Synthesis of Deuterated Phosphatidylinositol Phosphates

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DPhil Thesis

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Funded by EPSRC and AstraZeneca *via*

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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.

Acknowledgements

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 DPhils, (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.

To those that trained me when I first joined the lab, Dr's Corinna Kaul, Sonia Diab, Laura Jennings, Tim Rooney, David Hewings, and Diane Swallow, I will always appreciate the lengths you went to make sure I wouldn't cause too much trouble. Dr Lingbing Kong, I am eternally grateful for your presence in the lab, you may have been quiet at the start when I first met you but that is most definitely not the case anymore... Best of luck in your new job at University of Sussex and all your future endeavours, hopefully as a PI. Dr Liam O'Connor, for all the banter along the way and for the fun we had at Pacifichem in Hawaii. Dr's Samuel Greyer and Angelina Sekirnik, I will miss you two together as opposite faces of the same coin. To Sarah Collins and Larissa See for brightening up G12 everyday. To Charles Evans for always being keen to get stuck into whatever needed doing. To Dr Anthony Chan for his unique perspective on British culture, all the best in finding your next Post-Doc position. To Catherine Haslam and Corentine (Coco) Laurin for taking on some of the more horrible jobs around the labs last year, and for generally smiling all the time. To Dr Ewen Calder for the chemistry advice you give and for being a good laugh both in and out of the lab. Dr James Clayton for keeping the labs running

smoothly. To the various DTC/CDT students who have joined the group for their rotations (Mus, Reece, Amy, Claire, Joe, Isabel), I hope you enjoy the rest of the projects and good luck!

The group is not complete without the Part II's, and looking after them is always challenging as they invent new ways in which to damage themselves or other people but it has been a pleasure to supervise several of them. Calvin, glad you managed to finish without ingesting cyanide, likewise for Jay. Both of you were brilliant to have around, both in the lab and in the pub, and saved me from fixing many things around the lab which I greatly appreciate. I'm glad to see both of you doing well after you left Oxford. Good luck also to Fern, Jessie and Thanh in their PhD projects coming up in various places across Europe, it was fun having you around in the final year. Finally, to Jesse and his family, thoughts are with you all. It was an absolute pleasure having you working next to me the final year. To all those who read my thesis, in particular the stellar job Stuart did, but also those who read chapters prior to them getting anywhere near Stuart (although any mistakes remain my own): Michael Brand, Sarah Collins, Lingbing Kong, Charles Evans, Larissa See, Corentine Laurin, Catherine Haslam, and Ewen Calder. To all those in the department without whom the department would not run. The NMR team for their help, support and guidance, in particular Dr Barbara Odell and Tina Jackson. They have been invaluable in doing many of the NMR studies (in particular ^{2}H NMR and T_1 times) and fun to chat to, but also Professor Tim Claridge, Dr Nick Rees and Maria Marshall who have provided advice and dealt with some rather unusual requests. Enjoy your retirement Barbara, it is well earned! To the x-ray crystallography team, Professor Richard Cooper and Dr's Amber Thompson and Kirsten Christensen, thank you for providing data on several structures. To the mass spectrometry team, Dr James Wickens and Colin Sparrow, thanks for keeping everything running like a well oiled machine. Also to the stores staff, especially Leigh and Paul, who are often overlooked but nonetheless have always made sure everything gets to the right place. Finally, the department would be constantly broken without the expert hands of Alan, Barry, Jude, Debbie, Keith and of course, Ron.

Abbreviations

AAA	Asymmetric allylic alkylation
ar.	Aromatic (IR, NMR)
Ac	Acetyl (protecting group)
Bn	Benzyl (protecting group)
Bz	Benzoyl (protecting group)
Cne	2-Cyanoethyl (protecting group)
COSY	Correlation spectroscopy (NMR)
DAG	Diacylglycerol
DCC	*N,N'*-Dicyclohexylcarbodiimide
DHP	3,4-Dihydro-2*H*-pyran
DKR	Dynamic Kinetic Resolution
DMAP	*N,N*-Dimethyl-4-aminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
e.e.	Enantiomeric excess
eq.	Equivalents
$E^{+/-}$	Electron ionisation (mass spectroscopy)
EDC·HCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ER	Endoplasmmic reticulum
$ES^{+/-}$	Electrospray ionisation (mass spectroscopy)
Et	Ethyl
$F^{+/-}$	Field ionisation (mass spectroscopy)
h	hour(s)
HMBC	Heteronuclear multiple-bond correlation spectroscopy (NMR)
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy (NMR)
IR	Infrared Spectroscopy
LRMS	Low-resolution mass spectrometry
*m*CPBA	3-Chloroperbenzoic acid
Me	Methyl

min	minute(s)
m.p.	Melting point
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy (NMR)
PI*N*K*	Phosphatidylinositol *N*-kinase
PKC	Protein kinase C
PLC	Phospholipase C
PMB	*p*-Methoxybenzyl (protecting group)
PMBCl	*p*-Methoxybenzyl chloride
PPL	Pig pancrease lipase
PtdIns	Phosphatidylinositol
PtdIns*N*P*	Phosphatidylinositol *N*-phosphate
PtdIns*N*P_2*	Phosphatidylinositol *N*-bisphosphate
*p*TSA	4-Toluenesulfonic acid
R_f	Retention factor
TBABr	Tetrabutylammonium bromide
TBDMS	^{t}Butyldimethylsilyl (protecting group)
TBDPS	^{t}Butyldiphenylsilyl (protecting group)
TFA	Trifluoroacetic
TfOH	Triflic acid
THABr	Tetrahexylammonium bromide
THF	Tetrahydrofuran
THP	Tetrahydropyranyl (protecting group)
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TMSBr	Trimethylsilyl bromide
Troc	2,2,2-Trichloroethyl carbonate (protecting group)

**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.

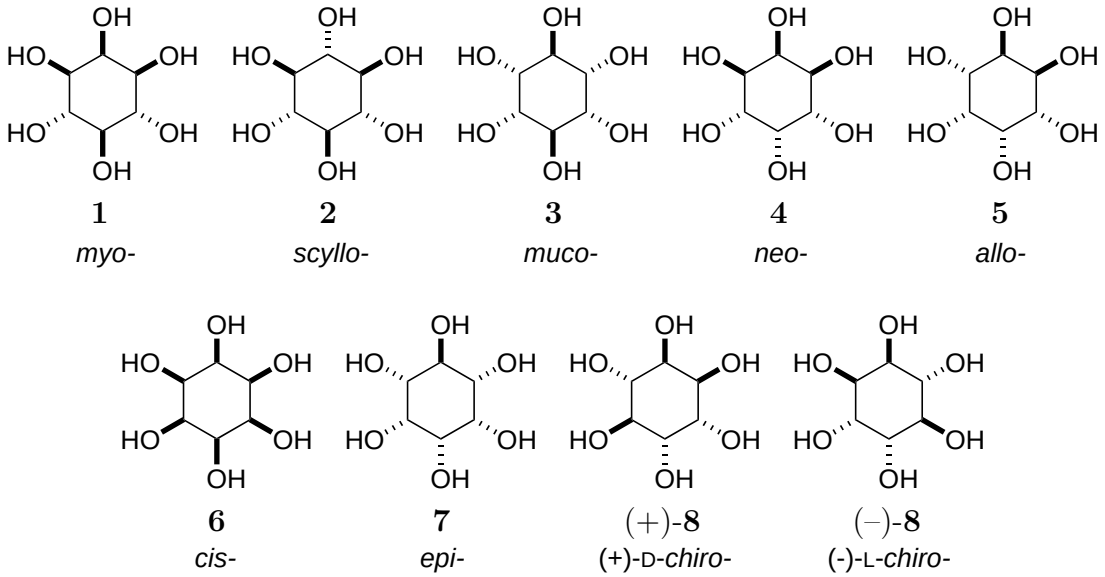


Figure 1.1 The nine isomers of inositol: *myo*-inositol **1**, *scyllo*-inositol **2**, *muco*-inositol **3**, *neo*-inositol **4**, *allo*-inositol **5**, *cis*-inositol **6**, *epi*-inositol **7**, (+)-D-*chiro*-inositol **8**, and (−)-L-*chiro*-inositol **8**.

1.1.1 Structure and Numbering of *myo*-Inositol

Inositols are a common building block for many messengers in biological systems, with the chemical formula $C_6H_{12}O_6$. Unlike typical carbohydrates of the formula of $C_n(H_2O)_n$ 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**.[2] Derivatives of **1** have been of particular interest for both biologists and chemists alike.[1–3] 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).[4]

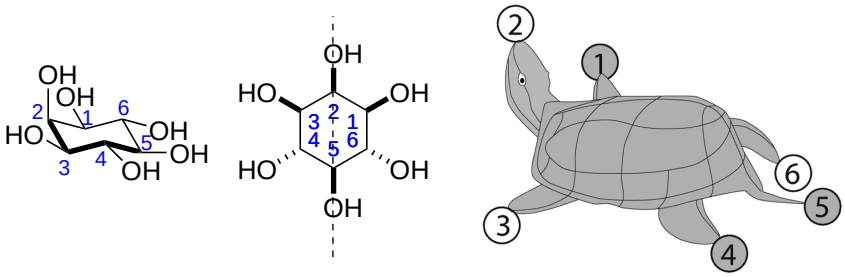


Figure 1.2 Numbering of *myo*-inositol ring shown in both the flat and chair forms. The D-numbering is usually used throughout the literature to avoid confusion as recommended by IUPAC, and is used throughout this work.[5] Turtle image used with permission (see appendix, page 547).[4]

myo-Inositol systems are numbered using the D-*myo*-inositol 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).[4–6] 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 (PtdInsP_n).

1.1.2 Phosphatidylinositol Phosphates (PtdInsP_n)

PtdInsP_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 PtdInsP_n in biological systems.[1,10,11] PtdInsP_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 PtdInsP_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 PtdInsP_n (Figure 1.4). The next most common PtdInsP_n are PtdIns(4,5)P_2 and its precursor PtdIns(4)P at around 0.2-1 mol%, with all the other PtdInsP_n found in only trace amounts.[1,13]

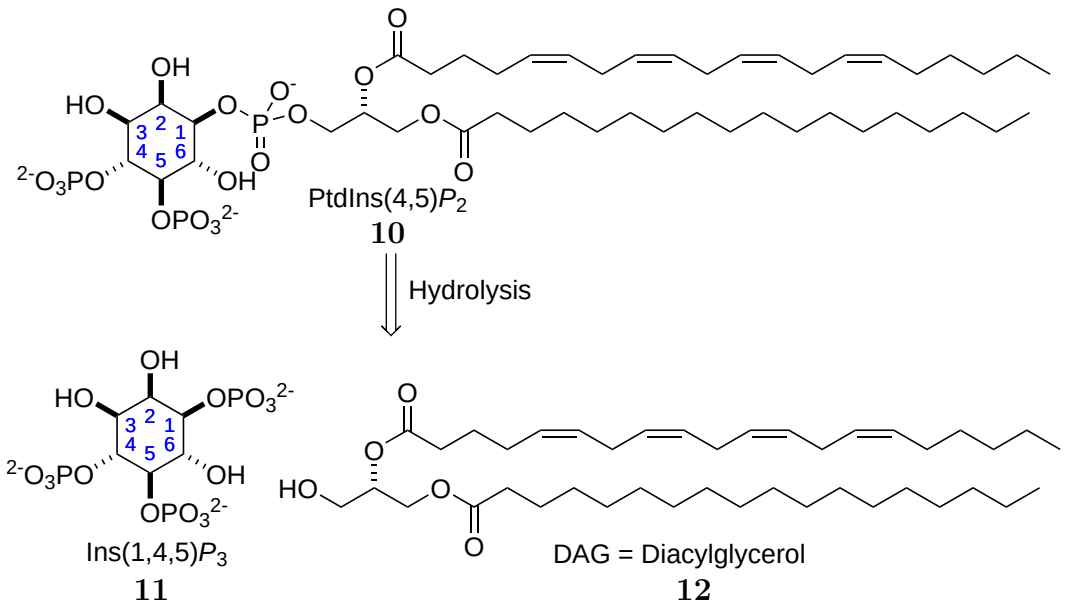


Figure 1.3 Hydrolysis of PtdIns(4,5)P_2 **10** in cellular systems by protein kinase C (PKC) leads to Ins(1,4,5)P_3 and DAG, both of which act on intracellular targets.[1,7]

1.1.3 Structure of PtdInsP_n

PtdInsP_n comprise a phosphorylated *myo*-inositol group linked to two lipid chains by a glycerol moiety (Figure 1.3).[14] Each part of the PtdInsP_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.[1] 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 PtdInsP_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]

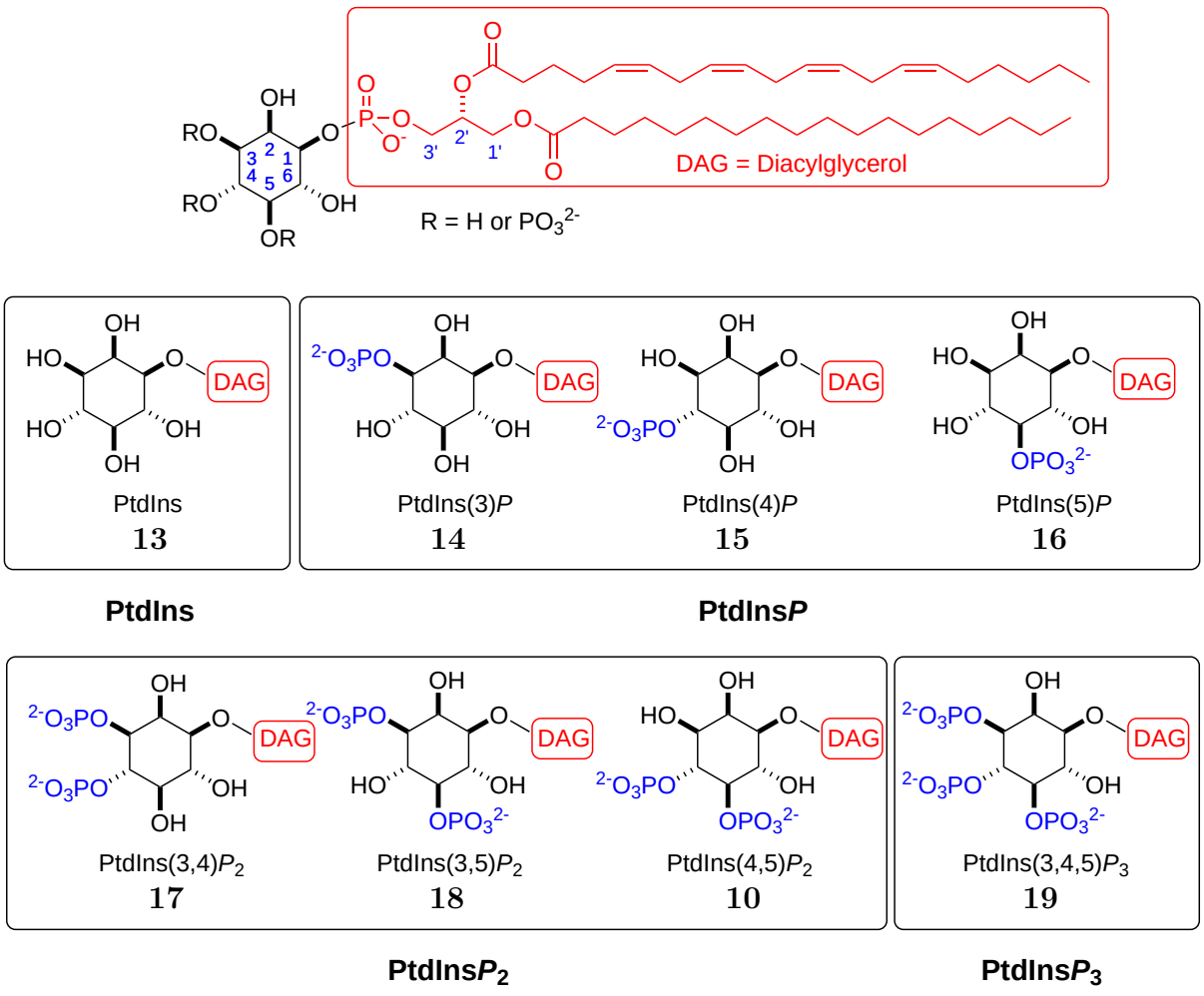


Figure 1.4 General structure of PtdInsP_n (top) comprising a *myo*-inositol headgroup, glycerol linker and two lipids. Phosphorylation of PtdIns **13** leads to seven PtdInsP_n, each with different biological activity. The structures shown contain the two most common lipid tails, an arachidonic acid and a stearic acid chain.

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.[1] 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).[15] 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.[16] This is of particular importance when concerned with anchoring of PtdInsP_n into different sub-cellular compartments and hence is important to consider when designing new probes.[1,3]

Table 1.1 Fatty acid composition of phospahtidylinositol in different tissues in rats, showing the predominant two species in all cases to be 18:0 and 20:4.[15]

Fatty Acid[a]	Liver	Kidney	Brain	Sciatic Nerve
16:0	6.7	9.2	10.8	9.4
16:1	0.4	0.5	N.D.	2.0
18:0	**41.3**	**38.8**	**33.8**	**35.0**
18:1	4.3	4.6	14.3	16.5
18:2	4.1	3.6	0.6	1.8
20:1	N.D.	N.D.	1.1	N.D
20:3	2.8	2.3	N.D.	3.6
20:4	**33.6**	**37.0**	**34.7**	**22.3**
20:5	0.3	0.3	N.D.	N.D.
22:4	0.6	1.0	0.9	2.4
22:5	1.5	0.3	N.D.	N.D.
22:6	3.1	1.5	2.9	1.5

[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 PtdInsP_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 (MPAK) and receptor for activated C kinase 1 (RACK1).[20,21] This leads to downstream effects that are

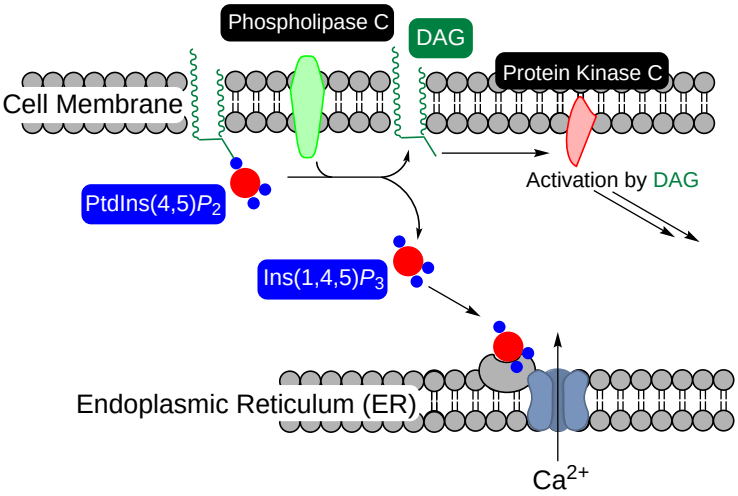
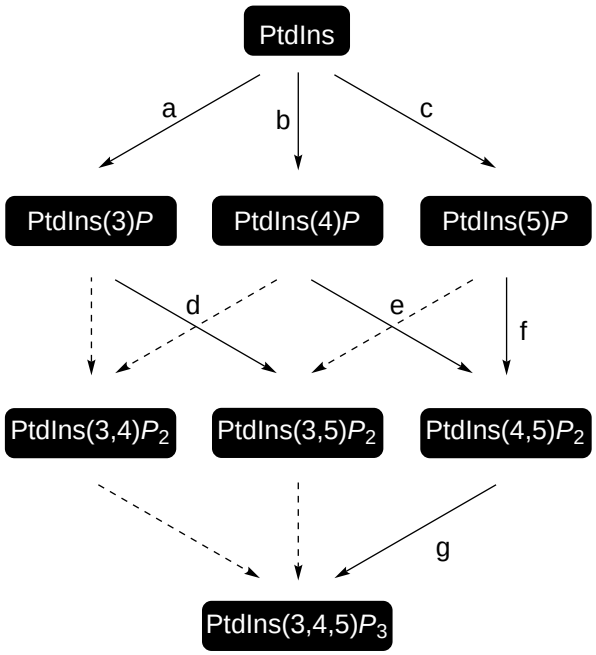


Figure 1.5 The Ca^{2+} signalling pathway involving PtdIns(4,5)P_2 has been thoroughly studied.[1,17] Hydrolysis of PtdIns(4,5)P_2 **10** at the cell membrane by phospholipase C (PLC) leads to release of Ins(1,4,5)P_3 **11** into the cytoplasm, with the remaining diacylglycerol (DAG) remaining in the 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.[1] 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.[22]

1.2.2 Biosynthesis of PtdInsP_n

The biosynthesis of the family of 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**.[23,24] The selective phosphorylation of PtdIns **13** is mediated by a family of phosphatidylinositol kinases (PtdIns$N$K, where the N denotes the site of phosphorylation, typically the 3-, 4- or 5-positions of the *myo*-inositol ring, Scheme 1.1). These PtdInsP_n can then be further phosphorylated by a second set of kinases, the PtdInsP_n kinases (PtdInsPNK). A constant basal level of PtdInsP_n is maintained by these kinases, with inhibition of any of the kinases causing an overall drop in the level of PtdInsP_n and a concomitant increase in the concentration of precursors.



Scheme 1.1 PtdIns can by phosphorylated by a series of kinases to give the family of PtdInsP_n. Solid arrows represent known kinases while dotted lines indicate suspected transformations where the kinases have not yet been isolated or characterised.[1] Kinases: a. PtdIns3K; b. PtdIns4K; c. PtdIns5K; d. PtdInsP5K3; e. PtdInsP5K1; f. PtdInsP5K2; g. PtdInsP5K3.[1]

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.[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.[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.[25] There has so far been limited success with PtdIns3K inhibitors, with only one compound approved by the FDA. Idelalisib **20** (Zydelig®, 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.[25–27]

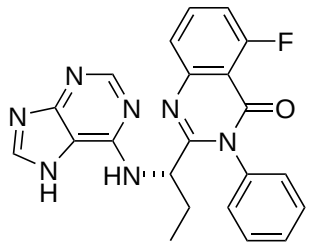


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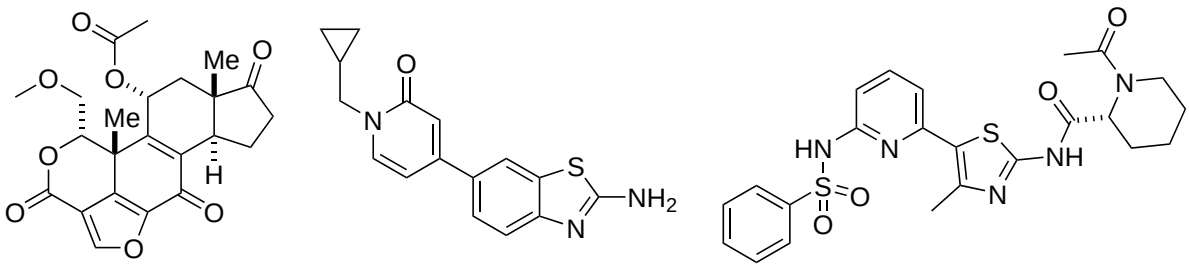
Figure 1.6 Structure of Idelalisib **20** (Zydelig®), a PtdIns3Kδ inhibitor approved by the FDA and MHRA.[25–27]

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.[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.[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.[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).[30] Type I PtdIns4K were wrongly assigned when first discovered, and are actually PtdIns3K.[1] 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.[31] These two types of PtdIns4K are further divided each into α- and β- isoforms.



21 **22** **23**

Figure 1.7 Structures of a covalent, natural-product inhibitor of PtdIns4K Wortmannin **21**, as well as a type III α-selective, **22**, and a type III β-selective, **23**, inhibitors developed by AstraZeneca.[30,32]

During the course of their work, AstraZeneca developed two different inhibitors of PtdIns4K that could target the IIIα- and IIIβ-subtypes with 100-1000 fold selectivity for one isoform over the other (**22** and **23**, Figure 1.7, Table 1.2).[32] 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 PtdInsP_{n} pathway. Using mass-spectrometry, the whole-cell levels of Ins$P$ and PtdInsP_2 were measured and compared to a basal cell level. No attempt was made to distinguish between the different isomers of Ins$P$ and PtdInsP_2 due to the use of mass spectrometry to quantify the species. The α-isoform inhibitor **22** revealed an accumulation of Ins$P$, a precursor to the pathway, and basal levels of PtdInsP_2 dropped substantially, suggesting significant inhibition of the kinase (Table 1.2). Conversely, the β-isoform inhibitor **23**

revealed a diminished effect on these two biomarkers compared to **22**.[32]

Table 1.2 Using recombinant protein, pIC_{50} values were obtained for compounds **22** and **23** (Figure 1.7) showing selectivity for one isoform of PtdIns4K type III over the other in biochemical assays. Inhibition of the β isoform by **23** did not give a drop in basal PtdInsP_2 levels, as measured by tandem mass spectrometry.[32]

Compound	PtdIns4Kα pIC_{50}	PtdIns4Kβ pIC_{50}	Cellular PtdInsP_2 (Basal, %)
22	8.2	5.9	0
23	5.1	7.8	19

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.[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_2 levels is observed. Alternatively, the reduction of basal PtdInsP_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)P_2 **10** and PtdIns(3,5)P_2 **18**), therefore while one PtdInsP_n is depleted, another may increase in concentration *via* feedback mechanisms.[34] In order to understand the origin of these results, new biologically relevant PtdIns(4,5)P_2-based probes are required.

1.3 Examples of Previous Probes

As the pathways involving PtdIns(4,5)P_2 **10** have been heavily studied over the past forty years, there are many examples of probes based on the structure of endogenous InsP_n and PtdInsP_n. Typical examples to probe PtdIns(4,5)P_2 **10** binding in biological systems have retained the Ins(1,4,5)P_3 motif, replacing the lipid chains with different reporter groups to distinguish between endogenous PtdInsP_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 PtdInsP_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 PtdInsP_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)P_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)P_2 **10** to profilin required the lipid chains.[39] More recently, similar work on PtdIns(3,4,5)P_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. PtdInsP_n have also been incorporated onto beads to create affinity columns that can be used to isolate and purify proteins that bind the inositol

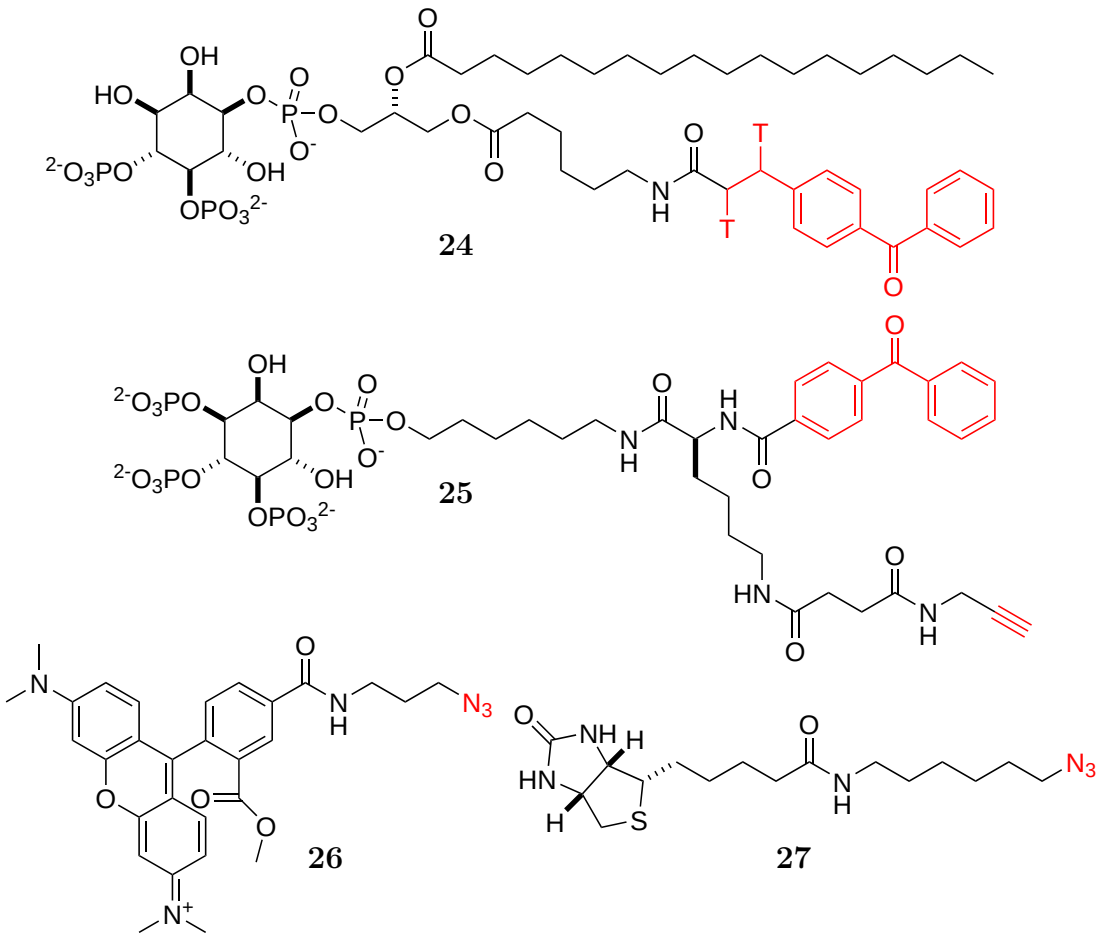


Figure 1.8 Two examples of photoaffinity probes synthesised in order to understand binding partners of PtdIns(4,5)P_2 **10** in biological systems.[39,40] In some cases, a 'clickable' linker is also incorpated for further work using fluorescent groups or biotin tags.

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 PtdIns$P$ (all isomers), using [^{32}P]-ATP.[42] Tritium (^{3}H) has been incorporated into benzophenone-tagged

PtdIns(4,5)P_2 **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 ^{18}F as a radiotracer, for use in monitoring metabolism of diacylglycerols.[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 ^{32}P and ^{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).[44] ^{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.[45] An alternative to radioisotopes is the use of stable isotopes in PtdInsP_n. Deuterium has been used to replace hydrogen in the lipids of PtdInsP_n, as perdeuteration of the fatty acid lipid chains is possible and perdeuterated fatty acids can be purchased from several companies including, Sigma Aldrich.[46,47] PtdInsP_n incorporating these isotopically-labelled lipids have found use in solid-state NMR studies of phospholipid bilayers.[46,47] *C*-Perdeuterated *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).[48,49] A patent exists for point-deuteration of the *myo*-inositol ring in PtdInsP_n, however, no further literature using these molecules is available.[50] Currently, only one large-scale chemical method exists for the perdeuteration of *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.[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 PtdInsP_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.[3] 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.[46,47] Once hydrolysed by PLC, the Ins(1,4,5)P_3 **11** 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 **11**. 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 occuring ^{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 Amelié Joffrin (Conway Group, University of Oxford) was also underway to produce deuterated PtdIns4P **15**.[51]

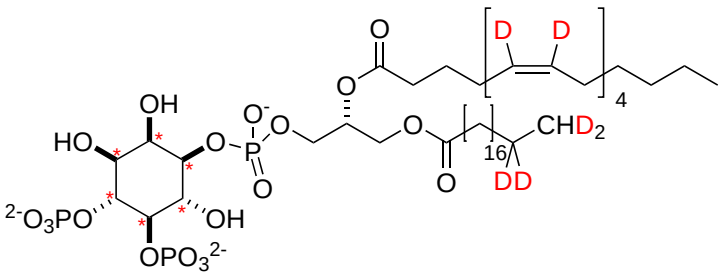
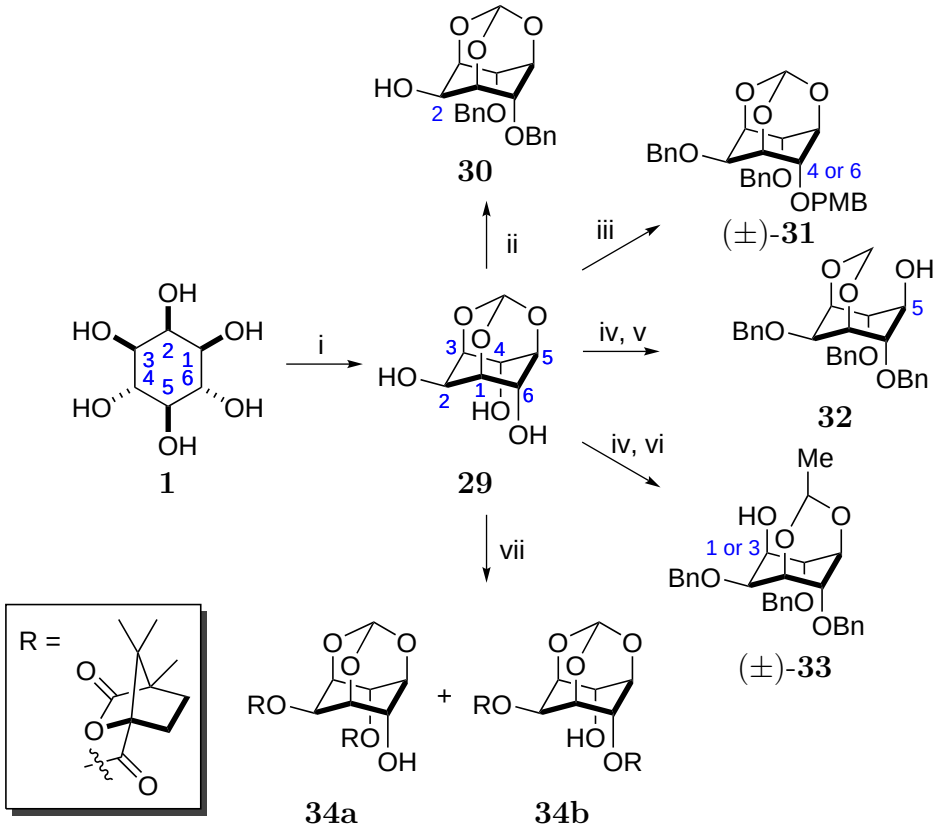


Figure 1.9 The planned sites of deuterium incorporation into PtdIns(4,5)P_2 **28**, highlighted in red.

1.4 Previous Synthesis of *myo*-Inositol Derivatives

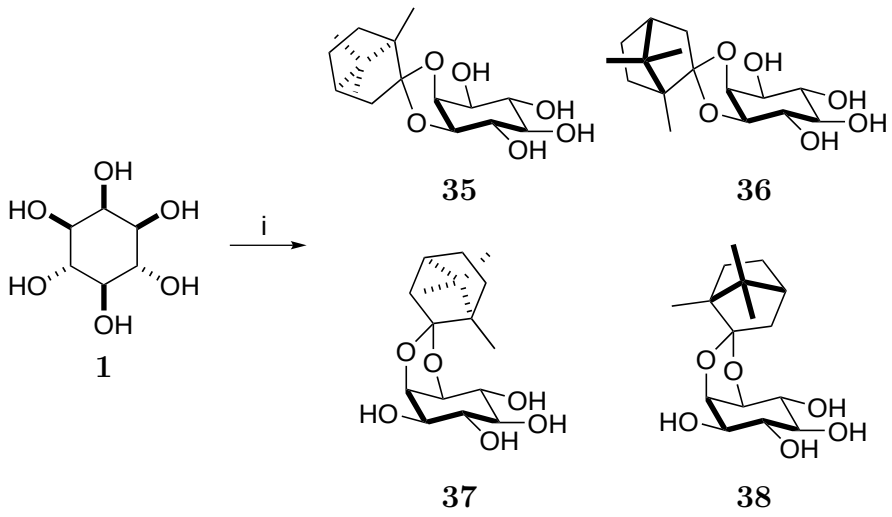
1.4.1 Syntheses from *myo*-Inositol

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 Examples of selective protection of *myo*-inositol systems *via* the orthoformate derivative **29**.[41,52,53] *Reagents & conditions*: i. $CH(OEt)_3$, *p*TSA, DMF, reflux, 83%;[52] ii. NaH, BnBr, DMF, 68%;[52] iii. NaH, PMBCl, DMF then NaH, BnBr, DMF, 65%;[41] iv. NaH, BnBr, DMF, 50%;[41] v. DIBAL-H, CH_2Cl_2, hexanes, 96%;[41] vi. Me_3Al, CH_2Cl_2, hexanes, 78%;[41] (–)-(1*S*)-camphanic acid chloride, 4-dimethylaminopyridine, NEt_3, CH_2Cl_2, 1 h, 60% ((–)-**34a**), 20% ((+)-**34b**).[53]

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.[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).[41,52] Furthermore, selective opening of the orthoester can differentiate between the 1-, 3- and 5-positions, making this intermediate very powerful.[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).[53]



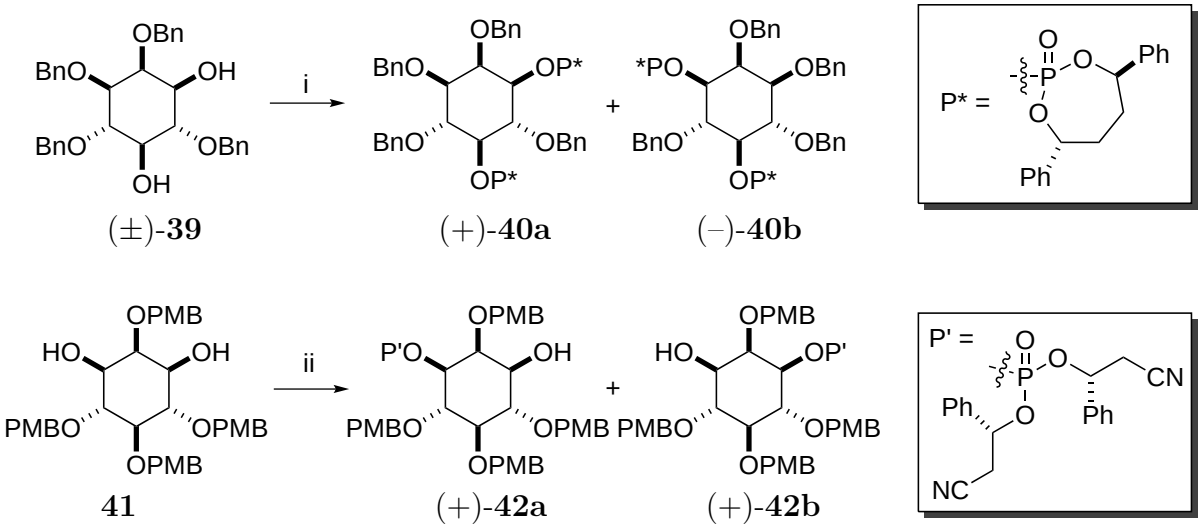
Scheme 1.3 Chiral derivatisation by Bruzik *et al.* using a camphor acetal led to four separable diastereomers, allowing optically active *myo*-inositol derivatives to be synthesised.[56] *Reagents & conditions*: i. D-Camphor dimethylacetal, TMSOTf, DMSO, reflux, 31% (**35**).[56]

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).[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).[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.[56] 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.[56] In this manner, some of the first enantioselective syntheses of InsP_n were achieved.[56]

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.[58–60] 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).[58] 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.[59,60] 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.[59,60]



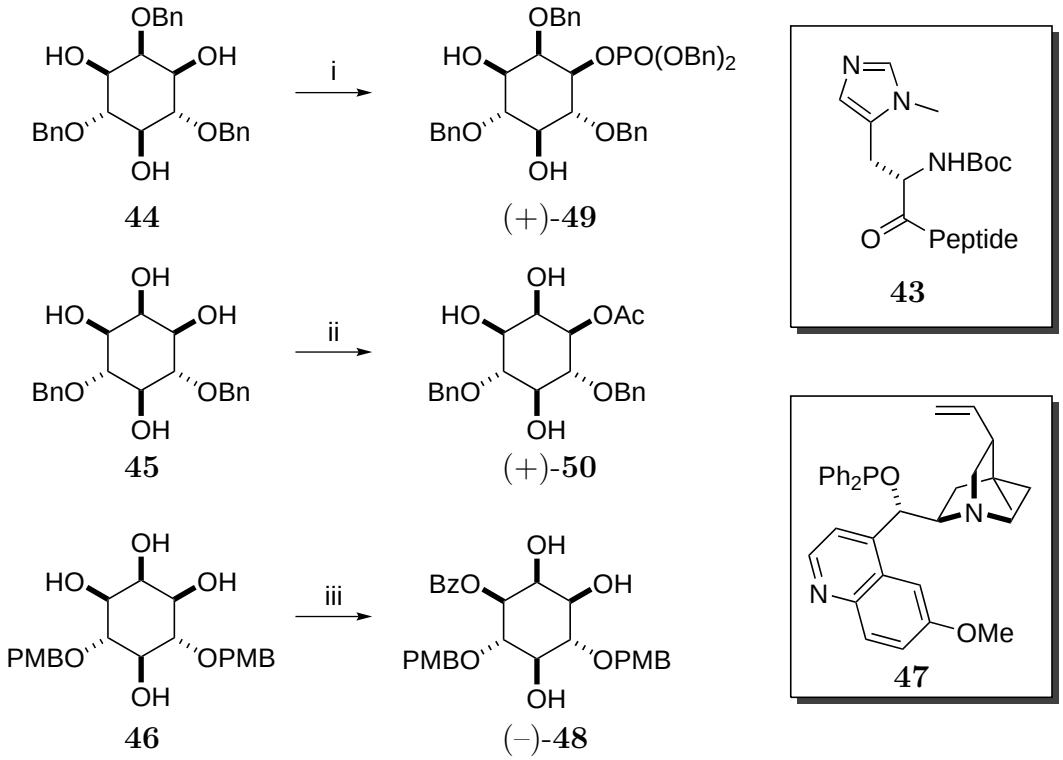
Scheme 1.4 Two examples of using chiral protecting groups on the phosphorus group to allow for separation of diastereomers of *myo*-inositol derivatives.[58,59] *Reagents & conditions*: i. Phosphoramidite, 1*H*-tetrazole, $CHCl_3$, 20 h then *m*CPBA, 1 h, 11-52%; ii. Phosphoramidite, 5-(*p*-F-phenyl)-1*H*-tetrazole in MeCN 1 h then *m*CPBA, 1 h, 13%.

Enantioselective Synthesis from *myo*-Inositol

Diastereomeric resolution of *myo*-inositol **1** using chiral auxiliaries is possible, however, enantioselective synthesis starting from *myo*-inositol derivatives is less common. Jordan *et al.* developed peptidic organocatalysts such as **43** (Scheme 1.5) to selectively phosphorylate the 1-position over the 3-position in **44**, presumably by generating a chiral pocket around *myo*-inositol in a similar manner to enzymes.[61] While an elegant piece of work, synthesis of the required peptides is not trivial and each *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 (> 90% yield and > 99% e.e.), however, only one of the two enantiomers can be generated.[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.[62] There are also limitations on which protecting groups may be incorporated. Lauber *et al.* showed organocatalysis to be a possibility on *myo*-insoitol 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.[51,63]

Limitations of *myo*-Inositol as a starting point

There are limitations in our case to starting with *myo*-inositol **1** to synthesised deuterated *myo*-inositol derivatives. A key aspect of the project was to develop an efficient, short and enantioselective synthesis of PtdIns(4,5)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 *myo*-inositol **1** that could be used on large scale (discussed in detail in section 1.5).[48] It was prudent, therefore, to consider other methods for generating enantiopure *myo*-inositol derivatives from different starting points other than *myo*-inositol.

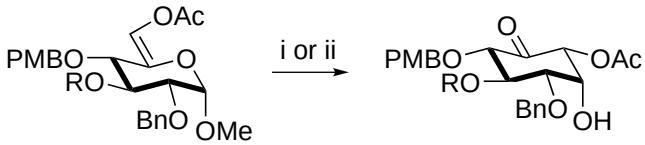


Scheme 1.5 Enantioselective synthesis of optically pure *myo*-inositol derivatives has been shown to be possible using peptides, enzymes and organocatalysts.[61–63] *Reagents & conditions*: i. $ClPO(OBn)_2$, NEt_3, PhMe, **43**, 65%; ii. Lipozyme TP-IL, vinyl acetate, 99%; iii. BzCl, DIPEA, **47**, propionitrile, 99%.

1.4.2 Syntheses from Other Starting Points

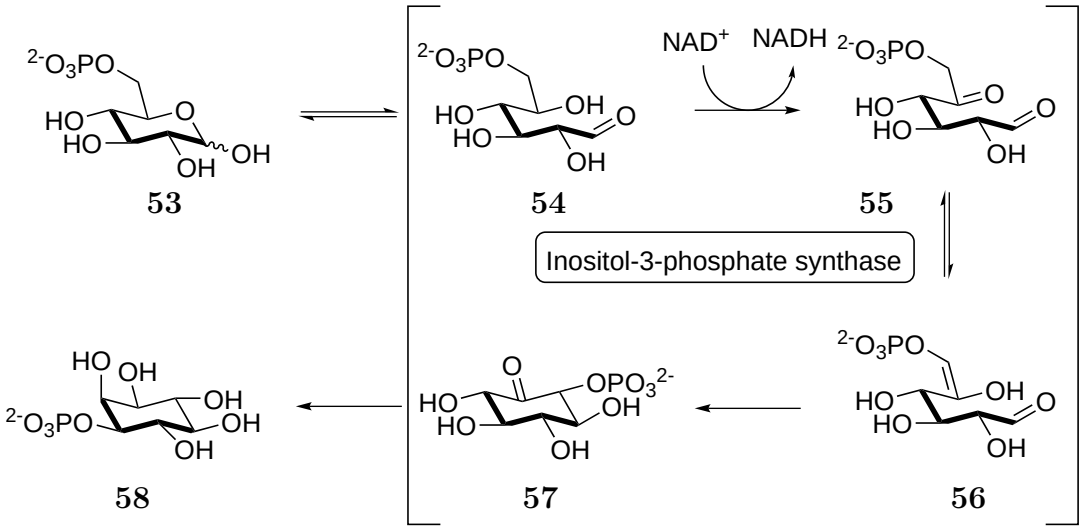
Many investigators have discussed routes to optically enriched *myo*-inositol derivatives starting from both achiral and chiral precursors, cyclic and acyclic.[64–67] By careful consideration of the different starting points, a robust route to deuterated *myo*-inositol derivatives should be achievable.

Ferrier Rearrangements of Glucose



R = PMB (–)-**51a** R = PMB (–)-**52a**
R = TIPS (–)-**51b** R = TIPS (–)-**52b**

Scheme 1.6 Two examples of the synthesis of *myo*-inositol derivatives *via* a Ferrier rearrangement.[66,68] Reagents & conditions: i. $PdCl_2$, dioxane, H_2O, 60 °C, 6 h; ii. $Hg(OAc)_2$, acetone, H_2O then 35% aq. NaCl.



Scheme 1.7 Biosynthetic pathway proposed by Barnett *et al.* for the interconversion of D-glucose-6-phosphate **53** into D-*myo*-inositol-3-phosphate **58** by inositol-3-phosphate synthase.[69,70]

Many groups, including our own, have used a synthetic route that takes inspiration from the natural source of *myo*-inositols 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]

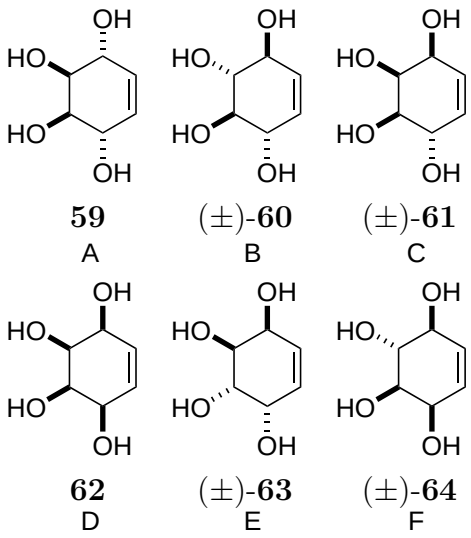
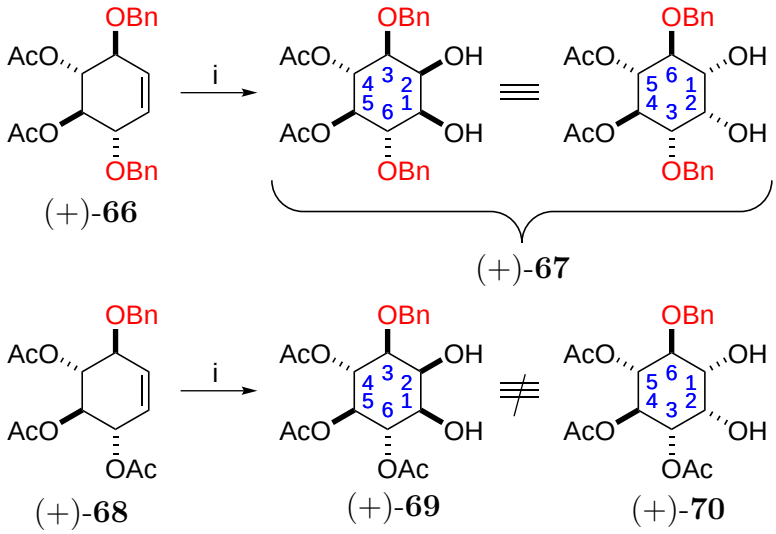


Figure 1.10 Family of six conduritols based on cyclohex-5-ene-1,2,3,4-tetraol with varying relative stereochemistry - only two are found in nature (A and B): Conduritol A (**59**), Conduritol B ((±)-**60**), Conduritol C ((±)-**61**), Conduritol D (**62**), Conduritol E ((±)-**63**), Conduritol F ((±)-**64**). Conduritol B (±)-**60** can be oxidised to give *myo*-inositol derivatives.[74–76]

As with inositol derivatives, they can be found in a number of naturally derived products.[77] 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.*.[75,76] 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.[75] Non-symmetric conduritol B derivatives can also be used, however, a mixture of isomers may be produced upon *syn*-dihydroxylation (Scheme 1.8).[76] There are a number of enantioselective syntheses of conduritol B derivatives (Scheme 1.9, Scheme 1.10).[64,67,78,79]

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

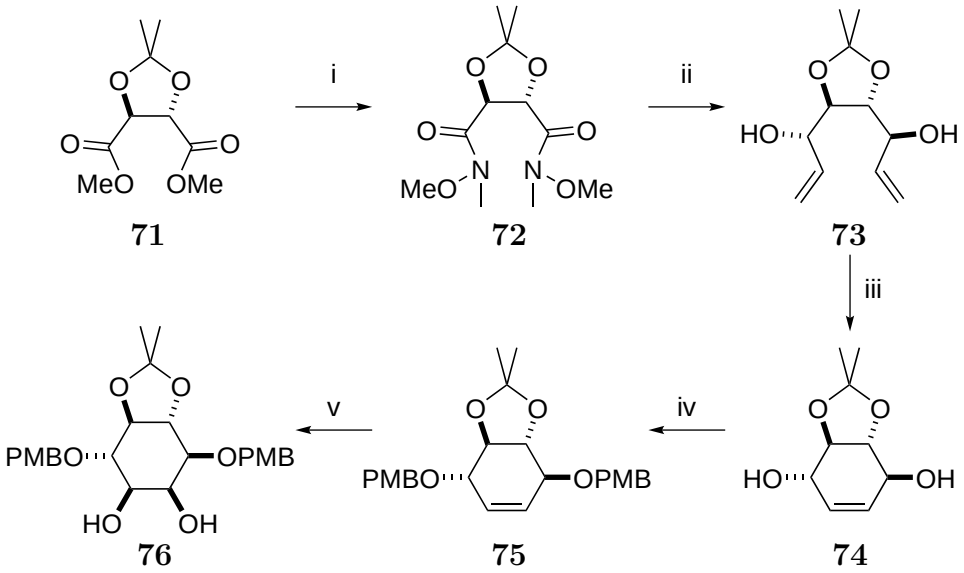


Scheme 1.8 When a non-symmetric conduritol B derviative ((+)-**68**) undergoes a *syn*-dihydroxylation, two different isomers ((+)-**69** and (+)-**70**) are formed, while with a C_2 symmetric conduritol B ((+)-**66**), only one product is produced ((+)-**67**). *Reagents & conditions*: i. $RuCl_3{\cdot}H_2O$, $NaIO_4$, H_2O, MeCN, 8 min, 99%.[75]

for synthesising conduritol B and *myo*-inositol derivatives (Scheme 1.9).[78] 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).[78] 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*-dihydoxylation to give **76**.[78,80] This route is similar to Hyldtoft's zinc-mediated ring-closing metathesis, which started from carbohydrates.[80] It was hypothesised that deuterated PtdIns(4,5)P_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_4 derivatives, not the D_6 desired, as there was no obvious manner in which to produce D_3-vinylmagnesium bromide, or to subsequently deuterate the two alkene positions at a later stage.

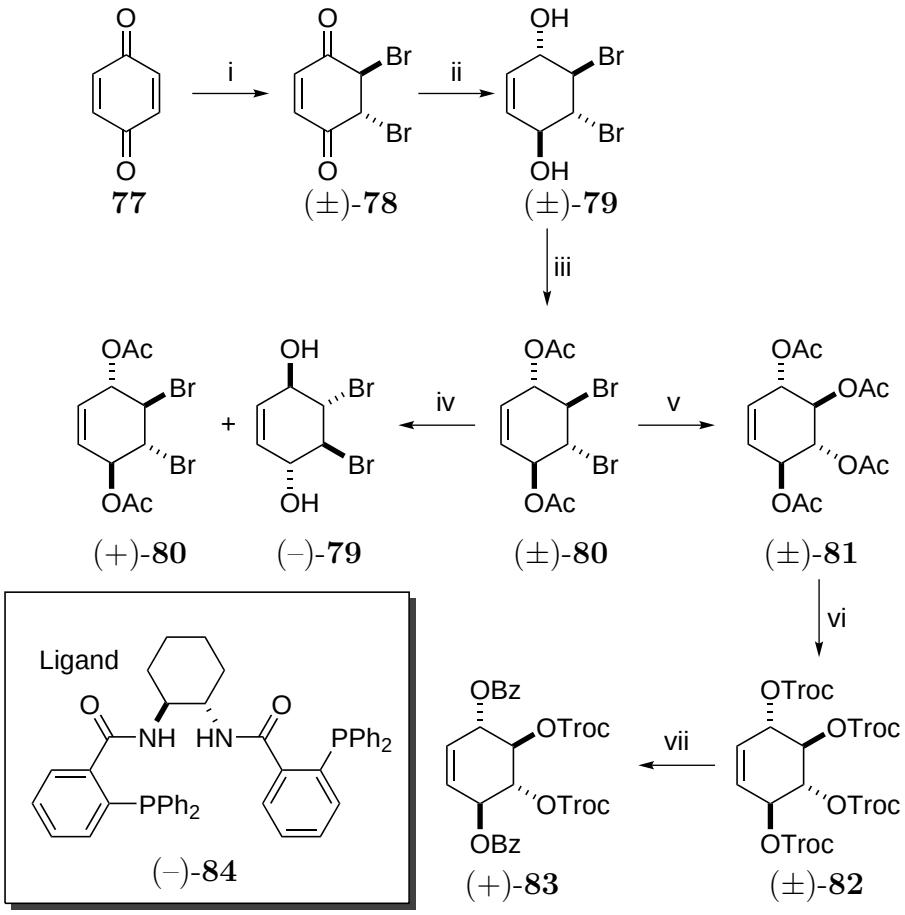
Asymmetric Syntheses of Conduritol B Derivatives

Many groups have used *p*-benzoquinone **77** as a start point for producing conduritol B derivatives and, as an achiral precursor, there have been many attempts to gener-



Scheme 1.9 Synthesis of *myo*-inositol derivatives **76** from commercially available, optically pure tartarate derivatives **71**.[78] *Reagents & conditions*: i. $CH_3NHOCH_3{\cdot}HCl$, $AlMe_3$, CH_2Cl_2, –10 ℃; ii. Vinylmagnesium bromide, THF, –78 ℃ to –5 ℃ then $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, –78 ℃; iii. Grubbs cat. 2nd generation, CH_2Cl_2, reflux; iv. PMBCl, $BnEt_3N^+Cl^-$, 50% aqueous KOH, toluene, 50 ℃; v. K_2OsO_4, K_2CO_3, $K_3Fe(CN)_6$, methanesulfonamide, quinuclidine, ^{t}BuOH, H_2O.

ate optically pure conduritol B derivatives from **77**.[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).[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).[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).[64,81] This route from Trost *et al.* had high potential for efficient synthesis of deuterated PtdIns(4,5)P_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_3 **11** using this methodology. As such, this approach was chosen to be the focus for generating single enantiomers of *myo*-inositol derivatives.[64] Despite the potential of this reaction in the synthesis of conduritol B and *myo*-inositol derivatives, the kinetic resolution of (±)-**81** had only been reported twice in



Scheme 1.10 Examples of enantioselective synthesis of conduritol B derivatives found in the literature starting from *p*-benzoquinone.[64,79–81] *Reagents & conditions*: i. Br_2, $CHCl_3$, 0 ℃, 1 h; ii. $NaBH_4$, Et_2O, H_2O, 0 ℃, 1 h; iii. Ac_2O, pyridine, 12 h, 61% over three steps; iv. Pig pancreas lipase, 0.1 M phosphate buffer, Et_2O, 4 days, 26% ((+)-**80**), 47% ((−)-**79**); v. KOAc, reflux, 3 days, 57%; vi. NEt_3, MeOH, H_2O, 1 h, then TrocCl, pyridine, DMAP, CH_2Cl_2, 1 h, 90%; vii. BzOH, (*S,S*)-ligand (−)-**84**, tetrahexylammonium bromide, $[Pd(\eta^3\text{-allyl})Cl]_2$, CH_2Cl_2, 1 M aqueous NaOH, 18 h, 80%.

the literature subsequent to the original publications and not the DKR.[65,84]

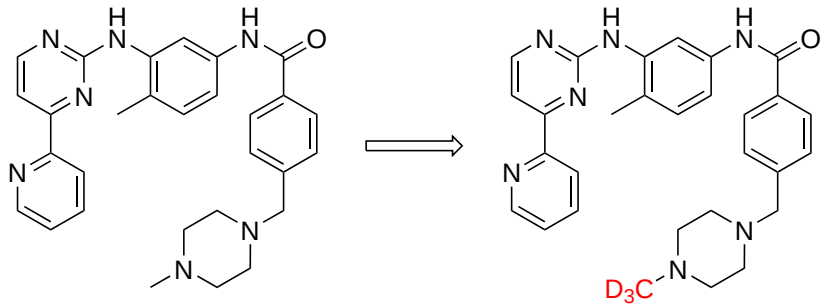
1.4.4 Previous Syntheses of PtdInsP_n

There have been multiple previous syntheses of PtdIns(4,5)P_2 **10** and related compounds, both with saturated (typically stearoyl or palmitoyl) and unsaturated (typically arachidonic) chains attached to the glycerol group.[3,41,85–90] The challenge with PtdInsP_n, as compared to InsP_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 PtdInsP_n derivatives rely heavily on the use of benzyl groups as a protecting group strategy.[3,41,90] This is due to the fact that hydrogenolysis of the benzyl groups is traceless,

removing the need to purify the final PtdInsP_n. 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]

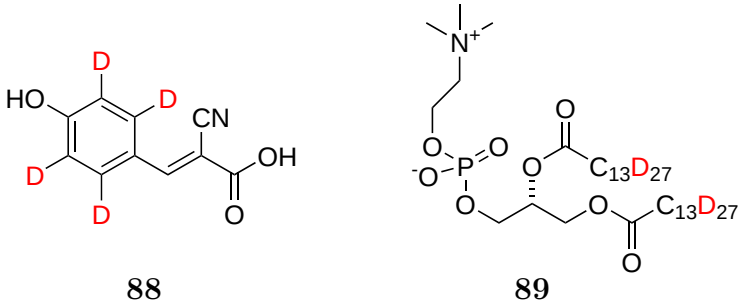


86 **87**

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.[93] 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.[94] 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.[47,95] 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**).[94,95]

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 *cf.* hydrogen due to the increased mass. This is observed by the shift in the ^{13}C NMR for carbon atoms attached to deuterium *vs* hydrogen, both when the deuterium atom is attached (α) or neighbouring (β) 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 *ca.* 7 times slower than the same process with hydrogen, while a secondary effect (SKIE) can be observed of *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.

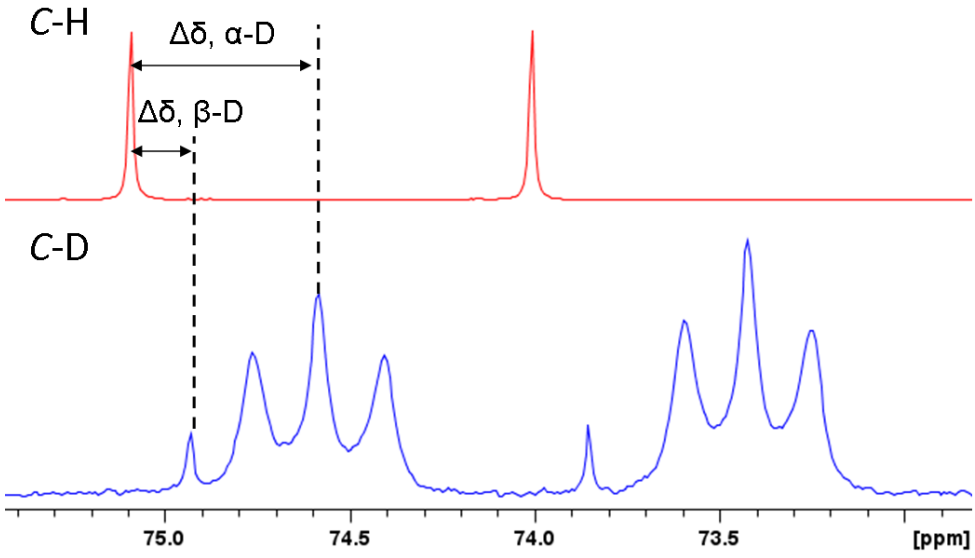
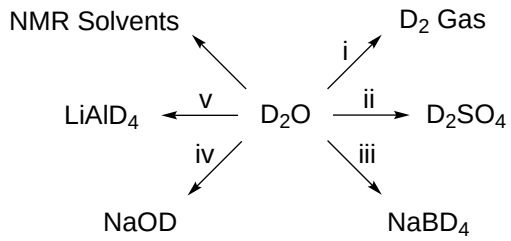


Figure 1.12 ^{13}C NMR of protonated (top, red) and deuterated (bottom, blue) versions of the same molecule, showing the shift upfield when deuterium is incorporated *vs.* when a proton is attached to the secondary carbon atoms (indicated by $\Delta\delta$). There is also an effect on the carbon atom when the D atom is β to the carbon, rather than α. This is caused by the small decrease in shielding of the carbon by the more electropositive deuterium atom.



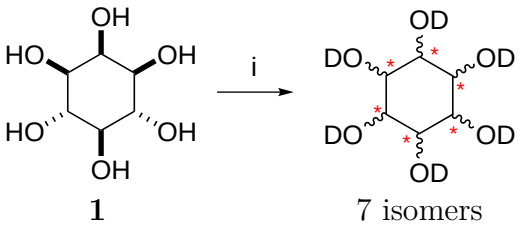
Scheme 1.12 Examples of deuterated reagents available commercially for producing deuterated compounds. The source of all deuterium reagents is D_2O, produced *via* the Girdler-Sulfide process. *Reagents & conditions*: i. Electolysis;[96] ii. Sulfur trioxide;[97] iii. $BH_3{\cdot}NMe_3$, D_2SO_4 then Na metal;[98] iv. Na metal; v. D_2 gas, lithium metal then $AlBr_3$.[99]

The primary source of all deuterium reagents is D_2O, isolated through the Girdler-Sulfide process.[100] The majority of D_2O is used in nuclear reactors as a neutron damper, however, the chemical industries are beginning to become more prevalent users, especially the pharmaceutical industry. Through chemical manipulation, D_2O can be made into a variety of useful reagents, typically NMR solvents, but also reactive species such as $NaBD_4$ or D_2SO_4 (Scheme 1.12). There has also been a move toward electrolysis of D_2O to produce D_2 gas and with the increasing use of equipment such as H-Cube®, convenient *in situ* production of D_2 gas for incorporation into organic molecules with high deuterium enrichment is possible.[96,101] Due to the relatively high expense of D_2O, other deuterated reagents are generally very expensive to produce and it is difficult to keep the enrichment high during chemical synthesis. Subsequent reactive steps during the synthesis of complex deuterated molecules must be chosen such that the incorporation is not diminished.

1.5.2 Previous Synthesis of D_6-*myo*-Inositol

There are few previous examples of D_6-*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 *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 *myo*-inositol **1** (Scheme 1.13).[48] While only taking one step to form **90** in high enrichment

(98-99% D_6 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.[103] 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).[48,49,103] This significantly limits the chemical synthesis of deuterated *myo*-inositol derivatives starting from D_6-*myo*-inositol **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.



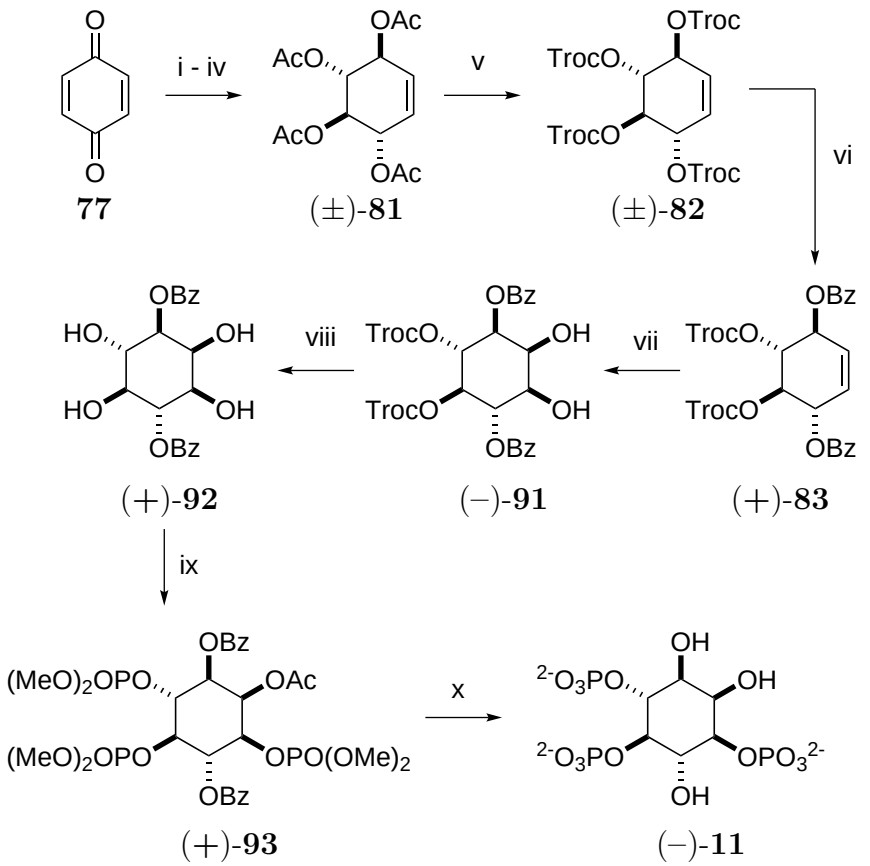
Scheme 1.13 Synthesis of D_6-*myo*-inositol **90** from *myo*-inositol **1** was described by Sasaki *et al.*, however, it was difficult to separate the isomers formed requiring multiple ion-exchange chromatography runs and crystallisations, resulting in low yields and purity.[48] A red asterisk indicates a carbon atom attached to deuterium. *Reagents & conditions*: i. Raney-Ni, D_2O, 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)P_2 **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



Scheme 1.14 Synthesis of Ins(1,4,5)P_3 (–)-**11** as described by Trost *et al.* utilising a palladium catalysed allylic alkylation.[64] *Reagents & conditions*: i. Br_2, $CHCl_3$; ii. $NaBH_4$, Et_2O, H_2O; iii. Ac_2O, K_2CO_3; iv. AcOH, 35% over four steps; v. NEt_3, H_2O, MeOH then TrocCl, DMAP, pyridine, CH_2Cl_2, 90%; vi. BzOH, tetrahexylammonium bromide, (–)-(1*S*,2*S*)-1,2-bis[*o*-(diphenylphosphanyl)benzoylamino]cyclohexane (–)-**84**, [Pd(η^3-allyl)Cl]$_2$, 1 M NaOH, CH_2Cl_2, 85%; vii. OsO_4, NMO, quinuclidine, CH_2Cl_2, 83%; viii. Zn, AcOH, THF, 89%; ix. $(MeO)_2PCI$, $i Pr_2NEt$, DMF, then AcCl, DMAP then H_2O_2; x. 30% HBr/AcOH then LiOH or KOH.

produce a single enantiomer.

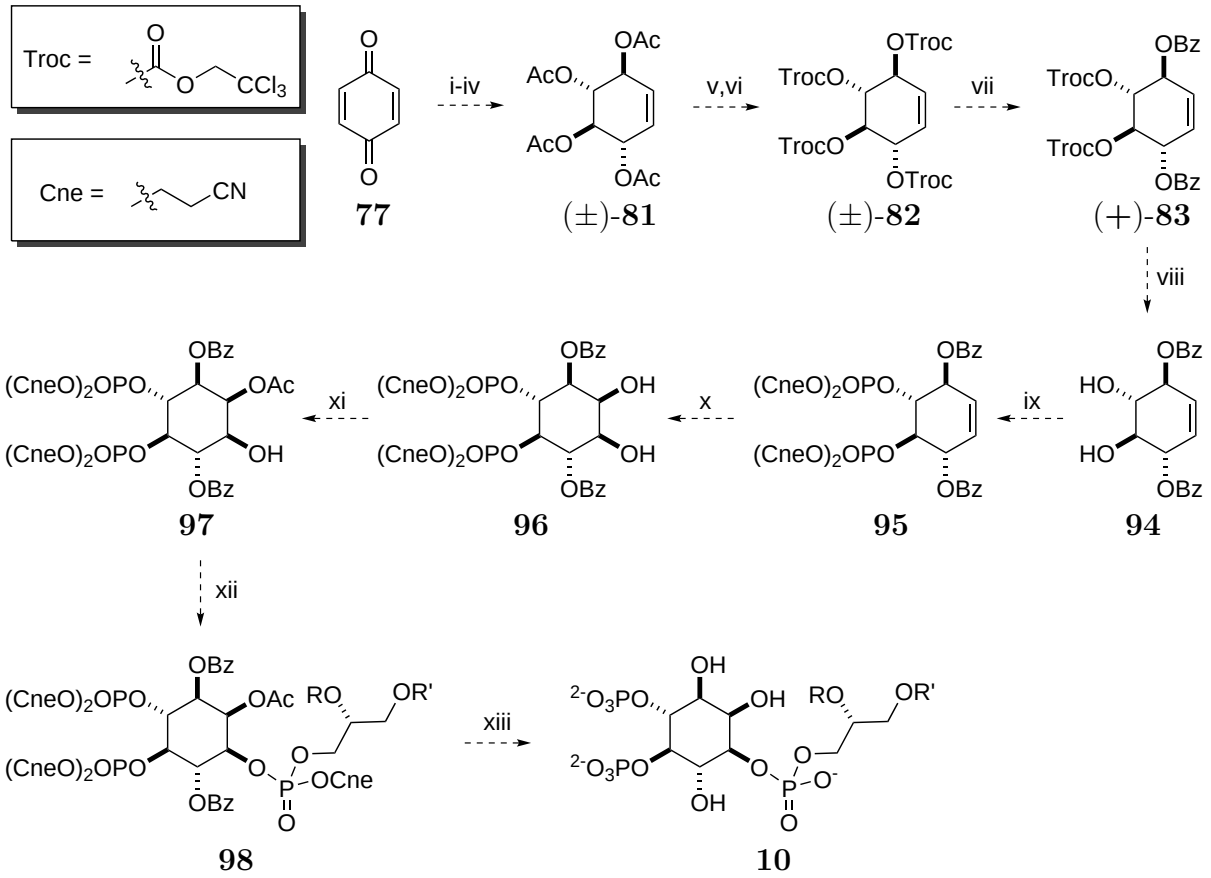
3. A protecting group strategy that allowed for the use of unsaturated lipid chains in PtdIns(4,5)P_2 **10** such as arachidonic acid.

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)P_3 (–)-**11** in an asymmetric manner, as well as related aminocyclitols (Scheme 1.14).[64,81] 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.[75] 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.[75] 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



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.[64,75] 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_2O, H_2O; iii. Ac_2O, K_2CO_3; iv. AcOH, reflux; v. NEt_3, MeOH, H_2O; vi. TrocCl, pyridine, 4-dimethylaminopyridine, CH_2Cl_2; vii. Benzoic acid, (*S,S*)-ligand (–)-**84**, tetrahexylammonium bromide, [Pd(η^3-allyl)Cl]$_2$, 1 M aqueous NaOH, CH_2Cl_2; viii. Zn, AcOH, THF; ix. Phosphoramidite, 1*H*-tetrazole in MeCN, CH_2Cl_2 then *m*CPBA; x. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, H_2O; xi. $CHC(OEt)_3$, *p*TSA, THF then 80% *v/v* aqueous AcOH; xii. Phosphoramidite, 1*H*-tetrazole in MeCN, CH_2Cl_2 then *m*CPBA; xiii. Basic hydrolysis e.g. NaOH, NEt_3 or LiOH.

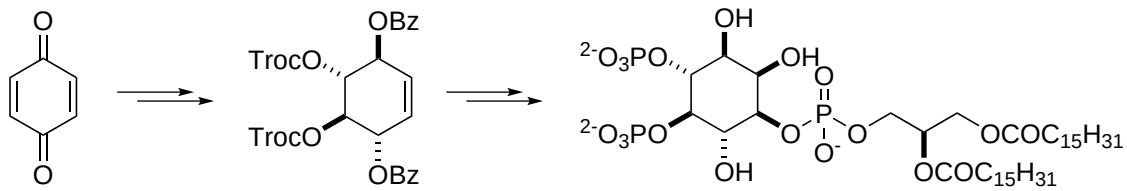
clean deprotection by 30% HBr/AcOH.[64] This had been previously described by Meek *et al.*[104] Methyl phosphate esters are relatively unstable and it was thought a more stable protecting group would be easier to work with. Benzyl esters have typically been used in phosphatidylinositol phosphate synthesis, 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.[105–107] They are base-labile *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).[64,81]



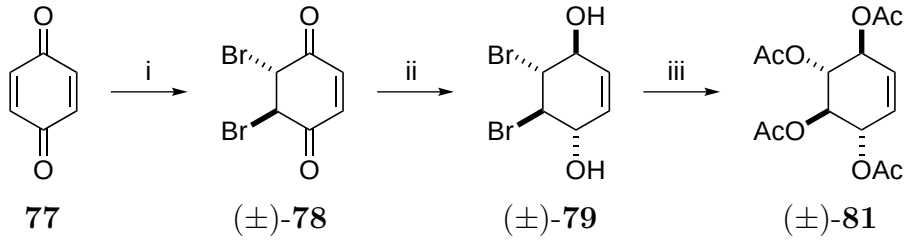
77 (+)-**83** (−)-**10**

Scheme 2.1 General scheme to generate enantiopure PtdInsP_2 **10** from *p*-benzoquinone.

2.2 Synthesis of Conduritol B Derivatives

2.2.1 Synthesis of Conduritol B tetracetate

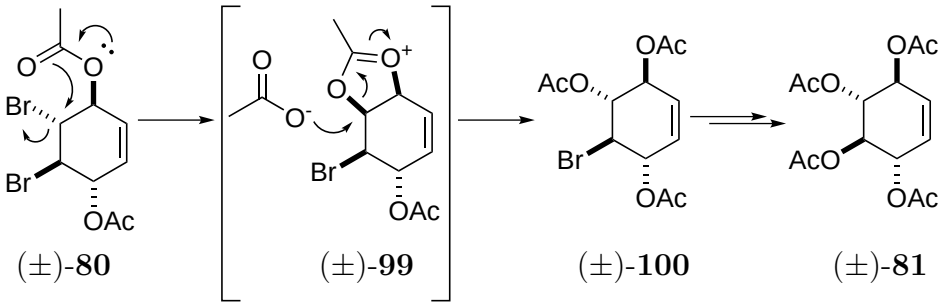
The racemic synthesis of conduritol B derivatives has been well documented.[67,75,82,108,109] Starting from *p*-benzoquinone, a modification of the method from Guo *et al.* was used to synthesise (±)-**81** (Scheme 2.2).[64,81,82] Bromination of **77** proceeded well within an hour at 0 ℃ with no further purification required.[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_2O/H_2O) reduction with $NaBH_4$ led to (±)-**79**, which was also found to be unstable during crystallisation and column chromatography, with both methods resulting in epoxide formation.[110] Early attempts and literature reports of the reduction utilised 2.5 equivalents of $NaBH_4$ (relative to **77**), however, after some optimisation, it was found that 1.0 equivalents of $NaBH_4$ was sufficient for complete reaction to be observed.



Scheme 2.2 Synthesis of the tetracetate (±)-**81** from *p*-benzoquinone **77**. *Reagents & conditions*: i. Br_2, $CHCl_3$, 0 ℃, 1 h; ii. $NaBH_4$, Et_2O, H_2O, 0 ℃, 1 h; iii. Ac_2O, K_2CO_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 *et al.*[64] The two hydroxyl groups on (±)-**79** were acetylated using acetic anhydride and K_2CO_3, followed by direct addition of acetic acid to the mixture, and heating under reflux for three days.[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 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.[74]

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).[76] This is in contrast to a *cis-trans-cis* configuration, which is the product observed when wet acetic acid is used (Woodward product).[111] 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 cystals 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-

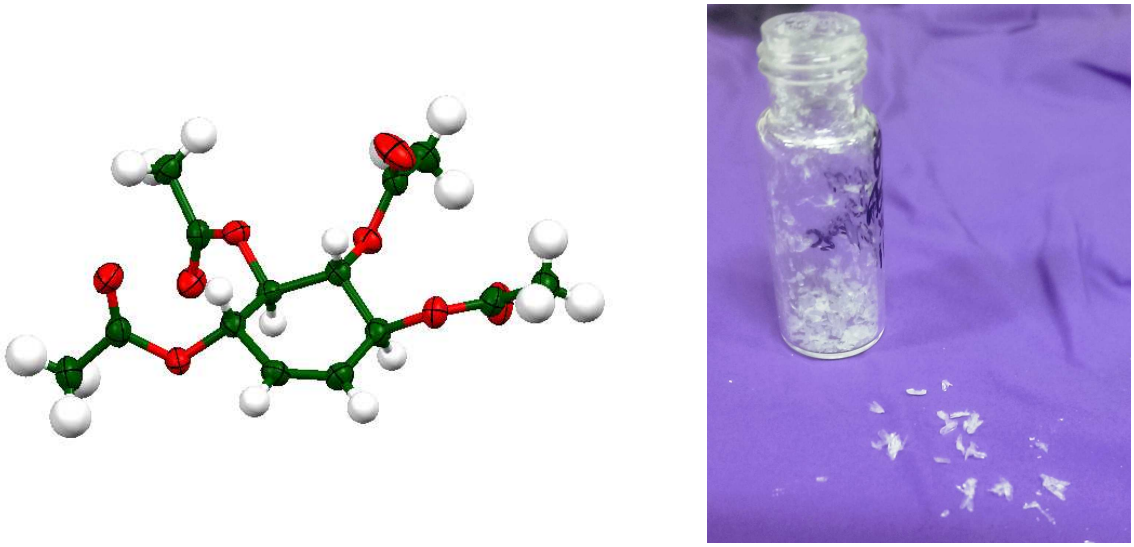


Figure 2.1 A crystal structure of (±)-**81**, right, was obtained by Prof. Richard Cooper, Chemical Crystallography Lab Oxford, from the crystals show in the image on the right.

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).[112] 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.

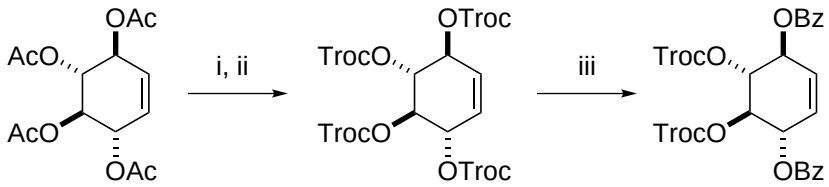
Crystal	Average Measured Rotation	Concentration / (mg mL^{-1})	Specific Rotation / 10^{-1} ° cm^2 g^{-1}
1	-0.009	0.4	–22.5
2	+0.003	0.5	+6.0
3	+0.025	1.1	+22.7
4	+0.003	1.2	+2.5
5	+0.003	1.0	+3.0

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.[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.[113,115]

2.3 Trost Asymmetric Allylic Alkylation

2.3.1 Initial Reproduction

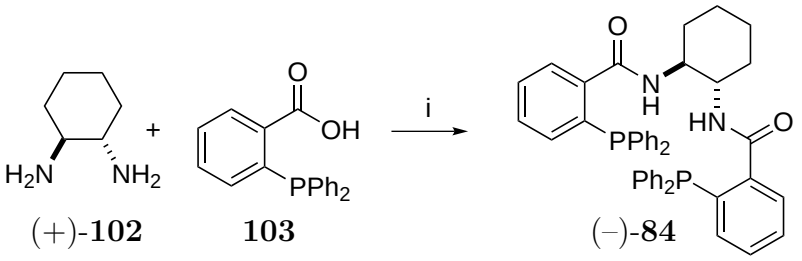
Once the synthesis of (±)-**81** was established, efforts began to generate a single enantiomer from the racemate, using palladium-catalysed chemistry. The tetracetate (±)-**81** had been shown to participate in an asymmetric allylic alkylation (AAA), leading to a kinetic resolution in which one enantiomer reacted with a nucleophile, while the other enantiomer remained unreacted.[64] The two products could then be separated by column chromatography. Trost *et al.* have also shown that changing the acetates to either methylcarbonates or 2,2,2-trichloroethylcarbonates (Troc) effected a dynamic kinetic resolution (DKR).[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 (*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.



(±)-**81** (±)-**82** (+)-**83**

Scheme 2.4 Synthesis of an enantiomerically pure derivative (+)-**83**, a useful derivative for the synthesis of inositols. *Reagents & conditions*: i. NEt_3, H_2O, MeOH, 1 h; ii. $ClCO_2CH_2CCl_3$, DMAP, pyridine, CH_2Cl_2, 20 min, 88% (2 steps); iii. BzOH, tetrahexylammonium bromide, $[Pd(\eta^3\text{-allyl})Cl]_2$, (−)-**84**, 1 M aqueous NaOH, CH_2Cl_2, 81%, > 99% e.e.

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).



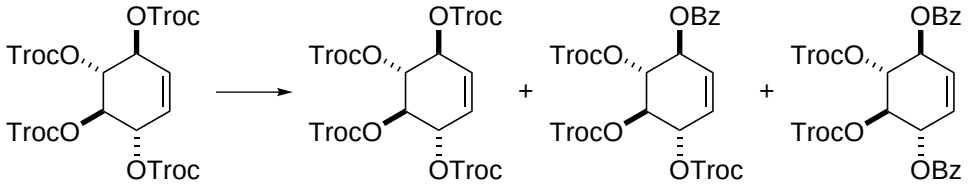
(+)-**102** **103** (–)-**84**

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, CH_2Cl_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 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_2Cl_2 (except in entries 5 & 6 where 6.0 mL CH_2Cl_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 aqueous phase was degassed by freeze/thaw methods with Argon; [e] Both phases were degassed by freeze/thaw methods with Argon; [f] The eq. of tetrahexylammonium bromide, ligand (–)-**84** and [Pd(η^3-allyl)Cl]$_2$ were doubled; [g] The reaction was performed on a Schlenk system using N_2.



(±)-**82** (±)-**82** (+)-**104** (+)-**83**

Entry	(±)-**82**	Ligand[a]	Time	Conversion (e.e.)[b]			Yield
	mmol	eq.	h	(±)-**82**	(+)-**104**	(+)-**83**	(+)-**83**
1[c]	0.54	0.075	18	79	21	0	-
2[c]	0.54	0.075	18	54	37	9	-
3[c,d]	0.54	0.075	18	85	15	0	-
4	0.54	0.075	18	0	0	100	36 (> 99)
5	2.25	0.075	18	69	31	0	-
6	2.25	0.075	18	80	20	0	-
7[e]	0.54	0.075	18	21	25	54	-
8[f]	0.54	0.150	18	61	39	0	-
9	0.54	0.150	2.5	0	0	100	57 (> 99)
10[g] (n=2)	0.54	0.150	1	0	0	100	-
11 (n=2)	2.29	0.150	1	0	0	100	81 (> 99)

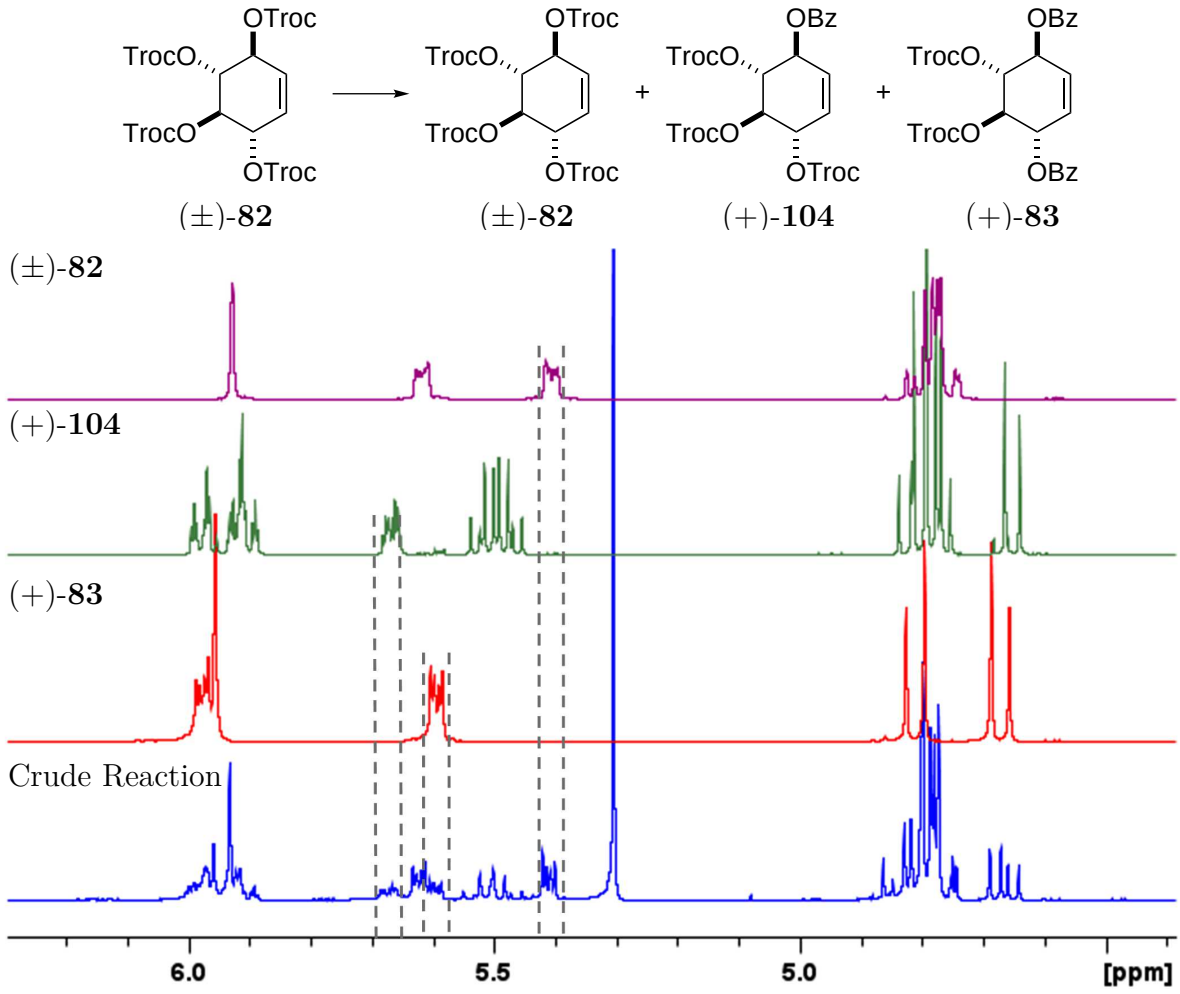


Figure 2.2 Illustration of how conversions were calculated from ^{1}H NMR analysis of reaction mixtures. As the peak highlighted for (+)-**83** (5.6 ppm) overlapped with one from (±)-**82**, the integration of the two peaks together was taken and the integration from the peak highlighted for (±)-**82** (5.4 ppm) was subtracted. Top (purple): (±)-**82**; upper middle (green): (+)-**104**; lower middle (red): (+)-**83**; bottom (blue): example crude reaction mixture, entry 2, Table 2.4.

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

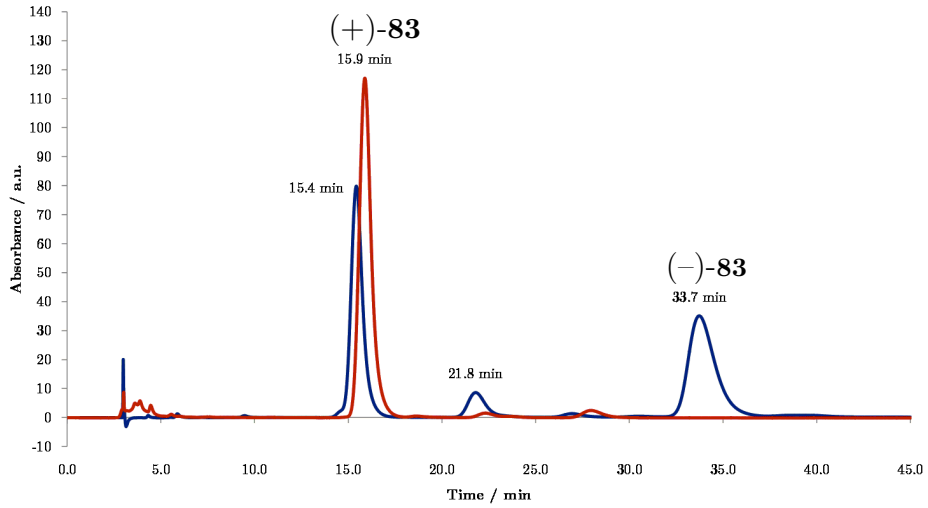
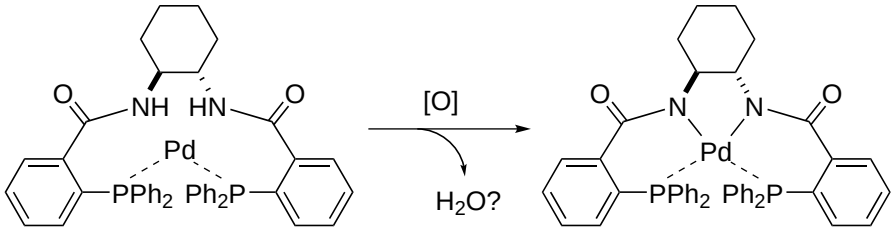


Figure 2.3 Chiral HPLC traces on a ChiralPak® AD-H in 90:10 heptane/isopropanol of the single enantiomer (+)-**83** (red) compared to a sample of racemic (±)-**83** (blue) prepared using triphenylphosphine. For comparison, the retention time reported by Trost *et al.* was 13.1 min for (+)-**83** while for (−)-**83**, the retention time was reported as 29.1 min using the same conditions on a ChiralPak® AD column.

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



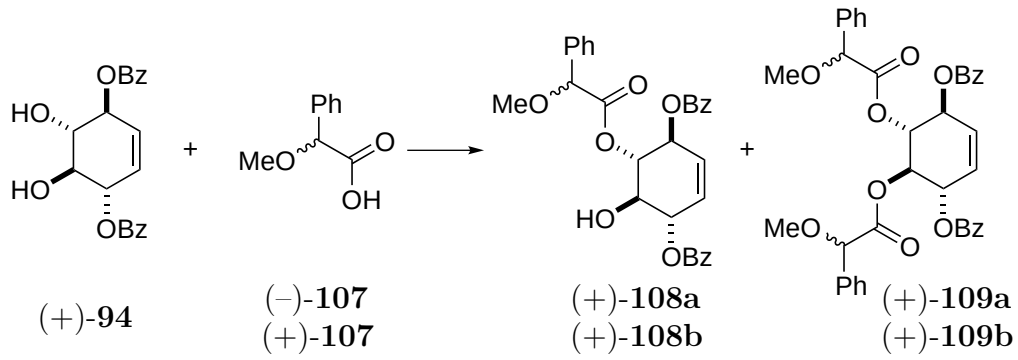
105 **106**

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 $[Pd(\eta^3\text{-allyl})Cl]_2$, 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]



(+)-**94** (−)-**107** (+)-**107** (+)-**108a** (+)-**108b** (+)-**109a** (+)-**109b**

Scheme 2.7 Derivatisation of (+)-**94** with each enantiomer of α-methoxymethylphenylacetic acid **107** (MPA) gave the mono- (+)-**108** and di-substituted (+)-**109** compounds the could be chromatographically separated for use in ^{1}H NMR studies. *Reagents & conditions*: EDC·HCl, DMAP, CH_2Cl_2, 1 h.

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 to due insignificant differences in electron densities between the two enantiomers.[121] 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 Seco *et al.* showing that various NMR experiments can be used to both calculate the e.e. of compounds and obtain absolute stereochemical assignments.[122] 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.[123] 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 ab-

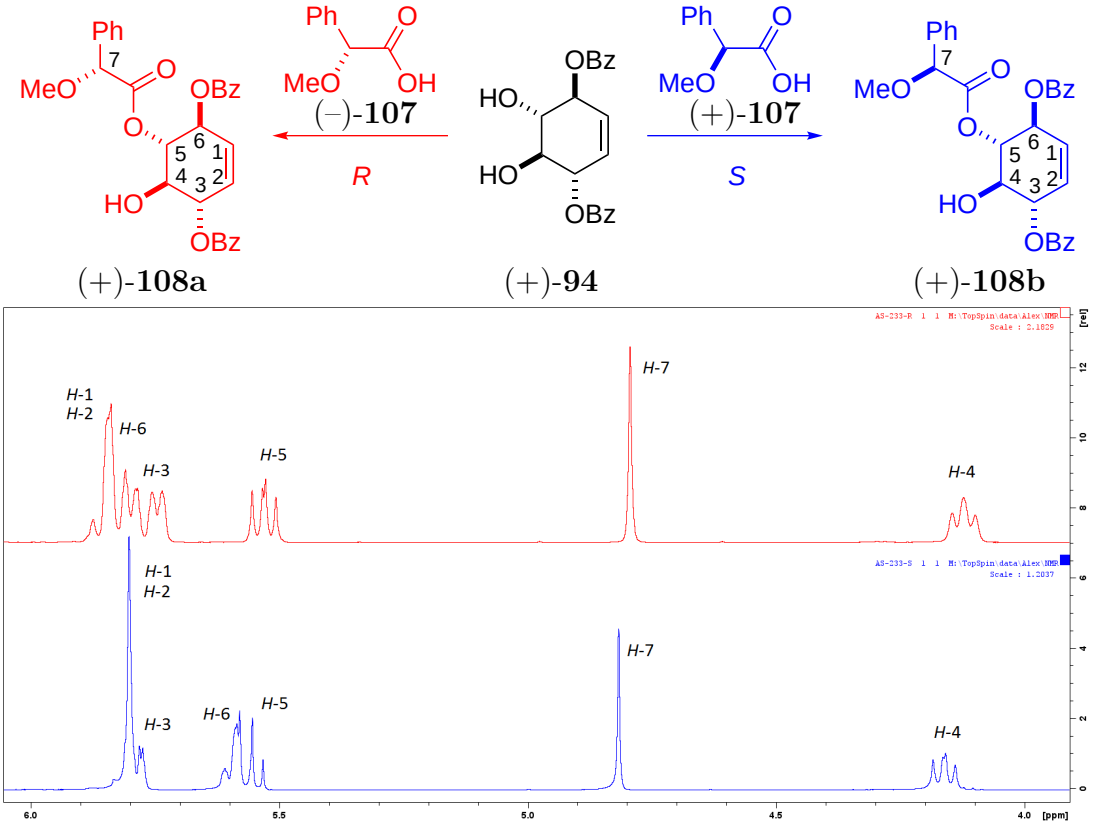


Figure 2.4 Mono-substitution of (+)-**94** with (*R*)- and (*S*)-enantiomers of MPA ((−)-**107** and (+)-**107** respectively) using conditions shown above (Scheme 2.7) gave two diasteromers ((+)-**108a**, red, and (+)-**108b**, blue) that provided different ^{1}H NMR spectra that could be used to determine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

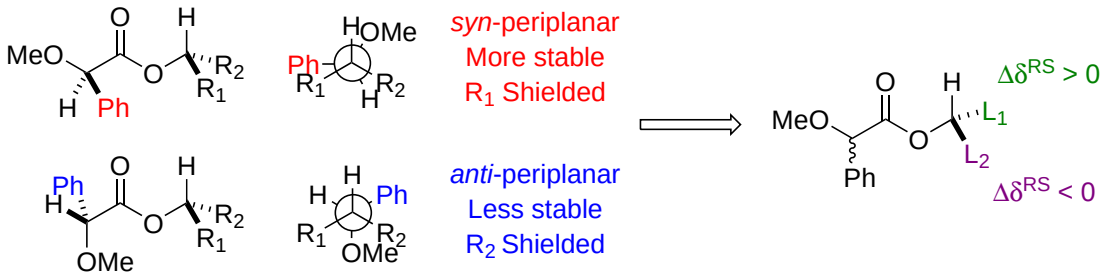
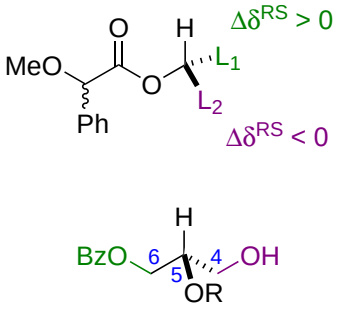


Figure 2.5 Two possible conformations of the MPA esters, *syn*- and *anti*-periplanar. It is well known from computational modelling that the *syn*-periplanar conformer is more stable and is observed on an NMR timescale, enabling the model shown to be derived.[122]

solute 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 α-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-substitued 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 hydoxyl moiety led to the same compound.

Table 2.3 Difference in δ values for the *R* and *S* diastereomers ($\Delta\delta^{RS}$) leads to the assignment of absolute stereochemistry using the model above (Figure 2.5). In cases where multiplets were observed in the ^{1}H NMR spectrum, the center of the peak was determined in combination with COSY, HSQC and HMBC. From this it was possible to show the stereochemistry was as shown, leading to the overall structure of (+)-**94**.

Position	δR **108a**	δS **108b**	$\Delta\delta^{RS}$	L_1 or L_2
1	5.84	5.80	+0.04	L_1
2	5.84	5.80	+0.04	L_1
3	5.74	5.78	–0.04	L_2
4	4.12	4.16	–0.04	L_2
5	5.53	5.56	–0.03	N/A
6	5.80	5.60	+0.20	L_1



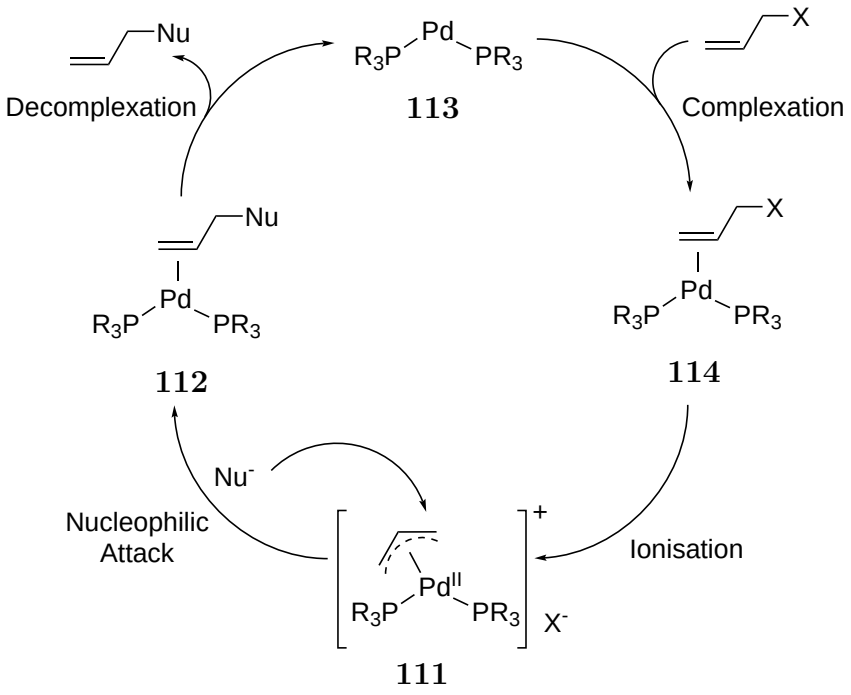
The ^{1}H NMR spectrum of (+)-**108a** and (+)-**108b**, in combination with COSY, HSQC and HMBC experiments, were fully assigned, paying particular attention to correct assignment of the inositol ring (Figure 2.4). From extensive modelling of systems containing a MPA ester, it is well known that the *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 proximty 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 (±)-**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 *myo*-inositol derivatives, it was prudent to understand the scope and limitations of the reaction, especially the increased ligand concentration inmproving 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 η^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 (±)-**82** is

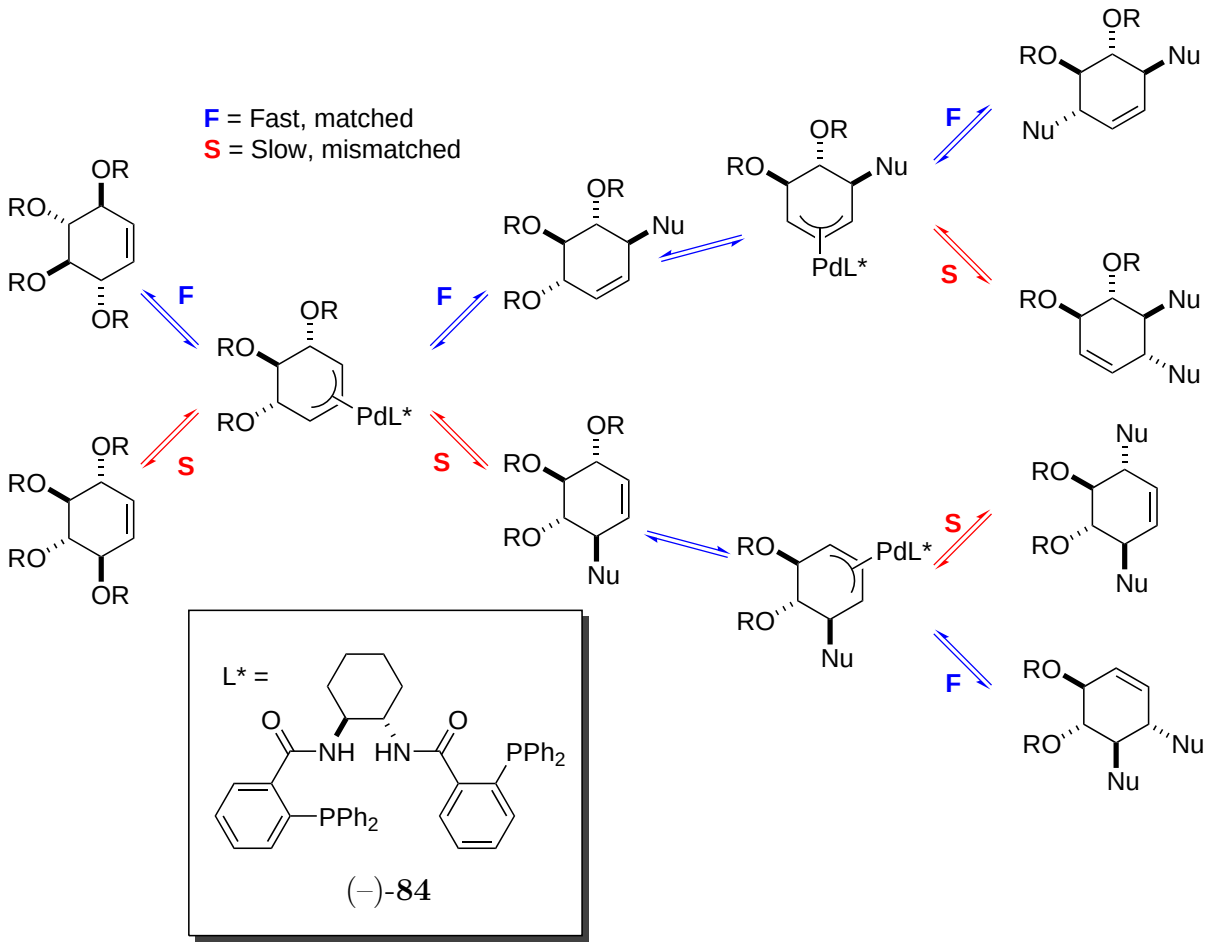


Scheme 2.8 Basic mechanism of the Tsuji-Trost allylic alkylation reaction relying on a shuttling between Pd^0 and Pd^{II} complexes. When 'soft' nucleophiles are used, a Type 2 process is usually observed where the nucleophile attacks the allyl group directly, leading to retention of stereochemistry.[125]

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 η^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.[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.[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.[64] Upon coordination of the double bond in (±)-**82** to a Pd^0 species complexed to ligand, there are two possibilities for ionisation of each enantiomer of (±)-**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.[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).[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.[118] This process then happens a second time, driving a second enantioselective step which leads to the high enantiomeric excesses observed (> 99%).



Scheme 2.9 Mechanism of the Trost asymmetric allylic alkylation, starting from the Pd(0) complex $[Pd(allyl)Cl]_2$. 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 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(η^3-allyl)Cl]$_2$, 0.2 eq. tetrahexylammonium bromide, 1.5 mL 1 M aqueous NaOH and 1.5 mL CH_2Cl_2. [a] (–)-**84**; [b] Conversions were calculated using ^{1}H NMR (see appendix, page 279), e.e. was determined by chiral HPLC; [c] Tetracetate (±)-**81** was used as the starting material.

Entry	(±)-**82**	Ligand[a]	Time	Conversion (e.e.)[b]		
	mmol	eq.	h	(±)-**82**	(+)-**104**	(+)-**83**
1	0.50	0.050	1	100	0	0
2	0.50	0.075	1	38	43 (92)	19
3	0.50	0.100	1	10	14	76
4	0.50	0.125	1	4	4	92 (> 99)
5	0.50	0.150	1	0	0	100 (> 99)
6	0.50	0.075	15	7	8	85
7	0.50	0.100	15	6	7	87
8[c]	0.50	0.150	15	52	0	48

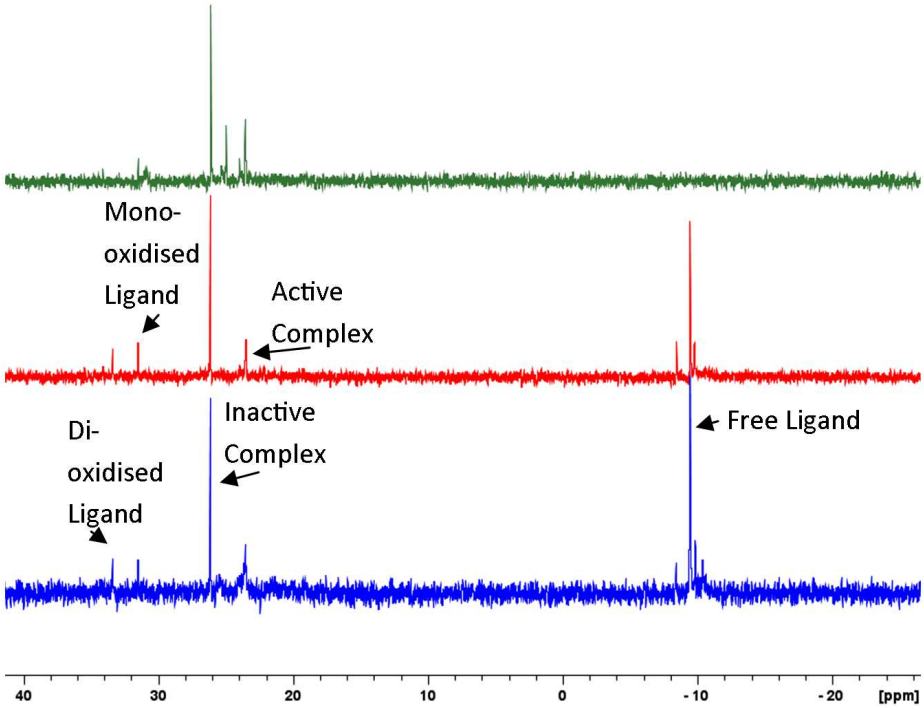


Figure 2.6 Partial ^{31}P NMR spectra for mixtures of [Pd(η^3-allyl)Cl]$_2$ and the ligand (–)-**84** in 1:2 (top, green), 1:3 (middle, red), 1:6 (bottom, blue) molar ratios in an NMR tube filled with Ar.

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 Pd^{II} complex with *P,N* coordination.[119] This complex can be isolated as a yellow solid and is bench stable, however, it is

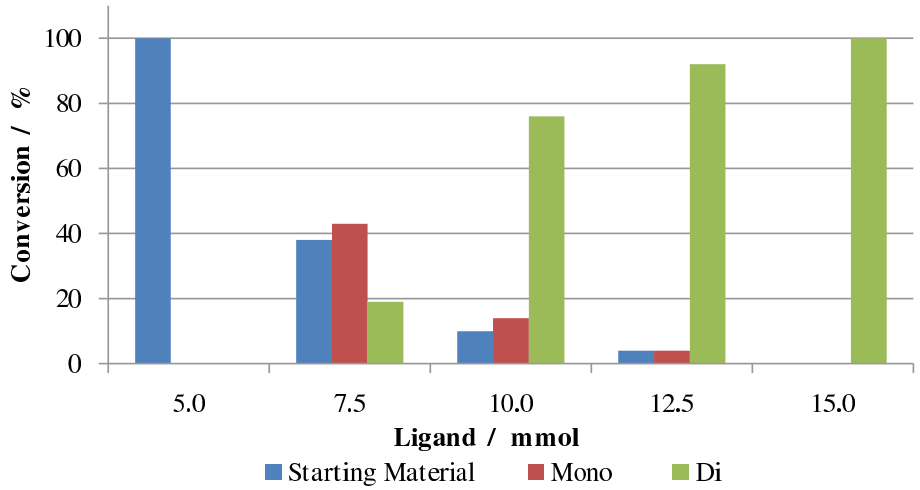


Figure 2.7 As the amount of ligand relative to palladium increases (entries 1-5, Table 2.4), the conversion after 1 h (as measured by ^{1}H NMR) can be seen to increase, showing a higher rate of reaction. Starting material: (±)-**82**; Mono: (+)-**104**; Di: (+)-**83**.

completely inactive in allylic alkylations (Scheme 2.6).[120] 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 Pd^{II}-Pd^0 systems.[132] Not only did triphenylphospine serve to reduce the Pd^{II} 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'.[133] 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.[65,84] 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.

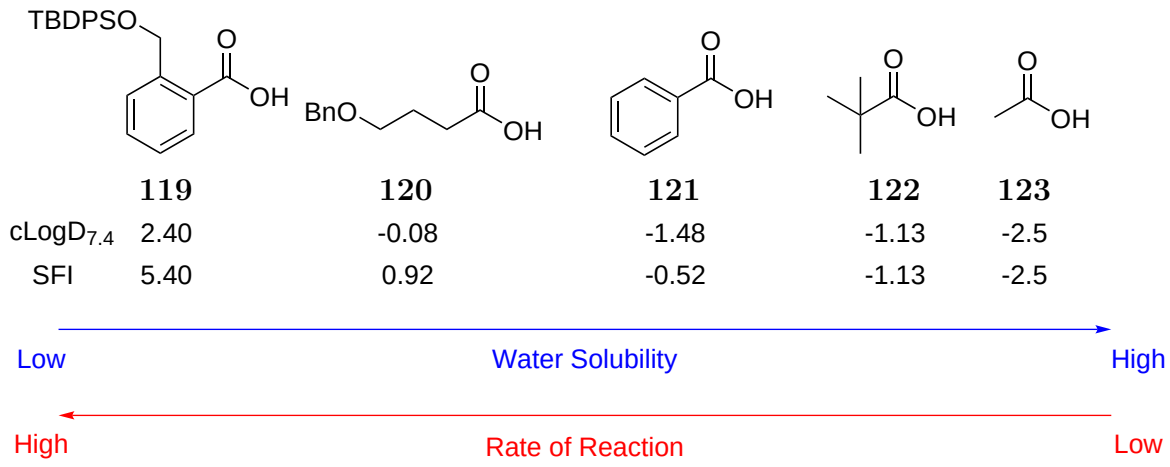
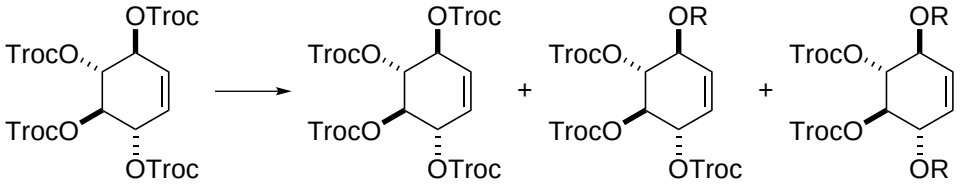


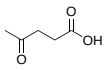
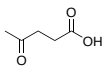
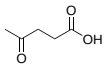
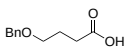
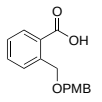
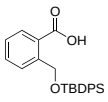
Figure 2.8 As the nucleophile solubility in aqueous media increases from **119** to acetic acid **123**, the rate of reaction in the asymmetric allylic alkylation reduces until the point where acetic acid no longer acts as a nucleophile in the reaction. $cLogD_{7.4}$ was determined using ACD I-Lab 2.0 (http://ilab.cds.rsc.org, *accessed 25/06/2016*). Solubility forecast index (SFI) = $cLogD_{7.4}$ + number of aromatic rings.[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. $[Pd(\eta^3\text{-allyl})Cl]_2$, 0.15 eq. ligand (–)-**84**, 0.2 eq. tetrahexylammonium bromide, 3.0 eq. 1 M aqueous NaOH and 1.5 mL CH_2Cl_2. [a] (–)-**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 α-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.



(±)-**82** (±)-**82** Mono- Di-

Entry	(±)-**82** mmol	Nucleophile	Time	Conversion (e.e.)[b] % (±)-**82**	Mono-	Di-	Yield %
1	0.5		15	100	0	0	-
2	0.5		1	82	18	0	-
3	0.5		1	60	33	17	-
4	0.5		15	14	32	54 (> 99)[c]	37 ((+)-**117**)
5[d]	0.5		15	9	16	75	57 ((+)-**118**)
6	0.5		1	18	64	18	33 ((+)-**115**)
7[e]	0.5		1	14	64	22	-
8	0.5		15	0	25	75	-
9	0.5		1	0	0	100 (> 99)	81
10	0.5		1	0	0	100	-
11	0.5		1	0	0	100 (> 99)	47
12	0.5		1	0	0	100 (> 99)	74

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 *myo*-inositol derivatives was crucial to ongoing synthesis of PtdInsP_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 PtdInsP_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.[41]

2. Conversion from the conduritol B system to a *myo*-inositol system *via* a *syn*-dihydroxylation.[74–76]

3. A robust asymmetric synthesis of the glycerol chains.[41]

All three features have been incorporated in the many syntheses of both inositol and phosphatidylinositol derivatives documented in the literature.[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

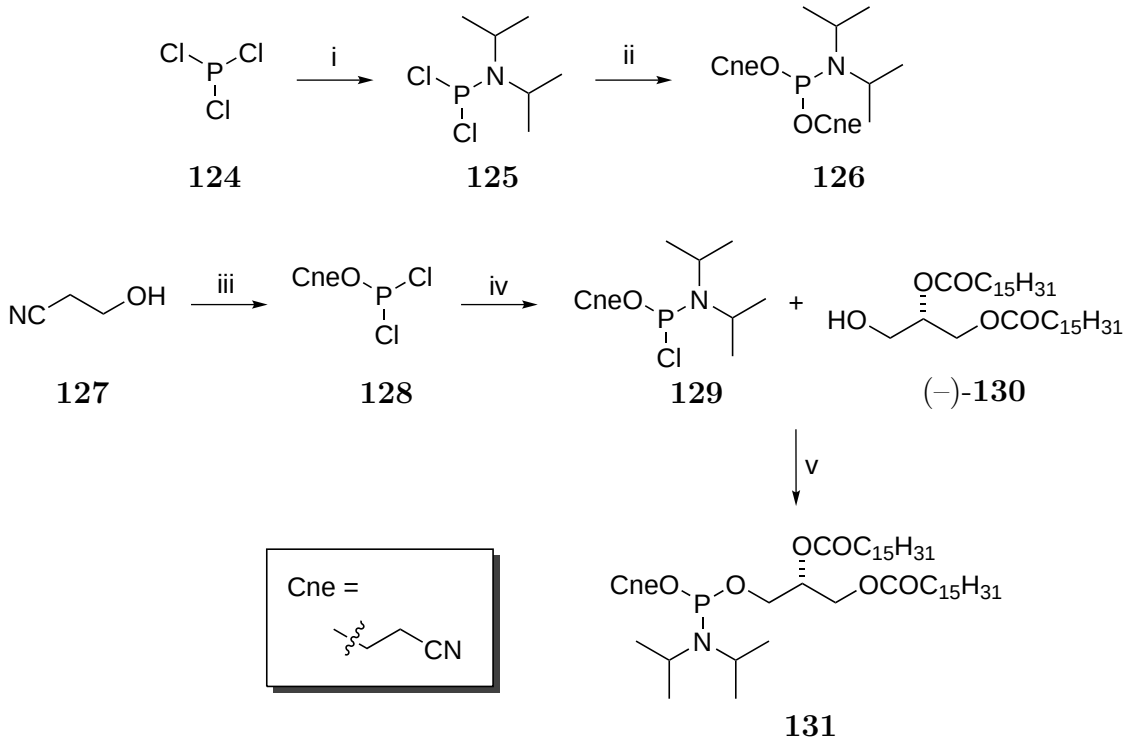
There has been a wealth of literature published on the phosphorylation of hydroxyl functionalities, in particular on nucleotides for oligionucleotide synthesis. A recent comprehensive review was published by Roy and Caruthers.[138] While designed for oligionucleotide

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 P(III) oxidation state. These compounds have been found to be significantly more reactive than the related P(V) compounds.[138] This reactivity makes them more useful, however, it also makes 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 ℃ under an inert atmosphere.

3.2.1 Preparation of Phosphoramidites

Phosphoramidites were prepared from distilled PCl_3 **124** (Scheme 3.1). To form **125**, addition of two equivalents of diisopropylamine to a solution of of PCl_3 led to a single product with only traces of the disubstituted phosphorus compound observed. The resulting diisoproylamine hydrochloride salt was removed by filtration, leaving a product that was > 90% pure, as determined by ^{31}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 ℃ 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 g) relatively easily.

The phosphoramidite **126** could be prepared from **125** by stirring with 3-hydroxypropionitrile and diisoproylethylamine (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 ℃, and the cost was comparatively high compared to other similar reagents. For these reasons,



Scheme 3.1 The synthesis of phosphoramidites **126** and **131**, used in the synthesis of PtdIns(4,5)P_2 derivatives. *Reagents & conditions*: i. Diisopropylamine, Et_2O, –78 °C, 1 h then room temperature, 3 h, 67%; ii. 3-Hydroxypropionitrile, diisoproylethylamine, CH_2Cl_2, 1 h, 67%; iii. PCl_3 (5 eq.), MeCN, 1 h; iv. Diisopropylamine, 0 °C then room temperature, 18 h, 44% over two steps; v. Diisoproylethylamine, CH_2Cl_2, 1 h, 56%.

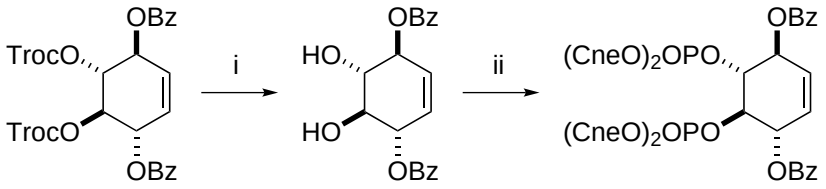
the compound was prepared using a modification of the method by Nielsen *et al.*[140] 3-Hydroxypropionitrile was reacted with 5 equivalents of PCl_3, followed by removal of excess PCl_3 *in vacuo*, to give **128**. Using the large excess of PCl_3 prevents over-reaction to the di- or tri-substituted compound (*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 *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 1*H*-tetrazole, forming a tetrazolium intermediate which is highly reactive.[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.[142] 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, phosphorthioates can be used to slow metabolism of phosphodiester moieties, expanding the scope of related probes.[143] Oxidation to P(V) is typically achieved using H_2O_2 or *m*CPBA. 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 *m*CPBA (*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).[64,81] The two free hydroxyl groups were phosphitylated using **126** in the presence of 1*H*-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 difficultly 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 *m*CPBA gave (+)-**95**.



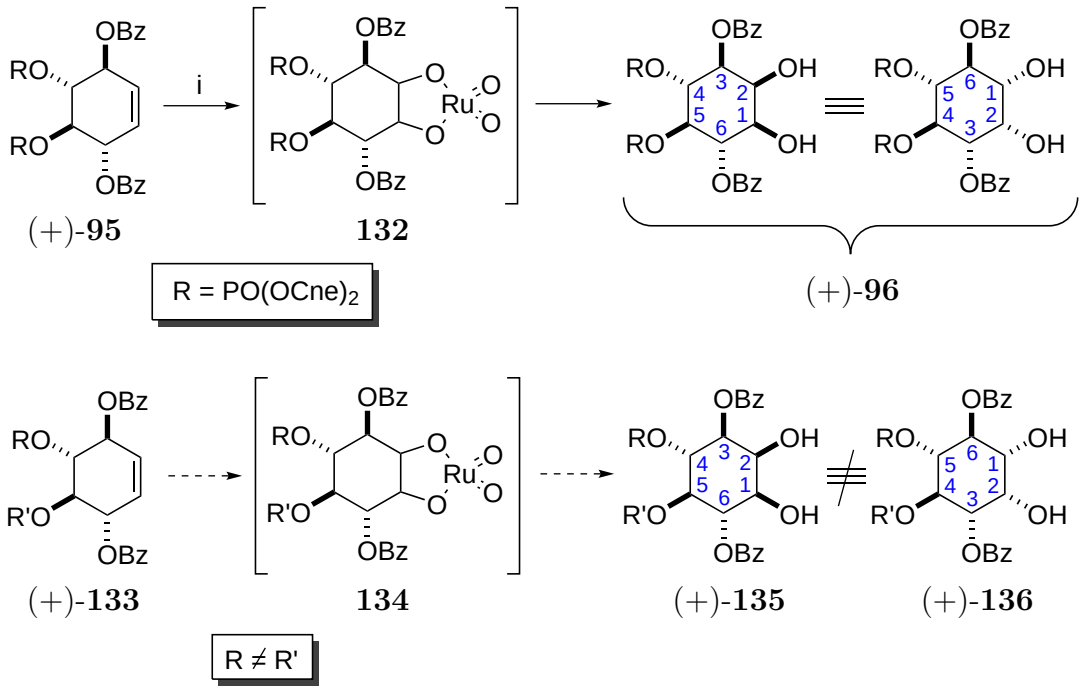
(+)-**83** (+)-**94** (+)-**95**

Scheme 3.2 Synthesis of a diphosphorylated conduritol B derivative (+)-**95** from a single enantiomer of a conduritol B derviative such as (+)-**83** in a similar manner to Trost *et al.* and Podeschwa *et al.*[64,75] *Reagents & conditions*: i. Zn, AcOH, THF, 2 h, 70%; ii. **126**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h then *m*CPBA, –78 ℃, 1 h, 59%.

3.3 Formation of Inositol Derivatives

3.3.1 Dihydroxylation of Conduritol B

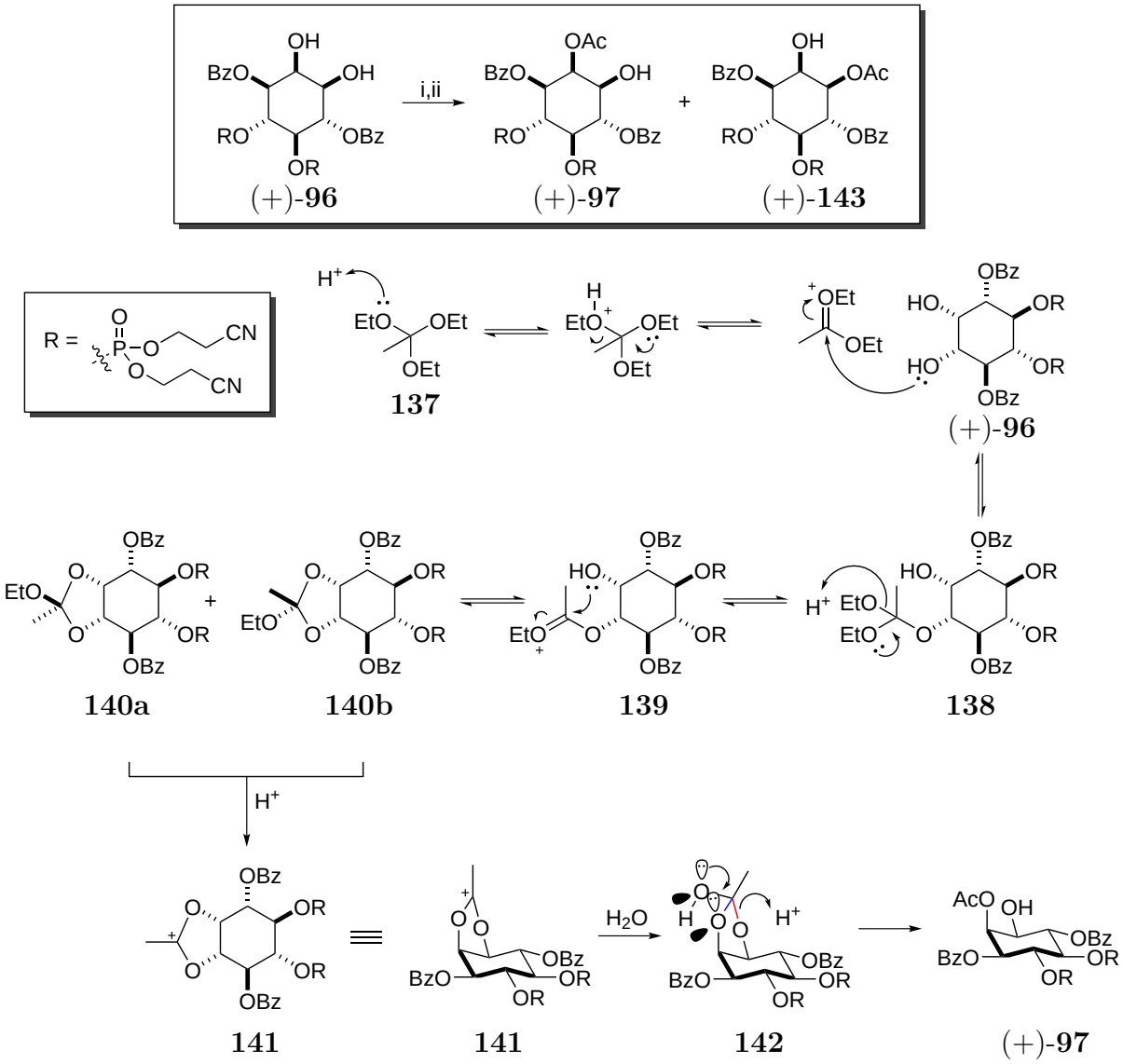
In order to form an inositol derivative from a conduritol B derivative, such as (+)-**95**, it is well documented that a *syn*-dihydroxylation of the double bond can be achieved by OsO_4, or $NaIO_4$ catalysed by $RuCl_3$ in a mixture of MeCN and H_2O.[64,75,76,81] While the use of OsO_4 is preferable 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 selectively, 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]



Scheme 3.3 Using a combination of $RuCl_3$, $NaIO_4$, MeCN, and H_2O leads to a *syn*-dihydroxylation *via* a ruthenium complex **132** giving a single product (+)-**96**, due to the C_2 symmetry of (+)-**95**. If the starting material lacked C_2 symmetry, a mixture of two regioisomers would be obtained. *Reagents & conditions*: $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, H_2O, 8 min, 88%.

3.3.2 Selective Acetylation of 2-position

Once the *syn*-dihydroxylation of (+)-**95** was complete to furnish a *myo*-inositol derviative (+)-**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.[75] A selective esterification at the kinetically stable axial 2-position (*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**.[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 *trans*-decalin-*cis*-2,3-diol.[144] Even as recently as 2012, there are still publications devoted to the selective acetylation of the 2-position in *myo*-inositol.[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 **142** leads to ring-opening onto the axial position.[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.[144] Alternatively, the selectivity may be driven by the orientation of lone pairs on the oxygen atoms in the intermediate **142**.[147] The lone pairs need to be *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 *anti*-periplanar to the broken bond.[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).[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. $CH_3C(OEt)_3$, 4-toluenesulfonic acid, THF, 18 h; ii. 80% aqueous AcOH, 1 h, 38% over two steps.

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.[75] 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*

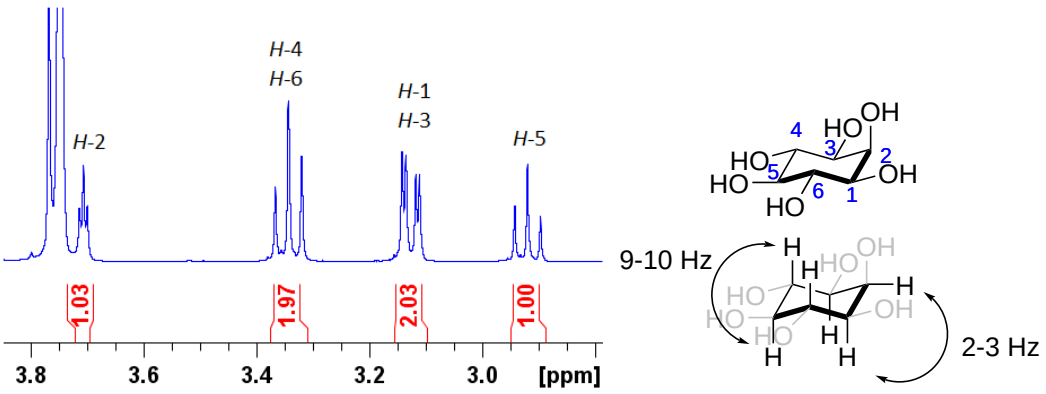


Figure 3.1 Expected coupling constants (as observed in ^{1}H NMR) for inositol peaks around *myo*-inositol. Large splittings caused by axial-axial coupling of protons are typically around 9-10 Hz while axial-equatorial splittings are around 2-3 Hz, giving a diagnostic pattern in ^{1}H NMR spectra.

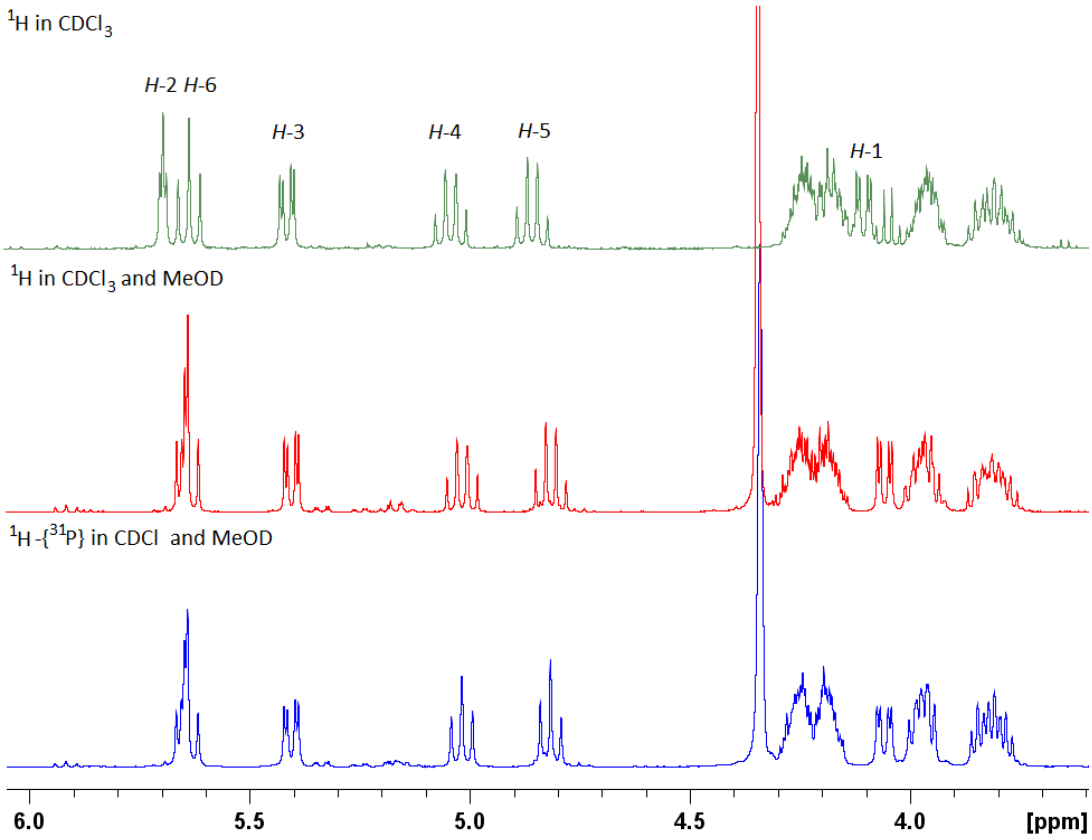


Figure 3.2 Overlay of selected portions of three ^{1}H NMR spectra of (+)-**97** in differing solvents showing the splitting patterns, allowing identification of the peaks, in combination with 2D NMR data. Top (green): A sample of (+)-**97** in $CDCl_3$. Middle (red): A sample of (+)-**97** in 10% MeOD 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**.

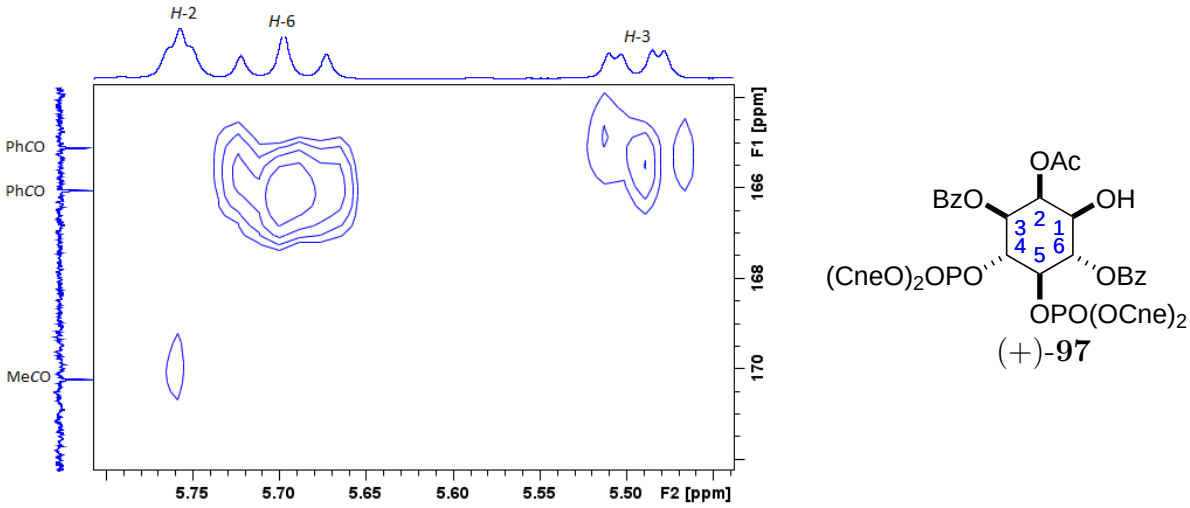


Figure 3.3 Selected portion of the ^{1}H-^{13}C HMBC spectrum of (+)-**97** centred around the inositol peaks (^{1}H) and the carbonyl peaks (^{13}C) showing correlation between the acetate carbonyl at 170 ppm and the doublet of doublets at 5.76 ppm (assigned to the 2-position proton from 2D ^{1}H NMR experiments), supporting the structural assignment of the inositol ring.

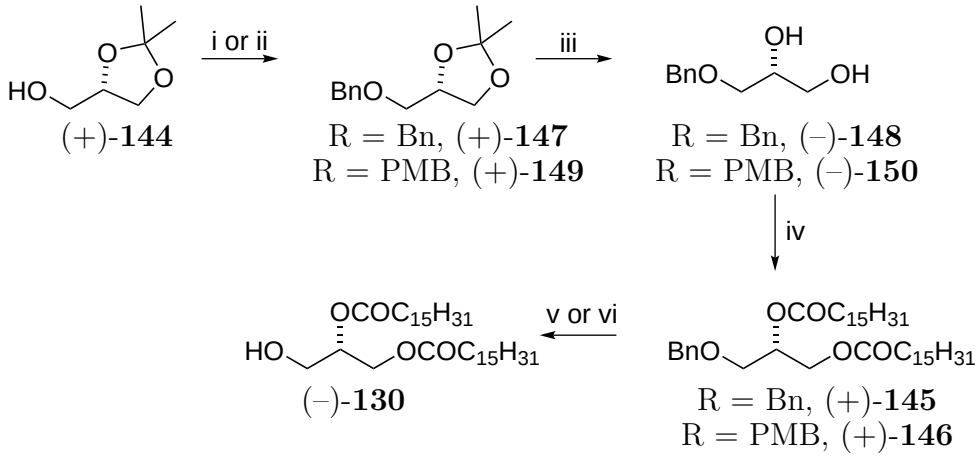
2-3 Hz) can be attributed to the 2-position where the equatorial proton is coupling to two axial protons. The other doublet of doublet is one of the 4-, 5- or 6-positions, given these three protons all couple to two neighbouring axial protons, giving large (9-10 Hz) couplings. There are two doublet of 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 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 asssignment (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

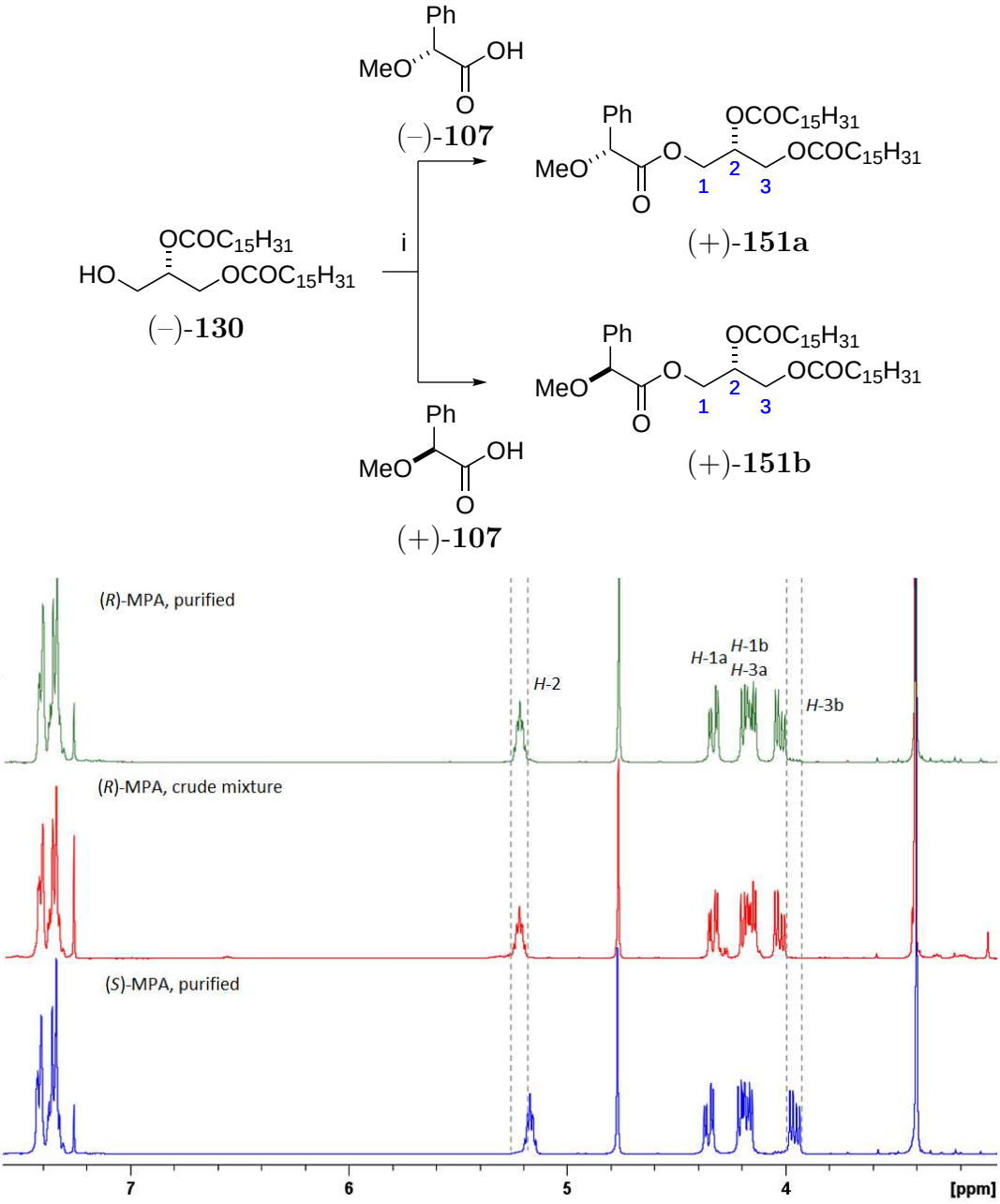
3.4.1 Synthesis of Glycerol Derivatives

Prior to introduction of the phosphatidyl moiety, a robust synthesis of 1,2-dipalmitoyl *sn*-glycerol (–)-**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.



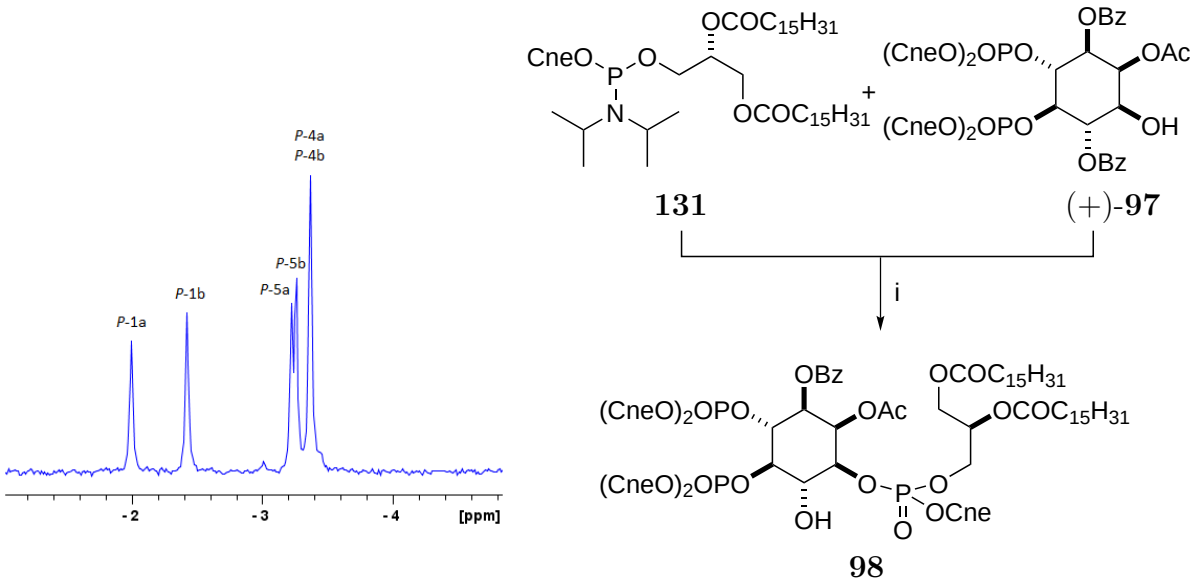
Scheme 3.5 Synthesis of (–)-1,2-dipalmitoyl *sn*-glycerol (–)-**130** for use in preparing PtdIns(4,5)P_2 **10**. *Reagents & conditions*: i. BnBr, NaH, DMF, 18 h, 92% (R = Bn); ii. PMBCl, DMF, 18 h, 93% (R = PMB); iii. 1 M aqueous HCl, THF, 18 h, 93% (R = Bn & PMB); iii. Palmitoyl chloride, DMAP, *N,N*-diisopropylethylamine, 18 h, 95% (R = Bn), 69% (R = PMB); v. H_2, Pd/C, AcOH, EtOH, 1 h, 100% (R = Bn); vi. DDQ, CH_2Cl_2, H_2O, 3 h, 69% (R = PMB).



Scheme 3.6 Partial ^{1}H 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, CH_2Cl_2, 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

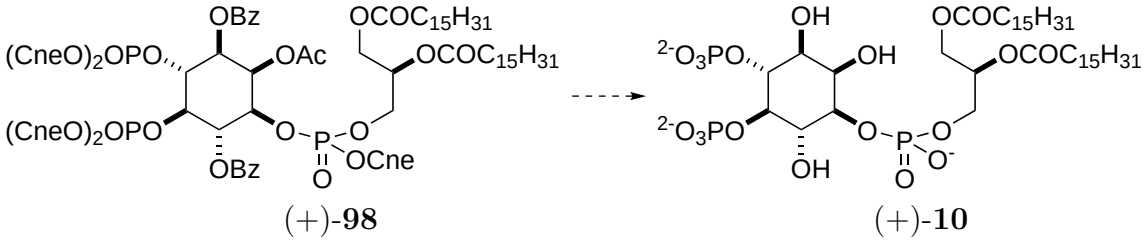


Scheme 3.7 Partial ^{31}P NMR spectrum of (+)-**98**, showing the presence of two diastereomers (labelled a and b) caused by a stereogenic phosphorus atom at the 1-position. For this reason, there is a large chemical shift of the 1-position between the two diastereomers, however, the effect diminishes further away from the stereogenic phosphorus centre. *Reagents & conditions*: i. 3-4% 1*H*-tetrazole in MeCN, CH_2Cl_2, 2 h then *m*CPBA, –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 **10**.

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

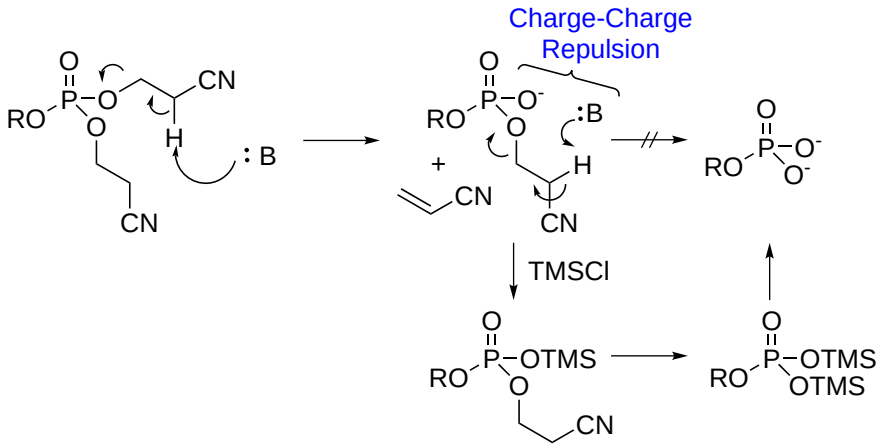
Once the synthesis of a fully-protected PtdIns(4,5)P_2 1,2-dipalmitoyl derivative (+)-**98** had been obtained, the synthesis then turned to the final step - deprotection of the phosphate and hydroxyl moieties. The 2-cyanoethyl groups had been used in previous PtdInsP_n syntheses, and were removed without migration of the phosphorus centres.[107] While acetate and benzoate protecting groups had been used successfully in the synthesis of InsP_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.



Scheme 3.8 Planned deprotection of fully-protected 1,2-dipalmitoyl PtdInsP_2 (+)-**98**.

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 Mechanism for the deprotection of the 2-cyanoethyl groups from the phosphate moities. 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 PtdInsP_n derivatives.[107] A stronger base is required in this case (TMG) as using a weaker base such as 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}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}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}P NMR spectrum (Figure 3.4).

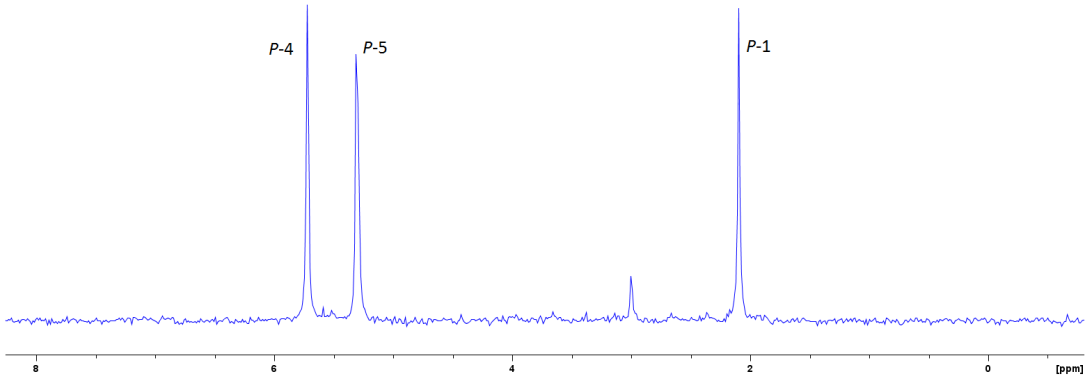


Figure 3.4 ^{31}P NMR of the product after removal of the 5 cyanoethyl groups, giving three sharp peaks in the spectrum. The benzoates are still attached at this stage, however, the acetate appeared to be no longer present at the 2-position.

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.[104] This had been replicated by Trost *et al.*[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.

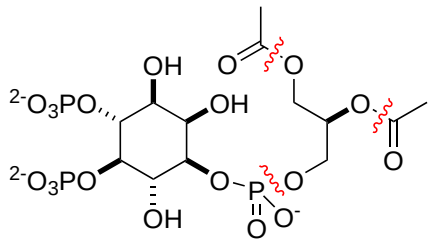


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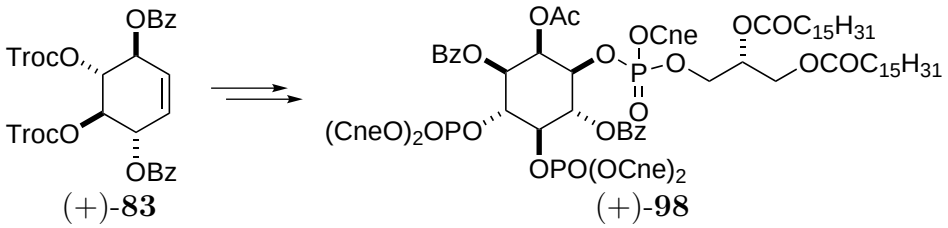
Figure 3.5 Proposed sites of hydrolysis caused by base-catalysed deprotection conditions in this system. Both lipid esters are susceptible to hydrolysis as is the phosphodiester (highlighted in red).

These data did not bode well for future base deprotection conditions, as LiOH is a mild method for hydrolysis of esters (*cf* use of NaOH or KOH). This reaction was repeated

twice with the same result. Changing the conditions to use 1 M NH_3 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)P_2 derivative (+)-**98**. Phosphorylation of hydroxyl moeities 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 acheived, subsequent deprotection of the benzoate protecting groups was unsuccessful with hydolysis 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.



(+)-**83** (+)-**98**

Scheme 3.10 The conduritol B derivative (+)-**83**, synthesised *via* Trost asymmetric allylic alkylation, was converted into a fully protected PtdIns(4,5)P_2 derivative (+)-**98**, however, deprotection of the benzoate groups in the presence of lipid chains was unsuccessful.[64,75]

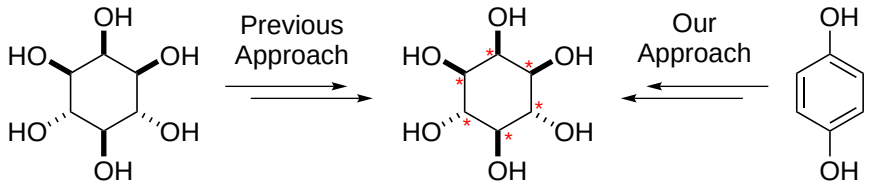
Chapter 4

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 Inositols

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. D_7-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 D_6-*myo*-inositol **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

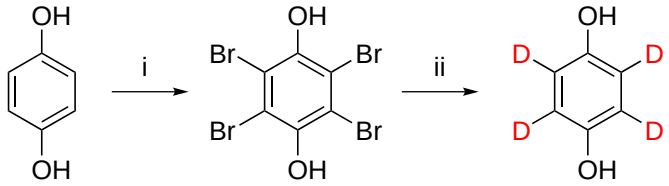


Scheme 4.1 Previous approaches toward D_6-*myo*-inositol **154** started from *myo*-inositol **1**, requiring separation of multiple isomers. Our approach starts from quinol **153**. All deuterium atoms from this point on are highlighted in red, either as "D" or as an asterisk.

separation of epimers (Scheme 4.1).[48] Consequently, a route that tolerates multi-gram syntheses was required toward 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**.[48]



153 **155** **156**

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_2O, reflux, 2 h, 92%; ii. Zn, Pd/C (10% *w/w*), D_2O, 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.[153,154] 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_2O. Therefore, tetrabromoquinol **155** was synthesised in 92% yield using bromine in AcOH (Scheme 4.2).[155] 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.[153] In combination with work by Kurita *et al.* on the *in situ* generation of D_2 gas from D_2O, it may have been possible to achieve deuterium incorporation.[156] 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.[156] Mukhopadhyay *et al.* had described a debromination using Zn in combination with Pd/C in H_2O under reflux conditions.[154] During their studies, they had replaced H_2O with D_2O 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_2O 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^+).

Entry	Quinol **153** / mmol	Conditions	Time / h	Incorporation/%				
				D_0	D_1	D_2	D_3	D_4
1	10	2:5 D_2SO_4/D_2O	48	100	0	0	0	0
2	19	2:1 $AcCl/D_2O$, 3 eq. Zn	24	1	3	18	41	37
3	20	AcOD, 3 eq. Zn	24	67	27	6	0	0
4	10	1:1 $AcOD/D_2O$, 6 eq. Zn	96	100	0	0	0	0
5	5	1:1 $AcOD/D_2O$, 4 eq. $ZnCl_2$	24	100	0	0	0	0
6	182	1:50 D_2SO_4/D_2O	3 × 24	0	0	0	7	93

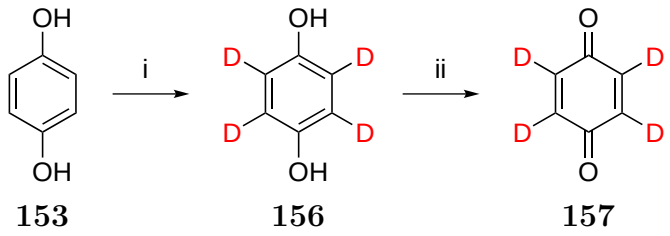
Zhao *et al.* described a synthesis of D_4-*p*-benzoquinone **157** that proceeded by deuteration of quinol **153** by exchange under acidic conditions followed by oxidation, however, there was only a limited procedure described.[157] Replicating this work by dissolving quinol **153** in 3.4 M D_2SO_4 in D_2O 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.[157,158] The deuterium source was prepared *in situ* by the addition of D_2O 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

was only 37% D_4 (D_4 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).

$$2\,\mathrm{AcCl} + 2\,\mathrm{D_2O} \longrightarrow 2\,\mathrm{AcOD} + 2\,\mathrm{DCl} \xrightarrow{\mathrm{Zn}} 2\,\mathrm{AcOD} + \mathrm{ZnCl_2} + \mathrm{D_2} \tag{4.1}$$

To optimise the conditions, the reactive components in the reaction were tested individually. D_1-AcOD was purchased and the reaction was repeated with mixtures of D_1-AcOD, Zn and D_2O (entries 3 and 4, Table 4.1). D_4-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, $ZnCl_2$ and D_2O 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 D_2O. Formation of DCl through this method required slow addition of AcCl to D_2O 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 D_2SO_4 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).[157,159] 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 D_2SO_4 in D_2O, the first iteration produced a similar result to that of Desiraju *et al.* using AcCl and D_2O (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% D_4 and the remaining 7% D_3 (Scheme 4.3). This method allowed for large amounts of D_4-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_2O_2 in isopropanol in the presence of catalytic iodine at 55 ℃ was a potential possibility to avoid the use of lead compounds.[160] The risk of using aqueous H_2O_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.

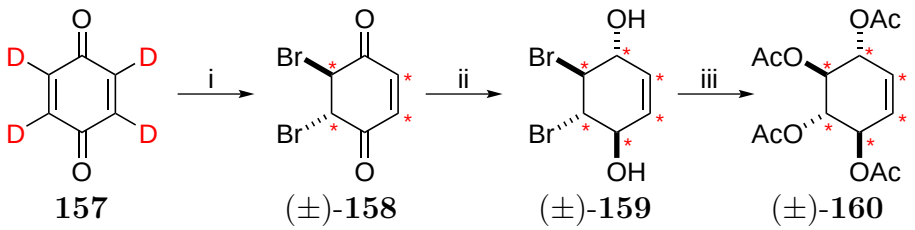


153 **156** **157**

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_2SO_4, D_2O, reflux, 3 × 24 h, 95%, 93% D_4; ii. 35% *w/w* aqueous H_2O_2, I_2, isopropanol, 45 ℃, 2 h, 89%.

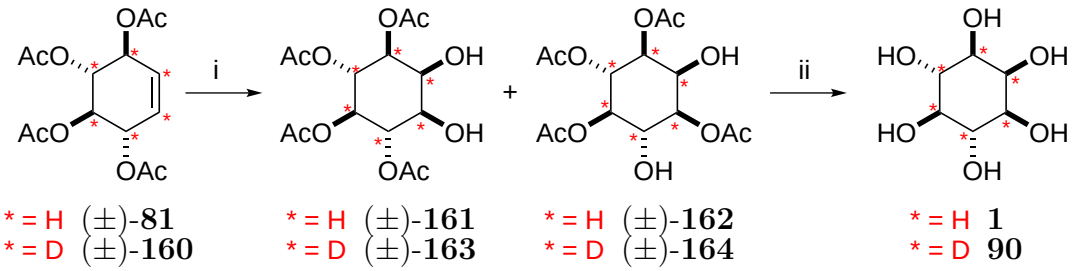
4.1.2 Preparation of D_6-*myo*-inositol

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



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_2O, Et_2O, 0 °C, 2 h; iii. Ac_2O, K_2CO_3, 2 h then AcOH, reflux, 45 h, 29% over 3 steps, 90% D_6, 10% D_5

epimerisation i.e. a proton exchange, does not occur, it is unlikely that loss of deuterium will be observed. Similarly to tetracetate (±)-**81** (chapter 2), D_4-*p*-benzoquinone **157** was brominated using Br_2 followed by reduction with $NaBD_4$ in D_2O and Et_2O. 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 (±)-**160** in 29% yield over the 3 steps (Scheme 4.4).[64,111] The lower yield could potentially be attributed to some iodine remaining from the earlier oxidation step. Mass spectrometry studies of the tetracetate (±)-**160** revealed the incorporation had remained constant from the diol (±)-**159** to (±)-**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 (±)-**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 (±)-**81**.



Scheme 4.5 Synthesis of *myo*-inositol **1** or D_6-*myo*-inositol **90** from (±)-**81** or (±)-**160** respectively. A mixture of inseparable compounds were observed after the *syn*-dihydroxylation, however, this did not matter for the final step. *Reagents & conditions*: $NaIO_4$, $RuCl{\cdot}3H_2O$, MeCN, H_2O, 4-8 min; ii. NEt_3, H_2O, MeOH, 2-18 h, 82% (**1**), 50% (**90**) over two steps.

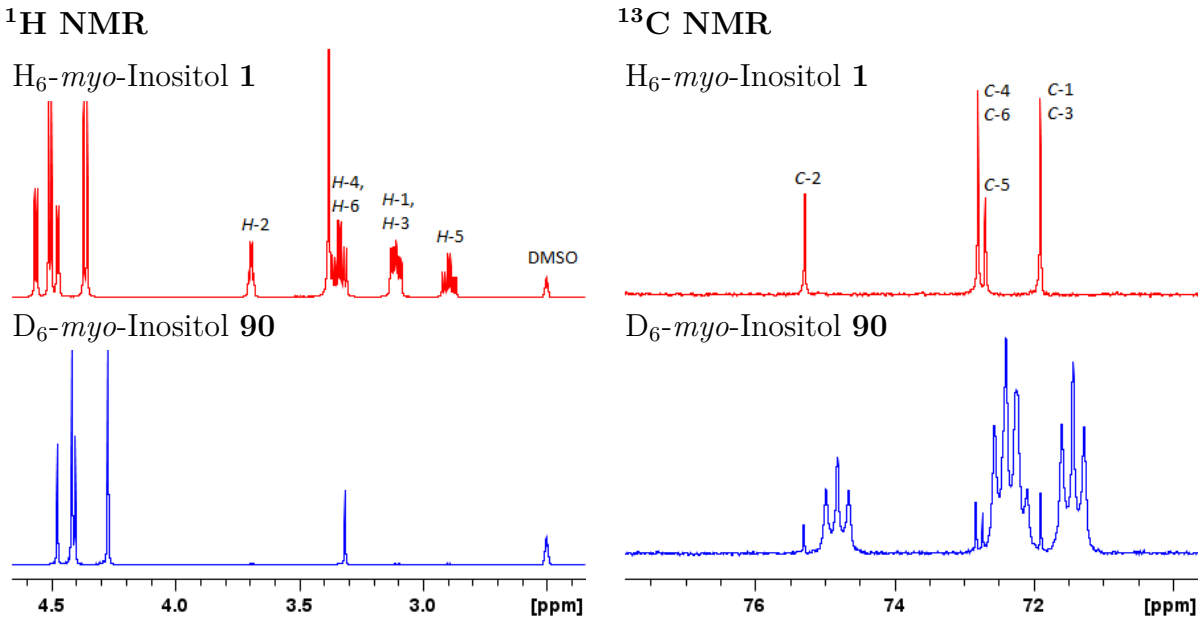


Figure 4.1 Comparison of ^{1}H NMR (left) and ^{13}C NMR (right) data for H$_6$-*myo*-inositol **1** (red, top) with D$_6$-*myo*-inositol **90** (blue, bottom). A small residual signal is seen for each resonance in the deuterated version as the material has 10% D$_5$ present.

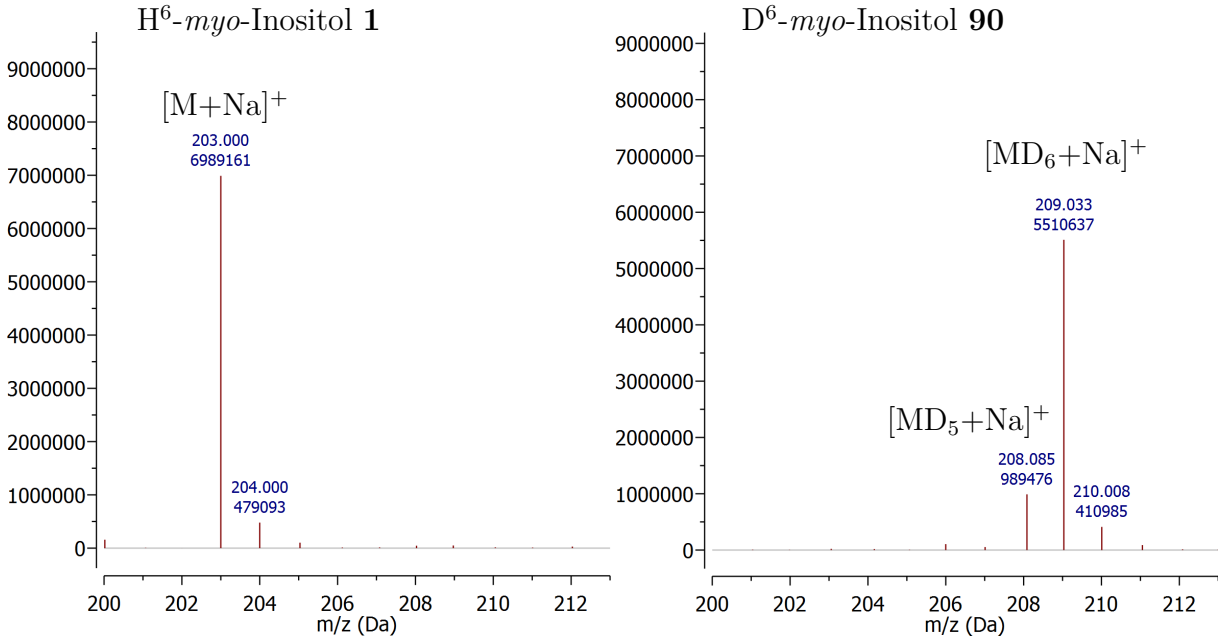
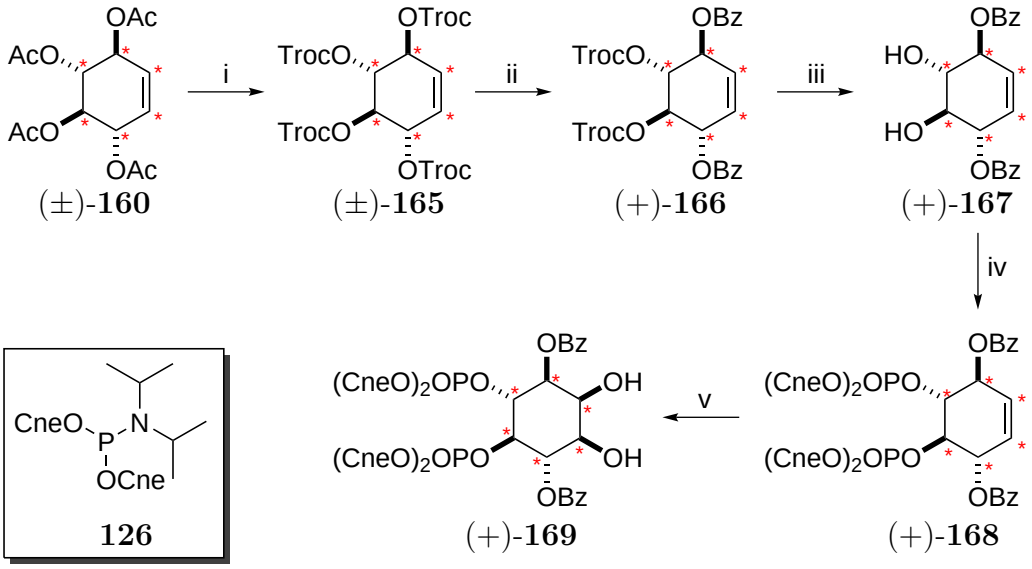


Figure 4.2 Mass spectrometry data comparing synthesised *myo*-inositol **1** with **90**. Both samples were injected at a concentrated of 1 mg ml^{-1} in a 9:1 mixture of MeOH/H$_2$O. The deuterium incorporation of **90** can be determined by comparing the relative intensity of *m/z* 208.0 to 209.0. Absolute intensities are shown below the mass.

To synthesise D_6-*myo*-inositol **90** from the tetracetate (±)-**160**, a *syn*-dihydroxylation was performed to produce a tetracetylinositol derivative (±)-**163** (Scheme 4.5).[75] The chemistry was first attempted with the protonated analogue (±)-**81** to confirm the structure was as expected, and to compare this method of synthesising *myo*-inositol **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 (±)-**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 ℃. Despite the migration product being inseparable from the desired product (±)-**163**, this was not an issue as subsequent deprotection of the acetates in either product in the mix led to *myo*-inositol **1**. Purification from the two step procedure was possible without chromatography as the product **1** was highly crystalline, with characterisation data matching purchased samples. Repeating the same procedures with the deuterated analogue (±)-**160** led to D_6-*myo*-inositol **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 **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. NEt_3, H_2O, MeOH, 1 h then TrocCl, pyridine, DMAP, CH_2Cl_2, 0 °C, 2 h, 85%; ii. BzOH, tetrahexylammonium bromide, $[Pd(allyl)Cl]_2$, (–)-**84**, 1 M aqueous NaOH, CH_2Cl_2, 69%, > 99% e.e.; iii. Zn, AcOH, THF, 2 h, 89%, 90% D_6; iv. **126**, 3-4% 1*H*-tetrazole in MeCN, CH_2Cl_2, 24 h then *m*CPBA, –78 °C, 1 h, 55%, 90% D_6; v. $RuCl_3{\cdot}3H_2O$, $NaIO_4$, MeCN, H_2O, 5 min, 30%, 89% D_6. Cne = 2-Cyanoethyl.

Once the synthesis of D_6-tetracetate (±)-**160** and D_6-*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

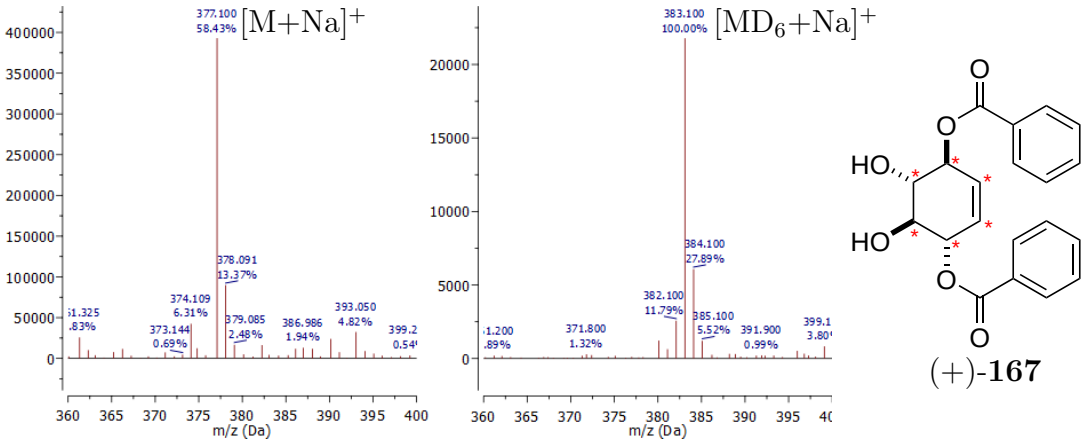


Figure 4.3 Mass spectra showing the shift in mass caused by incorporation of deuterium at the six positions indicated by red asterisks on the structure shown, in electrospray ionisation (ES^+) showing the $[M+Na]^+$ ion. Left: (+)-**94** (H_6); Right: (+)-**167** (D_6).

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 derivatives 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 (^2H) NMR

There have been many reported molecules throughout the literature that contain deuterium within their structure.[91] Evidence for incorporation has usually been provided by suppression of the relevant signal in the ^1H 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 PtdInsP_n. In addition, the use of deuterium attached to tertiary carbon centres causes

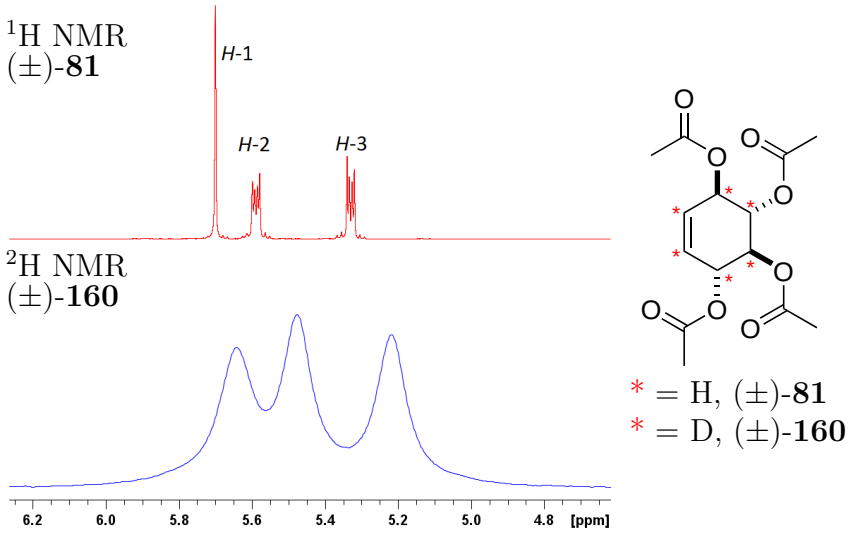


Figure 4.4 ^{1}H NMR (top) *vs.* ^{2}H NMR (bottom) for conduritol B tetraacetate with either deuterium ((±)-**160**) or hydrogen ((±)-**81**) around the six-membered ring. The spectra can be superimposed to assign the ^{2}H NMR, however, there is some shift in signals, presumably caused by the presence 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.

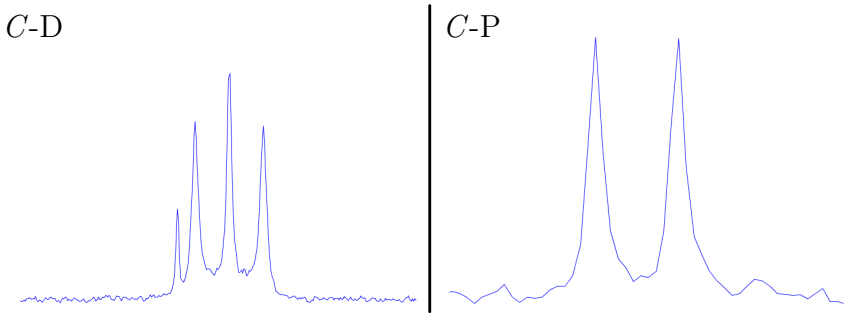


Figure 4.5 Splitting observed in ^{13}C NMR spectra caused by the coupling of either deuterium (left) or phosphorus (right) to a carbon centre. In the case of deuterium splitting, the carbon signal often experiences an isotopic shift of *ca.* 0.3 ppm upfield with a small peak where residual protonated species are left due to methods for incorporation not leading to 100% deuterium.

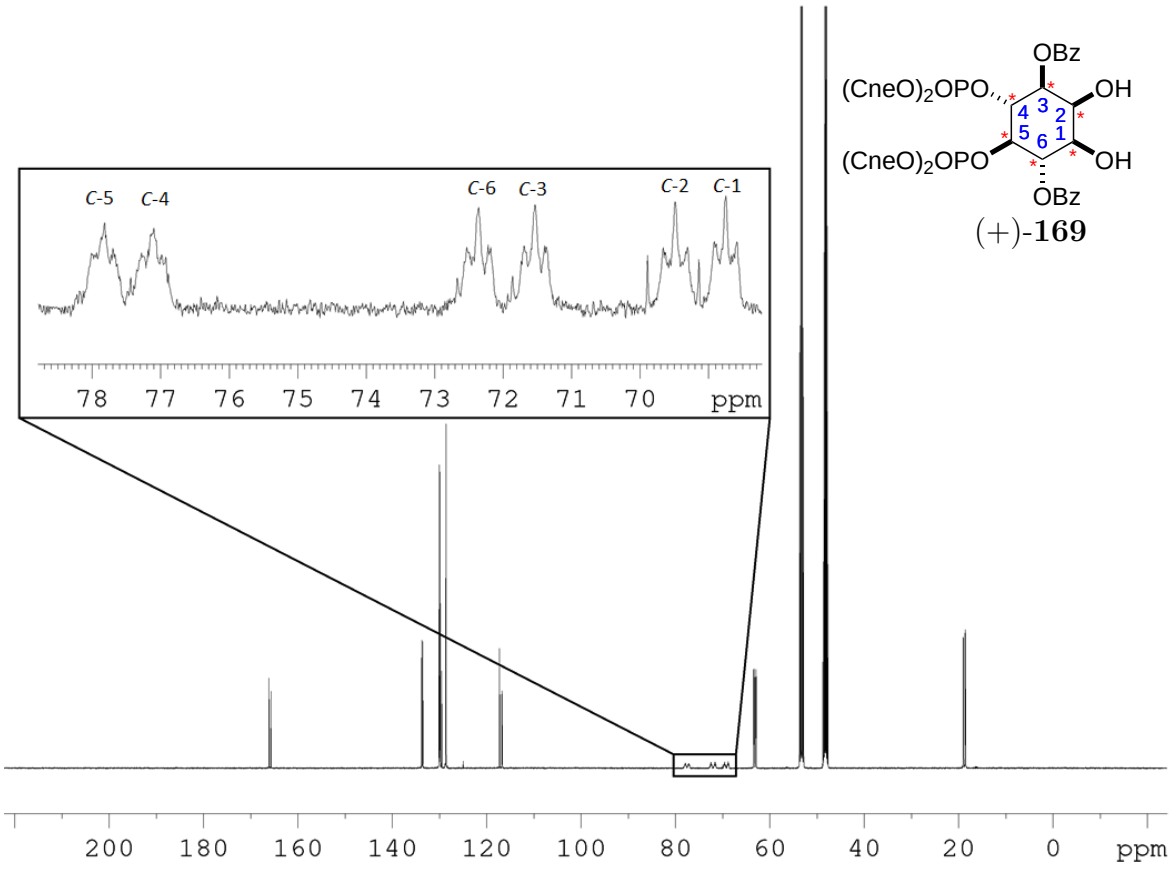
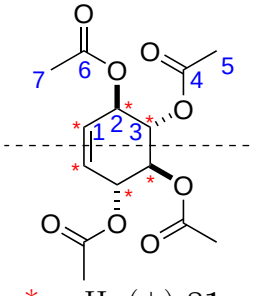


Figure 4.6 ^{13}C NMR spectrum of (+)-**169** showing the coupling of deuterium or phosphorus to a carbon centre in the inositol ring. In the case of deuterium splitting, the carbon signal often experiences an isotopic shift of *ca.* 0.3 ppm upfield with a small peak where residual protonated species 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_2Cl_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 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 (±)-**81** and deuterated (±)-**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

Table 4.2 Spin-lattice (T_1) times for carbon atoms in protonated ((±)-**81**) *vs* deuterated ((±)-**160**) analogues of the same compound. A significant increased is seen for carbon atoms attached to a deuterium atom. With thanks to Dr Barbara Odell for obtaining these data. [a] In these cases, the two carbon atoms were sufficiently close that the value was measured as an average of the two carbon signals.

Position	T_1 times / s	
	(±)-**81**	(±)-**160**
1	0.95	4.85
2 & 3[a]	1.11	8.59
4 & 6[a]	5.73	6.30
5 & 7[a]	3.19	3.57
$CDCl_3$	16.46	16.68



* = H, (±)-**81**
* = D, (±)-**160**

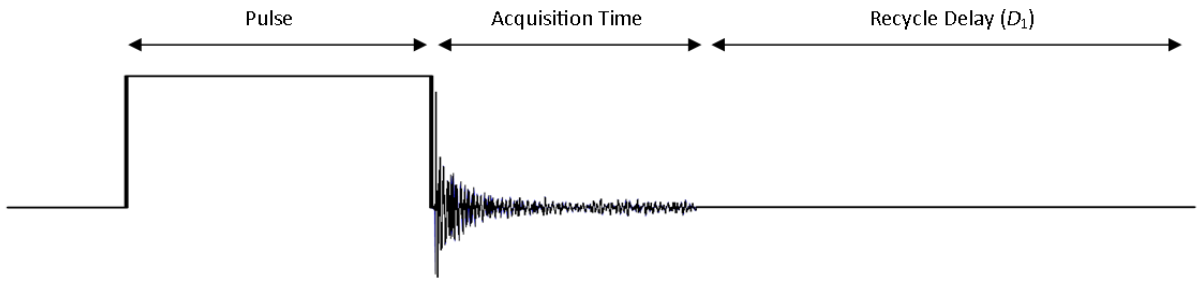


Figure 4.7 Schematic representation of a simple ^{13}C NMR pulse sequence, illustrating the recovery delay required for the highest amplitude signal.

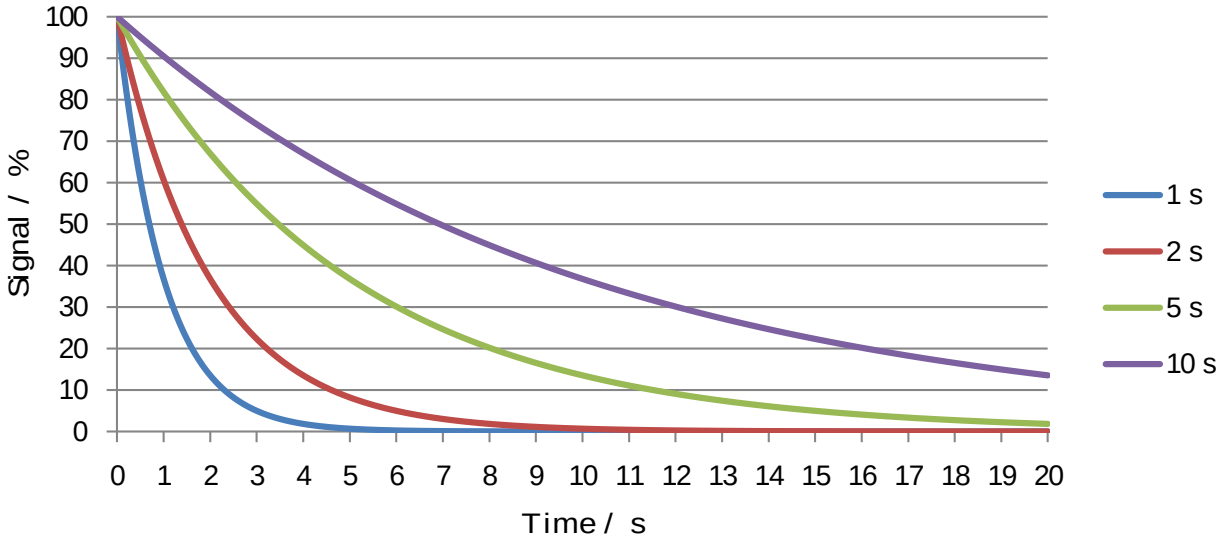


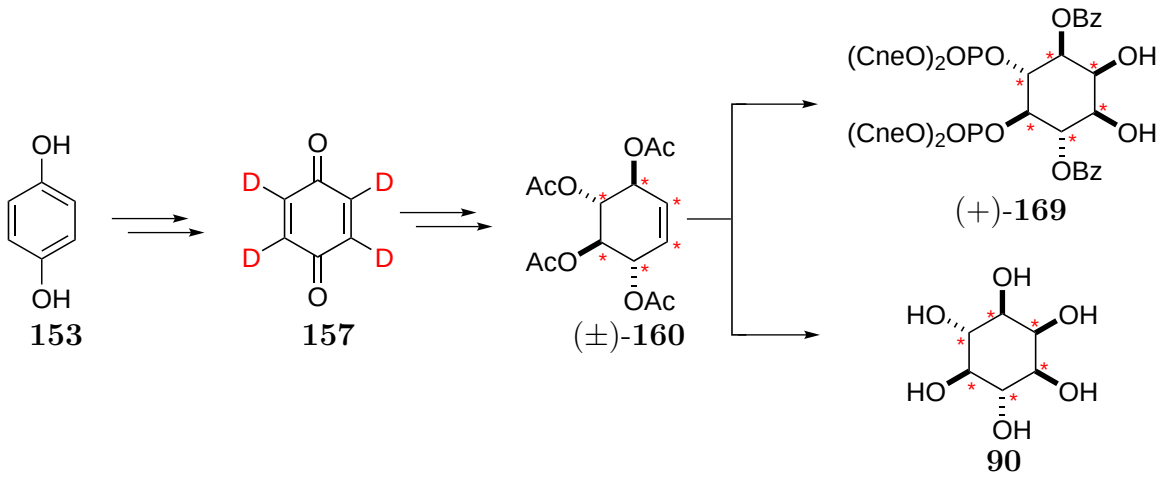
Figure 4.8 Schematic showing the signal relaxtion follwing RF excitation during an NMR experiment for different T_1 times. The T_1 time has an effect on choice of recycle delay time (D_1) as if too short a delay time is chosen, full relaxation is not achieved and a suppressed signal is observed.

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-

enriched starting materials (>90% D_4). Using D_4-*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 D_6-*myo*-inositol **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 D_6-*myo*-inositol **90** was established, allowing access to an expensive starting material in large quantities (> 1 g). From here, a robust synthesis of PtdIns(4,5)P_2 **10** was required, using these available starting materials.



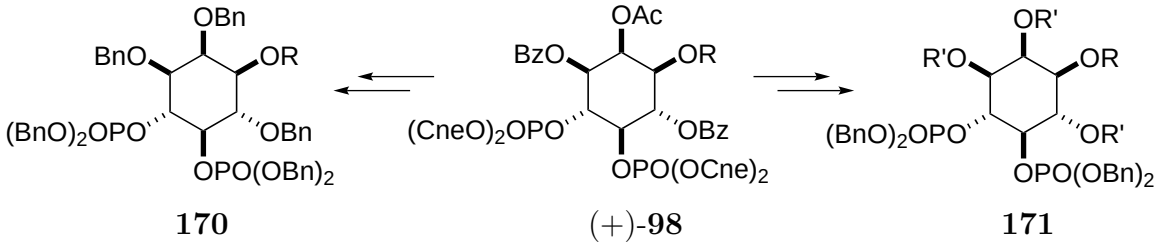
Scheme 4.7 Starting from quinol, D_4-*p*-benzoquinone **157** was prepared, leading to D_6-*myo*-inositol **90** and related derivatives (+)-**169**.

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).



170 (+)-**98** **171**

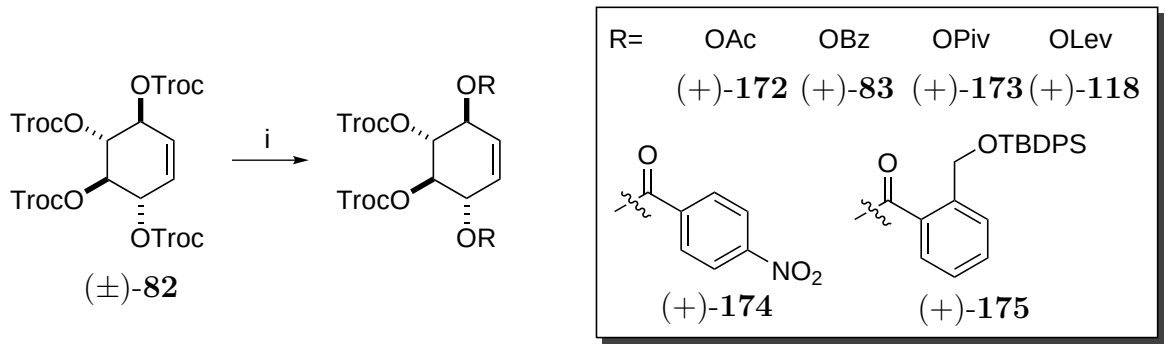
Scheme 5.1 Two different protecting group strategies were required to access PtdInsP_n with either saturated (left) or unsaturated (right) lipid chains. R denotes the phospholipid group while R' denotes a generic protecting group.

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).[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.[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

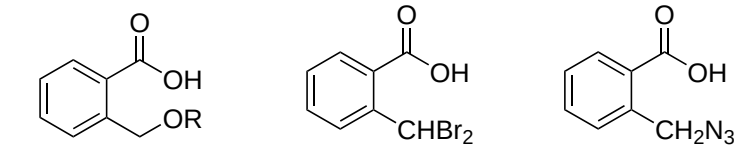
During the original replication of the Trost work (Chapter 2), a variety of different carboxylate groups were used in an attempt to understand solubility effects on the system (Scheme 5.2).[64,81] These groups were chosen as they had been used in previous literature for the protection of hydroxyl groups.[163] 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.



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. *Reagents & conditions*: ROH, THABr, $[Pd(\eta^3\text{-allyl})Cl]_2$, (*S,S*)-ligand (–)-**84**, CH_2Cl_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.[163] 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).[163–167] 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.[168] The TBDPS group was used preferentially, as the PMB derivative was hypothesised to be less stable than the TBDPS derivative.

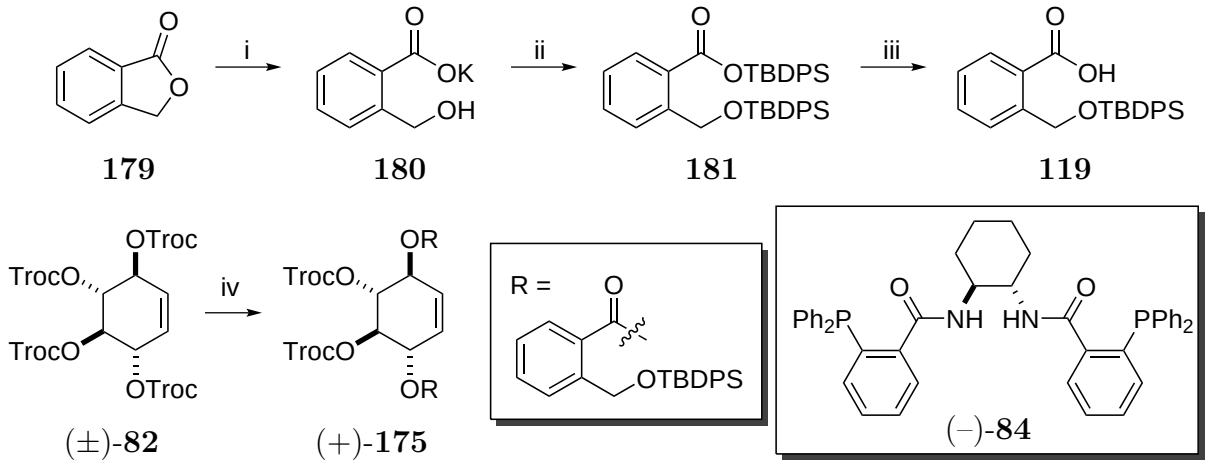


R = TBDPS **119**
R = PMB **176**

177 **178**

Figure 5.1 Examples of benzoate derivatives that can be cleaved by markedly different conditions to those of a benzoate group.[163–167]

The TBDPS-protected benzoic acid **119** was synthesised in 67% yield over three steps from phthalide, using the method from Guerlavais-Dagland *et al.* (Scheme 5.3).[164] 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.[64,164] *Reagents & conditions*: i. KOH, MeOH, H_2O, reflux, 90 min; ii. TBDPSCl, imidazole, pyridine, 18 h; iii. K_2CO_3, MeOH, THF, H_2O, 1 h then $KHSO_4$, 67% over 3 steps; iv. **119**, Tetrahexylammonium bromide, (*S,S*)-ligand (–)-**84**, $[Pd(\eta^3\text{-allyl})Cl]_2$, CH_2Cl_2, 1 M aqueous NaOH, 1 h, 74%, >99% e.e.

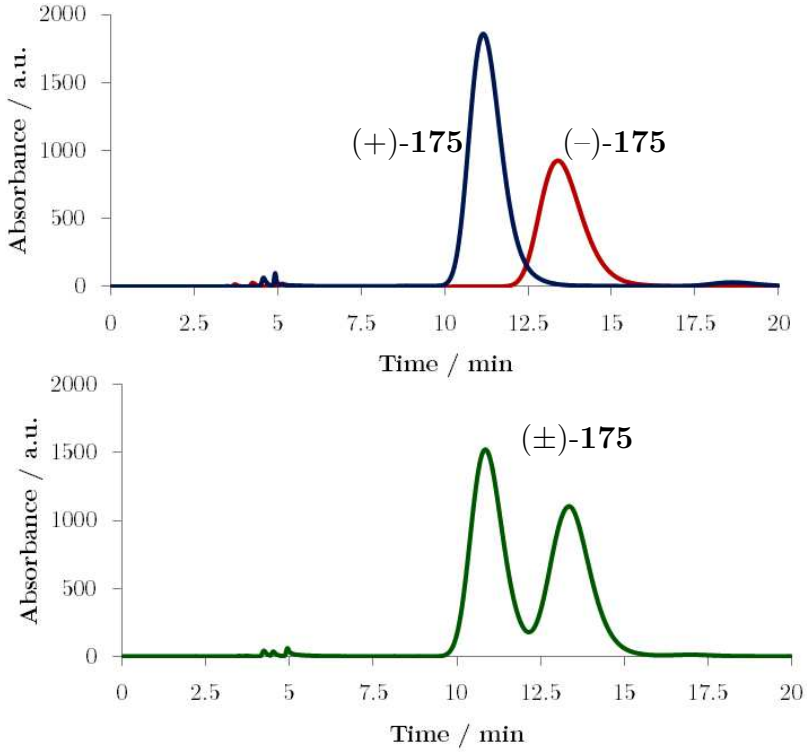


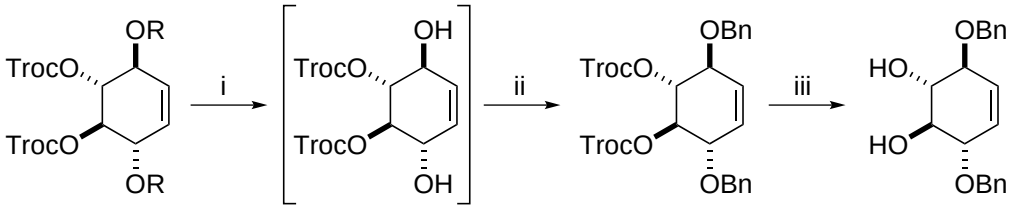
Figure 5.2 Chiral HPLC (ChiralPak® AD-H column, 0.5% isopropyl alcohol in hexane) overlay of (+)-**175** (top, blue) and (–)-**175** (top, red) *cf* a mix of the two compounds in the same sample (bottom, green).

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.[41,66,169] It is well known that deprotection of poly benzylated PtdInsP_n was possible using hydrogenolysis, removing the need for purification of unstable products at the final step.[41,66,169]

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_2Cl_2 and TFA to give (+)-**182** (Scheme 5.4).[168] 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).

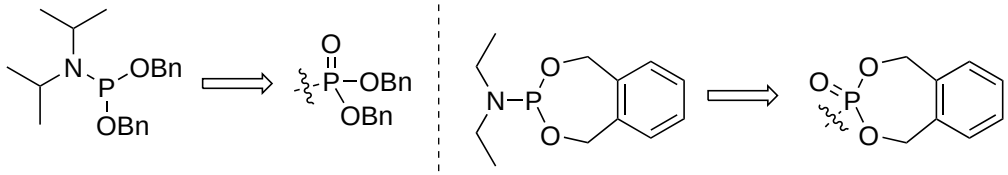


(+)-**175** (+)-**182** (+)-**183** (+)-**184**

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_2Cl_2, 1 h; ii. Benzyl 2,2,2-trichloroacetimidate, TfOH, 1,4-dioxane, 18 h, 62% over two steps; iii. Zn, AcOH, THF, 1 h, 88%.

5.3.2 Benzyl Phosphate Derivatives

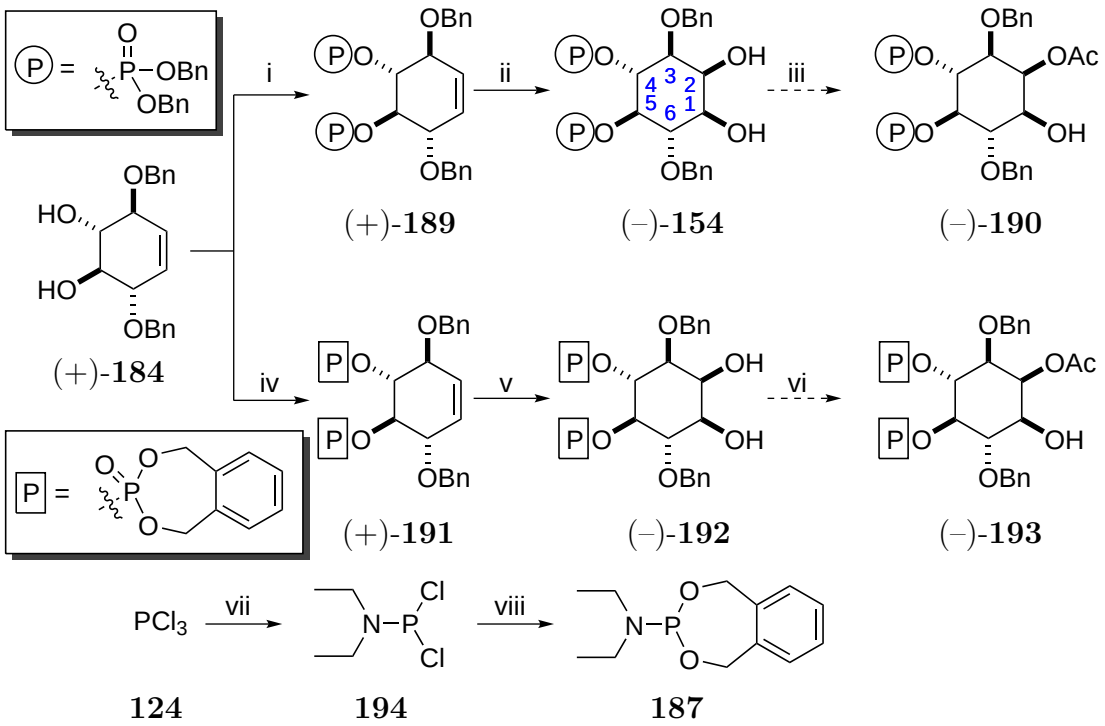
There were two protecting group options available for phosphate groups that can be deprotected using hydrogenolysis. While dibenzylphosphates (**186**, Figure 5.3) can be synthesised using a commercially available reagent (dibenzyl *N,N*-diisopropylphosphoramidite **185**), a protecting group based on 1,2-benzenedimethanol has often been used (**188**, Figure 5.3).[41,75,170,171] The *o*-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 *syn*-dihydroxylation of (+)-**189** gave the *myo*-inositol derivative (–)-**154**.



185 **186** **187** **188**

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.

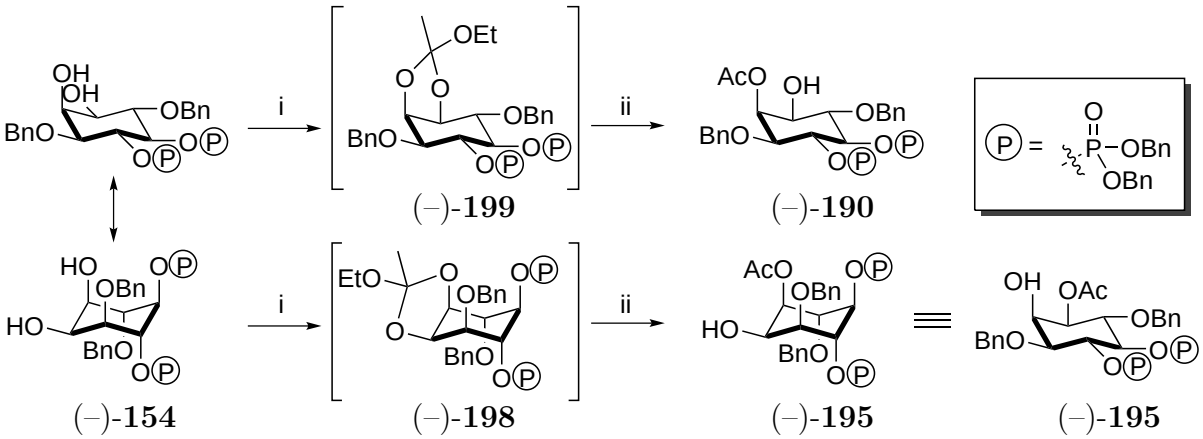
To phosphorylate the 1-position of (–)-**154** exclusively with the phospholipid, the 2-position required protection (Scheme 5.5). While introduction of a benzyl group at the 2-position would be advantageous, there were no literature routes for a high-yielding single step introduction of the benzyl at the 2-position. Most routes rely on protection of the 1-position first using organotin chemistry.[135,172,173] The *cis*-diol is first reacted with di(*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



Scheme 5.5 Two routes toward fully protected *myo*-inositol derivatives were unsuccessful due to the poor regioselectivity of the acetylation in the final step shown. *Reagents & conditions*: i. Dibenzyl *N,N*-diisopropylphosphoramidite **185**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 2 h then –78 ℃, *m*CPBA, then room temperature, 1 h, 72%; ii. $NaIO_4$, $RuCl_3{\cdot}H_2O$, MeCN, H_2O, 0 ℃, 4 min, 58%; iii. $CH_3C(OEt)_3$, *p*TSA, THF, 18 h then 80% aqueous AcOH, 1 h; iv. **187**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h then –78 ℃, *m*CPBA, then room temperature, 2 h, 31%; v. $NaIO_4$, $RuCl_3{\cdot}H_2O$, MeCN, H_2O, 4 min, 67%; vi. $CH_3C(OEt)_3$, *p*TSA, THF, 18 h then 80% aqueous AcOH, 1 h; vii. $HNEt_2$, Et_2O, –78 ℃ then room temperature, 18 h; viii. DIPEA, 1,2-benzenedimethanol, –78 ℃ then toom temperature, 18 h, used crude, *ca* 86% over two steps.

reduced selectively, however, this route was particularly low yielding.[75] An acetate group could be selectively placed at the 2-position in a one-pot two-step procedure to synthesise (–)-**190** (Scheme 5.5).[75] Attempts to selectively acetylate the axial 2-position in (–)-**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 *myo*-inositol ring flipped, i.e the two bulky groups were placed axially.[174] 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 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.[174] This flip is thought to lead to the opposite regioselectivity in the subsequent ring opening, leading to inseparable products. *Reagents & conditions*: $CH_3C(OEt)_3$, *p*TSA, 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 ^{1}H 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 ℃ 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-

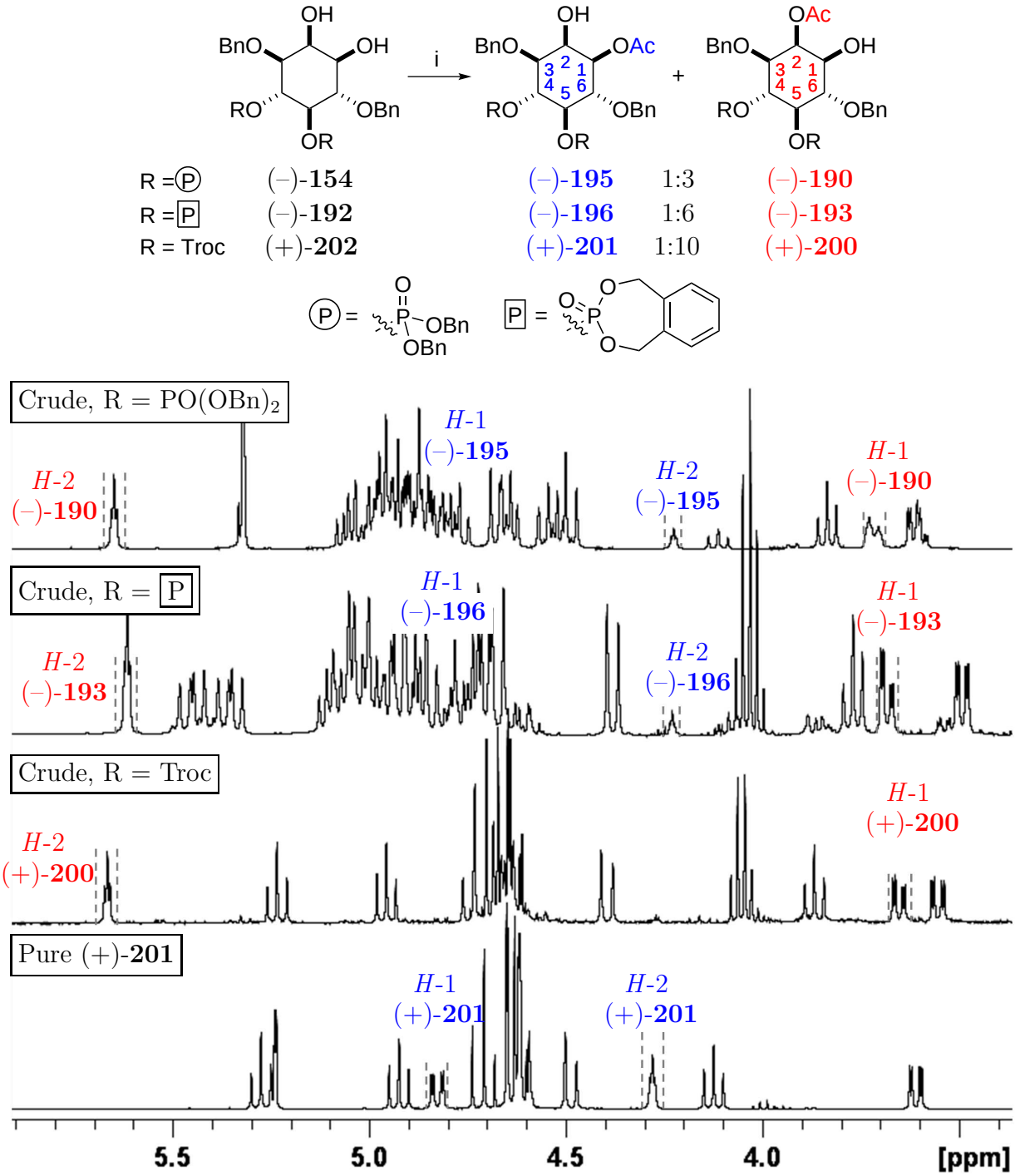


Figure 5.4 Comparison of crude ^{1}H NMR data for acetylation reactions with different substitutions at the 4- and 5-positions (top three) compared to a pure sample of the 1-acetate (+)-**201** (R = Troc). For each compound, the signals for *H*-1 and *H*-2 are labelled, as determined by 2D NMR analysis. 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*: $CH_3C(OEt)_3$, *p*TSA, THF, 1 h; ii. 80% *v/v* Aq. AcOH, 1 h.

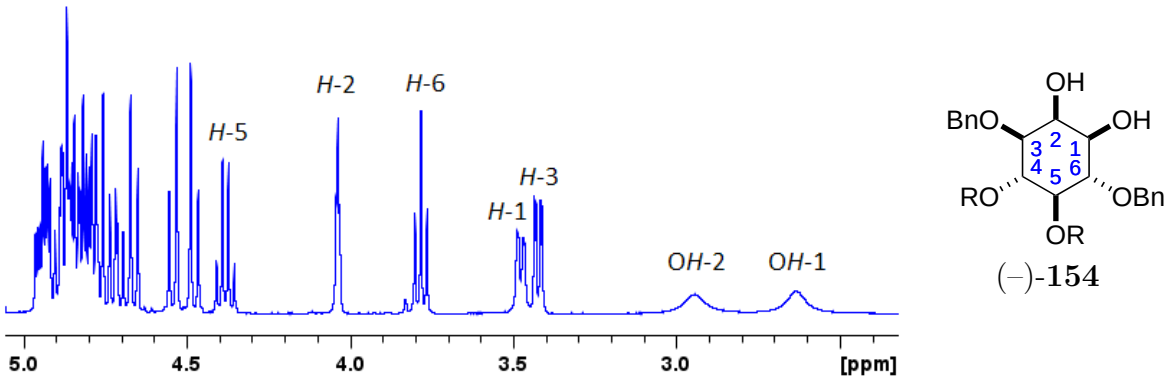
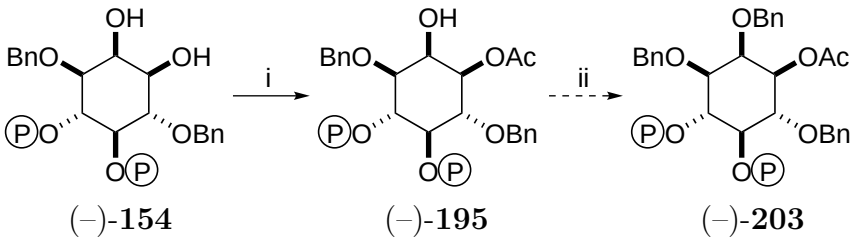


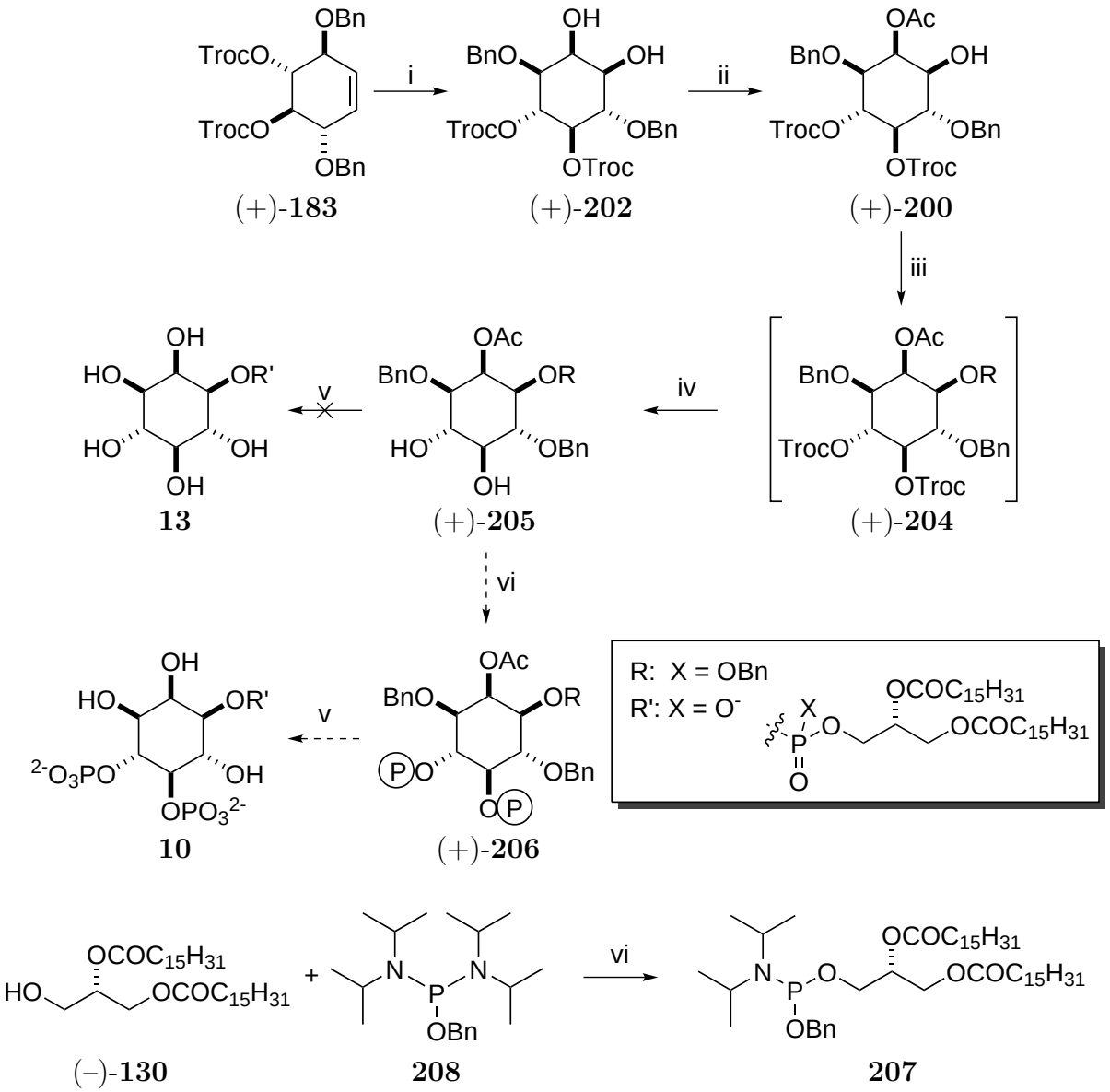
Figure 5.5 Partial ^{1}H NMR spectrum of (–)-**154** revealing only a single conformer under standard conditions. R = $OPO(OBn)_2$

ramidite **187** was prepared from PCl_3 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.



Scheme 5.7 Selective protection of the 1-position with an acetate was possible using AcCl, however, subsequent protection of the 2-position with a benzyl group was not possible. *Reagents & conditions*: i. AcCl, DMAP, pyridine, CH_2Cl_2, 1 h, 53%; ii. Benzyl 2,2,2-trichloroacetimidate, TfOH, dioxane, 18 h *or* NaH, BnBr, DMF, 2 h.

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 sterics 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. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, H_2O, 4 min, 44%; ii. $CH_3C(OEt)_3$, *p*TSA, THF, 1 h then 80% aq. AcOH, 0 °C, 1 h, 86%; iii. Phosphoramidite **207**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 1 h then *m*CPBA, 1 h; iv. Zn, THF, AcOH, 48 h, 62% over two steps; v. Pd Black, H_2, ^{t}BuOH, H_2O, 18 h then aqueous base; vi. Bis(benzyloxy) *N,N*-diisopropylphosphoramidite, 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h then *m*CPBA, 1 h; vi. 1*H*-tetrazole in MeCN, CH_2Cl_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).

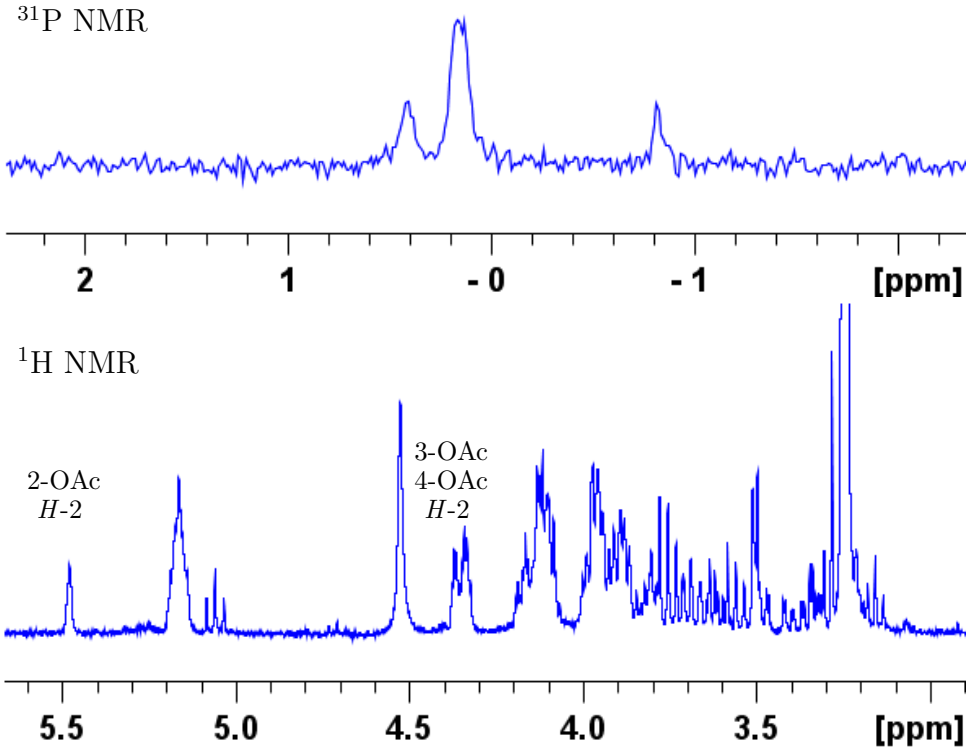
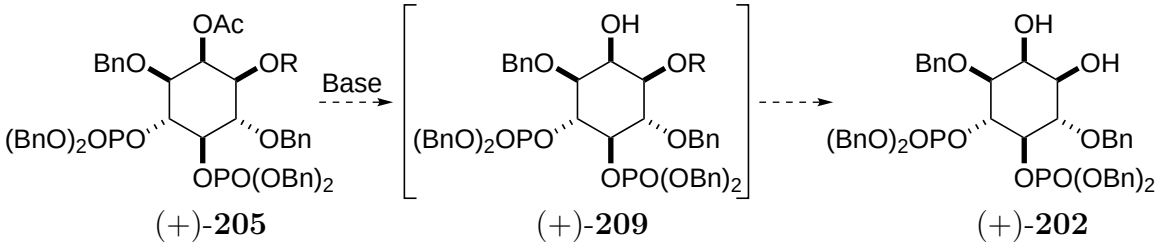


Figure 5.6 Partial ^{31}P NMR (top) and ^{1}H NMR (bottom) spectra in D_4-MeOD of the deprotection by hydrogenolysis of (+)-**205**. Several products, most likely resulting from acetate migration, were observed. Subsequent removal of the acetate also caused hydrolysis of the phospholipid.

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-actetate (*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.[176] 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.



(+)-**205** (+)-**209** (+)-**202**

Scheme 5.9 Hydrolysis of the acetate both pre- and post-hydrogenolysis of the benzyl groups led to rapid hydrolysis 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.

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.[177] 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.[176]

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.[147,172,173] 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.[178] Podeschwa *et al.* had described a route where a benzyl acetal was reduced to give a 2-benzyl protecting group.[75] 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.[75]

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.[179,180] 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.[180] 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_2CO_3, the solution turned dark brown (albeit at a slower rate with K_2CO_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 *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 *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**).[180] The OMB group may be directing the THP protection to the 2-position, improving the regioselectivity in their system and explaining the lower

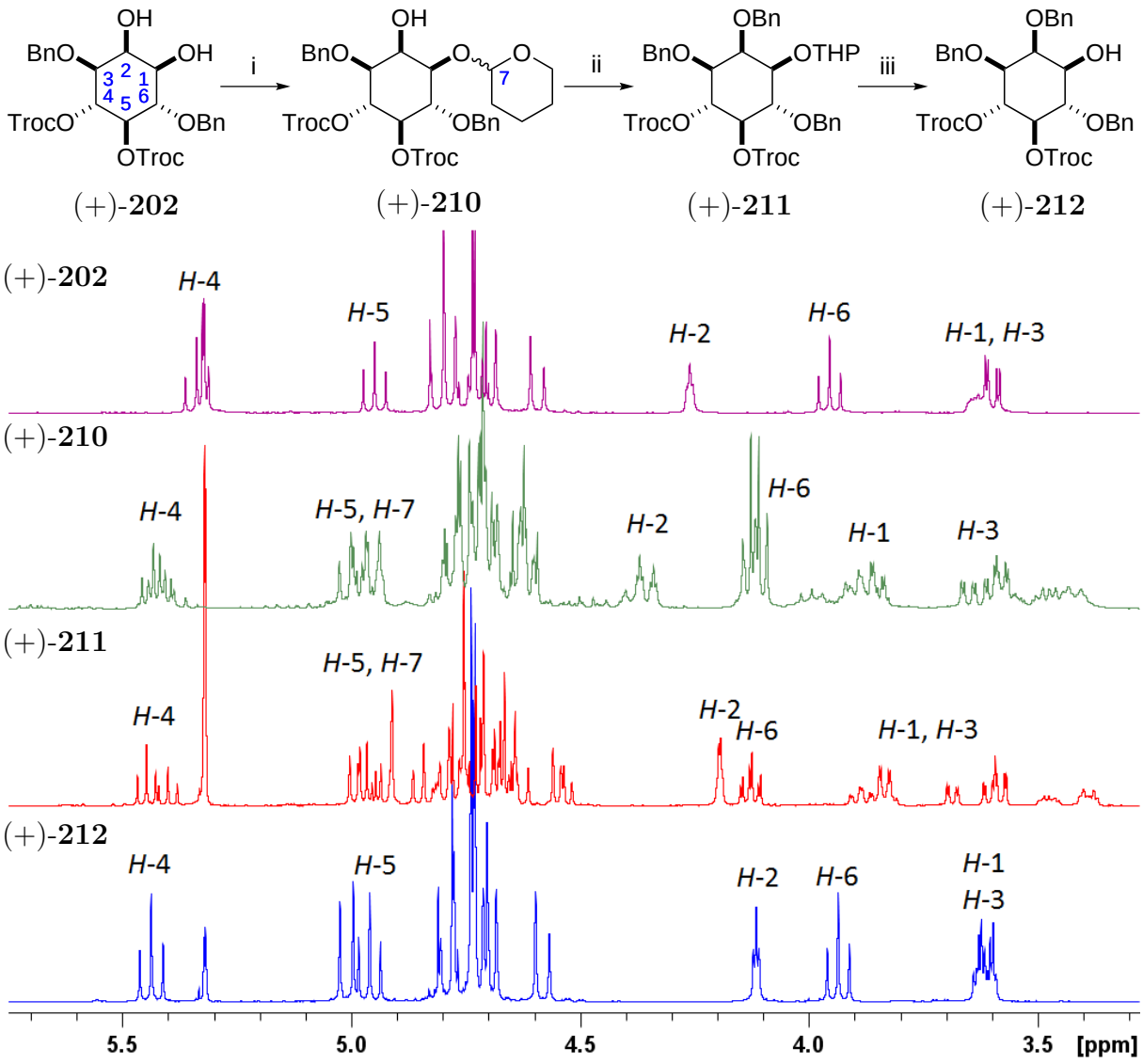


Figure 5.7 Selective benzylation of the diol (+)-**202** was achieved by selective protection of the 1-position using a THP group followed by benzylation and deprotection of the THP. Analysis of intermediate steps ((+)-**210** and (+)-**211**) by ^{1}H NMR analysis (shown) was complicated by the presence of two diastereomers. *Reagents & conditions*: i. DHP, PPTS, CH_2Cl_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%.

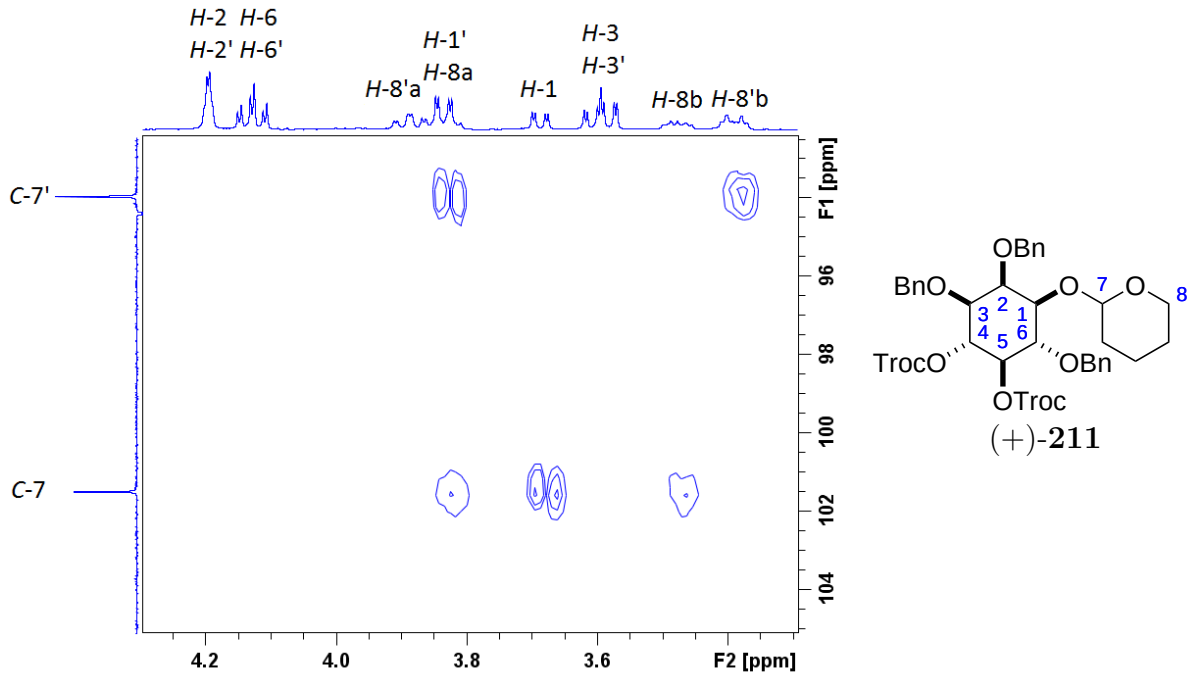


Figure 5.8 Analysis of (+)-**211** by ^{1}H-^{13}C HMBC revealed that the THP group was attached at the 1-position, with correlation between the anomeric carbon on the THP group to the 1-position proton. No correlation was observed from the 2-position on the inositol ring to any of the THP carbon atoms. The two carbon atoms shown (*C*-7 and *C*-7' are the anomeric carbon atoms on the THP ring of either diastereomer.

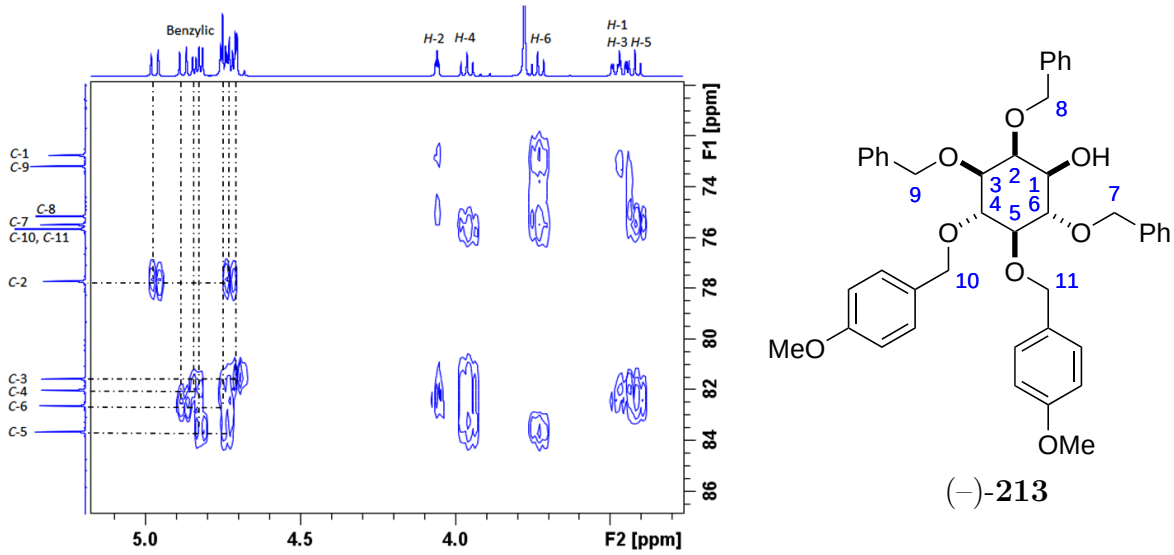
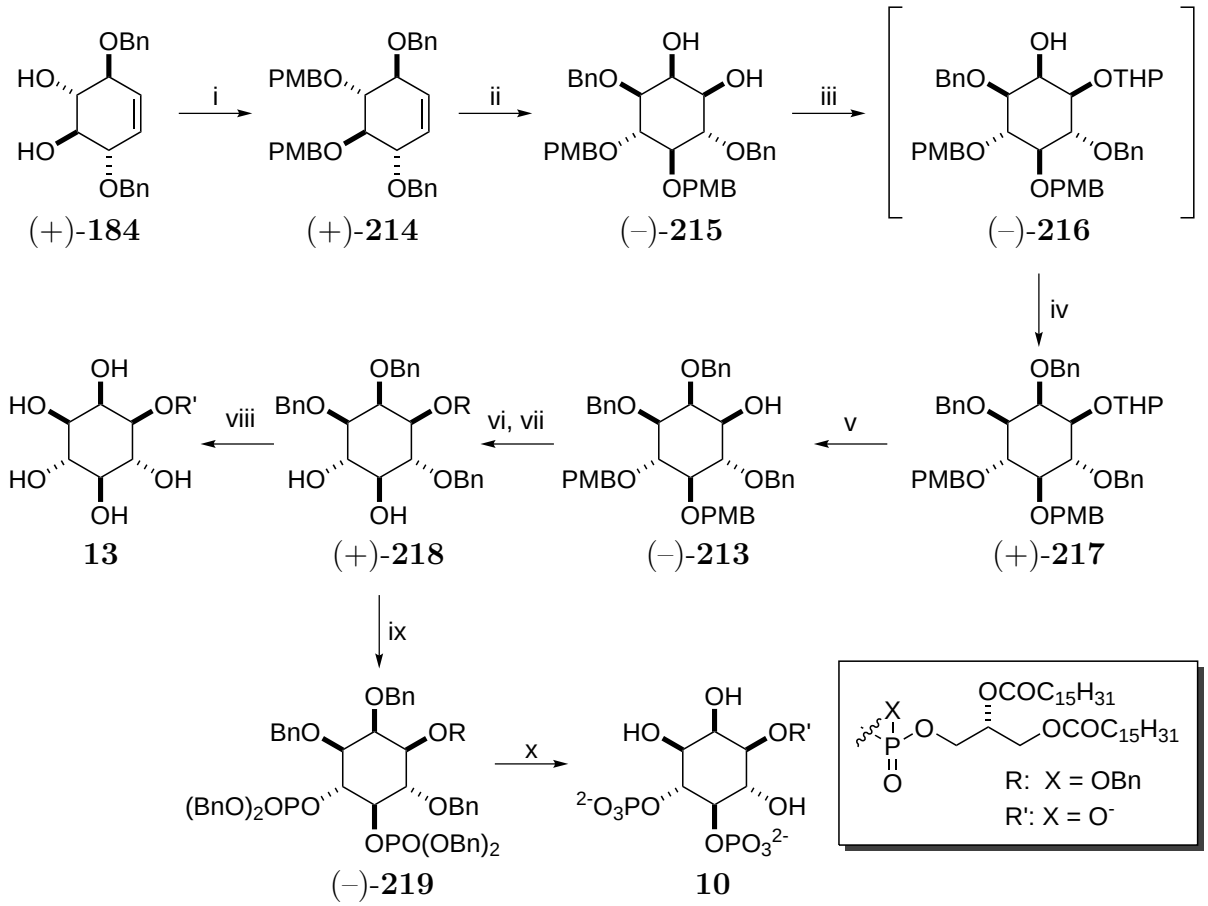


Figure 5.9 ^{1}H-^{13}C HMBC data for (−)-**213** in the inositol/benzylic region of the spectra, showing correlation from the benzylic protons of the PMB and Bn groups to all carbons except *C*-1 on the inositol ring.



Scheme 5.10 Route leading to PtdIns **13** and PtdIns(4,5)P_2 **10** with dipalmitoyl lipid chains. *Reagents & conditions*: i. NaH, DMF, 0 ℃, 30 min then 4-methoxybenzyl chloride, 2 h, 68%; ii. $RuCl_3{\cdot}3H_2O$, $NaIO_4$, MeCN, H_2O, 4 min, 100%; iii. 3,4-Dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 18 h; iv. NaH, DMF, 0 ℃, 30 min then BnBr, 2 h, 26% over 2 steps; v. 80% *v/v* Aq. AcOH, THF, 55 ℃, 2 h, 100%; vi. Phosphoramidite **207**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 2 days then *m*CPBA, –78 ℃, 1 h; vii. DDQ, CH_2Cl_2, H_2O, 2 h, 35% over 2 steps; viii. Pd black, H_2, ^{t}BuOH, H_2O, 18 h, 67%; ix. Bis(benzyloxy) *N,N*-diisopropylphosphoramidite, 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h then *m*-CPBA, –78 ℃, 1 h, 78%; x. Pd black, H_2, ^{t}BuOH, H_2O, 18 h, 89%.

regioselectivity in our system.[180] Subsequent deprotection of the THP group gave the fully-protected inositol system (–)-**213**, with the regiochemistry confirmed using ^{1}H-^{13}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 H_2 gas in the presence of Pd black gave PtdIns **13** as a sodium salt, another PtdInsP_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)P_2 derivative. Subsequent hydrogenolysis of (–)-**219** led to PtdIns(4,5)P_2 **10** as a pentasodium salt (Scheme 5.10).

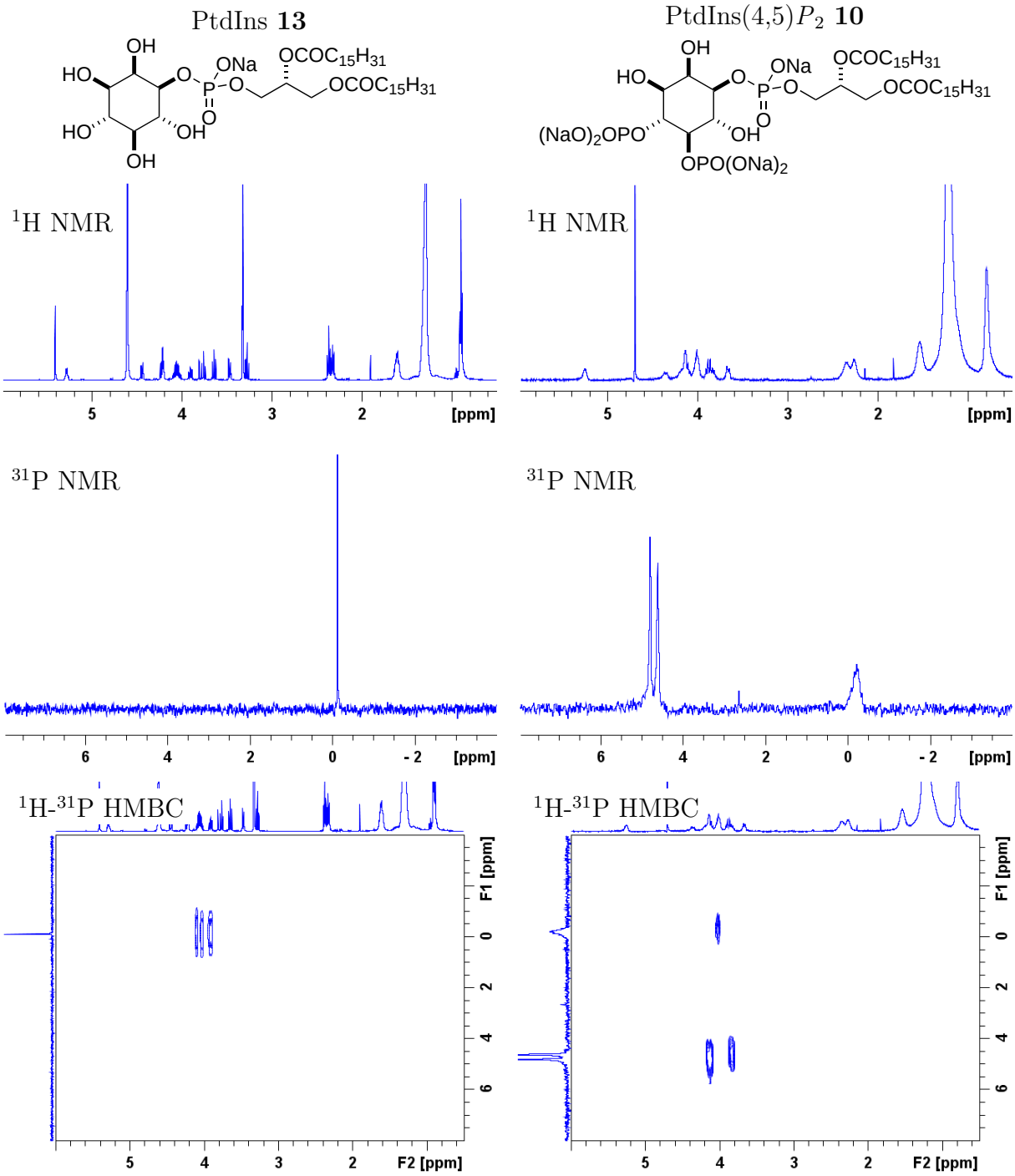
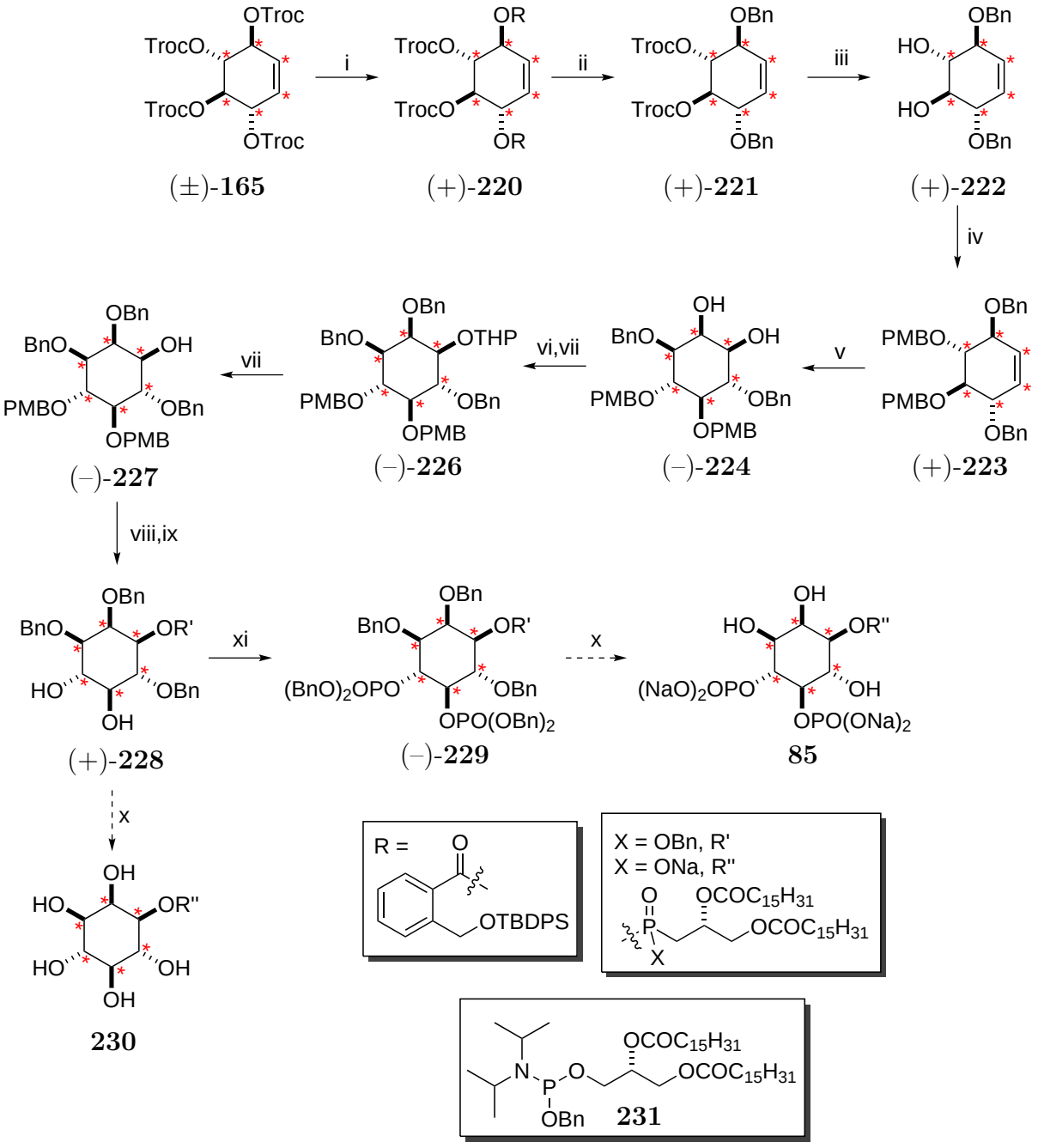


Figure 5.10 Comparison of NMR data for the two products, PtdIns **13** and PtdIns(4,5)P_2 **10**. With the singly charged PtdIns **13**, the peaks are sharp and well resolved as the product is fully soluble in a mixture of CD_2Cl_2 and D_4-MeOD. With PtdIns(4,5)P_2 **10**, the amphiphilic nature of the molecule makes it difficult to find solvents that fully dissolve the molecule, however, reasonable quality data could be obtained in D_2O.

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_2Cl_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 D_6-PtdIns **230** and D_6-PtdIns(4,5)P_2 **85** with 84% D_6, 16% D_5 incorporation. Red asterisks indicate deuterated carbon atoms. *Reagents & conditions*: i. ROH **119**, tetrahexylammonium bromide, [Pd(η^3-allyl)Cl]$_2$, (*S,S*)-ligand (−)-**84**, 1 M aqueous NaOH, CH_2Cl_2, 2 h, 79%; ii. 1:9 *v/v* TFA/CH_2Cl_2, 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. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, H_2O, 6 min, 66%; vi. 3,4-Dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 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), 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h, then *m*CPBA, 2 h; x. DDQ, CH_2Cl_2, H_2O, 1 h 53% (two steps); xi. H_2, Pd Black, $NaHCO_3$, H_2O, ^{t}BuOH, 24-48 h; xii. Bis(benzyloxy) *N,N*-diisopropylphosphoramidite, 1*H*-tetrazole in MeCN, 6 h then *m*CPBA, 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_2Cl_2/D_4-MeOD for **230** and D_2O 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 D_6-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 D_6-PtdInsP_2 **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 D_2O. Analysis of this sample by high resolution mass spectrometry (ES^-) revealed a number of masses which could be attributed to the D_6-*myo*-inositol ring by the distinctive isotope incorporation (85% D_6, 15% D_5, 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

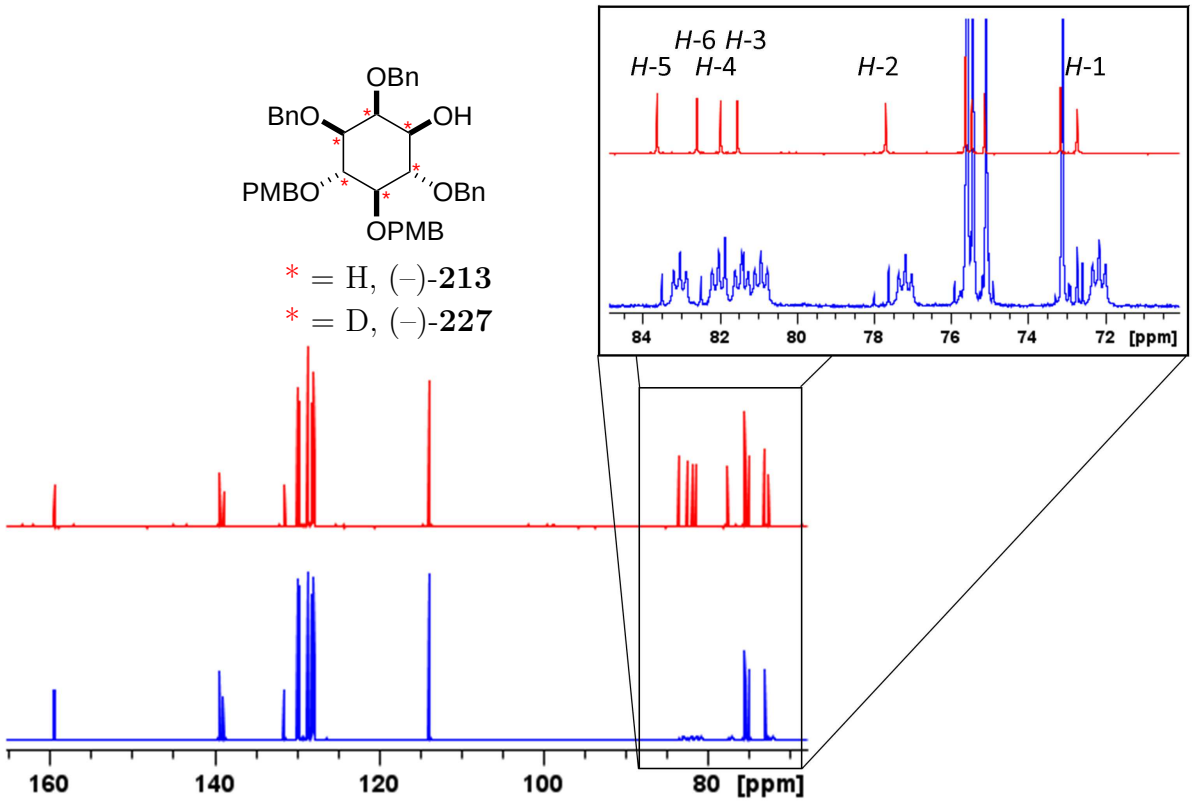


Figure 5.11 Overlay of ^{13}C NMR spectra for the protonated analogue (–)-**213** (top, red) *vs* the deuterated analogue (–)-**227** (blue, bottom), showing the carbon signals directly compare for the two compounds. A small upfield shift is observed for the deuterated carbons (zoomed section).

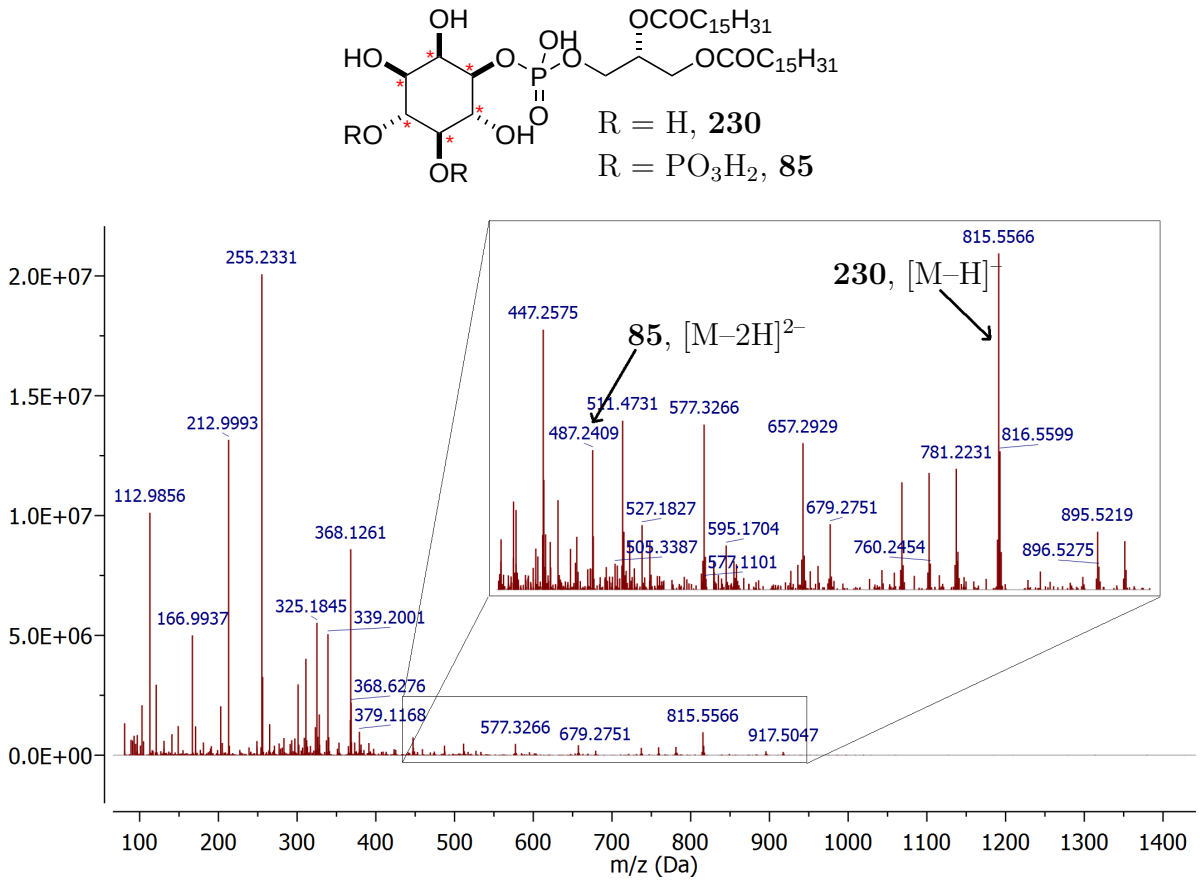


Figure 5.12 High resolution mass spectrum (ES⁻) of the product from deprotection of (–)-**229** (Scheme 5.11), with peaks highlighted as shown by Table 5.1. Multiple peaks consistent with hydrolysis products could be assigned with a high degree of certainty. See table for assignment.

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 $[M\text{-}2H]^{2-}$ where M is the structure shown above (R = PO_3H_2, **85**), however, many hydrolysis products could also be observed.

Mass Detected	Species	Expected Mass	Abundance	% of Max
368.1261	$[M–COC_{15}H_{31}–H]^{2-}$	368.1260	8596121	100
447.2575	$[M–PO_3H–2H]^{2-}$	447.2576	741520	8.6
487.2409	$[M–2H]^{2-}$	487.2408	397993	4.6
577.3266	$[M–COC_{15}H_{31}–2(PO_3H)]^{-}$	577.3265	470889	5.5
657.2929	$[M–COC_{15}H_{31}–PO_3H]^{-}$	657.2929	418196	4.9
737.2593	$[M–COC_{15}H_{31}]^{-}$	737.2592	306354	3.6
759.2414	$[M–COC_{15}H_{31}–H+Na]^{-}$	759.2412	332836	3.9
781.2231	$[M–COC_{15}H_{31}–2H+2Na]^{-}$	781.2231	344914	4.0
815.5566	$[M–2(PO_3H)–H]^{-}$	815.5562	959204	11.1
895.5219	$[M–(PO_3H)–H]^{-}$	895.5225	165105	1.9
917.5047	$[M–(PO_3H)–2H+Na]$	917.5045	138402	1.6

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 D_6-(±)-*myo*-inositol 1-phosphate.[183] During their work, they reported the efficient synthesis of H_6-(±)-*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 D_6-*myo*-inositol 1-phosphate derivative

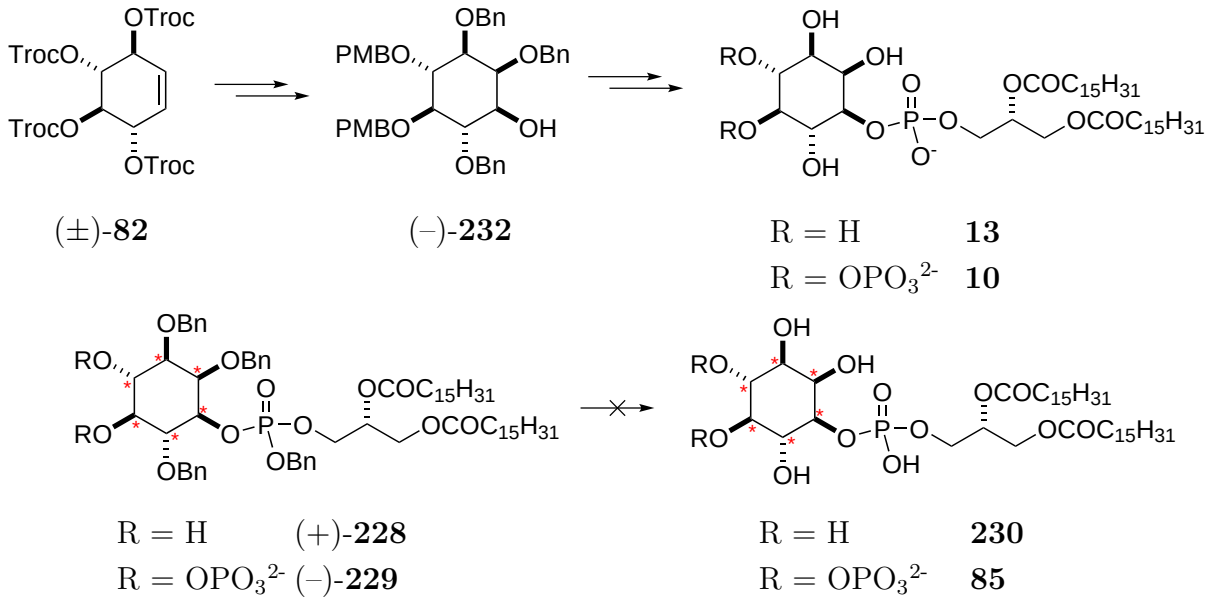
*"for unknown reasons, repeated attempts to perform this reaction on [$^2H_6$]*myo*-inositol resulted in yields of 10% or less."*[183]

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.[183] No attempt was made by the authors to isolate any of these products in pure form.[183] 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.[184–186] In addition, PtdIns **13** and PtdIns(4,5)P_2 **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 D_6-*myo*-inositol **90** in media for biological studies, however, only D_6-PtdIns was analysed and not any PtdInsP_n.[187,188] Further work is required to understand these effects in order to produce the required probes, by potentially using more simple systems (e.g. D_6-*myo*-inositol 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)P_2 **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**.[41] This same methodology was then applied to D_6-*myo*-inositol derivatives with some success, leading to the fully protected D_6-PtdIns (+)-**228** and D_6-PtdIns(4,5)P_2 (–)-**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 D_6-*myo*-inositol phosphate derivatives previously reported.[183] Further work is required to understand the hydrolysis of the phos-



Scheme 5.12 Synthesis of PtdIns **13** and PtdIns(4,5)P_2 **10** was possible from enantiopure (+)-**175**, however, deprotection of the fully protected D_6-PtdIns **230** and D_6-PtdIns(4,5)P_2 **85** resulted in partial hydrolysis of the phosphates, making full characterisation difficult.

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

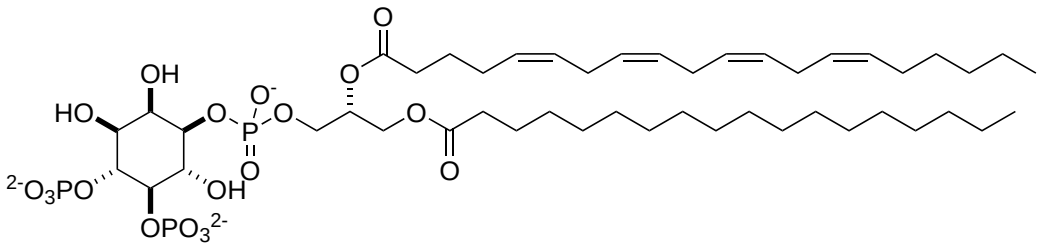


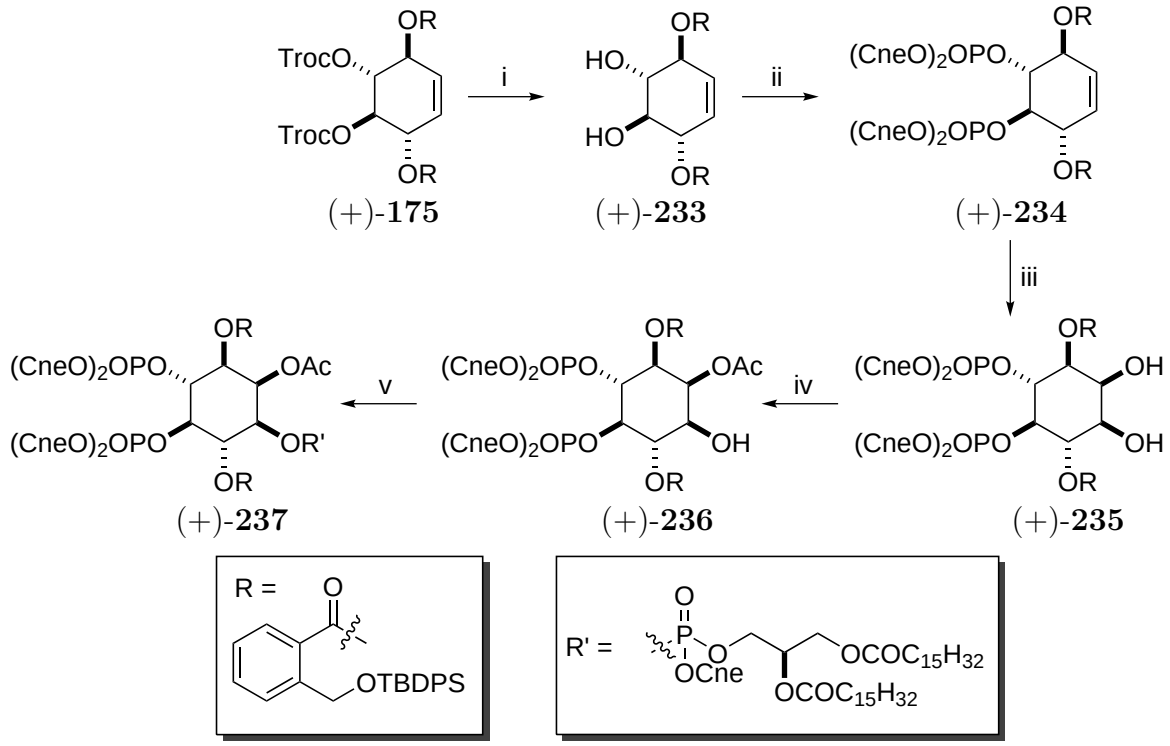
Figure 6.1 Target molecule incorporating unsaturated lipid chains onto the glycerol backbone.

could potentially allow acid-catalysed deprotection of the benzoate derivatives, rather than base-mediated hydrolysis, which was unsuccessful with the phospholipid present (Chapter 3). By the use of proximity assisted protecting groups, the use of basic hydrolysis could be avoided.

6.2 Use of Proximity Assisted Protecting Groups

6.2.1 Synthesising a Fully Protected PtdIns(4,5)P_2 Derivative

Starting from (+)-**175**, synthesised using the Trost asymmetric allylic alkylation, it was possible to synthesise a fully protected PtdIns(4,5)P_2 precursor (+)-**237** (Scheme 6.1) in an analogous manner to that described for the benzoate derivative (+)-**98** (Chapter 3). The sythesis 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



Scheme 6.1 Synthesis of (+)-**237** using a proximity-assisted protecting group strategy. *Reagents & conditions*: Zn, AcOH, THF, 0 ℃, 4 h then H_2O, 18 h, 74%; ii. **126**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 2 h, then *m*CPBA, –78 ℃ then room temperature, 1 h, 90%; iii. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, H_2O, 8 min, 83%; iv. $CH_3C(OEt)_3$, *p*TSA, 18 h then 80% *v/v* aqueous AcOH, 1 h, 50%; v. **131**, 1*H*-tetrazole in MeCN, CH_2Cl_2, 1 h, then *m*CPBA, –78 ℃ then room temperature, 30 min, 76%.

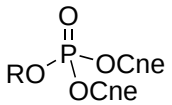
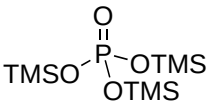
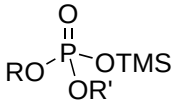
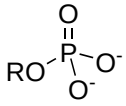
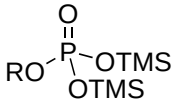
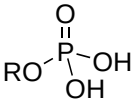
of (+)-**237** was achieved (Scheme 6.1) in 21% yield over five steps. The acetate protecting group was used in the first instance on the 2-position, despite the fact that it was not possible to remove in previous synthetic endeavours. This is because the installation of the acetate onto the 2-position was high yielding, allowing for rapid evaluation of the proximity-assisted protecting groups (*cf* the THP protecting group strategy, Chapter 5).

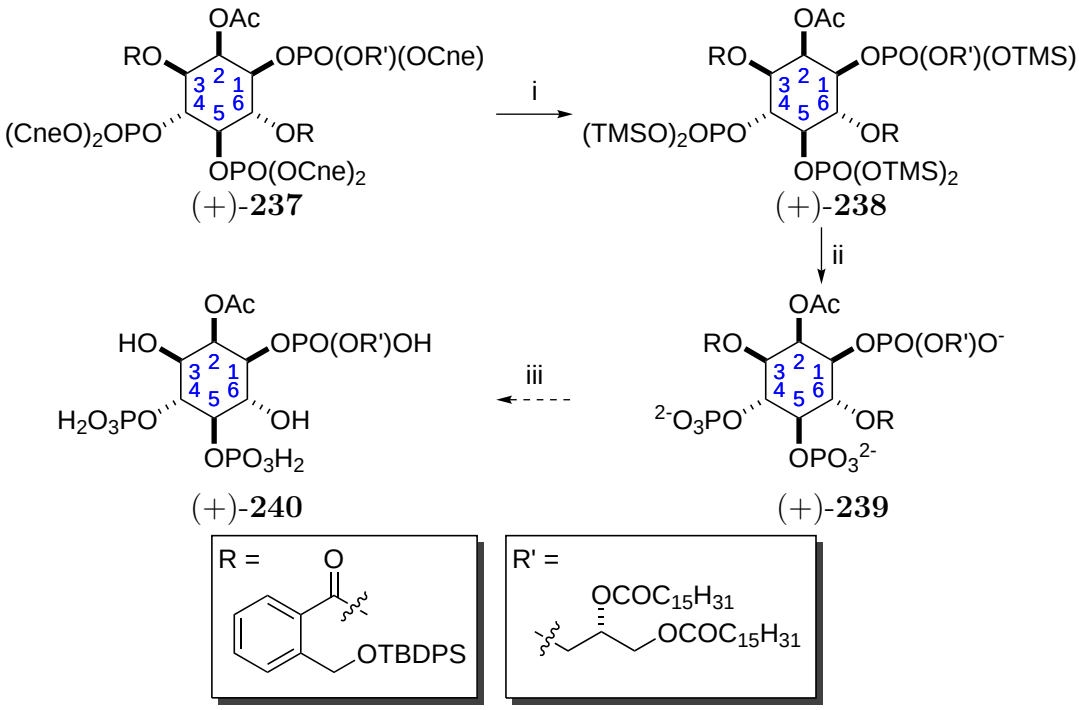
6.3 Deprotection of PtdIns(4,5)P_2 Derivative

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_2O 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 6.1 Indicative shifts (in $CDCl_3$) of phosphate esters in ^{31}P NMR during deprotection.[189]

Species	^{31}P NMR Shift / ppm	Species	^{31}P NMR Shift / ppm
	−3		−25
	−11		−3–0
	−19		0–5



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_2Cl_2, 18 h; ii. MeOH, 1 h; iii. 1:9 TFA/CH_2Cl_2, 18 h.

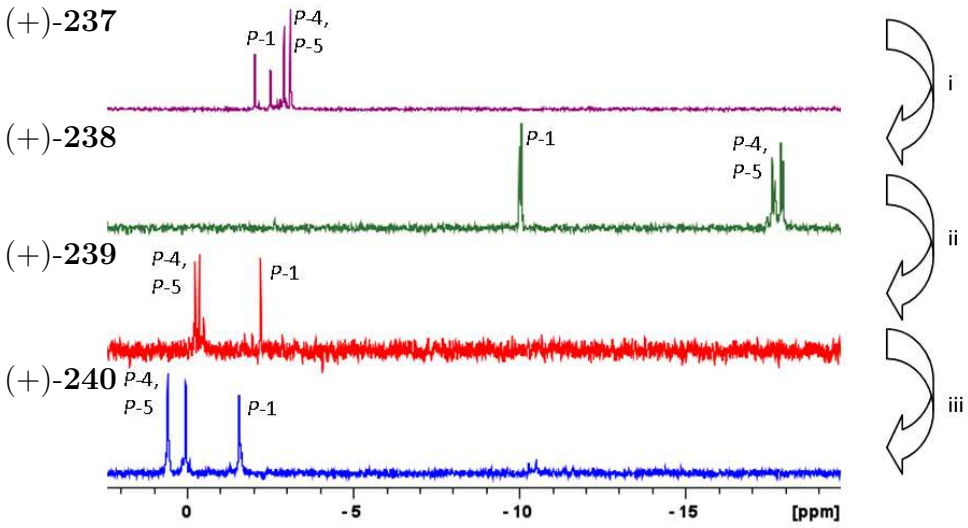
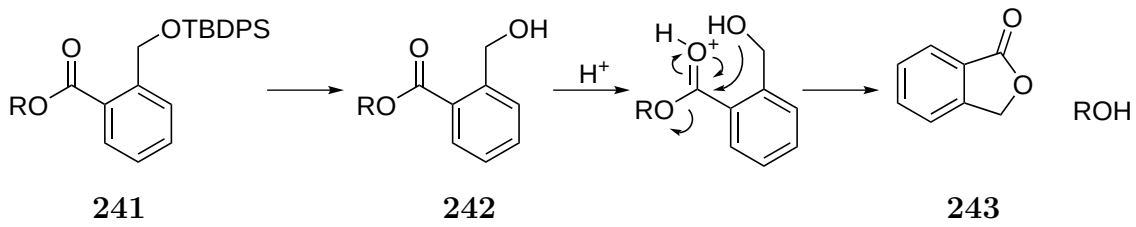


Figure 6.2 Deprotection of the 2-cyanoethyl groups (see Scheme 6.2) was monitored by ^{31}P NMR analysis in $CDCl_3$, as the ^{1}H NMR becomes increasingly complicated as more deprotection steps are carried out. Top (purple): starting material (+)-**237**; upper middle (green): TMS-protected (+)-**238**; lower middle (red): deprotonated (+)-**239**; bottom (blue): Protonated (+)-**240**. *Reagents & conditions*: Barton's base, trimethylsilyl chloride, CH_2Cl_2, 18 h; ii. MeOH, 1 h; iii. 1:9 TFA/CH_2Cl_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.[164,168] 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).



241 **242** **243**

Scheme 6.3 Once the TBDPS group has been removed from **241**, rapid cyclisation of the resulting free primary alcohol causes deprotection of the ester. This cyclisation reaction is especially fast under acidic conditions, given no intermediates are observed with the free primary hydroxyl group which can also be used to remove the TBDPS in a single-pot, two step method.

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.*[190] 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

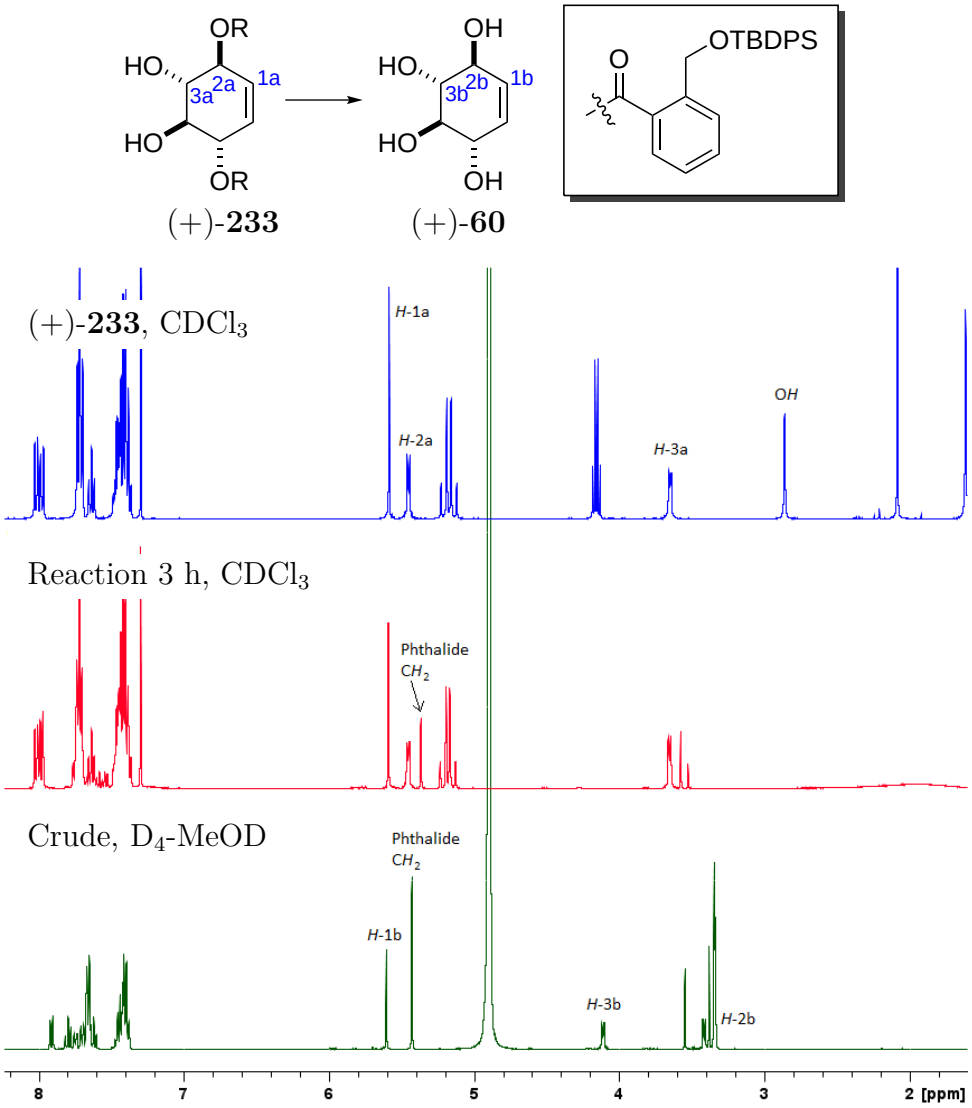
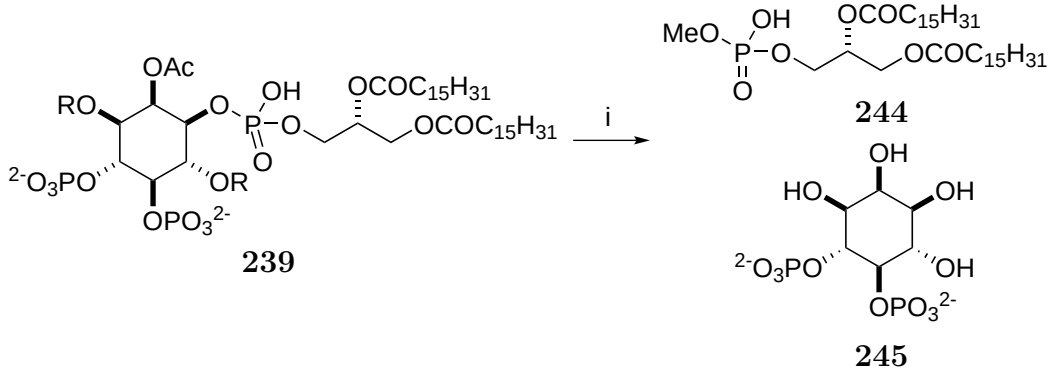


Figure 6.3 Deprotection of two proximity assisted protecting groups using TMSBr in MeOH as an anhydrous source of HBr, analysed using ^{1}H NMR. Top (blue): Starting material (+)-**233** in $CDCl_3$; Middle (red): Reaction mixture after 3 h in $CDCl_3$; Bottom (green): Reaction mixture after 18 h in D_4-MeOD. *Reagents & conditions*: 2 eq. TMSBr, MeOH, 18 h, not isolated or TFA/$CH_2Cl_2$1:9, 1 h, not isolated.

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.



Scheme 6.4 Using TMSBr in MeOH overnight resulted in cleavage of the phosphate ester to give the presumed methylphosphate glycerol ester **245** and InsP_2 **244**. *Reagents & conditions*: TMSBr, MeOH, 18 h, not isolated.

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).[168] 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_2Cl_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/CH_2Cl_2 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 suspended in $CDCl_3$, filtered and ^{1}H 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).

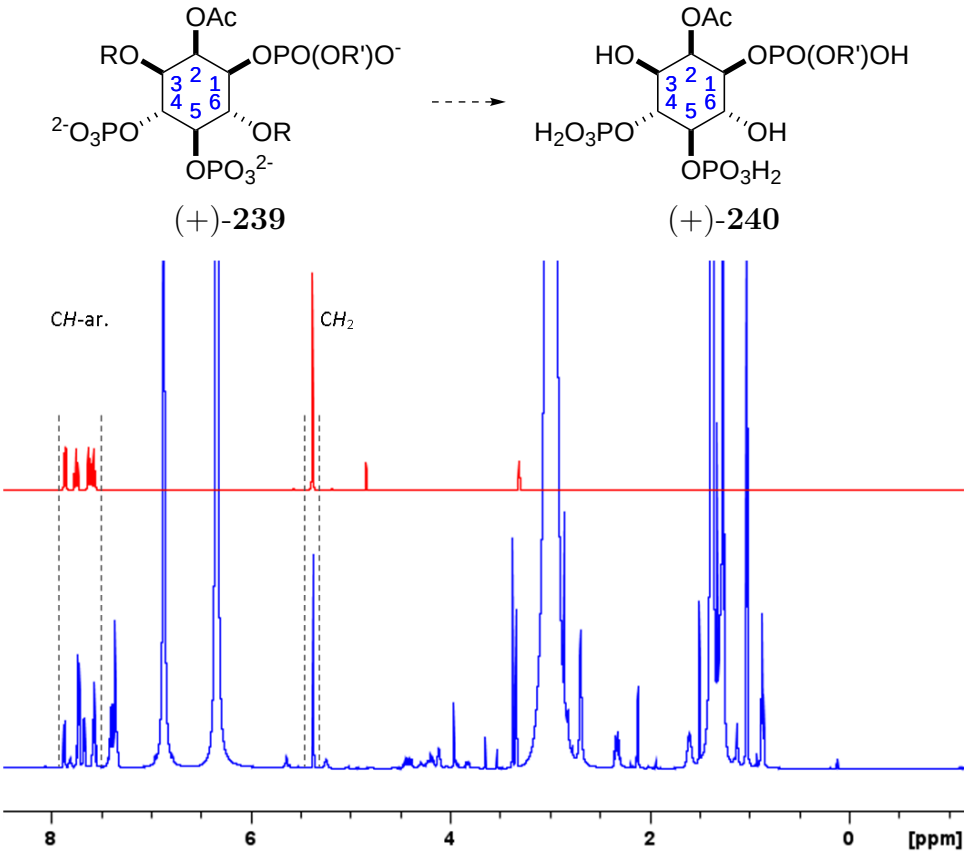


Figure 6.4 Comparison of the ^{1}H NMR spectra in D_4-MeOD of an authentic sample of phthalide **179** (top, red) *vs.* the crude reaction mixture after stirring (+)-**239** in a 1:9 mixture of TFA in CH_2Cl_2 for 1 h (bottom, blue). This shows at least a partial deprotection could be achieved.

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.[38,136,191] Triethylammonium bicarbonate (TEAB) buffer was chosen for elution, as it can be prepared by bubbling CO_2 gas through an aqueous solution of NEt_3, 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).[38,136,191] Interestingly, upon ^{1}H NMR analysis of the solid dissolved in D_2O (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

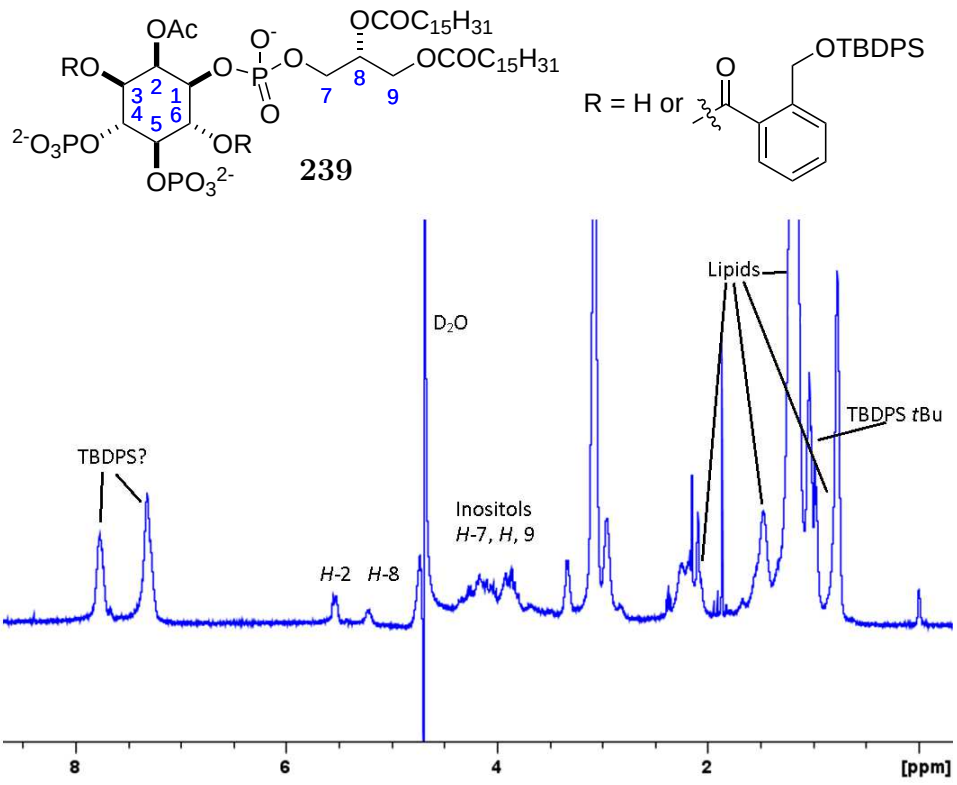
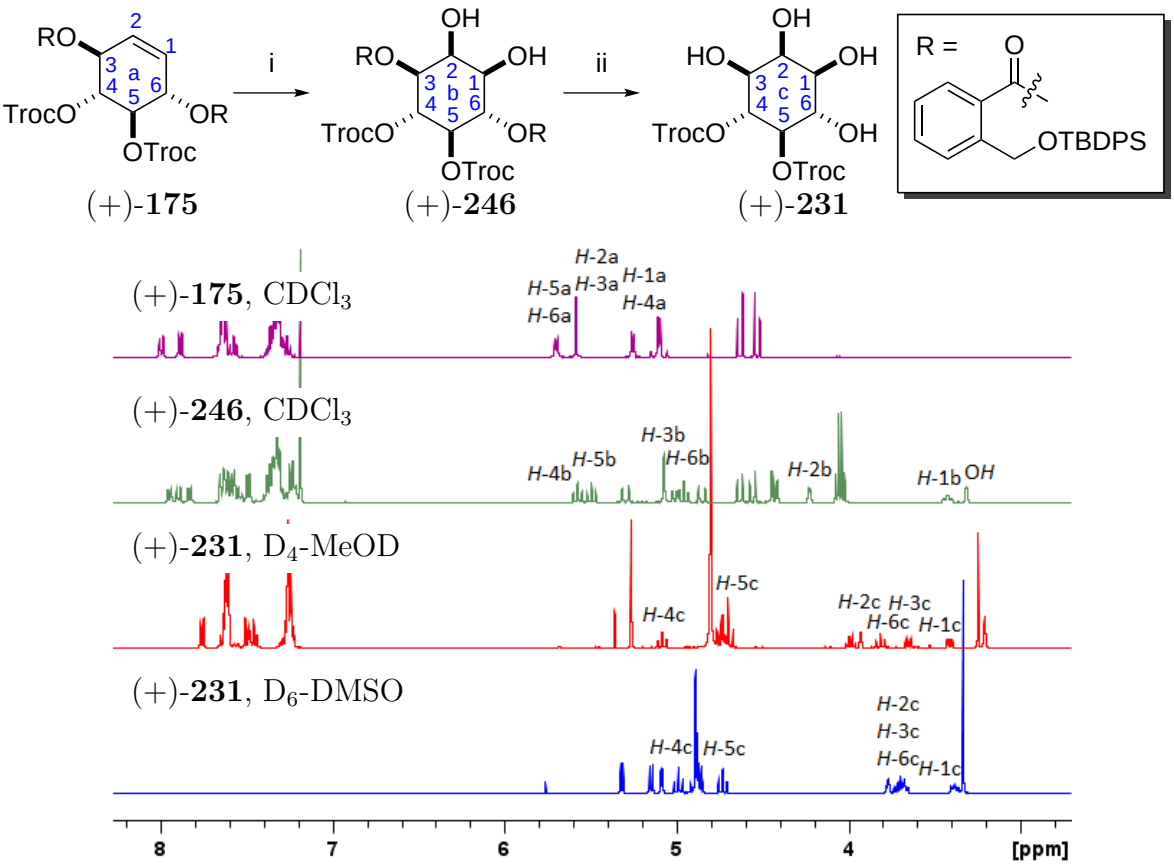


Figure 6.5 Selected region of ^{1}H NMR spectrum in D_2O (with water supression) of the residue isolated after ion-exchange column chromatography in the 1.0 M and 1.25 M TEAB fractions, revealing the presence of residual aromatic resonances in the spectrum.

^{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_2Cl_2 mixtures for 48 h, including the use of a 1:1 TFA/CH_2Cl_2 mix, or the use of 2 M HCl in Et_2O/CH_2Cl_2, were also unsuccessful.

6.3.3 Test Systems to Understand the Deprotection

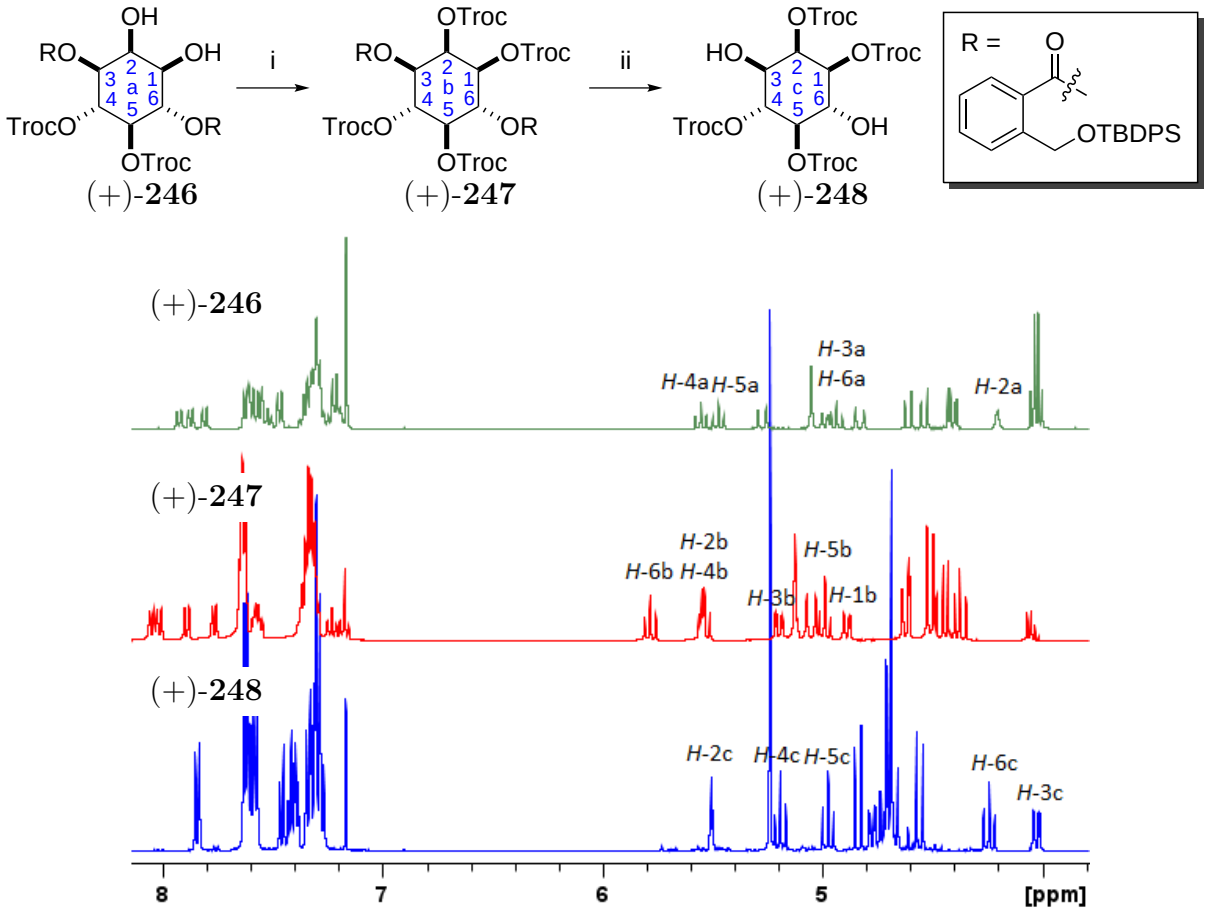
To begin to understand the complex deprotection, several test systems were investigated to probe which groups are tolerated by the proximity assisted protecting groups. Conditions were initially found using the conduritol B derivative (+)-**175** (Scheme 6.5), however, the proximity-assisted protecting groups in this system were masking allylic alcohols, rather than the secondary alcohols found in *myo*-inositol derivatives. Using a sample of



Scheme 6.5 Dihydroxylation of (+)-**175** led to the first test system used to confirm the potential problems observed when working with a proximity assisted protecting group in a full PtdInsP_n system. Complete deprotection of (+)-**246** was observed in under an hour under acidic conditions by ^{1}H NMR analysis. Top (purple): (+)-**175**; Upper middle (green): (+)-**246**; Lower middle (red): Crude reaction mixture post-deprotection containing (+)-**231**; Bottom (blue): Pure sample of (+)-**231**. *Reagents & conditions*: i. $NaIO_4$, $RuCl_3{\cdot}3H_2O$, MeCN, EtOAc, H_2O, 4 min; ii. TFA, CH_2Cl_2, 1 h, 34% over two steps.

(+)-**175**, a *syn*-dihydroxylation was performed to form the *myo*-inositol derivative (+)-**246** (Scheme 6.5). Upon treatment with 1:9 TFA in CH_2Cl_2, complete deprotection was observed in one hour. In the ^{1}H 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, ^{1}H NMR analysis (in D_6-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 ^{31}P 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

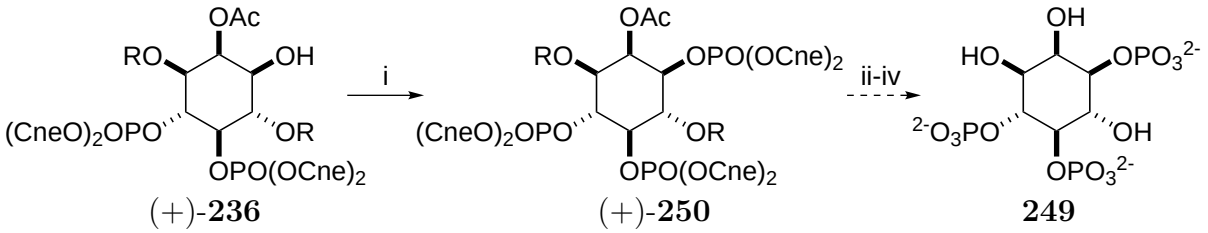
group participation of the two free hydroxyl groups may be assisting in the deprotection of (+)-**246** (*cf.* phospholipid hydrolysis, Chapter 5). To test this hypothesis, the two free hydroxyl groups were protected with Troc groups to give (+)-**247** and the same deprotection conditions were used 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 CH_2Cl_2, complete deprotection of the proximity assisted groups was observed in one hour, as observed by ^{1}H NMR analysis in $CDCl_3$. Top (green): (+)-**246**; Middle (red): (+)-**247**; Bottom (blue): (+)-**248**. *Reagents & conditions*: i. TrocCl, DMAP, pyridine, CH_2Cl_2, 18 h, not isolated; ii. TFA, CH_2Cl_2 1:9, 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)P_3 **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)P_3 derivative (+)-

250 (Scheme 6.7). In a similar manner to previous deprotections of PtdInsP_n derivatives, the phosphate groups were deprotected first. The resulting material was then stirred in a 1:9 mixture of TFA and CH_2Cl_2, initially for 1 h. Analysis of the crude material by ^{31}P NMR and ^1H 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 PtdInsP_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 ^1H NMR in D_2O revealed aromatic signals. No other inositol-like products were isolated from the ion exchange column.



(+)-**236** (+)-**250** **249**

Scheme 6.7 Synthesis of an InsP_3 derivative (+)-**250**, leading to further understanding of the deprotection of the proximity assisted protecting groups. *Reagents & conditions*: i. **126**, 3-4% 1*H*-tetrazole in MeCN, CH_2Cl_2, 18 h then *m*CPBA, –78 °C, then room temperature 1 h, 70%; ii. Barton's base, TMSCl, CH_2Cl_2, 18 h; iii. MeOH, 1 h; iv. 1:9 TFA/CH_2Cl_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_2Cl_2 once the phosphates

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 InsP_3 derivative (+)-**250** or PtdInsP_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_2Cl_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 **244** 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).

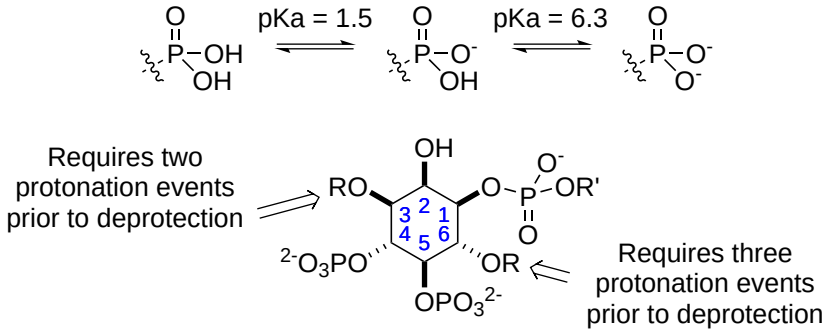


Figure 6.6 Phosphate monoesters have two pK_a values, 1.5 and 6.3 in aqueous solution, for the two protons. For the deprotection of the proximity assisted protecting groups, it is likely that the phosphates need to be non-charged for the reaction to be successful. On the 6-position, where the group is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

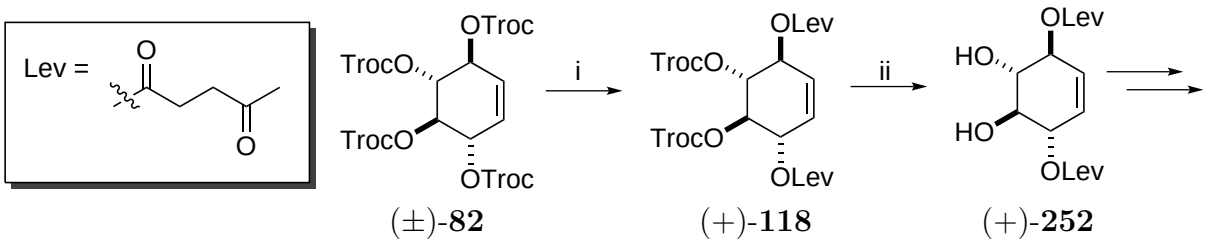
6.3.5 Other Deprotection Conditions

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.[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 synthesising PtdIns(3,4,5)P_3 **19** and PtdIns(3,5)P_2 **18**.[88,169] 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).[64,81] 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 concentration, 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 potentially 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).



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.[88,169] *Reagents & conditions*: i. Levulinic acid, (*S,S*)-ligand (–)-**84**, [Pd(η^3-allyl)Cl]$_2$, tetrahexylammonium bromide, 1 M aq. NaOH, CH_2Cl_2, 24 h, 57%; ii. Zn, 80% aq. AcOH, THF, 1 h, 92%.

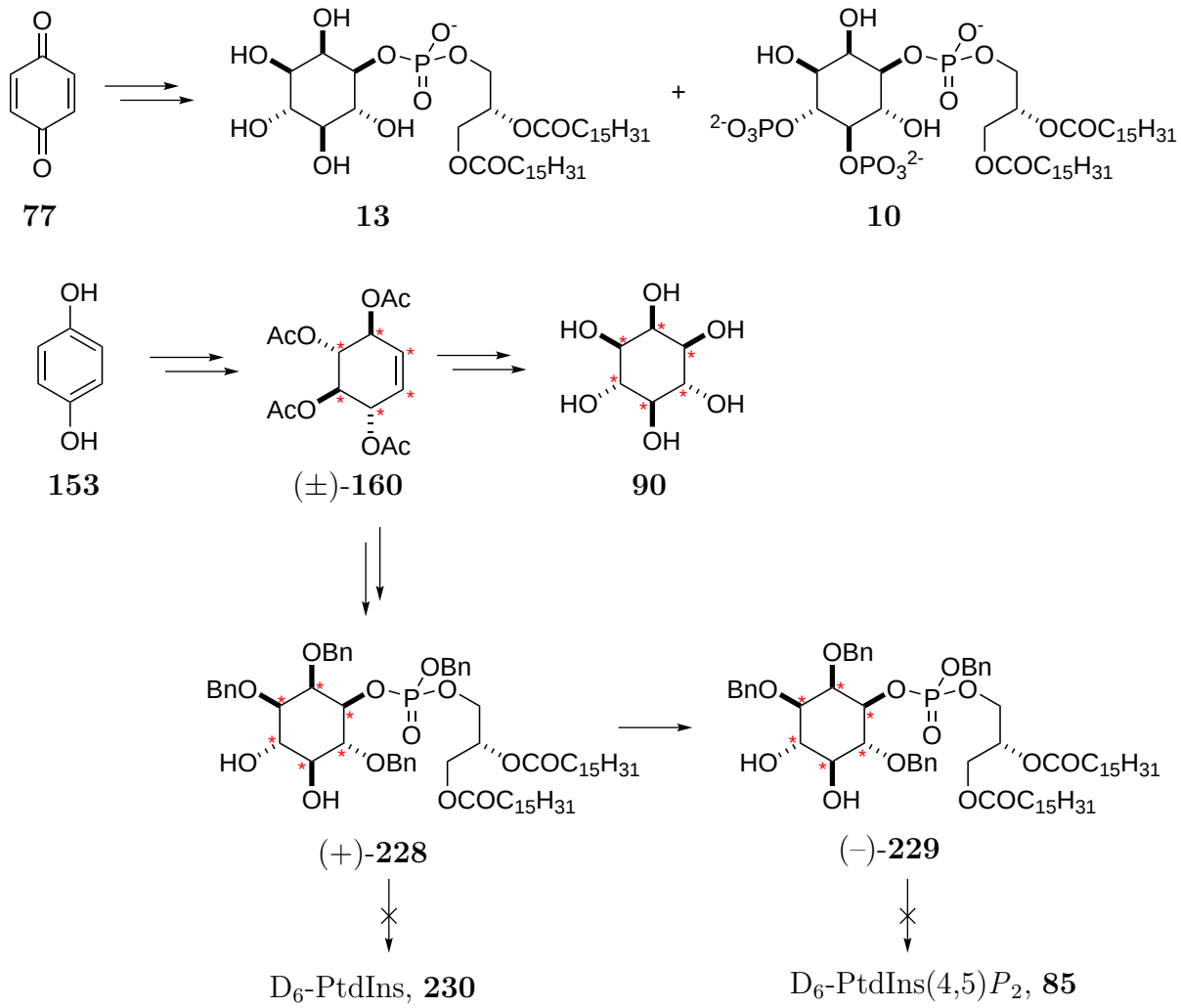
6.4 Conclusions

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 unsuccessful. 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_{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 *et al.* have already shown that it is possible to remove these groups in the presence of unsaturated systems.[88,169] This approach would enable rapid, efficient synthesis of deuterated PtdIns(4,5)P_2 with unsaturated lipid chains. Secondly, the Lev group opens the potential for reliably synthesising a mono-protected derivative (+)-**255** from the Trost asymmetric allylic alkylation. With a derivative such as this, other PtdInsP_{n} derivatives could be efficiently synthesised using this methodology.

6.5 Summary & Future Work

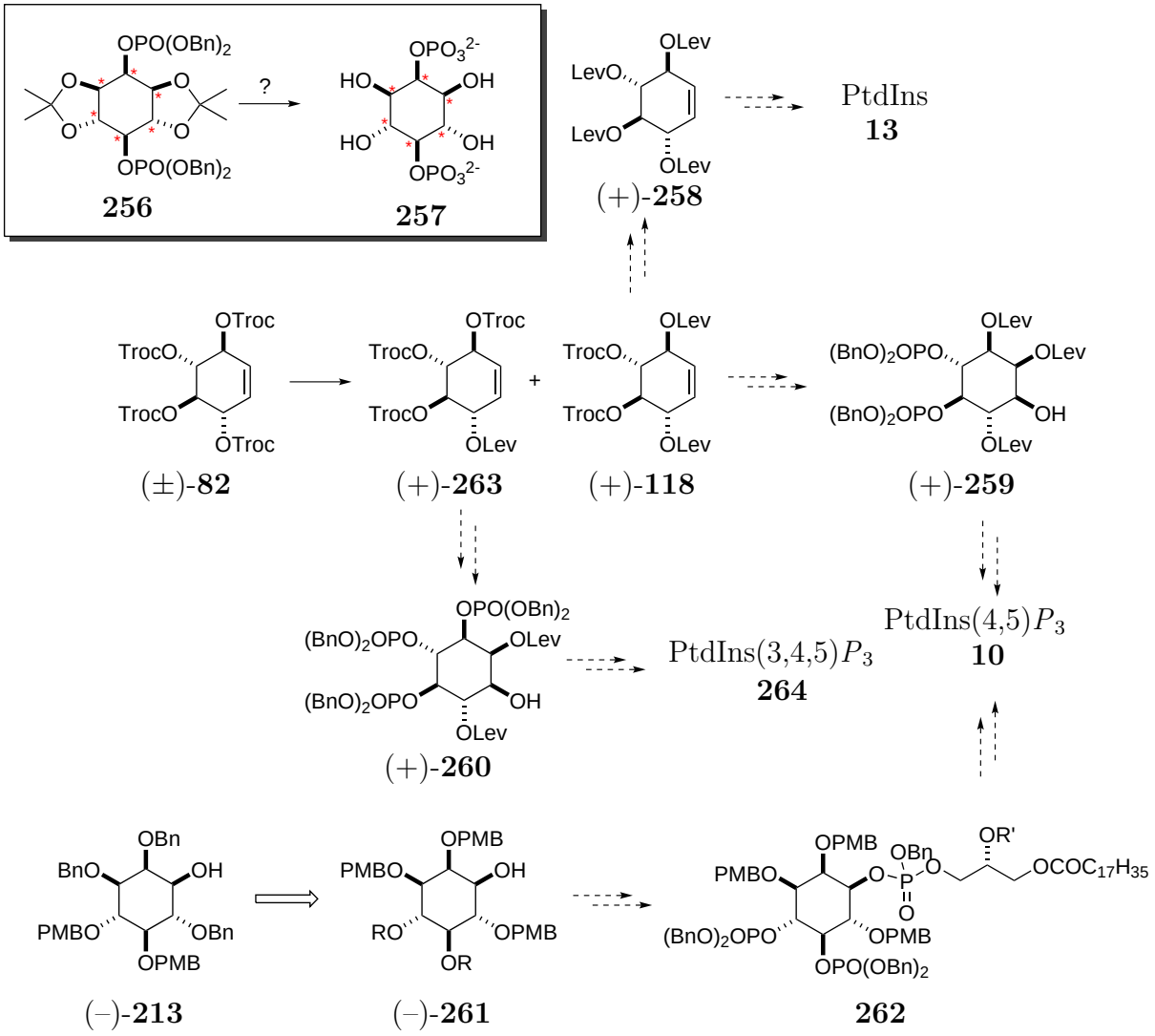
A route starting from *p*-benzoquinone **77** toward a single enantiomer of PtdIns **13** and PtdIns(4,5)P_2 **10** with C_{16} saturated lipid chains has been developed. The key enantioselective step used a palladium-catalysed Trost asymmetric allylic alkylation as a dynamic kinetic resolution to afford 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.[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).[196]



Scheme 6.10 Possible future work based on the work described. First, the hydrogenolysis of D_6-*myo*-inositol 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 δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ(TMS) = 0.00. The spectra are calibrated using the solvent peak with the data provided by Fulmer *et al.*[197] 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 n*H*. 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 δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ(TMS) = 0.00. The spectra are calibrated using the solvent peak with the data provided by Fulmer *et al.*[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_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_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 δ in units of parts per million (ppm) relative to 85% phosphoric acid as an external reference where $\delta(H_3PO_4)$ = 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 δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ(TMS) = 0.00 ppm. The spectra are calibrated using the solvent peak with the data provided by Fulmer *et al.*[197] 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_{254} aluminium-supported chromatography sheets, unless otherwise stated. Visualisation was by absorption of UV light (λ_{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 ℃ unless otherwise stated.

In vacuo refers to removal of solvent on a Buchi® rotary evaporator under reduced pressure in a water bath at 40 ℃ 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 $NaBD_4$ of 90% chemical purity.

Benzyloxy bis(*N,N*-diisopropyl)phosphoramidite 208 was prepared by Amelié 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.*[198] except in the cases of tetrahydrofuran which was distilled from sodium / benzophenone and *N,N*-dimethylformamide which was purchased from Sigma Aldrich UK in a SureSeal® 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® AD-H column (5 μm, 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 μm, 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 dissolveing in either a 1:1 mixture of isopropanol/hexane or in neat $CHCl_3$. Flow rates was kept constant throughut all runs at 1.0 mL min^{-1}.

Table 7.1 Timings and concentrations used in the method for the analytical normal phase HPLC column where B is the most polar solvent. Min and max indicate the lowest and highest concentration used respectively (typically 0 and 100% respectively).

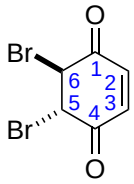
Time Start / min	Time End / min	Start Concentration B %	End Concentration B %
0	1	Min	Min
1	16	Min	Max
16	21	Max	Max
21	22	Max	Min
22	30	Min	Min

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.

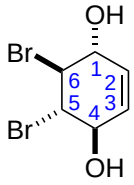
7.2 Enantioselective Synthesis

(±)-*trans*-5,6-Dibromocyclohex-2-ene-1,4-dione ((±)-78)[67]



The procedure from Adelt *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 ℃ 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 ℃ *via* a dropping funnel. The solution was stirred at 0 ℃ 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 *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 ℃ (from isopropanol) {lit.[67] 82-83 ℃}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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]

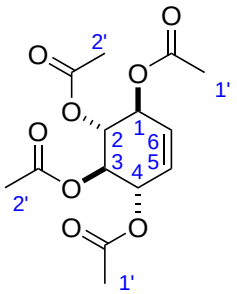
(±)-*trans*-5,6-Dibromocyclohex-2-ene-1,4-diol ((±)-79)[67]



The procedure from Adelt *et al.* was used.[67] A solution of (±)-**78** (13.4 g, 50 mmol, 1.0 eq.) in Et_2O (225 mL) was cooled to –5 ℃ 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_2O (3 × 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 ($[M^{79}Br^{81}Br–H]^-$, 100%), 272.6 ($[M^{81}Br_2–H]^-$, 82%). These data are in good agreement with the literature.[67]

(±)-(1*RS*,2*SR*,3*SR*,4*RS*)-Cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate ((±)-81)[80,109]



A modification of the procedure from Guo *et al.* was used.[82] To a solution of (±)-**79** (10.99 g, crude) in Ac_2O (300 mL) was added solid K_2CO_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 Et_2O (3 × 200 mL). The organic components were combined, dried with $MgSO_4$, 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 Et_2O, and dropwise addition of boiling petroleum ether until the solution was cloudy, followed by cooling to –20 ℃ for 1 h to afford the title compound as colourless needles (5.54 g, 35% over 3 steps): R_f 0.85 (Et_2O/petroleum ether 1:1); m.p. 84-85 ℃ (from Et_2O/petroleum ether), 88-89 ℃ (from EtOH) {lit.[109] 85-85.5 ℃, lit.[199] 86-88 ℃, lit.[200] 92-93 ℃}; ^{1}H NMR (400 MHz; $CDCl_3$) 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]

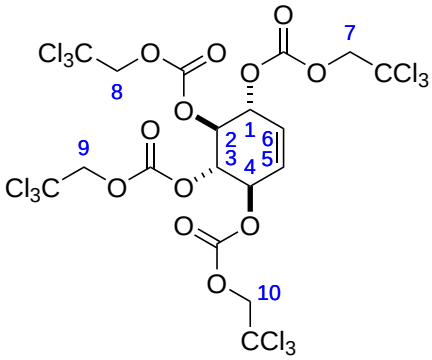
Multistep Procedure from p-*benzoquinone:*

To a solution of *p*-benzoquinone (10.8 g, 100 mmol, 1.0 eq.) in CH_2Cl_2 (300 mL) at 0 ℃ was added a solution of Br_2 (5.15 mL, 100 mmol, 1.0 eq.) in CH_2Cl_2 (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 Et_2O (450 mL), cooled to 0 ℃ and a solution of $NaBH_4$ (3.78 g, 100 mmol, 1.0 eq.) in H_2O (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 ℃. 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 Et_2O (3 × 300 mL), combined, dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford a colourless solid ((±)-**79**). The solid was dissolved in Ac_2O (500 mL) and K_2CO_3 (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_2O (500 mL) and water (500 mL), and the organic components were washed with water (2 × 500 mL), dried with Na_2SO_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).

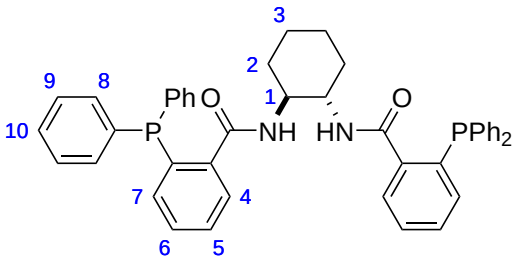
(±)-(1*SR*,2*RS*,3*RS*,4*SR*)-Cyclohex-5-ene-1,2,3,4-tetrayl tetrakis(2',2',2'-trichloroethyl) tetracarbonate ((±)-82)[64]



The procedure from Trost *et al.* was used.[64,81] To a solution of (±)-**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 × 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_2Cl_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 ℃, 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 ℃ 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_2Cl_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_2SO_4, filtered, and concentrated *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_2O/petroleum ether 1:2); m.p. 187-188 °C (from Et_2O/petroleum ether) {lit.[64] 186 °C}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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 $[M+H]^+$ ($C_{18}H_{13}O_{12}{}^{35}Cl_{12}$ requires 840.6666). These data are in good agreement with the literature.[64]

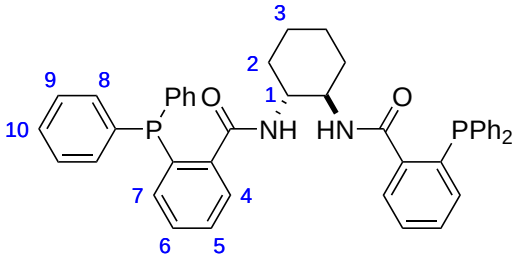
(−)-(1*S*,2*S*)-1,2-Bis(2-(diphenylphosphanyl)benzoylamino)cyclohexane ((−)-84)[116]



The procedure from Fuchs *et al.* was used.[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_2Cl_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 *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); $[\alpha]_D^{20} = -58.9$ (c 1.0, $CHCl_3$) {lit.[116] +55.6 ((*R,R*)-enantiomer, c 2.3, CH_2Cl_2)}; m.p. 139-141 °C (from MeCN) {lit.[116] 134-136 °C}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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, N*H*), 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; $CDCl_3$) δ –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]

(+)-(1*R*,2*R*)-1,2-Bis(2-(diphenylphosphanyl)benzoylamino)cyclohexane ((+)-84)[116]



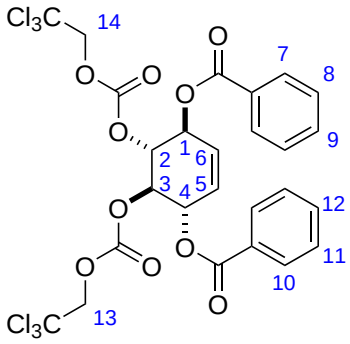
(+)-**84** was prepared in a similar manner to (–)-**84** using (–)-(*R,R*)-1,2-diaminocyclohexane (135 mg, 1.18 mmol, 1.0 eq.) to afford the title compound as a colourless solid (417 mg, 51%): $[\alpha]_D^{20} = +57.8$ (c 1.0, $CHCl_3$) {lit.[116] +55.6 (c 2.3, CH_2Cl_2)}; Chiral HPLC (10% isopropanol/hexane 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 Alkylations

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(η^3-allyl)Cl]$_2$ (0.025 eq.) were degassed

on a Schlenk system (3 × N_2/vacuum cycles). CH_2Cl_2 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 $NaHCO_3$ (20 mL) and the organic components were extracted with CH_2Cl_2 (20 mL × 2). The organic components were dried with $MgSO_4$, filtered through a plug of silica, and concentrated *in vacuo*. Conversions were calculated by ^{1}H 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).

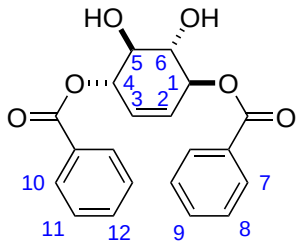
(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyl dibenzoate ((+)-83)[64]



A modification of the procedure from Trost *et al.* was used.[64,81] 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(η^3-allyl)Cl]$_2$ (14 mg, 0.04 mmol, 0.03 eq.) were degassed on a Schlenk system (3 × vacuum/N_2 cycles) and dissolved in CH_2Cl_2 (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. ^{1}H NMR analysis of the reaction mixture indicated the reaction was complete. Saturated aqueous $NaHCO_3$ (5 mL) was added and the product was extracted using CH_2Cl_2 (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 ℃ (from MeOH) {lit.[64] 141-143 ℃}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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, d, *J* 12.0, *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 ([$M^{35}Cl_5{}^{37}Cl$+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® 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]

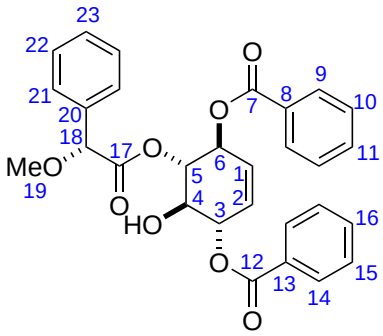
(+)-(1*S*,4*S*,5*S*,6*S*)-5,6-Dihydroxycyclohex-2-ene-1,4-diyl dibenzoate ((+)-94)[64,81]



The procedure from Trost *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_2CO_3 until effervescence was

no longer observed (3 × 30 mL). The organic components were dried with $MgSO_4$, 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%): R_f 0.54 (EtOAc/petroleum ether 1:1); $[\alpha]_D^{20} = +208.8$ (*c* 1.0, $CHCl_3$) {lit.[64] +206.8 (*c* 2.11, $CHCl_3$)}; m.p. 144-148 °C (from MeOH/water) {lit.[64] 153 °C (from EtOAc/petroleum ether)}; ^{1}H NMR (400 MHz; $CDCl_3$) 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, O*H*); *m/z* (ES^+) 377.1 ($[M+Na]^+$, 100%). These data are in good agreement with the literature.[64,81]

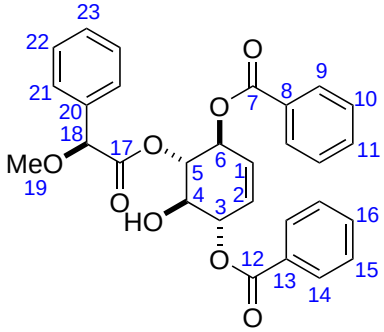
(+)-(1*S*,4*S*,5*R*,6*S*)-5-Hydroxy-6-((*R*)-2-methoxy-2-phenylacetoxy)cyclohex-2-ene-1,4-diyl dibenzoate ((+)-108a)



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-dimethylaminopyridine (8 mg, 0.07 mmol, 0.5 eq.) in CH_2Cl_2 (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 $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL), dried with $MgSO_4$, 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%): R_f 0.18 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20} = +148.6$ (*c*

1.0, $CHCl_3$); m.p. 131-133 ℃ (from $CHCl_3$); $\bar{\nu}_{max}$ (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-H alkyl, 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; $CDCl_3$) δ 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), 3.32 (3H, s, *H*-19), 2.30 (1H, br s, O*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 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 $[M+Na]^+$ ($C_{29}H_{26}O_8Na$ 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%.

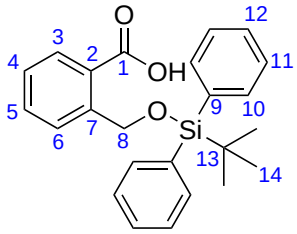
(+)-(1*S*,4*S*,5*R*,6*S*)-5-Hydroxy-6-((*S*)-2-methoxy-2-phenylacetoxy)cyclohex-2-ene-1,4-diyl dibenzoate ((+)-108b)



To prepare (+)-**108b**, the same procedure as **108a** was performed using (+)-(*S*)-α-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, $CHCl_3$); $\bar{\nu}_{max}$ (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]$^+$ ($C_{29}H_{26}O_8Na$ 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%.

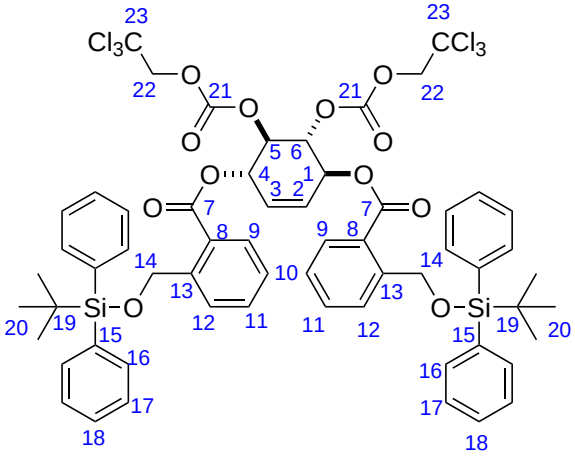
2-(((*t*Butyldiphenylsilyl)oxy)methyl)benzoic acid (119)[201]



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 ^{t}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_2Cl_2 (3 × 150 mL), combined, dried with Na_2SO_4, filtered and concentrated *in*

vacuo. The resulting oil was dissolved in a mixture of MeOH (200 ml) and THF (70 mL) and an aqueous solution of K_2CO_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_2O (6 × 100 mL), combined, dried with Na_2SO_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 ℃ (from hexane); ν_{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; $CDCl_3$) δ 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; $CDCl_3$) δ 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]

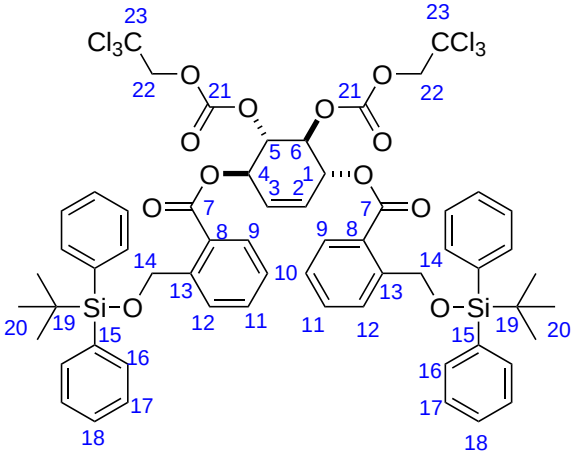
(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyl bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-175)



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 *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_f 0.79 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20}$ = +94.7 (*c* 1.0, $CHCl_3$); m.p. 138-142 °C (from EtOH); $\bar{\nu}_{max}$ (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),

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); ^{13}C NMR (101 MHz; CD_2Cl_2) 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-OBzCH$_2$OTBDPS]$^+$, 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%.

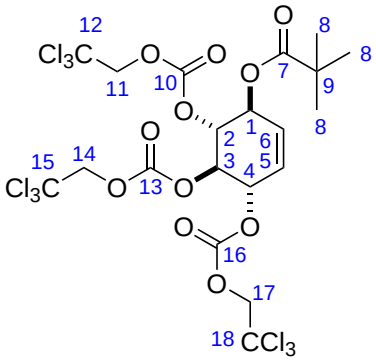
(–)-(1*R*,4*R*,5*S*,6*S*)-5,6-Bis(((2,2,2-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyl bis(2-(((^{t}butyldiphenylsilyl)oxy)methyl)benzoate) ((–)-175)



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%): $[\alpha]_D^{20}$ = –93.5 (*c* 1.0, $CHCl_3$); 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 (R_f, m.p., ^{1}H NMR, ^{13}C NMR, IR, NP-HPLC)

matched data for the opposite enantiomer (+)-**175**.

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

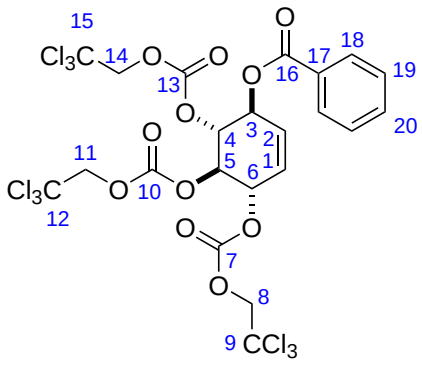


Tetratroc (±)-**82** (424 mg, 0.5 mmol, 1.0 eq.), pivalic acid (179 mg, 1.75 mmol, 3.5 eq.), [Pd(η^3-allyl)Cl]$_2$ (4.6 mg, 0.0125 mmol, 0.025 eq.), (*S,S*)-ligand (–)-**84** (52 mg, 0.075 mmol, 0.15 eq.), and tetrahexylammonium bromide (43 mg, 0.1 mmol, 0.2 eq.) were degassed using a Schlenk system (3 × vacuum/N_2 cycles). CH_2Cl_2 (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. ^{1}H 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 $NaHCO_3$ (20 mL) and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic components were dried with $MgSO_4$, 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% Et_2O in petroleum ether to afford the title compound as a colourless solid (123 mg, 33%): R_f 0.53 (Et_2O/petroleum ether 1:4); $[\alpha]_D^{20}$ = +68.0 (*c* 1.0, $CHCl_3$); m.p. 127-128 °C (from H_2O); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; $CDCl_3$) 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,

H-14, *H*-17), 1.78 (9H, s, *H*-8); ^{13}C NMR (101 MHz; $CDCl_3$) 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 $[M^{35}Cl_9+NH_4]^+$ ($C_{20}H_{25}O_{11}N^{35}Cl_9$ requires 769.8619); *m/z* (ES$^+$) 778.5* ($[M+NH_4]^+$, 100%).

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

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

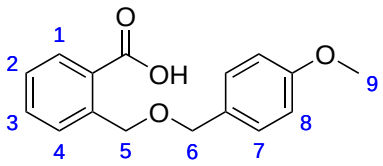


Tetratroc (±)-**82** (424 mg, 0.5 mmol, 1.0 eq.), BzOH (214 mg, 1.75 mmol, 3.5 eq.), $[Pd(\eta^3\text{-allyl})Cl]_2$ (4.6 mg, 0.013 mmol, 0.025 eq.), (*S,S*)-ligand (–)-**84** (26 mg, 0.038 mmol, 0.075 eq.), and tetrahexylammonium bromide (43 mg, 0.1 mmol, 0.2 eq.) were placed under an atmosphere of nitrogen using Schlenk apparatus (3 × vacuum/N_2 cycles). CH_2Cl_2 (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. ^{1}H 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 $NaHCO_3$ (10 mL) and the organic components were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic components were washed with saturated aqueous NaCl (10 mL), dried with $MgSO_4$, 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%): R_f 0.26 (Et_2O/petroleum ether 1:4); $[\alpha]_D^{20}$ = +94.3 (*c* 1.0, $CHCl_3$); m.p. 146-148 °C (from MeOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; $CDCl_3$) 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, t, *J* 7.6, *H*-19), 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); ^{13}C NMR (101 MHz; $CDCl_3$) 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 $[M^{35}Cl_9{+}NH_4]^+$ ($C_{22}H_{21}{}^{35}Cl_9NO_{11}$ requires 789.8306); *m/z* (ES^+) 797.7* ($[M{+}NH_4]^+$, 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 ^{35}Cl and ^{37}Cl in the molecule hence the most prominent peak is given.*

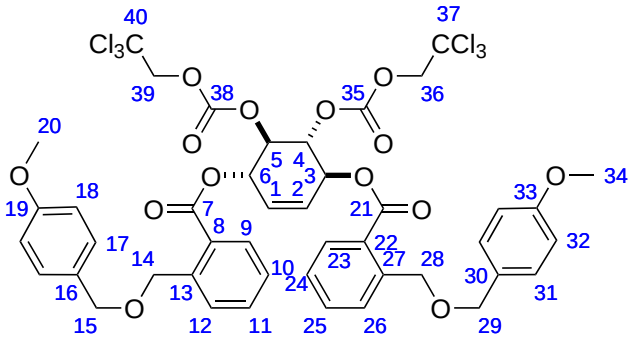
2-(((4-Methoxybenzyl)oxy)methyl)benzoic acid (176)[168]



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 CH_2Cl_2 (3 ×

150 mL), combined, dried with Na_2SO_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_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 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]

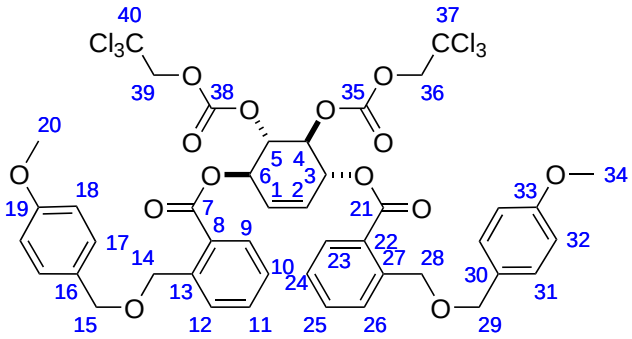
(+)-(3*S*,4*S*,5*R*,6*R*)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclo-hex-2-ene-1,4-diyl-bis(2-(((*p*-methoxybenzyl)oxy)methyl)benzoate) ((+)-253)



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 $[Pd(\eta^3\text{-allyl})Cl]_2$ (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_2Cl_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_2Cl_2 (3 × 30 mL). The combined organic components were dried with Na_2SO_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

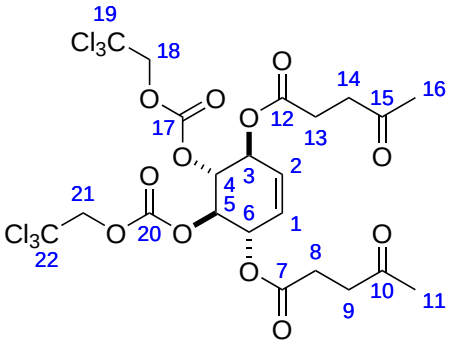
to afford the title compound as a colourless oil (2.57 g, 92%): R_f 0.36 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25}$ = +97.0 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 1771 (C=O, m), 1720 (C=O, m), 1613 (C=C, w), 1514 (C=C, w), 1288 (C-O, m), 1246 (C-O, s), 1174 (C-O, w), 1133 (C-O, w), 1065 (C-O, m), 1035 (C-O, m); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.95 (2H, dd, *J* 7.8, 1.3, *H*-9, *H*-23), 7.74 (2H, d, *J* 7.8, *H*-12, *H*-26), 7.59 (2H, ddd, *J* 7.8, 7.8, 1.3, *H*-11, *H*-25), 7.37 (2H, dd, *J* 7.8, 7.8, *H*-10, *H*-24), 7.33 (4H, dt, *J* 8.7, 1.8, *H*-17, *H*-31), 6.91 (4H, dt, *J* 8.7, 1.8, *H*-18, *H*-32), 5.97 (2H, dd, *J* 5.3, 2.5, *H*-4, *H*-5), 5.87 (2H, s, *H*-1, *H*-2), 5.56 (2H, dd, *J* 5.3, 2.5, *H*-3, *H*-6), 4.95 (2H, d, *J* 14.4, *H*-14a, *H*-28a), 4.90 (2H, d, *J* 14.4, *H*-14b, *H*-28b), 4.81 (2H, d, *J* 12.0, *H*-36a, *H*-39a), 4.70 (2H, d, *J* 12.0, *H*-36b, *H*-39b), 4.57 (4H, s, *H*-15, *H*-29), 3.80 (6H, s, *H*-20, *H*-34); ^{13}C NMR (101 MHz; $CDCl_3$) δ 165.7 (*C*-7, *C*-21), 159.3 (*C*-19, *C*-33), 153.5 (*C*-35, *C*-38), 141.7 (*C*-13, *C*-27), 133.0 (*C*-11, *C*-25), 130.7 (*C*-9, *C*-23), 130.5 (*C*-16, *C*-30), 129.3 (*C*-17, *C*-31), 127.7 (*C*-12, *C*-26), 127.2 (*C*-1, *C*-2), 127.0 (*C*-10, *C*-24), 126.8 (*C*-8, *C*-22), 113.7 (*C*-18, *C*-32), 94.2 (*C*-37, *C*-40), 76.9 (*C*-28, *C*-14), 76.0 (*C*-3, *C*-6), 72.5 (*C*-15, *C*-29), 71.7 (*C*-4, *C*-5), 69.9 (*C*-36, *C*-39), 55.3 (*C*-20, *C*-34); HRMS *m/z* (ES^+) Found 1025.0450 $[M+Na]^+$ ($C_{44}H_{40}{}^{35}Cl_6NaO_{14}$ requires 1025.0441); *m/z* (ES^+) 1024.9 ($[M^{35}Cl_6+Na]^+$, 50%), 1027.0 ($[M^{35}Cl_5{}^{37}Cl+Na]^+$, 100%), 1028.9 ($[M^{35}Cl_4{}^{37}Cl_2+Na]^+$, 87%), 1030.9 ($[M^{35}Cl_3{}^{37}Cl_3+Na]^+$, 47%), 1032.9 ($[M^{35}Cl_2{}^{37}Cl_4+Na]^+$, 13%); Chiral HPLC (50% isopropanol alcohol/hexane, 1.0 mL min^{-1}) Retention Time 38.7 min (–)-**253**, > 99% e.e., (other enantiomer Retention Time = 52.1 min (+)-**253**).

(–)-(3*R*,4*R*,5*S*,6*S*)-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%): $[\alpha]_D^{20}$ = –104.1 (*c* 1.0, $CHCl_3$); 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 (R_f, ^1H NMR, ^{13}C NMR, MS, NP-HPLC) matched data for the opposite enantiomer (+)-**253**.

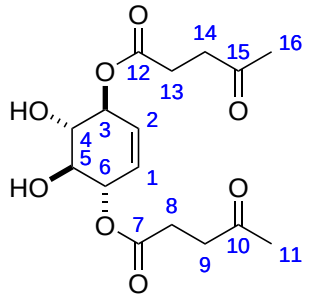
(+)-(3*S*,4*R*,5*R*,6*S*)-4,5-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-3,6-diyl bis(levulinate) ((+)-118)



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 $[Pd(\eta^3\text{-allyl})Cl]_2$ (15.0 mg, 0.041 mmol, 0.025 eq.) were degassed

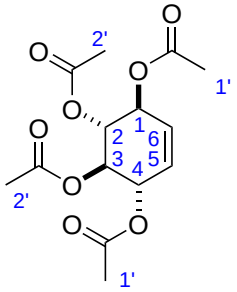
on a Schlenk system (3 × vacuum/N_2 cycles). The solid was dissolved in CH_2Cl_2 (5.0 mL) and aqueous NaOH (2 M, 2.4 mL, 4.8 mmol, 3.0 eq.) and the reaction mixture was stirred vigourously for 24 h. ^{1}H NMR analysis of the reaction mixture indicated a 54% conversion to (+)-**118**, with 32% mono-reacted (+)-**263** and 14% starting material (±)-**82**. The reaction mixture was diluted with saturated aqueous NaCl (50 mL) and the organic components were extracted with CH_2Cl_2 (2 × 50 mL). The organic components were combined, dried with Na_2SO_4, 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%): R_f 0.74 (EtOAc/petroleum ether 1:1); $[\alpha]_D^{25}$ = +63.2 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; CD_2Cl_2) 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); ^{13}C NMR (101 MHz; CD_2Cl_2) 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-CH_2CH_3]$^+$ ($C^{20}H^{19}Cl_6O_{12}$ 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 ^{1}H NMR.*

(+)-(3*S*,4*S*,5*S*,6*S*)-4,5-Dihydroxycyclohex-2-ene-3,6-diyl bis(levulinate) ((+)-252)



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 CH_2Cl_2 to afford the title compound as a colourless film (294 mg, 92%): R_f 0.12 (EtOAc); $[\alpha]_D^{25} = +135.8$ (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; CD_2Cl_2) 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, O*H*), 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); ^{13}C NMR (101 MHz; CD_2Cl_2) 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 $[M+Na]^+$ ($C_{16}H_{22}O_8$ requires 365.1212); *m/z* (ES^-) 377.1 ($[M+Cl]^-$, 13%), 387.1 ($[M+HCO_2H–H]^-$, 100%), (ES^+) 365.1 ($[M+Na]^+$, 100%).

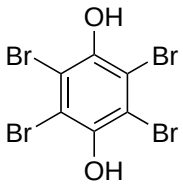
(+)-(1*S*,2*R*,3*R*,4*S*)-Cyclohex-5-ene-1,2,3,4-tetrayl tetraacetate ((+)-81)[80]



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_2Cl_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_2Cl_2 (2 × 25 mL), combined, dried with Na_2SO_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, followed by crystallisation from EtOH to afford the title compound as colourless plate-like crystals (72 mg, 23%): $[\alpha]_D^{20}$ = +182.6 (*c* 1.0, $CHCl_3$) {lit.[80] –182 (enantiomer (–)-**81**, *c* 0.7, $CHCl_3$)}; m.p. 123-125 ℃ (from EtOH) {lit.[80] 117-118 ℃}. All other data (R_f, LRMS, ^{1}H NMR) matched data for the racemate (±)-**81**. These data are in agreement with the literature.[80]

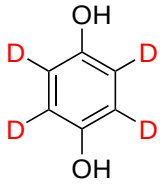
7.3 Deuterated *myo*-Inositol

2,3,5,6-Tetrabromoquinol (155)[155,202]



The procedure from Head was used.[155] Quinol (2.20 g, 50 mmol, 1.0 eq.) was suspended in AcOH (40 mL) and the suspension was cooled to 0 ℃. 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 a orange solid (7.96 g, 93%): R_f 0.32 (CH_2Cl_2); m.p. 242-243 ℃ (decomposed, from AcOH) {lit.[155] 243-244 ℃, decomposed}; ^{1}H NMR (400 MHz; D_6-DMSO) δ 9.96 (2H, s, O*H*); ^{13}C NMR (101 MHz; D_6-DMSO) δ 146.9 (*C*-OH), 115.9 (*C*-Br); *m/z* (ES^-) 421.6 ($[M^{79}Br_4–H]^-$, 88%), 423.6 ($[M^{79}Br_3{}^{81}Br–H]^-$, 100%), 425.6 ($[M^{79}Br_2{}^{81}Br_2–H]^-$, 92%), 427.6 ($[M^{79}Br{}^{81}Br_3–H]^-$, 23%). These data are in good agreement with the literature.[155,202]

2,3,5,6-Tetradeuteroquinol (156)[158]



Method A

A suspension of **155** (7.95 g, 18.7 mmol, 1.0 eq.) in D_2O (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% D_4): R_f 0.51 (EtOAc/petroleum ether 1:1); m.p. 169-170 ℃ (from EtOAc) {lit.[158] 171-173 ℃}; $\bar{\nu}_{max}$ (thin film)/cm^{-1} 3245 (O-H, w), 1409 (C=C, s), 1315 (C=C, m), 1220 (C-O, m), 1126 (C-O, s); ^{1}H NMR (400 MHz; D_6-DMSO) δ 8.63 (2H, s, O*H*); ^{13}C NMR (126 MHz; D_6-DMSO) δ 150.1 (*C*-O), 115.8 (t_D, J_D 23.8, *C*-D); ^{2}H NMR (77 MHz; DMSO; D_6-DMSO) δ 6.58; HRMS *m/z* (F^+) Found 114.0621 $[M]^+$ ($C_6H_2O_2D_4$ 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 B[158]

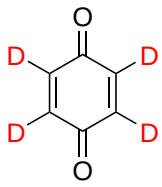
The procedure from Desiraju *et al.* was used.[158] Acetyl chloride (40 mL, 56 mmol, 2.9 eq) was cooled to 0 ℃ in an ice bath and D_2O (20 mL, 111 mmol, 5.8 eq) was added, dropwise, over a period of 1 h (SLOWLY - care must be taken to avoid large release of HCl gas). The solution was stirred at 0 ℃ for 10 min then zinc powder (4.0 g, 61 mmol, 3.2 eq.) was added, portionwise, at 0 ℃ 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 Et_2O (3 × 150 mL) and the combined organic components were was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound as a colourless solid (1.81 g, 86%, D_4 46%, D_3 36%, D_2 17%, D_1 < 1%, D_0 not observed). Full data was

not obtained on this partially deuterated sample.

Method C[159]

The procedure from Zimmermann *et al.* was used.[159] A suspension of quinol (20.0 g, 18.1 mmol, 1.0 eq.) and D_2SO_4 (1 mL, 96-98 wt.% in D_2O, 99.5% D, 13.7 mmol, 0.75 eq.) in D_2O (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_2O (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a colourless solid. This procedure was repeated (heated under reflux in fresh D_2O and D_2SO_4 followed by extraction) twice more to afford the title compound as a colourless solid (19.72 g, 95%, D_6 93%, D_5 7%). All other data matched earlier data.

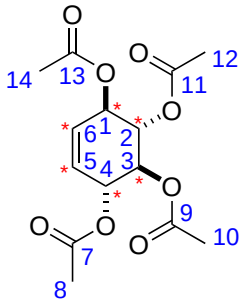
2,3,5,6-Tetradeuterobenzoquinone (157)[160]



The procedure from Ikemoto *et al.* was used.[160] To a solution of D_4-quinol **156** (1.14 g, 10.0 mmol, 1.0 eq., > 95% D_4) and iodine (126 mg, 1.0 mmol, 0.1 eq.) in isopropanol (5 mL) was added aqueous H_2O_2 (35% *w/w*, 1.7 ml, 20 mmol, 2.0 eq.) and the solution was heated to 45 ℃ 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_4): R_f 0.59 (EtOAc/petroleum ether 1:4); m.p. 112-114 ℃ (sublimed, from isopropanol) {lit.[203] 113 ℃ (from H_2O)}; $\bar{\nu}_{max}$ (thin film)/cm^{-1} 1638 (C=C, s), 1558 (C=C, m), 1264 (C=O, m), 1238 (C=O, m); ^{2}H NMR (77 MHz; DMSO; D_6-DMSO) δ 6.87; ^{13}C NMR (126 MHz; D_6-DMSO) δ 188.3 (*C*-O), 136.6 (t_D, J_D 25.8,

C-D); HRMS *m/z* (F^+) Found 112.0462 $[M]^+$ ($C_6D_4O_2$ requires 112.0462). These data are in good agreement with the literature.[160,203]

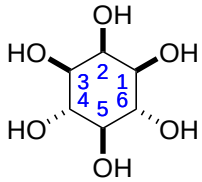
(±)-(1*RS*,2*SR*,3*SR*,4*RS*)-Cyclohex-5-ene-1,2,3,4-tetrayl-D_6 tetracetate ((±)-160)



A solution of D_4-benzoquinone **157** (2.90 g, 25.9 mmol, 1.0 eq., D_4 93%, D_3 7%) in $CHCl_3$ (75 mL) was cooled to 0 ℃ and a solution of bromine (1.33 mL, 25.9 mmol, 1.0 eq.) in $CHCl_3$ (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 ℃. 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 Et_2O (110 mL), and the solution was cooled to 0 ℃. A solution of $NaBD_4$ (2.28 g, 54.4 mmol, 2.1 eq.) in D_2O (40 mL) was added, portionwise, over a period of 5 min with vigorous stirring. The reaction mixture was stirred vigorously at 0 ℃ 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 Et_2O (2 × 100 mL), combined, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting colourless solid (7.08 g) was dissolved in Ac_2O (75 mL) and K_2CO_3 (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 anaylsis of the reaction mixture ($[M+K]^+$ = 383.1, no brominated species observed) indicated the reaction was

complete. The reaction was cooled down to 0 ℃, MeOH (50 mL) was added to quench Ac_2O and the reaction was stirred at 0 ℃ for 2 h. The reaction mixture was concentrated *in vacuo* (Büchi water bath at 60 ℃) 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, D_6 90%, D_5 10%): R_f 0.16 (EtOAc/petroleum ether 1:4); m.p. 81-83 ℃ (from EtOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.05 (6H, s, *H*-8, *H*-14), 2.03 (6H, s, *H*-10, *H*-12); ^{13}C NMR (126 MHz; $CDCl_3$) δ 170.3 (*C*-7, *C*-13), 169.9 (*C*-9, *C*-11), 127.0 (t_D, J_D 25.2, *C*-5, *C*-6), 71.0 (t_D, J_D 23.0, *C*-1, *C*-4), 70.8 (t_D, J_D 23.0, *C*-2, *C*-3), 20.9 (*C*-8, *C*-14), 20.6 (*C*-10, *C*-12); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-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 $[MD_5+Na]^+$ ($C_{14}H_{13}D_5O_8Na$ requires 342.1213), 343.1265 $[MD_6+Na]^+$ ($C_{14}H_{12}D_6O_8Na$ requires 343.1271); *m/z* (ES$^+$) 342.1 ($[MD_5+Na]^+$, 11%) 343.1 ($[MD_6+Na]^+$, 100%).

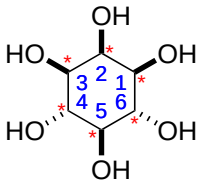
myo-Inositol (1)[204–206]



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 $NaIO_4$ (1.08 g, 5.05 mmol, 1.5 eq.) and $RuCl_3{\cdot}3H_2O$ (45 mg, 0.17 mmol, 0.05 eq.) in H_2O (8 mL) and the mixture was stirred vigorously for 8 min. TLC analysis (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL) was added and the organic components were extracted with EtOAc (3 × 100 mL), combined, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting solid was dissolved in a mixture of MeOH (14 mL) and H_2O (6 mL), NEt_3

(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 *in vacuo* to give a brown solid. The product was crystallised from 1:1 EtOH/H_2O, filtered and the crystals washed with Et_2O (20 mL) to afford the title compound as colourless needles (496 mg, 82%): R_f 0.81 (1:1 EtOH/H_2O); m.p. 220-221 ℃ (from 1:1 EtOH/H_2O) {lit.[204] 220-221 ℃ (from aq. EtOH)}; ^{1}H NMR (400 MHz; D_6-DMSO) δ 4.56 (1H, d, *J* 4.3, O*H*-5), 4.51 (2H, d, *J* 4.5, O*H*-4, O*H*-6), 4.48 (1H, d, *J* 3.1, O*H*-2), 4.36 (2H, d, *J* 5.5, O*H*-1, O*H*-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) δ 75.3 (*C*-5), 72.8 (*C*-4, *C*-6), 72.7 (*C*-2), 71.9 (*C*-1, *C*-3); *m/z* (ES^+) 203.1 ($[M+Na]^+$, 100%). These data are in good agreement with the literature, as well as in comparison to commercial sources of *myo*-inositol **1**.[204–206]

D_6-*myo*-Inositol (90)

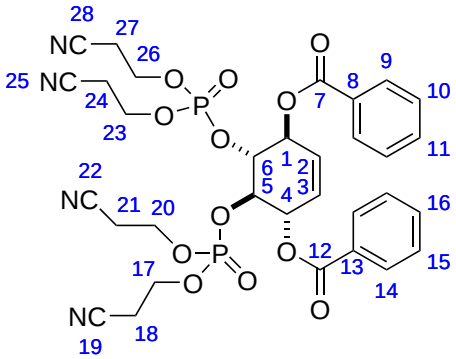


To a vigorously stirred solution of (±)-**160** (1.96 g, 6.11 mmol, 1.0 eq., 90% D_6, 10% D_5) in MeCN (60 mL) at 0 ℃ was added a solution of $RuCl_3{\cdot}3H_2O$ (80 mg, 0.31 mmol, 0.05 eq.) and $NaIO_4$ (1.96 g, 9.18 mmol, 1.5 eq.) in H_2O (15 mL) and the resulting solution was stirred at 0 ℃ for 4 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ (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_2SO_4, filtered, and concentrated *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_2O 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_2O); m.p. 226-229 °C (from EtOH/H_2O) {H_{12}-*myo*-inositol, see **1**, 220-221 °C (from EtOH/H_2O)}; $\bar{\nu}_{max}$ (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) δ 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) δ 74.6 (t_D, J_D 20.4, *C*-2), 72.2 (t_D, J_D 20.4, *C*-4, *C*-6), 72.1 (t_D, J_D 20.4, *C*-5), 71.3 (t_D, J 20.4, *C*-1, *C*-3); ^{2}H NMR (77 MHz; DMSO; D_6-DMSO) δ 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 $[MD_5+Na]^+$ ($C_6H_7O_6D_5Na$ requires 208.0840), 209.0903 $[MD_6+Na]^+$ ($C_6H_6O_6D_6Na$ requires 209.0902); *m/z* (ES^+) 208.1 ($[MD_5+Na]^+$, 11%) 209.1 ($[MD_6+Na]^+$, 100%).

7.4 First Route Development

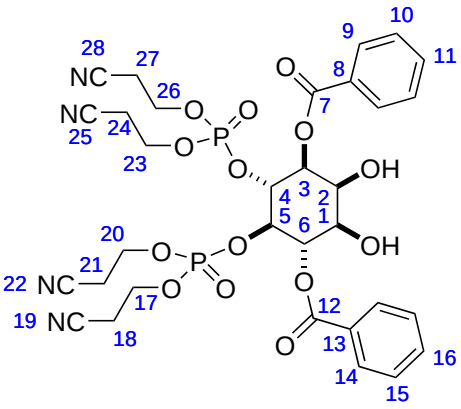
(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diyl dibenzoate ((+)-95)



To a solution of phosphoramidite **126** (606 mg, 2.24 mmol, 5.6 eq.) in CH_2Cl_2 (20 mL) under N_2 was added 1*H*-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 ℃ 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 $Na_2S_2O_3$ (10% *w/v*, 20 mL) was added. The organic components were extracted with CH_2Cl_2 (2 × 20 mL), combined, washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 1-5% MeOH in CH_2Cl_2 to afford the title compound as a colourless oil (172 mg, 59%): R_f 0.23 (MeOH/CH_2Cl_2 1:19); $[\alpha]_D^{20}$ = +130.9 (*c* 1.0, $CHCl_3$); ν_{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 $[M+Na]^+$ ($C_{32}H_{32}N_4O_{12}P_2Na$ 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%.

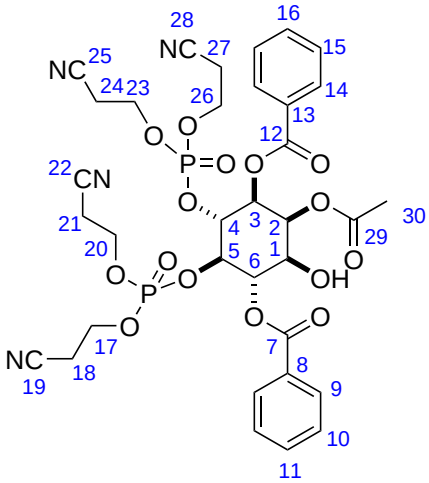
(+)-3,6-Dibenzoyl-4,5-bis(bis(2-cyanoethoxy)phosphoryl)-D-*myo*-inositol ((+)-96)



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 $RuCl_3 \cdot 3H_2O$ (17 mg, 0.066 mmol, 0.4 eq.) and $NaIO_4$ (53 mg, 0.25 mmol, 1.5 eq.) in H_2O (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 $Na_2S_2O_3$ (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 Na_2SO_4, 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%): R_f 0.33 (EtOAc); $[\alpha]_D^{20}$ = +35.8 (*c* 1.0, $CHCl_3$); m.p. 76-80 °C (from MeOH); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 1721 (C=O, m), 1266 (C-H alkyl, s), 1108 (C-O, m), 1026 (C-O, s); ^{1}H NMR (400 MHz; $CDCl_3$) 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, O*H*-2), 3.21 (1H, br s, O*H*-1), 2.76-2.56 (4H, m, *H*-18, *H*-27), 2.36-2.18 (4H, m, *H*-21, *H*-24); ^{13}C NMR (101 MHz; $CDCl_3$) 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; $CDCl_3$) δ –3.33 (*P*-4), –3.45 (*P*-5); HRMS *m/z* (ES^+) Found 783.1429 $[M+Na]^+$ ($C_{32}H_{34}N_4O_{14}P_2Na$ 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)-D-*myo*-inositol ((+)-97)

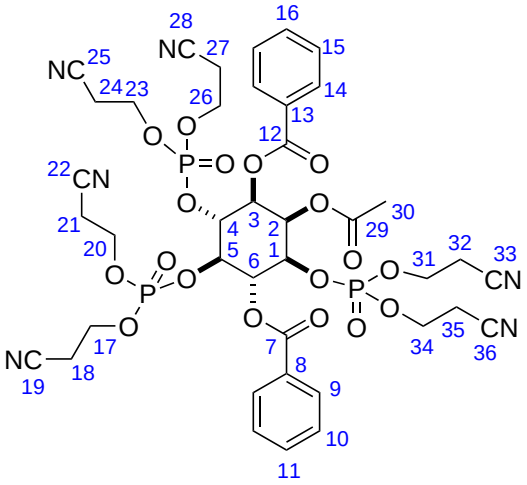


To a solution of (+)-**96** (528 mg, 0.7 mmol, 1.0 eq.) in anhydrous THF (20 mL) under an atmosphere of Ar was added triethylorthoacetate (0.38 mL, 2.1 mmol, 3.0 eq.) and *p*-toluenesulfonic acid (13 mg, 0.07 mmol, 0.1 eq.), and the reaction mixture was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The solution was concentrated *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 *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

Na_2SO_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); $[\alpha]_D^{20}$ = +31.1 (*c* 1.0, $CHCl_3$); m.p. 145-148 ℃ (from H_2O); $\bar{\nu}_{max}$ (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 $[M+Na]^+$ ($C_{34}H_{36}N_4O_{15}P_2Na$ 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-*myo*-inositol ((+)-267)

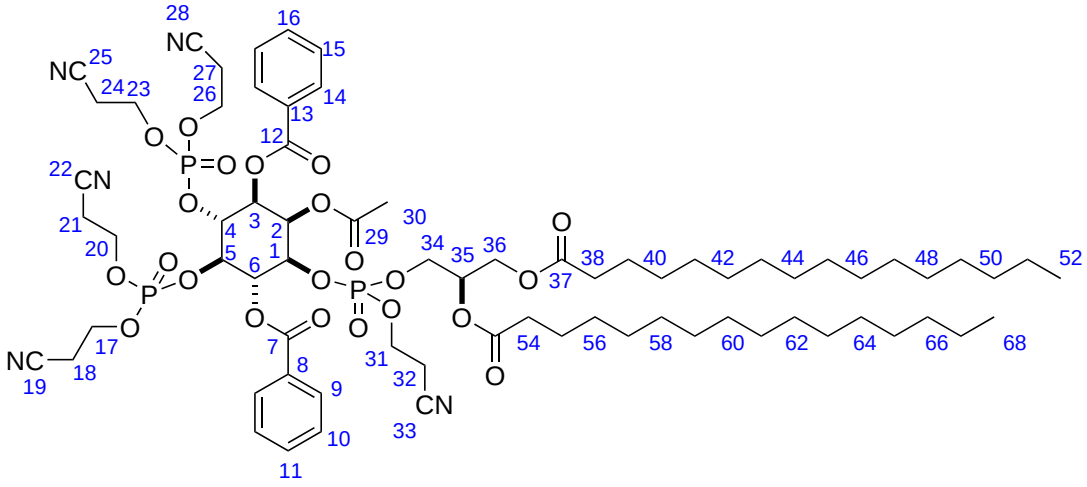


To a solution of (+)-**97** (60 mg, 0.075 mmol, 1.0 eq.) and phosphoramidite **126** (40 mg, 0.15 mmol, 2.0 eq.) in CH_2Cl_2 (5 mL) under an atmosphere of argon was added 1*H*-tetrazole (3-4 wt.% in MeCN, 0.35 mL, 0.15 mmol, 2.0 eq.) and the solution was stirred at room temperature for 48 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated the reaction was complete. The solution was cooled to –78 ℃ 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 CH_2Cl_2 (40 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na_2SO_4, 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 $CHCl_3$ gradient (25 CV) followed by a second column using $CHCl_3$, 0.5% EtOH in $CHCl_3$, 1.0% EtOH in $CHCl_3$, 2.0% EtOH in $CHCl_3$, 4.0% EtOH in $CHCl_3$ and 6.0% EtOH in $CHCl_3$ to afford the title compound as a colourless film (26 mg, 35%); R_f 0.11 (MeOH/$CHCl_3$ 1:19); $[\alpha]_D^{20}$ = +0.8 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.20 (2H, d, *J* 7.7,

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 $[M+Na]^+$ ($C_{40}H_{43}O_{18}N_6NaP_3$ requires 1011.1739); *m/z* (ES^+) 989.2 ($[M+H]^+$, 100%), (ES^-) 934.2 ($[M\text{-}CH_2CH_2CN]^-$, 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-D-*myo*-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 CH_2Cl_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 °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 $Na_2S_2O_3$ (10% *w/v*, 10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic components were washed with saturated aqueous $NaHCO_3$ (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was columned using silica gel flash column chromatography on a Biotage system twice, first using 4% EtOH in CH_2Cl_2 then 3% EtOH in $CHCl_3$ 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/$CHCl_3$ 1:19); $[\alpha]_D^{20}$ = +4.6 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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}H NMR (400 MHz; $CDCl_3$) *Diastereomer A** 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), 5.17 (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); ^{13}C NMR (126 MHz; $CDCl_3$) *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, J_P 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, J_P 5.6, *C*-34), 62.2 (d, J_P 5.8, *C*-20), 62.1 (d, J_P 5.8, *C*-17), 61.6 (d, J_P 4.8, *C*-23), 61.5 (d, J_P 4.8, *C*-26), 61.4 (d, J_P 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, J_P 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, J_P 5.6, *C*-34), 62.2 (d, J_P 5.8, *C*-20), 62.1 (d, J_P 5.8, *C*-17), 61.6 (d, J_P 4.8, *C*-23), 61.5 (d, J_P 4.8, *C*-26), 61.3 (d, J_P 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,

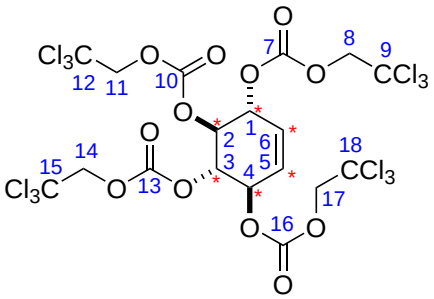
28.5, 28.34, 28.29, 28.12, 28.10, 28.05 (*C*-(40-49), *C*-(56-65)), 23.8 (*C*-55), 23.7 (*C*-39), 21.7 (*C*-51, *C*-67), 19.67 (*C*-30), 18.44 (*C*-21), 18.39 (*C*-18), 17.93 (*C*-24), 17.88 (*C*-27), 17.42 (*C*-32), 13.2 (*C*-52, *C*-68); ^{31}P NMR (162 MHz; $CDCl_3$) *Diastereomer A** δ –2.00 (*P*-1), –3.23 (*P*-5), –3.37 (*P*-4), *Diastereomer B** –2.42 (*P*-1), –3.26 (*P*-5), –3.37 (*P*-4); HRMS *m/z* (ES^+) Found 1058.6438 $[M+Na]^+$ ($C_{72}H_{106}N_5O_{22}P_3Na$ requires 1508.6435); *m/z* (ES^+) 1058.8 $[M+Na]^+$.

**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.*

***These peaks appeared under the solvent signal and were determined using HSQC and HMBC data and as such appear as multiplets in the range given.*

7.5 Deuterated Inositol Derivatives

(±)-(1*R*,2*S*,3*S*,4*R*)-Cyclohex-5-ene-1,2,3,4-tetrayl-D_6 tetrakis(2',2',2'-trichloroethyl) tetracarbonate ((±)-165)

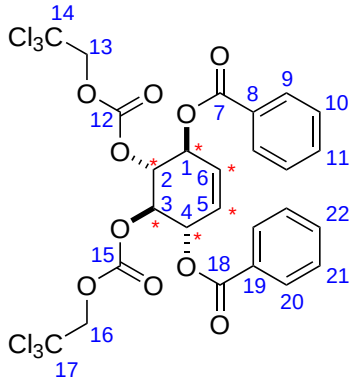


A solution of compound (±)-**160** (1.0 g, 3.1 mmol, 1.0 eq.) and triethylamine (1.31 mL, 9.4 mmol, 3.0 eq., 90% D_6, 10% D_5) in a mixture of MeOH (14 mL) and water (6 mL) was stirred at room temperature for 1 h. TLC analysis of the reaction mixture of the reaction mixture (1:4 EtOAc/petroleum ether) 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_2Cl_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 ℃. 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 ℃ for 2 h. ^{1}H NMR analysis of the reaction mixture indicated the reaction was complete. The reaction was diluted with CH_2Cl_2 (75 mL) and the organic components were washed with water (50 mL), aqueous HCl (1 M, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was suspended in boiling EtOH (*ca.* 50 mL), cooled to 0 ℃ and filtered to afford the title compound as a colourless solid (2.24 g, 85%): R_f 0.63 (EtOAc/petroleum ether 1:4); m.p. 190-191 ℃ (from EtOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.84-4.73 (8H, m, *H*-8, *H*-11, *H*-14, *H*-17); ^{13}C NMR (126 MHz; $CDCl_3$) δ 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); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-DMSO) δ 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 [M^{35}Cl$_9$-$CO_2CH_2CCl_3$]$^+$ ($C_{15}H_6D_6Cl_9O_9$ requires 656.8060); *m/z* (E$^+$) 461.8 ([M^{35}Cl$_9$-2×(OTroc)+H]$^+$, 656.8 ([M^{35}Cl$_9$-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 ^{1}H NMR.

(+)-(1*R*,4*S*,5*S*,6*R*)-2,3-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclo-hex-5-ene-1,4-diyl-D_6 dibenzoate ((+)-166)

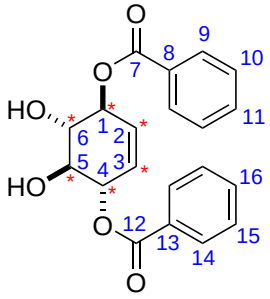


D_6-Tetratroc (±)-**165** (1.28 g, 1.50 mmol, 1.0 eq), BzOH (627 mg, 5.13 mmol, 3.4 eq.), (*S,S*)-ligand (–)-**84** (154 mg, 0.222 mmol, 0.15 eq.), tetrahexylammonium bromide (129 mg, 0.30 mmol, 0.2 eq.), and [Pd(η^3-allyl)Cl]$_2$ (14 mg, 0.04 mmol, 0.03 eq.) were degassed on a Schlenk system (3 × vacuum/N_2 cycles). CH_2Cl_2 (4.5 mL) and aqueous NaOH (1 M, 4.5 mL, 3.5 eq.) were added and the reaction mixture was stirred vigorously under N_2 for 90 min. ^{1}H NMR analysis of the reaction mixture indicated the reaction was complete. Saturated aqueous $NaHCO_3$ (50 mL) was added and the organic components were extracted using CH_2Cl_2 (2 × 30 mL). The organic components were combined, filtered under vacuum through a plug of silica and the silica was washed with CH_2Cl_2 (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%): R_f 0.57 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20}$ = +175.0 (*c* 1.0, $CHCl_3$); m.p. 143-146 ℃ (from EtOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; $CDCl_3$) 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); ^{13}C NMR (126 MHz; $CDCl_3$) 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 (t_D,

J_D 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); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-DMSO) δ 5.88 (*D*-2, *D*-3, *D*-5, *D*-6), 5.49 (*D*-1, *D*-4); HRMS *m/z* (E^+) Found 707.8966 $[M]^+$ ($C_{26}H_{14}D_6{}^{35}Cl_6O_{10}$ requires 707.9564); *m/z* 707.8 ($[M]^+$, 100%); Chiral HPLC (10% isopropanol/heptane isocratic, 1.0 mL min^{-1}) Retention Time = 11.6 min (+)-**166**, > 99% e.e. (other enantiomer not observed); NP-HPLC (0-10% isopropanol/hexane) Retention Time = 3.6 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 ^{1}H NMR.

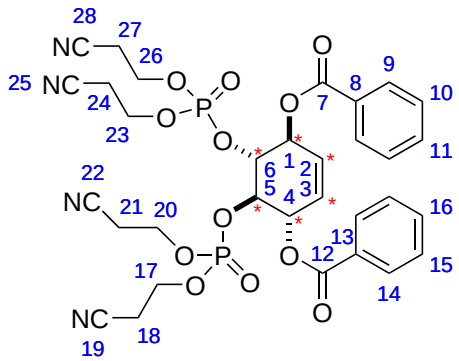
(+)-(1*S*,4*S*,5*S*,6*S*)-5,6-Dihydroxycyclohex-2-ene-1,4-diyl-D_6 dibenzoate ((+)-167)



A solution of (+)-**166** (1.65 g, 2.3 mmol, 1.0 eq.) in glacial AcOH (5 mL) and THF (5 mL) was cooled to 0 ℃ 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 $NaHCO_3$ (50 mL) was added, the suspension was stirred for 10 min and the organic components were extracted using EtOAc (3 × 50 mL). The combined organic components were dried with Na_2SO_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_2CO_3 was added until no effervesence was seen on addition. The phases were separated and the organic components were extracted

using EtOAc (50 mL), combined, dried with Na_2SO_4, 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%, D_6 90%, D_5 10%): R_f 0.78 (EtOAc/petroleum ether 1:1); $[\alpha]_D^{20}$ = +217.4 (*c* 1.0, $CHCl_3$); m.p. 143-147 ℃ (from $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; $CDCl_3$) 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*); ^{13}C NMR (126 MHz; $CDCl_3$) 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 (t_D, J_D 24.7, *C*-1, *C*-2), 74.4 (t_D, J_D 22.4, *C*-3, *C*-6), 73.4 (t_D, J_D 22.4, *C*-4, *C*-5); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-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 $[MD_5+Na]^+$ ($C_{20}H_{13}D_5NaO_6$ requires 382.1315), 383.1361 $[MD_6+Na]^+$ ($C_{20}H_{12}D_6NaO_6$ requires 383.1372); *m/z* (ES^+) 382.1 ($[MD_5+Na]^+$, 11%), 383.1 ($[MD_6+Na]^+$, 100%), (ES^-) 405.1 ($[M+formic\ acid-H]^-$, 100%); NP-HPLC (0-30% isopropanol/hexane) Retention Time = 8.6 min, 98.0%.

(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diyl-D_6 dibenzoate ((+)-168)



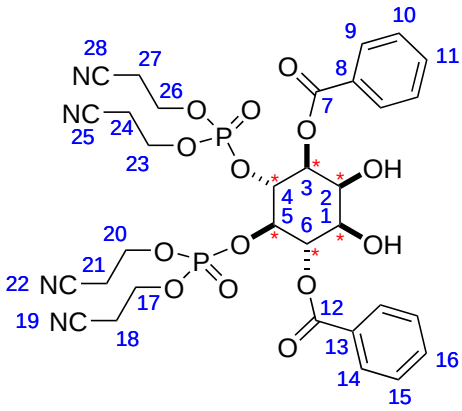
To a solution of (+)-**167** (741 mg, 2.06 mmol, 1.0 eq., D_6 90%, D_5 10%) and phosphoramidite **126** (2.24 g, 8.24 mmol, 4.0 eq.) in CH_2Cl_2 (40 mL) under an atmosphere of

N_2 was added 1*H*-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 ℃, 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 CH_2Cl_2 (60 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), saturated aqueous NaCl (50 mL), dried with Na_2SO_4, 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 CH_2Cl_2 followed by a second column in 2% EtOH in $CHCl_3$ to afford the title compound as a colourless film (833 mg, 55 %, D_6 89%, D_5 11%). The product was typically isolated with a 0.6% phosphoramidite impurity (by ^{31}P NMR) that was removed in the subsequent reaction: R_f 0.50 (EtOH/$CHCl_3$ 1:9); $[\alpha]_D^{20}$ = +122.7 (*c* 1.0, $CHCl_3$); m.p. 97-100 ℃ (from EtOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR* (400 MHz; $CDCl_3$) 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); ^{1}H NMR* (400 MHz; CD_2Cl_2) δ 8.12 (4H, dd, *J* 8.1, 1.4, *H*-9, *H*-14), 7.63 (2H, tt, *J* 7.5, 1.4, *H*-11, *H*-16), 7.50 (4H, t, *J* 7.5, *H*-10, *H*-15), 4.33-4.17 (4H, m, *H*-17, *H*-26), 4.14-4.04 (2H, m, *H*-20a, *H*-23a), 4.02-3.92 (2H, m, *H*-20b, *H*-23b), 2.81-2.60 (4H, m, *H*-21, *H*-24), 2.46-2.31 (4H, m, *H*-18, *H*-27); ^{13}C NMR* (126 MHz, $CDCl_3$) 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 (t_D, J_D 21.0, *C*-2, *C*-3), 116.9 (*C*-19, *C*-28), 116.4 (*C*-22, *C*-25), 71.7 (t_D, J_D 21.0, *C*-1, *C*-4), 63.0 (d, J_P 5.7, *C*-17, *C*-26), 62.6 (d, J_P 5.2, *C*-20, *C*-23), 19.4 (d, J_P 7.8, *C*-18, *C*-27), 19.2 (d, J_P 7.8, *C*-21, *C*-24); ^{13}C NMR* (126 MHz; CD_2Cl_2) 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 (t_D, J_D 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_D, 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; $CDCl_3$) δ –3.15; ^{2}H NMR (77 MHz; $CHCl_3$; D_6-DMSO) δ 5.90 (*D*-2, *D*-3, *D*-5, *D*-6), 4.91 (*D*-1, *D*-4); HRMS *m/z* (ES^+) Found 754.1678 $[MD_5+Na]^+$ ($C_{32}H_{27}D_5N_4O_{12}P_2Na$ requires 754.1704), 755.1736 $[MD_6+Na]^+$ ($C_{32}H_{26}D_6N_4O_{12}P_2Na$ requires 755.1761); *m/z* (ES^-) 677.2 ($[MD_5\text{-}CH_2CH_2CN]^-$, 11%), 678.2 ($[MD_6\text{-}CH_2CH_2CN]^-$, 100%); NP-HPLC (0-100% hexane/isopropanol) Retention Time = 19.0 min, 89.5%.

** A second set of NMR data was obtained in CD_2Cl_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-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 $RuCl_3{\cdot}3H_2O$ (29 mg, 0.11 mmol, 0.1 eq.) in H_2O (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 *in vacuo* to *ca.* 10 mL and aqueous $Na_2S_2O_3$ (10% *w/v*, 100 mL) was added. The organic components were extracted with EtOAc (3 × 100 mL), washed with saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage sys-

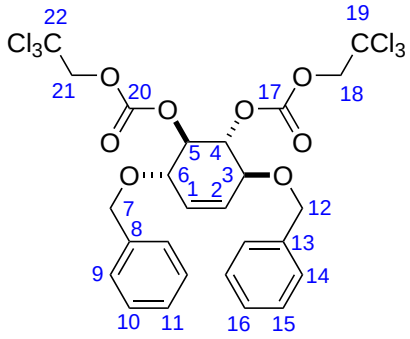
tem using 10% EtOH in $CHCl_3$, followed by crystallisation from $CHCl_3$ to afford the title compound as a colourless solid (250 mg, 30%, 89% D_6, 11% D_5); R_f 0.29 (EtOH/$CHCl_3$ 1:9); $[\alpha]_D^{20}$ = +31.6 (*c* 1.0, MeOH); m.p. 99-104 ℃ (from $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 3365 (O-H, w), 1717 (C=O, m), 1281 (C-H, s), 1264 (C-H, s), 1209 (C-O, m), 1110 (C-O, m), 1026 (C-O, s), 1000 (C-O, s), 945 (P-O, m); ^{1}H NMR* (400 MHz; $CDCl_3$/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); ^{1}H NMR* (400 MHz; CD_2Cl_2/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); ^{13}C NMR* (126 MHz; $CDCl_3$/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, J_P 5.8, *C*-17), 63.2 (d, J_P 5.8, *C*-20), 62.9 (d, J_P 5.2, *C*-23), 62.8 (d, J_P 5.2, *C*-26), 18.9 (d, J_P 7.9, *C*-18, *C*-27), 18.5 (d, J_P 7.8, *C*-21, *C*-24); ^{13}C NMR* (126 MHz; CD_2Cl_2/MeOD 1:1) δ 166.0 (*C*-12), 165.6 (*C*-7), 133.7 (*C*-16), 133.5 (*C*-11), 130.0 (*C*-14), 129.9 (*C*-13), 129.8 (*C*-9), 129.4 (*C*-8), 128.6 (*C*-15), 128.5 (*C*-10), 117.2 (*C*-22, *C*-25), 116.7 (*C*-19), 116.6 (*C*-28), 78.3-77.5 (m, *C*-5), 77.5-76.8 (m, *C*-4), 72.4 (t_D, J_D 19.6, *C*-6), 71.6 (t_D, J_D 19.8, *C*-3), 69.5 (t_D, J_D 21.9, *C*-2), 68.8 (t_D, J_D 21.9, *C*-1), 63.3 (d, J_P 5.7, *C*-17), 63.2 (d, J_P 5.7, *C*-26), 62.9 (d, J_P 5.1, *C*-23), 62.8 (d, J_P 5.1, *C*-20), 18.9 (d, J_P 7.9, *C*-18, *C*-27), 18.5 (d, J_P 7.8, *C*-21, *C*-24); ^{31}P NMR (162 MHz; $CDCl_3$/MeOD 1:1) δ –3.51 (*P*-4), –3.68 (*P*-5); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-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 [MD_5-CH_2CH_2CN]$^-$ ($C_{29}H_{25}D_5N_3O_{14}P_2$ requires 711.1522), 712.1578 [MD_6-CH_2CH_2CN]$^-$ ($C_{29}H_{24}D_6N_3O_{14}P_2$ requires 712.1585); *m/z* (ES^-) 711.1 ([MD_5-CH_2CH_2CN]$^-$, 7%), 712.1 ([MD_6-CH_2CH_2CN]$^-$, 100%), 800.1 ([MD_5+Cl]$^-$, 3%), 801.1 ([MD_6+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_2Cl_2 for ^1H 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)

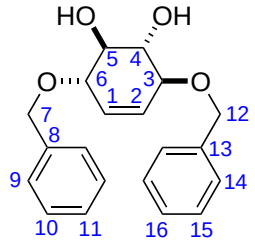


To a solution of (+)-**175** (1.78 g, 1.43 mmol, 1.0 eq.) in CH_2Cl_2 (36 mL) was added trifluoroacetic acid (4 mL) and the reaction mixture was stirred at room temperature for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture 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 ℃. 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_2SO_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, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; CD_2Cl_2) 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); ^{13}C NMR (101 MHz; CD_2Cl_2) 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).

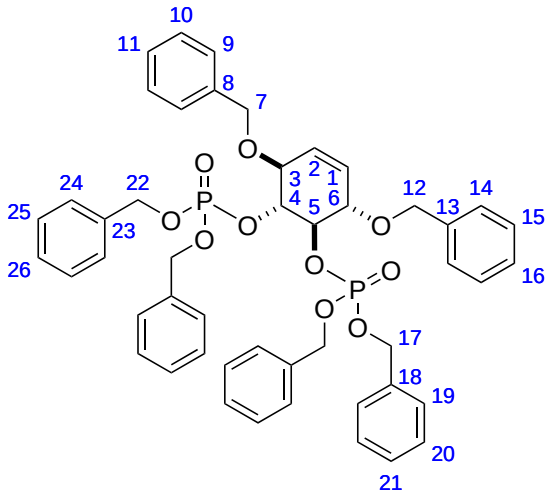
(+)-(3*S*,4*S*,5*S*,6*S*)-3,6-Bis(benzyloxy)-cyclohex-1-ene-4,5-diol ((+)-184)[74]



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 ($MeOH/CH_2Cl_2$ 1:9); $[\alpha]_D^{25}$ = +124.8 (*c* 1.0, Acetone) {lit.[74] +130 (*c*. 1.6, Acetone)}; ^{1}H NMR (400 MHz; $CDCl_3$) 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, O*H*); *m/z* (ES^+) 349.2 ($[M+Na]^+$, 100%). These data are in agreement with the literature.[74]

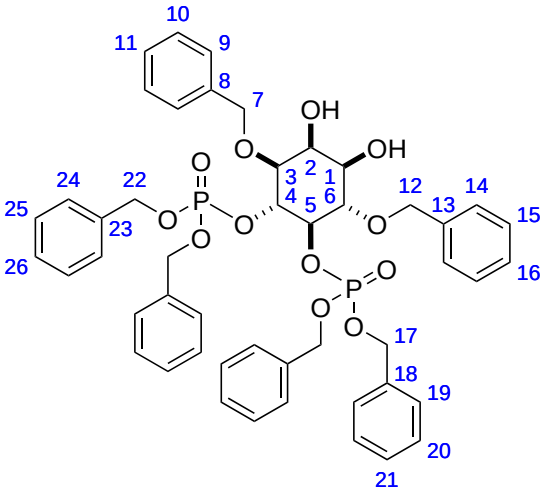
(+)-Tetrabenzyl-((3*S*,4*R*,5*R*,6*S*)-3,6-bis(benzyloxy)-cyclohex-4-ene-1,2-diyl) bis(phosphate) ((+)-189)



To a solution of diol **184** (272 mg, 0.83 mmol, 1.0 eq.) and dibenyl *N,N*-diisopropylphosphoramidite **185** (1.12 mL, 3.33 mmol, 4.0 eq.) in CH_2Cl_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_2Cl_2) indicated the reaction was complete. The reaction mixture was cooled to –78 ℃ 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_2Cl_2 (100 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *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_2Cl_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, $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 1497 (C=C, w), 1446

(C=C, m), 1386 (C-H ar., m), 1070 (C-O, s), 1017 (C-O, s); ^{1}H NMR (500 MHz; CD_2Cl_2) δ 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_2Cl_2) δ 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. × 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_2Cl_2) δ –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%.

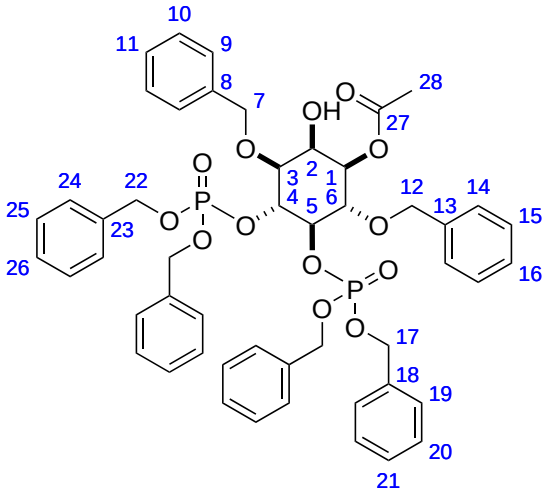
(–)-3,6-Di-*O*-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-D-*myo*-inositol ((–)-154)



To a solution of (+)-**189** (490 mg, 0.58 mmol, 1.0 eq.) in MeCN (6 mL) at 0 ℃ was added a solution of $NaIO_4$ (186 mg, 0.87 mmol, 1.5 eq.) and $RuCl_3{\cdot}3H_2O$ (8 mg, 0.03 mmol, 0.05 eq.) in H_2O (1.5 mL). The reaction mixture was stirred vigorously for 4 min at 0 ℃. TLC analysis of the reaction mixture (EtOAc) indicated the reaction was complete. The reaction was quenched with aqueous $Na_2S_2O_3$ (10% *w/v*, 20 mL). The organic components were extracted using EtOAc (3 × 30 mL), combined, washed with saturated aqueous NaCl (30 mL), dried with Na_2SO_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); $[\alpha]_D^{25}$ = –19.7 (*c* 2.0, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) δ 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_2Cl_2) δ 139.1 (*C*-13), 138.0 (*C*-8), 136.7-136.4 (m, *C*-18, *C*-23), 128.9-127.8 (m, *C*-ar. × 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_2Cl_2) δ –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%.

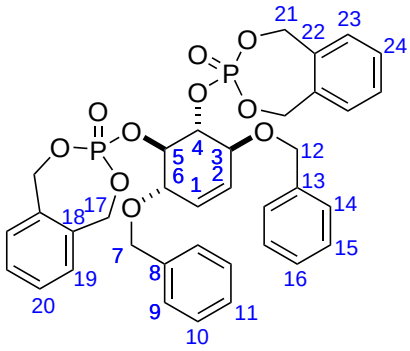
(–)-1-Acetyl-3,6-di-*O*-benzyl-4,5-bis(bis(benzyloxy)phosphoryl)-D-*myo*-inositol ((–)-195)



To a solution of (–)-**154** (138 mg, 0.157 mmol, 1.0 eq.) in CH_2Cl_2 was added 4-dimethyl-

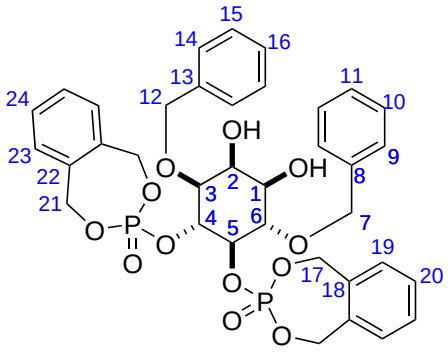
aminopyridine (1 mg, 0.008 mmol, 0.05 eq.), pyridine (0.020 mL, 0.25 mmol, 1.5 eq.), and acetyl chloride (0.020 mL, 0.28 mmol, 1.8 eq.) and the resulting suspension was stirred at room temperature for 1 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. 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 $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, 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); $[\alpha]_D^{25}$ = –20.5 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*), 1.93 (3H, s, *H*-28); ^{13}C NMR (126 MHz; CD_2Cl_2) 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, 128.7, 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); ^{31}P NMR (162 MHz; CD_2Cl_2) δ –1.46 (*P*-5), –1.50 (*P*-4); HRMS *m/z* (ES^+) Found 923.2949 $[M+H]^+$ ($C_{50}H_{53}O_{13}P_2$ 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%.

(+)-(3*S*,4*R*,5*R*,6*S*)-3,6-Bis(benzyloxy)-4,5-bis(oxy(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl))cyclohex-2-ene ((+)-191)[75]



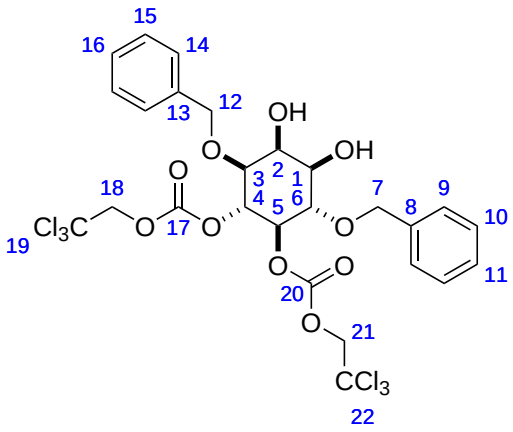
To a solution of (+)-**184** (377 mg, 1.16 mmol, 1.0 eq.) and phosphoramidite **187** (1.10 g, 4.62 mmol, 4.0 eq.) in CH_2Cl_2 (15 mL) under an atmosphere of Ar was added 1*H*-tetrazole (3-4% in MeCN, 10.75 mmol, 4.62 mL, 4.0 eq.) and the reaction mixture was stirred at room temperature for 18 h. TLC 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_2Cl_2 (100 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na_2SO_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); $[\alpha]_D^{25}$ = +22.9 (*c* 0.65, $CHCl_3$) {lit.[75] +21.5 (*c*. 0.65, $CHCl_3$)}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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; $CDCl_3$) δ –1.41; *m/z* (ES$^+$) 691.1 ([M+H]$^+$, 100%), 713.1 ([M+Na]$^+$, 54%). These data are in agreement with the literature.[75]

(–)-3,6-Di-*O*-benzyl-4,5-bis-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-D-*myo*-inositol ((–)-192)[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 $RuCl_3{\cdot}3H_2O$ (4.5 mg, 0.017 mmol, 0.05 eq.) in H_2O (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 $Na_2S_2O_3$ (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_2SO_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, 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, $CHCl_3$) {lit.[75] –32.0 (*c* 1.0, $CHCl_3$)}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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, dd, *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, O*H*-1), 3.02 (1H, br s, O*H*-2); ^{31}P NMR (162 MHz; $CDCl_3$) δ –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.[75]

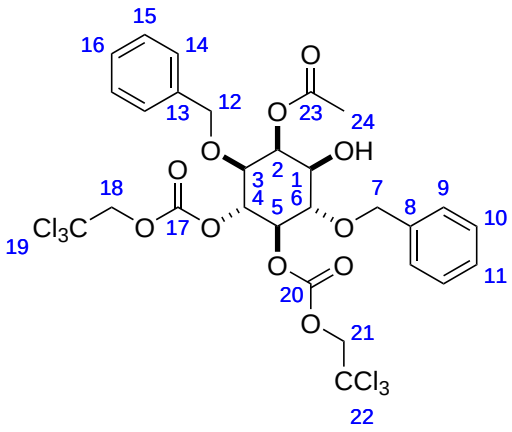
(+)-3,6-Di-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-*myo*-inositol ((+)-202)



To a solution of (+)-**183** (965 mg, 1.43 mmol, 1.0 eq.) in MeCN (16 mL) was added a solution of $RuCl_3{\cdot}3H_2O$ (19 mg, 0.07 mmol, 0.05 eq.) and $NaIO_4$ (457 mg, 2.15 mmol, 1.5 eq.) in H_2O (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 $Na_2S_2O_3$ (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_2SO_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); $[\alpha]_D^{25} = +10.4$ (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) δ 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, O*H*-2), 2.52 (1H, br d, *J* 6.3, O*H*-1); ^{13}C NMR (126 MHz; CD_2Cl_2) δ 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,

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 $[M^{35}Cl_6$+Formic acid-H$]^-$ ($C_{27}H_{27}{}^{35}Cl_6O_{12}$ requires 752.9639); *m/z* (ES⁻) 753.0 ($[M^{35}Cl_6$+Formic acid-H$]^-$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 6.9 min, 85.9%.

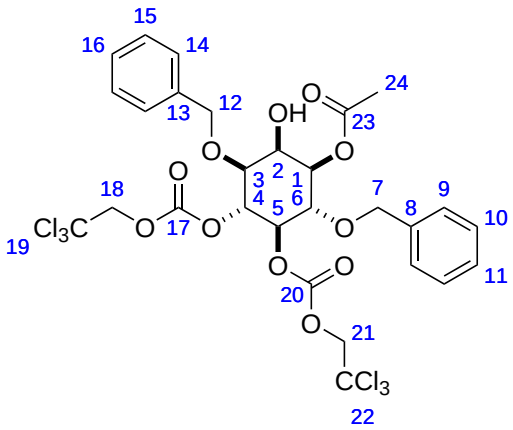
(+)-2-Acetyl-3,6-di-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-*myo*-inositol ((+)-200)



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 $NaHCO_3$ (2 × 50 mL), saturated aqueous NaCl (2 × 50 mL), dried with Na_2SO_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 foam (395 mg, 86%) that was used without further

purification: R_f 0.60 (EtOAc/petroleum ether 1:2); $[\alpha]_D^{25}$ = +22.5 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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*-18, *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); ^{13}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 $[M^{35}Cl_6+Na]^+$ ($C_{28}H_{28}{}^{35}Cl_6O_{11}Na$ requires 772.9655); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 6.1 min, 92.6%.

(+)-1-Acetyl-3,6-di-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-*myo*-inositol ((+)-201)

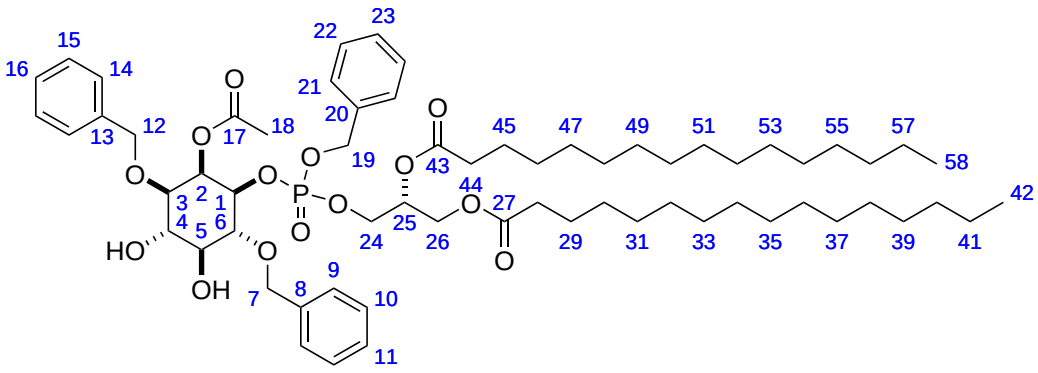


To a solution of (+)-**202** (276 mg, 0.39 mg, 1.0 eq.) in CH_2Cl_2 (2 mL) was added pyridine (62 μL, 0.78 mmol, 2.0 eq.) followed by AcCl (55 μL, 0.78 mmol, 2.0 eq.) and the reaction mixture was stirred at room temperature for 10 min. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) 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 $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na_2SO_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 the title compound as a colourless oil (240 mg, 82%): R_f 0.28 (EtOAc/petroleum ether 1:2); ^{1}H NMR (400 MHz; CD_2Cl_2) 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, O*H*), 2.05 (3H, s, *H*-24); ^{13}C NMR (101 MHz; CD_2Cl_2) 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. $\times$ 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)-D-*myo*-inositol (205)



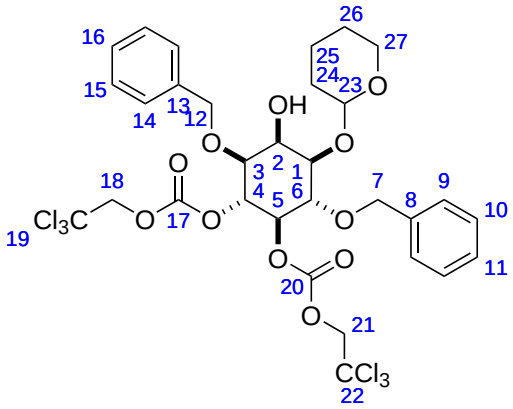
To a solution of (+)-**200** (93 mg, 0.12 mmol, 1.0 eq.) and phosphoramidite **207** (250 mg, 0.31 mmol, 2.5 eq.) in CH_2Cl_2 (5 mL) under an atmosphere of Ar was added a solution of 1*H*-tetrazole (3-4 wt.% in MeCN, 0.72 mL, 0.31 mmol, 2.5 eq.) and the reaction mixture was stirred at room temperature 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 ℃, 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: R_f 0.48 (EtOAc/petroleum ether 1:1); $[\alpha]_D^{25}$ = +10.9 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (400 MHz; CD_2Cl_2) *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

(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_2Cl_2) *Diastereomer A** δ 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, 127.85, 127.77, 127.75, 127.7, 127.6 (*C*-ar × 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** δ 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, 127.85, 127.77, 127.75, 127.7, 127.6 (*C*-ar × 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_2Cl_2) *Diastereomer A** δ –1.41, *Diastereomer B** δ –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.*

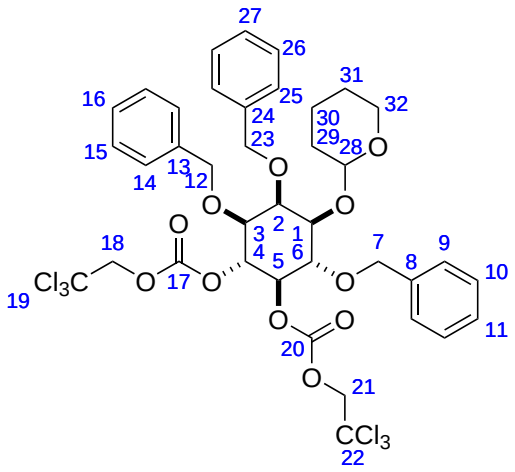
(+)-3,6-Di-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-1-*O*-(2*H*-tetrahydropyranyl)-D-*myo*-inositol ((+)-210)



To a solution of (+)-**202** (853 mg, 1.20 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) under an atmosphere of Ar was added 3,4-dihydro-2*H*-pyran (0.13 mL, 1.4 mmol, 1.2 eq.) followed by pyridinium *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 *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: R_f 0.89 (EtOAc/petroleum ether 1:1); ^{1}H NMR (400 MHz; $CDCl_3$) *Diastereomer A* δ 7.37-7.23 (10H, m, *H*-ar.), 5.43 (1H, dd, *J* 10.0, *H*-4), 5.03-4.92 (2H, m, *H*-5, *H*-23), 4.81-4.59 (8H, m, *H*-7, *H*-12, *H*-18, *H*-21), 4.37 (1H, dd, *J* 2.6, 2.6, *H*-2), 4.16-4.11 (1H, m, *H*-6), 3.94-3.87 (1H, m, *H*-27a), 3.85 (1H, dd, *J* 10.0, 2.6, *H*-1), 3.62-3.56 (1H, m, *H*-3), 3.52-3.36 (1H, m, *H*-27b), 2.67 (1H, br s, O*H*), 1.95-1.35 (6H, m, *H*-24, *H*-25, *H*-26), *Diastereomer B* δ 7.37-7.23 (10H, m, *H*-ar.), 5.42 (1H, dd, *J* 10.0, *H*-4), 5.03-4.92 (1H, m, *H*-5), 4.81-4.59 (9H, m, *H*-7, *H*-12, *H*-18, *H*-21, *H*-23), 4.34 (1H, dd, *J* 2.6, 2.6, *H*-2), 4.16-4.11 (1H, m, *H*-6), 3.94-3.87 (1H, m, *H*-27a), 3.65 (1H, dd, *J* 10.0, 2.6, *H*-1), 3.62-3.56 (1H, m, *H*-3), 3.52-3.36 (1H, m, *H*-27b), 2.60 (1H, br s, O*H*), 1.95-1.35 (6H, m, *H*-24, *H*-25, *H*-26); ^{13}C NMR (101 MHz; $CDCl_3$) *Diastereomer*

A δ 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* δ 153.61, 153.58 (*C*-17, *C*-20), 138.0 (*C*-8), 137.0 (*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), 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).

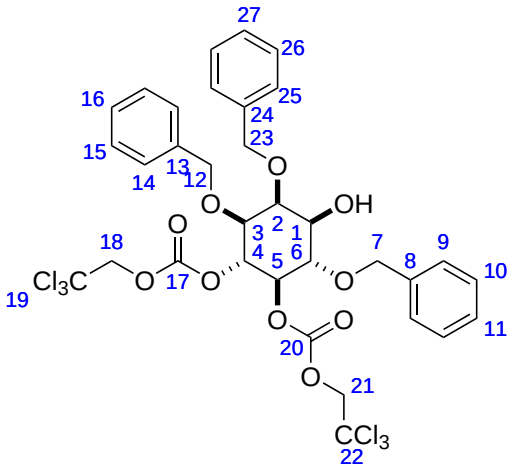
(+)-2,3,6-Tri-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-1-*O*-(2*H*-tetrahydropyranyl)-D-*myo*-inositol ((+)-211)



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 μL, 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_2SO_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 (14 mg, 14%): R_f 0.74 (EtOAc/petroleum ether 1:3); $[\alpha]_D^{25}$ = +11.8 (*c* 0.88, $CHCl_3$); $\bar{\nu}_{max}$ (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), 1021 (C-O, m); ^{1}H NMR (500 MHz; CD_2Cl_2) *Diastereomer A* δ 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), *Diastereomer B* δ 7.47-7.24 (15H, m, *H*-ar), 5.40 (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), 4.53 (1H, d, *J* 11.7, *H*-12b), 4.19 (1H, dd, *J* 2.1, 2.1, *H*-2), 4.13 (1H, dd, *J* 10.0, 10.0, *H*-6), 3.85-3.80 (1H, m, *H*-32a), 3.84 (1H, dd, *J* 10.0, 2.1, *H*-1), 3.58 (1H, dd, *J* 10.0, 2.1, *H*-3), 3.51-3.45 (1H, m, *H*-32b), 1.90-1.38 (6H, m, *H*-29, *H*-30, *H*-31); ^{13}C NMR (126 MHz; CD_2Cl_2) *Diastereomer A* δ 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. × 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* δ 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, 128.96, 128.9 (*C*-ar. × 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 $[M^{35}Cl_6+Na]^+$ ($C_{38}H_{40}{}^{35}Cl_6NaO_{11}$ 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%.

(+)-2,3,6-Tri-*O*-benzyl-4,5-bis(2',2',2'-trichloroethylcarbonate)-D-*myo*-inositol ((+)-212)

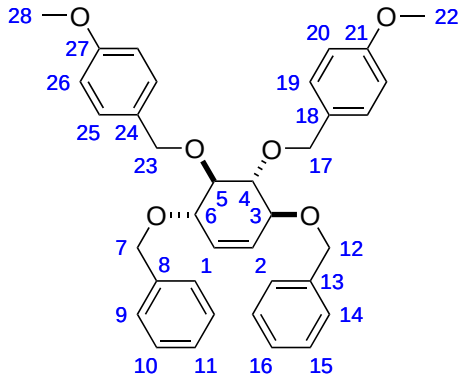


A solution of (+)-**211** (115 mg, 0.13 mmol, 1.0 eq.) was dissolved in a mixture of THF (0.4 mL) and aqueous AcOH (80% *v/v*, 2.0 mL) and the reaction mixture was stirred at 50 °C for 2 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The organic components were washed with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous NaCl (20 mL), dried with Na_2SO_4, 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, $CHCl_3$); $\bar{\nu}_{max}$ (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; CD_2Cl_2) δ 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, O*H*); ^{13}C NMR (101 MHz; CD_2Cl_2) δ 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,

C-22), 80.0 (*C*-6), 78.6 (*C*-5), 78.1 (*C*-3), 77.4 (*C*-4), 77.3 (*C*-18, *C*-21), 76.6 (*C*-2), 75.6 (*C*-7), 75.5 (*C*-23), 73.0 (*C*-12), 72.4 (*C*-1).

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

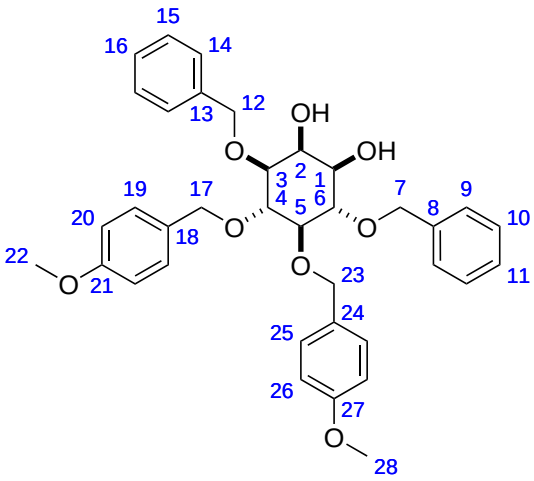
(+)-(3*R*,4*S*,5*S*,6*R*)-3,6-Bis(benzyloxy)-4,5-bis((4-methoxybenzyl)oxy)-cyclohex-1-ene ((+)-214)



To a solution of (+)-**184** (491 mg, 1.5 mmol, 1.0 eq.) in anhydrous DMF (5 mL) under an atmosphere of N_2 at 0 ℃ was added NaH (60% dispersion in oil, 480 mg, 12.0 mmol, 8.0 eq.) and the suspension was stirred at 0 ℃ 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 Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% Et_2O in hexane to afford the title compound as a colourless oil (579 mg, 68%): R_f 0.41 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25} = +70.1$ (*c* 0.92, $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 3032 (C-H, m), 2903 (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); ^{1}H NMR (500 MHz; CD_2Cl_2) δ 7.35-7.26 (10H, m, *H*-ar.), 7.25 (4H, dt, *J* 8.5, 2.0, *H*-19, *H*-25), 6.83 (4H, dt, *J* 8.5, 2.0, *H*-20, *H*-26), 5.75 (2H, s, *H*-1, *H*-2), 4.83 (2H, d, *J* 10.8, *H*-17a, *H*-23a), 4.76 (2H, d, *J* 10.8, *H*-17b, *H*-23b), 4.67 (4H, s, *H*-7, *H*-12), 4.18 (2H, dd, *J* 5.1, 2.2, *H*-3, *H*-6), 3.78 (6H, s, *H*-22, *H*-28), 3.65 (2H, dd, *J* 5.1, 2.2, *H*-4, *H*-5); ^{13}C NMR (126 MHz; CD_2Cl_2) δ 159.6 (*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), 128.2 (*C*-11, *C*-16), 128.0 (*C*-1, *C*-2), 127.9 (*C*-9, *C*-14), 113.9 (*C*-20, *C*-26), 83.7 (*C*-4, *C*-5), 80.5 (*C*-3, *C*-6), 75.3 (*C*-17, *C*-23), 72.5 (*C*-7, *C*-12), 55.6 (*C*-22, *C*-28); HRMS *m/z* (ES$^+$) Found 589.2557 [M+Na]$^+$ ($C_{36}H_{38}O_6$ requires 589.2560); *m/z* (ES$^+$) 589.2 ([M+Na]$^+$, 100%); NP-HPLC (2-10% isopropanol/hexane) Retention Time = 2.4 min, 98.6%.

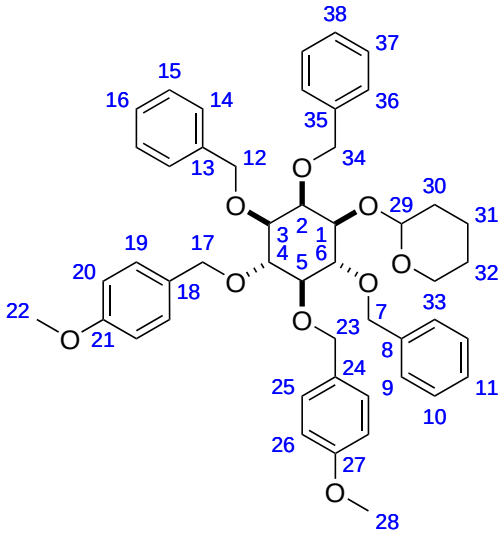
(−)-3,6-Di-*O*-benzyl-4,5-bis-*O*-(4-methoxybenzyl)-D-*myo*-inositol ((−)-215)



To a vigorously stirred solution of (+)-**214** (272 mg, 0.48 mmol, 1.0 eq.) in MeCN (5 mL) was added a solution of $NaIO_4$ (133 mg, 0.62 mmol, 1.3 eq.) and $RuCl_3{\cdot}3H_2O$ (12 mg, 0.048 mmol, 0.1 eq.) in H_2O (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 $Na_2S_2O_3$ (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); $[\alpha]_D^{25}$ = –29.5 (*c* 0.58, $CHCl_3$) {lit.[135] –32.2 (*c* 2.5 in $CHCl_3$)}; m.p.[b] 126-128 °C (from MeOH); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*-2), 2.42 (1H, d, *J* 5.6, O*H*-1); ^{13}C NMR (126 MHz; CD_2Cl_2) 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 $[M+Na]^+$ ($C_{36}H_{40}O_8Na$ 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*-tetrahydropyranyl)-D-*myo*-inositol ((–)-217)



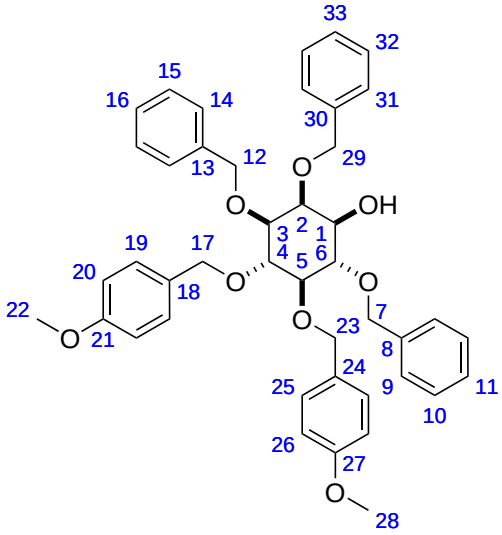
To a solution of (–)-**215** (346 mg, 0.58 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) under an atmosphere of Ar was added 3,4-dihydro-2*H*-pyran (79 μL, 0.87 mmol, 1.5 eq.) and pyridinium *p*-toluenesulfonate (15 mg, 0.06 mmol, 0.1 eq.) and the reaction solution was stirred at room temperature for 18 h. TLC analysis of the reaction mixture (1:1 EtOAc/petroleum ether) indicated some starting material (–)-**215** remained, some product and some di-reacted material was present. The reaction mixture was concentrated *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 mineral 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_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 7-60%

Et_2O in hexane to afford the title compound as a colourless oil (115 mg, 26%, 2 steps): R_f 0.21 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25} = +3.1$ (*c* 0.88, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) *Diastereomer A** δ 7.50-7.24 (15H, m, *H*-ar.), 7.22 (4H, d, *J* 8.7, *H*-19, *H*-25), 6.82 (4H, dt, *J* 8.7, 3.0, *H*-20, *H*-26), 4.96 (1H, d, *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*-2), 4.03-3.91 (2H, m, *H*-4, *H*-6), 3.89-3.83 (1H, m, *H*-30a), 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., *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); ^{13}C NMR (126 MHz; CD_2Cl_2) *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. $\times$ 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. $\times$ 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 $[M+Na]^+$ ($C_{48}H_{54}O_9$ 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.

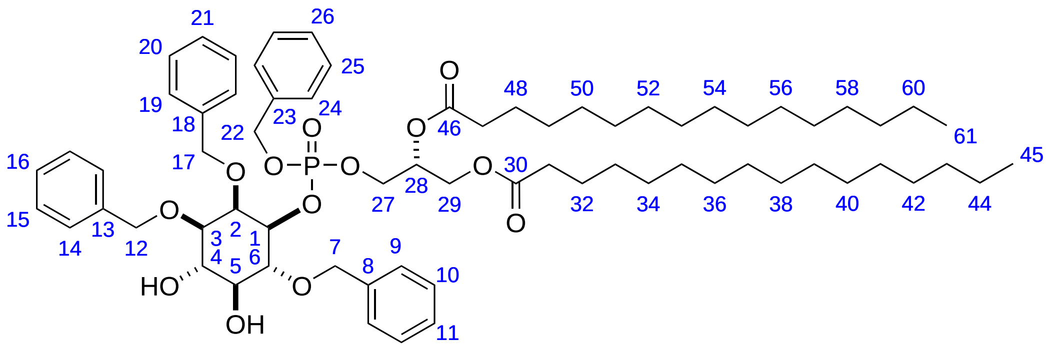
(–)-4,5-Bis-*O*-(4-methoxybenzyl)-2,3,6-Tri-*O*-benzyl-D-*myo*-inositol ((–)-213)



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%): R_f 0.53 (EtOAc/petroleum ether 1:2); $[\alpha]_D^{25}$ = –13.1 (*c* 1.0, $CHCl_3$) {lit.[135] –13.9 (*c.* 3.4 in $CHCl_3$)}; $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*); ^{13}C NMR (126 MHz; CD_2Cl_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), 128.73, 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)



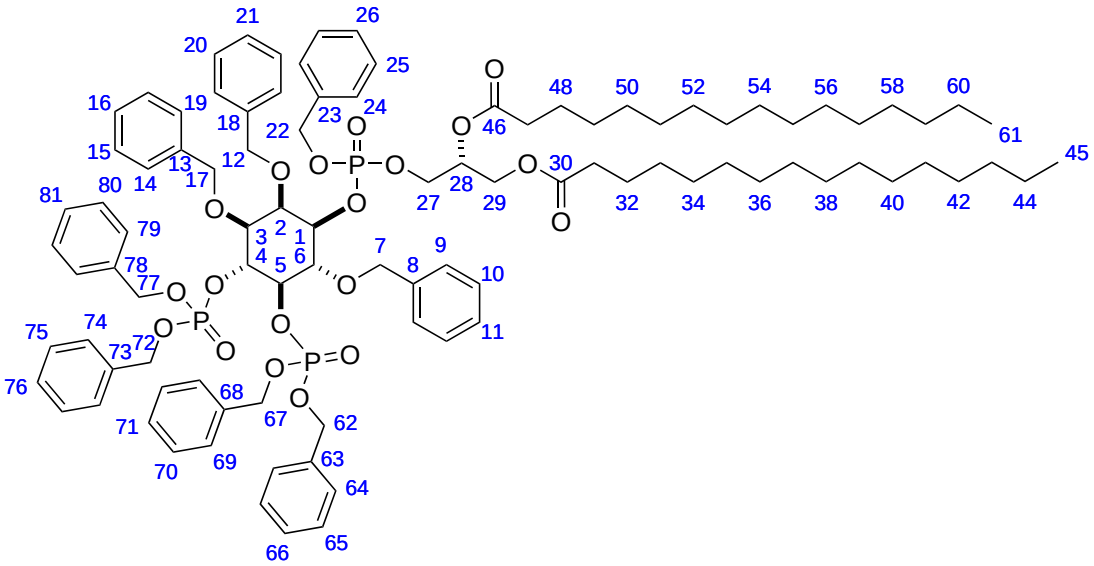
To a solution of (–)-**213** (104 mg, 0.151 mmol, 1.0 eq.) and phosphoramidite **207** (304 mg, 0.378 mmol, 2.5 eq.) in CH_2Cl_2 (3 mL) under an atmosphere of argon was added 1*H*-tetrazole (3-4 wt.%, 0.88 mL, 0.378 mmol, 2.5 eq.) and the reaction solution was stirred at room temperature for 48 h. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The solution was cooled to –78 °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_2Cl_2 (50 mL), the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica

gel flash column chromtography on a Biotage system using 5-40% EtOAc in petroleum ether to afford a colourless oil. The oil was dissolved in CH_2Cl_2 (10 mL), H_2O (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. ^{1}H NMR analysis of the reaction mixture indicated the reaction was complete. The mixture was diluted with CH_2Cl_2 (50 mL), the organic components were washed with saturated aqueous $NaHCO_3$ (50 mL), dried with Na_2SO_4, 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% Et_2O in hexane to afford the title compound as a colourless oil (62 mg, 35%) as a *ca.* 1:1 mixture of inseparable diastereomers: R_f 0.13 (EtOAc/petroleum ether 1:3); $[\alpha]_D^{25} = +3.2$ (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) *Diastereomer A** δ 7.40-7.23 (20H, m, *H*-ar.), 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, O*H*), 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*-ar.), 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, O*H*), 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); ^{13}C NMR (126 MHz; CD_2Cl_2) *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, 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), 79.1 (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** δ 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_2Cl_2) *Diastereomer A** δ –1.68, *Diastereomer B** δ –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-dipalmitoyl)-*sn*-glycerol)-(benzyloxy)phosphoryl)-D-*myo*-inositol ((–)-219)[41]



To a solution of (+)-**268** (48 mg, 0.041 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) under an atmosphere of Ar was added dibenzyl-*N,N*-diisopropylphosphoramidite (68 μL, 0.21 mmol, 5.0 eq.) followed by 1*H*-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_2Cl_2 (50 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL) and saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *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); $[\alpha]_D^{25} = -3.8$ (*c* 0.55, $CHCl_3$) {lit.[41] –4.3 (*c* 0.53, $CHCl_3$)}; $\bar{\nu}_{max}$ (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_2Cl_2) *Diastere-*

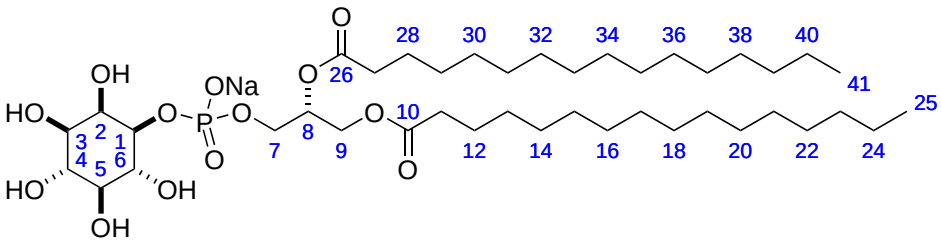
*omer A** δ 7.42-7.10 (38H, m, *H*-ar.), 7.05-7.02 (2H, m, *H*-ar.), 5.11 (1H, dddd, *J* 5.5, 5.5, 5.5, 5.5, *H*-28), 5.07-4.49 (18H, m, *H*-4, *H*-5, *H*-7, *H*-12, *H*-17, *H*-22, *H*-62, *H*-67, *H*-72, *H*-77), 4.40-4.28 (2H, m, *H*-1, *H*-2), 4.19-3.86 (5H, m, *H*-6, *H*-27, *H*-29), 3.56 (1H, dd, *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); ^{13}C NMR (126 MHz; CD_2Cl_2) *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, J_P 6.7, *C*-78), 136.0 (d, J_P 6.7, *C*-23), 129.1-127.6 (m, *C*-ar. $\times$ 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, 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)), 25.21 (*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, J_P 6.7, *C*-78), 136.1 (d, J_P 6.7, *C*-23), 129.1-127.6 (m, *C*-ar. $\times$ 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, 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); ^{31}P NMR (162 MHz; CD_2Cl_2) *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 $[M^{12}C_{97}+H]^+$ ($^{12}C_{97}H_{129}NaO_{19}P_3$ requires 1691.8413), 1692.8375 $[M^{12}C_{96}{}^{13}C+H]^+$ ($^{12}C_{96}{}^{13}CH_{129}NaO_{19}P_3$ requires 1692.8447); *m/z* (ES^+) 1691.6 ($[M+H]^+$, 100%), 1692.6 ($[M^{13}C+H]^+$, 80%), 1708.8 ($[M+NH_4]^+$, 20%), 1709.8 ($[M^{13}C+NH_4]^+$, 21%), 1713.7 ($[M+Na]^+$, 28%), 1714.7 ($[M^{13}C+Na]^+$, 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.*

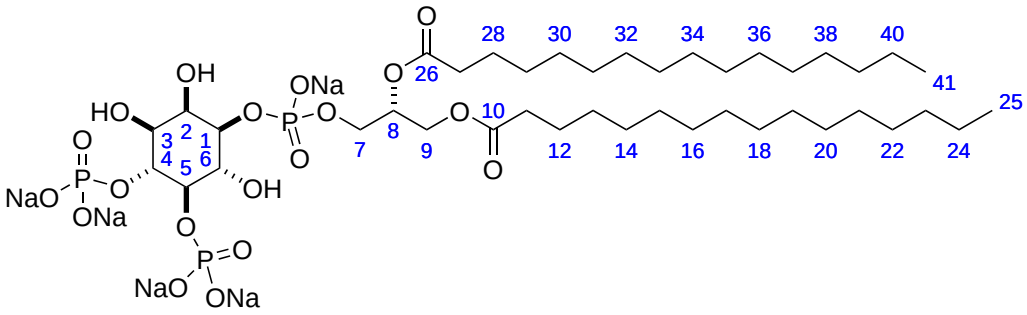
***As the number of carbon atoms is close to 100, the major peak in mass spectrometry is no longer $^{12}C_{97}$ but is $^{12}C_{96}{}^{13}C_1$ and hence this mass is included for clarity.*

Phosphatidylinositol monosodium salt (13)[41]



To a solution of (+)-**268** (8 mg, 0.007 mmol, 1.0 eq.) in ^{t}BuOH (1.2 mL) and H_2O (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_2Cl_2/D_4-MeOD) δ 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_2Cl_2/D_4-MeOD) δ –0.13 (*P*-1); HRMS *m/z* (ES$^-$) Found 809.5188 [M–H]$^-$ ($C_{41}H_{80}O_{19}P_3$ requires 809.5185). These data are in good agreement with the literature.[86]

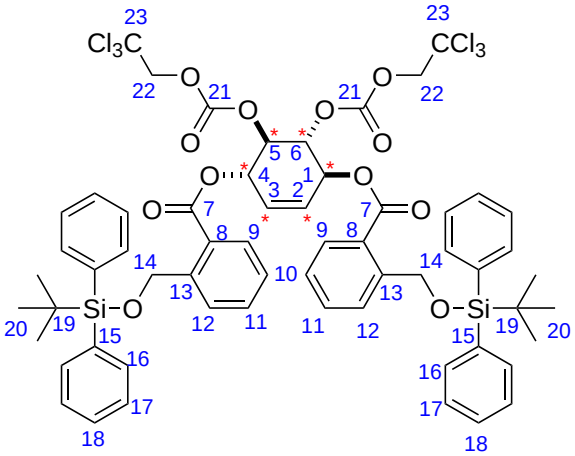
Phosphatidylinositol-(4,5)-bisphosphate pentasodium salt (10)[41]



To a solution of (+)-**219** (28 mg, 0.017 mmol, 1.0 eq.) in ^{t}BuOH (3.0 mL) and H_2O (0.5 mL) under an atmosphere of N_2 was added $NaHCO_3$ (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_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 (50 mL) was added. The suspension was filtered through a plug of Celite® and lyophilised to afford the title compound as a colourless powder (16 mg, 89%): ^{1}H NMR (400 MHz; D_2O) δ 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); ^{31}P NMR (162 MHz; D_2O) δ 4.78 (*P*-4), 4.59 (*P*-5), –0.23 (br s, *P*-1); HRMS *m/z* (ES^-) Found 969.4512 $[M–H]^-$ ($C_{41}H_{80}O_{19}P_3$ requires 969.4512). These data are in good agreement with the literature.[41,89]

7.7 Deuterated Benzylated Derivatives

(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis(((2',2',2'-trichloroethoxy)carbonyl)oxy)cyclohex-2-ene-1,4-diyl-D_6 bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-269)



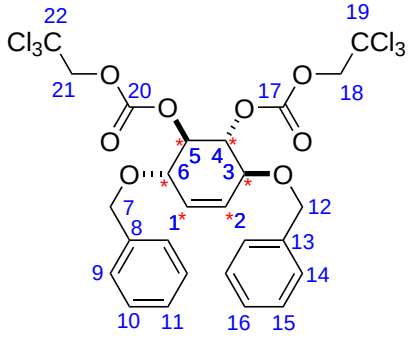
Tetratroc (±)-**165** (853 mg, 1.0 mmol, 1.0 eq.), benzoate derivative **119** (1.37 g, 3.5 mmol, 3.5 eq.), (*S,S*)-ligand (–)-**84** (104 mg, 0.15 mmol, 0.15 eq.), tetrahexylammonium bromide (86 mg, 0.2 mmol, 0.2 eq.), and [Pd(η^3-allyl)Cl]$_2$ (9.2 mg, 0.025 mmol, 0.025 eq.) were degassed on a Schlenk system (3 × vacuum/N_2 cycles). CH_2Cl_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_2Cl_2 (2 × 30 mL). The combined organic components were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% CH_2Cl_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, $CHCl_3$); m.p. 135-137 °C (from MeOH); $\bar{\nu}_{max}$ (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_2Cl_2) δ 8.08 (2H,

dd, *J* 7.9, 1.0, *H*-12), 7.97 (2H, dd, *J* 7.6, 1.3, *H*-9), 7.74-7.70 (8H, m, *H*-16), 7.69 (2H, ddd, *J* 7.9, 7.6, 1.0, *H*-11), 7.47-7.38 (12H, m, *H*-17, *H*-18), 7.36 (2H, dd, *J* 7.6, 7.6, *H*-10), 5.20 (2H, d, *J* 16.2, *H*-14a), 5.15 (2H, d, *J* 16.2, *H*-14b), 4.73 (2H, d, *J* 11.9, *H*-22a), 4.62 (2H, d, *J* 11.9, *H*-22b), 1.15 (18H, s, *H*-20); ^{13}C NMR* (126 MHz; CD_2Cl_2) δ 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 (t_D, J_D 22.1, *C*-1, *C*-4), 71.4 (t_D, J_D 22.1, *C*-5, *C*-6), 64.8 (*C*-14), 27.1 (*C*-20), 19.6 (*C*-19); ^{2}H NMR (77 MHz; $CHCl_3$; D_6-DMSO) δ 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^{-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 ^{13}C signals were observed and matched the shifts for (+)-**175**.*

(+)-(1*R*,2*R*,3*S*,6*S*)-3,6-Bis(benzyloxy)cyclohex-4-ene-1,2-diyl-D_6 bis(2',2',2'-trichloroethyl) bis(carbonate) ((+)-221)

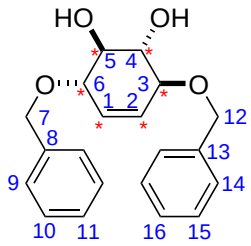


To a solution of (+)-**269** (6.32 g, 5.0 mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) was added

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 N_2. 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 $NaHCO_3$ (100 mL), saturated aqueous NaCl (100 mL), dried with Na_2SO_4, 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: R_f 0.60 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25} = +73.6$ (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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); ^{13}C NMR (126 MHz; CD_2Cl_2) 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); ^{2}H NMR (77 MHz; $CHCl_3$; $CDCl_3$) 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 $[M+Na]^+$ ($C_{26}H_{18}D_6{}^{35}Cl_6NaO_8$ requires 702.9871); *m/z* (ES^+) 702.8 ($[M^{35}Cl_6+Na]^+$, 100%).

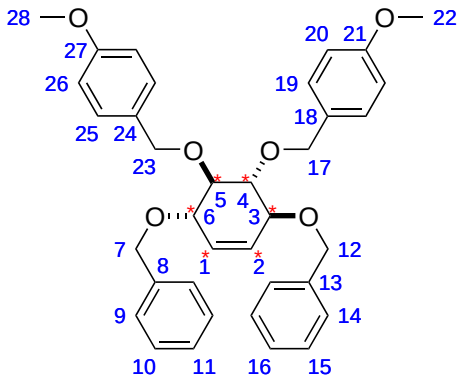
Deuterium incorporation of this compound was not calculated due to complexities arising from multiple Cl isotopes within the mass spectrum, however, no hydrogen-deuterium exchange was observed by ^{1}H NMR.

(+)-(3*S*,4*S*,5*S*,6*S*)-3,6-Bis(benzyloxy)cyclohex-1-ene-4,5-diol-D_6 ((+)-222)



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); $\bar{\nu}_{max}$ (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_2Cl_2) δ 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_2Cl_2) δ 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 (t_D, J_D 24.7, *C*-1, *C*-2), 78.7 (t_D, J_D 22.1, *C*-3, *C*-6), 74.2 (t_D, J_D 22.5, *C*-4, *C*-5), 71.7 (*C*-7, *C*-12); ^{2}H NMR (77 MHz; $CHCl_3$; $CDCl_3$) δ 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 $[MD_5+Na]^+$ ($C_{20}H_{17}D_5O_4$ requires 354.1730), 355.1783 $[MD_6+Na]^+$ ($C_{20}H_{16}D_6O_4$ 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%.

(+)-(3*S*,4*R*,5*R*,6*S*)-3,6-Bis(benzyloxy)-4,5-bis(4-methoxybenzyloxy)-cyclohex-1-ene-D_6 ((+)-223)

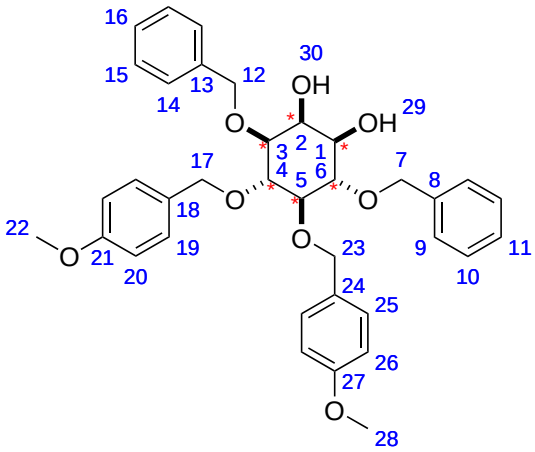


To a solution of (+)-**222** (124 mg, 0.37 mmol, 1.0 eq., 84% D_6, 16% D_5) in anhydrous DMF (1.5 mL) under an atmosphere of Ar was added NaH (60% dispersion in mineral oil, 89 mg, 1.5 mmol, 4.0 eq.) and the suspension was stirred at room temperature for 10 min. After this time, 4-methoxybenzyl chloride (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 × 30 mL), combined, washed with aqueous LiCl (0.5 M, 30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 5-40% Et_2O 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, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) δ 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_2Cl_2) δ 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 (t_D, J_D 21.0, *C*-4, *C*-5), 79.9 (t_D, 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); ^{2}H NMR (77 MHz; $CHCl_3$; $CDCl_3$) 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 $[MD_5+Na]^+$ ($C_{36}H_{33}D_5NaO_6$ requires 594.2874), 595.2933 $[MD_6+Na]^+$ ($C_{36}H_{32}D_6NaO_6$ requires 595.2937); *m/z* (ES^+) 594.3 ($[MD_5+Na]^+$, 20%), 595.3 ($[MD_6+Na]^+$, 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 ^{13}C signals were observed and matched the shifts for (+)-**214**.*

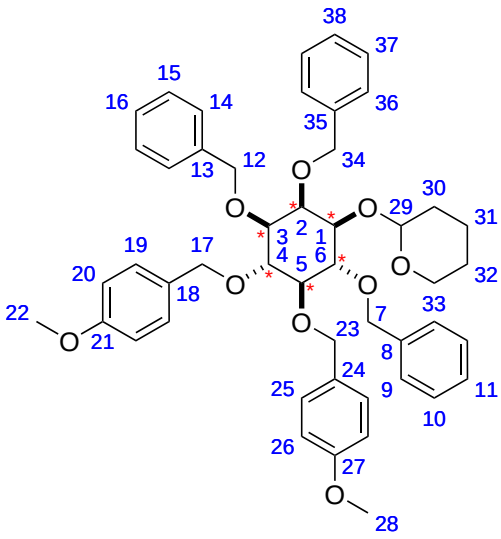
(−)-3,6-Di-*O*-benzyl-4,5-bis-*O*-(4-methoxybenzyl)-D-*myo*-inositol-D_6 ((−)-224)



To a solution of (+)-**223** (120 mg, 0.21 mmol, 1.0 eq., 84% D_6, 16% D_5) in MeCN (2 mL) was added a solution of $NaIO_4$ (66 mg, 0.31 mmol, 1.5 eq.) and $RuCl_3{\cdot}3H_2O$ (2.6 mg, 0.01 mmol, 0.05 eq.) in H_2O (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 $Na_2S_2O_3$ (10% *w/v*, 30 mL) was added and the organic components were extracted with CH_2Cl_2 (3 × 25 mL), dried with Na_2SO_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 colourless needles (84 mg, 66%, 84% D_6, 16% D_5): R_f 0.38

(EtOAc/petroleum ether 1:1); $[\alpha]_D^{25}$ = –29.6 (*c* 1.0, $CHCl_3$); m.p. 123-124 ℃ (from EtOAc); $\bar{\nu}_{max}$ (thin film)/cm^{-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); ^{1}H NMR (500 MHz; CD_2Cl_2) δ 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, O*H*-2), 2.56 (1H, s, O*H*-1); ^{13}C NMR (126 MHz; CD_2Cl_2) δ 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_D, J_D 20.3, *C*-5), 81.3 (t_D, J_D 20.3, *C*-6), 81.0 (t_D, J_D 20.3, *C*-4), 80.0 (t_D, J_D 20.3, *C*-3), 75.59, 75.58 (*C*-17, *C*-23), 75.4 (*C*-7), 72.8 (*C*-12), 71.7 (t_D, J_D 20.3, *C*-1), 69.1 (t_D, J_D 20.3, *C*-2), 55.6 (*C*-22, *C*-28); ^{2}H NMR (77 MHz; $CHCl_3$; $CDCl_3$) δ 4.17 (*D*-2), 3.93 (*D*-4), 3.82 (*D*-6), 3.45 (*D*-1, *D*-3, *D*-5); HRMS *m/z* (ES^+) Found 628.2930 $[MD_5+Na]^+$ ($C_{36}H_{35}D_5NaO_8$ requires 628.2929), 629.2990 $[MD_6+Na]^+$ ($C_{36}H_{34}D_6NaO_8$ requires 629.2992); *m/z* (ES^+) 628.4 ($[MD_5+Na]^+$, 20%), 629.3 ($[MD_6+Na]^+$, 100%); NP-HPLC (0-100% isopropanol/hexane) Retention Time = 7.8 min, 96.8%.

(+)-4,5-Bis-*O*-(4-methoxybenzyl)-2,3,6-Tri-*O*-benzyl-1-*O*-(2*H*-tetrahydropyranyl)-D-*myo*-inositol-D_6 ((+)-226)



To a solution of (–)-**224** (423 mg, 0.70 mmol, 1.0 eq.) in CH_2Cl_2 (7.0 mL) under an atmosphere of Ar was added 3,4-dihydro-2*H*-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_2SO_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

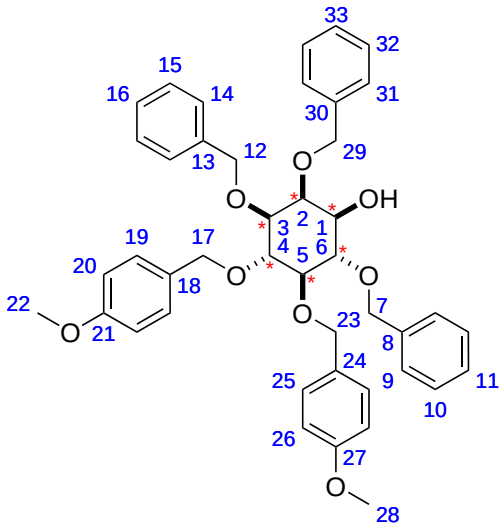
combined organic components were washed with aqueous LiCl (0.5 M, 50 mL) and saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 7-60% Et_2O in hexane, with mixed fractions 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_f 0.39 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25} = +2.3$ (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) *Diastereomer A** δ 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), *Diastereomer B** δ 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), 5.06 (1H, d, *J* 10.5, *H*-7a), 4.93-4.71 (10H, m, *H*-7b, *H*-12, *H*-17, *H*-23, *H*-29, *H*-34), 4.60-3.95 (1H, m, *H*-30a), 3.82 (6H, s, *H*-22, *H*-28), 3.44-3.37 (1H, m, *H*-30b), 1.98-1.40 (6H, m, *H*-31, *H*-32, *H*-33); ^{13}C NMR (126 MHz; CD_2Cl_2) *Diastereomer A** δ 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** δ 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* δ 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**.*

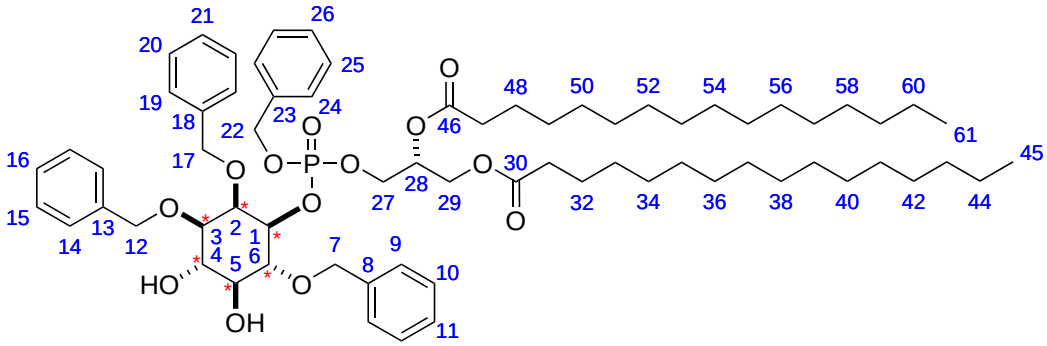
(−)-4,5-Bis-*O*-(4-methoxybenzyl)-2,3,6-tri-*O*-benzyl-D-*myo*-inositol-D_6 ((−)-227)



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); $[\alpha]_D^{25}$ = –13.9 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_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, O*H*); ^{13}C NMR (126 MHz; CD_2Cl_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 $[MD_5+Na]^+$ ($C_{43}H_{41}D_5NaO_8$ requires 718.3399), 719.3455 $[MD_6+Na]^+$ ($C_{43}H_{40}D_6NaO_8$ 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-dipalmitoyl)-*sn*-glycerol)-(benzyloxy)phosphoryl)-D-*myo*-inositol-D_6 ((−)-228)



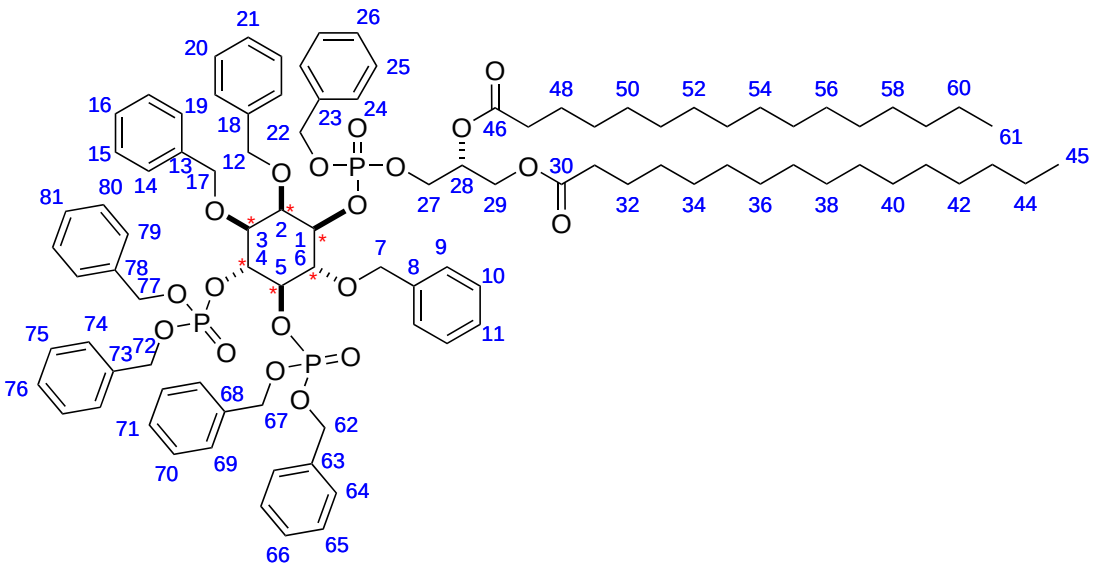
To a solution of (–)-**227** (71 mg, 0.10 mmol, 1.0 eq., 84% D_6, 16% D_5) and phosphoramidite **207** (206 mg, 0.26 mmol, 2.5 eq.) in CH_2Cl_2 (2 mL) under an atmosphere of Ar was added 1*H*-tetrazole (3-4 wt.% in MeCN, 0.59 mL, 0.26 mmol, 2.5 eq.) and the reaction mixture was stirred at room temperature 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 °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_2Cl_2 (50 mL), the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The intermediate was purified using silica gel flash column chromatography on a Biotage system using 12-100% Et_2O in hexane. The resulting oil was dissolved in CH_2Cl_2 (10 mL) and water (10 mL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (185 mg, 0.41 mmol, 4.0 eq.) was added and the biphasic 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 CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatgoraphy on a Biotage system using 5-40% EtOAc in petroleum ether to afford the title compound as a colourless

oil (64 mg, 53%, 84% D_6, 16% D_5): R_f 0.11 (EtOAc/petroleum ether 1:3); $[\alpha]_D^{25}$ = +5.4 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) *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, O*H*), 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, O*H*), 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); ^{13}C NMR (126 MHz; CD_2Cl_2) *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 (t_D, J_D 19.0, *C*-2), 75.51 (*C*-7), 75.4 (*C*-17), 74.5 (t_D, J_D 19.0, *C*-5), 72.65 (*C*-12), 72.1 (t_D, 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 (t_D, J_D 19.0, *C*-2), 75.46 (*C*-7), 75.4 (*C*-17), 74.5 (t_D, J_D 19.0, *C*-5), 72.71 (*C*-12), 72.1 (t_D, J_D 19.1, *C*-4), 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); ^{31}P

NMR (162 MHz; CD_2Cl_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 $[MD_5+H]^+$ ($C_{69}H_{99}D_5O_{13}P$ requires 1176.7523), 1177.7566 $[MD_6+H]^+$ ($C_{69}H_{98}D_6O_{13}P$ 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-dipalmitoyl)-*sn*-glycerol)-(benzyloxy)phosphoryl-D-*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_2Cl_2 (1 mL) under an atmosphere of Ar was added 1*H*-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

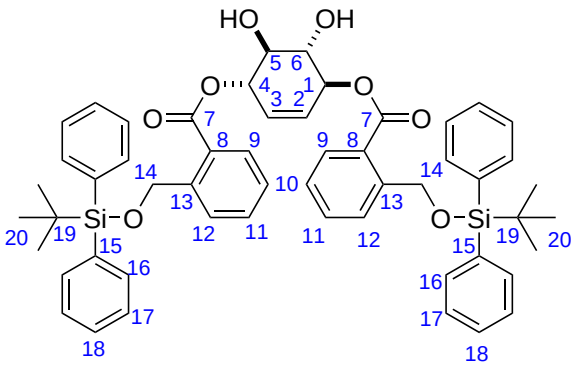
complete. The reaction suspension was cooled to –78 ℃, 3-chloroperbenzoic acid (77%, 24 mg, 0.14 mmol, 5.0 eq.) was added, and the suspension was stirred at room temperature for 2 h. ^{31}P NMR analysis indicated the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_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_2O in hexane, 100% Et_2O 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); $[\alpha]_D^{25}$ = –3.1 (*c* 0.66, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) *Diastereomer A* δ* 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), 4.14 (1H, dd, *J* 11.9, 4.3, *H*-27a), 4.08-3.85 (3H, m, *H*-27b, *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), *Diastereomer B* δ* 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_2Cl_2) *Diastereomer A* δ* 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. × 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* δ* 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

(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*-67, *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); ^{31}P 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); ^{2}H 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 $[MD_5+H]^+$ ($C_{97}H_{125}D_5O_{19}P_3$ requires 1696.8712), 1697.8722 $[MD_6+H]^+$ ($C_{97}H_{124}D_6O_{19}P_3$ 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

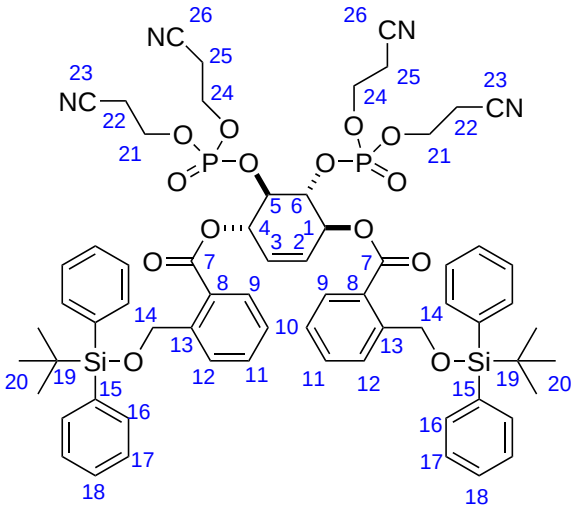
(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Dihydroxycyclohex-2-ene-1,4-diyl bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-233)



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 ℃, 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 $NaHCO_3$ (3 × 100 mL), dried with Na_2SO_4, 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%): R_f 0.23 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20}$ = +79.1 (*c* 1.0, $CHCl_3$); m.p.[a] 60-63 ℃ (from CH_2Cl_2); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*), 1.12 (18H, s, *H*-20); ^{13}C NMR (126 MHz; CD_2Cl_2) 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 $[M+Na]^+$ ($C_{54}H_{58}O_8Si_2Na$ 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%.

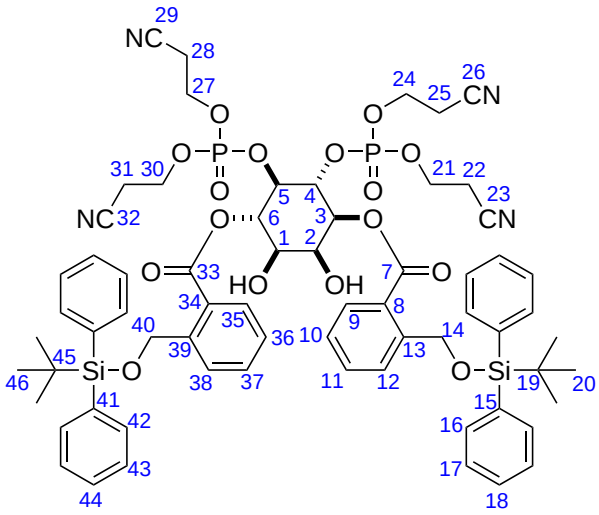
(+)-(1*S*,4*S*,5*R*,6*R*)-5,6-Bis((bis(2-cyanoethoxy)phosphoryl)oxy)cyclohex-2-ene-1,4-diyl bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate) ((+)-234)



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 1*H*-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. ^{31}P NMR analysis indicated the reaction was complete. Aqueous $Na_2S_2O_3$ (10% *w/v*, 30 mL) was added and the organic components were extracted with CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 2-10% MeOH in $CHCl_3$ to afford the title compound as a colourless film (253 mg, 90%). The product was isolated with a 5% impurity (by ^{31}P 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: R_f 0.78 (MeOH/$CHCl_3$ 1:9); $[\alpha]_D^{20}$ = +72.3 (*c* 1.4, $CHCl_3$); $\bar{\nu}_{max}$ (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_2Cl_2) δ 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_2Cl_2) δ 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_2Cl_2) δ –2.89; HRMS m/z (ES^+) Found 1263.4114 $[M+H]^+$ ($C_{66}H_{73}N_4O_{14}P_2Si_2$ requires 1263.4132); m/z (ES^-) 1208.5 ($[M\text{-}CH_2CH_2CN]^-$, 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-(((*t*butyl diphenylsilyl)oxy)methyl)benzoyl)-D-*myo*-inositol ((+)-235)

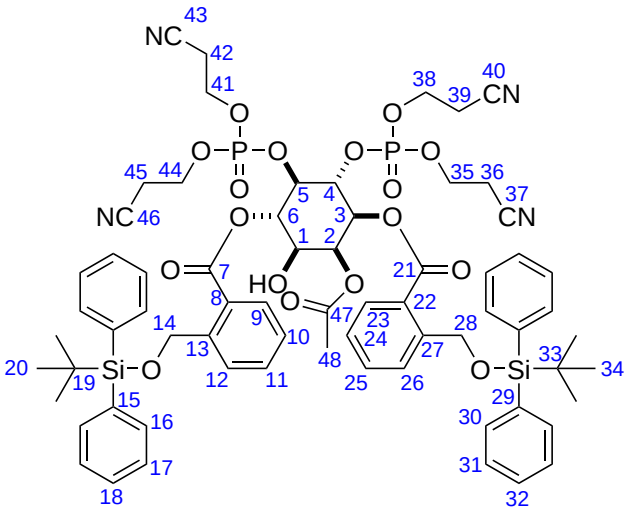


To a vigorously stirred solution of (+)-**234** (782 mg, 0.62 mmol, 1.0 eq.) in MeCN (6 mL) was added a solution of $RuCl_3{\cdot}3H_2O$ (8.0 mg, 0.031 mmol, 0.05 eq.), and $NaIO_4$ (199 mg,

0.93 mmol, 1.5 eq.) in H_2O (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/CH_2Cl_2) indicated the reaction was complete. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ (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 Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 0-5% MeOH in $CHCl_3$ to afford the title compound as a colourless film (671 mg, 83%): R_f 0.34 (MeOH/$CHCl_3$ 1:9); $[\alpha]_D^{25} = +35.8$ (*c* 2.1, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*-2), 3.50 (1H, td, *J* 9.4, 2.5, *H*-1), 2.67-2.50 (5H, m, O*H*-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); ^{13}C NMR (126 MHz; CD_2Cl_2) 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, J_P 5.2, 5.2, *C*-5), 76.9 (dd, J_P 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, J_P 5.8, *C*-21), 63.3 (d, J_P 5.5, *C*-30), 62.9 (d, J_P 4.7, *C*-27), 62.7 (d, J_P 4.7, *C*-24), 27.1, 27.0 (*C*-20, *C*-46), 19.7 (d, J_P 8.0), 19.6, 19.5 (*C*-19, *C*-45), 19.3 (d, J_P 7.2), 19.2 (d, J_P 7.2, *C*-22, *C*-25, *C*-28, *C*-31); ^{31}P

NMR (162 MHz; CD_2Cl_2) δ –2.92 (*P*-4), –3.15 (*P*-5); HRMS *m/z* (ES^-) Found 1295.4088 $[M\text{-}H]^-$ ($C_{66}H_{73}N_4O_{16}P_2Si_2$ requires 1295.4041); *m/z* (ES^-) 1331.5 ($[M+Cl]^-$, 10%) 1341.5 ($[M+formic\ Acid\text{-}H]^-$, 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-(((*t*butyl-diphenyl-silyl)oxy)methyl)benzoyl)-D-*myo*-inositol ((+)-236)

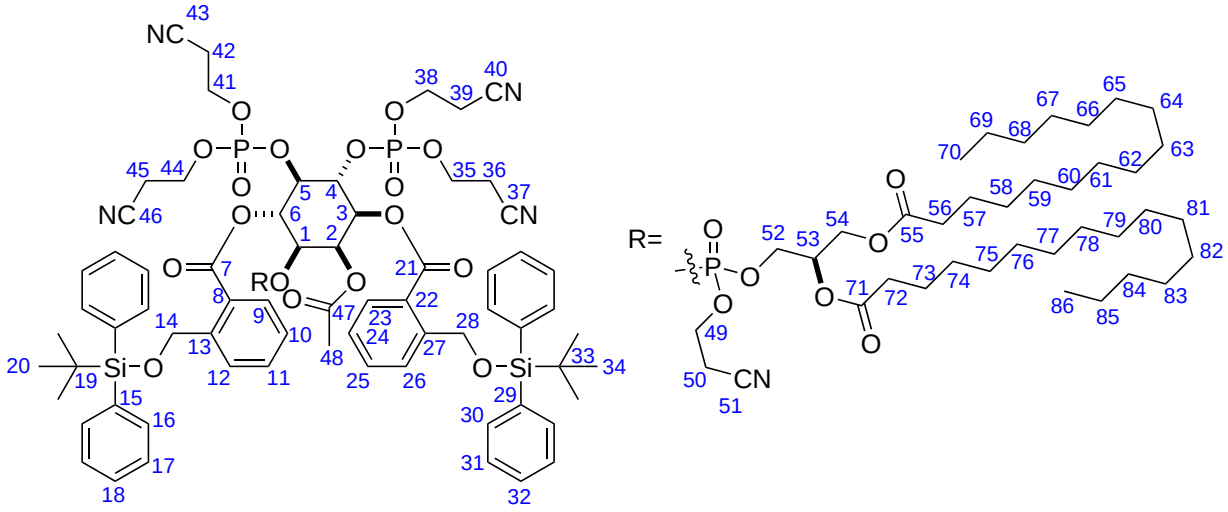


To a solution of (+)-**235** (1.00 g, 0.77 mmol, 1.0 eq.) in anhydrous THF (30 mL) under an atmosphere of Ar was added triethylorthoacetate (1.41 mL, 7.7 mmol, 10.0 eq.) followed by *p*-toluenesulfonic acid monohydrate (14 mg, 0.08 mmol, 0.1 eq.) and the solution was stirred at room temperature overnight. TLC analysis of the reaction mixture (1:9 $MeOH/CH_2Cl_2$) 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 $MeOH/CH_2Cl_2$) 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_2SO_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 $CHCl_3$ 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*-toluenesulfonic 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 Et_2O and filtered to afford the title compound as a colourless solid (520 mg, 50%): R_f 0.41 (MeOH/$CHCl_3$ 1:9); $[\alpha]_D^{25}$ = +21.2 (*c* 1.0, $CHCl_3$); m.p. 85-89 ℃ (from Et_2O); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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, O*H*) 2.16-2.05 (7H, m, *H*-36, *H*-39, *H*-48), 1.15 (9H, s, *H*-20), 1.13 (9H, s, *H*-34); ^{13}C NMR (126 MHz; CD_2Cl_2) 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, J_P 5.2, 5.2, *C*-5), 77.0 (dd, J_P 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, J_P 5.8, *C*-41), 63.4 (d, J_P 5.8, *C*-44), 62.9 (d, J_P 5.0, *C*-35), 62.8 (d, J_P 5.0, *C*-38), 27.1 (*C*-20), 27.0 (*C*-34), 20.9 (*C*-48), 19.72 (d, J_P 7.8, *C*-42), 19.71 (d, J_P 7.8, *C*-45), 19.64 (*C*-33), 19.58 (*C*-19), 19.3 (d, J_P 7.7, *C*-36), 19.2 (d, J_P 7.7, *C*-39); ^{31}P NMR (162 MHz; CD_2Cl_2) δ –3.08 (*P*-5), –3.25 (*P*-4); HRMS *m/z* (ES^+) Found 1361.4056 $[M+Na]^+$ ($C_{68}H_{76}N_4NaO_{17}P_2Si_2$ 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-(((*t*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 CH_2Cl_2 (10 mL) under an atmosphere of N_2 was added 1*H*-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/$CHCl_3$) 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 CH_2Cl_2 (100 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 50 mL), saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried with Na_2SO_4, 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: R_f 0.52 (MeOH/$CHCl_3$ 1:19); $[\alpha]_D^{26}$ = +5.7

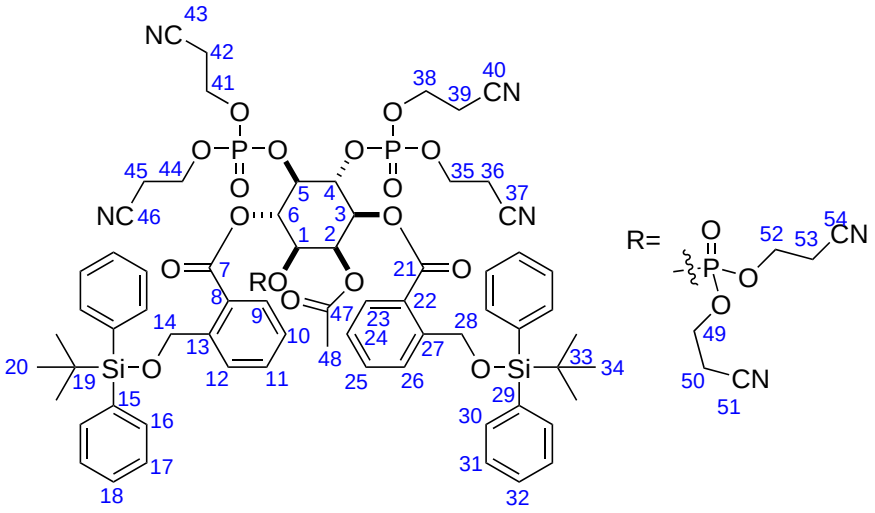
(*c* 3.1, $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 2959 (C-H, m), 2925 (C-H, s), 2854 (C-H, s), 1729 (C=O, s), 1470 (C-H, w), 1428 (C-H, w), 1282 (C-H, s), 1247 (C-H, s), 1218 (C-H, s), 1168 (C-H, w), 1135 (C-O, s), 1112 (C-O, s), 1065 (C-O, s), 1044 (C-O, s), 1028 (C-O, s), 1004 (C-O, s); ^{1}H NMR (700 MHz; CD_2Cl_2) *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); ^{13}C NMR (126 MHz; CD_2Cl_2) *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, J_P 4.2, 4.2, *C*-4), 76.8-76.6 (m, *C*-5), 73.5 (d, J_P 4.8, *C*-1), 70.3 (*C*-6), 69.4 (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), 63.6 (*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), 164.5 (*C*-21), 145.5 (*C*-27), 145.41 (*C*-13), 135.92 (*C*-17), 135.86 (*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); ^{31}P 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.*

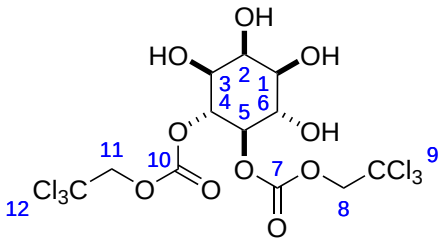
(+)-2-Acetoxy-1,4,5-tris((bis(2-cyanoethoxy)phosphoryl)oxy)-3,6-bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate) D-*myo*-inositol ((+)-250)



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 CH_2Cl_2 (1 mL) was added 1*H*-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/CH_2Cl_2) 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. ^{31}P NMR analysis indicated the reaction was complete. The resulting solution was diluted with CH_2Cl_2 (50 mL) and the organic components were washed with aqueous $Na_2S_2O_3$ (10% *w/v*, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried with Na_2SO_4, 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%): R_f 0.50 (MeOH/CH_2Cl_2 1:19); $[\alpha]_D^{25}$ = +4.6 (*c* 1.0, $CHCl_3$); $\bar{\nu}_{max}$ (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); ^{1}H NMR (500 MHz; CD_2Cl_2) 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* 9.8, 9.3, 9.3, *H*-4), 4.75 (1H, ddd, *J* 9.9, 9.9, 3.0, *H*-1), 4.65 (1H, ddd, *J* 9.4, 9.4, 9.4, *H*-5), 4.25-4.15 (2H, m, *H*-41), 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*-38), 2.68-2.49 (6H, m, *H*-39, *H*-42, *H*-45), 2.19 (3H, s, *H*-48), 2.18-2.00 (6H, m, *H*-36, *H*-50, *H*-53), 1.16 (9H, s, *H*-20), 1.15 (9H, s, *H*-34); ^{13}C NMR (126 MHz; CD_2Cl_2) δ 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_2Cl_2) δ –2.91 (*P*-1), –3.06 (*P*-5),– 3.22 (*P*-4); HRMS *m/z* (ES^+) Found 1547.4289 $[M+Na]^+$ ($C_{74}H_{83}N_6O_{20}P_3Si_2Na$ 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%.

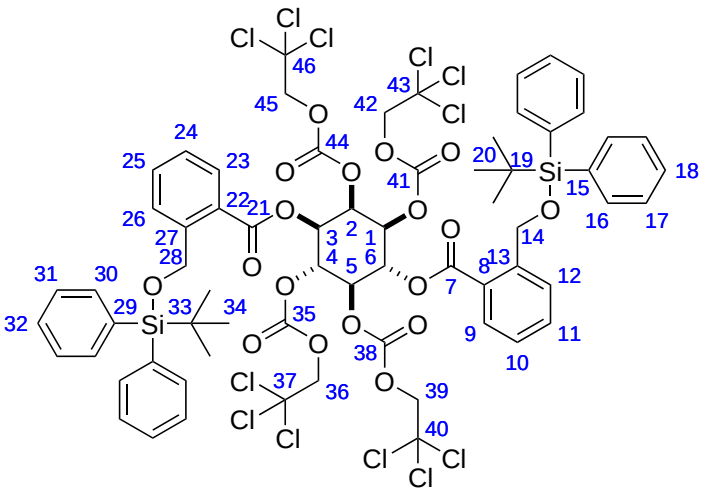
(+)-4,5-Bis(2',2',2'-trichloroethylcarbonate) D-*myo*-inositol ((+)-231)



To a solution of (+)-**175** (124 mg, 0.1 mmol, 1.0 eq.) in MeCN (1 mL) was added a solution of $NaIO_4$ (32 mg, 0.15 mmol, 1.5 eq.) and $RuCl_3{\cdot}3H_2O$ (1.7 mg, 0.005 mmol, 0.05 eq.) in a solution of H_2O (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 $Na_2S_2O_3$ (10% *w/v*, 30 mL). The organic components were extracted with EtOAc (50 mL), washed with saturated aqueous NaCl (30 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (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_2Cl_2 to afford the title compound as a colourless foam (18 mg, 34%): R_f 0.10 (MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25} = +11.8$ (*c* 0.5, $CHCl_3$/MeOH 1:1); $\bar{\nu}_{max}$ (thin film)/cm^{-1} 3362 (O-H, m), 1766 (C=O, s), 1264 (C-O, s), 1235 (C-O, s), 1131 (C-O, m), 1046 (C-O, m); ^{1}H NMR (500 MHz; D_6-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); ^{13}C NMR (126 MHz; D_6-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).

(+)-3,6-Bis(2-(((*t*butyldiphenylsilyl)oxy)methyl)benzoate)-1,2,4,5-tetrakis-(2',2',2'-trichloroethylcarbonate)-D-*myo*-inositol ((+)-247)



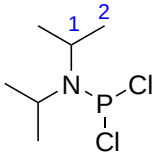
To a solution of (+)-**175** (124 mg, 0.10 mmol, 1.0 eq.) in MeCN (1 mL) was added a solution of $NaIO_4$ (32 mg, 0.15 mmol, 1.5 eq.) and $RuCl_3{\cdot}3H_2O$ (1.7 mg, 0.005 mmol, 0.05 eq.) in H_2O (0.25 mL) and the reaction mixture was stirred vigorously for 8 min. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. Aqueous $Na_2S_2O_3$ (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 CH_2Cl_2 (3 × 30 mL), combined, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The oil was dissolved in CH_2Cl_2 (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 $NaHCO_3$ (20 mL), saturated aqueous NaCl (20 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product as purified using silica gel flash column chromatography on a Biotage system using 2-20% Et_2O in petroleum ether to afford the title compound as a colourless oil (140 mg, 86%): R_f 0.46 (Et_2O/petroleum ether 1:4);

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.14 (1H, d, *J* 8.0, *H*-23), 8.11 (1H, d, *J* 8.0, *H*-9), 7.98 (1H, dd, *J* 8.0, 1.2, *H*-12), 7.86 (1H, dd, *J* 8.0, 1.2, *H*-26), 7.76-7.63 (10H, m, *H*-10, *H*-16, *H*-24, *H*-30), 7.48-7.37 (12H, m, *H*-17, *H*-18, *H*-31, *H*-32), 7.32 (1H, dd, *J* 8.0, 8.0, *H*-11), 7.26 (1H, dd, *J* 8.0, 8.0, *H*-25), 5.87 (1H, dd, *J* 10.3, 10.3, *H*-6), 5.66-5.59 (2H, m, *H*-2, *H*-4), 5.28 (1H, dd, *J* 10.3, 3.0, *H*-3), 5.21 (2H, s, *H*-28), 5.18 (1H, d, *J* 16.8, *H*-14a), 5.09 (1H, d, *J* 16.8, *H*-14b), 5.07 (1H, dd, *J* 10.3, 10.3, *H*-5), 4.98 (1H, dd, *J* 10.3, 3.0, *H*-1), 4.71 (1H, d, *J* 11.9, *H*-36a), 4.70 (1H, d, *J* 11.9, *H*-39a), 4.63-4.58 (3H, m, *H*-39b, *H*-45), 4.56 (1H, d, *J* 11.9, *H*-42a), 4.50 (1H, d, *J* 11.9, *H*-36b), 4.45 (1H, d, *J* 11.9, *H*-42b), 1.16 (18H, s, *H*-20, *H*-34); ^{13}C NMR (101 MHz; $CDCl_3$) δ 164.2, 164.0 (*C*-7, *C*-21), 153.3, 153.1, 153.0, 152.8 (*C*-35, *C*-38, *C*-41, *C*-44), 145.6 (*C*-27), 145.2 (*C*-13), 135.6, 135.5 (*C*-16, *C*-28), 134.0, 139.9 (*C*-10, *C*-24), 133.5, 133.4 (*C*-15, *C*-29), 131.2 (*C*-12), 130.7 (*C*-26), 129.8 (*C*-18, *C*-32), 126.5, 126.4 (*C*-9, *C*-11, *C*-25), 126.2 (*C*-23), 124.1, 123.9 (*C*-8, *C*-22), 94.0, 93.92, 93.90, 93.7 (*C*-37, *C*-40, *C*-43, *C*-46), 77.1, 77.0, 76.9, 76.8 (*C*-36, *C*-39, *C*-42, *C*-45), 75.0 (*C*-5), 73.8 (*C*-4), 72.7 (*C*-1), 72.6 (*C*-2), 68.7 (*C*-6), 68.3 (*C*-3), 64.2 (*C*-14), 63.9 (*C*-28), 27.01, 26.98 (*C*-20, *C*-34), 19.5 (*C*-19, *C*-33).

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

7.9 Phosphoramidite Preparations

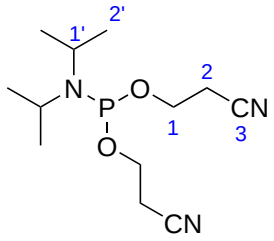
Dichloro-*N,N*-diisopropylphosphoramidite (125)[52]



A solution of PCl_3 (8.7 mL, 100 mmol, 1.0 eq.) in anhydrous Et_2O (500 mL) under an atmosphere of N_2 was cooled to –78 ℃ 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 ℃ followed by a further 3 h at room temperature. ^{31}P NMR

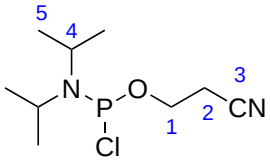
analysis of the reaction mixture indicated the reaction was complete. The precipitate was filtered under N_2 using a Schlenk filtration apparatus and the filtrate was concentrated *in vacuo* to afford the title compound as a colourless oil (13.62 g, 67%). The compound was stored as a crystalline solid at –20 ℃ and the purity checked by ^{31}P NMR prior to use: ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.93-3.80 (2H, m, *H*-1), 1.21 (12H, d, *J* 6.8, *H*-2); ^{31}P NMR (162 MHz; $CDCl_3$) δ 169.46; *m/z* (ES^+) 239.2 ($[M+K]^+$, 100%). These data are in good agreement with the literature.[52]

Bis(2-cyanoethyoxy)-*N,N*-diisopropylphosphoramidite (126)[207]



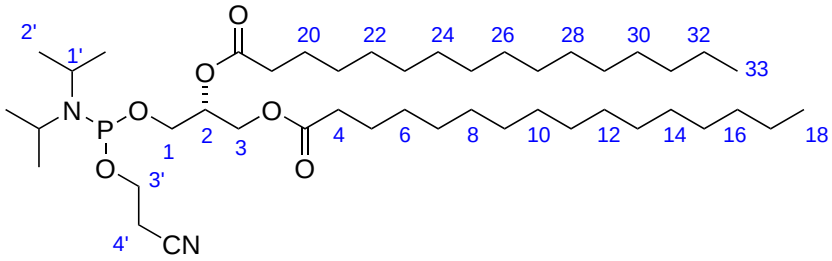
A solution of 3-hydroxypropionitrile (0.70 mL, 14 mmol, 2.0 eq.) and freshly distilled diisopropylethylamine (3.7 mL, 21 mmol, 3.0 eq.) in anhydrous CH_2Cl_2 (10 mL) under an atmosphere of Ar was cooled to 0 ℃ and **125** (1.41 g, 7 mmol, 1.0 eq.) was added, dropwise, over 5 min. The reaction mixture was stirred at room temperature for 1 h. ^{31}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 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}H NMR (400 MHz; $CDCl_3$) δ 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}C NMR (101 MHz; $CDCl_3$) δ 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}P NMR (162 MHz; $CDCl_3$) δ 149.15; *m/z* (ES^+) 403.3 ($[2M–2(O(CH_2)_2CN)+H]^+$, 100%). These data are in good agreement with the literature.[207]

2-Cyanoethyoxy *N,N*-diisopropylchlorophosphoramidite (129)[140,208]



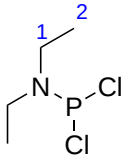
The procedure from Nielsen and Dahl was used.[140] To a solution of PCl_3 (17.5 mL, 200 mmol, 5.0 eq.) in anhydrous MeCN (20 mL) under an atmosphere of Ar was added 3-hydroxypropionitrile (2.7 mL, 40 mmol, 1.0 eq.). The solution was stirred at room temperature for 1 h. ^{31}P NMR analysis indicated the reaction was complete. The reaction mixture was concentrated *in vacuo* and the resulting oil was redissolved in anhydrous Et_2O (30 mL). Freshly distilled diisopropylamine (11.3 mL, 80.0 mmol, 2.0 eq.) was added, dropwise, at –10 ℃ 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_2O (100 mL). The filtrate was concentrated *in vacuo* to give a yellow oil. The product was purified by vacuum distillation (130–135 ℃, 1.2 mBar {lit.[140] 105-107 ℃, 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 ℃: ^{1}H NMR (400 MHz; $CDCl_3$) δ 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; $CDCl_3$) δ 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; $CDCl_3$) δ 179.94. These data are in good agreement with the literature.[140,208]

2-Cyanoethyoxy-*N,N*-diisopropyl-(1,2-dipalmitoyl-*sn*-glycerol)phosphor-amidite (131)[209]



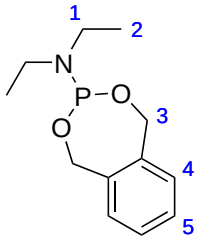
The procedure from Xu *et al.* was used.[209] A solution of freshly distilled diisopropylethylamine (0.10 mL, 0.57 mmol, 4.0 eq.) and (–)-**130** (81 mg, 0.14 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (2 mL) under an atmosphere of Ar was cooled to 0 ℃ and phosphoramidite **129** (62 μl, 0.28 mmol, 2.0 eq.) 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 *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; $CDCl_3$) δ 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; $CDCl_3$) *Diastereomer A* δ 149.60, *Diastereomer B* δ 149.45. These data are in good agreement with the literature.[209]

Dichloro *N,N*-diethylphosphoramidite (194)[175]



The procedure from Gregory *et al.* was used.[175] To a solution of PCl_3 (4.36 mL, 50 mmol, 1.0 eq.) in anhydrous Et_2O (300 mL) under an atmosphere of N_2 on a Schlenk system at –78 ℃ was added a solution of freshly distilled diethylamine (10.4 mL, 100 mmol, 2.0 eq.) in anhydrous Et_2O (100 mL) *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. ^{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_2O (100 mL). The filtrate was concentrated *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 ℃ as an oil and the purity checked by ^{31}P NMR prior to use: ^1H NMR (400 MHz; $CDCl_3$) δ 3.36 (2H, q, *J* 7.0, *H*-1a), 3.33 (2H, q, *J* 7.1, *H*-1b), 1.19 (6H, t, *J* 7.1, *H*-2); ^{31}P NMR (162 MHz; $CDCl_3$) δ 162.58. These data are in good agreement with the literature.[175]

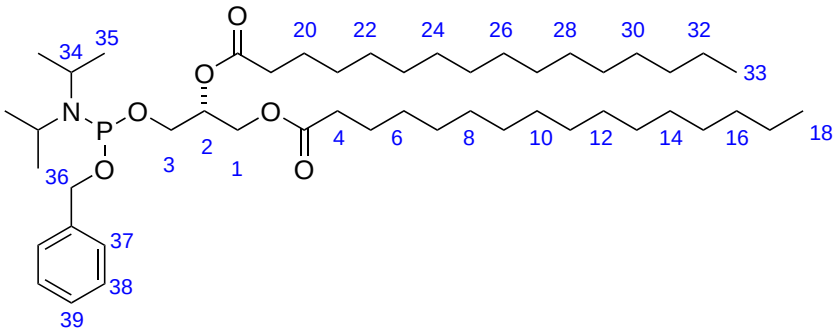
(1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (187)[175]



The procedure from Gregory *et al.* was used.[175] To a solution of **194** (1.75 g, 10.0 mmol, 1.0 eq.) in anhydrous Et_2O (80 mL) under an atmosphere of N_2 at –78 ℃ was added, *via* cannula, a solution of *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_2O (60 mL) over a period of 20 min. The reaction mixture was warmed to room temperature and stirred for 18 h. ^{31}P NMR analysis of the reaction mixture indicated the reaction was complete. The resulting suspension was filtered under N_2 using a Schlenk filter, followed by concentration *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; $CDCl_3$) δ 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; $CDCl_3$) δ 145.33. These data are in good agreement with the literature.[175]

Benzyloxy-*N,N*-diisopropyl-(1,2-dipalmitoyl-*sn*-glycerol)phosphoramidite (207)[152]

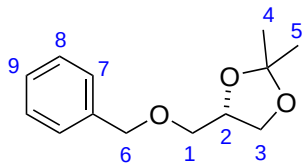


The procedure from Johns *et al.* was used.[152] A mixture of benzyloxy bis(*N,N*-diisopropyl)-phosphoramidite **208** (from A. Joffrin,[51] synthesised by the procedure from Johns et al.,[152] 0.375 g, 1.10 mmol, 2.5 eq.) and 1*H*-tetrazole (3-4 wt.% in MeCN, 3.07 mL, 1.32 mmol, 3.0 eq.) in CH_2Cl_2 (25 mL) was stirred at room temperature under an atmosphere of Ar for 10 min. To this solution was added a solution of (–)-**130** (350 mg, 0.44 mmol, 1.0 eq.) in CH_2Cl_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_2Cl_2 (50 mL), the organic components were washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated *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; $CDCl_3$) δ 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* δ 148.88, *Diastereomer B* δ 148.73. These data are in good agreement with the literature.[152]

7.10 Glycerol Preparations

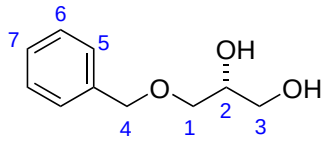
(+)-(*S*)-1,2-Isopropylidene-3-*O*-benzyl-*sn*-glycerol ((+)-147)[210]



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 ℃ and sodium hydride (60% suspension in mineral oil, 480 mg, 12.0 mmol, 1.2 eq.) was added. The suspension was stirred at 0 ℃ 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_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a Biotage system using 5% Et_2O in petroleum ether to afford the title compound as a colourless oil (2.05 g, 92%): R_f 0.34 (Et_2O/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; $CDCl_3$) δ 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),

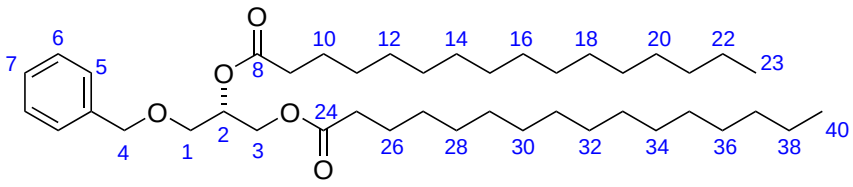
3.47 (1H, dd, *J* 9.8, 6.2, *H*-1b), 1.42 (3H, s, *H*-4), 1.37 (3H, s, *H*-5); *m/z* (ES^+) 223.1 ($[M+H]^+$, 57%), 245.1 ($[M+Na]^+$, 100%). These data are in good agreement with the literature.[210]

(–)-(*R*)-3-*O*-Benzyl-*sn*-glycerol ((–)-148)[210]



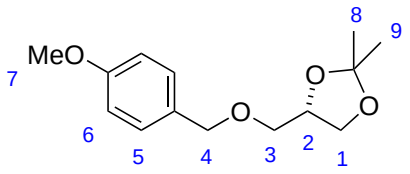
To a solution of (+)-**147** (2.00 g, 9.0 mmol, 1.0 eq.) in THF (10 mL) was added aqueous HCl (1 M, 4.0 mL) and the solution was stirred at room temperature overnight. TLC analysis of the reaction mixture (1:4 EtOAc/petroleum ether) indicated the reaction was complete. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ until pH 9. The product was extracted with EtOAc (3 × 100 mL), washed with saturated aqueous NaCl (100 mL), dried Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound as a colourless oil (1.52 g, 93%): R_f 0.13 (EtOAc/petroleum ether 1:1); $[\alpha]_D^{25}$ = –1.2 (*c* 5.3, $CHCl_3$) [lit.[210] +5.9 (*c* 1.0, $CHCl_3$), lit.[211] +7.5 (neat)]; ^{1}H NMR (400 MHz; $CDCl_3$) 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%.

(+)-(*S*)-3-*O*-Benzyl-1,2-dipalmitoyl-*sn*-glycerol ((+)-145)[149,211]



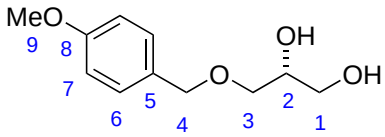
To a solution of (–)-**148** (1.31 g, 7.19 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) was added 4-dimethylaminopyridine (8 mg, 0.07 mmol, 0.01 eq.) and *N,N*-diisopropylethylamine (3.1 mL, 18.0 mmol, 2.5 eq.). The solution was cooled to 0 ℃ and palmitoyl chloride (5.50 mL, 18.0 mL, 2.5 eq.) was added, dropwise, 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 CH_2Cl_2 (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 CH_2Cl_2 (2 × 50 mL). The combined organic components (*ca.* 200 mL) were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified using silica gel flash column chromatography on a biotage system using 5% Et_2O in petroleum ether followed by 10% Et_2O in petroleum ether to afford the title compound as a colourless solid (4.52 g, 95%): R_f 0.49 (Et_2O/petroleum ether 1:9); $[\alpha]_D^{25}$ = +5.8 (*c* 3.3, $CHCl_3$) {lit.[211] +6.0 (*c* 8.5, $CHCl_3$)}; m.p. 38-39 ℃ (from Et_2O) {lit.[211] 42.0-42.5 ℃ (from EtOH), lit.[149] 64.0-65.5 ℃ (from EtOAc)}; ^{1}H NMR (400 MHz; $CDCl_3$) 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)[150]



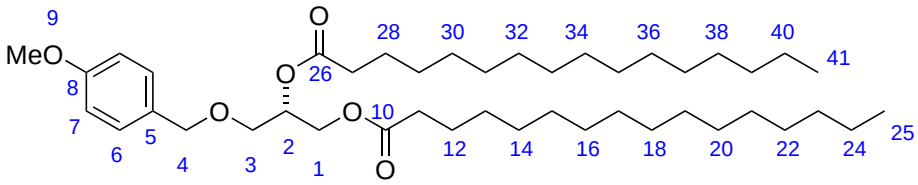
A solution of (+)-(*S*)-1,2-isopropylidene *sn*-glycerol (1.98 g, 15.0 mmol, 1.0 eq.) in anhydrous DMF (30 mL) under an atmosphere of Ar was cooled to 0 ℃ and sodium hydride (60% suspension in mineral oil, 720 mg, 18 mmol, 1.2 eq.) was added. The reaction mixture was stirred at 0 ℃ for 10 min followed 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 $NaHCO_3$ (100 mL), saturated aqueous NaCl (3 × 100 mL), aqueous LiCl (0.5 M, 50 mL) and saturated aqueous NaCl (100 mL), dried with Na_2SO_4, 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%): R_f 0.78 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20}$ = +18.8 (*c* 2.4, $CHCl_3$) {lit.[150] +21.42 (*c* 2.04, $CHCl_3$)}; ^{1}H NMR (400 MHz; $CDCl_3$) 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]

(–)-(*R*)-3-*O*-(4-Methoxybenzyl)-*sn*-glycerol ((–)-150)[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 × 20 mL). The combined organic components were dried with Na_2SO_4, filtered and concentrated *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; $CDCl_3$) δ 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, O*H*-2), 2.16 (1H, dd, *J* 6.7, 5.5, O*H*-1); *m/z* (ES$^+$) 235.1 ([M+Na]$^+$, 100%). These data are in good agreement with the literature.[150]

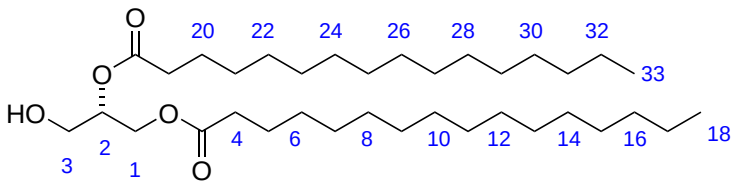
(+)-(*S*)-1,2-Dipalmitoyl-3-*O*-(4-methoxybenzyl)-*sn*-glycerol ((+)-146)



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_2Cl_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_2Cl_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_2Cl_2in petroleum ether to afford the title compound as a waxy solid (217 mg, 69%): R_f 0.84 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{20}$ = +6.0 (*c* 1.0, $CHCl_3$); m.p. 53-54 ℃ (from CH_2Cl_2/petroleum ether); $\bar{\nu}_{max}$ (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 $[M+Na]^+$ ($C_{43}H_{76}O_6Na$ requires 668.5642); *m/z* (ES^+) 551.1 ($[M–OPMB]^+$, 100%), 712.1 ($[M+Na]^+$, 56%).

(–)-(*S*)-1,2-Dipalmitoyl-*sn*-glycerol ((–)-130)[212]



Method A

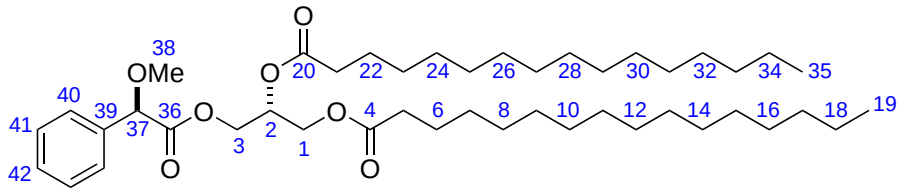
The procedure from Gu *et al.* was used.[89] To a solution of (+)-**145** (659 mg, 1.0 mmol, 1.0 eq.) in a mixture of glacial AcOH (2 mL) and EtOH (10 mL) under an atmosphere

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.[212] 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 ℃ (from EtOAc) {lit.[212] 66-67 ℃, lit.[149] 64.5-65.5 ℃}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 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, O*H*), 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]

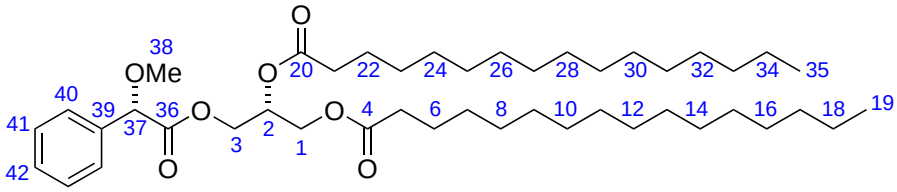
(+)-(*R*)-3-((*R*)-2-Methoxy-2-phenylacetoxy)-1,2-dipalmitoyl *sn*-glycerol ((+)-151a)



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-dimethylaminopyridine (1.9 mg, 0.01 mmol, 0.1 eq.) in CH_2Cl_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_2Cl_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_2SO_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); $[\alpha]_D^{26}$ = +7.5 (*c* 4.4, $CHCl_3$); $\bar{\nu}_{max}$ (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; $CDCl_3$) δ 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; $CDCl_3$) δ 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

(*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$^+$) Found 739.5478 [M+Na]$^+$ ($C_{44}H_{76}O_7$ requires 739.5483); *m/z* (ES$^+$) 739.5 ([M+Na]$^+$, 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*)-α-methoxyphenylacetic acid to afford the title compound as a colourless film (35 mg, 55%): R_f 0.63 (EtOAc/petroleum ether 1:4); $[\alpha]_D^{25}$ = +8.8 (*c* 3.2, $CHCl_3$); $\bar{\nu}_{max}$ (thin film)/cm^{-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); ^{1}H NMR (400 MHz; $CDCl_3$) δ 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); ^{13}C NMR (101 MHz; $CDCl_3$) δ 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), 68.6 (*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$^+$) Found 739.5477 [M+Na]$^+$ ($C_{44}H_{76}O_7Na$ requires 739.5483); *m/z* (ES$^+$) 739.5 ([M+Na]$^+$, 100%).

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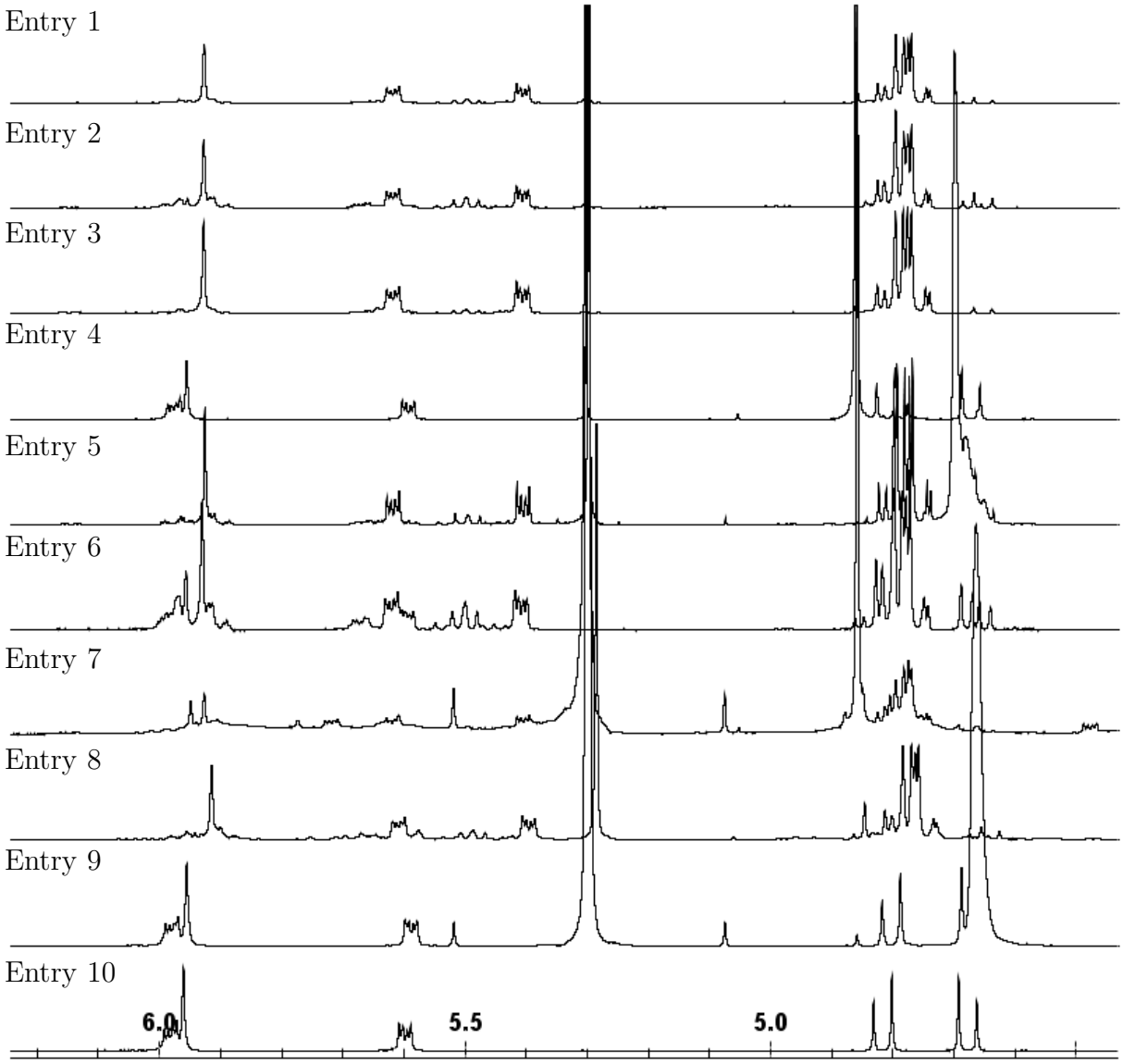
Appendix

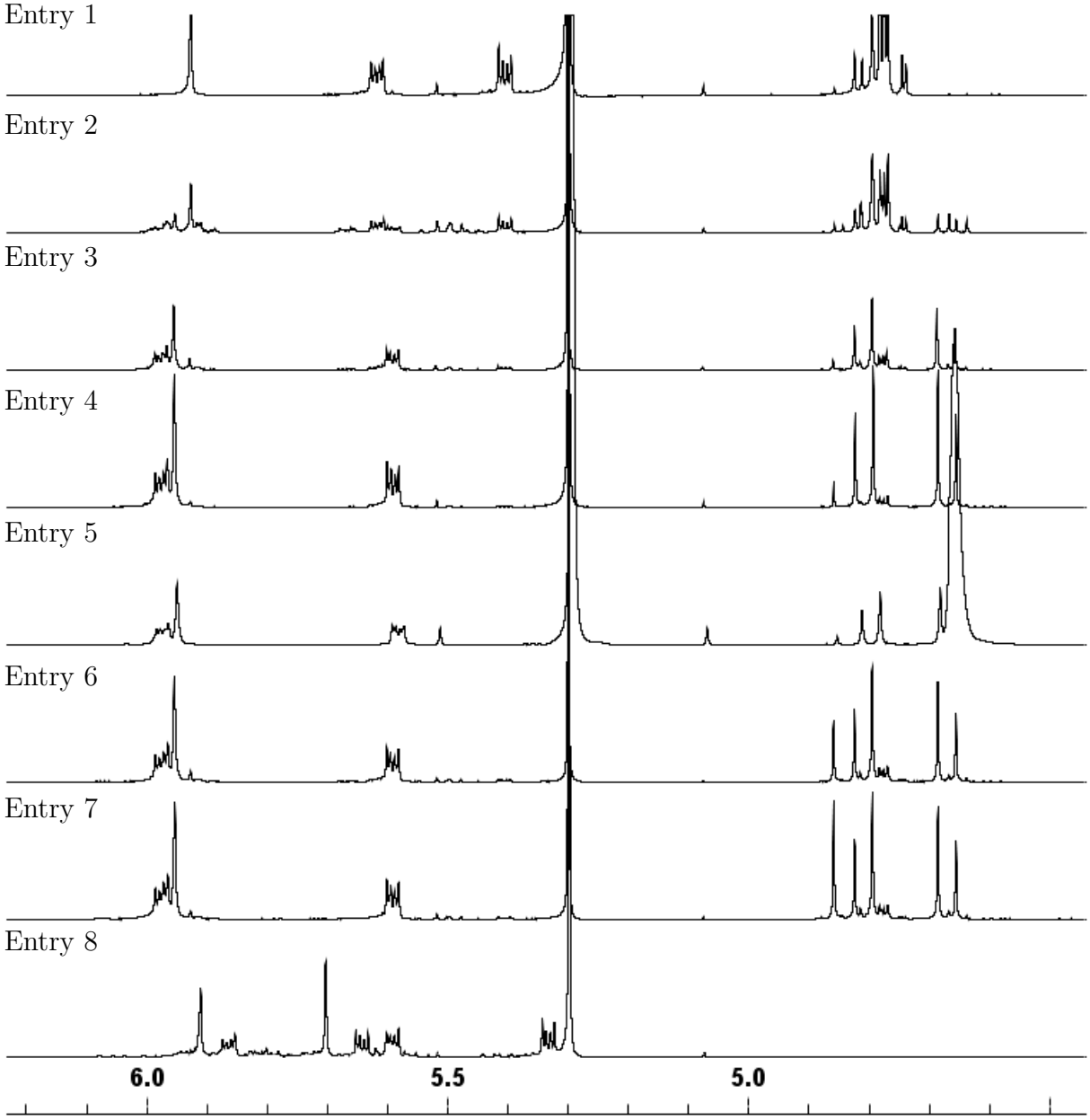
Selected Spectra

*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 (±)-**81** and (±)-**160** can be found on pages 533 and 540 respectively. Permissions for images can be found at the end of the appendix.*

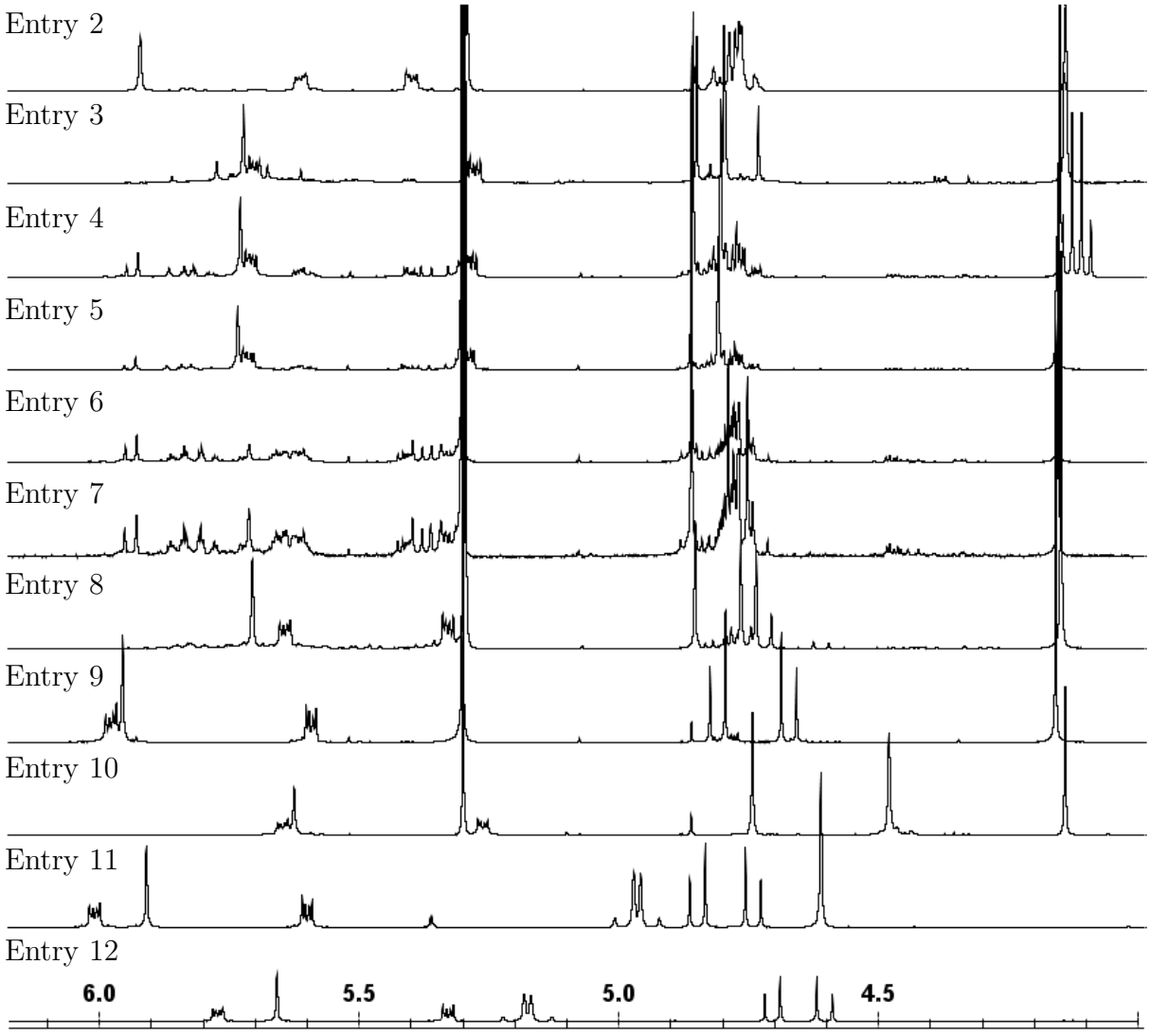
^{1}H NMR Data for Table 2.2



^{1}H NMR Data for Table 2.4



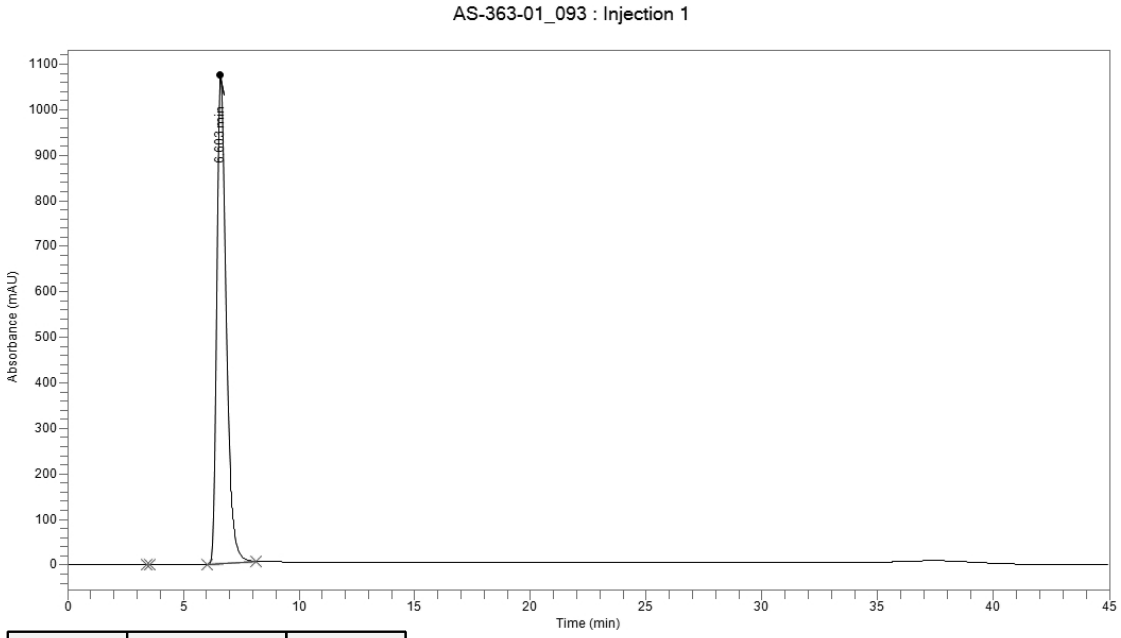
^{1}H NMR Data for Table 2.5



Chiral HPLC of ligand (–)-84

AS-363-01_093

Sample Name	AS-363-01_093	Sample Description	ADH column
Acquisition Method	EE determination 90:10 Hex:IPA 254 nm	Acquisition Date/Time	7/7/2015 3:43 pm
Batch Group/Name	Alex/EE determination 90:10 Hex:IPA 254 nm	Batch Description	ADH column



Time	Area	Area %
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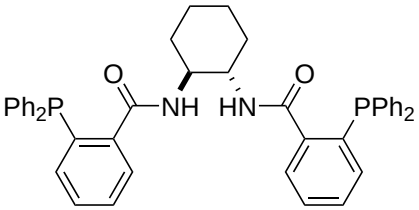
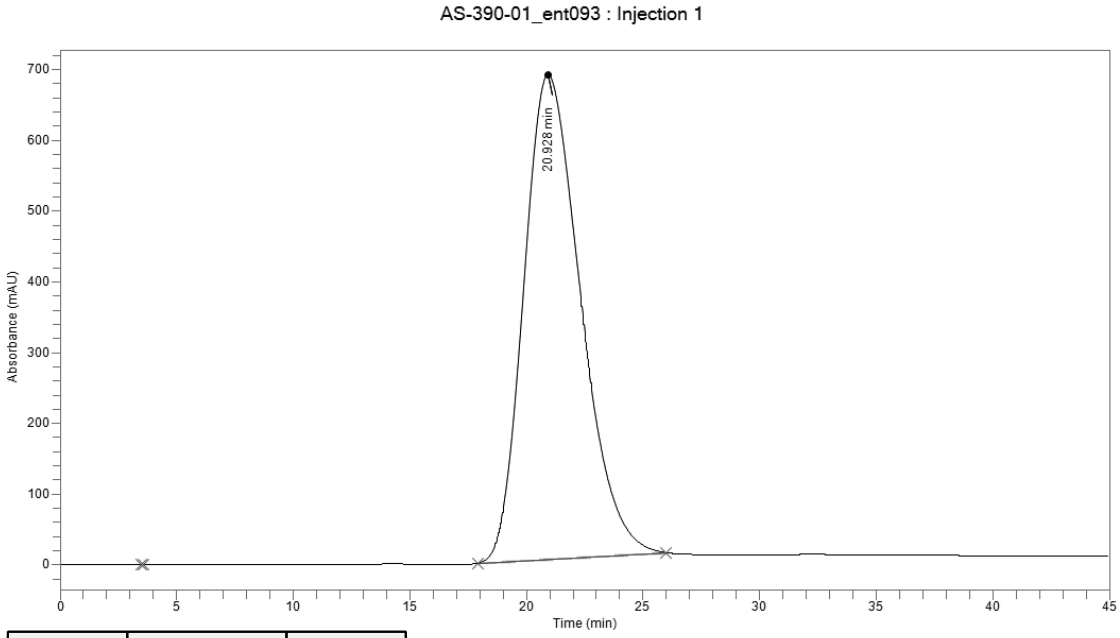
6.603	30153858	99.99
Total	30156931.8	100.00



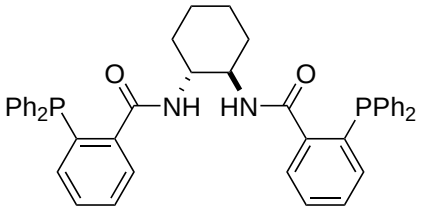
Chiral HPLC of ligand (+)-84

AS-390-01_ent093

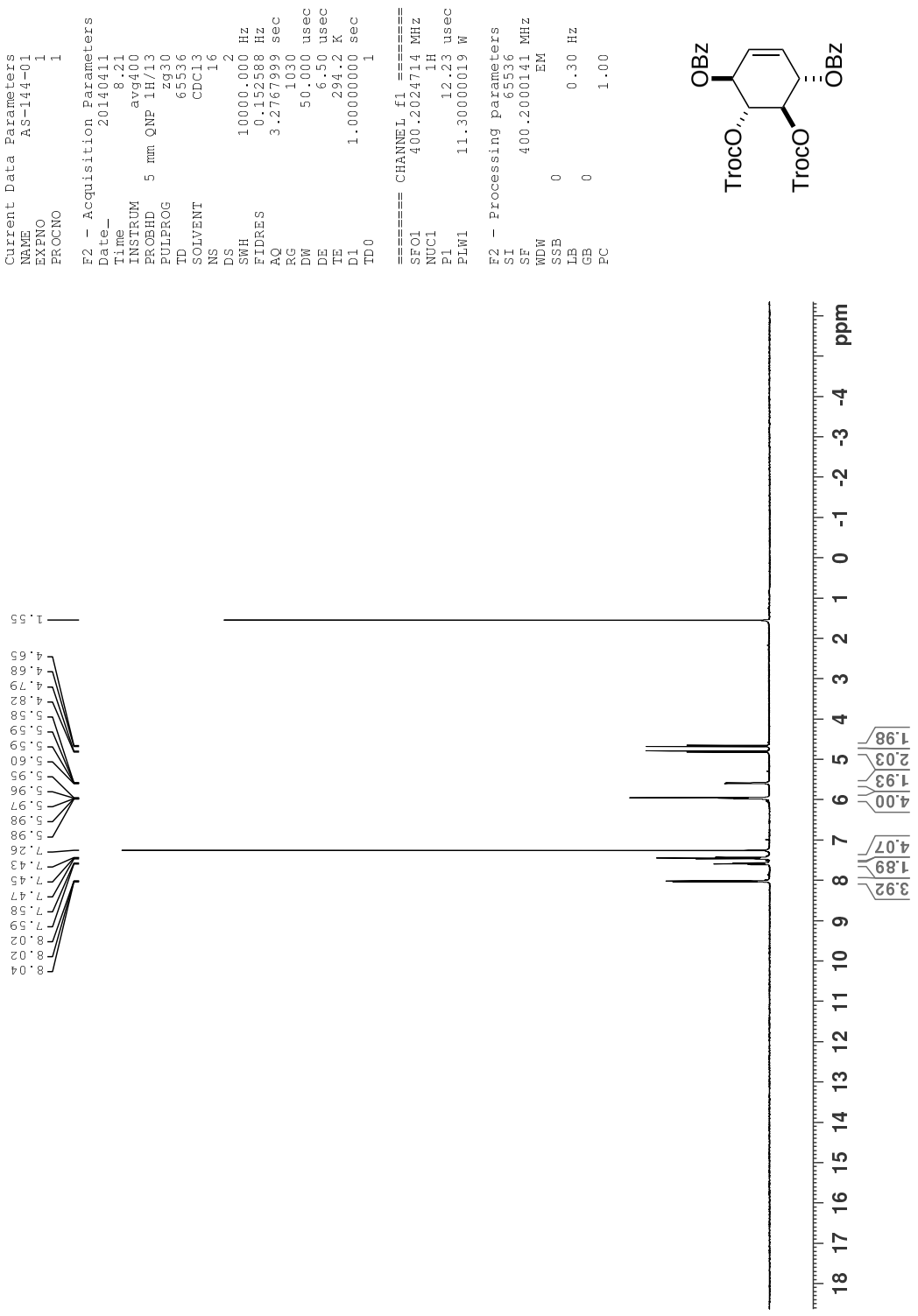
Sample Name	AS-390-01_ent093	Sample Description	ADH column
Acquisition Method	EE determination 90:10 Hex:IPA 254 nm	Acquisition Date/Time	7/7/2015 4:29 pm
Batch Group/Name	Alex/EE determination 90:10 Hex:IPA 254 nm	Batch Description	ADH column



Time	Area	Area %
3.518	4637.8	0.00
20.928	115206986	100.00
Total	115211623.5	100.00



^{1}H NMR of (+)-83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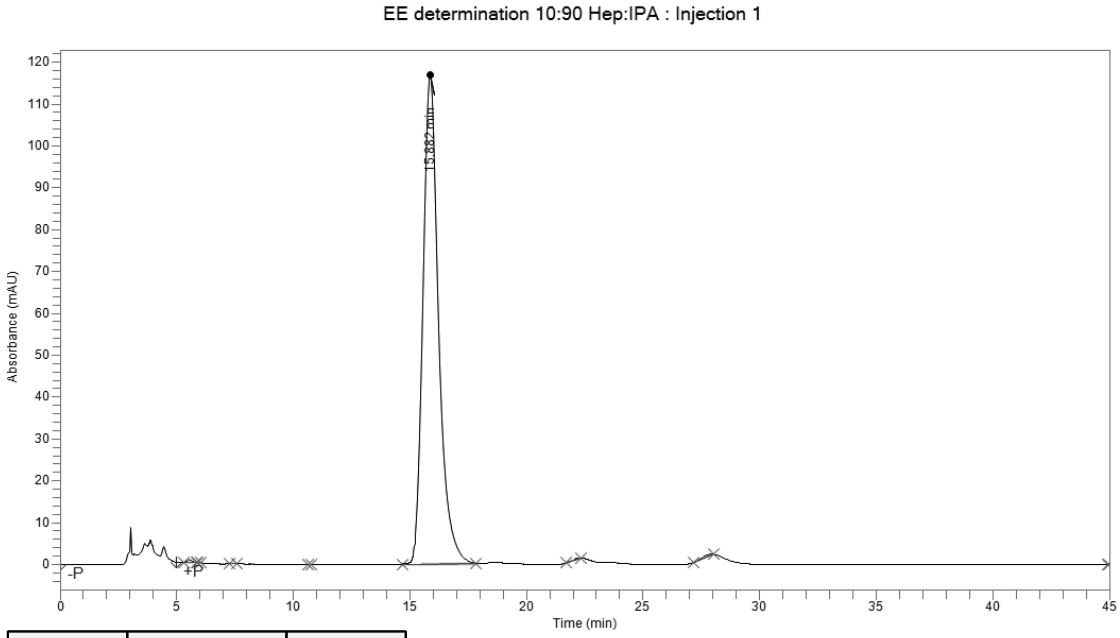
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140411
Time 8.21
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 1030
DW 50.000 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000141 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
TrocO
TrocO
OBz
1.55
4.65
4.68
4.79
4.82
5.58
5.59
5.59
5.60
5.95
5.96
5.97
5.98
5.98
7.26
7.43
7.45
7.47
7.58
7.59
8.02
8.02
8.04
1.98
2.03
1.93
4.00
4.07
1.89
3.92
ppm

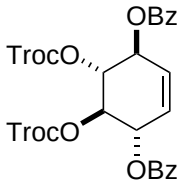
Chiral HPLC of (+)-83

EE determination 10:90 Hep:IP

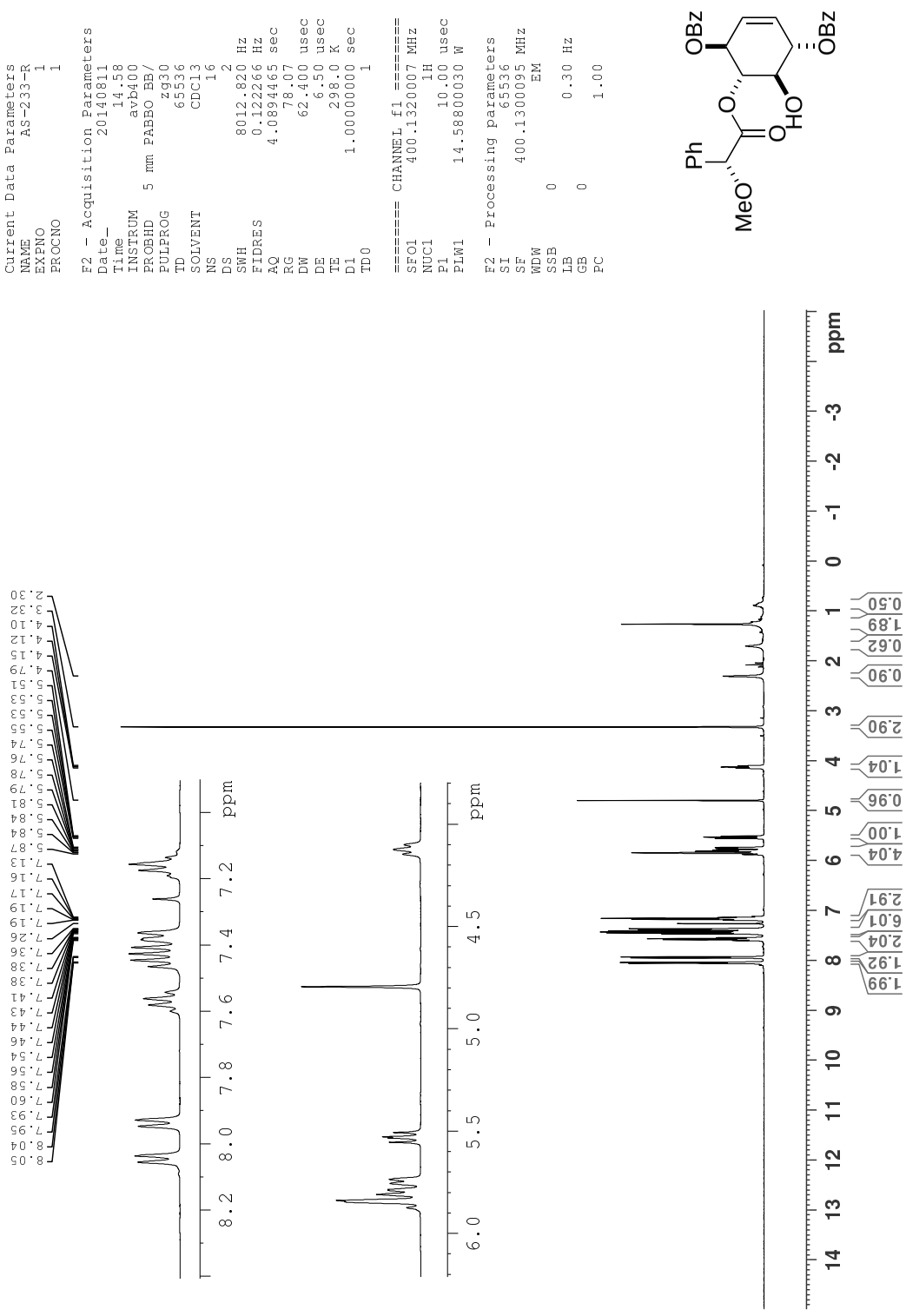
Sample Name	EE determination 10:90 Hep:IPA	Sample Description	AS-168-01
Acquisition Method	EE determination 10:90 Hep:IPA	Acquisition Date/Time	6/20/2014 11:09 am
Batch Group/Name	Alex/EE determination 10:90 Hep:IPA	Batch Description	ADH column



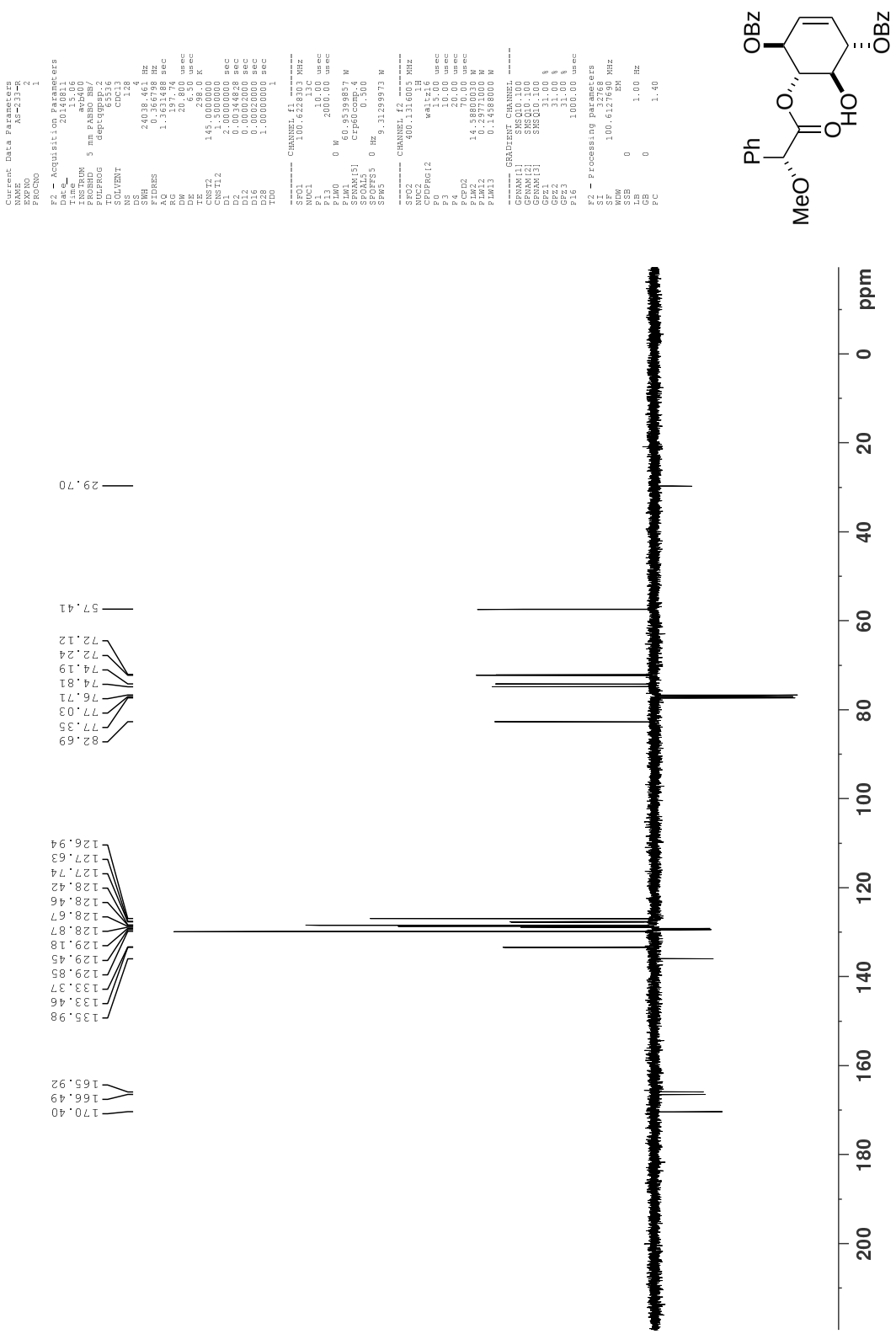
Time	Area	Area %
5.551	9900.3	0.18
5.965	112.79	0.00
7.528	304.12	0.01
10.772	137	0.00
15.882	5362155	99.49
22.299	4283.1	0.08
27.949	12967	0.24
44.933	24.802	0.00
Total	5389883.3	100.00



^{1}H NMR of (+)-108a



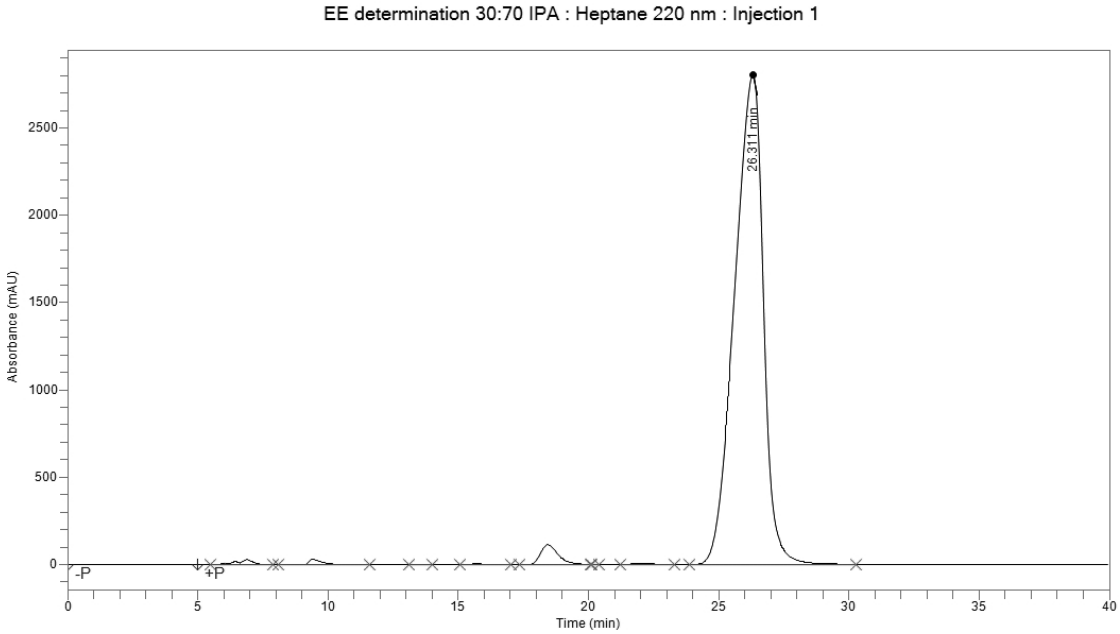
^{13}C NMR of (+)-108a

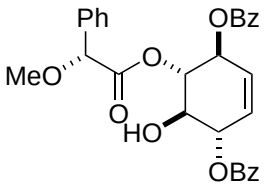


Chiral HPLC of (+)-108a

EE determination 30:70 IPA : H

Sample Name	EE determination 30:70 IPA : Heptane 220 nm	Sample Description	AS-233-R
Acquisition Method	EE determination 30:70 IPA : Heptane 220 nm	Acquisition Date/Time	8/14/2014 2:06 pm
Batch Group/Name	Alex/EE determination 30:70 IPA : Heptane 220 nm	Batch Description	ADH column



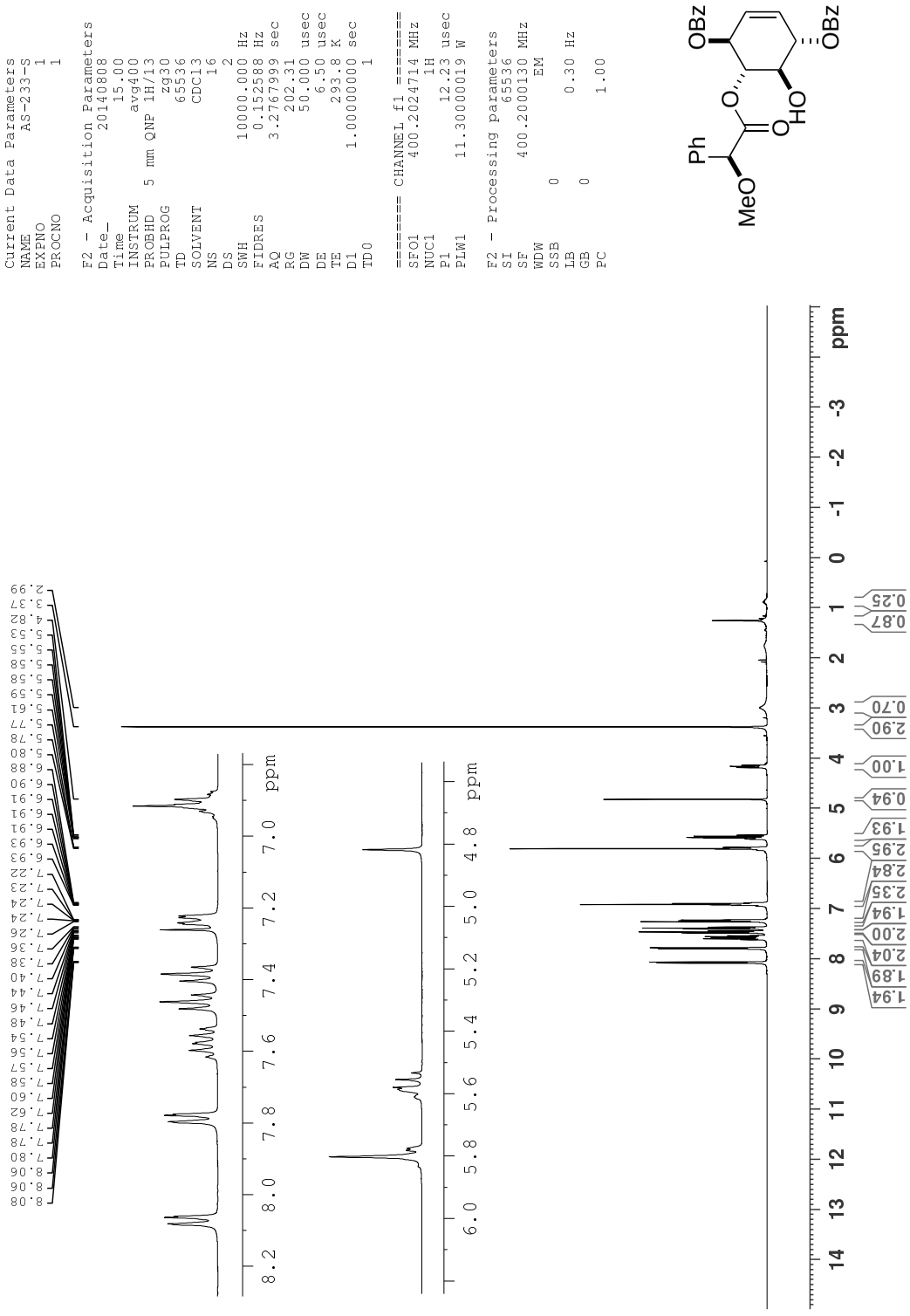


Chiral HPLC of (+)-108a (cont.)

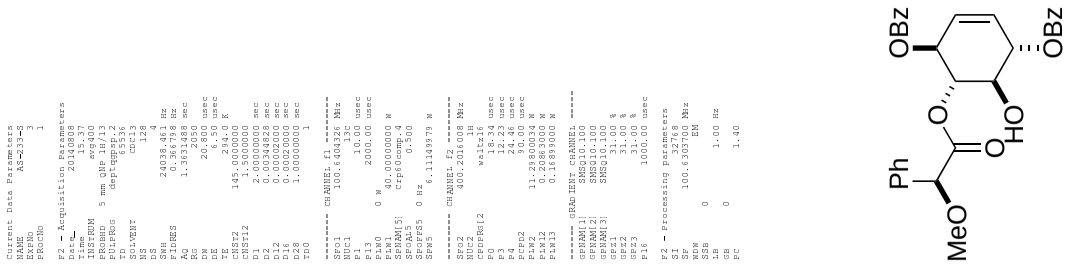
EE determination 30:70 IPA :

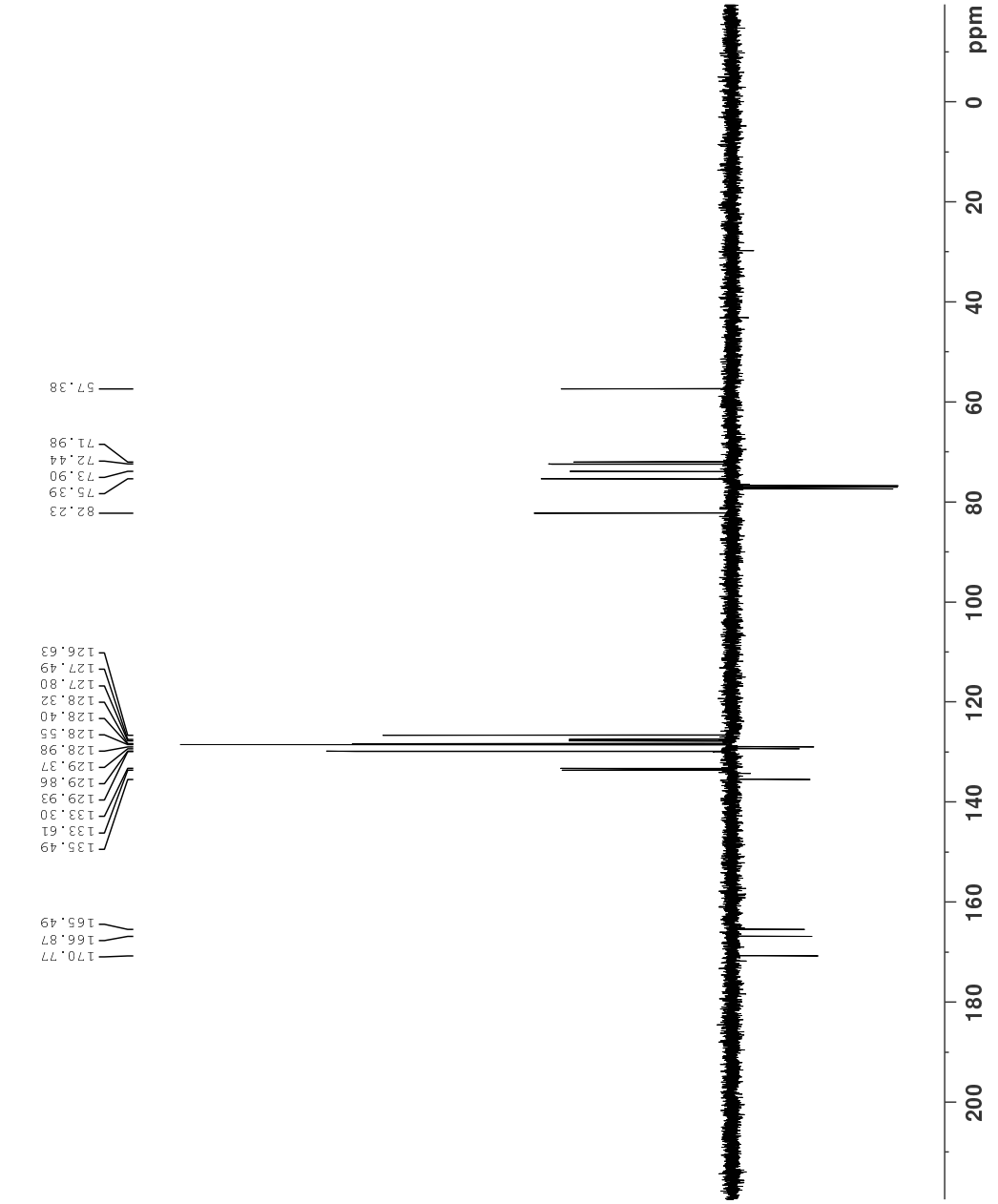
Time	Area	Area %
5.930	97703	0.04
6.423	435175	0.20
6.888	895668	0.40
8.361	16534	0.01
8.963	101449	0.05
9.409	1172397	0.53
10.883	0	0.00
13.634	25166	0.01
15.718	266942	0.12
18.434	5436053	2.45
20.340	524.39	0.00
22.027	298867	0.13
26.311	213551410	96.07
Total	222297888	100.00

^{1}H NMR of (+)-108b



^{13}C NMR of (+)-108b



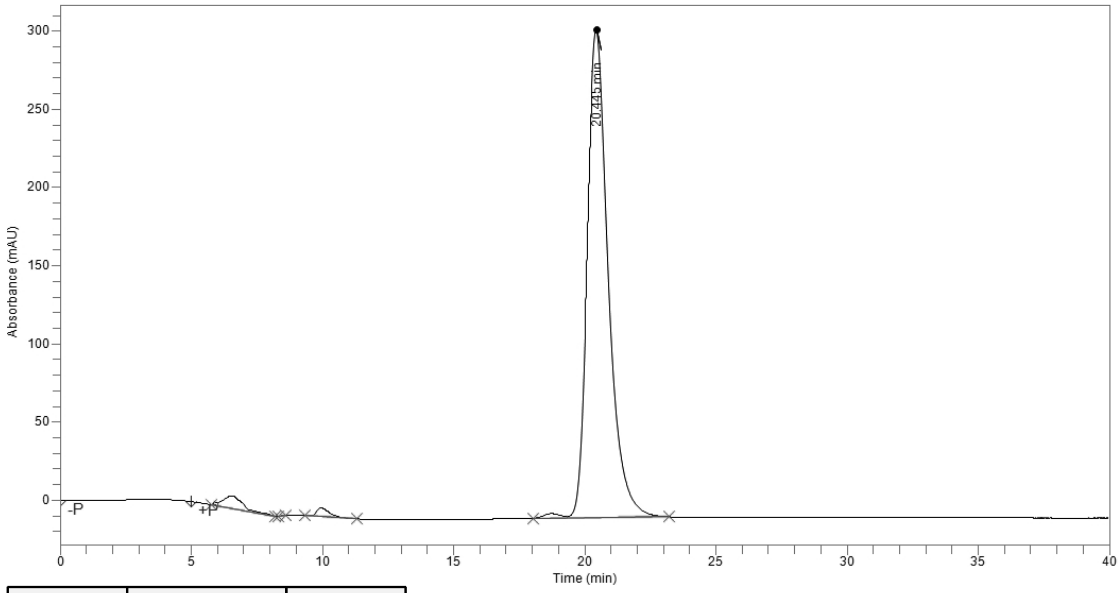


Chiral HPLC of (+)-108b

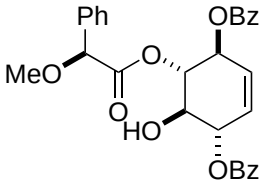
EE determination 30:70 IPA : H

Sample Name	EE determination 30:70 IPA : Heptane 220 nm	Sample Description	AS-233-S
Acquisition Method	EE determination 30:70 IPA : Heptane 220 nm	Acquisition Date/Time	8/14/2014 7:57 pm
Batch Group/Name	Alex/EE determination 30:70 IPA : Heptane 220 nm	Batch Description	ADH column

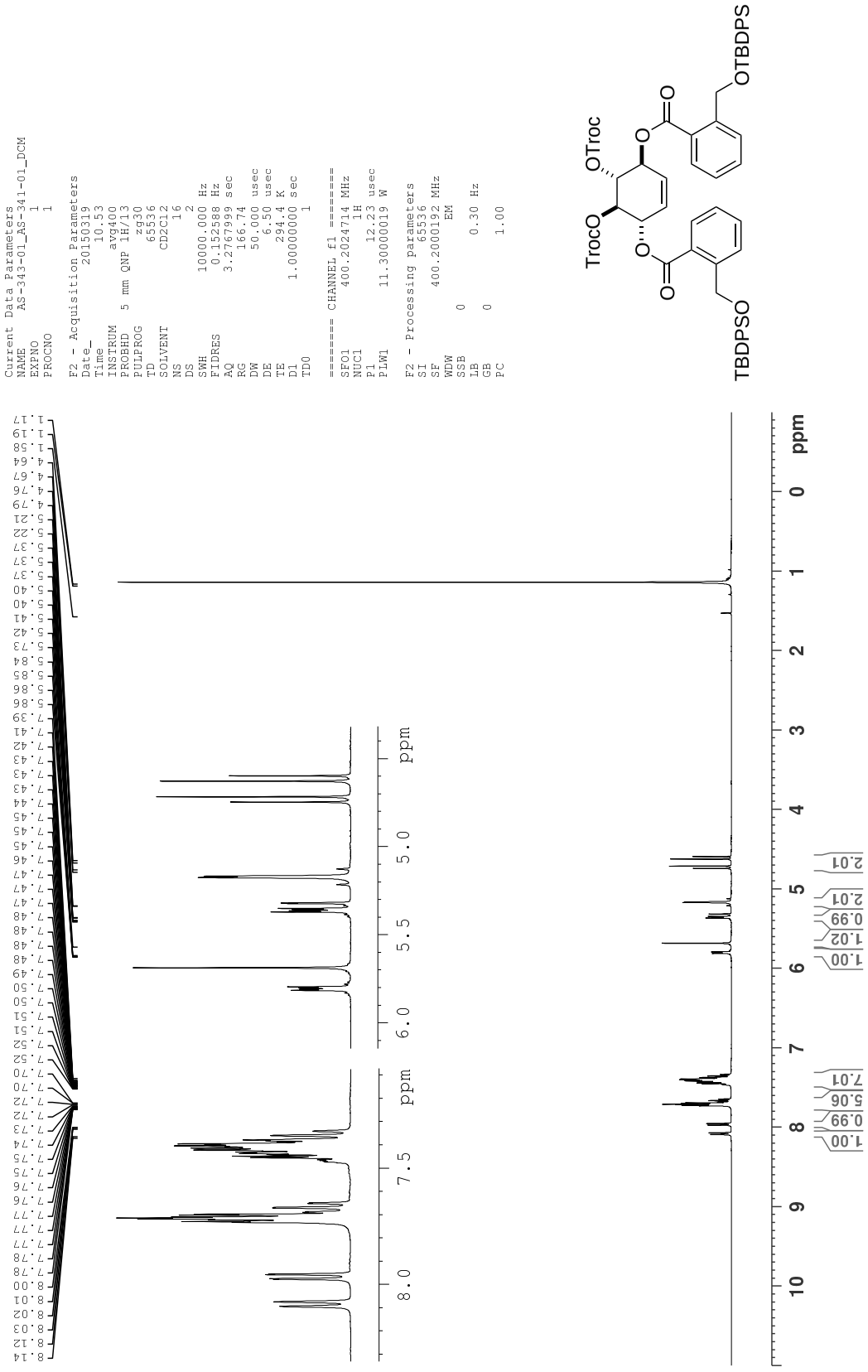
EE determination 30:70 IPA : Heptane 220 nm : Injection 1



Time	Area	Area %
5.887	24659	0.13
6.593	414669	2.26
8.576	1138	0.01
9.930	209848	1.15
18.736	121505	0.66
20.445	17539351	95.78
Total	18311170	100.00



^{1}H NMR of (+)-175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NAME AS-343-01_AS-341-01_DCM
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PROCNO 1
F2 - Acquisition Parameters
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Time_ 10.53
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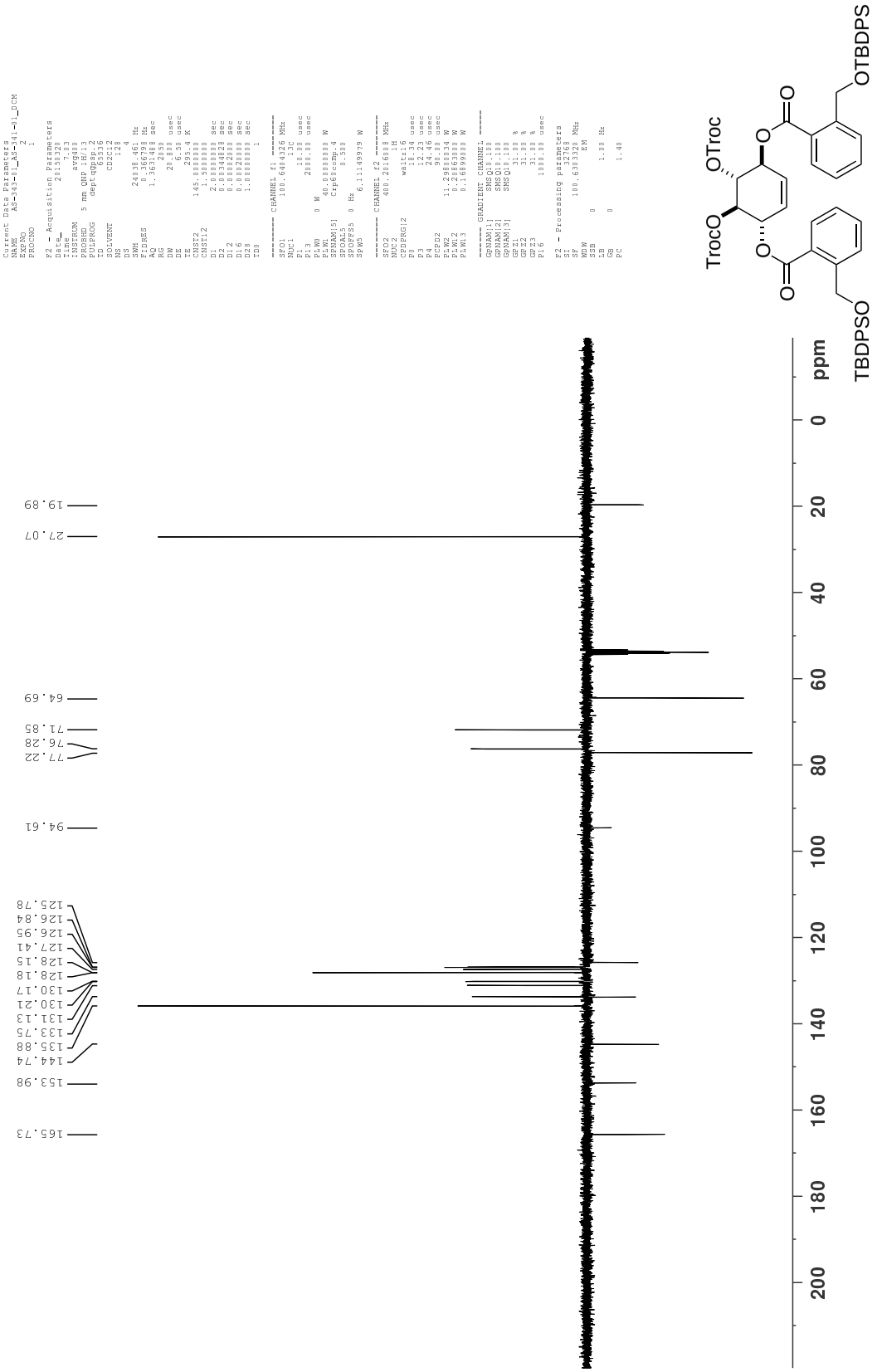
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 166.74
DW 50.000 usec
DE 6.50 usec
TE 294.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000192 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTroc
TrocO
OTBDPS
TBDPSO
ppm
1.00
0.99
5.06
7.01
1.00
1.02
0.99
2.01
2.01

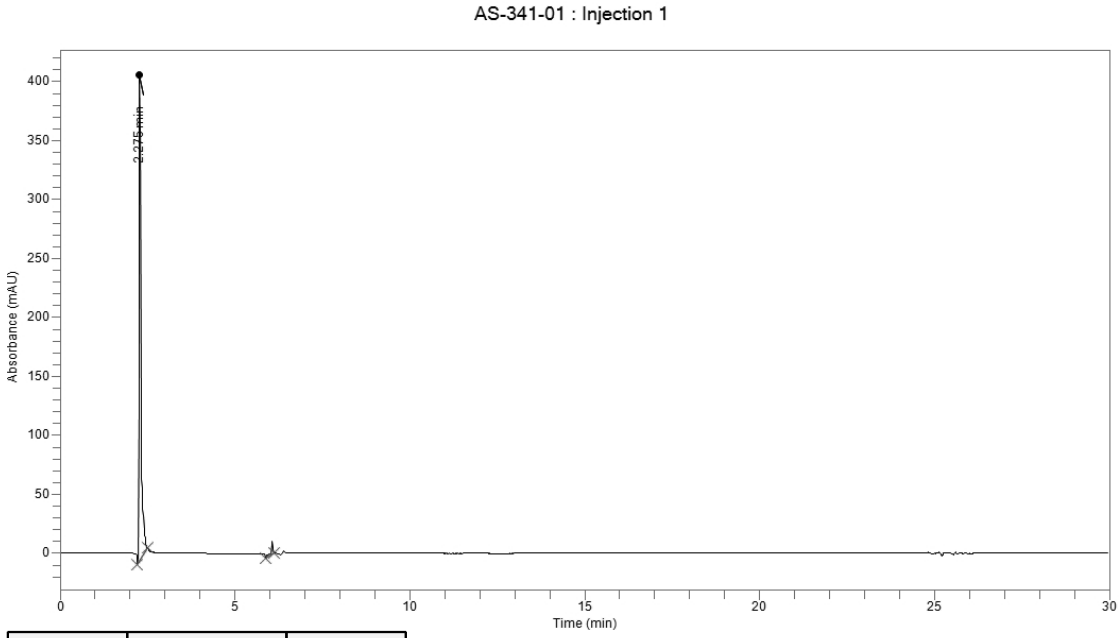
^{13}C NMR of (+)-175



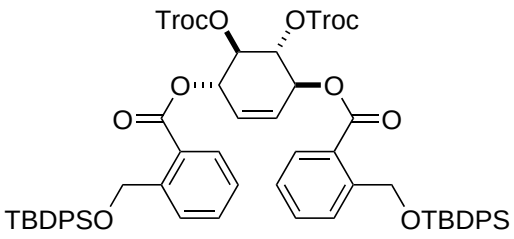
HPLC of (+)-175

AS-341-01

Sample Name	AS-341-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	4/13/2015 3:12 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 04-17-2015 13-16-11	Batch Description	Normal Phase silica column



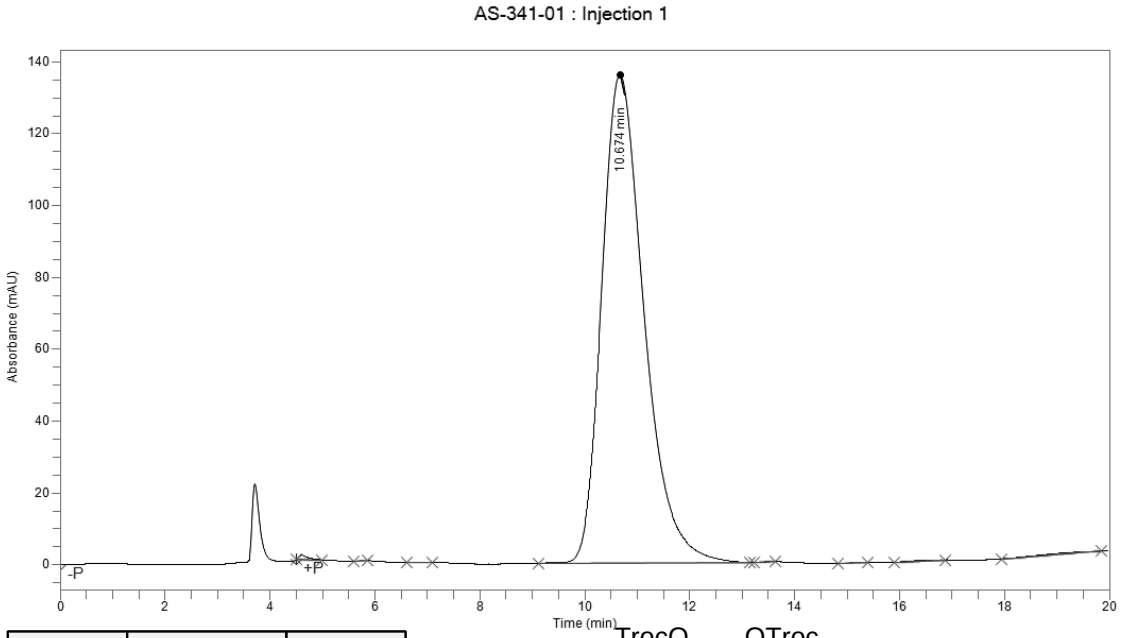
Time	Area	Area %
2.275	1408466	97.40
6.069	37533	2.60
Total	1445999	100.00



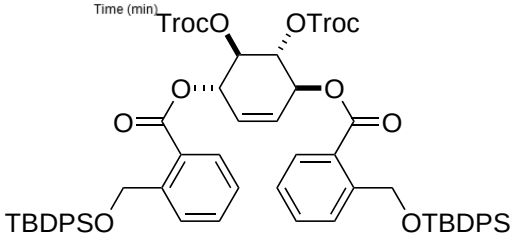
Chiral HPLC of (+)-175

AS-341-01

Sample Name	AS-341-01	Sample Description	ADH column
Acquisition Method	EE determination 100 A 220 nm 20 min 1% IPA	Acquisition Date/Time	7/7/2015 6:17 pm
Batch Group/Name	Alex/EE determination 100 A 220 nm 20 min 1% IPA	Batch Description	ADH column



Time	Area	Area %
4.604	15066	0.20
5.832	661.4	0.01
6.944	2006.6	0.03
10.674	7583636	99.38
13.522	879.3	0.01
15.374	1905.7	0.02
16.794	5460.1	0.07
19.803	21411	0.28
Total	7631026	100.00



Chiral HPLC of (–)-175

AS-394-01

Sample Name	AS-394-01	Sample Description	ADH column
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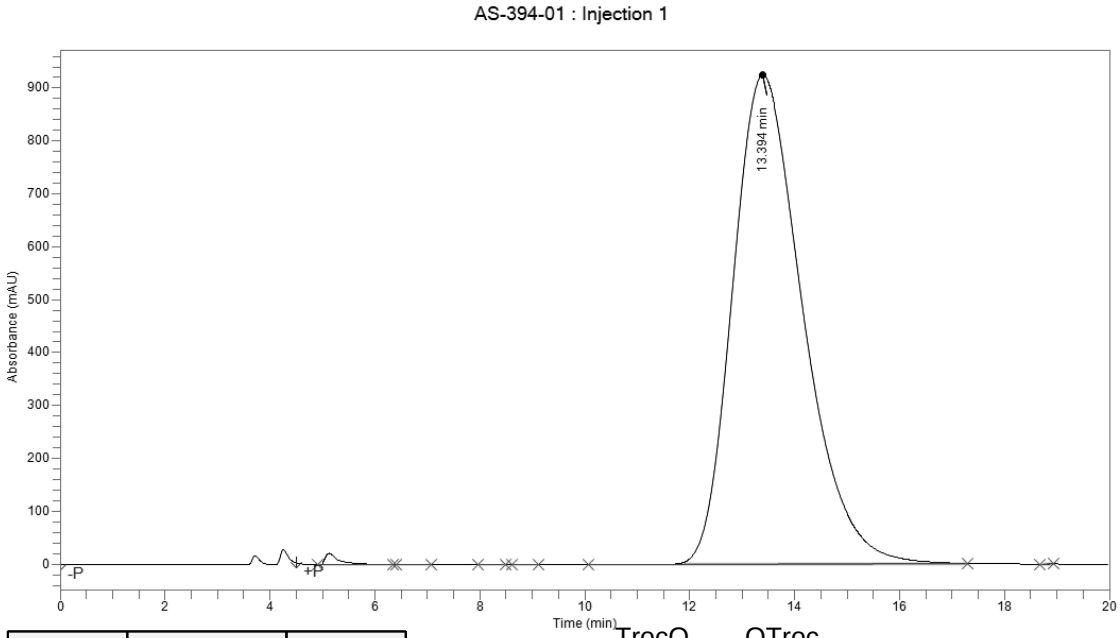
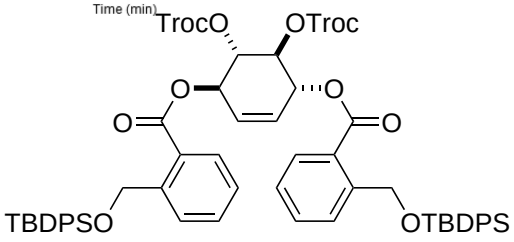
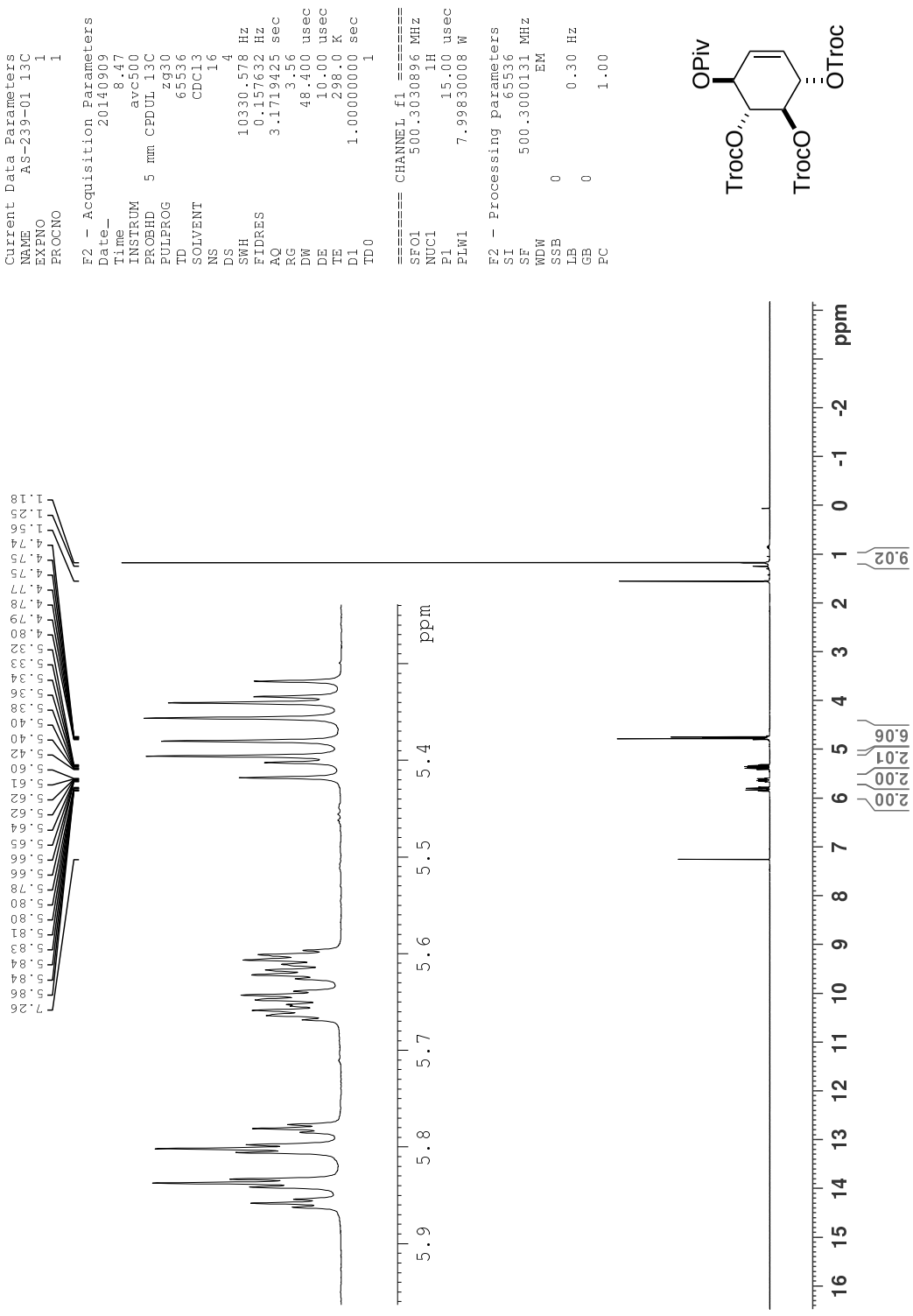
Batch Group/Name	Alex/EE determination 100 A 220 nm 20 min 1% IPA	Batch Description	ADH column



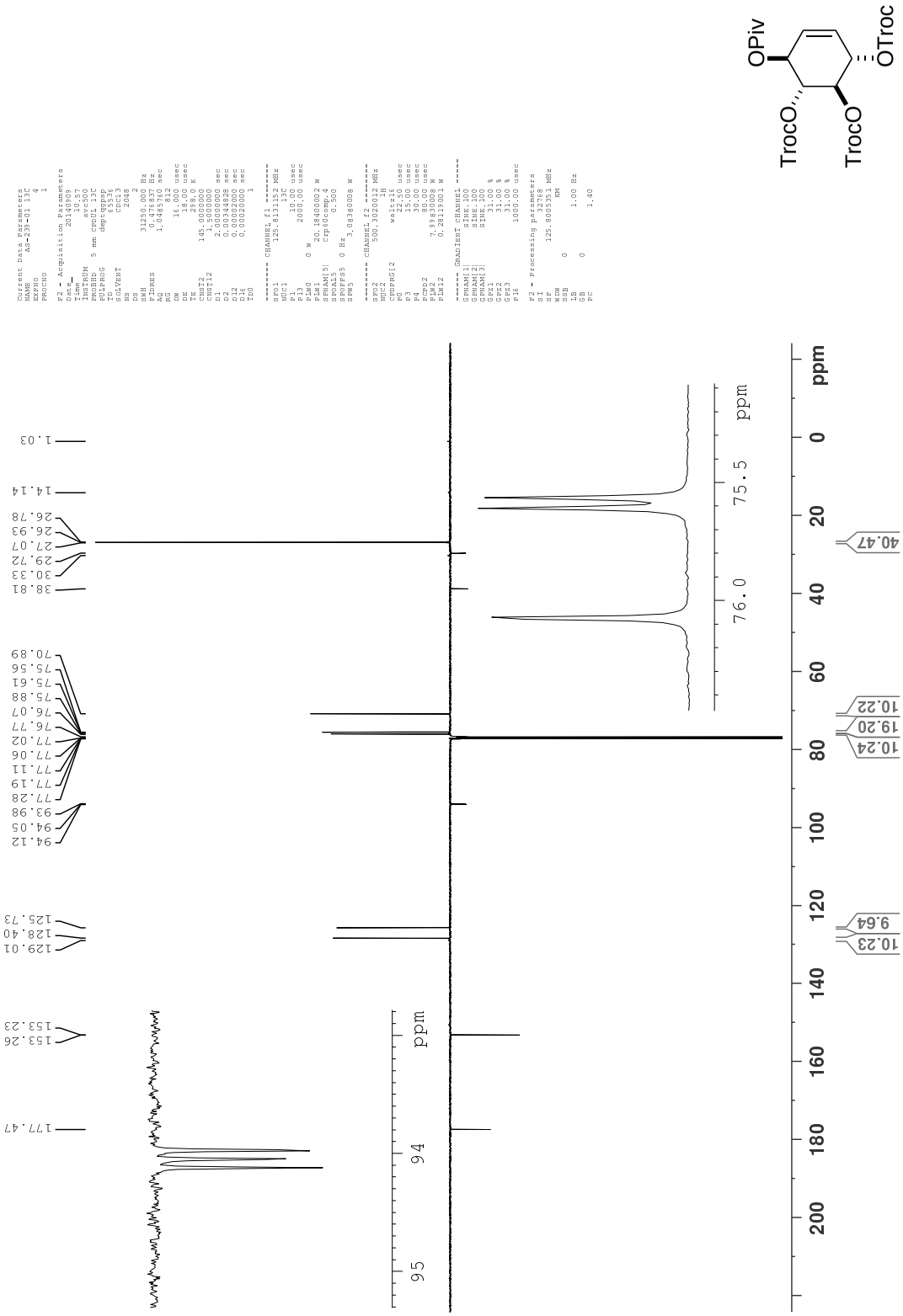
Time	Area	Area %
5.133	416522	0.48
6.683	6180.5	0.01
8.175	5161.9	0.01
9.081	2371	0.00
10.784	44433	0.05
13.394	85578492	99.45
18.892	464.75	0.00
Total	86053625	100.00



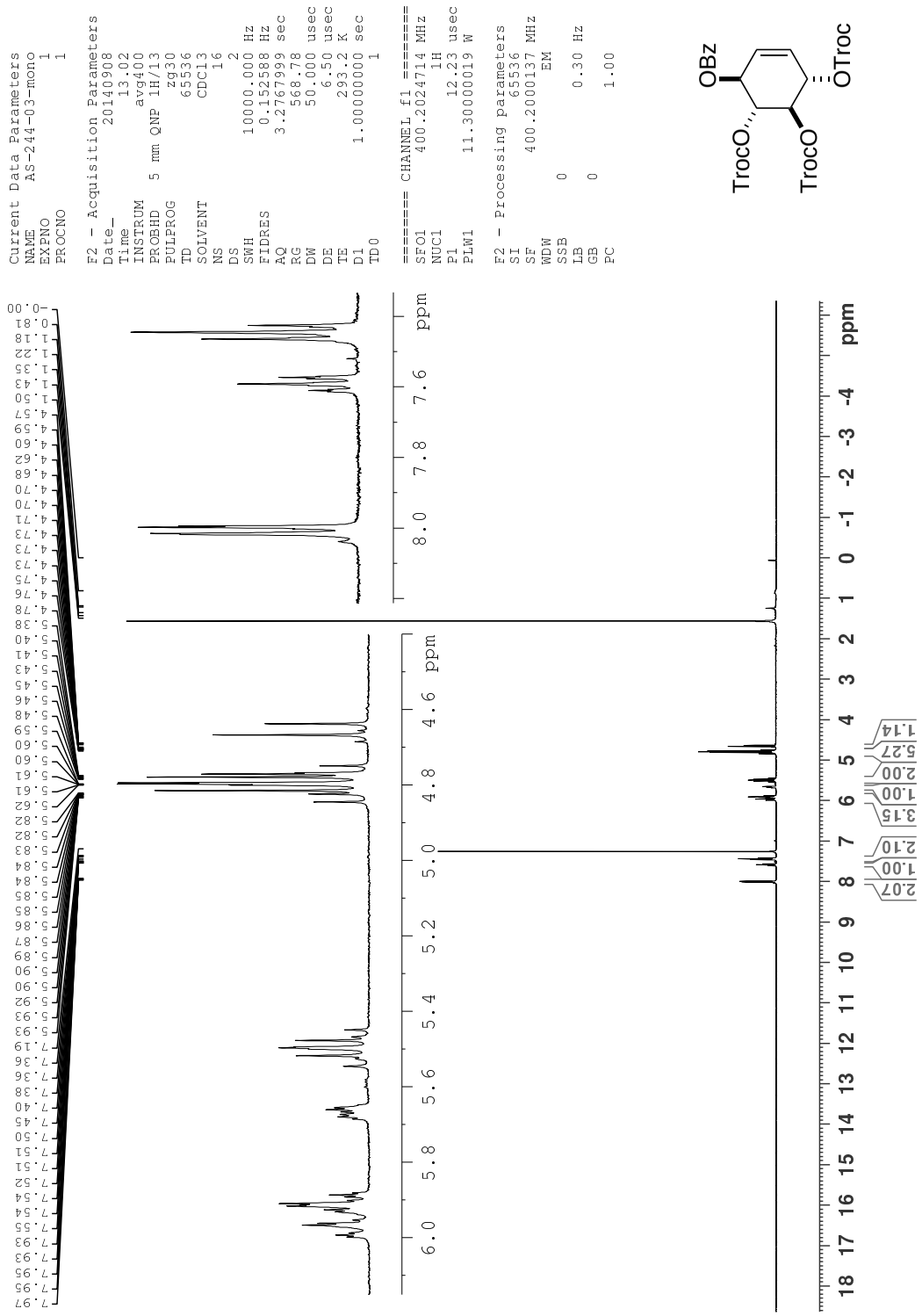
^{1}H NMR of (+)-115


Current Data Parameters
NAME AS-239-01 13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140909
Time 8.47
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000131 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OPiv
TrocO
TrocO
OTroc
ppm
9.02
6.06
2.01
2.00
2.00

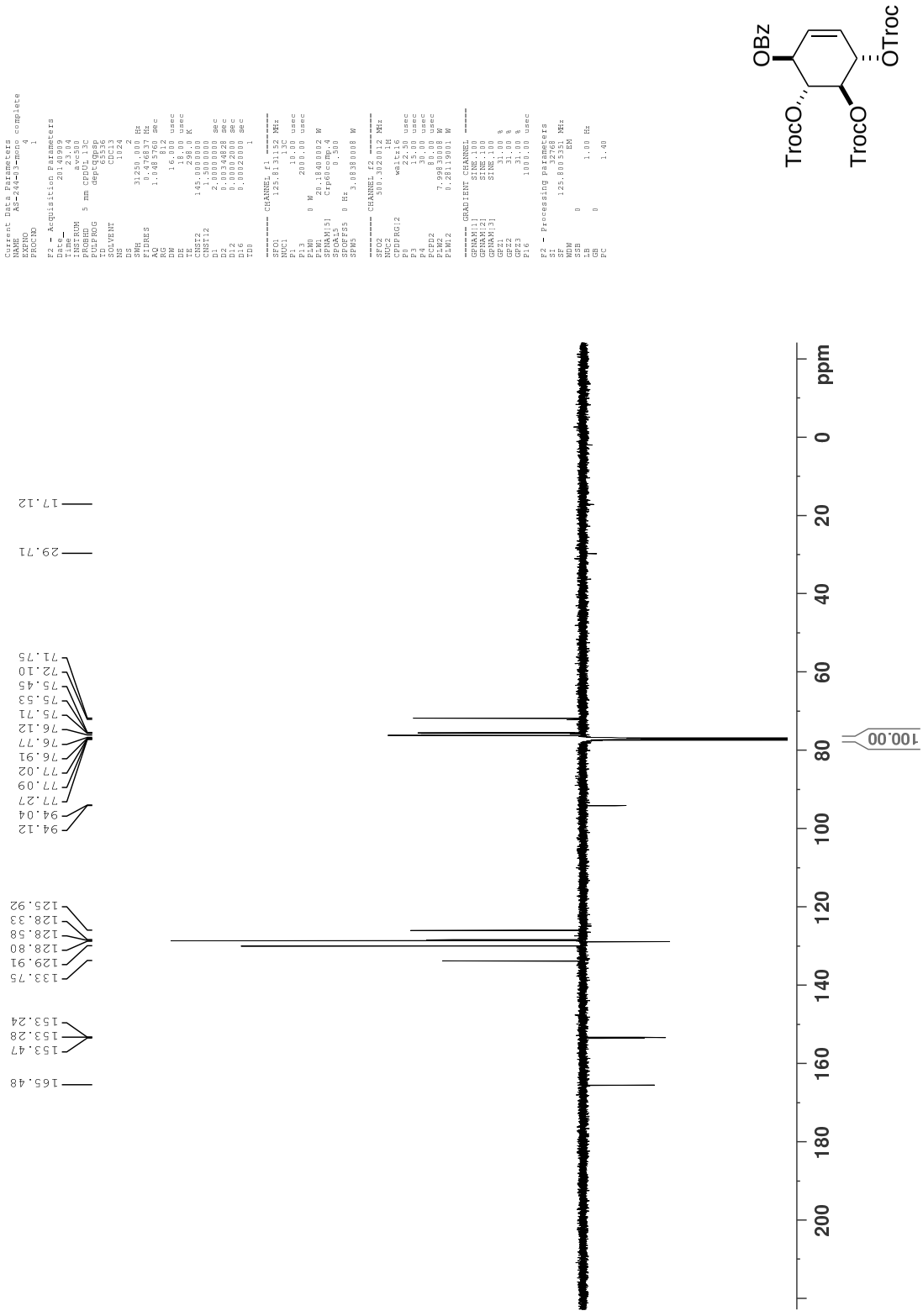
^{13}C NMR of (+)-115



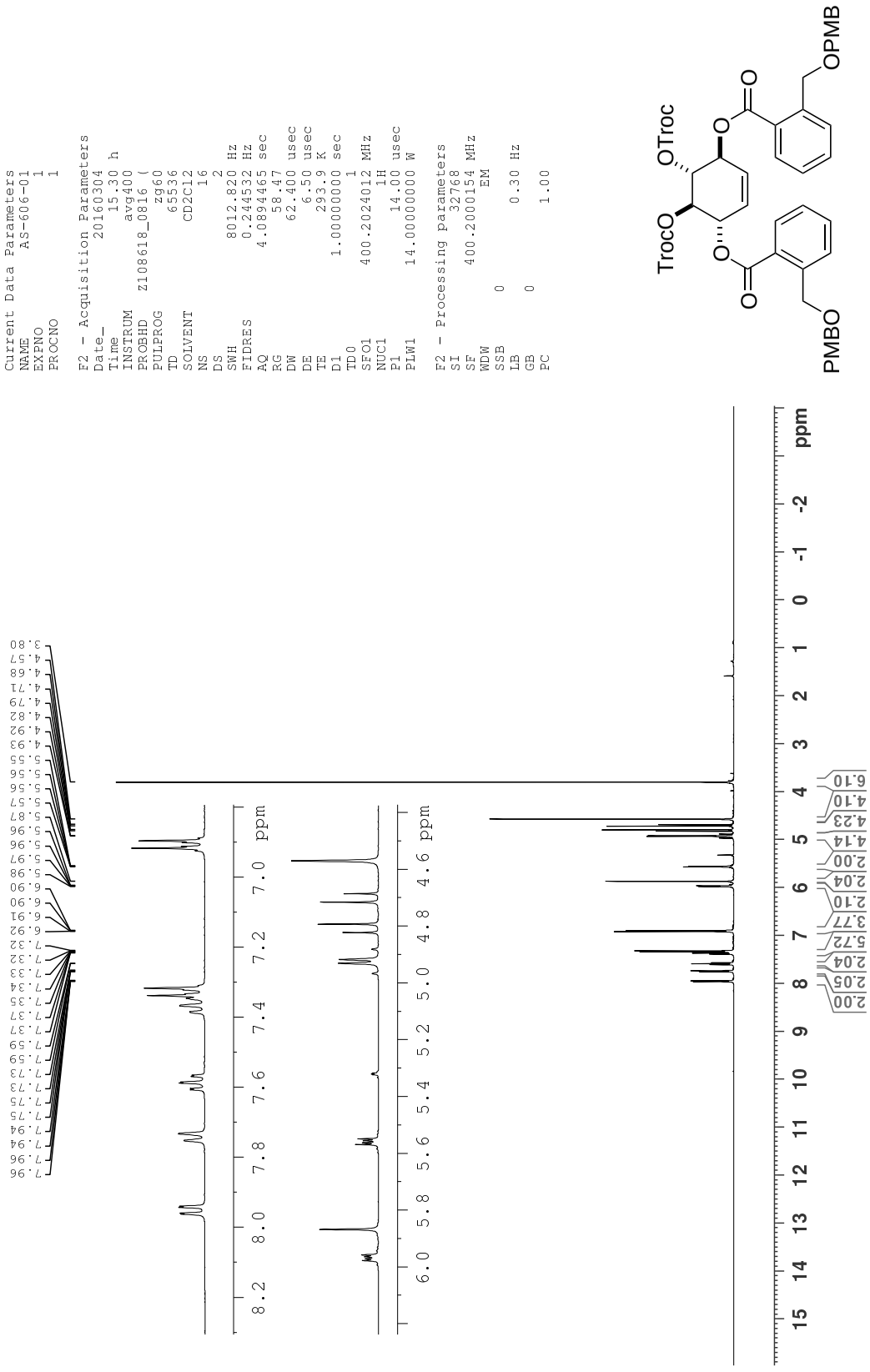
^{1}H NMR of (+)-104



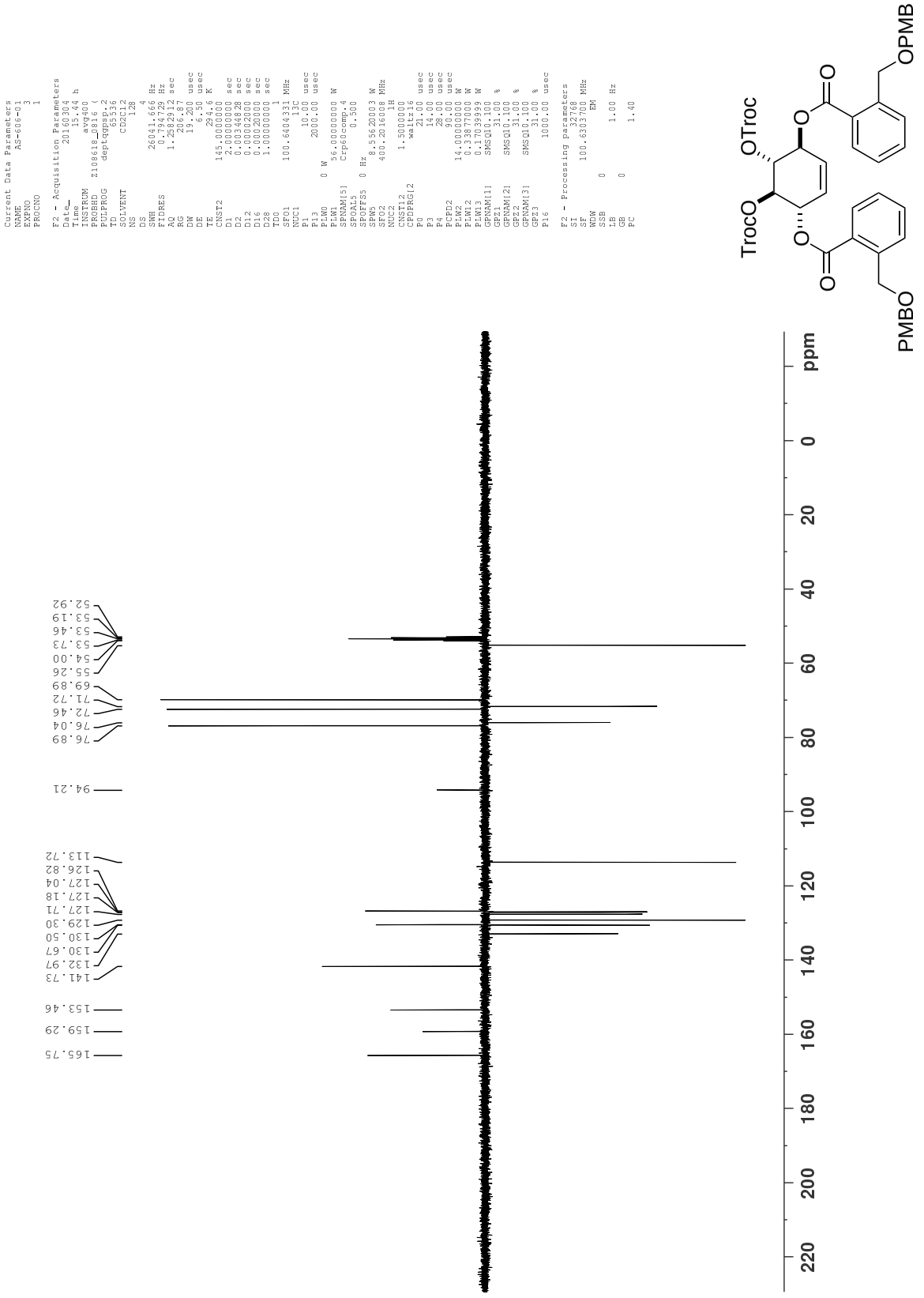
^{13}C NMR of (+)-104



^{1}H NMR of (+)-253


Current Data Parameters
NAME AS-606-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160304
Time 15.30 h
INSTRUM avg400
PROBHD Z108618_0816 (
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 58.47
DW 62.400 usec
DE 6.50 usec
TE 293.9 K
D1 1.00000000 sec
TD0 1
SFO1 400.2024012 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 32768
SF 400.2000154 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTroc
TrocO
OPMB
PMBO
ppm

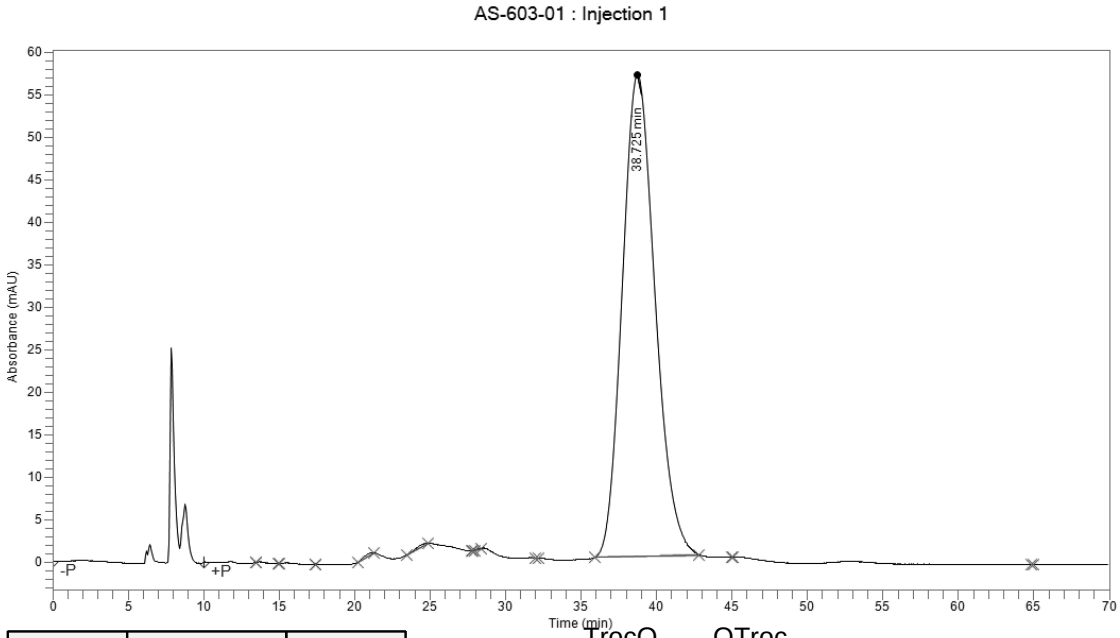
^{13}C NMR of (+)-253



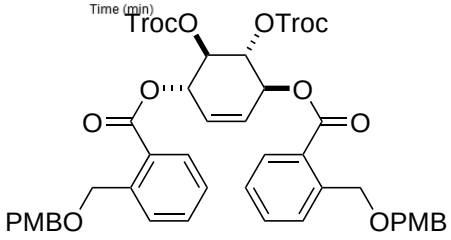
Chiral HPLC of (+)-253

AS-603-01

Sample Name	AS-603-01	Sample Description	ADH column
Acquisition Method	EE determination 50:50 Hep:IPA 254 nm 1h	Acquisition Date/Time	6/6/2016 9:18 pm
Batch Group/Name	Alex/EE determination 50:50 Hep:IPA 254 nm 1h	Batch Description	ADH column



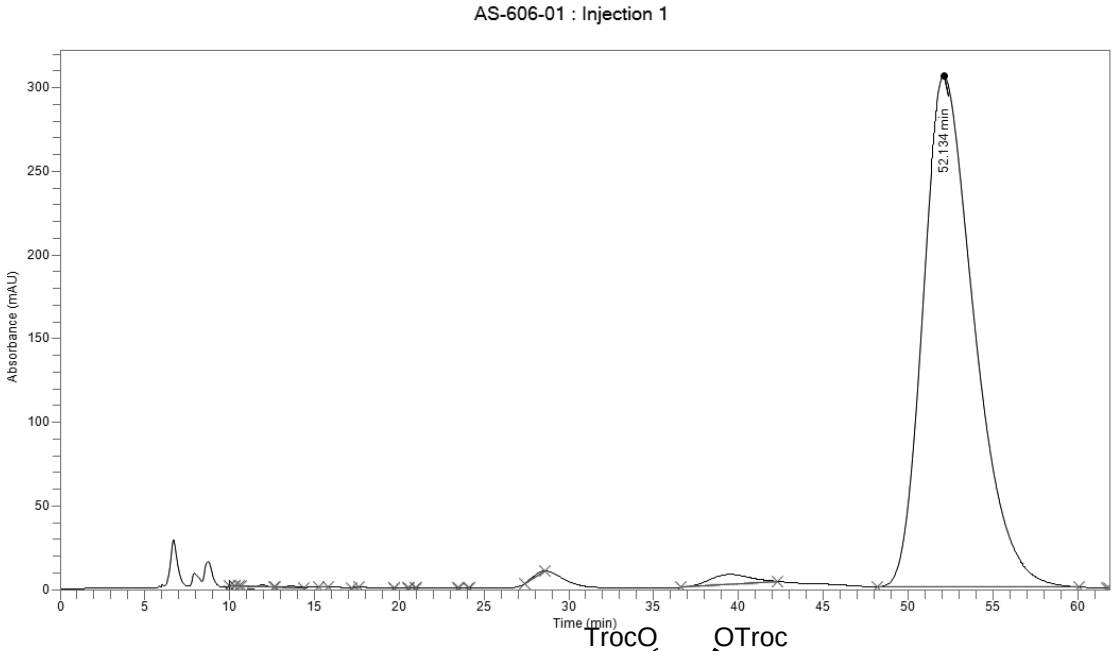
Time	Area	Area %
13.501	48.719	0.00
14.978	48.424	0.00
17.394	31.298	0.00
21.176	10625	0.12
24.798	12453	0.15
27.789	37.291	0.00
28.358	614.75	0.01
32.021	120.47	0.00
38.725	8498248	99.72
44.980	59.053	0.00
64.840	102.75	0.00
Total	8522388.676	100.00



Chiral HPLC of (–)-253

AS-606-01

Sample Name	AS-606-01	Sample Description	ADH column
Acquisition Method	EE determination 50:50 Hep:IPA 254 nm 1h	Acquisition Date/Time	6/6/2016 8:15 pm
Batch Group/Name	Alex/EE determination 50:50 Hep:IPA 254 nm 1h	Batch Description	ADH column

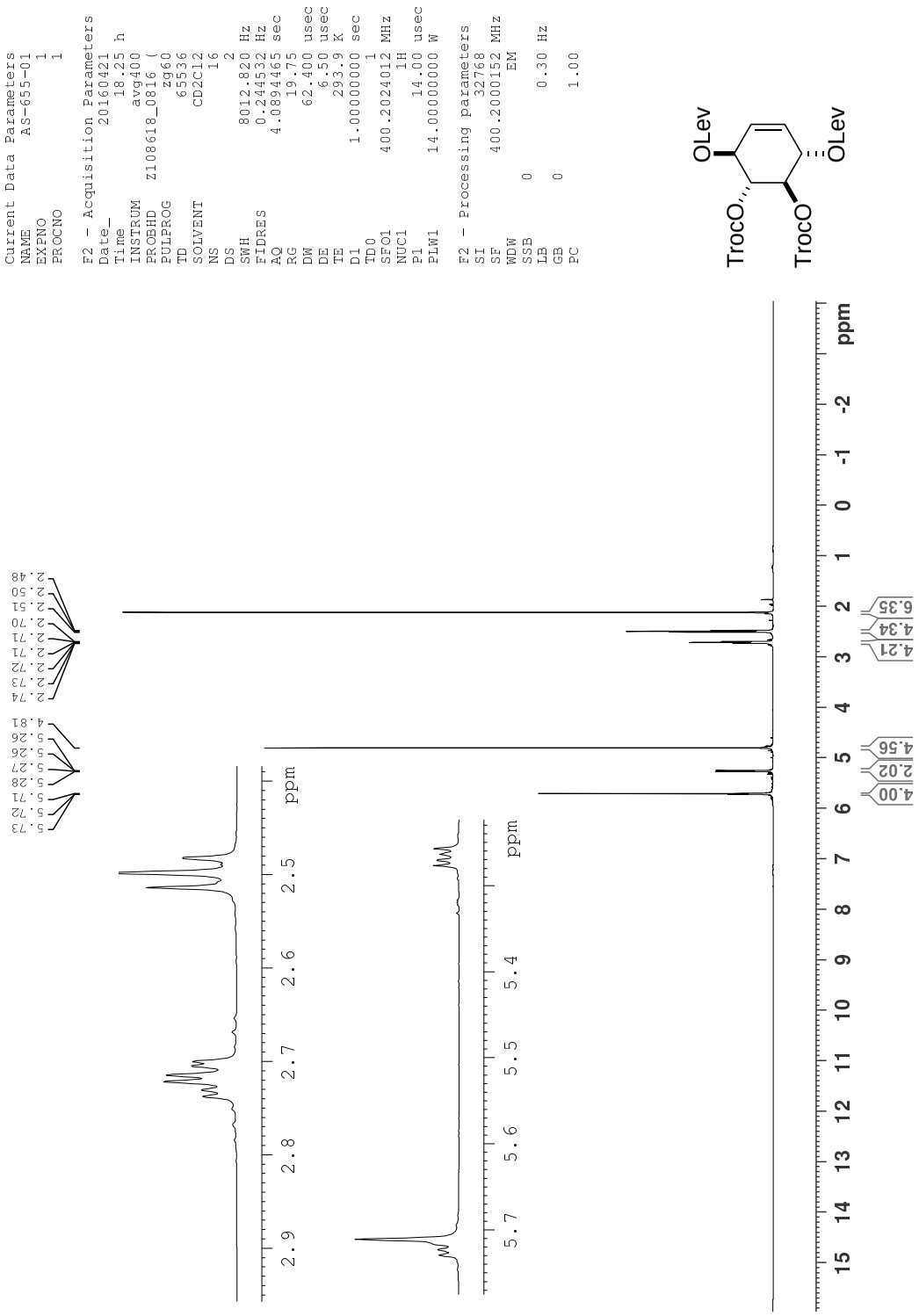


Chiral HPLC of (–)-253 (cont.)

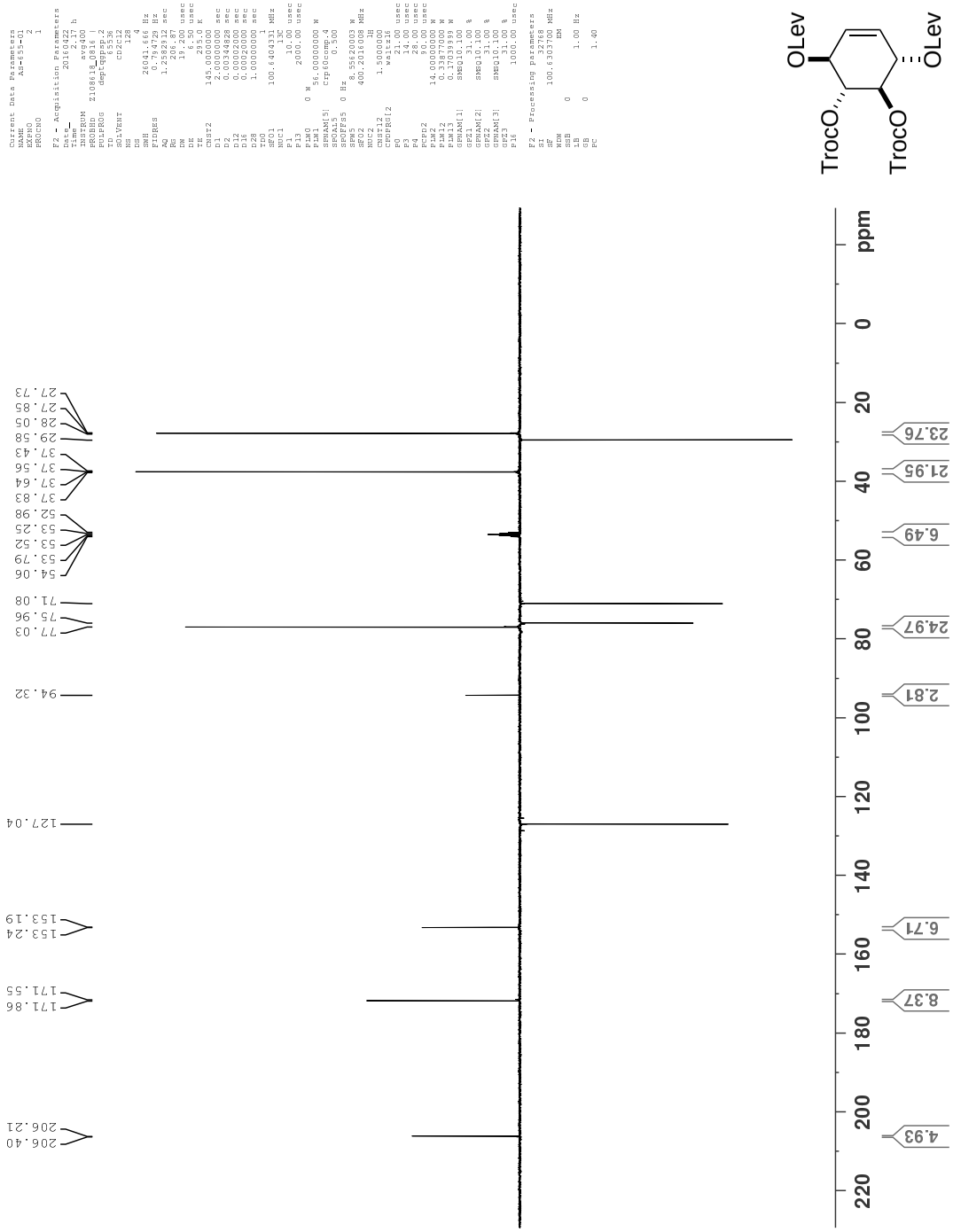
AS-606-01

Time	Area	Area %
10.070	1613.3	0.00
10.480	380.89	0.00
10.890	2610.6	0.00
11.948	42971	0.07
13.042	5521.7	0.01
13.620	35903	0.06
15.659	1239.7	0.00
15.801	529.25	0.00
17.396	317.88	0.00
17.602	450.99	0.00
19.692	38.68	0.00
20.550	88.875	0.00
20.969	50.786	0.00
23.492	31.298	0.00
24.134	28.346	0.00
28.574	56037	0.09
39.431	968503	1.48
52.134	64144889	98.29
61.767	64.959	0.00
Total	65261270.3	100.00

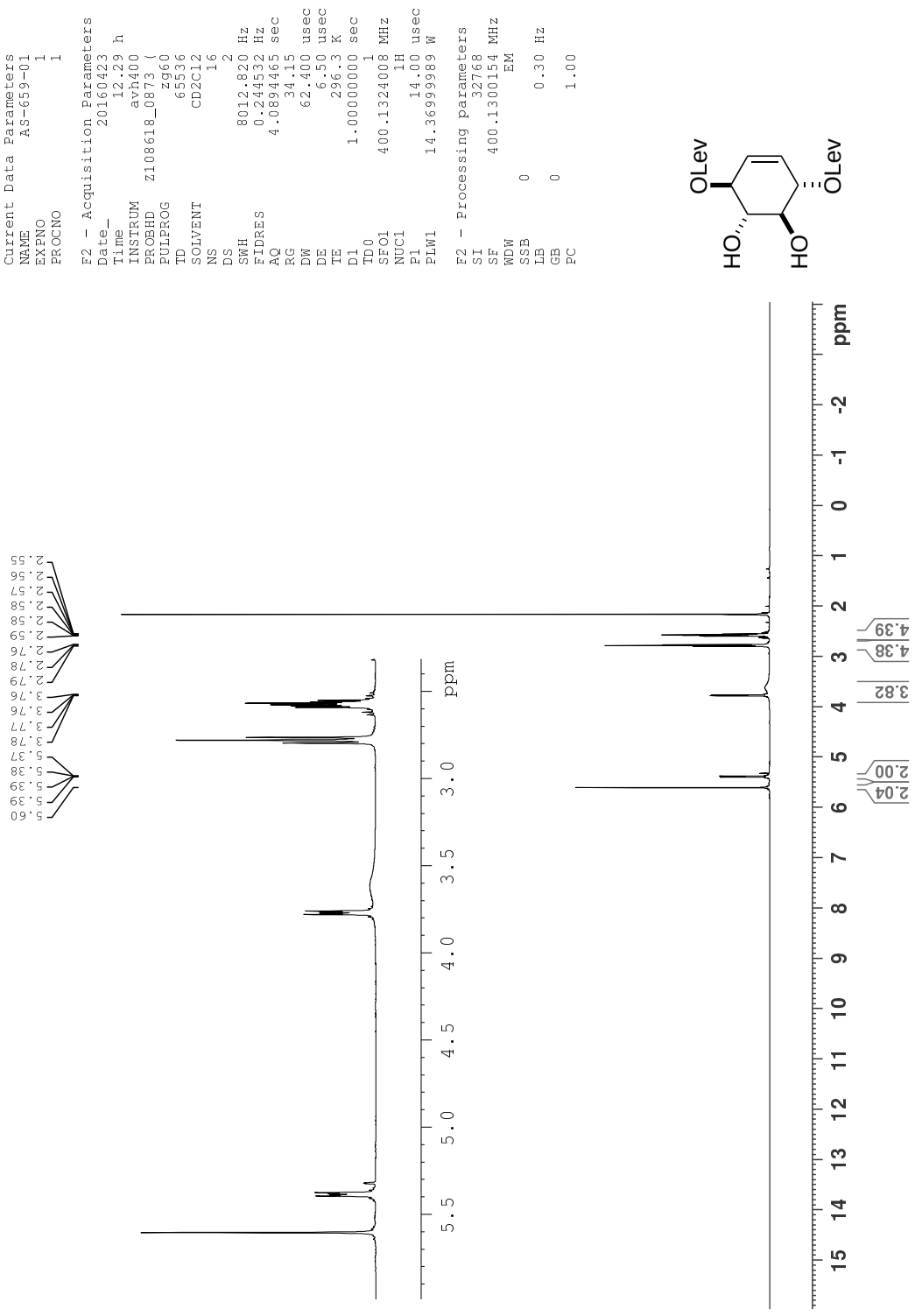
^{1}H NMR of (+)-118


Current Data Parameters
NAME AS-655-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160421
Time 18.25 h
INSTRUM avg400
PROBHD Z108618_0816 (
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 19.75
DW 62.400 usec
DE 6.50 usec
TE 293.9 K
D1 1.00000000 sec
TD0 1
SFO1 400.2024012 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 32768
SF 400.2000152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OLev
TrocO
TrocO
OLev
ppm
4.00
2.02
4.56
4.21
4.34
6.35

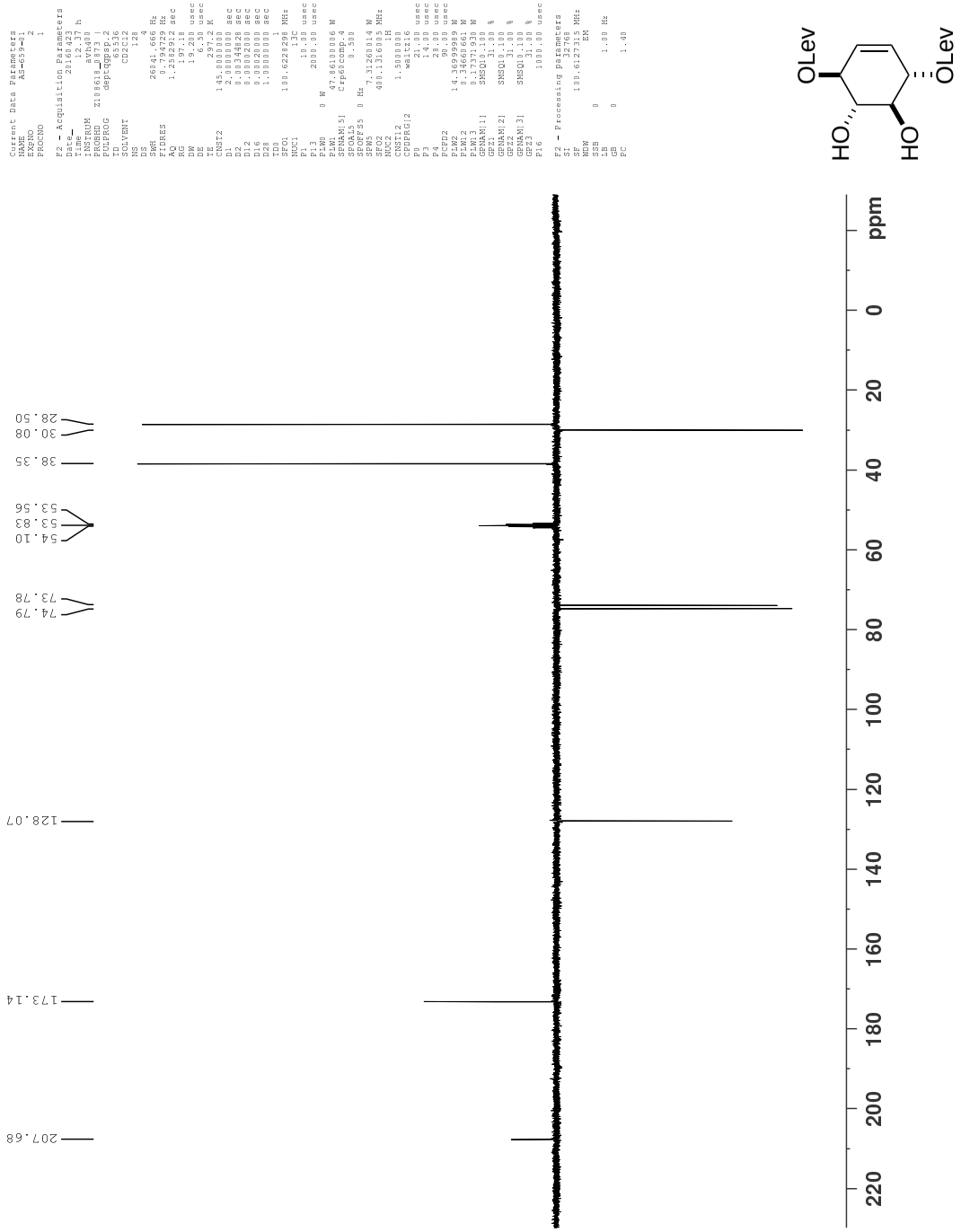
^{13}C NMR of (+)-118



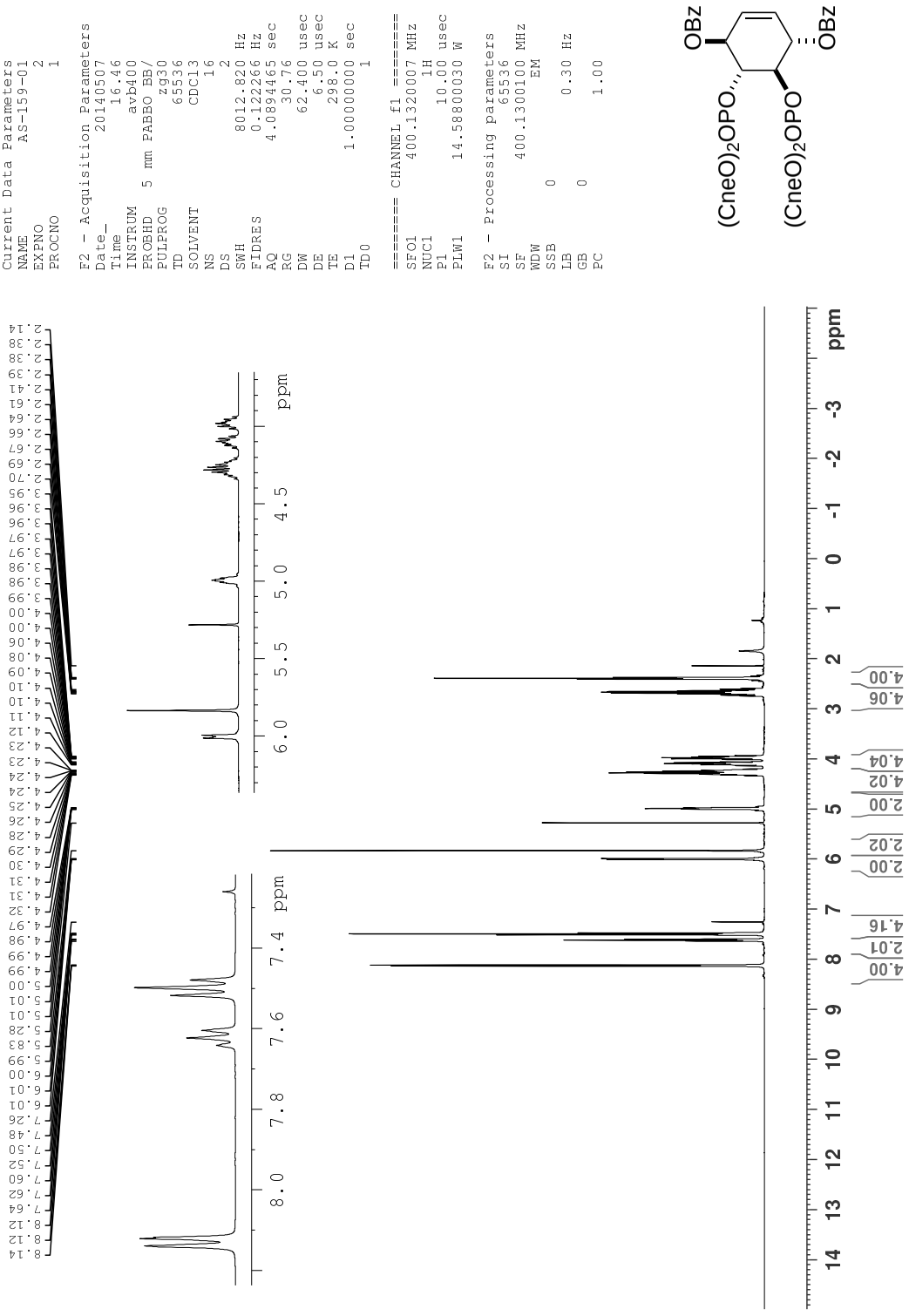
^{1}H NMR of (+)-252


Current Data Parameters
NAME AS-659-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160423
Time 12.29 h
INSTRUM avh400
PROBHD Z108618_0873 (
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 34.15
DW 62.400 usec
DE 6.50 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324008 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.36999989 W
F2 - Processing parameters
SI 32768
SF 400.1300154 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OLev
HO
HO
OLev
ppm
4.39
4.38
3.82
2.04
2.00

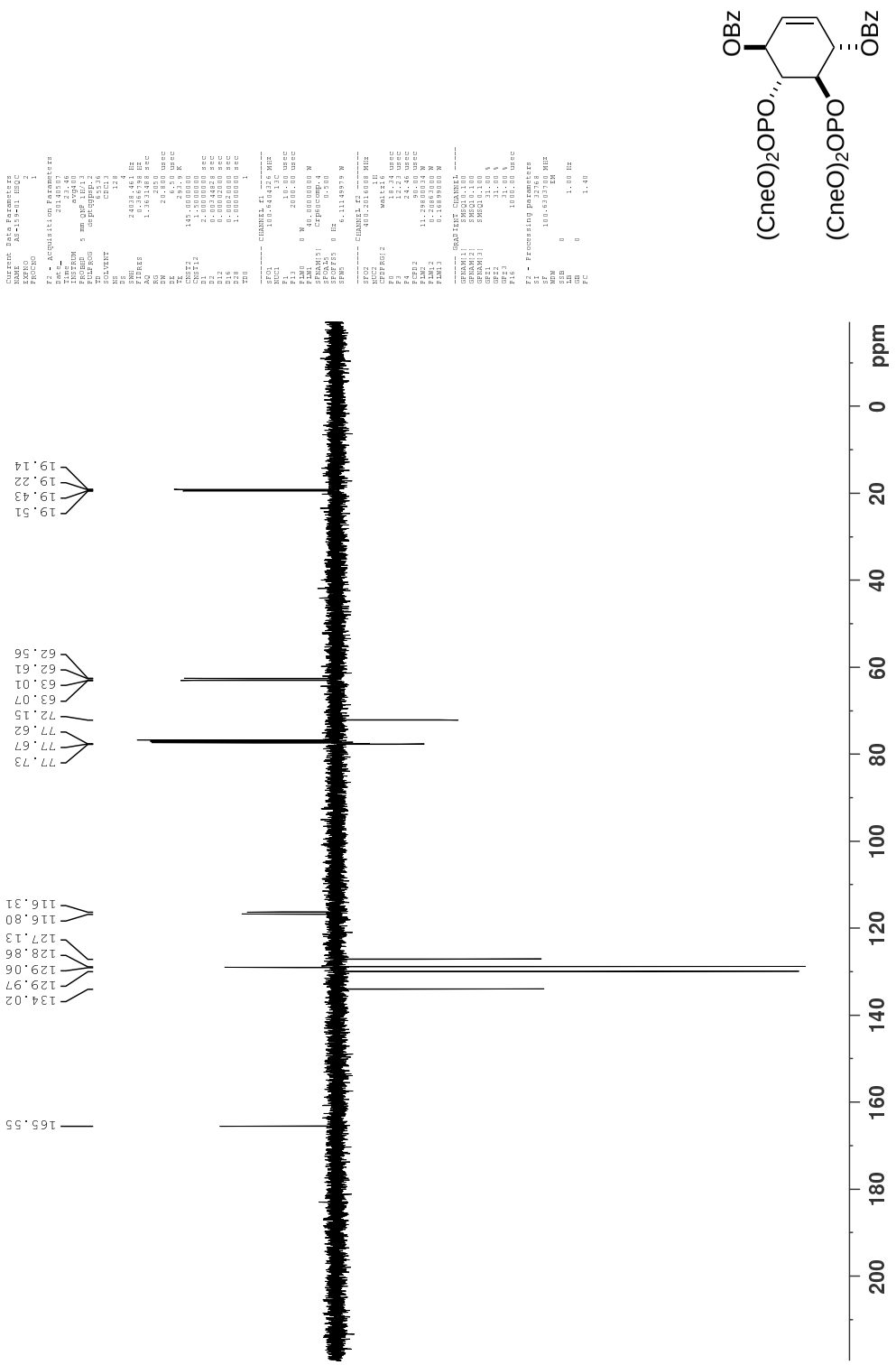
^{13}C NMR of (+)-252



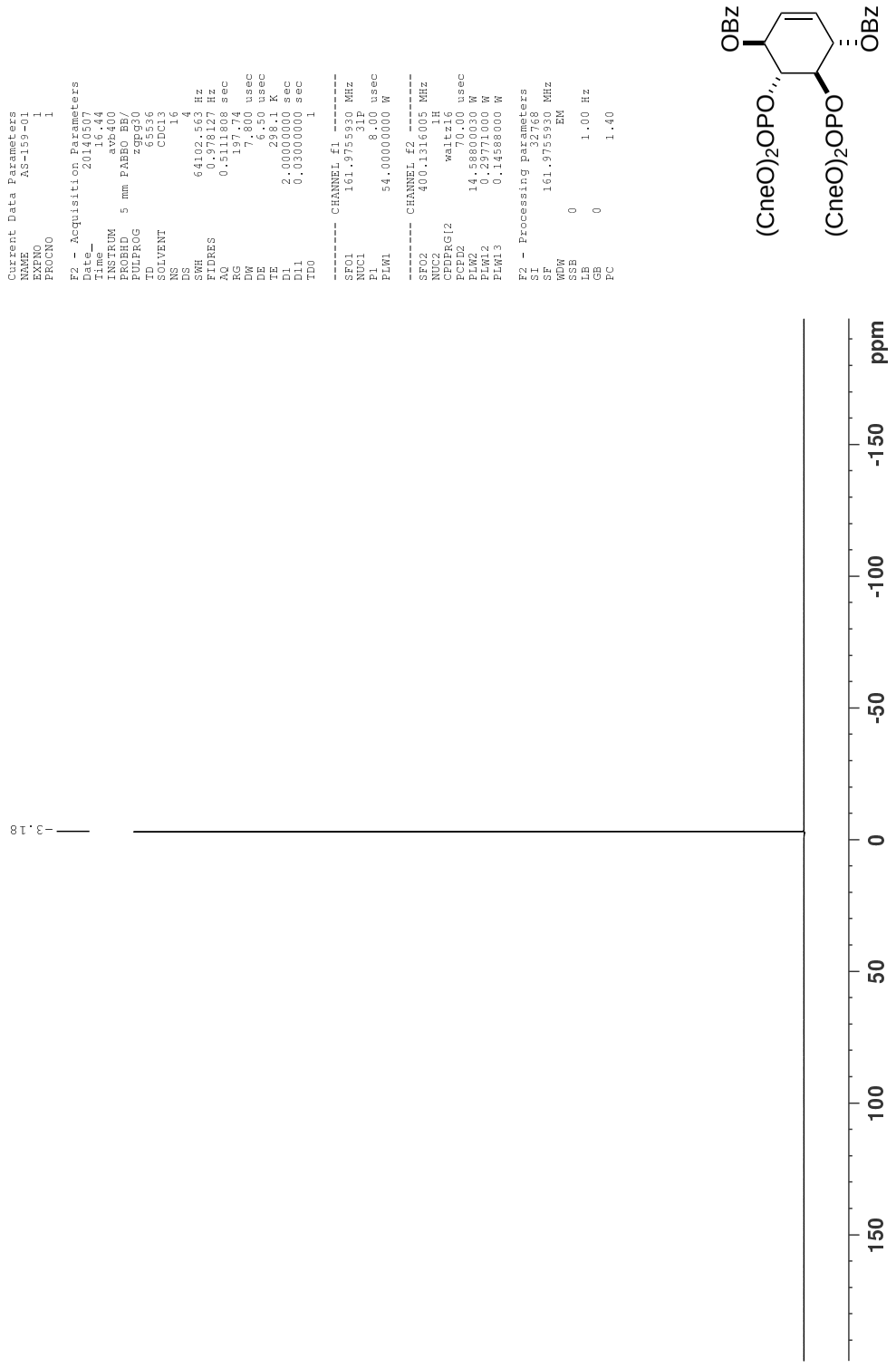
^{1}H NMR of (+)-95


Current Data Parameters
NAME AS-159-01
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140507
Time 16.46
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 30.76
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.13200007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.13001100 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
(CneO)2OPO
(CneO)2OPO
OBz
ppm
4.00
4.06
4.04
4.02
2.00
2.02
2.00
4.16
2.01
4.00

^{13}C NMR of (+)-95


OBz
OBz
(CneO)2OPO
(CneO)2OPO
19.14
19.22
19.43
19.51
62.56
62.61
63.01
63.07
72.15
77.62
77.67
77.73
116.31
116.80
127.13
128.86
129.06
129.97
134.02
165.55
ppm
0
20
40
60
80
100
120
140
160
180
200

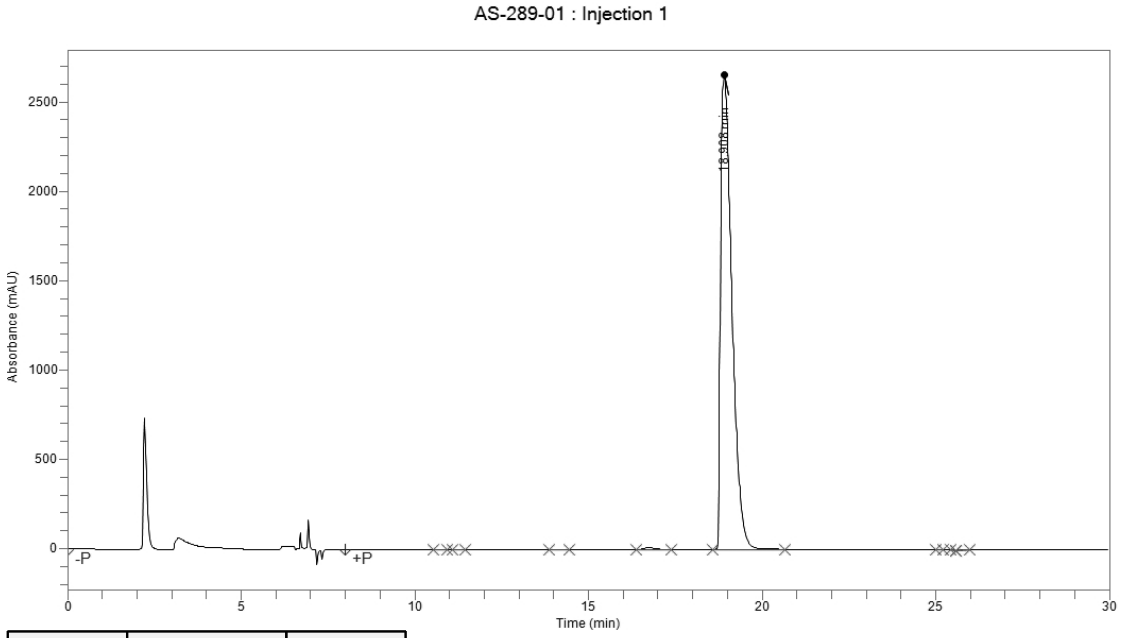
^{31}P NMR of (+)-95


Current Data Parameters
NAME AS-159-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140507
Time_ 16.44
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 64102.563 Hz
FIDRES 0.978127 Hz
AQ 0.5111808 sec
RG 197.74
DW 7.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 161.9755930 MHz
NUC1 31P
P1 8.00 usec
PLW1 54.00000000 W
CHANNEL f2
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 14.58800030 W
PLW12 0.29771000 W
PLW13 0.14588000 W
F2 - Processing parameters
SI 32768
SF 161.9755930 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OBz
OBz
(CneO)2OPO
(CneO)2OPO
-3.18
150
100
50
0
-50
-100
-150
ppm

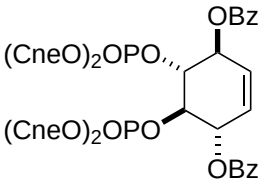
HPLC of (+)-95

AS-289-01

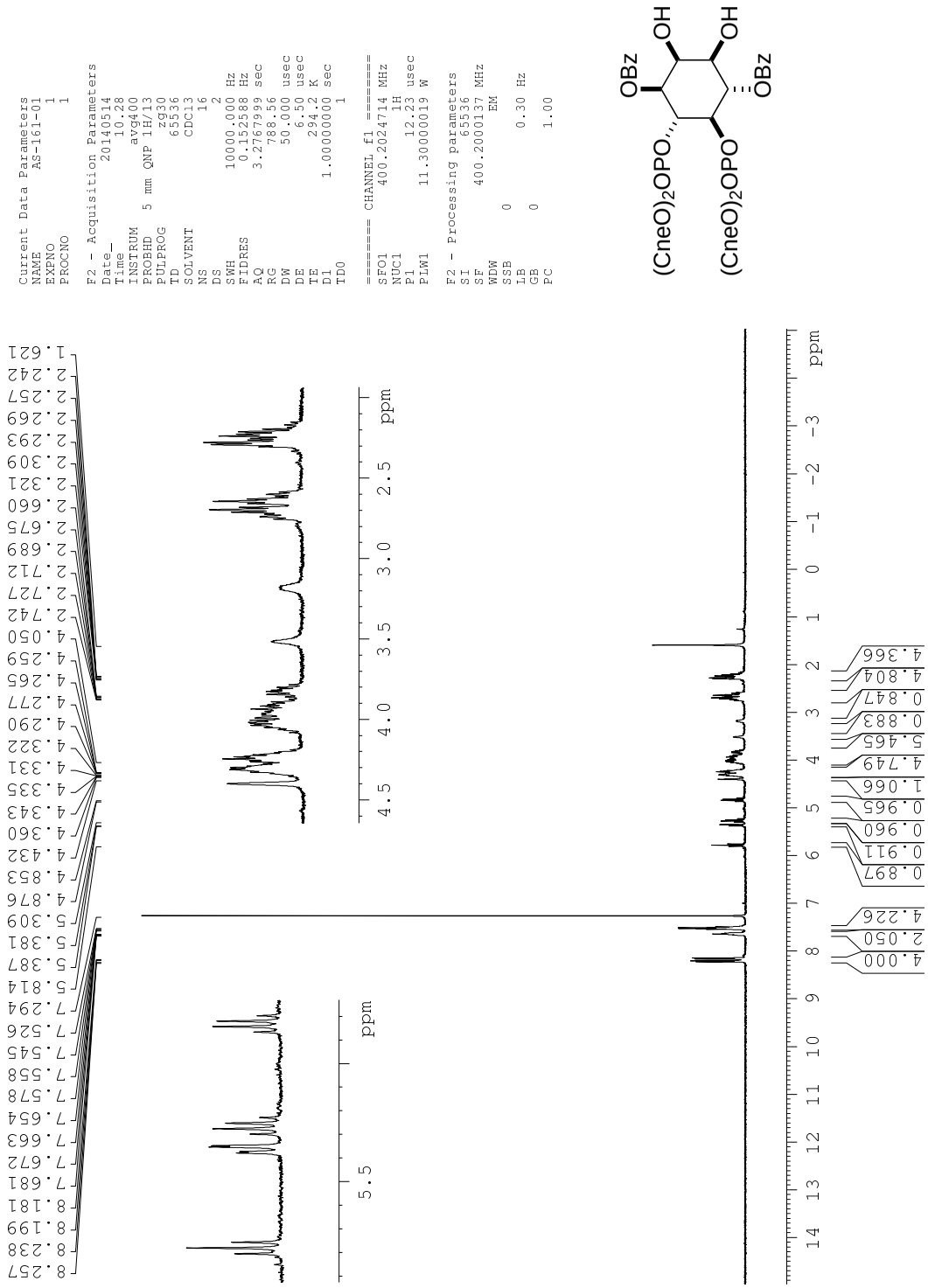
Sample Name	AS-289-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity	Acquisition Date/Time	12/10/2014 12:19 pm
Batch Group/Name	Alex/Normal Phase Purity - Copy 12-10-2014 13-12-15	Batch Description	Normal Phase silica column



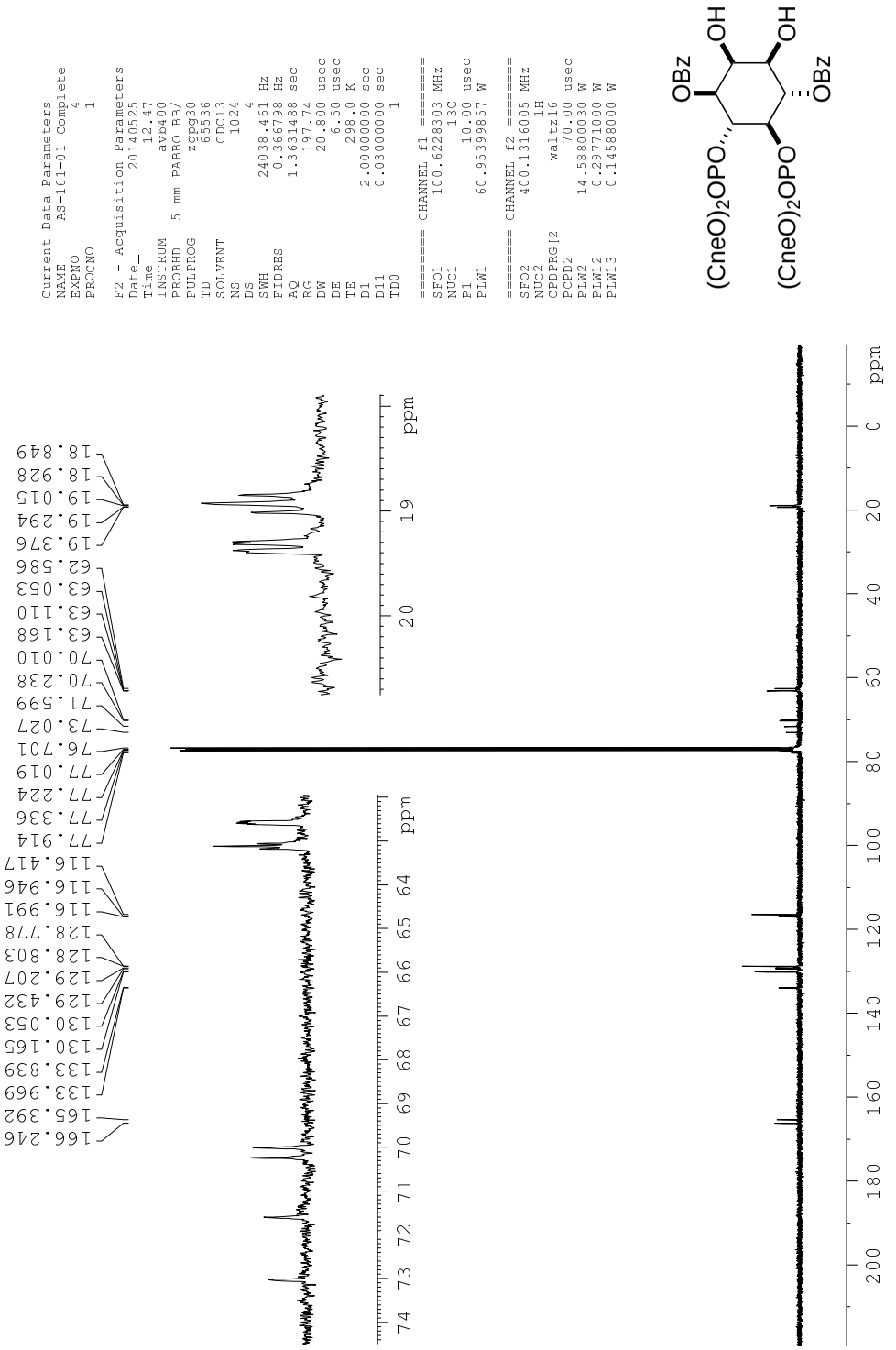
Time	Area	Area %
10.701	10035	0.02
11.260	7165.4	0.01
14.161	28295	0.05
16.743	232441	0.38
18.908	60947960	99.46
25.076	5797.6	0.01
25.455	7214.8	0.01
25.638	4061.7	0.01
25.861	37079	0.06
Total	61280050	100.00



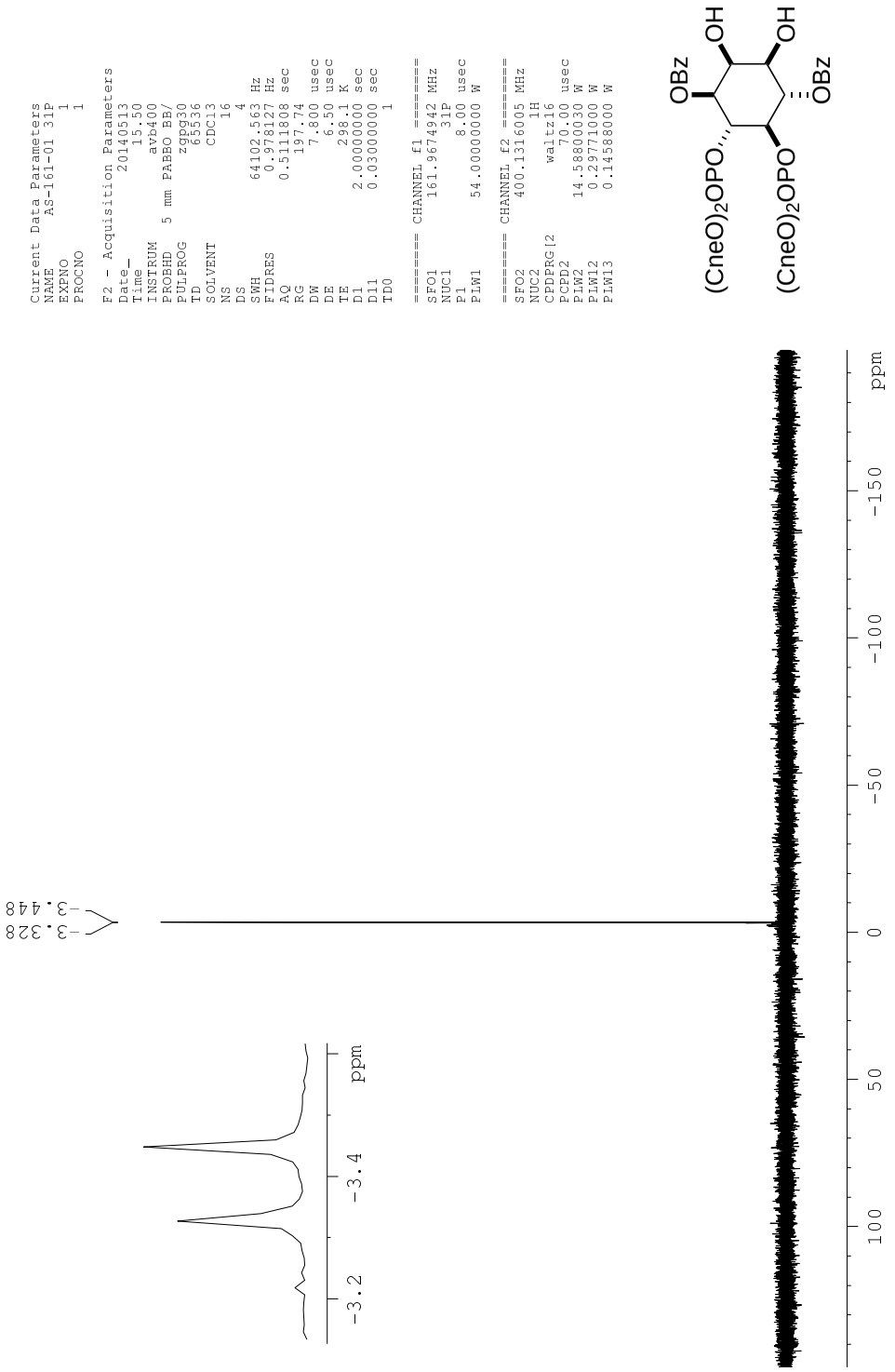
^{1}H NMR of (+)-96


Current Data Parameters
NAME AS-161-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140514
Time 10.28
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 788.56
DW 50.000 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000137 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
OH
OH
OBz
(CneO)2OPO
(CneO)2OPO
8.257
8.238
8.199
8.181
7.681
7.672
7.663
7.654
7.578
7.558
7.545
7.526
7.294
5.814
5.387
5.381
5.309
4.876
4.853
4.432
4.360
4.343
4.335
4.331
4.322
4.290
4.277
4.265
4.259
4.050
2.742
2.727
2.712
2.689
2.675
2.660
2.321
2.309
2.293
2.269
2.257
2.242
1.621
ppm
5.5
4.5
4.0
3.5
3.0
2.5
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
4.000
2.050
4.226
0.897
0.911
0.960
0.965
1.066
4.749
5.465
0.883
0.847
4.804
4.366

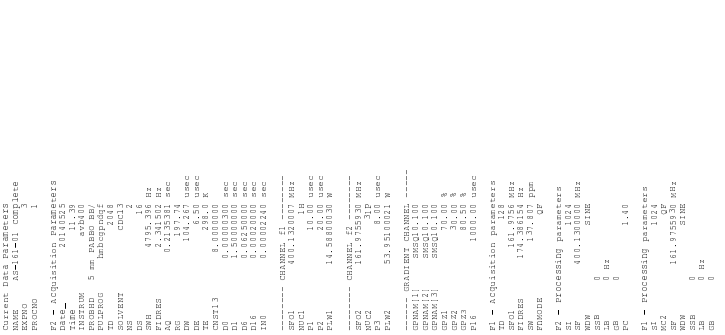
^{13}C NMR of (+)-96

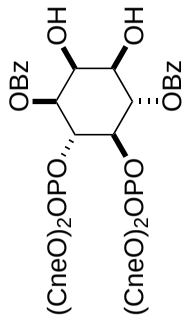

Current Data Parameters
NAME AS-161-01 Compiete
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140525
Time_ 12.47
INSTRUM av b400
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.36631488 sec
RG 197.74
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228303 MHz
NUC1 13C
P1 10.00 usec
PLW1 60.95399857 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 14.58800030 W
PLW12 0.29771000 W
PLW13 0.14588000 W
OBz
OH
OH
OBz
(CneO)2OPO
(CneO)2OPO
166.246
165.392
133.969
133.839
130.165
130.053
129.432
129.207
128.803
128.778
116.991
116.946
116.417
77.914
77.336
77.224
77.019
76.701
73.027
71.599
70.238
70.010
63.168
63.110
63.053
62.586
19.376
19.294
19.015
18.928
18.849
ppm
ppm
ppm

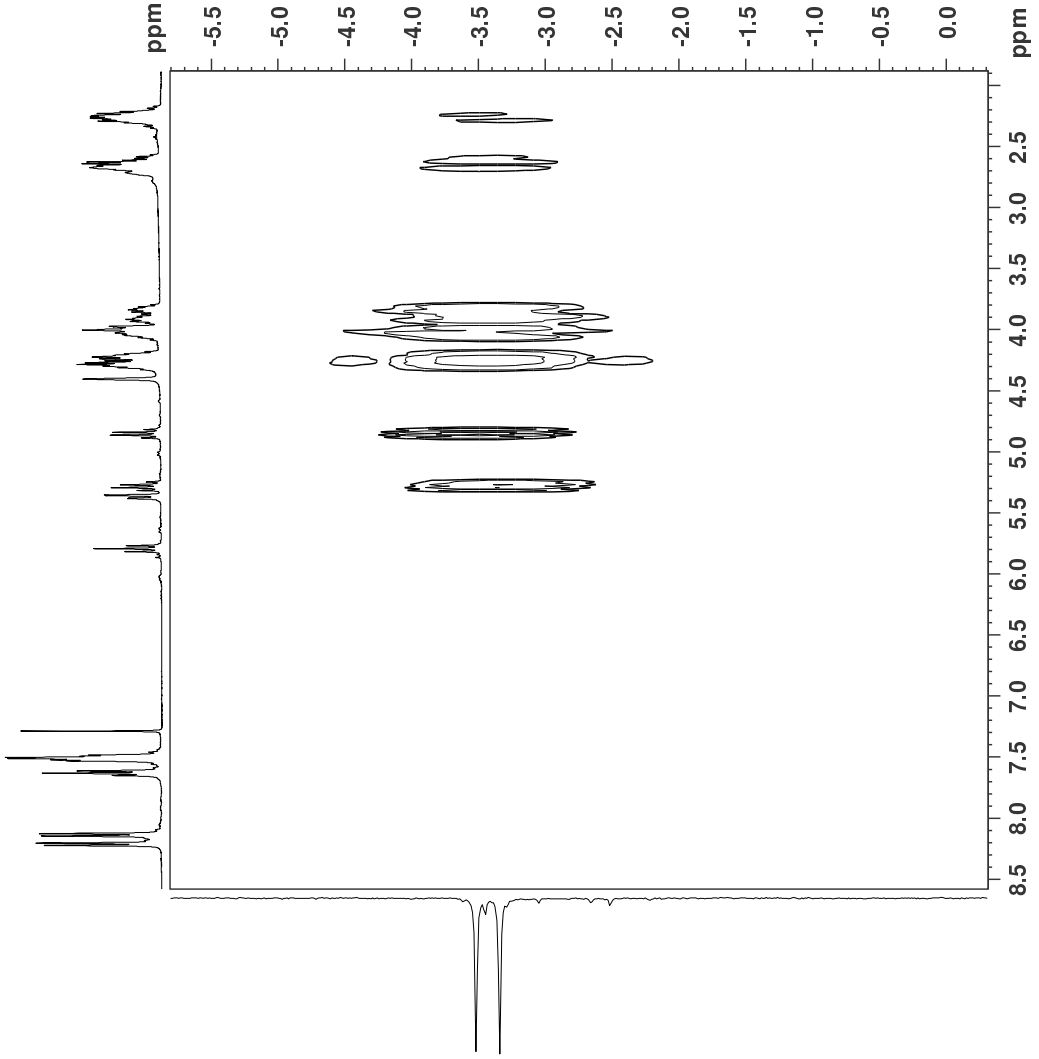
^{31}P NMR of (+)-96


Current Data Parameters
NAME AS-161-01 31P
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140513
Time 15.50
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 64102.563 Hz
FIDRES 0.978127 Hz
AQ 0.5111808 sec
RG 197.74
DW 7.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 161.96744942 MHz
NUC1 31P
P1 8.00 usec
PLW1 54.00000000 W
======== CHANNEL f2 ========
SFO2 400.13160005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 14.58800030 W
PLW12 0.29771000 W
PLW13 0.14588000 W
OBz
OH
OH
OBz
(CneO)2OPO
(CneO)2OPO
-3.328
-3.448
-3.2
-3.4
ppm
100
50
0
-50
-100
-150
ppm

^{1}H-^{31}P HMBC NMR of (+)-96



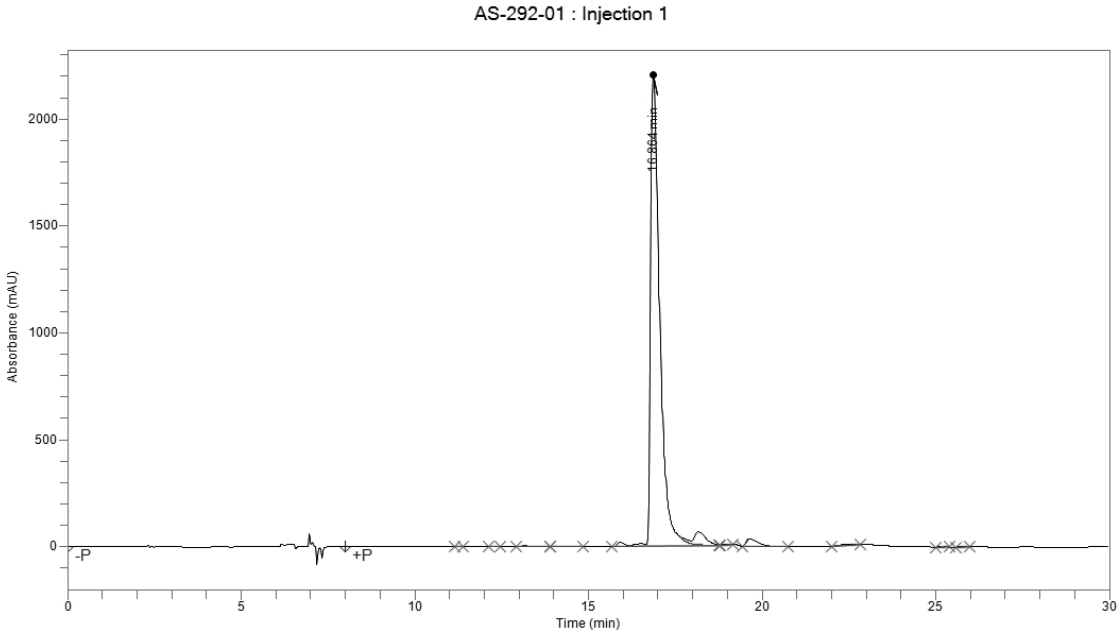


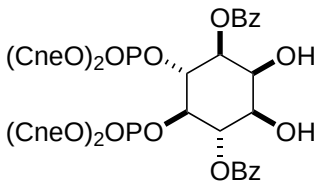


HPLC of (+)-96

AS-292-01

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



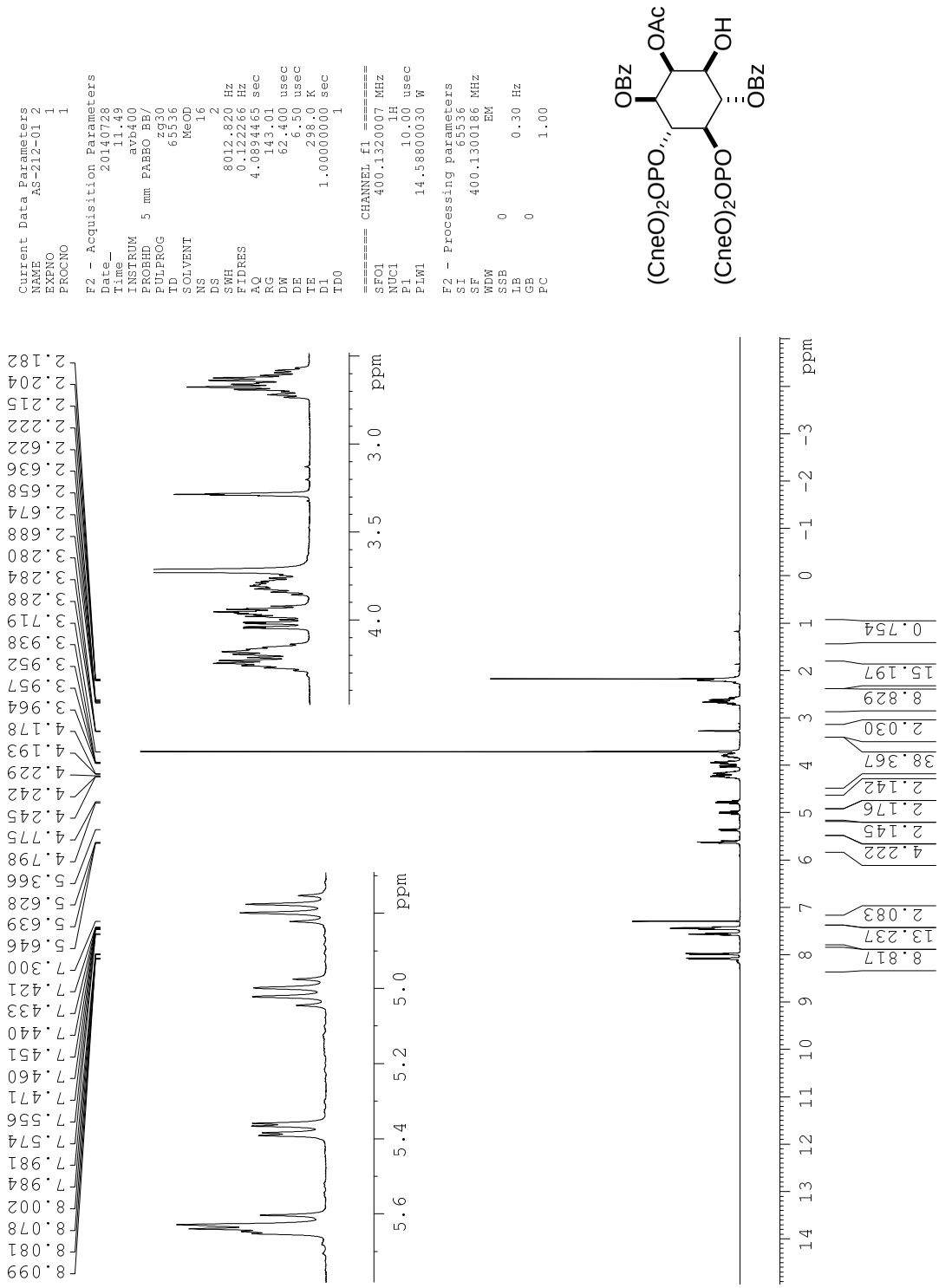


HPLC of (+)-96 (cont.)

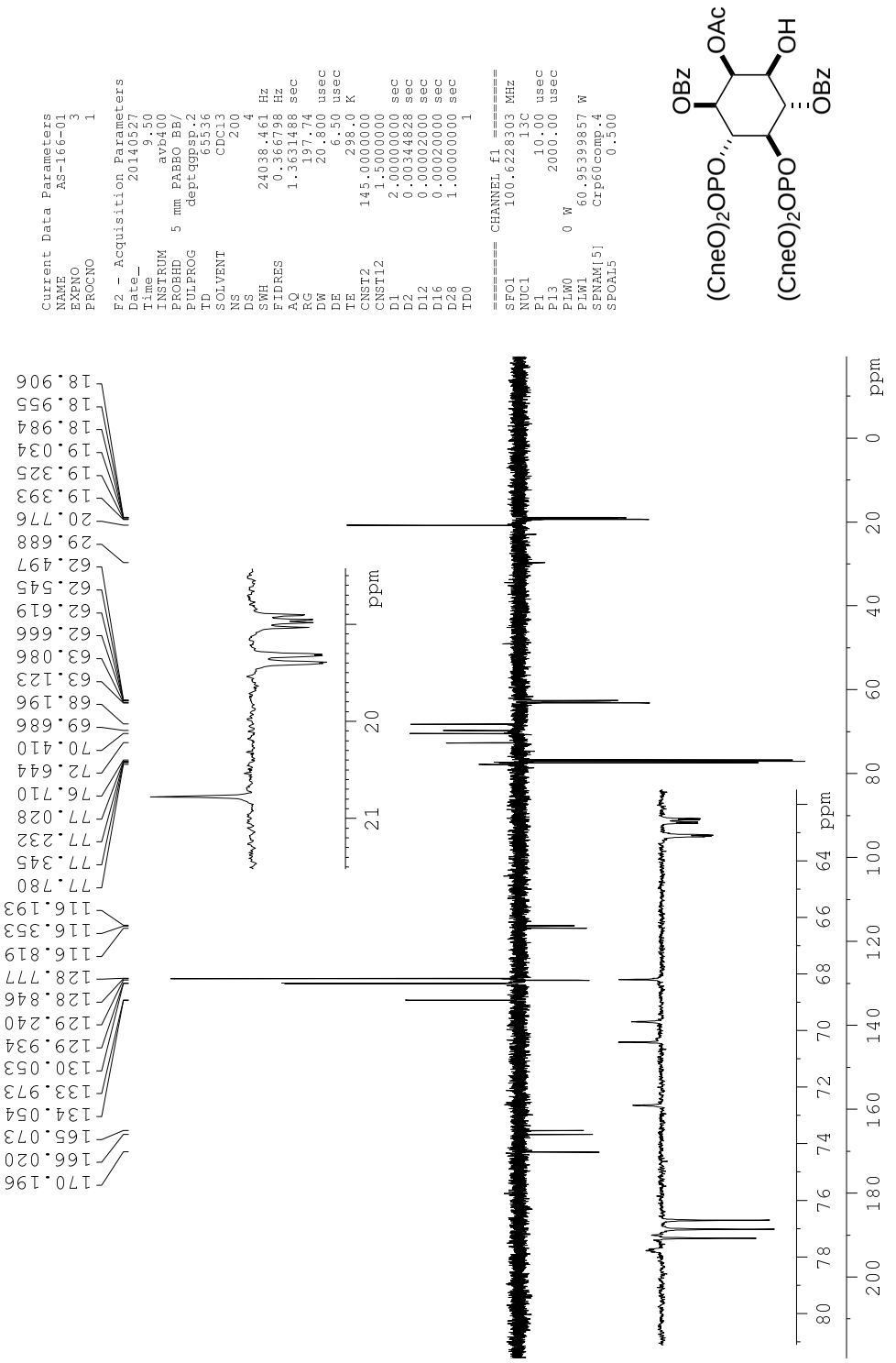
AS-292-01

Time	Area	Area %
11.266	2805	0.01
12.267	7594.3	0.02
13.148	94380	0.21
13.608	29059	0.07
14.061	16774	0.04
14.452	57552	0.13
15.912	306114	0.69
16.521	266907	0.61
16.864	40609537	92.19
18.172	1540549	3.50
18.956	28034	0.06
19.647	912151	2.07
22.472	132833	0.30
25.080	7302.8	0.02
25.308	3055.9	0.01
25.649	9296	0.02
25.739	3921.4	0.01
25.840	23018	0.05
Total	44050883.1	100.00

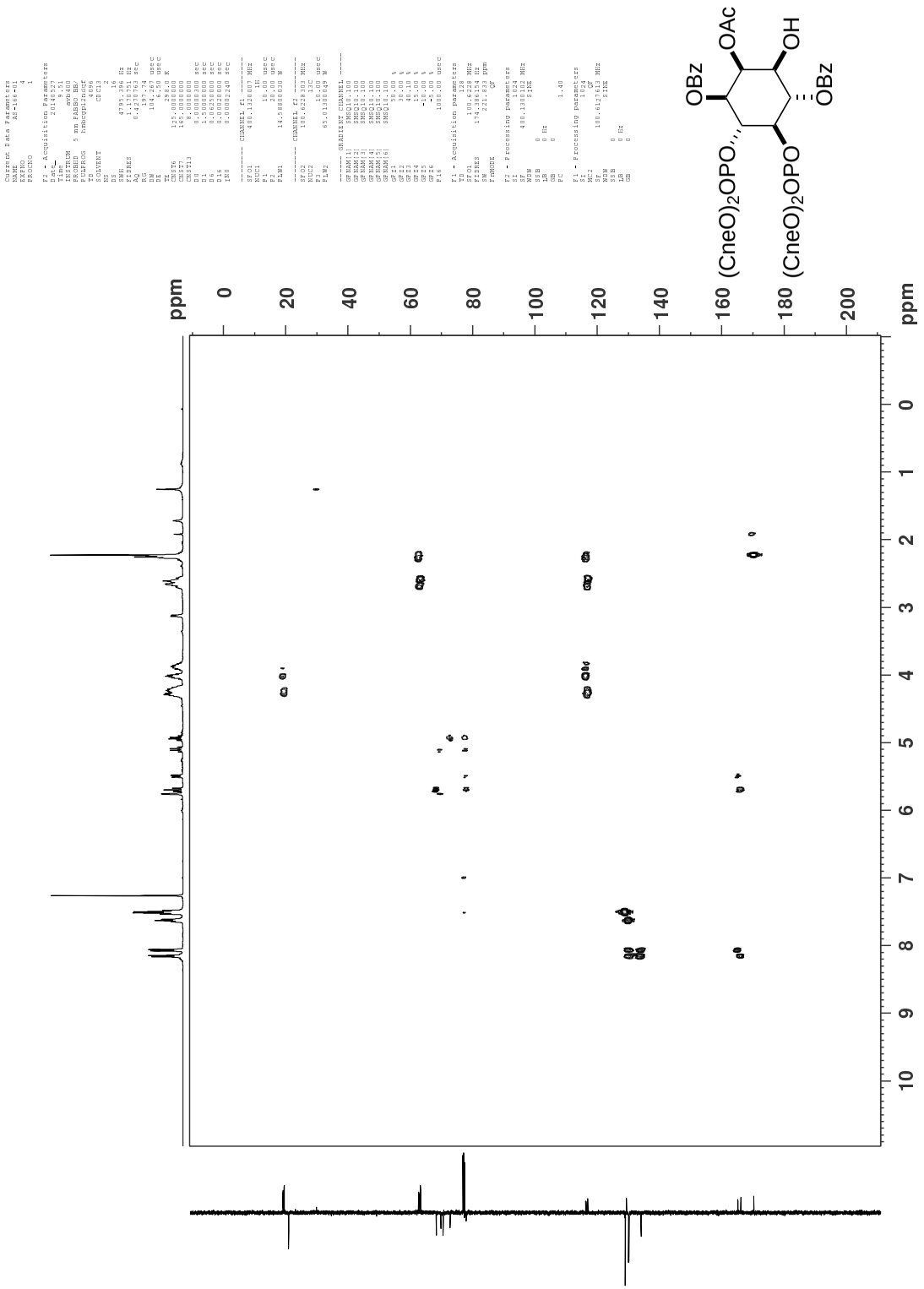
^{1}H NMR of (+)-97


Current Data Parameters
NAME AS-212-01 2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140728
Time 11.49
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 143.01
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1320007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.1300186 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
OAc
OH
OBz
(CneO)2OPO
(CneO)2OPO
8.817
13.237
2.083
4.222
2.145
2.176
2.142
38.367
2.030
8.829
15.197
0.754
ppm

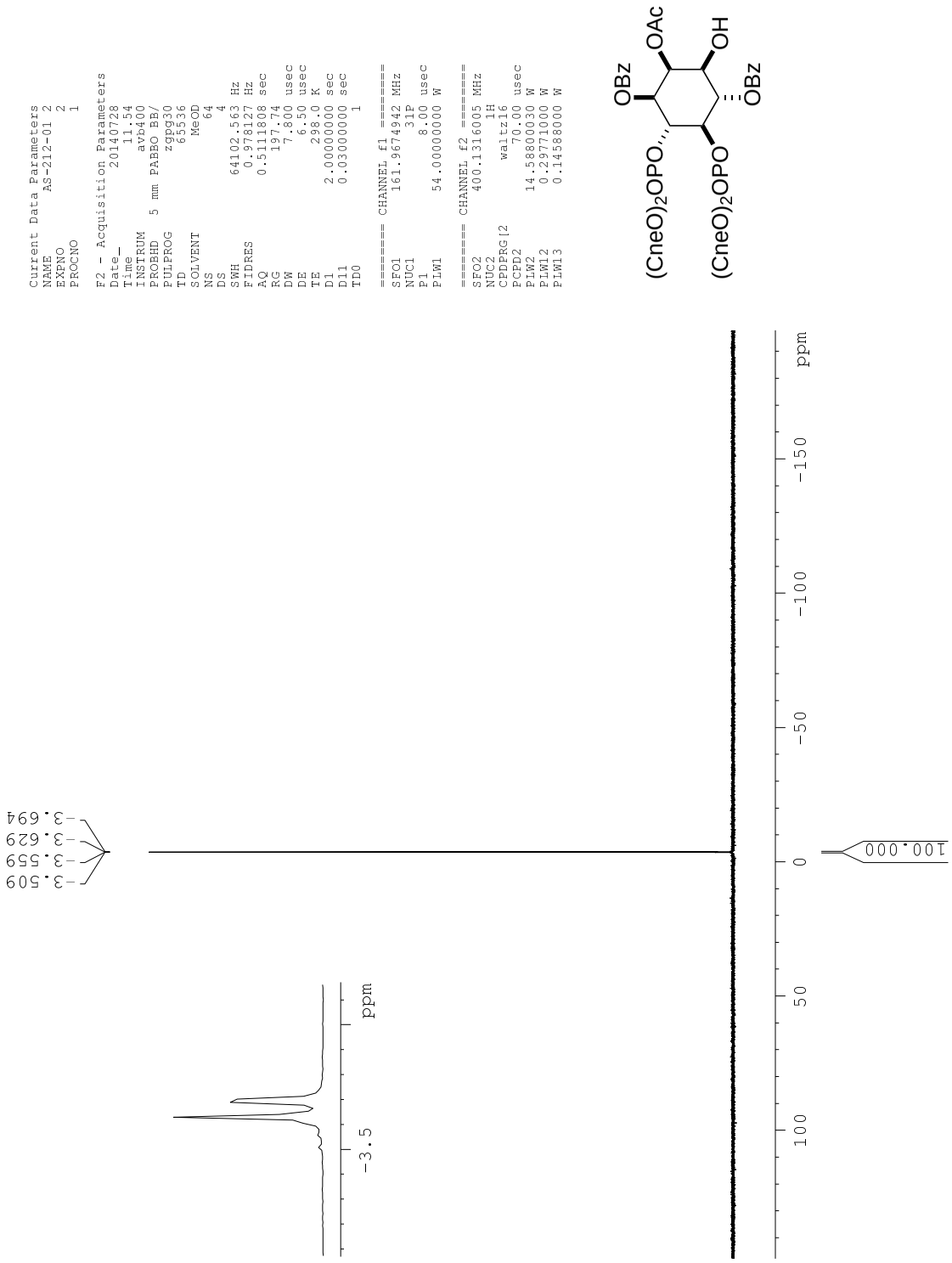
^{13}C NMR of (+)-97


Current Data Parameters
NAME AS-166-01
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140527
Time_ 9.50
INSTRUM av b400
PROBHD 5 mm PABBO BB/
PULPROG deptqgpsp.2
TD 65536
SOLVENT CDCl3
NS 200
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 197.74
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
CNST2 145.0000000
CNST12 1.5000000
D1 2.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
D16 0.00020000 sec
D28 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228303 MHz
NUC1 13C
P1 10.00 usec
P13 2000.00 usec
PLW0 0 W
PLW1 60.95399857 W
SPNAM[5] Crp60comp.4
SPOAL5 0.500
OBz
OAc
OH
OBz
(CneO)2OPO
(CneO)2OPO
18.906
18.955
18.984
19.034
19.325
19.393
20.776
29.688
62.497
62.545
62.619
62.666
63.086
63.123
68.196
69.686
70.410
72.644
76.710
77.028
77.232
77.345
77.780
116.193
116.353
116.819
128.777
128.846
129.240
129.934
130.053
133.973
134.054
165.073
166.020
170.196
ppm
21
20
ppm
ppm

^{1}H-^{13}C HMBC NMR of (+)-97



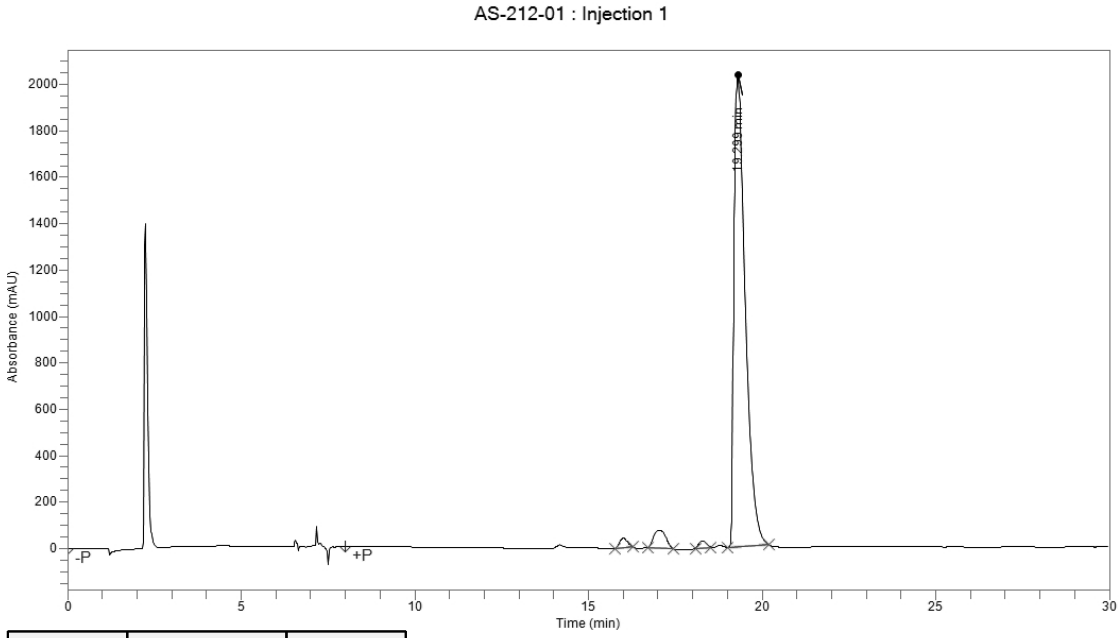
^{31}P NMR of (+)-97


Current Data Parameters
NAME AS-212-01 2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140728
Time_ 11.54
INSTRUM av b400
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 64
DS 4
SWH 64102.563 Hz
FIDRES 0.978127 Hz
AQ 0.5111808 sec
RG 197.74
DW 7.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 161.96749942 MHz
NUC1 31P
P1 8.00 usec
PLW1 54.00000000 W
======== CHANNEL f2 ========
SFO2 400.13160005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 14.58800030 W
PLW12 0.29771000 W
PLW13 0.14588000 W
OBz
OAc
OH
OBz
(CneO)2OPO
(CneO)2OPO
-3.509
-3.559
-3.629
-3.694
100.000
ppm
-3.5
ppm

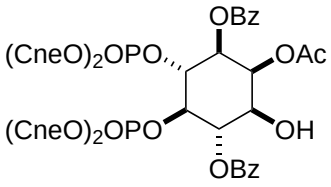
HPLC of (+)-97

AS-212-01

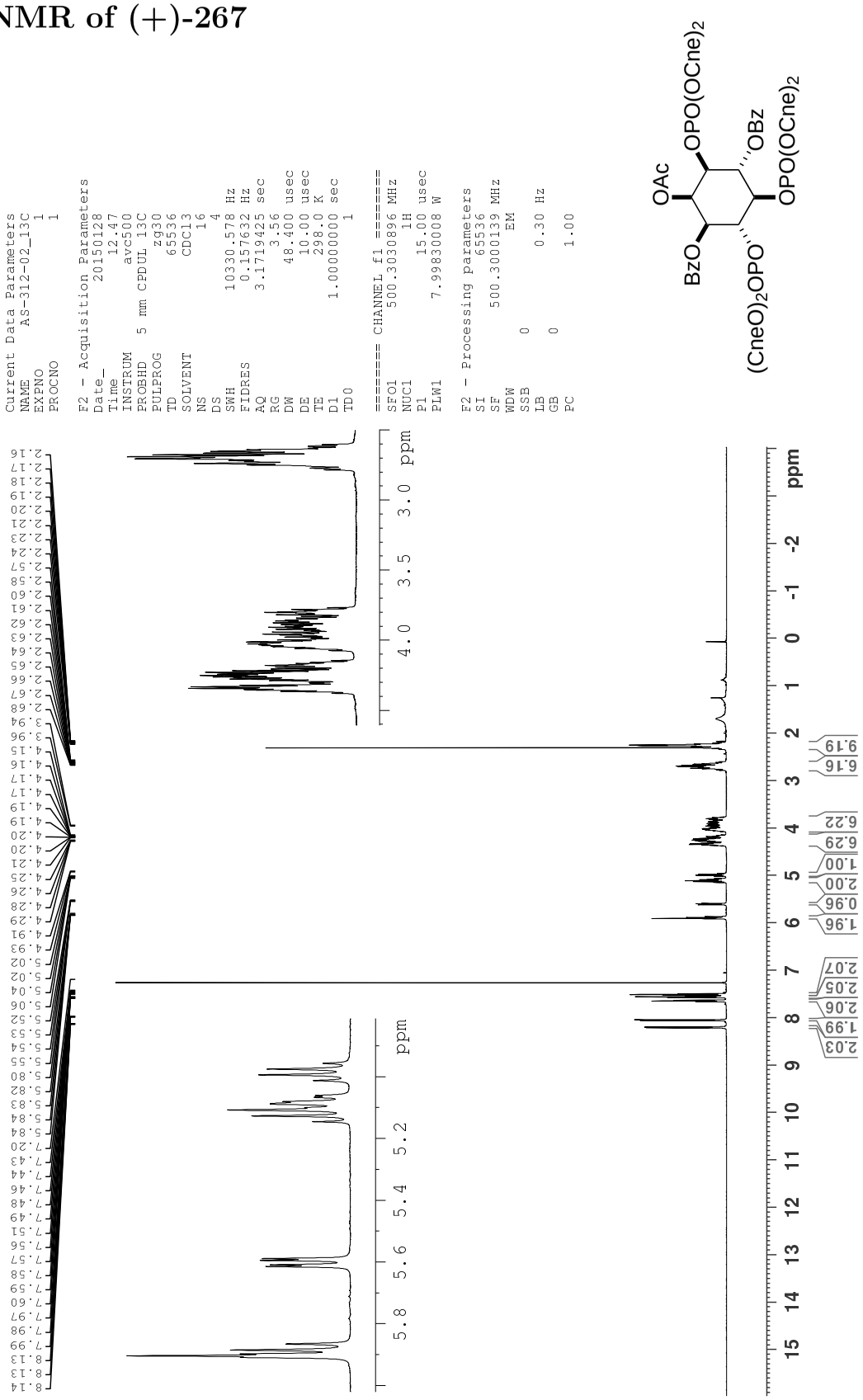
Sample Name	AS-212-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity	Acquisition Date/Time	12/11/2014 12:21 pm
Batch Group/Name	Alex/Normal Phase Purity - Copy 06-03-2016 11-38-03	Batch Description	Normal Phase silica column



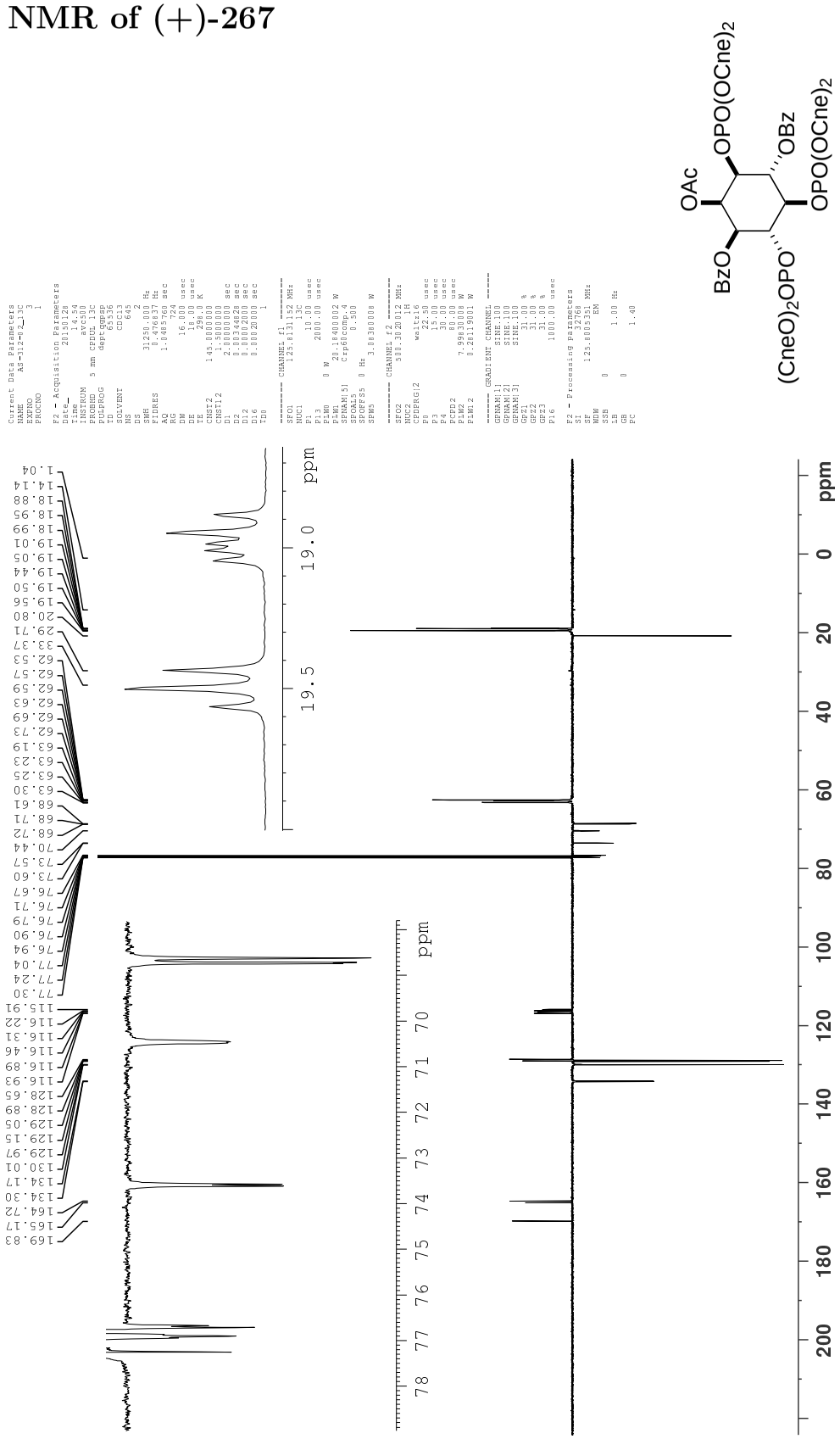
Time	Area	Area %
16.006	670829	1.36
17.055	1942938	3.94
18.276	428334	0.87
19.299	46226249	93.83
Total	49268352	100.00



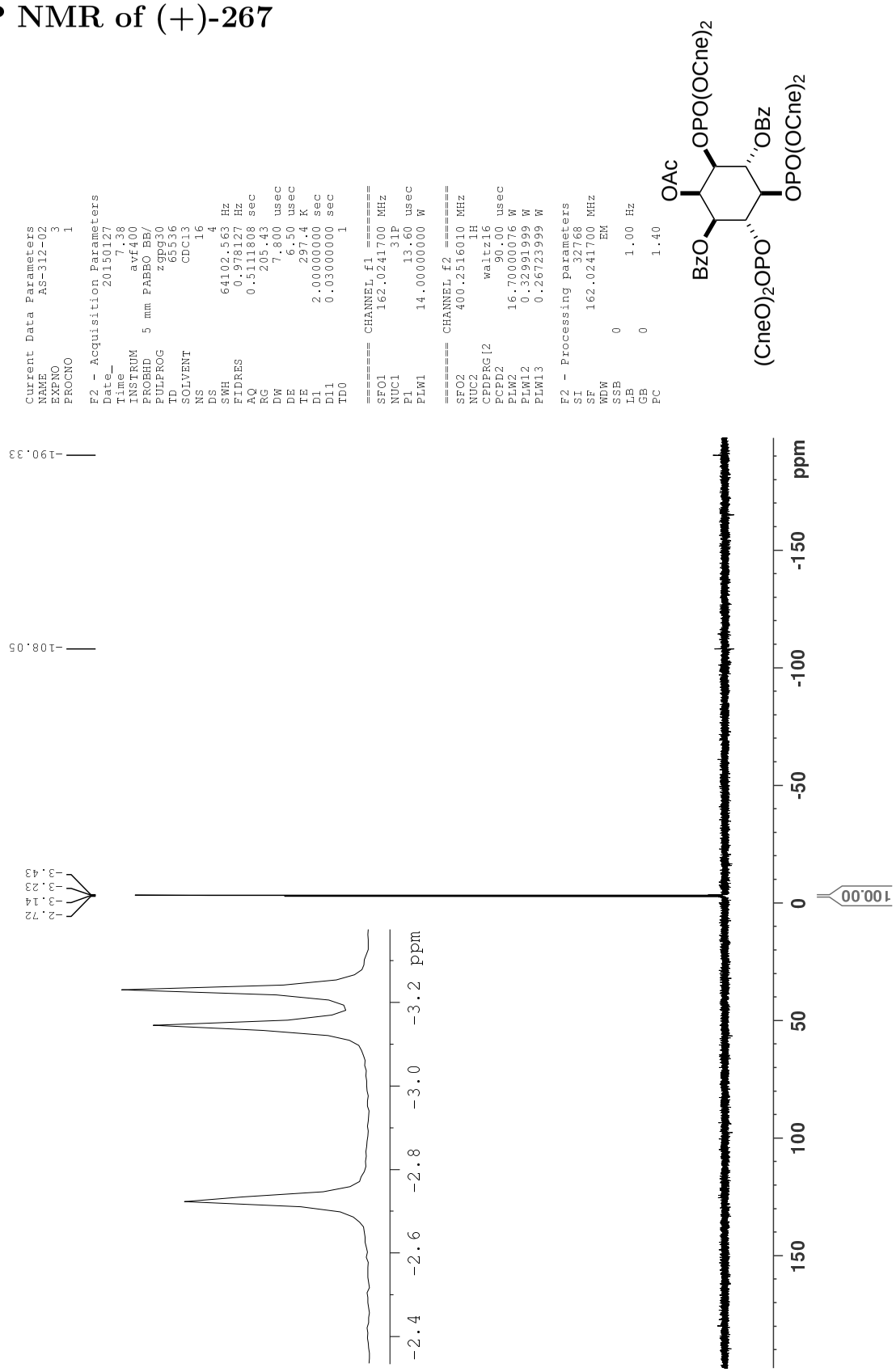
^{1}H NMR of (+)-267


OAc
OPO(OCne)2
OBz
BzO
(CneO)2OPO
OPO(OCne)2
Current Data Parameters
NAME AS-312-02_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150128
Time 12.47
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000139 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
9.19
6.16
6.22
6.29
1.00
2.00
0.96
1.96
2.07
2.05
2.06
1.99
2.03

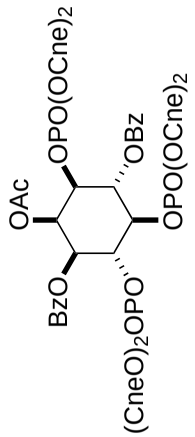
^{13}C NMR of (+)-267

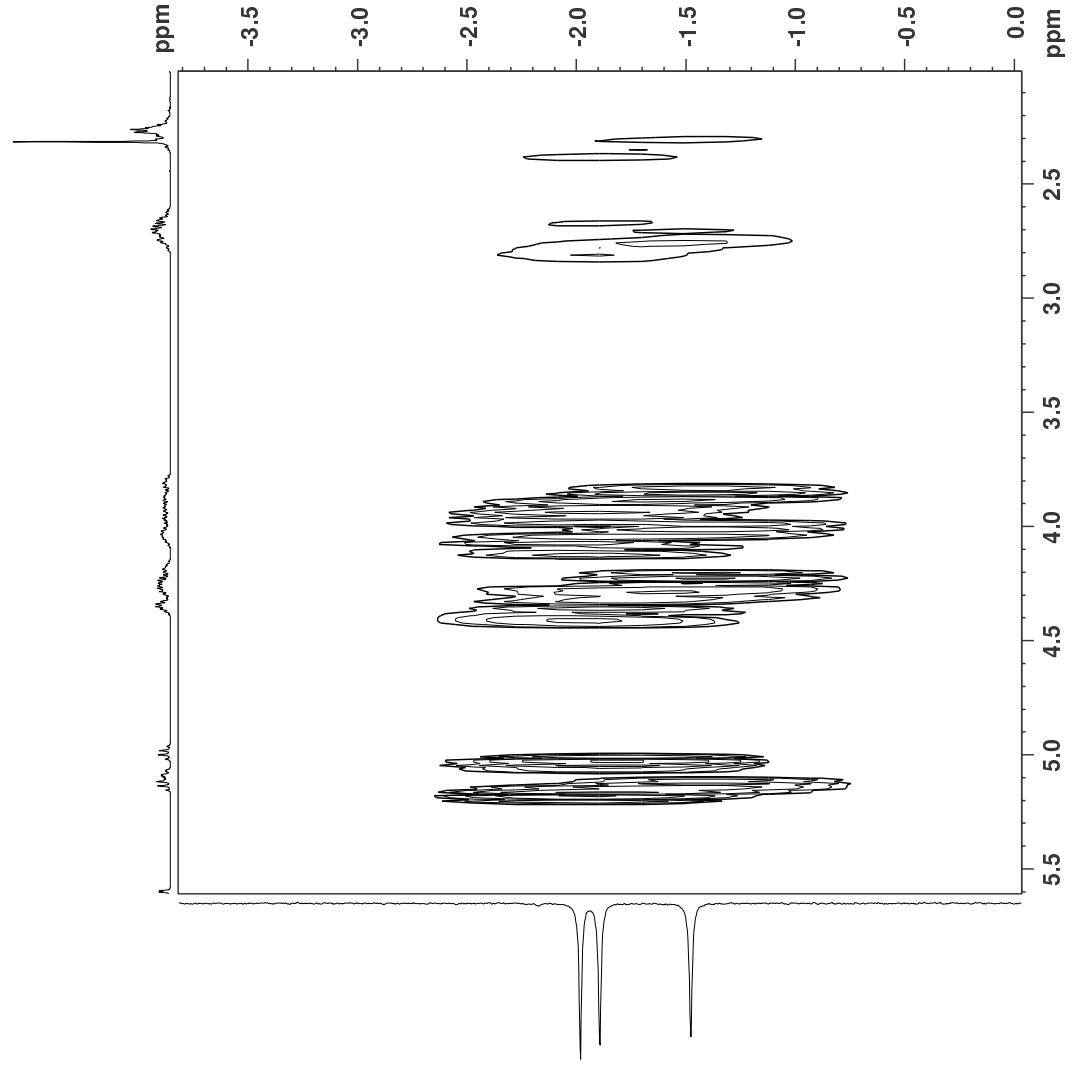


^{31}P NMR of (+)-267

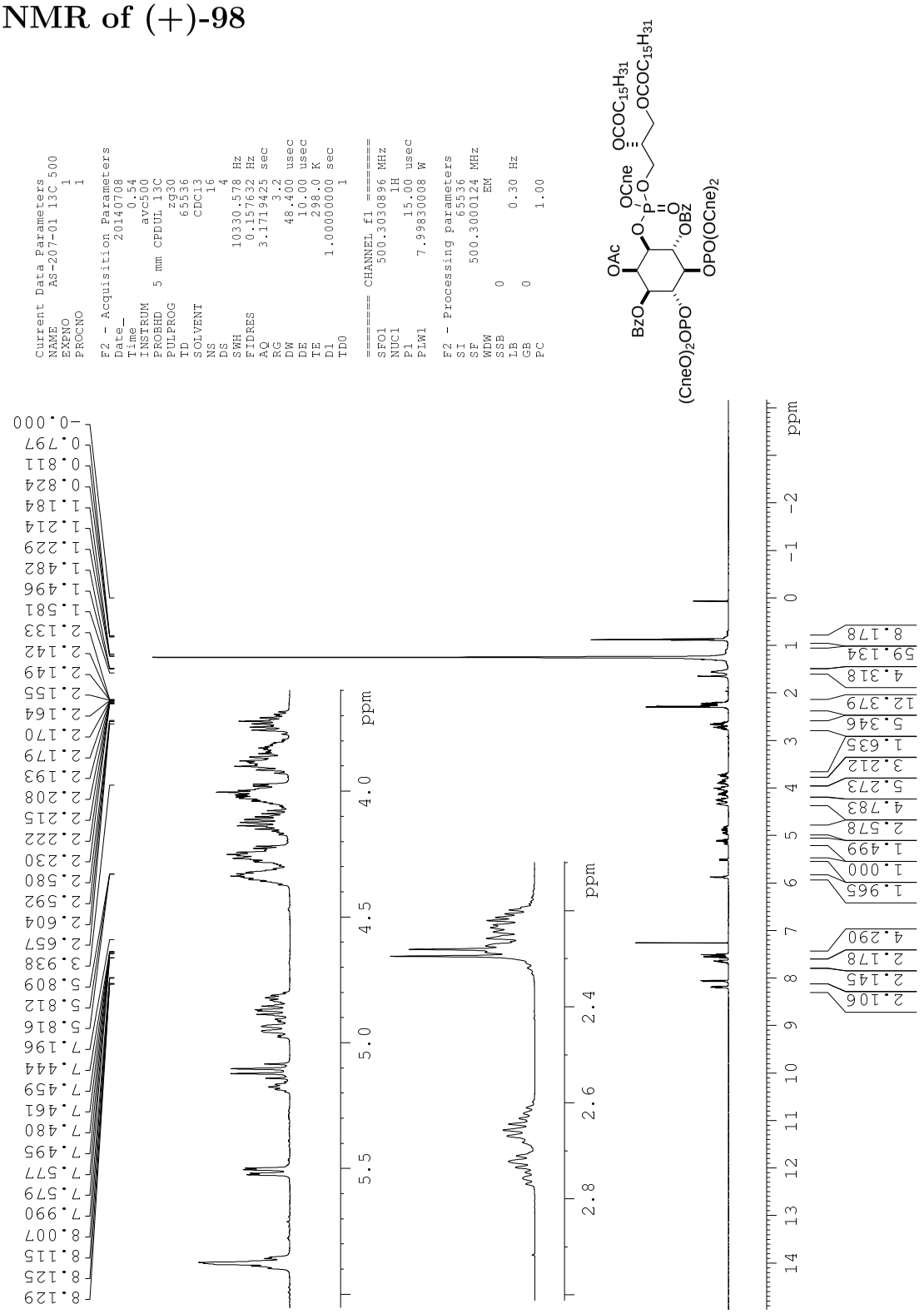


^{1}H-^{31}P HMBC NMR of (+)-267

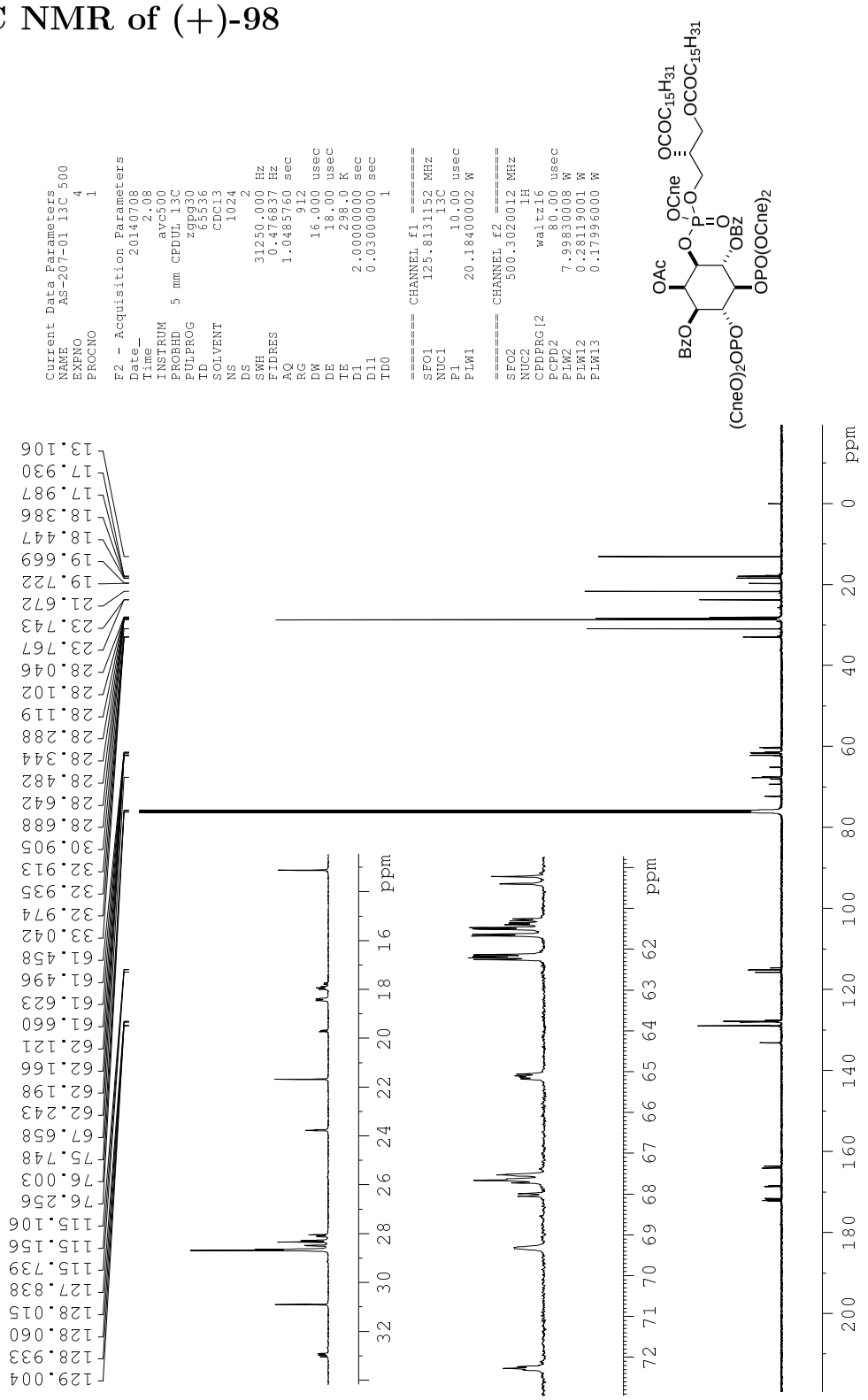




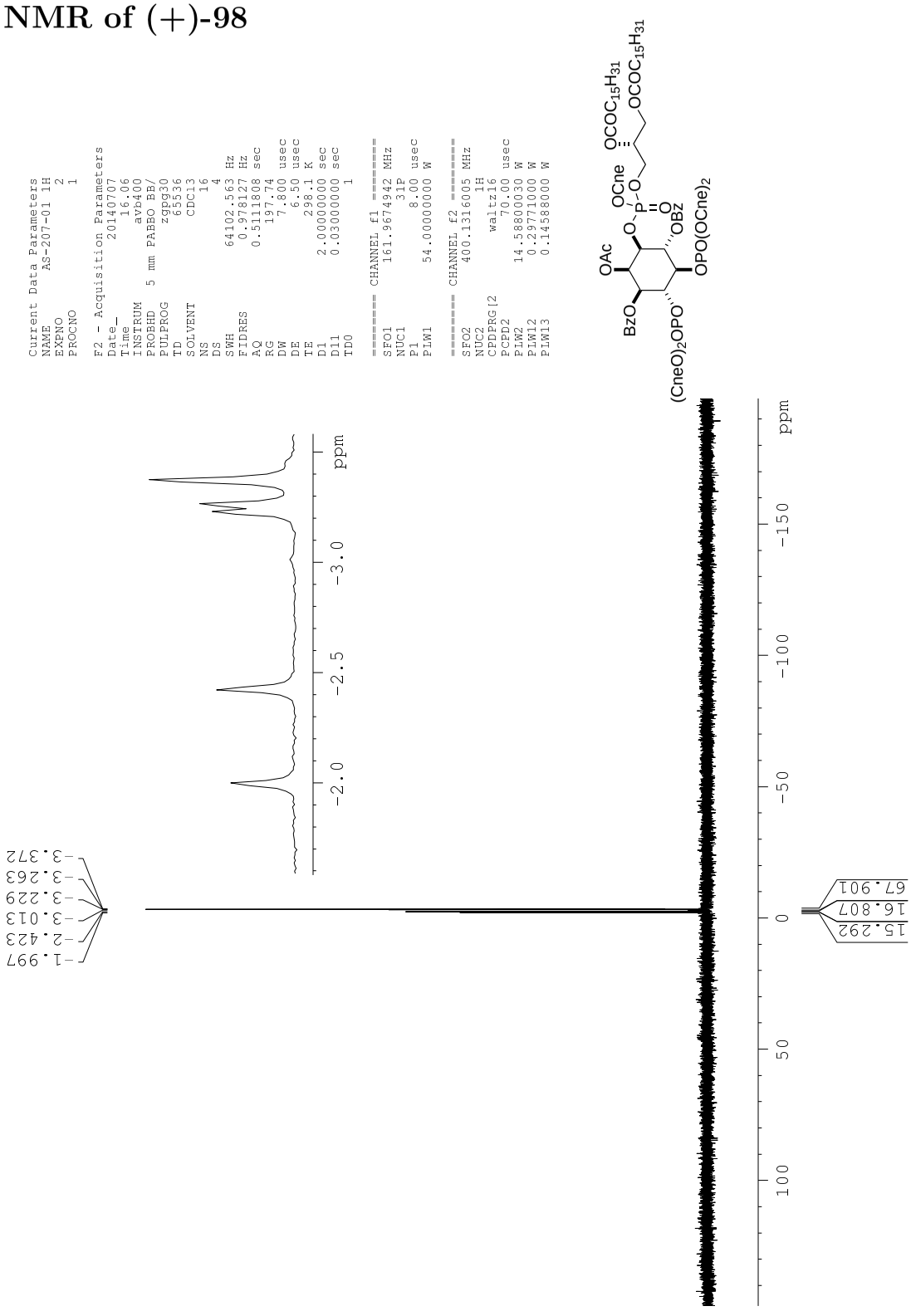
^{1}H NMR of (+)-98


Current Data Parameters
NAME AS-207-01 13C 500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140708
Time_ 0.54
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000124 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OAc
OCne
OCOC15H31
OCOC15H31
BzO
OBz
(CneO)2OPO
OPO(OCne)2
ppm

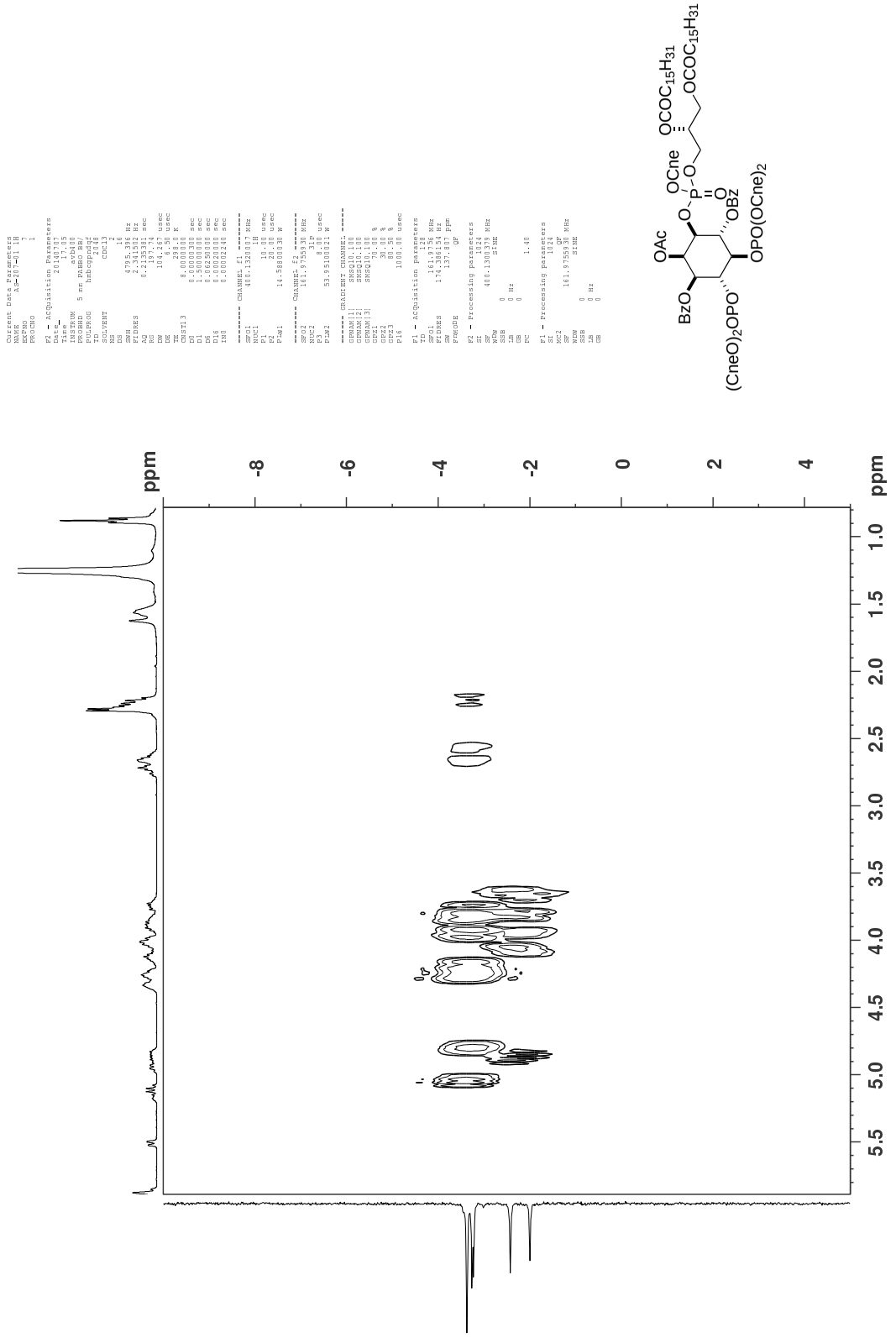
^{13}C NMR of (+)-98


Current Data Parameters
NAME AS-207-01 13C 500
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140708
Time 2.08
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.04857600 sec
RG 912
DW 16.000 usec
DE 18.00 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.81311520 MHz
NUC1 13C
P1 10.00 usec
PLW1 20.18400002 W
SFO2 500.30200120 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 7.99830008 W
PLW12 0.28119001 W
PLW13 0.17996000 W
OAc
BzO
OCne
OCOC15H31
OCOC15H31
OBz
OPO(OCne)2
(CneO)2OPO
ppm

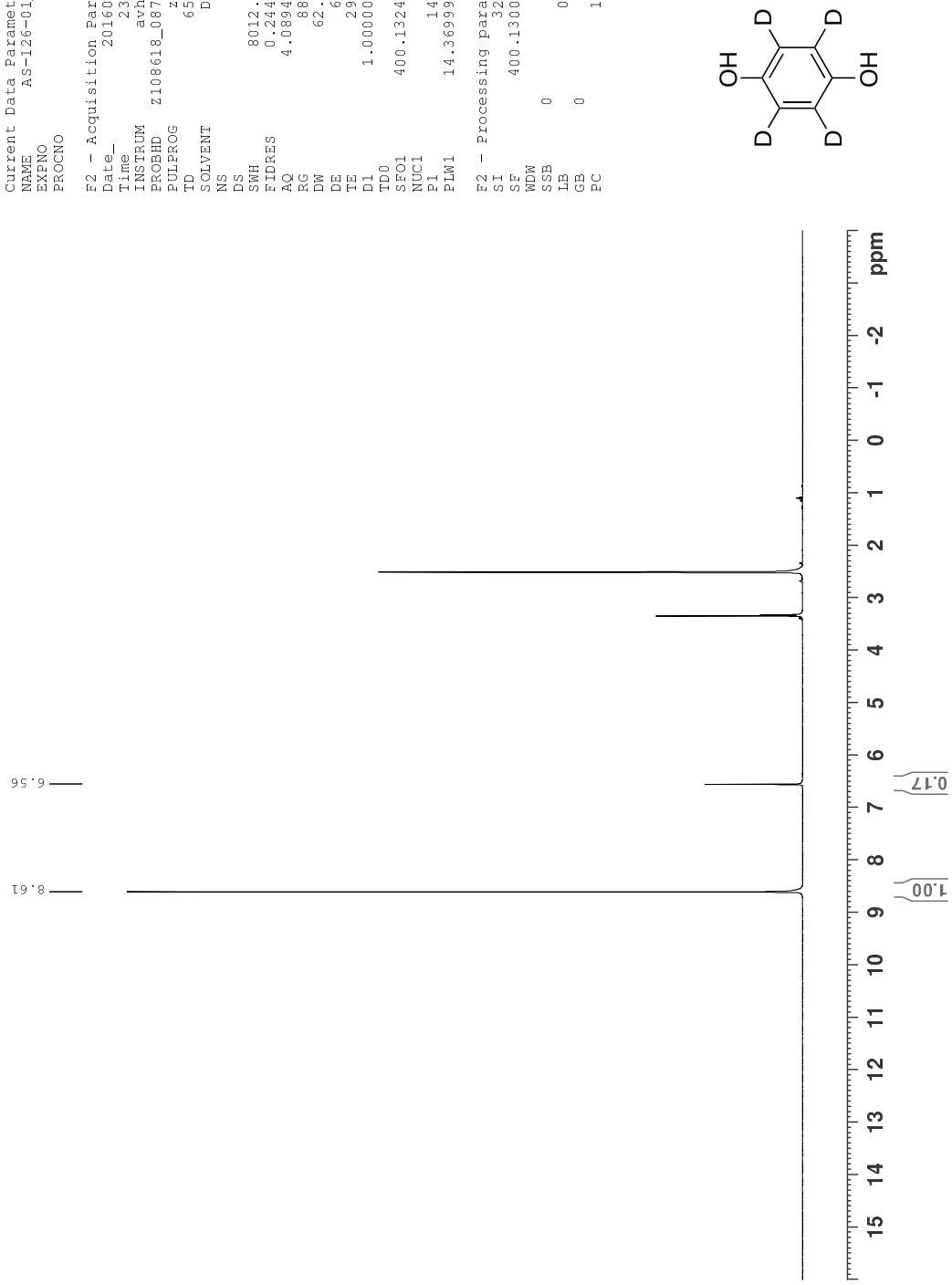
^{31}P NMR of (+)-98


Current Data Parameters
NAME AS-207-01 1H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140707
Time_ 16.06
INSTRUM av b400
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 16
DS 4
SWH 64102.563 Hz
FIDRES 0.978127 Hz
AQ 0.5111808 sec
RG 197.74
DW 7.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 161.9674942 MHz
NUC1 31P
P1 8.00 usec
PLW1 54.00000000 W
======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 14.58800030 W
PLW12 0.29771000 W
PLW13 0.14588000 W
OAc
OCne
OCOC15H31
OCOC15H31
BzO
OBz
(CneO)2OPO
OPO(OCne)2
-3.372
-3.263
-3.229
-3.013
-2.423
-1.997
15.292
16.807
67.901
ppm
-2.0
-2.5
-3.0
100
50
0
-50
-100
-150

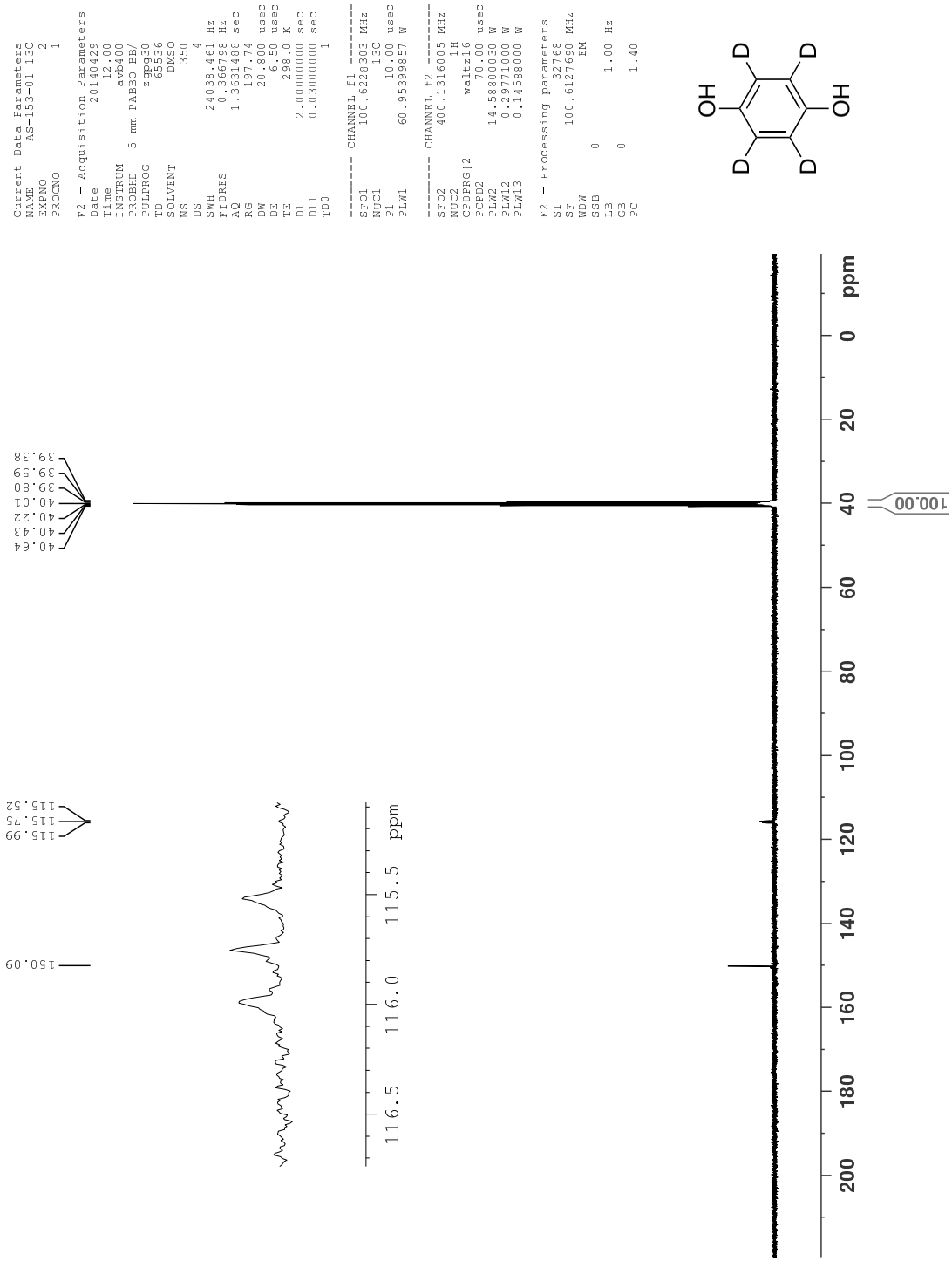
^{1}H-^{31}P HMBC NMR of (+)-98



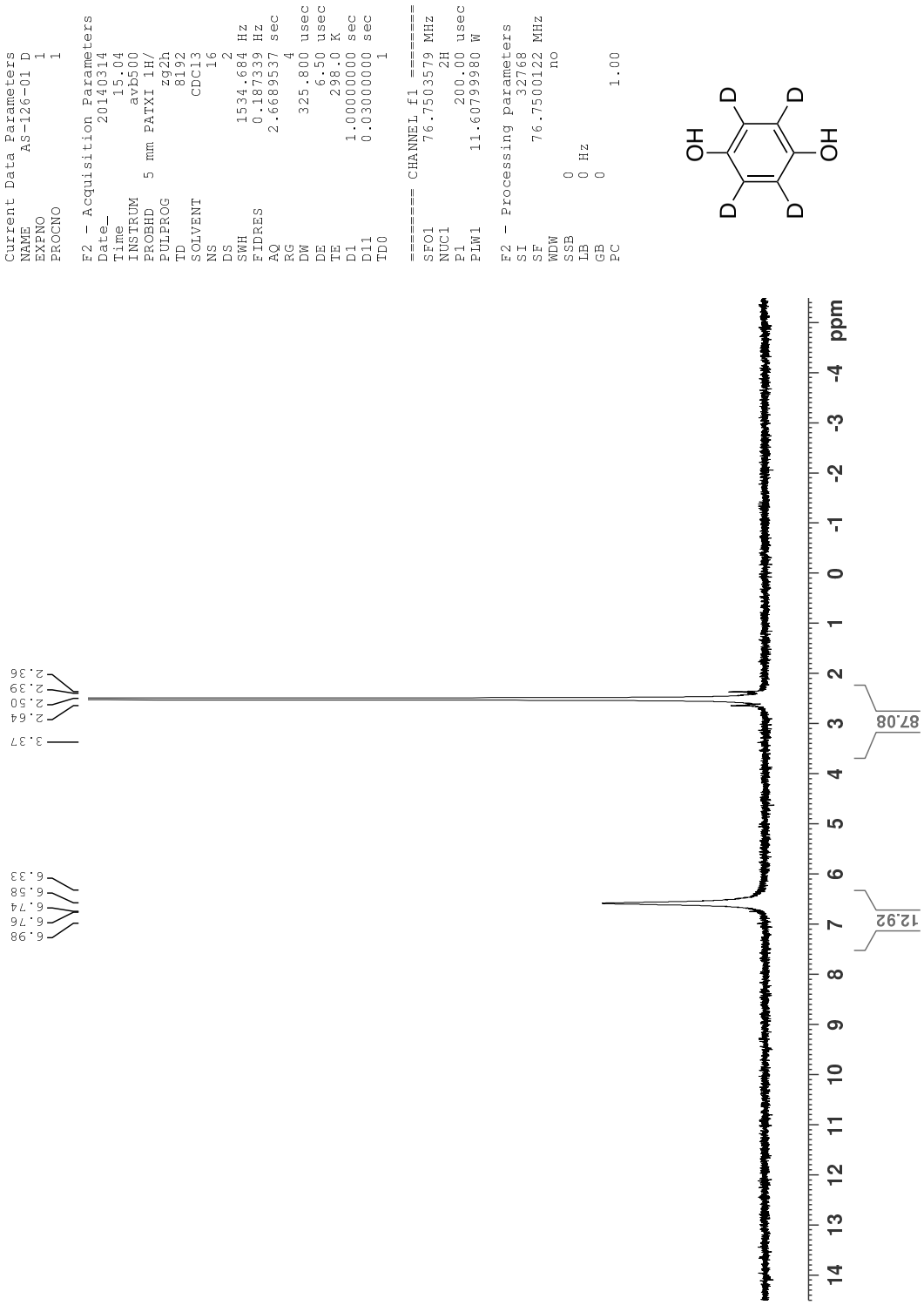
^{1}H NMR of 156


Current Data Parameters
NAME AS-126-01_1H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160418
Time 23.12 h
INSTRUM avh400
PROBHD z108618_0873 (
PULPROG zg60
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 88.17
DW 62.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324008 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.36999989 W
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
D
D
D
D
OH
6.56
8.61
0.17
1.00
ppm
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

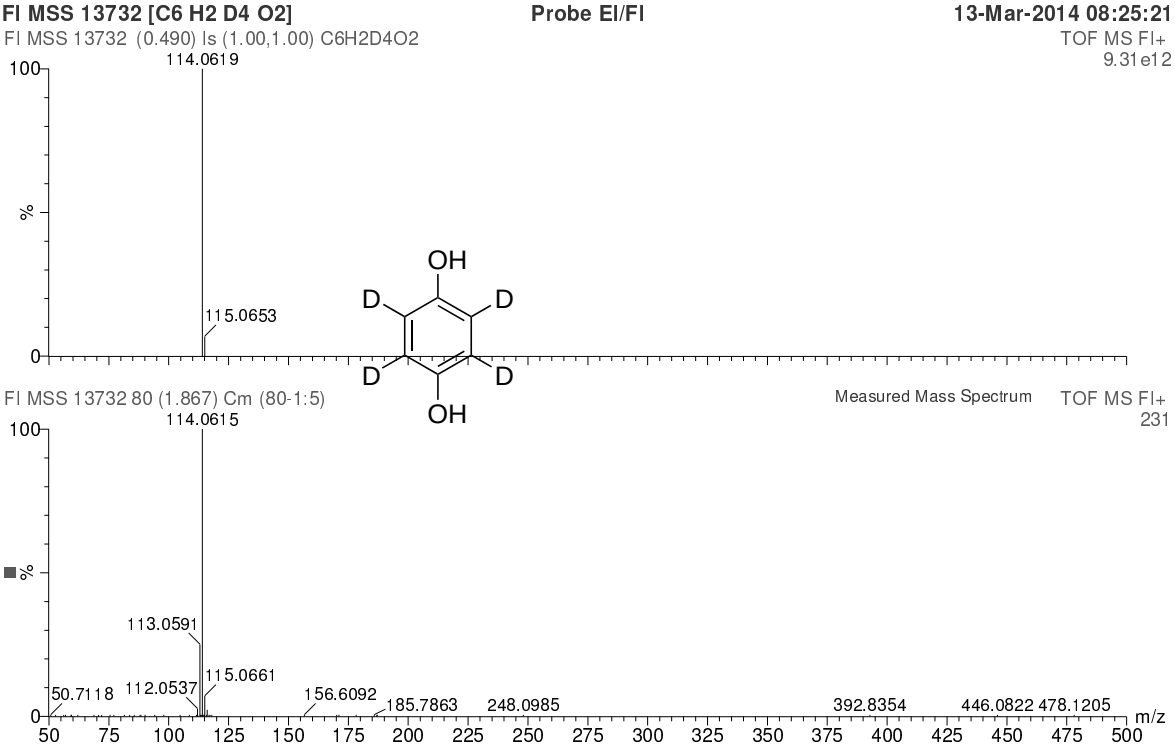
^{13}C NMR of 156



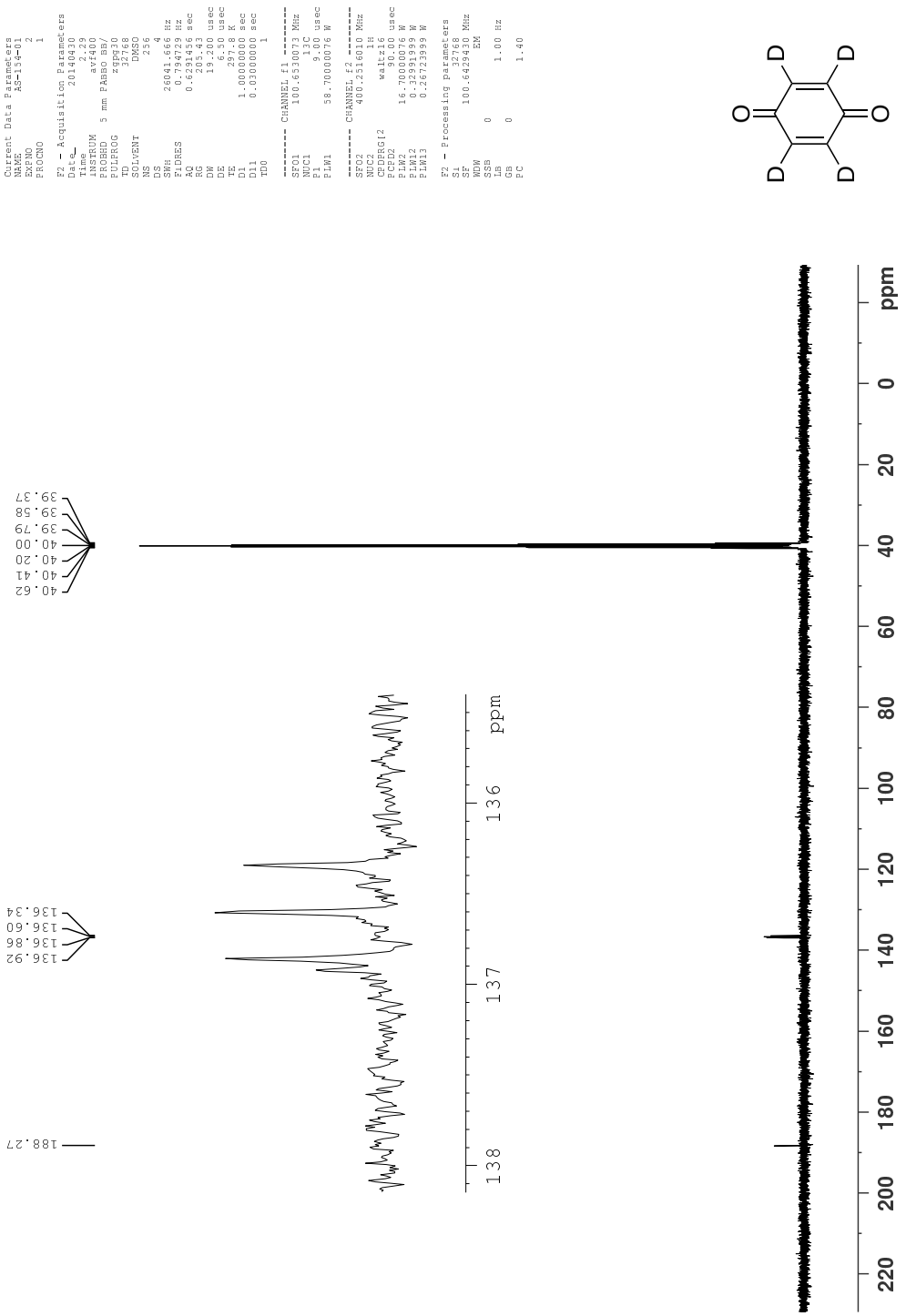
^{2}H NMR of 156


Current Data Parameters
NAME AS-126-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140314
Time 15.04
INSTRUM avb500
PROBHD 5 mm PATXI 1H/
PULPROG zg2h
TD 8192
SOLVENT CDC13
NS 16
DS 2
SWH 1534.684 Hz
FIDRES 0.187339 Hz
AQ 2.66889537 sec
RG 4
DW 325.800 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7503579 MHz
NUC1 2H
P1 200.00 usec
PLW1 11.60799980 W
F2 - Processing parameters
SI 32768
SF 76.7500122 MHz
WDW no
SSB 0
LB 0 Hz
GB 0
PC 1.00
OH
D
D
D
D
OH
6.98
6.76
6.74
6.58
6.33
3.37
2.64
2.50
2.39
2.36
12.92
87.08
ppm

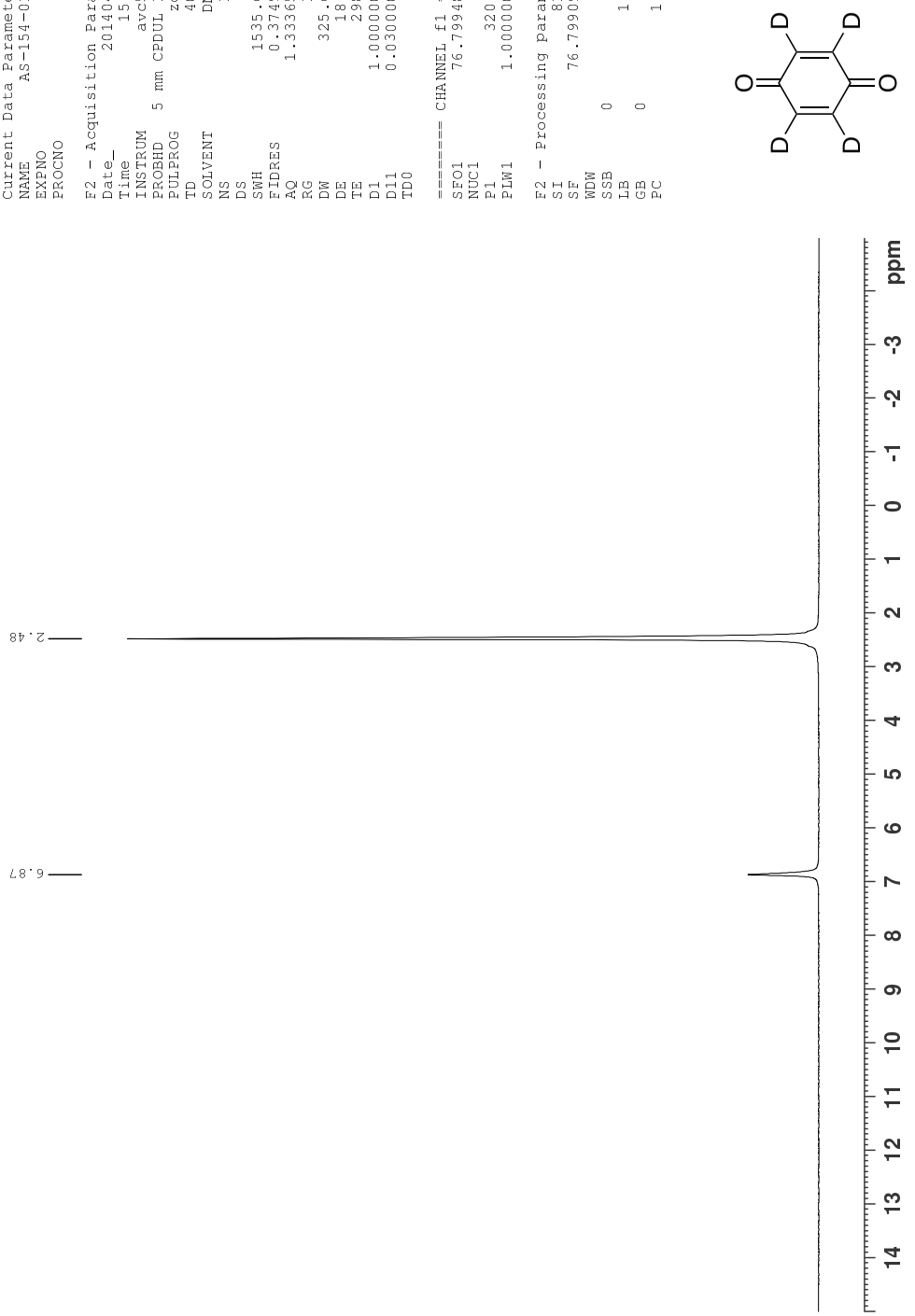
Mass spectrum of 156



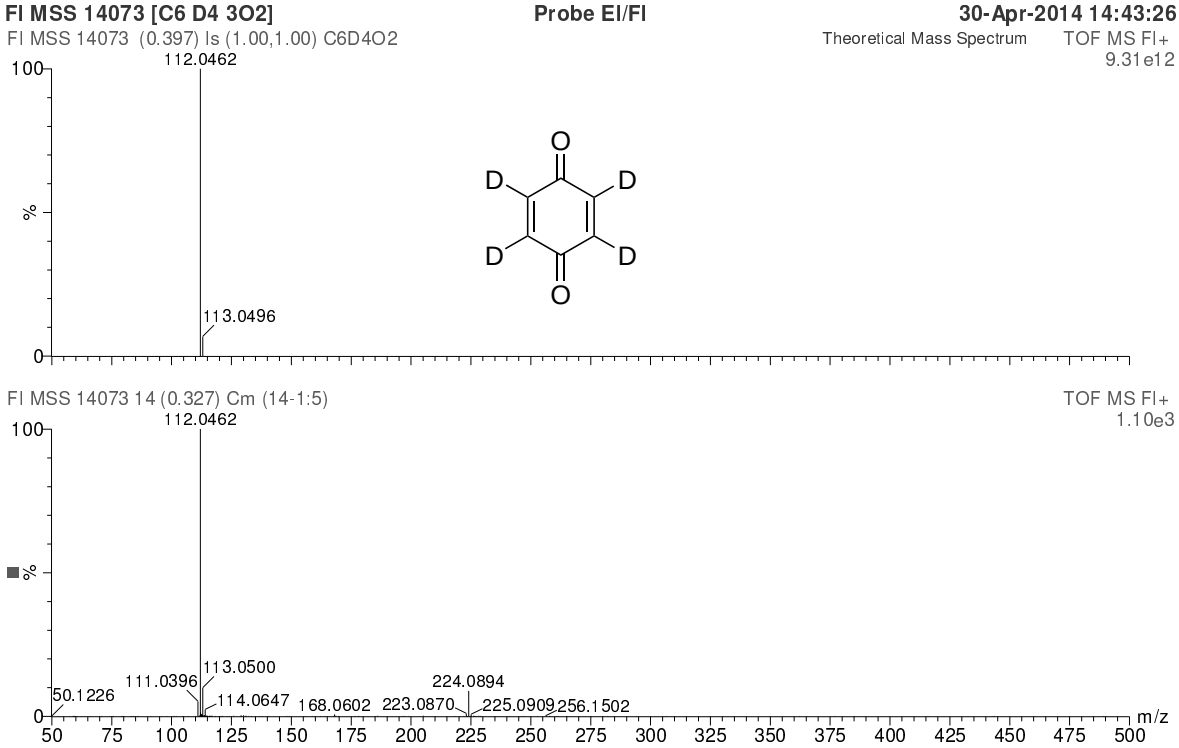
^{13}C NMR of 157



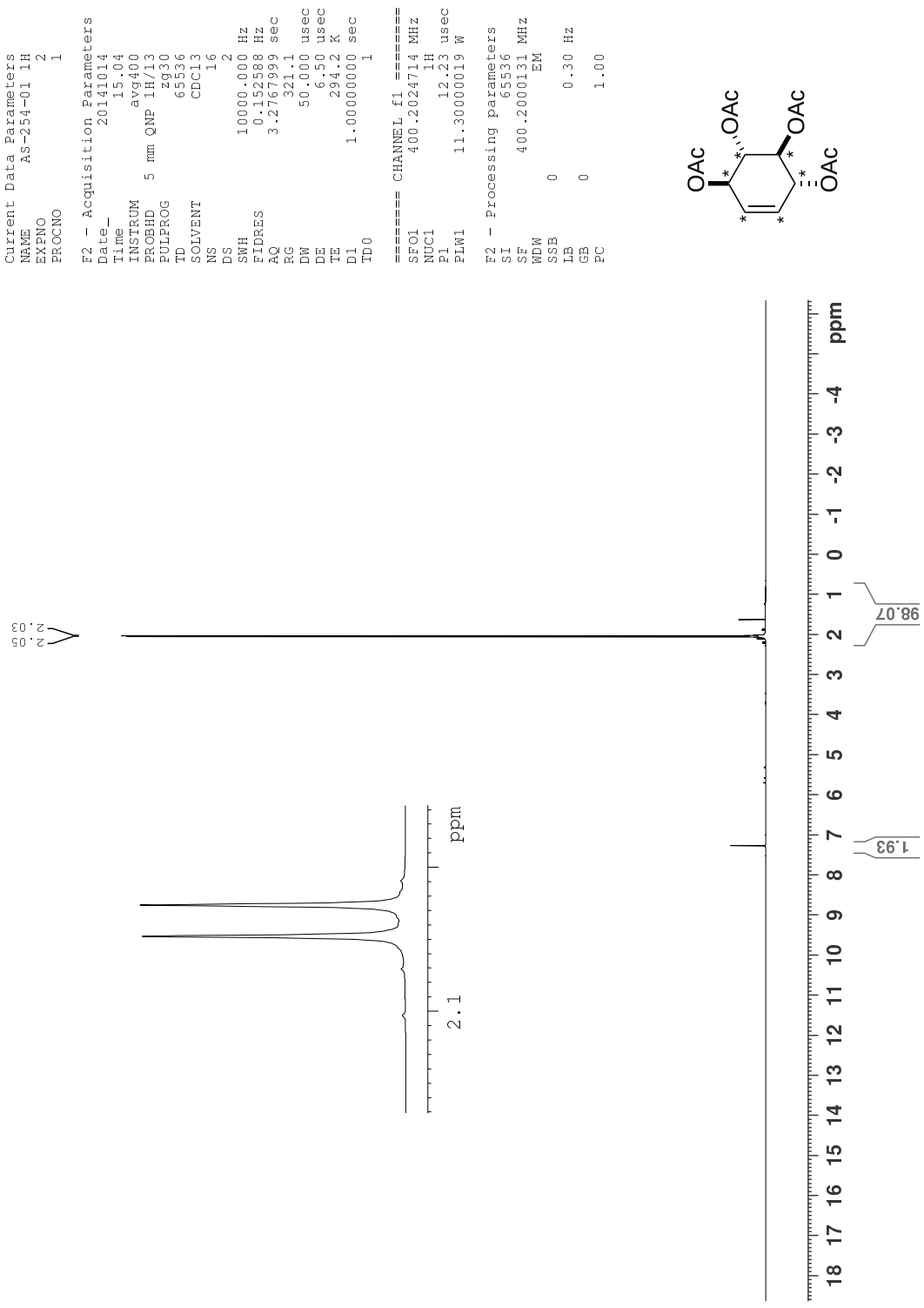
^{2}H NMR of 157


Current Data Parameters
NAME AS-154-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140429
Time 15.06
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT DMSO
NS 191
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33365576 sec
RG 1.6
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994801 MHz
NUC1 2H
P1 320.00 usec
PLW1 1.00000000 W
F2 - Processing parameters
SI 8192
SF 76.7990951 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
D
D
O
O
D
D
2.48
6.87
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3

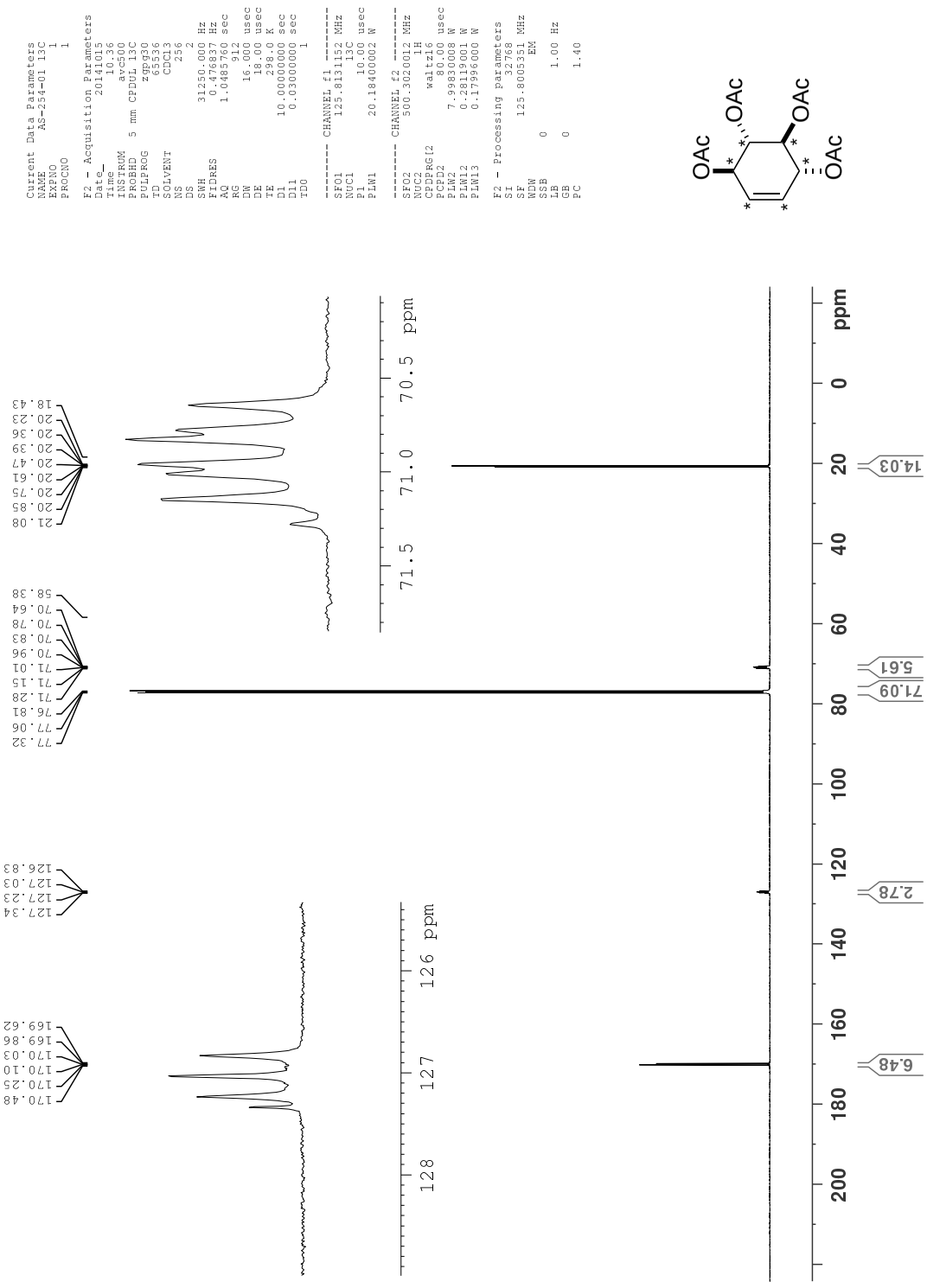
Mass spectrum of 157



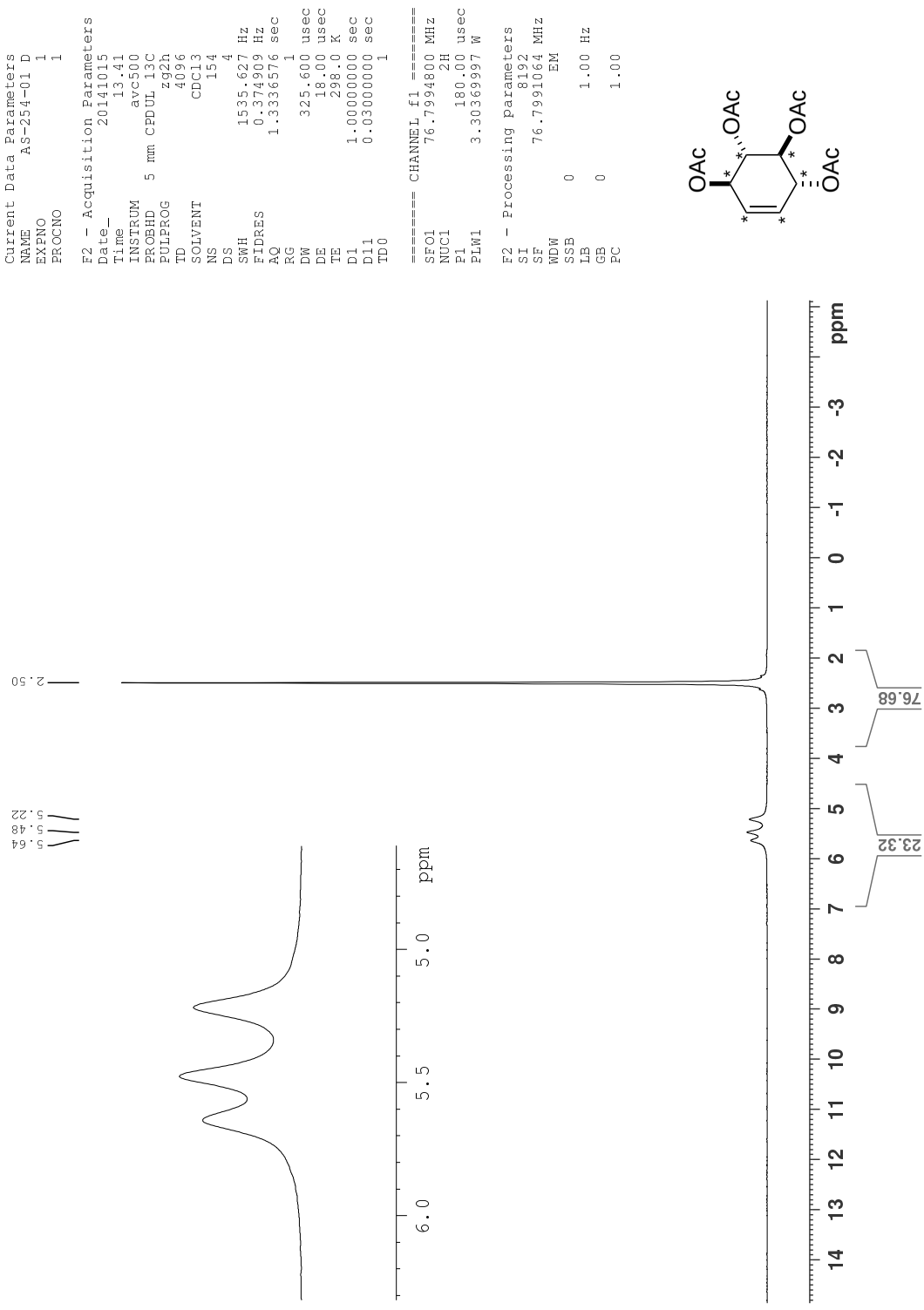
^{1}H NMR of (±)-160


Current Data Parameters
NAME AS-254-01 1H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141014
Time 15.04
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 321.1
DW 50.000 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000131 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OAc
OAc
OAc
OAc
2.05
98.07
1.93
2.1
ppm
18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 ppm

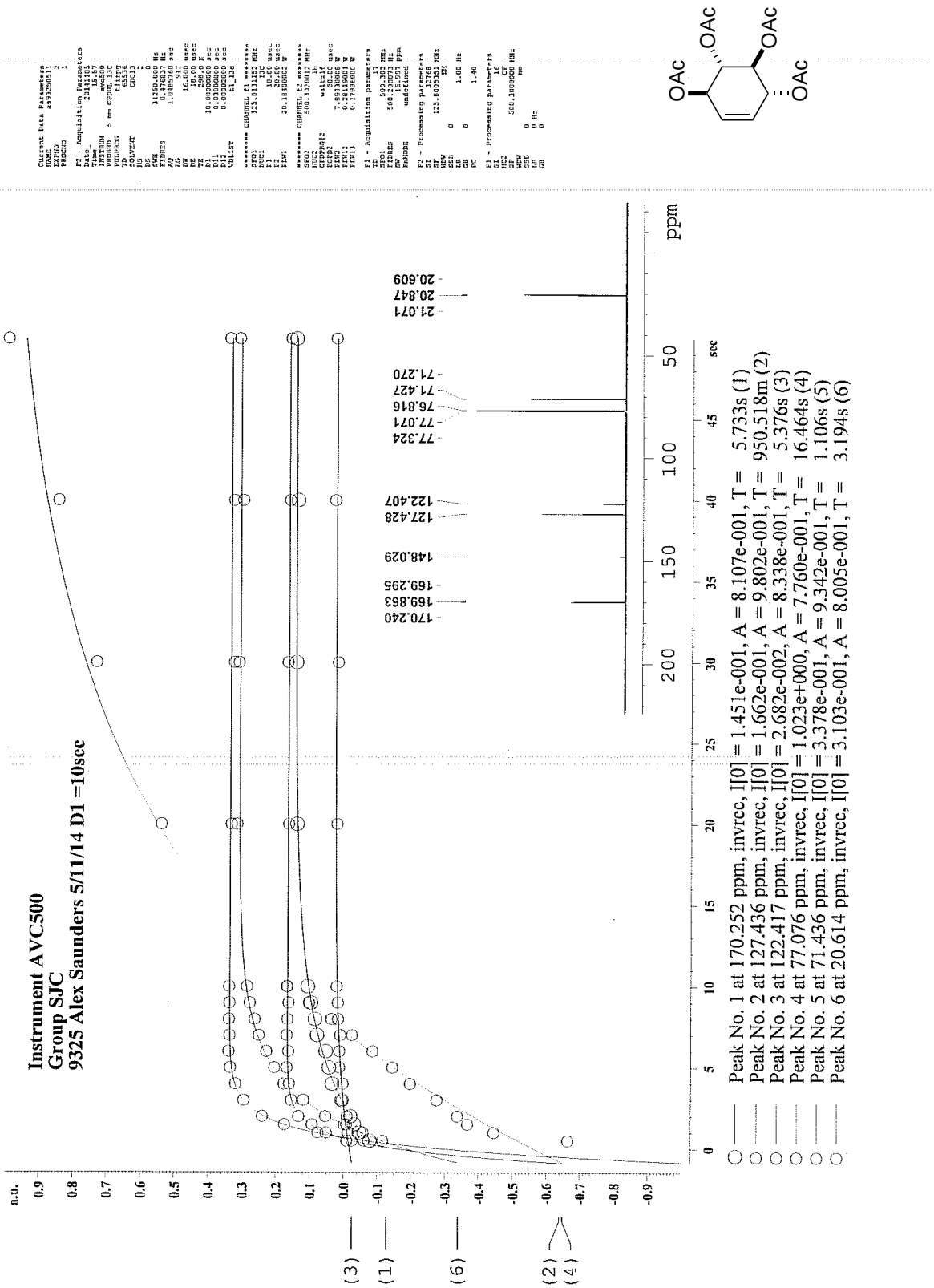
^{13}C NMR of (±)-160



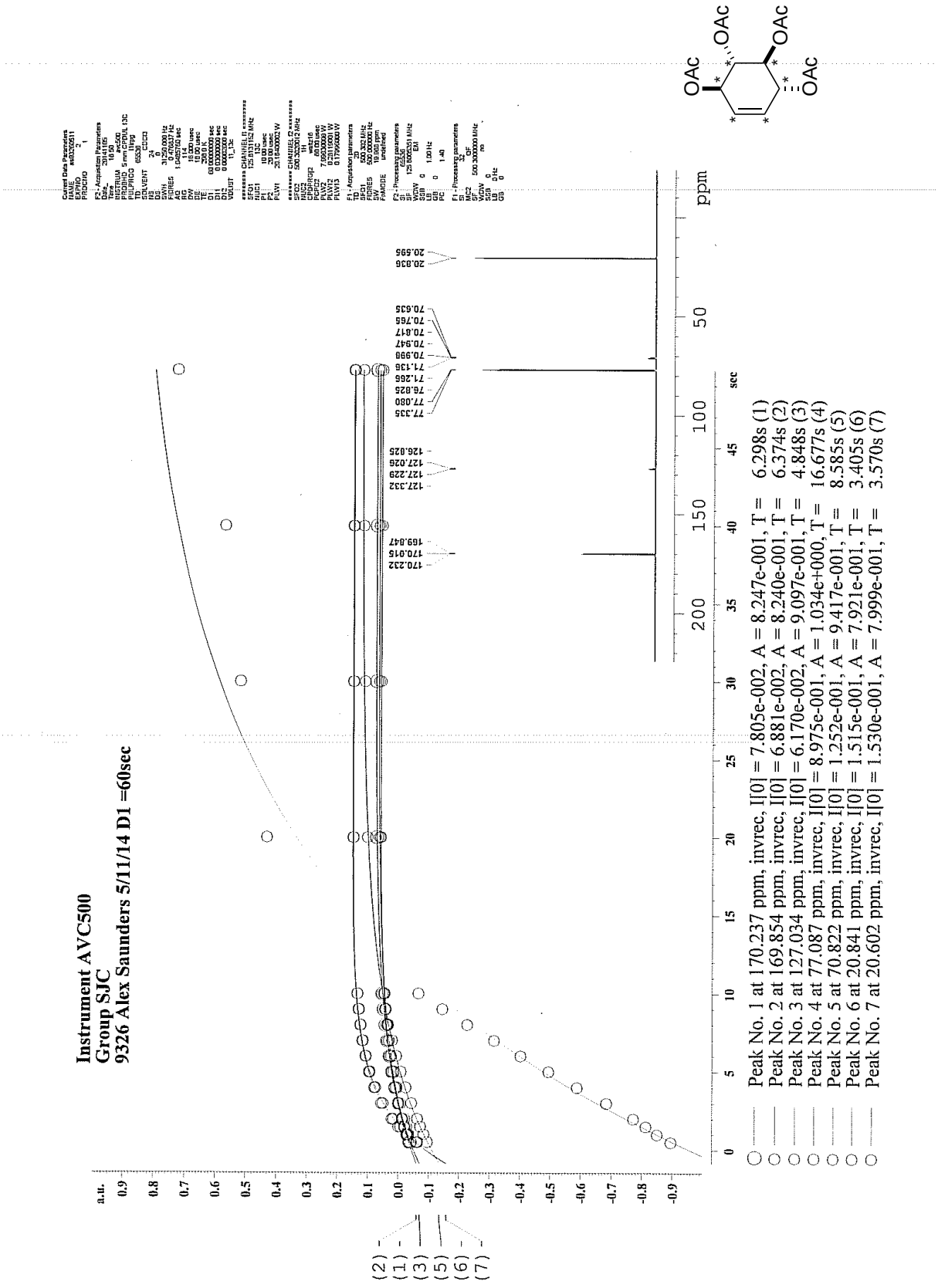
^{2}H NMR of (±)-160


Current Data Parameters
NAME AS-254-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141015
Time 13.41
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 154
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33366576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991064 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OAc
OAc
OAc
OAc
2.50
5.64
5.48
5.22
76.68
23.32
ppm
6.0
5.5
5.0
ppm

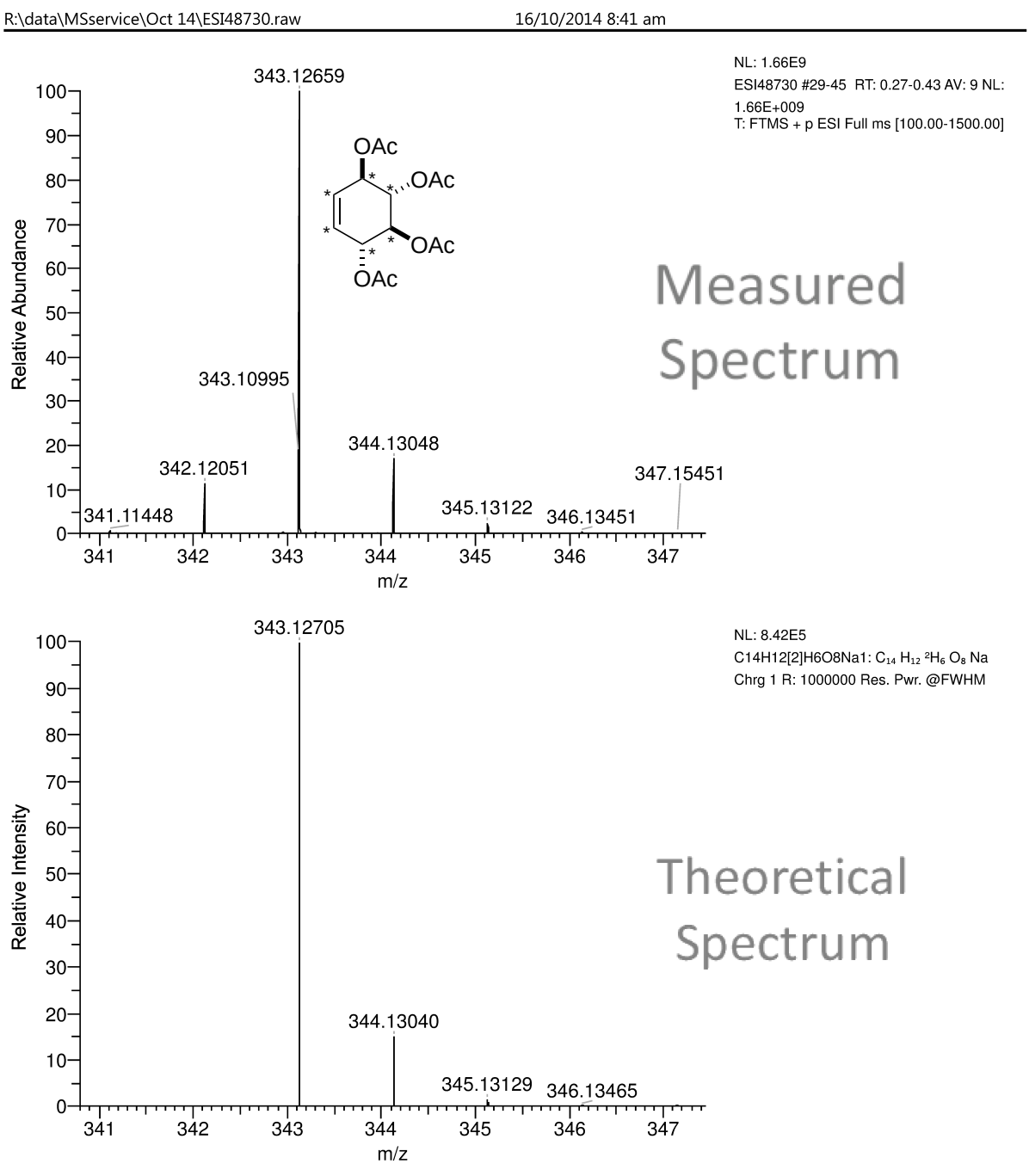
T_1 Times for (±)-81



T_1 Times for (±)-160

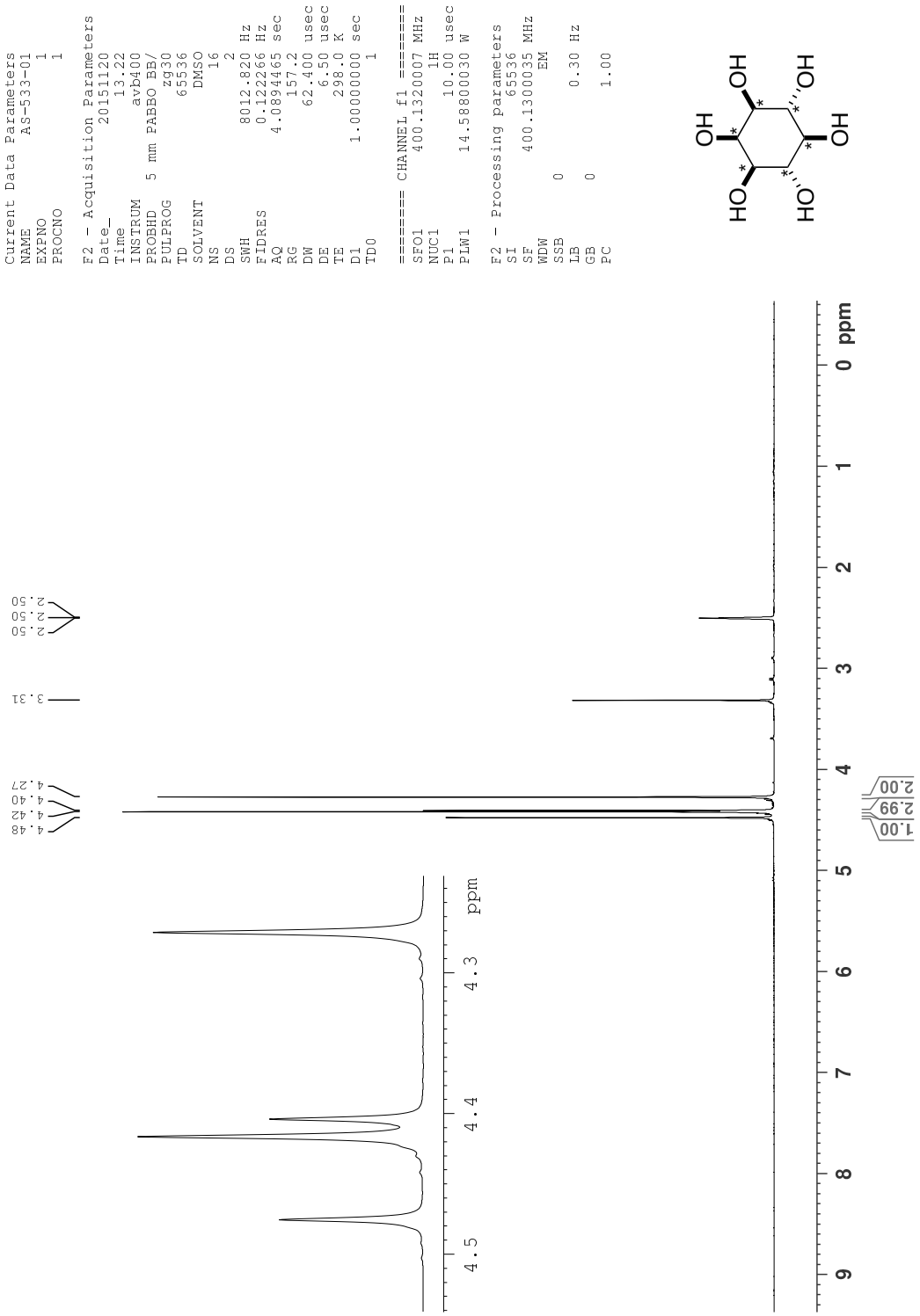


Mass spectrum of (±)-160

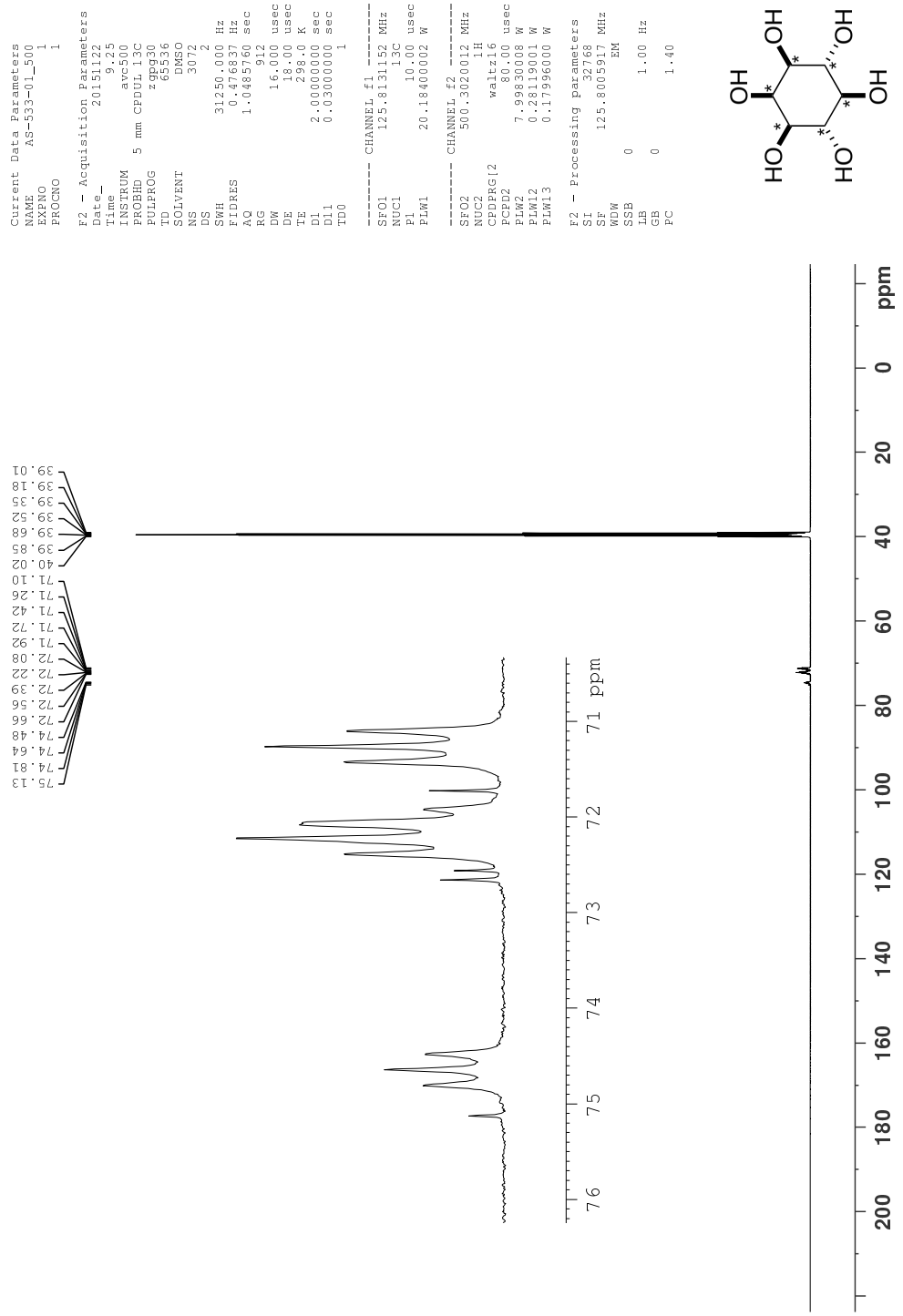


m/z	Formula	RDB	Delta ppm	Theo. Mass
343.12659	$C_{14}H_{12}{}^{2}H_{6}O_{8}{}^{23}Na$	5.5	-1.35	343.12705

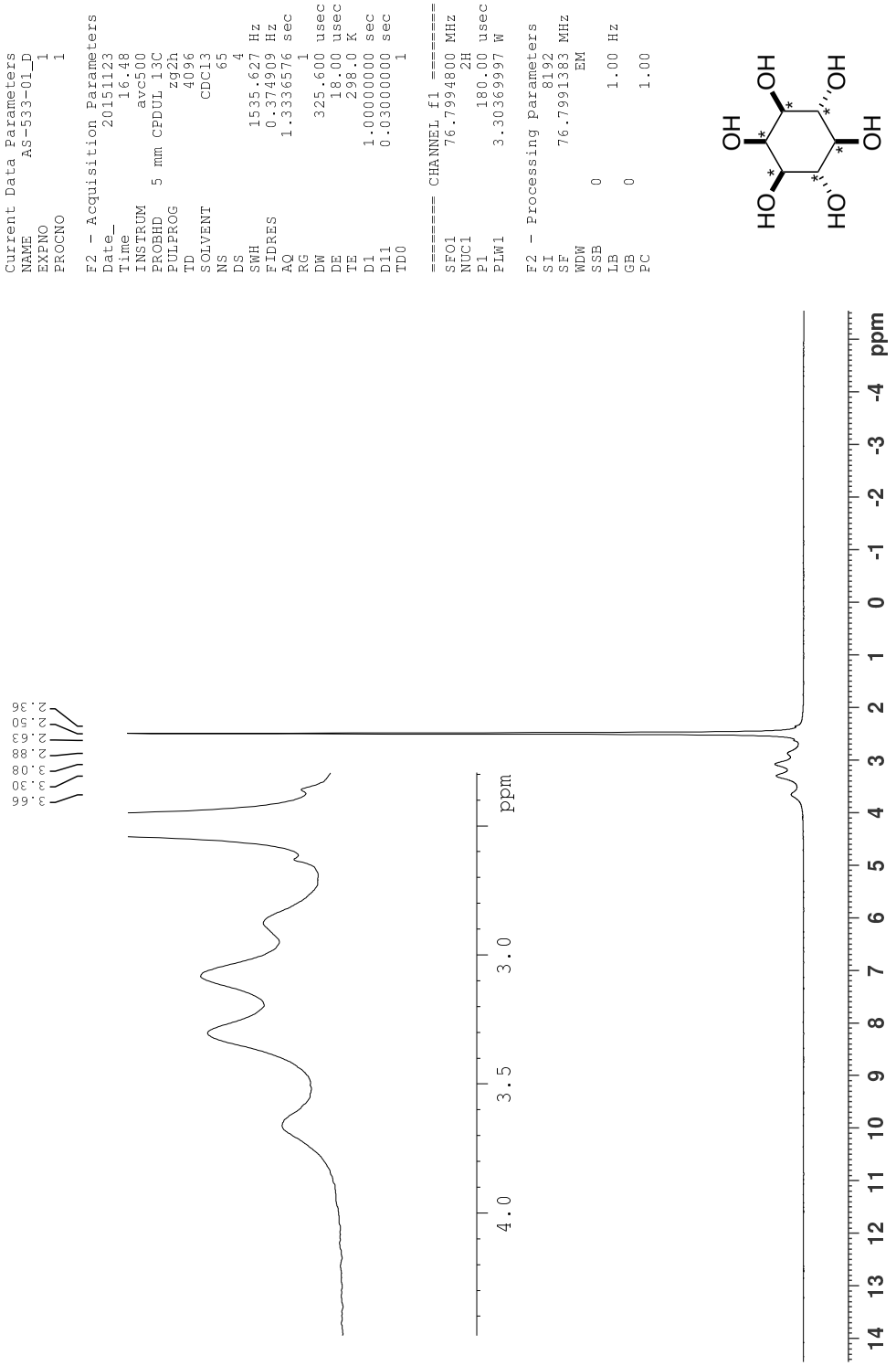
^{1}H NMR of 90


Current Data Parameters
NAME AS-533-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20151120
Time 13.22
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 157.2
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1320007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.1300035 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
HO
4.48
4.46
4.42
4.27
3.31
2.50
2.50
2.50
1.00
2.99
2.00
0 ppm
4.5
4.4
4.3

^{13}C NMR of 90

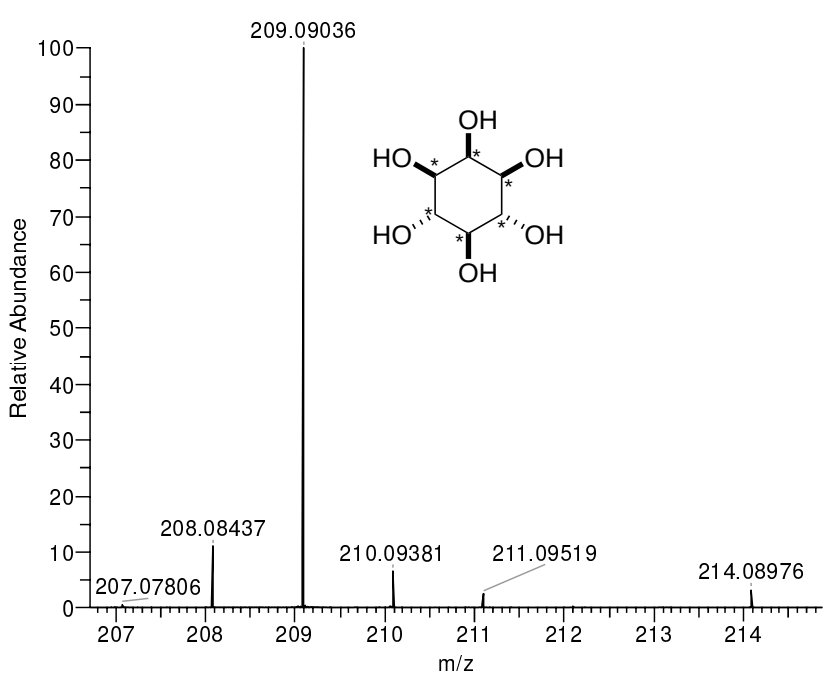

Current Data Parameters
NAME AS-533-01_500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20151122
Time_ 9.25
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3072
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.0485760 sec
RG 912
DW 16.000 usec
DE 18.00 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
--------- CHANNEL f1 ---------
SFO1 125.8131152 MHz
NUC1 13C
P1 10.00 usec
PLW1 20.18400002 W
--------- CHANNEL f2 ---------
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 80.00 usec
PLW2 7.99830008 W
PLW12 0.28119001 W
PLW13 0.17996000 W
F2 - Processing parameters
SI 32768
SF 125.8005917 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OH
HO
39.01
39.18
39.35
39.52
39.68
39.85
40.02
71.10
71.26
71.42
71.72
71.92
72.08
72.22
72.39
72.56
72.66
74.48
74.64
74.81
75.13
76 75 74 73 72 71 ppm
200 180 160 140 120 100 80 60 40 20 0 ppm

^{2}H NMR of 90


Current Data Parameters
NAME AS-533-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20151123
Time 16.48
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 65
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991383 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OH
HO
ppm

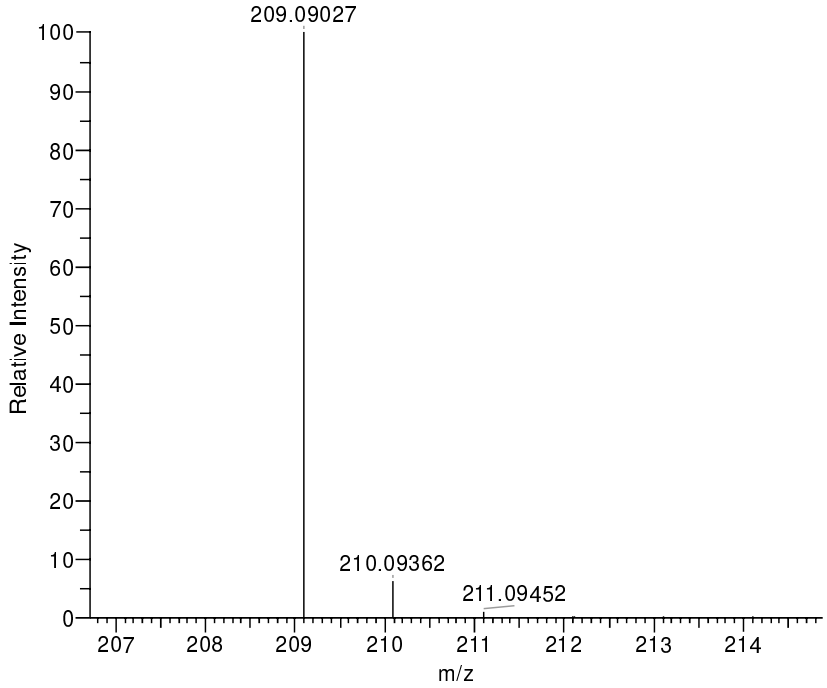
Mass spectrum of 90

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



NL: 1.44E7
ESI54796 #11-26 RT: 0.12-0.29 AV: 8 NL: 1.44E+007
T: FTMS {1,1} + p ESI Full lock ms [80.00-1600.00]

Measured Spectrum

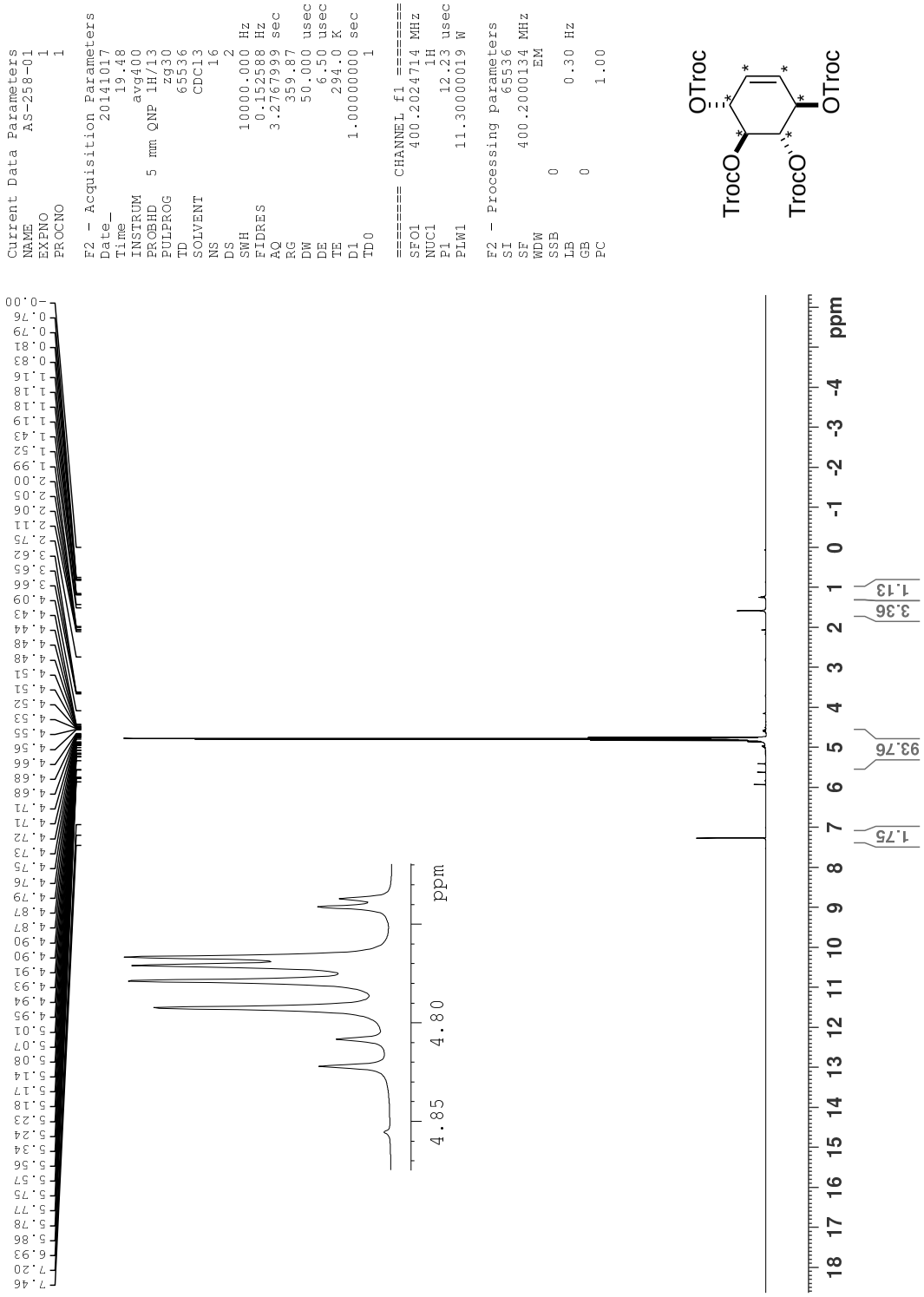


NL: 9.23E5
C6H6[2]H6O6Na1: $C_6H_6{}^2H_6O_6Na$ Chrg 1 R: 1000000 Res. Pwr. @FWHM

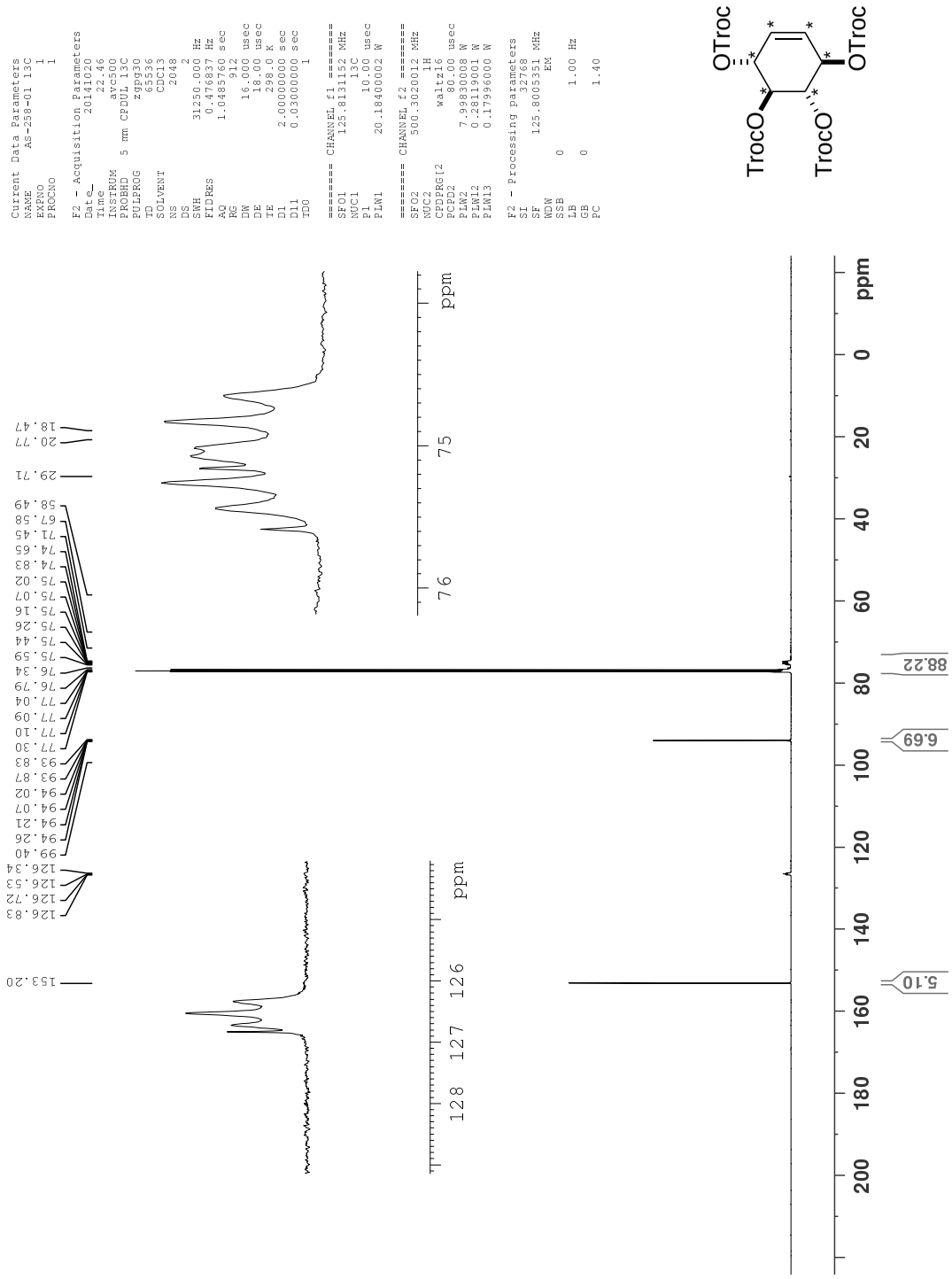
Theoretical Spectrum

Index	m/z	Formula	Score	RDB	Delta ppm	OriginalFormula	Theo. Mass
1	209.09036	$C_6H_6{}^2H_6O_6{}^{23}Na$	0	0.5	0.44	C6H6[2]H6O6...	209.09027

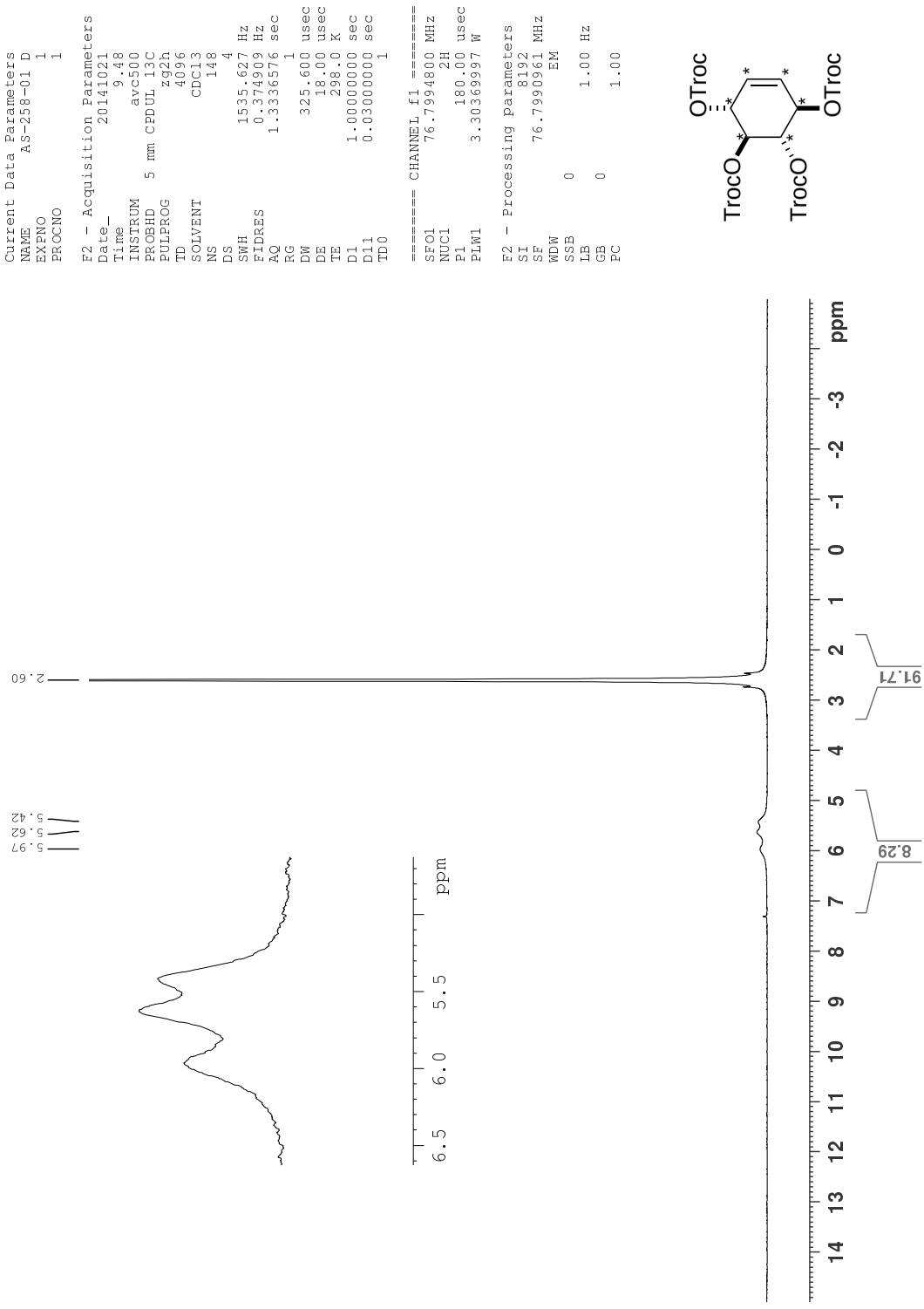
^{1}H NMR of (±)-165


Current Data Parameters
NAME AS-258-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141017
Time 19.48
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 359.87
DW 50.000 usec
DE 6.50 usec
TE 294.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000134 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTroc
TrocO
TrocO
OTroc
1.13
3.36
93.76
1.75
ppm
4.85
4.80
ppm

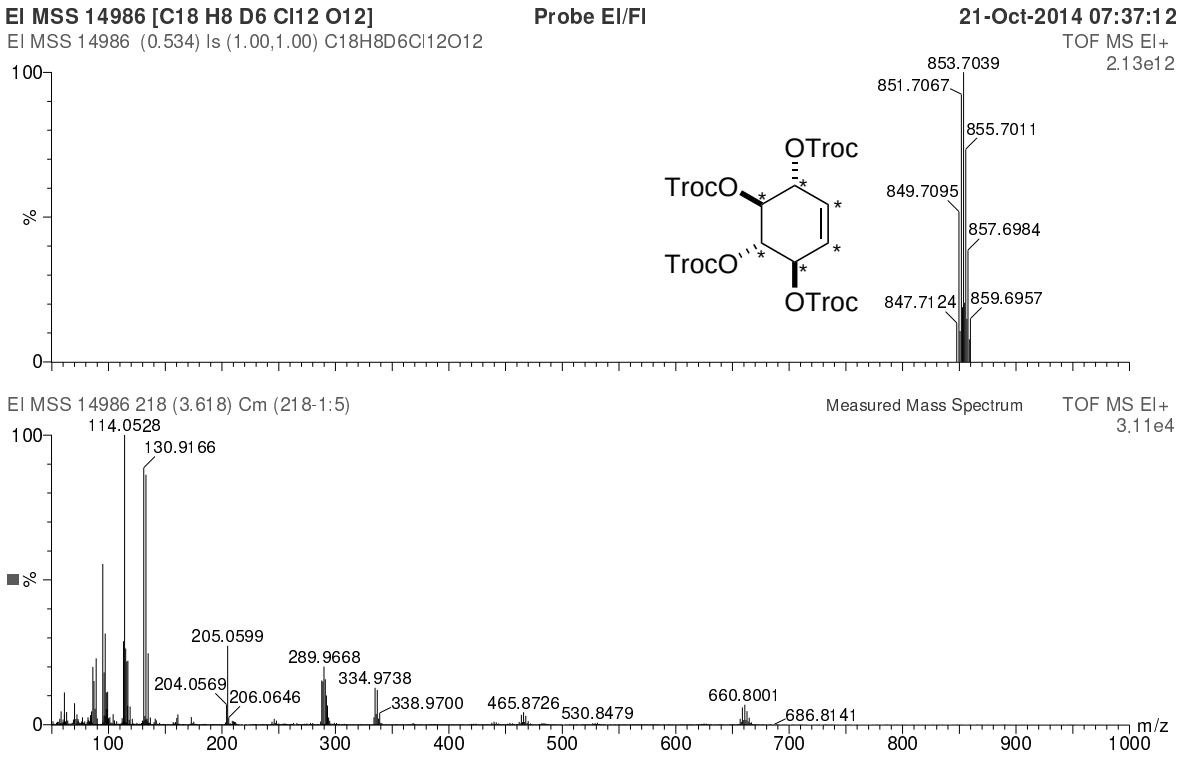
^{13}C NMR of (±)-165



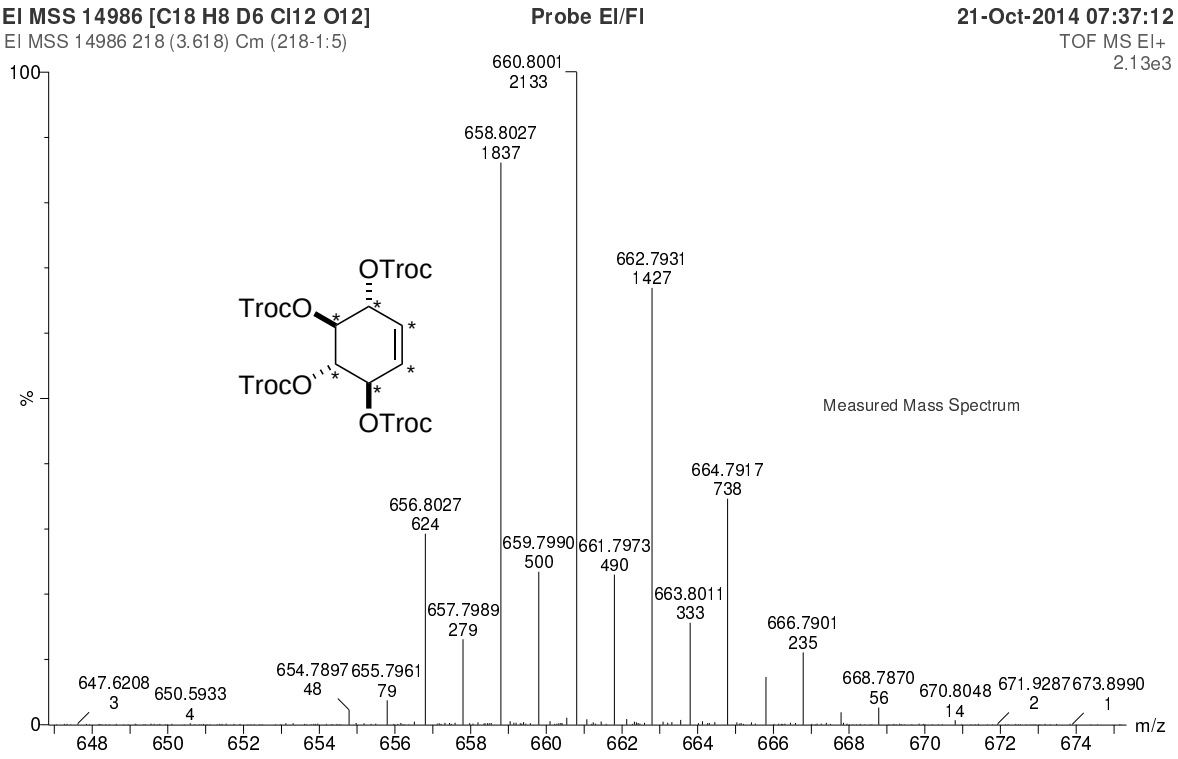
^{2}H NMR of (±)-165


Current Data Parameters
NAME AS-258-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141021
Time 9.48
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 148
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33936576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990961 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OTroc
TrocO
TrocO
OTroc
2.60
5.97
5.62
5.42
91.71
8.29
ppm
6.5 6.0 5.5
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

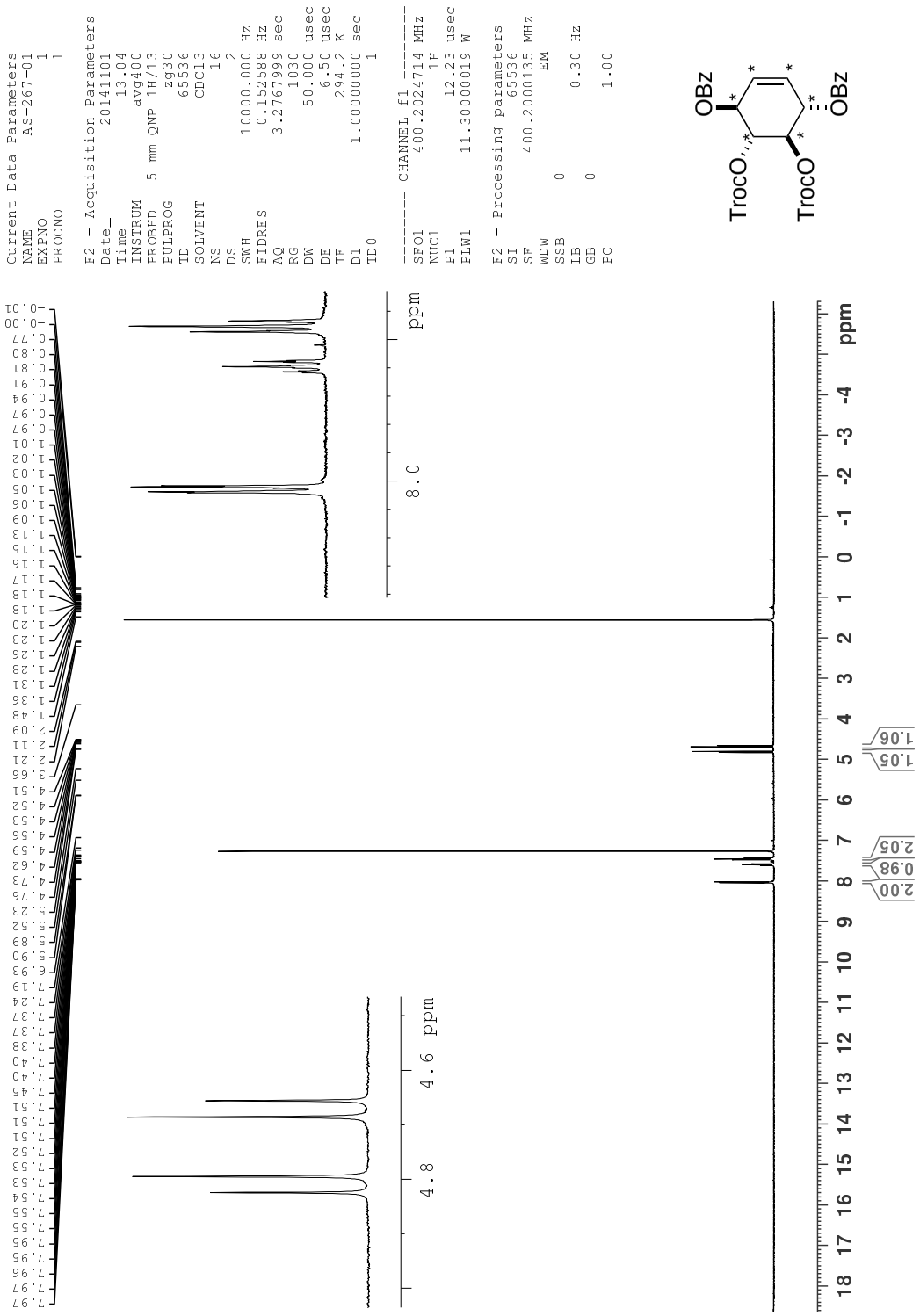
Mass spectrum of (±)-165



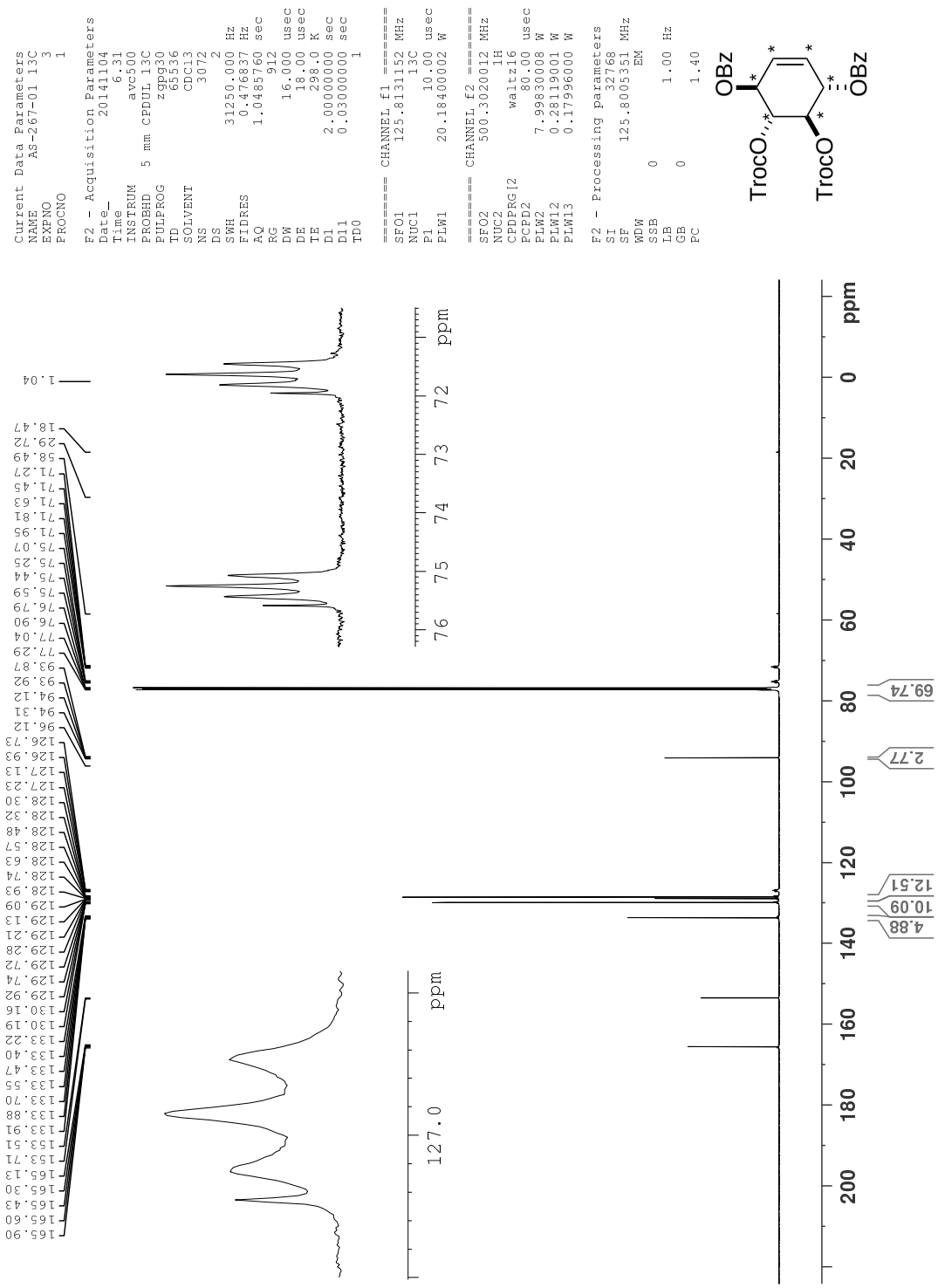
Mass spectrum of (±)-165 (cont.)



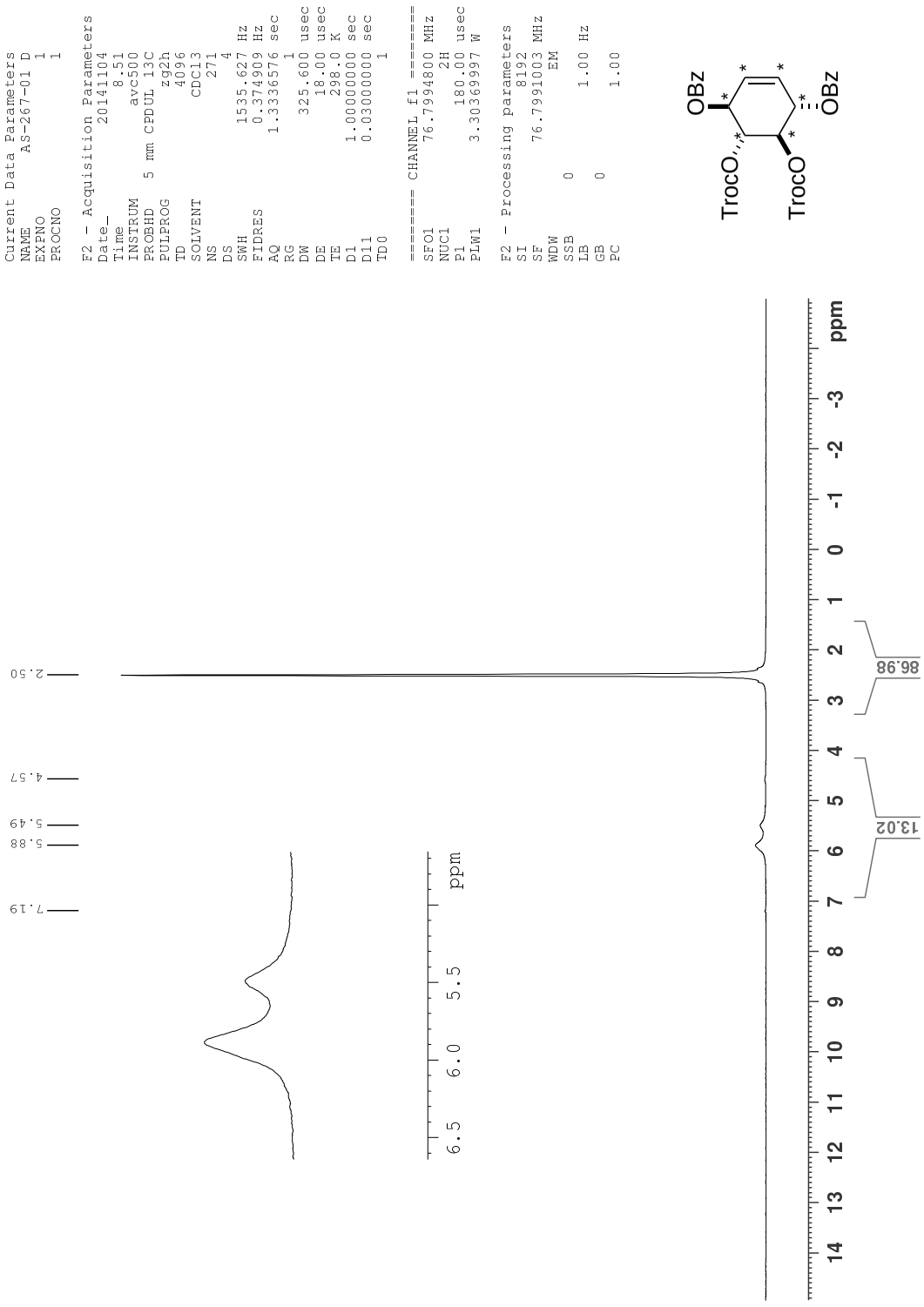
^{1}H NMR of (+)-166


Current Data Parameters
NAME AS-267-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141101
Time 13.04
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 1030
DW 50.000 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
TrocO
OBz
TrocO
8.0
ppm
4.8
4.6
ppm
1.06
1.05
2.05
0.98
2.00
ppm

^{13}C NMR of (+)-166



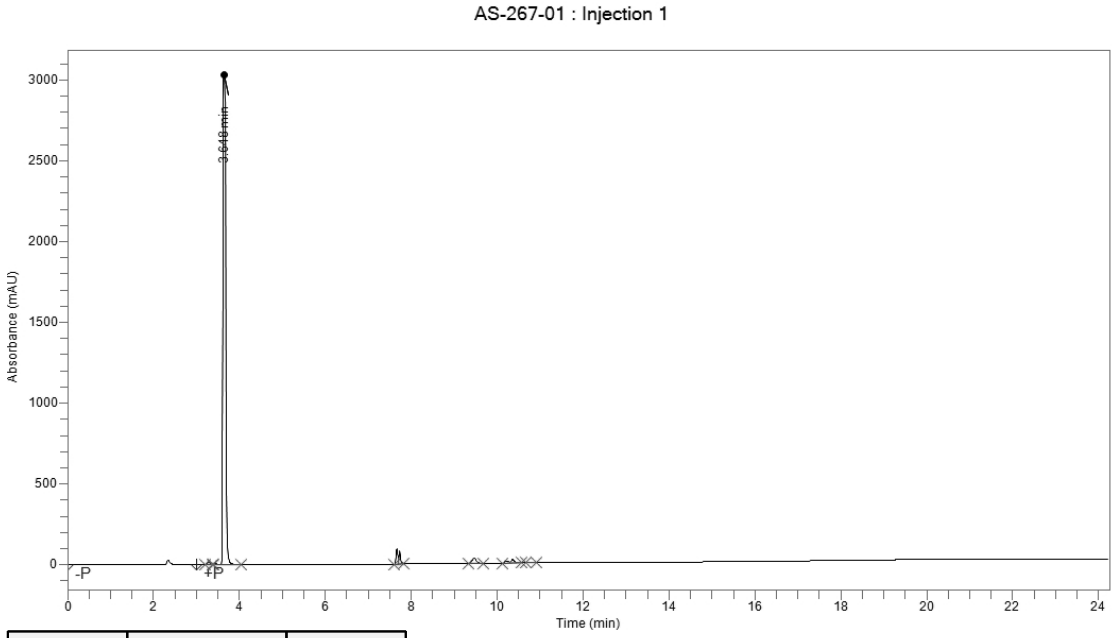
^{2}H NMR of (+)-166


Current Data Parameters
NAME AS-267-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141104
Time 8.51
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 271
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991003 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OBz
TrocO
TrocO
OBz
2.50
4.57
5.49
5.88
7.19
86.98
13.02
ppm
6.5
6.0
5.5
ppm

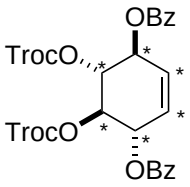
HPLC of (+)-166

AS-267-01

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



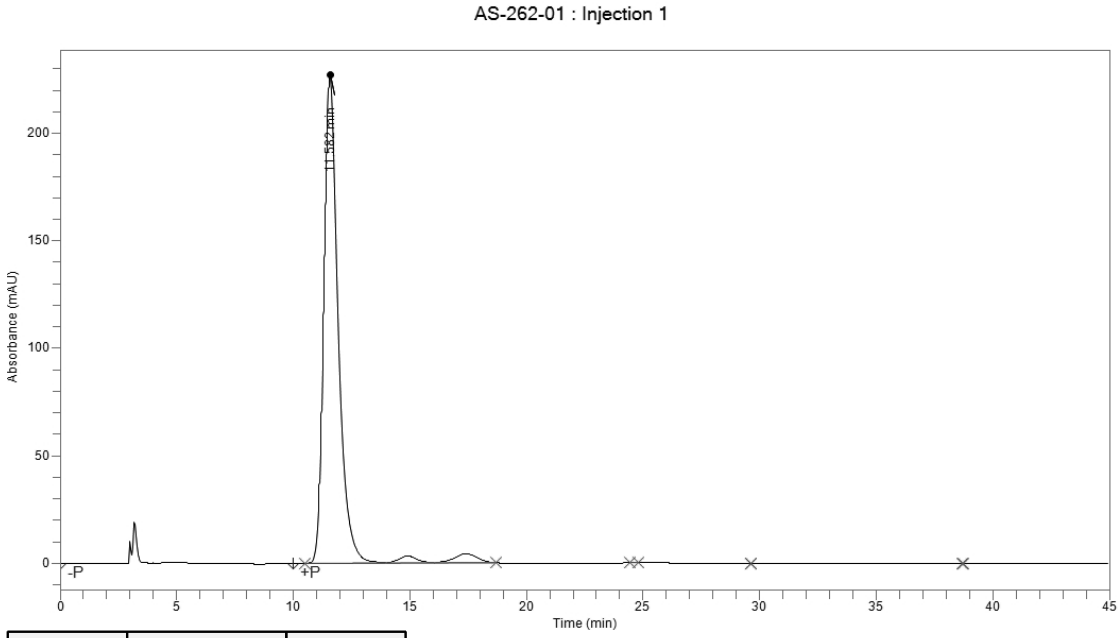
Time	Area	Area %
3.281	67775	0.52
3.446	32997	0.25
3.648	11992820	92.51
7.666	267326	2.06
7.729	186701	1.44
9.468	222426	1.72
10.199	65629	0.51
10.359	109520	0.84
10.767	18164	0.14
Total	12963357	100.00



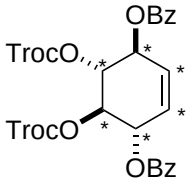
Chirla HPLC of (+)-166

AS-262-01

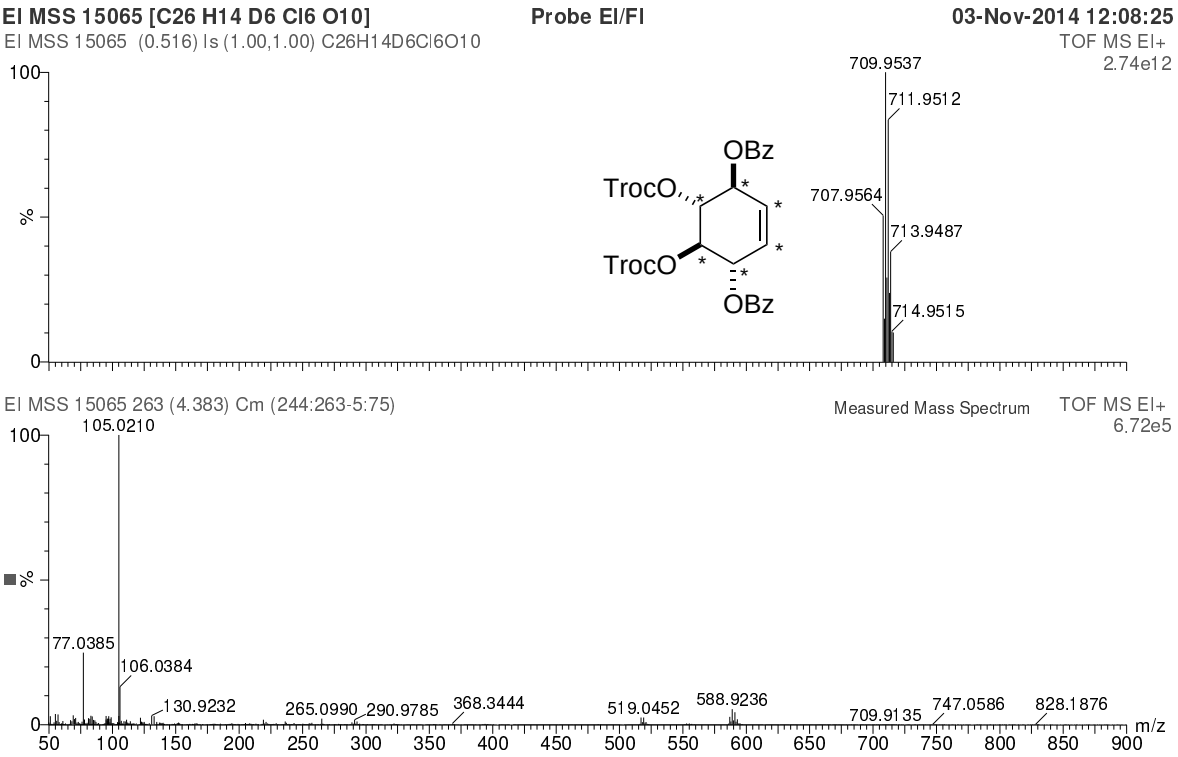
Sample Name	AS-262-01	Sample Description	ADH column
Acquisition Method	EE determination 90:10 Hep:IPA 220 nm	Acquisition Date/Time	10/28/2014 5:07 pm
Batch Group/Name	Alex/EE determination 90:10 Hep:IPA 220 nm	Batch Description	ADH column



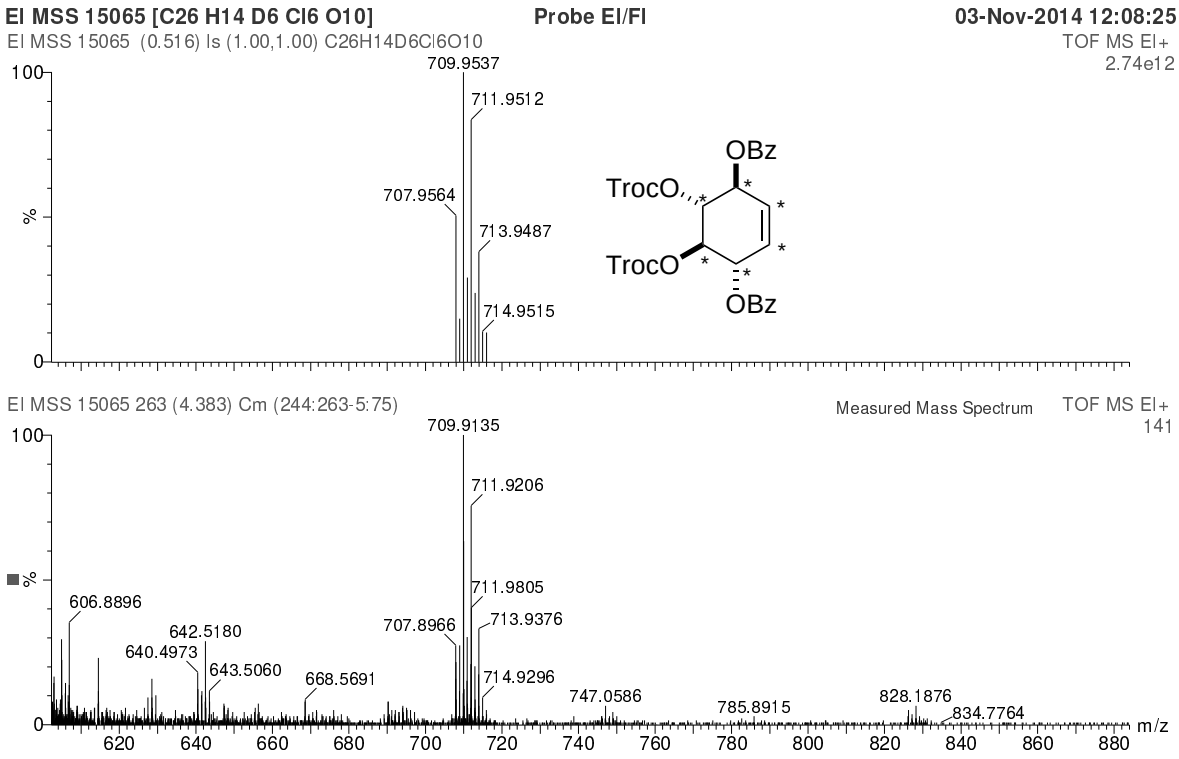
Time	Area	Area %
11.582	9931614	95.30
14.886	192303	1.85
17.387	297020	2.85
24.777	361.7	0.00
29.622	24.212	0.00
38.690	46.062	0.00
Total	10421370	100.00



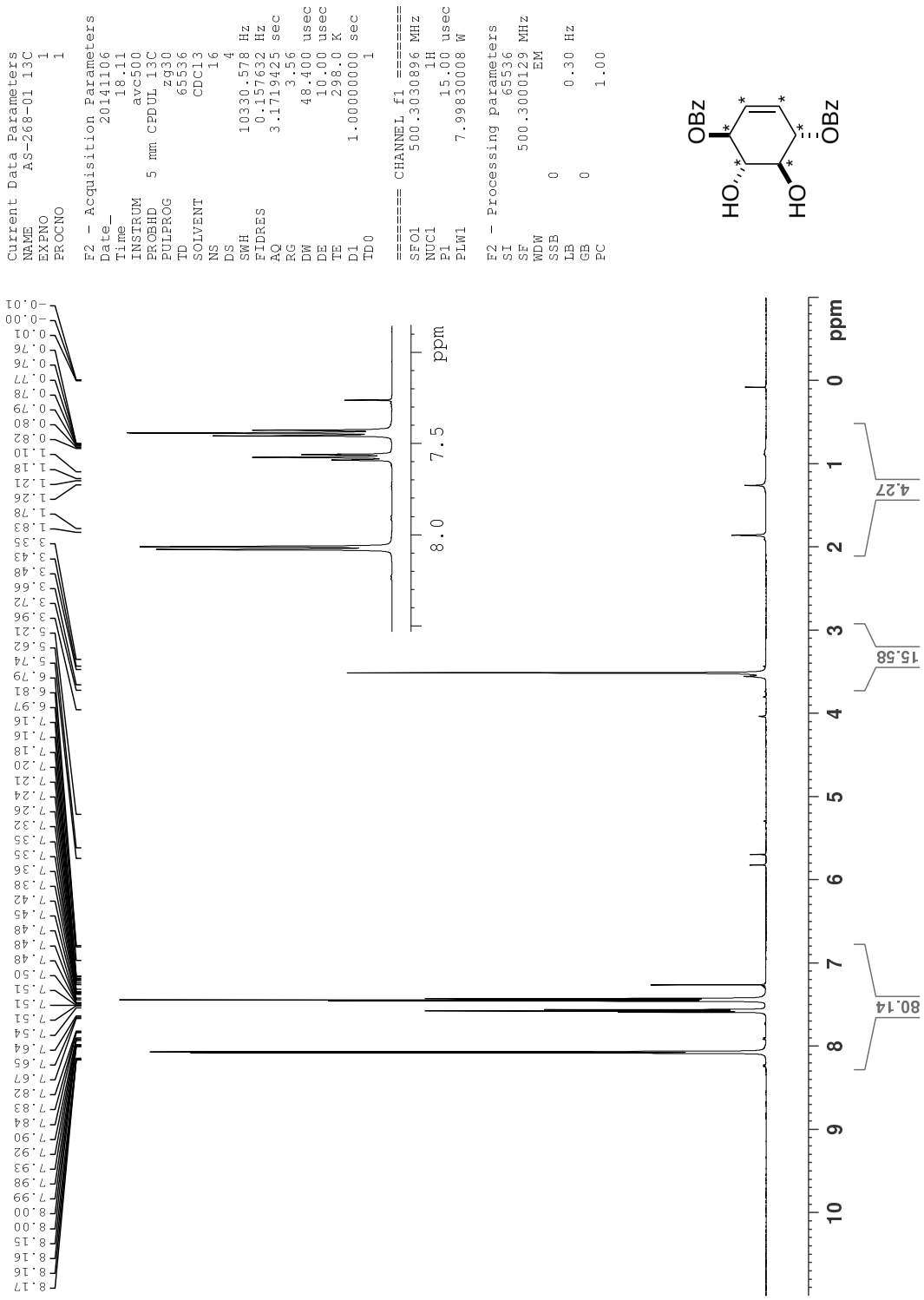
Mass spectrum of (+)-166



Mass spectrum of (+)-166 (cont.)



^{1}H NMR of (+)-167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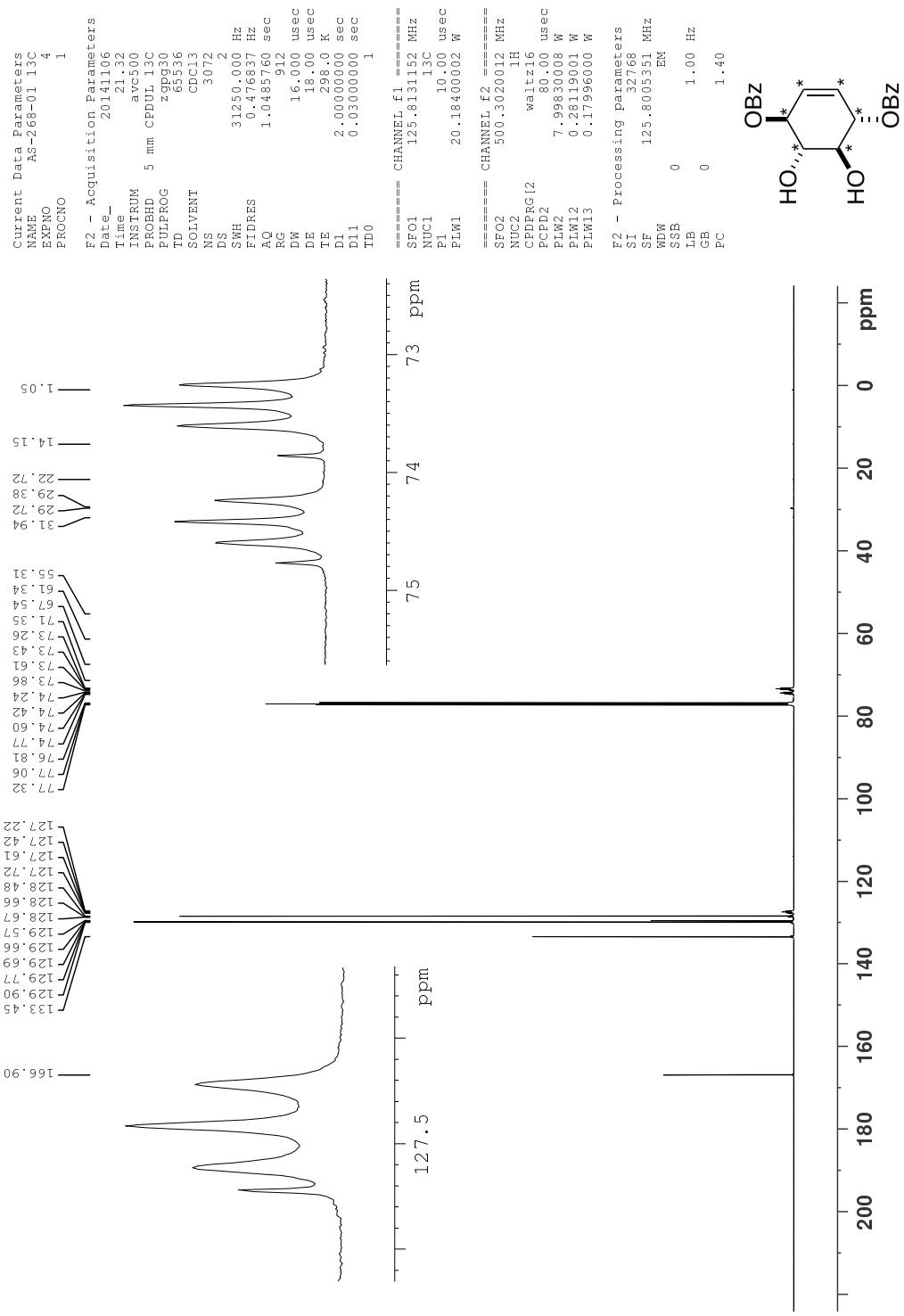
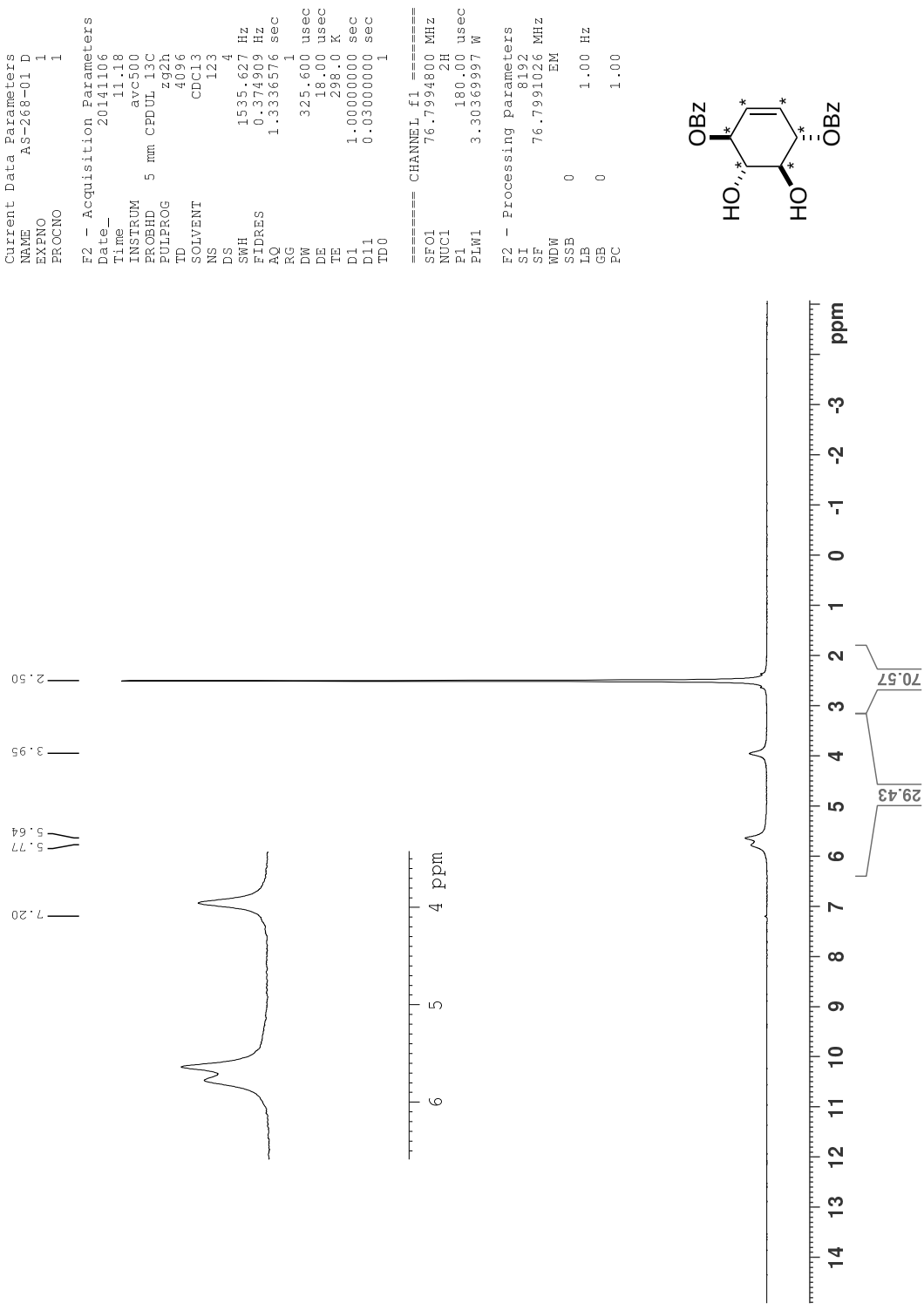
NAME AS-268-01 13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141106
Time 18.11
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
HO
HO
OBz
ppm
4.27
15.58
80.14

^{13}C NMR of (+)-167



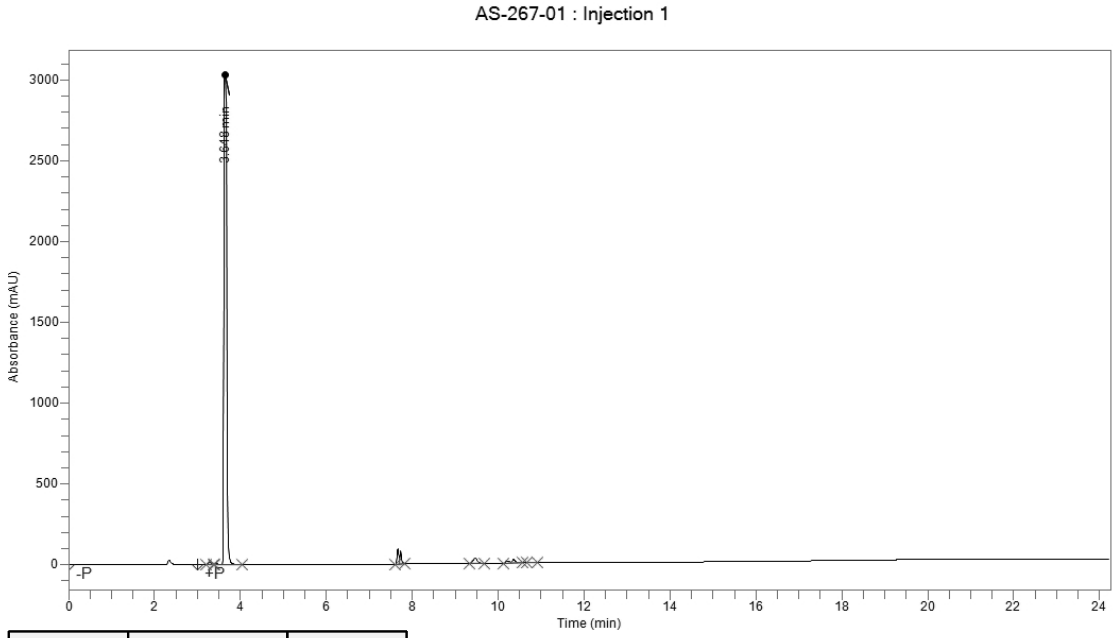
^{2}H NMR of (+)-167


Current Data Parameters
NAME AS-268-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141106
Time 11.18
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 123
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33366576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991026 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OBz
HO
HO
OBz
7.20
5.77
5.64
3.95
2.50
70.57
29.43
ppm

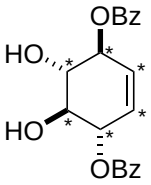
HPLC of (+)-167

AS-267-01

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

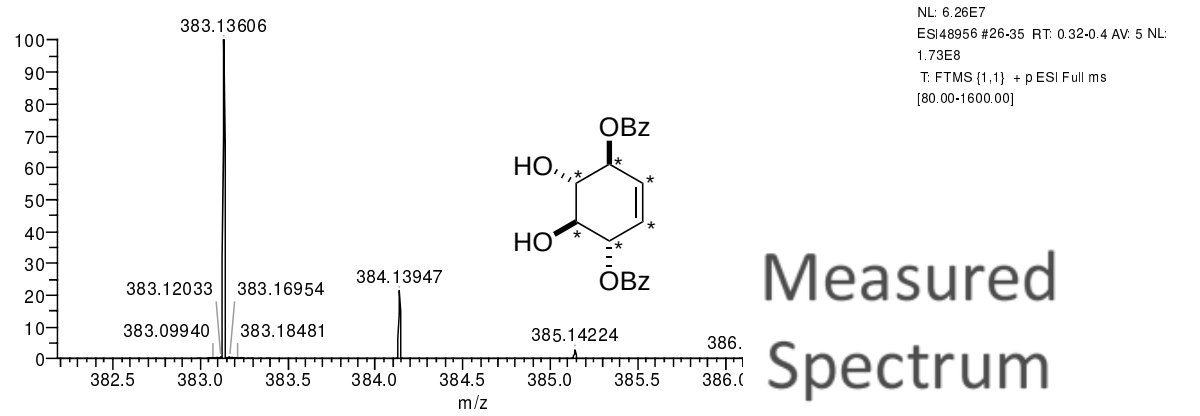


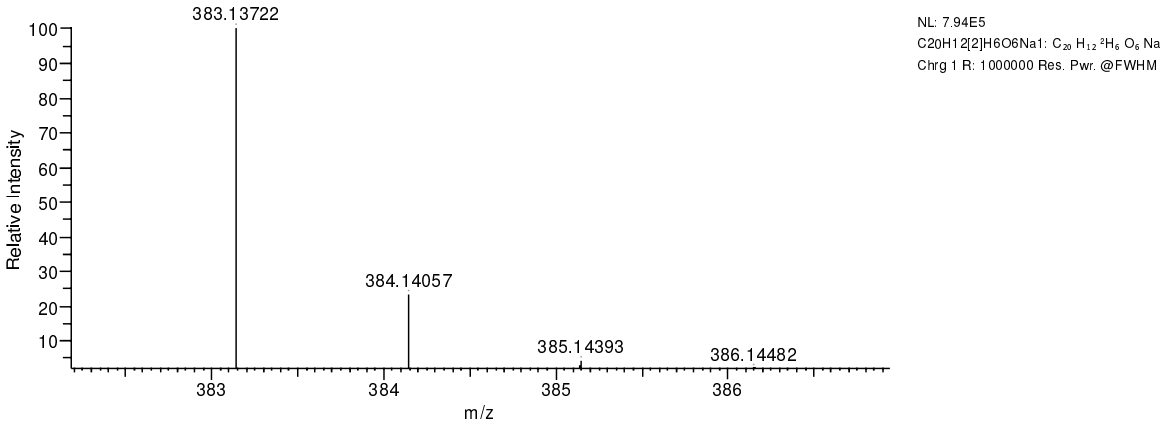
Time	Area	Area %
3.281	67775	0.52
3.446	32997	0.25
3.648	11992820	92.51
7.666	267326	2.06
7.729	186701	1.44
9.468	222426	1.72
10.199	65629	0.51
10.359	109520	0.84
10.767	18164	0.14
Total	12963357	100.00



Mass spectrum of (+)-167

Y:\data\Nov 14\ESI48956.raw 05/11/2014 10:44:40



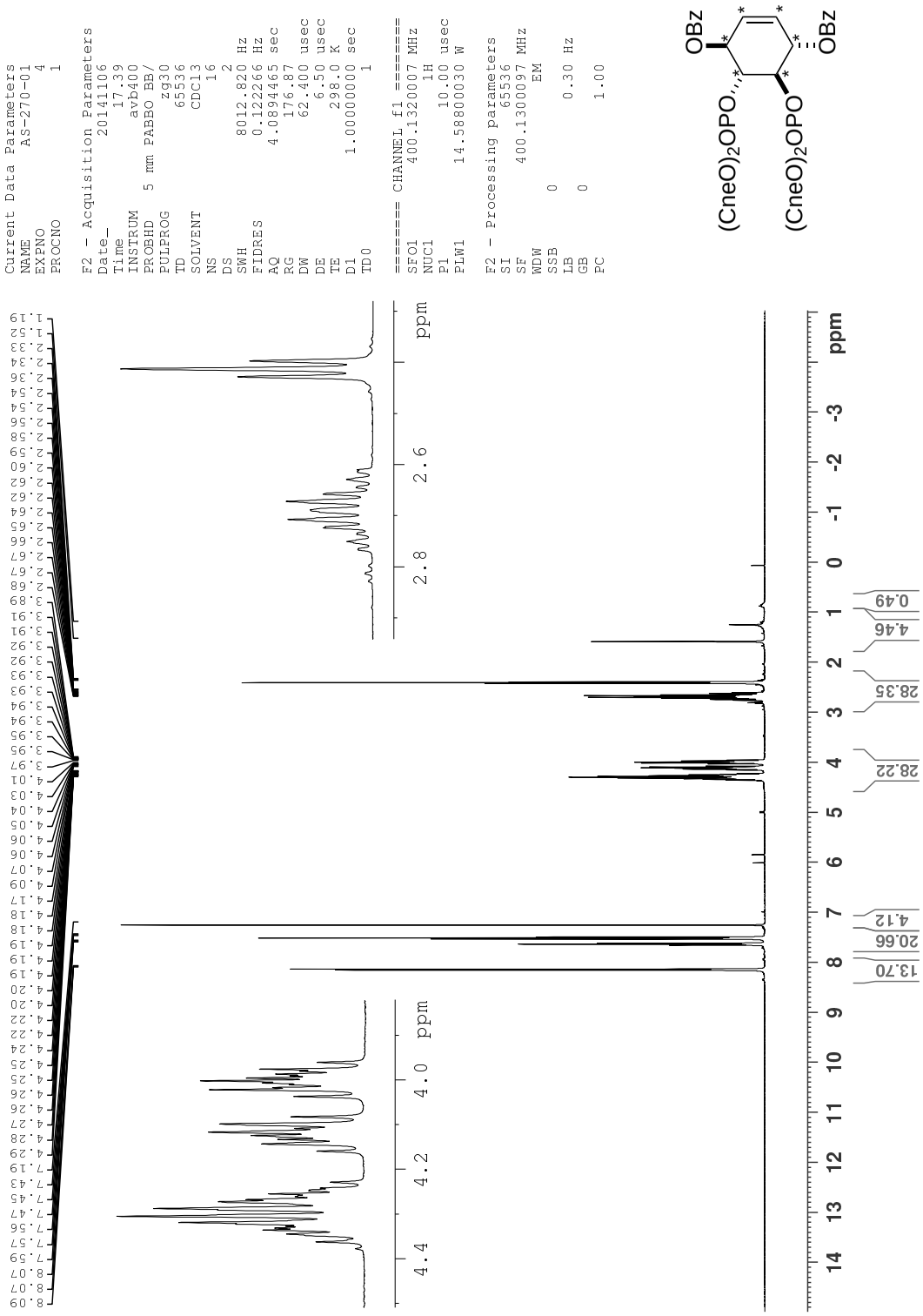


m/z	Formula	RDB	Delta ppm	Theo. Mass
383.13605	$C_{20}H_{12}{}^{2}H_{6}O_{6}{}^{23}Na$	11.5	-3.06	383.13722

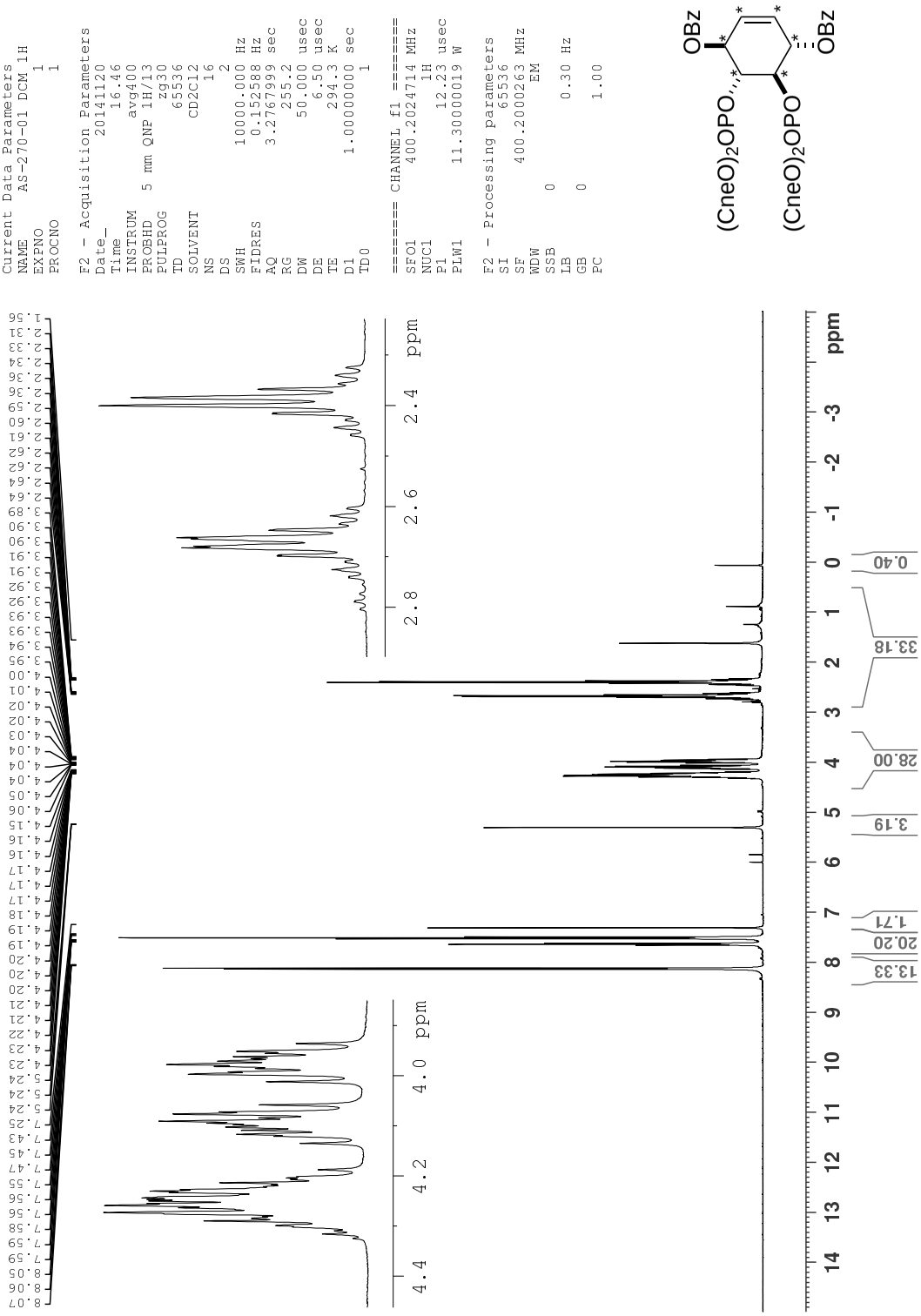
Theoretical Spectrum

ScanNumber	m/z	Intensity	Relative	SegmentNumber	IsPrecursor
26 - 35	239.118057030611	33286229.3202389	19.0972453955542	1	false
26 - 35	240.121271899837	4321874.47240507	2.47958086733835	1	false
26 - 35	361.154310293894	16006562.5641531	9.18341486763298	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	64682743.5813294	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	2.12091570397377	1	false
26 - 35	742.276784679122	38157241.3898286	21.8918819379727	1	false
26 - 35	743.282464852945	174298589.303292	100	1	false
26 - 35	744.286331777758	73753881.1137985	42.3146747249121	1	false
26 - 35	745.289427034589	18318051.8654463	10.5095812528761	1	false
26 - 35	812.31879229906	8050641.97733623	4.61887959593725	1	false
26 - 35	813.324817407215	38666710.5014354	22.184178687845	1	false
26 - 35	814.328402949405	17495175.0234815	10.0374736785957	1	false
26 - 35	815.331390099558	4789137.06278326	2.74766254960894	1	false
26 - 35	847.309474290933	3886323.11151905	2.22969280879065	1	false
26 - 35	883.367113370915	5370598.91455034	3.08126355813764	1	false

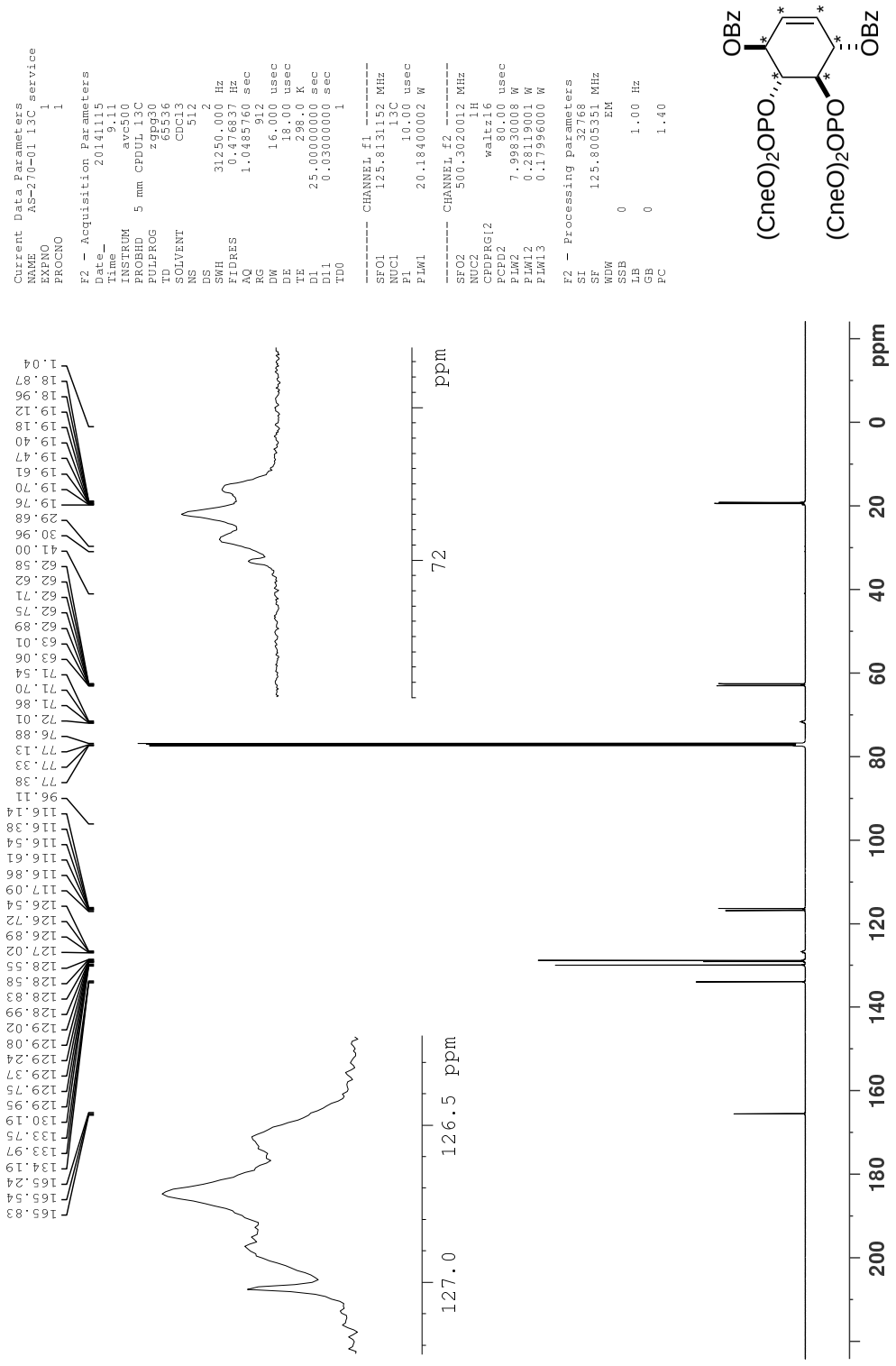
^{1}H NMR of (+)-168


Current Data Parameters
NAME AS-270-01
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141106
Time 17.39
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.08944465 sec
RG 176.87
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.13200007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.13000097 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
OBz
(CneO)2OPO
(CneO)2OPO
ppm
0.49
4.46
28.35
28.22
4.12
20.66
13.70

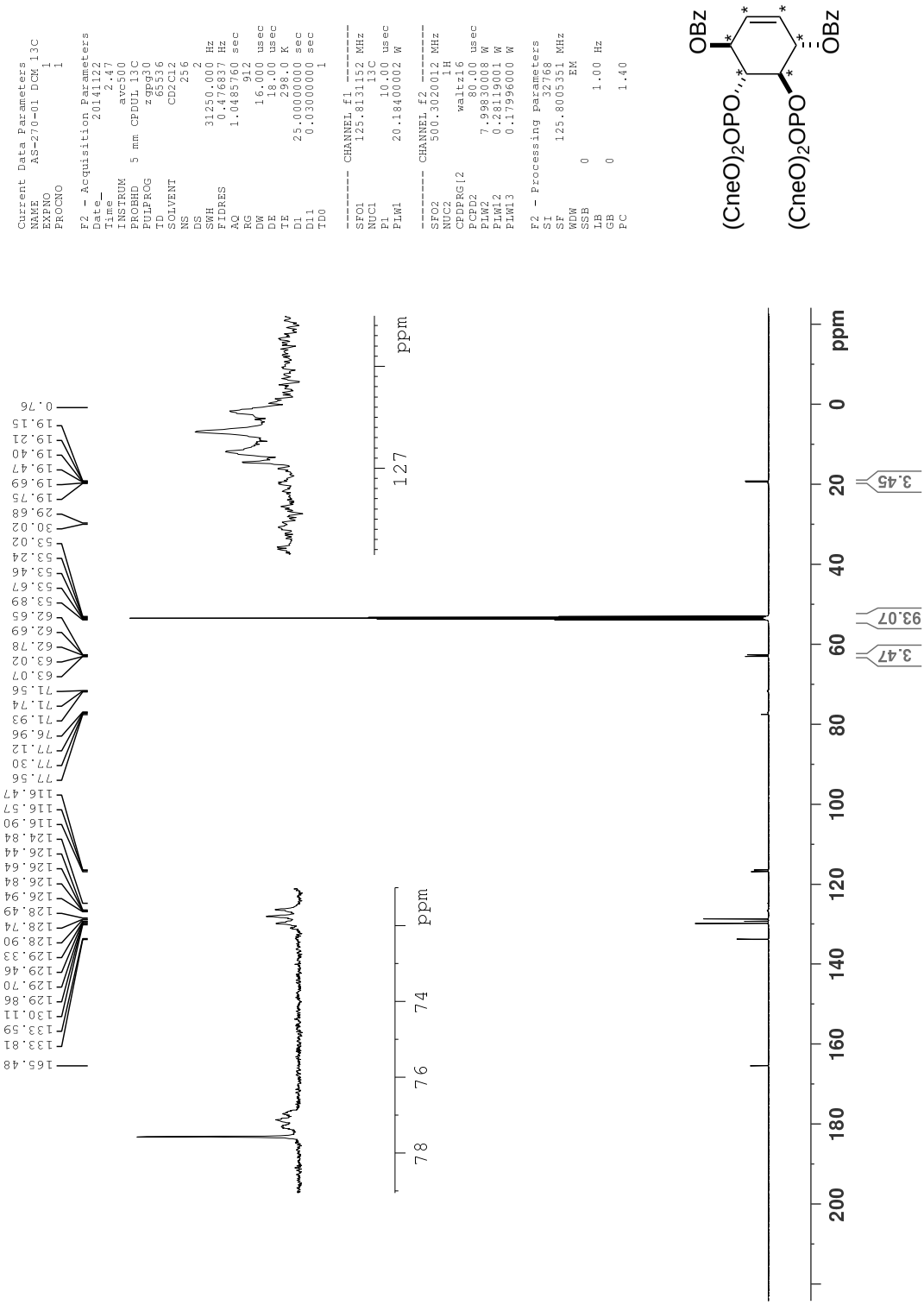
^{1}H NMR (in CD_2Cl_2) of (+)-168



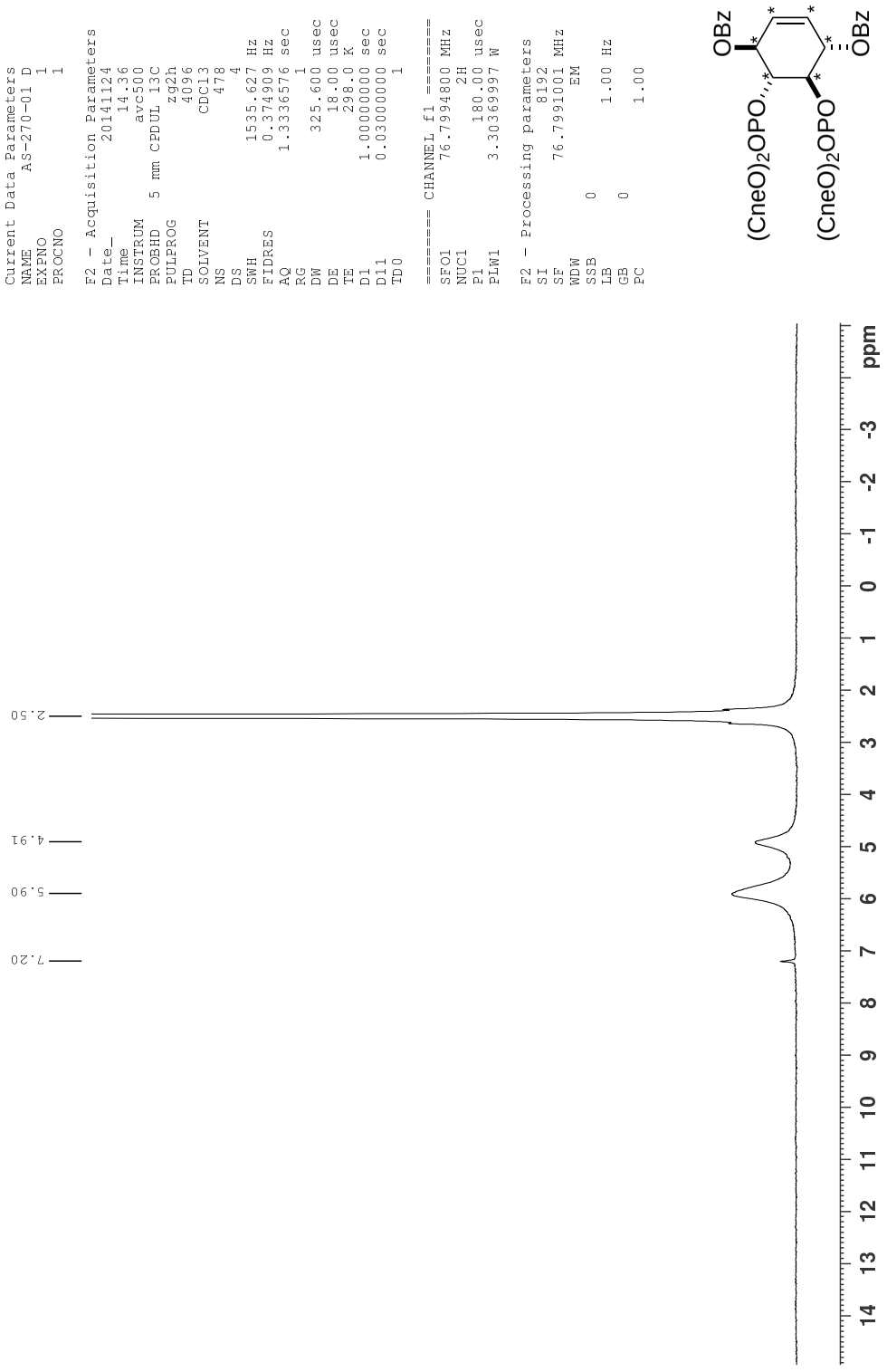
^{13}C NMR of (+)-168



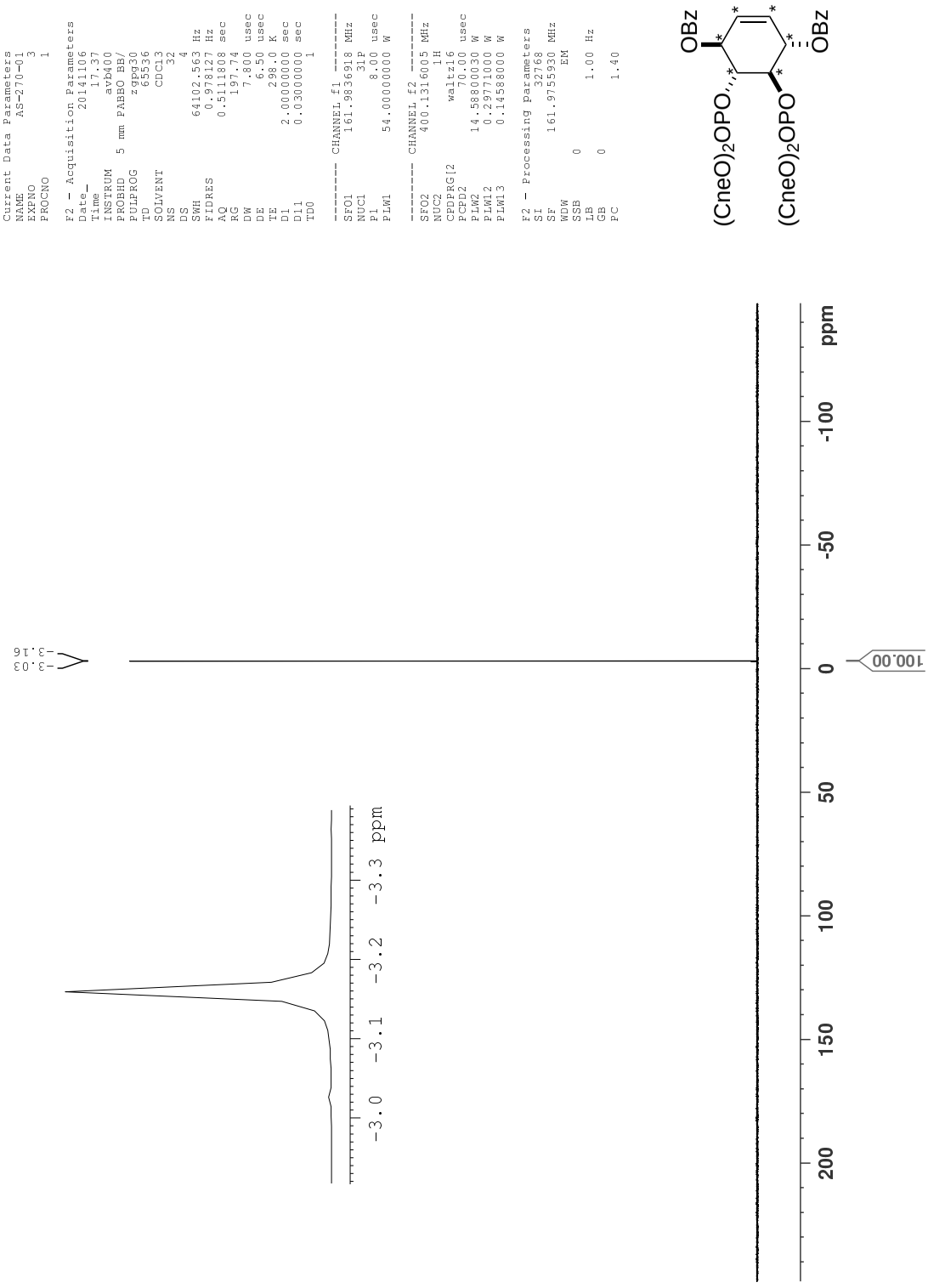
^{13}C NMR (in CD_2Cl_2) of (+)-168



^{2}H NMR of (+)-168


Current Data Parameters
NAME AS-270-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141124
Time 14.36
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 478
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991001 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OBz
(CneO)2OPO
(CneO)2OPO
OBz
2.50
4.91
5.90
7.20
ppm

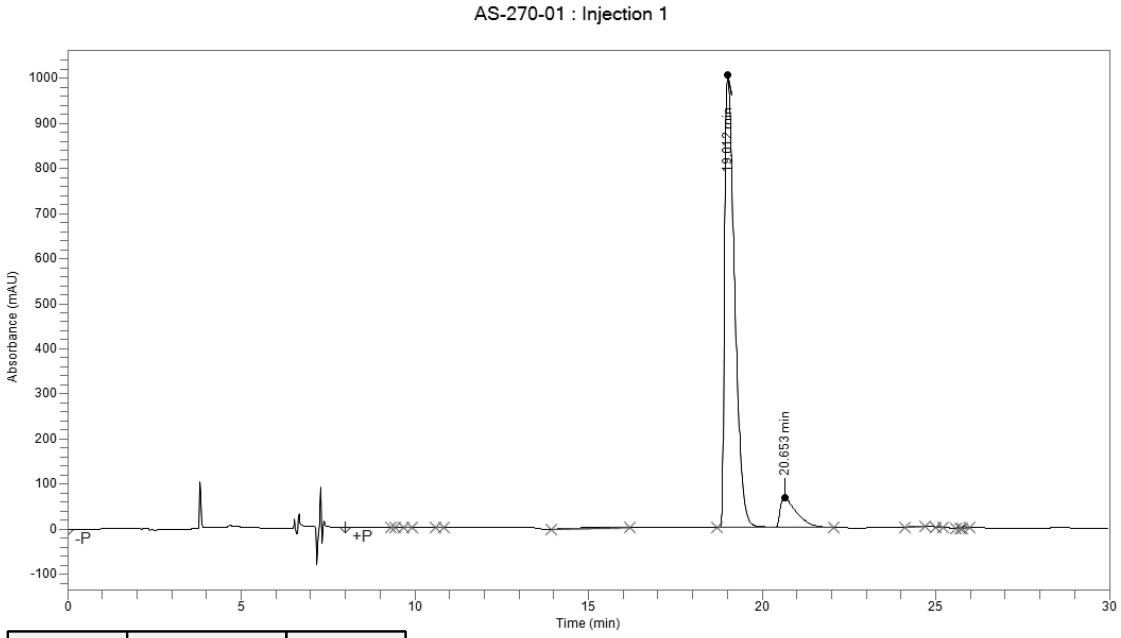
^{31}P NMR of (+)-168



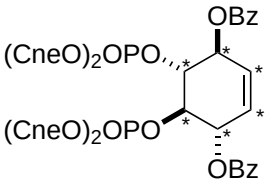
HPLC of (+)-168

AS-270-01

Sample Name	AS-270-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity	Acquisition Date/Time	12/10/2014 2:13 pm
Batch Group/Name	Alex/Normal Phase Purity - Copy 12-10-2014 16-24-08	Batch Description	Normal Phase silica column

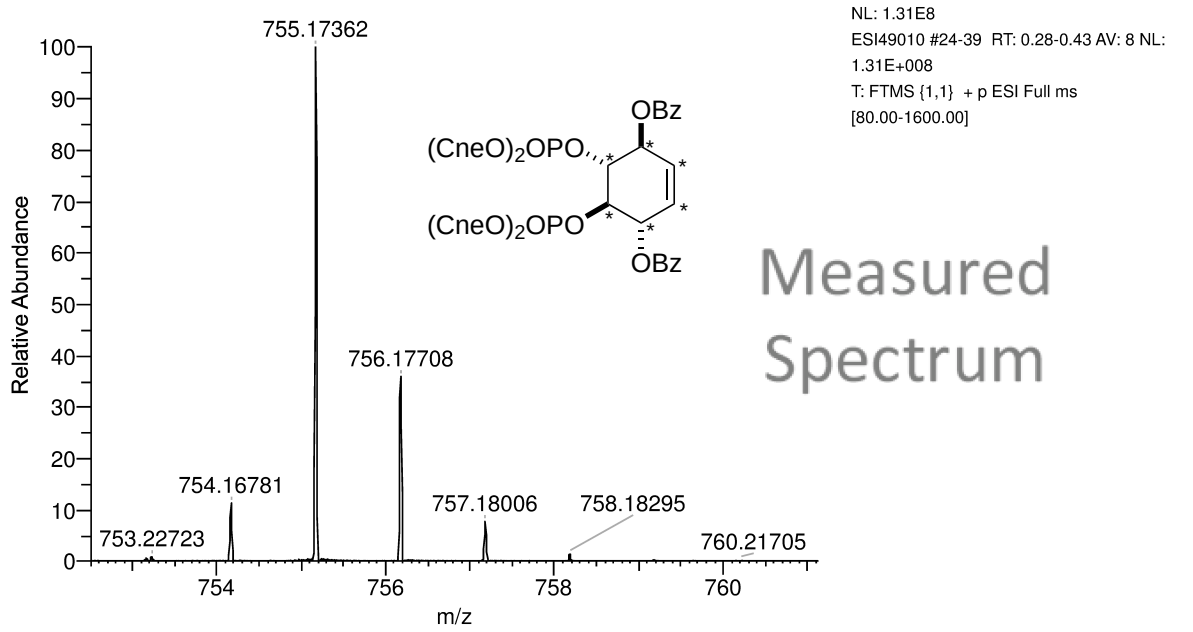


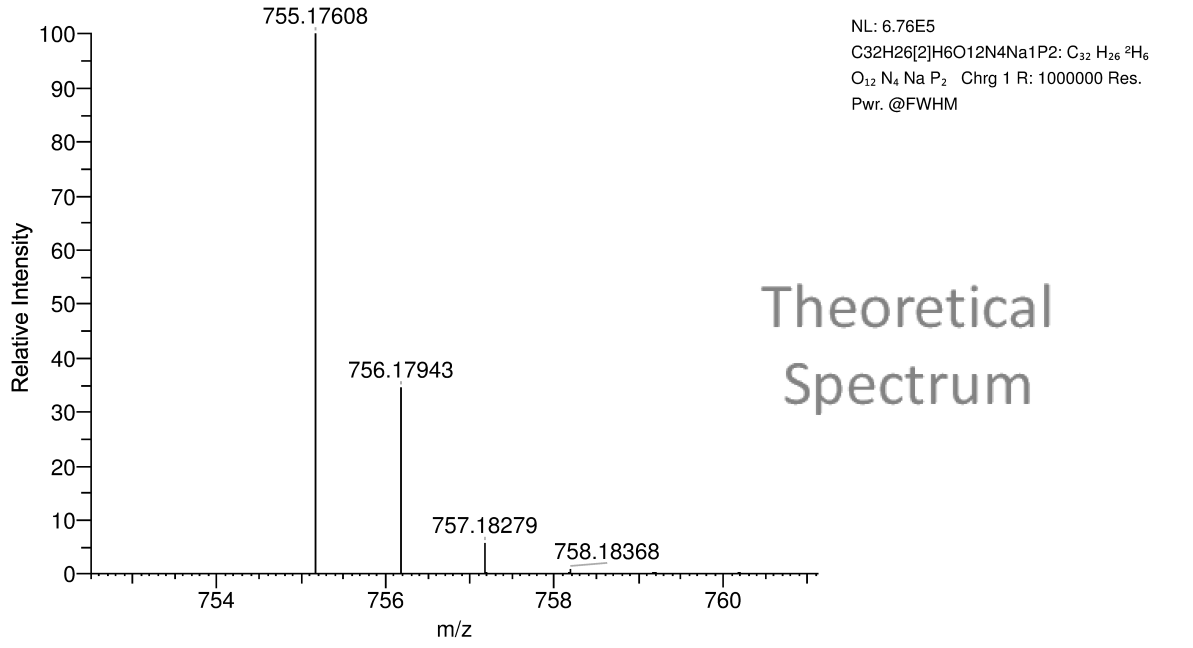
Time	Area	Area %
9.394	693.88	0.00
9.819	5735.6	0.03
10.716	2902.5	0.01
16.113	145848	0.64
19.012	20438033	89.51
20.653	2185100	9.57
24.639	16621	0.07
25.079	9698.8	0.04
25.644	5064.6	0.02
25.841	22768	0.10
Total	22832465	100.00



Mass spectrum of (+)-168

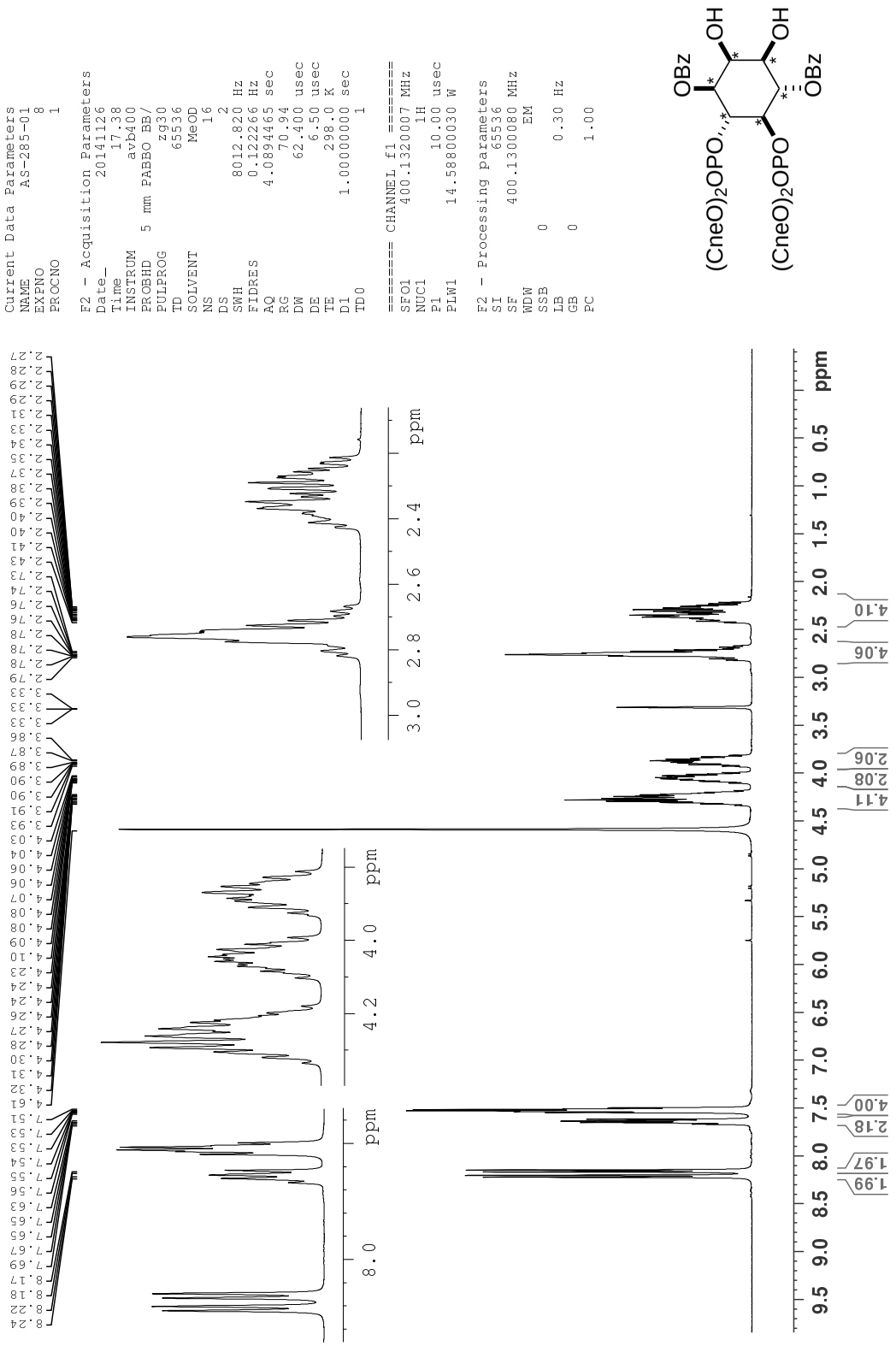
S:\data\Nov 14\ESI49010.raw 10/11/2014 8:21 am



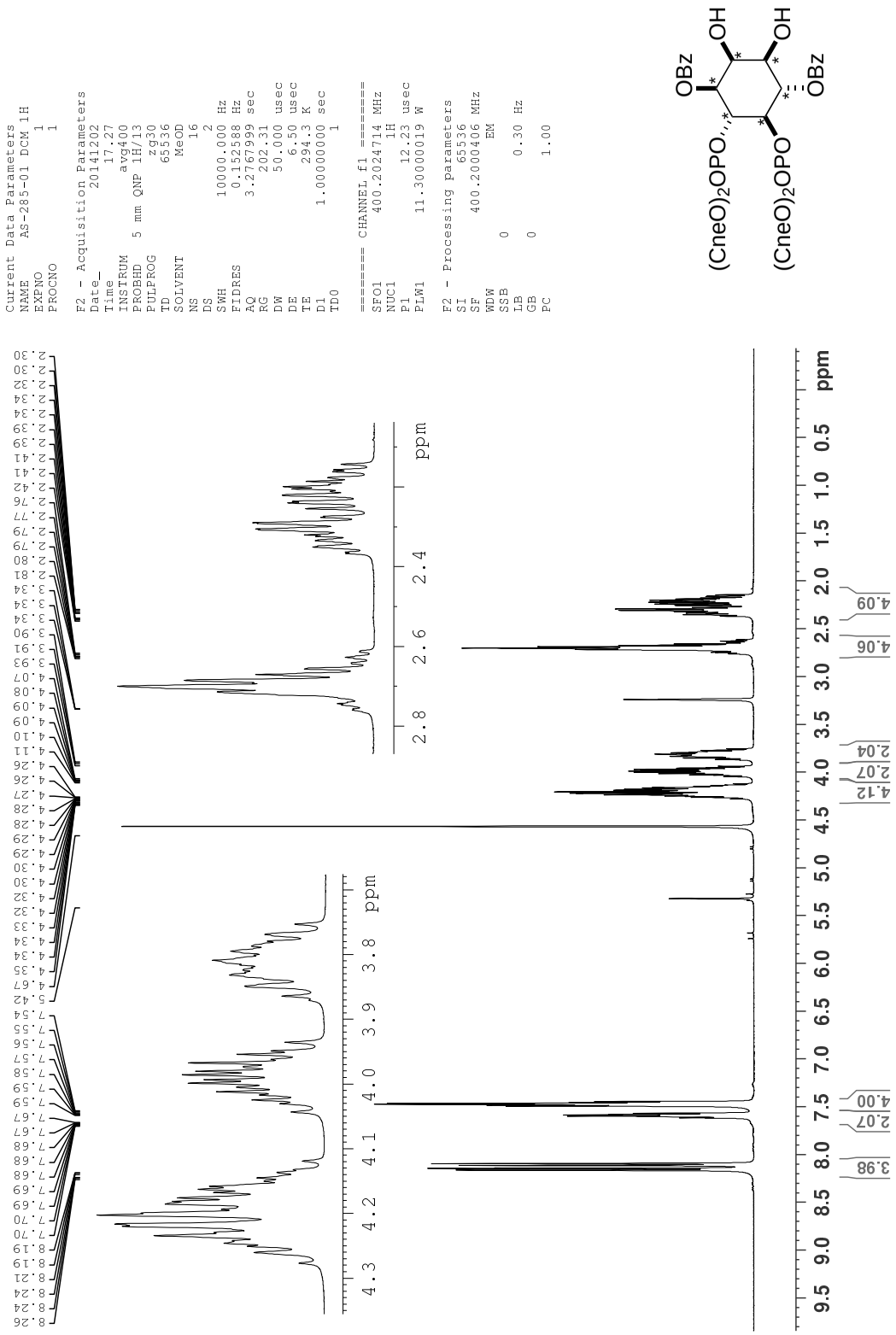


m/z	Formula	RDB	Delta ppm	Theo. Mass
755.17365	$C_{32}H_{26}{}^{2}H_{6}O_{12}N_{4}{}^{23}NaP_{2}$	19.5	-3.22	755.17608

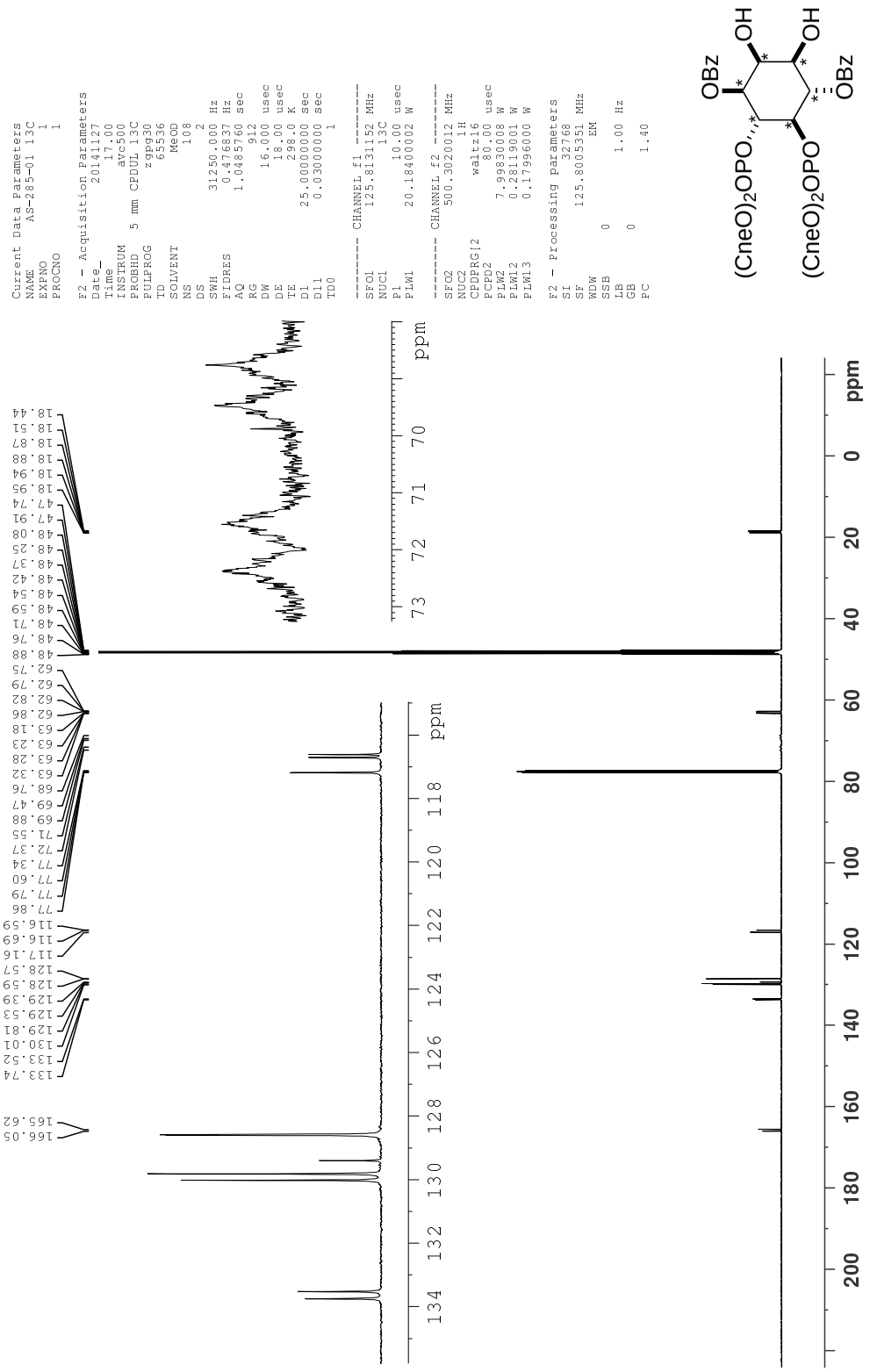
^{1}H NMR of (+)-169


Current Data Parameters
NAME AS-285-01
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141126
Time 17.38
INSTRUM avb400
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.08944465 sec
RG 70.94
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.13200007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.13000080 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBz
OH
OH
OBz
(CneO)2OPO
(CneO)2OPO
4.10
4.06
2.06
2.08
4.11
4.00
2.18
1.97
1.99
ppm

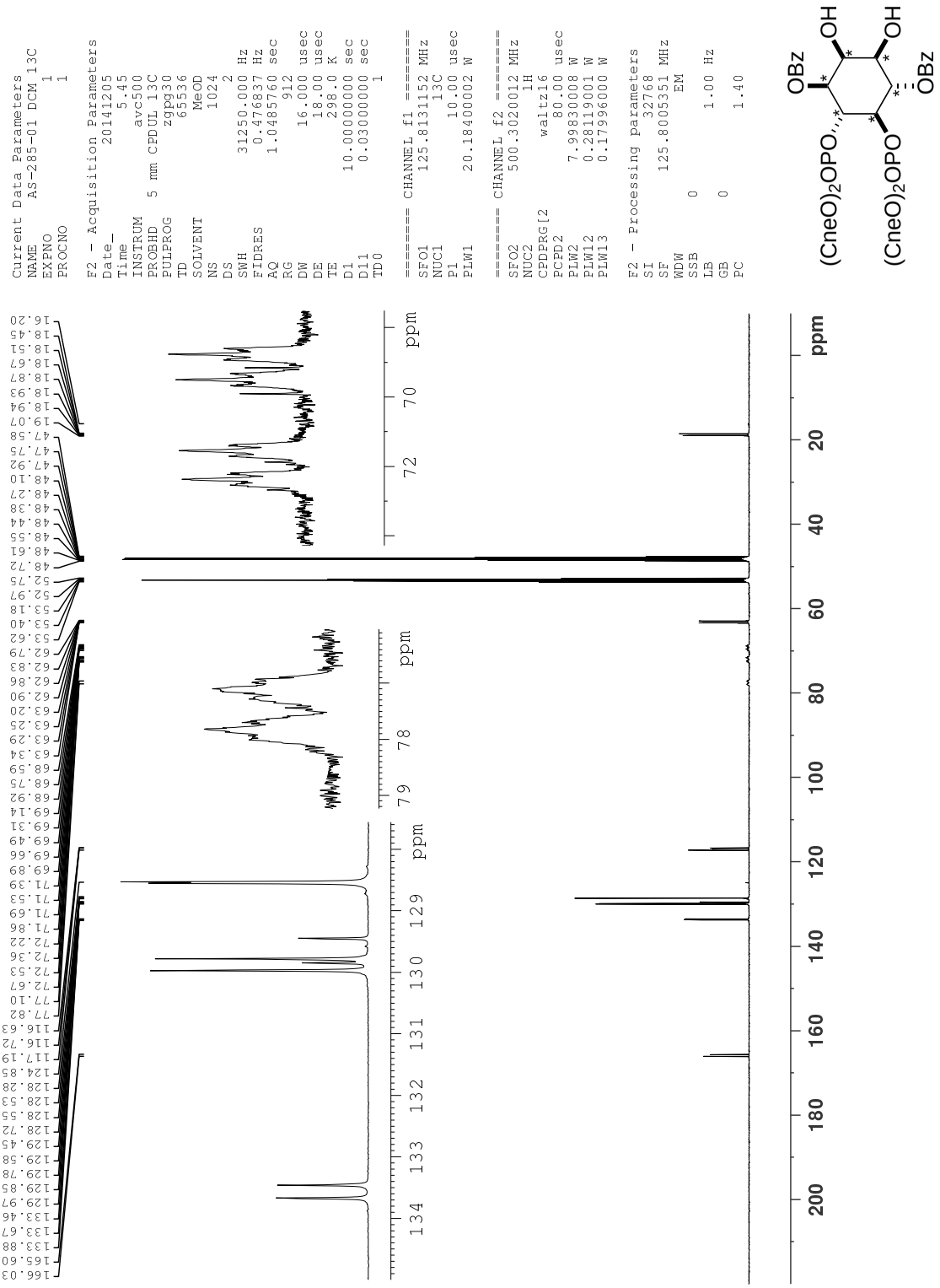
^{1}H NMR (in CD_2Cl_2) of (+)-169



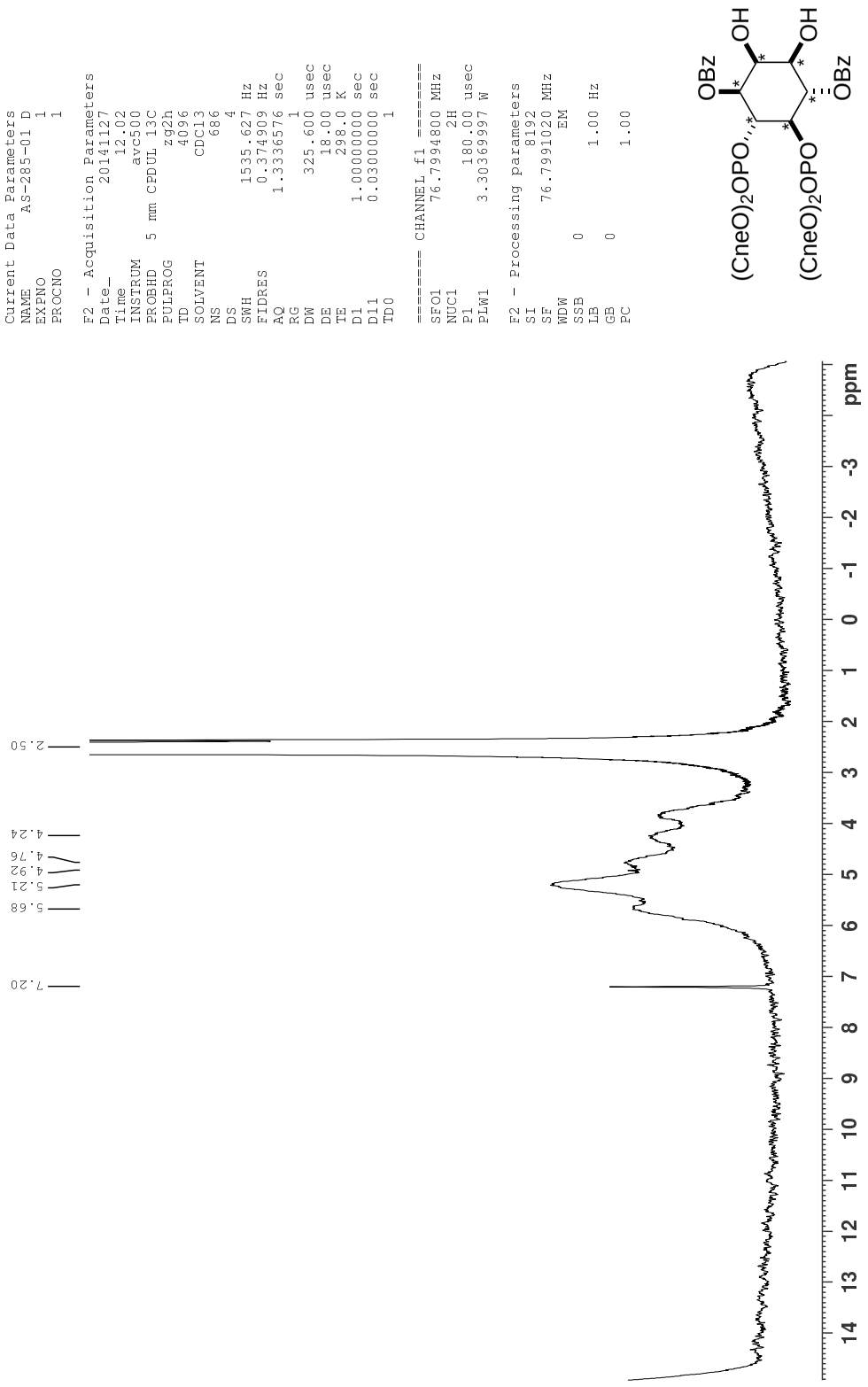
^{13}C NMR of (+)-169



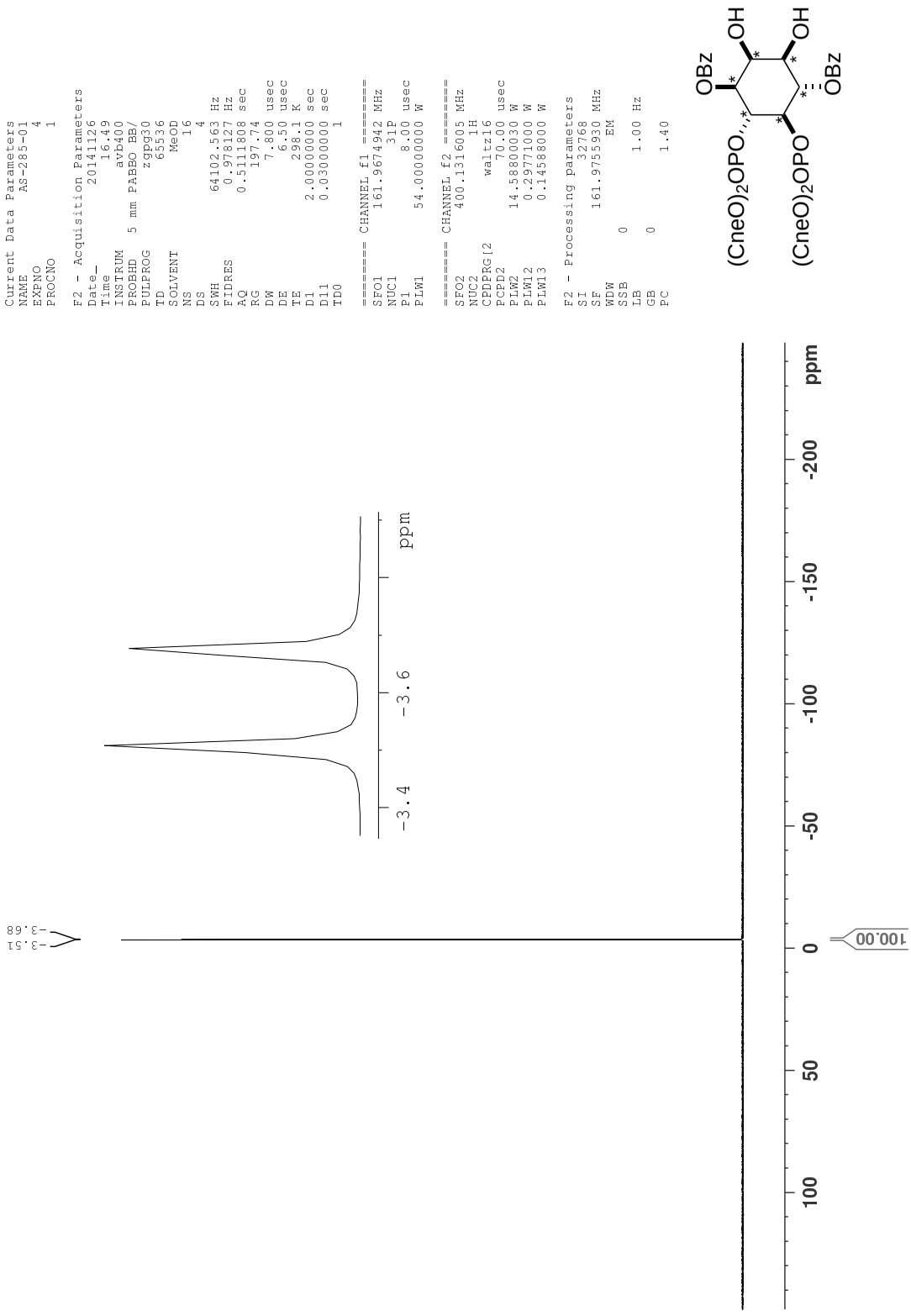
^{13}C NMR (in CD_2Cl_2) of (+)-169



^{2}H NMR of (+)-169


Current Data Parameters
NAME AS-285-01 D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141127
Time 12.02
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 686
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7991020 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OBz
OH
OH
OBz
(CneO)2OPO
(CneO)2OPO
2.50
4.24
4.76
4.92
5.21
5.68
7.20
ppm

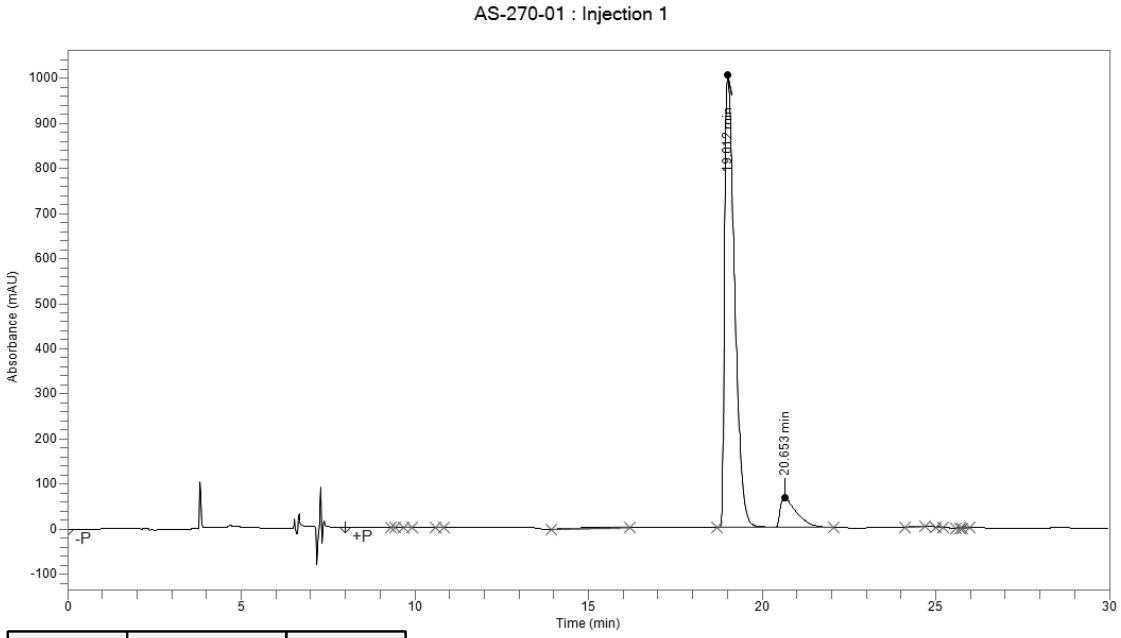
^{31}P NMR of (+)-169



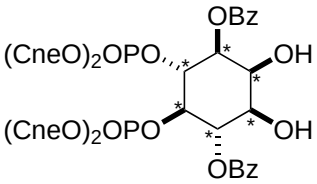
HPLC of (+)-169

AS-270-01

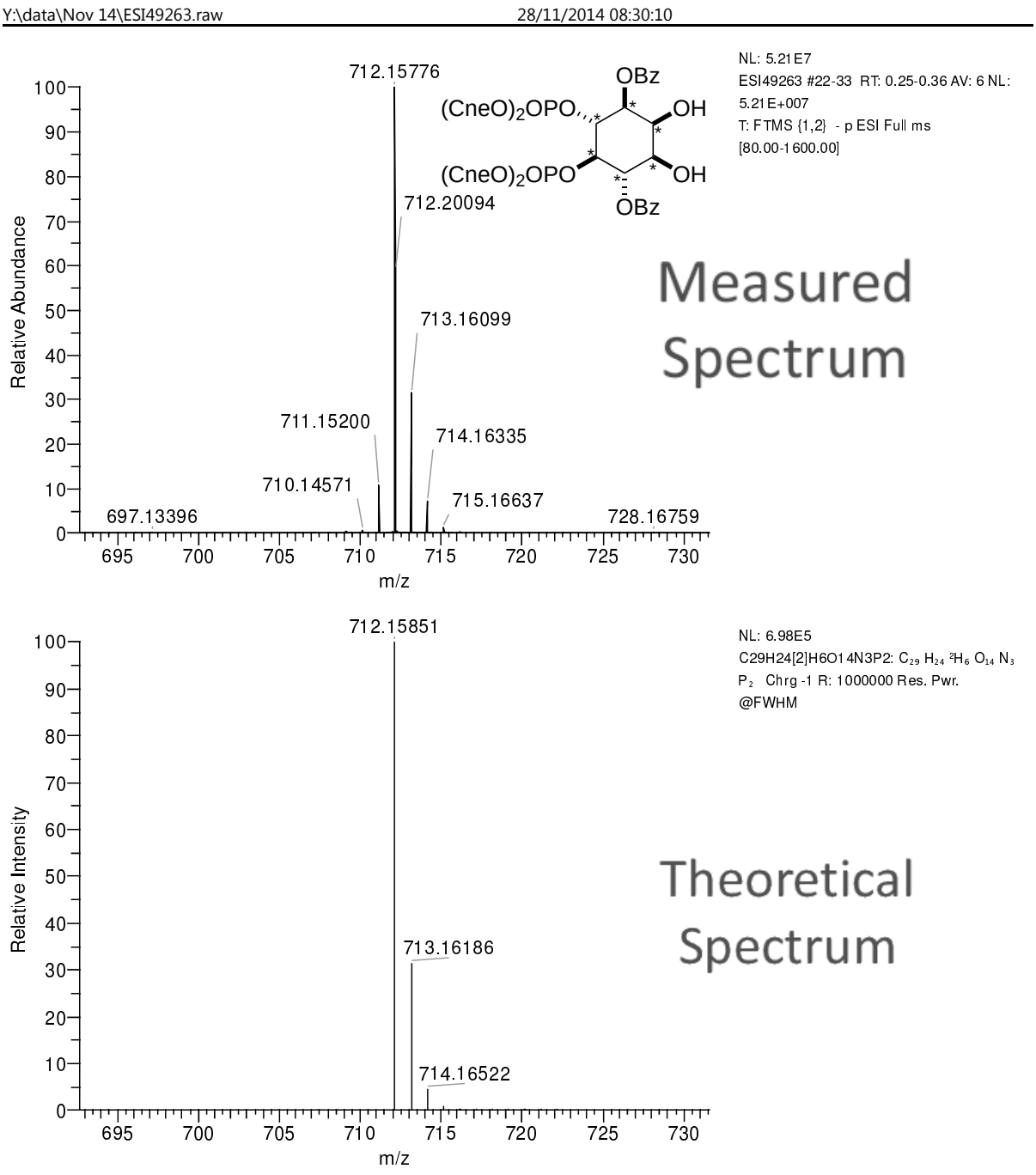
Sample Name	AS-270-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity	Acquisition Date/Time	12/10/2014 2:13 pm
Batch Group/Name	Alex/Normal Phase Purity - Copy 12-10-2014 16-24-08	Batch Description	Normal Phase silica column



Time	Area	Area %
9.394	693.88	0.00
9.819	5735.6	0.03
10.716	2902.5	0.01
16.113	145848	0.64
19.012	20438033	89.51
20.653	2185100	9.57
24.639	16621	0.07
25.079	9698.8	0.04
25.644	5064.6	0.02
25.841	22768	0.10
Total	22832465	100.00

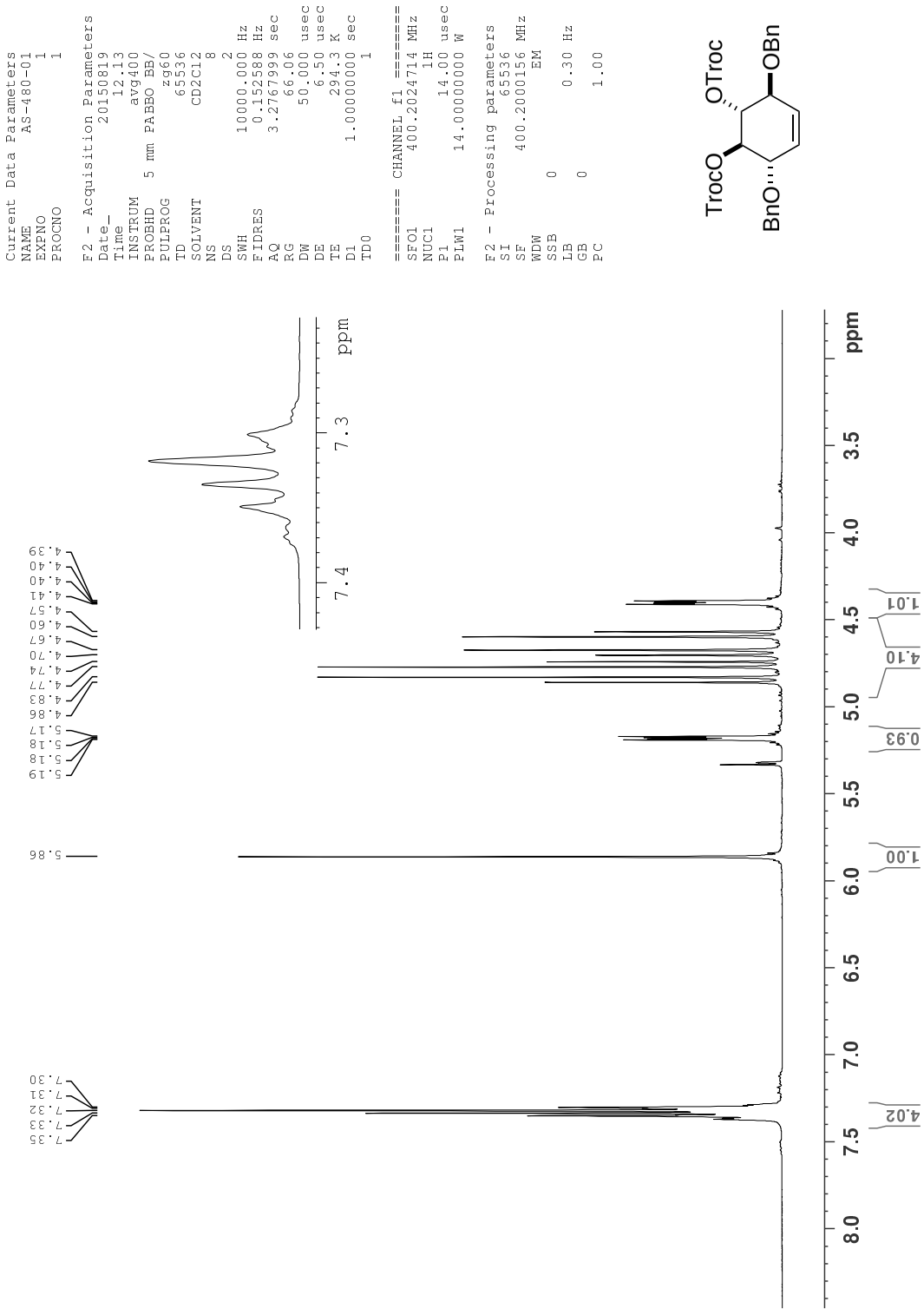


Mass spectrum of (+)-169

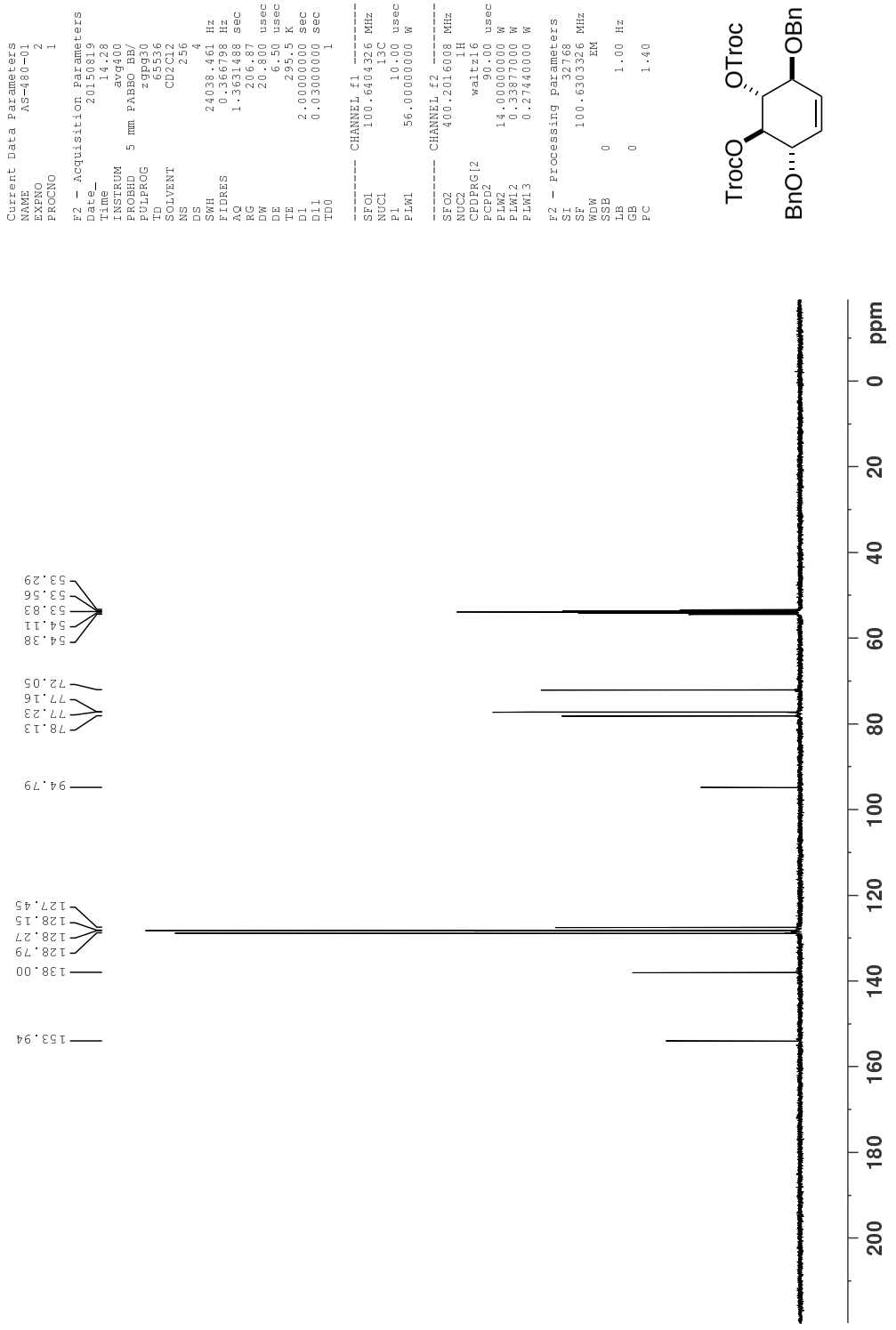


m/z	Formula	RDB	Delta ppm	Theo. Mass
712.15778	$C_{29}H_{24}{}^{2}H_6O_{14}N_3P_2$	17.5	-1.03	712.15851

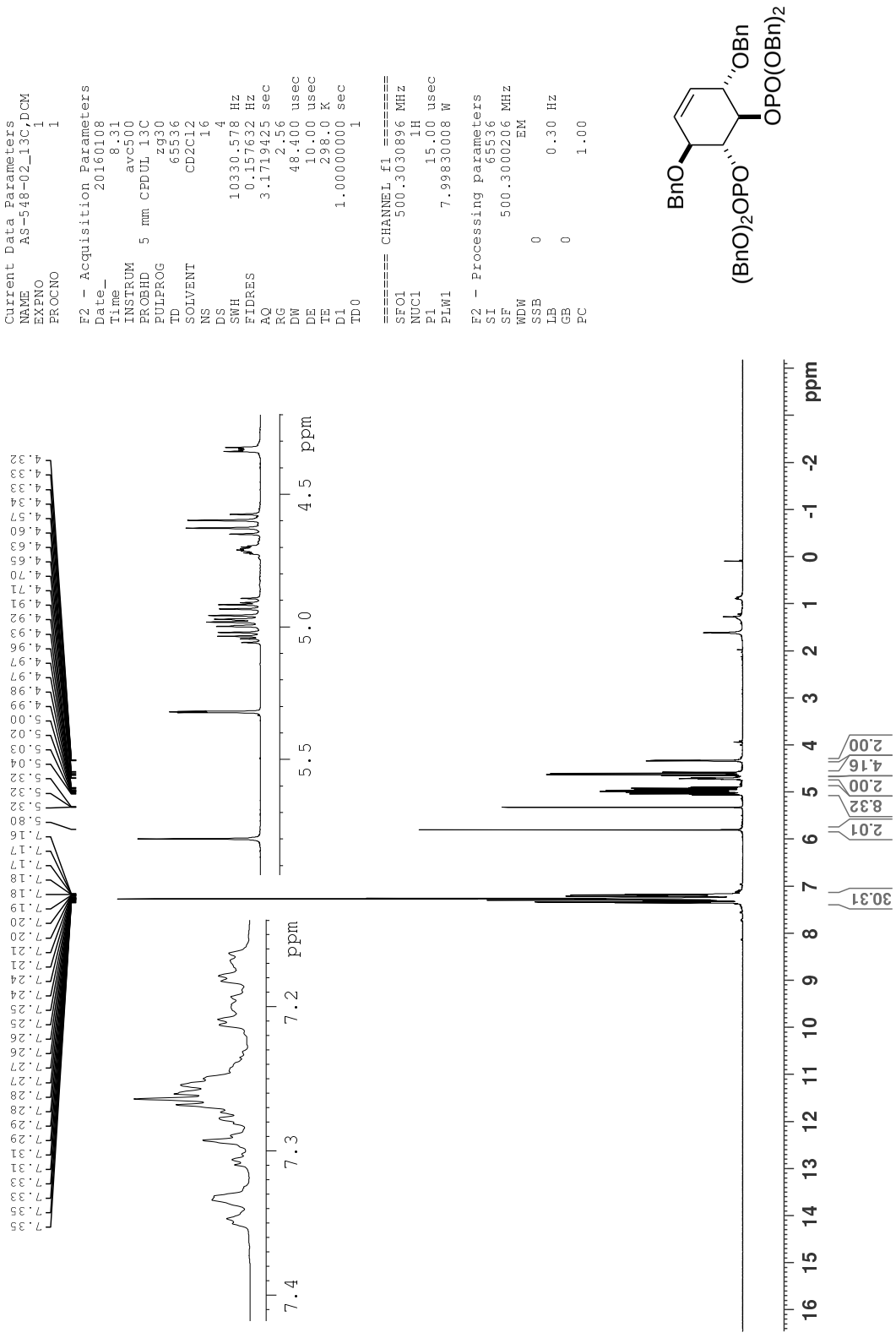
^{1}H NMR of (+)-183


Current Data Parameters
NAME AS-480-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150819
Time 12.13
INSTRUM avg400
PROBHD 5 mm PABBO BB/
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 8
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 66.06
DW 50.000 usec
DE 6.50 usec
TE 294.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 65536
SF 400.2000156 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTroc
OBn
TrocO
BnO
7.4
7.3
ppm
7.35
7.33
7.32
7.31
7.30
5.86
5.19
5.18
5.18
5.17
4.86
4.83
4.77
4.74
4.70
4.67
4.60
4.57
4.41
4.40
4.40
4.39
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
4.02
1.00
0.93
4.10
1.01

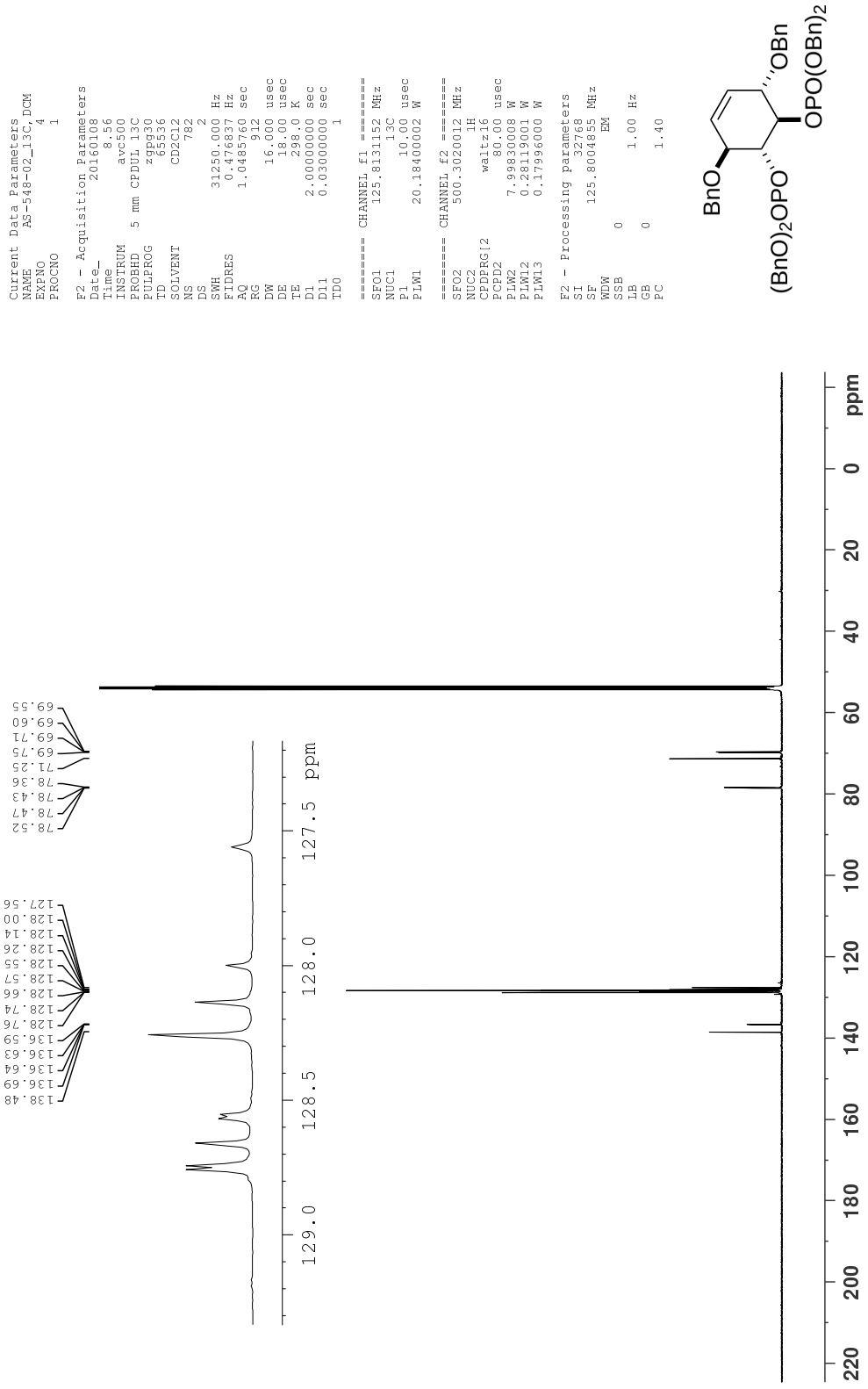
^{13}C NMR of (+)-183



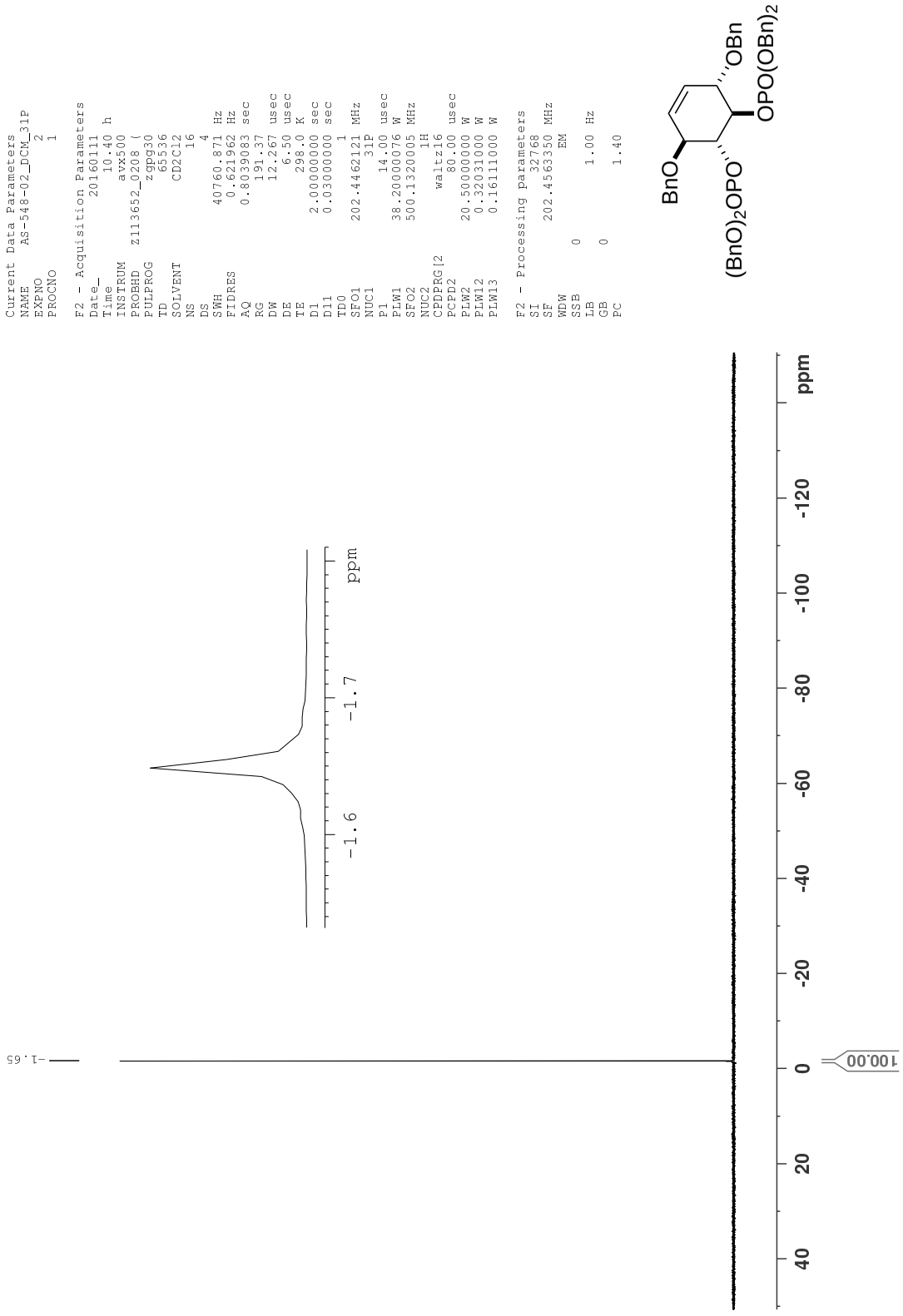
^{1}H NMR of (+)-189


Current Data Parameters
NAME AS-548-02_13C,DCM
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160108
Time 8.31
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 2.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
BnO
(BnO)2OPO
OPO(OBn)2
OBn
30.31
2.01
8.32
2.00
4.16
2.00
ppm

^{13}C NMR of (+)-189



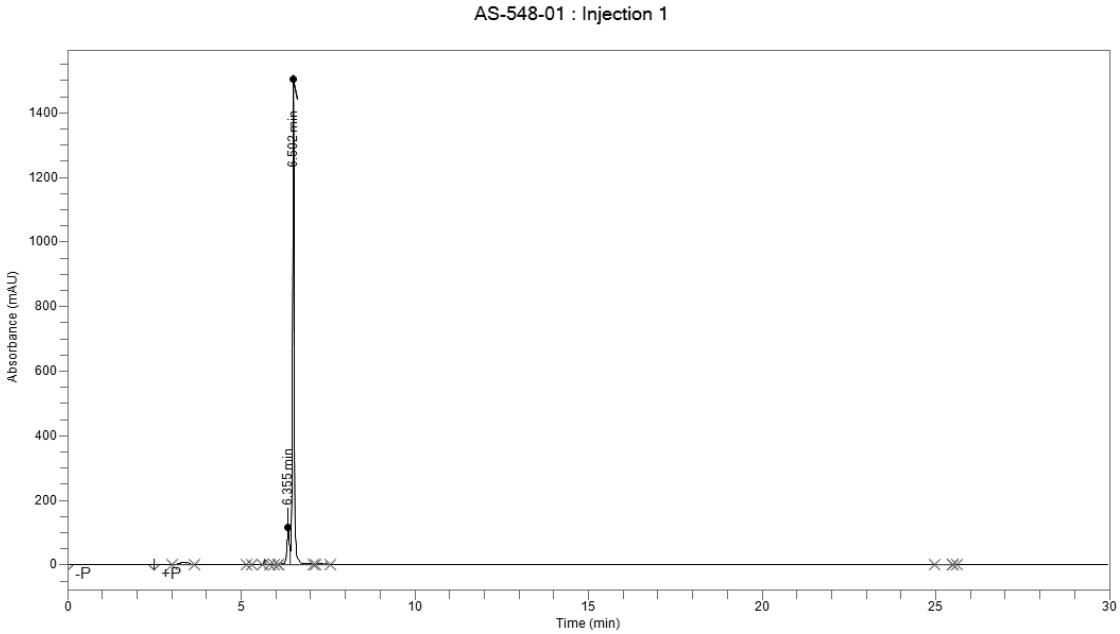
^{31}P NMR of (+)-189

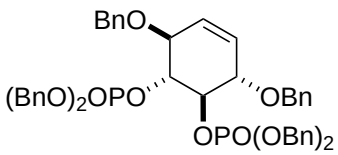


HPLC of (+)-189

AS-548-01

Sample Name	AS-548-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	3/10/2016 5:50 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-57-28	Batch Description	Normal Phase silica column



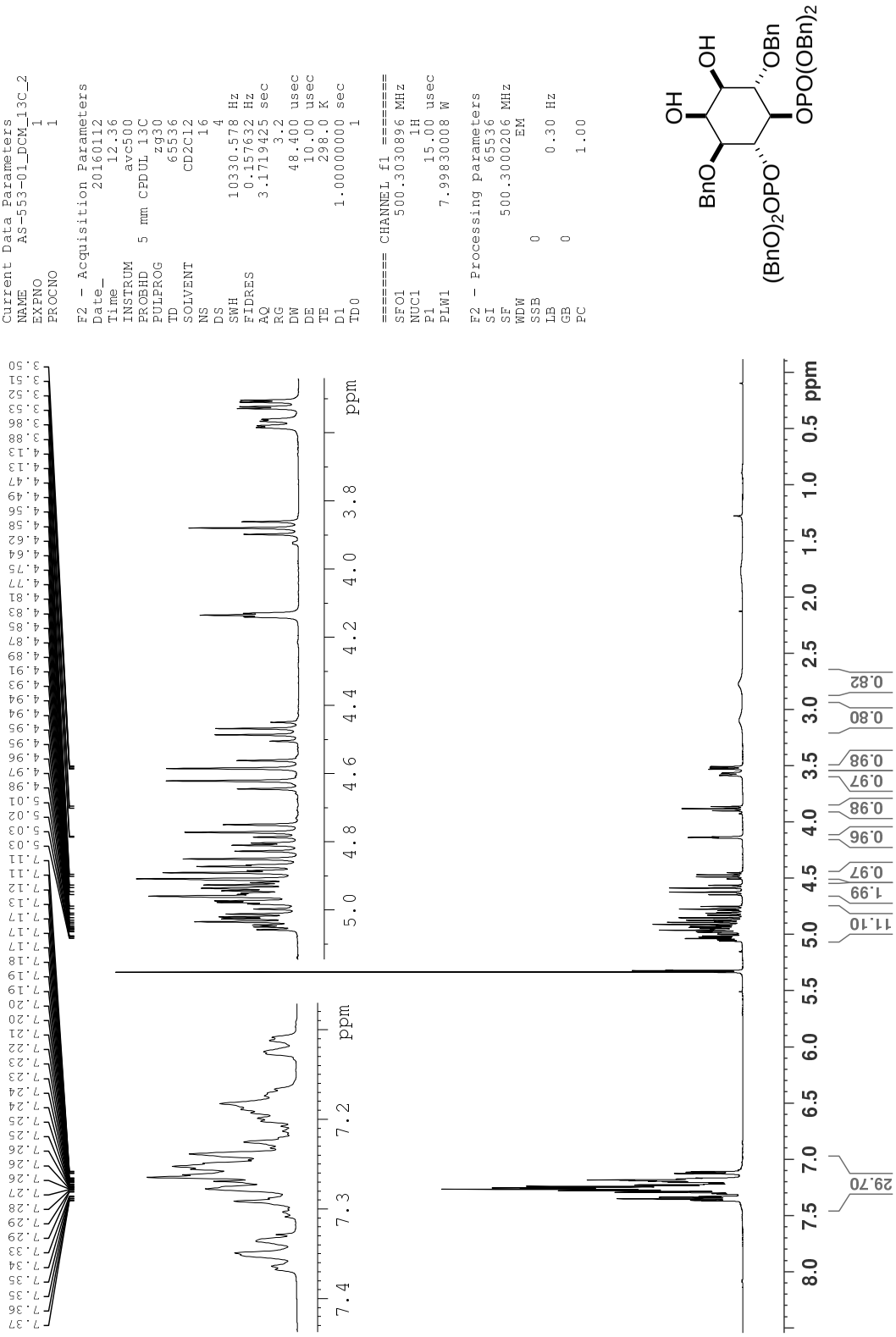


HPLC of (+)-189 (cont.)

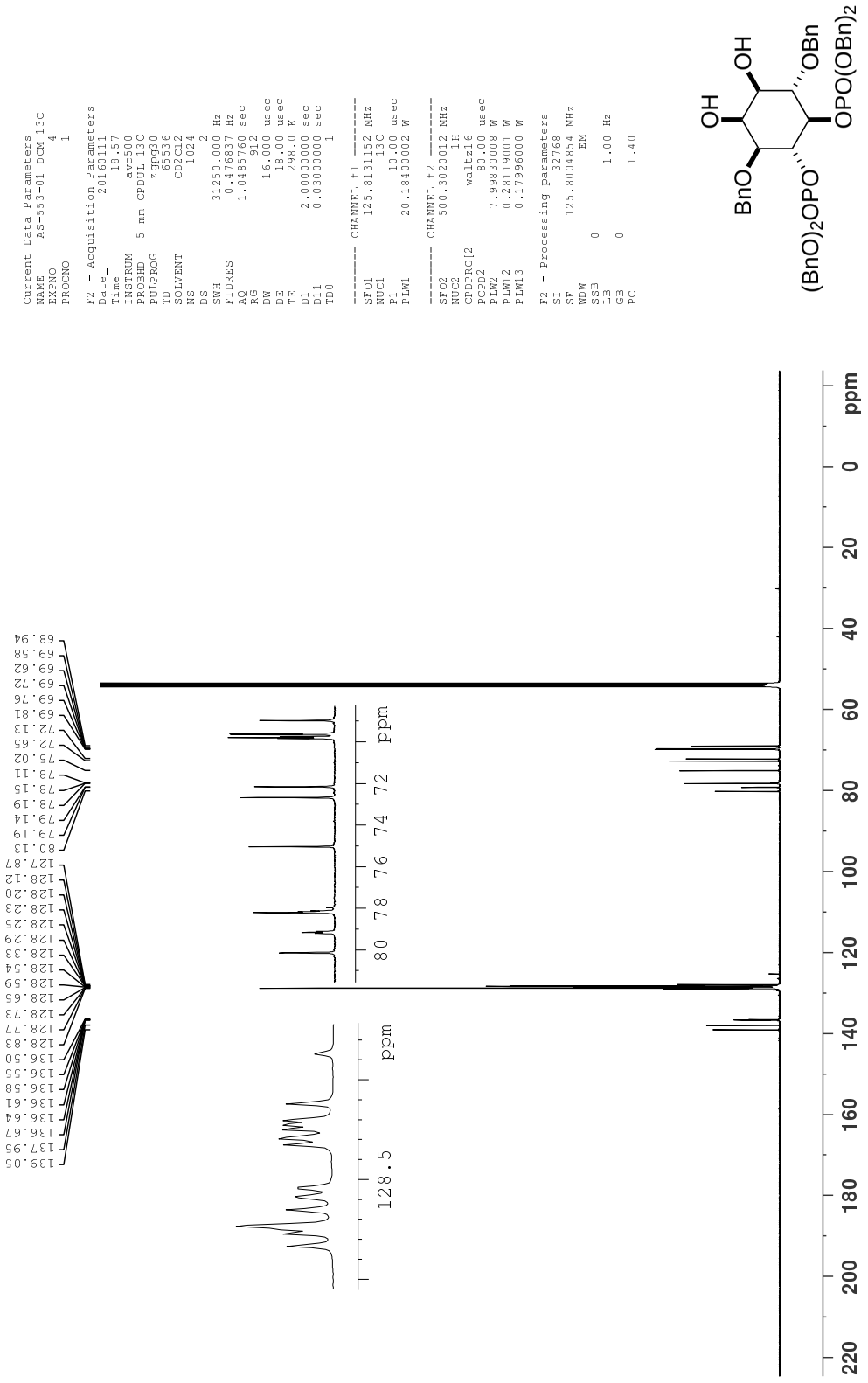
AS-548-01

Time	Area	Area %
3.323	98736	1.58
3.453	47840	0.77
5.234	2794	0.04
5.660	37043	0.59
5.991	2032.2	0.03
6.191	8976	0.14
6.355	585523	9.36
6.502	5366059	85.82
6.880	15451	0.25
6.970	15737	0.25
7.244	8260.9	0.13
7.308	16566	0.26
7.440	19424	0.31
25.111	9099.1	0.15
25.248	7365.5	0.12
25.398	9779.6	0.16
25.555	1679.6	0.03
Total	6252367	100.00

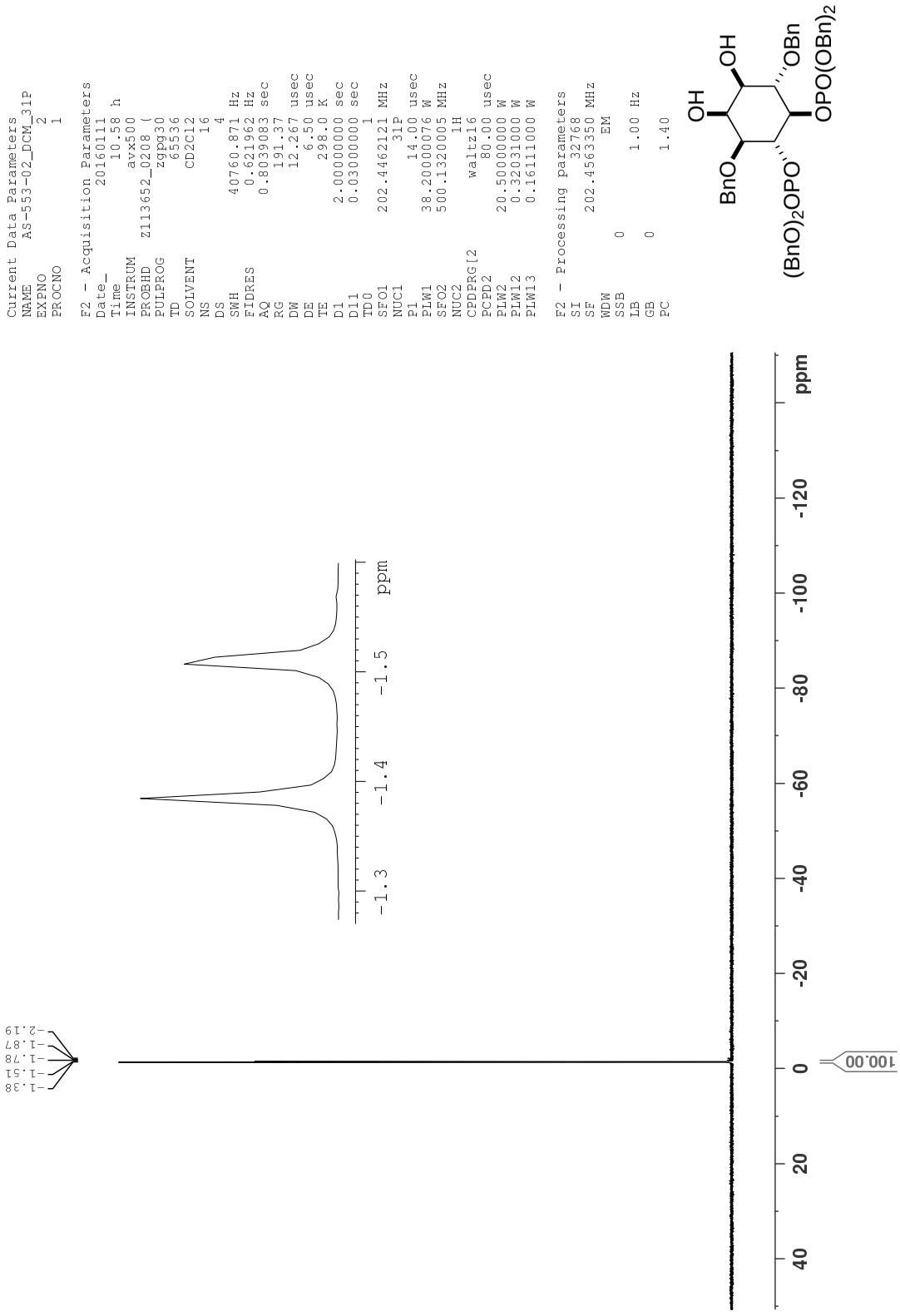
^{1}H NMR of (–)-154


Current Data Parameters
NAME AS-553-01_DCM_13C_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160112
Time 12.36
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OH
BnO
OBn
OPO(OBn)2
(BnO)2OPO
ppm
29.70
11.10
1.99
0.97
0.96
0.98
0.97
0.98
0.80
0.82

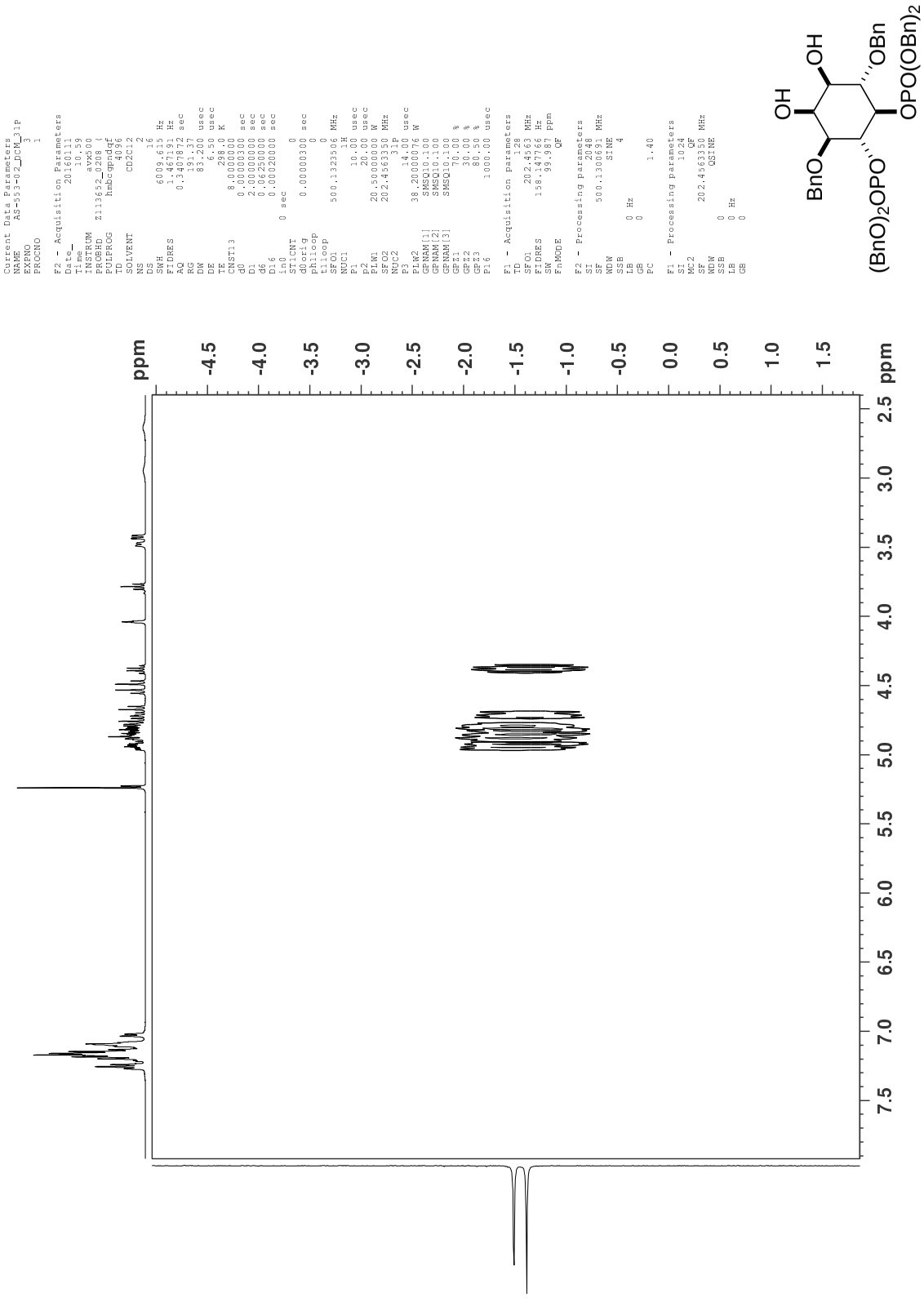
^{13}C NMR of (–)-154



^{31}P NMR of (–)-154



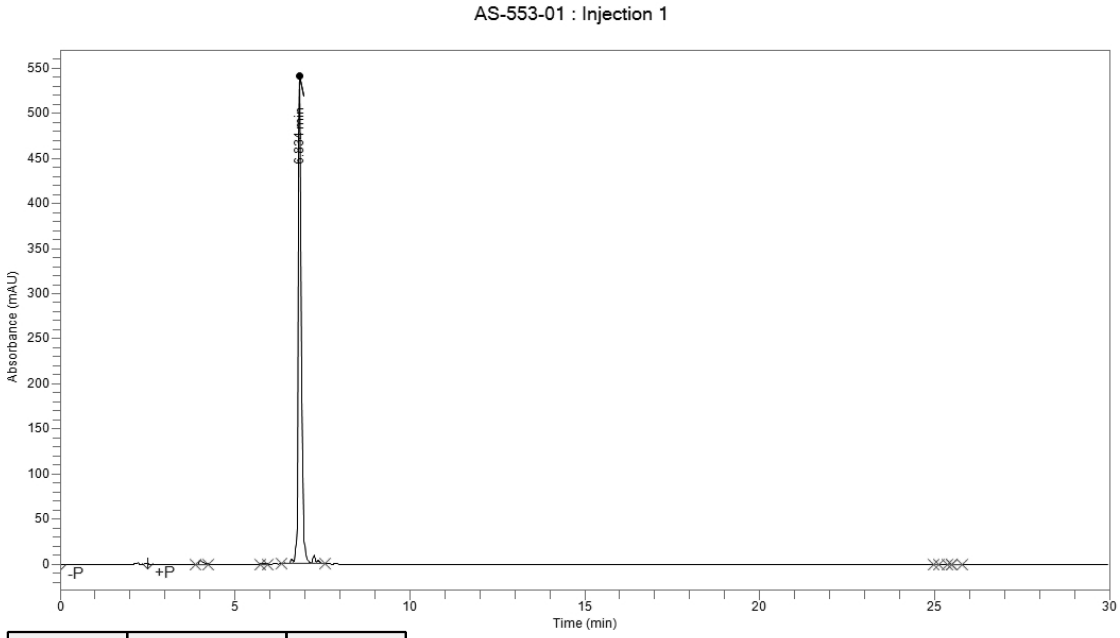
^{1}H-^{31}P HMBC NMR of (–)-154



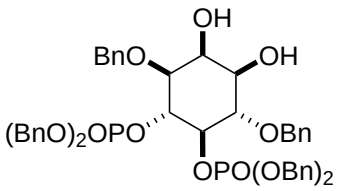
HPLC of (–)-154

AS-553-01

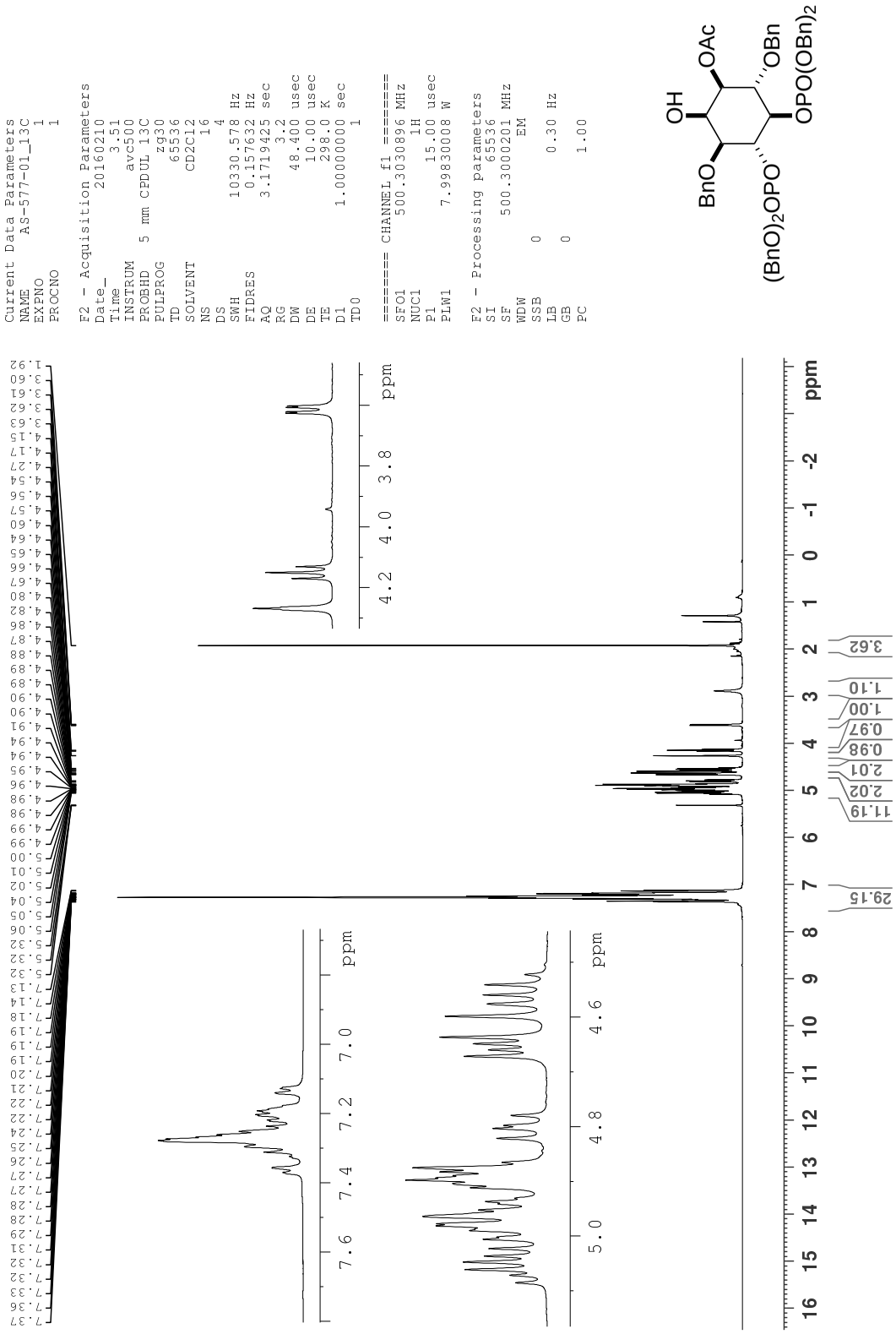
Sample Name	AS-553-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	3/10/2016 3:44 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-57-28	Batch Description	Normal Phase silica column



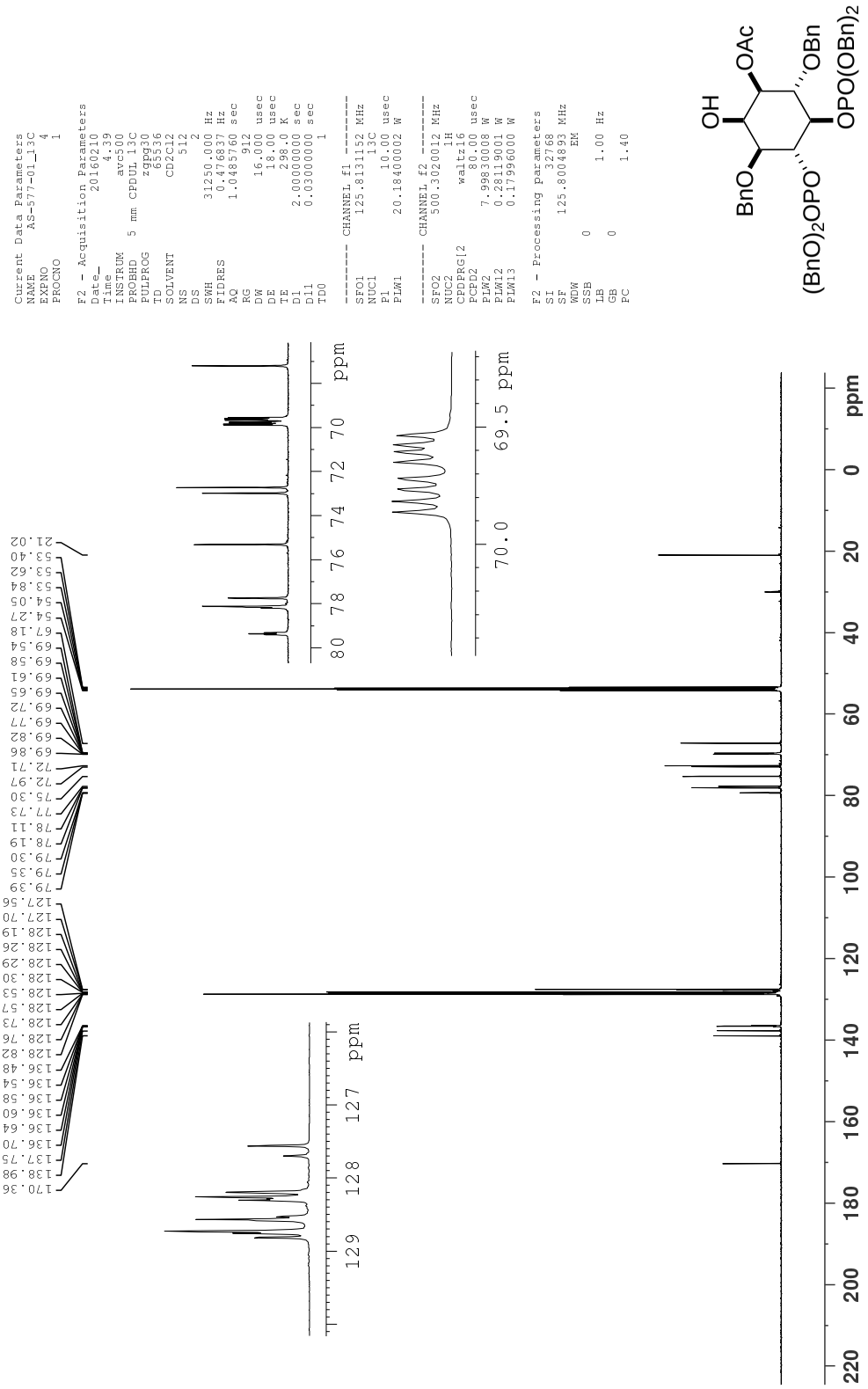
Time	Area	Area %
4.017	31027	0.90
5.813	5813.8	0.17
6.415	5541.6	0.16
6.615	24447	0.71
6.834	3281435	95.60
7.255	49255	1.44
7.377	22728	0.66
25.085	4157.4	0.12
25.427	3030.9	0.09
25.738	4868.2	0.14
Total	3432303	100.00



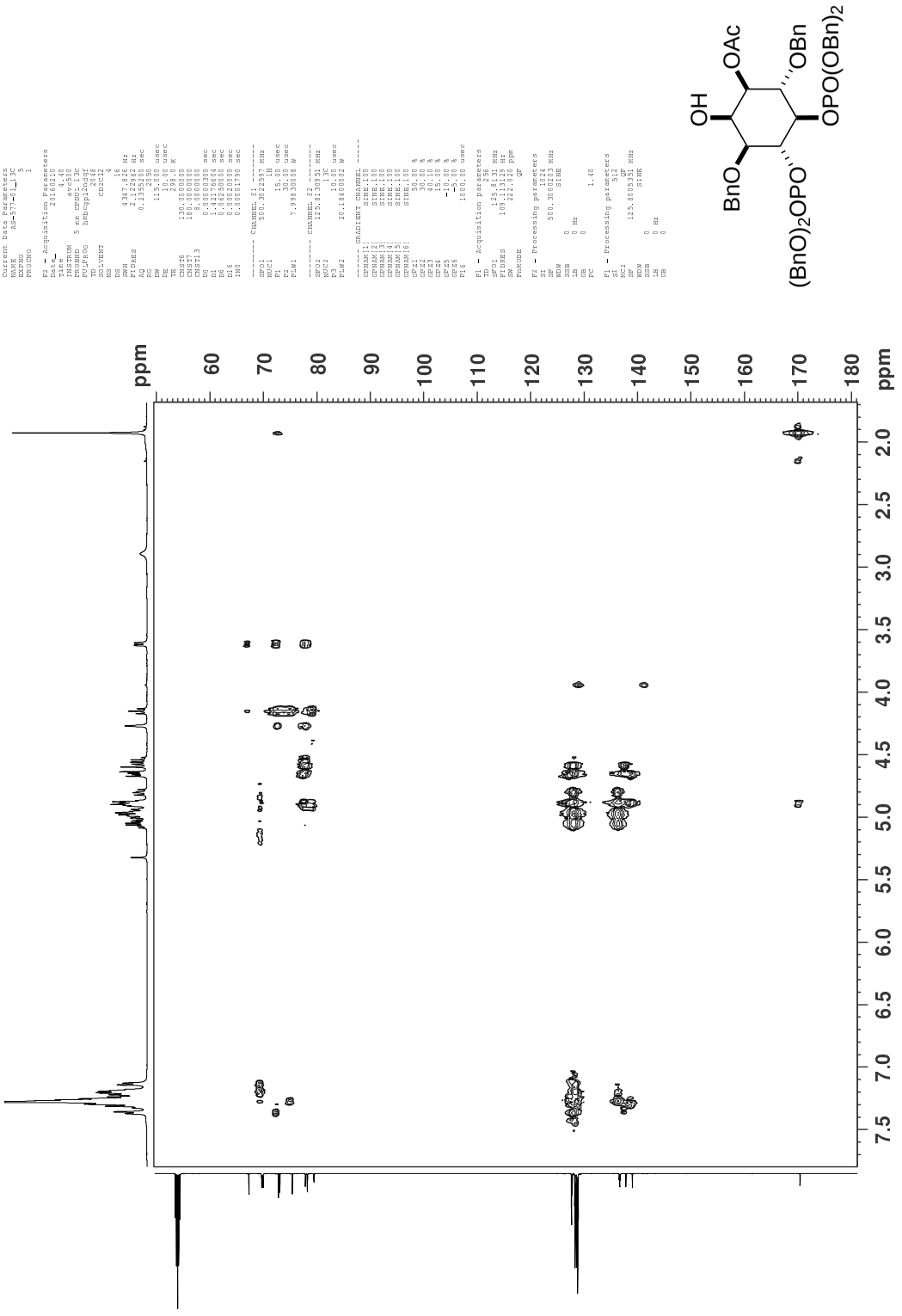
^{1}H NMR of (–)-195


Current Data Parameters
NAME AS-577-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160210
Time 3.51
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000201 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OAc
OBn
OPO(OBn)2
BnO
(BnO)2OPO
3.62
1.10
1.00
0.97
0.98
2.01
2.02
11.19
29.15
ppm

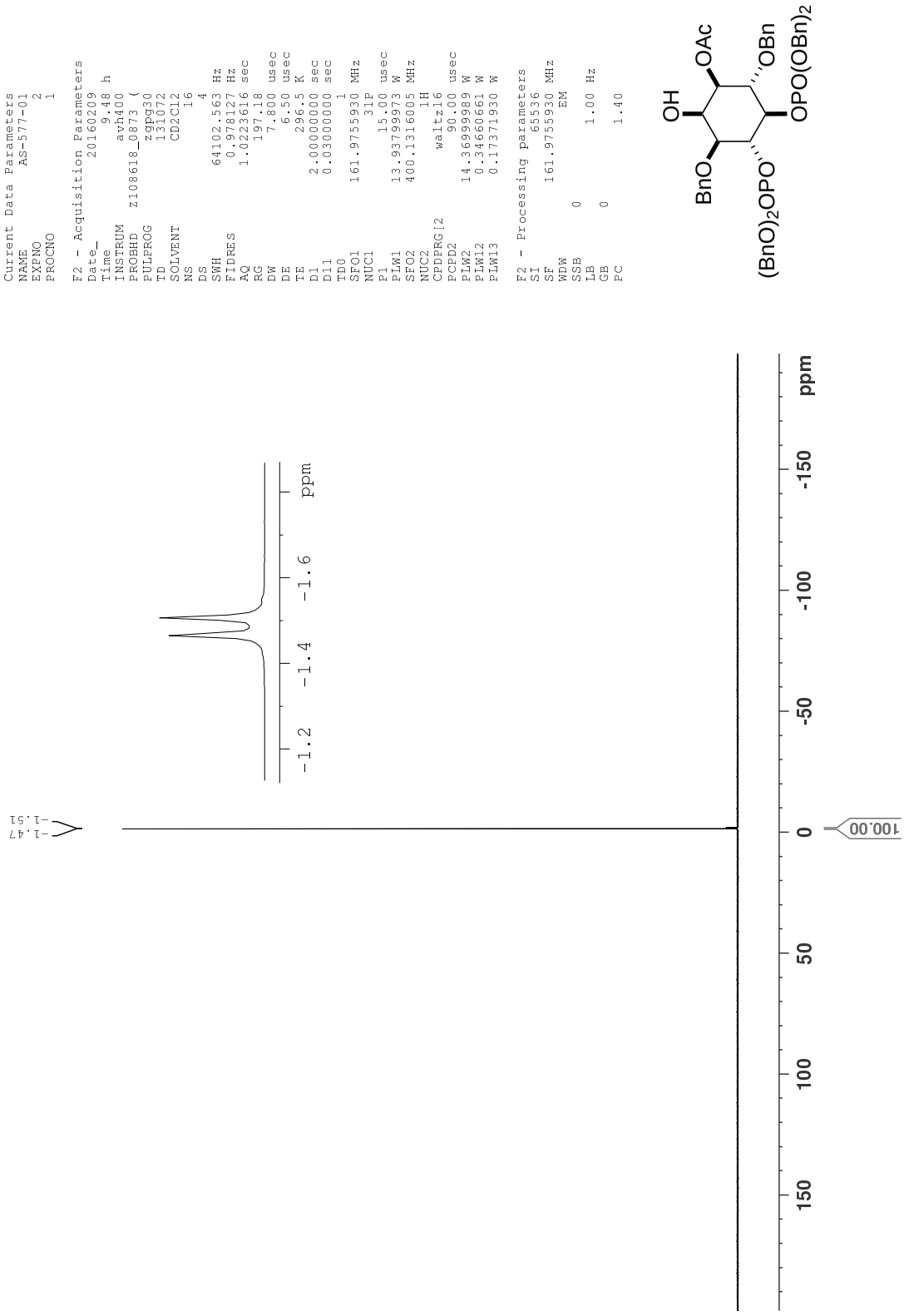
^{13}C NMR of (–)-195



^{1}H-^{13}C HMBC NMR of (–)-195



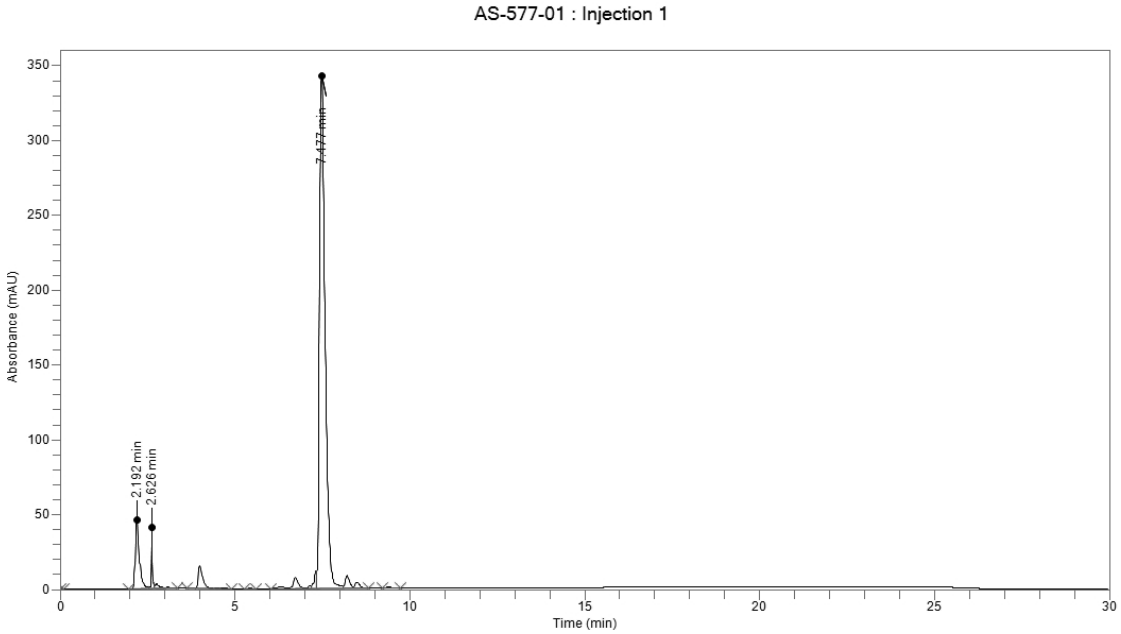
^{31}P NMR of (–)-195

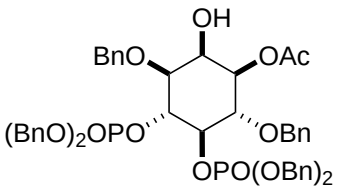


HPLC of (–)-195

AS-577-01

Sample Name	AS-577-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-30	Acquisition Date/Time	7/16/2016 5:58 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-30	Batch Description	Normal Phase silica column



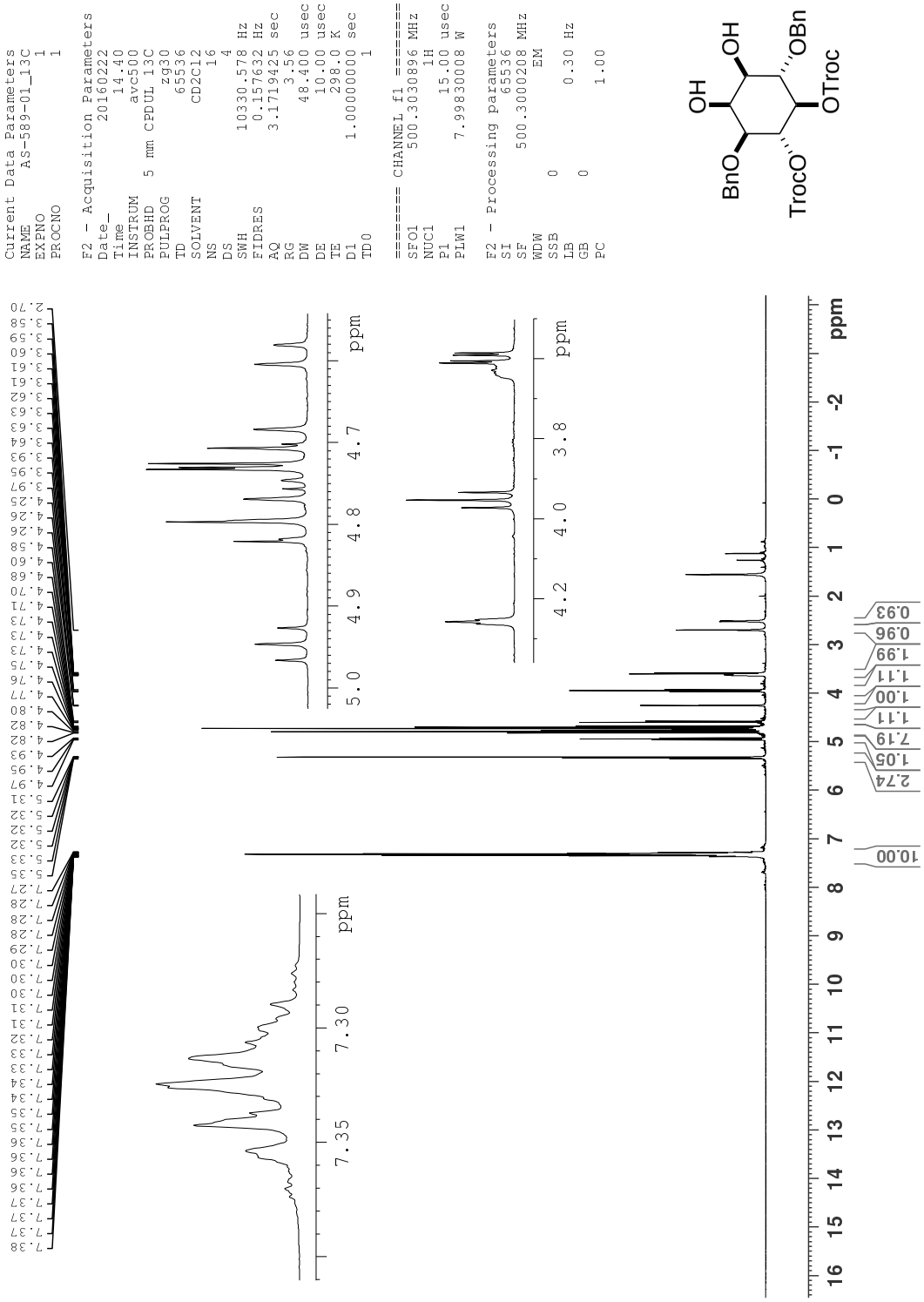


HPLC of (–)-195 (cont.)

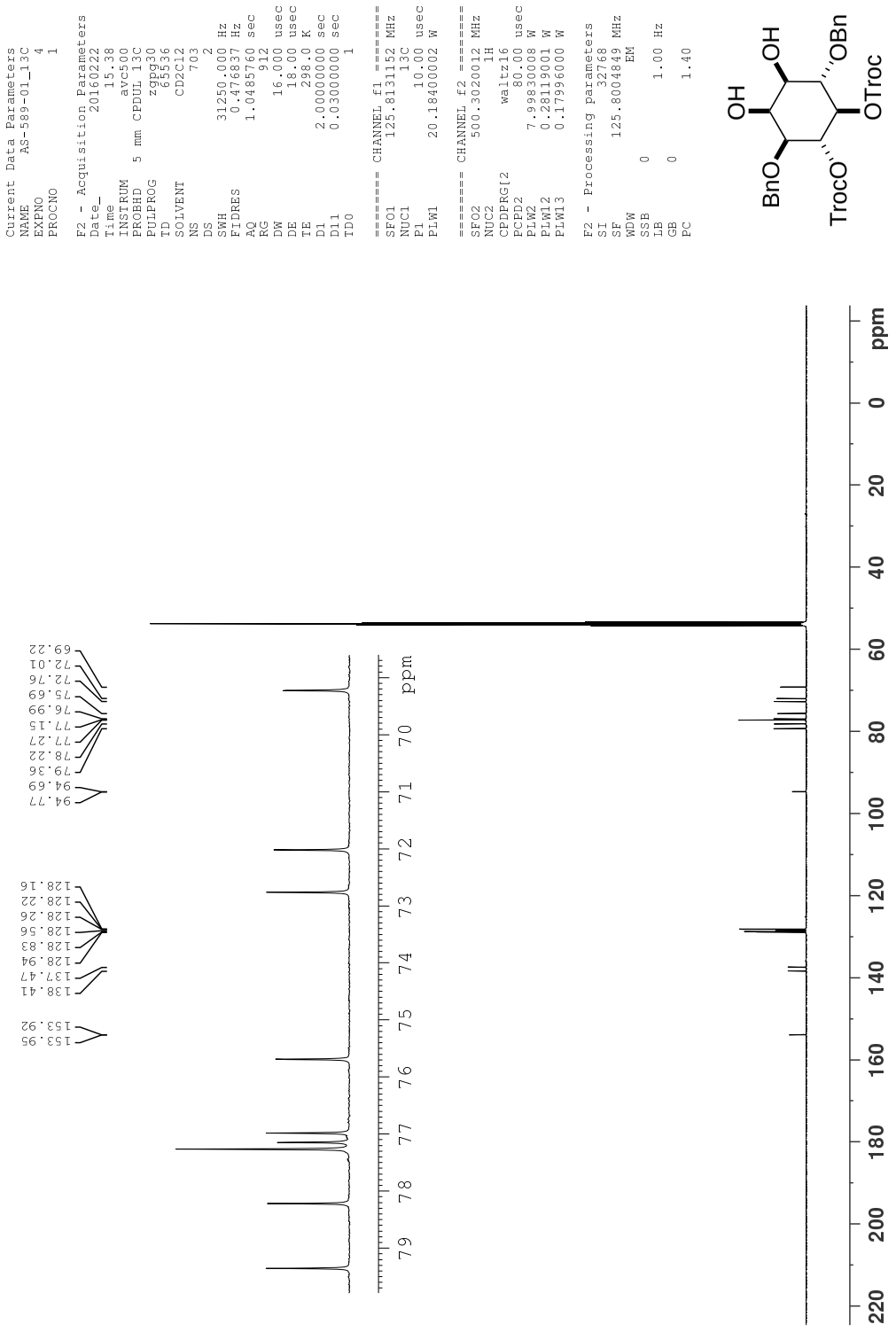
AS-577-01

Time	Area	Area %
0.029	250.98	0.01
2.192	359422	7.65
2.626	86117	1.83
2.768	32429	0.69
3.098	7097.4	0.15
3.222	3077.4	0.07
3.788	3287.3	0.07
3.986	138104	2.94
4.493	4674.4	0.10
4.663	7818.9	0.17
5.427	1734	0.04
6.317	15862	0.34
6.718	73266	1.56
7.151	10574	0.23
7.318	57362	1.22
7.477	3782308	80.53
8.208	71918	1.53
8.489	34865	0.74
9.378	6795.6	0.14
Total	4696962.74	100.00

^{1}H NMR of (+)-202


Current Data Parameters
NAME AS-589-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160222
Time 14.40
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000208 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OH
OBn
BnO
TrocO
OTroc
ppm
10.00
2.74
1.05
7.19
1.11
1.00
1.11
1.99
0.96
0.93

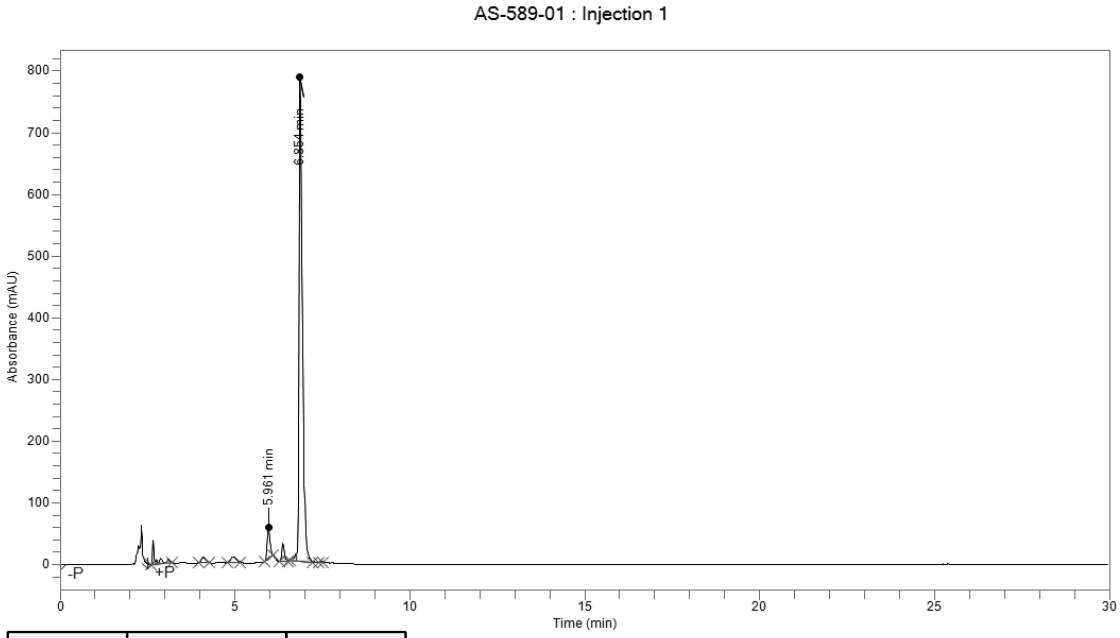
^{13}C NMR of (+)-202



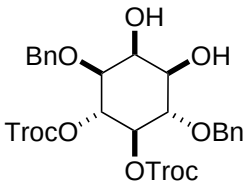
HPLC of (+)-202

AS-589-01

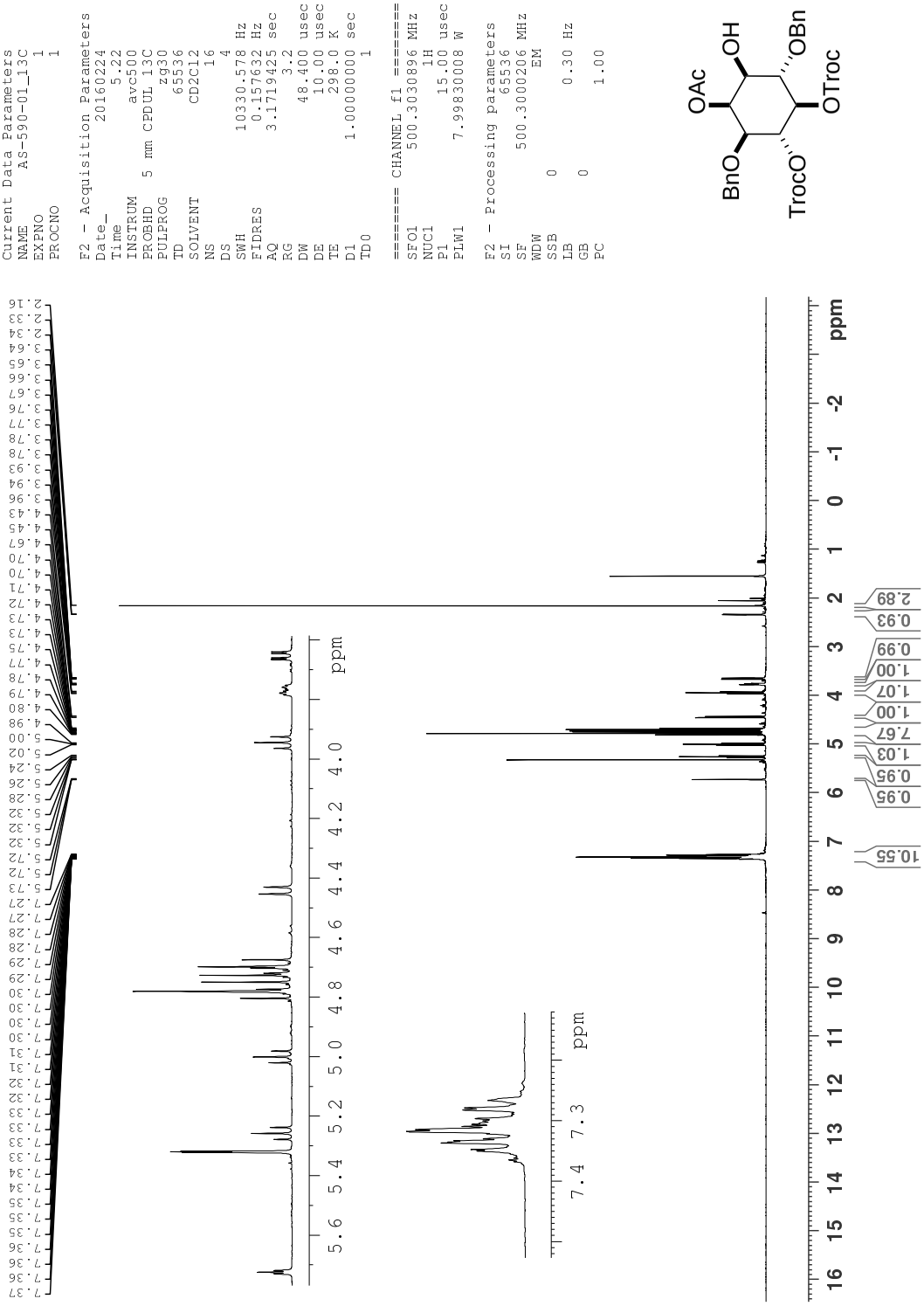
Sample Name	AS-589-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	3/10/2016 6:23 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-57-28	Batch Description	Normal Phase silica column



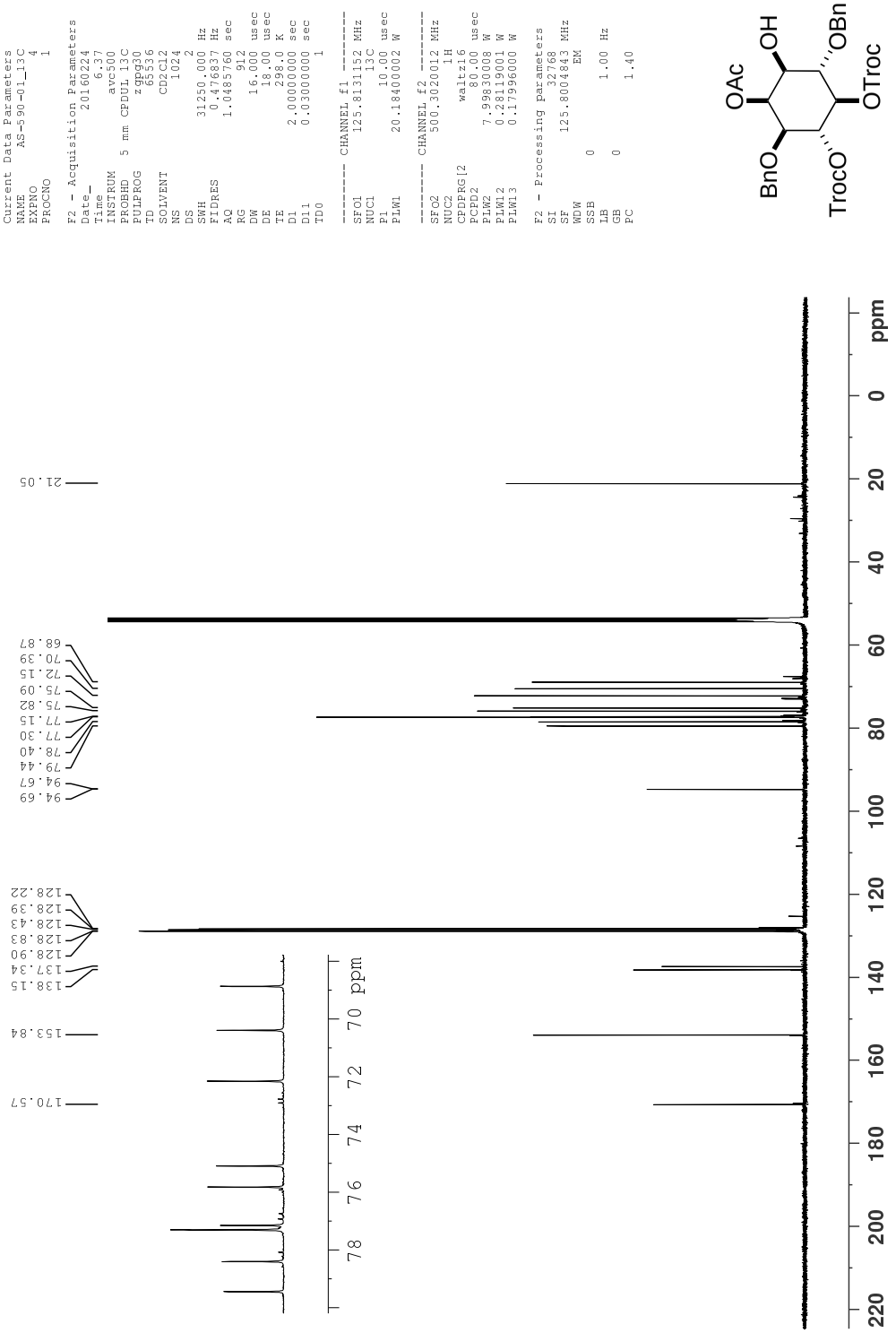
Time	Area	Area %
2.660	79792	1.32
2.751	23094	0.38
2.879	49602	0.82
3.107	32551	0.54
4.089	73681	1.22
4.944	97860	1.62
5.961	287264	4.75
6.367	144860	2.39
6.642	16337	0.27
6.735	38821	0.64
6.854	5195961	85.89
7.461	9441.1	0.16
Total	6049264	100.00



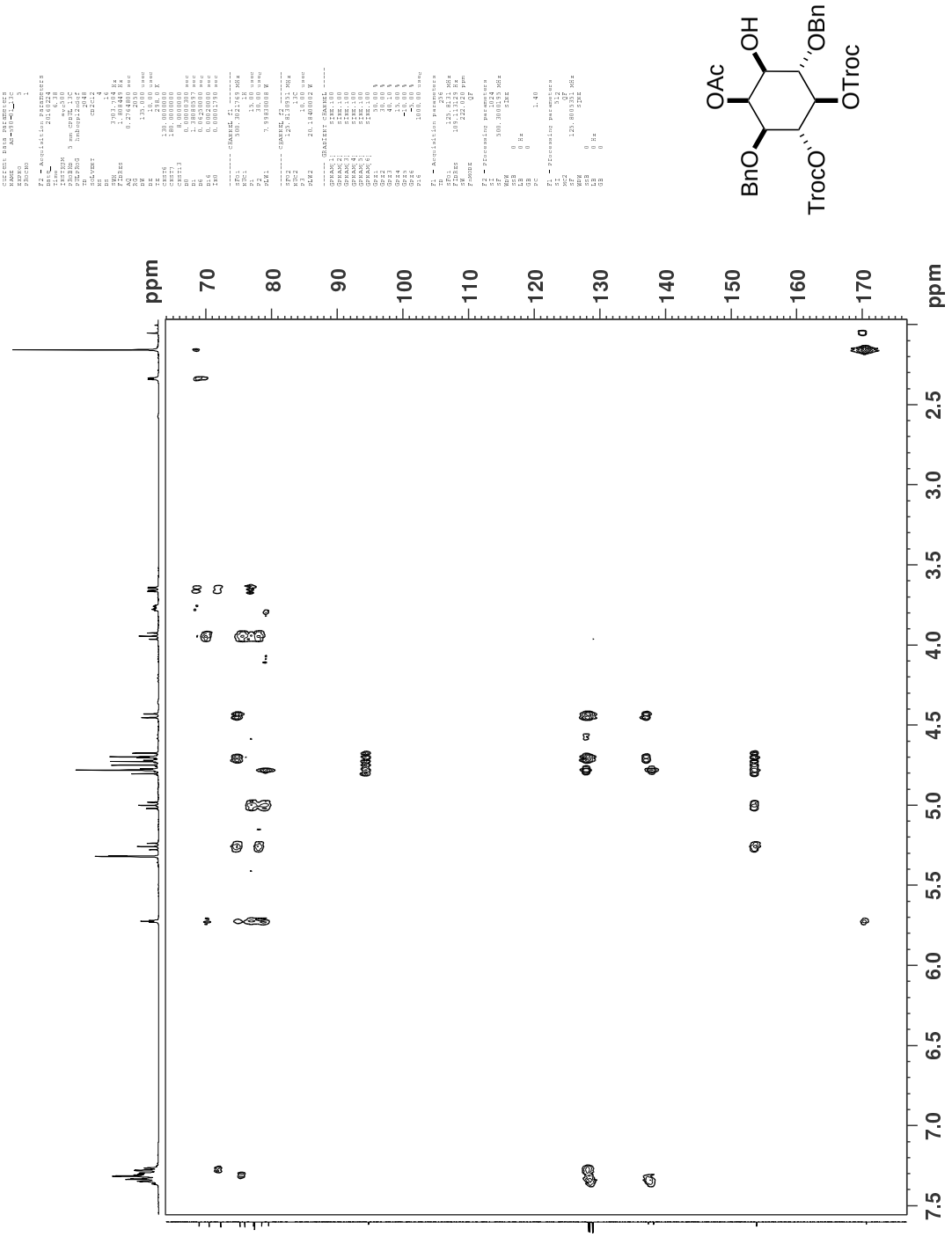
^{1}H NMR of (+)-200


Current Data Parameters
NAME AS-590-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160224
Time 5.22
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OAc
OH
OBn
BnO
TrocO
OTroc
ppm
10.55
0.95
0.95
1.03
7.67
1.00
1.07
1.00
0.99
0.93
2.89

^{13}C NMR of (+)-200



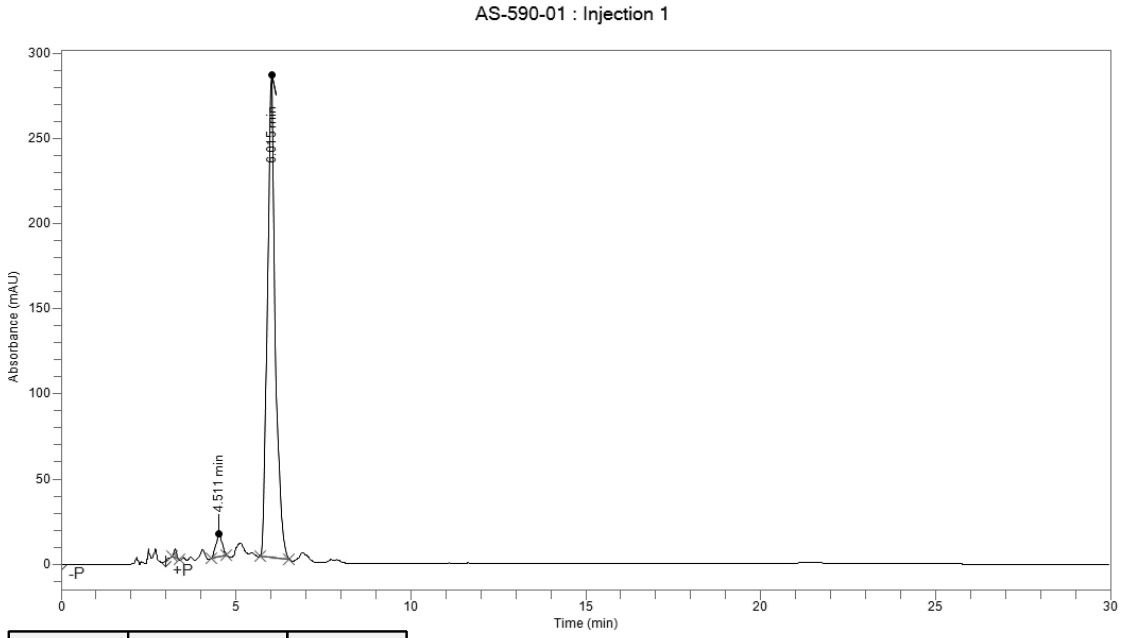
^{1}H-^{31}C HMBC NMR of (+)-200



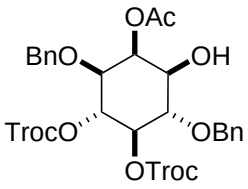
HPLC of (+)-200

AS-590-01

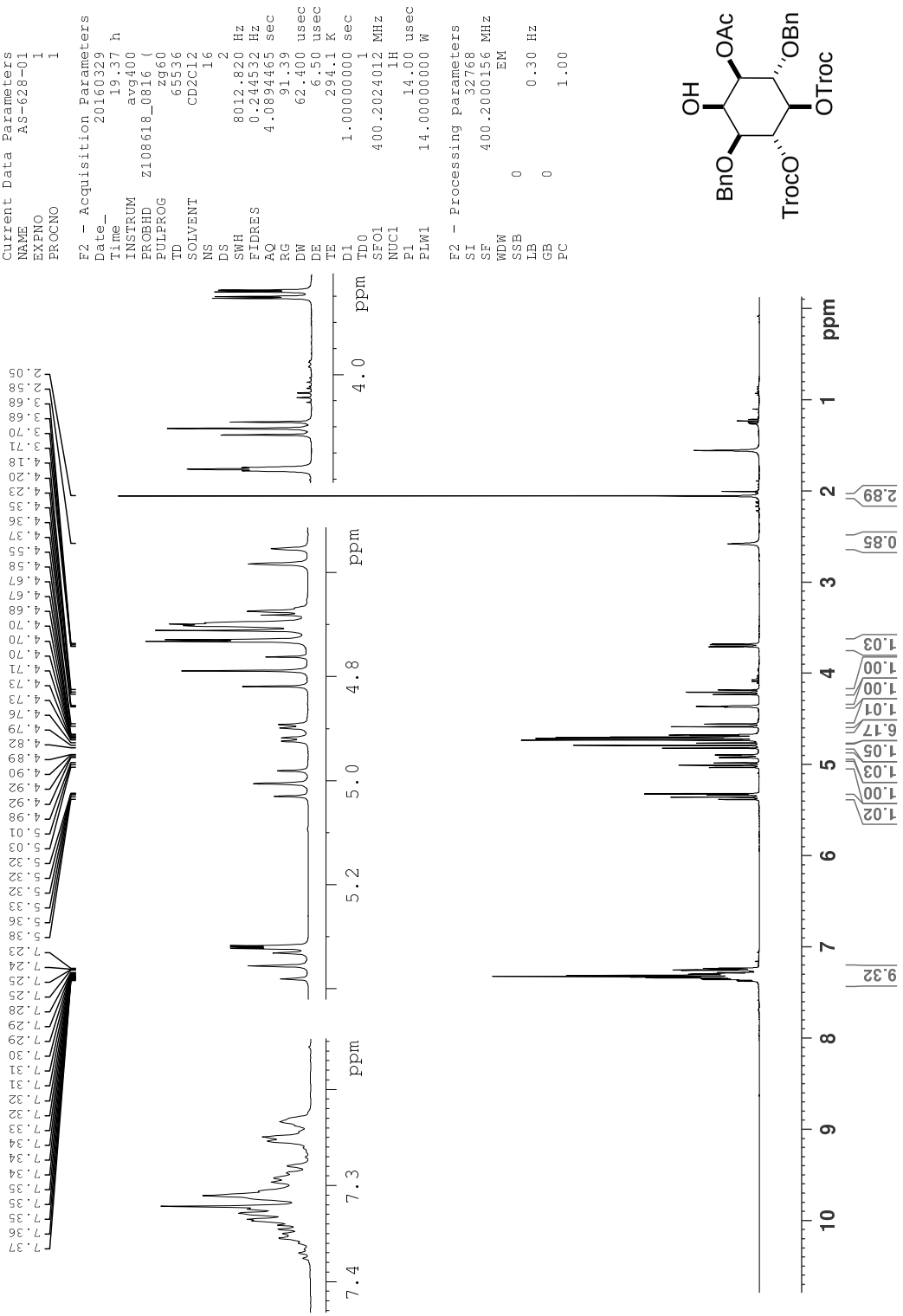
Sample Name	AS-590-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/4/2016 4:56 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



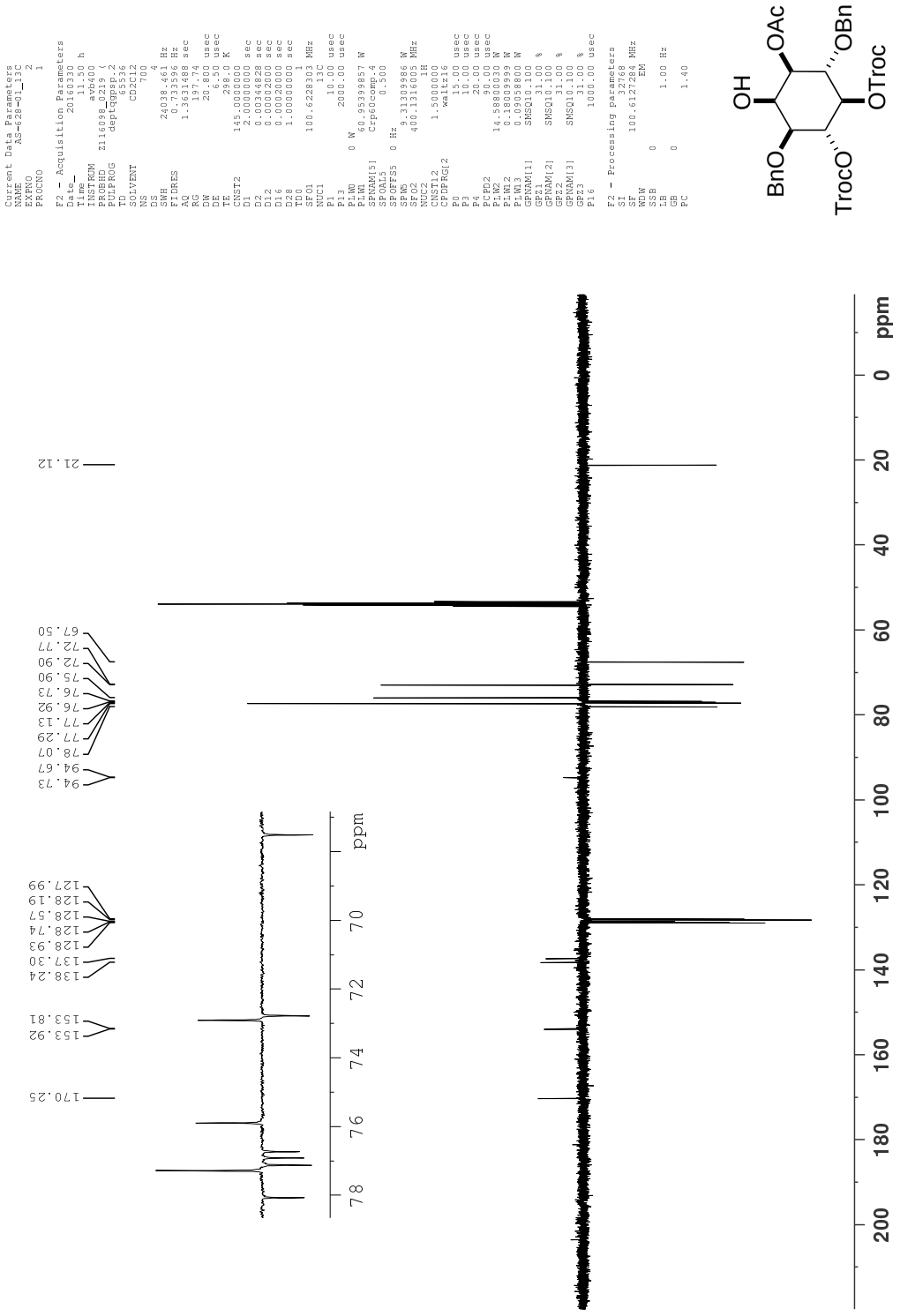
Time	Area	Area %
3.264	30909	0.68
4.511	169177	3.71
6.015	4363030	95.62
Total	4563117	100.00



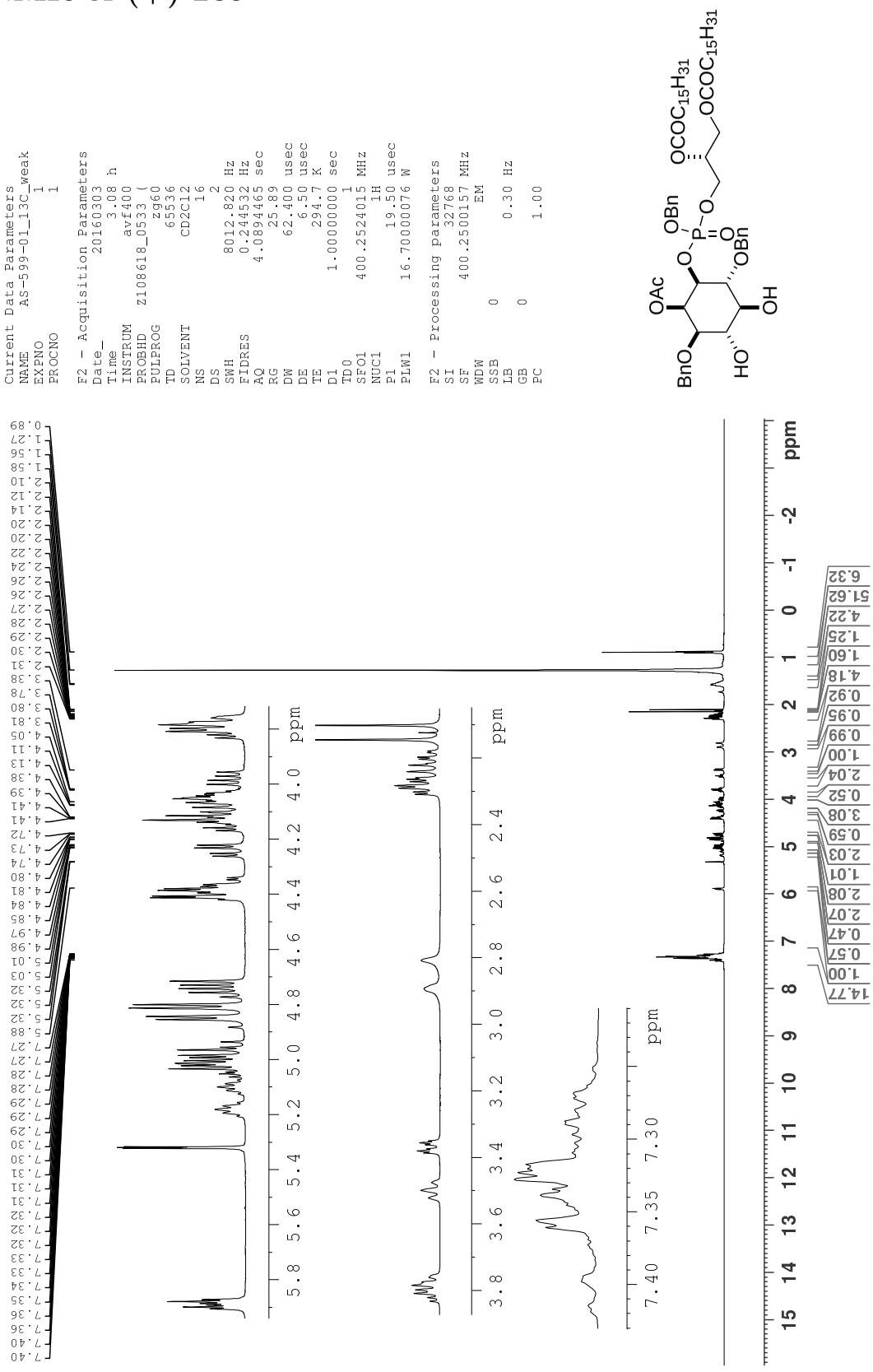
^{1}H NMR of (+)-201


OH
OAc
OBn
BnO
TrocO
OTroc
Current Data Parameters
NAME AS-628-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160329
Time 19.37 h
INSTRUM avg400
PROBHD Z108618_0816 (
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 91.39
DW 62.400 usec
DE 6.50 usec
TE 294.1 K
D1 1.00000000 sec
TD0 1
SFO1 400.2024012 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 32768
SF 400.2000156 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
2.89
0.85
1.03
1.00
1.00
1.01
6.17
1.05
1.03
1.00
1.02
9.32

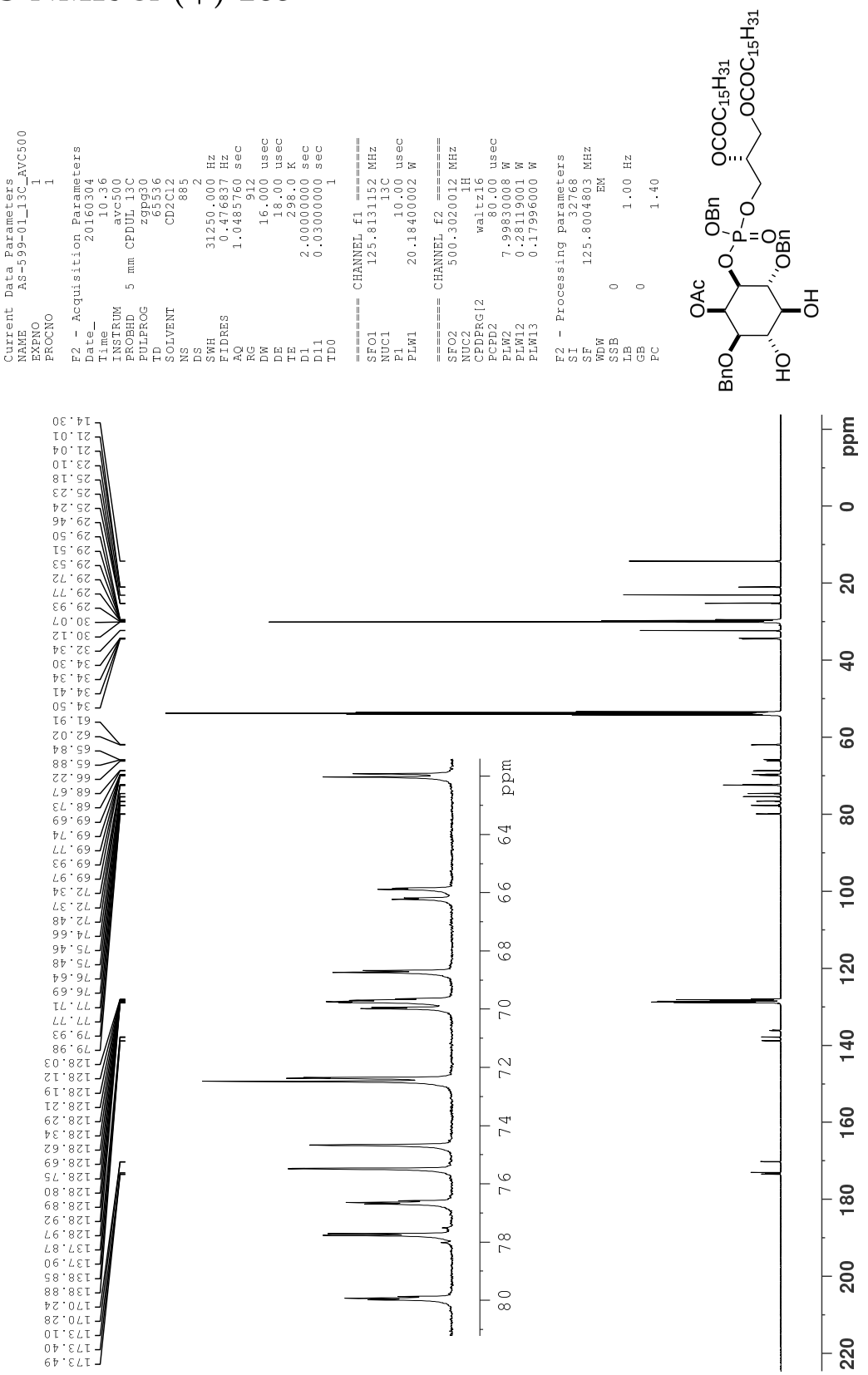
^{13}C NMR of (+)-201



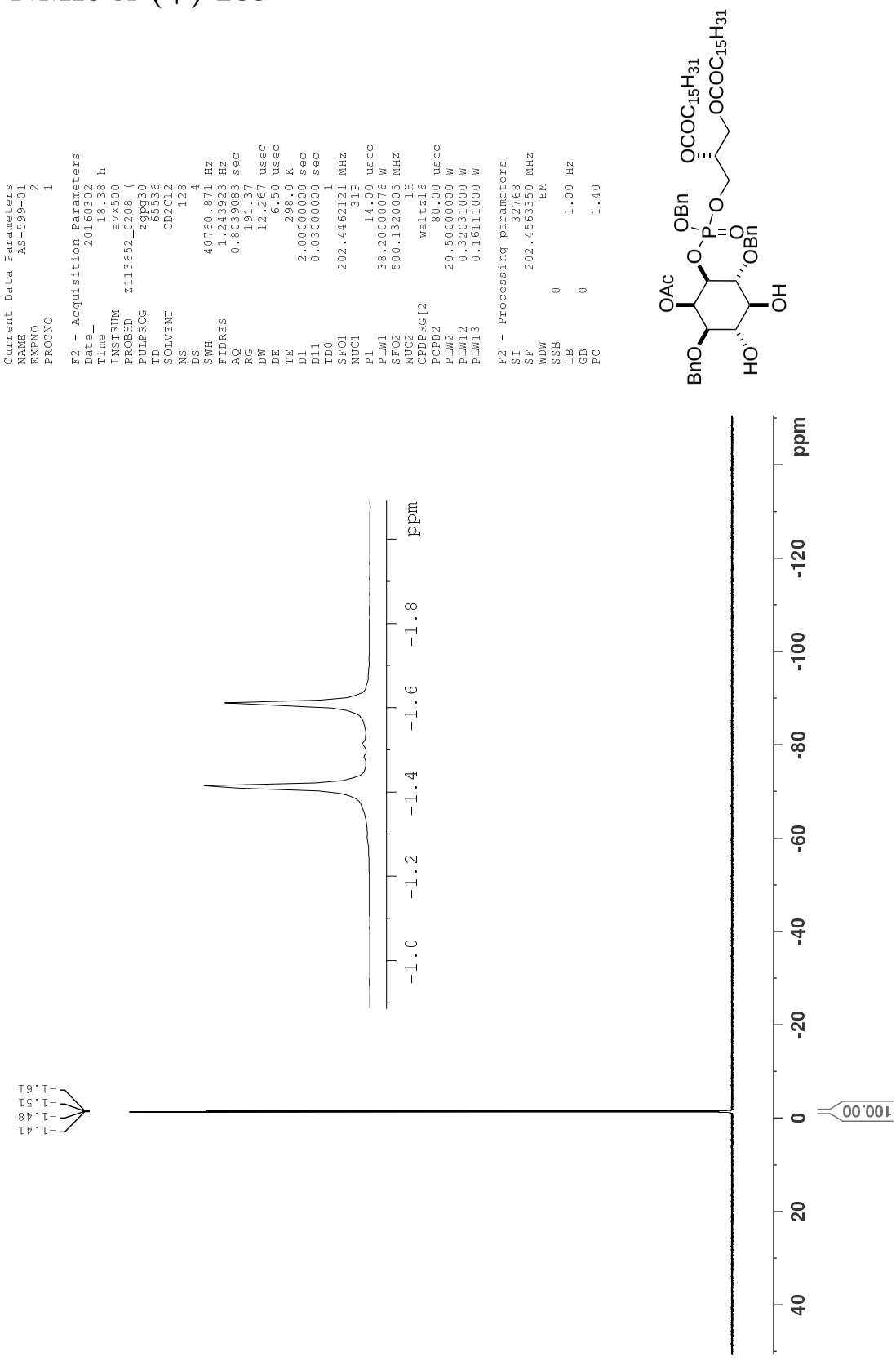
^{1}H NMR of (+)-205


Current Data Parameters
NAME AS-599-01_13C_weak
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160303
Time 3.08 h
INSTRUM avf400
PROBHD Z108618_0533 (
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 25.89
DW 62.400 usec
DE 6.50 usec
TE 294.7 K
D1 1.00000000 sec
TD0 1
SFO1 400.2524015 MHz
NUC1 1H
P1 19.50 usec
PLW1 16.70000076 W
F2 - Processing parameters
SI 32768
SF 400.2500157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OAc
OBn
OCOC15H31
OCOC15H31
BnO
HO
OBn
OH
ppm

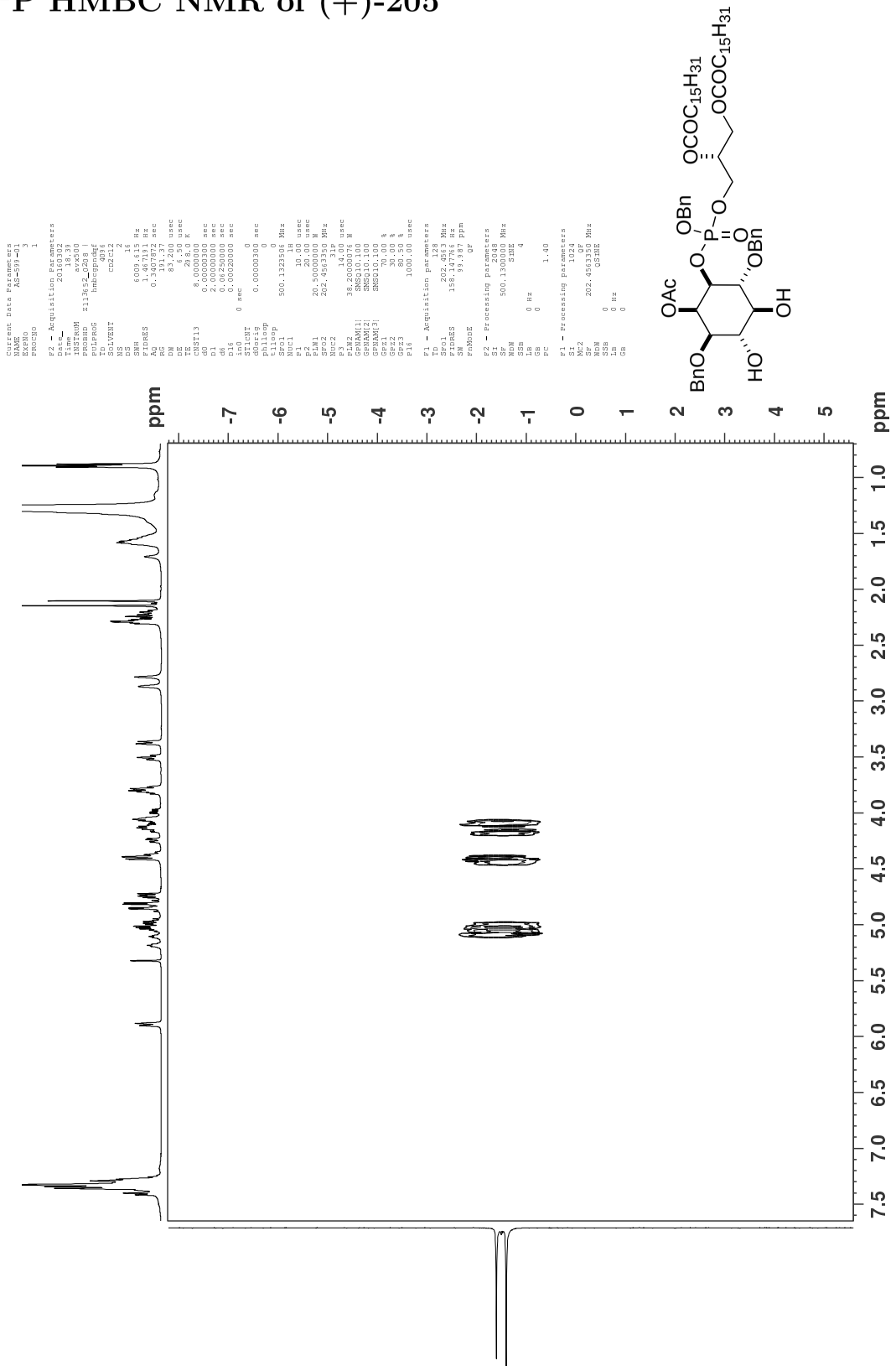
^{13}C NMR of (+)-205



^{31}P NMR of (+)-205



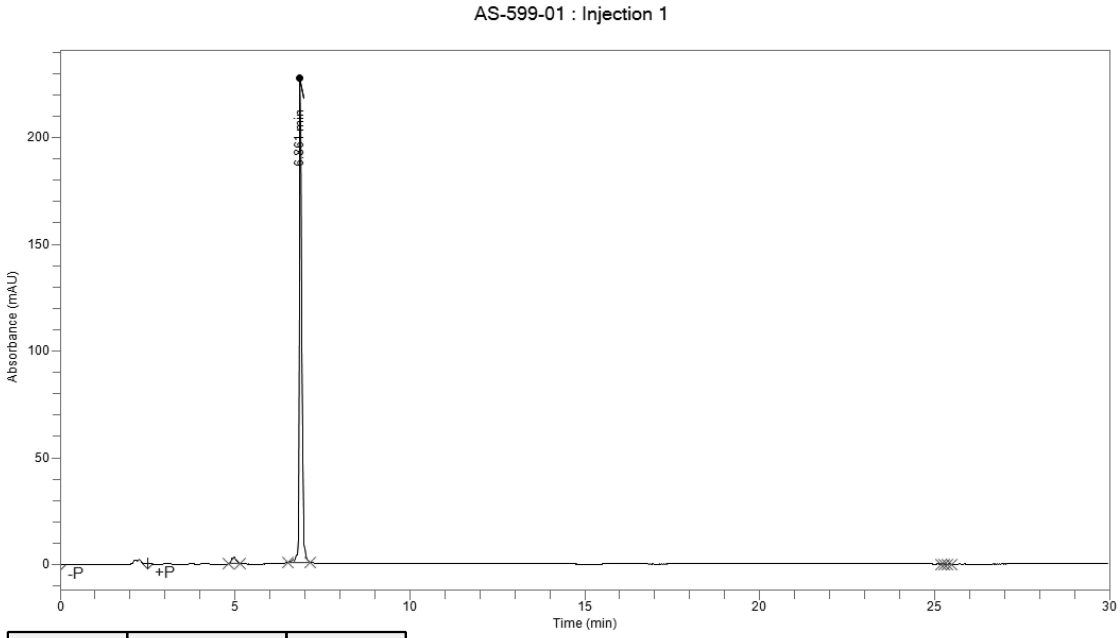
^{1}H-^{31}P HMBC NMR of (+)-205



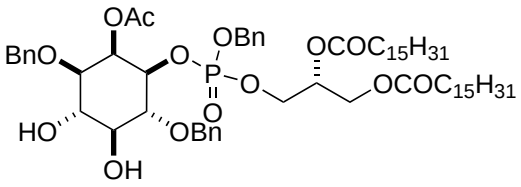
HPLC of (+)-205

AS-599-01

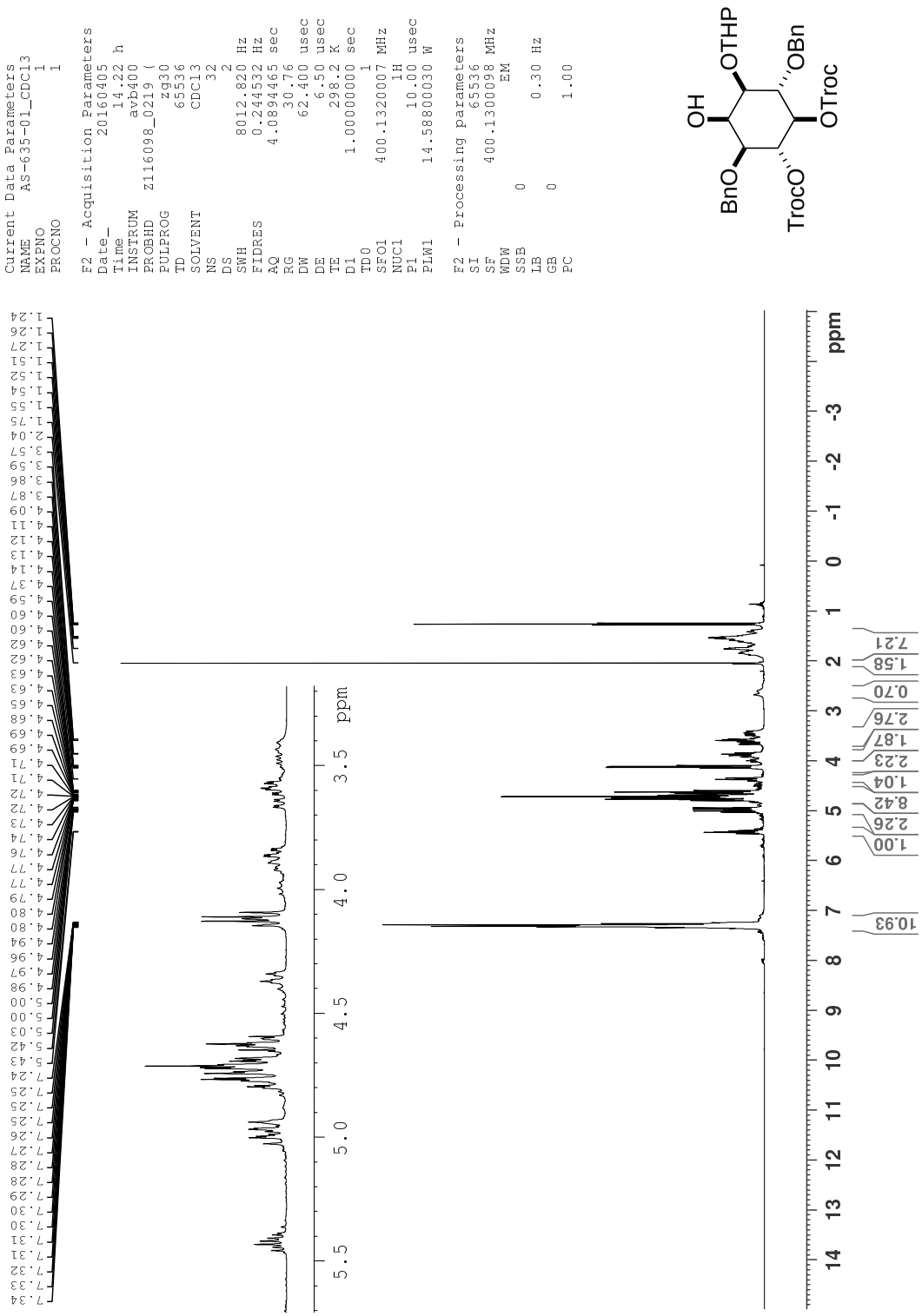
Sample Name	AS-599-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	3/10/2016 1:26 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 03-16-2016 17-22-00	Batch Description	Normal Phase silica column



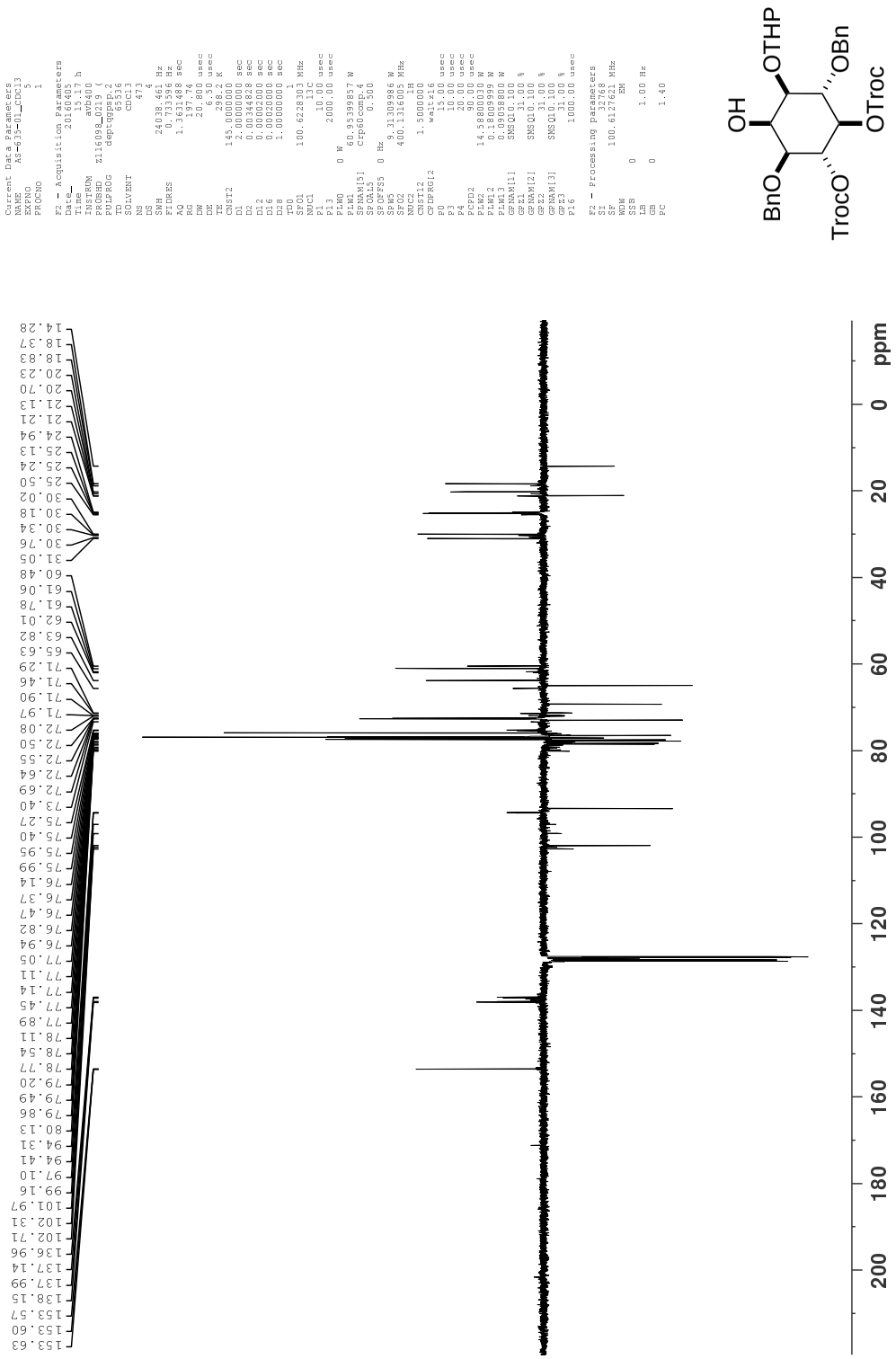
Time	Area	Area %
4.959	29050	2.54
6.572	1078.7	0.09
6.663	7214.5	0.63
6.861	1100904	96.36
25.249	2053.6	0.18
25.428	2249.2	0.20
Total	1142550	100.00



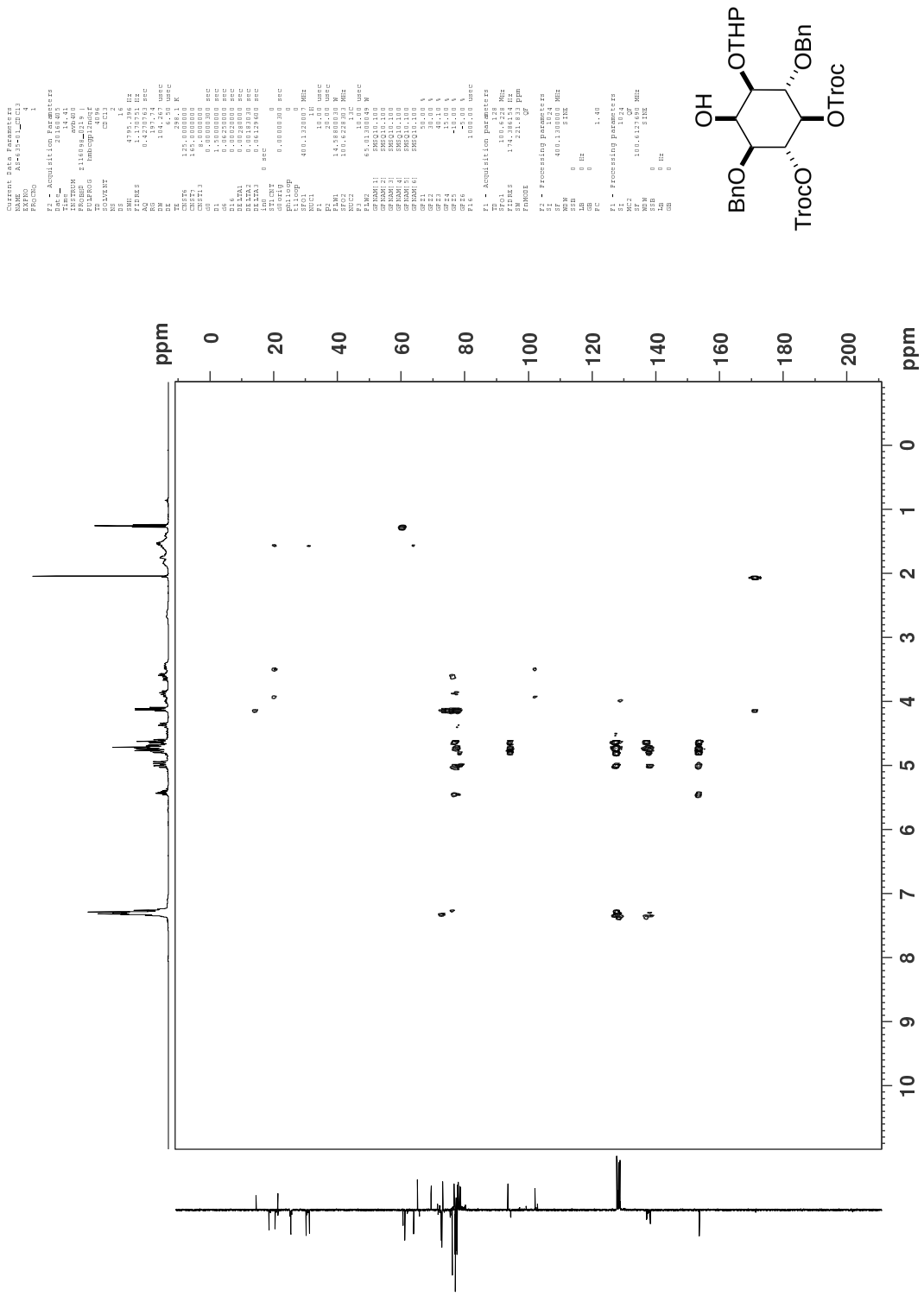
^{1}H NMR of (+)-210


Current Data Parameters
NAME AS-635-01_CDC13
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160405
Time 14.22 h
INSTRUM avb400
PROBHD Z116098_0219 (
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.08944465 sec
RG 30.76
DW 62.400 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
SFO1 400.1320007 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
F2 - Processing parameters
SI 65536
SF 400.1300098 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OTHP
OBn
OTroc
BnO
TrocO
ppm
7.21
1.58
0.70
2.76
1.87
2.23
1.04
8.42
2.26
1.00
10.93

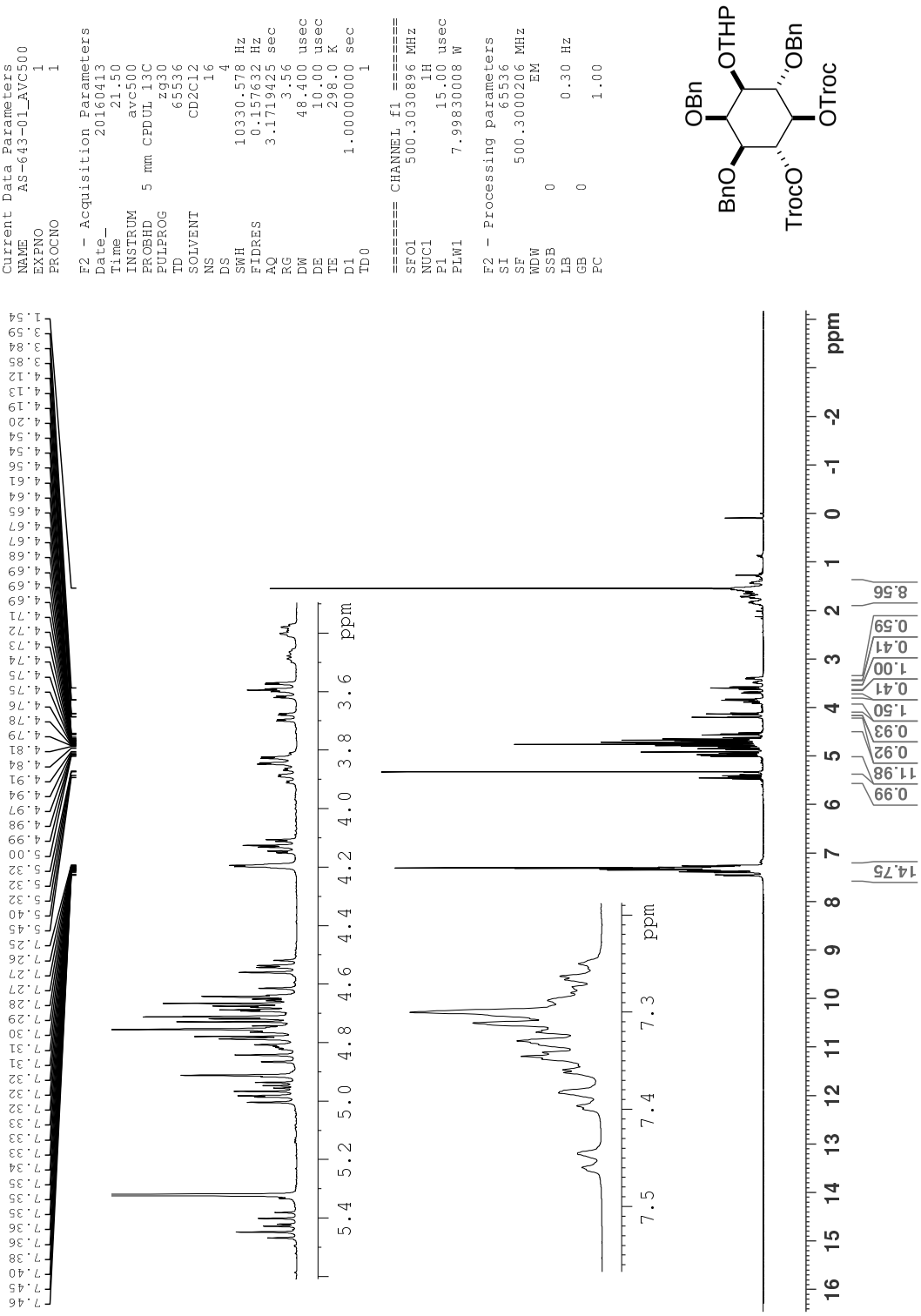
^{13}C NMR of (+)-210



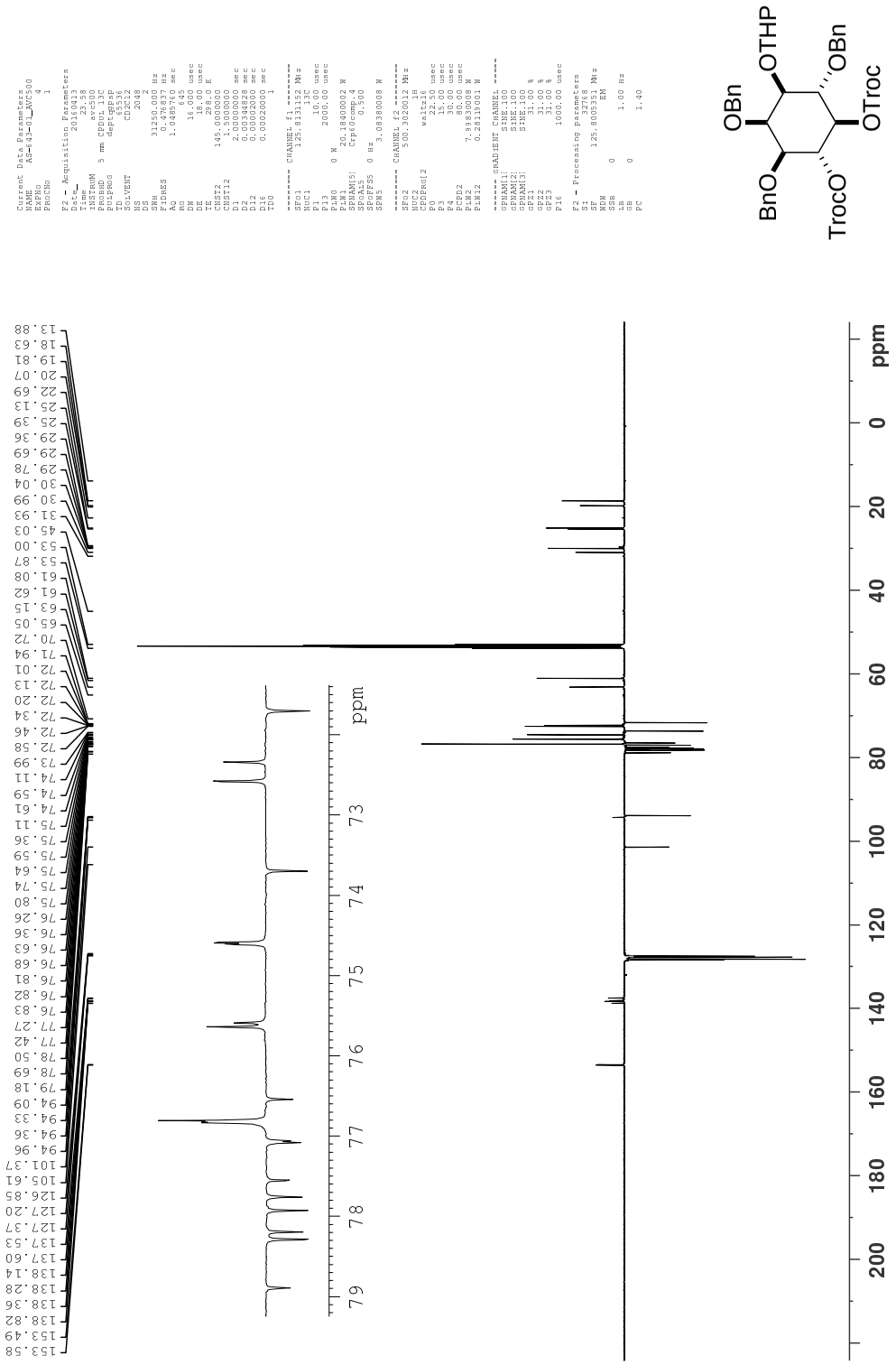
^{1}H-^{13}C HMBC NMR of (+)-210



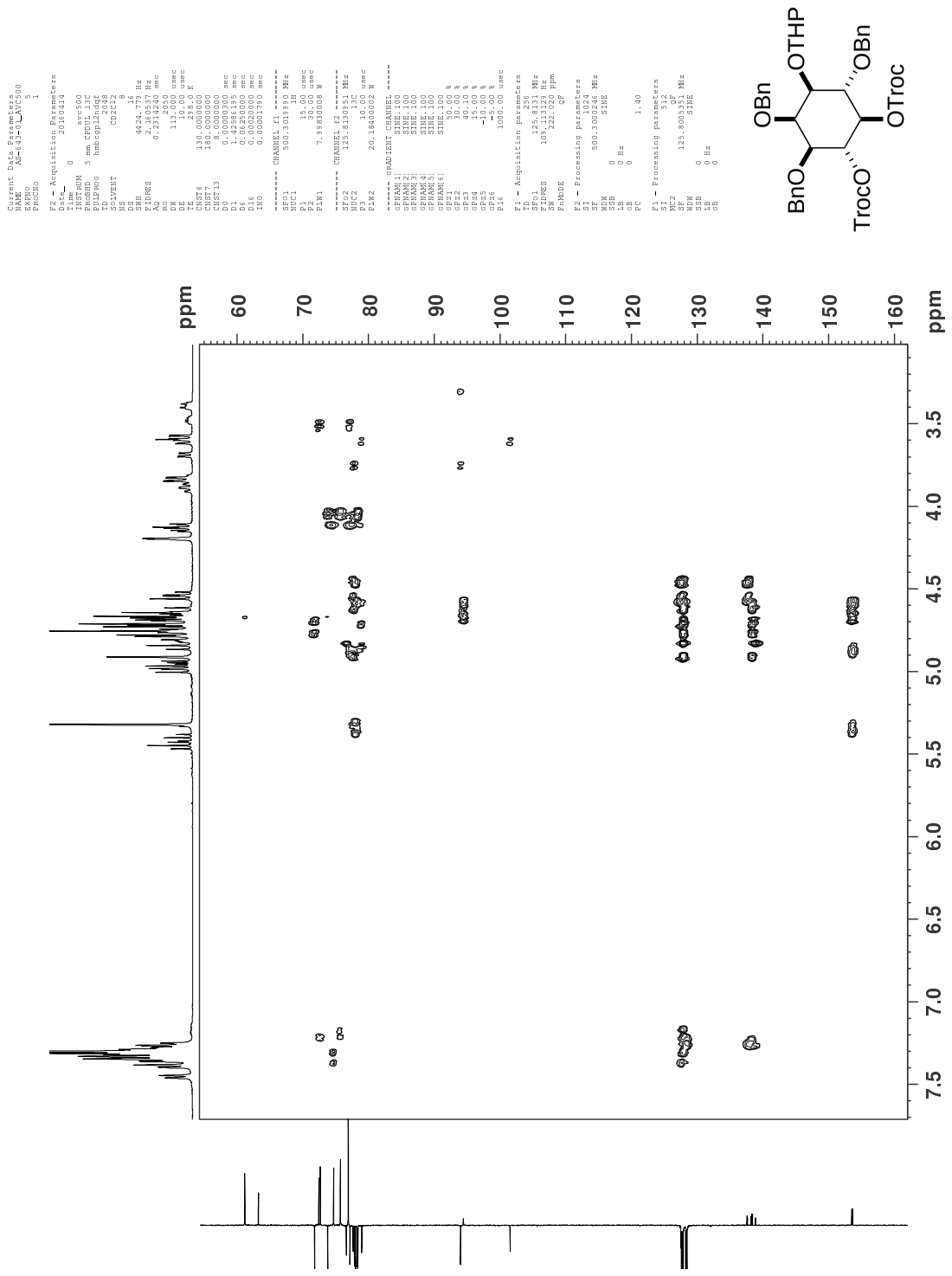
^{1}H NMR of (+)-211


Current Data Parameters
NAME AS-643-01_AVC500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160413
Time 21.50
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OTHP
OBn
BnO
TrocO
OTroc
ppm
8.56
0.59
0.41
1.00
0.41
1.50
0.93
0.92
11.98
0.99
14.75

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



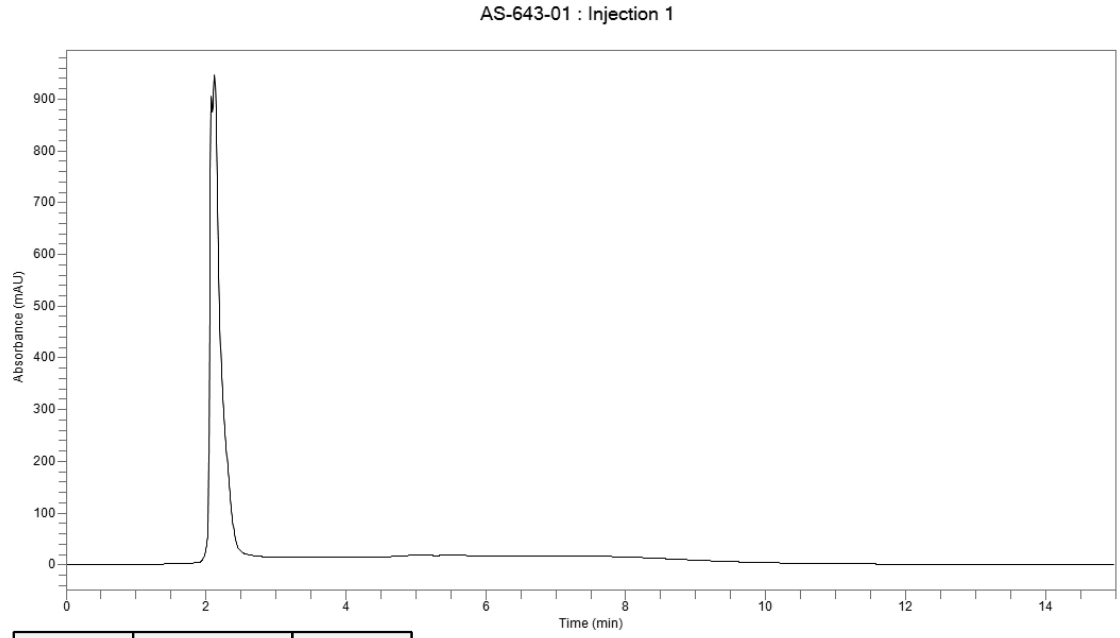
^{1}H-^{13}C HMBC NMR of (+)-211



HPLC of (+)-211

AS-643-01

Sample Name	AS-643-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 220nm Isocratic 2%	Acquisition Date/Time	6/3/2016 3:00 pm
Batch Group/Name	Alex/Normal Phase Purity 220nm Isocratic 2%	Batch Description	Normal Phase silica column



Time	Area	Area %
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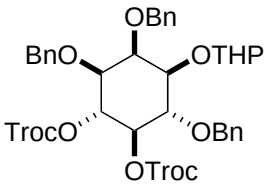
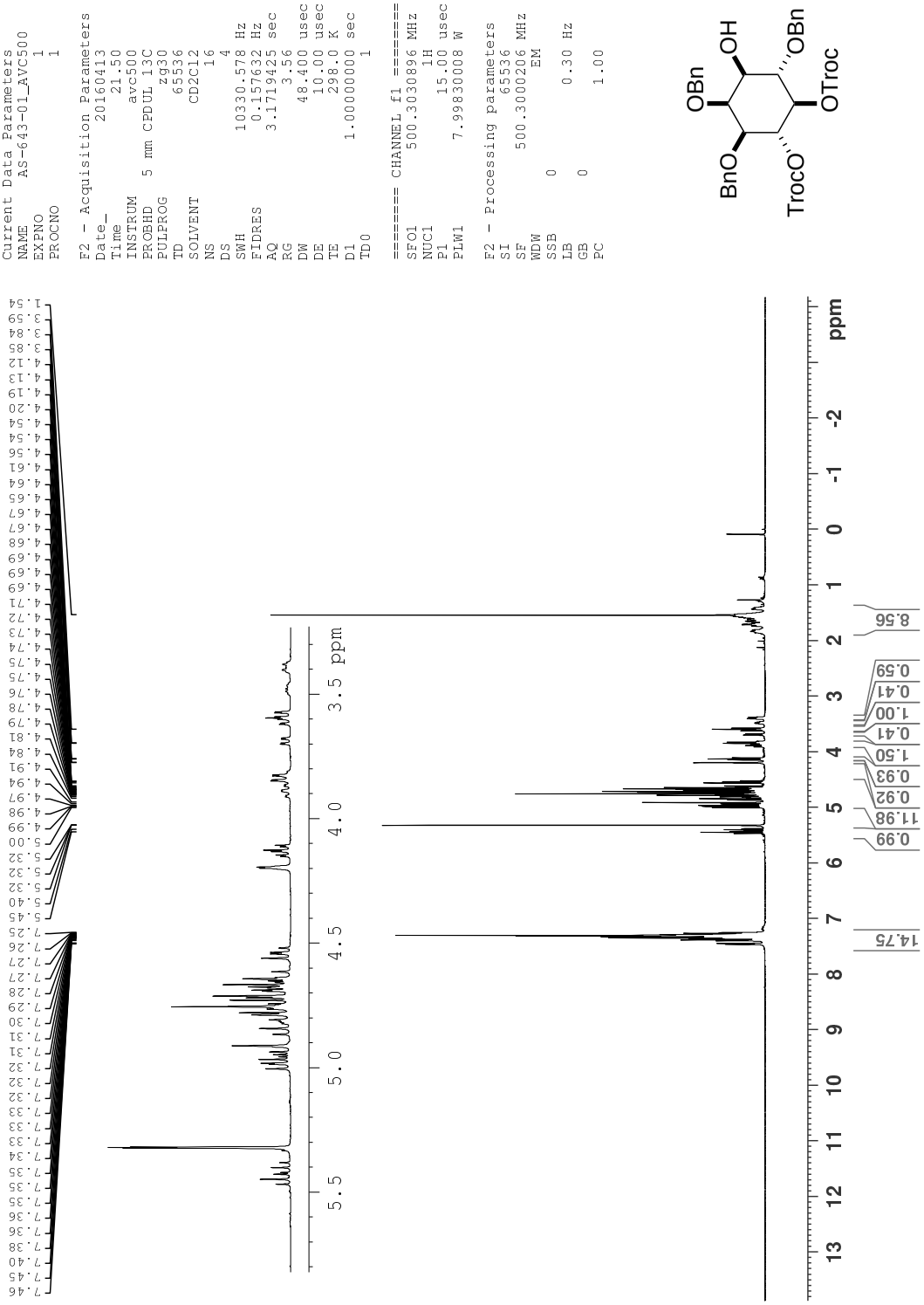
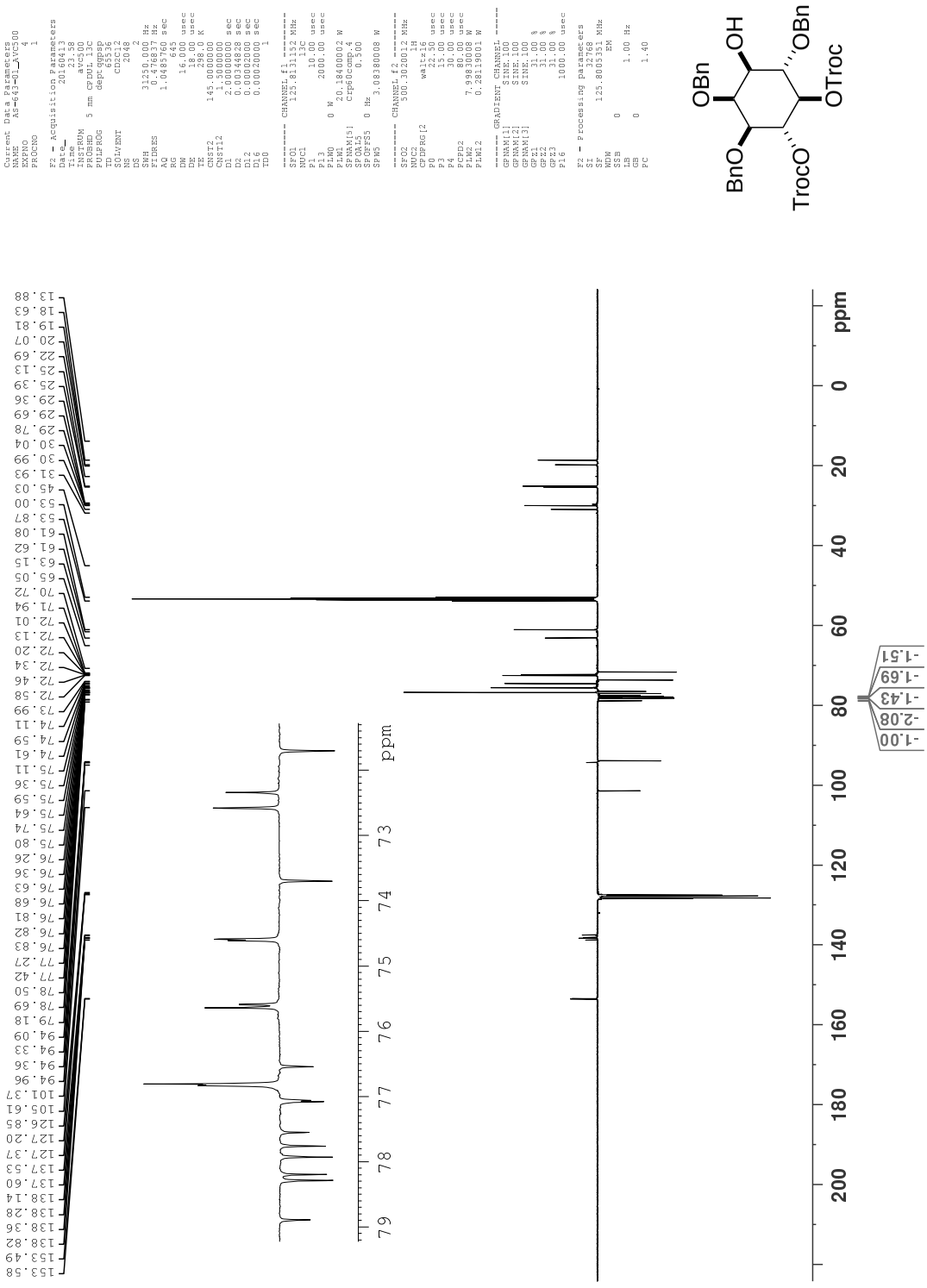
Total	0	



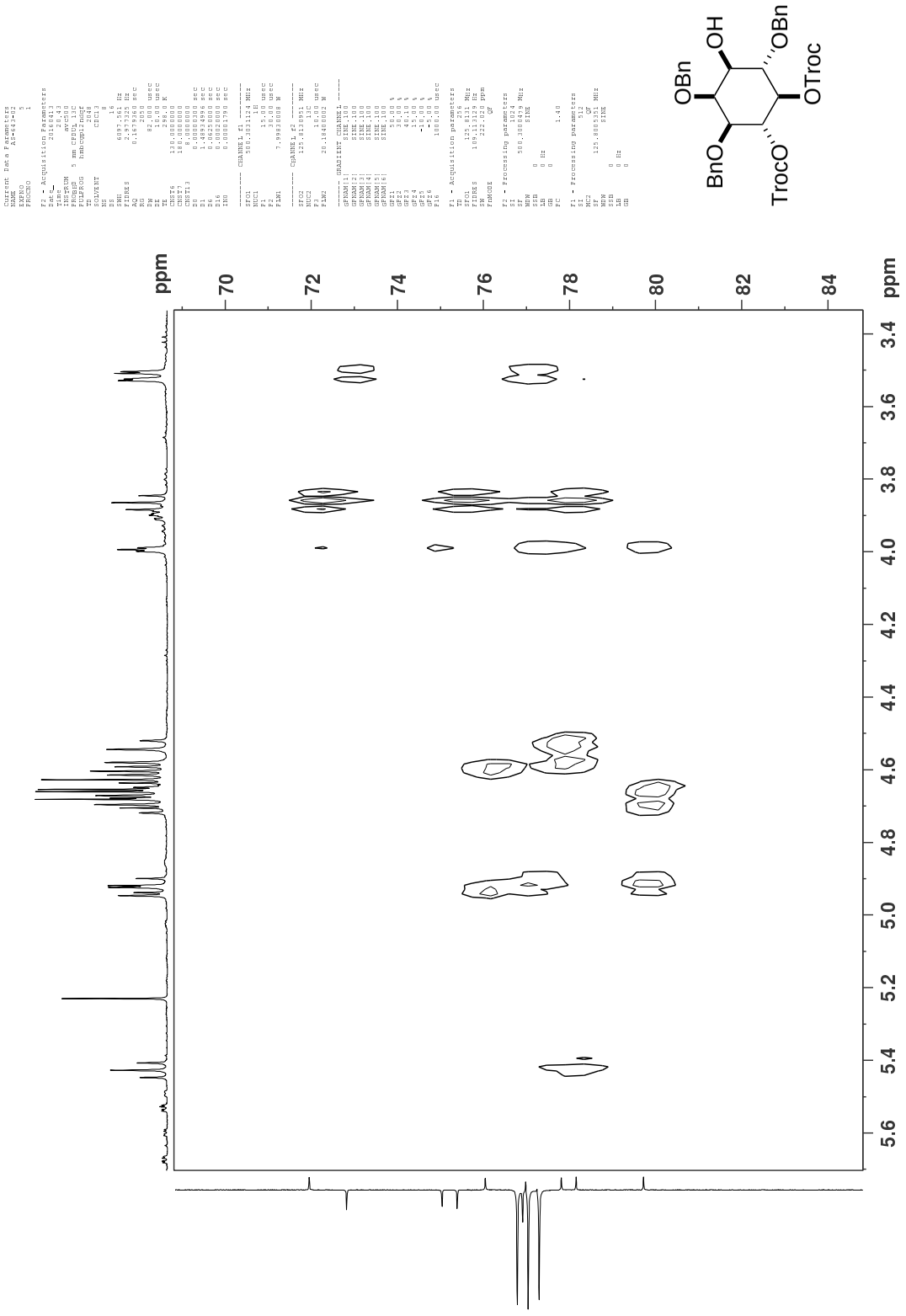
^{1}H NMR of (+)-212


Current Data Parameters
NAME AS-643-01_AVC500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160413
Time 21.50
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OH
OBn
BnO
TrocO
OTroc
ppm
8.56
0.59
0.41
1.00
0.41
1.50
0.93
0.92
11.98
0.99
14.75

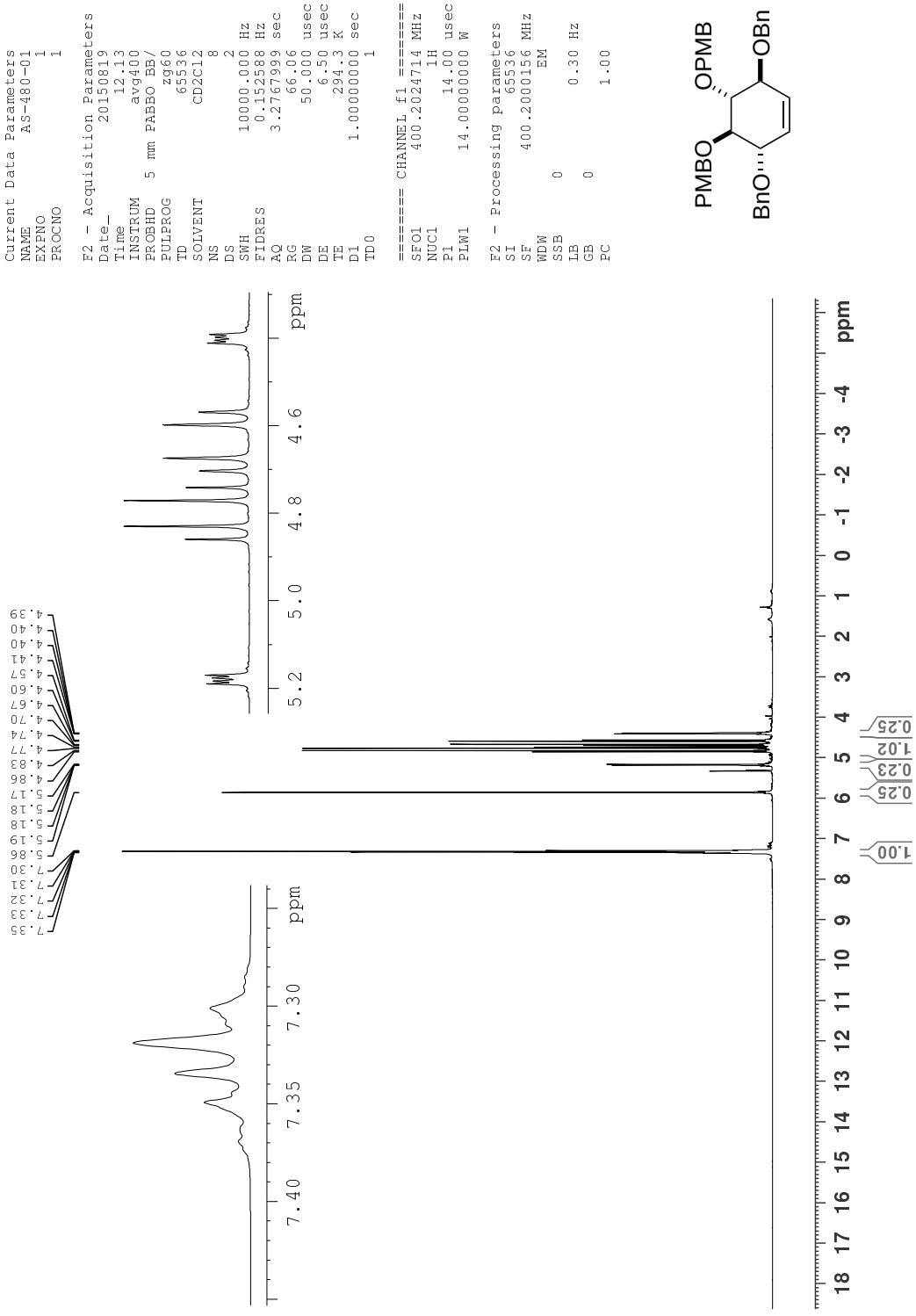
^{13}C NMR of (+)-212



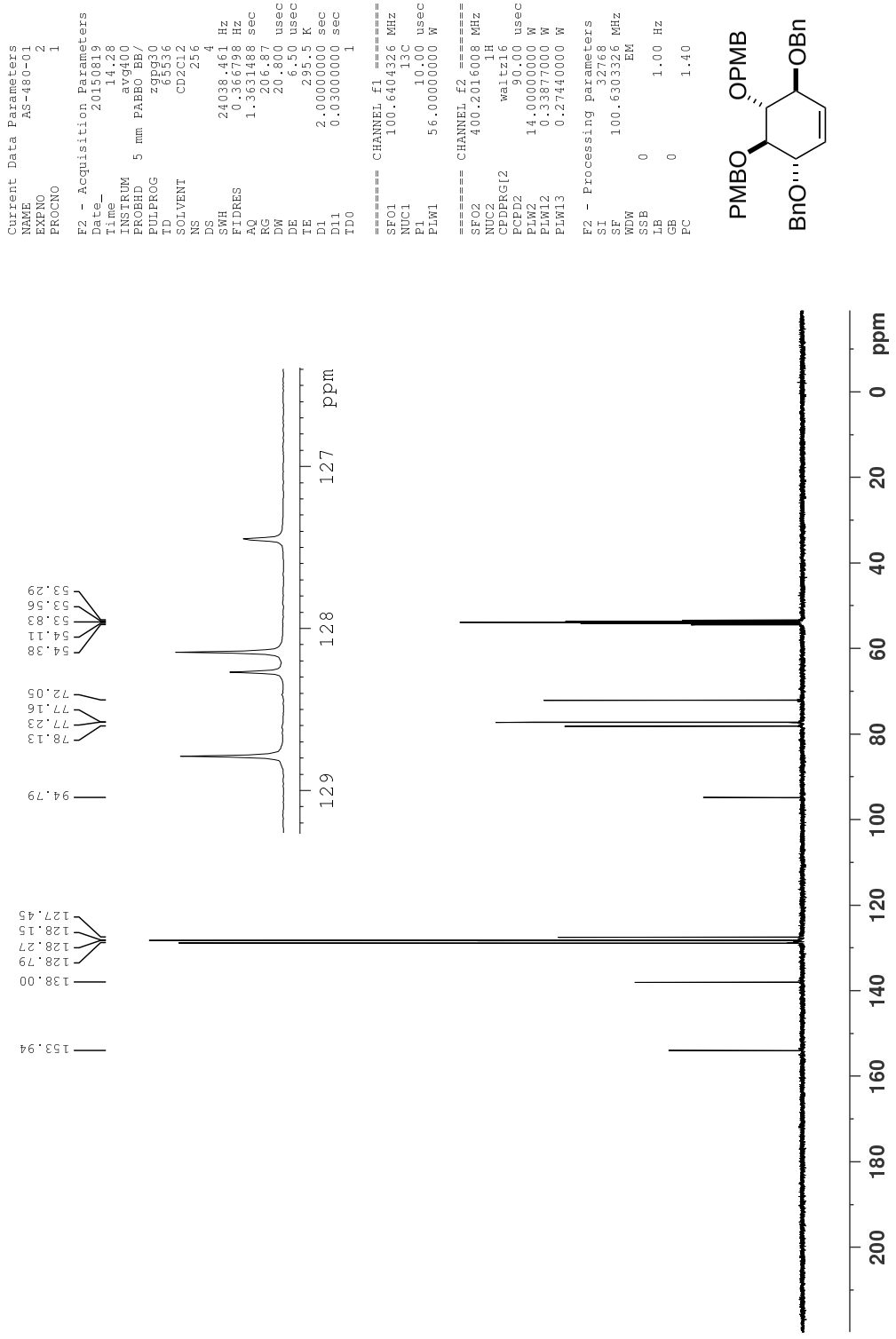
^{1}H-^{13}C HMBC NMR of (+)-212



^{1}H NMR of (+)-214


Current Data Parameters
NAME AS-480-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150819
Time 12.13
INSTRUM avg400
PROBHD 5 mm PABBO BB/
PULPROG zg60
TD 65536
SOLVENT CD2Cl2
NS 8
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 66.06
DW 50.000 usec
DE 6.50 usec
TE 294.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 65536
SF 400.2000156 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OPMB
OBn
PMBO
BnO
ppm
1.00
0.25
0.23
1.02
0.25

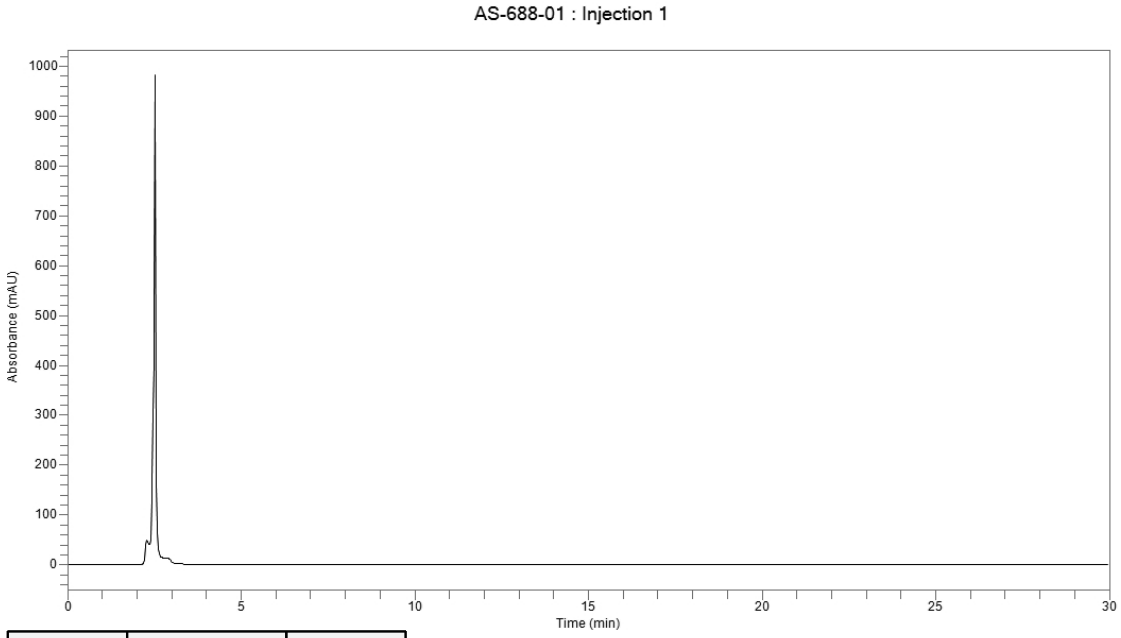
^{13}C NMR of (+)-214



HPLC of (+)-214

AS-688-01

Sample Name	AS-688-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/6/2016 11:35 am
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



Time	Area	Area %
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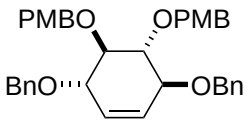
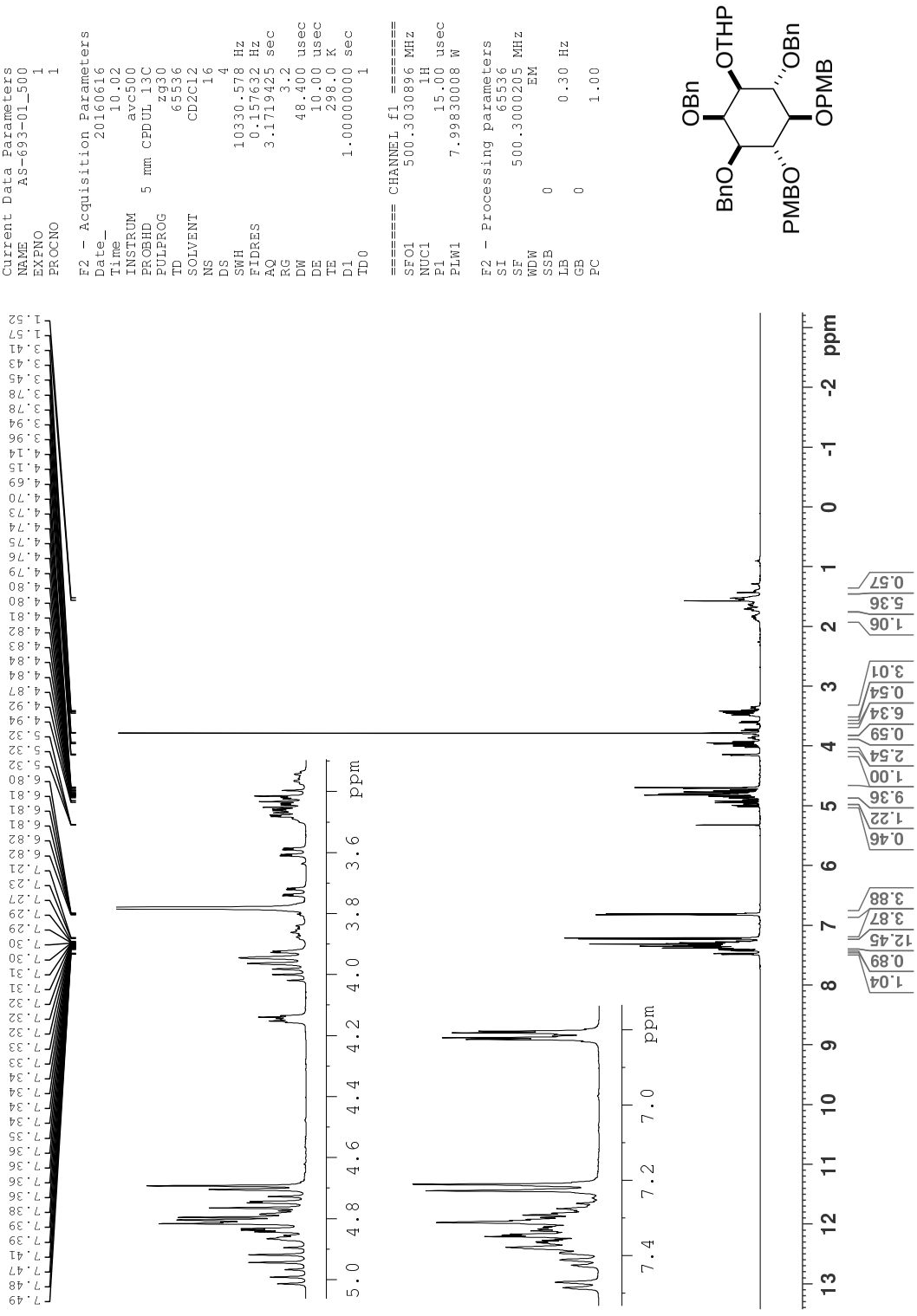
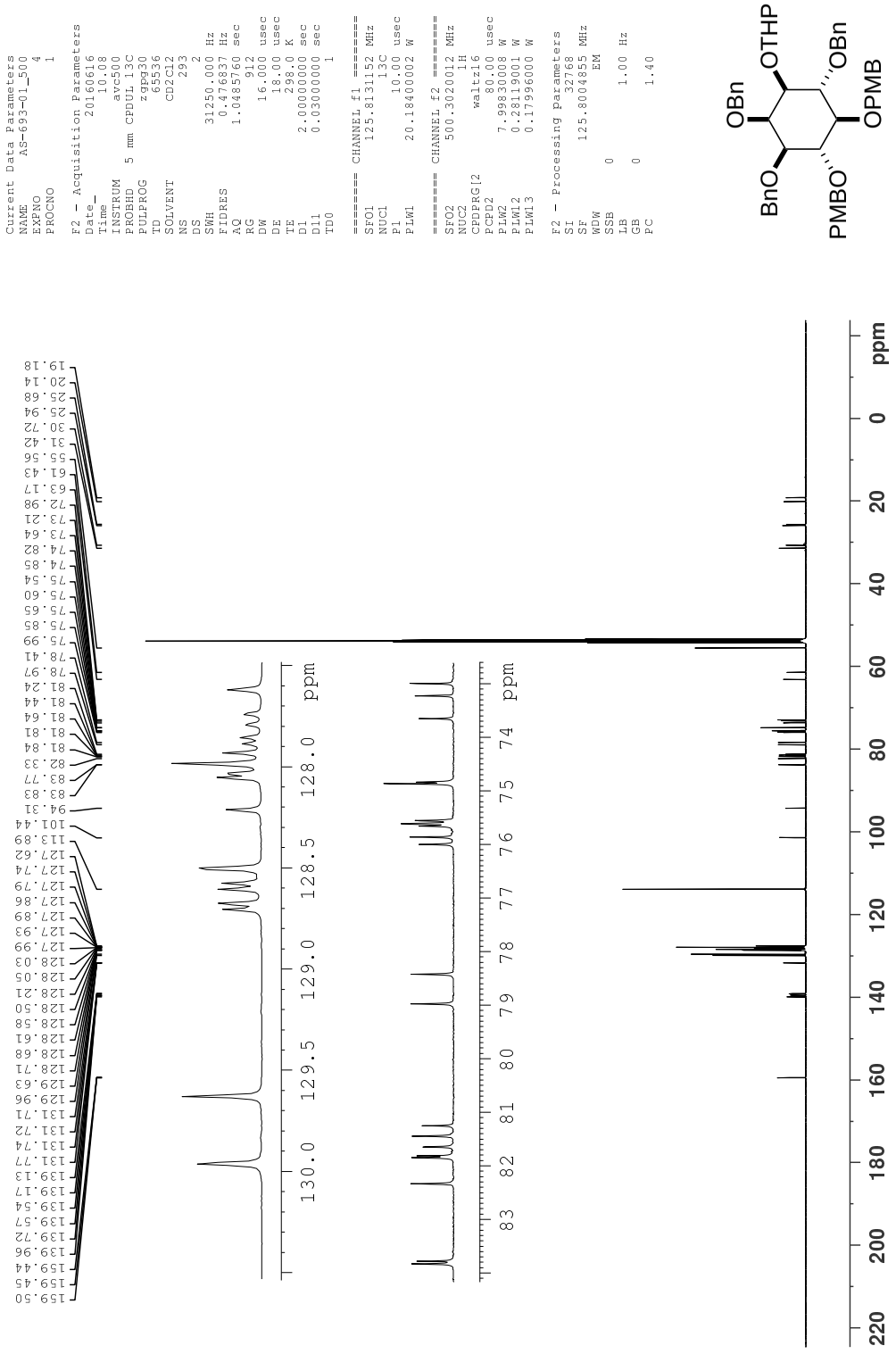
Total	0	



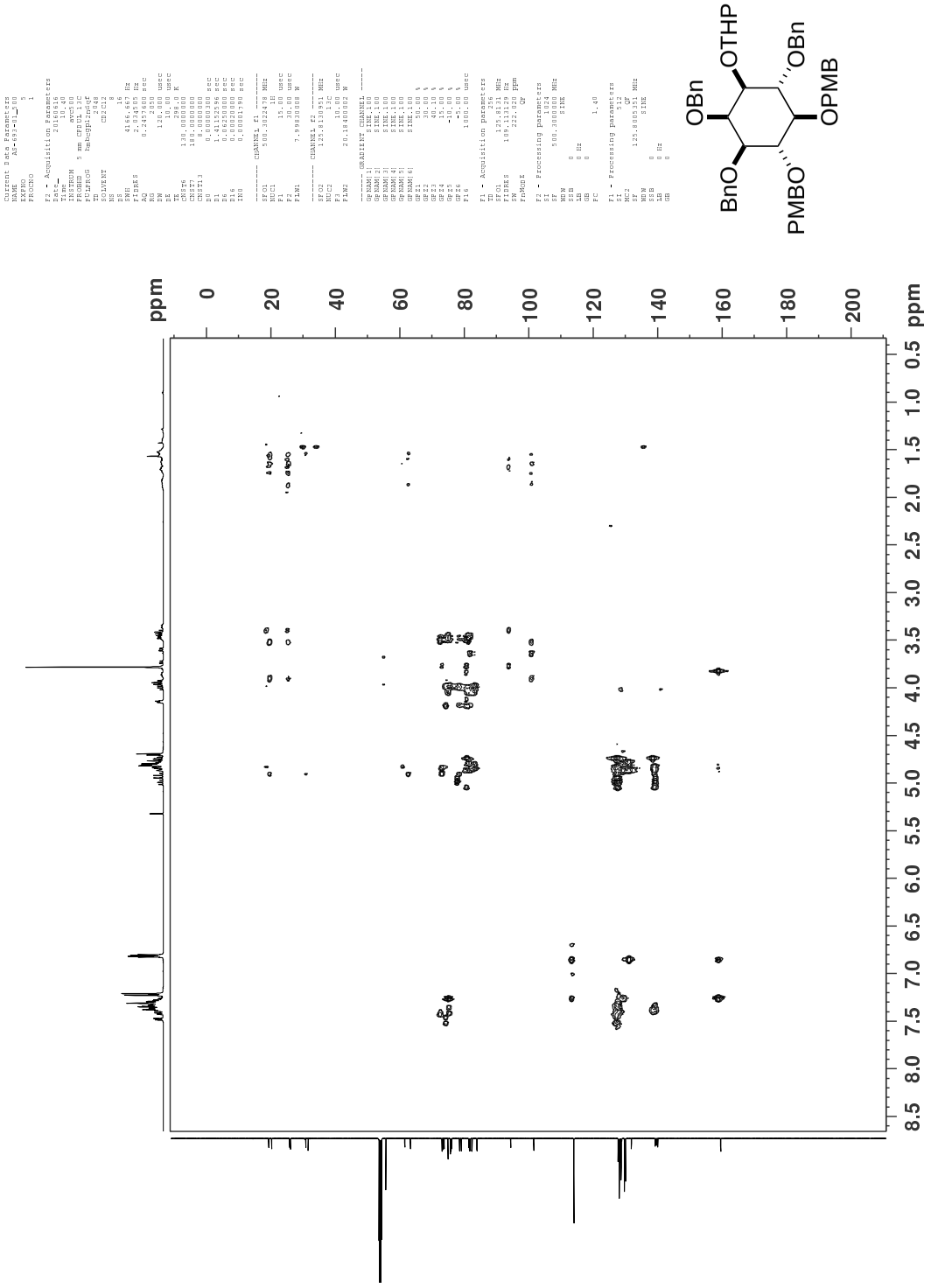
^{1}H NMR of (–)-217


Current Data Parameters
NAME AS-693-01_500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160616
Time_ 10.02
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OTHP
BnO
OBn
PMBO
OPMB
ppm
0.57
5.36
1.06
3.01
0.54
6.34
0.59
2.54
1.00
9.36
1.22
0.46
3.88
3.87
12.45
0.89
1.04

^{13}C NMR of (–)-217



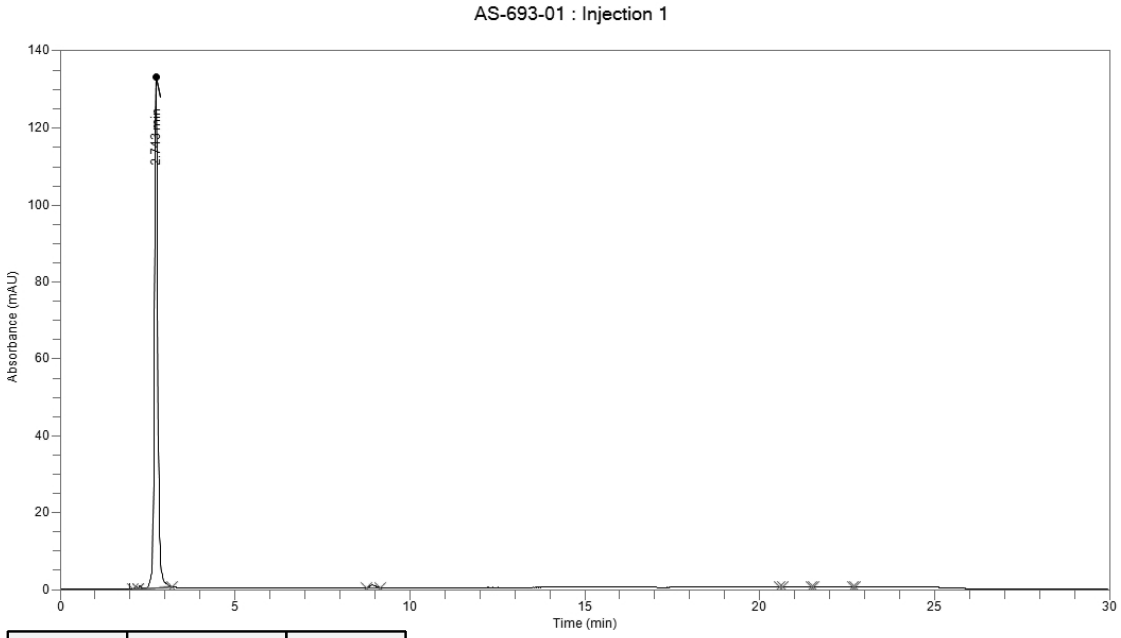
^{1}H-^{13}C HMBC NMR of (–)-217



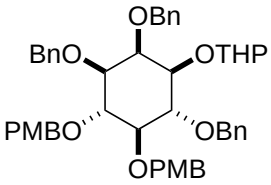
HPLC of (–)-217

AS-693-01

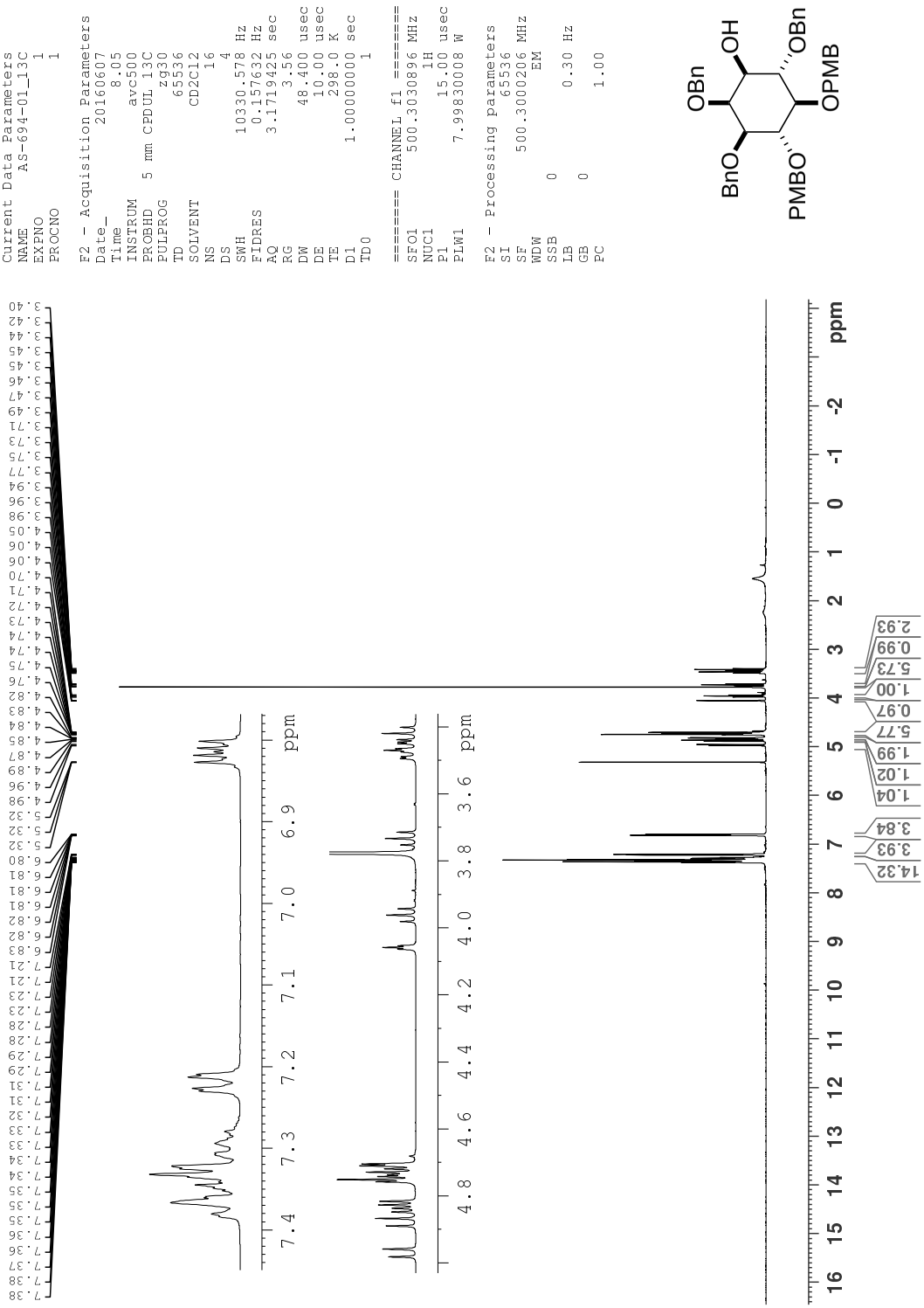
Sample Name	AS-693-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/28/2016 6:00 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



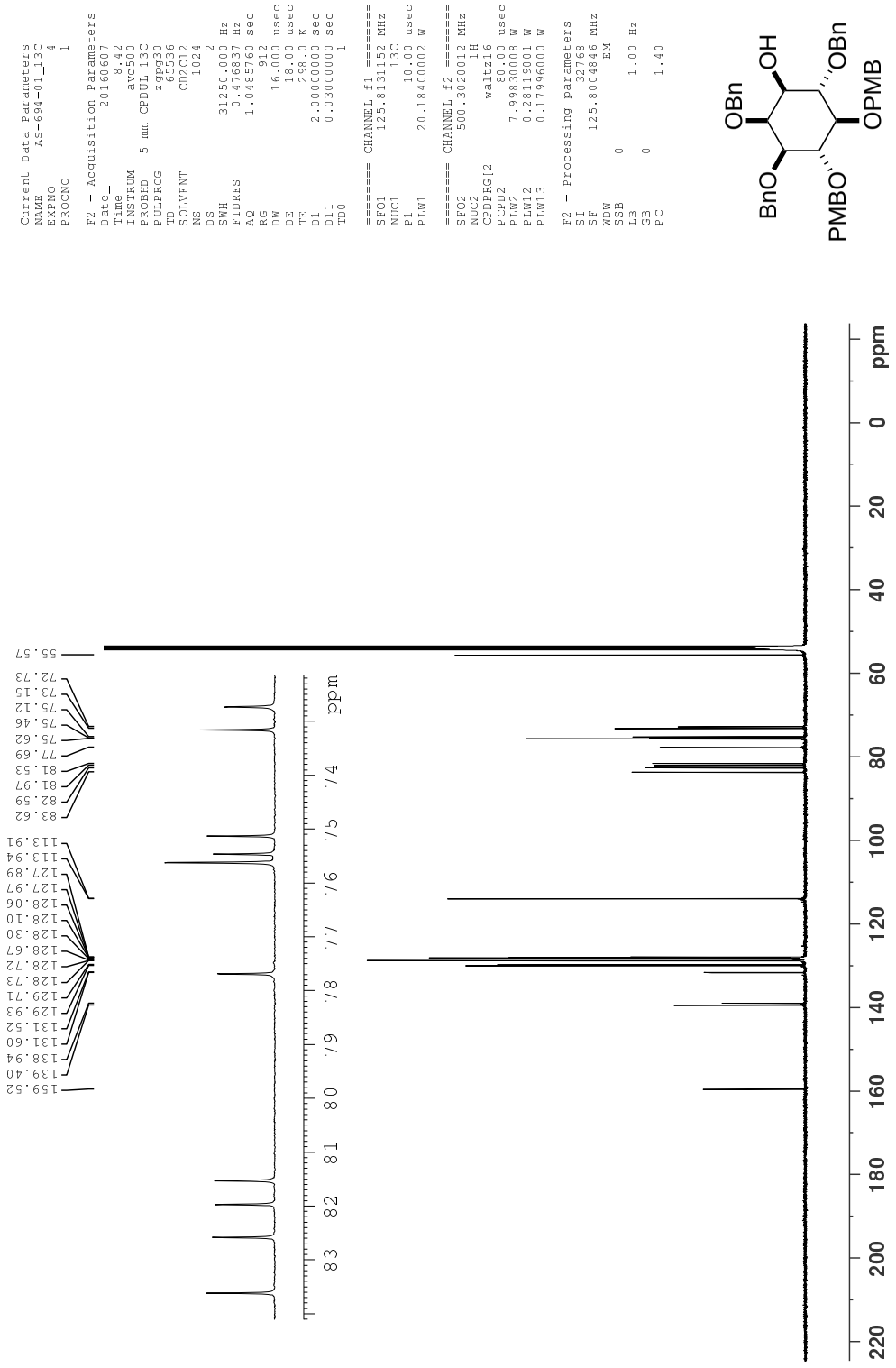
Time	Area	Area %
2.177	2225.6	0.25
2.277	3326.1	0.37
2.406	537.69	0.06
2.743	885822	98.47
8.924	7058.3	0.78
20.627	332.17	0.04
21.521	212.59	0.02
22.690	62.744	0.01
Total	899576.9	100.00



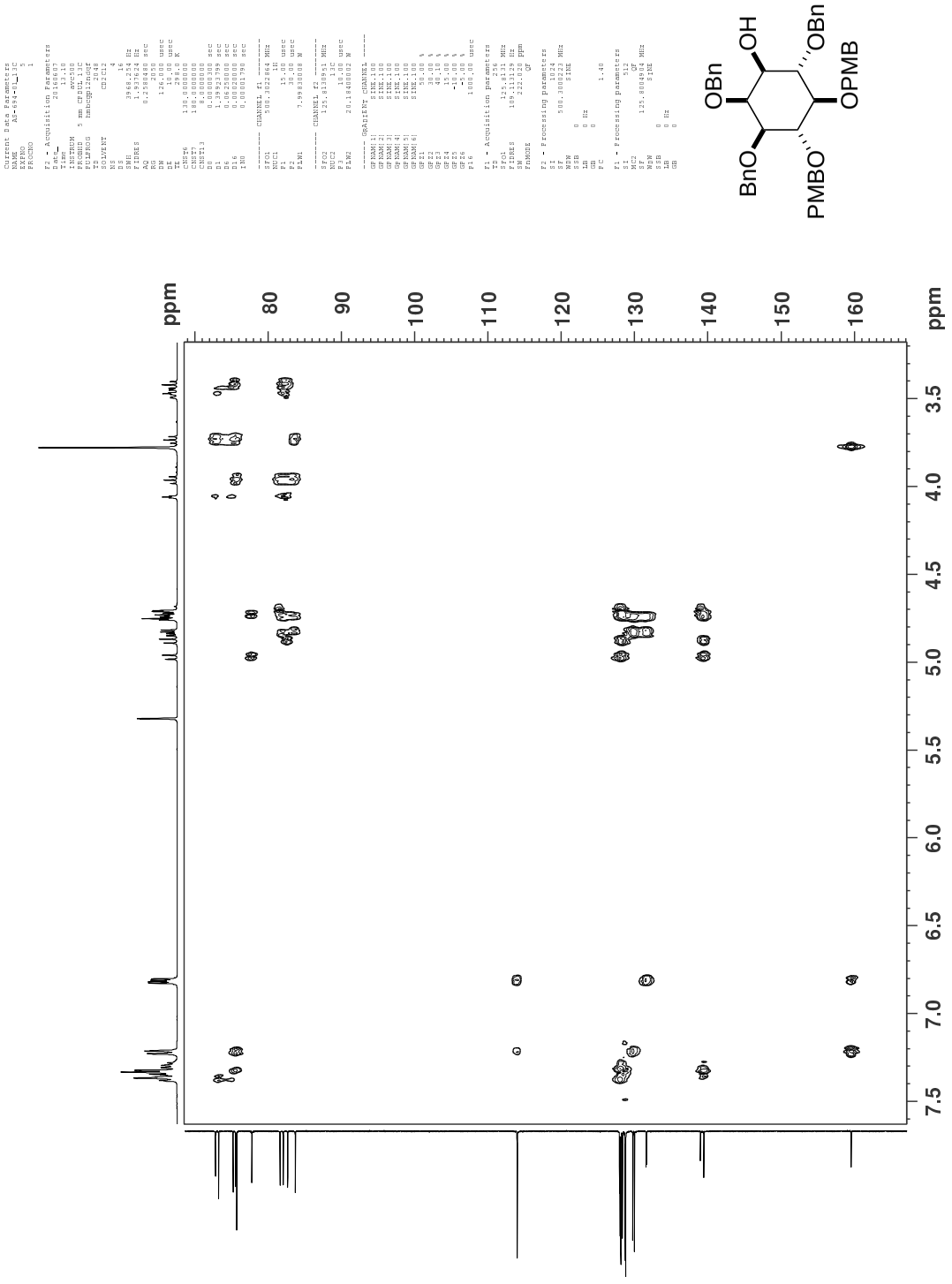
^{1}H NMR of (–)-213


Current Data Parameters
NAME AS-694-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160607
Time 8.05
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OH
OBn
BnO
PMBO
OPMB
ppm
14.32
3.93
3.84
1.04
1.02
1.99
5.77
0.97
1.00
5.73
0.99
2.93

^{13}C NMR of (–)-213



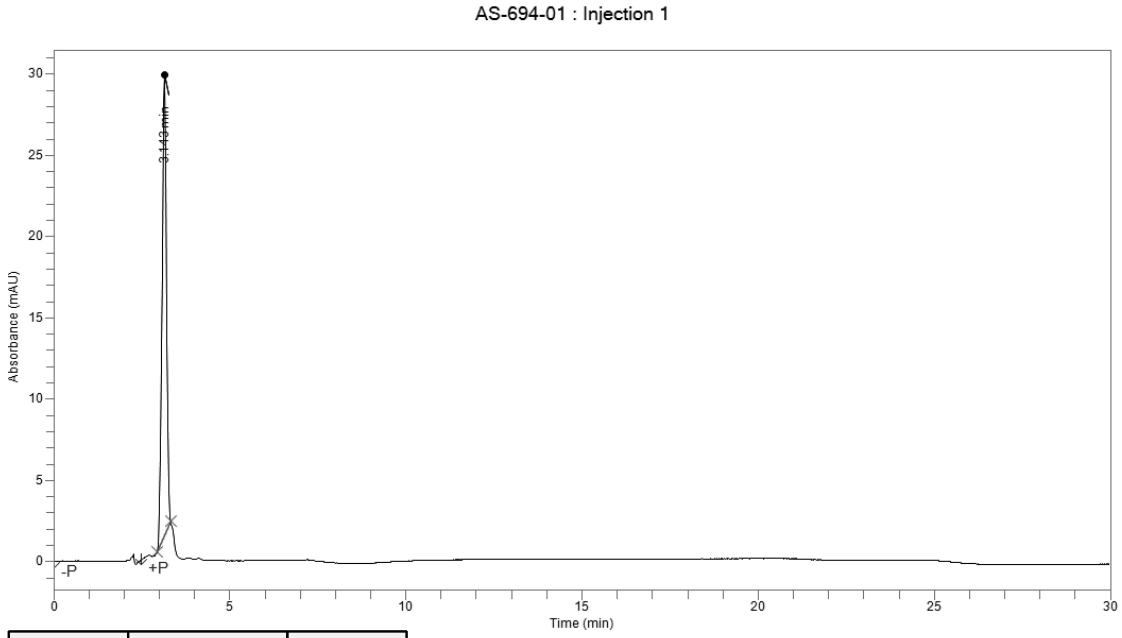
^{1}H-^{13}C HMBC NMR of (–)-213



HPLC of (–)-213

AS-694-01

Sample Name	AS-694-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/4/2016 3:41 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



Time	Area	Area %
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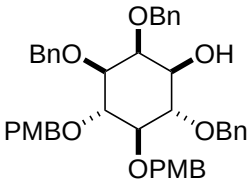
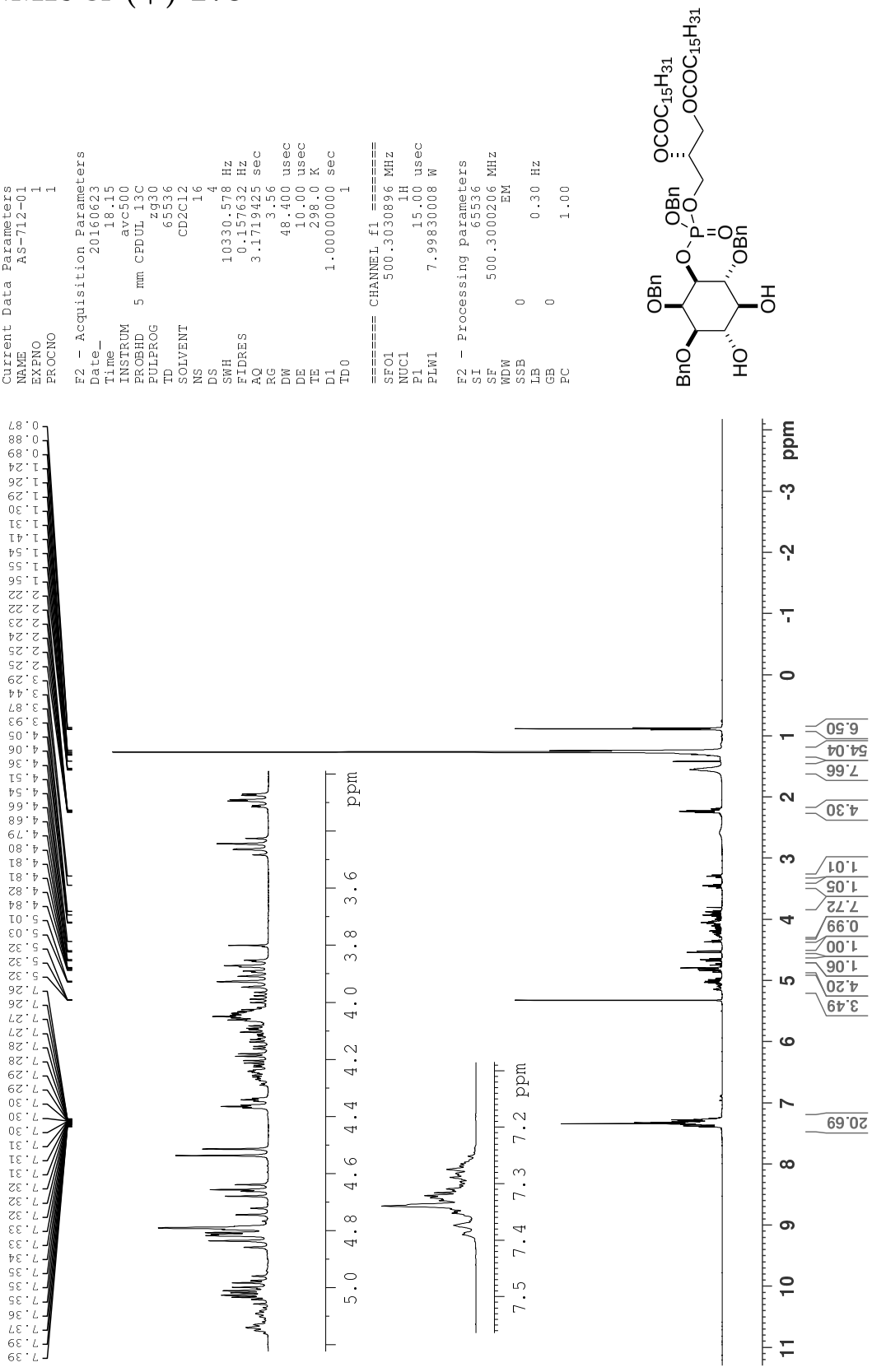
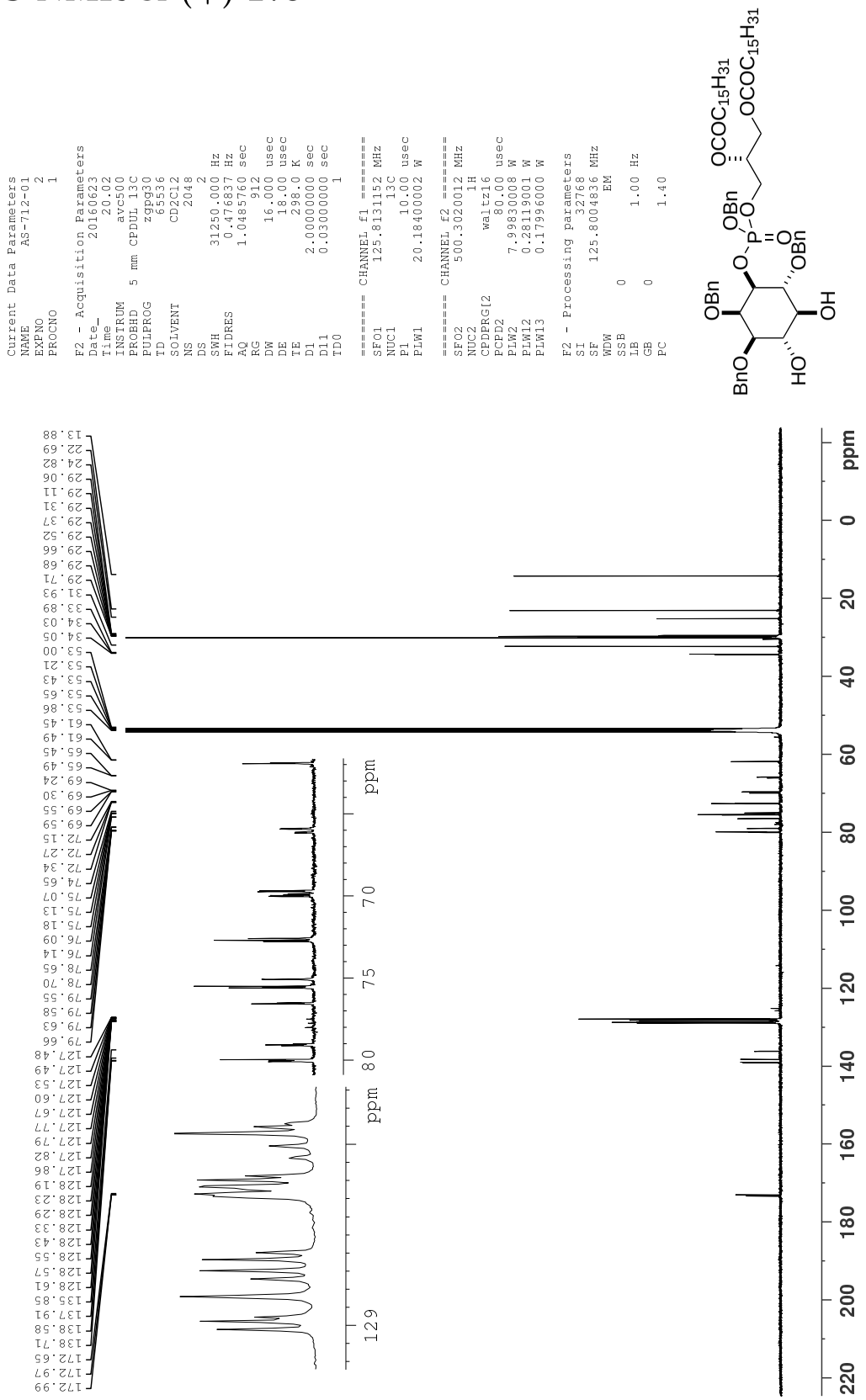
Total	245477	100.00



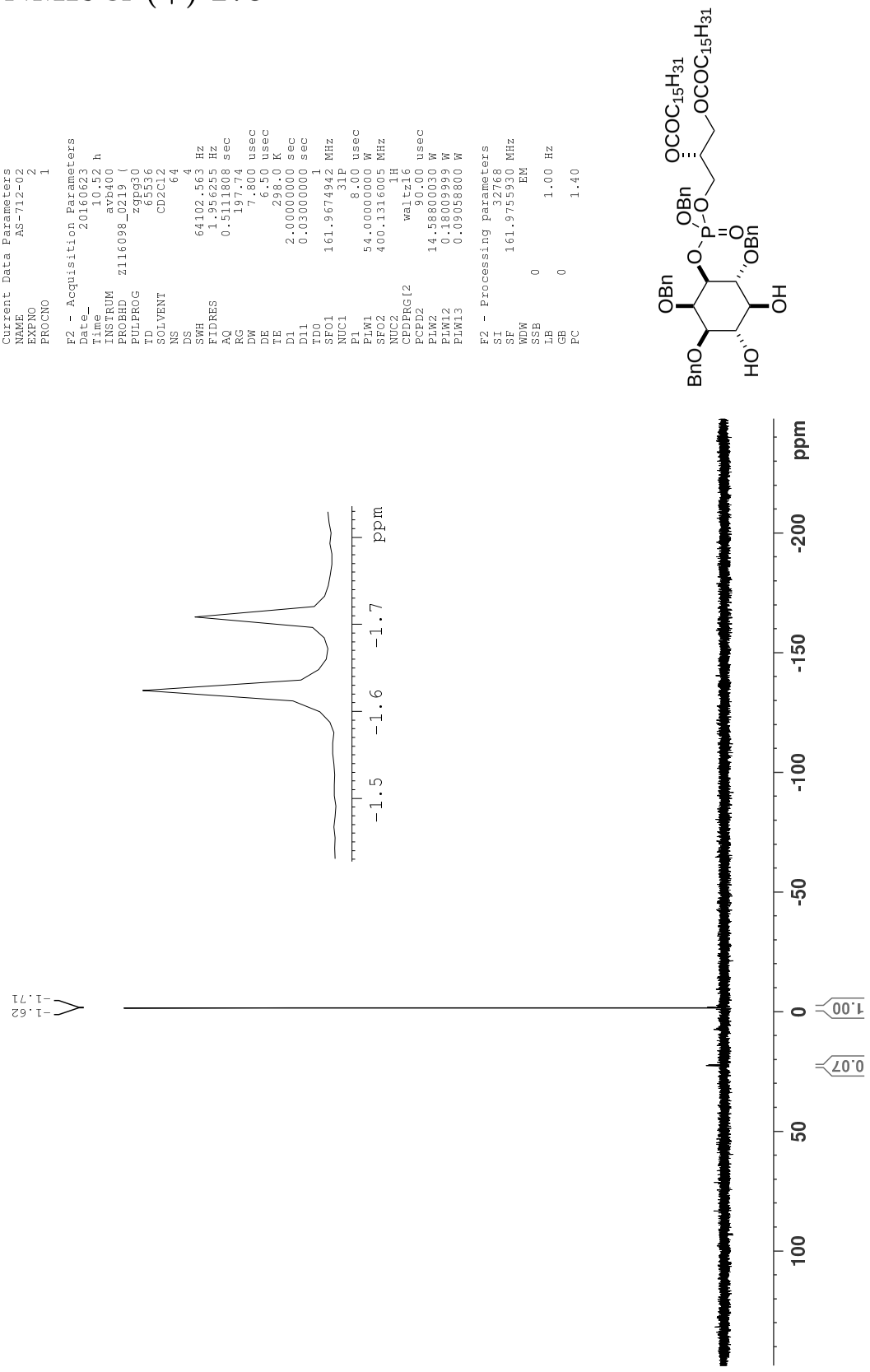
^{1}H NMR of (+)-270


Current Data Parameters
NAME AS-712-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160623
Time 18.15
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OBn
OCOC15H31
OCOC15H31
O
P
O
OBn
OH
BnO
HO
ppm
20.69
7.72
7.66
7.30
7.29
7.28
7.27
7.26
5.32
5.03
4.81
4.80
4.79
4.68
4.66
4.54
4.51
4.36
4.06
4.05
3.93
3.87
3.44
3.29
2.25
2.24
2.23
2.22
1.56
1.55
1.54
1.41
1.31
1.30
1.29
1.26
1.24
0.89
0.88
0.87
3.49
4.20
1.06
1.00
0.99
7.72
1.05
1.01
4.30
54.04
6.50

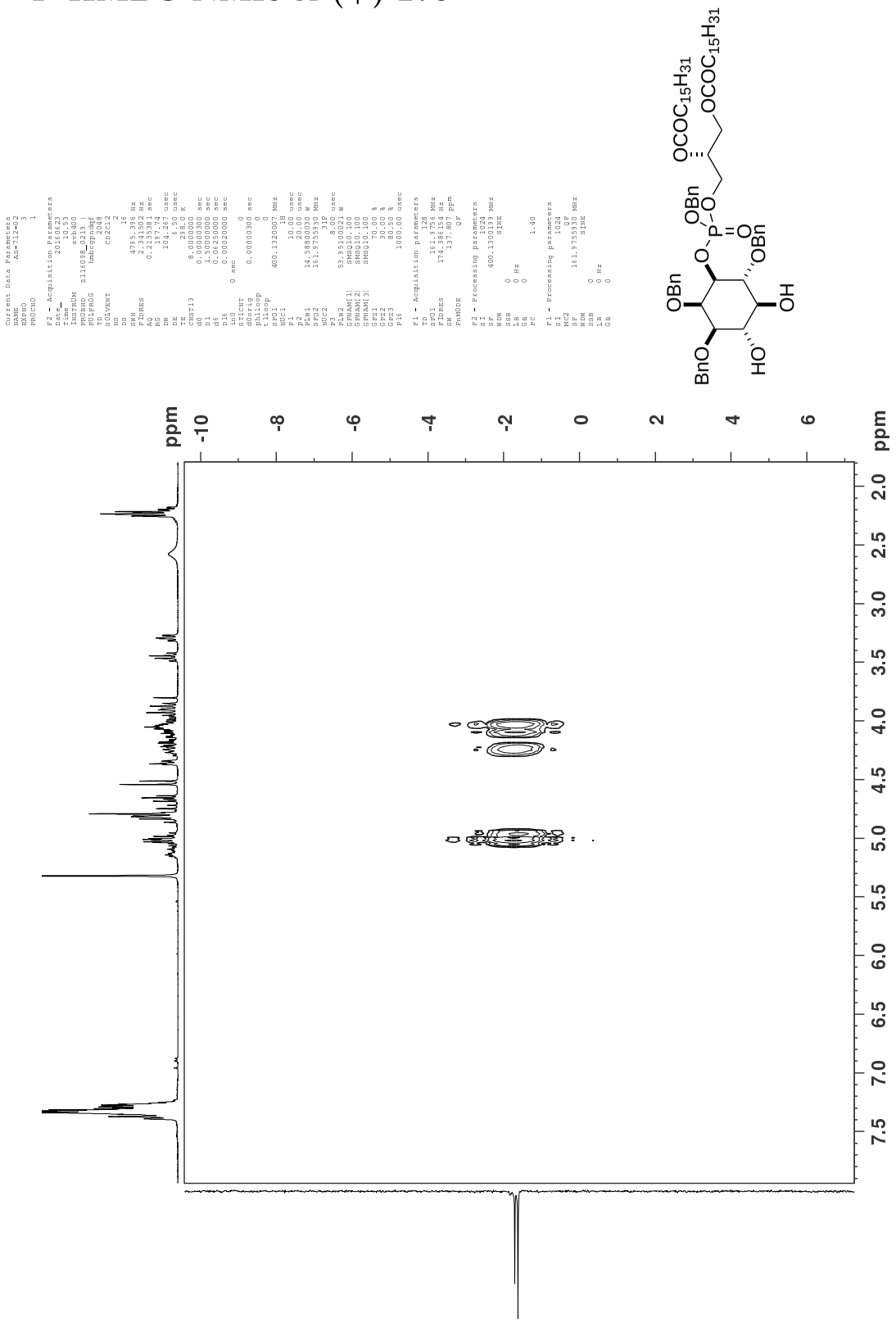
^{13}C NMR of (+)-270



^{31}P NMR of (+)-270



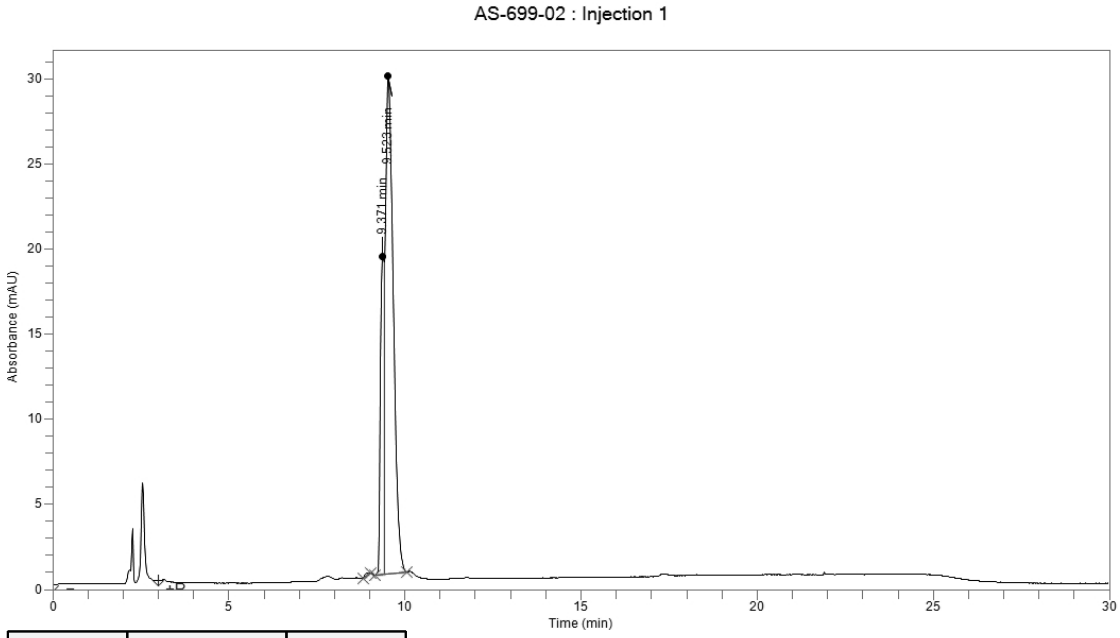
^{1}H-^{31}P HMBC NMR of (+)-270



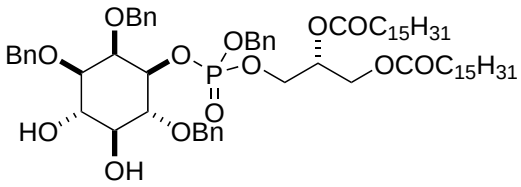
HPLC of (+)-270

AS-699-02

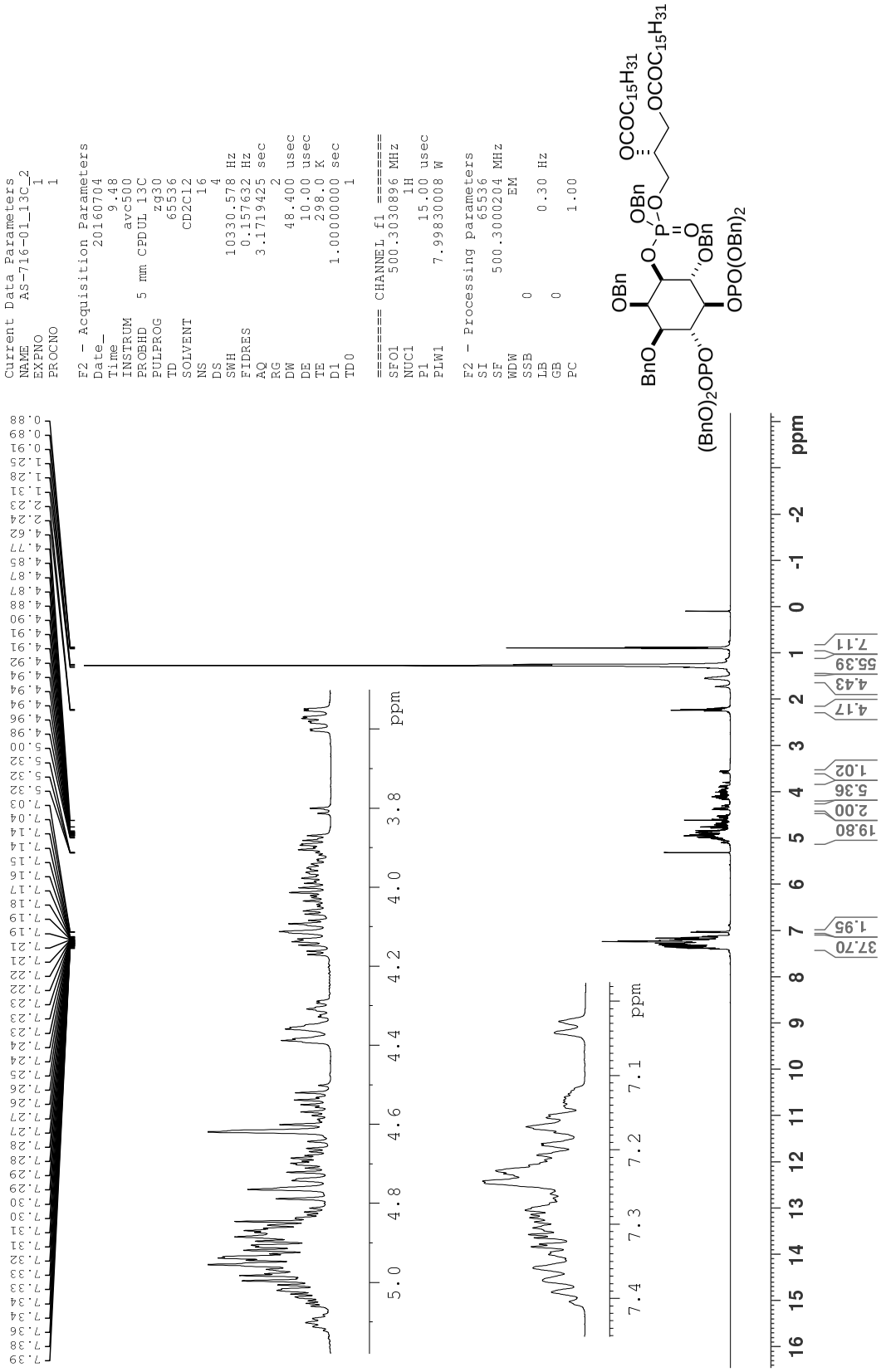
Sample Name	AS-699-02	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/28/2016 7:11 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



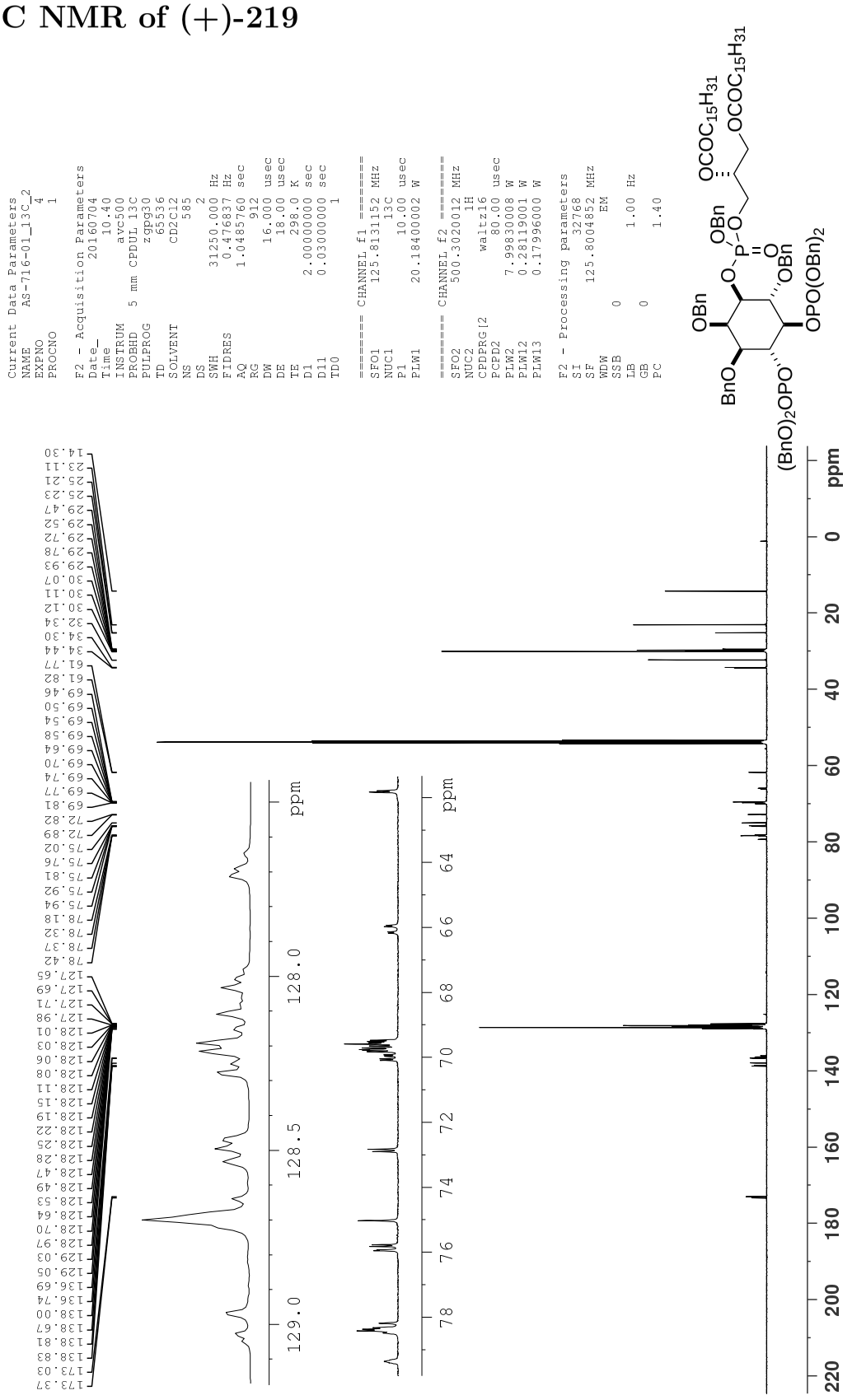
Time	Area	Area %
8.989	915.33	0.16
9.371	127337	21.68
9.523	459129	78.17
Total	587381.19	100.00



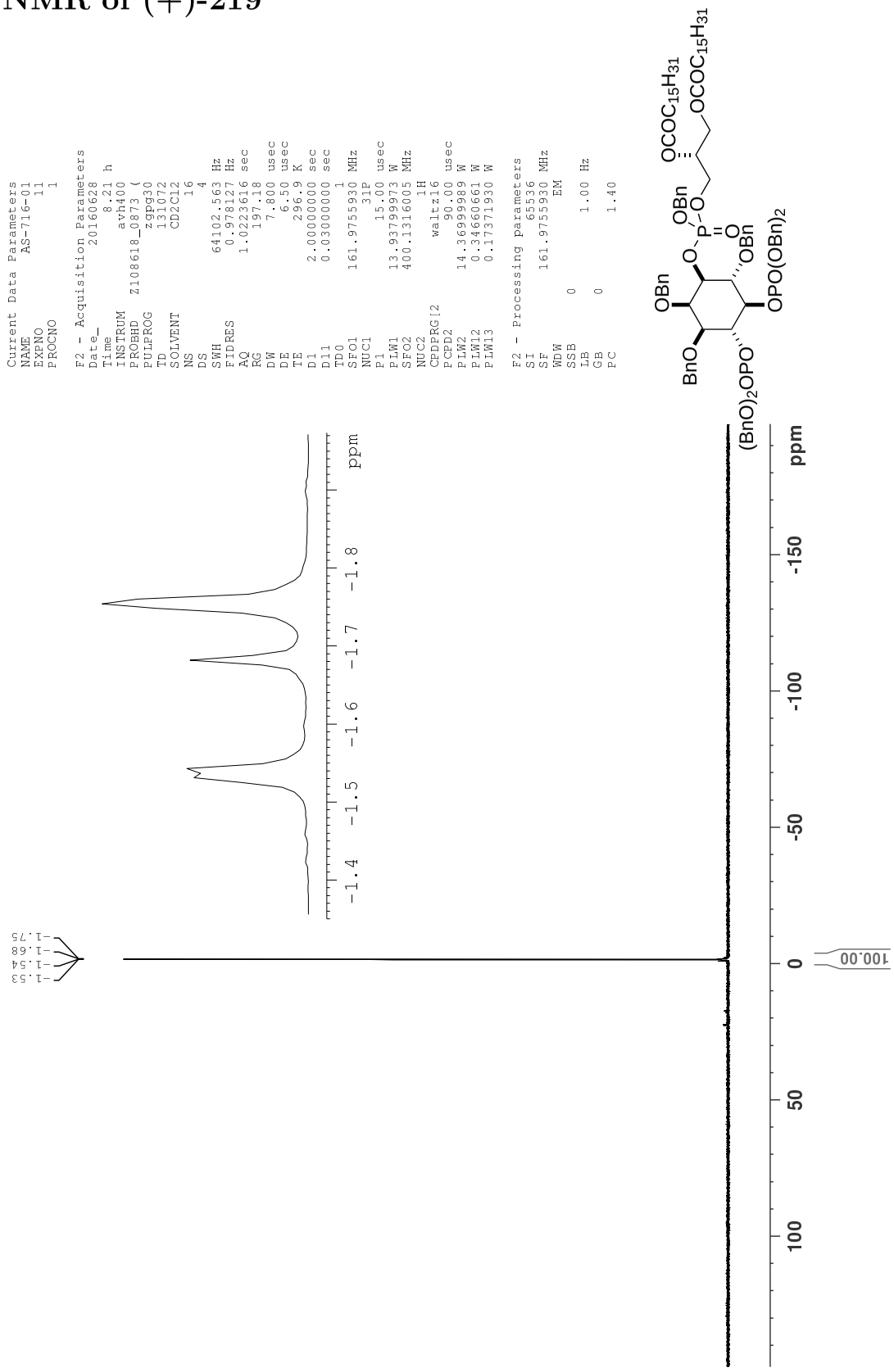
^{1}H NMR of (+)-219


Current Data Parameters
NAME AS-716-01_13C_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160704
Time 9.48
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000204 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
BnO
(BnO)2OPO
OBn
O
P=O
OBn
OPO(OBn)2
OCOC15H31
OCOC15H31
ppm
19.80
2.00
5.36
1.02
1.95
37.70
4.17
4.43
55.39
7.11

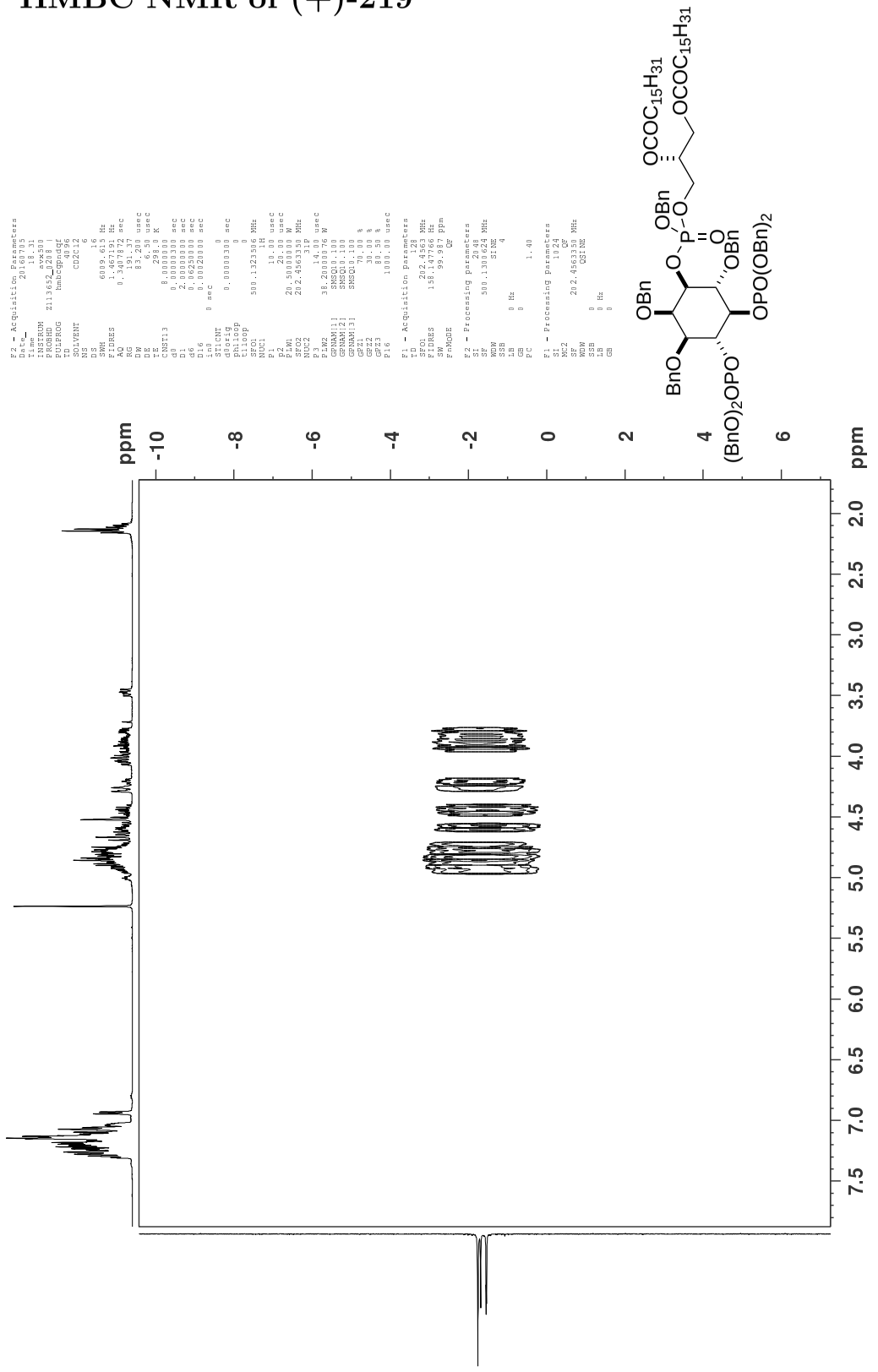
^{13}C NMR of (+)-219



^{31}P NMR of (+)-219



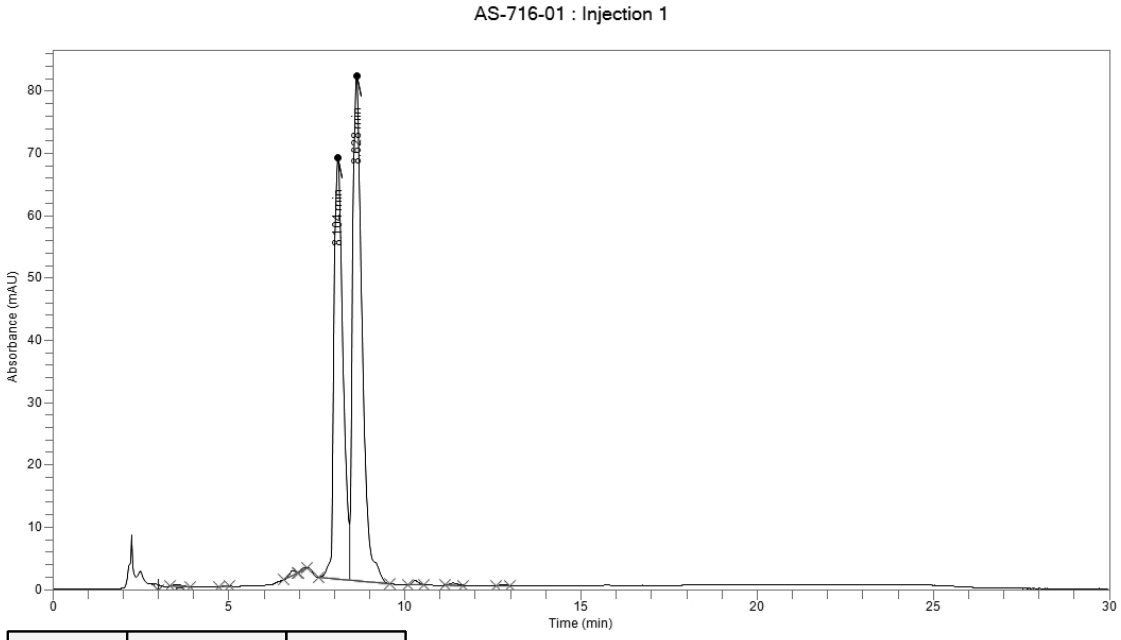
^{1}H-^{31}P HMBC NMR of (+)-219



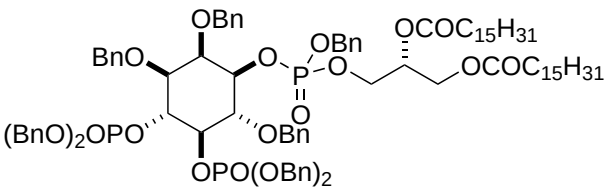
HPLC of (+)-219

AS-716-01

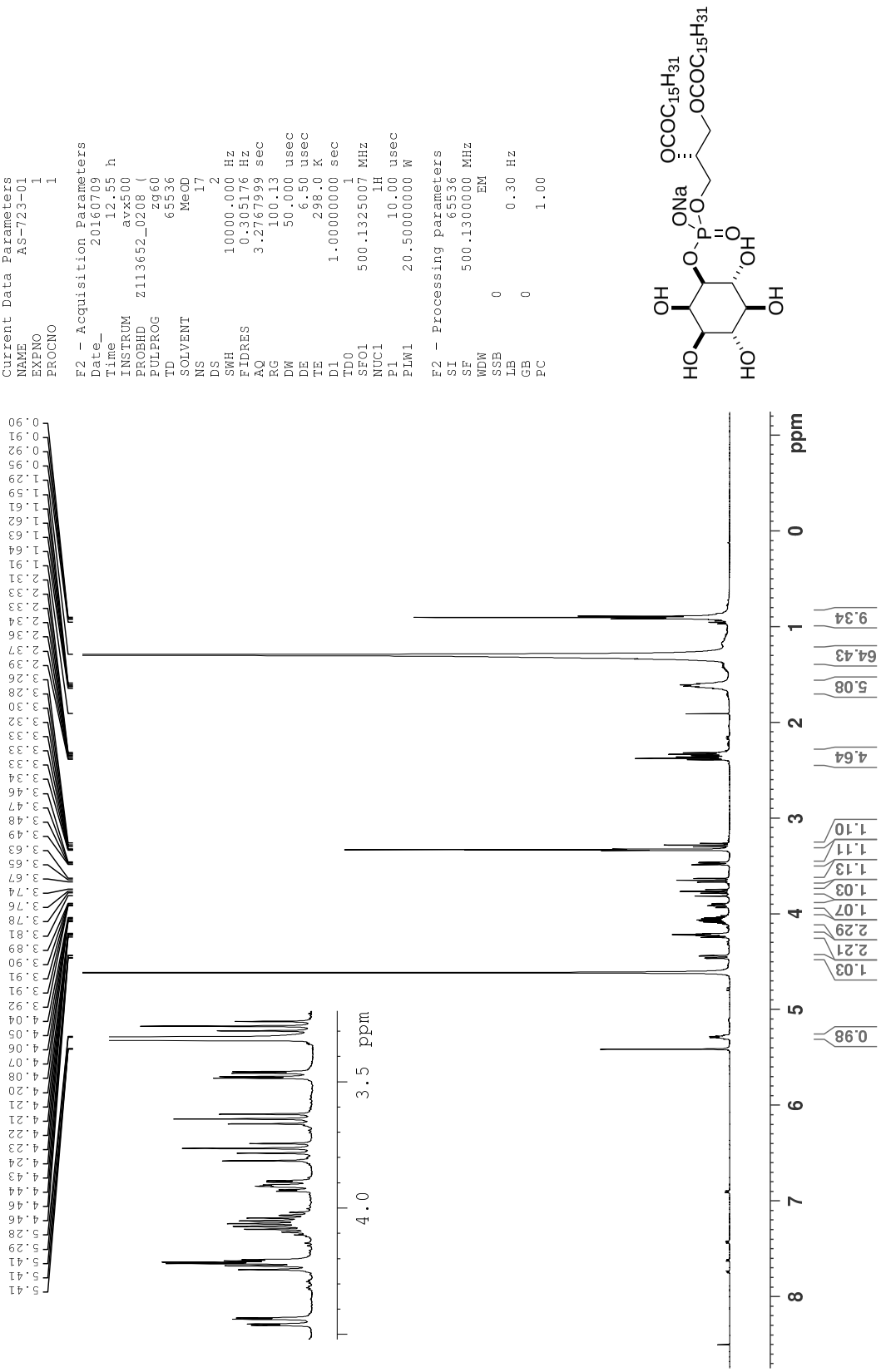
Sample Name	AS-716-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/29/2016 10:59 am
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column



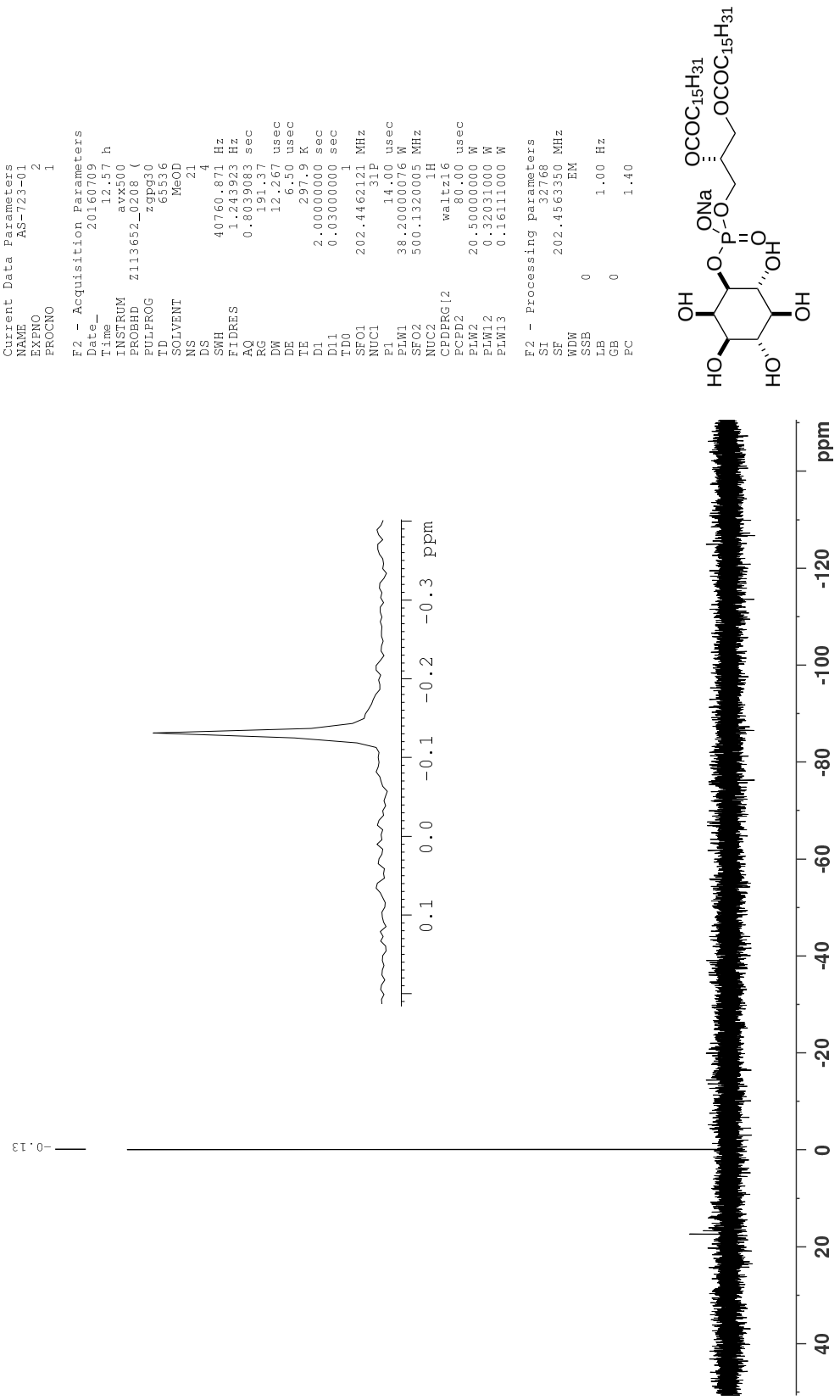
Time	Area	Area %
3.504	6061.8	0.22
4.877	1183.3	0.04
6.819	8189	0.30
7.162	1973.9	0.07
8.104	1195373	43.52
8.628	1518669	55.29
10.279	7353.6	0.27
11.369	5115.5	0.19
12.767	2645.6	0.10
Total	2746564.4	100.00



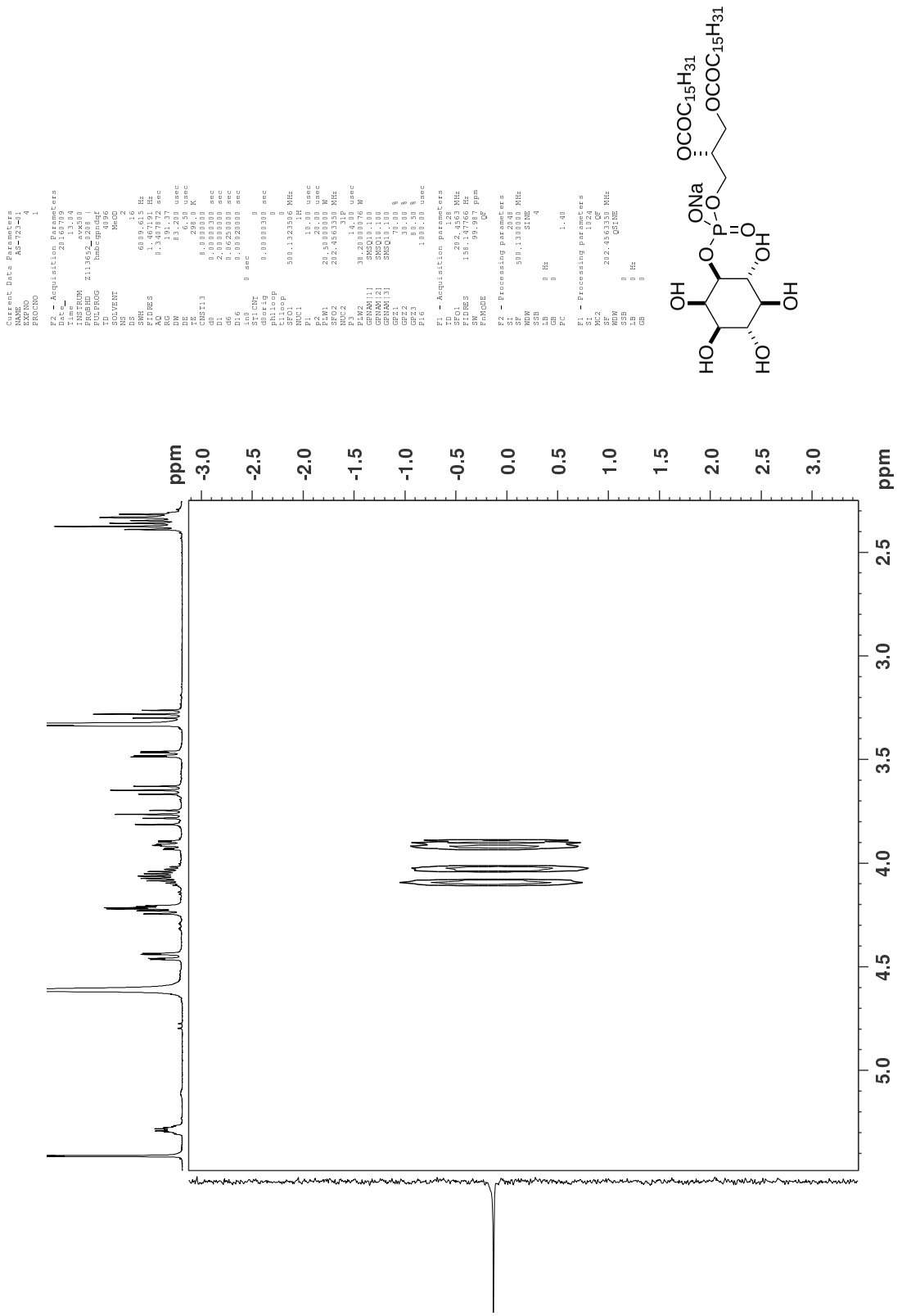
^{1}H NMR of 13


Current Data Parameters
NAME AS-723-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160709
Time 12.55 h
INSTRUM avx500
PROBHD Z113652_0208 (
PULPROG zg60
TD 65536
SOLVENT MeOD
NS 17
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 100.13
DW 50.000 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
PLW1 20.50000000 W
F2 - Processing parameters
SI 65536
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCOC15H31
ONa
OCOC15H31
P
O
OH
HO
ppm
9.34
64.43
5.08
4.64
1.10
1.11
1.13
1.03
1.07
2.29
2.21
1.03
0.98
4.0
3.5 ppm

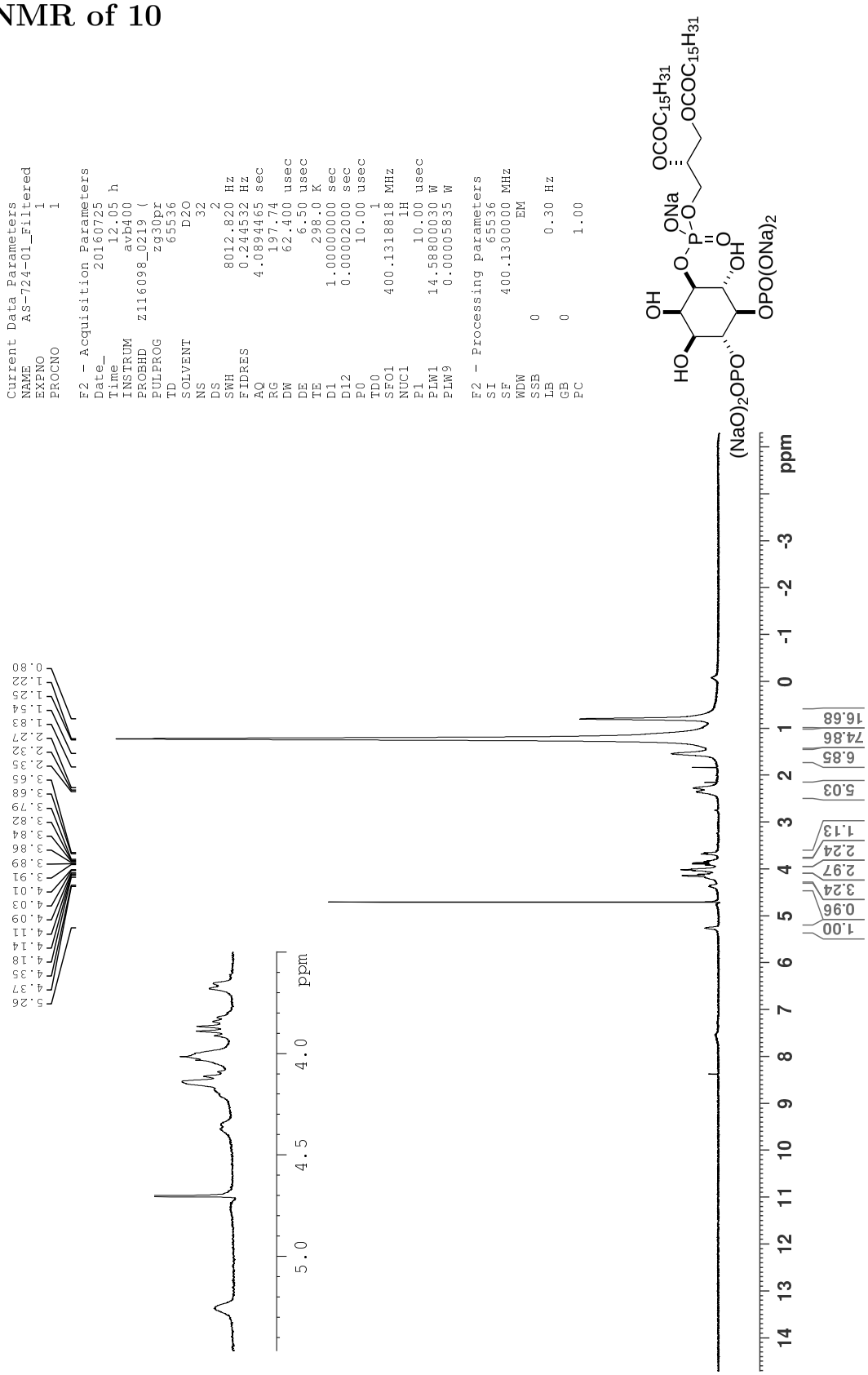
^{31}P NMR of 13


Current Data Parameters
NAME AS-723-01
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160709
Time 12.57 h
INSTRUM avx500
PROBHD Z113652_0208 (
PULPROG zgpg30
TD 65536
SOLVENT MeOD
NS 21
DS 4
SWH 40760.871 Hz
FIDRES 1.243923 Hz
AQ 0.8039083 sec
RG 191.37
DW 12.267 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 202.4462121 MHz
NUC1 31P
P1 14.00 usec
PLW1 38.20000076 W
SFO2 500.1320005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 20.50000000 W
PLW12 0.32031000 W
PLW13 0.16111000 W
F2 - Processing parameters
SI 32768
SF 202.4563350 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OCOC15H31
ONa
OCOC15H31
O
P
O
OH
OH
OH
HO
HO
-0.13
0.1
0.0
-0.1
-0.2
-0.3
ppm
40
20
0
-20
-40
-60
-80
-100
-120
ppm

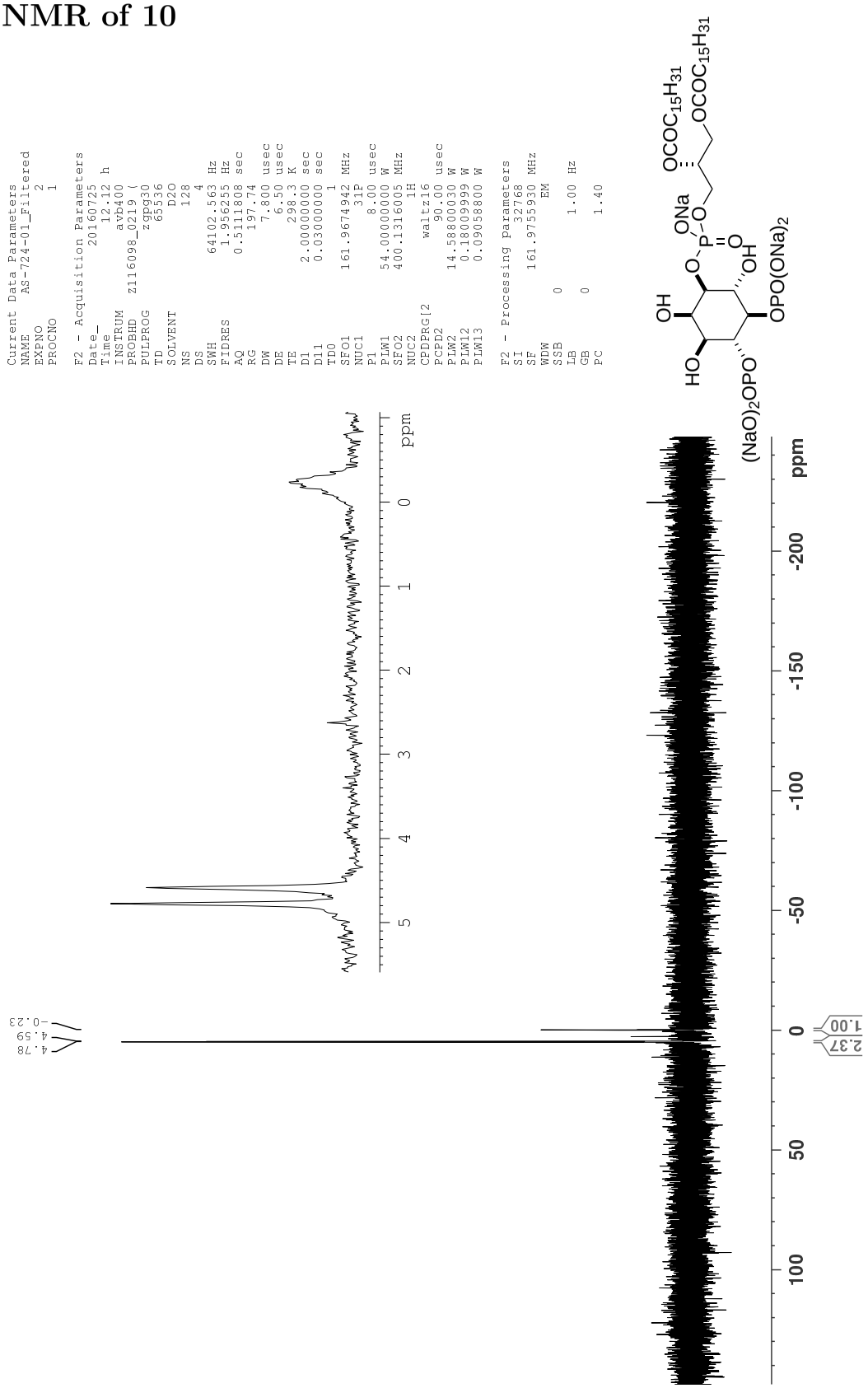
^{1}H-^{31}P NMR of 13



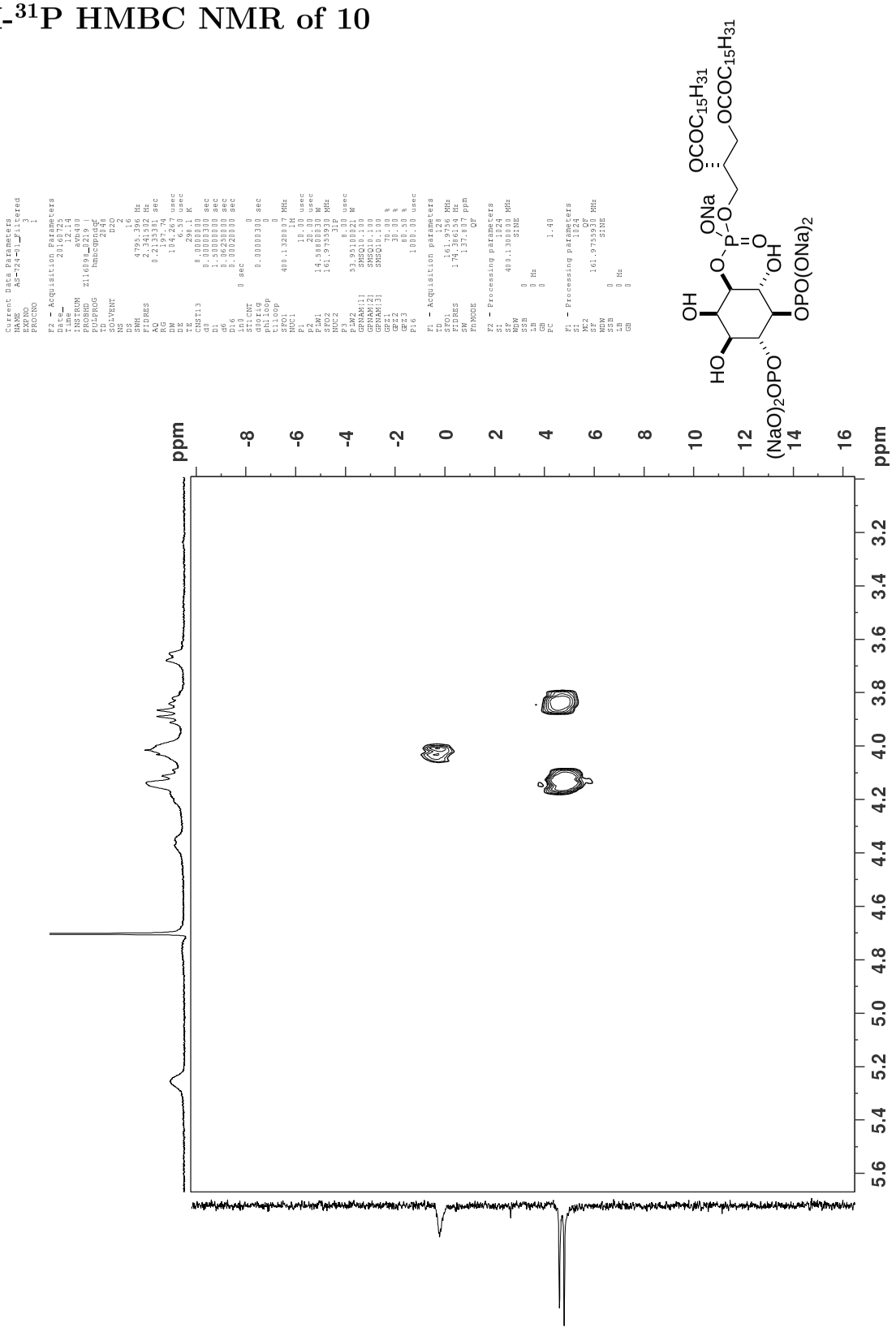
^{1}H NMR of 10


Current Data Parameters
NAME AS-724-01_Filtered
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160725
Time 12.05 h
INSTRUM avb400
PROBHD z116098_0219 (
PULPROG zg30pr
TD 65536
SOLVENT D2O
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 197.74
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
D12 0.00002000 sec
P0 10.00 usec
TD0 1
SFO1 400.1318818 MHz
NUC1 1H
P1 10.00 usec
PLW1 14.58800030 W
PLW9 0.00005835 W
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCOC15H31
OCOC15H31
ONa
O
P
O
O
OH
OH
HO
(NaO)2OPO
OPO(ONa)2
ppm
16.68
74.86
6.85
5.03
1.13
2.24
2.97
3.24
0.96
1.00

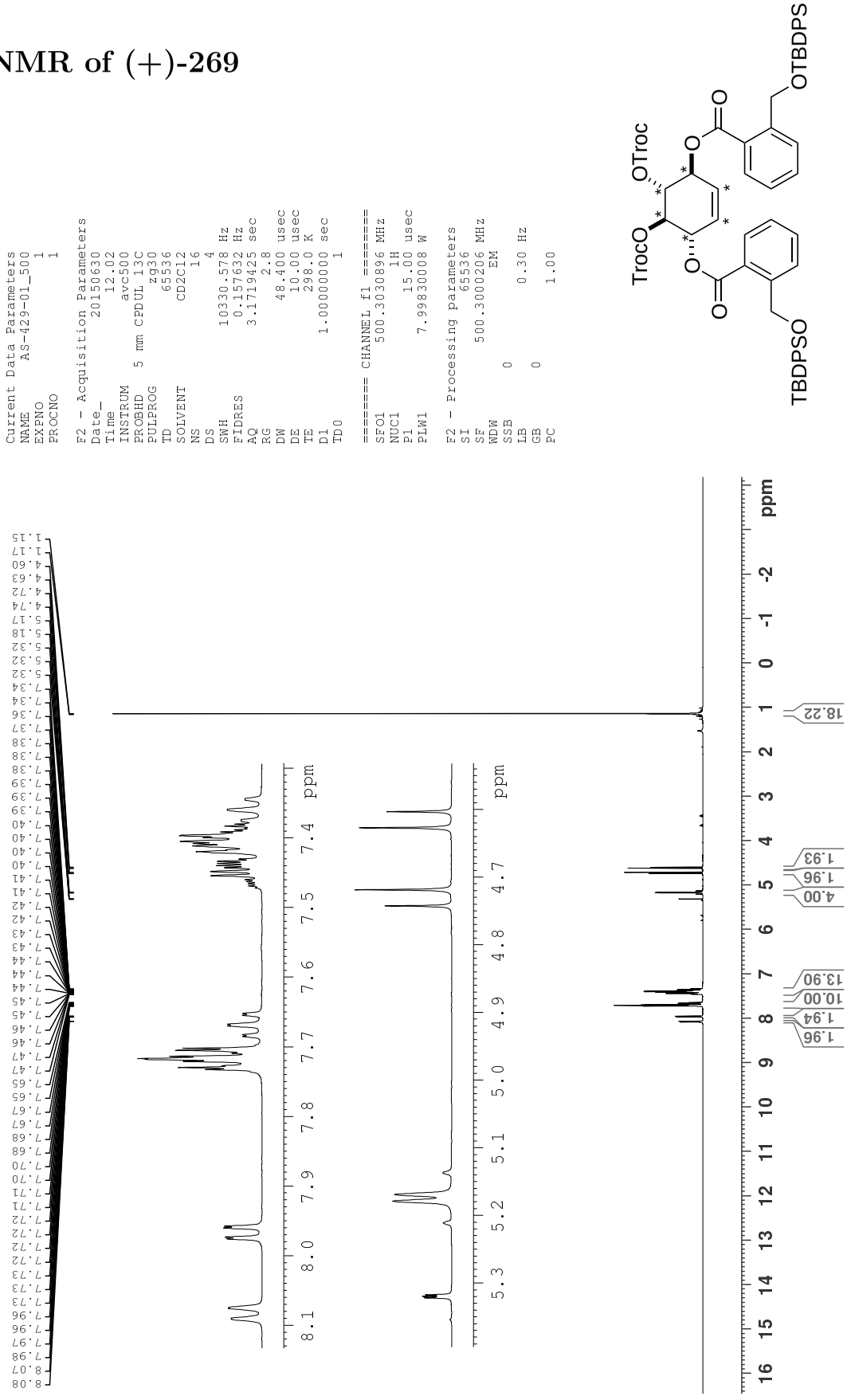
^{31}P NMR of 10


Current Data Parameters
NAME AS-724-01_Filtered
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160725
Time 12.12 h
INSTRUM avb400
PROBHD z116098_0219 (
PULPROG zgpg30
TD 65536
SOLVENT D2O
NS 128
DS 4
SWH 64102.563 Hz
FIDRES 1.956255 Hz
AQ 0.5111808 sec
RG 197.74
DW 7.800 usec
DE 6.50 usec
TE 298.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 161.9674942 MHz
NUC1 31P
P1 8.00 usec
PLW1 54.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 14.58800030 W
PLW12 0.18009999 W
PLW13 0.09058800 W
F2 - Processing parameters
SI 32768
SF 161.9755930 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
4.78
4.59
-0.23
ppm
5 4 3 2 1 0
100 50 0 -50 -100 -150 -200 ppm
1.00
2.37
OCOC15H31
OCOC15H31
ONa
O
P
O
OH
OH
HO
OPO(ONa)2
(NaO)2OPO

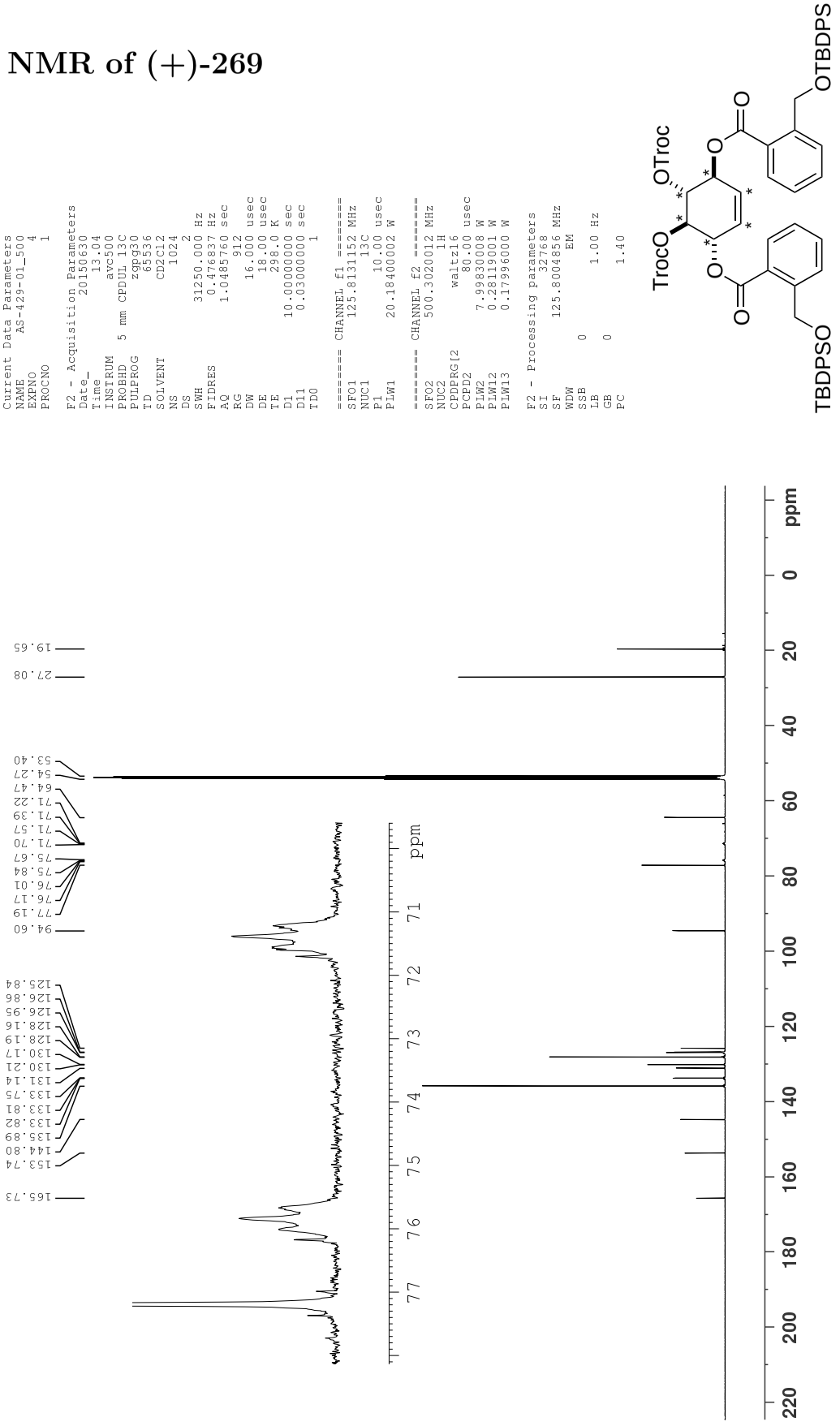
^{1}H-^{31}P HMBC NMR of 10



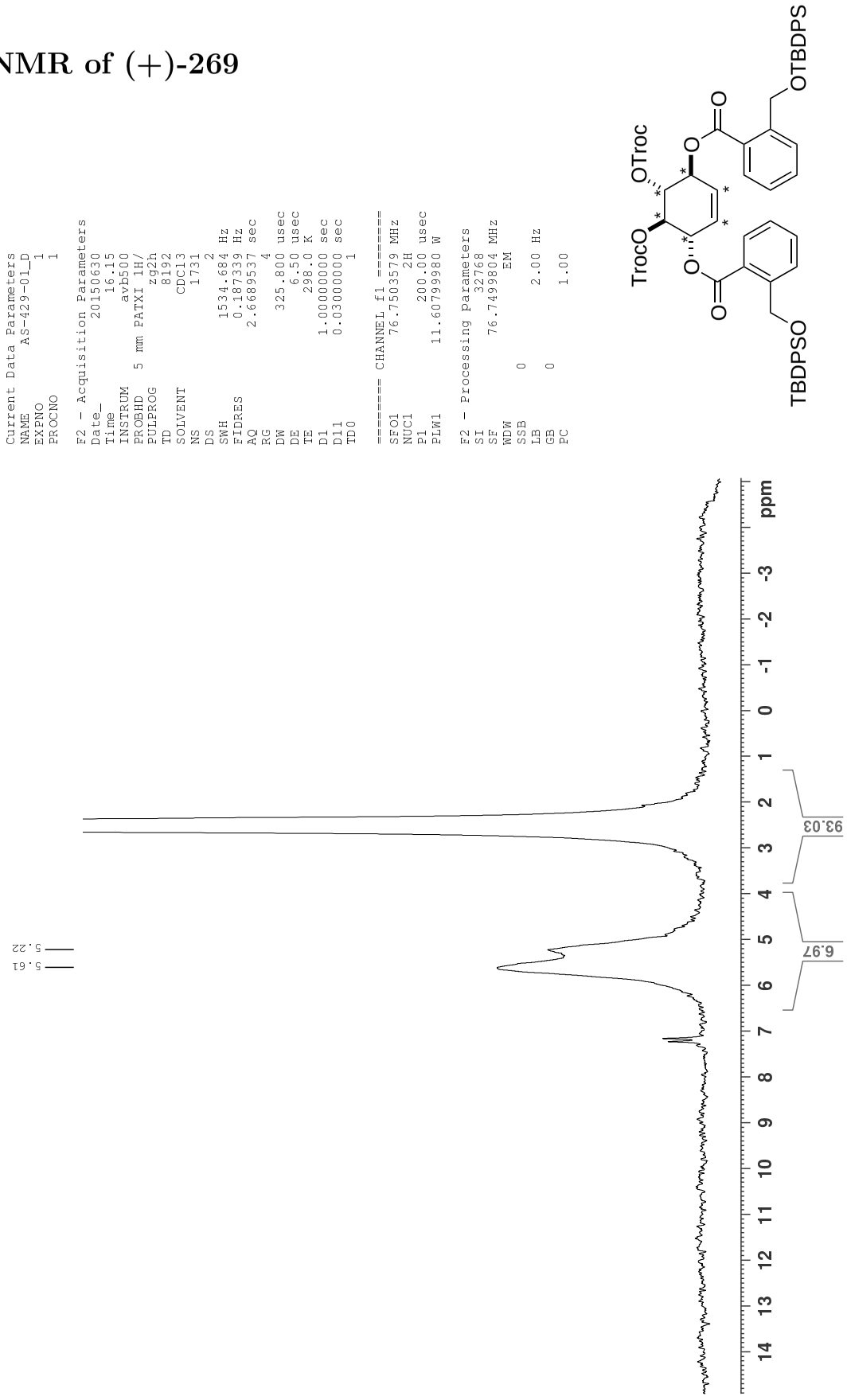
^{1}H NMR of (+)-269


OTBDPS
OTroc
TrocO
TBDPSO
Current Data Parameters
NAME AS-429-01_500
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150630
Time 12.02
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 2.8
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
18.22
4.00
1.93
1.96
13.90
10.00
1.94
1.96
ppm

^{13}C NMR of (+)-269



^{2}H NMR of (+)-269

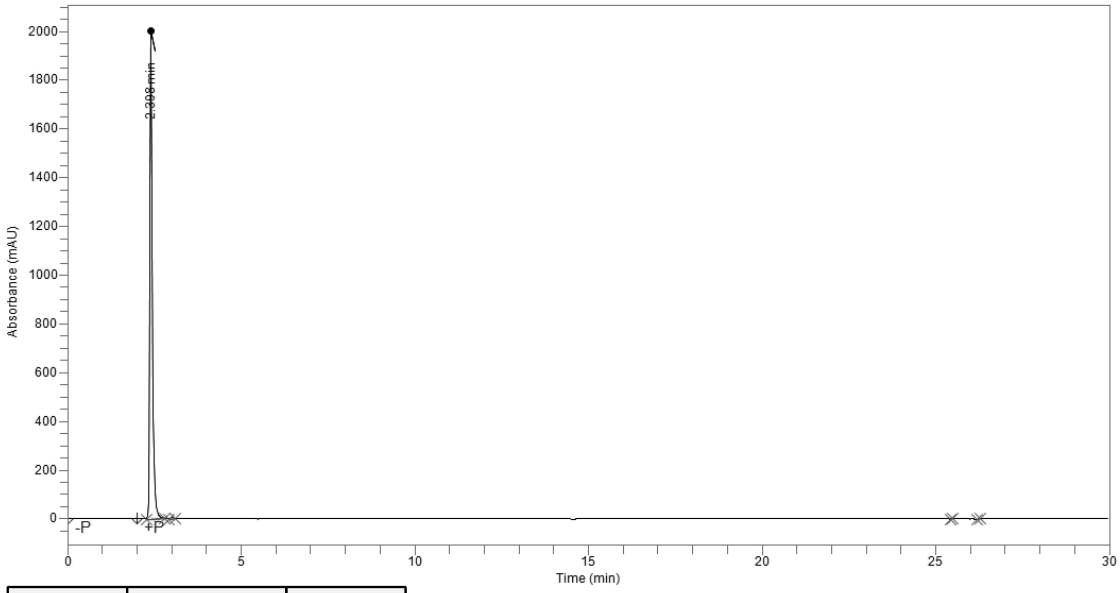

Current Data Parameters
NAME AS-429-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150630
Time 16.15
INSTRUM avb500
PROBHD 5 mm PATXI 1H/
PULPROG zg2h
TD 8192
SOLVENT CDCl3
NS 1731
DS 2
SWH 1534.684 Hz
FIDRES 0.187339 Hz
AQ 2.6689537 sec
RG 4
DW 325.800 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7503579 MHz
NUC1 2H
P1 200.00 usec
PLW1 11.60799980 W
F2 - Processing parameters
SI 32768
SF 76.7499804 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
OTroc
TrocO
OTBDPS
TBDPSO
5.61
5.22
93.03
6.97
ppm

HPLC of (+)-269

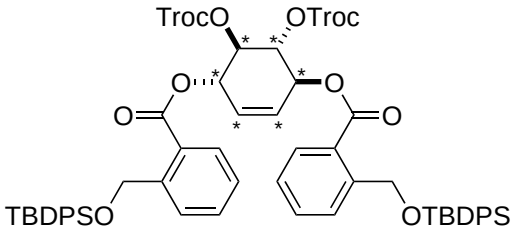
AS-429-01

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

AS-429-01 : Injection 1



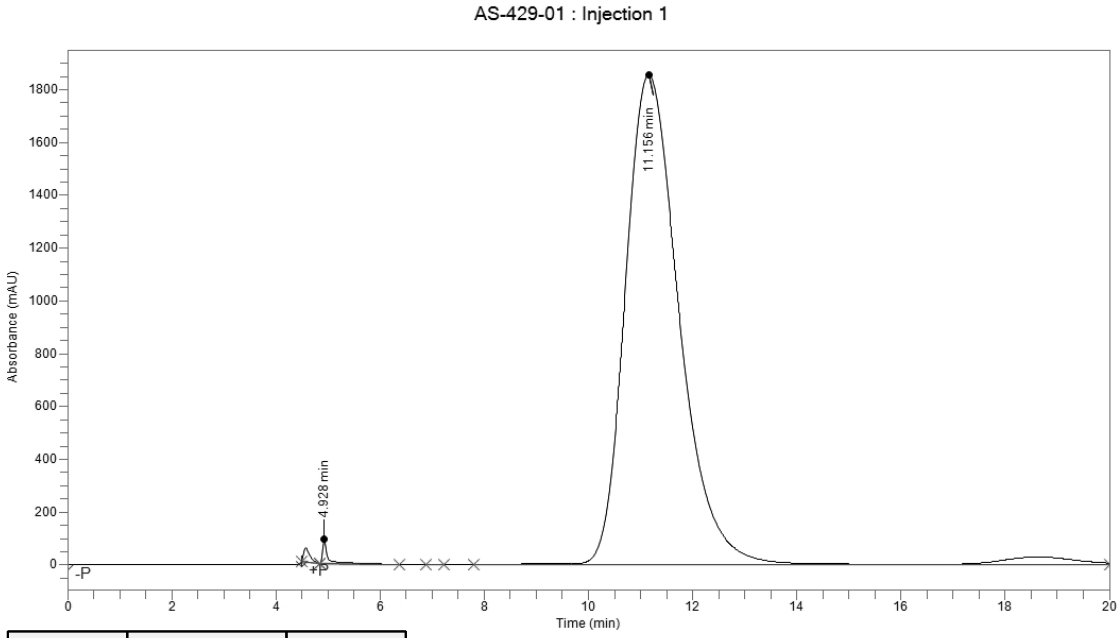
Time	Area	Area %
2.398	9848506	99.25
2.994	59588	0.60
25.470	6194	0.06
26.235	8635.8	0.09
Total	9922924	100.00



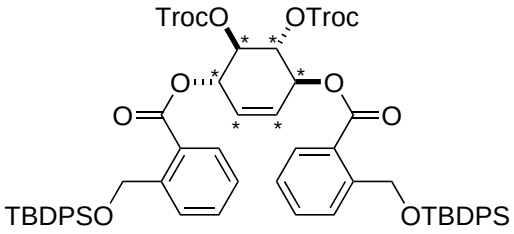
HPLC of (+)-269

AS-429-01

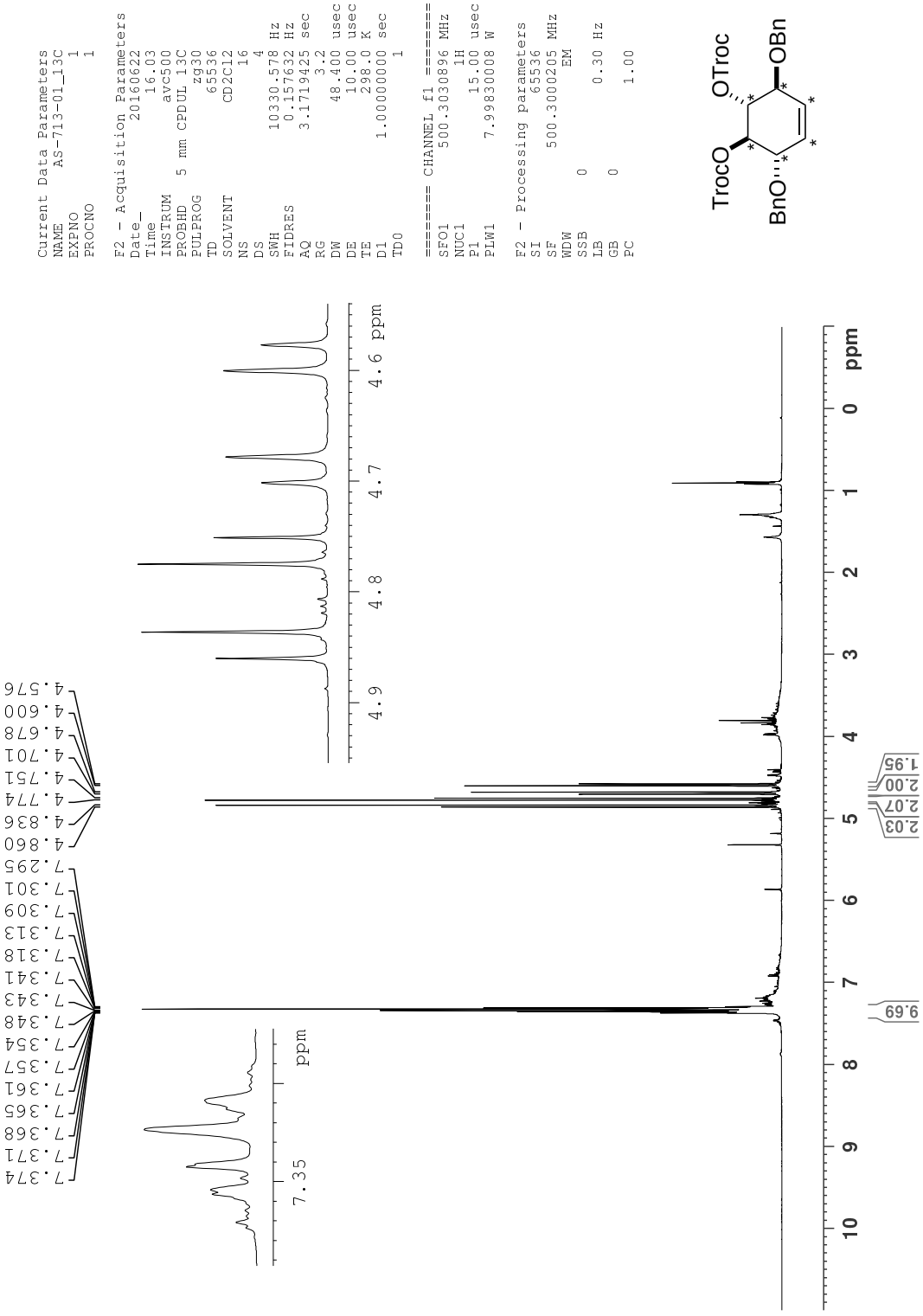
Sample Name	AS-429-01	Sample Description	ADH column
Acquisition Method	EE determination 100 A 220 nm 20 min 1% IPA	Acquisition Date/Time	7/7/2015 5:34 pm
Batch Group/Name	Alex/EE determination 100 A 220 nm 20 min 1% IPA	Batch Description	ADH column



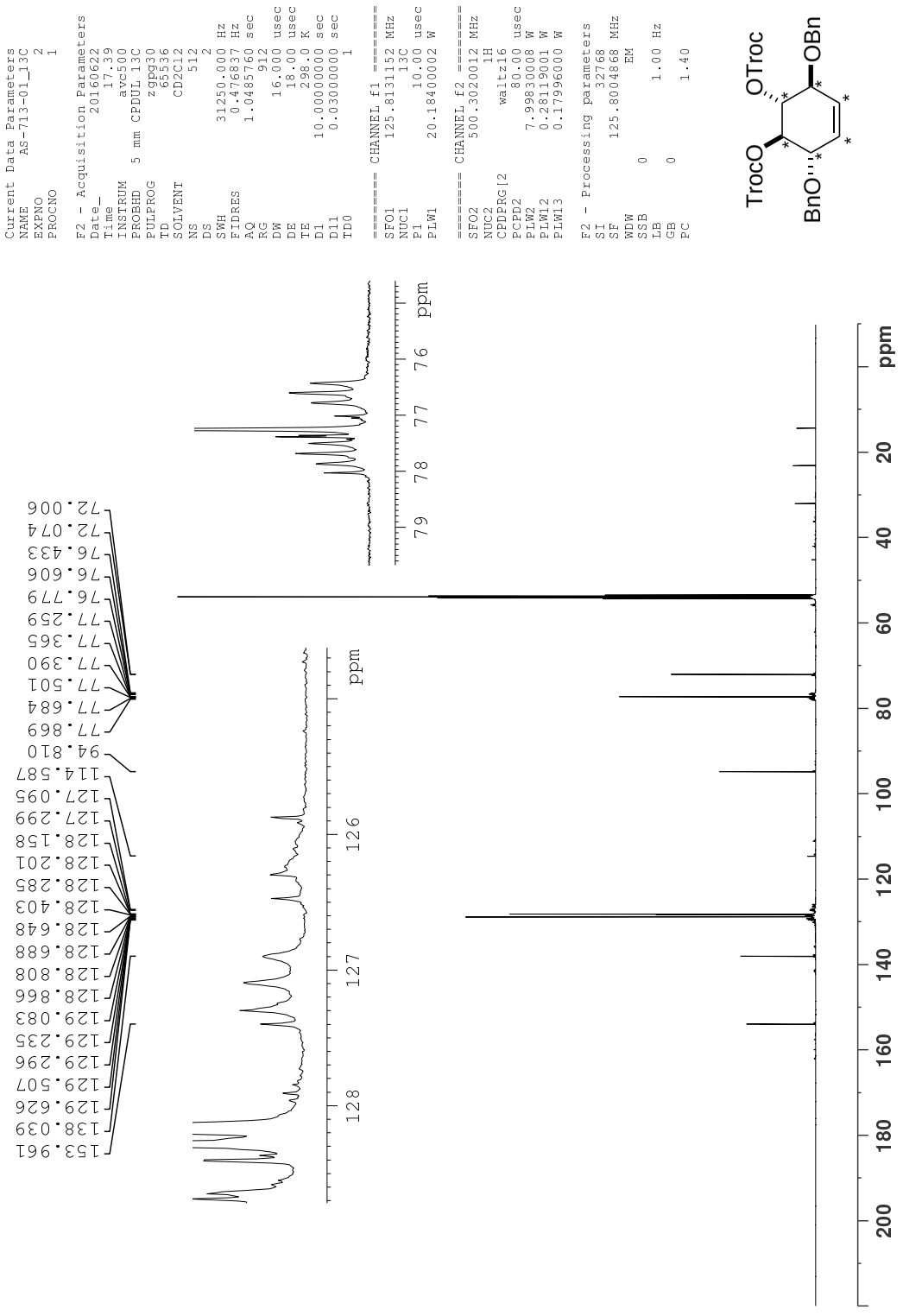
Time	Area	Area %
4.578	441006	0.32
4.928	643063	0.47
7.214	509.04	0.00
9.361	235347	0.17
11.156	132143151	97.04
18.630	2712400	1.99
Total	136175476	100.00



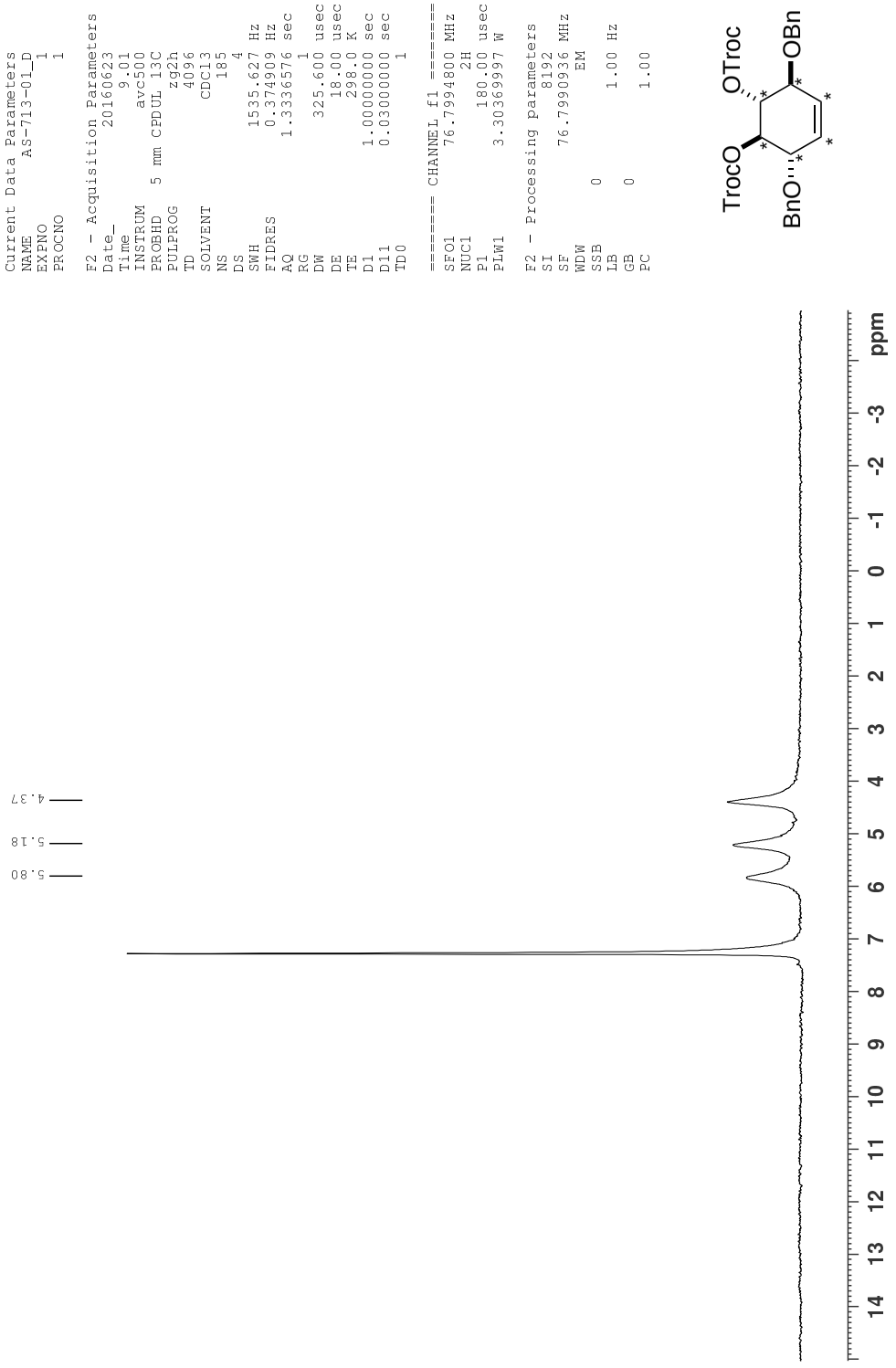
^{1}H NMR of (+)-221


Current Data Parameters
NAME AS-713-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160622
Time_ 16.03
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
TrocO
OTroc
BnO
OBn
4.576
4.600
4.678
4.701
4.751
4.774
4.836
4.860
7.295
7.301
7.309
7.313
7.318
7.341
7.343
7.348
7.354
7.357
7.361
7.365
7.368
7.371
7.374
4.9
4.8
4.7
4.6 ppm
7.35 ppm
1.95
2.00
2.07
2.03
9.69
ppm

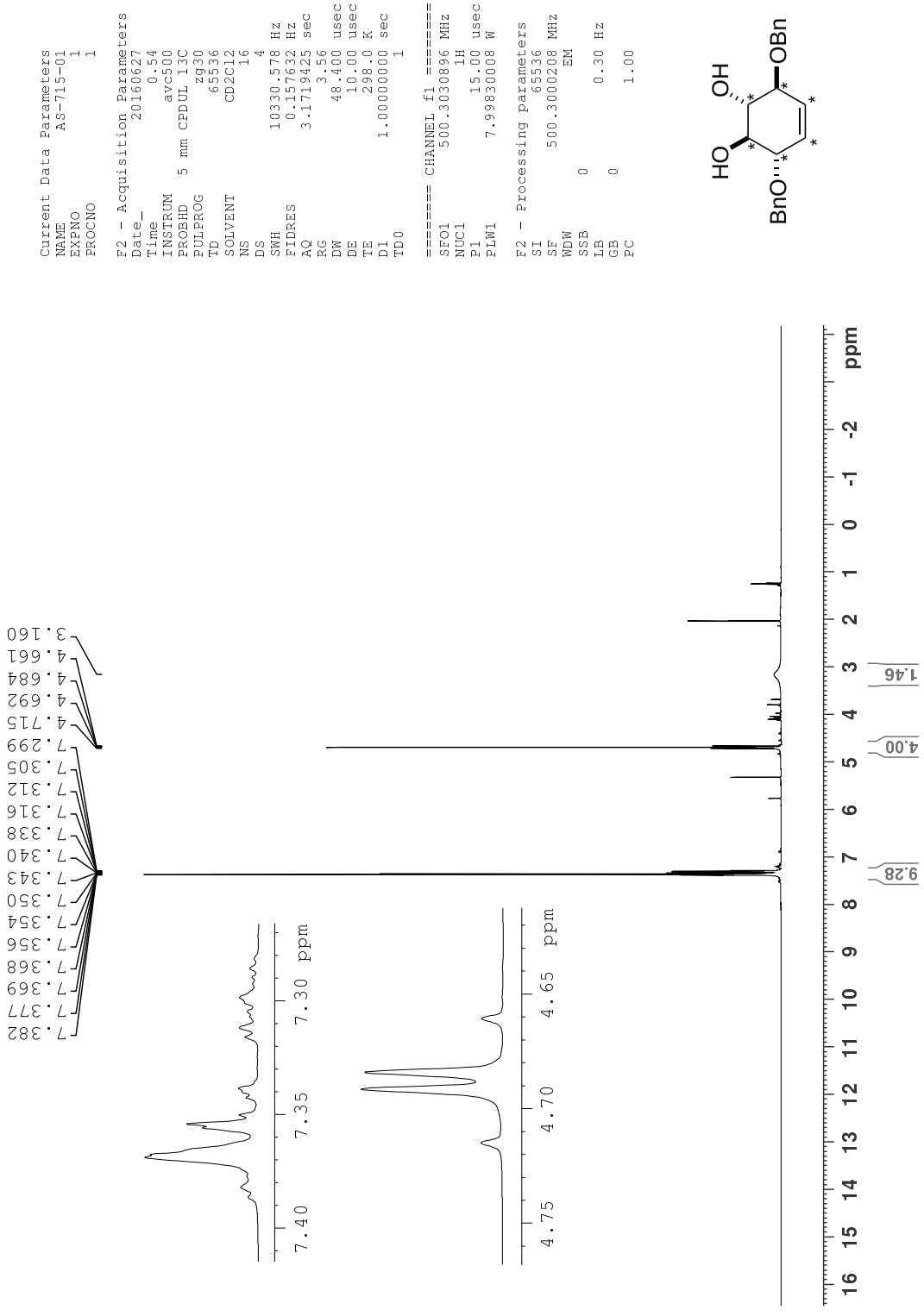
^{13}C NMR of (+)-221



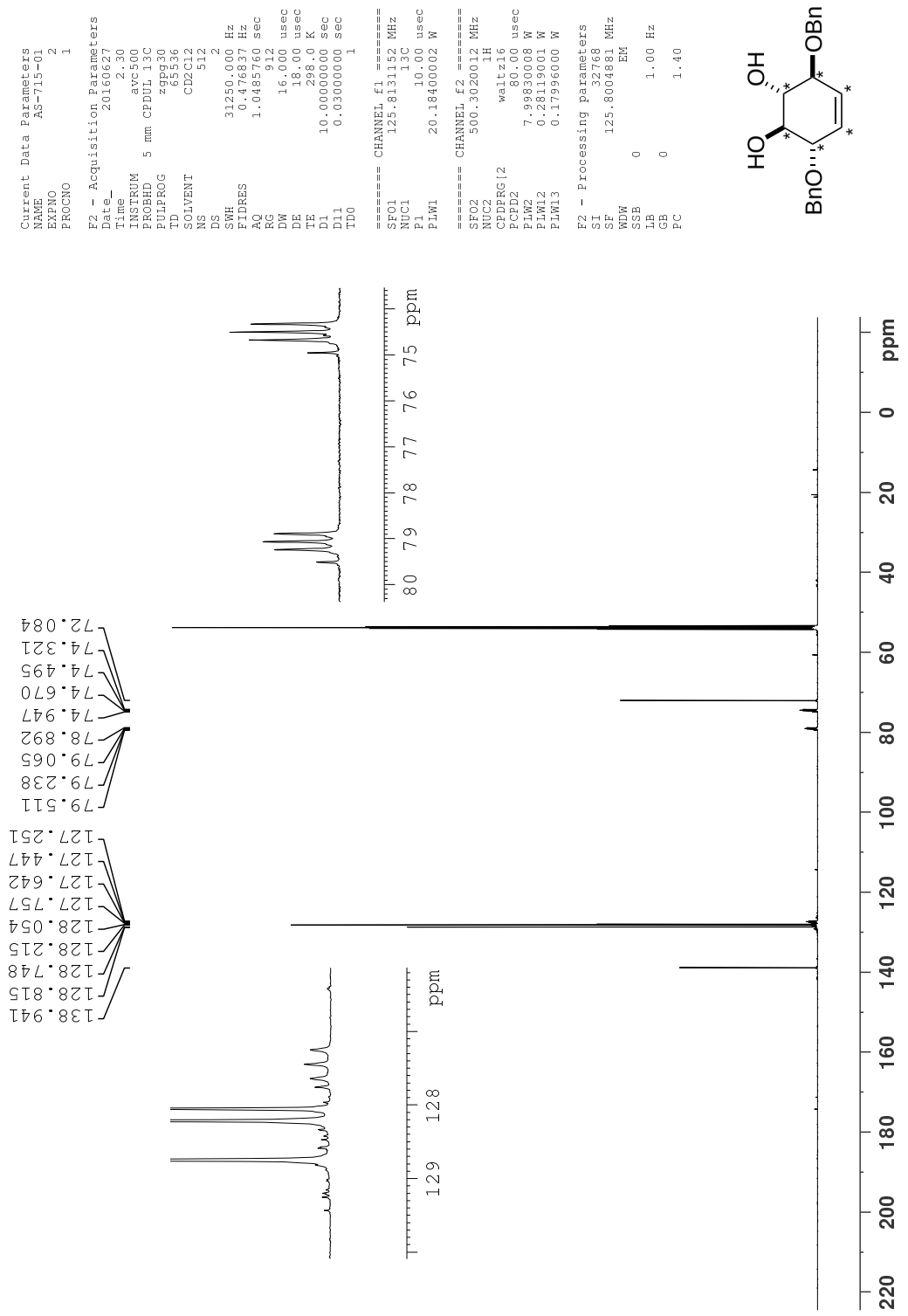
^{2}H NMR of (+)-221


Current Data Parameters
NAME AS-713-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160623
Time 9.01
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 185
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990936 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OTroc
OBn
TrocO
BnO
4.37
5.18
5.80
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3

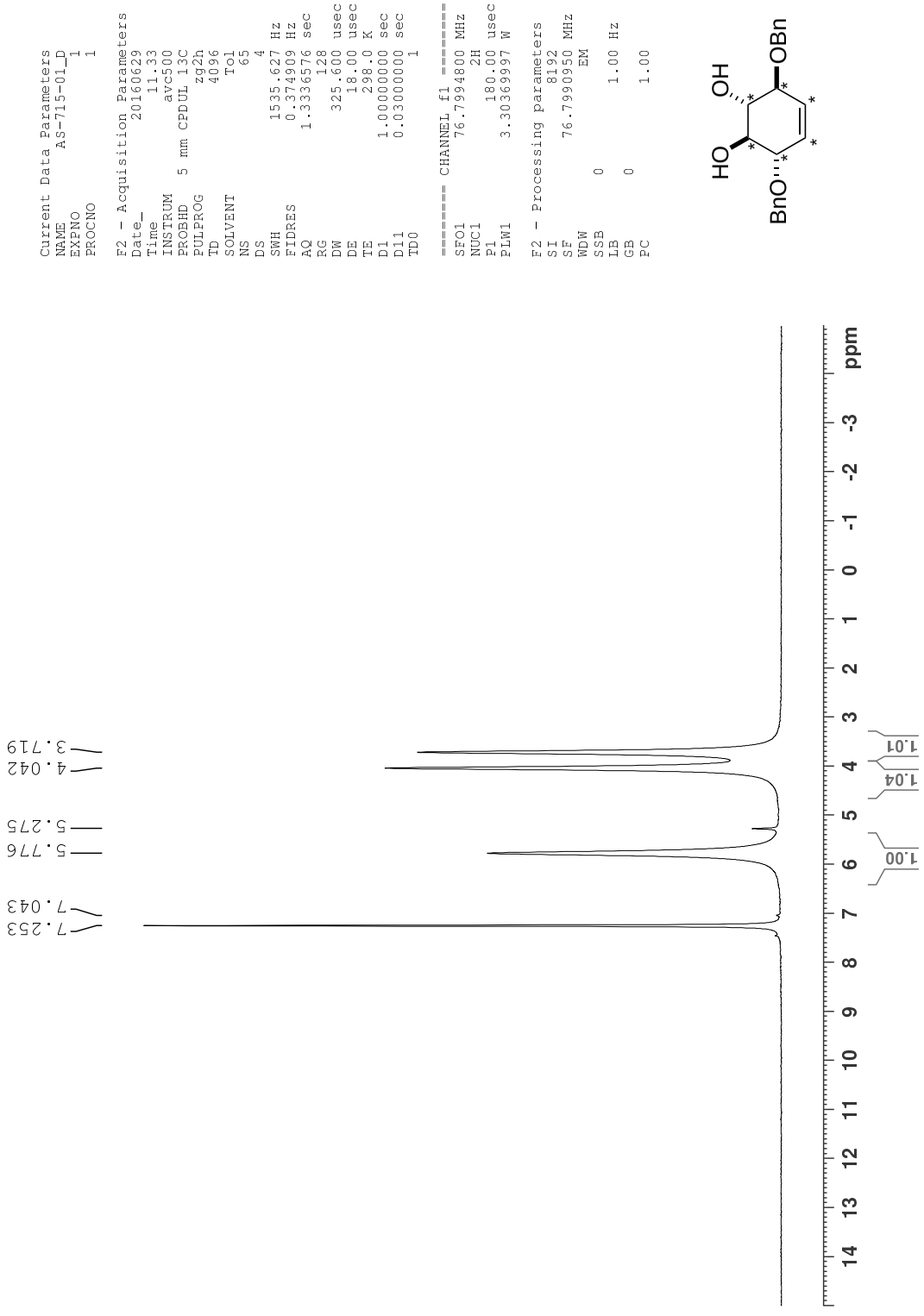
^{1}H NMR of (+)-222


Current Data Parameters
NAME AS-715-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160627
Time 0.54
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000208 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OBn
HO
BnO
7.382
7.377
7.369
7.368
7.356
7.354
7.350
7.343
7.340
7.338
7.316
7.312
7.305
7.299
4.715
4.692
4.684
4.661
3.160
9.28
4.00
1.46
ppm
7.40
7.35
7.30 ppm
4.75
4.70
4.65 ppm

^{13}C NMR of (+)-222



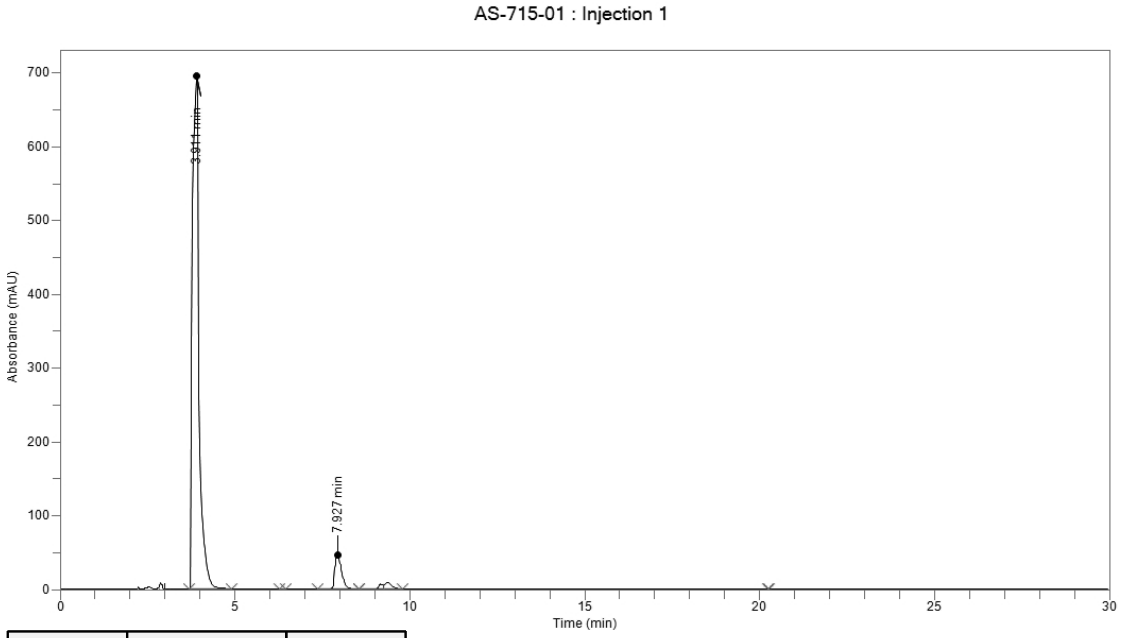
^{2}H NMR of (+)-222


Current Data Parameters
NAME AS-715-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160629
Time 11.33
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 40960
SOLVENT Tol
NS 65
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 128
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990950 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OH
OBn
HO
BnO
7.253
7.043
5.776
5.275
4.042
3.719
1.00
1.04
1.01
ppm

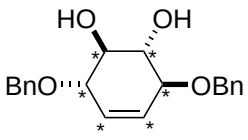
HPLC of (+)-222

AS-715-01

Sample Name	AS-715-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	6/28/2016 7:44 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column

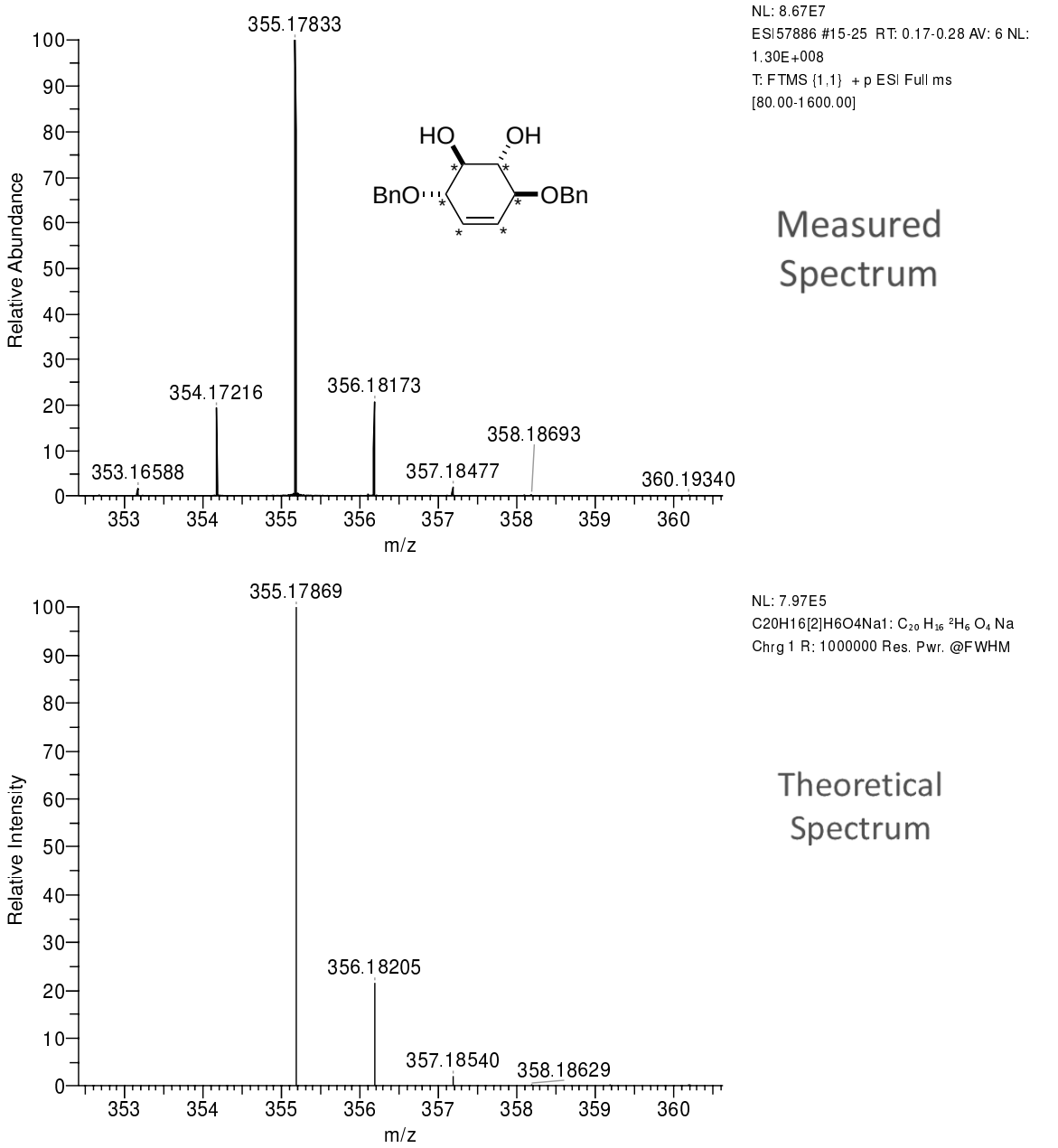


Time	Area	Area %
3.911	9043115	91.81
6.416	822.32	0.01
7.531	6136.9	0.06
7.927	621208	6.31
8.684	4617	0.05
9.162	56119	0.57
9.347	117810	1.20
20.256	239.17	0.00
Total	9850068	100.00



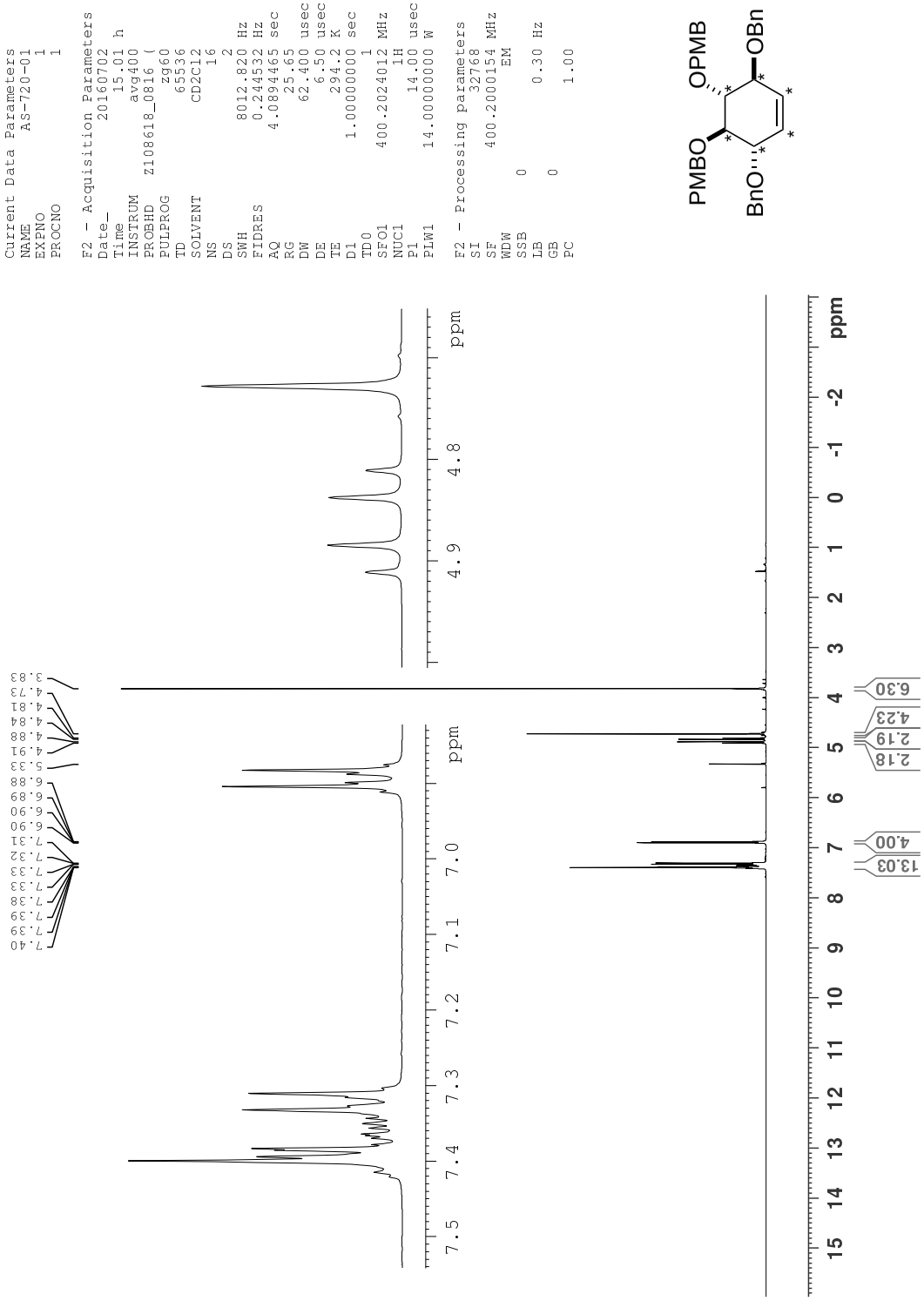
Mass spectrum of (+)-222

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

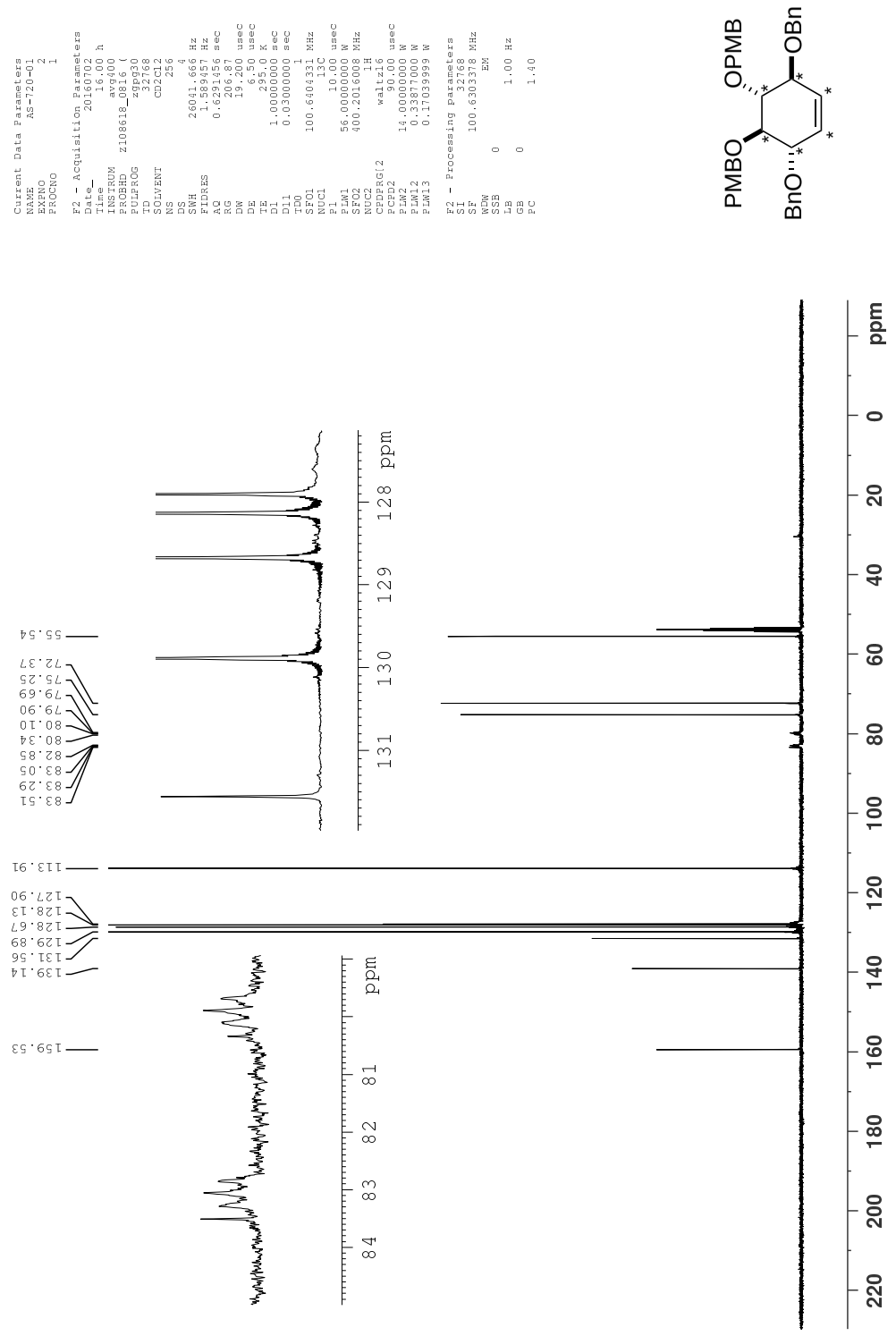


m/z	Formula	RDB	Delta ppm	Theo. Mass
355.17831	$C_{20}H_{16}{}^{2}H_{6}O_{4}{}^{23}Na$	9.5	-1.06	355.17869

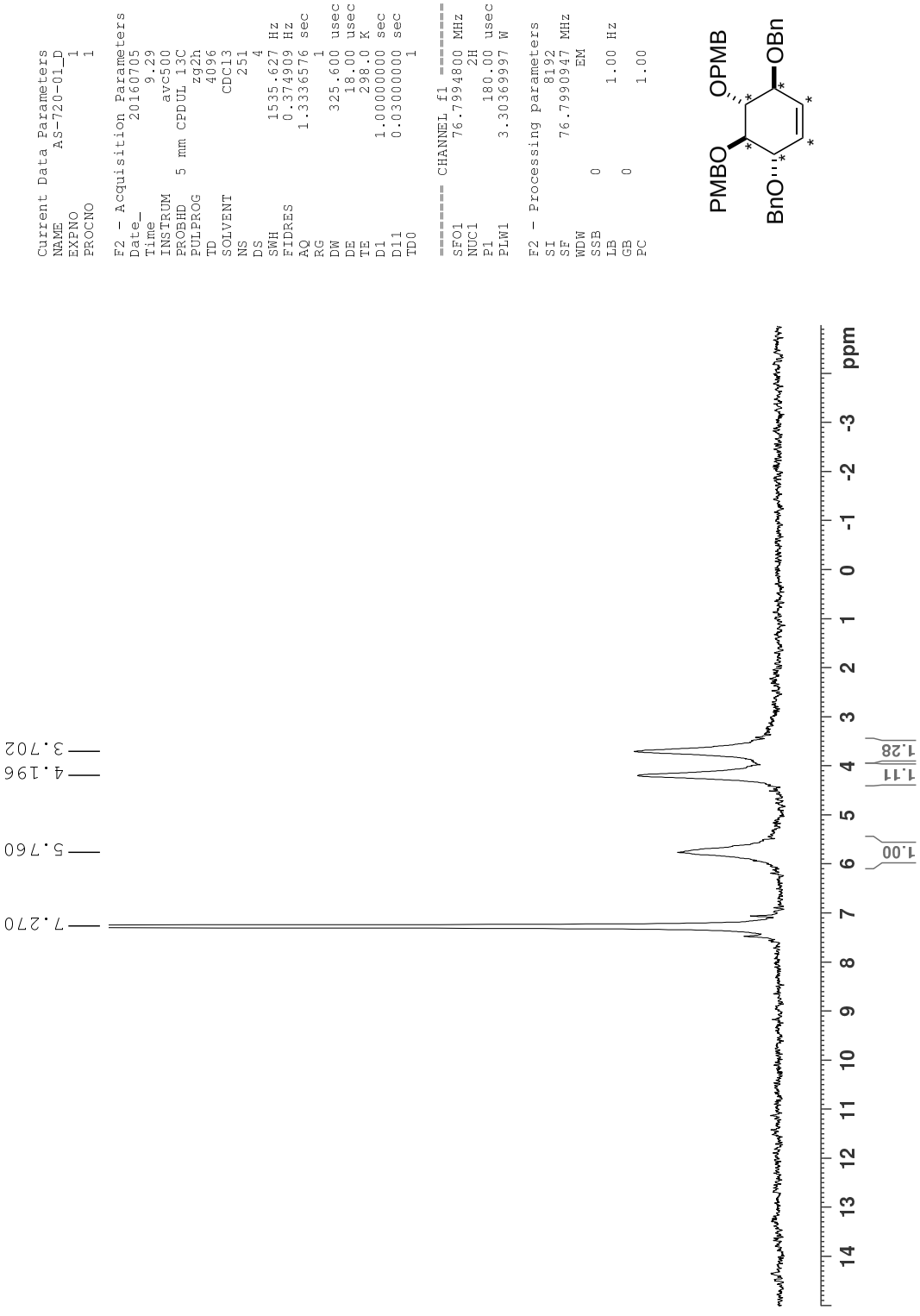
^{1}H NMR of (+)-223


Current Data Parameters
NAME AS-720-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160702
Time 15.01 h
INSTRUM avg400
PROBHD Z108618_0816 (
PULPROG zg60
TD 65536
SOLVENT CD2C12
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 25.65
DW 62.400 usec
DE 6.50 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
SFO1 400.2024012 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.00000000 W
F2 - Processing parameters
SI 32768
SF 400.2000154 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OPMB
OBn
PMBO
BnO
7.40
7.39
7.39
7.38
7.33
7.33
7.32
7.31
6.90
6.90
6.89
6.88
5.33
4.91
4.88
4.84
4.81
4.73
3.83
6.30
4.23
2.19
2.18
13.03
4.00
ppm

^{13}C NMR of (+)-223



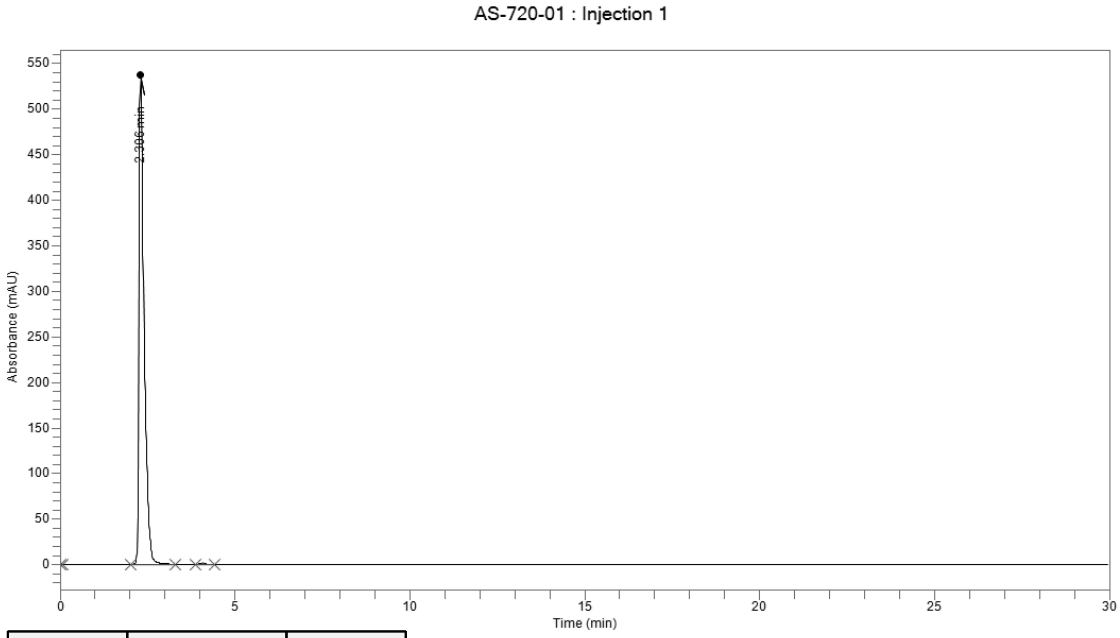
^{2}H NMR of (+)-223


Current Data Parameters
NAME AS-720-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160705
Time 9.29
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 251
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990947 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OPMB
OBn
PMBO
BnO
7.270
5.760
4.196
3.702
1.00
1.11
1.28
ppm

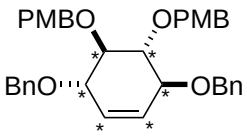
HPLC of (+)-223

AS-720-01

Sample Name	AS-720-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	7/16/2016 3:41 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column

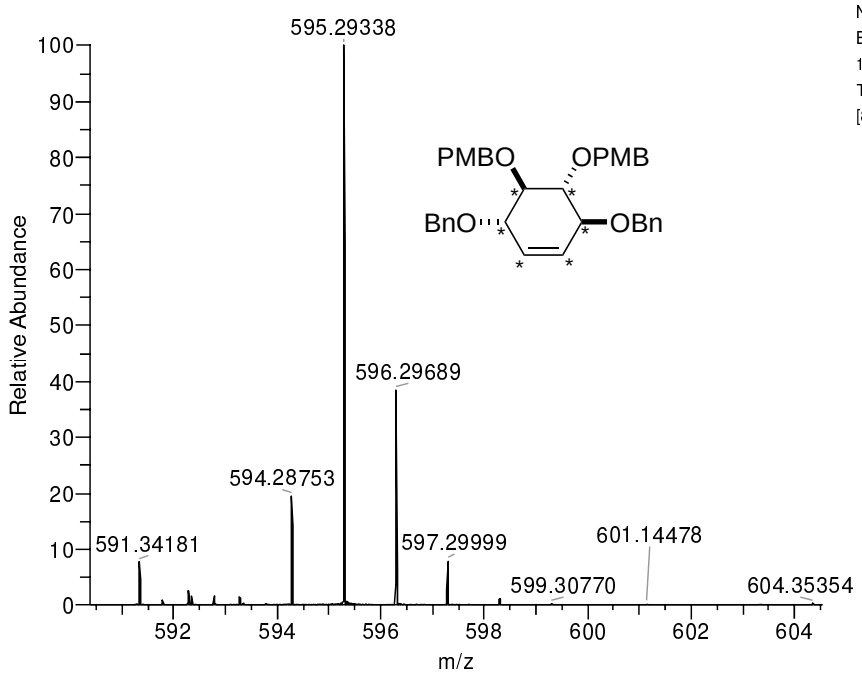


Time	Area	Area %
0.017	63.482	0.00
2.306	5705097	99.60
4.083	22682	0.40
Total	5727842.458	100.00



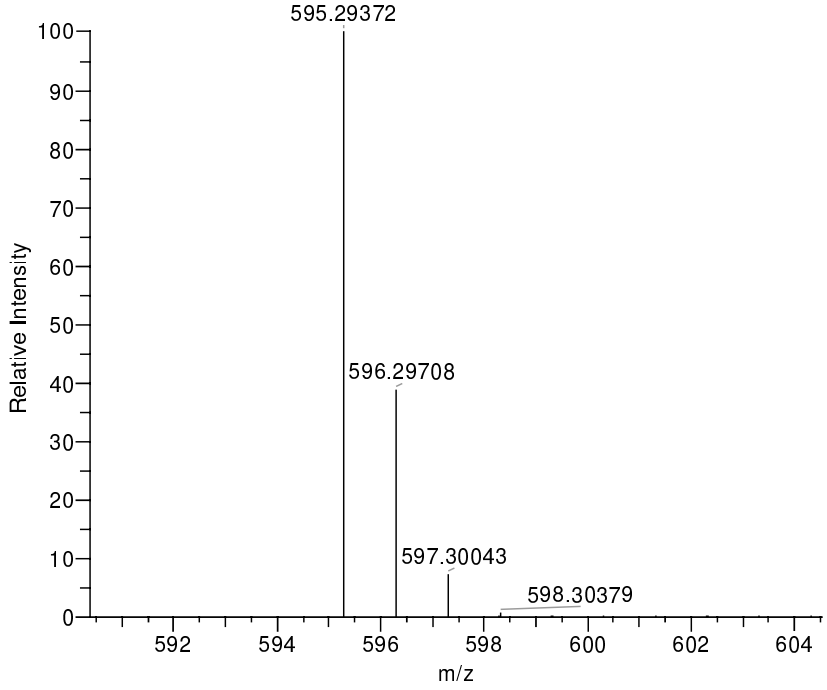
Mass spectrum of (+)-223

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



NL: 1.77E7
ESI57974 #11-26 RT: 0.12-0.29 AV: 8 NL: 1.77E+007
T: FTMS {1,1} + p ESI Full lock ms [80.00-1600.00]

Measured Spectrum

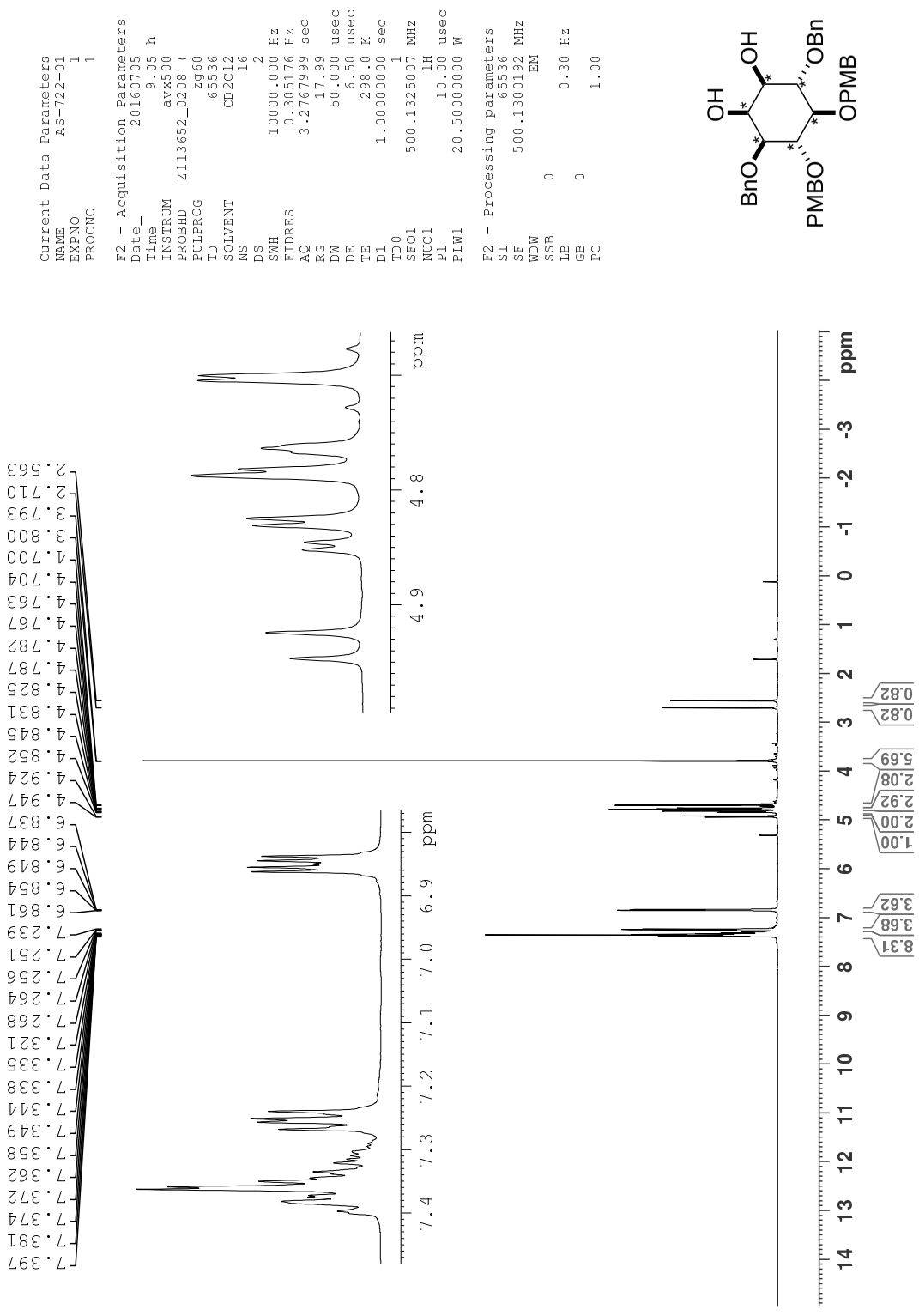


NL: 6.67E5
C36H32[2]H6O6Na1: $C_{36}H_{32}{}^{2}H_{6}O_{6}Na$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

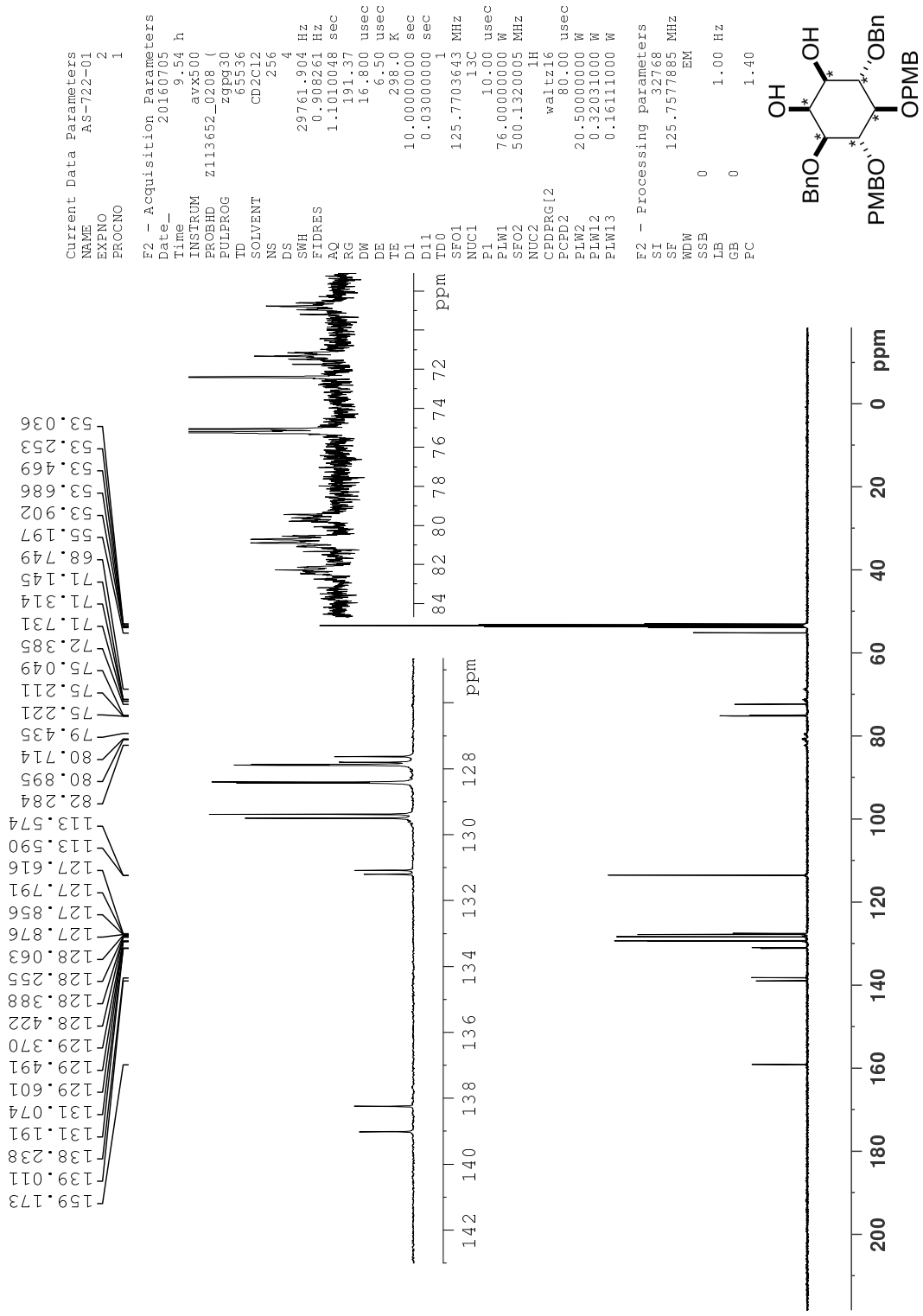
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
595.29340	$C_{36}H_{32}{}^{2}H_{6}O_{6}{}^{23}Na$	17.5	-0.55	595.29372

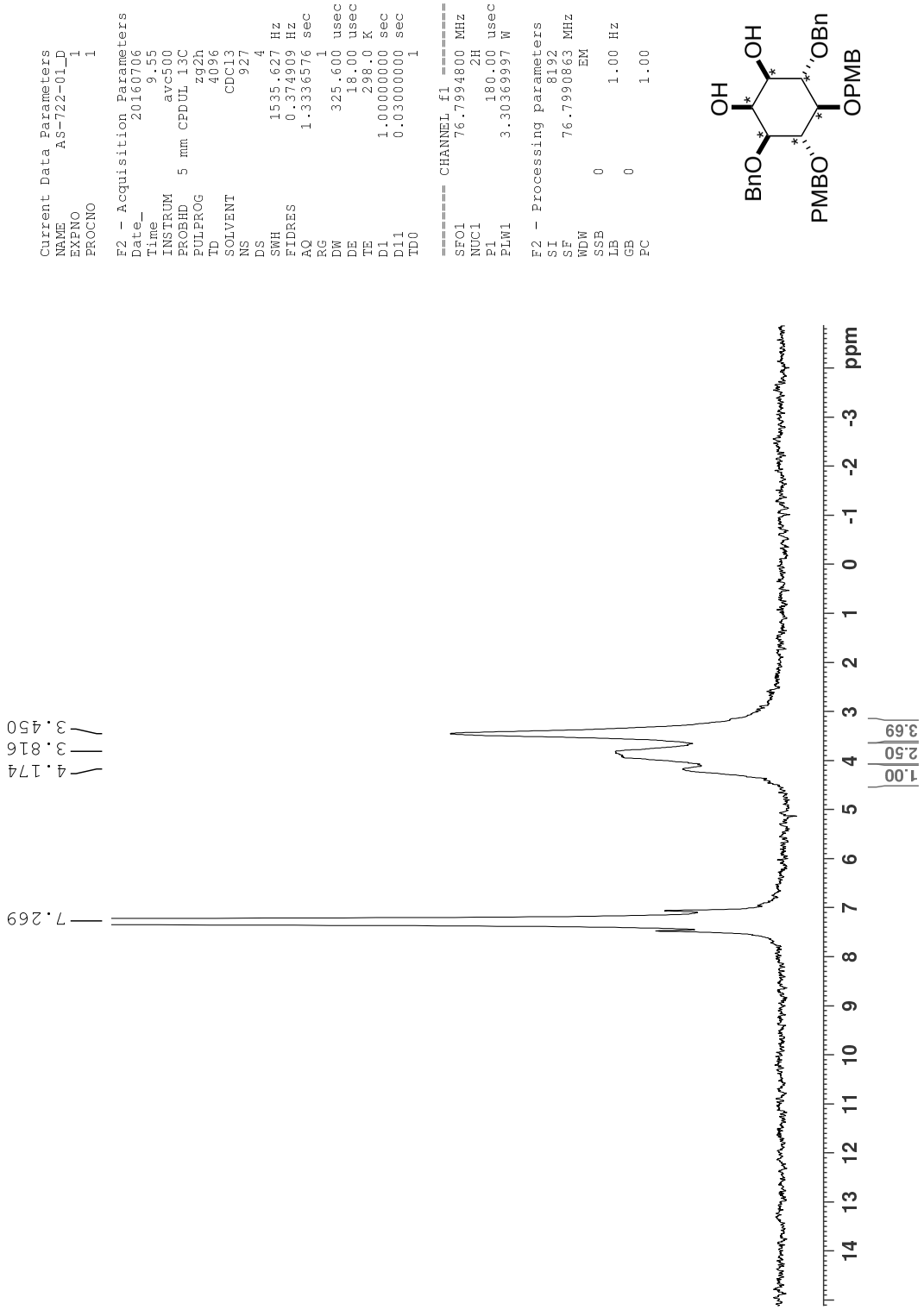
^{1}H NMR of (–)-224


Current Data Parameters
NAME AS-722-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160705
Time 9.05 h
INSTRUM avx500
PROBHD z113652_0208 (
PULPROG zg60
TD 65536
SOLVENT CD2C12
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 17.99
DW 50.000 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
PL1 20.50000000 W
F2 - Processing parameters
SI 65536
SF 500.1300192 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
OH
BnO
PMBO
OBn
OPMB
ppm
0.82
5.69
2.08
2.92
2.00
1.00
3.62
3.68
8.31

^{13}C NMR of (–)-224



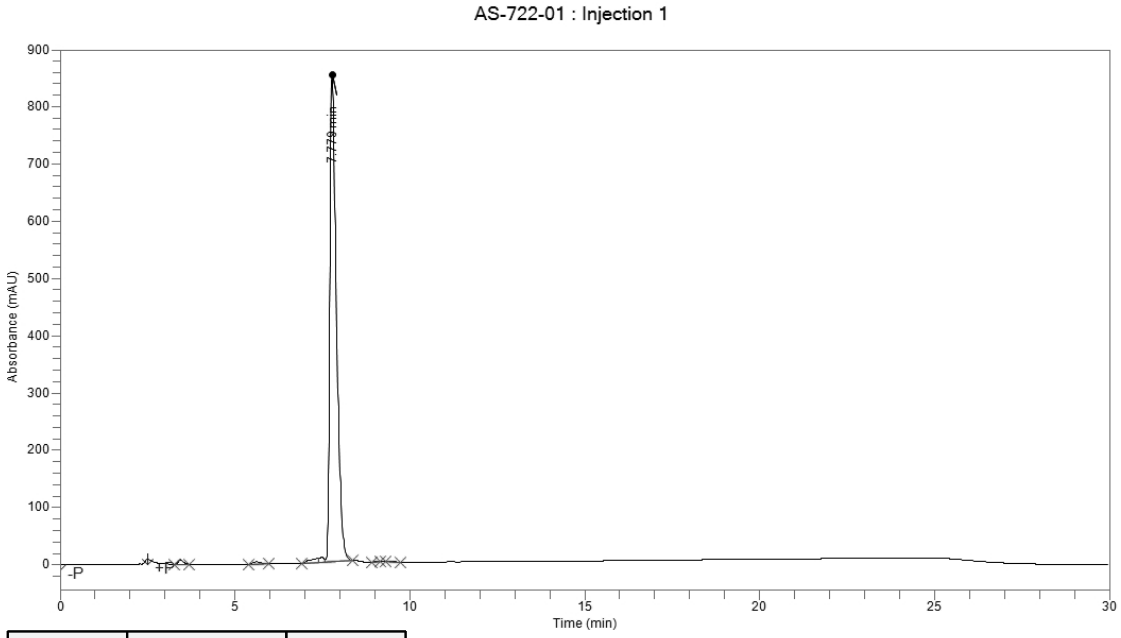
^{2}H NMR of (–)-224


Current Data Parameters
NAME AS-722-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160706
Time 9.55
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 927
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990863 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OH
OH
BnO
PMBO
OBn
OPMB
7.269
4.174
3.816
3.450
1.00
2.50
3.69
ppm

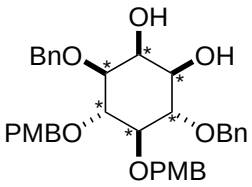
HPLC of (–)-224

AS-722-01

Sample Name	AS-722-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 220nm 2-10	Acquisition Date/Time	7/12/2016 3:33 pm
Batch Group/Name	Alex/Normal Phase Purity 220nm 2-10	Batch Description	Normal Phase silica column

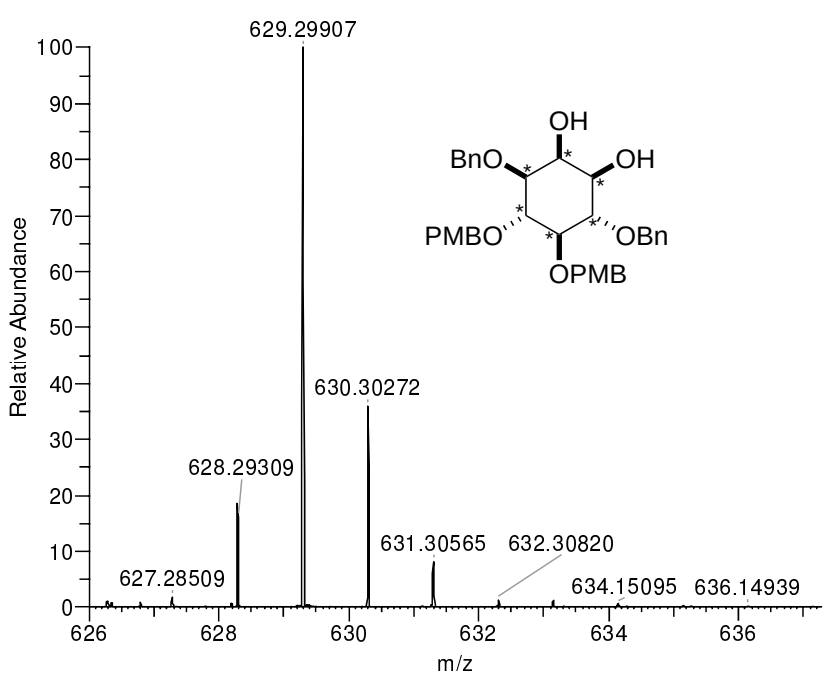


Time	Area	Area %
3.447	72579	0.63
5.629	63871	0.55
7.353	119775	1.03
7.485	87348	0.75
7.779	11230873	96.84
9.109	3947	0.03
9.436	19074	0.16
Total	11597467	100.00



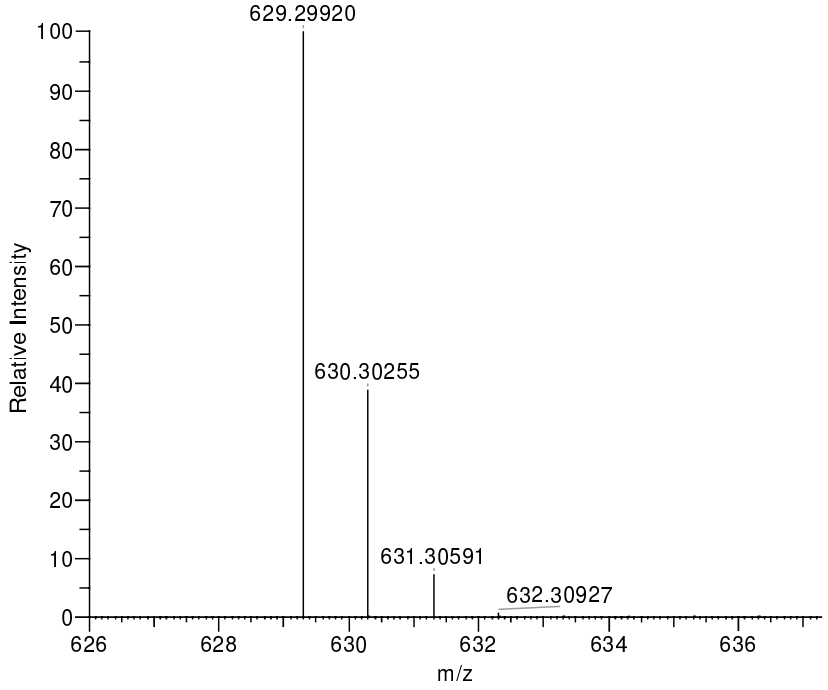
Mass spectrum of (–)-224

W:\data\July 16\ESI58002.raw 05/07/2016 8:05 am



NL: 1.03E7
ESI58002 #12-27 RT: 0.14-0.3 AV: 8 NL: 8.05E+007
T: FTMS {1,1} + p ESI Full ms [80.00-1600.00]

Measured Spectrum

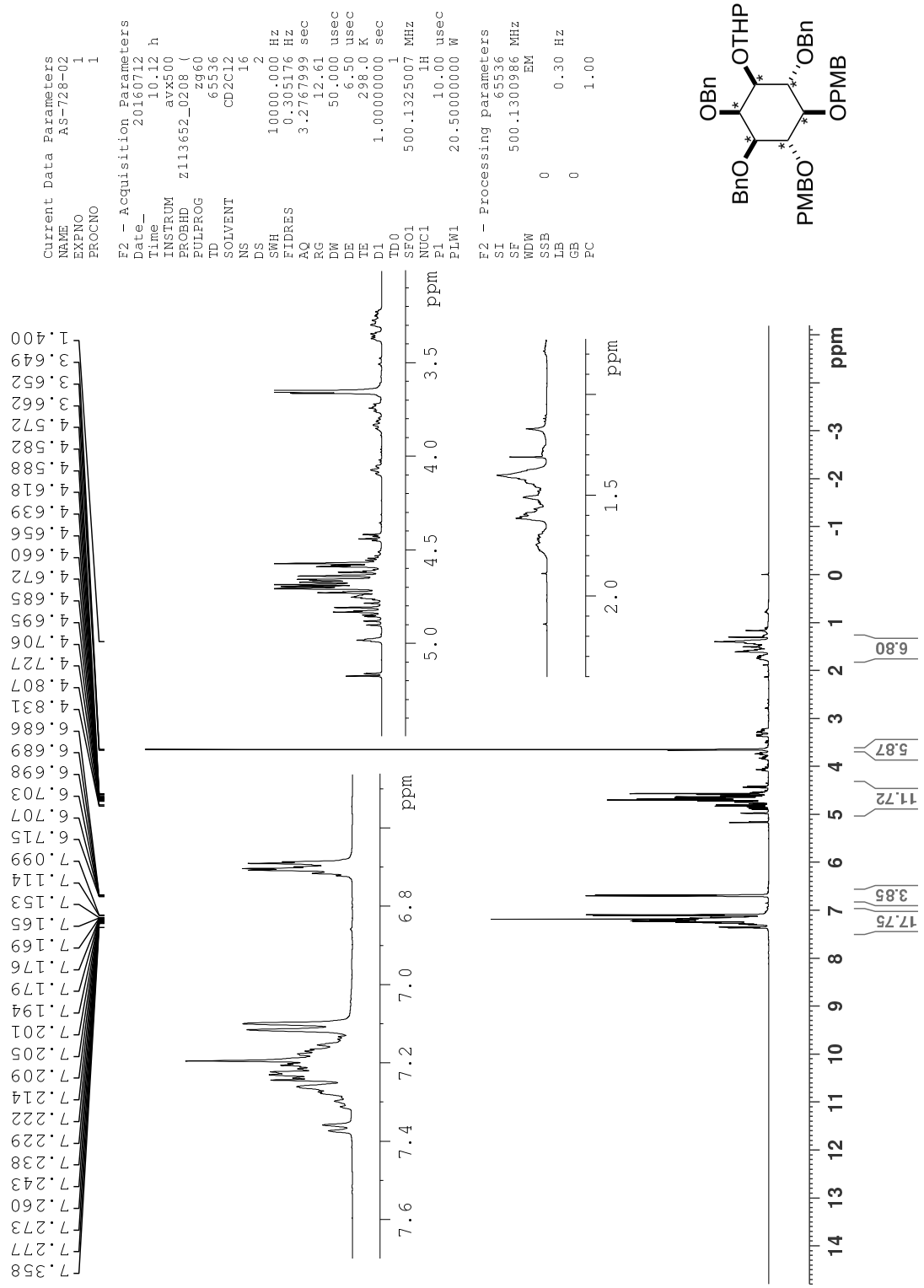


NL: 6.63E5
C36H34[2]H6O8Na1: $C_{36}H_{34}{}^{2}H_{6}O_{8}Na$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

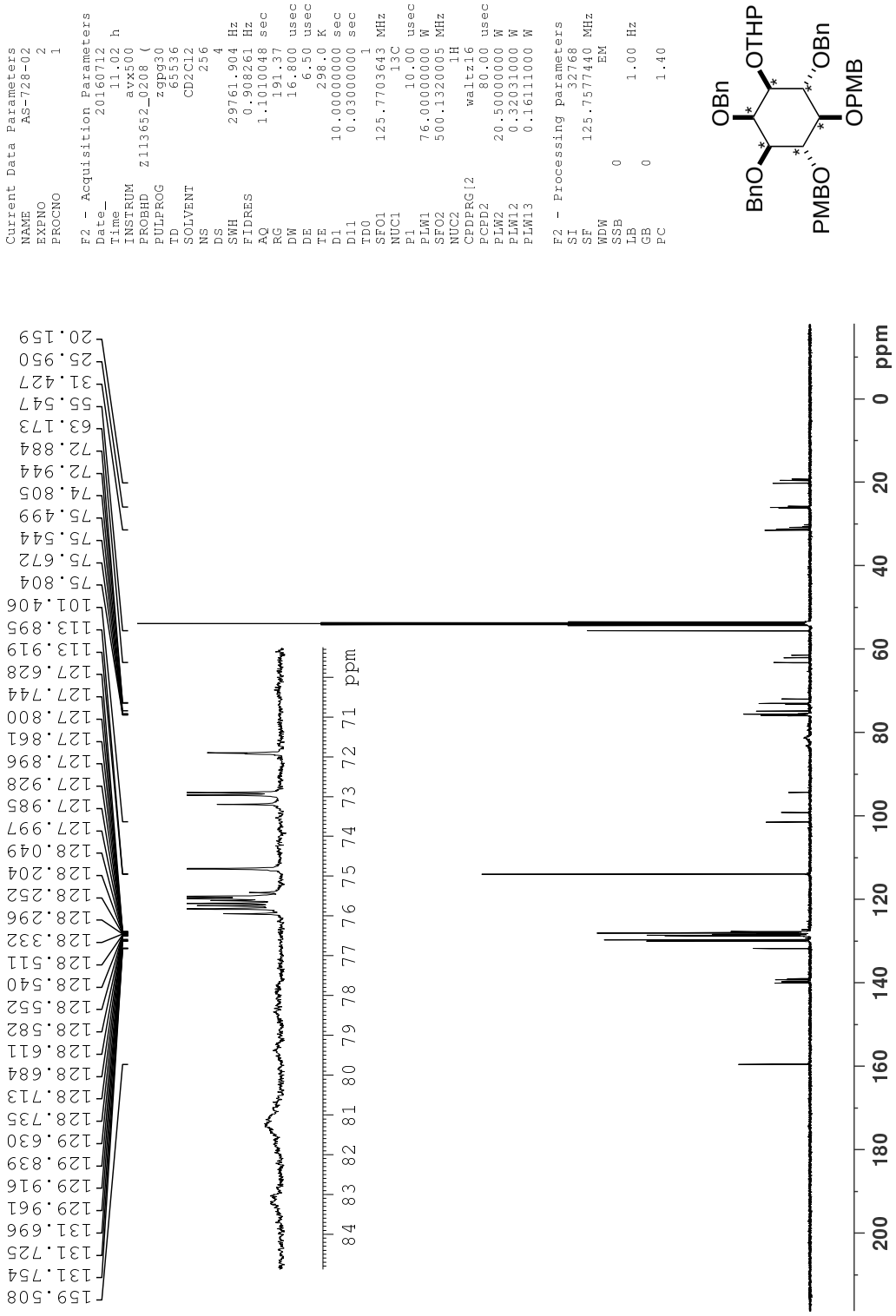
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
629.29907	$C_{36}H_{34}{}^{2}H_{6}O_{8}{}^{23}Na$	16.5	-0.2	629.29920

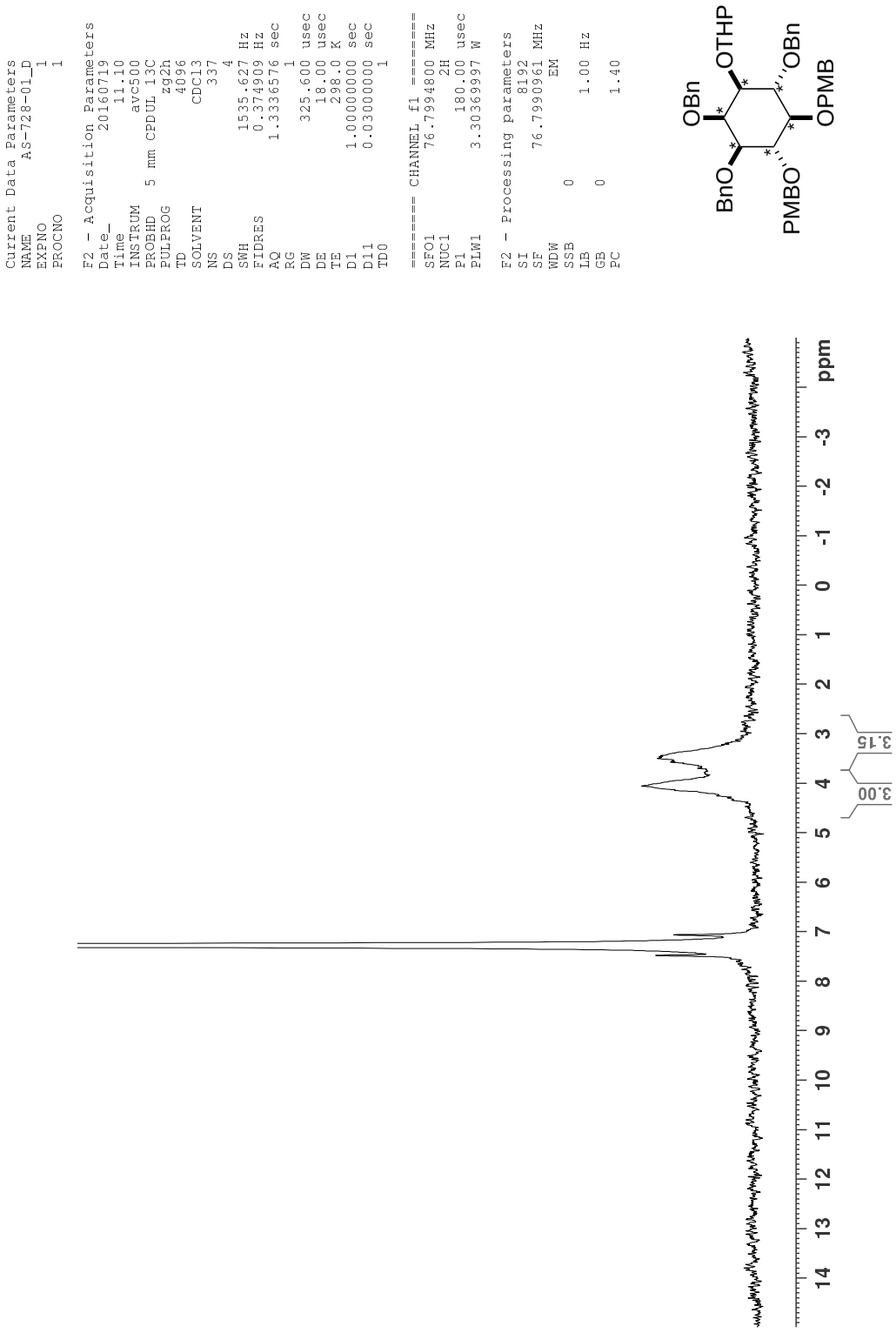
^{1}H NMR of (–)-226



^{13}C NMR of (–)-226



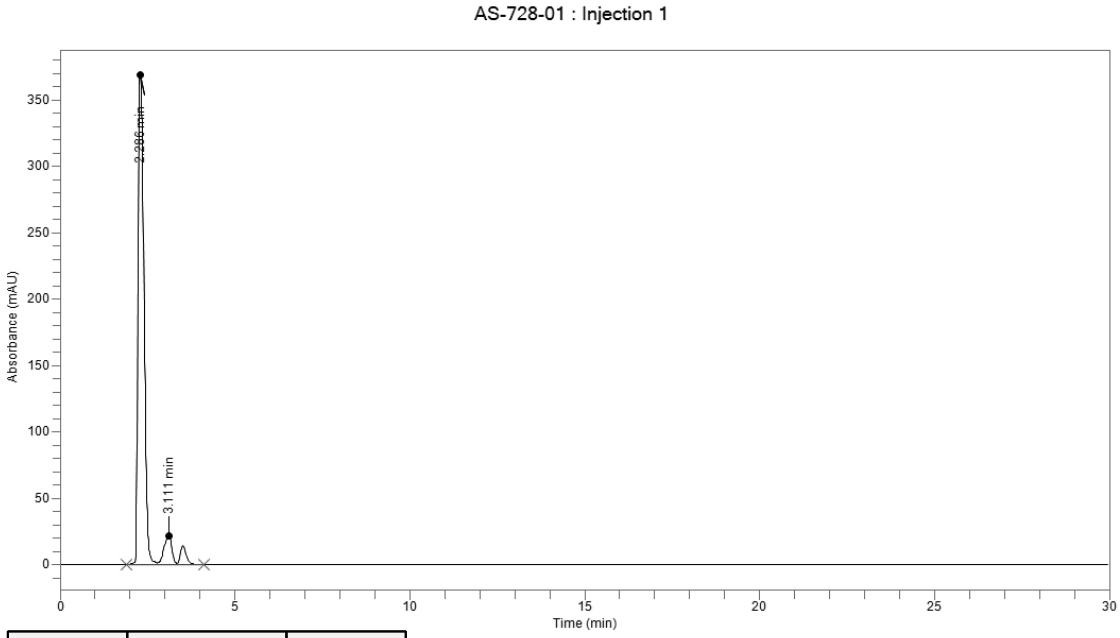
^{2}H NMR of (–)-226


Current Data Parameters
NAME AS-728-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160719
Time 11.10
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 337
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990961 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OBn
OTHP
BnO
PMBO
OBn
OPMB
3.15
3.00
ppm

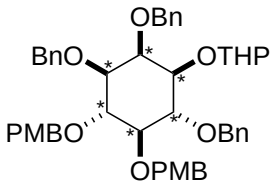
HPLC of (–)-226

AS-728-01

Sample Name	AS-728-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	7/16/2016 4:22 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column

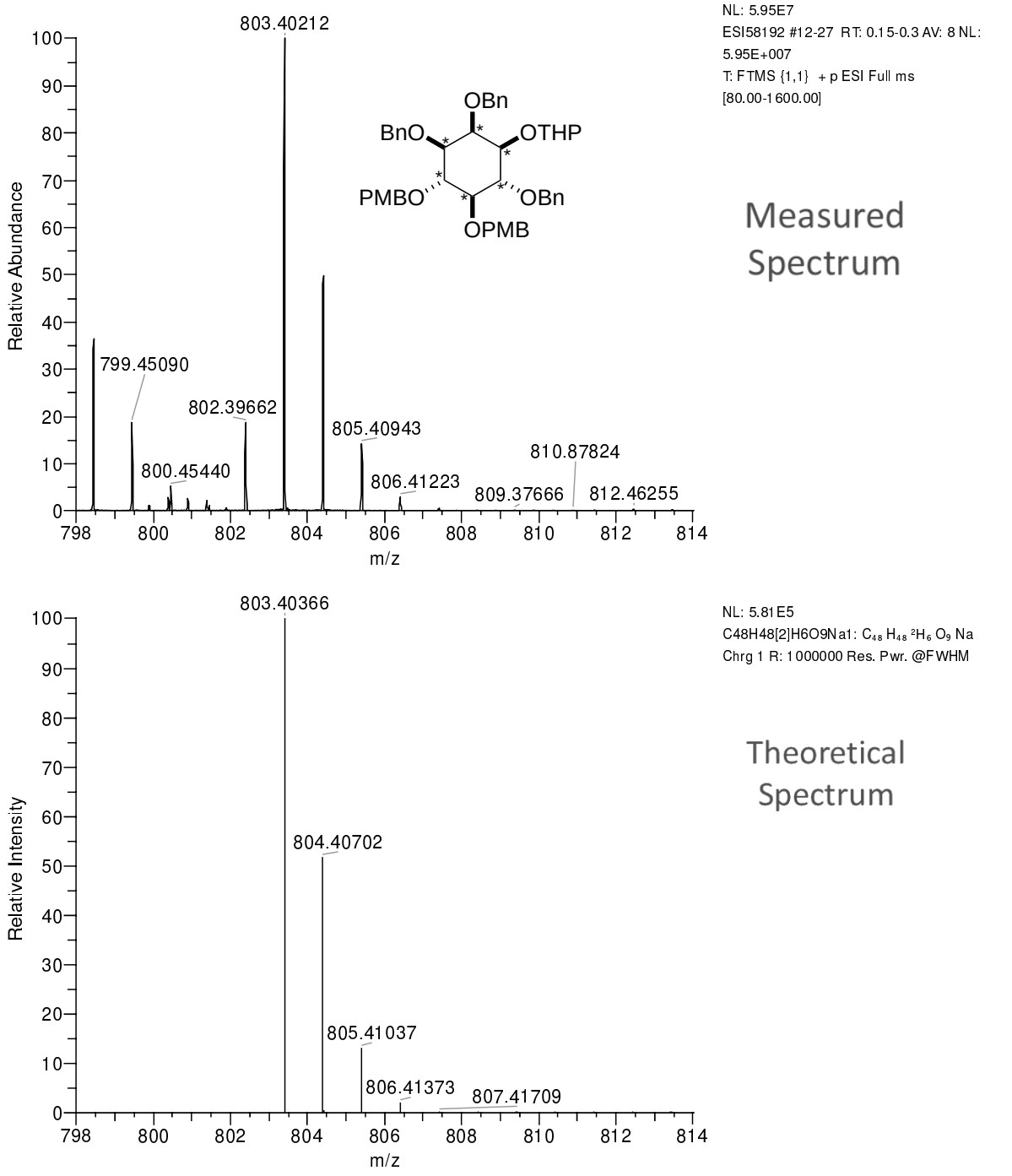


Time	Area	Area %
2.286	4505760	89.76
3.111	343076	6.83
3.513	171065	3.41
Total	5019901	100.00



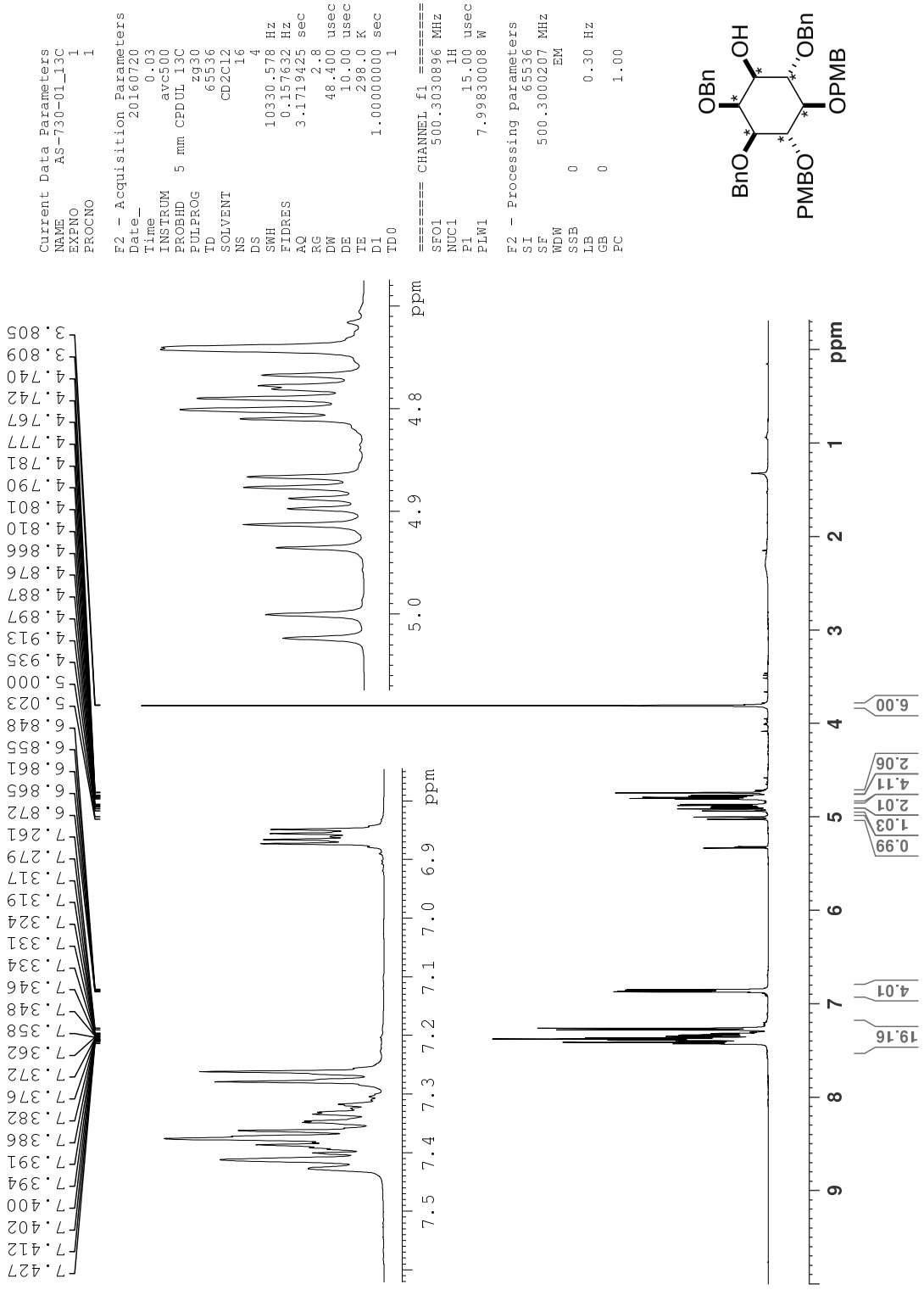
Mass spectrum of (–)-226

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

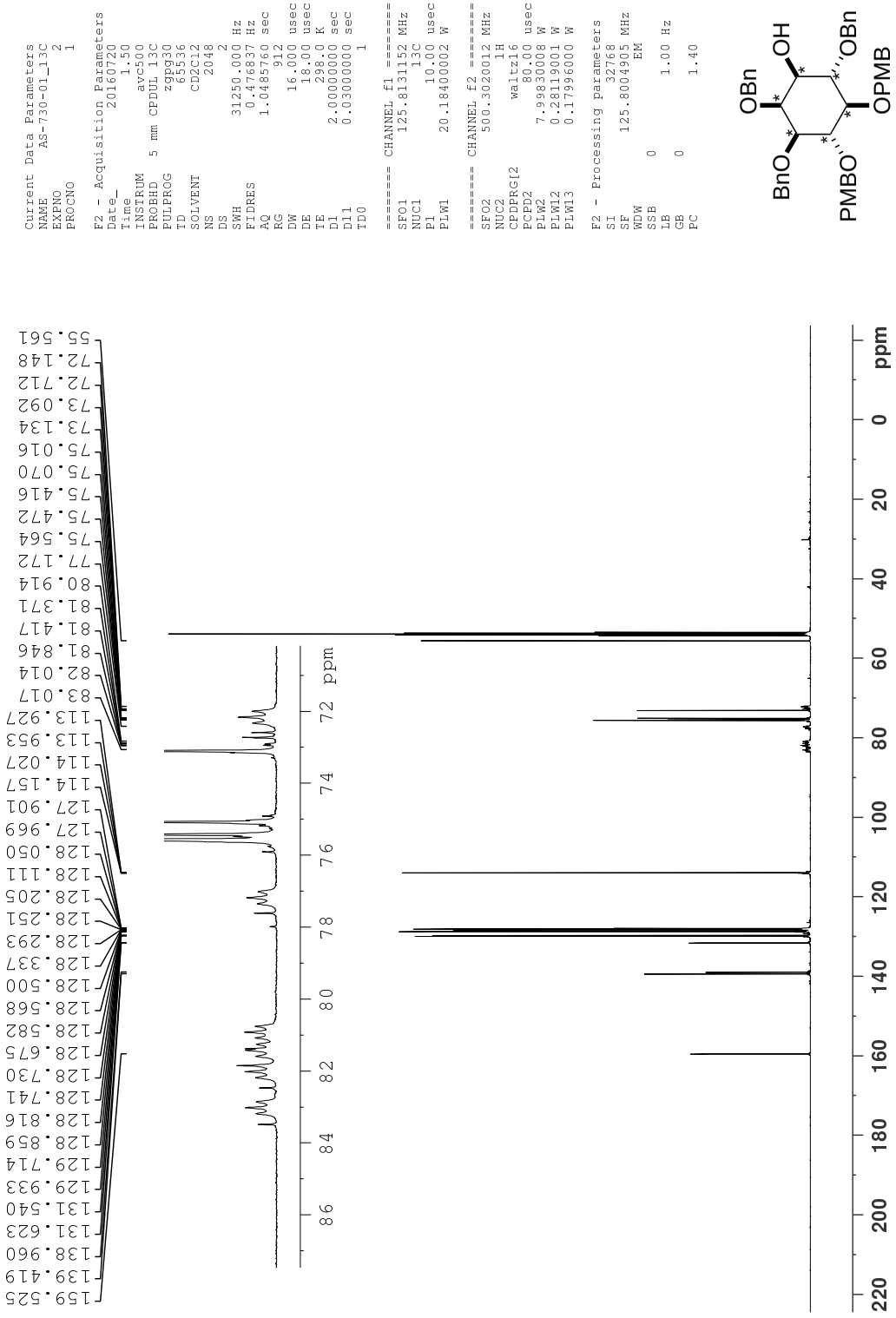


m/z	Formula	RDB	Delta ppm	Theo. Mass
803.40210	$C_{48}H_{48}{}^{2}H_{6}O_{9}{}^{23}Na$	21.5	-1.95	803.40366

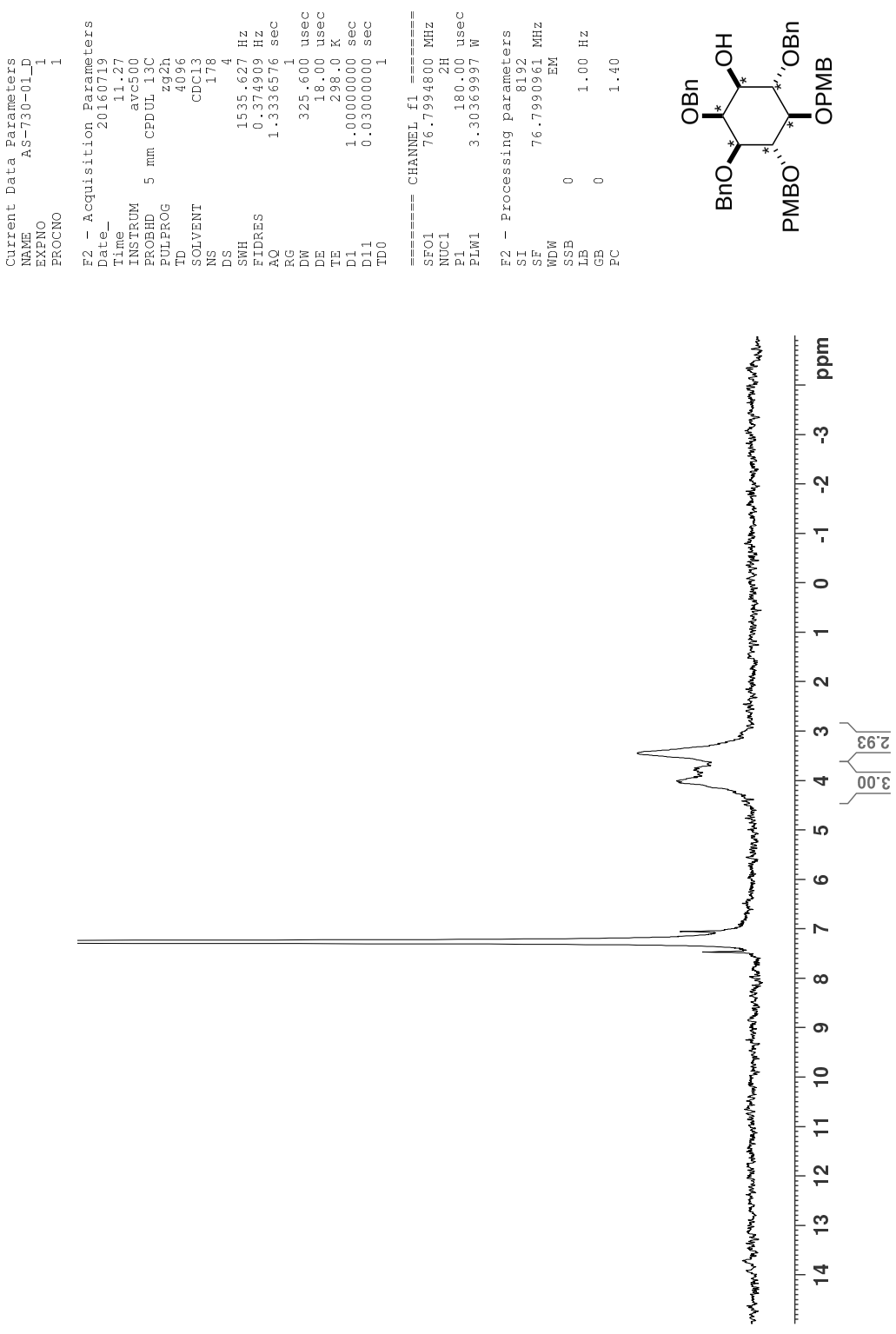
^{1}H NMR of (–)-227


Current Data Parameters
NAME AS-730-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160720
Time_ 0.03
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 2.8
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000207 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OH
OBn
BnO
PMBO
OPMB
ppm
6.00
0.99
1.03
2.01
4.11
2.06
4.01
19.16

^{13}C NMR of (–)-227



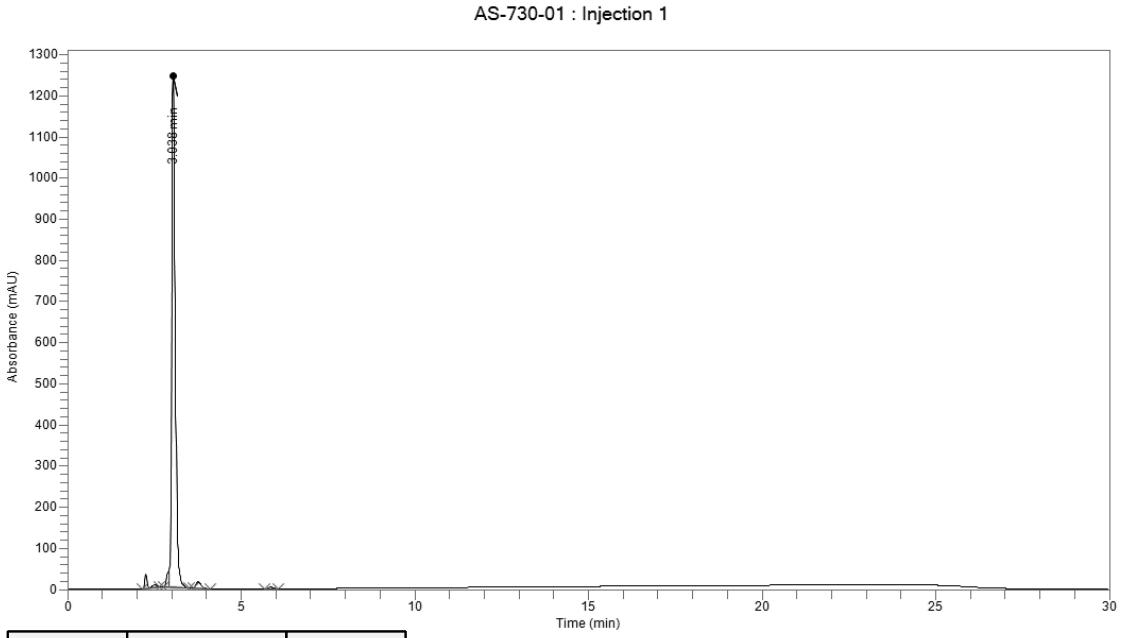
^{2}H NMR of (–)-227


Current Data Parameters
NAME AS-730-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160719
Time 11.27
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 178
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.3336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990961 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
OBn
OH
BnO
PMBO
OBn
OPMB
3.00
2.93
ppm

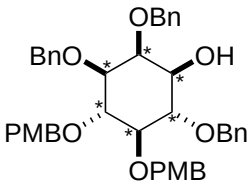
HPLC of (–)-227

AS-730-01

Sample Name	AS-730-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 220nm 2-10	Acquisition Date/Time	7/29/2016 1:22 pm
Batch Group/Name	Alex/Normal Phase Purity 220nm 2-10	Batch Description	Normal Phase silica column

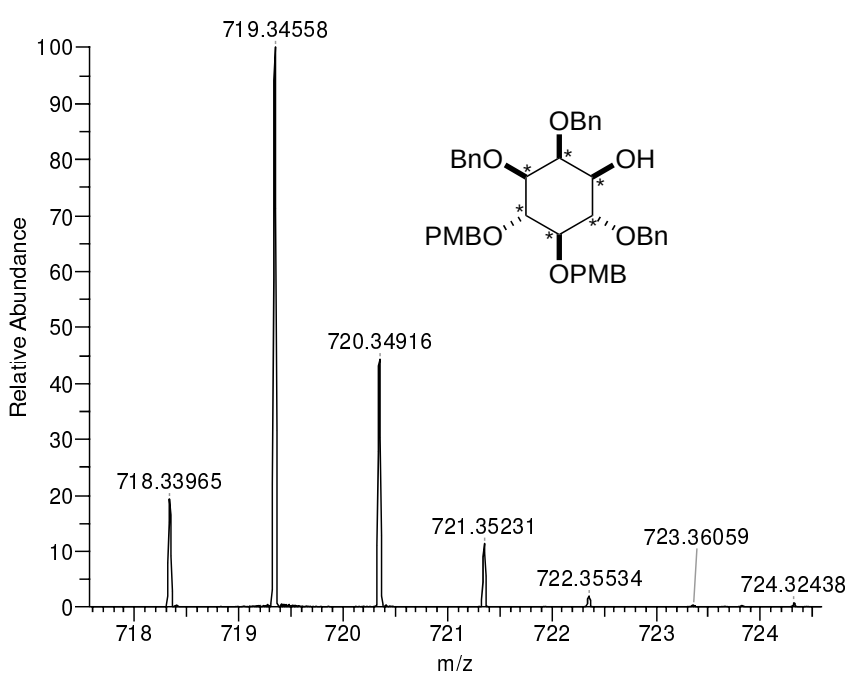


Time	Area	Area %
2.255	159843	1.70
2.511	58821	0.62
2.897	161445	1.71
3.038	8835537	93.83
3.769	159026	1.69
5.844	41951	0.45
Total	9416623	100.00



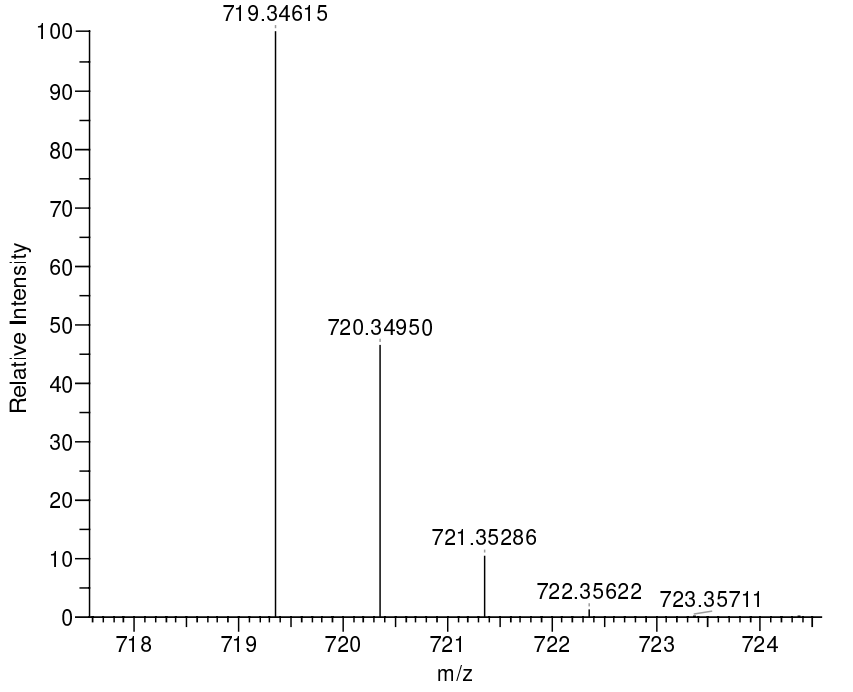
Mass spectrum of (–)-227

W:\data\July 16\ESI58204.raw 20/07/2016 8:26 am



NL: 7.37E6
ESI58204 #12-27 RT: 0.14-0.3 AV: 8 NL: 1.06E+007
T: FTMS {1,1} + p ESI Full lock ms [80.00-1600.00]

Measured Spectrum

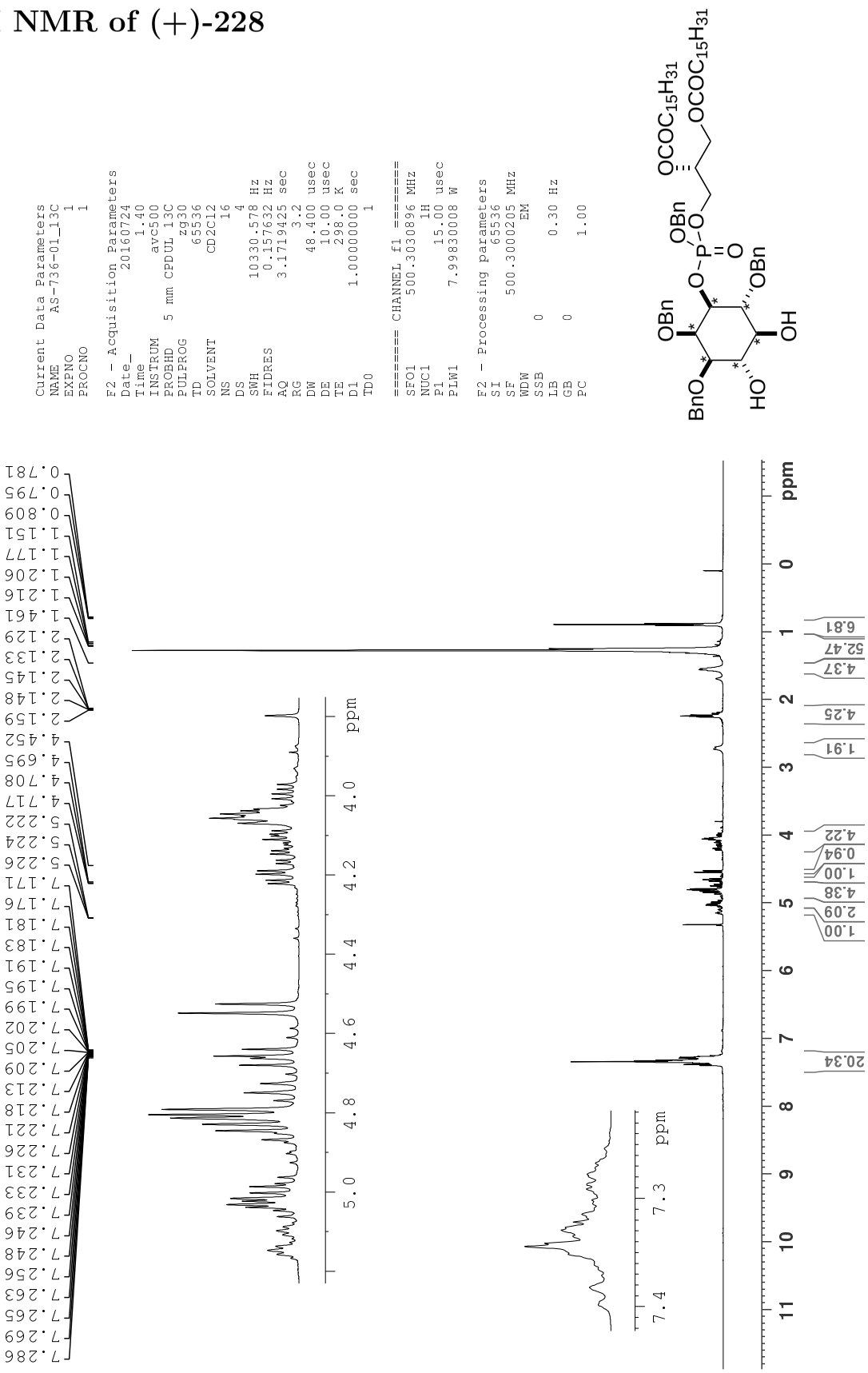


NL: 6.15E5
C43H40[2]H6O8Na1: $C_{43}H_{40}{}^{2}H_{6}O_{8}Na$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

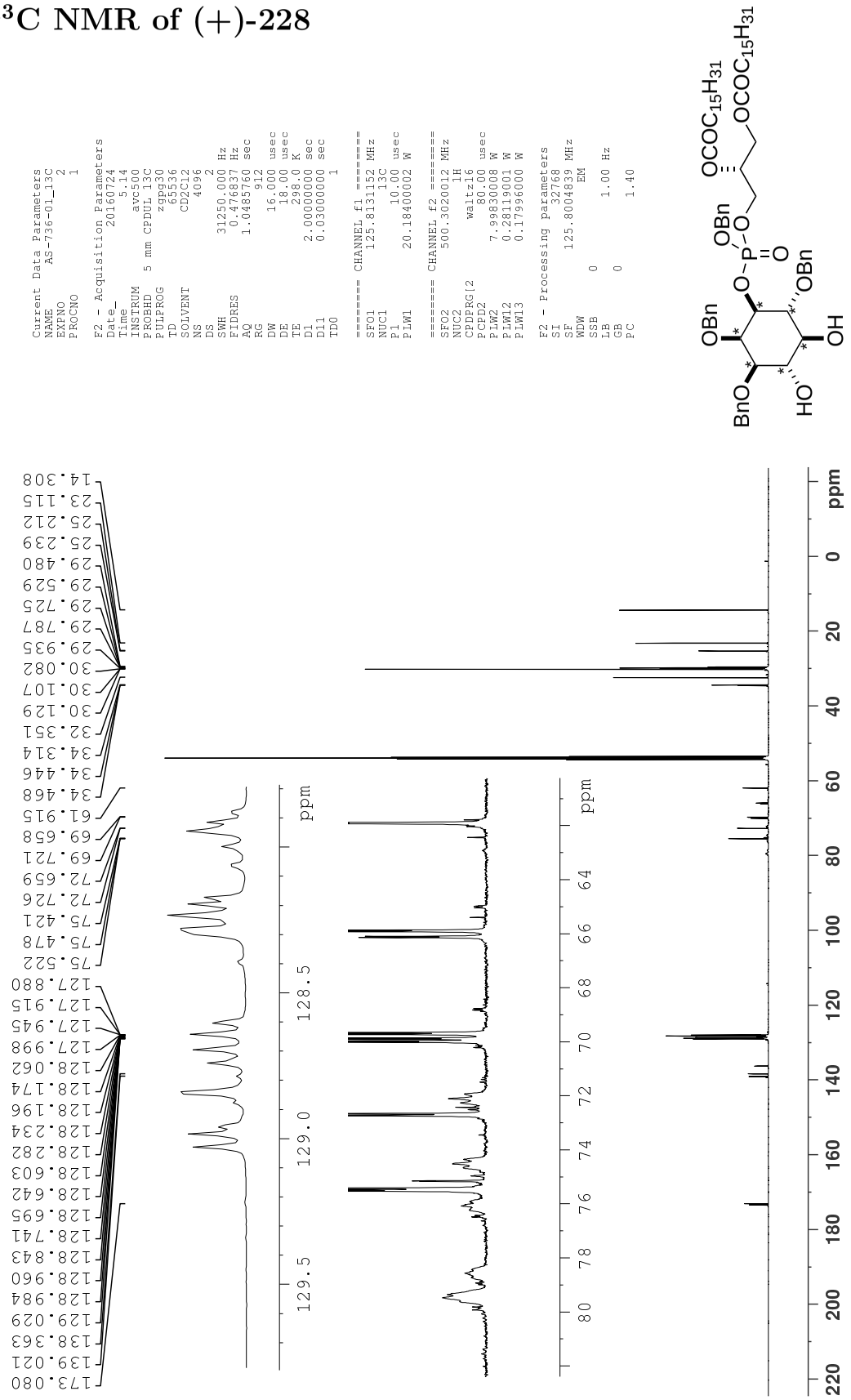
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
719.34558	$C_{43}H_{40}{}^{2}H_{6}O_{8}{}^{23}Na$	20.5	-0.79	719.34615

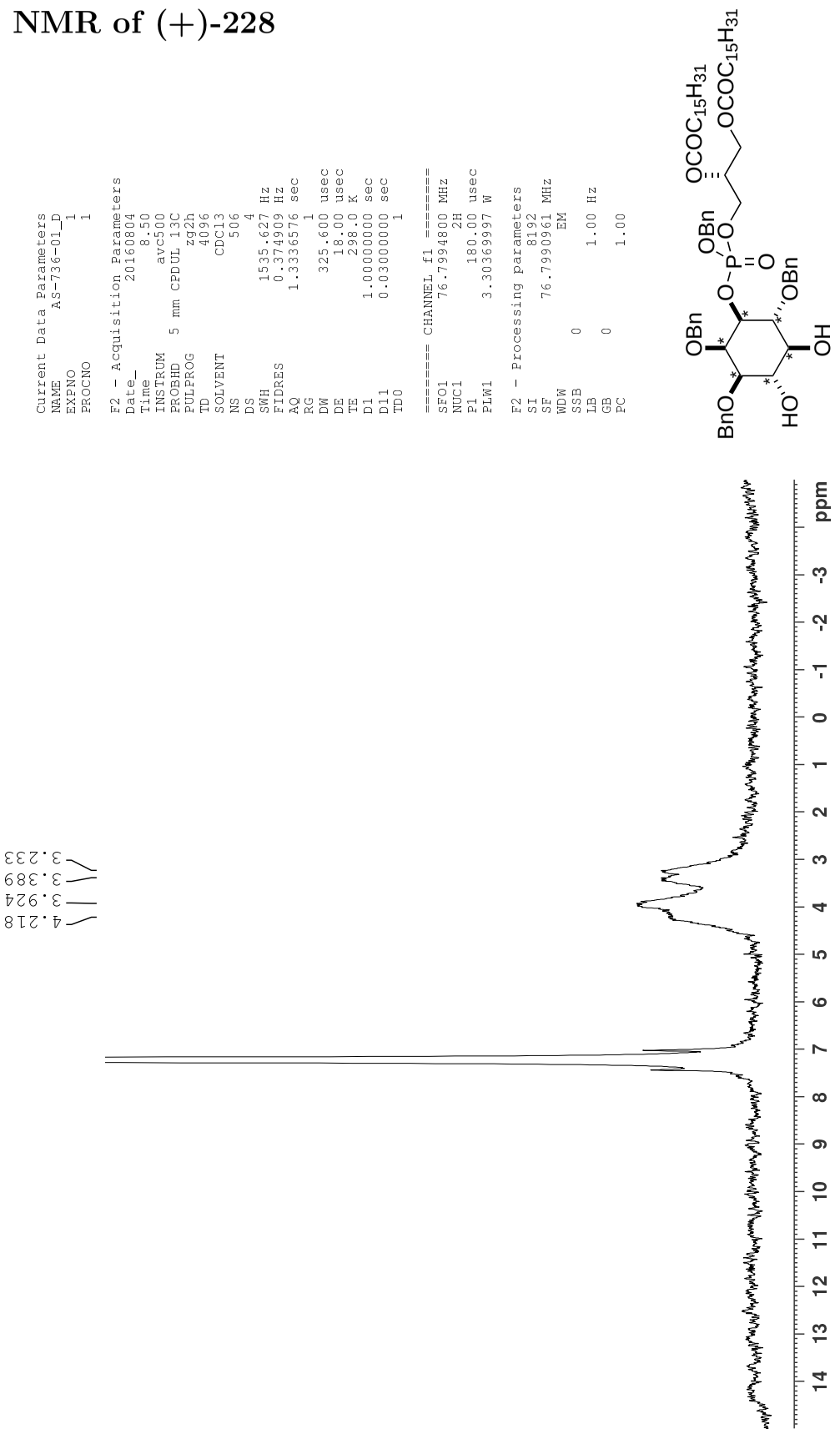
^{1}H NMR of (+)-228


Current Data Parameters
NAME AS-736-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160724
Time_ 1.40
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.1576632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
OBn
OCOC15H31
OCOC15H31
O-P=O
BnO
HO
OBn
OH
ppm
6.81
52.47
4.37
4.25
1.91
4.22
0.94
1.00
4.38
2.09
1.00
20.34

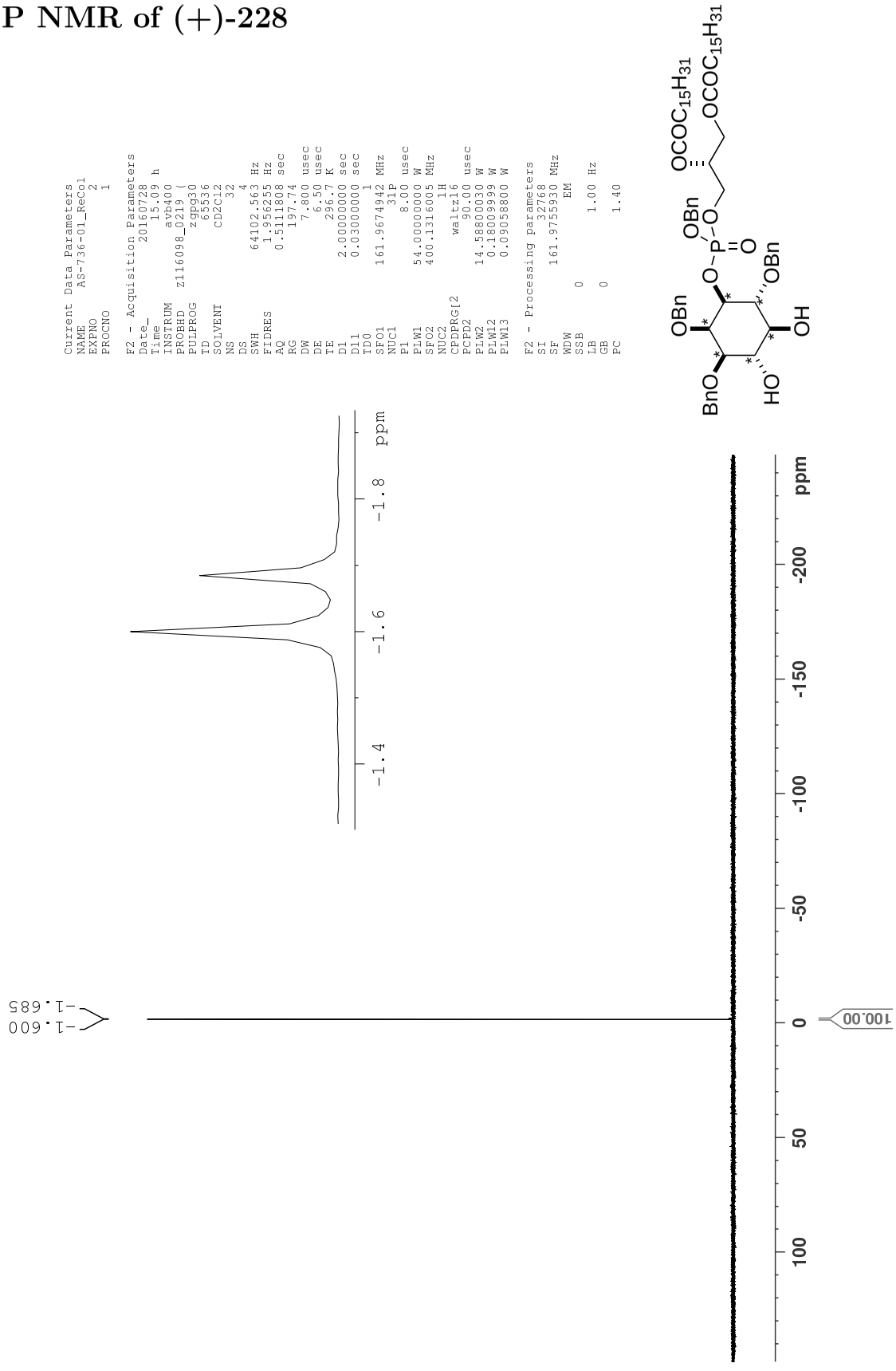
^{13}C NMR of (+)-228



^{2}H NMR of (+)-228


Current Data Parameters
NAME AS-736-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160804
Time 8.50
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 506
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990961 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
4.218
3.924
3.389
3.233
OBn
OBn
OCOC15H31
OCOC15H31
BnO
HO
OBn
OH
ppm

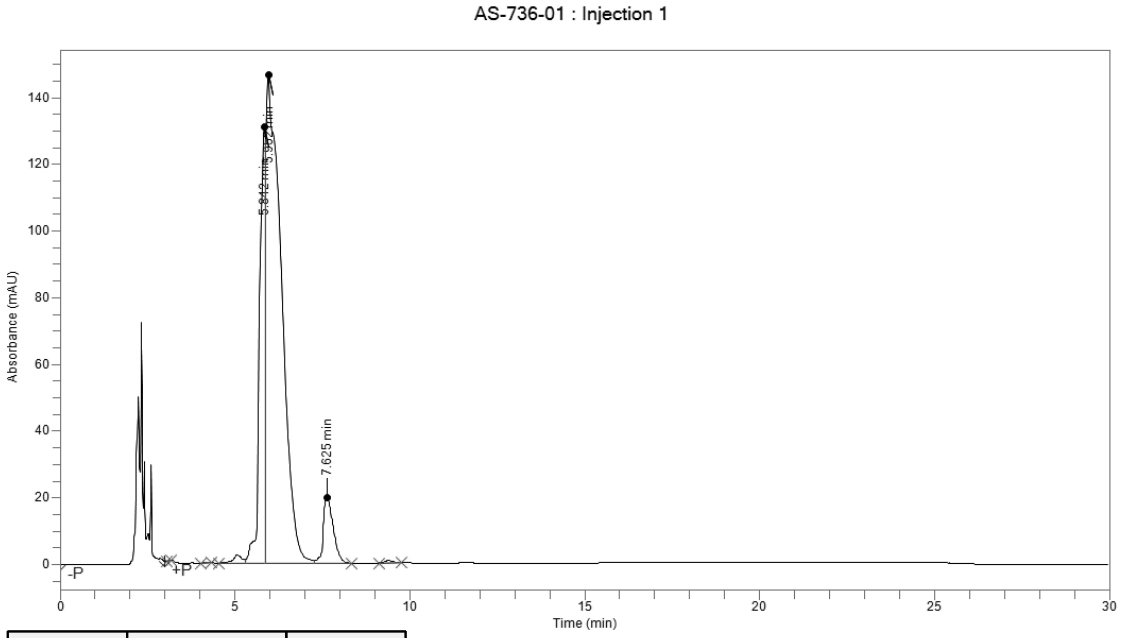
^{31}P NMR of (+)-228



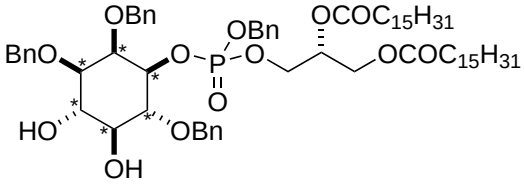
HPLC of (+)-228

AS-736-01

Sample Name	AS-736-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	8/4/2016 10:15 am
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column

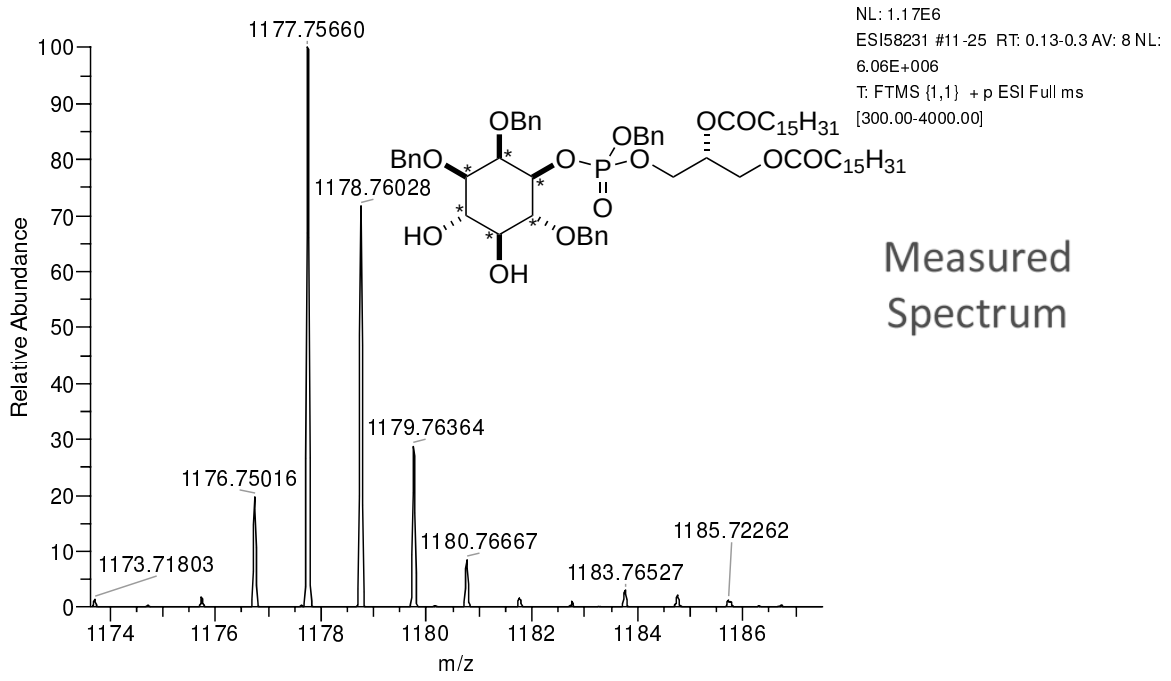


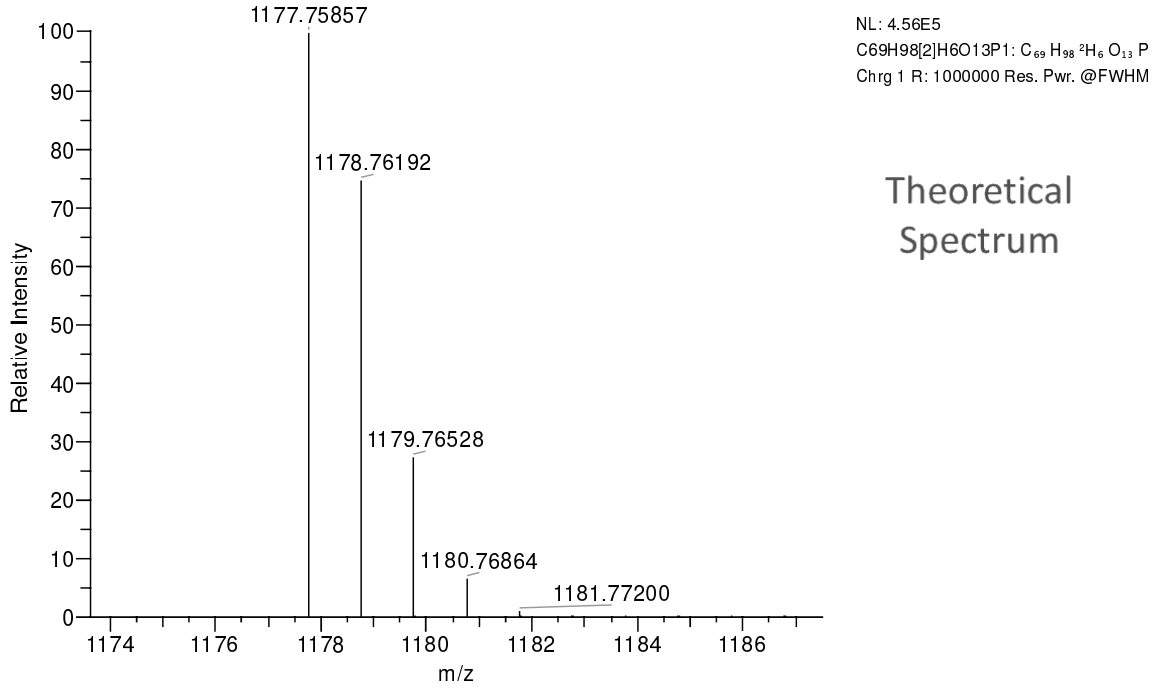
Time	Area	Area %
3.130	818.63	0.01
4.158	1913.3	0.03
5.067	45691	0.72
5.842	1441960	22.78
5.952	4423063	69.89
7.625	403116	6.37
9.374	12063	0.19
Total	6328625.06	100.00



Mass spectrum of (+)-228

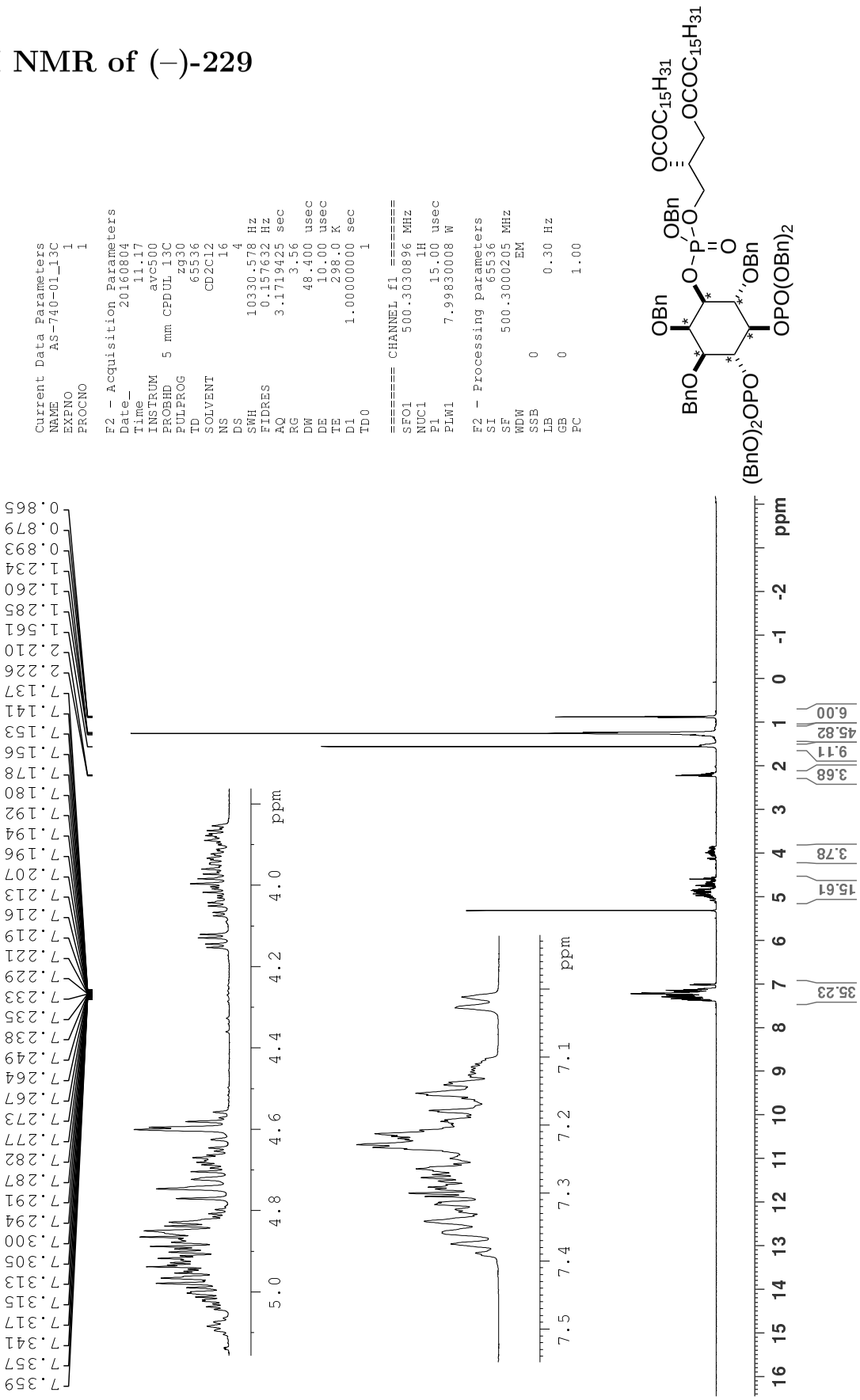
W:\data\July 16\ESI58231.raw 25/07/2016 8:42 am



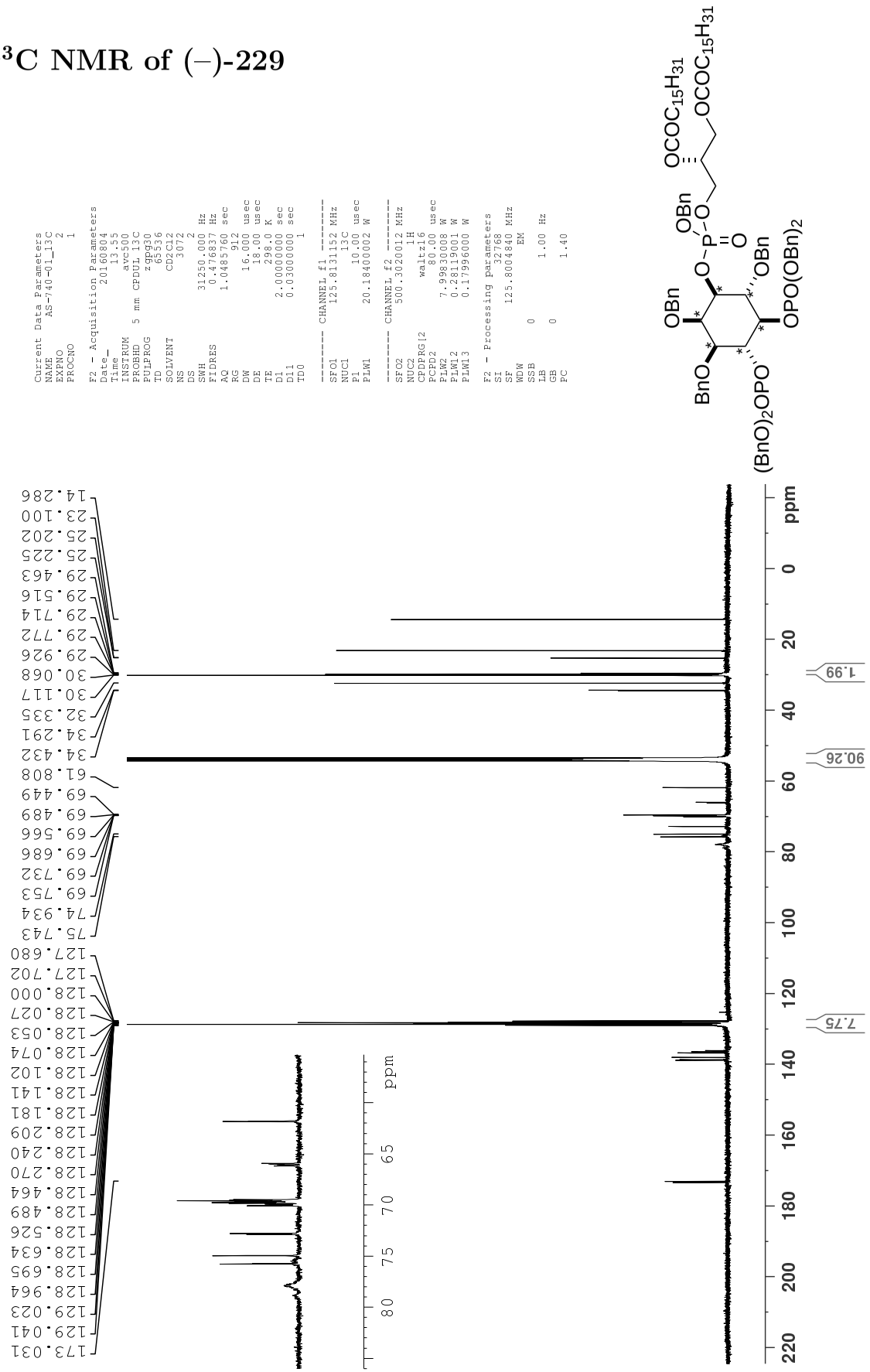


m/z	Formula	RDB	Delta ppm	Theo. Mass
1177.75659	$C_{69}H_{98}{}^{2}H_{6}O_{13}P$	18.5	-1.68	1177.75857

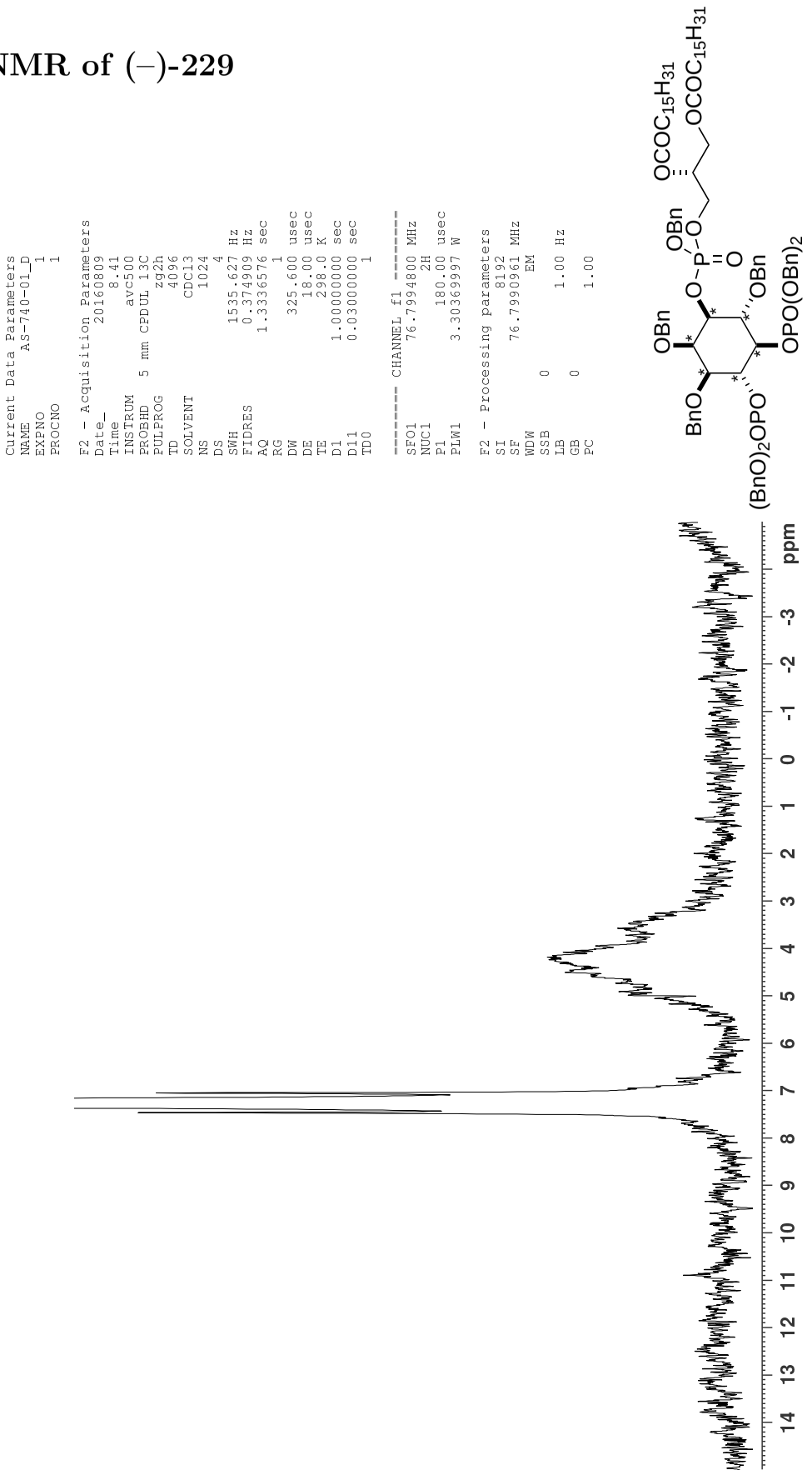
^{1}H NMR of (–)-229


Current Data Parameters
NAME AS-740-01_13C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160804
Time_ 11.17
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCOC15H31
OBn
OCOC15H31
O
P
O
OBn
OBn
BnO
OBn
OPO(OBn)2
(BnO)2OPO
ppm
35.23
15.61
3.78
3.68
9.11
45.82
6.00

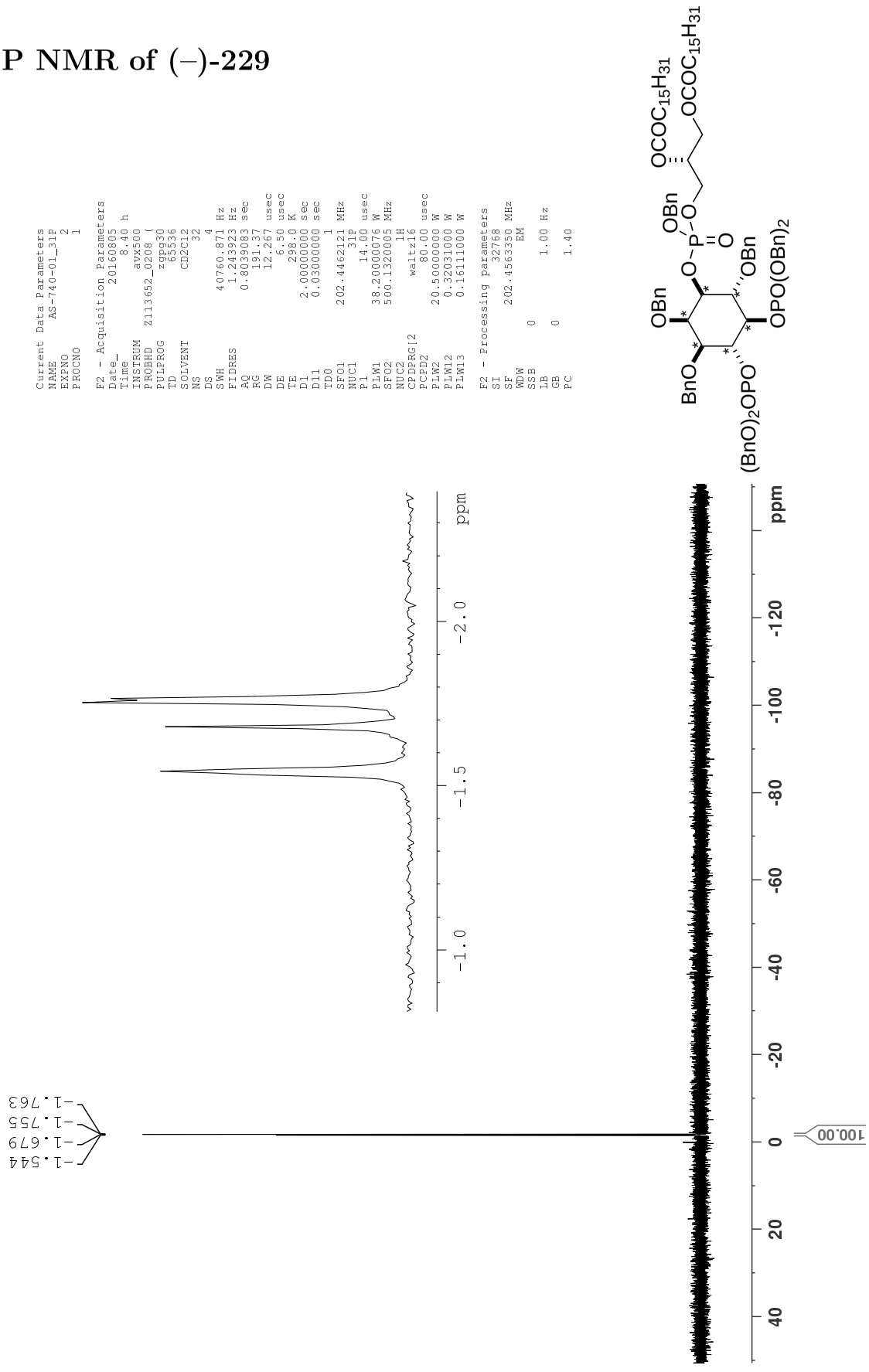
^{13}C NMR of (–)-229



^{2}H NMR of (–)-229


Current Data Parameters
NAME AS-740-01_D
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160809
Time 8.41
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg2h
TD 4096
SOLVENT CDC13
NS 1024
DS 4
SWH 1535.627 Hz
FIDRES 0.374909 Hz
AQ 1.33336576 sec
RG 1
DW 325.600 usec
DE 18.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 76.7994800 MHz
NUC1 2H
P1 180.00 usec
PLW1 3.30369997 W
F2 - Processing parameters
SI 8192
SF 76.7990961 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
OCOC15H31
OBn
OCOC15H31
O~P=O
OBn
OBn
OBn
BnO
OPO(OBn)2
(BnO)2OPO
ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3

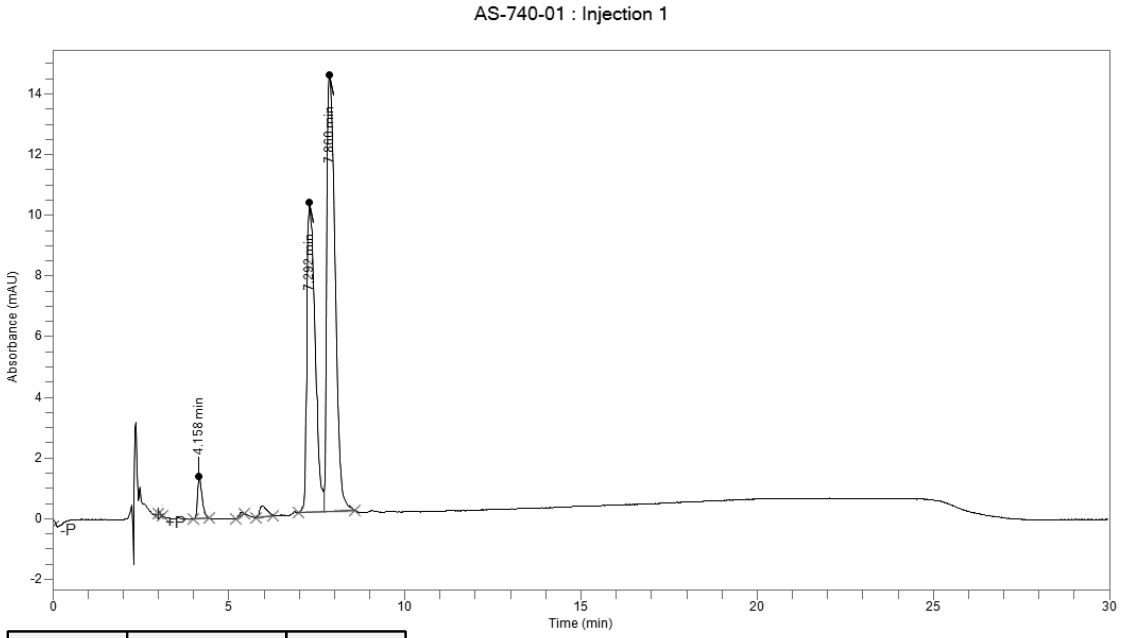
^{31}P NMR of (–)-229



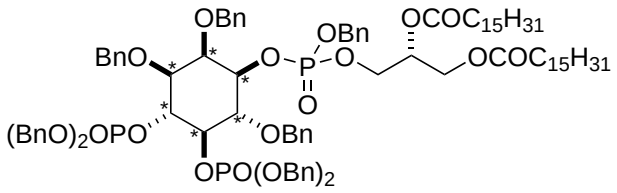
HPLC of (–)-229

AS-740-01

Sample Name	AS-740-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 2-10	Acquisition Date/Time	8/5/2016 11:45 am
Batch Group/Name	Alex/Normal Phase Purity 254nm 2-10	Batch Description	Normal Phase silica column

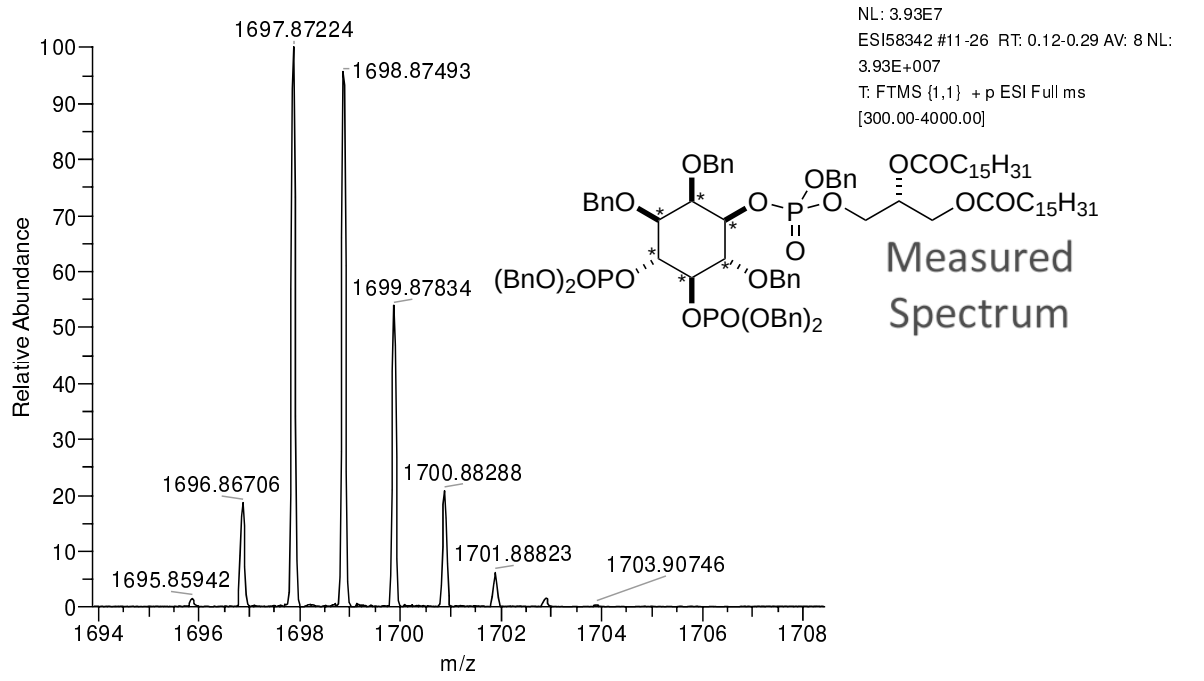


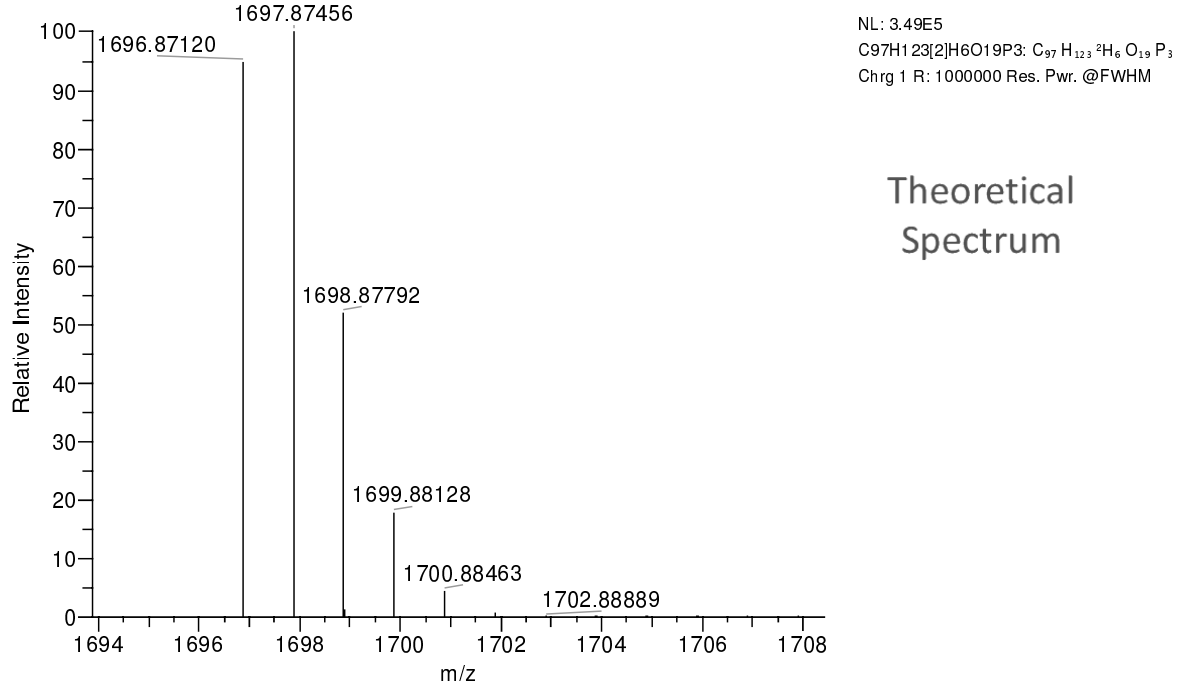
Time	Area	Area %
3.031	286.41	0.07
4.158	12406	2.96
5.369	724.88	0.17
5.949	5052	1.20
7.292	165928	39.54
7.860	235206	56.05
Total	419603.34	100.00



Mass spectrum of (–)-229

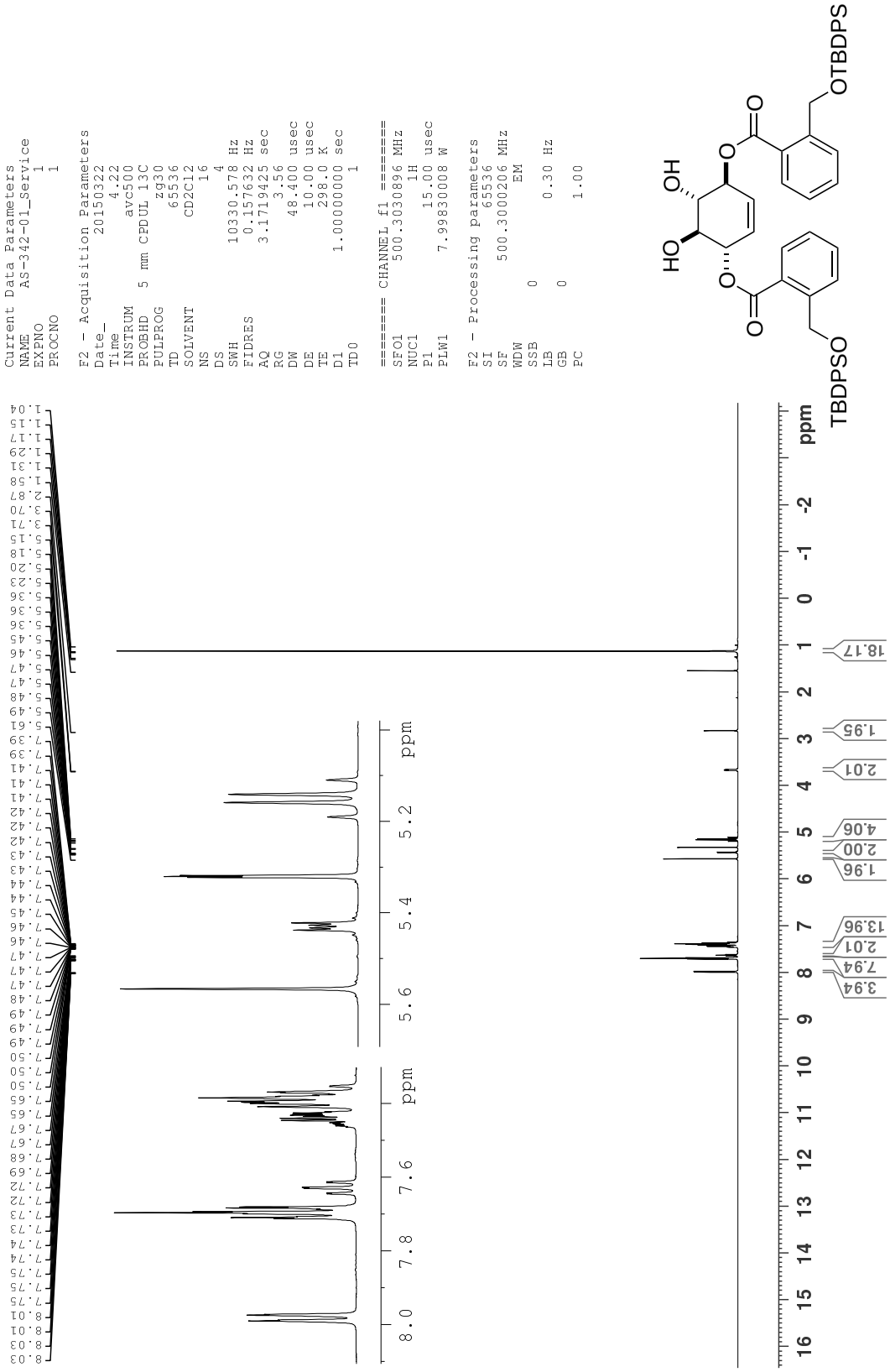
W:\data\July 16\ESI58342.raw 29/07/2016 7:59 am



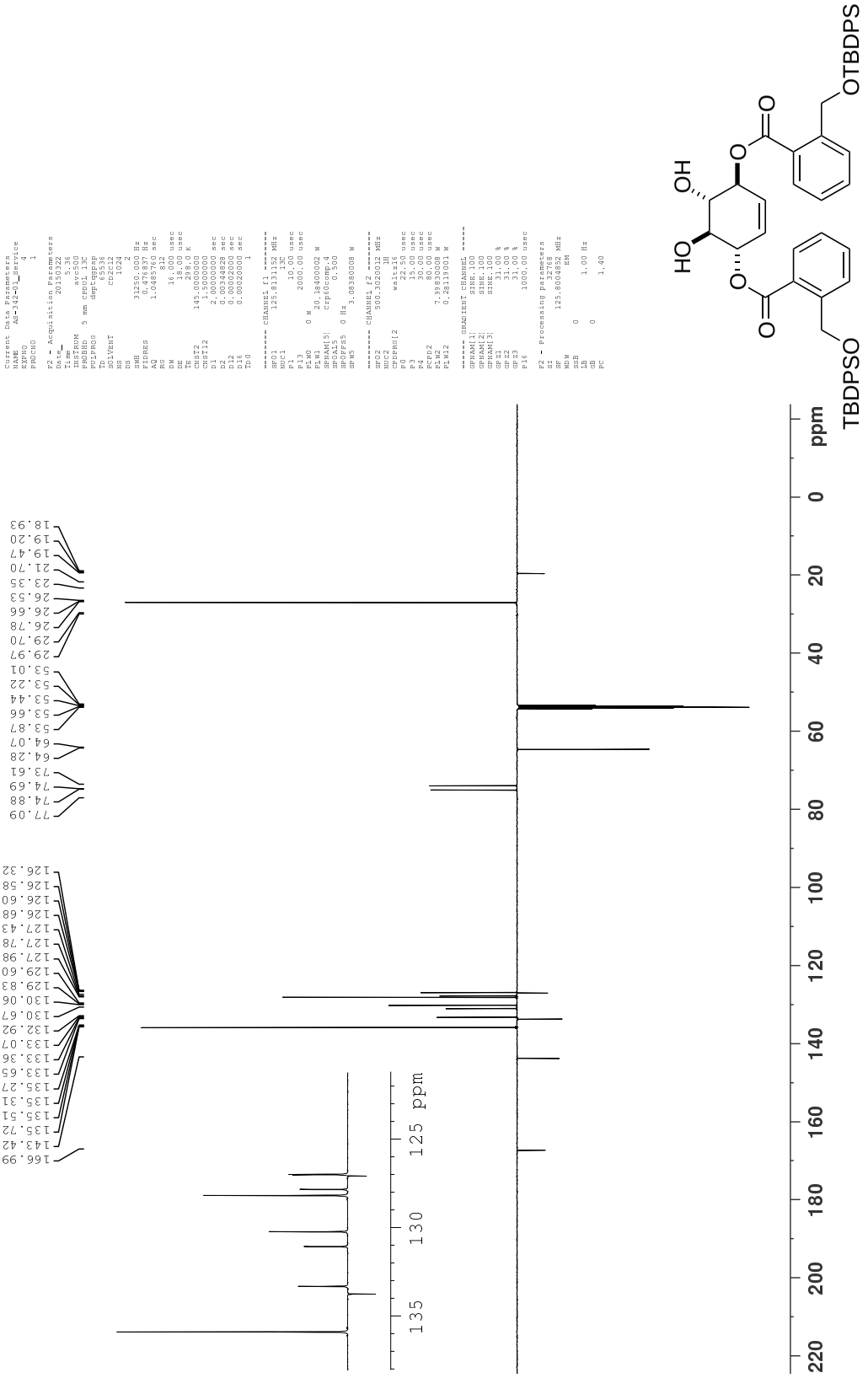


m/z	Formula	RDB	Delta ppm	Theo. Mass
1696.86707	$C_{97}H_{123}{}^{2}H_{6}O_{19}P_{3}$	35	-2.44	1696.87120

^{1}H NMR of (+)-233


Current Data Parameters
NAME AS-342-01_Service
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150322
Time 4.22
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OH
HO
O
O
O
O
OTBDPS
TBDPSO
ppm
18.17
1.95
2.01
4.06
2.00
1.96
13.96
2.01
7.94
3.94

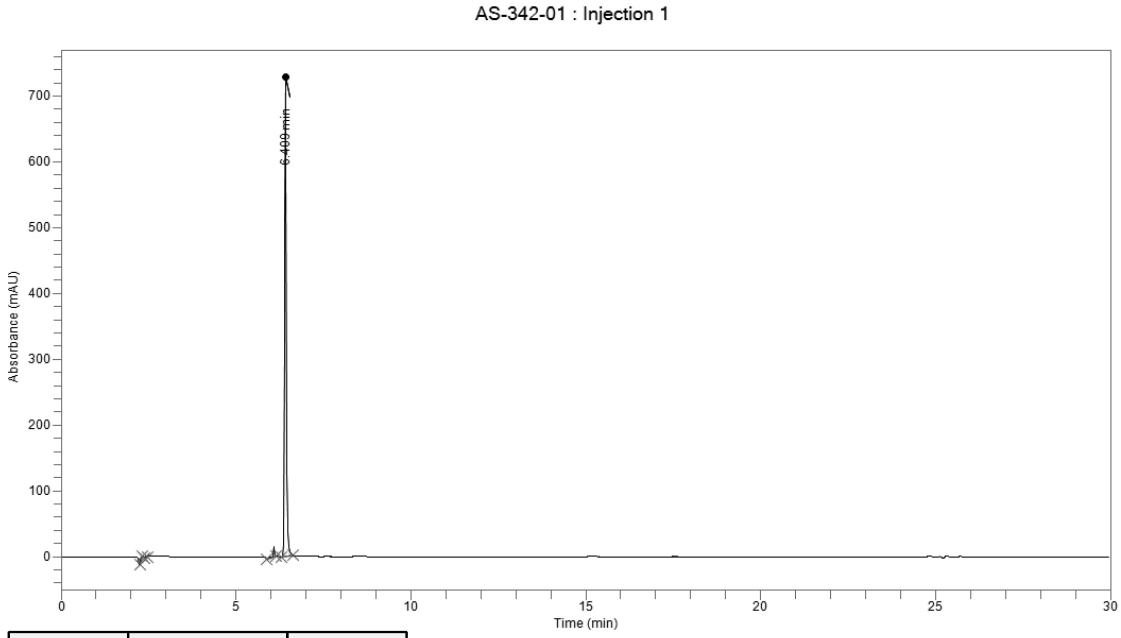
^{13}C NMR of (+)-233



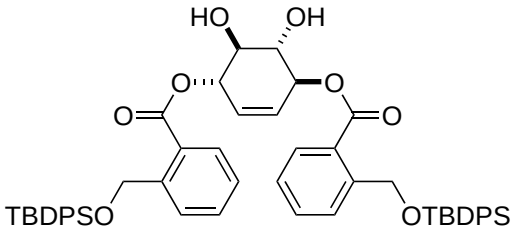
HPLC of (+)-233

AS-342-01

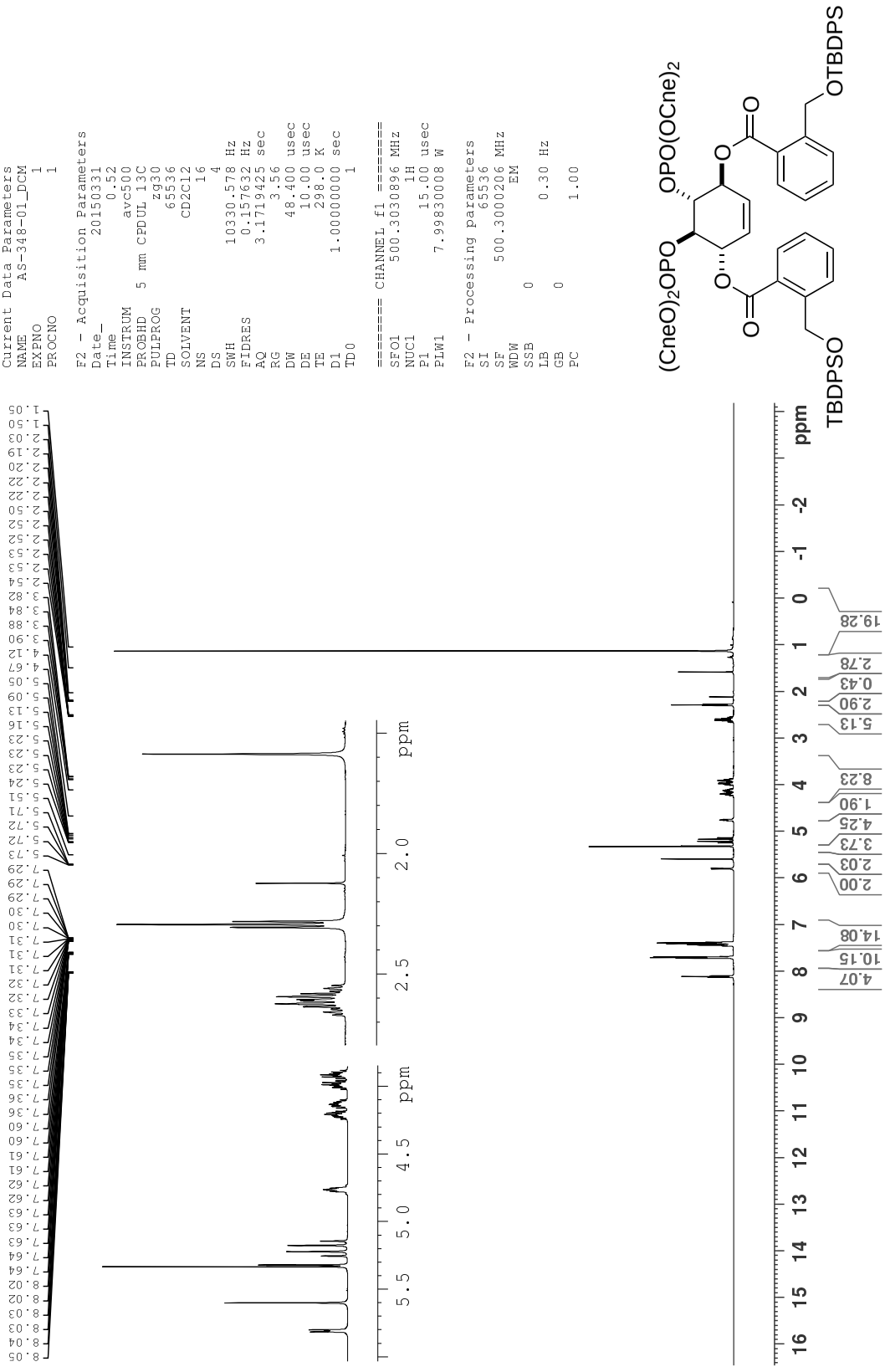
Sample Name	AS-342-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	4/13/2015 2:06 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 04-17-2015 13-16-11	Batch Description	Normal Phase silica column



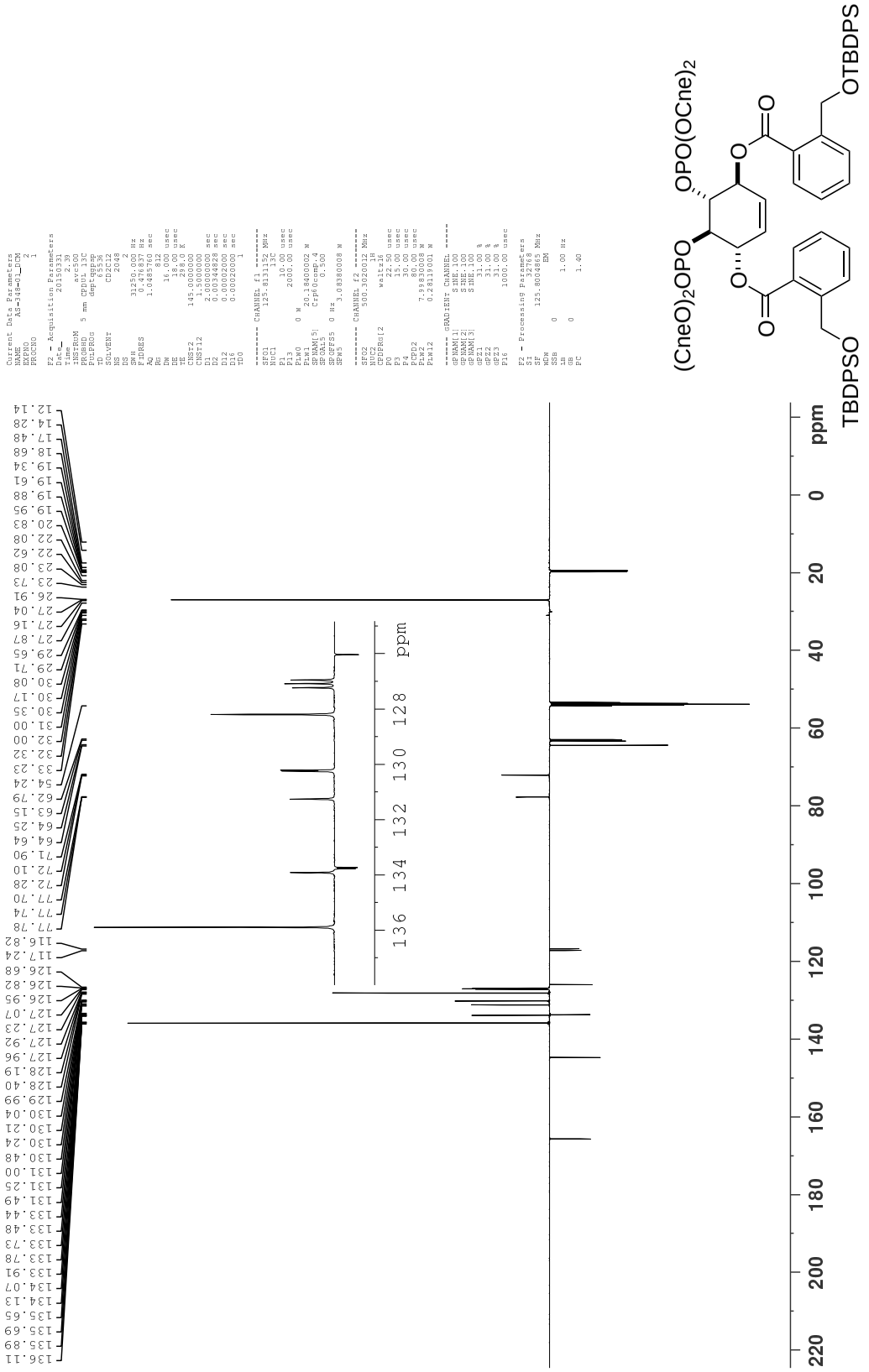
Time	Area	Area %
2.315	14864	0.58
2.436	5826.3	0.23
6.085	43981	1.71
6.409	2512282	97.49
Total	2576952	100.00



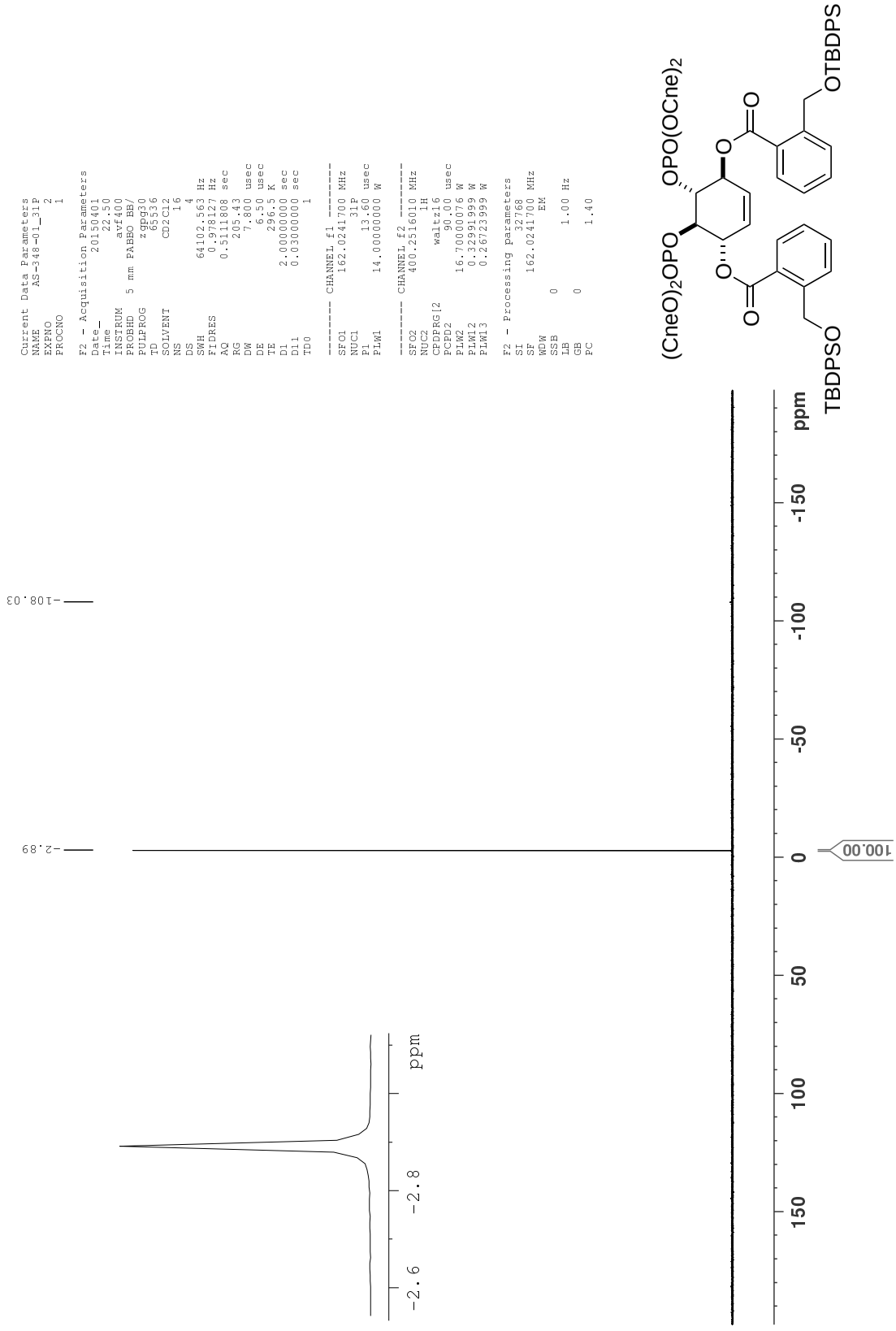
^{1}H NMR of (+)-234


Current Data Parameters
NAME AS-348-01_DCM
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150331
Time 0.52
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
(CneO)2OPO
OPO(OCne)2
OTBDPS
TBDPSO
ppm
19.28
2.78
0.43
2.90
5.13
8.23
1.90
4.25
3.73
2.03
2.00
14.08
10.15
4.07

^{13}C NMR of (+)-234



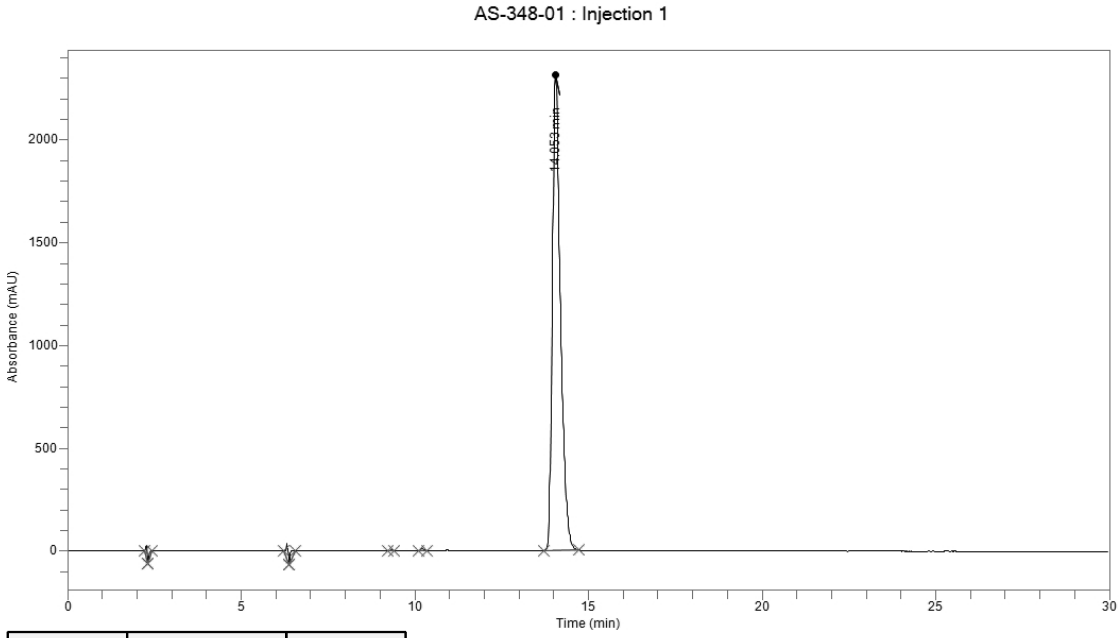
^{31}P NMR of (+)-234



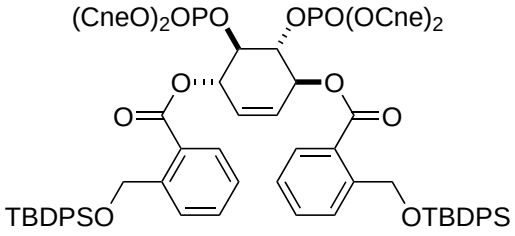
HPLC of (+)-234

AS-348-01

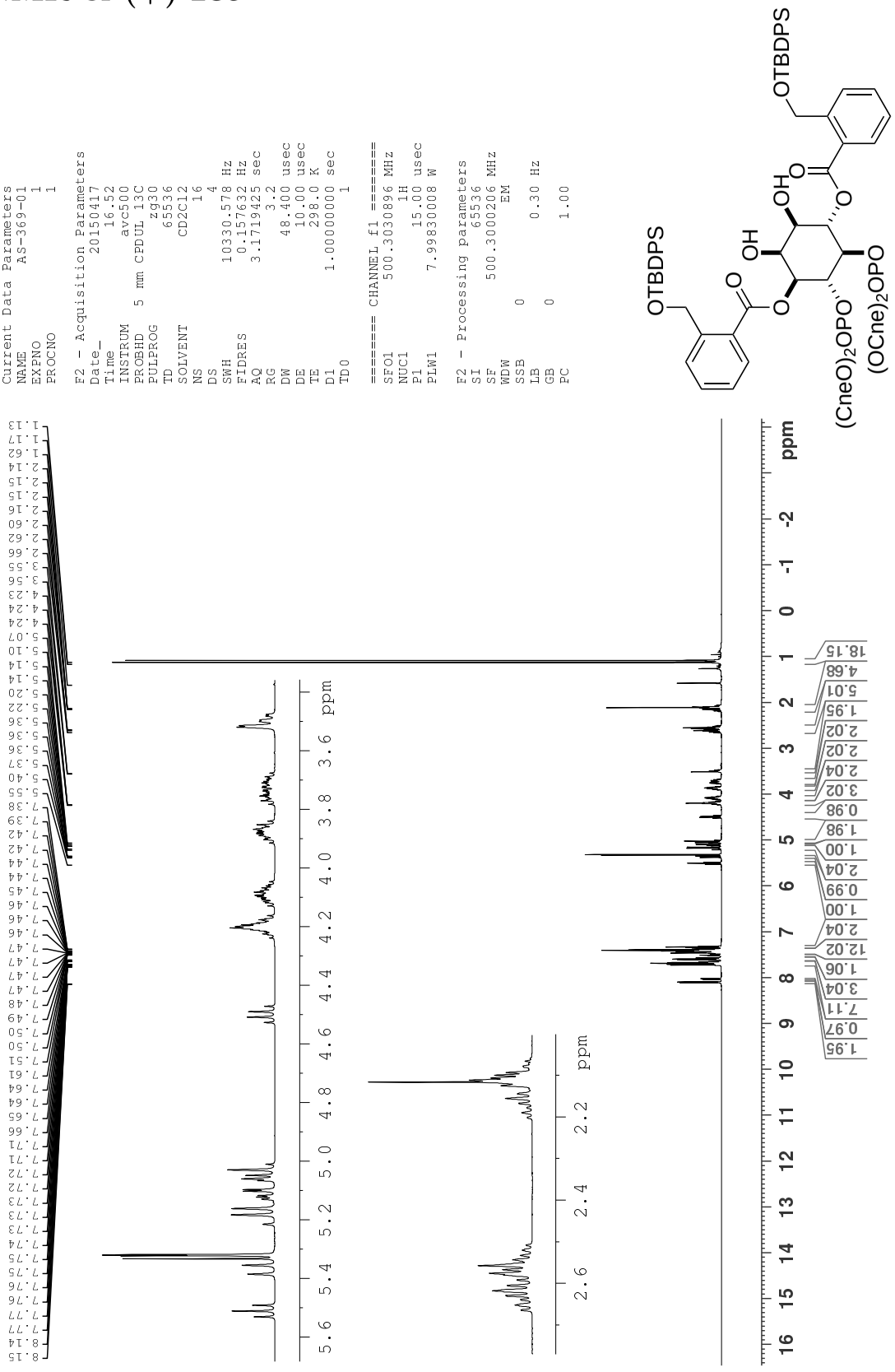
Sample Name	AS-348-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	4/22/2015 3:48 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 04-22-2015 17-00-58	Batch Description	Normal Phase silica column



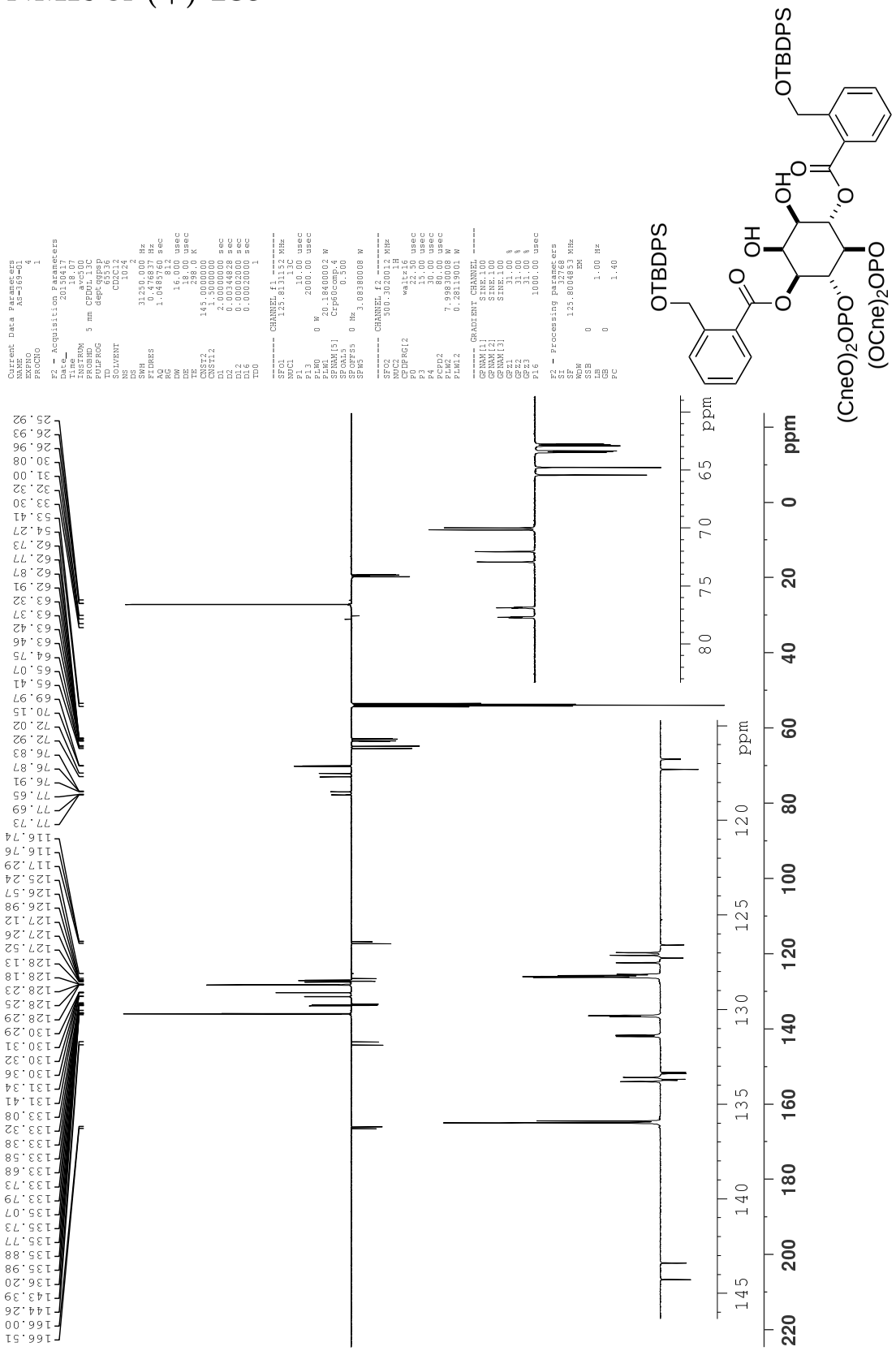
Time	Area	Area %
2.269	208182	0.53
2.411	120463	0.31
6.308	327284	0.84
6.509	282885	0.73
9.323	28377	0.07
10.218	64238	0.16
14.053	37901185	97.35
Total	38932614	100.00



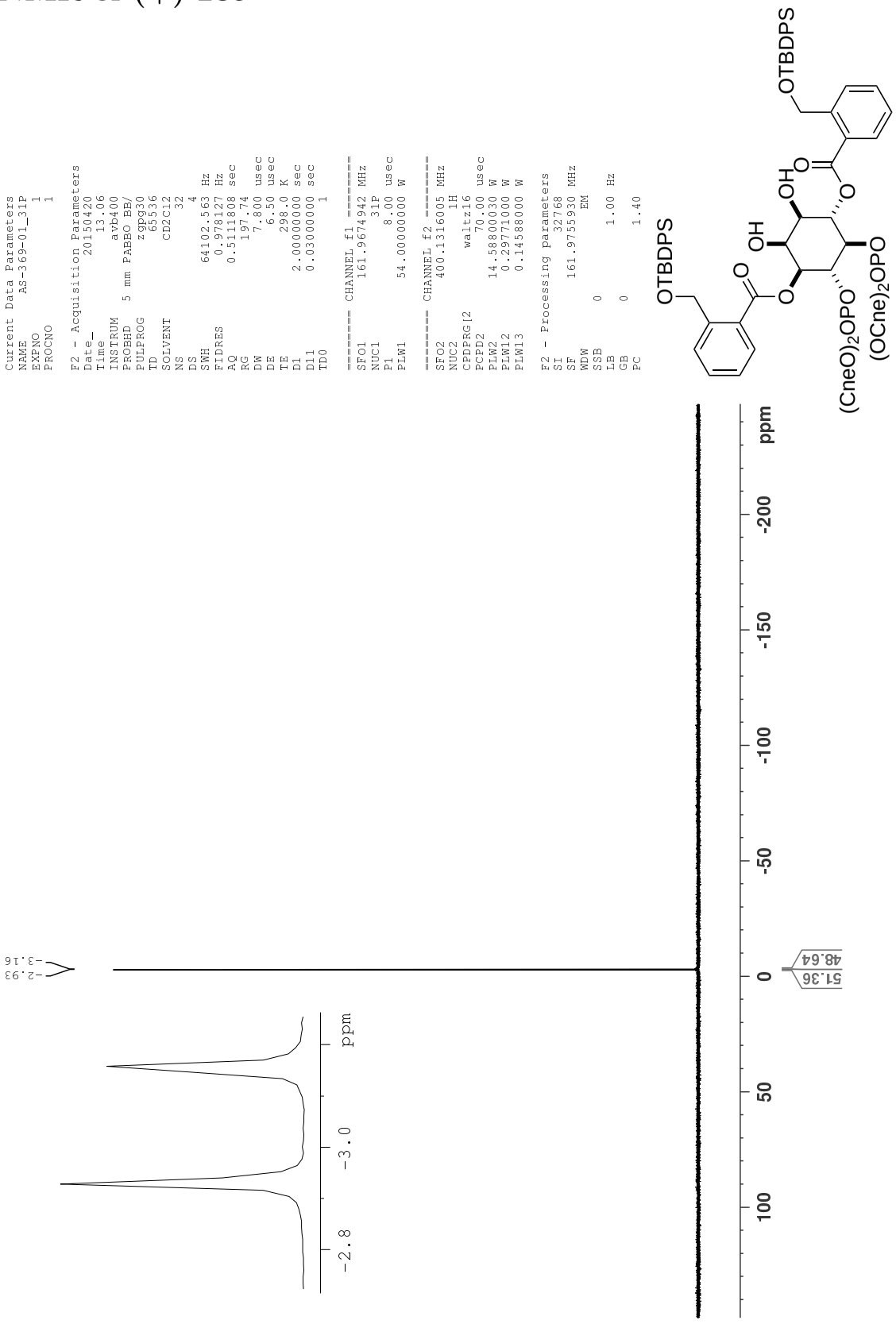
^{1}H NMR of (+)-235


Current Data Parameters
NAME AS-369-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150417
Time 16.52
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2Cl2
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000206 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTBDPS
OH
OH
O
O
O
O
OTBDPS
(CneO)2OPO
(OCne)2OPO
ppm

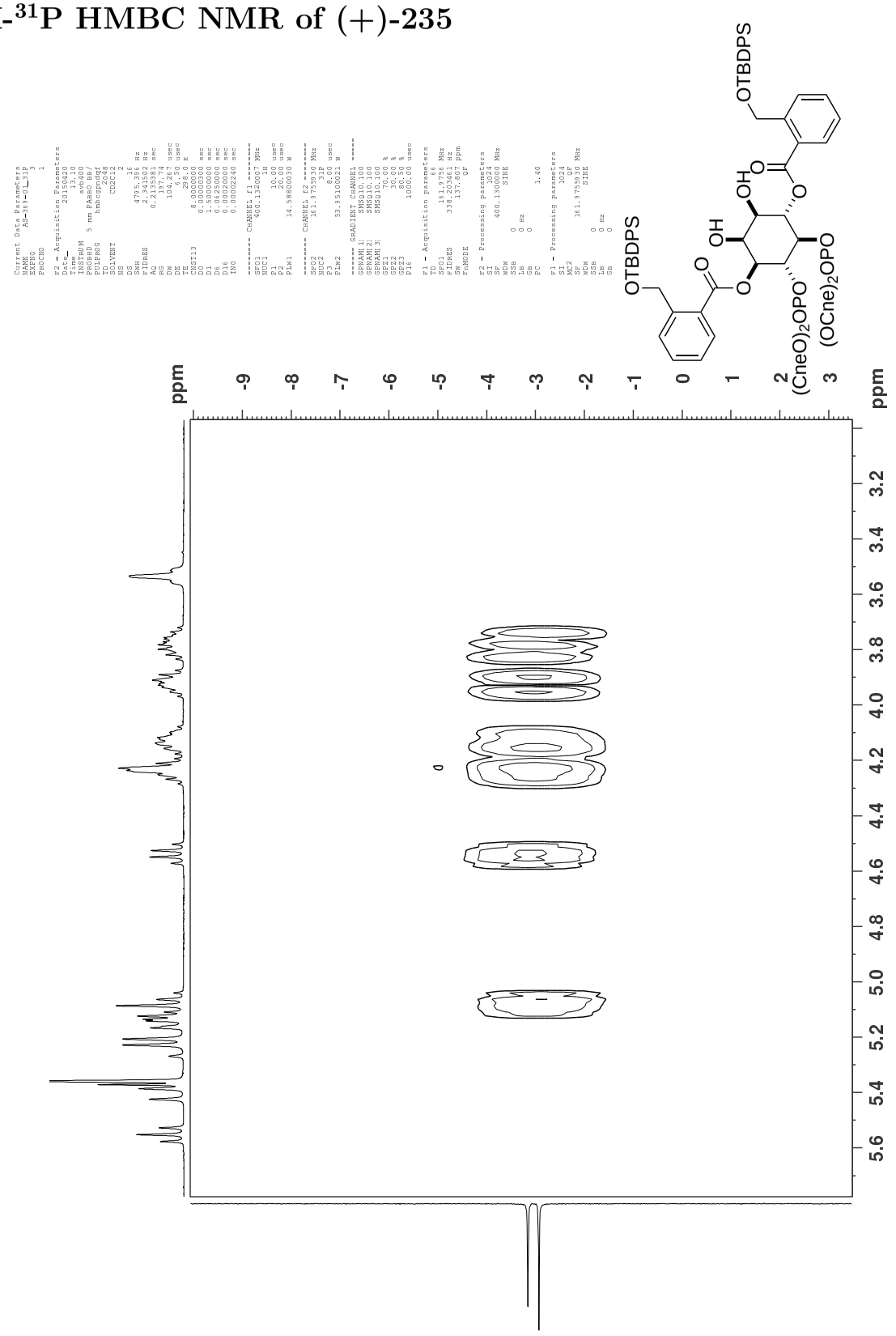
^{13}C NMR of (+)-235



^{31}P NMR of (+)-235



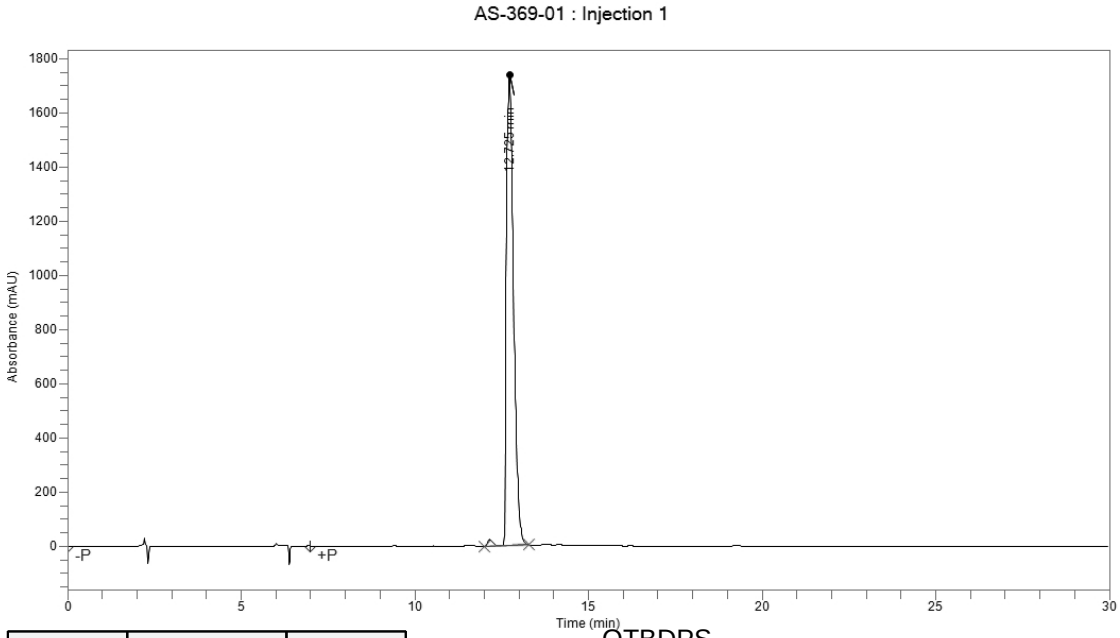
^{1}H-^{31}P HMBC NMR of (+)-235



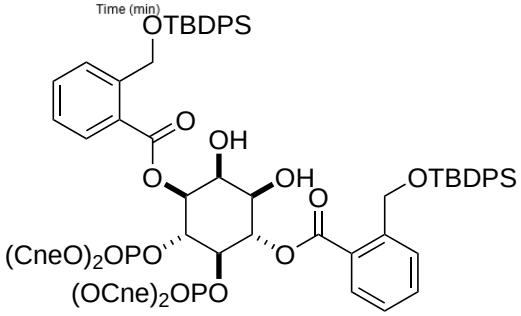
HPLC of (+)-235

AS-369-01

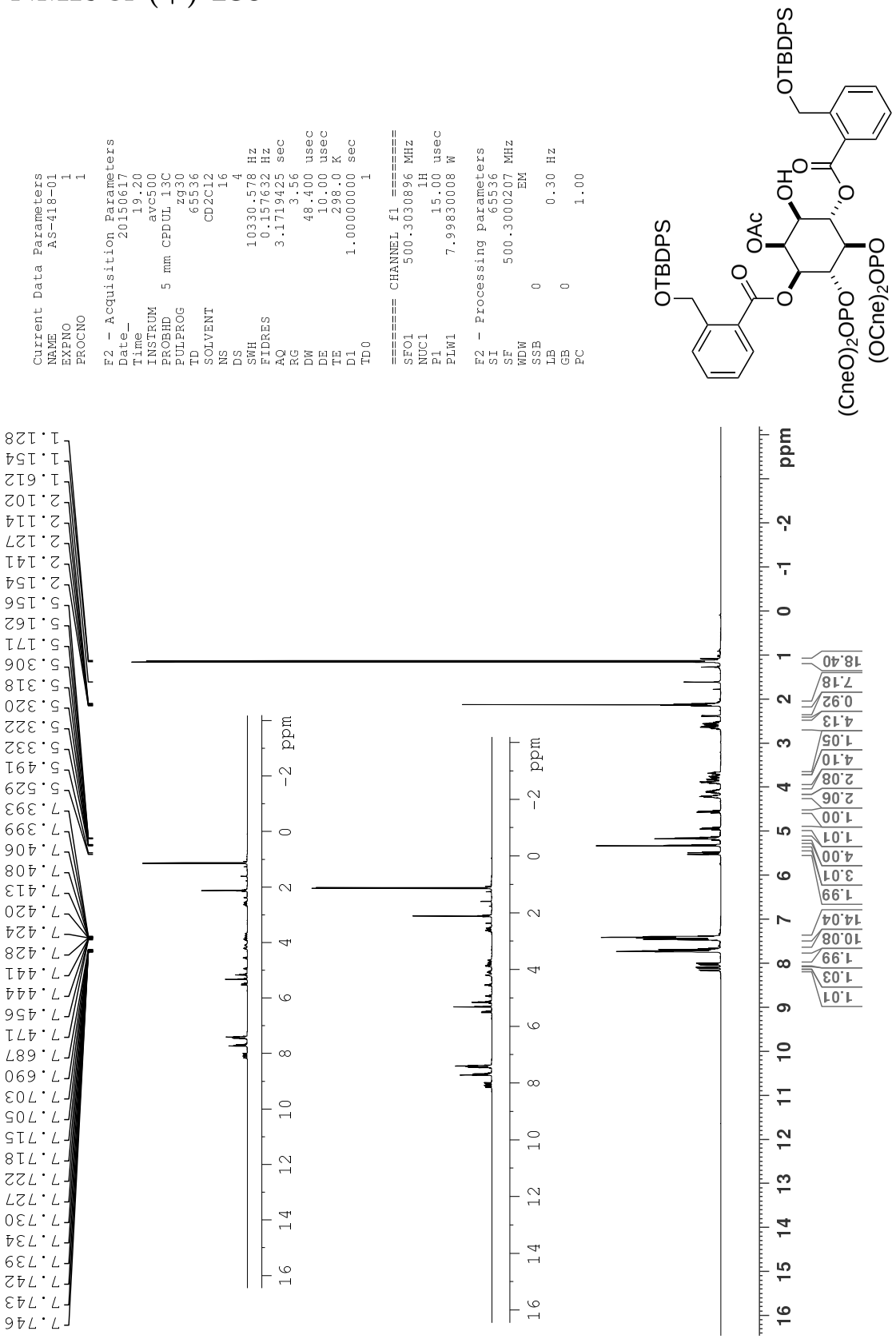
Sample Name	AS-369-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	4/22/2015 4:56 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm	Batch Description	Normal Phase silica column



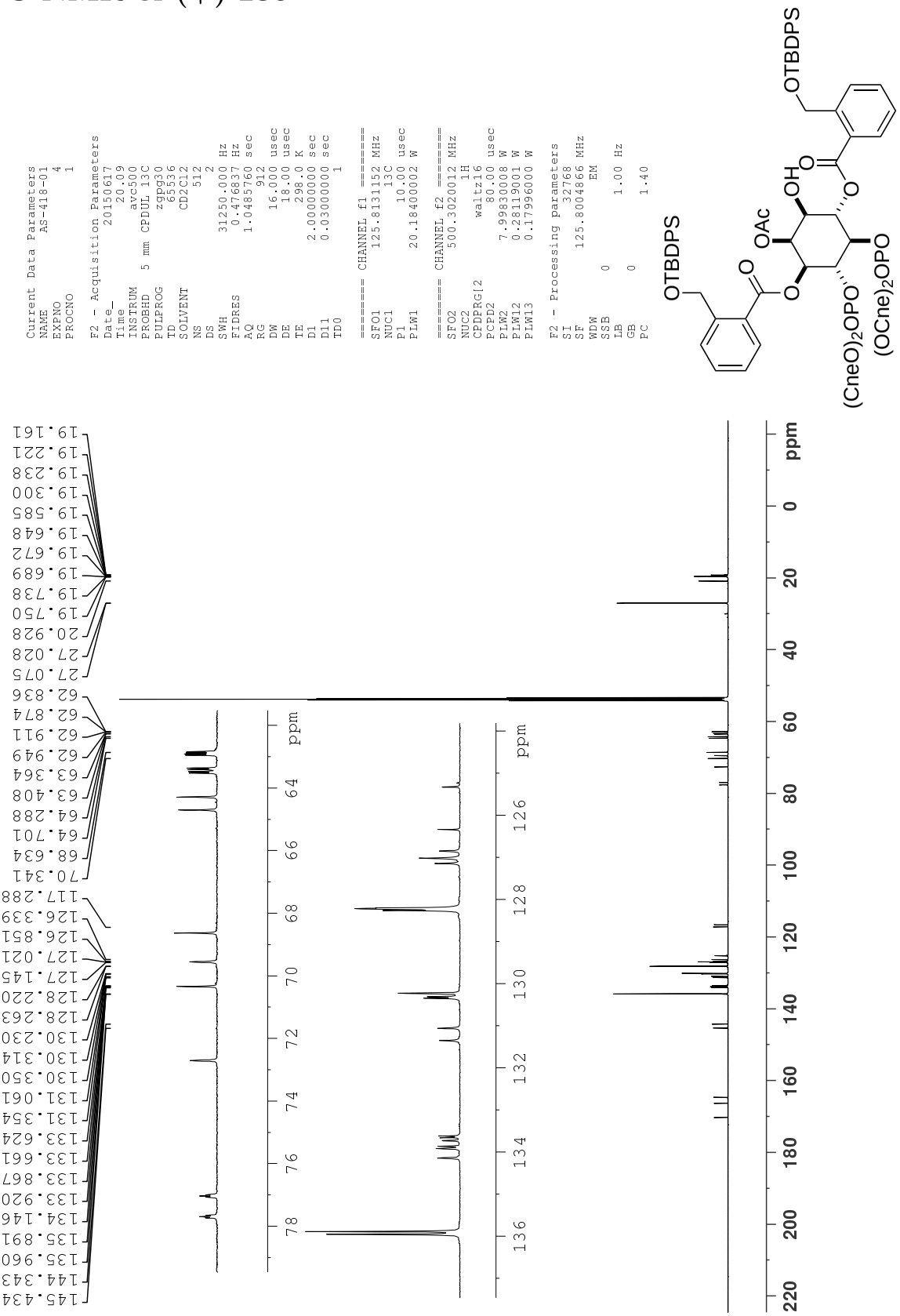
Time	Area	Area %
12.142	238485	0.93
12.725	25290981	99.07
Total	25529466	100.00



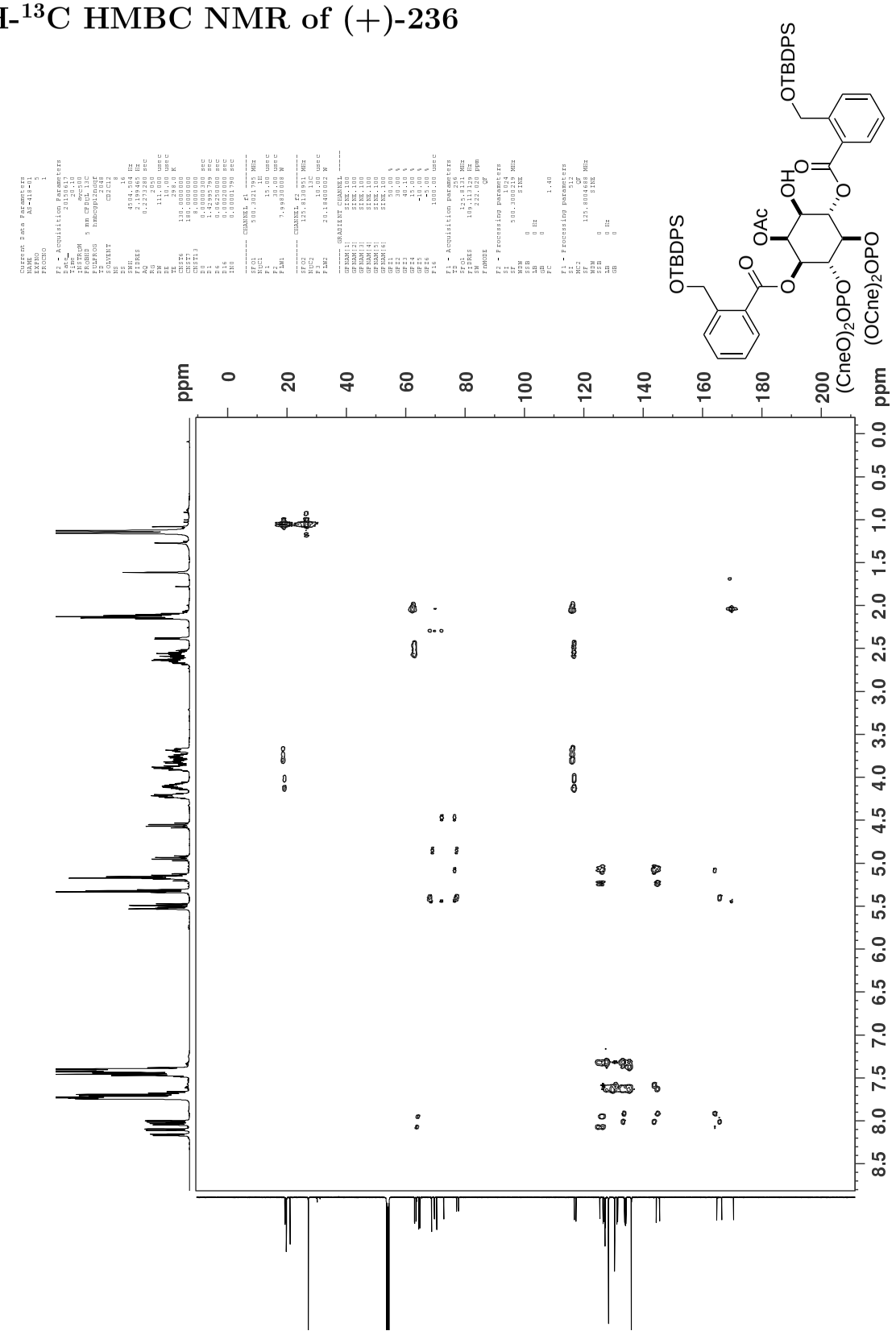
^{1}H NMR of (+)-236


Current Data Parameters
NAME AS-418-01
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150617
Time_ 19.20
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000207 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTBDPS
OAc
OH
O
(CneO)2OPO
(OCne)2OPO
OTBDPS
ppm

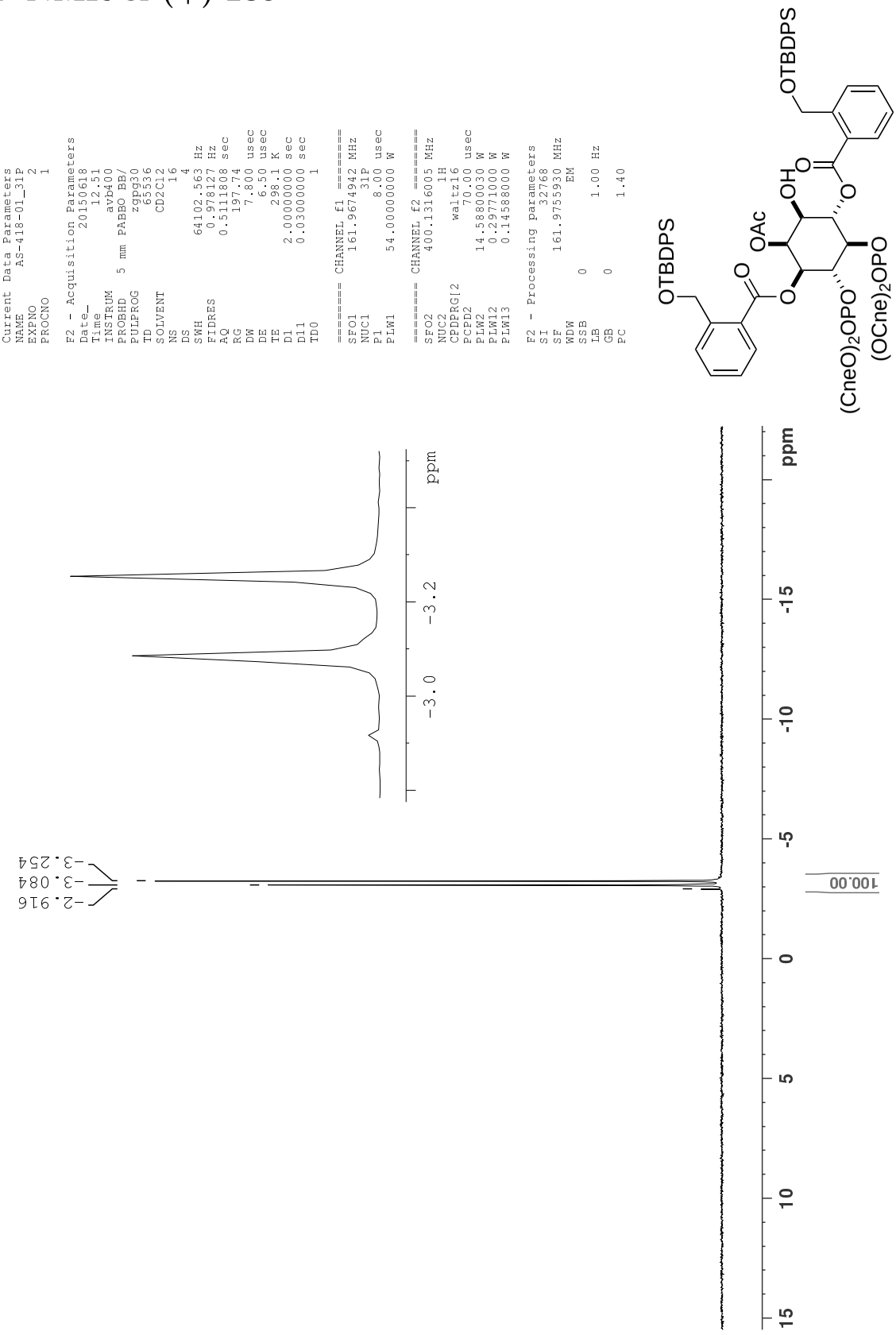
^{13}C NMR of (+)-236



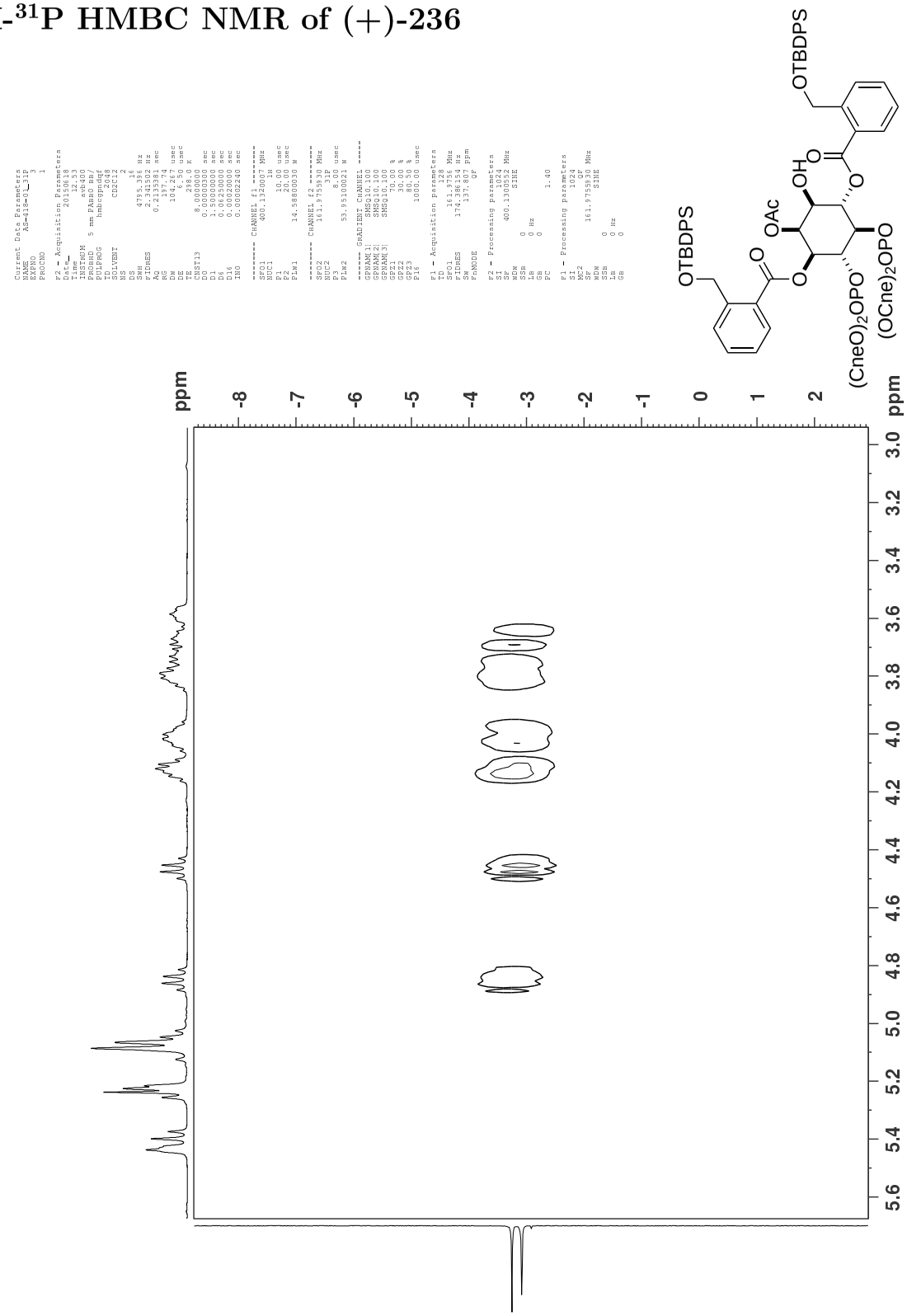
^{1}H-^{13}C HMBC NMR of (+)-236



^{31}P NMR of (+)-236



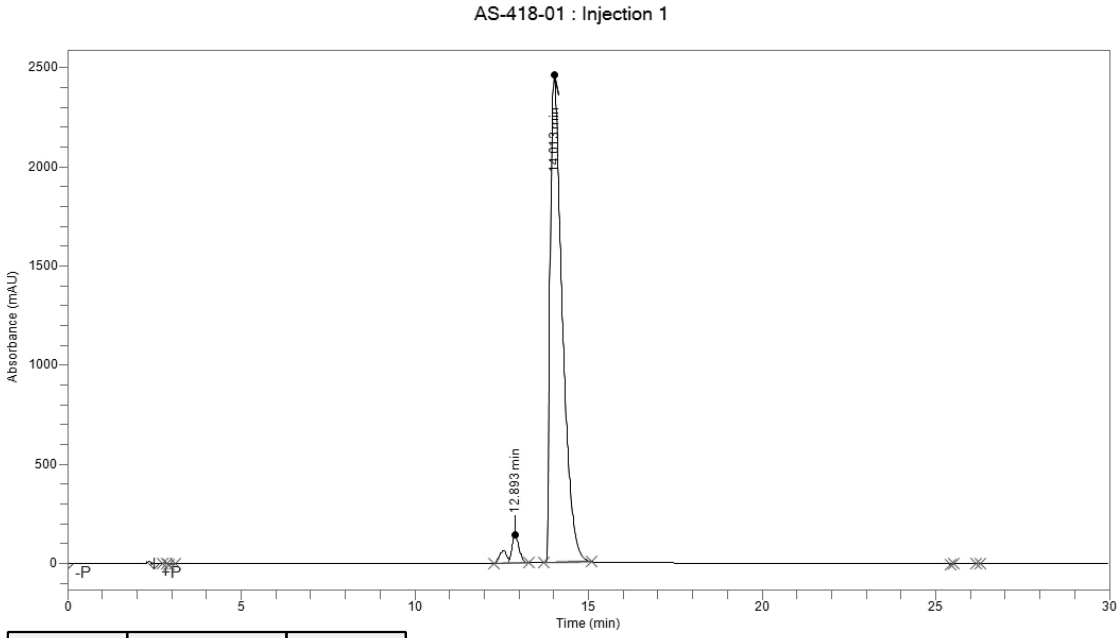
^{1}H-^{31}P HMBC NMR of (+)-236



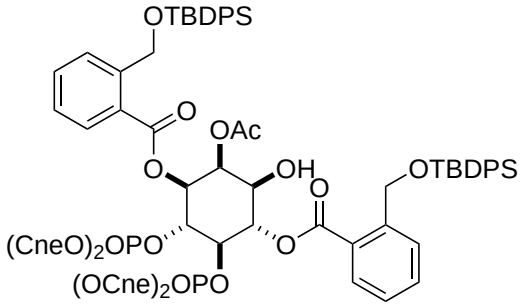
HPLC of (+)-236

AS-418-01

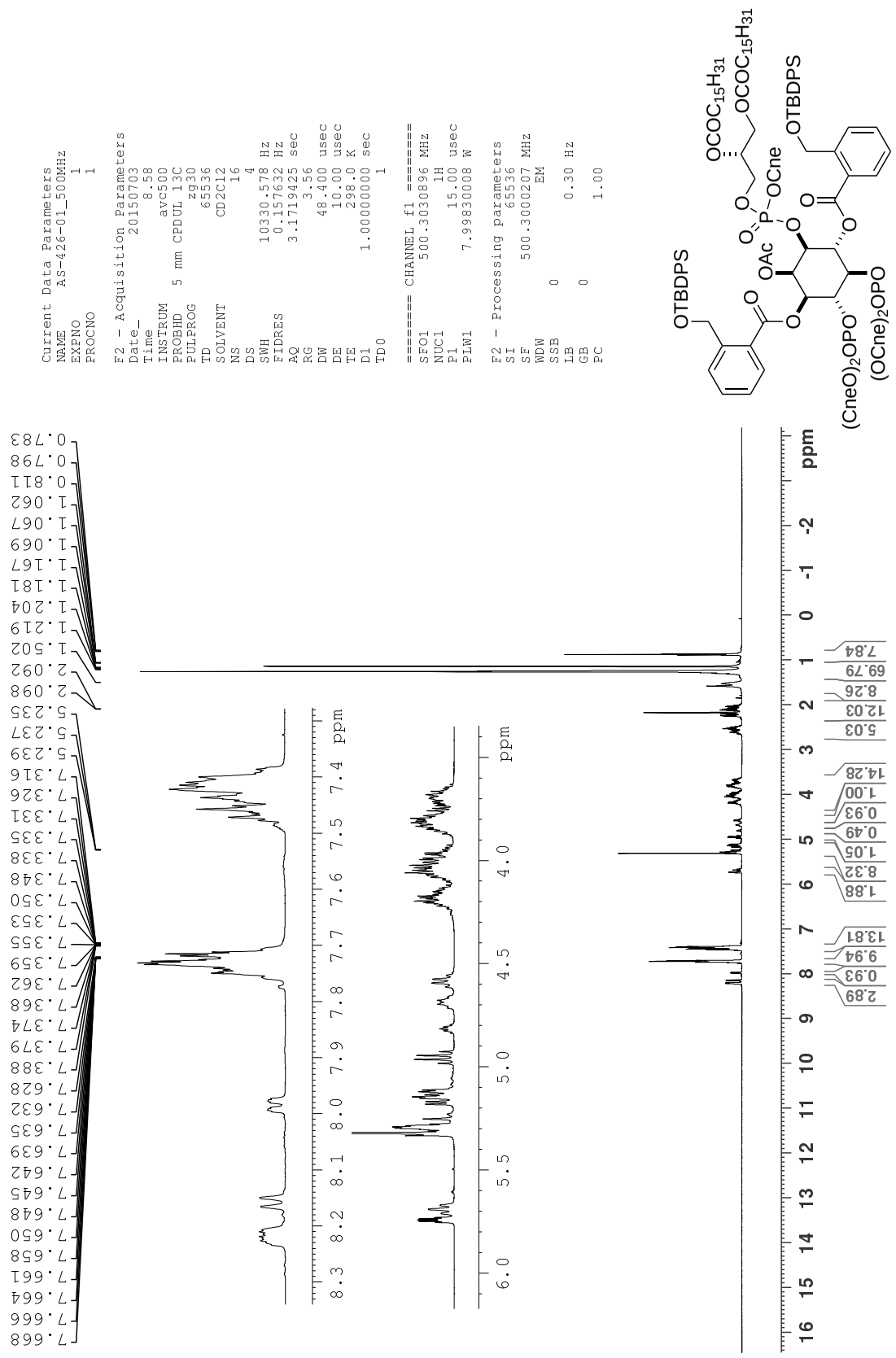
Sample Name	AS-418-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	7/7/2015 12:29 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 07-07-2015 15-09-58	Batch Description	Normal Phase silica column



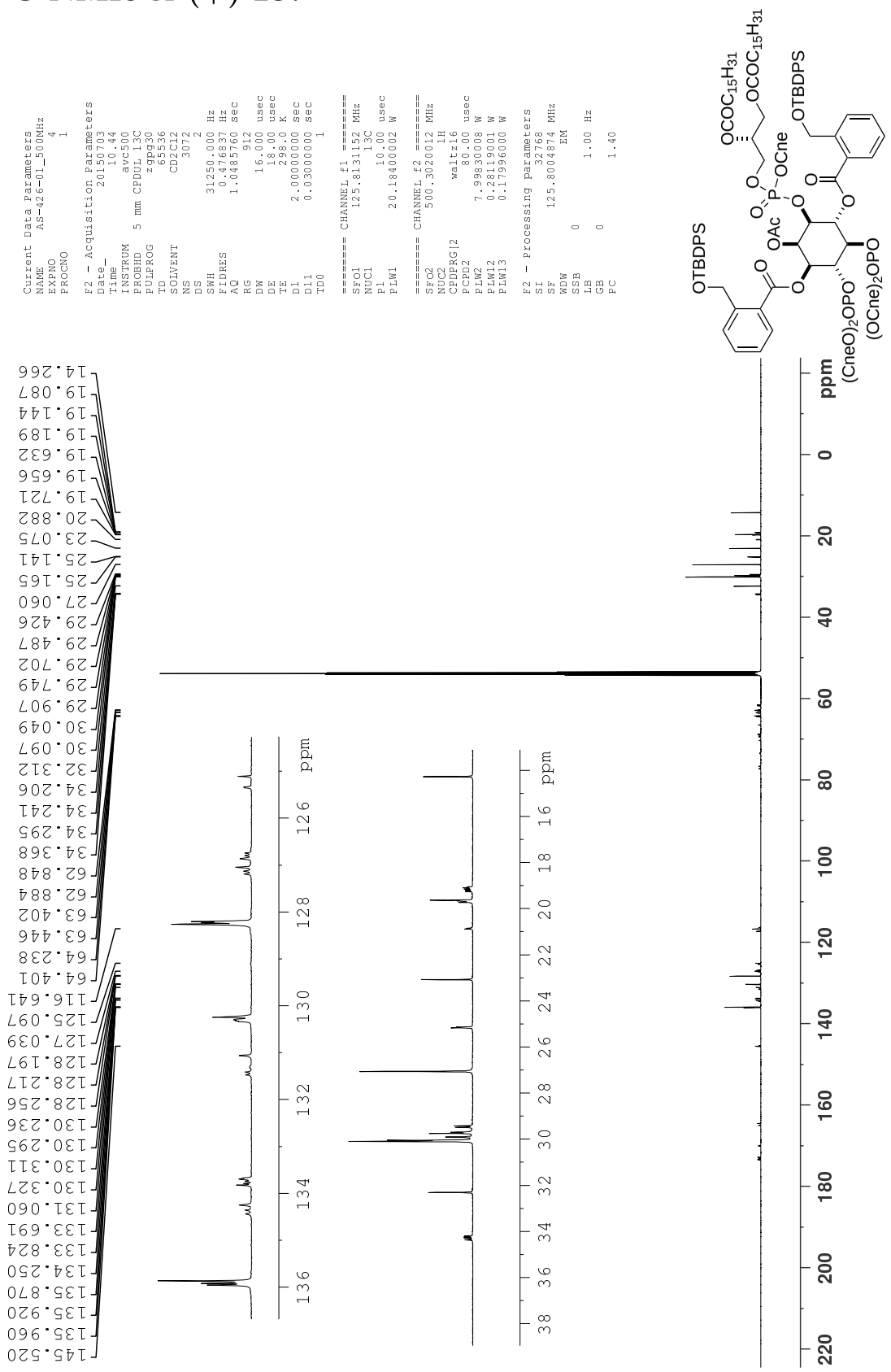
Time	Area	Area %
2.798	23970	0.04
3.069	28535	0.05
12.549	943712	1.49
12.893	2029186	3.21
14.013	60181066	95.18
25.495	10906	0.02
26.233	9983	0.02
Total	63227358	100.00



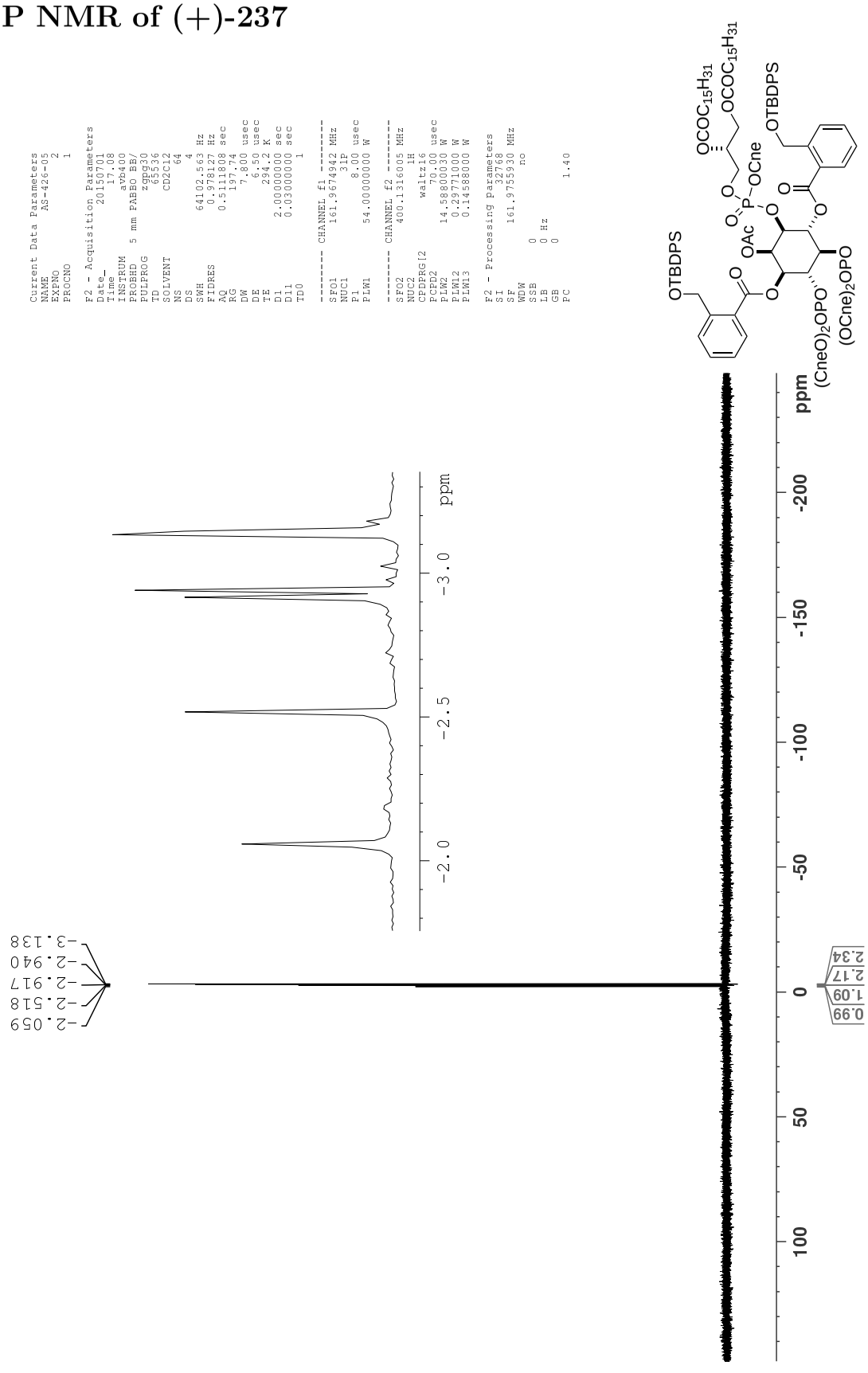
^{1}H NMR of (+)-237


Current Data Parameters
NAME AS-426-01_500MHz
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150703
Time_ 8.58
INSTRUM avc500
PROBHD 5 mm CPDUL 13C
PULPROG zg30
TD 65536
SOLVENT CD2C12
NS 16
DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.17719425 sec
RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 500.3030896 MHz
NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
SI 65536
SF 500.3000207 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OTBDPS
OCOC15H31
OCOC15H31
OTBDPS
OAc
OCne
(CneO)2OPO
(OCne)2OPO
ppm

^{13}C NMR of (+)-237



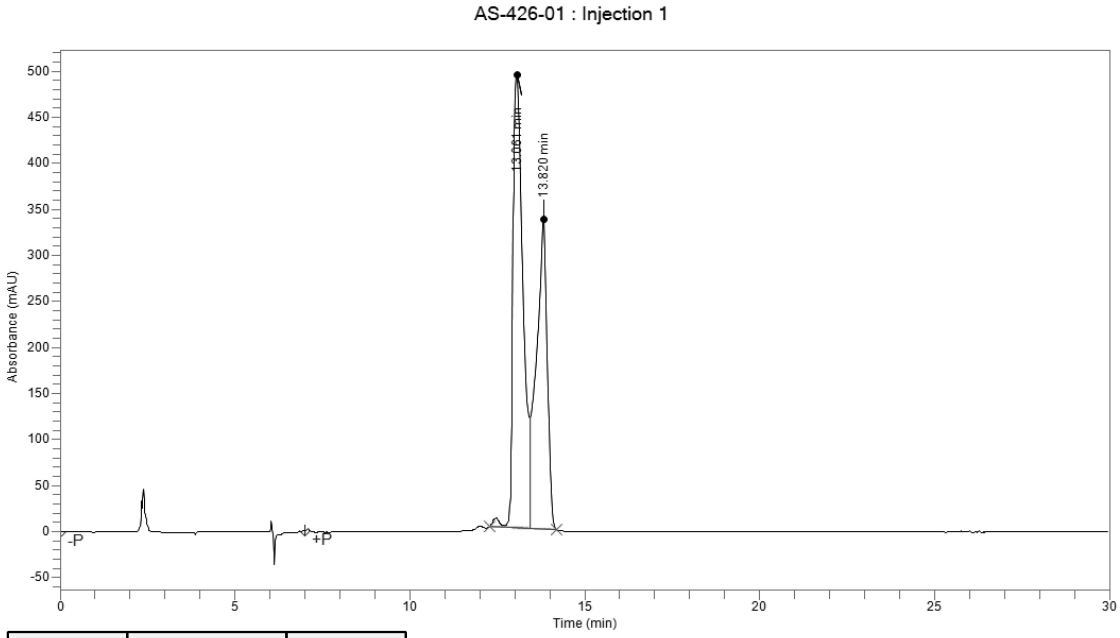
^{31}P NMR of (+)-237



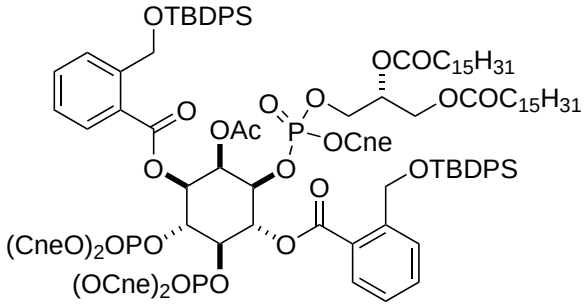
HPLC of (+)-237

AS-426-01

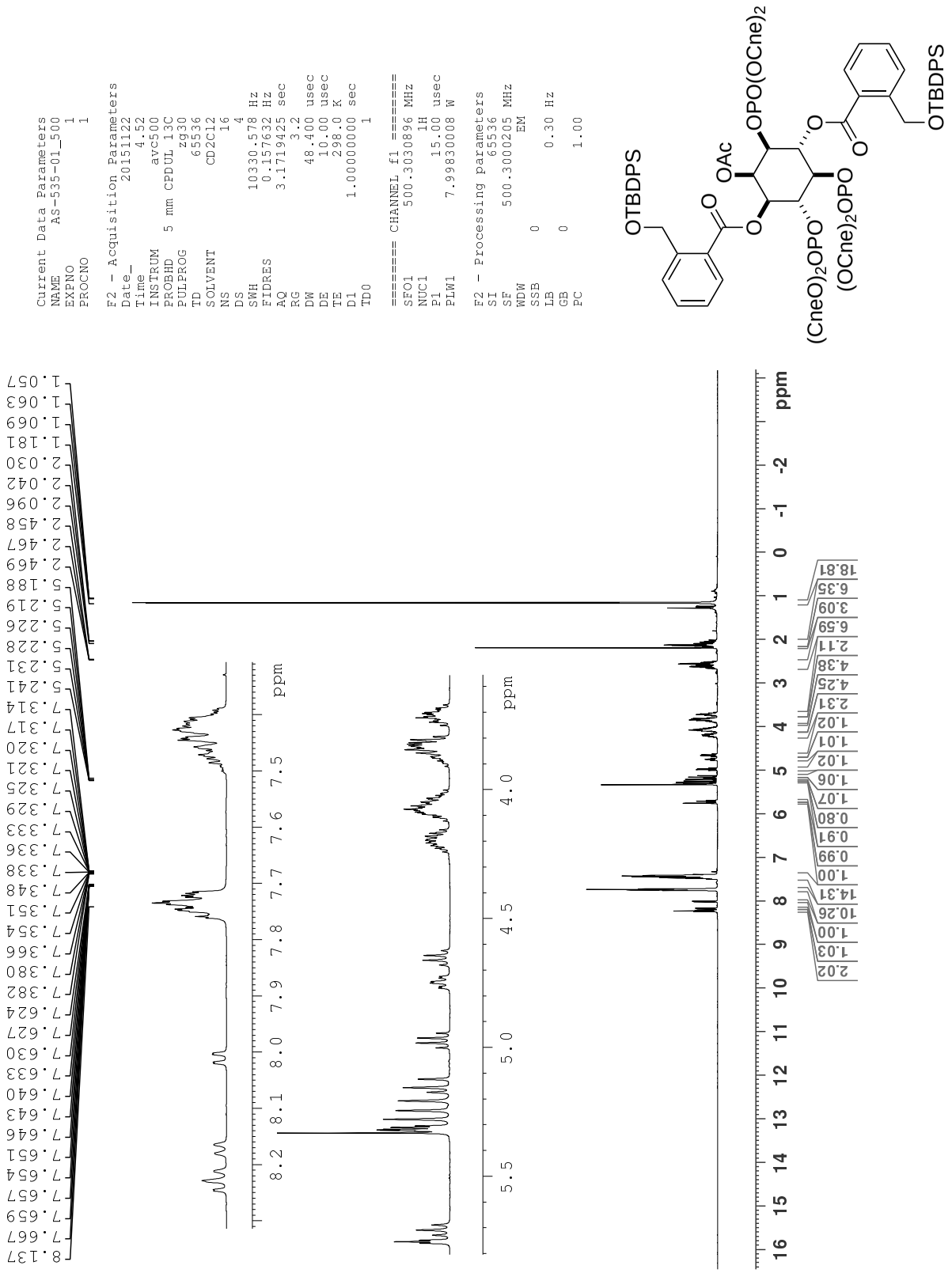
Sample Name	AS-426-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm	Acquisition Date/Time	7/3/2015 3:08 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm - Copy 07-07-2015 12-16-05	Batch Description	Normal Phase silica column



Time	Area	Area %
12.461	128529	0.75
13.061	9791575	56.92
13.820	7281659	42.33
Total	17201764	100.00



^{1}H NMR of (+)-250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PULPROG zg30
TD 65536
SOLVENT CD2C12
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DS 4
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 3.2
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
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NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
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SF 500.3000205 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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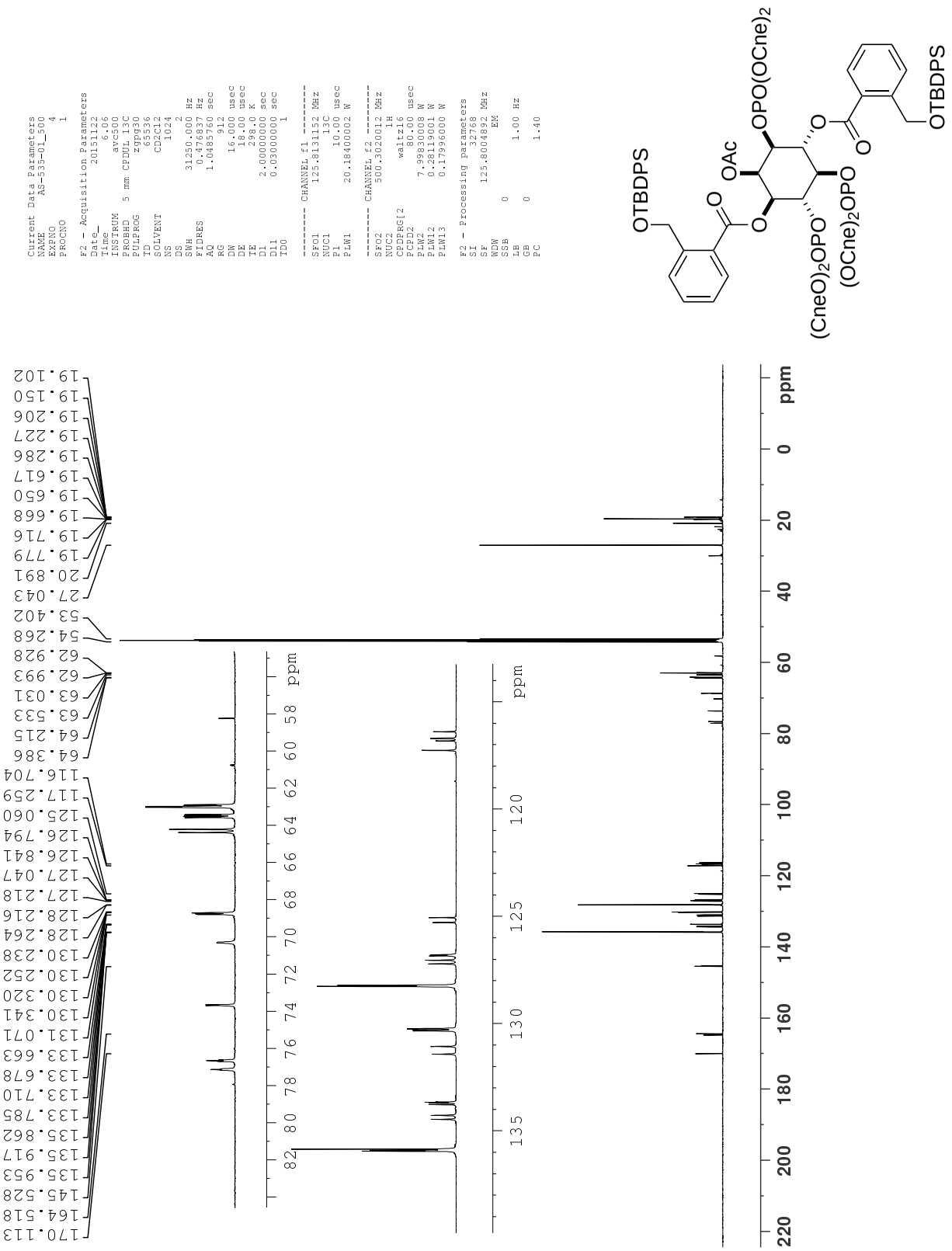
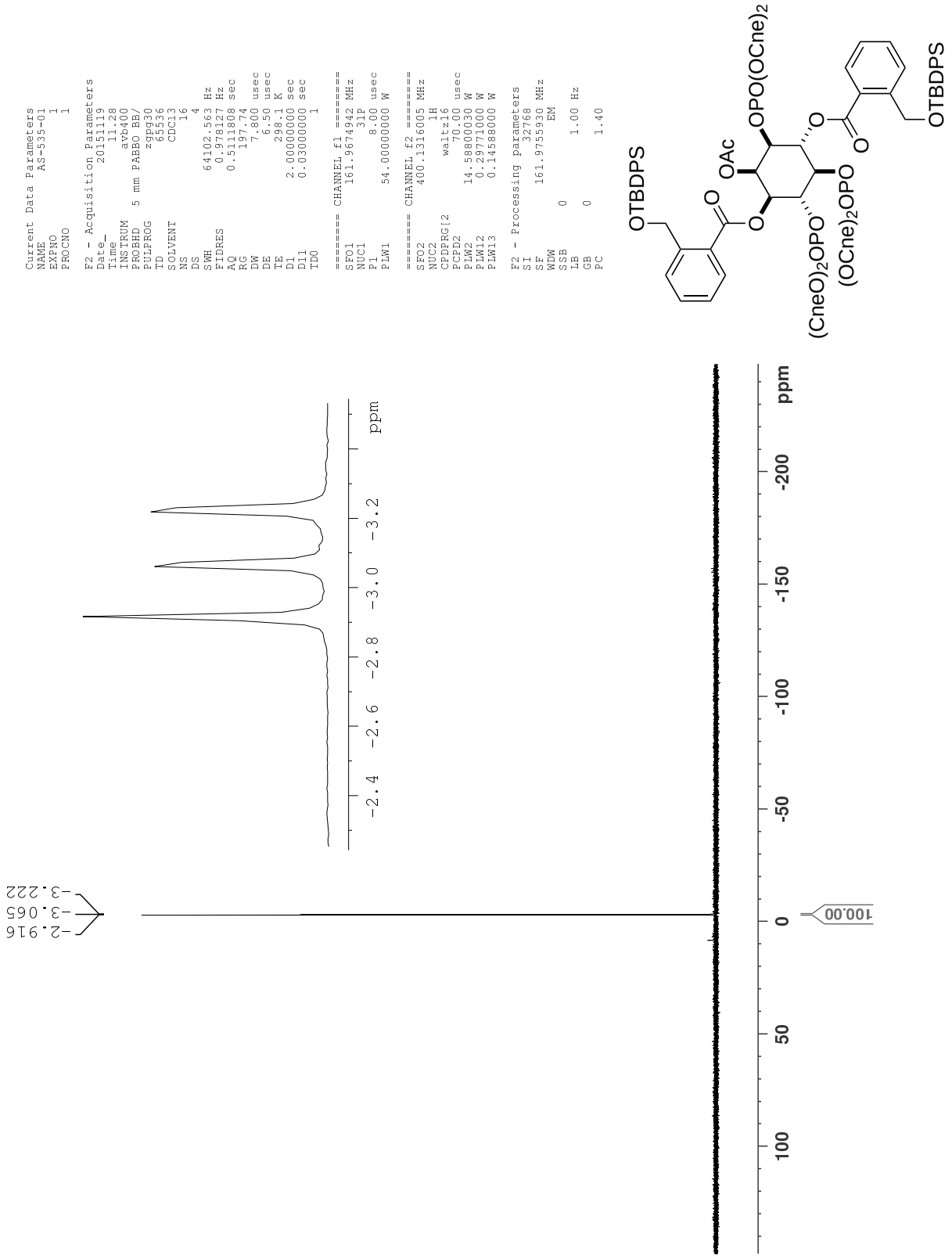
OPO(OCne)2
(CneO)2OPO
(OCne)2OPO
OTBDPS
ppm

^{13}C NMR of (+)-250



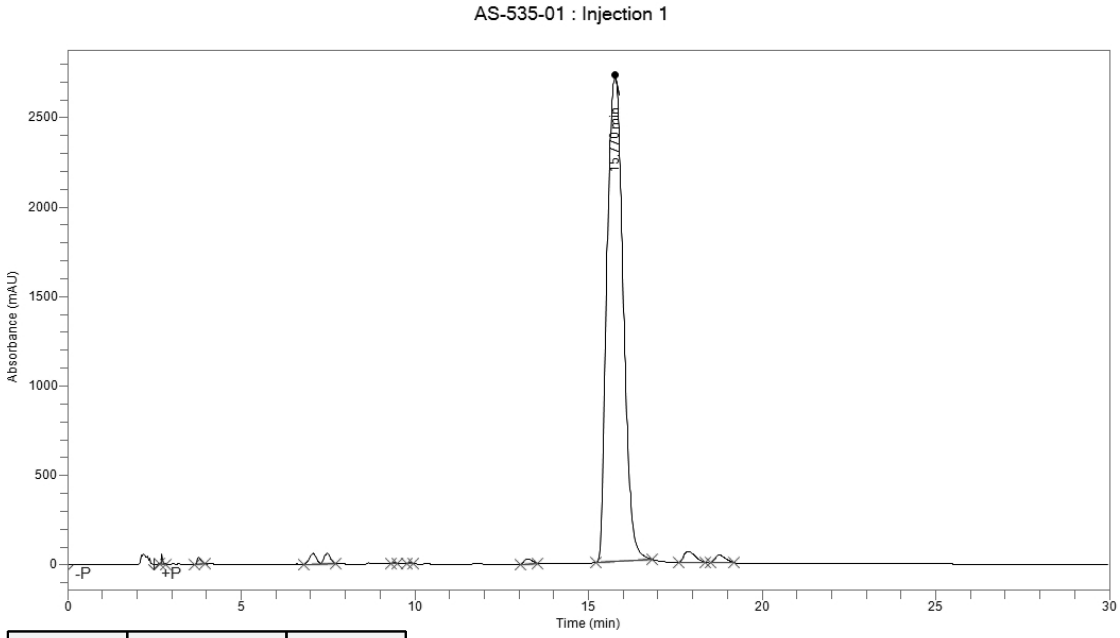
^{31}P NMR of (+)-250



HPLC of (+)-250

AS-535-01

Sample Name	AS-535-01	Sample Description	Normal Phase silica column
Acquisition Method	Normal Phase Purity 254nm 5-95	Acquisition Date/Time	7/16/2016 5:00 pm
Batch Group/Name	Alex/Normal Phase Purity 254nm 5-95	Batch Description	Normal Phase silica column



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7.072	798414	0.85
7.476	720833	0.77
9.399	48490	0.05
9.862	46995	0.05
13.250	380971	0.41
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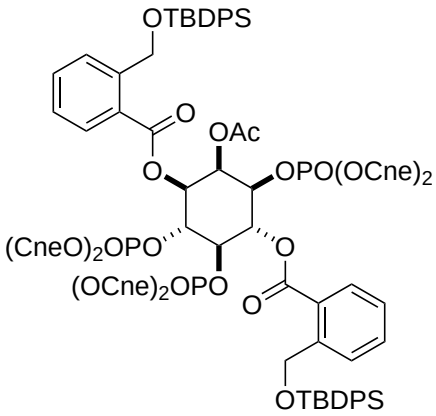
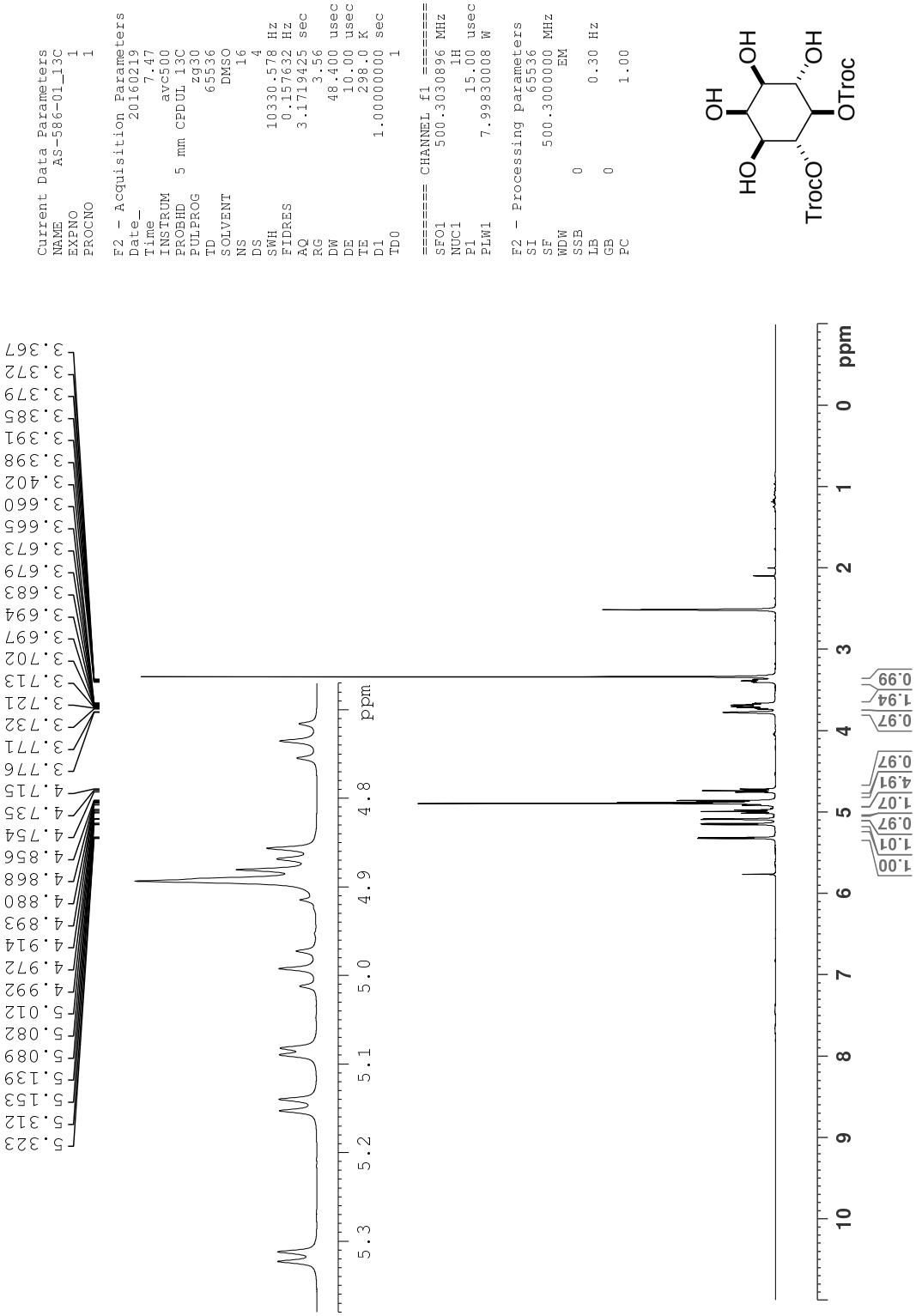
17.884	1402668	1.50
18.764	875610	0.93
Total	93769930	100.00



^{1}H NMR of (+)-231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FIDRES 0.157632 Hz
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RG 3.56
DW 48.400 usec
DE 10.00 usec
TE 298.0 K
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TD0 1
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NUC1 1H
P1 15.00 usec
PLW1 7.99830008 W
F2 - Processing parameters
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SSB 0
LB 0.30 Hz
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PC 1.00
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OH
HO
TrocO
OH
OTroc
ppm
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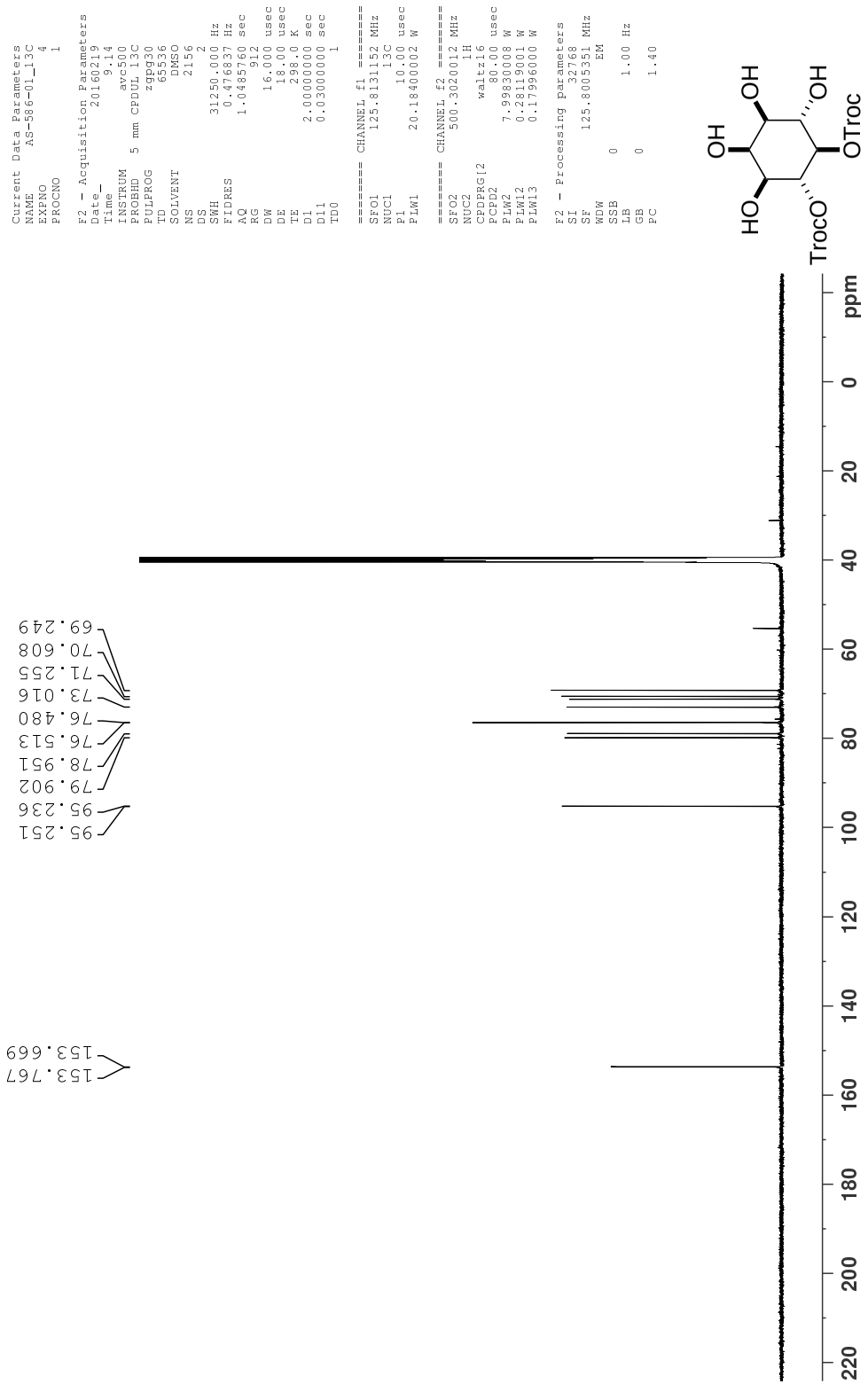
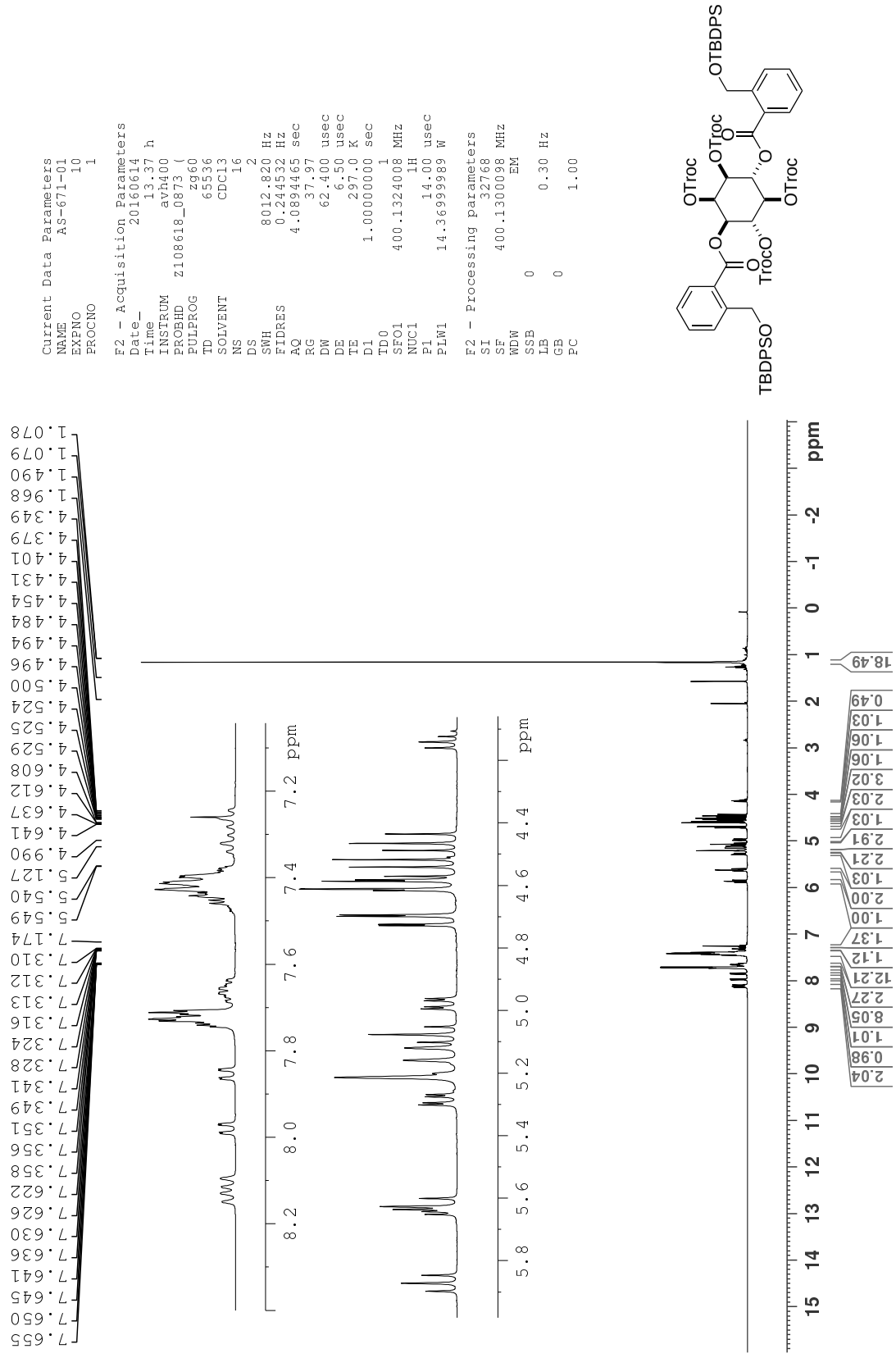
4.91
1.07
0.97
1.01
1.00

^{13}C NMR of (+)-231



^{1}H NMR of (+)-247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OTroc
OTroc
OTroc
TrocO
TBDPSO
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EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
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Time 13.37 h
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PROBHD Z108618_0873 (
PULPROG zg60
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 37.97
DW 62.400 usec
DE 6.50 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324008 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.36999989 W
F2 - Processing parameters
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SSB 0
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GB 0
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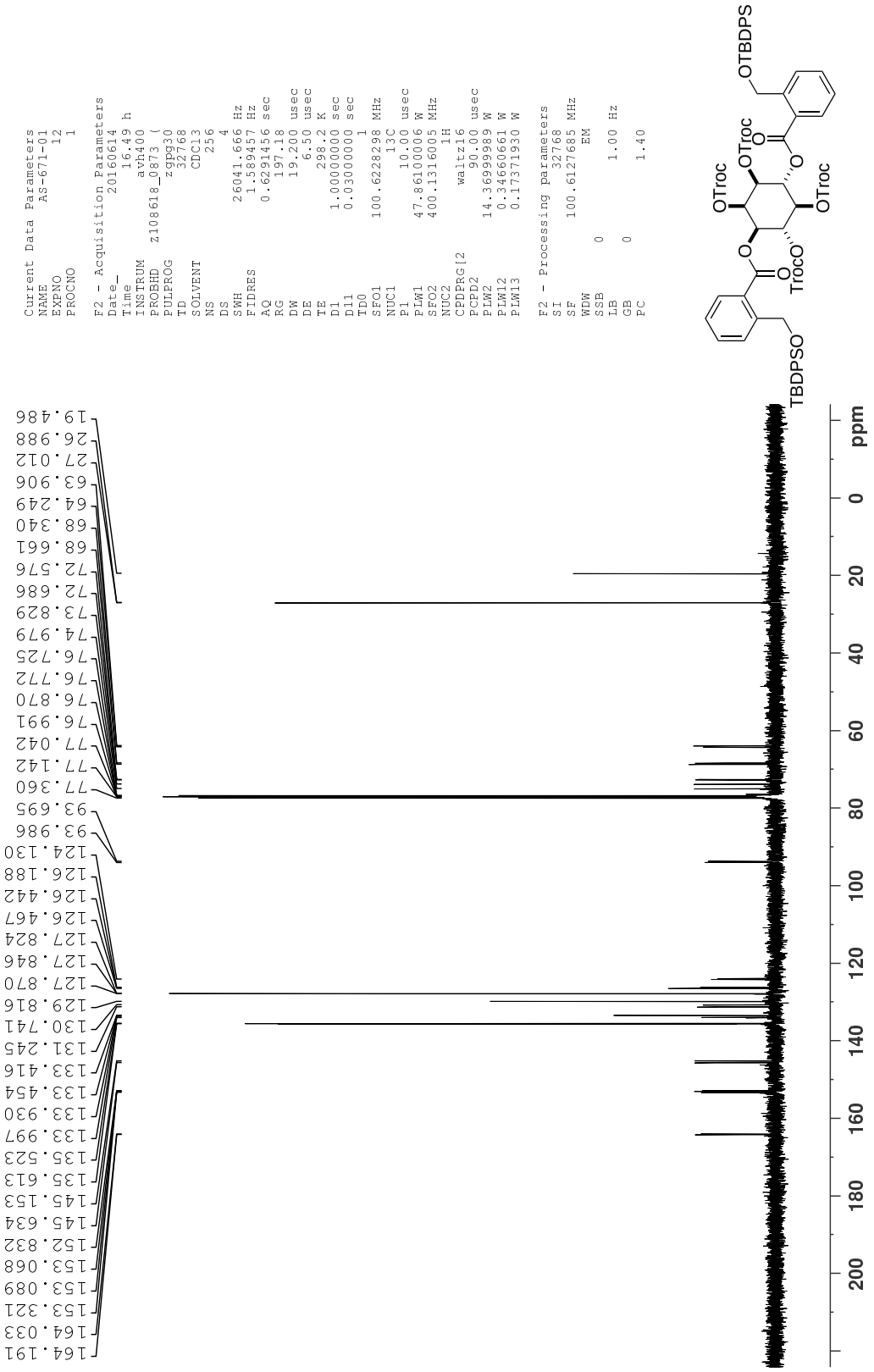
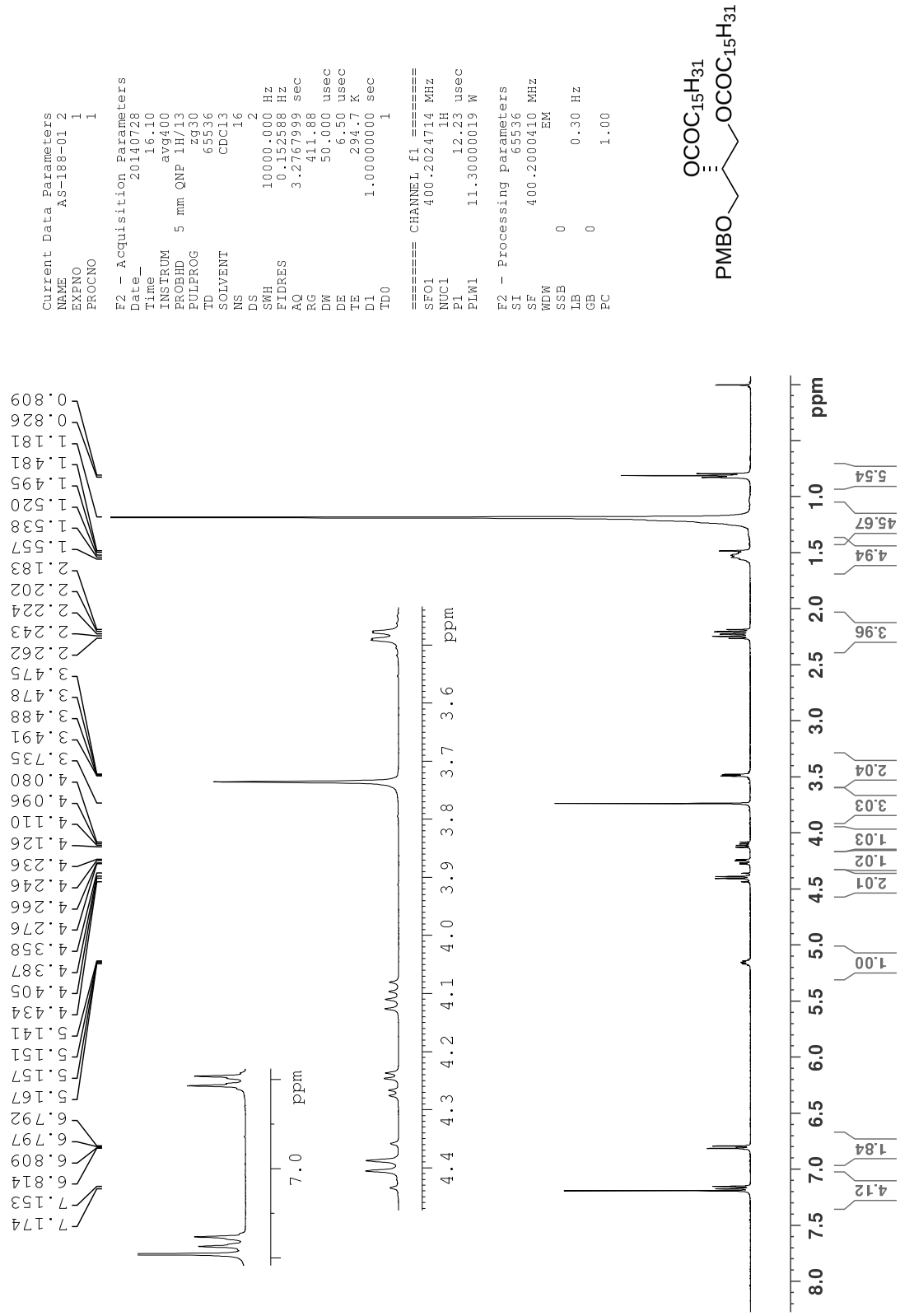
ppm

^{13}C NMR of (+)-247



^{1}H NMR of (+)-146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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
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Time_ 16.10
INSTRUM avg400
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 411.88
DW 50.000 usec
DE 6.50 usec
TE 294.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.2024714 MHz
NUC1 1H
P1 12.23 usec
PLW1 11.30000019 W
F2 - Processing parameters
SI 65536
SF 400.2000410 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OCOC15H31
OCOC15H31
PMBO
7.174
7.153
6.814
6.809
6.797
6.792
5.167
5.157
5.151
5.141
4.434
4.405
4.387
4.358
4.276
4.266
4.246
4.236
4.126
4.110
4.096
4.080
3.735
3.491
3.488
3.478
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2.262
2.243
2.224
2.202
2.183
1.557
1.538
1.520
1.495
1.481
1.181
0.826
0.809
ppm
7.0
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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1.84
1.00
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1.03
3.03
2.04
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45.67
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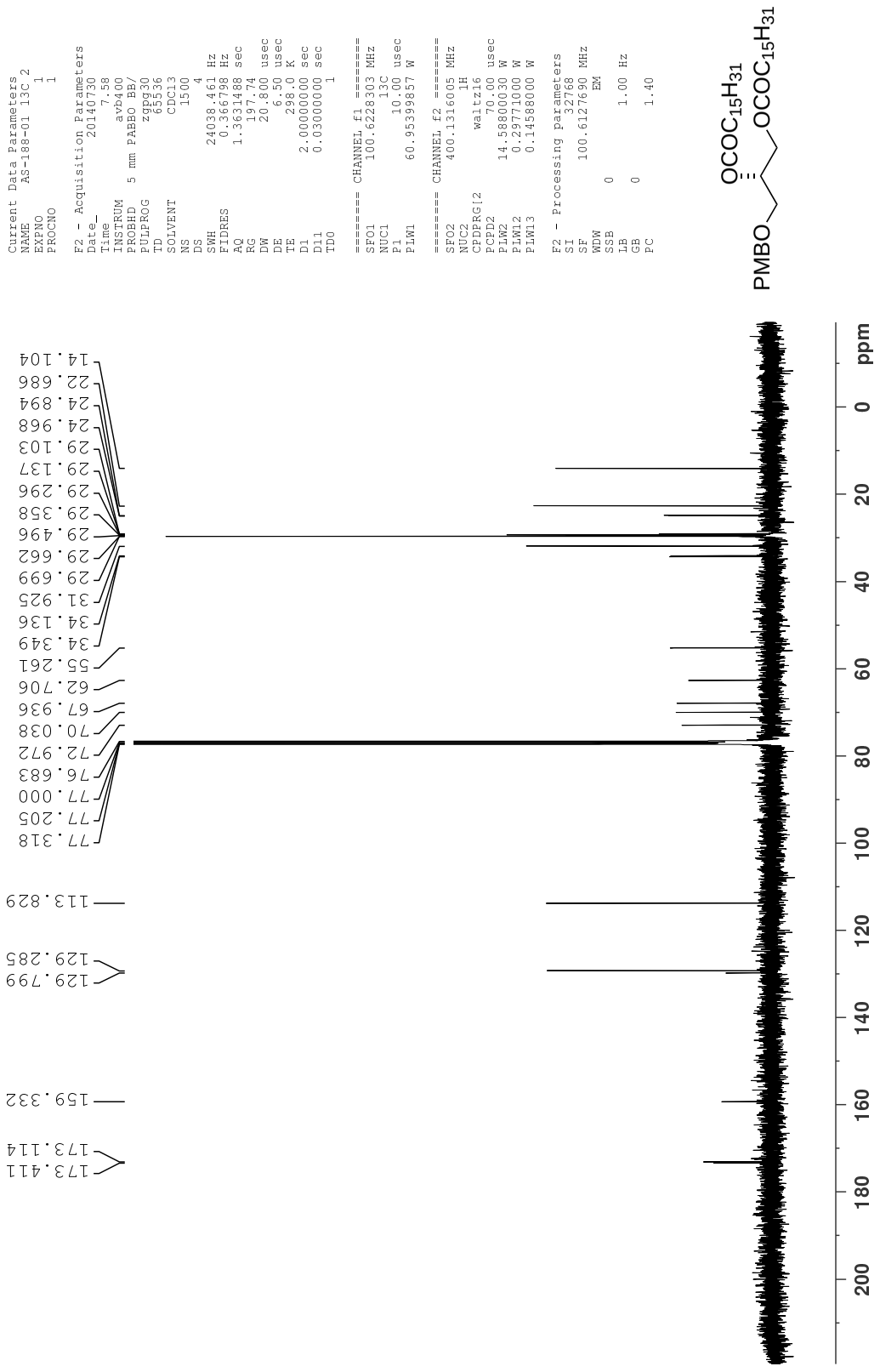
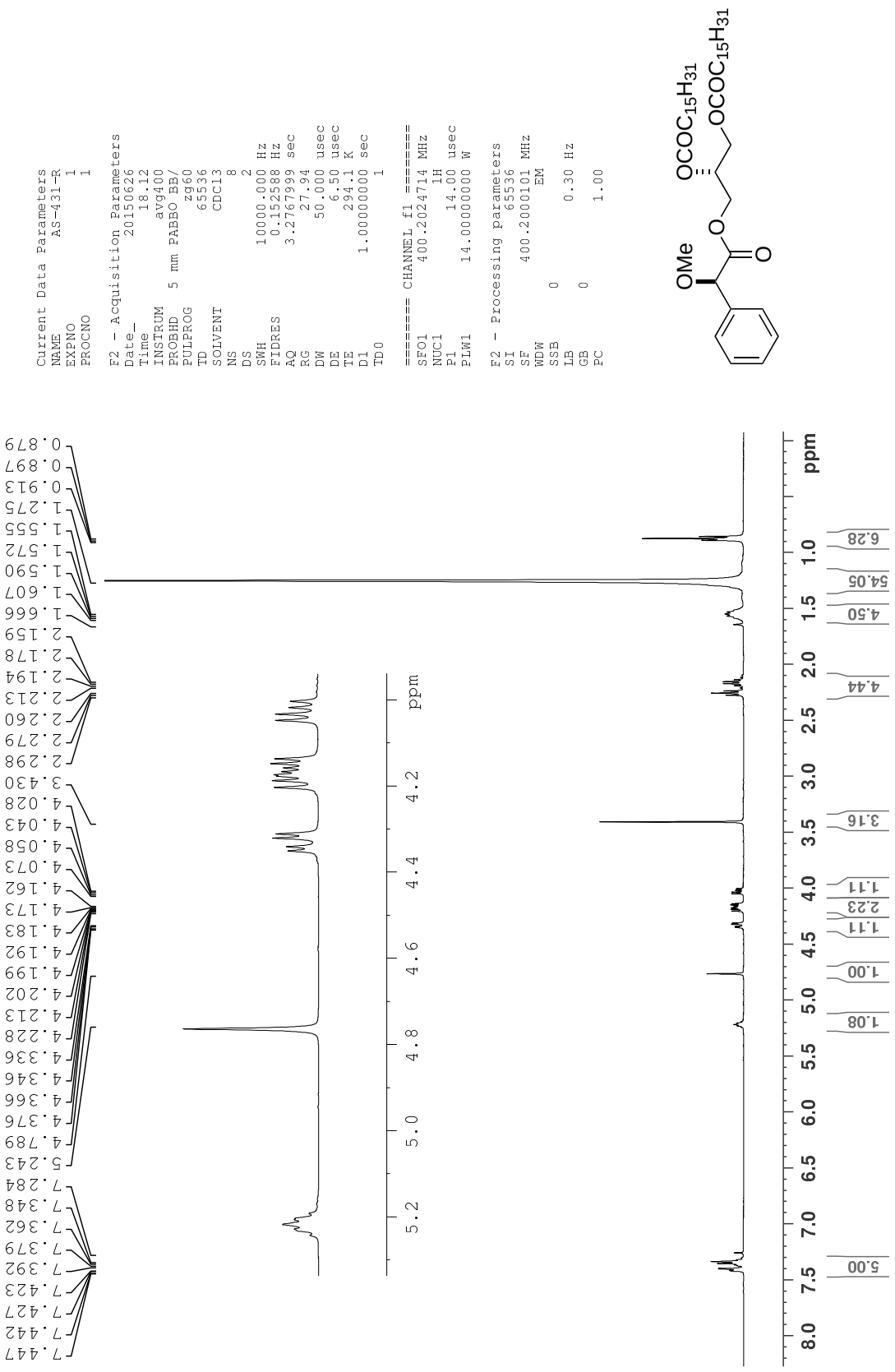
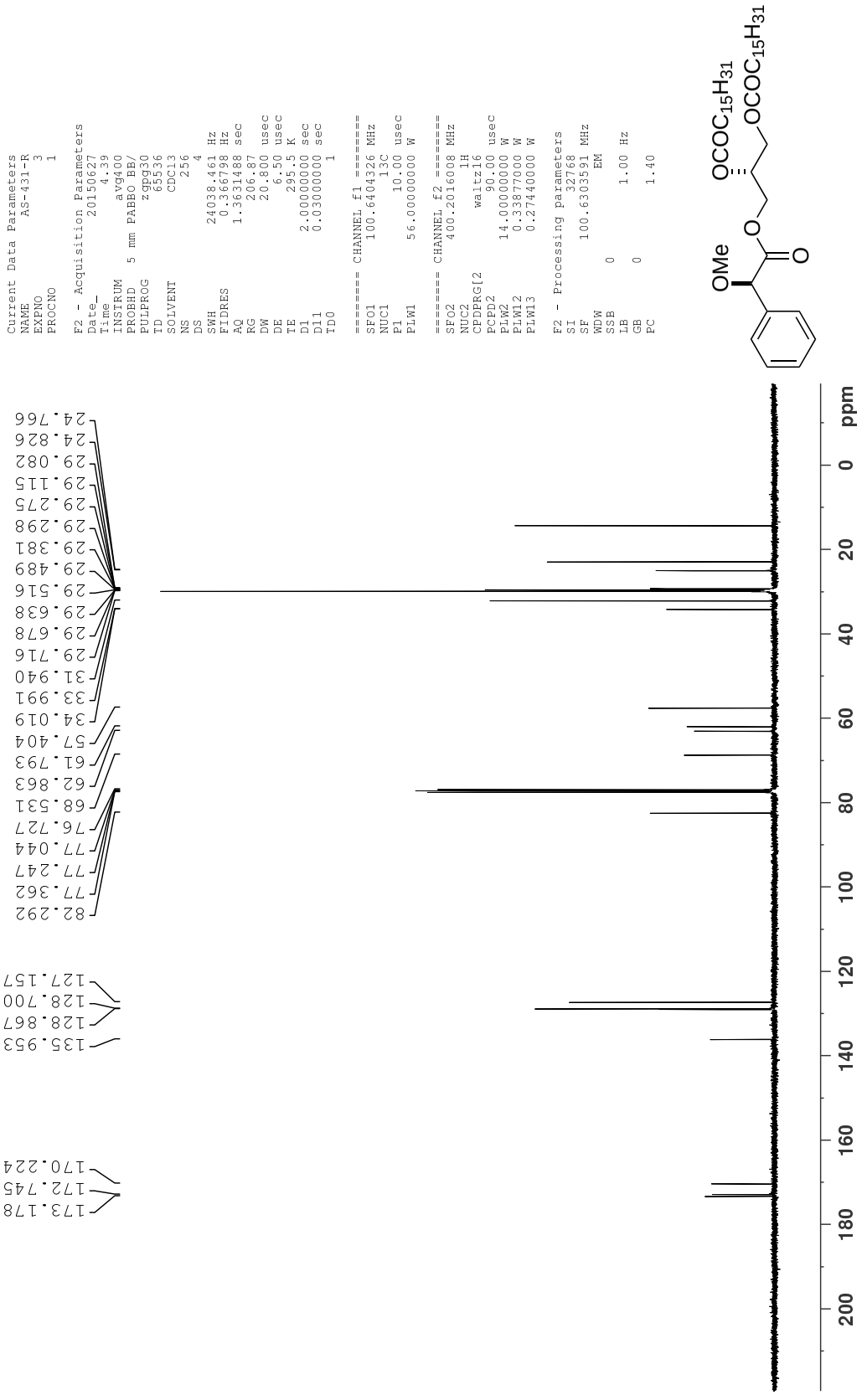
^{13}C NMR of (+)-146



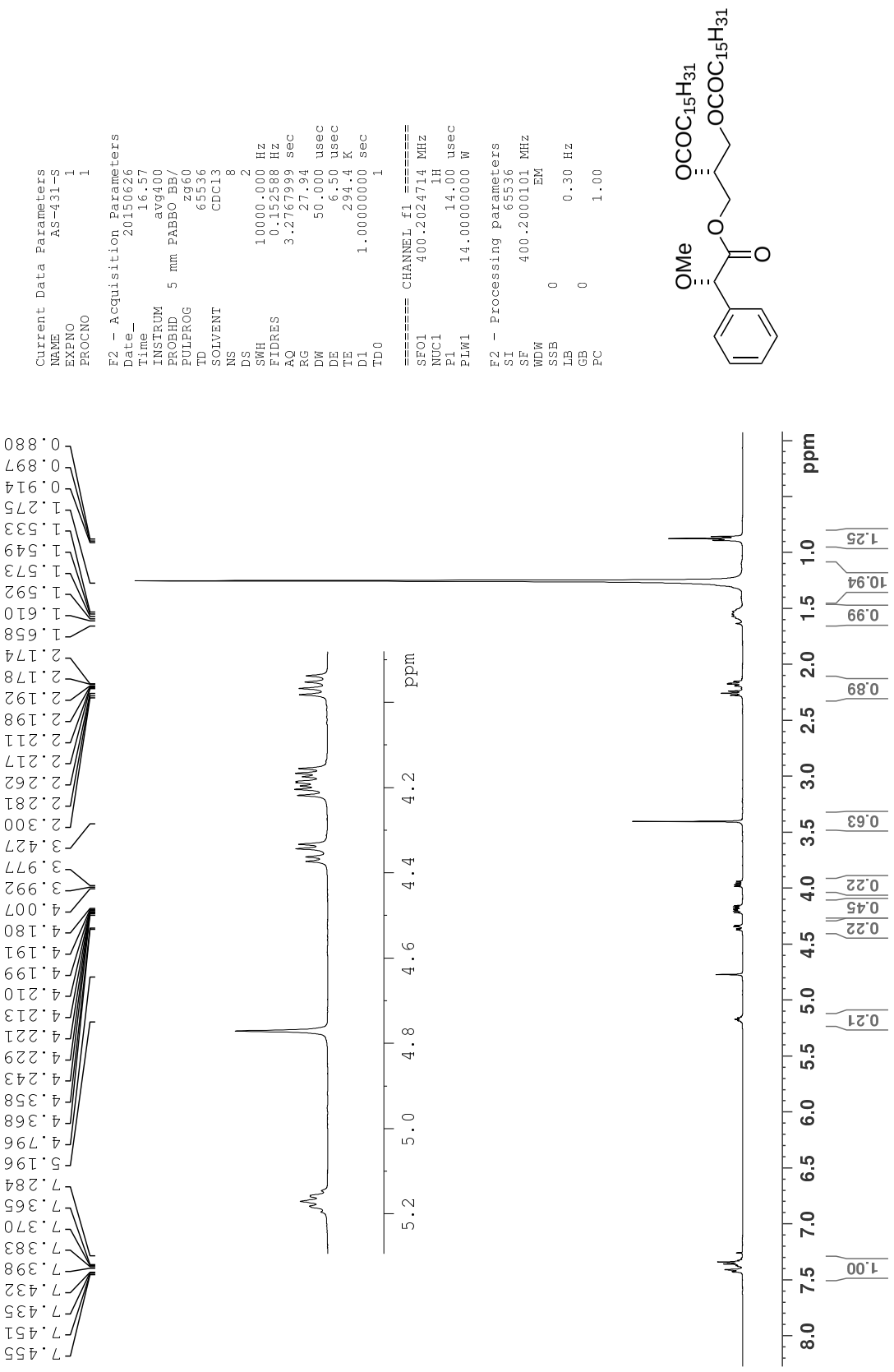
^{1}H NMR of (+)-151a



^{13}C NMR of (+)-151a



^{1}H NMR of (+)-151b



^{13}C NMR of (+)-151b

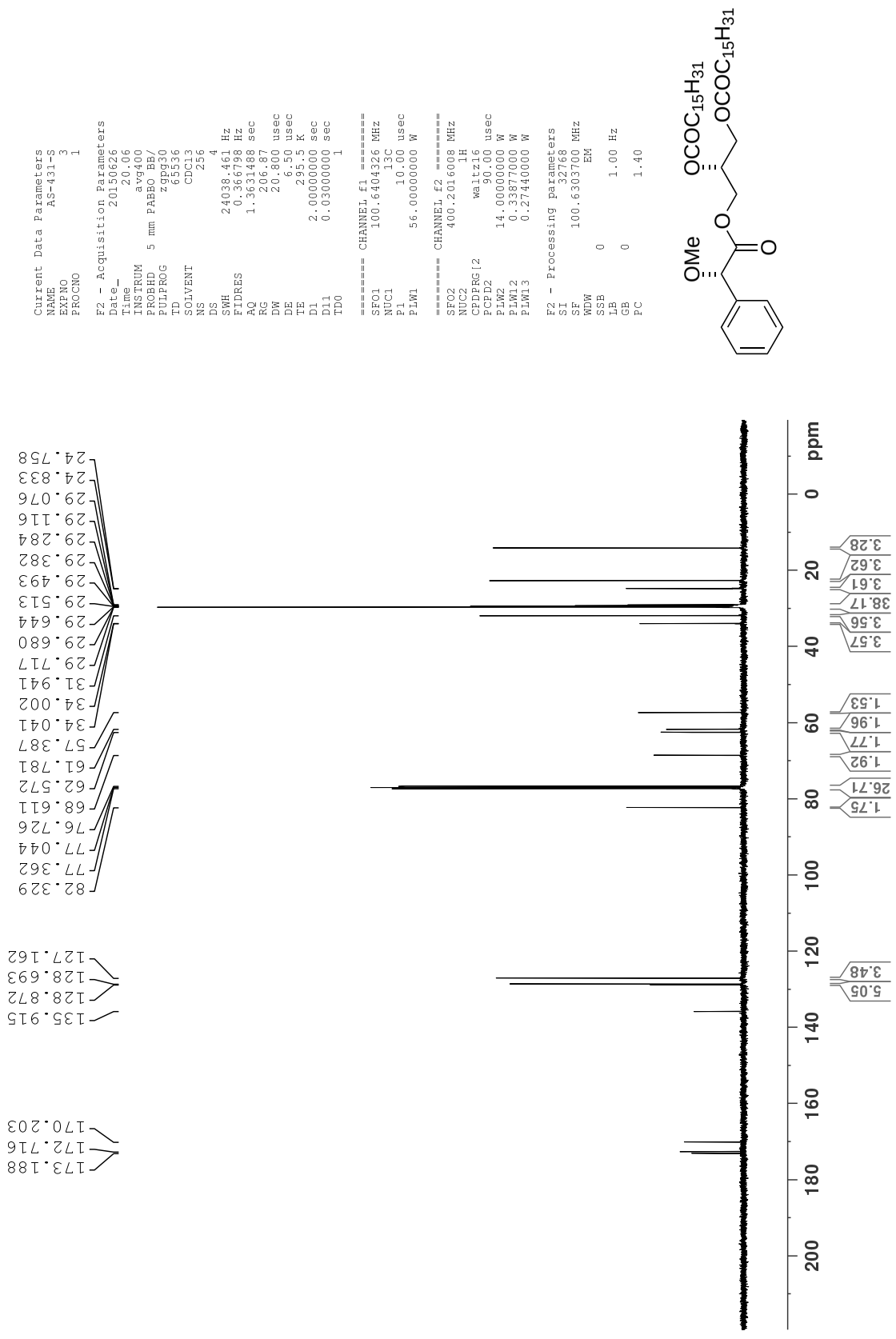


Table 1. Crystal data and structure refinement for 6617.

Identification code	6617	
Empirical formula	C14 H18 O8	
Formula weight	314.29	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.4164(2) Å	α= 90°.
	b = 6.6513(2) Å	β= 96.9535(17)°.
	c = 11.2592(2) Å	γ = 90°.
Volume	774.33(3) $Å^3$	
Z	2	
Density (calculated)	1.348 Mg/m^3	
Absorption coefficient	0.956 mm^{-1}	
F(000)	332	
Crystal size	0.23 x 0.16 x 0.15 mm^3	
Theta range for data collection	3.955 to 76.044°.	
Index ranges	-13<=h<=13, -8<=k<=8, -11<=l<=14	
Reflections collected	8925	
Independent reflections	3187 [R(int) = 0.017]	
Completeness to theta = 74.523°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.87 and 0.73	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2322 / 1 / 200	
Goodness-of-fit on F^2	1.0108	
Final R indices [I>2sigma(I)]	R1 = 0.0229, wR2 = 0.0590	
R indices (all data)	R1 = 0.0230, wR2 = 0.0591	
Absolute structure parameter	0.24(13)	
Largest diff. peak and hole	0.10 and -0.10 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6617. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3953(1)	227(2)	8615(1)	33
C(2)	5204(1)	-160(2)	8843(1)	32
C(3)	6233(1)	1169(2)	8457(1)	29
C(4)	5694(1)	3214(2)	8051(1)	27
C(5)	4422(1)	2988(2)	7244(1)	27
C(6)	3409(1)	2026(2)	7929(1)	30
O(7)	7194(1)	1443(2)	9493(1)	32
C(8)	8452(1)	1528(2)	9311(1)	35
O(9)	8821(1)	1324(2)	8349(1)	45
C(10)	9285(2)	1950(3)	10456(1)	48
O(11)	6575(1)	4210(2)	7350(1)	29
C(12)	7346(1)	5670(2)	7879(1)	29
O(13)	7341(1)	6174(2)	8903(1)	38
C(14)	8200(1)	6503(2)	7028(1)	35
O(15)	4012(1)	4978(2)	6881(1)	31
C(16)	3695(1)	5359(2)	5707(1)	32
O(17)	3767(1)	4129(2)	4941(1)	57
C(18)	3266(2)	7465(2)	5521(1)	43
O(19)	2339(1)	1276(2)	7098(1)	33
C(20)	1298(1)	2466(2)	6801(1)	35
O(21)	1223(1)	4163(2)	7136(1)	50
C(22)	286(1)	1377(3)	5996(1)	42

Table 3. Bond lengths [Å] and angles [°] for 6617.

C(1)-C(2)	1.323(2)	O(19)-C(20)	1.3516(18)
C(1)-C(6)	1.497(2)	C(20)-O(21)	1.195(2)
C(1)-H(11)	0.925	C(20)-C(22)	1.492(2)
C(2)-C(3)	1.4940(19)	C(22)-H(221)	0.947
C(2)-H(21)	0.956	C(22)-H(222)	0.930
C(3)-C(4)	1.5207(19)	C(22)-H(223)	0.940
C(3)-O(7)	1.4536(15)		
C(3)-H(31)	0.943	C(2)-C(1)-C(6)	123.91(13)
C(4)-C(5)	1.5215(18)	C(2)-C(1)-H(11)	120.2
C(4)-O(11)	1.4419(15)	C(6)-C(1)-H(11)	115.9
C(4)-H(41)	0.952	C(1)-C(2)-C(3)	123.62(13)
C(5)-C(6)	1.5222(18)	C(1)-C(2)-H(21)	119.5
C(5)-O(15)	1.4343(17)	C(3)-C(2)-H(21)	116.8
C(5)-H(51)	0.973	C(2)-C(3)-C(4)	111.37(11)
C(6)-O(19)	1.4538(16)	C(2)-C(3)-O(7)	106.85(10)
C(6)-H(61)	0.960	C(4)-C(3)-O(7)	108.80(11)
O(7)-C(8)	1.3521(16)	C(2)-C(3)-H(31)	111.1
C(8)-O(9)	1.1996(17)	C(4)-C(3)-H(31)	107.4
C(8)-C(10)	1.490(2)	O(7)-C(3)-H(31)	111.4
C(10)-H(101)	0.940	C(3)-C(4)-C(5)	110.78(10)
C(10)-H(102)	0.945	C(3)-C(4)-O(11)	109.83(10)
C(10)-H(103)	0.961	C(5)-C(4)-O(11)	106.48(10)
O(11)-C(12)	1.3520(16)	C(3)-C(4)-H(41)	111.0
C(12)-O(13)	1.2014(16)	C(5)-C(4)-H(41)	110.4
C(12)-C(14)	1.4914(19)	O(11)-C(4)-H(41)	108.2
C(14)-H(141)	0.970	C(4)-C(5)-C(6)	110.21(10)
C(14)-H(142)	0.959	C(4)-C(5)-O(15)	106.69(10)
C(14)-H(143)	0.962	C(6)-C(5)-O(15)	109.38(10)
O(15)-C(16)	1.3470(17)	C(4)-C(5)-H(51)	110.9
C(16)-O(17)	1.1972(18)	C(6)-C(5)-H(51)	109.3
C(16)-C(18)	1.478(2)	O(15)-C(5)-H(51)	110.3
C(18)-H(181)	0.972	C(5)-C(6)-C(1)	110.81(11)
C(18)-H(182)	0.951	C(5)-C(6)-O(19)	109.98(10)
C(18)-H(183)	0.974	C(1)-C(6)-O(19)	105.67(11)

C(5)-C(6)-H(61)	109.7	H(142)-C(14)-H(143)	110.6
C(1)-C(6)-H(61)	111.8	C(5)-O(15)-C(16)	118.82(10)
O(19)-C(6)-H(61)	108.8	O(15)-C(16)-O(17)	123.32(13)
C(3)-O(7)-C(8)	117.99(10)	O(15)-C(16)-C(18)	110.54(12)
O(7)-C(8)-O(9)	123.66(13)	O(17)-C(16)-C(18)	126.14(14)
O(7)-C(8)-C(10)	110.51(12)	C(16)-C(18)-H(181)	110.0
O(9)-C(8)-C(10)	125.82(13)	C(16)-C(18)-H(182)	106.9
C(8)-C(10)-H(101)	111.5	H(181)-C(18)-H(182)	108.7
C(8)-C(10)-H(102)	108.5	C(16)-C(18)-H(183)	108.9
H(101)-C(10)-H(102)	110.6	H(181)-C(18)-H(183)	110.7
C(8)-C(10)-H(103)	109.9	H(182)-C(18)-H(183)	111.5
H(101)-C(10)-H(103)	108.9	C(6)-O(19)-C(20)	119.17(11)
H(102)-C(10)-H(103)	107.4	O(19)-C(20)-O(21)	123.82(13)
C(4)-O(11)-C(12)	118.17(9)	O(19)-C(20)-C(22)	110.65(13)
O(11)-C(12)-O(13)	123.52(12)	O(21)-C(20)-C(22)	125.53(14)
O(11)-C(12)-C(14)	110.66(11)	C(20)-C(22)-H(221)	107.7
O(13)-C(12)-C(14)	125.81(12)	C(20)-C(22)-H(222)	108.0
C(12)-C(14)-H(141)	108.8	H(221)-C(22)-H(222)	110.7
C(12)-C(14)-H(142)	105.4	C(20)-C(22)-H(223)	108.4
H(141)-C(14)-H(142)	108.7	H(221)-C(22)-H(223)	109.6
C(12)-C(14)-H(143)	109.9	H(222)-C(22)-H(223)	112.2
H(141)-C(14)-H(143)	113.1		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6617. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	31(1)	37(1)	32(1)	4(1)	6(1)	-5(1)
C(2)	36(1)	32(1)	29(1)	4(1)	6(1)	0(1)
C(3)	28(1)	33(1)	25(1)	-1(1)	4(1)	3(1)
C(4)	28(1)	30(1)	24(1)	-1(1)	6(1)	-2(1)
C(5)	29(1)	26(1)	26(1)	-2(1)	2(1)	3(1)
C(6)	25(1)	35(1)	30(1)	-5(1)	2(1)	0(1)
O(7)	26(1)	40(1)	28(1)	1(1)	1(1)	4(1)
C(8)	29(1)	33(1)	42(1)	6(1)	4(1)	2(1)
O(9)	32(1)	61(1)	44(1)	1(1)	11(1)	0(1)
C(10)	33(1)	60(1)	48(1)	5(1)	-6(1)	-2(1)
O(11)	31(1)	32(1)	25(1)	-1(1)	6(1)	-4(1)
C(12)	24(1)	28(1)	33(1)	0(1)	0(1)	4(1)
O(13)	35(1)	45(1)	35(1)	-10(1)	5(1)	-9(1)
C(14)	31(1)	36(1)	40(1)	3(1)	5(1)	-1(1)
O(15)	36(1)	29(1)	27(1)	0(1)	2(1)	4(1)
C(16)	28(1)	38(1)	29(1)	-1(1)	-3(1)	0(1)
O(17)	83(1)	51(1)	32(1)	-9(1)	-14(1)	16(1)
C(18)	47(1)	43(1)	39(1)	8(1)	1(1)	5(1)
O(19)	25(1)	35(1)	38(1)	-5(1)	1(1)	0(1)
C(20)	27(1)	41(1)	36(1)	0(1)	6(1)	2(1)
O(21)	35(1)	46(1)	67(1)	-11(1)	-2(1)	9(1)
C(22)	31(1)	55(1)	39(1)	-4(1)	1(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 6617.

	x	y	z	U(eq)
H(11)	3355	-631	8889	40
H(21)	5483	-1367	9257	39
H(31)	6602	597	7811	34
H(41)	5583	4045	8719	28
H(51)	4532	2169	6548	30
H(61)	3083	3007	8443	33
H(101)	10168	1889	10358	70
H(102)	9086	1009	11035	73
H(103)	9094	3263	10743	73
H(141)	8527	7798	7323	53
H(142)	8911	5582	7050	53
H(143)	7737	6568	6236	53
H(181)	2989	7703	4677	62
H(182)	3995	8294	5766	66
H(183)	2562	7723	5996	64
H(221)	-532	1790	6196	66
H(222)	405	6	6126	66
H(223)	364	1743	5202	66

Table 6. Hydrogen bonds for 6617 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(10)-H(102)...O(21)#1	0.945	2.452	3.379(2)	166.75
C(14)-H(142)...O(21)#2	0.959	2.577	3.501(2)	161.77
C(14)-H(143)...O(17)#3	0.962	2.571	3.326(2)	135.52
C(18)-H(181)...O(11)#3	0.972	2.582	3.458(2)	149.77

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

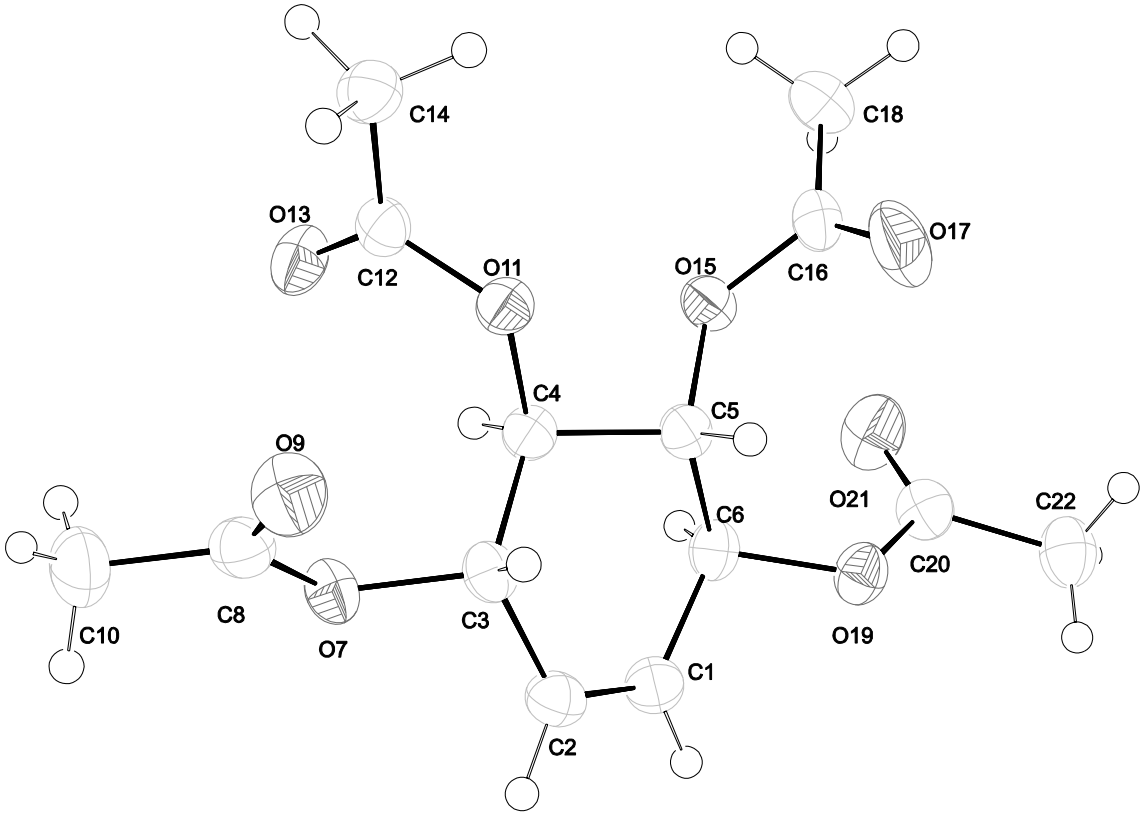


Table 1. Crystal data and structure refinement for 6614.

Identification code	6614	
Empirical formula	C14 H18 O8	
Formula weight	314.29	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.4422(4) Å	α= 90°.
	b = 6.6743(4) Å	β= 97.050(3)°.
	c = 11.2392(3) Å	γ = 90°.
Volume	777.39(6) $Å^3$	
Z	2	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.953 mm^{-1}	
F(000)	332	
Crystal size	0.25 x 0.10 x 0.01 mm^3	
Theta range for data collection	3.963 to 76.396°.	
Index ranges	-13<=h<=13, -7<=k<=8, -13<=l<=14	
Reflections collected	15703	
Independent reflections	2977 [R(int) = 0.046]	
Completeness to theta = 74.868°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.53	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2962 / 1 / 200	
Goodness-of-fit on F^2	1.0030	
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.1143	
R indices (all data)	R1 = 0.0441, wR2 = 0.1182	
Absolute structure parameter	0.3(2)	
Largest diff. peak and hole	0.16 and -0.21 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6614. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6044(2)	9776(4)	1385(2)	37
C(2)	4791(2)	10149(3)	1156(2)	37
C(3)	3769(2)	8819(3)	1547(2)	33
C(4)	4307(2)	6785(3)	1949(2)	31
C(5)	5581(2)	7002(3)	2759(2)	31
C(6)	6592(2)	7980(3)	2072(2)	34
O(7)	2807(1)	8551(3)	508(1)	36
C(8)	1549(2)	8472(4)	692(2)	39
O(9)	1184(1)	8684(3)	1655(1)	51
C(10)	715(2)	8043(5)	-458(2)	53
O(11)	3431(1)	5791(2)	2653(1)	33
C(12)	2665(2)	4337(3)	2124(2)	33
O(13)	2666(1)	3821(3)	1098(1)	43
C(14)	1809(2)	3505(4)	2976(2)	39
O(15)	5996(1)	5032(2)	3116(1)	35
C(16)	6303(2)	4643(4)	4297(2)	36
O(17)	6220(2)	5856(3)	5065(1)	63
C(18)	6741(2)	2545(4)	4479(2)	48
O(19)	7659(1)	8719(3)	2908(1)	38
C(20)	8699(2)	7539(4)	3190(2)	40
O(21)	8777(2)	5851(3)	2857(2)	58
C(22)	9714(2)	8637(5)	4005(2)	47

Table 3. Bond lengths [Å] and angles [°] for 6614.

C(1)-C(2)	1.326(3)	O(19)-C(20)	1.347(3)
C(1)-C(6)	1.501(3)	C(20)-O(21)	1.193(3)
C(1)-H(11)	0.942	C(20)-C(22)	1.504(3)
C(2)-C(3)	1.495(3)	C(22)-H(221)	0.951
C(2)-H(21)	0.944	C(22)-H(222)	0.957
C(3)-C(4)	1.517(3)	C(22)-H(223)	0.949
C(3)-O(7)	1.454(2)		
C(3)-H(31)	0.971	C(2)-C(1)-C(6)	123.69(19)
C(4)-C(5)	1.524(2)	C(2)-C(1)-H(11)	119.7
C(4)-O(11)	1.442(2)	C(6)-C(1)-H(11)	116.6
C(4)-H(41)	0.967	C(1)-C(2)-C(3)	123.7(2)
C(5)-C(6)	1.528(2)	C(1)-C(2)-H(21)	118.6
C(5)-O(15)	1.427(3)	C(3)-C(2)-H(21)	117.7
C(5)-H(51)	0.978	C(2)-C(3)-C(4)	111.55(15)
C(6)-O(19)	1.453(2)	C(2)-C(3)-O(7)	106.53(14)
C(6)-H(61)	0.980	C(4)-C(3)-O(7)	108.85(17)
O(7)-C(8)	1.356(2)	C(2)-C(3)-H(31)	110.0
C(8)-O(9)	1.199(3)	C(4)-C(3)-H(31)	110.2
C(8)-C(10)	1.495(3)	O(7)-C(3)-H(31)	109.6
C(10)-H(101)	0.945	C(3)-C(4)-C(5)	110.92(16)
C(10)-H(102)	0.958	C(3)-C(4)-O(11)	109.80(15)
C(10)-H(103)	0.960	C(5)-C(4)-O(11)	106.41(14)
O(11)-C(12)	1.348(2)	C(3)-C(4)-H(41)	110.8
C(12)-O(13)	1.204(2)	C(5)-C(4)-H(41)	109.4
C(12)-C(14)	1.495(2)	O(11)-C(4)-H(41)	109.4
C(14)-H(141)	0.968	C(4)-C(5)-C(6)	110.23(14)
C(14)-H(142)	0.954	C(4)-C(5)-O(15)	107.04(16)
C(14)-H(143)	0.957	C(6)-C(5)-O(15)	109.33(15)
O(15)-C(16)	1.352(2)	C(4)-C(5)-H(51)	110.8
C(16)-O(17)	1.194(3)	C(6)-C(5)-H(51)	108.3
C(16)-C(18)	1.479(4)	O(15)-C(5)-H(51)	111.1
C(18)-H(181)	0.967	C(5)-C(6)-C(1)	110.95(15)
C(18)-H(182)	0.968	C(5)-C(6)-O(19)	109.95(14)
C(18)-H(183)	0.956	C(1)-C(6)-O(19)	106.00(17)

C(5)-C(6)-H(61)	109.4	H(142)-C(14)-H(143)	111.4
C(1)-C(6)-H(61)	112.6	C(5)-O(15)-C(16)	118.74(15)
O(19)-C(6)-H(61)	107.9	O(15)-C(16)-O(17)	123.4(2)
C(3)-O(7)-C(8)	117.93(14)	O(15)-C(16)-C(18)	110.50(18)
O(7)-C(8)-O(9)	123.68(19)	O(17)-C(16)-C(18)	126.1(2)
O(7)-C(8)-C(10)	110.38(17)	C(16)-C(18)-H(181)	109.6
O(9)-C(8)-C(10)	125.92(19)	C(16)-C(18)-H(182)	109.8
C(8)-C(10)-H(101)	110.7	H(181)-C(18)-H(182)	110.9
C(8)-C(10)-H(102)	108.8	C(16)-C(18)-H(183)	107.8
H(101)-C(10)-H(102)	109.8	H(181)-C(18)-H(183)	108.3
C(8)-C(10)-H(103)	110.5	H(182)-C(18)-H(183)	110.4
H(101)-C(10)-H(103)	109.3	C(6)-O(19)-C(20)	119.09(17)
H(102)-C(10)-H(103)	107.8	O(19)-C(20)-O(21)	124.2(2)
C(4)-O(11)-C(12)	118.13(14)	O(19)-C(20)-C(22)	110.2(2)
O(11)-C(12)-O(13)	123.90(17)	O(21)-C(20)-C(22)	125.5(2)
O(11)-C(12)-C(14)	110.74(16)	C(20)-C(22)-H(221)	109.1
O(13)-C(12)-C(14)	125.34(19)	C(20)-C(22)-H(222)	109.4
C(12)-C(14)-H(141)	108.7	H(221)-C(22)-H(222)	111.3
C(12)-C(14)-H(142)	110.2	C(20)-C(22)-H(223)	107.7
H(141)-C(14)-H(142)	111.0	H(221)-C(22)-H(223)	109.4
C(12)-C(14)-H(143)	107.4	H(222)-C(22)-H(223)	109.9
H(141)-C(14)-H(143)	108.0		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6614. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	37(1)	41(1)	35(1)	2(1)	6(1)	-5(1)
C(2)	42(1)	39(1)	30(1)	4(1)	5(1)	0(1)
C(3)	33(1)	40(1)	26(1)	1(1)	4(1)	3(1)
C(4)	32(1)	38(1)	24(1)	-1(1)	5(1)	0(1)
C(5)	33(1)	33(1)	26(1)	-2(1)	2(1)	1(1)
C(6)	33(1)	38(1)	31(1)	-2(1)	4(1)	1(1)
O(7)	33(1)	47(1)	28(1)	2(1)	3(1)	6(1)
C(8)	35(1)	41(1)	42(1)	7(1)	3(1)	1(1)
O(9)	38(1)	69(1)	47(1)	2(1)	12(1)	-1(1)
C(10)	39(1)	66(2)	50(1)	5(1)	-6(1)	0(1)
O(11)	37(1)	37(1)	25(1)	-1(1)	7(1)	-3(1)
C(12)	28(1)	36(1)	34(1)	2(1)	2(1)	4(1)
O(13)	42(1)	53(1)	36(1)	-11(1)	6(1)	-11(1)
C(14)	34(1)	42(1)	41(1)	4(1)	7(1)	-1(1)
O(15)	42(1)	38(1)	26(1)	0(1)	3(1)	5(1)
C(16)	33(1)	45(1)	28(1)	0(1)	-3(1)	1(1)
O(17)	91(1)	60(1)	31(1)	-9(1)	-15(1)	18(1)
C(18)	51(1)	52(2)	40(1)	10(1)	1(1)	7(1)
O(19)	32(1)	41(1)	40(1)	-5(1)	2(1)	0(1)
C(20)	35(1)	48(1)	38(1)	-1(1)	7(1)	2(1)
O(21)	41(1)	55(1)	75(1)	-13(1)	-1(1)	11(1)
C(22)	37(1)	63(2)	41(1)	-3(1)	2(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 6614.

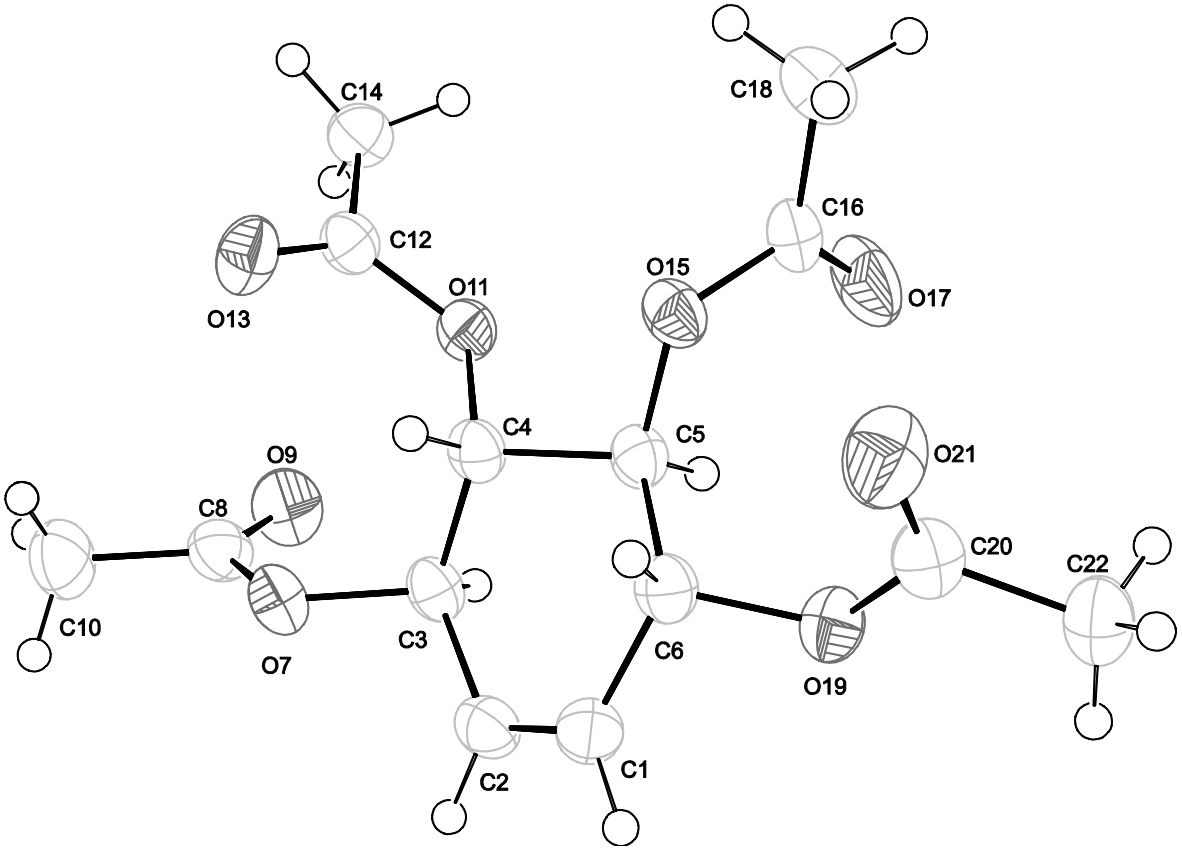
	x	y	z	U(eq)
H(11)	6642	10668	1109	44
H(21)	4523	11327	732	43
H(31)	3374	9455	2188	38
H(41)	4434	5960	1267	36
H(51)	5475	7837	3454	36
H(61)	6934	6980	1556	38
H(101)	-167	8087	-346	78
H(102)	888	9021	-1041	80
H(103)	913	6748	-760	79
H(141)	1457	2241	2664	58
H(142)	2282	3334	3751	59
H(143)	1108	4422	2999	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 °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(10)-H(102)...O(21)#1	0.958	2.441	3.379(3)	166.37
C(14)-H(142)...O(17)#2	0.954	2.538	3.331(3)	140.70
C(18)-H(181)...O(11)#2	0.967	2.587	3.455(3)	149.30

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z #2 -x+1,y-1/2,-z+1



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August 19, 2011

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