Towards the Total Synthesis of Domoic acid and the Isodomoic acids.

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences.

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School of Chemistry
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ABSTRACT

Total Synthesis of the Isodomoic Acids

A submission for the degree of Doctor of Philosophy at the University of Manchester,
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The isodomoic acids are a series of trisubstituted pyrrolidine-based carboxylic acids containing an octadienoic side chain at the C4 carbon.

These natural products display a number of interesting biological and neurological properties which have fuelled recent interest into finding a synthetic source. They are known to induce neuronal degeneration, similar to the effect of diseases such as Huntington’s disease and epilepsy. Thus, their use as a pharmacological model could be invaluable and perhaps provide further insight into the pathogenesis of such diseases.

This thesis describes the total synthesis of isodomoic acids B, E and F using a stereodivergent route. The key step in the synthesis is a dearomatising cyclisation mediated by chiral lithium amide 2 to form a dearomatised product 3 which possesses the same relative stereochemistry present in the isodomoic acids.

The synthesis of intermediate alkyne 4 from the dearomatised product 3 will also be discussed as well as the selective functionalisation of alkyne 4 to form the trisubstituted E-alkene. The preparation of the side chains are also described within this work. The thesis will conclude with the efforts to functionalise the alkyne intermediate to attain the trisubstituted Z-alkene which would lead to isodomoic acids A and D and domoic acid.
DECLARATION

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

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Finally, I would like to thank my mother for all her support over the years and to Michael for his devoted presence and finally thank you to my closest friends Dr. Chelsea Walton and Mubina Mohammed.

PREFACE

The author graduated from the University of Strathclyde with a Master of Science Chemistry (MSci) in Chemistry with a year in Industry. This industrial year was carried out at Bayer CropScience, Frankfurt, Germany working on the development and production of compound libraries for agrochemical research.
In 2009, the author joined the research group of Prof. Jonathan Clayden at the University of Manchester working “Towards the Total Synthesis of the Isodomoic acids and Domoic acid”. The research carried out here is embodied within this thesis.
ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tr>
<td>4-methoxy TEMPO</td>
<td>4-methoxy-2,2,6,6-tetramethyl-1-piperidinoxy, free radical</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>approx.</td>
<td>approximately</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>BCN</td>
<td>benzyl 5 norbornene-2, 3-dicarboximido carbonate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc-ON</td>
<td>2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile</td>
</tr>
<tr>
<td>bpt</td>
<td>boiling point</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
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<td>calc.</td>
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<td>cat.</td>
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</tr>
<tr>
<td>Chz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>COSY</td>
<td>correlated spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadiene</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAI-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylamino pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
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<tr>
<td>DMPU</td>
<td>N,N’-dimethyl-N,N’-propylene urea</td>
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<td>dimethylsulfide</td>
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<td>ee</td>
<td>enantiomeric excess</td>
</tr>
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<td>EI</td>
<td>electron impact</td>
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<td>hexamethylphosphoramide</td>
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<td>HRMS</td>
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<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>ICl</td>
<td>iodine monochloride</td>
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<tr>
<td>imid</td>
<td>imidazole</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>isopropyl alcohol</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis (trimethylsilyl)amide</td>
</tr>
<tr>
<td>Kᵢ</td>
<td>dissociation constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
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<tr>
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<td>N-bromosuccinimide</td>
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<td>n-BuLi</td>
<td>n-butyl lithium</td>
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<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
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<tr>
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<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
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<tr>
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<td>pyridinium p-toluenesulfonate</td>
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<td>pyridine</td>
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<td>pyridinium</td>
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<tr>
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</tr>
<tr>
<td>recryst.</td>
<td>recrystallised</td>
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<tr>
<td>Rᶠ</td>
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<tr>
<td>Rᵣ</td>
<td>retention time</td>
</tr>
<tr>
<td>rt</td>
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<tr>
<td>Super hydride</td>
<td>lithium triethylborohydride</td>
</tr>
<tr>
<td>t-Am</td>
<td>tert-amyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>τ-BuLi</td>
<td>tert-butyl lithium</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropryanyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilane</td>
</tr>
<tr>
<td>tol.</td>
<td>toluene</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl-4-toluenesulfonyl-</td>
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<tr>
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1 Introduction

1.1 The Kainoids

The isodomoic acids belong to a class of non-proteinogenic amino acids known as the kainoids. These dicarboxylic acids consist of a pyrrolidine core with three contiguous stereogenic centres, where variation of the C4 substituent gives rise to the various members of the kainoid acid family (Figure 1).

![Figure 1: General structure of the kainoids](image)

The parent member of the group, (−)-α-kainic acid (1) and its C4 epimer allokanic acid (2), were first isolated in 1953 from the algae Digenea simplex and have also been found in other related algae (Figure 2).¹

![Figure 2: Kainic acid and allokanic acid](image)

Domoic acid (3) and the isodomoic acids (4-11) are a series of structurally related isomers differing only in the geometry and regiochemistry of their octadienoic side chains at the C4 carbon (Figure 3). Domoic acid 3 was first isolated from the Japanese marine algae Chondria armata which also proved to be the source of other members of the kainoid family, such as isodomoic acids A-D and G and H.², ³ Isodomoic acids E and F were later found to be present in the edible mussels, Mytulis edulis (Figure 3).⁴
Additional members of the kainoid amino acid family include the more complex domoilactones A (12) and B (13) which contain a five membered lactone at the C4 position, and the acromelic acids A-E (14-18) which carry a functionalised 2-pyridone at the C4 position (Figure 4). The acromelic acids A-E (14-18) were isolated in small quantities from the poisonous Japanese mushroom *Clitocybe acromelalga*, though since then total syntheses of acromelic acids A, B and E have been reported.
1.1.1 Biological activity

The kainoids display interesting biological activity, namely their anthelmintic and insecticidal properties but more importantly due to their neuroexcitatory effects. This neuroexcitatory behaviour can be extremely potent, inducing a similar effect to diseases that cause neuronal degeneration such as Huntington’s disease, senile dementia and epilepsy. Thus their use as a pharmacological model could serve as an invaluable tool and perhaps provide further insight into the functioning and eventually the cure for such diseases.

Furthermore, the isolation of the kainoids from natural sources has been restricted by their scarcity, which has resulted in high prices for the kainoids and the need for efficient synthetic routes to its members.

The potent biological activity of the kainoids is due to their structural similarity to glutamic acid (Figure 5), a mammalian central nervous system neurotransmitter. Glutamic
acid is present in all cells and participates in protein and nucleotide metabolism as well as energy regulation, and acts at two classes of receptors.\textsuperscript{16} These consist of the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs). The iGluRs can be further divided into three sub-groups; the kainate (KA) receptors, the 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) receptors and the N-methyl-D-aspartic acid (NMDA) receptors.\textsuperscript{17}

The kainoid mode of action is proposed to be through binding to the brain’s KA receptors, causing depolarisation and neuronal damage.\textsuperscript{16-19} They display the highest affinity for the KA receptors and a moderate affinity for the AMPA receptors, but a low affinity for the NMDA receptors.\textsuperscript{19} However the 4-unsubstituted kainoid, trans-2-carboxy-3-pyrrolidine-3-acetic acid (CPAA) is an agonist at the NMDA receptor (Figure 5)\textsuperscript{20}

\begin{figure}
\centering
\includegraphics[width=0.6\textwidth]{figure5.png}
\caption{Structural comparison of the kainoids, CPAA and glutamic acid}
\end{figure}

The C4 substituent has been determined to be critical for biological activity, and both the nature and configuration of the substituent is significant.\textsuperscript{21, 22} This has also been confirmed by other researchers and summarized in the findings of Hampson who have stated two prerequisites for high affinity binding at the KA receptor. Firstly, unsaturation at the C1’-C2’ chain, and secondly, that the double bond must be in the Z configuration.\textsuperscript{16, 19, 23, 24} Confirmation of the importance of the C4 substituent was observed in the increased neuroexcitatory effects of domoic acid (3) in comparison to kainic acid (1). Similarly, allokainic acid (2) exhibits significantly reduced neuroexcitatory properties as well as weaker anthelmintic effects compared to kainic acid (1).\textsuperscript{25} The acromelates and analogues display even greater biological activity than kainic acid though they exhibit a different mode of action.\textsuperscript{26}

Domoic acid (3) has also been determined as the causative agent of Amnesic Shellfish Poisoning (ASP), an illness caused by its ingestion.\textsuperscript{27} In 1987, an outbreak of ASP from contaminated mussels, resulted in the death of three people and the poisoning of
more than 150. Symptoms of the poisoning includes vomiting and diarrhoea, followed in some cases by short term memory loss and even coma. These outbreaks occur when populations of domoic acid-producing algae become concentrated and pose a threat to sea mammals, birds and people. Since this incident, measures have been taken to ensure that these toxic algae do not accumulate, such as employing methods of bacterial biodegradation.

1.2 Kainic acid, domoic acid and analogues

Many syntheses of kainic acid (1) have been reported both racemically and asymmetrically. In 1982 Oppolzer reported the first enantioselective synthesis and since then several more syntheses have been reported. Similarly, the total synthesis of allokainic acid (2), the C4 epimer of kainic acid has also been reported several times since its first synthesis by Deschong in 1986.

On the other hand, domoic acid (3) has only been synthesised once by Ohfune, along with two domoic analogues, using a stereoselective Diels-Alder reaction as the key step. The synthesis began with N-tert-butoxycarbonyl-L-pyroglutamic acid (19) which is converted into silyl ether (20) in four steps (Scheme 1). The key Diels-Alder reaction with diene (21) furnished cycloadduct (22) as a single stereoisomer as justified by Woodward-Hoffmann rules.

The bicyclic compound (22) then underwent ozonolysis to open the six-membered ring, and conversion of the carboxylic acid to the methyl ester was carried out using diazomethane, followed by protection of the aldehyde as ketal (23). Reduction of the amide was carried out with borane-dimethylsulfide complex also resulting in the reduction of the C3 ester to the alcohol. The silyl ether was deprotected and the diol oxidised and methylated to afford a diester.

Aldehyde (24) was obtained through removal of the ketal protecting group. The methoxymethylene group was introduced by a Wittig olefination with (25), followed by hydroxyselenation with PhSeCl to yield diene (26). Compound (26) was oxidised to the carboxylic acid followed by esterification with diazomethane and the synthesis was
completed with the removal of the protecting groups to afford (−)-domoic acid (3) (Scheme 1).

Scheme 1: Total synthesis of (−)-domoic acid

The corresponding Z-enal (28) could be formed under different reaction conditions in a 2:1 ratio Z:E (28:24), analogous steps were then taken to afford a protected form of isodomoic acid E (29) (Scheme 2).
1.2.1 Semi-synthesis and biosynthesis of domoic acid

Wright and co-workers have explored the biosynthesis of domoic acid using $^{13}$C labelled precursors (Scheme 3). $^{37}$ $^{13}$C labelled acetate was fed to domoic acid-producing algae, *Nitzschia pungens*, since compounds (30) and (31) can be derived from this compound. Condensation of glutamate derivative, geranyl diphosphate (30) with acid (31) led to formation of domoic acid (3), and this process has been suggested as a possible biosynthetic route to the kainoids (Scheme 3).

The irradiation of a dilute sample of domoic acid with ultraviolet light ($\lambda = 250$ nm) for nine to twelve minutes was found to increase the abundance of the isodomoic acids, suggesting that domoic acid itself is synthesised by the mollusc and that the isodomoic acids are subsequently formed as a result of other processes. $^{4}$ It was also proposed that this process could be a general route to all of the kainoids.

Conway *et al.* have carried out a semi-synthetic route to kainoid analogues through modification of the isopropenyl side chain of kainic acid (1). Analogue (32) was prepared...
through the palladium catalysed coupling of kainic acid (1) with 3-nitroaniline (Scheme 4). \(^{38}\)

\[
\begin{array}{c}
\text{kainic acid 1} \\
\text{CO}_2\text{H} \\
\text{CO}_2\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\begin{array}{c}
\text{O}_2\text{N} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\end{array}
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{CO}_2\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\]

Reagent and conditions: (a) Pd(OAc)\(_2\), 3-nitroaniline, MeCN, \(t\)-butyl nitrite, 60 °C, 3-16 h

**Scheme 4: Palladium catalysed modification of kainic acid**

Biological testing found that despite both analogues being active, they were considerably less potent than the natural kainoids. This work has not been extended to the other kainoid syntheses and has proven to be a very inefficient and low yielding method for preparing analogues.

1.2.2 *Domoic acid analogues*

Baldwin has also reported the synthesis of a domoic acid analogue (33) structurally similar to isodomonic acid C (Figure 6). \(^{39}\)

\[
\text{HO}_2\text{C} \\
\text{HO}_2\text{C} \\
\text{CO}_2\text{H} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\text{\text{Ph}} \\
\]

**Figure 6: Domoic acid analogue**

The synthesis uses a cobalt-mediated cyclisation that has been used in a previous synthesis of kainic acid to form the pyrrolidine core. \(^{40}\) Alcohol (36) was prepared in four steps from (34) following a reductive amination with citral and protection of the amine as the \(N\)-phenyl carbamate. This was followed by reduction of the ester to the aldehyde then conversion to alcohol (36) with tert-butyllithioacacetate (Scheme 5).
Removal of the silyl protecting group was carried out with \( p-TsOH \) and the resulting diol was cyclised to give oxazolidinone (37). Iodide (38) was then formed after treatment of (37) with triflic anhydride and sodium iodide. Compound (38) then underwent cobalt-mediated cyclisation affording (39), which was hydrolysed with potassium hydroxide. The amine was protected as its Boc carbamate and the methyl ester formed with diazomethane. The alcohol intermediate was oxidised and esterified to afford diester (40). The final stages of the synthesis were hydrolysis of the methyl esters and formation of the alcohol by treatment with trifluoroacetic acid. Deprotection of the amine also under acidic conditions afforded the kainoid analogue (33), which Baldwin reported as having moderate activity at the kainate receptor site (Scheme 5).\(^\text{39}\)

**Scheme 5: Synthesis of a domoic acid analogue**
1.3 Synthesis of the isodomoic acids

At the beginning of the project few syntheses of the isodomoic acids had been completed. Isodomoic acid C was one of the first to be synthesised by Clayden et al., followed by the total syntheses of isodomoic acids G and H by Montgomery and Denmark. The work described in this thesis has contributed to the first total synthesis of isodomoic acids B, E and F which will be discussed at a later stage.

1.3.1 Isodomoic acids G and H

Isodomoic acids G (10) and H (11) differ from the other isodomoic acids as they contain an exocyclic alkene at the C4 position (Figure 7).

![Isodomoic acids G and H](image)

Montgomery carried out the first total synthesis and stereochemical definition of isodomoic acid G. This was later extended and revised to carry out the total synthesis of isodomoic acid H. Both syntheses were performed using a nickel-catalysed cyclisation of an alkynyl enone with an alkenylzirconium. Within a single cyclisation, control of the stereochemistry at the C2 and C3 positions was achieved, as well as formation of the characteristic exocyclic double bond. Furthermore reversal of the order in which the methyl and alkenyl groups were placed enabled Montgomery to form both the E and Z isomers.

The synthesis begins with the preparation of oxazolidinones (45) and (47) from amine (41) (Scheme 6). THP protection of (42), followed by N-butynylation and
deprotection afforded alcohol (44). A similar reaction was employed involving the N-propargylation of (43) to afford (47) via alcohol (46) which will be discussed later in the synthesis of isodomoic acid H (11).

Scheme 6: Isodomoic acids G and H: Route to cyclisation precursors

Evans’ alkylation of oxazolidinone (48) produced coupling precursor (49) which underwent in situ hydrozirconation (Scheme 7). Coupling of the intermediate vinyl zirconium species with (45), and treatment with Ni(COD)$_2$ afforded pyrrolidine (50). Isodomoic acid G (10) was then synthesised after methanolysis of the oxazolidinone and deprotection with TBAF to give diol (52) which was then oxidised to the diacid using Dess-Martin periodinane and NaClO$_2$. Hydrolysis then afforded isodomoic acid G (10) (Scheme 7).
Completion of the synthesis of isodomoic acid H (11) began with formation of E-vinyl iodide (53) from treatment of (49) with Schwartz’s reagent and N-iodosuccinimide (Scheme 8). Sonogashira coupling of vinyl iodide (53) and terminal alkyne (47) afforded enyne (54) which cyclised in the presence of dimethylzinc and Ni(COD)₂ to give (55) as a single isomer. The following steps are the same as described for isodomoic acid G (10); methanolysis to afford ester (56), silyl ether deprotection with TBAF, followed by oxidation and lastly a global hydrolysis to afford isodomoic acid H (11) (Scheme 8).
In 2009, Denmark reported the synthesis of isodomoic acids G and H using a stereodivergent alkenylsilane iodination step. The synthesis started with lactone (57) which was opened with TMSI, followed by esterification to give the amino ester (58). Iodide (58) was then converted to selenide (59) and N-alkylated under Mitsunobu conditions to afford (60). This was then followed by oxidative elimination with $\text{H}_2\text{O}_2$ to give enyne (61) in 95% yield.

A rhodium catalysed carbonylative silylcarbocyclization of (61) was carried out forming aldehyde (62) as an 8:1 mixture of diastereoisomers. As a result the aldehyde was
reduced to the alcohol and the isomers then separated. Methyl ester (63) was then formed after oxidation and esterification with diazomethane (Scheme 9).

Scheme 9: Enyne formation for carbonylative silylcarbocyclization

The key iododesilylation step was mediated by iodine monochloride (ICl) which caused inversion of the double bond configuration to afford iodide (66). The inversion was proposed to be due to anchimeric participation of the carbonyl group at C7 via a five-membered oxocarbenium ion (64). Rotation of this bond with the silyl group antiperiplanar to the C-O bond results in the observed stereochemical outcome (Scheme 10).
This step was then followed by palladium catalysed coupling with silanol (67) to produce the protected isodomoic acid (68), which was finally deprotected with LiOH and sodium amalgam affording isodomoic acid H (11) (Scheme 11).

Reagents and conditions: (a) (67), Pd_2(dba)_3-CHCl_3 5 mol%, TBAF-8H_2O, 92%; (b) i LiOH, reflux, quant; ii Na/Hg, NaH_2PO_4, rt, 56%.

Scheme 10: *Iododesilylation*

Scheme 11: *Total synthesis of isodomoic acid H*
For the synthesis of isodomoic acid G (10) a non-coordinating substrate was required at C7 in order to make the iodination reaction retentive. For this reason TIPS protection of primary alcohol (69) served as a non-participating functional group, and the iododesilylation was carried out affording E-vinyl iodide (70) followed by deprotection, oxidation and esterification of the primary alcohol (Scheme 12).

The synthesis was continued by palladium catalysed coupling of iodide (70) with (67) to afford ester (71), which was deprotected in two steps affording isodomoic acid G (10) (Scheme 12).

Scheme 12: Total synthesis of isodomoic acid G

1.4 Dearomatising cyclisation of benzamides

The dearomatising cyclisation of lithiated aromatic amides is a reaction that was developed within the Clayden group.47 It was discovered during an attempted ortho lithiation of amide (72) wherein the expected products (74) and (75) were obtained as the minor products while the major product was tricyclic lactam (73) (Scheme 13).48
Scheme 13: Discovery of the dearomatizing cyclisation reaction

This cyclisation reaction occurs after a benzylic deprotonation of benzamide (76) with t-BuLi. Cyclisation of the newly formed organolithium (77) onto the aromatic ring forms an extended enolate (78) which can either be protonated or alkylated (Scheme 14).

Scheme 14: Mechanism of the dearomatizing cyclisation reaction

Optimisation of this reaction found that better yields were obtained when bulky groups were present on the amide, whereas carbonyl protecting groups led to rearrangement products rather than the desired cyclisation.\footnote{49} It was observed that cyclisation with a cumyl group was equally as feasible as with a t-butyl group and resulted in easier deprotection.\footnote{49, 50} Also, use of a para-methoxy substituted benzamide (81) meant that the enol ether (82) could be easily hydrolysed to the stable enone (83) (Scheme 15).
Dearomatising cyclisation with p-methoxy benzamides

The significant potential of this cyclisation reaction was soon realised as the dearomatised product possessed the relative stereochemistry that was observed in the kainic acid family (Figure 8). Since then the reaction has been successfully applied to a number of total syntheses of the kainoids which will be discussed presently.\(^{41, 46, 51-54}\)

**Scheme 15: Dearomatising cyclisation with p-methoxy benzamides**

The significant potential of this cyclisation reaction was soon realised as the dearomatised product possessed the relative stereochemistry that was observed in the kainic acid family (Figure 8). Since then the reaction has been successfully applied to a number of total syntheses of the kainoids which will be discussed presently.\(^{41, 46, 51-54}\)

**Figure 8: Structural comparison of the dearomatised product with the kainoids**

### 1.5 Syntheses of kainoids using the dearomatising cyclisation reaction

#### 1.5.1 Synthesis of (±)-kainic acid

The synthesis of (±)-kainic acid (1) reported in 2000 made use of the previously discussed dearomatising cyclisation reaction.\(^{52}\) Cumylamine (83) was acylated with p-anisoyl chloride and then alkylated with benzylbromide. Lithiation with \(t\)-BuLi and HMPA formed the cyclic product (81) (Scheme 16). It was later discovered that LDA was basic enough to carry out the benzylic lithiation and the reaction could be carried out at 0 °C, avoiding the use of carcinogenic and pyrophoric chemicals.\(^{49}\)
Completion of the synthesis from the cyclised product (81) involved *in situ* hydrolysis of the enol ether to form the enone (82), followed by conjugate addition of methyl cuprate to afford ketone (84). The phenyl group which is essential for clean cyclisation was to be converted to the acid at a later stage, however re-protection of the amine was necessary first and acid hydrolysis removed the N-cumyl group which was re-protected as the N-Boc carbamate. A ruthenium catalysed oxidation of the phenyl group was performed and the resulting acid was esterified with TMSCHN$_2$ forming methyl ester (85) (Scheme 16).

A regioselective Baeyer-Villiger oxidation formed lactone (86), which was subsequently opened with sodium hydroxide, followed by a selenium mediated elimination to give disubstituted alkene (88). The final steps included borohydride reduction of the amide followed by an acidic deprotection to furnish (±)-kainic acid (1).$^{52}$
Scheme 16: Total synthesis of (±)-kainic acid

Reagents and conditions: (a) i p-anisoyl chloride, Et₃N, CH₂Cl₂; ii NaH, BuBr, DMF, rt, 18 h, 82% over 2 steps; (b) i t-BuLi (2 eq), HMPA (12 eq), THF, -40 °C, 60 h; ii aq NH₄Cl; (c) 1M HCl (aq), THF, 94% over 3 steps; (d) i Me₂CuLi, TMSCI, THF, -78 °C, 1 h; ii TFA reflux; 6 h, 64% over 2 steps; iii Boc₂O, Et₃N, DMAP, CH₂Cl₂, 92%; (e) i NaIO₄, cat. RuCl₃, 1:1 acetone-H₂O; ii Me₃SiClN₂, PhH, MeOH, 57% over 2 steps; (f) m-CPBA, CH₂Cl₂, 76%; (g) i NaOH, MeOH, reflux, 2 h; ii Me₂SiClN₂, PhH, MeOH, 71% over 2 steps; (h) i o-NO₂C₆H₄SeCN, Bu₃P, THF, rt; ii H₂O₂, py, THF, -40 °C, 69% over 2 steps; (i) NaH(OMe)₂, THF, 79%; (j) 10:1 TFA-H₂O, reflux, 4 h, 60%
1.5.2 Synthesis of an acromelic acid analogue

The synthesis of acromelic analogue (98) reported in 2001 is a short but effective route that uses the dearomatising cyclisation methodology developed within the Clayden group.\textsuperscript{51,47} The synthesis was initially carried out racemically\textsuperscript{51} (Scheme 17) and later asymmetrically.\textsuperscript{55}

In the racemic synthesis, amide (90) was deprotonated with \textit{t}-BuLi and cyclised to form enolate (91) which upon protonation afforded the cyclised product as a single diastereoisomer. Deprotection of the amide and hydrolysis of the enol ether was then carried out with trifluoroacetic acid affording ketone (93). Boc-protection of the free amide was carried out before ruthenium catalysed oxidation of the phenyl ring to the acid followed by a diazomethane work-up to obtain ester (94).

Baeyer-Villiger oxidation afforded lactone (95) which was opened to phenol (96) using sodium methoxide. Selective reduction of the lactam carbonyl group was carried out using NaBH(OMe)\textsubscript{3} and triethylsilane to give (97). The final step was ester hydrolysis to yield the target acromelic acid analogue (98) (Scheme 17).
Reagents and conditions: (a) i-i-BuLi, THF, -78 °C, 2h; ii-DMPU, 6 eq, -78 °C, 16 h, 88%; iii-NH₄Cl, H₂O; (b) CF₃CO₂H, H₂O, 3 h, 87%; (c) Boc₂O, DMAP (cat.), MeCN, 80%; (d) i-RuCl₃, NaIO₄, H₂O, EtOAc, MeCN, 4 h, ii-CH₃N₂, 52% 2 steps; (e) m-CPBA, 16 h, 52% (f) NaOMe, MeOH, 0 °C, 85%; (g) i-NaBH(OH)₂, THF; ii-BF₃·OEt₂, Et₃SiH, CH₂Cl₂, 25% over 2 steps; (h) 6 M HCl, 1 h, quant.

**Scheme 17: Racemic synthesis of an acromelic analogue**

### 1.6 Enantioselective dearomatising cyclisation

Dearomatising reactions using LDA resulted in a racemic product, but chiral lithium amides such as (99) and (100) (Figure 9) can be used to promote asymmetric cyclisations, thus allowing control over the absolute stereochemistry of the product.⁴⁷, ⁵⁶
Chiral amide (99) was found to be more effective than (100), as it produced both higher yields and ee's and was easily separated from the desired product. Thus amide (99) was used for the cyclisation step during the synthesis of (−)-kainic acid (1)\textsuperscript{53, 54} and (−)-isodomoic acid C (6).\textsuperscript{41}

### 1.6.1 Synthesis of (−)-kainic acid

The synthesis of (−)-kainic acid (1) from the enantioselectively dearomatised product (101) was completed in nine steps (Scheme 18).\textsuperscript{53, 54} The enantiomeric excess of the cyclised product (102) could be improved to >99% ee after recrystallisation from ethyl acetate. The remaining steps of the synthesis were analogous to those shown for the racemic natural product (Scheme 18).

![Scheme 18: Total synthesis of (−)-kainic acid](attachment:scheme_18.png)

Reagents and conditions: (a) i Me₂CuLi, TMSICl, -78 °C, 84% ii TFA, 84%; iii Boc₂O, Et₃N, DMAP, CH₂Cl₂, quant.; (b) i NaIO₄, cat. RuCl₃, 1:1 MeCN, H₂O, EtOAc; ii CH₂N₂, 67% over 2 steps; (c) i m-CPBA, CH₂Cl₂, 48 h, 88%; ii NaOMe, -78 °C, quant.; iii o-NO₂C₆H₄SeCN, Bu₃P, THF, rt; iv H₂O₂, py, THF, -40 °C, quant.; v DIBAH, -78 °C; Et₂SiH, BF₃·OEt₂, CH₂Cl₂, 44% over 2 steps; vi LiOH, H₂O; TFA, CH₂Cl₂, 80% over 2 steps
1.6.2 Total synthesis of (−)-isodomoic acid C

In 2005, a total synthesis of (−)-isodomoic acid C (6) was carried out within the group. The key step of the synthesis was the previously discussed dearomatising cyclisation reaction mediated by enantioselective deprotonation using a chiral base. The synthetic route began in a similar fashion to that of (±)-kainic acid (1) (Scheme 16), starting with N-benzyl benzamide (80). Cyclisation to enone (82) was performed on a gram scale using the chiral amide (99) (Scheme 19). The side chain of the isodomoic acid was then introduced by conjugate addition of mixed cuprate (103) to afford ketone (104). The cumyl protecting group was removed with formic acid resulting in desilylation and formylation of the primary hydroxyl group. The pyrrolidine was then protected as the N-Boc derivative before ruthenium mediated oxidation of the phenyl ring and methylation to afford the methyl ester (106). Replacement of the formate group with a TBDPS group was necessary for the remaining steps of the synthesis. Regioselective Baeyer-Villiger reaction with m-CPBA furnished lactone (107) as a single isomer, which was hydrolysed with NaOMe.

A selenium mediated elimination gave the desired alkene (109), and the amide was reduced using DIBAl-H then treatment of the intermediate with triethylsilane and boron trifluoride to afford Boc protected amine (110) (Scheme 19).

Silyl ether (110) was deprotected with TBAF and the primary alcohol was oxidised to the aldehyde. The remaining steps of the synthesis were a selective Horner-Wadsworth-Emmons olefination using phosphonate ester (111) followed by deprotection to give (−)-isodomoic acid C (6) (Scheme 19).

- 44 -
Scheme 19: Total synthesis of (-)-isodomoic acid C
2 Project aims

The aim of this project was the synthesis of the isodomoic acids, and the main objective has been the identification and synthesis of a suitable intermediate through which all the isodomoic acids could be accessed selectively without the need to redesign a synthetic route for each isomer.

The isodomoic acids can be grouped according to the geometry at the C1’-C2’ double bond (Figure 10). A trisubstituted E double is common to isodomoic acids B, E, and F while isodomoic acids A, D and domoic acid share a trisubstituted Z double bond.

![Trisubstituted alkenes of the isodomoic acids](image)

Figure 10: Trisubstituted alkenes of the isodomoic acids

An alkyne was chosen as an intermediate since this functionality could be used to provide the various trisubstituted double bonds. A disconnection of the octadienoic side chain and the pyrrolidine core would reveal the alkyne intermediate and a side chain to which it could be coupled (Scheme 20).
Thus the initial aim of the project was to develop a stereodivergent route from an enantiopure alkyne intermediate 112) and prepare the side chains that were to be used as coupling partners.

2.1 Route toward an alkyne intermediate.

2.1.1 Previous routes to the alkyne intermediate

Integral to the synthetic route to the alkyne is the dearomatising cyclisation reaction, and, as mentioned previously, this reaction had been used as the key step in a number of syntheses of the kainoids (Chapter 1, section 1.4).\textsuperscript{47,48} Since the de aromatised product shares the same relative stereochemistry as the kainoids it was decided to exploit this en route to the alkyne, which could be accessible after a few key transformations (Scheme 21).
Work has been carried out previously in an attempt to synthesise the intermediate alkyne (112). One of the routes investigated involved an Eschenmoser fragmentation as its key step and began with dearomatised product (117) (Scheme 22).

Protection of cyclised product (117) as the N-Boc carbamate (118) was followed by ketone reduction and elimination under mild acidic conditions to afford alkene (119). Treatment of the alkene with t-BuOOH formed epoxide (120), in preparation for the upcoming Eschenmoser fragmentation and also served to protect the double bond during oxidation of the aryl ring. The final step of the synthesis was fragmentation of methyl ester (121) to afford alkyne (122) (Scheme 22).
Although the alkyne could be prepared from this synthesis, it did suffer from irreproducible yields as well as low enantiomeric excesses when the cyclisation step was attempted enantioselectively.

As a result another synthetic route was proposed (Scheme 23).\(^5^9\) It was anticipated that after formation of the dearomatised product (82), a Baeyer-Villiger oxidation would enable the formation of lactone (124) which could then be converted to the alkyne (129) by ring opening and elimination.

Deearomatising cyclisation using LDA produced the desired amide (82) and after Baeyer-Villiger oxidation lactone (124) was produced regioselectively. Hydrogenation of the double bond and reprotection of the amine as the Boc carbamate was followed by ring-opening of the lactone to afford (127). The trichloroacetic acid protecting group was necessary during the oxidation of the phenyl ring as the silyl protecting groups were found

---

Reagents: (a) 3-methoxybenzyl bromide, K₂CO₃, DMF, rt, 18 h, 95%; (b) 2,4-dimethoxybenzoyl chloride, Et₃N, CH₂Cl₂, rt, 18 h, 86%; (c) i LDA, DMPU, THF, 0 °C; ii 1M HCl, 64%; (d) i TFA, reflux, 1.5 h, quant. ii LDA, Boc-ON, THF, 0 °C, 5 h, 80%; (e) i Super-H, THF, 0 °C, rt, 24 h; ii PTSA, MeOH, rt, 1.5 h iiii Et₃SiH, BF₃, OEt₂, CH₂Cl₂, -78 °C, 2 h, 48%; (f) t-BuOOH, DBU, THF, 0 °C, 30 mins; (g) RuCl₃, NaIO₄, EtOAc/H₂O/CH₂N, 0 °C, 2 h, 42%; (h) mesitylsulfonyl hydrazine, EtOH, reflux, 4 h, 15%.

**Scheme 22: Eschenmoser fragmentation route**
to be labile under such conditions. The final steps of the synthesis were to include the reduction of lactam (127) and deprotection of the primary alcohol followed by conversion to alkyne (129). Though many conditions were attempted, the reduction and elimination reactions were both unsuccessful.\textsuperscript{59}

Scheme 23: Baeyer-Villiger route

\textbf{2.2 The Silicon mediated fragmentation route}

A successful route to the alkyne intermediate was eventually achieved through a silicon-mediated fragmentation. The retrosynthetic pathway (Scheme 24) includes many of the same steps used in the previously explored routes (Schemes 22 and 23).\textsuperscript{59} The final steps to the desired alkyne involve a Peterson type fragmentation of lactone (132) to form alkene (131) which is cleaved and followed by a homologation to the target compound.\textsuperscript{60}
This synthetic route was designed and optimised by post-doctoral researcher Dr. Gilles Lemière, and the enantiopure alkyne was obtained in 16 steps. Further material was made during the course of the project following the route originally described by Lemière.

Starting from commercially available cumylamine (83), benzamide (80) was made, followed by a dearomatising cyclisation mediated by chiral lithium amide (99) (Scheme 25). During the re-synthesis of the alkyne it was necessary to purify benzamide (80) under basic conditions to prevent cleavage of the cumyl group. The dearomatising cyclisation reaction could be increased up to a 5 gram scale compared to the previous 2.5 gram limit without any significant changes in yield or enantioselectivity (current yields in brackets, Scheme 25). In addition, the chiral amine could be recovered and after further purification used in subsequent cyclisations.

The subsequent steps were followed as described by Lemière. Silylcupration of enone (82) was performed with freshly distilled reagents using trimethylsilyl chloride as a trapping agent. The resulting silyl enol ether is a stable intermediate which can then be hydrolysed during work up with HCl to afford ketone (134) as a single diastereoisomer (Scheme 25). Removal of the cumyl group under acidic conditions and reprotection as Boc carbamate (135) was a necessary step for ruthenium catalysed oxidation of the phenyl ring. The resulting acid was then esterified to form the t-butyl ester (136) as this was found to be
more resistant under the subsequent reductive conditions than the corresponding methyl esters.

Reduction of lactam (136) proved to be the most challenging part of this synthetic route and in the past numerous attempts to do so failed under the different reaction conditions and reagent combinations tried by former PhD student Sedehizadeh. The lactam was eventually reduced using super hydride (LiEt₃BH) and boron trifluoride etherate in the presence of triethylsilane, although these conditions resulted in the concomitant reduction of the ketone. This was an unavoidable step, but was resolved through re-oxidation of the alcohol to ketone (137) with Dess-Martin periodinane.

Lactam reduction is carried out in two steps; firstly with super hydride to form an intermediate hemiaminal which is then further reduced using triethylsilane and boron trifluoride etherate. Purification of the hemiaminal was not possible by column chromatography so the crude reaction mixture was carried through to the next step. It was found that the order of addition of the reagents was an important factor; triethylsilane has to be added several minutes prior to the addition of the boron trifluoride etherate and these reagents subsequently added again after 30 minutes.

During the re-synthesis of the enantiopure alkyne this reaction was found to be irreproducible despite closely following the reaction conditions set out by Lemière. For this reason the enantiopure alkyne has not yet been successfully re-synthesised, however in Lemière’s previous work following a successful lactam reduction, a regioselective Baeyer-Villiger oxidation was performed affording lactone (138) as a single isomer (see Appendix 1. The selectivity is due to the presence of silicon which aids in stabilising the developing ß positive charge, thereby causing preferential migration. Ring-opening of lactone (138) was mediated by TBAF and the resulting acid was esterified as the t-butyl ester with Boc₂O. Ozonolysis of alkene (139) then furnished aldehyde (140).
The Seyferth-Gilbert homologation is a well known reaction used in the formation of alkynes from aldehydes.\textsuperscript{63} It offers a milder alternative to the Corey-Fuchs reaction and so can tolerate a wider range of functional groups. The mechanism proceeds similarly to the Horner-Wadsworth-Emmons reaction forming a diazoalkene which can then undergo $\alpha$-elimination followed by carbene rearrangement to give the alkyne (Scheme 26).
The Ohira-Bestmann reagent (141) (Scheme 27) is a modified version of the reagent used in the Seyferth-Gilbert homologation and is more suitable for sensitive substrates.\textsuperscript{64, 65} Using this reagent the dimethylphosphonodiazomethane (143) is formed \textit{in situ} (Scheme 27).

Homologation of aldehyde (140) to the target alkyne (144) was carried out using the Ohira-Bestmann reagent (141) (Scheme 28). Epimerisation at the C4 position was observed under standard reaction conditions with potassium carbonate at 0 °C. In order to avoid this sodium methoxide was used to form anion (143) at -78 °C prior to addition to aldehyde (140), and the target alkyne (144) was obtained in 89% yield as a single diastereoisomer (Scheme 28).\textsuperscript{66}
2.3 The model alkyne

In order to facilitate the development of reaction conditions for functionalisation of the alkyne, a model compound (148) which closely resembles the enantiopure alkyne (144) was made. The model substrate not only has the alkyne functionality but also the carbamate protecting group, which is an important factor for optimisation as previous attempts at functionalisation had failed due to the presence of this protecting group.\(^{58}\)

The model substrate (148) was designed and first synthesised by post-doctoral researcher Dr. Julie Toueg, and was prepared in three steps starting from commercially available N-Boc pyrrolidinone (145) (Scheme 29).\(^{58}\)

Enol ether (146) was formed after treatment of ketone (145) with the Ohira-Bestmann reagent (141) in methanol. This was followed by hydrolysis with trichloroacetic acid to furnish aldehyde (147) and in the final step the Ohira-Bestmann reagent (141) was used once more to afford the model alkyne (148).

![Scheme 29: Synthesis of model alkyne](image-url)
Repetition of the reaction conditions described by Toueg were largely unsuccessful and the route to the model alkyne (148) was found to be extremely capricious (observed yields in brackets, Scheme 29).

As a result attempts to improve the synthesis were carried out; the described synthesis does not involve purification of any of the intermediates. Purification after the first step was attempted but low yields of the enol ether (146) were consistently obtained. Likewise aldehyde (147) was also purified which required more care during column chromatography, nevertheless purification did nothing to improve the overall yields that were obtained.

Attempts to optimise the reaction through variation of the reaction conditions had little effect on the reaction. There is literature precedent for the use of Cs$_2$CO$_3$ for low yielding homologations, however this too did not have the desired effect and no improvement was observed.

Hydrolysis of the enol ether (146) was carried out with a 90% solution of formic acid with extended reaction times forming aldehyde (147), but again with no change in the yield. Enol ether (146) was also prepared through a Wittig olefination with (methoxymethyl)triphenylphosphonium chloride, however this method produced varied yields (Scheme 30). Hydrolysis of the enol ether (146) followed by homolagation with the Ohira-Bestmann reagent (141) formed the model alkyne (148) in 29% yield from the aldehyde.

\[ \text{Scheme 30: Wittig olefination of N-Boc pyrrolidinone} \]

The Corey-Fuchs reaction was also investigated as an alternative method of forming alkyne (148). In this case the yields were still disappointingly low as the alkyne was only obtained in 8% yield over 3 steps (Scheme 31).
Based on these results the method of forming the model alkyne (148) outlined by Toueg was used despite the low yield it afforded.\(^{58}\)

### 2.3.1 Altering the protecting group

At a later stage during the project it became necessary to change the protecting group as the carbamate group was incompatible with reaction conditions (Chapter 5, section 5.4.1).

The tosyl group offers extra stability under acidic reaction conditions (See Chapter 5, section 5.4.1) and unlike the carbamate group is stable to acidic and mild basic conditions. It can also be removed through reductive methods, or with sodium amalgam as demonstrated in the final stages of the total synthesis of isodomoic acid H.\(^{44},^{71}\) It was anticipated that protecting the amine as its N-tosyl derivative would result in improved yields during the preparation of the alkyne in addition to less complex NMR spectra.

As neither the free amine nor the N-tosyl pyrrolidinone were commercially available, this had to be prepared from N-Boc pyrrolidinone (145). However the first attempts to do so through deprotection of the ketone were unsuccessful. Isolation of the intermediate was difficult as the free amine (149) proved to be unstable, particularly during purification by column chromatography. A one-pot deprotection and re-protection reaction was then tried without prior purification of the free amine but had similar results (Scheme 32).
Scheme 32: Re-protection of N-Boc pyrrolidinone

As a result an alternate route had to be used, starting from N-Boc protected alkyne (148) which was first deprotected with TFA. Since purification of the free amine was still unsuccessful re-protection had to be carried out immediately. The N-tosyl protected model alkyne (152) was made in two steps from the N-Boc protected model (148) in 63% over two steps (Scheme 33).

Scheme 33: Synthesis of tosyl protected model alkyne
3 Synthesis of the side chains

Each isodomoic acid consists of a pyrrolidine core and an eight-membered carbon side chain in various geometrical arrangements. Isodomoic acids A and B share a common side chain as do isodomoic acid E, domoic acid and isodomoic acids D and F (Figure 11).

Figure 11: domoic acid and the isodomoic acids side chains
This chapter will discuss the preparation of the side chains of the isodomoic acids, which are to be coupled to the pyrrolidine core during the final stages of the synthesis.

### 3.1 Preparation of the alkenyl side chains

A retrosynthetic route to the alkenyl side chains of isodomoic acids E, D, F and domoic acid was proposed (Scheme 34), making use of the commercially available (S)-Roche ester (methyl (S)-(+)-3-hydroxy-2-methylpropionate) (156).

Reduction of ester (156) to aldehyde (155) would then provide an intermediate through which the side chains could be prepared. Wittig olefination was proposed to provide the Z alkene (153) required for isodomoic acids D and F, whilst a Takai olefination would furnish the corresponding E alkene (154) for isodomoic acid E and domoic acid.

The synthesis began with the protection of the hydroxyl group of (S)-Roche ester (156) as silyl ether (157). Partial reduction of the ester (157) to the aldehyde was attempted initially using DIBAI-H at -78 °C as outlined in a reported synthesis, but despite these precautions mixtures of the desired aldehyde (158) and the fully reduced product, alcohol (159) were observed (Scheme 35).
The two products were separable by column chromatography, but complete reduction of ester (157) to alcohol (159) followed by an oxidation to the desired aldehyde (158) was considered more straightforward. Accordingly, reduction was carried out using DIBAI-H at -40 °C affording alcohol (159) in 82%. Aldehyde (158) was obtained after oxidation of the alcohol; however oxidation under Swern oxidation conditions or with IBX afforded consistently low yields which were attributed to the volatility of the aldehyde (Scheme 36).\(^73\)

**Scheme 36: Alternate route to aldehyde**

3.1.1 **Wittig Olefination: Z-Alkene coupling partner**

The formation of Z alkene (160) was planned using Wittig olefination\(^74\) of aldehyde (158) with iodomethyltriphenylphosphonium iodide which in turn was prepared according to a literature procedure from triphenylphosphine and diiodomethane (Scheme 37).\(^75\)
Scheme 37: Wittig formation of Z-iodoalkene

Under these reaction conditions however, alkene (160) could only be obtained in moderate yields as a mixture of geometrical isomers even after column chromatography.

3.1.2 Takai olefination E-alkene coupling partner

The Takai olefination reaction has been used to form E alkenes from aldehydes using iodoform and chromium(II) salts (Figure 12).

Figure 12: Mechanism of Takai olefination

E-Iodoalkene (161) was obtained under these reaction conditions, however moderate yields and selectivities were observed using this method (Scheme 38).

Scheme 38: Takai olefination

Variation of the reaction conditions (Table 1) found that moderate improvements in the yield could be obtained when the reaction time was extended.
Table 1: Takai olefination of aldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time</th>
<th>Yield</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>E:Z</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>45</td>
<td>77:23</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>62</td>
<td>92:8</td>
</tr>
</tbody>
</table>

Change of protecting group

In an effort to improve the yields the protecting group was changed to the tert-butyl diphenylsilyl (TBDPS) group. Protection of the (S)-Roche ester (156) was carried out in a similar manner with the TBDPS group and aldehyde (164) was prepared under Swern oxidation conditions according to literature procedures (Scheme 39).\textsuperscript{78, 79} The yields obtained with the new protecting group were noticeably higher than with the previously used TBDMS group, suggesting that perhaps volatility may have been accountable for the low yields.

Similarly, DIBAl-H reduction of the TBDPS protected ester (162) resulted in a significant improvement in the isolated yield. Aldehyde (164) was then obtained in an improved 88% yield from alcohol (163) corresponding with literature reports (Scheme 39).\textsuperscript{78}
Scheme 39: Preparation of TBDPS protected aldehyde

Wittig olefination were performed several times on the different silyl protected aldehydes, however low yields and selectivity were still an evident problem (Scheme 40, Table 2).

Scheme 40: Wittig olefination of aldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting group</th>
<th>Yield %</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBDMS</td>
<td>25</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>TBDPS</td>
<td>34</td>
<td>87:13</td>
</tr>
</tbody>
</table>

*Z:E ratio measured from ^1^H NMR spectra
Similar results were observed with the Takai olefination and the new protecting group (Scheme 41, Table 3).

\[
\begin{array}{cccc}
RO & \overset{\text{a}}{\underset{\text{H}}{\longrightarrow}} & RO & \overset{\text{a}}{\underset{\text{H}}{\longrightarrow}} \\
158 & R = \text{TBDMS} & 161 & R = \text{TBDMS} \\
164 & R = \text{TBDPS} & 166 & R = \text{TBDPS}
\end{array}
\]

Reagents and conditions: (a) CrCl₂, CH₂Cl₂, dioxane, THF, 0 °C - rt, 5 h

Scheme 41: Takai olefination with different silyl protecting groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protecting group</th>
<th>Yield %</th>
<th>Selectivity E:Z*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBDMS</td>
<td>62</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>TBDPS</td>
<td>25</td>
<td>94:6</td>
</tr>
</tbody>
</table>

*E:Z ratio measured from ¹H NMR spectra

Both methods of olefination led to appreciable formation of the undesired isomers which were inseparable by column chromatography and the low yields obtained were unacceptable. For these reasons alternative methods of forming the iodoalkenes were sought.

### 3.2 An alternative intermediate

The preparation of alkenes from alkynes has already been seen within the project during the synthesis of the enantiopure alkyne for the pyrrolidine core of the isodomoic acids (Chapter 2). A similar strategy was therefore proposed for the synthesis of the coupling partners as an alkyne would be accessible from aldehyde (164) in a single step by
means of homologation. Further transformation of the alkyne would then form the required Z or E alkenes (Scheme 42).

![Diagram of the homologation process](attachment:homologation_diagram.png)

**Scheme 42: Alternative intermediate to side chains**

Homologation of aldehyde (164) was first tried with the Ohira-Bestmann reagent (141). This reagent had been previously used to form the enantiopure alkyne for the pyrrolidine core (Chapter 2, section 2.2) and in the synthesis of the model alkyne (148) (Chapter 2, section 2.3); surprisingly however this reagent produced poor results and the alkyne was not formed.

Based on this result, aldehyde (164) was subjected to other standard homologation reaction conditions. The Corey-Fuchs reaction is another well known way of preparing alkynes from aldehydes and can do so without the racemisation of stereogenic centres. Under these reaction conditions alkyne (169) was successfully formed in 64% yield (Scheme 43).

![Diagram of the Corey-Fuchs homologation process](attachment:corey_fuchs_diagram.png)

**Scheme 43: Corey-Fuchs homologation of TBDPS protected aldehyde**

- Reagents and conditions: (a) i. CBr₄, PPh₃, Zn, CH₂Cl₂, 0 °C - rt, 4 h, ii. n-BuLi, -78 °C, THF, 1 h, 64%
3.3 Coupling partner for isodomoic acid E and domoic acid

Functionalisation of the alkyne intermediate (169) to form the E alkene is necessary for the preparation of the side chains of isodomoic acid E and domoic acid (Scheme 44).

![Chemical structure](image)

Proposed steps: (a) deprotection, oxidation; (b) addition

X = halide

**Scheme 44: Proposed route to E alkene from alkyne intermediate**

*Hydrozirconation*

E alkenes can be prepared selectively through a hydrozirconation reaction using Schwartz’s reagent (Cp₂ZrHCl).⁸⁰ Treatment of the alkyne (169) with Schwartz’s reagent formed the E vinyl zirconium (170), which was quenched with iodine, forming the E-iodoalkene (171) as a single isomer (Scheme 45). This was then followed by removal of the silyl ether protecting group with TBAF and oxidation with Jones’ reagent forming the carboxylic acid in a modest 36% yield. Esterification with t-butanol then provided the t-butyl ester (172) coupling partner in six steps from the starting methyl ester (156) (Scheme 45).⁸¹
Scheme 45: Synthesis of E-iodoalkene coupling partner for domoic acid and isodomoic acid E

3.4 Coupling partner for isodomoic acids D and F

Methods of transforming alkyne intermediate (169) to the Z alkene (153) were then explored (Scheme 46).

Proposed steps: (a) deprotection, oxidation; (b) addition

\( X = \text{halide} \)

Scheme 46: Route to the Z alkene from intermediate alkyne

Hydroindination

One such method has been reported by Takami who have demonstrated a one step reduction of alkynes to Z alkenes (Scheme 47). Treatment of indium chloride with DIBAl-H forms a dichloroindium complex, HInCl₂ which is subsequently added to the
alkyne in the presence of a catalytic amount of triethylborane acting as a radical initiator. The resulting alkenylindium is then quenched with iodine to give the Z-iodoalkene.

\[
\text{DIBAI-H} + \text{InCl}_3 \\
\text{HInCl}_2 \quad \text{cat. Et}_3\text{B} \quad \text{THF, -78 °C} \\
\begin{array}{c}
\text{R} \quad \text{H} \\
\text{R} \quad \text{InCl}_3 \\
\end{array} \quad \text{I}_2 \\
\begin{array}{c}
\text{R} \quad \text{I} \\
\end{array}
\]

**Scheme 47: Hydroindination of terminal alkyne**

Alkyne (169) was subjected to the conditions outlined by Takami, but despite several attempts only the starting material was recovered (Scheme 48). Based on this lack of reactivity this reaction was not pursued any further.

\[
\begin{array}{c}
\text{TBDPSO} \quad \text{a} \\
\text{169} \\
\end{array} \quad \begin{array}{c}
\text{TBDPSO} \\
\text{165} \\
\end{array}
\]

Reagents and conditions: (a) InCl₃, DIBAIH, Et₃B, I₂, -78 °C

**Scheme 48: Attempted hydroindination of intermediate alkyne**

**Diimide reduction**

Another alternative that was investigated was the use of diimide reagent nitrobenzylsulfonylhydrazide (NBSH) (173) which is easily prepared from hydrazine monohydrate and o-nitrobenzylsulfonyl chloride (Scheme 49). NBSH is a mild reducing reagent making it attractive for substrates with sensitive functional groups. The diimide is generated after *in situ* elimination of o-nitrobenzenesulfinic acid in a polar solvent such as acetonitrile.
In order to form the required Z-iodoalkene, iodination of terminal alkyne (169) would have to be carried out prior to diimide reduction (Scheme 50).

![Scheme 49: Diimide formation from NBSH](image)

Reagents and conditions: (a) N$_2$H$_4$, H$_2$O, THF, -30 °C; (b) alkene substrate, Et$_3$N, MeCN

Scheme 50: Retrosynthesis of Z-iodoalkyne

The initial conversion of alkyne (169) to iodoalkyne (174) was carried out with NIS (Scheme 51). The iodoalkyne (174) was then treated with NBSH (173) affording a mixture of the Z-iodoalkene (165) and a by-product which proved difficult to separate by column chromatography. This was found to be the alkane (175) obtained from over-reduction of the product.

![Scheme 51: Diimide reduction](image)

Reagents and conditions: (a) NIS, AgNO$_3$, acetone, 2.5 h, rt, 88%; (b) NBSH (173) (1.65 eq), Et$_3$N, i-PrOH/THF, 32 h

In an effort to prevent formation of the alkane (175), the reaction was carried out using one equivalent of NBSH (173) and reducing the reaction time. In this case a 2:1 mixture of the desired alkene (165) and the starting iodoalkyne (174) was observed. As separation by column chromatography was difficult, deprotection of the crude mixture was
attempted using TBAF (Scheme 52). Unfortunately the pure product could still not be isolated which meant that this route to the Z-iodoalkene was not continued.

\[
\begin{array}{cccccccccc}
 & & & & & & & & & & \\
& & & & & & & & & & \\
& & & & & & & & & & \\
\text{TBDPSO} & & & & & & & & & & \text{HO-}
\end{array}
\]

Reagents and conditions: (a) TBAF, THF, 0 °C

**Scheme 52: Deprotection of mixture obtained from diimide reduction**

**Hydroboration**

Hydroboration of alkynes followed by protonolysis has also been reported to furnish Z-alkenes.\(^{84}\) Similar to the diimide reduction, halogenation of the terminal alkyne is required prior to reduction (Scheme 53).

\[
\begin{array}{cccccccccc}
R & \equiv & X & a & \rightarrow & R & \equiv & X & b & \rightarrow & R & \equiv & H
\end{array}
\]

X = halogen
Chx₂ = dicyclohexylborane

Reagents: (a) Chx₂BH; (b) AcOH

**Scheme 53: Hydroboration and protonolysis of iodoalkynes**

Hydroboration of iodoalkyne (174) was carried out with dicyclohexylborane followed by protonolysis of the boron substituted alkene intermediate with acetic acid (Scheme 54). Using this method Z-iodoalkene (176) was finally formed in 78%. The remaining steps of the synthesis were analogous to that of the E-iodoalkene (166), including deprotection of the silyl protecting group, oxidation of the primary alcohol to carboxylic acid (178) and finally esterification to afford the side chain (179) in six steps from the starting ester (156) (Scheme 54).\(^{81}\)
Scheme 54: Synthesis of Z-iodoalkene coupling partner for isodomoic acids F and D

3.5 Coupling partner for isodomoic acids A and B

The final side chain to be prepared was the allylic side chain of isodomoic acids A and B (Figure 13).

A retrosynthetic route was proposed starting from commercially available isoprene monoepoxide (183) (Scheme 55). The key steps of this route involved ring-opening of the epoxide with TiCl₄ to give an allylic alcohol which would first be protected and then undergo halogen exchange to the iodide under standard Finkelstein reaction conditions. The next steps would be analogous to those used for previous coupling partners; deprotection and oxidation of the primary alcohol, followed by esterification to form the desired ester (180) (Scheme 55).
The first step in this synthetic route however yielded unsatisfactory results. Conversion to the alcohol (184) was slow, and attempts to improve the yield, including varying reaction times and the amount of TiCl₄ resulted in even lower yields as well as the formation of other unknown by-products (Scheme 54). Attempts to carry out purification by column chromatography only resulted in degradation of the alcohol. Due to these initial results this route was also not pursued any further.

![Scheme 55: Proposed steps to allylic side chain](image1)

An alternate option from a literature reported route was investigated starting from commercially available methyl 2-bromopropionate (187). The key steps are shown retrosynthetically involving a Wittig olefination to form carboxylic acid (186) which is then reduced to the alcohol and lastly brominated to give the side chain (185) (Scheme 57).

![Scheme 56: Ring opening of isoprene monoepoxide with TiCl₄](image2)

Wittig olefination of ester (187) with glyoxylic monohydrate proceeded well and acid (186) was obtained without purification in 59% yield (Scheme 58). The acid was then...
reduced with borane dimethyl sulfide complex to give alcohol (188) which was brominated with phosphorous tribromide to afford the requisite side chain (185) as a single geometrical isomer in 67% yield.

\[ \begin{array}{cccc}
\text{Br} & \text{MeO}_2\text{C} & \text{O} & \text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} & \text{187} & \text{186} & \text{188} & \text{185} \\
\end{array} \]

Reagents and conditions: (a) i PPh₃, MeCN, 59 °C 18 h; ii OHC-CO₂H monohydrate, Et(i-Pr)₂, MeCN, 0 °C, rt, 36 h, 59%; (b) BH₃-Me₂S, THF, rt, 16 h, 57%; (c) PBr₃, CCl₄, 0 °C, 1 h, 67%.

**Scheme 58: Synthesis of methyl ester**

For the ease of a global deprotection at the end of the synthesis the corresponding t-butyl ester (189) was also synthesised and prepared in the same manner as the methyl analogue (185) (Scheme 58). In this case longer reaction times were necessary, especially during the Wittig olefination and poor yields were observed in all three steps. The remaining steps proceeded without problem although with similarly low yields, affording side chain (192) in a modest 13% yield (Scheme 59).

\[ \begin{array}{cccc}
\text{Br} & \text{t-BuO₂C} & \text{O} & \text{t-BuO₂C} \\
\text{CO}_2\text{t-Bu} & \text{189} & \text{190} & \text{191} & \text{192} \\
\end{array} \]

Reagents and conditions: (a) i PPh₃, MeCN, 59 °C 18 h; ii OHC-CO₂H monohydrate, Et(i-Pr)₂, MeCN, 0 °C, rt, 72 h, 33% (b) BH₃-Me₂S, THF, rt, 16 h, 68%; (c) PBr₃, CCl₄, 0 °C, 1 h, 13%.

**Scheme 59: Synthesis of coupling partner for isodomoic acids A and B**
4 Functionalisation of the alkyne intermediate to the E-alkene

Various methods of carbometalation have been investigated in attempts to functionalise model alkyne (148) though all with disappointing results. The failure of these methods was attributed to the presence of the carbamate group; however functionalisation was achieved through syn stannylcupration, a method which has been shown to be tolerable of the nitrogen protecting group.

Treatment of model alkyne (148) with Bu$_3$Sn(Bu)Cu(CN)Li$_2$ formed trans stannane (193), followed by methylation with methyl iodide to afford the trisubstituted alkyne (194) (Scheme 60).

\[
\text{CuCN} \xrightarrow{\text{a}} \text{Bu}_3\text{CuCNLi}_2 \\
\text{148} \xrightarrow{\text{b}} \left[ \text{Bu}_3\text{SnCu(Bu)CNLi}_2 \right] \xrightarrow{\text{c}} \text{194}
\]

Reagents and conditions: (a) BuLi, THF, 15 min., -78 °C; (b) Bu$_3$SnH, 10 min., -60 °C; (c) Mel, 2 h, 0 °C, 41%

Scheme 60: Syn stannylcupration of model alkyne

Palladium catalysed coupling between the methyl ester side chain of isodomoic acid B (185) with the newly functionalised alkyne (194) was then attempted (Scheme 61).

\[
\text{194} \xrightarrow{\text{MeO}_3\text{C}} \text{CO}_2\text{Me} \xrightarrow{\text{185}} \text{195}
\]

Scheme 61: Coupling reaction of functionalised model alkyne with allylic coupling partner
Table 3: Optimisation of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_2$, AsPh$_3$, THF, 60 °C</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>PdCl$_2$(CH$_3$CN)$_2$, DMF, rt</td>
<td>87</td>
</tr>
</tbody>
</table>

The coupled product was obtained in a moderate 68% yield with AsPh$_3$ (Table 3, Entry 1) however double bond isomerisation was observed under these conditions. Changing the reaction conditions and coupling with PdCl$_2$(CH$_3$CN)$_2$ at room temperature, however yielded the desired coupled product as a single isomer in 87% (Table 3, Entry 2).

The above conditions were repeated, coupling functionalised alkyne (194) with the side chain of isodomoic acid E (172). In order to facilitate NMR analysis the carbamate group was removed under acidic conditions, to afford amine (196) in 55% yield (Scheme 62).

![Scheme 62: Coupling reaction of functionalised model alkyne with E-iodoalkene coupling partner](image)

Reagents and conditions: (a) i 172, PdCl$_2$(CH$_3$CN)$_2$ (2 mol%), 18 h, DMF, rt, 55%; ii TFA, CH$_2$Cl$_2$, rt, 16 h, quant.

**4.1 Total synthesis of isodomoic acids B, E, F**

With successful functionalisation conditions established on the model alkyne this was now transferred to the enantiopure alkyne (144) (Scheme 63). Stannane (198) was prepared after syn stannylcupration of alkyne (144) followed by methylation.
Confirmation of the relative and absolute stereochemistry of the alkyne intermediate and the regiochemistry of the stannylcupration was assessed by protodestannylation and a global deprotection. Treatment of stannane (198) with TFA resulted in the formation of (–)-kainic acid (1), (Scheme 64).

Stille coupling of stannane (198) with the coupling partners (192), (172), and (179) afforded the isodomoic acids, which were deprotected under acidic conditions furnishing the three natural products as their TFA salts (Scheme 65). The free amine was regenerated after purification by ion exchange chromatography, and comparison of the $^1$H and $^{13}$C NMR of the synthetic products were found to be a match to the spectroscopic data in the literature (Tables 4-6).
Scheme 65: Total synthesis of isodoomic acids B, E, F

Reagents and conditions: (a) PdCl₂(CH₃CN)₂ (3 mol%), DMF, 50 °C; (b) TFA, CH₂Cl₂
Table 4: $^1$H (D$_2$O) Spectroscopic comparison of natural$^6$ and synthetic (–)-isodomoic acid B.$^{46}$

<table>
<thead>
<tr>
<th>Natural isodomoic acid B</th>
<th>TFA salt of synthetic isodomoic acid B</th>
<th>Synthetic neutralised isodomoic acid B</th>
</tr>
</thead>
<tbody>
<tr>
<td>(360 MHz)</td>
<td>(500 MHz)</td>
<td>(400 MHz)</td>
</tr>
<tr>
<td>6.70 (1H, t, $J = 7.0$, $H2'$)</td>
<td>6.77 (1H, t, $J = 7.5$)</td>
<td>6.73 (1H, t, $J = 7.5$)</td>
</tr>
<tr>
<td>5.35 (1H, t, $J = 7.0$, $H4'$)</td>
<td>5.29 (1H, t, $J = 7.1$)</td>
<td>5.23 (1H, t, $J = 7.1$)</td>
</tr>
<tr>
<td>4.04 (1H, d, $J = 3.5$, $H2$)</td>
<td>4.33 (1H, bs)</td>
<td>4.02 (1H, d, $J = 3.9$, )</td>
</tr>
<tr>
<td>3.60 (1H, dd, $J = 12.0$, 7.0, $H5$)</td>
<td>3.63 (1H, dd, $J = 11.8$, 7.1)</td>
<td>3.56 (1H, dd, $J = 12.1$, 7.5)</td>
</tr>
<tr>
<td>3.46 (1H, dd, $J = 12.0$, 12.0, $H5$)</td>
<td>3.48 (1H, dd, $J = 11.8$, 10.0)</td>
<td>3.42 (1H, dd, $J = 11.9$, 10.3)</td>
</tr>
<tr>
<td>2.99 (1H, dddd, $J = 8.6$, 7.5, 7.0, 3.5, $H3$)</td>
<td>3.20-3.12 (2H, m)</td>
<td>3.07-3.00 (2H, m)</td>
</tr>
<tr>
<td>2.91 (3H, m, $H4$ and $H3'$)</td>
<td>3.00 (2H, dd, $J = 7.2$, 7.2)</td>
<td>2.96 (2H, dd, $J = 7.5$, 7.5)</td>
</tr>
<tr>
<td>2.38 (2H, d, $J = 7.0$, $H6$)</td>
<td>2.55 (1H, dd, $J = 17.0$, 6.6)</td>
<td>2.43-2.40 (2H, m)</td>
</tr>
<tr>
<td></td>
<td>2.49 (1H, dd, $J = 17.0$, 6.9)</td>
<td></td>
</tr>
<tr>
<td>1.82 (3H, s, $H5'$-CH$_3$)</td>
<td>1.84 (3H, s)</td>
<td>1.80 (3H, s)</td>
</tr>
<tr>
<td>1.72 (3H, s, $H1'$-CH$_3$)</td>
<td>1.71 (3H, s)</td>
<td>1.67 (3H, s)</td>
</tr>
</tbody>
</table>
Table 5: $^1$H (D$_2$O) Spectroscopic comparison of natural and synthetic (−)-isodomoic acid E.$^{46}$

<table>
<thead>
<tr>
<th>Natural isodomoic acid E at pH 1.8 (300 MHz)</th>
<th>TFA salt of synthetic isodomoic acid E (400 MHz)</th>
<th>Synthetic neutralised isodomoic acid E (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.55 (1H, dd, $H3'$)</td>
<td>6.55 (1H, dd, $J = 15.2$, 10.5)</td>
<td>6.54 (1H, dd, $J = 15.1$, 10.5)</td>
</tr>
<tr>
<td>5.95 (1H, d, $H2'$)</td>
<td>5.95 (1H, d, $J = 10.5$)</td>
<td>5.94 (1H, d, $J = 10.6$)</td>
</tr>
<tr>
<td>5.87 (1H, dd, $H4'$)</td>
<td>5.87 (1H, dd, $J = 15.3$, 8.0)</td>
<td>5.87 (1H, dd, $J = 15.3$, 7.5)</td>
</tr>
<tr>
<td>4.36 (1H, d, $H2$)</td>
<td>4.32 (1H, d, $J = 4.0$)</td>
<td>4.14 (1H, bs)</td>
</tr>
<tr>
<td>3.72 (1H, dd, $H5$)</td>
<td>3.72 (1H, dd, $J = 12.0$, 7.2)</td>
<td>3.70 (1H, dd, $J = 11.3$, 7.1)</td>
</tr>
<tr>
<td>3.58 (1H, dd, $H5$)</td>
<td>3.57 (1H, dd, $J = 11.8$, 10.3)</td>
<td>3.55 (1H, dd, $J = 11.2$)</td>
</tr>
<tr>
<td>3.38 (1H, dq, $H5'$)</td>
<td>3.38 (1H, dq, $J = 7.1$, 7.1)</td>
<td>3.38 (1H, dq, $J = 7.1$, 7.1)</td>
</tr>
<tr>
<td>3.26 (1H, dddd, $H3$)</td>
<td>3.28-3.18 (2H, m)</td>
<td>3.12-3.20 (2H, m)</td>
</tr>
<tr>
<td>3.23 (1H, ddd, $H4$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.57 (1H, dd, $H6$)</td>
<td>2.57 (1H, dd, $J = 16.9$, 7.0)</td>
<td>2.48 (2H, d, $J = 6.9$)</td>
</tr>
<tr>
<td>2.53 (1H, dd, $H6$)</td>
<td>2.53 (1H, dd, $J = 17.0$, 7.0)</td>
<td></td>
</tr>
<tr>
<td>1.85 (3H, s, $H1'$-CH$_3$)</td>
<td>1.85 (3H, s)</td>
<td>1.85 (3H, s)</td>
</tr>
<tr>
<td>1.33 (3H, d, $H5'$-CH$_3$)</td>
<td>1.33 (3H, d, $J = 7.0$)</td>
<td>1.32 (3H, d, $J = 7.0$)</td>
</tr>
</tbody>
</table>
Table 6: $^1$H (D$_2$O) Spectroscopic comparison of natural and synthetic (–)-isodomoic acid F.\textsuperscript{46}

<table>
<thead>
<tr>
<th>Natural isodomoic acid F at pH = 1.6 (300 MHz)</th>
<th>TFA salt of synthetic isodomoic acid F (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.47 (1H, dd, $H3^\prime$)</td>
<td>6.47 (1H, dd, $J = 11.0, 11.0$)</td>
</tr>
<tr>
<td>6.19 (1H, d, $H2^\prime$)</td>
<td>6.19 (1H, bd $J = 11.0$)</td>
</tr>
<tr>
<td>5.60 (1H, dd, $H4^\prime$)</td>
<td>5.60 (1H, dd, $J = 10.2, 10.2$)</td>
</tr>
<tr>
<td>4.39 (1H, d, $H2$)</td>
<td>4.43 (1H, d, $J = 5.0$)</td>
</tr>
<tr>
<td>3.77 (1H, dd, $H5$)</td>
<td>3.78-3.71 (2H, m)</td>
</tr>
<tr>
<td>3.73 (1H, dq, $H5^\prime$)</td>
<td></td>
</tr>
<tr>
<td>3.63 (1H, dd, $H5$)</td>
<td>3.63 (1H, dd, $J = 1.9, 9.8$)</td>
</tr>
<tr>
<td>3.32 (1H, ddd, $H4$)</td>
<td>3.36-3.25 (2H, m)</td>
</tr>
<tr>
<td>3.27 (1H, dddd, $H3$)</td>
<td></td>
</tr>
<tr>
<td>2.63 (1H, dd, $H6$)</td>
<td>2.64 (1H, dd, $J = 17.0, 7.0$)</td>
</tr>
<tr>
<td>2.53 (1H, dd, $H6$)</td>
<td>2.53 (1H, dd, $J = 17.0, 7.0$)</td>
</tr>
<tr>
<td>1.87 (3H, s, $H1^\prime$-CH$_3$)</td>
<td>1.87 (3H, s)</td>
</tr>
<tr>
<td>1.33 (3H, d, $H5^\prime$-CH$_3$)</td>
<td>1.33 (3H, d, $J = 7.0$)</td>
</tr>
</tbody>
</table>

4.1.1 Pharmacology

Due to collaboration with a chemical neuroscience research group we were able to carry out bioanalysis of the synthetic isodomoic acids.\textsuperscript{90} Assessment of the binding affinities of the isodomoic acids were determined from 1 mg samples of the isodomoic acids at the three glutamate subtype receptors. The inhibition dissociation constant ($K_i$) of domoic acid, which possess a Z trisubstituted double bond and isodomoic acids B and E with $E$ trisubstituted double bond are compared in Table 7.
Isodomoic acids B and E display a greater binding affinity to the KA receptor compared to domoic acid, and the reverse is observed at the AMPA and NMDA receptors. This however this is not unexpected as most KA antagonists display reduced activity at the AMPA and NMDA receptors.\textsuperscript{19}

Table 7: Binding affinities at the ionotropic glutamate receptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding, IC\textsubscript{50}/K\textsubscript{i} in µM glutamate receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domoic acid</strong></td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Molecule" /></td>
<td>9</td>
</tr>
<tr>
<td><strong>Isodomoic acid B</strong></td>
<td><img src="image2" alt="Molecule" /></td>
</tr>
<tr>
<td><strong>Isodomoic acid E</strong></td>
<td><img src="image3" alt="Molecule" /></td>
</tr>
</tbody>
</table>

KA: Kainate receptor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDA: N-methyl-D-aspartate receptor
As discussed previously, the geometry of the C4 side chain has been shown to be an important factor in binding at the KA receptor (Chapter 1, section 1.1).\textsuperscript{16, 21} There should therefore be a difference in the pharmacological profile of the \textit{Z} trisubstituted alkenes and the \textit{E} trisubstituted alkenes.\textsuperscript{23} At this point the results obtained show that the \textit{E} trisubstituted isodomoic acids B and E share similar affinities at the kainate receptors.

In the same manner it would be equally interesting to determine if the \(K_i\)'s of the other \textit{Z} trisubstituted isodomoic acids, A and D would be comparable to that of domoic acid; and in addition, to examine if these results correlate with what has been already reported about the importance of double bond configuration.
5 Functionalisation of the alkyne intermediate to the Z alkene

Isodomoic acids A and D and domoic acid share a common trisubstituted Z double bond, and as such it was expected that functionalisation of alkyne intermediate (144) would establish the required geometry. This could then be followed by coupling to the requisite side chain and finally a global deprotection to form the three natural products (Scheme 66).

Scheme 66: Functionalisation of the alkyne intermediate to Z trisubstituted alkene

This chapter describes the research carried out towards functionalisation of the alkyne intermediate to form the Z trisubstituted alkene. Analogous to the steps taken to functionalise alkyne (144) for the synthesis of the E trisubstituted alkene (Chapter 4), model alkyne (148) was used as a test substrate (Figure 14).
5.1 Carbonylation

While the \( E \) trisubstituted alkene can be made from the alkyne through \( \text{syn} \) carbometallation methods, the \( Z \) trisubstituted alkene is more challenging and would require \( \text{anti} \) addition. For this reason installation of the side chain should be carried out prior to functionalisation of the alkyne (Scheme 67).

One approach that was investigated to form the trisubstituted alkene required was through an acetylenic aldehyde (207) which can be prepared from model alkyne (148) (Scheme 68). Conjugate addition to this aldehyde would lead to alkene (206) and following this, similar to Ohfune’s synthesis of domoic acid (Chapter 1, section 1.2), an olefination would then furnish domoic acid and isodomoic acid D.
The key step in this proposed route is the formation of a Z alkene from the acetylenic aldehyde. Although it is known for compounds of this type to undergo 1,2-addition it has also been shown that compounds similar to aldehyde (208) can undergo 1,4-addition with cuprates.\textsuperscript{91, 92} The reaction proceeds via an allene intermediate (209) which upon protonation forms the Z alkene (210) (Scheme 69).\textsuperscript{93, 94}

Aldehyde (207) was formed by initial deprotonation of terminal alkyne (148) with \textit{n}-BuLi followed by nucleophilic addition to DMF (Scheme 70). Despite high yields being reported for this type of reaction, low yields were obtained with this substrate, even with extra measures taken to ensure anhydrous conditions and incorporating the reverse extraction methods as described.\textsuperscript{95}
Scheme 70: Synthesis of acetylenic aldehyde

Conjugate addition was then conducted on a small scale and analysis of the crude mixture by mass spectrometry showed that the product (211) had been formed, although the compound could not be isolated by column chromatography (Scheme 71). Though this was promising, the low yield obtained in the previous step meant that this route would not be feasible and so this particular step was not examined any further.

Scheme 71: Conjugate addition to acetylenic aldehyde

As an alternative intermediate, alkynoates were investigated (Scheme 72). Conjugate addition to alkynoates is well preceded (more so than to alkynals) and the Z isomer can be obtained preferentially by varying the reaction conditions.95, 96

Scheme 72: Proposed synthesis of Z trisubstituted alkene from an alkynoate ester
The alkynoate was prepared and obtained in an acceptable 51% yield from model alkyne (148) by addition of methyl chloroformate after deprotonation with n-BuLi (Scheme 73).

![Scheme 73: Synthesis of alkynoate](image)

Another method of preparing alkynoates from terminal alkynes is through a palladium catalysed addition of carbon monoxide (Scheme 74). 97, 98

![Scheme 74: Palladium catalysed carbonylation of terminal alkynes](image)

The mechanism proposed by Yamamoto begins with a catalytic source of Pd(II), A (Figure 15). Methoxycarbonyl palladium species B is then formed from Pd(II) complex A and carbon monoxide. The resulting species then reacts with the terminal alkyne to form Pd(II) species C. Finally, a reductive elimination forms the alkynoate product and Pd(0) species D, which is oxidised back to Pd(II). 99

Stoichiometric Cu(II) salts are generally used as the oxidant, although other oxidising agents such as quinones have been used. The presence of a base is also required as an acid scavenger and to prevent the formation of side products. 97
Consequently alkynoate (214) was obtained in an improved yield of 61% through this palladium catalysed carbonylation reaction. Conjugate addition of methyl cuprate to alkynoate (214) however, afforded \( E \)-alkene (215) as a single double bond isomer in 82% yield (Scheme 75).³⁴

![Catalytic carbonylation mechanism](image)

**Figure 15: Catalytic carbonylation mechanism**

Reagents and conditions: (a) \( \text{PdCl}_2, \text{CuCl}_2, \text{CO}, \text{NaOAc}, \text{MeOH}, 6 \text{ h, rt, 61\%} \); (b) \( \text{Me}_2\text{CuLi}, \text{Et}_2\text{O}, 2.5 \text{ h, rt, 82\%} \)

**Scheme 75: Carbonylation and conjugate addition to model alkynoate**

It was found that addition of an excess of methyllithium led to a side product that was identified as alkene (216) (Scheme 76), which is formed as a result of addition of methyllithium to the ester group of alkene (215).
Scheme 76: *Formation of side product during carbonylation*

Examination of the alkene geometry by nOe experiments confirmed the presence of the *E* isomer presumably formed as the more stable product (Figure 16). When alkene proton Hₐ was irradiated there was no nOe signal between proton Hₐ and the methyl group as would be expected for the *Z* alkene. Instead irradiation of proton Hₐ had a positive nOe with the methine proton of the pyrrolidine ring Hₐ, indicating that the *E* isomer had been formed. Similarly irradiation of the alkene proton Hₖ of the side product (216) showed a positive nOe with the methine group Hₖ of the pyrrolidine ring as well as the methyl group confirming that the *E* isomer had been formed too (Figure 16).

**Figure 16: Diagnostic 2D nOe peaks**

Based on these results this particular route was not investigated any further.
5.2 Enyne cross-metathesis

Enyne cross metathesis involves the intermolecular addition of an alkene across an alkyne resulting in a conjugated diene. Cross metathesis of terminal alkynes and ether vinyl ether (EVE) has been reported by Castagnolo to form crotonaldehydes in the presence of CuSO₄ (Scheme 77). The reaction uses water as a co-solvent and can be completed in short reaction times under microwave irradiative conditions.

Initial metathesis mediated by Grubbs 2nd generation catalyst forms a diene (218), which can be considered as a masked aldehyde. The aldehyde is thus formed after hydrolysis of this enol ether by CuSO₄ which acts as a weak acid. Enol-keto equilibration then forms the observed aldehyde (220) (Scheme 77).

Scheme 77: Synthesis of crotonaldehydes through enyne cross metathesis

Mixtures of the diene and aldehyde were observed by Castagnolo, and in all cases a 2:1 mixture of E/Z isomers was obtained which can then be separated by standard chromatographic methods. Though not relevant in this case, the pure E isomer could be obtained through isomerisation of the Z aldehyde using catalytic iodine (Scheme 78).
Installation of the internal methyl group as well as establishing the correct alkene geometry could be achieved in a single step through this reaction and after separation of the isomers, lead to the framework required for domoic acid and isodomoic acid D (Scheme 79).

Accordingly model alkyne (148) was subjected to the described conditions and irradiated to 80 °C for two 10 minute runs (Scheme 80). Several products were observed by TLC analysis and purification had to be carried out by gravity column chromatography in order to obtain adequate separation of the products. Two products were isolated from the reaction mixture and were identified as aldehyde (222) and diene (223) in 39% and 16% yield respectively (Scheme 80). The \(^1\)H NMR spectrum of aldehyde (222) showed that two isomers were present in an 88:12 mixture which unfortunately could not be separated by column chromatography.
Determination of the double bond configuration was carried out by an nOe experiment. Irradiation of alkene proton H$_a$ showed a positive nOe with both methylene protons of the pyrrolidine ring, indicating that the E isomer was the major stereoisomer (Figure 17).

Figure 17: Diagnostic 2D nOe peaks observed for aldehyde

The methods discussed in this section have proved unsuitable in terms of procurement of the Z trisubstituted alkene. It is evident that the E alkene is formed preferentially but these reactions could however provide alternative ways of making the trisubstituted E alkene present in isodomoic acids B, E and F.
5.3 Hydrotitanation

In 1989 Kulinkovich reported the cyclopropanation of esters mediated by a titanium(II) complex 1 (Scheme 81). Complex 1 is formed from the reaction of titanium(IV) alkoxides with two equivalents of an alkyl Grignard reagent.

Scheme 81: Cyclopropanation of esters

The mechanism for formation of the titanium(II) complex 1 involves two successive transmetallation of the Grignard reagent followed by a fast disproportionation to give the active species complex 1 (Scheme 82). Complex 1 can be represented as either (A), a titanium(IV)-cyclopropane complex or (B), a (η²-olefin) titanium(II) complex.

Scheme 82: Formation of titanium complexes

This titanium(II) complex has been shown to mediate four types of reaction, (Figure 18) namely: 1) generation of titanium-alkyne complexes and their further manipulation; 2) generation of titanium allyl, propargyl or allenyl complexes, from allylic alcohols or propargylic alcohols; 3) intramolecular nucleophilic acyl substitution with unsaturated esters; 4) the formation of titanacyclic compounds from the inter- and intramolecular coupling of dienes, eynes and diynes with complex 1.
These reactions all have in common the coordination of an unsaturated carbon-carbon bond with complex 1 creating an alkene/alkyne-titanium complex that can be further used as a carbanion source.

It was the first of these reactions exploiting alkyne-titanium complexes that appeared potentially useful to the project. The formation of η²-alkyne titanium complexes from the reaction of Ti(Oi-Pr)₂ with internal alkynes was first reported by Sato. Complex 1, formed from i-PrMgX and titanium isopropoxide, undergoes a ligand exchange of the coordinated propene with the alkyne to form a η²-alkyne-titanium intermediate (226) (Scheme 83). This intermediate can be viewed as a vicinal vinylic dianion, free to react.
with electrophiles. These complexes can then be trapped, for example with deuterium oxide, forming alkenes with exclusively the Z configuration (Scheme 83).

![Scheme 83: Hydrotitanation of internal alkynes using complex 1](image)

One of the major advantages of this reaction is that the titanium-alkyne complex (226) is not only formed in situ but can then be quenched consecutively with two different electrophiles, such as aldehydes, ketones, imines, and halides (Scheme 84).

Titanium isoproponoxide and i-PrMgCl have been found to be the most suitable reagents for this reaction though other alkyl Grignards have also been investigated, but have often resulted in poorer yields. These reagents are inexpensive and commercially available and furthermore titanium(IV) alkoxides are non-toxic, making them practical as well as applicable to large-scale synthesis.

![Scheme 84: Formation of alkenes through hydrotitanation](image)

Excellent levels of regioselectivity can be attained through the presence of a directing group such as a silyl ether or stannyl group on the starting alkyne. These groups enable the preparation of highly regioselective di-, tri- and tetra-substituted alkenes from alkynes by placing the electrophile on the carbon β- to the directing group.

In addition to this, the use of s-BuOH allows protonation to take place exclusively on the carbon α to the silyl or stannyl group, leaving (β-silylalkenyl)titanium species (231) to react with the next electrophile (Scheme 85).
The targeted natural products would therefore be prepared in four steps from the alkyne intermediate using this method (Scheme 86). The proposed synthesis starts from model alkyne (148), which after formation of stannane (235) would undergo functionalisation through hydrotitanation to give trisubstituted alkene (234). A palladium catalysed coupling with the appropriate side chain would then provide the protected natural product.

This route would be quite advantageous as the key functionalisation step would involve the important stereoselective reduction and methylation in a single one pot reaction.

Attempts to make the starting compound, stannyl alkyne (235) were unsuccessful, (Scheme 87) varying reaction conditions (Table 8) and times still had no effect and only starting material was recovered.109
Although all methods that could have been used to form stannane (235) had not been fully exhausted, it was decided to use an alternative substrate such as silyl protected alkyne (236) (Scheme 88). This compound had already been synthesised by a previous member within the project and hydrotitanation has already been shown to work on silyl alkynes in the same manner.\textsuperscript{58, 108}

Alkyne (236) was prepared from trimethylsilyl chloride and model alkyne (148) in good yield and the silyl alkyne was then subjected to the conditions stated in the literature (Scheme 88).\textsuperscript{58, 108}

Initial \textsuperscript{1}H NMR analysis of the crude reaction mixture showed the presence of new vinylic signals and that reduction of the triple bond had occurred. The absence of a signal for the methyl group implied however, that the reaction had proceeded without

### Table 8: Stannane formation attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-BuLi (1.1); SnBu(_3)Cl (1.1)</td>
<td>40 min. -78°C, 1.5 h rt</td>
<td>148</td>
</tr>
<tr>
<td>2</td>
<td>(n)-BuLi (1.2); SnBu(_3)Cl (1.2)</td>
<td>1 h -78°C, 2 hr rt</td>
<td>148</td>
</tr>
<tr>
<td>3</td>
<td>(n)-BuLi (1.2); SnBu(_3)Cl (2.0)</td>
<td>1 h -78°C, 2 hr rt</td>
<td>148</td>
</tr>
<tr>
<td>4</td>
<td>EtMgBr (1.2); SnBu(_3)Cl (1.2)</td>
<td>1 h -78°C, 1 h rt</td>
<td>148</td>
</tr>
<tr>
<td>5</td>
<td>(t)-BuLi (2 eq); SnBu(_3)Cl (2.0)</td>
<td>1 h -78°C, 1 h rt</td>
<td>148</td>
</tr>
</tbody>
</table>
methylation, forming compound (237), and this was also confirmed by $^{13}$C NMR and mass spectroscopy. Furthermore the non-methylated product (237) was found to be inseparable from the starting material (236) with which it was isolated as a 1:1 mixture.

![Scheme 88: Hydrotitanation of silyl alkyne](image)

Reagents and conditions: (a) n-BuLi, Me$_3$SiCl, THF, -78 °C, 75%; (b) Ti(Oi-Pr)$_2$, t-PrMgCl 2 eq, t-BuOH, Mel or MeOTf

Reactions with primary alkyl halides are difficult as titanium species are weakly nucleophilic. A number of experiments were carried out in an effort to methylate the intermediate, including use of a stronger methylating agent such as methyl triflate, however the same result was observed (Scheme 88).

The Z configuration of compound (237) was supported by nOe experiments; irradiation of either of the alkene protons, H$_a$ or H$_b$ during an nOe experiment indicated no positive nOe with any of the protons in the pyrrolidine ring as would have been expected if the E isomer was present (Figure 19).

![Figure 19: Diagnostic 2D nOe peaks observed for silyl alkene](image)

Comparison of the vinylic coupling constants with cis vinylsilanes in the literature corroborated the presence of the Z isomer. Cis silyl alkenes usually have coupling constants between 13-16 Hz while trans vinyl silanes are range from 17-19 Hz. The coupling constant between proton H$_a$ and H$_b$ was found to be $J = 14$ Hz, suggesting that it is the cis isomer.
5.3.1 Other methods of hydrotitanation

Due to this lack of reactivity, methods of transmetallation were then explored. Sato has reported both catalytic and stoichiometric copper transmetallations with Knochel’s salt ((Li$_2$Cu(CN)Cl)$_2$) (242), allowing the reaction with allyl halides and other electrophiles such as halogens to take place (Scheme 89).$^{108}$

![Scheme 89: Synthetic applications of the alkenyl titanium reagent](image)

Though the transmetallation with primary alkyl halides have not been reported, it was hoped that the reactivity of the intermediate copper species would be similar to the cyanocuprate used to functionalise the intermediate alkyne to form the trisubstituted $E$-alkene (Scheme 90 and Chapter 4).$^{88}$
Scheme 90: Functionalisation of enantiopure alkyne to the E trisubstituted alkene

The reaction was repeated in the hope of methylating the intermediate titanium species through copper mediated transmetallation (Scheme 91).

Scheme 91: Hydrotitanation and transmetallation of silyl alkyne

Table 9: methylation attempts with Knochel’s salt

<table>
<thead>
<tr>
<th>Entry</th>
<th>Li₂Cu(CN)Cl₂ (eq)</th>
<th>Reagent (eq)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>MeI (1.1)</td>
<td>236</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>MeI (2.2)</td>
<td>237</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>MeI (1.1)</td>
<td>237</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>MeI (20)</td>
<td>237</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>MeOTf (20)</td>
<td>237</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>MeI (25)</td>
<td>237</td>
</tr>
<tr>
<td>7</td>
<td>1.1*</td>
<td>MeI (20)</td>
<td>237</td>
</tr>
</tbody>
</table>

Additive: 4:1 Li₂Cu(CN)Cl₂:DMPU

Initial attempts using a sub-stoichiometric amount of Knochel’s salt showed no reaction and only starting material was recovered (Table 9, Entry 1) and disappointingly,
the same result as before was observed with stoichiometric amounts of the cuprate. The addition of an excess of methyl iodide also had no effect, again resulting in the non-methylated product (237) (Entry 2). This product was still obtained when 25 equivalents of methyl iodide was used (Entry 6). As before, methylation with methyl triflate was attempted also using up to 20 equivalents, but again with the same results (Entries 4-6). These results were still obtained despite using new reagents and additional drying of the reaction solvents. Additives such as HMPA have been reported to enhance the rate of reactions with cuprates. DMPU was chosen as a less toxic option and added in a 4:1 mixture with Knochel’s salt (Entry 7). Despite this change the non-methylated product was formed once more.

In the past, the presence of the Boc carbamate group has proved to be problematic especially when trying to functionalise the alkyne. For this reason, further test reactions were carried out with silyl alkyne (247) to ascertain whether the protecting group was interfering with the reactivity. Alkyne (247) was prepared from commercially available oct-1-yne and subjected to the conditions described above using methyl iodide or methyl triflate as the methylating agent. The same results were observed and non-methylated product (248) was formed (Scheme 92).

![Scheme 92: Hydrotitanation of 1-trimethylsilyloct-1-yne](image)

Compound (250) was obtained in 32% yield during another test reaction with Knochel’s salt (242) and allyl bromide, showing that transmetallation had occurred (Scheme 93). It appears that the nature of the electrophile is important for substitution to occur and it has been suggested this substitution takes place via an S_N2’ type mechanism.
When alkyne (236) was subjected to the same transmetallation conditions with allyl bromide as the electrophile, no reaction occurred and starting material was recovered (Scheme 94).

This lack of reactivity led to the examination of different organocopper reagents for the methylation step. Gilman and mixed higher order cyanocuprates can undergo substitution with both primary and secondary electrophiles. Transmetallation was then attempted with cyanocuprate Me₂Cu(CN)Li₂ followed by the addition of methyl iodide. After 16 hours at room temperature no change was observed by TLC analysis or ¹H NMR. Heating the reaction mixture at reflux for several hours also had no effect on the reaction and the starting material was recovered (Scheme 95).

Scheme 93: **Hydrotitanation and transmetallation of 1-trimethylsilyloct-1-ynes**

Scheme 94: **Attempted hydrotitanation and transmetallation of silyl alkyne with allyl bromide**

Scheme 95: **Hydrotitanation and transmetallation with Me₂Cu(CN)Li₂**
Despite these disappointing results it was hoped that titanium-mediated chemistry would still allow functionalisation of the alkyne in some way. One avenue not yet examined was the use of a halogen as the electrophile (Scheme 96).

\[ \text{C}_4\text{H}_3 = \text{SiMe}_3 \xrightarrow{a} \text{C}_4\text{H}_3 \text{SiMe}_3 \xrightarrow{b} \text{C}_4\text{H}_3 \text{SiMe}_3 \]

Reagents and conditions: (a) Ti(i-OPr)_4, i-MgPrCl 2 eq, s-BuOH Et_2O, (b) I_2

**Scheme 96: Hydrotitanation and iodination of 1-trimethylsilyloct-1-yn**

Accordingly, silylalkyne (236) was subjected to these new conditions and the reaction monitored by TLC. Starting material was still present in the reaction mixture one hour after addition of the iodine, and no significant change was observed after 16 hours. The crude $^1$H NMR spectrum however did show a new vinylic signal and compound (253) was isolated in 23% yield after purification by column chromatography (Scheme 97).

\[ \text{H} \]

Reagents and conditions: (a) Ti(Oi-Pr)_4, i-PrMgCl 2 eq, s-BuOH, I_2, Et_2O, 23%

**Scheme 97: Hydrotitanation and iodination of silyl alkyne**

This was the first promising result observed using this methodology, but in order to attain the targeted compounds an extra step would have to be taken to install the methyl group, followed by a final palladium-catalysed coupling to the side chain (Scheme 98).

\[ \text{Me} \]

Possible route: (a) silylation; (b) hydrotitanation; (c) i methylation, ii side chain coupling, iii global deprotection

**Scheme 98: Proposed synthesis of Z trisubstituted alkene through hydrotitanation and iodination**
The low yields and incomplete reactions obtained through this chemistry made it capricious and unreliable. For these reasons hydrotitanation of model alkyne (148) was not explored any further.
5.4 **Iodo-deboronation**

Z-iodoalkenes can be accessed in a single step from *E*-vinyl haloboronate esters through isomerisation of the double bond (Scheme 99). These products can be obtained through an iodo-deboronation reaction and in this manner Z-iodoalkenes can be made with high levels of regioselectivity.

![Scheme 99: Iodo-deboronation of alkenyl haloboronate esters induced by iodine](image)

This transformation can be performed with iodine, although Whiting has shown iodine monochloride (ICl) to be a more potent reagent. Further development of this reaction by Whiting has shown that the isomerisation can be controlled by the order of addition of the reagents, ICl and NaOMe. Retention of the *E*-alkenyl boronate stereochemistry is observed when NaOMe is added first, followed by addition of ICl to afford the *E*-iodoalkene. Conversely, inversion of the double bond geometry occurs when ICl is added first (Scheme 100).

![Scheme 100: Regioselectivity of ICl induced iodo-deboronation](image)

Product formation is also dependent on the temperature so that the reaction can be tailored to afford either the iodide or chloride. Conducting the reaction at lower temperatures favours formation of the chloride, while at room temperature formation of the iodide was observed.

- 106 -
The proposed mechanism begins with the addition of ICl across the alkene double bond to form a stable iodonium ion (259) (Scheme 101). This is then opened by the chloride counter ion to give the thermodynamically favoured intermediate (262) with the chloride ion attacking away from the boron. At lower temperatures however, boron-chloride complex (260) is formed thereby allowing access to the Z chloride (266) after a base-mediated elimination. Alternatively intermediate (262) can undergo elimination to afford Z-iodoalkene (265) or interconversion to diastereoisomer (263) which after elimination forms E-iodoalkene (264).

Scheme 101: Mechanism of iodo- and chloro-deboronation

This ICl induced iodo-deboronation reaction has been used successfully towards the total synthesis of viridenomycin, and carried out selectively forming either the E-iodoalkene (271) or the Z-iodoalkene (268) as required (Scheme 102).
Scheme 102: Use of iodo-deboronation in total synthesis of viridenomycin

The boronate ester starting material can be prepared by treatment of terminal alkynes with boron tribromide (BBr₃). The intermediate bromoborane (273) is then trapped in situ with pinacol to form the boronate ester (274) with high selectivity (Scheme 103).¹²³

\[ \begin{align*}
\text{272} & \xrightarrow{a} \text{273} & \text{274} \\
\text{Br} & \quad \text{H} & \quad \text{B(pin)} \\
& \quad \text{BBr₂} & \quad > 98 \% \\
\end{align*} \]

Reagents and conditions: (a) BBr₃ 1.1 eq. -78 °C to rt, 2 h; (b) pinacol 1.2 eq. -78 °C to rt, 1 h

Scheme 103: Synthesis of boronate esters

This approach had been briefly explored within the group by Toueg, in the hope of forming the trisubstituted E-alkene for isodomoic acids B, E and F from haloborated derivative (275).⁵⁸ Toueg’s strategy was to subsequently carry out methylation though
Negishi coupling with MeZnCl followed by Suzuki coupling to the side chains (Scheme 104).

Scheme 104: Previously proposed work: sequential and selective functionalisation of bromovinylboronate

An attempt to form the boronate ester (282) followed by a Negishi coupling with MeZnCl and allyl bromide were unsuccessful and the coupled product (283) was not isolated (Scheme 105). Moreover, the acidic reaction conditions of the first step resulted in removal of the N-Boc protecting group. Despite this, new allylic signals were observed in the $^1$H NMR spectrum of the crude reaction mixture.

Toueg’s initial result with this reaction has prompted our recent investigation into this methodology and to begin with a more robust protecting group would need to be
employed to undergo the first step. Whiting had experienced problems with the N-Boc group during an iodo-deboronation in a previous total synthesis (Scheme 106); they too saw cleavage of the carbamate protecting group under the reaction conditions.\textsuperscript{124}

![Scheme 106](image)

**Scheme 106**: Unsuccessful iodo-deboronation of N-Boc protected amine

The use of ICl has had some precedent in the synthesis of the isodomoic acids (Chapter 1, section 1.3.1). Denmark has successfully used this reagent to carry out an iodo-desilylation of silane (63) during the total synthesis of isodomoic acid H (Scheme 107) where complete double bond inversion was observed affording the Z-iodoalkene (66) in 86% yield.\textsuperscript{44}

![Scheme 107](image)

**Scheme 107**: ICl mediated Iodo-desilylation in the synthesis of isodomoic acid H

### 5.4.1 Haloboration

A pre-emptive change of the protecting group appeared to be a sensible measure before the next steps could be taken. Performing a re-protection at this stage is not particularly step efficient and would pose a problem during the route to the enantiopure alkyne intermediate (144). However as these reactions were to be carried out on model alkyne (152) this was not considered to be an immediate problem.
The strategy was to form boronate ester (289) after haloboration of the N-tosyl protected alkyne (152) (Scheme 108). Iodo-deboronation of ester (289) would form dihalogenated alkene (287) which would undergo initial palladium-catalysed coupling at the more reactive terminal halide to the side chain followed by a second coupling to install the internal methyl group.125 Alternatively initial methylation of the boronate ester (287) followed by iodo-deboronation would provide iodide (288) which could then undergo coupling to the appropriate side chain. A global deprotection would then furnish the natural product (Scheme 108).

![Scheme 108: Retrosynthetic synthesis of Z trisubstituted alkenes through haloboration and iodo-deboronation](image)

Proposed steps: (a) i Pd coupling, ii deprotection; (b) iodo-deboronation (c) i methylation, ii iodo-deboronation (d) haloboration

Changing the protecting group was carried out as discussed earlier (Chapter 2, section 2.3.1) and haloboration of the tosyl protected model alkyne (152) was attempted. Repetition of the conditions used by Toueg afforded no product and only starting material was recovered from these reactions (Scheme 109).58

![Scheme 109: Haloboration of model alkyne](image)

Reagents and conditions: (a) i BBr₃, CH₂Cl₂, -78 C - rt; ii i-PrOH, rt
Based on this lack of reactivity, pinacol was used as the trapping agent as hindered boronate esters are reportedly better for iodo-deboronation.\textsuperscript{122} However this too was problematic as attempts to form the boronate ester were difficult. Analysis of the $^1$H NMR spectrum and mass spectrometry of the crude reaction mixture indicated the presence of the desired boronate ester (291) as well as a side product in a 1:1 ratio identified as terminal alkene (292), along with a small amount of the starting alkyne (152) present indicating that the reaction had reached completion (Scheme 110).

![Scheme 110: Haloboration of model alkyne](image)

The possible cause of this alkene side product was de-boronation of the boronate ester product (291) under the acidic reaction conditions, and so a basic work-up and purification were employed. Despite these precautions alkene (292) was still present, so preparation of the boronate ester via the boronic acid (294) was attempted (Scheme 111 and Table 10, Entry 3) resulting in a slight improvement in the amount of alkene (292) present in the $^1$H NMR spectrum of the crude reaction mixture.\textsuperscript{126}
A test reaction with octyne was carried out to investigate whether the alkene formation was substrate specific, but even in this case the starting alkyne (246) was still present along with the alkene side product (296) (Scheme 112).

Reagents and conditions: (a) BBr₃ (1 M in CH₂Cl₂) 2 eq, -78 °C, 1 h; rt 1 h, pinacol, 3 eq, rt, 1.5 h CH₂Cl₂

Scheme 112: Haloboration of oct-1-yne

A second test reaction was carried out on the crude mixture in the hope of separating the two compounds after treatment with ICl. However, mass spectrometry of the crude reaction mixture indicated that the starting materials were still present (Scheme 113).
Following these results various reaction conditions were tried in an effort to reduce the formation of the alkene side product (292) (Scheme 114, Table 10).

**Scheme 113: Attempted iodo-deboronation reaction**

**Scheme 114: Attempted haloboration of model alkyne**
<table>
<thead>
<tr>
<th>Entry</th>
<th>BBr$_3$ (eq)</th>
<th>Reaction time after addition (h)</th>
<th>Pinacol (eq)</th>
<th>Reaction time after addition (h)</th>
<th>Ratio of products$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1$^b$</td>
<td>2</td>
<td>1.2</td>
<td>1</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>1.1$^b$</td>
<td>2</td>
<td>1.2</td>
<td>4</td>
<td>67:33</td>
</tr>
<tr>
<td>3</td>
<td>1.0$^b$</td>
<td>0.25</td>
<td>1.1</td>
<td>16</td>
<td>62:38</td>
</tr>
<tr>
<td>4</td>
<td>1.1$^b$</td>
<td>2</td>
<td>1.2</td>
<td>1$^c$</td>
<td>81:19</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
<td>1$^c$</td>
<td>71:29</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>1.5</td>
<td>3</td>
<td>1$^c$</td>
<td>75:25</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.5</td>
<td>3.5</td>
<td>1$^c$</td>
<td>98:2</td>
</tr>
<tr>
<td>8</td>
<td>1.5$^b$</td>
<td>2</td>
<td>3.5</td>
<td>16$^c$</td>
<td>78:22</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2</td>
<td>3.5</td>
<td>1.5$^b$</td>
<td>99:1</td>
</tr>
</tbody>
</table>

$^a$ determined from $^1$H NMR spectrum of crude reaction mixture; $^b$ 1 M solution of BBr$_3$; $^c$ basic quench with a saturated aqueous solution of NaHCO$_3$

Lowering the reaction temperature after addition of boron tribromide as well as extending the reaction time after the addition of pinacol to 4 hours did have a positive effect on the product to side product ratio (Entry 2). Extending the reaction time to 16 hours after addition of pinacol had no significant change (Entry 3) though a significant decrease in side-product formation was observed when an excess of pinacol was used (Entries 7-8), with 3.5 equivalents of pinacol providing the best result (Entry 9).

Boron tribromide proved to be very unstable despite extra precautions being taken to store the reagent. Molar solutions of the reagent were significantly easier and safer to handle and so were used in preference.

Analysis of the reaction by $^1$H NMR spectroscopy after addition of boron tribromide still showed presence of the alkene (292) (89:11 dibromoborane:alkene)
After addition of pinacol only the alkene peak of the product at 5.90 ppm could be observed in the $^1$H NMR spectrum of the crude reaction mixture yet, disappointingly, no product was isolated after purification.

The remaining problem was the persistence of the starting alkyne (152) in the reaction mixture. Attempts to separate it from the product boronate ester through column chromatography were unsuccessful. TLC analysis showed that the starting alkyne and the product had very similar $R_f$ values which meant that the pure boronate ester could not be isolated.

Refluxing the reaction mixture after addition of boron tribromide still showed the presence of the starting material (152) in the $^1$H NMR spectrum. The addition of 3 equivalents of boron tribromide followed by a further 2 equivalents after 1 hour resulted in the formation of a second side product identified as dibromide (297) (Scheme 116). This was presumably caused by bromination of alkyne (152) from the excess boron tribromide in the reaction mixture.

The trans configuration of dibromide (297) was later confirmed by comparison with the same product that was synthesised during another part of the project (see Chapter 5, section 5.7.1, Scheme 135).
The results obtained thus far were particularly promising but do require further optimisation of the reaction conditions. Further work would include formation and isolation of the boronate ester before the aforementioned iodo-deboronation step which is integral for functionalisation of the alkyne.
5.5 *Palladium catalysed chemistry*

While some methods of palladium catalysed chemistry such as carbomagnesiation and Negishii coupling had already been explored by previous group members these had been relatively unsuccessful.\(^{58}\) Other means of palladium catalysed coupling however had not been investigated and some of the efforts to further explore this area will be discussed in the following section.

5.5.1 *Dihalogenated alkenes*

The terminal halide of 1,2-dihalogenated alkenes has been shown to be more reactive thereby allowing selective coupling to this position (Scheme 117).\(^{125, 127, 128}\)

**Scheme 117**: *Reported palladium catalysed coupling reactions with 1,2-dihalogenated alkenes*
This methodology had been briefly explored by other group members, attempting to selectively carry out two consecutive coupling reactions by exploiting the difference in reactivity of the two halides; allowing coupling of the side chain first, followed by methylation (Scheme 118).\(^{58}\)

\[\text{Scheme 118: Proposed functionalisation of dihalogenated alkene}\]

Unfortunately the dihalogenated alkene was found to be unreactive under these reaction conditions; an issue that was later attributed to the presence of the carbamate protecting group.

### 5.6 Stille coupling

Dibromide (312) was prepared in good yield after treatment of model alkyne (148) with pyridinium tribromide (Scheme 119).\(^{58}\)

\[\text{Scheme 119: Preparation of dibromoalkene derivative}\]
Stille coupling of dibromide (312) with vinyl stannane was attempted, and surprisingly enyne (313) was formed as a result of Sonogashira coupling instead of the expected alkene (314) (Scheme 120). Enyne (313) is presumably formed after elimination to the alkyne followed by Sonogashira coupling with vinyl stannane.

\[
\text{Scheme 120: Stille coupling of dibromoalkene}
\]

This reaction was repeated using model alkyne (148) as the substrate, and the same result was obtained under identical reaction conditions, again forming enyne (313) (Scheme 121). This reactivity had been observed previously and highlights one of the problems associated with coupling to 1,2-dihalogenated systems.

\[
\text{Scheme 121: Sonogashira coupling with model alkyne}
\]

Since this particular mode of palladium catalysed chemistry did not provide the expected result, other reactions were then investigated.

5.7 **Suzuki coupling**

Suzuki coupling appears to be a more viable option in comparison to previous methods which were found to be incompatible with the \(N\)-carbamate protecting group.\textsuperscript{58}
Experiments were carried out in order to ascertain firstly whether the dibromide (312) would react under Suzuki reaction conditions and more importantly whether it could be performed in a selective manner. An initial test reaction with phenyl boronic acid and dibromide (312) yielded an unusual result, and bis coupled product (315) was obtained in 17% yield (Scheme 122).

Scheme 122: Suzuki coupling with dibromoalkene

Further attempts to make the mono coupled product (316) were unsuccessful despite variation of the reaction conditions. Furthermore the bis-coupled product (315) could only be formed in low yields, due to poor conversion of the starting dibromide (312). This result helps to exclude a proposed route suggested during the haloboration work in the previous section (Chapter 5, section 5.4.1, Scheme 108) as a selective coupling to a dihalogenated alkene would not be possible. However this unexpected result prompted further research into the reactivity of these compounds, in particular the use of Suzuki type reaction conditions for coupling.

5.7.1 Potassium alkyl and vinyl trifluoroborates

Organotrifluoroborates present a useful alternative to the boronate esters and boronic acids. These compounds have expanded the versatility of the Suzuki coupling reaction to include use of sp\(^2\) and sp\(^3\) coupling partners.\(^{129}\) The trifluoroborate essentially acts as a protected boronic acid which is hydrolysed during the reaction to the reactive boronic acid which can then proceed following the usual catalytic cycle (Scheme 123).\(^{130, 131}\)
These trifluoroborates are both air and moisture stable, and easily prepared in good yields. The reactions can be carried out in an aqueous or organic medium and can tolerate a variety of functional groups including esters and silyl ethers.\textsuperscript{130, 132} Molander has recently shown that Suzuki-Miyaura cross coupling reactions can be carried out with alkenyl and alkyl trifluoroborates, and more importantly, these reactions can be used to form various trisubstituted alkenes in a one-pot reaction, requiring only a change of catalyst and an elevation in temperature (Scheme 124).\textsuperscript{132}

These trifluoroborates are both air and moisture stable, and easily prepared in good yields. The reactions can be carried out in an aqueous or organic medium and can tolerate a variety of functional groups including esters and silyl ethers.\textsuperscript{130, 132} Molander has recently shown that Suzuki-Miyaura cross coupling reactions can be carried out with alkenyl and alkyl trifluoroborates, and more importantly, these reactions can be used to form various trisubstituted alkenes in a one-pot reaction, requiring only a change of catalyst and an elevation in temperature (Scheme 124).\textsuperscript{132}

This methodology would involve a simple one-pot reaction starting from dibromide (312) leading directly to the protected isodomoic acid. Global deprotection would conclude
the total synthesis and furnish the natural products in a very step economic fashion (Scheme 125).

![Scheme 125: Proposed synthetic route to the Z trisubstituted isodomoic acids](image)

Preparation of the *trans* trifluoroborate coupling partner can be carried out through the haloboration of alkynes (Scheme 126) as described in the literature.\(^{133}\)

![Scheme 126: Preparation of trans vinyl trifluoroborates](image)

Preparation of the corresponding *cis* isomers has not been demonstrated in the literature, however a probable route to the *Z* alkenyl trifluoroborate would stem from the previously prepared *Z*-iodoalkene (321) (Chapter 3 section 3.4, Scheme 54).\(^{81}\) Borylation of the organolithium or the Grignard would then provide access to the trifluoroborate. An analogous route can be proposed for preparation of the allylic trifluoroborate starting from bromide (324) (Scheme 127).

![Scheme 127: Proposed synthetic route to the trifluoroborate coupling partners](image)
Test reactions

Ascertaining the reactivity of dibromide (312) with the trifluoroborates was the first concern. For this reason initial reactions were carried out using potassium trans oct-1-enyl trifluoroborate (327). This was prepared after haloboration of oct-1-yne then treatment of the resulting bromoborane with potassium hydrogen fluoride (Scheme 128).\(^{133}\)

\[
\begin{align*}
\text{C}_9\text{H}_{13} & \quad \text{a} \quad \text{BF}_3\text{K} \\
\text{C}_6\text{H}_{13} & \\
246 & \quad 327
\end{align*}
\]

Reagents and conditions: (a) i BHBr\(_2\)-SMes\(_2\), CH\(_2\)Cl\(_2\); ii KHF\(_2\), Et\(_2\)O/H\(_2\)O, 85%

Scheme 128: Preparation of trans oct-1-enyl trifluoroborate

Potassium methyltrifluoroborate was prepared from trimethyl boroxine and potassium hydrogen fluoride according to literature procedures (Scheme 129).\(^{134}\)

\[
\begin{align*}
\text{O}^- & \quad \text{B} & \quad \text{O}^- \\
\text{B} & \quad \text{O}^- & \quad \text{B} \\
\text{a} & \\
\text{CH}_3\text{BF}_3\text{K} & \\
328
\end{align*}
\]

Reagents and conditions: (a) KHF\(_2\), MeCN/H\(_2\)O, 0 °C - rt, 77%

Scheme 129: Preparation of potassium methyltrifluoroborate

The first reaction carried out with potassium trans oct-1-enyl trifluoroborate (327) and with MeBF\(_3\)K (328) showed that a reaction had occurred, but the product did not correspond to the expected product (330). Mass spectrometry indicated that the mixture contained alkene (329) as well as the unreacted starting material (Scheme 130).

\[
\begin{align*}
\text{Br} & \quad \text{a} \quad \text{Boc} & \quad \text{Br} \\
\text{Br} & \quad \text{a} \quad \text{C}_6\text{H}_{13} & \quad \text{Boc} \\
\text{Boc} & \quad \text{Boc} & \quad \text{C}_6\text{H}_{13} \\
312 & \quad 329 & \quad 330
\end{align*}
\]

Reagents and conditions: (a) i (327), Pd(PPh\(_3\))\(_4\), C\(_6\)H\(_5\)CO\(_2\), 60 °C; ii (328), Pd(dppf).CH\(_2\)Cl\(_2\), C\(_6\)H\(_5\)CO\(_2\), 90 °C, toluene/H\(_2\)O

Scheme 130: Suzuki coupling of dibromoalkene with trifluoroborates

- 124 -
In order to explore the transformation in more detail, reactions were carried out using only potassium trans oct-1-enyl trifluoroborate (327) (Scheme 131, Table 11). It was anticipated that the bis(alkenyl) product (331) or bromide (332) would be formed. Surprisingly neither product was formed, and $^1$H NMR and mass spectrometry indicated that alkene (329) was present. Unfortunately purification by column chromatography was problematic and alkene (329) could not be isolated. Table 11 shows some of the attempts to carry out this coupling reaction.

![Reaction diagram]

Reagents and conditions: (a) (327), Pd(PPh$_3$)$_4$ (7 mol%), Cs$_2$CO$_3$ 3 eq, toluene/H$_2$O

**Scheme 131: Palladium catalysed coupling with potassium trans oct-1-enyl trifluoroborate**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature °C</th>
<th>Time h</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>2</td>
<td>329$^a$</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>4.5</td>
<td>329</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>1.5-16</td>
<td>329$^b$</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>16</td>
<td>329</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>16*</td>
<td>329</td>
</tr>
</tbody>
</table>

$^*$degassed solvents using ultrasonic bath under vacuum; $^a$ trace product; $^b$ starting material (312) present

The first reaction under these conditions showed that small amounts of (329) had been formed after 2 hours (Entry 1). The reaction time was then lengthened (Entry 2) and (329) was identified as the major product. Monitoring the reaction by TLC analysis...
indicated that starting material was still present after 2 hours, though the appearance of a new product was observed when the reaction was left for longer. The reaction was continued for 16 hours at 65 °C, without further change and alkene (329) was again observed (Entry 3). Further variation of reaction conditions such as extending the reaction times and higher temperatures (Entries 4 and 5) still had no effect on the reaction. Extra precautions taken to degas the solvents before use also had no significant effect (Entry 5).

A similar reaction was carried out using potassium methyltrifluoroborate (328) (Scheme 132) as the coupling partner, however in this case there was no reaction and only starting material (312) was recovered despite varied reaction conditions.

![Scheme 132: Suzuki coupling with potassium methyltrifluoroborate](image)

Methylation of this substrate continues to be a recurring problem within the project and this methodology too appears to be unproductive.

**Alternative catalysts**

Until this point the catalysts used for this reaction had been prescribed by literature reports, but due to the lack of reactivity with potassium methyltrifluoroborate, more reactive catalysts were sought. Johnson Matthey catalyst Pd-132 (PdCl$_2$(amphos)$_2$) (Figure 20), is known to work for challenging couplings and with low catalysts loadings. This catalyst has also been used in a number of Suzuki reactions and very recently with alkyltrifluoroborates.

![Figure 20: Pd-132 catalyst](image)
Methylation with potassium methyltrifluoroborate (328) and 1 mol% of Pd-132 was attempted but unfortunately had the same result and again only starting material was recovered (Scheme 133).

Scheme 133: Methylation with Pd-132

An analogous reaction was repeated with trans oct-1-enyl trifluoroborate (327) using 1 mol% of Pd-132 but also resulted in alkene product (329). It was found that raising the catalyst loading to 2 mol% resulted in formation of alkyne (335) through Sonogashira coupling (Scheme 134).

Scheme 134: Suzuki coupling with potassium trans oct-1-enyl trifluoroborate

An alternate protecting group: tosyl amide

The decision to alter the protecting group was due to the complex NMR spectra caused by the carbamate group and also to potentially aid in purification and isolation of the products. Tosyl protected dibromide (297) can be accessed in two ways; either from the tosyl protected alkyne (152) after bromination, or alternatively deprotection of the Boc protected dibromide (312) followed by re-protection (Scheme 135).
Scheme 135: Synthesis of tosyl protected dibromoalkene

The same reaction conditions were thus repeated on the newly protected dibromide (297), however with no change in the result as only alkene (336) was observed (Scheme 136). Table 12 shows the reaction conditions that were tried.

Scheme 136: Suzuki coupling of dibromoalkene and trans oct-1-yl trifluoroborate
Table 12: Coupling reactions of dibromoalkene 297 with trans oct-1-enyl trifluoroborate (327)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-132 mol%</th>
<th>Temperature °C</th>
<th>Time h</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>90</td>
<td>16</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>90</td>
<td>16</td>
<td>33:67</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>90-100*</td>
<td>22</td>
<td>17:83</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>100</td>
<td>16</td>
<td>20:80</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>110</td>
<td>16</td>
<td>53:47</td>
</tr>
</tbody>
</table>

*16 h at 90 °C then 6 h at 100 °C; 297:336 determined from crude ¹H NMR

These attempts still led to the predominant formation of alkene (336). A catalyst loading of 0.5 mol% Pd-132 had no effect and only starting material was recovered (Entry 1). Using 1 mol% of Pd-132, formation of compound (336) was observed but with starting material still present. The same was observed with an increase in temperature and lengthening the reaction time (Entry 3). In comparison to the carbamate protected amide (312), using a higher catalyst loading did not result in formation of an alkyne, but the alkene (336) and starting material (297) were still present in almost equal quantities in the ¹H NMR spectrum of the crude reaction mixture (Entry 5). Unfortunately the change of protecting group has had no effect on the purification and despite using gravity column chromatography, impure products were still obtained.

A reaction was carried out at reflux using 1 mol% of Pd-132 and monitored by ¹H NMR by taking samples of the crude reaction mixture at 6 hour intervals for 42 hours, but this also had no significant change in result.

To conclude, while the coupling of a vinyl trifluoroborate to our substrate is a promising start, this result is hindered by the lack of reactivity during the methylation step as well as the inability to isolate any of the reaction products. Furthermore the debromination that occurs during the reaction would not allow us to use this particular methodology in reaching the target compounds.

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5.8 Further work

In conclusion, this thesis describes the first total synthesis of three members of the kainoid family; isodomoic acids B, E and F using a stereodivergent route from an enantiopure alkyne intermediate.

It is anticipated that once the required trisubstituted Z double bond is successfully attained from this enantiopure intermediate, synthesis of the remaining isomers can be completed.

5.8.1 Functionalisation of the alkyne intermediate

Functionalisation of alkyne (144) remains the main objective of the project and formation of the Z trisubstituted double bond is required in order to reach the targeted natural products (Scheme 137).

The most promising means of achieving this appears to be through haloboration/iodo-deboronation as discussed earlier (Chapter 5, section 5.4), however as the boronate ester could not be isolated further investigation and optimisation is needed (Scheme 138).
Scheme 138: Retrosynthetic route to the isodomoic acids via haloboration/iodo-deboronation

Methylation of the boronate ester would have to take place prior to iodo-deboronation since coupling to the dihalogenated alkene was found to be unselective. This would then be followed by a final coupling to the appropriate side chain.

Once successful functionalisation of the model alkyne has been completed it will be transferred to the enantiopure alkyne and it is hoped that another stereodivergent synthesis from this intermediate will afford the remaining isodomoic acids.

5.8.2 Palladium catalysed chemistry

An attempt to carry out a Stille coupling on substrate (312), led to the formation of enyne (313) through Sonogashira coupling (Scheme 139).
This result does point to another avenue that could be investigated further to reach our targeted compounds (Scheme 140).

**Scheme 139: Enyne formation from dibromoalkene**

**Scheme 140: Enyne functionalisation**

5.8.3 **Redevelopment of the route**

The alkyne intermediate (144) has been shown to be a useful intermediate through which isodomoic acids B, E and F have already been synthesised and it is hoped that subsequent isomers will be made from this intermediate. There are currently sixteen synthetic steps to the enantiopure alkyne (144), which is both time consuming and affords very little material. Moreover the reproducibility of certain steps for example the lactam reduction makes re-synthesis of this intermediate a challenge (Chapter 2, section 2.2).

Previous members of the group have focused on the development of other routes to the alkyne starting from cumylamine. Though an ideal starting material which already possesses the trans relative stereochemistry required for the kainoids is trans-4-hydroxyl L-proline (346) (Figure 21). The obvious challenge though is the control of the relative stereochemistry at the three contiguous stereocenters.
Figure 21: Relative stereochemistry of the kainoids and trans-4-hydroxy L-proline

Few kainoid syntheses have been reported using this starting material, though in 2006 Poisson reported a concise synthesis of (−)-kainic acid from proline (346) in 14 steps. One of the key steps of this synthesis is a diastereoselective enolate alkylation to introduce the C3 substituent (Scheme 141). The N-Boc protecting group was found to be unsuitable and was replaced with the N-fluorophenyl (Pf) group, though this also had to be changed for a benzyloxycarbonyl (Cbz) group prior to the cupration step. Alkylation was carried out after an oxidation of the C4 hydroxyl group to the ketone, enolate formation, and then addition of bromoacetate. The selectivity of the reaction was controlled by the temperature and the trans product was obtained in a dr of 16:1 when carried out at -40 °C.

Introduction of the isoprenyl moiety at the C4 carbon was achieved with retention of stereochemistry through cuprate substitution. Poisson and co-workers report that stringent reaction conditions must be followed in order for the substitution to take place, and that the carbamate group plays a role in the reaction, yet offer no mechanistic insight.
The use of hydroxyproline (346) is an attractive starting material and could allow us to follow an analogous route for the formation of the intermediate alkyne (112) and the remaining kainoids (Scheme 142).

Scheme 141: Synthesis of (−)-kainic acid from hydroxyproline

Scheme 142: Possible synthesis of kainoids from hydroxyproline
6 Experimental

6.1 General Experimental

NMR spectra were recorded on a Bruker Ultrashield 300, 400 or 500 MHz spectrometer. The chemical shifts (δ) are reported in ppm downfield of tetramethylsilane. Solvents were used as internal standard when assigning NMR spectra (\(^1\)H NMR δ: CDCl\(_3\) 7.27 ppm; D\(_2\)O 4.87 ppm; toluene d\(_8\) 2.30 ppm; DMSO d\(_6\) 2.46; \(^{13}\)C NMR δ: CDCl\(_3\) 77.0 ppm; toluene d\(_8\) 20.4 ppm; DMSO 39.7 ppm). Coupling constants (J) are given in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (b) or any combination of these.

Low and high resolution mass spectra were recorded by the staff at the University of Manchester. EI and CI were recorded on a Fisons VG Trio 2000 and high resolution mass spectra (HRMS) were recorded on a Kratos Concept-IS mass spectrometer, and are accurate to ± 0.001.

Infrared spectra were recorded on an ATi Matson Genesis Series Fourier Transform spectrophotometer or a Thermo Scientific Nicolet iS5 iD5 ATR spectrometer. Only absorption maxima of interest are reported. All samples were run as an evaporated film on a sodium chloride plate or as a solid on ATR. Absorption maxima (\(\nu_{\text{max}}\)) are quoted in wavenumbers (cm\(^{-1}\)).

Melting points were determined using a Stuart Scientific SMPIO or a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter using a cell with pathlength of 0.25 dm. Concentrations (c) are given in grams per 100 cm\(^3\).

Chiral HPLC measurements were carried out using a Hewlett Packard Series 1050 instrument with a diode array detector, using β-gem chiral stationary phases using a
mixture of hexane and isopropanol (IPA) as the eluent. Absorption was measured at 254 or 214 nm.

Microwave irradiations were conducted using a Biotage Initiator microwave unit. All the experiments were performed using a pre-stirring option for 30 seconds.

Analytical thin layer chromatography (TLC) were carried out on pre-coated UV$_{254}$ plates (Macherey-Nagel) with visualisation by ultraviolet light at 254 nm, potassium permanganate or dodecamolybdophosphoric acid (PMA). Column chromatography was carried out using Fluorochem Davisil 40–63 µm 60 Å silica under a positive pressure using compressed air unless otherwise stated.

Tetrahydrofuran (THF) was distilled from sodium wire and benzophenone and subsequently stored under a nitrogen atmosphere. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. HMPA was distilled over calcium hydride under reduced pressure and subsequently stored over 4 Å molecular sieves. Petroleum ether (Petrol) refers to the fraction of light petroleum ether boiling between 40 and 65 °C. $n$-Butyl lithium was obtained from Acros as a solution in hexanes (2.5 M), methyllithium in Et$_2$O (1.6 M). The organolithium solutions were titrated prior to use against a solution of $N$-benzylbenzamide.

Toluene and Et$_2$O were collected under inert conditions from an Innovative Technologies PureSolve PS-MP-5 solvent purification system. Anhydrous methanol was obtained commercially. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

All experiments were performed in anhydrous conditions under an atmosphere of nitrogen unless otherwise noted in the experimental text. Apparatus were flame-dried with a Bunsen burner and standard techniques were employed in handling air sensitive materials.
N-Benzyl-4-methoxy-N-(2-phenylpropan-2-yl)benzamide\textsuperscript{52} (80)

\[ \text{N-Benzyl-4-methoxy-N-(2-phenylpropan-2-yl)benzamide} \]

\[ \text{p-Anisoyl chloride (4.30 ml, 33.30 mmol, 1.12 eq), benzyl-(1-methyl-1-phenyl-ethyl)-amine (123) (6.70 g, 29.73 mmol, 1.00 eq) and triethylamine (5.50 ml, 44.60 mmol, 1.50 eq) were dissolved in dichloromethane (60 ml) and stirred for 18 h at rt. The reaction was quenched by the addition of water (77 ml) and extracted with dichloromethane (2 x 80 ml). The combined organic phases were washed with brine, dried (MgSO}_4\text{) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (8:2 Petrol: EtOAc and 5% triethylamine) to afford the title compound (7.97 g, 95\%) as a white solid. All spectroscopic data were consistent with literature values.}\textsuperscript{52}

\[ \text{R}_F\text{ 0.19 (Petrol:EtOAc 8:2); } ^1\text{H NMR (CDCl}_3\text{, 300 MHz) } \delta 7.49-7.21 \text{ (12H, m, ArH), 6.84-6.81 (2H, m, ArH), 4.81 (2H, s, CH}_2\text{Ph); 3.51 (3H, s, O(CH}_3\text{)), 1.73 (6H, s, (CH}_3\text{)_2); } ^1\text{C NMR (CDCl}_3\text{, 75 MHz) } \delta 173.0 \text{ (C=O), 160.4 (ArC), 148.8 (ArC), 139.8 (ArC), 130.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.1 (ArC), 126.8 (ArCH), 126.1 (ArCH), 124.4 (ArCH), 113.5 (ArCH), 62.3 (C(CH}_3\text{)_2), 55.2 (OCH}_3\text{), 52.3 (CH}_2\text{Ph), 28.5 ((CH}_3\text{)_2); MS m/z (ES}^+\text{) 382 (MNa}^+\text{).} \]

NMR reference: 2013-02-16-jpc-26
(3S,3aS,7aR)-3-phenyl-2-(2-phenylpropan-2-yl)-2,3,3a,4-tetrahydro-1H-isooindole-1,5(7aH)-dione\(^52\) (82)

To a suspension of \((R)\)-propyl (1-phenylethyl)amine (99) (1.7 g, 10.44 mmol, 1.5 eq) in THF (120 ml) at 0 °C was added \(n\)-BuLi (3.6 ml of a 2.5 M solution in hexanes, 9.05 mmol, 1.30 eq) dropwise. The mixture was stirred for 15 min resulting in a clear yellow solution which was then cooled to -78 °C. A solution of benzamide (80) (2.5 g, 6.96 mmol, 1.00 eq) in THF (20 ml) was added dropwise and the reaction stirred for 30 min. at -78 °C before being slowly warmed to -20 °C over 4 h. The reaction was quenched with a saturated aqueous solution of NH\(_4\)Cl (2 ml) followed by the addition of 3 M HCl (20 ml) and the phases separated. The aqueous phase was extracted with Et\(_2\)O (3 x 20 ml) and the combined organic fractions were washed with brine, dried (MgSO\(_4\)) and concentrated in vacuo. (The chiral amine can be recovered after basification with KOH and extraction with EtOAc) The crude residue was purified by column chromatography (6:4 Petrol-EtOAc) to give the title compound as a white solid (1.59 g, 66%). Recrystallisation from EtOAc (5 ml) afforded the title compound (859 mg, 54%) of ee > 99% (Analytical HPLC (β-Gem, Regis) eluting with IPA and hexane (30:70)). All spectroscopic data were consistent with literature values.\(^52\)

\(R_f\) 0.18 (Petrol:EtOAc 6:4); \(^1H\) NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.38-7.16 (10H, m, ArH), 6.85 (1H, dd, \(J = 4.9, 10.2\), CH=CHCO), 6.09 (1H, dd, \(J = 2.2, 10.2\), CH=CHCO), 4.43 (1H, d, \(J = 2.2\), CPh), 3.65-3.60 (1H, m, CHCON), 2.83-2.45 (3H, m, COCH\(_2\), CHPhCH\(_3\)), 1.78 (3H, s, CH\(_3\)), 1.45 (3H, s, CH\(_3\)); \(^{13}C\) NMR (CDCl\(_3\), 75 MHz) \(\delta\) 196.5 (C=O), 171.5 (NC=O), 145.9 (C), 144.3 (CH=CH), 141.4 (C), 130.2 (COCH=CH), 129.0 (ArCH), 128.1 (ArCH), 126.9 (ArCH), 125.8 (ArCH), 125.2 (ArCH), 67.2 (CHPh), 59.9 (C(CH\(_3\))\(_2\)Ph), 42.3 (CH), 41.4 (CH), 39.0 (CH\(_2\)CO), 28.2 (CH\(_3\)), 27.1 (CH\(_3\)); MS \(m/z\) (ES\(^+\)) 368 (MNa\(^+\)).

NMR reference: 2012-10-16-jpc-50
A mixture of (R)-phenylethylamine (50 ml, 388 mmol, 1.00 eq), 2-bromopropane (56.4 ml, 600 mmol, 1.50 eq), K₂CO₃ (83.0 g, 600 mmol, 1.50 eq) and potassium iodide (33.2 g, 200 mmol, 0.50 eq) in ethanol (120 ml) was heated at reflux for 8 days. The mixture was cooled to rt and water (400 ml) and NaOH (20 g) were added. The mixture was then extracted with Et₂O (3 x 200 ml). The organic phases were combined and washed with water, dried (MgSO₄) and concentrated in vacuo. The crude oil was initially purified by distillation (bpt 60 °C/3 mmHg) through a Vigreux column to afford a colourless oil. The amine was poured into hot 2 M HCl (120 ml) and cooled to afford the hydrochloride salt as a white solid (~ 19 g) which was collected by filtration. The free amine was regenerated by stirring the salt with 2 M KOH (aq) (120 ml), saturated with NaCl (s) and extracted with Et₂O (3 x 50 ml). The combined organic phases were dried (MgSO₄) and the solvent was removed in vacuo. The residue was purified by distillation to afford the title compound (20.39 g, 32%) as a colourless oil which was stored over 4 Å molecular sieves. All spectroscopic data were consistent with literature values.¹³⁹

Rᵥ 0.45 (CH₂Cl₂:MeOH 9:1, 5% NH₃ (aq)); [α]²⁰D +62.4 (c = 1, CHCl₃) [lit.¹⁴⁰ [α]D +61.4 (c = 0.71, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.26 (5H, m, ArH), 3.87 (1H, q, J = 6.6, CH(CH₃)), 2.59 (1H, septet, J = 6.2, CH(CH₃)₂), 1.32 (3H, d, J = 6.6, CH₃), 1.00 (3H, d, J = 6.2, CH₃), 0.97 (3H, d, J = 6.2, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 146.1 (ArC), 128.4 (ArCH), 126.7 (ArCH), 126.4 (ArCH), 55.1 (CH(CH₃)NH), 44.5 (CH(CH₃)₂), 24.9 (CH₃), 24.1 (CH₃(CHCH₃)), 22.2 (CH₃(CHCH₃)); MS m/z (ES⁺) 164 (MH⁺).

NMR reference: 2010-12-21-jpc-48
Benzyl-(1-methyl-1-phenyl-ethyl)-amine\textsuperscript{52} (123)

Benzyl bromide (2.20 ml, 18.49 mmol, 1.00 eq), potassium carbonate (3.40 g, 24.59 mmol, 1.33 eq) and cumylamine (2.66 ml, 18.49 mmol, 1.00 eq) were dissolved in anhydrous DMF (25 ml) and left to stir for 18 h under nitrogen. The reaction was diluted with Et\textsubscript{2}O (35 ml) and washed with water (2 x 35 ml). The phases were separated and the organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent removed under reduced pressure to afford the title compound (3.94 g, 94\%) as a colourless oil. All spectroscopic data were consistent with literature values.\textsuperscript{52}

R\textsubscript{f} 0.67 (Petrol:EtOAc 3:1); \textsuperscript{1}H NMR (300 MHz; CDCl\textsubscript{3}) \(\delta\) 7.58-7.23 (10H, m, ArH), 3.51 (2H, s, CH\textsubscript{2}), 1.57 (6H, s, (CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (75 MHz; CDCl\textsubscript{3}) \(\delta\) 147.7 (ArC), 141.1 (ArC), 128.3 (ArCH), 128.2 (ArCH), 126.8 (ArCH), 124.7 (ArCH), 126.3(ArCH), 125.9 (ArCH), 56.3 (C(CH\textsubscript{3})\textsubscript{2}), 47.6 (CH\textsubscript{2}N), 29.7 (CH\textsubscript{3})\textsubscript{2}; MS m/z (ES\textsuperscript{+}) 226 (MH\textsuperscript{+}).


(3S,7S)-3-Phenyl-2-(2-phenylpropan-2-yl)-7-(trimethylsilyl)hexahydro-1H-isoindole-1,5(6H)-dione\textsuperscript{46} (134)

A solution of HMPA (4.79 ml, 27.5 mmol, 6.30 eq) and HMDS (2.06 ml, 10.85 mmol, 2.50 eq) was cooled to 0 °C. Methyl lithium (6.37 ml of a 1.6 M solution in hexanes, 10.19 mmol, 2.30 eq) was added dropwise and the red solution was left to stir for 15 min. at the
same temperature. After this time, THF (20 ml) was added followed by the addition in one portion of copper cyanide (428 mg, 4.77 mmol, 1.10 eq) and the reaction was left to stir for 30 min. at 0 °C. After this time the reaction was cooled to -78 °C and a solution of enone (82) (1.5 g, 4.34 mmol, 1.00 eq) and TMSCl (1.71 ml, 13.47 mmol, 3.10 eq) in THF (18 ml) was added dropwise. The mixture was allowed to stir at -78 °C for 30 min. and then quenched with an aqueous saturated solution of NH₄OH/NH₄Cl (1/1 v/v) solution. Et₂O was added, the phases were separated and the aqueous layer was extracted twice with Et₂O. The organic phases were combined and washed with an aqueous saturated solution of NH₄OH/NH₄Cl, brine, dried (MgSO₄) and concentrated under reduced pressure to afford the silyl enol ether intermediate.

The enol intermediate was dissolved in THF (30 ml) and HCl 3 M (~15 ml) was added at room temperature. The reaction was allowed to stir for 15 min. and the aqueous layer was extracted twice with Et₂O. The organic phases were combined and washed with a saturated aqueous solution of NaHCO₃, brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 8:2) gave the title compound (1.36 g, 74%) as a white solid. All spectroscopic data were consistent with literature values.⁴⁶ [Synthesed from dearomatised product (82) (> 99% ee)]

R₉ 0.25 (Petrol:EtOAc 8:2); ¹H NMR (CDCl₃, 300 MHz) δ 7.42-7.21 (10H, m, ArH), 4.39 (1H, s, CHPh), 3.03-2.99 (1H, m, CHCO), 2.55 (1H, dd, J = 4.9, 14.7, CHHCHCHPh), 2.45-2.38 ((1H, m, CHCHPh), 2.35-2.25 (2H, m, CHHCHSi + CHHCHCHPh), 2.11-2.03 (1H, m, CHHCHSi), 1.86 (3H, s, CH₃), 1.71-1.64 (1H, m, CHSi(CH₃)₃), 1.52 (3H, s, CH₃), 0.03 (9H, s, Si(CH₃)₃); ¹³C NMR (CDCl₃, 75 MHz) δ 211.2 (C=O), 175.5 (NC=O), 146.0 (ArC), 141.9 (ArC), 129.0 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.0 (ArCH), 125.6 (ArCH), 125.4 (ArCH), 67.4 (CHPh), 59.3 (C(CH₃)₂Ph), 43.0 (CHCHPh), 42.9 (CH₂CHCHPh), 39.6 (CHCON), 38.6 (CH₂CHSi(CH₃)₃), 28.0 (CH₃), 27.1 (CH₃), 20.0 (CHSi(CH₃)₃), -2.6 (C(Si(CH₃)₃)); MS m/z (ES⁺) 442 (MNa⁺).

NMR reference 2010-08-02-jpc-1
Lactam (134) (553 mg, 1.32 mmol, 1.00 eq) was dissolved in TFA (5.39 ml). The reaction was heated at reflux for 1 h and then allowed to cool to rt. The TFA was removed under reduced pressure and the crude residue was dissolved in CH$_2$Cl$_2$. The organic phase was washed twice with a saturated aqueous solution of NaHCO$_3$, brine, dried (MgSO$_4$) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 1:1) gave the title compound (338 mg, 85%) as a white solid. All spectroscopic data were consistent with literature values. [Synthesied from dearomatised product (82) (> 99% ee)]

R$_f$ 0.58 (Petrol:EtOAc 1:1); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.38-7.34 (2H, m, ArH), 7.31-7.25 (3H, m, ArH), 7.13 (1H, br s, NH), 4.32 (1H, d, J = 2.8, CHCHPh), 2.76-2.65 (2H, m, NCOH + NCHPhCH), 2.58 (1H, dd, J = 6.1, 16.1, COCHH), 2.47 (1H, dd, J = 9.6, 16.1, COCHH), 2.38 (1H, dd, J = 5.2, 15.5, SiCHCHH), 2.12 (1H, dd, J = 10.2, 15.5, SiCHCHH), 1.61 (1H, ddd, J = 10.2, 7.2, 5.2, SiCH), 0.00 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 211.1 (C=O), 178.6 (NC=O), 140.4 (ArC), 128.9 (ArCH), 128.0 (ArCH), 125.4 (ArCH), 61.7 (CHPh), 45.3 (CHCON), 41.7 (CH$_2$CHCHPh), 39.6 (CHCHPh), 39.2 (CH$_2$CHSi), 20.6 (CHSi), -2.5 (Si(CH$_3$)$_3$); MS m/z (ES$^+$) 324 (MNa$^+$).

NMR reference: 2013-02-25-jpc-58
(1S,4S)-tert-Butyl 3,6-dioxo-1-phenyl-4-(trimethylsilyl)hexahydro-1H-isoinole-2(3H)-carboxylate\(^6\) (135)

(3S, 7S)-3-Phenyl-7-(trimethylsilyl)hexahydro-1H-isoinole-1,5(6H)-dione (214 mg, 0.71 mmol, 1.00 eq) was dissolved in CH\(_2\)Cl\(_2\) (6 ml). Boc\(_2\)O (186 mg, 0.85 mmol, 1.2 eq), triethylamine (0.1 ml, 0.71 mmol, 1.00 eq) and DMAP (17 mg, 0.14 mmol, 0.2 eq) was added and the reaction was allowed to stir for 18 h. The reaction was quenched with water and extracted with CH\(_2\)Cl\(_2\). The organic layer was washed with water, brine, dried (MgSO\(_4\)) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 4:1) gave the title compound (206 mg, 72%) as a white solid. All spectroscopic data were consistent with literature values.\(^6\) [Synthesised from dearomatised product (82) (> 99% ee)]

\(R_f\) 0.31 (Petrol:EtOAc 4:1); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.42-7.30 (3H, m, ArH), 7.21-7.19 (2H, m, ArH), 4.81 (1H, s, CHPh), 2.97-2.93 (1H, m, NCOCH), 2.72-2.66 (1H, m, CH\(_2\)HCHSi), 2.61-2.55 (1H, m, CHCHPh), 2.50-2.41 (2H, m, CHHCHSi + CH\(_2\)CHCHPh), 2.14 (1H, dd, \(J = 9.1, 15.5\), CHHCHPh), 1.80-1.73 (1H, m, CHSi), 1.34 (9H, s, C(CH\(_3\)\(_3\)), 0.00 (9H, s, Si(C\(_3\)H\(_3\)\(_3\))); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 210.1 (C=O), 175.0 (NCO), 149.7 (ArC), 139.8 (ArC), 129.0 (ArCH), 128.0 (ArCH), 124.7 (ArCH), 83.4 (C(CH\(_3\)\(_3\)), 65.3 (CHPh), 42.6 (CH\(_2\)CHSi), 41.1 (CHCHPh), 40.8 (NCOCH), 38.6 (CH\(_2\)CHCHPh), 27.7 (C(CH\(_3\)\(_3\)), 20.0 (CHSi(CH\(_3\)\(_3\)), -2.6 (C(SiCH\(_3\)\(_3\))); MS m/z (ES\(^+\)) 424 (MNa\(^+\)).

NMR reference: 2012-08-22-jpc-28
(1S,4S)-Di-tert-butyl 3,6-dioxo-4-(trimethylsilyl)hexahydro-1H-isindole-1,2(3H)-dicarboxylate (136)

To a solution of NaIO₄ (5.84 g, 27.32 mmol, 18.00 eq) in distilled water (16 ml) and acetonitrile (8 ml), RuCl₃·xH₂O (32 mg, 0.15 mmol, 0.10 eq) was added in one portion. A solution of lactam (135) (609 mg, 1.52 mmol, 1.00 eq) in EtOAc (8 ml) was added dropwise. The reaction was allowed to stir for 24 h. After this time the reaction was filtered over a pad of celite™, the layers separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, brine, dried (MgSO₄) and concentrated under reduced pressure. The remaining starting material was recovered by column chromatography (Petrol-EtOAc 4:1) and the column was flushed with EtOAc to obtain the acid intermediate (317 mg).

The crude acid was dissolved in CH₂Cl₂ (7 ml), to which DCC (497 mg, 2.37 mmol, 1.56 eq), DMAP (29 mg, 0.24 mmol, 0.20 eq) and t-BuOH (0.29 ml, 3.00 mmol, 2.00 eq) were added and the reaction was allowed to stir for 18 h. After this time the reaction was filtered and water was added. The aqueous layer was extracted twice with CH₂Cl₂. The organic layer was washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 4:1) gave the title compound (409 mg, 63%) as a colourless oil. All spectroscopic data were consistent with literature values. [Synthesed from dearomatised product (82) (> 99% ee)]

R_f 0.23 (Petrol-EtOAc 8:2); ¹H NMR (CDCl₃, 500 MHz) δ 4.12 (1H, s, NCH), 2.89-2.86 (1H, m, COCH), 2.72-2.67 (1H, m, CHCHCO₂), 2.55 (1H, dd, J = 5.1, 15.8, COCHH), 2.41 (1H, dd, J = 6.0, 15.8, SiCHCHH), 2.28 (1H, dd, J = 12.6, 15.8, COCHH), 2.17 (1H, dd, J = 8.6, 15.8, SiCHCHH), 1.75-1.73 (1H, m, CHSi), 1.51 (9H, s, (CH₃)₃), 1.48 (9H, s, (CH₃)₃), 0.04 (9H, s, Si(CH₃)₃); ¹³C NMR (CDCl₃, 125 MHz) δ 209.2 (C=O), 173.9 (NC=O), 168.9 (CO₂C(CH₃)₃), 149.4 (NCO₂C(CH₃)₃), 83.7 (C(CH₃)₃), 82.9 (C(CH₃)₃), 73.9 (NCH), 209.2 (C=O), 173.9 (NC=O), 168.9 (CO₂C(CH₃)₃), 149.4 (NCO₂C(CH₃)₃), 83.7 (C(CH₃)₃), 82.9 (C(CH₃)₃),
63.4 (CHCO₂), 42.1 (CH₂CHCH), 41.7 (CHCHSi), 38.3 (CH₂CO), 36.1 (CHCHN), 27.9 2(C(CH₃)₃), 19.7 (CHSi), -2.7 (Si(CH₃)₃); MS m/z (ES⁺) 448 (MNa⁺).

NMR reference: 2013-03-12-jpc-27

Dimethyl (1-diazo-2-oxopropyl)phosphonate (Ohira-Bestmann reagent)⁵⁸,⁶⁵ (141)

K₂CO₃ (4.99 g, 36.12 mmol, 1.20 eq) was added to a solution of dimethyl (2-oxopropyl)phosphonate (5.00 g, 30.10 mmol, 1.00 eq) and p-acetamidobenzenesulfonyl azide (7.96 g, 33.11 mmol, 1.10 eq) in acetonitrile (100 ml) at 0 °C. The reaction was allowed to warm to rt and stirred for 16 h. The reaction was then filtered and the solvent removed under reduced pressure. The residue was dissolved in chloroform and stirred for 1 h. The suspension was then filtered and the filtrate evaporated. The crude residue was purified by column chromatography (Petrol-EtOAc 1:1 then 2:8) to afford the title compound (4.39 g, 76%) as a yellow oil. All spectroscopic data were consistent with literature values.⁵⁸,⁶⁵

Rᵥ 0.40 (Petrol:EtOAc 2:8); ¹H NMR (300 MHz; CDCl₃) δ 3.84 (6H, d, Jₜ-P = 12.0, (CH₃)₂), 2.27 (3H, s, CH₃); ¹³C NMR (75 MHz; CDCl₃) δ 190.0 (C=O), 53.6 (O(CH₃)₂), 27.1 (CH₃); MS m/z (ES⁺) 215 (80%, MH⁺).

\[ \pm \text{tert-Butyl 3(methoxymethylene)pyrrolidine-1-carboxylate (146)} \]

Method 1\textsuperscript{69}

To a suspension of (methoxymethyl)triphenylphosphonium chloride (18.51 g, 53.99 mmol, 5.00 eq) in THF (64 ml) at 0 °C was added NaHMDS (57.23 ml of a 1 M solution in THF 57.23 mmol, 1.00 eq) and the mixture stirred at 0 °C for 30 min. The deep red reaction mixture was then cooled to -78 °C and a solution of N-Boc pyrrolidinone (2.00 g, 10.80 mmol, 1.00 eq) in THF (56 ml) was added slowly. The reaction was kept at this temperature for 1 h then allowed to warm to rt and stirred under nitrogen for 16 h. The reaction was diluted with ether and a saturated aqueous solution of NH\textsubscript{4}Cl. The organic layer was separated and the aqueous layer extracted with ether. The combined organic phases were washed with brine, dried (MgSO\textsubscript{4}) and the solvent removed. The crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (597 mg, 26%) as a pale yellow oil.

Method 2\textsuperscript{58}

N-Boc pyrrolidinone (2.0 g, 10.80 mmol, 1.00 eq) was dissolved in anhydrous MeOH (64 ml) and K\textsubscript{2}CO\textsubscript{3} (3.0 g, 22 mmol, 2.00 eq) was added. The reaction mixture was cooled to 0 °C and a solution of Ohira-Bestmann reagent (141) (2.54 g, 12.12 mmol, 1.10 eq) in MeOH (16 ml) was added dropwise. The reaction was warmed to rt and stirred for 16 h, and quenched with a saturated aqueous solution of NH\textsubscript{4}Cl (3 ml) and extracted with Et\textsubscript{2}O (3 x 25 ml). The combined organic extracts were washed with brine, dried (MgSO\textsubscript{4}) and concentrated. The crude residue was adsorbed onto silica and purified by column chromatography (8:2 Petrol-EtOAc) to afford the title compound (857 mg, 37%) as pale yellow oil.
Rf 0.10 (Petrol:EtOAc 9:1); IR νmax(film/cm⁻¹) 1692 (C=O); ¹H NMR (300 MHz; CDCl₃) δ minor isomer 5.96 (1H, br s, C=CH), 5.90-5.87 (1H, m, C=CH), 3.89-3.85 (2H, m, CH₂N), 3.56-3.55 (3H, m, OCH₃), 3.39-3.37 (2H, m, CH₂N), 2.50 (0.68H, t, J = 7.2, CH₂), 2.40 (1.32H, t, J = 7.2, CH₂), 1.43 (9H, s, (CH₃)₃); ¹³C NMR (300 MHz; CDCl₃) δ 154.5 (C=O), 139.3(C=CH), 114.5 (C=CH), 79.1 (C(CH₃)₃), 59.6 (OCH₃), 46.1 (CH₂N), 45.3 (CH₂N), 28.4 (C(CH₃)₃), 28.3 (CH₂); MS m/z (ES⁺) 236 (MNa⁺); HRMS Found MNa⁺ 236.1250, C₁₁H₁₉O₃NNa requires MNa⁺ 236.1257.


± tert-Butyl 3-formylpyrrolidine-1-carboxylate (147)

Method 1

Enol ether (146) (50 mg, 0.24 mmol, 1.00 eq) was dissolved in CH₂Cl₂ (22 ml) and trichloroacetic acid (383 mg, 2.34 mmol, 10.00 eq) was slowly added to the solution. Three drops of water were then added and the mixture stirred at rt for 45 min. The reaction was cooled to 0 °C before being quenched with a saturated aqueous solution of NaHCO₃. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed once more with NaHCO₃, dried (MgSO₄) and the solvent removed to afford the title compound (32 mg, 70%) as a colourless oil.

Method 2

Enol ether (146) (50 mg, 0.24 mmol, 1.00 eq) was added to a 90% solution of formic acid (1 ml). After stirring for 2 h at rt, EtOAc (2 ml) and aqueous saturated NaHCO₃ (2 ml) were added. The phases were separated and the aqueous phase extracted with EtOAc (3 x 3
148

ml), washed with brine, dried (MgSO₄) and concentrated. The title compound (20 mg, 44%) was obtained without further purification as a colourless oil.

R_f 0.29 (Petrol:EtOAc 8:2); ^1H NMR (CDCl₃; 300 MHz) δ 9.70 (1H, d, J = 1.5, CHO), 3.74-3.68 (1H, m, CHCHHN), 3.56-3.50 (1H, m, CH₂CHHN), 3.41-3.36 (2H, m, CHCHHN + CH₂CHHN), 3.09-2.99 (1H, m, CH₂CH₂N), 2.26-2.06 (2H, m, CH₂CH₂N), 1.47 (9H, s, (CH₃)₃); ^13C NMR (CDCl₃; 75 MHz) δ 200.6 (C(CHO)), 154.4 (CO), 79.8 (C(CH₃)₃), 50.5 (CH₂N), 49.6 (CHCH₂N), 45.0 (CH₂N), 28.4 (C(CH₃)₃), 27.3 (CH₂CH₂N); MS m/z (ES^+) 222 (MNa^+).

NMR reference: proton 2013-02-12-jpc-39/carbon 2013-02-12-jpc-48

\[ \text{Boc} \]

\[ \pm \text{tert-Butyl 3-ethynlypyrrolidine-1-carboxylate}^{58} \ (148) \]

Method 1^{58}

K₂CO₃ (1.57 g, 11.34 mmol, 2.00 eq) was added to a solution of N-Boc-3-pyrrolidinone (1.05 g, 5.67 mmol, 1.00 eq) in dry MeOH (33 ml). The reaction mixture was cooled to 0°C and a solution of the Ohira-Bestmann reagent (141) (1.20 g, 6.24 mmol, 1.10 eq) in MeOH (8 ml) was added dropwise via cannula. The reaction mixture was warmed to rt and stirred for 16 h, then quenched by the addition of a saturated aqueous solution of NH₄Cl (3 ml) and extracted with Et₂O (3 x 10 ml). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated. The crude enol ether was then dissolved in CH₂Cl₂ (55 ml) and trichloroacetic acid (9.0 g, 55 mmol, 10.00 eq) was added portion wise to the reaction mixture and stirred for 30 min. It was then cooled down to 0 °C and carefully quenched by addition of a saturated aqueous solution of NaHCO₃ (10 ml), and extracted with EtOAc (4 x 10 ml). The combined organic extracts were washed again with saturated
aqueous NaHCO₃, dried (MgSO₄) and concentrated. The residue was then dissolved in dry MeOH (20 ml) and K₂CO₃ (3.0 g, 22 mmol, 4.00 eq) was added, the reaction mixture was cooled then to 0 °C and a solution of the Ohira-Bestmann reagent (141) (1.58 g, 8.22 mmol, 1.50 eq) in MeOH (8 ml) was added dropwise via cannula. The reaction was warmed to rt and stirred for 16 h, then quenched with a saturated aqueous solution of NH₄Cl (2 ml) and extracted with Et₂O (3 x 10 ml). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated. The crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (354 mg, 32% over 3 steps) as a white solid.

Method 2

A solution of Ohira-Bestmann reagent (141) (624 mg, 3.25 mmol, 1.50 eq) in dry methanol (2 ml) was added to a mixture of aldehyde (147) (432 mg, 2.17 mmol, 1.00 eq) and K₂CO₃ (1.20 g, 8.56 mmol, 4.00 eq) in methanol (6 ml) at 0 °C. The reaction was warmed to rt and stirred for 16 h. The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl and extracted with Et₂O. The combined organic extracts were washed with brine, dried (MgSO₄) and the solvent removed. The residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (126 mg, 30% over 2 steps) as a white solid.

Method 3

N-Boc-3-pyrrolidinone (500 mg, 2.70 mmol, 1.00 eq) was dissolved in anhydrous MeOH (16 ml) and K₂CO₃ (750 mg, 5.43 mmol, 2.00 eq) was added. The reaction mixture was cooled to 0 °C and a solution of Ohira-Bestmann reagent (141) (635 mg, 3.31 mmol, 1.20 eq) in MeOH (4 ml) was added dropwise. The reaction was warmed to rt and stirred for 16 h, and then quenched with a saturated aqueous solution of NH₄Cl (3 ml) then extracted with Et₂O (3 x 5 ml). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated. The crude enol ether was dissolved in CH₂Cl₂ (28 ml) and trichloroacetic acid (5.00 g, 30.60 mmol, 10.00 eq) was added in portions to the solution.
Three drops of water were then added and the mixture stirred at rt for 30 min. The reaction was cooled to 0 °C before being quenched with a saturated aqueous solution of NaHCO₃. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed once more with NaHCO₃, dried (MgSO₄) and the solvent removed to afford the crude aldehyde (586 mg).

CBr₄ (2.41 g, 7.26 mmol, 2.65 eq) in CH₂Cl₂ (2.5 ml) was added to a suspension of zinc powder (475 mg, 7.26 mmol, 2.65 eq) and triphenylphosphine (1.90 g, 7.26 mmol, 2.65 eq) in CH₂Cl₂ (7.5 ml) at 0 °C. The mixture was stirred for 20 min at this temperature then aldehyde (147) (586 mg, 2.74 mmol, 1.00 eq) in CH₂Cl₂ (2.5 ml) was added slowly and the reaction stirred for 4 h at rt. The reaction mixture was then poured into pentane, filtered and the solvent removed in vacuo. The residue was dissolved in THF (5 ml) and cooled to -78 °C. n-BuLi (2.74 ml of a 2.5 M solution in hexanes, 6.85 mmol, 2.50 eq) was added and the reaction stirred for 1 h before being quenched with NaHCO₃. The reaction was then extracted with Et₂O, washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (41 mg, 8% (over 3 steps)) as a white solid. All spectroscopic data were consistent with literature values.⁵⁸

**Rf** 0.19 (Petrol:EtOAc 9:1); **¹H NMR** (DMSO, 400 MHz; 120 °C) δ 3.54-3.50 (1H, m, CHHN), 3.42-3.36 (1H, m, CH₂CHHN), 3.30-3.23 (1H, m, CH₂CHHN), 3.21-3.17 (1H, m, CHHN), 3.05-2.97 (1H, m, CHCH₂N), 2.73 (1H, d, J = 2.2, CCH), 2.16-2.08 (1H, m, CHHCH₂N), 1.89-1.80 (1H, m, CHHCH₂N), 1.43 (9H, s, (CH₃)₃); **¹³C NMR** (DMSO, 100 MHz; 392 K) δ 152.9 (C=O), 84.4 (C(CH₃)₃), 77.9 (CCH), 70.8 (CCH), 50.8 (CH₂N), 44.1 (CH₂CH₂N), 31.1 (CH₂), 28.0 (CHCCH), 27.6 (C(CH₃)₃); **MS m/z (ES⁺)** 218 (MNa⁺).

NMR reference: 2013-02-01-admin-5
\( \pm 3\text{-Ethynyl-1-tosylpyrrolidine} \) (152)

tert-Butyl 3-ethynylpyrrolidine-1-carboxylate (148) (150 mg, 0.77 mmol, 1.00 eq) was stirred in a mixture of CH\(_2\)Cl\(_2\)/TFA (3:1) at rt for 2 h. The solvent was removed in vacuo. Et\(_2\)O (~1 ml) was added and the solvent was removed again under reduced pressure. This was repeated twice more. The residue was dissolved in CH\(_2\)Cl\(_2\) (2 ml) and washed twice with a saturated aqueous solution of NaHCO\(_3\), dried (MgSO\(_4\)) and the solvent removed. The residue was dissolved in CH\(_2\)Cl\(_2\) followed by the addition of triethylamine (107 µl, 0.77 mmol, 1.00 eq), DMAP (9 mg, 0.08 mmol, 0.10 eq) and tosyl chloride (176 mg, 0.92 mmol, 1.20 eq). The mixture was stirred at rt for 16 h, diluted with water (1 ml) and extracted with CH\(_2\)Cl\(_2\), dried (MgSO\(_4\)) and concentrated. The crude yellow residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (120 mg, 63% (over 2 steps)) as a yellow solid.

\( \text{R} \_F \ 0.15 \) (Petrol:EtOAc 9:1); \( \text{Mpt} \ 78\text{-}80 ^\circ \text{C} \); \( \text{IR} \ \nu_{\text{max}} \ \text{(neat/cm}^{-1}) \) 1343 (S=O); \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) 7.73-7.71 (2H, m, ArH), 7.34-7.32 (2H, m, ArH), 3.59 (1H, dd, \( J = 7.3, 10.0 \), CHHN), 3.39-3.29 (2H, m, CH\(_2\)N), 3.17 (1H, dd, \( J = 7.3, 10.0 \), CHHN), 2.87-2.79 (1H, m, CHCH), 2.44 (3H, s, ArCH\(_3\)), 2.13-2.05 (1H, m, CHH(CH\(_2\)N)), 1.99 (1H, d, \( J = 2.5 \), CCH), 1.88-1.79 (1H, m, CHH(CH\(_2\)N)); \( ^{13}\text{C NMR} \) (CDCl\(_3\), 100 MHz) \( \delta \) 143.6 (ArC), 133.6 (ArC), 129.7 (ArCH), 127.6 (ArCH), 83.0 (CCH), 70.3 (CCH), 53.2 (CH\(_2\)N), 47.0 (CH\(_2\)N), 32.2 (CH\(_2\)), 29.3 (CH), 21.5 (CH\(_3\)); \text{MS} \ \text{m/z} \ (\text{ES}^+) \ 272 \ (\text{MNa}^+); \text{HRMS:} \ \text{Found} \ 
\text{MNa}^+ \ 272.0712, \ C_{13}H_{15}NO_2NaS \ \text{requires} \ 
\text{MNa}^+ \ 272.0716.

NMR reference: 2011-12-07-jpc-60
(S)-3-(tert-Butyl dimethylsilanyloxy)-2-methyl-propionic acid methyl ester\textsuperscript{72} (157)

To a solution of methyl (S)-(+)-3-hydroxy-2-methyl propionate (0.93 ml, 8.46 mmol, 1.00 eq) in CH$_2$Cl$_2$ (16 ml) at 0 °C was added triethylamine (1.41 ml, 10.15 mmol, 1.20 eq) followed by tert-butylidemethylsilyl chloride (1.53 g, 10.15 mol, 1.20 eq) and DMAP (51.3 mg, 0.42 mmol, 0.05 eq) in CH$_2$Cl$_2$ (4 ml). The reaction was stirred at rt for 12 h before being quenched with water (10 ml) and CH$_2$Cl$_2$ (20 ml). The title compound (1.86 g, 94%) was obtained as a pale yellow oil. All spectroscopic data were consistent with literature values.\textsuperscript{72}

R$_F$ 0.90 (Petrol:EtOAc 1:1); \textsuperscript{1}H NMR (300 MHz; CDCl$_3$) δ 3.79-3.74 (1H, m, CH$_2$), 3.67 (3H, s, OCH$_3$), 3.65-3.62 (1H, m, CHH), 2.70-2.59 (1H, m, CH), 1.13 (3H, d, J = 7.2, CH$_3$), 0.87 (9H, s, (CH$_3$)$_3$), 0.03 (6H, s, Si(CH$_3$)$_2$); \textsuperscript{13}C NMR (75 MHz; CDCl$_3$) δ 175.5 (CO$_2$CH$_3$), 65.2 (SiOCH$_2$), 51.5 (OCH$_3$), 42.5 (CH$_2$CHCH$_3$), 25.8 (C(CH$_3$)$_3$), 18.2 (C(CH$_3$)$_3$), 13.4 (CH$_3$), -5.1(Si(CH$_3$)$_2$); MS m/z (ES$^+$) 255 (MNa$^+$).


(S)-3-(tert-Butyldimethylsilanyloxy)-2-methylpropionaldehyde\textsuperscript{73} (158)

DMSO (1.77 ml, 24.93 mmol, 2.80 eq) was added dropwise to a solution of oxaly chloride (1.71 ml, 19.59 mmol, 2.20 eq) in CH$_2$Cl$_2$ (18 ml) at -78 °C and the mixture was stirred for 15 min. A solution of (R)-3-(tert-butylidemethylsilanyloxy)-2-methyl-propan-1-ol (159) (1.8 g, 8.90 mmol, 1.00 eq) in CH$_2$Cl$_2$ (6 ml) was added dropwise to the reaction flask. The reaction was stirred for 1 h, then triethylamine (6.21 ml, 44.52 mmol, 5.00 eq) was added

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and the resultant mixture gradually warmed to rt, then stirred for 30 min. The white reaction mixture was quenched with water (25 ml) and extracted with CH₂Cl₂ (2 x 100 ml). The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (1.10 g, 61%) as a colourless oil. All spectroscopic data were consistent with literature values.

\[ R_f \text{ 0.83 (Petrol:EtOAc 1:1); } ^1H \text{ NMR (300 MHz; CDCl}_3\text{) } \delta \text{ 9.69 (1H, s, CHO), 3.90-3.78 (2H, m, CH}_2\text{), 2.60-2.48 (1H, m, CH(CH}_3\text{))}, 1.10 \text{ (3H, d, J = 7.1, CH}_3\text{), 0.88 (9H, s, (CH}_3\text{)_3}), 0.06 (6H, s, Si(CH}_3\text{)_2}); ^{13}C \text{ NMR (75 MHz; CDCl}_3\text{) } \delta \text{ 204.6 (CHO), 63.4 (CH}_2\text{), 48.8 (CH(CH}_3\text{)), 25.8 (CH}_3\text{)_3}, 18.2 (C(CH}_3\text{)_3)}, 10.3 (CH}_3\text{), -5.6 (Si(CH}_3\text{)_2}); MS m/z (Cl) 201 (M–H), 145 (M–t-Bu). \]

NMR reference: proton 2010-02-04-jpc-27/carbon 2010-02-04-jpc-25

\[ \text{TBDMOSO} \text{OH} \]

\((R)-3-\text{(tert-Butyldimethylsilanyloxy)-2-methylpropan-1-ol}^{141} \text{ (159)}\)

To a solution of (S)-3-\((\text{tert-butyldimethylsilanyloxy)-2-methylpropionic acid methyl ester} \text{ (157)}\) (1.00 g, 4.30 mmol, 1.00 eq) in toluene (30 ml) at -40 °C was added DIBAl-H (8.6 ml of a 1 M solution in toluene, 8.6 mmol, 2.00 eq). The reaction was stirred at this temperature for 3 h before quenching with methanol (1 ml) and Rochelle’s salt (35 ml). The mixture was stirred vigorously for 30 min. before adding water (11 ml) and Et₂O (4 ml). The resultant cloudy mixture was stirred for approx. 30 min. until clear. The aqueous layer was extracted with Et₂O (3 x 15 ml) and the combined organic phases were dried (Na₂SO₄), filtered and the solvent removed \textit{in vacuo}. The title compound (720 mg, 82%)
was obtained without further purification as a colourless oil. All spectroscopic data were consistent with literature values.\textsuperscript{141}

\textbf{R}_F 0.50 (Petrol:EtOAc 4:1); \textsuperscript{1}H NMR (300 MHz; CDCl\textsubscript{3}) \(\delta\) 3.67-3.44 (4H, m \(\text{CH}_2\)\textsubscript{2}), 1.95-1.79 (1H, m, \(\text{CH}\)), 0.83 (9H, s, \(\text{CH}_3\)\textsubscript{3}), 0.76 (3H, d, \(J = 6.9\), \(\text{CH}_3\)), 0.00 (6H, s, Si(\(\text{CH}_3\))\textsubscript{2}); \textsuperscript{13}C NMR (75 MHz; CDCl\textsubscript{3}) \(\delta\) 68.7 (\(\text{CH}_2\)OH), 68.3 (\(\text{CH}_2\)OH), 37.0 (\(\text{CH}(\text{CH}_3)\)), 25.8 (\(\text{C}(\text{CH}_3)\)), 18.2 (\(\text{C}(\text{CH}_3)\)), 13.1 (\(\text{CH}_3\)), -5.6 (Si(\(\text{CH}_3\))\textsubscript{2}); MS \(m/z\) (ES\textsuperscript{+}) 205 (MH\textsuperscript{+}).


\begin{center}
\includegraphics[width=0.2\textwidth]{iodomethyltriphenylphosphonium-iodide.png}
\end{center}

\textbf{Iodomethyltriphenylphosphonium iodide}\textsuperscript{142}

To a suspension of triphenylphosphine (5.00 g, 19.06 mmol, 1.00 eq) in toluene (5 ml) was added diiodomethane (2.0 ml, 6.64 mmol, 1.30 eq). The mixture was kept at 45-50 °C for 15 h. The white crystals formed were washed with toluene and dried \textit{in vacuo} for 4 h to afford the title compound (7.78 g, 77%) as a white solid. All spectroscopic data were consistent with literature values.\textsuperscript{142}

\textbf{R}_F 0.65 (Petrol:EtOAc 8:2); Mpt 210 °C dec; \textsuperscript{1}H NMR (300 MHz; DMSO) \(\delta\) 7.96- 7.76 (15H, m, \(\text{ArH}\)), 5.10 (2H, d, \(J_{\text{P-H}} = 8.4\), \(\text{CH}_2\)\textsubscript{2}); \textsuperscript{13}C NMR \(\delta\) (75 MHz; DMSO) 135.2 (\(\text{ArCH}\)), 133.8 (\(\text{ArCH}\)), 130.3 (\(\text{ArCH}\)), 130.1 (\(\text{ArCH}\)), 118.9 (\(\text{ArCH}\)), 117.7 (\(\text{ArC}\)), 18.4 (\(\text{CH}_2\)); MS \(m/z\) (ES\textsuperscript{+}) 403 (M).

(R,Z)-tert-Butyl((4-iodo-2-methylbut-3-en-1-yl)oxy)dimethylsilane (160)

NaHMDS (3.11 ml of a 1 M solution in THF, 3.11 mmol, 2.10 eq) was added dropwise to a suspension of iodomethyltriphenylphosphonium iodide (1.18 g, 2.22 mmol, 1.50 eq) in THF (20 ml). The red solution was stirred for 5 min. at rt before being cooled to -78 °C and DMPU (1.36 ml, 11.27 mmol, 7.60 eq) was added. The mixture was stirred for 15 min. and (S)-3-(tert-Butyldimethylsilanyloxy)-2-methylpropionaldehyde (158) (300 mg, 1.48 mmol, 1.00 eq) in THF (6 ml) was added dropwise to the solution. The reaction was stirred for 3 h at -78 °C then allowed to warm to rt. The reaction was quenched with a saturated aqueous solution of NaHCO₃, diluted with Et₂O and filtered through celite, which was washed with Et₂O. The filtrate was washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The crude residue was purified by column chromatography (Petrol then Petrol-EtOAc 9:1) to afford the title compound E:Z 7:93, (119 mg, 25%) as a colourless oil.

**Rf** 0.78 (Petrol:EtOAc 9:1); [α]²⁵D -33.6 (c = 1, CHCl₃); **IR** ʋ_max(film/cm⁻¹) 2955 (C-H), 1606 (C=C); **¹H NMR** (400 MHz; CDCl₃) δ 6.20 (1H, d, J = 7.3, CHI), 6.05 (1H, dd, J = 7.3, 8.6, CH=CHI), 3.58-3.54 (1H, m, CHH), 3.52-3.58 (1H, m, CHH), 2.73-2.63 (1H, m, CH(CH₃)), 1.03 (3H, d, J = 6.8, CH₃), 0.90 (9H, s, (CH₃)₃), 0.06 (6H, s, Si(CH₃)₂); **¹³C NMR** (100 MHz; CDCl₃) δ 149.9 (C=CHI), 81.6 (C=CHI), 66.2 (CH₂), 42.1 (CH(CH₃), 29.7 (C(CH₃)₃), 25.9 (C(CH₃)₃), 15.6 (CH₃), -5.3 (Si(CH₃)₂); **MS** m/z (GCMS-EI) 269 (M−t-Bu); **HRMS** Found M⁺ 327.0633, C₁₁H₂₃IOSiH requires M⁺ 327.0636.

tert-Butyl-((E)-(R))-4-iodo-2-methyl-but-3-enyloxy)-dimethyl-silane\textsuperscript{143} (161)

To a suspension of CrCl\(_2\) (2.09 g, 17.04 mmol, 5.30 eq) in THF (13 ml) and dioxane (5.24 ml) at 0 °C was added dropwise a solution of (S)-3-(tert-Butyldimethylsilanyloxy)-2-methyl propionaldehyde (158) (574 mg, 2.84 mmol, 1.00 eq) and iodoform (1.97 g, 5.00 mmol, 1.76 eq) in THF (10 ml). The reaction was stirred at 0 °C for 1 h and at rt for 16 h then quenched with a saturated aqueous solution of NH\(_4\)Cl (3 ml) and extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine then dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was purified by column chromatography (Petrol then Petrol-EtOAc 9:1) to afford the title compound E:Z 92:8 (573 mg, 62%) as a pale yellow oil. All spectroscopic data were consistent with literature values.\textsuperscript{143}

R\(_F\) 0.66 (Petrol:EtOAc 9:1); \(^1^H\) NMR (300 MHz; CDCl\(_3\)) \(\delta\) 6.49 (1H, dd, \(J = 7.5, 14.5,\) HC=CH\(_I\)), 6.06 (1H, d, \(J = 14.5,\) HC=CH\(_I\)), 3.48-3.45 (2H, m, CH\(_2\)), 2.44-2.31 (1H, m, CH(CH\(_3\))), 1.00 (3H, d, \(J = 6.8,\) CH\(_3\)), 0.90 (9H, s, (CH\(_3\))\(_3\)), 0.05 (6H, s, Si(CH\(_3\))\(_2\)); \(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta\) 149.1 (HC=CH\(_I\)), 75.0 (HC=CH\(_I\)), 66.9 (CH\(_2\)), 43.1 (CH(CH\(_3\))), 25.9 (C(CH\(_3\))\(_3\)), 18.3 (C(CH\(_3\))\(_3\)), 15.5 (CH\(_3\)), -5.3 (Si(CH\(_3\))\(_2\); MS \(m/z\) (GCMS-EI) 268 (M–t-Bu).

NMR reference: 2010-02-25-jpc-56
To a solution of (S)-Roche ester (0.93 ml, 8.47 mmol, 1.00 eq) and imidazole (605 mg, 8.89 mmol, 1.05 eq) in DMF (10 ml) at 0 °C was added TBDPSCl (2.31 g, 8.89 mmol, 1.05 eq) over 10 min. The solution was stirred for 2 h before quenching with water (4 ml) and pentane (20 ml). The aqueous layer was extracted with pentane (2 x 15 ml) and the combined organic layers were washed with brine, dried (MgSO₄) and the solvent removed. The crude residue was purified by column chromatography (Petrol 100%, then 9:1 Petrol-EtOAc) to afford the title compound (2.54 g, 84%) as a colourless oil. All spectroscopic data were consistent with literature values.

**Rₚ** 0.45 (Petrol:EtOAc 9:1); [α]ᵢᵈ₂ +12.0 (c = 1, CHCl₃) [lit. ¹⁴⁴ [α]ᵢᵈ₂ +12.9 (c = 1.0, CHCl₃)]; ¹H NMR (300 MHz; CDCl₃) δ 7.68-7.65 (4H, m, ArH), 7.44-7.36 (6H, m, ArH), 3.87-3.73 (2H, m, CH₂), 3.70 (3H, s, CH₃), 2.79-2.67 (1H, m, CH) 1.17 (3H, d, J = 6.9, CH₃), 1.04 (9H, s, (CH₃)₃); ¹³C NMR (75 MHz; CDCl₃) δ 175.4 (C=O), 135.6 (ArCH), 133.6 (ArC), 129.7 (ArCH), 127.7 (ArCH), 65.9 (CH₂OSi), 51.5 (CH₃OCO), 42.5 (CHCH₃), 26.7 (C(CH₃)₃), 19.3 (C(CH₃)₃), 13.5 (CH₃); MS m/z (ES⁺) 379 (MNa⁺).

NMR reference: proton 2010-01-29-jpc-36/carbon 2010-01-29-jpc-54

(R)-3-[(tert-butyldiphenyl)silyloxy]-2-methylpropanol⁷⁹ (163)

To a solution of methyl (2S)-3-(tert-butyldiphenylsilyloxy)-2-methylpropionate (162) (15.48 g, 43.41 mmol, 1.00 eq) in CH₂Cl₂ (176 ml) at -40 °C was added dropwise DIBAl-
H (108.5 ml of a 1 M solution in toluene, 109 mmol, 2.50 eq). The mixture was stirred for 2 h at -40 °C then poured into an aqueous solution of Rochelle’s salt and the mixture stirred vigorously until the organic phase was clear. The aqueous phase was extracted with ether (3 x 150 ml) and the combined organic layers were washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The crude residue was purified by column chromatography (9:1 Petrol-EtOAc) to afford the title compound (14.15 g, 99%) as a colourless oil. All spectroscopic data were consistent with literature values. López\textsuperscript{79}

\[ R_F \] 0.13 (Petrol:EtOAc 9:1); \([\alpha]^{25}_D +6.0 \ (c = 1.0, \ CHCl_3) \ [lit.]^{70} \ [\alpha]^{25}_D +5.8 \ c = 1.25, CHCl_3]; \textsuperscript{1}H NMR (500 MHz; CDCl₃) \( \delta \) 7.68-7.68 (4H, m, ArH), 7.47-7.40 (6H, m, ArH), 3.75-3.72 (1H, m, C₃H), 3.69-3.68 (2H, m, CH₂), 3.62-3.59 (1H, m, CHH), 2.48 (1H, br s, OHH), 2.04-1.96 (1H, m, CH(CH₃)), 1.07 (9H, s, (CH₃)₃), 0.84 (3H, d, \( J = 6.9, \ CH_3 \)); \textsuperscript{13}C NMR (75 MHz; CDCl₃) \( \delta \) 135.6 (ArC₃H), 133.2 (ArC), 129.8 (ArCH), 127.8 (ArCH), 68.7 (CH₂), 67.6 (CH₂), 37.4 (CHCH₃), 26.9 (C(CH₃)₃), 19.2 (C(CH₃)₃), 13.2 (CH₃); MS \textit{m/z} (ES⁺) 351.0 (MNa⁺).


\[
\text{TBDPSO} \text{H} \\
\text{O}
\]

\[(2S)-3-(\text{tert}-\text{Butyldiphenylsilylsilyloxy})-2\text{-methyl}^{78} (164)\]

DMSO (3.0 ml, 42.66 mmol, 2.80 eq) was added to a solution of oxalyl chloride (2.06 ml, 23.61 mmol, 2.20 eq) in CH₂Cl₂ (172 ml) at -78 °C followed by stirring for 30 min. \((S)-3-[(\text{tert}-\text{Butyldiphenyl}silyloxy]-2\text{-methylpropanol} \textbf{(163)}\) (5.0 g, 15.23 mmol, 1.00 eq) in CH₂Cl₂ (6 ml) was added dropwise and the mixture stirred for 1 h 20 min. Triethylamine (10.0 ml, 71.75 mmol, 5.00 eq) was then added and the mixture was stirred at rt for 30 min. The reaction was quenched with a saturated aqueous solution of NaHCO₃ and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried
(MgSO₄), filtered and the solvent removed. The residue was purified by column chromatography (9:1 Petrol-EtOAc) to afford the title compound (4.39 g, 88%) as a white solid-colourless oil. All spectroscopic data were consistent with literature values.

\[ \text{R}_F 0.34 \ (\text{Petrol}:\text{EtOAc} \ 9:1); \ [\alpha]^{25}_D +24.0 \ (c = 1.0, \text{CHCl}_3) \ [\text{lit.}^{144} [\alpha]^{25}_D +26.3 \ c = 0.57 \ \text{CHCl}_3]; \]

\[ \text{H NMR} \ (300 \text{ MHz; CDCl}_3) \delta 9.70 (1\text{H, d, } J = 1.8, \text{CHO}), 7.62-7.56 (4\text{H, m, ArH}), 7.37-7.29 (6\text{H, m, ArH}), 3.92-3.81 (2\text{H, m, C}_2H_2), 2.22-2.44 (1\text{H, m, CH}), 1.03 (3\text{H, d, } J = 6.9, \text{CH}_3), 0.97 (9\text{H, s, (CH}_3)_3); \text{C NMR} \ (75 \text{ MHz; CDCl}_3) \delta 204.4 (\text{C}=\text{O}), 135.6 (\text{ArCH}), 133.2 (\text{ArC}), 129.8 (\text{ArCH}), 127.7 (\text{ArCH}), 64.1 (\text{CH}_2\text{OSi}), 48.8 ((\text{C(CH}_3)_3), 26.6 (\text{C(CH}_3)_3), 19.2 (\text{C(CH}_3)_3), 10.3 (\text{CH}_3); \text{MS m/z (GCMS-EI)} 269 (M}–t-\text{Bu}).

NMR reference: proton 2010-06-08-jpc-56/carbon 2010-02-03-jpc-54

\[
\begin{align*}
\text{TBDPSO} & \quad \text{I} \\
(R,Z)-4-\text{Iodo-2-methylbut-3-enyl oxy) (tert-butyl)diphenylsilane (165)}
\end{align*}
\]

Method 1

To a suspension of iodomethyltriphenylphosphonium iodide (1.18 g, 2.23 mmol, 1.50 eq) in THF (10 ml) was added NaHMDS (5.22 ml of a 0.6 M solution in toluene, 3.13 mmol, 2.10 eq) at rt. After stirring for 5 min., the solution was cooled down to -78 °C and DMPU (1.36 ml, 11.32 mmol, 7.60 eq) was added. The mixture was stirred for approx. 15 min. and a solution of (2S)-3-(tert-butyldiphenylsilylsilyloxy)-2-methylpropanal (164) (486 mg, 1.40 mmol, 1.00 eq) in THF (6 ml) was added dropwise. The reaction was stirred for 3 h at this temperature before being diluted with Et₂O (5 ml) and filtered through celite. The filter cake was rinsed with more Et₂O. The organic layer was washed with a saturated aqueous solution of NH₄Cl and brine, dried (MgSO₄), filtered and the solvent removed. The residue was purified by column chromatography (Petrol-EtO 95:5) to afford the title compound \( \text{E:Z 13:87 (226 mg, 34%)} \) as a colourless oil.
Method 2

((R)-4-Iodo-2-methylbut-3-ynyl oxy)(tert-butyl)diphenylsilane (174) (1.00 g, 2.23 mmol, 1.00 eq) was dissolved in i-PrOH (5 ml) and THF (5 ml) and treated with triethylamine (0.42 ml, 2.99 mmol, 1.34 eq) and nitrobenzenesulfonylhydrazine (173) (544 mg, 2.54 mmol, 1.14 eq). The mixture was stirred for 15 h at rt before being quenched with water (10 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine, dried (MgSO₄) and the solvent removed in vacuo.

Method 3

A solution of BH₃-SMe₂ (1.97 ml of a 2 M solution in toluene, 3.93 mmol, 3.00 eq) was added to a stirred solution of cyclohexene (0.80 ml, 7.87 mmol, 6.00 eq) in Et₂O (4 ml) at 0 °C. The reaction mixture was stirred at rt for 1 h before adding (R)-tert-butyl((4-iodo-2-methylbut-3-yn-1-yl)oxy)diphenylsilane (174) (588 mg, 1.31 mmol, 1.00 eq) in Et₂O (2.5 ml) at 0 °C. After 1 h glacial acetic acid (1.30 ml, 22.71 mmol, 17.00 eq) was added and the reaction stirred for 30 min. at 0 °C. Et₂O (9 ml) was added followed by a saturated aqueous solution of NaHCO₃ (4 ml) at 0 °C. The aqueous layer was washed with brine, dried (MgSO₄), filtered and the solvent removed in vacuo. The crude residue was purified by column chromatography (Petrol 100% then Petrol-EtOAc 98:2) to afford the title compound (460 mg, 78%) as a yellow oil.

RF 0.70 (Petrol:EtOAc 9:1); [α]D²⁰ -57.4 (c = 1.0, CHCl₃); IR νmax(film)/cm⁻¹ 1688 (C=C), 1426 (Si-Ar); ¹H NMR (300 MHz; CDCl₃) δ 7.69-7.66 (4H, m, ArH), 7.43-7.36 (6H, m, ArH), 6.21 (1H, d, J = 7.3, CH), 6.10-6.05- (1H, m, CH), 3.60-3.58 (2H, m, CH₂), 2.84-2.70 (1H, m, CH), 1.07-1.05 (12H, m, (CH₃)₃ + CH₃); ¹³C NMR (75 MHz; CDCl₃) δ 143.9 (CH=CHI), 135.6 (ArCH), 133.7 (ArC), 129.6 (ArCH), 127.6 (ArCH), 81.7 (C=CHI), 67.0 (CH₂OSi), 42.2 (CH(CH₃)), 26.8 (C(CH₃), 19.3 (C(CH₃)₃), 15.7 (CH₃); MS m/z (GCMS-EI) 393 (M–t-Bu); HRMS Found (M–t-Bu+ 393.0168, C₁₇H₁₈OISi M–t-Bu+ requires 393.0166.

A solution of (2S)-3-((tert-butyldiphenylsilylsilyloxy)-2-methylpropanal (164) (574 mg, 2.84 mmol, 1.00 eq) and iodoform (1.97 g, 5.00 mmol, 1.76 eq) in THF (3 ml) was slowly added to a suspension of CrCl₂ (2.09 g, 17.04 mmol, 6.00 eq) at 0 °C in THF (20 ml) and dioxane (5.24 ml). The mixture was stirred at this temperature for 1 h and at rt for 16 h before being quenched with a saturated aqueous solution of NH₄Cl (5 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (Petrol 100%, then Petrol-EtOAc 2:1) to afford the title compound (573 mg, 62%) as an orange oil.

Rf 0.60 (Petrol:EtOAc 9:1); [α]₂²² +11.4 (c = 0.7, CHCl₃); IR νmax (film/cm⁻¹) 2928 (C-H), 2855 (C-H); ¹H NMR (300 MHz; CDCl₃) δ 7.68-7.64 (4H, m, ArH), 7.45-7.37 (6H, m, ArH), 6.5 (1H, dd, J = 7.7, 14.5, CHCHI), 6.09-6.04 (1H, m, C=CHI), 3.52 (2H, d, J = 6.2, CH₂), 2.47-2.36 (1H, m, CH), 1.05 (9H, s, (CH₃)₃), 1.01 (3H, d, J = 6.8, CH₃); ¹³C NMR (100 MHz; CDCl₃) δ 149.1 (CH=CHI), 135.6 (ArCH), 133.6 (ArC), 129.6 (ArCH), 127.7 (ArCH), 75.2 (C=CHI), 67.5 (CH₂OSi), 43.0 (CHCH₃), 26.8 (C(CH₃)₃), 19.2 (C(CH₃)₃), 15.6 (CH₃); MS m/z (ES⁺) 473 (MNa⁺); HRMS Found M⁺, 451.0958 C₂₁H₂₇OISi M⁺ requires 451.0949.

NMR reference: proton 2010-03-05-jpc-31/carbon 2010-03-09-jpc-48
(R)-tert-Butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane (169)

CBr₄ (10.49 g, 31.63 mmol, 3.00 eq) in CH₂Cl₂ (27 ml) was added to a suspension of zinc powder (2.06 g, 31.53 mmol, 3.00 eq) and triphenylphosphine (11.06 g, 42.16 mmol, 4.00 eq) in CH₂Cl₂ (10 ml) at 0 °C and the mixture was stirred for 20 min. A solution of (S)-3-(tert-butyldimethylsilanyloxy)-2-methyl-propionaldehyde (164) (3.44 g, 10.54 mmol, 1.00 eq) in CH₂Cl₂ (10 ml) was then added and the mixture stirred for 4 h at rt. The reaction mixture was poured into pentane (132 ml) filtered to remove the precipitate and concentrated in vacuo. The residue was dissolved in THF (19 ml) and cooled to -78 °C. n-BuLi (11.42 ml of a 2.4 M solution in hexanes, 27.41 mmol, 2.60 eq) was added to the solution and stirred for 1 h before being quenched with a saturated aqueous solution of NaHCO₃ (22 ml). The aqueous layer was extracted with ether (2 x 22 ml) and the organic layers were combined and washed with brine, dried (MgSO₄) and concentrated. The crude residue was purified by column chromatography (100% pentane then 95:5 pentane-EtOAc) to afford the title compound (2.81 g, 64%) as an orange oil.

R₅ 0.24 (Pentane); [α]²⁸D +3.2 (c = 1.2, CHCl₃); IR νmax (film/cm⁻¹) 1427 (Si-Ar); H NMR (400 MHz; CDCl₃) δ 7.62-7.59 (4H, m ArH), 7.36-7.28 (6H, m, ArH), 3.66 (1H, dd, J = 5.7, 9.6, CHH), 3.47 (1H, dd, J = 7.6, 9.6, CHH), 2.65-2.52 (1H, m, CH), 1.95 (1H, d, J = 2.4, CCH), 1.16 (3H, d, J = 6.9, CH₃), 0.99 (9H, s, (CH₃)₃); C NMR (75 MHz; CDCl₃) δ 135.6 (ArCH), 133.6 (ArC), 129.6 (ArCH), 127.6 (ArCH), 86.5 (CCH), 69.0, (CH₂), 67.4 (CCH), 28.8 (C(CH₃), 26.8 (C(CH₃)₃), 19.3 (C(CH₃)₃), 17.3 (CH₃); MS m/z (ES⁺) 345.0 (MNa⁺); HRMS Found MNa⁺ 345.1632, C₂₁H₂₆ONaSi requires MNa⁺ 345.1645.

NMR reference: proton 2010-06-10-jpc-17/carbon 2010-03-30-jpc-54
To a solution of (R)-tert-butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane (169) (1 g, 3.10 mmol, 1.00 eq) in CH₂Cl₂ (11 ml) was added Schwartz’s reagent (960 mg, 3.72 mmol, 1.20 eq) with stirring over 25 min. Iodine (983 mg, 3.87 mmol, 1.20 eq) was then added and the reaction stirred for 30 min. before being quenched with a saturated aqueous solution of Na₂SO₃ (16 ml). The aqueous phase was extracted with CH₂Cl₂ (2 x 10 ml), washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The crude silyl ether (1.40 g) was not purified but carried on in the following step.

**[H]** NMR (crude) (300 MHz; CDCl₃) δ 7.59-7.56 (4H, m, ArH), 7.36-7.29 (6H, m, ArH), 6.45-6.38 (1H, m, CH), 6.00 (1H, d, J = 14.4, CH), 3.44 (2H, d, J = 6.3, CH₂), 2.39-2.27 (1H, m, ArH), 0.98 (9H, s, (CH₃)₃), 0.92 (3H, d, J = 6.9, CH₃).

NMR reference: 2013-03-20-jpc-27

The crude product (1.4 g, 3.10 mmol, 1.00 eq) was dissolved in THF (5 ml). TBAF (4.65 ml) was added dropwise to the above mixture and the reaction stirred for 1 h before being quenched with water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried (MgSO₄) and the solvent removed. The residue was purified by column chromatography (Petrol-EtOAc 75:25) to afford the title compound (510 mg, 82%) as a colourless oil.

* Rf 0.21 (Petrol-EtOAc 8:2); [α]D +15.4 (c = 1.1, CHCl₃); IR v max (film/cm⁻¹) 3328 (OH), 2960 (C-H), 2871 (C-H); \( ^1H \) NMR (300 MHz; CDCl₃) δ 6.47 (1H, dd, J = 14.6, 7.9, CH=CHI), 6.09 (1H, d, J = 14.6, CH=CHI), 3.54-3.44 (2H, m, CH₂), 2.50-2.36 (1H, m, CH), 1.56 (1H, br s, CH₂OH), 1.04 (3H, d, J = 6.9, CH₃); \( ^13C \) NMR (75 MHz; CDCl₃) δ 148.5 (CH=CHI), 76.0 (CH=CHI), 66.5 (CH₂OH), 43.3 (CHCH₃), 15.5 (CH₃); MS m/z (GCMS-EI) 213 (MH⁺).
Jones reagent was prepared by the addition of H\textsubscript{2}SO\textsubscript{4} (2.3 ml) to a solution of CrO\textsubscript{3} (2.78 g) in H\textsubscript{2}O (7.7 ml). (R, E)-4-Iodo-2-methylbut-3-en-1-ol (171) (520 mg, 2.45 mmol, 1.00 eq) was dissolved in acetone (15 ml) and cooled to -10 °C. Jones reagent (3 ml) was added dropwise to the mixture and the reaction stirred for 1 h. i-PrOH (1.9 ml, 24.50 mmol, 10.00 eq) was added to the reaction followed by water (30 ml). The aqueous phase was washed with EtOAc (3 x 50 ml) and then washed with brine, dried (MgSO\textsubscript{4}) and the solvent removed. The residue was purified by column chromatography (Petrol-EtOAc 7:3) to afford the title compound (200 mg, 36%) as a yellow oil.

\textbf{R\textsubscript{F}} 0.55 (Petrol:EtOAc 7:3); \textbf{[α]\textsuperscript{23}D} \textsuperscript{-21.2 (c = 0.98, CHCl\textsubscript{3})}; \textbf{IR} \nu_{\text{max}} \text{ (film/cm}^{-1}) \text{ 2980 (C=O), 1706 (C=O); \textbf{\textsuperscript{1}H NMR} (400 MHz; CDCl\textsubscript{3}) \delta 6.63 (1H, dd, J \textsuperscript{8.0, 14.4, CH}), 6.31 (1H, d, J = 14.4, CH), 3.24-3.17 (1H, m, CH), 1.32 (3H, d, J = 7.2, CH\textsubscript{3}); \textbf{\textsuperscript{13}C NMR} (100 MHz; CDCl\textsubscript{3}) \delta 178.8 (C=O), 143.1 (CH=CHI), 78.2 (CH=CHI), 45.7 (CHCH\textsubscript{3}), 16.3 (CH\textsubscript{3}); \textbf{MS} m/z (ES\textsuperscript{-}) 225 (M\textsuperscript{-}); \textbf{HRMS} Found M\textsuperscript{-} 224.9426, C\textsubscript{5}H\textsubscript{6}O\textsubscript{2} requires M\textsuperscript{-} 224.9418.
(R, E)-tert-Butyl 4-iodo-2-methylbut-3-enoate (172)

TFAA (252 µl, 1.8 mmol, 5.00 eq) was slowly added to a solution of (R,E)-4-iodo-2-methylbut-3-enoic acid (80 mg, 0.35 mmol, 1.00 eq) in t-BuOH (1 ml) and the mixture was stirred for 1 h at rt. The reaction was quenched with a saturated aqueous solution of NaHCO₃ and the aqueous layer was extracted with ethyl acetate (3 x 2 ml), washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (48 mg, 49%) as a colourless oil.

**Rf** 0.80 (Petrol:EtOAc 8:2); \([\alpha]^{25}_D\) −3.2 (c = 1, CHCl₃); **IR** \(\nu_{\text{max}}\)(film)/cm\(^{-1}\) 1723 (C=O); **\(^1\)H NMR** (400 MHz; CDCl₃) \(\delta\) 6.60 (1H, dd, \(J = 7.8, 14.4, \text{CH}\)), 6.19 (1H, d, \(J = 14.4, \text{CH}\)), 3.06-2.99 (1H, m, \(\text{CH}\)), 1.41 (9H, s, \(\text{CH}_3\)), 1.24 (3H, s, \(\text{CH}_3\)); **\(^{13}\)C NMR** (100 MHz; CDCl₃) \(\delta\) 172.0 (C=O), 144.6 (CH=CHI), 81.0 (CH=CHI), 47.0 (CH(CH₃)), 27.0 (CH₃), 16.5 (CH₃), missing (C(CH₃)); **MS** (GCMS-EI) 224 (M–t-Bu); **HRMS** Found M–Or-Bu\(^+\) 208.9448, C₉H₁₅O requires M–Or-Bu\(^+\) 208.9458.

NMR reference: 2010-07-26-jpc-28

-o-Nitrobenzenesulfonylhydrazide (NBSH)\(^3\) (173)

Hydrazine monohydrate (2.75 ml, 56.38 mmol, 2.50 eq) was added dropwise to a solution of o-nitrobenzenesulfonyl chloride (5.00 g, 22.55 mmol, 1.00 eq) in THF (25 ml) at -30 °C.
and stirred for 30 min. EtOAc (45 ml) was added and the mixture washed with 10% aqueous NaCl (5 x 34 ml). The organic phases were dried (MgSO₄) and slowly added to hexane (270 ml). The white precipitate was filtered and washed with hexane then dried in vacuo for 16 h. The title compound (2.70 g, 55%) was obtained as a pale yellow solid. All spectroscopic data were consistent with literature values.

\[ R_f \] 0.48 (EtOAc:hexane 2:1); \(^1\)H NMR (500 MHz; CD₃CN) \( \delta \) 8.11-8.09 (1H, m, ArH), 7.91-7.84 (3H, m, ArH), 5.97 (1H, br s, NH), 3.90 (2H, br s, NH₂); \(^1^3\)C NMR (300 MHz; CD₃CN) \( \delta \) 135.7 (ArCH), 133.6 (ArCH), 133.4 (ArCH), 133.0 (ArC), 131.2 (ArC), 126.0 (ArCH); MS m/z (ES⁺) 240.0 (50%, MNa⁺).

NMR reference: proton 2010-04-20-jpc-6/carbon 2010-04-23-jpc-6

(R)-tert-Butyl((4-iodo-2-methylbut-3-yn-1-yl)oxy)diphenylsilane (174)

(R)-tert-Butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane (169) (1.00 g, 3.11 mmol, 1.00 eq) was dissolved in acetone (13 ml) and treated with N-iodosuccinimide (770 mg, 3.42 mmol, 1.10 eq) and AgNO₃ (53 mg, 0.31 mmol, 0.10 eq). The mixture was stirred at rt for 2.5 h then diluted with hexane (21 ml) and filtered through a pad of celite. Water (7 ml) was added and the aqueous layer was extracted with hexane (2 x 4 ml). The organic layers were combined, washed with brine, dried (MgSO₄) and the solvent removed in vacuo to afford the title compound (1.28 g, 92%) as a yellow oil which turned crystalline on standing.

\[ R_f \] 0.27 (pentane); Mpt 56 °C; \([\alpha]^{26}_D \] +6.3 (c = 1, CHCl₃); IR \( \nu_{max} \) (film/cm\(^{-1}\)) 1427 (Si-Ar); \(^1\)H NMR (500 MHz; CDCl₃) \( \delta \) 7.69-7.46 (4H, m, ArH), 7.46-7.39 (6H, m, ArH), 3.72-3.69 (1H, m, CHH), 3.57-3.54 (1H, m, CHH), 2.86-2.79 (1H, m, CH), 1.22 (3H, d, \( J = 6.6, \)

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(R,Z)-4-Iodo-2-methylbut-3-en-1-ol (176)

TBAF (2.16 ml of a 1 M solution in THF, 2.16 mmol, 1.50 eq) was added dropwise to a solution of (R,Z)-4-iodo-2-methylbut-3-enyl (tert-butyl)diphenylsilane (165) (628 mg, 1.44 mmol, 1.00 eq) in THF (0.8 ml) at 0 °C. The mixture was stirred at for 2 h at rt and the solvent was removed in vacuo. The crude residue was purified by column chromatography (Petrol-EtOAc 75:25) to afford the title compound (204 mg, 67%) as a pale yellow oil.

Jones reagent was prepared by adding H$_2$SO$_4$ (0.44 ml) to a solution of CrO$_3$ (1.48 g) in water (1.48 ml). 0.58 ml of this solution was added dropwise to a solution of (R,Z)-4-iodo-2-methylbut-3-en-1-ol (176) (100 mg, 0.47 mmol, 1.00 eq) in acetone (1.47 ml) at 0 °C. The mixture was stirred for 1 h at this temperature then i-PrOH (0.35 ml, 4.70 mmol, 10.00 eq) and water were added. The aqueous phase was extracted three times with EtOAc and then washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography (Petrol-EtOAc 75:25) to afford the title compound (52 mg, 49%) as a pale yellow oil.

$\text{R}_F$ 0.21 (Petrol:EtOAc 7:3); $[\alpha]^{24}_D$ -61.4 ($c = 1$, CHCl$_3$); IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 2981 (CO$_2$H), 1706 (C=O); $^1$H NMR (300 MHz; CDCl$_3$), $\delta$ 6.43 (1H, d, $J = 7.7$, CHI), 6.33 (1H, dd, $J = 7.7$, 8.7, CH=CH), 3.58-3.48 (1H, m, CHCH$_3$), 1.34 (3H, d, $J = 7.2$, CH$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 178.3 (C=O), 139.2 (CH=CH), 84.3 (CH=CH), 30.9 (CH(CH$_3$), 16.6 (CH$_3$); MS $m/z$ (ES$^+$) 225 (M); HRMS Found M–H$^+$ 224.9416, C$_5$H$_6$O$_2$I requires M–H$^+$ 224.9418.

NMR reference: 2010-07-14-jpc-19

TFAA (0.19 ml, 1.37 mmol, 5.00 eq) was added dropwise to a stirred solution of (R,Z)-4-iodo-2-methylbut-3-enoic acid (178) (62 mg, 0.27 mmol, 1.00 eq) in t-BuOH (0.8 ml).
mixture was stirred for 1.5 h at rt and monitored by TLC. The reaction was cooled to 0 °C and further TFAA (0.11 ml, 0.81, 3.00 eq) was added and the mixture stirred for 30 min. The reaction was quenched with a saturated aqueous solution of NaHCO₃ and the aqueous layer was extracted with EtOAc (3 x 3 ml), washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by column chromatography (Petrol-EtOAc 7:3) to afford the title compound (18 mg, 38% brsm) as a colourless oil.

Rᵥ 0.67 (Petrol:EtOAc 7:3); [α]²¹ D -17.2 (c = 0.5, CHCl₃); IR ν max(film)/cm⁻¹ 1723 (C=O); 

¹H NMR (300 MHz; CDCl₃) δ 6.35-6.27 (2H, m, CH₂), 3.40-3.39 (1H, m, CH), 1.46 (9H, s, (CH₃)₃), 1.26 (3H, d, J = 7.1, CH₃); 

¹³C NMR (75 MHz; CDCl₃) δ 172.7 (C=O), 140.5 (CH=CH), 83.1 (CH=CH₂), 80.9 (C(CH₃)₃), 46.5 (CH(CH₃)), 28.0 ((CH₃)₃), 16.8 (CH₃); 

MS m/z (ES⁻) 225 (M–t-Bu).

NMR reference: 2010-07-19-jpc-40

(E)-3-Chloro-2-methyl-prop-2-en-1-ol⁸⁵ (184)

Titanium tetrachloride (17.83 ml of a 1 M solution in CH₂Cl₂, 17.83 mmol, 3.00 eq) in CH₂Cl₂ was cooled to -78 °C. Isoprene monoxide (0.59 ml, 5.94 mmol, 1.00 eq) in CH₂Cl₂ (3 ml) was added dropwise and the reaction was stirred for 2 h at -78 °C. The reaction was quenched with 1 M HCl (7 ml) and warmed to room temperature. The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 12 ml). The combined organic phases were washed with brine and dried (Na₂SO₄), filtered and the solvent removed in vacuo. The crude product was purified by column chromatography (Petrol-EtOAc 1:1) to afford the title compound (212 mg, 30%) as a light brown oil. All spectroscopic data were consistent with literature values.¹⁴⁶
**RF** 0.43 (Petrol:EtO 7:3); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 5.74 (1H, tq, J = 7.8, 1.5, =CH), 4.13 (2H, d, J = 7.8, CH$_2$Cl), 4.07 (2H, s, CH$_2$OH), 1.74 (3H, s, CH$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 141.2 (CH$_3$C=CH), 120.4 (CH$_3$C=CH), 67.5 (CH$_2$OH), 40.1 (CH$_2$Cl), 13.5 (CH$_3$); MS (ES$^+$) 143 ([M$^{35}$Cl]+Na$^+$).


![MeO$_2$C=CHBr](image)

(E)-4-Bromo-2-methylbut-2-enoate$^{86,147}$ (185)

Phosphorous tribromide (71 μl, 0.76 mmol, 0.33 eq) in CCl$_4$ (0.6 ml), was added to a solution of (E)-methyl 4-hydroxy-2-methylbut-2-enoate (188) (300 mg, 2.31 mmol, 1.00 eq) in CCl$_4$ (7 ml) at 0 °C. The reaction was stirred at rt for 1 h and quenched with a saturated aqueous solution of NaHCO$_3$ (0.5 ml). The aqueous layer was extracted with pentane (2 x 2ml), the combined organic phases were washed with brine and dried (MgSO$_4$) and the solvent removed in vacuo to afford the title compound (300 mg, 67%) as a pale yellow oil. All spectroscopic data were consistent with literature values.$^{86,147}$

**RF** 0.61 (Petrol:EtOAc 7:3); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 6.93 (1H, tq, J = 8.6, 1.5, C=CH), 4.04 (2H, d, J = 8.6, CH$_3$), 3.77 (3H, s, CH$_3$), 1.93 (3H, s, CH$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$ 167.7 (CO$_2$CH$_3$), 135.0 (CH$_3$C=CHCH$_2$), 131.9 (CH$_3$C=CHCH$_2$), 52.2 (OCH$_3$), 26.0 (CH$_2$Br), 12.2 (CH$_3$); MS m/z (EI) 113 (M–[H$_{79}$Br]).

NMR reference: 2010-03-05-ejt-19
Triphenylphosphine (7.14 g, 27.24 mmol, 0.91 eq) was added to a solution of 2-bromopropionate (3.34 ml, 29.94 mmol, 1.00 eq) in acetonitrile (41 ml) and the mixture was heated to 65 °C for 24 h. The reaction was cooled to 0 °C and diisopropylethylamine (4.74 ml, 27.24 mmol, 0.91 eq) was added followed by portion-wise addition of glyoxylic acid monohydrate (2.51 g, 27.24 mmol, 0.91 eq). The reaction was stirred for 2 h at 0 °C and 72 h at rt. EtOAc (34 ml) was added to the reaction mixture and extracted with an aqueous saturated solution of NaHCO₃ until no more gas was evolved. The aqueous phase was washed with EtOAc (5 x 10 ml) and acidified to pH 1-2 with conc. HCl and then extracted with EtOAc (5 x 10 ml). The combined organic phases were dried (MgSO₄) and the solvent removed to afford the title compound (2.54 g, 59%) as a white solid. All spectroscopic data were consistent with literature values.⁸⁶,¹⁴⁷

Rₓ 0.86 (Petrol:EtOAc 1:1); Mpt 80-82 °C; IR νₓ_max(film/cm⁻¹) 2914 (CO₂H), 1720 (C=O); ¹H NMR (300 MHz; CDCl₃) δ 6.74 (1H, q, J = 1.5), 3.76 (3H, s, CO₂CH₃), 2.26 (3H, d, J = 1.5, CH₃); ¹³C NMR (75 MHz; CDCl₃) δ 170.3 (CO₂H), 167.3 (CO₂CH₃), 146.0 (CH₃C=), 125.7 (CH₃C=), 52.7 (CO₂CH₃), 14.6 (CH₃); MS m/z (ES⁻) 143.0 (MH⁻); HRMS Found M⁺ 143.0350, C₆H₈O₄ requires M⁺ 143.0349.

NMR reference: proton 2010-01-29-jpc-58/carbon 2010-01-29-jpc-46
To a solution of (E)-3-(methoxycarbonyl)but-2-enoic acid (186) (1.00 g, 6.93 mmol, 1.00 eq) in THF (20 ml) was added BH$_3$-Me$_2$S (3.82 ml of a 2 M solution in toluene, 7.63 mmol, 1.10 eq) at -15 °C. The reaction was gradually allowed to warm to rt and stirred for 16 h before being quenched with methanol (2 ml). The solvent was removed in vacuo then more methanol was added and the solvent removed again. This was repeated once more and the crude residue was purified by column chromatography (EtOAc-Petrol 7:3) to afford the title compound (565 mg, 63%) as a colourless oil. All spectroscopic data were consistent with literature values.\(^{86,147}\)

R$_F$ 0.47 (EtOAc:Petrol 7:3); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 6.83 (1H, tq, $J = 6.0, 1.5, C=CH$), 4.36 (2H, dd, $J = 6.0, 1.1, CH_2OH$), 3.75 (3H, s, CO$_2$CH$_3$), 1.84 (3H, s, CH$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 168.1 (CO$_2$CH$_3$), 140.2 (C=CCH$_2$), 128.5 (C=CCH$_2$), 59.7 (CH$_2$), 51.9 (OCH$_3$), 12.7 (CH$_3$); MS m/z (ES$^+$) 153 (MNa$^+$).

NMR reference: 2010-02-25-jpc-57

To a solution of tert-butyl methyl-2-bromopropionate (7.94 ml, 47.83 mmol, 1.00 eq) in acetonitrile (65 ml) was added triphenylphosphine (11.41 g, 43.52 mmol, 0.91 eq). The mixture was heated to 65 °C for 24 h. The reaction was cooled to 0 °C and
diisopropylethylamine (15.17 ml, 87.05 mmol, 1.82 eq) was added followed by portion-wise addition of glyoxylic acid monohydrate (8.01 g, 87.05 mmol, 1.82 eq). The reaction was stirred for 2 h at 0 °C and 72 h at rt. EtOAc (34 ml) was added and the mixture was extracted with a saturated aqueous solution of NaHCO₃ until no more gas was evolved. The aqueous phase was washed with EtOAc (5 x 10 ml) and acidified to pH 1-2 with conc. HCl and then extracted with EtOAc once more (5 x 10 ml) The combined organic phases were dried (MgSO₄) and the solvent removed to afford the title compound (3.00 g, 33%) as an orange oil.

\[
R_f \ 0.55 \ (\text{Petrol:EtOAc \ 1:1}); \ IR \ \nu_{\text{max}}(\text{film/cm}^{-1}) \ 2980 \ (\text{CO}_2\text{H}), 1699 \ (\text{C}=\text{O}); \ \text{H NMR} \ (300 \ \text{MHz}; \text{CDCl}_3) \ \delta \ 6.72-6.71 \ (1\text{H}, \text{m, CH}), 2.23 \ (3\text{H, d, } J = 3.0, \text{CH}_3), 1.51 \ (9\text{H, s, (CH}_3)_3); \ \text{C NMR} \ (75 \ \text{MHz}; \text{CDCl}_3) \ \delta \ 171.6 \ (\text{C}=\text{O}), 166.0 \ (\text{CO}_2\text{(CH}_3)_3), 148.0 \ (\text{CH}=\text{CCH}_3), 124.8 \ (\text{CH}=\text{CCH}_3), 82.2 \ (\text{C(CH}_3)_3), 27.9 \ (\text{CH}_3), 14.6 \ (\text{CH}_3); \ \text{MS} \ m/z \ (\text{ES}^-) \ 185 \ (\text{MH}^-); \ \text{HRMS} \ \text{Found} \ M^-H^+ \ 185.0819, \ C_9\text{H}_{13}\text{O}_4 \text{requires} \ M^-H^+ \ 185.0817.
\]


\[(E)-\text{tert-Butyl 4-hydroxy-2-methylbut-2-enoate (191)}\]

To a solution of (E)-3-(tert-butoxycarbonyl)but-2-enoic acid (190) (1.00 g, 5.37 mmol, 1.00 eq) in THF (20 ml) was added dropwise BH₃-Me₂S (2.96 ml of a 2 M solution in toluene, 5.91 mmol, 1.10 eq) at -15 °C. The reaction was gradually allowed to warm to rt and stirred for 16 h before being quenched with methanol (2 ml). The solvent was removed \textit{in vacuo} more methanol was added and the solvent removed again. This was repeated once more and the crude residue was purified by column chromatography (Petrol-EtOAc 7:3) to afford the title compound (631 mg, 68%) as a yellow oil.
Rf 0.61 (EtOAc:Petrol 7:3); IR $\nu_{\text{max}}$(film/cm$^{-1}$) 3500 (OH), 1708 (C=O); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 6.74 (1H, t, $J = 6.2$, C=CH), 4.35 (2H, d, $J = 6.2$, CH$_2$OH), 1.81 (3H, s, CH$_3$), 1.50 (9H, s, (CH$_3$)$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$ 166.9 (C=O), 138.7 (CH$_3$C=CH), 130.2 (CH$_3$C=CH), 80.5 (C(CH$_3$)$_3$), 59.8 (CH$_2$), 28.0 (CH$_3$)$_3$, 12.7 (CH$_3$); MS $m/z$ (GCMS-EI) 98 (M--t-Bu, – OH); HRMS Found MH$^+$ 173.1166, C$_9$H$_{17}$O$_3$ requires MH$^+$ 173.1172.


\[
\text{Phosphorous tribromide (22 µl, 0.24 mmol, 0.33 eq) in CCl}_4 (0.2 \text{ ml}), was added to a solution of (E)-tert-butyl 4-hydroxy-2-methylbut-2-enoate (191) (120 mg, 0.70 mmol, 1.00 eq) in CCl}_4 (2 \text{ ml}) at 0 °C. The reaction was stirred at rt for 2 h and quenched with a saturated aqueous solution of NaHCO$_3$ (0.5 ml). The aqueous layer was extracted with pentane (2 x 2 ml), the combined organic phases were washed with brine and dried (MgSO$_4$) and the solvent removed in vacuo. The crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (35 mg, 21%) as a pale yellow oil.}

Rf 0.71 (Petrol:EtOAc 7:3); IR $\nu_{\text{max}}$(film/cm$^{-1}$) 1707 (C=O); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 6.82 (1H, tq, $J = 8.5$, 1.5, C=CH), 4.02 (2H, d, $J = 8.5$, CH$_2$), 1.88 (3H, s, CH$_3$), 1.49 (9H, s, (CH$_3$)$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ 166.4 (C=O), 133.8 (CH=CH$_2$), 80.9 (C(CH$_3$)$_3$, 28.0 (CH$_3$)$_3$, 26.4 (CH$_2$), 12.2 (CH$_3$), missing (CH$_3$)C=C; MS (GCMS-EI) 176 ([M$^{79}$Br]$^+$.t-Bu).

± tert-Butyl 3-(3-oxoprop-1-yn-1-yl)pyrrolidine-1-carboxylate (207)

To a solution of tert-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (30 mg, 0.15 mmol, 1.00 eq) in THF (0.4 ml) at -40 °C was added n-BuLi (68 µl of a 2.5 M solution in hexanes, 0.17 mmol, 1.10 eq) over 2 min. resulting in a yellow solution. Anhydrous DMF (23 µl, 0.30 mmol, 2.00 eq) was added in one portion and the reaction warmed to rt for 45 min. A 10% solution of aqueous KH$_2$PO$_4$ (0.81 ml) and MTBE (0.75 ml) was added and the mixture stirred vigorously with cooling to 5 °C. The organic phase was washed with water. Then the aqueous phase was extracted with MTBE, dried (MgSO$_4$) and the solvent removed in vacuo. The crude product was purified by column chromatography (Petrol-EtOAc 8:2) to afford the title compound (9 mg, 27%) as a yellow oil.$^9$5

R$_f$ 0.14 (Petrol:EtoAc 8:2); IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 2239 (C=O), 2210 (C=O), 1694 (C=O); $^1$H NMR (400 MHz; toluene, 100 °C) δ 8.76 (1H, s, CHO), 3.35-3.26 (1H, m, CHCHHN), 3.24-3.20 (1H, m, CH$_2$CHHN), 3.14-3.10 (1H, m, CHCHHN), 3.04-2.97 (1H, m, CH$_3$CHHN), 2.43-2.36 (1H, m, CHCC), 1.57-1.45 (2H, m, CH$_2$CH$_2$N), 1.42 (9H, s, (CH$_3$)$_3$); $^{13}$C NMR (100 MHz; toluene, 100 °C) δ 174.9 (CHO), 154.0 (CO), 96.0 (CCCHO), 82.8 (C(CH$_3$)$_3$), 79.1 (CCCHO), 51.2 (CH$_3$N), 45.3 (CH$_2$N), 31.9 (CH$_2$CH$_2$N), 30.0 (CH), 28.8 (CH$_3$)$_3$; MS $m/z$ (ES$^+$) 246 (MNa$^+$); HRMS Found MNa$^+$ 246.1110, C$_{12}$H$_{17}$O$_3$NNa requires MNa$^+$ 246.1101.

NMR reference: 2011-02-03-admin-58
± tert-Butyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)pyrrolidine-1-carboxylate (214)

Method 1

tert-Butyl 3-ethynylpyrrolidine-1-carboxylate (148) (100 mg, 0.51 mmol, 1.00 eq) in dry methanol (1.2 ml) was added to a mixture of PdCl₂ (5.1 mg, 0.03 mmol, 0.06 eq) and CuCl₂ (137 mg. 1.02 mmol, 2.00 eq) in methanol (4 ml) and the reaction was stirred at rt under an atmosphere of CO. After 6 h the reaction mixture was filtered through celite and the solvent removed. The residue was dissolved in EtOAc (2 ml) and washed with water, brine and dried (MgSO₄), the solvent was removed in vacuo. The crude residue was purified by column chromatography (Petrol-EtOAc 8:2 then 6:4) to afford the title compound (78 mg, 61%) as a colourless oil.

Method 2

n-BuLi (1.02 ml of a 1.89 M solution in hexanes, 1.92 mmol, 2.50 eq) was slowly added to a solution of tert-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (150 mg, 0.77 mmol, 1.00 eq) dissolved in Et₂O (3 ml) at -78 °C. The reaction was stirred for 1 h at this temperature before the addition of methyl chloroformate (178 µl, 2.31 mmol, 3.00 eq). The reaction was then stirred for 2.5 h at -78 °C and then warmed to rt. The reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc (2 x 2 ml), washed with brine, dried (MgSO₄) and the solvent removed. The crude residue was purified by column chromatography (Petrol-EtOAc 8:2) to afford the title compound (101 mg, 51% brsm) as a colourless oil.

Rᵥ 0.20 (Petrol:EtOAc 4:1); IR νmax(film/cm⁻¹) 2240 (CC), 1718 (C=O), 1705 (C=O); ¹H NMR (400 MHz; toluene, 100 °C) δ 3.37-3.31 (4H, m, OC₃H₃ + CH₂CH₂N), 3.26-3.19 (1H, m, CH₂CHHN), 3.16-3.11 (1H, m, CHCH₂HN), 3.04-2.96 (1H, m, CH₂CHHN), 2.43-2.35 (1H, m, CHCH₂N), 1.56-1.43 (2H, m, CH₂CH₂N), 1.41 (9H, s, (CH₃)₃); ¹³C NMR
(100 MHz; toluene, 100 °C) δ 154.0 (CO₂CH₃), 153.7 (C=O), 88.4 (CO₂CH₃), 79.2 (C(CH₃)₃), 74.9 (CO₂CH₃), 51.8 (OCH₃), 51.2 (CH₂N), 45.3 (CH₂N), 31.9 (CH₂CH₂N), 29.8 (CHCC), 28.8 (C(CH₃)₃); MS m/z (ES⁺) 276 (MNa⁺); HRMS Found MNa⁺ 276.1204, C₁₃H₁₉O₄NNa requires MNa⁺ 276.1206.


± (E)-tert-Butyl 3-(4-methoxy-4-oxobut-2-en-2-yl)pyrrolidine-1-carboxylate (215)

To a solution of CuI (19 mg, 0.10 mmol, 1.00 eq) in Et₂O at 0 °C was added MeLi (0.16 ml of a 1.25 M solution in Et₂O, 20 mmol, 2.00 eq). A solution of tert-butyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)pyrrolidine-1-carboxylate (214) (25 mg, 0.10 mmol, 1.00 eq) was added dropwise to the above mixture, and the reaction was stirred for 2.5 h at rt. The reaction was quenched with a saturated aqueous solution of NaHCO₃, and extracted with Et₂O, washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The title compound (22 mg, 82%) was obtained without purification as a yellow oil.

Rₛ 0.15 (Petrol:EtOAc 4:1); IR v_max(film)/cm⁻¹; 1696 (C=O); ¹H NMR (300 MHz; CDCl₃) δ 5.60 (1H, s, C=C=CH), 3.70 (3H, s, OCH₃), 3.57-3.29 (4H, m, (CH₂)₂N), 2.04 (3H, s, CH₂C=CH), 2.07-2.03 (1H, m, CHCH₂N), 1.87-1.82 (2H, m, CH₂CH₂N), 1.46 (9H, s, (CH₃)₃); ¹³C NMR (100 MHz; toluene, 100 °C) δ 166.7 (CO₂CH₃), 157.6 (CH₃C=CH), 154.3 (CO), 116.2 (C=CH), 79.0 (C(CH₃)₃), 50.3 (OCH₃), 49.9 (CH₂N), 45.9 (CH₂N), 40.0 (CHCH₂N), 30.3 (CH₂CH₂N), 28.9 (CH₃), 17.0 (CH₃); MS m/z (ES⁺) 292 (MNa⁺); HRMS Found MNa⁺ 292.1509, C₁₄H₂₃NO₄Na requires MNa⁺ 292.1520.

± (E)-tert-Butyl 3-(4-oxopent-2-en-2-yl)pyrrolidine-1-carboxylate (216)

To a solution of CuI (56 mg, 0.30 mmol, 1.5 eq) in Et₂O at 0 °C was added MeLi (0.61 ml of a 0.97 M solution in Et₂O, 0.59 mmol, 3.00 eq). The solution was stirred at 0 °C for 30 min. then cooled to -78 °C then a solution of tert-butyl 3-(3-methoxy-3-oxoprop-1-yn-1-yl)pyrrolidine-1-carboxylate (214) (50 mg, 0.20 mmol, 1.00 eq) in THF (0.5 ml) was added dropwise to the above mixture, and the reaction was stirred at -78 °C for 5 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl, and extracted with Et₂O, washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The residue was purified by column chromatography (Petrol-EtOAc 4:1) to afford the title compound (13 mg, 26%) and (E)-tert-butyl 3-(4-methoxy-4-oxobut-2-en-2-yl)pyrrolidine-1-carboxylate (215) (14 mg, 25%) as yellow oils.

Rf 0.18 (Petrol:EtOAc 4:1); IR νmax(film)/cm⁻¹ 1690 (C=O); ¹H NMR (300 MHz; CDCl₃) δ 6.10 (1H, s, C=CH), 3.63-3.51 (2H, m, CH₂CHHN + CHCHHN), 3.37-3.26 (1H, m, CH₂CHHN), 3.23-3.08 (1H, m, CHCHHN), 2.89-2.78 (1H, m, CHCH₂N), 2.20 (3H, s, CH₃C=C), 2.14 (3H, s, COCH₃), 2.09-2.01 (1H, m, CHHCH₂N), 1.91-1.77 (1H, m, CHHCH₂N), 1.48 (9H, s, (CH₃)₃); ¹³C NMR (100 MHz; DMSO, 100 °C) δ 197.5 (COCH₃), 154.1 (CH₂C=CH), 153.1 (COC(CH₃)₃), 123.0 (CH₂C=CH), 77.8 (C(CH₃)₃), 48.7 (CH₂N), 46.2 (CHCH₂N), 44.8 (CH₂N), 30.8 (COCH₃), 28.8 (CH₂CH₂N), 27.7 (C(CH₃)₃), 16.4 (CH₃); MS m/z (ES⁺) 276 (50%, MNa⁺); HRMS Found MNa⁺, 276.1569, C₁₄H₂₃NO₃Na requires MNa⁺ 276.1571.

NMR reference: proton 2012-04-12-jpc-12/carbon 2012-04-27-admin-12
\[ \pm (E)\text{-}\text{tert-Butyl 3-}(4\text{-}\text{oxobut-2-en-2-yl})\text{pyrrolidine-1-carboxylate (222)}\]

tert-Butyl 3-ethynylpyrrolidine-1-carboxylate (148) (30 mg, 0.15 mmol, 1.00 eq), Hoyveda Grubbs catalyst 2\textsuperscript{nd} generation (13 mg, 0.02 mmol, 0.10 eq), \(\text{CuSO}_4\) (77 mg, 0.31 mmol, 2.00 eq) and ethyl vinyl ether (132 \(\mu\)l, 1.38 mmol, 9.00 eq) were placed in a microwave vial with \(t\text{-}\text{BuOH (0.75 ml) and water (0.75 ml). The vial was sealed and heated in the microwave at 80 °C for (2 x 10 min) at 400 W. The reaction was extracted with \(\text{Et}_2\text{O (2 x 2 ml) and the organic phases washed with brine, dried (MgSO}_4\) and concentrated in vacuo. The crude residue was purified by gravity column chromatography (Petrol:EtOAc 8:2) to afford the title compound (15 mg, 39%) as a yellow oil.\]}

R\(_F\) 0.39 (Petrol:EtOAc 7:3); IR \(\nu_{max}\) (film/cm\(^{-1}\)) 1692 (C=O); \(^1\text{H NMR}\) (400 MHz; CDCl\(_3\)) \(\delta\) 10.04 (1H, d, \(J = 7.8\), CHO), 5.91 (1H, dt, \(J = 7.8, 1.2\), C=CH), 3.69-3.49 (2H, m, \(\text{CH}_2\text{CH}_2\text{N}\)), 3.41-3.30 (1H, m, CHHN), 3.24-3.17 (1H, m, CHHN), 2.97-2.88 (1H, m, CHC=C), 2.21 (3H, s, CH\(_3\)), 2.15-2.09 (1H, m, CHHCH\(_2\text{N}\)), 1.90-1.82 (1H, m, CHHCH\(_2\text{N}\)), 1.47 (9H, s, (CH\(_3\)))\(_3\); \(^{13}\text{C NMR}\) (100 MHz; CDCl\(_3\), 25 °C) \(\delta\) 2 rotamers: 191.2 (CHO), 161.3 (CH\(_3\)C=CH), 154.4 (C=O), 126.8 (CH\(_3\)C=CH), 79.6 (C(CH\(_3\))\(_3\)), 49.2 (0.5C (CH\(_2\)CH\(_2\)N)), 48.9 (0.5C (CH\(_2\)CH\(_2\)N)), 47.6 (0.5C (CHCH\(_2\)N)), 46.8 (0.5C (CHCH\(_2\)N)), 45.5 (0.5C (CHCH\(_2\)N)), 45.3 (0.5C (CHCH\(_2\)N)), 29.8 (0.5C (CH\(_2\)CH\(_2\)N)), 29.7 (0.5C (CH\(_2\)CH\(_2\)N)), 28.5 (C(CH\(_3\))\(_3\)), 16.2 (CH\(_3\)C=CH); MS \(m/z\) (ES\(^{+}\)) 262 (MNa\(^{+}\)); HRMS Found MNa\(^{+}\) 262.1412, \(C_{13}\text{H}_{23}\text{NO}_3\text{Na}\) requires MNa\(^{+}\) 262.1414.

NMR reference: 2012-10-19-admin-13

Compound 223 (7 mg, 16%) was also isolated from the same reaction mixture.
\[ \pm (E)\text{-}\text{tert-Butyl 3-((trimethylsilyl)ethynyl)pyrrolidine-1-carboxylate} \]

**± (E)-tert-Butyl 3-(4-ethoxybuta-1,3-dien-2-yl)pyrrolidine-1-carboxylate (223)**

\[ R_F \ 0.68 \text{ (Petrol:EtOAc 7:3); } \text{IR } \nu_{\text{max}} \text{ (film/cm}^{-1}) \ 1696 (\text{C}=\text{O}); \]  \[ ^1\text{H NMR} \text{ (300 MHz; CDCl}_3) \]  \[ \delta \ 6.63 (1H, d, J = 13.0, \text{C}=\text{CHOEt}), \ 5.52 (1H, d, J = 13.0, \text{CH}=\text{CHOEt}), \ 4.87-4.72 (2H, m, \text{CH}), \ 3.69-3.41 (2H, m, \text{OCH}_2\text{CH}_3), \ 3.38-3.03 (4H, m, 2(\text{CH}_2\text{N})), \ 2.92-2.85 (1H, m, \text{CHCH}_2\text{N}), \ 2.09-1.99 (1H, m, \text{CHHCH}_2\text{N}), \ 1.93-1.78 (1H, m, \text{CHHCH}_2\text{N}), \ 1.47 (9H, s, (\text{CH}_3)_3), \ 1.33-1.28 (3H, m, \text{OCH}_2\text{CH}_3); \]  \[ ^{13}\text{C NMR} \text{ (100 MHz; DMSO, 100 °C) } \delta \ 153.1 (\text{C}=\text{O}), \ 150.9 (\text{CH}=\text{CHOEt}), \ 142.7 (\text{C}=\text{CH}_2), \ 109.3 (=\text{CH}_2), \ 99.2 (\text{CH}=\text{CHOEt}), \ 77.9 (\text{C}(\text{CH}_3)_3), \ 71.5 (\text{CH}_2\text{CH}_3), \ 55.6 (\text{CH}_2\text{N}), \ 48.5 (\text{CH}_2\text{N}), \ 44.7 (\text{CHCH}_2\text{N}), \ 30.7 (\text{CH}_2\text{CH}_2\text{N}), \ 27.7 (\text{C}(\text{CH}_3)_3), \ 15.3 (\text{CH}_2\text{CH}_3); \]  \[ \text{MS (ES}^+\text{) 290 (MNa}^+\text{)}. \]


\[ \pm \text{tert-Butyl 3-((trimethylsilyl)ethynyl)pyrrolidine-1-carboxylate}^{58} \text{ (236)} \]

\[ n\text{-BuLi (0.24 ml of a 2.5 M solution in hexanes, 0.61 mmol, 1.20 eq,) was added dropwise to a solution of tert-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (100 mg, 0.51 mmol, 1.00 eq) in THF (2.6 ml) at -78 °C and the mixture stirred for 40 min. at this temperature. TMSCl (0.13 ml, 1.02 mmol, 2.00 eq) was added to the above mixture and the reaction stirred for a further 1.5 h at -78 °C. The reaction was quenched with a saturated aqueous solution of NH}_4\text{Cl, extracted with EtOAc, washed with brine and dried (MgSO}_4\text{).} \]

- 180 -
crude residue was purified by column chromatography (Petrol-EtO 9:1) to afford the title compound (102 mg, 75%) as a colourless oil. All spectroscopic data were consistent with literature values.\textsuperscript{58}

R\textsubscript{f} 0.20 (Petrol:EtOAc 9:1); \textsuperscript{1}H NMR (400 MHz; DMSO, 100 °C) \( \delta \) 3.51 (1H, dd, \( J = 7.2, 10.3 \), C\( HH\)HNCHCCSiMe\(_3\)), 3.41-3.35 (1H, m, C\( HH\)HNCH\(_2\)), 3.27-3.20 (1H, m, C\( HH\)HNCH\(_2\)), 3.16 (1H, dd, \( J = 7.2, 10.3 \), C\( HH\)HNCH\(_2\)), 2.14-2.07 (1H, m, C\( HH\)CH\(_2\)), 1.86-1.78 (1H, m, C\( HH\)CH\(_2\)), 1.42 (9H, s, C(CH\(_3\))\(_3\)), 0.14 (9H, s, Si(CH\(_3\))\(_3\)). \textsuperscript{13}C NMR (400 MHz; DMSO, 100 °C) \( \delta \) 153.0 (C\( =O\)), 107.3 (C\( Si(CH_3)\)), 84.9 (CCSiMe\(_3\)), 77.9 (C(CH\(_3\))\(_3\)), 51.0 (CH\(_2\)), 44.2 (CH\(_2\)), 31.3 (CH\(_2\)), 29.2 (CH(CCSiMe\(_3\))), 27.7 (C(CH\(_3\))\(_3\)), -0.6 (Si(CH\(_3\))\(_3\)); MS m/z (ES\(^+\)) 290 (MNa\(^+\)).


\( \pm \) (Z)-\textit{tert}-butyl 3-(2-(trimethylsilyl)vinyl)pyrrolidine-1-carboxylate (237)

\textit{i}-PrMgCl (0.11 ml of a 2 M solution in Et\(_2\)O, 0.22 mmol, 2.00 eq) was added to a stirred solution of \textit{tert}-butyl 3-((trimethylsilyl)ethynyl)pyrrolidine-1-carboxylate (236) (30 mg, 0.11 mmol, 1.00 eq) and Ti(Oi-Pr\(_4\)) (33 µl, 0.11 mmol, 1.00 eq) in Et\(_2\)O (1.2 ml) at -78 °C. The mixture was warmed to -50 °C over 30 min. and stirred at 50 °C for 2 h. The reaction was cooled to -78 °C and MeI (5 µl, 0.08 mmol, 0.71 eq) was added and the reaction stirred at this temperature for 1 h before being quenched with water (0.12 ml) and warmed to rt. The mixture was filtered through celite, dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The title compound was obtained as an inseparable 1:1 mixture (39 mg) with the starting material (236) as a yellow oil.\textsuperscript{108}

R\textsubscript{f} 0.44 (Petrol:EtOAc 8:2); IR \( \nu_{\text{max}} \)(film)/cm\(^{-1}\) 2964 (C=C), 2880 (C-H), 1698 (C=O), 1403 (C=C-Si); \textsuperscript{1}H NMR (400 MHz; toluene, 100 °C) \( \delta \) 5.98 (1H, dd, \( J = 9.5, 14.0 \), - 181 -
CH=CHSiMe$_3$, 5.47 (1H, d, J = 14.0, CH=CHSiMe$_3$), 3.41-3.30 (2H, m, CH$_2$N), 3.09-2.96 (2H, m, CH$_2$N), 2.58-2.50 (1H, m, CH), 1.71-1.55 (2H, m, CH$_2$CH$_2$N), 1.45 (9H, s, (CH$_3$)$_3$), 0.13 (9H, s, Si(CH$_3$)$_3$) (Only product peaks reported); $^{13}$C NMR (100 MHz; toluene, 100 °C) $\delta$ 154.4 (CH=CSi(CH$_3$)$_3$), 149.5 (2C=O), 130.9 (CH=CSi(CH$_3$)$_3$), 78.9 (C(CH$_3$)$_3$), 52.3 (CH$_2$N), 46.1 (CH$_2$N), 43.1 (CHCH$_2$N), 33.0 (CH$_2$CH$_2$N), 28.9 (C(CH$_3$)$_3$), 0.43 (Si(CH$_3$)$_3$) (Only product peaks reported); MS m/z (ES$^+$) 292 (60%, MNa$^+$); HRMS Found MNa$^+$ 292.1700, C$_{14}$H$_{27}$O$_2$NNaSi requires MNa$^+$ 292.1704.

NMR reference: 2011-03-09-admin-41

Li$_2$Cu(CN)Cl$_2$

Knochel’s salt$^{148}$ (242)

CuCN (896 mg, 10 mmol, 1.00 eq) and LiCl (848 mg, 20 mmol, 2.00 eq) were placed in a Schlenck flask under vacuum for 5 h at 140 °C. After cooling the flask to rt, THF (10 ml) was added and the mixture stirred for 24 h resulting in a clear green solution.

1-Trimethylsilyloct-1-yne$^{116}$ (247)

A solution of $n$-BuLi (1.3 ml of a 2.5 M solution in hexanes, 3.26 mmol, 1.20 eq) was added dropwise to a solution of octyne (300 mg, 2.72 mmol, 1.00 eq) in THF at −78 °C. The mixture was stirred for 40 min. at this temperature. TMSCl (690 µl, 5.44 mmol, 2.00 eq) was added and the reaction mixture stirred for 1.5 h at -78 °C. The reaction mixture was then filtered to remove the LiCl and the solvent removed to afford the title compound (394 mg, 79%) as a colourless oil. All spectroscopic data were consistent with literature values.$^{116}$

R$_F$ 0.25 (hexane); $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ 2.25-2.20 (2H, m, CH$_2$), 1.57-1.26 (8H, m, (CH$_2$)$_4$), 0.92-0.88 (3H, m, CH$_3$), 0.15 (9H, s, (CH$_3$)$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ -182 -
A solution of i-PrMgCl (102 µl of a 2 M solution in Et₂O, 0.34 mmol, 1.25 eq) was added to a stirred solution of 1-trimethylsilyloct-1-yne (247) (50 mg, 0.27 mmol, 1.00 eq) and Ti(i-Pr)₄ (343 µl, 0.34 mmol, 1.25 eq) in Et₂O (4 ml) at -78 °C. The mixture was warmed to -50 °C over 30 min. and stirred at 50 °C for 2 h followed by the addition of s-BuOH (300 µl, 0.30 mmol, 1.10 eq). Li₂Cu(CN)Cl₂ (242) (300 µl of a 1 M solution in THF, 0.30 mmol, 1.10 eq) was added and the reaction warmed to −25 °C over 1 h. Allyl bromide (26 µl, 0.30 mmol, 1.10 eq) was added and the mixture was warmed to 0 °C over 1.5 h and stirred at 0 °C for 1 h, followed by stirring at rt for 1 h. The reaction was quenched with 1 M HCl and extracted with Et₂O. The combined organic phases were washed with a saturated aqueous solution of NaHCO₃, dried (MgSO₄) and the solvent removed. The crude product was purified by column chromatography (hexane) to afford the title compound (21 mg, 32%) as a colourless oil. All spectroscopic data were consistent with literature values.

**RF** 0.24 (hexane); **¹H NMR** (300 MHz; CDCl₃) δ 5.87-5.74 (1H, m, CH), 5.20 (1H, s, CH), 5.02-4.99 (2H, m, C=CH), 2.81 (2H, dd, J = 1.2, 6.9, CH₂), 2.13-2.08 (2H, m, CH₂), 1.39-1.29 (8H, m, (CH₂)₄), 0.89 (3H, t, J = 7.2, CH₃), 0.09 (9H, s, Si(CH₃)₃); **¹³C NMR** (75 MHz; CDCl₃) δ 158.0 (C), 136.9, (CH₂=C), 124.3 (CHSiMe₃), 115.9 (=CH₂), 43.5 (CH₂), 36.2 (CH₂), 31.8 (CH₂), 29.6 (CH₂), 29.0 (CH₂), 22.6 (CH₂), 14.1 (CH₃), 0.4 (Si(CH₃)₃); **MS** m/z (ES⁺) 225 (MH⁺).

NMR reference: 2011-04-14-jpc-44
\( \pm (E)-\text{tert-Butyl 3-}(1\text{-iodo-2-(trimethylsilyl)vinyl})\text{pyrrolidine-1-carboxylate (253)} \)

\( i\text{-PrMgCl (95 µl of a 2 M solution in Et}_2\text{O, 0.18 mmol, 2.50 eq) was added to a stirred solution of tert-butyl 3-((trimethylsilyl)ethynyl)pyrrolidine-1-carboxylate (236) (20 mg, 0.08 mmol, 1.00 eq) and Ti(Oi-Pr)\text{4 (28 µl, 0.09 mmol, 1.25 eq) in Et}_2\text{O (1 ml) at -78 °C. The mixture was warmed to -50 °C over 30 min. and stirred at 50 °C for 2 h. s-BuOH (90 µl of a 1 M solution in Et}_2\text{O, 0.08 mmol, 1.20 eq) was added at -50 °C and the mixture was stirred for 1 h at this temperature. Iodine (38 mg, 0.15 mmol, 2.00 eq) in THF (0.2 ml) was added and the reaction was warmed to rt and stirred for 16 h. The reaction was quenched with 1 M HCl and the aqueous phase extracted with Et}_2\text{O. The combined organic phases were then washed with saturated aqueous solutions of NaHCO}_3\text{ and Na}_2\text{S}_2\text{O}_3 \text{then dried (MgSO}_4\text{) and the solvent removed under vacuum. The crude product was purified by column chromatography (PE-EtOAc 9:1) to afford the title compound (4.4 mg, 23% brsm (7.2 mg)) as a colourless oil.}^{108} \)

R\text{F} 0.29 (Petrol:EtOAc 9:1); \text{IR} \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 1700 (C=O); \text{1H NMR (300 MHz; CDCl}_3\text{)} \delta 6.58 (1H, s, CH(SiCH}_3\text{)), 3.64-3.15 (4H, m (CH}_2\text{)2N), 2.40-2.30 (1H, m, CHCH}_2\text{N), 1.99-1.85 (2H, m, CH}_2\text{CH}_2\text{N), 1.47 (9H, s, (CH}_3\text{)3), 0.16 (9H, s, Si(CH}_3\text{)3); 13C NMR (100 MHz; toluene, 100 °C) \delta 158.7 (C=O), 109.0 (C=CSi(CH}_3\text{)3), 133.4 (C=CSi(CH}_3\text{)3), 78.9 (C(CH}_3\text{)3), 51.5 (CH}_2\text{N), 46.1 (CH}_2\text{N), 43.1 (CHCH}_2\text{N), 32.8 (CH}_2\text{CH}_2\text{N), 27.4 (C(CH}_3\text{)3), 0.00 (Si(CH}_3\text{)3); MS m/z (ES\text{+}) 418 (MNa\text{+}); HRMS Found MH\text{+} 396.0861, C\text{14H}_2\text{7O}_2\text{NSi requires MH\text{+} 396.0851.} \)

\[ \pm (E)-3-(1,2\text{-Dibromovinyl})-1\text{-tosylpyrrolidine} \text{ (297)} \]

Method 1

Pyridinium tribromide (156 mg, 0.49 mmol, 1.4 eq) was added to a solution of tert-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (87 mg, 0.35 mmol, 1.00 eq) in CH\(_2\)Cl\(_2\) (0.7 ml). The reaction mixture was stirred in the dark for 3 days then filtered through celite. The filter cake was rinsed with pentane and Et\(_2\)O and the filtrate evaporated to give the title compound (133 mg, 93%) as a yellow oil.

Method 2

\((E)\)-tert-butyl 3-(1,2-dibromovinyl)pyrrolidine-1-carboxylate (312) (422 mg, 1.19 mmol, 1.00 eq) was stirred at room temperature in a mixture of CH\(_2\)Cl\(_2\)/TFA (3:1) for 2 h at rt. The solvent was removed \textit{in vacuo} and the residue was dissolved in CH\(_2\)Cl\(_2\) (3 ml) and washed twice with a saturated aqueous solution of NaHCO\(_3\), washed with brine, dried (MgSO\(_4\)) and then concentrated. The residue was dissolved in CH\(_2\)Cl\(_2\) (4.2 ml) and triethylamine (249 µl, 1.79 mmol, 1.50 eq) was added followed by the addition of DMAP (14.5 mg, 0.12 mmol, 0.10 eq) and tosyl chloride (454 mg, 2.38 mmol, 2.00 eq). The mixture was stirred at room temperature for 16 h, diluted with water (3 ml) and extracted with CH\(_2\)Cl\(_2\), dried (MgSO\(_4\)) and concentrated. The crude yellow residue was purified by column chromatography (Petrol-EtOAc 9:1 then 8:2) to afford the title compound (207 mg, 42\% (over 2 steps)) as a yellow oil.

\( R_F \) 0.34 (Petrol:EtOAc 8:2); \( \text{IR} \ \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1346 (S=O); \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) 7.74-7.68 (2H, m, Ar\( \text{H} \)), 7.35-7.29 (2H, m, Ar\( \text{H} \)), 6.48 (1H, s, BrC=CH), 3.56-3.49 (2H, m, CBr\( \text{CHCH}_2\text{N} + \text{CBrCHCHHN} \)), 3.45-3.42 (1H, m, CH\(_2\)CHH\(_2\)N), 3.32-3.26 (1H, m, \( \text{CHHCH}_2\text{N} \)), 3.17-3.10 (1H, m, CBrCHCHHN), 2.45 (3H, s, CH\(_3\)), 2.01-1.85 (2H, m, -185-)
\[
\text{± (}E\text{-}\text{tert-Butyl 3-(1,2-dibromovinyl)pyrrolidine-1-carboxylate}^{58} (312)
\]

Pyridinium tribromide (330 mg, 1.03 mmol, 1.40 eq) was added to a solution of \textit{tert}-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (144 mg, 0.74 mmol, 1.00 eq) in \(\text{CH}_2\text{Cl}_2\) (1.5 ml). The reaction mixture was stirred in the dark for 3 days then filtered through celite. The filter cake was rinsed with pentane and \(\text{Et}_2\text{O}\) and the filtrate evaporated to give the title compound (238 mg, 91%) without any further purification as an orange oil. All spectroscopic data were consistent with literature values.\(^{58}\)

\[ \text{RF} \ 0.55 \ (\text{Petrol:EtOAc 8:2); } \]^1\text{H NMR} \ (\text{CDCl}_3, 400 \text{ MHz}) \ \delta \ 6.53 \ (1\text{H}, \text{s, CHBr}), \ 3.63-3.49 \ (3\text{H}, \text{m, CH}_2\text{N} + \text{CH}), \ 3.36-3.22 \ (2\text{H}, \text{m, CH}_3\text{N}), \ 2.09-2.00 \ (2\text{H}, \text{m, CH}_2), \ 1.47 \ (9\text{H}, \text{s, (CH}_3)_3); \]
\[ ^{13}\text{C NMR} \ (\text{DMSO}, 75 \text{ MHz; 100 °C}) \ \delta \ 152.9 \ (\text{C}=\text{O}), \ 126.7 \ (\text{BrC}=\text{CHBr}), \ 103.8 \ (\text{C}=\text{CHBr}), \ 78.0 \ (\text{C}(\text{CH}_3)_3), \ 48.2 \ (\text{CH}_2\text{CH}_2\text{N}), \ 44.5 \ (\text{CHCH}_2\text{N}), \ 41.6 \ (\text{CHCH}_2), \ 29.2 \ (\text{CH}_2\text{CH}_2\text{N}), \ 27.6 \ (\text{C}(\text{CH}_3)_3); \]
\[ \text{MS } m/\text{z} \ (\text{ES}^+) \ 378 \ ([\text{M}^{79}\text{Br}^{81}\text{Br}]^{+}\text{Na}^+). \]

Method 1

To a solution of tert-butyl 3-(but-3-en-1-yn-1-yl)pyrrolidine-1-carboxylate (148) (30 mg, 0.154 mmol, 1.00 eq) in toluene (1 ml) was added vinyl stannane (89 µl, 0.307 mmol, 2.00 eq), CuCl (46 mg, 0.462 mmol, 3.00 eq) and Pd(PPh$_3$)$_4$ (36 mg, 0.03 mmol, 0.20 eq). The reaction was refluxed for 24 h then quenched with aqueous KF. EtOAc was added and the mixture filtered through celite. The solvent was removed in vacuo and the crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (10 mg, 32%) as an oil.

Method 2

To a solution of (E)-tert-butyl 3-(1,2-dibromovinyl)pyrrolidine-1-carboxylate (312) (30 mg, 0.08 mmol, 1.00 eq) in toluene (1 ml) was added vinyl stannane (37 µl, 0.12 mmol, 1.50 eq), CuCl (25 mg, 0.25 mmol, 3.00 eq) and Pd(PPh$_3$)$_4$ (20 mg, 0.02 mmol, 0.20 eq). The reaction was refluxed for 24 h then quenched with aqueous KF. EtOAc was added and the mixture filtered through celite. The solvent was removed in vacuo and the crude residue was purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (4 mg, 25 % brsm) as an oil.

R$_F$ 0.40 (Petrol:EtOAc 8:2); IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 1690 (C=O); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.78 (1H, ddd, $J$ = 2.0, 11.0, 17.6, CH=CH$_2$), 5.59 (1H, dd, $J$ = 2.2, 17.6, CH=CHH), 5.42 (1H, dd, $J$ = 2.2, 11.0, CH=CHH), 3.67-3.59 (1H, m, CHHN), 3.54-3.47 (1H, m, CH$_2$CHHN), 3.34-3.24 (2H, m, CH$_2$CHHN + CHHN), 3.08-3.04 (1H, m, CHCC), 2.19-2.11 (1H, m, CHHCH$_2$N), 1.95-1.93 (1H, m, CHHCH$_2$N), 1.47 (9H, s, (CH$_3$)$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$ 2 rotamers: 154.3 (C=O), 126.5 (CH=CH$_2$), 117.0 (CH=CH$_2$), 90.1
(CC), 80.5 (CC), 79.4 (C(CH₃)₃), 51.6 (0.5C (CH₂N)), 51.2 (0.5C (CH₂N)), 45.2 (0.5C (CH₂CH₂N)), 44.9 (0.5C (CH₂CH₂N)), 32.7 (0.5C (CH₂CH₂N)), 32.0 (0.5C (CH₂CH₂N)), 30.5 (0.5C (CHCC)), 29.7 (0.5C (CHCC)), 28.5 (C(CH₃)₃); MS m/z (ES⁺) 244 (MNa⁺);

HRMS Found MNa⁺ 244.1313, C₁₃H₁₉NO₂Na requires MNa⁺ 244.1308.


± (E)-tert-Butyl 3-(1,2-diphenylvinyl)pyrrolidine-1-carboxylate (315)

To a solution of tert-butyl 3-ethynylpyrrolidine-1-carboxylate (148) (40 mg, 0.11 mmol, 1.00 eq) in DME (0.69 ml) and water (140 µl) was added P(o-tolyl)₃ (3 mg, 0.01 mmol, 0.10 eq), Na₂CO₃ (36 mg, 0.34 mmol, 3.00 eq) and Pd(OAc)₂ (3 mg, 0.01 mmol, 0.10 eq). The mixture was stirred at 80 °C for 16 h and then filtered through NaHCO₃ and silica and flushed with EtOAc. The solvent was removed in vacuo and the crude residue purified by column chromatography (Petrol-EtOAc 9:1) to afford the title compound (7 mg, 17%) as a yellow oil.

Rᶠ 0.27 (Petrol:EtOAc 9:1); IR ν_max(film/cm⁻¹) 1694 (C=O); ¹H NMR (400 MHz; CDCl₃) δ 7.36-7.29 (3H, m, ArH), 7.13-7.06 (5H, m, ArH), 6.89-6.86 (2H, m, ArH), 6.47 (1H, s, PhC=CHPh), 3.61-3.58 (1H, m, CHCHHN), 3.51-3.47 (1H, m, CH₂CHHN), 3.34-3.28 (1H, m, CH₂CHHN), 3.23-3.15 (2H, m, CH₂CHHN + CHCH₂N), 2.08-2.02 (1H, m, CHHCH₂N), 1.92-1.82 (1H, m, CHHCH₂N), 1.46 (9H, s, (CH₃)₃); ¹³C NMR (100 MHz; CDCl₃) δ 154.6 (C=O), 136.7 (PhC=CHPh), 129.1 (ArCH), 128.7 (ArCH), 127.9 (ArCH), 127.2 (ArC), 126.5 (PhC=CHPh), 79.1(C(CH₃)₃), 47.4 (CH₂N), 47.0 (CH₂N), 32.0 (CH₂CH₂N), 30.5 (CHCH₂N), 28.5 (C(CH₃)₃); MS m/z (ES⁺) 372 (MNa⁺); HRMS Found MNa⁺ 372.1932, C₂₃H₂₇NO₂Na requires MNa⁺ 372.1934.
Potassium trans-1-Oct-1-etyl trifluoroborate (327)

To a solution of octyne (2.68 ml, 18.15 mmol, 1.00 eq) in CH$_2$Cl$_2$ (9 ml) at 0 °C was added HBBr$_2$-SMe$_2$ (19.97 ml of a 1 M solution in CH$_2$Cl$_2$, 19.97 mmol, 1.10 eq) and the reaction stirred at room temperature for 4 h. The reaction mixture was added to a mixture of Et$_2$O (20 ml) H$_2$O (7 ml) at 0 °C and stirred for 15 min at rt. The aqueous layer was separated and the organic layer was washed with water, brine and dried (MgSO$_4$) and concentrated in vacuo to yield the boronic acid intermediate as a white solid (2.45 g). KHF$_2$ (3.24 mg, 41.50 mmol, 2.30 eq) was added to the boronic acid intermediate in Et$_2$O (27 ml) followed by the slow addition of H$_2$O (13 ml). The mixture was stirred for 3 h at rt then concentrated in vacuo. The white residue was dissolved in acetone, filtered and concentrated. The resulting white solid was purified by dissolving in hot acetone and precipitating with Et$_2$O to afford the title compound as a white solid (3.28 g, 83%).

R$_f$ 0.30 (Petrol:EtOAc 8:2); Mpt 290 °C; $^1$H NMR (DMSO, 300 MHz) δ 5.45 (1H, dt, $J$ = 6.2, 17.4, CH(C$_6$H$_{13}$)), 5.19 (1H, d, $J$ = 17.4, CH(BF$_3$K)), 1.87-1.85 (2H, m, CH$_2$(CH)), 1.24 (8H, s, (CH$_2$)$_4$), 0.85 (3H, t, $J$ = 6.4, CH$_3$) $^{13}$C NMR (DMSO, 75 MHz) δ 133.5 (CHC(C$_6$H$_{13}$)), 133.4 (CHBF$_3$K), 35.4 (CH$_2$CH), 31.3 (CH$_2$), 29.2 (CH$_2$), 28.5 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ -132.4.

MeBF$_3$K

Potassium Methyltrifluoroborate$^{134}$ (328)

Trimethylboroxine (1.90 ml, 13.62 mmol, 3.00 eq) was added to KHF$_2$ (6.33 g, 81.00 mmol, 6.00 eq) in MeCN (67 ml), the mixture was cooled to 0 °C and stirred for 30 min. H$_2$O (1.5 ml) was added and the reaction stirred for 3 h at rt. The solvent was removed and the solid thoroughly dried then triturated in acetone/methanol (1:1) (34 ml) filtered and washed with acetone/MeOH (1:1) (34 ml) then a 1:2 mixture (34 ml). The solid was dried on a high vacuum to afford the title compound as a white solid (3.86 g, 77%). All spectroscopic data were consistent with literature values.$^{134}$

R$_f$ 0.25 (Petrol:EtOAc 8:2); $^1$H NMR (D$_2$O, 500 MHz) δ -0.16 (3H, s, CH$_3$); $^{13}$C NMR (D$_2$O, 125 MHz) δ -1.14-1.4 (CH$_3$); $^{19}$F NMR (D$_2$O, 376 MHz) δ -132.0; MS m/z (ES$^-$) 82 (M–K$^+$).

NMR reference: 2013-02-23-jpc-35
APPENDIX 1

Conclusion of the alkyne route and total synthesis of isodomoic acids B, E, F\(^{89}\)

\[
\begin{align*}
\text{Lactam (136)} & \quad (380 \text{ mg, 0.890 mmol, 1.00 eq}) \text{ was dissolved in THF (9 ml) and cooled to 0} \\
& \quad \text{°C. Super hydride (3.6 ml of a 1 M solution in THF, 3.56 mmol, 4.00 eq) was added} \\
& \quad \text{dropwise and the solution was allowed to stir for 1 h. After this time the reaction was} \\
& \quad \text{quenched with a saturated aqueous solution of NaHCO} \text{3 at 0} \quad \text{°C and 10 drops of H}_2\text{O}_2 \\
& \quad \text{(30%) were added. The reaction was allowed to stir 30 min at room temperature. The} \\
& \quad \text{organic phase was extracted twice with EtOAc, and the combined organic layers were} \\
& \quad \text{washed with water, brine, dried (MgSO}_4\text{) and concentrated under reduced pressure to} \\
& \quad \text{afford the crude aminol intermediate.} \\
& \end{align*}
\]

The crude aminol was dissolved in CH\(_2\)Cl\(_2\) (6 ml) and cooled to -78 °C. Freshly distilled
BF\(_3\)-OEt\(_2\) (125 μl, 0.979 ml, 1.10 eq) and Et\(_3\)SiH (160 μl, 0.979 ml, 1.10 eq) were added and the reaction was stirred for 30 min. After this time BF\(_3\)-OEt\(_2\) (125 μl, 0.979 mmol, 1.10 eq) and Et\(_3\)SiH (160 μl, 0.979 mmol, 1.10 eq) were added again and the reaction was left to stir for 2 h. After this time the reaction was quenched with a saturated aqueous solution of NaHCO\(_3\) and allowed to warm to room temperature. The organic phase was extracted twice with CH\(_2\)Cl\(_2\) and the combined organic layers were washed with brine, dried (MgSO\(_4\)) and concentrated under reduced pressure. The alcohols were purified by column chromatography (Petrol-EtOAc 1:1) to afford the intermediate alcohol (250 mg).

The alcohol (250 mg, 0.605 mmol, 1.00 eq) was dissolved in CH\(_2\)Cl\(_2\) (2 ml). Dess-Martin periodinane (4 ml of a 0.3 M solution in CH\(_2\)Cl\(_2\), 1.2 mmol, 2.00 eq) was added dropwise
and the reaction was allowed to stir for 2 h. After this time the reaction was quenched with a saturated aqueous solution of NaHCO₃ and the organic phase was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 3:1) gave the title compound (181 mg, 50% over 3 steps) as a colourless oil.

\[ [\alpha]^{D}_{25} = 95.2 \ (c = 1 \ in \ CHCl_3); \ \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1} \ 1739 \ (C=O), \ 1733 \ (C=O), \ 1702 \ (C=O); \ \text{\^{1}H NMR} \ (400 \ \text{MHz}; \ \text{CDCl}_3) \ \delta \ 2 \ \text{rotamers}: \ 3.94 \ (0.3H, \ \text{bs}, \ \text{NCH}), \ 3.84 \ (0.7H, \ \text{dd}, \ J = 1.5, \ \text{NCH}), \ 3.78 \ (0.7H, \ \text{dd}, \ J = 7.0, \ 10.5, \ \text{CH}_3\text{HN}), \ 3.68 \ (0.3H, \ \text{dd}, \ J = 7.5, \ 10.3, \ \text{CH}_3\text{HN}), \ 3.29-3.25 \ (1H, \ m, \ \text{CH}_3\text{HbN}), \ 2.60-2.53 \ (2H, \ m, \ \text{CHCHSi} + \ \text{CHCHN}), \ 2.46-2.42 \ (2H, \ m, \ \text{CH}_2\text{CHCHN}), \ 2.29 \ (1H, \ dd, \ J = 4.5, \ 15.9, \ \text{CH}_2\text{HCHSi}), \ 2.10 \ (1H, \ dd, \ J = 12.5, \ 16.0, \ \text{CH}_3\text{bCHSi}), \ 1.46 \ (9H, \ \text{bs}, \ t-Bu), \ 1.43 \ (9H, \ \text{bs}, \ t-Bu), \ 1.11-1.05 \ (1H, \ m, \ CHSi), \ 0.03 \ (9H, \ s, \ 3 \ \text{SiCH}_3); \ \text{\^{13}C NMR} \ (100 \ \text{MHz}; \ \text{CDCl}_3) \ \delta \ 211.6, \ 171.2, \ 154.0, \ 81.6, \ 80.3, \ 64.8, \ 52.0, \ 43.4, \ 41.0, \ 38.7, \ 35.3, \ 28.3 \ (3C), \ 28.0 \ (3C), \ 23.9, \ -2.9 \ (3C); \ \text{MS} \ m/z \ (E^+) \ 412 \ (80\%, \ \text{MH}^+), \ 434.4 \ (\text{MNa}^+); \ \text{HRMS} \ \text{Found MH}^+ \ 412.2505, \ C_{21}H_{27}NO_5Si \ \text{requires MH}^+ \ 412.2514.

(1S,3aR,4R,8aS)-di-tert-Butyl hexahydro-4-(trimethylsilyl)-7-oxo-1H-oxepino[4,5-c]pyrrole-1,2(7H)-dicarboxylate

Ketone (137) (288 mg, 0.7 mmol, 1.00 eq) was dissolved in CH₂Cl₂ (5 ml). m-CPBA (240 mg, 1.4 mmol, 2.00 eq) was added in one portion and the reaction was left to stir for 2 days. The reaction was quenched with sodium thiosulfite and extracted with CH₂Cl₂. The organic layer was washed twice with a saturated aqueous solution of NaHCO₃ and brine, dried (MgSO₄) and concentrated under reduced pressure to give 288 mg of an inseparable mixture of the title compound (83%) and the overoxidised by-product (10%) as a white solid.
Mpt: 191-195 °C; [α]D 25 = -4.4°(c = 1 in CHCl3); IR νmax (film)/cm⁻¹: 1733 (C=O), 1728 (C=O), 1705 (C=O); ¹H NMR (400 MHz; CDCl3) δ 2 rotamers: 4.63-4.57 (1H, m, OCHaH), 4.28-4.23 (1H, m, OCHaHb), 3.99 (0.35H, s, NCHCO₂t-Bu), 3.84 (0.65H, s, NCHCO₂t-Bu), 3.69 (0.65H, J = 10.7, 8.4, NCHaHCO₂t-Bu), 3.61 (0.35H, J = 10.5, 8.6, NCHaHCO₂t-Bu), 3.40 (0.65H, J = 10.6, 10.6, NCHHbCO₂t-Bu), 2.99 (0.65H, J = 13.3, 13.3, CHaHCO₂t-Bu), 2.95 (0.35H, J = 13.5, 13.5, CHaHCO₂t-Bu), 2.75-2.69 (1H, m, NCH₂CH), 2.58 (1H, J = 13.6, 1.3, CHHbCO₂t-Bu), 2.52 (1H, dd, J = 13.0, 5.4, NCHCH), 1.47-1.43 (18H, m, 2 t-Bu), 1.13 (0.65H, bs, CHSiMe₃), 1.08 (0.35H, bs, CHSiMe₃), 0.00 (9H, s, Si(CH₃)₃); ¹³C NMR (100 MHz; CDCl₃) δ 2 rotamers: 173.2, 173.1, 170.5, 170.2, 154.4, 154.1, 81.9, 81.8, 80.4, 80.2, 66.9, 66.6, 66.1, 65.9, 48.5, 48.3, 40.3, 39.3, 36.7, 35.9, 35.6, 35.4, 28.2, 27.9 (2C), 27.8, 27.3, 27.2, -2.0 (6C); MS m/z (ES⁺) 450 (MNa⁺); HRMS Found MNa⁺ 450.2286, C₂₁H₃₇NO₆Si requires MNa⁺ 450.2282.

(2S,3S,4R)-di-tert-Butyl 3-((tert-butoxycarbonyl)methyl)-4-vinylpyrrolidine-1,2-Dicarboxylate (139)

To a solution of lactone (138) (165 mg, 0.38 mmol, 1.00 eq) in THF (3.5 ml) was added tetrabutylammonium fluoride (199 mg, 0.76 mmol, 2.00 eq) dropwise at 0 °C. The mixture was stirred for 5 min and then the cold bath was removed and the stirring continued for 2 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure to give the acid intermediate.

To a solution of the intermediate acid in t-BuOH (4 ml) was added DMAP (14 mg, 0.11 mmol, 0.30 eq) and Boc₂O (163 mg, 0.76 mmol, 2.00 eq). The reaction was allowed to stir overnight at room temperature and the mixture was concentrated under reduced pressure.
Purification by column chromatography (Petrol-EtOAc 9:1) gave the title compound (94 mg, 70% over 2 steps) as a colourless oil.

\([\alpha]_D^{25} = -3.6 \, (c = 1 \, \text{in CHCl}_3)\); IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1735 (C=O), 1723 (C=O), 1700 (C=O); \(^1\text{H NMR} \) (400 MHz; CDCl\(_3\) \( \delta \) 2 rotamers: 5.68-5.59 (1H, m, CH\(_2=CH\)), (1H, m, CH\(_{\text{trans}}\)=CH), (1H, m, CH\(_{\text{cis}}\)=CH), (1H, m, CH\(_{\text{trans}}\)=CH), (1H, m, CH\(_{\text{cis}}\)=CH), (1H, m, CH\(_{\text{trans}}\)=CH), (1H, m, CH\(_{\text{cis}}\)=CH); 3.84 (0.35H, d, \( J = 6.0 \), NCHCO\(_2t\)-Bu), 3.80 (0.65H, d, \( J = 5.7 \), NCHCO\(_2t\)-Bu), 3.60 (0.65H, \( J = 10.8 \), NCH\(_a\)HCO\(_2t\)-Bu), 3.56 (0.35H, \( J = 10.7 \), 6.5, NCH\(_b\)HCO\(_2t\)-Bu), 3.43 \( J = 10.8 \), 5.4 \( J = 10.7 \), 5.4, NCH\(_b\)HCO\(_2t\)-Bu), 3.33 (0.35H, \( J = 10.8 \), 5.0, NCH\(_b\)HCO\(_2t\)-Bu), 3.06-2.97 (1H, m, =CHCH), 2.68-2.62 (1H, m, NCHCH), 2.37-2.26 (2H, m, CH\(_2\)CO\(_2t\)-Bu), 1.45-1.41 (27H, m, 3 t-Bu); \(^13\text{C NMR} \) (100 MHz; CDCl\(_3\) \( \delta \) 2 rotamers: 171.3, 171.2, 171.0, 171.0, 154.1, 153.8, 134.9, 134.5, 117.8, 117.7, 81.3, 81.2, 80.7, 80.7, 79.9, 79.7, 63.7, 63.7, 50.2, 49.5, 44.1, 44.0, 43.1, 43.0, 35.0, 34.9, 28.3, 28.2, 28.0 (3C), 27.9; MS \( m/z \) (ES\(^+\)) 434 (MNa\(^+\)); HRMS Found MH\(^+\) 412.2694, C\(_{22}\)H\(_{35}\)NO\(_6\) requires MH\(^+\) 412.2694.

\[
\begin{align*}
\text{(2S,3S,4R)-di-tert-Butyl 3-((tert-butoxycarbonyl)methyl)-4-formylpyrrolidine-1,2-dicarboxylate}\quad(140)
\end{align*}
\]

In a three-neck round bottom flask, alkene (139) (130 mg, 0.32 mmol, 1.00 eq) was dissolved in dry CH\(_2\)Cl\(_2\) (5 ml) and the solution cooled down to -78 °C. O\(_3\) was bubbled through the solution for 15 min. After the appearance of a deep blue colour, the mixture was allowed to stir 5 more min. O\(_2\) (CAUTION: highly explosive!) was bubbled through the mixture for 5 min at the same temperature until total disappearance of the blue colour. N\(_2\) was then flushed through the mixture for 5 min and then Me\(_2\)S (1 ml, 15.80 mmol, 49.00 eq) was added. The solution was then warmed up to rt and allowed to stir for 24 h. The solvents were removed under reduced pressure to give the crude aldehyde (140) (128 mg, 98%).

- 194 -
[α]^{25}D = −3.8 (c = 1 in CHCl₃); IR νmax (film)/cm⁻¹ 1735 (C=O), 1727 (C=O), 1703 (C=O);

H NMR (400 MHz; CDCl₃) δ 2 rotamers: 9.70 (1H, d, J = 1.3, COH), 3.97 (0.35H, d, J = 4.6, NCHCO₂t-Bu), 3.91 (0.65H, d, J = 5.4, NCHCO₂t-Bu), 3.84 (0.65H, J = 11.4, 5.4, NCHAHCO₂t-Bu), 3.76 (0.35H, J = 11.2, 6.4, NCHAHCO₂t-Bu), 3.60 (0.65H, J = 11.4, 7.3, NCHHbCO₂t-Bu), 3.56 (0.35H, J = 11.2, 7.5, NCHHbCO₂t-Bu), 3.36-3.28 (1H, m, =CHCH), 3.00-2.87 (1H, m, NCHCH), 2.55-2.41 (2H, m, CH₂CO₂t-Bu), 1.46-1.401 (27H, m, 3t-Bu);

C NMR (100 MHz; CDCl₃) δ 2 rotamers: 199.9, 199.9, 170.7, 170.6, 170.5, 170.5, 154.0, 153.7, 81.8, 81.8, 81.5, 81.4, 80.4, 80.3, 64.5, 64.3, 51.6, 50.6, 44.9, 44.8, 42.0, 40.6, 35.1, 35.0, 28.3, 28.2, 28.0, 27.9 (2C), 27.9; MS m/z (ES^+): 436 (MNa^+), 468 (50%, M(MeOH)Na^+); HRMS Found MNa^+ 436.2308, C_{21}H_{35}NO_{7} requires MNa^+ 436.2307.

(2S,3S,4S)-di-tert-butyl 3-((tert-butoxycarbonylmethyl)-4-ethynylpyrrolidine-1,2-dicarboxylate (2S,3S,4S)-di-tert-butyl 3-((tert-butoxycarbonylmethyl)-4-ethynylpyrrolidine-1,2-dicarboxylate)

To a solution of the Ohira-Bestmann reagent (141) (188 mg, 0.99 mmol, 4.00 eq) in THF (4 ml) at -78 °C was added a solution of freshly prepared NaOMe (500 μl of a 2 M solution in MeOH, 0.99 mmol, 4.00 eq) in dry THF (1 ml). To this yellow mixture, a solution of aldehyde (140) (100 mg, 0.24 mmol, 1.00 eq) in dry THF (3 ml) was added dropwise. The reaction was allowed to stir for 1 h at the same temperature and then warmed to rt over 1 h. After this time, the reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 85:15) gave the title compound (88 mg, 89%) as a colourless oil.
[α]$_D^{25}$ = −4.1 ($c = 1$ in CHCl$_3$); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1738 (C=O), 1732 (C=O), 1700 (C=O);

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 2 rotamers: 3.93 (0.35H, d, $J = 5.5$, NCHCO$_2$-Bu), 3.87 (0.65H, d, $J = 5.6$, NCHCO$_2$-Bu), 3.70-3.59 (1.65H, m, NCH$_2$HCO$_2$-Bu + NCHHbCO$_2$-Bu), 3.53-3.49 (0.35H, m, NCH$_2$HCO$_2$-Bu), 3.32-2.23 (1H, m, CHCCH), 2.77-2.72 (1H, m, CHHCO$_2$-Bu), 2.68-2.62 (1H, m, NCHCH), 2.47-2.40 (1H, m, CHHCO$_2$-Bu), 2.17 (1H, d, $J = 2.4$, CCH), 1.46-1.43 (27H, m, 3 t-Bu); $^{13}$C NMR (100 MHz; CDCl$_3$) $\delta$ 2 rotamers: 171.0, 170.9, 170.8 (2C), 154.0, 153.7, 81.5 (2C), 81.0 (3C), 80.8, 80.3, 80.0, 72.9, 72.9, 63.4, 63.3, 51.3, 50.8, 43.5, 42.3, 35.5, 35.4, 32.7, 32.0, 28.3 (3C), 28.3(3C), 28.0 (6C), 28.0 (3C), 27.9 (3C); MS $m/z$ (ES$^+$) 432 (MNa$^+$); HRMS Found MNa$^+$ 432.2371, C$_{22}$H$_{35}$NO$_6$ requires MNa$^+$ 432.2357.

(2S,3S,4S)-di-tert-butyl-3-(((tert-butoxycarbonyl)methyl)-4-((E)-1-(tributylstannyl)prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate$^{46}$ (198)

To a mixture of CuCN (27 mg, 0.3 mmol, 3.50 eq) in THF (1.5 ml) at -78 °C was added BuLi (375 µl of a 1.6 M solution in hexanes, 0.6 mmol, 7.00 eq) and the mixture was stirred for 15 min affording a colourless solution. The mixture was warmed to -60 °C and Bu$_3$SnH (161 µl, 0.6 mmol, 7.00 eq) was added and the yellow solution that resulted was stirred for 10 min before being cooled again to -78 °C. Alkyne (144) (35 mg, 0.086 mmol, 1.00 eq) in THF (200 µl) was added slowly to the reaction. The reaction was slowly warmed to -10 °C for approximately 40 min. and MeI (78 µl, 1.2 mmol, 14.00 eq) was then added. The reaction was stirred for 2 h at 0 °C then quenched with a solution of NH$_4$Cl/NH$_4$OH (1/1 v/v) and extracted twice with ether. The combined organic layers were washed with a solution of NH$_4$Cl/NH$_4$OH (1/1), brine and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 98:2) gave the title compound (40 mg, 65%) as a colourless oil.
\(^1\)H NMR (500 MHz; CDCl\(_3\)) \(\delta\) 2 rotamers: 5.48 (0.7H, s, \(J_{Sn-H} = 64.0\), CH\(\text{Sn}\)), 5.44 (0.3H, s, \(J_{Sn-H} = 64\), CH\(\text{Sn}\)), 4.00 (1H, bs, NCH\(\text{H}\)), 3.62 (0.7H, \(J = 10.5\), 7.5, NCH\(\text{aHb}\)), 3.58 (0.3H, dd, \(J = 9.9\), 7.5, NCH\(\text{aHb}\)), 3.52 (0.7H, \(J = 10.0\), 10.0, NCH\(\text{aHb}\)), 3.41 (0.3H, bt, \(J = 9.5\), NCH\(\text{aHb}\)), 3.08 (1H, m, NCH\(\text{CH}\)), 2.75-2.66 (1H, m, NCH\(\text{CH}\)), 2.17-2.04 (2H, m, CH\(_2\)CO\(_2\)t-Bu), 1.71 (3H, s, =CCH\(\text{H}\)), 1.47-1.43 (33H, m, 3CH\(_2\) + 3r-Bu), 1.35-1.24 (6H, m, 3CH\(_2\)), 0.93-0.82 (15H, m, 3CH\(_2\)Sn + 3CH\(_3\));

\(^{13}\)C NMR (125 MHz; CDCl\(_3\)) \(\delta\) 2 rotamers: 171.5, 171.4 (2C), 171.3, 154.2, 154.0, 150.1, 149.4, 125.9, 125.6, 81.2 (2C), 80.8, 80.7, 79.8, 79.7, 64.3 (2C), 49.1, 48.3, 47.7, 42.9, 41.7, 34.6, 34.6, 29.2 (\(J_{Sn-C} = 20\) Hz, 6C), 28.4 (3C), 28.3 (3C), 28.0 (6C), 28.0 (3C), 28.0 (3C), 27.3 (\(J_{Sn-C} = 56\) Hz, 6C), 24.6, 24.5, 13.7 (6C), 10.2 (\(J_{Sn-C} = 333\) Hz, 6C); HRMS Found M\(Na^+\) 734.3722, C\(_{35}\)H\(_{65}\)NO\(_6\)\(^{116}\)Sn requires M\(Na^+\) 734.3728.

\((-\)Kainic acid (1)\)

To a solution of stannane (198) (5.0 mg, 0.007 mmol, 1.00 eq) in CH\(_2\)Cl\(_2\) (0.5 ml) was added TFA (0.5 ml) at rt. The reaction was allowed to stir for 15 h. After this time the reaction was concentrated under reduced pressure. The crude product was dissolved in water and added to a column containing Dowex-50 H\(^+\) (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with a 1 M solution of NH\(_4\)OH then concentrated under reduced pressure. The residue was passed through a column of Amberlite CG-50 and eluted with water. The solvent was removed \textit{in vacuo} to afford \((-\)kainic acid (1) (1.5 mg, quant.) as a white solid. All spectroscopic data were consistent with literature values.\(^35\)

\([\alpha]^{25}_D = -14.0\) (\(c = 0.15\) in H\(_2\)O) [lit.\(^35\) \(\alpha\)_D = -13.9 (\(c = 0.18\), H\(_2\)O)].
(2S,3S,4S)-di-tert-Butyl 3-(2-(tert-butoxy)-2-oxoethyl)-4-((2E,5E)-7-(tert-butoxy)-6-methyl-7-oxohepta-2, 5-dien-2-yl)pyrrolidine-1,2-dicarboxylate (199)

To a solution of stannane (198) (19.0 mg, 0.0266 mmol, 1.00 eq) and bromide (192) (12.5 mg, 0.053 mmol, 2.00 eq) in degassed DMF (250 μl) was added PdCl₂(CH₃CN)₂ (50 μl of a 0.015 M solution in DMF, 0.00075 mmol, 3 mol%). The reaction was stirred for 5 h at rt and water was added. The aqueous layer was extracted twice with EtOAc. The organic layers were combined and washed with water, brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 95:5 to 9:1) gave the title compound (11.0 mg, 71%) as a colourless oil.

¹H NMR (500 MHz; CDCl₃, 25 °C) δ 2 rotamers: 6.60-6.53 (1H, m, COC=CH), 5.14-5.09 (1H, m, CHC=CH), 3.98 (0.3H, d, J = 4.5, NCH), 3.97 (0.7H, d, J = 4.5, NCH), 3.61 (0.7H, dd, J = 13.5, 9.5, NCHaH), 3.57 (0.3H, dd, J = 13.5, 9.5, NCHaH), 3.47 (0.7H, dd, J = 13.0, 10.0, NCHHb), 3.39 (0.3H, dd, J = 13.5, 10.0, NCHHb), 3.02-2.94 (1H, m, CH), 2.87 (2H, bt, J = 7.0, CHCH₂CH), 2.76-2.69 (1H, m, CH), 2.16-2.11 (2H, m, CH₂CO), 1.80 (3H, bs, CH₃), 1.61 (3H, bs, CH₃), 1.50-1.43 (36H, m, 4t-Bu); MS m/z (ES⁺) 602 (MNa⁺); HRMS Found MNa⁺ 602.3672, C₃₂H₅₃NO₈ requires MNa⁺ 602.3663.

(−)-isodomoic acid B₄⁶ (5)

To a solution of diene (199) (11.0 mg, 0.0190 mmol, 1.00 eq) in CH₂Cl₂ (0.5 ml) was added TFA (0.5 ml) at rt. The reaction was allowed to stir 15 h. After this time the reaction was concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid B (8.0 mg, quant.) as an oil.
\([\alpha]^{25}_D = +2.8 \ (c = 1.0 \ \text{in} \ H_2O).\)

The salt was dissolved in water and added to a column containing Dowex-50 H\(^+\) (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with a 1 M solution of \(\text{NH}_3\text{OH}\) then concentrated under reduced pressure. The residue was passed through a column of Amberlite CG-50 and eluted with water. The solvent was removed \textit{in vacuo} to afford \((-\)-isodomoic acid B (5) (5.8 mg, quant.)

\([\alpha]^{D}_{25} = 0 \ (c = 1.0 \ \text{in} \ H_2O) \ [\text{lit}^9 \ [\alpha]^{25}_D = -8.1 \ (c = 0.14 \ \text{in} \ H_2O)]; \ MS \ m/z \ (E^+) 310 (M–H\(^+\)); \ HRMS \text{ Found M–H}^+ 310.1304, C_{15}H_{21}NO_6 \text{ requires M–H}^+ 310.1296. \ \text{^1H NMR} \text{ and } ^{13}\text{C NMR} \text{ data are reported in Table 4 (Chapter 4, section 4.1) and Table 13.}

\textbf{Table 13:} \ \textsuperscript{13}C (D\(_2\)O) Spectroscopic comparison of natural\(^9\) and synthetic \((-\)-isodomoic acid B\(^{46}\)

<table>
<thead>
<tr>
<th>Natural isodomoic acid B (90 MHz)</th>
<th>Synthetic neutralised isodomoic acid B (100 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>176.3 \ (C8)</td>
<td>176.3</td>
</tr>
<tr>
<td>173.1 \ (C5'-CO(_2)H)</td>
<td>173.3</td>
</tr>
<tr>
<td>173.0 \ (C7)</td>
<td>172.4</td>
</tr>
<tr>
<td>142.6 \ (C4')</td>
<td>142.6</td>
</tr>
<tr>
<td>132.2 \ (C1')</td>
<td>132.0</td>
</tr>
<tr>
<td>125.5 \ (C5')</td>
<td>128.4</td>
</tr>
<tr>
<td>125.3 \ (C2')</td>
<td>125.6</td>
</tr>
<tr>
<td>65.7 \ (C2)</td>
<td>65.0</td>
</tr>
<tr>
<td>47.8 \ (C5)</td>
<td>47.8</td>
</tr>
<tr>
<td>47.3 \ (C4)</td>
<td>47.5</td>
</tr>
<tr>
<td>41.6 \ (C3)</td>
<td>41.4</td>
</tr>
<tr>
<td>33.9 \ (C6)</td>
<td>33.8</td>
</tr>
<tr>
<td>28.1 \ (C3')</td>
<td>28.1</td>
</tr>
<tr>
<td>16.8 \ (C1'-CH(_3))</td>
<td>16.8</td>
</tr>
<tr>
<td>12.5 \ (C5'-CO(_2)H)</td>
<td>12.5</td>
</tr>
</tbody>
</table>
(2S,3S,4S)-di-tert-Butyl 3-(2-(tert-butoxy)-2-oxoethyl)-4-((S,2E,4E)-7-(tert-butoxy)-6-methyl-7-oxohepta-2, 4-dien-2-yl)pyrrolidine-1,2-dicarboxylate (200)

To a solution of stannane (198) (19 mg, 0.0266 mmol, 1.00 eq) and E-vinyl iodide (172) (11 mg, 0.040 mmol, 1.50 eq) in degassed DMF (250 μl) was added PdCl₂(CH₃CN)₂ (50 μl of a 0.015 M solution in DMF, 0.00075 mmol, 3 mol%). The reaction was stirred for 48 h at 50 °C then water was added. The aqueous layer was extracted twice with EtOAc. The organic layers were combined and washed with water, brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 98:2 to 95:5) gave the title compound (7.9 mg, 51%) as a colourless oil.

¹H NMR (500 MHz; CDCl₃) δ 2 rotamers: 6.33-6.27 (1H, m, CO₂t-BuCHCH=), 5.75 (1H, bd, J = 13.5, CH=CHCH=), 5.70- 5.62 (1H, m, CHC=CH), 3.98 (0.3H, d, J = 5.0, NCH), 3.96 (0.7H, d, J = 4.5, NCH), 3.64 (0.7H, dd, J = 13.5, 9.0, NCHaH), 3.58 (0.3H, dd, J = 13.5, 9.0, NCHaH), 3.51 (0.7H, dd, J = 13.5, 10.5, NCHHb), 3.43 (0.3H, dd, J = 13.0, 9.5, NCHHb), 3.11-2.98 (2H, m, 2CH), 2.78-2.73 (1H, m, CH), 2.19-2.13 (2H, m, CH₂CO), 1.70 (3H, bs, CH₃), 1.47-1.44 (36H, m, 4t-Bu), 1.23 (3H, d, J = 9.0, CHCH₃); MS m/z (ES⁺) 602 (MNa⁺); HRMS Found MNa⁺ 602.3664, C₃₂H₅₃NO₈ requires MNa⁺ 602.3663.
To a solution of diene (200) (7.9 mg, 0.0136 mmol, 1.00 eq) in CH$_2$Cl$_2$ (0.5 ml) was added TFA (0.5 ml) at rt. The reaction was allowed to stir for 15 h. After this time the reaction was concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid E (5.8 mg, quant.)

$[\alpha]^{25}_D = -5.1$ (c = 1 in H$_2$O).

The salt was dissolved in water and added to a column containing Dowex-50 H$^+$ (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with a 1 M solution of NH$_4$OH and concentrated under reduced pressure. The residue was passed through a column of amberlite CG-50 and eluted with water. The solvent was removed in vacuo to afford ($-$)-isodomoic acid E (8) (4.2 mg, quant.).

$[\alpha]^{25}_D = -20.0$ (c = 0.5 in H$_2$O) [lit$^4$ $[\alpha]^{25}_D = -19.5$ (H$_2$O, c not reported)]; MS m/z (ES$^-$) 310 (M–H$^+$); HRMS Found M–H$^+$ 310.1286, C$_{15}$H$_{21}$NO$_6$ requires M–H$^+$ 310.1296. $^1$H NMR and $^{13}$C NMR data are reported in Table 5 (Chapter 4, section 4.1) and Table 14.
Table 14: $^{13}$C (D$_2$O) Spectroscopic comparison of natural$^4$ and synthetic (−)-isodomoic acid E.$^{46$

<table>
<thead>
<tr>
<th>Natural isodomoic acid E (75 MHz)</th>
<th>Synthetic neutralised isodomoic acid E (100 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>181.9 ($C5^\prime$-CO$_2$H)</td>
<td>182.0</td>
</tr>
<tr>
<td>177.7 ($C6$-CO$_2$H)</td>
<td>177.8</td>
</tr>
<tr>
<td>173.3 ($C2$-CO$_2$H)</td>
<td>173.9</td>
</tr>
<tr>
<td>135.6 ($C4^\prime$)</td>
<td>135.3</td>
</tr>
<tr>
<td>134.2 ($C1^\prime$)</td>
<td>134.2</td>
</tr>
<tr>
<td>130.0 ($C2^\prime$)</td>
<td>129.6</td>
</tr>
<tr>
<td>129.5 ($C3^\prime$)</td>
<td>129.5</td>
</tr>
<tr>
<td>66.1 ($C2$)</td>
<td>66.4</td>
</tr>
<tr>
<td>49.6 ($C4$)</td>
<td>49.5</td>
</tr>
<tr>
<td>49.2 ($C5$)</td>
<td>48.8</td>
</tr>
<tr>
<td>45.0 ($C5^\prime$)</td>
<td>45.0</td>
</tr>
<tr>
<td>43.3 ($C3$)</td>
<td>43.3</td>
</tr>
<tr>
<td>35.3 ($C6$)</td>
<td>35.3</td>
</tr>
<tr>
<td>18.9 ($C5^\prime$-CH$_3$)</td>
<td>18.9</td>
</tr>
<tr>
<td>18.7 ($C1^\prime$-CH$_3$)</td>
<td>18.7</td>
</tr>
</tbody>
</table>

NMR reference: 2010-07-30-jpc-13

(2S, 3S,4S)-di-tert-butyl 3-(2-((tert-butoxy)-2-oxoethyl)-4-((R, 2E, 4Z)-7-(tert-butoxy)-6-methyl-7-oxohepta-2, 4-dien-2-yl)pyrrolidine-1,2-dicarboxylate (201)

To a solution of stannane (198) (23 mg, 0.032 mmol, 1.00 eq) and Z-vinyl iodide (179) (14 mg, 0.046 mmol, 1.4 eq) in degassed DMF (250 μl) was added PdCl$_2$(CH$_3$CN)$_2$ (50 μl of a 0.023 M solution in DMF, 0.00075 mmol, 2 mol% ). The reaction was stirred for 48 h at
50 °C and water was added. The aqueous layer was extracted twice with EtOAc. The organic layers were combined and washed with water, brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography (Petrol-EtOAc 98:2 to 95:5) gave the title compound (9.0 mg, 49%) as a colourless oil.

**¹H NMR** (500 MHz: CDCl₃) δ 6.28-6.20 (1H, m, CO₂t-BuCHCH=), 5.75 (1H, m, CH=CHCH=), 5.49-5.38 (1H, m, CHC=CH), 3.99 (1H, bd, J = 4.4, NCH), 3.71- 3.36 (3H, m, NCH₃ + CH), 3.10-3.01 (1H, m, CH), 2.81-2.73 (1H, m, CH), 2.19-2.13 (2H, m, CH₂CO), 1.73 (3H, bs, CH₃), 1.48-1.43 (36H, m, 4t-Bu), 1.18 (3H, d, J = 9.2, CHCH₃); **MS** m/z (ES⁺) 602 (MNa⁺); **HRMS** Found MNa⁺ 602.3672, C₃₂H₅₃NO₈ requires MNa⁺ 602.3664.

![Image](image)

**(-)-isodomoic acid F₄₆ (9)**

To a solution of diene (20₁) (9.0 mg, 0.016 mmol, 1.00 eq) in CH₂Cl₂ (0.5 ml) was added TFA (0.5 ml) at rt. The reaction was stirred for 15 h then concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid F (9) (6.5 mg, quant.) as an oil.

[α]₂⁵ⁿ = −20.4 (c = 1 in H₂O) [lit⁴ for neutral amino acid [α]₂⁵ⁿ = −85 (H₂O, c not reported)]; **MS** m/z (ES⁻) 310 (M⁻H⁺); **HRMS** Found M⁻H⁺ 310.1287, C₁₅H₂₁NO₆ requires M⁻H⁺ 310.1296. **¹H NMR** and **¹³C NMR** data are reported in Table 6 (Chapter 4, section 4.1) and Table 15.

The salt was dissolved in water and added to a column containing Dowex-50 H⁺ (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with a 1 M solution of NH₃OH then concentrated under reduced pressure. The residue was passed through a column of amberlite CG-50 and eluted with water. The solvent was removed in vacuo to afford (−)-isodomoic acid F (9) (4.5 mg, 95%).
Table 15: $^{13}$C (D$_2$O) Spectroscopic comparison of natural and synthetic (–)-isodomoic acid F.$^{46}$

<table>
<thead>
<tr>
<th>Natural isodomoic acid F (75 MHz)</th>
<th>Synthetic neutralised isodomoic acid F (100 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>181.8 (C5'-CO$_2$H)</td>
<td>182.1</td>
</tr>
<tr>
<td>177.6 (C6'-CO$_2$H)</td>
<td>177.8</td>
</tr>
<tr>
<td>173.1 (C2'-CO$_2$H)</td>
<td>173.7</td>
</tr>
<tr>
<td>136.7 (C1')</td>
<td>136.7</td>
</tr>
<tr>
<td>133.1 (C4')</td>
<td>133.0</td>
</tr>
<tr>
<td>127.8 (C3')</td>
<td>127.8</td>
</tr>
<tr>
<td>125.2 (C2')</td>
<td>124.9</td>
</tr>
<tr>
<td>66.0 (C2)</td>
<td>66.3</td>
</tr>
<tr>
<td>50.0 (C4)</td>
<td>49.9</td>
</tr>
<tr>
<td>49.3 (C5)</td>
<td>48.9</td>
</tr>
<tr>
<td>43.3 (C3)</td>
<td>43.3</td>
</tr>
<tr>
<td>40.7 (C5')</td>
<td>40.6</td>
</tr>
<tr>
<td>35.3 (C6)</td>
<td>35.3</td>
</tr>
<tr>
<td>19.7 (C5'-CH$_3$)</td>
<td>19.7</td>
</tr>
<tr>
<td>18.6 (C1'-CH$_3$)</td>
<td>18.6</td>
</tr>
</tbody>
</table>

NMR reference: 2010-07-27-jpc-17
APPENDIX 2

Table 16: Binding data for isodomoic acids B and E

<table>
<thead>
<tr>
<th>Natural product</th>
<th>Binding IC$_{50}$/Ki in µm</th>
<th>Binding Ki in µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MW</td>
<td>AMPA</td>
</tr>
<tr>
<td>domoic acid (3)</td>
<td>311.33</td>
<td>0.47</td>
</tr>
<tr>
<td>isodomoic acid B (5)</td>
<td>311.33</td>
<td>&gt;10</td>
</tr>
<tr>
<td>isodomoic E (8)</td>
<td>311.33</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
APPENDIX 3

Spectra

\[(E\)-\textit{tert}-Butyl 4-bromo-2-methylbut-2-enoate \(192)]\
(R,E)- tert-Butyl 4 iodo-2-methylbut-3-enoate (172)
(R,Z)-tert-Butyl 4-iodo-2-methylbut-3-enoate (179)
Isodomoic acid B (5)
Isodomoic acid E (8)
Isodomoic acid F (9)
REFERENCES


