Synthesis of Deuterated Phosphatidylinositol Phosphates

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DPhil Thesis
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DECLARATION OF AUTHORSHIP

Name: ALEX SAUNDERS  Candidate Number: 397138
College: ST ANNE’S  Supervisor: PROF. STUART CONWAY

Title of Thesis: SYNTHESIS OF DEUTERATED PHOSPHATIDYLINOSITOL PHOSPHATES

Word Count:

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I have read and understood the Education Committee’s information and guidance on academic good practice and plagiarism at https://www.ox.ac.uk/students/academic/guidance/skills?wssl=1. ✓

The dissertation I am submitting is entirely my own work except where otherwise indicated. ✓

It has not been submitted, either partially or in full, either for this Honour School or qualification or for another Honour School or qualification of this University (except where the Special Regulations for the subject permit this), or for a qualification at any other institution. ✓

I have clearly indicated the presence of all material I have quoted from other sources, including any diagrams, charts, tables or graphs. ✓

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I have acknowledged appropriately any assistance I have received in addition to that provided by my supervisor. ✓

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Abstract

Phosphatidylinositol phosphates (PtdInsP_n) are intracellular signalling molecules that are important in many key biological processes, in particular Ca^{2+} signalling pathways. Dysfunction of these processes has been implicated in numerous diseases including diabetes and many cancers. Some aspects of PtdInsP_n signalling have been heavily investigated; PTEN, PKC/Akt, PtdIns3K and PtdIns4K are all important therapeutic targets that have seen much attention in industrial endeavours. Inositol-based probes and tool compounds for these targets typically incorporate a fluorescent tag or photo-crosslinking group, usually at the lipid tails. It is increasingly apparent that the nature of the lipid chains plays a key role in determining the sub-cellular localisation of the PtdInsP_n and hence modification of the lipids is potentially detrimental to the biological function of the tool compounds. An additional challenge in the development of inositol-based tools compounds is the difficult and lengthy syntheses that are employed to obtain the target compounds. To address this, we have developed a novel asymmetric route that allows rapid synthesis of PtdIns and PtdIns(4,5)P_2. This route has been designed to allow incorporation of multiple deuterium atoms onto the myo-inositol ring (C-perdeuterated). To achieve this, we began with the aromatic compound quinol and built up the myo-inositol ring piecewise, allowing for deuterium incorporation. This methodology utilised a Pd-catalysed dynamic kinetic resolution on a conduritol B derivative to form optically-pure myo-inositol derivatives in high e.e. (>99%) toward the synthesis of D_6-PtdIns(4,5)P_2.

The incorporation of deuterium into these compounds should be minimally disruptive to their biological activity, while the difference in molecular mass between the endogenous and tool compounds enables their use in a range of biological assays. In addition, the incorporation of the deuterium onto the myo-inositol ring will allow for the detection of downstream effects relating to the myo-inositol ring post-hydrolysis of PtdIns(4,5)P_2 to be observed, which is currently not possible with other probes.
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First and foremost, I would like to thank Professor Stuart Conway who has been my supervisor throughout and provided guidance on completing this project, for which I will be forever grateful. To the other third year DPhil, (Dr) Michael Brand who has been a great friend and colleague during my time here in Oxford. I will miss our time spent down in Gloucester Green market at lunches, usually solving our chemistry problems! (Dr) Amélie Joffrin, thanks for being a co-conspirator on inositol chemistry and for providing phosphoramidites in return for D$_6$-myo-inositol. Thanks to AstraZeneca for their support throughout, in the form of Dr Hitesh Sanganee (Chemistry) and Dr Vikki Flemington (Biology). For funding me, I would like to thank AstraZeneca, EPSRC and of course the SABS-IDC programme. The staff associated with the SABS-IDC are outstanding, especially the (ex-)director Professor Charlotte Deane, the senior administrator Samantha Miles and the SABS administrator Annette Miller.

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Asymmetric allylic alkylation</td>
</tr>
<tr>
<td>ar.</td>
<td>Aromatic (IR, NMR)</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl (protecting group)</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl (protecting group)</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl (protecting group)</td>
</tr>
<tr>
<td>Cne</td>
<td>2-Cyanoethyl (protecting group)</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy (NMR)</td>
</tr>
<tr>
<td>DAG</td>
<td>Diacylglycerol</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-Dihydro-2H-pyran</td>
</tr>
<tr>
<td>DKR</td>
<td>Dynamic Kinetic Resolution</td>
</tr>
<tr>
<td>DMAP</td>
<td>$N,N$-Dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>EDC·HCl</td>
<td>$N$-(3-Dimethylaminopropyl)-$N'$-ethylcarbodiimide</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>E$^+/-$</td>
<td>Electron ionisation (mass spectroscopy)</td>
</tr>
<tr>
<td>EDC·HCl</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ER</td>
<td>Endoplasmic reticulum</td>
</tr>
<tr>
<td>ES$^+/-$</td>
<td>Electrospray ionisation (mass spectroscopy)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>F$^+/-$</td>
<td>Field ionisation (mass spectroscopy)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple-bond correlation spectroscopy (NMR)</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single-quantum correlation spectroscopy (NMR)</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
</tr>
<tr>
<td>LRMS</td>
<td>Low-resolution mass spectrometry</td>
</tr>
<tr>
<td>mCPBA</td>
<td>3-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy (NMR)</td>
</tr>
<tr>
<td>PINK*</td>
<td>Phosphatidylinositol N-kinase</td>
</tr>
<tr>
<td>PKC</td>
<td>Protein kinase C</td>
</tr>
<tr>
<td>PLC</td>
<td>Phospholipase C</td>
</tr>
<tr>
<td>PMB</td>
<td>p-Methoxybenzyl (protecting group)</td>
</tr>
<tr>
<td>PMBCl</td>
<td>p-Methoxybenzyl chloride</td>
</tr>
<tr>
<td>PPL</td>
<td>Pig pancrease lipase</td>
</tr>
<tr>
<td>PtdIns</td>
<td>Phosphatidylinositol</td>
</tr>
<tr>
<td>PtdInsNP*</td>
<td>Phosphatidylinositol N-phosphate</td>
</tr>
<tr>
<td>PtdInsNP₂*</td>
<td>Phosphatidylinositol N-bisphosphate</td>
</tr>
<tr>
<td>pTSA</td>
<td>4-Toluene sulfonic acid</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
</tr>
<tr>
<td>TBABr</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBDMS</td>
<td>'Butyldimethylsilyl (protecting group)</td>
</tr>
<tr>
<td>TBDPS</td>
<td>'Butyldiphenylsilyl (protecting group)</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic</td>
</tr>
<tr>
<td>TfOH</td>
<td>Triffic acid</td>
</tr>
<tr>
<td>THABr</td>
<td>Tetrahexylammonium bromide</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyranyl (protecting group)</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMSCl</td>
<td>Trimethylsilyl chloride</td>
</tr>
<tr>
<td>TMSBr</td>
<td>Trimethylsilyl bromide</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-Trichloroethyl carbonate (protecting group)</td>
</tr>
</tbody>
</table>

*In these cases, N refers to an integer i.e. 3, 4 or 5*
Chapter 1

Introduction

Inositides have been of interest to biologists and chemists alike due to their involvement in many biological pathways.¹ Their inositol core, at the heart of many signalling molecules, is of interest to chemists due to the synthetic challenges afforded in using these structures in synthetic endeavours. For these reasons, there is still a concerted effort from a chemical biology perspective to produce new probes based on the inositol core.

![Diagram of inositol isomers](image)

**Figure 1.1** The nine isomers of inositol: myo-inositol 1, scyllo-inositol 2, muco-inositol 3, neo-inositol 4, allo-inositol 5, cis-inositol 6, epi-inositol 7, (+)-D-chiro-inositol 8, and (−)-L-chiro-inositol 8.
CHAPTER 1. INTRODUCTION

1.1.1 Structure and Numbering of myo-Inositol

Inositol is a common building block for many messengers in biological systems, with the chemical formula C$_6$H$_{12}$O$_6$. Unlike typical carbohydrates of the formula of C$_n$(H$_2$O)$_n$ such as glucose, the ring consists of all carbons and there is no anomeric centre (Figure 1.1). There are nine possible isomers of inositol: myo- 1, scyllo- 2, muco- 3, neo- 4, cis- 6, allo-5, epi- 7, (+)-D-chiro- 8, and (-)-L-chiro- 8 (Figure 1.1). The most abundant inositol in eukaryotic cells is myo-inositol 1. Derivatives of 1 have been of particular interest for both biologists and chemists alike. In the most stable conformation of myo-inositol 9, there are five equatorial hydroxyl groups, while the remaining hydroxyl is axial (Figure 1.2). The structure of myo-inositol has light-heartedly been likened to a turtle - the axial hydroxyl is the head and the 5 other hydroxyls are the flippers and tail (Figure 1.2).

Figure 1.2 Numbering of myo-inositol ring shown in both the flat and chair forms. The L-numbering is usually used throughout the literature to avoid confusion as recommended by IUPAC, and is used throughout this work. Turtle image used with permission (see appendix, page 547).

myo-Inositol systems are numbered using the D-myoinositol nomenclature as recommended by IUPAC, where the most common modification (phosphorylation) occurs at the 1-position (right flipper of the turtle) and the positions are then labelled as shown above (Figure 1.2). There is a plane of symmetry in myo-inositol 1 running from the 2-to 5-position (shown by the dotted line), making myo-inositol achiral and meso. Derivatisation of myo-inositol on either side of the line of symmetry (on the 1-, 3-, 4-, or 6-positions) such that the symmetry is broken leads to a racemic mixture of compounds. This requires either asymmetric synthesis or resolution to synthesise the optically pure derivatives found in natural systems. One class of structures containing the myo-inositol core are phosphatidylinositol phosphates (PtdIns$P_n$).
1.1.2 Phosphatidylinositol Phosphates (PtdIns\(P_n\))

PtdIns\(P_n\) are complex intracellular signalling molecules found in the membranes of eukaryotic cells.\(^1\) They are involved in a number of biological processes, not only Ca\(^{2+}\) signalling, but also as membrane anchors and other related structural functions.\(^1,8,9\) There have been many reviews written on the role of PtdIns\(P_n\) in biological systems.\(^1,10,11\) PtdIns\(P_n\) have been of particular interest since the early 1980s, when their involvement in Ca\(^{2+}\) signalling through hydrolysis of PtdIns(4,5)\(P_2\) \(10\) to form inositol (1,4,5)-trisphosphate \(11\) (Ins(1,4,5)\(P_3\)) became apparent (Figure 1.3).\(^7\) The first syntheses of Ins(1,4,5)\(P_3\) \(11\) were published in 1986, allowing significant progress to be made in understanding the role of these molecules in biological pathways.\(^12\) Since then, there has been a concerted effort from both academic and industrial groups to unravel these complexities.\(^1\) The most abundant PtdIns\(P_n\) found in eukaryotic cells is PtdIns at around 10-20 mol\% of the total cellular phospholipids, and acts as a precursor to all the other PtdIns\(P_n\) (Figure 1.4). The next most common PtdIns\(P_n\) are PtdIns(4,5)\(P_2\) and its precursor PtdIns(4)\(P\) at around 0.2-1 mol\%, with all the other PtdIns\(P_n\) found in only trace amounts.\(^1,13\)

![Diagram](image.png)

**Figure 1.3** Hydrolysis of PtdIns(4,5)\(P_2\) \(10\) in cellular systems by protein kinase C (PKC) leads to Ins(1,4,5)\(P_3\) and DAG, both of which act on intracellular targets.\(^1,7\)
1.1.3 Structure of PtdIns$P_n$

PtdIns$P_n$ comprise a phosphorylated *myo*-inositol group linked to two lipid chains by a glycerol moiety (Figure 1.3). Each part of the PtdIns$P_n$ structure is necessary for the biological activity, with changes to phosphorylation position or number, lipid saturation, or lipid length, altering the activity of the molecules. An important factor in determining the biological activity is the phosphorylation pattern on the inositol headgroup (Figure 1.4). In total, there are seven members of the family of PtdIns$P_n$ in addition to PtdIns 13 (three monophosphates, three bisphosphates and one trisphosphate) with combinations of phosphorylation at the 3-, 4- and 5-positions.$^{1,3}$

![Figure 1.4 General structure of PtdIns$P_n$ (top) comprising a *myo*-inositol headgroup, glycerol linker and two lipids. Phosphorylation of PtdIns 13 leads to seven PtdIns$P_n$, each with different biological activity. The structures shown contain the two most common lipid tails, an arachidonic acid and a stearic acid chain.](image-url)
While initially thought to be of less importance than the phosphorylation pattern, the lipid chains also confer some effects of biological importance, other than just anchoring the phosphatidylinositol species into lipid membranes. Lin et al. measured the fatty acid composition of phosphatidylinositols in different tissues in rats and found varied levels of some lipids when compared between tissues (Table 1.1). The most predominant fatty acids in all tissues were the 18:0 (18 carbons, 0 unsaturated bonds, stearic acid) along with 20:4 (arachidonic acid) fatty acids. Not only are there tissue level effects from the fatty acid composition, but there may also be effects on subcellular localisation. It has been shown the nature of the lipid chain changes the physical properties of lipid bilayers in cellular systems, potentially affecting the biological results obtained in model systems. This is of particular importance when concerned with anchoring of PtdIns\(P_n\) into different sub-cellular compartments and hence is important to consider when designing new probes.

<table>
<thead>
<tr>
<th>Fatty Acid(^a)</th>
<th>Liver</th>
<th>Kidney</th>
<th>Brain</th>
<th>Sciatic Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:0</td>
<td>6.7</td>
<td>9.2</td>
<td>10.8</td>
<td>9.4</td>
</tr>
<tr>
<td>18:0</td>
<td>41.3</td>
<td>38.8</td>
<td>33.8</td>
<td>35.0</td>
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<tr>
<td>18:2</td>
<td>4.1</td>
<td>4.6</td>
<td>14.3</td>
<td>16.5</td>
</tr>
<tr>
<td>18:3</td>
<td>N.D.</td>
<td>N.D.</td>
<td>1.1</td>
<td>N.D.</td>
</tr>
<tr>
<td>20:1</td>
<td>2.8</td>
<td>2.3</td>
<td>N.D.</td>
<td>3.6</td>
</tr>
<tr>
<td>20:3</td>
<td>33.6</td>
<td>37.0</td>
<td>34.7</td>
<td>22.3</td>
</tr>
<tr>
<td>20:5</td>
<td>0.3</td>
<td>0.3</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>22:4</td>
<td>0.6</td>
<td>1.0</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>22:5</td>
<td>1.5</td>
<td>0.3</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>22:6</td>
<td>3.1</td>
<td>1.5</td>
<td>2.9</td>
<td>1.5</td>
</tr>
</tbody>
</table>

\(^a\) For fatty acid composition, the first number relates to the carbon chain length while the second is the number of unsaturated bonds in the chain. N.D. is not determined.
### 1.2 Biological Relevance of PtdIns$P_n$  

#### 1.2.1 $Ca^{2+}$ Signalling

$Ca^{2+}$ signalling in eukaryotic cells is a process that regulates the activity of a large number of proteins.\(^{18}\) The role of PtdIns(4,5)$P_2$ 10 in $Ca^{2+}$ signalling is well known (Figure 1.5).\(^{1}\) A typical example would be the activation of a G-protein coupled receptor on an extracellular membrane by an endogenous ligand such as a hormone.\(^{19}\) The receptor then activates phosphatidylinositol protein lipase C (PLC), causing hydrolysis of PtdIns(4,5)$P_2$ 10 (Figure 1.3), releasing $Ins(1,4,5)P_3$ 11 and a diacylglycerol (DAG) moiety. The DAG remains localised in the membrane, recruiting protein kinase C (PKC) to the extracellular membrane. The aqueous-soluble $Ins(1,4,5)P_3$ 11 diffuses across the cytoplasm to $InsP_3$ receptors found in the endoplasmic reticulum (ER), activating ion channels in the ER leading to release of $Ca^{2+}$ into the cytoplasm. In combination with the recruitment of PKC to the extracellular membrane, increase in $Ca^{2+}$ concentration causes activation of PKC. Activated PKC then catalyses the phosphorylation of protein substrates and activation of a number of targets, including mitogen-activated protein kinase (MAPK) and receptor for activated C kinase 1 (RACK1).\(^{20,21}\) This leads to downstream effects that are

![Figure 1.5](image-url)  

**Figure 1.5** The $Ca^{2+}$ signalling pathway involving PtdIns(4,5)$P_2$ has been thoroughly studied.\(^{1,17}\) Hydrolysis of PtdIns(4,5)$P_2$ 10 at the cell membrane by phospholipase C (PLC) leads to release of $Ins(1,4,5)P_3$ 11 into the cytoplasm, with the remaining diacylglycerol (DAG) remaining in the membrane. The $Ins(1,4,5)P_3$ interacts with $InsP_3$ receptors on the surface of the endoplasmic reticulum, causing release of intracellular $Ca^{2+}$ into the cytoplasm.
linked to biological activities as diverse as homeostasis, sensory transduction, and cardiac effects. This Ca$^{2+}$ signalling pathway is ubiquitous throughout eukaryotic cells and errors in this pathway can lead to diseases including cancers, diabetes and neurological conditions.

### 1.2.2 Biosynthesis of $\text{PtdInsP}_n$

The biosynthesis of the family of $\text{PtdInsP}_n$ begins by the condensation of diacylglycerols with *myo*-inositol by phosphatidylinositol synthases, found in the membrane of the endoplasmic reticulum, to give PtdIns 13. The selective phosphorylation of PtdIns 13 is mediated by a family of phosphatidylinositol kinases (PtdInsN$^\text{NK}$, where the $N$ denotes the site of phosphorylation, typically the 3-, 4- or 5-positions of the *myo*-inositol ring, Scheme 1.1). These PtdIns$^\text{P}_n$ can then be further phosphorylated by a second set of kinases, the PtdIns$^\text{P}_n$ kinases (PtdInsP$^\text{NK}$). A constant basal level of PtdIns$^\text{P}_n$ is maintained by these kinases, with inhibition of any of the kinases causing an overall drop in the level of PtdIns$^\text{P}_n$ and a concomitant increase in the concentration of precursors.

![Scheme 1.1](image)

**Scheme 1.1** PtdIns can by phosphorylated by a series of kinases to give the family of PtdIns$^\text{P}_n$. Solid arrows represent known kinases while dotted lines indicate suspected transformations where the kinases have not yet been isolated or characterised. Kinases: a. PtdIns3K; b. PtdIns4K; c. PtdIns5K; d. PtdInsP5K3; e. PtdInsP5K1; f. PtdInsP5K2; g. PtdInsP5K3.
1.2.3 PtdIns3K and PtdIns4K as Therapeutic Targets

Two kinases related to the biosynthesis of PtdIns(4,5)P$_2$ 10, PtdIns3K and PtdIns4K, have shown therapeutic potential.\textsuperscript{22} It is known that aberrant behaviour in these two kinases is linked to a number of diseases, including cancers, diabetes, and neurological conditions such as Alzheimer’s disease, and Down syndrome.\textsuperscript{22} There have been numerous examples of PtdIns3K inhibitors reaching clinical trials, with over 30 compounds in phases 1 and 2 and over 30 known isoform selective compounds in preclinical work.\textsuperscript{25} There has so far been limited success with PtdIns3K inhibitors, with only one compound approved by the FDA. Idelalisib 20 (Zydelig\textsuperscript{\textregistered}, Figure 1.6) was approved by the FDA for three blood cancers in 2014, however, recent reports (May 2016 and September 2016) have seen new guidance from the British Medicines and Healthcare products Regulatory Agency (MHRA) for Idelalisib. This guidance is due to increased mortality while taking the drug, caused by increased prevalence of serious infections.\textsuperscript{25-27}

![Figure 1.6](image)

**Figure 1.6** Structure of Idelalisib 20 (Zydelig\textsuperscript{\textregistered}), a PtdIns3K$\delta$ inhibitor approved by the FDA and MHRA.\textsuperscript{25-27}

PtdIns4K is also a desirable therapeutic target due to the potentially widespread therapeutic implications, but research has been more limited on this kinase compared to PtdIns3K.\textsuperscript{22} Pharmaceutical companies and the academic community are attempting to utilise the knowledge gained from problems in previous PtdIns3K programmes in order to achieve higher success rates with PtdIns4K.\textsuperscript{28} One area of particular interest is the side-effects of drugs caused by PtdIns3K and PtdIns4K inhibitors, that may be potentially caused by poor selectivity over other kinases, however, to some extent it may also be related to sub-type and isoform specificities, a challenging task to unravel.\textsuperscript{29}
1.2.4 Subtype Specific Inhibitors of PtdIns4K from AstraZeneca

Within mammalian cells there are two PtdIns4K types, defined by the sensitivity of each type to Wortmannin (21, Figure 1.7). These are type II (Wortmannin insensitive) and type III (Wortmannin sensitive). Type I PtdIns4K were wrongly assigned when first discovered, and are actually PtdIns3K. Type III PtdIns4K have generally been easier to target than type II, due to having a known positive control (Wortmannin) and type III possess a catalytic domain that is more similar to PtdIns3K than type II, consequently type III have been more widely studied. These two types of PtdIns4K are further divided each into \( \alpha \)- and \( \beta \)- isoforms.

During the course of their work, AstraZeneca developed two different inhibitors of PtdIns4K that could target the III\(\alpha\)- and III\(\beta\)- subtypes with 100-1000 fold selectivity for one isoform over the other (22 and 23, Figure 1.7, Table 1.2). The two inhibitors were developed to be selective for either isoform using biochemical assays with recombinant protein of either isoform of type III PtdIns4K (Table 1.2). Either inhibitor was then incubated with cells prior to addition of platelet-derived growth factor (PDGF), an activator of the PtdIns4K pathway. Using mass-spectrometry, the whole-cell levels of InsP and PtdInsP\(_2\) were measured and compared to a basal cell level. No attempt was made to distinguish between the different isomers of InsP and PtdInsP\(_2\) due to the use of mass spectrometry to quantify the species. The \( \alpha \)-isoform inhibitor 22 revealed an accumulation of InsP, a precursor to the pathway, and basal levels of PtdInsP\(_2\) dropped substantially, suggesting significant inhibition of the kinase (Table 1.2). Conversely, the \( \beta \)-isoform inhibitor 23
revealed a diminished effect on these two biomarkers compared to 22.\textsuperscript{32}

<table>
<thead>
<tr>
<th>Compound</th>
<th>PtdIns4Kα pIC\textsubscript{50}</th>
<th>PtdIns4Kβ pIC\textsubscript{50}</th>
<th>Cellular PtdInsP\textsubscript{2} (Basal, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>8.2</td>
<td>5.9</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>5.1</td>
<td>7.8</td>
<td>19</td>
</tr>
</tbody>
</table>

This methodology for measuring biological activity of 22 and 23 has several limitations. To quantify the data, the phospholipids were extracted using a method by Clark et al., processed and analysed.\textsuperscript{33} Using this method, all phospholipids in the cells are extracted, providing a whole-cell basal level rather than sub-cellular compartment levels. The β-isomer inhibitor 23 could potentially not be penetrating subcellular membranes to a sufficient extent to reach sites where PtdIns4KIIIβ is expressed, hence no effect on the whole-cell PtdInsP\textsubscript{2} levels is observed. Alternatively, the reduction of basal PtdInsP\textsubscript{2} in one area of the cell may be masked by a concomitant increase in other subcellular compartments, potentially due to a feedback system. In addition, mass spectrometry only isolates the masses, and cannot easily differentiate between different isomers (for instance between PtdIns(4,5)\textsubscript{2} 10 and PtdIns(3,5)\textsubscript{2} 18), therefore while one PtdInsP\textsubscript{n} is depleted, another may increase in concentration \textit{via} feedback mechanisms.\textsuperscript{34} In order to understand the origin of these results, new biologically relevant PtdIns(4,5)\textsubscript{2}-based probes are required.
1.3 Examples of Previous Probes

As the pathways involving PtdIns(4,5)\(_2\) have been heavily studied over the past forty years, there are many examples of probes based on the structure of endogenous Ins\(P_n\) and PtdIns\(P_n\). Typical examples to probe PtdIns(4,5)\(_2\) binding in biological systems have retained the Ins(1,4,5)\(_3\) motif, replacing the lipid chains with different reporter groups to distinguish between endogenous PtdIns\(P_n\) and synthetic probes. It has often been assumed that replacing the lipids with other hydrophobic groups, such as benzophenone, doesn’t affect the biological activity to any great extent, as the lipids are merely anchors into lipid membranes. Many reviews exist on the subject, showing the breadth of probes already synthesised.\(^3,35,36\) A few probe designs will be discussed here.

1.3.1 Photoaffinity, Fluorescent and Tagged Probes

Photoaffinity probes with reactive tags are particularly useful in determining binding partners of different biological messengers.\(^3,37\) In general, the design requires three components: 1) a group to bind to the endogenous protein of interest (with binding affinity not disrupted in the probe compared to endogenous PtdIns\(P_n\)), 2) a way of covalently linking to the protein in question, and 3) a method to observe the result.\(^38\) In this manner, proteins binding to endogenous PtdIns\(P_n\) can be identified. Chaudary et al. used a benzophenone tag in combination with a tritium tag (\(24\), Figure 1.8) to probe the binding of PtdIns(4,5)\(_2\) to profilin (Figure 1.8).\(^39\) By synthesising different probes, both with and without saturated lipid chains, it was possible to show that the binding of PtdIns(4,5)\(_2\) to profilin required the lipid chains.\(^39\) More recently, similar work on PtdIns(3,4,5)\(_3\)\(^19\) used a benzophenone photoaffinity group in combination with a ‘clickable’ acetylene (\(25\), Figure 1.8).\(^40\) This allowed the authors to bind proteins covalently with the probe and subsequently incorporate fluorescent groups (\(26\)), or a biotin tag for protein pull-down (\(27\)) post-reaction with the binding partner.\(^40\) This strategy removes potential issues with the reporter group disrupting biological activity, by introducing the reporter group after the binding event had occurred. PtdIns\(P_n\) have also been incorporated onto beads to create affinity columns that can be used to isolate and purify proteins that bind the inositol
1.3. EXAMPLES OF PREVIOUS PROBES

Figure 1.8 Two examples of photoaffinity probes synthesised in order to understand binding partners of PtdIns(4,5)P$_2$ in biological systems.$^{39,40}$ In some cases, a 'clickable' linker is also incorporated for further work using fluorescent groups or biotin tags.

phosphate headgroup, in a similar manner to ion-exchange chromatography.$^{41}$ These are just a small selection of possible tags that have been used in previous work.$^3$ A significant problem with these designs, however, is that the chemical and physical properties of the probes can substantially differ from the endogenous PtdInsP$_n$.$^{39}$

1.3.2 Isotopic Labelling

Isotopes have also been used in producing probes for PtdInsP$_n$ pathways. There are several isotopes that can be incorporated into PtdInsP$_n$, namely $^2$H, $^3$H, $^{32}$P, $^{18}$O, $^{13}$C, and $^{14}$C, with varying levels of difficulty. The key benefit of using isotopes is the difference in chemical properties from the endogenous molecules is minimised. Knowles et al. showed that $^{32}$P could be incorporated biosynthetically into PtdInsP (all isomers), using [$^{32}$P]-ATP.$^{42}$ Tritium ($^3$H) has been incorporated into benzophenone-tagged
PtdIns(4,5)\(P_2\) \textsuperscript{24,39} Both of these methods allow radiometric assays to be used for visualisation of data, providing a background against non-specific binding to proteins not of interest. Other groups have labelled the diacylglycerol group with \textsuperscript{18}F as a radiotracer, for use in monitoring metabolism of diacylglycerols.\textsuperscript{43} While used in biology regularly, there are severe limitations to radioactive isotopes as labels. Practically, they are much more challenging to work with, both from a health and safety perspective, but also from a chemistry perspective. With \textsuperscript{32}P and \textsuperscript{18}F, the synthesis must be robust and rapid once the radioisotope has been incorporated, otherwise there is a risk the probes could decay too quickly for subsequent use in assays (half lives of ca 14 days and 110 minutes, respectively).\textsuperscript{44} \textsuperscript{3}H has a significantly longer half life (ca 12 years), however, the majority of tritium is sourced through tritium gas, limiting the synthetic methods available for incorporation into probes.\textsuperscript{45} An alternative to radioisotopes is the use of stable isotopes in PtdIns\(P_n\). Deuterium has been used to replace hydrogen in the lipids of PtdIns\(P_n\), as perdeuteration of the fatty acid lipid chains is possible and perdeuterated fatty acids can be purchased from several companies including, Sigma Aldrich.\textsuperscript{46,47} PtdIns\(P_n\) incorporating these isotopically-labelled lipids have found use in solid-state NMR studies of phospholipid bilayers.\textsuperscript{46,47} \(C\)-Perdeuterated \textit{myo}-inositol has been used in biological systems to study cell walls in plants, however, its use has been limited by the high price of the material (\£120 for 10 mg, Sigma Aldrich, 2014).\textsuperscript{48,49} A patent exists for point-deuteration of the \textit{myo}-inositol ring in PtdIns\(P_n\), however, no further literature using these molecules is available.\textsuperscript{50} Currently, only one large-scale chemical method exists for the perdeuteration of \textit{myo}-inositol, but it is limited by the requirement to separate isomers of inositol, a challenging task that will be discussed in section 1.5.

### 1.3.3 Limitations of Previous Probes

While previous probes have aided in understanding the biological activity of PtdIns(4,5)\(P_2\), there are some limitations to these probes. It is increasingly apparent that the lipid tails are important for correct biological function.\textsuperscript{1,16} Removing or changing the lipids may be masking some of the biological effects of these molecules, in particular when concerned with sub-cellular effects of the PtdIns\(P_n\). This will affect the results obtained with a probe
in which the lipids have been exchanged for other groups. To circumvent this problem, minimally disrupted, biologically relevant probes are needed to tease apart the complex network of kinases.

### 1.3.4 Our Approach

It was hypothesised that the use of deuterium would enable the synthesis of minimally disrupted probes that more closely mimic the endogenous molecules than previous probes. Many of the chemical properties of deuterium are comparable to hydrogen, while the increased mass allows for use of mass-spectrometry and solid state or solution state NMR to distinguish between protonated and deuterated molecules. While previous work had relied on the use of deuterium on the lipid chains, this would limit the groups that could be monitored by mass-spectrometry. Once hydrolysed by PLC, the Ins(1,4,5)P$_3$ produced from PtdIns(4,5)P$_2$ with deuterium only on the lipid chains (cf 28, Figure 1.9) would be untraceable and indistinguishable from endogenous Ins(1,4,5)P$_3$. To allow for full analysis of the biological samples, the deuterium would need incorporation at the inositol headgroup, and on both lipid chains (Figure 1.9). A minimum of four deuterium atoms were required on each group for mass-spectrometry studies in order for the analysis to not be complicated by the naturally occurring $^{13}$C isotopes found in organic molecules. In the case of the inositol headgroup, all six positions would require deuteration for ease of analysis - there was a risk that fewer than six deuterium atoms would lead to complications involving enantiomers of isotopically-labelled inositols. A concurrent project by Amélié Joffrin (Conway Group, University of Oxford) was also underway to produce deuterated PtdIns4P.

![Figure 1.9](image-url) The planned sites of deuterium incorporation into PtdIns(4,5)P$_2$ 28, highlighted in red.
CHAPTER 1. INTRODUCTION

1.4 Previous Synthesis of myo-Inositol Derivatives

1.4.1 Syntheses from myo-Inositol

Most of the syntheses of myo-inositol derivatives in the literature start from myo-inositol 1. While very cheap and readily available, this presents several synthetic challenges. In “normal” sugar chemistries involving glucose-like structures, selective protection of the five hydroxyl groups can usually be achieved by either starting from the anomeric centre, or the primary hydroxyl group, and working around the structure from either end. In the case of myo-inositol 1, the difference between the hydroxyl groups is more subtle. In addition, the meso- nature of myo-inositol means that some form of enantiodiscrimination is required to synthesise optically pure myo-inositol derivatives, such as those found in natural systems.

![Scheme 1.2](image_url)
Two common synthetic methods are typically used as first steps in syntheses from myo-inositol 1. A patent from 1966 suggested that treatment of myo-inositol 1 or scyllo-inositol 2 with triethylorthoformate led to adamantane-like structures.\textsuperscript{54,55} This is a mainstay in inositol chemistry, as it is possible to differentiate between the six positions. The 4- and 6-positions in the orthoformate 29 can be selectively protected over the 2-position (Scheme 1.2).\textsuperscript{41,52} Furthermore, selective opening of the orthoester can differentiate between the 1-, 3- and 5-positions, making this intermediate very powerful.\textsuperscript{41,52} In addition, Riley et al. showed that derivatisation of free hydroxyl groups in orthoformate derivatives with camphor esters allows resolution to give \((-\))-34a and \((+\))-34b, generating single enantiomers once the chiral auxiliary was removed (Scheme 1.2).\textsuperscript{53}

\begin{center}
\textbf{Scheme 1.3} Chiral derivatisation by Bruzik et al. using a camphor acetal led to four separable diastereomers, allowing optically active myo-inositol derivatives to be synthesised.\textsuperscript{56} \textit{Reagents & conditions:} i. \(\pi\)-Camphor dimethylacetal, TMSOTf, DMSO, reflux, 31\% (35).\textsuperscript{56}
\end{center}

The axial 2-position hydroxyl group in myo-inositol 1 can be used as a starting point for selective protection of myo-inositol 1. Acetals of cis-diols preferentially form over those of trans-diols, allowing selective protection of the 1- and 2-positions simultaneously (or the 2- and 3-positions).\textsuperscript{57} This protection strategy was used by Bruzik and Tsai to good effect in combination with a camphor group to form a camphor acetal (Scheme 1.3).\textsuperscript{56} This group not only selectively protected the cis-diol, but also allowed a resolution of the inositol system to be achieved (Scheme 1.3), with one diastereomer 35 crystallising
preferentially over the other three. Once the 1- and 2-positions are protected, the most reactive position becomes the 3-position, due to the steric relief offered by the neighbouring axial hydroxyl, leaving only three positions to discriminate. In this manner, some of the first enantioselective syntheses of Ins$_nP_n$ were achieved.

Resolution at Phosphorus

The use of phosphoramidites protected with chiral non-racemic groups to effect a resolution during phosphitylation has also been used with limited success. Durantie et al. used a chiral benzyl derivative to effect resolution of (±)-39 to give bisphosphate derivatives such as Ins(1,5)$P_2$ 40a or Ins(3,5)$P_2$ 40b (Scheme 1.4). Despite high diastereotopic ratios obtained (d.r. > 99:1), the yields were very low with only a 11-24% yield (with the exception of one case with a 52% yield) of the desired diastereomer. Alternatively, Capolicchio et al. used a chiral non-racemic 2-cyanoethyl derivative on the phosphate group with excellent d.r., however, only a 13% yield of either diastereomer relative to the myo-inositol derivative (±)-41, was obtained. Another limitation of both these routes is that the compound d.r. in both cases is improved by crystallisation, which is not always possible with myo-inositol derivatives, and it was noted that separation of the two diastereomers in some cases was very challenging.

![Scheme 1.4](image)

**Scheme 1.4** Two examples of using chiral protecting groups on the phosphorus group to allow for separation of diastereomers of myo-inositol derivatives. Reagents & conditions: i. Phosphoramidite, 1H-tetrazole, CHCl$_3$, 20 h then mCPBA, 1 h, 11-52%; ii. Phosphoramidite, 5-(p-F-phenyl)-1H-tetrazole in MeCN 1 h then mCPBA, 1 h, 13%.
Enantioselective Synthesis from \textit{myo}-Inositol

Diastereomeric resolution of \textit{myo}-inositol 1 using chiral auxiliaries is possible, however, enantioselective synthesis starting from \textit{myo}-inositol derivatives is less common. Jordan \textit{et al.} developed peptidic organocatalysts such as 43 (Scheme 1.5) to selectively phospho-rylate the 1-position over the 3-position in 44, presumably by generating a chiral pocket around \textit{myo}-inositol in a similar manner to enzymes.\textsuperscript{61} While an elegant piece of work, synthesis of the required peptides is not trivial and each \textit{myo}-inositol derivative requires a different peptide, limiting the practicality of this approach. Enzymes have been used to generate high enantiomeric excess by the installation of an acetate protecting group onto 45 with excellent yield (\textbf{> 90\%} yield and \textbf{> 99\%} e.e.), however, only one of the two enantiomers can be generated.\textsuperscript{62} In order to obtain the opposite enantiomer, extensive protecting group manipulation is required, potentially limiting the isomers that can be synthesised by this route.\textsuperscript{62} There are also limitations on which protecting groups may be incorporated. Lauber \textit{et al.} showed organocatalysis to be a possibility on \textit{myo}-inositol derivatives such as 46. Using quinidine derivatives such as 47 (Scheme 1.5) in combination with acylating reagents meant it was possible to enantioselectively install a benzoyl group on the 3-position in 46 to give (–)-48, however, previous experience within the group suggested these results were difficult to reproduce in our hands.\textsuperscript{51,63}

Limitations of \textit{myo}-Inositol as a starting point

There are limitations in our case to starting with \textit{myo}-inositol 1 to synthesised deuterated \textit{myo}-inositol derivatives. A key aspect of the project was to develop an efficient, short and enantioselective synthesis of PtdIns(4,5)\textit{P}_2 10 while avoiding resolution. This approach would allow deuterium to be incorporated into highly complex molecules at a reasonable cost. In addition, there were no methods for the direct deuteration of \textit{myo}-inositol 1 that could be used on large scale (discussed in detail in section 1.5).\textsuperscript{48} It was prudent, therefore, to consider other methods for generating enantiopure \textit{myo}-inositol derivatives from different starting points other than \textit{myo}-inositol.
1.4.2 Syntheses from Other Starting Points

Many investigators have discussed routes to optically enriched myo-inositol derivatives starting from both achiral and chiral precursors, cyclic and acyclic.64–67 By careful consideration of the different starting points, a robust route to deuterated myo-inositol derivatives should be achievable.

Ferrier Rearrangements of Glucose

Scheme 1.5  Enantioselective synthesis of optically pure myo-inositol derivatives has been shown to be possible using peptides, enzymes and organocatalysts.61–63 Reagents & conditions: i. ClPO(OBn)2, NEt3, PhMe, 43, 65%; ii. Lipozyme TP-IL, vinyl acetate, 99%; iii. BzCl, DIPEA, 47, propionitrile, 99%.

Scheme 1.6  Two examples of the synthesis of myo-inositol derivatives via a Ferrier rearrangement.66,68 Reagents & conditions: i. PdCl2, dioxane, H2O, 60 °C, 6 h; ii. Hg(OAc)2, acetone, H2O then 35% aq. NaCl.
Many groups, including our own, have used a synthetic route that takes inspiration from the natural source of myo-inositol in cellular systems, D-glucose-6-phosphate \(53\).\(^{66,68,71,72}\) Inositol-3-phosphate synthase catalyses the reaction of \(53\) to inositol 3-phosphate \(58\) by the route shown (Scheme 1.7), followed by hydrolysis of the phosphate to give myo-inositol \(1\).\(^{69,70}\) Ferrier reported a chemical equivalent of the biotransformation of glucose in the presence of mercury(II) chloride in 1979 to give carbocycles that could be turned into myo-inositol derivatives.\(^{72}\) Takahashi et al. had reported the use of palladium(II) chloride to achieve a similar transformation toward many different inositol derivatives, avoiding the need for toxic mercury salts.\(^{68}\) Our group has some experience of using a Ferrier rearrangement for synthesising myo-inositol derivatives, however, it was noted that palladium(II) chloride was not as high yielding as mercury(II) salts (Hg(OAc)\(_2\)) in the reaction and subsequent removal of the mercury salts was difficult.\(^{66,73}\) In addition, for deuterated analogues the cost of D\(_7\)-glucose was still higher than desirable for a starting material to be used in a multistep synthesis (£330/g, Sigma-Aldrich, August 2015). This meant this method was discounted as a viable option.

### 1.4.3 Conduritol B Derivatives

Conduritol B belongs to a family of molecules comprising the cyclohex-5-ene-1,2,3,4-tetraol structure with varying relative stereochemistry (conduritol A-F, \(65\), Figure 1.10).\(^{77}\)
As with inositol derivatives, they can be found in a number of naturally derived products. Conduritol B derivatives are of interest to inositol chemists as they can be reacted, via a syn-dihydroxylation of the double bond, to give myo-inositol derivatives (Scheme 1.8). The use of conduritol B derivatives in the synthesis of myo-inositol derivatives was shown to be effective by the synthesis of all isomers of myo-inositol polyphosphates by Podeschwa et al. The use of optically pure, $C_2$ symmetric, conduritol B derivatives leads to a single enantiomer of a myo-inositol derivative during oxidation (Scheme 1.8), as the two faces of the $C_2$ symmetric system are the same, therefore there is no need to control for facial selectivity. Non-symmetric conduritol B derivatives can also be used, however, a mixture of isomers may be produced upon syn-dihydroxylation (Scheme 1.8). There are a number of enantioselective syntheses of conduritol B derivatives (Scheme 1.9, Scheme 1.10).

**Tartaric Acid Derivatives**

Chiral non-racemic starting materials have been used to synthesise protected enantiopure conduritol B derivatives, negating the requirement of enantioselective synthesis or diastereomeric resolution. Tartaric acid derivatives have been used as a starting point...
for synthesising conduritol B and myo-inositol derivatives (Scheme 1.9). These starting materials are readily available, at reasonable cost, and confer optical purity from the start of the synthesis. To achieve an enantiopure synthesis of the myo-inositol portion of a glycosylphosphatidylinositol, Conrad et al. described a synthetic process where a tartarate dimethyl ester 71 was reacted to form a divinyl species 73 via a Weinreb amide 72 (Scheme 1.9). From here, it was possible employ a ring-closing metathesis to give an optically pure conduritol B derivative 74, followed by protection to give 75 and a syn-dihydroxylation to give 76. This route is similar to Hyldtoft’s zinc-mediated ring-closing metathesis, which started from carbohydrates. It was hypothesised that deuterated PtdIns(4,5)P\textsubscript{2} would be difficult to synthesise using these methods, due to difficulties in deuteration and subsequent resolution of tartaric acid. In addition, this would only lead initially to D\textsubscript{4} derivatives, not the D\textsubscript{6} desired, as there was no obvious manner in which to produce D\textsubscript{3}-vinylmagnesium bromide, or to subsequently deuterate the two alkene positions at a later stage.

**Asymmetric Syntheses of Conduritol B Derivatives**

Many groups have used \textit{p}-benzoquinone 77 as a start point for producing conduritol B derivatives and, as an achiral precursor, there have been many attempts to gener-
ate optically pure conduritol B derivatives from 77.\textsuperscript{64,79–81} The conduritol B scaffold is obtained by bromination, reduction and acetylation to generate a dibromo diacetyl conduritol B derivative (±)-80 (Scheme 1.10).\textsuperscript{64,82} Several groups have used pig pancreatic lipase (PPL), a commercially available enzyme which hydrolyses the acetates of one enantiomer while leaving the other enantiomer intact, to provide both enantiomers in a single step that can be chromatographically separated (Scheme 1.10).\textsuperscript{67,79,83} Once again, this results in half the material not being used, a significant downside for deuterated analogues. Trost et al. reported a dynamic kinetic resolution (DKR) performed on a racemic conduritol B derivative (±)-82 that produces a single enantiomer of (+)-83 in 80% yield, while differentiating between the allylic and other alcohols (Scheme 1.10).\textsuperscript{64,81} This route from Trost et al. had high potential for efficient synthesis of deuterated PtdIns(4,5)P\textsubscript{2} 85 as the potential yield for the dynamic kinetic resolution is 100%. The original report of this system had included a synthesis of Ins(1,4,5)P\textsubscript{3} 11 using this methodology. As such, this approach was chosen to be the focus for generating single enantiomers of \textit{myo}-inositol derivatives.\textsuperscript{64} Despite the potential of this reaction in the synthesis of conduritol B and \textit{myo}-inositol derivatives, the kinetic resolution of (±)-81 had only been reported twice in
1.4. Previous Syntheses of PtdIns$P_n$

There have been multiple previous syntheses of PtdIns$(4,5)P_2$ and related compounds, both with saturated (typically stearoyl or palmitoyl) and unsaturated (typically arachidonic) chains attached to the glycerol group.\(^3,4,1,8,85-90\) The challenge with PtdIns$P_n$, as compared to Ins$P_n$ without the glycerol-lipid group, is that the final molecules are unstable to many conditions.\(^3,87-90\) For this reason, the predominant methods for synthesising PtdIns$P_n$ derivatives rely heavily on the use of benzyl groups as a protecting group strategy.\(^3,4,90\) This is due to the fact that hydrogenolysis of the benzyl groups is traceless, in contrast to other groups such as trifluoromethyl, which can undergo hydrogenolysis to give a trace of the desired product.\(^91,92\)
removing the need to purify the final PtdInsP₅. The literature for incorporation of unsaturated lipid chains, which are not stable to hydrogenolysis, is much more limited.⁸⁵,⁸⁶ In this case, the majority of the routes use acidic methods to remove the protecting groups, with purification by trituration or other non-chromatographic methods. Designing a synthesis to incorporate unsaturated lipid chains is particularly challenging, and careful choice of protecting group is required.

### 1.5 Deuterium in Synthesis

Deuterium is an isotope that has been incorporated into biologically active molecules as it retains many of the same chemical properties (electronics, shape, size) as hydrogen while having some notable differences, namely in the kinetics of reactions, mass and nuclear spin. These effects are used in the study of biologically active molecules through mass spectrometry, solid state NMR and for metabolism studies. The use of deuterium in pharmaceutically active molecules is becoming more widespread as deuterium can be incorporated at metabolic weak points, slowing the metabolism through the kinetic isotope effect.⁹¹ This has been exemplified through the deuteration of a methyl group in Imatinib (Gleevec®, ⁸⁶, Scheme 1.11), an approved anti-cancer drug. The methyl group on the piperazine was trideuterated to prevent oxidation by CYP enzymes and subsequent demethylation.⁹²

![Scheme 1.11](image)

**Scheme 1.11** Deuteration of the methyl group in Gleevec® led to slower metabolism in *in vitro* assays due to the kinetic isotope effect of deuterium.⁹²

In combination with metabolism studies, deuterated molecules are often used in mass
spectrometry studies, usually as analytical standards (Figure 1.11). Incorporating deuterium into analytes of interest produces a mass spectrometry standard - the deuterium atoms shift the mass but it is generally assumed that the ionisation potential is not changed by the deuterium atoms, if the placement of deuterium atoms is carefully selected.\(^9\) In a similar manner, \(^{13}\)C incorporation can also be used for mass spectrometry standards, however, the cost of producing \(^{13}\)C labelled molecules is significantly higher, and their synthesis more challenging than for deuterium incorporation. In addition, there is usually a requirement of a mass shift of at least 4 Daltons to avoid complications caused by naturally occurring \(^{13}\)C isotope incorporation into molecules (approximately 1.1% per carbon atom in the molecule of interest). Alternatively, the change in mass caused by deuterium incorporation lends it to incorporation into the matrix (e.g. 88, Figure 1.11) used in matrix assisted laser desorption ionisation (MALDI), shifting the mass of the matrix peaks by 4-6 Daltons, allowing for peaks that would normally be obscured by the matrix ions to be observed.\(^9\) Deuterium incorporation can also allow for the study of phospholipids and other molecules in membranes by solid state NMR (89, Figure 1.11), allowing for the ordering and packing of the molecules to be determined in a rigid system, such as that found in lipid bilayers.\(^4\)\(^7\)\(^9\)\(^5\) Solid state NMR studies are possible due to the change in spin state of the nucleus from spin \(I=1/2\) in hydrogen to \(I=1\) in deuterium. This change in spin state causes changes in the spin-spin relaxation properties, driven by quadrupolar relaxation, that make solid state NMR possible. The effects of deuterated organic molecules in solution state NMR (but not solid state NMR) are discussed in detail in Chapter 4.

\(88\)

\(89\)

**Figure 1.11** Examples of deuterated species used in either mass spectrometry studies (88) or for solid state \(^2\)H NMR studies (89).\(^9\)\(^4\)\(^9\)\(^5\)
1.5.1 Chemistry of Deuterium

The chemistry of deuterium is similar to that of hydrogen. The change in mass does affect the electronics in a small manner, namely that deuterium has a slightly reduced electron density \textit{cf.} hydrogen due to the increased mass. This is observed by the shift in the $^{13}$C NMR for carbon atoms attached to deuterium \textit{vs} hydrogen, both when the deuterium atom is attached ($\alpha$) or neighbouring ($\beta$) to the carbon atom (Figure 1.12). This difference in electronics is small, and generally does not affect all but the most sensitive chemical methods. The main effect observed moving from hydrogen to deuterium is the kinetic isotope effect, caused by a lowering of the zero-point energy in deuterium. Typically, the primary kinetic isotope effect (PKIE) caused by deuterium results in reactions proceeding \textit{ca.} 7 times slower than the same process with hydrogen, while a secondary effect (SKIE) can be observed of \textit{ca.} 1.4 times slower in close proximity to deuterium. These effects are often used in mechanistic studies of chemical reactions to identify the rate-limiting step. These effects, along with the possibility of hydrogen-deuterium exchange, should be considered when designing syntheses to incorporate deuterium atoms into complex molecules.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{$^{13}$C NMR of protonated (top, red) and deuterated (bottom, blue) versions of the same molecule, showing the shift upfield when deuterium is incorporated \textit{vs.} when a proton is attached to the secondary carbon atoms (indicated by $\Delta\delta$). There is also an effect on the carbon atom when the D atom is $\beta$ to the carbon, rather than $\alpha$. This is caused by the small decrease in shielding of the carbon by the more electropositive deuterium atom.}
\end{figure}
1.5. DEUTERIUM IN SYNTHESIS

1.5.1 Previous Synthesis of D_6-\textit{myo}-inositol

There are few previous examples of D_6-\textit{myo}-inositol 90 (Scheme 1.13) in the literature, despite the obvious high utility of the compound in the analysis of biological pathways. Sherman et al. showed in 1969 during their studies on the production of \textit{myo}-inositol from glucose-6-phosphate that this could also be accomplished enzymatically with D_7-glucose-6-phosphate to give D_6-inositol-1-phosphate (see Ferrier rearrangement, section 1.4.2).^{102} The main limitation to such procedures is the use of D_7-glucose, an expensive compound in its own right (£330/g, Sigma-Aldrich, August 2015). Sasaki et al. described a chemical procedure for the production of 90 using Raney-Nickel in D_2O starting with \textit{myo}-inositol 1 (Scheme 1.13).^{48} While only taking one step to form 90 in high enrichment...
(98-99% D₆ on carbon), six isomers of inositol are formed through the isomerisation process, requiring difficult ion-exchange chromatography and multiple crystallisations to separate all the isomers completely. Koch and Stuart had reported a similar procedure toward deuterated sugar species. It was noted in this publication that the isomerisation rate is significantly slower than the hydrogen-deuterium exchange reaction, however, the rate of isomerisation is sufficiently fast to prevent high incorporations without multiple isomers being produced. These results from Sasaki and Koch likely explain the high cost of 90 from commercial suppliers - the cost from Sigma-Aldrich was found to be £120 for 10 mg (March 2015). This significantly limits the chemical synthesis of deuterated myo-inositol derivatives starting from D₆-myoinositol 90, especially from commercial sources as multi-step syntheses of myo-inositol derivatives generally need multiple grams of starting material in order to reach final products. This shows the benefit of using other starting materials in the synthesis of complex deuterated myo-inositol derivatives.

Scheme 1.13 Synthesis of D₆-myoinositol 90 from myoinositol 1 was described by Sasaki et al., however, it was difficult to separate the isomers formed requiring multiple ion-exchange chromatography runs and crystallisations, resulting in low yields and purity. A red asterisk indicates a carbon atom attached to deuterium. Reagents & conditions: i. Raney-Ni, D₂O, reflux, 12-24 h, yields not quoted.

1.6 Aims & Initial Plan

A set of key attributes for a synthesis were defined based on what would be required in the overall synthesis of PtdIns(4,5)P₂ 10 and its deuterated derivatives. The main considerations for a viable synthetic route were as follows:

1. Synthetically tractable and short, based on the wealth of previous literature available.

2. An asymmetric route using enantioselective chemistry rather than resolution to
produce a single enantiomer.

3. A protecting group strategy that allowed for the use of unsaturated lipid chains in PtdIns(4,5)P2 10 such as arachidonic acid.

4. The ability to incorporate deuterium at a later stage of the project with minimal changes to the synthetic route.

5. Low-cost with regard to the ability to later incorporate deuterium.

A route had already been used by Trost et al. to good effect to produce Ins(1,4,5)P3 (−)-11 in an asymmetric manner, as well as related aminocyclitols (Scheme 1.14). This route fitted the initial considerations detailed above and as such a synthetic route
was chosen to develop (Scheme 1.15). The original literature route required two minor modifications to be utilised for our means. Firstly, the route was modified to include removal of the trichloroethylcarbonate (Troc) groups and phosphorylation prior to syn-dihydroxylation. This would allow discrimination between the 4- and 5-phosphate groups vs. the 1-phosphatidyl group. Once this was completed, selective protection of the 2-position, as had been used by Podeschwa et al. to give (+)-97 (Scheme 1.15), would leave the 1-position free to be derivatised with a phospholipid group. The second modification to the route was the nature of the protecting groups on the phosphate groups. In the original Trost publication, methyl phosphate esters had been used, allowing for a

![Chemical structures and reactions](image)

**Scheme 1.15** Planned synthesis of PtdIns(4,5)P$_2$ based on work by Podeschwa et al. and Trost et al. with some minor modifications to enable the use of unsaturated lipid chains. Initially, R=R'=C$_{15}$H$_{31}$ with the ability to add unsaturated lipids once optimised. Compounds 94-98 and the final product 10 are single enantiomers of unknown optical rotation. Reagents & conditions: i. Br$_2$, CHCl$_3$; ii. NaBH$_4$, Et$_2$O, H$_2$O; iii. Ac$_2$O, K$_2$CO$_3$; iv. AcOH, reflux; v. NEt$_3$, MeOH, H$_2$O; vi. TrocCl, pyridine, 4-dimethylaminopyridine, CH$_2$Cl$_2$; vii. Benzoic acid, (S,S)-ligand (–)-84, tetrahexylammonium bromide, [Pd(η$^3$-allyl)Cl]$_2$, 1 M aqueous NaOH, CH$_2$Cl$_2$; viii. Zn, AcOH, THF; ix. Phosphoramidite, 1H-tetrazole in MeCN, CH$_2$Cl$_2$ then mCPBA; x. NaIO$_4$, RuCl$_3$·3H$_2$O, MeCN, H$_2$O; xi. CHC(OEt)$_3$, pTSA, THF then 80% v/v aqueous AcOH; xii. Phosphoramidite, 1H-tetrazole in MeCN, CH$_2$Cl$_2$ then mCPBA; xiii. Basic hydrolysis e.g. NaOH, NEt$_3$ or LiOH.
clean deprotection by 30% HBr/AcOH.\textsuperscript{64} This had been previously described by Meek \textit{et al.}\textsuperscript{104} Methyl phosphate esters are relatively unstable and it was thought a more stable protecting group would be easier to work with. Benzyl esters have typically been used in phosphatidylinositol phosphate synthesis, with deprotection by hydrogenolysis due to the ease of purification at the final stage. They were not appropriate in this case due to the unsaturated lipid chains present in the final molecules. 2-Cyanoethyl protecting groups were chosen as 2-cyanoethyl (Cne) phosphate esters have been used to good effect in oligonucleotide synthesis since the 1960s, and in more recent phosphoinositide chemistry.\textsuperscript{105–107} They are base-labile \textit{via} an elimination mechanism, allowing for the use of unsaturated lipid chains. To this end, a total synthesis was designed (Scheme 1.15).
Chapter 2

Enantioselective Synthesis of Conduritol B Derivatives

2.1 Introduction

Prior to developing any synthesis of myo-inositol derivatives, it was essential to ensure that enantioselectivity could be achieved in order to reach optically pure final products. While literature procedures existed for the generation of conduritol B derivatives, these procedures needed some optimisation to be used successfully, in particular for the generation of single enantiomers using a Trost asymmetric allylic alkylation reaction (Scheme 2.1).\textsuperscript{64,81}

\begin{align*}
\begin{array}{c}
77 \\
\text{TrocO, TrocO, OBz} \\
\text{TrocO, OBz} \\
\text{(+)-83} \\
\text{(-)-10}
\end{array}
\end{align*}

\textbf{Scheme 2.1} General scheme to generate enantiopure PtdInsP\(_2\) 10 from \textit{p}-benzoquinone.
2.2 Synthesis of Conduritol B Derivatives

2.2.1 Synthesis of Conduritol B tetracetate

The racemic synthesis of conduritol B derivatives has been well documented.\textsuperscript{67,75,82,108,109} Starting from \textit{p}-benzoquinone, a modification of the method from Guo \textit{et al.} was used to synthesise (±)-81 (Scheme 2.2).\textsuperscript{64,81,82} Bromination of 77 proceeded well within an hour at 0 °C with no further purification required.\textsuperscript{67} The resulting dibromide (±)-78 was unstable, with increasing amounts of unidentified products observed when left standing on the bench in air. This meant (±)-78 was used immediately in the next reaction without further purification. A biphasic (Et\textsubscript{2}O/H\textsubscript{2}O) reduction with NaBH\textsubscript{4} led to (±)-79, which was also found to be unstable during crystallisation and column chromatography, with both methods resulting in epoxide formation.\textsuperscript{110} Early attempts and literature reports of the reduction utilised 2.5 equivalents of NaBH\textsubscript{4} (relative to 77), however, after some optimisation, it was found that 1.0 equivalents of NaBH\textsubscript{4} was sufficient for complete reaction to be observed.

\begin{equation}
\begin{array}{c}
\text{77} \quad \text{i} \quad \text{Br}_2, \text{CHCl}_3, 0 \degree \text{C}, 1 \text{ h} \quad \text{ii} \quad \text{NaBH}_4, \text{Et}_2\text{O}, \text{H}_2\text{O}, 0 \degree \text{C}, 1 \text{ h} \quad \text{iii} \quad \text{Ac}_2\text{O}, \text{K}_2\text{CO}_3, 2 \text{ h} \text{then} \text{AcOH, reflux, 96 h, 33\% over 3 steps.}
\end{array}
\end{equation}

\textbf{Scheme 2.2} Synthesis of the tetracetate (±)-81 from \textit{p}-benzoquinone 77. Reagents & conditions: i. Br\textsubscript{2}, CHCl\textsubscript{3}, 0 °C, 1 h; ii. NaBH\textsubscript{4}, Et\textsubscript{2}O, H\textsubscript{2}O, 0 °C, 1 h; iii. Ac\textsubscript{2}O, K\textsubscript{2}CO\textsubscript{3}, 2 h then AcOH, reflux, 96 h, 33% over 3 steps.

As the intermediates ((±)-78 and (±)-79) thus far had proven unstable, the synthesis was continued without purification from (±)-79 in a one-pot, two step, procedure as described by Trost \textit{et al.}\textsuperscript{64} The two hydroxyl groups on (±)-79 were acetylated using acetic anhydride and K\textsubscript{2}CO\textsubscript{3}, followed by direct addition of acetic acid to the mixture, and heating under reflux for three days.\textsuperscript{64} Post-workup, crystallisation of (±)-81 was possible from the crude, however, the yield was improved by column chromatography prior to crystalli-
sation, leading to 35-40% over the three steps.

![Scheme 2.3](image)

Scheme 2.3 The neighbouring acetates displace the bromide to form a cationic cyclic intermediate (±)-99 that undergoes S\(_{N2}\) by an acetate anion, leading to overall retention of stereochemistry.\(^7^4\)

The reaction to produce (±)-81 from (±)-101 proceeds by a displacement of the bromides, through neighbouring attack of the acetates, followed by attack of potassium acetate leading to the more thermodynamically stable all trans configuration (Prévost product, Scheme 2.3).\(^7^6\) This is in contrast to a cis-trans-cis configuration, which is the product observed when wet acetic acid is used (Woodward product).\(^1^1^1\) The Woodward product is formed under wet conditions because the water hydrolyses the cyclic acetal (±)-99 formed by neighbouring group participation, giving a free hydroxyl that can subsequently be acetylated, leading to the syn-acetate. Under the conditions used to produce (±)-81, typical dry conditions were not necessary (under inert atmosphere with distilled reagents) as the acetic anhydride used in large excess acts as a drying agent throughout the reaction.

2.2.2 Confirming the Relative Stereochemistry

Due to the complexity of forming the multiple stereogenic centres in (±)-81, it was prudent to confirm the relative stereochemistry prior to continued synthesis. While \(^1^H\) NMR tentatively suggested the relative stereochemistry was as predicted, the relative ease of growing crystals of the product led to the use of small molecule X-ray crystallography (Figure 2.1, also see appendix page 533, by Prof. Richard Cooper, Chemical Crystallography Lab Oxford). Interestingly, while the crystals were prepared from a bulk racemate, the crystal structure contained only one molecule in the unit cell, with a non-centrosymmetric space group (P2\(_1\)). The space group and unit cell together suggests only a single enan-
tiomer was found in the individual crystal rather than both enantiomers. This observation could be explained by one of two explanations - either the crystals were formed as single enantiomers with spontaneous resolution or the crystals are twinned (less likely than spontaneous resolution).

Further evidence for spontaneous resolution was provided by taking five individual crystals from the bulk and measuring the optical rotation. In two of the five cases, a non-zero (although small) specific rotation was observed suggesting that some crystals were optically active and therefore enantioenriched (Table 2.1), albeit at a low level (the specific rotation of a sample with > 99% e.e. was found to be +182.6, suggesting an e.e. of around 10% in the most enriched cases). Complete resolution is unlikely

Table 2.1 Measured optical rotations and calculated specific rotations of individual crystals of (±)-81 showing that some crystals have optical activity suggesting some spontaneous enantioenrichment during crystallisation.

<table>
<thead>
<tr>
<th>Crystal</th>
<th>Average Measured Rotation</th>
<th>Concentration / (mg mL(^{-1}))</th>
<th>Specific Rotation / (10^1\ \circ\ cm^2\ g^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.009</td>
<td>0.4</td>
<td>-22.5</td>
</tr>
<tr>
<td>2</td>
<td>+0.003</td>
<td>0.5</td>
<td>+6.0</td>
</tr>
<tr>
<td>3</td>
<td>+0.025</td>
<td>1.1</td>
<td>+22.7</td>
</tr>
<tr>
<td>4</td>
<td>+0.003</td>
<td>1.2</td>
<td>+2.5</td>
</tr>
<tr>
<td>5</td>
<td>+0.003</td>
<td>1.0</td>
<td>+3.0</td>
</tr>
</tbody>
</table>
as crystals usually contain many domains formed during crystallisation and it is unlikely that all domains contain the same enantiomer. This has been observed with amino acids whereby some crystallise as a single enantiomer more readily than the racemate, while others crystallise best as a racemate.\textsuperscript{113,114} In cases where the single enantiomer crystallises more readily, enantioenrichment can occur leading to high e.e. values, which has implications for the origins of homochirality.\textsuperscript{113,115}

\section*{2.3 Trost Asymmetric Allylic Alkylation}

\subsection*{2.3.1 Initial Reproduction}

Once the synthesis of (±)-81 was established, efforts began to generate a single enantiomer from the racemate, using palladium-catalysed chemistry. The tetracetate (±)-81 had been shown to participate in an asymmetric allylic alkylation (AAA), leading to a kinetic resolution in which one enantiomer reacted with a nucleophile, while the other enantiomer remained unreacted.\textsuperscript{64} The two products could then be separated by column chromatography. Trost \textit{et al.} have also shown that changing the acetates to either methylcarbonates or 2,2,2-trichloroethylcarbonates (Troc) effected a dynamic kinetic resolution (DKR).\textsuperscript{64,81} These DKR reactions were potentially higher yielding, a key consideration for more expensive deuterated substrates. The use of Troc groups in our synthesis (\textit{cf.} the methylcarbonates) was attractive as the Troc groups could be removed by reductive methods (Zn, AcOH) in the presence of the benzoates, unlike the methylcarbonates.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_2.4}
\caption{Synthesis of an enantiomerically pure derivative (+)-83, a useful derivative for the synthesis of inositols. \textit{Reagents \& conditions}: i. NE\textsubscript{T}\textsubscript{3}, H\textsubscript{2}O, MeOH, 1 h; ii. ClCO\textsubscript{2}CH\textsubscript{2}CCl\textsubscript{3}, DMAP, pyridine, CH\textsubscript{2}Cl\textsubscript{2}, 20 min, 88\% (2 steps); iii. BzOH, tetrahexylammonium bromide, [Pd(η\textsuperscript{3}-allyl)Cl]\textsubscript{2}, (−)-84, 1 M aqueous NaOH, CH\textsubscript{2}Cl\textsubscript{2}, 81\%, > 99\% e.e.}
\end{figure}
The ligand \( (-)-84 \) and its enantiomer \( (+)-84 \) were commercially available, however, the cost was high given the quantities required over the course of the project. It was found that the ligand could be synthesised from cheap, readily available starting materials by using the method described by Fuchs et al.\(^{116}\) A relatively straightforward amide coupling was conducted on gram scale (Scheme 2.5), also ensuring the ligand was of high purity.\(^{116}\) All other components were commercially available. Once the necessary reagents were available, the DKR reaction was undertaken as described by Trost et al. however there was little success on initial attempts (Table 2.2).

![Scheme 2.5](image)

**Scheme 2.5** Synthesis of the ligand \( (-)-84 \) was possible at a significantly lower cost than purchasing the ligand using an amide coupling as described by Fuchs et al.\(^{116}\) **Reagents & conditions:** EDC·HCl, \( N,N \)-dimethyl-4-aminopyridine, \( \text{CH}_2\text{Cl}_2 \), 18 h, 89%.

Tetrabutylammonium bromide (TBABr, *cf.* tetrahexylammonium bromide THABr) had been used in first attempts as literature precedent suggested this only affected the enantiomeric excess to a small extent and should not affect reliability or yield (entries 1-3, Table 2.2).\(^{117}\) These reactions using TBABr showed poor conversion with large amounts of starting material remaining (54-85% by \(^1\)H NMR analysis, Figure 2.2). It should be noted that freeze/thaw degassing of the reaction solvents in combination with Schlenk techniques was used in entry 3 with no improvement in conversion. At this stage tetrahexylammonium bromide was used as described (entry 4). The reaction proceeded with complete conversion to the product \( (+)-83 \). The enantiomeric excess was confirmed by chiral HPLC prior to continuing any further synthesis using a ChiralPak\(^{®}\) AD-H column which corroborated the published retention time (red, Figure 2.3). Triphenylphosphine was used to prepare a sample of the racemate in a similar manner, replacing the chiral ligand \( (-)-84 \) (0.15 equivalents) with \( \text{PPh}_3 \) (0.3 equivalents). As can be seen by the
HPLC trace (blue, Figure 2.3), the reaction does not tolerate well the use of achiral ligands (e.g. PPh$_3$), with two new peaks appearing in the spectrum despite a single product by $^1$H NMR analysis. A similar effect was observed when using a racemic batch of the ligand (±)-84 prepared from racemic amine (±)-102. This effect is due to the complexity of many different potential ionisations of the palladium complexes (Scheme 2.9). Discussions with Prof. Guy Lloyd-Jones (University of Edinburgh) revealed that he had observed similar effects in trying to prepare racemic products on an earlier publication.$^{118}$

Table 2.2 Optimisation of the Trost asymmetric allylic alkylation. All reactions were performed under an atmosphere of argon unless otherwise stated. Reagents & conditions: All reactions were performed using the general procedure with 3.5 eq. BzOH, 0.025 eq. [Pd(η$_3$-allyl)Cl]$_2$, 0.2 eq. tetrahexylammonium bromide, 3.0 eq. 1 M aqueous NaOH and 1.5 mL CH$_2$Cl$_2$ (except in entries 5 & 6 where 6.0 mL CH$_2$Cl$_2$ was used). $^a$ (–)-84; $^b$ Conversions were calculated using $^1$H NMR (see appendix, page 278), e.e. was determined by chiral HPLC; $^c$ Tetrabutylammonium bromide was used; $^d$ The eq. of tetrahexylammonium bromide, ligand (–)-84 and [Pd(η$_3$-allyl)Cl]$_2$ were doubled; $^e$ The reaction was performed on a Schlenk system using N$_2$.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>(±)-82</th>
<th>Ligand$^a$</th>
<th>Time</th>
<th>Conversion (e.e.$^b$)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol</td>
<td>eq.</td>
<td>h</td>
<td>(±)-82   (+)-104   (+)-83</td>
<td>(+)-83</td>
</tr>
<tr>
<td>1$^c$</td>
<td>0.54</td>
<td>0.075</td>
<td>18</td>
<td>79       21       0</td>
<td>-</td>
</tr>
<tr>
<td>2$^c$</td>
<td>0.54</td>
<td>0.075</td>
<td>18</td>
<td>54       37       9</td>
<td>-</td>
</tr>
<tr>
<td>3$^{c,d}$</td>
<td>0.54</td>
<td>0.075</td>
<td>18</td>
<td>85       15       0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.54</td>
<td>0.075</td>
<td>18</td>
<td>0        0        100</td>
<td>36 (&gt; 99)</td>
</tr>
<tr>
<td>5</td>
<td>2.25</td>
<td>0.075</td>
<td>18</td>
<td>69       31       0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2.25</td>
<td>0.075</td>
<td>18</td>
<td>80       20       0</td>
<td>-</td>
</tr>
<tr>
<td>7$^e$</td>
<td>0.54</td>
<td>0.075</td>
<td>18</td>
<td>21       25       54</td>
<td>-</td>
</tr>
<tr>
<td>8$^f$</td>
<td>0.54</td>
<td>0.150</td>
<td>18</td>
<td>61       39       0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0.54</td>
<td>0.150</td>
<td>2.5</td>
<td>0        0        100</td>
<td>57 (&gt; 99)</td>
</tr>
<tr>
<td>10$^g$ (n=2)</td>
<td>0.54</td>
<td>0.150</td>
<td>1</td>
<td>0        0        100</td>
<td>-</td>
</tr>
<tr>
<td>11 (n=2)</td>
<td>2.29</td>
<td>0.150</td>
<td>1</td>
<td>0        0        100</td>
<td>81 (&gt; 99)</td>
</tr>
</tbody>
</table>
In later attempts to determine enantiopurity of novel substrates, the opposite enantiomer of the ligand (+)-84 was prepared and used. This enabled easier purification of products and made it easier to interpret chiral HPLC data.

As the reaction had been used to produce a single enantiomer of (+)-83, it was scaled up to enable more material to be produced for subsequent chemistry (entries 5 and 6). The reaction, however, did not work with (+)-83 not observed by $^1$H NMR analysis. This is despite the scale being similar to the reported scale (1.50 mmol vs. 2.25 mmol in our case) and prior successful attempts on 0.5 mmol scale. Degassing the solvents by
bubbling through \( N_2 \) did not improve the reaction conversion. At this point it became prudent to go back to the original scale to check the reliability (entry 7). Despite some conversion to \((+)-83\) being observed, the conversion was not the 100% that had previously been achieved (entry 4). The decision was taken to consult the original authors regarding possible sources of unreliability. Dr Erik Hembre (post-doctoral researcher on the original paper) suggested that this reaction was particularly sensitive to oxygen. This was despite every attempt to exclude oxygen from our system, even by freeze/thaw degassing of solvents on a Schlenk system with \( N_2 \) or Ar. This had been previously described by Amatore et al. and Tsarev et al. in which an inactive Pd\( ^{II} \) complex was formed in the presence of traces of oxygen.\(^{119,120}\) To circumvent this problem, the amount of catalyst and ligand was doubled to 5 mol% and 15 mol% respectively with no improvement in conversion to \((+)-83\) (entry 8).

Dr Hembre then provided his post-doctoral report containing unpublished data on the reaction. The reaction had been thoroughly studied by Dr Hembre, however, it was noted that the ratio of ligand to palladium in the reaction was never changed, presumably as in other similar reactions a 3:1 molar ratio was optimal - in many cases in the literature
2.3. TROST AAA  
CHAPTER 2. ENANTIOSELECTIVE SYNTHESIS

Scheme 2.6 Activation of the $N$-$H$ bond in the active complex 105 leads to a rapid oxidation in air by oxygen, presumably releasing water in the process, to give the highly stable tetracoordinate Pd$^{II}$ complex 106.$^{119,120}$

this appears to be the case. Increasing the amount of ligand two-fold without changing the palladium concentration (6:1 molar ratio ligand (−)-84 to [Pd($\eta^3$-allyl)Cl]$_2$, 2.5 mol% Pd precatalyst) caused the reaction not only to reach 100% conversion, but also to occur at a much faster rate than had been reported in the literature (completed at 2.5 h when checked by $^1$H NMR analysis cf. 18 h for other reactions that had been successful, entry 9). It transpired after two more reactions, the reliability issue appeared to be resolved with similar results obtained on three different days. Indeed, this reaction was performed on many occasions throughout the project ($n$>10) on scales ranging from 100 mg to 10 g of (±)-82 with no other problems observed at this increased ligand concentration. The reaction rate was significantly faster than literature reports, such that the reaction was found to be complete after just 1 h (by $^1$H NMR analysis). In addition, there was no change to the e.e. as determined by both optical rotation and chiral HPLC. Scale up was attempted again with the new ligand concentration and the reaction proceeded well with complete conversion (entry 11). The fact that the reliability issue had been resolved enabled synthesis to continue as described on any necessary scale (up to 10 g of (±)-82).

2.3.2 Determination of Absolute Stereochemistry

Regardless of the fact the product (+)-83 was a literature compound, it was deemed prudent to confirm the absolute configuration of the product at an early stage of the project. Chiral HPLC had shown a single enantiomer with the same retention time as the reported values and the specific rotation matched in magnitude and direction, however, no attempt was made to determine absolute stereochemistry in the original publication.$^{64}$
There are several methods available for absolute stereochemical assignment. X-Ray crystallography can be used if the absolute stereochemistry of one stereogenic centre is known or there are heavy atoms (e.g. Cl) in the structure that show large electron densities, allowing for absolute configuration to be determined - only light atoms in the structure (H, N, C, O) make the determination difficult due to insignificant differences in electron densities between the two enantiomers. The relative configuration of the racemate (±)-81 had already been determined by crystallisation and subsequent X-ray diffraction analysis (performed by Prof. Richard Cooper, Chemical Crystallography lab, University of Oxford). Attempts to crystallise (+)-83 provided plate-like crystals, however, X-ray crystallography showed the Troc groups had degraded during crystallisation, leaving the dihydroxy compound (+)-94 that could not be used for absolute stereochemical assignment. As crystallography was not possible, other techniques were sought.

A comprehensive review of NMR stereochemical assignment techniques was available from Secco et al. showing that various NMR experiments can be used to both calculate the e.e. of compounds and obtain absolute stereochemical assignments. Chiral solvating agents (e.g. trisdipivalomethanatoeuropium(III)) do not irreversibly modify the structure being studied, while providing a chiral environment for NMR studies that causes two diasteromeric complexes to form. This can act as a useful method for separating two enantiomers in NMR studies (in particular for determining e.e.), however, it is very difficult to
show absolute configuration using these reagents. This left chiral derivatisation agents to determine absolute stereochemistry. By reacting the compound of interest with the two optically pure enantiomers of a chiral reagent of known stereochemistry, the two resulting diastereomers can be analysed by $^1$H NMR, and hence absolute stereochemical determination can be made. Mosher’s acid (±)-110 (α-methoxy-α-trifluoromethylphenylacetic acid, MTPA) has been used in combination with chiral secondary alcohols to determine the absolute stereochemistry at the 5-position.

![Figure 2.4](image1.png)

Figure 2.4 Mono-substitution of (+)-94 with (R)- and (S)-enantiomers of MPA ((–)-107 and (+)-107 respectively) using conditions shown above (Scheme 2.7) gave two diasteromers ((+)-108a, red, and (+)-108b, blue) that provided different $^1$H NMR spectra that could be used to determine absolute stereochemistry at the 5-position.

![Figure 2.5](image2.png)

Figure 2.5 Two possible conformations of the MPA esters, syn- and anti-periplanar. It is well known from computational modelling that the syn-periplanar conformer is more stable and is observed on an NMR timescale, enabling the model shown to be derived.
soluble stereochemistry, due to the fact that $^1$H and $^{19}$F NMR studies can be used in the structural determination, however, it is known that there are a significant number of exceptions that have been found to rules designed to predict absolute stereochemistry.$^{122,124}$ For this reason, the more reliable $\alpha$-methoxyphenylacetic acid (±)-107 (MPA) was used to derivatise (+)-94 (Scheme 2.7). Absolute stereochemical assignment was achieved by reaction of the two enantiomers of MPA (–)-107 and (+)-107 in the presence of $N$-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide hydrochloride (EDC·HCl) and DMAP, to give mixtures of the mono- (108) and di-substituted (109) compounds (Scheme 2.7), which could be chromatographically separated. The mono-substituted diastereomers (+)-108a and (+)-108b were used as it was believed the use of a di-substituted compound would lead to complexities in the $^1$H NMR studies - the two phenyl groups in a di-substituted compound could interact, making the analysis less reliable. In addition, the use of the mono-substituted (+)-108 was possible due to the $C_2$ symmetry of the starting material (+)-94 meaning substitution on either free hydroxyl moiety led to the same compound.

<table>
<thead>
<tr>
<th>Position</th>
<th>$\delta R$ 108a</th>
<th>$\delta S$ 108b</th>
<th>$\Delta \delta^{RS}$</th>
<th>L$_1$ or L$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.84</td>
<td>5.80</td>
<td>+0.04</td>
<td>L$_1$</td>
</tr>
<tr>
<td>2</td>
<td>5.84</td>
<td>5.80</td>
<td>+0.04</td>
<td>L$_1$</td>
</tr>
<tr>
<td>3</td>
<td>5.74</td>
<td>5.78</td>
<td>–0.04</td>
<td>L$_2$</td>
</tr>
<tr>
<td>4</td>
<td>4.12</td>
<td>4.16</td>
<td>–0.04</td>
<td>L$_2$</td>
</tr>
<tr>
<td>5</td>
<td>5.53</td>
<td>5.56</td>
<td>–0.03</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>5.80</td>
<td>5.60</td>
<td>+0.20</td>
<td>L$_1$</td>
</tr>
</tbody>
</table>

The $^1$H NMR spectrum of (+)-108a and (+)-108b, in combination with COSY, HSQC and HMBC experiments, were fully assigned, paying particular attention to correct assignment of the inositol ring (Figure 2.4). From extensive modelling of systems containing a MPA ester, it is well known that the syn-periplanar conformer is energetically more favourable than the anti-periplanar conformer.$^{122}$ This means over NMR timescales, the
conformation is predominately the syn-conformation (top, Figure 2.5). When derivatised with \((-\)-(R)-107\) to afford \((+)-108a\), the phenyl group in the ester will be in close proximity to L\(_2\) groups in the model (Figure 2.5), causing shielding of the groups in that locality. Conversely, when derivatised with \((+)-(S)-107\) to give \((+)-108b\), the L\(_1\) groups will be shielded relative to \((+)-108a\). By calculation of \(\Delta\delta^{RS}\), the model can be populated as per the table shown (Table 2.3), showing which groups belong to L\(_1\) and L\(_2\), revealing the absolute stereochemistry. It was shown that the stereocenter adjacent to the MPA derivatisation was as drawn in both \((+)-108a\) and \((+)-108b\). From this, the rest of the stereogenic centres were then assigned based on an all-trans relationship determined for \((\pm)-81\), as observed by the crystal structure. These data and analysis enabled the synthesis to continue in the knowledge that the absolute stereochemistry was confirmed.

### 2.4 Mechanistic Insights

As the Trost asymmetric allylic alkylation had proved crucial in providing key intermediates in the synthesis of optically pure \(\text{myo}\)-inositol derivatives, it was prudent to understand the scope and limitations of the reaction, especially the increased ligand concentration improving reliability. This reaction and other similar reactions have been studied in depth. The basic mechanism of allylic alkylations is well accepted (Scheme 2.8), however, there are further complexities when considering asymmetric versions incorporating \(C_2\) symmetric substrates. In a simple mechanism, coordination of the palladium-ligand catalytic species to the substrate alkene is followed by ionisation, leading to an \(\eta^3\)-allyl palladium species 111. A nucleophile then attacks the allyl species, giving the product 112 which subsequently is displaced and exchanged for a new substrate or a solvent molecule.\(^{125}\)

In the asymmetric version of the reaction, the mechanism is further complicated by the ligand in the palladium complex. Trost et al. developed a series of modular bidentate ligand systems, based on \(C_2\)-symmetric backbones combined with tertiary phosphines to replace the triphenylphosphine used in early systems.\(^{126-128}\) In the case where \((\pm)-82\) is
used as a substrate, the ligand provides a chiral environment in two key stages of the reaction - both the ionisation with loss of a Troc group to give an $\eta^3$-allyl species, and the subsequent reaction of the nucleophile. This dual effect leads to the high enantioselectivity and the dynamic kinetic resolution observed in the reaction (Scheme 2.9). The mechanism by which the enantioselectivity exists was first described by Trost et al. as a "flap-and-wall" model.\textsuperscript{129} This was later shown to be a simplification by Butts et al., however, it still serves as a useful model for the prediction of enantioselectivity.\textsuperscript{118}

When a chiral, $C_2$ symmetric, ligand such as \((-\)-84 is used the reaction becomes significantly more complex to study with many different kinetics for different diastereomeric complexes that are formed.\textsuperscript{64} Upon coordination of the double bond in \((\pm)-82\) to a Pd$^0$ species complexed to ligand, there are two possibilities for ionisation of each enantiomer of \((\pm)-82\), caused by the fact that the coordination to palladium causes the compound to lose its $C_2$ symmetry. Due to the chiral "pocket" formed by the ligand, in conjunction with other electronic effects involving the N-H of the amide in the ligand, one Troc group is
preferentially lost over the other.\textsuperscript{118} In the case of the Troc derivative (±)-82, the energy barrier is low enough and the kinetics fast enough that both enantiomers ("matched" and "mis-matched", although the "mis-matched" ionisation is slower) react to form a common intermediate (Scheme 2.9).\textsuperscript{64,81} This is the driving force for the observed DKR. In the tetraacetate (±)-81, the "mis-matched" ionisation is sufficiently slow that only a kinetic resolution can be observed. From a combination of the chiral pocket and through hydrogen bonding from the nitrogen amides in (–)-84, the nucleophile is directed to react in an enantiotopic manner.\textsuperscript{118} This process then happens a second time, driving a second enantioselective step which leads to the high enantiomeric excesses observed (> 99%).

\textbf{Scheme 2.9} Mechanism of the Trost asymmetric allylic alkylation, starting from the Pd(0) complex [Pd(allyl)Cl]\textsubscript{2}. In our case (Scheme 2.4), this mechanism proceeds twice on the substrate to give the di-substituted product (+)-83.
Ligand Rate Effects

As the reaction appeared to show some ligand concentration effects, further experiments were undertaken to understand how these effects manifest (Table 2.4). While the ligand confers enantioselectivity in the reaction, its role is two-fold, as can be seen by the increase in rate of reaction upon addition of extra ligand (entries 1-5, Table 2.4 and Figure 2.7). There are several explanations of this based in the current literature, of which a combination of effects is probably the true representation of the situation. It has been known for many years that there are multiple coordination modes of for these ligands in palladium chemistry, most notably whereby there is a $P,O$ coordination mode as opposed to $P,P$. This was discussed in detail by Lloyd-Jones et al. where it was confirmed that at a 1:2 ligand to palladium ratio, a $P,O$ coordination mode was observed.$^{130}$ As the amount of ligand increased from 1:1 to higher ratios, not only was a monomeric $P,P$ complex formed, but also oligomeric complexes as observed by $^{31}P$ NMR. It was found that at high ratios of ligand to palladium, the concentration of monomeric species begins to decrease. Lloyd-Jones et al. suggested that the oligomeric species may be catalytically active but not as enantioselective as the monomer.$^{131}$ While increasing the ligand in our case increased the

<table>
<thead>
<tr>
<th>Entry</th>
<th>(±)-82</th>
<th>Ligand$^a$</th>
<th>Time</th>
<th>Conversion (e.e.)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol</td>
<td>eq.</td>
<td>h</td>
<td>(±)-82 (±)-104 (±)-83</td>
</tr>
<tr>
<td>1</td>
<td>0.50</td>
<td>0.050</td>
<td>1</td>
<td>100 0 0</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>0.075</td>
<td>1</td>
<td>38 43 (92) 19</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>0.100</td>
<td>1</td>
<td>10 14 76</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
<td>0.125</td>
<td>1</td>
<td>4 4 92 (&gt; 99)</td>
</tr>
<tr>
<td>5</td>
<td>0.50</td>
<td>0.150</td>
<td>1</td>
<td>0 0 100 (&gt; 99)</td>
</tr>
<tr>
<td>6</td>
<td>0.50</td>
<td>0.075</td>
<td>15</td>
<td>7 8 85</td>
</tr>
<tr>
<td>7</td>
<td>0.50</td>
<td>0.100</td>
<td>15</td>
<td>6 7 87</td>
</tr>
<tr>
<td>8$^c$</td>
<td>0.50</td>
<td>0.150</td>
<td>15</td>
<td>52 0 48</td>
</tr>
</tbody>
</table>

Table 2.4  Observing rate effects caused by increasing the [ligand] within the Trost asymmetric allylic alkylation with no change to any other components. All reactions were performed under an atmosphere of $N_2$ using Schlenk techniques, using the general procedure with 3.5 eq. BzOH, 0.025 eq. $[Pd(\eta^1$-allyl)Cl]$_2$, 0.2 eq. tetrahexylammonium bromide, 1.5 mL 1 M aqueous NaOH and 1.5 mL CH$_2$Cl$_2$.$^a$ Conversions were calculated using $^1H$ NMR (see appendix, page 279), e.e. was determined by chiral HPLC;$^c$ Tetracetate (±)-81 was used as the starting material.
rate of reaction, no decrease in enantioselectivity was observed suggesting other effects were in play. Interestingly, when the original ligand concentration was used (entry 6) or a slightly increased concentration of ligand (entry 7), the reaction could be left for longer, leading to higher conversions, however, complete conversion was still not observed with these concentrations of ligand. Given that the higher ligand concentration substantially improved the reaction rate, it was thought this effect could potentially be used to allow a DKR to be performed on the tetracetate (±)-81. One explanation for the kinetic resolution in this system may be that with the less reactive acetates, the "mis-matched" ionisation is sufficiently slow that the catalyst is oxidised faster than the ionisation. With a higher ligand concentration, only a kinetic resolution was observed with enantiopure starting material remaining (entry 8).

Amatore et al. had previously discussed the oxidation of the palladium complex 105 to 106 via the loss of two protons leads to a highly stable PdII complex with P,N coordination. This complex can be isolated as a yellow solid and is bench stable, however, it is
completely inactive in allylic alkylations (Scheme 2.6). It is likely that the ligand can act as a terminal reductant of the inactive complex 106. Csákai et al. had shown that phosphines can act as reductants in PdII-Pd0 systems. Not only did triphenylphosphine serve to reduce the PdII system, bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp) could also achieve this reduction. This could also be replicated in this more complex asymmetric system (Figure 2.6). It may be possible to add other terminal reductants to the system to prevent the use of extra ligand, however, this was not the focus of the work.

**Nucleophile Scope**

The scope of the nucleophile in this reaction was of interest as using alternative nucleophiles to benzoic acid would enable different protecting group strategies at a later date. It is well known within allylic alkylations that the pKa of the nucleophile is crucial for the reaction in that it needs to be below ca. 25 to work sufficiently well, i.e. the nucleophile needs to be 'soft'. The nature of the nucleophile, however, appears to be more complex than just this effect. Use of different nucleophiles led to different conversion rates. This could potentially be used to good effect in order to not only generate products with different protecting groups, but also produce a reliable route to a mono-reacted product thus expanding the synthetic scope of the reaction. Pivalic acid had been used by sev-
eral groups in combination with the tetracetate (±)-81 to give a mono-reacted product rather than a di-substitution. With the Troc version (±)-82, the reaction proceeded past 50% conversion (cf. the kinetic resolution with the tetracetate (±)-81) as expected to give the mono-substituted product (+)-115 (entry 6, Table 2.5). The purification, however, was complicated by the presence of di-substituted product (+)-116 which was close running during column chromatography and hence led to a poor yield of 32% - using (±)-82 may not be an improvement on using the tetracetate (±)-81. It was not possible to change the relative proportions of the the species (unreacted (±)-82, mono-substituted (+)-115 and di-substituted (+)-116) by lowering the equivalents of pivalic acid (entry 7). This suggests the reaction of the mono-substituted intermediate occurs at a similar rate to that of the starting material and as such, it is difficult to control the relative proportions of the products by number of equivalents alone. The reaction could be pushed further to furnish the di-product, however, the rate of reaction was sufficiently slow even with the increased ligand concentration, complete conversion was not achieved.

![Figure 2.8](image)

Figure 2.8 As the nucleophile solubility in aqueous media increases from 119 to acetic acid 123, the rate of reaction in the asymmetric allylic alkylation reduces until the point where acetic acid no longer acts as a nucleophile in the reaction. \textit{cLogD}_{7.4} was determined using ACD I-Lab 2.0 (http://ilab.cds.rsc.org, accessed 25/06/2016). Solubility forecast index (SFI) = \textit{cLogD}_{7.4} + number of aromatic rings.\textsuperscript{134}

Changing the nucleophile to acetic acid led to essentially no reaction (entry 2, Table 2.5) - this was proposed as a reason that the tetracetate (±)-81 underwent kinetic resolution, not DKR as the reaction of the acetate may be reversible, however, this is not the case. There
Table 2.5 Investigation of nucleophile scope in the Trost asymmetric allylic alkylation. All reactions were performed under an atmosphere of N$_2$ on a Schlenk system unless otherwise stated. All reactions were performed using the general procedure with 3.5 eq. nucleophile, 0.025 eq. [Pd($\eta^3$-allyl)Cl]$_2$, 0.15 eq. ligand (--)-$\text{-84}$, 0.2 eq. tetrabutylammonium bromide, 3.0 eq. 1 M aqueous NaOH and 1.5 mL CH$_2$Cl$_2$. $^a$ (--)-$\text{-84}$; $^b$ Conversions were calculated using $^1$H NMR (see appendix, page 280), e.e. was determined by chiral HPLC; $^c$ E.e was determined by removal of the two troc groups, esterification with $\alpha$-methoxyphenylacetic acid and analysis by $^1$H NMR; $^d$ The aqueous phase concentration was increased, using 0.75 mL of 2 M aqueous NaOH; $^e$ 1.5 eq. of Pivalic acid were used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(±)-$\text{-82}$ Nucleophile</th>
<th>Time</th>
<th>Conversion (e.e.)$^b$ %</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO$_2$ &amp; NaOH</td>
<td>15</td>
<td>100 0 0 0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>1</td>
<td>82 18 0 0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>BOC</td>
<td>1</td>
<td>60 33 17</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$COOH</td>
<td>15</td>
<td>14 32 54 (&gt;$99)^c$</td>
<td>37</td>
</tr>
<tr>
<td>5$^d$</td>
<td>HO$_2$ &amp; NaOH</td>
<td>15</td>
<td>9 16 75</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$COOH</td>
<td>1</td>
<td>18 64 18</td>
<td>33</td>
</tr>
<tr>
<td>7$^e$</td>
<td>HO$_2$ &amp; NaOH</td>
<td>1</td>
<td>14 64 22</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>BOC</td>
<td>15</td>
<td>0 25 75</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>BOC</td>
<td>1</td>
<td>0 0 100 (&gt;99)</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>CH$_2$COOH</td>
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<td>0 0 100</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>BOC</td>
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<td>0 0 100 (&gt;99)</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td>BOC</td>
<td>1</td>
<td>0 0 100 (&gt;99)</td>
<td>74</td>
</tr>
</tbody>
</table>
are two potentially competing effects that could explain this trend. Either the change in electronics going from benzoate to acetate was detrimental or there was a solubility-driven effect, given that the reaction was biphasic. This suggested there may be a link between the rate of reaction and the solubility of the nucleophile in aqueous solution - more aqueous soluble nucleophiles were less available for reaction, despite the use of a phase transfer catalyst. To confirm the solubility theory, 4-\(O\)-benzyloxybutyric acid 120 was used as a nucleophile as it has similar electronic properties to acetic acid while being less soluble in aqueous media (entry 11). The reaction proceeded to completion within an hour, as observed with the benzoate and other more lipophilic nucleophiles, suggesting these effects were solubility driven (Figure 2.8). Finally, the size of the nucleophile was considered. As pivalic acid was sterically demanding, it was thought that the size of the nucleophile was irrelevant. This was the case in that a large nucleophile such as 119 could be employed without any detriment to enantioselectivity. These proximity-assisted protecting group were crucial to later studies using this system where a different protecting group strategy was used.

2.5 Conclusions

The generation of optically pure \textit{myo}-inositol derivatives was crucial to ongoing synthesis of PtdIns\(P_2\) as without a single enantiomer, further synthetic efforts were futile. While initially temperamental, the Trost asymmetric allylic alkylation starting with a racemic \(C_2\) symmetric conduritol B derivative (±)-82 was optimised to be significantly more robust with high yields (> 80%) and high e.e. (> 99%). The benzoate nucleophile could be exchanged for other nucleophiles, a key feature in future synthetic endeavours. In addition, the observation that mono-substituted products could be synthesised by careful choice of nucleophile may lead to the synthesis of other PtdIns\(P_n\) compounds.
Chapter 3

First Protecting Group Strategy

3.1 Introduction

While an enantioselective synthetic route toward conduritol B intermediates had been optimised, there were three key components needed to transform the system from a conduritol B system to a phosphatidylinositol derivative:

1. Phosphorylation of the hydroxyl groups, with both protected phosphates and with protected phosphatidyl moieties.\(^\text{41}\)

2. Conversion from the conduritol B system to a myo-inositol system via a syn-dihydroxylation.\(^\text{74–76}\)

3. A robust asymmetric synthesis of the glycerol chains.\(^\text{41}\)

All three features have been incorporated in the many syntheses of both inositol and phosphatidylinositol derivatives documented in the literature.\(^\text{41,86,135–137}\) All that was required was successful optimisation of previously described chemistry in the context of this system.

3.2 Phosphorylation Chemistry

There has been a wealth of literature published on the phosphorylation of hydroxyl functionalities, in particular on nucleotides for oligonucleotide synthesis. A recent comprehensive review was published by Roy and Caruthers.\(^\text{138}\) While designed for oligonucleotide...
synthesis, the phosphoramidite and \( H \)-phosphonate methods have been used in the synthesis of inositol-derived phosphates.\(^{86,139}\) In both methods, the phosphorus centre is in the \( \text{P(III)} \) oxidation state. These compounds have been found to be significantly more reactive than the related \( \text{P(V)} \) compounds.\(^{138}\) This reactivity makes them more useful, however, it also makes \( \text{P(III)} \) reagents sensitive to hydrolysis and oxidation. Despite the fact that \( H \)-phosphonates were discovered earlier, and are more resistant to oxidation in air than phosphoramidites, phosphoramidites are used more commonly due to fewer side reactions than typically occur with \( H \)-phosphonates. Also, many of the more stable phosphoramidites (although still unstable compared to normal, benchtop, reagents) can be stored at \(-20\, ^\circ\text{C}\) under an inert atmosphere.

### 3.2.1 Preparation of Phosphoramidites

Phosphoramidites were prepared from distilled \( \text{PCl}_3 \) \(^{124}\) (Scheme 3.1). To form \(^{125}\), addition of two equivalents of diisopropylamine to a solution of of \( \text{PCl}_3 \) led to a single product with only traces of the disubstituted phosphorus compound observed. The resulting diisopropylamine hydrochloride salt was removed by filtration, leaving a product that was \( > 90\% \) pure, as determined by \(^{31}\text{P}\) NMR analysis. Further purification was not deemed necessary, nor prudent, as the compound was unstable to water, oxygen, and high temperatures. It was convenient that this compound was solid at \(-20\, ^\circ\text{C}\) allowing it to be stored for periods greater than six months in the freezer, under an atmosphere of argon, and the compound could be prepared in large quantities (\( > 10 \text{ g} \)) relatively easily.

The phosphoramidite \(^{126}\) could be prepared from \(^{125}\) by stirring with 3-hydroxypropionitrile and diisoproyethyleneamine (Scheme 3.1), followed by purification using rapid silica column chromatography. It was noted that even when stored under vacuum or argon at room temperature, \(^{126}\) was prone to decomposition in as little as 48 hours, therefore the reagent was prepared fresh each time. In the case of phospholipids, the phosphoramidite \(^{129}\) was used as a precursor. Initially, compound \(^{129}\) was purchased from Sigma Aldrich, however, it was found that the compound was not easily stored, even at \(-20\, ^\circ\text{C}\), and the cost was comparatively high compared to other similar reagents. For these reasons,
the compound was prepared using a modification of the method by Nielsen et al.\textsuperscript{140} 3-Hydroxypropionitrile was reacted with 5 equivalents of PCl\textsubscript{3}, followed by removal of excess PCl\textsubscript{3} \textit{in vacuo}, to give 128. Using the large excess of PCl\textsubscript{3} prevents over-reaction to the di- or tri-substituted compound (\textit{cf} reacting with an amine where no over-reaction is observed). Subsequent reaction with two equivalents of diisopropylamine led to the product 129, which was distilled \textit{in vacuo} to give 129 in reasonable yield (44\%). This process allowed large quantities of 129 to be made as needed, rather than relying on expensive, unreliable commercial sources. Subsequent reaction of 129 with a free hydroxyl on a glycerol chain such as (–)-130 yielded the phosphoramidite 131, a useful phosphitylation reagent to install phospholipids. Reaction of the phosphoramidites with hydroxyl functionalities was achieved in the presence of \textit{1H}-tetrazole, forming a tetrazolium intermediate which is highly reactive.\textsuperscript{141} Multiple equivalents of the phosphoramidites were required for each hydroxyl (2-3 equivalents per hydroxyl moiety) in order to ensure complete conversion to the respective products.
Oxidation of P(III) intermediates

There are many routes to P(V) by oxidation of P(III) compounds, each of which has slightly different characteristics. In InsP_n chemistry, both oxidation to yield P=O and P=S bonds have been used to good effect - while natural substrates contain phosphates, phosphorothioates can be used to slow metabolism of phosphodiester moieties, expanding the scope of related probes. Oxidation to P(V) is typically achieved using H_2O_2 or mCPBA. Despite the use of double bonds in various parts of the molecules, in particular with the conduritol B derivative (+)-94, no epoxidation was observed as the oxidation of P(III) compounds is significantly faster than epoxidation, while sub-stoichiometric mCPBA (ca. 0.9 equivalents relative to the total phosphoramidite) was used.

### 3.2.2 Phosphorylation of Conduritol B Intermediates

With the enantioselective synthesis of the conduritol B intermediates complete, the two remaining Troc groups could be removed, as described in Chapter 2 using reductive methods (Scheme 3.2). The two free hydroxyl groups were phosphitylated using 126 in the presence of 1H-tetrazole, giving the P(III) intermediate. While multiple equivalents of 126 were required to effect complete conversion, a balance was required between this and the difficulty in purifying the compound once oxidised. This balance was required because the oxidised phosphoramidite was difficult to separate from the product (+)-95. In the end, four equivalents (two per hydroxyl) proved optimal - increasing the equivalents of 126 made the compound difficult to purify, while less resulted in incomplete reaction. Once reacted, in situ oxidation with mCPBA gave (+)-95.

![Scheme 3.2](image_url)

**Scheme 3.2** Synthesis of a diphosphorylated conduritol B derivative (+)-95 from a single enantiomer of a conduritol B derivative such as (+)-83 in a similar manner to Trost et al. and Podeschwa et al. Reagents & conditions: i. Zn, AcOH, THF, 2 h, 70%; ii. 126, 1H-tetrazole in MeCN, CH_2Cl_2, 18 h then mCPBA, –78 °C, 1 h, 59%.


3.3 Formation of Inositol Derivatives

3.3.1 Dihydroxylation of Conduritol B

In order to form an inositol derivative from a conduritol B derivative, such as (+)-95, it is well documented that a syn-dihydroxylation of the double bond can be achieved by OsO$_4$, or NaIO$_4$ catalysed by RuCl$_3$ in a mixture of MeCN and H$_2$O.$^{64,75,76,81}$ While the use of OsO$_4$ is preferable chemically, as there is little risk of cleavage to the diol, the high toxicity of OsO$_4$ makes use of NaIO$_4$ more practical. Despite there being two faces to oxidise on the double bond in (+)-95, there is no need to control facial selectivity as oxidation on either face leads to the same product, due to the $C_2$ symmetry of (+)-95 (Scheme 3.3).$^{75}$

In cases where the $C_2$ symmetry has not been maintained, as in (+)-133, the generation of a ruthenium complex may have some facial selectivity, however, there is generally poor selectivity and a mix of two regioisomers is obtained ((+)-135 and (+)-136) - in many cases the resulting regioisomers can be separated by column chromatography.$^{76}$

\[
\text{Scheme 3.3 Using a combination of RuCl$_3$, NaIO$_4$, MeCN, and H$_2$O leads to a syn-dihydroxylation via a ruthenium complex 132 giving a single product (+)-96, due to the } C_2 \text{ symmetry of (+)-95. If the starting material lacked } C_2 \text{ symmetry, a mixture of two regioisomers would be obtained. Reagents & conditions: NaIO$_4$, RuCl$_3$·3H$_2$O, MeCN, H$_2$O, 8 min, 88%}.\]
3.3.2 Selective Acetylation of 2-position

Once the syn-dihydroxylation of (+)-95 was complete to furnish a myo-inositol derivative (+)-96, a method was required for the selective protection of the axial 2-hydroxyl group over the equatorial 1-hydroxyl group. To achieve this, a selective acetylation on the axial 2-position using the methods described by Podeschwa et al. was employed.\textsuperscript{75} A selective esterification at the kinetically stable axial 2-position (\textit{cf} the more thermodynamically stable equatorial 1-position) was achieved by reacting (+)-96 with triethylorthoacetate in the presence of sub-stoichiometric acid under anhydrous conditions to form a 1,2-orthoester, followed by acidic hydrolysis. This process gave the acetate at the 2-position (+)-97.\textsuperscript{75} Selective opening of orthoesters in inositol and related diol systems has been known since a 1969 publication describing the selectivity between anti-dihydroxyl systems in \textit{trans}-decalin-\textit{cis}-2,3-diol.\textsuperscript{144} Even as recently as 2012, there are still publications devoted to the selective acetylation of the 2-position in \textit{myo}-inositol.\textsuperscript{145} The mechanism for formation of the orthoester and subsequent opening is shown (Scheme 3.4). There are two potential explanations for the selectivity observed in the ring opening. It is generally accepted that equatorial hydroxyl groups are more nucleophilic than axial hydroxyl groups. It is possible that protonation of the equatorial hydroxyl group in \textsuperscript{142} leads to ring-opening onto the axial position.\textsuperscript{146} While this may explain some of the selectivity, the difference in pKa of the two groups is likely small (< 1 pKa unit) and may not be the full explanation.\textsuperscript{144} Alternatively, the selectivity may be driven by the orientation of lone pairs on the oxygen atoms in the intermediate \textsuperscript{142}.\textsuperscript{147} The lone pairs need to be \textit{anti}-periplanar to the bond that is broken. By careful examination of all the possible confirmations of the orthoester and the lone pairs, this is best achieved when both oxygen atoms remaining in the ester group at the end have a lone pair orbital \textit{anti}-periplanar to the broken bond.\textsuperscript{148} In our case, upon hydrolysis of the orthoester to give (+)-97, correct alignment can be most efficiently achieved from the axial oxygen lone pair, a lone pair on the hydroxyl and with the equatorial oxygen bond (highlighted in red).\textsuperscript{144,147,148} This effect leads to selective protection of the 2-position. Typical regioselectivities observed by $^1$H NMR analysis of the crude product were in the order of 10:1 of the 2-position vs the
Scheme 3.4  Mechanism for the selective protection of the 2-position in (+)-96 using an orthoester followed by acidic hydrolysis to give a 10:1 regioselectivity for the 2-position over the 1-position. Two possible explanations for the selective opening are either protonation of the equatorial hydroxyl group preferentially over the axial or anti-periplanar overlap of lone pairs on the two oxygen atoms in the orthoester leads to breaking of the equatorially placed oxygen-carbon bond. 

Reagents & conditions: i. CH$_3$C(OEt)$_3$, 4-toluenesulfonic acid, THF, 18 h; ii. 80% aqueous AcOH, 1 h, 38% over two steps. 

(+) -96  (++) -97  (++) -143
1-position, however, separation of the two regioisomers was particularly difficult. Given that it is possible to heat compounds containing a 2-acetate under acidic conditions to give the 1-acetate, the 2-acetate may be the kinetic product while the 1-acetate is the thermodynamic product. Attempts to further improve the regioselectivity by cooling the reaction to 0 °C to drive formation of the kinetic product were unsuccessful.

**Determining Regioselectivity**

It was necessary to confirm the regioselectivity of the reaction in the context of our system by the use of a variety of 1D and 2D NMR techniques. The coupling constants in myo-inositol rings are diagnostic when taken in combination with the chemical shift (Figure 3.1). In addition, coupling of other NMR active nuclei such as $^{31}$P can be used to elucidate structure. From the $^1$H NMR data alone, it is possible to get an indication of the assignment. This is because the six protons on the inositol ring give characteristic signals in the $^1$H NMR (Figure 3.1). The coupling constants are different for the different positions due to the difference between axial-axial couplings (9-10 Hz) vs axial-equatorial couplings (2-3 Hz). From these coupling constants it is possible to assign the $^1$H NMR of (+)-97. The multiplet at 5.69-5.59 in the lower two NMR spectra (Figure 3.2) is a combination of two doublet of doublets, as can been seen from the top spectrum in CDCl$_3$ alone - MeOD had to be added for full NMR data as the compound slowly crystallises from CDCl$_3$. The doublet of doublets with small couplings (5.59 ppm, top spectrum, ca
Figure 3.2  Overlay of selected portions of three $^1$H NMR spectra of (+)-97 in differing solvents showing the splitting patterns, allowing identification of the peaks, in combination with 2D NMR data. Top (green): A sample of (+)-97 in CDCl$_3$. Middle (red): A sample of (+)-97 in 10% MeOD in CDCl$_3$; Bottom (blue): A sample of (+)-97 in 10% MeOD in CDCl$_3$ using a $^1$H-{$^{31}$P} NMR experiment, showing two peaks are coupling to $^{31}$P nuclei, consistent with the structure (+)-97.

Figure 3.3  Selected portion of the $^1$H-$^{13}$C HMBC spectrum of (+)-97 centred around the inositol peaks ($^1$H) and the carbonyl peaks ($^{13}$C) showing correlation between the acetate carbonyl at 170 ppm and the doublet of doublets at 5.76 ppm (assigned to the 2-position proton from 2D $^1$H NMR experiments), supporting the structural assignment of the inositol ring.
2-3 Hz) can be attributed to the 2-position where the equatorial proton is coupling to two axial protons. The other doublet of doublet is one of the 4-, 5- or 6-positions, given these three protons all couple to two neighbouring axial protons, giving large (9-10 Hz) couplings. There are two doublet of doublet of doublets at 5.02 and 4.82 ppm, caused by splitting to two protons and one phosphorus atom, each of which can be attributed to the 4- and 5-positions. This assignment was confirmed by $^1$H-$^{31}$P NMR where these two peaks coalesced into a doublet of doublets (bottom spectrum), confirming the coupling to phosphorus. The last peak in the spectra at 5.41 ppm shown was attributed to the 3-position, with one small and one large coupling. Given the chemical shift of the 2-position was so far downfield and the 1-position had remained upfield (4.06 ppm), it was highly likely that the acetate was indeed on the 2-position. The assignment of the $^1$H NMR was confirmed using a combination of $^1$H-$^1$H COSY and $^1$H-$^{31}$P HMBC experiments. Once the $^1$H NMR spectra had been assigned, it was a simple case of using $^1$H-$^{13}$C HMBC NMR analysis to show the acetate carbonyl carbon was coupling to the 2-position proton as shown, proving the structural assignment (Figure 3.3). With a fully-protected inositol ring system available, next was to install the phospholipid at the 1-position.

3.4 Synthesis of Protected PtdIns(4,5)P$_2$

3.4.1 Synthesis of Glycerol Derivatives

Prior to introduction of the phosphatidyl moiety, a robust synthesis of 1,2-dipalmitoyl $sn$-glycerol $\left(\text{--}\right)$130 was required. The asymmetric synthesis of 1,2-disubstituted glycerol derivatives has been well documented within the literature.41,89,149–152 Most syntheses start from commercially available 1,2-isopropylidene-$sn$-glycerol 144, which is available optically pure as either enantiomer. A typical synthesis comprised protection of the free hydroxyl group, deprotection of the acetal, reaction with two lipid chains, and finally deprotection of the first hydroxyl group. The choice of the first protecting group is crucial. In early literature syntheses, a benzyl group was used (Scheme 3.5).149 This proved to be highly effective, with no migration observed between the alcohols during the course of the synthesis. Deprotection of $(+)$-145 was straightforward using hydrogenolysis to remove
the benzyl group, giving an 81% yield over the four steps, with no change in enantiomeric excess (as measured by derivatisation with an MPA ester, Scheme 3.6 - this was described in detail in chapter 2). While convenient in early stages of the project when saturated lipid chains were used, a different route was required for unsaturated systems. In preparation for this, the benzyl group was exchanged for a 4-methoxybenzyl (PMB) protecting group in order to avoid hydrogenolysis methods for deprotection, allowing the use of unsaturated chains. While many of the steps proceeded very similarly (cf. the benzyl route), the final deprotection of (+)-146 proved problematic. In order to remove the PMB group, use of DDQ was possible, however, the compound then required column chromatography to remove DDQ-related debris. During column chromatography, the silica caused a migration from the 2-position to the 3-position, giving a symmetrical product that behaved very similarly to (–)-130, making purification difficult, and lowering the yield. Using DDQ would be a potential route for incorporation of unsaturated lipid chains at a later date. A high e.e. was maintained for (–)-130 (as measured by derivatisation with an MPA ester, Scheme 3.6), suggesting migration between the two primary alcohols does not occur.

Scheme 3.5 Synthesis of (–)-1,2-dipalmitoyl sn-glycerol (–)-130 for use in preparing PtdIns(4,5)P₂ 10. Reagents & conditions: i. BnBr, NaH, DMF, 18 h, 92% (R = Bn); ii. PMBCl, DMF, 18 h, 93% (R = PMB); iii. 1 M aqueous HCl, THF, 18 h, 93% (R = Bn & PMB); iv. Palmitoyl chloride, DMAP, N,N-diisopropylethylamine, 18 h, 95% (R = Bn), 69% (R = PMB); v. H₂, Pd/C, AcOH, EtOH, 1 h, 100% (R = Bn); vi. DDQ, CH₂Cl₂, H₂O, 3 h, 69% (R = PMB).
3.4 PROTECTED PTDINS(4,5)P₂

CHAPTER 3. FIRST STRATEGY

Scheme 3.6 Partial ¹H NMR spectrum of the glycerol derivative (–)-130 derivatised with optically pure (+)-(S)-α-methoxyphenylacetic acid (+)-107 or (–)-(R)-α-methoxyphenylacetic acid (–)-107 in order to generate enantiomeric excess of the product showing > 99% e.e. (described in detail in an earlier chapter). Top (Green): Pure (+)-151a; Middle (Red): Crude reaction mixture (no column chromatography), (+)-151a; Bottom (Blue): Pure (+)-151b. Reagents & conditions: Glycerol (–)-130, Acid (+)-107 or (–)-107 EDC·HCl, DMAP, CH₂Cl₂, 2 h, 79% ((+)-151a), 55% ((+)-151b).
3.4.2 Phosphatidylation of Protected myo-Inositol

Once the fully-protected inositol derivative (+)-97 had been synthesised, the next step was to install the phospholipid moiety. This was done using the phosphoramidite 131 (Scheme 3.7). Subsequent oxidation of the P(III) centre led to a fully protected PtdInsP$_2$ compound (+)-98. Extensive NMR studies were used to confirm the structure, however, these were complicated by the presence of a new stereogenic centre at the P(V) atom. As the oxidation conditions were achiral, a 1:1 mixture of two diastereomers was observed, typical in both P(III) and P(V) systems. In P(III) systems, the phosphorus atom can still be stereogenic as the lone pair on the phosphorus atom prevents inversion of the tetrahedral structure. This is best exemplified with 131, where two phosphorus resonances are observed at 149 ppm, caused by formation of diastereomers when the stereogenic phosphorus centre is placed next to the chiral glycerol group. Attempts to separate the diastereomers in (+)-98 were unnecessary as once the phosphorus had been deprotected and a free phosphate was obtained, the phosphorus centre is no longer stereogenic due to resonance between the P-OH and P=O bonds. As such, five peaks were observed in

![Scheme 3.7](image)

**Scheme 3.7** Partial $^{31}$P NMR spectrum of (+)-98, showing the presence of two diastereomers (labelled a and b) caused by a stereogenic phosphorus atom at the 1-position. For this reason, there is a large chemical shift of the 1-position between the two diastereomers, however, the effect diminishes further away from the stereogenic phosphorus centre. **Reagents & conditions:** i. 3-4% 1H-tetrazole in MeCN, CH$_2$Cl$_2$, 2 h then mCPBA, -78 °C then room temperature, 2 h, 49%.
the $^{31}$P NMR spectrum (Scheme 3.7) - two for the 1-position, one for the 4-position and two for the 5-position. A large difference in chemical shift was expected between the two diastereomers for the 1-position in (+)-98 as this is the stereogenic centre. As you move further away from the stereogenic centre, the difference between the two diastereomers becomes smaller such that the chemical shift for the 4-position in the two diastereomers is the same. As a robust synthesis to (+)-98 had been accomplished, it was then necessary to consider the multi-step deprotection of the protecting groups to afford PtdIns(4,5)$P_2$.

### 3.4.3 Deprotection of Fully-Protected PtdIns(4,5)$P_2$

Once the synthesis of a fully-protected PtdIns(4,5)$P_2$ 1,2-dipalmitoyl derivative (+)-98 had been obtained, the synthesis then turned to the final step - deprotection of the phosphate and hydroxyl moieties. The 2-cyanoethyl groups had been used in previous PtdIns$P_n$ syntheses, and were removed without migration of the phosphorus centres.\(^{107}\) While acetate and benzoate protecting groups had been used successfully in the synthesis of Ins$P_n$ derivatives, no literature existed in which benzoates had been removed in the presence of the glycerol moiety.\(^{64,81,104}\) This was a potential problem, seen from the outset, which it was hoped could be avoided by careful control of conditions.

There was a balance to be achieved during base hydrolysis - removal of the 2-cyanoethyl, acetate and benzoate groups while leaving the other carbonyl and phosphate esters, particularly related to the glycerol and lipids, intact. This meant rather than using sodium or potassium hydroxide, lithium hydroxide was used as a slightly weaker base. Upon stirring the protected PtdIns(4,5)$P_2$ (+)-98 in MeOH with aqueous LiOH, some deprotection was observed, however, it was noted that only one cyanoethyl group was removed.
from each phosphorus centre. This was unsurprising as once one cyanoethyl group has been removed, the negative charge prevents deprotonation of the second cyanoethyl by charge-charge repulsion (Scheme 3.9).

![Scheme 3.9](image)

**Scheme 3.9** Mechanism for the deprotection of the 2-cyanoethyl groups from the phosphate moieties. In the case of bis(2-cyanoethyl)phosphates as depicted, removal of one protection group leads to a negatively charged oxygen, preventing removal of the second. This can be avoided by use of TMSCl, masking the negative charge and subsequent hydrolysis of the di-TMS esters.

To remove both cyanoethyl groups, Gaffney *et al.* used a combination of trimethylsilylchloride (TMSCl) and \(N,N',N',N\)-tetramethylguanidine (TMG) in their synthesis of PtdIns\(P_n\) derivatives. A stronger base is required in this case (TMG) as using a weaker base such as \(\text{NEt}_3\) led to one cyanoethyl being removed but not the second, even in the presence of TMSCl. Using TMG worked to good effect, swapping the five cyanoethyl groups for TMS esters. This was easily monitored by \(^{31}\text{P}\) NMR analysis, as the TMS groups shift the phosphorus resonances upfield to ca. 
\(-11\) ppm and \(-18\) ppm for the mono- and di-TMS phosphates, respectively. Conveniently, the acetate was also removed under these conditions, as shown by the loss of a peak at ca. \(5.8\) ppm in the \(^1\text{H}\) NMR spectrum, caused by an upfield shift of the 2-inositol proton upon deprotection. At this stage, the reaction mixture was concentrated *in vacuo*, leaving large amounts of TMG present in the mixture. Addition of MeOH led to deprotection of the TMS esters leaving free phosphates, presumably as a TMG salt, giving three sharp peaks in the \(^{31}\text{P}\) NMR spectrum (Figure 3.4).
Once removal of the cyanoethyl groups was complete, deprotection of the benzoates was considered. The removal of benzoate groups was likely to be difficult in the presence of the two esters on the lipid chains. Two sets of conditions were considered as likely to be mild enough to confer some selectivity. Meek et al. had used LiOH in MeOH to remove benzoates in the presence of phosphates, albeit without lipids, in their synthesis of Ins(1,4,5)P$_3$.\textsuperscript{104} This had been replicated by Trost et al.\textsuperscript{64} Stirring the cyanoethyl-deprotected material with LiOH showed some removal of the benzoates in the $^1$H NMR spectrum, by the production of benzoic acid, however, there was also hydrolysis of the lipid chains from the glycerol (Figure 3.5) apparent.

These data did not bode well for future base deprotection conditions, as LiOH is a mild method for hydrolysis of esters (\textit{cf} use of NaOH or KOH). This reaction was repeated
twice with the same result. Changing the conditions to use 1 M NH₃ in MeOH did not improve the result with a mixture of products observed. These reactions suggested the removal of benzoates in the presence of lipid esters would be difficult and significant optimisation of conditions was probably required. Using milder conditions for hydrolysis, such as ammonium hydroxide in water, resulted in no reaction unless heated, at which point the molecules were prone to hydrolyse multiple phosphate esters (Figure 3.5). Given that the lipids appeared to hydrolyse at a similar rate to the benzoates, it was felt that an alternative protecting group strategy would be required rather than attempt to optimise conditions in the high likelihood it would not be successful.

3.5 Conclusions

From the generation of a single enantiomer of (+)-83, the compound was manipulated into synthesising a fully protected PtdIns(4,5)P₂ derivative (+)-98. Phosphorylation of hydroxyl moieties was optimised using well traversed phosphoramidite chemistry while starting with (+)-1,2-isopropylidene sn-glycerol (+)-144 led to 1,2-dipalmitoyl sn-glycerol (−)-130 required for the phospholipid moiety. With the fully protected (+)-98 available, while deprotection of the cyanoethyl and acetate moieties was easily achieved, subsequent deprotection of the benzoate protecting groups was unsuccessful with hydrolysis of the lipids observed. Given that it was unlikely that we would be able to find conditions whereby the benzoates could be removed in the presence of the lipid esters, an alternative protecting group strategy was required.

![Scheme 3.10](image-url)  
**Scheme 3.10** The conduritol B derivative (+)-83, synthesised via Trost asymmetric allylic alkylation, was converted into a fully protected PtdIns(4,5)P₂ derivative (+)-98, however, deprotection of the benzoate groups in the presence of lipid chains was unsuccessful.  

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Chapter 4

Deuterated myo-Inositol Derivatives

Throughout this chapter and future chapters, including the experimental, a red asterisk next to a carbon atom indicates a carbon atom with a deuterium atom attached.

4.1 Synthesis of Deuterated Inositolhs

Deuterium is a stable isotope that is commonly used in biologically relevant probes. The use of deuterium in complex sugars, and pseudo-sugars such as myo-inositol, has been precluded by the high cost of deuterated sugars available from commercial sources (e.g. D₇-glucose). This cost is unsurprising since sugars contain multiple stereogenic centres that must be controlled or conserved during incorporation. The separation of sugar isomers is typically difficult, usually requiring several chromatographic steps and multiple crystallisations to acquire pure products. While syntheses of D₆-myoinositol 90 have been reported, and the compound is commercially available, the cost was prohibitively high (£12/mg, Sigma-Aldrich) presumably as previous synthetic routes required laborious

Scheme 4.1 Previous approaches toward D₆-myoinositol 154 started from myo-inositol 1, requiring separation of multiple isomers. Our approach starts from quinol 153. All deuterium atoms from this point on are highlighted in red, either as “D” or as an asterisk.
4.1. DEUTERATED INOSITOL  

CHAPTER 4. $\text{D}_6$-MYO-INOSITOLS

separation of epimers (Scheme 4.1). Consequently, a route that tolerates multi-gram syntheses was required toward $\text{D}_6$-myo-inositol 90 and its derivatives.

4.1.1 Deuteration of $p$-Benzoquinone

As a suitable synthetic starting point had already been determined to generate myo-inositol derivatives (see previous chapters), it was necessary to consider the routes to generate $C$-perdeuterated derivatives. The starting material, $p$-benzoquinone 77, had been chosen as it appeared more susceptible to deuteration than myo-inositol 1. As a suitable synthetic starting point had already been determined to generate myo-inositol derivatives (see previous chapters), it was necessary to consider the routes to generate $C$-perdeuterated derivatives. The starting material, $p$-benzoquinone 77, had been chosen as it appeared more susceptible to deuteration than myo-inositol 1.48

![Scheme 4.2](image)

**Scheme 4.2** Synthesis of $D_4$-quinol 156 via tetrabromoquinol 155 was possible with high enrichment however chemical yield was low. Reagents & conditions: i. Br$_2$, AcOH, 24 h then H$_2$O, reflux, 2 h, 92%; ii. Zn, Pd/C (10% w/w), D$_2$O, reflux, 24 h, 20%, 95% D$_4$, 5% D$_3$.

There are many conditions for the reductive debromination of aromatic compounds reported in the literature. This approach was thought to be a potential method for incorporation of deuterium by replacing the hydrogen source for a deuterium source such as D$_2$O. Therefore, tetrabromoquinol 155 was synthesised in 92% yield using bromine in AcOH (Scheme 4.2). Several methods were attempted for reductive debromination. Ramanathan and Jimenez described the reductive debromination of aryl bromides via hydrogenolysis with Pd/C and H$_2$. In combination with work by Kurita et al. on the in situ generation of D$_2$ gas from D$_2$O, it may have been possible to achieve deuterium incorporation. Applying this methodology to our system resulted in a lower incorporation than expected (up to 30% D$_4$). Kurita et al. had used this methodology for reductive bromination of aryl systems in a similar manner to our system, however, attempts to replicate the reported work directly in our hands to the same level of incorporation was not possible. Mukhopadhyay et al. had described a debromination using Zn in combination with Pd/C in H$_2$O under reflux conditions. During their studies, they had replaced H$_2$O with D$_2$O to study kinetics of the debromination. We subsequently applied
this method to our tetrabromoquinol 155 system with high deuterium incorporation observed. Unfortunately, the reaction produced a by-product that was not an intermediate species in the reaction. This was potentially a homo-dimer side-product (as judged by by mass spectrometry, as the lack of protons precluded analysis by $^1$H NMR), which was not easily removed by non-chromatographic techniques - ideally, the use of chromatography was to be avoided to enable facile application to larger scale synthesis. In addition, the yield for this reaction was low (20%), and optimisation of these conditions was not attempted as other literature methods had presented themselves. As reductive bromination had not resulted in high yielding procedures, an alternative was required.

Table 4.1 Examples of conditions used in attempts to fully deuterate quinol 153 under acidic conditions. As the two phenolic protons are exchangeable, H$_2$O was used in each workup to give OH, therefore no D$_5$ or D$_6$ could be observed by mass spectrometry. All reactions were heated under reflux for the given times. Deuterium incorporations were determined by mass-spectrometry (Field ionisation, F$^+$).

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</tbody>
</table>

Zhao et al. described a synthesis of D$_4$-p-benzoquinone 157 that proceeded by deuteration of quinol 153 by exchange under acidic conditions followed by oxidation, however, there was only a limited procedure described. Replicating this work by dissolving quinol 153 in 3.4 M D$_2$SO$_4$ in D$_2$O and heating under reflux conditions was not successful, with no deuterium incorporation observed (entry 1, Table 4.1). Desiraju et al. described a method where the hydrogen atoms in quinol 153 were exchanged for deuterium, in a similar manner to Zhao et al., but this time in the additional presence of zinc powder. The deuterium source was prepared in situ by the addition of D$_2$O to acetyl chloride followed by addition of zinc powder and heating under reflux conditions for 24 h (entry 2, Table 4.1). In this case, a high chemical yield was achieved (95%), however, the enrichment
4.1. DEUTERATED INOSITOL

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was only 37% D₄ (D₄ is quoted throughout for 156 as the two phenolic protons are exchangeable), with longer reaction times showing no improvement in enrichment. It was therefore necessary to consider the reaction prior to addition of the quinol 153 (Equation 4.1).

\[ 2 \text{AcCl} + 2 \text{D}_2\text{O} \rightarrow 2 \text{AcOD} + 2 \text{DCl} \quad \text{Zn} \rightarrow 2 \text{AcOD} + \text{ZnCl}_2 + \text{D}_2 \] (4.1)

To optimise the conditions, the reactive components in the reaction were tested individually. D₁-AcOD was purchased and the reaction was repeated with mixtures of D₁-AcOD, Zn and D₂O (entries 3 and 4, Table 4.1). D₁-AcOD was unnecessary given that AcCl was used in the original procedure. When AcOD was used, only limited or no incorporation was observed after heating under reflux conditions for 24 h. Similarly, no reaction was observed when AcOD, ZnCl₂ and D₂O was used (entry 5, Table 4.1). This result suggested that the reactive component in the reaction mixture was DCl, produced from the reaction of AcCl and D₂O. Formation of DCl through this method required slow addition of AcCl to D₂O at 0 °C to prevent a sudden large release of DCl from the reaction mixture therefore a method which used a commercially available source of deuterated acid would be more advantageous. Zimmermann et al. had used D₂SO₄ in a similar manner to Zhao et al., however, the procedure was more detailed than in Zhao’s case and used lower concentration of acid (0.3 M cf 3.4 M, entry 6, Table 4.1). In this case, Zimmermann detailed that the reaction was performed three times sequentially using fresh reagents to achieve high incorporation. This method was successfully replicated. Using 20 g of quinol 153 in 50 mL of 0.3 M D₂SO₄ in D₂O, the first iteration produced a similar result to that of Desiraju et al. using AcCl and D₂O (entry 2, Table 4.1). Following an aqueous extraction of the deuterated quinol, the reaction was performed again on the material to further improved the deuteration, and then a third time to give an overall incorporation of 93% D₄ and the remaining 7% D₃ (Scheme 4.3). This method allowed for large amounts of D₄-quinol 156 to be synthesised, requiring only aqueous extraction for purification. This enrichment level was sufficient for our purposes - further enrichment was likely possible by further repeats. This was deemed unnecessary.
Two methods were available for the oxidation of D$_4$-quinol 156 to give D$_4$-benzoquinone 157 (Scheme 4.3).$^{157,160}$ Zhao et al. had used lead (IV) oxide in organic solvent to avoid the risk of loss of deuterium during the oxidation. This was successful but generated large amounts of toxic lead waste. Alternatively, a patent for the oxidation of quinol 153 using aqueous H$_2$O$_2$ in isopropanol in the presence of catalytic iodine at 55 °C was a potential possibility to avoid the use of lead compounds.$^{160}$ The risk of using aqueous H$_2$O$_2$ was that the enrichment would be diminished and expensive deuterated reagents would be required to prevent this loss. This was not the case, with no loss of deuterium observed and a 89% chemical yield. In addition, purification was facile in that the product crystallised from solution upon cooling allowing for simple filtration of the D$_4$-$p$-benzoquinone 157. These procedures led to the synthesis of D$_4$-$p$-benzoquinone 157 in 85% yield over two steps with a 93% D$_4$ incorporation, 7% D$_3$, using methods that were easily scaleable (>20 g) and low cost.

![Scheme 4.3](image)

**Scheme 4.3** Synthesis of D$_4$-benzoquinone 157 via acid-catalysed hydrogen-deuterium exchange of quinol 153 followed by oxidation with hydrogen peroxide. *Reagents & conditions:* i. D$_2$SO$_4$, D$_2$O, reflux, 3 × 24 h, 95%, 93% D$_4$; ii. 35% w/w aqueous H$_2$O$_2$, I$_2$, isopropanol, 45 °C, 2 h, 89%.

### 4.1.2 Preparation of D$_6$-myo-inositol

Once a reliable route to D$_4$-$p$-benzoquinone 157 had been achieved, it was necessary to show that subsequent chemistry would not lower the deuterium incorporation. It was hypothesised that once the deuterated version of the tetracetate (±)-81 (Scheme 4.4) had been synthesised, it was unlikely that hydrogen-deuterium exchange would be a problem. During the course of previous synthesis of myo-inositol and conduritol B derivatives detailed in the previous chapter, no epimerisation of the alcohols was observed during synthesis by NMR analysis. This observation is unsurprising as the protons adjacent to the hydroxyl groups are not acidic except under very strongly basic conditions. If
epimerisation i.e. a proton exchange, does not occur, it is unlikely that loss of deuterium will be observed. Similarly to tetracetate ($\pm$)-81 (chapter 2), D$_4$-p-benzoquinone 157 was brominated using Br$_2$ followed by reduction with NaBD$_4$ in D$_2$O and Et$_2$O. The reduction worked well, providing material with 90% D$_6$ enrichment with the remaining material D$_5$ - the small decrease in incorporation from 93% D$_4$ to 90% D$_6$ is due to NaBD$_4$ being of 98% deuterium enrichment. Subsequent reaction under conditions reported by Trost et al. produced ($\pm$)-160 in 29% yield over the 3 steps (Scheme 4.4). The lower yield could potentially be attributed to some iodine remaining from the earlier oxidation step. Mass spectrometry studies of the tetracetate ($\pm$)-160 revealed the incorporation had remained constant from the diol ($\pm$)-159 to ($\pm$)-160 at 90% D$_6$, 10% D$_5$, and only traces of the D$_4$ and below, suggesting no exchange of deuterium for hydrogen during the reactions, despite the use of glacial AcOH rather than AcOD. Comparison of an x-ray crystal structure obtained of ($\pm$)-160 by Dr Kirsten Christensen (Chemical Crystallography Lab Oxford, full structure in appendix page 540) showed no significant differences in bond lengths or angles compared to the protonated analogue ($\pm$)-81.

**Scheme 4.4** Synthesis of D$_6$-myo-inositol 90 from D$_4$-p-benzoquinone 157. 
Reagents & conditions: i. Br$_2$, CHCl$_3$, 0 °C, 3 h; ii. NaBD$_4$, D$_2$O, Et$_2$O, 0 °C, 2 h; iii. Ac$_2$O, K$_2$CO$_3$, 2 h then AcOH, reflux, 45 h, 29% over 3 steps, 90% D$_6$, 10% D$_5$.

**Scheme 4.5** Synthesis of myo-inositol 1 or D$_6$-myo-inositol 90 from ($\pm$)-81 or ($\pm$)-160 respectively. A mixture of inseparable compounds were observed after the syn-dihydroxylation, however, this did not matter for the final step. Reagents & conditions: NaIO$_4$, RuCl$_3$-3H$_2$O, MeCN, H$_2$O, 4-8 min; ii. NEt$_3$, H$_2$O, MeOH, 2-18 h, 82% (1), 50% (90) over two steps.
**4.1. DEUTERATED INOSITOL**

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**Figure 4.1** Comparison of $^1$H NMR (left) and $^{13}$C NMR (right) data for H$_6$-myo-inositol 1 (red, top) with D$_6$-myo-inositol 90 (blue, bottom). A small residual signal is seen for each resonance in the deuterated version as the material has 10% D$_5$ present.

**Figure 4.2** Mass spectrometry data comparing synthesised myo-inositol 1 with 90. Both samples were injected at a concentration of 1 mg ml$^{-1}$ in a 9:1 mixture of MeOH/H$_2$O. The deuterium incorporation of 90 can be determined by comparing the relative intensity of m/z 208.0 to 209.0. Absolute intensities are shown below the mass.
To synthesise D$_6$-myo-inositol $\mathbf{90}$ from the tetracetate ($\pm$)-$\mathbf{160}$, a syn-dihydroxylation was performed to produce a tetracetylinositol derivative ($\pm$)-$\mathbf{163}$ (Scheme 4.5).$^{75}$ The chemistry was first attempted with the protonated analogue ($\pm$)-$\mathbf{81}$ to confirm the structure was as expected, and to compare this method of synthesising myo-inositol $\mathbf{1}$ to commercially available material. This approach was taken because structure elucidation would be challenging on the deuterated molecule. All of the usual 2D NMR techniques (COSY, HSQC, HMBC) used to elucidate structural features of small molecules are not possible without protons, and the corresponding techniques for deuterium nuclei are generally not available. This is due to the face that deuterium nuclei are quadrupolar therefore possess a fast relaxation time (short $T_1$), hence spin coupling between deuterium nuclei is not observed. During the syn-dihydroxylation of ($\pm$)-$\mathbf{81}$, two products were observed in the crude (Scheme 4.5). An acetate migrated during the reaction, presumably from the 6-position to the 1-position as migration onto the axial 2-position is less likely. This was not prevented by shorter reaction times during the syn-dihydroxylation or lowering the temperature to 0 °C. Despite the migration product being inseparable from the desired product ($\pm$)-$\mathbf{163}$, this was not an issue as subsequent deprotection of the acetates in either product in the mix led to myo-inositol $\mathbf{1}$. Purification from the two step procedure was possible without chromatography as the product $\mathbf{1}$ was highly crystalline, with characterisation data matching purchased samples. Repeating the same procedures with the deuterated analogue ($\pm$)-$\mathbf{160}$ led to D$_6$-myo-inositol $\mathbf{90}$. $^1$H NMR and mass spectrometry analysis confirmed the isotopic enrichment had been preserved throughout the process (Figure 4.1), giving material of 90% D$_6$, remaining 10% D$_5$ incorporation around the ring by mass spectrometry analysis (Figure 4.2). No significant difference in the ionisation intensity were observed by mass spectrometry, once the D$_5$ incorporation had been included. This material could then be used in future synthesis of myo-inositol derivatives using routes described in the literature. D$_6$myo-inositol $\mathbf{90}$ produced by this route was used by another DPhil student in the group (Amélie Joffrin) in order to produce deuterated PtdIns(4)P.$^{51}$
4.1.3 Application to myo-Inositol Derivatives

Scheme 4.6 Synthesis of deuterated myo-inositol derivatives was possible without loss of deuterium during synthesis. Reagents & conditions: i. NEt₃, H₂O, MeOH, 1 h then TrocCl, pyridine, DMAP, CH₂Cl₂, 0 °C, 2 h, 85%; ii. BzOH, tetrahexylammonium bromide, [Pd(allyl)Cl]₂, (–)-84, 1 M aqueous NaOH, CH₂Cl₂, 69%, > 99% e.e.; iii. Zn, AcOH, THF, 2 h, 89%, 90% D₆; iv. 126, 3-4% 1H-tetrazole in MeCN, CH₂Cl₂, 24 h then mCPBA, –78 °C, 1 h, 55%, 90% D₆; v. RuCl₃·3H₂O, NaIO₄, MeCN, H₂O, 5 min, 30%, 89% D₆. Cne = 2-Cyanoethyl.

Once the synthesis of D₆-tetracetate (±)-160 and D₆-myo-inositol 90 was complete, the synthesis of protected myo-inositol derivatives could be achieved.⁶⁴,⁷⁵,⁸¹ The tetracetate (±)-160 was converted to the tetratroc derivative (±)-165, and the Trost asymmetric allylic alkylation was performed with relative ease (Scheme 4.6). Despite expecting a

Figure 4.3 Mass spectra showing the shift in mass caused by incorporation of deuterium at the six positions indicated by red asterisks on the structure shown, in electrospray ionisation (ES⁺) showing the [M+Na]⁺ ion. Left: (+)-94 (H₆); Right: (+)-167 (D₆).

81
kinetic isotope effect to be observed, the reactions proceeded in a similar manner to the
protonated version with no noticeable rate effect and no change in enantioselectivity (as
measured by chiral HPLC and specific rotation). Mass spectrometry analysis of deriva-
tives incorporating one or more Troc protecting groups was complicated by the multiple
peaks in the spectrum, caused by up to twelve chlorine atoms. To show incorporation
of deuterium was not diminished, the Troc groups were removed to afford (+)-167 and
mass spectrometric analysis showed the enrichment had remained at 90% D$_6$ (Figure 4.3).
Phosphorylation and syn-dihydroxylation of (+)-167 produced the first fully deuterated
myo-inositol derivative (+)-169 in > 99% e.e., with no loss in deuterium incorporation at
any point, within experimental error. No further synthesis from (+)-169 was attempted,
as it had already been shown that the benzoate deprotection was not possible in the
presence of the phosphatidyl moiety, however, this was a positive step towards showing
the deuterium atoms were not labile. In addition, normal synthetic transformations used
on conduritol B and myo-inositol derivatives were possible in protonated, rather than
deuterated, solvents without any modification to the procedures and without loss of the
deuterium atoms through exchange mechanisms.

4.2 NMR Techniques

Throughout the synthesis of deuterated derivatives, many of the normal NMR techniques
such as $^{13}$C experiments had to be modified to produce high quality structural data to
confirm the correct compound had been synthesised. In addition to modification of the
standard experiments, several non-standard methods were used in order to elucidate the
structure of synthesised compounds.

4.2.1 Deuterium ($^2$H) NMR

There have been many reported molecules throughout the literature that contain deu-
terium within their structure.$^{91}$ Evidence for incorporation has usually been provided
by suppression of the relevant signal in the $^1$H NMR, splitting of the relevant carbon
or disappearance of the signal in the $^{13}$C NMR, and mass-spectrometry analysis. While
adequate when only one or two protons have been exchanged for deuterium, in our case
it was prudent to prove there were multiple deuterium environments in our molecules, especially in cases where there were up to six different environments. $^2$H NMR provided the answer (Figure 4.4), showing there were deuterium atoms in different environments and providing evidence for multiple sites of incorporation. There are several limitations to $^2$H NMR: due to deuterium being spin $I=1$, the nucleus is quadrupolar and hence exhibits rapid relaxation following spin excitation by an RF pulse.$^{161,162}$ As a result of this, the peaks observed in the spectrum for $^2$H NMR are significantly broadened and normal 2D NMR techniques are not possible. The chemical shifts of the $^1$H NMR can be used as a guide when assigning the $^2$H NMR as it is not possible through 2D NMR techniques.

### 4.2.2 Carbon ($^{13}$C) NMR

While decoupling of $^1$H nuclei in $^{13}$C NMR is standard, the decoupling of other nuclei is much less common. Deuterium, as a spin $I=1$ nucleus, leads to a 1:1:1 splitting of adjacent carbon atoms, however, typically a small signal is also seen for the protonated carbon as full deuteration is almost never achieved, (e.g. Figure 4.5), while $^{31}$P leads to the standard 1:1 doublet as a spin $I=1/2$ nucleus. This leads to a significant complication in the $^{13}$C spectra of compounds containing both phosphorus and deuterium, as found in deuterated PtdIns$P_n$. In addition, the use of deuterium attached to tertiary carbon centres causes

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**Figure 4.4** $^1$H NMR (top) vs. $^2$H NMR (bottom) for conduritol B tetraacetate with either deuterium ((±)-160) or hydrogen ((±)-81) around the six-membered ring. The spectra can be superimposed to assign the $^2$H NMR, however, there is some shift in signals, presumably caused by the presence of $D_6$-DMSO which is used to calibrate the $^2$H NMR spectrum, and isotopic shift caused by the change in mass in the nuclei.
Figure 4.5 Splitting observed in $^{13}$C NMR spectra caused by the coupling of either deuterium (left) or phosphorus (right) to a carbon centre. In the case of deuterium splitting, the carbon signal often experiences an isotopic shift of ca. 0.3 ppm upfield with a small peak where residual protonated species are left due to methods for incorporation not leading to 100% deuterium.

Figure 4.6 $^{13}$C NMR spectrum of (+)-169 showing the coupling of deuterium or phosphorus to a carbon centre in the inositol ring. In the case of deuterium splitting, the carbon signal often experiences an isotopic shift of ca. 0.3 ppm upfield with a small peak where residual protonated species are left due to methods for incorporation not leading to 100% deuterium incorporation. Number of scans: 1024, D$_1$: 10 s, 50 mg in 0.4 mL CD$_2$Cl$_2$. Cne = 2-Cyanoethyl.
the carbon nucleus to act in a similar fashion to a quaternary carbon nucleus, in that
the relaxation of carbons attached to a deuterium atom is much slower (\( T_1 \) is increased, Table 4.2), leading to a degradation in the signal. The suppression of the signal is caused by poor spin-spin coupling of quadrupolar nuclei to \(^{13}\)C, hence the return to an equilibrium state is slowed, causing a significant reduction of the signal associated with a deuterated carbon (Figure 4.8).\(^{161,162} \) The relaxation times of primary through to tertiary \(^{13}\)C are significantly shorter relative to quaternary \(^{13}\)C, hence the associated quaternary carbon has a tendency to become suppressed relative to other carbon centres throughout an NMR experiment. In simple molecules, such as \( \text{D}_4\)-quinol 156, where all the carbon centres are quaternary, this is not an issue as all the centres behave in a similar manner such that relative signal strength from the different carbon centres is roughly the same. When the molecular complexity increased such that there were non-quaternary centres within the molecule, particularly in latter synthetic steps (as in (+)-169, Figure 4.6), the signals at some centres were significantly stronger than the deuterated quaternary centres. In order to observe the suppressed deuterated carbon atoms, significantly more scans than usual (3072 vs. 256) were required to enable sufficient signal-to-noise to fully resolve the signal.

To find the optimum experimental parameters for measuring \(^{13}\)C NMR on deuterated compounds, the spin-lattice (\( T_1 \)) relaxation times of the \(^{13}\)C atoms in protonated (\( \pm\))-81 and deuterated (\( \pm\))-160 (highlighted by red asterisks in Table 4.2) were measured using the inbuilt "inversion-recovery" method on Bruker’s TopSpin v 3.1 software by Dr Barbara

\[
\begin{array}{c|cc}
\text{Position} & \text{\( T_1 \) times / s} & \text{\( \pm\)}-81 & \text{\( \pm\)}-160 \\
\hline
1 & 0.95 & 4.85 \\
2 & \text{\& 3}^a & 1.11 & 8.59 \\
4 & \text{\& 6}^a & 5.73 & 6.30 \\
5 & \text{\& 7}^a & 3.19 & 3.57 \\
\text{CDCl}_3 & 16.46 & 16.68 \\
\end{array}
\]

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<table>
<thead>
<tr>
<th>Position</th>
<th>( T_1 ) times / s</th>
<th>( \pm)81</th>
<th>( \pm)160</th>
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<tr>
<td>1</td>
<td>0.95</td>
<td>4.85</td>
<td></td>
</tr>
<tr>
<td>2 &amp; 3(^a)</td>
<td>1.11</td>
<td>8.59</td>
<td></td>
</tr>
<tr>
<td>4 &amp; 6(^a)</td>
<td>5.73</td>
<td>6.30</td>
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<tr>
<td>5 &amp; 7(^a)</td>
<td>3.19</td>
<td>3.57</td>
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<tr>
<td>CDCl(_3)</td>
<td>16.46</td>
<td>16.68</td>
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5 & \text{\& 7}^a & 3.19 & 3.57 \\
\text{CDCl}_3 & 16.46 & 16.68 \\
\end{array}
\]
Figure 4.7  Schematic representation of a simple $^{13}$C NMR pulse sequence, illustrating the recovery delay required for the highest amplitude signal.

Figure 4.8  Schematic showing the signal relaxation following RF excitation during an NMR experiment for different $T_1$ times. The $T_1$ time has an effect on choice of recycle delay time ($D_1$) as if too short a delay time is chosen, full relaxation is not achieved and a suppressed signal is observed.
Odell (University of Oxford). The results were directly compared for the protonated and deuterated versions (Table 4.2). The $T_1$ times of carbons 4-7, the acetate groups, were unaffected within experimental error (Table 4.2), however, where hydrogen had been exchanged for deuterium, the $T_1$ times were ca. 5 and 8 times longer for positions 1 and 2/3 respectively. This result meant the experimental parameters for the $^{13}$C NMR experiments on molecules containing deuterium could be tailored such that the signals for deuterated carbons were not attenuated. The recycle delay time ($D_1$, Figure 4.7) is used to ensure a long enough time period between RF pulses for equilibrium to be reached, maximising the signal received. Prior to this result, the $^{13}$C NMR method used had required 3072 scans with the standard $D_1$ time of 2 s to enable a high enough signal-to-noise ratio in order to reliably see the deuterated carbons - in these cases it was noted that the signal-to-noise ratio was so high that $^{13}$C-$^{13}$C coupling could be observed as satellites of the main peaks. Typically in any NMR experiment using a 90° pulse sequence, a $D_1$ time is chosen to be ca. 5 times the $T_1$ to ensure the spin state is > 99% relaxed prior to the next pulse sequence, enhancing signal to noise (Figure 4.8). This would mean a $D_1$ time of up to 45 s to ensure the best spectrum, significantly lengthening the $^{13}$C NMR experiments. In our $^{13}$C NMR sequences, a 30° pulse sequence was used as while the signal generated is smaller, the subsequent delay time required for full relaxation is also less. It was found that the optimal delay time appeared to be 10 s for a 30° pulse, with longer $D_1$ leading to no improvement in relative signal strength, while shorter $D_1$ times lead to saturation of the signal over time and subsequently the relative signal strength was diminished at deuterated carbon centres. By increasing the $D_1$, a spectrum where the signal intensities for deuterated carbon atoms were comparable to other carbon atoms could be obtained with fewer scans (1024 scans) for the same amount of NMR time used for 3072 scans.

4.3 Conclusions

To synthesise $D_6$-myo-inositol 90 and derivatives, the deuteration of $p$-benzoquinone 77 was optimised starting from readily available quinol, generating highly deuterium-
4.3. CONCLUSIONS

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enriched starting materials (>90% D₄). Using D₄-p-benzoquinone, a route was developed toward conduritol B tetracetate (±)-160, a key intermediate in the synthesis of deuterated myo-inositol derivatives (Scheme 4.7). From here, a syn-dihydroxylation was performed on (±)-160 followed by deprotection, giving a reliable route toward D₆-myoinositol 90 (Scheme 4.7). This new route avoid the need for complex purification of isomers, requiring only a single chromatographic step in the synthesis and two crystallisations, allowing for large scale synthesis to be possible. Alternatively, using a Trost asymmetric allylic alkylation followed by phosphorylation and syn-dihydroxylation, an optically pure deuterated and phosphorylated myo-inositol derivative (+)-169 was prepared, showing that the deuterium atoms were not exchangeable, hence this synthetic route was highly desirable. To elucidate structural features, NMR techniques were developed to fully characterise these complex deuterated derivatives. In addition, a robust route toward the highly valuable D₆-myoinositol 90 was established, allowing access to an expensive starting material in large quantities (> 1 g). From here, a robust synthesis of PtdIns(4,5)P₂ 10 was required, using these available starting materials.

Scheme 4.7  Starting from quinol, D₄-p-benzoquinone 157 was prepared, leading to D₆-myoinositol 90 and related derivatives (+)-169.
Chapter 5

Benzyl Protection Strategy

5.1 Introduction

While a route toward a fully protected PtdIns(4,5)P$_2$ derivative (+)-98 had been achieved (see Chapter 3), it was found that deprotection of (+)-98 was not possible using the previous protecting group strategy. Therefore, an alternative route was required toward PtdIns(4,5)P$_2$ 10 that ensured a final product could be obtained. Several options were available in changing the protecting group strategy. To synthesise final products with saturated lipid chains, a benzyl protecting group strategy would allow for facile deprotection by hydrogenolysis (170, Scheme 5.1). This would access saturated derivatives (discussed in this chapter), however, a different route would be required to synthesise unsaturated lipid derivatives (discussed in the following chapter).

Scheme 5.1  Two different protecting group strategies were required to access PtdInsP$_n$ with either saturated (left) or unsaturated (right) lipid chains. R denotes the phospholipid group while R' denotes a generic protecting group.
5.2 Selection of New Nucleophile

The Trost asymmetric allylic alkylation had proved a useful reaction to generate optically pure myo-inositol derivatives (Chapter 2).\textsuperscript{64,81} Benzoic acid and pivalic acid had both been used in previous literature as nucleophiles, however, both groups require strongly basic conditions for deprotection.\textsuperscript{64,65,81,84} Removal of the benzoate groups in the presence of the Troc groups is difficult as the Troc groups are liable to cyclise under basic conditions adjacent to a free hydroxyl group. To develop an efficient synthesis, a group that was orthogonal to the Troc groups was required. In addition, careful choice of the protecting group may allow for a synthesis of derivatives with unsaturated lipid chains at a later date, without the need to change the protecting group for a different one in subsequent steps.

5.2.1 Carboxylate Nucleophiles

During the original replication of the Trost work (Chapter 2), a variety of different carboxylate groups were used in an attempt to understand solubility effects on the system (Scheme 5.2).\textsuperscript{64,81} These groups were chosen as they had been used in previous literature for the protection of hydroxyl groups.\textsuperscript{163} Of particular interest were the proximity-assisted protecting groups as the properties of the groups could be tuned, allowing deprotection under mild conditions that should be tolerant to many other functionalities.

\begin{center}
\includegraphics[width=\textwidth]{scheme52.png}
\end{center}

\textbf{Scheme 5.2} Use of other nucleophiles in the Trost asymmetric allylic alkylation limited the protecting group strategies that could be used in future synthesis (see Chapter 2 for full details). Piv: Pivalic acid; Lev: Levulinic acid. \textit{Reagents & conditions:} ROH, THABr, \([\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2\), \((S,S)\)-ligand \((\pm)\text{-84}, \text{CH}_2\text{Cl}_2, 1\) M aqueous NaOH, 1-18 h.
5.2.2 Proximity Assisted Protecting Groups

Proximity assisted protecting groups such as (+)-175 (Scheme 5.2) are alternatives to standard protecting groups. These proximity assisted groups focus on an intramolecular ring-closing mechanism to drive the deprotection. The intramolecular reaction makes the conditions required for deprotection milder than those needed for standard groups. There are many examples of benzoate derivatives that can be removed by conditions different to those used for a standard benzoate. These conditions can be acidic (119 and 176), hydrolysis under silver-promoted conditions (177), or reductive methods (178, Figure 5.1). In our system, a major limitation to the incorporation of many of the proximity assisted benzoate derivatives groups was the intended use of the unsaturated skipped-alkene arachidonic acid chain in later synthetic endeavours. For this reason, the two groups of particular interest were 119 and 176 (Figure 5.1), as they could both be removed in a number of ways, most notably acidic conditions. The TBDPS group was used preferentially, as the PMB derivative was hypothesised to be less stable than the TBDPS derivative.

![Figure 5.1: Examples of benzoate derivatives that can be cleaved by markedly different conditions to those of a benzoate group.](image)

The TBDPS-protected benzoic acid 119 was synthesised in 67% yield over three steps from phthalalide, using the method from Guerlavais-Dagland et al. (Scheme 5.3). The intermediates required no purification as the product 119 was readily crystallised from hexane, avoiding column chromatography. When 119 was used in the Trost reaction, no significant detrimental effect was seen on the yield compared to using benzoic acid (74% cf 80% for the benzoate derivative (+)-83, Chapter 2), and the sterically demanding TBDPS group had no effect on the e.e. (>99% e.e. in both cases, Figure 5.2).
Scheme 5.3  Synthesis of a proximity assisted protecting group for use in the Trost asymmetric allylic alkylation. \textsuperscript{64,164}  
Reagents & conditions:  
i. KOH, MeOH, H\textsubscript{2}O, reflux, 90 min;  
ii. TBDPSCl, imidazole, pyridine, 18 h;  
iii. K\textsubscript{2}CO\textsubscript{3}, MeOH, THF, H\textsubscript{2}O, 1 h then KHSO\textsubscript{4}, 67\% over 3 steps;  
iv. 119, Tetrahexylammonium bromide, (S,S)-ligand (–)-84, [Pd(η\textsuperscript{3}-allyl)Cl\textsubscript{2}], CH\textsubscript{2}Cl\textsubscript{2}, 1 M aqueous NaOH, 1 h, 74\%, >99\% e.e.

Figure 5.2  Chiral HPLC (ChiralPak\textsuperscript{®} AD-H column, 0.5\% isopropyl alcohol in hexane) overlay of (+)-175 (top, blue) and (–)-175 (top, red) of a mix of the two compounds in the same sample (bottom, green).
5.3 Benzylated Derivatives

To ensure that a deuterated PtdIns(4,5)P$_2$ derivative with saturated lipid chains could be synthesised, it was necessary to consider at this stage the introduction of benzyl groups into the synthesis. This approach had more literature precedent than routes where unsaturated lipid chains derivatives had been synthesised. It is well known that de-protection of poly benzylated PtdInsP$_n$ was possible using hydrogenolysis, removing the need for purification of unstable products at the final step.

5.3.1 Incorporation of Benzyl Ethers

As a route toward an acid-sensitive benzoate derivative (+)-175 had been optimised, the proximity-assisted protecting group was removed in the presence of the Troc groups by stirring at room temperature in a 9:1 mixture of CH$_2$Cl$_2$ and TFA to give (+)-182 (Scheme 5.4). Attempts to purify this compound from the mixture of phthalide and TBDPS debris were low yielding, as (+)-182 was poorly soluble in most solvent systems. As this was the case, the introduction of the benzyl groups was completed in a two-step, one-pot procedure. Benzyl 2,2,2-trichloroacetimidate in the presence of triflic acid was used to incorporate the benzyl groups without cyclisation of the Troc groups, resulting in (+)-183 in 62% yield over the two steps. The Troc groups were then removed to give (+)-184 (Scheme 5.4).

![Scheme 5.4](image)

**Scheme 5.4** Removal of the proximity assisted groups was possible under acidic conditions, followed by benzylation using a trichloroacetimidate allowed for a one-pot, two-step introduction of benzyl groups into the synthesis of PtdIns(4,5)P$_2$. **Reagents & conditions:** i. 1:9 v/v TFA/CH$_2$Cl$_2$, 1 h; ii. Benzyl 2,2,2-trichloroacetimidate, TIOH, 1,4-dioxane, 18 h, 62% over two steps; iii. Zn, AcOH, THF, 1 h, 88%.
5.3.2 Benzyl Phosphate Derivatives

There were two protecting group options available for phosphate groups that can be deprotected using hydrogenolysis. While dibenzylphosphates (186, Figure 5.3) can be synthesised using a commercially available reagent (dibenzyl N,N-diisopropylphosphoramidite 185), a protecting group based on 1,2-benzenedimethanol has often been used (188, Figure 5.3).\(^{41,75,170,171}\) The \(\alpha\)-xylene derivative 188 has been used as it creates a phosphorus centre that is less sterically hindered than the dibenzyl phosphate 186 and is removed under the same conditions.\(^75\) This can aid both in the introduction of the phosphate using phosphoramidite 187 and can prevent steric issues in later synthesis. The dibenzyl derivative (+)-189 was synthesised first due to commercial availability of dibenzyl N,N-diisopropylphosphoramidite 185 (Scheme 5.5). Subsequent \textit{syn}-dihydroxylation of (+)-189 gave the \textit{myo}-inositol derivative (–)-154.

\[
\begin{align*}
\text{185} & \iff \text{186} \\
\text{187} & \iff \text{188}
\end{align*}
\]

Figure 5.3 Two examples of phosphate protecting groups that can be removed using hydrogenolysis and the phosphoramidites used to prepare compounds containing these groups. The dibenzyl phosphoramidite 185 was preferentially used as it is commercially available.

To phosphorylate the 1-position of (–)-154 exclusively with the phospholipid, the 2-position required protection (Scheme 5.5). While introduction of a benzyl group at the 2-position would be advantageous, there were no literature routes for a high-yielding single step introduction of the benzyl at the 2-position. Most routes rely on protection of the 1-position first using organotin chemistry.\(^{135,172,173}\) The \textit{cis}-diol is first reacted with \textit{di}(\textit{n}-butyl)tin oxide, producing a tetracoordinate tin species, activating the equatorial hydroxyl group for reaction with a suitable electrophile such as acetyl chloride or 4-methoxybenzyl chloride.\(^{135,147}\) This relies on toxic organotin reagents which require complete removal prior to biological testing. Alternatively, a benzylorthoester could be
Reduced selectively, however, this route was particularly low yielding. An acetate group could be selectively placed at the 2-position in a one-pot two-step procedure to synthesise \((-\text{-190})\) (Scheme 5.5). Attempts to selectively acetylate the axial 2-position in \((-\text{-154})\) using triethylorthoacetate followed by hydrolysis (as described in Chapter 3) were successful, however, the regioselectivity was not as previously observed. A 1:3 regioselectivity was observed for the 1- vs the 2-position (Figure 5.4, cf 1:9 in Chapter 3) and the two regioisomers could not be separated by column chromatography or crystallisation. The poor regioselectivity may be due to the increased steric bulk of the dibenzyl phosphate group at the 4- and 5-positions. Painter et al. noted that when two TBDMS groups were placed on the 4- and 5-positions, the conformation of the \(\text{myo-}\)inositol ring flipped, i.e the two bulky groups were placed axially. If the opposite conformer (predominantly axial, lower scheme, Scheme 5.6) reacted to form the orthoester, the system becomes locked in
place and can no longer interchange without breaking one of the orthoester bonds. Upon hydrolysis, the acetate still preferentially maintains the axial positioning but this is now on the 1-position (Scheme 5.6).

![Scheme 5.6](image)

**Scheme 5.6** When the two large phosphate groups neighbour one another at the 4- and 5-positions, the conformation can flip to give the diaxial species shown. This flip is thought to lead to the opposite regioselectivity in the subsequent ring opening, leading to inseparable products. *Reagents & conditions: CH₃C(OEt)₃, pTSA, THF, 1 h; ii. 80% v/v Aq. AcOH, 1 h.*

It was possible that the large phosphate groups were causing this ring flip to happen in our system, however, only a single conformer was observed by ¹H NMR analysis of (+)-154 under standard conditions (Figure 5.5). To improve regioselectivity, it was hypothesised that temperature could be a crucial aspect to controlling the population of conformations during the reactions. However, cooling the orthoester to –40 °C and adding aqueous acetic acid to the orthoester at a reduced temperature or performing the orthoester formation at this reduced temperature made no difference to the regioselectivity. To selectively protect the 1,2-diol, (–)-154 was acetylated at the 1-position by stirring with acetyl chloride in pyridine. Only the equatorial hydroxyl group was protected with an acetate to give (–)-195 in 53% yield (Scheme 5.7). Subsequent reaction of (–)-195 with benzyl 2,2,2-trichloroacetimidate or using NaH/BnBr caused multiple unidentified products to form and this was not pursued further.

As it was the case that the dibenzylphosphate groups were impacting on regioselectivity, the less sterically demanding 1,2-benzenedimethanol derivative was used. The phospho-
Figure 5.4 Comparison of crude $^1$H NMR data for acetylation reactions with different substitutions at the 4- and 5-positions (top three) compared to a pure sample of the 1-acetate (+)-201 ($R = \text{Troc}$). For each compound, the signals for $H-1$ and $H-2$ are labelled, as determined by 2D NMR analysis. This shows the size of the protecting group on the 4- and 5-positions has a direct impact on regioselectivity during the acylation. Reagents & conditions: $\text{CH}_3\text{C(OEt)}_3$, $p\text{TSA}$, THF, 1 h; ii. 80% v/v Aq. AcOH, 1 h.
ramidite 187 was prepared from PCl₃ as a crude mixture (Scheme 5.5), as described by Gregory et al.¹⁷⁵ Diol (+)-184 was phosphitylated with 187 followed by oxidation to give (+)-191, and subsequently underwent a syn-dihydroxylation to give diol (–)-192 in 21% yield over two steps (Scheme 5.5). Upon selective acetylation using the orthoester and subsequent hydrolysis, the regioselectivity was better than previously observed with (–)-154 at ca. 1:6 for 1-acetate vs 2-acetate (Figure 5.4), however, the products could not be separated.

The bulky phosphate groups had proved detrimental to the selective acetylation at the 2-position, therefore an alternative route was sought. Podeschwa et al. used smaller groups such as acetates at the 4- and 5-positions to get the highest regioselectivity.⁷⁵,⁷⁶ Hence, it was hypothesised that Troc groups would behave in a more similar manner to acetates in terms of steric than the phosphate groups, as the carbonyl is planar (cf tetrahedral phosphates) and the trichloroethyl groups can rotate away from one another. Oxidation of (+)-183 to give (+)-202 and subsequent selective acetylation (Scheme 5.8) proceeded...
Scheme 5.8 Phospholipidation of (+)-200 followed by removal of the Troc groups led to a protected PtdIns derivative (+)-205. Deprotection of this derivative was unsuccessful therefore phosphorylation to give the PtdIns(4,5)P$_2$ derivative (+)-205 was not undertaken.

Reagents & conditions: i. NaIO$_4$, RuCl$_3$·3H$_2$O, MeCN, H$_2$O, 4 min, 44%; ii. CH$_3$C(OEt)$_3$, pTSA, THF, 1 h then 80% aq. AcOH, 0 $^\circ$C, 1 h, 86%; iii. Phosphoramidite 207, 1H-tetrazole in MeCN, CH$_2$Cl$_2$, 1 h then mCPBA, 1 h; iv. Zn, THF, AcOH, 48 h, 62% over two steps; v. Pd Black, H$_2$, tBuOH, H$_2$O, 18 h then aqueous base; vi. Bis(benzyloxy) N,N-diisopropylphosphoramidite, 1H-tetrazole in MeCN, CH$_2$Cl$_2$, 18 h then mCPBA, 1 h; vii. 1H-tetrazole in MeCN, CH$_2$Cl$_2$, 18 h, 79%.
with higher regioselectivity using the Troc groups, affording (+)-200 in 86% yield with 1:10 regioselectivity. Only small amounts of the 1-acetate was present in the mixture (Figure 5.4).

![NMR Spectra](image)

**Figure 5.6** Partial $^{31}$P NMR (top) and $^1$H NMR (bottom) spectra in D$_4$-MeOD of the deprotection by hydrogenolysis of (+)-205. Several products, most likely resulting from acetate migration, were observed. Subsequent removal of the acetate also caused hydrolysis of the phospholipid.

With the selective acetylation possible with high regioselectivity, this new route where the phosphates are introduced last had the added benefit of providing two final compounds instead of one. Phosphitylation with the phospholipid using the phosphoramidite 207 and subsequent oxidation led to (+)-204 (Scheme 5.8). Purification of this intermediate was particularly difficult, however, upon removal of the two Troc groups to give (+)-205, the compound could be isolated and purified. At this stage, it was prudent to consider deprotection conditions for (+)-205 to give PtdIns 13, as the chemistry required for the deprotection would be very similar for (+)-205, and the related PtdIns(4,5)P$_2$ derivative (+)-206. The three benzyl groups in (+)-205 were removed by hydrogenolysis using H$_2$ gas in the presence of Pd black, with complete deprotection observed after 18 h - no
aromatic signals remained in the $^1$H NMR spectrum. $^{31}$P NMR studies revealed at least three products in the mixture (Figure 5.6) and there were four peaks observed at 2.0-2.1 ppm in the $^1$H NMR, consistent with the presence of multiple acetate groups. It was hypothesised that these products were likely the 2-acetate ($H$-2 5.48 ppm, Figure 5.6), a migration product (3-acetate and possibly 4-acetate, $H$-2 4.35 ppm), and fully deprotected PtdIns(4,5)$P_2$ 10. To coalesce the three products into one, the acetates required removal. As has been discussed in Chapter 3, benzoates had proved difficult to remove, however, in this case there was limited literature precedent for the removal of acetates in the presence of phospholipids. Use of mild conditions such as aqueous NEt$_3$ (as had been used to hydrolyse the tetracetate (±)-81, Chapter 2) resulted in no product after 18 h, while stronger aqueous bases such as LiOH or NaOH resulted in cleavage of the phospholipid. Use of catalytic NaOMe in MeOH also resulted in cleavage of the phospholipid.

Once the phosphates had been deprotected, monitoring of the acetate deprotection became more difficult as the products were not soluble in many solvents used for NMR, and they did not move off the base-line by TLC, thus the order of deprotection was reversed (acetate then phosphates). The fully protected system (±)-205 was subjected to the same hydrolysis conditions (NEt$_3$ in aqueous MeOH, NaOH in aqueous MeOH or NaOMe in MeOH). In the first instance with NEt$_3$, no reaction was observed, despite leaving the reaction for 18 h. With the harsher conditions, hydrolysis of the 1-phosphate was observed, as had been seen with the deprotected phosphate compound (Scheme 5.9). Careful monitoring of the reaction by TLC suggested the deacetylated product was produced, however, it appeared there was then rapid cleavage of the phospholipid in this material. The cleavage of the phospholipid appeared to be faster than the deacetylation.

Scheme 5.9 Hydrolysis of the acetate both pre- and post-hydrogenolysis of the benzyl groups led to rapid hydrolysis of the phospholipid.
This hydrolysis is probably similar to the base-catalysed hydrolysis of the phosphate group in RNA, where there is participation of the 2-position in the cleavage upon deprotection of the acetate. Consultation with the literature showed that while acetates may be deprotected in the presence of phospholipids, this is generally only done in systems where the hydroxyl groups on either side of the phosphate are not free hydroxyls, preventing hydrolysis.

5.4 Fully Benzylated Derivatives

As the acetate was difficult to remove in the presence of the phospholipid, benzylation of the 2-position was required. There was no literature precedent for a single step protection with a benzyl group, despite the obvious utility of this transformation. Selective protection of the 1-position in 1,2-cis diol systems such as (−)-202 is possible with a benzyl ether using di(n-butyl)tin oxide. Use of PMBCl in place of BnBr would allow selective protection of the 1-position with a PMB group followed by protection of the 2-position with a benzyl group, however, this relied on the use of toxic tin compounds. Podeschwa et al. had described a route where a benzyl acetal was reduced to give a 2-benzyl protecting group. This required separation of endo- and exo-isomers, which in their case was done through crystallisation. It was also noted in the publication that the crystallisation performed worse with a single enantiomer than with a racemate. This route could potentially take significant optimisation in our system.

Alternatively, Saito et al. had shown that selective protection of the 1-position was possible using a tetrahydropyranyl (THP) group without the need for organotin complex formation. In addition, the following step in their synthesis was to introduce a benzyl group at the 2-position followed by removal of the THP ether. Incorporation of the THP group was achieved in our system starting from (+)-202, giving (+)-210 as a mixture of the two diastereomers (Figure 5.7). The complication of a mixture of diastereomers made determination of regiochemistry from the THP group to the inositol ring at this stage difficult. Benzylation with NaH and BnBr provided (+)-211, however,
the yield was low (14% over the two steps). In addition, the reaction was unreliable and on several occasions \( n = 5 \), the starting material \((+)-211\) was observed to break down into many different uncharacterised products prior to addition of BnBr. A small amount of product \((+)-211\) was isolated for full characterisation. The regiochemistry of \((+)-211\) was confirmed by 2D NMR techniques, including \(^1\)H-\(^{13}\)C HMBC NMR analysis, clearly indicating a coupling from \( H-2 \) to a benzylic position (Figure 5.8). Removal of the THP group using aqueous acetic acid gave a single product \((+)-212\).

While these reactions, and the subsequent NMR analysis, confirmed that the regiochemistry was as previously described, the reactivity of \((+)-210\) in the presence of NaH was problematic. Upon addition of the base, whether that be NaH or \( K_2 CO_3 \), the solution turned dark brown (albeit at a slower rate with \( K_2 CO_3 \)), and following reaction with BnBr many uncharacterised products were observed by \(^1\)H NMR analysis, only a small proportion of which was the desired product. In addition, without addition of the BnBr and subsequent reprotonation with weak aqueous acid, the starting material \((+)-210\) was not reisolated, nor \((+)-202\) from loss of the THP group potentially by the weak acid. This suggests the base was degrading \((+)-211\), presumably due to the Troc groups. This observation was despite the fact that limited literature precedence suggested Troc groups were tolerant of strong base.\(^{181,182}\) Attempts to use acidic methodology to introduce the benzyl group with a trichloroacetimidate were unsuccessful due to the poor stability of the THP under acidic conditions (PPTS, TFA, TfOH).

As it appeared likely that the Troc groups may be hampering the introduction of the benzyl group, other non-bulky protecting groups on the 4- and 5-positions to replace the Troc groups were required. Saito \textit{et al.} had shown that the THP and benzyl groups could be incorporated into similar systems in the presence of PMB groups.\(^{180}\) As this was the case, the Troc groups were removed from the conduritol B derivative \((+)-183\) and replaced with PMB groups to afford \((+)-214\) (Scheme 5.10). The \textit{syn}-dihydroxylation was performed quantitatively and subsequently a THP group was placed at the 1-position,
albeit as a complex mixture of the regioisomers and diastereomers. Subsequent benzylation of the free hydroxyl using NaH and BnBr gave \((+)\)-217 in 26\% yield over the two steps - most of the yield was lost due to the mix of regioisomers formed during the THP protection and the subsequent purification. In Saito’s system, the 3-position is protected by a benzoate group while the 6-position is protected by a 2-methoxybenzyl (OMB) group (cf two benzyls in \((+)\)-215). The OMB group may be directing the THP protection to the 2-position, improving the regioselectivity in their system and explaining the lower

![Figure 5.7](image_url)

**Figure 5.7** Selective benzylation of the diol \((+)\)-202 was achieved by selective protection of the 1-position using a THP group followed by benzylation and deprotection of the THP. Analysis of intermediate steps ((+)-210 and (+)-211) by \(^1\)H NMR analysis (shown) was complicated by the presence of two diastereomers. Reagents & conditions: i. DHP, PPTS, CH\(_2\)Cl\(_2\), 2 h; ii. NaH, DMF, 10 min then BnBr, 72 h, 14\% over two steps; iii. 80\% aq. AcOH, THF, 50 °C, 2 h, 34\%.
Figure 5.8 Analysis of (+)-211 by $^1$H-$^{13}$C HMBC revealed that the THP group was attached at the 1-position, with correlation between the anomic carbon on the THP group to the 1-position proton. No correlation was observed from the 2-position on the inositol ring to any of the THP carbon atoms. The two carbon atoms shown (C-7 and C-7') are the anomic carbon atoms on the THP ring of either diastereomer.

Figure 5.9 $^1$H-$^{13}$C HMBC data for (–)-213 in the inositol/benzylic region of the spectra, showing correlation from the benzylic protons of the PMB and Bn groups to all carbons except C-1 on the inositol ring.
regioselectivity in our system. Subsequent deprotection of the THP group gave the fully-protected inositol system $(-)-213$, with the regiochemistry confirmed using $\text{H}-^{13}\text{C}$ HMBC NMR (Figure 5.9). From $(-)-213$, it was possible to phosphitylate with the phospholipid 207 followed by oxidation, however, phosphoramidite impurities led to a difficult separation. Removal of the two PMB groups using DDQ allowed for easier purification to give $(+)-218$. Two final compounds were synthesised from this point. Hydrogenolysis of $(+)-218$ using $\text{H}_2$ gas in the presence of Pd black gave PtdIns 13 as a sodium salt, another PtdIns$P_n$ of interest. Alternatively, the two free hydroxyl groups in $(+)-218$ were phosphitylated with bis(benzyloxy) $N,N$-diisopropylphosphoramidite to give $(-)-219$, a
PtdIns(4,5)\(_2\) derivative. Subsequent hydrogenolysis of (-)-219 led to PtdIns(4,5)\(_2\) 10 as a pentasodium salt (Scheme 5.10).

Figure 5.10 Comparison of NMR data for the two products, PtdIns 13 and PtdIns(4,5)\(_2\) 10. With the singly charged PtdIns 13, the peaks are sharp and well resolved as the product is fully soluble in a mixture of CD\(_2\)Cl\(_2\) and D\(_4\)-MeOD. With PtdIns(4,5)\(_2\) 10, the amphiphilic nature of the molecule makes it difficult to find solvents that fully dissolve the molecule, however, reasonable quality data could be obtained in D\(_2\)O.
While high quality $^1$H and $^{31}$P NMR data could be obtained for PtdIns 13, the same was not true for the trisphosphate PtdIns(4,5)$P_2$ 10 (Figure 5.10). The presence of lipid chains, in combination with charged phosphates, makes getting these complex molecules fully into solution challenging. With PtdIns 13, where there is only a single negative charge, the compound is soluble in a mixture of CD$_2$Cl$_2$ and D$_4$-MeOD, giving sharp peaks in the NMR spectrum due to the fact all parts of the molecule are fully solvated (Figure 5.10). As the charge increases from a mono-charged PtdIns 13 to the penta-charged PtdIns(4,5)$P_2$ 10, solvation of the headgroup in deuterated aqueous solvent is possible, however, the lipid chains are less well solvated. This leads to a significant broadening of the signals in the $^1$H NMR of PtdIns(4,5)$P_2$ 10. In the $^{31}$P NMR spectrum, the peaks remain sharp for the 4- and 5-positions as the headgroup is fully solvated and only broaden for the 1-position (Figure 5.10). To prevent the signals from broadening further, the samples were filtered directly prior to NMR analysis to remove fine particulates from the samples such as those caused by remaining palladium. Salt form can play a role in the quality of data obtained - the sodium salt was chosen as it is more soluble in aqueous solution, which is crucial for biological studies, but the NMR data can be of lower quality than with other salts such as ammonium or triethylammonium. Organic salts such as triethylammonium mask the phosphate charge enough to allow the phospholipids into organic deuterated solvents such as mixtures of CDCl$_3$ and D$_4$-MeOD, giving sharper peaks in NMR spectra.\(^{41}\)

### 5.5 Deuterated PtdIns Derivatives

With the synthesis of PtdIns 13 and PtdIns(4,5)$P_2$ 10 complete with dipalmitoyl lipid chains (Scheme 5.10), work began on the deuterated analogues. A robust route was available toward the D$_6$-tetratroc derivative (±)-165 (Chapter 4), and the Trost chemistry was possible on the deuterated material, thus the same route as for the protonated analogue was performed using deuterium-enriched material (Scheme 5.11). As deuterium enrichment is batch dependent, the incorporation in this batch was slightly lower than the first batch described (ca. 84% D$_6$, 16% D$_5$, traces $\leq$ D$_4$ cf 90% D$_6$, 10% D$_5$ in Chapter 4),
Scheme 5.11  Route toward deuterated analogues D₆-PtdIns 230 and D₆-PtdIns(4,5)P₂ 85 with 84% D₆, 16% D₅ incorporation. Red asterisks indicate deuterated carbon atoms. *Reagents & conditions* i. ROH 119, tetrahexylammonium bromide, [Pd(η₃-allyl)Cl]₂, (S,S)-ligand (-) 84, 1 M aqueous NaOH, CH₂Cl₂, 2 h, 79%; ii. 1:9 v/v TFA/CH₂Cl₂, 3 h then benzyl 2,2,2-trichloroacetimidate, TfOH, 1,4-dioxane, 66 h, 76%; iii. Zn, AcOH, THF, 1 h, 64%; iv. NaH, DMF, 10 min then PMBCl, 1 h, 59%; v. NaIO₄, RuCl₃·3H₂O, MeCN, H₂O, 6 min, 66%; vi. 3,4-Dihydro-2H-pyran, pyridinium p-toluenesulfonate, CH₂Cl₂, 24 h; vii. NaH, DMF, 15 min then BnBr, 18 h, 24% (two steps); viii. 80% v/v Aqueous AcOH, 55 °C, 2 h, 86%; ix. Phosphoramidite 231 (Scheme 5.8), 1H-tetrazole in MeCN, CH₂Cl₂, 18 h, then mCPBA, 2 h; x. DDQ, CH₂Cl₂, H₂O, 1 h 53% (two steps); xi. H₂, Pd Black, NaHCO₃, H₂O, ¹BuOH, 24-48 h; xii. Bis(benzyloxy) N,N-diisopropylphosphoramidite, 1H-tetrazole in MeCN, 6 h then mCPBA, 2 h, 22%.
however, this was still sufficient for our purposes. As with the previous synthetic route that had been taken as far as a myo-inositol derivative, no loss of deuterium was observed by mass spectrometry or $^1$H NMR analysis during any of the synthetic steps. Due to the lack of protons for structural assignment, the spectra were compared to the protonated analogues in order to confirm the correct compound had been synthesised and isolated. This was particularly important in the case of the THP protection to afford (–)-226 and on to (–)-227 (Scheme 5.11) where two potential regioisomers could be isolated. Due to the lack of protons on the myo-inositol ring, the structures were best analysed by comparing the $^{13}$C NMR spectra of the protonated (–)-213 vs deuterated (–)-227 compounds (Figure 5.11). With all compounds, the $^{13}$C NMR spectra could be overlaid and the signals matched, with the exception of the deuterated carbon atoms where a small upfield shift was observed (see Chapter 4 for full details). No significant kinetic isotope effect was observed during any of the reactions. Following through to the conclusion of the synthetic route led to the fully protected derivatives D$_6$-PtdIns (+)-228 and D$_6$-PtdIns(4,5)P$_2$ (–)-229 in similar yields to the protonated route, with the deuterium enrichment retained throughout (84% D$_6$, 16% D$_5$, Scheme 5.11).

### 5.5.1 Deprotection of Deuterated Analogues

As with the protonated analogues (+)-218 and (–)-219 (Scheme 5.10), the deprotection of the D$_6$ analogues (+)-228 and (–)-229 was attempted using hydrogenolysis (Scheme 5.11). It was challenging to analyse the reactions and determine the end point of the reaction due to the many potential intermediates, therefore the reactions were left for 48 h (cf 24 h for (+)-218 and (–)-219) in order to ensure completion of the reactions as it was hypothesised there could potentially be a kinetic isotope effect from the deuterium atoms on the ring. Following the standard workup for these reactions and lyophilisation of the aqueous solutions, attempts were made to analyse the resulting products. Interestingly, the products did not behave in a similar manner to the protonated analogues in that the same deuterated solvent systems (1:1 CD$_2$Cl$_2$/D$_4$-MeOD for 230 and D$_2$O for 85) would not dissolve the products. Furthermore, analysis of the products by high resolution mass spectrometry indicated that the same mass was observed in both samples (815.5592 and
815.5564, respectively, [M–H]− 230). This suggested that both samples contained some D₆-PtdIns 230. As no high quality NMR data could be obtained on either sample due to the reluctance of the products to dissolve in any solvent system, including three component mixtures as described earlier, the reaction was repeated on (–)-229 to attempt to synthesise D₆-PtdInsP₂ 85 again. In this attempt, the reaction was only left for 24 h, as had been done with the protonated analogue (–)-219. Once again, the product from the reaction was not soluble in D₂O. Analysis of this sample by high resolution mass spectrometry (ES⁻) revealed a number of masses which could be attributed to the D₆-myo-inositol ring by the distinctive isotope incorporation (85% D₆, 15% D₅, Figure 5.12 and Table 5.1).

As can be seen in the mass spectrometry data, many hydrolysis products were observed, which can be assigned with high degree of certainty given the use of a high resolution method. This did not provide evidence to when this hydrolysis had occurred, given that

Figure 5.11 Overlay of ¹³C NMR spectra for the protonated analogue (–)-213 (top, red) vs the deuterated analogue (–)-227 (blue, bottom), showing the carbon signals directly compare for the two compounds. A small upfield shift is observed for the deuterated carbons (zoomed section).
5.5. DEUTERATED DERIVATIVES

CHAPTER 5. BENZYL PROTECTION

![Chemical structure](image)

**Figure 5.12** High resolution mass spectrum (ES$^-$) of the product from deprotection of (−)-229 (Scheme 5.11), with peaks highlighted as shown by Table 5.1. Multiple peaks consistent with hydrolysis products could be assigned with a high degree of certainty. See table for assignment.

**Table 5.1** Masses observed in the high resolution mass spectrum (ES$^-$) of the product from deprotection of (−)-229. A small peak could be observed for the [M-2H]$^{2-}$ where M is the structure shown above (R = PO$_3$H$_2$, 85), however, many hydrolysis products could also be observed.

<table>
<thead>
<tr>
<th>Mass Detected</th>
<th>Species</th>
<th>Expected Mass</th>
<th>Abundance</th>
<th>% of Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>368.1261</td>
<td>[M−COC$<em>{15}$H$</em>{31}$−H]$^{2-}$</td>
<td>368.1260</td>
<td>8596121</td>
<td>100</td>
</tr>
<tr>
<td>447.2575</td>
<td>[M−PO$_3$H−2H]$^{2-}$</td>
<td>447.2576</td>
<td>741520</td>
<td>8.6</td>
</tr>
<tr>
<td>487.2409</td>
<td>[M−2H]$^{2-}$</td>
<td>487.2408</td>
<td>397993</td>
<td>4.6</td>
</tr>
<tr>
<td>577.3266</td>
<td>[M−COC$<em>{15}$H$</em>{31}$−2(PO$_3$H)]$^{-}$</td>
<td>577.3265</td>
<td>470889</td>
<td>5.5</td>
</tr>
<tr>
<td>657.2929</td>
<td>[M−COC$<em>{15}$H$</em>{31}$−PO$_3$H]$^{-}$</td>
<td>657.2929</td>
<td>418196</td>
<td>4.9</td>
</tr>
<tr>
<td>737.2593</td>
<td>[M−COC$<em>{15}$H$</em>{31}$]$^{-}$</td>
<td>737.2592</td>
<td>306354</td>
<td>3.6</td>
</tr>
<tr>
<td>759.2414</td>
<td>[M−COC$<em>{15}$H$</em>{31}$−H+Na]$^{-}$</td>
<td>759.2412</td>
<td>332836</td>
<td>3.9</td>
</tr>
<tr>
<td>781.2231</td>
<td>[M−COC$<em>{15}$H$</em>{31}$−2H+2Na]$^{-}$</td>
<td>781.2231</td>
<td>344914</td>
<td>4.0</td>
</tr>
<tr>
<td>815.5566</td>
<td>[M−2(PO$_3$H)−H]$^{-}$</td>
<td>815.5562</td>
<td>959204</td>
<td>11.1</td>
</tr>
<tr>
<td>895.5219</td>
<td>[M−(PO$_3$H)−H]$^{-}$</td>
<td>895.5225</td>
<td>165105</td>
<td>1.9</td>
</tr>
<tr>
<td>917.5047</td>
<td>[M−(PO$_3$H)−2H+Na]</td>
<td>917.5045</td>
<td>138402</td>
<td>1.6</td>
</tr>
</tbody>
</table>
it could be during the reaction, during isolation or during preparation and running of the mass spectrometry. The same sample preparation and method of mass spectrometry was used for this sample compared to the protonated analogue 10 and no significant fragmentation was observed in the mass spectrum of 10, suggesting it was likely to have occurred during the reaction or subsequent isolation. At this point, it was discovered that Ghosh and Sherman had reported the attempted synthesis of D₆-(±)-myo-inositol 1-phosphate. During their work, they reported the efficient synthesis of H₆-(±)-myo-inositol 1-phosphate with hydrogenolysis under acidic conditions as a final deprotection step with a 95% yield. Conversely, it was reported by Ghosh and Sherman that when the reaction sequence was attempted on the D₆-myoinositol 1-phosphate derivative “for unknown reasons, repeated attempts to perform this reaction on [²H₆]myo-inositol resulted in yields of 10% or less.”

From this statement, it is likely that the authors experienced a similar result to that we observed here. These results suggest there may potentially an inherent instability in phosphate groups attached to deuterated myo-inositol. The same paper did synthesise a mixture of the mono-phosphates (both using protonated and deuterated myo-inositol) and analysed the mixture by GCMS, with similar proportions of the monophosphate isomers observed both with deuterated and protonated myo-inositol. No attempt was made by the authors to isolate any of these products in pure form. Examples could be found of the synthesis of phosphate groups neighbouring a deuterated carbon with the phosphate on a primary hydroxyl group, however, few examples exist of phosphates on secondary hydroxyl groups adjacent to deuterated carbon atoms, and even fewer still for phosphates on carbocycles, especially with multiple sites of deuteration close to the phosphate. In addition, PtdIns 13 and PtdIns(4,5)P₂ 10 are known to be susceptible to hydrolysis normally in aqueous solution and this may be exacerbated by the incorporation of deuterium onto the ring. Several groups have reported the use of D₆-myoinositol 90 in media for biological studies, however, only D₆-PtdIns was analysed and not any PtdInsₚₜ. Further work is required to understand these effects in order to produce the required probes, by potentially using more simple systems (e.g. D₆-myoinositol 1-phosphate) to
study the effects of deuterium incorporation onto carbocycles affecting the hydrolysis of phosphate groups. Time limitations prevented this work from being carried out.

5.6 Conclusions

Starting from the tetratroc derivative (±)-82, a route was developed that led to enantiopure PtdIns 13 and PtdIns(4,5)P₂ 10 with saturated lipid chains by the use of a benzyl protecting group strategy (Scheme 5.12). A key part of this methodology avoided the need to use extensive regioselective protection of the hydroxyl groups on myo-inositol by building up the structure from a conduritol B scaffold, with only a single regioselective step requiring control in the synthesis. Hydrogenolysis of the fully protected scaffold, as with previous literature, led to the sodium salts of the two products 13 and 10. This same methodology was then applied to D₆-myo-inositol derivatives with some success, leading to the fully protected D₆-PtdIns (+)-228 and D₆-PtdIns(4,5)P₂ (–)-229 derivatives. Unfortunately, at this stage it was found that hydrogenolysis of the compounds appeared to lead to cleavage of the phosphate esters, meaning pure products could not be isolated. This is similar to results reported on D₆-myo-inositol phosphate derivatives previously reported. Further work is required to understand the hydrolysis of the phos-
phates in simpler and more easily managed systems to explore possible routes to generate
D$_6$-myo-inositol derivatives.
Chapter 6

Unsaturated Lipid Protection

Strategy

6.1 Introduction

With the synthesis of PtdIns 13 and PtdIns(4,5)P_2 10 achieved with saturated lipid chains, focus turned to the synthesis of PtdIns(4,5)P_2 derivatives with unsaturated lipids. These compounds are important targets because the most common lipids found in mammalian PtdInsP_n are stearic acid (18:0) and arachidonic acid (20:4). The saturated lipids had been used first as the deprotection conditions for saturated systems (hydrogenolysis) limits the need for purification of the PtdInsP_n, however, hydrogenolysis is not compatible with the arachidonic acid lipid. Developing a route to remove protecting groups in the presence of the hydrolytically unstable phospholipid group is particularly challenging. As has already been described in Chapters 2 and 5, proximity-assisted benzoate derivatives

![Figure 6.1](target-molecule-unsaturated-lipid-chains.png)

**Figure 6.1** Target molecule incorporating unsaturated lipid chains onto the glycerol backbone.
6.2 Use of Proximity Assisted Protecting Groups

6.2.1 Synthesising a Fully Protected PtdIns(4,5)P₂ Derivative

Starting from (+)-175, synthesised using the Trost asymmetric allylic alkylation, it was possible to synthesise a fully protected PtdIns(4,5)P₂ precursor (+)-237 (Scheme 6.1) in an analogous manner to that described for the benzoate derivative (+)-98 (Chapter 3). The synthesis of the TBDPS analogue was attempted first (cf. the PMB analogue, Figure 2.8, Chapter 2) as there were some concerns regarding the stability of the PMB derivative during the removal of the Troc groups using AcOH. In this manner, the synthesis
of (+)-237 was achieved (Scheme 6.1) in 21% yield over five steps. The acetate protecting group was used in the first instance on the 2-position, despite the fact that it was not possible to remove in previous synthetic endeavours. This is because the installation of the acetate onto the 2-position was high yielding, allowing for rapid evaluation of the proximity-assisted protecting groups (cf the THP protecting group strategy, Chapter 5).

6.3 Deprotection of PtdIns(4,5)P$_2$ Derivative

6.3.1 Deprotection of Phosphates

Once the synthesis of (+)-237 had been achieved, deprotection conditions were required to afford PtdIns(4,5)P$_2$ 10. The 2-cyanoethyl groups were exchanged for TMS esters by stirring overnight at room temperature with Barton’s base (2-$t$-butyl-1,1,3,3-tetramethylguanidine) in the presence of TMSCl overnight.$^{189}$ The deprotection of the cyanoethyl groups was monitored using $^{31}$P NMR, as the shift of the phosphorus peaks is diagnostic when silyl esters are produced (Table 6.1).$^{189}$ The resulting solid from the reaction was suspended in Et$_2$O and filtered, as this removed the majority of the insoluble Barton’s base as the HCl salt, making subsequent analysis and purification of crude material easier. Following this, the crude was stirred in MeOH to remove the TMS esters.

<table>
<thead>
<tr>
<th>Species</th>
<th>$^{31}$P NMR Shift / ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO$^-$P$^\text{OC}$$^\text{Cne}$</td>
<td>-3</td>
</tr>
<tr>
<td>RO$^-$P$^\text{OTMS}$</td>
<td>-11</td>
</tr>
<tr>
<td>RO$^-$P$^\text{OTMS}$</td>
<td>-19</td>
</tr>
</tbody>
</table>

Table 6.1 Indicative shifts (in CDCl$_3$) of phosphate esters in $^{31}$P NMR during deprotection.$^{189}$

<table>
<thead>
<tr>
<th>Species</th>
<th>$^{31}$P NMR Shift / ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMSO$^-$$^\text{P}$$^\text{OTMS}$</td>
<td>-25</td>
</tr>
<tr>
<td>RO$^-$P$^\text{O}$</td>
<td>-3.0</td>
</tr>
<tr>
<td>RO$^-$P$^\text{OH}$</td>
<td>0.5</td>
</tr>
</tbody>
</table>
### Scheme 6.2
Deprotection scheme attempted for deprotection of the (+)-237 to afford PtdIns(4,5)P$_2$ derivatives with unsaturated lipid chains. *Reagents & conditions*: i. Barton’s base, trimethylsilyl chloride, CH$_2$Cl$_2$, 18 h; ii. MeOH, 1 h; iii. 1:9 TFA/CH$_2$Cl$_2$, 18 h.

### Figure 6.2
Deprotection of the 2-cyanoethyl groups (see Scheme 6.2) was monitored by $^{31}$P NMR analysis in CDCl$_3$, as the $^1$H NMR becomes increasingly complicated as more deprotection steps are carried out. Top (purple): starting material (+)-237; upper middle (green): TMS-protected (+)-238; lower middle (red): deprotonated (+)-239; bottom (blue): Protonated (+)-240. *Reagents & conditions*: Barton’s base, trimethylsilyl chloride, CH$_2$Cl$_2$, 18 h; ii. MeOH, 1 h; iii. 1:9 TFA/CH$_2$Cl$_2$, 18 h, not isolated.
6.3.2 Removal of Proximity-Assisted Benzoate Derivatives

Once the phosphate groups had been deprotected, the next step was to remove the proximity-assisted protecting groups. Previous literature suggested that the TBDPS-protected species such as 241 could be deprotected using strongly acidic conditions, or using sources of fluoride. While both sets of conditions should be tolerated by the unsaturated lipid chains, the acidic conditions were attempted first as previous experience in the group suggested that fluoride sources in combination with phosphate esters can be problematic. To find suitable conditions for the deprotection, compounds containing the TBDPS-benzoate group were used as model substrates for (+)-237, in particular (+)-175 and (+)-233 (Scheme 6.1).

Trimethylsilyl bromide (TMSBr) in MeOH as an anhydrous source of HBr has been successful in removing silyl ethers from alkyl alcohols by Shah et al. In addition, the acid would likely promote rapid ring closing, in order to effect complete deprotection (Scheme 6.3). When these conditions were investigated using (+)-233 with two equivalents of TMSBr, complete deprotection of the two proximity-assisted protecting groups to give (+)-60 was observed overnight at room temperature (Figure 6.3), as determined by $^1$H NMR analysis. The reaction proceeded significantly faster using a 1:9 ratio of TMSBr/MeOH, with complete conversion observed in under an hour. The product of this reaction was not purified, however, the crude $^1$H NMR data were consistent with the expected products. Phthalide 243 was produced, as can be seen by comparing the crude $^1$H NMR to an authentic sample of 243 (Figure 6.3), and there was an upfield...
shift of the protons on the conduritol B ring, consistent with loss of the ester groups. Interestingly, the crude reaction mixtures produced very clean spectra. After three hours with two equivalents of TMSBr (middle spectrum, Scheme 6.3), the only two conduritol B derivatives observed were the starting material (+)-233 and the product (+)-60. No significant amount of intermediates were observed, suggesting the slowest step is removal of the first TBDPS group and subsequent removal of the second group is significantly faster. As these conditions appeared to work on a test system, the conditions were used on the full system 239.
Using TMSBr in MeOH 1:9 for 1 h with 239 (Scheme 6.2), indicated that deprotection had occurred by $^1$H NMR analysis, with production of phthalide 243 observed. There were still three strong signals by $^{31}$P NMR analysis, suggesting no migration of the phosphate groups nor the production of other phosphate byproducts. Further analysis by $^1$H-$^{31}$P HMBC and $^1$H-$^1$H COSY correlation experiments suggested, however, that while two peaks of the $^{31}$P signals were associated with the inositol ring ($P$-4 and $P$-5, Scheme 6.4), the third signal was only associated with the glycerol chain and not the inositol ring.

Using mass spectrometry analysis, it was apparent that acid-mediated transesterification of the 1-phosphate had occurred under the conditions, leading to 244 and 245 (ES$^+$, [M+H]$^+$ 663.56, expected 663.48 for 245, Scheme 6.4). Reanalysis of the $^1$H-$^{31}$P HMBC data showed a correlation between a doublet (due to $^{31}$P-$^1$H coupling) at 4.51 ppm in the $^1$H NMR and one of the phosphorus peaks, providing more evidence for this hypothesis.

As treatment with TMSBr in MeOH had resulted in methanolysis of the phosphate ester, different solvent conditions were considered to prevent the transesterification. Li et al. had described the use of different forms of proximity assisted protecting groups with PMB-protected hydroxyl groups (cf the TBDPS moiety). With the PMB-protected analogues, it was possible to deprotect the groups under anhydrous solvent conditions using a 1:9 mixture of TFA in CH$_2$Cl$_2$. In the test system using (+)-175 (Figure 6.3), the conditions proved successful, with conversion to product in an hour. These conditions
were therefore investigated for the deprotection of 239. Stirring 239 (Scheme 6.2) in 1:9 TFA/CH₂Cl₂ for 1 h resulted in a mixture of compounds that were difficult to analyse by NMR and mass spectrometry techniques (Figure 6.4). When the crude mixture was sus-
pended in CDCl₃, filtered and ¹H NMR analysis was undertaken on the filtrate, phthalide 179 was present in the sample, indicating that some deprotection of the proximity-assisted protecting groups had occurred (Figure 6.4).

![Chemical structure](image)

**Figure 6.4** Comparison of the ¹H NMR spectra in D₄-MeOD of an authentic sample of phthalide 179 (top, red) vs. the crude reaction mixture after stirring (+)-239 in a 1:9 mixture of TFA in CH₂Cl₂ for 1 h (bottom, blue). This shows at least a partial deprotection could be achieved.

Ion-exchange column chromatography was used to purify the samples in order to determine the outcome of these reactions. Diethylaminoethyl (DEAE) sepharose gel was effective at purifying PtdInsP_n in previous work from other research groups.⁴⁸,¹³⁶,¹⁹¹ Tri-ethy lammonium bicarbonate (TEAB) buffer was chosen for elution, as it can be prepared by bubbling CO₂ gas through an aqueous solution of NEt₃, while the buffer can be re-
moved post-column by lyophilisation. Elutions were performed first with THF to remove organic impurities, then aqueous solutions of TEAB up to a maximum concentration of 2 M. From the THF flush, phthalide 179 was isolated, providing further evidence that some deprotection had occurred. Upon lyophilisation of all the aqueous fractions, some solid was observed in fractions around 1.0 M to 1.2 M TEAB, as expected for a pentacharged species (when compared to literature concentrations that had previously been documented). Interestingly, upon $^1$H NMR analysis of the solid dissolved in D$_2$O (Figure 6.5), it was immediately apparent that complete deprotection of 239 had not occurred. There were broad peaks in the $^1$H NMR spectrum between 7 and 8 ppm, indicative of aromatic protons still remaining in the sample (Figure 6.5). There were several hypotheses for the presence of these peaks in the purified sample:

1. Complete deprotection had occurred and the ion-exchange had been unsuccessful in removing the aromatic impurities (TBDPS debris).

2. Only partial deprotection had occurred, potentially as a result of short reaction times.

3. A stronger acid was required to protonate the phosphates prior to deprotection of the proximity-assisted protecting groups.

4. Deprotection of the proximity-assisted protecting groups had been successful, producing phthalide in the process, however, the TBDPS groups had transferred on to one or more of the free hydroxyl groups on the inositol system or onto the phosphate groups.

The first hypothesis was tested by repeating the reaction and ion-exchange purification, using a slower gradient of buffer, but the same result was observed. It is unlikely that the aromatic residues would be retained by the resin as the TBDPS debris is uncharged. In addition, the use of THF to wash the resin prior to elution with aqueous buffers prevented issues of solubility of the TBDPS or phthalide debris in aqueous solvents. This wash was likely to have removed all uncharged protecting group debris, which was confirmed by
6.3. DEPROTECTIONS

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Figure 6.5  Selected region of $^1$H NMR spectrum in D$_2$O (with water suppression) of the residue isolated after ion-exchange column chromatography in the 1.0 M and 1.25 M TEAB fractions, revealing the presence of residual aromatic resonances in the spectrum.

$^1$H NMR analysis of the THF fractions. The potential for the debris to be trapped by the lipids of the product (as micelle formation occurs at higher concentrations of PtdIns(4,5)P$_2$) was thought to be low, as the ability of the product 10 to form micelles in a polar organic solvent such as THF is likely to be much lower than in aqueous solution.$^{192}$ Repeating the deprotection of (+)-239 with TFA/CH$_2$Cl$_2$ mixtures for 48 h, including the use of a 1:1 TFA/CH$_2$Cl$_2$ mix, or the use of 2 M HCl in Et$_2$O/CH$_2$Cl$_2$, were also unsuccessful.

6.3.3 Test Systems to Understand the Deprotection

To begin to understand the complex deprotection, several test systems were investigated to probe which groups are tolerated by the proximity assisted protecting groups. Conditions were initially found using the conduritol B derivative (+)-175 (Scheme 6.5), however, the proximity-assisted protecting groups in this system were masking allylic alcohols, rather than the secondary alcohols found in myo-inositol derivatives. Using a sample of
(+)-175, a syn-dihydroxylation was performed to form the myo-inositol derivative (+)-246 (Scheme 6.5). Upon treatment with 1:9 TFA in CH₂Cl₂, complete deprotection was observed in one hour. In the ¹H NMR spectrum, production of phthalide 243 was observed, while a shift upfield of the two peaks for H-3 and H-6 was observed, consistent with the removal of esters. Post-purification, ¹H NMR analysis (in D₆-DMSO) showed that no aromatic residues were present and the hydroxyl protons were observed, therefore no migration of the TBDPS groups onto the inositol ring had occurred (Scheme 6.5).

In addition, the TBDPS groups had not migrated onto phosphorus in (+)-240, as ³¹P NMR analysis showed the phosphorus signals to be around 0 ppm (cf. TMS groups, Table 6.1). Given that the proximity-assisted groups could be removed from the inositol ring in (+)-246, but not in (+)-239, it was possible that some form of neighbouring...
group participation of the two free hydroxyl groups may be assisting in the deprotection of (+)-246 (cf. phospholipid hydrolysis, Chapter 5). To test this hypothesis, the two free hydroxyl groups were protected with Troc groups to give (+)-247 and the same deprotection conditions were used on this system. Once again, complete deprotection was observed in 1 hour (Scheme 6.6). These results disproved all but hypothesis three.

![Scheme 6.6 Protection of the two hydroxyl groups in (+)-246 with Troc groups gave a second test system with no free hydroxyl groups adjacent to the proximity-assisted protecting groups (+)-247. Upon stirring in TFA and CH₂Cl₂, complete deprotection of the proximity assisted groups was observed in one hour, as observed by ¹H NMR analysis in CDCl₃. Top (green): (+)-246; Middle (red): (+)-247; Bottom (blue): (+)-248. Reagents & conditions: i. TrocCl, DMAP, pyridine, CH₂Cl₂, 18 h, not isolated; ii. TFA, CH₂Cl₂:9, 1 h, not isolated.]

As deprotection was achieved in two systems not containing a phosphate group, a third test system was considered. This system would lead to Ins(1,4,5)P₃ 249, such that problems caused by the lipid chains in 10 could be eliminated as a cause. The free hydroxyl group in (+)-236 was phosphorylated to give a fully protected Ins(1,4,5)P₃ derivative (+)-
In a similar manner to previous deprotections of PtdIns$P_n$ derivatives, the phosphate groups were deprotected first. The resulting material was then stirred in a 1:9 mixture of TFA and CH$_2$Cl$_2$, initially for 1 h. Analysis of the crude material by $^{31}$P NMR and $^1$H NMR suggested that deprotection was incomplete, therefore the material was left for a further 24 h under these conditions. Isolation of an inositol product from the crude post-reaction was possible using DEAE/TEAB ion-exchange chromatography. Interestingly, as the buffer concentration was increased to around 1.25 M TEAB, foaming of the aqueous solution was noticed at the base of the column. This had been experienced when working with the PtdIns$P_2$ system and was expected for phospholipids - the charged phosphates in combination with the lipid chains made for an amphiphilic molecule that was detergent-like in aqueous solution. In the case of Ins(1,4,5)$P_3$ 249, foaming should not have been observed, as 249 is highly water soluble and not amphiphilic. The foaming suggested complete deprotection had not been accomplished, with the aromatic TBDPS protecting groups acting as the hydrophobic region in the amphiphile, and further deprotection was not achieved by increased reaction times. Furthermore, analysis of the purified sample by $^1$H NMR in D$_2$O revealed aromatic signals. No other inositol-like products were isolated from the ion exchange column.

Scheme 6.7  Synthesis of an Ins$P_3$ derivative (+)-250, leading to further understanding of the deprotection of the proximity assisted protecting groups. Reagents & conditions: i. 126, 3-4% 1H-tetrazole in MeCN, CH$_2$Cl$_2$, 18 h then mCPBA, −78 °C, then room temperature 1 h, 70%; ii. Barton’s base, TMSCl, CH$_2$Cl$_2$, 18 h; iii. MeOH, 1 h; iv. 1:9 TFA/CH$_2$Cl$_2$, 1-72 h.

### 6.3.4 Acidity of Phosphate Groups

When the deprotection conditions had been attempted on the Ins(1,4,5)$P_3$ derivative (+)-250, only partial deprotection was observed, therefore the lipids chain were unlikely to be preventing deprotection. Solubility of the phospholipids in CH$_2$Cl$_2$ once the phosphates
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had been deprotected was one possible explanation, however, no precipitate nor cloudiness in the reactions had been observed. Given the amphiphilic nature of these molecules, it was possible that micelles were forming preventing access of the acid to the protecting group. Repeating the reactions with either the Ins\(P_3\) derivative (+)-250 or PtdIns\(P_2\) derivative (+)-237 in 1:9 TFA/MeCN led to the same result. In addition, dilution of the reactions ten-fold, while keeping the same 1:9 ratio of TFA to CH\(_2\)Cl\(_2\) or MeCN, had no impact.

In the test systems that had achieved full deprotection (Scheme 6.5, Scheme 6.6), the compounds (+)-246 and (+)-247 had been uncharged. This suggests a protonation event of the proximity-assisted protecting group under strongly acidic conditions was rapid. In the systems using either the PtdIns(4,5)\(P_2\) derivative (+)-237 or Ins(1,4,5)\(P_3\) derivative (+)-250, the pK\(_a\) of the free phosphates is low. For a phosphate monoester group, the pK\(_a\) of the first deprotonation is ca 1.5, while the second is ca 6.3 in aqueous solution (Figure 6.6).\(^{193}\) The pK\(_a\) of TFA is 0.65 in aqueous solution.\(^{194}\) In our molecules, one of the protecting groups requiring removal is proximal to one phosphate group (3-position) while the second is proximal to two phosphate groups (6-position, Figure 6.6). It is possible that the pKa of the phosphate groups means that they remain partially charged, even under the acidic conditions provided by the TFA. While the equilibrium lies toward the phosphates being protonated in the presence of TFA, there are multiple phosphate groups so the probability that all three phosphates are uncharged at any one point in solution is small. For the 3-position, having one phosphate moiety in proximity is tolerated as there will likely be occasions where the phosphate group is uncharged, allowing protonation and deprotection of the ester. With the 6-position, however, there requires an extra protonation event to occur at the 1-position. This situation reduces the probability of both neighbouring phosphates to the 6-position being uncharged at the same time, therefore deprotection at the 6-position could potentially be slow. Attempts to confirm, by NMR analysis, that the remaining proximity-assisted protecting group was placed at the 6-position was unsuccessful due to small amounts of material and broaden-
ing of the signals. The acidity theory was supported by the fact that Ins(4,5)P$_2$ had been obtained when TMSBr in MeOH caused methanolysis of the lipid chain, removing the second neighbouring phosphate to the 6-position and allowing complete deprotection (Scheme 6.4).

![Diagram](image)

**Figure 6.6** Phosphate monoesters have two pK$_a$ values, 1.5 and 6.3 in aqueous solution, for the two protons. For the deprotection of the proximity assisted protecting groups, it is likely that the phosphates need to be non-charged for the reaction to be successful. On the 6-position, where the group is flanked by two phosphates, this is unlikely to be achieved in solution, even under strongly acidic conditions.

### 6.3.5 Other Deprotection Conditions

As acidic methods to remove the proximity-assisted protecting groups had proved unsuccessful, it was necessary to consider other methods. Tetrabutylammonium fluoride had been avoided as it is difficult to obtain completely dry and is highly basic when in the presence of water.\textsuperscript{195} It was used in the test system successfully with (+)-175, however, it did indeed lead to hydrolysis of the glycerol phosphate when applied to the full system (+)-239. Use of other conditions to remove the TBDPS group, such as HF·NEt$_3$ or HF·pyridine, were unsuccessful with no reaction occurring. Several attempts were made to remove the proximity assisted protecting groups prior to deprotection of the phosphates, however, multiple new phosphate peaks were observed by $^{31}$P NMR analysis. This suggested the phosphate triester groups were migrating during the reaction, as expected when adjacent to a free hydroxyl group under acidic conditions.

### 6.3.6 Other Future Protecting Group Strategies

Given the lack of success with a TBDPS-protected derivative, other systems were considered, however, due to time constraints they were not fully explored. An alternative
proximity assisted protecting group that has been much more widely used in “normal”
sugar chemistry is a levulinic acid derivative (Lev, 251, Scheme 6.8). This group has also
been applied in inositol chemistry by Watanabe et al. on multiple occasions, when syn-
thesising PtdIns(3,4,5)P_3 19 and PtdIns(3,5)P_2 18. The Lev group can be removed
using hydrazine under buffered conditions, forming a non-polar six-membered product
that can be removed by trituration. Levulinic acid was used in the Trost asymmetric
allylic alkylation, however, the high water solubility of sodium levulinate prevented the
original conditions from Trost et al. from being used (Chapter 2). To improve the
reaction conversion, the concentration of the nucleophile was increased two-fold by using
2 M aqueous NaOH, halving the aqueous solvent volume. Even with this increased con-
centration, the reaction required 18 h (cf. 1 h for previous reactions) and did not reach
complete conversion to the di-substituted product (+)-118 (Scheme 6.8). This could po-
tentially be a useful observation for future work, as the mono-substituted product would
be a useful intermediate in synthesising other PtdInsP_n, for instance PtdIns(3)P and
PtdIns(3,4,5)P_3 19 (Scheme 6.10).

\[
\text{Lev} = \begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{TrocO} \\
\text{TrocO}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{TrocO} \\
\text{TrocO}
\end{array} \\
\begin{array}{c}
\text{OTroc} \\
\text{OTroc}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{O} \\
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\begin{array}{c}
\text{Lev} \\
\text{Lev}
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\]

\[ \text{Reagents & conditions: i. Levulinic acid, (S,S)-ligand (-)-84, [Pd(η^3-allyl)Cl]_2, tetrahexylammonium bromide, 1 M aq. NaOH, CH}_2\text{Cl}_2, 24 h, 57\%; ii. Zn, 80\% aq. AcOH, THF, 1 h, 92\%}. \]

Scheme 6.8 Alternative protecting groups to TBDPS proximity assisted protecting
group. PMB protection in place of the TBDPS is likely to lead to a similar problem in deprotection of a fully protected derivative. Levulinoyl (Lev) groups have been used in previous synthesis, however, they are prone to be highly polar making working with these intermediates more challenging. Reagents & conditions: i. Levulinic acid, (S,S)-
ligand (-)-84, [Pd(η^3-allyl)Cl]_2, tetrahexylammonium bromide, 1 M aq. NaOH, CH}_2\text{Cl}_2, 24 h, 57\%; ii. Zn, 80\% aq. AcOH, THF, 1 h, 92\%.

6.4 Conclusions

While a novel route toward PtdIns(4,5)P_2 with unsaturated chains was developed as far
as generating a fully protected derivative (+)-237, deprotection of this species was unsuc-
cessful. The use of proximity assisted protecting groups remains an interesting concept.
In this case, it had proved difficult to remove the groups when two free phosphates were
neighbouring to the proximity-assisted protecting group. There are multiple possibilities for future work to generate unsaturated lipid derivatives by this method with careful choice of protecting group, such that the phosphate groups are no longer a problem. While the PMB-analogue had been avoided at first, a few structures were made with this group, which seemed to suggest they were not as unstable as initially thought. This may be interesting in that there are many different conditions for removing PMB groups that do not rely on acidity, namely oxidative methods such as DDQ or ceric ammonium nitrate that could be conducive to unsaturated lipid chains. These conditions may open up the potential for these groups to be used successful in the synthesis of PtdInsP\textsubscript{n} with unsaturated lipid chains. Other protecting groups using a proximity-assisted deprotection mechanism could be incorporated into the synthesis, such as Levulinic acid derivatives. While slower to react in the Trost asymmetric allylic alkylation, they provide a two-fold improvement. Watanabe \textit{et al.} have already shown that it is possible to remove these groups in the presence of unsaturated systems\textsuperscript{88,169} This approach would enable rapid, efficient synthesis of deuterated PtdIns(4,5)P\textsubscript{2} with unsaturated lipid chains. Secondly, the Lev group opens the potential for reliably synthesising a mono-protected derivative (\(\text{+})\textsuperscript{255}\) from the Trost asymmetric allylic alkylation. With a derivative such as this, other PtdInsP\textsubscript{n} derivatives could be efficiently synthesised using this methodology.
6.5 Summary & Future Work

A route starting from \( p \)-benzoquinone 77 toward a single enantiomer of PtdIns 13 and PtdIns(4,5)\( P_2 \) 10 with C\(_{16} \) saturated lipid chains has been developed. The key enantioselective step used a palladium-catalysed Trost asymmetric allylic alkylation as a dynamic kinetic resolution to afford a single enantiomer of a conduritol B derivative. Protecting group manipulation gave fully protected PtdIns and PtdIns(4,5)\( P_2 \) derivatives that were deprotected using hydrogenolysis to give PtdIns 13 and PtdIns(4,5)\( P_2 \) 10 (Scheme 6.9). With the endogenous analogues of 13 and 10 synthesised, work towards deuterated ana-

Scheme 6.9  Summary of the work achieved. An enantioselective route toward PtdIns 13 and 10 was possible, with hydrogenolysis as a final step. A route toward D\(_6\)-PtdIns 230 and D\(_6\)-PtdIns(4,5)\( P_2 \) was developed giving fully protected systems (+)-228 and (−)-229, however, the final deprotections led to hydrolysis of the phosphates. A by-product of the deuterated route was a new synthesis of D\(_6\)-myo-inositol 90 that was possible on large scale.
logues was attempted. A novel route to D$_6$-myo-inositol 90 was developed based on the route developed for PtdIns 13 and PtdIns(4,5)P$_2$ 10 in 12% overall yield from quinol 153 with $>$85% D$_6$, remaining D$_5$ C-perdeuteraion. This D$_6$-myo-inositol synthesis 90 will be invaluable for synthesising large quantities of material for using in biological studies. From this route, a synthesis of D$_6$-PtdIns 230 and D$_6$-PtdIns(4,5)P$_2$ 85 was developed, however, the final step (hydrogenolysis) was unsuccessful.

With the synthesis of the endogenous molecules 13 and 10 complete, the next step would be to understand the final hydrogenolysis of (+)-228 and (–)-229 more thoroughly (Scheme 6.9), in order to unravel at which point the hydrolysis of the final D$_6$ products is occurring. This could be achieved by using test systems such as 257, which are easier to synthesise, and thus the deprotection could be optimised on a simpler system (Scheme 6.10). If it is found that the phosphates on a deuterated ring are more susceptible to hydrolysis, other suitable systems such as phosphothioates could be used.\textsuperscript{143} Once this is complete, the route could be extended to allow for a synthesis that includes unsaturated lipid chains. This may be done either by developing the Lev route, discussed briefly in Chapter 6 (Scheme 6.8), or by exchanging the benzyl groups for PMB groups and global deprotection by TMSBr (Scheme 6.10).\textsuperscript{196}
Scheme 6.10  Possible future work based on the work described. First, the hydrogenolysis of D₆-myoinositol phosphate derivatives requires further work to understand possible hydrolysis of the phosphates (shown in box). Once this is possible, unsaturated lipid chain derivatives could be synthesised using either of the two routes pictured, either using Lev groups or PMB groups.
Chapter 7

Experimental

7.1 General Experimental

$^1$H NMR spectra were measured on a Bruker AVIIIHD 400 nanobay (400 MHz), Bruker AVIIIHD 500 (500 MHz), Bruker AVII 500 (500 MHz) with He cryoprobe or and AVIII 700 (700 MHz) with inverse TCI cryprobe spectrometer in the stated solvents as a reference for the internal deuterium lock. The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where $\delta$(TMS) = 0.00. The spectra are calibrated using the solvent peak with the data provided by Fulmer et al. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); qn (quintet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); qt (quartet of triplets), m (multiplet) or combinations thereof. The number of protons ($n$) for a given resonance signal is indicated by $nH$. Where appropriate, coupling constants ($J$) are quoted in Hz, are recorded to the nearest 0.1 Hz and were determined by analysis using Bruker TopSpin v3.2 software. Spectra were assigned using COSY, NOESY, HSQC and HMBC experiments as necessary.

$^{13}$C NMR spectra were measured on a Bruker AVIIIHD 400 nanobay (101 MHz), Bruker AVIIIHD 500 (126 MHz) or Bruker AVII 500 (126 MHz) with He cryoprobe spectrometer in the stated solvents as a reference for the internal deuterium lock using either the standard $^{13}$C experiment or a DEPTQ pulse sequence with broadband proton decoupling.
The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where $\delta$(TMS) = 0.00. The spectra are calibrated using the solvent peak with the data provided by Fulmer et al.\textsuperscript{197} Signals are quoted to 1 decimal place unless peaks are indistinguishable, in which case 2 decimal places are used. The multiplicity of each signal is singlet unless indicated by: d (doublet); t (triplet); q (quartet); qn (quintet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); qt (quartet of triplets), m (multiplet) or combinations thereof. A subscript D (e.g. t\textsubscript{D}) indicates splitting caused by an $I = 1$ nucleus such as deuterium and as such splitting intensities are as for $I = 1$ nucleus (e.g. t\textsubscript{D} = 1:1:1 split). Where appropriate, coupling constants ($J_P$ for $^{31}$P coupling and $J_D$ for $^2$H coupling) are quoted in Hz, are recorded to the nearest 0.1 Hz and were determined by analysis using Bruker TopSpin v3.2 software. Spectra were assigned using HSQC and HMBC experiments as necessary.

$^{31}$P NMR spectra were measured on a Bruker AVIIIHD 400 nanobay (162 MHz) or Bruker AVIIIHD 500 (202 MHz) spectrometer in the stated solvents as a reference for the internal deuterium lock with broadband proton decoupling. The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to 85\% phosphoric acid as an external reference where $\delta$(H\textsubscript{3}PO\textsubscript{4}) = 0.00 ppm. Signals are singlets unless otherwise stated. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); qn (quintet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); qt (quartet of triplets), m (multiplet) or combinations thereof. Where appropriate, coupling constants ($J$) are quoted in Hz, are recorded to the nearest 0.1 Hz and were determined by analysis using Bruker TopSpin v3.2 software. Spectra were assigned using $^1$H-$^{31}$P HMBC experiments as necessary.

$^2$H NMR were measured on a Bruker AVII 500 (77 MHz) with He cryoprobe spectrometer spectrometer in the stated solvents using a single drop of the relevant deuterated
solvent as a reference for the internal deuterium lock. Signals are broad singlets. The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where $\delta$(TMS) = 0.00 ppm. The spectra are calibrated using the solvent peak with the data provided by Fulmer et al. Spectra are assigned based on the $^1$H shift of the relevant protonated compound.

**Mass spectra** were acquired on either an Agilent 6120 spectrometer, Waters LCT Premier (low resolution) or Bruker MicroTOF spectrometer (high resolution) using the ionisation method specified (ES: electrospray, E: electron, F: field desorption) from solutions of methanol, where $m/z$ values are reported in Daltons.

**Melting points** were determined using either a Leica Galen III hot stage microscope or a Griffin capillary tube melting point apparatus and are uncorrected.

**Infrared spectra** were obtained from neat samples, either as solids or liquids, using a diamond ATR module. The spectra were recorded on a Bruker Tensor 27 spectrometer. Absorption maxima are reported in wavenumbers (cm$^{-1}$) and reported as s (strong), m (medium), w (weak) or br (broad).

**Specific optical rotations** were measured using either a PerkinElmer Model 241 or Schmidt + Haensch UniPol L2000 polarimeter using a sodium lamp at 589 nm and a path length of 1.0 dm. The concentration (c) is expressed in g/100 mL (equivalent to g/0.1 dm$^3$). Specific rotations are denoted and are given in implied units of 10$^{-1}$ deg cm$^2$ g$^{-1}$ at the temperature stated.

**Analytical thin layer chromatography (TLC)** was carried out on normal phase Merck silica gel 60 F$\text{254}$ aluminium-supported chromatography sheets, unless otherwise stated. Visualisation was by absorption of UV light ($\lambda_{\text{max}}$ 254 nm) and thermal development after dipping in either an ethanolic solution of ninhydrin, an alkali aqueous solution
of potassium permanganate or an acidic aqueous solution of ceric ammonium molybdate.

**Celite® 545** was purchased from Sigma Aldrich as the sodium carbonate treated form, flux calcined.

**Silica gel flash column chromatography** was performed either manually using VWR Prolabo silica gel 60 (240-400 mesh) under a positive pressure of nitrogen or on a Biotage SP1 automated column chromatography system using KP-Sil® SNAP Flash Silica Cartridges. CV refers to the number of column volumes as set on the Biotage system.

**Petroleum Ether** refers to the fraction in the boiling point range 40-60 °C unless otherwise stated.

**In vacuo** refers to removal of solvent on a Buchi® rotary evaporator under reduced pressure in a water bath at 40 °C unless otherwise stated.

**Lyophilisation** was performed on a CHRIST Alpha 1-2 LD unit.

**Chemicals** were purchased from Acros UK, Apollo Scientific, Enamine, Sigma Aldrich UK, Alfa Aesar UK, Fisher UK, Fluka UK, Fluorochem, Merck, Argo International Limited or TCI-Europe and were as used as supplied unless otherwise stated.

**Deuterium Oxide and Sodium Borodeuteride** were purchased from Sigma Aldrich or Alfa Aesar and contained 99.9% D and 98% D incorporation respectively with the NaBD₄ of 90% chemical purity.

**Benzyloxy bis(N,N-diisopropyl)phosphoramidite 208** was prepared by Amelie Joffrin using the method of Johns *et al.* ⁵¹,¹⁵²
Anhydrous solvents were prepared from stocks by passing through a column of activated basic alumina as described by Grubbs et al.\textsuperscript{198} except in the cases of tetrahydrofuran which was distilled from sodium / benzophenone and \textit{N,N}-dimethylformamide which was purchased from Sigma Aldrich UK in a SureSeal\textsuperscript{®} bottle. In all other cases, solvents were used as supplied as HPLC or analytical grade.

**Analytical high-performance liquid chromatography (HPLC)** was performed on a PerkinElmer Flexar system with a Binary LC Pump and UV/VIS LC Detector set at 220 nm or 254 nm unless otherwise stated. For determination of enantiomeric purity (Chiral HPLC), a ChiralPak\textsuperscript{®} AD-H column (5 \( \mu \)m, 4.6 \( \times \) 150 mm) was employed using an isocratic method of 45 min at concentrations as stated. Samples were injected by dissolving in a 1:1 mixture of isopropanol/hexane. Flow rates are as indicated. For determination of general purity (NP-HPLC), a HyperSil Gold Silica normal phase column (5 \( \mu \)m, 4.6 \( \times \) 150 mm) was employed, using a gradient method of 30 min (detailed in Table 7.1) at concentrations as stated. Samples were injected by dissolving in either a 1:1 mixture of isopropanol/hexane or in neat CHCl\(_3\). Flow rates was kept constant throughout all runs at 1.0 mL min\(^{-1}\).

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**Deuterium atoms** attached to carbon atoms, where not explicitly stated in a chemical structure, are indicated by a red asterisk next to the relevant carbon atom.
Deuterium Incorporation of products is shown with the yield with the mass spectrometry techniques used to calculate the incorporation shown. All incorporations are $^{13}$C corrected.
7.2 Enantioselective Synthesis

(±)-trans-5,6-Dibromocyclohex-2-ene-1,4-dione ((±)-78)\(^67\)

![Chemical structure](image)

The procedure from Adelt \textit{et al.} was used.\(^67\) A solution of \(p\)-benzoquinone (5.4 g, 50 mmol, 1.0 eq.) in CHCl\(_3\) (150 mL) was cooled to 0 °C and bromine (2.58 mL, 50 mmol, 1.0 eq.) in CHCl\(_3\) (50 mL) was added, dropwise, over a period of 30 min at 0 °C via a dropping funnel. The solution was stirred at 0 °C for 1 h producing a bright red solution. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The solvent was removed \textit{in vacuo} to afford the title compound as a light yellow solid (13.4 g, 100%) which was used without further purification: \(R_f\) 0.54 (EtOAc/petroleum ether 1:4); m.p. 84-85 °C (from isopropanol) {lit.\(^67\) 82-83 °C}; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 6.72 (2H, t, \(J\) 0.8, \(H\)-2, \(H\)-3), 4.80 (2H, t, \(J\) 0.8, \(H\)-5, \(H\)-6); \(m/z\) (ES\(^–\)) 264.8 ([M\(^{79}\)Br\(_2\)–H]\(^–\), 51%), 266.8 ([M\(^{79}\)Br\(^{81}\)Br–H]\(^–\), 100%), 268.8 ([M\(^{81}\)Br\(_2\)–H]\(^–\), 47%). These data are in good agreement with the literature.\(^67\)

(±)-trans-5,6-Dibromocyclohex-2-ene-1,4-diol ((±)-79)\(^67\)

![Chemical structure](image)

The procedure from Adelt \textit{et al.} was used.\(^67\) A solution of (±)-78 (13.4 g, 50 mmol, 1.0 eq.) in Et\(_2\)O (225 mL) was cooled to –5 °C and a solution of NaBH\(_4\) (4.73 g, 125 mmol, 2.5 eq.) in water (75 mL) was added portionwise over a period of 10 min.
The resulting biphasic mixture was stirred vigorously for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The phases were separated and organic components were extracted using Et$_2$O (3 x 100 mL). The combined organic components were dried with MgSO$_4$, filtered, and concentrated in vacuo to afford the title compound as a colourless solid (10.99 g, crude), which was used without further purification. An analytical sample was prepared by crystallisation from 1:1 acetone/pentane: R$_{f}$ 0.32 (EtOAc/petroleum ether 1:2); m.p. 149-150 °C (from acetone/pentane) [lit.$^{67}$ 149 °C]; $^{1}$H NMR (400 MHz; D$_6$-acetone) δ 5.75 (2H, s, H-2, H-3), 4.89 (2H, dt, J 6.4, 1.1, O-H), 4.52 (2H, dd, J 5.4, 2.6, H-5, H-6), 4.23 (2H, dd, J 5.4, 2.6, H-1, H-4); m/z (ES$^-$) 268.6 ([M$^{79}$Br$_2$H$^-$], 71%), 270.6 ([M$^{79}$Br$^{81}$BrH$^-$], 100%), 272.6 ([M$^{81}$Br$_2$H$^-$], 82%). These data are in good agreement with the literature.$^{67}$

($\pm$)-(1RS,2SR,3SR,4RS)-Cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate

$^{80,109}$

A modification of the procedure from Guo et al. was used.$^{82}$ To a solution of ($\pm$)-79 (10.99 g, crude) in Ac$_2$O (300 mL) was added solid K$_2$CO$_3$ (34.6 g, 250 mmol, 6.0 eq. relative to p-benzoquinone) portionwise over 10 min at 0 °C. The reaction mixture was stirred for at room temperature for 2 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. Glacial AcOH (300 mL) was added and the reaction mixture was heated under reflux for 96 h. Mass spectrometry analysis of the reaction mixture showed the reaction was complete ([M+K]$^+$ = 337.1, no brominated species observed). The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting oil was suspended in saturated aqueous NaHCO$_3$
(200 mL) and the product was extracted using Et₂O (3 × 200 mL). The organic components were combined, dried with MgSO₄, filtered, and concentrated in vacuo. The resulting oil was azeotroped three times with cyclohexane. The crude was purified using silica gel flash column chromatography on a Biotage system using 5-40% EtOAc/petroleum ether. The product was crystallised by dissolving in boiling Et₂O, and dropwise addition of boiling petroleum ether until the solution was cloudy, followed by cooling to −20 °C for 1 h to afford the title compound as colourless needles (5.54 g, 35% over 3 steps): R_f 0.85 (Et₂O/petroleum ether 1:1); m.p. 84-85 °C (from Et₂O/petroleum ether), 88-89 °C (from EtOH) {lit.¹⁰⁹ 85-85.5 °C, lit.¹⁹⁹ 86-88 °C, lit.²⁰⁰ 92-93 °C}; ¹H NMR (400 MHz; CDCl₃) δ 5.73 (2H, s, H-5, H-6), 5.62 (2H, dd, J 5.5, 2.6, H-1, H-4), 5.36 (2H, dd, J 5.5, 2.6, H-2, H-3), 2.09 (6H, s, H-1'), 2.07 (6H, s, H-2'); m/z (ES⁺) 337.1 ([M+Na]⁺, 100%). These data are in good agreement with the literature.⁸⁰,¹⁰⁹

**Multistep Procedure from p-benzoquinone:**

To a solution of p-benzoquinone (10.8 g, 100 mmol, 1.0 eq.) in CH₂Cl₂ (300 mL) at 0 °C was added a solution of Br₂ (5.15 mL, 100 mmol, 1.0 eq.) in CH₂Cl₂ (100 mL) via a dropping funnel over a period of 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. After this time, the solution was concentrated in vacuo to afford a yellow solid ((±)-78). The solid was dissolved in Et₂O (450 mL), cooled to 0 °C and a solution of NaBH₄ (3.78 g, 100 mmol, 1.0 eq.) in H₂O (150 mL) was added dropwise via a dropping funnel over 1 h. The reaction mixture was stirred vigorously for a further 1 h at 0 °C. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The phases were separated and the organic components were extracted using Et₂O (3 × 300 mL), combined, dried with Na₂SO₄, filtered and concentrated in vacuo to afford a colourless solid ((±)-79). The solid was dissolved in Ac₂O (500 mL) and K₂CO₃ (69.2 g, 500 mmol, 5.0 eq.) was added, portionwise, over 30 min. The reaction suspension was stirred at room temperature for 2 h, after which time glacial AcOH (500 mL) was added. The reaction mixture was heated to reflux for 48 h, cooled, and concentrated in vacuo. Mass spectrometry analysis of the
reaction mixture ([M+K]$^+$ = 337.1, no brominated species observed) showed the reaction was complete. The resulting brown solid was partitioned between Et$_2$O (500 mL) and water (500 mL), and the organic components were washed with water ($2 \times 500$ mL), dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% EtOAc in petroleum ether, followed by crystallisation from EtOH to afford the title compound as colourless needles (9.98 g, 32% from $p$-benzoquinone). Data matched those given above.

X-ray crystallographic data for this compound can be found in the appendix (page 533).

$(\pm)-(1SR,2RS,3RS,4SR)$-Cyclohex-5-ene-1,2,3,4-tetrayl tetrakis(2',2',2'-trichloroethyl) tetracarbonate ((\pm)-82)$

The procedure from Trost et al. was used.$^{64,81}$ To a solution of $(\pm)$-81 (6.28 g, 20.0 mmol, 1.0 eq.) in a mixture of MeOH (70 mL) and water (30 mL) was added triethylamine (16.7 mL, 120 mmol, 6.0 eq.). The reaction mixture was stirred at room temperature for 3 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. After this time, the reaction mixture was concentrated in vacuo, azeotroped with toluene ($3 \times 50$ mL), and dried under high vacuum for 18 h. The resulting solid was placed under an atmosphere of N$_2$, suspended in anhydrous CH$_2$Cl$_2$ (100 mL), and 4-dimethylaminopyridine (1.22 g, 10.0 mmol, 0.5 eq.) and freshly distilled pyridine (9.7 mL, 120 mmol, 6.0 eq.) were added. The suspension was cooled to 0 °C, 2,2,2-trichloroethyl chloroformate (16.5 mL, 120 mmol, 6.0 eq.) was added, dropwise, over 5 min, and the reaction mixture was stirred at 0 °C for 2 h, during which time
the reaction mixture turned red. \(^1\)H NMR analysis of the reaction mixture showed the reaction was complete. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (100 mL) and the organic components were washed with water (100 mL), aqueous HCl (1 M, 100 mL), saturated aqueous NaHCO\(_3\) (100 mL), saturated aqueous NaCl, dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The resulting solid was suspended in boiling EtOH (ca. 250 mL), cooled to room temperature, and filtered to afford the title compound as a colourless solid (15.96 g, 94\%): R\(_f\) 0.36 (Et\(_2\)O/petroleum ether 1:2); m.p. 187-188°C (from Et\(_2\)O/petroleum ether) \{lit.\(^64\) 186°C\}; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.96 (2H, s, H-5, H-6), 5.65 (2H, dd, J 5.5, 2.4, H-1, H-4), 5.44 (2H, dd, J 5.5, 2.4, H-2, H-3), 4.84-4.74 (8H, m, H-7, H-8, H-9, H-10); HRMS m/z (ES\(^+\)) Found 840.6674 [M+H]\(^+\) (C\(_{18}\)H\(_{13}\)O\(_{12}\)Cl\(_{12}\) requires 840.6666). These data are in good agreement with the literature.\(^64\)

\((-\)-(1\(S\),2\(S\))-1,2-Bis(2-(diphenylphosphanyl)benzoylamino)cyclohexane (\((-\)-84)\(^\text{116}\)

\[
\text{\(-\)-(1\(S\),2\(S\))-1,2-Bis(2-(diphenylphosphanyl)benzoylamino)cyclohexane (\(-\)-84)\(^\text{116}\)
}

The procedure from Fuchs \textit{et al.} was used.\(^\text{116}\) A solution of diphenylphosphine benzoic acid (1.02 g, 3.33 mmol, 2.2 eq.), EDC·HCl (700 mg, 3.65 mmol, 2.4 eq.), 4-dimethylaminopyridine (181 mg, 1.50 mmol, 1.0 eq.) and (+)-(\(S\),\(S\))-1,2-diaminocyclohexane (175 mg, 1.50 mmol, 1.0 mmol) in CH\(_2\)Cl\(_2\) (25 mL) was stirred under an atmosphere of N\(_2\) at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. After this time, the solvent was removed \textit{in vacuo} to leave ca. 1 mL of solvent and the product was purified by silica gel flash column chromatography using 30\% EtOAc in petroleum ether under a flow of N\(_2\). The resulting glassy solid was triturated with minimal MeCN and filtered to afford
the title compound as a colourless solid (941 mg, 89%): \( R_f = 0.37 \) (petroleum ether/EtOAc 2:1); \([\alpha]^{20}_D = -58.9 \) (c 1.0, CHCl\(_3\)) \{lit.\(^{116}\) +55.6 ((\(R,R\))-enantiomer, c 2.3, CH\(_2\)Cl\(_2\))\}; m.p. 139-141 °C (from MeCN) \{lit.\(^{116}\) 134-136 °C\}; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 7.59-7.55 (2H, m, H-4), 7.32-7.18 (24H, m, H-5, H-6, H-8, H-9, H-10), 6.93-6.89 (2H, m, H-7), 6.29 (2H, d, \( J = 7.3 \), NH), 3.81-3.73 (2H, m, H-1), 1.90-1.82 (2H, m, H-2a), 1.68-1.60 (2H, m, H-2b), 1.27-1.15 (4H, m, H-3); \(^{31}\)P NMR (162 MHz; CDCl\(_3\)) \( \delta \) −9.69; m/z (ES\(^+\)) 691.3 ([M+H]\(^+\), 100%); Chiral HPLC (10% isopropanol/hexane isocratic, 1.0 mL min\(^{-1}\)) Retention Time = 6.6 min (−)-\(84\), > 99% e.e. (other enantiomer not observed, Retention Time = 20.9 min (+)-\(84\)). These data are in good agreement with the literature.\(^{116}\)

\((+)-(1R,2R)-1,2\)-Bis(2-(diphenylphosphanyl)benzoylamo)no)cyclohexane ((+)-\(84\))\(^{116}\)

\((+)-84\) was prepared in a similar manner to (−)-\(84\) using (−)-(\(R,R\))-1,2-diaminocyclohexane (135 mg, 1.18 mmol, 1.0 eq.) to afford the title compound as a colourless solid (417 mg, 51%): \([\alpha]^{20}_D = +57.8 \) (c 1.0, CHCl\(_3\)) \{lit.\(^{116}\) +55.6 (c 2.3, CH\(_2\)Cl\(_2\))\}; Chiral HPLC (10% isopropanol/hexane isocratic, 1.0 mL min\(^{-1}\)) Retention Time = 20.9 min (+)-\(84\), > 99% e.e. (other enantiomer not observed, Retention Time = 6.6 min (−)-\(84\). All other data (R\(_f\), LRMS, \(^1\)H NMR, m.p.) matched data for the opposite enantiomer (−)-\(84\). These data are in good agreement with the literature.\(^{116}\)

**General Procedure for Trost Asymmetric Allylic Alkylation**

Tetratroc (±)-\(82\) (1.0 eq.), nucleophile (1.8 or 3.5 eq.), ligand (−)-\(84\) (0.05-0.15 eq.), tetrahexylammonium bromide (0.2 eq.), and [Pd(\(\eta^3\)-allyl)Cl\(_2\)] (0.025 eq.) were degassed
on a Schlenk system (3 × N₂/vacuum cycles). CH₂Cl₂ followed by aqueous NaOH (1 M, 3.0 eq.) were added and the biphasic mixture was stirred vigorously for the stated length of time. After this time, the reaction mixture was diluted with saturated aqueous NaHCO₃ (20 mL) and the organic components were extracted with CH₂Cl₂ (20 mL × 2). The organic components were dried with MgSO₄, filtered through a plug of silica, and concentrated in vacuo. Conversions were calculated by ¹H NMR from the integrations of the crude mixture and comparing to isolated samples of the starting material (±)-82, the mono-reacted product (+)-104 and the di-reacted product (+)-83 (see appendix, page 278-280).

(+)-(1S,4S,5R,6R)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyldibenzoate ((+)-83)

A modification of the procedure from Trost et al. was used. Tetratroc (±)-82 (1.27 g, 1.50 mmol, 1.0 eq), BzOH (642 mg, 5.26 mmol, 3.5 eq.), (S,S)-ligand (–)-84 (154 mg, 0.222 mmol, 0.15 eq.), tetrahexylammonium bromide (129 mg, 0.30 mmol, 0.2 eq.), and [Pd(η³-allyl)Cl]₂ (14 mg, 0.04 mmol, 0.03 eq.) were degassed on a Schlenk system (3 × vacuum/N₂ cycles) and dissolved in CH₂Cl₂ (4.5 mL). Aqueous NaOH (1 M, 4.5 mL, 3.0 eq.) was added and the reaction mixture was stirred vigorously for 2 h. ¹H NMR analysis of the reaction mixture indicated the reaction was complete. Saturated aqueous NaHCO₃ (5 mL) was added and the product was extracted using CH₂Cl₂ (2 × 10 mL). The organic components were combined, and filtered under vacuum through a plug of silica. The filtrate was concentrated in vacuo to give a colourless oil. The product
was precipitated from cold MeOH (7 mL) and filtered to afford the title compound as a colourless solid (852 mg, 81%): \( R_f = 0.63 \) (EtOAc/petroleum ether 1:4); \( [\alpha]_{D}^{20} = +186.0 \) (c 1.0, CHCl\(_3\)) \{lit.\( ^{64} \) +177.1 (c 1.22, CHCl\(_3\))\}; m.p. 146-148 °C (from MeOH) \{lit.\( ^{64} \) 141-143 °C\}; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \): 8.03 (4H, dd, \( J = 8.4, 1.3 \), H-7, H-10), 7.59 (2H, tt, \( J = 7.5, 1.1 \), H-9, H-12), 7.45 (4H, tt, \( J = 7.5, 1.1 \), H-8, H-11), 5.98 (2H, dd, \( J = 5.3, 2.4 \), H-2, H-3), 5.96 (2H, s, H-5, H-6), 5.59 (2H, dd, \( J = 5.3, 2.4 \), H-1, H-4), 4.81 (2H, s, H-13a, H-14a), 4.67 (2H, d, \( J = 12.0 \), H-13b, H-14b); \( m/z \) (ES\(^-\)) 746.9 ([M\(^{35}\)Cl\(_6\)+formic acid–H\(^-\)], 45%), 748.9 ([M\(^{35}\)Cl\(_3\)\(^{37}\)Cl\(_3\)+formic acid–H\(^-\)], 100%), 750.9 ([M\(^{35}\)Cl\(_4\)\(^{37}\)Cl\(_2\)+formic acid–H\(^-\)], 94%), 752.9 ([M\(^{35}\)Cl\(_3\)\(^{37}\)Cl\(_3\)+formic acid–H\(^-\)], 31%); Chiral HPLC (10% isopropanol/heptane isocratic, 1.0 mL min\(^{-1}\)) Retention Time = 15.9 min (+)-83, > 99% e.e. (other enantiomer not observed, Retention Time = 33.3 min (–)-83) \{lit.\( ^{64} \) (ChiralPak\(^\circledR\) AD column, 10% isopropanol/heptane isocratic) Retention Time = 13.5 min (+)-83, Retention Time = 29.1 min (–)-83\}. These data are in good agreement with the literature.\( ^{64} \)

\((+)-(1S,4S,5S,6S)-5,6-Dihydroxycyclohex-2-ene-1,4-diyl dibenzoate\n((+)-94)\(^{64,81}\)

The procedure from Trost \textit{et al.} was used.\( ^{64} \) Zinc dust (677 mg, 10.4 mmol, 6.3 eq.) was suspended in a mixture of glacial AcOH (5 mL) and THF (5 mL). Compound (+)-83 (1.21 g, 1.7 mmol, 1.0 eq.) was added and the suspension was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (75 mL) and the organic components were washed with saturated aqueous K\(_2\)CO\(_3\) until effervescence was
no longer observed (3 × 30 mL). The organic components were dried with MgSO₄, filtered and concentrated *in vacuo*. The title compound was crystallised from 3:2 MeOH/water to afford the title compound as colourless needles (424 mg, 70%): Rf 0.54 (EtOAc/petroleum ether 1:1); [α]D²⁰ = +208.8 (c 1.0, CHCl₃) {lit. +206.8 (c 2.11, CHCl₃)}; m.p. 144-148 °C (from MeOH/water) {lit. 153 °C (from EtOAc/petroleum ether)}; ¹H NMR (400 MHz; CDCl₃) δ 8.08-8.11 (4H, m, H-7, H-10), 7.60 (2H, tt, J 7.5, 1.3, H-9, H-12), 7.47 (4H, t, J 7.5, H-8, H-11), 5.86 (2H, s, H-2, H-3), 5.71 (2H, dd, J 5.3, 2.5, H-5, H-6), 4.06 (2H, dd, J 5.3, 2.2, H-1, H-4), 3.27 (2H, br s, OH); m/z (ES⁺) 377.1 ([M+Na]⁺, 100%). These data are in good agreement with the literature.⁶⁴,⁸¹

(−)-(1S,4S,5R,6S)-5-Hydroxy-6-((R)-2-methoxy-2-phenylacetoxy)cyclohex-2-ene-1,4-diyl dibenzoate ((−)-108a)

A solution of (+)-⁹⁴ (50 mg, 0.14 mmol, 1.0 eq.), (−)-(R)-α-methoxyphenylacetic acid (23 mg, 0.14 mmol, 1.0 eq.), EDC·HCl (33 mg, 0.21 mmol, 1.5 eq.) and 4-dimethylamino-pyridine (8 mg, 0.07 mmol, 0.5 eq.) in CH₂Cl₂ (1 mL) was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:2 EtOAc/petroleum ether) indicated the reaction was complete. The solution was diluted with EtOAc (20 mL) and the organic components were washed with aqueous HCl (1 M, 10 mL), saturated aqueous NaHCO₃ (10 mL), and saturated aqueous NaCl (10 mL), dried with MgSO₄, filtered, and concentrated *in vacuo*. The product was purified by silica gel flash column chromatography on a Biotage system using 20% EtOAc in petroleum ether to afford the title compound as a colourless solid (32 mg, 46%): Rf 0.18 (EtOAc/petroleum ether 1:4); [α]D²⁰ = +148.6 (c
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1.0, CHCl$_3$; m.p. 131-133 °C (from CHCl$_3$); $\bar{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$ 2920 (C-H, w), 1753 (C=O, s), 1721 (C=O, s), 1601 (C=C, w), 1452 (C-C ar., w), 1365 (C-H alkyl, m), 1255 (C=O, s), 1217 (C-O, s), 1166 (C-O, s), 1109 (C-O, s), 1069 (C-O, s), 1027 (C-O, s);

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 8.05 (2H, d, $J = 7.4$, H-14), 7.94 (2H, d, $J = 7.4$, H-9), 7.58 (1H, t, $J = 7.4$, H-16), 7.56 (1H, t, $J = 7.4$, H-11), 7.49-7.34 (6H, m, H-10, H-15, H-21), 7.20-7.11 (3H, m, H-22, H-23), 5.89-5.71 (4H, m, H-1, H-2, H-3, H-6), 5.53 (1H, dd, $J = 8.3$, 10.8, H-5), 4.79 (1H, s, H-18), 4.12 (1H, t, $J = 9.1$, H-4), 4.79 (1H, t, $J = 9.1$, H-4), 3.32 (3H, s, H-19), 2.30 (1H, br s, O-H);

$^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 170.4 (C-17), 169.5 (C-12), 165.9 (C-7), 136.0 (C-20), 133.5 (C-16), 133.4 (C-11), 129.8 (C-9, C-14), 129.4 (C-8), 129.2 (C-13), 128.9 (C-23), 128.7 (C-22), 128.5 (C-10), 128.4 (C-15), 127.7 (C-1), 127.6 (C-2), 126.9 (C-21), 82.7 (C-18), 74.8 (C-3), 74.2 (C-5), 72.2 (C-4), 72.1 (C-6), 57.4 (C-19); HRMS m/z (ES$^+$) Found 525.1505 [M+Na$^+$] + (C$_{29}$H$_{26}$O$_8$Na requires 525.1520); m/z (ES$^+$) 525.1 ([M+Na$^+$], 100%); Chiral HPLC (30% isopropanol/heptane isocratic, 0.5 mL min$^{-1}$) Retention Time = 26.3 min, 96%.

(+)-(1$S,4S,5R,6S$)-5-Hydroxy-6-((S)-2-methoxy-2-phenylacetoxy)cyclohex-2-ene-1,4-diyldibenzooate ((+)-108b)

To prepare (+)-108b, the same procedure as 108a was performed using (+)-(S)-$\alpha$-methoxyphenylacetic acid on the same scale to afford the title compound as a colourless film (38 mg, 54%): $R_f$ 0.11 (EtOAc/petroleum ether 1:4); $[\alpha]_{D}^{20}$ = +182.8 (c 1.0, CHCl$_3$); $\bar{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$ 1759 (C=O, m), 1720 (C=O, s), 1602 (C=C, w), 1452 (C-C ar., w), 1264 (C-H alkyl, s), 1176 (C-O, s), 1108 (C-O, s), 1070 (C-O, s), 1027 (C-O, s); $^1$H NMR
(400 MHz; CDCl$_3$) δ 8.07 (2H, d, $J$ 8.3, $H$-14), 7.79 (2H, d, $J$ 8.3, $H$-9), 7.60 (1H, t, $J$ 7.6, $H$-16), 7.56 (1H, t, $J$ 7.6, $H$-11), 7.46 (2H, t, $J$ 7.6, $H$-15), 7.38 (2H, t, $J$ 7.6, $H$-10), 7.23 (2H, dd, $J$ 7.6, 1.7, $H$-21), 6.95-6.87 (3H, m, $H$-22, $H$-23), 5.83-5.77 (3H, m, $H$-1, $H$-2, $H$-3), 5.62-5.53 (2H, m, $H$-5, $H$-6), 4.82 (1H, s, $H$-18), 4.16 (1H, dd, $J$ 10.1, 8.0, $H$-4), 3.37 (3H, s, $H$-19), 2.99 (1H, br s, OH); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 170.8 ($C$-17), 166.9 ($C$-12), 165.5 ($C$-7), 135.5 ($C$-20), 133.6 ($C$-16), 133.3 ($C$-11), 129.92 ($C$-14), 129.85 ($C$-9), 129.4 ($C$-13), 129.0 ($C$-8), 128.5 ($C$-22, $C$-23), 128.4 ($C$-10), 128.3 ($C$-15), 127.8 ($C$-1), 127.5 ($C$-2), 126.6 ($C$-21), 82.2 ($C$-18), 75.4 ($C$-3), 73.9 ($C$-6), 72.4 ($C$-4), 72.0 ($C$-5), 57.4 ($C$-19); HRMS m/z (ES$^+$) Found 525.1511 [M+Na]$^+$ (C$_{29}$H$_{26}$O$_8$Na requires 525.1520); m/z (ES$^+$) 525.1 ([M+Na]$^+$, 100%); Chiral HPLC (30% isopropanol/heptane isocratic, 0.5 mL min$^{-1}$) Retention Time = 20.5 min, 96%.

2-(((4-Butyldiphenylsilyl)oxy)methyl)benzoic acid (119)$^{201}$

![Chemical Structure Image]

The procedure from Dagland et al. was used.$^{201}$ A solution of phthalide (2.68 g, 20.0 mmol, 1.0 eq.) and KOH (1.12 g, 20.0 mmol, 1.0 eq.) in MeOH (17 mL) and water (3 mL) was heated to reflux for 90 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to room temperature and the solution was concentrated in vacuo. The resulting oil was azeotroped with toluene (3 × 50 mL), resulting in a colourless solid. The solid was suspended in pyridine (50 ml) under an atmosphere of Ar, and imidazole (3.00 g, 44.0 mmol, 2.2 eq.) and 4-butyldiphenylsilyl chloride (11.3 mL, 44.0 mmol, 2.2 eq.) were added. The reaction mixture was stirred at room temperature for 24 h. After this time, the solution was diluted with saturated aqueous NaHCO$_3$ (200 mL) and the organic components were extracted with CH$_2$Cl$_2$ (3 × 150 mL), combined, dried with Na$_2$SO$_4$, filtered and concentrated in
The resulting oil was dissolved in a mixture of MeOH (200 ml) and THF (70 mL) and an aqueous solution of K$_2$CO$_3$ (7.0 g in 70 mL) was added causing a colourless precipitate to be observed. The suspension was stirred at room temperature for 1 h. After this time, the suspension was concentrated in vacuo to ca. one quarter of the original volume, and diluted with with saturated aqueous NaCl (200 mL). The organic components were extracted with Et$_2$O (6 × 100 mL), combined, dried with Na$_2$SO$_4$, filtered and concentrated in vacuo. The solid was crystallised from hexane to afford the title compound as colourless cubic crystals (6.29 g, 81%): R$_f$ 0.21 (EtOAc/petroleum ether 1:4); m.p. 155-156 °C (from hexane); $\nu$$_{\text{max}}$ (thin film)/cm$^{-1}$ 2929 (C-H, w), 2857 (C-H, w), 1686 (C=O, s), 1471 (C-C, m), 1426 (C-H ar., m), 1413 (C-C, m), 1267 (C-O, s), 1197 (C-H ar., s), 1106 (C-H ar., s), 1092 (C-H ar., s), 1059 (C-H ar., s); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 8.06 (1H, d, J 7.8, H-3), 7.95 (1H, d, J 7.9, H-6), 7.70 (4H, dd, J 7.8, 1.2, H-10), 7.63 (1H, t, J 7.9, H-4), 7.44-7.34 (7H, m, H-5, H-11, H-12), 5.17 (2H, s, H-8), 1.13 (9H, s, H-14); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 172.0 (C-1), 143.9 (C-7), 135.6 (C-10), 133.5 (C-4), 133.3 (C-9), 131.5 (C-3), 129.8 (C-12), 127.8 (C-11), 126.9 (C-6), 126.8 (C-5), 126.5 (C-2), 64.3 (C-8), 26.9 (C-14), 19.5 (C-13); m/z (ES$^-$) 389 ([M-H]$^-$, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 2.4 min, 98.1%. These data are in good agreement with the literature.$^{201}$
Tetratroc (±)-82 (848 mg, 1.0 mmol, 1.0 eq.), benzoic acid derivative 119 (1.37 g, 3.5 mmol, 3.5 eq.), [Pd(η^3-allyl)Cl]_2 (9.2 mg, 0.025 mmol, 0.025 eq), (S,S)-ligand (–)-84 (104 mg, 0.15 mmol, 0.15 eq.), and tetrahexylammonium bromide (86 mg, 0.2 mmol, 0.2 eq.) were degassed on a Schlenk system (3 × vacuum/N_2 cycles). CH_2Cl_2 (3.0 mL) followed by aqueous NaOH (1 M, 3.0 mL, 3.0 eq.) were added. The reaction mixture was stirred vigorously for 1 h. \(^1\)H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was diluted with saturated aqueous NaHCO_3 (50 mL) and the organic components were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic components were dried with MgSO_4, and filtered through a plug of silica. The silica was washed with CH_2Cl_2 (50 mL) and the filtrate was concentrated \textit{in vacuo}. The product was purified using silica gel flash column chromatography on a Biotage system using 2-20% EtOAc in petroleum ether, followed by crystallisation from EtOH to afford the title compound as a colourless solid (920 mg, 74%): R_t 0.79 (EtOAc/petroleum ether 1:4); [α]_D^{20} = +94.7 (c 1.0, CHCl_3); m.p. 138-142 °C (from EtOH); \(\tilde{\nu}\) max (thin film)/cm\(^{-1}\) 2959 (C-H, w), 2931 (C-H, w), 2858 (C-H, w), 1773 (C=O, m), 1720 (C=O, m), 1472 (C-C, w), 1428 (C-H ar., w), 1288 (C-O, s), 1244 (C-O, s), 1132 (C-O, s), 1113 (C-H ar., s), 1060 (C-H ar., s), 1012 (C-H ar., w); \(^1\)H NMR (400 MHz; CD_2Cl_2) δ 8.08 (2H, d, J 7.8, H-12), 7.97 (2H, dd, J 7.9, 1.1, H-9), 7.74-7.69 (8H, m, H-16),
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7.67 (2H, ddd, J 7.7, 7.7, 1.1, H-11), 7.48-7.37 (12H, m, H-17, H-18), 7.36 (2H, t, J 7.7, 7.7, H-10), 5.81 (2H, dd, J 5.3, 2.6, H-5, H-6), 5.69 (2H, s, H-2, H-3), 5.36 (2H, dd, J 5.4, 2.6, H-1, H-4), 5.19 (2H, d, J 16.0, H-14a), 5.14 (2H, d, J 16.0, H-14b), 4.73 (2H, d, J 12.0, H-22a), 4.61 (2H, d, J 12.0, H-22b), 1.14 (18H, s, H-20); 13C NMR (101 MHz; CD2Cl2) δ 165.7 (C-7), 153.7 (C-21), 144.8 (C-13), 135.9 (C-16), 133.81 (C-15a), 133.79 (C-15b), 133.75 (C-11), 131.1 (C-9), 130.21 (C-18a), 130.17 (C-18b), 128.18 (C-17a), 128.15 (C-17b), 127.4 (C-2, C-3), 127.0 (C-10), 126.8 (C-12), 125.8 (C-8), 94.6 (C-23), 77.2 (C-22), 76.3 (C-1, C-4), 71.9 (C-5, C-6), 64.5 (C-14), 27.1 (C-20), 19.6 (C-19); m/z (MALDI) 849.21 ([M-OBzCH2OTBDPS]+, 100%), 1261.54 ([M+Na]+, 6%); Chiral HPLC (1% isopropanol/hexane isocratic, 1.0 mL min⁻¹) Retention Time 10.7 min (+)-175, > 98% e.e., (other enantiomer Retention Time = 13.4 min (-)-175); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 2.3 min, 97.4%.

(−)(1R,4R,5S,6S)-5,6-Bis((2,2,2-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diy1 bis(2-(((t-butyldiphenylsilyl)oxy)methyl)benzoate) ((−)-175)

Compound (−)-175 was prepared in a similar manner to (+)-175 on 0.5 mmol scale (with respect to (±)-82) using (R,R)-ligand (+)-84 to afford (−)-175 as a colourless solid (309 mg, 50%): [α]D₂₀ = −93.5 (c 1.0, CHCl₃); Chiral HPLC (1% isopropanol/heptane, 1.0 mL min⁻¹) Retention Time 12.4 min (−)-175, > 98% e.e., (other enantiomer Retention Time = 9.4 min (+)-175). All other data (Rf, m.p., ¹H NMR, ¹³C NMR, IR, NP-HPLC)
matched data for the opposite enantiomer (+)-175.

(+)-(1S,2R,3R,4S)-2,3,4-Tris((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-5-en-1-yl pivalate ((+)-115)

Tetratroc (±)-82 (424 mg, 0.5 mmol, 1.0 eq.), pivalic acid (179 mg, 1.75 mmol, 3.5 eq.), [Pd(η³-allyl)Cl]₂ (4.6 mg, 0.0125 mmol, 0.025 eq.), (S,S)-ligand (–)-84 (52 mg, 0.075 mmol, 0.15 eq.), and tetrahexylammonium bromide (43 mg, 0.1 mmol, 0.2 eq.) were degassed using a Schlenk system (3 × vacuum/N₂ cycles). CH₂Cl₂ (1.5 mL) followed by aqueous NaOH (1 M, 1.5 mL, 3.0 eq.) were added and the reaction mixture was stirred vigourously for 1 h. ¹H NMR analysis of the reaction mixture indicated a 64% conversion to (+)-115, with 18% remaining of (±)-82 and 18% of the disubstituted product (+)-265. The reaction mixture was diluted with saturated aqueous NaHCO₃ (20 mL) and the product was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic components were dried with MgSO₄, filtered through a plug of silica and concentrated in vacuo to give a yellow oil. The product was purified using silica gel flash column chromatography on a Biotage system using 10% Et₂O in petroleum ether to afford the title compound as a colourless solid (123 mg, 33%): Rᵣ 0.53 (Et₂O/petroleum ether 1:4); [α]²⁰_D = +68.0 (c 1.0, CHCl₃); m.p. 127-128 °C (from H₂O); ʋ_max (thin film)/cm⁻¹: 1764 (C=O, s), 1737 (C=O, s), 1436 (C=C, s), 1384 (C-H, s), 1297 (C-O, s), 1268 (C-H, s), 1246 (C-O, s), 1229 (C-O, s), 1136 (C-O, s), 1068 (C-O, w), 1009 (C-O, w); ¹H NMR (400 MHz; CDCl₃) δ 5.85 (1H, ddd, J 10.4, 1.9, 1.9, H-4), 5.79 (1H, ddd, J 10.4, 1.9, 1.9, H-5), 5.68-5.59 (2H, m, H-3, H-6), 5.40 (1H, dd, J 11.2, 7.9, H-1), 5.34 (1H, dd, J 11.2, 7.9, H-2), 4.81-4.73 (6H, m, H-11,
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H-14, H-17), 1.78 (9H, s, H-8); 13C NMR (101 MHz; CDCl3) δ 177.5 (C-7), 153.3 (C-10, C-13), 153.2 (C-16), 128.4 (C-5), 125.7 (C-4), 94.1 (C-12), 94.05 (C-15), 93.98 (C-18), 77.1 (C-11, C-14), 77.0 (C-17), 76.1 (C-6), 75.60 (C-1), 75.56 (C-2), 70.9 (C-3), 38.8 (C-9), 26.9 (C-8); HRMS m/z (ES+) Found 769.8602 [M+35Cl9+NH4]+ (C20H25O11N35Cl9 requires 769.8619); m/z (ES+) 778.5* ([M+NH4]+, 100%).

* Multiple peaks were observed in the spectrum due to multiple combinations of 35Cl and 37Cl in the molecule hence the most prominent peak is given.

(+)-(3S,4R,5R,6S)-4,5,6-Tris(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-1-en-3-yl benzoate ((+)-104)

Tetratroc (±)-82 (424 mg, 0.5 mmol, 1.0 eq.), BzOH (214 mg, 1.75 mmol, 3.5 eq.), [Pd(η3-allyl)Cl]2 (4.6 mg, 0.013 mmol, 0.025 eq.), (S,S)-ligand (–)-84 (26 mg, 0.038 mmol, 0.075 eq.), and tetrahexylammonium bromide (43 mg, 0.1 mmol, 0.2 eq.) were placed under an atmosphere of nitrogen using Schlenk apparatus (3 × vacuum/N2 cycles). CH2Cl2 (1.5 mL) followed by aqueous NaOH (1 M, 1.5 mL, 3.0 eq.) were added and the biphasic mixture was stirred vigourously for 1 h. 1H NMR analysis of the reaction mixture indicated 38% starting material (±)-82, 43% monosubstituted (+)-104 and 19% disubstituted (+)-83. The reaction mixture was diluted with saturated aqueous NaHCO3 (10 mL) and the organic components were extracted with CH2Cl2 (3 × 10 mL). The combined organic components were washed with saturated aqueous NaCl (10 mL), dried with MgSO4, filtered through a plug of silica, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5% EtOAc in petroleum
ether. The resulting oil was dissolved in MeOH (ca. 5 mL) causing a colourless solid to precipitate which was filtered to afford the title compound as a colourless solid (81 mg, 21%): Rf 0.26 (Et2O/petroleum ether 1:4); [α]20D = +94.3 (c 1.0, CHCl3); m.p. 146-148°C (from MeOH); νmax (thin film)/cm⁻¹ 1762 (C=O, s), 1747 (C=O, s), 1722 (C=O, s), 1386 (C-H, w), 1337 (C-O, m), 1294 (C-H, s), 1245 (C-O, s), 1099 (C-O, w), 1068 (C-O, w), 1010 (C-O, w); ¹H NMR (400 MHz; CDCl3) δ 8.01 (2H, dd, J 8.6, 1.2, H-18), 7.59 (1H, tt, J 7.4, 1.4, H-20), 7.44 (2H, m, H-1, H-2, H-3), 6.01-5.88 (3H, m, H-1, H-2, H-3), 5.69-5.64 (1H, m, H-6), 5.55-5.44 (2H, m, H-4, H-5), 4.85-4.63 (6H, m, H-8, H-11, H-14); ¹³C NMR (101 MHz; CDCl3) δ 165.5 (C-16), 153.5, 153.3, 153.2 (C-7, C-10, C-13), 133.7 (C-20), 129.9 (C-18), 128.8 (C-17), 128.6 (C-19), 128.3 (C-2), 125.9 (C-1), 94.1, 94.0 (C-9, C-12, C-15), 77.1, 76.9 (C-8, C-11, C-14), 76.1 (C-6), 75.5, 75.4 (C-4, C-5), 71.8 (C-3); HRMS m/z (ES⁺) Found 789.8288 [M⁺Cl9+NH₄⁺]⁺ (C₂₂H₂₁⁺Cl₉N⁺O₁₁ requires 789.8306); m/z (ES⁺) 797.7⁺ ([M+NH₄⁺]⁺, 100%); Chiral HPLC (20% isopropanol/heptane, 0.5 mL min⁻¹) Retention Time = 22.6 min, 92.6%.

* Multiple peaks were observed in the spectrum due to multiple combinations of ³⁵Cl and ³⁷Cl in the molecule hence the most prominent peak is given.

2-(((4-Methoxybenzyl)oxy)methyl)benzoic acid (176)¹⁶⁸

![Chemical Structure](image-url)

The procedure from Li et al. was used.¹⁶⁸ A suspension of phthalide 243 (2.68 g, 20.0 mmol, 1.0 eq.), KOH (4.49 g, 80.0 mmol, 4.0 eq.), and p-methoxybenzyl chloride (6.78 mL, 50.0 mmol, 2.5 eq.) in toluene (70 mL) was heated under reflux for 48 h. After this time, the reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The aqueous soluble components were extracted using water (3 × 150 mL). The combined aqueous layers were acidified to pH 1 using aqueous HCl (1 M) causing a milky solution to form. The organic components were extracted with CH₂Cl₂ (3 ×
150 mL), combined, dried with Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the title compound as a colourless solid (5.47 g, 100%) that was used without further purification: R$_f$ 0.54 (EtOAc/petroleum ether 1:1); m.p. 101-103 °C (from CH$_2$Cl$_2$); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 8.08 (1H, dd, $J$ 7.5, 1.4, H-1), 7.67 (1H, d, $J$ 7.5, H-4), 7.58 (1H, ddd, $J$ 7.5, 7.5, 1.4, H-3), 7.40 (1H, ddd, $J$ 7.5, 7.5, 1.3, H-2), 7.32 (2H, dt, $J$ 8.8, 2.2, H-7), 6.90 (2H, dt, $J$ 8.8, 2.2, H-8), 4.93 (2H, s, H-5), 4.61 (2H, s, H-6), 3.81 (3H, s, H-9); m/z (ES$^+$) 295.0 ([M+Na]$^+$, 100%), (ES$^-$) 271.0 ([M–H]$^-$, 100%). These data are in agreement with the literature.$^{168}$

(+)-(3S,4S,5R,6R)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclo-hex-2-ene-1,4-diy1-bis(2-(((p-methoxybenzyl)oxy)methyl)benzoate) ((+)-253)

Tetratroc (±)-82 (2.36 g, 2.78 mmol, 1.0 eq.), (S,S)-ligand (−)-84 (289 mg, 0.35 mmol, 0.15 eq.), benzoic acid derivative 176 (2.65 g, 8.21 mmol, 3.5 eq.), tetrahexylammonium bromide (239 mg, 0.47 mmol, 0.2 eq.), and [Pd($\eta^3$-allyl)Cl]$_2$ (25.6 mg, 0.059 mmol, 0.025 eq.) were degassed on a Schlenk system (3 × vacuum/N$_2$ cycles). The solid was dissolved in CH$_2$Cl$_2$ (8 mL), aqueous NaOH (1 M, 8 mL, 3.4 eq.) was added and the reaction mixture was stirred vigorously at room temperature for 3 h. $^1$H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was diluted with saturated aqueous NaHCO$_3$ (50 mL) and the organic components were extracted using CH$_2$Cl$_2$ (3 × 30 mL). The combined organic components were dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 15% EtOAc in petroleum ether
to afford the title compound as a colourless oil (2.57 g, 92%): 

\begin{align*}
\text{Rf} & = 0.36 \text{ (EtOAc/petroleum ether 1:4)}; \\
\alpha_{25}^{\text{D}} & = +97.0 \text{ (c 1.0, CHCl}_3); \\
\nu_{\text{max}} & \text{ (thin film)/cm}^{-1} 1771 \text{ (C=O, m), 1720} \\
& \text{ (C=O, m), 1514} \text{ (C=C, w), 1288} \text{ (C-O, m), 1246} \text{ (C-O, s), 1174} \\
& \text{ (C-O, w), 1133} \text{ (C-O, w), 1065} \text{ (C-O, m), 1035} \text{ (C-O, m);} \\
^{1}\text{H NMR (400 MHz; CDCl}_3) & \delta 7.95 \text{ (2H, dd, } J = 7.8, 1.3, \text{ H-9, H-23), 7.74} \\
& \text{ (2H, d, } J = 7.8, \text{ H-12, H-26), 7.59} \text{ (2H, ddd, } J = 7.8, \\
& \text{ 7.8, 1.3, H-11, H-25), 7.37} \text{ (2H, dd, } J = 7.8, 7.8, \text{ H-10, H-24), 7.33} \\
& \text{ (4H, dt, } J = 8.7, 1.8, \text{ H-17, H-31), 6.91} \text{ (4H, dt, } J = 8.7, 1.8, \\
& \text{ H-18, H-32), 5.97} \text{ (2H, dd, } J = 5.3, 2.5, \text{ H-4, H-5), 5.87} \\
& \text{ (2H, s, H-1, H-2), 5.56} \text{ (2H, dd, } J = 5.3, 2.5, \text{ H-3, H-6), 4.95} \\
& \text{ (2H, d, } J = 14.4, \text{ H-14a, H-28a), 4.90} \text{ (2H, d, } J = 14.4, \text{ H-14b, H-28b), 4.81} \\
& \text{ (2H, d, } J = 12.0, \text{ H-36a, H-39a), 4.70} \text{ (2H, d, } J = 12.0, \text{ H-36b, H-39b), 4.57} \\
& \text{ (4H, s, H-15, H-29), 3.80} \text{ (6H, s, H-20, H-34);} \\
^{13}\text{C NMR (101 MHz; CDCl}_3) & \delta 165.7 \text{ (C-7, C-21), 159.3} \text{ (C-19, C-33), 153.5} \\
& \text{ (C-35, C-38), 141.7} \text{ (C-13, C-27), 133.0} \text{ (C-11, C-25), 130.7} \\
& \text{ (C-9, C-23), 130.5} \text{ (C-16, C-30), 129.3} \text{ (C-17, C-31), 127.7} \\
& \text{ (C-12, C-26), 127.2} \text{ (C-1, C-2), 127.0} \text{ (C-10, C-24), 126.8} \text{ (C-8, C-22), 113.7} \\
& \text{ (C-18, C-32), 94.2} \text{ (C-37, C-40), 76.9} \text{ (C-28, C-14), 76.0} \\
& \text{ (C-3, C-6), 72.5} \text{ (C-15, C-29), 71.7} \text{ (C-4, C-5), 69.9} \text{ (C-36, C-39), 55.3} \\
& \text{ (C-20, C-34); HRMS } m/z \text{ (ES}^+) \text{ Found 1025.0450} [\text{M+Na}^+] \text{ (C}_{44}\text{H}_{40}\text{Cl}_{6}\text{NaO}_{14} \text{ requires 1025.0441); } m/z \text{ (ES}^+) \text{ 1024.9} \\
& \text{ ([M}^{35}\text{Cl}_{6}+\text{Na}^+]^+, 50\%), 1027.0} \text{ ([M}^{35}\text{Cl}_{3}^{37}\text{Cl+Na}^+]^+, 100\%), 1028.9} \\
& \text{ ([M}^{35}\text{Cl}_{4}^{37}\text{Cl}_{2}+\text{Na}^+]^+, 87\%), 1030.9} \text{ ([M}^{35}\text{Cl}_{5}^{37}\text{Cl}_{3}+\text{Na}^+]^+, 47\%), 1032.9} \text{ ([M}^{35}\text{Cl}_{6}^{37}\text{Cl}_{4}+\text{Na}^+]^+, 13\%); Chiral HPLC} \\
& \text{ (50\% isopropanol alcohol/hexane, 1.0 mL min}^{-1}) \text{ Retention Time 38.7 min } (-)-253, > 99\%} \\
& \text{ e.e., (other enantiomer Retention Time = 52.1 min } (+)-253).
(-)-(3R,4R,5S,6S)-5,6-Bis((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclo-hex-2-ene-1,4-diyl-bis(2-((p-methoxybenzyl)oxy)methyl)benzoate) ((-)-253)

Compound (-)-253 was prepared in a similar manner to (+)-253 on 0.5 mmol scale (with respect to tetratroc (±)-82 using (R,R)-ligand (+)-84 to afford (-)-253 as a colourless foam (234 mg, 47%); [α]D20 = −104.1 (c 1.0, CHCl3); Chiral HPLC (50% isopropanol/hexane, 1.0 mL min⁻¹) Retention Time 52.1 min (-)-253, >96% e.e., (other enantiomer Retention Time = 38.7 min (+)-253). All other data (Rf, 1H NMR, 13C NMR, MS, NP-HPLC) matched data for the opposite enantiomer (+)-253.

(+)-(3S,4R,5R,6S)-4,5-Bis((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-3,6-diyl bis(levulinate) (((+)-118)

Tetratroc (±)-82 (1.38 g, 1.63 mmol, 1.0 eq.), levulinic acid (661 mg, 5.69 mmol, 3.5 eq.), (S,S)-ligand (−)-84 (170 mg, 0.25 mmol, 0.15 eq.), tetrahexylammonium bromide (140 mg, 0.32 mmol, 0.2 eq.), and [Pd(η³-allyl)Cl]2 (15.0 mg, 0.041 mmol, 0.025 eq.) were degassed
on a Schlenk system (3 × vacuum/N₂ cycles). The solid was dissolved in CH₂Cl₂ (5.0 mL) and aqueous NaOH (2 M, 2.4 mL, 4.8 mmol, 3.0 eq.) and the reaction mixture was stirred vigourously for 24 h. ¹H NMR analysis of the reaction mixture indicated a 54% conversion to (+)-118, with 32% mono-reacted (+)-263 and 14% starting material (±)-82. The reaction mixture was diluted with saturated aqueous NaCl (50 mL) and the organic components were extracted with CH₂Cl₂ (2 × 50 mL). The organic components were combined, dried with Na₂SO₄, filtered through a plug of silica, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 7-70% EtOAc in petroleum ether (30-40 boiling point range) to afford the title compound as a colourless oil (642 mg, 57%): Rf 0.74 (EtOAc/petroleum ether 1:1); [α]²⁵_D = +63.2 (c 1.0, CHCl₃); νmax (thin film)/cm⁻¹ 1772 (C=O, s), 1744 (C=O, s), 1718 (C=O, s), 1372 (C-O, m), 1282 (C-O, s), 1233 (C-O, s), 1150 (C-O, s); ¹H NMR (400 MHz; CD₂Cl₂) δ 5.72 (2H, m, H-3, H-6), 5.71 (2H, s, H-1, H-2), 5.27 (2H, dd, J 5.3, 2.5, H-4, H-5), 4.81 (4H, s, H-18, H-21), 2.72 (2H, t, J 6.4, H-8a, H-13a), 2.71 (2H, t, J 6.4, H-8b, H-13b), 2.50 (4H, t, J 6.4, H-9, H-14), 2.12 (6H, s, H-11, H-16); ¹³C NMR (101 MHz; CD₂Cl₂) δ 206.2 (C-10, C-15), 171.9 (C-17, C-20), 153.2 (C-7, C-12), 127.0 (C-1, C-2), 94.3 (C-19, C-22), 77.0 (C-18, C-21), 76.0 (C-4, C-5), 71.1 (C-6, C-3), 37.7 (C-8, C-13), 29.6 (C-11, C-16), 27.9 (C-9, C-14); HRMS m/z (E⁺) 660.8008 [M-CH₂CH₃]+ (C²⁰H₁₉Cl₆O₁₂ requires 660.9002). Enantiomeric excess of (+)-118 was determined to be > 99% by removal of the two Troc groups to give (+)-252, derivatisation with 2.2 eq. (−)-R-α-methoxyphenylacetic acid in the presence of EDC-HCl and analysis of the crude material by ¹H NMR.
To a solution of (+)-118 (642 mg, 0.93 mmol, 1.0 eq.) in THF (6 mL) and AcOH (6 mL) was added activated zinc powder (1.82 mg, 27.8 mmol, 33.0 eq.), and the reaction suspension was stirred vigorously for 1 h. TLC analysis of the reaction mixture (EtOAc) showed the reaction was complete. The suspension was diluted with EtOAc (100 mL), filtered through a plug of Celite®, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 0-10% MeOH in CH₂Cl₂ to afford the title compound as a colourless film (294 mg, 92%): Rᵢ 0.12 (EtOAc); [α]²⁵°D = +135.8 (c 1.0, CHCl₃); νᵥmax (thin film)/cm⁻¹ 3449 (O-H, m), 2924 (C-H, w), 1733 (C=O, s), 1715 (C=O, s), 1409 (C-H, m), 1365 (C-H, m), 1207 (C-O, m), 1157 (C-O, s), 1059 (C-O, m), 1031 (C-O, m); ¹H NMR (400 MHz; CD₂Cl₂) δ 5.61 (2H, s, H-1, H-2), 5.39 (2H, dd, J 5.4, 2.5, H-3, H-6), 3.77 (2H, dd, J 5.4, 2.5, H-4, H-5), 3.61 (2H, br s, OH), 2.78 (4H, t, J 6.4, H-9, H-14), 2.60-2.54 (4H, m, H-8, H-13), 2.16 (6H, s, H-11, H-16); ¹³C NMR (101 MHz; CD₂Cl₂) δ 207.3 (C-10, C-15), 172.8 (C-7, C-12), 127.5 (C-1, C-2), 74.3 (C-3, C-6), 73.5 (C-4, C-5), 38.0 (C-9, C-14), 29.6 (C-11, C-16), 28.2 (C-8, C-13); HRMS m/z (ES⁺) Found 365.1205 [M+Na]+ (C₁₆H₂₂O₈ requires 365.1212); m/z (ES⁻) 377.1 ([M+Cl]⁻, 13%), 387.1 ([M+HCO₂H–H]⁻, 100%), (ES⁺) 365.1 ([M+Na]+, 100%).
(+)-(1S,2R,3R,4S)-Cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate ((+)-81)\(^80\)

Tetracetate (±)-81 (314 mg, 1.0 mmol, 1.0 eq.), benzoic acid derivative 119 (585 mg, 1.5 mmol, 1.5 eq.), tetrahexylammonium bromide (86 mg, 0.2 mmol, 0.2 eq.), (R,R)-ligand (+)-84 (70 mg, 0.1 mmol, 0.1 eq.), and [Pd(η\(^3\)-allyl)Cl]\(_2\) (9.6 mg, 0.025 mmol, 0.025 eq.) were degassed on a Schlenk system (3 × vacuum/N\(_2\) cycles). CH\(_2\)Cl\(_2\) (3 mL) and aqueous NaOH (1 M, 3.0 mL, 3.0 mmol, 3.0 eq.) were added and the reaction mixture was stirred vigorously for 5 h. \(^1\)H NMR analysis of the reaction mixture indicated the reaction had reached 48% conversion to (–)-266 with 52% remaining starting material (+)-81. The reaction mixture was diluted with saturated aqueous NaHCO\(_3\) (25 mL) and the organic components were extracted with CH\(_2\)Cl\(_2\) (2 × 25 mL), combined, dried with Na\(_2\)SO\(_4\), filtered and concentrated \(\text{in vacuo}\). The product was purified using silica gel flash column chromatography on a Biotage system using 2-20% EtOAc in petroleum ether, followed by crystallisation from EtOH to afford the title compound as colourless plate-like crystals (72 mg, 23%): \(\alpha\)\(^{20}\)\(_D\) = +182.6 (c 1.0, CHCl\(_3\)) \{lit.\(^80\) –182 (enantiomer (–)-81, c 0.7, CHCl\(_3\))\}; m.p. 123-125 °C (from EtOH) \{lit.\(^80\) 117-118 °C\}. All other data (R\(_f\), LRMS, \(^1\)H NMR) matched data for the racemate (±)-81. These data are in agreement with the literature.\(^80\)
7.3 Deuterated myo-Inositol

2,3,5,6-Tetrabromoquinol (155)\textsuperscript{155,202}

The procedure from Head was used.\textsuperscript{155} Quinol (2.20 g, 50 mmol, 1.0 eq.) was suspended in AcOH (40 mL) and the suspension was cooled to 0 °C. To this suspension was added a solution of bromine (4.3 mL, 167 mmol, 3.3 eq.) in AcOH (10 mL), dropwise, via a dropping funnel over a period of 30 min. The reaction mixture was warmed to room temperature and stirred for 24 h. Water (10 mL) was added and the reaction was heated under reflux for 2 h. The resulting suspension was cooled to room temperature and the precipitate was filtered to afford the title compound as an orange solid (7.96 g, 93%): R\textsubscript{f} 0.32 (CH\textsubscript{2}Cl\textsubscript{2}); m.p. 242-243 °C (decomposed, from AcOH) \{lit.\textsuperscript{155} 243-244 °C, decomposed\}; \textsuperscript{1}H NMR (400 MHz; D\textsubscript{6}-DMSO) \(\delta\) 9.96 (2H, s, O\textsubscript{H}); \textsuperscript{13}C NMR (101 MHz; D\textsubscript{6}-DMSO) \(\delta\) 146.9 (C-OH), 115.9 (C-Br); m/z (ES\textsuperscript{-}) 421.6 ([M\textsuperscript{79}Br\textsubscript{4}–H]\textsuperscript{-}, 88%), 423.6 ([M\textsuperscript{79}Br\textsubscript{3}\textsuperscript{81}Br–H]\textsuperscript{-}, 100%), 425.6 ([M\textsuperscript{79}Br\textsubscript{2}\textsuperscript{81}Br\textsubscript{2}–H]\textsuperscript{-}, 92%), 427.6 ([M\textsuperscript{79}Br\textsubscript{3}–H]\textsuperscript{-}, 23%). These data are in good agreement with the literature.\textsuperscript{155,202}

2,3,5,6-Tetradeuteroquinol (156)\textsuperscript{158}

\textit{Method A}

A suspension of 155 (7.95 g, 18.7 mmol, 1.0 eq.) in D\textsubscript{2}O (50 mL) was heated under reflux
for 30 min. After this time, the suspension was cooled to room temperature and Pd/C (10% w/w, 710 mg, 0.67 mmol, 0.036 eq.) and powdered zinc dust (2.39 g, 36.5 mmol, 1.95 eq.) were added. The reaction mixture was heated under reflux for 4 h. Further zinc dust (1.19 g, 18.3 mmol, 0.95 eq.) was added to the reaction mixture and continued heating under reflux for 18 h. The reaction mixture was cooled to room temperature and was diluted with MeOH (50 mL). The suspension was filtered through Celite® followed by a plug of silica and the resulting filtrate was concentrated in vacuo to give a brown oil. The product was purified using silica gel flash column chromatography on a Biotage system using a 5-40% EtOAc in petroleum ether to afford the title compound as a brown crystalline solid (420 mg, 20%, > 95% D₄): R_f 0.51 (EtOAc/petroleum ether 1:1); m.p. 169-170 °C (from EtOAc) {lit.¹⁵⁸ 171-173 °C}; ν_max (thin film)/cm⁻¹ 3245 (O-H, w), 1409 (C=C, s), 1315 (C=C, m), 1220 (C-O, m), 1126 (C-O, s); ¹H NMR (400 MHz; D₆-DMSO) δ 8.63 (2H, s, OH); ¹³C NMR (126 MHz; D₆-DMSO) δ 150.1 (C-O), 115.8 (tD, J D 23.8, C-D); ²H NMR (77 MHz; DMSO; D₆-DMSO) δ 6.58; HRMS m/z (F+) Found 114.0621 [M]+ (C₆H₂O₂D₄ requires 114.0619); NP-HPLC (5-95% isopropanol/hexane) Retention Time = 4.8 min, 98.5%. These data are in good agreement with the literature.¹⁵⁸

Method B¹⁵⁸

The procedure from Desiraju et al. was used.¹⁵⁸ Acetyl chloride (40 mL, 56 mmol, 2.9 eq) was cooled to 0 °C in an ice bath and D₂O (20 mL, 111 mmol, 5.8 eq) was added, dropwise, over a period of 1 h (SLOWLY - care must be taken to avoid large release of HCl gas). The solution was stirred at 0 °C for 10 min then zinc powder (4.0 g, 61 mmol, 3.2 eq.) was added, portionwise, at 0 °C over a period of 10 min. Once addition was complete, quinol (2.1 g, 19 mmol, 1.0 eq.) was added to the solution and the reaction mixture was heated under reflux for 18 h. The solution was cooled to room temperature and water (80 mL) was added. The product was extracted with Et₂O (3 × 150 mL) and the combined organic components were was washed with saturated aqueous NaHCO₃ (3 × 50 mL), dried with MgSO₄, filtered, and concentrated in vacuo to afford the title compound as a colourless solid (1.81 g, 86%, D₄ 46%, D₃ 36%, D₂ 17%, D₁ < 1%, D₀ not observed). Full data was
not obtained on this partially deuterated sample.

Method C\textsuperscript{159}

The procedure from Zimmermann \textit{et al.} was used.\textsuperscript{159} A suspension of quinol (20.0 g, 18.1 mmol, 1.0 eq.) and D\textsubscript{2}SO\textsubscript{4} (1 mL, 96-98 wt.% in D\textsubscript{2}O, 99.5% D, 13.7 mmol, 0.75 eq.) in D\textsubscript{2}O (50 mL) was placed under an atmosphere of nitrogen and the reaction suspension was heated under reflux for 24 h. The reaction suspension was cooled to room temperature and the product was extracted using Et\textsubscript{2}O (3 × 100 mL). The combined organic extracts were dried with MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo} to give a colourless solid. This procedure was repeated (heated under reflux in fresh D\textsubscript{2}O and D\textsubscript{2}SO\textsubscript{4} followed by extraction) twice more to afford the title compound as a colourless solid (19.72 g, 95%, D\textsubscript{6} 93%, D\textsubscript{5} 7%). All other data matched earlier data.

2,3,5,6-Tetradeterobenzoquinone (157)\textsuperscript{160}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{2_3_5_6-Tetradeterobenzoquinone.png}
\caption{2,3,5,6-Tetradeterobenzoquinone (157)}
\end{figure}

The procedure from Ikemoto \textit{et al.} was used.\textsuperscript{160} To a solution of D\textsubscript{4}-quinol 156 (1.14 g, 10.0 mmol, 1.0 eq., > 95% D\textsubscript{4}) and iodine (126 mg, 1.0 mmol, 0.1 eq.) in isopropanol (5 mL) was added aqueous H\textsubscript{2}O\textsubscript{2} (35% w/w, 1.7 ml, 20 mmol, 2.0 eq.) and the solution was heated to 45 °C for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled in an ice bath for 30 min and the solid was filtered to afford the title compound as yellow needles (986 mg, 89%, > 95% D\textsubscript{4}): R\textsubscript{f} 0.59 (EtOAc/petroleum ether 1:4); m.p. 112-114 °C (sublimed, from isopropanol) \{lit.\textsuperscript{203} 113 °C (from H\textsubscript{2}O)\}; \bar{\nu}_{\text{max}} (thin film)/cm\textsuperscript{-1} 1638 (C=C, s), 1558 (C=C, m), 1264 (C=O, m), 1238 (C=O, m); \textsuperscript{2}H NMR (77 MHz; DMSO; D\textsubscript{6}-DMSO) \delta 6.87; \textsuperscript{13}C NMR (126 MHz; D\textsubscript{6}-DMSO) \delta 188.3 (C-O), 136.6 (t, J\textsubscript{D} 25.8,
CHAPTER 7. EXPERIMENTAL

7.3. D₆-MYO-INOSITOL

C-D); HRMS m/z (F⁺) Found 112.0462 [M⁺] (C₆D₄O₂ requires 112.0462). These data are in good agreement with the literature.¹⁶⁰,²⁰³

(±)-(1RS,2SR,3SR,4RS)-Cyclohex-5-ene-1,2,3,4-tetrayl-D₆ tetracetate ((±)-160)

A solution of D₄-benzoquinone 157 (2.90 g, 25.9 mmol, 1.0 eq., D₄ 93%, D₃ 7%) in CHCl₃ (75 mL) was cooled to 0 °C and a solution of bromine (1.33 mL, 25.9 mmol, 1.0 eq.) in CHCl₃ (75 mL) was added dropwise via a dropping funnel over a period of 2 h. The reaction mixture was stirred at room temperature for a further 1 h at 0 °C. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The solvent was removed in vacuo, the resulting yellow solid was dissolved in Et₂O (110 mL), and the solution was cooled to 0 °C. A solution of NaBD₄ (2.28 g, 54.4 mmol, 2.1 eq.) in D₂O (40 mL) was added, portionwise, over a period of 5 min with vigorous stirring. The reaction mixture was stirred vigorously at 0 °C for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The phases were separated and the organic components were extracted from the aqueous layer using Et₂O (2 × 100 mL), combined, dried with MgSO₄, filtered, and concentrated in vacuo. The resulting colourless solid (7.08 g) was dissolved in Ac₂O (75 mL) and K₂CO₃ (21.3 g, 154 mmol, 6.0 eq.) was added. The suspension was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. Glacial AcOH (75 mL) was added and the reaction mixture was heated under reflux for 45 h. Mass spectrometry analysis of the reaction mixture ([M+K]⁺ = 383.1, no brominated species observed) indicated the reaction was
complete. The reaction was cooled down to 0 °C, MeOH (50 mL) was added to quench Ac₂O and the reaction was stirred at 0 °C for 2 h. The reaction mixture was concentrated in vacuo (Büchi water bath at 60 °C) to give a brown oil. The product was purified using silica gel flash column chromatography using 20% EtOAc in petroleum ether followed by crystallisation from EtOH to afford the title compound as colourless crystals (2.40 g, 29% over three steps, D₆ 90%, D₅ 10%): Rₚ 0.16 (EtOAc/petroleum ether 1:4); m.p. 81-83 °C (from EtOH); νmax (thin film)/cm⁻¹ 1745 (C=O, s), 1431 (C-H, w), 1372 (C-H, m), 1241 (C-H, s), 1222 (C-H, s), 1196 (C-O, s), 1118 (C-O, m), 1091 (C-O, m), 1023 (C-O, s), 969 (C-H, m), 954 (C-D, m); ¹H NMR (400 MHz; CDCl₃) δ 2.05 (6H, s, H-8, H-14), 2.03 (6H, s, H-10, H-12); ¹³C NMR (126 MHz; CDCl₃) δ 170.3 (C-7, C-13), 169.9 (C-9, C-11), 127.0 (tₚ, Jₚ 25.2, C-5, C-6), 71.0 (tₚ, Jₚ 23.0, C-1, C-4), 70.8 (tₚ, Jₚ 23.0, C-2, C-3), 20.9 (C-8, C-14), 20.6 (C-10, C-12); ²H NMR (77 MHz; CHCl₃; D₆-DMSO) δ 5.65 (D-5, D-6), 5.48 (D-1, D-4), 5.22 (D-2, D-3); HRMS m/z (ES⁺) Found 342.1204 [MD₅+Na]⁺ (C₁₄H₁₃D₅O₈Na requires 342.1213), 343.1265 [MD₆+Na]⁺ (C₁₄H₁₂D₆O₈Na requires 343.1271); m/z (ES⁺) 342.1 ([MD₅+Na]⁺, 11%) 343.1 ([MD₆+Na]⁺, 100%).

myo-Inositol (1)²⁰⁴–²⁰⁶

To a vigorously stirred solution of (±)-81 (1.06 g, 3.37 mmol, 1.0 eq.) in MeCN (32 mL) was added a solution of NaIO₄ (1.08 g, 5.05 mmol, 1.5 eq.) and RuCl₃·3H₂O (45 mg, 0.17 mmol, 0.05 eq.) in H₂O (8 mL) and the mixture was stirred vigorously for 8 min. TLC analysis (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous Na₂S₂O₃ (10% w/v, 50 mL) was added and the organic components were extracted with EtOAc (3 × 100 mL), combined, dried with Na₂SO₄, filtered, and concentrated in vacuo. The resulting solid was dissolved in a mixture of MeOH (14 mL) and H₂O (6 mL), NEt₃
(5.64 mL, 40.4 mmol, 12.0 eq.) was added and the reaction solution was stirred at room temperature for 2 h. After this time, the reaction solution was concentrated \textit{in vacuo} to give a brown solid. The product was crystallised from 1:1 EtOH/H$_2$O, filtered and the crystals washed with Et$_2$O (20 mL) to afford the title compound as colourless needles (496 mg, 82%): $R_f$ 0.81 (1:1 EtOH/H$_2$O); m.p. 220-221 °C (from 1:1 EtOH/H$_2$O) \{lit.\textsuperscript{204} 220-221 °C (from aq. EtOH)\}; $^1$H NMR (400 MHz; D$_6$-DMSO) $\delta$ 4.56 (1H, d, $J$ 4.3, OH-5), 4.51 (2H, d, $J$ 4.5, OH-4, OH-6), 4.48 (1H, d, $J$ 3.1, OH-2), 4.36 (2H, d, $J$ 5.5, OH-1, OH-3), 3.69 (1H, dt, $J$ 3.1, 2.8, H-2), 3.33 (2H, ddd, $J$ 9.2, 9.2, 4.5, H-4, H-6), 3.11 (2H, ddd, $J$ 9.2, 5.5, 2.8, H-1, H-3), 2.89 (1H, td, $J$ 9.2, 4.3, H-5); $^{13}$C NMR (101 MHz; D$_6$-DMSO) $\delta$ 75.3 (C-5), 72.8 (C-4, C-6), 72.7 (C-2), 71.9 (C-1, C-3); $m/z$ (ES\textsuperscript{+}) 203.1 ([M+Na]$^+$, 100%). These data are in good agreement with the literature, as well as in comparison to commercial sources of \textit{myo}-inositol \textsuperscript{1,204-206}

\textbf{D$_6$-\textit{myo}-Inositol (90)}

![Image of \textit{myo}-inositol structure]

To a vigorously stirred solution of (±)-160 (1.96 g, 6.11 mmol, 1.0 eq., 90% D$_6$, 10% D$_5$) in MeCN (60 mL) at 0 °C was added a solution of RuCl$_3$·3H$_2$O (80 mg, 0.31 mmol, 0.05 eq.) and NaIO$_4$ (1.96 g, 9.18 mmol, 1.5 eq.) in H$_2$O (15 mL) and the resulting solution was stirred at 0 °C for 4 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was quenched with aqueous Na$_2$S$_2$O$_3$ (10% w/v, 50 mL) and the organic components were extracted with EtOAc (3 × 50 mL). The organic components were washed with saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The resulting solid was dissolved in a mixture of MeOH (21 mL) and water (9 mL), NEt$_3$ (10.2 mL, 73.0 mmol, 12.0 eq.) was added and the reaction solution was stirred at room temperature for 2 h.
After this time, the reaction solution was concentrated in vacuo and the resulting solid crystallised from 1:1 EtOH/H$_2$O to afford the title compound as colourless cubes (621 mg, 55%, 90% D$_6$, 10% D$_5$): R$_f$ 0.82 (1:1 EtOH/H$_2$O); m.p. 226-229 ºC (from EtOH/H$_2$O) {H$_{12}$-myo-inositol, see 1, 220-221 ºC (from EtOH/H$_2$O)}; $\tilde{\nu}$$_{\text{max}}$ (thin film)/cm$^{-1}$ 3215 (O-H, br m), 1413 (C-H, m), 1365 (C-H, m), 1201 (C-H, s), 1144 (C-O, m), 1107 (C-O, m); $^1$H NMR (400 MHz; D$_6$-DMSO) $\delta$ 4.47 (1H, s, O-H$_5$), 4.42 (2H, s, O-H$_4$, O-H$_6$), 4.40 (1H, s, O-H$_2$), 4.27 (2H, s, O-H$_1$, O-H$_3$); $^{13}$C NMR (126 MHz; D$_6$-DMSO) $\delta$ 74.6 (t, $^J$D$_{20.4}$, C$_2$), 72.2 (t, $^J$D$_{20.4}$, C-4, C-6), 72.1 (t, $^J$D$_{20.4}$, C-5), 71.3 (t, $^J$D$_{20.4}$, C-1, C-3); $^2$H NMR (77 MHz; DMSO; D$_6$-DMSO) $\delta$ 3.66 (D-2), 3.33 (D-4, D-6), 3.08 (D-1, D-3), 2.88 (D-5); HRMS m/z (ES$^+$) Found 208.0843 [MD$_5$+Na]$^+$ (C$_6$H$_7$O$_6$D$_5$Na requires 208.0840), 209.0903 [MD$_6$+Na]$^+$ (C$_6$H$_6$O$_6$D$_6$Na requires 209.0902); m/z (ES$^+$) 208.1 ([MD$_5$+Na]$^+$, 11%) 209.1 ([MD$_6$+Na]$^+$, 100%).

### 7.4 First Route Development

(+)-(1S,4S,5R,6R)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diyl dibenzoate ((+)-95)

![chemical structure](image_url)

To a solution of phosphoramidite 126 (606 mg, 2.24 mmol, 5.6 eq.) in CH$_2$Cl$_2$ (20 mL) under N$_2$ was added 1H-tetrazole (3-4 wt.% in MeCN, 5.2 mL, 2.24 mmol, 5.6 eq.) and the solution was stirred at room temperature for 10 min. Diol (+)-94 (142 mg, 0.4 mmol, 1.0 eq.) was added and the solution was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was
complete. The solution was cooled to −78 °C and 3-chloroperbenzoic acid (77%, 502 mg, 2.24 mmol, 5.6 eq.) was added. The solution was warmed to room temperature and stirred for 1 h. After this time, aqueous Na$_2$S$_2$O$_3$ (10% w/v, 20 mL) was added. The organic components were extracted with CH$_2$Cl$_2$ (2 × 20 mL), combined, washed with saturated aqueous NaHCO$_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 1-5% Me OH in CH$_2$Cl$_2$ to afford the title compound as a colourless oil (172 mg, 59%): R$_f$ 0.23 (MeOH/CH$_2$Cl$_2$ 1:19); [α]$_D^{20}$ = +130.9 (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1719 (C=O, m), 1255 (C-H, s), 1097 (C-O, s), 1028 (C-O, s); $^1$H NMR (400 MHz; CDCl$_3$) δ 8.15 (4H, dd, J 8.1, 1.1, H-9, H-14), 7.64 (2H, dd, J 7.4, 7.4, H-11, H-16), 7.52 (4H, dd, J 7.4, 7.4, H-10, H-15), 6.03 (2H, dd, J 5.6, 2.4, H-5, H-6), 5.86 (2H, s, H-2, H-3), 5.07-4.97 (2H, m, H-1, H-4), 4.37-4.22 (4H, m, H-17, H-26), 4.17-4.08 (2H, m, H-20a, H-23a), 4.05-3.95 (2H, m, H-20b, H-23b), 2.77-2.61 (4H, m, H-18, H-27), 2.42 (4H, t, J 6.4, H-21, H-24); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 165.6 (C-7, C-12), 134.0 (C-11, C-16), 130.0 (C-9, C-14), 129.1 (C-8, C-13), 128.9 (C-10, C-15), 127.1 (C-2, C-3), 116.8 (C-22, C-25), 116.3 (C-19, C-28), 77.7 (t, J$\_P$ 5.7, C-5, C-6), 72.2 (C-1, C-4), 63.0 (d, J$\_P$ 5.6, C-20, C-23), 62.6 (d, J$\_P$ 5.6, C-17, C-26), 19.5 (d, J$\_P$ 8.0, C-18, C-27), 19.2 (d, J$\_P$ 8.0, C-21, C-24); $^{31}$P NMR (162 MHz; CDCl$_3$) δ -3.20; HRMS m/z (ES$^+$) Found 749.1355 [M+Na]$^+$ (C$_{32}$H$_{32}$N$_4$O$_{12}$P$_2$Na requires 749.1384); m/z (ES$^+$) 727.2 ([M+H]$^+$, 35%), 749.2 ([M+Na]$^+$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 18.9 min, 99.5%.
To a vigorously stirred solution of (+)-95 (120 mg, 0.17 mmol, 1.0 eq.) in MeCN (5 mL) was added, dropwise, a solution of RuCl₃·3H₂O (17 mg, 0.066 mmol, 0.4 eq.) and NaIO₄ (53 mg, 0.25 mmol, 1.5 eq.) in H₂O (1 mL) over a period of 2 min. The reaction mixture was stirred for 1 h at room temperature. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous Na₂S₂O₃ (10% w/v, 10 mL) was added, causing the solution to become green, and the organic components were extracted with EtOAc (3 × 20 mL). The combined organic components were dried with Na₂SO₄, filtered, and concentrated in vacuo. The resulting oil was dissolved in MeCN (20 mL), washed with hexane (10 mL) and concentrated in vacuo to afford the title compound as a colourless foam (111 mg, 88%): Rᵣ 0.33 (EtOAc); [α]²⁰<sub>D</sub> = +35.8 (c 1.0, CHCl₃); m.p. 76-80 °C (from MeOH); νₘₐₓ (thin film)/cm⁻¹ 1721 (C=O, m), 1266 (C-H alkyl, s), 1108 (C-O, m), 1026 (C-O, s); ¹H NMR (400 MHz; CDCl₃) δ 8.25 (2H, d, J 7.7, H-9), 8.19 (2H, d, J 7.9, H-14), 7.71-7.64 (2H, m, H-11, H-16), 7.59-7.51 (4H, m, H-10, H-15), 5.81 (1H, dd, J 9.8, 9.8, H-6), 5.40 (1H, dd, J 10.1, 2.5, H-3), 5.30 (1H, ddd, J 9.4, 9.4, 9.4, H-4), 4.87 (1H, ddd, J 9.2, 9.2, 9.2, H-5), 4.43 (1H, s, H-2), 4.40-4.21 (4H, m, H-17, H-26), 4.12-3.81 (5H, m, H-1, H-20, H-23), 3.55 (1H, br s, OH-2), 3.21 (1H, br s, OH-1), 2.76-2.56 (4H, m, H-18, H-27), 2.36-2.18 (4H, m, H-21, H-24); ¹³C NMR (101 MHz; CDCl₃) δ 166.3 (C-12), 165.4 (C-7), 134.0 (C-16), 133.8 (C-11), 130.2 (C-14), 130.1 (C-9), 129.4 (C-13), 129.2 (C-8), 128.80 (C-15), 128.78 (C-10), 117.04...
(C-19), 116.98 (C-28), 116.4 (C-22, C-25), 77.9 (dd, \( J_P \) 5.4, 5.4, C-5), 77.2 (m, C-4), 73.0 (C-6), 71.6 (C-3), 70.2 (C-2), 70.0 (C-1), 63.2 (d, \( J_P \) 5.9, C-20 or C-23), 63.1 (d, \( J_P \) 5.9, C-20 or C-23), 62.60 (d, \( J_P \) 4.2, C-17 or C-26), 62.55 (d, \( J_P \) 3.4, C-17 or C-26), 19.38 (d, \( J_P \) 8.2, C-18), 19.35 (d, \( J_P \) 8.2, C-21) 19.0 (d, \( J_P \) 8.3, C-24) 18.9 (d, \( J_P \) 8.3, C-27); \(^{31}\)P NMR (162 MHz; CDCl\(_3\)) \( \delta \) –3.33 (P-4), –3.45 (P-5); HRMS \( m/z \) (ES\(^{+}\)) Found 783.1429 [M+Na]\(^{+}\) (C\(_{32}\)H\(_{34}\)N\(_4\)O\(_{14}\)P\(_2\)Na requires 783.1439); \( m/z \) (ES\(^{+}\)) 799.1 ([M+K]\(^{+}\), 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 16.9 min, 92.2%.

\((+)-2\)-Acetyl-3,6-dibenzoyl-4,5-bis(bis(2-cyanoethoxy)phosphoryl)-\(\alpha\)-myo-inositol \((+)-97\)

To a solution of \((+)-96\) (528 mg, 0.7 mmol, 1.0 eq.) in anhydrous THF (20 mL) under an atmosphere of Ar was added triethylorthoacetate (0.38 mL, 2.1 mmol, 3.0 eq.) and \( p \)-toluenesulfonic acid (13 mg, 0.07 mmol, 0.1 eq.), and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The solution was concentrated \textit{in vacuo} and the resulting oil was dissolved in aqueous AcOH (80% \( v/v \), 10 mL). The solution was stirred at room temperature for 1 h and then concentrated \textit{in vacuo}. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The resulting oil was dissolved in EtOAc (75 mL) and the organic components were washed with saturated aqueous NaHCO\(_3\) (30 mL), saturated aqueous NaCl (30 mL), dried with
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Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5% EtOH in CHCl$_3$ to give a light yellow oil. The product was precipitated by dissolving the oil in MeOH (ca. 5 mL) and dropwise addition of water until no more precipitate was observed on addition (ca. 10 mL). The suspension was concentrated in vacuo at 100 mBar to remove MeOH and the solid was filtered to afford the title compound as a colourless solid (210 mg, 38%): R$_f$ 0.31 (EtOAc); [α]$^D_{20}$ = +31.1 (c 1.0, CHCl$_3$); m.p. 145-148 °C (from H$_2$O); ν$_{\max}$ (thin film)/cm$^{-1}$ 1727 (C=O, s), 1270 (C-H, s), 1108 (C-O, m), 1072 (C-O, s), 1030 (C-O, s); $^1$H NMR (400 MHz; MeOD/CDCl$_3$ 1:9) δ 8.09 (2H, d, $J$ 7.4, H-14), 7.99 (2H, d, $J$ 7.4, H-9), 7.57 (2H, dd, $J$ 7.4, 7.4, H-11, H-16), 7.48-7.41 (4H, m, H-10, H-15), 5.66-5.59 (2H, m, H-2, H-6), 5.37 (1H, dd, J 10.0, 2.8, H-3), 5.01 (1H, ddd, J 9.4, 9.4, 9.4, H-4), 4.79 (1H, ddd, J 9.4, 9.4, 9.4, H-5), 4.29-4.12 (4H, m, H-17, H-20), 4.03 (1H, dd, J 10.1, 2.8, H-1), 4.00-3.91 (2H, m, H-23), 3.85-3.74 (2H, m, H-26), 2.74-2.56 (4H, m, H-18, H-21), 2.29-2.14 (7H, m, H-24, H-27, H-30); $^{13}$C NMR (101 MHz; MeOD/CDCl$_3$ 1:9) δ 170.2 (C-29), 166.0 (C-12), 165.1 (C-7), 134.1 (C-16), 134.0 (C-11), 130.1 (C-14), 130.0 (C-9), 129.2 (C-8, C-13), 128.8 (C-10, C-15), 116.8 (C-19), 116.8 (C-22), 116.4 (C-25), 116.2 (C-28), 77.9-77.7 (m, C-5), 77.4-77.2* (m, C-4), 72.6 (C-3), 70.4 (C-2), 69.7 (C-6), 68.2 (C-1), 63.2 (d, J$^P$ 8.2, C-17 or C-20), 63.1 (d, J$^P$ 8.2, C-17 or C-20), 62.6 (d, J$^P$ 9.8, C-23 or C-26), 62.5 (d, J$^P$ 9.7, C-23 or C-26), 20.8 (C-30), 19.5 (d, J$^P$ 8.2, C-18 or C-21), 19.4 (d, J$^P$ 8.6, C-18 or C-21), 19.0 (d, J$^P$ 7.2, C-24 or C-27), 18.9 (d, J$^P$ 7.2, C-24 or C-27); $^{31}$P NMR (162 MHz; MeOD/CDCl$_3$ 1:9) δ -3.63 (P-5), -3.69 (P-4); HRMS m/z (ES$^+$) Found 825.1518 [M+Na]$^+$ (C$_{34}$H$_{36}$N$_4$O$_{15}$P$_2$Na requires 825.1545); m/z (ES$^+$) 803.2 ([M+H]$^+$, 42%), 825.1 ([M+Na]$^+$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 19.3 min, 93.8%.

*In this case, the carbon signal was within the solvent peak however HSQC and HMBC data confirmed the peak shift.
(+)-2-Acetoxy-3,6-dibenzoyl-1,4,5-tris(bis(2-cyanoethoxy)phosphoryl)-
D-myoinositol ( (+)-267)

To a solution of (+)-97 (60 mg, 0.075 mmol, 1.0 eq.) and phosphoramidite 126 (40 mg, 0.15 mmol, 2.0 eq.) in CH₂Cl₂ (5 mL) under an atmosphere of argon was added 1H-tetrazole (3-4 wt.% in MeCN, 0.35 mL, 0.15 mmol, 2.0 eq.) and the solution was stirred at room temperature for 48 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The solution was cooled to −78 °C and 3-chloroperbenzoic acid (77%, 26 mg, 0.15 mmol, 2.0 eq.) was added. The solution was stirred at room temperature for 1 h. The reaction solution was diluted with CH₂Cl₂ (40 mL) and the organic components were washed with aqueous Na₂S₂O₃ (10% w/v, 50 mL), saturated aqueous NaHCO₃ (50 mL), saturated aqueous NaCl (50 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system twice, first using a 0-10% EtOH in CHCl₃ gradient (25 CV) followed by a second column using CHCl₃, 0.5% EtOH in CHCl₃, 1.0% EtOH in CHCl₃, 2.0% EtOH in CHCl₃, 4.0% EtOH in CHCl₃ and 6.0% EtOH in CHCl₃ to afford the title compound as a colourless film (26 mg, 35%); Rₜ 0.11 (MeOH/CHCl₃ 1:19); [α]D²⁰ = +0.8 (c 1.0, CHCl₃); ¯νmax (thin film)/cm⁻¹ 2918 (C-H, w) 2850 (C-H, w) 2361 (C≡N, w) 2255 (C≡N, w), 1733 (C=O, m), 1270 (C-H, s), 1097 (C-O, s), 1073 (C-O, s), 1032 (C-O, s); ¹H NMR (500 MHz; CDCl₃) δ 8.20 (2H, d, J 7.7,
7.4. FIRST ROUTE DEVELOPMENT

H-9), 8.05 (2H, d, J 7.8, H-14), 7.64 (2H, dd, J 7.4, 7.4, H-11, H-16), 7.56 (2H, dd, J 7.7, 7.7, H-10), 7.51 (2H, dd, J 7.8, 7.8, H-15), 5.91-5.86 (2H, m, H-2, H-6), 5.60 (1H, dd, J 10.0, 2.9, H-3), 5.12 (1H, ddd, J 9.6, 9.6, 9.6, H-4), 5.10-5.05 (1H, m, H-1), 4.98 (1H, ddd, J 9.4, 9.4, 9.4, H-5), 4.38-4.14 (6H, m, H-17a, H-20a, H-23a, H-26a, H-31a, H-34a), 4.08-3.76 (6H, m, H-17b, H-20b, H-23b, H-26b, H-31b, H-34b), 2.79-2.60 (6H, m, H-18a, H-21a, H-24a, H-27a, H-32a, H-35a), 2.34-2.16 (9H, m, H-18b, H-21b, H-24b, H-27b, H-30, H-32b, H-35b); $^{13}$C NMR (126 MHz; CDCl$_3$) δ 169.8 (C-29), 165.2 (C-12), 164.7 (C-7), 134.3 (C-16), 134.2 (C-11), 130.01 (C-9), 129.97 (C-14), 129.2 (C-10), 129.0 (C-8), 128.8 (C-15), 128.7 (C-13), 116.93 (C-19), 116.89 (C-22), 116.4 (C-25), 116.3 (C-28), 116.2 (C-33), 115.9 (C-36), 76.8-76.7* (m, C-5), 76.7-76.6* (m, C-4), 73.6 (d, J$_P$ 4.8, C-1), 70.5 (d, J$_P$ 3.0, C-6), 68.7 (d, J$_P$ 2.3, C-2), 68.6 (C-3), 63.3 (d, J$_P$ 5.7, C-17), 63.2 (d, J$_P$ 5.7, C-20), 62.7 (d, J$_P$ 4.9, C-23), 62.6 (d, J$_P$ 5.3, C-26, C-31), 62.5 (d, J$_P$ 4.9, C-34), 20.8 (C-30), 19.5 (d, J$_P$ 7.8, C-18), 19.4 (d, J$_P$ 7.8, C-21), 19.03 (d, J$_P$ 8.0, C-24), 18.98 (d, J$_P$ 8.0, C-27, C-32), 18.9 (d, J$_P$ 8.0, C-35); $^{31}$P NMR (162 MHz; CDCl$_3$) δ –1.48 (P-1), –1.89 (P-5), –1.98 (P-4); HRMS m/z (ES$^+$) Found 1011.1735 [M+Na]$^+$ (C$_{40}$H$_{49}$O$_{18}$N$_6$NaP$_3$ requires 1011.1739); m/z (ES$^+$) 989.2 ([M+H]$^+$, 100%), (ES$^-$) 934.2 ([M-CH$_2$CH$_2$CN]$^-$, 100%).

* These peaks appeared under the solvent signal and were determined by a combination of HSQC and DEPTQ data and as such appear as multiplets in the region given.
(+)-2-Acetoxy-4,5-bis(bis(2-cyanoethoxy)phosphoryl)-1-((1,2-dipalmitoyl-
-sn-glycerol)-(2-cyanoethoxy)phosphoryl)-3,6-dibenzoyl-\( \text{d-mylo-} \)
inositol

\((+)-98\)

To a solution of (+)-97 (31 mg, 0.039 mmol, 1.0 eq.) and 131 (60 mg, 0.078 mmol, 2.0 eq.) in \( \text{CH}_2\text{Cl}_2 \) (3 mL) under an atmosphere of Ar was added 1\( H \)-tetrazole (3-4 wt.% in MeCN, 0.18 mL, 0.078 mmol, 2 eq.) and the solution was stirred for 2 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The solution was cooled to \(-78^\circ \text{C}\), 3-chloroperbenzoic acid (77%, 13 mg, 0.078 mmol, 2.0 eq.) was added and the solution was stirred at room temperature for 2 h. After this time, aqueous \( \text{Na}_2\text{S}_2\text{O}_3 \) (10% \( \text{w/v} \), 10 mL) was added and the product was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 \( \times \) 10 mL). The combined organic components were washed with saturated aqueous \( \text{NaHCO}_3 \) (10 mL), dried with \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated \( \text{in vacuo} \). The product was columned using silica gel flash column chromatography on a Biotage system twice, first using 4% EtOH in \( \text{CH}_2\text{Cl}_2 \) then 3% EtOH in \( \text{CHCl}_3 \) to afford the title compound as a colourless film (29 mg, 49%) as a 1:1 mixture of inseparable diastereomers: \( R_f \) 0.67 (EtOH/\( \text{CHCl}_3 \) 1:19); \([\alpha]_{D}^{20} = +4.6 \) (c 1.0, \( \text{CHCl}_3 \)); \( \tilde{\nu}_{\text{max}} \) (thin film)/cm\(^{-1}\) 2918 (C-H alkyl, s), 2851 (C-H alkyl, s), 1735 (C=O, s), 1467 (w), 1271 (C-H, s), 1221 (m), 1032 (C-O, s); \(^1\text{H} \text{NMR} \) (400 MHz; CDCl\(_3\) ) Diastereomer \( \text{A}^\ast \) \( \delta \) 8.21-8.17 (2H, m, \( H-9 \)), 8.06 (2H, d, \( J \) 8.2, \( H-14 \)), 7.69-7.62 (2H, m, \( H-11 \), \( H-16 \)), 7.58-7.49 (4H,
5.90-5.84 (2H, m, H-2, H-6), 5.51 (1H, dd, J 10.0, 2.6, H-3), 5.17 (1H, dddd, J 5.0, 5.0, 5.0, 5.0, H-35), 5.11 (1H, ddd, J 9.5, 9.5, 9.5, H-4), 4.98-4.91 (1H, m, H-1), 4.91-4.83 (1H, m, H-5), 4.39-3.96 (10H, m, H-17, H-20, H-31, H-34, H-36), 3.94-3.67 (4H, m, H-23, H-26), 2.79-2.59 (4H, m, H-18, H-21), 2.34-2.15 (13H, m, H-24, H-27, H-30, H-32, H-38, H-54), 1.61-1.49 (4H, m, H-39, H-55), 1.34-1.17 (48H, m, H-(40-51), H-(56-67)), 0.91-0.86 (6H, m, H-52, H-68), Diastereomer B* δ 8.21-8.17 (2H, m, H-9), 8.06 (2H, d, J 8.2, H-14), 7.69-7.62 (2H, m, H-11, H-16), 7.58-7.49 (4H, m, H-10, H-15), 5.90-5.84 (2H, m, H-2, H-6), 5.51 (1H, dd, J 10.0, 2.6, H-3), 5.11 (1H, ddd, J 9.5, 9.5, 9.5, H-4), 4.98-4.91 (1H, m, H-1), 4.91-4.83 (1H, m, H-5), 4.82 (1H, dddd, J 5.0, 5.0, 5.0, 5.0, H-35), 4.39-3.96 (8H, m, H-17, H-20, H-31, H-34), 3.94-3.67 (6H, m, H-23, H-26, H-36), 2.79-2.59 (6H, m, H-18, H-21, H-32), 2.34-2.15 (11H, m, H-24, H-27, H-30, H-38, H-54), 1.61-1.49 (4H, m, H-39, H-55), 1.34-1.17 (48H, m, H-(40-51), H-(56-67)), 0.91-0.86 (6H, m, H-52, H-68); 13C NMR (126 MHz; CDCl3) Diastereomer A* δ 172.3 (C-37), 171.8 (C-53), 168.7 (C-29), 164.65 (C-12), 164.1 (C-7), 133.24 (C-16), 133.16 (C-11), 129.0 (C-9), 128.9 (C-14), 128.1 (C-10), 127.8 (C-15), 127.60 (C-8), 127.59 (C-13), 115.8 (C-19), 115.7 (C-22), 115.2 (C-28), 115.1 (C-25), 114.7 (C-33), 76.2-76.1** (m, C-5), 75.7-75.6** (m, C-4), 72.3 (d, Jp 5.1, C-1), 69.4-69.2 (m, C-6), 68.04 (C-35), 67.72 (C-3), 67.7 (C-2), 65.2 (d, Jp 5.6, C-34), 62.2 (d, Jp 5.8, C-20), 62.1 (d, Jp 5.8, C-17), 61.6 (d, Jp 4.8, C-23), 61.5 (d, Jp 4.8, C-26), 61.4 (d, Jp 5.1, C-31), 60.4 (C-36), 33.04, 32.97, 32.94, 32.91 (C-38, C-54), 30.9 (C-50, C-66), 28.7, 28.6, 28.5, 28.34, 28.29, 28.12, 28.10, 28.05 (C-(40-49), C-(56-65)), 23.8 (C-55), 23.7 (C-39), 21.7 (C-51, C-67), 19.72 (C-30), 18.44 (C-21), 18.39 (C-18), 18.0 (C-24), 17.93 (C-27), 17.8 (C-32), 13.2 (C-52, C-68), Diastereomer B* δ 172.1 (C-37), 171.6 (C-53), 168.4 (C-29), 164.63 (C-12), 164.1 (C-7), 133.24 (C-16), 133.12 (C-11), 129.0 (C-9), 128.9 (C-14), 128.0 (C-10), 127.8 (C-15), 127.60 (C-8), 127.59 (C-13), 115.8 (C-19), 115.7 (C-22), 115.2 (C-28), 115.1 (C-25), 114.7 (C-33), 76.2-76.1** (m, C-5), 75.7-75.6** (m, C-4), 72.2 (d, Jp 5.1, C-1), 69.4-69.2 (m, C-6), 67.98 (C-35), 67.66 (C-3), 67.5 (C-2), 65.1 (d, Jp 5.6, C-34), 62.2 (d, Jp 5.8, C-20), 62.1 (d, Jp 5.8, C-17), 61.6 (d, Jp 4.8, C-23), 61.5 (d, Jp 4.8, C-26), 61.3 (d, Jp 5.1, C-31), 60.2 (C-36), 33.04, 32.97, 32.94, 32.91 (C-38, C-54), 30.9 (C-50, C-66), 28.7, 28.6,
7.5 Deuterated Inositol Derivatives

(±)-(1R,2S,3S,4R)-Cyclohex-5-ene-1,2,3,4-tetrayl-D$_6$tetrakis(2’,2’,2’-tri-chloroethyl) tetracarbonate ((±)-165)

A solution of compound (±)-160 (1.0 g, 3.1 mmol, 1.0 eq.) and triethylamine (1.31 mL, 9.4 mmol, 3.0 eq., 90% D$_6$, 10% D$_5$) in a mixture of MeOH (14 mL) and water (6 mL) was stirred at room temperature for 1 h. TLC analysis of the reaction mixture of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was concentrated in vacuo and was dried under high vacuum overnight. The solid was placed under an atmosphere of N$_2$ and suspended in anhydrous CH$_2$Cl$_2$ (25 mL). Freshly distilled pyridine (1.51 ml, 18.7 mmol, 6.0 eq.) and 4-dimethylaminopyridine
(195 mg, 1.6 mmol, 0.5 eq.) were added to the suspension and the suspension was cooled to 0 °C. Trichloroethyl chloroformate (2.57 mL, 18.7 mmol, 6.0 eq.) was added, dropwise, over a period of 10 min and the reaction was stirred at 0 °C for 2 h. ¹H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction was diluted with CH₂Cl₂ (75 mL) and the organic components were washed with water (50 mL), aqueous HCl (1 M, 50 mL), saturated aqueous NaHCO₃ (50 mL) and saturated aqueous NaCl (50 mL), dried with MgSO₄, filtered, and concentrated *in vacuo*. The resulting solid was suspended in boiling EtOH (ca. 50 mL), cooled to 0 °C and filtered to afford the title compound as a colourless solid (2.24 g, 85%): Ṕ_r 0.63 (EtOAc/petroleum ether 1:4); m.p. 190-191 °C (from EtOH); Ṓ_ν_max (thin film)/cm⁻¹ 1761 (C=O, s), 1435 (C-H, s), 1376 (C-H, s), 1286 (C-H, s), 1255 (C-H, s), 1235 (C-O, s), 1204 (C-O, s), 1156 (C-O, m), 1134 (C-O, m), 1099 (C-O, m), 1087 (C-O, m), 1063 (C-O, m), 1049 (C-O, m), 1022 (C-O, m), 1013 (C-O, m); ¹H NMR (400 MHz; CDCl₃) ᵈ 4.84-4.73 (8H, m, H-8, H-11, H-14, H-17); ¹³C NMR (126 MHz; CDCl₃) ᵈ 153.2 (C-7, C-10, C-13, C-16), 126.5 (t_D, J_D 24.4, C-5, C-6), 94.1 (C-12, C-15), 94.0 (C-9, C-18), 77.11 (C-8, C-17), 77.09 (C-11, C-14), 75.3 (t_D, J_D 21.9, C-1, C-4), 74.8 (t_D, J_D 23.3, C-2, C-3); ²H NMR (77 MHz; CHCl₃; D₆-DMSO) ᵈ 5.97 (D-5, D-6), 5.63 (D-1, D-4), 5.42 (D-2, D-3); HRMS m/z (E⁺) Found 656.8027 [M³⁵Clᵹ⁻CO₂CH₂CCl₃]⁺ (C₁₅H₆D₆Cl₉O₉ requires 656.8060); m/z (E⁺) 461.8 ([M³⁵Clᵹ⁻2×(OTroc)+H]⁺, 656.8 ([M³⁵Clᵹ⁻OTroc]⁺, 100%).

Deuterium incorporation of this compound was not calculated due to complexities arising from multiple Cl isotopes within the mass spectrum, however, no hydrogen-deuterium exchange was observed by ¹H NMR.
(+)-(1R,4S,5S,6R)-2,3-Bis(((2’’,2’’-trichloroethoxy)carbonyl)oxy)cyclo-hex-5-ene-1,4-diyl-D₆ dibenzoate ((+)-166)

D₆-Tetratroc (±)-165 (1.28 g, 1.50 mmol, 1.0 eq), BzOH (627 mg, 5.13 mmol, 3.4 eq.), (S,S)-ligand (–)-84 (154 mg, 0.222 mmol, 0.15 eq.), tetrahexylammonium bromide (129 mg, 0.30 mmol, 0.2 eq.), and [Pd(η³-allyl)Cl]₂ (14 mg, 0.04 mmol, 0.03 eq.) were degassed on a Schlenk system (3 × vacuum/N₂ cycles). CH₂Cl₂ (4.5 mL) and aqueous NaOH (1 M, 4.5 mL, 3.5 eq.) were added and the reaction mixture was stirred vigorously under N₂ for 90 min. ¹H NMR analysis of the reaction mixture indicated the reaction was complete. Saturated aqueous NaHCO₃ (50 mL) was added and the organic components were extracted using CH₂Cl₂ (2 × 30 mL). The organic components were combined, filtered under vacuum through a plug of silica and the silica was washed with CH₂Cl₂ (100 mL). The filtrate was concentrated in vacuo to give a colourless oil. The product was crystallised from EtOH to afford the title compound as colourless needles in two batches (combined 733 mg, 69%): R₉ 0.57 (EtOAc/petroleum ether 1:4); [α]D₂⁰ = +175.0 (c 1.0, CHCl₃); m.p. 143-146 °C (from EtOH); v̅ₘₐₓ (thin film)/cm⁻¹ 1762 (C=O, s), 1717 (C=O, s), 1380 (C-H, m), 1286 (C-H, s), 1270 (C-H, s), 1232 (C-O, s), 1198 (C-O, s), 1177 (C-O, m), 1110 (C-O, m), 1087 (C-O, m), 1069 (C-O, m), 1055 (C-O, m), 1026 (C-O, m), 1012 (C-O, m), 1005 (C-O, m); ¹H NMR (400 MHz; CDCl₃) δ 8.03 (4H, m, H-9, H-20), 7.60 (4H, m, H-10, H-21), 7.45 (2H, m, H-11, H-22), 4.81 (2H, d, J 11.8, H-13a, H-16a), 4.67 (2H, d, J 11.8, H-13b, H-16b); ¹³C NMR (126 MHz; CDCl₃) δ 165.6 (C-7, C-18), 153.5 (C-12, C-15), 133.7 (C-8, C-19), 129.9 (C-10, C-21), 128.9 (C-11, C-22), 128.6 (C-9, C-20), 126.9 (tD,
7.5. \textit{D}_6-\text{INOSITOL DERIVATIVES} \quad \textit{CHAPTER 7. EXPERIMENTAL}

\[ J_D \quad 24.8, \ C-5, \ C-6), \ 94.1 \ (C-13, \ C-16), \ 76.9 \ (C-14, \ C-17), \ 75.3 \ (t_D, \ J_D \ 23.0, \ C-2, \ C-3), \]
\[ 71.6 \ (t_D, \ J_D \ 22.4, \ C-1, \ C-4); \textsuperscript{2}H \text{ NMR} \ (77 \text{ MHz}; \text{CHCl}_3; \text{D}_6-\text{DMSO}) \delta \ 5.88 \ (D-2, \ D-3, \ D-5, \ D-6), \ 5.49 \ (D-1, \ D-4); \text{HRMS} \ m/z \ (E^+) \text{ Found} \ 707.8966 \ [M]^+ \text{ (C}_{26}\text{H}_{14}\text{D}_{6}\text{Cl}_6\text{O}_{10} \text{ requires} \ 707.9564); \ m/z \ 707.8 \ ([M]^+, \ 100\%); \text{Chiral HPLC} \ (10\% \text{ isopropanol/heptane isocratic,} \ 1.0 \text{ mL min}^{-1} \text{) Retention Time} = 11.6 \text{ min} \ (+)-\text{166}, \ >99\% \text{ e.e. (other enantiomer not observed); NP-HPLC} \ (0-10\% \text{ isopropanol/hexane}) \text{ Retention Time} = 3.6 \text{ min,} \ 92.5\%.

Deuterium incorporation of this compound was not calculated due to complexities arising from multiple Cl isotopes within the mass spectrum, however, no hydrogen-deuterium exchange was observed by \textsuperscript{1}H NMR.

\[ (+)-(1\text{S},4\text{S},5\text{S},6\text{S})-5,6-\text{Dihydroxycyclohex-2-ene-1,4-diyl-D}_6 \text{ dibenzoate} \]
\[ ((+)-\text{167}) \]

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

A solution of (+)-\text{166} \ (1.65 g, 2.3 mmol, 1.0 eq.) in glacial AcOH \ (5 mL) and THF \ (5 mL) was cooled to 0°C and Zn dust \ (902 mg, 13.8 mmol, 6.0 eq.) was added, portionwise, over 5 min. The reaction mixture was stirred at room temperature for 2 h. TLC analysis of the reaction mixture indicated the reaction was complete. Saturated aqueous NaHCO\textsubscript{3} \ (50 mL) was added, the suspension was stirred for 10 min and the organic components were extracted using EtOAc \ (3 \times 50 mL). The combined organic components were dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The resulting oil was azeotroped three times with cyclohexane. The resulting solid was partitioned between EtOAc \ (100 mL) and water \ (75 mL), and K\textsubscript{2}CO\textsubscript{3} was added until no effervescence was seen on addition. The phases were separated and the organic components were extracted
using EtOAc (50 mL), combined, dried with Na₂SO₄, filtered, and concentrated in vacuo.

The product was purified by dissolving in minimal boiling 1:1 MeOH/water, cooling to room temperature, concentrating in vacuo to remove MeOH (ca. 100 mBar), and filtering to afford the title compound as a colourless solid (741 mg, 89%, D₆ 90%, D₅ 10%): Rₚ 0.78 (EtOAc/petroleum ether 1:1); [α]₀³⁰ = +217.4 (c 1.0, CHCl₃); m.p. 143-147 °C (from CHCl₃); vₚ max (thin film)/cm⁻¹ 3372 (O-H, br), 1714 (C=O, s), 1451 (C-H, w), 1314 (C-H, m), 1283 (C-H, s), 1225 (C-O, m), 1209 (C-O, m), 1196 (C-O, m), 1181 (C-O, m), 1108 (C-O, s), 1096 (C-O, s), 1067 (C-O, m), 1028 (C-O, m), 1009 (C-O, m); ¹H NMR (500 MHz; CDCl₃) δ 8.07 (4H, dd, J 8.0, 1.1, H-9, H-14), 7.57 (2H, tt, J 7.4, 1.2, H-11, H-16), 7.44 (4H, dd, J 7.8, 7.8, H-10, H-15), 3.51 (2H, s, O-H); ¹³C NMR (126 MHz; CDCl₃) δ 166.9 (C-7, C-12), 133.5 (C-11, C-16), 129.9 (C-9, C-14), 129.6 (C-8, C-13), 128.5 (C-10, C-15), 127.4 (tD, JD 24.7, C-1, C-2), 74.4 (tD, JD 22.4, C-3, C-6), 73.4 (tD, JD 22.4, C-4, C-5); ²H NMR (77 MHz; CHCl₃; D₆-DMSO) δ 5.77 (D-2, D-3), 5.64 (D-5, D-6), 3.95 (D-1, D-4); HRMS m/z (ES⁺) Found 382.1299 [MD₅+Na]⁺ (C₂₀H₁₆D₅NaO₆ requires 382.1315), 383.1361 [MD₆+Na]⁺ (C₂₀H₁₂D₆NaO₆ requires 383.1372); m/z (ES⁺) 382.1 ([MD₅+Na]⁺, 11%), 383.1 ([MD₆+Na]⁺, 100%), (ES⁻) 405.1 ([M+formic acid-H]⁻, 100%); NP-HPLC (0-30% isopropanol/hexane) Retention Time = 8.6 min, 98.0%.

(+)-(1S,4S,5R,6R)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diy-D₆ dibenzoate ((+)-168)

To a solution of (+)-167 (741 mg, 2.06 mmol, 1.0 eq., D₆ 90%, D₅ 10%) and phosphoramidite 126 (2.24 g, 8.24 mmol, 4.0 eq.) in CH₂Cl₂ (40 mL) under an atmosphere of
N₂ was added 1H-tetrazole (3-4 wt.% in MeCN, 19.2 mL, 8.24 mmol, 4.0 eq.), and the solution was stirred at room temperature for 24 h, during which time the reaction mixture turned cloudy. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The suspension was cooled to −78 °C, 3-chloroperbenzoic acid (77%, 1.42 g, 8.24 mmol, 4.0 eq.) was added and stirred at room temperature for 1 h. The reaction mixture was diluted with CH₂Cl₂ (60 mL) and the organic components were washed with aqueous Na₂S₂O₃ (10% w/v, 50 mL), saturated aqueous NaHCO₃ (2 × 50 mL), saturated aqueous NaCl (50 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography twice on a Biotage system, using first 3% EtOH in CH₂Cl₂ followed by a second column in 2% EtOH in CHCl₃ to afford the title compound as a colourless film (833 mg, 55 %, D₆ 89%, D₅ 11%). The product was typically isolated with a 0.6% phosphoramidite impurity (by ³¹P NMR) that was removed in the subsequent reaction: Rf 0.50 (EtOH/CHCl₃ 1:9); [α]₀²⁰ = +122.7 (c 1.0, CHCl₃); m.p. 97-100 °C (from EtOH); νmax (thin film)/cm⁻¹ 1720 (C=O, m), 1283 (P=O, s), 1207 (C-O, m), 1108 (C-O, m), 1085 (P-O, m), 1071 (C-O, m), 1028 (P-O, s), 1006 (C-O, s); 1H NMR* (400 MHz; CDCl₃) δ 8.15 (4H, dd, J 8.2, 1.2, H-9, H-14), 7.65 (2H, tt, J 7.4, 1.2, H-11, H-16), 7.52 (4H, t, J 7.4, H-10, H-15), 4.38-4.22 (4H, m, H-17, H-26), 4.17-4.07 (2H, m, H-20a, H-23a), 4.05-3.95 (2H, m, H-20b, H-23b), 2.83-2.60 (4H, m, H-21, H-24), 2.41 (4H, t, J 6.2, H-18, H-27); 13C NMR* (126 MHz, CDCl₃) δ 165.5 (C-7, C-12), 134.0 (C-11, C-16), 130.0 (C-9, C-14), 129.1 (C-8, C-13), 128.8 (C-10, C-15), 126.7 (tD, J₆ 21.0, C-2, C-3), 116.9 (C-19, C-28), 116.4 (C-22, C-25), 71.7 (tD, J₆ 21.0, C-1, C-4), 63.0 (d, J₆ 5.7, C-17, C-26), 62.6 (d, J₆ 5.2, C-20, C-23), 19.4 (d, J₆ 7.8, C-18, C-27), 19.2 (d, J₆ 7.8, C-21, C-24); ¹³C NMR* (126 MHz; CD₂Cl₂) δ 165.5 (C-7, C-12), 133.8 (C-11, C-16), 129.9 (C-9, C-14), 129.3 (C-8, C-13), 128.7 (C-10, C-15), 126.6 (tD, J₆ 25.0, C-2, C-3), 116.9 (C-19, C-28), 116.5 (C-22, C-25), 77.4-76.8 (m, C-5,
C-6), 71.7 (t, J_D 22.8, C-1, C-4), 63.1 (d, J_P 5.7, C-17, C-26), 62.7 (d, J_P 5.2, C-20, C-23), 19.4 (d, J_P 7.7, C-18, C-27), 19.2 (d, J_P 7.7, C-21, C-24); \(^{31}\)P NMR (162 MHz; CDCl\(_3\)) \(\delta -3.15;\) \(^{2}\)H NMR (77 MHz; CHCl\(_3\); D\(_6\)-DMSO) \(\delta 5.90 (D-2, D-3, D-5, D-6), 4.91 (D-1, D-4);\) HRMS \(m/z\) (ES\(^+\)) Found 754.1678 [MD\(_5\)+Na]+ (C\(_{32}\)H\(_{27}\)D\(_5\)N\(_4\)O\(_{12}\)P\(_2\)Na requires 754.1704), 755.1736 [MD\(_6\)+Na]+ (C\(_{32}\)H\(_{26}\)D\(_6\)N\(_4\)O\(_{12}\)P\(_2\)Na requires 755.1761); \(m/z\) (ES\(^-\)) 677.2 ([MD\(_5\)-CH\(_2\)CH\(_2\)CN]\(^-\), 11%), 678.2 ([MD\(_6\)-CH\(_2\)CH\(_2\)CN]\(^-\), 100%); NP-HPLC (0-100% hexane/isopropanol) Retention Time = 19.0 min, 89.5%.

* A second set of NMR data was obtained in CD\(_2\)Cl\(_2\) for \(^1\)H and \(^{13}\)C due to the fact that a key carbon peak (C-5 and C-6) was obscured by the solvent peak in CDCl\(_3\).

(+)\-4,5-Bis(bis(2-cyanoethoxy)phosphoryl)-3,6-dibenzoyl-\textit{d-myo}-inositol-D\(_6\)
((+)\-169)

To a vigorously stirred solution of (+)\-168 (800 mg, 1.1 mmol, 1.0 eq., 89% D\(_6\), 11% D\(_5\)) in MeCN (50 mL) was added, dropwise, over a period of 5 min, a solution of NaIO\(_4\) (584 mg, 2.73 mmol, 2.5 eq.) and RuCl\(_3\)·3H\(_2\)O (29 mg, 0.11 mmol, 0.1 eq.) in H\(_2\)O (5 mL) and the reaction mixture was stirred vigorously for 5 min. TLC analysis of the reaction mixture (1:9 EtOH/CHCl\(_3\)) indicated the reaction was complete. The solution was concentrated \textit{in vacuo} to ca. 10 mL and aqueous Na\(_2\)S\(_2\)O\(_3\) (10% \textit{w/v}, 100 mL) was added. The organic components were extracted with EtOAc (3 \times 100 mL), washed with saturated aqueous NaCl (50 mL), dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The product was purified using silica gel flash column chromatography on a Biotage sys-
tem using 10% EtOH in CHCl₃, followed by crystallisation from CHCl₃ to afford the title compound as a colourless solid (250 mg, 30%, 89% D₆, 11% D₅); Rₚ 0.29 (EtOH/CHCl₃ 1:9); [α]₁⁰⁰° = +31.6 (c 1.0, MeOH); m.p. 99-104 °C (from CHCl₃); νₘₐₓ (thin film)/cm⁻¹ 3365 (O-H, w), 1717 (C=O, m), 1026 (C-O, s), 1000 (C-O, s), 945 (P-O, m); ¹H NMR* (400 MHz; CDCl₃/MeOD 1:1) δ 8.21 (2H, d, J 7.1, H-9), 8.16 (2H, d, J 7.6, H-14), 7.68-7.60 (2H, m, H-11, H-16), 7.56-7.49 (4H, m, H-10, H-15), 4.35-4.18 (4H, m, H-17, H-26), 4.11-3.98 (2H, m, H-20), 3.94-3.81 (2H, m, H-23), 2.83-2.66 (4H, m, H-18, H-27), 2.44-2.20 (4H, m, H-21, H-24); ¹H NMR* (400 MHz; CD₂Cl₂/MeOD 1:1) δ 8.15 (2H, d, J 7.8, H-9), 8.10 (2H, d, J 7.8, H-14), 7.62-7.56 (2H, m, H-11, H-16), 7.50-7.44 (4H, m, H-10, H-15), 4.29-4.11 (4H, m, H-17, H-26), 4.05-3.93 (2H, m, H-20a, H-23a), 3.88-3.75 (2H, m, H-20b, H-23b), 2.78-2.60 (4H, m, H-18, H-27), 2.37-2.13 (4H, m, H-21, H-24); ¹³C NMR* (126 MHz; CDCl₃/MeOD 1:1) δ 166.1 (C-12), 165.6 (C-7), 133.7 (C-16), 133.5 (C-11), 130.0 (C-14), 129.8 (C-9, C-13), 129.4 (C-8), 128.59 (C-15), 128.57 (C-10), 117.2 (C-22), 116.7 (C-25), 116.6 (C-19, C-28), 72.7-72.0 (m, C-6), 72.0-71.2 (m, C-3), 69.7-69.1 (m, C-2), 69.1-68.5 (m, C-1), 63.3 (d, Jₚ 5.8, C-17), 63.2 (d, Jₚ 5.8, C-20), 62.9 (d, Jₚ 5.2, C-23), 62.8 (d, Jₚ 5.2, C-26), 18.9 (d, Jₚ 7.9, C-18, C-27), 18.5 (d, Jₚ 7.8, C-21, C-24); ³¹P NMR (126 MHz; CD₂Cl₂/MeOD 1:1) δ -3.51 (P-4), -3.68 (P-5); ²H NMR (77 MHz; CHCl₃; D₆-DMSO) δ 5.66 (D-6), 5.20 (D-3, D-4), 4.74 (D-5), 4.24 (D-2), 3.84 (D-1); HRMS m/z (ES⁻) Found 711.1520 [MD₅-CH₂CH₂CN⁻] (C₂₀H₂₅D₅N₃O₁₄P₂ requires 711.1522), 712.1578 [MD₆-CH₂CH₂CN⁻] (C₂₀H₂₅D₆N₃O₁₄P₂ requires 712.1585); m/z (ES⁻) 711.1 ([MD₅-CH₂CH₂CN⁻], 7%), 712.1 ([MD₆-CH₂CH₂CN⁻], 100%), 800.1 ([MD₅+Cl⁻], 3%), 801.1 ([MD₆+Cl⁻], 19%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 16.9
min, 100.0%.

* A second set of NMR data was obtained in CD$_2$Cl$_2$ for $^1$H and $^{13}$C due to the fact that key carbon peaks (C-4 and C-5) were obscured by the solvent peak in CDCl$_3$.

### 7.6 Benzylated Derivatives

(+)-(1$^R$,2$^R$,3$^S$,6$^S$)-3,6-Bis(benzyloxy)-cyclohex-4-ene-1,2-diyl bis((2',2',2'-trichloroethyl)carbonate) ((+)-183)

To a solution of (+)-175 (1.78 g, 1.43 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (36 mL) was added trifluoroacetic acid (4 mL) and the reaction mixture was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was concentrated in vacuo and placed under an atmosphere of Ar. The solid was dissolved in anhydrous dioxane (20 mL), benzyl 2,2,2-trichloroacetimidate (1.07 mL, 5.74 mmol, 4.0 eq.) was added and the solution was cooled to 0 °C. Triflic acid (0.05 mL) was added and the reaction was stirred at room temperature for 3 h. $^1$H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was diluted with EtOAc (200 mL). The organic components were washed with saturated aqueous NaHCO$_3$ (100 mL), saturated aqueous NaCl (100 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 8% EtOAc in petroleum ether followed by 12% EtOAc in petroleum ether to afford the title compound as a colourless oil (600 mg, 62%) that was used without further purification: $R_f$ 0.52 (EtOAc/petroleum ether 1:4); $[\alpha]_{D}^{25} = +72.5$ (c 2.9, CHCl$_3$); $\bar{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$
1772 (C=O, s), 1383 (C-H, w), 1259 (C-O, s), 1230 (C-O, s), 1067 (C-O, m), 1008 (C-O, m); ¹H NMR (400 MHz; CD₂Cl₂) δ 7.38-7.28 (10H, m, H-9, H-10, H-11, H-14, H-15, H-16), 5.86 (2H, s, H-1, H-2), 5.18 (2H, dd, J 5.5, 2.4, H-3, H-6), 4.85 (2H, d, J 12.0, H-18a, H-21a), 4.76 (2H, d, J 12.0, H-18b, H-21b), 4.69 (2H, d, J 11.7, H-7a, H-12a), 4.58 (2H, d, J 11.7, H-7b, H-12b), 4.40 (2H, dd, J 5.5, 2.4, H-4, H-5); ¹³C NMR (101 MHz; CD₂Cl₂) δ 153.9 (C-17, C-20), 138.0 (C-8, C-13), 128.8 (C-10, C-15), 128.3 (C-11, C-16), 128.1 (C-9, C-14), 127.4 (C-1, C-2), 94.8 (C-19, C-22), 78.1 (C-3, C-6), 77.23 (C-4, C-5), 77.16 (C-18, C-21), 72.1 (C-7, C-12).

Mass spectrometry data were not obtained due to the poor ionisation of the compound in various techniques (ESI, EI, FI and MALDI).

(+)-(3S,4S,5S,6S)-3,6-Bis(benzyloxy)-cyclohex-1-ene-4,5-diol ((+)-184)⁷⁴

To a solution of (+)-183 (716 mg, 1.06 mmol, 1.0 eq.) in a mixture of glacial AcOH (5 mL) and THF (5 mL) was added zinc powder (2.08 g, 31.8 mmol, 30.0 eq.) and the suspension was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The suspension was filtered through a plug of Celite® and the plug was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo and the resulting oil was azeotroped with cyclohexane (3 × 20 mL). The product was purified using silica gel flash column chromatography on a Biotage system using 12-100% EtOAc in petroleum ether to afford the title compound as a colourless oil (304 mg, 88%): \( R_f \) 0.10 (MeOH/CH₂Cl₂ 1:9); \([\alpha]_D^{25} = +124.8 \) (c 1.0, Acetone) {lit.⁷⁴ +130 (c. 1.6, Acetone)}; ¹H NMR (400 MHz; CDCl₃) δ 7.40-7.27 (10H, m, H-ar.), 5.74 (2H, s, H-1, H-2), 4.71 (4H, s, H-7, H-12), 4.05 (2H, dd, J 5.1, 2.4,
$H-3$, $H-6$), 3.73 (2H, dd, $J$ 5.1, 2.4, $H-4$, $H-5$), 3.23 (OH, br s, OH); \textit{m/z} (ES$^+$) 349.2 ([M+Na]$^+$, 100%). These data are in agreement with the literature.$^{74}$

$\left(\text{+}\right)$-Tetrabenzyld-$\left(3S,4R,5R,6S\right)$-3,6-bis(benzyloxy)-cyclohex-4-ene-1,2-diyld) bis(phosphate) $\left(\left(\text{+}\right)-189\right)$

To a solution of diol 184 (272 mg, 0.83 mmol, 1.0 eq.) and dibenzyl $N,N$-diisopropylphosphoramidite 185 (1.12 mL, 3.33 mmol, 4.0 eq.) in CH$_2$Cl$_2$ (10 mL) under an atmosphere of Ar was added 1$H$-tetrazole (3-4 wt.\% in MeCN, 7.74 mL, 3.33 mmol, 4.0 eq.) and the reaction solution was stirred at room temperature for 2 h, during which time the reaction mixture became cloudy. TLC analysis of the reaction mixture (1:19 MeOH/CH$_2$Cl$_2$) indicated the reaction was complete. The reaction mixture was cooled to $-78^\circ$C 3-chloroperbenzoic acid (77%, 746 mg, 3.33 mmol, 4.0 eq.) was added and the reaction mixture was stirred at room temperature for 1 h. After this time, the reaction was diluted with CH$_2$Cl$_2$ (100 mL) and the organic components were washed with aqueous Na$_2$S$_2$O$_3$ (10% \textit{w/v}, 50 mL), saturated aqueous NaHCO$_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The product was purified twice using silica gel flash column chromatography on a Biotage system using 5-50% EtOAc in petroleum ether then 0-5% MeOH in CH$_2$Cl$_2$ to afford the title compound as a colourless oil (503 mg, 72%) that was used without further purification: $R_f$ 0.81 (EtOAc); $[\alpha]_D^{25} = +48.7$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1497 (C=C, w), 1446
(C=\text{C}, \text{m}), 1386 (C-O, s), 1017 (C-O, s); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) $\delta$ 7.36-7.15 (30H, m, H-ar.), 5.80 (2H, s, H-1, H-2), 5.04 (2H, dd, J 11.7, 7.0, H-17a), 4.98 (4H, dd, J 12.1, 8.1, H-17b, H-22a), 4.91 (2H, dd, J 12.1, 8.5, H-22b), 4.73-4.69 (2H, m, H-4, H-5), 4.64 (2H, d, J 11.3, H-7a, H-12a), 4.59 (2H, d, J 11.3, H-7b, H-12b), 4.33 (2H, dd, J 5.0, 2.3, H-3, H-6); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) $\delta$ 138.5 (C-8, C-13), 136.7 (d, J$_P$ 7.7, C-23), 136.6 (d, J$_P$ 7.2, C-18), 128.76, 128.75, 128.7, 128.57, 128.56, 128.3, 128.1, 128.0 (C-ar. $\times$ 30), 127.6 (C-1, C-2), 78.5 (dd, J$_P$ 5.5, C-4, C-5), 78.4 (C-3, C-6), 71.3 (C-7, C-12), 69.7 (d, J$_P$ 5.8, C-17), 69.6 (d, J$_P$ 5.8, C-22); $^{31}$P NMR (162 MHz; CD$_2$Cl$_2$) $\delta$ -1.65 (P-4, P-5); HRMS $m/z$ (ES$^+$) Found 847.2793 [M+H]$^+$ (C$_{48}$H$_{48}$O$_{10}$P$_2$ requires 847.2795); $m/z$ (ES$^+$) 847.1 ([M+H]$^+$, 99%), 869.1 ([M+Na]$^+$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 6.5 min, 85.8%.

(−)-3,6-Di-O-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-d-myoinositol (−)-154

To a solution of (+)-189 (490 mg, 0.58 mmol, 1.0 eq.) in MeCN (6 mL) at 0 °C was added a solution of NaIO$_4$ (186 mg, 0.87 mmol, 1.5 eq.) and RuCl$_3$·3H$_2$O (8 mg, 0.03 mmol, 0.05 eq.) in H$_2$O (1.5 mL). The reaction mixture was stirred vigorously for 4 min at 0 °C. TLC analysis of the reaction mixture (EtOAc) indicated the reaction was complete. The reaction was quenched with aqueous Na$_2$S$_2$O$_3$ (10% $w/v$, 20 mL). The organic components were extracted using EtOAc (3 $\times$ 30 mL), combined, washed with saturated aqueous NaCl (30 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified
using silica gel flash column chromatography on a Biotage system using 12-100% EtOAc in petroleum ether to afford the title compound as a colourless oil (295 mg, 58%): \( R_f \) 0.35 (EtOAc/petroleum ether 1:9); \( [\alpha]_{25}^{25} \) = \(-19.7 \) (c 2.0, CHCl\(_3\)); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3379 (O-H, w), 3064 (C-H ar., w), 3033 (C-H ar., w), 2895 (C-H ar., w), 1497 (C=C, w), 1455 (C=C, w), 1377 (C-H, w), 1267 (C-H, m), 1215 (C-O, m), 1072 (C-O, s), 1013 (C-O, s); \( ^1\)H NMR (500 MHz; CD\(_2\)Cl\(_2\)) \( \delta \) 7.39-7.10 (30H, m, H-ar.), 5.06-4.74 (11H, m, H-4, H-12, H-17, H-22), 4.63 (1H, d, J 11.8, H-7a), 4.57 (1H, d, J 11.8, H-7b), 4.48 (1H, ddd, J 9.3, 9.3, 9.3, H-5), 4.13 (1H, dd, J 2.7, 2.7, H-2), 3.88 (1H, dd, J 9.3, 9.3, H-6), 3.57 (1H, dd, J 9.3, 2.7, H-1), 3.52 (1H, dd, J 9.3, 2.7, H-3), 3.10 (1H, br s, O-H-2), 2.77 (1H, br s, O-H-1); \( ^{13}\)C NMR (126 MHz; CD\(_2\)Cl\(_2\)) \( \delta \) 139.1 (C-13), 138.0 (C-8), 136.7-136.4 (m, C-18, C-23), 128.9-127.8 (m, C-ar. \times 30), 80.1 (C-6), 79.2 (dd, J\(_P\) 5.8, 5.8, C-5), 78.20 (C-3), 78.16 (dd, J\(_P\) 5.2, 5.2, C-4), 75.0 (C-12), 72.7 (C-7), 72.1 (C-1), 69.8, 69.7, 69.6 (C-17, C-22), 68.9 (C-2); \( ^{31}\)P NMR (162 MHz; CD\(_2\)Cl\(_2\)) \( \delta \) -1.38 (P-5), -1.51 (P-4); HRMS m/z (ES\(^+\)) Found 881.2855 [M+H\(^+\)] (\( C_{48}H_{51}O_{12}P_2 \) requires 881.2850); m/z (ES\(^+\)) 881.1 ([M+H\(^+\), 100%] 903.1 ([M+Na\(^+\), 51%]; NP-HPLC (0-100% isopropanol/hexane) Retention Time = 6.8 min, 95.6%.

\((-\))-1-Acetyl-3,6-di-O-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-\( \alpha \)-myo-inositol ((\(-\))-195)

To a solution of \((-\))-154 (138 mg, 0.157 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) was added 4-dimethyl-
aminopyridine (1 mg, 0.008 mmol, 0.05 eq.), pyridine (0.020 mL, 0.25 mmol, 1.5 eq.), and acetyl chloride (0.020 mL, 0.28 mmol, 1.8 eq.) and the resulting suspension was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (50 mL) and the the organic components were washed with aqueous HCl (1 M, 30 mL), saturated aqueous NaHCO₃ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using a 12-100% EtOAc in petroleum ether to afford the title compound as a colourless film (76 mg, 53%): R_f 0.61 (EtOAc/petroleum ether 1:1); [α]_D^25 = −20.5 (c 1.0, CHCl₃); ν_max (thin film)/cm⁻¹ 3356 (O-H, w), 3033 (C-H ar., w), 1741 (C=O, m), 1498 (C=C, m), 1455 (C=C, m), 1370 (C-H, m), 1270 (C-H, m), 1022 (C-H ar., s); ^1H NMR (500 MHz; CD₂Cl₂) δ 7.40-7.10 (30H, m, H-ar.), 5.10-4.77 (11H, m, H-1, H-4, H-12a, H-17, H-22), 4.69-4.62 (2H, m, H-7a, H-12b), 4.61-4.51 (2H, m, H-5, H-7b), 4.27 (1H, dd, J 2.5, 2.5, H-2), 4.15 (1H, dd, J 9.9, 9.9, H-6), 3.61 (1H, dd, J 9.7, 2.5, H-3), 2.89 (1H, br s, OH), 1.93 (3H, s, H-28); ^13C NMR (126 MHz; CD₂Cl₂) δ 170.4 (C-27), 139.0 (C-13), 137.7 (C-8), 136.7 (d, J_P 7.7 C-18 or C-23), 136.61 (d, J_P 7.7, C-18 or C-23), 136.56 (d, J_P 7.7, C-18 or C-23), 136.5 (d, J_P 7.7, C-18 or C-23), 128.81, 128.75, 128.6, 128.5, 128.30, 128.28 , 128.25 , 128.19, 127.7, 127.6 (C-ar. × 30), 79.3 (dd, J_P 6.1, 6.1, C-5), 78.14 (dd, J_P 6.1, 6.1, C-4), 78.10 (C-3), 77.7 (C-6), 75.3 (C-12), 73.0 (C-1), 72.7 (C-7), 69.8 (d, J_P 5.8, C-17 or C-22), 69.7 (d, J_P 5.8, C-17 or C-22), 69.6 (d, J_P 5.8, C-17 or C-22), 69.5 (d, J_P 5.8, C-17 or C-22), 67.2 (C-2), 21.0 (C-28); ^31P NMR (162 MHz; CD₂Cl₂) δ -1.46 (P-5), -1.50 (P-4); HRMS m/z (ES⁺) Found 923.2949 [M+H]^+ (C₅₀H₃₃O₁₃P₂ requires 923.2956); m/z (ES⁺) 923.2 ([M+H]^+, 100%), 945.2 ([M+Na]^+, 24%); NP-HPLC (2-30% isopropanol/hexane) Retention Time = 7.5 min, 80.5%.
To a solution of (+)-184 (377 mg, 1.16 mmol, 1.0 eq.) and phosphoramidite 187 (1.10 g, 4.62 mmol, 4.0 eq.) in CH$_2$Cl$_2$ (15 mL) under an atmosphere of Ar was added 1H-tetrazole (3-4% in MeCN, 10.75 mmol, 4.62 mL, 4.0 eq.) and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (EtOAc) indicated the reaction was complete. The reaction mixture was cooled to -78 °C, 3-chloroperbenzoic acid (77%, 1.04 g, 4.62 mmol, 4.0 eq.) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with CH$_2$Cl$_2$ (100 mL) and the organic components were washed with aqueous Na$_2$S$_2$O$_3$ (10% w/v, 50 mL), saturated aqueous NaHCO$_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 12-100 % EtOAc in petroleum ether to afford the title compound as a colourless oil (245 mg, 31%): $R_f$ 0.62 (EtOAc/cyclohexane 3:1); $[\alpha]^{25}_D$ = +22.9 (c 0.65, CHCl$_3$) {lit.$^{75}$ +21.5 (c. 0.65, CHCl$_3$)}; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.45-7.40 (4H, m, H$_{10}$, H$_{15}$), 7.38-7.24 (12H, m, H$_{ar}$), 7.21-7.17 (2H, m, H$_{11}$, H$_{16}$), 5.79 (2H, ddd, J 7.45-7.40 (4H, m, H$_{10}$, H$_{15}$), 7.38-7.24 (12H, m, H$_{ar}$), 7.21-7.17 (2H, m, H$_{11}$, H$_{16}$), 5.79 (2H, s, H$_{1}$, H$_{2}$), 5.53 (2H, dd, J 14.5, 10.4), 5.24-5.00 (6H, m, H$_{17}$, H$_{21}$), 4.96 (2H, dddd, J 5.6, 5.6, 2.9, 2.9, H$_{4}$, H$_{5}$), 4.72 (2H, d, J 12.2, H$_{7a}$, H$_{12a}$), 4.68 (2H, d, J 12.2, H$_{7b}$, H$_{12b}$), 4.39 (2H, dd, J 5.6, 2.9, H$_{3}$, H$_{6}$); $^{31}$P NMR (162 MHz; CDCl$_3$) $\delta$ -1.41; $m/z$ (ES$^+$) 691.1 ([M+H]$^+$, 100%), 713.1 ([M+Na]$^+$, 54%). These data are in agreement with the literature.$^{75}$
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(–)-3,6-Di-O-benzyl-4,5-bis-O-(3-oxo-1,5-dihydro-3λ5-2,4,3-benzodioxaphosphepin-3-yl)-D-myo-inositol ((–)-192)\(^\text{75}\)

To a vigorously stirred solution of (+)-191 (240 mg, 0.35 mmol, 1.0 eq.) in MeCN (4 mL) was added a solution of NaIO\(_4\) (111 mg, 0.52 mmol, 1.5 eq.) and RuCl\(_3\)·3H\(_2\)O (4.5 mg, 0.017 mmol, 0.05 eq.) in H\(_2\)O (1 mL) and the reaction mixture was stirred vigorously for 4 min. TLC analysis of the reaction mixture (1:2 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched with aqueous Na\(_2\)S\(_2\)O\(_3\) (10% w/v, 30 mL). The organic components were extracted with EtOAc (3 × 30 mL), washed with saturated aqueous NaCl (2 × 10 mL), dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The product was purified using silica gel flash column chromatography on a Biotage system using 12-100% EtOAc in petroleum ether, followed by a second column using 0-10% MeOH in CHCl\(_3\) to afford the title compound as a colourless film (171 mg, 67%): R\(_f\) 0.66 (MeOH/CHCl\(_3\) 1:9); \([\alpha]_{D}^{25} = -33.0 (c 1.0, \text{CHCl}_{3})\) \{lit.\(^\text{75} -32.0 (c 1.0, \text{CHCl}_{3})\}; \text{H NMR (400 MHz; CDCl}_{3}\) \(\delta 7.44-7.06 (18H, m, H-ar.), 5.53-5.49 (2H, m), 5.16-4.92 (7H, m, H-4, H-17, H-21), 4.85 (1H, d, J 11.4, H-7a), 4.81 (1H, d, J 11.4, H-7b), 4.74-4.63 (3H, m, H-5, H-12), 4.15 (1H, d, J 2.4, 2.4, H-2), 3.90 (1H, dd, J 9.6, 9.6, H-6), 3.58 (1H, d, J 9.0, H-1), 3.48 (1H, dd, J 9.6, 2.6, H-3), 3.37 (1H, br s, OH-1), 3.02 (1H, br s, OH-2); \(^{31}\)P NMR (162 MHz; CDCl\(_3\)) \(\delta -0.31 (P-4), -0.88 (P-5); m/z (ES\(^{+}\)) 725.1 ([M+H]\(^+\), 100%), 747.1 ([M+Na]\(^+\), 16%). These data are in agreement with the literature.\(^\text{75}\)
(+)-3,6-Di-O-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-myo-inositol ((+)-202)

To a solution of (+)-183 (965 mg, 1.43 mmol, 1.0 eq.) in MeCN (16 mL) was added a solution of RuCl$_3$·3H$_2$O (19 mg, 0.07 mmol, 0.05 eq.) and NaIO$_4$ (457 mg, 2.15 mmol, 1.5 eq.) in H$_2$O (4 mL) and the reaction mixture was stirred vigorously for 4 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched with aqueous Na$_2$S$_2$O$_3$ (10% w/v, 100 mL). The organic components were extracted with EtOAc (3 × 50 mL), combined, washed with saturated aqueous NaCl (2 × 30 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 12-100% EtOAc in petroleum ether to afford the title compound as a colourless foam (449 mg, 44%): $R_f$ 0.34 (EtOAc/petroleum ether 1:1); $[\alpha]^{25}_D = +10.4$ (c 1.0, CHCl$_3$); $\bar{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$ 3448 (O-H, w), 2957 (C-H ar., w), 2877 (C-H ar., w), 1771 (C=O, s), 1454 (C=C, m), 1374 (C-H, m), 1262 (C-H, s), 1234 (C-O, s), 1133 (C-O, m), 1065 (C-O, m), 1002 (C-O, m); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) $\delta$ 7.39-7.27 (10H, m, H-ar), 5.34 (1H, dd, $J$ 9.8, 9.8, H-4), 4.95 (1H, dd, $J$ 9.8, 9.8, H-5), 4.82-4.68 (7H, m, H-7, H-12a, H-18, H-21), 4.59 (1H, d, $J$ 11.7, H-12b), 4.26 (1H, dd, $J$ 2.7, 2.7, H-2), 3.95 (1H, dd, $J$ 9.8, 9.8, H-6), 3.65-3.59 (1H, m, H-1), 3.60 (1H, dd, $J$ 9.8, 2.7, H-3), 2.70 (1H, br s, OH-2), 2.52 (1H, br d, $J$ 6.3, OH-1); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) $\delta$ 153.94, 153.92 (C-17, C-20), 138.4 (C-8), 137.5 (C-13), 128.9, 128.8, 128.6, 128.3, 128.22, 197
128.16 (C-ar. × 10), 94.8, 94.7 (C-19, C-22), 79.4 (C-6), 78.2 (C-5), 77.3 (C-18, C-21), 77.2 (C-3), 77.0 (C-4), 75.7 (C-7), 72.8 (C-12), 72.0 (C-1), 69.2 (C-2); HRMS m/z (ES⁻) Found 752.9631 [M+Cl₆+Formic acid-H]⁻ (C₂₇H₂₇Cl₆O₁₂ requires 752.9639); m/z (ES⁻) 753.0 ([M+Cl₆+Formic acid-H]⁻, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 6.9 min, 85.9%.

(+)-2-Acetyl-3,6-di-O-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-myo-inositol ((+)-200)

A solution of (+)-202 (436 mg, 0.61 mmol, 1.0 eq.), triethylorthoacetate (3.4 mL, 18 mmol, 30 eq.) and 4-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol, 0.1 eq.) in anhydrous THF (15 mL) under an atmosphere of Ar was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was concentrated in vacuo and the flask was cooled to 0 °C. A 0 °C pre-cooled solution of aqueous AcOH (80% v/v, 15 mL) was added to the flask and the solution was stirred at 0 °C for 1 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (150 mL) and the organic components were washed with water (2 × 50 mL), saturated aqueous NaHCO₃ (2 × 50 mL), saturated aqueous NaCl (2 × 50 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% EtOAc in petroleum ether to afford a colourless foam (395 mg, 86%) that was used without further
purification: R_f 0.60 (EtOAc/petroleum ether 1:2); [α]_{D}^{25} = +22.5 (c 1.0, CHCl_3); ν_{max} (thin film)/cm\(^{-1}\) 3503 (O-H, w), 3032 (C-H ar., w), 2957 (C-H ar., w), 1773 (C=O, s), 1454 (C-H, w), 1373 (C-H, m), 1230 (C-O, s), 1134 (C-O, m), 1071 (C-O, m), 1005 (C-O, m);

\(^1\)H NMR (500 MHz; CD_2Cl_2) δ 7.38-7.23 (10H, m, H-ar.), 5.72 (1H, dd, J 3.0, 3.0, H-2), 5.26 (1H, dd, J 10.0, 10.0, H-4), 5.00 (1H, dd, J 10.0, 10.0, H-5), 4.81-4.67 (7H, m, H-7, H-12a, H-21), 4.44 (1H, d, J 11.6, H-12b), 3.94 (1H, dd, J 10.0, 10.0, H-6), 3.77 (1H, ddd, J 10.0, 3.0, 3.0, H-1), 3.65 (1H, dd, J 10.0, 3.0, H-3), 2.34 (1H, d, J 3.6, O\_H), 2.15 (3H, s, H-24); \(^1\)C NMR (126 MHz; CD_2Cl_2) δ 170.6 (C-23), 153.8 (C-17, C-20), 138.1 (C-8), 137.3 (C-13), 128.42, 128.38, 128.2 (C-ar. × 10), 94.68, 94.66 (C-19, C-22), 79.4 (C-6), 78.4 (C-5), 77.3 (C-18, C-21), 77.1 (C-4), 75.8 (C-7), 75.1 (C-3), 72.2 (C-12), 70.4 (C-1), 68.9 (C-2), 21.0 (C-24); HRMS m/z (ES\(^{+}\)) Found 772.9660 [M\(^{35}\)Cl_6+Na]\(^{+}\) (C_{28}H_{35}Cl_6O_{11}Na requires 772.9655); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 6.1 min, 92.6%.

\((\pm)-1\)-Acetyl-3,6-di-O-benzyl-4,5-bis(2’,2’,2’-trichloroethylcarbonate)-\(\alpha\)-myo-inositol ((\pm)-201)

To a solution of (+)-202 (276 mg, 0.39 mg, 1.0 eq.) in CH_2Cl_2 (2 mL) was added pyridine (62 µL, 0.78 mmol, 2.0 eq.) followed by AcCl (55 µL, 0.78 mmol, 2.0 eq.) and the reaction mixture was stirred at room temperature for 10 min. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic components were washed
with aqueous HCl (1 M, 50 mL), saturated aqueous NaHCO₃ (50 mL), saturated aqueous NaCl (50 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% EtOAc in petroleum ether to afford the title compound as a colourless oil (240 mg, 82%): Rf 0.28 (EtOAc/petroleum ether 1:2); ¹H NMR (400 MHz; CD₂Cl₂) δ 7.38-7.22 (10H, m, H-ar.), 5.36 (1H, dd, J 10.1, 10.1, H-6), 5.00 (1H, dd, J 10.1, 10.1, H-5), 4.91 (1H, dd, J 10.1, 2.7, H-3), 4.80 (1H, d, J 12.0, H-18a), 4.75 (1H, d, J 12.0, H-21a), 4.74-4.67 (5H, m, H-7, H-12a, H-18b, H-21b), 4.57 (1H, d, J 11.6, H-12b), 4.36 (1H, dd, J 2.7, 2.7, H-2), 4.21 (1H, dd, J 10.1, 10.1, H-4), 3.69 (1H, dd, J 10.1, 2.7, H-1), 2.57 (1H, br s, OH), 2.05 (3H, s, H-24); ¹³C NMR (101 MHz; CD₂Cl₂) δ 170.3 (C-23), 153.9, 153.8 (C-17, C-20), 138.2 (C-8), 137.3 (C-13), 128.9, 128.7, 128.6, 128.2, 128.0 (C-ar. × 10), 94.73, 94.67 (C-19, C-22), 78.1 (C-5), 77.3 (C-18, C-21), 77.1 (C-1), 76.9 (C-4), 76.7 (C-6), 75.9 (C-7), 72.9 (C-12), 72.8 (C-3), 67.5 (C-2), 21.1 (C-24).

Mass spectrometry data were not obtained due to the poor ionisation of the compound in various techniques (ESI, EI, FI and MALDI).

(+)-2-Acetyl-3,6-di-O-benzyl-1-(((1,2-dipalmitoyl-sn-glycerol)(benzyl) phosphoryl)oxy)-α-mylo-inositol (205)

To a solution of (+)-200 (93 mg, 0.12 mmol, 1.0 eq.) and phosphoramidite 207 (250 mg, 0.31 mmol, 2.5 eq.) in CH₂Cl₂ (5 mL) under an atmosphere of Ar was added a solution of 1H-tetrazole (3-4 wt.% in MeCN, 0.72 mL, 0.31 mmol, 2.5 eq.) and the reaction mixture was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:3
EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to –78 °C, 3-chloroperbenzoic acid (77%, 69 mg, 0.31 mmol, 2.5 eq.) was added and the reaction mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The resulting oil was purified using silica gel flash column chromatography on a Biotage system using 5-40% EtOAc in petroleum ether to give a mixture of three phospholipid products as a colourless oil (ca. 250 mg). The oil was dissolved in a mixture of AcOH (2 mL) and THF (2 mL), zinc powder (300 mg) was added and the reaction suspension was stirred at room temperature for 48 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The suspension was filtered through a pad of Celite®, the pad was washed with EtOAc (50 mL), and the filtrate concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 30% EtOAc in petroleum ether followed by 50% EtOAc in petroleum ether to afford the title compound as a colourless film (84 mg, 62%) as a ca. 1.8:1 mixture of diastereomers: Rf 0.48 (EtOAc/petroleum ether 1:1); [α]D25 = +10.9 (c 1.0, CHCl3); νmax (thin film)/cm–1 3405 (O-H, w), 2923 (C-H ar., s), 2853 (C-H ar., s), 1745 (C=O, s), 1456 (C-H, m), 1375 (C-O, m), 1232 (C-O, s), 1115 (C-O, s), 1017 (C-O, s); 1H NMR (400 MHz; CD2Cl2) Diastereomer A*: δ 7.43-7.23 (15H, m, H-ar), 5.90 (1H, dd, J 2.6, 2.6, H-2), 5.18 (1H, dddd, J 5.2, 5.2, 5.2, 5.2, H-25), 5.07-4.93 (2H, m, H-19), 4.87 (1H, d, J 11.1, H-7a), 4.83 (1H, d, J 11.1, H-7b), 4.74 (1H, d, J 11.1, H-12a), 4.43-4.33 (2H, m, H-1, H-12b), 4.24 (1H, dd, J 12.0, 2.4, H-26a), 4.18-4.01 (3H, m, H-24, H-26b), 3.84-3.74 (2H, m, H-4, H-6), 3.50 (1H, dd, J 9.4, 9.4, H-5), 3.38 (1H, dd, J 9.8, 2.6, H-3), 2.89 (1H, br s, O-H-5), 2.81 (1H, br s, O-H-4), 2.32-2.17 (4H, m, H-28, H-44), 2.14 (3H, s, H-18), 1.62-1.48 (4H, m, H-29, H-45), 1.38-1.18 (48H, m, H-(30-41), H-(46-57)), 0.92-0.86 (6H, m, H-42, H-58); Diastereomer B*: δ 7.43-7.23 (15H, m, H-ar), 5.88 (1H, dd, J 2.6, 2.6, H-2), 5.10 (1H, dddd, J 5.2, 5.2, 5.2, 5.2, H-25), 5.07-4.93 (2H, m, H-19), 4.83 (1H, d, J 11.1, H-7a), 4.79 (1H, d, J 11.1, H-7b), 4.73 (1H, d, J 11.1, H-12a), 4.43-4.33 (2H, m, H-1, H-12b), 4.18-4.01 (3H, m, H-24, H-26a), 3.98 (1H, dd, J 12.0, 2.4, H-26b), 3.84-3.74 (2H, m, H-4, H-6), 3.50 (1H, dd, J 9.4, 9.4, H-5), 3.37 (1H, dd, J 9.8, 2.6, H-3), 2.89 (1H, br s, O-H-5), 2.81 (1H, br s, O-H-4), 2.32-2.17
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CHAPTER 7. EXPERIMENTAL

(4H, m, H-28, H-44), 2.10 (3H, s, H-18), 1.62-1.48 (4H, m, H-29, H-45), 1.38-1.18 (48H, m, H-(30-41), H-(46-57)), 0.92-0.86 (6H, m, H-42, H-58); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$)

Diastereomer A* $\delta$ 173.1 (C-27), 172.7 (C-43), 169.84 (C-17), 138.4 (d, $J_P$ 5.0, C-8), 137.4 (d, $J_P$ 4.0, C-13), 135.8 (d, $J_P$ 7.6, C-20), 128.53, 128.49, 128.45, 128.4, 128.31, 128.25, 128.2, 127.90, 127.77, 127.75, 127.7, 127.6 (C-ar $\times$ 15), 79.53 (d, $J_P$ 6.5, C-6), 77.33 (C-3), 76.24 (d, $J_P$ 6.7, C-1), 75.04 (C-7), 74.2 (C-5), 72.0 (C-4), 71.93 (C-12), 69.53 (C-25), 69.4-69.2 (m, C-19), 68.3 (C-2), 65.8 (d, $J_P$ 5.2, C-24), 61.6 (C-26), 34.1 (C-44), 33.90 (C-28), 31.9 (C-41, C-57), 29.7, 29.6, 29.5, 29.33, 29.28, 29.1-29.0 (m, C-(30-39), C-(46-55)), 24.80 (C-45), 24.7 (C-29), 22.7 (C-40, C-56), 20.60 (C-18), 13.9 (C-42, C-58), Diastereomer B* $\delta$ 173.0 (C-27), 172.7 (C-43), 169.80 (C-17), 138.4 (d, $J_P$ 5.0, C-8), 137.4 (d, $J_P$ 4.0, C-13), 135.7 (d, $J_P$ 7.6, C-20), 128.53, 128.49, 128.45, 128.4, 128.31, 128.25, 128.2, 127.90, 127.77, 127.75, 127.7, 127.6 (C-ar $\times$ 15), 79.46 (d, $J_P$ 6.5, C-6), 77.27 (C-3), 76.17 (d, $J_P$ 6.7, C-1), 75.02 (C-7), 74.2 (C-5), 72.0 (C-4), 71.90 (C-12), 69.49 (C-25), 69.4-69.2 (m, C-19), 68.2 (C-2), 65.4 (d, $J_P$ 5.2, C-24), 61.5 (C-26), 34.0 (C-44), 33.86 (C-28), 31.9 (C-41, C-57), 29.7, 29.6, 29.5, 29.33, 29.28, 29.1-29.0 (m, C-(30-39), C-(46-55)), 24.79 (C-45), 24.7 (C-29), 22.7 (C-40, C-56), 20.57 (C-18), 13.9 (C-42, C-58); $^{31}$P NMR (162 MHz; CD$_2$Cl$_2$)

Diastereomer A* $\delta$ -1.41, Diastereomer B* $\delta$ -1.61; HRMS m/z (ES$^+$) Found 1123.6848 [M+H]$^+$ (C$_{64}$H$_{100}$O$_{14}$P requires 1123.6845); m/z (ES$^+$) 1140.7 ([M+NH$_4$]$^+$, 100%), 1145.6 ([M+Na]$^+$, 68%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 6.9 min, 96.4%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A while the lower is diastereomer B.
(+)-3,6-Di-\textit{O}-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-1-\textit{O}-(2\textit{H}-tetrahydropyranyl)-\textit{d}-\textit{myo}-inositol ((+)-210)

To a solution of (+)-202 (853 mg, 1.20 mmol, 1.0 eq.) in \textit{CH}_2\textit{Cl}_2 (20 mL) under an atmosphere of Ar was added 3,4-dihydro-2\textit{H}-pyran (0.13 mL, 1.4 mmol, 1.2 eq.) followed by pyridinium \textit{p}-toluenesulfonate (30 mg, 0.12 mmol, 0.1 eq.) and the reaction mixture was stirred at room temperature for 90 min. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated some starting material (+)-200 remained, some product (+)-210 and some di-reacted compound. The reaction was concentrated \textit{in vacuo} and purified using silica gel flash column chromatography on a Biotage system using 5-40\% EtOAc in petroleum ether to afford the title compound as a colourless foam (753 mg) that was used without further purification as a mixture of diastereomers and an unknown impurity. Selected data: \textit{R}_f 0.89 (EtOAc/petroleum ether 1:1); \textit{^1}H NMR (400 MHz; CDCl\textsubscript{3}) \textit{Diastereomer A} \delta 7.37-7.23 (10H, m, \textit{H}-ar.), 5.43 (1H, dd, \textit{J} 10.0, \textit{H}-4), 5.03-4.92 (2H, m, \textit{H}-5, \textit{H}-23), 4.81-4.59 (8H, m, \textit{H}-7, \textit{H}-12, \textit{H}-18, \textit{H}-21), 4.37 (1H, dd, \textit{J} 2.6, 2.6, \textit{H}-2), 4.16-4.11 (1H, m, \textit{H}-6), 3.94-3.87 (1H, m, \textit{H}-27a), 3.85 (1H, dd, \textit{J} 10.0, 2.6, \textit{H}-1), 3.62-3.56 (1H, m, \textit{H}-3), 3.52-3.36 (1H, m, \textit{H}-27b), 2.67 (1H, br s, \textit{OH}), 1.95-1.35 (6H, m, \textit{H}-24, \textit{H}-25, \textit{H}-26); \textit{Diastereomer B} \delta 7.37-7.23 (10H, m, \textit{H}-ar.), 5.42 (1H, dd, \textit{J} 10.0, \textit{H}-4), 5.03-4.92 (1H, m, \textit{H}-5), 4.81-4.59 (9H, m, \textit{H}-7, \textit{H}-12, \textit{H}-18, \textit{H}-21, \textit{H}-23), 4.34 (1H, dd, \textit{J} 2.6, 2.6, \textit{H}-2), 4.16-4.11 (1H, m, \textit{H}-6), 3.94-3.87 (1H, m, \textit{H}-27a), 3.65 (1H, dd, \textit{J} 10.0, 2.6, \textit{H}-1), 3.62-3.56 (1H, m, \textit{H}-3), 3.52-3.36 (1H, m, \textit{H}-27b), 2.60 (1H, br s, \textit{OH}), 1.95-1.35 (6H, m, \textit{H}-24, \textit{H}-25, \textit{H}-26); \textit{^13}C NMR (101 MHz; CDCl\textsubscript{3}) \textit{Diastereomer
7.6. BENZYLATED DERIVATIVES

$\delta$ 153.64, 153.61 ($C$-17, $C$-20), 138.2 ($C$-8), 137.1 ($C$-13), 128.7, 128.6, 128.5, 128.34, 128.28, 128.2, 127.82, 127.76, 127.75, 127.68, 127.64, 127.63 ($C$-ar. × 15), 102.0 ($C$-23), 94.4 ($C$-19, $C$-22), 78.5 ($C$-6), 77.83 ($C$-5), 77.1 ($C$-3), 76.9 ($C$-18, $C$-21), 76.5 ($C$-4), 76.0 ($C$-7), 73.0 ($C$-1), 72.7 ($C$-12), 69.3 ($C$-2), 63.8 ($C$-27), 31.1 ($C$-25), 25.3 ($C$-26), 21.2 ($C$-24), Diastereomer B $\delta$ 153.61, 153.58 ($C$-17, $C$-20), 138.0 ($C$-8), 137.0 ($C$-13), 128.7, 128.6, 128.34, 128.28, 128.2, 127.82, 127.76, 127.75, 127.68, 127.64, 127.63 ($C$-ar. × 15), 94.3 ($C$-19, $C$-22), 93.5 ($C$-23), 78.3 ($C$-1), 77.81 ($C$-5), 77.6 ($C$-6), 77.1 ($C$-3), 76.9 ($C$-18, $C$-21), 76.4 ($C$-4), 76.0 ($C$-7), 72.6 ($C$-12), 65.0 ($C$-2), 61.0 ($C$-27), 30.0 ($C$-25), 25.2 ($C$-26), 18.4 ($C$-24).

(+)-2,3,6-Tri-O-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-1-O-(2$H$-tetrahydropyranyl)-$\alpha$-myo-inositol ((+)-211)

To a solution of (+)-210 (86 mg, 0.11 mmol, 1.0 eq.) in anhydrous DMF (1.0 mL) under an atmosphere of Ar was added NaH (60% dispersion in mineral oil, 5.0 mg, 0.13 mmol, 1.1 eq.) and the mixture was stirred at room temperature for 10 min. Benzyl bromide (15 $\mu$L, 0.13 mmol, 1.1 eq.) was added and the reaction mixture was stirred at room temperature for 72 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NaCl (30 mL), aqueous LiCl (0.5 M, 30 mL), saturated aqueous NaCl (30 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo.

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The product was purified using silica gel flash column chromatography on a Biotage system using 2-20% EtOAc in petroleum ether to afford the title compound as a colourless film (14 mg, 14%): \( R_f \) 0.74 (EtOAc/petroleum ether 1:3); \( [\alpha]_D^{25} = +11.8 \) (c 0.88, CHCl\(_3\)); \( \tilde{\nu}_{\text{max}} \) (thin film)/cm\(^{-1}\) 1774 (C=O, s), 1497 (C=C, m), 1454 (C=C, m), 1370 (C-H, m), 1259 (C-H, s), 1232 (C-O, s), 1123 (C-O, m), 1065 (C-O, m); \(^1\)H NMR (500 MHz; CD\(_2\)Cl\(_2\)) Diastereomer A \( \delta \) 7.47-7.24 (15H, m, H-ar), 5.45 (1H, dd, \( J = 10.0, 10.0, \) H-4), 5.01-4.61 (11H, m, H-5, H-7, H-12a, H-18, H-21, H-23, H-28), 4.55 (1H, d, \( J = 11.7, \) H-12b), 4.20 (1H, dd, J 2.1, 2.1, H-2), 4.12 (1H, dd, J 10.0, 10.0, H-6), 3.89 (1H, dt, J 10.8, 2.7, H-32a), 3.69 (1H, dd, J 10.0, 2.1, H-1), 3.61 (1H, dd, J 10.0, 2.1, H-3), 3.42-3.36 (1H, m, H-32b), 1.90-1.38 (6H, m, H-29, H-30, H-31); \(^13\)C NMR (126 MHz; CD\(_2\)Cl\(_2\)) Diastereomer A \( \delta \) 155.0, 154.9 (C-17, C-20), 140.2 (C-24), 139.6 (C-8), 138.9 (C-13), 129.81, 129.78, 129.7, 129.6, 129.3, 129.19, 129.16, 129.1, 129.02, 128.96, 128.9 (C-ar. \( \times \) 15), 102.9 (C-28), 95.8, 95.7 (C-19, C-22), 80.3 (C-6), 79.7 (C-1), 79.6 (C-5), 79.3 (C-3), 78.47 (C-4), 78.24, 78.20 (C-18, C-21), 77.9 (C-2), 77.02 (C-7), 76.01 (C-23), 74.0 (C-12), 64.6 (C-32), 31.5 (C-29), 26.5 (C-31), 20.0 (C-30), Diastereomer B \( \delta \) 155.0, 154.9 (C-17, C-20), 139.8 (C-24), 139.7 (C-8), 139.0 (C-13), 129.81, 129.78, 129.7, 129.6, 129.3, 129.19, 129.16, 129.1, 129.02, 128.9, 128.9 (C-ar. \( \times \) 15), 95.8, 95.7 (C-19, C-22), 95.3 (C-28), 79.6 (C-5), 79.2 (C-6), 78.9 (C-3), 78.45 (C-4), 78.22, 78.20 (C-18, C-21), 76.99 (C-7), 75.99 (C-23), 75.1 (C-1), 73.8 (C-12), 73.1 (C-2), 62.5 (C-32), 32.5 (C-29), 26.8 (C-31), 21.3 (C-30); HRMS m/z (ES\(^+\)) Found 905.0593 [M\(^{35}\)Cl\(_6\)+Na\(^+\)] \( \pm \) (C\(_{38}\)H\(_{40}\)\(^{35}\)Cl\(_6\)NaO\(_{11}\) requires 905.0594); m/z (ES\(^+\)) 900.0 ([M\(^{35}\)Cl\(_6\)+NH\(_4\)\(^+\)], 100%); NP-HPLC (2% isopropanol/hexane isocratic) Retention Time = 2.1 min, 100.0%. 

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A solution of (+)-211 (115 mg, 0.13 mmol, 1.0 eq.) was dissolved in a mixture of THF (0.4 mL) and aqueous AcOH (80% v/v, 2.0 mL) and the reaction mixture was stirred at 50 °C for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The organic components were washed with water (20 mL), saturated aqueous NaHCO₃ (20 mL), saturated aqueous NaCl (20 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 2-30% EtOAc in petroleum ether to afford the title compound as a colourless film (35 mg, 34%): \( R_f \) 0.49 (EtOAc/petroleum ether 1:4); \([\alpha]_{D}^{25}\) = +14.9 (c 1.0, CHCl₃); \( \bar{\nu}_{\text{max}} \) (thin film)/cm⁻¹ 3031 (C-H ar., w), 2881 (C-H ar., w), 1772 (C=O, s), 1497 (C-H, w) 1454 (w), 1372 (m), 1260 (C-O, s), 1233 (C-O, s), 1133 (C-O, m), 1068 (C-O, m), 1004 (C-O, m); \(^1\)H NMR (400 MHz; CD₂Cl₂) \( \delta \) 7.40-7.27 (15H, m, H-ar.), 5.44 (1H, dd, \( J \) 10.0, 10.0, \( H \)-4), 5.01 (1H, d, \( J \) 11.5, \( H \)-23a), 4.96 (1H, dd, \( J \) 10.0, 10.0, \( H \)-5), 4.82-4.67 (8H, m, \( H \)-7, \( H \)-12a, \( H \)-18, \( H \)-21, \( H \)-23b), 4.58 (1H, d, \( J \) 12.0, \( H \)-12b), 4.12 (1H, dd, \( J \) 2.7, 2.7, \( H \)-2), 3.94 (1H, dd, \( J \) 10.0, 10.0, \( H \)-6), 3.65-3.59 (2H, m, \( H \)-1, \( H \)-3), 2.30 (1H, d, \( J \) 7.4, OH); \(^{13}\)C NMR (101 MHz; CD₂Cl₂) \( \delta \) 154.0, 153.9 (C-17, C-20), 138.6 (C-24), 138.4 (C-8), 137.7 (C-13), 128.9, 128.84, 128.80, 128.4, 128.33, 128.25, 128.2, 128.1 (C-ar. × 15), 94.8, 94.7 (C-19, 206
Mass spectrometry data were not obtained due to the poor ionisation of the compound in various techniques (ESI, EI, FI and MALDI).

\((+)-(3R,4S,5S,6R)-3,6\text{-Bis(benzyloxy)}-4,5\text{-bis((4-methoxybenzyl)oxy)}\text{-cyclohex-1-ene}\ (\text{(+)-214})

To a solution of (+)-184 (491 mg, 1.5 mmol, 1.0 eq.) in anhydrous DMF (5 mL) under an atmosphere of \(\text{N}_2\) at 0 \(^\circ\text{C}\) was added NaH (60% dispersion in oil, 480 mg, 12.0 mmol, 8.0 eq.) and the suspension was stirred at 0 \(^\circ\text{C}\) for 10 min. After this time, 4-methoxybenzyl chloride (0.81 mL, 6.0 mmol, 4.0 eq.) was added and the reaction mixture was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (100 mL) and the organic components were washed with aqueous HCl (1 M, 50 mL), saturated aqueous NaHCO\(_3\) (50 mL), aqueous LiCl (0.5 M, 50 mL) and saturated aqueous NaCl (50 mL). Further product was backextracted from the combined aqueous phases using EtOAc (50 mL). The combined organic components were dried with \(\text{Na}_2\text{SO}_4\), filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% Et\(_2\)O in hexane to afford the title compound as a colourless oil (579 mg, 68%): \(R_f\) 0.41 (EtOAc/petroleum ether 1:4); \([\alpha]^{25}_D = +70.1\ (c 0.92, \text{CHCl}_3); \bar{\nu}_{\text{max}}\ (\text{thin film})/\text{cm}^{-1} 3032 (\text{C-H, m}), 2903 (\text{C-H, m}),\)
2859 (C-H, m), 2836 (C-H, m), 1613 (C=C, m), 1514 (C=C, s), 1454 (C=C, m), 1302 (C-O, m), 1248 (C-O, s), 1174 (C-O, m), 1146 (C-O, m), 1084 (C-O, s), 1070 (C-O, s), 1034 (C-O, m); \textsuperscript{1}H NMR (500 MHz; CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\) 7.35-7.26 (10H, m, -ar.), 7.25 (4H, dt, \(J\) 8.5, 2.0, -19, -25), 6.83 (4H, dt, \(J\) 8.5, 2.0, -20, -26), 5.75 (2H, s, -1, -2), 4.83 (2H, d, \(J\) 10.8, -17a, -23a), 4.76 (2H, d, \(J\) 10.8, -17b, -23b), 4.67 (4H, s, -7, -12), 4.18 (2H, dd, \(J\) 5.1, 2.2, -3, -6), 3.78 (6H, s, -22, -28), 3.65 (2H, dd, \(J\) 5.1, 2.2, -4, -5); \textsuperscript{13}C NMR (126 MHz; CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\) 159.6 (-21, -27), 139.1 (-8, -13), 131.6 (-18, -24), 129.9 (-19, -25), 128.7 (-10, -15), 128.2 (-11, -16), 128.0 (-1, -2), 127.9 (-9, -14), 113.9 (-20, -26), 83.7 (-4, -5), 80.5 (-3, -6), 75.3 (-17, -23), 72.5 (-7, -12), 55.6 (-22, -28); HRMS \(m/z\) (ES\textsuperscript{+}) Found 589.2557 [M+Na]\textsuperscript{+} (C\textsubscript{36}H\textsubscript{38}O\textsubscript{6} requires 589.2560); \(m/z\) (ES\textsuperscript{+}) 589.2 ([M+Na]\textsuperscript{+}, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 2.4 min, 98.6%.

\((-\text{-}3,6\text{-Di-O-benzyl-4,5-bis-O-(4-methoxybenzyl)-D-myoinositol (}-\text{-215)}}\)

To a vigorously stirred solution of (+)-214 (272 mg, 0.48 mmol, 1.0 eq.) in MeCN (5 mL) was added a solution of NaIO\textsubscript{4} (133 mg, 0.62 mmol, 1.3 eq.) and RuCl\textsubscript{3}\cdot3H\textsubscript{2}O (12 mg, 0.048 mmol, 0.1 eq.) in H\textsubscript{2}O (1.3 mL) and the reaction mixture was stirred vigorously at room temperature for 4 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (10% w/v, 50 mL) was added and the reaction mixture was stirred at room temperature for
10 min. The organic components were extracted with EtOAc (3 × 50 mL), combined, filtered through a plug of silica, and concentrated in vacuo to afford the title compound as a slightly brown crystalline solid (307 mg, 100%) that was used without further purification: R_f 0.32 (EtOAc/petroleum ether 1:1); [α]D25 = −29.5 (c 0.58, CHCl₃) {lit.¹³⁵ −32.2 (c 2.5 in CHCl₃)}; m.p.³¹ 126-128 °C (from MeOH); ν_max (thin film)/cm⁻¹ 3447 (O-H, br m), 3032 (C-H ar., w), 2908 (C-H ar., m), 2836 (C-H ar., m), 1613 (C=C, m), 1514 (C=C, s), 1455 (C-H, m), 1360 (C-H, m), 1302 (C-O, m), 1248 (C-O, s), 1070 (C-O, s), 1033 (C-O, s); ¹H NMR (500 MHz; CD₂Cl₂) δ 7.38-7.27 (10H, m, H-9, H-10, H-11, H-14, H-15, H-16), 7.25-7.20 (4H, m, H-19, H-25), 6.84-6.80 (4H, m, H-20, H-26), 4.92 (1H, d, J 11.3, H-7a), 4.81 (1H, d, J 10.1, H-17a), 4.80 (1H, d, J 10.1, H-23a), 4.75 (2H, d, J 10.1, H-17b, H-23b), 4.74 (1H, d, J 11.3, H-7b), 4.71 (1H, d, J 11.5, H-12a), 4.68 (1H, d, J 11.5, H-12b), 4.27 (1H, dd, J 2.7, 2.7, H-2), 3.87 (1H, dd, J 9.3, 9.3, H-4), 3.78 (3H, s, H-22), 3.77 (3H, s, H-28), 3.74 (1H, dd, J 9.3, 9.3, H-6), 3.49-3.43 (2H, m, H-1, H-5), 3.42 (1H, dd, J 9.3, H-3), 2.53 (1H, s, OH-2), 2.42 (1H, d, J 5.6, OH-1); ¹³C NMR (126 MHz; CD₂Cl₂) δ 159.6 (C-21, C-27), 139.3 (C-13), 138.6 (C-8), 131.5, 131.4 (C-18, C-24), 129.9, 129.8 (C-19, C-25), 128.78, 128.77 (C-9, C-14), 128.3 (C-10, C-15), 128.2, 128.0 (C-11, C-16), 114.0, 113.9 (C-20, C-26), 83.2 (C-5), 81.8 (C-6), 81.6 (C-4), 80.6 (C-3), 75.6 (C-17, C-23), 75.5 (C-7), 72.8 (C-12), 72.2 (C-1), 69.6 (C-2), 55.6 (C-22, C-28); HRMS m/z (ES⁺) Found 623.2611 [M+Na]⁺ (C₃₆H₄₀O₈Na requires 623.2615); m/z (ES⁺) 623.2 ([M+Na]⁺, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 9.6 min, 94.9%. These data are in good agreement with the literature.¹³⁵
(+)-4,5-Bis-\(O\)-(4-methoxybenzyl)-2,3,6-Tris-\(O\)-benzyl-1-\(O\)-(2\(H\)-tetrahydro-
pyranyl)-\(d\)-\(\text{myo}\)-inositol ((–)-217)

To a solution of (–)-215 (346 mg, 0.58 mmol, 1.0 eq.) in \(\text{CH}_2\text{Cl}_2\) (6 mL) under an
atmosphere of Ar was added 3,4-dihydro-2\(H\)-pyran (79 \(\mu\)L, 0.87 mmol, 1.5 eq.) and
pyridinium \(p\)-toluenesulfonate (15 mg, 0.06 mmol, 0.1 eq.) and the reaction
solution was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1
EtOAc/petroleum ether) indicated some starting material (–)-215 remained, some prod-
uct and some di-reacted material was present. The reaction mixture was concentrated
\textit{in vacuo} and purified using silica gel flash column chromatography on a Biotage system
using 5-40\% EtOAc in petroleum ether. The resulting film was dissolved in anhydrous
DMF (4 mL) under an atmosphere of Ar and cooled to 0 °C. NaH (60\% dispersion in min-
eral oil, 70 mg, 1.74 mmol, 3.0 eq.) was added and the suspension was stirred at 0 °C for
30 min. After this time, benzyl bromide (0.21 mL, 1.74 mmol, 3.0 eq.) was added and the
reaction mixture was stirred at room temperature for 2 h. TLC analysis of the reaction
mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction
suspension was diluted with EtOAc (50 mL) and the organic components were washed
with aqueous HCl (1 M, 50 mL), saturated aqueous NaHCO\(_3\) (50 mL), saturated aqueous
NaCl (50 mL), dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The product was
purified using silica gel flash column chromatography on a Biotage system using 7-60\%
Et₂O in hexane to afford the title compound as a colourless oil (115 mg, 26%, 2 steps): R₇
0.21 (EtOAc/petroleum ether 1:4); [α]⁺²⁵ = +3.1 (c 0.88, CHCl₃); νmax (thin film)/cm⁻¹
3032 (C-H, w), 2933 (C-H, m), 1613 (C=C, m), 1514 (C=C, s), 1398 (C-H, m), 1302
(C-H, m), 1248 (C-H, s), 1173 (C-O, m), 1126 (C-O, s), 1071 (C-O, s), 1031 (C-O, s); ¹H
NMR (500 MHz; CD₂Cl₂) Diastereomer A* δ 7.50-7.24 (15H, m, H-ar.), 4.96 (1H, d, J
8.7, H-19, H-25), 6.82 (4H, dt, J 8.7, 3.0, H-20, H-26), 4.91 (1H, dd, J 11.0, H-34a), 4.91
(1H, d, J 11.0, H-34b), 4.89-4.68 (9H, m, H-7, H-12, H-17, H-23, H-29), 4.15 (1H, dd, J
2.3, 2.3, H-1), 3.89-3.83 (1H, m, H-2), 4.03-3.91 (1H, m, H-4, H-6), 3.79-3.77 (6H, m,
H-22, H-28), 3.60 (1H, dd, J 10.0, 2.3, H-1), 3.51-3.38 (3H, m, H-3, H-5, H-30b), 1.93-
1.36 (6H, m, H-31, H-32, H-33), Diastereomer B* δ 7.50-7.24 (15H, m, H-ar.), 7.22 (4H,
d, J 8.7, H-19, H-25), 6.81 (4H, dt, J 8.7, 3.0, H-20, H-26), 5.00 (1H, d, J 11.0, H-7a),
4.89-4.68 (10H, m, H-7b, H-12, H-17, H-23, H-29, H-34), 4.14 (1H, dd, J 2.3, 2.3, H-2),
4.03-3.91 (3H, m, H-4, H-6, H-30a), 3.79-3.77 (6H, m, H-22, H-28), 3.73 (1H, dd, J 10.0,
2.3, H-1), 3.51-3.38 (2H, m, H-3, H-5), 3.37-3.33 (1H, m, H-30b), 1.93-1.36 (6H, m, H-
31, H-32, H-33); ¹³C NMR (126 MHz; CD₂Cl₂) Diastereomer A* δ 159.50 (C-21), 159.45
(C-27), 140.0 (C-35), 139.6, 139.2 (C-8, C-13), 131.73, 131.71 (C-18, C-24), 129.6 (C-19,
C-25), 128.70, 128.57, 128.5, 128.2, 128.05, 127.98, 127.9, 127.88, 127.8, 127.6 (C-ar. ×
15), 113.9 (C-20, C-26), 101.4 (C-29), 83.82 (C-5), 82.3 (C-6), 81.84 (C-4), 81.6 (C-3),
79.0 (C-1), 75.9 (C-7), 75.64 (C-17), 75.59 (C-23), 74.9 (C-34), 73.6 (C-2), 73.2 (C-12),
63.2 (C-30), 55.6 (C-22, C-28), 31.4 (C-33), 25.9 (C-32), 20.1 (C-31), Diastereomer B* δ
159.50 (C-21), 159.4 (C-27), 139.7 (C-35), 139.5, 139.1 (C-8, C-13), 131.8, 131.72 (C-18,
C-24), 130.0 (C-19, C-25), 128.67, 128.60, 128.5, 128.2, 128.03, 127.98, 127.9, 127.85,
127.7, 127.6 (C-ar. × 15), 113.9 (C-20, C-26), 94.3 (C-29), 83.77 (C-5), 81.80 (C-4),
81.4 (C-3), 81.2 (C-6), 78.4 (C-2), 76.0 (C-7), 75.59 (C-17), 75.5 (C-23), 74.9 (C-34),
74.8 (C-1), 73.0 (C-12), 61.4 (C-30), 55.6 (C-22, C-28), 30.7 (C-33), 25.7 (C-32), 19.2
(C-31); HRMS m/z (ES⁺) Found 797.3654 [M+Na]⁺ (C₄₈H₅₄O₉ requires 797.3660); m/z
(ES⁺) 797.4 ([M+Na]⁺, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time
= 2.7 min, 98.5%.

*As the two diastereomers cannot be distinguished using the available NMR techniques,
the higher shift of each pair is recorded as diastereomer A while the lower is diastereomer B.

(-)-4,5-Bis-O-(4-methoxybenzyl)-2,3,6-Tri-O-benzyl-d-myoinositol ((-)-213)

To a solution of (-)-217 (115 mg, 0.148 mmol, 1.0 eq) in THF (1 mL) was added aqueous AcOH (80% v/v, 5 mL) and the reaction mixture was stirred at 55 °C for 2 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to room temperature and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 7-60% EtOAc in petroleum ether to afford the title compound as a colourless oil (103 mg, 100%): Rf 0.53 (EtOAc/petroleum ether 1:2); [α]D^25 = -13.1 (c 1.0, CHCl₃) {lit.¹³⁵ -13.9 (c. 3.4 in CHCl₃}); νmax (thin film)/cm⁻¹ 3555 (O-H, w), 3031 (C-H ar., w), 2909 (C-H, w), 2836 (C-H, w), 1613 (C=C, m), 1514 (C=C, s), 1497 (C=C, m), 1360 (C-O, m), 1302 (C-O, m), 1248 (C-O, s), 1174 (C-O, m), 1130 (C-O, m), 1071 (C-O, s), 1034 (C-O, s); ¹H NMR (500 MHz; CD₂Cl₂) δ 7.40-7.26 (15H, m, H-ar.), 7.24-7.20 (4H, m, H-19, H-25), 6.84-6.79 (4H, m, H-20, H-26), 4.97 (1H, d, J 11.6, H-29a), 4.88 (1H, d, J 11.6, H-7a), 4.84 (1H, d, J 10.5, H-23a), 4.83 (1H, d, J 10.5, H-17a), 4.77-4.68 (6H, m, H-7b, H-12, H-17b, H-23b, H-29b), 4.06 (1H, dd, J 2.6, H-2), 3.96 (1H, dd, J 9.5, 9.5, H-4), 3.78 (3H, s, H-28), 3.77 (3H, s, H-22), 3.73 (1H, dd, J 9.5, 9.5, H-6), 3.48 (1H,
dd, J 9.5, 2.6, H-1), 3.46 (1H, dd, J 9.5, 2.6, H-3), 3.42 (1H, dd, J 9.5, 9.5, H-5), 2.24 (1H, br s, OH); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) $\delta$ 159.5 (C-21, C-27), 139.4, 138.9 (C-8, C-13, C-30), 131.6, 131.5 (C-18, C-24), 129.9, 129.7 (C-19, C-25), 128.73, 128.72, 128.67 (C-10, C-15, C-32), 128.3, 128.10, 128.06, 128.0, 127.9 (C-9, C-11, C-14, C-16, C-31, C-33), 113.93, 113.91 (C-20, C-26), 83.6 (C-5), 82.6 (C-6), 82.0 (C-4), 81.5 (C-3), 77.7 (C-2), 75.6 (C-17, C-23), 75.5 (C-7), 75.1 (C-29), 73.2 (C-12), 72.7 (C-1), 55.6 (C-22, C-28); HRMS m/z (ES$^+$) Found 713.3080 [M+Na]$^+$ (C$_{43}$H$_{46}$O$_8$ requires 713.3084); m/z (ES$^+$) 713.3 ([M+Na]$^+$, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 3.1 min, 100.0%. These data are in good agreement with the literature.$^{135}$

(+)-2,3,6-Tri-O-benzyl-1-(1,2-dipalmitoyl-sn-glycerol)-(2-benzyloxy)-phosphoryl)-D-myo-inositol ((+)-218)

To a solution of (–)-213 (104 mg, 0.151 mmol, 1.0 eq.) and phosphoramidite 207 (304 mg, 0.378 mmol, 2.5 eq.) in CH$_2$Cl$_2$ (3 mL) under an atmosphere of argon was added 1H-tetrazole (3-4 wt.%, 0.88 mL, 0.378 mmol, 2.5 eq.) and the reaction solution was stirred at room temperature for 48 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The solution was cooled to $-78^\circ$C, 3-chloroperbenzoic acid (77%, 85 mg, 0.378 mmol, 2.5 eq.) was added and the reaction suspension was stirred at room temperature for 1 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL), the organic components were washed with aqueous Na$_2$S$_2$O$_3$ (10% w/v, 50 mL), saturated aqueous NaHCO$_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica
gel flash column chromatography on a Biotage system using 5-40% EtOAc in petroleum ether to afford a colourless oil. The oil was dissolved in CH₂Cl₂ (10 mL), H₂O (10 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (137 mg, 0.603 mmol, 4.0 eq.) were added and the biphasic mixture was stirred vigorously for 2 h. ¹H NMR analysis of the reaction mixture indicated the reaction was complete. The mixture was diluted with CH₂Cl₂ (50 mL), the organic components were washed with saturated aqueous NaHCO₃ (50 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The product was purified twice using silica gel flash column chromatography using a Biotage system using 7-60% EtOAc in petroleum ether followed by 30% Et₂O in hexane to afford the title compound as a colourless oil (62 mg, 35%) as a ca. 1:1 mixture of inseparable diastereomers: Rf 0.13 (EtOAc/petroleum ether 1:3); [α]D²⁵ = +3.2 (c 1.0, CHCl₃); νmax (thin film)/cm⁻¹: 3439 (O-H, w), 2924 (C-H ar., s), 2853 (C-H ar., s), 1744 (C=O, s), 1497 (C-H, m), 1455 (C-H, m), 1158 (C-O, s), 1116 (C-O, s), 1023 (C-O, s); ¹H NMR (500 MHz; CD₂Cl₂) Diastereomer A* δ 7.40-7.23 (20H, m, H-ар.), 5.14 (1H, dddd, J 5.5, 5.5, 5.5, 5.5, H-28), 5.06-4.95 (2H, m, H-22), 4.84 (1H, d, J 11.6, H-17a), 4.83-4.77 (3H, m, H-7, H-17b), 4.67 (1H, d, J 11.6, H-12a), 4.53 (1H, d, J 11.6, H-12b), 4.37 (1H, dd, J 2.6, 2.6, H-2), 4.29-4.23 (1H, m, H-1), 4.20 (1H, dd, J 11.9, 4.4, H-29a), 4.13-4.01 (3H, m, H-27, H-29b), 3.93 (1H, dd, J 9.7, 9.7, H-4), 3.87 (1H, dd, J 9.7, 9.7, H-6), 3.44 (1H, dd, J 9.7, 9.7, H-5), 3.29 (1H, dd, J 9.7, 2.6, H-3), 2.58 (2H, br s, OΗ), 2.27-2.17 (4H, m, H-31, H-47), 1.62-1.48 (4H, m, H-32, H-48), 1.33-1.22 (48H, m, H-(33-44), H-(49-60)), 0.90-0.86 (6H, m, H-45, H-61), Diastereomer B* δ 7.40-7.23 (20H, m, H-ар.), 5.09 (1H, dddd, J 5.5, 5.5, 5.5, 5.5, H-28), 5.06-4.95 (2H, m, H-22), 4.83-4.77 (3H, m, H-7, H-17a), 4.73 (1H, d, J 11.6, H-17b), 4.65 (1H, d, J 11.6, H-12a), 4.53 (1H, d, J 11.6, H-12b), 4.34 (1H, dd, J 2.6, 2.6, H-2), 4.29-4.23 (1H, m, H-1), 4.15 (1H, dd, J 11.9, 4.4, H-29a), 4.13-4.01 (2H, m, H-27), 3.99 (1H, dd, J 11.9, 4.4, H-29b), 3.93 (1H, dd, J 9.7, 9.7, H-4), 3.88 (1H, dd, J 9.7, 9.7, H-6), 3.47 (1H, dd, J 9.7, 9.7, H-5), 3.31 (1H, dd, J 9.7, 2.6, H-3), 2.58 (2H, br s, OΗ), 2.27-2.17 (4H, m, H-31, H-47), 1.62-1.48 (4H, m, H-32, H-48), 1.33-1.22 (48H, m, H-(33-44), H-(49-60)), 0.90-0.86 (6H, m, H-45, H-61); ¹³C NMR (126 MHz; CD₂Cl₂) Diastereomer A* δ 173.39 (C-30), 173.1 (C-46), 139.11, 138.98 (C-8, C-18), 138.3 (C-13), 136.3 (d, Jp 7.6,
C-23), 129.01, 128.96, 128.9, 128.8, 128.73, 128.68, 128.62, 128.58, 128.28, 128.26, 128.22, 128.18, 128.16, 128.1, 128.0, 127.92, 127.89, 127.87 (C-ar. × 20), 80.1-79.9 (m, C-3, C-6), 79.1 (d, $J_P 6.7$, C-1), 76.54 (C-2), 75.6 (C-7), 75.47 (C-17), 75.0 (C-5), 72.67 (C-12), 72.6 (C-4), 70.0 (d, $J_P 5.8$, C-22), 69.7 (C-28), 65.9 (d, $J_P 5.4$, C-27), 61.9 (C-29), 34.5 (C-47), 34.3 (C-31), 32.3 (C-44, C-60), 30.11, 30.08, 30.06, 29.9, 29.8, 29.50 (C-(33-42), C-(49-58)), 25.2 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61), Diastereomer B* $\delta$ 173.37 (C-30), 173.1 (C-46), 139.10, 139.01 (C-8, C-18), 138.3 (C-13), 136.2 (d, $J_P 7.6$, C-23), 129.01, 128.96, 128.9, 128.8, 128.73, 128.68, 128.62, 128.58, 128.28, 128.26, 128.22, 128.18, 128.16, 128.1, 128.0, 127.92, 127.89, 127.87 (C-ar. × 20), 80.1-79.9 (m, C-3, C-6), 79.0 (d, $J_P 6.7$, C-1), 76.49 (C-2), 75.53 (C-7), 75.47 (C-17), 75.0 (C-5), 72.74 (C-12), 72.6 (C-4), 69.9 (d, $J_P 5.8$, C-22), 69.6 (C-28), 66.1 (d, $J_P 5.4$, C-27), 61.8 (C-29), 34.4 (C-47), 34.3 (C-31), 32.3 (C-44, C-60), 30.11, 30.08, 30.06, 29.9, 29.7, 29.46 (C-(33-42), C-(49-58)), 25.2 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61); $^{31}$P NMR (162 MHz; CD$_2$Cl$_2$) Diastereomer A* $\delta$ –1.68, Diastereomer B* $\delta$ –1.77; HRMS $m/z$ (ES$^+$) Found 1193.6973 [M+Na]$^+$ (C$_{69}$H$_{103}$NaO$_{13}$P requires 1193.7028); $m/z$ (ES$^+$) 1171.7 ([M+H]$^+$, 100%) 1193.6 ([M+Na]$^+$, 36%); NP-HPLC (2-10% isopropanol/hexane) Diastereomer A Retention Time = 9.4 min, 21.7%, Diastereomer B Retention Time = 9.5 min, 78.2%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A, while the lower is diastereomer B.
(-)-2,3,6-Tri-O-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-1-(((1,2-dipalmityloyl)-sn-glycerol)-(benzyloxy)phosphoryl)-D-myoinositol ((–)-219)\(^{41}\)

To a solution of (+)-268 (48 mg, 0.041 mmol, 1.0 eq.) in CH\(_2\)Cl\(_2\) (2 mL) under an atmosphere of Ar was added dibenzyl-N,N-diisopropylphosphoramidite (68 \(\mu\)L, 0.21 mmol, 5.0 eq.) followed by 1H-tetrazole (3-4 wt.% in MeCN, 0.48 mL, 0.21 mmol, 5.0 eq.) and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:2 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to –78 °C, 3-chloroperbenzoic acid (77%, 35 mg, 0.21 mmol, 5.0 eq.) was added and the suspension was stirred at –78 °C for 1 h then at room temperature for 1 h. After this time, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (50 mL) and the organic components were washed with aqueous Na\(_2\)S\(_2\)O\(_3\) (10% \(w/v\), 50 mL) and saturated aqueous NaCl (50 mL), dried with Na\(_2\)SO\(_4\), filtered, and concentrated \emph{in vacuo}. The product was purified using silica gel flash column chromatography using petroleum ether followed by 10%, 20%, 30% and 100% EtOAc in petroleum ether to afford the title compound as a colourless film (54 mg, 78%) as a ca. 1:1 mixture of inseparable diastereomers: \(R_f\) 0.55 (EtOAc/petroleum ether 1:1); \([\alpha]^{25}_D\) = –3.8 (\(c\) 0.55, CHCl\(_3\)); \{lit.\}\(^{41}\) –4.3 (\(c\) 0.53, CHCl\(_3\)); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2924 (C-H ar., s), 2853 (C-H ar., m), 1743 (C=O, m), 1456 (C-H, m), 1276 (C-H, m), 1019 (C-O, s); \(^1\)H NMR (500 MHz; CD\(_2\)Cl\(_2\)) \emph{Diastere-}
**CHAPTER 7. EXPERIMENTAL**

7.6. BENZYLATED DERIVATIVES

omer A* δ 7.42-7.10 (38H, m, H-ar.), 7.05-7.02 (2H, m, H-ar.), 5.11 (1H, dddd, J 5.5, 5.5, 5.5, 5.5, H-28), 5.07-4.49 (18H, m, H-4, H-5, H-7, H-12, H-17, H-22, H-62, H-67, H-72, H-77), 4.40-4.28 (2H, m, H-1, H-2), 4.19-3.86 (5H, m, H-6, H-27, H-29), 3.56 (1H, dd, J 9.9, 2.0, H-3), 2.27-2.18 (4H, m, H-31, H-47), 1.60-1.49 (4H, m, H-32, H-48), 1.35-1.21 (48H, m, H-(33-44), H-(49-60)), 0.91-0.87 (6H, m, H-45, H-61), Diastereomer B* δ 7.42-7.10 (38H, m, H-ar.), 7.05-7.02 (2H, m, H-ar.), 5.07-4.49 (19H, m, H-4, H-5, H-7, H-12, H-17, H-22, H-28, H-62, H-67, H-72, H-77), 4.40-4.28 (2H, m, H-1, H-2), 4.19-3.86 (5H, m, H-6, H-27, H-29), 3.59 (1H, dd, J 9.9, 2.0, H-3), 2.27-2.18 (4H, m, H-31, H-47), 1.60-1.49 (4H, m, H-32, H-48), 1.35-1.21 (48H, m, H-(33-44), H-(49-60)), 0.91-0.87 (6H, m, H-45, H-61); 13C NMR (126 MHz; CD2Cl2) Diastereomer A* δ 173.4 (C-30), 173.0 (C-46), 138.82 (C-8), 138.67 (C-18), 138.00 (C-13), 136.8-136.6 (m, C-63, C-68, C-73), 136.4 (d, Jp 6.7, C-78), 136.0 (d, Jp 6.7, C-23), 129.1-127.6 (m, C-ar. × 40), 79.4 (br s, C-5), 78.5-78.1 (m, C-1, C-3, C-4, C-6), 75.94 (C-2), 75.81 (C-12), 75.0 (C-7), 72.8 (C-17), 70.1-69.4 (m, C-22, C-28, C-62, C-67, C-72, C-77), 65.9 (d, Jp 5.1, C-27), 61.81 (C-29), 34.3 (C-31, C-47), 32.3 (C-44, C-60), 30.3-29.4 (C-33-42), (C-49-58), 15.21 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61), Diastereomer B* δ 174.3 (C-30), 173.0 (C-46), 138.80 (C-8), 138.69 (C-18), 138.01 (C-13), 136.8-136.6 (m, C-63, C-68, C-73), 136.4 (d, Jp 6.7, C-78), 136.1 (d, Jp 6.7, C-23), 129.1-127.6 (m, C-ar. × 40), 79.4 (br s, C-5), 78.5-78.1 (m, C-1, C-3, C-4, C-6), 75.92 (C-2), 75.76 (C-12), 75.0 (C-7), 72.9 (C-17), 70.1-69.4 (m, C-22, C-28, C-62, C-67, C-72, C-77), 66.1 (d, Jp 5.1, C-27), 61.77 (C-29), 34.4 (C-31, C-47), 32.3 (C-44, C-60), 30.3-29.4 (C-33-42), (C-49-58), 25.23 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61); 31P NMR (162 MHz; CD2Cl2) Diastereomer A* δ −1.55 (P-5), −1.77 (P-1, P-4), Diastereomer B* δ −1.54 (P-5), −1.70 (P-1), −1.77 (P-4); HRMS** m/z (ES+) Found 1691.8342 [M12C97+H]+ (12C97H129NaO19P3 requires 1691.8413), 1692.8375 [M12C9613C+H]+ (12C9613CH129NaO19P3 requires 1692.8447); m/z (ES+) 1691.6 ([M+H]+, 100%), 1692.6 ([M13C+H]+, 80%), 1708.8 ([M+NH4]+, 20%), 1709.8 ([M13C+NH4]+, 21%), 1713.7 ([M+Na]+, 28%), 1714.7 ([M13C+Na]+, 31%); NP-HPLC (2-10% isopropanol/hexane) Diastereomer A Retention Time = 8.1 min, 43.5%, Diastereomer B Retention Time = 8.6 min, 55.3%. These data are in agreement with the
literature.41

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A, while the lower is diastereomer B.

**As the number of carbon atoms is close to 100, the major peak in mass spectrometry is no longer $^{12}\text{C}_{97}$ but is $^{12}\text{C}_{96}^{13}\text{C}_1$ and hence this mass is included for clarity.

Phosphatidylinositol monosodium salt (13)41

To a solution of (+)-268 (8 mg, 0.007 mmol, 1.0 eq.) in $^4\text{BuOH}$ (1.2 mL) and H$_2$O (0.2 mL) under an atmosphere of N$_2$ was added NaHCO$_3$ (0.6 mg, 0.007 mmol, 1.0 eq.) followed by palladium black (14 mg, 0.14 mmol, 20 eq.). The suspension was stirred at room temperature for 10 min. The atmosphere was exchanged for H$_2$ using balloons (3 × balloons) and the reaction suspension was stirred for 24 h. After this time, the flask was flushed with N$_2$ and water (30 mL) was added. The suspension was filtered through a plug of Celite® and lyophilised to afford the title compound as a colourless powder (3.9 mg, 67%): $^1$H NMR (500 MHz; 1:1 CD$_2$Cl$_2$/D$_4$-MeOD) $\delta$ 5.31-5.26 (1H, m, H-8), 4.45 (1H, dd, J 12.1, 2.6, H-9a), 4.25-4.20 (2H, m, H-2, H-9b), 4.11-4.01 (2H, m, H-7), 3.91 (1H, ddd, J 10.8, 8.5, 2.8, H-1), 3.76 (1H, dd, J 9.6, 9.6, H-6), 3.65 (1H, dd, J 9.6, 9.6, H-4), 3.47 (1H, dd, J 9.6, 2.8, H-3), 3.28 (1H, dd, J 9.6, 9.6, H-5), 2.37 (2H, t, J 7.5, H-11), 2.33 (2H, dd, J 7.9, 6.8, H-27), 1.66-1.57 (4H, m, H-12, H-28), 1.37-1.25 (48H, m, H-(13-24), H-(29-40)), 0.92-0.88 (6H, m, H-25, H-41); $^{31}$P NMR (202 MHz; 1:1 CD$_2$Cl$_2$/D$_4$-MeOD) $\delta$ –0.13 (P-1); HRMS $m/z$ (ES) Found 809.5188 [M–H]$^-$ (C$_{41}$H$_{86}$O$_{19}$P$_3$ requires 809.5185). These data are in good agreement with the literature.86
Phosphatidylinositol-(4,5)-bisphosphate pentasodium salt (10)\textsuperscript{41}

To a solution of (+)-\textsuperscript{219} (28 mg, 0.017 mmol, 1.0 eq.) in \textsuperscript{4}BuOH (3.0 mL) and H\textsubscript{2}O (0.5 mL) under an atmosphere of N\textsubscript{2} was added NaHCO\textsubscript{3} (6.9 mg, 0.083 mmol, 5.0 eq.) followed by palladium black (35 mg, 0.35 mmol, 20 eq.). The suspension was stirred at room temperature for 10 min. The atmosphere was exchanged for H\textsubscript{2} using balloons (3 \times balloons) and the reaction suspension was stirred for 24 h. After this time, the flask was flushed with N\textsubscript{2} and water (50 mL) was added. The suspension was filtered through a plug of Celite\textsuperscript{6} and lyophilised to afford the title compound as a colourless powder (16 mg, 89%): \textsuperscript{1}H NMR (400 MHz; D\textsubscript{2}O) \(\delta\) 5.26 (1H, br s, \(H\)-8), 4.36 (1H, br d, \(J\) 10.0, \(H\)-2), 4.23-4.08 (3H, m, \(H\)-4, \(H\)-9), 4.08-3.97 (3H, m, \(H\)-1, \(H\)-7), 3.92-3.79 (2H, m, \(H\)-5, \(H\)-6), 3.72-3.63 (1H, br d, \(J\) 10.0, \(H\)-3), 2.35 (2H, br s, \(H\)-11), 2.27 (2H, br s, \(H\)-27), 1.54 (4H, br s, \(H\)-12, \(H\)-28), 1.22 (48H, br s, \(H\)-(13-24), \(H\)-(29-40)), 0.80 (6H, br s, \(H\)-25, \(H\)-41); \textsuperscript{31}P NMR (162 MHz; D\textsubscript{2}O) \(\delta\) 4.78 (\(P\)-4), 4.59 (\(P\)-5), –0.23 (br s, \(P\)-1); HRMS m/z (ES\textsuperscript{-}) Found 969.4512 [M–H]\textsuperscript{-} \((C_{41}H_{80}O_{19}P_{3}\text{ requires }969.4512)\). These data are in good agreement with the literature.\textsuperscript{41,89}
7.7 Deuterated Benzylated Derivatives

\[ (+)- (1S,4S,5R,6R)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyl-D_6 \text{ bis}(2-(((\text{butyldiphenylsilyl})oxy)methyl)benzoate) \] ((+)-269)

Tetratroc \((\pm)-165\) (853 mg, 1.0 mmol, 1.0 eq.), benzoate derivative \(119\) (1.37 g, 3.5 mmol, 3.5 eq.), \((S,S)\)-ligand \((-)-84\) (104 mg, 0.15 mmol, 0.15 eq.), tetrahexylammonium bromide (86 mg, 0.2 mmol, 0.2 eq.), and \([\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2\) (9.2 mg, 0.025 mmol, 0.025 eq.) were degassed on a Schlenk system (3 \(\times\) vacuum/N\(_2\) cycles). CH\(_2\)Cl\(_2\) (3.0 mL) and aqueous NaOH (1 M, 3.0 mL, 3.0 eq.) were added and the reaction mixture was stirred vigorously for 2 h. \(^1\)H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was diluted with NaHCO\(_3\) (50 mL) and the organic components were extracted with CH\(_2\)Cl\(_2\) (2 \(\times\) 30 mL). The combined organic components were dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% CH\(_2\)Cl\(_2\) in petroleum ether, followed by crystallisation from EtOH to afford the title compound as a colourless solid (984 mg, 79%): R\(_f\) 0.82 (EtOAc/petroleum ether 1:4); \([\alpha]_{D}^{25} = +94.1\ (c\ 1.0, \text{CHCl}_3)\); m.p. 135-137 °C (from MeOH); \(\tilde{\nu}_{\text{max}}\) (thin film)/cm\(^{-1}\) 2960 (C-H ar., w), 2930 (C-H ar., w), 2894 (C-H ar., w), 2857 (C-H, w), 1774 (C=O, s), 1719 (C=O, s), 1428 (C-O, m), 1379 (C-O, m), 1290 (C-O, s), 1260 (C-O, s), 1228 (C-O, s), 1205 (C-O, s), 1134 (C-O, s), 1111 (C-O, s), 1060 (C-O, s), 1046 (C-O, s); \(^1\)H NMR (500 MHz; CD\(_2\)Cl\(_2\)) \(\delta\) 8.08 (2H,
7.7. \textit{D}_6-\text{BENZYLATED DERIVATIVES}

dd, \textit{J} 7.9, 1.0, \textit{H}-12), 7.97 (2H, dd, \textit{J} 7.6, 1.3, \textit{H}-9), 7.74-7.70 (8H, m, \textit{H}-16), 7.69 (2H, ddd, \textit{J} 7.9, 7.6, 1.0, \textit{H}-11), 7.47-7.38 (12H, m, \textit{H}-17, \textit{H}-18), 7.36 (2H, dd, \textit{J} 7.6, 7.6, \textit{H}-10), 5.20 (2H, d, \textit{J} 16.2, \textit{H}-14a), 5.15 (2H, d, \textit{J} 16.2, \textit{H}-14b), 4.73 (2H, d, \textit{J} 11.9, \textit{H}-22a), 4.62 (2H, d, \textit{J} 11.9, \textit{H}-22b), 1.15 (18H, s, \textit{H}-20); \textit{^13}C \ NMR* (126 MHz; CD\textsubscript{2}Cl\textsubscript{2}) \delta 165.7 (C-7), 153.7 (C-21), 144.8 (C-13), 135.9 (C-16), 133.82 (C-9), 133.80, 133.75 (C-15), 131.1 (C-11), 130.21, 130.17 (C-18), 128.19, 128.16 (C-17), 127.3-127.1 (m, C-2, C-3), 127.0 (C-10), 126.9 (C-12), 125.8 (C-8), 94.6 (C-23), 77.19 (C-22), 75.8 (\textit{t}, \textit{J}_D 22.1, \textit{C}-1, \textit{C}-4), 71.4 (\textit{t}, \textit{J}_D 22.1, \textit{C}-5, \textit{C}-6), 64.8 (C-14), 27.1 (C-20), 19.6 (C-19); \textit{^2}H \ NMR (77 MHz; CHCl\textsubscript{3}; D\textsubscript{6}-DMSO) \delta 5.62 (D-2, D-3, D-5, D-6), 5.22 (D-1, D-4); Chiral HPLC (1\% isopropanol/hexane isocratic, 1.0 mL min\textsuperscript{-1}) Retention Time 11.2 min (+)-175, > 98\% e.e.; NP-HPLC (0-100\% isopropanol/hexane) Retention Time = 2.4 min, 99.3\%.

Mass spectrometry data were not obtained due to the poor ionisation of the compound in various techniques (ESI, EI, FI and MALDI).

*For the carbon multiplet at 127.3-127.1, the signal was broad, weak and partially obscured by two neighbouring peaks however the presence can be confirmed by comparing to the protonated analogue (+)-175. All other \textit{^13}C signals were observed and matched the shifts for (+)-175.

(+)-(1\textit{R},2\textit{R},3\textit{S},6\textit{S})-3,6-Bis(benzyloxy)cyclohex-4-ene-1,2-diyl-D\textsubscript{6} bis(2\textquoteright,2\textquoteright,2\textquoteright-trichloroethyl) bis(carbonate) ((+)-221)

To a solution of (+)-269 (6.32 g, 5.0 mmol, 1.0 eq.) in CH\textsubscript{2}Cl\textsubscript{2} (60 mL) was added
trifluoroacetic acid (6 mL) and the reaction solution was stirred at room temperature for 3 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was concentrated in vacuo and the residue was dissolved in anhydrous dioxane (60 mL) under an atmosphere of N₂. Benzyl 2,2,2-trichloroacetimidate (3.71 mL, 20.0 mmol, 4.0 eq.) and triflic acid (0.1 mL) were added and the reaction mixture was stirred at room temperature for 18 h. Further benzyl 2,2,2-trichloroacetimidate (0.92 mL, 5.0 mmol, 1.0 eq.) and triflic acid (0.05 mL) were added and stirring continued for 48 h. After this time, the reaction mixture was diluted with EtOAc (100 mL) and the organic components were washed with saturated aqueous NaHCO₃ (100 mL), saturated aqueous NaCl (100 mL), dried with Na₂SO₄, filtered and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 2-10% EtOAc in petroleum ether to afford the title compound as a colourless oil (2.58 g, 76%) that was used without further purification: Rₜ 0.60 (EtOAc/petroleum ether 1:4); [α]²⁵D = +73.6 (c 1.0, CHCl₃); ν_max (thin film)/cm⁻¹ 1771 (C=O, s), 1497 (C-H, w), 1454 (C=C, w), 1377 (C-H, w), 1285 (C-H, s), 1266 (C-H, s), 1225 (C-O, s), 1044 (C-O, w); ¹H NMR (500 MHz; CD₂Cl₂) δ 7.38-7.29 (10H, m, H-ar.), 4.85 (2H, d, J 11.8, H-18a, H-21a), 4.76 (2H, d, J 11.8, H-18b, H-21b), 4.69 (2H, d, J 11.5, H-7a, H-12a), 4.59 (2H, d, J 11.5, H-7b, H-12b); ¹³C NMR (126 MHz; CD₂Cl₂) δ 153.9 (C-17, C-20), 138.0 (C-8, C-13), 128.8 (C-10, C-15), 128.3 (C-11, C-16), 128.1 (C-9, C-14), 127.1 (t_d, J_D 24.9, C-1, C-2), 94.8 (C-19, C-22), 77.7 (t_d, J_D 24.0, C-3, C-6), 77.2 (C-4, C-5), 76.6 (t_d, J_D 22.2, C-18, C-21), 72.0 (C-7, C-12); ²H NMR (77 MHz; CHCl₃; CDCl₃) δ 5.80 (D-1, D-2), 5.18 (D-3, D-6), 4.37 (D-4, D-5); HRMS m/z (ES⁺) Found 702.9871 [M+Na]⁺ (C₂₆H₁₈D₆³⁵Cl₆NaO₈ requires 702.9871); m/z (ES⁺) 702.8 ([M³⁵Cl₆+Na]⁺, 100%)

Deuterium incorporation of this compound was not calculated due to complexities arising from multiple Cl isotopes within the mass spectrum, however, no hydrogen-deuterium exchange was observed by ¹H NMR.
(+)-(3S,4S,5S,6S)-3,6-Bis(benzyloxy)cyclohex-1-ene-4,5-diol-D$_6$ ((+)-222)

![Structural diagram](image)

To a solution of (+)-221 (395 mg, 0.58 mmol, 1.0 eq.) in glacial AcOH (3.0 mL) and THF (3.0 mL) was added zinc powder (1.51 g, 23 mmol, 40 eq.) and the suspension was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction suspension was diluted with EtOAc (50 mL), filtered through a pad of Celite®, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 7-60% EtOAc in petroleum ether to afford the title compound as a colourless oil (124 mg, 64%, 84% D$_6$, 16% D$_5$): $R_f$ 0.44 (EtOAc/petroleum ether 1:1); [$\alpha$]$^D_{25}$ = +112.3 (c 1.0, CHCl$_3$), +114.9 (c 1.0, Acetone); $\tilde{\nu}$$_{\text{max}}$ (thin film)/cm$^{-1}$ 3409 (O-H, m), 2981 (C-H ar., s), 2887 (C-H ar., m), 1454 (C=C, m), 1383 (C-H, m), 1252 (C-H, m), 1157 (C-O, m), 1084 (C-O, m), 1061 (C-O, m), 1027 (C-O, m); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) $\delta$ 7.39-7.33 (8H, m, H-ar.), 7.32-7.28 (2H, m, H-ar.), 4.70 (2H, d, J 11.7, H-7a, H-12a), 4.67 (2H, d, J 11.7, H-7b, H-12b); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) $\delta$ 138.6 (C-8, C-13), 128.4 (C-10, C-15), 127.8 (C-9, C-14), 127.7 (C-11, C-16), 127.1 (tD, J$_D$ 24.7, C-1, C-2), 78.7 (tD, J$_D$ 22.1, C-3, C-6), 74.2 (tD, J$_D$ 22.5, C-4, C-5), 71.7 (C-7, C-12); $^2$H NMR (77 MHz; CHCl$_3$; CDCl$_3$) $\delta$ 5.81 (D-1, D-2), 4.07 (D-3, D-6), 3.75 (D-4, D-5); HRMS m/z (ES$^+$) Found 354.1721 [MD$_5$+Na]$^+$ (C$_{20}$H$_{17}$D$_5$O$_4$ requires 354.1730), 355.1783 [MD$_6$+Na]$^+$ (C$_{20}$H$_{16}$D$_6$O$_4$ requires 355.1786); m/z (ES$^+$) 354.2 ([MD$_5$+Na]$^+$, 19%), 355.2 ([MD$_6$+Na]$^+$, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 3.9 min, 91.8%.
To a solution of (+)-222 (124 mg, 0.37 mmol, 1.0 eq., 84% D$_6$, 16% D$_5$) in anhydrous DMF (1.5 mL) under an atmosphere of Ar was added NaH (60% dispersion in mineral oil, 89 mg, 1.5 mmol, 4.0 eq.) and the suspension was stirred at room temperature for 10 min. After this time, 4-methoxybenzyl chloride (0.20 mL, 1.5 mmol, 4.0 eq.) was added and the reaction suspension was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched by dropwise addition of aqueous HCl (1 M, 20 mL). The organic components were extracted with CHCl$_3$ (3 x 30 mL), combined, washed with aqueous LiCl (0.5 M, 30 mL) and saturated aqueous NaCl (30 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% Et$_2$O in hexane to afford the title compound as a colourless oil (125 mg, 59%, 84% D$_6$, 16% D$_5$): R$_f$ 0.48 (EtOAc/petroleum ether 1:4); [$\alpha$]$^D_{25}$ = +69.1 (c 1.0, CHCl$_3$); $\tilde{\nu}$$_{\max}$ (thin film)/cm$^{-1}$ 1612 (C-H, w), 1514 (C-H, s), 1456 (C-O, w), 1248 (C-O, s), 1207 (C-O, m), 1173 (C-O, m), 1086 (C-O, m), 1067 (C-O, s), 1036 (C-O, m); $^1$H NMR (400 MHz; CD$_2$Cl$_2$) $\delta$ 7.43-7.30 (14H, m, H-ar.), 6.89 (4H, dt, J 8.7, 2.5, H-20, H-26), 4.90 (2H, d, J 10.8, H-17a, H-23a), 4.82 (2H, d, J 10.8, H-17b, H-23b), 4.73 (4H, s, H-7, H-12), 3.83 (6H, s, H-22, H-28); $^{13}$C NMR (101 MHz; CD$_2$Cl$_2$) $\delta$ 159.5 (C-21, C-27), 139.1 (C-8, C-13), 131.6 (C-18, C-24), 129.9 (C-19, C-25), 128.7 (C-10, C-15), 128.1 (C-11, C-16), 128.0-127.8* (m, C-1, C-2), 127.9 (C-9, C-14),
113.9 (C-20, C-26), 83.0 (tD, J_D 21.0, C-4, C-5), 79.9 (tD, J_D 21.0, C-3, C-6), 75.3 (C-17, C-23), 72.4 (C-7, C-12), 55.5 (C-22, C-28); ²H NMR (77 MHz; CHCl₃; CDCl₃) δ 5.76 (D-1, D-2), 4.20 (D-3, D-6), 3.70 (D-4, D-5); HRMS m/z (ES⁺) Found 594.2875 [MD₅+Na][MD₆+Na]⁺ (C₃₆H₃₃D₁₀NaO₆ requires 594.2874), 595.2933 [MD₆+Na][MD₆+Na]⁺ (C₃₆H₃₂D₁₀NaO₆ requires 595.2937); m/z (ES⁺) 594.3 ([MD₅+Na][MD₅+Na]⁺, 20%), 595.3 ([MD₆+Na][MD₆+Na]⁺, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 2.3 min, 99.6%.

*For the carbon peak at 128.0-127.8, the signal was weak and obscured by two neighbouring peaks, however, the presence can be confirmed by comparing to the protonated analogue (+)-214. All other ¹³C signals were observed and matched the shifts for (+)-214.*

(−)-3,6-Di-O-benzyl-4,5-bis-O-(4-methoxybenzyl)-d-myoinositol-D₆ (−)-224

To a solution of (+)-223 (120 mg, 0.21 mmol, 1.0 eq., 84% D₆, 16% D₅) in MeCN (2 mL) was added a solution of NaIO₄ (66 mg, 0.31 mmol, 1.5 eq.) and RuCl₃·3H₂O (2.6 mg, 0.01 mmol, 0.05 eq.) in H₂O (0.5 mL), and the reaction mixture was stirred vigorously for 6 min. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous Na₂S₂O₃ (10% w/v, 30 mL) was added and the organic components were extracted with CH₂Cl₂ (3 × 25 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 12-100% EtOAc in petroleum ether to afford the title compound as colourless needles (84 mg, 66%, 84% D₆, 16% D₅): Rᶠ 0.38
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(EtOAc/petroleum ether 1:1); $\alpha_2^D = -29.6$ (c 1.0, CHCl\textsubscript{3}); m.p. 123-124 °C (from EtOAc); $\tilde{\nu}_{\text{max}}$ (thin film)/cm\textsuperscript{-1} 3445 (O-H, w), 2860 (C-H ar., w), 2837 (C-H ar., w), 1612 (C-H, m), 1514 (C-H, s), 1454 (C-H, m), 1383 (C-H, m), 1332 (C-H, m), 1248 (C-O, s), 1209 (C-O, m), 1173 (C-O, m), 1065 (C-O, s), 1030 (C-O, s); \textsuperscript{1}H NMR (500 MHz; CD\textsubscript{2}Cl\textsubscript{2}) $\delta$ 7.41-7.27 (10H, m, H-ar.), 7.26-7.22 (4H, m, H-19, H-25), 6.88-6.83 (4H, m, H-20, H-26), 4.94 (1H, d, J 11.3, H-7a), 4.84 (1H, d, J 10.5, H-17a), 4.83 (1H, d, J 10.5, H-23a), 4.80-4.75 (3H, m, H-7b, H-17b, H-23b), 4.72 (1H, d, J 11.5, H-12a), 4.69 (1H, d, J 11.5, H-12b), 3.80 (3H, s, H-22), 3.79 (3H, s, H-28), 2.71 (1H, s, OH-2), 2.56 (1H, s, OH-1); \textsuperscript{13}C NMR (126 MHz; CD\textsubscript{2}Cl\textsubscript{2}) $\delta$ 159.5 (C-21, C-27), 139.4 (C-13), 138.6 (C-8), 131.6, 131.4 (C-18, C-24), 129.9, 129.7 (C-19, C-25), 128.79, 128.75 (C-9, C-14), 128.24, 128.22 (C-10, C-15), 128.16, 128.0 (C-11, C-16), 114.0, 113.9 (C-20, C-26), 82.7 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-5), 81.3 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-6), 81.0 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-4), 80.0 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-3), 75.59, 75.58 (C-17, C-23), 75.4 (C-7), 72.8 (C-12), 71.7 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-1), 69.1 (t\textsubscript{D}, J\textsubscript{D} 20.3, C-2), 55.6 (C-22, C-28); \textsuperscript{2}H NMR (77 MHz; CHCl\textsubscript{3}; CDC\textsubscript{13}) $\delta$ 4.17 (D-2), 3.93 (D-4), 3.82 (D-6), 3.45 (D-1, D-3, D-5); HRMS m/z (ES\textsuperscript{+}) Found 628.2930 [MD\textsubscript{5}+Na]\textsuperscript{+} (C\textsubscript{36}H\textsubscript{35}D\textsubscript{5}NaO\textsubscript{8} requires 628.2929), 629.2990 [MD\textsubscript{6}+Na]\textsuperscript{+} (C\textsubscript{36}H\textsubscript{34}D\textsubscript{6}NaO\textsubscript{8} requires 629.2992); m/z (ES\textsuperscript{+}) 628.4 ([MD\textsubscript{5}+Na]\textsuperscript{+}, 20%), 629.3 ([MD\textsubscript{6}+Na]\textsuperscript{+}, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 7.8 min, 96.8%.
To a solution of (–)-224 (423 mg, 0.70 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (7.0 mL) under an atmosphere of Ar was added 3,4-dihydro-2H-pyran (96 µL, 1.05 mmol, 1.5 eq.) and pyridinium p-toluenesulfonic acid (35 mg, 0.14 mmol, 0.2 eq.) and the solution was stirred at room temperature for 24 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated some starting material (–)-224 remained, some product was formed and some di-reacted product had formed. The reaction solution was diluted with EtOAc (50 mL) and the organic components were washed with saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The intermediate was purified using silica gel flash column chromatography on a Biotage system using 5-100% EtOAc in petroleum ether to give the intermediate (267 mg) and re-isolated starting material (–)-224 (88 mg). The intermediate was dissolved in anhydrous DMF (3.0 mL) under an atmosphere of N$_2$, NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol, 3.0 eq.) was added and the suspension was stirred at room temperature for 15 min. After this time, benzyl bromide (0.25 mL, 2.1 mmol, 3.0 eq.) was added and the reaction mixture stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with saturated aqueous NaCl (50 mL) and extracted with CHCl$_3$ (3 × 50 mL). The
combined organic components were washed with aqueous LiCl (0.5 M, 50 mL) and saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 7-60% Et$_2$O in hexane, with mixed fractions repurified under the same conditions to afford the title compound as a colourless oil (129 mg, 24% over two steps, 86% D$_6$, 14% D$_5$) as an inseparable mixture of diastereomers: $R_t$ 0.39 (EtOAc/petroleum ether 1:4); $[\alpha]_{D}^{25} = +2.3$ (c 1.0, CHCl$_3$); $\bar{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$ 2941 (C-H ar., m), 1612 (C-H, m), 1514 (C-H, s), 1454 (C-H, m), 1381 (C-H, m), 1302 (C-O, m), 1248 (C-O, s), 1211 (C-O, s), 1069 (C-O, s), 1030 (C-O, s); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) Diastereomer A* $\delta$ 7.56-7.30 (15H, m, H-ar.), 7.27 (4H, d, J 8.4, H-19, H-25), 6.86 (4H, d, J 8.4, H-20, H-26), 5.01 (1H, d, J 11.5, H-34a), 4.96 (1H, d, J 11.5, H-34b), 4.93-4.71 (9H, m, H-7, H-12, H-17, H-23, H-29), 3.94-3.87 (1H, m, H-30a), 3.82 (6H, s, H-22, H-28), 3.56-3.45 (1H, m, H-30b), 1.98-1.40 (6H, m, H-31, H-32, H-33); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) Diastereomer A* $\delta$ 159.51 (C-21), 159.46 (C-27), 140.0 (C-35), 139.60, 139.19 (C-8, C-13), 131.76, 131.74 (C-18, C-24), 129.6 (C-19, C-25), 128.72, 128.60, 128.5, 128.2, 128.1, 128.01, 127.94, 127.90, 127.82, 127.6 (C-ar. × 15), 113.9 (C-20, C-26), 101.4 (C-29), 83.2 (t$_D$, J$_D$ 19.3, C-5), 82.1-80.4 (m, C-3, C-4, C-6), 78.4 (t$_D$, J$_D$ 19.1, C-1), 75.8 (C-7), 75.61 (C-17), 75.56 (C-23), 74.8 (C-34), 73.2-73.0** (m, C-2), 73.0 (C-12), 63.2 (C-30), 55.6 (C-22, C-28), 31.4 (C-33), 26.0 (C-32), 20.2 (C-31), Diastereomer B* $\delta$ 159.51 (C-21), 159.45 (C-27), 139.7 (C-35), 139.55, 139.16 (C-8, C-13), 131.79, 131.72 (C-18, C-24), 130.0 (C-19, C-25), 128.69, 128.62, 128.5, 128.2, 128.1, 128.00, 127.94, 127.87, 127.76, 127.6 (C-ar. × 15), 113.9 (C-20, C-26), 94.3 (C-29), 83.2 (t$_D$, J$_D$ 19.3, C-5), 82.1-80.4 (m, C-3, C-4, C-6), 77.9 (t$_D$, J$_D$ 19.1, C-2), 76.0 (C-7), 75.56 (C-17), 75.5 (C-23), 74.8 (C-34), 74.3 (t$_D$, J$_D$ 20.5, C-1), 73.2 (C-12), 61.4 (C-30), 55.6 (C-22, C-28), 30.7 (C-33), 25.7 (C-32), 19.2 (C-31); $^2$H NMR (77 MHz; CHCl$_3$; CDCl$_3$) Diastereomer A & B $\delta$ 4.05 (D-2, D-4, D-6), 3.49 (D-
1, D-3, D-5); HRMS m/z (ES\(^+\)) Found 802.3966 [MD\(_5\)+Na\(^+\)] (C\(_{48}H_{49}D_5NaO_9\) requires 802.3974), 803.4021 [MD\(_6\)+Na\(^+\)] (C\(_{48}H_{48}D_6NaO_9\) requires 803.4037); m/z (ES\(^+\)) 802.4 ([MD\(_5\)+Na\(^+\)], 17%), 803.4 ([MD\(_6\)+Na\(^+\)], 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 2.3 min, 89.8%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A while the lower is diastereomer B.

**For the carbon multiplet at 73.2-73.0, the signal was broad, weak and partially obscured by two neighbouring peaks, however, the presence can be confirmed by comparing to the protonated analogue (+)-217. All other \(^{13}\)C signals were observed and matched the shifts for (+)-217.

(−)-4,5-Bis-O-(4-methoxybenzyl)-2,3,6-tri-O-benzyl-D\(_6\)-myo-inositol-D\(_6\)

(−)-227

To a solution of (+)-226 (129 mg, 0.165 mmol, 1.0 eq., 84% D\(_6\), 16% D\(_5\)) in THF (1 mL) was added aqueous AcOH (80% v/v, 5 mL) and the reaction mixture was warmed to 55 °C for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to room temperature and concentrated in vacuo. The product was purified using silica gel flash column chromatography.
on a Biotage system using 12-100% EtOAc in petroleum ether to afford the title compound as a colourless film (99 mg, 86%, 84% D$_6$, 16% D$_5$): R$_f$ 0.69 (EtOAc/petroleum ether 1:2); [α]$^2_D$ = −13.9 (c 1.0, CHCl$_3$); ν$_{max}$ (thin film)/cm$^{-1}$ 3030 (C-H ar., w), 2864 (C-H ar., w), 1612 (C-H, m), 1512 (C-H, s). 1454 (C-H, m), 1381 (C-H, m), 1302 (C-O, m), 1246 (C-O, s), 1207 (C-O, s), 1172 (C-O, s), 1061 (C-O, s), 1028 (C-O, s); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) δ 7.45-7.30 (15H, m, H-ar.), 7.27 (4H, d, J 8.5, H-19, H-25), 6.88-6.84 (4H, m, H-20, H-26), 5.01 (1H, d, J 11.7, H-29a), 4.93 (1H, d, J 11.7, H-7a), 4.89 (1H, d, J 10.6, H-23a), 4.88 (1H, d, J 10.6, H-17a), 4.83-4.76 (4H, m, H-7b, H-17b, H-23b, H-29b), 4.74 (2H, s, H-12), 3.81 (3H, s, H-28), 3.80 (3H, s, H-22), 2.29 (1H, br s, OH); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) δ 159.5 (C-21, C-27), 139.4, 138.9 (C-8, C-13, C-30), 131.6, 131.5 (C-18, C-24), 129.9, 129.7 (C-19, C-25), 128.72, 128.71, 128.66 (C-10, C-15, C-32), 128.3, 128.1, 128.03, 127.95, 127.9 (C-9, C-11, C-14, C-16, C-31, C-33), 113.93, 113.91 (C-20, C-26), 82.3 (t$_D$, J$_D$ 21.1, C-5), 82.0 (t$_D$, J$_D$ 21.1, C-6), 81.4 (t$_D$, J$_D$ 21.1, C-4), 80.9 (t$_D$, J$_D$ 20.3, C-3), 77.2 (t$_D$, J$_D$ 21.9, C-2), 75.5 (C-17, C-23), 75.4 (C-7), 75.1 (C-29), 73.1 (C-12), 72.1 (t$_D$, J$_D$ 21.6, C-1), 55.5 (C-22, C-28); $^2$H NMR (77 MHz; CHCl$_3$; CDCl$_3$) δ 4.03 (D-2, D-4), 3.79 (D-6), 3.46 (D-1, D-3, D-5); HRMS m/z (ES$^+$) Found 718.3396 [MD$_5$+Na$^+$] (C$_{43}$H$_{41}$D$_5$NaO$_8$ requires 718.3399), 719.3455 [MD$_6$+Na$^+$] (C$_{43}$H$_{40}$D$_6$NaO$_8$ requires 719.3461); m/z (ES$^+$) 718.4 ([(MD$_5$+Na$^+$), 20%], 719.4 ([MD$_6$+Na$^+$], 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 3.0 min, 93.8%.
(+)-2,3,6-Tri-\(O\)-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-1-((1,2-dipalmityloyl)-\(sn\)-glycerol)-(benzyloxy)phosphoryl)-\(\nu\)-myo-inositol-D\(_6\) ((–)-228)

To a solution of (–)-227 (71 mg, 0.10 mmol, 1.0 eq., 84% D\(_6\), 16% D\(_5\)) and phosphoramidite 207 (206 mg, 0.26 mmol, 2.5 eq.) in CH\(_2\)Cl\(_2\) (2 mL) under an atmosphere of Ar was added 1\(H\)-tetrazole (3-4 wt.% in MeCN, 0.59 mL, 0.26 mmol, 2.5 eq.) and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction suspension was cooled to \(-78^\circ\)C, 3-chloroperbenzoic acid (77%, 57 mg, 0.26 mmol, 2.5 eq.) was added, and the reaction mixture was stirred at room temperature for 2 h. \(^{31}\)P NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (50 mL), the organic components were washed with aqueous Na\(_2\)S\(_2\)O\(_3\) (10\% \(w/v\), 30 mL), saturated aqueous NaHCO\(_3\) (30 mL) and saturated aqueous NaCl (30 mL), dried with Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The intermediate was purified using silica gel flash column chromatography on a Biotage system using 12-100\% EtOAc in petroleum ether to afford the title compound as a colourless
oil (64 mg, 53%, 84% D₆, 16% D₅): Rₖ 0.11 (EtOAc/petroleum ether 1:3); [α]²⁵ᵣ = +5.4 (c 1.0, CHCl₃); νmax (thin film)/cm⁻¹ 3421 (O-H, br w), 2924 (C-H ar., s), 2853 (C-H ar., s), 1744 (C=O, s), 1497 (C-H, m), 1455 (C-H, m), 1274 (C-H, m), 1211 (C-H, m), 1118 (C-O, m), 1086 (C-O, m), 1027 (C-O, s); 1H NMR (500 MHz; CD₂Cl₂) Diastereomer A* δ 7.40-7.23 (20H, m, H-ar.), 5.14 (1H, dddd, J 5.3, 5.3, 5.3, 5.3, H-28), 5.07-4.95 (2H, m, H-22), 4.87-4.69 (4H, m, H-7, H-17), 4.67 (1H, d, J 11.7, H-12a), 4.53 (1H, d, J 11.7, H-12b), 4.20 (1H, dd, J 12.0, 5.3, H-29a), 4.14-3.95 (3H, m, H-27, H-29b), 2.63 (2H, br s, OH), 2.27-2.21 (4H, m, H-31, H-47), 1.60-1.48 (4H, m, H-32, H-48), 1.36-1.18 (48H, m, H-(33-44), H-(49-60)), 0.93-0.83 (6H, m, H-45, H-61), Diastereomer B* δ 7.40-7.23 (20H, m, H-ar.), 5.09 (1H, dddd, J 5.3, 5.3, 5.3, 5.3, H-28), 5.07-4.95 (2H, m, H-22), 4.87-4.69 (4H, m, H-7a, H-17, H-12a), 4.64 (1H, d, J 11.7, H-12a), 4.53 (1H, d, J 11.7, H-12b), 4.15 (1H, dd, J 12.0, 5.3, H-29a), 4.14-3.95 (3H, m, H-27, H-29b), 2.63 (2H, br s, OH), 2.27-2.18 (4H, m, H-31, H-47), 1.60-1.48 (4H, m, H-32, H-48), 1.36-1.18 (48H, m, H-(33-44), H-(49-60)), 0.93-0.83 (6H, m, H-45, H-61); 13C NMR (126 MHz; CD₂Cl₂) Diastereomer A* δ 173.41 (C-30), 173.1 (C-46), 139.1, 139.01 (C-8, C-18), 138.4 (C-13), 136.3 (C-23), 129.02, 128.97, 128.95, 128.83, 128.73, 128.68, 128.63, 128.59, 128.3, 128.22, 128.18, 128.16, 128.1, 128.0, 127.93, 127.90, 127.87 (C-ar. × 20), 79.8-79.1 (m, C-3, C-6), 78.9-78.3 (m, C-1), 76.0 (tD, J_D 19.0, C-2), 75.51 (C-7), 75.4 (C-17), 74.5 (tD, J_D 19.0, C-5), 72.65 (C-12), 72.1 (tD, J_D 19.1, C-4), 70.0 (d, J_P 6.1, C-22), 69.7 (C-28), 65.9 (d, J_P 5.5, C-27), 61.90 (C-29), 34.45 (C-47), 34.3 (C-31), 32.3 (C-44, C-60), 30.12, 30.09, 30.07, 29.9, 29.8, 29.7, 29.51, 29.47 (C-(33-42), C-(49-58)), 25.2 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61), Diastereomer B* δ 173.39 (C-30), 173.1 (C-46), 139.1, 139.04 (C-8, C-18), 138.4 (C-13), 136.2 (C-23), 129.02, 128.97, 128.95, 128.83, 128.73, 128.68, 128.63, 128.59, 128.3, 128.22, 128.18, 128.16, 128.1, 128.0, 127.93, 127.90, 127.87 (C-ar. × 20), 79.8-79.1 (m, C-3, C-6), 78.9-78.3 (m, C-1), 76.0 (tD, J_D 19.0, C-2), 75.46 (C-7), 75.4 (C-17), 74.5 (tD, J_D 19.0, C-5), 72.71 (C-12), 72.1 (tD, J_D 19.1, C-4), 70.0 (d, J_P 6.1, C-22), 69.7 (C-28), 69.8 (d, J_P 6.1, C-22), 69.6 (C-28), 66.1 (d, J_P 5.5, C-27), 61.90 (C-29), 34.43 (C-47), 34.3 (C-31), 32.3 (C-44, C-60), 30.12, 30.09, 30.07, 29.9, 29.8, 29.7, 29.51, 29.47 (C-(33-42), C-(49-58)), 25.2 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61), 31P
NMR (162 MHz; CD$_2$Cl$_2$) Diastereomer A * δ -1.60, Diastereomer B* δ -1.68; $^2$H NMR (77 MHz; CHCl$_3$; CDCl$_3$) Diastereomer A & B δ 4.18 (D-1, D-2), 3.95 (D-4, D-6), 3.43 (D-5), 3.24 (D-3); HRMS m/z (ES$^+$) Found 1176.7501 [MD$_6$+H$^+$] (C$_{69}$H$_{99}$D$_5$O$_{13}$P requires 1176.7523), 1177.7566 [MD$_6$+H$^+$] (C$_{69}$H$_{98}$D$_6$O$_{13}$P requires 1177.7585); m/z (ES$^+$) 1176.7 ([MD$_5$+H$^+$], 18%), 1177.7 ([MD$_6$+H$^+$], 100%), 1193.7 ([MD$_5$+NH$_4^+$], 4%), 1194.7 ([MD$_6$+NH$_4^+$], 25%), 1198.7 ([MD$_5$+Na$^+$], 3%), 1199.7 ([MD$_6$+Na$^+$], 15%); NP-HPLC (2-10% isopropanol/hexane) Diastereomer A Retention Time = 5.8 min, 22.8%, Diastereomer B Retention Time = 6.0 min, 69.9%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A, while the lower is diastereomer B.

(–)-2,3,6-Tri-O-benzyl-4,5-bis(bis(benzyloxy)phosphoryl-1-((1,2-dipalmityloyl)-sn-glycerol)-(benzyloxy)phosphoryl)-$\alpha$-myo-inositol-D$_6$ ((–)-229)

To a solution of (–)-227 (32 mg, 0.027 mmol, 1.0 eq., 84% D$_6$, 16% D$_5$) and dibenzyl-$N,N$-diisopropylphosphoramidite (46 µL, 0.14 mmol, 5.0 eq.) in CH$_2$Cl$_2$ (1 mL) under an atmosphere of Ar was added 1H-tetrazole (3-4 wt.% in MeCN, 0.32 mL, 0.14 mmol, 5.0 eq.) and the reaction mixture was stirred at room temperature for 6 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was
complete. The reaction suspension was cooled to $-78^\circ C$, 3-chloroperbenzoic acid (77%, 24 mg, 0.14 mmol, 5.0 eq.) was added, and the suspension was stirred at room temperature for 2 h. $^{31}P$ NMR analysis indicated the reaction was complete. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL), the organic components were washed with aqueous Na$_2$S$_2$O$_3$ (10% w/v, 30 mL), saturated aqueous NaHCO$_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography three times. Firstly, using 20%, 30%, 50% and 100% EtOAc in petroleum ether, secondly using 30-60% EtOAc in petroleum ether and finally using 50% Et$_2$O in hexane, 100% Et$_2$O and 100% EtOAc to afford the title compound as a colourless film (10 mg, 22%, 84% D$_6$, 16% D$_5$): $R_f$ 0.84 (EtOAc/petroleum ether 1:1); [$\alpha$]$_D^{29}$ = $-3.1$ (c 0.66, CHCl$_3$); $\tilde{\nu}_{\text{max}}$ (thin film)/cm$^{-1}$ 2923 (C-H ar., s), 2853 (C-H ar., m), 1743 (C=O, m), 1456 (C-H, m), 1279 (C-H, m), 1215 (C-H, m), 1015 (C-O, s); $^1$H NMR (500 MHz; CD$_2$Cl$_2$) Diastereomer A* $\delta$ 7.42-7.10 (38H, m, H-ar.), 7.02 (2H, d, $J$ 7.5, H-ar.), 5.09 (1H, dddd, $J$ 5.5, 5.5, 5.5, 5.5, H-28), 5.07-4.55 (16H, m, H-7, H-12, H-17, H-22, H-62, H-67, H-72, H-77), 2.25-2.15 (4H, m, H-31, H-47), 1.60-1.49 (4H, m, H-32, H-48), 1.35-1.21 (48H, m, H-(33-44), H-(49-60)), 0.91-0.87 (6H, m, H-45, H-61), Diastereomer B* $\delta$ 7.42-7.10 (38H, m, H-ar.), 7.02 (2H, d, $J$ 7.5, H-ar.), 5.07-4.55 (17H, m, H-7, H-12, H-17, H-22, H-28, H-62, H-67, H-72, H-77), 4.09-3.85 (5H, m, H-27, H-29), 2.25-2.15 (4H, m, H-31, H-47), 1.60-1.49 (4H, m, H-32, H-48), 1.35-1.21 (48H, m, H-(33-44), H-(49-60)), 0.91-0.87 (6H, m, H-45, H-61); $^{13}$C NMR (126 MHz; CD$_2$Cl$_2$) Diastereomer A* $\delta$ 173.4 (C-30), 173.0 (C-46), 138.83 (C-8), 138.66 (C-18), 138.00 (C-13), 136.8-136.6 (m, C-63, C-67, C-72), 136.4 (d, $J_P$ 7.0, C-77), 136.05 (d, $J_P$ 7.0, C-23), 129.1-127.6 (m, C-ar. $\times$ 40), 79.3-78.6 (m, C-5), 78.3-77.4 (m, C-1, C-3, C-4, C-6), 75.74 (C-12), 75.70-75.2 (m, C-2), 75.0 (C-7), 72.77 (C-17), 70.1-69.4 (m, C-22, C-28, C-62, C-67, C-72, C-77), 65.9 (d, $J_P$ 5.1, C-27), 61.81 (C-29), 34.3 (C-31, C-47), 32.3 (C-44, C-60), 30.3-29.4 (C-(33-42), C-(49-58)), 25.20 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61), Diastereomer B* $\delta$ 174.3 (C-30), 173.0 (C-46), 138.81 (C-8), 138.69 (C-18), 138.02 (C-13), 136.8-136.6 (m, C-63, C-67, C-72), 136.4 (d, $J_P$ 7.0, C-77), 136.08
CHAPTER 7. EXPERIMENTAL  7.8. ALTERNATIVE PROTECTING GROUP

(d, J_p 7.0, C-23), 129.1-127.6 (m, C-ar. × 40), 79.3-78.6 (m, C-5), 78.3-77.4 (m, C-1, C-3, C-4, C-6), 75.69 (C-12), 75.70-75.2 (m, C-2), 75.0 (C-7), 72.84 (C-17), 70.1-69.4 (m, C-22, C-28, C-62, C-72, C-77), 66.1 (d, J_p 5.1, C-27), 61.77 (C-29), 34.4 (C-31, C-47), 32.3 (C-44, C-60), 30.3-29.4 (C-(33-42), C-(49-58)), 25.23 (C-32, C-48), 23.1 (C-43, C-59), 14.3 (C-45, C-61); 31P NMR (162 MHz; CD_2Cl_2) Diastereomer A* δ –1.54 (P-5), –1.76 (P-1, P-4), Diastereomer B* δ –1.54 (P-5), –1.68 (P-1), –1.75 (P-4); 2H NMR (77 MHz; CHCl_3; CDCl_3) Diastereomer A & B δ 4.22 (D-1, D-2, D-4, D-5, D-6), 3.48 (D-3); HRMS m/z (ES+) Found 1696.8670 [MD_5+H]^+ (C_97H_{125}D_5O_{19}P_3 requires 1696.8712), 1697.8722 [MD_6+H]^+ (C_97H_{124}D_6O_{19}P_3 requires 1697.8745); m/z (ES+) 1696.7 ([MD_5+H]^+, 24%), 1697.7 ([MD_6+H]^+, 100%), 1713.8 ([MD_5+NH_4]^+, 1%), 1714.8 ([MD_6+NH_4]^+, 2%), 1718.7 ([MD_5+Na]^+, 12%), 1719.7 ([MD_6+Na]^+, 2%); NP-HPLC (2-10% isopropanol/hexane) Diastereomer A Retention Time = 7.3 min, 39.5%, Diastereomer B Retention Time = 7.9 min, 56.1%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A, while the lower is diastereomer B.

7.8 Alternative Protecting Group

(+)-(1S,4S,5R,6R)-5,6-Dihydroxycyclohex-2-ene-1,4-diyl bis(2-((t-butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-233)

![Chemical Structure](image)

To a solution of (+)-175 (2.48 g, 2.0 mmol, 1.0 eq.) in glacial AcOH (15 mL) and THF
(15 mL) was added zinc powder (3.27 g, 50.0 mmol, 25.0 eq.) at 0 °C, portionwise, over a period of 5 min. The reaction suspension was stirred at room temperature for 4 h, after which time water (1 mL) was added. The reaction suspension continued to be stirred for a further 18 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The solution was filtered through a plug of Celite® and the plug was washed with EtOAc (100 mL). The filtrate was washed with saturated aqueous NaHCO₃ (3 × 100 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 10% EtOAc in petroleum ether followed by 20% EtOAc in petroleum ether to afford the title compound as a colourless foam (1.32 g, 74%): Rf 0.23 (EtOAc/petroleum ether 1:4); [α]₂⁰ D = +79.1 (c 1.0, CHCl₃); m.p.a 60-63 °C (from CH₂Cl₂); νmax (thin film)/cm⁻¹ 3423 (O-H, br w), 2957 (C-H, w), 2931 (C-H, w), 2893 (C-H, w), 2857 (C-H, w), 1715 (C=O, s), 1428 (C-H ar., m), 1249 (C-O, s), 1133 (C-O, s), 1112 (C-O, s), 1061 (C-O s); ¹H NMR (500 MHz; CD₂Cl₂) δ 7.98 (4H, d, J 7.8, H-9, H-12), 7.70 (8H, tt, J 6.5, 1.4, H-16), 7.63 (2H, ddd, J 7.7, 7.7, 1.4, H-10), 7.46-7.34 (14H, m, H-11, H-17, H-18), 5.57 (2H, s, H-2, H-3), 5.43 (2H, dd, J 5.4, 2.6, H-1, H-4), 5.17 (2H, d, J 15.8, H-14a), 5.12 (2H, d, J 15.8, H-14b), 3.66 (2H, d, J 7.2, 1.7, H-5, H-6), 2.83 (2H, s, OMe), 1.12 (18H, s, H-20); ¹³C NMR (126 MHz; CD₂Cl₂) δ 167.4 (C-7), 143.8 (C-13), 135.9 (C-16), 133.8 (C-15), 133.3 (C-10), 131.1 (C-9), 130.2 (C-18), 128.2 (C-17), 127.8 (C-2, C-3), 127.1 (C-8), 126.99, 126.97 (C-11, C-12), 75.1 (C-1, C-4), 74.0 (C-5, C-6), 64.7 (C-14), 27.1 (C-20), 19.6 (C-19); HRMS m/z (ES⁺) Found 913.3567 [M+Na]⁺ (C₅₄H₅₈O₈Si₂Na requires 913.3587); m/z (ES⁺) 913.1 ([M+Na]⁺, 100%); NP-HPLC (0-100% isopropanol/hexane, 1.0 mL min⁻¹) Retention Time = 6.4 min, 97.5%.
(+)-(1S,4S,5R,6R)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diy l bis(2-((‘butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-234)

To a solution of (+)-233 (178 mg, 0.2 mmol, 1.0 eq.) and phosphoramidite 126 (0.20 mL, 0.8 mmol, 4.0 eq.) under an atmosphere of Ar was added 1H-tetrazole (3-4 wt.% in MeCN, 1.9 mL, 0.8 mmol, 4.0 eq.) and the reaction solution was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Water (0.5 mL) was added and the reaction was stirred for a further 30 min. The reaction solution was cooled to −78 °C, 3-chloroperbenzoic acid (77%, 179 mg, 0.8 mmol, 4.0 eq.) was added and the solution was stirred at room temperature for 1 h. 31P NMR analysis indicated the reaction was complete. Aqueous Na₂S₂O₃ (10% w/v, 30 mL) was added and the organic components were extracted with CH₂Cl₂ (30 mL), washed with saturated aqueous NaHCO₃ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 2-10% MeOH in CHCl₃ to afford the title compound as a colourless film (253 mg, 90%). The product was isolated with a 5% impurity (by 31P NMR) relating to oxidised phosphoramidite, however, some clean column fractions could be obtained for data and the impurity was more easily removed in the next step: Rf 0.78 (MeOH/CHCl₃ 1:9); [α]D²⁰ = +72.3 (c 1.4, CHCl₃); ν max (thin film)/cm⁻¹ 2932 (C-H, w), 2857 (C-H, w), 2361 (C≡N, w), 1717 (C=O, m),
1245 (C-O, s), 1133 (C-O, s), 1111 (C-O, s), 1047 (C-O, s); \(^1\)H NMR (500 MHz; CD\(_2\)Cl\(_2\))
\[\delta 8.13 (2H, d, J 7.4, H-12), 8.11 (2H, d, J 4.7, H-9), 7.74-7.68 (10H, m, H-10, H-16),
7.48-7.37 (14H, m, H-11, H-17, H-18), 5.81 (2H, dd, J 5.4, 2.3, H-1, H-4), 5.60 (2H, s, H-2, H-3), 5.24 (2H, d, J 16.1, H-14a), 5.16 (2H, d, J 16.1, H-14b), 4.76 (2H, tt, J 5.4, 2.3, H-5, H-6), 4.25-4.18 (2H, m, H-21), 4.16-4.09 (2H, m, H-27), 4.02-3.95 (2H, m, H-24),
3.94-3.87 (2H, m, H-30), 2.68-2.54 (4H, m, H-22, 28), 2.29 (4H, t, J 6.3, H-25, H-31), 1.14 (18H, s, H-20);
\(^13\)C NMR (126 MHz; CD\(_2\)Cl\(_2\))
\[\delta 165.7 (C-7), 144.8 (C-13), 135.9 (C-16),
133.9 (C-10), 133.8, 133.7 (C-15), 131.3 (C-9), 130.24, 130.21 (C-18), 128.2 (C-17), 127.2 (C-2, C-3), 127.1 (C-11), 127.0 (C-12), 126.0 (C-8), 117.2 , 116.8 (C-23), 77.7 (dd, J\(_P\) 5.4, 5.4, C-5, C-6), 72.1 (C-1, C-4), 64.5 (C-14), 63.3 (d, J\(_P\) 5.6, C-21, C-27), 63.0 (d, J\(_P\) 5.6, C-24, C-30), 27.0 (C-20), 19.8 (d, J\(_P\) 8.0, C-22, C-28), 19.6 (C-19), 19.5 (d, J\(_P\) 8.0, C-25, C-31);
\[^{31}\]P NMR (162 MHz; CD\(_2\)Cl\(_2\))
\[\delta -2.89; HRMS m/z (ES\(^+\)) Found 1263.4114 [M+H]\(^+\) (C\(_{66}\)H\(_{73}\)N\(_4\)O\(_{14}\)P\(_2\)Si\(_2\) requires 1263.4132); m/z (ES\(^-\)) 1208.5 ([M-CH\(_2\)CH\(_2\)CN]\(^-\), 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 14.1 min, 97.4%.

(+)-4,5-Bis((bis(2-cyanoethoxy)phosphoryl)-3,6-bis(2-((‘butyl diphenylsilyl)oxy)methyl)benzoyl)-\(\nu\)-myo-inositol ((+)-235)

\[\begin{align*}
\text{NC} & \quad \text{CN} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{Si} & \quad \text{Si} \\
\end{align*}\]

To a vigorously stirred solution of (+)-234 (782 mg, 0.62 mmol, 1.0 eq.) in MeCN (6 mL) was added a solution of RuCl\(_3\)-3H\(_2\)O (8.0 mg, 0.031 mmol, 0.05 eq.), and NaIO\(_4\) (199 mg,
0.93 mmol, 1.5 eq.) in H₂O (1.5 mL) and the reaction mixture was stirred vigorously at room temperature for 8 min. TLC analysis of the reaction mixture (1:9 MeOH/CH₂Cl₂) indicated the reaction was complete. The reaction mixture was quenched with aqueous Na₂S₂O₃ (10% w/v, 50 mL) and the organic components were extracted with EtOAc (3 × 50 mL). The combined organic components were washed with saturated aqueous NaCl (50 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 0-5% MeOH in CHCl₃ to afford the title compound as a colourless film (671 mg, 83%): Rf 0.34 (MeOH/CHCl₃ 1:9); [α]D²⁵ = +35.8 (c 2.1, CHCl₃); νmax (thin film)/cm⁻¹ 3045 (O-H, w), 2931 (C-H, w), 2858 (C-H, w), 1722 (C=O, m), 1276 (C-O, m), 1251 (C-O, m) 1062 (C-O, s), 1046 (C-O, s); ¹H NMR (500 MHz; CD₂Cl₂) δ 8.11 (2H, d, J 7.9, H-9, H-35), 8.03 (1H, d, J 7.9, H-38), 7.74-7.67 (6H, m, H-17, H-43), 7.67 (1H, td, J 7.6, 1.3, H-37), 7.62-7.59 (2H, m, H-16), 7.58 (1H, d, J 7.9, H-12), 7.52 (1H, td, J 7.6, 1.3, H-11), 7.49-7.37 (12H, m, H-10, H-17, H-18, H-36, H-42, H-44), 7.33 (2H, t, J 7.2, H-16), 5.51 (1H, dd, J 9.8, 9.8, H-6), 5.37 (1H, d, J 15.2, H-14a), 5.2 (1H, d, J 15.9, H-40a), 5.15 (1H, d, J 15.9, H-40b), 5.11 (1H, dd, J 10.1, 2.5, H-3), 5.05 (1H, d, J 15.2, H-14b), 5.04 (1H, ddd, J 9.2, 9.2, 9.2, H-4), 4.50 (1H, ddd, J 9.2, 9.2, 9.2, H-5), 4.24-4.16 (3H, m, H-2, H-21), 4.13-4.04 (2H, m, H-24), 3.92-3.83 (2H, m, H-27), 3.79-3.67 (2H, m, H-30), 3.52 (1H, d, J 2.5, OH-2), 3.50 (1H, td, J 9.4, 2.5, H-1), 2.67-2.50 (5H, m, OH-1, H-22, H-25), 2.21-2.06 (4H, m, H-28, H-31), 1.13 (9H, s, H-46), 1.09 (9H, s, H-20); ¹³C NMR (126 MHz; CD₂Cl₂) δ 166.5 (C-33), 166.0 (C-7), 144.3 (C-39), 143.4 (C-13), 136.0 (C-17, C-43), 135.9 (C-16), 133.8 (C-37), 133.72, 133.68 (C-41), 133.6 (C-11), 133.4, 133.3 (C-15), 131.4 (C-35), 131.3 (C-9), 130.4, 130.32, 130.31, 130.29 (C-18, C-44), 128.29, 128.25, 128.23, 128.18, 128.1 (C-10, C-12, C-17, C-36, C-42), 127.5 (C-16), 127.3 (C-8), 127.1 (C-42), 127.0 (C-38), 126.6 (C-34), 117.3, 116.8, 116.7 ((C-23, C-26, C-29, C-32), 77.7 (dd, Jp 5.2, 5.2, C-5), 76.9 (dd, Jp 5.2, 5.2, C-4), 72.9 (C-6), 72.0 (C-3), 70.1 (C-2), 70.0 (C-1), 65.4 (C-14), 67.8 (C-40), 63.4 (d, Jp 5.8, C-21), 63.3 (d, Jp 5.5, C-30), 62.9 (d, Jp 4.7, C-27), 62.7 (d, Jp 4.7, C-24), 27.1, 27.0 (C-20, C-46), 19.7 (d, Jp 8.0), 19.6, 19.5 (C-19, C-45), 19.3 (d, Jp 7.2), 19.2 (d, Jp 7.2, C-22, C-25, C-28, C-31); ³¹P
NMR (162 MHz; CD$_2$Cl$_2$) $\delta$ –2.92 (P-4), –3.15 (P-5); HRMS $m/z$ (ES$^-$) Found 1295.4088 [M-H]$^-$ (C$_{66}$H$_{73}$N$_4$O$_{16}$P$_2$Si$_2$ requires 1295.4041); $m/z$ (ES$^-$) 1331.5 ([M+Cl]$^-$, 10%) 1341.5 ([M+formic Acid-H]$^-$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 12.7 min, 99.1%.

(+)-2-Acetyl-4,5-bis(bis(2-cyanoethoxy)phosphoryl)-3,6-bis(2-((( tert-butyl-diphenyl-silyl)oxy)methyl)benzoyl)-D-myo-inositol ((+)-236)

To a solution of (+)-235 (1.00 g, 0.77 mmol, 1.0 eq.) in anhydrous THF (30 mL) under an atmosphere of Ar was added triethyl orthoacetate (1.41 mL, 7.7 mmol, 10.0 eq.) followed by p-toluenesulfonic acid monohydrate (14 mg, 0.08 mmol, 0.1 eq.) and the solution was stirred at room temperature overnight. TLC analysis of the reaction mixture (1:9 MeOH/CH$_2$Cl$_2$) indicated the reaction was complete. The solution was concentrated in vacuo, the oil was dissolved in aqueous AcOH (80% v/v, 20 mL), and the solution was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:9 MeOH/CH$_2$Cl$_2$) indicated that the reaction was complete. The reaction mixture was concentrated in vacuo and the resulting oil was dissolved in EtOAc (100 mL). The organic components were washed with water (50 mL), saturated aqueous NaHCO$_3$ (2 × 50 mL), saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting colourless film was purified using silica gel flash column chromatography on
a Biotage system using 0-5% MeOH in CHCl₃ to give a ca. 1:1 mix of starting material and product. The combined material was subjected to the same conditions, workup and purification with double the amount of reagents (triethylorthoacetate 2.82 mL, 15.4 mmol, 20 eq.; p-toluenesulfonylic acid monohydrate 28 mg, 0.16 mmol, 0.2 eq.) giving a colourless film with a ca. 10:1 mixture of regioisomers, where the acetate was on the 2- and 1-positions respectively. The colourless film was triturated with Et₂O and filtered to afford the title compound as a colourless solid (520 mg, 50%): Rf 0.41 (MeOH/CHCl₃ 1:9); [α]D²⁵ = +21.2 (c 1.0, CHCl₃); m.p. 85-89 °C (from Et₂O); νmax (thin film)/cm⁻¹ 2962 (C-H, w), 2931 (C-H, w), 2848 (C-H, w), 1753 (C=O, m), 1723 (C=O, m), 1298 (C-O, s), 1277 (C-O, s), 1257 (C-O, s), 1246 (C-O, s), 1221 (C-O, s), 1134 (C-O, s), 1111 (C-O, s), 1063 (C-O, s), 1043 (C-O, s), 1004 (C-O, m); ¹H NMR (500 MHz; CD₂Cl₂) δ 8.16 (1H, d, J 7.9, H-26) 8.10 (1H, dd, J 7.9, 1.2, H-9) 8.04 (1H, d, J 7.9, H-12) 8.00 (1H, dd, J 7.9, 1.2, H-23) 7.76-7.65 (10H, m, H-11, H-17, H-25, H-31), 7.49-7.37 (14H, m, H-10, H-16, H-18, H-24, H-30, H-32), 5.53 (1H, dd, J 2.9, 2.9, H-2) 5.49 (1H, dd, J 9.9, 9.9, H-6) 5.35-5.30 (1H, m, H-28a), 5.21-5.13 (4H, m, H-3, H-14, H-28b), 4.94 (1H, ddd, J 9.9, 9.2, 9.2, H-4) 4.56 (1H, ddd, J 9.9, 9.2, 9.2, H-5) 4.25-4.18 (2H, m, H-41), 4.15-4.05 (2H, m, H-44), 3.93-3.72 (4H, m, H-35, H-38), 3.71-3.66 (1H, m, H-1), 2.69-2.51 (4H, m, H-42, H-45), 2.38 (1H, d, J 6.8, OH) 2.16-2.05 (7H, m, H-36, H-39, H-48), 1.15 (9H, s, H-20), 1.13 (9H, s, H-34); ¹³C NMR (126 MHz; CD₂Cl₂) δ 170.4 (C-47), 166.4 (C-7), 164.7 (C-21), 145.4 (C-27), 144.3 (C-13), 136.0 (C-31), 135.9 (C-17), 134.1, 133.92, 133.86, 133.73, 133.66, 133.6 (C-11, C-15, C-25, C-29), 131.4 (C-9), 131.1 (C-23), 130.34, 130.31, 130.2 (C-18, C-32), 128.3, 128.2 (C-16, C-30), 127.1 (C-24), 127.0 (C-10, C-12), 126.9 (C-26), 126.3 (C-8), 125.3 (C-22), 117.28 (C-40), 117.26 (C-43), 116.74 (C-37), 116.69 (C-46), 77.7 (dd, Jₚ 5.2, 5.2, C-5), 77.0 (dd, Jₚ 5.2, 5.2, C-4), 72.7 (C-6), 70.3 (C-2), 69.6 (C-3), 68.6 (C-1), 64.7 (C-14), 64.3 (C-28), 63.5 (d, Jₚ 5.8, C-41), 63.4 (d, Jₚ 5.8, C-44), 62.9 (d, Jₚ 5.0, C-35), 62.8 (d, Jₚ 5.0, C-38), 27.1 (C-20), 27.0 (C-34), 20.9 (C-48), 19.72 (d, Jₚ 7.8, C-42), 19.71 (d, Jₚ 7.8, C-45), 19.64 (C-33), 19.58 (C-19), 19.3 (d, Jₚ 7.7, C-36), 19.2 (d, Jₚ 7.7, C-39); ³¹P NMR (162 MHz; CD₂Cl₂) δ -3.08 (P-5), -3.25 (P-4); HRMS m/z (ES⁺) Found 1361.4056 [M+Na]+ (C₆₈H₇₆N₄NaO₁₇P₂Si₂ requires 1361.4111);
m/z (ES⁻) 1383.5 ([M+formic acid-H]⁻, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 14.0 min, 95.2%.

(+)-2-Acetyl-4,5-bis(bis(2-cyanoethoxy)phosphoryl)-1-(((1,2-dipalmitoyl-sn-glycerol)(2-cyanoethoxy)phosphoryl)oxy)-3,6-bis(2-(((butyldiphenylsilyl)oxy)-methyl)benzoyl)-d-myo-inositol ((+)-237)

To a solution of (+)-236 (218 mg, 0.16 mmol, 1.0 eq.) and phosphoramidite 131 (375 mg, 0.49 mmol, 3.0 eq.) in CH₂Cl₂ (10 mL) under an atmosphere of N₂ was added 1H-tetrazole (3-4 wt.% in MeCN, 1.14 mL, 0.49 mmol, 3.0 eq.) and the reaction solution was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:9 MeOH/CHCl₃) indicated the reaction was complete. The reaction solution was cooled to –78 °C 3-chloroperbenzoic acid (77%, 84 mg, 0.49 mmol, 3.0 eq.) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction solution was diluted with CH₂Cl₂ (100 mL) and the organic components were washed with aqueous Na₂S₂O₃ (10% w/v, 50 mL), saturated aqueous NaHCO₃ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 40-100% EtOAc in petroleum ether to afford the title compound as a colourless oil (252 mg, 76%) as a 1:1 mixture of inseparable diastereomers: Rₜ 0.52 (MeOH/CHCl₃ 1:19); [α]D²⁶ = +5.7
(c 3.1, CHCl₃); ν max (thin film)/cm⁻¹ 2959 (C-H, m), 2925 (C-H, s), 2854 (C-H, s), 1729 (C=O, s), 1470 (C-H, w), 1428 (C-H, w), 1282 (C-H, s), 1247 (C-H, s), 1218 (C-H, s), 1168 (C-H, w), 1135 (C-O, s), 1112 (C-O, s), 1065 (C-O, s), 1044 (C-O, s), 1028 (C-O, s), 1004 (C-O, s); ¹H NMR (700 MHz; CD₂Cl₂) Diastereomer A* δ 8.24-8.19 (2H, m, H-9, H-12), 8.16 (1H, d, J 7.9, H-26), 8.00-7.97 (1H, m, H-23), 7.78-7.70 (10H, m, H-11, H-17, H-25, H-31), 7.50-7.38 (14H, m, H-10, H-16, H-18, H-24, H-30, H-32), 5.75 (1H, dd, J 2.9, 2.9, H-2), 5.72-5.66 (1H, m, H-6), 5.34-5.22 (3H, m, H-3, H-28), 5.19-5.10 (3H, m, H-14, H-53), 4.95 (1H, ddd, J 9.6, 9.6, 9.6, H-4), 4.72-4.64 (1H, m, H-1), 4.58 (1H, ddd, J 9.6, 9.6, 9.6, H-5), 4.30-3.92 (10H, m, H-41, H-44, H-49, H-52, H-54), 3.88-3.62 (4H, m, H-35, H-38), 2.68-2.46 (5H, m, H-42, H-45, H-50a), 2.29-2.19 (4H, m, H-56, H-72), 2.18 (3H, s, H-48), 2.15-1.98 (5H, m, H-50b, H-36, H-39), 1.64-1.47 (4H, br m, H-57, H-73) 1.33-1.20 (48H, m, H-(58-69), H-(74-85)), 1.15 (9H, s, H-20), 1.14 (9H, s, H-34), 0.90-0.86 (6H, m, H-70, H-86) Diastereomer B* 8.24-8.19 (2H, m, H-9, H-12), 8.16 (1H, d, J 7.9, H-26), 8.00-7.97 (1H, m, H-23), 7.78-7.70 (10H, m, H-11, H-17, H-25, H-31), 7.50-7.38 (14H, m, H-10, H-16, H-18, H-24, H-30, H-32), 5.74 (1H, dd, J 2.9, 2.9, H-2), 5.72-5.66 (1H, m, H-6), 5.34-5.22 (3H, m, H-3, H-28), 5.19-5.10 (2H, m, H-14), 4.95 (1H, ddd, J 9.6, 9.6, 9.6, H-4), 4.81 (1H, dddd, J 4.5, 4.5, 4.5, 4.5, H-53), 4.72-4.64 (1H, m, H-1), 4.58 (1H, ddd, J 9.6, 9.6, 9.6, H-5), 4.30-3.92 (7H, m, H-41, H-44, H-49, H-52a), 3.88-3.62 (7H, m, H-35, H-38, H-52b, H-54), 2.68-2.46 (5H, m, H-42, H-45, H-50a), 2.29-2.19 (4H, m, H-56, H-72), 2.17 (3H, s, H-48), 2.15-1.98 (5H, m, H-50b, H-36, H-39), 1.64-1.47 (4H, br m, H-57, H-73), 1.33-1.20 (48H, m, H-(58-69), H-(74-85)), 1.15 (9H, s, H-20), 1.14 (9H, s, H-34), 0.90-0.86 (6H, m, H-70, H-86); ¹³C NMR (126 MHz; CD₂Cl₂) Diastereomer A* δ 173.4 (C-55), 173.0 (C-71), 170.0 (C-49), 165.0 (C-7), 164.5 (C-21), 145.5 (C-27), 145.44 (C-13), 135.95 (C-17), 135.86 (C-31), 134.44 (C-11), 134.2 (C-25), 133.82, 133.79, 133.70, 133.69 (C-15, C-29), 131.5 (C-9), 131.1 (C-23), 130.4-130.3 (br m, C-18), 130.2 (C-32), 128.3 (C-30), 128.21 (C-16), 127.2 (C-10), 127.0 (C-24), 126.9 (C-26), 126.8 (C-12), 125.3 (C-8), 125.1 (C-22), 117.22 (C-43), 117.19 (C-46), 116.7 (C-37), 116.6 (C-40), 77.21 (dd, Jₚ 4.2, 4.2, C-4), 76.8-76.6 (m, C-5), 73.5 (d, Jₚ 4.8, C-1), 70.3 (C-6), 69.4 (d, Jₚ 7.8, C-53), 68.9-68.7 (m, C-2, C-3), 66.6-66.4 (m, C-54), 64.4 (C-28),
7.8. ALTERNATIVE PROTECTING GROUP  

64.2 (C-14), 63.6 (C-41), 63.5 (C-44), 63.00 (C-35), 62.96 (C-38), 62.78 (C-49), 61.7 (C-52), 34.4 (C-72), 34.24 (C-56), 32.3 (C-68, C-84), 30.1, 30.0, 29.9, 29.8, 29.7, 29.5 (C-(58-67), C-(74-83)), 27.1 (C-20, C-34), 25.2, 25.1 (C-57, C-73), 23.1 (C-69, C-85), 20.9 (C-48), 19.7 (d, J_P 8.4, C-42, C-45), 19.6 (C-19, C-33), 19.2 (d, J_P 7.2, C-36), 19.11 (d, J_P 7.5, C-39), 19.08 (d, J_P 6.7, C-50), 14.3 (C-70, C-86), Diastereomer B* 173.3 (C-55), 172.8 (C-71), 169.9 (C-47), 164.9 (C-7), 145.5 (C-27), 145.41 (C-13), 135.92 (C-31), 134.36 (C-11), 134.2 (C-25), 133.82, 133.74, 133.69, 133.67 (C-15, C-29), 131.4 (C-9), 131.1 (C-23), 130.4-130.3 (br m, C-18), 130.2 (C-32), 128.3 (C-30), 128.19 (C-16), 127.1 (C-10), 127.0 (C-24), 126.9 (C-26), 126.7 (C-12), 125.3 (C-8), 125.1 (C-22), 117.22 (C-43), 117.19 (C-46), 116.7 (C-37), 116.6 (C-40, C-51), 77.21 (dd, J_P 4.2, 4.2, C-4), 76.8-76.6 (m, C-5), 73.4 (d, J_P 5.1, C-1), 70.3 (C-6), 69.1 (d, J_P 7.8, C-53), 68.9-68.7 (m, C-2, C-3), 66.6-66.4 (m, C-54), 64.4 (C-28), 64.2 (C-14), 63.44 (C-41), 63.40 (C-44), 62.9 (C-35), 62.84 (C-38), 62.7 (C-49), 61.5 (C-52), 34.3 (C-72), 34.20 (C-56), 32.3 (C-68 84), 30.1, 30.0, 29.9, 29.8, 29.7, 29.4 (C-(58-67), C-(74-83)), 27.1 (C-20, C-34), 25.2, 25.1 (C-57, C-73), 23.1 (C-69, C-85), 20.8 (C-48), 19.7 (d, J_P 8.4, C-42, C-45), 19.6 (C-19, C-33), 19.2 (d, J_P 7.2, C-36), 19.11 (d, J_P 7.5, C-39), 19.08 (d, J_P 6.7, C-50), 14.3 (C-70, C-86); ^31P NMR (162 MHz; CD_2Cl_2) Diastereomer A* δ –0.12 (P-1), –0.98 (P-5), –1.20 (P-4), Diastereomer B* –0.59 (P-1), –1.00 (P-5), –1.20 (P-4); HRMS m/z (ES^+) Found 2039.9408 [M+NH_4]^+ (C_{106}H_{146}N_5O_{24}P_3Si_2 requires 2039.9453); m/z** (ES^+) 2023.1 ([M+H]^+, 68%), 2024.1 ([M^{13}C+H]^+, 100%), 2045.1 ([M+Na]^+, 45%), 2046.1 ([M^{13}C+Na]^+, 78%); NP-HPLC (0-100% isopropanol/hexane) Diastereomer A Retention Time = 13.1 min, 56.9%, Diastereomer B Retention Time = 13.8 min, 42.3%.

*As the two diastereomers cannot be distinguished using the available NMR techniques, the higher shift of each pair is recorded as diastereomer A while the lower is diastereomer B.

**As the number of carbon atoms is greater than 100, the major peak in mass spectrometry is no longer ^{12}C_{106} but is ^{12}C_{105}^{13}C_1 and hence this mass is included for clarity.
(+)-2-Acetoxy-1,4,5-tris((bis(2-cyanoethoxy)phosphoryl)oxy)-3,6-bis(2-((‘butyldiphenylsilyl)oxy)methyl)benzoate) d-myo-inositol ((+-250)

To a solution of (+)-236 (65 mg, 0.05 mmol, 1.0 eq.) and phosphoramidite 126 (30 mg, 0.10 mmol, 2.2 eq.) in CH₂Cl₂ (1 mL) was added 1H-tetrazole (3-4 wt.% in MeCN, 0.23 mL, 0.10 mmol, 2.0 eq.) and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:9 MeOH/CH₂Cl₂) indicated the reaction was complete. The reaction was cooled to –78 °C, 3-chloroperbenzoic acid (77%, 17 mg, 0.10 mmol, 2.0 eq.) was added and the reaction mixture was stirred at room temperature for 1 h. ³¹P NMR analysis indicated the reaction was complete. The resulting solution was diluted with CH₂Cl₂ (50 mL) and the organic components were washed with aqueous Na₂S₂O₃ (10% w/v, 30 mL), saturated aqueous NaHCO₃ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 40-100% EtOAc in petroleum ether to afford the title compound as a colourless glassy solid (53 mg, 70%): Rf 0.50 (MeOH/CH₂Cl₂ 1:19); [α]₂⁵° = +4.6 (c 1.0, CHCl₃); νₘₐₓ (thin film)/cm⁻¹ 2932 (C-H, w), 2857 (C-H, w), 2360 (C≡N, m), 2341 (C≡N, m), 1756 (C=O, m), 1730 (C=O, m), 1473 (C-H, w), 1428 (C≡C, w), 1278 (C-H, m), 1248 (C-H, m), 1220 (C-O, m), 1134 (C-O, m), 1112 (C-O, m), 1063 (C-O, s), 1042 (C-O, s), 1007 (C-O, s); ¹H NMR (500 MHz; CD₂Cl₂) δ 8.24 (1H, dd, J 8.1, 1.3, H-23), 8.22 (1H, d, J 8.4, H-26), 8.17
(1H, d, J 7.9, H-12), 8.01 (1H, dd, J 7.9, 1.3, H-9), 7.77-7.70 (10H, m, H-11, H-16, H-25, H-30), 7.51-7.38 (14H, m, H-10, H-17, H-18, H-24, H-31, H-32), 5.75 (1H, dd, J 3.0, 3.0, H-2), 5.71 (1H, dd, J 10.0, 10.0, H-6), 5.34-5.30 (1H, m, H-3), 5.26 (2H, d, J 16.0, H-14a, H-28a), 5.19 (1H, d, J 16.0, H-28b), 5.14 (1H, d, J 16.0, H-14b), 4.97 (1H, ddd, J 9.9, 9.9, 9.9, H-4), 4.75 (1H, ddd, J 9.9, 9.9, 3.0, H-1), 4.65 (1H, ddd, J 9.4, 9.4, H-5), 4.25-4.15 (2H, m, H-3), 4.13-4.00 (4H, m, H-44, H-49), 3.92-3.78 (4H, m, H-35, H-52), 3.76-3.66 (2H, m, H-11, H-25, H-30, H-31, H-32, H-33, H-34, H-35, H-52), 3.76-3.66 (2H, m, H-3), 2.68-2.49 (6H, m, H-10, H-17, H-18, H-24, H-31, H-32, H-33, H-34, H-35, H-52), 2.19 (3H, s, H-36, H-50, H-53), 1.16 (9H, s, H-20), 1.15 (9H, s, H-34); \(^{13}\)C NMR (126 MHz; CD\(_2\)Cl\(_2\)) \(\delta\) 170.1 (C-47), 164.9 (C-21), 164.5 (C-7), 145.5 (C-13), 145.4 (C-27), 136.0, 135.91 (C-16), 135.86 (C-30), 134.5 (C-11), 134.3 (C-25), 133.8, 133.71, 133.68, 133.66 (C-15, C-29), 131.4 (C-23), 131.1 (C-9), 130.34, 130.32, 130.25, 130.24 (C-18, C-32), 128.3, 128.2 (C-17, C-31), 127.2 (C-24), 127 (C-10), 126.84, 126.79 (C-12, C-26), 125.3 (C-22), 125.1 (C-8), 117.3 (C-43, C-46), 116.8 (C-40), 116.70 (C-37), 116.69 (C-51), 116.4 (C-54), 77.1 (dd, J\(_P\) 5.2, 5.2, C-5), 76.7 (dd, J\(_P\) 5.2, 5.2, C-4), 73.7 (d, J\(_P\) 5.1, C-1), 70.3 (C-6), 68.8 (C-2), 68.7 (C-3), 64.4 (C-28), 64.2 (C-14), 63.6 (d, J\(_P\) 5.9, C-41), 63.4 (d, J\(_P\) 5.5, C-44), 63.0 (d, J\(_P\) 4.8, C-35, C-38, C-52), 62.9 (d, J\(_P\) 4.8, C-49), 30.1 (C-19, C-33), 27.0 (C-20, C-34), 20.9 (C-48), 19.8-19.6, 19.3-19.1 (m, C-36, C-39, C-42, C-45, C-50, C-53); \(^{31}\)P NMR (162 MHz; CD\(_2\)Cl\(_2\)) \(\delta\) -2.91 (P-1), -3.06 (P-5), -3.22 (P-4); HRMS \(m/z\) (ES\(^+\)) Found 1547.4289 [M+Na]\(^+\) (C\(_{74}H_{83}N_6O_20P_3Si_2Na\) requires 1547.4305); \(m/z\) (ES\(^+\)) 1525.4 ([M+H]\(^+\), 30%), 1547.4 ([M+Na]\(^+\), 100%); NP-HPLC (5-95% isopropanol/hexane) Retention Time = 15.8 min, 95.0%. 

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(+)-4,5-Bis(2’,2’,2’-trichloroethylcarbonate) d-<i>myo</i>-inositol ((+)-231)

To a solution of (+)-<i>175</i> (124 mg, 0.1 mmol, 1.0 eq.) in MeCN (1 mL) was added a solution of NaIO<sub>4</sub> (32 mg, 0.15 mmol, 1.5 eq.) and RuCl<sub>3</sub>·3H<sub>2</sub>O (1.7 mg, 0.005 mmol, 0.05 eq.) in a solution of H<sub>2</sub>O (0.25 mL) and the reaction mixture was stirred vigorously at room temperature for 4 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10% w/v, 30 mL). The organic components were extracted with EtOAc (50 mL), washed with saturated aqueous NaCl (30 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The resulting oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), TFA (0.5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. TLC of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was concentrated in vacuo and the product was purified using silica gel flash column chromatography on a Biotage system using 0-10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to afford the title compound as a colourless foam (18 mg, 34%): R<sub>f</sub> 0.10 (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1:9); [α]<sub>D</sub><sup>25</sup> = +11.8 (c 0.5, CHCl<sub>3</sub>/MeOH 1:1); ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 3362 (O-H, m), 1766 (C=O, s), 1264 (C-O, s), 1235 (C-O, s), 1131 (C-O, m), 1046 (C-O, m); <sup>1</sup>H NMR (500 MHz; D<sub>6</sub>-DMSO) δ 5.30 (1H, d, J 5.4, O-H-6), 5.13 (1H, d, J 6.6, O-H-3), 5.07 (1H, d, J 3.8, O-H-2), 4.98 (1H, dd, J 9.9, 9.9, H-4), 4.91-4.84 (5H, m, H-8 H-11, O-H-1), 4.72 (1H, dd, J 9.9 9.9, H-5), 3.78-3.74 (1H, m, H-2), 3.73-3.64 (1H, m, H-3, H-6), 3.41-3.34 (1H, m, H-1); <sup>13</sup>C NMR (126 MHz; D<sub>6</sub>-DMSO) δ 153.3 (C-7), 153.2 (C-10), 94.78, 94.76 (C-9, C-12), 79.4 (C-5), 78.5 (C-4), 76.04, 76.01 (C-8, C-11), 72.5 (C-2), 70.8 (C-1), 70.1 (C-6), 68.8 (C-3). Mass spectrometry data were not obtained due to the poor ionisation of the compound in various techniques (ESI, EI, FI and MALDI).
To a solution of (+)-175 (124 mg, 0.10 mmol, 1.0 eq.) in MeCN (1 mL) was added a solution of NaIO₄ (32 mg, 0.15 mmol, 1.5 eq.) and RuCl₃·3H₂O (1.7 mg, 0.005 mmol, 0.05 eq.) in H₂O (0.25 mL) and the reaction mixture was stirred vigorously for 8 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous Na₂S₂O₃ (10% w/v, 30 mL) was added and the suspension was stirred at room temperature for 5 min. After this time, the organic components were extracted with CH₂Cl₂ (3 × 30 mL), combined, dried with Na₂SO₄, filtered and concentrated in vacuo. The oil was dissolved in CH₂Cl₂ (1 mL), 4-dimethylaminopyridine (1.2 mg, 0.01 mmol, 0.1 eq.), pyridine (24 µL, 0.30 mmol, 3.0 eq.) and trichloroethyl chloroformate (41 µL, 0.30 mmol, 3.0 eq.) were added and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:2 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (50 mL) and the organic components were washed with aqueous HCl (1 M, 20 mL), saturated aqueous NaHCO₃ (20 mL), saturated aqueous NaCl (20 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 2-20% Et₂O in petroleum ether to afford the title compound as a colourless oil (140 mg, 86%): Rₜ 0.46 (Et₂O/petroleum ether 1:4);
7.9 Phosphoramidite Preparations

Dichloro-\(N, N\)-diisopropylphosphoramidite (125)\(^{52}\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{P} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

A solution of \(\text{PCl}_3\) (8.7 mL, 100 mmol, 1.0 eq.) in anhydrous \(\text{Et}_2\text{O}\) (500 mL) under an atmosphere of \(\text{N}_2\) was cooled to \(-78^\circ\text{C}\) and freshly distilled diisopropylamine (28.0 mL, 200 mmol, 2.0 eq.) was added, dropwise, over a period of 20 min. The reaction mixture was stirred for 1 h at \(-78^\circ\text{C}\) followed by a further 3 h at room temperature. \(^{31}\text{P}\) NMR
analysis of the reaction mixture indicated the reaction was complete. The precipitate was filtered under \( \text{N}_2 \) using a Schlenk filtration apparatus and the filtrate was concentrated \textit{in vacuo} to afford the title compound as a colourless oil (13.62 g, 67\%). The compound was stored as a crystalline solid at \(-20\) °C and the purity checked by \( ^{31}\text{P} \) NMR prior to use: \( ^1\text{H} \) NMR (400 MHz; CDCl\(_3\)) \( \delta \) 3.93-3.80 (2H, m, \( H-1 \)), 1.21 (12H, d, \( J 6.8, H-2 \)); \( ^{31}\text{P} \) NMR (162 MHz; CDCl\(_3\)) \( \delta \) 169.46; \( m/z \) (ES\(^+\)) 239.2 ([M+K]\(^+\), 100\%). These data are in good agreement with the literature.\(^{52}\)

**Bis(2-cyanoethoxy)-\(N,N\)-diisopropylphosphoramidite (126)\(^{207}\)**

A solution of 3-hydroxypropionitrile (0.70 mL, 14 mmol, 2.0 eq.) and freshly distilled diisopropylethylamine (3.7 mL, 21 mmol, 3.0 eq.) in anhydrous CH\(_2\)Cl\(_2\) (10 mL) under an atmosphere of Ar was cooled to 0 °C and \( 125 \) (1.41 g, 7 mmol, 1.0 eq.) was added, dropwise, over 5 min. The reaction mixture was stirred at room temperature for 1 h. \( ^{31}\text{P} \) NMR analysis of the reaction mixture indicated the reaction was complete. The product was purified using rapid silica gel flash column chromatography using 50% EtOAc in petroleum ether under a flow of \( \text{N}_2 \) (the phosphoramidite is unstable to air) to afford the title compound as a colourless oil (1.27 g, 67\%): \( R_f \) 0.32 (EtOAc/petroleum ether 1:3); \( ^1\text{H} \) NMR (400 MHz; CDCl\(_3\)) \( \delta \) 3.97-3.80 (4H, m, \( H-1 \)), 3.70-3.58 (2H, m, \( H-1' \)), 2.68 (4H, t, \( J 6.3, H-2 \)), 1.22 (12H, d, \( J 6.9, H-2' \)); \( ^{13}\text{C} \) NMR (101 MHz; CDCl\(_3\)) \( \delta \) 117.7 (C-3), 58.5 (d, \( J_P 18.6, C-1 \)), 43.3 (d, \( J_P 12.2, C-1' \)), 24.6 (d, \( J_P 7.4, C-2' \)), 20.5 (C-2); \( ^{31}\text{P} \) NMR (162 MHz; CDCl\(_3\)) \( \delta \) 149.15; \( m/z \) (ES\(^+\)) 403.3 ([2M–2(O(CH\(_2\))\(_2\)CN)+H]\(^+\), 100\%). These data are in good agreement with the literature.\(^{207}\)
2-Cyanoethoxy $N,N$-diisopropylchlorophosphoramidite (129)$^{140,208}$

The procedure from Nielsen and Dahl was used.$^{140}$ To a solution of PCl$_3$ (17.5 mL, 200 mmol, 5.0 eq.) in anhydrous MeCN (20 mL) under an atmosphere of Ar was added 3-hydroxypropionitrile (2.7 mL, 40 mmol, 1.0 eq.). The solution was stirred at room temperature for 1 h. $^{31}$P NMR analysis indicated the reaction was complete. The reaction mixture was concentrated $\textit{in vacuo}$ and the resulting oil was redissolved in anhydrous Et$_2$O (30 mL). Freshly distilled diisopropylamine (11.3 mL, 80.0 mmol, 2.0 eq.) was added, dropwise, at $-10$ $^\circ$C over a period of 10 min. The resulting suspension was stirred at room temperature for 18 h. $^{31}$P NMR analysis indicated the reaction was complete. The yellow suspension was filtered under vacuum using a Schlenk filtration apparatus with a flow of N$_2$ and the resulting filter cake was washed with anhydrous Et$_2$O (100 mL). The filtrate was concentrated $\textit{in vacuo}$ to give a yellow oil. The product was purified by vacuum distillation (130–135 $^\circ$C, 1.2 mBar {lit.$^{140}$ 105-107 $^\circ$C, 1.3 mBar}) to afford the title compound as a colourless oil (4.17 g, 44%) with a purity of 92% by $^{31}$P NMR. The product was used without further purification and was stored for extended periods at $-20$ $^\circ$C: $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 4.05 (2H, dt, $J$ 6.5, 6.1, $H$-1), 3.80 (2H, d septet, $J$ 11.3, 6.8, $H$-4), 2.75 (2H, t, $J$ 6.1, $H$-2), 1.27 (12H, d, $J$ 6.8, $H$-5); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 116.9 ($C$-3), 60.4 (d, $J_P$ 19.4, $C$-1), 46.2 (d, $J_P$ 13.0, $C$-4), 24.2-23.0 (m, $C$-5), 19.9 (d, $J_P$ 6.7, $C$-2); $^{31}$P NMR (162 MHz; CDCl$_3$) $\delta$ 179.94. These data are in good agreement with the literature.$^{140,208}$
2-Cyanoethoxy-\(N,N\)-diisopropyl-(1,2-dipalmitoyl-\(sn\)-glycerol)phosphor-amidite (131)

The procedure from Xu et al. was used. A solution of freshly distilled diisopropylethylamine (0.10 mL, 0.57 mmol, 4.0 eq.) and (–)-130 (81 mg, 0.14 mmol, 1.0 eq.) in anhydrous CH\(_2\)Cl\(_2\) (2 mL) under an atmosphere of Ar was cooled to 0 °C and phosphoramidite 129 (62 µl, 0.28 mmol, 2.0 eq.) was added. The solution was stirred at room temperature for 2 h. \(^{31}\)P NMR analysis of the reaction mixture indicated the reaction was complete. The reaction mixture was concentrated \textit{in vacuo}. The product was purified using rapid silica gel flash column chromatography under a flow of N\(_2\) using 20% EtOAc in petroleum ether to afford the title compound as a colourless oil (60 mg, 56%): R\(_f\) 0.78 (EtOAc/petroleum ether 1:4); \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 5.19 (1H, m, H-2), 4.39-4.29 (1H, m, H-1a), 4.17 (1H, ddd, \(J\) 11.5, 11.5, 6.6, H-1b), 3.90-3.51 (6H, m, H-3, H-1’, H-3’), 2.63 (2H, t, \(J\) 6.4, H-4’), 2.36-2.27 (4H, m, H-4, H-19), 1.67-1.56 (4H, m, H-5, H-20), 1.35-1.21 (48H, m, H-(6-17), H-(21-32)), 1.18 (12H, t, \(J\) 5.9, H-2’), 0.91-0.85 (m, H-18, H-33, 6H); \(^{31}\)P NMR (162 MHz; CDCl\(_3\)) \textit{Diastereomer A} \(\delta\) 149.60, \textit{Diastereomer B} \(\delta\) 149.45. These data are in good agreement with the literature.

Dichloro \(N,N\)-diethylphosphoramidite (194)
The procedure from Gregory *et al.* was used.\textsuperscript{175} To a solution of PCl\textsubscript{3} (4.36 mL, 50 mmol, 1.0 eq.) in anhydrous Et\textsubscript{2}O (300 mL) under an atmosphere of N\textsubscript{2} on a Schlenk system at –78 °C was added a solution of freshly distilled diethylamine (10.4 mL, 100 mmol, 2.0 eq.) in anhydrous Et\textsubscript{2}O (100 mL) \textit{via} cannula over 30 min. After addition was complete, the reaction mixture was warmed slowly to room temperature and the resulting suspension was stirred at room temperature for 18 h. \textsuperscript{31}P NMR analysis of the reaction mixture indicated the reaction was complete. The solution was filtered using a Schlenk filter and the filter cake was washed with anhydrous Et\textsubscript{2}O (100 mL). The filtrate was concentrated \textit{in vacuo} to afford the title compound as a colourless oil (6.96 g, crude) that was used without further purification. The product was stored at –20 °C as an oil and the purity checked by \textsuperscript{31}P NMR prior to use: \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \textit{δ} 3.36 (2H, q, \textit{J} 7.0, H-1a), 3.33 (2H, q, \textit{J} 7.1, H-1b), 1.19 (6H, t, \textit{J} 7.1, H-2); \textsuperscript{31}P NMR (162 MHz; CDCl\textsubscript{3}) \textit{δ} 162.58. These data are in good agreement with the literature.\textsuperscript{175}

\textbf{(1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (187)}\textsuperscript{175}

![Chemical structure](image)

The procedure from Gregory *et al.* was used.\textsuperscript{175} To a solution of 194 (1.75 g, 10.0 mmol, 1.0 eq.) in anhydrous Et\textsubscript{2}O (80 mL) under an atmosphere of N\textsubscript{2} at –78 °C was added, \textit{via} cannula, a solution of \textit{N,N}-diisopropylethylamine (3.48 mL, 20.0 mmol, 2.0 eq.) and 1,2-benzenedimethanol (1.40 g, 10.0 mmol, 1.0 eq.) in a mixture of THF (15 mL) and Et\textsubscript{2}O (60 mL) over a period of 20 min. The reaction mixture was warmed to room temperature and stirred for 18 h. \textsuperscript{31}P NMR analysis of the reaction mixture indicated the reaction was complete. The resulting suspension was filtered under N\textsubscript{2} using a Schlenk filter, followed by concentration \textit{in vacuo} to give a colourless oil (3.28 g, crude) that was used without
further purification (ca. 63% product by $^{31}$P NMR): $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.28-7.16 (4H, m, H-4, H-5), 5.16 (2H, dd, J 13.8, 6.8, H-3a), 4.89 (2H, dd, J 19.6, 13.8, H-3b), 3.16 (4H, dq, J 10.0, 7.2, H-1), 1.08 (6H, t, J 7.2, H-2); $^{31}$P NMR (162 MHz; CDCl$_3$) $\delta$ 145.33. These data are in good agreement with the literature.$^{175}$

**Benzzyloxy-\textit{N},\textit{N}-diisopropyl-(1,2-dipalmitoyl-\textit{sn}-glycerol)phosphoramidite (207)$^{152}$**

![Chemical Structure](Image)

The procedure from Johns \textit{et al.} was used.$^{152}$ A mixture of benzzyloxy bis(\textit{N},\textit{N}-diisopropyl)-phosphoramidite 208 (from A. Joffrin,$^{51}$ synthesised by the procedure from Johns \textit{et al.},$^{152}$ 0.375 g, 1.10 mmol, 2.5 eq.) and 1\textit{H}-tetrazole (3-4 wt.% in MeCN, 3.07 mL, 1.32 mmol, 3.0 eq.) in CH$_2$Cl$_2$ (25 mL) was stirred at room temperature under an atmosphere of Ar for 10 min. To this solution was added a solution of (\textit{--})-130 (350 mg, 0.44 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (10 mL), dropwise, over a period of 10 min and the resulting reaction mixture was stirred at room temperature for 18 h. $^{31}$P NMR analysis of the reaction mixture indicated the reaction was complete. After this time, the reaction mixture had turned cloudy. The mixture was diluted with CH$_2$Cl$_2$ (50 mL), the organic components were washed with saturated aqueous NaHCO$_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The product was purified using rapid silica gel flash column chromatography with 80:15:5 hexane/EtOAc/NEt$_3$ to afford the title compound as a colourless oil (280 mg, 79%) which was used without further purification as a 1:1 mixture of diastereomers: $R_f$ 0.85 (EtOAc/petroleum ether 1:4); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.37-7.29 (5H, m, H-37, H-38, H-39), 5.19 (1H, dddd, J 5.0
5.0, 5.0, 5.0, $H-2$), 4.79-4.59 (2H, m, $H-36$), 4.34 (1H, ddd, $J$ 8.2, 3.8, 3.8, $H-1a$), 4.20-4.13 (1H, m, $H-1b$), 3.83-3.56 (4H, m, $H-3$, $H-34$), 2.29 (2H, t, $J$ 7.5, $H-19$), 2.28 (2H, t, $J$ 7.5, $H-4$), 1.65-1.55 (4H, m, $H-5$, $H-20$), 1.32-1.21 (48H, m, $H-(6-17)$, $H-(21-32)$), 1.20-1.16 (12H, m, $H-35$), 0.90-0.86 (6H, m, $H-18$, $H-33$); $^{31}$P NMR (162 MHz; CDCl$_3$) 

Diastereomer A $\delta$ 148.88, Diastereomer B $\delta$ 148.73. These data are in good agreement with the literature.$^{152}$

7.10 Glycerol Preparations

(+)-(S)-1,2-Isopropylidene-3-O-benzyl-sn-glycerol ((+)-147)$^{210}$

A solution of (+)-(S)-1,2-isopropylidene sn-glycerol (1.32 g, 10.0 mmol, 1.0 eq.) in anhydrous DMF (20 mL) under an atmosphere of Ar was cooled to 0 °C and sodium hydride (60% suspension in mineral oil, 480 mg, 12.0 mmol, 1.2 eq.) was added. The suspension was stirred at 0 °C for 1 h. After this time, benzyl bromide (1.43 mL, 12.0 mmol, 1.2 eq.) was added and the reaction mixture was stirred at room temperature overnight. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with EtOAc (300 mL), the organic components were washed with saturated aqueous NaCl (3 × 100 mL) and aqueous LiCl (0.5 M, 50 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 5% Et$_2$O in petroleum ether to afford the title compound as a colourless oil (2.05 g, 92%): $R_f$ 0.34 (Et$_2$O/petroleum ether 1:9); $[\alpha]_{D}^{25} = +17.5$ (c 4.3, CHCl$_3$) {lit.$^{210}$ +21.9 (c 1.0, CHCl$_3$)}; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.39-7.25 (5H, m, $H-7$, $H-8$, $H-9$), 4.6 (1H, d, $J$ 11.9, $H-6a$), 4.55 (1H, d, $J$ 11.9, $H-6b$), 4.31 (1H, dddd, $J$ 6.2, 6.2, 6.2, 6.2, $H-2$), 4.06 (1H, dd, $J$ 8.2, 6.2, $H-3a$), 3.74 (1H, dd, $J$ 8.2, 6.2, $H-3b$), 3.56 (1H, dd, $J$ 9.8, 6.2, $H-1a$),
3.47 (1H, dd, J 9.8, 6.2, H-1b), 1.42 (3H, s, H-4), 1.37 (3H, s, H-5); m/z (ES⁺) 223.1 ([M+H]⁺, 57%), 245.1 ([M+Na]⁺, 100%). These data are in good agreement with the literature.²¹⁰

(−)-(R)-3-O-Benzyl-sn-glycerol (−)-148)²¹⁰

To a solution of (+)-147 (2.00 g, 9.0 mmol, 1.0 eq.) in THF (10 mL) was added aqueous HCl (1 M, 4.0 mL) and the solution was stirred at room temperature overnight. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched by addition of saturated aqueous NaHCO₃ until pH 9. The product was extracted with EtOAc (3 × 100 mL), washed with saturated aqueous NaCl (100 mL), dried Na₂SO₄, filtered, and concentrated in vacuo to afford the title compound as a colourless oil (1.52 g, 93%): R₅ 0.13 (EtOAc/petroleum ether 1:1); [α]D²⁵ = −1.2 (c 5.3, CHCl₃) [lit.²¹⁰ +5.9 (c 1.0, CHCl₃), lit.²¹¹ +7.5 (neat)]; ¹H NMR (400 MHz; CDCl₃) δ 7.39-7.28 (5H, m, H-5, H-6, H-7), 4.55 (2H, s, H-4), 3.92-3.87 (1H, m, H-2), 3.71 (1H, dd, J 11.5, 4.1, H-1a), 3.63 (1H, dd, J 11.5, 5.5, H-1b), 3.59 (1H, dd, J 9.6, 4.1, H-3a), 3.54 (1H, dd, J 9.6, 6.4, H-3b); m/z (ES⁺) 205.1 ([M+Na]⁺, 100%). These data are in partial agreement with the literature - while all spectroscopic data matched the literature, the specific rotation was found to be different, despite multiple readings taken on different batches of (−)-148.²¹⁰ Taking (−)-148, subjecting it to further reactions to produce (+)-145 (see below) and measuring the specific rotation of (+)-145 was in agreement with the literature.²¹¹ In addition, derivatisation of (−)-146 with either enantiomer of α-methoxyphenylacetic acid to give (+)-151a or (+)-151b showed the e.e was > 99%.
To a solution of (−)-148 (1.31 g, 7.19 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL) was added 4-dimethylaminopyridine (8 mg, 0.07 mmol, 0.01 eq.) and N,N-diisopropylethylamine (3.1 mL, 18.0 mmol, 2.5 eq.). The solution was cooled to 0 °C and palmitoyl chloride (5.50 mL, 18.0 mL, 2.5 eq.) was added, dropwise, over 10 min. The reaction mixture was stirred at room temperature for 18 h, during which time it turned from colourless, to red, and then finally to yellow. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and the organic components were washed with aqueous HCl (1 M, 50 mL) and saturated aqueous NaCl (50 mL). Further product was extracted from the combined aqueous layers using CH₂Cl₂ (2 × 50 mL). The combined organic components (ca. 200 mL) were dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a biotage system using 5% Et₂O in petroleum ether followed by 10% Et₂O in petroleum ether to afford the title compound as a colourless solid (4.52 g, 95%): Rf 0.49 (Et₂O/petroleum ether 1:9); [α]²⁵_D = +5.8 (c 3.3, CHCl₃) {lit.²¹¹ +6.0 (c 8.5, CHCl₃)}; m.p. 38-39 °C (from Et₂O) {lit.²¹¹ 42.0-42.5 °C (from EtOH), lit.¹⁴⁹ 64.0-65.5 °C (from EtOAc)}; ¹H NMR (400 MHz; CDCl₃) δ 7.38-7.24 (5H, m, H-5, H-6, H-7), 5.25 (1H, dddd, J 6.7, 5.2, 4.3, 3.8, H-2), 4.57 (1H, d, J 11.9, H-4a), 4.52 (1H, d, J 11.9, H-4b), 4.35 (1H, dd, J 11.9, 3.8, H-3a), 4.19 (1H, dd, J 11.9, 6.7, H-3b), 3.59 (2H, d, J 5.2, H-1), 2.32 (2H, t, J 7.5, H-9), 2.28 (2H, t, J 7.5, H-25), 1.66-1.54 (4H, m, H-10, H-26), 1.35-1.21 (48H, m, H-(11-22), H-(27-38)), 0.91-0.85 (6H, m, H-23, H-40); m/z (ES⁺) 681.5 ([M+Na]⁺, 100%). These data are in good agreement with the literature.¹⁴⁹,²¹¹
(+)-(S)-1,2-Isopropylidene-3-O-(4-methoxybenzyl)-sn-glycerol ((+)-149)

A solution of (+)-(S)-1,2-isopropylidene sn-glycerol (1.98 g, 15.0 mmol, 1.0 eq.) in anhydrous DMF (30 mL) under an atmosphere of Ar was cooled to 0 °C and sodium hydride (60% suspension in mineral oil, 720 mg, 18 mmol, 1.2 eq.) was added. The reaction mixture was stirred at 0 °C for 10 min followed by room temperature for 1 h. After this time, 4-methoxybenzyl chloride (2.44 mL, 18 mmol, 1.2 eq.) was added and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. Water (5 mL) was added, dropwise, to quench excess sodium hydride and the resulting suspension was diluted with EtOAc (300 mL). The organic components were washed with saturated aqueous NaHCO₃ (100 mL), saturated aqueous NaCl (3 × 100 mL), aqueous LiCl (0.5 M, 50 mL) and saturated aqueous NaCl (100 mL), dried with Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by silica gel flash column chromatography using 30% EtOAc in petroleum ether to afford the title compound as a colourless oil (2.29 g, 93%): Rᵣ 0.78 (EtOAc/petroleum ether 1:4); [α]_D²⁰⁺ = +18.8 (c 2.4, CHCl₃) {lit. ¹⁵⁰ +21.42 (c 2.04, CHCl₃)}; ¹H NMR (400 MHz; CDCl₃) δ 7.26 (2H, d, J 8.6, H-5), 6.88 (2H, d, J 8.6, H-6), 4.53 (1H, d, J 11.6, H-4a), 4.48 (1H, d, J 11.6, H-4b), 4.28 (1H, dddd, J 6.5, 6.5, 5.8, 5.8, H-2), 4.05 (1H, dd, J 8.3, 6.5, H-1a), 3.80 (3H, s, H-7), 3.72 (1H, dd, J 8.3, 6.5, H-1b), 3.52 (1H, dd, J 9.9, 5.8, H-3a), 3.43 (1H, dd, J 9.9, 5.8, H-3b), 1.42 (3H, s, H-8), 1.36 (3H, s, H-9); m/z (ES⁺) 527.3 ([2M+Na]⁺, 100%). These data are in good agreement with the literature.¹⁵⁰
The procedure from Pilkington and Barker was used.\(^{150}\) To a solution of (+)-149 (800 mg, 3.2 mmol, 1.0 eq.) in THF (4 mL) was added aqueous HCl (1 M, 2 mL) and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched by addition of saturated aqueous NaHCO\(_3\) (20 mL) and the product was extracted with EtOAc (3 \(\times\) 20 mL). The combined organic components were dried with Na\(_2\)SO\(_4\), filtered and concentrated \(\text{in vacuo}\) to afford the title compound as a colourless oil (624 mg, 93\%): \(R_f\) 0.12 (EtOAc/petroleum ether 1:1); \([\alpha]_{D}^{20} = -0.64\) (c 2.5, CHCl\(_3\)) {lit.\(^{150}\) \(-0.73\) (c 2.48, CHCl\(_3\))}; \(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 7.28-7.24 (2H, m, \(H-6\)), 6.91-6.86 (2H, m, \(H-7\)), 4.49 (2H, s, \(H-4\)), 3.91-3.84 (1H, m, \(H-2\)), 3.81 (3H, s, \(H-9\)), 3.70 (1H, ddd, \(J\ 10.9, 6.9, 3.8, H-1a\)), 3.63 (1H, dd, \(J\ 10.9, 5.3, H-1b\)), 3.58-3.49 (2H, m, \(H-3\)), 2.64 (1H, d, \(J\ 5.0, OH-2\)), 2.16 (1H, dd, \(J\ 6.7, 5.5, OH-1\)); \(m/z\) (ES\(^+\)) 235.1 ([M+Na]\(^+\), 100\%). These data are in good agreement with the literature.\(^{150}\)

\(\text{(+)-(S)-1,2-Dipalmitoyl-3-O-(4-methoxybenzyl)-sn-glycerol ((+)-146)}\)

A solution of (–)-150 (106 mg, 0.5 mmol, 1.0 eq.), \(N,N'\)-dicyclohexylcarbodiimide (227 mg, 1.1 mmol, 2.2 eq.), 4-dimethylaminopyridine (137 mg, 1.1 mmol, 2.2 eq.) and palmitic acid (282 mg, 1.1 mmol, 2.2 eq.) in CH\(_2\)Cl\(_2\) (10 mL) was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the
reaction was complete. The solution was diluted with CH$_2$Cl$_2$ (ca. 40 mL) and the organic components were washed with aqueous HCl (1 M, 25 mL), saturated aqueous NaHCO$_3$ (25 mL), saturated aqueous NaCl (25 mL), dried with MgSO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography using 50% CH$_2$Cl$_2$ in petroleum ether to afford the title compound as a waxy solid (217 mg, 69%): R$_f$ 0.84 (EtOAc/petroleum ether 1:4); [α]$_D^{20}$ = +6.0 (c 1.0, CHCl$_3$); m.p. 53-54 °C (from CH$_2$Cl$_2$/petroleum ether); ν$_{max}$ (thin film)/cm$^{-1}$ 2916 (C-H alkyl, s), 2849 (C-H alkyl, s), 1730 (C=O, s), 1514 (C=C, m), 1471 (C=C, m), 1244 (C-O, m), 1160 (C-O, s), 1109 (C-O, s), 1030 (C-O, m); $^1$H NMR (400 MHz; CDCl$_3$) δ 7.16 (2H, d, J 8.7, H-6), 6.80 (2H, d, J 8.7, H-7), 5.19-5.12 (1H, m, H-2), 4.42 (1H, d, J 11.7, H-4a), 4.39 (1H, d, J 11.7, H-4b), 4.26 (1H, dd, J 11.9, 3.7, H-1a), 4.10 (1H, dd, J 11.9, 6.5, H-1b), 3.74 (3H, s, H-9), 3.48 (2H, dd, J 5.2, 1.0, H-3), 2.24 (2H, t, J 7.6, H-27), 2.20 (2H, t, J 7.6, H-11), 1.59-1.46 (4H, m, H-12, H-28), 1.25-1.15 (48H, m, H-(13-24), H-(29-40)), 0.81 (6H, m, H-25, H-40); $^{13}$C NMR (101 MHz; CDCl$_3$) δ 177.4 (C-26) 173.1 (C-10), 159.3 (C-8), 129.8 (C-5), 129.3 (C-6), 113.8 (C-7), 73.0 (C-4), 70.0 (C-3), 67.9 (C-2), 62.7 (C-1), 55.3 (C-9), 34.3 (C-27), 34.1 (C-11), 31.9 (C-23, C-39), 29.8-29.6 (m), 29.5, 29.4, 29.3, 29.14, 29.10 (C-(13-22), C-(29-38)), 25.0 (C-28), 24.9 (C-12), 22.7 (C-24, C-40), 14.1 (C-25, C-41); HRMS m/z (E$^+$) Found 668.5432 [M+Na]$^+$ (C$_{43}$H$_{76}$O$_6$Na requires 668.5642); m/z (ES$^+$) 551.1 ([M–OPMB]$^+$, 100%), 712.1 ([M+Na]$^+$, 56%).

(−)-(S)-1,2-Dipalmitoyl-sn-glycerol (−)-130$^{212}$

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Method A

The procedure from Gu et al. was used. To a solution of (+)-145 (659 mg, 1.0 mmol, 1.0 eq.) in a mixture of glacial AcOH (2 mL) and EtOH (10 mL) under an atmosphere
of $N_2$ was added Pd/C (10% w/w, 100 mg, 0.1 eq.). The suspension was stirred at room
temperature for 5 min before the atmosphere of $N_2$ was replaced with $H_2$ (3 × balloons).
The reaction suspension was stirred at room temperature for 1 h. TLC analysis of the
reaction mixture (1:9 EtOAc/petroleum ether) indicated the reaction was complete. The
reaction suspension was diluted with EtOAc (50 mL) and the mixture was filtered through
a plug of Celite®. The filter cake was washed with EtOAc (50 mL) and the filtrate was
concentrated in vacuo to afford the title compound as a colourless solid (570 mg, 100%).

Data is shown below.

Method B

The procedure from Vilchéze and Bittman was used. A biphasic mixture of (+)-
146 (194 mg, 0.28 mmol, 1.0 eq.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
(DDQ, 77 mg, 0.34 mmol, 1.2 eq.) in $CH_2Cl_2$ (8 mL) and water (8 mL) was stirred vigourously
at room temperature for 2 h. After this time, further DDQ (38 mg, 0.17 mmol, 0.6 eq.)
was added and the reaction mixture stirred for 1 h. The biphasic solution was diluted
with $CH_2Cl_2$ (ca. 50 mL), the aqueous layer was removed and the organic components
were washed with saturated aqueous NaHCO$_3$ (3 × 20 mL) until the organic solution was
colourless. The organic components were dried with MgSO$_4$, filtered and concentrated
in vacuo. The resulting solid was subjected to the reaction again with DDQ (77 mg,
0.34 mmol, 1.2 eq.) in $CH_2Cl_2$ (8 mL) and water (8 mL) and the same workup was
performed. The product was purified using silica gel flash column chromatography on
a Biotage system using 15% EtOAc in petroleum ether to afford the title compound as
a colourless waxy solid (98 mg, 61%): $R_f$ 0.07 (EtOAc/petroleum ether 1:19); $[\alpha]_D^{20}$ =
-2.6 (c 1.0, CHCl$_3$) {lit.$^{212}$ -2.69 (c 3.9 CHCl$_3$)}; m.p. 63-64 °C (from EtOAc) {lit.$^{212}$
66-67 °C, lit.$^{149}$ 64.5-65.5 °C}; $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 5.12 (1H, dddd,
$J$ 5.0, 5.0, 5.0, 5.0, $H$-2), 4.35 (1H, dd, $J$ 11.9, 5.0, $H$-1a), 4.27 (1H, dd, $J$ 11.9, 5.0, $H$-1b), 3.76
(2H, d, $J$ 5.0, $H$-3), 2.34 (2H, t, $J$ 7.8, $H$-19), 2.32 (2H, t, $J$ 7.8, $H$-4), 2.06 (1H, br s,
OH), 1.65 (4H, m, $H$-5, $H$-20), 1.29 (48H, m, $H$-(6-17), $H$-(21-32)), 0.91 (6H, m, $H$-18,
$H$-33); m/z (ES$^+$) 551.1 ([M-OH]$^+$, 100%). These data are in good agreement with the
literature.$^{212}$
(+)-(R)-3-(((R)-2-Methoxy-2-phenylacetoxy)-1,2-dipalmitoyl sn-glycerol
((+)-151a)

A solution of (–)-130 (50 mg, 0.09 mmol, 1.0 eq.), (–)-(R)-α-methoxyphenylacetic acid (28 mg, 0.17 mmol, 2.2 eq.), EDC-HCl (35 mg, 0.18 mmol, 2.4 eq.) and 4-dimethylamino-pyridine (1.9 mg, 0.01 mmol, 0.1 eq.) in CH$_2$Cl$_2$ (1 mL) was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction solution was diluted with CH$_2$Cl$_2$ (30 mL) and the organic components were washed with aqueous HCl (1 M, 20 mL), saturated aqueous NaHCO$_3$ (20 mL) and saturated NaCl (20 mL), dried with Na$_2$SO$_4$, filtered, and concentrated in vacuo. The product was purified using silica gel flash column chromatography on a Biotage system using 2-20% EtOAc in petroleum ether to afford the title compound as a colourless film (50 mg, 79%): R$_f$ 0.59 (EtOAc/petroleum ether 1:4); [α]$^\text{D}_{26}$ = +7.5 (c 4.4, CHCl$_3$); $\tilde{\nu}$$_{\text{max}}$ (thin film)/cm$^{-1}$ 2916 (C-H, s), 2849 (C-H, s), 1749 (C=O, s), 1731 (C=O, s), 1467 (C-H, m), 1286 (C-H, m), 1266 (C-H, m), 1245 (C-H, m), 1225 (C-O, s), 1198 (C-O, s), 1176 (C-O, s), 1148 (C-O, s), 1118 (C-O, s), 1097 (C-O, s), 1089 (C-O, m), 1019 (C-O, m); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.43-7.29 (5H, m, H$_{-40}$, H$_{-41}$, H$_{-42}$), 5.22 (1H, dddd, J 4.5, 4.5, 4.5, 4.5, H$_{-2}$), 4.76 (1H, s, H-37), 4.33 (1H, dd, J 11.9, 4.5, H-1a), 4.18 (1H, dd, J 11.9, 4.5, H-1b), 4.16 (1H, dd, J 11.9, 4.5, H-3a), 4.03 (1H, dd, J 11.9, 4.5, H-3b), 3.41 (3H, s, H-38), 2.25 (2H, t, J 7.7, H-5), 2.18 (1H, ddd, J 7.6, 7.6, 7.6, H-21a), 2.14 (1H, ddd, J 7.6, 7.6, 7.6, H-21b), 1.62-1.48 (4H, m, H-6, H-22), 1.32-1.21 (48H, m, H-(7-18), H-(23-34)), 0.90-0.85 (6H, m, H-19, H-35); $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 173.3 (C-20), 172.9 (C-4), 170.3 (C-36), 136.1 (C-39), 129.0 (C-42), 128.8 (C-40), 127.3 (C-41), 82.4 (C-37), 68.7 (C-2), 63.0 (C-1), 61.9 (C-3), 57.5 (C-38), 34.13 (C-21), 34.1 (C-5), 32.1 (C-34), 29.82 (C-18), 29.79, 29.75, 29.63, 29.6, 29.5, 29.41, 29.38, 29.23, 29.19

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(C-(7-16), C-(23-32)), 24.94 (C-22), 24.88 (C-6), 22.8 (C-17, C-33), 14.3 (C-19, C-35); HRMS m/z (ES\textsuperscript{+}) Found 739.5478 [M+Na]\textsuperscript{+} (C\textsubscript{44}H\textsubscript{76}O\textsubscript{7} requires 739.5483); m/z (ES\textsuperscript{+}) 739.5 ([M+Na]\textsuperscript{+}, 100%).

(+)-(R)-3-((S)-2-Methoxy-2-phenylacetoxy)-1,2-dipalmitoyl sn-glycerol

\((+)-151b\)

\((+)-151b\) was prepared in a similar manner to \((+)-151a\) using \((+)-(S)\)-\(\alpha\)-methoxyphenylacetic acid to afford the title compound as a colourless film (35 mg, 55%): R\textsubscript{f} 0.63 (EtOAc/petroleum ether 1:4); \([\alpha]\textsubscript{\text{D}}\textsuperscript{25} = +8.8 (c 3.2, CHCl\textsubscript{3}); \nu\textsubscript{max} (thin film)/cm\textsuperscript{-1} 2922 (C-H, s), 2852 (C-H, s), 1741 (C=O, s), 1467 (C-H, m), 1237 (C-O, m), 1168 (C-O, s), 1117 (C-O, s); \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \(\delta\) 7.44-7.30 (5H, m, H-40, H-41, H-42), 5.17 (1H, dddd, J 5.1, 5.1, 5.1, 5.1, H-2), 4.77 (1H, s, H-37), 4.35 (1H, dd, J 11.9, 5.1, H-1a), 4.19 (1H, dd, J 11.9, 5.1, H-1b), 4.17 (1H, dd, J 11.9, 5.1, H-3a), 3.96 (1H, dd, J 11.9, 5.1, H-3b), 3.40 (3H, s, H-38), 2.26 (2H, dd, J 7.6, H-5), 2.17 (1H, dd, J 7.6, H-21a), 2.16 (1H, dd, J 7.6, H-21b), 1.62-1.48 (4H, m, H-6, H-22), 1.35-1.17 (48H, m, H-(7-18), H-(23-34)), 0.93-0.82 (6H, m, H-19, H-35); \textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}) \(\delta\) 173.2 (C-20), 172.7 (C-4), 170.2 (C-36), 135.9 (C-39), 128.9 (C-42), 128.7 (C-40), 127.2 (C-41), 82.3 (C-37), 66.8 (C-2), 62.6 (C-1), 61.8 (C-3), 57.4 (C-38), 34.04 (C-21), 34.00 (C-5), 31.9 (C-34), 29.71 (C-18), 29.68, 29.6, 29.51, 29.49, 29.4, 29.3, 29.11, 29.08 (C-(7-16), C-(23-32)), 24.83 (C-22), 24.75 (C-6), 22.7 (C-17, C-33), 14.1 (C-19, C-35); HRMS m/z (ES\textsuperscript{+}) Found 739.5477 [M+Na]\textsuperscript{+} (C\textsubscript{44}H\textsubscript{76}O\textsubscript{7}Na requires 739.5483); m/z (ES\textsuperscript{+}) 739.5 ([M+Na]\textsuperscript{+}, 100%).
Bibliography


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BIBLIOGRAPHY

255–256.


Appendix

Selected Spectra

NMR Spectra (\(^1\)H, \(^{13}\)C and, where applicable, \(^{31}\)P, \(^2\)H, \(^1\)H-\(^{13}\)C HMBC and \(^1\)H-\(^{31}\)P HMBC) are reported for all compounds where the data has not been previously reported. For relevant compounds, HPLC and mass spectrometry data have been included. The compounds appear in the order that they can be found in the Experimental section of this dissertation. Asterisks indicate deuterium atoms attached to the indicated carbon atoms. Crystallographic data for (\(\pm\))-81 and (\(\pm\))-160 can be found on pages 533 and 540 respectively. Permissions for images can be found at the end of the appendix.
$^1$H NMR Data for Table 2.2

Entry 1

Entry 2

Entry 3

Entry 4

Entry 5

Entry 6

Entry 7

Entry 8

Entry 9

Entry 10
$^1$H NMR Data for Table 2.4

Entry 1

Entry 2

Entry 3

Entry 4

Entry 5

Entry 6

Entry 7

Entry 8
$^1$H NMR Data for Table 2.5

Entry 2

Entry 3

Entry 4

Entry 5

Entry 6

Entry 7

Entry 8

Entry 9

Entry 10

Entry 11

Entry 12
Chiral HPLC of ligand (−)-84

AS-363-01_093

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Chiral HPLC of ligand (+)-84

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7/7/2015
Chiral HPLC of (+)-83

EE determination 10:90 Hep:IP

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10.772 | 137 | 0.00
15.882 | 5362155 | 99.49
22.299 | 4283.1 | 0.08
27.949 | 12967 | 0.24
44.933 | 24,802 | 0.00
**Total** | **5389883.3** | **100.00**
H NMR of (+)-108a

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FWMH:  0.12226 Hz
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NS:  78.57
DW:  52.400 usec
DE:  6.50 usec
TE:  2.98-0 K
DI:  1.00000000 sec
TDS:  1

--- CHANNEL 1 ---

F2 - Processing parameters
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DF:  400.11 MHz
WDW:  600.11 MHz
SSB:  0
LB:  0.30 Hz
PC:  1.00
Chiral HPLC of (+)-108a

### EE determination 30:70 IPA : H

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![Graph of EE determination 30:70 IPA : Heptane 220 nm]
Chiral HPLC of (+)-108a (cont.)

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EE determination 30:70 IPA:
CHAPTER 9. APPENDIX

C NMR of (+)-108b
Chiral HPLC of (+)-108b

EE determination 30:70 IPA : H

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9.930 | 209848 | 1.15
18.736 | 121505 | 0.66
20.445 | 17539351 | 95.78
Total | 18311170 | 100.00

![Graph of EE determination 30:70 IPA : Heptane 220 nm Injection 1](image)
H NMR of (+)-175
$^{13}$C NMR of (+)-175
HPLC of (+)-175

AS-341-01

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\[ \text{Troc} \quad \text{OTroc} \]

\[ \text{OTBDPSO} \]

\[ \text{AS-341-01 : Injection 1} \]
Chiral HPLC of (+)-175

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- Batch Group/Name: Alex/EE determination
- Batch Description: ADH column
- Acquisition Date/Time: 7/7/2015 6:17 pm
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Chiral HPLC of (−)-175

AS-394-01

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TrocO

OTBDPS

OTBDPS

O

O

O

O

O

O
H NMR of (+)-115
13C NMR of (+)-115
**1H NMR of (+)-104**

Current Data Parameters

- **NAME**: Ag-144-03-senno
- **EXPNO**: 1
- **PROCNO**: 1

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- **Date**: 20160926
- **Tm**: 13.02
- **INSTM**: av900
- **FREQMOD**: 5 mm QNP 1H/13
- **PULPROG**: zg30
- **TD**: 65536
- **SOLVENT**: CDCl3
- **NS**: 16
- **DS**: 2
- **SNH**: 100.9202 AO00 1256 Hz
- **F1RES**: 0.15200 Hz
- **AQ**: 3.7247999 sec
- **NS**: 248.78
- **DM**: 500.00 usec
- **DE**: 6.50 usec
- **TE**: 293.2 K
- **DI**: 1.00000000 sec
- **TDS**: 1

--------- CHANNEL F1 ---------

**nrfr**: 1.00000000 Hz
**nuc**: 1H
**f1**: 12.22 usec
**flm1**: 11.30000019 N

**F2 - Processing parameters**
- **Sr**: 65536
- **SR**: 400.2000317 Mm
- **mow**: Em
- **ssb**: 0
- **lb**: 0.3 Hz
- **gb**: 0
- **pc**: 1.00

![1H NMR Spectrogram](image-url)
CHAPTER 9. APPENDIX

C NMR of (+)-104

[Chemical structure image]

13C NMR of (+)-104
H NMR of (+)-253

Current Data Parameters
NAME  Ao-256-01
PROCNO  1

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Date   20160314
Tskm   15.30 h
INSTM   av9016
PRGNO   101816
TD     65536
SOLVENT   CDCl3
NS    16
DS     2
SNR    8011.82 C Hz
F1RES   2.449532 Hz
AQ    4.0994e+05
jG    38.47
jW    52.400 usec
DE    6.50 usec
TE    293.9 K
DI     1.00000000 sec
TD1    1
SM1    400.2024012 MHz
NUC1   1H
D1     14.00 usec
PLM1   14.00000000 N

F3 - Processing parameters
G1     12768
SF    400.2000154 MHz
HDM    1
SDB    0
LM     0.30 Hz
GB     0
FC     1.00

1H NMR of (+)-253
CHAPTER 9. APPENDIX

C NMR of (+)-253

TrocO

PMBO

OPMB

O

O

OPMBP

TrocO

OTroc
Chiral HPLC of (+)-253

**AS-603-01**

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![Graph of AS-603-01: Injection 1](image-url)
Chiral HPLC of \((-\)-253

### AS-606-01

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![HPLC Chromatogram](image)

![Chemical Structure](image)
Chiral HPLC of (–)-253 (cont.)

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H NMR of (+)-118

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PROCNO: 1

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PROCNO: Z10818_0816
RFTT: 2048
TD: 65536
SOLVENT: CH2Cl2
NS: 16
NS: 2
GM: 8012.824 Hz
TDRES: 0.244532 Hz
AQ: 4.0384000 sec
RG: 19.75
DM: 42.400 usec
HR: 6.00 usec
TR: 293.8 K
DS: 1.0000000 sec
TDS: 1
SFO: 400.204012 MHz
NUC1: 1H
PI: 14.00 usec
pix1: 14.00000000 W

F2 - Processing parameters
ST: 32768
SF: 400.204012 MHz
SDB: 0
SSB: 0
LS: 0.30 Hz
PC: 1.00
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-118

$^{13}$C NMR of (+)-118

- 206.48
- 206.21
- 171.14
- 171.15
- 153.24
- 153.19
- 127.14
- 94.32
- 77.01
- 75.91
- 71.01
- 54.01
- 53.79
- 53.22
- 52.21
- 52.91
- 37.81
- 37.64
- 37.51
- 37.41
- 21.51
- 28.01
- 27.43
- 27.71
H NMR of (+)-252
**13C NMR of (+)-252**

- 207.18
- 173.14
- 128.17
- 74.79
- 73.74
- 54.31
- 53.83
- 53.54
- 38.35
- 38.04
- 28.51

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**Appendix 9.1. Compound (+)-252**

[Diagram of 13C NMR spectrum for (+)-252]
H NMR of (+)-95

Current Data Parameters
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EXPID  2
PROCNO  1

F2 - Acquisition Parameters
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PROCNO   5 mm FABBO BB/
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SMN    gg12.00 Hz
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TR    298.0 K
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TDS    1

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pl    10.00 usec
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F2 - Processing parameters
SH    65536
SF   400.1310160 MHz
SWIN   EM
SSm   0
LS    0.30 Hz
GB    0
PC    1.00

(CneO)2OPO

\(\text{OBz}\)

---

(CneO)2OPO

\(\text{OBz}\)
13C NMR of (+)-95
CHAPTER 9. APPENDIX

$\text{P NMR of } (+)-\text{ Compound}$
HPLC of (+)-95

**AS-289-01**

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**AS-289-01 : Injection 1**

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<td>25.861</td>
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<td><strong>61280050</strong></td>
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*(CneO)_{2}OP O_{3}O(CneO)_{2}O*
H NMR of (+)-96

Current Data Parameters
NAME: AI-161-96
SPECTR: 1
PROCDB: 1

TI - Acquisition Parameters
Sweep: 10149014
SW1: 15.20
NMRST: 0.004
PDST: 5.0 ms
PW 18.3 kHz
DG0: 0.01 sec
DG1: 1.0000000 sec
PD0: 1

--- CHANNEL 1 ---
SPOL: 400.202414 MHz
SW1: 1 Hz
PHI: 1.2236 Hz
PLMI: 11.30000019 W

TI - Processing Parameters
ST: 65336
SF: 400.200000 MHz
UDW: 2 Hz
USB 0
LB: 0.01 Hz
GC 0
GC 1.01

O
OBz

Obz

OH

(Cno)2PO

OH

(Cno)2PO
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-96

C NMR of (+)-96

![NMR Spectrum Image]

13C NMR of (+)-96
31P NMR of (+)-96

Current Data Parameters
NAME  31P     AD-141-01
SPFBO  1
PRFBO  1

FID - Acquisition Parameters
Sample  70140013
STIM  70140013
INSTRUM  eppos
PRFBO  5 mm FABSD B8
FIDPFG  -90.00
TE  65336
SOLVENT  d8c6-d3
NS  16
SR  4
SWH  64102-56.3 Hz
FIDRES  1.978127 Hz
AQ  0.3111801 sec
BG  107.74
DW  7.801 usec
PF  6.51 usec
TE  29.8 K
G1  2.100000000001 usec
G11  0.130000000001 sec
TD0  1

------- CHANNEL 1 -------
SF01  161.9674941 MHz
BSC1  34
P1  8.01 usec
F1ML  34-100000001 W

------- CHANNEL 2 -------
SF02  406.1316085 MHz
BSC2  18
CPEP[2]  wait=6
CPD2  72.01 usec
F2ML  14.88880005 W
F2ML2  0.2977100 W
F2ML3  0.1288000 W

\[
\text{(CneO)OPO}_2\text{OBz} \quad \text{OH} \\
\text{(CneO)OPO}_2\text{OBz} \\
\]

\[
\text{OBz} \quad \text{OH} \\
\text{OBz} \\
\]

\[
\text{OBz} \quad \text{OH} \\
\text{OBz} \\
\]
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-96

$\text{H}^1$ NMR of (+)-96
HPLC of (+)-96

AS-292-01

Sample Name: AS-292-01
Acquisition Method: Normal Phase Purity
Batch Group/Name: Alex/Normal Phase Purity - Copy 12-10-2014 17-20-36
Sample Description: Normal Phase silica column
Acquisition Date/Time: 12/10/2014 4:25 pm
Batch Description: Normal Phase silica column

AS-292-01: Injection 1

![Graph showing HPLC results for AS-292-01]

Chemical structure of (+)-96:

\[
\begin{align*}
\text{(CneO)_{2}OPO}_{2} & \quad \text{OH} \\
\text{(CneO)_{2}OPO} & \quad \text{OHz} \\
\text{OH} & \quad \text{OBz}
\end{align*}
\]
HPLC of (+)-96 (cont.)

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<th>Area</th>
<th>Area %</th>
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<tbody>
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<td>2805</td>
<td>0.01</td>
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<td>12.267</td>
<td>7594.3</td>
<td>0.02</td>
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<td>13.148</td>
<td>94380</td>
<td>0.21</td>
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<td>13.608</td>
<td>29059</td>
<td>0.07</td>
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<td>14.061</td>
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<td>16.864</td>
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<td><strong>Total</strong></td>
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</table>
CHAPTER 9. APPENDIX

H NMR of (+)-97
C NMR of (+)-97

13C NMR of the compound (+)-97 is shown in the figure. The spectrum displays resonances at various chemical shifts, indicating the presence of multiple functional groups and atomic environments in the molecule. Key peaks at 77.780 ppm, 77.345 ppm, and 77.232 ppm correspond to carbon atoms with distinct environments. The spectrum provides valuable insights into the molecular structure and chemical bonding of the compound.
CHAPTER 9. APPENDIX

H-13C HMBC NMR of (+)-97
P NMR of (+)-97
HPLC of (+)-97

AS-212-01

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<th>AS-212-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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**Diagram:**

![HPLC Graph](image)
H NMR of (+)-267

\[
\begin{align*}
&\text{BzO} \quad \text{OPO} \quad \text{OAc} \\
&\text{OPO}\text{(OCne)}_2 \quad \text{OPO}\text{(OCne)}_2 \\
&\text{15} \quad 14 \quad 13 \quad 12 \quad 11 \quad 10 \quad 9 \quad 8 \quad 7 \quad 6 \quad 5 \quad 4 \quad 3 \quad 2 \quad 1 \quad 0 \quad -1 \quad -2 \\
&\text{ppm}
\end{align*}
\]

\[
\begin{align*}
&\text{1.26} \quad \text{1.28} \\
&2.03 \quad 1.96 \quad 2.00 \quad 2.06 \quad 2.05 \quad 1.99 \quad 2.02 \quad 2.07 \\
&5.16 \quad 5.19
\end{align*}
\]

\[
\begin{align*}
&\text{8.14} \quad 8.13 \quad 7.99 \quad 7.96 \quad 7.60 \quad 7.59 \quad 7.57 \quad 7.56 \\
&7.54 \quad 7.48 \quad 7.46 \quad 7.44 \quad 7.43 \quad 7.10 \quad 5.84 \quad 5.84 \\
&5.83 \quad 5.82 \quad 5.80 \quad 5.55 \quad 5.54 \quad 5.53 \quad 5.52 \quad 5.51 \\
&5.50 \quad 5.49 \quad 5.48 \quad 4.99 \quad 4.98 \quad 4.97 \quad 4.96 \\
&4.95 \quad 4.94 \quad 4.93 \quad 4.92 \quad 4.91 \\
\end{align*}
\]

\[
\begin{align*}
&\text{3.2} \quad 3.2 \quad 3.2 \quad 3.2 \quad 3.2 \quad 3.2 \\
&\text{ppm}
\end{align*}
\]

\[
\begin{align*}
&\text{1H NMR of (+)-267}
\end{align*}
\]

CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-267
C NMR of (+)-267
P NMR of (+)-267

[Diagram of NMR谱图]

-2.72
-3.22
-3.41

-100.00 ppm

-100.23

31p NMR of (+)-267
CHAPTER 9. APPENDIX

H-31P HMB-C NMR of (+)-267

1H-31P HMB-C NMR of (+)-267

9.1. COMPOUND (+)-267

H NMR of (+)-98
CHAPTER 9. APPENDIX

13C NMR of (+)-98
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-98

P NMR of (+)-98

Current Data Parameters
NAME  AE-217-01 18
SWEET  1
PROCNO  1

PRO - Acquisition Parameters
Data  20180701
Time  14:06
INSTRUM  a-4001
PROBHS  5 mm PABBO BR/PS DET0
SOLVENT  CDCl3
NS  16
SE  4
SWH  64102.930 Hz
FBWES  0.798127 Hz
AQ  0.3111000 sec
BG  197.74
SW  7.801 usec
DE  6.81 usec
TE  298.1 K
T1  2.10000000 sec
gg  0.13000000 usec
TDU  1

------- CHANNEL f1 -------
SFO1  161.967444 MHz
B1C1  31P
P1  8.01 usec
PLWD  24.10000000 W

------- CHANNEL f2 -------
SFO2  400.131400 MHz
B1C2  1H
CPEPF1: 0 waittime
CP2R2  76.01 usec
PLMD  14.38800031 W
PLMD2  0.09771000 W
PLMD3  0.1458800 W

31P NMR of (+)-98
$^{1}H$-HMBC NMR of (+)-98
13C NMR of 156
✸✝ ☛✞
✆✝ ✆✷

✡✠ ✟✝
✆✷ ✆✷

❈✔✕✕✖✗✘ ✙✚✘✚ ✛✚✕✚✜✖✘✖✕✢
◆✣✤✥
✣✦✧★✩✪✧✫★ ✙
✥❊✛◆✬
★
✛P✬❈◆✬
★
❋✩ ✧ ✣✭✮✔✯✢✯✘✯✰✗ ✛✚✕✚✜✖✘✖✕✢
✙✚✘✖❉
✩✫★✱✫✳★✱
❚✯✜✖
★✴✵✫✱
■◆✦❚P✹✤
✚✿❀✴✫✫
✛P✬❁❂✙ ✴ ✜✜ ✛✣❚❊■ ★❂❃
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❆❇✩●
❚✙
❍★❏✩
✦✬❄❙✥◆❚
❈✙❈❑✳
◆✦
★✪
✙✦
✩
✦▲❂
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❋■✙P✥✦
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✣❖
✩✵✪✪❍❏✴✳▼ ✢✖✭
✱
P❅
✳✩✴✵❍✫✫ ✔✢✖✭
✙▲
✙✥
✪✵✴✫ ✔✢✖✭
❚✥
✩❏❍✵✫ ◗
✙★
★✵✫✫✫✫✫✫✫✫ ✢✖✭
✙★★
✫✵✫✳✫✫✫✫✫✫ ✢✖✭
❚✙✫
★
❘❘❘❘❘❘❘❘ ❈❂✣◆◆✥❄ ❯★ ❘❘❘❘❘❘❘❘
✦❋✬★
▼✪✵▼✴✫✳✴▼❏ ✤❂❆
◆✹❈★
✩❂
✛★
✩✫✫✵✫✫ ✔✢✖✭
✛❄▲★
★★✵✪✫▼❏❏❏❍✫ ▲
❋✩ ✧ ✛✕✰✭✖✢✢✯✗❇ ❱✚✕✚✜✖✘✖✕✢
✳✩▼✪❍
✦■
✦❋
▼✪✵▼✴✫✫★✩✩ ✤❂❆
▲✙▲
✗✰
✦✦❁
✫
❄❁
✫ ❂❆
❅❁
✫
✛❈
★✵✫✫
✞✝
✆✷

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D
OH

9.1. COMPOUND 156

OH

H NMR of 156

☞✠ ✝✝
✆✞ ✆✞

CHAPTER 9. APPENDIX

2

☞✟ ✸✞ ✸☛
✆✞ ✆✞ ✆✞


Mass spectrum of 156
CHAPTER 9. APPENDIX 9.1. COMPOUND 157

C NMR of 157

[Diagram of a 13C NMR spectrum showing peak assignments]
H NMR of Compound 157

Chemical shifts and coupling constants can be found in the attached table.
Mass spectrum of 157
§ 1. COMPOUND (±)-160

CHAPTER 9. APPENDIX

H NMR of (±)-160

H NMR of (±)-160
CHAPTER 9. APPENDIX 9.1. COMPOUND (±)-160

13C NMR of (±)-160
$T_1$ Times for (+)-81
Peak No. 1 at 170.237 ppm, inavg, [I0] = 7.805e-002, A = 8.247e-001, T = 6.298s (1)
Peak No. 2 at 169.854 ppm, inavg, [I0] = 6.881e-002, A = 8.240e-001, T = 6.374s (2)
Peak No. 3 at 127.034 ppm, inavg, [I0] = 6.170e-002, A = 9.097e-001, T = 4.848s (3)
Peak No. 4 at 77.087 ppm, inavg, [I0] = 8.975e-001, A = 1.034e+000, T = 16.677s (4)
Peak No. 5 at 70.822 ppm, inavg, [I0] = 1.252e-001, A = 9.417e-001, T = 8.585s (5)
Peak No. 6 at 20.841 ppm, inavg, [I0] = 1.515e-001, A = 7.921e-001, T = 3.405s (6)
Peak No. 7 at 20.602 ppm, inavg, [I0] = 1.530e-001, A = 7.999e-001, T = 3.570s (7)
Mass spectrum of (±)-160

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<th>Delta ppm</th>
<th>Theo. Mass</th>
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<tr>
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<td>C_{14}H_{20}O_{8}^{2+}Na</td>
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<td>-1.35</td>
<td>343.12705</td>
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H NMR of 90
CHAPTER 9. APPENDIX

9.1. COMPOUND 90

Mass spectrum of 90

W:\data\Nov 15\ESI54796.raw 23/11/2015 8:46 am

Measured Spectrum

Theoretical Spectrum

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<td>209.09027</td>
</tr>
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</table>
CHAPTER 9. APPENDIX

$\text{H NMR of (±)-165}$
Appendix 9.1: Compound (±)-165

$^{13}$C NMR of (±)-165

---

**Acquisition Parameters**
- Spectrometer: 600 MHz
- Chemical Shift: 15.0 ppm
- Sample: 10 mg/mL
- Solvent: CDCl$_3$

**Processing Parameters**
- Spectra: 128
- Fourier Transform: 2D
- Water suppression: STWAD
- Spin decoupling: NOE

**Spectral Data**
- ppm: 127.1
- Resonance: 2H

---

**Spectrum**

- Peaks at 127.1 ppm
- Additional peaks at various ppm values

---

**Structure**

![Compound Structure](chart.png)
9.1. COMPOUND (+)-165

CHAPTER 9. APPENDIX

2H NMR of (+)-165

Current Data Parameters
NAME  Ali-251-01 S
EXPN0  1
PROCNO  1

F2 - Acquisition Parameters
Date_  20141021
Time  9.40
INSTRUM  avc560
PROBHD  5 mm CPDUL 11C
FREQUENCY  zg2h
TD  4096
SOLVENT  ccc13
MS  148
DS  4
SMN  1535.627 Hz
FIDRES  0.374969 Hz
AQ  1.3336576 sec
RG  1
DM  325.600 usec
RE  18.600 usec
TE  298.6 K
D1  1.00000000 sec
D11  0.03000000 sec
TD0  1

F2 - Processing parameters
SF  8192
F  76.7990981 MHz
MDF  0
LS  1.00 Hz
PB  0
PC  1.00
Mass spectrum of (±)-165
Mass spectrum of (±)-165 (cont.)
**1H NMR of (+)-166**

**Current Data Parameters**
- **NAME:** Ac-267-01
- **EXPNO:** 1
- **PROCNO:** 1

**F1 - Acquisition Parameters**
- **Date:** 20141011
- **T1:** 13.04
- **INSTRUM:** avd400
- **FREQUNIT:** 5 mm GND 1H/13
- **PULPROG:** zg30
- **TD:** 6536
- **SOLVENT:** (CDCl3)
- **DS:** 10
- **SNH:** 10020.0 Hz
- **FREQUENCY:** 0.15258 Hz
- **AQ:** 3.2744999 usec
- **NG:** 50.0000 usec
- **DE:** 6.30 usec
- **TE:** 290-2 K
- **DG:** 1.0000000 usec

**F2 - Processing parameters**
- **St:** 45554
- **SR:** 400.0000115 MHz
- **MHW:** 2 MHz
- **SSB:** 0
- **LB:** 0.30 Hz
- **PC:** 1.00

**Diagram:**
- Compound structure with peaks at specific ppm values.
- Integration data indicated at the bottom of the spectrum.

**Note:** The image provides detailed spectral data and structure representation for compound (+)-166.
C NMR of (+)-166

Current Data Parameters
NAME A5=267-01 13C
PROTON 1
F2 - Acquisition Parameters
Date_ 20141104
Time_ 6:31
SYSTEM ac500
FREQOE 500.1360 Hz
FZPAC 1.32
T2 600.36
SOLVENT CDCl3
NS _ 32
DS _ 2
SNR 31.250000 Hz
RESOLUTION 1.476873 Hz
AQ 1.0465760 sec
RG 912
DM 16.00000 usec
DE 16.000 usec
TE 29.500000 sec
D11 0.0000000 sec
T20 1
------ CHANNEL f1 ------
SP10 125.8131972 MHz
M01 13C
P1 13.00000 usec
F10 20.166200002 MHz
------ CHANNEL f2 ------
SP20 500.3020120 MHz
M02 1H
CPE100 16
PE10 80.000 usec
P1NM 7.8393000 MHz
P1NM 0.2313000 MHz
P2NM 7.4196000 MHz
F2 - Processing parameters
D5 125.8005351 MHz
DEW DM
IAS 0 1.000 Hz
GB 0 1.00
F1 1.40

Troco

OBz

OBz

CHAPTER 9. APPENDIX

9.1. COMPOUND (+)-166
CHAPTER 8

APPENDIX 8.1: COMPOUND (±) 166

H NMR of (+)-166

13.02
86.88

TrocO

OBz

OBz

Current Data Parameters

- Instrument: Proton NMR
- Solvent: DMSO-d_6
- Temperature: 25°C
- Field Strength: 600 MHz

Acquisition Parameters

- Time Lapse: 8.51 s
- Number of Scans: 1024
- Pulse Width: 10.0 µs
- Spin-Lock Time: 1000 ms
- Off-Cycle Delay: 50 ms

Chemical Shifts

- 7.19 ppm
- 5.88 ppm
- 5.19 ppm
- 4.57 ppm
- 2.50 ppm

CH NMR of (+)-166
HPLC of (+)-166

**AS-267-01**

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<td>0.25</td>
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<td>3.648</td>
<td>11992820</td>
<td>92.51</td>
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<td>7.666</td>
<td>267326</td>
<td>2.06</td>
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<tr>
<td>7.729</td>
<td>186701</td>
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<td>9.468</td>
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<td>1.72</td>
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<td>65629</td>
<td>0.51</td>
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<td>10.359</td>
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<td>0.14</td>
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Sample Name: AS-267-01  Sample Description: Normal Phase silica column
Acquisition Method: Normal Phase Purity 0-10  Acquisition Date/Time: 12/8/2014 2:29 pm
Batch Group/Name: Alex/Normal Phase Purity 0-10  Batch Description: Normal Phase silica column

![Graph of AS-267-01 Injection 1]
Chiral HPLC of (+)-166

### AS-262-01

<table>
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<th>Sample Description</th>
<th>ADH column</th>
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<td>Acquisition Date/Time</td>
<td>10/28/2014 5:07 pm</td>
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<td>Batch Description</td>
<td>ADH column</td>
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</table>

#### AS-262-01 : Injection 1

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<tbody>
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<td>95.30</td>
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<td>14.886</td>
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<td>1.85</td>
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<td>17.387</td>
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<td>2.85</td>
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<td>24.777</td>
<td>361.7</td>
<td>0.00</td>
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<td><strong>100.00</strong></td>
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</tbody>
</table>

![Graph of AS-262-01 Injection 1 with Time (min) on the x-axis and Absorbance (mAU) on the y-axis, showing a single peak at around 11.582 min with Area 9931614 and Area % 95.30. The compound structure with OBz and TrocO groups is also shown.](image-url)
Mass spectrum of (+)-166
Mass spectrum of (+)-166 (cont.)
**Current Data Parameters**

**NAME**: AS-268-01 13C

**EXPN0**: 1

**FREQ**: 1

**P2 - Acquisition Parameters**

**Date**: 20141106

**Time**: 10:11

**P2 - Processing parameters**

**SH**: 65536

**FID**: 500.3000123 MHz

**NRM**: 0

**HSM**: 0

**LB**: 0.30 Hz

**GB**: 1.00

**NMR of (+)-167**
C NMR of (+)-167

Current Data Parameters
NAME  Acet/13C
MODE  1
F2 - Acquisition Parameters
DAT  20141106
Time  21:32
INST/INSTR  agl200
PROG/PROG  5 mm CDPUL 13C
PULSER  zpg20
TE  65.36
SOLVENT  CDC13
NS  3072
PS  2
DS  31260.00 Hz
FIDRES  4.036837 Hz
AQ  1.0400000 sec
DG  912
SW  16.00 us
DE  16.00 us
TE  298.0 K
D1  2.0000000000 sec
D2  0.0000000000 sec
TR  1
--------- CHANNEL 1 ----------
FIDU  128  813112 MHz
NOC1  13C
P  20.00 usec
PLM  20.18403022 M
--------- CHANNEL 2 ----------
FIDU  500  3001012 MHz
NOC2  1H
CUPM2  16
FCPS2  48.00 usec
PM2  7.9383009 M
PM3  0.1996003 M
F2 - Processing parameters
S1  32768
SF  125  80003551 MHz
MWM  EM
SNR  0
LB  0
LB  0
PC  1.00
Current Data Parameters
NAME   AI-268-01 D
EXPNO   1
PROCNO   1

F2 - Acquisition Parameters
Date_   20141106
Time_   11:18
INSTRUM_ avance 600
FIELD   5 mm WINDBL 13C
FREQPROG_ zg2b
TD   4096
SOLVENT_ cccc13
NS   123
DM   1535.62 Hz
P1RES   0.374939 Hz
AQ   1.33357 sec
RG   1
DM   325.600 usec
HS   18.60 usec
TR   298.0 K
D1   1.00000000 sec
D11   0.03000000 sec
TD2   1

-------- CHANNEL F1 --------
SPC1   76.999886 MHz
NC1   28
F1   180.00 usec
dw1   3.3069979 W

F2 - Processing parameters
SP   8192
SF   76.9991028 MHz
NWM   3 MHz
DSM   0
LS   0.00 Hz
GB   0
PC   1.00
HPLC of (+)-167

AS-267-01

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<td>10.767</td>
<td>18164</td>
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<td><strong>Total</strong></td>
<td>12963357</td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

12/8/2014 2:29 pm
9.1. COMPOUND (+)-167

CHAPTER 9. APPENDIX

Mass spectrum of (+)-167

Theoretical Spectrum

Scan Number | m/z     | Intensity | Relative  | Segment Number | IsPrecursor |
-------------|---------|-----------|-----------|----------------|-------------|
26 - 35      | 239.11805703611 | 32862229.320239 | 19.0972453955542 | 1 false |
26 - 35      | 240.12718199837 | 4321874.47240507 | 2.47958086733835 | 1 false |
26 - 35      | 361.154310293894 | 1600562.5641531 | 9.1831486763298 | 1 false |
26 - 35      | 378.180907242041 | 7117071.73352948 | 4.08326410556614 | 1 false |
26 - 35      | 382.129910808787 | 7308266.68320661 | 4.1929580224483 | 1 false |
26 - 35      | 383.136055956447 | 6468274.5813294 | 37.1103081441335 | 1 false |
26 - 35      | 384.139469580345 | 13722221.6041774 | 7.87282424890988 | 1 false |
26 - 35      | 453.177693416012 | 11400409.4246325 | 6.5407353382505 | 1 false |
26 - 35      | 741.271191785354 | 3696726.15233826 | 2.1209157039737 | 1 false |
26 - 35      | 742.276784679122 | 3815724.3898286 | 21.8918819379727 | 1 false |
26 - 35      | 743.28244852945 | 17429858.303292 | 100 | 1 false |
26 - 35      | 744.28631777758 | 73753881.1137985 | 42.314674249121 | 1 false |
26 - 35      | 745.289427034589 | 18318051.865446 | 10.509981258761 | 1 false |
26 - 35      | 812.31879229096 | 805641.97733623 | 4.6188795939725 | 1 false |
26 - 35      | 813.324817407215 | 38666710.5014354 | 22.184178687845 | 1 false |
26 - 35      | 814.328402949405 | 17495175.024381 | 10.0374736785957 | 1 false |
26 - 35      | 815.33190999558 | 4789137.06278326 | 2.7466254960894 | 1 false |
26 - 35      | 847.30947290933 | 3886323.11151905 | 2.2969280879065 | 1 false |
26 - 35      | 883.367113370195 | 5370598.91455034 | 3.08126355813764 | 1 false |
H NMR of (+)-168

Current Data Parameters
NAME: A0-270-01
EXPNO: 4
PROCNO: 1

F2 - Acquisition Parameters
Date: 20141126
Time: 17:39
INSTRUM: a02040
PROSHD: 5 mm VARPRO mm/
PULPROG: zg30
TD: 65536
SOLVENT: CDCl3
NS: 16
DS: 2
SNH: 8012.820 Hz
PWHM: 0.122246 Hz
AQ: 4.0394905 sec
NS: 176.87
DM: 52.400 usec
DE: 6.35 usec
TE: 298.0 K
DI: 1.00000000 sec
YSTD 1

-------- CHANNEL F1 --------

NCOL: 400.1120007 mHz
NC: 1H
F1: 10.56 usec
FLIM: 14.58800030 W

F2 - Processing parameters
St: 65536
SR: 400.11300097 mHz
MDW: 4 mHz
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

(CneO)2OP(O)(O)Bz

(CneO)2OP(O)(O)Bz
H NMR (in CDCl₃) of (+)-168
$^{13}$C NMR of (+)-168

Current Data Parameters

**Acquire Parameters**
- **Time:** 14.5 s
- **T1:** 2014115
- **Acquire:** 65565
- **SOLVENT:** CDCl$_3$
- **S:** 912

**Spectrometer Parameters**
- **FIDRES:** 0.476837 Hz
- **A9:** 1.000000000000000 sec
- **S:** 16,384.000000 sec
- **T2:** 19.600000 sec
- **Di:** 2560000000.000000 sec
- **Di:** 0.030000000 sec

---

**Chemical Shifts**

- **$^{13}$C NMR (ppm):**
  - 127.0 ppm
  - 126.5 ppm

---

**1H NMR**

- **Signal Analysis:**
  - Protons at various positions indicated

---

**Additional Information**

- **Formula:** (CneO)$_2$OPO$_2$OBz
- **Substituents:**
  - Oz
  - OH

---

**Structure Diagram**

![Structure Diagram](image)
C NMR (in CD$_2$Cl$_2$) of (+)-168

Current data parameters
NAME: AE27+13.CCH 13C
ENDPG
PRG: 1

F1 - Acquisition parameters

- FO: 126.0137 Hz
- F1: 1.9 GHz
- PW: 0.1448 sec
- RE: 911.114 sec
- DE: 15.0 Hz
- TE: 1.95 sec
- D1: 30.0000 sec

--- CHANNEL F1 ---

--- CHANNEL F2 ---

F1 - Processing parameters

- IF: 126.0137 Hz
- W1: 126.0137 Hz
- MW: 0.1448 sec
- RE: 911.114 sec
- DE: 15.0 Hz
- TE: 1.95 sec
- D1: 30.0000 sec

(CneO)$_2$OPO

(CneO)$_2$OPO
Current Data Parameters
        use=  E2
        E2=  3
        E2E2=  1

        F1 - Acquisition Parameters
        name=  "" 20141106
        Time=  17:37
        ZSTEM=  5 mm
        FREG=  5 mm
        XDMC=  0
        S=  800
        D=  0.50
        T=  298.5 K
        B1=  2.00000000 sec
        B11=  0.00000000 sec

        ---- CHANNEL 1 ----
        SP1=  161.986618 MHz
        MRI=  161.986618 MHz
        F1=  5.00 user
        FWM0=  546.00000000 W
        FWM1=  546.00000000 W
        FWM2=  546.00000000 W
        FWM3=  546.00000000 W

        F1 - Processing Parameters
        B1=  2776
        SF=  161.986618 MHz
        WSM=  69
        ES=  0
        GC=  0
        PC=  1.40
HPLC of (+)-168

AS-270-01

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<tr>
<th>Sample Name</th>
<th>AS-270-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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<td>5735.6</td>
<td>0.03</td>
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<td>19.012</td>
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<td>89.51</td>
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<td>20.653</td>
<td>2185100</td>
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![HPLC graph](chart.jpg)

(CneO)OPO

(CneO)OPO
Mass spectrum of (+)-168

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<th>Delta ppm</th>
<th>Theo. Mass</th>
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<td>-3.22</td>
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**CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-169**

**H NMR of (+)-169**

Current Data Parameters
- NAME: AO-265-01
- EXPNO: 9
- PROCNO: 1

**F2 - Acquisition Parameters**
- Data: 20141214
- Tsk: 17.38
- INSTRUM: av6.000
- RESOLUTION 5 mm VANDO sm/
- POLMAG 30
- SOLVENT: MeOD
- NS: 16
- DI: 2
- SNR: 8012.828 Hz
- DFSAM: 0.222226 Hz
- AQ: 4.084448 s
- AQ: 70.94
- DTH: 52.400 us
- E: 6.50 us
- TE: 298.0 K
- T1: 1.00000000 us
- T2D: 1

**--- CHANNEL F1 ---**
- F1: 400.112000 MHz
- F1: 1H
- F1: 10.00 us
- F1: 14.5880030 W

**F2 - Processing parameters**
- Sr: 625.54
- SN: 400.110000 MHz
- HSN: 10
- SSB: 0
- LB: 0.30 Hz
- FC: 1.00
H NMR (in CD₂Cl₂) of (+)-169

Current Data Parameters
NAME AS-283-01 OH
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141202
Time_ 17.27
INSTRM avg400
FOURS 5 mm QNP 1H/13
PULPROG e=30
TE 0.33 s
SOLVENT MeOD
NS 16
DS 2
SWN 10000.000 Hz
FRES 0.152588 Hz
AQ 3.2707999 sec
NS 200-31
SW 50.000 us
DE 6.25 us
TE 294.3 K
DI 1.0000000 sec
TR 1

--- CHANNEL F1 ---
F1 40.00014 MHz
NUS1 1H
F1 52.73 us
P1M 11.3000013 MHz

F2 - Processing parameters
ST 65536
Sr 40.000000498 MHz
MDR DM
ZMS 0
LH 0.20 Hz
DF 0
PC 1.00
**CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-169**

**13C NMR of (+)-169**

![13C NMR spectra](image)

**Current Data Parameters**
- Sample: 1
- Acquisition Parameters:
  - **F1**: 125.8391 MHz
  - **F1**: 1.05 GHz
  - **F1**: 11.8000 USEC
  - **F1**: 11.6000 USEC
- Processing Parameters:
  - **F1**: 125.8391 MHz
  - **F1**: 1.05 GHz
  - **F1**: 11.8000 USEC
  - **F1**: 11.6000 USEC

**Chemical Structures**

\[
(C\text{neO})_2\text{OP}O_{\ldots}\]

\[
\text{OBz}
\]

\[
\text{OBz}
\]

\[
(C\text{neO})_2\text{OP}O
\]

\[
\text{OBz}
\]

\[
\text{OBz}
\]
CHAPTER 9. APPENDIX

C NMR (in CDCl3) of (+)-169
**CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-169**

2H NMR of (+)-169

The provided NMR spectrum shows the chemical shifts and peak intensities for the compound (+)-169. The spectrum is used to identify and quantify the protons present in the molecule. The peaks at various ppm values correspond to different proton environments, providing detailed structural information. Additional data parameters include acquisition and processing conditions, which are crucial for interpreting the spectrum accurately.

**Current Data Parameters**
- **NAME**: A+287-01
- **EXPNO**: 1
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Date**: 20141117
- **Time**: 12:02
- **INSTRUM**: avw500
- **PROBHD**: 5 mm CPDPD 11C
- **F2FREQ**: 500 MHz
- **F2PROG**: zg2h
- **TD**: 4096
- **SOLVENT**: CDCl3
- **NS**: 664
- **DS**: 4
- **SNH**: 1535.6 GHz
- **FIRFRES**: 0.374959 Hz
- **AQ**: 1.1336574 sec
- **NS**: 1
- **DM**: 325.600 usec
- **DE**: 1.00 usec
- **TE**: 298.0 K
- **DI**: 1.00000000 sec
- **DI1**: 0.01000000 sec
- **TDS**: 1

**F1 - Processing parameters**
- **SNF1**: 76.799480 MHz
- **SNH1**: 28
- **F1**: 180.00 usec
- **PM1**: 3.30369997
- **SI**: 8192
- **NF**: 76.791020 MHz
- **MDN**: EDN
- **SSB**: 0
- **LB**: 1.00 Hz
- **GB**: 0
- **PC**: 1.00

The NMR spectrum is a key tool in organic chemistry for elucidating the molecular structure of compounds, particularly those with complex chemical functionalities like (+)-169.
HPLC of (+)-169

**AS-270-01**

<table>
<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Area %</th>
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<tbody>
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<td>0.00</td>
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<tr>
<td>9.819</td>
<td>5735.6</td>
<td>0.03</td>
</tr>
<tr>
<td>10.716</td>
<td>2902.5</td>
<td>0.01</td>
</tr>
<tr>
<td>16.113</td>
<td>145848</td>
<td>0.64</td>
</tr>
<tr>
<td>19.012</td>
<td>20438033</td>
<td>89.51</td>
</tr>
<tr>
<td>20.653</td>
<td>2185100</td>
<td>9.57</td>
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<td>24.639</td>
<td>16621</td>
<td>0.07</td>
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<td>25.079</td>
<td>9698.8</td>
<td>0.04</td>
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<td>25.644</td>
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<td><strong>100.00</strong></td>
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![Graph of AS-270-01 injection 1](image-url)

**Sample Name**: AS-270-01  
**Acquisition Method**: Normal Phase Purity  
**Batch Group/Name**: Alex/Normal Phase Purity - Copy 12-10-2014 16-24-08  
**Sample Description**: Normal Phase silica column  
**Acquisition Date/Time**: 12/10/2014 2:13 pm  
**Batch Description**: Normal Phase silica column
Mass spectrum of (+)-169
C NMR of (+)-183
H NMR of (+)-189

\[
\text{OBn} \quad \text{BnO} \quad \text{OPO(OBn)}_2 \quad \text{OBn}
\]
13C NMR of (+)-189

Current Data Parameters
NAME  AS-548617_13C_DCM
EXPER  4
PROCNO  1

F1 - Acquisition Parameters
Date  21.11.2018
Time  9.36
INSTRUM  av5000
PROBCH  5 mm CDUL 13C
POLPROG  zpgp350
TD  500000
SOLVENT  CCL4
NS  782
DS  2
SWM  31250.000 Hz
FIDRES  0.478637 Hz
AQ  1.1485760 sec
RG  912
DW  16.000 ussec
SE  15.000 ussec
TE  29.0° K
S1  2.015000000 sec
S11  0.0000000 sec
TE0  1

---------- CHANNEL F1 ----------
SF01  123.1111112 MHz
MC21  13C
FI  10.00 ussec
FW11  20.1400000 W

---------- CHANNEL F2 ----------
SF02  200.3020001 MHz
MC22  18
CF2PR[2]  wait.x16
FIW2  7.9800000 W
FW12  0.21129051 W
FW13  0.1996000 W

F2 - Processing parameters
S1  12768
SF  123.1111112 MHz
GYM  0°
SSB  1.00 Hz
LA  1.00 Hz
GB  1.40

![13C NMR Spectrogram]
31p NMR of (+)-189

$\text{OPO(OBn)}_2$
HPLC of (+)-189

AS-548-01

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<tr>
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<table>
<thead>
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<th>Sample Name</th>
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</thead>
<tbody>
<tr>
<td>Acquisition Method</td>
<td>Normal Phase Purity 254nm</td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-57-28</td>
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</tbody>
</table>

AS-548-01: Injection 1

\[
\begin{align*}
\text{BnO} & \quad \text{OPO(OBn)}_2 \\
(BnO)_2\text{OPO}^+ \quad \text{OBn} \\
\text{OPO(OBn)}_2
\end{align*}
\]
HPLC of (+)-189 (cont.)

<table>
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H NMR of (–)-154
13C NMR of (–)-154
H-31 PMBC NMR of (−)-154
HPLC of (−)-154

AS-553-01

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9.1. COMPOUND (–)-195

CHAPTER 9. APPENDIX
H-13C HMBC NMR of (–)-195
CHAPTER 9
APPENDIX

P NMR of (–)-195
HPLC of (−)-195

AS-577-01

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7/16/2016 5:58 pm
HPLC of (−)-195 (cont.)

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1H NMR of (+)-202
CHAPTER 9. APPENDIX

C NMR of (+)-202
HPLC of (+)-202

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Acquisition Method: Normal Phase Purity 254nm
Acquisition Date/Time: 3/10/2016 6:23 pm
Batch Group/Name: Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-57-28
Batch Description: Normal Phase silica column

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3/16/2016
9.1. COMPOUND (+)-200

CHAPTER 9. APPENDIX

H NMR of (+)-200

Current Data Parameters
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EXPNO    1
PROCNO   1

T2 - Acquisition Parameters
Date     20160224
T1        5.22
INSTRUM   avcc500
PROCRED   5 mm CDUDL 11C
FULLPROG  zg10
TD        65536
SOLVENT   cbr212
NS        16
DS        4
GMN       10136.578 Hz
FIDRES    0.157632 Hz
AQ        3.1719425 sec
RG        2.2
DM        48.400 usec
HE        10.66 usec
TR        298.0 K
DI        1.0000000 sec
TD2       1

--------- CHANNEL F1 ---------
SFO1      500.3030890 MHz
HCC1      15
dt        15.00 usec
plml      7.9800000 W

F2 - Processing parameters
SH        65536
SF        500.3000206 MHz
SNM       EM
SSt       0
LS        0.30 Hz
GB        0
FC        1.00

\[
\text{OAc} \quad \text{OH} \\
\text{BnO} \quad \text{OH} \\
\text{TrocO} \quad \text{OObn} \\
\text{Otroc}\]

1H NMR of (+)-200
13C NMR of (+)-200
CHAPTER 9. APPENDIX

HMBC NMR of (+)-200

Chemical shifts and connectivities are shown in the NMR spectrum. The spectrum is labeled with peaks corresponding to different functional groups and atoms. Notations such as H, C, and other chemical shifts are used to denote specific signals in the spectrum.
HPLC of (+)-200

AS-590-01

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6/4/2016
**H NMR of (+)-201**

Current Data Parameters

NAME: AS-428-11
EXPNO: 1
PROCNO: 1

T2 - Acquisition Parameters

- DATE: 20160329
- TIME: 19.37 h
- INSTRUM: AV8000
- PULSEP: Z106618_5816D
- FIELD: 9.400 T
- TD: 65536
- SOLVENT: cd2c12
- NS: 16
- sweep: 16
- FREQUENCY: 0.244532 Hz
- AQ: 4.054460 sec
- RG: 91.35
- DM: 62.406 usec
- TR: 2941.1 ms
- TE: 1.0000000 sec
- TDS: 1
- SFC: 400.2024012 MHz
- NUC: 1H
- 14.00 usec
- pix: 14.0000000 W

T2 - Processing parameters

- ST: 32768
- SF: 400.2000156 MHz
- BNM: 0
- SSB: 0
- BS 0.30 Hz
- PC: 1.00
C NMR of (+)-201

13C NMR of (+)-201
9.1. COMPOUND (+)-205

H NMR of (+)-205

Current Data Parameters
NAME   AS=539-51_13C_weak
EXPNO  I
PROCNO  1

r2 - Acquisition Parameters
Date  20160303
Time   3:08 h
INSTRUM  split
PROCNO  Z103618_5533 (c)
FIDFREQ  3560
TD       45536
SOLVENT  cm2c12
NS      16
GS      2
SMN   8012.220 Hz
FIDRES  0.2445 Hz
AQ  4-0396840 sec
RG      25.89
DM       62.406 usec
HE      6.53 usec
TR    294.7 K
TI   1.0000000 sec
TDS     1
SFQ1  400.2524013 MHz
NU1    18
FI  19.50 usec
pwml  16.70800076 W

r2 - Processing parameters
St    3276
SF    400-2500157 MHz
NSN    BN
SSN  0
LS  0
Gm  0
PC   1.00
C NMR of (+)-205

Current Data Parameters
NAME Ah09=1L30
EXPER 1
PROCDB 1
T2 - Acquisition Parameters
Data 20345054
T1 10.76
INSTRUM avcc00
PROCDB 2 mm CD2CD 12C
FILLPROG 1 mg CD2CD 12C
SOLVENT CD2C12
H5 88
ES 2
DM 31255.000 Hz
FIFHS 0.476837 Hz
AQ 1.048970 sec
h5 912
DM 16.000 uscc
EE 18.000 uscc
TE 290.0 sec
D1 0.00000000 sec
D13 0.00000000 sec
D15 1
----- CHANNEL 1 ----- 
SF01 125.833152 MHz
NEX1 125
P1 10.00 uscc
PLW1 10.18400002 W
----- CHANNEL 2 -----
SF02 300.1020012 MHz
NEX2 1
CFSPR [2] wait: 16
PCFS2 30.00 uscc
PLW2 7.98835035 W
PLW12 0.28310001 W
PLW13 0.17956000 W
F2 - Processing parameters
S1 32768
SF 125.8003883 MHz
INEC 
SSB 0
LB 1.00 Hz
CB 8
PC 1.40

\[
\text{BnO\AcO\BnO\AcO_{15}H_{31}}
\]

\[
\text{O\BnO\AcO_{15}H_{31}}
\]

\[
\text{O\BnO\AcO_{15}H_{31}}
\]
P NMR of (+)-205

Current Data Parameters
NAME  A15299-11
EXPCD  2
PROCNO  1
F1 - Acquisition Parameters
Data  20160302
Time  18.28 h
INSTRUM  av600
PROBENM  2113305_205
FULPROC  Topsp30
TD  65500
SOLVENT  CDCl3
NS  128
SS  4
DMN  40760.871 Hz
FIFRES  1.241923 Hz
AQ  0.83190783 sec
DG  131.37
DM  12.267 usec
DE  4.30 usec
TE  298.15 K
E1  2.00000000 sec
E11  0.10000000 sec
T1AS  2044421214 MHz
MXC1  31P
FLW1  38.20000076 W
FLO2  500.1320005 MHz
MCUS  15
NPSPROD2  9819 MHz
F1 - Processing Parameters
NF  32768
SF  204.25600000 MHz
WPM  0
NNB  0
LB  0
GB  1.00 Hz
PC  1.40

BnO
HO
Ac
OBn
OBn
OCOC15H31
OCOC15H31

HO

9.1. COMPOUND (+)-205

CHAPTER 9. APPENDIX
$^{1}H$-31P HMBC NMR of (+)-205
HPLC of (+)-205

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3/16/2016
H NMR of (+)-210
CHAPTER 9. APPENDIX

13C NMR of (+)-210
Appendix 9.1: Compound (+)-210

H NMR of (+)-210
H NMR of (+)-211

Current Data Parameters
NAME       AS-440-01-AVC500
EXPNO      1
PROCNO     1

F2 - Acquisition Parameters
Date       20160413
Time       21:50
INSTRUM     avc565
PROCBD     5 mm CFDUL 11C
FULFDG      zg10
TD          65536
SOLVENT    ch2cl2
NS          16
DS          4
SMN         40110.578 Hz
FRQRES      0.157632 Hz
AQ          3.1719025 sec
RG          3.56
DM          48.460 ussec
HE          10.60 ussec
TR          298.0 K
Di          1.0000000 sec
TDS         1

-------- CHANNEL F1 --------
FREQ       500.3030896 MHz
HOC1       1H
Di          15.00 ussec
PLINE      7.9880000 W

F2 - Processing parameters
SF          65536
SF          500.3000206 MHz
DFO        EM
SSm         0
LB          0.30 Hz
GB          0
PC          1.00
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-211

$^{13}$C NMR of (+)-211

![Carbon-13 NMR spectrum of (+)-211](image)
H-13C HMBC NMR of (+)-211

BnO

O

OTHP

OBn

TrocO

O

OBn

Troc
HPLC of (+)-211

AS-643-01

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H NMR of (+)-212

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PROCNO  1

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Time    21:50
INSTRUM Avance
PROCWD  5 mm CF30UL 13C
FQFWD   zg30
TD      65536
SOLVENT cb2c12
NS      16
SF      4
FIDRES  1.015378 Hz
AQ      0.177632 Hz
RG      3.56
DM      40.400 ussec
HE      10.66 ussec
TR      298.0 K
D1      1.000000 ussec
TDS     1

CHANNEL 1

F2 - Processing parameters
SF      65536
SF      500.00206 MHz
NBW    33.33 EM
SSM    0
LB     0.30 Hz
GB     0
PC     1.00
13C NMR of (+)-212

CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-212
**H NMR of (+)-214**

Current Data Parameters

NAME: AO-180-02
EXPNO: 1
PROCNO: 1

**F2 - Acquisition Parameters**

Date: 20100819
Time: 12:13
INSTRM: apo-400
PROBID: 5 mm FABBO mm/
PULPROG: zg60
TD: 65536
SOLVENT: CD2Cl2
NS: 8
DS: 2
SNR: 10060.000 Hz
FIFRES: 0.125588 Hz
AQ: 3.747999 sec
NS: 64
DW: 50.000 ussec
DS: 6.30 ussec
TE: 290.3 K
DI: 1.00000000 sec
TDS: 1

**---------------- CHANNEL F1 ----------------**

FREQ: 400.204714 MHz
NUC1: 1H
F1: 14.00 ussec
FLM1: 14.00000000 N

**F2 - Processing parameters**

S1: 65536
SF: 400.2000356 MHz
MNW: 8M
SISB: 8
LB: 0.30 Hz
GC: 1.00

**---------------- CHANNEL F2 ----------------**

**---------------- CHANNEL F3 ----------------**

PMBO

OPMB

BnO

OBn
CHAPTER 9. APPENDIX

C NMR of (+)-214

\[ \text{PMBO - OPMB} \]

\[ \text{BnO - OH} \]
HPLC of (+)-214

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PMBO

OPMB

BnO

OBn

427
**H NMR of (–)-217**

**Current Data Parameters**

**NAME**  AS-493-01_500
**EXPNO** 1
**PROCNO** 1

**F1 - Acquisition Parameters**

- **Date:** 20160616
- **Time:** 10:32
- **INSTRUM:** avance
- **FIELD:** 14.10 T
- **SOLVENT:** DMSO-d$_6$
- **NS:** 1
- **DS:** 8
- **DR:** 4000 Hz
- **T1:** 15.00 sec
- **TR:** 298.0 K
- **TD:** 1.00000000 sec

**F2 - Processing parameters**

- **SH:** 65536
- **SF:** 500.338025 MHz
- **CH:** 8
- **LS:** 0
- **LB:** 0.10 Hz
- **PC:** 1.00

**Diagram:**

A proton NMR spectrum showing peaks at various ppm values.
CHAPTER 9. APPENDIX 9.1. COMPOUND (–)-217
CHAPTER 9. APPENDIX

1H-13C HMBE NMR of \((-\text{-})-217\)
HPLC of (−)-217

AS-693-01

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-693-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
</tr>
</thead>
<tbody>
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<td>Acquisition Method</td>
<td>Normal Phase Purity 254nm 2-10</td>
<td>Acquisition Date/Time</td>
<td>6/28/2016 6:00 pm</td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase Purity 254nm 2-10</td>
<td>Batch Description</td>
<td>Normal Phase silica column</td>
</tr>
</tbody>
</table>

**AS-693-01 : Injection 1**

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<th>Area %</th>
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<tr>
<td>2.277</td>
<td>3326.1</td>
<td>0.37</td>
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<tr>
<td>2.406</td>
<td>537.69</td>
<td>0.06</td>
</tr>
<tr>
<td>2.743</td>
<td>885822</td>
<td>98.47</td>
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<tr>
<td>8.924</td>
<td>7058.3</td>
<td>0.78</td>
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<tr>
<td>20.627</td>
<td>332.17</td>
<td>0.04</td>
</tr>
<tr>
<td>21.521</td>
<td>212.59</td>
<td>0.02</td>
</tr>
<tr>
<td>22.690</td>
<td>62.744</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>899576.9</strong></td>
<td><strong>100.00</strong></td>
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</table>

6/28/2016
H NMR of (−)-213
C NMR of (–)-213

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn

Current Data Parameters
NAME: 213

$1^3$C NMR of (–)-213

pmr30

PMBO

OBn

OBn

OBn

OBn
$^{1}H$-$^{13}C$ HMBE NMR of (−)-213
HPLC of \((-\)-213

**AS-694-01**

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<thead>
<tr>
<th>Sample Name</th>
<th>AS-694-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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</table>

**Time** | **Area** | **Area %**
--- | --- | ---
3.143 | 245477 | 100.00
Total | 245477 | 100.00

![HPLC graph]

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{PMBO} & \quad \text{OPMB}
\end{align*}
\]
H NMR of (+)-270
31P NMR of (+)-270
$\text{H}^1$-31p HMBC NMR of (+)-270
HPLC of (+)-270

**AS-699-02**

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<tbody>
<tr>
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<tr>
<td>Batch Group/Name</td>
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<td>Sample Description</td>
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<tr>
<td>Acquisition Date/Time</td>
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<table>
<thead>
<tr>
<th>Time</th>
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<th>Area %</th>
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<tbody>
<tr>
<td>8.989</td>
<td>915.33</td>
<td>0.16</td>
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<tr>
<td>9.371</td>
<td>127337</td>
<td>21.68</td>
</tr>
<tr>
<td>9.523</td>
<td>459129</td>
<td>78.17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>587381.19</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

![HPLC chromatogram for AS-699-02]

**Molecular Structure**

\[
\text{OBnO}\quad \text{Phosphate ester} \quad \text{OCOC}_{15}H_{31}
\]

\[
\text{BnO} \quad \text{OBn} \quad \text{OCOC}_{15}H_{31}
\]

\[
\text{HO} \quad \text{OH} \quad \text{OBn}
\]

6/28/2016
1H-31P HMBC NMR of (+)-219
HPLC of (+)-219

AS-716-01

<table>
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<th>Sample Name</th>
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**Time | Area | Area %**
---|-----|------|
3.504 | 6061.8 | 0.22 |
4.877 | 1183.3 | 0.04 |
6.819 | 8189 | 0.30 |
7.162 | 1973.9 | 0.07 |
8.104 | 1195373 | 43.52 |
8.628 | 1518669 | 55.29 |
10.279 | 7353.6 | 0.27 |
11.369 | 5115.5 | 0.19 |
12.767 | 2645.6 | 0.10 |
**Total** | **2746564.4** | **100.00** |

![Graph](image)

445
Current Data Parameters
NAME   A5-723-01
EXPNO   1
PROCNO  1

T2 - Acquisition Parameters
Date_  20160709
Time   12:55 h
INSTRUM avx500
PROBID 2113652_0208
PULPROG zg900
TD     65336
SOLVENT MeOD
NS     17
SG     2
SMN    10000.000 Hz
FDRES  0.305176 Hz
AQ     1.2767999 sec
RN     105-13
DM     50.000 usec
SE     4.50 usec
TE     294.0 sec
SI     1.00000000 sec
TD0    1
SP01   500.1327007 MHz
MIQ1   1H
PI1    15.00 usec
PIw1   20.50000000 w

T2 - Processing parameters
SI     65336
SF     500.1300000 MHz
NEW    10
SUS    0
LS     0.30 Hz
Gb     0
PC     1.00
### Compound 13

**31P NMR of 13**

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</tr>
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<td>NMR</td>
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<td>F2 - Acquisition Parameters</td>
<td></td>
</tr>
<tr>
<td>Time</td>
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<td>FIDRES</td>
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<td>TR</td>
<td>150 s</td>
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<tr>
<td>T1</td>
<td>150 s</td>
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<td>SOLVENT</td>
<td>MeOD</td>
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<td>FIDRES</td>
<td>1.24392 Hz</td>
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<td>0.0030083 sec</td>
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<tr>
<td>D11</td>
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<td>TD</td>
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<td>CH</td>
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<tr>
<td>FC</td>
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**Diagram**

[Diagram of Compound 13]
$^{1}H$-31P NMR of 13
CHAPTER 9. APPENDIX 9.1. COMPOUND 10

H NMR of 10

Current Data Parameters
NAME   Ad-724-01_Filtredux
EXPNRO 1
PROCNO 1

F2 - Acquisition Parameters
Date    20160725
Time    12:05 h
INSTRUM Av6000
FREQMOD 2116098.0219
PULPROG zg10pr
TM      81536
SOLVENT D2O
DS      32
DSM 2
SNH    8012.820 Hz
FIDRES 0.24532 Hz
AQ     4.0894465 sec
PG     197.74
TM     62.400 usec
DS     6.50 usec
TE     293.0 K
D1     1.000000000 sec
D12    0.000000000 sec
PG     15.00 usec
T1   1
T01    406.1318818 mHz
MDC1   1H
F1     15.00 usec
TLP1   14.58800030 N
TLP2   0.000000000 N

F2 - Processing parameters
DS     65536
SP     400.1300000 mHz
MDW    EM
SSB    0
LB     0.30 Hz
GB     0
FC     1.00

\[
\begin{align*}
\text{HO} & \quad \text{O} \quad \text{P} \quad \text{Na} \\
\text{COC}_{15} \text{H}_{31} & \quad \text{OCOC}_{15} \text{H}_{31}
\end{align*}
\]
CHAPTER 9. APPENDIX

P NMR of 10
$^{1}H$-HMBC NMR of 10

**Π** ✁ **✸  ✄ **✂  ✹ ✻  ✁ ✒ ✄ ♣ ♣ ✆ ✗ ✙ ✚ ✛ ✜ ✢ ✡ ✟ ✞ ✟ ✣ ✎ ✤ ☚ ◆ ✤ ✙ ✖ ✘ ✙ ✖ ✘ ✖ ✙ ✗ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ ✖ ✙ ✘ ✘ ✘ THE 9° COMPOUND 10 APPEENDIX 9.1. COMPOUND 100 1H-HMBC NMR of 10
CHAPTER 9. APPENDIX

H NMR of (+)-269

Current Data Parameters
NAME      AS-429-01_500
EXPNO     1
PROCNO    1

F2 - Acquisition Parameters
Date_    20100530
Time_     12:02
INSTRNM   avx500
PROC1BD   5 mm CPDUL 11C
PULPROG   zg30
TD        65536
SOLVENT   cb2c12
NS        16
GS        4
SMN      10,136,578 Hz
FIDRES    0.177632 Hz
AQ        3.1719425 sec
RG        2.8
DM       49.400 usec
HE       10.60 usec
TR        298.0 K
DT        1.0000000 sec
TDS       1

--------- CHANNEL F1 ---------
SF01      500.3030886 MHz
HHC1     1h
d1       15.00 usec
pu1      7,993,00000 W

F2 - Processing Parameters
SH        65536
SF        500.300026 MHz
NCHN      ED
SSm       0
LS        0.30 Hz
GB        0
FC        1.00
C NMR of (+)-269

Current Data Parameters
NAME  AN-129-0L-250
FREQ  4
PROCH  1
F2 - Acquisition Parameters
Date: 21105630
Time: 13:04
FOURIER: 2910206006
FREQM: 5 mm CFSUL 13C
POLPOL: 2
TE 65536
SW/MW  CH2/2
D M 1124
DE 2
SMH 31225.00 Hz
FIDRES: 0.476337 Hz
AQ 1.480516 sec
PG 912
SW 16.100 usec
DE 18.00 usec
TE 294.0 K
D1 10.000000 sec
D11 10.000000 sec
D20 1

----- CHANNEL F1 ------
SFO1 125.413172 MHz
MODI 13C
F1 10.00 usec
POL1 20.14400102 W

----- CHANNEL F2 ------
SFO2 250.9000112 MHz
MODC 1H
CPMG/2 1/16
FCPC2 80.00 usec
PWM1 7.9930308 W
PWM2 0.23119101 W
PWM3 0.17960100 W

F2 - Processing parameters
SI 320
SH 125.413172 MHz
SD 0
LB 0
SB 0
PC 1.40
H NMR of (+)-269
HPLC of (+)-269

**AS-429-01**

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-429-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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<tbody>
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<td>Acquisition Method</td>
<td>Normal Phase Purity</td>
<td>Acquisition Date/Time</td>
<td>7/7/2015 1:32 pm</td>
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<tr>
<td></td>
<td>254nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Purity 254nm - Copy 07-07-2015 15-09-58</td>
<td>Batch Description</td>
<td>Normal Phase silica column</td>
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</tbody>
</table>

![Graph of AS-429-01: Injection 1](image)

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<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Area %</th>
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</thead>
<tbody>
<tr>
<td>2.398</td>
<td>9848506</td>
<td>99.25</td>
</tr>
<tr>
<td>2.994</td>
<td>59588</td>
<td>0.60</td>
</tr>
<tr>
<td>25.470</td>
<td>6194</td>
<td>0.06</td>
</tr>
<tr>
<td>26.235</td>
<td>8635.8</td>
<td>0.09</td>
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<tr>
<td>Total</td>
<td>9922924</td>
<td>100.00</td>
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**Chemical Structures**

[Chemical structure diagram]
HPLC of (+)-269

AS-429-01

<table>
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<tr>
<th>Time</th>
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<th>Area %</th>
</tr>
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<tr>
<td>4.578</td>
<td>441006</td>
<td>0.32</td>
</tr>
<tr>
<td>4.928</td>
<td>643063</td>
<td>0.47</td>
</tr>
<tr>
<td>7.214</td>
<td>509.04</td>
<td>0.00</td>
</tr>
<tr>
<td>9.361</td>
<td>235347</td>
<td>0.17</td>
</tr>
<tr>
<td>11.156</td>
<td>132143151</td>
<td>97.04</td>
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<tr>
<td>18.630</td>
<td>2712400</td>
<td>1.99</td>
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<tr>
<td>Total</td>
<td>136175476</td>
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AS-429-01: Injection 1
C NMR of (+)-221
H NMR of (+)-221

Current Data Parameters
NAME: Ac713-01_r
EXPNC: 1
PROCNC: 1

F2 - Acquisition Parameters
Date: 20160623
T1: 9.01
INSTRM: HE500
PROBID: 5 mm DEPT 13C
PULPROG: zg2h
TD: 4096
SOLVENT: CDCl3
DS: 4
SNH: 0.00000 Hz
RES: 0.00000 Hz
AQ: 1.333657 s
MS: 1
DM: 1.000000 usec
DE: 0.000000 usec
TE: 0.000000 K
D1: 1.0000000 usec
D2: 0.000000 usec
TDS: 1

-------- CHANNEL F1 --------
SF01: 76.790480 MHz
NC1: 28
F1: 180.00 usec
PLM1: 3.3039997 N

F2 - Processing parameters
SH: 8192
SF: 76.790936 MHz
MDM: 4
SSB: 0
LB: 0
GB: 0
PC: 1.00

\[
\text{BnO} \quad \text{TrocO} \\
\text{OTroc} \quad \text{OBn}
\]
1H NMR of (+)-222

**Current Data Parameters**
- **NAME**: Al-713-21
- **EXPNO**: 1
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Date**: 2016-04-27
- **Time**: 18:59
- **INSTRUM**: avc-500
- **PROBID**: 5 mm CPDFL 13C
- **POLEPOD**: 900
- **SS**: 65336
- **SOLVENT**: C6D12
- **DS**: 4
- **SM**: 10330.578 Hz
- **FIDRES**: 0.157632 Hz
- **AQ**: 3.171425 sec
- **PS**: 3.56
- **DN**: 48,400 usec
- **DE**: 16.00 usec
- **TE**: 238.0 µsec
- **DI**: 1.000000000 sec
- **ISO**: 1

**F2 - Processing parameters**
- **SF**: 65336
- **SP**: 500.300020 MHz
- **MD**: DM
- **SSB**: 0
- **TS**: 0.30 Hz
- **SC**: 1.00

**Chemical Shifts**:
- 7.40 ppm
- 7.35 ppm
- 7.30 ppm

**Resonances**:
- 4.75 ppm
- 4.70 ppm
- 4.65 ppm

**Structural Formula**:

\[
\begin{align*}
\text{HO} & \quad \text{BnO} \\
\text{OH} & \quad \text{OBn}
\end{align*}
\]
$^{13}C$ NMR of (+)-222
Chapter 9. Appendix

$^2$H NMR of (+)-222

Current Data Parameters
NAME     AM-705-01-D
EXPNO    1
PROCNO   1

F2 - Acquisition Parameters
Date: 20160629
Time: 11:33
Frequency: cm-500
PROBD 5 mm DEUTEROL 13C
T1 4.96 sec
T2 5000 Hz
SOLVENT Toluene
MS 65
DS 4
SW 1535.627 Hz
FIDRES 0.37409 Hz
AQ 1.333657 sec
NS 128
DN 325.00 usec
SE 16.00 usec
TE 298.0 K
SI 1.0000000000 sec
DIV 6.0000000000 sec
TDO 1

--------------- CHANNEL F1 ---------------
SFO1 76.799600 MHz
DC1 0 Hz
F1 180.00 usec
FAW 3.99393939 MHz

F2 - Processing parameters
SI 0.192
SF 76.7999950 MHz
NEW DM
SNM 0
TS 1.00 Hz
GR 0
VC 1.00
HPLC of (+)-222

AS-715-01

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-715-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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<tbody>
<tr>
<td>Acquisition Method</td>
<td>Normal Phase Purity 254nm 2-10</td>
<td>Acquisition Date/Time</td>
<td>6/28/2016 7:44 pm</td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase Purity 254nm 2-10</td>
<td>Batch Description</td>
<td>Normal Phase silica column</td>
</tr>
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</table>

**Time** | **Area** | **Area %**
---|---|---
3.911 | 9043115 | 91.81
6.416 | 822.32 | 0.01
7.531 | 6136.9 | 0.06
7.927 | 621208 | 6.31
8.684 | 4617 | 0.05
9.162 | 56119 | 0.57
9.347 | 117810 | 1.20
20.256 | 239.17 | 0.00
**Total** | **9850068** | **100.00**
Mass spectrum of (+)-222

S:\data\June 16\ESI57886.raw  27/06/2016  9:45 am

<table>
<thead>
<tr>
<th>m/z</th>
<th>Formula</th>
<th>RDB</th>
<th>Delta ppm</th>
<th>Theo. Mass</th>
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<tbody>
<tr>
<td>355.17831</td>
<td>C_{20}H_{16}O_{4}Na</td>
<td>9.5</td>
<td>-1.06</td>
<td>355.17869</td>
</tr>
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</table>
\[ \text{H NMR of (+)-223} \]
H NMR of (+)-223

Current Data Parameters
NAME   AR-720-01_D
EXPNO  1
PROCNO 1

F2 - Acquisition Parameters
Date    20160705
Time    9:39
INSTRUM  avc500
POWERS  5 mm CPMG 13C
POLNMSG  x20h
TE     5096
SOLVENT CDCl3
NS   256
DS   4
SNR    1535.627 Hz
FIDRES   0.374909 Hz
AQ    1.3336576 sec
RG     1
SN    325.600 usec
SE    18.00 usec
TE   234.0 Hz
DI    1.00000000 sec
D11  0.00000000 sec
TSD   1

---------- CHANNEL F1 ----------
SFO1    76.79968000 MHz
SFO1    2H
F1    180.00 usec
PNM1  3.30369997 W

F2 - Processing parameters
e1    8192
e2  15.9677 MHz
RM   20 MHz
SSB   0
LB    1.00 Hz
GB    0
PC    1.00

9.1. COMPOUND (+)-223
HPLC of (+)-223

### AS-720-01

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-720-01</th>
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<th>Normal Phase silica column</th>
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<tbody>
<tr>
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<td>Batch Group/Name</td>
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<td>Batch Description</td>
<td>Normal Phase silica column</td>
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**AS-720-01 : Injection 1**

<table>
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<th>Time</th>
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<th>Area %</th>
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<tbody>
<tr>
<td>0.017</td>
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<tr>
<td>2.306</td>
<td>5705097</td>
<td>99.60</td>
</tr>
<tr>
<td>4.083</td>
<td>22682</td>
<td>0.40</td>
</tr>
<tr>
<td>Total</td>
<td>5727842.458</td>
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</tr>
</tbody>
</table>

**Chemical Structure:**

- PMBO
- OPMB
- BnO
- OBn
Mass spectrum of (+)-223

W:\data\July 16\ESI57974.raw 04/07/2016 8:56 am

595.29340    C₆H₁₂²⁺Na²⁺   17.5    -0.55    595.29372
H NMR of (–)-224
C NMR of (–)-224

Current Data Parameters
NAME: A5-722-01
SPIN: 2
PROC: 1

F2 - Acquisition Parameters
Date: 2016-07-25
Time: 9:30 h
INSTRUM: avx500
RESOL: z13892_0201
POLP: 2
SOLVENT: CD2Cl2
NI: 256
NS: 4
SMH: 12961.904 Hz
FIDRES: 0.992461 Hz
AQ: 1.1010068 sec
BG: 191.39
SN: 16.890 ussec
DE: 4.50 ussec
TE: 156.0 sec
DI: 10.00000000 sec
DI1: 0.83000000 sec
TISO: 1
srl: 125.7703643 MHz
NOC: 13c
P1: 15.00 ussec
FPL1: 76.00000000 MHz
SFO2: 50.31320005 MHz
NOC2: 1H
CP55: \[\text{wali.146} \]
FCDP2: 65.00 ussec
PIM1: 20.00000000 MHz
PIM2: 0.32031000 MHz
PIM1: 0.16111000 MHz

F2 - Processing parameters
SI: 32768
SF: 125.7577885 MHz
MOM: 0
ssm: 0
sm: 0
L: 1.00 Hz
m: 0
PC: 1.00
H NMR of (–)-224

![H NMR spectrum of (–)-224](image)
HPLC of (−)-224

**AS-722-01**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Area</th>
<th>Area %</th>
</tr>
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<tbody>
<tr>
<td>3.447</td>
<td>72579</td>
<td>0.63</td>
</tr>
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<td>5.629</td>
<td>63871</td>
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<td>7.485</td>
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<td>7.779</td>
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<td>9.436</td>
<td>19074</td>
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![Graph](image)
Mass spectrum of (–)-224

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<td>16.5</td>
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</table>
CHAPTER 9
APPENDIX 9.1
COMPOUND (–)-226

H NMR of (–)-226
C NMR of (–)-226
2H NMR of (–)-226

Current Data Parameters
NAME  AN-728-01_d
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Data_  20160719
Time  11:10
INSTRUM  avci500
FD/DM  5 cm Cpeul 13C
POLAROG  1g8n
TE  1.696
SOLVENT  CDCl3
NS  137
DS  2
SNR  1535.627 Hz
FIDsRES  0.374909 Hz
AQ  1.333676 sec
BD  1
SN  325.600 usec
DE  18.00 usec
TE  294.0 µsec
DI  1.00000000 sec
D11  0.83000000 sec
DSO  1

--------- CHANNEL f1 ---------
SFO1  76.799400 MHz
NOC1  6H
F1  183.00 usec
FLM1  3.30369977 N

F2 - Processing parameters
SF  8192
SF  76.7993961 MHz
MOD  6M
SBB  0
LB  1.00 Hz
GB  0
FC  1.40
HPLC of (−)-226

**AS-728-01**

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<td>89.76</td>
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<td>3.111</td>
<td>343076</td>
<td>6.83</td>
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<tr>
<td>3.513</td>
<td>171065</td>
<td>3.41</td>
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<td><strong>5019901</strong></td>
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![HPLC Graph](image-url)
Mass spectrum of (–)-226

W:\data\July 16\ESI58192.raw 18/07/2016 8:09 am

Measured Spectrum

Theoretical Spectrum

<table>
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<th>Theo. Mass</th>
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<td>802.39662</td>
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<tr>
<td>805.40943</td>
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<td>806.41223</td>
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<td>809.37666</td>
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<td>810.87624</td>
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<td>806.41373</td>
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<td>807.41709</td>
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N.L.: 5.95E7
ESI58192 #12.27  RT: 0.15-0.3 AV: 8 N.L.: 5.95E-007
T: FTMS (1,1) + p ESI Full ms
[800.00-1600.00]
C NMR of (–)-227
2H NMR of (−)-227

Current Data Parameters
SAMPLE: AH-72C-1LD
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 2016-07-19
Time: 11:27
Instruments: av600
PFGSBD: 5 mm CPDUL 13C
PFGSBO: 400 MHz
ID: 10000
SOLVENT: CDCl3
NS: 178
SS: 0
SW: 1535.627 Hz
FIDRES: 0.375909 Hz
AQ: 1.3336756 sec
NS: 1
DN: 325.000 usec
EX: 18.00 usec
TE: 298.0 K
SI: 1.0000000 usec
DI: 1.0000000 sec
ID0: 1

--------- CHANNEL F1 --------
SPOL: 96.7991600 MHz
NC1: 2H
P1: 185.000 usec
P1wl: 3.30369997 MHz

F2 - Processing parameters
SI: 8192
SF: 96.7990961 MHz
SEM: 0
TS: 1.00 Hz
GR: 0
FC: 1.40
HPLC of (−)-227

AS-730-01

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<td>2.511</td>
<td>58821</td>
<td>0.62</td>
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<tr>
<td>2.897</td>
<td>161445</td>
<td>1.71</td>
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<td>3.038</td>
<td>8835537</td>
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<td>3.769</td>
<td>159026</td>
<td>1.69</td>
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<td>5.844</td>
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7/29/2016
Mass spectrum of (−)-227

W:\data\July 16\ESI58204.raw 20/07/2016 8:26 am

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NL: 7.37E6
ESI58204 #12-27 RT: 0.14-0.3 AV: 8 NL: 1.06E-6
T: FTMS [1,1] + p ESI Full lock ms [80.00-1600.00]
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-228

1H NMR of (+)-228

**Figure Description:**
- The figure shows a 1H NMR spectrum for compound (+)-228.
- The spectrum displays peaks at various ppm values, indicating the chemical shifts of different protons in the molecule.
- The spectrum is divided into sections showing different proton environments, with typical assignments for each peak.

**Chemical Structures:**
- The structure of compound (+)-228 is depicted with key functional groups and substituents.
- The structure includes benzyl (Bn), hydroxyl (OH), and ester (COOC) groups.

**Additional Information:**
- The NMR spectrum is labeled with specific chemical shifts, resonance frequencies, and relative intensities.
- The spectrum is used to identify and characterize the compound's proton environment, which is crucial for structural analysis and functional group assignment.

**Analysis:**
- The NMR data provides insights into the molecular structure, helping to confirm the identity of (+)-228 and understand its chemical properties.
C NMR of (+)-228
P NMR of (+)-228
HPLC of (+)-228

**AS-736-01**

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<table>
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<td>4.158</td>
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<td>5.842</td>
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![HPLC Graph](image_url)
Mass spectrum of (+)-228

<table>
<thead>
<tr>
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<tr>
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H NMR of (–)-229

1H NMR of (–)-229
H NMR of (–)-229
CHAPTER 9. APPENDIX

P NMR of (–)-229
HPLC of (–)-229

AS-740-01

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<td>5.949</td>
<td>5052</td>
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<td>7.292</td>
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<td>7.860</td>
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8/5/2016
# Mass spectrum of (–)-229

 Mass spectrum of (–)-229

![Mass spectrum of (–)-229](image)

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H NMR of (+)-233

Current Data Parameters
NAME    AG-142-61_overview
EXPAR   1
PROCNO  1

F2 - Acquisition Parameters
Data_   20150331
T1M     4.22
INSTRM   avc500
PROSHD  5 mm CPMG 13C
PULPROG 90
TD      65536
SOLVENT CD2Cl2
NS      16
DS      4
SNH     10136.578 Hz
PFRMRE  0.157632 Hz
AQ      3.1719425 nsec
AS      3.26
DM      48.400 nsec
DE      10.60 nsec
TE      298.0 K
DI      1.00000000 nsec
TDO     1

--------- CHANNEL F1 ---------
SFO1    500.3000000 MHz
NUCL    1H
F1      15.00 nsec
PLM1    7.99830000 N

F2 - Processing parameters
St      63596
SF      500.3000000 MHz
MDM     0
SSB     0
LB      0.30 Hz
BC      1.00
CHAPTER 9. APPENDIX

C NMR of (+)-233

[Image of a chemical structure and NMR spectrum]
HPLC of (+)-233

AS-342-01

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<td>43981</td>
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<td>6.409</td>
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4/17/2015
9.1. COMPOUND (+)-234

CHAPTER 9. APPENDIX

H NMR of (+)-234

Current Data Parameters
NAME  AS-348-01_DCM
EXPN0  1
PROCNO  1

F2 - Acquisition Parameters
Data_  20100331
Time_  0.52
INSTRM_ CPG500
PROC500  5 mm CPMG 11C
PFLDPOG  zgD
TD  65536
SOLVENT  ceb312
NS  16
DS  4
SMN  400100.75 Hz
TFRES  0.157632 Hz
AQ  3-1719025 sec
RG  3.56
DM  40.400 usec
EE  10.60 usec
TR  298.0 K
TI  1.0000000 sec
TDS  1

-------- CHANNEL F1 --------
SF01  500-3000886 MHz
DEC1  1H
ds  15.00 usec
PLNL  7.9880000 W

F2 - Processing parameters
SH  65536
SF  500-3000206 MHz
MED  8
SSm  0
LS  0.30 Hz
GB  0
PC  1.00

\[(\text{CneO})_2\text{OPO} \quad \text{OPo(OCne)}_2\]

\(\text{TBDPSO} \quad \text{OPO(OPO)(OCne)}\)

\(\text{OTBDPS} \quad \text{OPO(OPO)(OCne)}\)
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-234

13C NMR of (+)-234

$\text{C}^{13}$NMR of (+)-234
HPLC of (+)-234

**AS-348-01**

Sample Name: AS-348-01  
Sample Description: Normal Phase silica column

Acquisition Method: Normal Phase Purity 254nm  
Acquisition Date/Time: 4/22/2015 3:48 pm

Batch Group/Name: Alex/Normal Phase Purity 254nm - Copy 04-22-2015 17-00-58  
Batch Description: Normal Phase silica column

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(\(\text{CneO})_2\text{OPO} \rightleftharpoons \text{OPO}(\text{OCne})_2\)

TBDPSO  
OTBDPS
H NMR of (+)-235

Current Data Parameters
NAME  AS-169-41
EXPNR  1
PROCNR  1

F2 - Acquisition Parameters
Date  20100417
Time  16:52
INSTURM  avc350
PROCNR  5 nm CFPUL 13C
FULLNMR  zg10
TD  65536
SOLVENT  cb2c12
NS  16
NS  4
SMH  0.01330.578 Hz
FIDRES  0.157632 Hz
AQ  3-1719.625 sec
RG  3-2
DM  48.400 usec
DR  10.00 usec
TR  298.0 K
T1i  1.000000 sec
TDS  1

-------- CHANNEL f1 --------
F01  500.030686 MHz
H1Cl  1m
J1  15.00 usec
J2  2.000000 w

F2 - Processing parameters
SH  65536
SF  500.030000 MHz
N0M  EM
SSm  0
LB  0.30 Hz
GB  0
FC  1.00

Otbdps

Otbdpsoh

(CneO)2OPO

(Ocne)2OPO

(2)
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-235

$^{13}$C NMR of (+)-235

OTBDPS

$\text{(CneO)}_2\text{PO}^+$

(O$\text{Cne}$)$_2\text{OPO}$

$^{13}$C NMR of (+)-235

OTBDPS
CHAPTER 9

3P NMR of (+)-235

Current Data Parameters
NAME  A5369-01L-1P
EXPN  1
PROCHO  1

F2 - Acquisition Parameters
Dat  20150429
Time  13:06
INSTRUM  avn400
F normal  5 mm PAB/EM
F PULPROG  zggp30
TE  62.36
SOLVENT  CDCl3
NS  32
DS  4
SWH  64.102.563 Hz
FIBES  0.979127 Hz
AQ  0.511189 sec
NQ  197.74
BW  7.800 usec
DE  6.30 usec
TE  298.0 K
D1  2.00000000 sec
D11  0.30000000 sec
TE0  1

-------- CHANNEL F1 --------
Stoi  161.9674942 MHz
Res1  3.1P
F1  8.00 usec
PLRM  94.00000000 MHz

-------- CHANNEL F2 --------
Stoi  400.133605 MHz
Res2  1H
CpldF1 200 us
CpldF2  76.00 usec
F1AM  14.28000000 Hz
F1AM  0.29771000 MHz
F1LM  0.43800000 MHz

F3 - Processing parameters
S1  2768
S2  161.9755930 MHz
DEW  500
SNR  0
LB  1.00 Hz
GB  0
PC  1.40
$^{1}H$-NMR of (+)-235
HPLC of (+)-235

AS-369-01

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<tr>
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<th>Sample Description</th>
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<td>Batch Description</td>
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<th>Area %</th>
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4/22/2015
H NMR of (+)-236

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NAME: AS-G18-01
SPMHD: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20150617
Time: 19:20
INSTRUM: avc500
pW0MHz: 5 MHz, Cryst 13C
PULPROG: sq30
T1: 6536
SOLVENT: CD2Cl2
NS: 16
DS: 4
SM: 10330.578 Hz
FIDRES: 0.157632 Hz
AQ: 1.711425 sec
PG: 1.56
SN: 48,000 usec
DE: 15.00 usec
TE: 234.0 K
DI: 1.0000000 sec
TDO: 1

F2 - Processing parameters
SI: 6536
SP: 500.3005207 MHz
MEW: MHz
SSB: 0
LB: 0.30 Hz
GB: 0
PC: 1.00

\[\text{Current Data Parameters} \]
\[\text{NAME: AS-G18-01} \]
\[\text{SPMHD: 1} \]
\[\text{PROCNO: 1} \]

\[\text{F2 - Acquisition Parameters} \]
\[\text{Date: 20150617} \]
\[\text{Time: 19:20} \]
\[\text{INSTRUM: avc500} \]
\[\text{pW0MHz: 5 MHz, Cryst 13C} \]
\[\text{PULPROG: sq30} \]
\[\text{T1: 6536} \]
\[\text{SOLVENT: CD2Cl2} \]
\[\text{NS: 16} \]
\[\text{DS: 4} \]
\[\text{SM: 10330.578 Hz} \]
\[\text{FIDRES: 0.157632 Hz} \]
\[\text{AQ: 1.711425 sec} \]
\[\text{PG: 1.56} \]
\[\text{SN: 48,000 usec} \]
\[\text{DE: 15.00 usec} \]
\[\text{TE: 234.0 K} \]
\[\text{DI: 1.0000000 sec} \]
\[\text{TDO: 1} \]

\[\text{F2 - Processing parameters} \]
\[\text{SI: 6536} \]
\[\text{SP: 500.3005207 MHz} \]
\[\text{MEW: MHz} \]
\[\text{SSB: 0} \]
\[\text{LB: 0.30 Hz} \]
\[\text{GB: 0} \]
\[\text{PC: 1.00} \]
CHAPTER 9. APPENDIX

13C NMR of (+)-236
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-236

H-13C NMR of (+)-236
CHAPTER 9. APPENDIX

P NMR of (+)-236

Current Data Parameters
NAME  AC411=81_34P
EXPNO  2
PROCNO  1

F2 - Acquisition Parameters
Date_  20100618
Time_  12:51
ISOTYPE_  e00400
FREQNS_  3 mm PABO BR/ FURVO
OFFSPIN_  90°
TC_  65336
SOLVENT_  CD2Cl2
N1_  46
DS_  4
SW_  462.02263 Hz
F1 B3_  0.571027 Hz
AQ_  0.5111888 sec
ACQ_  195.74
SE_  7.800 usec
TE_  1.60 usec
TD1_  2.00000000 sec
TD2_  0.03000000 sec
TD0_  1

--------- CHANNEL f1 ---------
SP01_  161.967442 MHz
ND01_  34p
F1_  8.00 usec
P1m1_  54.00000000 W

--------- CHANNEL f2 ---------
SP02_  461.131660 MHz
ND02_  45p
CVPAC[2]_  157.46
CPA[2]_  75.00 usec
PIM2_  14.92880000 W
PIM2_  0.29710000 W
PIM13_  0.14588000 W

F2 - Processing parameters
ST_  32768
ST_  161.97559230 MHz
MDM_  32
SSB_  0
LB_  1.00 Hz
Gb_  0
FC_  1.40

---

OTBDPS

(CneO)2OPO

(OCne)2OPO

OTBDPS

Ac

Ac
H-P HMBC NMR of (+)-236

OTBDPS

OTBDPSOH

OAc
HPLC of (+)-236

AS-418-01

Sample Name                  AS-418-01          Sample Description          Normal Phase silica column
Acquisition Method           Normal Phase Purity 254nm
Batch Group/Name             Alex/Normal Phase Purity 254nm - Copy 07-07-2015 15-09-58

Batch Description

Acquisition Date/Time         7/7/2015 12:29 pm

Sample Description
Normal Phase silica column

Time | Area  | Area %
-----|-------|--------
2.798 | 23970 | 0.04   
3.069 | 28535 | 0.05   
12.549 | 943712 | 1.49   
12.893 | 2029186 | 3.21   
14.013 | 60181066 | 95.18  
25.495 | 10906 | 0.02   
26.233 | 9983  | 0.02   
Total  | 63227358 | 100.00

![HPLC Graph](image_url)
CHAPTER 9
APPENDIX 9.1
COMPOUND (+)-237

H NMR of (+)-237
CHAPTER 9

C NMR of (+)-237

13C NMR of (+)-237
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-237

31P NMR of (+)-237

spectroscopic parameters
HPLC of (+)-237

AS-426-01

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-426-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
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<td>Acquisition Method</td>
<td>Normal Phase Purity 254nm</td>
<td>Acquisition Date/Time</td>
<td>7/3/2015 3:08 pm</td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase Purity 254nm - Copy 07-07-2015 12-16-05</td>
<td>Batch Description</td>
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<table>
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<tr>
<th>Time</th>
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<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.461</td>
<td>128529</td>
<td>0.75</td>
</tr>
<tr>
<td>13.061</td>
<td>9791575</td>
<td>56.92</td>
</tr>
<tr>
<td>13.820</td>
<td>7281659</td>
<td>42.33</td>
</tr>
<tr>
<td>Total</td>
<td>17201764</td>
<td>100.00</td>
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![HPLC Graph](image)
H NMR of (+)-250
C NMR of (+)-250
P NMR of (+)-250

$\text{OTBDPS}$

$\text{OPO(OCne)_{2}}$

$\text{OAc}$

$\text{(-250)}$

$\text{ppm}$

$\text{-2.916}$

$\text{-3.065}$

$\text{-3.222}$

$\text{1H NMR of (+)-250}$

CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-250
HPLC of (+)-250

AS-535-01

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>AS-535-01</th>
<th>Sample Description</th>
<th>Normal Phase silica column</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition Method</td>
<td>Normal Phase Purity 254nm 5-95</td>
<td>Acquisition Date/Time</td>
<td>7/16/2016 5:00 pm</td>
</tr>
<tr>
<td>Batch Group/Name</td>
<td>Alex/Normal Phase Purity 254nm 5-95</td>
<td>Batch Description</td>
<td>Normal Phase silica column</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.718</td>
<td>107582</td>
<td>0.11</td>
</tr>
<tr>
<td>3.776</td>
<td>276827</td>
<td>0.30</td>
</tr>
<tr>
<td>7.072</td>
<td>798414</td>
<td>0.85</td>
</tr>
<tr>
<td>7.476</td>
<td>720833</td>
<td>0.77</td>
</tr>
<tr>
<td>9.399</td>
<td>48490</td>
<td>0.05</td>
</tr>
<tr>
<td>9.862</td>
<td>46995</td>
<td>0.05</td>
</tr>
<tr>
<td>13.250</td>
<td>380971</td>
<td>0.41</td>
</tr>
<tr>
<td>15.770</td>
<td>89111541</td>
<td>95.03</td>
</tr>
<tr>
<td>17.884</td>
<td>1402668</td>
<td>1.50</td>
</tr>
<tr>
<td>18.764</td>
<td>875610</td>
<td>0.93</td>
</tr>
<tr>
<td>Total</td>
<td>93769930</td>
<td>100.00</td>
</tr>
</tbody>
</table>

OTBDPS

\((\text{CneO})_2\text{OPO(OCne)}_2\)OAc

\((\text{OCne})_2\text{OPO}\)OAc

7/16/2016
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-231

1H NMR of (+)-231

Current Data Parameters
NAME: AS-584-01_13C
EPIPHO: 1
PROCENO: 1

F2 - Acquisition Parameters
Date: 20160219
Time: 7-27
INSTRUM: avc500
DSWTIME: 5 mm Cpmg 13C
POLP: e0
TD: 65536
SOLVENT: DMSO
NS: 16
DS: 4
SMH: 10330.578 Hz
FIDRES: 0.157632 Hz
AQ: 3.1717425 sec
RG: 1.56
SN: 48.400 usec
DE: 15.00 usec
TE: 234.0 K
DG: 1.00000000 sec
TD: 1

F2 - Processing parameters
SI: 65536
SP: 500.303996 MHz
MDM: 3M
SSB: 0
LB: 0.30 Hz
GB: 0
FC: 1.00
9.1. COMPOUND (+)-231

C NMR of (+)-231

[Diagram of 13C NMR spectrum]

Current Data Parameters
NAME AS-382a(+)-13C
EXPIRY 4
PROCNO 1

F2 - Acquisition Parameters
Data 20160218
Time 9:14
INSTRUM av2003
kHzppm 5 ns Cryst. 13C wppm=30
TD 65536
SOLVENT DMSO
NS 2156
DS 2
Freq 31250000 Hz
AQ 0.676837 Hz
AQ 1.6485760 sec
TE 912
DW 16000 usec
TE 18000 usec
TE 298 K
D1 2600000000 usec
D2 6030000000 usec

--- CHANNEL F1 ---
SFO1 125.613112 MHz
FUC1 13C
P1 1000 usec
FWM1 2018400002 W

--- CHANNEL F2 ---
SFO2 500.3020012 MHz
FUC2 1H
CFDPPS:2 1H wait=10
PCD1 8000 usec
PCD1 7.095000 w
FWM2 0.29819001 w
FWM13 0-17996000 W

F2 - Processing parameters
st 32748
st 125.613112 MHz
rms nm
SSB 0
LB 1.0 Hz
SB 0
PC 1.40
H NMR of (+)-247

Current Data Parameters
NAME A5-671-01
TSPRD 10
PROCRO 1

F2 - Acquisition Parameters
Data_ 20162614
Time 13:37 h
INSTRUM avb000
pwName z108618_0873 |
POLPXG xps0
TS 65536
SOLVENT CDCl3
NS 16
DS 2
SMM 8012.820 Hz
FIDRES 0.244332 Hz
AQ 4.0894465 sec
DG 37.97
DN 62.400 ussec
DE 7.50 ussec
TE 1.970 K
DI 1.0000000 sec
TD0 1
SFO1 400.1324008 MHz
NVO1 1H
PI 11.00 ussec
PIM 14.36999989 MHz

F2 - Processing parameters
SI 32768
SP 400.1324008 MHz
NDW EM
NBX 0
LB 0.30 Hz
GR 0
PC 1.00

TBDPSO O Troc O Troc O TBDPS O Troc
13C NMR of (+)-247
CHAPTER 9. APPENDIX 9.1. COMPOUND (+)-146

H NMR of (+)-146
CHAPTER 9. APPENDIX

C NMR of (+)-146

OCOC₆H₄

13C NMR of (+)-146
C NMR of (+)-151a

Current data parameters
NAME  As-151-
EXPPD  3
PROCNO  1
F2 - Acquisition Parameters
Date  2015-027
Time  4.79
INSTRUM  ag5000
FREQUS  5 mm PAMCO 88/
POLPROG  zpg30
TS  65556
SOLVENT  CDCl3
NS  256
SS  4
DMR  249.36.461 Hz
FDRRNG  0-365798 Hz
AQ  1.36514380 sec
BG  206.97
SM  20.890 usec
SE  6.50 usec
TE  2.95-1.0 K
S1  2.00000000 sec
S11  0.30001000 sec
TR2  1
------------ CHANNEL F1 ------------
SFO1  100.640326 MHz
NUC1  13C
f1  11.00 usec
FM1  56.00000000 W
------------ CHANNEL F2 ------------
SFO2  400.201608 MHz
NUC2  1H
CETMS [1] water16
F2[1]  91.00 usec
FM2  1.00000000 W
FM11  0.168376000 W
FM13  0.27441000 W
F2 - Processing parameters
SI  3765
SF  100.6303591 MHz
GWM
SBR  0
LB  1.00 Hz
GB  0
FC  1.40
H NMR of (+)-151b

CHARTER 9. APPENDIX 9.1. COMPOUND (+)-151b
C NMR of (+)-151b
### Table 1. Crystal data and structure refinement for 6617.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>6617</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C14 H18 O8</td>
</tr>
<tr>
<td>Formula weight</td>
<td>314.29</td>
</tr>
<tr>
<td>Temperature</td>
<td>150 K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54180 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.4164(2) Å, b = 6.6513(2) Å, c = 11.2592(2) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>774.33(3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.348 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.956 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>332</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.23 x 0.16 x 0.15 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.955 to 76.044°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=13, -8&lt;=k&lt;=8, -11&lt;=l&lt;=14</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>8925</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3187 [R(int) = 0.017]</td>
</tr>
<tr>
<td>Completeness to theta = 74.523°</td>
<td>99.6 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.87 and 0.73</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2322 / 1 / 200</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.0108</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0229, wR2 = 0.0590</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0230, wR2 = 0.0591</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.24(13)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.10 and -0.10 e.Å⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å²x $10^3$) for 6617. U(eq) is defined as one third of the trace of the orthogonalized $U^i$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
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<tbody>
<tr>
<td>C(1)</td>
<td>3953(1)</td>
<td>227(2)</td>
<td>8615(1)</td>
<td>33</td>
</tr>
<tr>
<td>C(2)</td>
<td>5204(1)</td>
<td>-160(2)</td>
<td>8843(1)</td>
<td>32</td>
</tr>
<tr>
<td>C(3)</td>
<td>6233(1)</td>
<td>1169(2)</td>
<td>8457(1)</td>
<td>29</td>
</tr>
<tr>
<td>C(4)</td>
<td>5694(1)</td>
<td>3214(2)</td>
<td>8051(1)</td>
<td>27</td>
</tr>
<tr>
<td>C(5)</td>
<td>4422(1)</td>
<td>2988(2)</td>
<td>7244(1)</td>
<td>27</td>
</tr>
<tr>
<td>C(6)</td>
<td>3409(1)</td>
<td>2026(2)</td>
<td>7929(1)</td>
<td>30</td>
</tr>
<tr>
<td>O(7)</td>
<td>7194(1)</td>
<td>1443(2)</td>
<td>9493(1)</td>
<td>32</td>
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<tr>
<td>C(8)</td>
<td>8452(1)</td>
<td>1528(2)</td>
<td>9311(1)</td>
<td>35</td>
</tr>
<tr>
<td>O(9)</td>
<td>8821(1)</td>
<td>1324(2)</td>
<td>8349(1)</td>
<td>45</td>
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<tr>
<td>C(10)</td>
<td>9285(2)</td>
<td>1950(3)</td>
<td>10456(1)</td>
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<td>O(11)</td>
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<td>7350(1)</td>
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<tr>
<td>C(12)</td>
<td>7346(1)</td>
<td>5670(2)</td>
<td>7879(1)</td>
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<tr>
<td>O(13)</td>
<td>7341(1)</td>
<td>6174(2)</td>
<td>8903(1)</td>
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<td>C(14)</td>
<td>8200(1)</td>
<td>6503(2)</td>
<td>7028(1)</td>
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<tr>
<td>O(15)</td>
<td>4012(1)</td>
<td>4978(2)</td>
<td>6881(1)</td>
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<td>C(16)</td>
<td>3695(1)</td>
<td>5359(2)</td>
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<td>O(17)</td>
<td>3767(1)</td>
<td>4129(2)</td>
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<tr>
<td>C(18)</td>
<td>3266(2)</td>
<td>7465(2)</td>
<td>5521(1)</td>
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<td>O(19)</td>
<td>2339(1)</td>
<td>1276(2)</td>
<td>7098(1)</td>
<td>33</td>
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<td>C(20)</td>
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<td>2466(2)</td>
<td>6801(1)</td>
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<td>O(21)</td>
<td>1223(1)</td>
<td>4163(2)</td>
<td>7136(1)</td>
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<td>C(22)</td>
<td>286(1)</td>
<td>1377(3)</td>
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Table 3. Bond lengths [Å] and angles [°] for 6617.

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<th>Bond</th>
<th>Length/Angle</th>
<th>Bond</th>
<th>Length/Angle</th>
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<tbody>
<tr>
<td>C(1)-C(2)</td>
<td>1.323(2)</td>
<td>O(19)-C(20)</td>
<td>1.3516(18)</td>
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<tr>
<td>C(1)-C(6)</td>
<td>1.497(2)</td>
<td>C(20)-O(21)</td>
<td>1.195(2)</td>
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<tr>
<td>C(1)-H(11)</td>
<td>0.925</td>
<td>C(20)-C(22)</td>
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<tr>
<td>C(2)-C(3)</td>
<td>1.4940(19)</td>
<td>C(22)-H(221)</td>
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<tr>
<td>C(2)-H(21)</td>
<td>0.956</td>
<td>C(22)-H(222)</td>
<td>0.930</td>
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<tr>
<td>C(3)-C(4)</td>
<td>1.5207(19)</td>
<td>C(22)-H(223)</td>
<td>0.940</td>
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<tr>
<td>C(3)-O(7)</td>
<td>1.4536(15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(3)-H(31)</td>
<td>0.943</td>
<td>C(2)-C(1)-C(6)</td>
<td>123.91(13)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.5215(18)</td>
<td>C(2)-C(1)-H(11)</td>
<td>120.2</td>
</tr>
<tr>
<td>C(4)-O(11)</td>
<td>1.4419(15)</td>
<td>C(6)-C(1)-H(11)</td>
<td>115.9</td>
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<tr>
<td>C(4)-H(41)</td>
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<td>C(1)-C(2)-C(3)</td>
<td>123.62(13)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.5222(18)</td>
<td>C(1)-C(2)-H(21)</td>
<td>119.5</td>
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<tr>
<td>C(5)-O(15)</td>
<td>1.4343(17)</td>
<td>C(3)-C(2)-H(21)</td>
<td>116.8</td>
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<td>C(5)-H(51)</td>
<td>0.973</td>
<td>C(2)-C(3)-C(4)</td>
<td>111.37(11)</td>
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<tr>
<td>C(6)-O(19)</td>
<td>1.4538(16)</td>
<td>C(2)-C(3)-O(7)</td>
<td>106.85(10)</td>
</tr>
<tr>
<td>C(6)-H(61)</td>
<td>0.960</td>
<td>C(4)-C(3)-O(7)</td>
<td>108.80(11)</td>
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9.1. X-RAY STRUCTURE FOR (+)-81

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for 6617. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^* a^* U^{11} + \ldots + 2hk a^* b^* U^{12} ]$

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<th>U^{11}</th>
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<th>U^{33}</th>
<th>U^{23}</th>
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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 6617.

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<tr>
<th>H(1)</th>
<th>x</th>
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<th>z</th>
<th>U(eq)</th>
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<td>597</td>
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<td>H(41)</td>
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<td>8719</td>
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<td>H(51)</td>
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<td>70</td>
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<td>H(102)</td>
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<td>1009</td>
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<td>H(103)</td>
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<td>10743</td>
<td>73</td>
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<td>H(141)</td>
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<td>7323</td>
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<td>H(142)</td>
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<td>66</td>
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Table 6. Hydrogen bonds for 6617 [Å and °].

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<th>D-H...A</th>
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<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
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</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+2    #2 x+1,y,z    #3 -x+1,y+1/2,-z+1
Table 1. Crystal data and structure refinement for 6614.

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</tr>
<tr>
<td>Wavelength</td>
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</tr>
<tr>
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<td>Space group</td>
<td>P 21</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
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<tr>
<td>Z</td>
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<td>Density (calculated)</td>
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<td>332</td>
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<tr>
<td>Crystal size</td>
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</tr>
<tr>
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<td>Index ranges</td>
<td>-13 ≤ h ≤ 13, -7 ≤ k ≤ 8, -13 ≤ l ≤ 14</td>
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<tr>
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<td>Completeness to theta = 74.868°</td>
<td>99.9 %</td>
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<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
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<td>Max. and min. transmission</td>
<td>0.99 and 0.53</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>2962 / 1 / 200</td>
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<tr>
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<td>R indices (all data)</td>
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<tr>
<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.16 and -0.21 e.Å⁻³</td>
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Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for 6614. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

<table>
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<th>z</th>
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Table 3. Bond lengths [Å] and angles [°] for 6614.

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C(22)-H(222) 0.957
C(22)-H(223) 0.949
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C(2)-C(1)-H(11) 119.7
C(6)-C(1)-H(11) 116.6
C(1)-C(2)-C(3) 123.7(2)
C(1)-C(2)-H(21) 118.6
C(3)-C(2)-H(21) 117.7
C(2)-C(3)-C(4) 111.55(15)
C(2)-C(3)-O(7) 116.6
C(4)-C(3)-O(7) 108.85(17)
C(2)-C(3)-H(31) 110.0
C(4)-C(3)-H(31) 110.2
C(3)-C(4)-C(5) 110.92(16)
C(3)-C(4)-O(11) 110.2
C(5)-C(4)-O(11) 106.41(14)
C(3)-C(4)-H(41) 110.8
C(5)-C(4)-H(41) 109.4
C(4)-C(5)-C(6) 110.95(15)
C(4)-C(5)-O(15) 109.95(14)
C(6)-C(5)-O(15) 106.00(17)
C(4)-C(5)-H(51) 109.6
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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10⁳) for 6614. The anisotropic displacement factor exponent takes the form: 

\[-2\pi^2 [ h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12} ]\]

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</table>
Table 5.  Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^{-3}$) for 6614.

| H(11)  | 6642 | 10668 | 1109 | 44   
| H(21)  | 4523 | 11327 | 732  | 43   
| H(31)  | 3374 | 9455  | 2188 | 38   
| H(41)  | 4434 | 5960  | 1267 | 36   
| H(51)  | 5475 | 7837  | 3454 | 36   
| H(61)  | 6934 | 6980  | 1556 | 38   
| H(101) | -167 | 8087  | -346 | 78   
| H(102) | 888  | 9021  | -1041| 80   
| H(103) | 913  | 6748  | -760 | 79   
| H(141) | 1457 | 2241  | 2664 | 58   
| H(142) | 2282 | 3334  | 3751 | 59   
| H(143) | 1108 | 4422  | 2999 | 57   
| H(181) | 7015 | 2316  | 5322 | 71   
| H(182) | 7437 | 2277  | 4006 | 72   
| H(183) | 6021 | 1692  | 4236 | 72   
| H(221) | 10544| 8245  | 3823 | 71   
| H(222) | 9587 | 10050 | 3906 | 71   
| H(223) | 9623 | 8265  | 4805 | 70   

Table 6. Hydrogen bonds for 6614 [Å and °].

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<th>d(H...A)</th>
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Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z    #2 -x+1,y-1/2,-z+1
To whom it may concern,

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Best wishes,

Sarah Crespi

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Suite 302
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