they appeared to suppress the effects of benzodiazepine-induced withdrawal, suggesting possible applications for CCK receptor antagonists in the treatment of withdrawal from drugs such as cocaine, alcohol and nicotine.

1.4.4 Role of CCK on feeding behaviour

Studies on the cerebral spinal fluid (CSF) of patients suffering from bulimia nervosa revealed similar findings to those patients suffering from anxiety disorders, leading to speculation that there may be a physiological connection between the two. This prompted investigation into the role of CCK in eating disorders. Peripherally administered CCK has been demonstrated to induce satiety and inhibit food consumption, even after fasting, in a range of animals, including humans.
The entry of food into the intestine triggers the release of CCK, which stimulates CCK₁ receptors in the periphery and in particular on the vagus nerve. These receptors transmit signals of fullness to the brain, terminating feeding behaviour and inducing satiety. CCK₁ agonists have therefore been suggested as having possible therapeutic applications in the treatment of obesity, and conversely, CCK₁ antagonists have been proposed for the treatment of eating disorders such as anorexia.

CCK₂ receptors in the periphery are primarily located in the stomach and smooth muscle cells throughout the gastrointestinal tract. Studies have shown that contraction of the stomach smooth muscles is stimulated by CCK, and that gastric emptying following food intake is inhibited by CCK₂ receptor antagonists. This has led to CCK₂ antagonists being proposed as a potential treatment for gastric ulcers.

1.4.5 Role of CCK in other peripheral functions

In the peripheral tissues it is thought that receptor antagonists may have a potential for treating pancreatitis, as they have been shown to inhibit the release of pancreatic amylase. Caerulein, an analogue of CCK, has been shown to cause pancreatitis in rats; studies have been undertaken which demonstrate that CCK receptor antagonists prevent this onset of caerulein-induced pancreatitis.

\[
\text{Pyr-Gln-Asp-Tyr(SO}_3\text{H)-Trp-Gly-Trp-Met-A}p-Phe-NH}_2
\]

4

The CCK analogue caerulein

CCK has also been shown to stimulate growth of the pancreas, leading to the investigation of CCK receptor antagonists as a potential treatment for pancreatic cancer.
CCK receptor antagonists may also have potential in treating biliary disorders. A form of biliary colic caused by contractions of the gallbladder when a gallstone obstructs the entrance has been shown to be successfully treated in patients by the administration of CCK receptor antagonists.27

1.5 CCK Receptor antagonists

A structurally diverse range of compounds have been found to act as CCK antagonists. Comprehensive structure-affinity relationship studies between these antagonists and CCK receptors have further highlighted regions of these molecules which may be modified, resulting in improved receptor affinity and selectivity in these second and third generation antagonists. CCK receptor antagonists can be grouped into five main categories: derivatives of cyclic nucleotides, derivatives of amino acids, peptides - partial sequences and derivatives of CCK, benzodiazepine derivatives, and dipeptoids, non-peptide molecules based on fragments of the CCK structure.27

1.5.1 Derivatives of cyclic nucleotides

Unsubstituted cyclic nucleotides do not show activity as CCK receptor antagonists, but butyryl derivatives of cyclic guanosine monophosphate and cyclic adenosine monophosphate have been proven to act as antagonists. Di-butyryl cyclic guanosine monophosphate (Bt2cGMP) 5 was the first discovered nucleotide antagonist of CCK receptors and is the most potent of this class of antagonists.27
Studies by Miller and Gaudreau have demonstrated that, unlike the majority of known CCK receptor antagonists, cyclic nucleotides act as non-competitive antagonists and indirectly regulate the binding of radioligands to CCK receptor sites by combining with CCK.

1.5.2 Derivatives of amino acids

Many of the amino acid-derived CCK receptor antagonists were originally developed as anti-gastrin compounds, however due to the structural similarity of CCK and gastrin, it has been shown that such agents are also effective CCK antagonists. Two of the earliest discovered amino acid derived antagonists, proglumide (D,L-4-benzamido-N,N-di-n-propylglutaramic acid) 6, which has been used medicinally throughout Europe and Japan since the 1970s to treat patients with peptic ulcers, and benzotript (N-p-chlorobenzoyl-L-tryptophan) 7 have been shown to act as more potent antagonists than the cyclic nucleotide derived agents. However they exhibit very poor selectivity between CCK\textsubscript{A} and CCK\textsubscript{B} receptors and so are of limited use in pharmacological studies into the effects of individual receptor action.
The amino acid-derived CCK receptor antagonists proglumide and benzotript

Following these studies, the L- and D- isomers of tryptophan itself were investigated and both proved to be effective, albeit weak, antagonists of the binding action of CCK. N-Acyl derivatives of tryptophan were also studied, and revealed an increase in potency with the addition of hydrophobic substituents, the most promising being N-carbobenzoxytryptophan (CBZ-tryptophan). No significant difference in potency arose as a result of the stereospecificity of the tryptophan moiety. Further testing of CBZ-amino acids revealed the importance of other structural features, with aromatic amino acids being more potent than aliphatic ones of comparable hydrophobicity.

Other research into glutamic acid derivatives yielded the analogues lorglumide (CR 1409) (DL-4-(3,4-dichlorobenzoylamino)-5-(di-n-pentylamino)-5-oxopentanoic acid) and loxiglumide (CR 1505) (DL-4-(3,4-dichlorobenzoylamino)-5-(N-(3-methoxypropyl)-N-pentylamino)-5-oxopentanoic acid)

The glutamic acid derived lorglumide and loxiglumide
Both compounds exhibited a highly potent antagonistic effect of a competitive nature on pancreatic CCK₁ receptors, and were active after oral administration.

Table 1 Inhibition of $[^{125}I]$CCK-33 binding to CCK receptors in rat pancreas and mouse cortex

<table>
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<th>Antagonist</th>
<th>IC$_{50}$ (µM) Rat pancreatic tissue (CCK₁)</th>
<th>IC$_{50}$ (µM) Mouse brain cortex (CCK₂)</th>
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</tr>
<tr>
<td>Loxlgumide</td>
<td>0.33</td>
<td>9.1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Further manipulation of the lorglumide structure led to the development of the potent and highly CCK₂ selective antagonist Spiroglumide (CR-2194) 10.

![Chemical Structure](image)

10

The potent and CCK₂ selective antagonist Spiroglumide
Spiroglumide (R-4-(3,5-dichlorobenzamido)-5-(8-azaspiro[4.5]decan-8-yl)-5-oxopentanoic acid) showed competitive and specific antagonism of the pentagastrin-stimulated gastric acid secretion in a number of animal models.\textsuperscript{64} Initial human trials were undertaken but discontinued due to the relatively low inhibitory potency,\textsuperscript{65} though spiroglumide remains the most potent CCK\textsubscript{2} antagonist among this class of compounds.

1.5.3 Peptides and pseudopeptide analogues

Many of the initial CCK receptor antagonists were peptides or pseudopeptides derived from modification of the amino acid sequence of CCK-7 and CCK-4.\textsuperscript{9} Initially their synthesis was based on the deletion or modification of the phenylalanine residue at the carboxy-terminal of CCK, but more recent studies have revealed a wide range of modifications which have led to increased potency and selectivity.

Several requirements must be satisfied in order for the peptide to act as an antagonist: the minimum sequence length necessary for antagonism is the tetrapeptide (the smallest sequence that the CCK receptors will recognise), the presence of a tryptophan residue 11, which has been shown to be important for binding to central and peripheral CCK receptors; and the presence of a terminal amide, which is an important determinant of the inhibitory potency of the antagonist.

\[
\begin{array}{c}
\text{HO-C} \\
\text{H}_2\text{N} \\
\text{H}
\end{array}
\]

11

L-Tryptophan
1.5.3.1 Peptides

The first peptidic CCK antagonist was the $N$-Boc derivative of the C-terminal tripeptide Boc-Met-Asp-Phe-NH$_2$, which inhibited the CCK-8-stimulated release of amylase from guinea pig pancreatic tissue with an IC$_{50}$ in the mM range $^{66}$ Other Boc protected fragments were also investigated, and deletion of the terminal phenylalanine residue from the peptides Boc-CCK-4 and Boc-CCK-7 resulted in both exhibiting antagonist activity. The most potent antagonist of this class, Cbz-CCK-27-32-NH$_2$ $^{12}$ is derived from deletion of the phenylalanine residue from the sulfated octapeptide CCK-8S. It has been demonstrated to be up to thirty times more potent than dibutyryl cyclic guanosine monophosphate (Bt$_2$cGMP)$^{67}$

$$\text{Cbz-Tyr(SO$_3$H)-Met-Gly-Trp-Met-Asp-NH$_2$}$$

The potent peptide CCK receptor antagonist Cbz-CCK-27-32-NH$_2$

It is also possible to synthesise specific CCK$_1$ or CCK$_2$ peptidic receptor antagonists, the combined replacement of the phenylalanine residue of Boc-CCK-7 by 2-phenylethyl ester or amide, and the L-tryptophan residue with D-tryptophan produced the most potent peptidic CCK$_1$ specific antagonist, with a binding affinity in the $10^{-8}$ M range $^{68}$

1.5.3.2 Pseudopeptides

Pseudopeptide analogues have also been synthesised by alteration or replacement of one or more residues of CCK fragments. The sulphate ester of the tyrosine residue of CCK-8 is critical to the biological activity of the peptide, however it is vulnerable to hydrolysis. To increase the stability of the molecule,
the sulfated tyrosine was substituted by the synthetic amino acid (LD)-Phe(\(\rho\)-CH\(_2\)SO\(_3\)Na), replacing the \(\text{OSO}_3\) group with the non-hydrolysable CH\(_2\)SO\(_3\)Na. The resulting peptide exhibited antagonist activity against both CCK\(_1\) and CCK\(_2\) receptors with a binding affinity in the nanomolar range.

Specific CCK\(_1\) and CCK\(_2\) receptors may also be synthesised. An examination of the effects of \(N\)-methylation of certain residues led to analogues exhibiting high CCK\(_1\) selectivity. Replacement of the terminal aspartic acid and tyrosine(SO\(_3\)H) residues of CCK-8 with 4-hydroxyphenylacetyl(SO\(_3\)H), together with inversion of chirality of the aspartic acid residue and \(N\)-methylation of either the phenylalanine or aspartic acid residues yielded the peptides ARL-15295 and ARL-15849.

\[4\text{-Hydroxyphenylacetyl(SO}_3\text{H)}\text{-Nle-Gly-Trp-Nle-D-Asp-(NMe)Phe-NH}_2\]  

\[13\]

\[4\text{-Hydroxyphenylacetyl(SO}_3\text{H)}\text{-Nle-Gly-Trp-Nle-(NMe)D-Asp-Phe-NH}_2\]  

\[14\]

The pseudopeptide CCK\(_1\) receptor antagonists ARL-15295 and ARL-15849 both act as potent CCK\(_1\) receptor antagonists. ARL-15295 exhibited a 2100-fold selectivity for CCK\(_1\) receptors and ARL-15849 a 6600-fold selectivity, both with binding activity in the nanomolar range.

Replacement of the methionine and phenylalanine residues with leucine or the unnatural norleucine has no effect on the antagonistic properties. Therefore many synthetic CCK antagonists include this replacement to avoid the issues of methionine instability. Further substitution involved replacement of the methionine residues of Boc-CCK-4 and Boc-CCK-7 with ornithine. Ornithine is a non-protein amino acid; not involved in the synthesis of proteins and so is not coded for by DNA. It is a byproduct of the action of the enzyme.
arginase on L-arginine 16 to produce urea, and so is an important part of the urea cycle to remove excess nitrogen from the body (Scheme 1)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \quad \text{CH}_2\text{CH} \quad \text{COOH} \\
\text{H}_2\text{N} & \quad \text{NH} \quad \text{CH}_2\text{CH} \quad \text{COOH} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{N} \quad \text{NH}_2 \\
\text{Arg} & \quad \text{ase} \\
\end{align*}
\]

Scheme 1

Ornithine substitution produced the CCK1 specific antagonists Boc-Trp-Orn(Z)-Asp-NH2 and Boc-Tyr(SO3H)-Nle-Gly-Trp-Orn(Z)-Asp-NH2, which exhibited binding potencies in the 10^{-7} M range. 73 Conversely, replacement of the methionine and phenylalanine residues of Boc-CCK-4 with the unnatural and hydrophobic amino acids phenylglycine and dimethylamide-l-naphthylalanine to increase metabolic stability and brain penetration yielded Boc-Phg-Asp-[1-Nal-N(CH3)2]-NH2, a CCK2-specific antagonist with a binding affinity of 3.9 x 10^{-8} M. 74 Similarly, the substitution of the norleucine-glycine peptide bond in Boc-[Nle]CCK-7 by the peptide bond surrogates $\Psi[\text{COCH}_2]$ or $\Psi[\text{HNCO}]$ resulted in the most potent CCK2 specific peptidic antagonists, with binding affinities in the subnanomolar range. 75

Many of these peptidic CCK receptor antagonists have been employed in clinical studies and have provided useful information about binding sites of the CCK receptors. However, despite the high potency and selectivity of some, their use is limited by a lack of oral availability, problems in crossing the blood-brain barrier, their partial agonist action and the fact that they are rapidly degraded by proteases. 77
1.5.4 Benzodiazepine derivatives

Benzodiazepines are widely used in medicine due to their anxiolytic, anticonvulsant and sedative action, and drugs such as flurazepam, diazepam (Valium) and temazepam contain benzodiazepines as the active ingredient. Benzodiazepines produce their effects by depressing the central nervous system through specific recognition sites on the GABA receptor complex.

The first effective nonpeptide CCK antagonist, asperlicin 17, was obtained as a fermentation product of the fungus *Aspergillus alliaceus*, and represented a major advance in the development of CCK receptor antagonist. Asperlicin was found to be a potent CCK₁ selective antagonist, exhibiting a 300 to 400-fold greater affinity for pancreatic, ileal and gallbladder CCK receptors than the peptide antagonists proglumide 6 and benzotript 7.

![Chemical structure of asperlicin](image)

**17**

The nonpeptide CCK antagonist asperlicin

Although asperlicin exhibited long lasting antagonistic activity *in vivo*, it had little pharmacological potential due to its lack of water solubility and poor oral bioavailability. A large number of asperlicin derivatives were synthesised with varying success, though the majority suffered from the same lack of oral activity. A new line of investigation by Evans *et al* highlighted the presence of both diazepam 18 and D-tryptophan 19 like moieties in the asperlicin structure.
By fusing these elements they were successful in creating a range of synthetic analogues containing a potent core structure.

These first generation compounds were designed to increase potency, selectivity and water solubility. The most notable of these, the 3-amido substituted benzodiazepine Devazepide (also known as L-364,718 and MK-329) is among the most potent CCK antagonists currently known, with subnanomolar affinity – comparable to the natural CCK-8 ligand.
Devazepide is also a specific CCK₁ receptor antagonist, exhibiting a 1000-fold selectivity for CCK₁ receptors.⁷⁹ These factors, along with good oral bioavailability, have resulted in Devazepide’s role as the most widely used CCK receptor antagonist in studies researching the physiological effects of CCK and its receptors.⁹ Phase I clinical trials involving Devazepide have been completed, in which it was shown to inhibit the CCK-induced contraction of the gallbladder in healthy volunteers,⁸¹ along with stimulating gastric motility and gastric emptying after ingesting meals.⁸² These trials were not continued, due to concerns over gallstone toxicity, and the Devazepide-induced hyperplasia of rat liver and bile ducts,⁹ however phase II clinical trials of Devazepide are currently being undertaken for the treatment of opioid-resistant neuropathic pain in patients.

Table 2 Inhibition of [¹²⁵I]CCK-33 binding to CCK receptors in rat pancreas and guinea pig brain cortex

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>IC₅₀ (nM) Rat tissue (CCK₁)</th>
<th>IC₅₀ (nM) Guinea pig brain cortex (CCK₂)</th>
<th>Selectivity CCK₂/CCK₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asperlicin</td>
<td>1,400</td>
<td>&gt;10⁵</td>
<td>&gt;71</td>
</tr>
<tr>
<td>Devazepide</td>
<td>0.08</td>
<td>270</td>
<td>3,375</td>
</tr>
</tbody>
</table>

Attempts to synthesise analogues of Devazepide with increased potency, CCK₁ selectivity or oral bioavailability have been unsuccessful, although one such modification, in which the 3-amido substituent is replaced with a urea derivative, led to the design of L-365,260 22, the first highly potent non-peptide selective CCK₂ receptor antagonist.⁸³
L-365,260 exhibited binding affinity in the nanomolar range with a 140-fold selectivity for CCK₂ receptors over CCK₁. In studies involving several animal species, it potently antagonised the gastrin-stimulated release of gastric acid with good duration, but in phase I clinical trials involving healthy volunteers, these actions were short lived with a much lower level of inhibition. Mixed results were achieved in phase II clinical trials of the drug, with some studies indicating reduction in the frequency and intensity of CCK-4 induced panic attacks in patients with panic disorders, but others reporting no significant effects.

Whilst these first generation benzodiazepine derived drugs have provided highly specific CCK₁ and CCK₂ receptors with increased oral bioavailability compared to the naturally occurring asperlicin, one explanation for the problems encountered lies with the low aqueous solubility of their crystalline forms. This has led to the development of second generation benzodiazepines. No further CCK₁ specific drugs have been developed that improve greatly on Devazepide, however a range of compounds based on the CCK₂-specific L-365,260, but incorporating an aminotetrazole unit attached to the phenylurea moiety have been synthesised. As well as showing a marked increase in aqueous solubility - up to ten times more soluble than L-365,260 - these compounds, including L-736,380 and L-738,425 are highly specific CCK₂ receptor antagonists, L-738,425 having a ratio of binding for CCK₂/CCK₁ that is over 250 times greater than the first generation molecule L-365,260.
Table 3. Inhibition of [125I]CCK-8 binding to CCK receptors in rat pancreas and guinea pig brain cortex

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>IC₅₀ (nM) Pancreatic tissue (CCK₁)</th>
<th>IC₅₀ (nM) Rat brain cortex (CCK₂)</th>
<th>Selectivity CCK₁/CCK₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-365,260</td>
<td>2700</td>
<td>8.1</td>
<td>300</td>
</tr>
<tr>
<td>L-736,380</td>
<td>400</td>
<td>0.05</td>
<td>8,000</td>
</tr>
<tr>
<td>L-738,425</td>
<td>4,070</td>
<td>0.11</td>
<td>37,000</td>
</tr>
</tbody>
</table>

Major drawbacks of the clinical applications of benzodiazepines include their sedative action, which can hinder attempts to study solely the effects of the CCK receptors, as well as issues of long-term dependence 56

1.5.5 Dipeptoids

The synthesis of dipeptoid CCK receptor antagonists was based on the finding that the tryptophan and phenylalanine residues were the minimum necessary sequence to exhibit antagonistic effects at micromolar concentrations. Structure-activity relationship (SAR) studies on the N-terminus of these dipeptide
fragments identified an increase in potency on replacement of the tryptophan residue with α-methyl tryptophan. Potency was also raised by increasing the bulk of the protecting group, with 2-adamantyloxy carbonyl substitution yielding the best results. Optimisation of the C-terminus led to the development of CI-988 25, formally known as PD 134308.

![Chemical structure of CI-988](image)

**25**

The dipeptoid CCK₂ receptor antagonist CI-988

CI-988 has been shown to act as a potent and selective CCK₂ receptor antagonist, with an IC₅₀ of 1.7 nM for the binding of [¹²⁵I]CCK-8S in mouse cerebral cortex, and a 2500-fold selectivity for CCK₂ receptors. Studies have been carried out to examine the effects of CI-988, which has been shown to exhibit potent anxiolytic effects in several models of animal anxiety, including the mouse black/white box test and the marmoset human threat test. However, these effects are yet to be confirmed in phase II clinical trials in patients with panic and anxiety disorders. This lack of anxiolytic effect in humans has been attributed to the compound’s low bioavailability, thought to be predominantly due to its high molecular weight. Analogues of CI-988 were synthesised with the aim of reducing molecular weight and improving aqueous solubility. As the substitution at the N-terminus had been demonstrated to be critical for binding affinity, modifications were made to the C-terminus. Two of these most notable analogues, PD-135,666 26 and PD-140,548 27 are diastereoisomeric dipeptoids.
PD-135,666 is a highly potent and selective CCK$_2$ receptor antagonist with an IC$_{50}$ of 0.15 nM for the binding of $[^{125}]$I CCK-8S in mouse cerebral cortex and a 170-fold selectivity for CCK$_2$ receptors. Conversely, PD-140,548 is a potent and selective CCK$_1$ receptor antagonist with an IC$_{50}$ of 2.82 nM for the binding of $[^{125}]$I CCK-8S in rat pancreatic membrane and a 95-fold selectivity for CCK$_2$ receptors.

These developments have allowed dipeptoid antagonists (dipeptide fragments of CCK) to be used in clinical trials to determine further the individual effects of both CCK$_1$ and CCK$_2$ receptors. In addition, dipeptoid antagonists have shown no signs of a sedative action, even at the highest doses administered, giving them an advantage over other selective antagonists, in particular the benzodiazepines.

1.5.6 Other groups of CCK receptor antagonists

Other classes of compounds are currently under investigation as potential CCK receptor antagonists. Among these are the quinazolino-based compounds, based on the quinazolino-1,4-benzodiazepin-5,13-dione structure in the naturally
occurring antagonist asperhein. The lack of asymmetric centres in these structures facilitated structural optimisation and led to the development of a class of compounds including the CCK₂ specific antagonist LY-202769 28.

![Chemical structure of LY-202769](https://via.placeholder.com/150)

The quinazolinone-based CCK₂ receptor antagonist LY-202769

These compounds exhibited good selectivity for CCK₂ receptors over CCK₁, with LY-202769 having an IC<sub>50</sub> of 9.3 nM for the binding of [¹²⁵I]CCK-8S in mouse cortical membranes.²⁷ However, a major drawback was their poor bioavailability (>5%), and further structural optimisation is ongoing.

Virginiamycin 29, is a naturally occurring macrolide antibiotic produced by fermentation of a strain of *Streptomyces olivaceus*. It was found to bind selectively to CCK₂ receptors in guinea pig brain tissue. Structural optimisation has led to two analogues that are potent CCK₂ receptor antagonists ²⁹.

![Chemical structure of Virginiamycin](https://via.placeholder.com/150)

Virginiamycin
As a result of screening for new structurally unique CCK receptor antagonists, tetronothiodin 30 was discovered.

1.6 Tetronothiodin

In 1992 a microbial screening process aimed at finding new binding inhibitors for cholecystokinin discovered the naturally occurring compound tetronothiodin 30. The screen looked for inhibitors of the binding between 125I-labelled Bolton Hunter CCK-8 and rat cerebral cortex membrane. Tetronothiodin was isolated from the fermentation broth of *Streptomyces* sp NR0489, a gram-positive bacterium of the *Streptomyces* genus. *Streptomyces* are widely found in soil and decaying vegetation, and produce a wide variety of enzymes and antibiotics, including erythromycin, tetracycline, and chloramphenicol.

Tetronothiodin is isolated from *Streptomyces* sp. NR0489, which was harvested from a soil sample. Following fermentation of the bacteria for ten days, the sample was centrifuged and the supernatant isolated. The pH was adjusted to neutral to allow column chromatography to be carried out, and the resulting solution was concentrated under reduced pressure. Extraction with organic solvents followed by further column chromatography yielded an active organic compound. Final purification using reverse phase preparative HPLC yielded 30 as a pale brown powder.

Its structure is completely different from previously known CCK antagonists, including those of microbial origin such as asperlicin, the cyclic nucleotides, amino acid derivatives and the peptoid antagonists.
1.6.1 Biological activity of tetronothiodin

Studies have been undertaken to investigate the binding properties of tetronothiodin at CCK1 and CCK2 receptors using \[^{125}\text{I}\]CCK-8 as a radiolabelled ligand. Tetronothiodin and the radioligand were incubated at 23 °C with samples of rat cerebral cortex membrane or rat pancreatic membrane. These studies have shown that tetronothiodin is a potent and selective antagonist of CCK2 receptors, inhibiting the binding of \[^{125}\text{I}\]CCK-8 to CCK2 receptors on the rat cerebral cortex membrane in a concentration-dependent manner. The binding affinity of tetronothiodin to the CCK2 receptors was up to four times greater than other previously mentioned known antagonists, derived from amino acids and benzodiazepines or peptoid antagonists, and only three times less potent than the natural ligand CCK-8 itself. By contrast, tetronothiodin did not inhibit the binding of \[^{125}\text{I}\]CCK8 to the CCK1 receptors found in the rat pancreatic membrane. The selectivity ratio of the binding affinity of tetronothiodin to CCK2 to CCK1 receptors was shown to be greater than 30,000 - two to three orders of magnitude greater than for other receptor antagonists mentioned above (Table 4). Tetronothiodin was thus shown to be a highly potent and highly selective CCK2 receptor antagonist, which may prove extremely useful in further studies into the physiological role of CCK2 receptors.
Table 4 Inhibition of [125I]CCK-8 binding to CCK receptors in rat pancreas and rat cerebral cortex

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>IC50 (nM) rat pancreatic tissue (CCK1)</th>
<th>IC50 (nM) rat cerebral cortex (CCK2)</th>
<th>CCK1/CCK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetronothiodin</td>
<td>&gt;100,000</td>
<td>3.6</td>
<td>&gt;30000</td>
</tr>
<tr>
<td>L-365,260</td>
<td>2700</td>
<td>8.1</td>
<td>300</td>
</tr>
<tr>
<td>Benzotript</td>
<td>82,000</td>
<td>40,000</td>
<td>2.05</td>
</tr>
<tr>
<td>Proglumide</td>
<td>6,100,000</td>
<td>&gt;300,000</td>
<td>&lt;20.33</td>
</tr>
<tr>
<td>Asperlicin</td>
<td>1,400</td>
<td>&gt;1,000,000</td>
<td>&lt;0.0014</td>
</tr>
</tbody>
</table>

An additional study by Kuwahara\(^1\) examined the effects of tetronothiodin on GH3 cells, a rat anterior pituitary tumour cell line also containing CCK2 receptors. CCK-8 has been shown to induce an increase in concentration of Ca\(^{2+}\) in the internal fluid of these cells. Autoradiographic studies demonstrated that tetronothiodin inhibited this increase in concentration and this acted as a selective antagonist of CCK2 receptors on GH3 cells. Tetronothiodin was determined to have an IC\(_{50}\) value of 3.6 nM ± 0.33 for CCK2 receptors.

1.6.2 Structural elucidation

The acidic nature of tetronothiodin 30 was evidenced by the isolation procedure, which involved extraction with ethyl acetate at pH 2 and back extraction with distilled water at pH 7.5. Tetronothiodin was found to be soluble in methanol, tetrahydrofuran, dimethylsulfoxide and alkaline water but insoluble in ether, chloroform, hexane and acidic water. The free form of the molecule is unstable in solution, gradually decomposing during NMR experiments over a period of 2
weeks in DMSO-$d_6$ or CD$_3$OD, though the corresponding alkaline metal salts are stable for at least 5 months under the same conditions.  

The molecular formula of 30 was determined to be C$_{31}$H$_{38}$O$_5$S based on positive-ion FAB-MS ($m/z$ 593 (M + Na)$^+$) and negative ion high resolution FAB-MS ($m/z$ 569.2237, calculated for (M - H)$^-$ 569.2210) data. Further qualitative analysis indicated the presence of sulfur, while the IR spectral data suggested the presence of a $\gamma$-lactone (1760 cm$^{-1}$) and carboxyl groups (3000–2300, 1728 cm$^{-1}$). The UV spectrum in methanol indicated absorption maxima at 233 and 273 nm, which were attributed to an $\alpha$-acetyltetronic acid chromophore, similar to kijanimicin and tetrocarcins. The molecular formula was further supported by both $^1$H NMR and $^{13}$C NMR spectra, which indicated the presence of 31 carbon signals.

Structural elucidation was carried out based on the NMR data obtained with the potassium salt of 30 in D$_2$O as all the carbon signals were clearly observed, while two signals were obscured by the large solvent signal in DMSO-$d_6$. Partial structures (Figure 1) were elucidated by interpretation of the $^1$H-$^1$H COSY spectra.

![Figure 1]
An allylic coupling was observed between H-8 and the methyl protons H-28, which connected the olefinic carbon C-8 and the olefinic quaternary carbon C-7. The fragments shown in figure 21 and the remaining quaternary carbons, C-4 ($\delta$ 85.6), C-26 ($\delta$ 195.5), C-30 ($\delta$ 200.6) and C-3 ($\delta$ 202.4) were connected to form a partial structure (Figure 2) based on the analysis of the $^{13}$C-$^1$H long range couplings obtained from HMBC experiments.

Figure 2

$E$-Stereochemistry was determined for each of the three disubstituted double bonds from the large coupling constants (15 Hz) observed for the corresponding olefinic proton signals. A hydroxyl group was located at C-16 by spin-spin coupling between the hydroxyl proton ($\delta$ 4.57) and H-16 ($\delta$ 3.55) of the sodium salt of 30 in DMSO-$d_6$.

The spectral data for 30 had suggested the presence of an $\alpha$-acetyltetronic acid moiety, with a clearly separated band at 1760 cm$^{-1}$ in the IR spectrum indicating the presence of a $\gamma$-lactone. The UV spectrum in methanol also indicated absorption maxima at 233 and 273 nm, which were attributed to an $\alpha$-acetyltetronic acid functionality, and these findings were confirmed by
comparison of the $^{13}$C NMR data of 30 with that of a carolic acid derivative 31 (Figure 3)

![Figure 3](image)

Thus allowed the carbon signals at δ 96.6, 177.2, 195.5 or 200.6 and 202.4 to be assigned to C-2, C-1, C-26 and C-3 respectively and confirm the presence of the α-acyltetronic acid. This moiety was attached to the cyclohexene ring at C-4 because of the long range coupling observed between H-5 and C-3.

A $^{13}$C-$^1$H coupling was observed between C-24 and H-23 although H-23 and H-24 were not coupled, suggesting a linkage between C-23 and C-24 via either a heteroatom or quaternary carbon atom or a ketone function to form a 5-membered ring. The cyclopentanone structure was ruled out due to the $^{13}$C chemical shift of C-30, which was not in agreement with the general trend that ketones in cyclopentanones are observed in the region lower than 210 ppm as well as analysis of the reduced derivative of 30. This suggested the presence of a sulfur atom between C-23 and C-24 to form a tetrahydrothiophene ring. This conclusion was corroborated by comparison of the $^{13}$C spectrum of 30 with that of (2α,3β,4α)-2-trimethylsilyltetrahydrothiophene-3,4-dicarboxylate 32 (Figure 4).
Confirmation of the tetrahydrothiophene ring left two possible structures for tetronothiolin, A and B (Figure 5)

In order to allocate the remaining carboxylic function to either C-26 or C-30, reduction of tetronothiolin with sodium borohydride was carried out, to give epimeric alcohols 33a and 33b (Figure 6) The molecular formulae of 33a and 33b were established to be C$_{31}$H$_{40}$O$_{5}$S by negative ion FAB-MS data, and the UV spectrum was unchanged, indicating that the \( \alpha \)-acyltetronic moiety remained unchanged and that one ketone not comprising part of the chromophore of 30 had been reduced to give the dihydro derivative

The newly observed proton signal (\( \delta \ 3.95 \)) was assigned to H-30 by \(^1\)H-\(^1\)H COSY experiments, which revealed it to be spin coupled only to H-23 This established the structure of the moiety to be represented by structure A in Fig 26 and confirmed the planar structure of tetronothiolin to be 30 (Figure 6).

---

**Figure 4**

**Figure 5**

**Figure 6**
1.6.3 Stereochemistry

Although the absolute stereochemistry of tetronothiodin remains unassigned, the relative stereochemistry of six of the eight stereocentres has been determined by a series of nOe and long-range selective proton experiments carried out on the sodium salt of tetronothiodin in DMSO-$d_6$. The nOe between $H$-9 and $H$-5b indicated the $cis$ dihedral relationship between these two protons (Figure 7), and the small coupling constant between $H$-9 and $H$-8 (2 Hz) determined by a homodecoupling experiment further supported the pseudoaxial orientation of $H$-9, as the figure was consistent with a dihedral angle between $H$-9 and the plane of the double bond of 70-80°. The $cis$ relationship between the methyl group on C-6 and $H$-5 was established from a strong nOe between $H$-5a and $H$-27 and a very weak nOe between $H$-5b and $H$-27.\(^{94}\)
Long range selective decoupling (LSDP) experiments using a double irradiation technique were used to determine the coupling constants between C-3 and the protons H-5b and H-9, and both were found to be less than 4 Hz. This indicated a cis relationship between C-3 and both H-5b and H-9, as the coupling constant between an axial proton and an axial carbon would be larger (6–9 Hz) due to the trans relationship.\textsuperscript{94}

The cis relationship between H-23 and H-25 was established by the NOE between these two protons (Figure 8) Treatment of the free acid of tetronothiodin with CD\textsubscript{3}OD for five hours resulted in the disappearance of H-25 from the \textsuperscript{1}H NMR spectrum. Upon treatment with CH\textsubscript{3}OH, the deuterium was exchanged for hydrogen with no epimerisation observed at C-25, indicating that only one configuration at C-25 was stable in solution. This allowed for a trans relationship to be assigned for the substituents on C-22 and C-25, as the less sterically hindered trans isomer is more stable than the cis isomer.\textsuperscript{94}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8.png}
\caption{Figure 8}
\end{figure}

The relative stereochemistry of six of the eight stereocentres has therefore been established by detailed spectroscopic analysis, although this is yet to be confirmed, along with the absolute stereochemistry, by X-ray crystallography. At present, the stereochemistry of the methyl substituent at C-21 and the hydroxy group at C-16 remains unknown. The structure of tetronothiodin 30 is therefore represented as shown below.
1.7 Synthesis of tetronothiodin

Our synthesis of tetronothiodin is based around a flexible and convergent approach, with the molecule disconnected into three units; the oxaspirobicyclic unit 34, the substituted tetrahydrothiophene moiety 35 and the macrocyclic framework 36 (Scheme 2)
1.7.1 Synthesis of the oxaspirobicyclic unit

1.7.1.1 Bimolecular Diels-Alder approach

Previous research within the Page group has investigated a number of synthetic routes towards the oxaspirobicyclic unit. The initial proposal involved a bimolecular Diels-Alder reaction between the hydroxydilene 37 and nitroethylene 38 (Scheme 3). This would be followed by a Nef reaction to yield the substituted cyclohexenone 40. However, the Nef reaction proved unsuccessful yielding none of the desired product, suggesting that the necessary deprotonation of the nitro compound 39 to form the nitronate anion was not occurring. All attempts to form the required nitronate anion by other means resulted in decomposition of the starting material, and so an alternative route was sought.

Scheme 3

A route starting from a bimolecular Diels-Alder reaction between the hydroxydilene 37 and phenyl vinyl sulfoxide 44 was envisaged, which involved as the key step a Pummerer rearrangement to allow formation of the substituted cyclohexenone 40 (Scheme 4) 95.
However, problems were encountered in the formation of the intermediate sulfide 46, and the route was abandoned.

Diels-Alder reactions utilising the chiral dienophile (R)-47 were also investigated within the Page group.

The steric bulk resulting from the tert-butyl substituent offers exceptional diastereofacial selectivity in the Diels-Alder reaction and in addition this class of dienophile has a tendency to undergo highly exo specific Diels-Alder reactions. This is due to the dipole moment formed in the transition states, as described by Berson\textsuperscript{96} who concluded that in Diels-Alder reactions between cyclopentadiene...
and methyl acrylate and related compounds, the dipole moments formed in the exo transition state would largely cancel each other out, whereas the dipole moments in the endo transition state would form a larger permanent dipole moment. This would increase the energy of the endo transition state, and make it unfavourable (Scheme 5).

\[
\text{benzene 60 °C, 15 h} \quad 85 \%
\]

A synthetic route towards the oxaspiro bicyclic unit 34 was devised, with the key step being a highly exo-selective and highly stereofacially selective Diels-Alder reaction between the hydroxydiene 37 and the chiral dienophile (R)-47 (Scheme 6).
However, problems were encountered with the Diels-Alder reaction which did not proceed as planned, despite a number of different reaction conditions being employed, possibly due to the instability of the diene to polymerisation, or the susceptibility of the dioxolane ring to acidic attack. The failure of this reaction pathway led to the discontinuation of this particular synthetic route, with other approaches considered.

### 1.7.1.2 An alternative Diels-Alder approach

One such approach again involved as a key step the use of a Diels-Alder reaction, with the synthetic route yielding 61, a diastereoisomer of the target oxaspirobicyclic moiety 34. (Scheme 7)
The previously synthesised hydroxydiene 55 was coupled with acrolein, which underwent a one-pot Diels-Alder reaction, followed by cyclisation of the resulting aldehyde. The Diels-Alder reaction in this instance was promoted by the interaction of the hydroxy function of 55 and the carbonyl of acrolein. Oxidation of the resulting Diels-Alder products gave 58 as a single isomer in good yield. Hydroxylation using (1S)-(+)-(camphorsulfonyl)oxazindine yielded the α-hydroxy lactone 59. Acylation with ethyl malonyl chloride to give 60 was followed by the addition of potassium bis(trimethylsilyl)amide to initiate a Dieckmann cyclisation (Scheme 8).
Finally, the primary alcohol of the Dieckmann cyclisation product was oxidised to yield the oxaspiroyclic product 61, a diastereoisomer of the desired target 34.

This incorrect stereochemistry arises as a result of the α-hydroxylation of 58 occurring exclusively from the less hindered face. Access to the lower face is blocked by the methyl substituent, resulting in a single, undesired stereoisomer.

1.7.1.3 The ring-opened approach

Recent research within the Page group has led to the successful completion of the formal synthesis of the desired spirocycle 34. In order to establish the correct stereochemistry at the hydroxy position in lactone 59, attention was moved away from the cis-fused bicyclic unit 58 as access to the desired lower face during α-hydroxylation is disfavoured. Instead, the decision was made to work with a ring-opened precursor in order to introduce the desired substitution with the correct stereochemistry prior to ring closure.
Hydroxydiene 55 was prepared in the same manner as in previous synthetic routes, before undergoing a Diels-Alder reaction with propenal. Sodium borohydride was then used to reductively ring open the resulting lactols 56 and 57 (Scheme 9).

The less hindered hydroxyl group of the resulting diol 62 required protection, to allow oxidation of the hydroxyl group closest to the ring. Tert-butyl diphenylsilyl chloride was chosen as the protecting reagent, as the bulky alkyl substituents would increase steric repulsion with the more hindered hydroxyl group and favour reaction at the desired site. Reaction with 1.2 equivalents of tert-butyl diphenylsilyl chloride in dichloromethane at ambient temperature led to a 60% yield of the desired mono-protected diol 63.

Several oxidative methods were investigated for the transformation of diol 63 to the required aldehyde 64, including the use of chromium (VI) reagents, hypervalent iodine (V) reagents and activated dimethyl sulfoxide, all with
limited or no success. Fetizon's reagent was subsequently employed, which utilizes silver carbonate adsorbed onto a Celite® support, and this provided a route through to the aldehyde 64 in moderate yield.

Although previous attempts to install the required hydroxyl group by α-hydroxylation of lactone 58 (Scheme 7) had resulted in the installation of the incorrect stereochemistry, it was felt that there was less steric hindrance to the desired bottom face of aldehyde 64, and so direct α-hydroxylation was attempted. However all approaches tried were unsuccessful, and so an indirect route was conceived (Scheme 10).

Aldehyde 64 was treated with trisopropyl silyl triflate to yield the silyl enol ether 65. This was then reacted with a solution of dimethyldioxirane in acetone to carry out the α-hydroxylation and afford an inseparable mixture of diastereoisomers 66 and 67. Further work would require removal of the silyl protecting group and oxidation to the α-hydroxy lactone 68 (Scheme 11), followed by a repeat of the earlier
work by Vahedi, outlined in Scheme 7, to yield the desired oxaspiro cyclic product 34

Scheme 7

Scheme 11

1.7.2 Synthesis of the tetrahydrothiophene moiety

1.7.2.1 Tetrahydrothiophenes in other natural products

Tetrahydrothiophenes are found in a wide variety of naturally occurring compounds, many of which are of great interest due to their biological activity. Some notable examples include the glucosidase inhibitors salacinol 70 and kotalanol 71. These compounds were extracted from the Hippocrateaceae plant *Salacia reticulate* WIGHT, widespread throughout Sri Lanka and South India, extracts of which have been traditionally used as a treatment for non-insulin-dependent diabetes.
These compounds with their unique zwitterionic structures, along with many analogues, have been synthesised by several groups including Yuasa and co-workers, whose synthesis of the tetrahydrothiophene moiety of both salacinol and kotalanol from the sugar D-xylofuranose is outlined in Scheme 12.

Scheme 12
Following synthetic routes described by Ingles\textsuperscript{103} and Van Es,\textsuperscript{104} the intermediates 76 and 77 were obtained. The \textit{cis} diol of D-xylofuranose was protected as the acetal, followed by conversion of the primary alcohol to the tosylate. Reaction with the sodium salt of benzyl mercaptan yielded 74, the remaining alcohol was then protected as the benzyl ether and the acetal removed to give the two isomers 76 and 77. Cyclisation by iodination using a mixture of iodine, triphenylphosphine and imidazole then produced the bicyclic 78 as a single product, suggesting equilibrium between 76 and 77 under the reaction conditions. Compound 78 was treated with sodium cyanoborohydride to initiate the one-pot hydrolysis and reduction to form the tetrahydrothiophene 79, and finally a Birch reduction produced the desired salacinol and kotalanol moiety 80.

Other naturally occurring compounds containing a tetrahydrothiophene ring include a class of potential inhibitors of HIV based on 4-thionucleosides (Figure 9).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Figure 9}
\end{figure}

There has been much synthetic interest in these compounds, with a number of synthetic routes published in the literature\textsuperscript{105, 106, 107, 108}. The synthesis of the tetrahydrothiophene moiety of 82 by Walker is outlined in scheme 13.
2-Deoxy-D-erythropentose 84 was reacted sequentially with 1% methanolic hydrochloric acid and silver carbonate, followed by sodium hydride, benzyl bromide and tetrabutylammonium iodide to give 85 in a 93% yield. Treatment of 85 with benzyl mercaptan under acidic conditions produced 3,5-di-o-benzyl-2-deoxy-D-erythro-pentose dibenzyl dithioacetal 86, which was converted to the mesylate 87. Cyclisation was effected by reaction with tetrabutylammonium iodide and barium carbonate to give the tetrahydrothiophene 88.

Possibly the best known naturally occurring product containing a tetrahydrothiophene ring is D-biotin 90. First isolated in 1941 from beef liver, D-biotin or vitamin H has attracted significant interest as a target for total synthesis, and numerous examples exist in the literature involving enzymatic resolution, chiral methods involving carbohydrates, cysteine or L-aspartic acid, or asymmetric synthesis.
One such synthesis by Chen$^{117}$ involved as the key steps a phosphoric acid catalysed cyclisation of a dicarboxylic acid to the anhydride followed by conversion with sodium sulfide to the corresponding thioanhydride (Scheme 14)

Another synthesis, by Marquet,$^{118}$ formed the tetrahydrothiophene ring by reaction of a dimesylate with sodium sulfide (Scheme 15)

1.7.2.2 Other syntheses of tetrahydrothiophenes

Other examples of synthetic routes for the formation of tetrahydrothiophenes can be found in the literature. In 2000, Overman$^{119}$ reported a new method for stereocontrolled synthesis of tetrahydrothiophenes by acid-promoted condensation of mercapto allylic alcohols 97 with aldehydes or by rearrangement of 5-alkenyl oxathiolanes such as 98 (Scheme 16) The differentiating feature of this synthetic route is that the key ring-closing step
involves formation of a carbon-carbon bond, rather than the formation of a carbon-sulfur bond as in most syntheses of substituted tetrahydrothiophenes

\[
\begin{align*}
\text{R}_2\text{COH} + \text{R}_3\text{CHO} & \quad \text{97} \\
\text{R}^2\text{MeO} - \text{R}^3\text{S} & \quad \text{98}
\end{align*}
\]

Scheme 16

A new synthetic route to the formation of tetrahydrothiophenes was reported by Jana in 2003.\textsuperscript{120} They reported the electrophile-promoted thioetherification of 1-sulfanyl and 2-sulfanylpentenol derivatives. The cycloetherification could be promoted either by iodine or selenium, and a range of yields and selectivities were obtained (Scheme 17).

\[
\begin{align*}
\text{PhSe} & \quad \text{OR} & \quad \text{104} \\
\text{[Se]} & \quad \text{R = Ac} & \quad \text{5-exo} \\
\text{PO} & \quad \text{S=Ph} & \quad \text{101} \\
\text{5-endo} & \quad \text{102} \\
\text{[I]} & \quad \text{R = H, Bn} & \quad \text{5-endo} \\
\text{PO} & \quad \text{S} & \quad \text{103} \\
\text{5-exo} & \quad \text{105} \\
\text{[I]} & \quad \text{R = Bn} & \quad \text{6-endo} \\
\text{OR} & \quad \text{106}
\end{align*}
\]

Scheme 17
With the 2-sulfanyl pentenol derivatives 102, 5-endo cyclisation always occurred, regardless of the electrophile. With 1-sulfanyl pentenol species 105, treatment with iodine provides the 6-endo product 106, while selenium electrophiles gave 5-exo tetrahydrothiophenes 104.

Recently, Benetti and Pollini have described the synthesis of 3,4-substituted tetrahydrothiophenes through tandem Michael-Henry and Michael-Michael reactions. They reacted 1,4-dithiane-2,5-diol 107 (the dimer of mercaptoacetaldehyde) with a nitroalkene generated in situ from the precursor 108, in a Michael reaction. This gave a suitable intermediate 109 able to undergo an intramolecular Henry reaction (Scheme 18).

They also performed a Wittig reaction between 107 and a stabilised phosphorane to yield 4-mercapto-2-butenoate 111, a suitable partner for the masked nitroalkene 108 in a tandem Michael-Michael reaction to form substituted tetrahydrothiophenes (Scheme 19).
1.7.2.3 Biosynthesis of tetrahydrothiophenes

Whilst no research has been carried out into the biosynthesis of tetrathiodin, the biosynthesis of another tetrahydrothiophene-containing compound, biotin, has been extensively investigated. Biotin is one of eight sulfur-containing cofactors – molecules which bind to enzymes and are required for the catalysis of biochemical reactions – found in living systems. These eight are coenzyme A 114, S-adenosylmethionine (SAM) 115, thiamine pyrophosphate 116, D-biotin 90, molybdothionin 117, lipoic acid 118, coenzyme M 119 and N-(7-mercaptoheptanoyl)threomine phosphate 120 (Figure 10).
Both thiamin 116 and biotin 90 are essential vitamins in the human diet. Thiamin, vitamin B₁, is an important cofactor in carbohydrate metabolism, whilst biotin, vitamin H or B₇, plays an important role in some enzymatic carboxylation reactions.

In contrast to the relatively simple formation of a carbon-sulfur bond in organic synthesis, which usually proceeds by nucleophilic attack of sulfur onto a carbon electrophile, the biosynthesis of a carbon-sulfur bond is more intricate. The sulfur source in the biosynthesis of both thiamin and biotin was initially thought to be cysteine, though in the case of biotin, recent studies have revealed the intermediate sulfur sources to be much more complex.¹²³, ¹²⁴, ¹²⁵

1.7.2.3.1 Biosynthesis of thiamin

The thiamin biosynthesis in Escherichia coli is illustrated in Scheme 20. The thiazole 121 is synthesised from tyrosine 122, cysteine 123 and deoxy-D-xylulose-5-phosphate 124 in a complex two-electron oxidative condensation, requiring the participation of at least six proteins.¹²²

[Scheme 20: Diagram illustrating the biosynthesis of thiamin 116]

The thiazole is then coupled with the pyrimidine 125, followed by phosphorylation to generate thiamin 116.
1.7.2.3.2 Biosynthesis of biotin

The biosynthesis of biotin in *Escherichia coli* and *Bacillus* species is thought to originate from pimelic acid 126, which is converted over a number of steps into dethiobiotin 127, with the key carbon-sulfur bond-forming step being the transformation of dethiobiotin 127 to biotin 90 (Scheme 21)\(^{126}\)

\[
\begin{align*}
\text{HO}_2\text{CCH}_2(\text{CH}_3)_2\text{COOH} &\rightarrow \begin{array}{c}
\text{HN} \\
\text{H}_3\text{C}
\end{array} \\
\text{CH}_2(\text{CH}_3)_4\text{COOH} &\rightarrow \begin{array}{c}
\text{O} \\
\text{HN}
\end{array} \\
&\begin{array}{c}
\text{H} \\
\text{H}
\end{array} \\
&\begin{array}{c}
\text{S} \\
\text{CH}_3(\text{CH}_3)_2\text{COOH}
\end{array}
\end{align*}
\]

Scheme 21

Contrary to initial beliefs, the sulfur source for the transformation of dethiobiotin to biotin is not cysteine, but biotin synthase.\(^{127}\) A sample of biotin synthase was obtained from *E. coli*, and was found to be a homodimer, consisting of two iron-sulfur clusters. It has been shown by radiolabelling studies that it is these clusters that provide the sulfur source for the reaction, and not cysteine.

The conversion of dethiobiotin 127 to biotin 90 requires stoichiometric quantities of biotin synthase, and utilizes S-adenosyl methionine (SAM) 115 as a co-substrate. The products of the reaction are D-biotin 90 and the SAM-derived products methionine 128 and deoxyadenosine 129 (Scheme 22)\(^{122}\).
1.7.2.3.3 Biosynthesis of tetronothiodin

To date there are no published studies of the biosynthesis or synthesis of tetronothiodin. This thesis details our work into the synthesis of the tetrahydrothiophene moiety 35 of tetronothiodin.
1.8 References

(1) Kuwahara, T; Kudoh, T, Nagase, H; Takamiya, M; Nakano, A., Ohtsuka, T; Yoshuzaki, H; Arisawa, M *Eur J Pharmacol* 1992, 221, 99-105
(2) Vanderhaegen, J -J ; Signeau, J C.; Gepts, W *Nature (Lond.)*, 1975, 257, 604-605
(4) Van Dijk, A.; Richards, J G, Trzeciak, A.; Gillessen, D; Mohler, H *J Neurosci*, 1984, 4, 1021-1033
(5) Deschesnes, R. J., Lorenz, L J, Haun, R. S.; Roos, B. A.; Collier, K J; Dixon, J. E.*Proc Natl Acad Sci USA*, 1984, 81, 726-731
(6) Charpentier, B.; Pelaprat, D, Dureux, C.; Dor, A.; Rebaud, M; Blanchard, J., Roques, B. *Proc Natl Acad Sci USA* 1985, 88, 1968-1972
(7) Brownstein, M J.; Rehfeld, J F *Ann N Y Acad Sci* 1985, 448, 9-10
(8) Inns, R B , Snyder, S H *Proc Natl Acad Sci USA* 1980, 77, 6917-6921
(9) Herranz, R *Med Res Rev* 2003, 23, 559-605
(14) Larsson, L. I., Rehfeld, J F *Brain Res* 1979, 165, 201-218
(17) Roques, B P ; Dureux, C, Gacel, G; Pelaprat, D; Ruiz-Gayo, M, Belleney, J, Fellion, E; Zaajac, J M, Fournie-Zaluski, M-C.; Dauge, V, Menant, I; Rossignol, P; Lux, B., Gerard, D; Begue, D, Sasaki, A; Morgat, J L *Ann N Y Acad Sci* 1985, 448 , 61-75
(23) Noble, F., Wank, S A ; Crawley, J N, Bradwejn, J.; Seroogy, M. H ; Roques, B. P. *Pharmacol Rev* 1999, 51, 745-781
(26) Wank, S A ; Pisegna, J R ; De Weerth, A. Proc Natl Acad Sci USA , 1992, 89, 8691-8695
(33) Penke, B , Hajnal, F ; Lonovics, J ; Holzinger, J; Kadar, G; Telegdy, T; Rivier, J. J. Med Chem , 1984, 27, 845-849
(37) Derrien, M, Dureux, C , Dauge, V, Roques, B P Brain Res 1993, 617, 181-188
(38) Gall, C ; Lauterborn, J.; Burks, D., Seroogy, K. Brain Res 1987, 403, 403-408
(40) Bradwejn, J.; de Montigny, C. Nature 1984, 312, 363-364
(41) Bradwejn, J; Koszycki, D; Payeur, R ; Bourn, M ; Borthwick, P Am J Psychiatry 1992, 149, 962-964
(47) Ladurelle, N ; Keller, G , Roques, B P, Dauge, V Brain Res 1993, 628, 254-262
(49) Schalling, M; Friberg, K ; Seroogy, K , Riederer, P.; Bird, E, Schiffmann, S. N ; Mailieux, P ; Vanderhaeghen, J J , Kuga, S., Goldstein, M Proc Natl Acad Sci USA 1990, 87, 8427-8431
(50) Farmery, S M; Owen, F; Poulter, M; Crow, T J Life Sci 1985, 36, 473-477

(51) Smadja, C ; Maldonado, R ; Turcaud, S ; Fourme-Zaluski, M. C.; Roques, B. P. Psychopharmacol 1995, 120, 400-408

(52) Wiesenfeld-Hallin, Z; Xu, X J ; Hughes, J , Horwell, D. C ; Hokfelt, T. Proc Natl Acad Sci USA 1990, 87, 7105-7109

(53) Fourme-Zaluski, M C ; Coric, P.; Turcaud, S.; Lucas, E ; Noble, F ; Maldonado, R ; Roques, B P. J Med Chem 1992, 35, 2474-2481


(55) Lydiard, R B; Brewerton, T. D ; Fossey, M D; Laraia, M. T.; Stuart, G; Bemfeld, MC; Ballenger, J. C Am J Psychiatry 1993, 150, 508-510


(57) Schick, R R; Schusdziarra, V.; Yaksh, T. L; Go, V. L W. Ann N Y Acad Sci 1994, 713, 242-254


(59) Saluja, A K; Saluja, M; Printz, H; Zavertnik, A; Sengupta, A; Steer, M L Proc Natl Acad Sci USA 1989, 86, 8968-8971

(60) Miller, L J; Reilly, W M; Rosenzweig, S A; Jameson, J D; Go, V L W. Gastroenterology, 1983, 84, 1505-1511


(65) Beltunger, J, Hidelbrand, P, Drewe, J, Christ, A; Hlobil, K; Ritz, M, D’Amato, M, Rovati, L, Beglinger, C Eur J Clin Invest 1999, 29, 153-159


(72) Lignon, M F.; Galas, M. C.; Rodriguez, M; Laur, J., Aumelas, A; Martinez, J J Biol Chem 1987, 262, 7226-7231
(73) Gonzalez-Muniz, R ; Bergeron, F , Marsenigne, I., Durneux, C., Roques, B P. J Med Chem 1990, 33, 3199-3204
(74) Corringer, P. J ; Weng, J H; Ducos, B ; Durneux, C , Boudeau, P , Bohme, A ; Roques, B P. J Med Chem 1993, 36, 166-172
(75) Mendre, C , Rodriguez, M , Lignon, M F ; Galas, M C , Gueudet, C.; Worms, P ; Martinez, J J Biol Chem 1990, 186, 213-222
(77) Comnger, P. J ; Weng, J H; Ducos, B ; Durneux, C , Boudeau, P , Bohme, A ; Roques, B P. J Med Chem 1993, 36, 166-172
(78) Mendre, C , Rodriguez, M , Lignon, M F ; Galas, M C , Gueudet, C.; Worms, P ; Martinez, J J Biol Chem 1990, 186, 213-222
(80) Evans, B E ; Bock, M. G ; Rlttle, K. E Proc Nat Acad Sci USA 1986, 83, 4918-4922
(86) Hughes, J, Boden, P; Costall, B, Domeney, A, Kelly, E, Horwell, D. C; Hunter, J C; Punock, R D, Woodruff, G. N Proc Natl Acad Sci USA 1990, 87, 6728-6732
(92) Watanabe, J ; Fujisaki, N , Fujimon, K , Anzai, Y , Oshima, S ; Sano, T , Ohitsuika, T; Watanabe, K , Okuda, T J Antibiotics 1992, 46, 1-10
(93) Ohitsuika, T, Kotaki, H, Nakayama, N; Itezono, Y, Shima, N; Kudoh, T; Kuwahara, T, Arisawa, M, Yokose, K J Antibiotics 1992, 46, 11-17
(95) Batchelor, K J, Loughborough University, 2001
(97) Hindley, S. J., Loughborough University, 1998
(98) Page, P C B., Vahedi, H ; Batchelor, K J, Hindley, S J, Edgar, M., Beswick, P. Synlett 2003, 1022-1024
(99) Dubert, O, Loughborough University, 2005
(101) Gallienne, E, Benazza, M ; Demaillly, G ; Bolte, J ; Lemaire, M. Tetrahedron 2005, 61, 4557-4568
(103) Ingles, D L.; Whistler, R. L. J Org Chem 1962, 27, 11, 3896-3898
(106) Monta, N.; Krause, N Angew Chem Int Ed 2006, 45, 1897-1899
(111) Ohn, H.; Emoto, S Tetrahedron Lett 1975, 2765-2766
(115) Chavan, S P; Ramakrishna, G., Gonnade, R G., Bhadbhade, M M Tetrahedron Lett 2004, 45, 7307-7310


(125) Gibson, K. J.; Pelletier, D. A.; Turner, I. M *Biochem Biophys Res Comm* 1999, 254, 632-635


Chapter 2

Results & Discussion
2. Results and Discussion

Our first approach towards the synthesis of the tetrahydrothiophene moiety 1 is outlined in scheme 1.

\[
\text{HO} \quad \text{C} \quad \text{O} \\
\text{H} \quad \text{H} \quad \text{X} \\
\text{S} \quad \text{H} \quad \text{H} \\
\text{HH} \quad \text{S} \quad \text{X} \\
1 \quad \text{2} \quad \text{3} \\
\text{OSO}_4 \quad t-\text{BuOOH} \\
\text{OR} \quad \text{R}^* \text{O} \\
\text{5} \quad \text{4} \\
\]

Scheme 1

As the α-keto acid functionality was potentially unstable to the reaction conditions employed in other transformations, we decided that this group would be best masked as the trimethylstilyl acetylene 2. As reported by Page, Such groups may be oxidised readily to the corresponding α-keto esters by treatment with a mixture of osmium tetroxide and t-butyl hydroperoxide (Scheme 2).

\[
\text{R} \quad \text{S} \quad \text{R}^* \\
\text{O} \quad \text{C} \quad \text{OR}^* \\
\text{R}^* \text{O} \\
\text{R}^* \text{OH} \\
1 \quad \text{2} \quad \text{3} \\
\text{OSO}_4 \quad t-\text{BuOOH} \\
\text{OR} \quad \text{R}^* \text{O} \\
\text{5} \quad \text{4} \\
\]

Scheme 2
The trimethylsilyl acetylene is reacted with osmium tetroxide (5 % w/w) and five equivalents of t-butyl hydroperoxide in an alcoholic solution at 0 °C, initially to form an α-keto acylsilane 8 (Scheme 3)

![Scheme 3](image)

Scheme 3

The more electrophilic carbonyl group of the α-keto acylsilane 8 is attacked by the alcohol, followed by a Brook-type rearrangement to give 10. Further osmium tetroxide-catalysed oxidation yields the α-keto ester 11.

### 2.1 Nitro-aldol route

We envisaged that installation of the branched alkyl chain could occur by a Grignard addition to ketone 5, followed by dehydration of the resulting alcohol. As shown in scheme 4, the ring-closing step in the synthesis of the tetrahydrothiophene would be achieved by the reaction between a dimesylate 12 and anhydrous sodium sulfide.
There are several literature examples of this dimesylate displacement to be found, including a total synthesis of the vitamin biotin, in which the key cyclisation of a dimesylate to the required tetrahydrothiophene is carried out in excellent yield using sodium sulfide (Scheme 5).

A key step in the synthesis would be a nitro-aldol reaction to form the β-nitroalcohol 15. Two molecules would be synthesised, a trimethylsilyl-protected alkynal 19 and a nitro compound with a protected diol 20 (Scheme 6). A stereo
controlled nitro-aldol reaction would then be carried out as the C-C bond forming step, introducing two new chiral centres. The stereochemistry at the nitro-carbon is not important, as the chirality of this carbon atom will be removed later, however the correct stereochemistry must be introduced at the other centre.

\[
\begin{align*}
19 & \quad 20 & \quad 15 \\
\text{nitro-aldol} & \text{nitro-aldol} & \text{nitro-aldol}
\end{align*}
\]

Scheme 6

A Nef reaction would then be carried out to oxidize the nitro group to the ketone 14, followed by deprotection of the diol and conversion of the two primary alcohols to the dimesylate 12.

2.1.1 Synthesis of the nitro component

In order to attempt the nitro-aldol reaction, (4R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 22 was synthesised from D-mannitol 21 (Scheme 7).
The two primary diols of D-mannitol were protected using two equivalents of 2-methoxypropene, and the resulting 1,2-dif[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethane-1,2-diol 22 was cleaved using sodium periodate\textsuperscript{5} to yield two equivalents of (4R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 23 (Scheme 8). A cyclic periodate intermediate 26 is formed, and this intermediate subsequently breaks down to yield two equivalents of aldehyde 23.

An initially poor yield resulting from the addition of sodium periodate to a solution of diol 22 and sodium bicarbonate in dichloromethane water (2:1), was improved significantly by utilising silica gel-bound sodium periodate\textsuperscript{6}.
The use of silica gel-bound sodium peroxidate provided a much cleaner and more efficient route to the aldehyde than the use of lead tetraacetate,\(^7\) which may also be used to effect such transformations, but which resulted in significant contamination of the product.

The aldehyde 23 was subsequently converted to the oxime 24 using an aqueous solution of hydroxylamine hydrochloride,\(^8\) and finally oxidised to give the desired (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane 20 by generation of perox trifluoroacetic acid from a mixture of urea-hydrogen peroxide and trifluoroacetic anhydride.\(^9\)

An alternative to the use of a large excess of perox trifluoroacetic acid is the methyltrioxorhenium-catalysed oxidation of oximes,\(^10\) which also employs the urea-hydrogen peroxide complex, although under milder conditions. However these conditions give best results when oxidising aromatic oximes and resulted in poor yields with this substrate.
2.1.2 Synthesis of the aldehyde

The required aldehyde 19 was prepared from 2-propyn-1-ol as shown in Scheme 9.

\[
\begin{align*}
\text{Alkyne 27} & \xrightarrow{1 \text{ eq } n-\text{BuLi, THF, } -78 \, ^\circ\text{C}} \text{2 eq } n-\text{BuLi, THF, } -78 \, ^\circ\text{C} \\
& \xrightarrow{2 \text{ TMSCL, } -78 \text{ to } 0 \, ^\circ\text{C}} \text{PCC, CH}_2\text{Cl}_2 \\
& \xrightarrow{} \text{79%} \\
\text{27} & \xrightarrow{} \text{28} & \xrightarrow{} \text{19} \\
\end{align*}
\]

Scheme 9

Alkyne 27 was deprotonated using two equivalents of n-butyllithium and protected with a trimethylsilyl chloride to give 28 in good yield, as described by Davison et al.\(^{11}\) A number of methods were investigated to carry out the oxidation of the primary alcohol to the aldehyde 19, and these are outlined below.

2.1.2.1 The Swern oxidation

The first oxidation attempt made use of the Swern oxidation. First reported in 1981,\(^{12}\) it involves the activation of dimethylsulfoxide by oxalyl chloride at low temperature, typically -78 to -40 °C (Scheme 10). The Swern oxidation is a generally high yielding reaction, affording aldehyde and ketones from primary and secondary alcohols respectively under mild conditions, with no over-oxidation observed. The products obtained are sometimes clean enough to be used without the need for further purification.
The initial adduct 31 between dimethylsulfoxide and oxalylchloride collapses to form the more reactive dimethylchlorosulfonium salt 32. This is attacked by an alcohol to produce the alkoxy sulfonium ion 34, which is deprotonated by a base, typically triethylamine, to form ylide 35. Finally this undergoes a rearrangement to yield the desired carbonyl compound, producing dimethylsulfide as a by-product. One advantage of the Swern oxidation is that this, along with the other byproducts produced, may be easily removed in vacuo, eliminating the need for further purification steps.

\[ \text{Scheme 10} \]

In the oxidation of primary alcohol 28, the Swern procedure was carried out at both \(-78\) °C and \(-40\) °C, however the optimum conditions only gave a poor yield of 23%, despite purification of all reagents prior to use (Scheme 11).
A variant on the Swern oxidation was also attempted, which allowed for the use of higher temperatures.

2.1.2.2 The variant Swern oxidation

An alternative to the classic Swern oxidation was reported by Giacomelli in 2001.\textsuperscript{13} It utilises 2,4,6-trichloro[1,3,5]triazine to activate dimethylsulfoxide, rather than oxalyl chloride as used in the Swern oxidation. The activation of dimethylsulfoxide using traditional reagents such as oxalyl chloride and thionyl chloride can result in violent and exothermic reactions, and is usually carried out at temperatures of $-78$ °C to prevent formation of undesirable byproducts, or decomposition of the dimethyl alkoxysulfonium salt. One major advantage of 2,4,6-trichloro[1,3,5]triazine is that the activation is extremely mild and may be carried out at 0 °C with no apparent decomposition. Typical reaction conditions involve a temperature of $-30$ °C to avoid the formation of any chloro-derived byproducts or thiomethyl ethers.

The addition of dimethylsulfoxide to 2,4,6-trichloro[1,3,5]triazine results in the formation of a dimethyl alkoxysulfonium species 38 (Scheme 12). This is attacked by an alcohol to yield a further alkoxysulfonium ion 34. Deprotonation
by a base, usually triethylamine, forms an ylide 35, which undergoes a rearrangement to yield the carbonyl species 36, liberating dimethylsulfide in the process

$$\text{S} \rightarrow 35 \rightarrow \text{Me}_2\text{S}$$

In this instance, the alcohol 28 was oxidised using 2,4,6-trichloro[1,3,5]triazine and dimethylsulfoxide at a temperature of -30 °C, resulting in a slightly increased yield of 38 %, compared to the standard Swern conditions, which produced a yield of 23 % (Scheme 13)
2.1.2.3 Oxidation using hypervalent iodine reagents

Following the limited success of the Swern type procedures, oxidation using hypervalent iodine reagents was investigated. Such reagents have the advantage of mild reaction conditions, the elimination of expensive and potentially toxic metals, and there is no production of toxic by-products. However, care must be taken when using such reagents as they may be explosive when dried.

2.1.2.3.1 Oxidation using Dess Martin periodinane (DMP)

The most commonly used hypervalent iodine reagent is Dess Martin periodinane (DMP) (1,1,1-triacetoxy-1,2-dihydro-1,2-benziodoxol-3(1H)-one)

\[
\text{Dess Martin periodinane (DMP)}
\]

Dess Martin periodinane has become a widely used oxidant for the selective conversion of primary and secondary alcohols to the corresponding carbonyl compounds under very mild conditions. The oxidative mechanism is not fully understood but is thought to proceed by displacement of one acetate ligand by the alcohol, forming an intermediate which collapses to form the carbonyl compound, acetic acid and a reduced iodine species.
Oxidation of the primary alcohol 28 was attempted using 1.5 equivalents of DMP in dichloromethane at ambient temperature (Scheme 14)

![Scheme 14](image)

However, none of the desired aldehyde was isolated from the reaction, with only a small quantity of unreacted starting material recovered.

**2.1.2.3.2 o-Iodoxybenzoic acid oxidation**

Oxidation using another hypervalent iodine oxidant, o-iodoxybenzoic acid (IBX) 41 was also attempted. IBX was chosen as it is an effective oxidant of primary alcohols with no over oxidation to the carboxylic acid 14. IBX is a precursor of Dess-Martin periodinane (DMP) 40 and is prepared from 2-iodobenzoic acid 42 (Scheme 15)

![Scheme 15](image)
One of the major advantages of IBX over other similar oxidants is its ability to tolerate moisture and water, and it is also easy to freshly prepare before use. The oxidation is based on a proposed two-step mechanism (Scheme 16) involving a fast pre-equilibrium step that forms an alkylxyiodinane oxide reactive intermediate 43 and a molecule of water through ligand exchange at iodine, followed by a rate-determining step to yield the carbonyl compound and iodosobenzoic acid 44.

\[
\begin{align*}
R^*-\text{OH} + \text{IBX} & \xrightarrow{\text{fast}} R'\left(\text{IO\textsubscript{3}}\text{OH}\right) + H_2O \\
\text{alkylxyiodinane oxide} \\
\end{align*}
\]

\[
\begin{align*}
\text{IBX} & \xrightarrow{\text{slow}} R^*-\text{R} + \text{IBX} + H_2O \\
\text{iodosobenzoic acid} \\
\end{align*}
\]

Scheme 16

Oxidation of the primary alcohol 28 with IBX was attempted using a procedure described by Frøgero\textsuperscript{14} using dimethylsulfoxide as a solvent at ambient temperature (Scheme 17).
However, none of the desired aldehyde 19 could be isolated from the reaction mixture. Oxidation was then attempted using a reaction with IBX at high temperature with ethyl acetate as a solvent, as described by More and Finney.\(^\text{16}\) Although a range of primary and secondary alcohols were reported to be oxidised efficiently and cleanly, with no need for purification of the products due to the insolubility of IBX and the reaction by-products, no oxidation was observed of the substrate 28 in this case (Scheme 18)

![Scheme 17](image_url)

![Scheme 18](image_url)
2.1.2.4 Oxidation using chromium (VI)

Oxidation methods utilizing chromium (VI) reagents were also investigated. There are many reported chromium (VI) reagents, although many early methods such as the Jones, Sarett or Collins oxidations involve the use of chromium trioxide with the associated problems of toxicity due to large excesses of oxidant required, the labour intensive preparation of reagents and the tendency to overoxidise primary alcohols to carboxylic acids.

Problems with these early chromium (VI) reagents led to the development of new oxidants such as pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) (Figure 1)

\[
\begin{align*}
\text{PDC} & \quad \text{PCC} \\
\begin{array}{c}
\text{[N]} \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{[N]} \\
\text{H}
\end{array}
\end{align*}
\]

These salts have the advantages of being commercially available, non-hygrosopic and therefore easier to handle and store, as well as being soluble in a wide range of organic solvents. They oxidise alcohols to aldehydes and ketones with no overoxidation, typically as solutions in dichloromethane or N,N-dimethylformamide by the process shown in Figure 2.
Oxidation of the alcohol 28 was attempted using pyridinium chlorochromate (PCC) in dichloromethane, as reported by Harrns and Gajewski, and this produced some of the desired aldehyde 19, but in poor yield (Scheme 19).

The poor yield was possibly a result of the poor form of the product, a very sticky solid was formed by the reaction, leading to problems in isolating the product from the chromium byproducts. The reaction was then attempted with a 1:1 mixture of PCC and celite in dichloromethane which resulted in a free flowing powdery product, from which the desired aldehyde 19 could be easily isolated, improving the yield significantly (Scheme 20).
2.1.2.5 Oxidation using manganese dioxide

The use of activated manganese dioxide as an oxidizing agent was first reported by Ball et al. in 1948,\textsuperscript{19} in the oxidation of vitamin A \textbf{45} to retinal \textbf{46} (Scheme 21).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme21.png}
\caption{Scheme 21}
\end{figure}

It has subsequently become a standard reagent for the oxidation of allylic alcohols in petroleum ether, acetone or chloroform,\textsuperscript{20,21,22} propargylic alcohols in dichloromethane,\textsuperscript{23,24} and benzylic or heterocyclic alcohols in chloroform or acetone\textsuperscript{25,26}.

Activated manganese dioxide has been prepared by many methods, including the reaction of aqueous solutions of manganese sulfate and potassium
permananate at varying pH values, the pyrolysis of manganese salts such as manganese carbonate or manganese nitrite, or by the reaction of an aqueous solution of manganese dichloride tetrahydrate with potassium permanganate to yield an extremely active form of manganese dioxide. All these preparations require the manganese dioxide to be dried thoroughly before use. Alternatively, activated manganese dioxide is now commercially available and may be purchased from chemical reagent suppliers.

The mechanism of activated manganese dioxide oxidation is not known, however it is thought to proceed via a proposed free radical process (Scheme 22).

![Scheme 22](image)

The substrate is adsorbed onto the surface of the oxide, followed by the formation of a coordinated complex. Transfer of a hydrogen atom then occurs, to yield the stable radical which undergoes intramolecular transfer followed by desorption to give the carbonyl product.

More recent developments include the use of activated manganese dioxide in tandem oxidation processes, where an alcohol is oxidised to the corresponding
aldehyde and then further functionalised via for instance a Wittig reaction, esterification, amide formation, or a range of other reactions in a one-pot process. Taylor utilised activated manganese dioxide in his tandem oxidation process-Wittig reactions as shown in Scheme 23.\(^33,34\)

\[
\begin{align*}
\text{Ph,}\text{P}=\text{CHCO}_2\text{Et} & \quad \text{Ph,}\text{P}=\text{CHCO}_2\text{Me} \\
81\% (E, Z, Z) & \quad 82\% (E, Z) \\
\text{54} & \quad \text{55} & \quad \text{56} & \quad \text{57}
\end{align*}
\]

Scheme 23

The oxidation of primary and secondary alcohols to the corresponding aldehydes by manganese dioxide is usually carried out in aliphatic or aromatic hydrocarbons, chlorinated hydrocarbons, THF or acetone, however oxidation has also been achieved under solvent-free conditions\(^35\) (Scheme 24)

\[
\begin{align*}
\text{Cl} & \quad \text{MnO}_2, \text{rt, 24 h} & \quad \text{CHO} \\
81\% & \quad \text{58} & \quad \text{59}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{MnO}_2, \text{rt, 24 h} \\
\text{60} & \quad \text{61}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{MnO}_2, \text{rt, 72 h} \\
\text{62} & \quad \text{63}
\end{align*}
\]

Scheme 24
Manganese dioxide oxidation of 28 was also attempted, using commercially available activated magnesium dioxide, dried overnight at 120 °C before use. The alcohol 28 and activated manganese dioxide were dissolved in dichloromethane and stirred at ambient temperature for twenty four hours (Scheme 25).

\[
\text{CH}_3\text{Si} = \text{CH}_2\text{CHOH} \xrightarrow{\text{MnO}_2, \text{DCM}, \text{rt}, 24 \text{ h}} \text{CH}_3\text{Si} = \text{CH}_2\text{COH}
\]

Scheme 25

None of the desired aldehyde 19 was obtained however, the starting alcohol 28 being the only product isolated from the reaction mixture.

Table 1 gives a summary of the oxidation methods attempted.

<table>
<thead>
<tr>
<th>Oxidising Agent</th>
<th>Solvent</th>
<th>Reaction Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO / (COCl)_2</td>
<td>THF</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>DMSO / 2,4,6-trichloro[1,3,5]triazine</td>
<td>THF</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>DMP</td>
<td>DCM</td>
<td>24</td>
<td>SM</td>
</tr>
<tr>
<td>IBX</td>
<td>DMSO</td>
<td>48</td>
<td>SM</td>
</tr>
<tr>
<td>IBX</td>
<td>EtOAc</td>
<td>48</td>
<td>SM</td>
</tr>
<tr>
<td>PCC</td>
<td>DCM</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>PCC/Celite</td>
<td>DCM</td>
<td>20</td>
<td>54</td>
</tr>
<tr>
<td>MnO_2</td>
<td>DCM</td>
<td>24</td>
<td>S.M</td>
</tr>
</tbody>
</table>

Table 1. Summary of oxidation attempts
2.1.3 The Nitro-aldol reaction

The nitro-aldol reaction is an important and useful reaction in organic synthesis, as it allows the formation of a new carbon-carbon bond and also generates a new disfunctional group, the β-nitroalcohol group. The nitro compound is deprotonated at the α-position to form the nitronate, which then undergoes nucleophilic addition to the aldehyde (Scheme 26).

Scheme 26. The nitro-aldol reaction

Molecules with a high degree of functionality may be joined together in this manner and additionally, two new stereocentres are generated at the junctions of the new carbon-carbon bond. Many options then exist for further transformation of the new β-nitroalcohol functionality. The nitro group may be removed or reduced to give a β-aminoalcohol and the alcohol may be oxidised to a ketone or removed by dehydration if acidic protons are available, to yield a nitroalkene. In this instance the nitro group will be removed using a Nef reaction and so the stereochemistry at this centre is not important. However, the stereochemistry at the other centre must be controlled, as this will become the 2-position of the tetrahydrothiophene ring.
2.1.3.1 Nitro-aldol reaction catalysts

There are many different methods for promoting the nitro-aldol reaction, most involving the use of catalysts such as organic or inorganic bases and quaternary ammonium salts, and in a wide range of organic solvents or under solventless conditions. For some time, 1,1,3,3-tetramethylguanidine (TMG) 64, and more recently cyclic analogues of the guanidines (Figure 3), have been used to catalyse the nitro-aldol reaction effectively in solvents such as diethyl ether or tetrahydrofuran, while amines such as triethylamine or dibutylmethylamine are widely used in alcoholic solvents. More recently, excellent yields have been achieved by the use of tetrabutylammonium fluoride trihydrate as a catalyst in organic solvents.37

![Figure 3](image)

Procedures have also been developed recently to perform nitro-aldol reactions in aqueous environments. Ballini has reported the use of cetyltrimethylammonium chloride as a phase transfer catalyst for promoting the nitro-aldol reaction in water using potassium hydroxide.38 Some other common catalysts include potassium or sodium hydroxide in alcoholic solvents, as well as aluminium and magnesium alkoxides.36, 39, 40 More recently, lithium...
aluminium hydride has been used to catalyse a wide range of nitro-aldol reactions, thought to occur through the mechanism shown (Scheme 27) [36].

Scheme 27. Catalytic cycle for lithium aluminium hydride catalysed nitro-aldol reaction

2.1.3.2 Asymmetric nitro-aldol reaction catalysts

As the nitro-aldol products contain two new stereocentres at the carbon-carbon bond junction, a number of asymmetric catalysts have been developed in order to produce optically enriched β-nitro alcohols. When used in conjunction with an efficient reduction of the nitro function, such catalysts can provide effective routes to aminoalcohols in high enantiomeric excesses
The most commonly used asymmetric catalysts employ the chiral ligands (S)-(-)-binaphthol or (R)-(+-)binaphthol in conjunction with lanthanum or samarium salts to promote the reaction between nitromethane and a range of aldehydes$^{41,42}$ (Scheme 28).

\[
\begin{align*}
\text{CH}_3\text{NO}_2 & \quad \text{CH}_3\text{NO}_2 \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\end{align*}
\]

\[
\begin{align*}
\text{R-} & \quad \text{S-} \\
\text{Binol} & \quad \text{Binol} \\
\end{align*}
\]

Scheme 28

Following their effectiveness as general nitro-aldol catalysts, several chiral guanidines have also been developed as asymmetric catalysts, and produce good enantiomeric excesses in the reaction between nitromethane and benzaldehyde$^{43,44}$ (Figure 4).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Figure 4
2.1.3.3 Attempted nitro-aldol reactions

We then carried out a series of nitro-aldol reactions between aldehyde 19 and the nitro compound 20, using a range of catalysts. First the reaction was carried out in methanol using potassium carbonate as a catalyst (Scheme 29)

The two components were dissolved in methanol at 0 °C and a catalytic amount of powdered potassium carbonate added. The solution was then stirred for eight hours, allowing to warm to ambient temperature. None of the desired product could be isolated from the reaction mixture. There were indications that the acidic workup had employed too harsh conditions, resulting in decomposition of the nitroalcohol 15.

Sodium hydroxide catalysis was then attempted, using ethanol as a solvent (Scheme 30). The aldehyde 19 and nitro compound 20 were dissolved in ethanol and cooled to 0 °C. 10 mol % of powdered sodium hydroxide was then added to catalyse the nitro-aldol reaction and the solution stirred for 16 hours, allowing to warm to ambient temperature.
No reaction was observed between aldehyde 19 and the nitro compound 20 under these conditions, with no identifiable products isolated from the reaction mixture.

The use of stochiometric *n*-butyllithium along with titanium tetrachloride in nitro-aldol reactions has been reported by Barrett, and attempts were made to utilise these reaction conditions (Scheme 31).

The two components were dissolved in tetrahydrofuran in the presence of the Lewis acid titanium tetrachloride, and cooled to -78 °C. *n*-Butyllithium was added dropwise and the resulting solution stirred at this temperature for 8 h. In this instance, however, the use of *n*-butyllithium in tetrahydrofuran led to a
breakdown of products, with none of the desired β-nitroalcohol 15 being recovered.

The conditions used in the attempted nitro-aldol reaction between aldehyde 19 and nitro compound 20 are summarised in Table 2 below.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>K₂CO₃</td>
<td>10 mol%</td>
<td>MeOH</td>
<td>0 °C - rt</td>
<td>SM</td>
</tr>
<tr>
<td>NaOH</td>
<td>10 mol%</td>
<td>EtOH</td>
<td>0 °C - rt</td>
<td>S.M.</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>Stochiometric</td>
<td>THF</td>
<td>-78 °C</td>
<td>S M</td>
</tr>
</tbody>
</table>

**Table 2. Summary of nitro-aldol reaction conditions**

2.1.3.4 Nitronate dianion

In order to determine whether successful deprotonation of the nitro component was occurring, a test reaction was carried out to form the nitronate dianion. Treatment of (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane 20 in a mixture of tetrahydrofuran and N,N'-dimethylpropyleneurea, with two equivalents of n-butylthium, as described by Seebach,⁴⁸ yielded the nitronate dianion 6⁹ (Scheme 32).

The addition of one equivalent of methyl iodide at -78 °C followed by acetic acid to quench the remaining anion, yielded (4S)-2,2-dimethyl-4-(1-nitroethyl)-1,3-dioxolane 70 in a 44 % yield, confirming that deprotonation of the nitro compound 20 is occurring at the required position.
The nitronate anion 69 was then reacted with aldehyde 19 under the same conditions, in an attempt to yield the desired β-nitroalcohol 15. None of the desired product or starting materials could be identified from the reaction mixture however.

As a result of the failure of the nitro-aldol reaction to yield any of the desired β-nitroalcohol 15 under the conditions tried, a decision was made to investigate alternative routes for the synthesis of the tetrahydrothiophene moiety 1.
2.2 Dicarboxylic acid cyclisation route

A second approach to the synthesis of the tetrahydrothiophene moiety 1 was based on the cyclisation of diesters, dicarboxylic acids or dicarboxylic acid chlorides to form thioanhydrides (Scheme 33)

\[
\begin{align*}
\text{HO} & \text{R'O} \quad \text{O} = \text{O} \quad \text{OR} \\
\text{O} & \text{OR} \quad \text{O} = \text{O} \\
\text{OR} & \text{OR} \quad \text{O} = \text{O} \\
\end{align*}
\]

Scheme 33

A few literature examples of the synthesis of thioanhydrides from dicarboxylic acids exist,\(^4^9,5^0\) albeit in moderate yields, but they often employ reagents that are impractical to handle, such as hydrogen sulfide or pyridinium hydrosulfides\(^5^1,5^2\). We therefore decided to investigate the synthesis of thioanhydrides from diesters and dicarboxylic acid chlorides.

The latter stages of the synthesis of 1 would remain as envisaged in the previous nitro-aldol approach, outlined in Scheme 1, therefore the target of the dicarboxylic acid chloride cyclisation would be the tetrahydrothiophene 5.
2.2.1 Diethyl-L-tartrate cyclisations

The first route investigated involved the cyclisation of diethyl-L-tartrate, either directly from the diester or via the dicarboxylic acid chloride. The resulting tetrahydrothiophene 74 would then be treated with one equivalent of a reducing agent such as lithium aluminium hydride to yield the thiolactone 73, followed by a stereocontrolled addition of the trimethylsilyl-protected alkyne by a Grignard type addition to give 72. Selective deprotection of the alcohol at the 3-position, followed by oxidation to the ketone, would yield the substituted tetrahydrothiophene 5 (Scheme 34).
To this end, diethyl(4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 77 was prepared from diethyl-L-tartrate 76 (Scheme 35)

Protection of the diethyl-L-tartrate diol with 2-methoxypropene yielded diethyl (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 77 as described by Murrer. The reaction proceeded cleanly, with no evidence of unwanted side
products such as dimethyl or ethyl methyl esters being formed, as reported with some other methods.  

Although the formation of 5,5-trans fused carbocycles is prohibited due to the steric strain, the formation of heteroatom-containing 5,5-trans fused rings has been successful. In 2001 Smith reported the synthesis of two diastereoisomers of a 5,5-trans-lactam (Scheme 36).

![Scheme 36](image)

More recently, Metzner achieved the synthesis of two 5,5-trans fused compounds with three heteroatoms incorporated into the rings. Ring closure of the dimesylates 83 and 85 is effected by reaction with sodium sulfide nonahydrate in dimethylsulfoxide to afford substituted tetrahydrothiophenes 84 and 86, with an acetal bridge forming 5,5-trans fused bicycles (Scheme 37).
Scheme 37

The 3D-models of the tetrahydrothiophenes 84 and 86 show a high degree of ring strain. It is clear that when there is a cis relationship between the two methyl groups and the acetyl moiety as in 84, the methyl groups are fixed in a pseudo-axial position. With a trans relationship between the methyl groups and the acetyl moiety as in 86, the methyl groups occupy a pseudo-equatorial position (Figure 5).
We attempted cyclisation of diethyl (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 77 to form the substituted tetrahydrothiophene 78 by a reaction with sodium sulfide (Scheme 35) The sodium sulfide was heated at high temperature under reduced pressure to eliminate water, and then ground to a powder. This was added to a solution of the diethyl ester 77 in acetonitrile and heated under reflux. The resulting solid was recrystallised from dichloromethane to yield colourless crystalline needles, however none of the desired product was isolated, the reaction instead leading to the probable formation of 2,2-dimethyl-5-thiocarboxy-[1,3]dioxolane-4-carboxylic acid 87 or a related salt, as suggested by the NMR spectrum.

An attempt was then made to obtain the desired tetrahydrothiophene 78 by cyclisation of the dicarboxylic acid chloride. The purified diethyl-(4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 77 was hydrolysed using lithium hydroxide to yield (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid 88. This was followed by conversion with oxalyl chloride in the presence of a catalytic quantity of N,N'-dimethylformamide to the diacid chloride 89, which was not isolated but reacted immediately with dried, powdered sodium sulfide in refluxing acetonitrile as described above. Unfortunately, once again none of the desired product could be isolated (Scheme 38).
2.2.2 Dibenzoyl-L-tartaric acid cyclisations

One possible barrier to the cyclisation of the above dicarboxylic acid chloride was the difficulty of formation of 5,5-trans fused rings. Although examples exist in the literature of such systems containing heteroatoms, there is still a high degree of strain in these molecules. To remove the need to form these highly strained structures, cyclisations of dibenzoyl-L-tartaric acid were investigated. Reaction of dibenzoyl-L-tartaric acid 90 with oxalyl chloride in dichloromethane in the presence of a catalytic quantity of N,N'-dimethylformamide gave tartaroyl chloride dibenzoate 91 in a good yield (Scheme 39).
Cyclisation to the tetrahydrothiophene 92 was then attempted using dried, powdered sodium sulfide in refluxing acetonitrile as described above. None of the desired product could be identified. Further attempts to cyclise to the tetrahydrothiophene were made, the reaction of tartaroyl chloride dibenzoate 91 with powdered sodium sulfide in toluene at -40 °C in the presence of pyridine yielded only starting material, and the cyclisation was also attempted in dichloromethane at 0 °C in the presence of zinc chloride, but again none of the desired product could be isolated.

There are also literature precedents for the formation of anhydrides from dicarboxylic acids and subsequent conversion to the corresponding thioanhydrides. The common opinion was that the formation of succinic type thioanhydrides from the corresponding anhydrides proceeded through ring opening of the anhydride by a hydrosulfide ion to form the intermediate sodium monothiosuccinate 94, which upon acidification underwent ring closure to yield the thioanhydride 95 (Scheme 40).
To this end, (2R, 3R)-D1-O-benzoyl tartaric anhydride 96 was obtained in excellent yield from the reaction of dibenzoyl-L-tartaric acid 90 with acetic anhydride in the presence of a catalytic quantity of phosphoric acid (Scheme 41). Attempts to convert the anhydride to the corresponding thioanhydride using sodium sulfide were again unsuccessful however, yielding only starting material.

During the course of his work on the synthesis of small to medium ring thioanhydrides, Schauble identified that acidification of sodium monothiosuccinate 94 with 10 % hydrochloric acid gave succinic anhydride 93 in an 86 % yield, accompanied by hydrogen sulfide, with no trace of the desired thioanhydride 95. This confirmed earlier findings by Marvel and Kraiman.
who noted that acidification of sodium monothiophthalate yielded only phthalic anhydride and hydrogen sulfide. Schauble reported that carrying out the reaction of sodium sulfide with 1.2 molar equivalents of succinic anhydride yielded 0.2 molar equivalents of succinic thioanhydride prior to acidification, suggesting that the formation of the thioanhydride was a result of the reaction of succinic anhydride with the intermediate sodium monothiosuccinate to form a mixed anhydride intermediate (Scheme 42, Path B), followed by intramolecular attack of the thiocarboxylate to form the desired thioanhydride 95.
As the thiocarboxylate is more nucleophilic than the carboxylate in the initial sodium monothiosuccinate intermediate 94, Path A would be more kinetically favourable. This suggests that the formation of the acyclic thioanhydride 97 would predominate over formation of the mixed acyclic anhydride 98. Therefore formation of the acyclic anhydrides must be reversible in order for synthesis of the thioanhydride 95 to occur.

Test reactions were carried out to repeat the literature work to ensure the validity of the method. Succinic anhydride 93 was synthesised in quantitative yield from succinic acid 100 by reaction with refluxing acetic anhydride in the presence of a catalytic amount of phosphoric acid (Scheme 43). This was then treated with 0.5 molar equivalents of dried, powdered sodium sulfide in a mixture of THF and water, which yielded the desired succinic thioanhydride 95.

\[
\text{O} \quad \text{Ac}_2\text{O} \quad \text{H}_2\text{PO}_4 \\
\text{H}_2\text{O} \quad \text{reflux, 2 h} \quad 97\% \\
\text{O} \quad 0.5 \text{ eq Na}_2\text{S} \\
\text{H}_2\text{O, THF, rt, 2 h} \quad 84\% \\
\text{O} \quad \text{S} \quad \text{O}
\]

Scheme 43

Similarly, phthalic anhydride 102 was obtained in the same manner from phthalic acid 101 in excellent yield, which upon treatment with 0.5 molar equivalents of sodium sulfide in THF and water was smoothly converted to phthalic thioanhydride 103 (Scheme 44).
Following these encouraging results, the cyclisation of dibenzoyl-L-tartaric acid 90 was repeated to yield (2R, 3R)-Dl-O-benzoyl tartaric anhydride 96 in the same manner as described previously. This was then reacted with 0.5 molar equivalents of dried, powdered sodium sulfide in a mixture of THF and water. Unfortunately, none of the desired thioanhydride 92 could be isolated, yielding instead a mixture of starting anhydride and unidentifiable products (Scheme 45).

A possible explanation for this is the complexity of the intermediate acyclic anhydrides formed in this instance (2R, 3R)-Dl-O-benzoyl tartaric anhydride 96 reacts with sodium sulfide to form the initial intermediate 104, which upon further reaction with another molecule of (2R, 3R)-Dl-O-benzoyl tartaric anhydride could form the two acyclic anhydrides 105 and 106 (Scheme 46, Paths A and B).
Scheme 46
Path A is again the kinetically favoured pathway, due to the higher nucleophilicity of the thiocarboxylate with respect to the carboxylate, and a number of possible cyclisation pathways arise from the intermediate 105. The kinetically disfavoured intermediate 106 is required in order to obtain the desired tetrahydrothiophene 92, but again, even if the disfavoured 106 forms in the reaction mixture, a number of other possible cyclisation routes arise.

Although many thioanhydrides were synthesised in this manner from the corresponding anhydrides by Schauble\textsuperscript{59} (Scheme 47), none were alkoxy substituted, or contained any additional carbonyl functionality

\[
\begin{align*}
\text{Na}_2S & \quad \text{THF} \quad \text{H}_2\text{O} \\
\text{96\%} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Na}_2S & \quad \text{THF} \quad \text{H}_2\text{O} \\
\text{99\%} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Na}_2S & \quad \text{THF} \quad \text{H}_2\text{O} \\
\text{80\%} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Na}_2S & \quad \text{THF} \quad \text{H}_2\text{O} \\
\text{92\%} & \\
\end{align*}
\]

\textbf{Scheme 47}
Progression to the desired tetrahydrothiophene 5 requires elimination of one of the carbonyl functions. Reduction of a variety of cyclic anhydrides to lactones has been reported by Narasimhan,\textsuperscript{61} using one equivalent of lithium borohydride in tetrahydrofuran (Scheme 48)

\[ \text{Cyclic Anhydride} \xrightarrow{\text{LiBH}_4, \text{THF, rt}} \text{Lactone} \]

\[ \text{THF}, \text{rt} \]
\[ \text{68\%} \]

Scheme 48

This procedure was carried out on the previously synthesised anhydride (2\(R\), 3\(R\))-Dl-O-benzoyl tartaric anhydride 96. The reaction proceeded smoothly to yield (3\(R\), 4\(S\))-bis(benzoyloxy)-2-furanone 107 in a 68% yield (Scheme 49)

\[ \text{Anhydride} \xrightarrow{\text{LiBH}_4, \text{THF, rt}} \text{Furanone} \]

\[ \text{THF}, \text{rt} \]
\[ \text{68\%} \]

Scheme 49
Using these methods, some simple thioanhydrides such as 95 and 103 were synthesised from their corresponding, readily available anhydrides. Anhydrides with more complex functionality such as 96 were also successfully partially reduced to yield the desired lactones, however conversion of any suitably functionalised anhydrides to the corresponding thioanhydride proved unsuccessful. As this conversion was central to the synthesis of the desired tetrahydrothiophene 1, an alternative route was sought.

2.3 Substituted butadiene cyclisations

During our ongoing research into the synthesis of substituted tetrahydrothiophenes, the cyclisation of 2,3-disubstituted 1,3-butadienes to yield 5-membered rings was investigated.

There are several examples in the literature of the cyclisation of 1,3-butadienes with sulfur dioxide\(^6\) or boron species,\(^6\)\(^3\),\(^4\) but no precedent could be found for the formation of tetrahydrothiophenes in this manner.

2.3.1 Butadiene synthesis

We envisaged that the required 2,3-disubstituted 1,3-butadienes would be synthesised by a Morita-Baylis-Hillman reaction, followed by dehydration of the resulting tertiary allylic alcohol (Scheme 50).
2.3.1.1 The Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillman reaction is one of a number of extremely important carbon-carbon bond forming reactions in organic chemistry. It produces densely functionalised products with the added advantages of atom efficiency, along with the fact that the new functional groups created by the reaction may be easily converted and reacted further, making it a very versatile and useful reaction.

First reported in a patent by Baylis and Hillman in 1972, the Baylis-Hillman reaction is a three component reaction involving the coupling of an activated alkene with a carbon electrophile, catalysed by a tertiary amine (Scheme 51).

\[ R^1, R^2 = EWG \]

\[ R = H, COOR, alkyl \]
\[ R' = aryl, alkyl, heteroaryl \]
\[ X = O, NTs, NOS_{Ph} \]
The reaction proceeds via a Michael addition of the amine to the activated alkene, followed by formation of the new carbon-carbon bond and finally elimination of the amine to yield the Baylis-Hillman product (Scheme 52)

A wide range of activated alkenes may participate in the Baylis-Hillman reaction, including alkyl vinyl ketones, acrylates, vinyl sulfones, acrylonitrile and vinyl phosphonates. β-Substituted activated alkenes such as crotonates or crotononitrile may also undergo Baylis-Hillman reactions, though increased pressure is required in the reactions.66,67 By far the most common electrophiles used in the Baylis-Hillman reaction are simple aldehydes, although some α-keto esters, nonenolizable 1,2-diketones and fluoro ketones have been used.68,69,70 Simple ketones however require high pressure in order to participate in Baylis-Hillman reactions.

Most Baylis-Hillman reactions employ the tertiary amine 1,4-diazabicyclo[2,2,2]octane (DABCO) 113 as a catalyst, though several other tertiary amines have also been utilised, including quinuclidine 114, 3-
hydroxyquinuclidine (3-HQD) 115, 3-quinuclidone 116 and indolizine 117 (Figure 6) 71, 72

Figure 6

One major drawback of the Baylis-Hillman reaction is the reaction rate. It is often a very slow reaction requiring several days to several weeks to achieve completion. As a result, extensive research has been carried out into means of accelerating the reaction rate.

Research by Aggarwal 73 has led to the use of the tertiary amine 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in stoichiometric quantities to increase the rate of reaction. A range of aldehydes were coupled with activated alkenes in this manner, with the reactions complete in 0.5-72 hours (Scheme 53).

\[
\text{RC(=O)H} + \text{EWG} \rightarrow \text{R-C(=O)EWG} \quad \text{rt, neat, 0.5-72 h, 17-95%}
\]

R = Ph, 2-(NO2)Ph, 2-(OMe)Ph, Et, t-Bu
EWG = CO2Me, CO2Et, CO2t-Bu, CN

Scheme 53

The choice of solvent employed in the Baylis-Hillman reaction is also vital in terms of the reaction rate. Protic organic solvents have been shown to accelerate
the reaction, either by increasing the stability of the enolate by hydrogen bonding, activation of the aldehyde though hydrogen bonding, or both. 74, 75 Recently aqueous conditions have been studied in an attempt to increase the rate of the Baylis-Hillman reaction.

The use of DABCO as a stochiometric catalyst by Hu in a mixture of dioxane-water has also been shown to increase the reaction rate dramatically, 76 and under these conditions even the usually sluggish acrylamide undergoes efficient transformations 77 (Scheme 54).

\[
\begin{align*}
\text{Scheme 54}
\end{align*}
\]

Tang also utilised an aqueous/solvent medium to promote the reaction rate. He achieved homogeneous mixtures of the substrates and trimethylamine catalyst in mixtures of polar solvents such as low carbon alcohols, tetrahydrofuran and acetonitrile with water 78 (Scheme 55).
In order to synthesise the necessary 2,3-disubstituted 1,3-butadienes, a Baylis-Hillman reaction was carried out between ethyl pyruvate 118 and methyl acrylate 119 with 10 mol % DABCO catalyst present (Scheme 56).

The reaction was carried out under solventless conditions at ambient temperature for fourteen days, and resulted in a poor yield of the 2-hydroxy-2-methyl-3-methylene succinate 120.

Dehydration of 120 to yield the desired diene was achieved via a one-pot procedure as described by Hoffmann, which proceeded in moderate yield to give 2,3-dimethylenesuccinic acid ethyl ester methyl ester 121 (Scheme 57).
The 2-hydroxy-2-methyl-3-methylene succinate 120 was treated with three equivalents of DABCO and half an equivalent of DMAP in dichloromethane. The solution was then cooled to 0 °C and methanesulfonyl chloride added dropwise. Stirring was continued at ambient temperature for twenty-four hours before the dropwise addition of ice water, resulting in the desired 2,3-dimethylenesuccinic acid ethyl ester methyl ester 121.

Attempts were then made to improve the yield of the Baylis-Hillman reaction. Using methyl pyruvate 122 and methyl acrylate 119 in order to yield the symmetrical diene, a range of conditions were investigated.

Reaction of methyl pyruvate 122 with methyl acrylate 119 in the presence of 10 mol % DABCO catalyst under solventless conditions for 14 days resulted in a poor yield of the desired dimethyl 3-hydroxy-3-methyl-2-methylenesuccinooate 123 (Scheme 58).
The two reagents were then heated to 60 °C under solventless conditions in the presence of 10 mol % DABCO catalyst in an attempt to increase the reaction rate (Scheme 59)

\[
\begin{align*}
\text{122} + \text{119} & \xrightarrow{\text{DABCO 10 mol\%}} \text{123} \\
& \text{60 °C, neat, 7 d, 12 %}
\end{align*}
\]

Scheme 59

After 7 days reaction time however, only a 12 % yield of the desired product could be isolated.

A range of solvents were then investigated, an aprotic solvent in the form of tetrahydrofuran, and methanol - a protic solvent. Methyl pyruvate 122 and methyl acrylate 123 were dissolved in the solvent along with 10 mol % of DABCO catalyst and stirred at ambient temperature for 14 days (Scheme 60)

\[
\begin{align*}
\text{122} + \text{119} & \xrightarrow{\text{DABCO 10 mol\%}} \text{123} \\
& \text{rt, solvent, 14 d, solvent = THF, 11 \%, solvent = MeOH, 21 \%}
\end{align*}
\]

Scheme 60

In the aprotic tetrahydrofuran the reaction proceeded poorly in 11 % yield. In the protic methanol, the reaction was slightly improved, with a 21 % yield of dimethyl 3-hydroxy-3-methyl-2-methylenesuccinate 123 recovered.
The reaction was then attempted using a stoichiometric quantity of catalyst. Methyl pyruvate 122 and methyl acrylate 119 were dissolved in a 1:1 mixture of 1,4-dioxane and water, and one equivalent of DABCO added (Scheme 61).

\[
\begin{align*}
\text{C} & \; \text{O} \quad + \quad \text{C} & \; \text{O} \\
122 & \quad 119
\end{align*}
\]

\[ \xrightleftharpoons[1 \text{ eq DABCO}][1,4\text{-dioxane} \; \text{H}_2\text{O} (1:1) \; \text{rt, 14 d} \; 10\%] \]

\[
\text{OH}
\]

Scheme 61

Stirring at ambient temperature for 14 days produced a disappointing 10\% yield of the desired product.

Finally, a stoichiometric amount of DBU was employed as a catalyst. Methyl pyruvate 122 and methyl acrylate 119 were reacted at ambient temperature under solventless conditions (Scheme 62).

\[
\begin{align*}
\text{C} & \; \text{O} \quad + \quad \text{C} & \; \text{O} \\
122 & \quad 119
\end{align*}
\]

\[ \xrightleftharpoons[1 \text{ eq DBU}][\text{rt, neat, 14 d} \; 16\%] \]

\[
\text{OH}
\]

Scheme 62

This resulted in a poor 16\% yield of the desired dimethyl 3-hydroxy-3-methyl-2-methylenesuccinate 123.
2.3.1.3 Vinylalumination reaction

An alternative to the Baylis-Hillman reaction was reported in 1998 by Ramachandran. As a result of several poor yields resulting from Baylis-Hillman reactions involving fluorinated aldehydes, Ramachandran developed a vinylalumination procedure to access Baylis-Hillman adducts, based on a report from 1988 by Tsuda involving the use of [α-(alkoxycarbonyl)vinyl]aluminium reagents.

Ramachandran formed the [α-(ethoxycarbonyl)vinyl]aluminium reagent 125 by reaction of ethylpropiolate 124 with 1.5 equivalents of a mixture of disobutylaluminium hydride (DIBAL) and hexamethylphosphoramide (HMPA) in tetrahydrofuran (Scheme 63).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{DIBAL} & \quad \text{N} & \quad \text{N} \\
\text{H} & \quad \text{THF, rt} & \quad \text{Bu}_2\text{Al} & \quad \text{N} \\
124 & \quad \text{CO}_2\text{Et} & \quad \text{H} & \quad \text{R} \\
125 & \quad \text{HO} & \quad \text{CO}_2\text{Et} \\
126
\end{align*}
\]

\[R = \text{H, CH}_3, \text{Ph} \]
\[R_F = \text{CF}_3, \text{C}_2\text{F}_5, \text{C}_3\text{F}_7\]

Scheme 63

This vinylaluminium intermediate 125 was then reacted with a range of fluorinated aldehydes and ketones to yield the corresponding Baylis-Hillman adducts in good to excellent yields, with no Lewis acid activation of any of the substrates required.
The scope of the vinylalumination reaction was expanded by Ramachandran in 1999, with the introduction of differently substituted non-fluorinated carbonyl compounds. They reported excellent yields from the reaction of the [α-(ethoxycarbonyl)vinyl]aluminium intermediate 125 with the α-keto esters methyl pyruvate and methyl benzoyl formate, pyruvomalonate and the α-acetylenic ketone 3-butyln-2-one (Scheme 64). These products are either unobtainable by the standard Baylis-Hillman procedure or are formed in extremely poor yields requiring extremely long reaction times or increased pressure.

Scheme 64

The Baylis-Hillman reaction is not compatible with β-substituted activated alkenes, and these compounds do not react to form the expected adducts. Such adducts may, however, be obtained by the vinylalumination reaction Reaction
of ethyl-2-butynoate 124 or ethyl phenylpropiolate 130 with the DIBAL/HMPA mixture yields the corresponding β-substituted vinylamminum intermediates. These may then be reacted with carbonyl compounds to yield the vinyl-substituted Baylis-Hillman adducts. The stereochemistry of the alkenes is exclusively Z (Scheme 65).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{DIBAL} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{P} \quad \text{N} \\
\text{R} & \quad \text{THF, rt} & \quad \text{R} & \quad \text{CO}_2\text{Et} & \quad \text{R} & \quad \text{CO}_2\text{Et} & \quad \text{R} & \quad \text{R}^2 \quad \text{R}^3 & \quad \text{HO} \quad \text{CO}_2\text{Et} \\
130 & & 132 & & 133 & & 134 & & 135
\end{align*}
\]

Scheme 65

A further improvement to the vinylamination reaction was reported by Ramachandran in 1999,83 with the replacement of the carcinogenic HMPA by N-methylmorpholine-N-oxide (NMO) 136. A range of potential replacements were investigated, including the common HMPA replacements 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) 137, 1,3-dimethyl-2-imidazolidinone (DMI) 138 and quinuclidine N-oxide (QNO) 139 (Figure 7).

\[
\begin{align*}
\text{O} & \quad \text{Me} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{O} \\
136 & & 137 & & 138 & & 139
\end{align*}
\]

Figure 7

As DMPU and DMI have the potential to be reduced by DIBAL, and QNO was considered uneconomical, they were discounted. NMO however, proved to be...
an extremely effective substitute for HMPA in the vinylalumination reaction, resulting in increased yields of the Baylis-Hillman adducts

2.3.1.4 Attempted vinylalumination reactions

To obtain the required dimethyl 3-hydroxy-3-methyl-2-methylenesuccinoate 123, a vinylalumination reaction was attempted (Scheme 66)

\[ \text{Methyl propiolate 140 was added to a solution of DIBAL and NMO in tetrahydrofuran.} \]

\[ \text{The resulting vinylaluminium intermediate 141 was then cooled to 0 °C and methyl pyruvate 122 added to give the desired compound 123 in a far superior yield to that achieved by the Baylis-Hillman reactions.} \]

To obtain the required 2,3-substituted butadiene 142, a dehydration reaction was carried out on 123, under the same conditions employed previously (Scheme 67)

\[ \text{Scheme 67} \]
The 2-hydroxy-2-methyl-3-methylene succinate 123 was treated with DABCO and DMAP in dichloromethane. The solution was then cooled to 0 °C and methanesulfonyl chloride added dropwise. Stirring was continued at ambient temperature for twenty four hours before the dropwise addition of ice water to yield dimethyl 2,3-dimethylenebutanedioate 142.

Diethyl 2,3-dimethylenebutanedioate 144 was prepared in the same manner. Ethyl propionate 124 was added to a solution of DIBAL and NMO in tetrahydrofuran to yield the vinylaluminum intermediate 125, which was subsequently reacted with ethyl pyruvate to yield the Baylis-Hillman adduct diethyl 3-hydroxy-3-methyl-2-methylenesuccinate 143 (Scheme 68).

\[
\text{\textbf{Scheme 68}}
\]

This was then dehydrated using DMAP and DABCO followed by methanesulfonyl chloride to give the desired diethyl 2,3-dimethylenebutanedioate 144 in 57% yield (Scheme 69).

\[
\text{\textbf{Scheme 69}}
\]
As the desired tetrahydrothiophene 1 requires substitution at the 2-position, the reaction to produce β-substituted vinylaluminium intermediates was then investigated. Ethyl phenylpropiolate 131 was reacted with a solution of DIBAL and NMO in tetrahydrofuran to yield the intermediate 133. Ethyl pyruvate 118 was then added to give 3-benzylidene-2-hydroxy-2-methylsuccinic acid diethyl ester 145 (Scheme 70).

Dehydration of 145 was then achieved using the same conditions employed previously. DMAP and DABCO were added to a solution of 3-benzylidene-2-hydroxy-2-methylsuccinic acid diethyl ester 145 in dichloromethane, followed by the dropwise addition of methanesulfonyl chloride. Upon workup, the desired 2-benzylidene-3-methylene succinic acid diethyl ester 146 was obtained (Scheme 71).
The use of other activated carbonyl compounds was also investigated. The \([\alpha-\text{(ethoxycarbonyl)vinyl}]\text{aluminium intermediate 125 was obtained in the usual manner by the reaction of ethyl propionate 124 with a solution of DIBAL and NMO. Pyruvamide 147 was then added dropwise to give ethyl 2-(1-cyano-1-hydroxyethyl)acrylate 148 (Scheme 72)\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \overset{\text{DIBAL, NMO}}{\longrightarrow} & \quad t-\text{Bu}_2\text{Al} & \quad \text{CN} \\
\text{H} & & \text{H} & \quad \text{OH} \\
124 & & 125 & \quad 147 \\
\text{THF, rt} & & \text{THF, 0 °C to rt} & 66\% \\
& & & 148
\end{align*}
\]

Scheme 72

Dehydration of 148 was then attempted. DABCO and DMAP were added to a solution of 148 in dichloromethane, followed by methanesulfonyl chloride (Scheme 73). None of the desired 3-cyano-2-methylene-but-3-enoic acid ethyl ester 149 could be isolated from the reaction.

\[
\begin{align*}
\text{NC} & \quad \text{CO}_2\text{Et} \\
\text{OH} & & \text{CN} \\
148 & & 149 \\
\text{1) DABCO, DMAP, DCM} & & \text{2) MsCl, DCM, 0 °C to rt} & \text{3) H}_2\text{O}
\end{align*}
\]

Scheme 73

2.3.2 Cyclisation reactions of substituted 1,3-butadienes

Although no literature precedent exists for the cyclisation of 2,3-disubstituted-1,3-butadienes to tetrahydrothiophenes, a cyclisation reaction was attempted
between dimethyl 2,3-dimethylenebutanedioate 142 and anhydrous sodium hydrogen sulfide in tetrahydrofuran in the presence of tetrabutylammonium iodide (Scheme 74).

![Scheme 74](image)

The reaction was stirred at ambient temperature for sixteen hours, but none of the desired tetrahydrothiophene 150 could be identified from the reaction mixture, with only starting material recovered.

Cyclisation was then attempted using sodium sulfide nonahydrate in a mixture of methanol and water (Scheme 75).

![Scheme 75](image)

After sixteen hours at ambient temperature, tetrahydrothiophene-3,4-dicarboxylic acid dimethyl ester 150 was isolated from the reaction mixture in a 48 % yield. A trans relationship was identified between the two carboxylate groups at the 3- and 4-positions by NMR spectroscopy.
Similarly, diethyl 2,3-dimethylenebutanedioate 144 underwent cyclisation with sodium sulfide nonahydrate (Scheme 76)

A solution of 144 and sodium sulfide nonahydrate was stirred in a mixture of methanol and water at ambient temperature for sixteen hours, to give the tetrahydrothiophene 151 in a 41 % yield. Again a trans relationship was later identified between the two carboxylate groups by X-ray crystallography.

A cyclisation was then attempted involving the substituted vinyl compound 3-benzylidene-2-hydroxy-2-methylsuccinic acid diethyl ester 146 (Scheme 77)

The substituted butadiene 146 was dissolved in a mixture of methanol and water at ambient temperature, and treated with sodium sulfide nonahydrate. After stirring for sixteen hours none of the desired 2-substituted tetrahydrothiophene 152 could be isolated from the reaction mixture, with only the starting butadiene 146 identified.
Due to this difficulty in installing substitution at the 2-position of the resulting tetrahydrothiophenes, as well as problems with the scope of substituents tolerated by both the vinylalumination reaction and the dehydration reaction, an alternative route to the formation of tetrahydrothiophenes was sought.

### 2.4 Thiocarbonyl ylide route

The final approach towards the synthesis of the tetrahydrothiophene moiety involved the use of thiocarbonyl ylides.

![Thiocarbonyl ylide](image)

Thiocarbonyl ylides are useful reactive intermediates for the formation of sulfur-containing heterocycles. They have been widely developed as synthetic intermediates since the first clear-cut evidence for their existence was published by Kellogg et al. in 1972. They can be represented by a series of resonance forms (Figure 8) which include a 1,3-dipolar structure.

![Resonance forms](image)
2.4.1 Generation of thiocarbonyl ylides

The existence of thiocarbonyl ylides was first suggested by Knott in 1955\(^8\) in relation to his work into the synthesis of novel dyes, generated by either 1,3-elimination if a suitable leaving group is present, or by deprotonation in the presence of a stabilised carbenium ion (Scheme 78).

\[
\begin{align*}
1,3\text{-elimination} & \quad \text{deprotonation} \\
\text{Scheme 78}
\end{align*}
\]

Early relatively stable thiocarbonyl ylides such as 154 and 155 were soon prepared following this procedure by Okawara amongst others, though less stable examples containing an adjacent carbonyl group such as 156 typically decompose through the rearrangement shown (Scheme 79)\(^8\)

\[
\begin{align*}
154 & \quad 155 & \quad 156 \\
\text{Scheme 79}
\end{align*}
\]

2.4.1.1 1,3,4-Thiadiazolidine precursors

A more flexible route to the formation of thiocarbonyl ylides was first published by Schonberg in 1967,\(^8\) involving the generation of 1,3,4-thiadiazolidines
through the 1,3-dipolar cycloaddition of a diazo compound to a thioke
tone. These thia
diazolidines were highly unstable, and decomposed immediately to
yield tetrasubstituted thuranes, but allowed for greater flexibility in the
substituents present (Scheme 80)

\[
\begin{align*}
R_2C=N-N+R_2C=S & \rightarrow [R_2C-N=N-R'] - N_2 \rightarrow [R_2S=O-R'] \rightarrow R_2S-R'
\end{align*}
\]

Scheme 80

A related pathway for the formation of thiocarbonyl ylides involved the
spontaneous condensation of some aldehydes and ketones such as
cyclohexanone with hydrazine and hydrogen sulfide at temperatures of -10 to -
20 °C to generate stable 1,3,4-thiadiazolidines. These could be readily
dehydrogenated using lead tetraacetate to give thiacarbonyl ylide precursors
(Scheme 81)

\[
\begin{align*}
\text{C} & + H_2S + H_2NNH_2 \rightarrow \text{N-S-N} \rightarrow \text{N-S-N}
\end{align*}
\]

Scheme 81

Upon heating to 100 °C, the thia
diazolidines lose nitrogen to form thuranes via a highly reactive and short lived thiacarbonyl ylide. Such ylides can be trapped by dialkyl azodicarboxylate 1,3-dipolarophiles to form substituted 1,3,4-thiadiazolidines, and were the first thiacarbonyl ylides lacking stabilising electron-withdrawing or conjugating substituents.
The scope of these early thiocarbonyl ylides generated by the thermolysis of thiaadiazolidines was, however, limited by difficulties in synthesising the necessary starting materials and lack of generality of the reactions. This led to the development of a new method of generating thiocarbonyl ylides, desilylation of α-halo(silylmethyl)sulfides.

2.4.1.2 α-Halo(silylmethyl)sulfide precursors

First reported by Achiwa in 1985, the thermal extrusion of trimethylsilyl bromide from bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide was a new method for the generation of thiocarbonyl ylides, the use of an organosilicon compound (Scheme 83)
The formation of the sulfonium cation in the initial step is stabilised by the β-
silicon atom, and the cleavage of the silicon-carbon bond is accelerated by
stabilisation of the resulting carbamion as a thiocarbonyl ylide intermediate 162.
These intermediates could be trapped by conjugated olefins, such as N-
methylmaleimide and dimethylfumarate, to form substituted
tetrahydrothiophenes in good yields.

These 2-(trimethylsilyl)-tetrahydrothiophene derivatives may be further transformed into
tetrahydrothiophenes by fluorodesilylation using caesium fluoride in a mixture of DMPU water⁴⁴ (Scheme 84)

2.4.1.3 Bis(silylmethyl)sulfoxide precursors

A novel thiocarbonyl ylide precursor was reported by Achiwa in 1986⁵. It produced the simplest thiocarbonyl ylide, thioformaldehyde S-methylide 168, by thermal release of disiloxane from bis(silylmethyl)sulfoxide 166. These
bis(silylmethyl)sulfoxides are easily obtained by oxidation of the corresponding bis(silylmethyl)sulfides 165 using m-chloroperoxybenzoic acid. Upon heating, these compounds release disiloxane by a mechanism related to the sila-Pummerer rearrangement to yield the previously unobtainable thioformaldehyde S-methyldide 168 (Scheme 85).

\[
\begin{align*}
\text{R}_3\text{Si} & \quad \text{S} \quad \text{SiR}_3 \quad \xrightarrow{\text{m-CPBA}} \quad \text{R}_3\text{Si} \quad \text{S} \quad \text{SiR}_3 \\
165 & \quad 166 \\
\text{rearrangement} & \quad 167 \\
\text{R}_3\text{Si} & \quad \text{S} \quad \text{O} \quad \text{SiR}_3 \\
169 & \quad 168
\end{align*}
\]

Scheme 85

The bis(silylmethyl)sulfoxides are, however, prone to undergo sila-Pummerer rearrangement with increasing temperature or acidity in solvent-free conditions, to form the unreactive compound 169 84.

Achiwa demonstrated that the resulting ylide intermediate, thioformaldehyde S-methyldide 168, underwent 1,3-dipolar cycloaddition with a range of conjugated dipolarophiles to yield substituted tetrahydrothiophenes (Scheme 86).

\[
\begin{align*}
\text{R}_3\text{Si} & \quad \text{S} \quad \text{SiR}_3 \\
166 & \quad 168
\end{align*}
\]

Scheme 86
2.4.1.4 Halomethyl trimethylsilylmethyl precursors

An alternative precursor for the preparation of thioformaldehyde S-methylide \(168\) was reported by Sakurai in 1986. The 1,3-elimination reaction of chloromethyl trimethylsilylmethyl sulfide \(170\), promoted by acid or fluoride ion, produced the thio carbonyl ylide thioformaldehyde S-methylide \(168\) (Scheme 87).

\[ \text{Scheme 87} \]

The 1,3-elimination occurs at ambient temperature in the presence of acid and fluoride ions to yield the thio carbonyl ylide \(168\), which then undergoes 1,3-dipolar cycloaddition with a range of activated dipolarophiles to give substituted tetrahydrothiophenes. No 1,3-elimination was observed under thermal conditions. No cycloaddition reaction was observed between \(168\) and cyclic dipolarophiles such as \(N\)-methylmaleimide and maleic anhydride.

2.4.2 Thiocarbonyl ylide synthesis

Initial investigations into the synthesis of thio carbonyl ylide synthesis concentrated on the \(\alpha\)-halo(silylmethyl)sulfide precursors, as the thiadiazolidine precursors did not offer sufficient flexibility of substitution.
A thiocarbonyl ylide precursor, bromo(trimethylsilyl)methyltrimethylsilylmethyl sulfide 161, was prepared in good yield over two steps from chloromethyltrimethylsilane 172 (Scheme 88).

Two equivalents of chloromethyltrimethylsilane 172 were reacted with an aqueous solution of sodium sulfide in the presence of tetrabutylammonium iodide to generate bis(trimethylsilylmethyl)sulfide 173, and this underwent bromination using N-bromosuccinimide to give the desired precursor 161.

Thermolysis of 161 causes elimination of trimethylsilylbromide to produce the ylide intermediate, trimethylsilylthioformaldehyde S-methylide 162, which was then trapped by a range of dipolarophiles in a 1,3-dipolar cycloaddition reaction to form substituted tetrahydrothiophene derivatives.

2.4.2.1 1,3-Dipolar cycloadditions

The 1,3-dipolar cycloaddition reaction is a very useful reaction in organic chemistry, allowing for the formation of various five-membered heterocycles with a high degree of chirality. It involves the reaction of a dipolarophile - typically an alkene or alkyne, or molecules containing heteroatom equivalents such as carbonyl or nitrile compounds – with a 1,3-dipolar compound. A wide
range of functionality may be tolerated in both the dipolarophile and 1,3-dipole, making the 1,3-dipolar cycloaddition a very versatile reaction for the synthesis of heterocycles.

A vast array of 1,3-dipoles exist, which can be divided into two types: allyl anions such as nitrones 174, carbonyl or thio carbonyl ylides 175, azomethine ylides 176, nitro compounds 177 or carbonyl imines 178, and linear propargyl/allenyl anions, such as nitrile oxides 179, nitrilimines 180, diazoalkanes 181 or azides 182 (Figure 9). Four π electrons from the 1,3-dipole and two π electrons from the dipolarophile are involved in a concerted pericyclic process, forming two new σ-bonds that join the termini of the original π systems (Scheme 89).

![Scheme 89](image_url)
The transition state is determined by the frontier molecular orbitals of the dipolarophile and 1,3-dipole, involving either a LUMO-dipole/HOMO-dipolarophile or HOMO-dipole/LUMO-dipolarophile interaction, depending on the nature of the two components, and this interaction largely determines the stereo- and regio-chemical outcome of the reaction, although in some cases steric factors may also have an influence.

The dipole may also be stabilised by resonance through the central atom X (if X = N, O, S), leading to a non-concerted pathway (Scheme 90). In this instance, the stereochemistry of the dipolarophile may not be conserved.

\[
\begin{array}{c}
R^1 \equiv \begin{array}{c}
\text{R}^1
\end{array}
\end{array}
+ \begin{array}{c}
R^1 \equiv X \equiv \begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\rightarrow \begin{array}{c}
\left[ R^1 \equiv \begin{array}{c}
\text{R}^1
\end{array} \right]
\end{array}
\begin{array}{c}
\rightarrow \begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\begin{array}{c}
\rightarrow \begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\begin{array}{c}
\rightarrow \begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\end{array}
\]

\text{Scheme 90}

In more recent years, asymmetric 1,3-dipolar cycloaddition reactions have become extremely important in the synthesis of enantiomerically pure heterocycles, with the ability to introduce up to four stereocentres in a stereoselective manner in a single step. The enantioselectivity may be controlled by the use of a chiral dipolarophile, chiral dipole or chiral catalyst.

A vast range of chiral 1,3-dipoles have been employed to great success, including Fišera’s use of chiral nitrones derived from L-valine with methyl acrylate in the synthesis of optically pure isoxazolidines, and chiral azomethine ylides utilised by Harwood as a key step in the preparation of enantiomerically pure β-hydroxy-α-amino acids (Scheme 91).
More common is the use of chiral dipolarophiles. A recent study by Brandl into the use of chiral acrylates and acrylamides in a 1,3-dipolar cycloaddition reaction with 2-t-butoxycarbonyl-1-pyrroline N-oxide achieved excellent stereo-control, with in some cases only a single diastereoisomer observed (Scheme 92).

Many 1,3-dipolar cycloaddition reactions employ a catalyst, and this often provides the best opportunity for stereo-control. They may be employed in two ways, achiral catalysts may be used to potentiate the stereo-control of a reaction involving a chiral 1,3-dipole or dipolarophile, or chiral catalysts may be utilised to introduce stereo-selectivity in a reaction involving achiral reactants.
The efficiency of a chiral catalyst relies on the ability of the enantiopure catalyst to distinguish between the two \( \pi \)-faces of the dipolarophile, as well as its ability to control endo/exo selectivity and regioselectivity. As it coordinates to one of the reactants, the catalyst lowers the energy difference between the HOMO of the electron-rich component and the LUMO of the electron-deficient component, leading to increased reactivity.

The most common achiral catalysts used in 1,3-dipolar cycloaddition reactions are Lewis acids, and such catalysts have been reported for the reactions of a wide variety of both electron-rich and electron-deficient dipolarophiles.\textsuperscript{99, 100, 101} Work by Tamura\textsuperscript{102} on the highly stereoselective synthesis of the sweetener (-)-
monatin involved as a key step the 1,3-dipolar cycloaddition of a chiral nitrone with an allylic alcohol, catalysed by magnesium bromide (Scheme 93), which yielded a single diastereoisomer in excellent yield.

Several chiral catalysts have also been used in 1,3-dipolar cycloaddition reactions, both Lewis acid based catalysts and organo-catalysts. Recently, Maruoka developed a chiral bis-titanium (IV) oxide catalyst for the cycloaddition of various nitrones and acrolein to yield isoxazolidines with excellent enantioselectivity (Scheme 94).

Scheme 93

Scheme 94
Chiral organic catalysts have also been used in conjunction with Lewis acids to provide excellent stereoselectivity. (S)-QUINAP has been used by Schreiber\textsuperscript{104} in conjunction with the Lewis acid silver acetate in the 1,3-dipolar cycloaddition of azomethine ylides with various \(\alpha,\beta\)-unsaturated esters, resulting in excellent enantioselectivity (Scheme 95).

\[
\text{CH}_2\text{CO}_2\text{Me} + \text{CO}_2\text{Pr}^\bullet \xrightarrow{\text{AgOAc}} \text{AgOAc} \quad \text{(S)-QUINAP} \quad \text{t-Pr}_2\text{NEt}
\]

\[
\begin{align*}
R = p\text{-MeOC}_6\text{H}_4, & \; 93 \%, \; \text{ee} = 95 \% \\
R = p\text{-BrC}_6\text{H}_4, & \; 89 \%, \; \text{ee} = 95 \% \\
R = o\text{-Tol}, & \; 95 \%, \; \text{ee} = 89 \%
\end{align*}
\]

Scheme 95

Some organo-catalysed cycloadditions require no Lewis acid. Work by Karlsson\textsuperscript{105} involving the 1,3-dipolar cycloaddition of nitrones to 1-cycloalkene-1-carboxaldehyde utilised a chiral pyrrolidinium salt catalyst to produce a range of substituted isoxazolidines in high enantio- and diastereoselectivity (Scheme 96).

\[
\begin{align*}
\text{CHO} + \text{Me}^\bigcirc \quad \xrightarrow{\text{catalyst}} & \quad \text{Me}^\bigcirc \text{N} = \bigcirc \text{Me} \\
\text{R} = \text{Ph}, & \; 49 \%, \; \text{de} = 94 \%, \; \text{ee} = 92 \% \\
\text{R} = c\text{-C}_4\text{H}_7, & \; 68 \%, \; \text{de} = 96 \%, \; \text{ee} = 99 \% \\
\text{R} = n\text{-Pr}, & \; 76 \%, \; \text{de} > 98 \%, \; \text{ee} = 57 \% \\
catalyst = & \quad \text{Scheme 96}
\end{align*}
\]

75
The catalytic effect is due to iminium salt formation between the catalyst and the \( \alpha,\beta \)-unsaturated aldehyde, resulting in a decrease in energy of the LUMO of the aldehyde.

2.4.3 1,3-Dipolar cycloaddition reactions of thiocarbonyl ylides

2.4.3.1 Cycloaddition reactions of \( \alpha \)-halo(silylmethyl)sulfide ylides

Treatment of bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide 161 with dimethyl fumarate, in \( N,N \)-dimethylformamide at 110 °C, as reported by Achiwa,\textsuperscript{106} yielded 2-(trimethylsilyl)-tetrahydrothiophene-3,4-dicarboxylic acid dimethyl esters 183 and 184 as an inseparable mixture of diastereoisomers in 84 % yield (Scheme 97).

\[ \text{Scheme 97} \]

In the desired tetrahydrothiophene 1, only one electron-withdrawing group is present in the 3- and 4-positions, position 3 requiring an alkyl chain. In order to investigate whether electron-withdrawing groups were necessary at both ends of the double bond in the dipolarophile for cycloaddition to occur, reaction of 161 with methyl acrylate was attempted under the same conditions (Scheme 98).
Bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide 161 was reacted with methyl acrylate, in \( N,N \)-dimethylformamide at 110 °C. This produced the isomers 5-(trimethylsilyl)-tetrahydrothiophene-3-carboxylic acid methyl esters 185 and 186 and 2-(trimethylsilyl)-tetrahydrothiophene-3-carboxylic acid methyl esters 187 and 188, all as mixtures of enantiomers, in 59 % overall yield.

### 2.4.3.1.1 Regioselectivity in α-halo(silylmethyl)sulfide ylide cyclisations

The regio- and stereoselectivity of 1,3-dipolar cycloadditions of thiocarbonyl ylides bearing a terminal trimethylsilyl group have been investigated by Achiwa,\(^{106, 107}\) who studied the effects of further substitution of the ylide precursor bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide 161 in the dipolar cycloaddition reaction with methyl acrylate (Scheme 99).
The regio- and stereoselectivity of the reactions are summarised in Table 3 below.

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Total Yield (%)</th>
<th>Regioselectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td><img src="image1" alt="Product 161" /></td>
<td>52</td>
<td>75</td>
</tr>
<tr>
<td>161</td>
<td><img src="image2" alt="Product 161" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SiMe₃</td>
<td><img src="image3" alt="Product 189" /></td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>189</td>
<td><img src="image4" alt="Product 189" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td><img src="image5" alt="Product 190" /></td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>190</td>
<td><img src="image6" alt="Product 190" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. The regioselectivity in 1,3-dipolar cycloadditions

Achiwa observed that with the unsubstituted ylide precursor bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide 161, the dipolar cycloaddition reaction generated the 2,3-substituted tetrahydrothiophene in preference to the 2,4-substituted regioisomer, both as mixtures of stereoisomers, in a ratio of 3:1. In the case of the bistrimethylsilyl substituted ylide precursor...
189 (R = SiMe₃), the regioselectivity was less pronounced, with a 7.6 ratio of 2,2,3-substitution versus 2,2,4-substitution. In the case of the phenyl-substituted ylide precursor 190 however, only a single regiosomer was observed, with 2,2,3-substitution and favouring a trans relationship between the phenyl and ester substituents.

These regioselectivities may be explained by frontier molecular orbital theory. The first point to determine is whether the interaction occurs between the HOMO of the dipole and the LUMO of the dipolarophile, or the LUMO of the dipole and the HOMO of the dipolarophile. The energy levels (in eV) for the HOMO and LUMO of the three thio carbonyl ylides and methyl acrylate, calculated by Achiwa, are shown in Figure 10, and the more favourable interactions between HOMO and LUMO are indicated.
In each case it is the interaction between the HOMO of the dipole and the LUMO of the dipolarophile which is relevant, as this provides the smallest gap in energy levels. The electron-donating trimethylsilyl group present in all the dipoles has the effect of raising the energy of both the HOMO and LUMO, while the electron-withdrawing ester group of methyl acrylate lowers the energy of its HOMO and LUMO, reducing the energy gap of this interaction. The secondary substitution of a phenyl or second trimethylsilyl group has only a smaller effect on the frontier molecular orbital energies.

In order to determine the regioselectivity of the reaction following identification of the interaction as HOMO dipole-LUMO dipolarophile, the coefficients representing the electron densities of the frontier molecular orbitals, i.e., the HOMO of the dipole and the LUMO of the dipolarophile, must be considered. The coefficients calculated by Achiwa are shown in Figure 11, which also indicates the more favourable orientation of the frontier molecular orbitals, with a large/large and small/small interaction.

![Figure 11](image)

The regioselectivities observed by Achiwa may be explained by these coefficients, the dipolarophile is highly polarised as a result of the electron-withdrawing ester functionality, and so there is a large difference in the size of...
the coefficients. In the case of the dipole, where \( R = H \) there is a reasonable difference in the size of the coefficients, leading to the regioselectivity indicated in Table 3 as a result of the large/large and small/small interactions. The size difference is not too large to be overcome however, accounting for the 3:1 ratio of products. In the bis(trimethylsilyl)-substituted ylide precursor there is only a very small difference between the coefficients of the dipole, leading to poor regioselectivity. Finally, where the dipole bears a phenyl substituent the difference in size of the coefficients is so great that it results in a single regioisomer.

2.4.3.2 Substituted \( \alpha \)-halo(silylmethyl)sulfide ylide cyclisations

As the desired tetrahydrothiophene 1 required substitution at the 2-position, a substituted ylide precursor was synthesised to investigate the 1,3-dipolar cycloaddition reactions of such compounds. Phenyl substitution was chosen as there were literature precedents for these cyclisations.\(^{106,107}\)

(Trimethylsilyl)benzyl trimethylsilylmethyl sulfide 194 was synthesised from benzyl thiol 191 as shown in Scheme 100.

\[
\begin{align*}
\text{Scheme 100}
\end{align*}
\]
Two equivalents of \( n \)-butyllithium were added to benzyl thiol 191 at 0 °C, in order to doubly deprotonate the benzyl thiol and produce the dianion species 192, as described by Seebach\(^{108}\). After cooling to -78 °C, one equivalent of chlorotrimethylsilane was added, to quench the carbamon and give 193. The solution was allowed to warm to 0 °C before the second electrophile, chloromethyl trimethylsilane, was added to yield (trimethylsilyl)benzyl trimethylsilylmethyl sulfide 194 in 72% yield.

Sulfide 194 was then brominated using \( N \)-bromosuccinimide as before, to yield the ylide precursor (trimethylsilyl)(bromo)benzyl trimethylsilylmethyl sulfide 195 (Scheme 101).

\[
\begin{align*}
\text{Sulfide 194} & \xrightarrow{\text{Br, CCl}_4, 82\%} \text{Ylide precursor 195} \\
\end{align*}
\]

Scheme 101

This ylide precursor was then subjected to the same conditions as described above, in the presence of dimethyl fumarate to effect the 1,3-dipolar cycloaddition, yielding the 2-phenyl tetrahydrothiophenes 197 and 198 as an inseparable mixture of diastereoisomers (Scheme 102).

\[
\begin{align*}
\text{Ylide precursor 195} & \xrightarrow{\text{DMF, 110 °C}} \text{Cycloaddition products 196, 197, 198} \\
\end{align*}
\]

Scheme 102
We envisaged that the α-keto acid functionality in the desired tetrahydrothiophene 1 would be masked as a trimethylsilyl protected acetylene as in previous synthetic routes. The ring-forming step in the synthesis would be a 1,3-dipolar cycloaddition between a thiocarbonyl ylide bearing a trimethylsilyl protected acetylene at the terminus 203, and a conjugated dipolarophile 202 (Scheme 103).

![Scheme 103]

The required ylide precursor 204 would be synthesised in a manner analogous to the preparation of the phenyl substituted ylide precursor 195. To this end, 3-
trimethylsilyl-prop-2-ynyl-S-thioacetate 207 was obtained in two steps from propargyl bromide 205 (Scheme 104)

![Scheme 104](image)

The reaction produced a reasonable yield over the two steps, but due to the instability of the bromo-compounds an alternative route was sought. Propargyl alcohol was deprotonated using two equivalents of n-butyllithium and protected with trimethylsilylchloride in the manner described above, to afford 28 in good yield. A Mitsunobu reaction was then carried out to yield the thioacetate 207 (Scheme 105).

![Scheme 105](image)

3-(1,1,1-Trimethylsilyl)prop-2-yn-1-ol 28 was added to a cold, stirring solution of triphenylphosphine and disopropyl azodicarboxylate, followed by the addition of thiolacetic acid to form the desired 3-trimethylsilyl-prop-2-ynyl-S-thioacetate 207 in good yield. This provided a much cleaner and more efficient
route to the thioacetate, which was then hydrolysed using a solution of lithium aluminium hydride in diethyl ether to give the desired thiol 208 (Scheme 106).

![Scheme 106](image)

However, subjecting the resulting thiol 208 to the same reaction conditions as utilised in the double deprotonation of benzyl thiol (Scheme 100) yielded none of the desired product α-(trimethylsilylethynyl)-bis(trimethylsilylmethyl)sulfide 211 (Scheme 107).

![Scheme 107](image)
Attempts were then made to install the trimethylsilyl and trimethylsilylmethyl groups sequentially rather than in a one-pot process. There are numerous reports in the literature of the synthesis of α-trimethylsilyl thiols,\textsuperscript{108, 109, 110} typically by double deprotonation of the thiol as described above, followed by the addition of one molar equivalent of chlorotrimethylsilane. The product of such a reaction involving benzyl thiol is exclusively α-trimethylsilyl benzyl thiol \textsuperscript{213}, rather than benzylthiotrimethylsilane \textsuperscript{212} as may have been expected in the case of the equivalent alcohols (Scheme 108). It is known that sulfur has an acidifying influence on proton-bearing α-carbon atoms, an effect not shared by oxygen atoms. Though this effect was originally thought to arise as a result of the larger size and availability of the 3d orbitals on the sulfur atom,\textsuperscript{111} more recent studies have revealed this plays a minor role if any, and the acidifying effect is due to the polarisability of the sulfur atom\textsuperscript{112}.

![Scheme 108](image)

Indeed, it has also been shown that benzylthiotrimethylsilane \textsuperscript{212} undergoes a base-catalysed Wittig-type [1,2]-sigmatropic shift rearrangement to yield α-trimethylsilyl benzyl thiol \textsuperscript{213} \textsuperscript{111}.
To this end, 3-trimethylsilyl-prop-2-yne-1-thiol 208 was treated with 2.2 equivalents of $n$-butyllithium before addition of one equivalent of chlorotrimethylsilane (Scheme 109). Upon workup, however, none of the desired product or starting material could be isolated.

As a result of the problems encountered during the attempted installation of the two trimethylsilyl groups required for activation of the α-halo(silylmethyl)sulfide ylide precursor 204, alternative methods of thio carbonyl ylide formation were investigated.

2.4.3.2 Cycloaddition reactions of bis(silylmethyl)sulfoxide ylides

As the trimethylsilyl group present in the 2-position of the tetrahydrothiophenes synthesised from the α-halo(silylmethyl)sulfide ylide precursors is not present in the desired tetrahydrothiophene 1, the bis(silylmethyl)sulfoxide ylide precursors were investigated. With these ylide precursors, both trimethylsilyl groups are removed in the course of unmasking the ylide, resulting in no unwanted substitution in the product tetrahydrothiophenes.
Bis(trimethylsilylmethyl)sulfide 173 was prepared from chloromethyltrimethylsilane 172 in the manner described above. This was then oxidised using \( m \)-chloroperoxybenzoic acid in cold dichloromethane to yield bis(trimethylsilylmethyl)sulfoxide 215 in a quantitative yield (Scheme 110).

\[
\begin{align*}
\text{172} & \xrightarrow{\text{H}_2\text{O, reflux}} \text{173} & \xrightarrow{\text{m-CPBA, DCM, -40}^\circ\text{C}} \text{215} \\
\text{Na}_2\text{S}_2, \text{t-Bu}_4\text{NI} & \xrightarrow{78\%} & \text{m-CPBA} & \xrightarrow{98\%}
\end{align*}
\]

Scheme 110

A 1,3-dipolar cycloaddition reaction was then carried out between the sulfoxide ylide precursor 215 and dimethyl fumarate, in \( N,N' \)-dimethylpropyleneurea at 100 °C, as described by Achirwa. The reaction proceeded smoothly to give tetrahydrothiophene-3,4-dicarboxylic acid dimethyl ester 150 in a 71 % yield (Scheme 111).

\[
\text{215} \xrightarrow{\text{DMPU, 100}^\circ\text{C}} \text{168} \xrightarrow{\text{MkO}_2\text{C, 71\%}} \text{150}
\]

(Scheme 111)

Aromatic- and aliphatic-substituted thioaldehyde \( S \)-methylides can also be generated from the corresponding sulfoxides. To prepare the phenyl-substituted thioaldehyde \( S \)-methylide precursor, (trimethylsilyl)benzyl trimethylsilylmethyl sulfide 194 was synthesised from benzyl thiol 191 as described above (Scheme 100).
The doubly deprotonated benzyl thiol was treated sequentially with one equivalent of chlorotrimethylsilane, followed by chloromethyl trimethylsilane to yield 194. This was then oxidised to the corresponding sulfoxide 216 using m-chloroperoxybenzoic acid in dichloromethane at –40 °C (Scheme 112).

Cycloaddition was then carried out between sulfoxide 216 and dimethyl fumarate. Thermal elimination of disiloxane yields the thio carbonyl ylide 217, which underwent a 1,3-dipolycycloaddition reaction to yield diastereoisomers 218 and 219 which were not separated, both as mixture of enantiomers (Scheme 113).
Using a substituted bis(silylmethyl)sulfoxide ylide precursor, a 2-substituted tetrahydrothiophene not bearing the 2-trimethylsilyl substituent was obtained. However, this synthetic route still encountered the same problem as the α-halo(silylmethyl)sulfide ylide precursor route when attempting to install the required trimethylsilyl protected acetylene functionality in the 2-position, which would later be unmasked as the α-keto acid in tetrahydrothiophene 1. Reaction of the dianion of 3-trimethylsilyl-prop-2-yne-1-thiol 208 with chlorotrimethylsilane and chloromethyl trimethylsilane failed to yield the thioether 211 required to obtain the necessary ylide precursor (Scheme 107).

Scheme 107
We therefore decided to investigate a further class of ylides halomethyl trimethylsilylmethyl ylides

2.4.3.3 Cycloaddition reactions of halomethyl trimethylsilylmethyl ylides

Halomethyl trimethylsilylmethyl ylide precursors have two major advantages over the two types of ylide precursor discussed above; they are activated by acid/flouride ions rather than thermally activated, and so reactions can be carried out at ambient temperatures, allowing for a wider range of functionality to be tolerated. They also have the advantage of utilising a halide leaving group, rather than a trimethylsilyl group. This means that only one $\beta$-trimethylsilyl group is required in the ylide precursors.

The simplest halomethyl trimethylsilylmethyl ylide precursor, chloromethyl(trimethylsilylmethyl)sulfide 170, was obtained from chloromethyltrimethylsilane 172 in reasonable yield (Scheme 114)

Chloromethyltrimethylsilane 172 was treated with thiourea in refluxing absolute ethanol to yield a white powder. This was then reacted with sodium hydroxide solution to give the thiol 220 in a 61% yield. Chloromethylation was then carried out as described by Evans,\textsuperscript{113} by bubbling gaseous hydrochloric acid through a solution of the thiol and 1,3,5-trioxane 221 at $-10$ °C to yield
chloromethyl(trimethylsilylmethyl)sulfide 170. This reaction was unpredictable, however, and it was hard to achieve a reasonable, reproducible yield as a result of the presence of a large quantity of a byproduct being formed. This byproduct was identified as the dimeric species 228, presumably formed through the pathway illustrated in Scheme 115.

Scheme 115
Attack of the intermediate 226 could occur by either a chloride ion to yield the desired ylide precursor 170, or by attack of another equivalent of trimethylsilylmethanethiol, giving rise to the observed undesired product 228. To avoid formation of this byproduct, alternative methods of chloromethylation were investigated, with the aim of lowering the concentration of trimethylsilylmethanethiol present to reduce the likelihood of reaction between trimethylsilylmethanethiol and the intermediate 226.

Work by Schmidt\textsuperscript{114} into the synthesis of 1-N-glycosylthiomethyl-1,2,3-triazoles involved as a key step the conversion of O-acyl protected glycosylthiols to the corresponding glycosylthiomethyl chlorides. The authors hypothesised that treating these thiols with dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) would lead to methylene-linked dimers of the glycosylthiols. However, when the reaction was carried out, good to excellent yields of the desired glycosylthiomethyl chlorides were observed (Scheme 116).

![Scheme 116](image-url)
Attempts were made to synthesise the required ylide precursor 170 under these conditions. Trimethylsilylmethanethiol 220 was dissolved in dichloromethane at ambient temperature and treated with one equivalent of DBU. However, this resulted in a 45% yield of the desired chloromethyl(trimethylsilylmethyl)sulfide 170 with a 37% yield of the dimeric species 228 (Scheme 117).

\[
\begin{align*}
\text{220} \quad &\xrightarrow{\text{1 eq DBU, DCM, rt, 5 h}} \quad \text{228} \\
( & \quad 45\% \quad + \quad 37\% )
\end{align*}
\]

Scheme 117

These findings were backed up by a report by Ono\textsuperscript{115} on the synthesis of sulfides and chloromethyl sulfides, which examined the stoichiometry of the reaction between thiophenol and both dichloromethane and bromochloromethane in the presence of DBU. The authors found that the reaction of thiophenol 229 with dichloromethane with one equivalent of DBU yielded bis(phenylthio)methane 230 in an 82% yield (Scheme 118).

\[
\begin{align*}
\text{229} \quad &\xrightarrow{\text{1 eq DBU, DCM, rt, 6 h}} \quad \text{230} \\
( & \quad 82\% )
\end{align*}
\]

Scheme 118
However, they also reported that the reaction of thiophenol with bromochloromethane in acetonitrile, in the presence of one equivalent of DBU produced α-chlorothioanisole 231 in 75 % yield (Scheme 119)

\[
\text{Scheme 119}
\]

These conditions were applied to the synthesis of chloromethyl(trimethylsilylmethyl)sulfide 170. Trimethylsilylmethanethiol was dissolved in acetonitrile and one equivalent of DBU added. This was then added to a solution of bromochloromethane, resulting in a 39 % yield of the desired sulfide and 27 % of the dimeric species 228 (Scheme 120)

\[
\text{Scheme 120}
\]

A further study of the synthesis of chloromethyl thioaromatics by Ramadas\textsuperscript{116} was discovered. A range of thioaromatics was reacted with bromochloromethane in acetone, in the presence of a catalytic quantity of potassium hydroxide and the ion-exchange resin Amberlite IRA 400 to give the corresponding (chloromethyl)thioaromatics in good yields (Scheme 121).
The desired ylide precursor 170 was then synthesised under these conditions. Trimethylsilylmethanethiol was dissolved in acetone and potassium hydroxide added. This mixture was then added dropwise to a solution of bromochloromethane and Amberlite IRA 400 in acetone, which yielded 13% of the desired ylide precursor 170 and 18% of the dimeric species 228 (Scheme 122).

\[
\begin{align*}
15 \text{ eq } \text{ClCH}_2\text{Br} & \quad 20 \text{ mol } \% \text{ KOH} \\
\text{Amberlite IRA 400} & \quad \text{acetone, } 10 \degree \text{C} \\
\quad & \quad 84 \% \\
\end{align*}
\]

\[
\begin{align*}
15 \text{ eq } \text{ClCH}_2\text{Br} & \quad 20 \text{ mol } \% \text{ KOH} \\
\text{Amberlite IRA 400} & \quad \text{acetone, } 10 \degree \text{C} \\
\quad & \quad 73 \% \\
\end{align*}
\]

\[
\begin{align*}
15 \text{ eq } \text{ClCH}_2\text{Br} & \quad 20 \text{ mol } \% \text{ KOH} \\
\text{acetone, } 10 \degree \text{C} & \quad \text{yielded } 13 \% \\
& \quad 18 \% \quad \text{Scheme 122}
\end{align*}
\]
A further method was found in the literature in a report by Li\textsuperscript{117} on the synthesis of polydentate ligands for biomimetic metal complexes. The authors reported the synthesis in quantitative yield of benzylchloromethylsulfide 232 from benzyl thiol 191, bromochloromethane and potassium hydroxide, using triethylbenzylammonium chloride (TEBAC) as a phase-transfer catalyst (Scheme 123). The bromochloromethane in this instance acts as both a reactant and solvent.

\[ \text{Scheme 123} \]

These conditions were subsequently applied to the synthesis of chloromethyl(trimethylsilylmethyl)sulfide 170. Trimethylsilylmethanethiol was dissolved in bromochloromethane, and a catalytic quantity of triethylbenzylammonium chloride added, followed by one equivalent of powdered potassium hydroxide. This procedure gave a 67% yield of the desired chloromethyl(trimethylsilylmethyl)sulfide 170 and only 21% of the unwanted byproduct 228 (Scheme 124).

\[ \text{Scheme 124} \]
As a result of the increased and reproducible yield, combined with the milder reaction conditions, this method was subsequently used for the synthesis of the ylide precursor 170.

Several 1,3-dipolar cycloaddition reactions were carried out with the ylide precursor 170. Dimethyl fumarate was initially chosen, as it had proved to be a very reliable dipolarophile with other ylide precursors Chloromethyl(trimethylsilylmethyl)sulfide 170 and dimethyl fumarate were dissolved in acetonitrile at ambient temperature, and caesium fluoride added. The reaction produced a colourless crystalline solid in good yield (Scheme 125)

![Scheme 125](image)

An X-ray crystal structure was obtained of tetrahydrothiophene 150 that clearly illustrates the trans relationship between the two ester groups in the 3- and 4-positions (Figure 12). The crystallography was carried out by Dr Mark Elsegood at Loughborough University, and revealed the C-S bond length in the molecule to be 1.82 Å, which corresponds to the standard C-S bond length of 1.83 Å.
Also visible from the X-ray crystal structure of 150 is the manner in which the molecules are arranged within the crystal, with hydrogen bonding between the ester functionality of one tetrahydrothiophene and the α-protons of another (Figure 13)
1,3-Dipolar cycloaddition reactions were carried out with a range of electron deficient dipolarophiles. The reaction between ylide precursor 170 and diethyl fumarate proceeded smoothly, to yield tetrahydrothiophene-3,4-dicarboxylic acid diethyl ester 151 in good yield (Scheme 126)

\[
\begin{align*}
\text{170} & \xrightarrow{\text{CsF, MeCN, rt}} \left[\text{H}_2\text{C} = \text{C} = \text{S} \right] \xrightarrow{\text{EtO}_2\text{C}} \text{168} \xrightarrow{67\%} \text{151}
\end{align*}
\]

Scheme 126

Cycloaddition reactions were also achieved with two electron-deficient vinyl sulfones. The reaction between chloromethyl(trimethylsilylmethyl)sulfide 170 and methylvinylsulfone proceeded in acetonitrile at ambient temperature, in the presence of caesium fluoride to give 3-methanesulfonyl tetrahydrothiophene 233 in a good yield (Scheme 127)

\[
\begin{align*}
\text{170} & \xrightarrow{\text{CsF, MeCN, rt}} \left[\text{H}_2\text{C} = \text{C} = \text{S} \right] \xrightarrow{\text{O}_2\text{S}} \text{168} \xrightarrow{68\%} \text{233}
\end{align*}
\]

Scheme 127

Similarly, the reaction between ylide precursor 170 and phenylvinylsulfone proceeded under the same conditions to give 3-benzenesulfonyl tetrahydrothiophene 234 in an excellent yield (Scheme 128)
In addition, an X-ray crystal structure of 234 was obtained, revealing the structure of the molecule (Figure 14).

The secondary arrangement and bonding between molecules within the crystal structure can also be observed, revealing hydrogen bonding between the sulfoxide functionality of one tetrahydrothiophene and the α-protons of another (Figure 15).
As the required tetrahydrothiophene 1 is substituted in the 2-position, it was necessary to synthesise substituted ylide precursors to install this 2-substitution in the product tetrahydrothiophenes.

α-Trimethylsilyl benzylthiol 213 was synthesised from benzyl thiol 191 in a manner analogous to the synthesis of (trimethylsilyl)benzyl trimethylsilylmethyl sulfide 194 described previously (Scheme 129).
Two equivalents of n-butyllithium were added to benzyl thiol at 0 °C, in order to doubly deprotonate the benzyl thiol and produce the dianion species 192. After cooling to −78 °C, one equivalent of chlorotrimethylsilane was added, and the solution allowed to warm to ambient temperature, to give α-trimethylsilyl benzylthiol 213 in an 82% yield.

Chloromethylation was then attempted, firstly using gaseous hydrochloric acid in the presence of 1,3,5-trioxane (Scheme 130), which again was subject to the limitations of un reproduceable yields, but formed the desired chloromethyl trimethylsilylphenylmethyl sulfide 235 in a 59% yield.

\[
\begin{array}{c}
\text{HCl(g)} \\
1,3,5-	ext{trioxane} \\
\text{(-10 °C)} \\
\text{59%}
\end{array}
\]

\[
213 \overset{\text{HCl(g)} \text{1,3,5-trioxane}}{\underset{-10 \text{ °C}}{\longrightarrow}} 235
\]

Scheme 130

This yield was subsequently improved by employing the optimised conditions determined previously, namely the reaction of α-trimethylsilyl benzylthiol 213 with bromochloromethane in the presence of potassium hydroxide and a catalytic quantity of TEBAC, which resulted in a 76% yield of the desired chloromethyl(trimethylsilyl)benzyl sulfide 235 (Scheme 131).

\[
\begin{array}{c}
\text{ClCH}_{2}\text{Br} \\
\text{KOH} \\
\text{TEBAC} \\
\text{76%}
\end{array}
\]

\[
213 \overset{\text{ClCH}_{2}\text{Br} \text{KOH} \text{TEBAC}}{\underset{76 \text{%}}{\longrightarrow}} 235
\]

Scheme 131
A 1,3-dipolar cycloaddition reaction was carried out between the substituted ylide precursor 235 and dimethyl fumarate. The two were dissolved in acetonitrile at ambient temperature, and caesium fluoride added. The cycloaddition proceeded smoothly to give a colourless oil in a 69% yield, from which a colourless crystalline solid formed upon standing (Scheme 132).

Scheme 132

An X-ray crystal structure was obtained of the resulting 2-substituted tetrahydrothiophene, which revealed a cis relationship between the 2-phenyl and 3-methyl ester substituents (Figure 16).
Attempts to install the trimethylsilyl-protected acetylene at the 2-position of the desired tetrahydrothiophene 200, by reaction of the ylide precursor 204 with a dipolarophile (Scheme 103), had been frustrated by the failure to install the α-trimethylsilyl group into the required thiol 214 (Scheme 109)

\[
\begin{align*}
\text{Si-} & \quad 2 \text{eq n-BuLi} \\
\text{TMEDA} & \quad \text{THF, 0 °C} \\
\text{Si-} & \quad 2 \text{L}^+ \\
\text{TMSCl} & \quad -75°C \text{ to rt}
\end{align*}
\]

**Scheme 109**

As 1,3-bistrimethylsilyl-prop-2-yne-1-thiol 214 was also required for the synthesis of the corresponding halomethyl trimethylsilylmethyl ylide precursor, an alternative route was sought. As the 1,3-dipolar cycloaddition reaction conditions for halomethyl trimethylsilylmethyl ylides are far milder than the conditions required for the activation of α-halo(silylmethyl)sulfide ylides and bis(silylmethyl)sulfoxide ylides, we decided to investigate the synthesis of an ylide precursor bearing an α-keto ester, rather than having this group masked as a trimethylsilyl-protected acetylene.

Attempts were made to synthesise ethyl mercaptopyruvate 237 from ethyl bromopyruvate 236, as described by both Reiter\textsuperscript{118} and Corey\textsuperscript{119} They describe the reaction of ethyl bromopyruvate 236 with a mixture of sodium, ethanol and hydrogen sulfide at 4 °C to yield ethyl mercaptopyruvate (Scheme 133)

\[
\begin{align*}
\text{Br} & \quad \text{Na, H}_2\text{S} \\
\text{EtOH, 4 °C} & \quad 64% \\
\text{O} & \quad \text{O} \\
\text{236} & \quad \text{237}
\end{align*}
\]

**Scheme 133**
Attempts were made to carry out this reaction without using hydrogen sulfide gas. Ethyl bromopyruvate 236 was reacted with anhydrous sodium hydrogen sulfide in ethanol, in the presence of a catalytic quantity of tetrabutylammonium iodide as a phase transfer catalyst. The reaction was stirred at 0 °C for two hours, followed by sixteen hours at ambient temperature. However, none of the desired product or starting material could be identified from the reaction (Scheme 134).

![Chemical structure of 236 and 237 with reaction conditions](image)

**Scheme 134**

An attempt was then made to synthesize the corresponding thioacetate from ethyl bromopyruvate, by reaction with potassium thioacetate as described above in the synthesis of 3-trimethylsilyl-prop-2-ynyl-S-thioacetate 207. To this end, ethyl bromopyruvate 236 was reacted with potassium thioacetate in tetrahydrofuran at 0 °C. However, none of the desired compound could be isolated, with the only product identifiable by mass spectrometry being the unwanted ethyl 2,3-bis(thioacetyl)acrylate 238 (Scheme 135).

![Chemical structure of 236 and 238 with reaction conditions](image)

**Scheme 135**
No further work was undertaken on the synthesis of the required ylide precursors, either the trimethylsilyl protected acetylene 239 or the unmasked α-keto ester 240.

\[
\text{\includegraphics[width=2cm]{239}} \quad \text{\includegraphics[width=2cm]{240}}
\]

Nonetheless, it is anticipated that further investigation into the α-keto ester ylide precursor 240 would lead to a successful synthesis of this molecule. Once conversion of ethyl bromopyruvate 236 to ethyl mercaptopyruvate 237 is achieved, the installation of the α-trimethylsilyl functionality via the dianion intermediate should proceed smoothly, due to the ability of the molecule to stabilise a negative charge at the α-position. Finally, chloromethylation using the established method would afford the desired ylide precursor 240.

2.4.4.1 Installation of the required dipolarophile substituents

The tetrahydrothiophenes synthesised currently have diester substitution at the 3- and 4- positions, or are mono esters with the other position unsubstituted. The desired tetrahydrothiophene moiety 199 requires an ester substituent at the 4-position and a branched alkyl chain at the 3-position. We envisaged that a suitable dipolarophile 202 would react with the α-keto acid-bearing ylide precursor 241 to install this substitution (Scheme 136).
2.4.4.2 Synthesis of the required dipolarophile

Synthesis of the reduced form of the required dipolarophile 202 was achieved in three steps from the commercially available 3-methyl-4-pentenoic acid 243 (Scheme 137)

Scheme 136

Scheme 137
Esterification of 3-methyl-4-pentenoic acid 243 using dimethyl sulfate and caesium carbonate in dichloromethane proceeded to give 244 in 78% yield. This was followed by reduction of the ester function to the corresponding alcohol 245 with lithium aluminium hydride, and finally a cross metathesis reaction with methyl acrylate and a catalytic amount of Grubbs’ second generation catalyst yielded 66% of the desired racemic dipolarophile 246.

Grubbs’ second generation ruthenium carbone complex 248 for the metathesis of olefins was first reported in 1999, and represented a marked improvement over the first generation catalyst 247 in terms of activity, air and water tolerance, and required catalyst loading. For these reasons, the second generation catalyst was chosen for this cross metathesis reaction:

A vast array of olefins may undergo cross metathesis reactions, including terminal olefins, allylic alcohols, acrylates, acrylamides, vinyl ketones, 1,1-disubstituted olefins and allyl halides, and the relative reactivity of each is determined by their ability to homodimerise (Scheme 138).
Olefins are categorised as Type I – those able to undergo rapid homodimerisation and whose homodimers play a role in cross metathesis as well as the initial olefin, Type II – those which undergo homodimerisation less slowly than Type I, and whose homodimers only sparingly participate in cross metathesis reactions, and Type III – which are unable to undergo homodimerisation by the catalyst, but which still take part in cross metathesis reactions with Type I and Type II olefins.

With the second generation Grubbs catalyst, terminal olefins are categorised as Type I, while acrylates are classed as Type II. In this instance however, we carried out the reaction between alcohol and methyl acrylate, which proceeded smoothly to yield the desired dipolarophile with no evidence of homodimerisation of the terminal olefin.

With the desired dipolarophile in hand, a 1,3-dipolar cycloaddition reaction was carried out with the unsubstituted chloromethyl ylide precursor (Scheme 139)
Scheme 139

Chloromethyl (trimethylsilylmethyl) sulfide 170 and the dipolarophile 246 were dissolved in acetonitrile at ambient temperature, and caesium fluoride added. The reaction yielded 62% of the desired tetrahydrothiophene as an inseparable mixture of diastereoisomers 249 and 250 in a 1:1.5 ratio, both as a mixture of enantiomers.

2.4.4.3 Synthesis of enantiomerically pure dipolarophiles

As the relative stereochemistry of the methyl group in the branched alkyl chain substituent is unknown in the target molecule tetronothiodin 251, the decision was taken to synthesise both enantiomers of the racemic dipolarophile 246. The resulting tetrahydrothiophenes could then be analysed and compared to an authentic sample of tetronothiodin to establish the relative stereochemistry of this centre.
In order to control the stereochemistry of the methyl group in the required dipolarophile, Evans' \( N \)-acyl oxazolidinone chiral auxiliaries were employed. First reported by Evans in 1982, these chiral oxazolidinones are widely used in asymmetric synthesis and consist of an optically pure \( N \)-acylated oxazolidinone bearing a bulky substituent, such as isopropyl, phenyl or benzyl. Used in aldol or alkylation reactions, they form chiral enolate intermediates. The pre-existing chirality from the auxiliary is then transferred to the aldol or alkylation product in a diastereoselective reaction, allowing the auxiliary to be removed to reveal the optically pure product (Scheme 140)

![Scheme 140](image)
In order to synthesise the enantiomerically pure dipolarophiles required, an alkylation reaction was envisaged between the chiral auxiliary \((R)\)-4-benzyl-3-propionyl-2-oxazolidinone 254 and a protected analogue of bromoethanol 253. Towards this end, bromoethanol was protected by the reaction with tertbutyldimethylsilyl chloride in dichloromethane, in the presence of imidazole and a catalytic amount of dimethylamino pyridine (DMAP) (Scheme 141). An enolate alkylation reaction was then carried out between the resulting 2-bromoethoxy tertbutyldimethylsilane 253 and the Evans auxiliary \((R)\)-4-benzyl-3-propionyl-2-oxazolidinone 254.

![Scheme 141](image)

The chiral auxiliary 254 was deprotonated using lithium bis(trimethylsilyl)amide in tetrahydrofuran at \(-78\,^\circ\text{C}\) and 2-bromoethoxy tertbutyldimethylsilane 253 added dropwise. None of the desired product could be isolated from the reaction mixture, however, with only the chiral auxiliary identifiable.

An alternative alkylation approach was then carried out, with the chiral auxiliary 254 deprotonated in the same manner, and reacted with allyl bromide 256, as described by Joulhè\textsuperscript{131} (Scheme 142)
The reaction proceeded smoothly to give the desired product 257 in a 77% yield. Ozonolysis was then carried out on 257 to install the required carbonyl functionality, and the resulting aldehyde protected as the acetal 259. Olefin 257 was dissolved in dichloromethane and cooled to -78°C. Ozone gas was then bubbled through the solution until a stable purple colour was achieved, at which point dimethylsulphide was added and the reaction allowed to reach ambient temperature to yield the aldehyde 258. This aldehyde functionality was then protected as the corresponding acetal 259 by reaction with ethylene glycol to allow further transformations of the molecule to be carried out (Scheme 143).
Cleavage of the chiral auxiliary was achieved using a solution of lithium aluminium hydride. Compound 259 was dissolved in tetrahydrofuran and cooled to 0 °C before the addition of lithium aluminium hydride. This cleaved the amide bond between the chiral auxiliary and the desired compound to give dioxolane 260 in a 72% yield. Oxidation of the primary alcohol with pyridinium chlorochromate in dichloromethane proceeded smoothly, to provide the target compound aldehyde 261 (Scheme 144).

![Scheme 144](image)

The final step in the synthesis of the optically pure desired dipolarophile was a Horner-Wadsworth-Emmons reaction between aldehyde 261 and triethyl phosphonoacetate 262 (Scheme 145).

![Scheme 145](image)
Triethyl phosphonoacetate 262 was deprotonated with sodium hydride in tetrahydrofuran at 0 °C and aldehyde 261 added. The Horner-Wadsworth-Emmons reaction proceeded in 73 % to yield the desired (S)-dipolarophile 263. As a stabilised reagent, triethyl phosphonoacetate was utilised, the required E-alkene was obtained.

With the synthesis of one enantiomer of the desired dipolarophile complete, attention was turned to the synthesis of the opposite enantiomer, [4R]-ethyl 5-[1,3]-dioxolan-2-yl-4-methyl-pent-2-enoate. The same synthetic route was utilised, starting from the Evans' auxiliary 264.

The chiral auxiliary 264 was deprotonated using sodium bis(trimethylsilyl)amide to form the chiral enolate, and reacted with allyl bromide 256 (Scheme 146).

The reaction yielded 80 % of the desired species 265. This was followed by ozonolysis to form the aldehyde 266, which was subsequently protected as the acetal 267 (Scheme 147).
Ozone gas was bubbled through a solution of the olefin 265 in cold dichloromethane until a stable purple colour was achieved. Dimethylsulfate was then added and the reaction warmed to give aldehyde 266 in 85% yield. The aldehyde functionality was then protected as the corresponding acetal 267 by reaction with ethylene glycol.

Removal of the chiral auxiliary was then achieved by dissolution of 267 in tetrahydrofuran and cooling to 0 °C, followed by the addition of lithium aluminium hydride to yield 268, with an optical rotation of +8.6° (Scheme 148). This compound has been previously synthesised by Clive,132 with an optical rotation of +8.873°.
Oxidation of the resulting primary alcohol of 268 with pyridinium chlorochromate in dichloromethane, provided 71% of the target compound aldehyde 269.

Finally, a Horner-Wadsworth-Emmons reaction between aldehyde 269 and the stabilised reagent triethyl phosphonoacetate 262 was carried out to yield the (R)-dipolarophile 270. Sodium hydride was used to deprotonate a solution of 262 in tetrahydrofuran at 0 °C, and aldehyde 269 added. The reaction proceeded to yield 75% of the desired (R)-dipolarophile 270 (Scheme 149).

\[
\begin{align*}
\text{NaH} & \quad \text{THF, 0 °C} \quad 75\% \\
\text{269} & \quad + \quad \text{262} \quad \rightarrow \quad \text{270}
\end{align*}
\]

**Scheme 149**

With both enantiomers of the required dipolarophile synthesised, a method of controlling the diastereoselectivity of the 1,3-dipolar cycloaddition reaction was sought.

### 2.4.5 Diastereomeric control in 1,3-dipolar cycloaddition reactions

There are various examples in the literature of chiral dipolarophiles being utilised to control diastereoselectivity in 1,3-dipolar cycloaddition reactions,
however the majority are concerned with $N$-oxide or nitrogen ylides\textsuperscript{123, 124, 125}. A chiral auxiliary is reacted with the dipolarophile to form a chiral dipolarophile, which then directs diastereoselectivity in the 1,3-dipolar cycloaddition reaction (Scheme 150). The most common chiral auxiliaries used in this manner are chiral oxazolidinones, diisopropyl tartrate and camphorsultam\textsuperscript{126}

\[ \text{[Y]} + \text{R=O, N, S} \stackrel{\text{Xc}}{\longrightarrow} \text{R, Y, Xc} + \text{R, Y, Xc} \]

\[ \text{Scheme 150} \]

A major and a minor diastereoisomer are produced by the 1,3-dipolar cycloaddition in this manner, determined by the chiral auxiliary used. In the case of the sultams, when not complexed or chelated to Lewis acids, they react with dipolar compounds in a conformation where the carbonyl oxygen and the sulfone are arranged \emph{trans} with respect to each other in relation to the C-N amide bond. In the case of (1S)-(−)-2,10-camphorsultam, the incoming dipolar species then attacks the \emph{re-re} face of the double bond of the dipolarophile due to unfavourable interactions between the dipole and the axially orientated oxygen of the sulfone. This yields the major diastereoisomer as shown (Scheme 151). Conversely, in a cycloaddition reaction with (1R)-(+)2,10-camphorsultam as a chiral auxiliary, the dipole attacks the \emph{si-si} face of the dipolarophile to avoid
interactions with the axial sulfone oxygen, resulting in the opposite diastereoisomer as the major product.

\[ \text{Scheme 151} \]

Work by Hogberg\textsuperscript{127} into the diastereoselective synthesis of \textit{trans}-3,4-disubstituted tetrahydrothiophenes involved the use of (1S)-(\textit{R})-2,10-camphorsultam as a chiral auxiliary, resulting in diastereoselectivities as high as 90:10 (Scheme 152).

\[ \text{Scheme 152} \]
We envisaged that a chiral auxiliary could be used to control the
diastereoselectivity of the 1,3-dipolar cycloaddition reaction between the
enantiomerically pure dipolarophiles obtained and the ylide precursor.

To test the efficiency of the chiral auxiliaries with these dipolarophiles, N-
acryloyl (1S)-(−)-2,10-camphorsultan 273 would be synthesised. This would be
reacted with the racemic alcohol 3-methyl-4-penten-1-ol 244 in a cross
metathesis reaction to yield a chiral dipolarophile

To this end, acryloyl chloride 272 was synthesised from acrylic acid 271, by
reaction with thionyl chloride in refluxing dichloromethane The acid chloride
was not isolated, but the solution concentrated in vacuo and added to a solution
of (1S)-(−)-2,10-camphorsultan and methyl magnesiumbromide as described by
Hogberg127 (Scheme 153)

\[
\begin{align*}
271 & \xrightarrow{\text{thionyl chloride}} 272 \\
 DCN & \text{reflux} \\
\end{align*}
\]

Scheme 153

None of the desired N-acryloyl (1S)-(−)-2,10-camphorsultan 273 could be
isolated, however, with only the starting material (1S)-(−)-2,10-camphorsultan
identifiable from the reaction mixture
An alternative approach was also investigated, as reported by Kim\textsuperscript{128} The authors described the synthesis of \(N\)-acyloyl (1S)-(\(-\))-2,10-camphorsultam 273, albeit in a low yield, by the deprotonation of (1S)-(\(-\))-2,10-camphorsultam using sodium bis(trimethylsilyl)amide, and subsequent reaction with acryloyl chloride. Following this method, sodium bis(trimethylsilyl)amide was added to a solution of the camphorsultam in tetrahydrofuran at \(-78^\circ \text{C}\), followed by a solution of acryloyl chloride 272 prepared as previously described (Scheme 154).

Unfortunately, none of the desired \(N\)-acyloyl (1S)-(\(-\))-2,10-camphorsultam 273 could be isolated.

Synthesis of \(N\)-acyloyl (1S)-(\(-\))-2,10-camphorsultam 273 directly from acrylic acid 271 was also attempted (Scheme 155).
1-Ethyl 3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), a carboxyl activating agent, was added to a solution of acrylic acid 271 in dichloromethane and (1S)-(−)-2,10-camphorsultam added. The reaction was stirred at ambient temperature for 16 h, but acrylic acid was the only identifiable product.

A further paper by Kim\textsuperscript{129} reported an improved synthesis of N-acryloyl (1S)-(−)-2,10-camphorsultam 273. The authors achieved a successful synthesis by employing triethylamine in the presence of copper chloride and copper powder, with a catalytic quantity of dimethylaminopyridine (DMAP). These conditions were repeated and resulted in a good yield of the desired product (Scheme 156).
With the acrylic chiral auxiliary in hand, a cross metathesis reaction was carried out with 3-methyl-4-pentenoic acid methyl ester 244 (Scheme 157). While no precedent could be found in the literature for cross metathesis reactions involving chiral sultam acrylamides, there was good evidence for a wide range of aromatic and aliphatic acrylamides participating in cross metathesis reactions.  

Scheme 157
The starting materials were refluxed in dichloromethane with Grubb's second generation catalyst for twenty-four hours. None of the desired chiral dipolarophile 274 could be isolated from the reaction mixture however, with the only identifiable products being the two starting materials and the product of homodimerisation of 3-methyl-4-pentenoic acid methyl ester.

In order to investigate the possibility of installing the chiral auxiliary after the cross metathesis reaction, 4-methyl-hex-2-enedioic acid 6-methyl ester 275 was synthesised from 3-methyl-4-pentenoic acid methyl ester 244 and acrylic acid 271 (Scheme 158).

\[
\begin{align*}
\text{244} & \quad + \quad \text{271} \quad \xrightarrow{\text{DCM, reflux, 24 h, 60\%}} \quad \text{275}
\end{align*}
\]

Scheme 158

In this case, the cross metathesis reaction proceeded smoothly to give the desired dipolarophile in 60% yield. It is envisaged that reaction of the acid chloride derivative of 275 with the chiral auxiliary (1S)-(−)-2,10-camphorsultam under the conditions described above, will yield the desired chiral dipolarophile 274 (Scheme 159).
2.4.6 Towards the synthesis of the desired tetrahydrothiophene

Synthesis of a number of tetrahydrothiophenes has been successful, using a number of ylide precursors to achieve the 1,3-dipolar cycloaddition reaction with various dipolarophiles.

Progress has been made towards the synthesis of the required ylide precursor. Substituted ylide precursors have been synthesised and used in successful 1,3-dipolar cycloaddition reactions to yield 2-substituted tetrahydrothiophenes. Due to the frustrated attempts to install the α-trimethylsilyl substituent into the acetyhmic thiol 208, an alternative ylide precursor was sought. Successful conversion of ethyl bromopyruvate 236 to ethyl mercaptopyruvate 237, possibly under the conditions described in the literature would leave only two further steps in the synthesis of the required ylide precursor 240 (Scheme 160)
The required dipolarophile to install the correct substitution at the 3- and 4-positions of the target molecule 199 has been synthesised as a racemic mixture, and a 1,3-dipolar cycloaddition reaction with the simplest thiocarbonyl ylide successfully carried out.

The two optically pure enantiomers of the target dipolarophile have also been synthesised, utilising Evans' chiral auxiliaries to install the chiral methyl substituent, the relative stereochemistry of which is unknown in the target molecule tetronothodin. These enantiomERICally pure dipolarophiles may be used to determine and assign the relative stereochemistry of this centre, leaving only one unassigned stereocentre in tetronothodin.
Progress has been made in the attempt to control the diastereoselectivity of the 1,3-dipolar cycloaddition reaction. There is good precedent in the literature for the use of camphorsultams as chiral auxiliaries in these reactions, affording excellent diastereomeric control. Installation of the chiral auxiliary (1S)-(−)-2,10-camphorsultam into the dipolarophile 4-methyl-hex-2-enedioic acid 6-methyl ester 275 following an established procedure will enable the diastereoselective synthesis of tetrahydrothiophenes with the required substitution at the 3- and 4-positions (Scheme 161).

Addition of the chiral auxiliary to the enantiomerically pure dipolarophiles 263 and 270 would enable the synthesis of both diastereomers of the tetrahydrothiophene with the correct substitution and stereochemistry at the 3- and 4-positions (Scheme 162).
Finally, reaction of the α-keto ester ylide precursor 240 with these chiral dipolarophiles, followed by hydrolysis of the chiral auxiliary and deprotection of the aldehyde, will complete the synthesis of both diastereomers of the desired tetrahydrothiophene moiety 199 (Scheme 163)
Scheme 163
2.9 References

(4) Lavielle, S; Bory, S, Moreau, B; Luche, M J; Marquet, A. *J Am Chem Soc* 1978, 1558-1563
(8) Larsen, K. E; Torsell, K B. G. *Tetrahedron* 1984, 40, 2985-2988
(10) Cardona, F, Soldani, G, Goti, A *Synlett* 2004, 9, 1553-1556
(17) Poos, G I, Arth, G E ; Beyler, R E, Sarett, L H. *J Am Chem Soc* 1053, 75, 2, 422-429
(19) Ball, S , Goodwin, T W, Morton, R A J *Biochem* 1948, 42, 516-523
(22) Bharucha, K R *J Chem Soc* 1956, 2446-2447
(23) Struve, G , Seltzer, S *J Org Chem* 1982, 47, 2109-2113
(36) Youn, S. W.; Kim, Y. H. Synlett 2000, 6, 880-882
(39) Ma, D, Pan, Q, Han, F Tetrahedron Lett 2002, 43, 9401-9403
(45) More, K, Funaki, Y Tetrahedron 1985, 41, 2369-2377
(48) Seebach, D, Lehr, F Helv Chim Acta 1979, 62, 2239-2257
(49) Lozzi, L, Ricci, A, Taddei, M. J Org Chem 1984, 49, 3408-3410
(51) Schauble, J H., Williams, J. D J Org Chem 1972, 37, 2514-2516
(52) Kodomari, M., Fukuda, M ; Yoshitomi, S Synthesis 1981, 637-640
(53) Murrer, B A; Brown, J M, Chalonen, P A, Nicholson, P N; Parker, D Synthesis 1979, 350-352
(60) Marvel, C S , Kraiman, E. A J Org Chem 1953, 18, 1664
(61) Narasimhan, S Heterocycles 1982, 18, 131-135

132
(62) Roversi, E; Monnat, F; Vogel, P Helv Chim Acta 2002, 85, 733-760
(63) Brown, H C; Negishi, E; Burke, P L J Am Chem Soc 1971, 93, 3400-3409
(64) Pope, A E; Skinner, D J J Chem Soc 1963, 3704-3708
(65) Baylis, A B; Hillman, M E D. German Patent 2155113, 1972
(66) van Rozendaal, E L M; Voss, B M W; Scheeran, H W. Tetrahedron 1993, 49, 6931-6936
(67) Ando, D; Bevan, C; Brown, J M; Price, D W. Chem Commun 1992, 592-594
(68) Basavaiah, D; Gowriswari, V V L Tetrahedron Lett 1987, 28, 4591-4592
(69) Basavaiah, D; Gowriswari, V V L Synth Commun 1989, 19, 2461-2465
(70) Yamamoto, K; Tagaki, M Tetrahedron 1991, 47, 8869-8882
(71) Drewes, S E; Roos, G H P. Tetrahedron 1988, 44, 4653-4670
(72) Langer, P. Angew Chem Int Ed 2000, 39, 3049-3052
(73) Aggarwaal, V K; Mereu, A Chem Commun 1999, 2311-2312
(74) Ameer, F; Drewes, S E; Freese, S; Kaye, P T Synth Commun 1988, 18, 495-500
(75) Aggarwal, V K; Mereu, A; Tarver, G J; McCague, R J Org Chem 1998, 63, 7183-7189
(76) Yu, C; Liu, B; Hu, L J Org Chem 2001, 66, 5413-5418
(78) Cai, J; Zhou, Z; Zhao, G; Tang, C Org Lett 2002, 26, 4723-4725
(79) Grundke, C; Hoffmann, H M R Chem Ber 1987, 120, 1461-1462
(80) Ramachandran, P V; Reddy, M V R; Rudd, M T; de Alanz, J R Tetrahedron Lett 1998, 39, 8791-8794
(81) Tsuda, T; Yoshida, T; Saegusa, T J Org Chem 1988, 53, 1037-1040
(82) Ramachandran, P V; Reddy, M V R; Rudd, M T Tetrahedron Lett 1999, 40, 627-630
(83) Ramachandran, P V; Reddy, M V R; Rudd, M T Chem Commun 1999, 1979-1980
(84) Aono, M; Terao, Y; Achiwa, K Heterocycles 1995, 40, 249-260
(85) Butler, J; Wassenaar, S; Kellogg, R M J Org Chem 1972, 37, 4045-4060
(87) Ueno, Y; Okawara, M Bull Chem Soc Japan 1972, 45, 1797-1800
(88) Schönberg, A; König, B; Singer, E Chem Ber 1967, 100, 767-771
(89) Barton, D H R; Willis, B J J Che Soc Chem Commun 1970, 1225-1227
(91) Terao, Y; Aono, M; Imai, N; Achiwa, K Chem Pharm Bull 1987, 35, 1734-1740
(92) Terao, Y; Aono, M; Achiwa, K Heterocycles 1988, 27, 981-1008
(93) Terao, Y; Tanaka, M; Imai, N, Achiwa, K. *Tetrahedron Lett* 1985, 26, 25, 3011-3014
(94) Aono, M; Terao, Y; Achiwa, K. *Heterocycles* 1986, 24, 313-315
(100) Zha, Q.; Han, F, Romero, D L. *J Org Chem* 2002, 67, 3317-3322
(102) Tamura, O; Shiro, T, Toyao, A, Ishibashi, H. *Chem Comm* 2003, 2678-2679
(106) Terao, Y; Aono, M, Achiwa, K *Heterocycles* 1986, 24, 6, 1571-1574
(107) Imai, N; Tokiwa, H, Aono, M.; Terao, Y., Akahoni, Y; Achiwa, K *Heterocycles* 1986, 24, 9, 2423-2427
(108) Geiß, K -H; Seebach, D, Seuring, B *Chem Ber* 1977, 110, 1833-1851
(111) Wright, A; West, R *J Am Chem Soc* 1974, 3222-3227
(113) Evans, D A, Mathre, D J *J Org Chem* 1985, 50, 1830-1835
(116) Ramadas, K, Janarthanan, N *Synth Comm* 1999, 29, 1003-1007
(117) Heinrich, L, Chottard, J-C, Li, Y *Synth Comm* 2001, 31, 1323-1333
(120) Scholl, M, Ding, S; Lee, C W, Grubbs, R H *Org Lett* 1999, 1, 953-956
(121) Chatterjee, A K, Choi, T.-L; Sanders, D P; Grubbs, R H *J Am Chem Soc* 2003, 125, 11360-11370
(130) Streuff, J.; Muñiz, K J Organomet Chem 2005, 690, 5973-5978
Chapter 3

Experimental
3. Experimental Detail

3.1 General experimental procedures

Chemicals were purchased from Aldrich Chemical co or Lancaster Ltd and used as supplied. Where procedures indicate the use of anhydrous conditions, glassware was dried overnight at 150 °C or flame dried. All solvents where necessary were dried, distilled and then stored over 4Å molecular sieves prior to use. Tetrahydrofuran was distilled from sodium (benzophenone being used as indicator), dichloromethane was distilled over calcium hydride, and ethyl acetate and light petroleum (40-60 °C) were distilled over calcium chloride. All other anhydrous solvents were obtained commercially. All reactions were carried out under a nitrogen atmosphere unless otherwise specified.

3.1.1 Purification methods

Thin layer chromatography was carried out using aluminium backed silica gel 60 plates containing fluorescent indicator, as supplied by Macherey-Nagel. In the absence of an aromatic chromophore, compounds were visualised using basic KMnO₄ solution, or an ethanolic solution of phosphomolybdic acid.

Flash column chromatography was performed using Davisil silica gel 60a. Hand bellows were used to apply pressure where needed. Samples were applied as liquids or pre-adsorbed onto silica gel.

Purification by vacuum distillation was achieved using a Buchi GKR-51 Kugelrohr for bulb-to-bulb distillations.
3.1.2 Spectra and analyses

Where IR spectra could not be acquired neat, samples were dissolved in dichloromethane. The instrument used was a Perkin-Elmer FT-IR Paragon 1000 spectrometer utilizing sodium chloride plates. Frequencies are reported in cm\(^{-1}\) and spectra were recorded in the range 4000-600 cm\(^{-1}\).

NMR spectra were recorded using a Bruker AC-400 spectrometer. Chemical shifts are quoted in parts per million (SiMe\(_4\), \(\delta = 0\)), using residual solvent signals as reference. Multiplicities are recorded as singlets (s), doublets (d), triplets (t), quartets (q), double doublets (dd), double doublet of doublets (ddd) or multiplets (m) and coupling values (\(J\)) are quoted in hertz (Hz).

Low and high-resolution mass spectra were acquired at the EPSRC national mass spectrometry service centre, Swansea. Melting points were determined on a Stuart Scientific SMP3 hot stage microscope and are uncorrected. Optical rotations were measured on an Optical Activity PolAAr 2001 polarimeter, operating at \(\lambda = 589\) nm, corresponding to the sodium line, (D) at 25 °C and are expressed in 10\(^{-1}\) deg cm\(^2\) g\(^{-1}\). The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used. Where comparison was made to literature rotations, these are indicated in the text.
3.2 Experimental procedures

1,2-Bis[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethane-1,2-diol 22

To a stirring solution of D-mannitol (10.00 g, 54.95 mmol) in anhydrous dimethyl formamide (250 ml) was added 2-methoxypropene (10.44 ml, 109.85 mmol) and p-toluenesulfonic acid (1.00 g, 5.50 mmol) and the mixture stirred for 20 h. Solution was then stirred with anhydrous sodium carbonate (5.0 g) for 1 h, filtered and the solvents removed under reduced pressure to yield a sticky residue. This was dissolved in diethyl ether (300 ml) and washed with distilled water (30 ml). The organic layer was then dried over magnesium sulfate, filtered and evaporated to yield a colourless crystalline solid (12.11 g, 84%), mp 121-123 °C (lit 1 mp 118-120 °C); [α]D 20 +21 ° (c = 1.0, EtOH) (lit 2 [α]D 25 +24 ° (c = 1.0, EtOH), νmax (DCM)/cm⁻¹: 3274 (br), 1371, 1211, 1066, δH (400 MHz, CDCl₃) 1.36 (6H, s, CH₃), 1.42 (6H, s, CH₃), 3.75 (2H, d, J = 6.5 Hz, C(OH)H), 3.99 (2H, dd, J = 5.4, 8.4 Hz, CH₂), 4.16 (2H, dd, J = 6.5, 8.4 Hz, CH₂), 4.16 (2H, m, CH₂CH), δC (100 MHz, CDCl₃) 25.20 (CH₃), 26.73 (CH₃), 63.18 (CH₂), 71.16 (C(OH)H), 75.24 (CH₂CH), 109.38 (C(CH₃)₂), m/z (EI) 263.1489 [(M+H)⁺, C₁₂H₂₂O₆ requires 263.1489] 263.2 (32%), 222.2 (9), 205.1 (8), 52.2 (10)
(4R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde 23

To a stirred solution of 1,2-di[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethane-1,2-diol (6.00 g, 22.94 mmol) and sodium bicarbonate (5.00 g, 59.50 mmol) in dichloromethane (60 ml) and distilled water (30 ml), was added sodium periodate (6.47 g, 29.47 mmol) portionwise over 30 min. The reaction was then stirred at ambient temperature for 3 h, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated at reduced pressure to yield a clear oil (4.30 g, 72%), $\left[\alpha_D\right]_{20}^{20} +67.4^\circ$ (c = 1.0, CHCl$_3$) (lit $^3$ $\left[\alpha_D\right]_{20}^{20} +70^\circ$ (c = 1.0, CHCl$_3$), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ : 1738 (C=O); $\delta_H$ (400 MHz, CDCl$_3$) 1.42 (3H, s, CH$_3$), 1.47 (3H, s, CH$_3$), 4.11 (1H, dd, J = 4.8, 8.8 Hz, CH$_2$), 4.18 (1H, dd, J = 7.4, 8.8 Hz, CH$_2$), 4.39 (1H, m, CH$_2$CH), 9.72 (1H, d, J = 1.8 Hz, CHO), $\delta_C$ (100 MHz, CDCl$_3$) : 25.11 (CH$_3$), 26.22 (CH$_3$), 65.55 (CH$_2$), 79.83 (CH$_2$CH), 111.26 (C(CH$_3$)$_3$), 201.81 (CHO)
(4S)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde oxime 24

(4R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.50 g, 11.50 mmol) was added to an aqueous solution of hydroxylamine hydrochloride (1.00 g, 15.05 mmol) and sodium bicarbonate (1.60 g, 19.10 mmol) and stirred for 16 h. The solution was then filtered and extracted with dichloromethane (3 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a clear oil (1.54 g, 89 %), \([\alpha_d]^20_0 + 68.6^\circ\) (c = 1.0, CHCl\(_3\)). \([\alpha_d]^29_0 + 69.8^\circ\) (c = 1.0, CHCl\(_3\)); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 3378 (br), 2987, 1663, 1457, 1375, \(\delta_\text{H}\) (400 MHz, CDCl\(_3\)). Major Configuration 1.40 (3H, s, CH\(_3\)), 1.45 (3H, s, CH\(_3\)), 3.88 (1H, dd, J = 6.4, 8.6 Hz, CH\(_2\)), 4.18 (1H, dd, J = 6.4, 8.6 Hz, CH\(_2\)), 4.65 (1H, q, J = 6.4 Hz, CH\(_2\)CH\(_2\)), 7.40 (1H, d, J = 7.0 Hz, C(N)H); Minor Configuration 1.40 (3H, s, CH\(_3\)), 1.45 (3H, s, CH\(_3\)), 3.81 (1H, dd, J = 7.0, 8.5 Hz, CH\(_2\)), 4.37 (1H, dd, J = 7.0, 8.5 Hz, CH\(_2\)), 5.11 (1H, dt, J = 4.1, 7.0 Hz, CH\(_2\)CH), 6.97 (1H, d, J = 4.1 Hz, C(N)H), \(\delta_C\) (100 MHz, CDCl\(_3\)). Major configuration: 25.44 (CH\(_3\)), 26.48 (CH\(_3\)), 67.33 (CH\(_2\)), 73.20 (CH\(_2\)CH), 110.23 (C(CH\(_3\))\(_2\)), 149.43 (C(N)H), Minor configuration: 25.23 (CH\(_3\)), 26.05 (CH\(_3\)), 67.83 (CH\(_2\)), 70.63 (CH\(_2\)CH), 109.67 (C(CH\(_3\))\(_2\)), 152.54 (C(N)H)
(4S)-2,2-Dimethyl-4-(nitromethyl)-1,3-dioxolane 25

To a stirred suspension of urea hydrogen peroxide (7.80 g, 82.70 mmol) in acetonitrile (100 ml) at 0 °C, was added trifluoroacetic anhydride (9.70 ml, 68.95 mmol) in acetonitrile (30 ml) dropwise, and stirred at this temperature for a further 30 min. This solution was then added dropwise to (4S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde oxime (1.00 g, 6.90 mmol) and sodium hydrogenphosphate (27.45 g, 192.93 mmol) in acetonitrile (150 ml) at 0°C and stirred for 4 h. The remaining solvents were then removed under reduced pressure and the resulting white residue dissolved in saturated sodium bicarbonate solution and extracted with diethyl ether (3 x 150 ml). The combined organic fractions were washed with a 5% sodium sulfite solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a clear oil (1.03 g, 90 %); [αD]_20^20 -16 3° (c = 1 0, CHCl_3) (lit. [αD]_20^20 -16 5° (c = 1 0, CHCl_3)), ε_max (thin film)/cm⁻¹: 3404 (br), 2986, 1559, 1374, 1086, 845, δ_H (400 MHz, CDCl_3) · 1.37 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.87 (1H, dd, J = 4.5, 9.1 Hz, CH_2), 4.20 (1H, dd, J = 6.2, 9.1 Hz, CH_2), 4.48 (2H, ddd, J = 7.0, 12.7, 39.4 Hz, CH_2NO_2), 4.73-4.77 (1H, m, CH_2CH), δ_C (100 MHz; CDCl_3) · 25.12 (CH_3), 26.91 (CH_3), 66.78 (CH_2(O-C)), 72.01 (CH_2CH), 77.42 (CH_2NO_2), 110.70 (C(CH_3)_2)
3-(1,1,1-trimethylsilyl)prop-2-yn-1-ol 28

\[
\begin{align*}
\text{HO} & \quad \text{Si} \\
\text{OH} & \quad \text{Si}
\end{align*}
\]

To a stirred solution of 2-propyn-1-ol (2.00 g, 34.44 mmol) in tetrahydrofuran (100 ml) at -78 °C, was added n-butyl lithium (30.50 ml, 76.37 mmol) dropwise and the reaction stirred at this temperature for 20 min before the dropwise addition of chlorotrimethylsilane (13.15 ml, 103.38 mmol). The solution was then allowed to warm to ambient temperature, hydrochloric acid (2M, 100 ml) was added and the reaction stirred for 16 h before extraction of the aqueous layer with diethyl ether (2 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a yellow oil (3.52 g, 79 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \): 3329 (br), 2959, 2176, 1251, 1042; \( \delta_H \) (400 MHz, CDCl\(_3\)) 0.15 (9H, s, CH\(_3\)), 2.40 (1H, s (br), OH), 4.24 (2H, s, CH\(_2\)), \( \delta_C \) (100 MHz, CDCl\(_3\)) -0.03 (CH\(_3\)), 51.68 (CH\(_2\)), 90.73 (C(SiMe\(_3\))), 104.16 (C(CH\(_2\)OH))
3-(1,1,1-trimethylsilyl)prop-2-ynal 19

A solution of 3-(1,1,1-trimethylsilyl)prop-2-yn-1-ol (4.00 g, 31.24 mmol) in dichloromethane (20 ml) was added dropwise to a stirring suspension of pyridinium chlorochromate (13.57 g, 62.48 mmol) and celite (26.9 g) in dichloromethane (150 ml). The solution was stirred for 20 h before being filtered through a pad of alumina oxide. The filtrate was evaporated under reduced pressure to yield a green oil. The oil was distilled using kugelrohr distillation apparatus at a temperature of 70-90 °C to yield a pale yellow oil (1.17 g, 54 %), ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2961, 2154, 1667, 1252; δ<sub>h</sub> (400 MHz, CDCl<sub>3</sub>): 0.25 (9H, s, CH<sub>3</sub>), 9.15 (1H, s, C(O)H), δ<sub>c</sub> (100 MHz, CDCl<sub>3</sub>): -0.73 (CH<sub>3</sub>), 102.38 (C(CO)), 103.21 (C(CSiMe<sub>3</sub>)), 176.94 (COH).
1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-1-nitro-4-trimethylsilyl-but-3-yn-2-ol 15

Method A

A solution of 3-(1,1,1-trimethylsilyl)prop-2-ynal (0.59 g, 4.65 mmol) and (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane (0.75 g, 4.65 mmol) in methanol (10 ml) was added to a stirring suspension of anhydrous potassium carbonate (0.06 g, 0.47 mmol) in methanol (5 ml) at 0 °C. The solution was stirred for 8 h while being allowed to warm to ambient temperature before being neutralised by the addition of conc. hydrochloric acid. The organic solvent was evaporated under reduced pressure and the resulting residue extracted with ice water (20 ml) and diethyl ether (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield an orange oil.

Method B

To a stirred solution of 3-(1,1,1-trimethylsilyl)prop-2-ynal (0.59 g, 4.65 mmol) and (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane (0.75 g, 4.65 mmol) in absolute ethanol (5 ml) at 0 °C was added an aqueous sodium hydroxide solution (0.02 g, 0.47 mmol in 5 ml). The solution was stirred for 16 h while being allowed to warm to ambient temperature before being neutralised by the addition of glacial acetic acid. The organic solvent was evaporated under reduced pressure and the resulting residue extracted with ice water (20 ml) and
diethyl ether (3 x 50 ml) The combined organic fractions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield an orange oil.

**Method C**

To a stirred solution of 3-(1,1,1-trimethylsilyl)prop-2-ynal (0.47 g, 3.72 mmol), (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane (0.60 g, 3.72 mmol) and titanium tetrachloride (0.71 g, 3.72 mmol) in tetrahydrofuran (10 ml) at -78 °C was added n-butyllithium (1.49 ml, 3.72 mmol) Stirring was continued at this temperature for 8 h before the solution was allowed to warm to ambient temperature The solution was washed with saturated sodium bicarbonate solution and extracted with diethyl ether (3 x 50 ml) The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield an orange oil.

**Method D**

To a stirred solution of (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane (0.60 g, 3.72 mmol) in THF DMPU (20 ml, 9.1) at -78 °C was added n-butyllithium (3.05 ml, 7.63 mmol) and stirring continued at this temperature for 3 h 3-(1,1,1-Trimethylsilyl)prop-2-ynal (0.47 g, 3.72 mmol) was added dropwise and stirred at -78 °C for 2 h, followed by the addition of acetic acid (0.22 ml, 3.72 mmol) at this temperature After warming to ambient temperature, the solution was washed with saturated sodium bicarbonate solution and extracted with diethyl ether (3 x 50 ml) The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield an orange oil.
To a stirred solution of (4S)-2,2-dimethyl-4-(nitromethyl)-1,3-dioxolane (0.25 g, 1.55 mmol) in THF DMPU (10 ml, 9:1) at -78 °C was added n-butyllithium (1.27 ml, 3.18 mmol) and stirring continued at this temperature for 3 h. Methyl iodide (0.10 ml, 1.55 mmol) was added dropwise and stirred at -78 °C for 2 h, followed by the addition of acetic acid (0.09 ml, 1.55 mmol) at this temperature. After warming to ambient temperature, the solution was washed with saturated sodium bicarbonate solution and extracted with diethyl ether (2 x 30 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (5:1), which yielded the desired product as a colourless crystalline solid (0.12 g, 44%), mp 88-92 °C, νmax (DCM)/cm⁻¹: 1375, 1559; δH (400 MHz, CDCl₃): 1.36 (3H, s, CH₃C(CH₃)), 1.43 (3H, s, CH₃C(CH₃)), 1.63 (3H, d, J = 6.7 Hz, CH₂CH), 3.90 (1H, dd, J = 4.6, 9.2 Hz, CH₂), 4.15 (1H, dd, J = 6.2, 9.2 Hz, CH₂), 4.46-4.41 (1H, m, CH₂CH), 4.55-4.49 (1H, m, CH₂CH), δC (100 MHz, CDCl₃): 15.37 (CH₂CH), 24.89 (CH₃C(CH₃)), 26.50 (CH₃C(CH₃)), 66.81 (CH₂), 76.15 (CH₂CH), 84.04 (CH₂CH), 110.51 (C(CH₃)₂)
Diethyl (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 77

To a stirred solution of diethyl-L-tartrate (5.00 g, 24.35 mmol) in acetone (100 ml) was added 2-methoxypropene (3.50 ml, 36.48 mmol) and p-toluenesulfonic acid (0.56 g, 2.44 mmol) and heated under reflux for 4 h. The reaction was then stirred with anhydrous sodium carbonate (5.00 g) for 30 min, before filtration. The filtrate was evaporated under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (4:1), which yielded a pale orange oil (4.72 g, 78 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 2987, 1757, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.32 (6H, t, \( J = 7.1 \) Hz, CH\(_2\)CH\(_3\)), 1.51 (6H, s, CH\(_3\)), 4.29 (4H, q, \( J = 7.1 \) Hz, CH\(_2\)CH\(_3\)), 4.78 (2H, s, CH(O)), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 14.09 (CH\(_3\)), 26.35 (CH\(_2\)CH\(_3\)), 61.90 (CH\(_2\)CH\(_3\)), 77.14 (CH(O)), 113.74 (C(CH\(_3\))\(_2\)), 169.66 (CO).
Method A

To a stirred solution of diethyl (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (3.00 g, 12.18 mmol) in acetonitrile (100 ml) was added sodium sulfide (2.85 g, 36.54 mmol), and the resulting solution was heated under reflux for 16 h. The reaction mixture was then allowed to cool to ambient temperature, filtered, and the remaining solvent removed under reduced pressure to yield an orange crystalline solid. This was recrystallised from dichloromethane to yield a colourless crystalline solid.

Method B

To a stirred solution of (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid (2.00 g, 10.52 mmol) in dichloromethane (40 ml) was added oxalyl chloride (8.01 g, 63.12 mmol) and N,N'-dimethylformamide (5 drops) and stirred at ambient temperature for 5 h. The organic solvent was removed under reduced pressure, and the resulting oil added to a suspension of sodium sulfide (2.46 g, 31.56 mmol) in acetonitrile (100 ml) and heated under reflux for 16 h. The cooled reaction mixture was then filtered and the remaining solvent removed under reduced pressure to yield a colourless solid.
To a stirred solution of diethyl (4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (1.50 g, 6.14 mmol) in tetrahydrofuran (40 ml) and distilled water (20 ml) was added lithium hydroxide (1.13 g, 27.48 mmol) and stirring continued at ambient temperature for 20 h. The organic solvent was removed under reduced pressure before the addition of distilled water (20 ml) and the solution acidified by the addition of 1 M hydrochloric acid solution. The mixture was extracted with ethyl acetate (3 x 100 ml), the combined organic fractions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a colourless crystalline solid (0.74 g, 59%), mp 94 °C (lit. 7 mp 92 °C), ν<sub>max</sub> (thin film)/cm<sup>-1</sup> : 3225 (br), 1726, 811 (400 MHz, CDCl<sub>3</sub>) 134 (6H, s, CH<sub>3</sub>), 461 (2H, s, CH(O)), 5.19 (2H, br, OH), δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 26.14 (CH<sub>3</sub>), 76.57 (CH(O)), 112.38 (C(CH<sub>3</sub>)<sub>2</sub>), 171.12 (CO)
(2R, 3R)-Tartaroyl chloride dibenzoate 91

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{Cl} \\
\hline
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{Cl}
\end{align*}
\]

To a stirred solution of dibenzoyl-L-tartaric acid (1.50 g, 4.19 mmol) in dichloromethane (50 ml) was added oxalyl chloride (1.20 ml, 13.95 mmol) and dimethylsulfide (2 drops). This solution was then stirred at ambient temperature for 8 h. The remaining solvent was removed under reduced pressure to yield a yellow oil (1.48 g, 89%); \(v_{\text{max}} \) (thin film)/cm\(^{-1}\) 1804, 1738, 1452, 1089, 706, \(\delta_H\) (400 MHz, CDCl\(_3\)) : 6.32 (2H, s, CH), 7.54-7.50 (4H, m, 4 x CH arom meta), 7.69-7.66 (2H, m, 2 x CH arom para), 8.11-8.08 (4H, m, 4 x CH arom ortho); \(\delta_C\) (100 MHz, CDCl\(_3\)) : 76.33 (CH), 127.23 (C arom ipso), 128.87 (CH arom meta), 130.29 (CH arom ortho), 134.60 (CH arom para), 164.44 (CO), 167.17 (CO)
(2R, 3R)-Di-O-benzoyl tartaric thioanhydride 92

To a stirred solution of (2R, 3R)-tartaroylchloride dibenzoate (1.10 g, 2.79 mmol) in acetonitrile (50 ml) was added sodium sulfide (0.44 g, 5.58 mmol) and the reaction was heated under reflux for 16 h. The cooled reaction mixture was then filtered and the remaining solvent removed under reduced pressure to yield a colourless solid.
(2R, 3R)-Di-O-benzoyl tartaric anhydride 96°

Dibenzoyl-L-tartaric acid (3.90 g, 10.88 mmol), acetic anhydride (6.67 ml, 70.72 mmol) and 85% phosphoric acid (0.07 ml, 1.09 mmol) were heated under reflux for 2 h. The solution was then cooled to ambient temperature and the resulting precipitate washed with distilled water to yield a colourless crystalline solid (3.64 g, 98%), mp 194-196 °C (lit° mp 192-195 °C), ν_max (DCM)/cm⁻¹ 1822, 1740, 1707, 1267, 713; δ_H (400 MHz, CDCl₃) 5.99 (2H, s, CH), 7.53-7.48 (4H, m, 4 x CH arom meta), 7.69-7.65 (2H, m, 2 x CH arom para), 8.10-8.07 (4H, m, 4 x CH arom ortho); δ_C (100 MHz, CDCl₃) 127.14 (C arom ipso), 128.82 (CH arom meta), 130.37 (CH arom ortho), 134.68 (CH arom para), 163.50 (CO), 165.49 (CO).
Succinic anhydride 93°

A solution of succinic acid (2.00 g, 16.94 mmol), acetic anhydride (10.39 ml, 0.11 mol) and phosgene (0.10 ml, 1.69 mmol) was heated under reflux for 2 h. Upon cooling to ambient temperature, a colourless precipitate formed. This precipitate was filtered and washed with distilled H2O to yield a colourless solid (1.65 g, 97 %), mp 121 °C (lit 9 mp 118 °C), νmax (DCM)/cm⁻¹ 1783, 1059, 919; δH (400 MHz; CDCl₃) 3.01 (4H, s, CH₂); δC (100 MHz; CDCl₃) 28.71 (CH₂), 170.89 (CO)
A solution of succinic anhydride (1.00 g, 9.99 mmol) and sodium sulfide (0.39 g, 5.00 mmol) in H$_2$O-THF (20 ml, 1:1) was stirred at ambient temperature for 2 h before addition of diethyl ether (40 ml). The aqueous layer was separated and extracted with diethyl ether (2 x 20 ml). The combined organic fractions were washed with H$_2$O (50 ml), sat. NaHCO$_3$ solution (50 ml) and brine (50 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a colourless crystalline solid (0.49 g, 84 %), mp 36-38 °C (lit. mp 30-31 °C), $\nu_{\text{max}}$ (DCM)/cm$^{-1}$ 1698, 994, 749, $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 3.10 (4H, s, CH$_2$), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) : 40.99 (CH$_2$), 200.67 (CO)
Phthalic anhydride 102

A solution of phthalic acid (2.00 g, 12.04 mmol), acetic anhydride (738 ml, 78.26 mmol) and phosphoric acid (0.07 ml, 1.20 mmol) was heated under reflux for 2 h. Upon cooling to ambient temperature, a colourless precipitate formed. This precipitate was filtered and washed with distilled H₂O to yield a yellow solid. This was recrystallised from ethyl acetate to yield a colourless crystalline solid (1.71 g, 94%), mp 134 °C (lit 11 mp 132 °C); νmax (DCM)/cm⁻¹ 1761, 1257, 904, 712, δH (400 MHz, CDCl₃) : 7.92 (2H, dd, J = 2.9, 5.5 Hz, 2 x CH arom) 8.04 (2H, dd, J = 2.9, 5.5 Hz, 2 x CH arom), δC (100 MHz, CDCl₃) : 126.05 (C arom), 131.69 (C arom), 136.36 (C arom), 163.09 (CO)
Phthalic thioanhydride 103

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\begin{align*}
\text{O} & \quad \text{O} \\
& \quad \text{S}
\end{align*}
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A solution of phthalic anhydride (1.00 g, 6.75 mmol) and sodium sulfide (0.26 g, 3.38 mmol) in H₂O THF (20 ml, 1:1) was stirred at ambient temperature for 2 h before addition of diethyl ether (40 ml). The aqueous layer was separated and extracted with diethyl ether (2 x 20 ml). The combined organic fractions were washed with H₂O (50 ml), sat. NaHCO₃ solution (50 ml) and brine (50 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a colourless crystalline solid (0.41 g, 75%), mp 106-107 °C (lit. 12 mp 105-5 °C), ν<sub>max</sub> (DCM)/cm<sup>-1</sup> 1690, 1265, 836, 712; δ<sub>II</sub> (400 MHz; CDCl₃) 7.82 (2H, dd, J = 3.1, 5.6 Hz, 2 × CH arom) 7.98 (2H, dd, J = 3.1, 5.6 Hz, 2 × CH arom), δ<sub>C</sub> (100 MHz, CDCl₃) 124.12 (C arom), 135.36 (C arom), 139.06 (C arom), 190.13 (CO), m/z (EI) 163.9926 [(M)<sup>+</sup>, C₈H₆O₂S requires 163.9927] 163.9 (100 %), 104.0 (90), 76.0 (70)
(3R, 4S)-bis(benzoyloxy)-2-furanone 10713

To a stirred solution of (2R, 3R)-dl-O-benzoyl tartaric anhydride (1.00 g, 2.94 mmol) in tetrahydrofuran (20 ml) was added dropwise a solution of lithium borohydride (0.036 g, 1.63 mmol) in tetrahydrofuran (5 ml) and stirred at ambient temperature for 30 min. An 18 % aqueous hydrochloric acid solution (15 ml) was then added dropwise and the resulting solution heated over a steam bath for 30 min. Upon cooling, the solution was saturated with sodium chloride, separated and the aqueous layer extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered and the organic solvent was removed under reduced pressure to yield a colourless foamy solid (0.65 g, 68 %), mp 146-150 °C (Lit.13 mp 142.5 °C), \( \nu_{\text{max}} \) (DCM)/cm: 1734, 1721, 1452, 1245, 1095, \( \delta_{\text{MHz}} \) (400 MHz; CDCl3): 4.27-4.21 (2H, m, CH), 6.01-6.00 (1H, m, CH), 6.07-6.06 (1H, m, CH), 7.50-7.46 (4H, m, 4 x CH arom meta), 7.62-7.60 (2H, m, 2 x CH arom para), 8.14-8.11 (4H, m, 4 x CH arom ortho), \( \delta_{C} \) (100 MHz, CDCl3): 62.47 (CH2), 71.10 (CH), 71.55 (CH), 128.50 (C arom ipso), 128.74 (CH arom meta), 130.14 (CH arom ortho), 133.89 (CH arom para), 165.70 (CO), 177.82 (CO)
2-Hydroxy-2-methyl-3-methylenesuccinic acid-1-ethyl ester-4-methyl ester

Ethyl pyruvate (400 ml, 36.00 mmol), methyl acrylate (486 ml, 54.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.61 g, 5.40 mmol) were stirred at ambient temperature for 14 days. The excess reagent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a red viscous oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (1:1), which yielded a colourless oil (132 g, 18%). $\nu_{\max }$ (thin film)/cm$^{-1}$: 3492 (br), 2986, 1734, 1634, 1447, 1019, $\delta_{\nu}$ (400 MHz; CDCl$_3$): 1.26 (3H, t, $J = 7.1$ Hz, CH$_3$CH$_2$), 1.61 (3H, s, CH$_3$COH), 3.77 (3H, s, OCH$_3$), 4.23 (2H, q, $J = 7.1$ Hz, CH$_2$CH$_2$), 5.98 (1H, s, 1 x CH$_2$=C), 6.37 (1H, s, 1 x CH$_2$=C), $\delta_C$ (100 MHz, CDCl$_3$): 14.04 (CH$_3$CH$_2$), 23.73 (CH$_3$COH), 52.14 (OCH$_3$), 62.08 (CH$_3$CH$_2$), 73.71 (COH), 125.73 (CH$_2$=C), 141.73 (CH$_2$=C), 166.56 (CO), 174.88 (CO); $m/z$ (EI) 220 1181 [(M+NH$_4$)$^+$, C$_9$H$_{18}$O$_5$N requires 220 1179] 220 1 (100%), 52.2 (28%)

2,3-Dimethylenesuccinic acid ethyl ester methyl ester 121

![Chemical structure]

To a stirred solution of 2-hydroxy-2-methyl-3-methylenesuccinic acid-1-ethyl ester-4-methyl ester (0.40 g, 1.98 mmol) in dichloromethane (5 ml) was added 1,4-diazabicyclo[2,2,2]octane (0.67 g, 5.94 mmol) and 4-dimethylaminopyridine (0.12 g, 0.99 mmol) The reaction mixture was then cooled to 0 °C and methanesulfonyl chloride (0.18 ml, 2.38 mmol) in dichloromethane (1 ml) added dropwise Stirring was then continued at ambient temperature for 24 h before the dropwise addition of ice cold distilled water until the solution remained clear The solution was then poured into diethyl ether (10 ml), separated and the aqueous layer extracted with diethyl ether (2 x 10 ml) The combined organic fractions were washed with a 4% aqueous hydrochloric acid solution (10 ml), saturated aqueous sodium hydrogen carbonate solution (10 ml) and brine (10 ml) and dried over magnesium sulfate The remaining solvent was removed under reduced pressure to yield a pale yellow oil This was purified by column chromatography using a mixture of light petroleum - diethyl ether (2:1), which yielded a colourless oil (0.16g, 44 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 2983, 1718, 1620, 1437, 1326, 1202, 1121, \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.28 (3H, t, \( J = 7.1 \) Hz, CH\(_3\)CH\(_2\)), 3.76 (3H, s, OCH\(_3\)), 4.22 (2H, q, \( J = 7.1 \) Hz, CH\(_3\)CH\(_2\)), 5.80-5.81 (2H, m, 2 x 1 of CH\(_2\)=C), 6.27 (1H, d, \( J = 1.4 \) Hz, 1 x CH\(_2\)=C), 6.28 (1H, d, \( J = 1.4 \) Hz, 1 x CH\(_2\)=C); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 14.11 (CH\(_3\)CH\(_2\)), 52.16 (OCH\(_3\)), 61.11 (CH\(_2\)CH\(_2\)), 127.66 (CH\(_2\)), 127.73 (CH\(_2\)), 138.62 (C=CH\(_2\)), 138.82 (C=CH\(_2\)), 165.74 (CO), 166.35 (CO)
Dimethyl 3-hydroxy-3-methyl-2-methylenesuccinoate 123

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\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \\
\end{align*}
\]

Method A

Methyl pyruvate (3 70 ml, 40 00 mmol), methyl acrylate (5.40 ml, 60 00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0 68 g, 6 00 mmol) were stirred at ambient temperature for 14 days. The excess reagent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield an orange viscous oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (1:1), which yielded a colourless oil (1 20 g, 16 %)

Method B

Methyl pyruvate (1 84 ml, 18 00 mmol), methyl acrylate (2 45 ml, 27 00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.30 g, 2 70 mmol) were stirred at 60 °C for 7 days. The excess reagent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a brown viscous oil. This was purified by column chromatography using a
mixture of light petroleum : diethyl ether (1:1), which yielded a colourless oil (0.41 g, 12 %)

Method C

A solution of methyl pyruvate (0.92 ml, 10.00 mmol), methyl acrylate (0.90 ml, 10.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.11 g, 1.00 mmol) in tetrahydrofuran (7 ml) was stirred at ambient temperature for 14 days. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange viscous oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (1:1), which yielded a colourless oil (0.21 g, 11 %)

Method D

A solution of methyl pyruvate (0.92 ml, 10.00 mmol), methyl acrylate (0.90 ml, 10.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.11 g, 1.00 mmol) in methanol (7 ml) was stirred at ambient temperature for 14 days. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange viscous oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (1:1), which yielded a colourless oil (0.40 g, 21 %)
Method E

A solution of methyl pyruvate (0.84 ml, 9.00 mmol), methyl acrylate (2.43 ml, 27.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (1.01 g, 9.00 mmol) in 1,4-dioxane: distilled water (40 ml, 1 l) was stirred at ambient temperature for 14 days. The reaction was then diluted with dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange viscous oil. This was purified by column chromatography using a mixture of light petroleum: diethyl ether (1:1), which yielded a colourless oil (0.17 g, 10%).

Method F

Methyl pyruvate (1.85 ml, 20.00 mmol), methyl acrylate (2.70 ml, 30.00 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.57 g, 30.00 mmol) were stirred at ambient temperature for 14 days. The excess reagent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50 ml) and washed with distilled water (3 x 25 ml). The organic fraction was dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield an orange viscous oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (1:1), which yielded a colourless oil (0.60 g, 16%).

Method G

To a stirred suspension of 4-methylmorpholine-N-oxide (6.65 g, 56.78 mmol) in tetrahydrofuran (100 ml) at ambient temperature was added
dibutylaluminium hydride (28.39 ml, 28.39 mmol) and stirring continued at this temperature for 2 h. The solution was then cooled to 0 °C and methyl propiolate (1.59 ml, 18.93 mmol) in tetrahydrofuran (10 ml) added dropwise. After stirring at this temperature for 3 h, methyl pyruvate (2.32 ml, 22.72 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was then quenched with a 10% aqueous hydrochloric acid solution (50 ml) and separated. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and distilled water (200 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (2:1), which yielded a colourless oil (2.52 g, 71 %), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 3495 (br), 2954, 1742, 1633, 1439, 1256, 1143, $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1.61 (3H, s, CH$_3$COH), 3.77 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.92 (1H, s, br, OH), 5.99 (1H, s, 1 x CH$_2$-C), 6.38 (1H, s, 1 x CH$_2$-C), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 23.73 (CH$_3$COH), 52.22 (OCH$_3$), 53.06 (OCH$_3$), 73.80 (COH), 125.79 (CH$_2$-C), 141.68 (CH$_2$-C), 166.58 (CO), 175.36 (CO), m/z (El) 189.0759 [(M+H)$^+$], C$_8$H$_{13}$O$_5$ requires 189.0757. 206.1 (100 %), 190.1 (25), 148.1 (16), 52.2 (55).
Dimethyl 2,3-dimethylenebutanedioate \[142^{15}\]

To a stirred solution of dimethyl 3-hydroxy-3-methyl-2-methylene succinate (0.24 g, 1.28 mmol) in dichloromethane (10 ml) was added 1,4-diazabicyclo[2,2,2]octane (0.43 g, 3.84 mmol) and 4-dimethylaminopyridine (0.08 g, 0.64 mmol). The reaction mixture was then cooled to 0 °C and methanesulfonyl chloride (0.12 ml, 1.54 mmol) in dichloromethane (2 ml) added dropwise. Stirring was then continued at ambient temperature for 24 h before the dropwise addition of ice cold distilled water until the solution remained clear. The solution was then poured into diethyl ether (20 ml), separated and the aqueous layer extracted with diethyl ether (2 x 10 ml). The combined organic fractions were washed with a 4% aqueous hydrochloric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (2:1), which yielded a colourless oil (0.12 g, 53%), \( v_{\text{max}} \) (thin film)/cm\(^{-1} \): 2989, 1725, 1617, 1437, 1199, 1120, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) : 3.76 (6H, s, 2 x O\(\text{CH}_3\)), 5.82 (2H, d, \(J = 13\) Hz, 2 x 1 of CH\(_2\)=C), 6.29 (2H, d, \(J = 13\) Hz, 2 x 1 of CH\(_2\)=C); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) : 52.23 (O\(\text{CH}_3\)), 127.96 (CH\(_2\)), 138.49 (C=CH\(_2\)), 166.23 (CO).
Diethyl 3-hydroxy-3-methyl-2-methylenesuccinate 143

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\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH} = \text{CH} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

To a stirred suspension of 4-methylmorpholine-N-oxide (6.95 g, 59.34 mmol) in tetrahydrofuran (100 ml) at ambient temperature was added dibutylaluminium hydride (29.67 ml, 29.67 mmol) and stirring continued at this temperature for 2 h. The solution was then cooled to 0 °C and ethyl propiolate (200 ml, 19.78 mmol) in tetrahydrofuran (10 ml) added dropwise. After stirring at this temperature for 3 h, ethyl pyruvate (2.64 ml, 23.74 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was then quenched with a 10% aqueous hydrochloric acid solution (50 ml) and separated. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and distilled water (200 ml). The organic fraction was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (2:1), which yielded a colourless oil (3.25 g, 76%), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 3488 (br), 2984, 1735, 1632, 1459, 1249, 1107, \( \delta_1 \) (400 MHz, CDCl\(_3\)): 1.26 (3H, t, \( J = 7.1 \text{ Hz}, \text{CH}_3\text{CH}_2\)), 1.30 (3H, t, \( J = 7.1 \text{ Hz}, \text{CH}_3\text{CH}_2\)), 1.60 (3H, s, \text{CH}_3\text{COH}), 3.91 (1H, s, br, OH), 4.19-4.26 (4H, m, 2 x \text{CH}_3\text{CH}_2), 5.96 (1H, s, 1 x \text{CH}_3=\text{C}), 6.37 (1H, s, 1 x \text{CH}_2=\text{C}), \delta_c (100 MHz, CDCl\(_3\)): 14.04 (\text{CH}_3\text{CH}_2), 14.08 (\text{CH}_3\text{CH}_2), 23.71 (\text{CH}_3\text{COH}), 61.23 (\text{CH}_3\text{CH}_2), 62.03 (\text{CH}_3\text{CH}_2), 73.70 (\text{COH}), 125.43 (\text{CH}_2=\text{C}), 141.97 (\text{CH}_2=\text{C}), 166.13 (\text{CO}), 174.95 (\text{CO}), \text{m/z (EI) 234} 1336 [(\text{M+NH}_4)^+], \text{C}_{10}\text{H}_{26}\text{O}_3\text{N requires 234 1336] 234 1 (90 %), 218 1 (100), 206 1 (94), 162 0 (54), 155 0 (30), 134 0 (40)
To a stirred solution of diethyl 3-hydroxy-3-methyl-2-methylene succinoate (0.24 g, 1.28 mmol) in dichloromethane (10 ml) was added 1,4-diazabicyclo[2,2,2]octane (0.43 g, 3.84 mmol) and 4-dimethylaminopyridine (0.08 g, 0.64 mmol). The reaction mixture was then cooled to 0 °C and methanesulfonyl chloride (0.12 ml, 1.54 mmol) in dichloromethane (2 ml) added dropwise. Stirring was then continued at ambient temperature for 24 h before the dropwise addition of ice cold distilled water until the solution remained clear. The solution was then poured into diethyl ether (20 ml), separated and the aqueous layer extracted with diethyl ether (2 x 10 ml). The combined organic fractions were washed with a 4% aqueous hydrochloric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (2:1), which yielded a colourless oil (0.12 g, 57%), ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2981, 1724, 1620, 1190, 1119, δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.76 (6H, s, 2 x OCH<sub>3</sub>), 5.82 (2H, d, J = 13 Hz, 2 x 1 of CH<sub>2</sub>=C), 6.29 (2H, d, J = 13 Hz, 2 x 1 of CH<sub>2</sub>=C), δ<sub>c</sub> (100 MHz, CDCl<sub>3</sub>) 52.23 (OCH<sub>3</sub>), 127.96 (CH<sub>2</sub>), 138.49 (C=CH<sub>2</sub>), 166.23 (CO)
3-Benzylidene-2-hydroxy-2-methylsuccinic acid diethyl ester

To a stirred suspension of 4-methylmorpholine-N-oxide (3.62 g, 30.94 mmol) in tetrahydrofuran (100 ml) at ambient temperature was added dibutylaluminium hydride (30.94 ml, 30.94 mmol) and stirring continued at this temperature for 1 h. The solution was then cooled to 0 °C and ethylphenyl propionate (3.00 ml, 18.20 mmol) in tetrahydrofuran (10 ml) added dropwise. After stirring at this temperature for 3 h, ethyl pyruvate (2.43 ml, 21.84 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was then quenched with a 10% aqueous hydrochloric acid solution (50 ml) and separated. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and distilled water (200 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (1:1), which yielded a colourless oil (3.16 g, 59%), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3485 (br), 2982, 1732, 1446, 1373, 1252, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\) ) 1.06 (3H, t, \( J = 6.8 \) Hz, CH\(_3\)CH\(_2\)), 1.31 (3H, t, \( J = 7.2 \) Hz, CH\(_3\)CH\(_2\)), 1.72 (3H, s, CH\(_3\)CHOH), 3.88 (1H, s, br, OH), 4.10 (2H, q, \( J = 7.2 \) Hz, CH\(_3\)CH\(_2\)), 4.27-4.33 (2H, m, CH\(_3\)CH\(_2\)), 7.01 (1H, s, C=CH), 7.26-7.32 (5H, m, CH\(_3\) arom.), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\) ) : 13.60 (CH\(_3\)CH\(_2\)), 14.08 (CH\(_3\)CH\(_2\)), 24.62 (CH\(_3\)COH), 61.06 (CH\(_3\)CH\(_2\)), 62.60 (CH\(_3\)CH\(_2\)), 75.16 (COH), 128.20 (CH...
arom.) 128.27 (CH arom), 128.30 (CH arom), 132.93 (C–CH), 135.31 (C arom), 136.41 (C=CH), 168.25 (C=O), 174.84 (C=O), m/z (EI) 310 1650 [(M+NH₄)⁺, C₁₆H₂₄O₃N requires 310.1649] 310.3 (100 %), 293.2 (26), 275.2 (52)
To a stirred solution of 3-benzylidene-2-hydroxy-2-methylsuccinic acid diethyl ester (1.50 g, 5.13 mmol) in dichloromethane (50 ml) was added 1,4-diazabicyclo[2,2,2]octane (1.73 g, 15.39 mmol) and 4-dimethylaminopyridine (0.31 g, 2.57 mmol). The reaction mixture was stirred at ambient temperature for 30 min, then cooled to 0 °C and methanesulfonyl chloride (0.48 ml, 6.16 mmol) in dichloromethane (5 ml) added dropwise. Stirring was then continued at ambient temperature for 24 h before the dropwise addition of ice cold distilled water until the solution remained clear. The solution was then separated and the aqueous layer extracted with dichloromethane (2 x 30 ml). The combined organic fractions were washed with a 4% aqueous hydrochloric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (1:1), which yielded a colourless oil (0.68 g, 48%), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \): 2981, 1713, 1618, 1448, 1198, 1055, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.22 (3H, t, \( J = 7.2 \) Hz, CH\(_3\)CH\(_2\)), 1.31 (3H, t, \( J = 7.1 \) Hz, CH\(_3\)CH\(_2\)), 4.21 (2H, q, \( J = 7.1 \) Hz, CH\(_2\)CH\(_2\)) 4.26 (2H, q, \( J = 7.2 \) Hz, CH\(_3\)CH\(_2\)), 5.65 (1H, d, \( J = 1.6 \) Hz, 1 x C=CH\(_2\)), 6.46 (1H, d, \( J = 1.6 \) Hz, 1 x C=CH\(_2\)), 7.30-7.32 (3H, m, CH arom.), 7.41-7.43 (2H, m, CH arom.), 7.79 (1H, s, (C=CHPh), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 14.10 (CH\(_3\)CH\(_2\)), 14.21 (CH\(_3\)CH\(_2\)), 61.11 (CH\(_3\)CH\(_2\)), 61.21 (CH\(_3\)CH\(_2\)), 128.43 (CH arom.), 128.99
(C arom), 129.19 (CH arom.), 130.02 (CH arom.), 130.29 (C=CH₂), 134.54 (C=CH₂), 136.39 (C=CHPh), 141.43 (C=CHPh), 166.11 (CO), 166.81 (CO), m/z (EI) 275.1282 [(M+H)+, C₁₆H₁₉O₄ requires 275.1278] 274 2 (60%), 229 2 (100), 129 1 (90), 77 1 (48), 51 2 (25)
Ethyl 2-(1-cyano-1-hydroxyethyl)acrylate 14816

To a stirred suspension of 4-methylmorpholine-N-oxide (3.43 g, 29.29 mmol) in tetrahydrofuran (100 ml) at ambient temperature was added diisobutylaluminium hydride (29.29 ml, 29.29 mmol) and stirring continued at this temperature for 1 h. The solution was then cooled to 0 °C and ethyl propionate (1.75 ml, 17.23 mmol) in tetrahydrofuran (10 ml) added dropwise. After stirring at this temperature for 3 h, pyruvonic acid (1.47 ml, 20.68 mmol) was added and the reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was then quenched with a 10% aqueous hydrochloric acid solution (50 ml) and separated. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and distilled water (200 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (2:1), which yielded a colourless oil (1.92 g, 66%); ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3422 (br), 2985, 1718, 1626, 1317, 1105, 83 (400 MHz, CDCl\textsubscript{3}) 1.37 (3H, t, J = 7.2 Hz, CH\textsubscript{3}CH\textsubscript{2}), 1.84 (3H, s, CH\textsubscript{3}CN(OH)), 4.34 (2H, q, J = 7.2 Hz, CH\textsubscript{3}CH\textsubscript{2}) 4.76 (1H, s, br, OH), 6.10 (1H, s, 1 x C=CH), 6.48 (1H, s, 1 x C=CH); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 14.03 (CH\textsubscript{3}CH\textsubscript{2}), 26.06 (CH\textsubscript{3}CN(OH)), 62.20 (CH\textsubscript{3}CH\textsubscript{2}), 67.61 (COH), 120.34 (C=NN), 127.38 (C=CH\textsubscript{2}), 138.66 (C=CH\textsubscript{2}), 165.70 (C=O)
To a stirred solution of ethyl 2-(1-cyano-1-hydroxyethyl)acrylate (1.75 g, 10.34 mmol) in dichloromethane (50 ml) was added 1,4-diazabicyclo[2,2,2]octane (3.47 g, 31.02 mmol) and 4-dimethylaminopyridine (0.63 g, 5.17 mmol). The reaction mixture was stirred at ambient temperature for 30 min, then cooled to 0 °C and methanesulfonyl chloride (0.96 ml, 12.41 mmol) in dichloromethane (5 ml) added dropwise. Stirring was then continued at ambient temperature for 24 h before the dropwise addition of ice cold distilled water until the solution remained clear. The solution was then separated and the aqueous layer extracted with dichloromethane (2 x 30 ml). The combined organic fractions were washed with a 4% aqueous hydrochloric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml) and dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield an orange oil.
Tetrahydrothiophene-3,4-dicarboxylic acid dimethyl ester 15018

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\end{align*}
\]

Method A

To a stirring solution of dimethyl 2,3-dimethylenedinitrile (0.89 g, 5.23 mmol) in methanol (10 ml) and distilled H2O (10 ml), was added sodium sulfide nonahydrate (1.26 g, 5.23 mmol). Stirring was continued at this temperature for 12 h before the addition of distilled H2O (50 ml). The reaction was extracted with diethyl ether (3 x 40 ml) and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum - diethyl ether (3:1), which yielded a colourless crystalline solid (0.51 g, 48%)

Method B

A solution of bis(trimethylsilylmethyl)sulfoxide (0.67 g, 3.00 mmol) and dimethyl fumarate (0.29 g, 2.00 mmol) in N,N'-dimethylpropyleneurea (6 ml) was heated to 100 °C and stirred at this temperature for 20 min. The solution was allowed to cool, diluted with toluene (50 ml) and washed with distilled water (2 x 30 ml). After drying over magnesium sulfate, the remaining solvents were removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum - diethyl ether (5:1), which yielded a colourless crystalline solid (0.29 g, 71%)
Method C

To a stirred solution of dimethyl fumarate (0.58 g, 4.00 mmol) and chloromethyltrimethylsilylmethylsulfide (0.88 g, 5.20 mmol) in acetonitrile (30 ml) at ambient temperature, was added caesium fluoride (1.82 g, 12.00 mmol). The solution was stirred for 24 h before being quenched with distilled H2O (100 ml). The aqueous phase was extracted with ethyl acetate (3 x 50 ml) and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (3:1), which yielded a colourless crystalline solid (0.62 g, 76 %), mp 53 °C (lit 18 mp 51-53 °C), v_max (DCM)/cm⁻¹ : 2951, 1734, 1436, 1265, 1197; δ_H (400 MHz, CDCl₃) : 3.11-3.19 (4H, m, 2 x CH₂), 3.47-3.51 (2H, m, 2 x CHCO), 3.73 (6H, s, 2 x CH₃); δ_C (100 MHz, CDCl₃) : 33.01 (CH₂), 50.48 (CH), 52.45 (CH₃), 172.42 (CO), m/z (El) 227 0349 [(M+Na)⁺, C₈H₁₂O₂NaS requires 227 0349] 222 1 (100 %), 205 1 (40), 52 2 (24).
Method A

To a stirred solution of diethyl 2,3-dimethylenedecarboxylic acid (0.63 g, 3.18 mmol) in methanol (10 ml) and distilled H₂O (10 ml), was added sodium sulfide nonahydrate (0.76 g, 3.18 mmol) Stirring was continued at this temperature for 12 h before the addition of distilled H₂O (50 ml) The reaction was extracted with diethyl ether (3 x 40 ml) before the combined organic fractions were dried over magnesium sulfate The remaining solvent was removed under reduced pressure to yield a pale yellow oil This was purified by column chromatography using a mixture of light petroleum diethyl ether (3:1), which yielded a clear oil (0.30 g, 41%)

Method B

To a stirred solution of diethyl fumarate (0.68 g, 3.95 mmol) and chloromethyltrimethylsilylmethylsulfide (0.87 g, 5.14 mmol) in acetonitrile (30 ml) at ambient temperature, was added caesium fluoride (1.80 g, 11.85 mmol) The solution was stirred for 24 h before being quenched with distilled H₂O (100 ml) The aqueous phase was extracted with ethyl acetate (3 x 50 ml) and the combined organic fractions were dried over magnesium sulfate The remaining solvent was removed under reduced pressure to yield a pale yellow oil This was
purified by column chromatography using a mixture of light petroleum diethyl ether (3 l), which yielded a clear oil (0.61 g, 67%); $\nu_{\text{max}}$ (DCM)/cm$^{-1}$ 2980, 1731, 1446, 1371, 1258, 1182, 1030, $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1.27 (6H, t, $J = 7.2$ Hz, CH$_3$), 3.09-3.19 (4H, m, SCH$_2$), 3.44-3.50 (2H, m, CH), 4.18 (4H, q, $J = 7.2$ Hz, CH$_2$CH$_3$), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 14.13 (CH$_3$), 33.03 (SCH$_2$), 50.66 (CH), 61.31 (CH$_2$CH$_3$), 171.97 (CO); $m/z$ (El) 233.0840 [(M+H)$^+$, C$_{10}$H$_{17}$O$_4$S requires 233.0842] 232.1 (17%), 158.0 (19), 85.0 (100)
To a stirred solution of 2-benzylidene-3-methylenesuccinic acid diethyl ester (0.57 g, 2.08 mmol) in methanol (10 ml) and distilled H₂O (10 ml), was added sodium sulfide nonahydrate (0.50 g, 2.08 mmol). Stirring was continued at this temperature for 12 h before the addition of distilled H₂O (50 ml). The reaction was extracted with diethyl ether (3 x 40 ml) and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield an orange oil.
Bis(trimethylsilylmethyl)sulfide 173

\[ \text{SiCl} \rightarrow \text{Si}_{3}\text{S}_{2} \]

To a stirred solution of sodium sulfide nonahydrate (5.16 g, 42.99 mmol) in distilled water (20 ml) was added chloromethyltrimethylsilane (6.00 ml, 42.99 mmol) and tetrabutylammoniumiodide (0.20 g, 0.50 mmol). The reaction mixture was heated under reflux for 16 h, the organic layer separated and the aqueous layer extracted with light petroleum (2 x 20 ml) and diethyl ether (20 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a clear oil (3.48 g, 78 %); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \): 2954, 1387, 1248, 849, \delta_{\text{H}} (400 MHz, CDCl\(_3\)) : 0.07 (18H, s, SiCH\(_3\)), 1.84 (4H, s, CH\(_2\)); \delta_{\text{C}} (100 MHz, CDCl\(_3\)) : -1.60 (SiCH\(_3\)), 23.97 (CH\(_2\)) ; \text{m/z (EI) } 207.1055 [(M+H)]\(^+\), \text{C}_{8}\text{H}_{22}\text{SS}_{2} \text{ requires } 207.1054] 207.1 (28%), 90.1 (27), 84.1 (21), 69.1 (46), 58.1 (100)
Bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide 161

\[
\begin{array}{c}
\text{Si} \quad \text{S} \quad \text{Si} \\
\text{Si}\quad \text{S} \quad \text{Si}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{Si} \quad \text{S} \quad \text{Si} \\
\text{Si} \quad \text{S} \quad \text{Br}
\end{array}
\]

To a stirred solution of bis(trimethylsilylmethyl)sulfide (0.45 g, 2.18 mmol) in carbon tetrachloride (15 ml) was added N-bromosuccinimide (1.64 g, 9.20 mmol) portionwise, and stirred at ambient temperature for 16 h. The solution was filtered to remove the precipitate and washed with petrol. The remaining solvent was removed under reduced pressure to yield a pale yellow oil (2.57 g, 98 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2955, 1387, 1250, 846; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 0.11 (9H, s, CH\(_3\)SiCH\(_2\)), 0.23 (9H, s, CH\(_3\)SiCHBr), 1.85 (1H, d, \( J = 12 \) Hz, CH\(_2\)), 2.31 (1H, d, \( J = 12 \) Hz, CH\(_2\)), 4.69 (1H, s, CHBr); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) -2.30 (CH\(_3\)SiCHBr), -1.57 (CH\(_3\)SiCH\(_2\)), 21.82 (CH\(_2\)), 58.67 (CHBr)
2-Trimethylsilyl-tetrahydrothiophene-3,4-dicarboxylic acid dimethyl ester 183 & 18419

A solution of bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide (0.30 g, 1.05 mmol) and dimethyl fumarate (0.10 g, 0.70 mmol) in N,N-dimethylformamide (2 ml) was stirred for 2 h at 110 °C. The solution was allowed to cool, diluted with toluene (50 ml) and washed with brine (2 x 30 ml). After drying over magnesium sulfate, the remaining solvents were removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (7:1), which yielded a pale yellow oil (0.16 g, 84%) as a 3:1 mixture of diastereoisomers, \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \): 2951, 1734, 1436, 1250, 1024, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)):

- **Major diastereomer**
  - 0.09 (9H, s, SiCH\(_3\)), 2.78 (1H, d, \( J = 11.7 \) Hz, CH\(_3\)SiCH), 2.27-3.02 (1H, m, CH\(_2\)SiCHCH), 3.02 (1H, dd, \( J = 10.5, 11.7 \) Hz, CH\(_3\)), 3.17 (1H, dd, \( J = 8.0, 10.5 \) Hz, CH\(_2\)), 3.42 (1H, ddd, \( J = 8.0, 10.5, 18.4 \) Hz, CH\(_2\)CH), 3.70 (3H, s, OCH\(_3\)), 3.72 (3H, s, OCH\(_3\))
- **Minor diastereomer**
  - 1.00 (9H, s, SiCH\(_3\)), 2.74 (1H, d, \( J = 7.5 \) Hz, CH\(_3\)SiCH), 3.12-3.17 (1H, m, CH\(_2\)SiCHCH), 3.26 (1H, dd, \( J = 7.7, 8.9 \) Hz, CH\(_2\)) 3.52-3.58 (1H, m, CH\(_2\)CH), 3.66 (1H, dd, \( J = 6.2, 7.7 \) Hz, CH\(_2\)), 3.70 (3H, s, OCH\(_3\)), 3.72 (3H, s, OCH\(_3\)), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\))

**Major diastereomer**

- \(-2.88 \) (SiCH\(_3\)), 32.83 (CHSi), 36.18 (CH\(_2\)), 52.16 (CHCO), 52.30 (CHCO), 53.41 (OCH\(_3\)), 54.31 (OCH\(_3\)), 172.21 (CO), 173.10 (CO)

**Minor diastereomer**

- \(-1.89 \) (SiCH\(_3\)), 32.94 (CHSi), 35.39 (CH\(_2\)), 50.68 (CHCO), 51.98 (CHCO), 52.40 (OCH\(_3\)), 52.56 (OCH\(_3\)), 172.31 (CO), 172.96 (CO), \( m/z \) (EI) 294 1191 [(M+NH\(_4\)]\(^+\), C\(_{11}\)H\(_{24}\)O\(_4\)NSSi requires 294 1190] 294 1 (36%), 277 1 (52), 90 0 (100)
5-Trimethylsilyl-tetrahydrothiophene-3-carboxylic acid methyl esters 185 & 186 & 2-trimethylsilyl-tetrahydrothiophene-3-carboxylic acid methyl esters 187 & 188

A solution of bromo(trimethylsilyl)methyl trimethylsilylmethyl sulfide (1.28 g, 4.50 mmol) and methyl acrylate (0.27 ml, 3.00 mmol) in N,N'-dimethylformamide (2 ml) was stirred for 2 h at 110 °C. The solution was allowed to cool, diluted with toluene (50 ml) and washed with brine (2 x 30 ml). After drying over magnesium sulfate, the remaining solvents were removed under reduced pressure to yield a brown oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (12 l), which yielded a clear oil (0.39 g, 59 %) as an inseparable mixture of isomers, ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2955, 1732, 1434, 1249, 1197, m/z (El) 219.3881 [(M+H)<sup>+</sup>, C<sub>9</sub>H<sub>19</sub>O<sub>2</sub>SSi requires 219.3885] 218.4 (24 %), 146 2 (18), 90 0 (100)
$\alpha$-(Trimethylsilyl)benzyl trimethylsilylmethyl sulfide 194$^{19}$

![Chemical structure](image)

To a stirred solution of benzyl mercaptan (117 ml, 1000 mmol) and $N,N,N',N'$-tetramethylethylenediamine (151 ml, 1000 mmol) in tetrahydrofuran (15 ml) at 0 °C, was added $n$-butyllithium (880 ml, 2200 mmol) dropwise. Stirring was continued at this temperature for 2 h to yield an orange solution. This was then cooled to -78 °C and chlorotrimethylsilane (133 ml, 10.50 mmol) was added dropwise. The solution was then allowed to warm to 0 °C and stirred at this temperature for 16 h, before the dropwise addition of chloromethyltrimethylsilane (154 ml, 1100 mmol). The reaction mixture was then stirred at ambient temperature for 4 h before being poured into a mixture of light petroleum, distilled water (75 ml, 1.2). The solution was separated and the aqueous layer extracted with light petroleum (20 ml). The combined organic fractions were washed with a 7% aqueous potassium carbonate solution (50 ml) and distilled water (50 ml), dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a pale pink oil. This was purified by column chromatography using light petroleum, which yielded a clear oil (2.03 g, 72%), $v_{\text{max}}$ (thin film)/cm$^{-1}$ 2954, 1596, 1491, 1448, 1249, 1066, 846, $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 0 04 (18H, s, CH$_3$), 1 51 (2H, dd, $J = 12.4$, 34.8 Hz, CH$_2$), 3 20 (1H, s, CHPh), 7 17-7 13 (1H, m, CH arom para), 7.30-7 24 (4H, m, 4 x CH arom ortho, meta), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) -2 60 (CH$_3$SiCHPh), -1 68 (CH$_3$SiCH$_2$), 18 64 (CH$_2$), 43 64 (CHPh), 125 21 (CH arom para), 128 06 (CH arom ortho), 128 19 (CH arom meta), 141 32 (C arom ipso)
α-(Trimethylsilyl)bromide benzyl trimethylsilymethyl sulfide 195

To a stirred solution of (trimethylsilyl)benzyl trimethylsilymethyl sulfide (1.75 g, 6.19 mmol) in carbon tetrachloride (15 ml) was added N-bromosuccinimide (1.10 g, 6.19 mmol) portionwise, and stirring continued at ambient temperature for 16 h. The resulting solution was filtered to remove the precipitate and washed with light petroleum. The remaining solvent was removed under reduced pressure to yield a yellow oil (1.84 g, 82%), ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2955, 1387, 1250, 846, δ<sub>H</sub> (400 MHz, CDCl₃) 0.11 (9H, s, CH₃SiCH₂), 0.23 (9H, s, CH₃SiC(Ph)Br), 1.85 (1H, d, J = 12.4 Hz, CH₂), 2.31 (1H, d, J = 12.4 Hz, CH₂), 7.18-7.34 (3H, m, 3 x CH arom), 7.61-7.65 (2H, m, 2 x CH arom), δ<sub>C</sub> (100 MHz, CDCl₃) -2.30 (CH₃SiC(Ph)Br), -1.57 (CH₃SiCH₂), 21.82 (CH₂), 58.67 (C(Ph)Br), 128.92 (CH arom), 129.99 (CH arom), 132.25 (CH arom), 142.76 (C arom).
A solution of α-(trimethylsilyl)benzyl trimethylsilylmethyl sulfide (1.00 g, 2.77 mmol) and dimethyl fumarate (0.27 g, 1.85 mmol) in N,N'-dimethylformamide (5 ml) was stirred for 2 h at 110 °C. The solution was allowed to cool, diluted with toluene (50 ml) and washed with brine (2 x 30 ml). After drying over magnesium sulfate, the remaining solvents were removed under reduced pressure to yield a brown oil. This was purified by column chromatography using a mixture of light petroleum: diethyl ether (7:1), which yielded a pale yellow oil (0.65 g, 67%) as a 1:5:1 mixture of diastereoisomers, $\nu$ max (thin film)/cm$^{-1}$: 2974, 1734, 1713, 1448, 1055, 798, $\delta$ H (400 MHz, CDCl$3$): Major diastereomer: 0.19 (9H, s, Si(CH$_3$)$_3$), 2.73-3.39 (4H, m, CH$_2$CHCH), 3.66 (3H, s, OCH$_3$), 3.69 (3H, s, OCH$_3$), 7.14-7.64 (5H, m, 5 x CH arom), Minor diastereomer: 0.19 (9H, s, Si(CH$_3$)$_3$), 2.73-3.39 (4H, m, CH$_2$CHCH), 3.52 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 7.14-7.64 (5H, m, 5 x CH arom), $\delta$ C (100 MHz, CDCl$3$): Major diastereomer -1.19 (SiCH$_3$), 31.83 (CH$_2$), 48.78 (CH$_2$CH), 52.41 (2 x OCH$_3$), 53.66 (C(Ph)Si(CH$_3$)$_3$), 58.71 (CH$_2$CHCH), 126.35 (CH arom), 127.72 (2 x CH arom), 128.34 (2 x CH arom), 140.07 (C arom), 171.11 (CO), 173.30 (CO), Minor diastereomer -1.19 (SiCH$_3$), 32.43 (CH$_2$), 50.79 (CH$_2$CH), 51.89 (OCH$_3$), 52.17 (OCH$_3$), 53.64 (C(Ph)Si(CH$_3$)$_3$), 60.57 (CH$_2$CHCH), 125.82 (CH arom), 127.37 (2 x CH arom), 128.01 (2 x CH arom), 143.59 (C arom), 171.77 (CO), 173.130 (CO), m/z (El) 353 1168 [(M+H)$^+$, C$_{17}$H$_{25}$O$_4$Si requires 353 1165] 352.1 (29%), 176.5 (67), 90 0 (100)
3-Bromo-1-(trimethylsilyl)propyne $206^{29}$

\[ \text{Br} \quad \text{Br} \quad \text{Si} \]

$n$-Butyllithium (220 ml, 55.00 mmol) was added dropwise to a stirred solution of propargyl bromide (5.5 ml, 50.00 mmol) in tetrahydrofuran (200 ml) at $-78 \, ^\circ\text{C}$. After stirring for 30 min, chlorotrimethylsilane (19.0 ml, 150.00 mmol) was added dropwise at $-78 \, ^\circ\text{C}$. The solution was then allowed to warm to ambient temperature and 4% aqueous hydrochloric acid (200 ml) added and stirred for 16 h. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (10:1), which yielded a colourless oil (7.31 g, 76%); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2959, 2178, 1251, 1205, 1041; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 0.18 (9H, s, CH$_3$), 3.91 (2H, s, CH$_2$), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) -0.42 (CH$_3$), 14.65 (CH$_2$), 92.30 (C(SiMe$_3$)), 99.94 (C(CH$_2$Br))
3-Trimethylsilyl-prop-2-ynyl S-thioacetate

\[
\begin{align*}
\text{Si} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{S}
\end{align*}
\]

Method A

To a stirred suspension of potassium thioacetate (0.60 g, 5.20 mmol) in tetrahydrofuran (10 ml) at 0 °C, was added 3-bromo-1-(trimethylsilyl)propyne (0.50 g, 2.60 mmol) dropwise and stirring continued at this temperature for 1 h. The solution was poured into distilled water (50 ml) and separated, and the aqueous layer extracted with diethyl ether (3 x 10 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the excess solvent removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum - diethyl ether (10:1), which yielded a pale yellow oil (0.30 g, 63 %).

Method B

To a stirred solution of triphenylphosphine (8.18 g, 31.20 mmol) in tetrahydrofuran (100 ml) at 0 °C was added disopropyl azodicarboxylate (6.14 ml, 31.20 mmol) and stirring maintained at this temperature for 30 min. A solution of 3-(1,1,1-trimethylsilyl)prop-2-yn-1-ol (2.00 g, 15.60 mmol) and thiolacetic acid (2.23 ml, 31.20 mmol) in tetrahydrofuran (50 ml) was then added dropwise over 10 min. The solution was stirred at 0 °C for 1 h, then allowed to warm to ambient temperature and stirred for a further 1 h. The solvent was removed under reduced pressure to yield an orange oil. This was
purified by column chromatography using a mixture of light petroleum · diethyl ether (10:1), which yielded a pale yellow oil (2.21 g, 76 %), νmax (thin film)/cm⁻¹: 2959, 2178, 1698, 1251, 1033, δH (400 MHz; CDCl₃) 0.15 (9H, s, SiCH₃), 2.36 (3H, s, (CO)CH₃), 3.69 (2H, s, CH₂), δC (100 MHz, CDCl₃) -0.17 (Si(CH₃), 18.61 (CH₂), 30.13 (CO)CH₃), 87.85 (C(SiCH₃)₂), 100.07 (C(CH₃)), 193.99 (C(O)H), m/z (EI) 186.0528 [(M+H)+, C₇H₁₄OSSi requires 186.0529] 185 1 (19 %), 171 0 (61), 144.0 (65), 127.0 (46), 73 0 (93), 53 0 (29), 43 0 (100)
To a stirred solution of lithium aluminium hydride (12.88 ml, 12.88 mmol) in anhydrous diethyl ether (50 ml) at -30 °C, was added 3-(trimethylsilyl)-prop-2-ynyl S-thioacetate (2.40 g, 12.88 mmol) in anhydrous diethyl ether (20 ml) dropwise. The solution was allowed to warm to ambient temperature and stirred for 1 h. After re-cooling to -30 °C, saturated aqueous ammonium chloride solution was added dropwise to destroy any remaining lithium aluminium hydride. The solution was poured into distilled water (100 ml) and separated, and the aqueous layer extracted with diethyl ether (3 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a yellow oil (1.79 g, 96 %).

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 2957, 2175, 1250, 1031, 842, $\delta_{11}$ (400 MHz; CDCl$_3$): 0.17 (9H, s, SiCH$_3$), 2.01 (1H, t, $J = 7.6$ Hz, SH), 3.30 (2H, d, $J = 7.6$ Hz, CH$_2$), $\delta_{12}$ (100 MHz, CDCl$_3$): -0.14 (SiCH$_3$), 13.23 (CH$_2$), 87.25 (C(SiMe$_3$), 103.73 (C(CH$_2$SII) ), $m/z$ (EI) 143 0342 [(M-H)$^+$, C$_8$H$_{11}$SSi requires 143 0345] 144 0 (52 %), 128.9 (100), 102.9 (65), 95.0 (50), 74.9 (65)
To a stirred solution of 3-trimethylsilyl-prop-2-yne-1-thiol (1.44 g, 10.00 mmol) and \(N,N,N',N'-\text{tetramethylethylenediamine}\) (1.51 ml, 10.00 mmol) in tetrahydrofuran (20 ml) at 0 °C, was added \(n\)-butyllithium (8.80 ml, 22.00 mmol) dropwise. Stirring was continued at this temperature for 2 h to yield an orange solution. This was then cooled to -78 °C and chlorotrimethylsilane (1.33 ml, 10.50 mmol) was added dropwise. The solution was then allowed to warm to 0 °C and stirred at this temperature for 16 h, before the dropwise addition of chloromethyltrimethylsilane (1.54 ml, 11.00 mmol). The reaction mixture was then stirred at ambient temperature for 4 h before being poured into a mixture of light petroleum and distilled water (100 ml, 1:2). The solution was separated and the aqueous layer extracted with light petroleum (30 ml). The combined organic fractions were washed with a 7% aqueous potassium carbonate solution (50 ml) and distilled water (50 ml), dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield an orange oil.
Bis(trimethylsilylmethyl)sulfoxide 215^21

\[
\begin{align*}
\text{Si} & \quad \text{S} \quad \text{Si}' \\
\text{Si} & \quad \text{S} \quad \text{Si}' \\
\end{align*}
\]

To a stirred solution of bis(trimethylsilylmethyl)sulfide (0.75 g, 3.63 mmol) in dichloromethane (5 ml) at -40 °C was added \( m \)-chloroperoxy benzoic acid (1.50 g, 4.36 mmol) in dichloromethane (20 ml) dropwise. The solution was stirred at this temperature for 3 h, then allowed to warm to ambient temperature, filtered and washed with cold dichloromethane. The combined organic fractions were washed with cold saturated sodium hydrogen carbonate solution (50 ml) and cold brine (50 ml), dried over magnesium sulfate, filtered and the remaining solvents removed under reduced pressure to yield a clear oil (0.82 g, 98%). \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2955, 1249, 1075, 847, 847 (400 MHz, CDCl\(_3\)) • 0.22 (18H, s, CH\(_3\)), 2.15 (2H, d, \( J = 13.6 \text{ Hz, 2 x 1 of CH}_2\)), 2.43 (2H, d, \( J = 13.6 \text{ Hz, 2 x 1 of CH}_2\)), \( \delta \)C (100 MHz, CDCl\(_3\)) • -0.83 (CH\(_3\)), 47.59 (CH\(_2\))
(Trimethylsilyl)benzyl trimethylsilylmethyl sulfoxide 216

\[
\text{Si} \quad \text{S} \quad \text{Si} \quad \text{S} \quad \text{Si} \quad \text{O} \quad \text{Si}
\]

To a stirred solution of (trimethylsilyl)benzyl trimethylsilylmethyl sulfide (2.00 g, 7.08 mmol) in dichloromethane (20 ml) at -40 °C was added m-chloroperoxy benzoic acid (2.93 g, 8.50 mmol) in dichloromethane (40 ml) dropwise. The solution was stirred at this temperature for 3 h, then allowed to warm to ambient temperature, filtered and washed with cold dichloromethane. The combined organic fractions were washed with cold saturated sodium hydrogen carbonate solution (100 ml) and cold brine (100 ml), dried over magnesium sulfate, filtered and the remaining solvents removed under reduced pressure to yield a clear oil (1.92 g, 91 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 2948, 1254, 1042, 783, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 0.19 (9H, s, CH\(_3\)SiCH\(_2\)), 0.27 (9H, s, CH\(_3\)SiCHPh), 2.04 (1H, d, \( J = 12.8 \text{ Hz} \), CH\(_2\)), 2.41 (1H, d, \( J = 12.8 \text{ Hz} \), CH\(_2\)) 4.27 (1H, s, CHPh) 7.21-7.39 (3H, m, 3 x CH arom), 7.61-7.66 (2H, m, 2 x CH arom), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) -0.22 (CH\(_3\)SiCHPh), -0.09 (CH\(_3\)SiCH\(_2\)), 33.84 (CH\(_2\)), 63.49 (CHPh), 127.23 (CH arom), 132.84 (CH arom), 133.63 (CH arom), 142.70 (C arom.).
2-Phenyl tetrahydrothiophene-3,4-dicarboxylic acid dimethyl esters 218 & 219

Method A

A solution of (Trimethylsilyl)benzyl trimethylsilylmethyl sulfoxide (1.79 g, 6.00 mmol) and dimethyl fumarate (0.59 g, 4.00 mmol) in N,N-dimethylpropyleneurea (15 ml) was heated to 100 °C and stirred at this temperature for 20 min. The solution was allowed to cool, diluted with toluene (100 ml) and washed with distilled water (2 x 50 ml). After drying over magnesium sulfate, the remaining solvents were removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (5 l), which yielded a colourless oil as a 1:1 mixture of diastereoisomers (0.71 g, 59 %)

Method B

To a stirred solution of dimethyl fumarate (0.36 g, 2.52 mmol) and chloromethyl trimethylsilylphenylmethyl sulfide (0.80 g, 3.27 mmol) in acetonitrile (20 ml) at ambient temperature, was added caesium fluoride (1.15 g, 7.56 mmol). The solution was stirred for 48 h before being quenched with distilled H2O (100 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 ml), and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure
to yield a viscous orange oil. This was purified by column chromatography using a mixture of light petroleum · diethyl ether (3 l), which yielded a colourless oil, which crystallised upon standing to yield a colourless crystalline solid in a colourless oil (0.49 g, 69 %); mp 73 °C, νmax (thin film)/cm⁻¹: 2958, 1731, 1436, 1265, δH (400 MHz; CDCl3) : cis-diastereomer 2.91-3.59 (4H, m, CH₂CH₂CH₂), 3.75 (3H, s, OCH₃), 4.03 (3H, s, OCH₃), 7.17-7.64 (5H, m, 5 x CH arom), trans-diastereomer : 2.78-3.39 (4H, m, CH₂CH₂CH₂), 3.62 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 7.15-7.66 (5H, m, 5 x CH arom), δC (100 MHz, CDCl3) : cis-diastereomer 33 32 (CH₂), 51.74 (CH₂CH₂), 53 45 (OCH₃), 67 23 (OCH₃), 54 72 (CHPPh), 59 17 (CH₂CH₂CH₂), 125 21 (CH arom), 128 02 (2 x CH arom), 128 27 (2 x CH arom), 140 17 (C arom), 171 32 (CO), 173 37 (CO), trans-diastereomer 33 43 (CH₂), 48 65 (CH₂CH₂), 53 68 (OCH₃), 54 15 (OCH₃), 52 12 (CHPPh), 56.78 (CH₂CH₂CH₂), 125 21 (CH arom), 127.67 (2 x CH arom), 127 81 (2 x CH arom), 141 32 (C arom), 169 56 (CO), 171.86 (CO), m/z (EI) 298 1108 [(M+NH₄)⁺, C₁₄H₂₀O₄NS requires 298 1108] 298 2 (100 %), 281.2 (35)
Trimethylsilylmethanethiol 220\textsuperscript{22}

\[
\begin{array}{c}
\text{Si} \\
\text{Cl} \longrightarrow \text{Si} \\
\text{SH}
\end{array}
\]

A stirred solution of chloromethyl trimethylsilane (10.00 ml, 71.66 mmol) and thiourea (10.91 g, 143.32 mmol) in anhydrous ethanol (100 ml) was heated under reflux for 48 h. The solvent was then removed under reduced pressure to yield a white powdery solid, which was dissolved in distilled water (100 ml) and treated with a 40 % sodium hydroxide solution (100 ml). The solution was extracted with diethyl ether (3 x 100 ml), acidified with concentrated hydrochloric acid and extracted with diethyl ether (2 x 100 ml). The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a clear oil (5.26 g, 61 %), \( \nu_{\text{max}} \) (thin film)/\text{cm}^{-1} 2954, 1249, 843; \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{3}) 0.10 (9H, s, CH\textsubscript{3}), 1.11 (1H, t, \( J = 6.9 \text{ Hz}, \text{SH} \)), 1.65 (2H, d, \( J = 6.9 \text{ Hz}, \text{CH}_2 \)), \( \delta_{\text{C}} \) (100 MHz, CDCl\textsubscript{3}) -248 (CH\textsubscript{3}), 824 (CH\textsubscript{2}), \( m/z \) (EI) 119 0344 [(M+H)+, C\textsubscript{4}H\textsubscript{11}Si requires 119 0345] 119 0 (16 %), 73 0 (100), 59 0 (10), 45 0 (19).
Chloromethyl trimethylsilylmethyl sulfide 170\textsuperscript{23}

\[
\begin{array}{c}
\text{Si-SH} \\
\rightarrow \\
\text{Si-S-Cl}
\end{array}
\]

Method A

Gaseous hydrogen chloride was bubbled through a solution of trimethylsilylmethanol (0.75 g, 6.23 mmol) and 1,3,5-trioxane (0.19 g, 2.14 mmol) at -10 °C for 1 h. The solution was allowed to warm to 0 °C and stirred for 2 h before being dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil (0.64 g, 61 %)

Method B

To a stirred solution of trimethylsilylmethanol (1.00 g, 8.31 mmol) in dichloromethane (150 ml) at ambient temperature, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.24 ml, 8.31 mmol) dropwise. Stirring was continued at this temperature for 16 h, before the reaction was quenched with distilled water (50 ml). The organic layer was separated, dried over magnesium sulfate, and the remaining solvent removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (10 l), which yielded a pale yellow oil (0.63 g, 45 %)
Method C

To a stirred solution of trimethylsilylmethanethiol (1.00 g, 8.31 mmol) in acetonitrile (50 ml) at ambient temperature, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.24 ml, 8.31 mmol) dropwise. Stirring was continued at this temperature for 30 min, and then the solution was added dropwise to a stirred solution of bromochloromethane (150 ml). After stirring at ambient temperature for 5 h, the reaction was quenched with distilled water (50 ml), and the organic layer was separated, dried over magnesium sulfate, and the remaining solvent removed under reduced pressure to yield an orange oil. This was purified by column chromatography using a mixture of light petroleum · diethyl ether (10:1), which yielded a pale yellow oil (0.55 g, 39%).

Method D

To a stirred solution of trimethylsilylmethanethiol (1.00 g, 8.31 mmol) in acetone (50 ml) at 10 °C, was added powdered potassium hydroxide (0.09 g, 1.66 mmol). Stirring was continued at this temperature for 30 min, before the dropwise addition of the solution to a stirred solution of bromochloromethane (0.81 ml, 12.47 mmol), and Amberlite IRA 400 (0.10 g) in acetone (50 ml) at 10 °C. Stirring was continued for a further 16 h, during which time the reaction was allowed to warm to ambient temperature, before the reaction was quenched with distilled water (100 ml), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 50 ml), and the combined organic fractions were dried over magnesium sulfate, and the remaining solvent removed under reduced pressure to yield a yellow oil. This was distilled using Kugelrohr apparatus to yield a pale yellow oil (0.18 g, 13%).
Method E

To a stirred solution of trimethylsilylmethanethiol (1.00 g, 8.31 mmol) in bromochloromethane (100 ml) at ambient temperature, was added triethylbenzylammonium chloride (0.19 g, 0.83 mmol) followed by powdered potassium hydroxide (0.47 g, 8.31 mmol). Stirring was continued at this temperature for 3 h before being the addition of a saturated ammonium chloride solution (50 ml). The solution was then separated and the aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was distilled using Kugelrohr apparatus to yield a clear oil (0.94 g, 67 %). $v_{\text{max}}$ (thin film)/cm$^{-1}$: 2954, 1338, 1250, 848, 723; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$): 0.12 (9H, s, SiCH$_3$), 2.03 (2H, s, CH$_2$Si), 4.73 (2H, s, CH$_2$Cl), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): -17.71 (SiCH$_3$), 17.99 (CH$_2$Si), 54.05 (CH$_2$Cl)
To a stirred solution of methylvinylsulfone (0.24 ml, 2.74 mmol) and chloromethyl trimethylsilylmethyl sulfide (0.60 g, 3.56 mmol) in acetonitrile (25 ml) at ambient temperature was added caesium fluoride (1.25 g, 8.22 mmol). Stirring was continued at this temperature for 48 h before the reaction was quenched with distilled water (50 ml). The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum – diethyl ether (1:4), which yielded a colourless crystalline solid (0.31 g, 68%), mp 56 °C, νmax (thin film)/cm⁻¹ 2928, 1293, 1135, 960, 771, δH (400 MHz; CDCl₃) 2.34-2.46 (1H, m, 1 x CH₂CH₂CHSO₂), 2.51-2.59 (1H, m, 1 x CH₂CH₂CHSO₂), 2.95 (3H, s, SO₂CH₃), 2.95-3.01 (1H, m, 1 x SCH₂CHSO₂), 3.04-3.09 (1H, m, 1 x SCH₂CHSO₂), 3.18-3.27 (2H, m, SCH₂CH₂), 3.61-3.63 (1H, m, CH₂O₂Cl₃), δC (100 MHz; CDCl₃) 30.48 (CH₂CH₂CHSO₂), 30.53 (SCH₂CHSO₂), 31.32 (CH₂CH₂), 39.92 (CH₃), 65.99 (CHSO₂CH₃), m/z (EI) 184.0461 [(M+NH₄)⁺, C₅H₁₄O₂NS₂ requires 184.0460] 184.0 (100%), 86.1 (20).
To a stirred solution of phenylvinylsulfone (0.46 g, 2.74 mmol) and chloromethyl trimethylsilylmethyl sulfide (0.60 g, 3.56 mmol) in acetonitrile (25 ml) at ambient temperature was added caesium fluoride (1.25 g, 8.22 mmol). The reaction was stirred at this temperature for 48 h before being quenched with distilled water (50 ml). The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined organic fractions were dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (2 : 1), which yielded a colourless crystalline solid (0.55 g, 87%), m.p 69 °C, \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 2938, 1445, 1305, 1147, 1085, 871 (400 MHz; CDCl\(_3\)) : 2.26-2.36 (1H, m, 1 x SCH\(_2\)CH\(_2\)), 2.40-2.47 (1H, m, 1 x SCH\(_3\)CH\(_2\)), 2.86-3.03 (3H, m, SCH\(_3\)CH\(_2\), 1 x SCH\(_2\)CH), 3.17 (1H, m, 1 x SCH\(_3\)CH), 3.63-3.71 (1H, m, CHSO\(_2\)Ph), 7.58-7.62 (2H, m, 2 x CH arom meta), 7.68-7.72 (1H, m, CH arom para), 7.91-7.93 (2H, m, 2 x CH arom ortho), 8.35 (100 MHz, CDCl\(_3\)) : 30.23 (SCH\(_2\)CH\(_2\)), 30.51 (SCH\(_3\)CH), 31.50 (SCH\(_2\)CH\(_2\)), 67.36 (CHSO\(_2\)Ph), 128.54 (CH arom ortho), 129.43 (CH arom meta), 134.11 (CH arom para), 138.23 (C arom); m/z (EI) 246.0617 [(M+NH\(_4\))^+, C\(_{10}\)H\(_{16}\)O\(_2\)NS\(_2\) requires 246.0617] 246.1 (100%), 86.0 (7)
α-Trimethylsilyl benzylmercaptan 213^24

\[
\text{\text{\text{-}}}^{\text{-}} \text{Si} \text{SH} \quad \text{\text{\text{-}}}^{\text{-}} \text{Si} \text{SH}
\]

To a stirred solution of benzyl mercaptan (3.00 ml, 25.52 mmol) and \(N,N,N',N'\)-tetramethylethlenediamine (3.86 ml, 25.52 mmol) in tetrahydrofuran (40 ml) at 0 °C, was added \(n\)-butyllithium (22.46 ml, 56.14 mmol) dropwise. Stirring was continued at this temperature for 2 h to yield an orange/red solution. This was then cooled to -78 °C and chlorotrimethylsilane (3.40 ml, 26.80 mmol) was added dropwise. The solution was then allowed to warm to 0 °C and stirred at this temperature for 16 h, before being poured into a mixture of light petroleum : distilled water (150 ml, 1:2). The solution was separated and the aqueous layer extracted with light petroleum (2 x 50 ml). The combined organic fractions were washed with a 7 % aqueous potassium carbonate solution (100 ml) and distilled water (100 ml), dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a pale yellow oil (4.17 g, 82 %). \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2954, 1596, 1492, 1448, 1249, 841; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 0.06 (9H, s, Si\(\text{CH}_3\)), 1.83 (1H, d, \(J = 6.9\) Hz, SH), 3.35 (1H, d, \(J = 6.9\) Hz, CHSH), 7.02-7.16 (1H, m, CH arom. para), 7.23-7.29 (4H, m, 4 x CH arom ortho, meta), \(\Delta C\) (100 MHz, CDCl\(_3\)) -3.06 (CH\(_3\)Si), 31.50 (CHSH), 125.54 (CH arom para), 127.41 (CH arom ortho), 128.15 (CH arom meta), 143.54 (C arom)
Chloromethyl trimethylsilylphenylmethyl sulfide 235

\[
\text{\lowercase{Si}--\text{S}--\text{H}} \rightarrow \text{\lowercase{Si}--\text{S}--\text{Cl}}
\]

Method A

Gaseous hydrogen chloride was bubbled through a solution of α-trimethylsilyl benzylmercaptan (2.00 g, 10.18 mmol) and 1,3,5-trioxane (0.32 g, 3.51 mmol) at -10 °C for 1 h. The solution was allowed to warm to 0 °C and stirred for 2 h before being dried over magnesium sulfate. The remaining solvent was removed under reduced pressure to yield a pale yellow oil (1.47 g, 59%).

Method B

To a stirred solution of α-trimethylsilyl benzylmercaptan (2.50 g, 12.73 mmol) in bromochloromethane (200 ml) at ambient temperature, was added trimethylbenzylammonium chloride (0.29 g, 1.27 mmol) followed by powdered potassium hydroxide (0.71 g, 12.73 mmol). Stirring was continued at this temperature for 3 h before being the addition of a saturated ammonium chloride solution (100 ml). The solution was then separated and the aqueous layer was extracted with dichloromethane (2 x 75 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a pale yellow oil (2.37 g, 76%).

\[\nu_{\text{max}} \text{ (thin film)/cm}^{-1}: 2954, 1596, 1492, 1449, 1249, 844, \delta_{\text{H}} \text{ (400 MHz, CDCl}_3\text{) 0.16 (9H, s, SiCH}_3\text{), 3.72 (1H, s, CHPh), 4.46 (1H, d, J = 11.2 Hz, CH}_2\text{Cl), 4.62 (1H, d, J = 11.2 Hz, CH}_2\text{Cl), 7.26-7.38 (5H, m, 5 x CH arom)}, \delta_{\text{C}} \text{ (100 MHz, }\text{)}\]
CDCl₃: -2.61 (CH₃Sn), 37.01 (CHPh), 49.02 (CH₂Cl), 125.99 (CH arom para), 128.29 (CH arom ortho), 128.43 (CH arom meta), 139.51 (C arom)
To a stirred solution of ethyl bromopyruvate (5.00 ml, 35.84 mmol) and tetrabutylammonium iodide (1.15 g, 3.58 mmol) in absolute ethanol (150 ml) at 0 °C, was added anhydrous sodium hydrogen sulfide (2.01 g, 35.84 mmol). Stirring was continued at this temperature for 2 h, before allowing the reaction to warm to ambient temperature and stir for a further 16 h. The solvent was then removed under reduced pressure, and the residue partitioned between dichloromethane (100 ml) and distilled water (100 ml). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 25 ml). The combined organic fractions were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil.
3-Methyl-4-pentenoic acid methyl ester 244

To a stirred solution of 3-methyl-4-pentenoic acid (3.19 ml, 26.28 mmol) in dichloromethane (50 ml) at ambient temperature was added caesium carbonate (10.28 g, 31.54 mmol) and dimethyl sulfate (2.99 ml, 31.54 mmol). Stirring was continued at ambient temperature for 48 h. The solution was then washed with distilled water (2 x 50 ml) and brine (2 x 50 ml), dried over magnesium sulfate, filtered and the remaining solvents removed under reduced pressure to yield a clear oil (2.64 g, 78 %), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 2961, 1735, 1437, 1200, 1008, $\delta_{\text{HH}}$ (400 MHz; CDCl$_3$) 1 06 (3H, d, $J = 6.8$ Hz, CH$_3$CH), 2 32 (2H, ddd, $J = 7.2$, 14.9, 37.6 Hz, CH$_2$(CO)), 2.72-2 65 (1H, m, CH$_3$CH), 3 66 (3H, s, OCH$_3$), 4 96 (1H, dt, $J = 14$, 10.4 Hz, CH=CH$_2$), 5 03 (1H, dt, $J = 14$, 17.2 Hz, CH=CH$_2$), 5 77 (1H, ddd, $J = 7.0$, 10.4, 17.2 Hz, CH=CH$_2$), $\delta_c$ (100 MHz, CDCl$_3$) 19 70 (CH$_3$CH), 34 40 (CH$_3$CH), 41 12 (CH$_2$(CO)), 51 46 (OCH$_3$), 113 36 (CH=CH$_2$), 142 44 (CH=CH$_2$), 172 99 (CO), m/z (EI) 129 0910 [(M+H)$^+$, C$_7$H$_{13}$O$_2$ requires 129 0910] 127 0 (10 %), 95.9 (55), 68 0 (82), 58.9 (37), 55 0 (65), 41 0 (100), 39 0 (49)
To a stirred solution of 3-methyl-4-pentenoic acid methyl ester (2.00 g, 15.60 mmol) in anhydrous diethyl ether (20 ml) at 0 °C, was added lithium aluminium hydride (31.20 ml, 31.20 mmol) dropwise. Stirring was maintained at this temperature for 2 h, before the solution was allowed to warm to ambient temperature and stirring continued for a further 16 h. Distilled water was then added dropwise to destroy any remaining lithium aluminium hydride before the solution was poured into distilled water (100 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a pale yellow oil. This was purified via Kugelrohr distillation to yield a clear oil (1.34 g, 86 %), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 3330 (br), 2959, 1639, 1434, 1419, 1374, 1053, 995, $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 1 03 (3H, d, J = 6.7 Hz, CH$_3$CH), 1 33 (1H, s, br, OH) 1 55–1 61 (2H, m, OHCH$_2$CH$_2$CH$_3$) 2 31 (1H, q, J = 7 0 Hz, CH$_3$CH), 3 66 (2H, t, J = 6 5 Hz, CH$_2$OH), 4 95 (1H, dt, J = 1 4, 10 1 Hz, CH=CH$_2$), 5 01 (1H, dt, J = 1 4, 17 3 Hz, CH=CH$_2$), 5 72 (1H, ddd, J = 7 4, 10 1, 17 3 Hz CH=CH$_2$), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) C 35 24 (CH$_2$CH), 39 68 (CH$_3$CH$_2$CH$_2$), 61 56 (CH$_2$OH), 113 43 (CH=CH$_2$), 144 59 (CH=CH$_2$), m/z (EI) 82 0775 [(M-H$_2$O)$^+$, C$_6$H$_{10}$ requires 82 0777] 82 0 (25 %), 67 0 (100), 56 0 (23), 55 0 (47), 40 9 (49)
6-Hydroxy-4-methyl-hex-2-enoic acid methyl ester 246

To a stirred solution of 3-methyl-4-penten-1-ol (1.60 g, 15.97 mmol) in anhydrous dichloromethane (30 ml) was added methyl acrylate (3.60 ml, 39.93 mmol) and benzyldene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (0.28 g, 0.33 mmol). The reaction was heated under reflux for 24 h, before being opened to the air to allow oxidation and stirred at ambient temperature for 16 h. The remaining solvent was removed under reduced pressure to yield a brown oil, which was purified by column chromatography using a mixture of light petroleum diethyl ether (1:1.5) to yield a pale yellow oil (0.31 g, 66%), v_max (thin film)/cm⁻¹ 3418 (br), 2954, 1722, 1654, 1436, 1275, δ_H (400 MHz, CDCl₃) 1.09 (3H, d, J = 6.9 Hz, CH₃CH), 1.44 (1H, s, br, OH), 1.65 (2H, q, J = 6.7 Hz, CH₂CH₂OH), 2.53 (1H, m, CH₃CH), 3.66 (2H, t, J = 2.9 Hz, CH₂OH), 3.73 (3H, s, OCH₃), 5.83 (1H, d, J = 15.7 Hz, CHCO), 6.88 (1H, dd, J = 8.1, 15.7 Hz, CH₃CHCH), δ_C (100 MHz, CDCl₃) · 19.42 (CH₃CH), 33.19 (CH₂CH), 38.61 (CH₂CH₂OH), 51.48 (OCH₃), 60.54 (CH₂OH), 119.67 (CHCO), 154.06 (CH₃CHCH), 167.22 (CO); m/z (El) 159 1016 [(M+H)⁺, C₈H₁₄OSSi requires 159 1016] 159 1 (27 %), 144 1 (100), 127 0 (36), 52 2 (36)
4-(3-(1-hydroxybutyl))-3-carboxymethyl tetrahydrothiophenes 249 & 250

To a stirred solution of 6-hydroxy-4-methyl-hex-2-enoic acid methyl ester (0.16 g, 1.00 mmol) and chloromethyl trimethylsilylmethyl sulfide (0.22 g, 1.30 mmol) in acetonitrile (8 ml) at ambient temperature, was added caesium fluoride (0.46 g, 3.00 mmol). Stirring was continued at this temperature for 24 h before the reaction was quenched with distilled water (100 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 ml), the combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (4:1), which yielded a clear oil (0.14 g, 62%) as a 1:1.5 inseparable mixture of diastereoisomers, νmax (thin film)/cm⁻¹ 3434 (br), 2949, 1732, 1435, 1268, 1163; m/z (EI) 241 0867 [(M+Na)+, C₁₀H₁₅O₃NaS requires 241 0869] 218 1 (100%), 186 0 (56), 171 1 (24), 158 0 (30)
2-Bromoethoxy tertbutyldimethylsilane 253

To a stirred solution of 2-bromoethanol (1.00 ml, 13.40 mmol) in dichloromethane (10 ml) at ambient temperature, was added imidazole (1.00 g, 14.74 mmol) and dimethylaminopyridine (0.16 g, 1.34 mmol). After 30 min, tertbutyldimethylsilyl chloride (2.22 g, 14.74 mmol) was added, and stirring continued at ambient temperature for 16 h. The reaction was then filtered through silica to remove the resulting precipitate, and the remaining solvent was removed under reduced pressure to yield a clear oil (3.19 g, 99%). 

$\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 2954, 1471, 1256, 837, 777, $\delta_{\text{II}}$ (400 MHz; CDCl$_3$): 0.09 (6H, s, SiCH$_3$), 0.91 (9H, s, C(CH$_3$)$_3$), 3.40 (2H, t, $J = 6.6$ Hz, CH$_2$Br), 3.89 (2H, t, $J = 6.6$ Hz, CH$_2$Si), $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): -5.27 (SiCH$_3$), 18.33 (C(CH$_3$)$_3$), 25.82 (C(CH$_3$)$_3$), 33.30 (CH$_2$Br), 63.50 (CH$_2$OSi), $m/z$ (EI) 223 0149 [(M-CH$_3$), C$_7$H$_{16}$OBrSi requires 223 0148] 224 9 (100%), 223 0 (94), 208.9 (8)
Lithium bis(trimethylsilyl)amide (5.15 ml, 5.25 mmol) was cooled to -78 °C and a solution of (R)-4-benzyl-3-propionyl-2-oxazolidinone (1.00 g, 4.29 mmol) in tetrahydrofuran (10 ml) added dropwise via syringe pump over 2 h, ensuring the internal temperature remained below -60 °C. After stirring for an additional 30 min at -78 °C, a solution of 2-bromoethoxy tertbutyldimethylsilane (2.05 g, 8.58 mmol) in tetrahydrofuran (5 ml) was added dropwise. The reaction was stirred for 16 h, allowing to warm to ambient temperature, before being poured into a saturated aqueous ammonium chloride solution (40 ml). The aqueous layer was separated and extracted with diethyl ether (3 x 30 ml), the combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a colourless solid. This was recrystallised from diethyl ether and light petroleum to yield a colourless crystalline solid which was identified as (R)-4-benzyl-3-propionyl-2-oxazolidinone.
A solution of sodium bis(trimethylsilyl)amide (12.86 ml, 25.72 mmol) in tetrahydrofuran (50 ml) was cooled to -78 °C. A solution of (R)-4-benzyl-3-propionyl-2-oxazolidinone (5.00 g, 21.43 mmol) in tetrahydrofuran (20 ml) was then added dropwise over 30 min and stirring continued at this temperature for 1 h. Allyl bromide (5.57 ml, 64.29 mmol) was then added dropwise and the reaction was stirred for 3 h, allowing to warm to ambient temperature. Saturated aqueous ammonium chloride solution (75 ml) was added, the aqueous layer was separated and extracted with diethyl ether (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (2:1), which yielded a viscous clear oil (4.51 g, 77 %), $[\alpha]_{D}^{20} +89^\circ$ (c = 1.0, CHCl$_3$) (lit $^{25}$ $[\alpha]_{D}^{20} +98^\circ$ (c = 1.0, CHCl$_3$), $\nu_{\max }$ (thin film)/cm$^{-1}$ 2976, 1779, 1699, 1386, 1210, 702; $\delta_{H}$ (400 MHz, CDCl$_3$) 1.19 (3H, d, $J = 6.8$ Hz, CH$_3$), 2.24 (1H, qt, $J = 11$, 7.0 Hz, CH$_3$CHCH$_2$), 2.53 (1H, qt, $J = 11$, 7.0 Hz, CH$_3$CHCH$_2$), 2.70 (1H, dd, $J = 9.8$, 13.3 Hz, PhCH$_2$), 3.29 (1H, dd, $J = 3.3$, 13.3 Hz, PhCH$_2$), 3.87 (1H, sextet, $J = 6.8$ Hz, CH$_3$CH), 4.14-4.21 (2H, m, OCH$_2$), 4.68 (1H, ddd, $J = 3.3$, 6.8, 10.7 Hz, NCH), 5.05-5.13 (2H, m, CH$_2$=CH), 5.83 (1H, tt, $J = 7.0$, 10.2, 17.1 Hz, CH$_2$=CH), 7.20-7.35 (5H, m, 5 x CH arom); $\delta_{C}$ (100 MHz, CDCl$_3$): 16.44 (CH$_3$), 37.14 (CH$_3$CH), 37.99 (CH$_3$CHCH$_2$), 38.10 (PhCH$_2$), 55.40 (NCH), 66.01 (OCH$_2$), 117.24 (CH$_2$=CH)
127.33 (CH arom para), 128.94 (CH arom ortho), 129.42 (CH arom meta), 135.26 (CH=CH), 135.37 (C arom. ipso), 153.12 (CO), 176.52 (CO); m/z (EI) 274 1438 [(M+H)^+], C_{16}H_{20}O_{3}N requires 274 1438] 273 2 (10 %), 97 0 (65), 91 0 (46), 69 1 (100), 41 1 (78)
[3S,4(4R)]-4-(4-Benzyl-2-oxo-oxazolidin-3-yl)-3-methyl-4-oxo-butyraldehyde 258

A solution of [4R,3(2S)]-4-benzyl-3-(2-methylpent-4-enoyl)-2-oxazolidinone (2.55 g, 9.33 mmol) was dissolved in dichloromethane (100 ml) at -78 °C and ozone gas bubbled through the solution for 1 h. Dimethyl sulfide (2.06 ml, 27.99 mmol) was then added and the solution stirred for a further 30 min, allowing to warm to ambient temperature. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum dichloromethane (1:2), which yielded a viscous clear oil (2.08 g, 81 %), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 2975, 1770, 1695, 1389, 1251, 1206, 704; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.24 (3H, d, \( J = 6.8 \) Hz, CH\(_3\)), 2.62 (1H, ddd, \( J = 0.8, 4.5, 18.6 \) Hz, CHOCH\(_2\)), 2.82 (1H, dd, \( J = 9.5, 13.4 \) Hz, PhCH\(_2\)), 3.13 (1H, dd, \( J = 9.5, 18.6 \) Hz, CHOCH\(_2\)), 3.30 (1H, dd, \( J = 3.3, 13.4 \) Hz, PhCH\(_2\)), 4.13-4.26 (3H, m, OCH\(_2\), CH\(_3\)CH), 4.62-4.69 (1H, m, NCH), 7.24-7.37 (5H, m, 5 x CH arom), 9.77 (1H, s, CHO), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) : 17.07 (CH\(_3\)), 32.43 (CH\(_3\)CH), 37.56 (PhCH\(_2\)), 47.67 (CHOCH\(_2\)), 55.35 (NCH), 66.07 (OCH\(_2\)), 127.27 (CH arom \textit{para}), 128.94 (CH arom \textit{ortho}), 129.48 (CH arom \textit{meta}), 135.40 (C arom ipso), 153.01 (CO), 175.83 (CO), 199.99 (CHO), m/z (El) 276 1232 [(M+H)*, C\(_{15}\)H\(_{18}\)O\(_4\)N requires 276 1230] 276 2 (8 %), 178 1 (50), 117 1 (28), 99 1 (100)
[4R,3(2S)‑4‑Benzy1‑3‑(3‑[1,3]‑dioxolan‑2‑yl‑2‑methylpropionyl)‑oxazolinin‑2‑one 259

A solution of [3S,4(4R)]‑4‑(4‑benzyl‑2‑oxo‑oxazolidin‑3‑yl)‑3‑methyl‑4‑oxo‑butyraldehyde (2.50 g, 9.08 mmol), ethylene glycol (0.66 ml, 11.80 mmol) and p‑toluenesulfonic acid (0.19 g, 0.98 mmol) in toluene (150 ml), was refluxed through a Soxhlet extractor equipped with 4Å molecular sieves for 4.5 h. The solution was then allowed to cool to ambient temperature, washed with a saturated aqueous ammonium chloride solution (100 ml) and brine (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a viscous yellow oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (2:3), which yielded a viscous clear oil (2.58 g, 89%); νmax (thin film)/cm−1 2971, 1779, 1699, 1387, 1245, 1208, 1020, 704, δH (75 MHz, CDCl3) 1.24 (3H, d, J = 7.0 Hz, CH3), 1.83 (1H, dt, J = 4.0, 14.2 Hz, CH3CHCH2), 2.35 (1H, ddd, J = 5.1, 9.2, 14.2 Hz, CH3CHCH2), 2.66 (1H, dd, J = 10.1, 13.3 Hz, PhCH2), 3.39 (1H, dd, J = 3.2, 13.3 Hz, PhCH2), 3.80–3.97, (4H, m, OCH2CH2O), 4.05–4.12 (1H, m, CH3CH), 4.13–4.19 (2H, m, OCH2), 4.64–4.70 (1H, m, NCH), 5.00 (1H, dd, J = 3.7, 5.1 Hz, CH3CHCH2CH), 7.24–7.36 (5H, m, 5 x CH arom.), δC (100 MHz, CDCl3) 18.32 (CH3), 32.79 (CH3CH), 37.51 (CH3CHCH2), 37.54 (PhCH2), 55.61 (NCH), 64.64 (OCH2CH2O), 65.10 (OCH2CH2O), 65.87 (OCH2), 102.82 (CH3CHCH2CH), 127.24 (CH arom. para), 128.93 (CH arom. ortho), 129.45
(CH arom meta), 135 69 (C arom upso), 153 10 (CO), 176 86 (CO), m/z (EI)
320 1493 [(M+H)⁺, C₁₇H₂₅O₃N requires 320.1492] 320 3 (100%), 143 0 (49)
To a stirred solution of lithium aluminium hydride (15.72 ml, 15.72 mmol) in tetrahydrofuran (20 ml) at 0 °C, was added a solution of [4R,3(2S)]-4-benzyl-3-(3-[1,3]-dioxolan-2-yl-2-methylpropionyl)-oxazolin-2-one (1.64 g, 5.14 mmol) in tetrahydrofuran (20 ml) Stirring was maintained at this temperature for 15 min before being allowed to warm to ambient temperature and stirred for 1 h. Celite (2 g) was added and the reaction re-cooled to 0 °C before being quenched with distilled water The solution was then filtered and the solid washed with ethyl acetate The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a clear oil This was purified by column chromatography using a mixture of light petroleum diethyl ether (1:2), which yielded a viscous clear oil (0.55 g, 72 %), $[\alpha]_{D}^{20} -8.5^\circ$ (c = 1.0, CHCl$_3$), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3415 (br), 2880, 1132, 1035, $\delta_{t}$ (400 MHz, CDCl$_3$) : 0.98 (3H, d, $J = 6.8$ Hz, CH$_3$), 1.73 (2H, dd, $J = 4.7$, 6.1 Hz, CH$_2$OCHCH$_2$), 1.88-1.96 (1H, m, CH$_3$CH), 2.42 (1H, s (br), OH), 3.43-3.58 (2H, m, OHCH$_2$), 3.86-4.01 (4H, m, OCH$_2$CH$_2$O), 4.96 (1H, t, $J = 4.7$ Hz, CH$_2$OCH), $\delta_{C}$ (100 MHz; CDCl$_3$) 17.74 (CH$_3$), 32.17 (CH$_3$CH), 38.10 (CH$_2$OCHCH$_2$), 64.82 (OCH$_2$CH$_2$O), 64.85 (OCH$_2$CH$_2$O), 68.16 (OHCH$_2$), 103.62 (CH$_2$OCH), $m/z$ (EI) 147 1017 [(M+H)$^+$, C$_7$H$_{13}$O$_3$ requires 147 1016] 147 1 (40 %), 133 0 (20), 85 2 (100), 73.1 (23)
(S)-β-Methyl-1,3-dioxolane-2-propanal 261

To a stirred solution of (S)-β-methyl-1,3-dioxolane-2-propanol (0.50 g, 3.42 mmol) in dichloromethane (100 ml) at ambient temperature, was added pyridinium chlorochromate (1.47 g, 6.84 mmol) and celite (1.47 g) and stirring was continued at this temperature for 16 h. The solution was then filtered, washed with ethyl acetate and the remaining solvent removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum / ethyl ether (2:1), which yielded a viscous clear oil (0.32 g, 66 %), $[\alpha]_D^{20} +14.1^\circ$ (c = 1.0, CHCl$_3$), $\nu_{\text{max}}$ (thin film)/cm$^{-1}$: 2882, 1723, 1148, 1031, $\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 1.15 (3H, d, $J = 7.2$ Hz, CH$_3$), 1.87 (1H, ddd, $J = 4.2, 4.4$ Hz, CH$_3$CHCH), 2.18 (1H, ddd, $J = 4.2, 8.0$ Hz, 14.4 Hz, CH$_3$CHCH), 2.56-2.65 (1H, m, CH$_3$CH), 3.80-3.99 (4H, m, OCH$_2$CH$_2$O), 4.98 (1H, t, $J = 4.2$ Hz, CH$_2$OCH), 9.59 (1H, d, $J = 2.0$ Hz, CHO); $\delta_C$ (100 MHz; CDCl$_3$): 14.21 (CH$_3$), 34.91 (CH$_3$CHCH), 41.77 (CH$_3$CH), 64.91 (OCH$_2$CH$_2$O), 65.05 (OCH$_2$CH$_2$O), 102.54 (CH$_2$OCH), 204.01 (CHO); $m/z$ (El) 143 0700 [(M-H)$^+$, C$_7$H$_{11}$O$_3$ requires 143 0703] 143 0 (30 %), 116.0 (5), 73 0 (100), 45 0 (39)
To a stirred solution of triethyl phosphonoacetate (0.41 ml, 1.99 mmol) in tetrahydrofuran (50 ml) at 0 °C, was added sodium hydride (0.08 g, 1.99 mmol) portionwise, followed by (S)-β-methyl-1,3-dioxolane-2-propanal (0.24 g, 1.66 mmol) and stirring continued at ambient temperature for 16 h. The reaction was then diluted with saturated aqueous sodium hydrogen carbonate solution (30 ml) and the aqueous layer was separated and extracted with ethyl acetate (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated to yield a clear oil. This was purified by column chromatography using a mixture of light petroleum diethyl ether (3:1), which yielded a viscous clear oil (0.26 g, 73 %), $\nu$ max (thin film)/cm$^{-1}$: 2962, 1717, 1650, 1179, 1034, δH (400 MHz, CDCl$_3$) 1.12 (3H, d, J = 6.8 Hz, CH$_3$CH), 1.29 (3H, t, J = 7.0 Hz, CH$_2$CH$_3$), 1.65-1.82 (2H, m, CH$_3$CHCH$_2$), 2.56-2.64 (1H, m, CH$_3$CH), 3.81-3.98 (4H, m, OCH$_2$CH$_2$O), 4.19 (2H, q, J = 7.0 Hz, CH$_2$CH$_3$), 4.85 (1H, dd, J = 4.4, 5.7 Hz, CH$_2$OCH), 5.82 (1H, dd, J = 1.2, 15.7 Hz, CH=CHCO), 6.90 (1H, dd, J = 7.9, 15.7 Hz, CH$_3$CHCH=CH), δC (100 MHz; CDCl$_3$) 14.27 (CH$_3$CH$_2$), 19.82 (CH$_3$CH), 32.68 (CH$_3$CH), 39.84 (CH$_3$CHCH$_2$), 60.25 (CH$_3$CH$_2$), 64.79 (OCH$_2$CH$_2$O), 64.82 (OCH$_2$CH$_2$O), 102.90 (CH$_2$OCH), 119.91 (CH=CHCO), 153.37 (CH$_3$CHCH=CH) 166.82 (CO); m/z (El) 215 1280 [(M+H)$^+$, 215 1278 requires 215 1278] 215.1 (38 %), 189 0 (30), 98 1 (24), 73 0 (100)
A solution of sodium bis(trimethylsilyl)amide (12.86 ml, 25.72 mmol) in tetrahydrofuran (50 ml) was cooled to -78 °C. A solution of (S)-4-benzyl-3-propionyl-2-oxazolidinone (5.00 g, 21.43 mmol) in tetrahydrofuran (20 ml) was added dropwise over 30 min and stirring continued at this temperature for 1 h. Allyl bromide (5.57 ml, 64.29 mmol) was then added dropwise and the reaction was stirred for 3 h, allowing to warm to ambient temperature. Saturated aqueous ammonium chloride solution (75 ml) was added, the aqueous layer was separated and extracted with diethyl ether (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and the remaining solvent was removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum/diethyl ether (2:1), which yielded a viscous clear oil (4.69 g, 80%); νmax (thin film)/cm⁻¹: 2977, 1778, 1698, 1385, 703, δH (400 MHz, CDCl₃): 1.19 (3H, d, J = 6.8 Hz, CH₃), 2.24 (1H, qt, J = 1.1, 7.0 Hz, CH₃CH₂), 2.53 (1H, qt, J = 1.1, 7.0 Hz, CH₃CHCH₂), 2.70 (1H, dd, J = 9.9, 13.3 Hz, PhCH₂), 3.29 (1H, dd, J = 3.2, 13.3 Hz, PhCH₂), 3.87 (1H, sextet, J = 6.8 Hz, CH₃CH), 4.14-4.21 (2H, m, OCH₂), 4.66-4.72 (1H, m, NCH), 5.05-5.13 (2H, m, CH₂=CH), 5.83 (1H, tdd, J = 7.0, 10.1, 17.1 Hz, CH₂=CH), 7.20-7.36 (5H, m, 5 x CH arom); δc (100 MHz, CDCl₃): 16.45 (CH₃), 37.15 (CH₃CH), 37.99 (CH₃CHCH₂), 38.10 (PhCH₂), 55.40 (NCH), 66.01 (OCH₂), 117.25 (CH₂=CH), 127.33 (CH arom. para), 128.95 (CH arom ortho), 129.42 (CH arom meta), 135.26 (CH₂=CH), 135.36
(C arom. ipso), 153.12 (C=O), 176.52 (C=O), m/z (EI) 274.1436 [(M+H)⁺, C₁₆H₂₀O₃N requires 274.1438] 273.2 (6 %), 97.1 (45), 91.0 (62), 69.2 (100), 41.2 (64)
A solution of \([4S,3(2R)]\)-4-benzyl-3-(2-methylpent-4-enoyl)-2-oxazolidinone (3.88 g, 14.20 mmol) was dissolved in dichloromethane (100 ml) at -78 °C and ozone gas bubbled through the solution for 1 h. Dimethyl sulfide (3.13 ml, 27.99 mmol) was then added and the solution stirred for a further 30 min, allowing to warm to ambient temperature. The remaining solvent was removed under reduced pressure to yield a pale yellow oil. This was purified by column chromatography using a mixture of light petroleum : dichloromethane (1:2), which yielded a viscous clear oil (3.32 g, 85 %), \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\): \(2971, 1776, 1695, 1388, 1251, 1205, 704, 704\) (400 MHz, CDCl\(_3\)) \(123\) (3H, d, \(J = 6.8\) Hz, CH\(_2\)), \(2.62\) (1H, ddd, \(J = 0.8, 4.5, 18.5\) Hz, CHOCH\(_3\)), \(2.81\) (1H, dd, \(J = 9.6, 13.5\) Hz, PhCH\(_2\)), \(3.13\) (1H, dd, \(J = 9.6, 18.5\) Hz, CHOCH\(_3\)), \(3.29\) (1H, dd, \(J = 3.3, 13.5\) Hz, PhCH\(_2\)), \(4.13-4.24\) (3H, m, OCH\(_2\), CH\(_3\)CH), \(4.64-4.70\) (1H, m, NCH), \(7.25-7.37\) (5H, m, 5 x CH ar), \(9.77\) (1H, s, CHO), \(\delta_c\) (100 MHz, CDCl\(_3\)) \(17.07\) (CH\(_3\)), \(32.43\) (CH\(_2\)CH), \(37.56\) (PhCH\(_2\)), \(47.67\) (CHOCH\(_2\)), \(55.35\) (NCH), \(66.07\) (OCH\(_2\)), \(127.27\) (CH ar para), \(128.94\) (CH ar ortho), \(129.48\) (CH ar meta), \(135.40\) (C ar ipso), \(153.01\) (CO), \(175.83\) (CO), \(199.99\) (CHO), m/z (EI) \(276\) 1231 [(M+H)\(^{+}\), \(C_{15}H_{18}O_{4}N\) requires \(276\) 1230] \(276\) 2 (12 %), \(195\) 0 (15), \(178\) 1 (75), \(148\) 1 (15), \(131\) 0 (110), 99.1 (55)
A solution of [3S,4(4R)]-4-(4-benzyl-2-oxo-oxazolin-3-yl)-3-methyl-4-oxo-butyraldehyde (3.90 g, 14.17 mmol), ethylene glycol (1.03 ml, 18.42 mmol) and p-toluenesulfonic acid (0.27 g, 1.42 mmol) in toluene (150 ml), was refluxed through a Soxhlet extractor equipped with 4Å molecular sieves for 4.5 h. The solution was then allowed to cool to ambient temperature, washed with a saturated aqueous ammonium chloride solution (100 ml) and brine (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a viscous yellow oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (2:3), which yielded a viscous clear oil (3.90 g, 86%), νmax (thin film)/cm⁻¹ 2969, 2881, 1777, 1695, 1384, 1201, 703, δH (400 MHz, CDCl₃) 1.24 (3H, d, J = 7.1 Hz, CH₃), 1.82 (1H, dt, J = 4.1, 14.1 Hz, CH₂CHCH₂), 2.35 (1H, ddd, J = 5.0, 9.2, 14.1 Hz, CH₂CHCH₂), 2.66 (1H, dd, J = 10.0, 13.2 Hz, PhCH₂), 3.39 (1H, dd, J = 3.2, 13.2 Hz, PhCH₂), 3.79-3.99, (4H, m, OCH₂CH₂O), 4.04-4.12 (1H, m, CH₃CH), 4.14-4.19 (2H, m, OCH₂), 4.63-4.70 (1H, m, NCH), 5.00 (1H, dd, J = 3.6, 5.0 Hz, CH₂CHCH₂CH₂), 7.24-7.36 (5H, m, 5 x CH arom), δC (100 MHz, CDCl₃) 18.32 (CH₃), 32.79 (CH₂CH), 37.51 (CH₂CH₂CH₂), 37.54 (PhCH₂), 55.61 (NCH), 64.64 (OCH₂CH₂O), 65.10 (OCH₂CH₂O), 65.87 (OCH₂), 102.82 (CH₂CHCH₂CH₂), 127.24 (CH arom para), 128.93 (CH arom ortho), 129.45 (CH arom meta).
135 69 (C arom. upso), 153 10 (CO), 176 86 (CO), m/z (EI) 320 1492 [(M+H)^+,
C_{17}H_{22}O_3N requires 320 1492] 320 3 (81%), 143 0 (100), 99 1 (42)
(R)-β-Methyl-1,3-dioxolane-2-propanol 26826

To a stirred solution of lithium aluminium hydride (42.51 ml, 42.51 mmol) in tetrahydrofuran (50 ml) at 0 °C, was added a solution of [4S,3(2R)]-4-benzyl-3-(3-[1,3]-dioxolan-2-yl-2-methylpropionyl)-oxazolin-2-one (4.53 g, 14.17 mmol) in tetrahydrofuran (50 ml). Stirring was maintained at this temperature for 15 min before being allowed to warm to ambient temperature and stirred for 1 h Celite (4.50 g) was added and the reaction re-cooled to 0 °C before being quenched with distilled water. The solution was then filtered and washed with ethyl acetate, dried over magnesium sulfate, filtered and the remaining solvent removed under reduced pressure to yield a clear oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (1:2), which yielded a viscous clear oil (1.45 g, 70%), [α]D20 +8.6° (c = 1.0, CHCl₃) (lit.26 [α]D25 +8.873° (c = 1.0, CHCl₃), v max (thin film)/cm⁻¹ : 3419 (br), 2885, 1136, 1037, δ₁H (400 MHz, CDCl₃) 0.98 (3H, d, J = 6.8 Hz, CH₃), 1.72 (2H, dd, J = 4.8, 6.5 Hz, CH₂OCH₂CH₃), 1.88-1.96 (1H, m, CH₂CH), 2.48 (1H, s (br), OH), 3.44-3.56 (2H, m, OHCH₂), 3.85-4.03 (4H, m, OCH₂CH₂O), 4.96 (1H, t, J = 4.8 Hz, CH₂OCH), ΔC (100 MHz, CDCl₃) 1774 (CH₃), 3217 (CH₃CH), 3811 (CH₂OCH₂CH₃), 6482 (OCH₂CH₂O), 6486 (OCH₂CH₂O), 6816 (OHC₆H₄), 10362 (CH₂OCH); m/z (El) 147 (100) [(M+H)+, C₇H₁₅O₃ requires 147 1016], 1471 (36%), 85.2 (100), 73.1 (41)
(R)-β-Methyl-1,3-dioxolane-2-propanol 269

To a stirred solution of (R)-β-methyl-1,3-dioxolane-2-propanol (0.50 g, 3.42 mmol) in dichloromethane (100 ml) at ambient temperature, was added pyridinium chlorochromate (1.47 g, 6.84 mmol) and celite (1.47 g) and stirring continued at this temperature for 16 h. The solution was then filtered, washed with ethyl acetate and the remaining solvent removed under reduced pressure to yield a yellow oil. This was purified by column chromatography using a mixture of light petroleum–diethyl ether (2:1), which yielded a viscous clear oil (0.35 g, 71%). $\left[\alpha\right]_{D}^{20} = -14.2^\circ$ (c = 1.0, CHCl₃) (lit $\left[\alpha\right]_{D}^{15} = -14.66^\circ$ (c = 1.3, CHCl₃), $\nu_{\text{max}}$ (thin film)/cm⁻¹: 2883, 1721, 1130, 1028, 743, $\delta_{\text{H}}$ (400 MHz, CDCl₃): 1.15 (3H, d, $J = 7.2$ Hz, CH₃), 1.77 (1H, ddd, $J = 4.4$, 5.4, 14.4 Hz, CH₃CH₂), 2.15 (1H, ddd, $J = 4.4$, 8.0, 14.4 Hz, CH₃CH₂), 2.57–2.65 (1H, m, CH₃CH₂), 3.81–3.99 (4H, m, OCH₂CH₂O), 4.98 (1H, t, $J = 4.4$ Hz, CH₂OCH), 9.59 (1H, d, $J = 2.4$ Hz, CHO), $\delta_{\text{C}}$ (100 MHz, CDCl₃): 14.21 (CH₃), 34.90 (CH₃CH₂), 41.77 (CH₃CH₂), 64.91 (OCH₂CH₂O), 65.05 (OCH₂CH₂O), 102.54 (CH₂OCH), 204.01 (CHO); m/z (EI) 143.0702 [(M-H)+, C₇H₁₁O₃ requires 143.0703] 143.0 (52%), 116.0 (100), 73.1 (28), 45.0 (41)
[4R]-Ethyl-5-[1,3]-dioxolan-2-yl-4-methyl-pent-2-enoate 270

To a stirred solution of triethyl phosphonoacetate (0.53 ml, 2.59 mmol) in tetrahydrofuran (50 ml) at 0 °C, was added sodium hydride (0.10 g, 2.59 mmol) portionwise, followed by (R)-β-methyl-1,3-dioxolane-2-propanal (0.31 g, 2.16 mmol) and stirring continued at ambient temperature for 16 h. The reaction was then diluted with saturated aqueous sodium hydrogen carbonate solution (30 ml) and the aqueous layer was separated and extracted with ethyl acetate (3 x 50 ml). The combined organic fractions were dried over magnesium sulfate, filtered and evaporated to yield a clear oil. This was purified by column chromatography using a mixture of light petroleum : diethyl ether (3:1), which yielded a viscous clear oil (0.35 g, 75 %), ν<sub>max</sub> (thin film)/cm⁻¹: 2961, 1718, 1653, 1179, 1035, δ<sub>H</sub> (400 MHz, CDCl₃) 1.12 (3H, d, J = 6.8 Hz, CH₃CH), 1.29 (3H, t, J = 7.0 Hz, CH₂CH₃), 1.68-1.85 (2H, m, CH₃CHCH₂), 2.56-2.62 (1H, m, CH₃CH), 3.82-3.98 (4H, m, OCH₂CH₂O), 4.19 (2H, q, J = 7.0 Hz, CH₂CH₃), 4.85 (1H, dd, J = 4.4, 5.7 Hz, CH₂OCH), 5.82 (1H, dd, J = 1.2, 15.7 Hz, CH=CHCO), 6.90 (1H, dd, J = 7.9, 15.7 Hz, CH₂CHCH=CH), δ<sub>C</sub> (100 MHz, CDCl₃) 14.27 (CH₃CH₂), 19.82 (CH₃CH), 32.68 (CH₃CH), 39.84 (CH₃CHCH₂), 60.25 (CH₂CH₂), 64.79 (OCH₂CH₂O), 64.82 (OCH₂CH₂O), 102.90 (CH₂OCH), 119.91 (CH=CHCO), 153.37 (CH₃CHCH=CH) 166.82 (CO), m/z (EI) 215 1280 [(M+H)<sup>+</sup>, C₁₁H₁₀O₄ requires 215 1278] 215 1 (38 %), 189 0 (30), 98 1 (24), 73 0 (100)
N-Acryloyl-(1S)-bornane-2,10-sultam 273

Method A

To a stirring solution of (1S)-(−)-2,10-camphorsultam (0.70 g, 3.25 mmol) in tetrahydrofuran (50 ml) at 0 °C was added methylmagnesiumbromide (1.14 ml, 3.41 mmol) and stirring was continued at this temperature for 30 min. A solution of acryloyl chloride (0.27 g, 3.02 mmol) in tetrahydrofuran (20 ml) was then added dropwise at 0 °C and stirred at this temperature for 2 h and then at ambient temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution (20 ml) and separated. The aqueous layer was extracted with ethyl acetate (2 x 50 ml) and the combined organic fractions were dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a colourless solid which was identified as starting material.

Method B

To a stirring solution of (1S)-(−)-2,10-camphorsultam (0.50 g, 2.33 mmol) in tetrahydrofuran (10 ml) at -78 °C was added sodium bis(trimethylsilyl)amide (1.20 ml, 2.40 mmol) dropwise and stirring was continued at this temperature for 2 h. A solution of acryloyl chloride (0.27 g, 3.03 mmol) in tetrahydrofuran (10 ml) was then added dropwise at -78 °C and stirred at this temperature for 5 h and then at ambient temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride solution (20 ml) and separated. The
aqueous layer was extracted with ethyl acetate (2 x 50 ml) and the combined organic fractions were dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a yellow oil.

**Method C**

A solution of acrylic acid (0.08 ml, 1.16 mmol), (1S)-(1)-2,10-camphorsultam (0.25 g, 1.16 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.33 g, 1.74 mmol) in dichloromethane (5 ml) was stirred at ambient temperature for 16 h. The solvent was removed to yield a viscous clear oil which was identified as starting material.
N-Acryloyl-(1S)-bornane-2,10-sultam 273²⁷

A solution of acryloyl chloride (168 g, 1858 mmol) in dichloromethane (20 ml) was added dropwise at ambient temperature to a stirring solution of (1S)-(−)-2,10-camphorsultam (200 g, 929 mmol), copper (I) chloride (0.92 g, 9.29 mmol), copper powder (0.59, 9.29 mmol) and triethylamine (1.29 ml, 9.29 mmol) in dichloromethane (50 ml). After stirring at this temperature for 30 min, 4-dimethylaminopyridine (0.34 g, 2.81 mmol) was added and the reaction stirred for a further 2 h before being diluted with dichloromethane (100 ml) and washed with saturated aqueous sodium hydrogen carbonate solution (2 x 100 ml) and brine (2 x 100 ml). The organic fraction was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a pale green solid. This was purified by flash silica chromatography using ethyl acetate to yield a colourless crystalline solid (198 g, 79%), mp 195 °C (lit.²⁷ mp 191-195 °C); v_max (DCM)/cm⁻¹ 2981, 1683, 1332, 1152, 1035, δ_H (400 MHz, CDCls) : 0.98 (3H, s, CH₃), 1.18 (3H, s, CH₃), 1.35-1.48 (2H, m, 1 x (CH₃)₂CCHCH₂CH₂, 1 x (CH₃)₂CCHCH₂CH₃), 1.88-1.95 (3H, m, 1 x (CH₃)₂CCHCH₂CH₂, 1 x (CH₃)₂CCHCH₂CH₂, 1 x (CH₃)₂CCHCH₂CH₂, 1 x (CH₃)₂CCHCH₂CH₂), 2.08-2.17 (2H, m, (CH₃)₂CCHCH₂CH₃), 3.49 (2H, q, J = 13.8 Hz, SO₂CH₃), 3.95 (1H, dd, J = 7.6, 5.2 Hz, (CH₃)₂CCHCH₂CH₂), 5.87 (1H, dd, J = 1.6, 10.4 Hz, 1 x CH₂=CH), 6.51 (1H, dd, J = 1.6, 16.8 Hz, 1 x CH₂=CH), 6.87 (1H, dd, J = 10.4, 16.8 Hz, CH₂=CH); δ_C (100 MHz, CDCl₃) : 19.90 (CH₃), 20.85 (CH₃), 26.47 ((CH₃)₂CCHCH₂CH₂), 32.87 ((CH₃)₂CCHCH₂CH₂), 38.41 ((CH₃)₂CCHCH₂CH₃), 44.67 ((CH₃)₂CCH), 47.81 ((CH₃)₂C), 48.56
(SO₂CH₂CCH₂), 53 11 (SO₂CH₂), 65 13 ((CH₃)₂CCHCH₂CHN), 127 73 (CH₂=CH), 131 42 (CH₂=CH), 163 83 (CO), m/z (El) 287 1425 [(M+NH₄)⁺, C₁₃H₂₃O₂N₂S requires 287.1424] 287 3 (100 %), 270 2 (12), 206 2 (15)
4-Methyl-hex-2-enedioic acid 6-methyl ester 275

\[ \text{O} \quad \text{C} \quad \text{O} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{CO} \]

To a stirring solution of 3-methyl-4-pentenoic acid methyl ester (2.00 g, 15.60 mmol) in anhydrous dichloromethane (30 ml) was added acrylic acid (3.21 ml, 46.80 mmol) and benzyldene-[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichlorotricyclohexylphosphine)metal ruthenium (0.27 g, 0.31 mmol) and heated under reflux for 24 h. The solution was then opened to the air to allow oxidation and stirred at ambient temperature for 16 h. The remaining solvent was removed under reduced pressure to yield a brown oil. This was purified by column chromatography using a mixture of light petroleum-diethyl ether (1:2), which yielded a clear oil (1.61 g, 60%), \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\): 2965 (br), 1734, 1696, 1437, 1416, 1285, 1173, \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 1.14 (3H, d, \( J = 6.8 \) Hz, CH\(_3\)CH), 2.42 (2H, ddd, \( J = 7.0, 15.5, 36.3 \) Hz, CH\(_2\)CHCH\(_2\)), 2.87-2.93 (1H, m, CH\(_3\)CH), 3.69 (3H, s, OCH\(_3\)), 5.84 (1H, dd, \( J = 1.2, 15.7 \) Hz, CHCO), 7.02 (1H, dd, \( J = 7.2, 15.7 \) Hz, CH\(_2\)CHCH), \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)): 18.92 (CH\(_3\)CH), 33.06 (CH\(_3\)CH), 39.96 (CH\(_3\)CHCH\(_2\)), 59.65 (OCH\(_3\)), 119.78 (CHCO), 154.64 (CH\(_2\)CHCH), 172.01 (CO), 172.21 (CO), m/z (El) 190.1074 [(M+NH\(_4^+\))\(^+\), C\(_8\)H\(_{16}\)O\(_4\)N requires 190.1074] 190 1 (100%), 116 1 (21)
3.3 References

(1) Schmld, C. R; Bryant, J. D. *Org. Synthesis* 1995, 72, 6-12
(2) Yokoyama, H ; Otaya, K.; Kobayashi, H ; Miyazawa, M ; Yamaguchi, S ; Hira, Y *Org Lett* 2000, 2, 2427-2429
(3) Wei, Y ; Bakthavatchalam, R. *Tetrahedron* 1993, 49, 2373-2390
(4) Larsen, K. E ; Torssell; K B G *Tetrahedron* 1984, 40, 2985-2988
(10) Jakobsen, H. J ; Larsen, E H; Lawesson, S O *Tetrahedron* 1963, 19, 1867-1882
(14) Basavaraj, D., Gowristwari, V V *Synth Commun* 1989, 19, 2461-2465
(18) Baker, B R ; Querry, M V ; Safir, S R , McEwan, W L , Bernstein, S J *Org Chem* 1947, 12, 174-185
(20) Verkruijssse, H D ; Brandsma, L. *Synth Commun* 1990, 20, 3375-3378
(21) Aono, M , Terao, Y ; Achlwa, K *Heterocycles* 1995, 40, 249-260
(22) Block, E , Laffitte, J. A , Eswarakrishnan, V J *Org Chem* 1986, 51, 3428-3435
(23) Heinrich, L , Chottard, J-C ; Li, Y *Synth Commun* 2001, 31, 1323-1333
(24) Geiß, K-H; Scebach, D, Seuring, B *Chem Ber* 1977, 110, 1833-1851
### Table 1. Crystal data and structure refinement for 150

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<td>Absorption correction</td>
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Largest and mean shift/su  0 000 and 0 000
Largest diff peak and hole  0 411 and -0.331 e Å\(^{-3}\)

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å\(^2\)) for 150

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<th>U(_{eq})</th>
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Table 3. Bond lengths [Å] and angles [°] for 150

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Table 4. Hydrogen coordinates and isotropic displacement parameters (Å²) for 150

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Table 5. Torsion angles [°] for 150.

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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5)–S(1)–C(2)–C(3)</td>
<td>-11 54(10)</td>
<td>S(1)–C(2)–C(3)–C(6)</td>
<td>159 19(9)</td>
<td></td>
</tr>
<tr>
<td>S(1)–C(2)–C(3)–C(4)</td>
<td>35 96(12)</td>
<td>C(6)–C(3)–C(4)–C(8)</td>
<td>68 04(13)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(3)–C(4)–C(8)</td>
<td>-168 24(10)</td>
<td>C(6)–C(3)–C(4)–C(5)</td>
<td>-172 26(10)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(3)–C(4)–C(5)</td>
<td>-48 54(13)</td>
<td>C(8)–C(4)–C(5)–S(1)</td>
<td>160 24(9)</td>
<td></td>
</tr>
<tr>
<td>C(3)–C(4)–C(5)–S(1)</td>
<td>38 52(12)</td>
<td>C(2)–S(1)–C(5)–C(4)</td>
<td>-15 47(10)</td>
<td></td>
</tr>
<tr>
<td>C(4)–C(3)–C(6)–O(1)</td>
<td>-2 25(18)</td>
<td>C(2)–C(3)–C(6)–O(1)</td>
<td>-122 66(14)</td>
<td></td>
</tr>
<tr>
<td>C(4)–C(3)–C(6)–O(2)</td>
<td>178 08(10)</td>
<td>C(2)–C(3)–C(6)–O(2)</td>
<td>57 67(14)</td>
<td></td>
</tr>
<tr>
<td>O(1)–C(6)–O(2)–C(7)</td>
<td>-2 18(19)</td>
<td>C(3)–C(6)–O(2)–C(7)</td>
<td>177 49(11)</td>
<td></td>
</tr>
<tr>
<td>C(3)–C(4)–C(8)–O(3)</td>
<td>26 69(17)</td>
<td>C(5)–C(4)–C(8)–O(3)</td>
<td>-90 85(15)</td>
<td></td>
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<tr>
<td>C(3)–C(4)–C(8)–O(4)</td>
<td>-155 98(11)</td>
<td>C(5)–C(4)–C(8)–O(4)</td>
<td>86 48(13)</td>
<td></td>
</tr>
<tr>
<td>O(3)–C(8)–O(4)–C(9)</td>
<td>4 17(19)</td>
<td>C(4)–C(8)–O(4)–C(9)</td>
<td>-173 19(10)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Crystal data and structure refinement for 219

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₁₄H₁₈O₄S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>280 33</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
</tbody>
</table>
Crystal system, space group
- orthorhombic, P2_12_12_1

Unit cell parameters
- a = 5.5031(7) Å, α = 90°
- b = 7.8587(10) Å, β = 90°
- c = 32.005(4) Å, γ = 90°
- V = 1384.1(3) Å³

Cell volume
- Z = 4

Calculated density
- 1.345 g/cm³

Absorption coefficient μ
- μ = 0.241 mm⁻¹

Absorption coefficient f₁
- f₁ = 592

F(000)
- Colourless, 0.50 × 0.14 × 0.04 mm³

Crystals of size
- 4227 (θ range 25° to 25° 81°)

Reflections for cell refinement
- Bruker APEX 2 CCD diffractometer
- ω rotation with narrow frames
- 2.55 to 26.41°

Data collection method
- h -6 to 6, k -9 to 9, l -39 to 40
- Completeness to θ = 26.41°: 99.9%
- Intensity decay: 0%
- Reflections collected: 12175
- Independent reflections: 2825 (Rint = 0.0554)
- Reflections with F² > 2σ: 2456

Absorption correction
- Semi-empirical from equivalents
- Min and max transmission: 0.889 and 0.990

Structure solution
- Direct methods
- Full-matrix least-squares on F²

Refinement method
- Weighting parameters a, b
- 0.0448, 1.1718
- Data / restraints / parameters: 2825 / 0 / 174
- Final R indices [F² > 2σ]: R1 = 0.0519, wR2 = 0.1184
- R indices (all data): R1 = 0.0629, wR2 = 0.1235

Goodness-of-fit on F²
- 1.104

Absolute structure parameter
- -0.01(14)

Largest and mean shift/su
- 0.000 and 0.000

Largest diff. peak and hole
- 0.455 and -0.266 e Å⁻³
Table 7. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for 219. \(U_{eq}\) is defined as one third of the trace of the orthogonalized \(U^j\) tensor.

<table>
<thead>
<tr>
<th>Atomic Symbol</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(U_{eq})</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>0.74298(16)</td>
<td>0.81799(10)</td>
<td>0.11653(3)</td>
<td>0.0310(2)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.6547(6)</td>
<td>0.5943(4)</td>
<td>0.10796(9)</td>
<td>0.0249(7)</td>
</tr>
<tr>
<td>C(3)</td>
<td>0.5287(6)</td>
<td>0.5413(4)</td>
<td>0.14944(10)</td>
<td>0.0285(7)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.4279(6)</td>
<td>0.6955(4)</td>
<td>0.17108(10)</td>
<td>0.0297(7)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.6310(6)</td>
<td>0.8288(4)</td>
<td>0.17019(10)</td>
<td>0.0305(7)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.5054(5)</td>
<td>0.5713(4)</td>
<td>0.06862(9)</td>
<td>0.0211(6)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.5785(6)</td>
<td>0.4506(4)</td>
<td>0.03949(10)</td>
<td>0.0284(7)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.4458(7)</td>
<td>0.4217(5)</td>
<td>0.00374(10)</td>
<td>0.0339(8)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.2310(7)</td>
<td>0.5102(4)</td>
<td>−0.00333(10)</td>
<td>0.0354(8)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.1558(6)</td>
<td>0.6297(4)</td>
<td>0.02533(10)</td>
<td>0.0316(8)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.2932(5)</td>
<td>0.6616(4)</td>
<td>0.06098(9)</td>
<td>0.0257(7)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.3374(6)</td>
<td>0.4057(5)</td>
<td>0.14303(10)</td>
<td>0.0283(7)</td>
</tr>
<tr>
<td>O(1)</td>
<td>0.1229(4)</td>
<td>0.4266(3)</td>
<td>0.15096(8)</td>
<td>0.0374(6)</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.4251(5)</td>
<td>0.2632(3)</td>
<td>0.12695(8)</td>
<td>0.0393(6)</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.2380(8)</td>
<td>0.1381(4)</td>
<td>0.11633(14)</td>
<td>0.0514(10)</td>
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<tr>
<td>C(14)</td>
<td>0.3527(7)</td>
<td>0.6569(4)</td>
<td>0.21580(10)</td>
<td>0.0312(7)</td>
</tr>
<tr>
<td>O(3)</td>
<td>0.4550(5)</td>
<td>0.5596(4)</td>
<td>0.23859(8)</td>
<td>0.0519(8)</td>
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<tr>
<td>O(4)</td>
<td>0.1605(5)</td>
<td>0.7475(3)</td>
<td>0.22674(7)</td>
<td>0.0383(6)</td>
</tr>
<tr>
<td>C(15)</td>
<td>0.0734(8)</td>
<td>0.7226(6)</td>
<td>0.26860(11)</td>
<td>0.0456(10)</td>
</tr>
</tbody>
</table>

Table 8. Bond lengths [Å] and angles [°] for 219

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)–C(5)</td>
<td>1.827(3)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(6)</td>
<td>1.514(4)</td>
<td></td>
</tr>
<tr>
<td>C(3)–C(4)</td>
<td>1.502(5)</td>
<td></td>
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<tr>
<td>C(4)–C(14)</td>
<td>1.520(4)</td>
<td></td>
</tr>
<tr>
<td>C(6)–C(11)</td>
<td>1.389(4)</td>
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<tr>
<td>C(7)–C(8)</td>
<td>1.376(5)</td>
<td></td>
</tr>
<tr>
<td>C(9)–C(10)</td>
<td>1.376(5)</td>
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</tr>
<tr>
<td>C(12)–O(1)</td>
<td>1.218(4)</td>
<td></td>
</tr>
<tr>
<td>O(2)–C(13)</td>
<td>1.463(4)</td>
<td></td>
</tr>
<tr>
<td>C(14)–O(4)</td>
<td>1.323(4)</td>
<td></td>
</tr>
<tr>
<td>C(5)–S(1)–C(2)</td>
<td>95.46(15)</td>
<td>C(6)–C(2)–C(3) 115.8(3)</td>
</tr>
<tr>
<td>C(6)–C(2)–S(1)</td>
<td>112.4(2)</td>
<td>C(3)–C(2)–S(1) 104.3(2)</td>
</tr>
<tr>
<td>C(4)–C(3)–C(12)</td>
<td>112.0(3)</td>
<td>C(4)–C(3)–C(2) 110.0(3)</td>
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<tr>
<td>C(12)–C(3)–C(2)</td>
<td>112.6(3)</td>
<td>C(3)–C(4)–C(14) 111.9(3)</td>
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Table 9. Hydrogen coordinates and isotropic displacement parameters (Å²) for 219

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>0.8066</td>
<td>0.5255</td>
<td>0.1050</td>
<td>0.030</td>
</tr>
<tr>
<td>H(3)</td>
<td>0.6566</td>
<td>0.4920</td>
<td>0.1680</td>
<td>0.034</td>
</tr>
<tr>
<td>H(4)</td>
<td>0.2844</td>
<td>0.7391</td>
<td>0.1552</td>
<td>0.036</td>
</tr>
<tr>
<td>H(5A)</td>
<td>0.7609</td>
<td>0.8002</td>
<td>0.1904</td>
<td>0.037</td>
</tr>
<tr>
<td>H(5B)</td>
<td>0.5671</td>
<td>0.9435</td>
<td>0.1767</td>
<td>0.037</td>
</tr>
<tr>
<td>H(7)</td>
<td>0.7225</td>
<td>0.3869</td>
<td>0.0443</td>
<td>0.034</td>
</tr>
<tr>
<td>H(8)</td>
<td>0.5013</td>
<td>0.3410</td>
<td>-0.0162</td>
<td>0.041</td>
</tr>
<tr>
<td>H(9)</td>
<td>0.1371</td>
<td>0.4884</td>
<td>-0.0277</td>
<td>0.042</td>
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<tr>
<td>H(10)</td>
<td>0.0092</td>
<td>0.6907</td>
<td>0.0208</td>
<td>0.038</td>
</tr>
<tr>
<td>H(11)</td>
<td>0.2413</td>
<td>0.7461</td>
<td>0.0803</td>
<td>0.031</td>
</tr>
<tr>
<td>H(13A)</td>
<td>0.1585</td>
<td>0.0985</td>
<td>0.1419</td>
<td>0.077</td>
</tr>
<tr>
<td>H(13B)</td>
<td>0.3132</td>
<td>0.0413</td>
<td>0.1020</td>
<td>0.077</td>
</tr>
<tr>
<td>H(13C)</td>
<td>0.1171</td>
<td>0.1908</td>
<td>0.0979</td>
<td>0.077</td>
</tr>
<tr>
<td>H(15A)</td>
<td>0.0126</td>
<td>0.6061</td>
<td>0.2716</td>
<td>0.068</td>
</tr>
<tr>
<td>H(15B)</td>
<td>-0.0583</td>
<td>0.8032</td>
<td>0.2743</td>
<td>0.068</td>
</tr>
<tr>
<td>H(15C)</td>
<td>0.2065</td>
<td>0.7416</td>
<td>0.2884</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Table 10. Torsion angles [°] for 219

<table>
<thead>
<tr>
<th></th>
<th>C(5)–S(1)–C(2)–C(6)</th>
<th>C(5)–S(1)–C(2)–C(3)</th>
<th>19(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(6)–C(2)–C(3)–C(4)</td>
<td>-98.9(3)</td>
<td>S(1)–C(2)–C(3)–C(4)</td>
<td>25.1(3)</td>
</tr>
<tr>
<td>C(6)–C(2)–C(3)–C(12)</td>
<td>26.7(4)</td>
<td>S(1)–C(2)–C(3)–C(12)</td>
<td>150.8(2)</td>
</tr>
<tr>
<td>C(12)–C(3)–C(4)–C(14)</td>
<td>66.6(4)</td>
<td>C(2)–C(3)–C(4)–C(14)</td>
<td>-167.5(3)</td>
</tr>
<tr>
<td>C(12)–C(3)–C(4)–C(5)</td>
<td>-172.8(3)</td>
<td>C(2)–C(3)–C(4)–C(5)</td>
<td>-46.8(3)</td>
</tr>
</tbody>
</table>

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C(3)–C(4)–C(5)–S(1) 452(3) C(14)–C(4)–C(5)–S(1) 166 7(2)
C(2)–S(1)–C(5)–C(4) −26 9(2) C(3)–C(2)–C(6)–C(11) 64 7(4)
S(1)–C(2)–C(6)–C(11) −55 0(3) C(3)–C(2)–C(6)–C(7) −113 0(3)
S(1)–C(2)–C(6)–C(7) 127 3(3) C(11)–C(6)–C(7)–C(8) 0 5(5)
C(2)–C(6)–C(7)–C(8) 178 4(3) C(6)–C(7)–C(8)–C(9) −1.8(5)
C(7)–C(8)–C(9)–C(10) 1 6(5) C(8)–C(9)–C(10)–C(11) 0 0(5)
C(7)–C(6)–C(11)–C(10) 1 0(4) C(2)–C(6)–C(11)–C(10) −176.7(3)
C(9)–C(10)–C(11)–C(6) −1 3(5) C(4)–C(3)–C(12)–O(1) 6.5(5)
C(2)–C(3)–C(12)–O(1) −118 0(4) C(4)–C(3)–C(12)–O(2) −175.1(3)
C(2)–C(3)–C(12)–O(2) 60 4(4) O(1)–C(12)–O(2)–C(13) 4 8(5)
C(3)–C(12)–O(2)–C(13) −173 6(3) C(3)–C(4)–C(14)–O(3) 35.1(5)
C(5)–C(4)–C(14)–O(3) −82 7(4) C(3)–C(4)–C(14)–O(4) −146.0(3)
C(5)–C(4)–C(14)–O(4) 96 1(3) O(3)–C(14)–O(4)–C(15) −0 7(5)
C(4)–C(14)–O(4)–C(15) −179 6(3)

Table 11. Crystal data and structure refinement for 234

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>C_{16}H_{12}O_{2}S_{2}</th>
</tr>
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<tbody>
<tr>
<td>Formula weight</td>
<td>228 32</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0 71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, Pbc</td>
</tr>
<tr>
<td>Cell volume</td>
<td>532 23(8) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1 425 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>0 470 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>240</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>colourless, 0 44 × 0 26 × 0 14 mm³</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>2124 (θ range 3 53 to 27 97°)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker APEX 2 CCD diffractometer</td>
</tr>
<tr>
<td>ω rotation with narrow frames</td>
<td>Bruker APEX 2 CCD diffractometer</td>
</tr>
<tr>
<td>h range for data collection</td>
<td>2 12 to 30 57°</td>
</tr>
<tr>
<td>l range for data collection</td>
<td>h −14 to 14, k −8 to 8, l −13 to 13</td>
</tr>
</tbody>
</table>
Completeness to θ = 30.57° 99.4%
Intensity decay 0%
Reflections collected 6007
Independent reflections 3156 (Rint = 0.0251)
Reflections with F²>2σ 2814
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.820 and 0.937
Structure solution direct methods
Refinement method Full-matrix least-squares on F²
Weighting parameters a, b 0.0391, 0.0051
Data restraints / parameters 3156 / 44 / 146
Final R indices [F²>2σ] R1 = 0.0336, wR2 = 0.0737
R indices (all data) R1 = 0.0399, wR2 = 0.0774
Goodness-of-fit on F² 1.038
Absolute structure parameter 0.02(7), so determined reliably
Largest and mean shift/su 0.002 and 0.000
Largest diff. peak and hole 0.209 and −0.237 e Å⁻³

Table 12. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for 234. Ueq is defined as one third of the trace of the orthogonalized Uij tensor

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Ueq</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>1.0558(19)</td>
<td>0.6435(3)</td>
<td>0.01939(17)</td>
<td>0.0275(3)</td>
</tr>
<tr>
<td>C(2)</td>
<td>1.0580(2)</td>
<td>0.8929(3)</td>
<td>−0.0263(2)</td>
<td>0.0364(4)</td>
</tr>
<tr>
<td>S(1)</td>
<td>1.22719(14)</td>
<td>0.9434(3)</td>
<td>−0.06284(18)</td>
<td>0.0418(3)</td>
</tr>
<tr>
<td>C(3)</td>
<td>1.3005(12)</td>
<td>0.6779(17)</td>
<td>0.0292(14)</td>
<td>0.0398(16)</td>
</tr>
<tr>
<td>C(4)</td>
<td>1.1988(2)</td>
<td>0.5861(4)</td>
<td>0.1145(2)</td>
<td>0.0406(5)</td>
</tr>
<tr>
<td>C(3X)</td>
<td>1.1979(16)</td>
<td>0.909(4)</td>
<td>−0.067(3)</td>
<td>0.067(7)</td>
</tr>
<tr>
<td>S(1X)</td>
<td>1.3193(8)</td>
<td>0.6910(15)</td>
<td>0.0309(10)</td>
<td>0.0483(16)</td>
</tr>
<tr>
<td>S(2)</td>
<td>0.92360(5)</td>
<td>0.58850(7)</td>
<td>0.11324(5)</td>
<td>0.02875(11)</td>
</tr>
<tr>
<td>O(1)</td>
<td>0.94943(15)</td>
<td>0.7325(2)</td>
<td>0.24040(13)</td>
<td>0.0367(3)</td>
</tr>
<tr>
<td>O(2)</td>
<td>0.91463(17)</td>
<td>0.3423(2)</td>
<td>0.13154(15)</td>
<td>0.0403(3)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.7692(2)</td>
<td>0.6866(3)</td>
<td>−0.00493(19)</td>
<td>0.0308(4)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.7106(2)</td>
<td>0.8950(3)</td>
<td>0.0199(2)</td>
<td>0.0388(4)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.5907(2)</td>
<td>0.9700(4)</td>
<td>−0.0766(3)</td>
<td>0.0500(6)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.5331(2)</td>
<td>0.8391(5)</td>
<td>−0.1977(3)</td>
<td>0.0525(6)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.5935(2)</td>
<td>0.6337(5)</td>
<td>−0.2213(3)</td>
<td>0.0516(6)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.7106(2)</td>
<td>0.5545(4)</td>
<td>−0.1257(2)</td>
<td>0.0391(5)</td>
</tr>
</tbody>
</table>

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### Table 13. Bond lengths [Å] and angles [°] for 234

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)–C(2)</td>
<td>1.508(3)</td>
<td>C(1)–C(4)</td>
</tr>
<tr>
<td>C(1)–S(2)</td>
<td>1.7854(18)</td>
<td>C(2)–C(3X)</td>
</tr>
<tr>
<td>C(2)–S(1)</td>
<td>1.815(2)</td>
<td>S(1)–C(3)</td>
</tr>
<tr>
<td>C(3)–C(4)</td>
<td>1.535(10)</td>
<td>C(4)–S(1X)</td>
</tr>
<tr>
<td>C(3X)–S(1X)</td>
<td>1.836(14)</td>
<td>S(2)–O(2)</td>
</tr>
<tr>
<td>S(2)–O(1)</td>
<td>1.4471(13)</td>
<td>S(2)–C(5)</td>
</tr>
<tr>
<td>C(5)–C(6)</td>
<td>1.382(3)</td>
<td>C(5)–C(10)</td>
</tr>
<tr>
<td>C(6)–C(7)</td>
<td>1.388(3)</td>
<td>C(7)–C(8)</td>
</tr>
<tr>
<td>C(8)–C(9)</td>
<td>1.371(4)</td>
<td>C(9)–C(10)</td>
</tr>
<tr>
<td>C(2)–C(1)–C(4)</td>
<td>107.79(15)</td>
<td>C(2)–C(1)–S(2)</td>
</tr>
<tr>
<td>C(4)–C(1)–S(2)</td>
<td>110.34(12)</td>
<td>C(1)–C(2)–C(3X)</td>
</tr>
<tr>
<td>C(1)–C(2)–S(1)</td>
<td>106.71(14)</td>
<td>C(2)–S(1)–C(3)</td>
</tr>
<tr>
<td>C(4)–C(3)–S(1)</td>
<td>108.1(5)</td>
<td>C(1)–C(4)–C(3)</td>
</tr>
<tr>
<td>C(1)–C(4)–S(1X)</td>
<td>107.2(3)</td>
<td>C(2)–C(3X)–S(1X)</td>
</tr>
<tr>
<td>C(4)–S(1X)–C(3X)</td>
<td>92.3(7)</td>
<td>O(2)–S(2)–O(1)</td>
</tr>
<tr>
<td>O(2)–S(2)–C(5)</td>
<td>109.07(10)</td>
<td>O(1)–S(2)–C(5)</td>
</tr>
<tr>
<td>O(2)–S(2)–C(1)</td>
<td>108.15(9)</td>
<td>O(1)–S(2)–C(1)</td>
</tr>
<tr>
<td>C(5)–S(2)–C(1)</td>
<td>104.25(8)</td>
<td>C(6)–C(5)–C(10)</td>
</tr>
<tr>
<td>C(6)–C(5)–S(2)</td>
<td>120.29(15)</td>
<td>C(10)–C(5)–S(2)</td>
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<td>C(5)–C(6)–C(7)</td>
<td>119.0(2)</td>
<td>C(6)–C(7)–C(8)</td>
</tr>
<tr>
<td>C(9)–C(8)–C(7)</td>
<td>120.1(2)</td>
<td>C(8)–C(9)–C(10)</td>
</tr>
</tbody>
</table>

### Table 14. Hydrogen coordinates and isotropic displacement parameters (Å²) for 234

<table>
<thead>
<tr>
<th>Hydrogen</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1)</td>
<td>1.0387</td>
<td>0.5432</td>
<td>-0.0681</td>
<td>0.033</td>
</tr>
<tr>
<td>H(2A)</td>
<td>1.0440</td>
<td>0.9969</td>
<td>0.0512</td>
<td>0.044</td>
</tr>
<tr>
<td>H(2B)</td>
<td>0.9831</td>
<td>0.9222</td>
<td>-0.1135</td>
<td>0.044</td>
</tr>
<tr>
<td>H(3A)</td>
<td>1.3138</td>
<td>0.5610</td>
<td>-0.0418</td>
<td>0.048</td>
</tr>
<tr>
<td>H(3B)</td>
<td>1.3920</td>
<td>0.7106</td>
<td>0.0950</td>
<td>0.048</td>
</tr>
<tr>
<td>H(4A)</td>
<td>1.2099</td>
<td>0.4171</td>
<td>0.1301</td>
<td>0.049</td>
</tr>
<tr>
<td>H(4B)</td>
<td>1.2134</td>
<td>0.6643</td>
<td>0.2088</td>
<td>0.049</td>
</tr>
<tr>
<td>H(3C)</td>
<td>1.2378</td>
<td>1.0652</td>
<td>-0.0448</td>
<td>0.081</td>
</tr>
<tr>
<td>H(3D)</td>
<td>1.1836</td>
<td>0.8832</td>
<td>-0.1721</td>
<td>0.081</td>
</tr>
<tr>
<td>H(6)</td>
<td>0.7518</td>
<td>0.9856</td>
<td>0.1017</td>
<td>0.047</td>
</tr>
</tbody>
</table>
Table 15. Torsion angles [°] for 234.

| Bond                  | 646°(10) | 166°3(10) | 161°15(11) | -62°(6) | -48°3(5) | -46°3(4) | 35°8(7) | -26°2(15) | 24°7(9) | 1°1(5) | -68°92(15) | 60°27(15) | 175°10(13) | 11°81(17) | -41°12(17) | 74°21(16) | 178°66(16) | 0°9(3) | 0°7(3) | -177°59(17) |
|-----------------------|----------|-----------|------------|---------|----------|----------|---------|-----------|--------|-------|-------------|-----------|-----------|-----------|-----------|-----------|---------|--------|-----------|