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Synthetic Studies Towards Analogues of Spirolaxine Methyl Ether

Doctor of Philosophy

By

Ivaylo Dimitrov

School of Chemical Sciences
University of Auckland
April 2012
Sed fortuna, quae plurimum potest cum in reliquis rebus tum praecipue in bello, parvis momentis magnas rerum commutationes efficit; ut tum accidit.

**Fortune, which has a great deal of power in other matters but especially in war, can bring about great changes in a situation through very slight forces.**

*The Civil War*, Book III, 68

Gaius Julius Caesar
ABSTRACT

*H. pylori* is a bacteria that infects a significant proportion of the human population. It is the primary agent responsible for gastric and duodenal ulcers and has been further linked with gastric cancer and mucosa-associated lymphoid tissue (MALT lymphoma). Eradication of *H. pylori* can cure these diseases; however the current therapies used are far from ideal. (+)-Spirolaxine methyl ether (15) exhibits potent activity against *H. pylori* and is therefore a promising drug candidate. The first enantioselective total synthesis of spirolaxine methyl ether (15) was achieved by Robinson and Brimble. This thesis reports the successful synthesis of eight analogues of spirolaxine methyl ether (15), with the aim of producing antibiotics with more pronounced activity than the parent natural product.

Specifically the goal is to obtain analogues where the length of the polymethylene carbon chain which links the spiroacetal and phthalide moieties is varied (Compounds 335-336) and at the same time replace the phthalide heterocycle with an indole (Compounds 337-339) and an oxindole (Compounds 340-342) ring systems. This strategy provides three sets of three analogues: one set with a longer polymethylene chain than the natural product and three different heterocycles (Compounds 336, 339, 342), a second set of three analogues with the same polymethylene chain length as in the natural product and the three different heterocycles (Compounds 338, 341) and finally a set of three compounds with a shorter polymethylene chain length than the natural product (Compounds 335, 337, 340) (Scheme 69). The information from the biological evaluation of these analogues of spirolaxine methyl ether (15) will be of considerable value to programs aimed at improving the anti-*H. pylori* profile of these compounds.
ACKNOWLEDGMENTS

First, I would like to thank my supervisor, Prof. Margaret Brimble for allowing me to be part of this great research group and giving me such an interesting research project. I am grateful for all your advice and immense knowledge of organic chemistry, incredible speed at proofreading everything and the hours spent on this thesis.

To the postdocs over the years, firstly thanks to Patrick O'Connor for getting me up and running in the lab all the way back in my honours year. Dan what can I say (you are awesome!) thanks for your ever cheerful enthusiastic mood, great invaluable chemistry advice and the small history talks, as our friend von Clausewitz said: "A prince or general can best demonstrate his genius by managing a campaign exactly to suit his objectives and his resources, doing neither too much nor too little." I'm waiting to be your referee for your firearms licence.

A thank you must go to Dr. Michael Schmitz for maintaining the NMR facilities (even after hours) and advice with spectra. Raisa Imatdieva thanks for the mass spectra and giving me my critical results so promptly. Anoma Ratnayake and her brief successor Morgan for being always so kind and helpful with chemicals and broken equipment and keeping the rot evaps (most crucially) and other equipment running.

To all friends on the 7th floor past and present (sorry can't put all the names) for making these 4 years a special Odyssey. Especially Kevin, Kris, Michael and Ubin what more can I say guys, you made the middle lab epic! Meder Man, Спасибо за все!!! Anaïs, we are out of coffee! Thanks for all the conversations, the seriousness, the silliness and all the laughs! Steph it's finally over nothing more for you to proof read! Thanks for being a great friend, all the best with learning Swiss-German, see you in Switzerland! Steffi und Dr. Miller Nun! Wenn ihr nicht da wart, hätte ich deutsch auf jeden Fall vergessen und wahrscheinlich viel weniger von Neuseeland gesehen! Danke für alles, ihr seid großartig! Geoff thanks for all the classical music talk, it was good to see you at the annual German plays! Orla thanks for doing the bio testing, Kim and Dom thanks for always being so nice, caring, kind and helpful, Paul thanks for soccer and the movies and your sarcastic british humour. Seb, Jack, Reentje, Raoul, Amanda, Greg, Joanna, Renata, Dan, Huimin, Xiaboa, Isi, Katie thanks guys!

Some personal friends need to be acknowledged as well for their friendship, which has been invaluable. Jonny, Graham, Jeff, Ogy and Brendan thanks guys!

Finally and most importantly I would like to thanks my parents, Stela and Ventzi, for your caring, understanding and always being there! For always helping me, having the right words and always supporting me in whatever I have wished to do! This thesis is dedicated to you! My grandparents, you have made me who I am, you have cared so much for me, I don't know how to thank you enough!

Ivo Dimitrov

November 2011
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<td>Å</td>
<td>angstrom</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<td>BINOL</td>
<td>1,1′-bi-2-naphthol</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>br</td>
<td>broad</td>
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<td>BT</td>
<td>benzothiazole</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>C</td>
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<td>cerium(IV) ammonium nitrate</td>
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<td>Corey-Bakshi-Shibata</td>
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<td>chemical ionisation</td>
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<td>d.e.</td>
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<td>Dess–Martin periodinane</td>
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<td>deoxyribonucleic acid</td>
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<td>isopinocampheylborane</td>
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<td>IR</td>
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<tr>
<td>LDA</td>
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<td>KHMDS</td>
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</tr>
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<td>m</td>
<td>multiplet or mili</td>
</tr>
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<td>m</td>
<td>meta</td>
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<td>MALAT</td>
<td>mucosa associated lymphoid tissue</td>
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<td>Description</td>
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<tr>
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<td>-------------</td>
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<td>minimum bactericidal concentration</td>
</tr>
<tr>
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<td>methyl</td>
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<td>megahertz</td>
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<td>MIC</td>
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<td>TBDPS</td>
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<tr>
<td>TBS</td>
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<td>tertiary</td>
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<td>TMS</td>
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<td>tosyl (toluenesulfonyl)</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Chapter I: Introduction

1.1 *Helicobacter pylori*

1.1.1 The bacteria in a historical context

The initial discovery of *Helicobacter pylori* occurred in 1875 when German physicians observed spiral bacteria in the lining of human stomachs, however they were unable to culture the microorganism.¹ Jarowski observed the rod like structure of the bacteria again in 1899 and named it *Vibrio rugula* and included it in the Polish Handbook of Gastric Diseases.² Subsequently these results were largely forgotten for the next forty years. In 1938 Doenges rediscovered the bacteria, he observed what he called “spirochaetes” in 43% of the 242 stomachs he examined at autopsy but drew no conclusion because autolysis had rendered specimens unsuitable for pathological diagnosis.³ In 1940 Freedburg and Barron concluded that these bacteria colonise tissue near benign or malignant ulcers as non-pathogenic opportunists.⁴ Yet again these results lived largely in obscurity for the next four decades until 1979 when Australian pathologist Robin Warren visualized the bacteria in the stomach of gastric ulcer patients and managed to isolate the microorganism with his colleague Barry Marshall. After numerous attempts they finally managed to colonize the bacteria in 1982⁵ and found it inhabited the interface between the gastric epithelium and the semipermeable gastric mucus layer.⁶ Due to similarities between the isolated organism and the bacteria of the genus *Campylobacter*, the bacterium was assigned as a new species belonging to the *Campylobacter* genus. Further RNA analysis, however, revealed that it did not belong to the genus *Campylobacter* and the new name *Helicobacter pylori* was assigned.⁷ Warren and Marshall proposed that most stomach ulcers and gastritis are caused by the infection by this bacteria and not by stress, poor diet and spicy food as had previously been contended.⁶ In order to demonstrate that *H. pylori* caused gastritis and was not merely a bystander, Marshall drank a culture of *H. pylori*. He became ill several days later with nausea and vomiting. An endoscopy ten days after inoculation revealed signs of gastritis and the presence of *H. pylori*. Marshall and Warren went on to show that antibiotics are effective in the treatment of many cases of gastritis. For this pioneering work Warren and Marshall were eventually recognized with the Nobel Prize for Medicine and Physiology in 2005.

1.1.2 Morphology and genetic variation

*H. pylori* bacteria are Gram-negative, microaerophilic rods that possess a helical shape (Scheme 1). Each bacterium is approximately 2.5-3.0 μm in length and 0.5 μm in width and usually possess up to five sheathed flagella arising from one end of the cell.⁵ These flagella enable *H. pylori* to penetrate and colonise the viscous gastric mucosal lining by propelling the bacterium in a spiralling motion.⁶ The organism is able to enter a coccoid form or a dormant state, which allows its survival in unfavourable conditions.
H. pylori has travelled on a unique evolutionary journey to occupy its niche. Its genome contains 1.65 million nucleotides which are estimated to code for approximately 1500 genes that individually encode a separate protein.\textsuperscript{9,10} Out of these genes, 55\% are shared with other organisms with the remaining 45\% being unique to the organism. Nearly every infected human being carries an individually distinguishable strain of H. pylori due to the longevity of the infection in the host, causing mutation of the bacteria or re-infection with new strains.\textsuperscript{11} The strains of H. pylori can be divided into cytotoxic (cag A-positive) and non-cytotoxic (cagA-negative) strains. The virulent (cagA-positive) strains contain cag pathogenicity island (cag PAI), a 40 kilobase segment of DNA, suspected to have been acquired from another organism which codes for the cytotoxic-associated antigen (CagA).\textsuperscript{12}

1.1.3 Epidemiology and transmission

H. pylori is the most common chronic infection in humans.\textsuperscript{13} It has been estimated that 50\% of the entire human population has been infected.\textsuperscript{14} The prevalence of infection with H. pylori exhibits a strong correlation with socio-economic conditions and is far greater in developing countries (80-90\%) than in developed countries (10-50\%).\textsuperscript{14,15}

It is widely believed that H. pylori is predominantly acquired in childhood through a combination of poor living conditions and close interpersonal contact with infected family members.\textsuperscript{16} The bacteria is contracted through oral ingestion.\textsuperscript{17} It has been found in samples of faeces and sometimes dental plaque but to date the precise mechanism of transmission is unclear.\textsuperscript{18,19}
Chapter I: Introduction

1.1.4 Colonisation and survival mechanisms

It is well established that *H. pylori* colonises on the surface of the gastric epithelium and the mucosal layer overlying the gastric epithelium. This thick semi-permeable mucosal lining is secreted by the stomach to protect the gastric epithelium from the actions of the acidic environment and digestive gastric juices. The bacteria is able to penetrate the mucosal surface of the stomach by several mechanisms. The flagella provide a powerful spiral movement to the organism complemented by the helicoidal shape. Secretion of the putative collagenase enzyme (HP0169) which digests the mucous and other substances act to decrease the mucosal viscosity and allow easier movement through the mucosa. The environment surrounding *H. Pylori* is extremely hostile, the stomach produces gastric juice containing ~0.17 M hydrochloric acid and protease enzymes. Inhabiting the mucosal layer which acts as a shield to the gastric epithelium provides the bacteria with a favourable niche. Furthermore, the bacteria bind tightly to gastric cells. The precise nature of the adhesion is unknown. The adhesin protein BabA which binds to fucosylated Lewis B blood group antigens on gastric epithelial cells is believed to be especially important in the process.

Another vital survival mechanism of all *H. pylori* strains is the abundant production of the enzyme urease. Urease catalyses the hydrolysis of urea present in gastric juice into carbon dioxide and ammonia.

\[
\text{CO(NH}_2\text{)}_2 + \text{H}_2\text{O} \xrightarrow{\text{urease}} \text{CO}_2 + 2\text{NH}_3
\]

The ammonia in effect buffers the acidic environment around the bacterium contributing to its survival in the acidic environment of the stomach which ranges in pH from 1-4. The bacterium can precisely maintain the pH environment surrounding it, as urease activity is controlled by UreI. UreI is a pH-gated urea channel which opens at low pH and closes at neutral pH, thus controlling the uptake of urea into the organism.

1.1.5 Inflammation and host immune response

The precise mechanisms of inflammation have been well investigated but not fully elucidated. The primary accepted mechanism is believed to be due to the toxins (VacA, Cag A, HP-NAP) produced by *H. pylori*, which are all major antigens in the immune response. Ammonia produced in the hydrolysis of urea, causes damage to gastric cells. Urease itself is inflammatory to the gastric mucosal layer. *H. pylori* also has an outer membrane structure which is enriched in lipopolysaccharide (LPS) antigens which are known inflammation mediators.

*H. pylori* infection triggers a host immune response that involves the accumulation of various leukocytes within the gastric mucosa. Neutrophils and monocytes are sent by the immune system
towards the site of infection, but are unable to pass through the epithelium cells to reach and eradicate the infection. The leukocytes adhere to the epithelial cells and produce cytotoxins which in conjunction with those produced by \textit{H. pylori} cause considerable gastric epithelial necrosis.\textsuperscript{29-31} Macrophages activated by \textit{H. pylori} antigens also participate in the inflammatory response. They produce pro-inflammatory cytokines that activate the T-helper lymphocytes.\textsuperscript{32}

The \textit{cagA}-positive strains of \textit{H. pylori} can translocate the CagA (cytotoxin associated gene A) protein into epithelial cells through a type IV secretion system.\textsuperscript{33} This causes a cascade of specific cellular responses inducing greater inflammation, thus increasing the risk of ulceration, atrophic gastritis, intestinal metaplasia and gastric cancer.\textsuperscript{34} Cag A can also cause alteration of the cytoskeleton of the host epithelial cell. The presence of cagPAI is associated with the secretion of the vacuolating toxin (\textit{vac A}).\textsuperscript{35} VacA is the cause of large vacuole formation in epithelial cells, leading to ulceration and tissue damage.

It appears that the inability of the host immune response to eliminate the \textit{H. pylori} infection is one of the primary causes in the development of inflammation and peptic ulcer disease.\textsuperscript{34} Thus the organism is able to persist without antibiotic intervention.

1.1.6 Pathology

\textit{H. pylori} colonises the antrum of the stomach and the duodenum for years or decades and produces continual inflammation in virtually all infected individuals.\textsuperscript{36} This continual inflammation is known as chronic superficial gastritis, which can eventually lead to hypergastrinemia (excess gastric acid secretion).\textsuperscript{24} Despite the chronic infection, the patient remains clinically silent, i.e., asymptomatic.\textsuperscript{24} However between 15-20\% of infected individuals will eventually develop gastric or duodenal disease and over 1\% will develop lymphoma or adenocarcinomas (gastric cancer).\textsuperscript{37} The main difference in the effects of the infection are attributed to the severity of the immunological reaction of the host, the strain of the organism, bacterial polymorphisms and environmental factors.\textsuperscript{38}

People who develop the more common antral-predominant gastritis are at a higher risk of developing duodenal ulcers, with approximately 95\% of all duodenal ulcers caused by \textit{H. pylori} infection.\textsuperscript{39,40} People who develop corpus-predominant gastritis are more likely to develop gastric ulcers, which can lead to atrophic gastritis and intestinal metaplasia, then dysplasia and finally adenocarcinoma.\textsuperscript{39} In total up to 80\% of gastric ulcers are the result of \textit{H. pylori} infection.\textsuperscript{16}

Most cases of peptic ulcer disease, gastric mucosal associated lymphoid tissue (MALT) lymphoma and distal stomach cancer, particularly intestinal adenocarcinoma, are caused by the progression of the \textit{H. pylori} infection. (Scheme 2). The progression of chronic superficial gastritis into atrophic gastritis is considered as a precursor to gastric cancer. Gastric cancer is the second most prevalent worldwide
cancer and the 14th overall cause of death.\textsuperscript{41} There are considerable geographical differences in cancer rates with China, Japan and South America having the highest rates and western Europe and USA displaying the lowest rates.\textsuperscript{41} \textit{H. pylori} is classified as a class 1 (Definite) carcinogen by the International Agency for Research on Cancer (IARC), a division of the World Health Organisation (WHO).\textsuperscript{42}

\begin{center}
\textbf{Scheme 2:} A model of \textit{H. pylori} infection and gastroduodenal pathology, reproduced from Suerbaum and Mechetti\textsuperscript{17}
\end{center}

\subsection{1.1.7 Treatments for \textbf{Helicobacter pylori}}

Current treatment of \textit{H. pylori} associated stomach and duodenal ulcers are aimed at the eradication of the bacteria rather than suppression of the ulcer. The Maastricht guidelines\textsuperscript{43,44} recommend treating all \textit{H. pylori} infected patients: those with active or inactive peptic ulcers, those with complicated ulcer disease, those following gastric surgery, those with low-grade mucosa associated lymphoid tissue (MALT) lymphoma, those with high grade mucosa associated tissue (MALT) lymphoma or those who are first degree relatives of gastric cancer patients. Bacterial elimination results in gastric or duodenal ulcer cure rates of 90\%.\textsuperscript{45} In patients with low grade MALT lymphoma, \textit{H. pylori} removal leads to a complete remission for 74\% of cases, although these patients should be monitored for the rest of their lives as atrophic changes in the gastric mucosa can progress to gastric cancer. With high-grade MALT lymphoma patients, \textit{H. pylori} eradication should also be used as a first line treatment.\textsuperscript{44}

The first report of antibiotic treatment for peptic ulcer diseases was a monograph published in 1951 in which Jose Solano reported his experience treating ulcer patients with penicillin and convalescent
patient serum. Ten years later John Lykoudis, a Greek practitioner, patented Elgano, an antibacterial combination of streptomycin and oxyquinolines among other components. The combination produced notable improvements in ulcer patients' symptoms. He treated more than 30000 patients for two decades despite lack of official approval, since no comparative trials were ever reported. The first 'official' *H. pylori* treatment was serendipitously performed by Barry Marshall in 1983. A patient included in a trial comparing the anti-ulcer effect of bismuth salts and cimetidine, developed periodontal disease while receiving bismuth and received five-day metronidazole treatment. *H. pylori* was not found in subsequent control endoscopy. Marshall later used this combination on many patients including himself. The first reliable therapy was triple therapy combining bismuth, tetracycline 3 and metronidazole 1 which was very effective, though it had a complicated schedule and frequent side effects. In 1993, Bell *et al.* first reported the high efficacy of triple therapy combining a proton pump inhibitor (PPI), amoxicillin 5 and metronidazole 1. Shortly afterwards Franco Bazzoli described a triple therapy combining PPI, clarithromycin 2 and metronidazole 1. Triple therapy combined simplicity, tolerability and efficacy and was quickly accepted as standard after large multicentre trials had demonstrated cure rates around 90%. Successful *H. pylori* eradication therapy still remains a challenge in medical practice. Currently a proton pump inhibitor-based triple therapy containing clarithromycin 2, amoxicillin 5 or nitroimidazole 6 for seven days is the recommended first-line treatment approach with an expected eradication success rate of ~80%. In the case of failure, a second-line treatment option of seven-day ranitidine, bismuth citrate, metronidazole 1 and tetracycline 3 based quadruple therapy is currently recommended, curing another 80% of patients leaving a subset of patients with persistent *H. pylori* infection. The efficacy of the antibiotics is significantly reduced in the acidity of the gastric lumen, therefore it is necessary to co-administer an acid-suppressant. Proton-pump inhibitors such as omeprazole 4, lansoprazole and esomeprazole or the histamine-2 receptor antagonist ranitidine are commonly used. The use of urease inhibitors to prevent *H. pylori* survival in the acidic stomach environment was abandoned due to the high toxicity of these compounds.

Although quadruple therapy (proton pump inhibitor, bismuth salt, metronidazole 1 and tetracycline 3) is highly effective in patients with at least one failed course of standard triple therapy some problems with this regimen still exist. First bismuth compounds are not available everywhere. Secondly patients could be intolerant to tetracycline. Finally, patient compliance could be suboptimal since the schedule of drug administration is complex with bismuth and tetracycline 3 to be taken four times daily, metronidazole three times daily and PPI twice daily.
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Scheme 3: The standard arsenal against *H. pylori*

1.1.8 Rescue therapies and novel agents

As a result of the inadequacies of first and second line treatments, sometimes it is necessary to resort to rescue options and novel agents. A study has shown that *H. pylori* has proven highly susceptible to rifabutin **10** *in vitro*.\(^5^5\) Therefore, rifabutin **10** in combination with amoxicillin or quinolone might be a potent second or third line eradication. Resistance to fluoroquinolones is low in most countries\(^5^6\) hence these are potential candidates for second line and rescue treatment.\(^5^2\)

Furazolidone **9** has also demonstrated high antimicrobial activity including against *H. pylori*.\(^5^7\) Furazolidone is considered as a potent substitute for metronidazole **1** resistant strains. Eradication regiments including furazolidone **9** in a triple or quadruple therapy first-line approach achieved 58-90% success in populations of high metronidazole **1** resistance.

Rifaximin **11** has broad spectrum antimicrobial activity including *H.pylori*. The drug is poorly absorbed by the gastric and intestinal mucosa, achieving a high concentration within the gastrointestinal tract with few systematic adverse effects.\(^5^8\) Its bactericidal effect is not significantly affected by the acidic environment. Due to these advantages rifaximin **11** is studied as a treatment for persistent *H. pylori* infection.

Tinidazole **7** is a nitroimidazole **6**, a metronidazole-like antimicrobial agent. It is effective against protozoa and anaerobic organisms, including *H. pylori*. Its activities are largely pH independent, an advantage in treatment of gastric infections. Tinidazole's advantages over metronidazole **1** include enhanced activity, favourable pharmacokinetics, and increased tolerability. A randomized blind study...
found tinidazole 7 based regimens resulted in eradication rates of more than 90% in metronidazole-susceptible strains. 59

Lactoferrin is a glycoprotein (molecular weight 80 kDa) that is a member of the transferrin family that binds two Fe\(^{3+}\) atoms with high affinity.\(^{60}\) It has shown antibacterial action against \(H.\) \textit{pylori} both \textit{in vitro} and \textit{in vivo} and has been evaluated in a few clinical trials with mixed success.

Plaunotol 8 is an acyclic diterpene alcohol originally isolated from the plant \textit{Croton sublyratus}, which is native of southeast Asia. \textit{In vitro} studies showed bactericidal action against \(H.\) \textit{pylori} by increasing membrane fluidity, leading to autolysis and deterioration of cell structure.\(^{61}\)

\[
\text{tinidazole 7} \quad \text{plaunotol 8} \quad \text{furazolidone 9}
\]

\[
\text{rifabutin 10} \quad \text{rifaximin 11}
\]

\textbf{Scheme 4:} Rescue therapies against \(H.\) \textit{pylori}

1.1.9 Limitations of current therapy

A problem with current therapy is that long term treatment using triple or quadruple therapy is far from ideal. This is due to the side effects caused by the treatment such as nausea, diarrhoea, sore mouth, taste disturbances and fungal diseases.\(^{62}\) The side effects can lead to patient non-compliance. Long term treatment is also associated with bismuth toxicity build up and drug resistance. After first-line treatment failures, the strain of the bacteria develops resistance to one or both antibiotics, this strain can then be passed to other people, thus increasing the prevalence of antibiotic resistant \(H.\)
pylori strains in the general population. \(^{63}\) In 2001, the first strain (Hardenberg strain) with stable amoxicillin \(^5\) resistance was discovered. \(^{64}\) Acquired resistance to clarithromycin \(^2\) and metronidazole \(^1\) after first-line therapy failure is 50-75\% and acquired resistance to metronidazole \(^1\) even higher with a frequency of approximately 90\%. \(^{64}\) The emerging resistance poses significant \textit{H. pylori} eradication problems.

A further limitation to current treatment is that after the course of antibiotics, there is no prevention to re-infection occurring. As a result the development of a vaccine is being extensively studied and trialled. Many studies have been carried on \textit{in vitro} and \textit{in vivo} models using mice, other rodents, monkeys and pigs as human substitutes. \(^{65}\) Clinical studies on human vaccination have experienced poor results so far, which indicates there is still a lot of work needed in this area. \(^{26}\)

Although current chemotherapy for \textit{H. pylori} is effective, it is at the same time far from ideal. The problems and limitations described above lead to the conclusion that there is a need for a safe and effective treatment for \textit{H. pylori} which achieves close to 100\% eradication as a first line monotherapy.

1.2 Novel anti-\textit{H. pylori} agents

1.2.1 Spirolaxine and the CJ compounds

Spirolaxine \((14)\) was first isolated in 1990 from a strain of the white-rot fungi \textit{Sporotrichum Laxum}. \(^{66}\) Subsequently the methyl ether \((15)\) was also isolated from \textit{S. Laxum}, \textit{S. Pruinosum} and \textit{Phanerochaete chrysosporium}. \(^{67}\) White rot fungi are the most efficient of all known lignin degraders. Spirolaxine contains a 7-methoxy-5-hydroxyphthalide nucleus linked through a polymethylene chain to a spiroacetal group (Scheme 5). In the original isolation article, \(^{66}\) spirolaxine \((14)\) was shown to possess weak bacteriostatic activity against \textit{Bacillus cereus}, \textit{Bacillus subtillis}, and \textit{Escherichia coli} and no antifungal activity against \textit{Asperigillus niger}, \textit{Botytris cinerea}, \textit{Cladosporium cucumerinum}, \textit{Saacharomyces cerevisiae}, however the compound was not tested against \textit{H. pylori}.

In 1997, in a screening program designed to discover \textit{H. pylori} specific antibacterial compounds Dekker et al. \(^{68}\) isolated seven new phthalide antibiotics from the basidiomycete \textit{Phanerochaete velutina} CL6387, which were named the CJ compounds (Scheme 5). The aim was to find compounds which were potent, caused less side-effects and did not disturb the normal gastro-intestinal microbial flora, which normally occurs in the standard antibiotic \textit{H. pylori} treatment.
Dekker et al.\textsuperscript{68} discovered that spiroacetal-containing compounds CJ-12,954 (13) and CJ-13,104 (12) showed most potent activity against \textit{H. pylori} (Scheme 6) and did not display antibacterial activity when tested against a panel of other microorganisms such as \textit{Bacillus searothermophilis}, \textit{Micrococcus luteus}, \textit{Staphylococcus aureus} and \textit{Pasteurella haemolytica}.\textsuperscript{68} Such high level of specificity suggested that the CJ and related compounds may exhibit less side effects and may not induce resistance in non-target organisms, which makes them prime candidates for anti-\textit{H. pylori} agents. Dekker et al.\textsuperscript{68} also noticed that the ring opening of the spiroacetal to a diketone (CJ-13,015) (16) reduces potency nearly tenfold. The monoketone (CJ-13,108)(20) is again fivefold less potent and after reduction of the ketone to a hydroxy group (CJ-13,104) (19) activity is lost (Scheme 6).
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**Scheme 6:** Anti-\( H. \text{pylori}\) activity of CJ compounds, spirolaxine (14), spirolaxine methyl ether (15) and the unnatural diastereomer (2''S)-spirolaxine methyl ether (21)\(^{68,69}\)

Dekker *et al.*\(^{68}\) also looked at spirolaxine (14) and found it to be of similar potency if not more potent than the 5,5-spiroacetal compounds (CJ-12,954 (13) and CJ-13,104 (12). However the authors did not mention the activity of spirolaxine methyl ether (15) which was also isolated from white-rot fungi.\(^{67}\)

Radcliff *et al.*\(^{69}\) reported the anti-\( H. \text{pylori}\) activity of spirolaxine methyl ether (15) and found it had similar potency to spirolaxine (14). Furthermore, they reported that the synthetic (2''S)-diastereomer of spirolaxine methyl ether (21) which was synthesised by Robinson *et al.*\(^{70}\) during the first total synthesis of spirolaxine methyl ether (15) was fourfold more potent than the natural compound (Scheme 6). At the outset of that work the absolute stereochemistry of spirolaxine methyl ether (15) had not yet been confirmed. Our research group\(^{70}\) was subsequently able to establish that the absolute stereochemistry of the natural product is \((3R, 2''R, 5''R, 7''R)\). This result suggests that the

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>MIC (µg/mL)</th>
<th>MBC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJ-12,954</td>
<td>13</td>
<td>Me</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>CJ-13,104</td>
<td>12</td>
<td>Me</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>CJ-13,015</td>
<td>16</td>
<td>Me</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>CJ-13,102</td>
<td>17</td>
<td>Me</td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>CJ-13,104</td>
<td>19</td>
<td>Me</td>
<td>12.5</td>
<td>50</td>
</tr>
<tr>
<td>CJ-13,108</td>
<td>20</td>
<td>Me</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>spirolaxine</td>
<td>14</td>
<td>H</td>
<td>0.2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>spirolaxine methyl ether</td>
<td>15</td>
<td>Me</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>unnatural (2''S)-spirolaxine methyl ether</td>
<td>21</td>
<td>Me</td>
<td>0.125</td>
<td>0.125</td>
</tr>
</tbody>
</table>

MIC = Minimum Inhibitory Concentration  
MBC = Minimum Bactericidal Concentration
stereochemistry of the 6,5-spiroacetal ring system is an important structural feature for the observed anti-\textit{H. pylori} activity and that the conversion of the methyl ether to a free phenol is not necessary for the activity.

### 1.2.2 Indole analogues of the simpler CJ compounds

Analogues of the simpler open chain CJ-compounds were synthesised by Wilson \textit{et al.}\textsuperscript{71} where the phthalide heterocycle had been replaced with an indole, which they considered a good bioisostere for the phthalide. The indole analogues however, were all found to be less active (or inactive at the concentrations tested) than their parent compounds (Scheme 7). The notable exception being the chain-shortened indole analogue of CJ-13,108 (20) which was twice as potent as the parent phthalide. This observation suggests that examination of the chain length in conjunction with bioisosteric replacement of the phthalide heterocycle provides an opportunity for future lead compound development.\textsuperscript{69}

![Scheme 7: anti-\textit{H. pylori} activity of indole analogues of simple CJ compounds](image-url)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(R_2)</th>
<th>anti-\textit{H. pylori} activity ((\mu\text{g/mL}))</th>
<th>anti-\textit{H. pylori} activity ((\mu\text{g/mL}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MIC</td>
<td>MBC</td>
</tr>
<tr>
<td>CJ-13,015</td>
<td></td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>CJ-13,102</td>
<td></td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>CJ-13,104</td>
<td></td>
<td>12.5</td>
<td>50</td>
</tr>
<tr>
<td>CJ-13,108</td>
<td></td>
<td>10</td>
<td>10-20</td>
</tr>
</tbody>
</table>

MIC = Minimum Inhibitory Concentration  
MBC = Minimum Bactericidal Concentration
1.3 Spiroacetal ring systems

1.3.1 Spiroacetals

Spiroacetal ring systems are a common sub-structural motif that are present inside a range of biologically active compounds isolated from many diverse origins. The structural complexity and pharmacological activity of spiroacetals have subsequently led to extensive investigation in their synthesis and reactivity. They are usually composed of two spiro-linked tetrahydrofuran or tetrahydropyran rings. The five main types of spiroacetal structures isolated from nature are shown below (Scheme 8).

![Scheme 8: Spiroacetal ring systems found in nature](image)

The most predominant spiroacetals in nature are the 6,6-spiroacetals (D) followed by 6,5-spiroacetals (B) and to a lesser extent 5,5-spiroacetal ring systems (A).

1.3.2 Stereochemistry of spiroacetal ring systems

Spiroacetals can exist as two enantiomers due to the presence of the stereogenic spiroacetal carbon (Scheme 9).

![Scheme 9: Enantiomeric forms of spiroacetals](image)

The two stereoisomers are able to interconvert under acidic conditions via a hydroxyalkyl oxonium ion intermediate (Scheme 10).

![Scheme 10: Spiroacetal ring opening under acidic conditions](image)
1.3.3 Anomeric effect

The anomeric effect is the propensity of heteroatom substituents at the anomeric C1 position of an oxygen containing ring to adopt the axial position as opposed to the traditionally predicted less hindered equatorial position.\textsuperscript{81,82}

It was first observed in 1955 by J. T. Edward that alkoxy groups at C-1 of pyranose rings are more stable in the axial rather than in the equatorial configuration.\textsuperscript{83} At the time the explanation given for this observation was due to the more favourable dipole alignment of unshared electrons in the $\alpha$-anomer $\text{B}$ by Lemieux et al.\textsuperscript{84} (Scheme 11).

\begin{center}
\textbf{Scheme 11:} Edward-Lemieux theory focused on unfavourable dipole interactions of the $\beta$-anomer
\end{center}

The theory of the anomeric effect evolved in 1968 into the "rabbit-ear effect", which stated that conformations of molecules, in which unshared electron pairs on non-adjacent atoms are parallel, are disfavoured\textsuperscript{85} (Scheme 12).

\begin{center}
\textbf{Scheme 12:} Electrostatic repulsion in the $\beta$-anomer of the "rabbit-ear effect" model
\end{center}

It is now widely accepted that the observed stabilisation of spiroacetals is due to the orbital overlap (hyperconjugation) between the non-bonding oxygen p-orbital (n) with the antibonding ($\sigma^*$) orbital of a carbon-oxygen bond. In order to overlap, the non-bonding orbital (n) must adopt an antiperiplanar arrangement with respect to the carbon-oxygen bond.\textsuperscript{86} Such overlap can be accommodated in two ways: the \textit{endo} anomeric effect and the \textit{exo} anomeric effect (Scheme 13).

\begin{center}
\textbf{Scheme 13:} Orbitals involved in n-$\sigma^*$ hyperconjugation
\end{center}
Deslongchamps et al.\textsuperscript{87} have conducted further studies on the anomeric effects of 6,6-spiroacetals. It was calculated that there is a ~2.4 kcal/mol for each axial O-R acetal in an unsubstituted 6,6-spiroacetal and allows the confident prediction that the orientation of such a spiroacetal is that which exists in the double anomerically stabilised bis-axial conformation \textbf{1} (Scheme 14).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme14.png}
\end{center}

\textbf{Scheme 14:} All four possible conformers of unsymmetrically substituted 6,6-spiroacetals\textsuperscript{79}

The anomeric effect provides a reliable method for predicting the configuration of unsubstituted 6,6-spiroacetals formed under thermodynamic conditions. The 6,6-spiroacetal ring system is relatively rigid and there is a clearly defined difference between the anomeric and non-anomeric conformations.\textsuperscript{79} Although it is possible for spiroacetals in natural products to exist in nonanomeric form, Pihko et al.\textsuperscript{88} have written a very comprehensive review on the nonanomeric spiroacetals found in nature, the reasons they form, their sources and synthetic strategies towards accessing them.

The analysis of 5,5-spiroacetal ring systems is much more complex than that of the six membered ring counterparts. Five membered rings are known to exhibit rapid pseudorotation and deformation in which the ring and its substituents may assume a continuous set of conformations.\textsuperscript{89} The more complex array of conformers adopted by five membered rings has implications on the degree of influence that the anomeric effect has over the configuration about the spirocentre. The 180º antiperiplanar arrangement required between a lone pair non-bonding oxygen orbital and the C-O bond for optimal anomeric stabilization is not attainable in the 5,5-spiroacetal. Instead, this dihedral angle for a \textit{bis} “pseudo-axial” conformation is only approximately 165º. Consequently, it is not easy to predict the conformation that a ring system will adopt upon spirocyclization, if one or two five membered rings are involved.\textsuperscript{79}
1.3.4 Hydrogen bonding and chelation effects

The conformation which the spiroacetal ring adopts may be further influenced by intramolecular hydrogen bonding of a polar spiroacetal substituent. Hydrogen bonding of H-O • • • H accounts for an energy stabilization of 5-10 kcal/mol\(^9^0\) and can either be matched with the anomeric effect or be mismatched. Chelating metals can have a similar effect. In each case, the thermodynamically favoured conformation will predominate under equili brating conditions.

An example of this is observed in the X-ray crystal structure of a 6,6-spiroacetal A bearing an axial 1,3-hydroxyl substituent, in this case the hydrogen bonding reinforces the anomeric effect (Scheme 15).\(^9^1\)

![Scheme 15: Hydrogen bonding of 6,6-spiroacetal with a 1,3-axial hydroxyl substituent](image)

Ireland et al.\(^9^2\) took advantage of H-bond stabilization to control the configuration of two stereocentres in the 6,5-spiroacetal of monensin 23 (Scheme 16). All four isomers of 22, when subjected to benzyl deprotection, followed by exposure to acid resulted in a single stereoisomer 23.

![Scheme 16: Ireland's synthesis of monensin spiroacetal ring system 23\(^9^2\)](image)

1.3.5 Steric effects

Large or sterically demanding substituents of 6,6-spiroacetals can have a profound influence on the conformation of the spiroacetal. Such substituents may favour formation of a non-anomerically stabilized conformer to minimize severe 1,3-diaxial interactions and prevent ring flipping to an anomerically stabilized conformation.

Exactly such an example was observed recently by Dias et al.\(^9^3\) in their efficient synthesis of the spirofungin spiroacetals 26 and 27 (Scheme 17). Open chain intermediate 25 was subjected to acid deprotection and concomitant spiroacetalisation by treatment with HF-pyridine to give a 30:70 mixture of anomic 26 and nonanomic 27 spiroacetals respectively. It was also observed that each
isolated pure spiroacetal led to the same 30:70 equilibrium mixture under very mild acidic conditions (CDCl$_3$). The instability of the doubly anomic structure in spirofungins is due to unfavourable steric interactions between axial C$_{19}$ side chain and the C$_{11}$ axial hydrogen (Scheme 17)

\[
\text{Spirofungin A 24}
\]

\[
\text{Scheme 17: Steric interactions causing the 6,6-spiroacetal of spirofungins to adopt a nonanomeric conformation}\]

1.3.6 Chiral substituents

As previously stated, the anomeric effect does not exert much stereocontrol over the formation of 5,5-spiroacetals. Nevertheless chiral centres in the spiroacetal precursor have been shown to induce the formation of one configuration over the other. Solladie et al.$^{94}$ used chiral sulfoxides inbuilt into precursor 28 which upon chelation to ZnBr$_2$ gave exclusively one spiroacetal diastereomer 30 (Scheme 18). The transition state 29 is shown where the two chelates are on opposite sides of the newly formed spiroacetal which is the favoured conformation under equilibrating thermodynamic conditions.

\[
\begin{align*}
\text{Reagents and conditions: a) ZnBr}_2, \text{CH}_2\text{Cl}_2, 60^\circ\text{C, 2 h, 76%} \\
\end{align*}
\]

\[
\text{Scheme 18: Solladie's use of chiral sulfoxide substituents to generate enantiopure 5,5-spiroacetal 30}\]

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1.4 Natural products containing 6,5-spiroacetal ring systems

1.4.1 Bacterial 6,5-spiroacetal containing metabolites

Polyether antibiotics constitute a large class of metabolites isolated from the fermentation broths of *Streptomyces* with many of them possessing 6,5-spiroacetals (Scheme 19). Nigericin (31), isolated in 1951, was among the first polyether antibiotics reported.\(^95,96\) However, it was not until monensin (32) was isolated from *Streptomyces cinnamomensis*, that the potent ionophoric and microbial activity of this class was discovered.\(^97\)

These compounds are characterised by the presence of substituted tetrahydrofurans, tetrahydropyrans and spiroacetal systems. Dainemycin (35) and the related lenoremycin (36) are unusual examples that contain two 6,5-spiroacetal systems (Scheme 19).\(^96\)

![Nigericin 31](image)

![Monensin 32](image)

![Etheromycin 33](image)

![Septamycin 34](image)

![Dianemycin 35](image)

![Lenoremycin 36](image)

**Scheme 19**: Selection of polyether antibiotics that contain a 6,5-spiroacetal moiety
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Reveromycin B (37) was isolated in 1991 from the soil actinomycete of the *Streptomyces* genus (Scheme 20).\(^9\) It contains a 6,5-spiroacetal at its core and is a potent inhibitor (IC\(_{50}\)=6 µg/mL) of the mitogenic activity induced by epidermal growth factor.\(^9\)

![Scheme 20: Reveromycin B (37)](image)

The rubromycins were isolated from *Streptomyces collinus* in 1969 and contain napthazarin and isocoumarin moieties linked through a rare bis-benzanulated 6,5-spiroacetal ring system (Scheme 21).\(^10\) Both β-rubromycin (38) and γ-rubromycin (39) inhibit human immunodeficiency virus reverse transcriptase\(^10\) as well as inhibiting human telomerase, an enzyme essential for effective replication of DNA.\(^10\)

![Scheme 21: Structures of β and γ-rubromycins](image)

1.4.2 Fungal 6,5-spiroacetal containing metabolites

The papulacandins are a family of C-arylglycosides that contain a benzannulated 6,5-spiroacetal ring system (Scheme 22). Papulacandins A (40), B (41), C (42) and D (43) have been isolated from fungi *Papularia sphaerosperma* and exhibit potent activity against *Candida albicans* and related microorganisms.\(^10\) More recently, Mer-WF3010 (44) was isolated from *Phialophora cyclamnis* and L-687,781 (45) from *Dictyochaeta simplex*.\(^10\) L-687,781 (45) has shown considerable activity against *Pneumocystis carinii*, an opportunistic pneumonic infection commonly encountered in AIDS patients.\(^10\)
1.4.3 Plant metabolites containing 6,5-spiroacetals

Saponins and sapogenins were isolated during the 1930s and 1940s primarily by Marker et al.\textsuperscript{107} from various plant species found predominantly in Mexico. Steroidal sapogenins represent the earliest isolated class of spiroacetal-containing natural products. Sapogenins are the aglycones of plant saponins and contain a fused 6,5-spiroacetal fused to the D-ring of the steroidal nucleus (Scheme 23).

The spiroacetal moiety is relatively well conserved in these compounds as most structural variation tends to occur in the steroidal skeleton. Their biological activity is wide ranging and has been extensively reviewed.\textsuperscript{108,109}
1.4.4 Marine natural products containing 6,5-spiroacetals

Marine dinoflagellates are known to produce highly toxic polycyclic ether compounds. As the plankton is a food source for shellfish, the toxins tend to accumulate in the glands of the shellfish and sporadically cause problems for humans that consume them.

A number of the compounds associated with diarrhetic shellfish poisoning contain a 6,5-spiroacetal moiety. Dinoflagellates, Dinophysis and Prorocentrum, are known to be primary sources of diarrhetic shellfish toxins.\textsuperscript{110-113}

Acanthifolicin (83) was isolated from the marine sponge Pandaros acanthifolium, in 1981, and was the first polyether carboxylic acid of marine origin.\textsuperscript{114} At the same time the related okadaic acid was also isolated from the sponge Halichidria okadai.\textsuperscript{110} Several diol esters (85-89) of okadaic acid and closely related derivatives known as dinophysistoxins (90-93) have also been reported (Scheme 24).\textsuperscript{111,112,115,116}
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Another class of shellfish toxins that contain a 6,5-spiroacetal unit are the ciguatoxins (Scheme 25). Originally isolated from the moray eel *Gymnothorax javanicus*, in 1967, the structure of ciguatoxin-1 (94) was not elucidated until 1989. The precursor gambiertoxin-4B (98) is produced by the dinoflagellate *Gambierdiscus toxicus*.
Ciguatoxin-2 (95) and its epimer ciguatoxin-3 (96) were subsequently isolated by Lewis et al.\textsuperscript{121} The ciguatoxins are produced through bio-modifications of the gambiertoxins and are the primary agents responsible for ciguatera shellfish poisoning, a disorder that is characterised by a multitude of gastrointestinal and neurological symptoms.\textsuperscript{120}

The pectenotoxins are a family of polycyclic ether diarrhetic shellfish toxins that possess a spiroacetal ring system embedded in a macrocyclic lactone (Scheme 26). Pectenotoxin-1 (99) and pectenotoxin-2 (100) were the first to be isolated in 1985 from the digestive glands of \textit{Patinopecten yessoensis}.\textsuperscript{122}

Pectenotoxin-2 proved to be the metabolite of the dinoflagellate \textit{Dinophysis fortii}.\textsuperscript{123} It has been proposed that pectenotoxin-2 is the parent compound and all other members of the family are
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produced via hepato-pancreatic oxidation in the shellfish. Pectenotoxin-2 exhibits extremely potent activity against human lung, colon and breast cancer cell lines.

All the structurally interesting naturally occurring spiroacetal motifs can be accessed synthetically and the following section will provide an overview of the synthetic methods to access spiroacetals.

1.5 Strategies for the synthesis of 6,5-spiroacetal ring systems

There is a vast array of methods available for the synthesis of spiroacetal ring systems. Depending on the synthesis compatibility requirements, a range of various functionalised spiroacetal precursors can be accessed. This section comprises a brief overview of the most common methods with relevant examples.

1. Acid catalysed spiroacetalisation of a dihydroxyketone
2. Metal mediated intramolecular hydroxylation of internal alkynes
3. Ring closing metathesis
4. Cyclic enol ethers
5. Oxidative methods
6. Hetero Diels-Alder Reaction
7. Acetal and hemiacetal intramolecular conjugate Michael addition
8. Carbonyl cascade

1.5.1 Cyclisation of a dihydroxyketone

The cyclisation of dihydroxyketones is by far the most predominantly encountered strategy for the synthesis of spiroacetals and a multitude of methods to construct this motif are available in the literature. It is common to unmask the protected ketone or diol functionalities in the presence of acid to induce concomitant cyclisation.

Smith et al. successfully applied a kinetically controlled acid-catalysed strategy to furnish the C(7-19) tricyclic spiroacetal fragment of the lituanines. The highlight of the synthesis was the remarkably facile 6-endo regioselective cyclisation of vinyl epoxide by simple elution thorough silica gel to yield the pyran ring. Selective oxidation with manganese (IV) oxide, followed by a palladium (0)-catalyzed 1,4-reduction using tributyltin hydride as the stoichiometric reductant, proceeded to give the saturated ketone-diol precursor which when exposed to p-toluenesulfonic acid furnished the tricyclic spiroacetal (Scheme 27).
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Scheme 27: Synthesis of the tricyclic spiroacetal core 107 of the lituarines

1.5.2 Metal-mediated double intramolecular hydroxylation of internal alkynes

Transition metal catalysed spiroacetalisation\textsuperscript{126,127} has recently emerged as a versatile method for the synthesis of spiroacetal moieties of natural products as exemplified by (+)-broussonetine G (110),\textsuperscript{128} azaspiracid (111),\textsuperscript{129} (+)-spirolaxine methyl ether (15),\textsuperscript{130} ushikulide A (112)\textsuperscript{131} and spirastrellolide F methyl ester (113)\textsuperscript{132} (Scheme 28). Compared with the conventional approach to prepare spiroacetals \textit{via} acid catalysed cyclisation of dihydroxyketones, the use of an alkyne as a dehydrated surrogate for a ketone avoids some potential sensitivity issues associated with the use of highly functionalised ketones.\textsuperscript{129,130}

\textit{Reagents and conditions:} a) silica gel column, 90%; b) MnO\textsubscript{2}, THF 77%; c) Pd(PPh\textsubscript{3})\textsubscript{4} (cat.), Bu\textsubscript{3}SnH; d) 10 mol% TsOH•H\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 87%, 2 steps
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Scheme 28: Recent natural product synthesis utilising metal catalysed spiroacetalisation

The methodology of metal catalysed spiroacetalisation was pioneered by Utimoto in 1983. Substituted 5,5-115, 5,6-117 and 5,7-119 spiroacetals were synthesised in high yield by the palladium catalyzed cyclization of the respective diols 114, 116 and 118 onto the inbuilt internal alkynes (Scheme 29). In the case of diol 118, the desired 6,6-spiroacetal product was not observed and only the 7,5-spiroacetal 119 was reported in 60% yield (Scheme 29).
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Scheme 29: Selected spiroacetals made by Utimoto

The regioselectivity of hydroalkylation was investigated when Liu and De Brabander repeated the work shown above and obtained mixtures of regioisomers when competing 6-exo-dig and 7-endo-dig additions were possible. The cyclisation was found to favour 6-exo-dig cyclisation over 7-endo-dig particularly when a platinum catalyst was used (Scheme 30).

Scheme 30: Preference for 6-exo cyclisation

Fang et al. used regiocontrolled gold(I) chloride catalysed spiroacetalisation to assemble both C19 and C34 spiroacetal domains of okadaic acid (84). During the synthesis of the C19 domain, alkyne
was exposed to a catalytic amount of AuCl, acid co-catalyst was initially avoided to prevent removal of the anisylidene protecting group. However, the Lewis acidity of AuCl itself triggered partial removal of the protecting group, but the in situ liberated hydroxyl groups did not seem to affect the spiroacetalisation step. Subsequent addition of p-toluenesulfonic acid in methanol to the reaction mixture helped to completely remove the anisylidene group affording spiroacetal 123 (Scheme 31).

Scheme 31: Synthesis of the C19 unit of okadaic acid (84)

In the synthesis of the C34 unit of okadaic acid (84) addition of the lithium acetylide derived from alkyne 125 reacted with aldehyde 124 to afford a mixture of C32 epimers (anti:syn = 1.0:1.5) (Scheme 32). Each epimer was separated and treated with p-toluenesulfonic acid to afford 1,3-syn triol 128 and 1,3-anti triol 132 as spiroacetal precursors. Aponick et al. reported that the relative 1,3-stereochemistry of the propargylic and nucleophilic hydroxyls within triols similar to 126 and 127 influences the gold catalysed spiroacetalisation selectivity. Therefore both syn and anti triols were treated with AuCl. The 1,3-syn triol 128 gave a mixture of the desired 6,6-spiroacetal 129 and two 5,7 spiroacetals 130 and 131, epimeric at C33, in the ratio 7.6:1.6:1.0. In contrast, the 1,3-anti triol 132 gave the desired unsaturated 6,6-spiroacetal 129 as the exclusive product.
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Reagents and conditions: a) °BuLi, THF, -78 °C, 75%; b) TsOH•H₂O, MeOH, 95-98%; c) AuCl (10 mol%) 4 Å MS, THF, 0 °C 65-82%

Scheme 32: Synthesis of the C34 unit of okadaic acid (84)

These later results suggest a kinetic preference for the C30 hydroxyl of the 1,3-syn triol 126 versus the C30 hydroxyl of the 1,3-anti triol 127 to participate in initial oxy-auration of alkyne via 5-exo addition at C33 (Scheme 33). The 5-exo cyclisation of 126 would afford an enol ether gold intermediate 134, protiodeauration of which, followed by capture of the primary hydroxyl, would lead to spiroacetals 130 and 131. However an analogous 5-exo cyclisation of 127 would proceed via a more sterically hindered all syn C30-32 trisubstituted five membered ring transition state 137 (Scheme 33). Alternatively, the primary hydroxyl of 127 likely initiates its spiroacetalisation via a less hindered 6-exo oxy-auration. The original C32 propargylic hydroxyl group of 126 is retained in 130 and 131, whereas it is eliminated in 129. This may reflect a concerted loss of gold hydroxide from an α-hydroxy vinyl gold species 139, whereas an allylic hydroxy vinyl gold intermediate 134 undergoes simple protiodeauration. Isomerisation of the resulting exocyclic allenyl ether intermediate 140 into a
vinyl substituted oxacarbenium ion 141 followed by addition of the C30 hydroxyl would afford 129 (Scheme 33).

Scheme 33: Proposed mechanism for gold mediated spiroacetalisation

Most recently Furstner et al.\textsuperscript{132} have utilised a gold catalyst 143 in their total synthesis of spirastrellolide F methyl ester (113) (Scheme 34) to transform alkyne 142 into enol ether 144 which upon acid treatment yielded the desired 6,6-spiroacetal 145.
1.5.3 Ring closing metathesis

Ring closing metathesis (RCM) can provide a valuable method for the preparation of oxygen containing heterocyclic compounds. The method was first used in 1998 to prepare pyranose spiroacetal derivatives. The resulting endocyclic double bond which may or may not be a component of the natural product, is amenable to a wide variety of functional group transformations.

Recently Hsung et al. employed a cyclic ketal tethered ring-closing metathesis strategy to construct the 6,6-spiroacetal core of (+)-aigialospirol in the total synthesis of the natural product.

When cyclic ketal 146 was exposed to 12.5 mol% of Grubb's first generation catalyst, RCM proceeded smoothly to give spiroacetal 147. However, NOE experiments revealed that the stereochemistry at the C6' spiroacetal centre was opposite to the one required by the natural product. Fortuitously removal of the acetonide group under acidic conditions, afforded completely epimerised...
C6’ stereocentre with the correct configuration, as a consequence of the hydrogen bonding between C4’-OH and the spiroacetal oxygen in 149 (Scheme 35).

**Scheme 35:** Cyclic ketal-tethered RCM and C6’ epimerisation

1.5.4 Cyclic enol ethers

Protonation of enol ethers results in the formation of an oxonium ion. In the presence of an alcohol, intramolecular cyclization can take place to form a spiroacetal. An unusual spiroacetalisation strategy in which a hydroxyalkene serves as a precursor to a cyclic enol was used in the synthesis of the ABCD trioxadispiroacetal subunit of azaspiracid-1 (Scheme 36) as reported by Li et al.137 Alkene 150 underwent iodoetherification to afford iodide 151. Elimination of the iodide 151 to the corresponding enol ether was followed by hydrolysis of the methyl acetal affording a free hemiacetal which underwent spirocyclisation with the oxonium ion 152 formed in situ to afford the desired bis-spiroacetal 153 (Scheme 36).
1.5.5 Oxidative techniques

1.5.5.1 Intramolecular hydrogen abstraction

Intramolecular hydrogen abstraction generates an alkoxy radical in hydroxyl substituted cyclic ethers thus enabling spiroacetalisation. Suarez et al. were the first to demonstrate this methodology in 1984. When iodosobenzene diacetate, PhI(OAc)2 is used in the presence of iodine, the reaction is called the Suarez oxidation. There is an extensive review on the synthesis of natural products containing spiroacetals using this method by Brimble et al.

The proposed mechanism for the radical cyclisation is represented below (Scheme 37). It involves “hypoiodite reaction” and the homolytic cleavage of alkyl hypoiodite species 155 and 159 which are generated in situ by reaction of alcohols 154 and 158 with PhI(OAc)2.
The first synthesis of a bis-spiroacetal ring system using a photochemical free radical cyclisation involved assembly of the unsaturated tricyclic core 164 of salinomycin by Baker and Brimble in 1985.\textsuperscript{141} Treatment of silyl ether 162 with CSA resulted in simultaneous silyl ether deprotection and acetal cyclisation to afford unsaturated spiroacetal 163. Alkoxy radical cyclisation on the unsaturated 6,6-spiroacetal 163 afforded bis-spiroacetal 164 as a single diastereomer, the conformation of which was stabilised by three anomeric effects (Scheme 38).

Reagents and conditions: a) CSA, CH$_2$Cl$_2$; b) I$_2$, PhI(OAc)$_2$, hv

Figure 38: Baker-Brimble’s synthesis of the bis-spiroacetal 164 unit of salinomycin

1.5.5.2 Furan oxidation

The Achmatowicz oxidative rearrangement of furan carbinols to dihydropyran hemiacetals has been used for the synthesis of 6,5-spiroacetals as reported by Balachari \textit{et al.}\textsuperscript{142} in their synthesis of the spiroacetal core of papulacandin-D (43) (Scheme 39). The key furyl alcohol 165 underwent Achmatowicz oxidative ring expansion followed by cyclisation of the resulting hemiacetal to afford enone 169. Reduction of enone 169 and protection with tert-butyldimethylsilyl chloride gave 170. Dihydroxylation using osmium tetroxide and N-methylmorpholine N-oxide followed by global deprotection provided the spiroacetal core 172 of papulacandin D (43) (Scheme 39).
Reagents and conditions: a) NBS, H\textsubscript{2}O, NaHCO\textsubscript{3} then dil. HCl, 38%; b) aq. NaBH\textsubscript{4}, 88%; c) TBDMSI, DMF, 64%; d) OsO\textsubscript{4}, NMO, t-BuOH/H\textsubscript{2}O, 75 \degree C, 20 h, 69%; e) DIBALH, 93%; f) TBAF, 93%

Scheme 39: Synthesis of the spiroacetal core 172 of papulacandin D (43)

1.5.5.3 Oxidative ring expansion

Baeyer-Villiger oxidative ring expansion has been used for the synthesis of oxaspirolactone (178) by Bueno et al.\textsuperscript{143} The photochemical [2+2] addition of chromium carbe complex 173 to a chiral alkene 174 afforded the spirofused cyclobutanone 175. Baeyer-Villiger oxidation followed by reductive elimination of the oxazolidinone provided butenolide 177, which upon hydrogenation afforded the desired oxaspirolactone (178)(Scheme 40).
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**Scheme 40:** Bayer-Villiger methodology in the synthesis of a 6,5 spiroacetal 178

1.5.6 Hetero Diels-Alder Methodology

The construction of 6,5-spiroacetal ring systems via catalytic enantioselective hetero Diels-Alder reaction has been investigated by Jørgensen et al. The methodology enables assembly of high complexity in a single step with control of up to three stereocentres simultaneously. Reaction of the keto ester 179 with electron rich methylene furan 180 in the presence of chiral bisoxazoline-Lewis acid copper (II) catalyst 181 afforded the corresponding spiroacetal carbohydrate derivatives 182 and 183 with considerable endo-diastereoselectivity (Scheme 41).

**Scheme 41:** Enantioselective hetero Diels-Alder reaction for the synthesis of 6,5-spiroacetal 183

1.5.7 Carbonyl Cascade Reactions

The carbonyl cascade strategy involves a carbonyl compound being attacked by a nucleophilic oxygen, thus forming the spiro carbon centre. The important difference during the carbonyl cascade...
reaction is that the oxygen of the carbonyl compound then acts as a nucleophile, contributing the second oxygen atom to the spiroacetal ring system upon cyclization with an electrophilic acceptor. Ruveda et al.\textsuperscript{145} used this strategy to form the 6,5-spiroacetal core of methyl grindelistrictate (188) (Scheme 42). Hydrolysis of the ester 184 with concomitant oxidative cleavage using sodium periodate provided aldehyde 186 which spontaneously cyclised in a cascade reaction to furnish hemiacetal 187. Methylation of the carboxylic acid using diazomethane, followed by oxidation of the hemiacetal with PCC yielded methyl grindelistrictate (188).

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {184};
\node (b) at (3,0) {185};
\node (c) at (6,0) {186};
\node (d) at (0,-3) {187};
\node (e) at (3,-3) {Methyl grindelistrictate (188)};

\draw[->] (a) -- node[above] {a} (b);
\draw[->] (b) -- (c);
\draw[->] (d) -- node[above] {b,c} (e);
\end{tikzpicture}
\end{center}

\textit{Reagents and conditions}: a) NaIO$_4$, K$_2$CO$_3$, aq. tBuOH; b) CH$_2$N$_2$, Et$_2$O; c) PCC, Al$_2$O$_3$, 75% 3 steps

\textbf{Scheme 42:} Construction of the 6,5-spiroacetal of methyl grindelistrictate (188) via carbonyl cascade

\subsection*{1.6 Previous reported syntheses of spirolaxine methyl ether (15)}

\subsection*{1.6.1 The first total synthesis of spirolaxine methyl ether (15)}

The first enantioselective total synthesis of spirolaxine methyl ether (15) was achieved by Robinson and Brimble.\textsuperscript{146} At the outset of the work it was necessary to consider the stereochemistry of the four stereogenic centres, the relative and absolute stereochemistry of which had not been established at that point. It was anticipated that the 6,5-spiroacetal would adopt the anomerically stabilized \textit{bis}-axial conformation and that the polymethylene side chain at C7" would occupy the thermodynamically preferred equatorial position. The stereochemistry of the remaining two stereo centres could not be predicted. Therefore a convergent and flexible synthetic strategy was adopted that would allow the stereochemistry at the C3 position of the phthalide and C2" position of the spiroacetal ring to be
varied. The retrosynthetic plan involved heterocycle activated Julia-Kocienski olefination of phthalide aldehyde 189 with sulfonyl spiroacetal 190. Phthalide aldehyde was made available via lactonisation of alcohol 191. Both enantiomers of alcohol 191 were accessed via asymmetric allylation, hence both enantiomers of phthalide aldehyde 189 were available. Sulfonyl spiroacetal 190 was prepared via acid-catalysed cyclisation of protected dihydroxyketone 192 which in turn was made by addition of lithium acetylide 194 to aldehyde 193. Both enantiomers of the acetylene 194 are commercially available from alcohol 195, thus facilitating the synthesis of the spiroacetal ring system with either (R) or (S) stereochemistry at the C2′ position. In turn aldehyde 193 was accessible in both enantiomeric forms from the chiral pool reagent (S)-aspartic acid (196) (Scheme 43).

Scheme 43: Retrosynthetic analysis of spirolaxine methyl ether (15) by Robinson and Brimble146

Their study initially focused on the synthesis of the (3R)-phthalide fragment 200. Accordingly, 2,4-dimethoxybenzoic acid (197) was treated with thionyl chloride and diethylamine to give benzamide 198. Directed ortho-lithiation of the benzamide 198 with tert-butyl lithium followed by the addition of
dimethylformamide afforded aldehyde 199. It was discovered that the asymmetric allylation of the benzaldehyde 199 using the allylboron reagent derived from (-)-B-allyldiisopinocamphylborane failed to take place. Allylboration of bromobenzaldehyde 202 was then investigated where the bromide could later be converted to an amide group The bromobenzaldehyde 202 was formed by reduction of 3,5-dimethoxybenzoic acid (201) with lithium aluminium hydride, followed by regioselective bromination using NBS and Dess-Martin oxidation. However allylboration of the bromobenzaldehyde 202 using (-)-B-allyldiisopinocampheyborane only afforded the benzylic alcohol 203 in 30% e.e. Catalytic asymmetric allylation of the bromobenzaldehyde 202 following a procedure reported by Carreira et al. 147 using allyltrimethylsilane in the presence of catalyst generated from titanium tetrafluoride and (R)-BINOL afforded the desired (R)-benzylic alcohol 203 with a modest 51% e.e (Scheme 44). At this stage, they postulated that the steric bulkiness of either the diethylamide or bromide substituents was preventing the formation of the desired benzylic alcohol with high enantioselectivity. Hence a new route was proposed whereby the asymmetric allylation occurred prior to the functionalisation at the ortho position which was causing the problem.

\[
\begin{align*}
&\text{Reagents and conditions: a) SOCl}_2, \text{reflux, 2 h then Et}_2\text{NH, CH}_2\text{Cl}_2, 0^\circ\text{C, 93%; b) } \text{i}^\text{BuLi}, -78^\circ\text{C, 0.25 h then DMF, 83%} \\
&\text{Reagents and conditions: a) LiAIH}_4, \text{THF, 0^\circ\text{C, to r.t. 12 h, 99%; b) NBS, CHCl}_3, \text{reflux, 12 h, 70%; c) Dess-Martin perodinane, py., CH}_2\text{Cl}_2, 96%; d) } (-)-\text{Ipc}_2\text{B(allyl), Et}_2\text{O, -78^\circ\text{C to r.t., 45%, 30% e.e.; e) TIF}_4 (10 mol%), R-} \\
&\text{BINOL (20 mol%), MeCN, 0^\circ\text{C, 0.25 h then CH}_2\text{Cl}_2, allyltrimethylsilane, 0^\circ\text{C, 1.5 h, 54%, 51% e.e.} \\
&\text{Scheme 44: First attempted synthesis of the phthalide unit of spirolaxine methyl ether by Brimble and Robinson}^{70}
\end{align*}
\]
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TiF₄-(R)-BINOL-derived Lewis acid-catalysed addition of allyltrimethylsilane to 3,5-dimethoxybenzaldehyde (204) provided homoallylic alcohol 205 in 76% yield and 86% e.e. Regioselective bromination of the aromatic ring using NBS afforded bromide 203 in preparation for the subsequent installation of the phthalide functionality at that position. Attempts to effect direct carboxylation of bromide 203 proved unsuccessful. However Castedo et al. have prepared a number of phthalides via internal trapping of carbamates derived from benzylic alcohols. Following this precedent alcohol 203 was converted to diethyl carbamate 206 by treatment with sodium hydride and diethyl carbamoyl chloride. Lithium-halogen exchange with tert-butyl lithium provided a mixture of the desired phthalide 200 and diethylamide 207. Treatment of this mixture with p-toluenesulfonic acid furnished the desired phthalide. Hydroboration then afforded the desired phthalide alcohol 208 which underwent Dess-Martin periodinane oxidation to give the desired phthalide aldehyde 189 (Scheme 45).

Reagents and conditions: a) TiF₄, (+)-BINOL, allyltrimethylsilane, CH₂Cl₂ : MeCN (97:3), -20 °C, 72 h, 78%, 86% e.e.; b) NBS, CHCl₃, reflux, 88%; c) NaH, THF, 0 °C then N,N-diethylcarbamoyl chloride, 82%; d) tBuLi, THF, -78 °C, 45 min; e) pTSA, 20 °C, 12 h, 76%, 2 steps; f) BH₃ • SMe₂, THF, 0 °C then NaOH, H₂O₂, 56%; g) DMP, CH₂Cl₂, 0 °C to r.t. 4 h, 85%.

Scheme 45: Second successful synthesis of the phthalide unit 189 of spirolaxine methyl ether (15) by Robinson and Brimble.
With the synthesis of phthalide aldehyde 189 in hand, attention next focused on synthesis of the spiroacetal fragment from (S)-aspartic acid (196). Bromide 209 was prepared by treating (S)-aspartic acid (196) with sodium nitrite in the presence of potassium bromide. The reaction proceeded with overall retention of stereochemistry and involved a double inversion sequence via the unstable α-lactone 215. Reduction of the two carboxylic acid groups with borane dimethylsulfide complex afforded bromodiol 210. The (R)-epoxide 211 was then prepared by one-pot intramolecular cyclisation and subsequent protection of the primary alcohol. Subsequent allylation of epoxide 211 proved difficult when allylmagnesium bromide was used, leading to the formation of an inseparable bromohydrin product. Treatment with allylmagnesium bromide in the presence of copper iodide or CuBr-SMe₂ complex also led to exclusive formation of bromohydrin 213. Finally when the higher-order diallylcyanocuprate prepared from lithium chloride, copper (I) cyanide and allyltributyltin was used the desired alcohol 212 was obtained in excellent yield (Scheme 46).

![Scheme 46: Synthesis of the spiroacetal unit of spirolaxine methyl ether 15 by Robinson and Brimble]

After silyl protection of the secondary alcohol 212, hydroboration of the alkene afforded the primary alcohol 217 which was successfully oxidised to aldehyde 193 using Dess-Martin periodinane. Aldehyde 193 was coupled with acetylene 219 in the presence of 'BuLi and lithium bromide while the
acetylene 219 itself was derived from silyl protection of the commercially available alcohol 218.

Oxidation of the acetylenic alcohol 220 using N-methylmorpholine-N-oxide and tetrapropylammonium perruthenate afforded the corresponding ynone 221 which was hydrogenated in the presence of Adam’s catalyst to furnish the protected dihydroxy ketone 222. Selective removal of the tert-butylidemethylsilyl ethers with camphorsulfonic acid and simultaneous cyclisation afforded the spiroacetal 223. Finally removal of the tert-butylidiphenylsilyl ether using tetra-n-butylammonium fluoride provided spiroacetal alcohol 224 (Scheme 47).

Scheme 47: Synthesis of the spiroacetal unit of spirolaxine methyl ether (15) by Robinson and Brimble70

Next coupling of the phthalide and spiroacetal units was first attempted via Wittig reaction between a phthalide aldehyde 189 and ylide 227, generated from a spiroacetal phosphonium salt. Unfortunately, formation of the spiroacetal phosphonium salt proved impossible even though the phthalide aldehyde 189 could be generated. The alternative strategy where the Wittig reaction is performed between a spiroacetal aldehyde 226 and a phthalide ylide 225 was unsuccessful as generation of the phthalide ylide 225 was not observed (Scheme 48).
Scheme 48: Attempts of coupling spiroacetal 208 and phthalide fragments 224, in the synthesis of spirolaxine methyl ether (15) by Robinson and Brimble.

Julia-Kocienski olefination was next tried to couple the phthalide and spiroacetal fragments (Scheme 49). Spiroacetal sulfone 229 was prepared by treating alcohol 224 with 2-mercaptobenzothiazole under Mitsunobu conditions, to give sulfide 228 which in turn was oxidised with mCPBA to the sulfone 229. Gratifyingly, when sulfone 229 was metallated with LDA and treated with phthalide aldehyde 189, olefin 230 was afforded. The alkene was smoothly hydrogenated over Adam's catalyst to afford the unnatural (2''S) diastereomer of spirolaxine methyl ether (21). The unnatural (2''S) stereochemistry was determined when NMR data was compared to the natural product. Due to the flexible nature of the synthesis the natural (2''R) diastereomer was also carried out simply by using the (R) enantiomer of acetylene 218 (Scheme 47). The unnatural (2''S) diastereomer was found to be four times more active against H. Pylori than the natural (2''R) diastereomer (Scheme 6).
Reagents and conditions: a) DEAD, PPh$_3$, 2-mercaptobenzothiazole; b) mCPBA, CH$_2$Cl$_2$, 51% 2 steps; c) LDA, THF, -78 °C; d) PtO$_2$, H$_2$, THF, 2 h, 40% 2 steps

Scheme 49: Successful first total synthesis of (2''S)-spirolaxine methyl ether 21 by Robinson and Brimble $^70$

1.6.2 Second total synthesis of spirolaxine methyl ether (15)

In 2006 Dallavalle et al.$^{149}$ reported the second total synthesis of spirolaxine methyl ether (15). Their retrosynthetic approach involved a condensation between a phosphonate 231 and aldehyde 232 using a Horner-Wadsworth-Emmons reaction. The spiroacetal was formed by oxidative cyclisation of a hydroxyalkyl-substituted tetrahydropyran 234. Tetrahydropyran 234 itself was synthesised by a Prins cyclisation between an unsaturated alcohol 235 and the hemiacetal 236 obtained by reduction of commercially available (R)-γ-valerolactone 237. The phosphonate 231 was prepared from dimethoxybenzoic acid 233 (Scheme 50).
Since the spiroacetal was assigned (R) configuration at C7'', the Prins reaction was carried out using enantiopure homoallylic (R)-alcohol 242, that bore a substituent to allow the coupling with the phthalide moiety. The asymmetric synthesis of alcohol 242 was carried out starting with monoprotection of 1,6-hexanediol 238, followed by TEMPO oxidation to aldehyde 240 which was treated with B-allyldisopinocamphenylborane 241 to afford the chiral alcohol 240. The C-2'' stereocentre was obtained from chiral lactol 236 partner. Hemiacetal 236 was obtained by reduction of commercially available (R)-γ-valerolactone (237). The Prins reaction was performed in the presence of titanium tetrachloride to afford the chlorotetrahydropyran 243. Reductive dechlorination using sodium borohydride, gave the tetrahydropyran 234. Protection of primary alcohol 234 followed by oxidative cyclisation mediated by mercuric oxide, iodine and light gave the desired spiroacetal moiety 245. PMB deprotection and TEMPO oxidation yielded the aldehyde precursor 232, ready for coupling to the phthalide unit via Horner-Wadsworth-Emmons reaction (Scheme 51).
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Reagents and conditions: a) TBDMSCl, Et$_3$N, DMAP, THF, r.t., 18 h, 57%; b) NaOCl, polymer-supported TEMPO, KBr, CH$_2$Cl$_2$, r.t., 6 h, 100%; c) -78 °C, 1 h then r.t., NaOH, H$_2$O$_2$, 1 h, reflux, 82%; d) TiCl$_4$, CH$_2$Cl$_2$, -78 °C, 4 h then -20 °C, 1 h, 63%; e) NaBH$_4$, DMSO, 130 °C, 8 h, 96%; f) PMBCl, NaH, DMF, r.t., 3 days, 59%; g) HgO, I$_2$, hv, cyclohexane, 9 h, 68%; h) CAN, CH$_3$CN/H$_2$O, r.t., 2 h, 68%; i) TEMPO, KBr, NaOCl, 3 h, 100%

Scheme 51: Synthesis of the spiroacetal unit of spirolaxine methyl ether (15) by Dallavalle et al.$^{149}$

The phthalide unit was obtained by converting 2,4-dimethoxybenzoic acid (197) into benzamide 247 upon treatment with thionyl chloride and diethylamine followed by formylation with DMF. The resulting formylbenzamide 247 was treated with tert-butyldimethylsilyl chloride and triethylphosphite to afford intermediate 248 which, upon desilylation with methanesulfonic acid, cyclised to the desired phosphonate 231. The Horner-Wadsworth-Emmons reaction between phthalide phosphonate 231 and spiroacetal-aldehyde 232 afforded the desired alkene 249. Hydrogenation of the double bond over palladium on charcoal led to a mixture of two isomers from which spirolaxine methyl ether (15) was isolated by preparative HPLC (Scheme 52).
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**Scheme 52:** Successful synthesis of spirolaxine methyl ether (15) by Dallavalle et al.\(^{149}\)

1.6.3 Third total synthesis of spirolaxine methyl ether (15)

The third total synthesis of spirolaxine methyl ether was completed by Trost and Weiss.\(^{130}\) Retrosynthetically they envisaged that the spiroacetal moiety could be formed through a transition metal catalysed cyclization of alkyne diol 251. Furthermore, a series of three alkyne additions were used to stitch the carbon framework together while establishing both the absolute and relative stereochemistry. The stereochemistry of the spiroacetal fragment was derived from R-(+)
propylene oxide 253 and a catalyst-controlled diastereoselective alkyne addition to \(\alpha,\beta\)-unsaturated aldehyde 254. The phthalide portion was accessed via enantioselective alkynylation of 3,5-dimethoxybenzaldehyde (204). Both subunits were obtained using stereocontrolled acetylide additions to unsaturated aldehydes as the key step (Scheme 53).
The synthesis began with enantioselective addition of terminal alkyne 258 to 3,5-dimethoxybenzaldehyde (204) in the presence of the commercially available (S,S)-ProPhenol ligand 259 which gave the chiral propargylic alcohol 260 in high yield and e.e.\(^{150}\) Hydrogenation of the alkyne over Adam’s catalyst followed by bromination with NBS, gave the desired bromo alcohol 261. Lithium-halogen exchange and CO\(_2\) trapping followed by acidic work up yielded the desired phthalide alcohol 262 with simultaneous silyl group cleavage. Oxidation of the primary alcohol, followed by Wittig olefination with (triphenylphosphoranylidene)acetaldehyde gave the desired enal 254 (Scheme 54).
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Reagents and conditions: a) Me$_2$Zn, PhMe; b) H$_2$, PtO$_2$, EtOAc, 100%; c) NBS, CHCl$_3$, 99%; d) $^4$BuLi, THF, -78 °C then CO$_2$, HCl/H$_2$O, 90%; e) TEMPO (5 mol%), bis(acetoxy)iodobenzene, 84%; f) (triphenylphosphoranylidene) acetaldehyde, PhH, 80 °C, 56%

Scheme 54: Synthesis of the phthalide unit 262 of spirolaxine methyl ether (15) by Trost and Weiss$^{130}$

The spiroacetal was formed late in the synthesis (Scheme 55). A second (S,S)-ProPhenol catalysed asymmetric alkynylation of enal 254 gave the desired propargylic alcohol 264. Silyl protection, global reduction to the fully saturated chain and acid hydrolysis of the diethyl acetal furnished the protected alkoxy aldehyde 265. Homologation of aldehyde 265 to terminal alkyne 266 was accomplished using the mild Ohira-Bestmann procedure. Addition of alkyne 266 to (R)-propylene oxide (253) assisted by Lewis acid, and subsequent treatment with HCl, removed the silyl group to provide diol 251. Finally, spiroacetalisation of alkyne diol 251 was performed in the presence of a palladium catalyst to yield spirolaxine methyl ether (15).
Reagents and conditions: a) Me₂Zn, (S,S)-ProPhenol, PhMe, 53%; b) TBDMSCl, imid., CH₂Cl₂, 71%; c) H₂, PtO₂, 91%; d) PPTS, wet acetone, 98%; e) Ohira-Bestmann reagent, K₂CO₃, MeOH, 75%; f) nBuLi, BF₃·Et₂O; g) HCl/H₂O, 51% (2 steps); h) [PdCl₂(PhCN)₂], THF/CH₂CN 3:1, 79%

Scheme 55: Synthesis of spirolaxine methyl ether (15) by Trost and Weiss³³⁰

The mechanistic rationale for the metal catalysed spiroacetalisation was investigated by de Brabander et al.¹²⁶ Initial coordination of the alkynol 267 to the Pd²⁺ activates it for intramolecular attack by the alcohol to yield the endo adduct 269. Deprotonation followed by reprotonation would then deliver the transient palladinated oxocarbenium species (270) onto which the alcohol cyclises to yield the spiroacetal 271 (Scheme 56).
1.6.4 Fourth total synthesis of spirolaxine methyl ether (15)

Phillips et al.\textsuperscript{51} used a Suzuki coupling between a borane-phthalide 272 and a bromo-spiroacetal 273 to form spirolaxine methyl ether (15). The phthalide moiety itself was obtained by a similar route to the one employed by Brimble and Robinson (Scheme 45).\textsuperscript{146} The spiroacetal was derived from a cyclopropanol 275 which was formed by Kulinkovich reaction between (R)-\(\gamma\)-valerolactone (237) and the readily available olefin 276 (Scheme 57).
**Scheme 57**: Retrosynthetic analysis of spirolaxine methyl ether (15) by Phillips and Keaton\textsuperscript{151}

Kulinkovich reaction of readily available olefin 276 with commercially available (R)-γ-valerolactone (237) afforded cyclopropanol 275 which was exposed to ferric nitrate and tributyltin hydride to give the desired ketone 274. Deprotection and simultaneous cyclisation yielded the spiroacetal alcohol 277. Alcohol 277 was then converted to primary bromide 273 using an Appel reaction. Treatment with 9-BBN followed by a sp\textsuperscript{3}-sp\textsuperscript{3} Suzuki coupling with spiroacetal bromide 273 afforded spirolaxine methyl ether (15) (Scheme 58).
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Reagents and conditions: a) c-C₆H₁₁MgBr, Ti(PrO)₄, PhMe, 92%; b) Fe(NO₃)₃, Bu₃SnH, DMF, 75%; c) HF, MeCN, 89%; d) NBS, PPh₃, CH₂Cl₂, 99%; e) (lpc)₂B(allyl), Et₂O, 75%; f) NBS, CHCl₃, 80%; g) NaH, Et₂NCOCl, THF, 82%; h) tBuLi, THF then p-TsOH, 79%; i) 9-BBN, THF; j) CsCO₃, Pd(OAc)₂, (5 mol%), Cy₃P (10 mol%), dioxane, 40 °C, 79%

Scheme 58: Total synthesis of spirolaxine methyl ether (15) by Phillips and Keaton

1.6.5 Fifth total synthesis of spirolaxine methyl ether (15)

The retrosynthetic analysis of spirolaxine methyl ether (15) by Yadav et al. is shown in Scheme 59. Following the example of Robinson and Brimble a heterocycle activated modified Julia-Kocienski olefination of phthalide aldehyde 189 with sulfonil spiroacetal 278 was used as the key step of the synthesis. Phthalide-aldehyde 189 was prepared via Alder-Rickert reaction between 1,4-unconjugated diene 279 and long-chain acetylenic dienophile 280. Sulfonil spiroacetal 278 was prepared via acid-catalyzed cyclization of protected dihydroxyketone 281, which in itself was synthesized starting from benzyl protected 1,5-pentanediol 284.
Phthalide-aldehyde 189 (Scheme 60) was synthesised from monobenzyl ether 282, which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester 285. Reduction of the ester 285 followed by Sharpless asymmetric epoxidation furnished epoxy alcohol 286. Reaction of epoxy-alcohol 286 with triphenylphosphine in carbon tetrachloride in the presence of NaHCO$_3$ gave chloride 287 which upon base-induced dehydrohalogenation, yielded alkynol 288. $^{153}$ Treatment of the silyl-ether protected alkyne 289 with butyl lithium followed by addition of methyl chloroformate gave a long-chain acetylenic ester 280. $^{154}$ Alder-Rickert reaction of diene 279 with acetylenic dienophile 280 afforded the aromatic precursor 290. Deprotection of silyl ether 290 yielded the benzyl-protected phthalide-alcohol which on debenzylation followed by oxidation with Dess-Martin periodinane gave the phthalide-aldehyde 189.
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Scheme 60: Synthesis of the phthalide unit 189 by Yadav et al.\textsuperscript{152}

Spiroacetal alcohol 277 was obtained from monoprotected alcohol 284 in nine steps using Sharpless asymmetric epoxidation and acid catalysed spiroacetalsisation as the key steps. Spiroacetal alcohol 277 was converted to sulfone 278 via coupling with 1-phenyltetrazole-5-thiol followed by oxidation with \textit{m}-CPBA. The key Julia-Kocienski olefination with aldehyde 189 and sulfone 278 afforded alkene 298 which upon reduction afforded spirolaxine methyl ether (15) (Scheme 61).
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1.6.6 Formal synthesis of spirolaxine methyl ether (15)

Recently Singh and Argade\textsuperscript{155} completed a formal synthesis of spirolaxine methyl ether (15). They opted to prepare the same common spiroacetal fragment 277 as Robinson and Brimble.\textsuperscript{146} Complementary to the Trost and Weiss alkyne strategy,\textsuperscript{130} the synthesis of the spiroacetal system 277 also began with TMS-protected acetylene 301. Regioselective ring opening of an enantiomerically pure (R)-epoxide 299 (derived from Jacobsen Hydrolytic Kinetic Resolution) with trimethylsilylacetylide 300 provided the required alkynol 302 (Scheme 62). Chemoselective O-benzyl protection of the resultant secondary alcohol 301 directly furnished the required acetylene derivative 302 which was condensed with the enantiomerically pure TBDPS-protected aldehyde 303 to yield
alcohol 305. Oxidation afforded the required alkyne 307. The chemoselective alkyne reduction of 307 was attempted under very mild catalytic hydrogenation conditions to provide the desired product 309. TBDPS deprotection of the corresponding dihydroxyketone 309 afforded the stable secondary alcohol 310. Dihydroxyketone obtained by catalytic hydrogenolysis of the two O-benzyl groups underwent concomitant spiroacetalization to furnish the common spiroacetal fragment 277. After initial work it was then realised that the spiroacetal 277 could be accessed directly from ketone 308 in which the R group was a benzyl group (Scheme 62).

![Scheme 62: Synthesis of spiroacetal fragment 277 via two partially separate routes](image)

**Reagents and conditions:** a) BF_3·OEt_2, nBuLi, THF, -78 °C, 1 h, 89%; b) NaH, BnBr, DMF, 4 h, 77%; c) nBuLi, THF, -78 °C, 1 h; d) TEMPO, PhI(OAc)_2, CH_2Cl_2; e) H_2, Pd/C, EtOAc, 1 h, 100%; f) TBAF, THF, 6 h, 92%; g) H_2, Pd/C, MeOH, 60 psi, 8 h 85%

Finally reaction of the acetylide 302 derived from 299 with commercially available enantiopure (R)-γ-valerolactone (237) provided alkynone 308 which upon subjecting to the catalytic hydrogenation conditions, directly furnished the spiroacetal 277. Thus, starting from epoxide 299, the desired (+)-spiroacetal 277 was obtained in just four steps (Scheme 63).
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Reagents and conditions: nBuLi, BF$_3$•OEt$_2$, THF, -78 °C, 1h, 82%; b) H$_2$, Pd/C, MeOH, 60 psi, 8 h, 87%

Scheme 63: Synthesis of spiroacetal fragment 277 via (R)-γ-valerolactone (237)

1.7 Summary of previous syntheses of spirolaxine methyl ether (XX)

To date there have been five enantioselective total syntheses and one formal synthesis of spirolaxine methyl ether (15) (Scheme 64).

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Type of synthesis</th>
<th>Total number of steps</th>
<th>Longest linear sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Robinson and Brimble$^{70,146}$</td>
<td>Convergent</td>
<td>23</td>
<td>16 steps</td>
</tr>
<tr>
<td>2006</td>
<td>Dallavalle$^{149}$ et al.</td>
<td>Diastereoselective</td>
<td>15</td>
<td>12 steps</td>
</tr>
<tr>
<td>2007</td>
<td>Trost and Weiss$^{130}$</td>
<td>Linear</td>
<td>15</td>
<td>14 steps</td>
</tr>
<tr>
<td>2007</td>
<td>Keaton and Phillips$^{151}$</td>
<td>Convergent</td>
<td>13</td>
<td>5 steps</td>
</tr>
<tr>
<td>2010</td>
<td>Yadav et al.$^{152}$</td>
<td>Convergent</td>
<td>22</td>
<td>13 steps</td>
</tr>
<tr>
<td>2011</td>
<td>Singh and Argade$^{155}$</td>
<td>Formal</td>
<td>11</td>
<td>4 steps</td>
</tr>
</tbody>
</table>

Scheme 64: Summary of previous syntheses of spirolaxine methyl ether (15)

Scheme 65 illustrates the key intermediates and steps in each synthesis of spirolaxine methyl ether (15):

Robinson and Brimble$^{70}$ synthesised the phthalide unit 189 starting with 3,5-dimethoxybenzaldehyde (204) in six steps and the spiroacetal coupling partner 190 in 14 steps starting from (S)-aspartic acid (196). Julia-Kocienski olefination was used as the key step to join the two fragments.

Dallavalle et al.$^{149}$ synthesised the phthalide unit 231 starting with 2,4-dimethoxybenzoic acid (197) in three steps. The spiroacetal coupling partner 246 was synthesised in eight steps from 1,6-hexanediol (238) with a Prins reaction between alcohol 242 and chiral pool derived lactol 236 as the key step. The two fragments were joined via a Horner Wadsworth-Emmons reaction.
Trost and Weiss\textsuperscript{130} used a series of three alkyne additions to stitch the carbon framework together, while establishing both the absolute and relative stereochemistry. They completed spirolaxine methyl ether (15) through a transition metal catalysed cyclisation of alkyne diol 251.

Keaton and Phillips\textsuperscript{151} synthesised the spiroacetal bromide 273 in four steps from cyclopropanol 275 which was formed by Kulinkovich reaction between ($R$)-$\gamma$-valerolactone (237) and readily available olefin 276. The phthalide alkene 200 was derived from the procedure of Robinson and Brimble\textsuperscript{70} and treated with 9-BBN to give the key coupling partner 272. The key step was a $sp^3$-$sp^3$ Suzuki coupling to stitch the two fragments.

Yadav et al.\textsuperscript{152} synthesised the phthalide aldehyde 189 from monobenzyl ether 282 in nine steps using the Alder-Rickert reaction between diene 279 and acetylene 280 as the key step. The spiroacetal sulfone 278 was synthesised in 11 steps from monoprotected alcohol 284. The fragments were joined via a modified Julia-Kocienski olefination.

Singh and Argade\textsuperscript{155} completed a formal synthesis of spirolaxine methyl ether (15) by accessing the common spiroacetal intermediate 277 of Robinson and Brimble\textsuperscript{146} in four steps starting from epoxide 299 (derived from Jacobsen Hydrolytic Kinetic Resolution).\textsuperscript{156}
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Scheme 65: Summary of previous syntheses of spirolaxine methyl ether (15)
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1.8 CJ-12,954 (13) and CJ-13,014 (12)

1.8.1 Synthesis of CJ-12,954 (13) and CJ-13,014 (12)

CJ-12,954 (13) and its diastereoisomer CJ-13,014 (12) are phthalide containing compounds isolated in 1997 by Dekker et al.\(^{68}\) from the basidiomycete Phanerochaete velutina CL6387 (Scheme 5). These two compounds are structurally related to spirolaxine methyl ether (15) in that they contain a 3,5-dimethoxyphthalide unit linked through a six carbon polymethylene chain to a 5,5-spiroacetal unit. They also exhibit potent, selective anti-\(H.\) pylori activity (Scheme 6). The first total synthesis of ent-CJ-12,954 (13) and ent-CJ-13,014 (12) was reported by Brimble and Bryant in 2006.\(^{157}\) The synthesis enabled assignment of the absolute configuration of the natural products CJ-12,954 (13) and CJ-13,014 (12) as 3\(R\),5\(R\),7\(R\) and 3\(R\),2\(R\),5\(R\),7\(R\), respectively.

They predicted that the control of the stereochemistry of the spirocentre in the 5,5-ring system would be more difficult to control hence their efforts were directed to the synthesis of a 1:1 mixture of heterocycle-activated sulfones 312 and 313 in preparation for union with (3\(S\))-phthalide aldehyde 311 using a modified Julia-Kocienski olefination (Scheme 66).

The synthesis of the phthalide unit hinged on synthesis of alcohol 315 via CBS-reduction of ketone 314. Alcohol 315 underwent regioselective bromination to bromide 316 and conversion to carbamate 317. Carbamate 317 was then transformed to phthalide aldehyde 311 via intramolecular acylation and hydroboration-oxidation of the olefin (Scheme 67).
Reagents and conditions: a) (R)-Me-CBS-oxazaborolidine, BH$_3$-SMe$_2$, 2 h, 92%, 94% e.e.; b) NBS, NH$_4$OAc, Et$_2$O, 24 h, 90%; c) NaH, THF, 0°C then N,N-diethylcarbamoyl chloride, 90%. d) tBuLi, THF, -78°C, 2 h then CSA, r.t., 12 h, 70%; e) 2-methyl-2-butene, BH$_3$-SMe$_2$, THF, 0°C then MeOH, NaOH (30%), H$_2$O$_2$, 71%; f) TPAP, NMO, CH$_2$Cl$_2$, 4 Å M.S. 6 h, r.t., 72%

Scheme 67: Synthesis of the phthalide unit 311 of CJ 12,954 (13) and CJ-13,014 (12)

The spiroacetal fragments were prepared starting with addition of (+)-B-allyldiisopinocampheylborane to aldehyde 319 thus affording (S)-alcohol 320 after peroxide work-up. Hydroboration to primary alcohol 322 and oxidation using Dess–Martin periodinane afforded aldehyde 323. Addition of aldehyde 323 to the lithium acetylide of 219 in the presence of lithium bromide, proceeded smoothly to furnish alcohol 324. Oxidation of the alcohol 324 to ynone 325 followed by reduction of the acetylene afforded saturated protected dihydroxyketone 326. Spirocyclization afforded an inseparable 1 : 1 mixture of spiroacetals 327 and 329. Lack of stereocontrol from the anomeric effect contributed to the observed formation of equal quantities of 5,5-spiroacetals 328 and 330 with (S)- and (R)-stereochemistry at the spirocentres, respectively. Spiroacetal alcohols 328 and 330 were converted to sulfides 331 and 332 and then treated with m-chloroperoxybenzoic acid to afford sulfones 312 and 313. Union with (3S)-phthalide-aldehyde 311 was achieved in the presence of potassium hexamethyldisilazide to afford a mixture of alkenes 333 and 334. Finally hydrogenation of the mixture of alkenes 333 and 334 over Adams’ catalyst afforded an inseparable 1 : 1 mixture of 13 and 12 (Scheme 68).
Reagents and conditions: a) allyl bromide, Mg, (+)-diisopinocampheylmethoxyborane, Et₂O, -78 °C to 20 °C, 82%; b) TBDMSCI, imid., DMAP, CH₂Cl₂, 20 °C, 12 h, 90%; c) 2-methyl-2-butene, BH₃-SMe₂, 0 °C, 76%; d) DMP, py., CH₂Cl₂, 20 °C, 77%; e) nBuLi, LiBr, THF, -78 °C, 84%; f) TPAP, NMO, 4 Å M.S., CH₂Cl₂, 20 °C, 94%; g) H₂, PtO₂, K₂CO₃, THF-MeOH (1:1), 94%; h) CSA, CH₂Cl₂, 20 °C, 4 h, 93%; i) TBDPS, THF-MeOH (1:1), 94%; j) 1-phenyl-1H-tetrazole-5-thiol, PPh₃, DEAD, 78%; k) **GPBA, NaHCO₃, CH₂Cl₂, 71%; l) KHMDS, THF, -78 °C, 84%; m) H₂, PtO₂, K₂CO₃, THF-MeOH (1:1)

Scheme 68: Synthesis of CJ 12,954 (13) and CJ-13,014 (12)
2.1 Aim of the current project

2.1.1 Analogues of spirolaxine methyl ether (15)

In light of our research group's successful first total synthesis of spirolaxine methyl ether (15)\textsuperscript{146} and its even more biologically active unnatural (2''S)-diastereomer 21 (Scheme 49),\textsuperscript{69} the aim of the current project is to synthesise analogues of the unnatural (2''S)-diastereomer 21 of spirolaxine methyl ether (15). Specifically the goal is to obtain analogues where the length of the polymethylene carbon chain which links the spiroacetal and phthalide moieties is varied (Compounds 335-336) and at the same time replace the phthalide moiety with two other heterocycles, namely an indole (Compounds 337-339) and an oxindole (Compounds 340-342) ring systems. This strategy provides three sets of three analogues: one set with a longer polymethylene chain than the natural product and three different heterocycles (Compounds 336, 339, 342), a second set of three analogues with the same polymethylene chain length as in the natural product and the three different heterocycles (Compounds 338, 341) and finally a set of three compounds with a shorter polymethylene chain length than the natural product (Compounds 335, 337, 340) (Scheme 69). The information obtained upon comparison of the biological profiles of these analogues of spirolaxine methyl ether (15) will be of considerable value to programs aimed at improving the pharmacological profile of these antibiotics. The ultimate goal is to develop a clinically useful anti-\textit{H. pylori} active compound for use in the eradication of peptic ulcers and associated diseases caused by the pathogen.

![Scheme 69: Synthetic targets for the current project](image-url)
2.2 Retrosynthetic analysis

2.2.1 Retrosynthetic analysis of phthalide analogues of the (2”S)-diastereomer of spirolaxine methyl ether (15)

The proposed retrosynthetic analysis for the phthalide analogues 343, was based on work carried out by Brimble and Robinson.\textsuperscript{146} It was envisaged that heterocycle-activated Julia-Kocienski olefination between phthalide aldehyde 189 and sulfone spiroacetals 344 would be the key step. Phthalide aldehyde 189 can be obtained via intramolecular lithiation and cyclisation of carbamate 206. Sulfone spiroacetals 344 can be prepared by acid-catalysed cyclisation of protected dihydroxyketone precursors 345 which in turn will be accessed by addition of lithium acetylide 347 to aldehydes 346. Aldehydes 346 will be obtained from epoxides 348, which are available from hydroxyalkenes 349 via epoxidation of the olefin followed by Jacobsen Hydrolytic Kinetic Resolution (Scheme 70).
2.2.2 Retrosynthetic analysis of the indole 350 and oxindole 351 analogues of (2''S)-diastereomer of spirolaxine methyl ether (21)

The indole and oxindole analogues (350, 351) of spirolaxine methyl ether (15) will be accessed via alkylation of either 4,6-dimethoxyindole (352) or 4,6-dimethoxyoxindole (354) respectively, with various spiroacetal iodides 353 (Scheme 71). The spiroacetal iodides 353 can be obtained from hydroxyalkenes 349 in a similar fashion as for the phthalide analogues 343 (Scheme 70).
2.3 Synthesis of oxindole 342 and indole 339 analogues of (2''S)-spirolaxine methyl ether (21) with a long polymethylene chain (eight carbons)

2.3.1 Synthesis of the spiroacetal iodide 359

A. Synthesis of aldehyde 357

The strategy for the synthesis of an eight carbon polymethylene chain spiroacetal iodide 359, is outlined in Scheme 72 and involves preparation of aldehyde 357 from epoxide 355 via olefin 356. Coupling of aldehyde 357 and (S)-acetylene 219 synthesised from commercially available (S)-but-3-yn-2-ol (218) will allow access to dihydroxyketone 358. Finally, acid catalysed cyclisation of dihydroxyketone 358 obtained after functional group manipulation will furnish spiroacetal iodide 359.
The synthesis commenced with readily available 9-decen-1-ol (360) which was stirred in the presence of 4-dimethylaminopyridine, imidazole and tert-butyldiphenylsilyl chloride in dichloromethane at room temperature for 12 h to afford the desired silyl ether 361 without further purification. The alkene 361 underwent smooth oxidation to the racemic epoxide 362 in the presence of m-CPBA in dichloromethane for 12 h (Scheme 73).

![Scheme 73: Synthesis of racemic epoxide 362]

In order to obtain enantiopure epoxide 355 from the racemic epoxide 362 it was decided to use a Hydrolytic Kinetic Resolution (HKR) procedure first developed by Jacobsen in 1997. The HKR of terminal epoxides catalysed by chiral (salen)CoIII·OAc complex 365 affords the unreacted epoxide and 1,2-diol product in highly enantioenriched form (Scheme 75). As such the HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access from inexpensive racemic materials. The reaction has several appealing features from a practical standpoint, including the use of water as a reactant and low loadings (0.2-2.0 mol%) of a recyclable commercially available catalyst. In addition the HKR displays extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to >99% e.e. The corresponding chiral 1,2-diols can be produced in good to high enantiomeric excess using 0.45 equivalents of water (Scheme 74).

![Scheme 74: Hydrolytic Kinetic Resolution]

Under standard conditions, catalyst 364 needs to be activated to the Acetyl CoIII complex 365 which is its active form. This is achieved by stirring 364 in toluene with acetic acid open to the air. The standard procedure then involves stirring the activated catalyst 365 with the racemic epoxide 362 neat in the presence of water. The catalyst selectively hydrolyses one of the enantiomers to the diol 363 while the other enantiomer 355 remains unreacted (Scheme 75). Applying these conditions on epoxide 362 only resulted in recovery of the starting material after 72 h (Scheme 75). Upon consulting the literature it was suggested that epoxide 362 is a non-polar...
substrate. When this is the case the polar activated-catalyst 365, non-polar epoxide 362 and water mixture are not very miscible. To circumvent this problem the reaction can be performed in a solvent rather than neat. Attempting the resolution again in the presence of 1.5 mol% of the catalyst 365, 0.5 equivalents of water and isopropanol as the solvent gratifyingly afforded chiral epoxide 355 in 99% e.e after 24 h at room temperature. The e.e. was determined by the synthesis of the Mosher’s ester of alcohol 366 (Scheme 84).

Scheme 75: HKR of racemic epoxide 362

Initial attempt to effect regioselective opening of the chiral epoxide 355 with allylmagnesium bromide proved problematic due to the formation of a 1:1 mixture of the desired product and bromohydrin 367 (Scheme 76). A similar undesired product was reported by Robinson and Brimble (Scheme 46) in the total synthesis of spirolaxine methyl ether (15).\textsuperscript{146}

Scheme 76: Bromohydrin 367 formation during opening of epoxide 355
Additionally Tiefenthal and Huston\textsuperscript{161} reported in 1951 that reaction of Grignard reagents with epoxides can result in halohydrins as the main product. Magnesium bromide (MgBr\textsubscript{2}) generated during the formation of the Grignard reagent can act as a Lewis acid, promoting nucleophilic attack by the halide. There are two possible mechanistic pathways: one involving solely the Grignard reagent, the other implicating MgBr\textsubscript{2}.\textsuperscript{161} The reaction is believed to proceed through a six-membered cyclic transition state which could be formed in two different ways (A or B) (Scheme 77).\textsuperscript{162}

\textbf{Scheme 77:} Possible transition states of the Grignard reaction

Transition state A depicts the reaction of epoxide 355 with the Mg-Alkyl bond forming the desired product 366, whereas transition state B presents the reaction with the Mg-Br bond forming bromohydrin 367. Epoxide opening catalysed by MgBr\textsubscript{2} is the second and more likely pathway for bromohydrin 367 formation (Scheme 78). In this pathway the magnesium coordinates with the oxirane oxygen atom withdrawing electron density from the ring and making it prone to nucleophilic attack by the bromide anion at the sterically and electronically favoured position (Scheme 78).

\textbf{Scheme 78:} MgBr\textsubscript{2} Lewis acid pathway

In order to overcome the bromohydrin side product formation, the opening of epoxide 355 was attempted with higher order allylic cuprate. In 1981 Lipschutz \textit{et al.}\textsuperscript{163} reported this strategy, which was also successfully applied by Robinson and Brimble.\textsuperscript{146}

Organocopper reagents play a prominent role among the many organometallic compounds which can be used for the selective C-C bond formation. Monoorganocopper compounds (RCu) and cuprates (R\textsubscript{2}CuLi) are usually prepared by transmetalation of organolithium or Grignard reagents with copper (I) salts. Lipschutz \textit{et al.}\textsuperscript{163,164} were the first to describe cyanocuprates, which were formed by the reaction of copper(I) cyanide (CuCN) with two equivalents of alkyl lithium. This higher order cyanocuprate seemed to differ considerably in terms of stability and reactivity compared to the Gilman cuprates (R\textsubscript{2}CuLi·LiX) that are prepared from copper(I) halides.
Lipschutz et al.\textsuperscript{165} attributed these differences to the cyano ligand which is tightly bound to the copper centre. Accordingly the reaction of CuCN with one equivalent of RLi would lead to the copper species RCu(CN)Li which is designated as a lower order cyanocuprate (Scheme 79), while the reaction with a second equivalent of RLi would lead to a higher order cuprate (R\textsubscript{2}Cu(CN)Li\textsubscript{2}).

\[
\text{CuCN} \xrightarrow{\text{RLi}} \text{RCu(CN)Li} \xrightarrow{\text{RLi}} \text{R}\textsubscript{2}Cu(CN)Li\textsubscript{2} \text{ or } \text{R}\textsubscript{2}CuLi•LiCN
\]

\textbf{Scheme 79: Lower order and higher order cyanocuprates}

The structure of these species was clarified by several spectroscopic experiments. Bertz\textsuperscript{166} observed a coupling between the cyanide ligand and the methyl group in the $^{13}$C-NMR spectra of isotopically labelled MeCu($^{13}$CN)Li. This is probably the most convincing proof that CN is directly bound to copper in the lower order cuprates.

In contrast the question of whether cyanocuprates exist as a higher order species R\textsubscript{2}Cu(CN)Li\textsubscript{2} (Scheme 79) or rather cyano-Gilman cuprates R\textsubscript{2}CuLi•LiCN is not entirely clear. Based on studies by Boche \textit{et al.}\textsuperscript{167} and Kronenburg \textit{et al.}\textsuperscript{168} the question of the thermodynamically most stable form of the reagent prepared from two equivalents of alkyl lithium and one equivalent of CuCN can be answered clearly in favour of the cyano-Gilman cuprates. Furthermore in cryogenic studies using THF solutions, cyano-Gilman like structures could be proven for several cyanocuprates.\textsuperscript{169,170} In organometallic chemistry however it is not uncommon that the most thermodynamically stable species of a given reagent is not the kinetically active one. This phenomenon can only occur if there is a fast equilibrium between different species. The existence of such equilibria has been spectroscopically proven for several organocuprates.\textsuperscript{171} In the case of the cyanocuprates an equilibrium between the cyano-Gilman and higher order species could exist. However such an equilibrium has not yet been verified.

In the case of the reaction with the long chain epoxide \textit{355}, the organocuprate reagent was obtained using the procedure developed by Lipschutz\textsuperscript{172} (Scheme 80).

\[
\text{CuCN} \xrightarrow{a} \text{Me}_2\text{Cu(CN)Li}_2 \xrightarrow{b} \text{Me}_2\text{Cu(CN)Li}_2
\]

\textit{Reagents and conditions: a) MeLi (2 eq.), THF, -78 °C - 0 °C, 20 min; b) allylSnBu\textsubscript{3} (2 eq.), THF, 0 °C, 30 min}

\textbf{Scheme 80: Generation of higher order cuprate for the opening of epoxide 355}

Allylic stannanes are highly prone to ligand exchange with the Me\textsubscript{2}Cu(CN)Li\textsubscript{2} species, which are formed by reacting CuCN with two equivalents of methyllithium at -78 °C in THF. Allyltributyltin reacts at -35 °C in THF to afford a mixed higher order cuprate (Scheme 81).\textsuperscript{172}
Chapter II: Discussion

\[ \text{Me}_2\text{Cu(CN)Li}_2 \overset{\text{a}}{\rightarrow} \text{Cu(Me)(CN)Li}_2 \]

**Reagents and conditions:** a) allylSnBu\textsubscript{3}, THF, \(-35^\circ\text{C}\)

**Scheme 81:** Low temperature generates mixed higher order cuprate

Mixed higher order cuprates have little synthetic use since the methyl ligand rather than the allyl ligand can competitively transfer to the electrophile. Hence a double transmetallation with a second equivalent of allyltributyltin is necessary to arrive at the diallyl cuprates. This reaction occurs at \(0^\circ\text{C}\) and it is very important to warm the reaction to \(0^\circ\text{C}\) from \(-78^\circ\text{C}\) (Scheme 82).\(^{172}\)

\[ \text{Me}_2\text{Cu(CN)Li}_2 \overset{\text{a}}{\rightarrow} \text{Cu(CN)Li}_2 \]

**Reagents and conditions:** a) allylSnBu\textsubscript{3} (2 eq), THF, \(0^\circ\text{C}, 30\text{ min}\)

**Scheme 82:** Transmetallation to higher order diallyl cuprate at \(0^\circ\text{C}\)

This higher order diallyl cuprate was generated \textit{in situ} by reacting CuCN with two equivalents of methyl lithium at \(-78^\circ\text{C}\) for 20 min in THF followed by warming of the reaction to \(0^\circ\text{C}\) and addition of two equivalents of allyltributyltin with further stirring for 30 min. The thus formed cuprate was then cannulated to a solution of the epoxide 355 in THF at \(-78^\circ\text{C}\). The reaction was then further stirred at \(0^\circ\text{C}\) for 1 h, to pleasingly afford secondary alcohol 366 in 82% yield after purification (Scheme 83).

\[ \text{TBDPSO} \overset{\text{a}}{\rightarrow} \text{TBDPSO} \]

**Reagents and conditions:** a) THF, \(0^\circ\text{C}, 1\text{ h}, 82\%\)

**Scheme 83:** Successful opening of epoxide 355 with higher order cuprate

The enantiomeric excess of alcohol 366 was determined by examining the \(^{19}\text{F}\) NMR spectrum of the corresponding Mosher's ester 368 (Scheme 84). Following a standard procedure,\(^{173}\) alcohol 366 was treated with \((R)\)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid in the presence of 4-(\(N,N\)-dimethylamino)pyridine and dicyclohexylcarbodiimide. After 72 h, thin layer chromatography revealed the disappearance of the starting material and the Mosher's ester 368 was isolated in 80% yield. The \(^{19}\text{F}\) NMR spectrum of the Mosher's ester 368 showed a resonance at \(\delta \sim 72.38\) as a single detectable peak, indicating > 99% e.e.
Having established the enantiomeric purity of alcohol 366, the alcohol 366 was reacted with tert-butyldimethylsilyl chloride, 4-dimethylaminopyridine and imidazole in dichloromethane at room temperature for 12 h to afford the desired silyl ether 356 on purification. (Scheme 85). Hydroboration of the alkene 356, using borane dimethylsulfide complex in tetrahydrofuran at 0 °C for 12 h followed by oxidative work up with H₂O₂ and NaOH, afforded alcohol 369 in 73% yield. Dess-Martin periodinane oxidation of the primary alcohol 369 in dichloromethane for 2 h at room temperature afforded the corresponding aldehyde 357 in 91% yield.

With the aldehyde 357 in hand, it was envisaged that spiroacetal alcohol 370 would be prepared from dihydroxyketone 358, which in turn could be accessed from union of aldehyde 357 with acetylene 219. Acetylene 219 was available from commercially sourced (S)-but-3-yn-2-ol 218 (Scheme 86).
Robinson and Brimble\textsuperscript{146} initially reported a problem when attempting to couple aldehyde 357 and acetylide 219 (Scheme 47). Simple treatment of the acetylene 219 with \(^n\)BuLi followed by the addition of the aldehyde 357 only resulted in a complex mixture, lowering the temperature to -90 °C and adding boron trifluoride etherate did not improve the results. It was postulated that enolate formation was occurring in preference to the desired nucleophilic addition. This was also observed by Brandsma et al.\textsuperscript{175} during the preparation of propargylic alcohols from lithium acetylides and ketones. They successfully overcame the problem by the inclusion of lithium bromide in the reaction. Consequently \(^n\)BuLi was used to deprotonate acetylene 219 at -78 °C in THF, half an equivalent of lithium bromide dissolved in THF was then cannulated to the reaction mixture and stirred at -78 °C for further 15 min. Aldehyde 357 was then added and the reaction mixture was warmed to room temperature over 6 h to give the desired secondary alcohol 371 in 76% yield on purification (Scheme 87)
Oxidation of the secondary alcohol 371 proceeded with tetrapropylammonium perruthenate and N-methylmorpholine N-oxide in dichloromethane for 2 h at room temperature in the presence of 4 Å molecular sieves to afford the corresponding ynone 372 in 86% yield. Hydrogenation of the alkyne functionality over Adam's catalyst (PtO₂) in MeOH/THF (1:1) for 6 h yielded dihydroxyketone 358 in excellent yield (Scheme 88).

![Scheme 88: Formation of dihydroxyketone 358](image)

**Reagents and conditions:** a) TPAP, NMO, CH₂Cl₂, 4Å M.S., 0 °C to r.t., 2 h, 86%; b) PtO₂, H₂, MeOH/THF (1:1), 6 h, 84%

Selective removal of the tert-butyldimethylsilyl ethers and concomitant cyclisation with camphorsulfonic acid in dichloromethane for 2 h at room temperature afforded spiroacetal 373 in 73% yield. Removal of the tert-butyldiphenylsilyl ether with tetrabutylammonium fluoride in THF for 2 h provided the desired spiroacetal alcohol 370 (Scheme 89). A molecular ion at m/z 285.24243 in the high resolution EI mass spectrum (285.24297 calculated for MH⁺) provided evidence for the successful formation of the spiroacetal alcohol 370.

![Scheme 89: Formation of spiroacetal 370](image)

**Reagents and conditions:** a) CSA, CH₂Cl₂, 3 h, 73%; b) TBAF, THF, 2 h, 87%
The structure of the spiroacetal alcohol 370 was confirmed by NMR studies (Scheme 90). Resonances at $\delta$ 4.20 and $\delta$ 3.80 in the $^1$H NMR spectrum were assigned to H2 and H7 respectively and their multiplicities were consistent with spiroacetal formation. Additionally, the quaternary carbon resonance in the $^{13}$C NMR at $\delta$ 105.8 assigned to C5 was characteristic of a spiro-centre. The anomeric effect would predict that the spiroacetal ring would adopt a thermodynamically most favoured configuration where both oxygen atoms of the spiroacetal ring adopt axial orientations. This was confirmed by the observation of a nOe between H7 and the protons of the methyl group at C2.

Scheme 90: Structure of spiroacetal alcohol 370 based on NMR data

2.3.2 Synthesis of the eight carbon polymethylene chain indole analogue 339

Having successfully synthesised spiroacetal alcohol 370, attention next turned towards its union with commercially available 4,6-dimethoxyindole (352) to complete the synthesis of the long polymethylene chain indole analogue 339. It was decided to adopt the methodology used by Wilson et al. in their synthesis of indole analogues of the simpler CJ compounds (Scheme 7). The alcohol functionality needed to be transformed into a halide for selective N-alkylation of the indole heterocycle 352 (Scheme 91). Consequently spiroacetal alcohol 370 was stirred with methanesulfonyl chloride in the presence of triethylamine in THF for 2 h at room temperature. The in situ generated mesylate 374 was refluxed with sodium iodide in THF for 12 h to afford spiroacetal iodide 359 in 67% yield. Following the procedure developed by Heaney and Ley, selective N-deprotonation of 4,6-dimethoxyindole (352) in DMSO with potassium hydroxide followed by the addition of spiroacetal iodide 359 yielded indole analogue 339 in 54% yield after stirring for 3 h at room temperature. Further substitution on the indole ring was not observed (Scheme 91). The formation of the indole analogue was supported by a triplet in the $^1$H NMR at $\delta$ 4.01 assigned to H1', a further resonance at $\delta$ 46.5 in the $^{13}$C NMR was assigned to C1'. A molecular ion at $m/z$ 443.30408 in the high resolution EI mass spectrum (443.30356 calculated for MH$^+$) provided evidence for the successful formation of the indole analogue 339.
2.3.3 Synthesis of the eight carbon polymethylene chain oxindole analogue 342

With the spiroacetal iodide 359 in hand, it was next decided to complete the long polymethylene chain oxindole analogue 342 (Scheme 93). The oxindole heterocycle 354 was accessed via condensation of dimethoxyaniline 375 with diethyl ketomalonate (376). The resulting species 377 was then reduced with tin chloride to afford 4,6-dimethoxyoxindole (354) in accordance with the method reported by Black et al. (Scheme 92).

Reagents and conditions: CH$_3$CO$_2$H, 100 $^\circ$C, 15 min, 93%; b) SnCl$_2$, HCl, CH$_3$CO$_2$H, reflux, 1 h then NaOH, reflux, 1.5 h, 87%

Scheme 92: Synthesis of dimethoxyoxindole 354

It was anticipated that $N$-alkylation of the oxindole ring would be more challenging, with the oxindole ring bearing an acidic proton alpha to a carbonyl group that renders C-alkylation side reactions possible. Nakazawa et al. have reported deprotonation of oxindoles with sodium hydride. Attempting deprotonation of oxindole 354 with two equivalents of sodium hydride followed by the addition of the iodide 359 only resulted in a complex mixture of multiple alkylation products. Hence iodide 359 was used as a limiting reagent and the oxindole 354 was used in excess (two equivalents) and deprotonation was carried out with just one equivalent of sodium hydride in DMF at room
temperature. This process resulted in smooth $N$-deprotonation, yielding the desired $N$-alkylated analogue $342$ in 68% yield (Scheme 93). The formation of the oxindole analogue $342$ was supported by a triplet in the $^1H$ NMR at $\delta$ 3.63 assigned to H1', a further resonance at $\delta$ 40.2 in the $^{13}C$ NMR was assigned to C1'. A molecular ion at $m/z$ 460.3049 in the high resolution ESI mass spectrum (460.3057 calculated for MH$^+$) provided evidence for the successful formation of the oxindole analogue $342$.

![Scheme 93: Successful completion of long polymethylene chain oxindole analogue 342](image)

**2.4 Synthesis of oxindole 341 and indole 338 analogues of (2''S)-spirolaxine methyl ether (21)**

Having successfully synthesised the long polymethylene chain indole $339$ and oxindole $342$ analogues, attention next turned to the synthesis of five carbon polymethylene chain oxindole $341$ and indole $338$ analogues of spirolaxine methyl ether (15). The five carbon polymethylene chain spiroacetal alcohol $378$ would also be used for the synthesis of the long chain (eight carbon) phthalide analogue $336$, since phthalide aldehyde $189$ has a three carbon polymethylene chain. The latter synthesis required conversion of the alcohol $378$ to a heterocyclic activated sulfone $379$ in order to carry out a Julia-Kocienski olefination (Scheme 94).
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Scheme 94: Common spiroacetal alcohol precursor 378 necessary for the synthesis of oxindole 341 indole 338 and phthalide 336 analogues

2.4.1 Synthesis of the spiroacetal alcohol 378

A. Synthesis of dihydroxyketone 383

The synthesis of the five carbon polymethylene chain spiroacetal 378 was envisaged to proceed in a similar fashion to the synthesis of the eight carbon chain spiroacetal 370, starting from 6-hepten-1-ol (380) (Scheme 95). However, 6-hepten-1-ol (380) is very expensive and large quantities of this material would be necessary to complete a twenty step synthesis.
Initially it was attempted to synthesise 6-hepten-1-ol (380). Bohlmann et al.\textsuperscript{181} successfully reacted the Grignard generated from 5-bromopent-1-ene (384) with ethylene oxide to yield 6-hepten-1-ol (380) (Scheme 96). Unfortunately these conditions required handling the gaseous highly flammable and mutagenic ethylene oxide, which made this route undesirable.

\begin{align*}
\text{Br} & \xrightarrow{\text{a}} \text{BrMg} & \xrightarrow{\text{b}} \text{HO}
\end{align*}

\textit{Reagents and conditions:} a) \text{THF, Mg, 0 \textdegree C, 0.5 h}; b) \text{ethylene oxide, 0.5 h, 5 \textdegree C}

\textbf{Scheme 96: Attempted synthesis of 6-hepten-1-ol (380)}

\textbf{B. Synthesis of dihydroxyketone 389}

An alternative route was established starting from readily available 4-penten-1-ol (386) as shown in Scheme 97. The resulting three carbon polymethylene chain spiroacetal aldehyde 390, would then be extended to the required five carbon polymethylene chain spiroacetal 378 \textit{via} a Horner-Wadsworth-Emmons reaction using triethyl phosphonoacetate 391.
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Scheme 97: Alternative route for the synthesis of spiroacetal alcohol 378

The synthesis commenced with readily available 4-penten-1-ol (386) which was protected as a tert-butylidiphenyl silyl ether 392 by stirring with tert-butylidiphenylsilyl chloride in the presence of 4-dimethylaminopyridine and imidazole in dichloromethane for 12 h at room temperature. The double bond was oxidised to the racemic epoxide 393 in the presence of m-CPBA in dichloromethane for 12 h (Scheme 98). Jacobsen’s Hydrolytic Kinetic Resolution (HKR) was then used to obtain enantiopure epoxide 387 as previously described (Scheme 75). The (R)-epoxide 387 was obtained in 86% yield and 99% e.e. as determined by conversion of the subsequently ring opened bis-homoallylic alcohol 394 to the Mosher’s ester. The chiral epoxide 387 was opened with a higher order diallylcyanocuprate via the procedure of Lipschutz as described previously for the ring opening of the long polymethylene chain epoxide 355 (Scheme 83). The resulting alcohol 394 was protected as tert-butyldimethyl silyl ether 395 by stirring with tert-butyldimethylsilyl chloride in the presence of 4-dimethylaminopyridine and imidazole in dichloromethane for 12 h at room temperature. (Scheme 98).

![Scheme 98: Synthesis of the secondary silyl protected alcohol 395](image)

Reagents and conditions: a) TBDPSCI, imid., DMAP, CH₂Cl₂, 12 h, 98%; b) m-CPBA, CH₂Cl₂, 0 °C to r.t., 12 h, 80%; c) (R,R)-SalenCoIII•OAc, H₂O, iPrOH, 24 h, 86%, 99% e.e.; d) CuCN, MeLi, AllylSnBu₃, THF, -78-0 °C, 70%; e) TBDMSOTf, imid., DMAP, CH₂Cl₂, 85%
Hydroboration-oxidation of alkene 395 using borane-dimethyl sulfide complex in THF at room temperature for 12 h, followed by oxidative work up with H₂O₂ and NaOH afforded primary alcohol 396 in 70% yield. Dess-Martin oxidation of the resulting alcohol 396 in dichloromethane for 2 h provided aldehyde 388 in 88% yield. The lithium acetylide was generated from acetylene 219 using °BuLi at -78 °C in THF for 15 min, then aldehyde 388 was added in the presence of lithium bromide (0.5 eq.) to afford secondary alcohol 397. Oxidation of the acetylenic alcohol 397 using tetrapropylammonium perruthenate and N-methylmorpholine N-oxide in the presence of 4 Å molecular sieves in dichloromethane for 2 h proceeded smoothly to give the corresponding ynone 398 in 79% yield. Hydrogenation of the triple bond over Adam's catalyst (PtO₂) in MeOH/THF (1:1) for 6 h yielded dihydroxyketone 389 in excellent yield (Scheme 99).

Scheme 99: Synthesis of the dihydroxyketone 389

C. Synthesis of Spiroacetal Alcohol 400

With dihydroxyketone 389 in hand, attention next turned to the spiroacetalisation step using similar conditions to those used earlier to execute the spiroacetalisation of the long polymethylene carbon chain dihydroxyketone 358 (Scheme 89). Gratifyingly, treatment of dihydroxyketone 389 with camphorsulfonic acid in dichloromethane at room temperature for 2 h, selectively removed the tert-butylidemethylsilyl ethers and enabled concomitant cyclisation to yield spiroacetal 399. Removal of the tert-butylidiphenylsilyl ether again proceeded smoothly using tetra-n-butylammonium fluoride in THF at room temperature for 3 h to give alcohol 400 (Scheme 100).
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Scheme 100: Synthesis of the spiroacetal 400

D. Synthesis of Spiroacetal Alcohol 378

Having obtained the three carbon polymethylene chain spiroacetal, the hydrocarbon chain was next extended to five carbons as present in spirolaxine methyl ether (15) using the Horner-Wadsworth-Emmons (HWE) reaction. Spiroacetal alcohol 400 was smoothly oxidised to the corresponding aldehyde 390 using Dess-Martin Periodinane in dichloromethane at room temperature for 2 h (Scheme 102). The most useful conditions for the HWE condensation between aldehyde 390 and triethyl phosphonoacetate 401 involved the use of the Masamune-Roush variant of the reaction due to its mild nature (Scheme 101) using the mild DBU base in the presence of lithium chloride in THF. Lithium cations affect the course of the Wittig reaction and its modified version, the HWE, in many important ways. The lithium cation forms tight complex with the carbanion derived from phosphonate 401 thereby enhancing its acidity (Scheme 101). The pKa value of the methylene of 402 in diglyme (Li⁺) is 12.2, therefore in the presence of a lithium salt, 401 could be deprotonated with an amine such as DBU (pKa 11.6) to generate the reactive carbanion 402 under mild conditions (Scheme 101).

Scheme 101: Effect of lithium cation on phosphonate 401

Reaction of spiroacetal aldehyde 390 with triethyl phosphonoacetate 401 under Masamune-Roush conditions using DBU in the presence of lithium chloride in THF at room temperature for 5 h, gratifyingly proceeded smoothly to yield alkene 403 in 70% yield. The E/Z ratio was not determined as the double bond was reduced in the next step. This procedure provided spiroacetal 403 bearing a five carbon polymethylene chain, analogous to that present in spirolaxine methyl ether (15) (Scheme 102).
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Reagents and condition: a) Dess-Martin periodinane, pyr., CH₂Cl₂, 2 h, 81%; b) LiCl, DBU, 5 h, r.t, 70%

Scheme 102: Extension of the carbon chain of spiroacetal 400 via HWE

Having successfully extended the carbon chain of spiroacetal 400 to the correct length of five carbons, further functional group manipulation was required to access the spiroacetal precursor 378. Consequently the double bond of alkene 403 was reduced in a power hydrogenator (150 psi) in the presence of Adam’s catalyst in THF/MeOH (1:1) over 6 h to yield ester 404. Initial reduction of the ester 404 with DIBALH in hexane only yielded aldehyde 405 which was further reduced with sodium borohydride to the desired alcohol 378. This was an unexpected result since it was assumed that DIBALH would be strong enough to afford alcohol 378 from the ester 404. The reaction was next attempted with the stronger reductant, lithium aluminium hydride in THF which proceeded smoothly in 15 min at room temperature to yield desired alcohol 378 in 94% yield on quenching with aqueous NaOH (2 M). Finally alcohol 378 was converted to iodide 406 in preparation for coupling with the 4,6-dimethoxyindole (352) and 4,6-dimethoxyoxindole (354) heterocycles. The alcohol 378 was reacted with methanesulfonyl chloride in THF at 0 °C for 1 h, the mesylate was then refluxed overnight with excess sodium iodide in THF to provide iodide 406 (Scheme 103).

Reagents and conditions: a) H₂ (150 psi), PtO₂, 12 h, r.t.,MeOH-THF (1:1), 86%; b) DIBALH, toluene, 4 h, -78 °C; c) NaBH₄, Et₂O, 2 h, 70% over two steps; d) LiAlH₄, THF, 0 °C, 15 min. then NaOH, 94%; e) MsCl, Et₃N, THF, 1 h, 0 °C then NaI, reflux 12 h, 60%

Scheme 103: Completion of spiroacetal iodide 406
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2.4.2 Synthesis of the five carbon polymethylene chain indole analogue 338 and oxindole analogue 341

With iodide 406 in hand, N-deprotonation of 4,6-dimethoxyindole (352) with potassium hydroxide at room temperature in DMSO followed by iodide 406 addition afforded the indole analogue 338 of the unnatural (2''S)-diastereomer of spirolaxine methyl ether (15) in 59% yield (Scheme 104). The formation of the indole analogue 338 was supported by a triplet in the $^1$H NMR at $\delta$ 4.01 assigned to H1', a further resonance at $\delta$ 46.5 in the $^{13}$C NMR was assigned to C1'. A molecular ion at m/z 402.2649 in the high resolution ESI mass spectrum (402.2639 calculated for MH$^+$) provided evidence for the successful formation of the indole analogue 338.

Additionally N-deprotonation of 4,6-dimethoxyoxindole 354 with one equivalent of sodium hydride in DMF at room temperature followed by addition of iodide 406 as the limiting reagent, gave the desired oxindole analogue 341 in 58% yield (Scheme 104). The formation of the oxindole analogue 341 was supported by a triplet in the $^1$H NMR at $\delta$ 3.63 assigned to H1', a further resonance at $\delta$ 40.2 in the $^{13}$C NMR was assigned to C1'. A molecular ion at m/z 418.2593 in the high resolution ESI mass spectrum (418.2588 calculated for MH$^+$) provided evidence for the successful formation of the oxindole analogue 341.

Reagents and conditions: a) KOH, DMSO, 2 h, r.t. 59%; b) NaH, DMF, 2.5 h, r.t, 58%

Scheme 104: Completion of exact oxindole 341 and indole 338 analogues of the unnatural spirolaxine methyl ether (15)

2.5 Synthesis of long polymethylene chain (eight carbons) phthalide analogue 336

2.5.1 Synthesis of phthalide aldehyde 189

With the five carbon polymethylene chain spiroacetal alcohol 378 in hand, it was aimed to complete the long chain (eight carbon) phthalide analogue 336 as well (Scheme 105). The phthalide aldehyde
189 prepared by Brimble and Robinson,\textsuperscript{146} was synthesised that would then lead to the eight carbon polymethylene chain analogue 336 when coupled to the five carbon polymethylene chain spiroacetal sulfone 379. Retrosynthetically the phthalide aldehyde 189 can be accessed \textit{via} cyclisation of carbamate 206, which in turn would be obtained from chiral allylic alcohol 205 (Scheme 105).

Starting with commercially available 3,5-dimethoxybenzaldehyde (204), the asymmetric allylation as described by Robinson and Brimble\textsuperscript{146} which was based on a procedure by Carreira and Gauthier\textsuperscript{147} was attempted. The method relied on using allyltrimethylsilane, which is significantly less reactive than the corresponding stannanes. A strong Lewis acid is required to perform the addition, which led to the development of chiral BINOL derived titanium complex 408, which due to the increased electronegativity of fluorine is a considerably more powerful Lewis Acid than the corresponding chloro and bromo congeners (Scheme 106).\textsuperscript{184} Additionally this catalyst is resistant to degradation by allyltrimethylsilane since the strength of the titanium-fluorine bond ($D_0$(Ti-F) = 140 kcal/mol) is greater than the strength of the silicon-fluorine bond ($D_0$(Si-F) = 135 kcal/mol). The catalyst is prepared \textit{in situ} from titanium tetrafluoride, and (R)-(−)-BINOL in acetonitrile. (Scheme 106).

(R)-BINOL in acetonitrile was treated with titanium tetrafluoride to afford a deep red solution of Lewis acid 408 (Scheme 106). The solvent was removed \textit{in vacuo} and the mixture dissolved in dichloromethane and acetonitrile (97:3), before cooling to 0 °C and adding allyltrimethylsilane. After
1.5 h, aldehyde 204 was introduced and the solution stirred at -20 °C for 70 h. The reaction was quenched with tetrabutylammonium fluoride. Unfortunately the homoallylic alcohol 205 was only isolated in 30% e.e as determined by chiral HPLC.

![Scheme 106: Asymmetric synthesis of allyl alcohol 205 by Robinson and Brimble](image)

Reagents and conditions: a) TiF₄ (5 mol%), (R)-(+)-BINOL (10 mol%), MeCN, 0 °C, 15 min., ii. CH₂Cl₂/MeCN (97:3), allyltrimethylsilane, 0 °C, 1.5 h, iii. -20 °C, 72 h, then TBAF, 70%, 86% e.e.

Scheme 106: Asymmetric synthesis of allyl alcohol 205 by Robinson and Brimble

Robinson and Brimble had already attempted to affect the same transformation using (-)-B-allyldiisopinocampheylborane under various conditions without much success. Bryant and Brimble successfully resolved the problem in their synthesis of CJ-12,954 and CJ-13,014 by performing a CBS reduction of allylic ketone 314 to the desired chiral alcohol 315 (Scheme 107).

![Scheme 107: CBS reduction of ketone 314 to yield allyl alcohol 315 by Bryant and Brimble](image)

Reagents and conditions: a) allylMgBr, Et₂O, -40 °C, 2 h, 88%; b) PCC, CH₂Cl₂, 4 h, r.t., 83% c) BH₃-SMe₂, 2 h, THF, -20 °C, 92%, 94% e.e.

Scheme 107: CBS reduction of ketone 314 to yield allyl alcohol 315 by Bryant and Brimble

In an attempt to avoid the extra oxidation-reduction steps from the CBS procedure, the literature was examined for other ways to install the stereochemistry at the benzylic position in a single step. A recent method by Singaram et al. whereby asymmetric allylation of aromatic aldehydes was achieved in the presence of indium metal, allyl bromide and a chiral amino alcohol 414 (Scheme 109) offered a promising alternative method. The first indium-mediated allylation reaction was performed by Butsugan et al. in which indium metal, allyl iodide and benzaldehyde 411 in DMF were used,
providing the racemic alcohol in 87% yield. Later Loh \textit{et al.}\cite{loh187} executed the first indium-mediated allylation of benzaldehyde 411 using (-)-cinchonidine 413 as the chiral director (Scheme 108).

![Scheme 108: First Indium mediated asymmetric allylation](image)

Singaram \textit{et al.}\cite{singaram185} discovered that commercially available (+)-(1S,2R)-2-amino-1,2-diphenylethanol (414) proved to be a very effective chiral mediator for the transformation using a range of aromatic aldehydes (Scheme 109).
The mechanism of this allylation has not yet been established. Gynane and Worrall\textsuperscript{188} suggested that alkylindium sesquihalides ($R_3\text{In}_2X_3$) are intermediates in the reaction of indium metal with various alkyl iodides based on mass and vibrational spectral analyses. Singaram et al.\textsuperscript{185} postulated transition state \textbf{417} as shown in Scheme \textbf{110}, based on spectroscopic studies.
Encouraged by these results, the asymmetric allylation of 3,5-dimethoxybenzaldehyde (204) in the presence of two equivalents each of pyridine, indium, allylbromide and (1R, 2S)-(-)-2-amino-1,2-diphenylethanol (418) in THF/hexane (5:1) was attempted at -78 °C. Gratifyingly, upon quenching the reaction after 2 h the desired chiral alcohol 205 was afforded in 88% yield and 96% e.e. as determined by chiral HPLC (Scheme 111). The chiral ligand was recovered by washing the aqueous layer with sodium hydroxide and extracting with ethyl acetate.

![Scheme 110: Transition state for indium mediated asymmetric allylation proposed by Singaram et al.](image)

**Scheme 110:** Transition state for indium mediated asymmetric allylation proposed by Singaram et al.\(^\text{185}\)

Having successfully obtained chiral alcohol 205, formation of the phthalide 200 proceeded smoothly. Selective ortho-bromination was achieved by refluxing alcohol 205 with NBS in chloroform overnight to yield bromide 203. Conversion of secondary alcohol 203 into carbamate 206 was successfully affected by stirring bromoalcohol 203 with sodium hydride in THF followed by the addition of N,N-diethylcarbamoyl chloride over 12 h at room temperature. Lithiation of the resulting bromide 206 with t-BuLi at -78 °C followed by ring closure in the presence of p-toluenesulfonic acid afforded allyl phthalide 200 in 70% yield (Scheme 112).
Chapter II: Discussion

Scheme 112: Preparation of phthalide alkene 200

All that remained to prepare phthalide heterocycle 200 as a coupling partner for the spiroacetal 379 (Scheme 105) was to transform the olefin to an alcohol and oxidise the resulting alcohol 208 to the corresponding aldehyde 189. The standard hydroboration conditions utilising borane-dimethyl sulfide complex stirring for 12 h, followed by oxidative work up with sodium hydroxide and hydrogen peroxide resulted in poor regioselectivity and variable low yields (15-30%). It was postulated that the highly oxygenated phthalide heterocycle 200 coordinates to the borane-dimethyl sulfide reagent resulting in undesirable side reactions. Therefore a more bulky borane was necessary to promote addition of the boron to the atom bearing the least bulky substituents and also to reduce its possible coordination to the oxygen atoms of the heterocycle. Bryant and Brimble\textsuperscript{157} had encountered a similar problem when synthesising the phthalide unit for CJ-12,954 (13) and CJ-13014 (12) and successfully used the bulky disiamylborane 419 generated \textit{in situ} from 2-methyl-2-butene (Scheme 67), to execute a similar hydroboration. The disiamylborane 419 was formed by stirring borane-dimethylsulfide complex with 2-methyl-2-butene at 0 °C for 5 h in THF and that was then added \textit{via cannula} to a solution of alkene 200. After stirring for 3 h at 0 °C and quenching with MeOH and sodium hydroxide/hydrogen peroxide, the desired alcohol 208 was obtained in 70% yield. Oxidation of the alcohol 208 with Dess-Martin periodinane in dichloromethane in the presence of pyridine for 3 h gave the desired phthalide aldehyde 189 coupling partner (Scheme 113).

Scheme 113: Completion of the synthesis phthalide aldehyde 189

\textit{Reagents and conditions:} a) THF, 0 °C, 3 h, then MeOH, NaOH, H$_2$O$_2$, 12 h r.t., 70%; b) DMP, pyr., CH$_2$Cl$_2$, 3 h, 85%
2.5.2 Coupling of phthalide aldehyde 189 with spiroacetal sulfone 379 using Julia olefination

With the phthalide aldehyde 189 and spiroacetal alcohol 378 in hand, the synthesis of the long polymethylene chain (eight carbon) analogue of the (2''S)-diastereomer of spirolaxine methyl ether (15) could be completed via Julia-Lythgoe olefination (Scheme 114). This strategy had been successfully used by Brimble and Robinson146 and Bryant and Brimble157 for the synthesis of spirolaxine methyl ether (15) and CJ-12,954 (13) and CJ-13,014 (12), respectively (Schemes 49 and 68).

The classical Julia olefination (also known as Julia-Lythgoe olefination) was first reported in 1973 by Julia and Paris,189 and involves reductive elimination of β-acyloxysulfones to form alkenes. The synthetic methodology was further developed by Lythgoe and Kocienski.190-193 Phenylsulfone 420 is treated with "BuLi to yield a metallate 421, which is added to aldehyde 422 to form β-alkoxysulfone 423 which undergoes reductive elimination with a one electron donor to give alkene 430 or 434 (Scheme 114). Keck et al.194 observed that using sodium-mercury amalgam as the single electron donor tends to yield E-isomers, whereas samarium iodide tends to give Z-isomers. In the proposed mechanism, when sodium-mercury amalgam is used, sodium methoxide deprotonates the sulfone 425 leading to a vinyl sulfone 426 which is then reduced to a vinyl radical 428. The vinyl radical 428 is then further reduced to a vinyl anion 429, which upon quenching gives alkene 430. The vinyl radical intermediate 428 is able to undergo equilibration which may lead to increased selectivity for the E-isomer. Alternatively, reduction with samarium iodide gives an alkyl radical 432 which is reduced to the alkyl anion 433, which then eliminates the acetate group to give the alkene 434. The Z selectivity presumably arises due to the lack of an isomerisation step when adopting this pathway (Scheme 114).
Chapter II: Discussion

Scheme 114: Classical Julia olefination mechanism\textsuperscript{194}

The modified Julia olefination (or one-pot olefination) was developed by Julia et al.\textsuperscript{195} by the replacement of the traditional phenylsulfone \textbf{420} with benzothiazol-2-yl sulfone \textbf{435}. Many other heterocyclic activators have been also investigated. Three heteroarylsulfones provide high levels of stereoselectivity: pyridin-2-yl sulfones \textbf{436},\textsuperscript{196} 1-phenyl-1\textit{H}-tetrazol-5-yl sulfones \textbf{437}\textsuperscript{197} and 1-\textit{tert}-butyl-1\textit{H}-tetrazol-5-yl sulfones \textbf{438}\textsuperscript{198} (Scheme 115). Benzothiazol-2-yl sulfones \textbf{435}, pyridin-2-yl sulfones \textbf{436} and 1-\textit{tert}-butyl-1\textit{H}-tetrazol sulfones \textbf{438}, primarily exhibit \textit{Z}-selectivity, whereas 1-phenyl-1\textit{H}-tetrazole-5-yl sulfones \textbf{437} generally adopt \textit{E}-selectivity.

\begin{center}
\begin{tabular}{c|c|c|c|c}
 benzothiazol-2-yl sulfone & pyridin-2-yl sulfone & 1-phenyl-1\textit{H}-tetrazol-5-yl sulfone & 1-\textit{tert}-butyl-1\textit{H}-tetrazol-5-yl sulfone \\
\textbf{435} (BT) & \textbf{436} (PYR) & \textbf{437} (PT) & \textbf{438} (TBT)
\end{tabular}
\end{center}

Scheme 115: Heterocyclic activated sulfones used in the modified Julia olefination

The modified Julia olefination proceeds \textit{via} a different mechanism from the classical olefination. The benzothiazole heterocycle \textbf{439} undergoes \textgreek{a}-lithiation before treatment with aldehyde \textbf{422} to give an
unstable intermediate 441 which undergoes a Smiles rearrangement via addition of the lithium alkoxide to the neighbouring C=N group. This results in a spirocyclic intermediate 442 which rearranges to 443 and then undergoes elimination of sulfur dioxide, benzothiazolone 444 and the desired alkene 445 (Scheme 116).

Scheme 116: Modified Julia olefination mechanism

Benzothiazol-2-yl sulfones 440 were found to predominantly exhibit Z-stereoselectivity. The stereoselectivity is explained in Scheme 117 where the syn stereochemistry displayed in 446 is favoured over the anti in 451. In the anti transition state there are unfavourable steric interactions between R₁ and R₂ groups. The syn adduct leads to a Z-product 434, whereas the anti stereochemistry leads to an E-product 430. However there are cases where this rule is not followed.

Scheme 117: Modified Julia olefination mechanism
Robinson and Brimble utilized benzothiazol-2-yl sulfones for the key coupling step in their synthesis of spirolaxine methyl ether (15) (Scheme 49). Although the reaction worked successfully, it was plagued by low yield, which is attributed to the instability of the benzothiazol-2-yl sulfones and their tendencies to undergo self-condensation which has been well documented in the literature. Treatment of sulfone with lithium diisopropylamide gives enolate, which can undergo self-condensation and yield (Scheme 118).

![Scheme 118: Self-condensation of BT-sulfones](image)

1-Phenyl-1H-tetrazol-5-yl sulfones (PT-sulfones) (Scheme 115) were developed by Kocienski et al. to provide a more stable alternative to the benzothiazol-2-yl sulfones in the modified Julia olefination. PT-sulfones proceed with predominantly E-selectivity due to their preferential kinetic addition to aldehydes to yield anti-alkoxysulfones, as opposed to the syn-alkoxysulfones formed when using benzothiazol-2-yl sulfones (Scheme 117). PT-sulfones were successfully used by Bryant and Brimble for the key coupling step in the synthesis of CJ-12,954 and CJ-13,014 resulting in high yields (Scheme 68).

Encouraged by this literature precedent, PT-sulfone spiroacetals was prepared using a Mitsunobu protocol. Treating spiroacetal alcohol with triphenylphosphine, 1-phenyl-1H-tetrazol-5-thiol and diethyl azodicarboxylate in THF for 12 h afford spiroacetal sulfide in 61% yield. Oxidation of the sulfide with m-CPBA in the presence of sodium bicarbonate in dichloromethane for 12 h gave the desired sulfone in 76% yield (Scheme 119).
Chapter II: Discussion

Reagents and conditions: a) PPh₃, DIAD, THF, 12 h, r.t., 61%; b) m-CPBA, CH₂Cl₂, NaHCO₃, 12 h, 76%

Scheme 119: Completion of the synthesis PT-spiroacetal sulfone 379

The final step was the Julia olefination between phthalide aldehyde 189 and spiroacetal sulfone 379. Potassium hexamethyldisilazide was added to a solution of sulfone 379 in THF at -78 °C and the mixture was stirred for 0.2 h. Phthalide aldehyde 189 was then added and stirred for 1.5 h at that temperature followed by 1 h at room temperature to afford alkene 464 in 68% as a mixture of E and Z isomers. The formation of the alkene 464 was supported by a multiplet in the ¹H NMR at δ 5.33-5.53 assigned to H3' and H4', further resonance at δ 132.2 and 128.1 in the ¹³C NMR were assigned to C4' and C3' respectively. A molecular ion at m/z 459.2727 in the high resolution ESI mass spectrum (459.2714 calculated for MH⁺) provided evidence for the successful formation of the olefin 464. The ratio of E to Z isomers was not determined as the resulting double bond was hydrogenated in the presence of Adam's catalyst in MeOH/THF (1:1) to yield the final long chain phthalide analogue 336 in 70% yield (Scheme 120). The formation of the phthalide analogue 336 was supported by a molecular ion at m/z 461.2887 in the high resolution ESI mass spectrum (461.2898 calculated for MH⁺).

Reagents and conditions: a) KHMDS, THF, 1.5 h, -78 °C then 1 h r.t., 67%; b) PtO₂, H₂, MeOH/THF (1:1), 6 h, 70%

Scheme 120: Completion of the synthesis of phthalide analogue 336
2.6 Synthesis of short chain (four carbon) indole 337 and oxindole 340 analogues

2.6.1 Synthesis of short chain spiroacetal iodide 470

The proposed synthesis of the four carbon short polymethylene chain spiroacetal 470 was envisaged to proceed in the same fashion as the synthesis of the eight carbon chain spiroacetal 359 (Scheme 72), starting with 5-hexen-1-ol (465). The strategy for the synthesis of four carbon polymethylene chain spiroacetal iodide 470, involved the preparation of aldehyde 468 from epoxide 466 via bis-homoallylic alcohol 467. Coupling of aldehyde 468 with (S)-acetylene 219 synthesised from commercially available (S)-but-3-yn-2-ol (218) would allow access to the dihydroxyketone 469. Finally acid catalysed cyclisation of dihydroxyketone 469 after functional group manipulation would furnish spiroacetal iodide 470 (Scheme 121).

Scheme 121: Plan for the synthesis short chain spiroacetal iodide 470

Stirring tert-butyldiphenylsilyl chloride, imidazole and DMAP with 5-hexen-1-ol (465) in dichloromethane for 12 h effected protection of the alcohol as tert-butyldiphenylsilyl ether 471. Oxidation of the olefin 471 with m-CPBA in dichloromethane over 12 h at room temperature yielded racemic epoxide 472 in 79% yield. HKR of the racemic epoxide following the earlier described procedure (Scheme 75) in the presence of isopropanol gave the desired chiral epoxide 466 in 99% e.e. as determined by chiral HPLC. Generation of the diallylcyanocuprate reagent in situ following previous work (Scheme 83) enabled the opening of the epoxide 466 to the bis-homoallylic alcohol 473 in 91% yield. Hydroboration oxidation of the alkene 473 using borane-dimethyl sulfide complex in THF over 12 h followed by Dess-Martin periodinane oxidation of the resulting primary alcohol 474 furnished aldehyde 468 in 66% overall yield. In accordance with the earlier work (Scheme 87)
coupling of aldehyde 468 with chiral acetylene 219 in the presence of lithium bromide resulted in secondary alcohol 475, which was oxidised to ynone 476 using N-methylmorpholine-N-oxide and tetrapropylammonium perruthenate. Hydrogenation of the triple bond over Adam's catalyst yielded the dihydroxyketone precursor 469 in 83% yield (Scheme 122).

Upon treatment of dihydroxyketone 469 with camphorsulfonic acid in dichloromethane for 3 h at room temperature, spiroacetal 477 was formed smoothly in 74% yield. Removal of the tert-butylsilyldiphenyl ether with tetra-n-butylammonium fluoride in THF for 2 h at room temperature gave spiroacetal alcohol 478. Treatment of the alcohol 478 with methanesulfonyl chloride in THF in the presence of triethylamine followed by reflux with sodium iodide, gave the desired iodide 470 (Scheme 123).
Chapter II: Discussion

Reagents and conditions: a) CSA, CH$_2$Cl$_2$, 3 h, r.t., 74%; b) TBAF, THF, 2 h, r.t. 92%; c) THF, MsCl, Et$_3$N, 0 °C-r.t then NaI, reflux, 12 h, 67%

Scheme 123: Synthesis of spiroacetals iodide 470

2.6.2 Completion of the short chain indole and oxindole analogues 337, 340

Finally the completion of the two short chain analogues was performed by reacting spiroacetals iodide 470 with 4,6-dimethoxyindole (352) and 4,6-dimethoxyoxindole (354) using the previously established method (Scheme 104). Accordingly, treatment of 4,6-dimethoxyindole (354) with potassium hydroxide in DMSO followed by the addition of iodide 470, provided analogue 337 after 2.5 h at room temperature. The formation of the indole analogue 337 was supported by a triplet in the $^1$H NMR at $\delta$ 4.02 assigned to H1', a further resonance at $\delta$ 46.5 in the $^{13}$C NMR was assigned to C1'. A molecular ion at $m/z$ 388.2473 in the high resolution ESI mass spectrum (388.2456 calculated for MH$^+$) provided evidence for the successful formation of the indole analogue 337 (Scheme 124).

Meanwhile treatment of 4,6-dimethoxyoxindole (354) with a single equivalent of sodium hydride in DMF followed by addition of iodide 470 for 2.5 h at room temperature provided analogue 340 (Scheme 124). The formation of the oxindole analogue 340 was supported by a triplet in the $^1$H NMR at $\delta$ 3.64 assigned to H1', a further resonance at $\delta$ 40.2 in the $^{13}$C NMR was assigned to C1'. A molecular ion at $m/z$ 404.2415 in the high resolution ESI mass spectrum (404.2431 calculated for MH$^+$) provided evidence for the successful formation of the oxindole analogue 340 (Scheme 124).
2.7 Synthesis of short chain (four carbon) phthalide analogue 335

2.7.1 Attempted synthesis of one carbon polymethylene chain spiroacetal 483

In order to synthesise a four carbon polymethylene chain phthalide analogue of spirolaxine methyl ether (15), using a similar strategy to that reported above (Scheme 120), first it was necessary to prepare one carbon methylene chain spiroacetal 483 from allyl alcohol 479, that would then be coupled to the three carbon polymethylene chain phthalide aldehyde 189 (Scheme 125).
A. Preparation of bis-homoallylic alcohol 487

tert-Butyldiphenylsilyl protection of allyl alcohol 484 proceeded smoothly in the presence of tert-butyldiphenylsilyl chloride, DMAP and imidazole in dichloromethane. m-CPBA epoxidation of the double bond in dichloromethane gave racemic epoxide 486. Following the earlier developed procedure (Scheme 75), HKR afforded chiral epoxide 480 in 81% e.e. as determined by chiral HPLC. Initial attempts at opening the epoxide with higher order diallylcyanocuprate using the earlier procedure (Scheme 83) proved troublesome. Stirring the epoxide 480 with the in situ formed diallylcyanocuprate for more than 1 h at 0 °C resulted in a complex mixture. Lowering the temperature to -20 °C resulted in recovery of starting material. Finally it was observed that stirring epoxide 480 with the preformed cuprate at 0 °C for precisely one hour did result in the desired product 487 in 67% yield (Scheme 126).

\[
\begin{align*}
&\text{HO} \quad \text{TBDSO} \quad \text{TBDSO} \quad \text{TBDSO} \quad \text{OH} \\
&\text{484} \quad \text{485} \quad \text{486} \quad \text{487} \\
&\text{488} \quad \text{489} \quad \text{490} \quad \text{491}
\end{align*}
\]

Reagents and conditions: a) TBDPSCI, imid., DMAP, CH\(_2\)Cl\(_2\), 12 h, r.t., 97%; b) m-CPBA, CH\(_2\)Cl\(_2\), r.t., 12 h, 99%; c) \(R,R\)-SalenCo\(\text{III}^+\)OAc, iPrOH, 24 h, 95%; d) CuCN, MeLi, allylSnBu\(_3\), -78-0 °C, 1 h, 67%

Scheme 126: Synthesis of secondary alcohol 487

B. Preparation of dihydroxyketone 482

tert-Butyldimethylsilyl protection of the secondary alcohol 487 using tert-butyldimethylsilyl chloride, DMAP and imidazole in dichloromethane for 12 h at room temperature proceeded smoothly. Hydroboration oxidation of the olefin 488 with borane-dimethyl sulfide complex in THF yielded alcohol 489 in 73% yield. Dess-Martin oxidation of the primary alcohol 489 in dichloromethane in the presence of pyridine for 3 h at room temperature provided the desired aldehyde 481. Following the earlier protocol (Scheme 87) the aldehyde 481 was coupled with acetylene 219 derived from (S)-but-3-yn-2-ol (218) in the presence of LiBr to give alcohol 490. N-methylmorpholine-\(N\)-oxide and tetrapropylammonium perruthenate oxidation of alcohol 490 in dichloromethane yielded ynone 491, which underwent smooth hydrogenation in the presence of Adam's catalyst in THF/MeOH (1:1) over 6 h to yield dihydroxyketone 482 (Scheme 127).
Chapter II: Discussion

Reagents and conditions: a) TBDMSCl, imid., CH₂Cl₂, DMAP, 12 h, 75%; b) BH₃•SMe², THF, 12 h, r.t., 73%; c) DMP, CH₂Cl₂, pyr., 3 h, r.t. 77%; d) 'BuLi, THF, -78-0 °C, LiBr, 6 h, 72%; e) TPAP, NMO, CH₂Cl₂, 2 h, r.t., 79%; f) H₂, PtO₂, MeOH:THF (1:1), 6 h, r.t., 89%

Scheme 127: Synthesis of dihydroxyketone 482

Attempts at effecting spiroacetalisation of dihydroxyketone 482 with camphorsulfonic acid proved futile. Use of different temperatures, reaction times and equivalents of acid only resulted in decomposition. At this point it was postulated that the one carbon methylene chain spiroacetal 492 is quite unstable and may be difficult to handle (Scheme 128). An alternative strategy to analogue 335 was therefore devised.

Scheme 128: Attempted synthesis of spiroacetal alcohol 492

2.7.2 Synthesis of two carbon polymethylene chain phthalide aldehyde 493

Having established that the synthesis of the one carbon methylene chain spiroacetal 492 was difficult, it was envisaged that the problem could be circumvented by forming a two carbon polymethylene chain phthalide aldehyde 493. Coupling this compound to a two carbon polymethylene chain spiroacetal sulfone 229, which had already been synthesised by Robinson and Brimble¹⁴⁶ (Scheme 49) would yield a four carbon polymethylene chain phthalide analogue 335 (Scheme 129).
Chapter II: Discussion

Scheme 129: Revised strategy to analogue 335

Serendipitously very recent work completed by Choi et al.\textsuperscript{200} in our group on the total synthesis of (-)-herbaric acid (494) produced the opposite enantiomer of the exact phthalide aldehyde 493 necessary for our proposed synthesis (Scheme 130). The planned retrosynthesis of (-)-herbaric acid (494) by Choi et al.\textsuperscript{200} involved oxidation and deprotection of the key aldehyde 495. Aldehyde 495 was derived from vinyl phthalide 496 via Wacker oxidation. In turn the chiral vinyl phthalide 496 was constructed by lactonization of carbamate 497, which in turn was derived using microwave-assisted kinetic resolution of benzylic alcohol 498 (Scheme 130).

Scheme 130: Retrosynthetic analysis of (-)-herbaric acid (494) by Choi et al.\textsuperscript{200}

Wacker oxidation of terminal alkenes predominantly forms methyl ketones, inferring that hydroxypalladation takes place following Markovnikov's rules.\textsuperscript{201} There are a few examples of so-called "reverse" Wacker transformations controlled by heteroatoms.\textsuperscript{202-206} The heteroatom-directed Wacker oxidation of the vinyl phthalide 496 relies on the bridging oxygen present in the lactone to provide an anchor enabling chelation to palladium, thereby facilitating delivery of water to the methylene carbon and affording the desired aldehyde 495 (Scheme 131).\textsuperscript{200}
Chapter II: Discussion

Following the procedure of Choi et al.\textsuperscript{200} we set about to construct the two carbon chain phthalide aldehyde 493. Accordingly, readily available 2-bromo-3,5-dimethoxybenzaldehyde (202)\textsuperscript{207,208} was treated with vinylimagnesium bromide in THF at -78 °C for 12 hours to afford racemic alcohol 499 in 85% yield.

Microwave-assisted chemoenzymatic resolution of the alcohol 499 using toluene and p-chlorophenyl acetate (502) as the solvent and acyl donor, respectively in a closed vessel reaction for 48 h led to a 43% yield of (R)-acetate 500 in 96% e.e. as determined by chiral HPLC together with (S)-alcohol 501 (Scheme 133). The stereochemistry of the products was evaluated using Kazlauskas’ rules.\textsuperscript{209} Kazlauskas's rule has traditionally been translated into an active site model for lipases consisting of two "pockets" of different sizes. When a secondary alcohol is resolved by a lipase, the fast-reacting enantiomer binds in the manner shown in Scheme 132. However, when the other enantiomer reacts with the lipase, its large-size substituent has to be accommodated in the small pocket (the stereoselectivity pocket), this is sterically unfavourable and hence accounts for the low reaction rate of that enantiomer.

Hydrolysis of the (R)-acetate 500 with potassium hydroxide in MeOH over 2 h, provided the chiral alcohol 503 in 87% yield. Deprotonation of the alcohol 503 with sodium hydride in THF, followed by addition of N,N-diethylcarbamoyl chloride over 12 h at room temperature resulted in carbamate 504 in 98% yield. Carbamate 504 was treated with "BuLi in THF at -78 °C leading to smooth lithium-
halogen exchange followed by acid-mediated lactonisation to deliver the key vinyl phthalide 505. Exposure of the alkene 505 to standard Wacker oxidation conditions of palladium (II) chloride, copper (I) chloride, oxygen and water in DMF for 2 h at room temperature delivered the desired aldehyde 493 coupling partner in 74% yield (Scheme 133).

Reagents and conditions: a) vinylmagnesium bromide, THF, 12 h, 78 °C, 85%; b) 502, 48 h, 55 °C, 300 W, microwave, 43%, 96% e.e.; c) KOH, MeOH, 2 h, 87%; d) N,N-diethylcarbamoyl chloride, THF, NaH, 0 °C- r.t. 12 h, 98%; e) nBuLi, THF, -78 °C, 1 h then HCl (4 M in dioxane), 12 h, r.t., 82%; f) PdCl₂, CuCl, O₂, DMF-H₂O, r.t., 2 h, 74%

Scheme 133: Synthesis of phthalide aldehyde 493

2.7.3 Synthesis of two carbon polymethylene chain spiroacetal sulfone 229

With the short chain phthalide aldehyde 493 in hand, it was next required to prepare the two carbon polymethylene chain spiroacetal sulfone 229 synthesised by Robinson and Brimble (Scheme 134) and then couple the two fragments to complete the synthesis of analogue 335.
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Scheme 134: Plan for the synthesis of spiroacetal sulfone 229

Following the procedure developed by Robinson and Brimble\(^7\) (Schemes 46 and 47), (S)-aspartic acid (196) was treated with sodium nitrite in the presence of potassium bromide and sulfuric acid to afford bromosuccinic acid 209, which was then reduced to the corresponding diol 210 with borane dimethylsulfide complex in methanol. Diol 210 was then treated with two equivalents of sodium hydride in THF to effect intramolecular cyclisation to epoxide 211 with simultaneous protection of the primary alcohol upon quenching with tert-butyldiphenylsilyl chloride. Epoxide 211 was opened with diallylcyanocuprate formed \textit{in situ} from CuCN, MeLi and allyltributyltin to afford secondary alcohol 212 in 98\% yield. Subsequent protection as a tert-butyldimethylsilyl ether 216 proceeded smoothly by treatment of alcohol 212 with tert-butyldimethylsilyl chloride in the presence of DMAP and imidazole (Scheme 47). Hydroboration oxidation of the double bond with borane-dimethyl sulfide in THF followed by Dess-Martin oxidation of the resulting primary alcohol 217 in dichloromethane in the presence of pyridine gave aldehyde 193. Coupling of the aldehyde 193 with the chiral acetylene 219 derived from (S)-but-3-yn-2-ol (218) in the presence of lithium bromide in THF afforded secondary alcohol 220. Alcohol 220 underwent smooth oxidation to ynone 221 in the presence of N-methylmorpholine-N-oxide and tetrapropylammonium perruthenate in dichloromethane in 97\% yield. Hydrogenation of the triple bond in the presence of Adam’s catalyst in MeOH/THF (1:1) furnished the dihydroxyketone 222 precursor which underwent camphorsulfonic acid catalysed cyclisation in dichloromethane to produce spiroacetal 223 in 86\% yield. Fluoride ion induced removal of the tert-butyldiphenylsilyl ether also occurred smoothly (Scheme 135) to afford spiroacetal alcohol 224.
2.7.4 Julia-Kocienski coupling of phthalide aldehyde 493 and spiroacetal sulfone 229

The last remaining task was to perform the coupling of the phthalide 493 and spiroacetal 229 fragments to complete the synthesis of analogue 335. Following the procedure established by Robinson and Brimble\(^\text{146}\) (Scheme 49), spiroacetal alcohol 224 was converted to sulfide 228 via treatment with 2-mercaptobenzothiazole under Mitsunobu conditions in the presence of triphenylphosphine, diethyl azodicarboxylate in THF. Oxidation of the sulfide 228 with \(m\)-chloroperoxybenzoic acid, in dichloromethane at 0 °C for 12 h provided spiroacetal sulfone 229 in 82% yield.

Gratifyingly, treatment of sulfone 229 with potassium hexamethyldisilazide in THF at -78 °C followed by the addition of phthalide aldehyde 493 and warming to room temperature over 2.5 h gave olefin 506 in 62% yield. The formation of the alkene 506 was supported by a multiplet in the \(^1\)H NMR
at δ 5.45-5.58 assigned to H2' and H3'. A molecular ion at m/z 403.2090 in the high resolution ESI mass spectrum (403.2115 calculated for MH+) provided evidence for the successful formation of the olefin 506. The ratio of E to Z isomers was not determined as the resulting double bond was hydrogenated in the subsequent step. The final reduction of the double bond was achieved by hydrogenation with Adam's catalyst in THF/MeOH (1:1) for 6 h. The reaction proceeded smoothly to furnish the desired analogue 335 in 77% yield (Scheme 136). The formation of the phthalide analogue 335 was supported by a molecular ion at m/z 405.2254 in the high resolution ESI mass spectrum (405.2272 calculated for M+) (Scheme 136).

\[
\begin{align*}
\text{HO} & \quad \text{a} \quad \text{Me} \\
\text{224} & \quad \text{228} & \quad \text{Me} \\
\text{c} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{493} \\
\text{MeO} & \quad \text{MeO} & \quad \text{506} & \quad \text{Me} \\
\text{MeO} & \quad \text{335} & \quad \text{Me} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{OMe}
\end{align*}
\]

Reagents and conditions: a) 2-mercaptobenzothiazole, Ph3P, DEAD, THF, 0 °C, 2 h, 70%; b) m-CPBA, NaHCO3, CH2Cl2, 0 °C to r.t., 12 h, 82%; c) KHMDS, THF, -78 °C-r.t. 2.5 h, 62%; d) H2, PtO2, THF:MeOH (1:1), 6 h, 77%

Scheme 136: Completion of short chain phthalide analogue 335

2.8 Conclusions and future work

2.8.1 Summary of the prepared analogues of spirolaxine methyl ether (15)

In conclusion eight analogues of the (2”S)-diastereomer of spirolaxine methyl ether (21) were synthesised. The indole 338 and oxindole 341 analogues of (2”S)-diastereomer of spirolaxine methyl ether (21) were synthesised in 20 steps. Indole 339 and oxindole 342 analogues with eight carbon polymethylene chain, three carbons longer than the natural product were synthesised in 15 steps and an eight carbon polymethylene chain phthalide analogue 336 in 25 linear steps. The short chain indole 337 and oxindole 340 with a four carbon polymethylene chain were synthesised in 15 linear steps, while the short chain phthalide analogue 335 was also prepared in 15 steps (Schemes 137 and 138).
Short (4 carbons) chain analogues

Long (8 carbons) chain analogues

Scheme 137: Synthesised analogues
Scheme 138: Summary of syntheses of the eight analogues
2.8.2 Biological results

The biological testing was performed by Fiona Radcliff, Orla Finch in the Fraser laboratory. The biological testing of the eight analogues was carried out as follows: *H. pylori* was cultured overnight in a microaerophilic atmosphere at 37 °C, 70 rpm in Brucella Broth. The compounds were weighed and dissolved in DMSO at 10 mg/mL. The compounds were then diluted with the equivalent quantity of DMSO in Brucella Broth. The absorbance was determined of the overnight culture at \( A_{570} \). The colony forming units (CFU)/mL was determined by plating serial dilutions of the culture onto quarter sections of Brucella agar and cultured for up to 5 days in a 37 °C CO₂ incubator. *H. Pylori* was transferred into petri dishes, 2 mL of culture per plate. Compound or control was added to each culture (0.5 mL/plate) and incubated for 24 h. Aliquots were taken of each to determine the \( A_{570} \) for each condition tested and the CFU/mL was quantified. The CFU/mL was determined after up to five days culture time by screening the plates to identify the highest dilution factor with visible signal colonies and enumerate the colonies. The analogues were tested in two independent experiments and the same minimum inhibitory concentration (MIC) value was obtained in both experiments, therefore there is no statistical error to report (Scheme 139).
Chapter II: Discussion

Scheme 139: Biological results

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>2.0</td>
</tr>
<tr>
<td>337</td>
<td>3.0</td>
</tr>
<tr>
<td>338</td>
<td>8.3</td>
</tr>
<tr>
<td>339</td>
<td>&gt;100</td>
</tr>
<tr>
<td>340</td>
<td>12.5</td>
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<tr>
<td>341</td>
<td>12.5</td>
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<tr>
<td>342</td>
<td>16.0</td>
</tr>
<tr>
<td>335</td>
<td>12.5</td>
</tr>
<tr>
<td>336</td>
<td>3</td>
</tr>
</tbody>
</table>

**MIC** (minimum inhibitory concentration)
In general for the indole analogues the anti-\textit{H. pylori} activity increases with decreasing chain length. There is less correlation between chain length and activity for the oxindole analogues, the short chain 340 and exact 341 oxindole analogues have the same activity, while the long chain analogue 342 is less active than either of them. However the trend is the same as for the indole analogues i.e. increasing chain length decreases activity. The data for the phthalide analogues is less informative, the short chain phthalide analogue is least active while the long chain phthalide analogue has nearly the same activity as the natural product. The two most active analogues were the chain shortened indole analogue 337 and chain lengthened phthalide analogue 336 that both displayed inhibitory activity of 3 \( \mu \)g/mL (spirolaxine methyl ether (15) 2 \( \mu \)g/mL) (Scheme 139). This is a very gratifying result since the indole analogue 337 is nearly as potent as spirolaxine methyl ether (15), yet easier to synthesise in just 16 total steps compared to the 23 total steps employed by Robinson and Brimble\textsuperscript{70} (Scheme 138).

### 2.8.3 Future work

Future analogue exploration of spirolaxine methyl ether (15) might lie in forming diastereomers of the natural product in order to improve its activity. The (2''\(S\))-diastereomer of spirolaxine methyl ether (21) was four times more potent than the parent (Scheme 6). Forming a (3\(S\))-diastereomer of spirolaxine methyl ether 507 or a (2''\(S\), 3\(S\))-diastereomer 508 could provide an interesting investigation (Scheme 140).

![Scheme 140: Future analogues](image)

Since a trend between the polymethylene chain length and the observed anti-\textit{H. pylori} activity was observed with the indole and oxindole analogues, there is potential for extending the work by bioisosteric replacements of the phthalide unit with other heterocycles, to form analogues with varying polymethylene chain lengths (Scheme 141). Obtaining a larger library of compounds would provide a clearer understanding of the correlation between chain length and activity. Dimethoxyindazole 510 could be a logical bioisostere to try as it is very similar in size to...
dimethoxyindole 352 yet it is different electronically due to the presence of a nitrogen atom at the 2 position. Isatin 511 could also be tried as it is similar in size to oxindole, yet different electronically due to the presence of an extra carbonyl at the C-3 position. An interesting analogue to explore would be the formation of a carba isostere of the phthalide heterocycle by replacing it with dimethoxyindane 509. Replacing the heteroatom with a methylene could improve chemical and biological stability.210 Evaluating all anti-H. pylori data would provide a clearer picture of the possible relationship between chain length, nature of the heterocycle and stereochemistry to afford the optimum anti-H. pylori activity.

Scheme 141: Future analogues
3.1 Synthesis of Long Chain Indole 339 and Oxindole 342 Analogues

1-(tert-Butyldiphenylsilyloxy)-decan-9-ene (361)

TBDPSO

tert-Butyldiphenylsilylchloride (7.30 mL, 28.0 mmol), 4-dimethylaminopyridine (0.14 g, 1.10 mmol) and imidazole (3.60 g, 42 mmol) were dissolved in CH$_2$Cl$_2$ (10 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this stirred solution was added 9-decen-1-ol (5.00 mL, 28.0 mmol) in CH$_2$Cl$_2$ (5 mL). After stirring for 12 h at room temperature, the white precipitate was filtered off and the solvent removed under reduced pressure to yield the title compound (10.8 g, 98%) as a yellow oil without further purification.

IR $\gamma_{\text{max}}$(film): 2928, 1472, 1427, 1389, 1107, 908, 822, 738, 687, 613 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.65-7.69 (4H, m, Si'tBuPh$_2$, o), 7.28-7.34 (6H, m, Si'tBuPh$_2$, m and p), 5.71-5.80 (1H, m, H9), 4.88-5.01 (2H, m, H10), 3.66 (2H, t, J 6.5, H1), 2.01 (2H, dt, J 7.4 and 6.9, H8), 1.56 (2H, tt, J 6.4 and 4.4, H2), 1.22-1.37 (10H, m, H3-7), 1.06 (9H, s, Si'tBuPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 138.9 (CH, C9), 135.5 (CH, Si'tBuPh$_2$, o), 134.1 (quat., Si'tBuPh$_2$), 129.4 (CH, Si'tBuPh$_2$, p), 127.5 (CH, Si'tBuPh$_2$, m), 114.2 (CH$_2$, C10), 63.9 (CH$_3$, C1), 33.8 (CH$_2$, C8), 32.6 CH$_2$, (CH$_3$, C2), 29.4 (CH$_2$, C4), 29.3 (CH$_2$, C5), 29.0 (CH$_2$, C6), 28.9 (CH$_2$, C7), 26.9 (CH$_3$, Si'tBuPh$_2$), 25.7 (CH$_2$, C3), 19.2 (quat., Si'tBuPh$_2$); m/z (EI): 337 (73), 199 (100), 183 (25), 135 (7), 123 (14), 105 (6), 77 (8), 55 (9) and 41 (13); HRMS (Cl): Found (MH)$^+$, 395.27762 C$_{26}$H$_{39}$OSi, requires 395.27702.

1-(tert-Butyldiphenylsilyloxy)-9-decanene oxide (362)

TBDPSO

meta-Chloroperoxybenzoic acid (10.3 g, 46.0 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL) under an atmosphere of nitrogen and cooled to 0 °C. A solution of alkene 361 (8.90 g, 23.0 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise. The solution was allowed to warm to room temperature over 12 h then saturated aqueous sodium sulfite solution (50 mL) was added to the reaction mixture and stirred until it became clear. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layer was then washed with NaOH solution (100 mL, 5 %) and brine (100 mL) and the solvent was removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (7.30 g, 78%) as a yellow oil.
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**IR** $\gamma_{\text{max}}$(film): 2930, 2855, 1588, 1471, 1427, 1388, 1360, 1258, 1215, 1187, 1111, 823, 739, 701 cm$^{-1}$; $^1\text{H}$ NMR (400 MHz, CDCl$_3$): 7.65-7.69 (4H, m, Si‘BuPh$_2$, o), 7.28-7.34 (6H, m, Si‘BuPh$_2$, m and p), 3.66 (2H, J 6.5, H1), 2.86-2.89 (1H, m, H9), 2.72 (1H, dd, J 4.8 and 5.2, H10a), 2.44 (1H, dd, J 2.8 and 5.2, H10b), 1.20-1.59 (14H, m, H2-8), 1.05 (9H, s, Si‘BuPh$_2$); $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$): 135.5 (CH, Si‘BuPh$_2$, o), 134.1 (quat., Si‘BuPh$_2$), 129.4 (CH, Si‘BuPh$_2$, p), 127.5 (CH, Si‘BuPh$_2$, m), 63.9 (CH$_2$, C1), 52.3 (CH, C9), 47.0 (CH$_2$, C10), 32.5 (CH$_2$, C8), 32.4 (CH$_2$, C2), 29.4 (CH$_2$, C4), 29.3 (CH$_2$, C5), 29.2 (CH$_2$, C6), 26.8 (CH$_3$, Si‘BuPh$_2$), 25.9 (CH$_2$, C7), 25.7 (CH$_2$, C3), 19.2 (quat., Si‘BuPh$_2$); $m/z$ (CI): 411 (6), 395 (18), 353 (21), 333 (80), 216 (30), 199 (52), 137 (79), 95 (85), 81 (100), 78 (50), 71 (14); HRMS (CI): Found (MH)$^+$, 411.27264 C$_{26}$H$_{39}$O$_2$Si, requires 411.27193.

(R)- 1-(tert-Butyldiphenylsilyloxy)-9-decanene oxide (355)

To a solution of (R,R)-SalenCo$^{\text{II}}$ (0.15 g, 0.24 mmol) in toluene (1.20 mL) was added glacial acetic acid (27.0 μL, 0.48 mmol) and the mixture was stirred open to the air for 1 h to form the active form of the catalyst (R,R)-SalenCo$^{\text{III}}$OAc over this period of time the colour changed from orange to dark brown. The solution was concentrated in vacuo to give a crude brown solid. To the resultant catalyst residue was added a solution of epoxide 362 (6.30 g, 16.0 mmol) in isopropanol (6 mL). The resultant solution was cooled to 0 °C and water (0.17 mL, 9.60 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 h. The isopropanol was removed under reduced pressure and the resulting chiral epoxide was purified by flash chromatography (hexanes/EtOAc 25:1) to afford the title compound (2.70 g, 80%) as a yellow oil; $[\alpha]_{\text{D}}$ +8.50 (c 1.30, CHCl$_3$). The spectroscopic data was identical to that reported above for epoxide 362.

(S)-13-(tert-Butyldiphenylsilyloxy)-tridec-1-en-5-ol (366)

CuCN (0.68 g, 7.60 mmol) was gently flame dried under vacuum, then dissolved in THF (8 mL) under an atmosphere of nitrogen. The mixture was cooled to -78 °C and MeLi (9.50 mL, 15.2 mmol, 1.6 M in THF) was added. The reaction was allowed to warm to 0 °C and further stirred at this temperature for 20 min. AllylSnBu$_3$ (5.03 g, 15.2 mmol) was added at 0 °C as a neat liquid in one portion and the solution continued to be stirred at this temperature for an additional 30 min. The reaction mixture was cooled to -78 °C and epoxide 355 (1.50 g, 3.80 mmol) in THF (5 mL) was cannulated to the resulting cuprate. The
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reaction was then warmed to 0 °C and stirred at that temperature for an additional hour. The solution was quenched by the addition of 10% ammonia solution in saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate filtered and the solvent removed in vacuo. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (1.40 g, 82%) as a yellow oil; [α]D +15.4 (c 1.30, CHCl3).

IR γmax(film): 3344 br (OH), 2928, 2855, 1462, 1427, 1109, 997, 910, 822, 739, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl3): 7.66-7.69 (4H, m, SiBuPh₂, o), 7.36-7.41 (6H, m, SiBuPh₂, m and p), 5.80-5.89 (1H, m, H12), 4.96-4.99 (2H, m, H13), 3.65 (2H, t, J 6.5, H1), 3.61-3.63 (1H, m, H9), 2.15-2.23 (2H, m, H11), 1.22-1.59 (16H, m, H2-8 and H10), 1.05 (9H, s, SiBuPh₂); ¹³C NMR (100 MHz, CDCl3): 138.6 (CH, C12), 135.5 (CH, SiBuPh₂, o), 134.1 (quat., SiBuPh₂), 129.4 (CH, SiBuPh₂, p), 127.5 (CH, SiBuPh₂, m), 114.7 (CH₂, C13), 71.5 (CH₂, C9), 63.9 (CH₂, C1), 37.5 (CH₂, C8), 36.9 (CH₂, C10), 36.4 (CH₂, C11), 32.5 (CH₂, C2), 30.1 (CH₂, C4), 29.6 (CH₂, C5), 29.5 (CH₂, C6), 29.3 (CH₂, C7), 26.8 (CH₃, SiBuPh₂), 25.7 (CH₂, C3), 19.2 (quat., SiBuPh₂); m/z (CI): 452 (1), 435 (9), 395 (11), 377 (9), 319 (5), 239 (10), 216 (21), 199 (100), 179 (23), 139 (39), 123 (42), 109 (55), 95 (71), 83 (62), 75 (7); HRMS (Cl): Found (MH)+, 453.31945 C₂₉H₄₅O₂Si, requires 453.31888.

(S)-(R)-13-(tert-Butyldiphenylsilyloxy)tridec-1-en-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (368)

Following a literature procedure¹⁷³ a solution of alcohol 366 (50.0 mg, 110 µmol) in CH₂Cl₂ (1 mL) was added to a suspension of (R)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (36.0 mg, 150 µmol), N,N-4-dimethylaminopyridine (2.70 µg, 20.0 µmol) and dicyclohexylcarbodiimide (55.0 mg, 270 µmol) in CH₂Cl₂ (1 mL). After stirring the mixture for 48 h, the dicyclohexylurea white precipitate was filtered off and the organic layer was washed with water. The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined extracts dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a crude oil. Purification by flash chromatography using (hexanes/diethyl ether 8:1) as the eluent to afforded the title compound (59.0 mg, 80%) as a yellow oil; [α]D -4.70 (c 1.20, CHCl3).
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IR  \( \gamma_{\text{max}} \) (film): 2930, 1742, 1462, 1451, 1261, 1167, 1106, 1017, 697, 613 cm\(^{-1}\); H NMR (300 MHz, CDCl\(_3\)): 7.66-7.69 (4H, s, Si' BuPh\(_2\), o), 7.55-7.58 (2H, m, ArH, o or m), 7.35-7.45 (9H, m, Si' BuPh\(_2\), m and p, and ArH, p and o or m), 5.80-5.89 (1H, m, H12), 5.11 (1H, quintet, J 6.3, H9), 4.94-4.99 (2H, m, H13), 3.66 (2H, t, J 6.5, H1), 3.57 (3H, s, OMe), 2.15-2.23 (2H, m, H11), 1.22-1.59 (16H, m, H2-8 and H10), 1.05 (9H, s, Si' BuPh\(_2\)); C NMR (75 MHz, CDCl\(_3\)): 166.2 (quat., C=O), 137.4 (CH, C12), 135.5 (CH, Si' BuPh\(_2\), o), 134.1 (quat., Si' BuPh\(_2\)), 129.4 (CH, Si' BuPh\(_2\), p), 127.5 (CH, Si' BuPh\(_2\), m), 125.3 (CF\(_3\)), 115.3 (CH\(_2\), C13), 78.2 (quat., CCF\(_3\)), 77.2 (CH, C9), 63.9 (CH\(_2\), C1), 55.40 (CH\(_3\), OMe), 33.7 (CH\(_2\), C8), 33.4 (CH\(_2\), C10), 32.9 (CH\(_2\), C2), 32.5 (CH\(_2\), C4), 29.6 (CH\(_2\), C5), 29.5 (CH\(_2\), C6), 29.3 (CH\(_2\), C7), 26.8 (CH\(_3\), Si' BuPh\(_2\)), 25.7 (CH\(_2\), C3), 19.2 (quat., Si' BuPh\(_2\)); F NMR (282 MHz, CDCl\(_3\)): \( \delta \) -72.38 (single detectable peak) greater than 99% ee.; m/z (FAB): 669 (1), 435 (7), 355 (8), 239 (13), 213 (18), 199 (79), 216 (21), 189 (54), 183 (34), 135 (100), 121 (30), 105 (42), 95 (55), 81 (53), 75 (29); HRMS (CI): Found (MH\(^+\)), 669.36034 C\(_{39}\)H\(_{52}\)F\(_3\)O\(_4\)Si, requires 669.35870.

(9S)-1-(tert-Butyldiphenylsilyloxy)-9-(tert-butylidemethylsilyloxy)-tridecan-12-ene (356)

\[
\text{TBDPSO}^+ - 13\text{OTBDMS}^- 
\]

tert-Butyldimethylsilylchloride (490 mg, 3.26 mmol), imidazole (260 mg, 3.78 mmol), N,N-dimethylaminopyridine (12.0 mg, 90.0 µmol) were dissolved in CH\(_2\)Cl\(_2\) (23 mL) under nitrogen atmosphere and cooled to 0 °C. To this stirred solution was added alcohol 366 (1.14 g, 12.0 mmol) in CH\(_2\)Cl\(_2\) (5 mL). After stirring for 12 h, brine (10 mL) was added and the aqueous layer extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate. The solvent was removed in vacuo and purification by flash chromatography (hexanes/EtOAc 40:1) afforded the title compound (1.10 g, 80%) as a yellow oil; \([\alpha]\)\(_D\) +5.70 (c 1.00, CHCl\(_3\)).

IR  \( \gamma_{\text{max}} \) (film): 2928, 1472, 1427, 1360, 1253, 1106, 833, 722, 739 697, 613, 519 cm\(^{-1}\); H NMR (300 MHz, CDCl\(_3\)): 7.69-7.72 (4H, m, Si' BuPh\(_2\), o), 7.37-7.44 (6H, m, Si' BuPh\(_2\), m and p), 5.84-5.87 (1H, m, H12), 4.96-4.99 (2H, m, H13), 3.68 (2H, t, J 6.5, H1), 3.66-3.67 (1H, m, H9), 2.09-2.14 (2H, m, H11), 1.28-1.61 (16H, m, H2-8 and H10), 1.08 (9H, s, Si' BuPh\(_2\)), 0.91 (9H, s, Si' BuMe\(_2\)), 0.04 (3H, s, Si' BuMe\(_2\)), 0.01 (3H, s, Si' BuMe\(_2\)); C NMR (75 MHz, CDCl\(_3\)): 139.1 (CH, C12), 135.5 (CH, Si' BuPh\(_2\), o), 134.2 (quat., Si' BuPh\(_2\)), 129.4 (CH, Si' BuPh\(_2\), p), 127.6 (CH, Si' BuPh\(_2\), m), 114.1 (CH\(_2\), C13), 71.8 (CH, C9), 63.9 (CH\(_2\), C1), 37.5 (CH\(_2\), C8), 36.2 (CH\(_2\), C11), 32.5 (CH\(_2\), C2), 29.8 (CH\(_2\), C10), 29.7 (CH\(_2\), C4), 29.6 (CH\(_2\), C5), 29.4 (CH\(_2\), C7), 26.9 (CH\(_3\), Si' BuPh\(_2\)), 25.9 (CH\(_3\), Si' BuMe\(_2\)), 25.7 (CH\(_2\), C3), 19.2 (quat., Si' BuMe\(_2\)), 18.1 (quat., Si' BuMe\(_2\)), -4.4 (CH\(_3\), Si' BuMe\(_2\)), -4.5 (CH\(_3\), Si' BuMe\(_2\)); m/z (EI): 566 (1), 509

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(11), 377 (12), 313 (6), 273 (7), 253 (100), 211 (15), 199 (40), 145 (21), 95 (132), 75 (94), 56 (19); HRMS (CI): Found M⁺, 566.39885 C₃₅H₅₈O₂Si₂, requires 566.39754.

(S)-5-(tert-Butyldimethylsilyloxy)-13-(tert-butyldiphenylsilyloxy)-tridecan-1-ol (369)

Alkene 356 (400 mg, 710 µmol) was dissolved in THF (6 mL) under an atmosphere of nitrogen and the solution was cooled to 0 °C. Borane dimethylsulfide complex (130 µL, 1.40 mmol) was added to the stirred solution dropwise and the solution was allowed to warm to room temperature over 12 h. Oxidative workup by addition of H₂O₂ (500 µL, 8.80 M) and aqueous NaOH (4.00 mL, 1 M) gave a biphasic mixture which was stirred for 40 min. The mixture was then extracted with diethyl ether (3 x 10 mL) and the combined extracts were dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave an oil that was purified by flash chromatography using (hexanes/EtOAc 15:1) to afford the title compound (0.30 g, 73%) as a yellow oil; [α]D +52.0 (c 1.30, CHCl₃).

IR γmax (film): 3346 br (OH), 2928, 2855, 1471, 1462, 1427, 1388, 1360, 1253, 1106, 772, 697, 613, 512 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.66-7.68 (4H, m, Si‘BuPh₂, o), 7.35-7.41 (6H, m, Si‘BuPh₂, m and p), 3.62-3.67 (5H, m, H₁, H₉, H₁₃), 1.44-1.58 (4H, m, H₈ and H₉), 1.25-1.43 (16H, m, H₂-7 and H₁₀-11), 1.05 (9H, s, Si‘BuPh₂), 0.91 (9H, s, Si‘BuMe₂), 0.04 (3H, s, Si‘BuMe₂), 0.01 (3H, s, Si‘BuMe₂); ¹³C NMR (100 MHz, CDCl₃): 135.5 (CH, Si‘BuPh₂, o), 134.2 (quat., Si‘BuPh₂), 129.4 (CH, Si‘BuPh₂, p), 127.6 (CH, Si‘BuPh₂, m), 72.2 (CH, C₉), 64.0 (CH₂, C₁), 63.0 (CH₂, C₁₃), 37.1 (CH₂, C₈), 36.8 (CH₂, C₂), 33.0 (CH₂, C₁₀), 32.6 (CH₂, C₄), 29.8 (CH₂, C₃), 29.6 (CH₂, C₁₂), 29.4 (CH₂, C₉), 26.9 (CH₃, Si‘BuPh₂), 25.9 (CH₃, Si‘BuMe₂), 25.8 (CH₂, C₆), 25.3 (CH₂, C₇), 21.4 (CH₃, C₁₁), 19.2 (quat., Si‘BuPh₂), 18.1 (quat., Si‘BuMe₂), -4.4 (CH₃, Si‘BuMe₂); m/z (EI): 584 (1), 511 (10), 395 (42), 371 (10), 239 (10), 199 (100), 183 (19), 135 (32), 109 (50), 95 (64) 75 (79), 69 (31). 55 (41), 41 (20); HRMS (EI): Found M⁺, 584.4078, C₃₅H₆₀O₃Si₂, requires 584.40810.

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(S)-5-(tert-Butyldimethylsilyloxy)-13-(tert-butyldiphenylsilyloxy)-tridecanal (357)

A solution of alcohol 369 (100 mg, 0.17 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise to a suspension of Dess-Martin periodinane (0.15 g, 0.34 mmol) and pyridine (41.0 mg, 0.51 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 2.5 h the solution was diluted with diethyl ether (10 mL) and filtered through Celite®. Removal of the solvent under reduced pressure, followed by flash chromatography (hexanes/EtOAc 20:1) afforded the title compound (90 mg, 91%) as a yellow oil; [α]$_D$ +12.0 (c 1.30, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2928, 1727, 1471, 1427, 1388, 1360, 1253, 1108, 833, 722, 739, 687, 613 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 9.77 (1H, t, $J$ 1.8, H19), 7.69-7.72 (4H, m, Si'tBuPh$_2$, o), 7.37-7.44 (6H, m, Si'tBuPh$_2$, m and p), 3.67 (2H, t, $J$ 6.3, H1), 3.65-3.69 (1H, m, H9), 2.41-2.45 (2H, td, $J$ 1.8 and 7.2, H12), 1.44-1.58 (4H, m, H8 and H9), 1.25-1.43 (16H, m, H2-7 and H10-11), 0.91 (9H, s, Si'tBuMe$_2$), 0.04 (3H, s, Si'tBuMe$_2$), 0.01 (3H, s, Si'tBuMe$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 202.6 (C=O, C13), 135.5 (CH, Si’tBuPh$_2$, o), 134.2 (quat., Si’tBuPh$_2$), 129.4 (CH, Si’tBuPh$_2$, p), 127.6 (CH, Si’tBuPh$_2$, m), 72.0 (CH, C9), 64.0 (CH$_5$, C1), 44.0 (CH$_5$, C12), 39.3 (CH$_4$, C10), 37.1 (CH$_2$, C8), 32.6 (CH$_2$, C4), 30.3 (CH$_2$, C2), 29.8 (CH$_2$, C5), 29.7 (CH$_2$, C6), 29.6 (CH$_2$, C7), 26.9 (CH$_3$, Si’tBuPh$_2$), 25.9 (CH$_3$, Si’tBuMe$_2$), 25.8 (CH$_3$, C3), 24.6 (CH$_3$, C11), 19.1 (quat., Si’tBuPh$_2$), 18.1 (quat., Si’tBuMe$_2$), -4.4 (CH$_3$, Si’tBuMe$_2$); m/z (CI): 582 (1), 525 (100), 511 (4), 467 (1), 393 (29), 365 (4), 337 (4), 273 (3), 258 (4), 253 (9), 239 (2), 215 (8), 199 (84), 183 (14), 177 (6), 159 (6), 139 (11), 135 (14), 105 (11), 95 (22), 75 (65); HRMS (EI): Found M$^+$ 583.39955 C$_{35}$H$_{59}$O$_3$Si$_2$, requires 583.40028.

(S)-(But-3-yn-2-yloxy)(tert-butyl)dimethylsilane (219)

Following an adaptation of the method used by Okamura et al.$^{174}$ to a solution of tert-butyldimethylsilylchloride (2.80 g, 19.7 mmol) and imidazole (2.70 g, 39.4 mmol) in diethyl ether (15 mL) under an atmosphere of nitrogen at 0 °C was added (S)-but-3-yn-2-ol (218) (1.03 mL, 13.1 mmol) in diethyl ether (10 mL). After stirring for 12 h, saturated aqueous ammonium chloride (20 mL) was added and the mixture extracted with diethyl ether (3 x 40 mL). The combined extracts were dried over magnesium sulfate filtered and concentrated under reduced pressure, followed by flash chromatography.
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(hexanes/diethyl ether 97:3) afforded the title compound (1.70 g, 70%) as a yellow oil. $[\alpha]_D$ -43.8 (c 1.30, CHCl$_3$) (lit. $^1$ -46.0 (c 0.090 in CHCl$_3$));

$^1$H NMR (300 MHz, CDCl$_3$): 4.47-4.54 (1H, q, $J$ 6.6, H2), 2.34 (1H, s, H4), 1.40 (3H, d, $J$ 6.6, H1), 0.89 (9H, s, Si$_{t}$BuMe$_2$), 0.12 (3H, s, Si$_{t}$BuMe$_2$), 0.10 (3H, s, Si$_{t}$BuMe$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 86.4 (quat., C3), 71.1 (CH, C4), 58.8 (CH, C2), 25.7 (CH$_3$, Si$_{t}$BuMe$_2$), 25.3 (CH$_3$, C1), 18.2 (quat., Si$_{t}$BuMe$_2$), -4.7 (CH$_3$, Si$_{t}$BuMe$_2$), -5.0 (CH$_3$, Si$_{t}$BuMe$_2$). The spectroscopic data were in agreement with that reported in the literature.$^{174}$

(16S,13R(and 13S),9S)-16,9-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-heptdec-14-yn-13-ol (371)

$n$-BuLi (0.61 mL, 0.97 mmol, 1.6 M) was added to a stirred solution of acetylene 219 (0.16 g, 0.89 mmol) in THF (5 mL), at -78 °C under an atmosphere of nitrogen. The resultant pale yellow solution was stirred for 30 min at this temperature. A solution of LiBr (40.0 mg, 0.41 mmol) in THF (5 mL) under an atmosphere of nitrogen was cannulated to the acetylene mixture. After 15 min a solution of aldehyde 357 (0.470 g, 0.810 mmol) in THF (5 mL) was added dropwise and the solution was allowed to slowly warm to room temperature over 6 h. Saturated ammonium chloride solution (10 mL) was added followed by extraction with diethyl ether (3 x 10 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 30:1) afforded the title compound (0.470 g, 75%) as a yellow oil; $[\alpha]_D$ -14.6 (c 1.30, CHCl$_3$).

IR $\gamma_{max}$(film): 2856, 2928, 1471, 1462, 1428, 1388, 1361, 1316, 1253, 1100, 1005, 832, 773, 738, 697, 687, 613, 520 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si$_{t}$BuPh$_2$, o), 7.35-7.42 (6H, m, Si$_{t}$BuPh$_2$, m and p), 4.54-4.57 (1H, qd, $J$ 6.3 and 1.5, H16), 4.38 (1H, m, H13), 3.65 (2H, t, J 6.3, H1), 3.64-3.65 (1H, m, H9), 1.52-1.73 (6H, m H10-12), 1.39-1.42 (3H, d, $J$ 3.6, H17), 1.22-1.39 (16H, m, H1-8), 1.05 (9H, s, Si$_{t}$BuPh$_2$), 0.91 (9H, s, Si$_{t}$BuMe$_2$), 0.88 (9H, s, Si$_{t}$BuMe$_2$), 0.13 (3H, s, Si$_{t}$BuMe$_2$), 0.12 (3H, s, Si$_{t}$BuMe$_2$), 0.05 (6H, s, Si$_{t}$BuMe$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 135.6 (CH, Si$_{t}$BuPh$_2$, o), 134.2 (quat., Si$_{t}$BuPh$_2$), 129.5 (CH, Si$_{t}$BuPh$_2$, p), 127.6 (CH, Si$_{t}$BuPh$_2$, m), 87.4 (quat., C15), 84.1 (quat., C14), 72.2 (CH, C9), 64.0 (CH$_2$, C1), 62.5 (CH, C13), 58.9 (CH, C16), 38.1 (CH$_2$, C8), 37.1 (CH$_2$, C12), 36.7 (CH$_2$, C10), 32.6 (CH$_2$, C2), 31.6 (CH$_3$, C17), 29.8 (CH$_2$, C5), 29.6 (CH$_2$, C6), 29.4 (CH$_2$, C7), 26.9 (CH$_3$, Si$_{t}$BuPh$_2$), 25.9 (CH$_3$, Si$_{t}$BuMe$_2$), 25.8 (CH$_3$, Si$_{t}$BuMe$_2$), 25.4 (CH$_3$, C3), 25.3 (CH$_2$, C4), 21.0
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(9S, 16S)-9,16-Bis(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)heptadec-14-yn-13-one (372)

Alcohol 371 (0.27 g, 0.35 mmol) was dissolved in CH₂Cl₂ (7 mL) and added to a slurry of 4 Å molecular sieves (1 g) in CH₂Cl₂ (5 mL) and the solution was cooled to 0 °C. To this stirred solution was added a solution of N-methylmorpholine-N-oxide (60.0 mg, 0.53 mmol) and tetrapropylammonium perruthenate (6.00 mg, 0.018 mmol) in CH₂Cl₂ (7 mL). After stirring for 2 h the reaction mixture was filtered through Celite® and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 30:1) afforded the title compound (0.23 g, 86%) as a yellow oil; [α]D -14.0 (c 1.00, CHCl₃).

IR γmax (film): 2928, 2856, 1679, 1471, 1462, 1428, 1388, 1361, 1252, 1102, 833, 773, 737, 697, 687, 613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.66-7.69 (4H, m, Si’BuPh₂, o), 7.35-7.42 (6H, m, Si’BuPh₂, m and p), 4.65 (1H, q, J 6.6, H16), 3.65 (2H, t, J 6.6, H1), 3.62-3.63 (1H, m, H9), 2.55 (2H, t, J 7.5, H12), 1.54-1.77 (4H, m, H8 and H10), 1.47 (3H, d J 6.6, H17) 1.22-1.48 (14H, m, H2-7 and H11), 1.06 (9H, s, Si’BuPh₂), 0.92 (9H, s, Si’BuMe₂), 0.91 (9H, s, Si’BuMe₂), 0.14 (3H, s, Si’BuMe₂), 0.13 (3H, s, Si’BuMe₂), 0.06 (6H, s, Si’BuMe₂); ¹³C NMR (100 MHz, CDCl₃): 187.7 (quat., C=O), 135.5 (CH, Si’BuPh₂, o), 134.2 (quat., Si’BuPh₂), 129.4 (CH, Si’BuPh₂, p), 127.5 (CH, Si’BuPh₂, m), 93.6 (quat., C15), 83.3 (quat., C14), 72.2 (CH, C9), 63.9 (CH₃, C1), 58.9 (CH, C16), 45.5 (CH₂, C12), 37.0 (CH₂, C10), 36.1 (CH₂, C8), 30.3 (CH₂, C2), 29.8 (CH₂, C5), 29.7 (CH₂, C3), 29.3 (CH₂, C7), 26.9 (CH₃, Si’BuPh₂), 25.9 (CH₃, Si’BuMe₂), 25.8 (CH₃, Si’BuMe₂), 25.7 (CH₃, C17), 25.6 (CH₂, C3), 25.2 (CH₂, C4), 24.5 (CH₂, C11), 19.2 (quat., Si’BuPh₂), 18.2 (quat., Si’BuMe₂), 18.1 (quat., Si’BuMe₂), -4.4 (CH₃, Si’BuMe₂), -4.6 (CH₃, Si’BuMe₂), -4.9 (CH₃, Si’BuMe₂), -5.0 (CH₃, Si’BuMe₂); m/z (FAB): 765 (1), 631 (1), 443 (1), 393 (5), 353 (1), 273 (2), 239 (3), 199 (7), 183 (3), 159 (6), 149 (4), 137 (9), 135 (17), 115 (6), 91 (7), 73 (100); HRMS (FAB): Found (MH)+, 765.51380 C₄₅H₇₁O₄Si₃, requires 765.51297.
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(9S, 16S)-9,16-Bis(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)heptadec-13-one (358)

Ynone 372 (43.0 mg, 0.0560 mmol) was dissolved in methanol/THF (5 mL, 1:1) and stirred under an atmosphere of hydrogen in the presence of PtO$_2$ (2.00 mg, 0.009 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite$^\circledR$ and the solvents removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 20:1) afforded the title compound (36.0 mg, 84%) as a yellow oil; [α]$_D^0$ +6.50 (c 3.00, CHCl$_3$).

IR $\gamma_{\text{max}}$ (film): 2928, 2855, 1716, 1462, 1428, 1388, 1361, 1253, 1109, 833, 772, 697, 613, 524 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si$^\text{t}$Bu$_2$Ph$_2$, o), 7.35-7.42 (6H, m, Si$^\text{t}$Bu$_2$Ph$_2$, m and p), 3.80-3.86 (1H, m, H$_{16}$), 3.65 (2H, t, $J$ 6.5, H$_1$), 3.61-3.62 (1H, m, H$_9$), 2.39-2.48 (4H, m, H$_{12}$ and H$_{14}$), 1.54-1.77 (4H, m, H$_8$ and H$_{10}$), 1.22-1.48 (16H, m, H$_{2-7}$, H$_{11}$ and H$_{15}$), 1.1 (3H, d, $J$ 6.2, H$_{17}$), 1.06 (9H, s, Si$^\text{t}$Bu$_2$Ph$_2$), 0.92 (9H, s, Si$^\text{t}$BuMe$_2$), 0.91 (9H, s, Si$^\text{t}$BuMe$_2$), 0.045 (6H, s, Si$^\text{t}$BuMe$_2$), 0.041 (3H, s, Si$^\text{t}$BuMe$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 211.1 (quat., C=O), 135.5 (CH, Si$^\text{t}$Bu$_2$Ph$_2$, o), 134.2 (quat., Si$^\text{t}$Bu$_2$Ph$_2$), 129.4 (CH, Si$^\text{t}$Bu$_2$Ph$_2$, p), 127.5 (CH, Si$^\text{t}$Bu$_2$Ph$_2$, m), 72.1 (CH, C9), 67.6 (CH, C16), 64.0 (CH$_2$, C1) 43.0 (CH$_2$, C12), 38.6 (CH$_2$, C14), 37.1 (CH$_2$, C8), 36.5 (CH$_2$, C10), 32.6 (CH$_2$, C3), 29.8 (CH$_2$, C2), 29.7 (CH$_2$, C5), 29.6 (CH$_2$, C6), 29.4 (CH$_2$, C7), 26.9 (CH$_3$, Si$^\text{t}$BuPh$_2$), 25.9 (CH$_3$, Si$^\text{t}$BuPh$_2$), 25.8 (CH$_3$, Si$^\text{t}$BuMe$_2$), 25.3 (CH$_2$, C4), 23.7 (CH$_2$, C15), 19.8 (CH$_2$, C11), 19.2 (CH$_2$, C6), 19.2 (quat., Si$^\text{t}$BuPh$_2$), 18.2 (quat., Si$^\text{t}$BuMe$_2$), 18.1 (quat., Si$^\text{t}$BuMe$_2$), -4.38 (CH$_3$, Si$^\text{t}$BuMe$_2$), -4.41 (CH$_3$, Si$^\text{t}$BuMe$_2$), -4.43 (CH$_3$, Si$^\text{t}$BuMe$_2$), -4.77 (CH$_3$, Si$^\text{t}$BuMe$_2$); m/z (FAB): 770 (1), 711 (1), 637 (1), 505 (5), 427 (1), 273 (2), 239 (3), 199 (10), 185 (5), 159 (6), 149 (5), 135 (16), 115 (6), 111 (8), 91 (10), 73 (100); HRMS (FAB): Found (MH)$^+$, 769.54516 C$_{45}$H$_{81}$O$_4$Si$_3$, requires 769.54427.
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*tert*-Butyl(8-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)octyloxy)diphenylsilane (373)

To a stirred solution of ketone 358 (0.22 g, 0.29 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C under an atmosphere of nitrogen was added camphorsulfonic acid (0.16 g, 0.64 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 2 h. Filtration through Celite$^\circledast$ followed by wash with CH$_2$Cl$_2$ (10 mL) and removal of the solvent under reduced pressure gave a crude product which was purified by flash chromatography (hexanes/diethyl ether 20:1) to afford the *title compound* (110 mg, 73%) as a yellow oil; [α]$_D$ +18.0 (c 1.60, CHCl$_3$).

**IR $\gamma_{\text{max}}$(film):** 2929, 2857, 1472, 1462, 1427, 1388, 1361, 1253, 1222, 1159, 1109, 1083, 1007, 974, 834, 822, 773, 700 cm$^{-1}$; **$^1$H NMR** (300 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si’BuPh$_2$, o), 7.35-7.42 (6H, m, Si’BuPh$_2$, m and p), 4.20-4.27 (1H, qd, $J$ 6.0, 1.8, H2), 3.78-3.86 (1H, m, H7), 3.65 (2H, t, $J$ 6.6, H1’), 1.96-2.02 (2H, m, H3b and H4b), 1.52-1.85 (10H, m, H9, H2’, H10, H3a, H4a, and H8’), 1.20-1.46 (12H, m, H8, H3’-7’), 1.28 (3H, d, $J$ 6.3, Me), 1.09 (9H, s, Si’BuPh$_2$); **$^{13}$C NMR** (75 MHz, CDCl$_3$): 135.5 (CH, Si’BuPh$_2$, o), 134.2 (quat., Si’BuPh$_2$), 129.4 (CH, Si’BuPh$_2$, p), 127.5 (CH, Si’BuPh$_2$, m), 105.8 (quat., C5), 76.6 (CH, C2), 69.8 (CH, C7), 64.1 (CH$_2$, C1’), 39.5 (CH$_2$, C4 or 10), 36.5 (CH$_2$, C4 or 10), 33.6 (CH$_2$, C8’), 32.6 (CH$_2$, C7’), 31.9 (CH$_2$, C3), 31.2 (CH$_2$, C8), 29.70 (CH$_2$, C3’), 29.6 (CH$_2$, C2’), 29.4 (CH$_2$, C4’), 26.9 (CH$_3$, Si’BuPh$_2$), 25.8 (CH$_2$, C5’), 25.7 (CH$_3$, C6’), 23.3 (CH$_3$, Me), 20.5 (CH$_3$, C9), 19.2 (quat., Si’BuPh$_2$); **$m/z$ (EI):** 522 (1), 465 (90), 447 (5), 409 (3), 387 (5), 365 (12), 337 (8), 199 (100), 183 (20), 167 (9), 155 (21), 149 (21), 135(15), 126 (14), 111 (75), 98 (52), 83 (20), 55 (39), 41 (30); **HRMS (EI):** Found M$^+$, 522.35205, C$_{33}$H$_{50}$O$_3$Si, requires 522.35292.
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8-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)octan-1-ol (370)

To a stirred solution of silyl ether 373 (230 mg, 0.44 mmol) in THF (8 mL) under an atmosphere of nitrogen was added tert-butylammonium fluoride (0.67 mL, 0.67 mmol, 1 M in THF). After stirring for 2 h at room temperature, brine (5 mL) was added and the mixture extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (110 mg, 87%) as a yellow oil; [α]D+50.4 (c 1.10, CHCl3).

IR γmax(film): 3365 br (OH), 2929, 2855, 1458, 1375, 1253, 1222, 1160, 1113, 1059, 1024, 973, 943, 873, 836, 773, 741, 700 cm⁻¹; 1H NMR (300 MHz, CDCl3): 4.14-4.23 (1H, qd, J 6.0, 1.8, H2), 3.73-3.79 (1H, m, H7), 3.59 (2H, t, J 6.6, H1'), 1.90-2.01 (1H, m, H3a), 1.78-1.83 (2H, m, H3b and H4b), 1.48-1.75 (9H, m, H9, H2', H10, H4a, H8'), 1.20-1.46 (12H, m, H8, H3'-7'), 1.28 (3H, d, J 6.3, Me); 13C NMR (75 MHz, CDCl3): 105.8 (quat., C5), 76.6 (CH, C2), 69.8 (CH, C7), 62.8 (CH2, C1'), 39.4 (CH2, C4), 37.1 (CH2, C8'), 36.4 (CH2, C2'), 33.6 (CH2, C10), 32.7(CH2, C3), 31.1 (CH2, C8), 29.7 (CH2, C5'), 29.6 (CH2, C4'), 29.5 (CH2, C6'), 29.4 (CH2, C4'), 26.5 (CH2, C3'), 22.3 (CH3, Me), 20.4 (CH2, C9); m/z (FAB): 285 (35), 269 (10), 199 (5), 154 (100), 136 (80), 124 (5), 111 (20), 101 (20), 95 (15), 89 (29), 81 (10), 71 (9); HRMS (EI): Found (MH)+, 285.24243, C17H33O3 requires 285.24297.

(2S)-7-(8-Iodoctyl)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)octan-1-ol (359)

To a solution of alcohol 370 (130 mg, 0.45 mmol) in THF (5 mL) at 0 °C was added dry triethylamine (0.15 mL, 1.1 mmol) followed by methanesulfonyl chloride (0.043 mL, 0.55 mmol) under an atmosphere of nitrogen. After stirring for 50 min at 0 °C, the precipitate was filtered off and washed with dry THF (3 mL). To the filtrate was added sodium iodide (210 mg, 1.40 mmol) and the resultant mixture was refluxed for 18 h giving a dark brown solution. Saturated aqueous Na2S2O3 (5 mL) was added. The crude product was extracted with diethyl ether (3 x 5 mL). The combined extracts were dried over magnesium sulfate,
filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 40:1) afforded the title compound (0.12 g, 67%) as a colourless oil; $[\alpha]_D +70.1$ (c 1.10, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 2925, 2853, 1456, 1374, 1221, 1162, 1073, 1024, 974, 944, 875, 835, 773, 702, 604, 541 cm$^{-1}$; **$^1$H NMR** (300 MHz, CDCl$_3$): 4.19-4.26 (1H, qd, $J = 6.0, 1.8$, H2), 3.77-3.82 (1H, m, H7), 3.18 (2H, t, $J = 6.9$, H1'), 1.77-1.86 (2H, m, H8'), 1.53-1.76 (10H, m, H3, H4, H10, H9, H2'), 1.20-1.42 (12H, m, H8, H3'-7'), 1.29 (3H, d, $J = 6.3$, Me); **$^{13}$C NMR** (75 MHz, CDCl$_3$): 105.8 (quat., C5), 76.6 (CH, C2), 69.8 (CH, C7), 39.5 (CH$_2$, C4), 36.5 (CH$_2$, C8'), 33.6 (CH$_2$, C7'), 33.5 (CH$_2$, C4'), 31.9 (CH$_2$, C10), 31.2 (CH$_2$, C3'), 31.1 (CH$_2$, C3), 30.5 (CH$_2$, C8), 29.5 (CH$_2$, C5'), 28.5 (CH$_2$, C2'), 25.7 (CH$_2$, C6'), 23.3 (CH$_3$, Me), 20.4 (CH$_2$, C9), 7.2 (CH$_2$, C1'); m/z (EI): 394 (8), 350 (2), 256 (2), 199 (40), 155 (14), 126 (13), 101 (100), 98 (42), 55 (20), 41 (18); **HRMS** (EI): Found M$^+$, 394.13655, C$_{17}$H$_{31}$IO$_2$, requires 394.13688.

**4,6-Dimethoxy-1-(7-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)-1H-indole (339)**

A solution of 4,6-dimethoxyindole (46.0 mg, 260 µmol) in DMSO (2 mL) was added dropwise to a stirred solution of powdered KOH (33.0 mg, 580 µmol) in DMSO (2 mL) and the mixture was stirred for 45 min at room temperature under an atmosphere of nitrogen. Iodide 359 (86.0 g, 220 µmol) dissolved in DMSO (1 mL) was added to the resultant green solution. After stirring the mixture for 2 h at room temperature, water (4 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined organic extracts were dried with brine (3 x 3 mL) and magnesium sulfate. The solvents were removed under reduced pressure, flash chromatography (hexanes/diethyl ether 40:1) afforded the title compound (52.0 mg, 54%) as a yellow oil; $[\alpha]_D +43.4$ (c 1.10, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 2927, 2854, 1622, 1587, 1499, 1455, 1373, 1249, 1209, 1146, 1068, 1049, 974, 936, 874, 804, 756, 732, 703, 627 cm$^{-1}$; **$^1$H NMR** (300 MHz, CDCl$_3$): 6.89 (1H, d, $J = 3.3$, H2), 6.51 (1H, d, $J = 3.0$, H1), 6.41 (1H, apparent s, H4), 6.23 (1H, d, $J = 1.5$, H6), 4.20-4.30 (1H, m, H2"), 4.01 (2H, t, $J = 7.2$, H1'), 3.93 (3H, s, OMe), 3.88 (3H, s, OMe), 3.81-3.83 (1H, m, H7"), 2.29-2.39 (2H, m, H3"), 1.91-2.06 (4H, m, H4" and H8"), 1.60-1.86 (6H, m, H10", H9" and H8"), 1.22-1.45 (12H, m, H2'-7"), 1.28 (3H, d, $J = 6.2$, Me); **$^{13}$C NMR** (75 MHz, CDCl$_3$): 155.2 (quat., C5), 153.7 (quat., C7), 137.2 (quat., C4a), 124.9 (CH, C2), 113.4 (quat., C7a), 105.8 (quat., C5"), 98.1 (CH, C1), 91.0 (CH, C6), 85.7 (CH, C4), 76.7 (CH, C2"), 69.7 (CH, C7"), 55.7 (CH$_3$, OMe), 55.2 (CH$_3$, OMe), 46.5 (CH$_2$, C1'), 39.4 (CH$_2$, C4"), 36.4 (CH$_2$, C8'), 33.6
(CH₂, C7), 31.8 (CH₂, C10"), 31.2 (CH₂, C3"), 29.9 (CH₂, C8"), 29.6 (CH₂, C3'), 29.4 (CH₂, C5'), 29.3 (CH₂, C4'), 26.9 (CH₂, C2'), 25.6 (CH₂, C6'), 23.3 (CH₃, Me), 20.4 (CH₂, C9''); m/z (EI): 443 (100), 429 (10), 399 (8), 343 (17), 315 (9), 289 (7), 232 (4), 190 (11), 155 (6), 98 (16), 55 (14), 41 (22); **HRMS** (EI): Found M⁺, 443.30408, C₂₇H₄₁NO₄, requires 443.30356.

3-Carbethoxy-4,6-dimethoxy-3-hydroxy-1H-oxindole (377)

![Chemical Structure](image)

Diethyl ketomalonate (4.5 mL, 30 mmol) was added dropwise to a solution of 3,5-dimethoxyaniline (375) (4.0 g, 26 mmol) in glacial acetic acid (16 mL) The reaction mixture was heated to 100 °C for 15 min. It was then allowed to cool to room temperature over 2.5 h. The solid was filtered off and washed with hexane (150 mL). Drying the solid in vacuo afforded the title compound (6.80 g, 92%) as a white powder; m.p. 189-194 °C.

**1H NMR** (400 MHz, d₆-DMSO): 10.43 (1H, s, NH), 6.39 (1H, s, OH), 6.16 (1H, d, J 2.0, ArH), 6.04 (1H, d, J 2.0, ArH), 4.07 (2H, q, J 7.0, OCH₂CH₃), 3.76 (3H, s, OMe), 3.70 (3H, s, OMe), 1.05 (3H, t, J 7.0, OCH₂CH₃). The spectroscopic data was in agreement with that reported in the literature.¹⁷⁸
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4,6-Dimethoxy-1H-oxindole (354)\textsuperscript{178}

Aqueous hydrochloric acid (6.8 mL, 82 mmol, 37\%) was added slowly to a stirred solution of 3-carbethoxy-4,6-dimethoxy-3-hydroxy-1H-oxindole (377) (6.70 g, 24 mmol) in glacial acetic acid (68 mL), followed by the addition of stannous chloride (5.6 g, 29 mmol). The reaction mixture was heated to reflux for 1 h and then cooled to room temperature, diluted with water (200 mL) and extracted with dichloromethane (6 \times 200 mL). The organic phase was then washed with brine (100 mL) and water (200 mL). Removal of the solvent \textit{in vacuo} yielded a pale yellow solid which was suspended in aqueous sodium hydroxide (62 mL, 474 mmol, 20\%). The mixture was refluxed for 1.5 h, cooled to room temperature and diluted with water (400 mL). The mixture was cooled to 0 °C and acidified with aqueous hydrochloric acid (37\%) to a pH 1-2. The resulting precipitate was filtered, washed with water (100 mL) and dried to yield the title compound (4.0 g, 87\%) as a pale yellow solid; m.p. 200-207 °C.

\textsuperscript{1}H NMR (400 MHz, d\textsubscript{6}-DMSO): 10.29 (1H, s, NH), 6.16 (1H, d, \textit{J} 2.0, ArH), 6.05 (1H, d, \textit{J} 2.0, ArH), 3.76 (3H, s, OMe), 3.73 (3H, s, OMe), 3.25 (2H, s, H8). The spectroscopic data was in agreement with that reported in the literature.\textsuperscript{178}

4,6-Dimethoxy-1-(7-((2\textsuperscript{S})-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)indolin-2-one (342)

NaH (2.60 mg, 0.11 mmol, 60\% w/w dispersion in mineral oil) was washed with pentane (3 \times 1 mL) under an atmosphere of nitrogen and dried \textit{in vacuo}. DMF (1mL) was added to the solid and the resulting slurry was stirred at room temperature. 4,6-Dimethoxyoxindole (354) (39.0 mg, 0.200 mmol) dissolved in DMF (1 mL) was added to the slurry, resulting in a red-brown mixture which was stirred at room temperature for 15 min. Iodide 359 (42.0 mg, 0.11 mmol) was dissolved in DMF (1 mL) and added to the mixture. After stirring for 2.5 h at room temperature, water (3 mL) was added. The solution was extracted with diethyl ether (3 \times 5 mL) and ethyl acetate (3 \times 5 mL). The combined organic extracts were dried with brine (3 \times 3 mL) and magnesium sulfate. The solvents were removed under reduced pressure, flash
chromatography (hexanes/EtOAc 5:1) afforded the title compound (32.0 mg, 68%) as a yellow oil; [α]_D +60.3 (c 1.10, CHCl₃).

IR: 2928, 2857, 1712, 1607, 1509, 1454, 1345, 1290, 1270, 1202, 1143, 1113, 1067, 974, 871, 787, 687 cm⁻¹; δH NMR (300 MHz, CDCl₃): 6.15 (1H, d, J 3.1, H4), 6.09 (1H, d, J 3.0, H6), 4.20-4.30 (1H, m, H2'), 3.82 (6H, s, OMe), 3.77-3.79 (1H, m, H7''), 3.63 (2H, t, J 6.0, H1'), 3.37 (2H, s, H1), 1.82-1.96 (2H, m, H3''), 1.57-1.69 (12H, m, H8', H10'', H4'', H6', H8'' and H2'), 1.13-1.42 (10H, m, H9'', H7', H4', H3' and H5'), 1.28 (CH₃, d, J 6.0, Me);

3.2 Synthesis of Indole 338 and Oxindole 341 Analogues

1-(tert-Butyldiphenylsilyloxy)-pent-4-ene (392)

\[
\text{TBDPSO}^1 \overline{\text{C}} \equiv \overline{\text{S}}^5
\]

tert-Butyldiphenylsilylchloride (15.9 mL, 58.0 mmol), 4-dimethylaminopyridine (280 mg, 2.30 mmol) and imidazole (5.90 g, 87 mmol) were dissolved in CH₂Cl₂ (20 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this stirred solution was added 4-pentene-1-ol (386) (6.00 mL, 58.0 mmol) in CH₂Cl₂ (5 mL). After stirring for 12 h at room temperature, the white precipitate was filtered off and the solvent removed under reduced pressure to yield the title compound (18.5 g, 98%) as a yellow oil. The protected alcohol was taken through to the next step without further purification.

IR: 2931, 2857, 1712, 1607, 1509, 1427, 1389, 1361, 1261, 1105, 969, 910, 822, 737, 686, 612 cm⁻¹; δH NMR (300 MHz, CDCl₃): 7.66-7.70 (4H, CH, SiBuPh₂, o), 7.38-7.46 (6H, CH, SiBuPh₂, m and p), 5.80-5.89 (1H, SiBuPh₂, o), 5.45-5.07 (2H, CH, H5), 3.72 (2H, t, J 6.3, H1), 2.19 (2H, dt, J 6.9 and 1.2, H3), 1.71 (2H, t, J 6.7 and 1.2, H2), 1.11 (9H, CH₃, SiBuPh₂); δC NMR (75 MHz, CDCl₃): 138.5 (CH, C4), 135.6 (CH, SiBuPh₂, o), 134.8 (quat., SiBuPh₂), 129.5 (CH, SiBuPh₂, p), 127.6 (CH, SiBuPh₂, m), 114.5 (CH₂, C5), 63.3 (CH₂, C1), 31.8 (CH₂, C3), 30.1 (CH₂, C4), 26.9 (CH₃, SiBuPh₂), 19.2 (quat., SiBuPh₂); m/z (Cl): 325 (5), 267 (100), 249 (7), 255 (11), 199 (80), 189 (29), 183 (41), 181 (22), 163
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(15), 123 (15), 105 (17), 77 (22), 41 (25); **HRMS** (Cl): Found (MH)$^+$, 325.19814, C$_{21}$H$_{29}$O$_2$Si, requires 325.19877.

1-(*tert*-Butyldiphenylsilyloxy)-4-pentene oxide (393)

![Structure](TBDPSO)  

*meta*-Chloroperoxybenzoic acid (19.0 g, 46.0 mmol) was dissolved in CH$_2$Cl$_2$ (250 mL) under an atmosphere of nitrogen and cooled to 0 °C. A solution of alkene 392 (18.5 g, 57.0 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise. The solution was allowed to warm to room temperature over 12 h, saturated sodium sulfite solution (60 mL) was added to the reaction mixture and stirred until it became clear. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 25 mL). The organic layer was then washed with an aqueous NaOH solution (80.0 mL, 2 M) and brine (100 mL) and the solvent was removed under reduced pressure. Purification by flash chromatography (hexanes/diethyl ether 25:1) afforded the **title compound** (15.5 g, 80%) as a yellow oil.

**IR** $\gamma_{\text{max}}$(film): 2930, 1471, 1427, 1389, 1360, 1258, 1215, 1187, 1104, 740, 694, 612 cm$^{-1}$; **$^1$H NMR** (400 MHz, CDCl$_3$): 7.66-7.68 (4H, m, Si$\text{BuPh}_2$, o), 7.37-7.43 (6H, m, Si$\text{BuPh}_2$, m and p), 2.90-2.95 (1H, m, H1), 2.74 (1H, dd, J 4.9 and 5.0, H5a), 2.46 (1H, dd, J 2.1 and 5.1, H5b), 2.74 (1H, dd, J 4.9 and 5.0, H5a), 2.46 (1H, dd, J 2.1 and 5.1, H5b), 1.63-1.75 (4H, m, H2 and H3), 1.06 (9H, s, Si$\text{BuPh}_2$); **$^{13}$C NMR** (100 MHz, CDCl$_3$): 135.5 (CH, Si$\text{BuPh}_2$, o), 133.8 (quat., Si$\text{BuPh}_2$), 129.6 (CH, Si$\text{BuPh}_2$, p), 127.6 (CH, Si$\text{BuPh}_2$, m), 63.4 (CH$_2$, C1), 52.1 (CH$_2$, C4), 47.1 (CH$_2$, C5), 28.9 (CH$_2$, C2 or C3), 28.8 (CH$_2$, C2 or C3), 26.8 (CH$_3$, Si$\text{BuPh}_2$), 19.2 (quat., Si$\text{BuPh}_2$); **m/z** (Cl): 341 (2), 283 (31), 253 (11), 223 (9), 205 (11), 199 (100), 183 (12), 139 (24), 91 (17), 85 (14), 78 (15); **HRMS** (Cl): Found (MH)$^+$, 341.19362, C$_{21}$H$_{29}$O$_2$Si, requires 341.19368.

(R)-1-(*tert*-Butyldiphenylsilyloxy)-4-pentene oxide (387)

![Structure](TBDPSO)  

To a solution of (R,R)-SalenCo$^{II}$ (0.41 mg, 0.68 mmol) in toluene (3.4 mL) was added glacial acetic acid (78.0 µL, 1.40 mmol) and the mixture was stirred open to the air for 1 h to form the active form of the catalyst (R,R)-SalenCo$^{III}$OAc over which time the colour changed from orange to a dark brown. The solution was concentrated *in vacuo* to give a crude brown solid. To the catalyst residue was added a solution of epoxide 393 (15.5 g, 45.5 mmol) in isopropanol (15 mL). The resultant solution was cooled to 0 °C and water (0.490 mL, 27.3 mmol) was added. The reaction was allowed to warm to room
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temperature and stirred for 24 h. The isopropanol was removed under reduced pressure and the resulting chiral epoxide was purified by flash chromatography (hexanes/diethyl ether 25:1) to afford the title compound (6.60 g, 86%) as a yellow oil; [α]D +10.0 (c 1.30, CHCl3). The spectroscopic data was identical to that reported above for epoxide 393.

(S)-1-(tert-Butyldiphenylsilyloxy)oct-7-en-4-ol (394)

CuCN (3.50 g, 39.0 mmol) was gently flame dried under vacuum then dissolved in THF (50 mL) under an atmosphere of nitrogen. The resultant slurry was cooled to -78 °C and MeLi (48.7 mL, 78.0 mmol, 1.6 M in THF) was added. The reaction was allowed to warm up to 0 °C and further stirred at this temperature for 20 min. AllylSnBu3 (25.7 g, 78.0 mmol) was then added at 0 °C as a neat liquid in one portion and the solution continued to be stirred at this temperature for an additional 30 min. The reaction mixture was then cooled to -78 °C and epoxide 387 (6.60 g, 19.0 mmol) in THF (25 mL) was cannulated to the resulting cuprate. The reaction was then warmed to 0 °C and stirred at that temperature for an additional hour. The solution was quenched by the addition of a solution of 10% ammonia in saturated aqueous ammonium chloride (40 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed in vacuo. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (5.20 g, 70%) as a yellow oil; [α]D +18.4 (c 1.3, CHCl3).

IR νmax(film): 3433 br (OH), 2930, 2857, 1472, 1147, 1106, 997, 909, 822, 739, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl3): 7.69-7.71 (4H, m, SiBuPh2, o), 7.38-7.45 (6H, m, SiBuPh2, m and p), 5.83-5.90 (1H, m, H7), 4.97-5.10 (2H, m, H8), 3.72 (2H, t, J 5.8, H1), 3.60-3.62 (1H, m, H4), 2.14-2.27 (2H, m, H6), 1.52-1.72 (6H, m, H2, H3 and H5), 1.08 (9H, s, SiBuPh2); ¹³C NMR (100 MHz, CDCl3): 138.6 (CH, C7), 135.5 (CH, SiBuPh2, o), 133.6 (quat., SiBuPh2), 129.6 (CH, SiBuPh2, p), 127.6 (CH, SiBuPh2, m), 114.6 (CH2, C8), 70.9 (CH, C4), 64.2 (CH2, C1), 36.4 (CH2, C5), 34.3 (CH2, C6), 30.1 (CH2, C3), 28.7 (CH2, C2), 26.8 (CH3, SiBuPh2), 19.1 (quat., SiBuPh2); m/z (Cl): 383 (7), 325 (11), 229 (11), 216 (10), 199 [100], 181 (15), 139 (22), 109 (95), 91 (12), 81 (16), 71 (11); HRMS (CI): Found (MH)+, 383.24090, C24H35O2Si, requires 383.24063.
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(S)-(S)-1-(tert-Butyldiphenylsilyloxy)oct-7-en-4-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

Following a literature procedure a solution of alcohol 394 (50.0 mg, 0.13 mmol) in CH$_2$Cl$_2$ (1 mL) was added to a suspension of (R)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (43 mg, 0.18 mmol), N,N-4-dimethylaminopyridine (3.2 mg, 0.026 mmol) and dicyclohexylcarbodiimide (65 mg, 0.31 mmol) in CH$_2$Cl$_2$ (1 mL). After stirring the mixture for 48 h, the dicyclohexylurea white precipitate was filtered off and the filtrate was washed with water. The aqueous layer was then extracted with diethyl ether (3 x 5 mL) and the combined organic extracts dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave an oil that was purified by flash chromatography using (hexanes/diethyl ether 8:1) as the eluent to afford the title compound (62.0 mg, 79%) as a yellow oil; [α]$_D$ -6.00 (c 1.10, CHCl$_3$).

$^1$H NMR (300 MHz, CDCl$_3$): 7.63-7.69 (4H, m, Si$^t$BuPh$_2$, o), 7.55-7.58 (2H, m, ArH, o or m), 7.35-7.42 (9H, m, Si$^t$BuPh$_2$, m and p, and ArH, p and o or m), 5.83-5.90 (1H, m, H7), 5.04 (1H, quintet, J 2.2, H4), 4.98-5.00 (2H, m, H8), 3.59 (2H, t, J 2.2, H1), 3.54 (3H, s, OMe), 1.90-1.94 (2H, m, H6), 1.70-1.77 (2H, m, H2), 1.54-1.58 (4H, m, H3 and H5), 1.07 (9H, s, Si$^t$BuPh$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 166.2 (quat., C=O), 137.4 (CH, C7), 135.5 (CH, Si$^t$BuPh$_2$, o), 133.7 (quat., Si$^t$BuPh$_2$), 129.4 (CH, Si$^t$BuPh$_2$, p), 127.5 (CH, Si$^t$BuPh$_2$, m), 126.7 (CF$_3$), 115.3 (CH$_2$, C8), 78.8 (quat., CCF$_3$), 70.9 (CH, C4), 63.2 (CH$_3$, C1), 55.6 (CH$_3$, OMe), 36.4 (CH$_2$, C5), 34.2 (CH$_2$, C3), 32.8 (CH$_2$, C6), 29.7 (CH$_2$, C2), 26.8 (CH$_3$, Si$^t$BuPh$_2$), 19.2 (quat., Si$^t$BuPh$_2$); $^{19}$F NMR (282 MHz, CDCl$_3$): δ -72.2 (single detectable peak) greater than 99% ee.
t-Butyldimethylsilylchloride (1.98 g, 13.0 mmol), imidazole (990 mg, 14.6 mmol), N,N-dimethylaminopyridine (70.0 mg, 590 µmol) were dissolved in CH₂Cl₂ (20 mL) under nitrogen atmosphere and cooled to 0 °C. To this stirred solution was added alcohol 394 (2.80 g, 7.30 mmol) in CH₂Cl₂ (10 mL). After stirring for 12 h, brine (40 mL) was added and the mixture extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate. Removal of the solvent in vacuo followed by flash chromatography (hexanes/EtOAc 40 :1) afforded the title compound (3.10 g, 85%) as a yellow oil; [α]D +8.0 (c 1.10, CHCl₃).

IR νmax (film): 2953, 2928, 2857, 1472, 1461, 1427, 1388, 1360, 1254, 1108, 1090, 1058, 1006, 908, 833, 801 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.69-7.69 (4H, m, Si'tBuPh₂, o), 7.34-7.42 (6H, m, Si'tBuPh₂, m and p), 5.78-5.84 (1H, m, H12), 4.93-5.04 (2H, m, H13), 3.65 (2H, t, J 6.3, H1), 3.68-3.70 (1H, m, H4), 2.05-2.10 (2H, m, H6), 1.48-1.61 (6H, m, H2, H3 and H5), 1.08 (9H, s, Si'tBuPh₂), 0.94 (9H, s, Si'tBuMe₂), 0.05 (3H, s, Si'tBuMe₂), 0.01 (3H, s, Si'tBuMe₂); ¹³C NMR (75 MHz, CDCl₃): 139.0 (CH, C7), 135.6 (CH, Si’tBuPh₂, o), 134.1 (quat., Si’tBuPh₂), 129.5 (CH, Si’tBuPh₂, p), 127.6 (CH, Si’tBuPh₂, m), 114.2 (CH₂, C8), 71.6 (CH, C4), 64.1 (CH₂, C1), 36.2 (CH₂, C5), 33.3 (CH₂, C6), 29.6 (CH₂, C3), 28.3 (CH₂, C2), 26.9 (CH₃, Si’BuPh₂), 25.9 (CH₃, Si’BuMe₂), 19.2 (quat., Si’BuPh₂), 18.1 (quat., Si’BuMe₂), -4.4 (CH₃, Si’BuMe₂), -4.5 (CH₃, Si’BuMe₂); m/z (FAB): 497 (1), 271 (7), 209 (14), 197 (21), 195 (19), 135 (51), 109 (20), 91 (19), 73 (100); HRMS (FAB): Found (MH)+, 497.32717 C₃₀H₄₉O₂Si₂, requires 497.32711.

(5S)-5-(t-Butyldimethylsilyloxy)-8-(t-Butyldiphenylsilyloxy)-octan-1-ol (396)

Alkene 395 (2.20 g, 4.40 mmol) was dissolved in THF (15 mL) under an atmosphere of nitrogen and the solution was cooled to 0 °C. Borane dimethylsulfide complex (0.800 mL, 8.80 mmol) was added to the stirred solution dropwise and the solution was allowed to warm to room temperature over 12 h. Oxidative workup by addition of H₂O₂ (3.00 mL, 8.80 M) and aqueous NaOH (2.60 mL, 1 M) gave a biphasic mixture which was stirred for 30 min. The mixture was extracted with diethyl ether (3 x 10 mL) and the combined extracts were dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a colourless oil that was purified by flash chromatography using (hexanes/diethyl
ether 8:1) as the eluent to afford the title compound (1.60 g, 70%) as a yellow oil; [α]_D +43.1 (c 1.20, CHCl₃).

IR \( \gamma_{\text{max}} \text{(film)}: 3346 \text{ br (OH)}, 2930, 2857, 1472, 1462, 1428, 1388, 1360, 1106, 1063, 1039, 1006, 938, 834, 773, 700 \text{ cm}^{-1} \); \(^1\text{H NMR} \) (300 MHz, CDCl₃): 7.66-7.68 (4H, m, Si‘BuPh₂, o), 7.34-7.41 (6H, m, Si‘BuPh₂, m and p), 3.66 (2H, t, J 6.3, H1), 3.62 (3H, m, H4 and H8), 1.35-1.61 (10H, m, H2, H3, H5, H6 and H7), 1.06 (9H, s, Si‘BuPh₂), 0.90 (9H, s, Si‘BuMe₂), 0.04 (3H, s, Si‘BuMe₂), 0.01 (3H, s, Si‘BuMe₂);

\(^{13}\text{C NMR} \) (75 MHz, CDCl₃): 135.6 (CH, Si‘BuPh₂, o), 134.1 (quat., Si‘BuPh₂), 129.5 (CH, Si‘BuPh₂, p), 127.6 (CH, Si‘BuPh₂, m), 72.0 (CH, C4), 64.1 (CH₂, C1), 63.0 (CH₂, C8), 36.7 (CH₂, C5), 33.3 (CH₂, C6), 32.9 (CH₂, C7), 28.4 (CH₂, C2), 26.9 (CH₃, Si‘BuPh₂), 25.9 (CH₃, Si‘BuMe₂), 21.5 (CH₂, C3), 19.2 (quat., Si‘BuPh₂), 18.1 (quat., Si‘BuMe₂), -4.4 (CH₃, Si‘BuMe₂); \( \text{m/z} \) (FAB): 515 (1), 325 (11), 199 (20), 135 (50), 127 (30), 109 (35), 91 (14), 81 (15), 73 (100); \(^{13}\text{HRMS} \) (FAB): Found MH⁺, 515.33804 C₃₀H₅₁O₅Si₂, requires 515.33768.

(R)-5-(tert-Butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)-octanal (388)

A solution of alcohol 396 (2.23 g, 4.34 mmol) in CH₂Cl₂ (25 mL) was added dropwise to a suspension of Dess-Martin periodinan (3.68 g, 8.70 mmol) and pyridine (1.02 g, 13.0mmol) in CH₂Cl₂ (15 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 2.5 h the solution was diluted with diethyl ether (20 mL) and filtered through Celite®. Removal of the solvent under reduced pressure, followed by flash chromatography (hexanes/Celite ether 15:1) afforded the title compound (1.95 g, 88%) as a yellow oil; [α]_D +21.2 (c 1.10, CHCl₃).

IR \( \gamma_{\text{max}} \text{(film)}: 3291, 2930, 2857, 1472, 1428, 1388, 1361, 1253, 1109, 1090, 834, 773, 738, 697, 687, 663 \text{ cm}^{-1} \); \(^1\text{H NMR} \) (400 MHz, CDCl₃): 9.76 (1H, t, J 1.8, H8), 7.65-7.68 (4H, m, Si‘BuPh₂, o), 7.34-7.42 (6H, m, Si‘BuPh₂, m and p), 3.67 (2H, t, J 6.0, H1), 3.65- 3.69 (1H, m, H4), 2.38- 2.44 (2H, td, J 1.5 and 7.2, H7), 1.40-1.70 (8H, m, H2, H3, H5 and H6), 1.06 (9H, s, Si‘BuPh₂), 0.91 (9H, s, Si‘BuMe₂), 0.04 (3H, s, Si‘BuMe₂), 0.01 (3H, s, Si‘BuMe₂); \(^{13}\text{C NMR} \) (100 MHz, CDCl₃): 202.6 (C=O, C8), 135.6 (CH, Si‘BuPh₂, o), 134.0 (quat., Si‘BuPh₂), 129.5 (CH, Si‘BuPh₂, m), 127.6 (CH, Si‘BuPh₂, p), 71.7 (CH, C4), 64.1 (CH, C1), 43.9 (CH₃, C7), 36.2 (CH₂, C5), 33.2 (CH₂, C6), 31.6 (CH₂, C3), 28.3 (CH₂, C2), 26.9 (CH₃, Si‘BuPh₂), 25.9 (CH₃, Si‘BuMe₂), 19.2 (quat., Si‘BuPh₂), 18.1 (quat., Si‘BuMe₂), -4.4 (CH₃, Si‘BuMe₂); \( \text{m/z} \) (FAB): 513 (1), 455 (3), 241 (2), 209 (4), 197 (14), 135 (35), 81 (14), 73 (100); \(^{13}\text{HRMS} \) (FAB): Found MH⁺ 513.32280 C₃₀H₅₁O₅Si₂, requires 513.32203.
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(11S, 8R(and S), 4S)-4,11-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-didec-9-yn-11-ol (397)

\[
\text{TBDPSO} \quad \text{OTBDMS} \quad \text{OH} \quad \equiv \quad \text{12} \quad \text{OTBDMS}
\]

\(n\)-BuLi (2.90 mL, 4.70 mmol, 1.60 M) was added to a stirred solution of acetylene 219 (0.79 g, 4.30 mmol) in THF (10 mL), at -78 °C under an atmosphere of nitrogen. The resultant pale yellow solution was stirred for 30 min. Anhydrous LiBr (0.160 g, 1.95 mmol) was dissolved in THF (5 mL) under an atmosphere of nitrogen and cannulated to the acetylide mixture. After 15 min a solution of the aldehyde 388 (2.00 g, 3.90 mmol) in THF (8 mL) was added dropwise and the solution was allowed slowly to warm to room temperature over 6 h. Saturated ammonium chloride solution (10 mL) was added followed by extraction with diethyl ether (3 x 10 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (2.10 g, 78%) as a yellow oil; [\(\alpha\)]<sub>D</sub>-19.3 (c 1.30, CHCl₃).

\[\text{IR } \gamma_{\text{max}}\text{(film): } 2856, 2929, 1472, 1462, 1389, 1361, 1336, 1253, 1102, 1005, 833, 773, 738, 698, 687, 664 \text{ cm}^{-1}; \text{^1H NMR} \text{ (300 MHz, CDCl}_3): } 7.65-7.68 \text{ (4H, m, Si'BuPh}_2, o), 7.34-7.37 \text{ (4H, m, Si'BuPh}_2, m \text{ and p), 4.54-4.57 (1H, qd, } J 6.6 \text{ and } 1.3, \text{ H11), 3.47 (1H, m, H7), 3.64-3.65 (1H, m, H4), 1.42-1.69 (6H, m, H7, H3 and H5), 1.38 (3H, d, J 2.7, H12), 1.09-1.40 (4H, m, H2 and H6), 1.05 (9H, s, Si'BuPh}_2), 0.91 (9H, s, Si'BuMe}_2), 0.88 (9H, s, Si'BuMe}_2), 0.12 (3H, s, Si'BuMe}_2), 0.11 (3H, s, Si'BuMe}_2), 0.02 (3H, s, Si'BuMe}_2), 0.01 (3H, s, Si'BuMe}_2); \text{^13C NMR} \text{ (75 MHz, CDCl}_3): } 135.6 \text{ (CH, Si'BuPh}_2, o), 134.1 \text{ (quat., Si'BuPh}_2), 129.5 \text{ (CH, Si'BuPh}_2, p), 127.6 \text{ (CH, Si'BuPh}_2, m), 87.4 \text{ (quat., C10), 84.1 (quat., C9), 71.9 (CH, C4), 64.1 (CH}_2, C1), 62.5 (CH, C8), 58.9 (CH, C11), 38.0 (CH}_2, C7), 36.6 \text{ (CH}_2, C5), 34.7 (CH}_2, C3), 33.2 (CH}_2, C2), 31.6 \text{ (CH}_3, C12), 26.9 \text{ (CH}_3, Si'BuPh}_2), 25.9 \text{ (CH}_3, Si'BuMe}_2), 25.8 \text{ (CH}_3, Si'BuMe}_2), 22.7 \text{ (CH}_3, C6), 19.1 \text{ (quat., Si'BuPh}_2), 18.2 \text{ (quat., Si'BuMe}_2), 18.1 \text{ (quat., Si'BuMe}_2), -4.4 \text{ (CH}_3, Si'BuMe}_2), -4.7 \text{ (CH}_3, Si'BuMe}_2), -4.9 \text{ (CH}_3, Si'BuMe}_2); m/z \text{ (FAB): } 697 \text{ (1), 273 (2), 235 (3), 219 (3), 199 (4), 165 (4), 154 (100), 136 (70), 89 (25), 73 (30); HRMS (FAB): Found MH}^+ 697.45094 \text{ C}_{40}H_{69}O_4Si_3, \text{ requires 697.45037.}
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(11S, 4S)-4,11-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-didec-9-yn-8-one (398)

Alcohol 397 (2.50 g, 3.60 mmol) was dissolved in CH₂Cl₂ (10 mL) and added to a slurry of 4 Å molecular sieves (1.50 g) in CH₂Cl₂ (5 mL) and the solution was cooled to 0 °C. To this stirred solution was added N-methylmorpholine-N-oxide (630 mg, 5.40 mmol) and tetrapropylammonium perruthenate (63 mg, 0.18 mmol) in CH₂Cl₂ (7 mL). After stirring for 2 h the reaction mixture was filtered through Celite® and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 20:1) afforded the title compound (1.90 g, 79%) as a yellow oil; [α]D -8.00 (c 1.00, CHCl₃).

IR γmax (film): 2954, 2857, 1679, 1472, 1462, 1428, 1389, 1361, 1252, 1103, 826, 774, 728, 687 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.66-7.69 (4H, m, Si’BuPh₂, o), 7.34-7.42 (6H, m, Si’BuPh₂, m and p), 4.65 (1H, q, J 6.6, H11), 3.65 (2H, t, J 6.6, H1), 3.62-3.63 (1H, m, H4), 2.54 (2H, t, J 7.5, H7), 1.44-1.69 (8H, m, H2, H3, H5 and H6), 1.48 (3H, d J 6.6, H12), 1.06 (9H, s, Si’BuPh₂), 0.93 (9H, s, Si’BuMe₂), 0.90 (9H, s, Si’BuMe₂), 0.14 (3H, s, Si’BuMe₂), 0.13 (3H, s, Si’BuMe₂), 0.06 (6H, s, Si’BuMe₂); ¹³C NMR (75 MHz, CDCl₃): 187.6 (quat., C=O), 135.6 (CH, Si’BuPh₂, o), 134.1 (quat., Si’BuPh₂), 129.5 (CH, Si’BuPh₂, p), 127.6 (CH, Si’BuPh₂, m), 93.7 (quat., C10), 83.3 (quat., C9), 71.7 (CH, C4), 64.1 (CH₂, C1), 58.8 (CH, C11), 45.5 (CH₂, C7), 36.0 (CH₂, C3), 33.3 (CH₂, C2), 28.3 (CH₂, C5), 26.9 (CH₃, Si’BuPh₂), 25.9 (CH₃, Si’BuMe₂), 25.7 (CH₃, Si’BuMe₂), 24.5 (CH₃, C12), 19.9 (CH₂, C6), 19.2 (quat., Si’BuPh₂), 18.2 (quat., Si’BuMe₂), 18.1 (quat., Si’BuMe₂), -4.4 (CH₃, Si’BuMe₂), -4.6 (CH₃, Si’BuMe₂), -4.9 (CH₃, Si’BuMe₂), -5.0 (CH₃, Si’BuMe₂); m/z (FAB): 695 (1), 637 (1), 505 (1), 273 (2), 199 (8), 165 (10), 154 (100), 136 (83), 73 (32); HRMS (FAB): Found (MH⁺), 695.43353 C₄₀H₆₀O₄Si₃, requires 695.43472.
(11S, 4S)-4,11-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)didec-8-one (389)

Ynone 398 (1.76 g, 2.40 mmol) was dissolved in methanol/THF (10 mL, 1:1), and stirred under a hydrogen atmosphere in the presence of PtO$_2$ (87.0 mg, 0.36 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvents removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 20:1) afforded the title compound (1.30 g, 74%) as a yellow oil; $[\alpha]_D^{+11.3}$ (c 2.00, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2928, 2856, 1716, 1472, 1462, 1428, 1360, 1253, 1106, 834, 772, 700, 687, 662 cm$^{-1}$;

$^{1}$H NMR (400 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si$_{\text{tBu}}$Ph$_2$, o), 7.35-7.42 (6H, m, Si$_{\text{tBu}}$Ph$_2$, m and p), 3.80-3.86 (1H, m, H$_{11}$), 3.65 (2H, t, $J_{6.5}$, H$_1$), 3.61-3.62 (1H, m, H$_4$), 2.37-2.47 (4H, m, H$_7$ and H$_9$), 1.54-1.77 (6H, m, H$_2$, H$_3$ and H$_6$), 1.22-1.48 (4H, m, H$_5$ and H$_{10}$), 1.1 (3H, d, $J_{6.2}$, H$_{12}$), 1.06 (9H, s, Si$_{\text{tBu}}$Ph$_2$), 0.92 (9H, s, Si$_{\text{tBu}}$Me$_2$), 0.91 (9H, s, Si$_{\text{tBu}}$Me$_2$), 0.045 (3H, s, Si$_{\text{tBu}}$Me$_2$), 0.030 (6H, s, Si$_{\text{tBu}}$Me$_2$), 0.021 (3H, s, Si$_{\text{tBu}}$Me$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 211.1 (quat., C=O), 135.6 (CH, Si$_{\text{tBu}}$Ph$_2$, o), 134.1 (quat., Si$_{\text{tBu}}$Ph$_2$), 129.5 (CH, Si$_{\text{tBu}}$Ph$_2$, m), 127.6 (CH, Si$_{\text{tBu}}$Ph$_2$, p), 71.9 (CH, C$_4$), 67.6 (CH, C$_{11}$), 64.1 (CH$_2$, C$_1$) 42.9 (CH$_2$, C$_7$), 42.4 (CH$_2$, C$_7$), 38.6 (CH$_2$, C$_{10}$), 36.4 (CH$_2$, C$_2$), 33.2 (CH$_2$, C$_3$), 28.3 (CH$_2$, C$_5$), 26.9 (CH$_3$, Si$_{\text{tBu}}$Ph$_2$), 25.9 (CH$_3$, Si$_{\text{tBu}}$Me$_2$), 25.8 (CH$_3$, Si$_{\text{tBu}}$Me$_2$), 23.7 (CH$_3$, C$_{12}$), 19.8 (CH$_2$, C$_6$), 19.2 (quat., Si$_{\text{tBu}}$Ph$_2$), 18.2 (quat., Si$_{\text{tBu}}$Me$_2$), 18.1 (quat., Si$_{\text{tBu}}$Me$_2$), -4.39 (CH$_3$, Si$_{\text{tBu}}$Me$_2$), -4.41 (CH$_3$, Si$_{\text{tBu}}$Me$_2$), -4.43 (CH$_3$, Si$_{\text{tBu}}$Me$_2$), -4.77 (CH$_3$, Si$_{\text{tBu}}$Me$_2$); m/z (FAB): 690 (1), 199 (2), 154 (100), 136 (75), 120 (12), 89 (25); HRMS (FAB): Found MH$^+$, 699.46626 C$_{40}$H$_{71}$O$_4$Si$_3$, requires 699.46602.

tert-Butyl(3-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)propoxy)diphenylsilane (399)

To a stirred solution of ketone 389 (300 mg, 0.43 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C under an atmosphere of nitrogen was added camphorsulfonic acid (240 mg, 0.91 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 3 h. Filtration through Celite®, removal of the solvent under
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reduced pressure followed by flash chromatography (hexanes/diethyl ether 30:1) afforded the title compound (130 mg, 70%) as a yellow oil; \([\alpha]_D^{+} 93.0\) (c 1.00, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 2929, 2857, 1472, 1462, 1388, 1361, 1253, 1222, 1159, 1109, 1083, 1007, 974, 834, 822, 773, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si'BuPh$_2$, o), 7.36-7.42 (6H, m, Si'BuPh$_2$, m and p), 4.20-4.27 (1H, qd, $J$ 5.9, 1.6, H2), 3.78-3.81 (1H, m, H7), 3.65-3.72 (2 H, m, H1'), 1.96-1.99 (2H, m, H3a and H4a), 1.48-1.76 (12H, m, H3', H2', H3b, H4b, H8, H9 and H10), 1.25 (3H, d, J 6.3, Me), 1.06 (9H, s, Si'BuPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 135.6 (CH, Si'BuPh$_2$, o), 134.1 (quat., Si'BuPh$_2$), 129.4 (CH, Si'BuPh$_2$, p), 127.5 (CH, Si'BuPh$_2$, m), 105.8 (quat., C5), 76.6 (CH, C2), 69.6 (CH, C7), 64.0 (CH$_2$, C1'), 39.4 (CH$_2$, C4), 33.6 (CH$_2$, C3'), 32.6 (CH$_2$, C10), 31.8 (CH$_2$, C3), 31.1 (CH$_2$, C8), 28.9 (CH$_2$, C2'), 26.9 (CH$_3$, Si'BuPh$_2$), 23.3 (CH$_3$, Me), 20.4 (CH$_2$, C9), 19.2 (quat., Si'BuPh$_2$); m/z (CI): 453 (100), 395 (59), 375 (7), 295 (5), 197 (23), 179 (11), 111 (62), 98 (19), 78 (9); HRMS (CI): Found MH$^+$, 453.28231, C$_{28}$H$_{41}$O$_3$Si, requires 453.28250.

3-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)propan-1-ol (400)

To a stirred solution of silyl ether 399 (400 mg, 0.88 mmol) in THF (10 mL) under an atmosphere of nitrogen was added tert-butylammonium fluoride (1.33 mL, 1.33 mmol, 1 M in THF). After stirring for 2 h at room temperature, brine (5 mL) was added and the mixture extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (160 mg, 86%) as a yellow oil; \([\alpha]_D^{+} 40.2\) (c 1.00, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 3419 br (OH), 2929, 2861, 1458, 1375, 1325, 1223, 1206, 1158, 1057, 1021, 973, 950, 874, 810 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 4.12-4.21 (1H, qd, J 7.1, 2.1, H2), 3.76-3.85 (1H, m, H7), 3.59 (2H, dt, J 6.0, 2.4, H1'), 2.72 (1H, br s, OH), 1.92-1.97 (2H, m, H3 and H4), 1.41-1.79 (12H, m, H3', H2', H3b, H4b, H8, H9 and H10), 1.25 (3H, d, J 6.3, Me); $^{13}$C NMR (75 MHz, CDCl$_3$): 106.0 (quat., C5), 76.6 (CH, C2), 69.9 (CH, C7), 62.8 (CH$_2$, C1'), 39.4 (CH$_2$, C4), 33.6 (CH$_2$, C3'), 33.1 (CH$_2$, C10), 31.7 (CH$_2$, C3), 30.9 (CH$_2$, C8), 29.0 (CH$_2$, C2'), 22.9 (CH$_3$, Me), 20.2 (CH$_2$, C9); m/z (CI): 237 (100)(M+Na)$^+$, 226 (5), 197 (5), 181 (6), 172 (4); HRMS (CI): Found (M+Na)$^+$, 237.1454, C$_{12}$H$_{22}$O$_3$Na, requires 237.1461.
A solution of alcohol 400 (100 mg, 0.47 mmol) in CH₂Cl₂ (5 mL) was added dropwise to a suspension of Dess-Martin periodinane (590 mg, 1.40 mmol) and pyridine (153 µL, 1.87 mmol) in CH₂Cl₂ (5 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 2 h the solution was diluted with diethyl ether (10 mL) and filtered through Celite®. Removal of the solvent under reduced pressure, followed by flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (80.0 mg, 81%) as a yellow oil; [α]₀⁺72.2 (c 1.90, CHCl₃).

IR γₓₓₓ(max film): 2925, 1732 (CO), 1462, 1375, 1206, 1111, 975, 950, 874, 811 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 9.71 (1H, t, J 1.6, H1'), 4.11-4.19 (1H, qd, J 7.1, 2.1, H2), 3.77-3.86 (1H, m, H7), 2.41-2.47 (1H, m, H2'), 1.91-1.97 (2H, m, H3₂ and H4₃), 1.52-1.76 (12H, m, H3', H2', H3₄, H4₅, H8, H9 and H10), 1.25 (3H, d, J 6.3, Me); ¹³C NMR (100 MHz, CDCl₃): 202.9 (C=O, C1'), 105.9 (quat., C5), 76.7 (CH, C2), 69.1 (CH, C7), 40.5 (CH₂, C2'), 39.3 (CH₂, C4), 33.4 (CH₂, C3'), 31.8 (CH₂, C10), 30.9 (CH₂, C3), 28.9 (CH₂, C8), 23.0 (CH₃, Me), 20.1 (CH₂, C9); m/z (Cl): 235 (100)(M+Na)+, 219 (5), 211 (11), 197 (9); HRMS (Cl): Found (M+Na)+, 235.1320, C₁₂H₂₀O₃Na, requires 235.1305.

Ethyl 5-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)pent-2-enoate (403)

In an adaptation of the procedure used by Ordonez et al.,¹⁸² to a solution of DBU (170 mg, 1.10 mmol) and LiCl (50.0 mg 1.10 mmol) in THF (5 mL) was added triethyl phosphonoacetate (0.16 mL, 0.39 mmol) at room temperature under an atmosphere of nitrogen. After stirring the resultant mixture for 5 min, aldehyde 390 (77.0 g, 0.36 mmol) in THF (3 mL) was added and the reaction was stirred for further a 5 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 mL) and the aqueous layer extracted with diethyl ether (3 x 5 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography
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(hexanes/diethyl ether 8:1) afforded the title compound (72.0 mg, 70%) as a yellow oil; \([\alpha]_D -30.5\) (c 1.20, CHCl\(_3\)).

**IR** \(\gamma_{\text{max}}\) (film): 2932, 1781 (CO), 1654, 1458, 1443, 1366, 1266, 1222, 1176, 1073, 1046, 975 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): 6.93-7.03 (1H, m, H3'), 5.77-5.83 (1H, m, H2'), 4.11-4.19 (1H, qd, \(J\) 7.1, 2.1, H2), 4.11-4.15 (2H, q, \(J\) 10.8, H6'), 3.77-3.86 (1H, m, H7), 2.33-2.40 (1H, m, H4a'), 1.94-2.02 (2H, m, H3a and H4a), 1.49-1.85 (12H, m, H5', H4', H3b, H4b, H8, H9 and H10), 1.28 (3H, t, \(J\) 7.2, H7'), 1.26 (3H, d, \(J\) 6.0, Me); \(^13\)C NMR (75 MHz, CDCl\(_3\)): 166.7 (C=O, C1'), 149.3 (CH, C3'), 121.1 (CH, C2), 105.9 (quat., C5), 76.6 (CH, C2), 69.1 (CH, C7), 59.9 (CH2, C6'), 39.4 (CH2, C4), 34.7 (CH2, C5'), 33.6 (CH2, C10), 31.9 (CH2, C3), 31.1 (CH2, C8), 28.5 (CH2, C4'), 23.2 (CH3, Me), 20.2 (CH2, C9), (CH3, C7'); \(m/z\) (EI): 305 (100)(M+Na)+, 283 (5), 265 (4), 237 (3); HRMS (EI): Found (M+Na)+ 305.1710, C\(_{16}\)H\(_{26}\)O\(_4\)Na, requires 305.1723.

**Ethyl 5-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentanoate (404)**

Alkene 403 (67.0 mg, 0.24 mmol) was dissolved in methanol/THF (5 mL, 1:1). The solution was hydrogenated using a power hydrogenator (150 psi) for 6 h in the presence of PtO\(_2\) (8.20 mg, 0.033 mmol). The catalyst was removed by filtration through a pad of Celite\(^\circledR\) and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 15:1) afforded the title compound (58.0 mg, 86%) as a yellow oil; \([\alpha]_D -5.70\) (c 2.00, CHCl\(_3\)).

**IR** \(\gamma_{\text{max}}\) (film): 2932, 2860, 1736 (CO), 1457, 1374, 1222, 1176, 1113, 1074, 1022, 974, 876 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): 4.19-4.25 (1H, qd, \(J\) 6.3, 2.7, H2), 4.11-4.15 (2H, q, \(J\) 7.3, H6'), 3.74-3.83 (1H, m, H7), 2.28 (2H, t, \(J\) 7.2, H2'), 1.95-1.98 (2H, m, H3a and H4a), 1.49-1.78 (14H, m, H3', H4', H5', H3b, H4b, H10, H9 and H8), 1.28 (3H, d, \(J\) 6.0, Me); \(^13\)C NMR (75 MHz, CDCl\(_3\)): 173.8 (C=O, C1'), 105.8 (quat., C5), 76.6 (CH, C2), 69.6 (CH, C7), 60.1 (CH2, C6'), 39.5 (CH2, C4'), 35.8 (CH2, C4), 32.6 (CH2, C5'), 31.9 (CH2, C10), 30.3 (CH2, C3), 24.9 (CH2, C4' or C3'), 24.8 (CH2, C4' or C3'), 22.6 (CH3, Me), 20.9 (CH2, C9), 14.9 (CH3, C7'); \(m/z\) (ESI): 307 (100)(M+Na)+, 285 (5), 239 (2), 148 (3), 101 (3); HRMS (ESI): Found (MH)+, 285.2043, C\(_{16}\)H\(_{26}\)O\(_4\) requires 285.2060.
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5-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentan-1-ol (378)

To a suspension of LiAlH₄ (3.00 mg, 0.074 mmol) in THF (3 mL) cooled to 0 °C was added dropwise a solution of ester 404 (20.0 mg, 0.074 mmol) in THF (1 mL). The solution was stirred for 15 min at room temperature. Aqueous NaOH solution (0.50 mL, 4 M) was then added dropwise over 5 min period. The white precipitate was filtered over a pad of Celite® and washed with THF (5 mL). The filtrate was dried over magnesium sulfate. The solvent was removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (16.0 mg, 94%) as a yellow oil; [α]D +30.5 (c 1.30, CHCl₃).

IR γ_max(film): 3364 br (OH), 2932, 2857, 1457, 1440, 1375, 1222, 1074, 1022, 945, 871, 810; ¹H NMR (300 MHz, CDCl₃): 4.20-4.25 (1H, qd, J 6.0, 2.0, H2), 3.79-3.81 (1H, m, H7), 3.63 (2H, t, J 6.6, H1'), 1.95-2.01 (2H, m, H3a and H4a), 1.31-1.79 (16H, m, H5', H4', H3', H2', H3a, H4a, H8, 9, and H10), 1.27 (3H, d, J 6.0, Me); ¹³C NMR (75 MHz, CDCl₃): 105.9 (quat., C5), 76.6 (CH, C2), 69.7 (CH, C7), 63.0 (CH₂, C'), 39.4 (CH₂, C4), 36.4 (CH₂, C5'), 33.6 (CH₂, C10), 32.8 (CH₂, C3), 31.9 (CH₂, C8), 31.2 (CH₂, C2'), 25.8 (CH₂, C3' or C4'), 25.5 (CH₂, C3' or C4'), 23.3 (CH₃, Me), 20.4 (CH₂, C9); m/z (ESI): 265 (100)(M+Na)+, 225 (40), 189 (10), 145 (3), 111 (5); HRMS (ESI): Found (M+Na)+, 265.1766, C₁₄H₂₆O₄Na, requires 265.1774.

(2S)-7-(5-Iodopentyl)-2-methyl-1,6-dioxaspiro[4.5]decan (406)

To a solution of alcohol 378 (70.0 mg, 0.29 mmol) in THF (2 mL) at 0 °C was added dry triethylamine (96.0 µL, 0.69 mmol) followed by methanesulfonyl chloride (27.0 µL, 0.35 mmol) under an atmosphere of nitrogen. After stirring for 60 min at 0 °C, the mixture was filtered and washed with dry THF (3 mL). To the filtrate was added sodium iodide (130 mg, 0.87 mmol) and the resultant mixture was refluxed for 12 h resulting in a dark brown solution. The reaction was quenched with aqueous saturated Na₂S₂O₃ (3 mL) the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined extracts were dried
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over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 50:1) afforded the title compound (61.0 mg, 60%) as a colourless oil; $[\alpha]_D +61.1$ (c 1.30, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2922, 2852, 1374, 1211, 1162, 1073, 1024, 974, 944, 875, 835, 773, 702 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 4.19-4.26 (1H, qd, $J$ 6.0, 1.8, H2), 3.77-3.82 (1H, m, H7), 3.18 (2H, t, $J$ 6.0, H1'), 1.81-1.98 (2H, m, H5'), 1.52-1.74 (10H, m, H3, H4, H10, H9 and H2'), 1.18-1.48 (4H, m, H8, H4'), 1.29 (3H, d, $J$ 6.0, Me), 0.82-0.90 (2H, m, H3'); $^{13}$C NMR (75 MHz, CDCl$_3$): 105.8 (quat., C5), 76.6 (CH, C2), 69.7 (CH, C7), 39.5 (CH$_2$, C4), 36.2 (CH$_2$, C5'), 33.6 (CH$_2$, C4'), 31.9 (CH$_2$, C10), 31.2 (CH$_2$, C3'), 30.6 (CH$_2$, C3), 30.4 (CH$_2$, C8), 30.3 (CH$_2$, C2'), 23.3 (CH$_3$, Me), 20.4 (CH$_3$, C9), 7.1 (CH$_3$, C1'); m/z (EI): 352 (5), 199 (40), 101 (100), 98 (42), 55 (20); HRMS (EI): Found M$^+$, 352.0888, requires 352.0899.

4,6-Dimethoxy-1-(5-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentyl)-1H-indole (338)

A solution of 4,6-dimethoxyindole (9.1 mg, 0.051 mmol) in DMSO (1 mL) was added dropwise to a stirred solution of powdered KOH (4.3 mg, 0.077 mmol) in DMSO (1 mL) and the resultant mixture was stirred for 50 min at room temperature under an atmosphere of nitrogen. Iodide 406 (10.0 mg, 0.029 mmol) dissolved in DMSO (1 mL) was added to the resultant green solution giving a brown solution upon addition. After stirring the mixture for 2 h at room temperature, water (4 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (3 x 3 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure, flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (6.80 mg, 59%) as a yellow oil; $[\alpha]_D +49.5$ (c 1.00, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2925, 2855, 1732, 1622, 1588, 1499, 1456, 1433, 1364, 1251, 1208, 1146, 1070, 1050, 976, 937, 878 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 6.89 (1H, d, $J$ 3.0, H2), 6.49 (1H, d, $J$ 3.0, H1), 6.39 (1H, apparent s, H4), 6.23 (1H, d, $J$ 3.0, H6), 4.20-4.30 (1H, m, H2''), 4.01 (2H, t, $J$ 6.0, H1'), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 3.80-3.83 (1H, m, H7''), 1.97-2.17 (2H, m, H3''), 1.71-1.81 (4H, m, H4'' and H5''), 1.52-1.79 (6H, m, H10'', H9'' and H8''), 1.22-1.45 (6H, m, H2'-4''), 1.22 (3H, d, $J$ 6.1, Me); $^{13}$C NMR (75 MHz, CDCl$_3$): 157.3 (quat., C5), 153.7 (quat., C7), 137.3 (quat., C4a), 124.9 (CH, C2), 113.6 (quat.,...
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C7a), 105.9 (quat., C5''), 98.1 (CH, C1), 91.0 (CH, C6), 85.6 (CH, C4), 76.7 (CH, C2''), 69.7 (CH, C7''), 55.8 (CH3, OMe), 55.3 (CH3, OMe), 46.5 (CH2, C1'), 39.4 (CH2, C4''), 36.3 (CH2, C5''), 33.6 (CH2, C4''), 31.9 (CH2, C10''), 31.2 (CH2, C3''), 30.3 (CH2, C8''), 29.7 (CH2, C3'), 29.4 (CH2, C4'), 27.1 (CH2, C2''), 23.3 (CH3, Me), 20.5 (CH2, C9''); 

m/z (ESI): 424 (100)(M+Na)+, 402 (40), 365 (1), 325 (5), 311 (9), 278 (2); HRMS (ESI): Found (MH)+, 402.2649, C24H36NO4, requires 402.2639.

4,6-Dimethoxy-1-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentyl)indolin-2-one (341)

NaH (1.20 mg, 0.051 mmol, 60% w/w dispersion in mineral oil) was washed with pentane (3 x 0.5 mL) under an atmosphere of nitrogen and dried in vacuo, then suspended in DMF (0.5 mL). A solution of 4,6-dimethoxyxindole (21.0 mg, 0.11 mmol) dissolved in DMF (0.5 mL) was added slowly to the slurry. The resulting red-brown mixture was stirred at room temperature for 15 min. A solution of iodide 406 (20.0 mg, 0.057 mmol) in DMF (0.5 mL) was added slowly to the reaction mixture. After stirring for 2.5 h at room temperature, water (1 mL) was added and the solution was extracted with diethyl ether (3 x 2 mL) and ethyl acetate (3 x 2 mL). The combined organic extracts were dried over magnesium sulfate. The solvents were removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 5:1) afforded the title compound (14.0 mg, 58%) as a yellow oil; [α]D +43.2 (c 1.50, CHCl3).

IR γmax(film): 2923, 2856, 1718, 1615, 1462, 1378, 1263, 1219, 1143, 1111, 1074, 974, 875, 810 cm⁻¹;

1H NMR (300 MHz, CDCl3): 6.16 (1H, d, J 1.8, H4), 6.09 (1H, d, J 1.8, H6), 4.19-4.24 (1H, m, H2''), 3.83 (6H, s, OMe), 3.77-3.79 (1H, m, H7''), 3.63 (2H, t, J 6.0, H1''), 3.38 (2H, s, H1), 1.87-1.96 (2H, m, H3''), 1.56-1.70 (10H, m, H5', H10", H4", H8" and H2''), 1.23-1.48 (6H, m, H9", H3' and H4''), 1.28 (CH3, d, J 6.0, Me); 13C NMR (75 MHz, CDCl3): 175.8 (quat., C=O), 161.4 (quat., C7), 156.0 (quat., C5), 146.4 (quat., C4a), 105.8 (quat., C5''), 103.1 (quat., C7a), 91.7 (CH, C4), 89.0 (CH, C6), 76.6 (CH, C2''), 69.8 (CH, C7''), 55.6 (CH3, OMe), 55.4 (CH3, OMe), 40.2 (CH2, 1'), 39.4 (CH3, C4''), 36.3 (CH2, C3''), 33.6 (CH2, C10''), 33.1 (CH2, C8''), 31.9 (CH2, C5'), 31.2 (CH3, C1), 29.7 (CH2, C2'), 27.7 (CH3, C4'), 27.1 (CH2, C3'), 25.5 (CH3, C9''), 23.3 (CH3, Me); m/z (ESI): 418 (10)(MH)+, 400 (100), 382 (10), 356 (10), 262 (55), 206 (30), 189 (25), 111 (5); HRMS (ESI): Found (MH)+, 418.2593, C24H36NO5, requires 418.2588.
3.3 Synthesis of Long Chain Phthalide Analogue (R)-1-(3,5-Dimethoxyphenyl)but-3'-en-1'-ol (205)

Following the procedure described by Singaram et al., indium powder (0.140 g, 1.20 mmol), (1R, 2S)-(-)-2-Amino-1,2-diphenylethanol (0.260 g, 0.120 mmol), pyridine (0.096 mL, 1.20 mmol) and allyl bromide (0.100 mL, 1.20 mmol) were dissolved in THF (10 mL) under an argon atmosphere. The mixture was stirred vigorously at room temperature for 30 min. Dry n-hexane (2 mL) was added and the mixture cooled to -78 °C, 3,5-dimethoxybenzaldehyde dissolved in THF (3 mL) was added dropwise and the reaction was stirred for 2 h. The mixture was quenched by the addition of saturated ammonium chloride (2 mL) and HCl (1M, 2 mL) and allowed to warm room temperature. The organic layer was diluted with n-hexane (5 mL), decanted, dried with anhydrous magnesium sulfate, filtered through a small plug of silica gel and evaporated under reduced pressure. NaOH (1 M, 5 mL) was added to the aqueous layer and it was further extracted with diethyl ether (3 x 5 mL) to recover the chiral amino alcohol (0.065 g, 68%) without further purification. Flash chromatography (hexanes/diethyl ether 7:1) yielded the title compound (0.11 g, 88%) as a yellow oil in 96% enantiomeric excess (chiral hplc); \([\alpha]_D^+38.8\) (c 1.60, CHCl₃).

**IR** \(\gamma_{\max}\) (film): 3434br (OH), 2937, 1598, 1463, 1429, 1204, 1154, 1059, 920, 838, 696 cm\(^{-1}\); **\(^1\)H NMR** (400 MHz, CDCl₃): 6.52 (2H, d, J 2.2, H2), 6.37 (1H, t, J 2.2, H4), 5.81 (1H, dddd J 17.2, 10.2, 7.1 and 7.1, H3'), 5.13-5.18 (2H, m, H4'), 4.66 (1H, dd, J 7.5 and 5.3, H1'), 3.79 (6H, s, OMe), 2.43-2.55 (2H, m, H2'), 2.10 (1H, br s, OH); **\(^13\)C NMR** (100 MHz, CDCl₃): 160.8 (quat., C3), 146.5 (quat., C1), 134.4 (CH, C3'), 118.3 (CH₂, C4'), 103.7 (CH, C2), 99.4 (CH, C4), 73.3 (CH, C1'), 55.3 (CH₃, OMe), 43.7 (CH₂, C2'); \(m/z\) (EI): 208 (M⁺, 23%), 167 (92), 139 (100), 124 (24), 77 (11), 41 (7); **HRMS** (EI): Found M⁺, 208.10973, C₁₂H₁₆O₃, requires 208.10994.

\(^{18}\)HPLC Conditions: IC-column, \(^1\)PrOH:hexane 1:9, flow rate 0.5 mL/min, retention times: 23.2 min (minor), 27.9 min (major)
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(R)-1'-{(2-Bromo-3,5-dimethoxyphenyl)but-3'-en-1'-ol (203)

![Chemical Structure](image)

Alcohol 205 (1.10 g, 5.30 mmol) and N-bromosuccinimide (940 mg, 5.30 mmol) were dissolved in chloroform (40 mL) and the mixture was refluxed for 12 h under an atmosphere of nitrogen. The solution was filtered through a pad of Celite® and the solvent removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 12:1) gave the title compound (1.41 g, 94 %) as an orange oil; \([\alpha]_D^+57.5\) (c 3.40, CHCl₃).

**IR** \(\gamma_{\text{max}}\) (film): 3435br (OH), 2939, 2839, 1589, 1454, 1431, 1323, 1200, 1160, 1071, 1052, 1022, 919, 838; **\(^1H\) NMR** (300 MHz, CDCl₃): 6.75 (1H, d, \(J = 2.8\), H6), 6.39 (1H, d, \(J = 2.8\), H4), 5.88 (1H, dddd, \(J = 17.1, 17.1, 10.1, 7.1\) and 7.1), 5.10-5.21 (3H, m, H4' and H1'), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 2.57-2.65 (1H, m, H2'ₐ), 2.40 (1H, br s, OH), 2.26-2.36 (1H, m, H2'ₐ); **\(^{13C\) NMR** (75 MHz, CDCl₃): 159.9 (quat., C1), 156.2 (quat., C5), 144.9 (quat., C1), 134.4 (CH, C3'), 118.3 (CH₂, C4'), 103.0 (CH, C6), 101.9 (quat., C2), 98.8 (CH, C4) 71.9 (CH, C1'), 56.2 (CH₃, OMe), 55.5 (CH₃, OMe), 41.8 (CH₂, C2'); \(m/z\) (EI): 288 (M\(^{[81\text{Br}]}\), 6%), 286 (M\(^{[79\text{Br}]}\), 6%), 247 (58), 245 (62), 207 (31), 166 (55), 138 (100); **HRMS** (EI): Found M⁺, 286.01990, C₁₂H₁₅⁷⁹BrO₃, requires 286.02046. Found M⁺, 288.019150, C₁₂H₁₅⁸¹BrO₃, requires 288.01841.

(R)-1-(2-Bromo-3,5-dimethoxyphenyl)but-3'-enyl diethylcarbamate (206)

![Chemical Structure](image)

To a suspension of NaH (200 mg, 7.90 mmol, 60% w/w dispersion in mineral oil) in THF (10 mL), at 0 °C, under an atmosphere of nitrogen was added a solution of bromoalcohol 203 (2.05 g, 7.20 mmol) in THF (6 mL) dropwise. After stirring for 0.5 h, N,N-diethylcarbamoyl chloride (1.40 mL, 10.8 mmol) was added dropwise. The mixture was stirred for 12 h before the addition of saturated ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts dried over magnesium sulfate. Removal of the solvent under reduced pressure and flash chromatography
(hexanes/diethyl ether 4:1) provided the *title compound* (2.30 g, 81%) as a yellow oil; [\(\alpha\)]\(_D\) -9.10 (c 1.60, CHCl\(_3\)).

**IR** \(\gamma_{\text{max}}\) (film): 2974, 2836, 1703 (CO), 1589, 1455, 1422, 1325, 1276, 1163, 1067, 1024, 920, 835; **\(^{1}\text{H} \)** NMR (300 MHz, CDCl\(_3\)): 6.52 (1H, d, \(J \) 2.8, H6), 6.42 (1H, d, \(J \) 2.8, H4), 6.10 (1H, dd, \(J \) 8.0 and 4.3, H1'), 5.82 (1H, m, H3'), 5.04-5.12 (2H, m, H4'), 3.85 (3H, s, OMe), 3.79 (3H, s, OMe), 3.33 (4H, br s, NCH\(_2\)CH\(_3\)), 2.47-2.68 (2H, m, H2') 1.11-1.26 (6H, m, NCH\(_2\)CH\(_3\)); **\(^{13}\text{C} \)** NMR (75 MHz, CDCl\(_3\)): 159.7 (quat., C3), 156.5 (quat., C5), 154.7 (quat., C=O), 142.7 (quat., C1), 133.6 (CH, C3'), 117.7 (CH, C4'), 103.4 (CH C6), 102.2 (quat., C2), 98.4 (CH, C4), 74.8 (CH, C1'), 56.3 (CH\(_3\), OMe), 55.3 (CH\(_3\), OMe), 41.9 (CH\(_2\), NCH\(_2\)CH\(_3\)), 41.3 (CH\(_2\), NCH\(_2\)CH\(_3\)), 39.6 (CH\(_2\), C2'), 41.3 (CH\(_2\), NCH\(_2\)CH\(_3\)), 39.6 (CH\(_2\), C2'), 14.3 (CH\(_2\), NCH\(_2\)CH\(_3\)), 13.4 (CH\(_2\), NCH\(_2\)CH\(_3\)); \(m/z\) (CI): 388 (M\(^{81}\)BrH\(^+\), 6), 386 (M\(^{79}\)BrH\(^+\), 6), 344 (2), 306 (31), 288 (4), 286 (4), 271 (100), 269 (97), 190 (13), 100 (22), 72 (24); **HRMS** (CI): Found (MH\(^+\)), 386.09538, C\(_{17}\)H\(_{25}\)BrNO\(_4\), requires 386.09669. Found (MH\(^+\)), 388.09559, C\(_{17}\)H\(_{25}\)BrNO\(_4\), requires 388.09465.

**\((R)-3\text{-}3\text{-}Allyl\text{-}5\text{-}7\text{-}dimethoxyisobenzofuran\text{-}1\text{-}3H\text{-}one\text{ (200)}\)**

To a stirred solution of \((R)	ext{-}carbamate\) 206 (1.55 g, 4.05 mmol) in THF (10 mL) at -78 °C under an atmosphere of nitrogen was added dropwise tert-butyllithium (5.50 mL, 8.80 mmol). After stirring for 45 min the reaction was quenched by the addition of methanol (5 mL) and the solution was allowed to warm to room temperature. A catalytic amount of \(p\)-toluenesulfonic acid (19.0 mg, 0.10 mmol) was added and the solution stirred for 12 h. The mixture was concentrated *in vacuo* and the residue purified by flash chromatography (hexanes/diethyl ether 1:1) to give the *title compound* (0.660 g, 70%) as a white solid; m.p. 95-98 °C; [\(\alpha\)]\(_D\) +31.5 (c 1.37, CHCl\(_3\)).

**IR** \(\gamma_{\text{max}}\) (film): 2948, 1750 (C=O), 1615, 1460, 1332, 1221, 1159, 1030, 839; **\(^{1}\text{H} \)** NMR (300 MHz, CDCl\(_3\)): 6.41 (1H, s, H6), 6.38-6.39 (1H, m, H4), 5.64-5.80 (1H, m, H2'), 5.30 (1H, dd, \(J \) 10.6 and 5.5, H3), 5.07-5.17 (2H, m, H3'), 3.91 (3H, s, OMe), 3.85 (3H, s, OMe), 2.63-2.70 (1H, m, H1'), 2.50-2.56 (1H, m, H1'), 2.50-2.56 (1H, m, H1'), 1.26-1.40 (6H, m, CH\(_3\)); **\(^{13}\text{C} \)** NMR (75 MHz, CDCl\(_3\)): 167.9 (quat., C1), 166.5 (quat., C5), 159.2 (quat., C7) 154.0 (quat., C3a), 131.1 (CH, C2'), 119.0 (CH\(_2\), C3'), 106.5 (quat., C7a), 98.4 (CH, C4), 97.6 (CH, C6), 78.6 (CH, C3), 55.7 (CH\(_3\), OMe), 55.7 (CH\(_3\), OMe), 38.4 (CH\(_2\), C1'); \(m/z\) (FAB): 235 (MH\(^+\)), 100, 203 (11), 193 (26); **HRMS** (FAB): Found MH\(^+\), 235.09691, C\(_{13}\)H\(_{25}\)BrNO\(_4\), requires 235.09703.
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(R)-3-Butyl-5,7-dimethoxyisobenzofuran-1-3H-one (208)

A solution of borane-dimethylsulfide complex (0.95 mL, 10.0 mmol) in THF (10 mL) was cooled to 0 °C under an atmosphere of nitrogen and 2-methyl-2-buten (2.12 mL, 20.0 mmol) was added dropwise over a 25 min period. The resultant solution was stirred at 0 °C for 5 h to form the disiamylborane. To a solution of alkene 200 (100 mg, 0.43 mmol) in THF (3 mL) was added disiamylborane (0.510 mL, 0.510 mmol) via canula and the resulting mixture stirred 0 °C for 3 h. Methanol (1 mL) was then added followed by NaOH (1 M, 0.20 mL) and H2O2 (0.10 mL, 8.80 M). The solution was allowed to warm to room temperature over 12 h then concentrated to a third of its volume before the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts were washed with water (1 x 5 mL), dried over magnesium sulfate and the solvent removed under reduced pressure. The crude oil was purified by flash chromatography (dichloromethane/acetone 9:1) to afford the title compound (75 mg, 70%) as a white solid; m.p. 117-118 °C; [α]D +40.6 (c 7.8, CHCl3).

IR γmax(film): 3305 br (OH), 2951, 1738 (C=O), 1603, 1430, 1340, 1204, 1160, 1053, 980, 840; 1H NMR (300 MHz, CDCl3): 6.41 (1H apparent s, H6), 6.40 (1H, d J 1.7, H4), 5.33 (1H, dd, J 7.2 and 3.7, H3), 3.92 (3H, s, OMe), 3.87 (3H, s, OMe), 3.62-3.75 (2H, m, H3, H3'), 2.08-2.21 (1H, m, H1',b), 1.63-1.82 (4H, m, H1'a, H2' and OH); 13C NMR (75 MHz, CDCl3): 168.4 (quat., C1), 166.8 (quat., C5), 159.6 (quat., C7), 155.0 (quat., C3a), 106.8 (quat., C7a), 98.8 (Ch, C4), 97.5 (CH, C6), 79.7 (CH, C3), 62.1 (CH2, C3'), 56.0 (CH3, OMe), 55.9 (CH3, OMe), 31.3 (CH2, C1'), 27.8 (CH2, C2'); m/z (EI): 252 (M+, 34%), 207 (30), 193 (100), 165 (21), 135 (9), 77 (8); HRMS (EI): Found M+, 252.09955, C13H16O5, requires 252.09977.

(R)-3-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanal (189)

A solution of alcohol 208 (63.0 mg, 0.25 mmol) in CH2Cl2 (3 mL) was added dropwise to a suspension of Dess-Martin periodinane (0.21 g, 0.50 mmol) and pyridine (0.06 mL, 0.75 mmol) in CH2Cl2 (5 mL) at 0 °C under an atmosphere of nitrogen. After stirring at room temperature for 3 h, the solution was filtered
through a pad of Celite® and washed with CH₂Cl₂ (2 x 3 mL). Removal of the solvent \textit{in vacuo} and purification by flash chromatography (hexanes/EtOAc 3:2) afforded the \textit{title compound} (53.0 mg, 85%) as a white solid; m.p. 99-102 °C; \([\alpha]_D^{\text{25}}+51.1\) (c 0.74, CHCl₃).

\textbf{IR} \(\gamma_{\text{max}}\) (film): 2951, 2928, 1755 (C=O), 1602 (C=O), 1463, 1338, 1218, 1158, 1028, 837, 734; \textbf{\(^1H\) NMR} (300 MHz, CDCl₃): 9.80 (1H, apparent s, H₃'), 6.43 (1H, s, H₆), 6.42 (1H, s, H₄), 5.34 (1H, dd, \(J\) 8.3 and 3.2, H₃), 3.94 (3H, s, OMe), 3.88 (3H, s, OMe), 2.75 (1H, dd, \(J\) 18.7 and 7.4, H₂'), 2.54 (1H, ddd, \(J\) 18.7, 8.3 and 5.1, H₂'), 2.44 (1H, dddd, \(J\) 14.4, 7.4, 7.4 and 3.2, H₁₅'), 1.88 (1H, dddd, \(J\) 14.4, 8.3, 8.3 and 5.1, H₁₆'), \textbf{\(^{13}C\) NMR} (75 MHz, CDCl₃): 200.7 (CH, C₃'), 168.4 (quat., C₁), 137.0 (quat., C₅), 159.7 (quat., C₇), 154.3 (quat., C₃a), 106.7 (quat., C₇a), 99.1 (CH, C₄), 97.4 (CH, C₆), 78.4 (CH, C₃), 56.0 (CH₃), 38.9 (CH₂, C₂'), 26.9 (CH₃, C₁'); \textbf{m/z} (EI): 250 (M⁺, 30), 206 (61), 193 (100), 165 (21), 135 (20), 77 (10); \textbf{HRMS} (EI): Found M⁺, 250.08333, C₁₃H₁₄O₅, requires 252.08412.

5-(5-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentylthio)-1-phenyl-1\(H\)-tetrazole (463)

To a stirred solution of 1-phenyl-1\(H\)-tetrazole-5-thiol (16.0 mg, 0.09 mmol) and triphenylphosphine (24.0 mg, 0.09 mmol) in THF (2 mL) under an atmosphere of nitrogen was added alcohol 378 (20.0 mg, 0.08 mmol). The mixture was cooled to 0 °C and a solution of diisopropyl azodicarboxylate (17.0 mg, 0.08 mmol) was added dropwise. The resulting bright yellow solution was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure and the resultant residue was purified by flash chromatography (hexanes/diethyl ether 7:1) to afford the \textit{title compound} (20.0 mg, 61%) as an yellow oil; \([\alpha]_D^{\text{25}}+64.3\) (c 1.2, CHCl₃).

\textbf{IR} \(\gamma_{\text{max}}\) (film): 2972, 2855, 1598, 1500, 1458, 1412, 1386, 1314, 1242, 1222, 1159, 1114, 1085, 1073, 1016, 974, 876, 809, 716, 694; \textbf{\(^1H\) NMR} (300 MHz, CDCl₃): 7.56-7.59 (5H, m, Ph, \(o\), \(m\), \(p\)), 4.18-4.25 (1H, qd, \(J\) 6.3, 1.5, H₂), 3.94 (2H, t, \(J\) 7.2, H₁'), 3.77-3.82 (1H, m, H₇), 1.81-1.97 (2H, m, H₅'), 1.52-1.74 (10H, m, H₃, H₄, H₁₀, H₉ and H₂'), 1.18-1.48 (4H, m, H₈, H₄'), 1.28 (3H, d, \(J\) 6.0, Me), 0.85-0.88 (2H, m, H₃'); \textbf{\(^{13}C\) NMR} (75 MHz, CDCl₃): 154.5 (quat., C₁a), 130.0 (CH, Ph, \(o\)), 130.0 (quat., Ph), 129.8 (CH, Ph, \(p\)), 123.9 (CH, Ph, \(m\)), 105.9 (quat., C₅), 76.7 (CH, C₂), 69.6 (CH, C₇), 39.4 (CH₃, C₄), 36.2 (CH₂, C₅'), 33.6 (CH₂, C₁₀), 33.4 (CH₂, C₁'), 31.9 (CH₃, C₃), 31.2 (CH₂, C₈), 30.3 (CH₂, C₂'), 28.7 (CH₂, C₃').
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25.2 (CH₂, C4') 23.3 (CH₃, Me), 20.4 (CH₂, C9); m/z (ESI): 425 (90)(M+Na)⁺, 403 (100)(MH)⁺, 385 (5), 230 (5), 177 (5), 145 (5); HRMS (ESI): Found (MH)⁺, 403.2165, C₂₁H₃₁N₄O₂S, requires 403.2162.

5-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentylsulfonyl)-1-phenyl-1H-tetrazole (379)

![Chemical structure of 5-((2S)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentylsulfonyl)-1-phenyl-1H-tetrazole (379)](image)

To a solution of sulfide 463 (20.0 mg, 0.05 mmol) dissolved in CH₂Cl₂ (2 mL) was added sodium bicarbonate (21 mg, 0.25 mmol) followed by m-chloroperoxybenzoic acid (22.0 mg, 0.12 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 12 h, then a saturated sodium bicarbonate solution (2 mL) was added followed by a solution of saturated sodium thiosulfate (2 mL). The resultant mixture was stirred for 1 h and the aqueous layer was extracted with diethyl ether (2 x 3 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude oil was purified by flash chromatography (hexanes/diethyl ether 3:2) to afford the title compound (16.0 mg, 76%); [α]D +29.0 (c 1.32, CHCl₃).

IR γ max (film): 2928, 2854, 1723, 1703, 1575, 1461, 1432, 1343, 1288, 1259, 1224, 1153, 1113, 1073, 1020, 974, 753, 702, 626; ¹H NMR (300 MHz, CDCl₃): 7.62-7.65 (2H, m, Ph, o), 7.56-7.60 (3H, m, Ph, m and p), 4.19-4.26 (1H, qd, J 6.0, 1.5, H2), 3.77-3.82 (1H, m, H7), 3.70-3.75 (2H, m, H1'), 1.96-1.98 (4H, m, H3 and H5'), 1.51-1.74 (8H, m, H4, H10, H9 and H2'), 1.18-1.43 (4H, m, H8, H4'), 1.28 (3H, d, J 6.0, Me), 0.85-0.88 (2H, m, H3'); ¹³C NMR (75 MHz, CDCl₃): 153.5 (quat., C1a), 131.4 (quat., Ph), 130.0 (CH, Ph, o), 129.8 (CH, Ph, p), 125.1 (CH, Ph, m), 105.9 (quat., C5), 76.7 (CH, C2), 69.5 (CH, C7), 56.0 (CH₂, C1'), 39.4 (CH₂, C4) 35.9 (CH₂, C2'), 33.6 (CH₂, C10), 31.9 (CH₂, C5'), 31.1 (CH₂, C3), 28.3 (CH₂, C3'), 25.1 (CH₂, C4'), 23.3 (CH₃, Me), 21.9 (CH₂, C8), 20.3 (CH₂, C9); m/z (ESI): 457(25)(M+Na)⁺, 452 (10), 435 (100)(MH)⁺, 282 (10), 219 (5); HRMS (ESI): Found (MH)⁺, 435.2070, C₂₁H₃₁N₄O₂S, requires 435.2061.
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(3R)-5,7-Dimethoxy-3-(7-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)hept-3-enyl)isobenzofuran-1(3H)-one (464)

To a solution of sulfone 379 (12.0 mg, 0.03 mmol) in THF (1 mL) under an inert atmosphere at -78 °C was added potassium hexamethyldisilazide (77.0 µL, 0.5 M in toluene, 0.04 mmol) dropwise. The mixture was stirred for 20 min at -78 °C then a solution of aldehyde 189 (13.0 mg, 0.05 mmol) in THF (1 mL) was added, and the mixture was stirred at that temperature for 1.5 h. The mixture was then warmed to room temperature and stirred for an additional hour. Diethyl ether (3 mL) was added followed by saturated aqueous sodium chloride (3 mL). The aqueous layer was extracted with diethyl ether (2 x 3 mL) and the combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude oil was purified by flash chromatography (hexanes/EtOAc 2:1) to afford the title compound (8.3 mg, 64%); [α]D +48.0 (c 1.60, CHCl₃).

IR γmax (film): 2923, 2853, 1733 (C=O), 1603, 1461, 1363, 1219, 1158, 1119, 1070, 1026, 974, 937, 809, 757, 689; ¹H NMR (300 MHz, CDCl₃): 6.40-6.41 (2H, m, H₄ and H₆), 5.33-5.53 (2H, m, (E)-H₃' and (Z)-H₃', (E)-H₄' and (Z)-H₄'), 5.30 (1H, dd, J 8.4 and 3.3, H₃), 4.18-4.25 (1H, qd, J 6.0, 1.5, H₂''), 3.94 (3H, s, OMe), 3.89 (3H, s, OMe), 3.85-3.80 (1H, m, H₇''), 1.94-2.04 (4H, m, (E)-H₂' and (Z)-H₂', (E)-H₅' and (Z)-H₅'), 1.58-1.70 (8H, m, H₁', H₈', H₃'' and H₄''), 1.25-1.43 (10H, m, H₆', H₇', H₈'', H₉'' and H₁₀''), 1.28 (3H, d, J 6.0, Me); ¹³C NMR (75 MHz, CDCl₃): 168.5 (quat., C₁), 166.7 (quat., C₅), 159.6 (quat., C₇), 155.2 (quat., C₃a), 132.2 (CH, (E)-C₄' and (Z)-C₄'), 128.1 (CH, (E)-C₃' and (Z)-C₃'), 107.0 (quat., C₇a), 105.8 (quat., C₅''), 98.7 (CH, C₄), 97.3 (CH, C₆), 79.2 (CH, C₃), 76.6 (CH, C₂''), 69.7 (CH, C₇''), 55.9 (CH₃, OMe), 55.8 (CH₃, OMe), 39.4 (CH₂, C₅'), 36.3 (CH₂, C₂'), 34.9 (CH₂, C₁'), 33.6 (CH₂, C₈'), 32.6 (CH₂, C₃''), 31.9 (CH₂, C₈'), 31.8 (CH₂, C₁₀'), 29.7 (CH₂, C₄''), 29.4 (CH₂, C₆'), 27.9 (CH₂, C₇'), 23.3 (CH₃, Me), 20.4 (CH₂, C₉''); m/z (ESI): 481(25)(M+Na)^+, 452 (100), 459 (45)(MH)^+, 413 (10), 373 (15), 301 (10), 267 (15), 245 (10), 219 (15), 149 (15); HRMS (ESI): Found (MH)^+, 459.2727 C₂₇H₃₈O₆ requires 459.2714.
(3R)-5,7-Dimethoxy-3-(7-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)isobenzofuran-1-(3H)-one (336)

Alkene 464 (8.40 mg, 0.02 mmol) was dissolved in methanol/THF (1 mL, 1:1) and hydrogenated under an atmosphere of hydrogen in the presence of PtO$_2$ (0.63 mg, 0.003 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite$^\text{®}$ and the filtrate concentrated in vacuo. Flash chromatography (hexanes/diethyl ether 1:3) afforded the title compound (5.80 mg, 69%) as a yellow oil; $[\alpha]_D^{\text{28}} +48.3$ (c 1.50, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 2926, 2854, 17543(C=O), 1604, 1495, 1461, 1433, 1337, 1219, 1158, 1028, 837; $^1\text{H NMR}$ (300 MHz, CDCl$_3$): 6.40-6.41 (2H, m, H4 and H6), 5.29 (1H, dd, $J$ 7.8 and 3.9, H3), 4.19-4.26 (1H, qd, $J$ 6.3, 1.8, H2$''$), 3.95 (3H, s, OMe), 3.89 (3H, s, OMe), 3.78-3.81 (1H, m, H7$''$), 1.95-2.00 (3H, m, H1$''_b$, H3$''_b$ and H4$''_b$), 1.58-1.67 (12 H, m, H1$'_a$, H3$'_a$, H4$'_a$, H9$''_a$, H8', H10', H8'' and H7'), 1.22-1.43 (13H, m, H2', H4', H3', H9$''_b$, H5', H6' and H7'), 1.29 (3H, d, $J$ 6.3, Me); $^{13}\text{C NMR}$ (75 MHz, CDCl$_3$): 168.5 (quat., C1), 166.7 (quat., C5), 159.6 (quat., C7), 155.2 (quat., C3a), 107.0 (quat., C7a), 105.8 (quat., C5$'$), 98.6 (CH, C4), 97.4 (CH, C6), 79.9 (CH, C3), 76.6 (CH, C2$''$), 69.8 (CH, C7$''$), 55.9 (CH$_3$, OMe), 55.8 (CH$_3$, OMe), 39.5 (CH$_2$, C4$''$), 36.5 (CH$_2$, C8$'$), 34.9 (CH$_2$, C1$'$), 33.6 (CH$_2$, C10$''$), 31.9 (CH$_2$, C3$''$), 31.2 (CH$_2$, C8$''$), 29.7 (CH$_2$, C2$'$) 29.5 (CH$_2$, C3$'$), 29.4 (CH$_2$, C7$''$), 29.3 (CH$_2$, C6$'$), 25.7 (CH$_2$, C5$'$), 24.6 (CH$_2$, C4$''$), 23.3 (CH$_3$, Me), 20.4 (CH$_2$, C9$''$); $m/z$ (ESI): 483 (100)(M+Na)$^+$, 461 (30)(MH)$^+$, 373 (20), 289 (10), 267 (9), 245 (10), 223 (5); HRMS (ESI): Found (MH)$^+$, 461.2887 C$_{27}$H$_{41}$O$_6$, requires 461.2898.
3.4 Synthesis of Short Chain Indole XX and Oxindole XX Analogues

1-(tert-Butyldiphenylsilyloxy)-hex-5-ene (471)

\[ \text{TBDPSO} \begin{array}{c}
\text{\_\_\_}\text{\_}\text{\_}\text{\_}\text{\_}
\end{array} \]

tert-Butyldiphenylsilylchloride (16.3 mL, 62.5 mmol), 4-dimethylaminopyridine (300 mg, 2.50 mmol) and imidazole (6.40 g, 93.75 mmol) were dissolved in CH\(_2\)Cl\(_2\) (20 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this stirred solution was added 6-heptene-1-ol (465) (7.50 mL, 62.5 mmol) in CH\(_2\)Cl\(_2\) (10 mL). After stirring for 12 h at room temperature, the white precipitate was filtered off and the solvent removed under reduced pressure to yield the title compound (21.1 g, 99%) as yellow oil without further purification.

IR \( \gamma_{\text{max}} \) (film): 2931, 2857, 1472, 1427, 1389, 1105, 997, 909, 822, 738, 689, 613 cm\(^{-1}\); \( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)): 7.66-7.70 (4H, m, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), o), 7.37-7.44 (6H, m, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), m and p), 5.77-5.86 (1H, m, H5), 4.94-5.03 (2H, m, H6), 3.69 (2H, t, J 6.0, H1), 2.07 (2H, dt, J 9.0 and 6.0, H4), 1.54-1.63 (2H, m, H3), 1.46-1.54 (2H, m, H2), 1.06 (9H, s, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \)); \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)): 138.9 (CH, C5), 135.6 (CH, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), o), 134.1 (quat., Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), 129.5 (CH, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), p), 127.6 (CH, Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \), m), 114.3 (CH\(_2\), C6), 63.8 (CH\(_2\), C1), 33.5 (CH\(_2\), C4), 32.0 (CH\(_2\), C2), 26.9 (CH\(_3\), Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \)), 25.1 (CH\(_2\), C3), 19.2 (quat., Si\( ^{t} \)Bu\( ^{2} \)Ph\( _2 \)); \( m/z \) (ESI): 361 (10)(M+N\( ^{+} \))\(^{+}\), 339 (30)(MH\(^{+}\))\(^{+}\), 257 (45), 239 (100), 179 (80), 135 (60), 123 (30); HRMS (ESI): Found (MH\(^{+}\))\(^{+}\), 339.2129 C\(_{22}\)H\(_{31}\)OSi, requires 339.2139.

1-(tert-Butyldiphenylsilyloxy)-5-hexene oxide (472)

\[ \text{TBDPSO} \begin{array}{c}
\text{\_\_\_}\text{\_}\text{\_}\text{\_}\text{\_}\text{\_}\text{\_}
\end{array} \]

meta-Chloroperoxybenzoic acid (22.9 g, 0.13 mol) was dissolved in CH\(_2\)Cl\(_2\) (100 mL) under an atmosphere of nitrogen and cooled to 0 °C. A solution of alkene 471 (22.5 g, 66.0 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added dropwise. The solution was allowed to warm to room temperature over 12 h, saturated sodium sulfite solution (80 mL) was then added to the reaction mixture and stirred until it became clear. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The organic layer was then washed with NaOH solution (100 mL, 5 %) and brine (100 mL) and the solvent was removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (18.7 g, 79%) as a yellow oil.
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IR \(\gamma_{\text{max}}\) (film): 2931, 2858, 1471, 1427, 1389, 1361, 1258, 1188, 1105, 822, 739, 686 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.66-7.68 (4H, m, Si\(_{\text{tBu}}\)Ph\(_2\), o), 7.37-7.45 (6H, m, Si\(_{\text{tBu}}\)Ph\(_2\), m and p), 2.90-2.95 (1H, m, H5), 2.74 (1H, dd, J 4.9 and 5.0, H6a), 2.46 (1H, dd, J 2.1 and 5.1, H6b), 1.55-1.64 (6H, m, H2-4), 1.08 (9H, s, Si\(_{\text{tBu}}\)Ph\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 135.5 (CH, Si\(_{\text{tBu}}\)Ph\(_2\), o), 133.9 (quat., Si\(_{\text{tBu}}\)Ph\(_2\)), 129.5 (CH, Si\(_{\text{tBu}}\)Ph\(_2\), p), 127.6 (CH, Si\(_{\text{tBu}}\)Ph\(_2\), m), 63.6 (CH\(_2\), C1), 52.3 (CH\(_2\), C5), 47.0 (CH\(_2\), C6), 32.3 (CH\(_2\), C2 or C4), 32.2 (CH\(_2\), C2 or C4), 26.6 (CH\(_3\), Si\(_{\text{tBu}}\)Ph\(_2\)), 22.3 (CH\(_2\), C3), 19.2 (quat., Si\(_{\text{tBu}}\)Ph\(_2\)); m/z (ESI): 377 (30)(M+Na)+, 277 (100), 259 (5), 235 (7), 157 (8), 129 (3); HRMS (ESI): Found (M+Na)+, 377.1901 C\(_{22}\)H\(_{30}\)NaO\(_2\)Si, requires 377.1907.

\((R)-1-(\text{tert-Butyldiphenylsilyloxy})-5\text{-hexene oxide (466)}\)

\[
\text{TBDPSO}^1\overbrace{\text{O}}^\text{O}
\]

To a solution of \((R,R)\)-SalenCo\(^{\text{II}}\) (0.48 g, 0.79 mmol) in toluene (4 mL) was added glacial acetic acid (0.09 mL, 1.58 mmol) and the mixture was stirred open to the air for 1 h to form the active form of the catalyst \((R,R)\)-SalenCo\(^{\text{III}}\)OAc over which time the colour changed from orange to a dark brown. The solution was then concentrated \textit{in vacuo} to give a crude brown solid. To the resultant catalyst residue was added epoxide 472 (18.7 g, 53.0 mmol) dissolved in isopropanol (19 mL). The resultant solution was cooled to 0 °C and water (0.57 mL, 32.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 h. The isopropanol was removed under reduced pressure and the resulting chiral epoxide was purified by flash chromatography (hexanes/diethyl ether 25:1) to afford the \textit{title compound} (7.56 g, 81%) as a yellow oil; \([\alpha]_D^{+}+15.3\) (c 1.20, CHCl\(_3\)). The spectroscopic data was identical to that reported above for epoxide 472, enantiomeric excess 99% (chiral hplc\(^{28}\)).

\((S)-5-(\text{tert-Butyldiphenylsilyloxy})\text{-non-1-en-5-ol (467)}\)

\[
\text{TBDPSO}^1\overbrace{\text{OH}}^\text{OH}
\]

CuCN (0.72 g, 8.00 mmol) was gently flame dried under vacuum then THF (10 mL) was introduced under an atmosphere of nitrogen thus forming a slurry. The mixture was cooled to -78 °C and MeLi (10.0 mL, 16.0 mmol, 1.6 M in THF) was added. The reaction was allowed to warm up to 0 °C and further stirred at this temperature for 20 min. AllylSnBu\(_3\) (5.30 g, 16.0 mmol) was then added at 0 °C as a neat liquid in one portion and the solution continued to be stirred at this temperature for an additional 30

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\(^{28}\) HPLC Conditions: AD-H column, hexane 100%, flow rate 0.5 mL/min, retention times: 28.7 min (major), 35.1 min (minor)
min. The reaction mixture was cooled to -78 °C and epoxide 466 (1.50 g, 4.00 mmol) in THF (7 mL) was cannulated to the resulting cuprate. The reaction was then warmed to 0 °C and stirred at that temperature for an additional hour. The solution was quenched by the addition of a solution of 10% ammonia solution in saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed in vacuo. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (1.44 g, 91%) as a yellow oil; [α]D +17.3 (c 1.32, CHCl₃).

IR γmax (film): 3365 br (OH), 2931, 2858, 1472, 1462, 1427, 1389, 1361, 1106, 997, 910, 822, 739, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.66-7.71 (4H, m, Si’BuPh₂, o), 7.38-7.43 (6H, m, Si’BuPh₂, m and p), 5.80-5.89 (1H, m, H₈), 4.96-5.08 (2H, m, H₉), 3.70 (2H, t, J 6.0, H₁), 3.60-3.62 (1H, m, H₅), 2.13-2.20 (2H, m, H₇), 1.38-1.59 (8H, m, H₂, H₃, H₄ and H₆), 1.06 (9H, s, Si’BuPh₂); ¹³C NMR (75 MHz, CDCl₃): 138.6 (CH, C₈), 135.5 (CH, Si’BuPh₂, o), 134.1 (quat., Si’BuPh₂), 129.5 (CH, Si’BuPh₂, p), 127.6 (CH, Si’BuPh₂, m), 114.7 (CH₃, C₉), 71.4 (CH, C₅), 63.8 (CH₂, C₁), 37.1 (CH₂, C₆), 36.4 (CH₂, C₇), 32.5 (CH₂, C₄), 30.1 (CH₂, C₂), 26.9 (CH₃, Si’BuPh₂), 21.9 (CH₃, C₃), 19.2 (quat., Si’BuPh₂); m/z (ESI): 419 (M+Na)+, 397 (100)(MH)+, 379 (10), 257 (10), 141 (45), 123 (100); HRMS (ESI): Found (M+Na)+, 397.2548 C₂₅H₃₇O₂Si, requires 397.2530.

(5S)-1-(tert-Butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)-non-8-ene (473)

tert-Butyldimethylsilylchloride (1.23 g, 8.20 mmol), imidazole (0.56 g, 8.20 mmol), N,N-4-dimethylaminopyridine (33.0 mg, 0.27 mmol) were dissolved in CH₂Cl₂ (15 mL) under nitrogen atmosphere and cooled to 0 °C. To this stirred solution was added a solution of alcohol 467 (2.16 g, 5.50 mmol) in CH₂Cl₂ (7 mL). After stirring for 12 h, brine (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate. The solvent was removed in vacuo, flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (2.21 g, 79%) as a yellow oil; [α]D +12.9 (c 1.80, CHCl₃).
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Si′BuPh₂, o), 134.1 (quat., Si′BuPh₂), 129.5 (CH, Si′BuPh₂, p), 127.6 (CH, Si′BuPh₂, m), 114.2 (CH₂, C9), 71.8 (CH, C5), 63.9 (CH₂, C1), 36.9 (CH₂, C6), 36.3 (CH₂, C4), 32.9 (CH₂, C2), 29.6 (CH₃, C7) 26.9 (CH₃, Si′BuPh₂), 25.9 (CH₃, Si′BuMe₂), 21.6 (CH₂, C3), 19.2 (quat., Si′BuPh₂), 18.1 (quat., Si′BuMe₂), -4.4 (CH₃, Si′BuMe₂), -4.5 (CH₃, Si′BuMe₂); m/z (ESI): 533 (9)(M+Na)+, 511 (5)(MH)+, 379 (50), 353 (20), 274 (5), 257 (20), 239 (10), 179 (15), 144 (10), 123 (100); HRMS (ESI): Found (MH)+, 511.3405; C₃₁H₅₁O₂Si₂, requires 511.3422.

(S)-5-(tert-Butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)nonan-9-ol (474)

Alkene 473 (1.63 g, 3.20 mmol) was dissolved in THF (10 mL) under an atmosphere of nitrogen and the solution was cooled to 0 °C. Borane dimethylsulfide complex (0.900 mL, 9.60 mmol) was added dropwise and the solution was allowed to warm to room temperature over 12 h. Oxidative workup by sequential addition of H₂O₂ (2.20 mL, 8.80 M) followed by aqueous NaOH (4.80 mL, 4 M) gave a biphasic mixture which was stirred for 30 min. The mixture was extracted with diethyl ether (3 x 10 mL) and the combined extracts dried over magnesium sulfate. Filtration, removal of the solvent under reduced pressure and purification by flash chromatography using (hexanes/EtOAc 25:1) as the eluent to afford the title compound (1.30 g, 77%) as a yellow oil; [α]D +37.3 (c 1.00, CHCl₃).

IR γmax(film): 3350 br (OH), 2930, 2857, 1472, 1462, 1428, 1388, 1360, 1255, 1105, 1005, 988, 833, 772, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.65-7.68 (4H, m, Si′BuPh₂, o), 7.37-7.40 (6H, m, Si′BuPh₂, m and p), 3.66 (5H, q, J 6.0, H1, H5, H9), 1.50-1.56 (4H, m, H6 and H4), 1.40-1.43 (8H, m, H2, H3, H7 and H8), 1.05 (9H, s, Si′BuPh₂), 0.88 (9H, s, Si′BuMe₂), 0.03 (3H, s, Si′BuMe₂), 0.02 (3H, s, Si′BuMe₂); ¹³C NMR (75 MHz, CDCl₃): 135.6 (CH, Si′BuPh₂, o), 134.2 (quat., Si′BuPh₂), 129.5 (CH, Si′BuPh₂, p), 127.6 (CH, Si′BuPh₂, m), 71.8 (CH, C5), 63.9 (CH₂, C1), 63.0 (CH, C9), 36.9 (CH₂, C6 or C4), 36.8 (CH₂, C6 or C4), 33.0 (CH₂, C7 or C8), 32.9 (CH₂, C7 or C8), 26.9 (CH₃, Si′BuPh₂), 25.9 (CH₃, Si′BuMe₂), 21.7 (CH₂, C2 or C3), 21.4 (CH₂, C2 or C3), 19.2 (quat., Si′BuPh₂), 18.1 (quat., Si′BuMe₂), -4.4 (CH₃, Si′BuMe₂), -4.5 (CH₃, Si′BuMe₂); m/z (ESI): 533 (30)(M+Na)+, 529 (10)(MH)+, 437 (6), 397 (18), 319 (100), 284 (5), 241 (10), 141 (25), 123 (21); HRMS (ESI): Found (MH)+, 529.3516; C₃₁H₅₁O₂Si₂, requires 529.3528.

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(R)-5-(tert-Butyldimethylsilyloxy)-1-(tert-butylidiphenylsilyloxy)nonanal (468)

A solution of alcohol 474 (1.62 g, 3.10 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise to a suspension of Dess-Martin periodinane (2.60 g, 6.14 mmol) and pyridine (0.74 mL, 9.20 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 3 h, the solution was diluted with diethyl ether (10 mL) and filtered through a pad of Celite®. Removal of the solvent under reduced pressure, followed by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (1.36 g, 84%) as a colourless oil; [α]$_D$ +18.3 (c 1.30, CHCl$_3$).

IR $\nu_{\text{max}}$ (film): 2930, 2857, 1727, 1472, 1462, 1428, 1388, 1361, 1254, 1106, 1006, 833, 772, 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 9.76 (1H, t, $J$ 3.0, H9), 7.67-7.70 (4H, m, Si'tBuPh$_2$, o), 7.36-7.43 (6H, m, Si'tBuPh$_2$, m and p), 3.67 (2H, t, $J$ 6.0, H1), 3.65-3.69 (1H, m, H5), 2.39-2.45 (2H, td, $J$ 3.0 and 9.0, H8), 1.54-1.68 (4H, m H4 and H6), 1.41-1.49 (6H, m, H2, H3 and H7), 1.06 (9H, s, Si'tBuPh$_2$), 0.90 (9H, s, Si'BuMe$_2$), 0.05 (6H, s, Si'BuMe$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 202.6 (quat., C9), 135.6 (CH, Si'tBuPh$_2$, o), 134.1 (quat., Si'BuPh$_2$), 129.5 (CH, Si'BuPh$_2$, p), 127.6 (CH, Si'BuPh$_2$, m), 71.8 (CH, C5), 63.8 (CH, C1), 44.0 (CH$_2$, C8), 36.8 (CH$_2$, C6 or C4), 36.3 (CH$_2$, C6 or C4), 32.8 (CH$_2$, C2), 26.9 (CH$_3$, Si'BuPh$_2$), 25.9 (CH$_3$, Si'BuPh$_2$), 21.6 (CH$_3$, C3), 19.2 (quat., Si'BuPh$_2$), 18.1 (quat., Si'BuMe$_2$), 17.9 (CH$_2$, C7), 4.4 (CH$_3$, Si'BuMe$_2$), 3.95 (100), 314 (50), 139 (15), 121 (11); HRMS (ESI): Found (MH)$^+$, 527.3363 C$_{31}$H$_{51}$O$_3$Si$_2$, requires 527.3371.

(5S, 9S(and R), 12S)-5,12-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butylidiphenylsilyloxy)-tridec-10-yn-9-ol (475)

n-BuLi (1.70 mL, 2.60 mmol, 1.60 M in THF) was added to a stirred solution of acetylene 219 (0.44 g, 2.40 mmol) in THF (6 mL), at -78 °C under an atmosphere of nitrogen and the resultant pale yellow solution was stirred for 30 min. Anhydrous LiBr (100 mg, 1.10 mmol) was dissolved in THF (2 mL) under an atmosphere of nitrogen and added via canula to the acetylide mixture. After 15 min a solution of the aldehyde 468 (1.16 g, 2.20 mmol) in THF (5 mL) was added dropwise and the solution was allowed...
slowly to warm to room temperature over 6 h. Saturated ammonium chloride solution (10 mL) was added followed by extraction with diethyl ether (3 x 5 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 25:1) afforded the *title compound* (1.10 g, 70%) as a yellow oil; [α]D -30.1 (c 1.10, CHCl3).

**IR** γ_max (film): 3380, 2930, 2857, 1472, 1462, 1428, 1389, 1361, 1253, 1101, 1005, 832, 773, 698, 687, 665 cm⁻¹

**1H NMR** (300 MHz, CDCl3): 7.66-7.68 (4H, m, Si’BuPh₂, o), 7.35-7.44 (6H, m, Si’BuPh₂, m and p), 4.52-4.56 (1H, qd, J 4.0 and 8.0, H12), 4.37 (1H, m, H9), 3.65 (2H, t, J 8.0, H1), 3.64-3.65 (1H, m, H5), 1.64-1.69 (2H, m, H8), 1.53-1.57 (4H, m, H6 and H6), 1.42-1.45 (6H, m, H2, H3 and H7) 1.41 (3H, d, J 8.0, H13), 1.05 (9H, s, Si’BuPh₂), 0.90 (9H, s, Si’BuMe₂), 0.12 (3H, s, Si’BuMe₂), 0.11 (3H, s, Si’BuMe₂), 0.04 (3H, s, Si’BuMe₂), 0.03 (3H, s, Si’BuMe₂);

**13C NMR** (100 MHz, CDCl3): 135.6 (CH, Si’BuPh₂, o), 134.1 (quat., Si’BuPh₂), 129.5 (CH, Si’BuPh₂, p), 127.6 (CH, Si’BuPh₂, m), 87.5 (quat., C11), 84.1 (quat., C10), 72.1 (CH, C5), 63.9 (CH₂, C1), 62.5 (CH, C9), 58.9 (CH, C12), 38.1 (CH₂, C8), 36.9 (CH₂ C6 or C4), 36.7 (CH₂ C6 or C4), 32.9 (CH₂, C3), 26.9 (CH₃, Si’BuPh₂), 25.9 (CH₃, Si’BuMe₂), 25.8 (CH₃, Si’BuMe₂), 25.4 (CH₃, C13), 21.7 (CH₂, C7), 20.9 (CH₂, C2), 19.2 (quat., Si’BuPh₂), 18.2 (quat., Si’BuMe₂), 18.1 (quat., Si’BuMe₂), -4.4 (CH₃, Si’BuMe₂), -4.5 (CH₃, Si’BuMe₂), -4.8 (CH₃, Si’BuMe₂); m/z (ESI): 749 (6)(M+K⁺), 733 (100)(M+Na)⁺, 711 (65)(MH)⁺, 579 (75), 561 (16), 501 (10), 429 (20), 369 (40), 323 (35), 249 (11), 173 (43); **HRMS** (ESI): Found (MH)⁺, 711.4641 C₄₁H₇₁O₄Si₃, requires 711.4655.

(5S, 12S)-5,12-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-tridec-10-yn-9-one (476)

Alcohol 475 (790 mg, 1.10 mmol) was dissolved in CH₂Cl₂ (10 mL) and added to a slurry of 4 Å molecular sieves (~1.00 g) in CH₂Cl₂ (5 mL). The solution was cooled to 0 °C then a solution of N-methylmorpholine-N-oxide (190 mg, 1.67 mmol) and tetrapropylammonium per ruthenate (19 mg, 0.06 mmol) in CH₂Cl₂ (5 mL) was added. After stirring for 2 h the reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 30:1) afforded the *title compound* (620 mg, 80%) as a yellow oil; [α]D -3.20 (c 1.00, CHCl₃).
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IR \( \gamma_{\text{max}} \) (film): 2930, 2857, 1769, 1472, 1463, 1428, 1389, 1361, 1252, 1103, 826, 773, 738, 686 cm\(^{-1}\); \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): 7.65-7.67 (4H, m, Si' BuPh\(_2\), o), 7.36-7.42 (6H, m, Si' BuPh\(_2\), m and p); 3.81-3.85 (1H, m, H12), 3.65 (2H, t, J 8.0, H1), 3.61-3.62 (1H, m, H5), 2.37-2.49 (4H, m, H8 and H10), 1.55-1.59 (6H, m, H6, H4 and H11), 1.39-1.44 (6H, m, H2, H3 and H7), 1.42 (3H, d, J 4.0, H13), 1.05 (9H, s, Si' BuPh\(_2\)), 0.91 (9H, s, Si' BuMe\(_2\)), 0.88 (9H, s, Si' BuMe\(_2\)), 0.14 (3H, s, Si' BuMe\(_2\)), 0.12 (3H, s, Si' BuMe\(_2\)), 0.04 (3H, s, Si' BuMe\(_2\)), 0.03 (3H, s, Si' BuMe\(_2\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): 187.6 (quat., C9), 135.6 (CH, Si' BuPh\(_2\), o), 134.1 (quat., Si' BuPh\(_2\)), 129.5 (CH, Si' BuPh\(_2\), p), 127.6 (CH, Si' BuPh\(_2\), m), 93.7 (quat., C11), 82.6 (quat., C10), 71.9 (CH, C5), 63.9 (CH, C1), 58.8 (CH, C12), 45.6 (CH\(_2\), C8), 36.8 (CH\(_2\), C6 or C4), 36.2 (CH\(_2\), C6 or C4), 32.8 (CH\(_2\), C2), 26.9 (CH\(_3\), Si' BuPh\(_2\)), 25.9 (CH\(_3\), Si' BuMe\(_2\)), 25.8 (CH\(_3\), Si' BuMe\(_2\)), 24.5 (CH\(_3\), C13), 21.6 (CH\(_2\), C3), 21.6 (CH\(_2\), C3), 19.8 (CH\(_2\), C7), 19.2 (quat., Si' BuPh\(_2\)), 18.2 (quat., Si' BuMe\(_2\)), 18.1 (quat., Si' BuMe\(_2\)), -4.4 (CH\(_3\), Si' BuMe\(_2\)), -4.5 (CH\(_3\), Si' BuMe\(_2\)), -4.8 (CH\(_3\), Si' BuMe\(_2\)); m/z (ESI): 731 (100)(M+Na); 709 (15)(MH); 631 (20), 577 (19), 499 (30), 445 (30), 367 (10); HRMS (ESI): Found (MH\(^{+}\)), 709.4482 C\(_{41}\)H\(_{60}\)O\(_3\)Si\(_3\), requires 709.4498.

(5S, 12S)-5,12-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-tridec-9-one (469)

Ynone 476 (620 mg, 0.88 mmol) was dissolved in methanol/THF (10 mL, 1:1) and stirred under an atmosphere of hydrogen in the presence of PtO\(_2\) (30.0 mg, 0.12 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite\textsuperscript{\textregistered} and the solvents removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (520 mg, 83%) as a yellow oil; [\(\alpha\]\(_D\)\(_{5}+18.4 \text{ (c 1.20, CHCl}_3\)].
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Si'BuMe$_2$, 18.1 (quat., Si'BuMe$_2$), -4.4 (CH$_3$, Si'BuMe$_2$), -4.5 (CH$_3$, Si'BuMe$_2$), -4.8 (CH$_3$, Si'BuMe$_2$); m/z (ESI): 735 (90)(M+Na)$^+$, 713 (50)(MH)$^+$, 605 (20), 581 (100), 451 (20), 373 (19); HRMS (ESI): Found (MH)$^+$, 713.4800 C$_{41}$H$_{73}$O$_4$Si$_3$, requires 713.4811.

tert-Butyl(4-((2S,5R,7R)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butoxy)diphenylsilane (477)

To a stirred solution of ketone 469 (520 mg, 0.73 mmol) in CH$_2$Cl$_2$ (7 mL) at 0 °C under an atmosphere of nitrogen was added camphorsulfonic acid (400 mg, 1.61 mmol). The resultant mixture was allowed to warm to room temperature and stirred at this temperature for 3 h. Filtration through a pad of Celite® then removal of the solvent under reduced pressure and flash chromatography (hexanes/diethyl ether 20:1) afforded the title compound (250 mg, 74%) as a yellow oil; [α]$_D$+67.8 (c 1.50, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2933, 2859, 1472, 1461, 1428, 1375, 1330, 1221, 1159, 1110, 1023, 974, 875, 822, 738, 686 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.68-7.73 (4H, m, Si'BuPh$_2$, o), 7.39-7.47 (6H, m, Si'BuPh$_2$, m and p), 4.25-4.30 (1H, qd, J 8.0 and 4.0, H2), 3.86-3.89 (1H, t, J 8.0, H7), 3.73 (2H, t, J 8.0, H1'), 1.97-2.03 (2H, m, H3), 1.67-1.73 (10H, m, H4, H4', H2', H3' and H8), 1.45-1.48 (4H, m, H9 and H10), 1.33 (3H, d, J 8.0, Me), 1.11 (9H, s, Si'BuPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 135.5 (CH, Si'BuPh$_2$, o), 134.1 (quat., Si'BuPh$_2$), 129.4 (CH, Si'BuPh$_2$, p), 127.5 (CH, Si'BuPh$_2$, m), 105.7 (quat., C5), 76.5 (CH, C2), 69.7 (CH, C7), 63.8 (CH$_2$, C1'), 39.4 (CH$_2$, C4), 36.2 (CH$_2$, C4'), 33.6 (CH$_2$, C10), 32.6 (CH$_2$, C3), 31.8 (CH$_2$, C8), 31.2 (CH$_2$, C2), 26.8 (CH$_3$, Si'BuPh$_2$), 23.3 (CH$_3$, Me), 22.1 (CH$_3$, C3'), 20.4 (CH$_2$, C9), 19.1 (quat., Si'BuPh$_2$); m/z (ESI): 489 (30)(M+Na)$^+$, 467 (45)(MH)$^+$, 389 (45), 211 (100), 175 (20), 111 (9); HRMS (ESI): Found (MH)$^+$, 467.2974 C$_{29}$H$_{57}$O$_4$Si, requires 467.2976.
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4-((2S,5R,7R)-2-Methyl-1,6-dioxaspiro[4.5]decan-7-yl)butan-1-ol (478)

To a stirred solution of silyl ether 477 (200 mg, 0.44 mmol) in THF (5 mL) under an atmosphere of nitrogen was added tert-butylammonium fluoride (0.66 mL, 0.66 mmol, 1 M in THF). After stirring for 2 h at room temperature, brine (5 mL) was added and the resultant mixture extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (92.0 mg, 92%) as a yellow oil; $\alpha_D^{+}+28.3$ (c 1.80, CHCl$_3$).

IR $\gamma_{max}$ (film): 3392, 2935, 2867, 1457, 1440, 1375, 1313, 1222, 1159, 1072, 1058, 1022, 974, 874, 857 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 4.15-4.20 (1H, qd, $J$ 8.0 and 4.0, H2), 3.74-3.78 (1H, m, H7), 3.57 (2H, t, $J$ 8.0, H1'), 2.32 (1H, br. s, OH), 1.93-1.99 (2H, m, H3), 1.52-1.72 (10H, m, H4, H4', H2', H3' and H8), 1.24-1.39 (4H, m, H9 and H10), 1.24 (3H, d, $J$ 8.0, Me); $^{13}$C NMR (100 MHz, CDCl$_3$): 105.8 (quat., C5), 76.6 (CH, C2), 69.8 (CH, C7), 62.4 (CH$_2$, C1'), 39.3 (CH$_2$, C4), 35.9 (CH$_2$, C4'), 33.5 (CH$_2$, C10), 32.6 (CH$_2$, C3), 31.7 (CH$_2$, C8), 31.0 (CH$_2$, C2'), 23.1 (CH$_3$, Me), 21.7 (CH$_2$, C3'), 20.2 (CH$_2$, C9); m/z (ESI): 251 (40)(M+Na)$^+$, 229 (3)(MH)$^+$, 211 (100), 193 (10), 193 (10), 175 (20), 111 (20); HRMS (ESI): Found (MH)$^+$, 229.1803 C$_{13}$H$_{25}$O$_3$, requires 229.1798.

(2S,5R,7S)-7-(4-Iodobutyl)-2-methyl-1,6-dioxaspiro[4.5]decane (470)

To a solution of alcohol 478 (45.1 mg, 0.19 mmol) in THF (3 mL) at 0 °C was added dry triethylamine (0.07 mL, 0.47 mmol) followed by methanesulfonyl chloride (0.0180 mL, 0.240 mmol) under an atmosphere of nitrogen. After stirring for 60 min at 0 °C, the mixture was filtered and washed with dry THF (3 mL). To the filtrate was added sodium iodide (89.0 mg, 0.59 mmol) and the resultant mixture was refluxed for 12 h resulting in a dark brown solution. The mixture was then filtered and a saturated aqueous solution of Na$_2$S$_2$O$_3$ (3 mL) was added. The crude product was extracted with diethyl ether (3 x 5 mL). The combined extracts were dried over magnesium sulfate and the solvent removed under reduced
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pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (45.0 mg, 67%) as a colourless oil; $[\alpha]_D +45.2$ (c 1.90, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2933, 2867, 1439, 1366, 1220, 1160, 1114, 1070, 1026, 1001, 972, 872, 811;
$^1$H NMR (300 MHz, CDCl$_3$): 4.18-4.25 (1H, m, H$_2$), 3.76-3.82 (1H, m, H$_7$), 3.18 (2H, t, $J$, 6.0, H$_1'$), 1.86-1.99 (2H, m, H$_4'$), 1.61-1.83 (10H, m, H$_4$, H$_4'$, H$_2'$, H$_3'$ and H$_8$), 1.39-1.42 (4H, m, H$_9$ and H$_10$), 1.27 (3H, d, $J$ 6.0, Me); $^{13}$C NMR (75 MHz, CDCl$_3$): 105.8 (quat., C$_5$), 76.6 (CH, C$_2$), 69.5 (CH, C$_7$), 39.4 (CH$_2$, C$_4$), 35.2 (CH$_2$, C$_4'$), 33.6 (CH$_2$, C$_10$), 31.9 (CH$_2$, C$_8$), 31.0 (CH$_2$, C$_2'$), 26.8 (CH$_2$, C$_3'$), 23.3 (CH$_3$, Me), 20.3 (CH$_2$, C$_9$), 6.9 (CH$_2$, C$_1'$); $m/z$ (ESI): 361 (45)(M+Na)$^+$, 339 (100)(MH)$^+$, 321 (79), 303 (22), 251 (5), 210 (9), 111 (6); HRMS (ESI): Found (MH)$^+$, 339.0811 C$_{13}$H$_{24}$O$_2$, requires 339.0815.

4,6-Dimethoxy-1-(4-((2S,5R,7R)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)-1H-indole (337)

A solution of 4,6-dimethoxyindole (352) (33.0 mg, 0.19 mmol) in DMSO (2 mL) was added dropwise to a stirred solution of powdered KOH (16.0 mg, 0.28 mmol) in DMSO (2 mL) and the resultant mixture was stirred for 45 min at room temperature under an atmosphere of nitrogen. Iodide 470 (35.0 mg, 0.10 mmol) dissolved in DMSO (1 mL) was added to the green solution resulting in a brown solution upon addition. After stirring the mixture for an additional 2.5 h at room temperature, water (5 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined extracts were washed with brine (3 x 3 mL) and dried over magnesium sulfate and concentrated in vacuo. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (30.0 mg, 75%) as a yellow oil; $[\alpha]_D +48.3$ (c 1.70, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2933, 2867, 1622, 1586, 1499, 1455, 1438, 1372, 1312, 1248, 1210, 1145, 1068, 1048, 1021, 973, 951, 935, 874, 855, 805, 757, 735, 704, 663; $^1$H NMR (300 MHz, CDCl$_3$): 6.88 (1H, d, $J$ 3.0, H$_2$), 6.48 (1H, d, $J$ 3.0, H$_1$), 6.40 (1H, apparent s, H$_4$), 6.23 (1H, d, $J$ 3.0, H$_6$), 4.20-4.30 (1H, m, H$_2''$), 4.02 (2H, t, $J$ 6.0, H$_1''$), 3.92 (3H, s, OMe), 3.87 (3H, s, OMe), 3.76-3.80 (1H, m, H$_7''$), 1.95-1.99 (2H, m, H$_4''$), 1.60-1.82 (10H, m, H$_4''$, H$_4'$, H$_2''$, H$_3'$ and H$_8''$), 1.39-1.44 (4H, m, H$_9''$ and H$_10''$), 1.25 (3H, d, $J$ 6.0, Me); $^{13}$C NMR (75 MHz, CDCl$_3$): 157.2 (quat., C$_5$), 153.8 (quat., C$_5$), 137.3 (quat., C$_4$a), 125.0 (CH, C$_2$), 113.6 (quat., C$_7$a), 105.8 (quat., C$_5''$), 98.1 (CH, C$_1$), 91.1 (CH, C$_6$), 85.6 (CH, C$_4$), 76.7 (CH, C$_2''$), 69.6 (CH, C$_7''$), 55.7 (CH$_3$, OMe), 55.3 (CH$_3$, OMe), 46.5 (CH$_2$, C$_1''$), 39.4 (CH$_2$, C$_4''$), 36.0 (CH$_2$, C$_3''$), 26.8 (CH$_2$, C$_2''$), 23.3 (CH$_3$, Me), 20.3 (CH$_2$, C$_9$), 6.9 (CH$_2$, C$_1'$); $m/z$ (ESI): 361 (45)(M+Na)$^+$, 339 (100)(MH)$^+$, 321 (79), 303 (22), 251 (5), 210 (9), 111 (6); HRMS (ESI): Found (MH)$^+$, 339.0811 C$_{13}$H$_{24}$O$_2$, requires 339.0815.
4,6-Dimethoxy-1-(4-((2S)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)indolin-2-one (340)

NaH (2.40 mg, 0.10 mmol, 60% w/w dispersion in mineral oil) was washed with pentane (3 x 1 mL) under an atmosphere of nitrogen and dried in vacuo. DMF (1 mL) was added to the solid. 4,6-Dimethoxyxindole (354) (36.0 mg, 0.190 mmol) in DMF (1 mL) was added to the slurry. The resulting red-brown mixture was stirred at room temperature for 15 min. Iodide 470 (34.0 mg, 0.100 mmol) was dissolved in DMF (1 mL) and then added to the anion. After stirring the mixture for 2.5 h at room temperature, water (3 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined extracts were dried over magnesium sulfate. The solvents were removed under reduced pressure, flash chromatography (hexanes/EtOAc 5:1) afforded the title compound (28.0 mg, 70%) as a yellow oil; \([\alpha]_D^\circ +38.4\) (c 1.60, CHCl₃).

**IR** \(\gamma_{\text{max}}\) (film): 2930, 2865, 1700, 1615, 1511, 1459, 1362, 1349, 1280, 1210, 1198, 1150, 1067, 971, 934, 873, 809, 798 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃): 6.15 (1H, d, \(J\ 3.0\), H₄), 6.09 (1H, d, \(J\ 3.0\), H₆), 4.19-4.24 (1H, m, H₂”), 3.82 (6H, s, OMe), 3.77-3.79 (1H, m, H₇”), 3.64 (2H, t, \(J\ 6.0\), H₁”), 3.36 (2H, s, H₁), 1.87-1.96 (2H, m, H₃”), 1.57-1.72 (10H, m, H₄”, H₄’, H₂’, H₃’ and H₈”), 1.39-1.43 (4H, m, H₉” and H₁₀”), 1.25 (3H, d, \(J\ 6.0\), Me); \(^13\)C NMR (75 MHz, CDCl₃): 175.8 (quat., C₂), 164.4 (quat., C₇), 155.9 (quat., C₅), 146.3 (quat., C₄a), 105.5 (quat., C₅”), 103.0 (quat., C₇a), 91.0 (quat., C₄), 89.0 (quat., C₆), 76.6 (CH, C₂”), 69.6 (CH, C₇”), 55.6 (CH₃, OMe), 55.4 (CH₃, OMe), 40.2 (CH₂, C₁’), 39.4 (CH₂, C₄”), 36.1 (CH₂, C₃”), 33.6 (CH₂, C₁0”), 33.1 (CH₂, C₄”), 31.8 (CH₂, C₁), 31.1 (CH₂, C₈”), 27.9 (CH₂, C₂”), 23.3 (CH₂, Me), 20.3 (CH₂, C₉”); \(m/z\) (ESI): 426 (100)(M+Na)+, 404 (85)(MH)+, 386 (10); HRMS (ESI): Found (MH)+, 404.2415 C₂₃H₄₅NO₅ requires 404.2431.
3.5 Synthesis of Short Chain Phthalide Analogue 335

1-(tert-Butyldiphenylsilyloxy)-prop-2-ene (485)

\[
\text{TBDPSO}^1\text{1-O}
\]

tert-Butyldiphenylsilylchloride (30.6 mL, 118 mmol), 4-dimethylaminopyridine (0.58 g, 4.72 mmol) and imidazole (12.0 g, 42.0 mmol) were dissolved in CH\(_2\)Cl\(_2\) (30 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this stirred solution was added allyl alcohol (8.0 mL, 118 mmol) in CH\(_2\)Cl\(_2\) (7 mL). After stirring for 12 h at room temperature, the white precipitate was filtered off and the solvent removed under reduced pressure to yield the title compound (34.0 g, 97%) as colourless oil without further purification.

IR \(\gamma_{\text{max}}\) (film): 3071, 2959, 2857, 1462, 1427, 1402, 1361, 1131, 1110, 1075, 915, 823, 698 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.68-7.73 (4H, m, Si^tBuPh\(_2\), o), 7.40-7.45 (6H, m, Si^tBuPh\(_2\), m and p), 5.93-6.05 (2H, m, H2), 5.41-5.47 (1H, m, H3a), 5.15-5.19 (2H, m, H3b), 4.27-4.28 (2H, m, H1), 1.14 (9H, s, Si^tBuPh\(_2\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)): 136.9 (CH, C2), 135.5 (CH, Si^tBuPh\(_2\), o), 133.7 (quat., Si^tBuPh\(_2\)), 129.6 (CH, Si^tBuPh\(_2\), p), 127.6 (CH, Si^tBuPh\(_2\), m), 113.9 (CH\(_2\)), 64.6 (CH\(_2\), C3), 64.6 (CH\(_2\), C1), 26.8 (CH\(_3\), Si^tBuPh\(_2\)), 19.2 (quat., Si^tBuPh\(_2\)); m/z (ESI): 319 (5)(M+Na), 297 (10)(MH), 239 (10), 181 (21), 137 (20), 123 (100); HRMS (ESI): Found (MH)^+ 297.1666 C\(_{19}\)H\(_{25}\)OSi, requires 297.1669.

1-(tert-Butyldiphenylsilyloxy)-3-propene oxide (486)

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\text{TBDPSO}^1\text{O}
\]

meta-Chloroperoxybenzoic acid (35.1 g, 203 mmol) was dissolved in CH\(_2\)Cl\(_2\) (120 mL) under an atmosphere of nitrogen and cooled to 0 °C. A solution of alkene 485 (30.1 g, 102 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added dropwise. The solution was allowed to warm to room temperature over 12 h, saturated sodium sulfite solution (100 mL) was added to the reaction mixture and stirred until it became clear. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The organic layer was then washed with aqueous NaOH solution (100 mL, 5 %), brine (100 mL) then dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (31.6 g, 99%) as a yellow oil.

IR \(\gamma_{\text{max}}\) (film): 3071, 2930, 2857, 1472, 1427, 1390, 1361, 1254, 1110, 1089, 1007, 998, 917, 822, 699, 612, 569 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.70-7.74 (4H, m, Si^tBuPh\(_2\), o), 7.38-7.48 (6H, m, Si^tBuPh\(_2\),
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m and p), 3.86-3.91 (1H, dd, J 3.0 and 12.0, H1a), 3.71-3.77 (1H, dd, J 6.0 and 12.0, H1b), 3.12-3.17 (1H, m, H2), 2.74-2.77 (1H, dd, J 3.0 and 6.0, H3a), 2.62-2.64 (1H, dd, J 3.0 and 6.0, H3b), 1.09 (9H, s, Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): 135.5 (CH, Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}, o), 133.3 (quat., Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}), 129.7 (CH, Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}, m), 64.3 (CH\textsubscript{2}, C1), 52.2 (CH, C2), 44.4 (CH\textsubscript{2}, C3), 26.7 (CH\textsubscript{3}, Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}), 19.2 (quat., Si\textsubscript{t}Bu\textsubscript{2}Ph\textsubscript{2}); m/z (ESI): 335 (100)(M+Na)+, 235 (10), 197 (10), 193 (23), 117 (23); HRMS (ESI): Found (M+Na)+, 335.1434 C\textsubscript{19}H\textsubscript{24}NaO\textsubscript{2}Si, requires 335.1438.

**(R)-1-(tert-Butyldiphenylsilyloxy)-3-propene oxide (480)**

![TBDPSO](attachment:monomer.png)

To a solution of (R,R)-SalenCo\textsuperscript{II} (0.90 g, 1.50 mmol) in toluene (7.5 mL) was added glacial acetic acid (0.17 mL, 3.03 mmol) and the mixture was stirred open to the air for 1 h to form the active form of the catalyst (R,R)-SalenCo\textsuperscript{II}OAc, over which time the colour changed from orange to a dark brown. The solution was concentrated in vacuo to give a crude brown solid. To the catalyst residue was added a solution of epoxide 486 (31.6 g, 101 mmol) in isopropanol (31 mL). The resultant solution was cooled to 0 °C and water (1.10 mL, 61.0 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 h. The isopropanol was removed under reduced pressure and the resulting chiral epoxide was purified by flash chromatography (hexanes/EtOAc 25:1) to afford the title compound XX (14.9 g, 95%) as a yellow oil; [\(\alpha\)]\textsubscript{D}+24.3 (c 1.60, CHCl\textsubscript{3}). The spectroscopic data was identical to that reported above for epoxide XX, enantiomeric excess 81% (chiral hplc\textsuperscript{38}).

**(R)-1-(tert-Butyldiphenylsilyloxy)hex-5-en-2-ol (487)**

![TBDPSO](attachment:monomer.png)

CuCN (1.05 g, 12.0 mmol) was gently flame dried under vacuum then THF (6 mL) was added under an atmosphere of nitrogen thus forming a slurry. The mixture was cooled to -78 °C and MeLi (15.0 mL, 24.0 mmol, 1.6 M in THF) was added. The reaction was then allowed to warm to 0 °C and further stirred at this temperature for 20 min. AllylSnBu\textsubscript{3} (7.40 g, 24.0 mmol) was then added at 0 °C as a neat liquid in one portion and the solution continued to be stirred at that temperature for an additional 30 min. The reaction mixture was cooled to -78 °C and epoxide 480 (1.87 g, 6.00 mmol) in THF (10 mL) was cannulated to the resulting cuprate. The reaction was then warmed to 0 °C and stirred at that temperature.

\textsuperscript{38} HPLC Conditions: AD-H column, hexane 100%, flow rate 0.5 mL/min, retention times: 14.3 min. (major), 17.1 min. (minor)
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for an additional hour. The solution was quenched by the addition of a solution of 10% ammonia solution in saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed in vacuo. Purification by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (1.40 g, 67%) as a yellow oil; $[\alpha]_D$ -21.4 (c 1.10, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 3411 br (OH), 3072, 2930, 2857, 1472, 1427, 1260, 1110, 997, 911, 822, 699, 607 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.65-7.73 (4H, m, Si'BuPh$_2$, o), 7.38-7.45 (6H, m, Si'BuPh$_2$, m and p), 5.76-5.83 (1H, m, H5), 4.93-5.03 (2H, m, H6), 3.72-3.76 (1H, m, H2), 3.65-3.69 (1H, dd, J 4.0 and 8.0, H1a), 3.48-3.53 (1H, dd, J 8.0 and 4.0 H1b), 2.05-2.20 (2H, m, H4), 1.43-1.60 (2H, m, H3), 1.08 (9H, s, Si'BuPh$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 138.3 (CH, C5), 135.5 (CH, Si'BuPh$_2$, o), 134.8 (quat., Si'BuPh$_2$), 129.8 (CH, Si'BuPh$_2$, p), 127.8 (CH, Si'BuPh$_2$, m), 114.7 (CH$_2$, C6), 71.4 (CH$_2$, C3), 31.9 (CH$_2$, C4), 26.8 (CH$_3$, Si'BuPh$_2$), 19.2 (quat., Si'BuPh$_2$); m/z (ESI): 377 (100)(M+Na)$^+$, 351 (10), 277 (12); HRMS (ESI): Found (M+Na)$^+$, 377.1917 C$_{22}$H$_{30}$NaO$_2$Si, requires 377.1907.

(2R)-1-(tert-Butyldiphenylsilyloxy)-2-(tert-butyldimethylsilyloxy)hex-5-ene (488)

TBDPSO

OTBDMS

tert-Butyldimethylsilylchloride (0.57 g, 3.80 mmol), imidazole (0.26 g, 3.80 mmol), N,N-4-dimethylaminopyridine (16.0 mg, 0.13 mmol) were dissolved in CH$_2$Cl$_2$ (10 mL) under nitrogen atmosphere and cooled to 0°C. To this stirred solution was added alcohol 487 (0.90 g, 2.55 mmol) in CH$_2$Cl$_2$ (8 mL). After stirring for 12 h, brine (20 mL) was added and the mixture extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. Flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (0.73 g, 75%) as a yellow oil; $[\alpha]_D$ -12.4 (c 1.50, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2956, 2932, 1474, 1465, 1431, 1395, 1364, 1257, 1111, 1077, 1053, 1001, 913, 836, 775, 699, 617 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.66-7.69 (4H, m, Si'BuPh$_2$, o), 7.37-7.43 (6H, m, Si'BuPh$_2$, m and p), 5.81-5.88 (1H, m, H5), 4.94-5.04 (2H, m, H6), 3.72-3.74 (1H, m, H2), 3.58-3.61 (1H, dd, J 4.8 and 10.0, H1a), 3.46-3.50 (1H, dd, J 6.8 and 9.0 H1b), 2.05-2.12 (2H, m, H4), 1.53-1.61 (2H, m, H3), 1.06 (9H, s, Si'BuPh$_2$), 0.89 (9H, s, Si'BuMe$_2$), 0.03 (3H, s, Si'BuMe$_2$), 0.02 (3H, s, Si'BuMe$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): 139.0 (CH, C5), 135.6 (CH, Si'BuPh$_2$, o), 133.7 (quat., Si'BuPh$_2$), 129.6 (CH, Si'BuPh$_2$, p), 127.8 (CH, Si'BuPh$_2$, m), 114.2 (CH$_2$, C6), 72.3 (CH, C2), 67.6 (CH$_2$, C1), 33.6 (CH$_2$, C3), 165.
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29.2 (CH₂, C4), 26.9 (CH₃, Si'BuPh₂), 25.9 (CH₃, Si'BuMe₂), 19.2 (quat., Si'BuPh₂), 18.1 (quat., Si'BuMe₂), -4.4 (CH₃, Si'BuMe₂), -4.8 (CH₃, Si'BuMe₂); m/z (ESI): 491 (55)(M+Na)+, 465 (15), 432 (30), 391 (60), 365 (40), 293 (85), 233 (100), 191 (15), 159 (60), 133 (25), 91 (10); HRMS (ESI): Found (M+Na)⁺, 491.2765 C₂₈H₄₄NaO₂Si₂, requires 491.2772.

(R)-5-(tert-Butyldimethylsilyloxy)-6-(tert-butyldiphenylsilyloxy)hexan-1-ol (489)

Alkene 488 (0.66 g, 1.40 mmol) was dissolved in THF (7 mL) under an atmosphere of nitrogen and the solution was cooled to 0 °C. Borane dimethylsulfide complex (0.320 mL, 4.20 mmol) was added dropwise to the stirred solution which was allowed to warm to room temperature over 12 h. Oxidative workup of sequential addition of H₂O₂ (0.95 mL, 8.80 M) followed by aqueous solution of NaOH (8.40 mL, 1 M) gave a biphasic mixture which was stirred for 30 min. The mixture was extracted with diethyl ether (3 x 5 mL) and the combined extracts were dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography using (hexanes/EtOAc 10:1) as the eluent to afford the title compound (0.50 g, 73%) as a yellow oil; [α]D⁻18.3 (c 1.40, CHCl₃).

IR γmax(film): 3352, 2929, 2857, 2929, 1472, 1462, 1428, 1389, 1361, 1252, 1105, 1048, 1005, 834, 774, 699, 613 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 7.65-7.66 (4H, m, Si'BuPh₂, o), 7.37-7.41 (6H, m, Si'BuPh₂, m and p), 3.69-3.71 (1H, m, H2), 3.60-3.63 (2H, m, H6), 3.55-3.60 (1H, dd, J 3.0 and 9.0, H1a), 3.43-3.49 (1H, dd, J 6.0 and 9.0 H1b), 1.66-1.73 (4H, m, H3 and H5), 1.40-1.55 (2H, m, H4), 1.05 (9H, s, Si'BuPh₂), 0.84 (9H, s, Si'BuMe₂), 0.00 (3H, s, Si'BuMe₂); ¹³C NMR (75 MHz, CDCl₃): 135.6 (CH, Si'BuPh₂, o), 133.6 (quat., Si'BuPh₂), 129.6 (CH, Si'BuPh₂, p), 127.6 (CH, Si'BuPh₂, m), 72.7 (CH, C2), 67.6 (CH₂, C1), 62.9 (CH₂, C6), 34.1 (CH₃, C3), 32.9 (CH₃, C5), 26.9 (CH₃, Si'BuPh₂), 25.8 (CH₃, Si'BuMe₂), 21.0 (CH₂, C4), 19.2 (quat., Si'BuPh₂), 18.1 (quat., Si'BuMe₂), -4.4 (CH₃, Si'BuMe₂); m/z (ESI): 509 (30)(M+Na)+, 487 (10)(MH)+, 331 (60), 277 (100); HRMS (ESI): Found (MH)+, 487.3062 C₂₈H₄₄O₃Si₂, requires 487.3058.
(R)-5-(tert-Butyldimethylsilyloxy)-6-(tert-butyldiphenylsilyloxy)hexanal (481)

A solution of alcohol 489 (0.40 g, 0.82 mmol) in CH₂Cl₂ (5 mL) was added dropwise to a suspension of Dess-Martin periodinane (0.69 g, 1.65 mmol) and pyridine (0.20 mL, 2.50 mmol) in CH₂Cl₂ (5 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 3 h the solution was diluted with diethyl ether (5 mL) and filtered through Celite®. Removal of the solvent under reduced pressure followed by flash chromatography (hexanes/EtOAc 25:1) afforded the title compound (0.300 g, 77%) as a yellow oil; [α]D +32.5 (c 1.60, CHCl₃).

IR γmax (film): 2954, 2857, 2929, 1727, 1472, 1462, 1428, 1389, 1253, 1105, 834, 823, 774, 700, 689, 613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 9.75 (1H, t, J 2.0, H6), 7.64-7.67 (4H, m, Si'tBuPh₂, o), 7.36-7.42 (6H, m, Si'tBuPh₂, m and p), 3.68-3.72 (1H, m, H2), 3.56-3.60 (1H, dd, J 5.2 and 10.0, H1a), 3.44-3.48 (1H, dd, J 6.8 and 10.0, H1b), 2.41-2.46 (2H, m, H5), 1.46-1.65 (2H, m, H3 and H4), 1.04 (9H, s, Si'tBuPh₂), 0.83 (9H, s, Si'tBuMe₂), 0.01 (3H, s, Si'tBuMe₂), -0.08 (3H, s, Si'tBuMe₂); ¹³C NMR (100 MHz, CDCl₃): 202.6 (quat., C6), 135.6 (CH, Si'tBuPh₂, o), 133.6 (quat., Si'tBuPh₂), 129.6 (CH, Si'tBuPh₂, p), 127.7 (CH, Si'tBuPh₂, m), 72.3 (CH, C2), 67.3 (CH₂, C1), 44.0 (CH₂, C5), 33.7 (CH₂, C3), 26.8 (CH₃, Si'tBuPh₂), 25.8 (CH₃, Si'tBuMe₂), 19.2 (quat., Si'tBuPh₂), 18.0 (quat., Si'tBuMe₂), 17.6 (CH₂, C4), -4.5 (CH₃, Si'tBuMe₂), -4.8 (CH₃, Si'tBuMe₂); m/z (ESI): 507 (90)(M+Na)⁺, 485 (10)(MH)⁺, 407 (100), 353 (75), 329 (65), 275 (40), 243 (30); HRMS (ESI): Found (MH)⁺, 485.2890 C₂₈H₄₅O₃Si₂, requires 485.2902.

(2S, 6S and 6R, 9S)-2,9-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-dec-7-yn-6-ol (490)

n-BuLi (0.40 mL, 0.67 mmol, 1.60 M in hexane) was added to a stirred solution of acetylene 219 (0.11 g, 0.61 mmol) in THF (4 mL), at -78 °C under an atmosphere of nitrogen and the resultant pale yellow solution was stirred for 30 min. Anhydrous LiBr (24 mg, 0.28 mmol) was dissolved in THF (2 mL) under an atmosphere of nitrogen and cannulated to the acetylide mixture. After 15 min a solution of aldehyde 481 (0.27 g, 0.56 mmol) in THF (5 mL) was added dropwise and the solution was allowed slowly to warm to room temperature over 6 h. Saturated aqueous ammonium chloride solution (10 mL)
was added followed by extraction with diethyl ether (3 x 5 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 30:1) afforded the title compound (0.27 g, 72%) as a yellow oil; [α]_D^20 -8.25 (c 1.30, CHCl_3).

IR γ\text{max}\ (\text{film}): 3348 (OH), 2929, 2857, 1472, 1462, 1389, 1361, 1335, 1252, 1101, 832, 774, 700, 689, 613 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.65-7.68 (4H, m, Si' BuPh\(_2\), o), 7.36-7.42 (6H, m, Si' BuPh\(_2\), m and p), 4.51-4.56 (1H, qd, J 4.0 and 8.0, H9), 4.37 (1H, m, H6), 3.70 (2H, m, H2 ), 3.56-3.60 (1H, dd, J 5.2 and 10.0, H1a), 3.44-3.48 (1H, dd, J 6.8 and 10.0, H1b), 1.66-1.71 (4H, m, H3 and H5), 1.43-1.50 (2H, m, H4), 1.40 (3H, d, J 8.0, H10), 1.05 (9H, s, Si' BuPh\(_2\)), 0.90 (9H, s, Si' BuMe\(_2\)), 0.84 (9H, s, Si' BuMe\(_2\)), 0.12 (3H, s, Si' BuMe\(_2\)), 0.11 (3H, s, Si' BuMe\(_2\)), 0.00 (3H, s, Si' BuMe\(_2\)), -0.07 (3H, s, Si' BuMe\(_2\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 135.6 (CH, Si' BuPh\(_2\), o), 133.7 (quat., Si' BuPh\(_2\)), 129.6 (CH, Si' BuPh\(_2\), p), 127.6 (CH, Si' BuPh\(_2\), m), 87.4 (quat., C8), 84.1 (quat., C7), 72.7 (CH, C2), 67.6 (CH, C1), 62.5 (CH, C6), 58.9 (CH, C9), 38.1 (CH\(_2\), C5 or C3), 34.0 (CH\(_2\), C5 or C3), 26.8 (CH\(_3\), Si' BuPh\(_2\)), 25.9 (CH\(_3\), Si' BuMe\(_2\)), 25.8 (CH\(_3\), Si' BuMe\(_2\)), 25.4 (CH\(_2\), C10), 20.7 (CH\(_2\), C4), 19.2 (quat., Si' BuPh\(_2\)), 18.2 (quat., Si' BuMe\(_2\)), 18.1 (quat., Si' BuMe\(_2\)), 4.4 (CH\(_3\), Si' BuMe\(_2\)), -4.5 (CH\(_3\), Si' BuMe\(_2\)), -4.8 (CH\(_3\), Si' BuMe\(_2\)); m/z (ESI): 691 (40)(M+Na)^+ , 669 (100)(MH)^+ , 573 (5), 513 (20), 459 (45), 327 (10), 263 (9), 209 (15); HRMS (ESI): Found (MH)^+ , 669.4178 C\(_{38}\)H\(_{65}\)O\(_4\)Si\(_3\), requires 669.4185.

(2S,9S)-2,9-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-dec-7-yn-6-one (491)

Alcohol 490 (192 mg, 0.29 mmol) was dissolved in CH\(_2\)Cl\(_2\) (5 mL) and added to a slurry of 4 Å molecular sieves (0.3 g) in CH\(_2\)Cl\(_2\) (5 mL) and the solution was cooled to 0 °C. To this stirred solution was added N-methylmorpholine-N-oxide (51.0 mg, 0.43 mmol) and tetrapropylammonium perruthenate (5.10 mg, 0.01 mmol) in CH\(_2\)Cl\(_2\) (5 mL). After stirring for 2 h the reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure. Flash chromatography (hexanes/EtOAc 30:1) afforded the title compound (150 mg, 79%) as a colourless oil; [α]_D^20 -8.30 (c 1.10, CHCl\(_3\)).

IR γ\text{max}\ (\text{film}): 2955, 2930, 2857, 1679 (C=O), 1472, 1463, 1428, 1389, 1361, 1253, 1104, 825, 775, 689, 613; \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.65-7.68 (4H, m, Si' BuPh\(_2\), o), 7.36-7.45 (6H, m, Si' BuPh\(_2\), m and p), 4.67 (1H, q, J 8.0, H9), 3.70 (2H, m, H2), 3.56-3.60 (1H, dd, J 4.0 and 8.0, H1a), 3.44-3.48 (1H, dd, J 8.0 and 12.0, H1b), 2.57 (2H, m, H5), 1.66-1.77 (4H, m, H3 and H4), 1.48 (3H, d, J 8.0, H10), 1.07 (9H,
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s, Si′BuPh2), 0.93 (9H, s, Si′BuMe2), 0.85 (9H, s, Si′BuMe2), 0.16 (3H, s, Si′BuMe2), 0.14 (3H, s, i′BuMe-
2), 0.02 (3H, s, Si′BuMe2), -0.06 (3H, s, Si′BuMe2); 13C NMR (100 MHz, CDCl3): 187.5 (quat., C6), 135.6 (CH, Si′BuPh2, o), 133.7 (quat., Si′BuPh2), 129.6 (CH, Si′BuPh2, p), 127.7 (CH, Si′BuPh2, m), 93.5 (quat. C8) 82.3 (quat., C7), 72.4 (CH2, C2), 67.4 (CH, C1), 58.8 (CH, C9), 45.6 (CH2, C5), 33.5 (CH2, C3), 26.8 (CH3, Si′BuPh2), 25.8 (CH3, Si′BuMe2), 25.7 (CH3, Si′BuMe2), 24.5 (CH2, C10), 19.5 (CH2, C4), 19.2 (quat., Si′BuPh2), 18.2 (quat., Si′BuMe2), 18.1 (quat., Si′BuMe2), -4.4 (CH3, Si′BuMe2), -4.5 (CH3, Si′BuMe2), -4.8 (CH3, Si′BuMe2); m/z (ESI): 689 (100)(M+Na)+, 589 (5), 535 (10), 457 (5), 353 (8); HRMS (ESI): Found (M+Na)+, 689.3783 C36H32NaO3Si3, requires 689.3848.

(2S,9S)-2,9-Bis-(tert-butyldimethylsilyloxy)-1-(tert-butyldiphenylsilyloxy)-dec-6-one (482)

Ynone 491 (150 mg, 0.23 mmol) was dissolved in methanol/THF (5 mL, 1:1) and stirred under an atmosphere of hydrogen in the presence of PtO2 (7.70 mg, 0.03 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvents removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 8:1) afforded the title compound (135 mg, 89%) as a yellow oil; [α]D+25.4 (c 1.10, CHCl3).

IR γmax (film): 2954, 2928, 2857, 1716 (C=O), 1472, 1462, 1428, 1361, 1253, 1111, 1068, 1004, 834, 773, 700, 613 cm−1; 1H NMR (400 MHz, CDCl3): 7.66-7.69 (4H, m, Si′BuPh2, o), 7.36-7.43 (6H, m, Si′BuPh2, m and p), 3.81-3.85 (1H, m, H9), 3.70 (2H, m, H2), 3.56-3.61 (1H, dd J 6.0 and 9.0, H1a), 3.44-3.50 (1H, dd, J 6.0 and 9.0, H1b), 2.39-2.50 (4H, m, H5 and H7), 1.58-1.75 (6H, m, H8, H3 and H4), 1.14 (3H, d, J 6.0, H10), 1.06 (9H, s, Si′BuPh2), 0.90 (9H, s, Si′BuMe2), 0.85 (9H, s, Si′BuMe2), 0.06 (3H, s, Si′BuMe2), 0.05 (3H, s, i′BuMe2), 0.01 (3H, s, Si′BuMe2), -0.06 (3H, s, Si′BuMe2); 13C NMR (75 MHz, CDCl3): 210.9 (quat., C6), 135.6 (CH, Si′BuPh2, o), 133.7 (quat., Si′BuPh2), 129.6 (CH, Si′BuPh2, p), 127.7 (CH, Si′BuPh2, m), 72.6 (CH, C2), 67.6 (CH, C1 or C9), 67.5 (CH, C1 or C9), 43.1 (CH2, C5 or C7), 43.0 (CH2, C5 or C7), 33.9 (CH2, C8), 33.2 (CH2, C3 or C4), 26.8 (CH3, Si′BuPh2), 25.9 (CH3, Si′BuMe2), 25.8 (CH3, Si′BuMe2), 23.7 (CH2, C10), .5 (CH2, C4), 19.2 (quat., Si′BuPh2), 18.2 (quat., Si′BuMe2), 18.1 (quat., Si′BuMe2), -4.4 (CH3, Si′BuMe2), -4.5 (CH3, Si′BuMe2), -4.6 (CH3, Si′BuMe2); m/z (ESI): 693 (100)(M+Na)+, 563 (20), 409 (2), 355 (5), 296 (2); HRMS (ESI): Found (MH)+, 671.4303 C36H32O3Si3, requires 671.4342.

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(2S)-2-Bromobutanedioic acid (209)

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

(S)-Aspartic acid (196) (20.0 g, 15.0 mmol) was dissolved in aqueous sulfuric acid (390.0 mL, 97.7 mmol, 2.50 M) with potassium bromide (82.3 g, 69.2 mmol) and the mixture cooled to -10 °C. To this solution was added sodium nitrite (18.7 g, 27.1 mmol) in water (39.0 mL). The resultant dark brown suspension was allowed to warm to room temperature over 5 h then extracted with ethyl acetate (4 x 600 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed in vacuo to give the title compound (27.2 g, 92%) as a white solid, that was used in the next step without further purification; m.p. 176-179 °C, (lit., xx 178-180 °C); \([\alpha]_D^{20}-38.1\) (c 1.00, H₂O), (lit., xx [\(\alpha\])_D^{20}-38.1\) (c 1.00, H₂O)).

\(^1\)H NMR\( (300\ MHz, CD_3OD)\): 4.56 (1H, dd, J 8.6 and 6.3, H2), 3.20 (1H, dd, J 17.2 and 8.6, H3a), 2.95 (1H, dd, J 17.2 and 6.3, H3b); \(^13\)C NMR\( (75\ MHz, CD_3OD)\): 173.1 (quat., C1), 172.3 (quat., C4), 40.8 (CH, C2), 40.1 (CH₂, C3). This data was in agreement with that reported in the literature.

(S)-2-Bromobutane-1,4-diol (210)

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

(S)-Bromosuccinic acid 209 (6.31 g, 32.1 mmol) was dissolved in THF (100 mL), under an inert atmosphere and cooled to -10 °C. Borane dimethylsulfide complex (9.62 mL, 96.2 mmol) was added dropwise and the solution allowed to warm to room temperature over 12 h. The reaction was quenched by the addition of methanol (50 mL) and the trimethylborate azeotropically removed in vacuo. The resultant residue was dissolved in methanol (50 mL) and the solvent concentrated in vacuo. This process was repeated three times. Flash chromatography (acetone/dichloromethane 1:1) afforded the title compound (5.25 g, 97%) as a yellow oil; \([\alpha]_D^{20}-31.2\) (c 1.02, CHCl₃), (lit., xx \([\alpha]_D^{20}-31.9\) (c 15.2, CHCl₃)).

\(^1\)H NMR\( (300\ MHz, CD_3OD)\): 4.81 (2H, br s, OH), 4.17-4.22 (1H, m, H2), 3.68-3.79 (4H, m, H1 and H4), 2.11-2.18 (1H, m, H3a), 1.86-1.94 (1H, m, H3b); \(^13\)C NMR\( (75\ MHz, CD_3OD)\): 67.9 (CH₂, C1), 60.5 (CH₂, C4), 54.7 (CH, C2), 39.0 (CH₂, C3). This data was in agreement with that reported in the literature.
Sodium hydride (2.35 g, 92.97 mmol 60% dispersion in oil) was suspended in dry THF (150 mL) under an atmosphere of nitrogen and cooled to 0 °C. A solution of (S)-bromodiol (5.24 g, 30.1 mmol) in THF (50 mL) was added dropwise. After 1 h, tert-butyldiphenylsilylchloride (8.90 mL, 34.1 mmol) was added and the mixture allowed to warm to room temperature. After stirring for 5 h saturated aqueous sodium bicarbonate (50 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 9:1) afforded the title compound (8.29 g, 82%) as a white solid; m.p. 38-40 °C, (lit., 38-40 °C); \( [\alpha]_D +5.9 \) (c 1.00, CHCl₃), (lit., \( [\alpha]_D +6.3 \) (c 1.00, CHCl₃)).

\(^1\)H NMR (300 MHz, CDCl₃): 7.66-7.69 (4H, m, Si\(_{\text{tBuPh}}\), o, 7.38-7.40 (6H, m, Si\(_{\text{tBuPh}}\), m and p), 3.83-3.84 (2H, m, H2), 3.10 (1H, m, H3), 2.76-2.78 (1H, m, H4a), 2.52 (1H, m, H4b), 1.74-1.79 (2H, m, H2), 1.06 (9H, s, Si\(_{\text{tBuPh}}\)); \(^{13}\)C NMR (75 MHz, CDCl₃): 135.5 (CH, Si\(_{\text{tBuPh}}\), o), 133.7 (quat., Si\(_{\text{tBuPh}}\), 129.6 (CH, Si\(_{\text{tBuPh}}\), p), 127.7 (CH, Si\(_{\text{tBuPh}}\), m), 60.9 (CH₂, C1), 50.1 (CH₂, C3), 47.2 (CH, C4), 35.7 (CH₂, C2), 26.8 (CH₃, Si\(_{\text{tBuPh}}\)), 19.2 (quat., Si\(_{\text{tBuPh}}\)). This data was in agreement with that reported in the literature.

(5S)-7-(tert-Butyldiphenylsilyloxy)hept-1-en-5-ol (212)

Allyltributyltin (22.8 mL, 73.6 mmol) was dissolved in THF (80 mL) and cooled to -78 °C under an atmosphere of nitrogen then methylithium (45.9 mL, 73.6 mmol, 1.60 M in THF) was added. The resultant solution was stirred for 2 h, then added via cannula to a mixture of anhydrous lithium chloride (1.56 g, 36.8 mmol) and copper (I) cyanide (3.29 g, 36.8 mmol in THF) at -78 °C. The resultant yellow solution was stirred for 3 h at -78 °C then (R)-epoxide (211) (8.00 g, 24.5 mmol) in THF (20 mL) was added dropwise. After stirring at -78 °C for 2 h, the solution was allowed to warm to -40 °C and quenched by the addition of a solution of 10% ammonia in saturated aqueous ammonium chloride (60 mL). The aqueous layer was extracted with ethyl acetate (3x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo to give a crude oil that was purified by flash
chromatography (hexanes/diethyl ether 9:1-7:3) to afford the title compound (20 g, 90%) as a yellow oil; [α]D -4.3 (c 1.05, CHCl3).

IR γmax (film): 3442 (OH), 3071, 2930, 2857, 1472, 1428, 1112, 997, 910, 822, 736, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl3): 7.68-7.69 (4H, m, Si'BuPh₂, o), 7.39-7.46 (6H, m, Si'BuPh₂, m and p), 5.77-5.89 (1H, m, H2), 4.95-5.07 (2H, m, H1), 3.85-3.92 (3H, m, H5 and H7), 2.17-2.27 (2H, m, H3), 1.53-1.70 (4H, m, H6 and H4), 1.05 (9H, s, Si'BuPh₂); ¹³C NMR (75 MHz, CDCl3): 138.6 (CH, C2), 135.5 (CH, Si'BuPh₂, o), 133.7 (quat., Si'BuPh₂), 129.6 (CH, Si'BuPh₂, p), 127.7 (CH, Si'BuPh₂, m), 114.6 (CH₂, C1), 71.1 (CH, C5) 63.4 (CH₂, C7), 38.3 (CH₂, C6), 36.6 (CH₂, C4), 29.8 (CH₂, C3), 26.8 (CH₃, Si'BuPh₂), 19.2 (quat., Si'BuPh₂); m/z (EI): 311 (6)(M-tBu)+, 229 (17), 199 (100), 139 (9), 95 (37); HRMS (CI, NH₃): Found (MH)+, 369.2253 C₂₃H₃₃O₂Si, requires 369.2250.

A solution of alcohol 212 (50.0 mg, 0.14 mmol) in CH₂Cl₂ (1 mL) ws added to a suspension of (S)-2-methoxy-2-trifluoromethyl-2-phenylacetylic acid (48.0 mg, 0.20 mmol), N,N-4-dimethylaminopyridine (3.00 mg, 0.03 mmol) and dicyclohexylcarbodiimide (70.0 mg, 0.34 mmol) in CH₂Cl₂ (1 mL). After stirring the mixture at room temperature for 72 h, the reaction was quenched by the addition of brine (2 mL) and the mixture diluted with the diethyl ether (5 mL). The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a crude oil that was purified by flash chromatography (hexanes/diethyl ether 9:1) to afford the title compound (65.0 mg, 82%) as a colourless oil;
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(5S)-7-(tert-Butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)hept-1-ene (216)

\[
\text{TBDPSO} \quad \text{OTBDMS} \quad \text{OTBDMS}
\]

tert-Butyldimethylsilyl chloride (2.53 g, 16.8 mmol), imidazole (1.14 g, 16.8 mmol), N,N-di-4-dimethylaminopyridine (80.0 mg, 0.64 mmol) were dissolved in CH\(_2\)Cl\(_2\) (90 mL) under nitrogen atmosphere and cooled to 0 °C. To this stirred solution was added alcohol 212 (4.75 g, 12.9 mmol) in CH\(_2\)Cl\(_2\) (10 mL). After stirring for 12 h, brine (30 mL) was added and the mixture extracted with CH\(_2\)Cl\(_2\) (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo. Flash chromatography (hexanes/diethyl ether 9:1) afforded the title compound (6.10 g, 98%) as a yellow oil; [\(\alpha\)]\(_D\) +3.70 (c 0.98, CHCl\(_3\)).

IR \(\gamma_{max}\) (film): 2928, 1471, 1427, 1255, 1111, 909, 835, 774, 736, 701 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.64-7.68 (4H, m, Si\(\text{BuPh}_2\), o), 7.34-7.45 (6H, m, Si\(\text{BuPh}_2\), m and p), 5.80 (1H, dddd, \(J 17.1, 10.3\) and 6.6, H2), 4.91-5.03 (2H, m, H1), 3.91 (1H, q, \(J 6.3\), H5), 3.72 (2H, td \(J 6.3\) and 2.4, H7), 2.03-2.11 (2H, m, H3), 1.70 (2H, m, H6), 1.43-1.59 (2H, m, H4), 1.05 (9H, s, Si\(\text{BuPh}_2\)), 0.85 (9H, s, Si\(\text{BuMe}_2\)), 0.04 (3H, s, Si\(\text{BuMe}_2\)), 0.01 (3H, s, Si\(\text{BuMe}_2\));

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 138.9 (CH, C2), 135.6 (CH, Si\(\text{BuPh}_2\), o), 133.9 (quat., Si\(\text{BuPh}_2\)), 129.5 (CH, Si\(\text{BuPh}_2\), p), 127.6 (CH, Si\(\text{BuPh}_2\), m), 114.2 (CH\(_2\), C1), 68.8 (CH, C5), 60.8 (CH\(_2\), C7), 39.8 (CH\(_2\), C6), 36.5 (CH\(_2\), C4), 29.5 (CH\(_2\), C3), 26.9 (CH\(_3\), Si\(\text{BuPh}_2\)), 25.9 (CH\(_3\), Si\(\text{BuMe}_2\)), 19.2 (quat., Si\(\text{BuPh}_2\)), 18.1 (quat., Si\(\text{BuMe}_2\)), -4.4 (CH\(_3\), Si\(\text{BuMe}_2\)), -4.5 (CH\(_3\), Si\(\text{BuMe}_2\)); m/z (EI): 425 (24)(M+\(^{13}\)Bu\(^+\)), 313 (57), 271 (52), 209 (70), 197 (50), 175 (39), 135 (86), 95 (100), 91 (65), 73 (44); HRMS (FAB): Found (MH\(^+\)) \(483.3117\), requires 483.31146.

(5S)-7-(tert-Butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)heptan-1-ol (217)

\[
\text{TBDPSO} \quad \text{OTBDMS} \quad \text{OH}
\]

Alkene 216 (5.75 g, 11.9 mmol) was dissolved in THF (30 mL) under an atmosphere of nitrogen and the solution was cooled to 0 °C. Borane dimethylsulfide complex (11.9 mL, 23.8 mmol) was added to the stirred solution dropwise and the solution was allowed to warm to room temperature over 12 h. Oxidative workup by addition of H\(_2\)O\(_2\) (6.77 mL, 8.80 M) and aqueous NaOH (29.8 mL, 2 M) gave a biphasic mixture which was stirred for 40 min. The mixture was extracted with diethyl ether (3 x 100 mL) and the combined extracts were dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a colourless oil that was purified by flash chromatography using (hexanes/diethyl ether 9:1) as a title compound (6.10 g, 98%).
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ether 9:1) as the eluent to afford the title compound (4.95 g, 83%) as a yellow oil; $[\alpha]_D +3.90$ (c 1.17, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 3346 (OH), 2930, 2858, 1471, 1427, 1256, 1112, 835, 774, 738, 701 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 7.63-7.68 (4H, m, SiBu$_2$H, o), 7.33-7.44 (6H, m, SiBu$_2$H, m and p), 3.86 (1H, q, J 6.2, H5), 3.71 (2H, t, J 6.2 and 1.7, H7), 3.62 (2H, t, J 6.6, H1), 1.68 (2H, m, H6), 1.53 (2H, q, J 6.6, H2), 1.31-1.46 (4H, m, H3 and H4), 1.04 (9H, s, SiMe$_3$), 0.00 (3H, s, SiMe$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): 135.6 (CH, SiBu$_2$H, o), 134.0 (quat., SiBu$_2$H), 129.6 (CH, SiBu$_2$H, p), 127.6 (CH, SiBu$_2$H, m), 69.2 (CH, C5), 63.0 (CH$_2$, C1), 61.0 (CH$_2$, C7), 39.8 (CH$_2$, C6), 37.1 (CH$_2$, C4), 33.0 (CH$_2$, C2), 26.9 (CH$_3$, SiBu$_2$H), 25.9 (CH$_3$, SiBu$_2$Me), 21.3 (CH$_3$, C3), 19.2 (quat., SiBu$_2$H), 18.1 (quat., SiBu$_2$Me), -4.4 (CH$_3$, SiBu$_2$Me), -4.6 (CH$_3$, SiBu$_2$Me); m/z (EI): 443 (1)(M$^+$Bu$^+$), 311 (67), 199 (31), 135 (37), 95 (100), 73(25); HRMS (FAB): Found (MH)$^+$, 501.32137, requires 501.32203.

(5S)-7-(tert-Butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)heptanal (193)

A solution of alcohol 217 (3.85 g, 7.69 mmol) in CH$_2$Cl$_2$ (40 mL) was added dropwise to a suspension of Dess-Martin periodinane (6.52 g, 15.4 mmol) and pyridine (1.86 mL, 23.1 mmol) in CH$_2$Cl$_2$ (40 mL) at 0 °C under an atmosphere of nitrogen. After stirring for 2 h the solution was diluted with diethyl ether (10 mL) and filtered through a pad of Celite®. Removal of the solvent under reduced pressure, followed by flash chromatography (hexanes/diethyl ether 4:1) afforded the title compound (3.30 g, 86%) as a yellow oil; $[\alpha]_D +1.50$ (c 1.05, CHCl$_3$).

IR $\gamma_{\text{max}}$(film): 2954, 2930, 2857, 1728 (C=O), 1472, 1428, 1255, 1111, 835, 774, 738, 701 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 9.73 (1H, t, J 1.8, H1), 7.63-7.67 (4H, m, SiBu$_2$H, o), 7.34-7.44 (6H, m, SiBu$_2$H, m and p), 3.88 (1H, q, J 5.6, H5), 3.71 (2H, t, J 6.1, H7), 2.37 (2H, t, J 7.3 and 1.8, H2), 1.61-1.74 (4H, m, H3 and H6), 1.41-1.54 (2H, m, H4), 1.04 (9H, s, SiBu$_2$H), 0.85 (9H, s, SiBu$_2$Me), 0.03 (3H, s, SiBu$_2$Me), 0.00 (3H, s, SiBu$_2$Me); $^{13}$C NMR (75 MHz, CDCl$_3$): 202.5 (CH, C1), 135.6 (CH, SiBu$_2$H, o), 133.9 (quat., SiBu$_2$H), 129.6 (CH, SiBu$_2$H, p), 127.6 (CH, SiBu$_2$H, m), 68.9 (CH, C5), 60.7 (CH$_2$, C7), 43.9 (CH$_2$, C2), 39.7 (CH$_2$, C6), 36.5 (CH$_2$, C4), 26.9 (CH$_3$, SiBu$_2$H), 25.9 (CH$_3$, SiBu$_2$Me), 19.1 (quat., SiBu$_2$H), 18.0 (quat., SiBu$_2$Me), 17.8 (CH$_3$, C3), -4.5 (CH$_3$, SiBu$_2$Me), -4.6 (CH$_3$, SiBu$_2$Me); m/z (EI): 441 (74)(M$^+$Bu$^+$), 271 (29), 255 (65), 241 (38), 209 (38), 199 (73), 135 (100), 111 (27), 91 (37); HRMS (CI, NH$_3$): Found (MH)$^+$, 499.30572, requires 499.30638.
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(2S, 9S)-2,9-bis-(tert-Butyldimethylsilyloxy)-11-(tert-butyldiphenylsilyloxy)undec-3-yn-5-ol (220)

n-BuLi (6.19 mL, 9.90 mmol, 1.60 M in hexane) was added to a stirred solution of acetylene 219 (1.67 g, 9.07 mmol) in THF (30 mL), at -78 °C under an atmosphere of nitrogen and the resultant pale yellow solution was stirred for 30 min. Anhydrous LiBr (0.36 g, 4.12 mmol) was dissolved in THF (5 mL) under an atmosphere of nitrogen and cannulated to the acetylide mixture. After 15 min a solution of the aldehyde 193 (4.11 g, 8.25 mmol) in THF (30 mL) was added dropwise and the solution was allowed slowly to warm to room temperature over 6 h. Saturated ammonium chloride solution (30 mL) was added followed by extraction with diethyl ether (3 x 100 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 9:1-7:3) afforded the title compound (4.85 g, 86%) as a yellow oil; [α]_D -12.6 (c 1.00, CHCl₃).

**IR** γ_max(film): 3400 (OH), 2954, 2930, 2857, 1472, 1462, 1428, 1254, 1104, 835, 775, 701 cm⁻¹; **¹H NMR** (300 MHz, CDCl₃): 7.64-7.68 (4H, m, Si₂BuPh₂, o), 7.35-7.44 (6H, m, Si₂BuPh₂, m and p), 4.54 (1H, qd, J 6.5 and 1.4, H2), 4.36 (1H, m, H5), 3.87 (1H, m, H9), 3.71 (2H, t, J 6.1, H11), 1.63-1.75 (4H, m, H6 and H10), 1.41-1.47 (4H, m, H7 and H8), 1.40 (3H, d, J 6.5, H1), 1.05 (9H, s, Si₂BuPh₂), 0.90 (9H, s, Si₂BuMe₂), 0.85 (9H, s, Si₂BuMe₂), 0.12 (3H, s, Si₂BuMe₂), 0.11 (3H, s, Si₂BuMe₂), 0.03 (3H, s, Si₂BuMe₂), 0.00 (3H, s, Si₂BuMe₂); **¹³C NMR** (75 MHz, CDCl₃): 135.6 (CH, Si₂BuPh₂, o), 133.9 (quat., Si₂BuPh₂), 129.6 (CH, Si₂BuPh₂, p), 127.6 (CH, Si₂BuPh₂, m), 87.4 (quat., C3), 84.1 (quat., C4), 69.2 (CH, C9), 62.4 (CH, C5), 60.9 (CH₂, C11), 59.0 (CH, C2), 39.8 (CH₂, C10), 38.0 (CH₂, C6), 36.5 (CH₂, C8), 26.9 (CH₃, Si₂BuPh₂), 25.9 (CH₃, Si₂BuMe₂), 25.8 (CH₃, Si₂BuMe₂), 25.4 (CH₃, C1), 20.8 (CH₂, C7), 19.2 (quat., Si₂BuPh₂), 18.1 (quat., Si₂BuMe₂), 18.1 (quat., Si₂BuMe₂), -4.5 (CH₃, Si₂BuMe₂), -4.6 (CH₃, Si₂BuMe₂), -4.9 (CH₃, Si₂BuMe₂); **m/z** (EI): 625 (1)(M⁺Bu), 493 (6), 441 (8), 361 (100); **HRMS** (FAB): Found (MH)+, 683.43080 C₃₉H₆₇O₄Si₃, requires 683.43472.
(2S, 9S)-2,9-Bis-(tert-butyldimethylsilyloxy)-11-(tert-butyldiphenylsilyloxy)undec-3-yn-5-one (221)

Alcohol 220 (5.70 g, 8.30 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and added to a slurry of 4 Å molecular sieves (1.00 g) in CH$_2$Cl$_2$ (8 mL) and the solution was cooled to 0 °C. To this stirred solution was added $N$-methylmorpholine-$N$-oxide (1.45 g, 12.4 mmol) and tetrapropylammonium perruthenate (0.15 g, 0.41 mmol) in CH$_2$Cl$_2$ (15 mL). After stirring for 2 h the reaction mixture was filtered through a pad of Celite®, washed with CH$_2$Cl$_2$ (2 x 20 mL) and the solvent removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 9:1-7:3) afforded the title compound (5.50 g, 97%) as a yellow oil; [α]$_D$-15.7 (c 0.498, CHCl$_3$).

IR $\gamma_{max}$ (film): 2955, 2930, 2857, 2213, 1680 (C=O), 1472, 1462, 1428, 1255, 1155, 1111, 836, 776, 738, 701 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 7.64-7.68 (4H, m, Si$'$/BuPh$_2$, o), 7.35-7.42 (6H, m, Si$'$/BuPh$_2$, m and p), 4.65 (1H, q, J 6.6, H2), 3.88 (1H, q, J 5.8, H9), 3.71 (2H, td, J 6.5 and 1.8, H11), 2.52 (2H, t, J 7.6, H6), 1.61-1.75 (4H, m, H7 and H10), 1.45 (3H, d, J 6.6, H1), 1.41-1.46 (2H, m, H8), 1.05 (9H, s, Si$'$/BuPh$_2$), 0.91 (9H, s, Si$'$/BuMe$_2$), 0.85 (9H, s, Si$'$/BuMe$_2$), 0.14 (3H, s, Si$'$/BuMe$_2$), 0.12 (3H, s, Si$'$/BuMe$_2$), 0.03 (3H, s, Si$'$/BuMe$_2$), 0.01 (3H, s, Si$'$/BuMe$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 187.5 (quat., C5), 135.6 (CH, Si$'$/BuPh$_2$, o), 133.9 (quat., Si$'$/BuPh$_2$), 129.6 (CH, Si$'$/BuPh$_2$, p), 127.6 (CH, Si$'$/BuPh$_2$, m), 93.6 (quat., C30, 82.3 (quat., C4), 68.9 (CH, C9), 60.8 (CH$_2$, C11), 58.8 (CH, C2), 45.5 (CH$_2$, C6), 39.7 (CH$_2$, C10), 36.4 (CH$_2$, C8), 26.9 (CH$_2$, Si$'$/BuPh$_2$), 25.9 (CH$_3$, Si$'$/BuMe$_2$), 25.7 (CH$_3$, Si$'$/BuMe$_2$), 24.5 (CH$_3$, C1), 19.6 (CH$_2$, C7), 19.1 (quat., Si$'$/BuPh$_2$), 18.1 (quat., Si$'$/BuMe$_2$), 18.0 (quat., Si$'$/BuMe$_2$), -4.5 (CH$_3$, Si$'$/BuMe$_2$), -4.6 (CH$_3$, Si$'$/BuMe$_2$), -5.0 (CH$_3$, Si$'$/BuMe$_2$); m/z (FAB): 623 (1)($M$-$t$/Bu)$^+$, 549 (1), 491 (1), 413 (2), 271 (3), 209 (7), 197 (18), 135 (32), 73 (100); HRMS (FAB): Found (MH)$^+$, 681.42118 C$_{39}$H$_{65}$O$_4$Si$_3$, requires 681.41907.
(2S, 9S)-2,9-Bis-(tert-butyldimethylsilyloxy)-11-(tert-butyldiphenylsilyloxy)undecan-5-one (222)

Ynone 221 (3.50 g, 5.10 mmol) was dissolved in methanol/THF (10 mL, 1:1), and stirred under an atmosphere of hydrogen in the presence of PtO₂ (0.17 g, 0.75 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite and the solvents removed under reduced pressure. Flash chromatography (hexanes/diethyl ether 9:1) afforded the title compound (3.30 g, 95%) as a yellow oil; [α]₀ -1.00 (c 3.60, CHCl₃).

IR γₘₚ(film): 2955, 2929, 2857, 1716 (C=O), 1472, 1428, 1255, 1111, 1005, 836, 774, 738, 701 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): 7.64-7.68 (4H, m, Si₄Bu₂Ph₂, o), 7.35-7.42 (6H, m, Si₄Bu₂Ph₂, m and p), 3.79-3.90 (2H, m, H₂ and H₉), 3.70 (2H, td, J 6.5, 1.7, H₁₁), 2.17-2.51 (4H, m, H₄ and H₆), 1.64-1.72 (4H, m, H₃ and H₁₀), 1.51-1.62 (2H, m, H₇), 1.36-1.44 (2H, m, H₈), 1.11 (3H, d, J 6.1, H₁), 0.88 (9H, s, Si₄Bu₂Me₂), 0.84 (9H, s, Si₄Bu₂Me₂), 0.04 (9H, s, Si₄Bu₂Me₂), -4.4 (CH₃, Si₄Bu₂Me₂), -4.6 (CH₃, Si₄Bu₂Me₂), -4.8 (CH₃, Si₄Bu₂Me₂); m/z (FAB): 685 (2)(MH)⁺, 553 (3), 495 (2), 421 (6), 343 (2), 297 (3), 269 (4), 239 (8), 197 (18), 135 (43), 73 (100); HRMS (FAB): Found (MH)⁺ 685.45024 C₃₉H₆₉O₄Si₃, requires 685.45037.

(2S,5R,7S)-7-[2'-(tert-Butyldiphenylsilyloxy)ethyl]-2-methyl-1,6-dioxaspiro[4.5]decane (223)

To a stirred solution of ketone 222 (4.50 g, 6.50 mmol) in CH₂Cl₂ (65 mL) at 0 ºC under an atmosphere of nitrogen was added camphorsulfonic acid (3.60 g, 14.4 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 2 h. Filtration through Celite then removal of the solvent under
reduced pressure followed by flash chromatography (hexanes/diethyl ether 4:1-3:2) afforded the title compound (2.50 g, 86%) as a yellow oil; $[\alpha]_D +117.1$ (c 0.50, CHCl$_3$).

**IR** $\gamma_{max}$(film): 2934, 2858, 1472, 1428, 1219, 1112, 736, 702 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 7.65-7.69 (4H, m, Si'BuPh$_2$, o), 7.33-7.44 (6H, m, Si'BuPh$_2$, m and p), 4.20 (1H, qdd, J 6.2, 6.2 and 1.9, H2), 4.00 (1H, dddd, J 11.5, 7.5, 5.3 and 2.2, H7), 3.75 (2H, t, J 6.8 H2'), 1.88-1.88 (1H, m, H9a), 1.59-1.76 (7H, m, H3b, H4b, H9b, H10 and H1'), 1.52-1.59 (1H, m, H8a), 1.22 (3H, d, J 6.2, Me), 1.13-1.19 (1H, m, H8b), 1.04 (9H, s, Si'BuPh$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): 135.6 (CH, Si'BuPh$_2$, o), 134.0 (quat., Si'BuPh$_2$), 129.5 (CH, Si'BuPh$_2$, p), 127.6 (CH, Si'BuPh$_2$, m), 105.7 (quat., C5), 76.6 (CH, C20. 66.9 (CH, C7), 60.9 (CH$_2$, C2'), 39.5 (CH$_2$, C1' or C4), 39.4 (CH$_2$, C1' or C4), 33.5 (CH$_2$, C10), 31.8 (CH$_2$, C3), 31.1 (CH$_2$, C8), 26.9 (CH$_3$, Si'BuPh$_2$), 23.4 (CH$_3$, Me), 20.4 (CH$_2$, C9), 19.2 (quat., Si'BuPh$_2$); m/z (EI): 381 (46)(M-tBu)$^+$, 303 (4), 295 (5), 281 (8), 199 (51), 165 (25), 111 (100), 85 (18), 83 (17), 55 (19); HRMS (CI, NH$_3$): Found (MH)$^+$, 439.26654 C$_{27}$H$_{39}$O$_3$Si, requires 439.26685.

(2S,5R,7S)-7-(2'-Hydroxyethyl)-2-methyl-1,6-dioxaspiro[4.5]decane (224)

| IR $\gamma_{max}$(film): 3435 (OH), 2934, 2871, 1456, 1439, 1377, 1221, 1159, 1115, 1069, 1027, 972, 947, 876, 862 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 4.24 (1H, qdd, J 6.3, 6.3 and 1.8, H2), 4.10 (1H, dddd, J 11.4, 8.8, 4.1 and 2.2, H7), 3.68-3.72 (2H, m, H2'), 1.88-2.03 (2H, m, H3a and H4a), 1.68-1.85 (1H, m, H9a), 1.68 (7H, m, H3b, H4b, H9b, H10 and H1'), 1.43-1.51 (1H, m, H8a), 1.25 (3H, d, J 6.3, Me), 1.15-1.29 (1H, m, H8b); $^{13}$C NMR (75 MHz, CDCl$_3$): 105.9 (quat., C5), 76.9 (CH, C2), 71.0 (CH, C7), 61.7 (CH$_2$, C2'), 39.3 (CH$_2$, C4), 37.9 (CH$_2$, C1'), 33.3 (CH$_2$, C10), 31.8 (CH$_2$, C3), 31.0 (CH$_2$, C8), 23.1 (CH$_3$, Me), 20.0 (CH$_2$, C9); m/z (EI): 185 (3)(M-Me)$^+$, 149 (7), 137 (14), 129 (17), 95 (18), 81 (52), 69 (100), 57 (37), 55 (36), 41 (49); HRMS (CI, NH$_3$): Found (MH)$^+$, 201.14858 C$_{11}$H$_{21}$O$_3$Si, requires 201.14907. |
(2''S, 5''R, 7''S)-2-[2''-(2''-Methyl-1'',6''-dioxaspiro[4.5]dec-7''-yl)ethylsulfonyl]-benzothiazole (228)

Triphenylphosphine (701 mg, 2.67 mmol) and mercaptobenzothiazole (596 mg, 3.60 mmol) were dissolved in THF (15 mL) and cooled to 0 °C under an atmosphere nitrogen. To this stirred solution was added alcohol 224 (357 mg, 1.80 mmol) in THF (5 mL). After stirring for 15 min, diethylazodicarboxylate (0.50 mL, 3.20 mmol) was added dropwise. The resultant bright yellow solution was stirred at 0 °C for 2 h. The reaction was quenched by the addition of brine (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash chromatography (hexanes/ diethyl ether 49:1-7:3) afforded the title compound (461 mg, 74%) as a yellow oil; [α]$_D$ +76.3 (c 1.00, CHCl$_3$).

**IR** $\gamma_{\text{max}}$(film): 2936, 2868, 1459, 1427, 1309, 1237, 1221, 1158, 1113, 1072, 994, 976, 876, 854 cm$^{-1}$; **$^1$H NMR** (400 MHz, CDCl$_3$): 7.85 (1H, dd, $J$ 7.9 and 1.0, H4), 7.74 (1H, dd, $J$ 7.9 and 1.0, H7), 7.39 (1H, td, $J$ 7.9 and 1.0, H5), 7.27 (1H, td, $J$ 7.9 and 1.0, H6), 4.23 (1H, qdd, $J$ 6.2, 6.2 and 1.9, H2''), 4.00 (1H, ddd, $J$ 11.3, 9.0, 3.8 and 2.3, H7''), 3.43-3.50 (1H, m, H1'a), 3.32-3.39 (1H, m, H1'a), 1.91-2.03 (4H, m, H3''a, H4''a and H2'), 1.70-1.90 (3H, m, H3''b, H4''b and H9''a), 1.56-1.69 (4H, m, H8''a, H9''b and H10''), 1.30 (3H, d, $J$ 6.2, Me), 1.18-1.28 (1H, m, H8''b); **$^{13}$C NMR** (100 MHz, CDCl$_3$): 167.4 (quat., C2), 153.4 (quat., C3a), 135.2 (quat., C7a), 125.9 (CH, C5), 124.0 (CH, C6), 121.5 (CH, C4), 120.9 (CH, C7), 105.9 (quat., C5''), 76.9 (CH, C2''), 68.5 (CH, C7''), 39.4 (CH$_2$, C4''), 36.0 (CH$_2$, C2''), 33.6 (CH$_2$, C10''), 32.0 (CH$_2$, C3''), 30.9 (CH$_2$, C8''), 30.1 (CH$_2$, C1'), 23.4 (CH$_3$, Me), 20.2 (CH$_2$, C9''); **m/z** (EI): 349 (17)(M$^+$), 334 (4)(M-Me), 182 (63), 167 (100), 125 (29), 111 (68), 98 (69), 83 (14), 55 (25), 43 (26), 41 (26); **HRMS** (EI): Found M$^+$, 349.11669 C$_{18}$H$_{23}$NO$_2$S$_2$, requires 349.11702.
(2''S,5''R,7''S)-2-[2'-(2''-Methyl-1'',6''-dioxaspiro[4.5]dec-7''yl)ethylsulfonyl]-benzothiazole (229)

To a solution of thioether 228 (461 mg, 1.30 mmol) in CH₂Cl₂ (5 mL) at 0 °C under an atmosphere of nitrogen was added sodium bicarbonate (554 mg, 6.60 mmol) and a solution of m-chloroperoxybenzoic acid (569 mg, 3.30 mmol) in CH₂Cl₂ (5 mL). After stirring for 12 h, saturated aqueous sodium bicarbonate (2 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resultant oil was purified by flash chromatography (hexanes/ diethyl ether 4:1-3:2) to afford the title compound (453 mg, 90%) as a white solid; m.p. 74-77 °C; [α]D +24.8 (c 0.40, CHCl₃).

IR γ_max(film): 2930, 2870, 1459, 1472, 1458, 1328 (SO), 1236, 1221, 1148 (SO), 1072, 1026, 977, 877, 855 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 8.22 (1H, dd, J 7.3 and 1.5, H₄), 8.01 (1H, dd, J 7.3 and 1.5, H₇), 7.64 (1H, td, J 7.3 and 1.5, H₅), 7.57 (1H, td, J 7.3 and 1.5, H₆), 4.19 (1H, qdd, J 6.2, 6.2 and 1.9, H₂''), 3.86-3.92 (1H, m, H₇''), 3.74 (1H, ddd, J 14.4, 11.3 and 4.8, H₁'a), 3.47 (1H, ddd, J 14.4, 11.3 and 4.8, H₁'b), 1.84-2.03 (4H, m, H₃''a, H₄''a and H₂'), 1.72-1.84 (1H, m, H₉''a), 1.59-1.72 (3H, m, H₃''b, H₄''b, H₉''b), 1.50-1.58 (3H, m, H₈''a and H₁₀''), 1.24 (3H, d, J 6.2, Me), 1.12 (1H, m, H₈''b); ¹³C NMR (100 MHz, CDCl₃): 165.7 (quat., C₂), 152.8 (quat., C₃a), 136.8 (quat., C₇a), 128.0 (CH, C₆), 127.6 (CH, C₅), 125.5 (CH, C₄), 122.3 (CH, C₇), 106.0 (quat., C₅''), 76.9 (CH, C₂''), 68.0 (CH, C₇''), 51.9 (CH₂, C₁'), 39.3 (CH₂, C₄''), 33.4 (CH₂, C₁₀''), 31.9 (CH₂, C₃''), 30.8 (CH₂, C₈''), 29.1 (CH₂, C₂'), 23.4 (CH₃, Me), 20.0 (CH₂, C₉''); m/z (EI): 381 (2)(M⁺), 366 (3)(M-Me), 282 (18), 217 (15), 189 (34), 149 (30), 135 (52), 98 (100), 55 (40), 41 (34); HRMS (EI): Found M⁺, 381.10540 C₁₈H₂₃NO₄S₂, requires 381.10685.
2-Bromo-3,5-dimethoxybenzaldehyde (202)

3,5-Dimethoxybenzaldehyde (204) (1.0 g, 6.02 mmol) was suspended in glacial acetic acid (5 mL) and cooled to 0 °C. A solution of bromine (320 µL, 6.25 mmol) in acetic acid (2 mL) was added dropwise to the reaction mixture. Once the addition was complete the suspension was warmed to room temperature over 5 min at which point the reaction had solidified and water (10 mL) was added. The solid was filtered and washed with water (5 mL), then it was dissolved in CH$_2$Cl$_2$ (8 mL) and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate, filtered through a plug of silica gel and eluted with CH$_2$Cl$_2$. The filtrate was concentrated in vacuo to yield a white solid which was dissolved in EtOAc (5 mL) and cooled to 5 °C at which point the dibrominated by-product precipitated out of solution. The solid was separated via filtration and the filtrate concentrated in vacuo to yield the title compound (1.09 g, 74%) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): 10.43 (1H, s, CHO), 7.06 (1H, d, $J$ 2.7, H6), 6.73 (1H, d, $J$ 2.7, H4), 3.93 (3H, s, OCH$_3$), 3.87 (3H, s, OCH$_3$); The $^1$H NMR data was in agreement with that reported in the literature.

1'-{(2-Bromo-3,5-dimethoxyphenyl)prop-2'-en-1'-ol (499)

A solution of vinylmagnesium bromide (15.1 mL, 15.1 mmol, 1 M in THF) was added dropwise to a solution of aldehyde 202 (1.05 g, 4.30 mmol) in THF (20 mL) cooled to -78 °C. The mixture was stirred at -78 °C for 12 h, before quenching with aqueous HCl (20 mL, 1 M). The reaction mixture was washed with saturated sodium bicarbonate (10 mL) and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. Flash chromatography (hexanes/EtOAc 5:1) afforded the title compound (1.00 g, 85%) as a yellow oil. The spectroscopic data was identical to the one reported in the literature.
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IR $\gamma_{\text{max}}$(film): 3398, 2938, 2839, 1584, 1452, 1417, 1198, 1157, 1019, 927, 836, 601 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 6.68 (1H, d, $J$ 3.0, H6), 6.36 (1H, d, $J$ 3.0 H4), 5.96 (1H, m, H2), 5.59 (1H, $t$ $J$ 1.5, H1'), 5.34 (1H, dt, $J$ 17.4 and 1.5, H3'a), 5.15 (1H, dt, $J$ 10.5, 1.5, H3'b), 3.86 (3H, s, OMe), 3.76 (3H, s, OMe), 2.72 (1H, br s, OH); $^{13}$C NMR (75 MHz, CDCl$_3$): 159.8 (quat., C5), 156.3 (quat., C3), 143.5 (quat, C1), 138.1 (CH, C2'), 115.4 (CH$_2$, C3'), 103.5 (CH, C6), 102.7 (quat, C2), 99.0 (CH, C4), 73.2 (CH, C1'), 56.2 (CH$_3$, OMe), 55.4 (CH$_3$, OMe); m/z (ESI): 295 (21)(M$^+$), 273 (4), 257 (21), 190 (1), 176 (100), 161 (2); HRMS (ESI): Found (M+Na)$^+$, 294.9927 C$_{11}$H$_{13}$BrNaO$_3$, requires 294.9940.

(R)-1'-(2-Bromo-3,5-dimethoxyphenyl)allyl acetate (500)$^{200}$

A mixture of alcohol 499 (2.00 g, 7.35 mmol) and p-chlorophenyl acetate (2.5 g, 14.7 mmol) in toluene (50 mL) was flushed with argon for 1 min followed by the addition of Novozyme 435$^{30}$ (100 mg). The resulting mixture was stirred at 55 $^\circ$C in a microwave reactor (single mode CEM Discovery$^{10}$ Focused Microwave Synthesis System) at 300 W for 48 h. The mixture was then filtered through cotton wool and washed with CH$_2$Cl$_2$ (2 x 5 mL). The combined organic extracts were concentrated in vacuo and the residue purified by flash chromatography (hexanes/EtOAc 9:1) to afford title compound (1.00 g, 43%, 96 % e.e.) as a yellow oil; $[\alpha]_D$$^+17.7$ (c 2.70, CH$_2$Cl$_2$). The spectroscopic data was identical to the one reported in the literature.$^{200}$

IR $\gamma_{\text{max}}$(film): 2941, 1740, 1586, 1454, 1323, 1223, 1161, 1061, 1020, 980, 605 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 6.61 (1H, d, $J$ 5.6 H1'), 6.58 (1H, d, $J$ 2.8 H6), 6.42 (1H, d, $J$ 2.8, H4), 5.95 (1H, m, H2'), 5.25 (2H, m, H3'), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 2.12 (3H, s, CH$_3$CO); $^{13}$C NMR (75 MHz, CDCl$_3$): 169.5 (quat., C=O), 160.0 (quat., C5), 156.7 (quat., C3), 140.2 (quat., C1), 134.5 (CH, C2'), 117.3 (CH$_2$, C3'), 104.4 (CH, C6), 103.4 (quat., C2), 99.0 (CH, C4), 74.9 (CH, C1'), 56.4 (CH$_3$, OMe), 55.5 (CH$_3$, OMe), 21.1 (CH$_3$, CH$_2$CO); m/z (ESI): 315 (34)(MH$^+$), 257 (50), 176 (100), 161 (2); HRMS (ESI): Found (M)$^+$, 315.0226 C$_{13}$H$_{16}$$_7^9$BrNaO$_4$, requires 315.0219.
(R)-1’-(2-Bromo-3,5-dimethoxyphenyl)prop-2’-en-1’-ol (503)

To a solution of acetate 500 (0.44 g, 1.40 mmol) in MeOH (5 mL), was added potassium hydroxide (0.094 g, 1.60 mmol). The resulting mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo and the residue purified by flash chromatography (hexanes/EtOAc 9:1) to afford the title compound (0.33 g, 87%) as a colourless oil; [α]D+35.6 (c 1.10, CH2Cl2). The spectroscopic data were identical to the one reported above for alcohol 499, enantiomeric excess 96% (chiral hplc).

(R)-1’-(2-Bromo-3,5-dimethoxyphenyl)allyl diethylcarbamate (504)

To a suspension of NaH (0.10 g, 4.13 mmol, 60% w/w dispersion in mineral oil) in THF (8 mL), at 0 °C, under an atmosphere of nitrogen was added a solution of bromoalcohol 503 (1.02 g, 3.75 mmol) in THF (15 mL) dropwise. After stirring for 0.5 h, N,N-diethylcarbamoyl chloride (0.76 mL, 5.63 mmol) was added dropwise. The mixture was stirred for 12 h before the addition of saturated ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure followed by flash chromatography (hexanes/EtOAc 4:1) gave the title compound (1.36 g, 98%) as a yellow oil; [α]D+6.41 (c 1.50, CH2Cl2). The spectroscopic data was identical to the one reported in the literature.

IR γmax(film): 2972, 1698, 1587, 1454, 1418, 1323, 1269, 1200, 1058, 995, 766 cm⁻¹; ¹H NMR (300 MHz, CDCl3): 6.49 (1H, t, J 2.8, H6), 6.47 (1H, d, J 1.6 H1’), 6.32 (1H, d, J 2.8 H4), 5.91 (1H, m, H2’), 5.15 (2H, m, H3’), 3.72 (3H, s, OMe), 3.68 (3H, s, OMe), 3.26 (2H, br s, NCH₂CH₃), 3.22 (2H, br s, NCH₂CH₃), 1.11 (3H, br s, NCH₂CH₃), 1.01 (3H, br s, NCH₂CH₃); ¹³C NMR (75 MHz, CDCl3): 159.5 (quat., C5), 156.2 (quat., C3), 154.0 (quat., C=O), 140.7 (quat., C1), 135.0 (CH, C2’), 115.8 (CH₂, C3’), 115.8 (CH₂, C3’).

HPLC Conditions: IC column, iPrOH:hexane, 3:97, flow rate 0.5 mL/min, retention times: 23.0 min. (minor), 27.6 min. (major)
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103.6 (CH, C6), 102.4 (quat., C2), 98.3 (CH, C4), 75.0 (CH, C1'), 55.8 (CH3, OMe), 54.9 (CH3, OMe), 41.5 (CH2, NCH2CH3), 40.9 (CH2, NCH2CH3), 13.8 (CH3, NCH2CH3), 13.0 (CH3, NCH2CH3), m/z (ESI): 394 (100)(M+Na)+, 350 (6), 318 (3), 140 (2); HRMS (ESI): Found (M+Na)+, 394.0624 C16H22BrNNaO4, requires 394.0623.

(R)-5,7-Dimethoxy-3-vinylisobenzofuran-1(3H)-one (505)200

Carbamate 504 (1.35 g, 3.60 mmol) was dissolved in THF (10 mL). The solution was cooled to -78 °C and n-BuLi (4.78 mL, 7.60 mmol, 1.6 M in THF) was added dropwise. The yellow solution was stirred at -78 °C for 1 h then warmed to room temperature. The reaction was quenched with water (10 mL), extracted with EtOAc (3 x 20 mL), the organic layer was dried with magnesium sulfate and concentrated in vacuo. The crude mixture was dissolved in dioxane (15 mL) and anhydrous HCl (6.30 mL, 25.2 mmol, 4M in dioxane) was added dropwise. The solution was stirred for 12 h and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc 7:3) to give the title compound (0.65 g, 82%) as a white solid; m.p. 84 °C; [α]D -24.1 (c 0.57, CH2Cl2). The spectroscopic data was identical to the one reported in the literature.200

IR γmax (film): 3093, 2951, 2842, 1751, 1596, 1461, 1417, 1330, 1213, 1156, 1050, 937, 690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 6.40 (1H, s, H4), 6.37 (1H, s H6), 5.79 (1H, m, H1'), 5.61 (1H, d, J 7.2, H3), 5.36 (2H, dt, J 10.2, 1.2 H2'), 3.92 (3H, s, OMe), 3.86 (3H, s, OMe); ¹³C NMR (75 MHz, CDCl₃): 167.9 (quat., C1), 166.8 (quat, C5), 159.5 (quat., C7), 153.5 (quat, C3a), 133.6 (CH, C1'), 119.4 (CH2, C2), 106.1 (quat., C7a), 99.0 (CH, C6), 98.0 (CH, C4), 80.6 (CH, C3), 55.9 (CH3, OMe), 55.8 (CH3, OMe); m/z (ESI): 221 (22)(MH)+, 178 (8), 162 (9); HRMS (ESI): Found (MH)+, 221.0805 C12H14O4, requires 221.0808.
(R)-2-(4,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetaldehyde (493)\textsuperscript{200}

\begin{align*}
\text{OMe} & \quad \text{MeO} \\
5 & \quad 4 \\
6 & \quad 2 \\
7a & \quad 1 \\
1' & \quad 2' \\
3a & \quad 7a
\end{align*}

A solution of vinylphthalide 505 (0.36 g, 1.60 mmol) in DMF (5 mL) was added to a mixture of palladium (II) chloride (0.15 g, 0.82 mmol), copper (I) chloride (0.21 g, 2.10 mmol) in DMF (3 mL) and water (2 mL). Oxygen gas was bubbled through the solution for 2 h. The reaction mixture was filtered through a silica pad, the residue washed with EtOAc (100 mL) and hexanes (50 mL). The volatile solvents were removed \textit{in vacuo} and the DMF under high vacuum at 40 °C. Flash chromatography (hexanes/EtOAc 1:1) afforded the title compound as a colourless oil (0.28 g, 74%); [\(\alpha\)]\textsubscript{D} +9.10 (c 0.50, CH\textsubscript{2}Cl\textsubscript{2}). The spectroscopic data was identical to the one reported in the literature.\textsuperscript{200}

\textbf{IR} \(\gamma_{\text{max}}\) (film): 2929, 2848, 1749, 1601, 1334, 1212, 1200, 1158, 1026, 839, 731, 699 cm\textsuperscript{-1}; \textbf{H NMR} (300 MHz, CDCl\textsubscript{3}): 9.81 (1H, t, \(J\) 3.0, C2'), 6.44 (1H, d, \(J\) 3.0, H4), 6.40 (1H, d, J 3.0, H6), 5.74 (1H, t, J 6.0 H3), 3.91 (3H, s, OMe), 3.85 (3H, s, OMe), 2.97 (2H, m, H1'); \textbf{13C NMR} (75 MHz, CDCl\textsubscript{3}): 198.0 (quat., C2'), 167.5 (quat., C1), 167.0 (quat., C5), 159.7 (quat., C7), 153.8 (quat., C3a), 106.2 (quat., C7a), 99.1 (CH, C4), 97.8 (CH, C6), 74.1 (CH, C3), 56.0 (CH\textsubscript{3}, OMe), 55.9 (CH\textsubscript{3}, OMe), 48.2 (CH\textsubscript{3}, C1'); \textbf{m/z} (ESI): 259 (18)(M+Na); 237 (2), 193 (9), 172 (7), 135 (2); \textbf{HRMS} (ESI): Found (M+Na), 259.0581 C\textsubscript{12}H\textsubscript{12}NaO\textsubscript{5}, requires 259.0577.

(3R)-5,7-Dimethoxy-3-(4'-(2''S,7''R)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)but-2-enyl)isobenzofuran-1-(3H)-one (506)

\begin{align*}
\text{OMe} & \quad \text{Me} \\
5 & \quad 3a \\
6 & \quad 7a \\
7 & \quad 7a
\end{align*}

To a solution of sulfone 229 (0.046 g, 0.12 mmol) in THF (2 mL) under an inert atmosphere at -78 °C was added potassium hexamethyldisilazide (0.300 mL, 0.5 M in toluene, 0.151 mmol) dropwise. The reaction was stirred at -78 °C for 20 min then aldehyde 493 (0.028 g 0.12 mmol) in THF (2 mL) was added dropwise to the mixture. The reaction was stirred at -78 °C for 1.5 h then warmed to room temperature and stirred for an additional hour. Diethyl ether (10 mL) was added followed by brine (8 mL). The
aqueous layer was extracted with ethyl acetate and the combined organic fractions dried over magnesium sulfate. Solvent removal under reduced pressure followed by flash chromatography (hexanes/EtOAc 4:1) afforded the title compound (30.1 mg, 62%) as a yellow oil; [α]D +38.2 (c 1.00, CHCl3).

IR γmax (film): 2928, 1751, 1602, 1459, 1432, 1332, 1212, 1156, 1027, 977, 878, 834, 690 cm⁻¹; \(^1^H\) NMR (300 MHz, CDCl₃): 6.41-6.44 (2H, m, H4 and H6), 5.45-5.58 (2H, m, (E)-H2' and (Z)-H2', (E)-H3' and (Z)-H3'), 5.26-5.32 (1H, m, H3), 4.12-4.15 (1H, H2''), 3.94 (3H, s, OMe), 3.88 (3H, s, OMe), 3.67-3.75 (1H, m, H7''), 2.52-2.69 (2H, m, H1'), 2.08-2.17 (2H, m, H4'), 1.56 (2H, m, H8''), 1.25 (3H, d, J 6.4 Me).

\[^{13}\]C NMR: 168.2 (quat., C1), 166.5 (quat., C5), 159.6 (quat., C7), 154.6 (quat., C4a*), 154.6 (quat., C4a), 131.9 (CH, C3*), 124.6 (CH, C3'), 130.5 (CH, C2'), 123.4 (CH, C2'), 107.1 (quat., C7a), 106.2 (quat., C5*), 98.8 (CH, C4*), 98.6 (CH, C4), 97.8 (CH, C6*), 97.7 (CH, C6), 79.3 (CH, C3*), 79.2 (CH, C3), 73.7 (CH, C2''), 69.8 (CH, C7''), 69.7 (CH, C7'), 55.9 (CH, OMe), 55.8 (CH, OMe), 39.5 (CH₂, C4*), 39.3 (CH₂, C4'), 38.0 (CH₂, C4**), 37.8 (CH₂, C4*), 34.4 (CH₂, C1*), 33.5 (CH₂, C10*), 33.4 (CH₂, C10'), 31.4 (CH₂, C3*), 31.3 (CH₂, C3'), 30.6 (CH₂, C3''), 30.5 (CH₂, C3'), 30.2 (CH₂, C8*), 30.1 (CH₂, C8'), 29.7 (CH₂, C1'), 21.2 (CH₃, Me), 20.3 (CH₂, C9'), 20.2 (CH₂, C9''), m/z (ESI): 425 (100)(M+Na), 403 (30), 385 (10); HRMS (ESI): Found (MH)+, 403.2090 C_{23}H_{31}O_{6}, requires 403.2115.

(3R)-5,7-Dimethoxy-3-(4-((2''S,7''R)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)isobenzofuran-1-(3H)-one (335)

Alkene 506 (13.0 mg, 0.032 mmol) was dissolved in THF/MeOH (2 mL, 1:1) and hydrogenated under an atmosphere of hydrogen in the presence of PtO₂ (0.63 mg, 0.0026 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvents removed under reduced pressure. Flash chromatography (hexanes/EtOAc 1:1) afforded the title compound (10.0 mg, 77%) as a yellow oil; [α]D +25.3 (c 1.50, CHCl₃).

IR γmax (film): 2935, 2865, 1754, 1604, 1494, 1458, 1336, 1219, 1158, 1053, 1026, 974, 875, 837, 690 cm⁻¹; \(^1^H\) NMR (300 MHz, CDCl₃): 6.39-6.40 (2H, m, H3 and H6), 5.26-5.30 (1H, dd, J 3.6, 7.8, H3), 3.67-3.75 (1H, m, H7''), 2.52-2.69 (2H, m, H1'), 2.08-2.17 (2H, m, H4'), 1.56 (2H, m, H8''), 1.25 (3H, d, J 6.4 Me); \[^{13}\]C NMR: 168.2 (quat., C1), 166.5 (quat., C5), 159.6 (quat., C7), 154.6 (quat., C4a*), 154.6 (quat., C4a), 131.9 (CH, C3*), 124.6 (CH, C3'), 130.5 (CH, C2'), 123.4 (CH, C2'), 107.1 (quat., C7a), 106.2 (quat., C5*), 98.8 (CH, C4*), 98.6 (CH, C4), 97.8 (CH, C6*), 97.7 (CH, C6), 79.3 (CH, C3*), 79.2 (CH, C3), 73.7 (CH, C2''), 69.8 (CH, C7''), 69.7 (CH, C7'), 55.9 (CH, OMe), 55.8 (CH, OMe), 39.5 (CH₂, C4*), 39.3 (CH₂, C4'), 38.0 (CH₂, C4**), 37.8 (CH₂, C4*), 34.4 (CH₂, C1*), 33.5 (CH₂, C10*), 33.4 (CH₂, C10'), 31.4 (CH₂, C3*), 31.3 (CH₂, C3'), 30.6 (CH₂, C3''), 30.5 (CH₂, C3'), 30.2 (CH₂, C8*), 30.1 (CH₂, C8'), 29.7 (CH₂, C1'), 21.2 (CH₃, Me), 20.3 (CH₂, C9'), 20.2 (CH₂, C9''), m/z (ESI): 425 (100)(M+Na), 403 (30), 385 (10); HRMS (ESI): Found (MH)+, 403.2090 C_{23}H_{31}O_{6}, requires 403.2115.

**This symbol (*) is used to denote mixture of (E) and (Z) isomers.**
4.20-4.22 (1H, m, H2’’), 3.94 (3H, s, OMe), 3.88 (3H, s, OMe), 3.75-3.78 (1H, m, H7’’), 1.95-2.03 (3 H, m, H1’a, H3’a and H4’a), 1.66-1.72 (9H, H1’b, H3’’b and H4’’b, H9’’, H10’’and H8’’), 1.58-1.62 (6H, m, H2’, H3’ and H4’), 1.26 (3H, d, J 6.4 Me); 13C NMR (75 MHz, CDCl3): 168.4 (quat., C1), 166.6 (quat., C5), 159.6 (quat., C7), 155.2 (quat., C4a), 107.0 (quat., C7a), 105.8 (quat., C5”), 98.6 (CH, C4), 97.4 (CH, C6), 79.9 (CH, C3), 76.6 (CH, C2”), 69.7 (CH, C7”), 55.9 (CH3, OMe), 55.8 (CH3, OMe), 39.4 (CH2, C4”), 36.2 (CH2, C4’), 34.8 (CH2, C1’), 34.7 (CH2, C1”), 33.6 (CH2, C10”), 31.9 (CH2, C3”), 31.1 (CH3, C8”), 25.5 (CH2, C3”), 24.7 (CH2, C2”), 23.3 (CH3, Me), 20.4 (CH2, C9’’); m/z (ESI): 427 (100)(M+Na)+, 405 (30)(M’+), 280 (10), 231 (15); HRMS (ESI): Found MH+, 405.2254, C23H33O6, requires 405.2272.
Chapter 3: Experimental
Appendix

$^{1}$H NMR spectrum of 355 at 400 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 355 at 100 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 356 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 356 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 357 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 357 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 371 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 371 at 75 MHz, CDCl$_3$
**Appendix**

$^1$H NMR spectrum of 373 at 300 MHz, CDCl$_3$

![NMR spectrum of 373 at 300 MHz, CDCl$_3$]

$^{13}$C NMR spectrum of 373 at 75 MHz, CDCl$_3$

![NMR spectrum of 373 at 75 MHz, CDCl$_3$]
Appendix

COSY spectrum of 373

NOESY spectrum of 373
Appendix

$^1$H NMR spectrum of 370 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 370 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of $\textbf{359}$ at 300 MHz, CDCl$_3$

\begin{center}
\includegraphics{hnmr_spectrum.png}
\end{center}

$^{13}$C NMR spectrum of $\textbf{359}$ at 75 MHz, CDCl$_3$

\begin{center}
\includegraphics{cnmr_spectrum.png}
\end{center}
Appendix

$^1$H NMR spectrum of 339 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 339 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 342 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 342 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 395 at 300 MHz, CDCl$_3$

![H NMR spectrum of 395 at 300 MHz, CDCl$_3$]

$^{13}$C NMR spectrum of 395 at 75 MHz, CDCl$_3$

![C NMR spectrum of 395 at 75 MHz, CDCl$_3$]
Appendix

\[ ^1\text{H NMR spectrum of 396 at 300 MHz, CDCl}_3 \]

\[ ^{13}\text{C NMR spectrum of 396 at 300 MHz, CDCl}_3 \]
$^1$H NMR spectrum of 388 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 388 at 300 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 397 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 397 at 300 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 398 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 398 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of $^{389}$ at 400 MHz, CDCl$_3$

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hnmr.png}
\caption{$^1$H NMR spectrum of $^{389}$ at 400 MHz, CDCl$_3$}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{cmr.png}
\caption{$^{13}$C NMR spectrum of $^{389}$ at 100 MHz, CDCl$_3$}
\end{figure}
Appendix

$^1$H NMR spectrum of 400 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 400 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 403 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 403 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 404 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 404 at 75 MHz, CDCl$_3$
\( ^1H \) NMR spectrum of 378 at 300 MHz, CDCl₃

\( ^{13}C \) NMR spectrum of 378 at 75 MHz, CDCl₃
Appendix

$^1$H NMR spectrum of **406** at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of **406** at 75 MHz, CDCl$_3$
Appendix

\(^1\)H NMR spectrum of 338 at 300 MHz, CDCl\(_3\)

\[^{13}\text{C} \) NMR spectrum of 338 at 75 MHz, CDCl\(_3\)
Appendix

$^1$H NMR spectrum of 341 at 400 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 341 at 100 MHz, CDCl$_3$
\( ^1 \)H NMR spectrum of 463 at 300 MHz, CDCl\(_3\)

\( ^{13} \)C NMR spectrum of 463 at 75 MHz, CDCl\(_3\)
$^1$H NMR spectrum of 379 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 379 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 464 at 300 MHz, CDCl$_3$

![H NMR spectrum of 464 at 300 MHz, CDCl$_3$](image)

$^{13}$C NMR spectrum of 464 at 75 MHz, CDCl$_3$

![C NMR spectrum of 464 at 75 MHz, CDCl$_3$](image)
Appendix

$^1$H NMR spectrum of 336 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 336 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 466 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 466 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 467 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 467 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 473 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 473 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 474 at 300 MHz, CDCl$_3$

TBDPSO \[ \text{OTBDMS} \text{OH} \]

$^{13}$C NMR spectrum of 474 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 468 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 468 at 75 MHz, CDCl$_3$
Appendix

\( ^1H \) NMR spectrum of 475 at 300 MHz, CDCl\(_3\)

\[ 
\text{OTBDMS} \quad \text{OH} \quad \text{TBDPSO} \quad \text{OTBDMS} 
\]

\[ 
\begin{array}{c}
0.881 \\
0.888 \\
0.895 \\
0.903 \\
1.040 \\
1.047 \\
1.262 \\
1.389 \\
1.406 \\
1.419 \\
1.424 \\
1.431 \\
1.446 \\
1.533 \\
1.541 \\
1.548 \\
1.554 \\
1.570 \\
1.643 \\
1.660 \\
1.677 \\
1.693 \\
2.047 \\
3.638 \\
3.654 \\
3.670 \\
4.098 \\
4.117 \\
4.134 \\
4.152 \\
4.358 \\
4.364 \\
4.367 \\
4.374 \\
4.377 \\
4.521 \\
4.524 \\
4.537 \\
4.540 \\
4.553 \\
4.557 \\
7.260 \\
7.353 \\
7.358 \\
7.361 \\
7.374 \\
7.377 \\
7.392 \\
7.397 \\
7.402 \\
7.406 \\
7.412 \\
7.419 \\
7.437 \\
7.657 \\
7.661 \\
7.666 \\
7.676 \\
7.680 \\
6.771 \\
6.086 \\
20.610 \\
10.981 \\
12.154 \\
3.530 \\
3.474 \\
0.648 \\
3.627 \\
1.061 \\
1.000 \\
6.756 \\
4.567 \\
140 \\
130 \\
120 \\
110 \\
100 \\
90 \\
80 \\
70 \\
60 \\
50 \\
40 \\
30 \\
20 \\
10 \\
ppm
\end{array} 
\]

\[ 
\begin{array}{c}
18.112 \\
18.218 \\
19.200 \\
20.931 \\
20.981 \\
21.697 \\
25.390 \\
25.800 \\
25.942 \\
26.861 \\
32.869 \\
36.714 \\
36.850 \\
37.971 \\
38.052 \\
58.954 \\
62.462 \\
62.496 \\
63.924 \\
72.133 \\
76.680 \\
76.999 \\
77.316 \\
84.107 \\
87.461 \\
87.486 \\
127.562 \\
129.474 \\
134.128 \\
135.562 \\
13.84 \\
13.44 \\
12.94 \\
12.54 \\
47.461 \\
48.147 \\
77.534 \\
76.681 \\
62.494 \\
62.534 \\
18.052 \\
16.785 \\
16.714 \\
16.845 \\
15.942 \\
15.896 \\
15.992 \\
15.020 \\
14.818 \\
4.382 \\
\end{array} 
\]

\[ 
13C NMR spectrum of 475 at 75 MHz, CDCl\(_3\)
Appendix

$^1$H NMR spectrum of 476 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 476 at 75 MHz, CDCl$_3$
$^{1}$H NMR spectrum of 469 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 469 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 477 at 400 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 477 at 100 MHz, CDCl$_3$
NOESY spectrum for 477
$^1$H NMR spectrum of 478 at 400 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 478 at 100 MHz, CDCl$_3$
$^1$H NMR spectrum of 470 at 400 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 470 at 100 MHz, CDCl$_3$
Appendix

\[ ^1H \text{ NMR spectrum of } \text{337} \text{ at 300 MHz, CDCl}_3 \]

\[ ^{13}C \text{ NMR spectrum of } \text{337} \text{ at 75 MHz, CDCl}_3 \]
$^1$H NMR spectrum of 340 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 340 at 75 MHz, CDCl$_3$
Appendix

$^1$H NMR spectrum of 506 at 300 MHz, CDCl$_3$

13C NMR spectrum of 506 at 75 MHz, CDCl$_3$
$^1$H NMR spectrum of 335 at 300 MHz, CDCl$_3$

$^{13}$C NMR spectrum of 335 at 75 MHz, CDCl$_3$