The Approaches toward the Synthesis of Pseudaminic acid Inhibitors

A thesis submitted in partial fulfilment of the degree of

Doctor of Philosophy

Ali Hussein Raheemah

Department of Chemistry

University of Sheffield

September 2018

Contents

Contents I

Declaration III

Acknowledgements IV

Abbreviations V

Abstract IX

1. Chapter 1: Introduction 1

1.1. Food poisoning 1

1.2. The state of modern antibiotics 1

1.3. Addressing the problem 2

1.4. Finding new targets 2

1.5. The flagella 3

1.6. Bacterial motility 5

1.6.1. S-Motility 6

1.6.2. A-Motility 6

1.7. Post-translational modification 7

1.8. Sialic acid 8

1.8.1. Synthesis of sialic acid inhibitor 10

1.9. Pseudaminic acid 13

1.10. Phosphonate compounds 16

1.11. Fluorinated phosphonates compounds 16

1.11.1. Background 16

1.12. General synthetic methods 22

1.12.1. Synthesis of (α-monofluoroalkyl)phosphonates 22

1.12.1.1. Electrophilic fluorination 22

1.12.1.2. Nucleophilic fluorination 23

1.12.1.3. Horner-Wadsworth Emmons olefination approach 24

1.12.1.4. Peterson olefination approach 26

1.13. Project Aims 27

2. Chapter 2: Results and discussion 28

2.1. β-Hydroxyphosphonate 28
2.1.1. Background 28
2.1.2. General Synthetic methods of β-hydroxyphosphonates 28
2.1.3. Synthesis of chiral β-hydroxyphosphonates 29
2.2. Asymmetric hydrogenation reaction 34
2.3. Chiral catalyst 37
2.4. Acid base titration 48
2.5. Chiral amine base 50

3. Conclusion 62

4. Experimental 65
4.1. General 65

5. References 129

Declaration

This dissertation records work carried out in the Department of Chemistry, University of Sheffield, between October 2014 and September 2018 and is original except where acknowledged by reference. No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Acknowledgements

First and foremost, I must thank almighty Allah for all the blessings that he has bestowed on us and extended my life to complete what I started before more than four years, a huge thanks goes to Prof. Simon Jones for giving me the opportunity to take up a PhD within his research group. I am extremely grateful for his full time supervision and his kind suggestions to enhance my knowledge in organic chemistry during my time in Sheffield.

I would also like to extend my thanks to my country, IRAQ, represented by the Ministry of Higher Education and Scientific Research for giving me this opportunity and for their financial support.

A big thank you to goes to my beloved wife (Aedah) without your helping, supporting me throughout these years and taking care of most of the hardships of caring for the family, I would not have finished what I started. Many thanks to my daughters, Narjis, Yasameen and Jannat to make my life happy. Thank you for being such a happy family.

All my deepest veneration goes to my parents and to my brother martyr (Ahmed) for everything that they have given to me. I would convey my regards to my brother, sisters and all my cousins for their constant support and always being in my side. Without them, it's impossible to finish my study.

I would also thank all professors and colleagues in Al-Mustansiriya University, especially my dear friend Dr. Ivan Hameed R. Tomi, as well as, Dr. Ahmed Al-Karawi, Dr. Amer, Dr. Ghazwan and Dr. Zeyad for their support and help over the past years.

My sincere appreciation goes to all my lab mates, over the years with a special mention going to Dr. Reeder, Dr. Dan C, Dan J, Jonny, Matt, Najwa, Shuwen Ma, Haneesh, Huda, J. Ferner Alex Field and Jenna, for their support, entertainment and knowledge. A big thank you goes to all the technical staff in the Department of Chemistry. In particular Rob Hansen (HPLC), Dr. Sandra Van Meurs (^{1}HNMR), Dr Craig C. Robertson (X-ray crystallography), Simon Thorpe and Sharon Spey (Mass Spec.) and Mr. Keith Owen.

I would like to thank all friends in the department of chemistry at the University of Sheffield, Ahmed M. Hsskia, Ibrahem Al-Aadily, Mehul V Makwana, Muhannad Al-Saedy, Omar M. Esmaeel and Ziad Alkayar.

Abbreviations

A. caviae	*Aeromonas caviae*
a.u	Atomic units
Ac	Acetyl
ACE	Angiotensin-converting-enzyme inhibitor
AcOH	Acetic acid
app.	Apparent
aq.	Aqueous
Ar	Aryl
atm	Atmosphere (pressure)
ATP	Adenosine 5′-triphosphate
b.p.	Boiling point
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINAP	Binaphthalene
BINAPO	Binaphthalene oxide
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
Br	Broad
BTEAC	Benzyltrimethylammonium chloride
Bz	Benzoyl
C or *c*	Concentration
C. jejuni	*Campylobacter jejuni*
calcd.	Calculated
Cbz	Carboxybenzyloxy
Conv.	Conversion
d	Doublet (NMR)
DAST	*N*,*N*-Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo (5.4.0)undec-7-ene
DCM	Dichloromethane
De	Diastereomeric excess
DEMP	Diethyl methylphosphonate
DKR	Dynamic Kinetic Resolution

DMAP	4-[*N*,*N*-Dimethylamino]pyridine
DMF	*N*,*N*'-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide
dr	Diastereoisomer ratio
E.coli	*Escherichia coli*
ee	Enantiomeric excess
EPSP	Excitatory postsynaptic potential
eq.	Equivalent(s)
er	Enantiomeric ratio
Et	Ethyl
EtOAc	Ethyl acetate
GlcNAc	*N*-acetylglucosamine
h	Hour(s)
H. pylori	*Helicobacter pylori*
HPLC	High performance liquid chromatography
$HSiCl_3$	Trichlorosilane
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i-Pr (IPA)	iso-Propyl
IR	Infra-red
KDA	Potassium diisopropylamide
KDN	2-Keto-3-deoxy-D-glycero-D-galacto-nononic acid
KDO	3-Deoxy-D-manno-2-octulopyranoseate
L	Ligand
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
Lit.	Literature
LPS	lipo-polysaccharide
m	Multiplet
M. xanthus	*Myxococcus xanthus*
m/z	Mass-to-charge ratio

ManNac	*N*-Acetylmannosamine
Me	Methyl
Me_3SiCl	Trimethylsilyl chloride
min	Minute(s)
mp	Melting point
MsCl	Methanesulfonyl chloride
N. gonorrhoeae	*Neisseria gonorrhoeae*
$NaBH_4$	Sodium borohydride
n-Bu	n-butyl
Neu	Neuraminic acid
Neu5Ac	*N*-acetylneuraminic acid
NMR	Nuclear magnetic resonance
Nu	Nucleophile
P	Para
P. aeruginosa	*Pseudomonas aeruginosa*
PEP	Phosphoenolpyruvate
Ph	Phenyl
pK_a	Acid dissociation constant
PNP	Purine nucleoside phosphorylase
ppm	Parts per million
Pse	Pseudaminic acid
PTP1B	Protein phosphotyrosine phosphotase
Pyr	Pyridine
Q	Quartet
rac	Racemic
Rt	Room temperature
s	Singlet
sec	Second(s)
Sias	Sialic acids
SM	Starting material
S_N2	substitution nucleophilic (bi-molecular)
t	Triplet
T	Temperature

TA	Tartaric acid
TBAF	Tetrabutylammonium fluoride
TBDMS-Cl	Tert-Butyldimethylchlorosilane
t-Bu	tert-Butyl
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
$Ti(O^iPr)_4$	Titanium (IV) propoxide
$TiCl_4$	Titanium tetrachloride
TIPS	Triisopropylsilyl
TLC	Analytical thin layer chromatography
TMS	Trimethylsilyl
TMSBr	Bromotrimethylsilane
TMSCl	Trimethylsilyl chloride
tol	Toluene
t_R	Retention time
Ts	*p*-Toluenesulfonyl
TsCl	*p*-Toluenesulfonyl chloride
TsOH	*p*-Toluenesulfonic acid
W	Watt
δ	Chemical shift
$[\alpha]_D^T$	Specific rotation

Abstract

Due to the increasing of resistance of bacteria to antibiotics, the search for other methods to deal with this important issue occupies the minds of many researchers. Meny research has been focused on synthesis of antibiotics designed to target the bacteria cell wall, some targeting bacteria DNA, and other the synthesis of bacterial protein inhibitors. Nevertheless, the bacterial flagella have not been targeted by antibiotics.

By inhibiting the growth of the flagella, this will prevent the bacteria motility inside the host's body and thus prevent them from forming the colonies, and as a result will reduce the risk of infections and diseases.

This study concentrated on the synthesis of pseudaminic acid inhibitors, an acid that is considered essential for the formation of bacterial flagella. The synthesis of six potential inhibitors was developed using different procedures.

Transfer hydrogenation reduction of *β*-ketophosphonates was achieved in excellent yield and high levels of enantioselectivity at 0.5 mol% catalyst loading. Protection of tertiary hydroxyl group was not achieved using the usual methods.

The furan ring has been successfully oxidized using a well-known method employing of $RuCl_3$ and $NaIO_4$ in a mixture of three different solvents and led to the corresponding carboxylic acid in excellent yield.

Various chiral amines were prepared and used as ligands and bases for an aldol condensation reaction. Unfortunately, none of these reactions was successful in attempts to form quaternary stereogenic centres.

Diethyl α-iodomethylphosphonate-carbonyl compound couplings *via* enantioselective aldol reaction mediated by SmI_2 with (*R*)-BINAPO was conducted using two equivalent of SmI_2 under dry conditions, from this coupling reaction were obtained only racemic mixture of β-hydroxyphosphonates.

1. Chapter 1: Introduction

1.1 Food poisoning

Food poisoning is a typical, yet upsetting and some of the time dangerous issue for people around the world. People contaminated with foodborne organisms might be manifestation-free or may have side effects extending from mellow intestinal distress to extreme drying out and haemorrhagic diarrhea.

Food poisoning can occur from more than 250 different diseases. Probably the most widely recognized illnesses are contaminations caused by microscopic organisms, such as *Campylobacter*, *Salmonella*, *Shigella*, *E. coli*, *Listeria*, *botulism*, and *norovirus*. For example, *Campylobacter* is a bacterium that causes acute diarrhea. Infections is often caused by ingestion of contaminated water, food, or non-pasteurized milk or through contact with contaminated pets, infants, or wild animals.[1]

It is known that the symptoms of bacterial infection can be delayed (incubation period) in the case of any person infected bacteria leading to food poisoning. This is because the bacteria need time to multiply within the intestines of the infected person, which depends on the quantity ingested and type of bacteria.

Treatment of food poisoning depends mostly on the source of the disease, if it is unknown, and the intensity of the symptoms. For the vast majority, the diseases disappear without medical intervention within a few days, although a few sorts of food poisoning may last longer. The treatment of food poisoning may include compensation for lost fluids or by taking antibiotics, as is the case of food poisoning caused by Listeria where intravenous antibiotics are taken during hospital treatment.

In view of the high resistance of bacterial strains to these antibiotics, there is a need to find alternative methods of treatment such infection.

1.2. The State of Modern Antibiotics

The discovery of antibiotics catalysed a revolution in medicine, but the issue of drug resistant microorganisms continues to grow. There are many ways in which microorganisms can acquire drug resistance and some evidence suggests that drug resistance can be naturally occurring.[2] However, a commonly accepted source of resistance is through inappropriate administration of antibiotics at doses that are too small and allow the surviving bacteria to acquire resistance. Additionally, the symptoms of a viral infection from a common cold are

often mistaken for bacterial infection and misdiagnosis can lead to other microorganisms present in the host acquiring resistance to drugs that are having no therapeutic effect.

1.3. Addressing the Problem

Due to the importance of antibiotics, and the nature of bacterial speciation, a large number of different classes of antibiotics have been developed. Antibacterial compounds are classified and categorised based on their chemical structure, which is intrinsically linked to the mechanism of their action against the desired target. The widespread use of an antibiotic is directly linked to more widespread resistance to the compound.[3]

Modification of existing treatments and compounds is one way in which bacterial resistance has been approached. For example, β-lactamase inhibitors are molecules that can be used cooperatively with β-lactam antibiotics, that protect them from being destroyed by β-lactamases, thereby enabling a therapeutic effect against resistant bacteria.[4]

1.4. Finding New Targets

Finding different ways of targeting the bacteria is also a successful approach. There is a large contingent of antibiotic classes that are designed to target the cell wall, including many penicillins, five different generations of cephalosporins, monobactams, carbapenems, and glycopeptides. *Streptococcus pneumoniae* is very contagious, Gram-positive bacterium that is considered to be the most significant pathogen in a considerable number of pneumococcal infections including community acquired pneumonia, bacteremia and bacterial meningitis.[5] This infection has been treated in a simple way by taking penicillin or other microbial agents. However, the first case of inactive penicillin in *S. pneumoniae* was diagnosed in 1967. Later, by the 1990s, increased resistance of pneumococcal pneumonia to penicillin and other antibiotics was observed.[6] The disturbance of the biosynthesis of the cell wall is a recognized mechanism of action for many of antibiotics used clinically. Nucleotidylyl transferases are considered attractive antimicrobial targets.[7] There are also bacterial protein synthesis inhibitors which target the ribosomes, such as aminoglycosides, lincosamides, and macrolides.[8] Other antibiotics have been created to target DNA gyrase, as well as polymyxins, which target the cell membrane.

A. caviae is known to cause gastroenteritis (inflammation of the stomach and small intestine) and *C. jejuni* is known to cause enteritis (inflammation of the small intestine). *H. pylori* is also known to cause enteritis, as well as stomach ulcers and has been associated with increased risk of gastric cancer.[9,10] When present in the stomach, *H. pylori* utilizes its flagella

and reaches the epithelial cells of the gastric wall through the gastric mucosa.[11] However, without the flagella, the bacteria are unable to perform this vital activity and they cease to be pathogenic.

Many facets of the bacterial cell have been used as targets for antibiotics, especially the cell wall. However, bacterial flagella have not yet been the target of any antibiotics. If progress can be made in this area, it will present a new strategy that can be used to battle bacteria.[12]

It has also been discovered that, in the case of *Aeromonas caviae*, *Helicobacter pylori* and *Campylobacter jejuni*, the flagellin proteins on the surface of the flagella are post-translationally glycosylated with oligosaccharides which are terminated by the molecule pseudaminic acid.[13] In this case, the glycosyl acceptor is the oxygen or nitrogen, (rarely) carbon atom of a polypeptide side chain.

1.5. The Flagella

Microscopic organisms such as bacteria can be transferred inside the surfaces using specific motility modes.[14] Flagella are a motility mode utilized for settlement amplification along a semisolid surface.[15] Though Type IV pili (TFP) which are thin filaments, also participate in swarming, these bacteria are often hyper flagellated, expressing multiple flagella even in types such as *P. aeruginosa* which usually has a single flagellum.[16]

Flagella are the microscopic 'tails' found on cells, and are an important movement organelle for several different microorganisms. *Eukaryotes* and *prokaryotes* can possess flagella, whereas *archaea* have the structurally (and etymologically) identical *archaellum*. Not every microorganism needs flagella for movement, for example *Myxococcus xanthus* uses gathering and sliding translocation processes to navigate outside of fluid media.[17] However, the proliferation and survival of microorganisms is significantly associated with the movement characteristics for every individual microorganism (Figure 1).

The flagellum is a helical filament, about 5µm in length, which spins and produces force by hydrodynamic drag opposing its rotation.[18] It is driven by a 50-nm rotary motor an integral part in the cell membrane. This motor is work by protons moving down an electrochemical gradient, and not directly by ATP. Measurements on *Streptococcus* cells show that it takes about 1200 protons to carry out one full flagellar rotation,[19] with typical rotation speeds being on the order of 100 Hz. Although the typical image of flagellar motility involves the flagellum oriented behind the bacterium and pushing it forward, in multiple flagellated cells such as *E. coli*, the flagella show cooperative behaviour. When all the flagella rotate in one direction, they are withdrawn together and form a flagellar package which leads the cell to move

forward. However, when one of the flagella changes direction, the flagellar package breaks apart and the cell tumbles, stood up its forward motion and rotating quickly. This randomizes the direction of motion.[20]

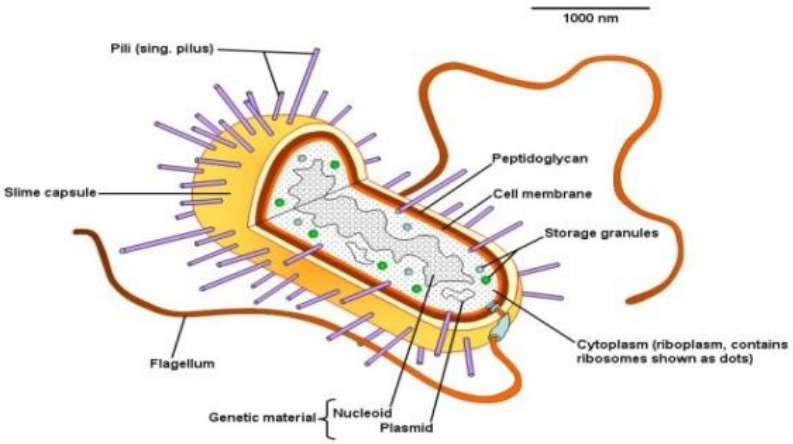


Figure 1: A cross section of the gram-negative bacterial cell.
http://cronodon.com/BioTech/Bacteria.html

As many as 50 genes are involved in the formation and function of the flagellum for bacteria such as *E. coli* and *C. jejuni*.[21] However, due to the large amount of energy consumption involved in synthesis and function of the flagella, environmental conditions largely regulate the expression of flagellar genes.

Bacterial flagella are simpler than eukaryotic flagella and can be divided into three main substructures: the basal body, the filament and the hook. The filament is composed solely of the protein flagellin and is around 20 nm in diameter. The hook work as a connector, attaching the basal body to the filament, which acts as a rotary motor (Figure 2). Proteins in the basal structure control rotation of the flagellum. The bacteria then modifies its movement patterns to account for changes in external chemical stimulus through a process known as chemotaxis.[22] This eventually allows the bacteria to accumulate in areas that are beneficial to survival, proliferation and infection.

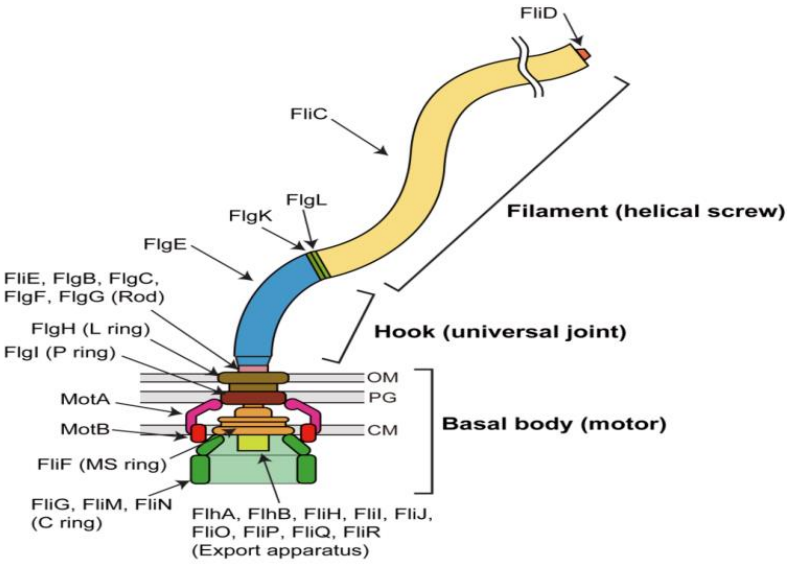


Figure 2: Schematic diagram of the bacterial flagellum. Adapted from (Morimoto Y. & Minamino T.)[23]

Bacterial flagella increase the number of host-pathogen interactions due to the motility they provide. However, in addition to the motility they offer, bacterial flagella offer other enhanced virulence properties, including modulation of immune system responses, adhesion, biofilm formation, and destructiveness factor emission.[24] Bacterial flagella have the ability to help virulence by translocating virulence proteins into host cells by using a type III secretion system (or injectisome).[25] Moreover, bacterial flagella also interact with the TLR-5 (toll-like receptor 5) signalling pathway that may lead to pro-inflammatory reactions.[13]

1.6. Bacterial Motility

In microscopic organisms such as bacteria, the capacity to move is a critical issue for a wide assortment of important biological functions, for example biofilm arrangement, virulence and fruiting body design. Although, the majority of bacteria move by utilizing these growths, typically periplasmic or external flagella, several bacteria apply other strategies for mobility, such as "gliding". This technique is a method of movement on hard surfaces without the help of flagella. Not every microorganism needs flagella for movement; for example, *Myxococcus xanthus* uses gathering and sliding translocation processes to navigate outside of fluid media. However, the proliferation and survival of microorganisms is significantly associated with the movement characteristics for every individual microorganism. A-Motility and S-motility are perfect for soil dwelling Gram-negative bacteria such as *M. xanthus*, flagella are basic and useful issues for the bacteria that resides in animals. Whereas A motility is usually described as motility of well-isolated cells or small cell groups, S motility is described as coordinated movement of large cell groups.[26] At present time, little is investigated regarding

motility of individual cells in the initial steps of biofilm formation, during which bacteria transformation from a free-swimming planktonic state to a surface-associated state and afterward forms microcolonies.

1.6.1. S-Motility

M. xanthus S-motility is usually defined as the organized movement of cells when moving in a groups of thousands together harmoniously on a solid surface without the help of flagella, which is similar to twitching motility in *Pseudomonas aeruginosa*,[27] which is driven by extension, adhesion, and retraction of polar type IV pili.[28] Behaviour and genetical analyses show that at least three main cellular ingredients are needed for S-motility: extracellular external fibril material, lipo-polysaccharide (LPS) *O*-antigen and type IV pili (TFP).[28] Studies on TFP of *N. gonorrhoeae*, *P. aeruginosa*, and *M. xanthus* using variable exploratory methodologies provided evidence that this mechanism of twitching movement or social slippage **(**S-motility) is created *via* withdrawal of pilli fibres, a system initially suggested by Bradley in 1972.[29, 30]

1.6.2. A-Motility

In 1979, Hodgkin and Kaiser reported the existence of a motility system which they named A-motility, where some *M. xanthus* cells were still able to move as isolated cells on the edge of colonies despite their lack of a functional S-motility system.[31] A (adventurous) motility, is driven by an uncharacterized engine hypothesized to be associated with slime secretion.[32] Recently, Wolgemuth *et al*. showed that a slime extrusion engine could theoretically produce enough force to drive a bacterium at the observed speed.[33] This model was consistent with the observation that in a *Phormidium sp*., a gliding cyanobacterium, the rates of slime secretion and cell movements were similar.[34,35] Over many years, the explanation of the A-motility has been suggested through the proposal of many models. However, the molecular basis of A-motility is still elusive.[17]

Biofilm formation depends strictly on the way that planktonic bacteria adjust their motility mechanisms close to a surface.[36] In *P. aeruginosa* biofilm formation,[37] two type of villi are responsible for movement; multiple type IV pili (TFP) and a single polar flagellum. Distortions in either flagellum or TFP function result in biofilm formation defects and drops in virulence. Type IV pili are approximately 6 nm in diameter and between 1 and 5 µm long, which typically form at cell poles.[38] The pili are inflexible, with a persistence length of 5 µm. The tip of the extended pilus then attaches to the surface,[30] but the remainder of the pilus

does not display any adhesive characteristics. In *P. aeruginosa*, this binding is unspecific, but for *M. xanthus* the pilus tip also functions as an exopolysaccharide sensor, and in *Neisseria* strains the pilus tip has specific interactions with human epithelial cells.[39]

In order to limit or prevent this movement and thus prevent the formation of bacterial colonies, it is necessary to know how to form the fibres and what depends on their composition. Studies have shown that *Caulobacter* flagellins are glycosylated, however there has been no confirmation of the chemical effect of this, the glycosylation was fundamental for fibre composition.[40] Glycosylation is the most important posttranslational modification occurring mainly in the cytosol, the endoplasmic reticulum, the Golgi apparatus and the sarcolemmal membrane. A rapidly growing family of genetic diseases is due to defects in protein N- and O-glycosylation, glycosylphosphatidylinositol glycosylation, and lipid glycosylation

1.7. Post-translational modification

The process by which proteins are modified throughout biosynthesis is known as post-translational modification. Post-translational modifications are modifications that occur on a protein, catalysed by enzymes, after its translation by ribosomes is complete and occurs at the peptide terminus of the amino acid chain, playing an important role in translocating them across biological membranes. These include secretory proteins in prokaryotes, and eukaryotes and proteins that are intended to be incorporated in various cellular and organelle membranes such as lysosomes, chloroplast, mitochondria and plasma membranes. Expression of proteins is important in diseased conditions. Posttranslational modifications play an important part in modifying the end product of expression and contribute towards biological processes and diseased conditions. The protein post translational modifications play a crucial role in generating the heterogeneity in proteins and also help in utilizing identical proteins for different cellular functions in different cell types. How a particular protein sequence will act in most of the eukaryotic organisms is regulated by these post translational modifications. Post-translational modification generally refers to the addition of a functional group covalently to a protein as in phosphorylation and neddylation, but also refers to proteolytic processing and folding processes necessary for a protein to mature functionally. Nevertheless, recent developments actually have detected that prokaryotic cells do possess the ability to achieve post-translational glycosylation.[41] Flagellins from *Campylobacter coli* VC167 and *Campylobacter jejuni* 81-176 are significantly glycosylated. The main configurations are an acetamidino-substituted

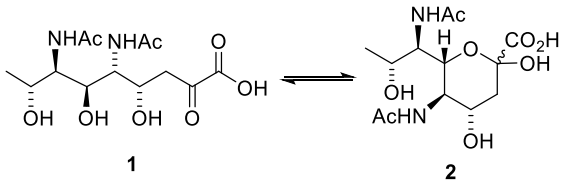
pseudaminic acid (PseAm) and pseudaminic acid (Pse5Ac7Ac); in addition to small amount of an *O*-acetylated form (Pse5Ac7Ac8OAc) and a dihydroxypropionyl form (Pse5Pr7Pr). The flagellin of *Campylobacter coli* VC167 includes Pse5Ac7Ac, in addition to a fundamentally and immunologically particular type of PseAm, that maybe Pse5Ac7Ac and PseAm, respectively, expanded by a deoxypentose.[42] Although initially thought to be limited to eukaryotes, there is an expanded familiarity with bacterial glycoproteins.[43-55] Campylobacter flagellins are vigorously glycosylated prokaryotic proteins characterized, with carbohydrates participating of the protein.[42, 56] *Campylobacter jejuni* (strain 81-176) flagellin has been seen to consist of 19 amino acids, which are *O*-connected to some monosaccharide analogues of pseudaminic acid (Pse),[56] a nine carbon sugar related to sialic acid (Neu5Ac).

1.8. Sialic Acids

Sialic acids are found across a vast array of different organisms, including vertebrates, bacteria, fungi, echinoderms, insects and molluscs. The name of these compounds does not relate to their monosaccharide structure but instead denotes their first isolation from human saliva. There are over 50 different structurally distinct variants.

The term sialic acid can be used to refer specifically to *N*-acetylneuraminic acid (Neu5Ac), which is not found in Nature, but functions as the structural foundation, along with KDN (3-deoxy-2-keto-D-galacto-D-glycero-2-nonulosonic acid). These may be modified in a number of ways to reach any of the other sialic acids, and therefore all currently known derivatives of KDN or Neu5Ac are sialic acids.[57] KDN, KDO [(±)-3-deoxy-D-manno-2-octulopyranosate] and Neu5Ac exist predominantly as the α-anomer. Amongst glycoproteins, sialic acids are often found on the distal end of glycan chains, which means that in the case of the bacterial flagellum especially, they are often able to interact with multiple environmental factors, including other cells. This tendency alludes to the possible roles of sialic acids in mediating host-bacteria interactions and, therefore, the possibility of exploitation by novel antibiotics.

Sialic acids are nonulosonic acids. These are 9-carbon α-keto acids formed from the oxidation of the 1-hydroxyl group of ketose to a carboxylic acid. The pyranose ring forms autonomously in solution via hemiketal formation.



Scheme 1: Cyclisation of legionaminic acid

Sialic acids (Sias) are O- and N- derivatives of 3,5-dideoxy-5-amino-D-galacto-D-glycero nonusolonic acid (neuraminic acid), and the only nine carbon sugars that exist in bacteria. Legionaminic acid is an example is found in *Legionella* LPS and probably helps adhesion to the membrane of alveolar macrophages in the human lung and to the membrane of amoebae in the natural environment.[57]

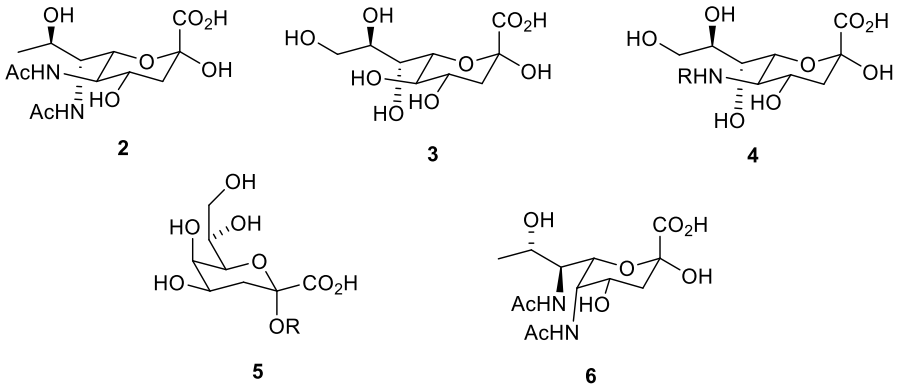
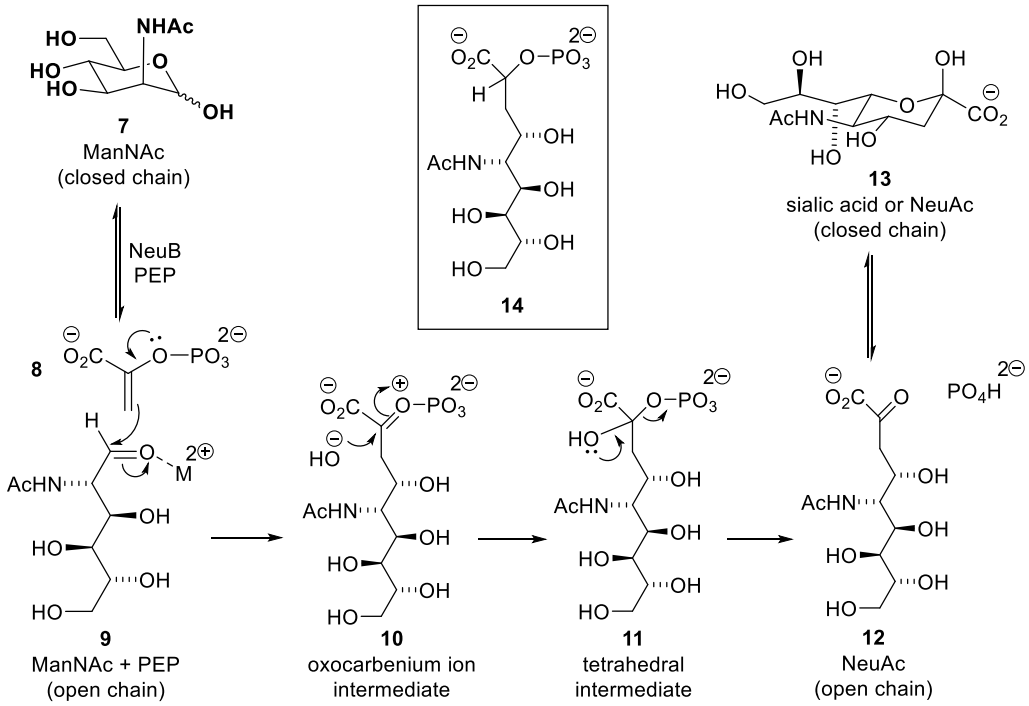


Figure 3: ''Structures of sialic acids: (**2**) 5,7-diamino-3,5,7,9-tetradeoxy-D-galacto D-glycero-nonulosonic acid (legionaminic acid), (**3**) 2-Keto-3-deoxy- D-galacto D-glycero-nonulosonic acid (KDN). (**4**) Neuraminic acid (Neu, R=H), *N*-acetylneuraminic acid (Neu5Ac, R=CH_3CO-) and *N*-glycolylneuraminic acid (Neu5Gc, R=$HOCH_2CO$-), Structures of the following sugars are also shown for comparison: (**5**) 2-keto-3-deoxy-D-manno-octulosonic acid (KDO) and (**6**) 5,7-diamino-3,5,7,9-tetradeoxy- L-manno-L-glycero- nonulosonic acid (pseudaminic acid)''.

It has been proved through mechanistic studies that the catalysis of bacterial sialic acid synthase needs a divalent metal ion.[58] The aldehyde at C-1 plays an important role in this process, which is thought to be produced by the action of the enzyme to catalyze the opening of ManNAc ring (Scheme 2). Baes on this, sialic acid is produced in just two steps starting from UDP-*N*-acetylglucosamine (UDP-GlcNAc).[59] Initially, hydrolysis with UDP-GlcNAc 2-epimerase gives UDP and ManNAc.[60] Then *N*-acetylneuraminic acid is prepared by reacting of phosphoenolpyruvate with ManNAc **7**.[61] The biosynthesis is different in mammals, where ManNAc 6-phosphate, then produces *N*-acetylneuraminic acid 9-phosphate.[62] The oxocarbenium ion **10** intermediate is then formed by attacking the C-3 carbon of PEP to the aldehyde. This step is accelerated by activating the carbonyl in the aldehyde with the help of the metal ion, which acts as an electrophilic catalyst. After the

tetrahedral intermediate **11** is produced by adding hydroxyl group to the oxocarbenium ion the phosphate is lost to form the sialic acid **12** (open chain form), which can easily cyclize in solution into the pyranose form.



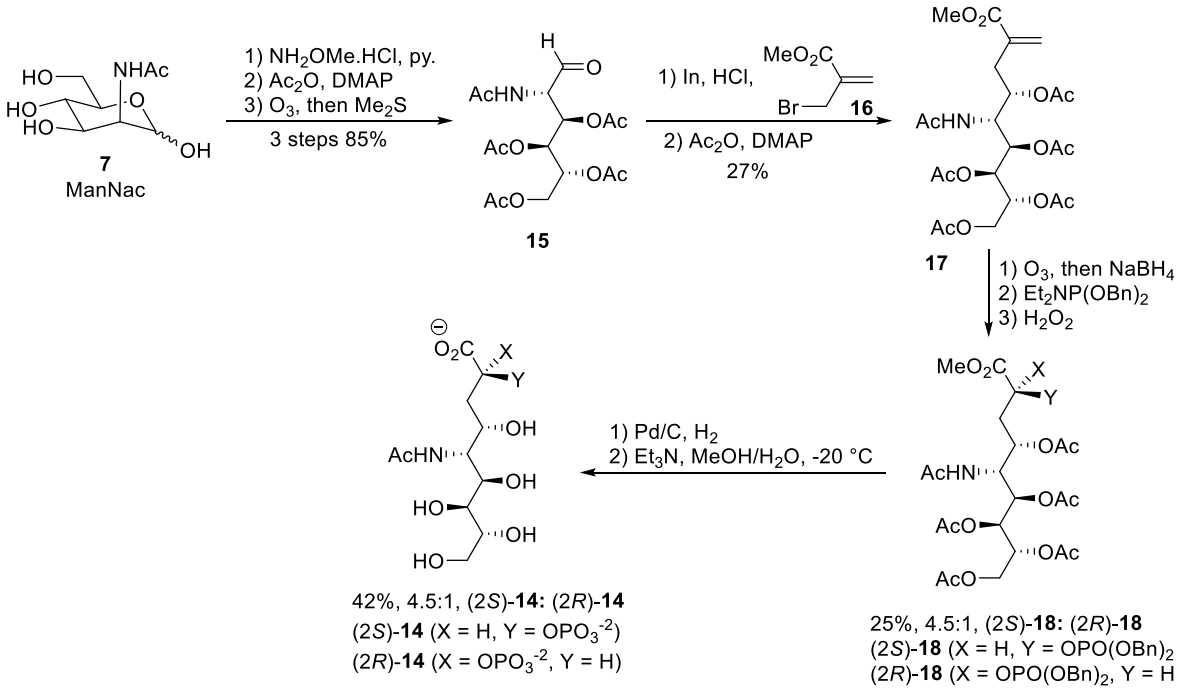
Scheme 2: The structure of inhibitor (**14**) and mechanism of the reaction catalyzed by sialic acid synthase

Tanner's group has prepared an inhibitor of sialic acid synthase (NeuB) **14**. They reported that this inhibitor imitates the tetrahedral intermediate which is synthesised in the reaction of sialic acid synthase (Scheme 3, **14** insert). A mixture of stereoisomers at C-2 of this compound was obtained (50:50) to examine the preferred orientation of groups inside the enzyme active site. It was found that the inhibitor affords (*R*)-configuration at C-2; this was known by the crystallographic analysis of a complex between the more strongly binding stereoisomer of the inhibitor **14** and sialic acid synthase. This indicates that the tetrahedral intermediate **11** holds the same configuration (*R*) at C-2 and that a hydroxide-metal bound is delivered to the *si* face of the intermediate **10** through catalysis.[63]

1.8.1. Synthesis of sialic acid inhibitors

The general strategy adopted by Tanner's group in the synthesis of sialic acid inhibitor included the addition of pyruvate unit that give a three-carbon atoms into the peracetylated open chain shape of ManNAc **7**. Firstly, the aldehyde of ManNAc was protected using hydroxylamine, and the hydroxyl groups were protected with acetic anhydride. To create the

aldehyde group, ozonolysis was used giving compound **15**.[63, 64] Addition of methyl bromomethylacrylate **16** by an indium-mediated, then acetylation using acetic anhydride, to gave compound **17** that was treated with ozone giving the ketone at C-2, reduced with sodium borohydride, then phosphorylated to give ester **18** as a mixture of two isomers (3:1) at C-4. The major isomer was purified by flash chromatography, and recrystallization, giving the desired configuration (*S*) at C-4 [65-67] (Scheme 3).



Scheme 3: Synthesis of inhibitor **14**

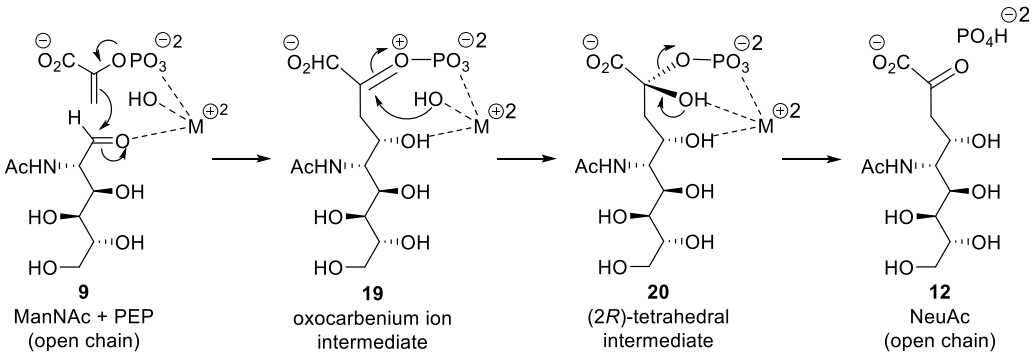
The reduction step was performed at -78 ˚C, giving a mixture of (2*S*)-**14**:(2*R*)-**14** (4.5:1), but at 25 ˚C, a mixture of (2*S*)-**18**:(2*R*)-**18** was obtained in a 1.2:1 ratio. This mixture was used in the subsequent reaction because these stereoisomers were non-separable by flash chromatography. Following hydrogenolysis, then treatement with triethylamine at -20 ˚C to hydrolyse the ester group, gave isomer **14** as a mixture of (2*S*)-**14**:(2*R*)-**14** (4.5:1) or (2*S*)-**14**:(2*R*)-**14** (1.2:1) based on the reaction conditions adopted to prepare compound **18**.

Kinetic constants for the inhibition of the *Neisseria meningitis* sialic acid synthase by compound **14** were acquired utilizing a consistently coupled assay for phosphate release.[68, 69] Initial investigations using a mixture of (2*S*)-**14**:(2*R*)-**14** in a 4.5:1 ratio demonstrated that compound **14** appear as a strong and moderate binding inhibitor. Thus, before each kinetic examination, the enzyme was preincubated for 20 min in the presence of the inhibitor, PEP, and Mn^{+2} to guarantee that binding equilibration had happened. Identical kinetic runs using

the 1.2:1 mixture of (2*S*)-**14**:(2*R*)-**14** brought about a similar reduction of rate. Furthermore, and the minor (2*R*)-isomer is responsible for no less than 80% of the inhibition.[63]

An analysis of the tetrahedral geometry at C-2 clearly indicates an (*R*)-configuration of the bound inhibitor and provides the basis for the assignment of stereochemistry of the tighter binding isomer. Assuming that this stereochemical preference reflects a resemblance to the tetrahedral intermediate, then the intermediate is also expected to bear an (*R*)-configuration at C-2. This would indicate that the reaction mechanism involves an attack of water onto the *si* face of the oxocarbenium ion intermediate **19** (Scheme 4). The (2*R*)-configuration orients the C-2 hydrogen of inhibitor **14** toward the Mn^{2+} ion and suggests that in the actual tetrahedral intermediate the C-2 hydroxyl may serve as a ligand for the metal. It also implies that the metal may play a dual role in catalysis, both as an electrostatic catalyst that activates the aldehyde of ManNAc and as a source of the activated water molecule that attacks the oxocarbenium ion intermediate (Scheme 4). In the NeuB·*N*-acetylmannositol·PEP·Mn^{2+} structure, the equatorial metal-bound water molecule (W_{eq}) is positioned 2.8 A˚ away from the *si* face of the bound PEP (3.1 A˚ away from C-2 of PEP) and is a likely candidate to play the role of the nucleophile. In the structure of NeuB·inhibitor **14**·Mn^{2+}, the electron density corresponding to the Mn^{2+} ion indicates only partial occupancy (50%) based on resulting maps and temperature factors. The partial occupancy of the metal cofactor indicates that the manganese ion binds weakly to the NeuB·inhibitor **14**·complex. This notion is further supported by the determination of NeuB·inhibitor **14** structures devoid of bound metal cofactor that were obtained during various soaking trials. The manganese ion of the NeuB·inhibitor **14**·Mn^{2+} complex was coordinated in the active site with a significantly distorted octahedral arrangement, whereas the previously reported NeuB·*N*-acetylmannositol ·PEP·Mn^{2+} complex displayed the much more regular octahedral geometry typical of Mn^{2+} binding coordination spheres. The partial occupancy and distorted geometry of the bound metal suggest that the binding of inhibitor **14** disturbs the coordination sphere and likely impairs binding somewhat. One explanation may lie in the fact that the C-2 hydrogen of the inhibitor is oriented toward the metal and thereby has displaced W_{eq} from its preferred position. In the normal reaction mechanism, the C-2 hydroxyl group of the tetrahedral intermediate would occupy this coordination site and no steric clash would result. An alternative explanation for the perturbed metal binding/geometry could be that a

conformational change normally accompanies the formation of the tetrahedral intermediate but that soaking with the inhibitor is not sufficient to induce the same change in the solid state. In this event, the active site would not be in an optimal conformation to bind both inhibitor **14** and the metal ion, and the metal binding could be impaired.[63]



Scheme 4: Revised mechanism of the reaction catalyzed by sialic acid synthase outlining the proposed stereochemistry of the tetrahedral intermediate and the dual role played by the Mn^{2+} ion.

While it is not conceivable to separate the tetrahedral intermediate created in the synthase reaction of sialic acid and define its stereochemistry specifically, the synthesis and characterization of another analogue could strengthen the discoveries of this investigation. Given the importance of the presence of some natural phosphonates in the environment, where bacteria have developed the capability to metabolize phosphonates as nutritional sources, some bacteria use phosphonates as one of the main sources of phosphorus for growth. Therefore, phosphonate compounds should be highlighted of view of possible synthetic methodology as well as the synthesis of a molecule contains both of phosphorus and fluorine atoms and study their effect on the pseudaminic acid biosynthesis.

1.9. Pseudaminic acid

Studies in the last years have discovered the presence of *N*- and *O*-glycosylations in a variety of different prokaryotic proteins. In particular, *O*-linked glycosylation by pseudaminic acid **6** is interesting. Additionally, Pse has been found linked to serine/threonine residues in the central domain of the protein in flagellin glycoproteins derived from different pathogenic bacteria such as *Helicobacter pylori* and *Campylobacter jejuni*, and this is important for bacteria to move inside the host cells. Furthermore, Pse has been distinguished as larger glycans. For example, an *O*-antigen polysaccharide from *Escherichia coli* has a trisaccharide

repeat that contains pseudaminic acid, and a trisaccharide from *Pseudomonas aeruginosa* appears to have modified Pse.

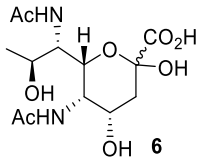


Figure 4: Pseudaminic acid **6**.

Synthetic pseudaminic acid exists as predominantly the β-anomer and the NMR and optical rotation data matches that of derivatives isolated from bacterial polysaccharides.[70] (Figure 5).

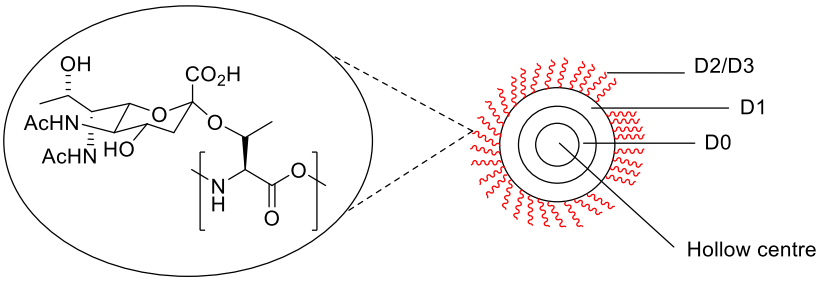


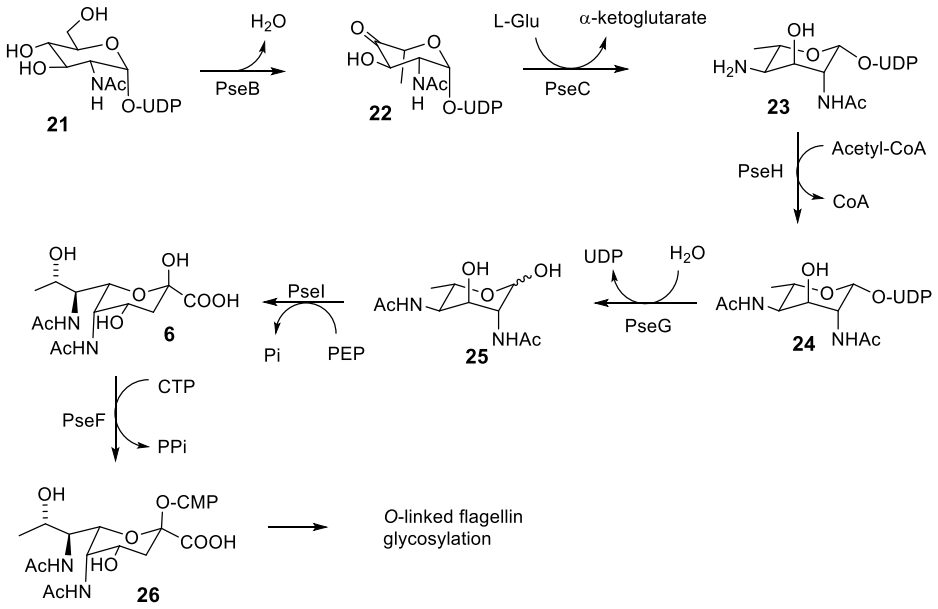
Figure 5: A cross-sectional representation of the flagellar glycosylation of *H. pylori*. The flagellar filament core is composed of four structurally distinct domains (D0-D4), which are formed from the polymerisation of flagellin subunits. Pseudaminic acid forms glycosidic bonds to the hydroxyl groups of threonine (pictured) and serine residues of the external D2/D3 domain.[71]

The role of pseudaminic acid is not clear but it has been shown to have an important role in the intervention of the interactions between the host and the pathogen.[72] Interrupting the biosynthetic pathway for the assembly and production of this compound (through generation of knock-out mutations) results in non-motile, non-pathogenic bacteria. It has been found that the gastrointestinal pathogens *Helicobacter pylori* and *Campylobacter jejuni* their flagellins modified with pseudaminic acid (Pse) or sialic acid-like sugar 3,5,7,9-tetradeoxy-5,7-diacetamido-L-manno-L-glycero-nonulosonic acid.[73]

The biosynthetic pathway that leads to the preparation of pseudaminic acid is well-mapped out, an important event being the condensation of 2,4-diNAc-6-deoxy-Alt with phosphoenol pyruvate.[74] This route is similar to that for stereoisomeric legionaminic acid, and also for sialic acid, a α-keto acid that has shown to be a virulence factor for pathogens such as *Neisseria meningitis.*

Biosynthetically both pseudaminic acid **6** and legionaminic acid **2** are synthesised from a nucleotide activated *N*-acetylglucosamine. The complete biosynthesis of pseudaminic acid

has been characterised within *Campylobacter jejuni* and *Helicobacter pylori* (Scheme 5). Within these bacteria, pseudaminic acid is generated from UDP-*N*-acetylglucosamine **21** in an efficient five step pathway (Scheme 5).[75-78] The first step in the pathway is catalysed by PseB an enzyme that has a dual function as a NAD(P)-dependant dehydratase and C-5 epimerase, converting UDP-a-D-GlcNAc **21** to UDP-2-acetamido-2,6-dideoxy-α-D-arabino-hexos-4-ulose, **22**.[78-81] Compound **22** is converted by PseC into UDP-4-amino-4,6-dideoxy-α-L-AltNAc **23** that, as can be seen in Scheme 5, rearranges the entire molecule converting **22** from a D-sugar to an L-sugar.[77, 78, 82] The intermediate **23** is then shuttled through a further two enzyme catalysed reactions, involving PseH and PseG,[83, 84] being converted into 2,4-diacetamindo-2,4,6-trideoxy-b-L-altropyranose **25**. Compound **25** is the substrate for PseI, the enzyme that converts it into pseudaminic acid **6** via an aldol condensation with phosphoenolpyruvate (PEP) (Scheme 5). In order to be incorporated into O-antigens, or utilised in O-linked protein glycosylation pathways, pseudaminic acid **6** must be activated as its CMP-linked derivative. This reaction is catalysed by PseF, a CMP-pseudaminic acid synthetase, which utilises CTP, producing CMP pseudaminic acid **26** and pyrophosphate (Scheme 5).[68, 78, 79]



Scheme 5: Pseudaminic acid biosynthesis.

1.10. Phosphonate compounds

In medicinal and biological systems chemistry, methylene phosphonates groups have been used as stable bioisoteres for phosphate such as in Tenofovir **27** (Figure 6) which is used in the antiviral nucleotide analogue as the cornerstones of anti-HIV therapy and used as non-hydrolysable mimics of phosphate esters, with *α*-halo-analogues being utilized since the 1980's.[85] In 1963, Myers *et al*. reported the synthesis of the first analogue of adenosine 5′-triphosphate, ATP (X=O) by the reaction between adenosine 5'-phosphoromorpholidate and methylene bisphosphonic acid to give 5'-adenylyl methylene- diphosphate (AMP-PCP) (X=CH_2) (Figure 6),[86] expecting that the P-O-P linkage of this analogue would be capable of group transfer or enzymic cleavage but the P-C-P bonds would not. Generally, AMP-PCP **28** and **29** (×=CH_2) have the functions properties may play rules as: (i) a metabolic substitute for ATP in operations including cleavage of the P-O-P bonds of the second pyrophosphate oxygen of adenosine triphosphate; (ii) adenosine triphosphate (ATP) inhibitor including cleavage of the terminal P-O-P bond of ATP; (iii) in the processes of metabolic substitute for ATP including binding or complexing actions of adenosine triphosphate which are not accompanied by cleavage of pyrophosphate bond.

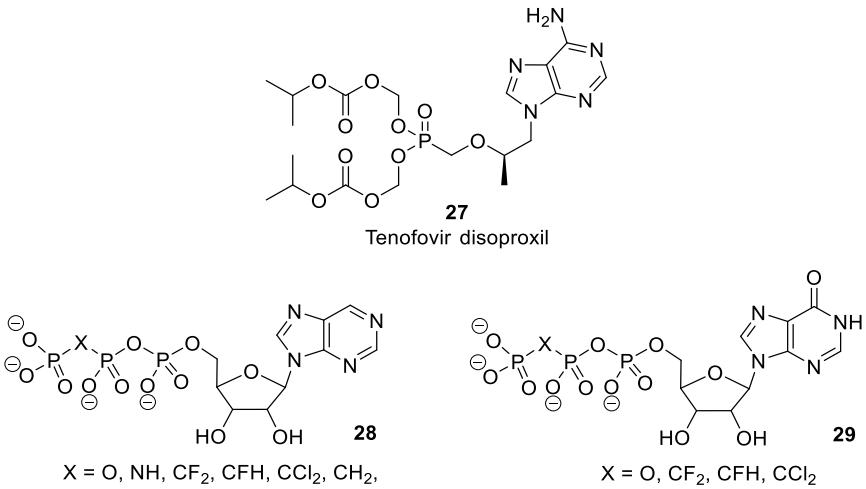


Figure 6: Adenosine 5′-triphosphate analogues.

1.11. Fluorinated Phosphonates compounds

1.11.1. Background

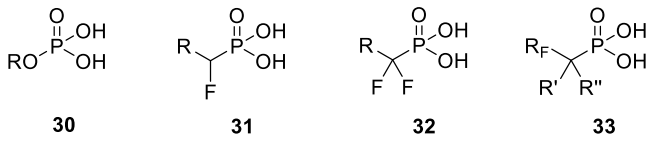
In the 1980s, Blackburn and Mckenna proposed that *α*-fluorination might function as good mimic natural phosphoates. However, *α*-monofluorination gives phosphonates with "matching" second pK_a values, in the previous decade the *α*,*α*-difluorinated phosphonates have received more attention. O'Hagan *et al*. and Berkowitz *et al*. stated that the enzyme-

binding affected by the stereochemistry of C-H-F bond and they gave details of the enzyme kinetics data and their related with *α*-monofluorinated phosphonates. This was additionally shows in structural information from the group of Tracey[87] and Barford/Burke[88] on protein phosphotyrosine phosphotase (PTP1B) complex with bound *α,α*- difluorinated inhibitors. Just one of these two prochiral fluorine atoms shows up to a clear interaction with the enzyme. To be specific, it is though that the pro-*R* (F_{si}) fluorine is occupied in an essential hydrogen bond with the amide NH.[89]

For many years it has been known that phosphonates can act as phosphate mimics.[90] In contrast to the phosphate group, in the biological environment, the phosphonate linkage is not easily hydrolysed. In a different sense, although the dramatically difference in the chemical properties of the corresponding compounds as the structural of C-C-P bonds with C-O-P bonds, has given other avenues to the systematic efficiency of biomedical and chemical investigations of phosphonic acids derivatives.[91-95]

The study of fluorinated alkyl phosphonates chemistry is a comparatively new field of research, which over the past two decades has developed remarkably. The purpose of fluorine replacement in the organic groups associated with phosphorus comes from the expected effect on biological, chemical and physical properties because of this substitution. Generally, combining fluorine as either an isoelectronic substitution for the hydroxyl group or as a bioisosteric substitution for hydrogen has significant results on lipophilicity, hydrogen bonding, metabolic degradation, and reactivity of organic molecules.[96-102]

A specific improvement of bioisostere designing in the chemistry of phosphonate has been reported by McKenna and Shen[103] and Blackburn and coworkers.[85] They proposed that by introducing halogens, especially fluorine, on *α*-carbon alkylphosphonates, it is possible to obtain predominant bioisosteres because these are alternative compounds should more precisely mimic the polar and steric feature of phosphate action (Figure 7).



30 **31** **32** **33**

R = Alk, Ar or Het; and R'' = H, Alk, Ar or R_F; R_F = any group containing fluorine

Figure 7: Phosphates naturally developed (**30**), Their Fluorinated Analogues (**31-33**).

In fact, *α*-monofluoro- and *α,α*-difluoroalkylphosphonates were found to be more effective analogues of phosphonates compared with the nonfluorinated congeners because the CHF

and CF_2 groups can both sterically and electronically mimic an oxygen, enabling the second dissociation constant, pK_a[2], to more closely mirror those of the phosphates due to the electron-withdrawing effect of fluorine. For example, the pK_a of the second deprotonation of a phosphate group is ca. 6.4. The CH_2-phosphonate has a corresponding pK_a of ca. 7.6 and is less acidic. The electron-withdrawing effect of the two fluorine atoms on the CF_2-phosphonate significantly lowers the pK_a to ca. 5.4, and the presence of only one fluorine atom in the CHF-phosphonate results in a pK_a of ca. 6.5, almost identical to that of the natural phosphate.[104-106] Theoretical studies also indicates that the electrostatic profile of a CHF phosphonate is close in magnitude to that of a phosphate.[107]

Unfortunately, the abundance of digestive phosphatases renders phosphate esters themselves impractical functional groups for drug design, with the exception of pro-drug applications (for example, Etopophos is a useful prodrug with enhanced water solubility).[108] For this reason, much like the peptidomimetic problem, the phosphate mimics problem has captured the attention of many in the bioorganic community. The rotian that replacement of the bridging oxygen in a phosphate ester or anhydride with a CH_2 should confer inertness to phosphatase cleavage is a well established one, and simple phosphonate analogues of biological phosphates continue to be of interest.[90, 92] In the 1980s Blackburn and coworkers [85, 104] and Mckenna and Shen [103] suggested that superior bioisosteres might be obtained by introducing α-halogenation, and in particular, α-fluorination, into such phosphonates (Figure 8).

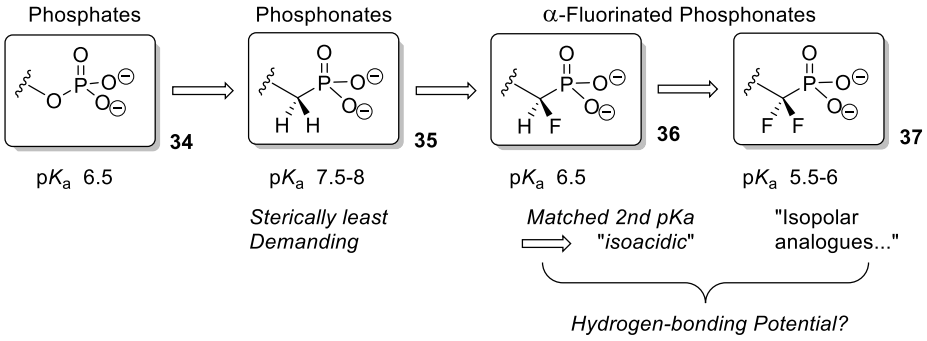


Figure 8: Fluorinated phosphonates as "phosphate isosteres"

Among other parameters that potentially favor α-fluorinated phosphonates over their nonfluorinated analogues are (a) reduced pK_a[109] (b) increased C-CX_2-P dihedral angle, (c) increased polarity of the bridging group (d) the possibility for C-F···H-X hydrogen

bonding[110-112] and (e) increased hydrolytic stability, as well as oxygen stability.[89] Sterics, on the other hand, tend to favor the simple phosphonate as literally the best isostere (in α-fluorinated phosphonates, the C-F bond is typically 1.3-1.5 Å, 30-50% longer than the corresponding C-H bond).

Indeed, α,α-difluorinated phosphonates are known to be especially effective phosphate isosteres in a number of the active sites (Figure 9). For example, Monsanto *et al*. found that phosphoenol pyruvate analogue **38** irreversibly inactivates EPSP synthase (Excitatory Postsynaptic Potential).[113] Burke *et al*. discovered that the difluorinated analogue of phosphotyrosine, when incorporated into an appropriate hexapeptide **40**, enhanced PTP1B-binding affinity 2000-fold relative to the CH_2-phosphonate-containing congener **39**.[114] Peptide **40** even reverses the impairment of insulin receptor function associated with the overexpression of PTP1B in some forms of diabetes.[115] Later, the CF_2-phosphonate analogue of phosphoserine,[116, 117] and then incorporated into peptide **41**, served as a useful bio-organic tool, allowing Appella and coworkers to induce otherwise unobtainable antibodies to the Ser[6]-phosphorylated form of the important human tumour suppressor protein p53, for the study of its regulation.[118]

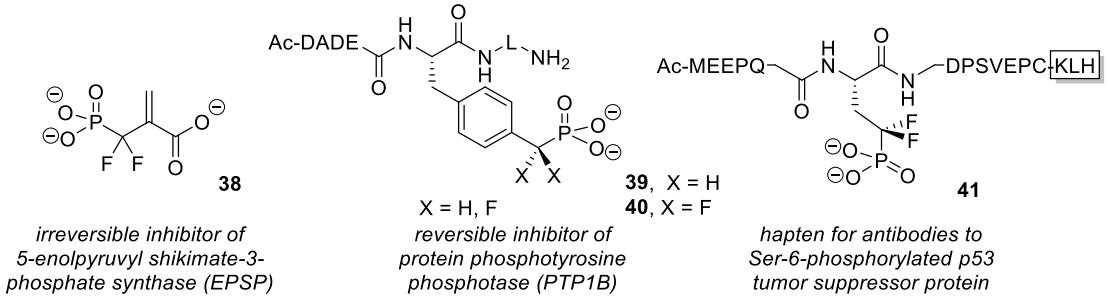


Figure 9: α,α-Difluorinated phosphonates as bioorganic tools.

Halazy and coworkers, working with a series of florinated analogue inhibitors of purine nucleoside phosphorylase.[119, 120] They found that, in this active site, one could gain an order of magnitude in binding affinity with α-difluoroination (**42** and **43**, Figure 10). Interestingly, however, placement of an additional CHF unit in the β-position (for example (CHF)CF_2-phosphonate, **44**) reduced K_i by another magnitude. The stereochemical dependence of this effect at the α-centre was not examined. The result suggests that when constructing phosphonate isosteres, both flanking CHF and CF_2 units should be considered, and where

possible it may even be advantageous to include both α- and β-fluorination in such phosphonates.

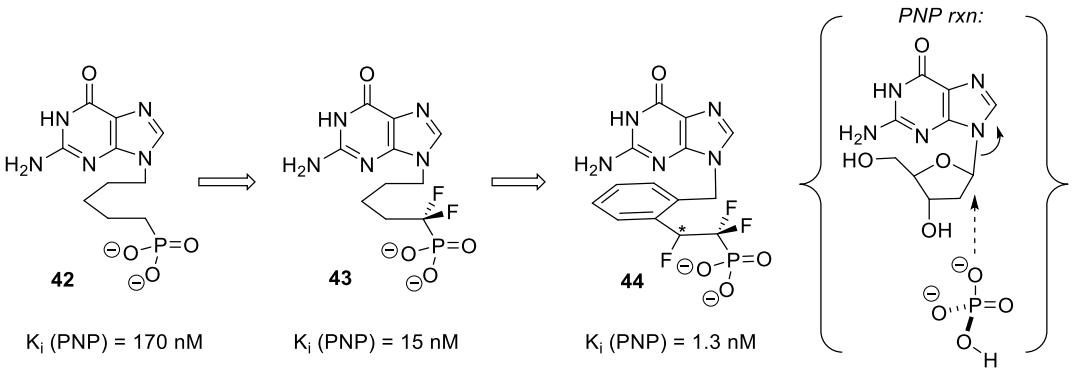


Figure 10: Bisubstrate Analogue Inhibitors for Human Erythrocyte PNP (Purine Nucleoside Phosphorylase).

However, it remains the case that placement of a single CHF unit α to the phosphoryl group results in a phosphonate that is essentially iso-acidic with the phosphate itself. So, although a fair number of (α-monofluoroalkyl)phosphonates have been reported (Figure 11),[121-132] somewhat surprisingly, the biological activity of this class of phosphate mimics remains much less explored than that of either their simple phosphonate or α,α-difluorinated congeners. Most importantly, the possible influence of the additional CHF stereocentre upon binding/activity has only recently begun to be examined.

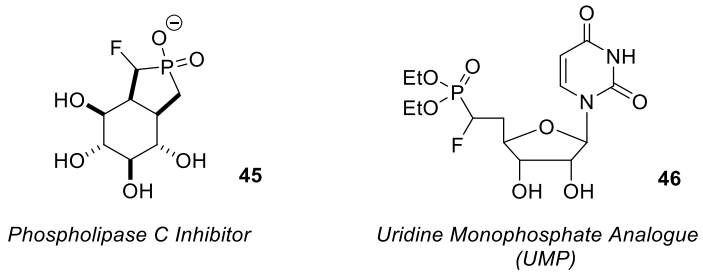


Figure 11: Bioisoteres of the monofluorinated phosphonate class.

L-Rhamnose-1C-phosphonate has been found to be a superior inhibitor than all of the ketosephosphonates, perhaps because of the low binding effectiveness from the existence of the C2 hydroxyl on the ketophosphonate. For the collection of ketophosphonates, being a single of fluorine atom at the position in C1 **49** enhanced inhibition by ~25% compared with the non-fluorinated **50** and **51** phosphonate while having two fluorine atoms **47** and **48** was deleterious to inhibition. (Figure 12)

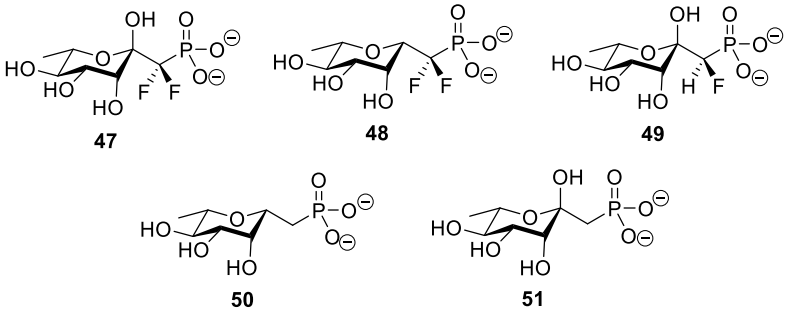
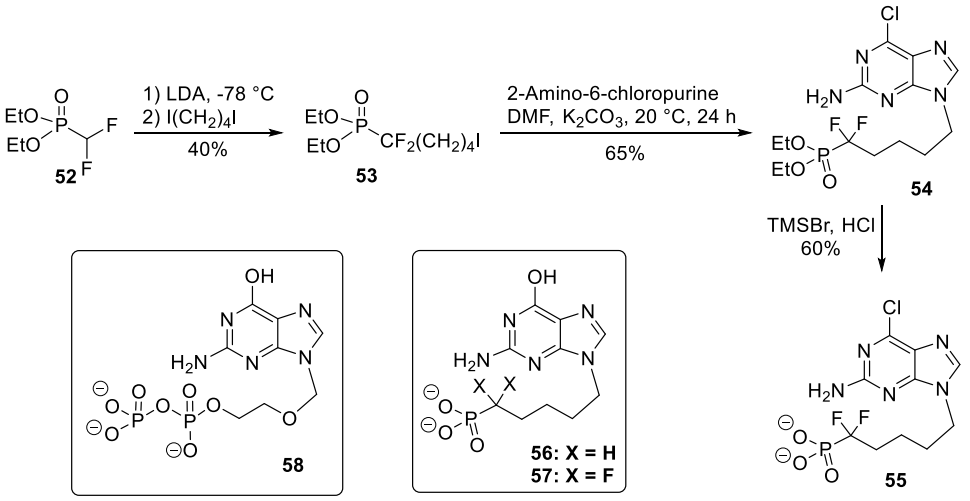


Figure 12: Ketophosphonate Analogue Compounds.

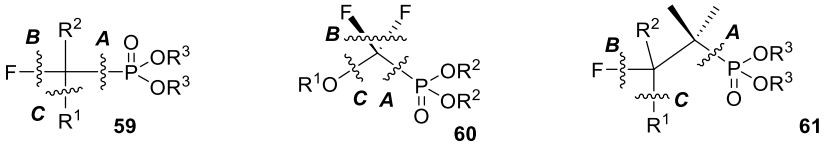
In 1991 Halazy *et al*. reported the synthesis of 9-(5,5-difluoro-5-phosphonopentyl) guanine **57**. It was synthesized as a potential multisubstrate analogue inhibitor of purine nucleoside phosphorylase (EC 2.4.2.1, PNP). As a key enzyme in the purine salvage pathway,[133] is believed to be a target for the design of immunosuppressive agents. PNP inhibitors might also be useful in the treatment of T-cell leukemia, gout,[134-137] and some parasitic diseases.[138] Based on the finding that the diphosphate derivative of acyclovir **58** is a very potent inhibitor of the human enzyme,[139, 140] (K_i = 8.7 nM, when determined in the presence of 1 mM orthophosphate), metabolically stable "multisubstrate" acyclic nucleotide analogues containing a purine and a phosphate-like moiety such as 9-phosphonoalkyl derivatives of hypoxanthine and guanine have been designed and synthesized.[141] It was proposed by Kent and Blackburn[142] that *α*-fluoro- and *α*,*α*-difluoroalkanephosphonates should mimic phosphate esters better than the corresponding phosphonates. This assumption was based on both electronic and steric considerations. So far, however, attempts to exploit the potential of fluorophosphonates as substrates or inhibitors of enzymes has not led to any significant improvement versus nonfluorinated phosphonates.[143-145] It was found that compounds **56** and **57** inhibited PNP prepared from rat erythrocytes, human erythrocytes, *Escherichia coli* and calf spleen (Scheme 6).



Scheme 6: Synthesis of analogue inhibitors of purine nucleoside phosphorylase.[119]

1.12. General Synthetic Methods

It is possible to synthesize fluorinated phosphonates by several recognized strategies (Figure 13) that include (a) electrophilic fluorination of phosphonate carbanions, (b) direct synthesis *via* trivalent derivatives of phosphorus and fluorohaloalkanes, (c) nucleophilic fluorination of functionalized phosphonate substrates, (d) radical approaches and (e) addition reactions catalysed by transition metals.



A: *synthesis via Arbuzov and Michaelis-Becker reaction, transition metal catalyzed and radical reaction*
B: *nucleophilic or electrophilic fluorination of phosphonate substrates*
C: *synthesis via fluorinated phosphonate carbanions and radical additions*

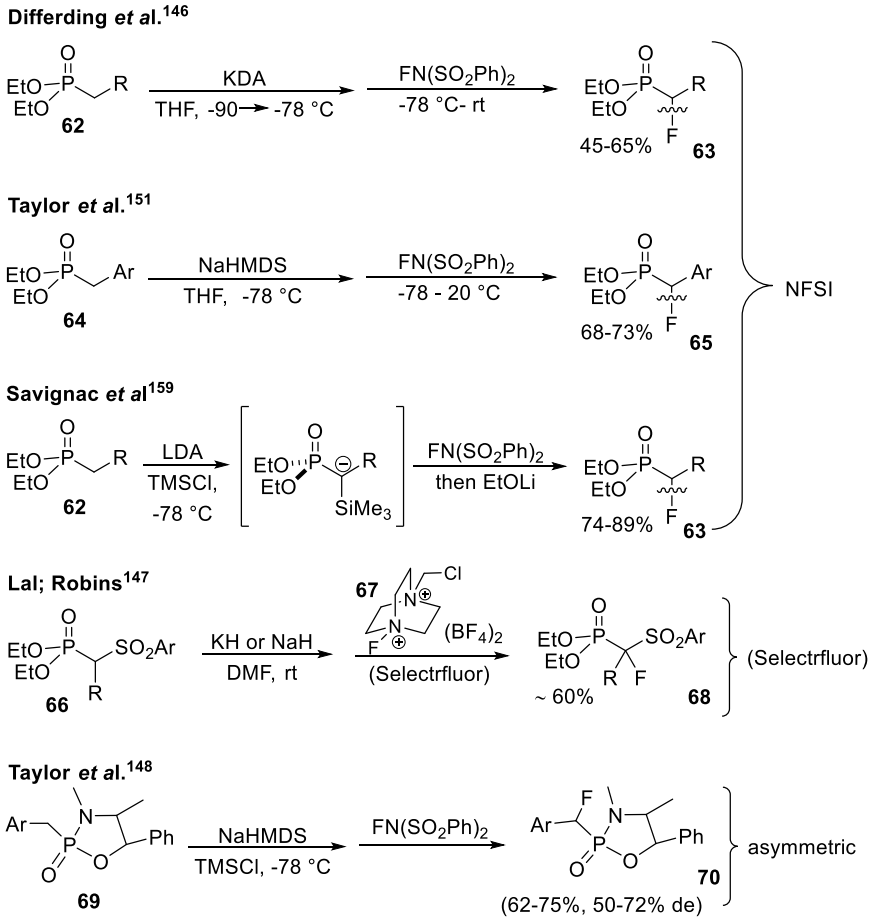
Figure 13: Diagrams of possible synthetic strategies to fluorinated phosphonates.

1.12.1. Synthesis of (*α*-monofluoroalkyl)phosphonates

1.12.1.1. Electrophilic fluorination

Through the synthetic methods of the *α*-monofluorinated phosphonates, two of the widely recognised methods include C-X bond disconnection. The previous decade has seen the evolution of electrophilic fluorination as a feasible process. One produces a carbanion *α* to phosphoryl unit and after that traps it with an X^+ equivalent. First electrophilic fluorination *α* to phosphorus was reported by Differding *et al*,[146] where KDA (potassium diisopropylamide) was used as a base to produce an "unstabilized" anion *α* to phosphorus.

NFSI was used as a source of fluorine cation F^+ and gives modest to good yield. Generally, in later work has been seen that the reaction proceeds more effectively when a stable α-phosphoryl anion $[(RO)_2P(O)C(Y)R^-]$ is used, when the Y group is either trialkylsilyl,[147] aryl,[148] or arenesulfonyl (Scheme 7). Selectfluor® has been successfully deployed as an alternative F^+ equivalent when Y is sulfonyl. Saviganc *et al*. have improved this chemistry, where a trimethylsilyl group is introduced in *situ* and used as an anion-stabilizing group, and extracted under basic conditions, then α-fluorination.[149, 150] Furthermore, Taylor *et al*. reported that reasonable to good ee's can be acquired by incorporation of an ephedrine ester/amide auxiliary to the phosphoryl centre.[151]

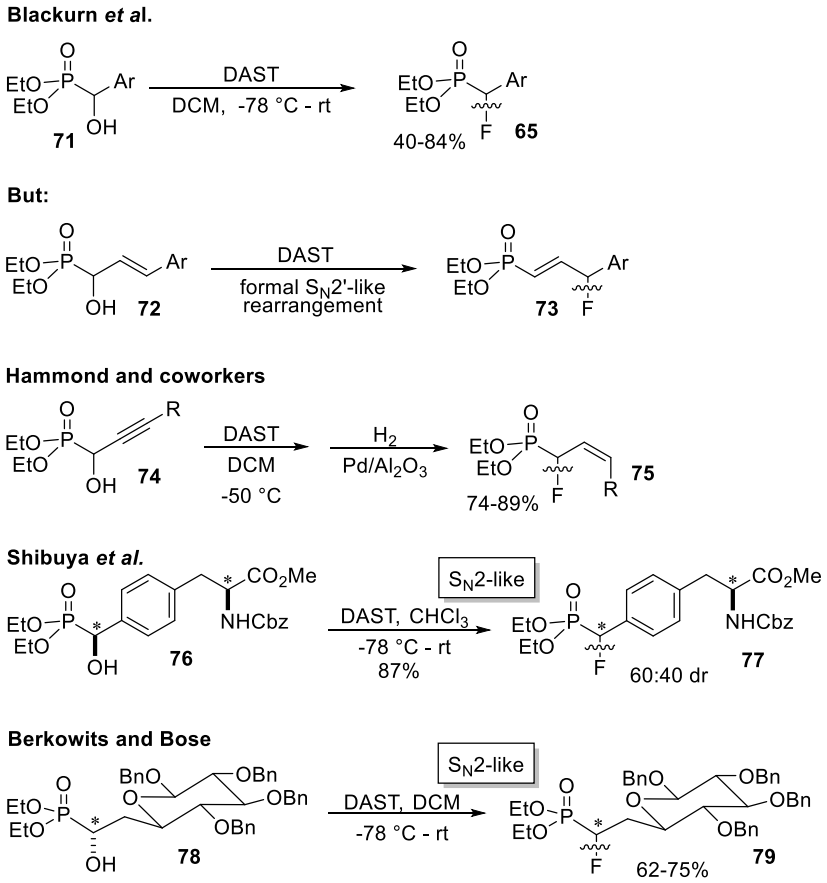


Scheme 7: Synthesis of (α-monofluoroalkyl)phosphonates.

1.12.1.2. Nucleophilic fluorination

Nucleophilic fluorination is an alternative route for the synthesis of α-monofluorinated phosphonates. Generally, this route includes reaction of an alcohol with DAST (*N*,*N*-diethylaminosulfur trifluoride) and apparently goes through a S(IV)-ester intermediate.

Blackburn and Kent were the first to employ this reaction to (α-hydroxyalkyl)phosphonates (Scheme 8).[142, 152] The reaction was observed to function admirably for benzylic substrates, but led to a rearrangement (formally an S_N2 displacement or [3,3]-sigmatropic shift) for cinnamyl-type or allyl systems. Subsequently, Hammond, reported that propargylic (α-hydroxy) phosphonates do afford pure substitution with DAST, without going with rearrangement. Finally, partial catalytic hydrogenation of the triple bond in **74** yielded the desired 1-fluoro -2-butenylphosphonates **75** (Scheme 8).[153-155]

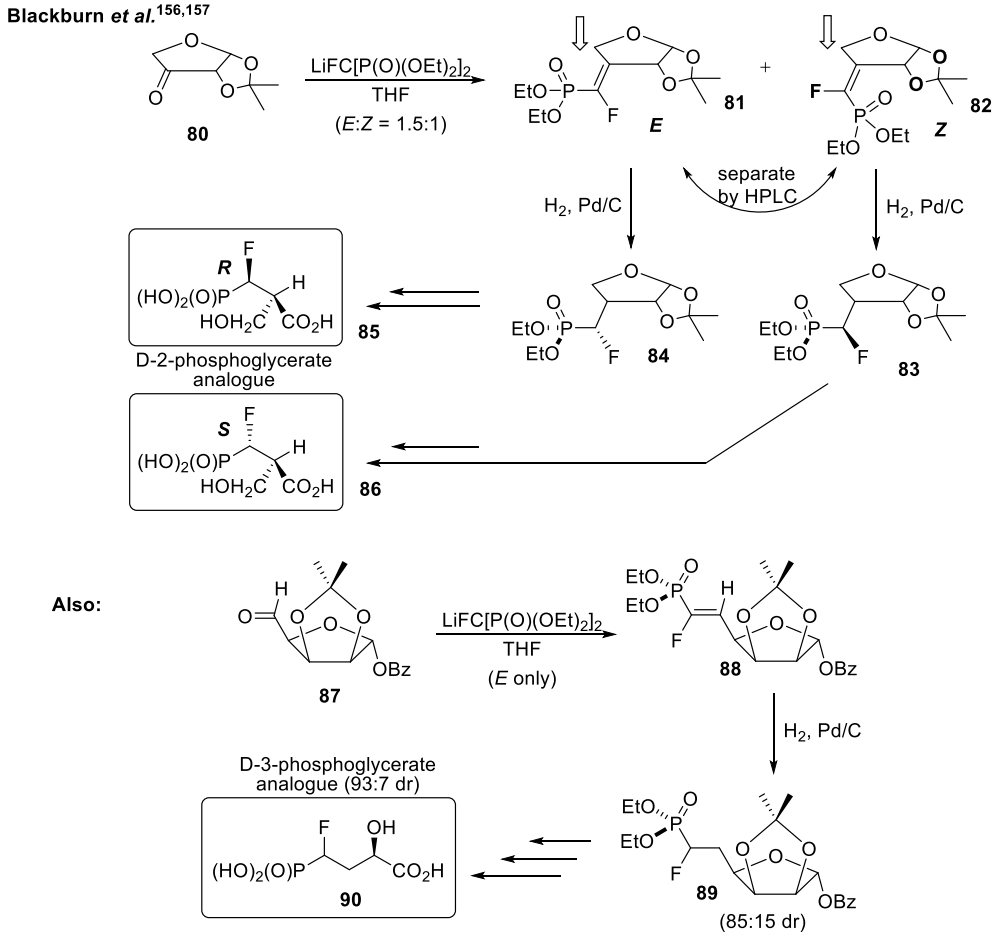


Scheme 8

1.12.1.3. Horner-Wadsworth-Emmons olefination approach

In the 1980s, Blackburn and Parratt were reported that tetraalkylfluoromethylenephosphonate anions undergo HWE-condensation with aldehydes and ketones producing protected, (α-fluoro)vinylphosphonates,[156, 157] as a mixture of geometric isomers. However, with aldehydes, a pronounced preference for the *E*-isomer is generally seen. Following this initial disclosure, the Sheffield group reported the application of this approach to the synthesis of monofluorophosphonate analogues of several glycolytic intermediates, including glyceraldehyde 3-phosphate,[131] 2-phosphoglycerate[130] and 3-phosphoglycerate.[158]

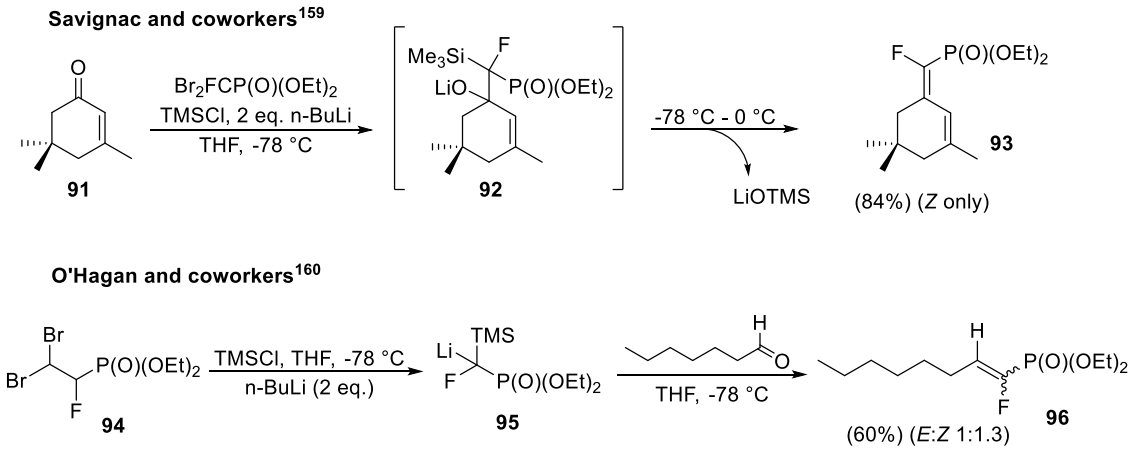
In order to access CHF-stereoisomers, Blackburn carried out the HWE reaction with carbonyl groups establishing on comparatively rigid acetonide-protected carbohydrate framworks. The scaffolding provided by the protected sugar then imposed a significant diastereofacial bias upon a subsequent double bond hydrogenation step. Provided that geometric isomers can be separated at the (α-fluoro)vinylphosphonates stage, this approach allows to obtain single stereoisomers of the target (α-monofluoroalkyl)phosphonates to be formed, with predictable CHF stereochemistry in some cases (for instance hydrogenation of **81** and **82** presumably occurs from the exposed convex face). Deprotection and periodate-mediated oxidative processing then allows one to extract the desired analogues of C_3-metabolites from these carbohydrate templates of higher carbon count.[158]



Scheme 9

1.12.1.4. Peterson olefination approach

In 1996, the group of Savignac and coworkers[159] and O'Hagan and coworkers[160] independently reported a complementary Peterson olefination entry into (*α*-fluoro)vinyl-phosphonates (Scheme 10). In fact, Blackburn and Parratt had actually first reported one example of a related Peterson approach some time earlier.[161] In a key development leading to the maturation of this chemistry, Savignac and coworkers had developed a procedure for the *in situ* generation and alkylation of the lithium anion of diethyl(*α*-trimethylsilyl) fluoromethyl-phosphonate (vide infra) **92**. The condensation of this anion with carbonyl compounds then followed as a logical and important extension of that chemistry. With aldehydes, the Peterson approach generally provides a higher percentage of the *Z*-isomer than the Horner-Wadsworth-Emmons approach. Nonetheless, it generally must be separated from the nearly equimolar quantity of the *E*-isomer. With cyclohexenones (**91-93**) or with *α*-substituted cyclohexenones, a marked preference for the *Z*-isomer is often seen.



Scheme 10

1.13. Project Aims

The overall aims of this work are to make pseudaminic acid inhibitors by preparation of tetrahedral intermediate inhibitors and evaluate it on bacteria. Coupled with the exploratory results provided by Tanner, where they have developed inhibitors of sialic acid synthase NeuB, it would make a good target to construct and evaluate tetrahedral intermediate inhibitors derived from a methylene-phosphonate pharmacophore (Figure 14).

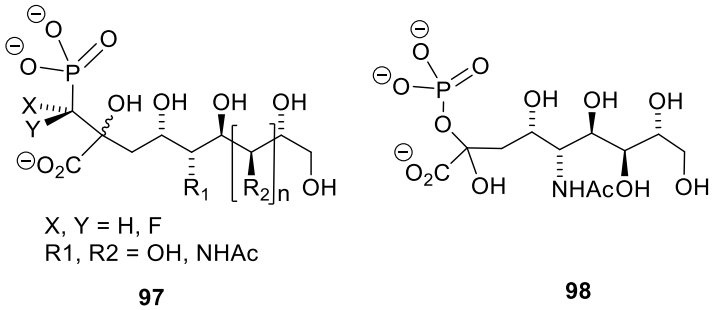


Figure 14: (**97**) target inhibitors for this proposal, (**98**) Tanner's inhibitor.

Initial work will be developing synthetic methodology to access a model of *β*-hydroxy phosphonates (Figure 15), including α-fluorinated species, in enantiomerically pure form, and to apply this developed methodology to the synthesis of *α*-fluoro-*β*-hydroxy poly-hydroxy and amino-polyhydroxy inhibitors.

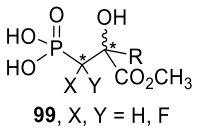


Figure 15: Representative chiral phosphonate compound.

After that, the progression will be focussed on accessing to *β*-hydroxyphosphonic acid which it has a similar moiety to the pseudaminic acids, which are considered more challenging than that *β*-hydroxyphosphonates. With this starting material in hand, work on this class of compound can possibly be evaluated on the bacteria to examine the inhibition of bacterial motility.

2. Chapter 2: Results and Discussion

2.1. *β*-Hydroxyphosphonate

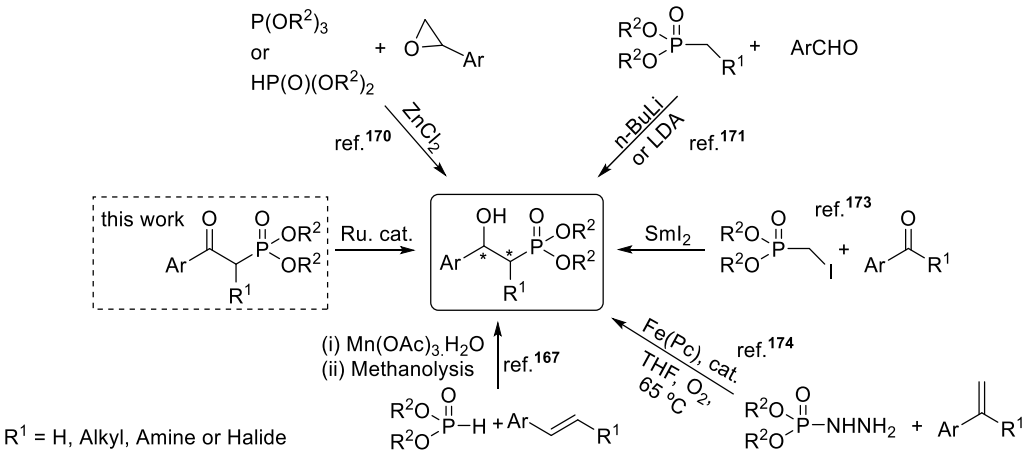
2.1.1. Background

Research in phosphonate biology and chemistry is based on the fact that the C-P bond in phosphonates[90] is not liable to hydrolytic processes of phosphatases, giving stability and longer period of activity under physiological conditions. Hydroxy phosphonic acids are an important class of compounds, some of which are obtained from Nature, which can be found in carbohydrates, nucleotides, phospholipids and amino acids.[85, 104, 162-165] Due to their biological applications and the ability to mimic the corresponding amino acids or hydroxy-carboxylic acids, chiral *β*-hydroxy phosphonates are an important type of compound that have received significant attention.[166] β-Hydroxy-phosphonates have been used in numerous applications including herbicides, horticultural agents, antioxidants, and moisture-resistant compounds.[167] Furthermore, the hydroxyl group can be converted into other functional groups, such as esters, ethers and amines, which all have distinctive biological effects. [168]

2.1.2. General Synthetic methods of *β*-hydroxyphosphonates

Chiral beta hydroxy phosphonic acids have acknowledged significant attention because of their unique physiological activities as well as their ability to mimic the corresponding hydroxy carboxylic acids or amino acids because they can be used as an intermediate in the syntheses of potentially significant peptide analogues, catalytic antibodies, and phosphonic acid-based antibiotics.[169] *β*-Hydroxyphosphonates have been previously prepared by numerous strategies (Scheme 11), that include the ring-opening of epoxides with phosphorus nucleophiles, reacting epoxides and triethyl phosphite with $ZnCl_2$ under mild conditions, to give a regioselective product in high yields (85-92%).[170] The reaction of aldehydes with alkylphosphonates through an aldol-like reaction with presence of strong base such as *n*-BuLi or DBU with diethyl phosphite,[171,172] gives racemic *β*-hydroxyphosphonates, that have been subjected to enzymatic kinetic resolution using *C. antarctica* lipase B (Novozym-435) to give product in >99% ee. The addition of α-halophosphonates to carbonyl compounds *via* Reformatsky-type reaction with SmI_2[173] results in a racemic mixture of *β*-hydroxyphosphonates in acceptable yield. Other procedures reported include using phosphorohydrazidates as radical precursors in iron-catalyzed aerobic oxidation to give phosphonyl radicals, [174] or by radical oxidative phosphonation of alkenes with H-phosphonates using $Mn(OAc)_3$-mediated radical oxidative phosphonation of alkenes with H-

phosphonates and H-phosphine oxide.[167] This method can be appropriate to large-scale preparations.



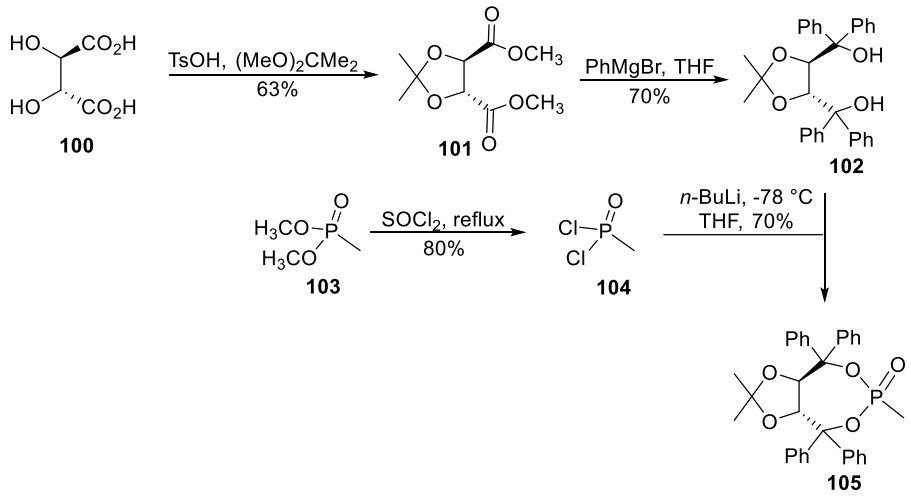
Scheme 11: Summery of synthetic routes to β-hydroxyphosphonates.

2.1.3. Synthesis of chiral *β*-hydroxyphosphonates

Generally, apart from enzymatic kinetic resolution,[175] the chirality in β position can be introduced in several ways, including, asymmetric addition of phosphonate carbanions or chiral phosphites to carbonyl compounds,[176] addition of chiral aldehydes to phosphorus nucleophiles,[177] or by asymmetric reduction of the corresponding prochiral *β*-ketophosphonates. In this work, the latter was investigated.

Although these methods have been used to access *β*-hydroxyphosphonates, the targets needed a tertiary stereogenic centre that asymmetric reduction could not deliver. Thus, an approach was first conducted using an auxiliary based method.

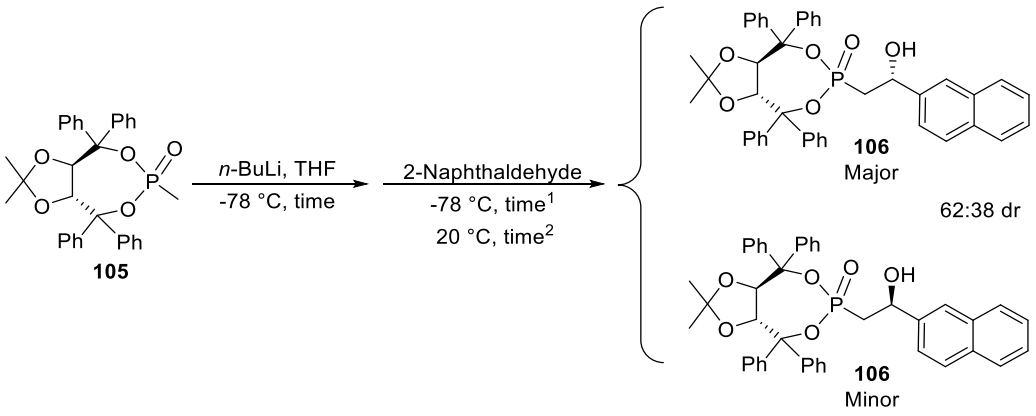
The synthetic route adopted was preparation of chiral methyl phosphonate **105** hoping to control the stereochemistry by use of the chiral auxiliary. TADDOL **102** was prepared by reaction of L-tartaric acid **100** with 2,2-dimethoxypropane (DMP) in the presence of *p*-toluene sulfonic acid to give (4*R*,5*R*)-dimethyl-2,3-*O*-isopropylidene-L-tartrate **101** in a good yield.[178] Reaction of this with an excess of phenyl magnesium bromide gave TADDOL **102**. Separately, methylphosphonic dichloride **104** was prepared by reaction of dimethyl methylphosphonate **103** and thionyl chloride for 12 h, followed by distillation under atmospheric pressure. This was reacted with TADDOL **102** that has been pre-treated with *n*-BuLi (2.5 eq.) at -78 °C to give methyl phosphonate **105** which matched the analytical data in the literature (70% yield) (Scheme 12).



Scheme 12: Synthesis of methyl phosphonate **105**.

First trial, *β*-naphthaldehyde was chosen as a model. In order to obtain the *β*-hydroxyphosphonate, phosphonate **105** was deprotonated with 1.0 equivalents of *n*-BuLi in THF at -78 °C, followed by addition of *β*-naphthaldehyde. After workup, to the alcohol **106** was obtained as a mixture of diastereoisomers (Scheme 13).

The reactions were conducted at -78 °C, and the lowest yield was achieved when the reaction was carry out at -40 °C (8%, entry 6, Table 1). It was also observed that increased reaction time after addition of aldehyde negatively affected the reaction yield (entries 1-5). However, when deprotonated for just 15 minutes followed by 30 minutes at -78 °C and 30 minutes at 20 °C after addition of *β*-naphthaldehyde, the yield was 61% (entry 7). Increasing reaction time with low temperature further improved this yield.



Scheme 13: Synthesis of *β*-hydroxyphosphonate *via* aldol reaction route.

Table 1: Optimisation of aldol reaction.[a]

Entry	Deprotonation time/min.	Time[1]/ min.	Time[2]/ min.	Yield/ %[b]	dr[c]
1	5	5	- [c]	25	ND[d]
2	15	15	-	35	ND
3	30	15	-	20	ND
4	60	60	-	15	ND
5	240	60	-	10	ND
6	240	120	60	8	ND
7	15	30	30	61	60:40
8	15	30	60	83	62:38

[a] Reaction conditions: **27** (0.1 mmol), *n*-BuLi (0.1 mmol), THF (5 mL), at -78 °C, in various time. Naphthaldehyde (0.1 mmol), in 1 mL THF. All reactions were conducted for different time and temperature. [b] Isolated yields. [c] Determined by 1 H NMR analysis. [c] The reaction was quenched at the same temperature after time[2] directly. [d] ND = no determined.

Two diastereoisomers were formed with a ratio of 62:38 (entry 8) dr, in total yield 83%. After separation and purification, the major and minor diastereoisomers were isolated in 46% and 25% yield respectively. The configurations at C-2 were established by X-ray analysis of the major diastereoisomer of compound **106** (Figure 16).

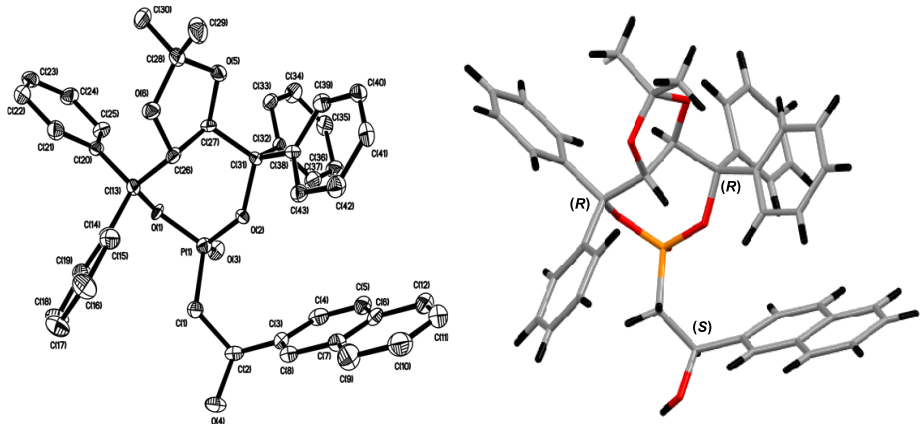


Figure 16: X-ray crystallography for compound **106**.

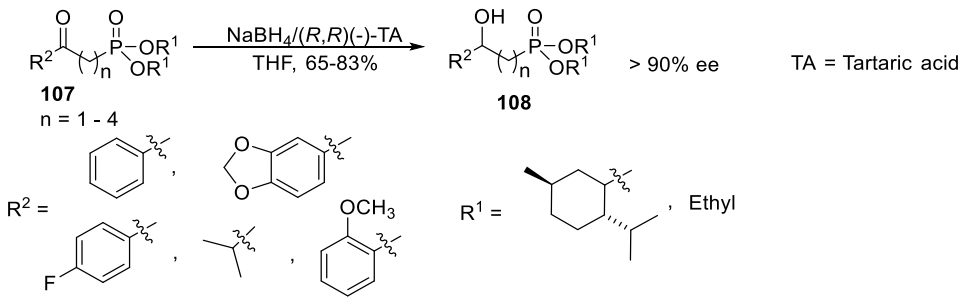
In order to help improve the diastereoisomer ratio, the reaction was conducted with additives, where after deprotonated starting material by *n*-BuLi at -78 °C for 15 minutes, following by adding *β*-naphthaldehyde at the same temperature. When using boron trifluoride diethyletherate or trimethyl borate, the conversion and yield were very low (entry 2 and entry 3**,** Table 2), whilst no reaction occurred when using titanium tetrachloride, titanium (IV) propoxide or zinc chloride (entries 4-7).

Table 2: Synthesis of *β*-hydroxyphosphonate.

Entry	Additive[a]	Conv./% [b]	Yield/% [c]	dr[b]
1	-	75	61	62 : 38
2	$BF_3.OEt_2$	25	15	62 : 38
3	$B(OMe)_3$	28	18	61 : 39
4	$TiCl_4$	0	-	-
5	$Ti(O^iPr)_4$	0	-	-
6	$ZnCl_2$ 0.1M in Et_2O	0	-	-
7	$ZnCl_2$	0	-	-

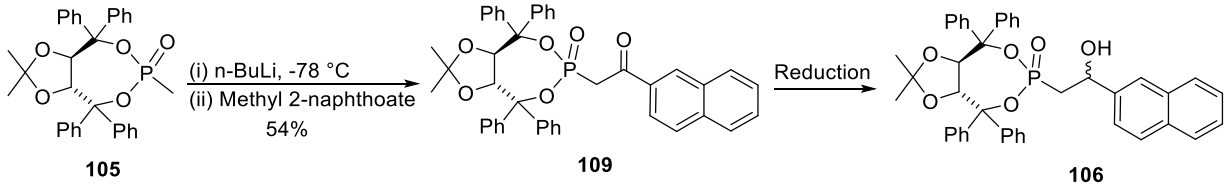
[a] (1 eq.) was added after deprotonated methyl phosphonate **27** with *n*-BuLi.
[b] Conversion and dr were determined by integration of appropriate signals in the ^{1}H NMR spectrum.
[c] Isolated yield.

In 2012, Nesterov *et al.* was developed a method for asymmetric reduction of *α*- and *β*-ketophosphonates using chiral complexes prepared from sodium borohydride and natural aminoacids or tartaric acids. Reduction of *α* or *β*-ketophosphonates by these reagents led to formation of chiral (*S*)- or (*R*)-hydroxyphosphonates. Reduction of chiral di-(1*R*,2*S*,5*R*)-menthylketophosphonates by the chiral complexes $NaBH_4$/(*R*,*R*)-proline or $NaBH_4$/(*R*,*R*)-tartaric acid due to the double matched asymmetric induction resulted in increased stereoselectivity of the reaction and led to the formation of hydroxyphosphonates up to 90% ee or higher. Dimenthyl 2-hydroxy-3- chloropropylphosphonate was utilized as a chiron for the preparation of a number of biologically active compounds in multigram quantity.[179, 180] (Scheme 14).



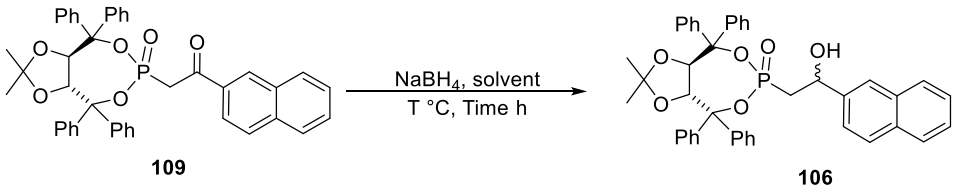
Scheme 14: Reduction of *β*-ketophosphonate using sodium borohydride and tartaric acids.[179]

In order to evaluate this method, the *β*-ketophosphonate substrate **109** was prepared by treatment of methyl phosphonate **105** with *n*-BuLi at -78 °C followed by addition of methyl 2-naphthoate at the same temperature. (Scheme 15)



Scheme 15: Synthesis and reduction of *β*-ketophosphonate.

Once synthesised, the asymmetric reduction was undertaken using a variety of conditions (Scheme 16, Table 3). Use of sodium borohydride-tartaric acid gave no reaction, but this complex has been reported to be is quite sensitive to moisture,[180] and might be the cause behind the failed reaction (Entry 1, Table 3). Low temperature reaction with only $NaBH_4$ gave the product with better diastereoisomer ratio (dr 75:25) than using MeOH and 100% conversion estimated by ^1H NMR analysis (Entry 2). When this reaction was performed at RT (Entry 3), the desired compound was obtained with a similar diastereoisomer ratio (dr 72:28). Use of methanol as solvent gave the product with lower dr (60:40) and conversion 50% (Entry 4). Mixtures of dichloromethane and methanol were used as solvent to overcome the problem of the low solubility of the starting material in methanol (Entry 5), leading to excellent conversion and a comparable diastereoisomer ratio (dr 68:32). The low stereoselectivity in all cases might be due to the distance of the chiral auxiliary from the ketone. Therefore, adding bulkier aryl groups to the chiral auxiliary (e.g. naphthyl) might lead to an increase in steric hindrance.



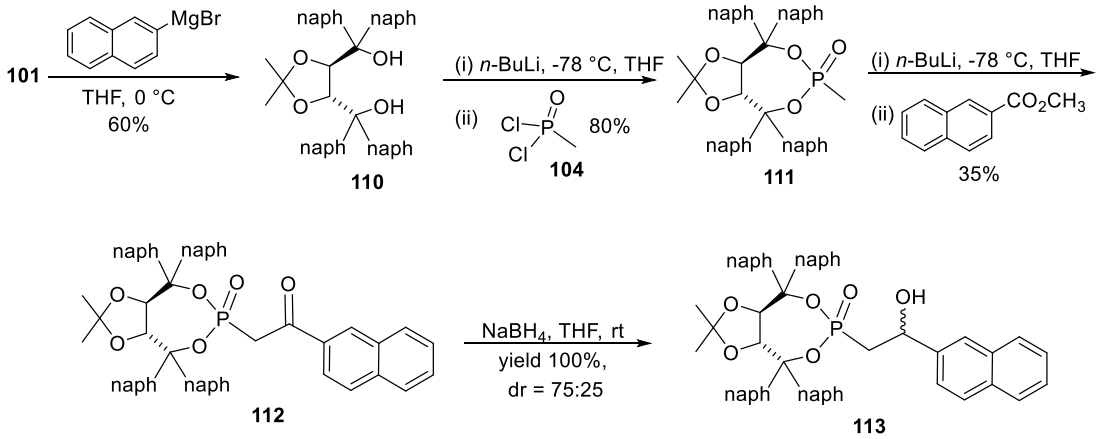
Scheme 16: Recduction of **109** with $NaBH_4$

Table 3: Reduction of *β*-ketophosphonate into *β*-hydroxyphosphonate.

Entry	Reducing agent	Solvent	T.°C	Time/h	Conv/%[b]	dr [b]
1	$NaBH_4$+TA[a]	THF	-30	16	0	-
2	$NaBH_4$	THF	-30	16	100	70:30
3	$NaBH_4$	THF	25	16	100	72:28
4	$NaBH_4$	MeOH	25	16	50	60:40
5	$NaBH_4$	DCM/MeOH	25	16	100	68:32

[a] TA: Tartaric Acid (1 eq.)
[b] Conversion and dr were determined integration of appropriate signals in the ^1H NMR spectrum

β-Ketonaphthylphosphonate **113** was synthesised from ester **101** by treatment with an excess of 2-naphthyl magnesium bromide at 0 °C to give diol **110**. This was treated with methylphosphonic dichloride **104** using *n*-BuLi at -78 °C. Naphthalene *β*-ketophosphonate **113** was then prepared by deprotonation of phosphonate **111** with *n*-BuLi at -78 °C, followed by addition of methyl 2-naphthoate giving the desired product. Subsequently, reduction to give the *β*-hydroxynaphthylphosphonate **113** using sodium borohydride, proceeded in complete conversion as estimated by ^{1}H NMR analysis but the diastereomeric ratio was almost the same as with the phenyl analogue (dr 75:25) (Scheme 17).

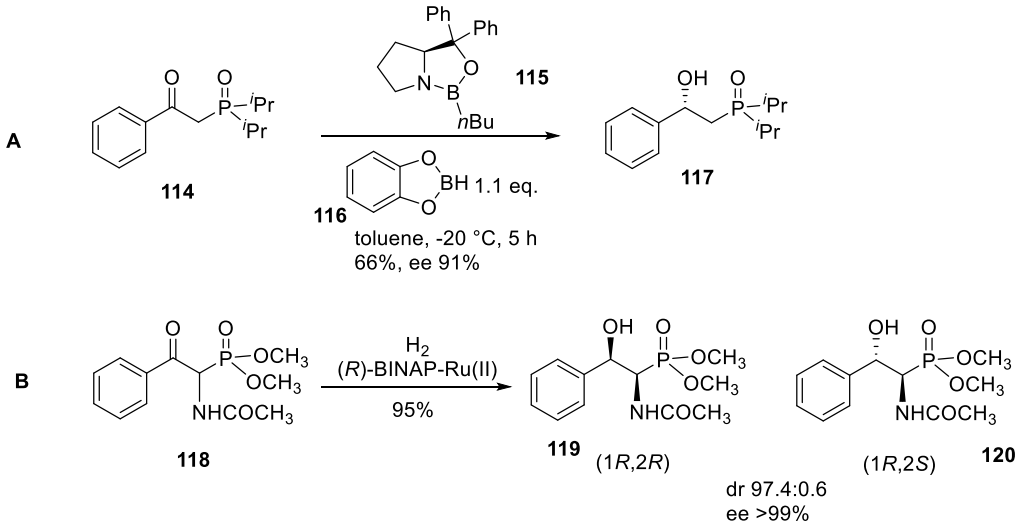


Scheme 17: Synthetic routes to *β*-hydroxynaphthylphosphonate.

Since an auxiliary approach failed to deliver the needed selectivity, previously used catalytic approaches were investigated.

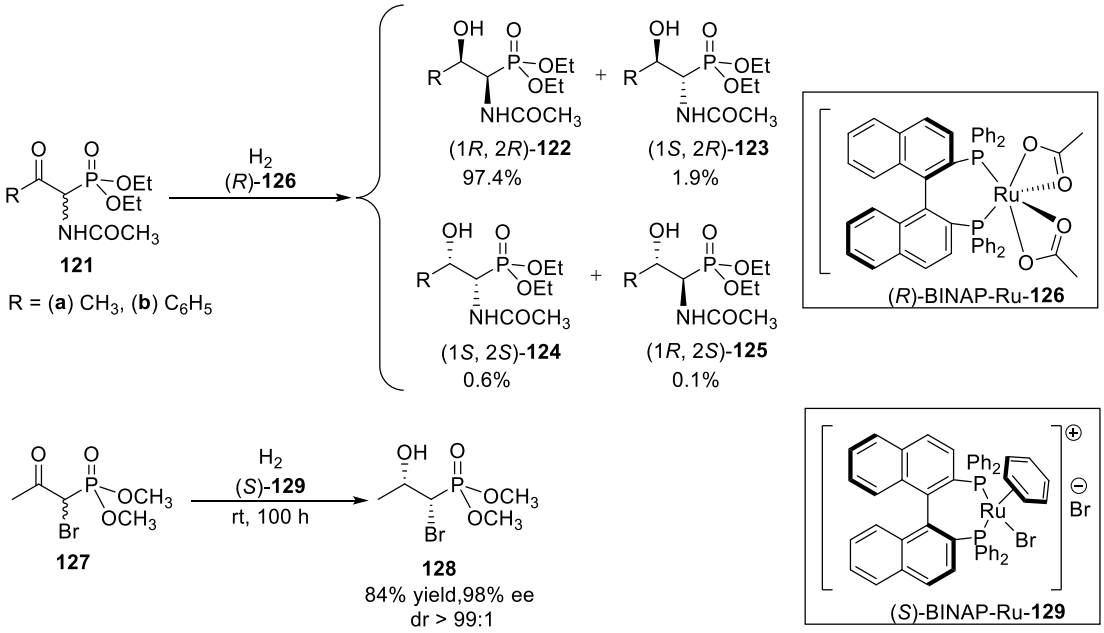
2.2. Asymmetric Hydrogenation Reaction

The asymmetric reduction of ketophosphonates has been studied by reduction with catecholborane or borane using chiral oxazaborolidine catalysts,[181,182] or using a chiral BINAP-Ru catalyst, (equation **B**)[183] (Scheme 18).



Scheme 18: Asymmetric reduction of *β*-ketophosphonates.[183]

Noyori and co-workers used derivatives of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in the reduction of various *β*-phenyl and *β*-alkylketophosphonates to prepare the corresponding *β*-hydroxyphosphonates. In 1995, Kitamura *et al.* reported that hydrogenation of a racemic *α*-substituted *β*-ketophosphonate **121** produced a mixture of four potential stereoisomers (1*R*,2*R*)-**122**, (1*S*,2*R*)-**123**, (1*S*,2*S*)-**124**, and (1*R*,2*S*)-**125** in a 97.4:1.9:0.6:0.1 ratio.[183] The hydrogenation of *β*-bromophosphonate **127** in methanol using (*S*)-BINAP-Ru-**129** catalyst at room temperature for 100 h, gave the desired stereoisomer, (l*R*,2*S*)-**128**, in 84% yield and 98% ee (Scheme 19).[184]



Scheme 19: Asymmetric Hydrogenation of *α*-substituted-*β*-ketophosphonates.[184]

In this case the absolute stereochemistry of the hydroxyl-bearing configuration C(2) stereogenic centre was established by a Felkin-Anh working model[185, 186] (Figure 17). In this, it is possible to have interactions between methanol or Ru atom with the carbonyl oxygen atom. The most stable transition state geometry (Figure 17) which leads to (l*S*,2*S*)-**128**, within the four possibilities, is where the carbonyl carbon approaches from the Re-face of the direction *anti* to the electronegative bromine atom with the hydride ion.

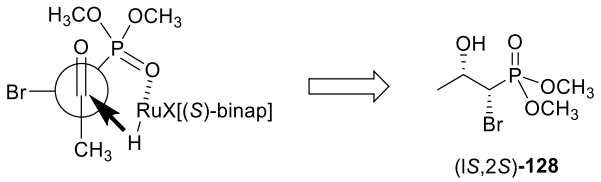
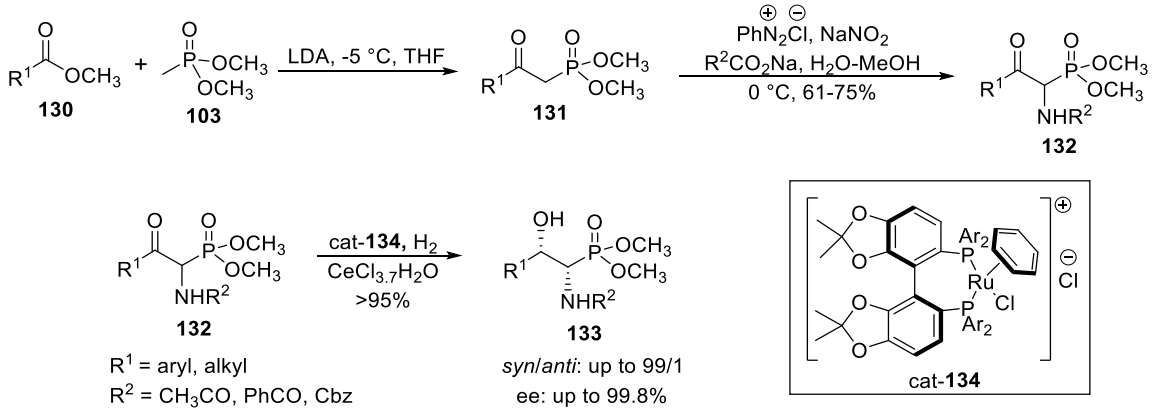


Figure 17

Asymmetric hydrogenation by a ruthenium-catalyzed dynamic kinetic resolution (DKR) is a good way to control two neighbouring stereogenic centres with excellent levels of diastereoselectivity and enantioselectivity in one chemical reaction.[187-191] In 1989, Noyori *et al.*[192] and Genet *et al.*[193] used chiral (*R*)-Ru catalysts, in the asymmetric reduction of the *β*-ketophosphonates in yields of up to 90% and with an ee of up to 90%. Genet and co-workers applied (*R*) and (*S*)-Ru-BINAP catalysts **134** to several *β*-keto- phosphonates substrates to give products in 70-100% yield and 92-99% ee.[194,195] In 2013, Zhang *et al.* prepared various *α*-amido-*β*-ketophosphonates **132** and then subjected them using chiral catalysts **134** in order to carry out asymmetric hydrogenation reactions *via* dynamic kinetic resolution to give the corresponding *β*-hydroxyphosphonates **133** in excellent enantioselectivity and diastereoselectivity (99.8% ee and up to 99:1 *syn*/*anti*) (Scheme 20).[196]



Scheme 20: Synthesis of *β*-hydroxy-*α*-amido phosphonates **133**.

2.3. Chiral catalyst

Until now, the only example was reported by Noyori in 1995 of an effective dynamic kinetic resolution of *R*-acetamido-*β*-ketophosphonate using a system of Ru-BINAP provided the corresponding *R*-acetamido-*β*-hydroxyphosphonate (*syn*, >98%).[183,184] Genet *et al.* also explored asymmetric hydrogenation reactions of *β*-ketothiophosphonates and *β*-ketophosphonates using the same Ru catalyst.[194] Recently Zhang *et al.* unveiled stereoselective reduction of an *α*-acylamido-*β*-ketophosphonates and *α*-alkyl-*β*-ketophosphonates[197] using a system of Ru-SunPhos as catalyst, in order to asymmetric hydrogenation of *β*-ketophosphonates which gave the corresponding *α*-alkyl-*β*-hydroxyphosphonates and *α*-acylamido-*β*-hydroxy phosphonates respectively in good to excellent enantioselectivities (up to 99.9% ee) and excellent diastereoselectivities (96:4) were obtained.

More recent efforts in this area have focused on the many ways to perform this reaction asymmetrically. In 2014, Son *et al.* reported many examples of asymmetric transfer hydrogenation reactions and dynamic kinetic resolution driven of a range of 2-substituted *α*-alkoxy-*β*-ketophosphonates **138**, to give the corresponding 2-substituted *α*-alkoxy-*β*-hydroxyphosphonates **139** and superb levels of enantio- and diastereoselectivity[198] (Figure 18, Scheme 21).

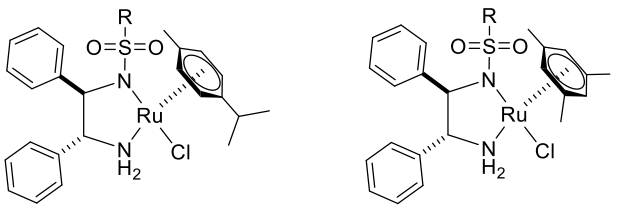
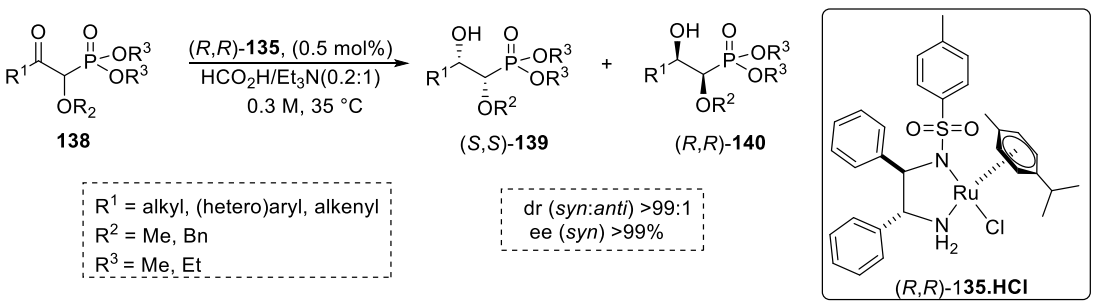
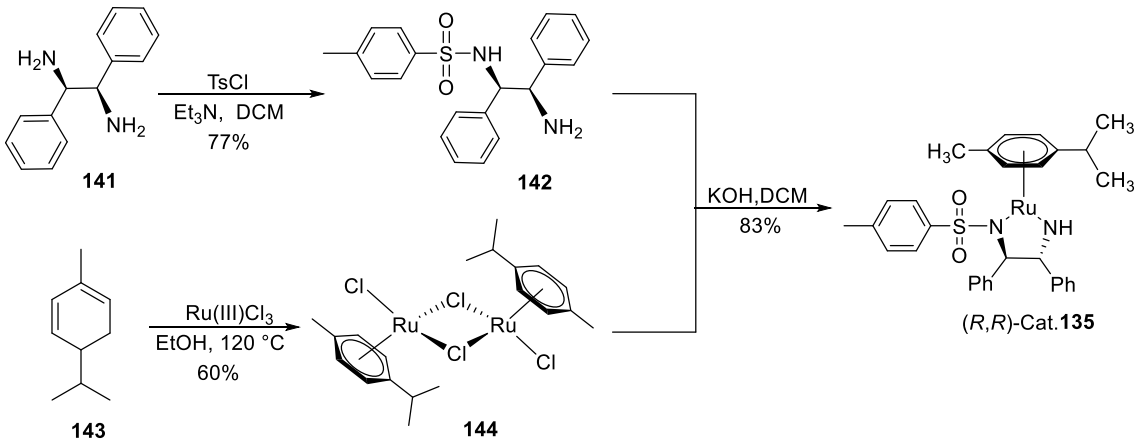


Figure 18: Noyori's Ru-catalyst.



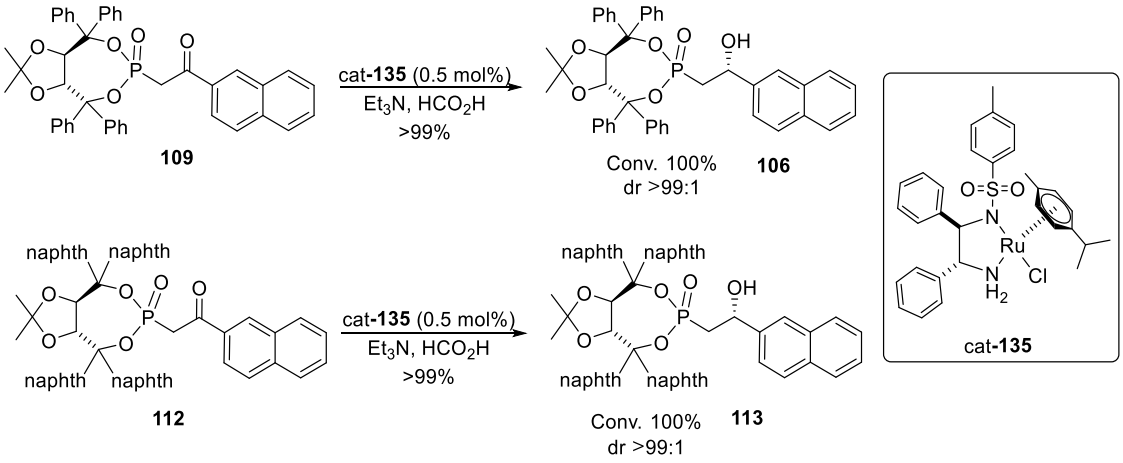
Scheme 21: Synthetic route of chiral β-hydroxyl group.[198]

Chiral ruthenium based catalyst (*R*,*R*)-**135** has been used widely for asymmetric hydrogenation reactions. This catalyst was synthesised in three steps with good yield. Firstly, (1*R*,2*R*)-1,2-diphenylethanediamine **141** was treated with *p*-toluene-sulfonyl chloride in the presence of triethylamine at 0 °C to rt for 36 h under an argon atmosphere to give **142** (TsDPEN). Compound **144** was prepared by heating *α*-phellandrene **143** with ruthenium(III) chloride at 120 °C for 4 h to afford the product as deep-red crystals. In the last stage, compounds **142** and **144** were stirred with KOH for 10 minutes to give **135** in high yield, which was dried under reduced pressure and stored in the fridge at 0-8 °C (Scheme 22).



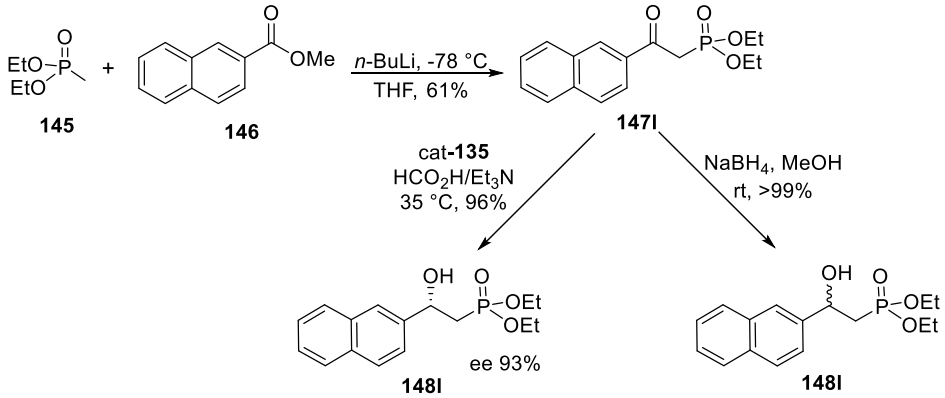
Scheme 22: Synthesis of Noyori catalyst **37**.

Ruthenium based catalyst (*R*,*R*)-**135** was employed in an asymmetric transfer hydrogenation reaction, where the *β*-ketophosphonates **109** or **112** were dissolved in dichloromethane and then Et_3N added, followed by formic acid at 35 °C overnight. This proceeded efficiently and gave the corresponding *β*-hydroxyphosphonates with complete diastereoselectivity (dr >99:1) as calculated by ^{1}H NMR and ^{31}P NMR analysis (Scheme 23).



Scheme 23: Asymmetric transfer hydrogenation reduction of *β*-ketophosphonates.

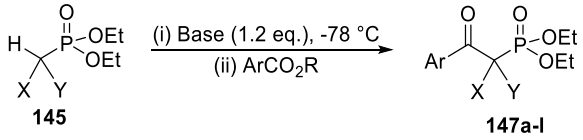
To investigate the effect of the naphthyl groups on the diastereoselectivity, the diethyl methyl phosphonate **145** was used as an achiral substrate. As the product **147l** was prepared in the past but in different ways and was not addressed to the use of ester with diethyl methyl phosphonate in the presence of *n*-BuLi at, where this mixture was cooled to -78 °C, then followed by addition of methyl 2-naphthoate **146** giving the *β*-ketophosphonate **147l** in good yield. Reduction of ketone **147l** with sodium borohydride gave a racemic mixture of *β*-hydroxynaphthylphosphonate **148** as, and when catalyst-**135** was used as a chiral catalyst, the product was obtained with 93% ee (Scheme 24).



Scheme 24: Synthesis of *β*-hydroxynaphthylphosphonate **52**.

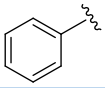
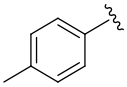
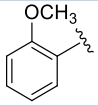
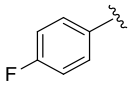
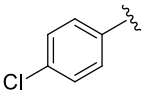
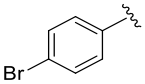
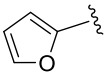
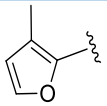
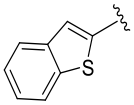
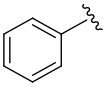
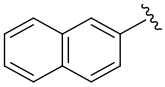
The stereodirecting group on the substrate did not have any effect on the selectivity of the reaction. Thus, a range of *β*-ketophosphonates were investigated as substrates. These were prepared by treatment of diethyl methyl phosphonate with *n*-BuLi at -78 °C or lithium bis(trimethylsilyl)amide (LiHMDS) at 0 °C in tetrahydrofuran (THF), followed by addition of various ester electrophiles, giving the corresponding *β*-ketophosphonates **150a-k** (Scheme

25, Table 4). In general, the yield was higher when using LiHMDS rather than *n*-BuLi, and in particular, the preparation of difluorophosphonate **150k** using *n*-BuLi failed, whereas it was successful with LiHMDS.



Scheme 25: Synthesis of *β*-ketophosphonates **147a-l**.

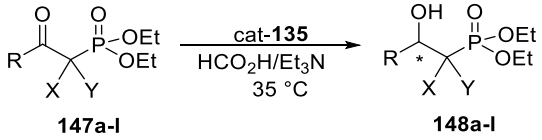
Table 4: Synthesis of *β*-ketophosphonates using *n*-BuLi and LiHMDS

Entry	Ar	R	X,Y	Yield/%[a]		147a-l
				n-BuLi	LiHMDS	
1		Et	H,H	61	70	**a**
2		Me	H,H	60	74	**b**
3		Me	H,H	30	87	**c**
4		Et	H,H	61	77	**d**
5		Et	H,H	65	74	**e**
6		Et	H,H	70	77	**f**
7		Et	H,H	55	60	**g**
8		Me	H,H	38	50	**h**
9		Me	H,H	54	61	**i**
10		Me	H,H	35	50	**j**
11		Et	F,F	-	85	**k**
12		Me	H,H	61	-	**l**

[a] Determined after purification by flash chromatography on silica gel

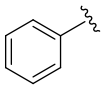
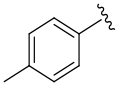
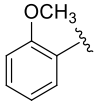
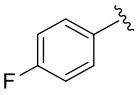
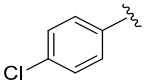
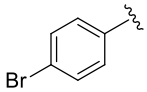
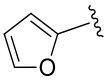
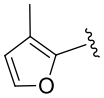
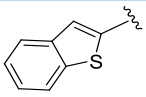
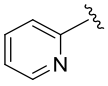
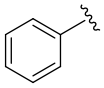
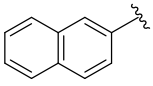
These *β*-ketophosphonates **147a-l** were reduced using the chiral ruthenium species (Scheme 26), affording the corresponding alcohols, **148a-l** in excellent ee 90-99% (Table 5). The

enantiomeric excess was not affected by changing the type of aromatic ring or substituents. However, enantioselective hydrogenation of the substrate bearing two fluorine atoms **147k** afforded the corresponding alcohol **148k** in only 20% ee (entry 12, Table 5).



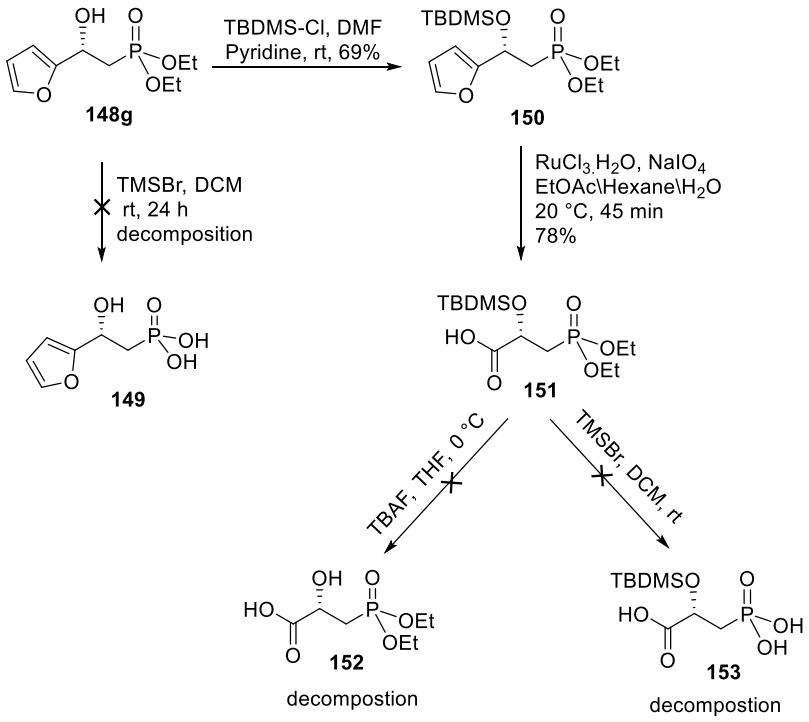
Scheme 26: Synthesis of *β*-hydroxyphosphonates.

Table 5: Asymmetric reduction of *β*-ketophosphonates.

Entry	Substrate		Yield% [a]	ee/% [b]	Configuration[c]
	R	X,Y			
1	 **148a**	H,H	85	90	*S*
2	 **148b**	H,H	91	96	*S*
3	 **148c**	H,H	76	93	*S*
4	 **148d**	H,H	84	97	*S*
5	 **148e**	H,H	93	92	*S*
6	 **148f**	H,H	91	97	*S*
7	 **148g**	H,H	82	98	*S*
8	 **148h**	H,H	79	98	*S*
9	 **148i**	H,H	94	>99	*S*
10	 **148j**	H,H	77	97	*S*
11	 **148k**	F,F	87	20	*S*
12	 **148l**	H,H	96	93	*S*

[a] Yield determined after purification by flash chromatography on silica gel
[b] Determined by chiral HPLC
[c] Determined by comparison with literature values

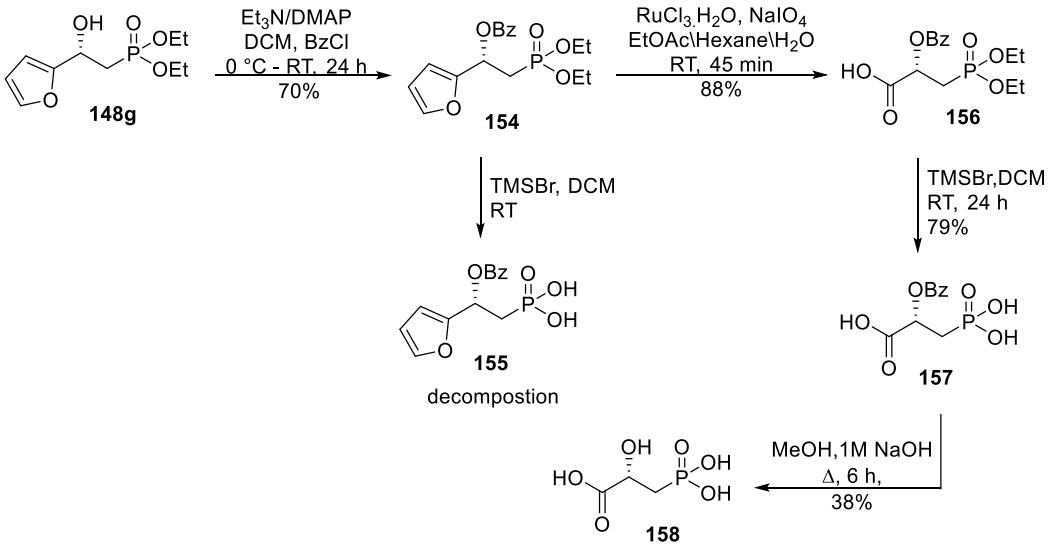
The low ee of difluoro substrate **148k** is most likely due to an enhanced electrophilicity of the carbon group, increasing the rate of any background reactive that is non selection. Compound **148g** was taken forward used because it contains a furan ring which can be oxidized to the corresponding carboxylic acid that is found in the target molecules.[199] The selected *β*-hydroxyphosphonate **148g** was treated with TMSBr and DCM to remove the ethyl groups, but this led to decomposition and thus, protection of the secondary alcohol with TBDMSCl was carried out in good yield.[200] With the protected *β*-hydroxyphosphonate **150** in hand, the furan ring was selectively oxidized with 8 equivalents of $NaIO_4$ and 0.5 mol% $RuCl_3$ as a catalyst in hexane/EtOAc/H_2O to give (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-(diethoxy phosphoryl) propanoic acid **151** in good yield. Phosphonate **151** was treated with TMSBr to hydrolyse the ethyl groups, but this led to decomposition. It is likely that the trimethylsilyl bromide, in addition to removing the ethyl groups, also deprotected the silyl group leading to decomposition as observed with **148g**. This was confirmed by attempting to remove the silyl group from **151** using tetrabutylammonium fluoride that immediately led to decomposition (Scheme 27).



Scheme 27: Synthesis of *β*-hydroxyphosphonate derivatives.

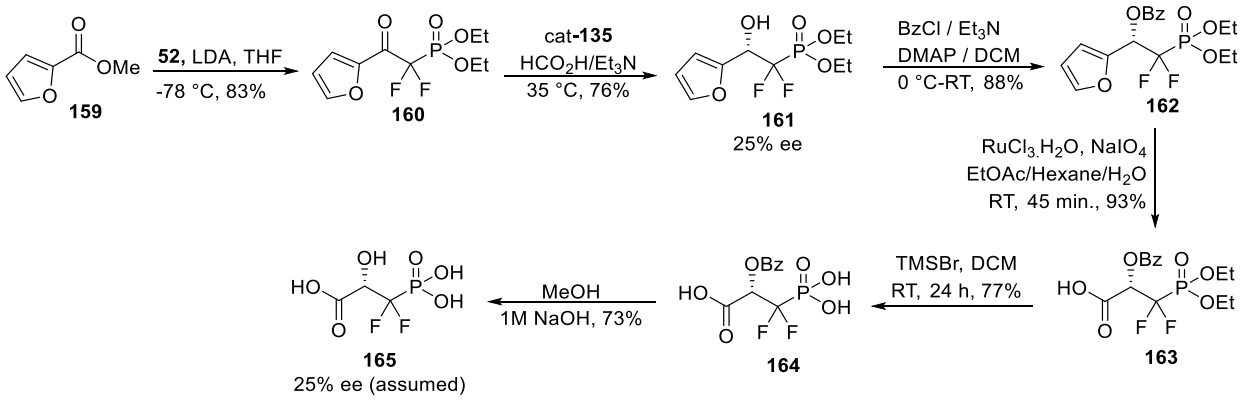
The protecting group was changed to benzoate by reacting the *β*-hydroxyphosphonate **148g** with benzoyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine at 0°

C. However, treatment of benzoate **154** with trimethylsilyl bromide in DCM at room temperature led to decomposition. Thus, the furan ring of compound **154** was oxidised using the previously employed reaction conditions to give the carboxylic acid **156** in good yield**,** followed by deprotection of ethyl groups using trimethylsilyl bromide in DCM at 25 °C, delivering target **157** in reasonable yield. Final deprotection of the benzoate group by heating with the mixture of methanol and 1M solution of sodium hydroxide gave the desired (*S*)-2-hydroxy-3-phosphonopropanoic acid **158** (Scheme 28).



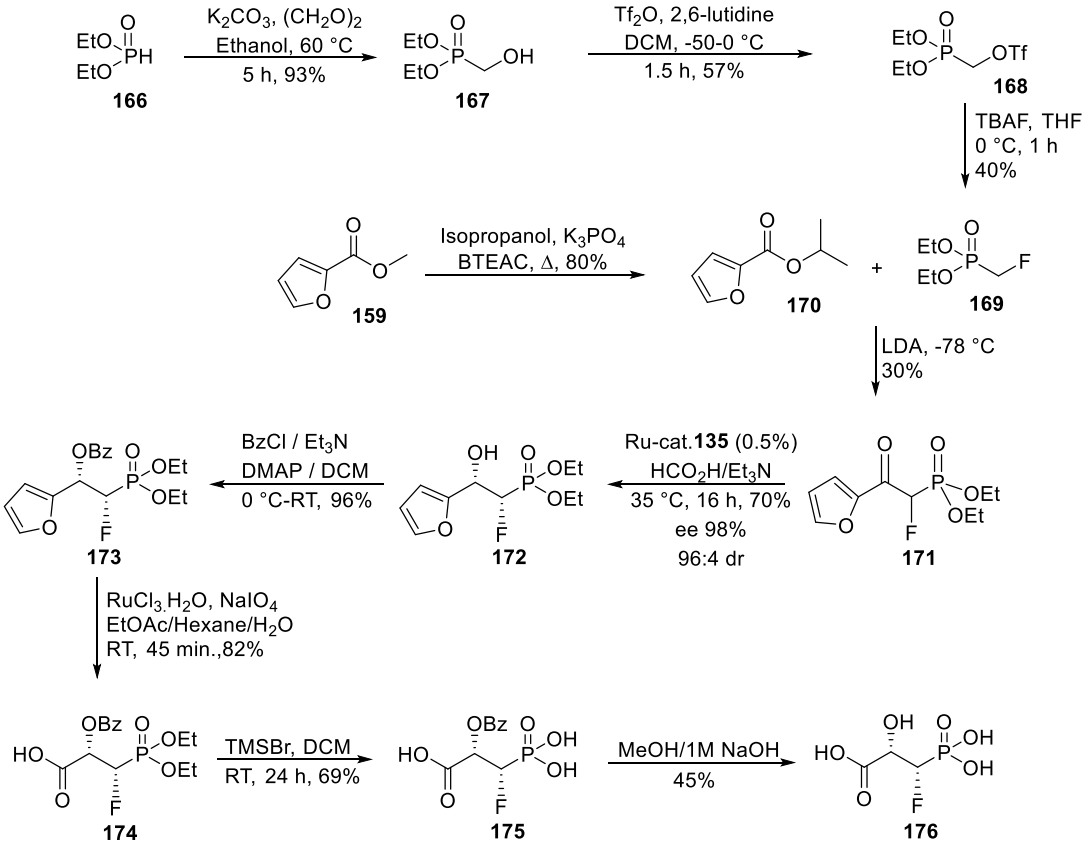
Scheme 28: Synthesis of (*S*)-2-hydroxy-3-phosphonopropanoic acid **158**.

For the preparation of difluoro analogue **165**, a similar strategy was adopted. The hydroxyl group of alcohol **161** was protected with benzoyl chloride with triethylamine and DMAP at 0 °C, followed by the oxidation of the furan ring with ruthenium chloride and sodium periodate at room temperature for 45 minutes to give the carboxylic acid **163** in excellent yield. Deprotection was carried out to remove the ethyl and benzoate groups by using TMSBr for 24-hour and a solution of 1M sodium hydroxide in methanol, respectively, giving 3,3-difluoro-2-hydroxy-3-phosphonopropanoic acid **165** (Scheme 29).



Scheme 29: Synthesis of 3,3-difluoro-2-hydroxy-3-phosphonopropanoic acid **165**.

For the preparation of monofluoro analogue **176**, a similar strategy was used, starting from diethyl (fluoromethyl)phosphonate **169.** This was accomplished starting with the preparation of diethyl (hydroxymethyl)phosphonate **169** by the reaction of diethyl phosphonate **166** with paraformaldehyde in ethanol under basic conditions in excellent yield, followed by treatment of this hydroxyphosphonate with trifluoromethane-sulfonic anhydride and 2,6-lutidine at -50 °C to give (diethoxyphosphoryl)methyl trifluoromethanesulfonate **168**. This was then reacted with tetrabutylammonium fluoride solution at 0 °C for 1 hour giving the monofluoride **169** but in low yield. Condensation of **169** with isopropyl furan-2-carboxylate was found to be better than with furan-2-carboxylate in terms of yield, but this was still very low. Reduction of the carbonyl group with the ruthenium-based catalyst gave a single isomer of *α*-fluoro-*β*-hydroxyphosphonate **172**, which was obtained in 70% yield, 98% ee and 96:4 dr. The hydroxyl group was protected with benzoyl chloride at 0 °C, followed by oxidation of the furan ring with ruthenium chloride and sodium periodate to give the carboxylic acid **174** in good yield. Deprotection of the ethyl and benzoate groups using TMSBr for 24-hours, followed by a solution of 1M sodium hydroxide in methanol, gave the (2*S*,3*S*)-3-fluoro-2-hydroxy-3-phosphonopropanoic acid **176** (Scheme 30).



Scheme 30: Synthesis of (2*S*,3*S*)-3-fluoro-2-hydroxy-3-phosphonopropanoic acid **176**.

The reduction of *α*-fluoro-*β*-ketophosphonate **171,** is highly stereoselective, with essentially one enantiomer and one diastereoisomer being obtained (*S*,*S*)-**172**. The chiral Ru-catalyst (*R*,*R*) usually delivers the (*S*) configuration in similar compounds that do not contain fluorine **148a-l.** (Figure 19). On the assumption that the resulting asymmetric centre is of (*S*)-configuration, and that the molecule is conformationally constrained due to the hydrogen bonding that leads to the formation of intramolecular six-membered ring.

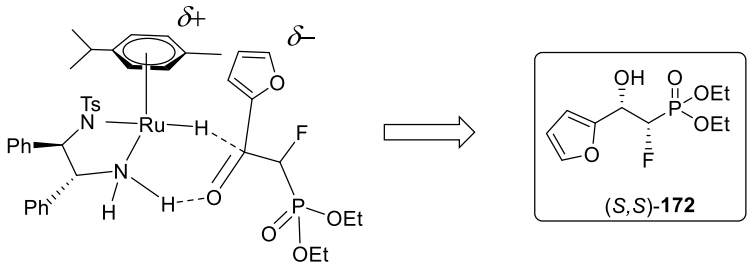


Figure 19: Plausible transition state model for the formation of compound **172.**

Although successful, in order to access analogues of the inhibitor, there is a need to access quaternary stereogenic centres by introducing other groups on the *β*-carbon atom. (Figure 20)

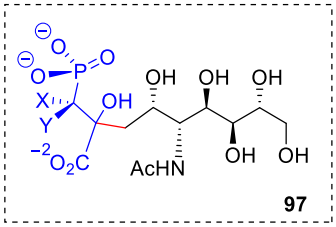
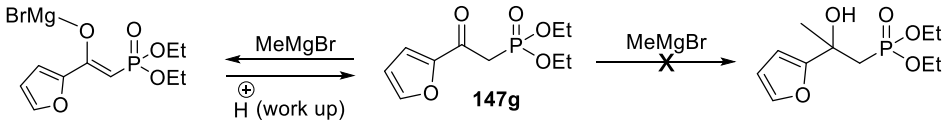


Figure 20: Structure of postulated pseudaminic acid inhibitor.

β-Ketophosphonate **147g** was treated with methyl magnesium bromide under a variety of conditions, (entries 1-4) but none gave the desired product, giving mostly recovered starting material. It is likely that the acidic *α* proton was deprotonated by the Grignard reagent (Scheme 31, Table 6).



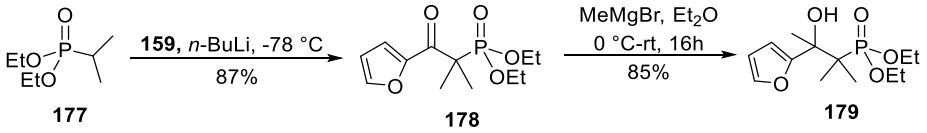
Scheme 31: Reaction of **147g** with methyl magnesium bromide.

Table 6: Adding of Grignard reagent to *β*-ketophosphonates **147g**.

Entry	Time	Temp/°C	Solvent	Conv./ %[a]
1	16 h	0 – rt	THF	0
2	16 h	0 – rt	Toluene	0
3	16 h	0 – rt	Et_2O	0
4	72 h	0 – rt	Et_2O	0
5	16 h	-78 – rt	Et_2O	0

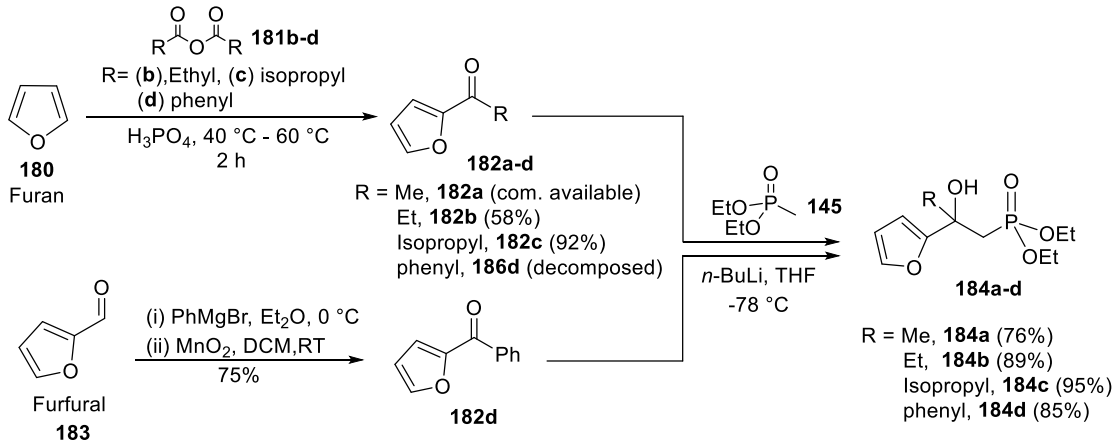
[a] Conversion determined by ^{1}H NMR and ^{31}P NMR

To show that the *α* proton was reacting with the Grignard reagent, *gem*-dimethyl analogue **178** was prepared by reaction of **177** with methyl furan-2-carboxylate in the presence of *n*-BuLi at -78 °C. Subsequently, ketone **178** was treated dropwise with methyl magnesium bromide at 0 °C and allowing the reaction to warm to room temperature overnight gave the *β*-hydroxyphosphonate **179** in good yield (Scheme 32).



Scheme 32: Synthesis of diethyl (3-(furan-2-yl)-3-hydroxy-2-methylbutan-2-yl)phosphonate **182**.

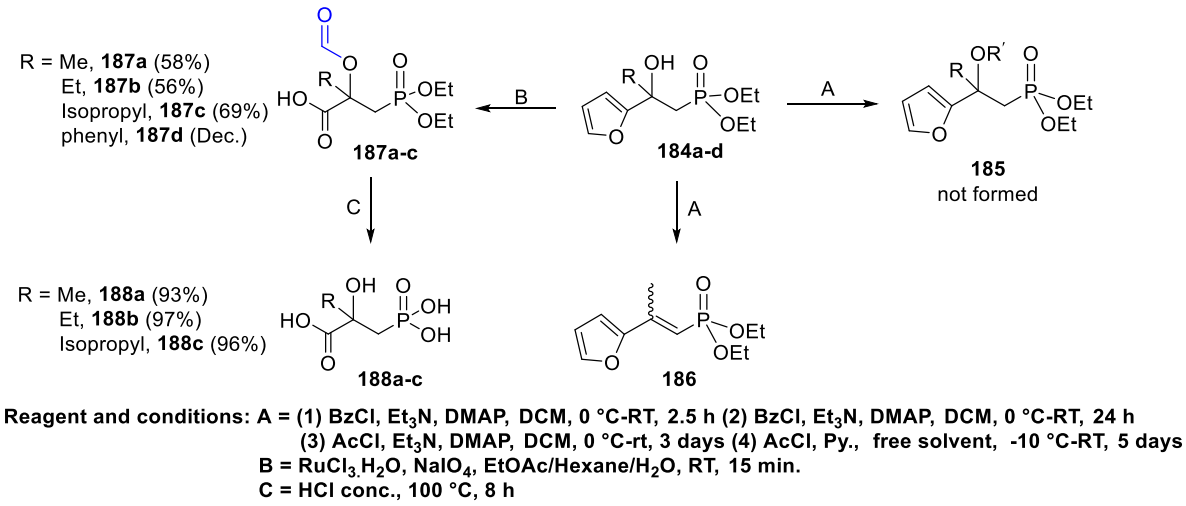
Since this approach was not successful and would not be applicable to the TADDOL approach, another strategy was adopted starting from ketones **182b-d**, (**182a** is a commercially available) that could then be used in an aldol reaction. 2-Furyl ethyl ketone **182b** and 2-furyl isopropyl ketone **182c** were prepared by treating furan **180** with propionic anhydride **181b** or isobutyric anhydride **181c** in the presence of phosphoric acid 98% at 40 ºC. Compound **182d** was not synthesized by the reaction with benzoic anhydride **181d** and furan, as this led to decomposition. Instead furfural **183** and phenyl magnesium bromide were reacted at 0 °C, followed by oxidation with manganese dioxide in DCM at room temperature to give **182d** in good yield. Ketones **182a-d** were all reacted with diethyl methylphosphonate **145** and *n*-BuLi at -78 °C, and gave *β*-hydroxyphosphonates **184a-d** in good yield. (Scheme 33)



Scheme 33: Synthesis of *β*-hydroxyphosphonates **184a-d**.

Preliminary attempts to protect the tertiary hydroxyl group as a benzoate ester all failed to generate product despite using various temperatures and reaction times. Instead of protecting the hydroxyl group, elimination of water occurred leading to the mixtures of *cis*/*trans* alkene **186a**. To get around this problem, oxidation of the furan **184a-d** to its acid derivatives **187a-d** was considered using $NaIO_4$ in a mixture of hexane/EtOAc/H_2O and a catalytic equivalent of $RuCl_3$.[201] Carboxylic acids **187a-c** were formed with good conversion after 15 minutes as the formate ester. This structure of compound **187a** was confirmed by the x-ray

crystallography (Figure 6). Removal of the ethyl and formate groups by heating to 100 °C in concentrated hydrochloric acid gave the final compounds as a pure carboxylic acid **188a-c,** which did not need any further purification (Scheme 34).



Scheme 34: Synthesis of 2-hydroxy-2-alkyl-3-phosphonic acids **188a-c**.

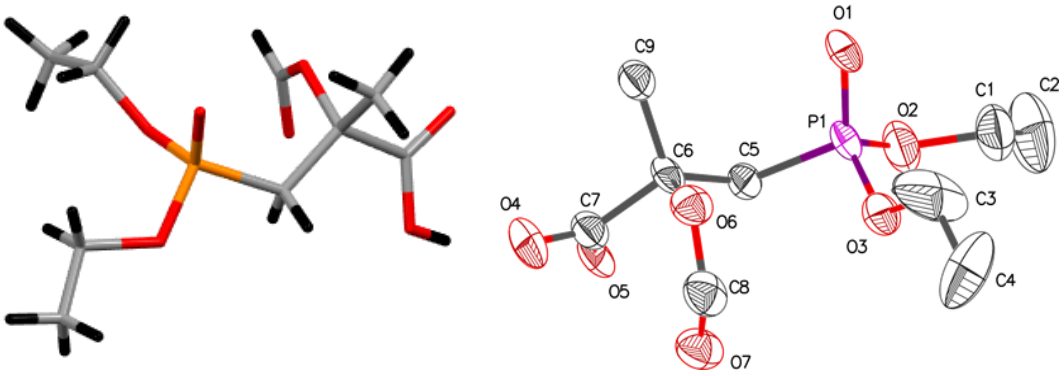
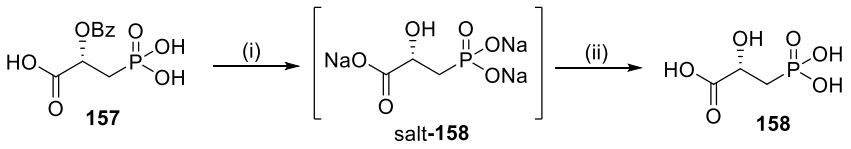


Figure 21: X-ray crystal structure for compound **187a**.

2.4. Acid Base Titration

The last step in the preparation of phosphate **158** was hydrolysis of benzoate ester **157** using 1M NaOH, giving the sodium salt of this compound. In order to determine and calculate the pH of this compound, needed for possible purification and biological studies, the titration was made by adding 0.1 M HCl in 0.1 mL increments after dissolving salt-**158** in water, and the pH measured after each addition. It was observed that there were three inflection points in pH value at 10.4, 4.85 and 2.1 (Scheme 35, Figure 22).



Reagents and conditions: (i) MeOH,1M NaOH, Δ 6 h, (ii) 0.1 M HCl, H_2O

Scheme 35: Titration curves for the non-fluorinated salt-**158**

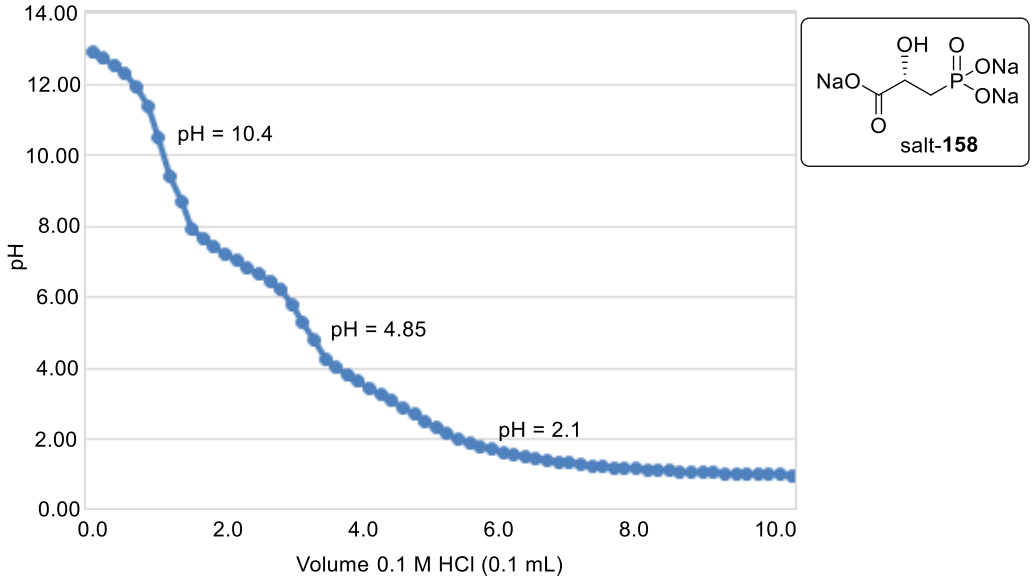


Figure 22: pH Titration curve of salt-**158** with hydrochloric acid (0.1 M).

In the case of compound **188b**, (Scheme 33 and 34), the last step was hydrolysis of the protecting groups by concentrated hydrochloric acid. Therefore, titration this time must be through adding a solution of sodium hydroxide (0.1 M), where it was added in 0.1 mL increments after dissolving **188b** in 10 mL H_2O, and the pH measured after each addition. It was noted that there were three inflection points in pH value at 3.0, 6.1 and 10.9; this confirms the existence of more than one acidic proton. It is though that the first pH (3.0) belong to the proton of one of the hydroxyl groups associated with phosphorus atom, Second one (6.1) belonging to carboxylic acid proton and the last value (10.9) belonging to another hydroxyl groups next to the phosphorus atom (Figure 23).

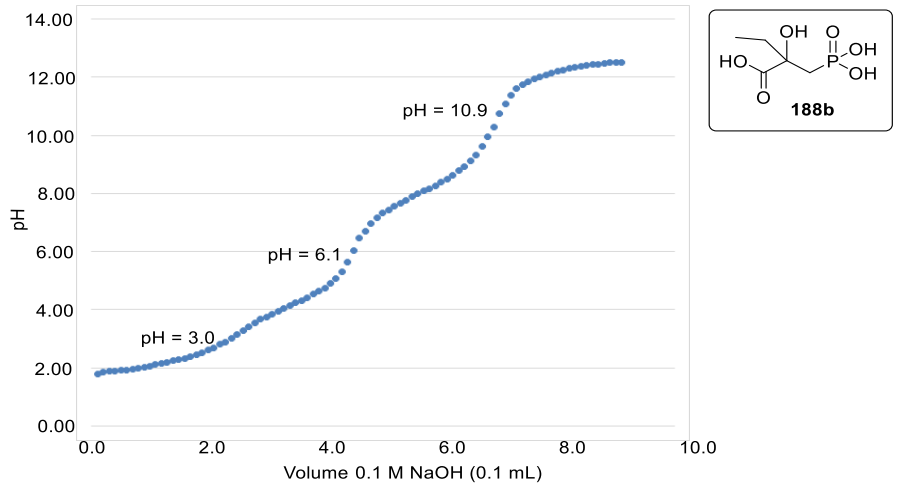


Figure 23: pH Titration curve of **188b** with NaOH (0.1 M).

After the failure to access quaternary stereogenic centres enantiomerically pure, an other strategy was employed, using a chiral amine synthesized as a ligand in an aldol condensation reaction.

2.5. *α*- Chiral Amine Bases

α-Chiral amines are amino compounds which have a stereogenic centre at the *α* position of the amino group (Figure 24). Chiral amines have broad application in asymmetric synthesis serving, in enantioselective deprotonation reactions as chiral bases[202] or for resolving racemic mixtures of acids. In organic synthesis, the enantiomerically pure amines that have an *α*-stereocentre plays a significant role in many important applications, such as: as chiral auxiliaries,[203] chiral resolving agents,[204] ligands in various asymmetric transformations[205] and in agrochemical and pharmaceutical industries.[206-209] Also they are productive in metal-complex catalysis as a chiral ligands.[210] In addition, chiral amines are predominant, fundamental parts of many drugs and drug candidates

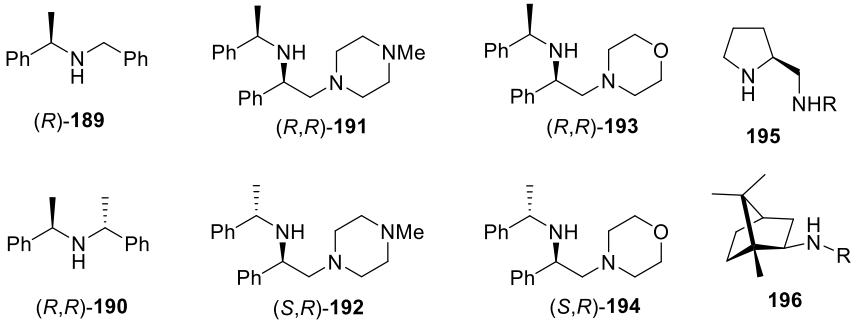
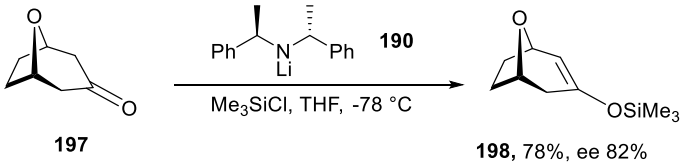


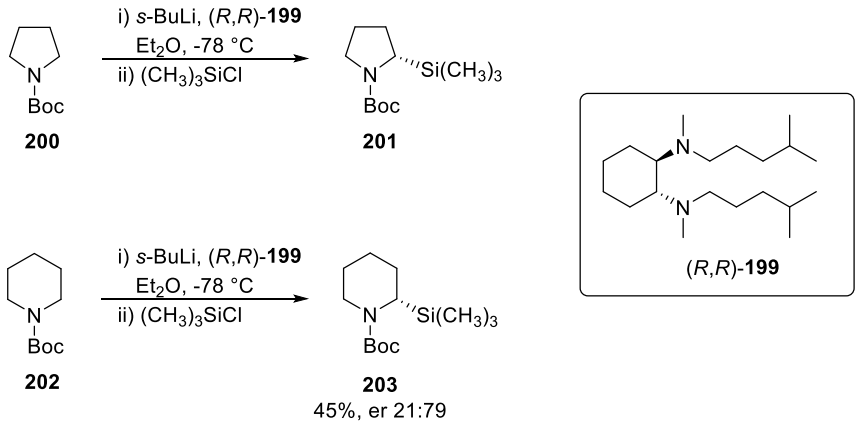
Figure 24: Chiral amines.

Chiral bases derived from the amine (*R*,*R*)-**190** have been used to deprotonate prochiral cyclic ketones selectively,[211] or diamines (*R*)-**191-195**, popularised by Koga.[212, 213] Generally, in the deprotonation of ketones two kinds of chiral base provide comparable enantioselectivity but (*R*,*R*)-**190** is more commonly used because it is readily available compared to the Koga bases, assumed to be due to the difficulty and length of their synthesis.[214, 215] For example, Simpkins *et al*. used *bis*-phenylethylamide **190** to break the symmetry in cyclic prochiral ketone **197** in good ee (Scheme 36).[216]



Scheme 36

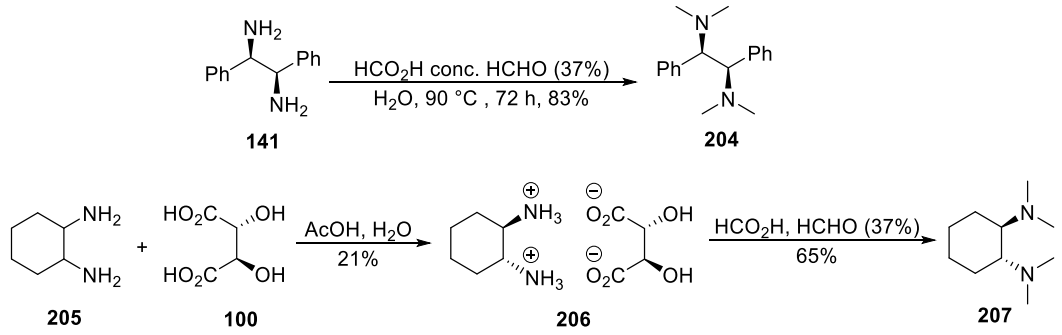
Privileged chiral ligands [217-219] are a class of compounds that widely give very high levels of enantioselectivity in asymmetric transformations, chiral diamines[2] exemplifying one such class. *trans*-1,2-Diaminocyclohexane derivatives **199**[220] have been used as chiral ligand in the asymmetric deprotonation of *N*-Boc pyrrolidine **200** and piperidine **202** (Scheme 37) with enantioselectivities comparable to those obtained with (-)-sparteine.[221, 222]



Scheme 37: Silylation of *N*-Boc pyrrolidine and *N*-Boc piperidine using ligand (*R*,*R*)-**203**.

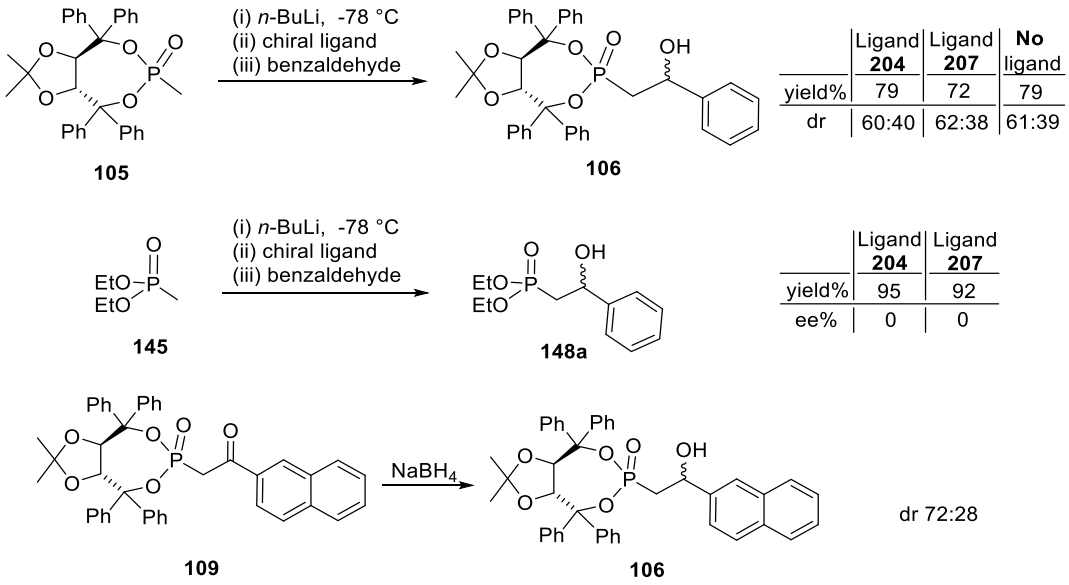
Recently, enantiomerically pure magnesium bisamides have been used in enantioselective deprotonations,[223] as an alternative to their well-established lithium counterparts.[216, 224, 225]
In this study, emphasis was placed on the preparation of chiral amines for use in an asymmetric phosphoaldol reaction. Two chiral amines were selected, the first being prepared

by heating a mixture of 1,2-diphenylethylenediamine **141** and 10 equivalents of formic acid with formaldehyde solution 37% in water at 90 °C for three days to give tetramethylbutane-2,3-diamine **204** in good yield. The second ligand was prepared by resolution of the *trans* isomers from a mixture of *cis* and *trans* 1,2-diaminocyclohexane **205** with tartaric acid **100** in acetic acid at 90 °C. Dissolving this salt in formic acid and formalin at room temperature gave (1*R*,2*R*)-N^1,N^1,N^2,N^2-tetramethylcyclohexane-1,2-diamine **207** in moderate yield. (Scheme 38)



Scheme 38: Synthesis of chiral amines ligands **204** and **207**.

The chiral ligands **204** and **207** were then evaluated for their ability to induce asymmetry in the addition of phosphonate compounds to benzaldehyde. Both gave a racemic mixture of compound **148a**, and produced diastereoisomers 62:38 with *β*-hydroxyphosphonate **106** (Scheme 39). Generally, comparing these results with the diastereoisomers obtained from reduction reaction of compound **109**, the diastereoisomers was (dr 72:28), and it was found that the stereodirectory group on the substrate did not have a big effect on the selectivity of the reaction.

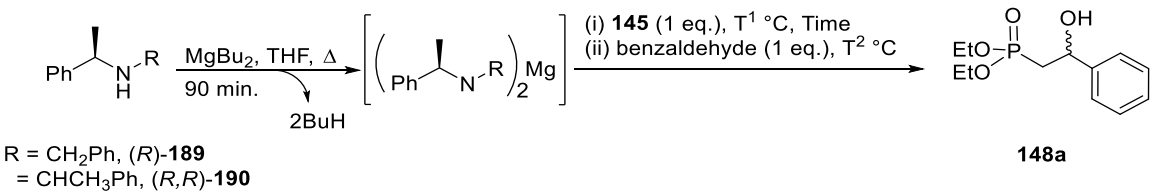


	Ligand **204**	Ligand **207**	No ligand
yield%	79	72	79
dr	60:40	62:38	61:39

	Ligand **204**	Ligand **207**
yield%	95	92
ee%	0	0

Scheme 39: Asymmetric addition of phosphonates compound to benzaldehyde in the presence of chiral ligands **204** and **207**.

Methodology was then trialled using Mg-mediated processes reported by Bassindale *et al.* [226] Using commercially available amines such as (*R*)-*N*-benzyl-α-methylbenzylamine **189** and (*R*)-*bis*[(*R*)-1-phenylethyl] amine **190** as their respective magnesium bisamides (Scheme 40). The two amines (*R*)-**189** and (*R,R*)-**190** were used in a Mg-mediated enantioselective deprotonation strategy for the phosphoaldol reaction.



Scheme 40: Synthesis of chiral magnesium amide and exploited in aldol reaction.

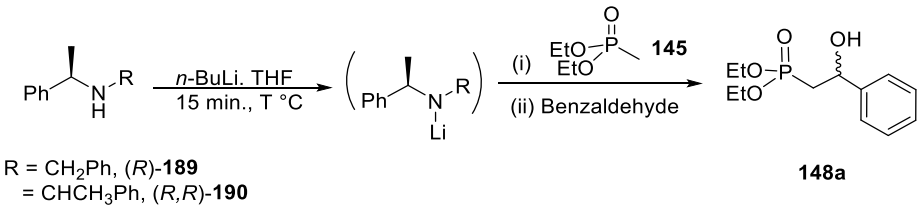
The established method[227] for bisamide formation required heating 2 equivalents of the amine and commercially available Bu_2Mg in THF for 90 min. These bases were used directly in phosphoaldol reactions with diethyl methylphosphonate and benzaldehyde. None of these attempts were successful, mostly leading to starting materials being recovered. (Table 7)

Table 7: Optimised conditions of aldol reaction.

Entry	Chiral amine	T[1]/°C	Time/min.	T[2]/°C	Conv./%[a]	ee/%[b]
1	(*R*)-**189**	-78	30	-78	0	-
2	(*R*)-**189**	0	60	-78	0	-
3	(*R*)-**189**	rt	60	-78	<10	0
4	(*R,R*)-**190**	rt	60	-78	<5	0

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.

n-BuLi was also used in a similar way with the bases **189** and **190** (Scheme 41). The results were not encouraging in terms of enantioselectivity, except for the chiral amine (*R,R*)-**190**, where the product **147a** was obtained in 49% yield and 18% ee from analysis of the HPLC of the crude mixture (Entry 3, Table 8). This was considered a positive sign and prompted further development. For the other entries, although reactivity increased, the reactions were unselective (Entry 5, Table 8)



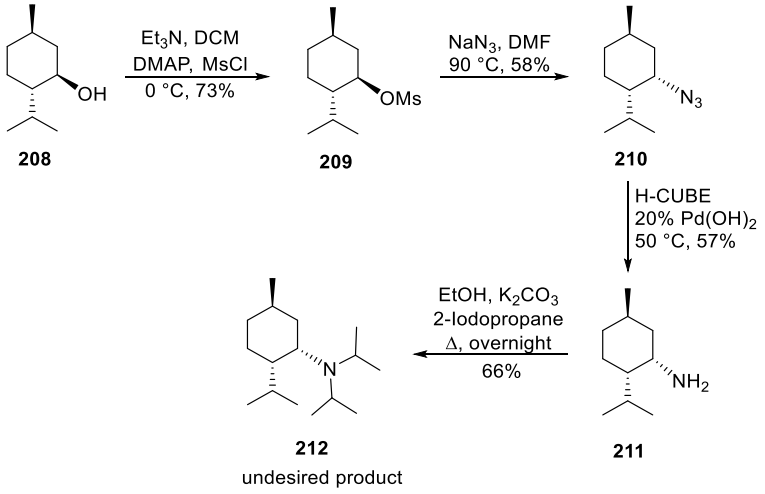
Scheme 41: Enantioselective addition reaction using chiral lithium bases.

Table 8: Phosphono aldol reaction with chiral amines.

Entry	Chiral amine	Equivalent of amine	T/ºC	Conv./%[a]	ee/%[b]
1	(*R*)-**189**	1	-78	68	0
2	(*R*)-**189**	2	-78	86	0
3	(*R*,*R*)-**190**	1	-78	49	18
4	(*R*,*R*)-**190**	2	-78	65	0
5	(*R*,*R*)-**190**	2	-78-0	100	0

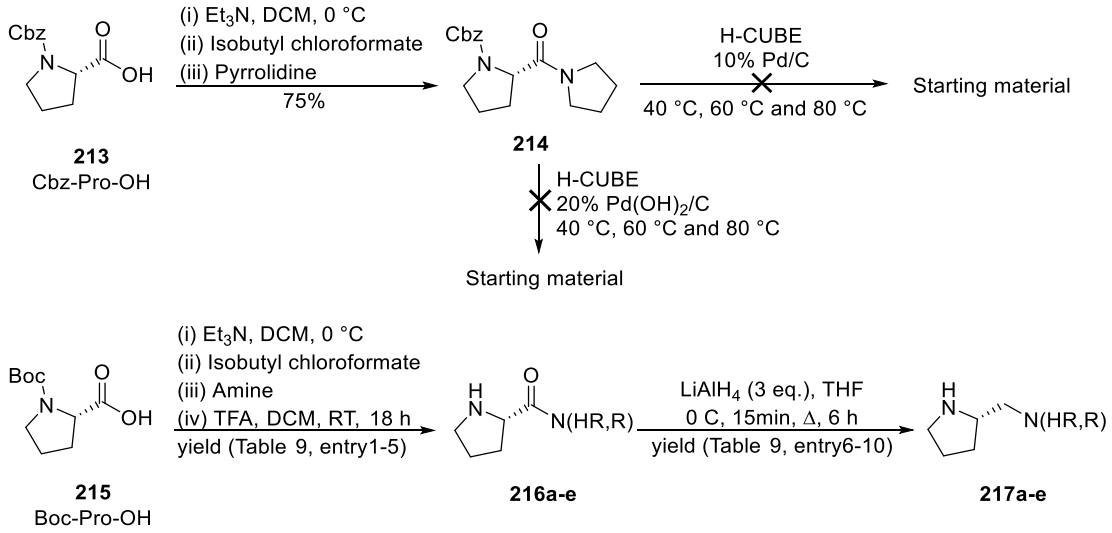
[a] Conversion determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC.

Based on the result obtained, a series of chiral amines were prepared. The first amine **211** derived from L-menthol **208** was obtained in a three-step synthesis, by mesylation, reaction with sodium azide and then H-Cube reduction with 10% $Pd(OH)_2/C$ at 50 ºC in methanol. Primary amine **211** was reacted with iodopropane in the presence of potassium carbonate to give the tertiary amine **212** as the main product, which was undesired as the goal was to prepare the secondary amine (Scheme 42).



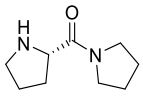
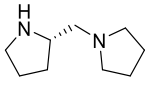
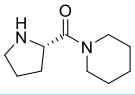
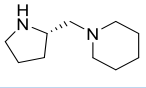
Scheme 42: Alkylation of amine **211** with alkyl halide.

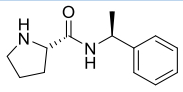
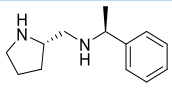
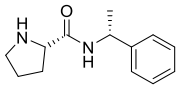
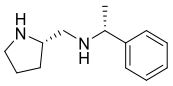
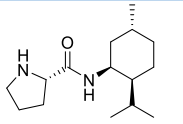
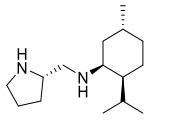
N-(PG)-L-Proline was used to prepare four chiral diamines **217a-e**. Initially, Cbz-Pro-OH **213** was reacted with isobutyl chloroformate in the presence of triethylamine at 0 ºC and then adding pyrrolidine (1 eq.) dropwise, giving the amide **214** in good yield. Hydrogenolysis of the benzyl group (Cbz) was attempted using the H-Cube with 10% $Pd(OH)_2/C$ and 20% $Pd(OH)_2$ at 50 ºC and 80 ºC for 6 hours in methanol. However, neither of these catalysts deprotected the benzyl group, giving only starting material. An alternative method was to change the protection group to the *tert*-butyloxycarbonyl group (Boc group), which is easy to remove with trifluoroacetic acid at room temperature. Reaction of *N*-(*tert*-butoxycarbonyl)-L-proline **215** (Boc-Pro-OH) with isobutyl chloroformate and triethylamine in dichloromethane as previously, followed by adding various amines, gave products that were treated with TFA to give the amides **216a-e** in reasonable yield. The final step was to reduce these amides to amines by heating with lithium aluminum hydride (3 eq.) in THF to give amines **217a-e** in acceptable yield (Scheme 43, Table 9).



Scheme 43: Synthesis of chiral diamines **217a-e**.

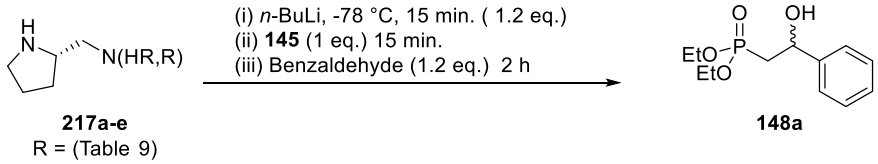
Table 9: Yields of amides and reduction using $LiAlH_4$ to the corresponding diamines.

Coupling Reaction			Reduction Reaction	
Entry	**Amide 216a-e**	**Yield/%[a]**	**Amine 217a-e**	**Yield/%[a]**
1	 **a**	51	 **a**	65
2	 **b**	59	 **b**	70

3	 **c**	85	 **c**	68
4	 **d**	70	 **d**	75
5	 **e**	80	 **e**	62

[a] Isolated yield.

After obtaining these amines, they were tested as a chiral diamine base. As noted in the diagram and table below, these amines were mixed with n-BuLi (1.2 eq.) at -78 °C. Diethyl methylphosphonate 145 (1 eq.) was added, and finally, benzaldehyde added dropwise. The results obtained (Table 10) indicate good conversion, but unfortunately, the enantioselectivity was zero in all cases (Scheme 44, Table 10).



217a-e
R = (Table 9)

148a

Scheme 44: Asymmetric aldol reaction using different chiral diamines as a bases.

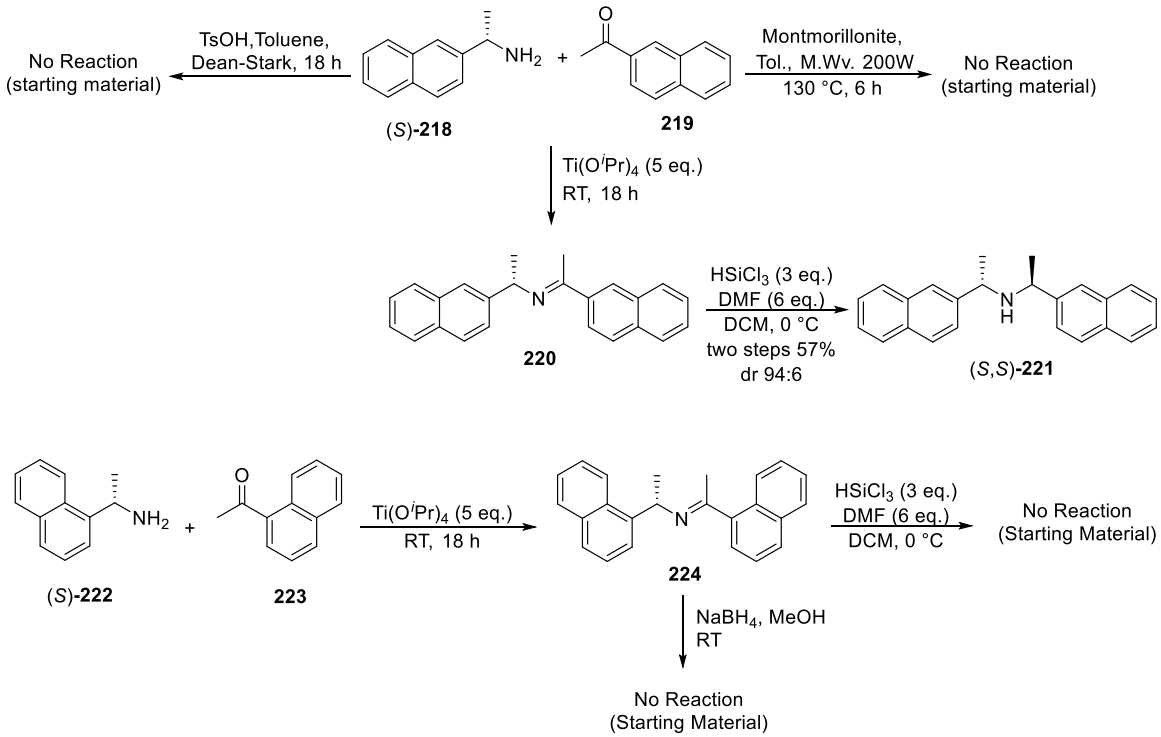
Table 10: Investigation of aldol reaction using chiral diamines.

Entry	Chiral Amine	Yield/%[a]	ee/%[b]
1	**217a**	68	0
2	**217b**	71	0
3	**217c**	76	0
4	**217d**	78	0
5	**217e**	63	0

[a] Isolated yield.
[b] Determined by chiral HPLC for pure product

In view of this, it was thought to prepare secondary amines with large bulky group such as a naphthalene ring. The target amine was accessed *via* the imine **220**. Attempts to react (1*S*)-1-(2-naphthyl)ethanamine (*S*)-**218** and 2-acetonaphthone **219** using a Dean-Stark apparatus in the presence of *p*-toluenesulfonic acid in toluene, or in a microwave with montmorillonite at 200 W at >130 ºC just gave starting materials. Following a literature procedure,[228, 229] amine and ketone were mixed in the presence of titanium (IV) isopropoxide. This time the

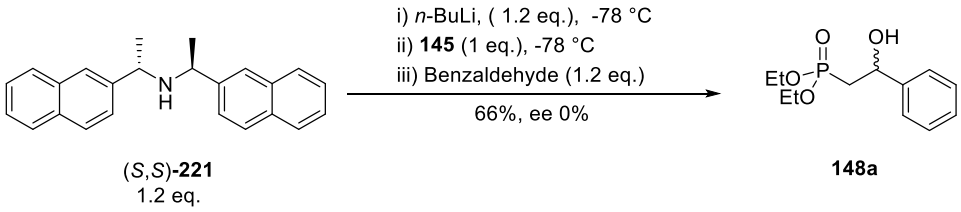
reaction was successful but was not purified using silica gel, as the imine decomposed, so it was washed using acetone and petroleum ether and used in subsequent reactions without any further purification. The imine **220** was then reduced using trichlorosilane and dimethylformamide in dichloromethane at 0 ºC and gave secondary amine (*S*,*S*)-**221** in reasonable yield and excellent dr, the stereochemistry being identical to the literature by comparing the H NMR signals and specific rotation (Scheme 45).[230]



Scheme 45: Synthesis of dinaphthyl amines

To prepare the other isomer **224**, amine (*S*)-**222** was mixed with ketone **223** using the same method as previous using titanium (IV) isopropoxide. The product was a mixture of the compound **224** and the starting materials. Because of the difficulty of purification the reaction was introduced in the reduction step directly using trichlorosilane and dimethylformamide. However, the reduction step was not successful possibly because of the steric hindrance around the imine. Reaction with sodium borohydride also failed.

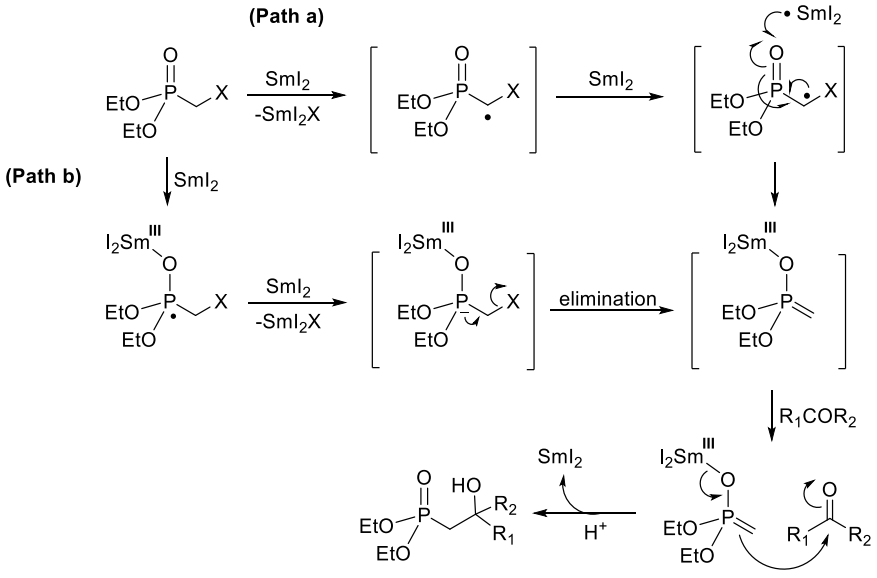
The chiral amine (*S*,*S*)-**221** was subjected to reaction with diethyl methylphosphonate after treatment with *n*-BuLi at -78 ºC, then benzaldehyde was added at the same temperature. The yield was acceptable but the enantiomeric excess was 0% (Scheme 46).



Scheme 46: Asymmetric aldol reaction using chiral amine (*S*,*S*)-**221**.

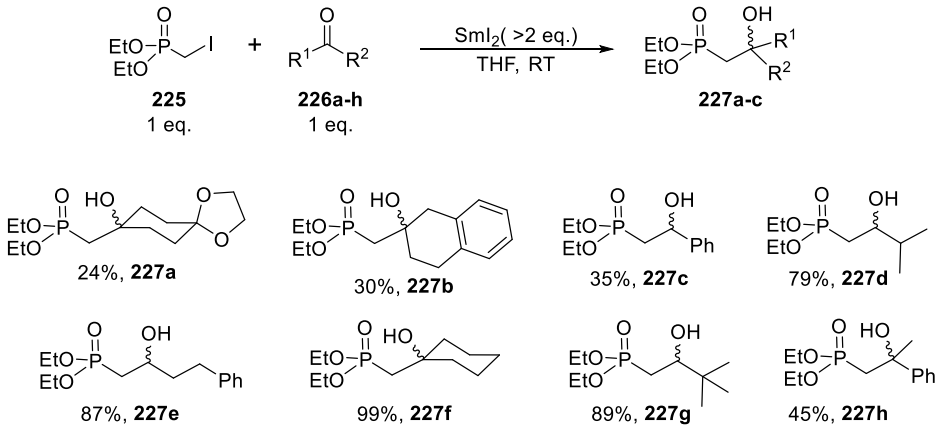
In view of all these negative results and lack of enantioselectivity, the previous reaction that gave 18% ee when using chiral amine 190 was repeated. The HPLC was measured, but this time the crude mixture was purified before doing the analysis. Unfortunately, the ee was 0%, and it was thought due to some impurities that may have affected the initial result and gave a wrong value due to the crude product being used in the HPLC without any purification.

After this method failed for making the key C-C bond needed to prepare chiral quaternary centre, an alternative synthetic strategy was adopted using samarium iodide based methodology. This strategy has been previously employed to prepare *β*-hydroxy-phosphonates using samarium(II) iodide to promote the reaction of *α*-halophosphonates and carbonyl compounds (aldehyde or ketones).[173, 231]



Scheme 47: Mechanism of SmI_2-mediated Reformatsky and aldol reactions.

Orsini *et al.*[231] stated the requirement of two equivalents of samarium iodide and the reactions progressed in very good yield for aliphatic aldehydes such as pivalaldehyde **226g** (89%) but the yield was decreased with an easily enolizable ketone such as acetophenone **226h** (Scheme 48).

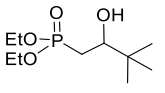
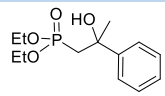
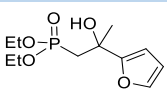


Scheme 48: Reformatsky-aldol reaction using SmI_2 (Orsini's work).[231]

So, in the first stage, these conditions were trialled in the synthesis of *β*-hydroxyphosphonates **227g** and **227h** as examples of aliphatic and aromatic *β*-hydroxyphosphonates, as well as synthesis of furan derivative **227i**, because of the need for the presence of this ring, as the source of the carboxylic acid.

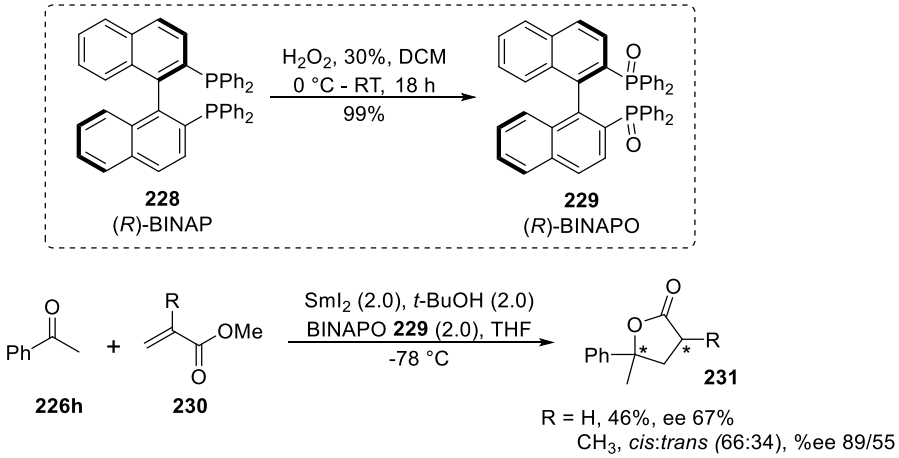
The previous conditions were followed with a change in the order of addition; that was imagned might give good conversion. Diethyl iodomethylphosphonate was added to samarium iodide solution, followed by the carbonyl compound. This led to production of diethyl methylphosphonate (50%) as a by-product and non-reacted diethyl iodomethylphosphonate (50%), while the product was not observed. However, Orsini's method was followed by mixing diethyl iodomethylphosphonate with an equimolar amount of carbonyl compound, followed by adding two equivalents of samarium iodide solution for 15 minutes, gave the products in a good yield with small quantities diethyl methylphosphonate and starting materials recovered (Table 11).

Table 11: Diethyl *α*-iodomethylphosphonate-carbonyl compounds couplings promoted by SmI_2.

Entry	Substrate 226g-i	Product 227g-i	Yield/ %[a]	Recovered diethyl methyl-phosphonate/ %[b]	Recovered diethyl iodomethyl-phosphonate/ %[b]	Orsini *et al.* Yield/ %
1	 **g**	 **g**	87	9	4	89
2	 **h**	 **h**	66	25	9	45
3	 **i**	 **i**	51	40	9	NA

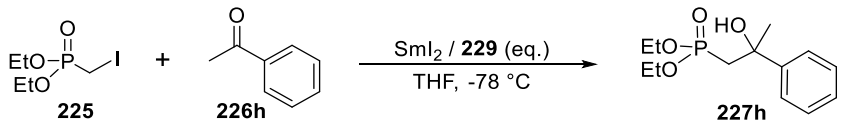
[a] Isolated yield, [b] Determined after purification

After the success of the preparation of these *β*-hydroxyphosphonates utilizing samarium iodide-mediated reaction additives were sought which may provide some control of the stereoselectivity. One of these additives is (*R*)-BINAPO, from a report by Mikami *et al*. that ketyl radicals can be adding to olefins mediated *via* enantioselective intermolecular addition.[232] They reported that 2,2'-bis(diphenylphosphinyl)-l,l'-binaphthyl, (*R*)-BINAPO **229** which was prepared by oxidation of (*R*)-BINAP **228** with hydrogen peroxide 30% at room temperature in excellent yield[233] is the best ligand can be used with SmI_2 in this type of reduction (Scheme 49).



Scheme 49: Enantioselective ketyl-olefin coupling reactions mediated by SmI_2 with (*R*)-BINAPO **229**.[232]

Using this idea, the reaction of diethyl iodomethylphosphonate with acetophenone was attempted in the presence of chiral ligand **229** (Scheme 50).



Scheme 50: Synthesis of *β*-hydroxyphosphonate mediated chiral ligand **229**.

Following the Buonomo procedure, reaction of equimolar quantity of diethyl iodomethylphosphonate **225** and acetophenone **226h** at -78 ˚C with (*R*)-BINAPO **229** in dry THF, with two equivalents of samarium iodide (SmI_2) was conducted. The conversion was observed to increase with a reduction in equivalents of the chiral ligand **229**, and the starting material was always observed. However, all of these trials led to the formation of a racemic mixture (Table 12).

Table 12: Enantioselective aldol reaction mediated by SmI_2 with (*R*)-BINAPO **229**

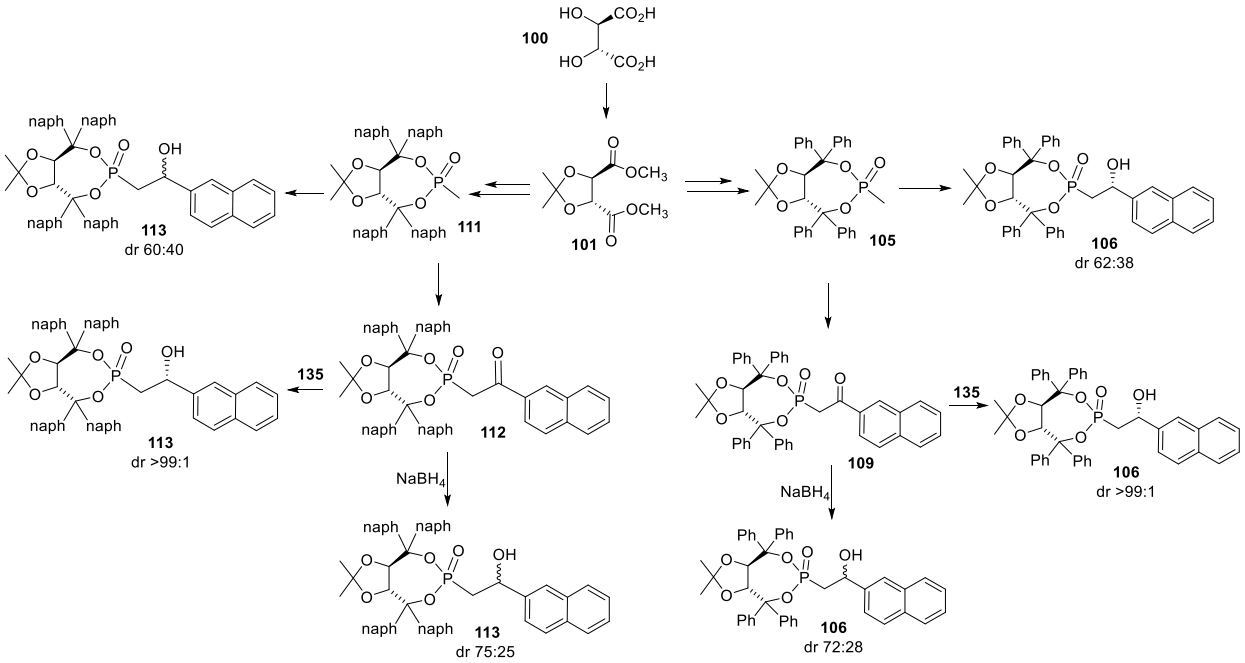
Entry	BINAPO/(eq.)	Conv./% [a]	Recovered of 145/%[b]	ee/% [c]
1	2	54	46	0
2	1	60	40	0
3	0.5	64	36	0
4	0.1	73	27	0

[a,b] Determined by ^{1}H NMR
[c] Determined by chiral HPLC: Lux 3u Cellulose-4, 5% IPA in hexane, 1 mL/min^{-1}@ 254 nm

This reaction was then repeated three times with the addition of *t*-BuOH as previously performed by Mikami *et al*. [232] under the same reaction conditions and order of addition. However, no control was achieved in the selectivity and the ee is still 0% due to the mixture of enantiomers was obtained.

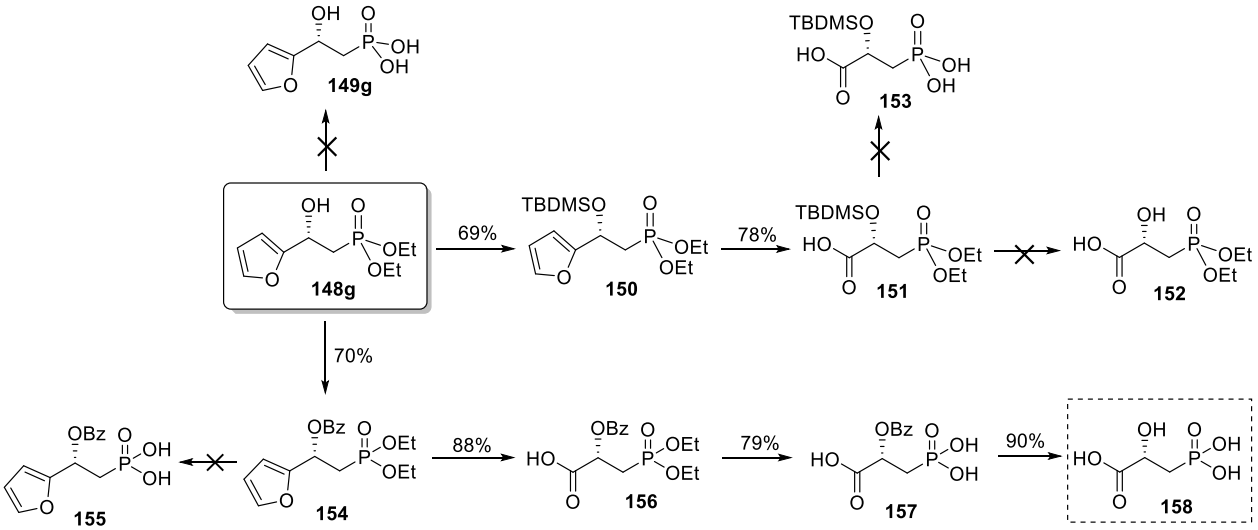
3. Conclusions

A method has been established for the synthesis of analogues of the pseudaminic acid inhibitor *β*-hydroxyphosphonate **161**, *α,α*-difluoro-β-hydroxyphosphonate **166** and *α*-fluoro-*β*-hydroxy phosphonate **178**. The method was first carried out using a synthesised chiral methyl phosphonate **105** starting material. The β-hydroxyphosphonates **106** and **113** were obtained similarly *via* aldol condensation in (dr 62:38) and (dr 60:40) respectively. (Scheme 51). Transfer hydrogenation reduction of *β*-ketophosphonates **109** and **112** using (*R,R*)-Ru catalyst has been developed. The asymmetric transfer hydrogenation reduction was performed with excellent diastereoisomer ratio (>99:1) (Scheme 51).



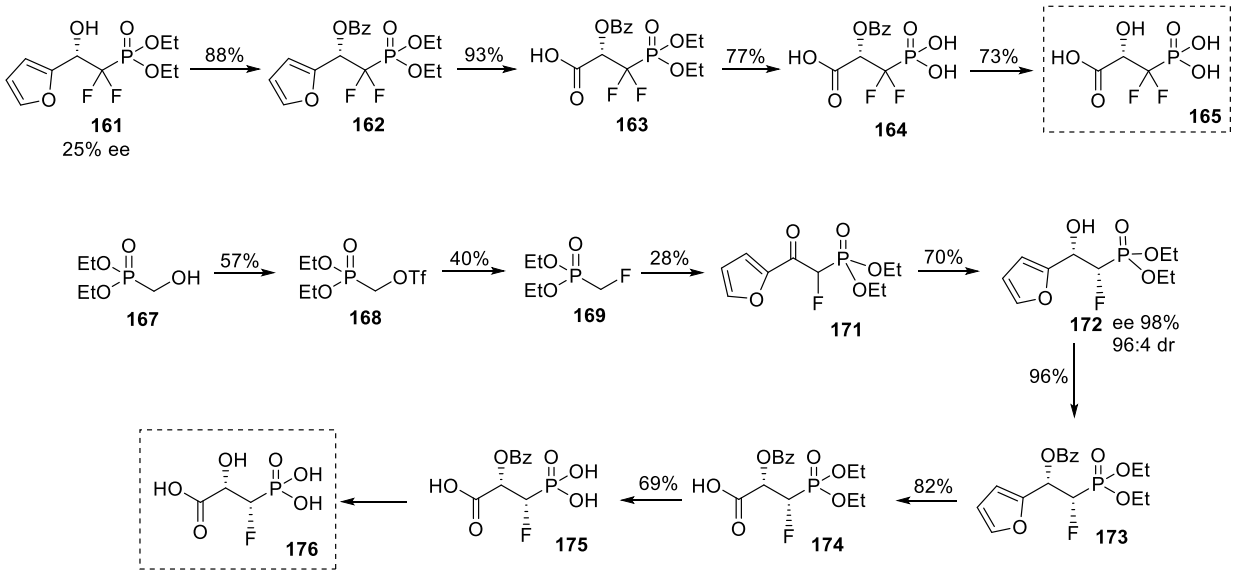
Scheme 51

This methodology has been used for the reduction of various *β*-ketophosphonates. Compound **148g** was chosen due to contains a furan ring ,which can be oxidized to corresponding carboxylic acid that is found in the target molecules. Synthesis of the phosphonic acid **158** proved problematic (Scheme 52). Since the hydrolysis products **152** and **155** were unable to be obtained due to decomposition, the oxidation reaction of the furan ring was investigated. The oxidation reactions using $RuCl_3$ and $NaIO_4$ were done before hydrolysis of the protection groups resulted in expected carboxylic acid formation **156**.



Scheme 52

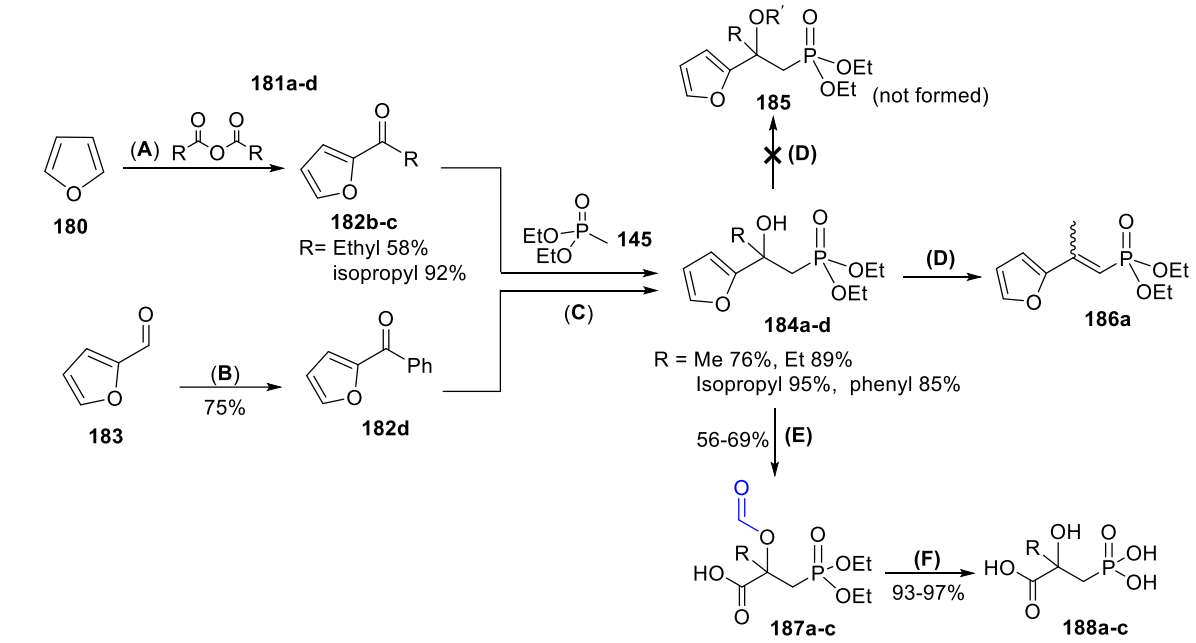
This methodology was applied to the synthesis of *α*-difluoro and monofluoro-*β*-hydroxyphosphonic acid **165** and **176**, where compound **176** took more steps for preparation of starting material (Scheme 53). However, the synthesis of these three compounds was successful but with racemic mixtures of two enantiomers, as well as, there were some difficulties in terms of purification because these three compounds are only soluble in water.



Scheme 53

The next stage was how to access quaternary stereogenic centres containing a hydroxyl group. *β*-ketophosphonates **147g** was treated with Grignard reagent, but this reaction failed and only starting materials were recovered. The strategy was then changed to the preparation of certain ketones containing the important furan ring and then reacting these with diethyl methylphosphonate **145**, giving *β*-hydroxyphosphonate that have a quaternary stereogenic

centres but unfortunately was non-selective. After many failed attempts to protect the hydroxyl group, the oxidation of furan ring was carried out using $NaIO_4$ and $RuCl_3$, giving the corresponding acids with unexpected protected phosphonates **187a-c** which were confirmed by X-ray crystallography analysis. Where these protection compounds **187a-c** are unknown compounds and have not been reported in the literature (Scheme 56).



Reagent and conditions: (**A**) H_3PO_4, 40 °C - 60 °C, 2 h (**B**) (i) PhMgBr, Et_2O, 0 °C (ii) MnO_2, DCM,RT (**C**) *n*-BuLi -78 °C, THF
(D) (**i**) BzCl, Et_3N, DMAP, DCM, 0 °C-RT, 2.5 h (**ii**) BzCl, Et_3N, DMAP, DCM, 0 °C-RT, 24 h
(**iii**) AcCl, Et_3N, DMAP, DCM, 0 °C-rt, 3 days (**iv**) AcCl, Py., free solvent, -10 °C-RT, 5 days
(**E**) $RuCl_3.H_2O$, $NaIO_4$, EtOAc/Hexane/H_2O, RT, 15 min. (**F**) HCl conc., 100 °C, 8 h

Scheme 54

Finally, for the synthesis enantiomerically pure of *β*-hydroxyphosphonate, many strategies have been explored, including synthesis of chiral amine ligands, magnesium amide bases and chiral lithium amine bases and used with the aldol reaction. Unfortunately, all of these procedures gave racemic mixtures of product. Later, another strategy was adopted using samarium iodide mediated aldol reaction with chiral ligand (BINAPO). However, this method only gave a racemic mixture (ee 0%).

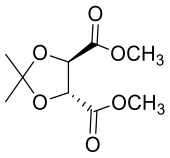
Future work includes the synthesis another chiral ligands and used with this coupling reaction between carbonyl compounds and iodomethylphosphonate.

4. Chapter 3: Experimental

4.1.General

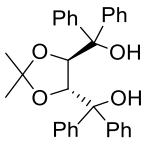
All dry reactions were performed under nitrogen at room temperature unless otherwise stated, using glassware, flame-dried under vacuum, with magnetic stirring. All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. 4Å Molecular sieves were activated by flame-drying under vacuum. Reactions that were performed at 0 °C used water/ice baths, -78 °C used acetone/dry ice bath, -10 °C used salt/ice/water bath and -20 °C used acetone/dry ice bath (by adding portionwise of dry ice to acetone). Tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide and diethyl ether solvents used in reactions were obtained from the departmental Grubbs solvent system and stored under a positive pressure of nitrogen. All other solvents were obtained from commercial suppliers and used without prior drying unless otherwise stated. Commercially available Grignard reagents were titrated against a standard solution of (-)-menthol using phenanthroline as an indicator. *n*-Butyllithium was titrated before use against a standard solution of benzophenone tosylhydrazone. Analytical thin layer chromatography (TLC) was carried out utilising aluminium backed Merck TLC plates (silica gel 60 F254) and visualised with UV light (254 nm) followed by either a potassium permanganate, phosphomolybdic acid or dinitrophenylhydrazine dip then exposed to heat. Flash column chromatography was performed using Flurochem Limited Silica Gel 40 – 60 μ 60Å as the stationary phase. The eluent for each purification is noted within the individual experimental procedures. All H, ^{13}C, ^{31}P and ^{19}F spectra were obtained using either a Bruker AC 250 or AC 400 spectrometer. ^{13}C NMR spectra were recorded using the JMOD or CPD method. The NMR solvent used is noted within the individual experimental procedures. Chemical shifts are expressed in parts per million (ppm). All *J*-values (*J*, $J_{C\text{-}H}$, $J_{C\text{-}C}$, $J_{C\text{-}P}$) measured in Hertz. High resolution mass spectrometry was performed by the University of Sheffield Mass Spec department on either a MicroMass LCT spectrometer operating in electrospray 98 mode or a MicroMass Prospec system operating in electron impact mode. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR using a Universal diamond ATR top-plate. Melting points were measuring on a Gallenkamp melting point apparatus and are uncorrected. The pH was measured using pH meter which had previously been calibrated with calibration buffers. H-cube® reactions were conducted using a ThalesNano H-cube® continuous-flow hydrogenation reactor with a pre-packed CatCart® cartridge. HPLC was carried out on a Gilson analytical system using a Lux 3u Cellulose-4, (4.8 mm × 250 mm) column, Cellulose-3 and Cellulose-2 with IPA and hexane as the solvents. The flow rate was 1.00 cm^3 per minute and the Shimadzu SPD-10A UV-Vis detector was set at 228 and 254 nm. All chemicals were used as received without further purification.

(4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate[178, 234] 101



A mixture of L-tartaric acid **100** (0.5 g, 3.33 mmol), 2,2-dimethoxypropane (1 mL, 0.8 g, 7.7 mmol), methanol (0.3 mL) and *p*-toluene sulfonic acid monohydrate (2.0mg, 0.01 mmol) was warmed to 35-40 °C with occasional swirling until a dark-red homogeneous solution was obtained. Additional 2,2-dimethoxypropane (0.5 mL, 0.4 g, 3.81 mmol) and cyclohexane (2.3 mL) were added. The mixture was heated at reflux with stirring overnight. The acetone–cyclohexane and methanol– cyclohexane azeotropes were slowly removed approximately 3 mL of the main solution. Additional 2,2-dimethoxypropane (0.03 mL, 0.025 g, 0.24 mmol) was added and the mixture heated at reflux for 15 min. After the mixture was cooled to room temperature, anhydrous potassium carbonate (5.0mg, 0.036 mmol) added and the mixture stirred until the reddish colour disappeared. Volatile materials were removed under reduced pressure to leave a yellow oil, and the residue was fractionally distilled under vacuum (bp 94–106°C, 0.4 mm) to afford the product **101** as a pale-yellow oil, (0.46 g, 63% yield). An analytical sample was obtained by further purification using flash chromatography on silica gel as a pale-yellow oil, eluting with ethyl acetate/petroleum ether (1:3); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.51 (6H, s, 2 × C*H*$_3$), 3.84 (6H, s, 2 × OC*H*$_3$), 4.83 (2H, s, 2 × C*H*-O); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 26.3(2 × *C*H$_3$), 52.8 (2 × O*C*H$_3$), 76.9 (2 × *C*H-O), 113.8 [*C*(CH$_3$)$_2$], 170.0 (2 × *C*=O).

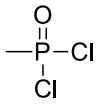
[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]bis(diphenylmethanol) [235] 102



A solution of bromobenzene (1.0 g, 0.66 ml 6.4 mmol) in dry THF (14 mL) was added dropwise over 45 minutes to Mg (0.2 g, 8.2mmol), with gentle heating. After complete addition, the reaction was heated at reflux for 1 h. The reaction mixture was cooled in an ice bath and a solution of dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **101** (0.3 g, 1.3 mmol) in dry THF (6 mL) was added. During the addition, the internal temperature was kept below 20 °C, and when the addition was complete, the mixture was heated at reflux for

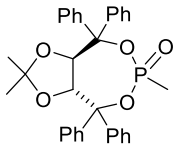
10 hr, and then cooled to room temperature. An aqueous saturated solution of NH_4Cl (10mL) was carefully added with cooling until the pH reached 7-8, and the mixture was extracted with ethyl acetate (3 ×20 mL). The combined organic layers were washed twice with brine (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting yellowish foam was purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to afford the compound **102** (0.42 g, 70%) as a white solid; mp 193-195°C, (lit.[236] 195-196 °C); $[\alpha]_D^{25}$ -61.0(*c* 1 in $CHCl_3$), lit.[235] $[\alpha]_D^{25}$ -60.6 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3439, 3208, 2896, 1601, 1495, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.18 (6H, s, 2 × C*H*$_3$), 3.98 (2H, s, 2 × O*H*), 4.63 (2H, s, 2 × C*H*-O), 7.25-7.39 (16H, m, ArC*H*), 7.53-7.57(4H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 27.2 (2 x *C*H$_3$), 78.2 (2 × *C*-OH) 80.9 (2 × *C*H-O), 109.6 [*C*(CH$_3$)$_2$], 127.3 (4 × Ar*C*H), 127.6 (4 × Ar*C*H), 127.7 (4 × Ar*C*H), 128.2 (4 × Ar*C*H), 128.7 (4 × Ar*C*H), 142.6 (2 × Ar*C*), 146.0(2 × Ar*C*); *m*/*z* (EI) 489.2037 [M+Na$^+$]. $C_{31}H_{30}O_4Na$ requires 489.2042.

Methylphosphonicdichloride.[237] 104



A mixture of (4.0 g, 32.3 mmol) of dimethyl methylphosphonate **103** and DMF (0.032 mL) was added dropwise to thionyl chloride (6 mL) and heated at reflux. Vigorous gas evolution indicated the progress of the reaction. After 12 h, the bath temperature was increased to 120 °C (bp 71-73 C/65 mbar[237]). Vacuum distillation of the crude product at atmospheric pressure (bp 163-165 °C) yielded the desired dichloride **104** (3.5 g, 82%) as colourless crystals; mp 30-35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.54 (3H, d, $J_{H\text{-}P}$ 16.4, C*H*$_3$P).

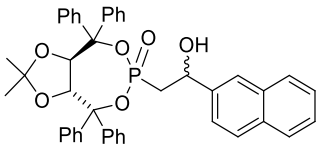
(3a*R*,8a*R*)-2,2,6-Trimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e] [1,3,2] dioxaphosphepine 6-oxide [238] 105



A solution of TADDOL **102** (1.00 g, 2.14 mmol) in dry THF (25 mL) was cooled to -78 °C, and *n*-BuLi in hexane (2.1 M, 2.55 mL, 5.36 mmol) was added dropwise at the same temperature. The solution was warmed to room temperature and stirred for 1 h, then cooled

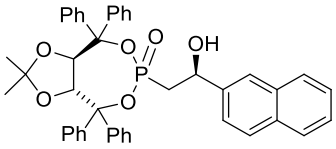
to -78 °C, and $MeP(O)Cl_2$ (1.37g, 10.29 mmol) dissolved in THF (2 mL) and added dropwise over 15 minutes. The mixture was stirred at room temperature for 3.5 h, the solvent removed under reduced pressure, and the crude material purified by flash column chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:2) to afford the product **105** (0.71 g, 63%) as a white solid; mp 243-244°C, (lit.[238] 240-242 °C); $[\alpha]_D^{25}$-286.8 (*c* 0.76 in $CHCl_3$), lit.[238] $[\alpha]_D^{25}$-287.5 (*c* 0.76 in $CHCl_3$); ν_{max}(ATR)/cm^{-1}: 3056, 3010, 2995, 2909, 2923, 1495, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.60 (3H, s, C*H*$_3$),0.67 (3H, s, C*H*$_3$),1.48 (3H, d, *J* 18.1, C*H*$_3$P), 5.23 (1H, d, *J* 7.9, C*H*-O), 5.53 (1H, d, *J* 7.9, C*H*-O), 7.25-7.62 (20H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.9 (d, $J_{C\text{-}P}$ 150.0, 2 × *C*H$_3$), 26.6 (d, $J_{C\text{-}P}$ 3.9, *C*H$_3$P), 79.1 (d, $J_{C\text{-}P}$ 2.6, *C*H-O), 79.7 (d, $J_{C\text{-}P}$ 1.5, *C*H-O), 87.2 (d, $J_{C\text{-}P}$ 8.5, *C*-O-P), 88.6 (d, $J_{C\text{-}P}$ 10.8, *C*-O-P), 114.2 [*C*(CH$_3$)$_2$], 126.8 (Ar*C*H), 127.1 (Ar*C*H), 127.2 (Ar*C*H), 127.6 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 129.2 (Ar*C*H),139.8 (d, $J_{C\text{-}P}$ 6.3, Ar*C*), 139.9 (d, $J_{C\text{-}P}$ 10.5, Ar*C*), 143.4 (Ar*C*), 144.2 (d, $J_{C\text{-}P}$ 3.4, Ar*C*);^{31}P NMR (162 MHz, $CDCl_3$) δ_P 21.52; *m*/*z* (EI) 549.1784 [M+Na^+]. $C_{32}H_{31}NaO_5P$ requires 549.1807.

(3a*R*,8a*R*)-6-[2-Hydroxy-2-(naphthalen-2-yl)ethyl]-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide 106



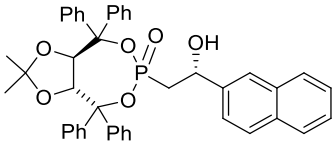
A pre cooled (-78 °C) solution of *n*-BuLi (1.8 Min hexane, 0.25mL, 0.45mmol) was added under argon at -78 °C to a stirred solution of methyl phosphonate **105** (0.23 g, 0.45 mmol) dissolved in dry THF (2 mL). After an additional 5 minutes at the same temperature, a solution of 2-naphthaldehyde (0.07 g, 0.45 mmol) in THF (1 mL) was introduced dropwise over 15 minutes, and the reaction was allowed to continue for another 0.5 h at -78 °C followed by another 0.5 h at room temperature. A saturated aqueous solution of NH_4Cl (20 mL) was added followed by water (20 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried with anhydrous $MgSO_4$, filtered and the residue which was obtained after removal of the solvent in vacuum was purified by flash chromatography on silica gel eluting with ethyl acetate/toluene (1:3) to afford two diastereoisomers (0.16 g, 62%).

(3a*R*,8a*R*)-6-((*S*)-2-Hydroxy-2-(naphthalen-2-yl)ethyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide 106



Minor isomer: White solid; yield 23%; $[\alpha]_D^{25}$ +164 (*c* 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.59 (3H, s, C*H*$_3$), 0.77 (3H, s, C*H*$_3$), 2.34-2.43 (2H, m, C*H*$_2$P), 4.15 (1H, s br, O*H*), 5.24 (1H, d, *J* 8.0, C*H*-O), 5.29-5.37 (1H, m, C*H*OH), 5.59 (1H, d, *J* 8.0, C*H*-O), 7.29-7.63 (23H, m, ArC*H*), 7.82-7.85 (4H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.5 (*C*H$_3$), 26.8 (*C*H$_3$), 37.5 (d, $J_{C\text{-}P}$ 140.1, *C*H$_2$P), 67.4 (d, $J_{C\text{-}P}$ 3.9, *C*HOH), 80.0 (d, $J_{C\text{-}P}$ 15.2, 2 × *C*H-O), 87.2 (d, $J_{C\text{-}P}$ 9.0, *C*-O-P), 88.4 (d, $J_{C\text{-}P}$ 11.1, *C*-O-P), 113.9 [*C*(CH$_3$)$_2$], 123.6 (Ar*C*H), 124.3 (Ar*C*H), 125.9 (Ar*C*H), 126.1 (Ar*C*H), 126.6 (2 × Ar*C*H), 127.0 (Ar*C*H), 127.2 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.6 (Ar*C*H), 127.8 (Ar*C*H), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H) 128.7 (Ar*C*H), 128.8 (2 × Ar*C*H), 128.9 (Ar*C*H), 129.0 (2 × Ar*C*H),132.5 (Ar*C*), 133.0 (Ar*C*), 140.0 (Ar*C*), 140.1 (Ar*C*), 140.3 (Ar*C*), 142.8 (Ar*C*), 144.0 (Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 22.31.

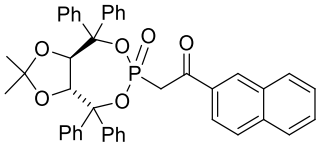
(3a*R*,8a*R*)-6-((*R*)-2-Hydroxy-2-(naphthalen-2-yl)ethyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide 106



Major isomer: White solid; yield 77%; $[\alpha]_D^{25}$ -160 (*c* 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.55 (3H, s, C*H*$_3$), 0.68 (3H, s, C*H*$_3$), 2.21 (1H, ddd, *J* 18.5, 15.3 and3.1, C*H*HP), 2.52 (1H, dt, *J* 9.8 and 15.3, CH*H*P), 4.23 (1H, d, *J* 2.6, O*H*), 5.17-5.21 (1H, m, C*H*OH), 5.26 (1H, d, *J* 7.9, C*H*-O), 5.58 (1H, d, *J* 7.8, C*H*-O), 7.13-7.85 (27H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.5 (*C*H$_3$), 26.8 (*C*H$_3$), 37.8 (d, $J_{C\text{-}P}$ 141.3, *C*H$_2$P), 68.5 (d, $J_{C\text{-}P}$ 4.0, *C*HOH), 79.0 (d, $J_{C\text{-}P}$ 7.9, 2 × *C*H-O), 88.0 (d, $J_{C\text{-}P}$ 9.2, *C*-O-P), 89.8 (d, $J_{C\text{-}P}$ 11.6, *C*-O-P), 114.5 [*C*(CH$_3$)$_2$], 123.5 (Ar*C*H), 124.3 (Ar*C*H), 125.9 (Ar*C*H), 126.1 (Ar*C*H), 126.7 (2 × Ar*C*H), 127.2 (Ar*C*H), 127.2 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.7 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.0 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H) 128.6 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.0 (Ar*C*H), 129.4 (2 × Ar*C*H),133.0 (Ar*C*),

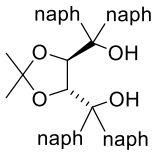
133.2 (Ar*C*), 139.4 (d, $J_{C\text{-}P}$ 10.1, Ar*C*), 139.6 (d, $J_{C\text{-}P}$ 4.5, Ar*C*), 140.6 (d, $J_{C\text{-}P}$ 16.1, Ar*C*), 143.2 (Ar*C*), 144.2 (d, $J_{C\text{-}P}$ 3.9, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.50; *m/z* (EI) 705.2382 [M+Na^+]. $C_{43}H_{39}NaO_6P$ requires 705.2362.

2-((3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-1-(naphthalen-2-yl)ethanone 109



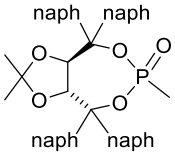
A stirred solution of methyl phosphonate **105** (0.51 g, 0.96 mmol) in dry THF (5 mL) was cooled to -78 °C, and *n*-BuLi (2.0 M in hexane, 0.48 mL, 0.96 mmol) was added dropwise by syringe over 15 minutes under an argon atmosphere. After stirring for additional 30 minutes at the same temperature, a solution of the methyl 2-naphthoate (0.18 g, 0.96 mmol) in dry THF (8 mL) was introduced dropwise over 15 minutes, and the reaction was allowed to continue stirring for 1 h at -78 °C. A saturated aqueous solution of NH_4Cl (10 mL) and water (10 mL) were added, the mixture was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with solution of NH_4Cl (30 mL), water (30 mL) and brine. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the residue which was obtained after removal of the solvent in vacuum was purified by flash chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:2) to afford the product **109** (0.35 g, 54% yield) as a white solid; mp 242-244 °C; $[\alpha]_D^{25}$ -194 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1}: 3060, 3024, 2985, 1676, 1493, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.48 (3H, s, C*H*$_3$), 0.82 (3H, s, C*H*$_3$), 3.79-3.96 (2H, m, C*H*$_2$P), 5.17 (1H, d, *J* 8.0, C*H*-O), 5.55 (1H, d, *J* 7.9, C*H*-O), 7.06-7.96 (m, 27H, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.6 (d, $J_{C\text{-}P}$ 63.2, 2 × *C*H$_3$), 40.2 (d, $J_{C\text{-}P}$ 139.1, *C*H$_2$P), 79.4 (d, $J_{C\text{-}P}$ 74.5, 2 × *C*H-O), 87.6 (d, $J_{C\text{-}P}$ 8.1, *C*-O-P), 90.5 (d, $J_{C\text{-}P}$ 11.6, *C*-O-P), 113.8 [*C*(CH$_3$)$_2$], 124.2 (Ar*C*H), 126.6 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 127.1 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.1 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 129.5 (2 × Ar*C*H), 130.0 (Ar*C*H), 131.4 (Ar*C*H),132.4 (Ar*C*), 134.0 (Ar*C*), 135.7 (Ar*C*), 139.4 (Ar*C*), 139.5 (Ar*C*), 143.4 (Ar*C*), 143.7 (Ar*C*), 191.0(d, $J_{C\text{-}P}$ 8.1, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 13.08; *m/z* (EI) 703.2260 [M+Na^+]. $C_{43}H_{37}NaO_6P$ requires 703.2225.

[(4*R*,5*R*)-2,2-Dimethyl-1,3-Dioxolane-4,5-diyl]Bis [di (naphthalen-2-yl) methanol] 110



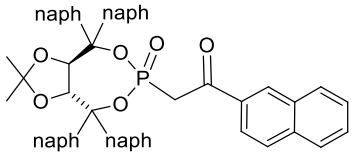
A solution of 2-bromonaphthalene (0.82 g, 4 mmol) in dry THF (5 mL) was added dropwise over 45 minutes to Mg (0.10 g, 4.2 mmol), with gentle heating. After complete addition, the reaction was heated at reflux for 1 h, then the reaction mixture was cooled in an ice bath, and a solution of dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **101** (0.17 g, 0.8 mmol) in dry THF (3 mL) was added. During the addition, the internal temperature was kept below 20 °C, and when complete the addition, the mixture was heated at reflux for 10 h. After cooling to room temperature, an aqueous saturated solution of NH_4Cl (10 mL) was carefully added with cooling until the pH reached 7-8, and the mixture was extracted with ethyl acetate (3 × 10 mL) The combined organic layers were washed twice with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated on a rotary evaporator. The resulting yellowish foam was purified by flash chromatography on silica gel, eluting with ethyl acetate/ toluene (1:6) to afford the compound **110** (0.32 g, 60% yield) as a white solid; mp 206-209°C, (lit.[239] 204-208 °C); $[\alpha]_D^{25}$-115.4 (*c* 1 in ethyl acetate), lit.[239] $[\alpha]_D^{25}$-116 (*c* 1 in ethyl acetate); ν_{max}(ATR)/cm^{-1}: 3492, 3059, 2991, 2936, 2895, 1632, 1597, 1505; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.20 (6H, s, 2 × C*H*$_3$), 4.27 (2H, s, 2 × O*H*), 5.00 (2H, s, 2 × C*H*-O), 7.26 (2H, dd, *J* 8.8 and 1.9, ArC*H*), 7.40-7.47 (4H, m, ArC*H*), 7.49-7.56 (7H, m, ArC*H*), 7.66-7.75 (7H, m, ArC*H*), 7.80 (2H, d, *J* 8.8, ArC*H*), 7.87-7.92 (4H, m, ArC*H*), 7.94 (2H, d, *J* 1.5, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 27.5 (2 × *C*H_3), 78.6 (2 × *C*-OH), 81.4 (2 × *C*H-O), 110.0 [*C*$(CH_3)_2$], 125.7 (2 × Ar*C*H), 125.9 (2 × Ar*C*H), 126.0 (2 × Ar*C*H), 126.1 (2 × Ar*C*H),126.1 (2 × Ar*C*H), 126.2 (2 × Ar*C*H), 126.8 (2 × Ar*C*H), 127.0 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.5 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.6 (4 × Ar*C*H), 132.6 (2 ×Ar*C*), 132.6 (2 × Ar*C*), 132.7 (2 × Ar*C*), 132.8 (2 ×Ar*C*), 140.6 (2 × Ar*C*), 142.4 (2 × Ar*C*); *m/z* (EI) 689.2659 [MNa^+]. $C_{47}H_{38}NaO_4$ requires 689.2668).

(3a*R*,8a*R*)-2,2,6-Trimethyl-4,4,8,8-tetra(naphthalen-2-yl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide 111



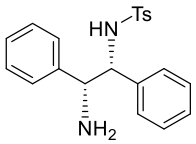
A solution of naphthyl diol **110** (0.75 g, 1.12 mmol) in dry THF (8 mL) was cooled to -78 °C, and *n*-BuLi (2.0 M in hexane, 1.6 mL, 3.37 mmol) was added dropwise at the same temperature. The solution was warmed to room temperature and stirred for 1 h, then cooled to -78 °C again, and **104** (0.29 g, 2.25 mmol) dissolved in THF (2 mL) and added dropwise over 15 minutes. The mixture was stirred at room temperature for 3.5 h. The solvent was removed under reduced pressure, and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate/ toluene (1:4) to afford the product **111** (0.65 g, 80%) as a white solid; mp 213-216 °C; $[\alpha]_D^{25}$-313(*c* 1, $CHCl_3$); ν_{max}(ATR)/cm^{-1}: 3056, 3022, 2994, 2936, 1632, 1601, 1505; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.64 (3H, s, C*H*$_3$), 0.72 (3H, s, C*H*$_3$), 1.60 (3H, d, *J* 18.0, C*H*$_3$P), 5.62 (1H, d, *J* 7.9, C*H*-O), 5.90 (1H, d, *J* 7.8, C*H*-O), 7.19-8.10 (28H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C14.0 (d, $J_{C\text{-}P}$ 149.2, 2 ×*C*H$_3$), 26.5 (*C*H$_3$P), 79.9 (d, $J_{C\text{-}P}$ 45.4, 2 × *C*H-O), 87.6 (d, $J_{C\text{-}P}$ 8.7, *C*-O-P), 88.9 (d, $J_{C\text{-}P}$ 10.5, *C*-O-P), 114.7 [*C*(CH$_3$)$_2$], 125.1 (Ar*C*H), 125.2 (Ar*C*H), 125.3 (Ar*C*H), 125.7 (Ar*C*H), 125.9 (Ar*C*H), 126.1 (Ar*C*H), 126.1 (2 × Ar*C*H), 126.3 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (2 × Ar*C*H), 126.8 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 127.7 (2 × Ar*C*H), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 × Ar*C*H), 128.8 (Ar*C*H), 128.9 (2 × Ar*C*H), 132.4 (Ar*C*), 132.5 (Ar*C*), 132.6 (Ar*C*), 132.7 (Ar*C*), 132.8 (Ar*C*), 133.0 (Ar*C*), 133.2 (Ar*C*), 137.1 (Ar*C*), 137.2 (Ar*C*), 137.3 (Ar*C*), 140.5 (Ar*C*),141.2 (Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 21.97; *m/z* (EI) 749.2440 [M+Na^+]. $C_{48}H_{39}NaO_5P$ requires 749.2433.

2-[(3a*R*,8a*R*)-2,2-Dimethyl-4,4,8,8- tetra(naphthalen-2-yl)]-6-oxidotetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-1-(naphthalen-2-yl)ethanone 112



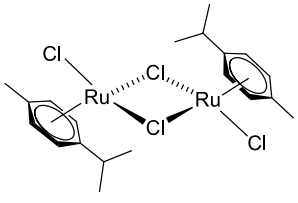
A stirred of solution methyl phosphonate **111** (0.35 g, 0.48 mmol) in dry THF (2 mL) was cooled to -78 °C, and *n*-BuLi (2.0 M in hexane,0.24 mL, 0.48 mmol) was added dropwise by syringe over 15 minutes under an argon atmosphere. After stirring for additional 30 minutes at the same temperature, a solution of methyl 2-naphthoate (0.89 g, 0.48 mmol) in dry THF (1mL) was introduced dropwise over 15 minutes, and the reaction was allowed to continue stirring for 1 h at -78 °C. A saturated aqueous solution of NH_4Cl (10 mL) and water (20 mL) were added, the mixture was extracted with (3 × 50 mL) of ethyl acetate. The combined extracts were washed with saturated aqueous solution of NH_4Cl (30 mL), water (30 mL) and brine (30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the residue obtained after removal of the solvent was purified by flash chromatography on silica gel eluting with ethyl acetate/ toluene (1:9) to afford the product **112** (0.15 g, 42% yield) as a white solid; mp 190-196 °C; $[\alpha]_D^{25}$-218 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1}: 3056, 2992, 2934, 1676, 1629, 1597, 1507; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.50 (3H, s, C*H*$_3$), 0.90 (3H, s, C*H*$_3$), 4.00 (2H, ddd, *J* 32.8, 23.6 and 14.1, C*H*$_2$P), 5.55 (1H, d, *J* 7.9, C*H*-O), 5.90 (1H, d, *J* 7.9, C*H*-O), 7.17-7.94 (35H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.9(d, $J_{C\text{-}P}$ 63.2, 2 × *C*H$_3$), 40.0 (d, $J_{C\text{-}P}$ 138.4, *C*H$_2$P), 79.8 (d, $J_{C\text{-}P}$ 43.2, 2 × *C*H-O), 88.0 (d, $J_{C\text{-}P}$ 8.1, *C*-O-P), 90.8 (d, $J_{C\text{-}P}$ 11.6, *C*-O-P), 114.2 [*C*(CH$_3$)$_2$], 124.0 (Ar*C*H), 125.0 (Ar*C*H), 125.1 (Ar*C*H), 125.3 (Ar*C*H), 125.4 (Ar*C*H), 125.7 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (Ar*C*H), 126.2 (Ar*C*H), 126.3 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (Ar*C*H), 126.7 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 128.0 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (2 × Ar*C*H), 129.1 (Ar*C*H) 129.9 (Ar*C*H), 131.4 (Ar*C*H), 132.4 (Ar*C*), 132.4 (Ar*C*), 132.5 (Ar*C*), 132.5 (Ar*C*), 132.7 (Ar*C*), 132.7 (Ar*C*), 132.8 (Ar*C*), 133.1 (Ar*C*), 133.8 (Ar*C*), 135.7 (Ar*C*), 136.9 (Ar*C*),136.9 (Ar*C*),137.0 (Ar*C*), 140.6 (Ar*C*),140.7 (Ar*C*), 190.8 (d, $J_{C\text{-}P}$ 8.3, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 13.24; *m/z* (EI) 903.2817 [M+Na$^+$]. $C_{59}H_{45}NaO_6P$ requires 903.2851.

(1*R*,2*R*)-*N*-tosyl-1,2-diphenylethanediamine (TsDPEN) [240] 142



A mixture of (1*R*,2*R*)-1,2-diphenylethanediamine **141** (0.33 g, 1.6 mmol) *p*-toluene-sulfonyl chloride (0.34 g, 1.6 mmol), and triethylamine (0.33 mL, 2.4 mmol) in dichloromethane (10 mL) was stirred at 0 °C for 30 minutes and then at room temperature for 36 h under argon atmosphere. The reaction was quenched by the addition of distilled water (20 mL), and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic phase was washed with saturated solution of $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), and then dried over sodium sulfate. After filtrate and removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (2:1), to afford the product **142** (0.43 g, 77% yield) as a white solid; mp 126-127 °C, (lit.[240] 127-128 °C); $[\alpha]_D^{25}$ -36 (*c* 1 in $CHCl_3$), lit.[241] $[\alpha]_D^{25}$ -36.7 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1}: 3340, 3286, 3084, 3062, 3028, 2933, 2860, 2165, 2021, 1974, 1595, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.45 (2H, s, broad, N*H*$_2$), 2.34 (3H, s, C*H*$_3$), 4.15 (1H, d, *J* 5.2, C*H*NH$_2$), 4.39 (1H, d, *J* 5.1, C*H*NH), 6.07 (1H, s, broad, N*H*), 6.99 (2H, d, *J* 7.8, ArC*H*), 7.10-7.20 (10H, m, ArC*H*), 7.33 (2H, d, *J* 8.3, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.4 (*C*H$_3$), 60.5 (*C*HNH$_2$), 63.1 (*C*HNH), 126.5 (2 × Ar*C*H), 126.9 (2 × Ar*C*H), 127.0 (2 × Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 137.1 (Ar*C*), 139.3 (Ar*C*), 141.4 (Ar*C*), 142.5 (Ar*C*); *m/z* (EI) 367.1476 (100%, MH$^+$. $C_{21}H_{22}N_2O_2S$ requires 367.1475), 367 (100), 350 (3).

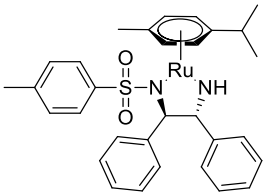
Di-µ-chloro-bis[chloro(η^6-1-isopropyl-4- methylbenzene) ruthenium (II)][241] 144



A solution of ruthenium(III) chloride hydrate (0.15 g, 0.7 mmol) in EtOH (7.5 mL), was treated with *α*-phellandrene **143** (0.43 g, 7.5 ml, 3.2 mmol) and heated at 120 °C for 4 h. The solution was allowed to cool to room temperature and the red-brown crystalline product was filtered off. Additional product was obtained by concentrating the orange-yellow filtrate

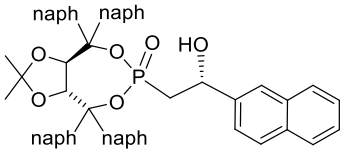
under reduced pressure to approximately the half-volume, refrigerating overnight and filtering off the crystals. Drying in vacuum afforded the product **144** (0.12 g, 60%) as deep-red crystals; mp decomp. >200 °C, (lit.[241] decomp. >205 °C); ν_{max}(ATR)/cm^{-1}: 3050, 2960, 2925, 2874, 1496, 1471; ^{1}H NMR (400 MHz, $CDCl_3$)δ_H 1.29 (12H, d, *J* 7.0, 4 × C*H*$_3$), 2.17 (6H, s, 2 × C*H*$_3$), 2.94[(2H, septet, *J* 6.9, 2 × C*H*$(CH_3)_2$], 5.35 (4H, d, *J* 5.9, ArC*H*), 5.49 (4H, d, *J* 5.9, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 18.9 (2 × *C*H$_3$), 22.1 (4 × *C*H$_3$), 30.6 [2 × C*H*$(CH_3)_2$], 80.5 (4 × Ar*C*H), 81.3 (4 × Ar*C*H), 96.8 (2 × Ar*C*), 101.3 (2 × Ar*C*).

(1*R*,2*R*)-(−)-*N*-Tosyl-1,2-diphenylethane-1,2-diamine[(η^6-1-isopropyl-4-methylbenzene) ruthenium(II)][241] 135



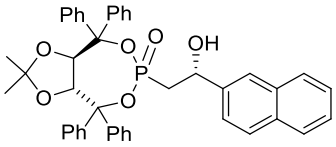
A mixture of **144** (0.67 g, 1.1 mmol), TsDPEN **142** (0.80 g, 2.2 mmol) and KOH (0.92 g, 16.4 mmol) in anhydrous DCM (15 mL) were stirred under an argon atmosphere at ambient temperature for 10 min. On addition of water (15 mL) the colour changed from orange to deep purple. The layers were separated and the purple organic layer was washed with water (15 mL), dried over CaH_2, filtrated and concentrated at 25 °C to dryness in vacuum to yield the product **135** (1.1 g, 91%) as a deep purple crystals that were kept in the fridge at 0-8 °C until needed; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, d, *J* 6.9, CHC*H*$_3$), 1.32 (3H, d, *J* 6.9, CHC*H*$_3$) 2.22 (3H, s, C*H*$_3$), 2.30 (3H, s, C*H*$_3$), 2.65-2-72 [1H, m, C*H*$(CH_3)_2$], 4.00 (1H, d, *J* 4.5, C*H*NH), 4.46 (1H, s, C*H*N-Ts), 5.33 (1H, d, *J* 4.4, ArC*H*), 5.41 (1H, d, *J* 5.9, ArC*H*), 5.55 (1H, d, *J* 5.9, ArC*H*), 5.72 (1H, d, *J* 5.8, ArC*H*), 6.89 (2H, d, *J* 8.1, ArC*H*), 7.08 (2H, d, *J* 6.9, ArC*H*), 7.13–7.22 (6H, m, ArC*H*), 7.31 (2H, d, *J* 8.2, ArC*H*), 7.41 (2H, d, *J* 6.2, ArC*H*); *m/z* (EI) 601.1454 (100%, MH$^+$. $C_{31}H_{35}N_2O_2S^{102}Ru$ requires 601.1463), 604 (10), 603 (^{104}Ru, 72), 602 (37), 600 (^{101}Ru, 80), 599 (^{99}Ru, 70), 598 (^{98}Ru, 64), 597 (8), 596 (^{96}Ru, 8), 595 (30).

(3a*R*,8a*R*)-6-((*R*)-2-Hydroxy-2-(naphthalen-2-yl)ethyl)-2,2-dimethyl-4,4,8,8-tetra(naphthalen-2-yl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2] dioxaphosphepine 6-oxide 113



The solution of *β*-ketonaphthylphosphonate **112** (0.881 g, 1 mmol) and (*R*,*R*)-catalyst (0.003 g, 0.005 mmol) in Et_3N (2.024 g, 2.85 mL, 20 mmol) was stirred for 10 min at room temperature. Formic acid (0.184 g, 0.15 mL, 4 mmol) was slowly added by syringe and the resulting mixture was then purged with nitrogen. The mixture was allowed to react at 35 °C for 16 h. After complete consumption of *β*-ketophosphonate, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The solution was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the product **113** as a whit solid. The product was purified by flash chromatography on silica gel, eluting with ethyl acetate (0.82 g, 97%); $[\alpha]_D^{25}$ -188 (*c* 1 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.57 (3H, s, C*H*$_3$), 0.73 (3H, s, C*H*$_3$), 2.21 (1H, ddd, *J* 18.2, 15.4 and 2.7, C*H*HP), 2.61 (1H, dt, *J* 10.3 and 15.6, CH*H*P), 4.38 (1H, br s, O*H*), 5.28 (1H, td, *J* 10.8 and 2.0, C*H*OH), 5.63 (1H, d, *J* 7.8, C*H*-O), 5.90 (1H, d, *J* 7.8, C*H*-O), 7.16 (1H, dd, *J* 8.7 and 1.8, ArC*H*), 7.23 (1H, dd, *J* 8.7 and 1.8, ArC*H*), 7.38 (1H, dd, *J* 8.7 and 1.8, ArC*H*), 7.42-8.00 (30H, m, ArC*H*), 8.22 (2H, dd, *J* 3.1 and 1.3, ArC*H*), 8.43 (1H, d, *J* 1.3, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.8 (*C*H$_3$), 27.0 (*C*H$_3$), 37.9 (d, $J_{C\text{-}P}$ 139.6, *C*H$_2$P), 68.4 (d, $J_{C\text{-}P}$ 3.9, *C*HOH), 79.5 (d, $J_{C\text{-}P}$ 17.1, 2 × *C*H-O), 88.5 (d, $J_{C\text{-}P}$ 9.2, *C*-O-P), 89.9 (d, $J_{C\text{-}P}$ 11.0, *C*-O-P), 115.0 [*C*(CH$_3$)$_2$], 133.4 (Ar*C*H), 124.0 (Ar*C*H), 125.0 (Ar*C*H), 125.3 (Ar*C*H), 125.5 (Ar*C*H), 125.8 (Ar*C*H), 126.0 (Ar*C*H), 126.1 (Ar*C*H), 126.2 (Ar*C*H), 126.2 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (Ar*C*H), 126.8 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.4 (Ar*C*H), 127.5 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 127.8 (Ar*C*H), 127.9 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 128.1 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 128.6 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 132.4 (Ar*C*), 132.5 (Ar*C*), 132.6 (Ar*C*), 132.7 (Ar*C*), 132.8 (Ar*C*), 133.1 (Ar*C*) 133.2 (Ar*C*), 133.3 (Ar*C*), 136.8 (Ar*C*), 136.9 (Ar*C*), 137.0 (Ar*C*), 140.3 (Ar*C*), 140.4 (Ar*C*), 140.6 (Ar*C*), 140.9 (Ar*C*);^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.6; *m/z* (EI) 905.2993 (100%, M+Na$^+$. $C_{59}H_{47}NaO_6P$ requires 905.3008), 905.6 (100).

(3a*R*,8a*R*)-6-((*R*)-2-Hydroxy-2-(naphthalen-2-yl)ethyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide 106



Same as the procedure for naphthalene **113**, by reacting **109** with Ru-cat-**135**.

98% yield; $[\alpha]_D^{25}$ -161 (*c* 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.54 (3H, s, C*H*$_3$), 0.69 (3H, s, C*H*$_3$), 2.21 (1H, ddd, *J* 18.4, 15.3 and 3.0, C*H*HP), 2.51 (1H, dt, *J* 9.8 and 15.2, CH*H*P), 4.24 (1H, d, *J* 2.6, O*H*), 5.19-5.20 (1H, m, C*H*OH), 5.24 (1H, d, *J* 7.7, C*H*-O), 5.57 (1H, d, *J* 7.7, C*H*-O), 7.15-7.84 (27H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.5 (*C*H_3), 26.7 (*C*H_3), 37.7 (d, $J_{C\text{-}P}$ 141.3, *C*H_2P), 68.6 (d, $J_{C\text{-}P}$ 4.0, *C*HOH), 79.1 (d, $J_{C\text{-}P}$ 7.8, 2 × *C*H-O), 88.1 (d, $J_{C\text{-}P}$ 9.1, *C*-O-P), 89.9 (d, $J_{C\text{-}P}$ 11.5, *C*-O-P), 114.5 [*C*$(CH_3)_2$], 123.7 (Ar*C*H), 124.3 (Ar*C*H), 125.8 (Ar*C*H), 126.1 (Ar*C*H), 126.6 (2 × Ar*C*H), 127.1 (Ar*C*H), 127.2 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H) 128.5 (Ar*C*H), 128.7 (2 × Ar*C*H), 128.5 (Ar*C*H), 129.3 (2 × Ar*C*H),132.5 (Ar*C*), 133.6 (Ar*C*), 139.3 (d, $J_{C\text{-}P}$ 10.1, Ar*C*), 139.5 (d, $J_{C\text{-}P}$ 4.5, Ar*C*), 140.2 (d, $J_{C\text{-}P}$ 16.1, Ar*C*), 143.2 (Ar*C*), 144.1 (d, $J_{C\text{-}P}$ 3.9, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.5.

General procedure (A) for the Synthesis of *β*-Ketophosphonates 147a-l

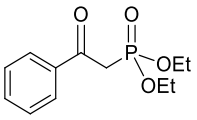
A solution of *n*-BuLi (2.3 Min hexane, 0.9 mL, 2.05 mmol) was added at -78 °C to a solution of diethyl methylphosphonate **145** (0.3 mL; 2.05 mmol) in dry THF (5 mL). After 1 h, the ester (2.05 mmol) in dry THF (2 mL) was added dropwise over 15 minutes. Two hours later, a saturated aqueous solution of NH_4Cl (10 mL) was added and stirred at room temperature for 1 h. Water (10 mL) and EtOAc (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:1-5:1) to afford the product.

General procedure (B) for the Synthesis of *β*-Ketophosphonates 147a-l

A solution of LiHMDS (1.0 M in THF, 22 mL, 22mmol) was cooled in an ice bath, and diethyl methylphosphonate **145** (1.5 mL, 10 mmol) was added. The ester (11 mmol) (either

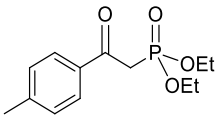
neat or dissolved in a minimal amount of THF) was added dropwise, maintaining the internal temperature of the reaction below 0 °C. The reaction was stirred at 0°C until complete consumption of the ester as determined by TLC. The reaction was then carefully quenched with HCl (6 M) to pH 4-5. EtOAc (20 mL) and H_2O (10mL) were added respectively, followed by extraction with EtOAc (3 × 50 mL), the combined organics were washed with H_2O (100 mL) and brine (100 mL), dried over ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (6:1).

Diethyl (2-oxo-2-phenylethyl) phosphonate [242, 243] 147a



General procedure **B** was followed. The product was isolated as a colourless oil, 70% yield; ν_{max}(ATR)/cm^{-1}: 3064, 2985, 2933, 2909, 1679, 1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (6H, t, *J* 7.3, 2 × C*H*$_3$), 3.64 (2H, d, $J_{H\text{-}P}$ 22.7, C*H*$_2$P), 4.11-4.19 (4H, m, 2 × OC*H*$_2$CH$_3$), 7.49 (2H, t, *J* 7.7, ArC*H*), 7.60 (1H, t, *J* 7.2, ArC*H*), 8.03 (2H, d, *J* 7.1, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_3$), 38.5 (d, $J_{C\text{-}P}$ 129.6, *C*H$_2$P), 62.6 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_2$O), 128.6 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 133.7 (Ar*C*H), 136.5 (Ar*C*), 192.0 (d, $J_{C\text{-}P}$ 6.8, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.86; *m*/*z* (EI) 257.0936 (100%, MH$^+$. $C_{12}H_{18}O_4P$ requires 257.0937), 229 (3), 201 (4).

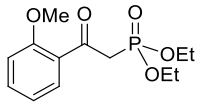
Diethyl [2-oxo-2-(*p*-tolyl) ethyl]phosphonate [244,245] 147b



General procedure **B** was followed. The product was isolated as a light yellow oil in 74% yield; ν_{max} (ATR)/cm^{-1} 3064, 3033, 2985, 2930, 2872, 1675, 1607, 1576; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (6H, t, *J* 7.0,2 × C*H*$_3$), 2.43 (3H, s, ArC*H*$_3$), 3.61 (2H, d, $J_{H\text{-}P}$ 22.7, C*H*$_2$P), 4.14(4H, pent, 2 × OC*H*$_2$CH$_3$), 7.28 (2H, d, *J* 7.8, ArC*H*), 7.92 (2H, d, *J* 8.3, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.2, 2 × *C*H$_3$), 21.7 (Ar*C*H$_3$), 38.4 (d, $J_{C\text{-}P}$ 130.0, *C*H$_2$P), 62.6 (d, $J_{C\text{-}P}$ 6.0, 2 × *C*H$_2$O), 129.2 (2 × Ar*C*H),129.3 (2 × Ar*C*H), 134.1

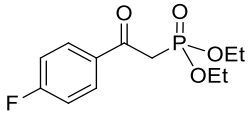
(Ar*C*), 144.6 (Ar*C*), 191.5 (d, $J_{C\text{-}P}$ 6.9, *C*=O); ^{31}P-NMR (162 MHz, $CDCl_3$) δ_P 20.16; *m*/*z* (EI) 271.1094 (100%, MH^+. $C_{13}H_{20}O_4P$ requires 271.1094), 243 (3), 215 (3).

Diethyl [2-(2-methoxyphenyl)-2-oxoethyl]phosphonate [242] 147c



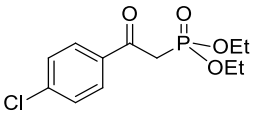
General procedure **B** was followed. The product was isolated as a colourless oil in 87% yield; ν_{max} (ATR)/cm^{-1} 3074, 2985, 2940, 2909, 2844, 1671, 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (6H, t, *J* 7.1,2 × C*H*$_3$), 3.83 (2H, d, $J_{H\text{-}P}$ 22.0, C*H*$_2$P), 3.94 (3H, s, OC*H*$_3$), 4.06-4.14 (4H, m, 2 × OC*H*$_2$CH$_3$), 6.97 (1H, d, *J* 8.4, ArC*H*), 7.01 (1H, td, *J* 7.5 and 0.9, ArC*H*), 7.49 (1H, t, *J* 7.8, ArC*H*), 7.72 (1H, dt, *J* 7.8 and 1.2, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, 2 × *C*H$_3$), 42.5 (d, $J_{C\text{-}P}$ 130.1, *C*H$_2$P), 55.6 (O*C*H$_3$), 62.2 (d, $J_{C\text{-}P}$ 6.3, 2 × *C*H$_2$O), 111.5 (Ar*C*H), 120.7 (Ar*C*H), 127.7 (Ar*C*), 130.9 (Ar*C*H), 134.2 (Ar*C*H), 158.6 (Ar*C*), 193.4 (d, $J_{C\text{-}P}$ 7.2, *C*=O); ^{31}P-NMR (162 MHz, $CDCl_3$) δ_P 21.17; *m*/*z* (EI) 287.1043 (100%, MH^+. $C_{13}H_{20}O_5P$ requires 287.1043), 309 (3), 277 (1), 259 (2), 259 (2), 231 (1), 212 (1), 191 (2), 163 (1).

Diethyl [2-(4-fluorophenyl)-2-oxoethyl]phosphonate [243,245] 147d



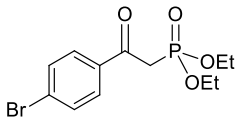
General procedure **B** was followed. The product was isolated as a pale yellow oil in 77% yield; ν_{max} (ATR)/cm^{-1} 3115, 3071, 2985, 2937, 2913, 2872, 1681, 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (6H, t, *J* 7.1, 2 × C*H*$_3$), 3.61 (2H, d, $J_{H\text{-}P}$ 22.8, C*H*$_2$P), 4.11-4.18(4H, m, 2 × OC*H*$_2$CH$_3$), 7.13-7.19 (2H, m, 2 × ArC*H*), 8.07 (2H, dd, *J* 9.0 and 5.4,2 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, 2 × *C*H$_3$), 38.6 (d, $J_{C\text{-}P}$ 129.3, *C*H$_2$P), 62.7 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_2$O), 115.7 (d, $J_{C\text{-}P}$ 21.8, 2 × Ar*C*H), 131.8 (d, $J_{C\text{-}P}$ 9.4, 2 × Ar*C*H), 164.8 (Ar*C*), 167.3 (Ar*C*F), 190.3 (d, $J_{C\text{-}P}$ 6.5, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.55; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -104.10; *m*/*z* (EI) 275.0847 (100%, MH^+. $C_{12}H_{17}FO_4P$ requires 275.0843), 297.1 (2), 247 (3), 219 (3).

Diethyl [2-(4-chlorophenyl)-2-oxoethyl]phosphonate [243,245] 147e



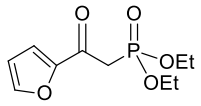
A mixture of triethylphosphite (2.2 mL, 12.84 mmol) and α-bromo-4-chloroacetophenone (1.0 g, 4.28 mmol) was heated to reflux at 180 °C under argon for 48 hours. Excess triethylphosphite was removed under reduced pressure at 40 °C. The residue was purified by column chromatography on silica gel eluting with EtOAc/petroleum ether (1:1). The product was isolated as a pale yellow oil (0.7 g, 74% yield); ν_{max} (ATR)/cm^{-1} 3067, 2984, 2933, 2906, 2868, 1682, 1548; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.23 (6H, t, J 7.1, 2 × CH_3), 3.55 (2H, d, $J_{H\text{-}P}$ 22.8, CH_2P), 4.02-4.13 (4H, m, 2 × OCH_2CH$_3$), 7.39 (2H, d, J 8.6, ArCH), 7.90 (2H, d, J 8.7, ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, 2 × CH$_3$), 38.5 (d, $J_{C\text{-}P}$ 129.6, CH$_2$P), 62.6 (d, $J_{C\text{-}P}$ 6.4, 2 × CH$_2$O), 128.8 (2 × ArCH), 130.4 (2 × ArCH), 134.7 (ArC), 140.1 (ArC),190.7 (d, $J_{C\text{-}P}$ 6.9, C=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.38; m/z (EI) 291.0545 (100%, MH$^+$. $C_{12}H_{17}{}^{35}ClO_4P$ requires 291.0547), 313 (1, M+Na$^+$), 293 (30, ^{37}Cl), 263 (3, MH$^+$-CH$_2$CH$_3$), 235 (3), 193 (2).

Diethyl [2-(4-bromophenyl)-2-oxoethyl]phosphonate [243,245] 147f



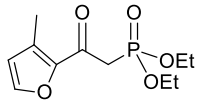
General procedure **B** was followed. The product was isolated as a pale yellow oil in 77% yield; ν_{max} (ATR)/cm^{-1} 3096, 2978, 2933, 2906, 1682, 1586; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (6H, t, J 7.0, 2 × CH_3), 3.60 (2H, d, $J_{H\text{-}P}$ 23.0, CH_2P), 4.11-4.18 (4H, m, 2 × OCH_2CH$_3$), 7.63 (2H, d, J 8.7, 2 × ArCH), 7.90 (2H, d, J 8.7, 2 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 5.9, 2 × CH$_3$), 38.6 (d, $J_{C\text{-}P}$ 129.3, CH$_2$P), 62.7 (d, $J_{C\text{-}P}$ 6.5, 2 × CH$_2$O), 129.1 (ArC), 130.6 (2 × ArCH), 131.9 (2 × ArCH),135.2 (ArC), 190.95 (d, $J_{C\text{-}P}$ 6.9, C=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.33; m/z (EI) 335.0041 (100%, MH$^+$. $C_{12}H_{17}{}^{79}BrO_4P$ requires 335.0042), 337 (98, ^{81}Br), 307 (2), 279 (2).

Diethyl [2-(furan-2-yl)-2-oxoethyl]phosphonate [242] 147g



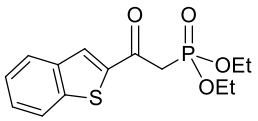
General procedure **B** was followed. The product was isolated as an orange oil in 60% yield; ν_{max} (ATR)/cm^{-1} 3125, 2985, 2933, 2906, 2868, 1673, 1568; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (6H, t, *J* 7.0, 2 × C*H*$_3$), 3.51 (2H, d, $J_{H\text{-}P}$ 22.6, C*H*$_2$P), 4.12-4.20 (4H, m, 2 × OC*H*$_2$CH$_3$), 6.60 (1H, dd, *J* 3.6 and 1.6, ArC*H*), 7.32 (1H, dd, *J* 3.6 and 0.6, ArC*H*), 7.64 (1H, dd, *J* 1.6 and 0.6, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.4, 2 ×*C*H$_3$), 38.2 (d, $J_{C\text{-}P}$ 129.8, *C*H$_2$P), 62.7 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_2$O), 112.8 (Ar*C*H), 119.0 (Ar*C*H), 147.1 (Ar*C*H), 152.2 (Ar*C*), 180.4 (d, $J_{C\text{-}P}$ 6.7, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.46; *m*/*z* (ESI$^+$) 247.0734 (100%, MH$^+$. $C_{10}H_{16}O_5P$ requires 247.0730), 219 (4), 191 (3), 179 (2), 123 (4).

Diethyl [2-(3-methylfuran-2-yl)-2-oxoethyl] phosphonate 147h



General procedure **B** was followed. The product was isolated as an orange oil in 50% yield; ν_{max} (ATR)/cm^{-1} 3108, 3055, 2985, 2933, 2906, 2868, 1666, 1584; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (6H, t, *J* 7.1, 2 × C*H*$_3$), 2.41 (3H, s, ArC*H*$_3$), 3.54 (2H, d, $J_{H\text{-}P}$ 22.3, C*H*$_2$P), 4.13-4.20 (4H, m, 2 × OC*H*$_2$CH$_3$), 6.42 (1H, d, *J* 1.4, ArC*H*), 7.45 (1H, d, *J* 1.5, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 11.9 (Ar*C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.3, 2 × *C*H$_3$), 38.2 (d, $J_{C\text{-}P}$ 130.4, *C*H$_2$P), 62.4 (d, $J_{C\text{-}P}$ 6.2,2 × *C*H$_2$O), 116.3 (Ar*C*H), 132.1 (Ar*C*), 144.9 (Ar*C*H), 148.9 (Ar*C*),181.8 (d, $J_{C\text{-}P}$ 7.0, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.52; *m*/*z* (EI) 261.0891 (100%, MH$^+$. $C_{11}H_{18}O_5P$ requires 261.0886), 233 (2), 179 (2), 123 (3).

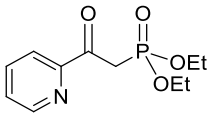
Diethyl [2-(benzo[*b*]thiophen-2-yl)-2-oxoethyl] phosphonate 147i



General procedure **B** was followed. The product was isolated as a colourless oil in 61% yield; ν_{max} (ATR)/cm^{-1} 3060, 2981, 2937, 2909, 1659, 1516; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (6H, t, *J* 7.0,2 × C*H*$_3$), 3.67 (2H, d, $J_{H\text{-}P}$ 22.6, C*H*$_2$P), 4.14-4.22 (4H, m, 2 × OC*H*$_2$CH$_3$), 7.43

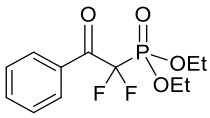
(2H, td, *J* 7.6 and 1.5, ArC*H*), 7.50 (2H, td, *J* 7.7 and 1.5, ArC*H*),8.13 (1H, s, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$6.3, 2 × *C*H_3), 39.4 (d, $J_{C\text{-}P}$ 129.7, *C*H_2P), 62.9 (d, $J_{C\text{-}P}$ 6.6, 2 × *C*H_2O), 122.9 (Ar*C*H), 125.1 (Ar*C*H), 126.3 (Ar*C*H), 127.8 (Ar*C*H), 131.6 (Ar*C*H), 139.0 (Ar*C*), 143.1 (Ar*C*), 143.2 (Ar*C*), 185.8 (d, $J_{C\text{-}P}$ 6.6, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 19.04; *m/z* (EI) 313.066 (100%, MH^+. $C_{14}H_{18}O_4PS$ requires 313.0658), 285 (1), 257 (1), 225 (1), 204 (1), 179 (1), 151 (2).

Diethyl [2-oxo-2-(pyridin-2-yl)ethyl] phosphonate [245] 147j



General procedure **B** was followed. The product was isolated as a yellow oil in 50% yield; ν_{max} (ATR)/cm^{-1} 3057, 2985, 2933, 2909, 1700, 1605, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (6H, t, *J* 7.1, 2 × C*H*$_3$), 4.04 (2H, d, $J_{H\text{-}P}$ 22.7, C*H*$_2$P), 4.16 (4H, pent, *J* 7.3, 2 × OC*H*$_2$CH$_3$), 7.50 (1H, ddd, *J* 7.6, 4.8 and 1.2, ArC*H*), 7.85 (1H, dt, *J* 1.7 and 7.7, ArC*H*), 8.09 (1H, dt, *J* 7.9 and 1.0, ArC*H*), 8.71 (1H, dq, *J* 4.7 and 0.8, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H_3), 35.9 (d, $J_{C\text{-}P}$ 129.9, *C*H_2P), 62.4 (d, $J_{C\text{-}P}$ 6.2,2 × *C*H_2O), 122.2 (Ar*C*H), 127.4 (Ar*C*H), 136.9 (Ar*C*H), 148.9 (Ar*C*H), 152.6 (Ar*C*),193.8(d, $J_{C\text{-}P}$ 6.8, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.73; *m/z* (EI) 258.0888 (100%, MH^+. $C_{11}H_{17}NO_4P$ requires 258.089), 230 (2).

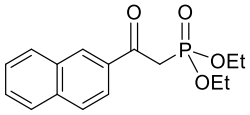
Diethyl (1,1-difluoro-2-oxo-2-phenylethyl)phosphonate [246]147k



A solution of diisopropylamine (0.45 mL, 3.18 mmol) in dry THF (2 mL) was cooled to -78 °C and then *n*-BuLi (1.41 mL, 2.28 M in hexanes, 3.19 mmol) was added dropwise via syringe. The resulting solution was allowed to warm to 0 °C for 25 min and then cooled to -78 °C before diethyl (difluoromethyl) phosphonate **149** (0.49 mL, 3.18 mmol) was added in THF (2 mL). After 30 min at -78 °C, ethyl benzoate (0.35 mL, 2.45 mmol) in THF (2 mL) was added, dropwise, via cannula over 15 minutes. After 1 hour, the reaction was quenched by the addition of HOAc (0.33 mL, 5.73 mmol), followed by saturated aqueous solution of NH_4Cl (8 mL). Following extraction with EtOAc (3 × 25 mL), the combined organics layers

were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (EtOAc/petroleum ether) (1:1) yielded the desired compound **150k** (0.75 g, 85%) as a pale yellow oil; ν_{max} (ATR)/cm^{-1} 3074, 2988, 2940, 2913, 1698, 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39 (6H, td, *J* 7.1 and 0.6, 2 × C*H*$_3$), 4.32-4.38 (4H, m, 2 × OC*H*$_2$CH$_3$), 7.55 (2H, t, *J* 7.8, ArC*H*), 7.64-7.69 (1H, m, ArC*H*), 8.15 (2H, dt, *J* 8.4 and 1.1, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.6, 2 × *C*H$_3$), 65.3 (d, $J_{C\text{-}P}$ 6.7,2 × *C*H$_2$O), 128 (d, $J_{C\text{-}F}$ 14.6, *C*F$_2$), 128.7 (Ar*C*H),130.3 (Ar*C*H), 130.4 (Ar*C*H), 130.4 (Ar*C*H), 132.0 (Ar*C*), 134.7 (Ar*C*H), 187.9 (td, $J_{C\text{-}P}$ 36.4 and 14.9, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 3.5 (t, $J_{P\text{-}F}$ 95.6, C-P); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -110.0 (d, $J_{P\text{-}F}$ 95.6, C-F); *m*/*z* (EI) 293.0748 (100%, MH^+. $C_{12}H_{16}F_2O_4P$ requires 293.0749), 265 (5), 237 (6), 217 (2).

Diethyl (2-(naphthalen-2-yl)-2-oxoethyl)phosphonate[243, 247-251]147l



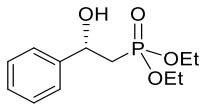
General procedure **A** was followed. The products was isolated as a colourless oil, 61% yield; ν_{max} (ATR)/ cm^{-1}: 3084, 2982, 2930, 2904, 1675, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (6H, t, *J* 7.0, 2 × C*H*$_3$), 3.78 (2H, d, *J* 22.7, C*H*$_2$P), 4.09-4.24 (4H, m, 2 × OC*H*$_2$CH$_3$), 7.58 (1H, ddd, *J* 8.0, 7.0 and 1.1, Ar*H*), 7.64 (1H, ddd, *J* 8.1, 6.9 and 1.2, Ar*H*), 7.91 (2H, t, *J* 8.4, Ar*H*), 8.01 (1H, d, *J* 8.1, Ar*H*), 7.08 (1H, dd, *J* 8.7 and 1.8, Ar*H*), 8.58 (1H, d, *J* 1.1, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (*C*H$_3$), 16.3 (*C*H$_3$), 38.6 (d, $J_{c\text{-}p}$ 129.9, *C*H$_2$P), 62.7 (d, $J_{c\text{-}p}$ 6.5, 2 × *C*H$_2$O), 124.2 (Ar*C*H), 126.9 (Ar*C*H), 127.8 (Ar*C*H), 128.5 (Ar*C*H), 128.9 (Ar*C*H), 129.8 (Ar*C*H), 131.5 (Ar*C*H), 132.4 (Ar*C*), 133.9 (Ar*C*), 135.8 (Ar*C*), 191.8 (d, $J_{c\text{-}p}$ 6.5, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 20.02.

General Procedure for the Asymmetric Transfer Hydrogenation of *β*-Ketophosphonates 147a-l to the *β*-Hydroxyphosphonates 148a-l

The solution of *β*-ketophosphonate **147a-l** (1 mmol, 1 eq.) and (*R*,*R*)-catalyst **135** (0.005 mmol, 0.005 eq.) in Et_3N (2.85 mL, 20 eq.) was stirred for 10 min at room temperature. Formic acid (0.15 mL, 4 eq.) was slowly added by syringe and the resulting mixture was then purged with nitrogen. The mixture was allowed to react at 35 °C for 16 h. After complete consumption of β-ketophosphonate, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The solution was dried over anhydrous $MgSO_4$, and concentrated under reduced

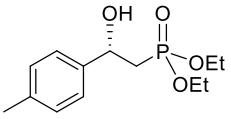
pressure to afford the product. The product was purified by flash chromatography on silica gel, eluting with ethyl acetate.

(*S*)-Diethyl (2-hydroxy-2-phenylethyl)phosphonate [174] 148a



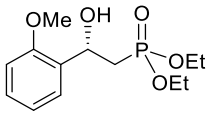
The product was isolated as a pale yellow oil (85%); $[\alpha]_D^{25}$ +30 (*c* 1 in $CHCl_3$, 90% ee); ν_{max}(ATR)/cm^{-1} 3346, 3031, 2986, 2933, 2909, 1493, 1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.37 (3H, t, *J* 7.1, C*H*$_3$), 2.15-2.30 (2H, m, C*H*$_2$P), 3.93 (1H, br s, O*H*), 4.05-4.22 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.13 (1H, ddd, *J* 11.2, 8.8 and 3.8, C*H*OH), 7.29-7.43 (5H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 35.9 (d, $J_{C\text{-}P}$ 136.0, *C*H$_2$P), 62.0 (d, $J_{C\text{-}P}$ 6.7, *C*H$_2$O), 62.1 (d, $J_{C\text{-}P}$ 6.2, *C*H$_2$O), 68.8 (d, $J_{C\text{-}P}$ 4.6, *C*HOH), 125.5 (2 × Ar*C*H), 127.7 (Ar*C*H), 128.5 (2 × Ar*C*H), 143.4 (d, $J_{C\text{-}P}$ 16.3, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.08; *m/z* (EI) 281.0919 (100%, M+Na^+. $C_{12}H_{19}NaO_4P$ requires 281.0932); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 8.1 min, t_R (minor) = 10.5 min.

(*S*)-Diethyl [2-hydroxy-2-(p-tolyl)ethyl]phosphonate 148b



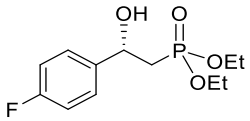
The product was isolated as a colourless oil (91%); $[\alpha]_D^{25}$ +30 (*c* 1 in $CHCl_3$, 96% ee); ν_{max}(ATR)/cm^{-1} 3339, 2983, 2908, 2868, 1515, 1443; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.36 (3H, t, *J* 7.1, C*H*$_3$), 2.13-2.29 (2H, m, C*H*$_2$P), 2.35 (3H, s, ArC*H*$_3$),3.85 (1H, br s, O*H*), 4.05-4.12 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.09 (1H, td, *J* 10.1 and 3.1, C*H*OH), 7.18 (2H, d, *J* 8.0, ArC*H*), 7.29 (2H, d, *J* 8.0, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.4 (d, $J_{C\text{-}P}$ 6.9, *C*H$_3$), 16.5 (d, $J_{C\text{-}P}$ 6.9, *C*H$_3$), 21.1 (ArC*H*$_3$), 35.9 (d, $J_{C\text{-}P}$ 135.7, *C*H$_2$P), 61.9 (d, $J_{C\text{-}P}$ 6.6, *C*H$_2$O), 62.0 (d, $J_{C\text{-}P}$ 6.3, *C*H$_2$O), 68.7 (d, $J_{C\text{-}P}$ 4.6, *C*HOH), 125.5 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 137.4 (Ar*C*), 140.5 (d, $J_{C\text{-}P}$ 16.5, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.18; *m/z* (EI) 295.1057 (100%, M+Na^+. $C_{13}H_{21}NaO_4P$ requires 295.1088); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 9.1 min, t_R (minor) = 13.1 min.

(*S*)-Diethyl [2-hydroxy-2-(2-methoxyphenyl) ethyl] phosphonate 148c



The product was isolated as a white solid (76%); mp 48-49 °C; $[\alpha]_D^{23}$ +47 (*c* 1 in $CHCl_3$, 93% ee); ν_{max}(ATR)/cm^{-1}: 3306, 2986, 2944, 2904, 2842, 1596, 1587, 1489; 1H NMR (400 MHz; $CDCl_3$) δ_H 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 2.21 (1H, dt, J_{H-P} 9.4 and 15.2, CH*H*P), 2.40 (1H, ddd, J_{H-P} 18.2, 15.3 and 3.0, C*H*HP), 3.86 (3H, s, OC*H*$_3$), 4.00–4.24 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.35 (1H, ddd, *J* 12.8, 9.6 and 3.1, C*H*OH), 6.88 (1H, d, *J* 8.2, ArC*H*), 7.01 (1H, dt, *J* 0.7 and 8.0, ArC*H*), 7.27 (1H, dt, *J* 1.8 and 8.0, ArC*H*), 7.53 (1H, dd, *J* 8.1 and 1.5, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, J_{C-P} 6.4, *C*H$_3$) 16.4 (d, J_{C-P} 6.2, *C*H$_3$), 33.7 (d, J_{C-P} 134.8, *C*H$_2$P), 55.2 (*C*H$_3$O), 61.8 (d, J_{C-P} 6.4, *C*H$_2$O), 61.9 (d, J_{C-P} 6.6, *C*H$_2$O), 64.6 (d, J_{C-P} 4.6, *C*HOH), 110.1 (ArC*H*), 120.8 (Ar*C*H), 126.2 (Ar*C*H), 128.4 (Ar*C*H), 131.4 (d, J_{C-P} 15.3, Ar*C*), 155.7 (Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.80; *m/z* (EI) 289.1201 (1%, MH^+ $C_{13}H_{22}O_5P$ requires 289.1199), 311 (1, M+Na^+), 271 (30, MH^+-H_2O), 243 (1), 227 (100, MH^+-H_2O and -OCH_2CH_3), 215 (1), 199 (8); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 13.3 min, t_R (minor) = 23.8 min.

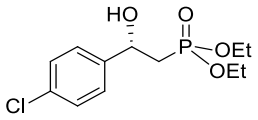
(*S*)-Diethyl [2-(4-fluorophenyl)-2-hydroxyethyl] phosphonate 148d



The product was isolated as a colourless oil (84%); $[\alpha]_D^{25}$ +35 (*c* 1 in $CHCl_3$, 97% ee); ν_{max}(ATR)/cm^{-1} 3346, 2986, 2909, 1604, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.33 (3H, t, *J* 7.1, C*H*$_3$), 1.37 (3H, t, *J* 7.1, C*H*$_3$), 2.15-2.22 (2H, m, C*H*$_2$P),4.07-4.24 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.11 (1H, ddd, *J* 11.6, 8.0 and 3.8, C*H*OH), 7.05 [2H, $(AX)_2$, ArC*H*], 7.38 [2H, $(AX)_2$, ArC*H*]; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.4 (d, J_{C-P} 6.5, *C*H$_3$), 16.5 (d, J_{C-P} 6.6, *C*H$_3$), 36.0 (d, J_{C-P} 136.0, *C*H$_2$P), 62.0 (d, J_{C-P} 6.7, *C*H$_2$O), 62.1 (d, J_{C-P} 6.3, *C*H$_2$O), 68.2 (d, J_{C-P} 4.4, *C*HOH), 115.3 (d, J_{C-P} 21.5, 2 × Ar*C*H), 127.2 (d, J_{C-P} 8.1, 2 × Ar*C*H), 139.2 (dd, J_{C-P} 16.3 and 3.4, Ar*C*), 162.3 (d, J_{C-F} 245.8, Ar*C*F); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.81; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -114.85; *m/z* (EI) 299.0824 (100%, M+Na^+. $C_{12}H_{18}FNaO_4P$

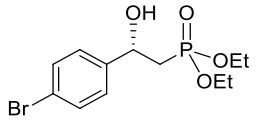
requires 299.0826); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 6.2 min, t_R (minor) = 8.7 min.

(*S*)-Diethyl [2-(4-chlorophenyl)-2-hydroxyethyl] phosphonate 148e



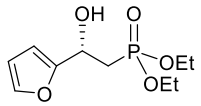
The product was isolated as a colourless oil (93%); $[\alpha]_D^{23}$ +27 (*c* 1 in $CHCl_3$, 92% ee); ν_{max}(ATR)/cm^{-1} 3345, 2985, 2909, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.37 (3H, t, *J* 7.1, C*H*$_3$), 2.14-2.20 (2H, m, C*H*$_2$P), 4.05-4.23 (5H, m, 2 × OC*H*$_2$CH$_3$), 5.10 (1H, ddd, *J* 11.3, 7.8 and 5.0, C*H*OH), 7.34 (4H, app s, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.1, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_3$), 35.9 (d, $J_{C\text{-}P}$ 136.2,*C*H$_2$P), 62.0 (d, $J_{C\text{-}P}$ 6.7,*C*H$_2$O), 62.2 (d, $J_{C\text{-}P}$ 6.4, *C*H$_2$O), 68.2 (d, $J_{C\text{-}P}$ 4.6, *C*HOH), 127.0 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 133.4 (Ar*C*), 142.0 (d, $J_{C\text{-}P}$ 20.8,Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.71; *m/z* (ESI$^+$) 315 (4, M+Na$^+$), 293.0708 (5%, MH$^+$. $C_{12}H_{19}{}^{35}ClO_4P$ requires 293.0704), 275 (100, MH$^+$-H$_2$O), 249 (3), 231 (4), 203 (3); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 6.4 min, t_R (minor) = 8.1 min.

(*S*)-Diethyl [2-(4-bromophenyl)-2-hydroxyethyl] phosphonate 148f



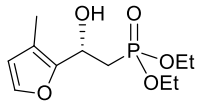
The product was isolated as a colourless oil (91%); $[\alpha]_D^{25}$ +27 (*c* 1 in $CHCl_3$, 97% ee); ν_{max}(ATR)/cm^{-1} 3323, 2983, 2908, 1482, 1439, 1394; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.37 (3H, t, *J* 7.1, C*H*$_3$), 2.14-2.20 (2H, m, C*H*$_2$P), 4.06-4.22 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.06-5.12 (1H, m, C*H*OH), 7.29 (2H, d, *J* 8.8, ArC*H*), 7.49 (2H, d, *J* 8.8, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_3$), 16.5 (d, $J_{C\text{-}P}$ 6.1, *C*H$_3$), 35.8(d, $J_{C\text{-}P}$ 136.3, *C*H$_2$P), 62.1 (d, $J_{C\text{-}P}$ 6.6, *C*H$_2$O), 62.2 (d, $J_{C\text{-}P}$ 6.3, *C*H$_2$O), 68.2 (d, $J_{C\text{-}P}$ 4.7, *C*HOH), 121.5 (Ar*C*), 127.3 (2 × Ar*C*H), 131.6 (2 × Ar*C*H), 142.5 (d, $J_{C\text{-}P}$ 16.4, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.66; *m/z* (EI) 337.0201 (8%, MH$^+$. $C_{12}H_{18}{}^{79}BrO_4P$ requires 337.0199), 359 (1, M+Na$^+$), 339 (7, ^{81}Br), 319 (100, MH$^+$-H$_2$O), 293 (3), 275 (3), 247 (2); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 7.0min, t_R (minor) = 8.5 min.

(*S*)-Diethyl [2-(furan-2-yl)-2-hydroxyethyl] phosphonate 148g



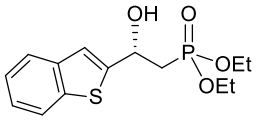
The product was isolated as a colourless oil (82%); $[\alpha]_D^{25}$ +18 (*c* 1 in $CHCl_3$, 98% ee); ν_{max}(ATR)/cm^{-1} 3326, 2983, 2930, 2908, 1505, 1443; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.33 (3H, t, *J* 6.2 C*H*$_3$), 1.36 (3H, t, *J* 6.2 C*H*$_3$), 2.29-2.45 (2H, m, C*H*$_2$P), 3.84 (1H, br s, O*H*), 4.06-4.21 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.14 (1H, ddd, *J* 13.0, 9.0 and 3.9, C*H*OH), 6.32 (1H, d, *J* 3.2, ArC*H*), 6.35 (1H, dd, *J* 3.2 and 1.8, ArC*H*), 7.39 (1H, d, *J* 3.1,ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.5, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 5.4, *C*H$_3$), 32.3 (d, $J_{C\text{-}P}$ 139.0, *C*H$_2$P), 62.0 (d, $J_{C\text{-}P}$ 6.5, *C*H$_2$O), 62.2 (d, $J_{C\text{-}P}$ 6.3, *C*H$_2$O), 63.1 (d, $J_{C\text{-}P}$ 4.2, *C*HOH), 106.2 (Ar*C*H), 110.3 (Ar*C*H), 142.1 (Ar*C*), 155.1 (d, $J_{C\text{-}P}$ 17.4, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.63; *m/z* (EI) 271.0703 (5%, M+Na^+. $C_{10}H_{17}NaO_5P$ requires 271.0706), 249 (3, MH^+), 231 (100, MH^+-H_2O), 203 (10), 187 (16); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228nm; t_R (major) = 11.8 min, t_R (minor) = 18.0 min.

(*S*)-Diethyl [2-hydroxy-2-(3-methylfuran-2-yl) ethyl] phosphonate 148h



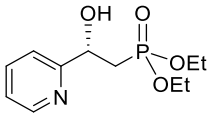
The product was isolated as a yellow oil (79%); $[\alpha]_D^{25}$ +16 (*c* 1 in $CHCl_3$, 98% ee); ν_{max}(ATR)/cm^{-1} 3340,2985, 2929, 2907, 2872, 1741, 1510, 1478; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.33 (3H, t, *J* 7.1 C*H*$_3$), 1.34 (3H, t, *J* 7.1 C*H*$_3$), 2.08 (3H, s, C*H*$_3$), 2.24 (1H, ddd, $J_{H\text{-}P}$ 19.0, 15.0 and 4.0, C*H*HP), 2.53 (1H, dt, $J_{H\text{-}P}$ 9.4 and 15.5, CH*H*P), 3.50 (1H, br s, O*H*), 4.05-4.19 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.12-5.19 (1H, m, C*H*OH), 6.20 (1H, d, *J* 1.5, ArC*H*), 7.29 (1H, d, *J* 1.5, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 9.67 (*C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 3.2, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 3.2, *C*H$_3$), 32.2 (d, $J_{C\text{-}P}$ 138.3, *C*H$_2$P), 61.0 (*C*HOH), 61.8 (d, $J_{C\text{-}P}$ 6.6, *C*H$_2$O), 62.1 (d, $J_{C\text{-}P}$ 6.1, *C*H$_2$O), 113.0 (Ar*C*H), 116.6 (Ar*C*), 141.3 (Ar*C*H), 149.2 (d, $J_{C\text{-}P}$ 14.8, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.72; *m/z* (EI) 263.1045 (2%, MH^+. $C_{11}H_{20}O_5P$ requires 263.1043), 245 (100, MH^+-H_2O), 217 (4), 201 (17), 189 (3), 173 (2); Chiral HPLC: Lux 3u Cellulose-4, 50% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 11.0 min, t_R (minor) = 16.6 min.

(*S*)-Diethyl [2-(benzo[*b*]thiophen-2-yl)-2-hydroxyethyl] phosphonate 148i



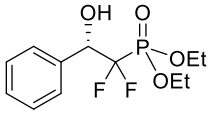
The product was isolated as a white solid (94%); mp 73-74 °C; $[\alpha]_D^{25}$ +13 (*c* 1 in $CHCl_3$, >99% ee); ν_{max}(ATR)/cm^{-1} 3339, 3058, 2979, 2930, 2904, 1462, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 2.38-2.44 (2H, m, C*H*$_2$P), 4.08-4.24 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.42-5.50 (1H, m, C*H*OH), 7.25 (1H, s, ArC*H*), 7.30-7.38 (2H, m, 2 × ArC*H*), 7.73 (1H, dd, *J* 7.2 and 2.0, ArC*H*), 7.83 (1H, dd, *J* 7.7 and 1.2, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.0, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 6.1, *C*H$_3$), 35.8 (d, $J_{C\text{-}P}$ 137.0, *C*H$_2$P), 62.1 (d, $J_{C\text{-}P}$ 6.6, *C*H$_2$O), 62.3 (d, $J_{C\text{-}P}$ 6.3, *C*H$_2$O), 65.8 (d, $J_{C\text{-}P}$ 4.3, *C*HOH), 120.0 (Ar*C*H), 122.5 (Ar*C*H), 123.6 (Ar*C*H), 124.3 (Ar*C*H), 124.4 (Ar*C*H), 139.4 (d, $J_{C\text{-}P}$ 6.0, Ar*C*), 147.8 (Ar*C*), 148.0 (Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.11; *m/z* (EI) 337.0638 (5%, [M+Na^+]. $C_{14}H_{19}NaO_4PS$ requires 337.0634), 297 (100, MH^+-H_2O), 253 (5); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 10.0 min, t_R (minor) = 11.8 min.

(*S*)-Diethyl [2-hydroxy-2-(pyridin-2-yl) ethyl] phosphonate 148j



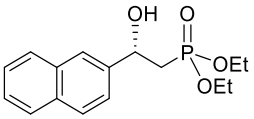
The product was isolated as a yellow oil (77%); $[\alpha]_D^{25}$ +45 (*c* 1 in $CHCl_3$, 97% ee); ν_{max}(ATR)/cm^{-1} 3329, 2985, 2932, 2907, 1588, 1570; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.35 (3H, t, *J* 7.1, C*H*$_3$), 2.23 (1H, dt, $J_{H\text{-}P}$ 9.3 and 15.3, CH*H*P), 2.50 (1H, ddd, $J_{H\text{-}P}$ 18.3, 15.3 and 3.2, C*H*HP), 4.05-4.21 (4H, m, 2 × OC*H*$_2$CH$_3$), 4.57 (1H, d, *J* 3.9, O*H*), 5.16 (1H, ddd, *J* 17.0, 9.3 and 3.9, C*H*OH), 7.21 (1H, ddd, *J* 7.5, 4.9 and 0.9, ArC*H*), 7.54 (1H, d, *J* 7.9, ArC*H*), 7.72 (1H, td, *J* 7.7 and 1.8, ArC*H*), 8.55 (1H, d, *J* 4.9, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.8, *C*H$_3$), 16.4 (d, $J_{C\text{-}P}$ 6.5, *C*H$_3$), 34.3 (d, $J_{C\text{-}P}$ 137.7, *C*H$_2$P), 62.0 (d, $J_{C\text{-}P}$ 7.1, *C*H$_2$O), 62.0 (d, $J_{C\text{-}P}$ 7.5, *C*H$_2$O), 69.0 (d, $J_{C\text{-}P}$ 4.6, *C*HOH), 120.2 (Ar*C*H), 122.5 (Ar*C*H), 136.9 (Ar*C*H), 148.6 (Ar*C*H), 161.6 (d, $J_{C\text{-}P}$ 15.5, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.18; *m/z* (EI) 282.0871 (100%, M+Na^+. $C_{11}H_{18}NaNO_4P$ requires 282.0862); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 15.3 min, t_R (minor) = 19.3 min.

(*S*)-Diethyl (1,1-difluoro-2-hydroxy-2-phenylethyl)phosphonate 148k



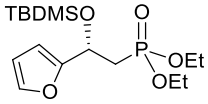
The product was isolated as a white solid (87%); mp 72-74 °C, (lit.[252] 74-75 °C), (lit.[253] 76-77° C); $[\alpha]_D^{23}$ +7 (*c* 1 in $CHCl_3$, 20% ee); ν_{max}(ATR)/cm^{-1} 3333,3063, 3035, 2985, 2936, 2918, 1496, 1478, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.2, C*H*$_3$), 1.36 (3H, t, *J* 7.2, C*H*$_3$), 3.88-4.00 (1H, m, O*H*),4.17-4.31 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.13 (1H, dq, *J* 20.0, 10.8 and 5.0, C*H*OH), 7.37-7.43 (3H, m, ArC*H*), 7.49-7.52 (2H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.2, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.2, *C*H$_3$), 64.9 (d, $J_{C\text{-}P}$ 7.0, *C*H$_2$O), 65.1 (d, $J_{C\text{-}P}$ 6.6, *C*H$_2$O), 73.6 (dq, $J_{C\text{-}P}$ 21.2, 40.9 and 4.5, *C*HOH), 128.1 (4 × Ar*C*H), 128.9 (Ar*C*H), 134.7 (d, $J_{C\text{-}P}$ 5.5, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 6.84 (dd, J_{PF} 105.1 and 99.6); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -125.2 (dd, $J_{P\text{-}F}$ 104.9 and 19.8), -124.4 (dd, $J_{F\text{-}F}$ 104.9 and 19.8), -115.1 (dd, $J_{P\text{-}F}$ 99.7 and 6.1), -114.3 (dd, $J_{F\text{-}F}$ 99.6 and 6.1); *m/z* (EI) 317.0730 (100%, M+Na^+. $C_{12}H_{17}F_2NaO_4P$ requires 317.0726); Chiral HPLC: Cellulose-1, 10% IPA in hexane, 1 mL/min^{-1}@ 254 nm; t_R (major) = 7.5 min, t_R (minor) = 9.7 min.

(*S*)-Diethyl (2-hydroxy-2-(naphthalen-2-yl)ethyl)phosphonate 148l



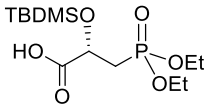
The product was isolated as a pale yellow oil, 96% yield; $[\alpha]_D^{25}$ +19 (*c* 0.75 in $CHCl_3$, 93% ee), lit.[166] $[\alpha]_D^{20}$ +20 (*c* 0.75 in $CHCl_3$, 95% ee); ν_{max}(ATR)/cm^{-1} 3341, 3056, 2983, 2930, 2907, 1601, 1508; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 2.27-2.34 (2H, m, C*H*$_2$P), 4.06-4.26 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.30 (1H, ddd, *J* 11.7, 7.7 and 4.2, C*H*OH), 7.46-7.52 (3H, m, ArC*H*), 7.82-7.89 (4H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.0, *C*H$_3$), 16.5 (d, $J_{C\text{-}P}$ 6.0, *C*H$_3$), 35.9 (d, $J_{C\text{-}P}$ 136.0, *C*H$_2$P), 62.0 (d, $J_{C\text{-}P}$ 6.7, *C*H$_2$O), 62.1 (d, $J_{C\text{-}P}$ 6.3, *C*H$_2$O), 69.0 (d, $J_{C\text{-}P}$ 4.6, *C*HOH), 123.6 (Ar*C*H), 124.3 (Ar*C*H), 126.0 (Ar*C*H), 126.2 (Ar*C*H), 127.7 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 133.0 (Ar*C*), 133.3 (Ar*C*), 140.8 (d, $J_{C\text{-}P}$ 16.3, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.07; *m/z* (EI) 331.1075 (100%, M+Na^+. $C_{16}H_{21}NaO_4P$ requires 331.1083); Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228 nm; t_R (major) = 10.1 min, t_R (minor) = 13.4 min.

(*S*)-Diethyl (2-((tert-butyldimethylsilyl)oxy)-2-(furan-2-yl)ethyl) phosphonate 150



A solution of TBDMS-Cl (0.68 g, 4.5 mmol) and pyridine (0.65 g, 0.66 mL, 8.2 mmol) in DMF (4 mL) was added to the solution of alcohol **148g** (1.02 g, 4.1 mmol) in DMF (4 mL). The mixture was stirred at 20 °C for 15 h and diluted with H_2O (25 mL). Aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with a saturated solution of citric acid (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give a crude oil. Purification by flash chromatography on silica gel, eluting with ethyl acetate gave **150** as an oil in (1.00 g, 69% yield); $[\alpha]_D^{25}$ +38 (*c* 1 in $CHCl_3$,); ν_{max}(ATR)/cm^{-1} 2980, 2957, 2931, 2902, 2857, 1503, 1474; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H -0.10 (3H, s, C*H*$_3$), 0.07 (3H, s, C*H*$_3$), 0.86 (9H, s, 3 × C*H*$_3$), 1.25 (3H, t, *J* 6.6, C*H*$_3$), 1.28 (3H, t, *J* 6.6, C*H*$_3$), 2.41 (2H, dd, *J* 17.7 and 6.8, C*H*$_2$P), 3.91-4.10 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.11 (1H, dt, *J* 8.1 and 6.8, C*H*-O), 6.23 (1H, d, *J* 3.2, ArC*H*), 6.31 (1H, dd, *J* 3.2 and 1.8, ArC*H*), 7.37 (1H, dd, *J* 1.8 and 0.7, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C -5.1 [Si(*C*H$_3$)$_2$], -5.1 [Si(*C*H$_3$)$_2$], 16.4 (d, $J_{C\text{-}P}$ 6.0, CH$_2$*C*H$_3$), 18.1 [*C*(CH$_3$)$_3$], 25.7 [C(*C*H$_3$)$_3$], 34.1 (d, $J_{C\text{-}P}$ 138.7, *C*H$_2$P), 61.4 (d, $J_{C\text{-}P}$ 6.3, 2 × *C*H$_2$O), 63.9 (*C*H-O), 106.7 (Ar*C*H), 110.1 (Ar*C*H), 141.7 (Ar*C*H), 155.4 (d, $J_{C\text{-}P}$ 8.4, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 26.78; *m/z* (ESI$^+$) 385 (10%, M+Na$^+$), 363.1755 (2%, MH$^+$. $C_{16}H_{32}O_5PSi$ requires 363.1751), 231 (100, M$^+$-TBDMSOH), 203 (10), 203 (10), 187 (16), 159 (5), 121 (3).

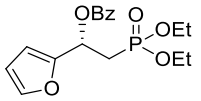
(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-(diethoxyphosphoryl)propanoic acid 151



$RuCl_3.H_2O$ (0.006 g, 0.03 mmol) was added to a solution of $NaIO_4$ (2.24 g, 10.5 mmol) in EtOAc (23 mL), hexane (15 mL) and H_2O (9 mL). After 10 min, furan **150** (0.21 g, 0.60 mmol) was added. The resultant mixture was stirred at RT for 45 min, then quenched with brine (15 mL). The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material did not require any purification, (0.18 g, 78% yield); $[\alpha]_D^{25}$ -2.1 (*c* 1 in $CHCl_3$,); ν_{max}(ATR)/cm^{-1} 2986, 2931, 2902, 2857, 1734, 1475; ^{1}H

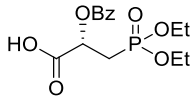
NMR (400 MHz, $CDCl_3$) δ_H 0.16 [3H, s, Si(CH_3)$_2$], 0.16 [3H, s, Si(CH_3)$_2$], 0.93 [9H, s, C(CH_3)$_3$], 1.34 (6H, td, *J* 7.1 and 1.9, 2 × CH_2CH_3), 2.26-2.44 (2H, m, CH_2P), 2.31 (1H, dd, J_{H-P} 15.7 and 5.5, C*H*HP), 2.39 (1H, dd, J_{H-P} 15.3 and 6.0, CH*H*P), 4.14 (4H, hex tet, 2 × OCH_2CH_3), 4.55 (1H, dt, *J* 20.9 and 5.7, C*H*-O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C -5.3 (CH_3), -5.1 (CH_3), 16.3 (d, J_{C-P} 6.0, CH_2CH_3), 16.4 (d, J_{C-P} 6.0, CH_2CH_3), 18.2 [$C(CH_3)_3$], 25.6 [C(CH_3)$_3$], 31.7 (d, J_{C-P} 141.5, CH_2P), 62.1 (d, J_{C-P} 6.4, CH_2O), 62.4 (d, J_{C-P} 6.4, CH_2O), 67.9 (d, J_{C-P} 4.3, CH-O), 173.5 (d, J_{C-P} 10.2, C=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 27.23; *m/z* (ESI$^+$) 363 (3, M$^+$+Na), 341.1545 (100%, MH$^+$. $C_{13}H_{30}O_6PSi$ requires 341.1544), 325 (1), 295 (1), 218 (1).

(*S*)-2-(Diethoxyphosphoryl)-1-(furan-2-yl)ethyl benzoate 154



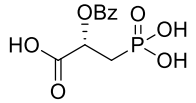
A solution of **148g** (1 g, 4.028 mmol), Et_3N (0.8 mL, 6.043 mmol), and DMAP (0.5 g, 4.028 mmol) in CH_2Cl_2 (40 mL), benzoyl chloride (0.7 mL, 6.043 mmol) was added at 0° C, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was acidified with 1 M HCl and neutralized with saturated $NaHCO_3$. After extraction with CH_2Cl_2 (3 × 50 mL), the organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluting with EtOAc. The product **154** was isolated as a pale yellow oil (1.1 g, 70% yield); $[\alpha]_D^{25}$ +73 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2983, 2934, 2907, 1720, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.24 (6H, dt, *J* 3.4 and 7.1, 2 × CH_3), 2.59-2.79 (2H, m, CH_2P), 4.00-4.11 (4H, m, 2 × OCH_2CH_3), 6.37 (1H, dd, *J* 3.3 and 1.8, ArC*H*), 6.42 (1H, dt, *J* 9.0 and 7.2, C*H*-O), 6.49 (1H, d, *J* 3.4, ArC*H*), 7.42-7.46 (3H, m, ArC*H*), 7.58 (1H, tt, *J* 11.1 and 1.2, ArC*H*), 8.08 (1H, dd, *J* 8.3 and 1.3, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (CH_3), 16.3 (CH_3), 29.9 (d, J_{C-P} 142.3, CH_2P), 61.8 (d, J_{C-P} 7.3, CH_2O), 64.3 (CH-O), 61.9 (d, J_{C-P} 7.3, CH_2O), 109.4 (ArCH), 110.5 (ArCH), 128.4 (2 × ArCH), 129.8 (2 × ArCH), 133.2 (ArCH), 142.8 (ArCH), 151.2 (ArC), 151.3 (ArC), 165.2 (C=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 24.97; *m/z* (EI$^+$) 391.1 (20, M+K$^+$), 375.0985 (100%, M+Na$^+$. $C_{17}H_{21}O_6NaP$ requires 375.0973), 294.1 (10), 253.1 (18).

(*S*)-2-(Benzoyloxy)-3-(diethoxyphosphoryl)propanoic acid 156



$RuCl_3$. H_2O (0.001 g, 0.047 mmol) was added to a solution of $NaIO_4$ (3.540 g, 16.555 mmol) in EtOAc (35 mL), hexane (23 mL) and H_2O (14 mL). After 10 min, furan **154** (0.333 g, 0.946 mmol) was added. The resultant mixture was stirred at RT for 45 min. and then quenched with brine (20 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phase washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the product **156** (0.28 g, 88% yield) as a brown solid that was no needs any purification; mp 128-131 °C; $[\alpha]_D^{25}$ -16 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 2990, 2976, 2909, 2539, 2159, 2034, 1974, 1746, 1722, 1601, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (3H, t, *J* 7.0 C*H*$_3$), 1.32 (3H, t, *J* 7.0 C*H*$_3$), 2.62 (2H, dd, *J* 18.2 and 6.3, C*H*$_2$P), 4.10-4.20 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.60 (1H, dt, *J* 19.0 and 6.3, C*H*-O), 7.46 (2H, t, *J* 7.7, ArC*H*), 7.56-7.62 (1H, m, ArC*H*), 8.12 (2H, dd, *J* 8.5 and 1.4, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.8, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.8, *C*H$_3$), 28.0 (d, $J_{C\text{-}P}$ 144.8, *C*H$_2$P), 62.7 (d, $J_{C\text{-}P}$ 1.7, *C*H$_2$O), 62.8 (d, $J_{C\text{-}P}$ 1.7, *C*H$_2$O), 67.5 (d, $J_{C\text{-}P}$ 5.4, *C*H-O), 128.4 (2 × Ar*C*H), 129.1 (Ar*C*), 130.0 (2 × Ar*C*H), 133.5 (Ar*C*H), 165.5 (*C*=O), 170.5 (d, $J_{C\text{-}P}$ 12.1, C=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 25.86; *m*/*z* (ESI^+) 331.0941 (100%, MH^+. $C_{14}H_{20}O_7P$ requires 331.0942), 209.1 (5), 181.1 (7).

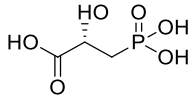
(*S*)-2-(Benzoyloxy)-3-phosphonopropanoic acid 157



A solution of **156** (0.2 g, 0.59 mmol) in CH_2Cl_2 (2 mL), TMSBr (0.3 mL, 2.35 mmol) was added and the mixture was stirred for 24 h at room temperature. The solvents were removed under reduced pressure residue, H_2O (5 mL) was added to the residue. After vigorously stirring for 15 minutes, the aqueous solution was neutralized with ammonium bicarbonate, washed with chloroform (3 × 15 mL) and concentrated under reduced pressure to provide the product **157** (0.15 g, 79%) as a grey solid; mp 195-199 °C; $[\alpha]_D^{25}$ -31 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3033, 2809, 1693, 1579, 1430; ^{1}H NMR (400 MHz, D_2O) δ_H 2.05-2.21 (2H, m, C*H*$_2$P), 5.05 (1H, td, *J* 10.8 and 3.5, C*H*-O), 7.46 (2H, t, *J* 7.6, ArC*H*), 7.60 (1H, t, *J* 7.5,

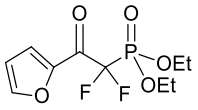
ArC*H*), 8.03 (2H, d, *J* 7.5, ArC*H*); ^{13}C NMR (100 MHz, D_2O) δ_C 30.6 (d, $J_{C\text{-}P}$ 132.9, *C*H_2P), 73.0 (d, $J_{C\text{-}P}$ 6.7, *C*H-O), 128.6 (2 × Ar*C*H), 129.2 (Ar*C*), 129.7 (2 × Ar*C*H), 133.8 (Ar*C*H), 168.3 (*C*=O), 177.7 (d, $J_{C\text{-}P}$ 16.0, C=O); ^{31}P NMR (162 MHz, CD_3OD) δ_P 18.20; *m*/*z* (ESI$^+$) 292.1 (3, M+H_2O), 275.0316 (100%, MH$^+$. $C_{10}H_{12}O_7P$ requires 275.0315), 266.0 (4), 257.0 (25, M$^+$-H_2O), 229.0 (4), 208.0 (1), 153.0 (4), 125.0 (10), 105.0 (9).

(*S*)-2-Hydroxy-3-phosphonopropanoic acid 158



A solution of **157** (0.25 g, 0.91 mmol) in MeOH (5 mL) and 1 M NaOH (0.4 g, 10 mmol) in H_2O (10 mL), the mixture was heated to reflux for 6 h. MeOH and water were removed under reduced pressure. The residue was washed with hot EtOH (3 x 50 mL). The solid obtained dried under vacuum for 4 h yielded **158** (0.2 g, 38%) as a semi solid; $[\alpha]_D^{25}$ -37 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3033, 1693, 1579, 1430; ^{1}H NMR (400 MHz, D_2O) δ_H 2.03 (1H, dd, *J* 16.0 and 8.4, C*H*HP), 2.20 (1H, dd, *J* 16.0 and 8.4, C*H*HP), 4.46 (1H, dt, *J* 19.2 and 4.1, C*H*-OH); ^{13}C NMR (100 MHz, D_2O) δ_C 33.6 (d, $J_{C\text{-}P}$ 126.1, *C*H_2P), 69.5 (d, $J_{C\text{-}P}$ 6.0, *C*H-O), 182.2 (d, $J_{C\text{-}P}$ 17.7, C=O); ^{31}P NMR (162 MHz, D_2O) δ_P 21.22.

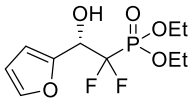
Diethyl (1,1-difluoro-2-(furan-2-yl)-2-oxoethyl)phosphonate 160



A solution of diisopropylamine (1.11 mL, 6.37 mmol) in dry THF (5 mL) was cooled to -78 °C and then *n*-BuLi (3.03 mL, 2.1 M in hexanes, 6.37 mmol) was added dropwise via syringe. The resulting solution was allowed to warm to 0 °C for 25 min and then cooled to -78 °C before diethyl (difluoromethyl)phosphonate **52** (1.00 mL, 6.37 mmol) was added in THF (5 mL). After 30 min at -78 °C, methyl 2-furoate (0.82 mL, 7.65 mmol) was added dropwise, via cannula over 15 minutes. After 1 hour, the reaction was quenched by the addition of HOAc (0.65 mL, 11.47 mmol), followed by a saturated aqueous solution of NH_4Cl (15 mL). Following extraction with EtOAc (3 × 25 mL), the combined organics layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/petroleum ether) (1:1) yielded

the compound **160** (1.5 g, 83%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39 (6H, t, *J* 7.1, 2 × C*H*$_3$), 4.29-4.37 (4H, m, 2 × OC*H*$_2$CH$_3$), 6.64-6.65 (1H, m, ArC*H*), 7.60-7.61 (1H, m, ArC*H*), 7.78-7.79 (1H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, J_{C-P} 5.6, 2 × *C*H3), 65.5 (*C*H$_2$O), 65.6 (*C*H$_2$O), 113.0 (Ar*C*H), 114.0 (dd, J_{C-F} 546.5 and 199.2, *C*F$_2$), 124.7 (Ar*C*H), 148.2 (Ar*C*), 149.5 (Ar*C*H), 175.2 (td, J_{C-P} 25.1 and 15.8, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 2.9 (t, J_{P-F} 96.7); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -113.8 (d, J_{P-F} 96.6); *m*/*z* (ESI$^+$) 305 (6%, M+Na$^+$), 283.0542 (100%, MH$^+$. $C_{10}H_{14}F_2O_5P$ requires 283.0541), 255 (10), 227 (9).

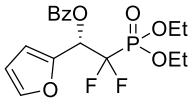
(*S*)-Diethyl (1,1-difluoro-2-(furan-2-yl)-2-hydroxyethyl)phosphonate 161



The solution of *β*-ketophosphonate **160** (1.250 g, 4.430 mmol) and Ru-(*R*,*R*)-catalyst (0.013 g, 0.022 mmol) in Et_3N (12.350 mL, 88.595 mmol) was stirred for 10 min at room temperature. Formic acid (0.669 mL, 17.719 mmol) was slowly added by syringe and the resulting mixture was then purged with nitrogen. The mixture was allowed to react at 35 °C for 16 h. After complete consumption of β-ketophosphonate, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to afford the product **161** (0.95 g, 76%, 25% ee) as a white solid; mp 69-74 °C; $[\alpha]_D^{25}$ +11 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3338, 2988, 2937, 2913, 2875, 1737, 1504; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.1, C*H*$_3$), 1.38 (3H, t, *J* 7.1, C*H*$_3$), 3.92 (1H, d, *J* 7.1, O*H*), 4.23-4.32 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.16 (1H, ddd, *J* 18.4, 12.1 and 6.9, C*H*OH), 6.42 (1H, dd, *J* 3.3 and 1.4, Ar*H*), 6.54 (1H, d, *J* 3.3, Ar*H*), 7.47 (1H, d, *J* 1.4, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, J_{C-P} 5.8, *C*H$_3$), 16.3 (d, J_{C-P} 5.4, *C*H$_3$), 65.1 (t, J_{C-P} 6.5, 2 × *C*H$_2$O), 68.6 (ddd, J_{C-P} 25.0 and 16.2, *C*HOH), 110.1 (Ar*C*H), 110.6 (Ar*C*H), 131.4 (Ar*C*), 143.2 (Ar*C*H); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 6.12 (t, J_{P-F} 100.6); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -123.1 (dd, J_{P-F} 304.7 and 101.5), -115.6 (dd, J_{F-F} 304.7 and 100.0); *m/z* (ESI$^+$) 323 (15%), 307.0522 (10, M+Na$^+$. $C_{10}H_{15}F_2O_5PNa$ requires 307.0517), 267 (100, MH$^+$-H$_2$O), 239 (10), 211 (5); Chiral

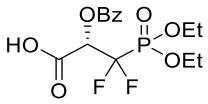
HPLC: Cellulose-1, 10% IPA in hexane, 1 mL/min^{-1}@ 254 nm; t_R (major) = 8.1 min, t_R (minor) = 11.5 min.

(*S*)-2-(Diethoxyphosphoryl)-2,2-difluoro-1-(furan-2-yl)ethyl benzoate 162



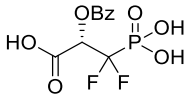
Benzoyl chloride (0.63 mL, 5.42 mmol) was added to a solution of alcohol **161** (1.40 g, 4.92 mmol), Et_3N (1.03 mL, 7.39 mmol), and DMAP (0.66 g, 5.42 mmol) in CH_2Cl_2 (30 mL), at 0° C, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with H_2O (30 mL). After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were separated and washed with saturated solution of $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (40-60) (1:1). The product **162** was isolated as a pale yellow oil (1.60 g, 88% yield); $[\alpha]_D^{25}$ +65 (*c* 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (6H, q, *J* 7.4, 2 × C*H*$_3$), 4.18-4.27 (4H, m, 2 × OC*H*$_2$CH$_3$), 6.43 (1H, dd, *J* 3.3 and 1.8, Ar*H*), 6.60 (1H, dq, *J* 15.7, 11.2 and 1.9, C*H*-O), 6.67 (1H, d, *J* 3.3, Ar*H*), 7.45-7.50 (3H, m, Ar*H*), 7.58-762 (1H, m, ArC*H*), 8.15 (2H, dd, *J* 8.5 and 1.4, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 5.6, 2 × *C*H$_3$), 64.8 (d, $J_{C\text{-}P}$ 4.9, 2 × *C*H$_2$O), 67.0-67.7 (m, *C*H-O), 110.7 (Ar*C*H), 112.3 (Ar*C*H), 118.0 (dd, $J_{C\text{-}P}$ 270.2 and 212.9, *C*F$_2$), 128.5 (2 × Ar*C*H), 128.9 (Ar*C*), 130.2 (2 × Ar*C*H), 133.6 (Ar*C*H), 143.9 (Ar*C*H), 145.5 (Ar*C*), 164.5 (*C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 4.8 (dd, $J_{P\text{-}F}$ 103.3 and 99.3, C-*P*); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -119.3 (ddd, $J_{P\text{-}F}$ 308.7, 103.3 and 15.8), -116.9 (ddd, $J_{P\text{-}F}$ 308.7, 99.0 and 10.9); *m*/*z* (ESI$^+$) 389.0965 (5%, MH$^+$. $C_{17}H_{20}F_2O_6P$ requires 389.0960), 267 (100), 239 (20), 211 (10), 191 (4), 163 (2), 137 (1), 109 (1).

(*S*)-2-(Benzoyloxy)-3-(diethoxyphosphoryl)-3,3-difluoropropanoic acid 163



$RuCl_3$. H_2O (0.03 g, 0.15 mmol) was added to a solution of $NaIO_4$ (11.32 g, 52.95 mmol) in EtOAc (110 mL), hexane (75 mL) and H_2O (45 mL). After 10 min, furan **162** (1.17 g, 3.02 mmol) was added. The resultant mixture was stirred at RT for 45 min. and then quenched with brine (150 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic phase washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the product **163** (1.0 g, 93% yield) as a dark oil which was used without purification; $[\alpha]_D^{25}$ -8 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 3383, 3071, 2992, 2933, 2868, 2618, 1744, 1603, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.38 (3H, t, *J* 7.2 C*H*$_3$), 1.40 (3H, t, *J* 7.2 C*H*$_3$), 4.33-4.40 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.75 (1H, dq, *J* 14.6, 7.1 and 11.1, C*H*-O), 7.48 (2H, t, *J* 7.6, ArC*H*), 7.63 (1H, tt, *J* 7.6 and 1.3, ArC*H*), 8.16 (2H, dd, *J* 8.5 and 1.3, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (*C*H$_3$), 16.3 (*C*H$_3$), 65.8 (d, $J_{C\text{-}P}$ 3.4, *C*H$_2$O), 65.9 (d, $J_{C\text{-}P}$ 3.4, *C*H$_2$O), 71.4 (t, $J_{C\text{-}P}$ 14.8, *C*H-O), 81.6 (t, $J_{C\text{-}P}$ 20.0, *C*F$_2$), 128.2 (Ar*C*), 128.5 (2 × Ar*C*H), 130.3 (2 × Ar*C*H), 134.0 (Ar*C*H), 164.6 (*C*=O), 165.3 (*C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 3.4 (t, $J_{P\text{-}F}$ 100.1, C-*P*); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -116.2 (dd, $J_{P\text{-}F}$ 300.0 and 100.6), -114.1 (dd, $J_{F\text{-}F}$ 303.1 and 99.1); *m*/*z* (ESI$^+$) 384 (3%, M$^+$+H_2O), 367.0756 (100, MH$^+$. $C_{14}H_{18}F_2O_7P$ requires 367.0753), 349 (10, M$^+$-H_2O), 245 (6), 217 (10).

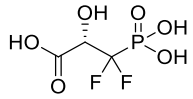
(*S*)-2-(Benzoyloxy)-3,3-difluoro-3-phosphonopropanoic acid 164



A solution of **163** (1.8 g, 4.91 mmol) in CH_2Cl_2 (30 mL), TMSBr (3.0 g, 2.6 mL, 19.66 mmol) was added and the mixture was stirred for 24 h at room temperature. The solvents were removed under reduced pressure, to the residue H_2O (80 mL) was added and vigorously stirring for 15 minutes, the aqueous solution was neutralized with ammonium bicarbonate, washed with chloroform (3 × 100 mL) and concentrated under reduced pressure to provide the product **164** (0.8 g, 77%) as a gummy oil; $[\alpha]_D^{25}$ -22 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3119, 3035, 2979, 1414; ^{1}H NMR (400 MHz, D_2O) δ_H 5.75 (1H, ddd, *J* 18.9, 11.1 and 8.1, C*H*-O),

7.48 (2H, t, *J* 8.1, ArC*H*), 7.63 (1H, tt, *J* 8.1 and 1.3, ArC*H*), 8.16 (2H, dd, *J* 8.2 and 1.3, ArC*H*); ^{13}C NMR (100 MHz, D_2O) δ_C 71.4 (t, $J_{C\text{-}P}$ 18.5, *C*H-O), 84.8 (t, $J_{C\text{-}P}$ 24.2, *C*F_2), 125.2 (Ar*C*), 127.2 (2 × Ar*C*H), 130.1 (2 × Ar*C*H), 132.5 (Ar*C*H), 160.2 (*C*=O), 164.7 (*C*=O); ^{31}P NMR (162 MHz, CD_3OD) δ_P 5.2 (t, $J_{P\text{-}F}$ 105.4, C-*P*); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -110.4 (dd, $J_{P\text{-}F}$ 288.0 and 95.6), -114.1 (dd, $J_{F\text{-}F}$ 286.1 and 97.0); *m*/*z* (ESI^+) 311.0062 (100%, $M+H^+$. $C_{10}H_9F_2O_7P$ requires 311.0160), 291 (70), 245 (40).

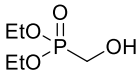
(*S*)-3,3-Difluoro-2-hydroxy-3-phosphonopropanoic acid 165



Same as the procedure for synthesis compound **158**, using previous compound **164**.

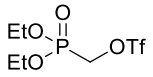
(73% yield) as a semi solid; $[\alpha]_D^{25}$ -54 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3030, 1687, 1569, 1425; ^{1}H NMR (400 MHz, D_2O) δ_H 4.22 (1H, dt, *J* 19.2 and 15.1, C*H*-OH) 7.10 (1H, t, *J* 52.0, C*H*F); ^{13}C NMR (100 MHz, D_2O) δ_C 67.8 (t, $J_{C\text{-}P}$ 18.5, *C*H-O), 180.0 (d, $J_{C\text{-}P}$ 15.7, C=O); ^{31}P NMR (162 MHz, D_2O) δ_P 11.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -122.7 (dd, $J_{P\text{-}F}$ 298.8 and 90.6), -116.7 (dd, $J_{F\text{-}F}$ 298.8 and 90.6).

Diethyl (hydroxymethyl)phosphonate [254] 167



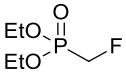
Diethyl phosphite **166** (6.44 mL, 50 mmol), paraformaldehyde (1.80 g, 60 mmol), were stirred in ethanol (20 mL), and anhydrous potassium carbonate (0.34 g, 2.5 mmol), at 60 °C for 5 h. The solution was cooled, filtered and the solvent removed under vacuum, to give crude material (7.9 gm, 93%), which was used in the next step without any further purification; ν_{max} (ATR)/cm^{-1} 3369, 2986, 2935, 2911, 1647; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.35 (6h, t, *J* 7.1, 2 × C*H*$_3$), 3.9 (2H, d, *J* 4.8, C*H*$_2$P), 4.13-4.22 (4H, m, 2 × OC*H*$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.4 (d, $J_{C\text{-}P}$ 5.5, 2 × C*H*$_3$), 57.0 (d, $J_{C\text{-}P}$ 15.4, *C*H$_2$P), 62.6 (d, $J_{C\text{-}P}$ 3.4, 2 × *C*H$_2$O) ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 24.36.

(Diethoxyphosphoryl)methyl trifluoromethanesulfonate [255] 168



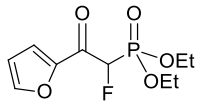
Trifluoromethanesulfonic anhydride (2.98 mL, 17.75 mmol) was added dropwise to a stirred solution of diethyl (hydroxymethyl)phosphonate **167** (2.57 g, 15.30 mmol) and 2,6-lutidine (2.19 mL, 18.80 mmol) in anhydrous CH_2Cl_2 (25 mL) at -50 °C under an argon atmosphere. The resulting mixture was allowed to warm to 0 °C over a period of 1.5 h, and then ether (150 mL) was added to the dark brown solution. The precipitates formed were removed by filtration. The ethereal solution was successively washed with water (150 mL), 1 N HCl (150 mL), and brine (150 mL), then dried over Na_2SO_4, and filtered. After concentration under reduced pressure, a yellow oil was obtained (2.65 g), which was used in the next step without further purification; ν_{max} (ATR)/cm^{-1} 2993, 2948, 2914, 2873, 1633, 1479; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40 (6H, t, *J* 7.1, 2 × C*H*$_3$), 4.26 (4H, app p, *J* 7.4, 2 × OC*H*$_2$CH$_3$), 4.63 (2H, d, *J* 8.8, C*H*$_2$P); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.8, 2 × *C*H$_3$), 64.0 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_2$O) 66.4 (d, $J_{C\text{-}P}$ 168.7, *C*H$_2$P), 118.5 (q, $J_{C\text{-}P}$ 320.5, *C*F$_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 12.23; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -73.94.

(Diethoxyphosphoryl)methyl trifluoromethanesulfonate [255] 169



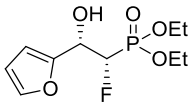
A solution of the triflate **168** (2.00 g, 6.66 mmol) in dry THF (10 mL) was cooled to 0 °C and a solution of tetrabutylammonium fluoride 1M in THF (8.9 mL) was added dropwise. After stirring at 0 °C for 1 h. The solvent was removed, and CH_2Cl_2 (15 mL) added. The organic layer was washed with water (3 × 30 mL), dried over $MgSO_4$, filtered and evaporated to give a crude oil, that was purified by flash chromatography eluting with ethyl acetate/petroleum ether (40-60) (1:1) as the eluent, to give **169** as a pale yellow oil (0.46 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.38 (6H, t, *J* 7.1, 2 × C*H*$_3$), 4.22 (4H, app pent, *J* 7.3, 2 × OC*H*$_2$CH$_3$), 4.70 (2H, dd, *J* 46.9 and 4.8, C*H*$_2$P); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.4 (d, $J_{C\text{-}P}$ 5.6, 2 × *C*H$_3$), 63.0 (d, $J_{C\text{-}P}$ 6.4, 2 × *C*H$_2$O), 76.6 (dd, $J_{C\text{-}P}$ 180.8 and 169.3, *C*H$_2$P); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 16.30 (d, $J_{P\text{-}F}$ 63.2); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -249.70 (dt, $J_{P\text{-}F}$ 62.9 and 46.9). All data is according with the literature.

Diethyl (1-fluoro-2-(furan-2-yl)-2-oxoethyl)phosphonate 171



A solution of diisopropylamine (0.82 mL, 5.878 mmol) in dry THF (4 mL) was cooled to -78 °C and then *n*-BuLi (2.80 mL, 2.1 M in hexanes, 5.878 mmol) was added dropwise via syringe. The resulting solution was allowed to warm to 0 °C for 25 min and then cooled to -78 °C before **169** (1.00 g, 5.878 mmol) was added in THF (4 mL). After 30 min at -78 °C, isopropyl 2-furoate **170** (0.75 mL, 7.054 mmol) was added dropwise via cannula over 15 minutes. After 1 hour, the reaction was quenched by the addition of HOAc (0.60 mL, 10.580 mmol), followed by a saturated aqueous solution of NH_4Cl (15 mL). Following extraction with EtOAc (3 × 40 mL), the combined organics layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (ethyl acetate/petroleum ether, 2:1) yielded the compound **171** (0.44 g, 30%) as a pale yellow oil; ν_{max} (ATR)/cm^{-1} 3133, 2986, 2938, 2914, 1685, 1568, 1465; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (3H, td, *J* 7.1 and 1.5, C*H*$_3$), 1.36 (3H, td, *J* 7.1 and 1.5, C*H*$_3$), 4.18-4.30 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.78 (1H, dd, *J* 47.0 and 13.0, C*H*F), 6.61-6.63 (1H, m, Ar*H*), 7.48-7.51 (1H, m, Ar*H*), 7.71 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 5.6, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 5.6, *C*H$_3$), 64.3 (d, $J_{C\text{-}P}$ 6.6, 2 x *C*H$_2$O), 89.7 (dd, $J_{C\text{-}P}$ 196.5 and 153.8, *C*HF), 112.8 (Ar*C*H), 121.5 (d, $J_{C\text{-}P}$ 7.0, Ar*C*H), 148.0 (Ar*C*H), 149.8 (Ar*C*), 179.0 (app d, $J_{C\text{-}P}$ 18.1, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 9.8 (d, $J_{P\text{-}F}$ 72.1); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -210.6 (dd, $J_{P\text{-}F}$ 71.6 and 47.3); *m*/*z* (ESI$^+$) 282 (6%, M+H$_2$O), 265.0640 (100, MH$^+$. $C_{10}H_{15}FO_5P$ requires 265.0636), 237 (7), 209 (5).

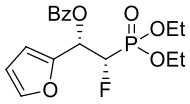
Diethyl [(1*S*,2*S*)- 1-fluoro-2-(furan-2-yl)-2-hydroxyethyl)]phosphonate 172



The solution of *β*-ketophosphonate **171** (0.42 g, 1.59 mmol) and Ru-(*R*,*R*)-catalyst (0.005 g, 0.008 mmol) in Et_3N (4.43 mL, 31.8 mmol) was stirred for 10 min at room temperature. Formic acid (0.24 mL, 6.36 mmol) was slowly added by syringe and the resulting mixture was then purged with nitrogen. The mixture was allowed to react at 35 °C for 16 h. After complete consumption of *β*-ketophosphonates, the reaction mixture was diluted with EtOAc

(20 mL) and washed with water (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:1) to afford the product **172** (0.3 g, 70%,) as a pale yellow oil; $[\alpha]_D^{25}$ +29 (*c* 1 in $CHCl_3$, 98% ee, 97% dr); ν_{max}(ATR)/cm^{-1} 3314, 2985, 3035, 2937, 2916, 2875, 1699, 1504, 1476; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.35 (3H, q, *J* 6.8, 2 x C*H*$_3$), 3.52 (1H, s, O*H*),4.11-4.29 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.03 (1H, dq, *J* 45.4, 5.5 and 3.9, C*H*F), 5.22 (1H, d, *J* 23.3, C*H*OH), 6.39 (1H, *J* 3.0 and 1.8, Ar*H*) 6.46 (1H, d, *J* 3.2, Ar*H*), 7.43 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (t, $J_{C\text{-}P}$ 5.6, 2 x *C*H$_3$), 63.5 (dd, $J_{C\text{-}P}$ 113.5 and 6.6, *C*HOH), 66.7 (d, $J_{C\text{-}P}$ 2.9, *C*H$_2$O), 66.9 (d, $J_{C\text{-}P}$ 2.9, *C*H$_2$O), 88.9 (dd, $J_{C\text{-}P}$ 189.5 and 167.8, *C*HF), 108.5 (Ar*C*H), 110.6 (Ar*C*H), 142.5 (Ar*C*H), 151.0 (dd, $J_{C\text{-}P}$ 11.5 and 4.6, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 15.22 (d, $J_{P\text{-}F}$ 77.3); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -219.9 (d, $J_{P\text{-}F}$ 77.7); *m/z* (ESI^+) 289.0611 (5%, M+Na^+. $C_{10}H_{16}FO_5NaP$ requires 289.0612), 249.1 (100%), 221.0 (8%), 193 (6%), 157 (12%), 137 (6%), 109 (10%). Chiral HPLC: Lux 3u Cellulose-4, 30% IPA in hexane, 1 mL/min^{-1}@ 228nm; t_R (major) = 9.4 min, t_R (minor) = 16.0 min.

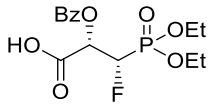
(1*S*,2*S*)-2-(Diethoxyphosphoryl)-2-fluoro-1-(furan-2-yl)ethyl benzoate 173



Benzoyl chloride (0.60 g, 0.5 mL, 4.282 mmol) was added to a solution of alcohol **172** (0.95 g, 3.57 mmol), Et_3N (0.54 g, 1.03 mL, 5.353 mmol), and DMAP (0.52 g, 4.282 mmol) in CH_2Cl_2 (20 mL), at 0° C, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with H_2O (30 mL). After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were separated and washed with saturated solution of $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (40-60) (1:1). The product **173** was isolated as a pale yellow oil (1.0 g, 96% yield); $[\alpha]_D^{25}$ +84 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3122, 3064, 2985, 2933, 2913, 2872, 1727, 1603, 1500, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (6H, q, *J* 6.8, 2 × C*H*$_3$), 4.05-4.20 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.31 (1H, dt, *J* 45.7 and 6.4, C*H*F), 6.39 (1H, dd, *J* 3.3 and 1.8, C*H*-O), 6.58 (1H, d, *J* 3.5, Ar*H*), 6.63

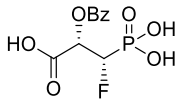
(1H, dd, *J* 6.7 and 4.2, Ar*H*), 7.46 (3H, t, *J* 7.7, Ar*H*), 7.58 (1H, t, *J* 7.4, Ar*H*), 8.12 (1H, dd, *J* 8.5 and 1.4, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.0, 2 × *C*H_3), 63.3 (d, $J_{C\text{-}P}$ 6.7, *C*H_2O), 63.6 (d, $J_{C\text{-}P}$ 6.7, *C*H_2O), 67.0 (dd, $J_{C\text{-}P}$ 19.7 and 7.4, C*H*-O), 87.5 (dd, $J_{C\text{-}P}$ 191.6 and 170.7, C*H*-F), 110.7 (Ar*C*H), 111.0 (Ar*C*H), 128.4 (2 × Ar*C*H), 129.5 (Ar*C*), 130.0 (2 × Ar*C*H), 133.3 (Ar*C*H), 143.3 (Ar*C*H), 147.6 (Ar*C*), 165.1 (*C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 13.21 (d, $J_{P\text{-}F}$ 76.0); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -214.2 (ddd, $J_{P\text{-}F}$ 76.1, 45.9 and 17.7); *m*/*z* (ESI^+) 403.1 (10%), 371.1053 (50%, MH^+. $C_{17}H_{21}FO_6P$ requires 371.1054), 351 (25%), 341 (20%), 319 (100%).

(2*S*,3*S*)-2-(Benzoyloxy)-3-(diethoxyphosphoryl)-3-fluoropropanoic acid 174



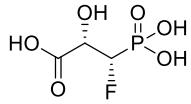
$RuCl_3$. H_2O (0.03 g, 0.15 mmol) was added to a solution of $NaIO_4$ (11.32 g, 51.97 mmol) in EtOAc (110 mL), hexane (75 mL) and H_2O (45 mL). After 10 min, furan **173** (1.10 g, 2.97 mmol) was added. The resultant mixture was stirred at RT for 45 min. and then quenched with brine (75 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic phase washed with brine (3 × 75 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the product **174** (0.85 g, 82% yield) as a gray solid which is used without further purification; mp 76-88 °C; $[\alpha]_D^{25}$ -27 (*c* 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3053, 2985, 2937, 2909, 2868, 1758, 1743, 1600, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (6H, q, *J* 7.7, 2 × C*H*$_3$), 4.17-4.27 (4H, m, 2 × OC*H*$_2$CH$_3$), 5.48 (1H, ddd, *J* 43.7, 8.1 and 2.0, C*H*-F), 5.84 (1H, dt, *J* 33.0 and 2.2, C*H*-O), 7.47 (2H, t, *J* 7.7, Ar*H*), 7.60 (1H, t, *J* 7.4, Ar*H*), 8.16 (2H, d, *J* 7.3, Ar*H*), 8.74 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.8, 2 × *C*H_3), 64.2 (t, $J_{C\text{-}P}$ 6.4, 2 × OCH_2CH$_3$), 70.4 (d, $J_{C\text{-}P}$ 18.7, *C*H-O), 87.2 (dd, $J_{C\text{-}P}$ 192.3 and 175.4, C*H*-F), 128.4 (2 × Ar*C*H), 128.7 (Ar*C*), 130.2 (2 × Ar*C*H), 133.6 (Ar*C*H), 165.0 (*C*=O), 168.7 (dd, $J_{C\text{-}P}$ 14.4 and 4.3, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 12.68 (d, $J_{P\text{-}F}$ 77.5); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -219.20 (ddd, $J_{P\text{-}F}$ 77.2, 43.9 and 33.2); *m*/*z* (ESI^+) 349.0846 (100%, MH^+. $C_{14}H_{19}FO_7P$ requires 349.0847), 331.1 (8%, M-H_2O), 227 (11), 199 (20).

(2*S*,3*S*)-2-(Benzoyloxy)-3-fluoro-3-phosphonopropanoic acid 175



A solution of **174** (0.8 g, 2.297 mmol) in CH_2Cl_2 (15 mL), TMSBr (1.4 g, 1.2 mL, 2.35 mmol) was added and the mixture was stirred for 24 h at room temperature. The solvents were removed under reduced pressure, to the residue H_2O (40 mL) was added and vigorously stirring for 15 minutes, the aqueous solution was neutralized with ammonium bicarbonate, washed with chloroform (3 × 50 mL) and concentrated under reduced pressure to provide the product **175** (0.15 g, 69%) as a grey solid; mp 195-199 °C; $[\alpha]_D^{25}$ -42 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3129, 3050, 2985, 1404; ^{1}H NMR (400 MHz, D_2O) δ_H 5.22 (1H, ddd, *J* 44.3, 8.0 and 2.0, C*H*-F), 5.50 (1H, d, *J* 35.9, C*H*-O), 7.49 (2H, t, *J* 7.7, Ar*H*), 7.60 (1H, t, *J* 7.4, Ar*H*), 8.20 (2H, d, *J* 7.3, Ar*H*); ^{13}C NMR (100 MHz, D_2O) δ_C 75.1 (d, $J_{C\text{-}P}$ 19.5, *C*H-O), 90.7 (dd, $J_{C\text{-}P}$ 184.6 and 159.1, *C*H-F),128.0 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 130.3 (Ar*C*), 132.7 (Ar*C*H), 166.6 (*C*=O), 172.9 (dd, $J_{C\text{-}P}$ 10.6 and 4.7, *C*=O); ^{31}P NMR (162 MHz, CD_3OD) δ_P 8.77 (d, $J_{C\text{-}P}$ 70.5); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -215.17; *m*/*z* (ESI^+) 291.0082 (100%, M-H^+. $C_{10}H_{12}O_7P$ requires 291.0075), 227 (80), 169 (60).

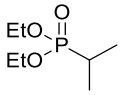
(2*S*,3*S*)-3-Fluoro-2-hydroxy-3-phosphonopropanoic acid 176



Same as the procedure for synthesis compound **158**, using previous compound **175**.

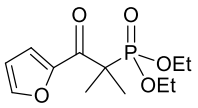
(45% yield) as a semi solid; $[\alpha]_D^{25}$ -51 (*c* 1 in D_2O); ν_{max} (ATR)/cm^{-1} 3030, 1687, 1569, 1425; ^{1}H NMR (400 MHz, D_2O) δ_H 4.22 (1H, dt, *J* 19.2 and 15.1, C*H*-OH) 7.10 (1H, t, *J* 52.0, C*H*F); ^{13}C NMR (100 MHz, D_2O) δ_C 33.6 (d, $J_{C\text{-}P}$ 126.1, *C*H_2P), 69.5 (d, $J_{C\text{-}P}$ 6.0, *C*H-O), 182.2 (d, $J_{C\text{-}P}$ 17.7, C=O); ^{31}P NMR (162 MHz, D_2O) δ_P 10.81 (d, $J_{C\text{-}P}$ 82.5); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -218.8 (d, $J_{P\text{-}F}$ 69.9).

Diethyl isopropylphosphonate [256] 177



A stirred solution of *n*-BuLi (2.1M in hexane, 5 mL, 0.011 mol), and dry THF (7 mL) cooled at -78 °C. Solution of diethyl ethylphosphonate (1.62 mL, 0.01 mol) in THF (2 mL) was added dropwise under argon over 20 minutes. After stirring for 10 minutes, iodomethan (0.68 mL, 0.011 mol) in THF (2 mL) was added dropwise over 20 minutes. After complete the addition, allow the reaction to reach room temperature gradually. Hydrolysis the reaction with water (10 mL), extracted with diethyl ether (4 x 30 mL), then dried over $MgSO_4$, and filtered. After concentration under reduced pressure, yellow oil was obtained, which was purified by column chromatography on silica gel eluting with DCM/Methanol (5%, MeOH) to give the product **177** (1 g, 55% yield) as a yellow oil; ν_{max} (ATR)/cm^{-1} 2993, 2948, 2914, 2873, 1479; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.16 (3H, d, *J* 7.1, CH_3), 1.20 (3H, d, *J* 7.3, CH_3), 1.32 (6H, t, *J* 7.1, 2 × CH_3), 1.87-2.00 [1H, m, CH(CH_3)$_2$], 4.05-4.15 (4H, m, 2 x OCH_2CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (*C*H_3), 16.3 (*C*H_3), 25.6 (d, $J_{C\text{-}P}$ 142.0, C*H*P), 64.0 (d, $J_{C\text{-}P}$ 6.4 2 × *C*H_2O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 35.4. All data is in accordance with the literature.

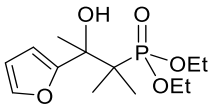
Diethyl (1-(furan-2-yl)-2-methyl-1-oxopropan-2-yl)phosphonate 178



A solution of diisopropylamine (1.9 mL, 13.32 mmol) in dry THF (10 mL) was cooled to -78 °C and then *n*-BuLi (6.5 mL, 2.1 M in hexanes, 13.32 mmol) was added dropwise via syringe. The resulting solution was allowed to warm to 0 °C for 25 min, and then cooled to -78 °C before diethyl isopropylphosphonate **177** (2.00 g, 11.10 mmol) dissolved in THF (10 mL) was added dropwise. After 30 min at -78 °C, methyl 2-furoate (1.4 mL, 13.32 mmol) was added dropwise via cannula over 15 minutes. After 1.5 hour, the reaction was quenched by the addition of HOAc (1.1 mL, 20.00 mmol), followed by a saturated aqueous solution of NH_4Cl (30 mL). Following extraction with EtOAc (3 × 50 mL), the combined organics layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc) yielded the compound **178** (1.40

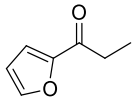
g, 87%) as a pale yellow oil; ν_{max} (ATR)/cm^{-1} 3132, 2985, 2937, 2909, 1730, 1662, 1559, 1463; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.27 (6H, t, *J* 7.0, 2 × C*H*$_3$), 1.62 (3H, s, C*H*$_3$), 1.66 (3H, s, C*H*$_3$), 4.10 (4H, pent, *J* 7.3, 2 × OC*H*$_2$CH$_3$), 6.52 (1H, dd, *J* 3.5 and 1.6, Ar*H*), 7.52 (1H, d, *J* 3.5, Ar*H*), 7.59 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 5.8, 2 x *C*H$_3$), 21.6 (d, $J_{C\text{-}P}$ 4.8, 2 x *C*H$_3$), 49.2 [d, $J_{C\text{-}P}$ 133.3, *C*(CH$_3$)$_2$], 62.7 (d, $J_{C\text{-}P}$ 7.2, 2 x *C*H$_2$O), 111.9 (Ar*C*H), 120.3 (Ar*C*H), 146.0 (Ar*C*H), 151.7 (Ar*C*), 187.3 (*C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 27.12; *m*/*z* (ESI$^+$) 275.1044 (100%, MH$^+$. $C_{12}H_{20}O_5P$ requires 275.1043).

Diethyl (3-(furan-2-yl)-3-hydroxy-2-methylbutan-2-yl)phosphonate 179



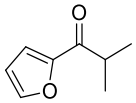
A solution of methyl magnesium bromide (1.4 mL, 2.6 M in Et_2O, 3.65 mmol) was added dropwise via cannula to a stirred solution of diethyl [(1-(furan-2-yl)-2-methyl-1-oxopropan-2-yl)]phosphonate **178** (0.50 g, 1.82 mmol) in Et_2O (10 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 1.5 h, it was allowed to warm to room temperature and stirred overnight, and quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and then concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel (ethyl acetate/petroleum, 1:1) gave *β*-hydroxyphosphonate **179** (0.45 g, 88%) as a yellow oil; ν_{max}(ATR)/cm^{-1} 3389, 3115, 2985, 2933, 2906, 1658, 1500, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.19 (3H, t, *J* 7.1, C*H*$_3$), 1.27 (3H, d, *J* 5.2, C*H*$_3$), 1.31 (3H, d, *J* 4.9, C*H*$_3$), 1.35 (3H, t, *J* 7.1, C*H*$_3$), 1.59 (3H, s, C*H*$_3$), 3.77-3.87 (1H, m, OC*H*HCH$_3$), 3.96-4.05 (1H, m, OCH*H*CH$_3$), 4.14 (2H, pent, *J* 7.2, OC*H*$_2$CH$_3$), 5.06 (1H, s, O*H*), 6.34 (2H, app d, *J* 1.0, Ar*H*), 7.35 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.0, *C*H$_3$), 16.5 (d, $J_{C\text{-}P}$ 5.8, *C*H$_3$), 19.5 (d, $J_{C\text{-}P}$ 3.1, *C*H$_3$), 19.6 (d, $J_{C\text{-}P}$ 3.2, *C*H$_3$), 23.2 (d, $J_{C\text{-}P}$ 7.0, *C*H$_3$), 44.1 [d, $J_{C\text{-}P}$ 134.2, *C*(CH$_3$)$_2$], 62.1 (d, $J_{C\text{-}P}$ 7.8, *C*H$_2$O), 62.2 (d, $J_{C\text{-}P}$ 7.8, *C*H$_2$O), 75.0 (*C*-OH), 106.6 (Ar*C*H), 110.0 (Ar*C*H), 141.1 (Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 35.27; *m*/*z* (ESI$^+$) 313.1170 (100%, M+Na$^+$. $C_{13}H_{23}O_5NaP$ requires 313.1181).

1-(Furan-2-yl)propan-1-one [257] 182b



A stirred mixture of propionic anhydride **181b** (13.10 g, 12.88 mL, 100 mmol) and furan **180** (3.40 g, 3.63 mL, 50 mmol) of furan was warmed to 40 ˚C. The heat source was removed, and ortho phosphoric acid (1.09 g, 0.61 mL, 10.20 mmol) was added in one portion, causing a slight rise in temperature which was allowed to subside and the mixture was kept at 60 ˚C for two hours. After cooling, water (20 mL) was added and the mixture stirred for one hour. The dark coloured organic layer was stirred for 24 hours with saturated sodium carbonate solution (150 mL). The mixture was diluted with water (150 mL), extracted with chloroform (3 × 100 mL), and the combined organic phases were washed with brine (2 × 150 mL), and dried over $MgSO_4$. After being filtered and concentrated, the residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc (8:2) to give the product **182b** (2.69 g, 58% yield) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3135, 2980, 2942, 2910, 2881, 1679, 1568, 1469; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.14 (3H, t, *J* 7.4, C*H*$_3$), 2.79 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 6.46 (1H, dd, *J* 3.6 and 1.4, Ar*H*), 7.11 (1H, d, *J* 3.6, Ar*H*), 7.52 (1H, d, *J* 1.4, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 7.9 (*C*H$_3$), 31.5 (*C*H$_2$CH$_3$), 112.0 (Ar*C*H), 116.6 (Ar*C*H), 146.1 (Ar*C*H), 152.5 (Ar*C*), 190.0 (*C*=O). All data is in accordance with the literature.

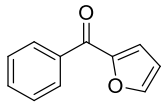
1-(Furan-2-yl)-2-methylpropan-1-one [257] 182c



A stirred mixture of isobutyric anhydride **181c** (9.95 mL, 60 mmol) and furan **180** (2.18 mL, 30 mmol) of furan was warmed to 40 ˚C. The heat was removed, and ortho phosphoric acid (0.35 mL, 6.12 mmol) was added in one portion, causing a slight rise in temperature which was allowed to subside and the mixture was kept at 60 ˚C for two hours. After cooling, water (12 mL) was added and the mixture stirred for one hour. The dark coloured organic layer was stirred for 24 hours with saturated sodium carbonate solution (60 mL). The mixture was diluted with water (150 mL), extracted with chloroform (3 × 200 mL), and the combined organic phases were washed with brine (2 × 250 mL), and dried over $MgSO_4$. After being

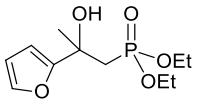
filtered and concentrated, the residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc (7:1) to give the product **182c** (1.87 g, 92% yield) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3133, 2973, 2935, 2877, 1671, 1566, 1467; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 (6H, d, *J* 6.9, 2 × C*H*$_3$), 3.34 [1H, hept, *J* 6.9, C*H*$(CH_3)_2$], 6.54 (1H, dd, *J* 3.5 and 1.5, Ar*H*), 7.20 (1H, d, *J* 3.5, Ar*H*), 7.59 (1H, d, *J* 1.5, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 18.7 (2 × *C*H_3), 36.2 [*C*$H(CH_3)_2$], 112.0 (Ar*C*H), 117.0 (Ar*C*H), 146.2 (Ar*C*H), 152.1 (Ar*C*), 193.6 (*C*=O). All data is in accordance with the literature.

Furan-2-yl(phenyl)methanone 182d



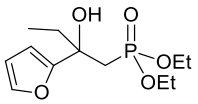
Furaldehyde **183** (2.4 g, 25 mmol) was added dropwise to the solution of phenyl magnesium bromide (2.46 M in Et2O) (11.1 mL, 27.5 mmol) in anhydrous Et_2O (50 mL). The reaction mixture stirred for a further 20 min, Saturated solution of NH_4Cl (75 mL) was added and extracted the mixture with Et_2O (3 × 75 mL). The layers were separated and the organic layer was washed with brine (150 mL), dried with Na_2SO_4, and concentrated in vacuum to afford alcohol (5.66 g, 65 %). To a solution of the alcohol (5.6 g, 32.1 mmol) in dry CH_2Cl_2 (100 mL), at room temperature, MnO_2 (28 g, 321.0 mmol) was added. After vigorous stirring overnight, the reaction mixture was filtered through a pad of Celite® and concentrated in vacuum to afford pure product **182d** (3.7 g, 75 %). ν_{max} (ATR)/cm^{-1} 3149, 3100, 3032, 1648, 1599, 1561,1465; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.59-6.61 (1H, m, Ar*H*), 7.24 (1H, dd, *J* 3.6 and 0.7, Ar*H*), 7.50 (2H, t, *J* 7.8, Ar*H*), 7.58-7.62 (1H, m, Ar*H*), 7.72 (1H, t, *J* 0.7, Ar*H*), 7.98 (2H, d, *J* 7.8, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 112.2 (Ar*C*H), 120.6 (Ar*C*H), 128.4 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 132.6 (Ar*C*H), 137.2 (Ar*C*), 147.1 (Ar*C*H), 152.3 (Ar*C*), 182.5 (*C*=O).

Diethyl (2-(furan-2-yl)-2-hydroxypropyl) phosphonate 184a



A solution of *n*-BuLi 2.1 M in hexane (3.6 mL, 7.527 mmol) was added dropwise via cannula to a stirred solution of diethyl methylphosphonate **145** (1.0 mL, 1.04 g, 6.842 mmol) in dry THF (10 mL) at -78 °C, over 20 minutes. After the reaction mixture was stirred for 30 minutes, **182a** in THF (2 mL) was added dropwise over 20 minutes, then stirred the reaction for 2 h at -78 ˚C. Quenched the reaction by addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and then concentrated in vacuum. Purification of the residue by flash column chromatography eluting with ethyl acetate, gave *β*-hydroxy phosphonate **184a** (1.2 g, 76%) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3376, 3146, 3119, 2985, 2933, 2909, 1504, 1446; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.17 (3H, ddd, *J* 7.1 and 1.5, C*H*$_3$), 0.94 (3H, ddd, *J* 7.1 and 1.5, C*H*$_3$), 1.63 (3H, s, C*H*$_3$), 2.26 (1H, ddd, *J* 16.4, 15.4 and 0.9, C*H*HP), 2.57 (1H, ddd, *J* 17.6, 15.6 and 1.8, C*H*HP), 3.96-3.71 (2H, m, OC*H*$_2$CH$_3$), 4.12-4.03 (2H, m, OC*H*$_2$CH$_3$), 4.98 (1H, s, O*H*), 6.32 (2H, s, Ar*H*), 7.35 (1H, d, *J* 1.0, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 29.6 (d, $J_{C\text{-}P}$ 13.9, *C*H$_3$), 37.4 (d, $J_{C\text{-}P}$ 136.6, *C*H$_2$P), 61.7 (d, $J_{C\text{-}P}$ 6.4, *C*H$_2$O), 61.9 (d, $J_{C\text{-}P}$ 6.4, *C*H$_2$O), 69.2 (d, $J_{C\text{-}P}$ 4.9, *C*-OH), 104.7 (Ar*C*H), 110.3 (Ar*C*H), 141.4 (Ar*C*H), 158.9 (d, $J_{C\text{-}P}$ 7.5, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.27; *m*/*z* (ESI^+) 285.0867 (6%, $M+Na^+$. $C_{11}H_{19}O_5P$ requires 285.0862), 245.1 (100%, M^+-H_2O), 217.1 (5) 189.1 (7).

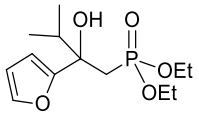
Diethyl (2-(furan-2-yl)-2-hydroxybutyl) phosphonate 184b



A solution of *n*-BuLi 1.25 M in toluene (6.6 mL, 8.21 mmol) was added dropwise via syringe to a stirred solution of diethyl methylphosphonate **145** (1.0 mL, 1.04 g, 6.84 mmol) in dry THF (10 mL) at -78 °C, over 20 minutes. After the reaction mixture was stirred for 30 minutes, **182b** THF (2 mL) was added dropwise over 20 minutes, then the reaction stirred for 2 h at -78 ˚C. Saturated aqueous NH_4Cl (20 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL), the combined organic extracts were dried over

$MgSO_4$, filtered and then concentrated under vacuum. Purification of the residue by flash column chromatography eluting with ethyl acetate, gave *β*-hydroxyphosphonate **184b** (1.69 g, 89%) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3396, 3146, 3112, 2978, 2933, 2882, 1507, 1442; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.82 (3H, t, *J* 7.4, C*H*$_3$), 1.15 (3H, t, *J* 7.1, C*H*$_3$), 1.32 (3H, t, *J* 7.1, C*H*$_3$), 1.87 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 2.26 (1H, t, *J* 15.5, C*H*HP), 2.51 (1H, dd, *J* 18.5 and 15.5, C*H*HP), 3.61-3.75 (1H, m, OC*H*HCH$_3$), 3.80-3.92 (1H, m, OCH*H*CH$_3$), 5.05 (1H, s, O*H*), 6.34-6.32 (1H, m, Ar*H*), 6.37 (1H, d, *J* 3.1, Ar*H*), 7.36 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 7.8 (d, $J_{C\text{-}P}$ 2.0, *C*H$_3$), 16.2 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 35.3 (d, $J_{C\text{-}P}$ 16.5, *C*H$_2$), 36.1 (d, $J_{C\text{-}P}$ 104.8, *C*H$_2$P), 61.6 (d, $J_{C\text{-}P}$ 6.4, *C*H$_2$O), 61.8 (d, $J_{C\text{-}P}$ 6.4, *C*H$_2$O), 72.0 (d, $J_{C\text{-}P}$ 5.3, *C*-OH), 106.3 (Ar*C*H), 110.2 (Ar*C*H), 141.3 (Ar*C*H), 157.8 (d, $J_{C\text{-}P}$ 5.9, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.92; *m*/*z* (ESI$^+$) 299.1009 (7%, M+Na$^+$. $C_{12}H_{21}O_5PNa$ requires 299.1019), 259 (100%, M$^+$-H_2O), 231 (5), 203 (4).

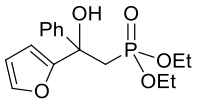
Diethyl (2-(furan-2-yl)-2-hydroxy-3-methylbutyl)phosphonate 184c



A solution of *n*-BuLi (2M in hexane, 4.1 mL, 8.21 mmol) was added dropwise via syringe to a stirred solution of diethyl methylphosphonate **145** (1.0 mL, 1.04 g, 6.84 mmol) in dry THF (10 mL) at -78 °C, over 20 minutes. After the reaction mixture was stirred for 30 minutes, **182c** (1.13 g, 8.21 mmol) in THF (2 mL) was added dropwise over 20 minutes, then stirred the reaction for 2 h at -78 ˚C. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and then concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel eluting with ethyl acetate/petroleum ether (40-60) (1:2) gave β-hydroxy phosphonate **184c** (1.4 g, 95%) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3393, 2978, 2913, 2879, 1504, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.85 (3H, d, *J* 6.8, C*H*$_3$), 0.94 (3H, d, *J* 6.8, C*H*$_3$), 1.12 (3H, t, *J* 7.1, C*H*$_3$), 1.31 (3H, t, *J* 7.1, C*H*$_3$), 2.00 [1H, sept, *J* 6.8, C*H*(CH$_3$)$_2$], 2.29 (1H, dd, *J* 16.6 and 15.2, C*H*HP), 2.53 (1H, dd, *J* 19.3 and 15.2, CH*H*P), 3.65-3.55 (1H, m, OC*H*HCH3), 3.83 (1H, dt, *J* 10.1 and 7.0, OCH*H*CH3), 4.06 (2H, pent d, *J* 7.2 and 1.8, OC*H*$_2$CH$_3$), 5.07 (1H, s, O*H*), 6.33 (1H, dd, *J* 3.0 and 1.0, Ar*H*), 6.38 (1H, d, *J* 3.0, Ar*H*), 7.36 (1H, d, *J* 1.0, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.3, *C*H$_3$), 16.5 (*C*H$_3$),

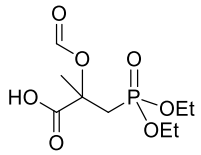
17.3 (*C*H_3), 33.7 (d, $J_{C\text{-}P}$ 138.1, *C*H_2P), 38.8 [d, $J_{C\text{-}P}$ 15.8, *C*$(CH_3)_2$], 61.6 (d, $J_{C\text{-}P}$ 6.4, *C*H_2O), 61.8 (d, $J_{C\text{-}P}$ 6.6, *C*H_2O), 74.0 (d, $J_{C\text{-}P}$ 6.0, *C*-OH), 106.9 (Ar*C*H), 110.2 (Ar*C*H), 141.2 (Ar*C*H), 157.8 (d, $J_{C\text{-}P}$ 3.7, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 29.97; *m*/*z* (ESI$^+$) 313.1177 (2%, M+Na$^+$. $C_{13}H_{23}O_5NaP$ requires 313.1175), 273 (100, M$^+$-H_2O), 245 (5).

Diethyl (2-(furan-2-yl)-2-hydroxy-2-phenylethyl)phosphonate 184d



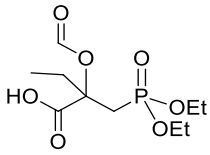
A solution of *n*-BuLi 1.25 M in toluene (6.56 mL, 8.211 mmol) was added dropwise via cannula to a stirred solution of diethyl methylphosphonate **145** (1.0 mL, 1.04 g, 6.84 mmol) in dry THF (10 mL) at -78 °C, over 10 minutes. After the reaction mixture was stirred for 30 minutes, furan-2-yl(phenyl)methanone **182d** (1.76 g, 10.26 mmol) in THF (2 mL) was added dropwise over 20 minutes, then stirred the reaction for 2 h at -78 ˚C. Quenched the reaction by addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and then concentrated in vacuum. Purification of the residue by flash column chromatography eluting with ethyl acetate, gave β-hydroxy phosphonate **184d** (1.87 g, 85%) as a yellow oil; ν_{max} (ATR)/cm^{-1} 3340, 3064, 3034, 2985, 2930, 2907, 1593, 1503, 1490, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.12 (3H, t, *J* 7.1, C*H*$_3$), 1.23 (3H, t, *J* 7.1, C*H*$_3$), 2.65 (1H, dd, *J* 16.8 and 15.4, C*H*HP), 3.00 (1H, dd, *J* 17.2 and 15.4, C*H*HP), 3.69-3.59 (1H, m, OC*H*HCH3), 3.91-3.79 (2H, m, OC*H*$_2$CH$_3$), 4.02-3.92 (1H, m, OC*H*HCH3), 5.84 (1H, s, O*H*), 6.27 (1H, dd, *J* 3.3 and 0.8, Ar*H*), 6.31 (1H, dd, *J* 3.3 and 1.8, Ar*H*), 7.29-7.26 (1H, m, Ar*H*) 7.40-7.34 (3H, m, Ar*H*) 7.58-7.55 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, $J_{C\text{-}P}$ 6.3, *C*H_3), 16.3 (d, $J_{C\text{-}P}$ 6.3, *C*H_3), 37.4 (d, $J_{C\text{-}P}$ 136.3, *C*H_2P), 61.8 (d, $J_{C\text{-}P}$ 3.8, *C*H_2O), 61.9 (d, $J_{C\text{-}P}$ 3.8, *C*H_2O), 72.5 (d, $J_{C\text{-}P}$ 4.0, *C*-OH), 106.5 (Ar*C*H), 110.4 (Ar*C*H), 125.5 (2 × Ar*C*H), 127.5 (Ar*C*H), 128.1 (2 × Ar*C*H), 142.1 (Ar*C*H), 144.1 (d, $J_{C\text{-}P}$ 10.5, Ar*C*), 157.8 (d, $J_{C\text{-}P}$ 11.2, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.00; *m*/*z* (ESI$^+$) 347.1026 (15%, M+Na$^+$. $C_{16}H_{21}NaO_5P$ requires 347.1019), 307 (100).

3-(Diethoxyphosphoryl)-2-(formyloxy)-2-methylpropanoic acid 187a



$RuCl_3$. H_2O (0.033 g, 0.16 mmol) was added to a solution of $NaIO_4$ (6.836 g, 32.03 mmol) in EtOAc (112 mL), hexane (75 mL) and H_2O (46 mL). After 10 min, furan **184a** (0.840 g, 3.20 mmol) was added. The resultant mixture was stirred at room temperature for 5 min. and then quenched with brine (100 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phase washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual crude was dissolved in DCM (5 mL), followed by adding hexane (100 mL) and Keep it in the fridge to precipitate the product **187a** as a brown solid (0.5 g, 58% yield), which is used without further purification; mp 97-98 °C; ν_{max} (ATR)/cm^{-1} 2987, 2935, 2908, 1729, 1447; ^{1}H NMR (400 MHz, DMSO) δ_H 1.22 (3H, t, *J* 7.0, C*H*$_3$), 1.23 (3H, t, *J* 7.0, C*H*$_3$), 1.67 (3H, s, CH_3), 2.36 (1H, dd, *J* 19.7 and 15.7, C*H*HP), 2.39 (1H, dd, *J* 17.7 and 15.8, CH*H*P), 3.95-4.00 (4H, m, 2 × OC*H*$_2$CH$_3$), 8.20 (1H, s, C*H*=O), 13.30 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (d, $J_{C\text{-}P}$ 6.2, 2 × *C*H$_3$), 23.8 (d, $J_{C\text{-}P}$ 5.6, *C*H$_3$), 32.8 (d, $J_{C\text{-}P}$ 142.8, *C*H$_2$P), 62.6 (dd, $J_{C\text{-}P}$ 13.5 and 6.6, 2 × *C*H$_2$O), 78.0 (d, $J_{C\text{-}P}$ 3.1, *C*-CH$_3$), 159.6 (*C*H=O), 172.6 (d, $J_{C\text{-}P}$ 11.5, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 24.42; *m*/*z* (ESI$^+$) 267.0651 (60%, M-H$^+$. $C_9H_{16}O_7P$ requires 267.0639), 239.1 (100%, M$^-$-CH=O), 221.1 [28, M$^-$-(CH=O and H_2O], 193 (1), 175 (2).

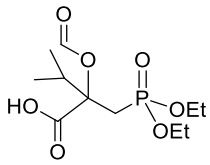
2-((Diethoxyphosphoryl)methyl)-2-(formyloxy)butanoic acid 187b



$RuCl_3$. H_2O (0.026 g, 0.126 mmol) was added to a solution of $NaIO_4$ (5.420 g, 25.337 mmol) in EtOAc (88 mL), hexane (60 mL) and H_2O (36 mL). After 10 min, furan **184b** (0.706 g, 2.533 mmol) was added. The resultant mixture was stirred at RT for 5 min. and then quenched with brine (100 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phase washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual crude was dissolved in DCM (5 mL),

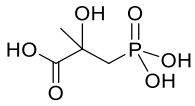
followed by adding hexane (100 mL) and Keep it in the fridge to precipitate the product **187b** as a gray solid (0.4 g, 56% yield), which is used without further purification; mp 127-130 °C; ν_{max} (ATR)/cm^{-1} 3055, 2986, 2941, 1731, 1424; ^{1}H NMR (400 MHz, DMSO) δ_H 0.83 (3H, t, *J* 7.5, CH_2CH_3), 1.22 (6H, q, *J* 6.9, 2 × CH_3), 2.05-2.15 (2H, m, CH_2CH_3), 2.39 (1H, dd, *J* 19.5 and 16.0, C*H*HP), 2.39 (1H, dd, *J* 17.9 and 16.0, CH*H*P), 3.93-4.00 (4H, m, 2 × OCH_2CH_3), 8.23 (1H, s, C*H*=O), 13.36 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 7.6 (CH_2CH_3), 16.2 (d, J_{C-P} 6.3, 2 × CH_3), 29.6 (d, J_{C-P} 6.3, CH_2CH_3), 30.0 (d, J_{C-P} 143.5, CH_2P), 62.5 (dd, J_{C-P} 6.0 and 4.8, 2 × CH_2O), 81.4 (d, J_{C-P} 4.2, *C*-CH_3), 159.8 (*C*H=O), 171.8 (d, J_{C-P} 11.8, *C*=O); ^{31}P NMR (162 MHz, DMSO) δ_P 24.35; *m*/*z* (ESI$^+$) 281.0800 (36%, M-H$^+$. $C_9H_{16}O_7P$ requires 281.0796), 253.1 (100%, M$^-$-CH=O), 235.1 [8, M$^-$-(CH=O and H_2O].

2-((Diethoxyphosphoryl)methyl)-2-(formyloxy)-3-methylbutanoic acid 187c



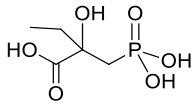
$RuCl_3$. H_2O (0.017 g, 0.085 mmol) was added to a solution of $NaIO_4$ (3.66 g, 17.140 mmol) in EtOAc (60 mL), hexane (40 mL) and H_2O (25 mL). After 10 min, furan **184c** (0.50 g, 1.714 mmol) was added. The resultant mixture was stirred at RT for 5 min. and then quenched with brine (45 mL). The aqueous phase was extracted with EtOAc (3 × 75 mL) and the combined organic phase washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual crude was dissolved in DCM (5 mL), followed by adding hexane (100 mL) and Keep it in the fridge to precipitate the product **187c** as a white solid (0.35 g, 69% yield), which is used without further purification; mp 125-126 °C; ν_{max} (ATR)/cm^{-1} 3056, 2987, 2942, 2911, 1733, 1423; ^{1}H NMR (400 MHz, CD_3CN) δ_H 1.00 (3H, d, *J* 6.9, CH_3), 1.04 (3H, t, *J* 6.9, CH_3), 1.29 (6H, dt, *J* 3.7 and 7.0, 2 × CH_3), 2.65 (1H, dd, *J* 19.2 and 16.3, C*H*HP), 2.74 [1H, pent, *J* 6.8, $CH(CH_3)_2$], 2.88 (1H, dd, *J* 18.9 and 16.5, CH*H*P), 4.03-4.10 (4H, m, 2 × OCH_2CH_3), 8.10 (1H, s, C*H*=O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2 (d, J_{C-P} 6.3, 2 × CH_3), 16.9 (CH_3), 17.3 (CH_3), 28.8 (d, J_{C-P} 143.7, CH_2P), 33.6 [d, J_{C-P} 4.8, $CH(CH_3)_2$], 62.5, (d, J_{C-P} 6.5, 2 × CH_2O), 83.6 (d, J_{C-P} 4.7, *C*-O), 160.2 (*C*H=O), 171.1 (d, J_{C-P} 13.7, *C*=O); ^{31}P NMR (162 MHz, CD_3CN) δ_P 24.62; *m*/*z* (ESI$^+$) 295.0960 (42%, M-H$^+$. $C_{11}H_{20}O_7P$ requires 295.0952), 267.1 (100%, M$^-$-CH=O), 221.1 [5, M$^-$-(CH=O and H_2O], 236 (1), 203 (1).

2-Hydroxy-2-methyl-3-phosphonopropanoic acid 188a



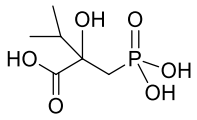
The acid **187a** (0.28 g, 1.044 mmol) was dissolved in concentrated hydrochloric acid (8 mL) and heated to 110 °C for 8 hours. The solvent was removed under vacuum. The resulting crude was diluted in water (20 mL) and lyophilized to obtain phosphonic acid **188a** (0.18 g, 93% yield); ^{1}H NMR (400 MHz, D_2O) δ_H 1.43 (3H, d, *J* 2.2, C*H*$_3$), 2.19 (1H, dd, *J* 17.4 and 15.6, C*H*HP), 2.37 (1H, dd, *J* 18.2 and 15.6, CH*H*P); ^{13}C NMR (100 MHz, D_2O) δ_C 26.9 (d, $J_{C\text{-}P}$ 12.5, *C*H_3), 37.0 (d, $J_{C\text{-}P}$ 135.2, *C*H_2P), 72.3 (d, $J_{C\text{-}P}$ 5.8, *C*-OH), 178.3 (d, $J_{C\text{-}P}$ 5.9, *C*=O); ^{31}P NMR (162 MHz, D_2O) δ_P 23.64; *m*/*z* (ESI$^+$) 183.0071 (100%, M-H$^+$. $C_4H_8O_6P$ requires 183.0064), 281.9 (2), 367 (35).

2-Hydroxy-2-(phosphonomethyl)butanoic acid 188b



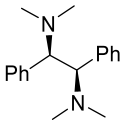
The acid **187b** (0.25 g, 0.885 mmol) was dissolved in concentrated hydrochloric acid (8 mL) and heated to 110 °C for 8 hours. The solvent was removed under vacuum. The resulting crude was diluted in water (20 mL) and lyophilized to obtain phosphonic acid **188b** (0.17 g, 97% yield); ^{1}H NMR (400 MHz, D_2O) δ_H 0.77 (3H, t, *J* 7.4, CH_2CH_3), 1.80-1.61 (2H, m, CH_2CH_3), 2.17 (1H, dd, *J* 17.1 and 15.9, C*H*HP), 2.35 (1H, dd, *J* 18.2 and 15.7, CH*H*P); ^{13}C NMR (100 MHz, D_2O) δ_C 6.9 (CH_2CH_3), 33.6 (d, $J_{C\text{-}P}$ 14.3, *C*H_2CH$_3$), 36.0 (d, $J_{C\text{-}P}$ 135.6, *C*H_2P), 75.5 (d, $J_{C\text{-}P}$ 6.5, *C*-OH), 177.7 (d, $J_{C\text{-}P}$ 4.8, *C*=O); ^{31}P NMR (162 MHz, D_2O) δ_P 24.26; *m*/*z* (ESI$^+$) 197.023 (100%, M-H$^+$. $C_5H_{10}O_6P$ requires 197.022), 419.0 (3), 395 (25), 295 (4), 225 (4).

2-Hydroxy-3-methyl-2-(phosphonomethyl)butanoic acid 188c



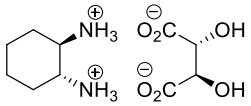
The acid **187c** (0.5 g, 1.687 mmol) was dissolved in concentrated hydrochloric acid (15 mL) and heated to 110° C for 8 hours. After cooling the solvent was removed under vacuum. The resulting material was diluted in water (20 mL) and lyophilized to obtain **188c** (0.34 g, 96% yield) as a yellow oil; ^{1}H NMR (400 MHz, CD_3OD) δ_H 0.95 (3H, d, *J* 6.8, C*H*$_3$), 0.99 (3H, d, *J* 6.8, C*H*$_3$), 2.01-1.91 [1H, m, C*H*$(CH_3)_2$], 2.36 (2H, ddd, *J* 37.8, 18.4 and 15.4, C*H*$_2$P); ^{13}C NMR (100 MHz, CD_3OD) δ_C 15.1 (*C*H_3), 16.1 (*C*H_3), 33.8 (d, $J_{C\text{-}P}$ 138.3, *C*H_2P), 36.7 [d, $J_{C\text{-}P}$ 14.5, C*H*$(CH_3)_2$], 76.6 (d, $J_{C\text{-}P}$ 6.8, *C*-OH), 176.2 (*C*=O); ^{31}P NMR (162 MHz, CD_3OD) δ_P 26.11; *m*/*z* (ESI$^+$) 423 (30), 211.0383 (100, M-H$^+$. $C_6H_{12}O_6P$ requires 211.0377).

(*R*,*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diphenylethylenediamine 204



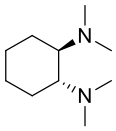
Solution of (1*R*,2*R*)-1,2-diphenylethylenediamine **141** (1.0 g, 4.71 mmol) in formic acid (97%, 1.8 mL, 47.10 mmol) and H_2O under reflux. Formalin (37%, 2.1 mL, 75.36 mmol) was added dropwise. After the mixture refluxed for 3 days, formic acid (1.8 mL) and formalin (2.1 mL) were added, and reflux was continued for 3 days. To the mixture 2M NaOH (pH 11) was added and extracted with EtOAc (3 × 50 mL) and the organic layer was washed with brine and then dried over Na_2SO_4. Concentration gave 2.86 g of product, which was chromatographed over silica gel (EtOAc/petroleum, 1:4) to yield **204** (1.11 g, 83%) as colourless oil. $[\alpha]_D^{20}$ -55.1 (*c* 1.1, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3035, 2991, 2886, 1450, 1035 ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.25 (12H, s, 4 × C*H*$_3$), 4.25 (2H, s, 2 × C*H*N), 6.95-7.19 (10H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 40.8 (4 × *C*H_3), 67.9 (2 × *C*HN), 127.3 (5 × Ar*C*H), 130.0 (5 × Ar*C*H), 133.9 (2 × Ar*C*).

(*R*,*R*)-1,2-Diaminocyclohexane tartrate salt [258] 206



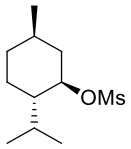
L-(+)-tartaric acid **100** (5.25 g, 35 mmol) was dissolved in distilled water (25 mL) and a mixture of cis/trans 1,2-diaminocyclohexane **205** added (12.22 ml, 100 mmol) so that the reaction temperature reached 70 °C. To this glacial acetic acid was added (5 mL) so that the reaction temperature reached 90 °C. The resulting slurry was stirred for a further 2 h, and then cooled to 5 °C for 2 h. The resulting precipitate was collected by vacuum filtration and washed with 5 °C distilled water (2 × 5 mL) and then methanol (5 × 5 mL). The crude product was then recrystallized by dissolving the compound in distilled water at 90 °C and leaving to cool to room temperature overnight. The purified product **206** was collected by vacuum filtration and dried under reduced pressure (7.4 g, 75% yield); mp 275 °C; $[\alpha]_D^{20}$ +12.5, (*c* 4, H_2O), lit.[258] $[\alpha]_D^{25}$ +12 (*c* 4, H_2O). (dec.) ^{1}H NMR (400 MHz, D_2O) δ_H 1.25 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.70 (2H, m, CH_2), 2.08 (2H, m, CH_2), 3.25 (2H, m, 2 x CHNH_3^+), 4.21 (2H, s, 2 x CHOH); ^{13}C NMR (100 MHz, D_2O) δ_C 22.8 (2 x CH$_2$), 29.3 (2 x CH$_2$), 52.2 (2 x CHNH$_3^+$), 73.9 (2 x CHOH), 178.5 (2 x C=O).

N^1,N^1,N^2,N^2-(1*R*,2*R*)-Tetramethylcyclohexane-1,2-diamine[259] 207



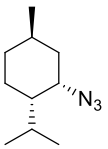
(*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate salt **206** (2 g, 7.56 mmol) was dissolved in formic acid 96% (3.0 mL) and formaldehyde 37% (1.3 mL) was added slowly at room temperature. The mixture was heated at reflux 2 h. After cooling, the reaction mixture was made basic until pH 14 and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product **207** as a colourless liquid (0.2 g, 65%) (85%[221]). The product was used without any farther purification; $[\alpha]_D^{20}$ -62.9, (*c* 1.05, $CHCl_3$), lit.[259] $[\alpha]_D^{25}$ -60 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05–1.15 (4H, m, 2 x CH_2), 1.70–1.79 (2H, m, CH_2), 1.80–1.90 (2H, m, CH_2), 2.26 (12H, s, 4 x CH_3), 2.35–2.40 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 22.9 (2 x CH$_2$), 25.6 (2 x CH$_2$), 40.2 (4 x CH$_3$), 63.9 (2 x CH).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl methanesulfonate[260] 209



(1*S*,2*R*,5*S*)-(+)-Menthol **208** (1 g, 6.41 mmol) was dissolved in methylene chloride (15 mL) and cooled to 0 °C. Triethylamine (2.7 mL, 19.21 mmol), dimethylaminopyridine (0.08 g, 0.64 mmol) were added. Finally, the Mesyl chloride (1.46 g, 12.82 mmol) was added dropwise. The solution was slowly warmed to room temperature and stirred for an additional 12 h. Once complete, the reaction was quenched with 1 M hydrochloric acid. The aqueous layer was extracted with methylene chloride (2 x 20mL), washed with K_2CO_3 (10%, 20mL) then dried over magnesium sulfate, filtered, concentrated in vacuum, and purified via flash column chromatography on silica gel using (EtOAc/petroleum ether, 1:3) as eluent to give product as a colorless oil **209** (1.1 g, 73% yield); $[\alpha]_D^{23}$ -78 (*c* 1 in ethanol), lit.[261] $[\alpha]_D^{25}$ -62.8 (*c* 1 in ethanol), lit.[262] $[\alpha]_D^{20}$ -63.5 (*c* 1 in ethanol); ν_{max} (ATR)/cm^{-1} 2958, 2934, 2872, 1417, 1456, 1352; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.85 (3H, d, *J* 6.9, C*H*$_3$), 0.91-0.87 (1H, m, C*H*CH$_3$) 0.95 (6H, dd, *J* 6.8 and 3.4, 2 x C*H*$_3$), 1.08 (1H, ddd, *J* 26.0, 13.2 and 3.5, C*H*H), 1.29 (1H, dd, *J* 23.2 and 12.0, C*H*H), 1.56–1.40 (2H, m, C*H*$_2$), 1.77–1.68 (2H, m, C*H*$_2$), 2.13–2.05 [1H, m, C*H*(CH$_3$)$_2$], 2.31–2.25 (1H, m, C*H*CH$_2$), 3.02 (3H, s, C*H*$_3$), 4.57 (1H, ddd, *J* 10.9 and 4.6, C*H*OMs); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.7 (*C*H$_3$), 20.8 (*C*H$_3$), 21.9 (*C*H$_3$), 23.1 (*C*H$_2$), 25.8 (*C*H$_3$), 31.6 (*C*H), 33.8 (*C*H$_2$), 39.1 (*C*H), 42.2 (*C*H$_2$), 47.4 (*C*H), 83.4 (CH).

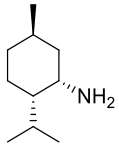
(1*S*,2*S*,4*R*)–2-Azido-1-isopropyl-4-methylcyclohexane[260] 210



Mesylated alcohol **209** (1.0 g, 4.26 mmol) and sodium azide (0.83 g, 12.78 mmol) were dissolved in dimethylformamide (17 mL) and heated to 90 °C for three days. Upon completion, the solution was cooled to room temperature and diluted with water (70 mL). This solution was extracted with diethyl ether (4 x 40 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude material was purified via flash

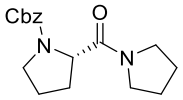
column chromatography on silica gel using 2.5% ethyl acetate/petroleum ether, to yield azide **210** (0.45 g, 58%) as a colourless oil. $[\alpha]_D^{23}$ +86 (*c* 1.6 in $CHCl_3$), lit.[261] $[\alpha]_D^{25}$ = +65.6° (c 1.6 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 2955, 2919, 2869, 2849, 2103, 1474, 1456; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87-0.82 (1H, m, C*H*CH_3), 0.91 (6H, d, *J* 6.7, 2 x C*H*$_3$), 0.95 (3H, d, *J* 6.6, C*H*$_3$), 1.27-1.13 (2H , m, C*H*$_2$), 1.58-1.49 [1H, m, C*H*$(CH_3)_2$]), 1.77-1.65 (4H, m, 2 x C*H*$_2$), 2.03 (1H, dq, *J* 14.0, 5.9 and 3.4,C*H*CH_2), 4.00 (1H, d, *J* 2.4, C*H*N_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.7 (C*H*$_3$), 20.9 (C*H*$_3$), 22.2 (C*H*$_3$), 24.9 (C*H*$_2$), 26.5 (C*H*), 29.5 (C*H*), 34.8(C*H*$_2$), 38.9 (C*H*$_2$), 47.3 (C*H*), 60.5 (C*H*).

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexanamine [260] 211



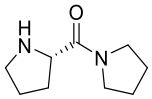
Menthyl azide **210** (0.055 M, 0.5 g, 2.76 mmol) was dissolved in MeOH (50 mL) and reduced to menthyl amine over 20% $Pd(OH)_2$ at 80 °C. The H-Cube flow rate was set at 1 mL/min with H_2 on Full mode. The reactor and CatCart catalyst cartridges (ThalesNano) were equilibrated with methanol for 10 min before measurements were made. The effluent from the reactor was collected from the start of the injection; the injection volume had passed through the reactor. This process was repeated twice, and the solution was set aside overnight to allow the solvent to evaporate to obtain the title product **211** as white crystals (0.24 gm, 57% yield); mp 86-88 °C, lit.[263] mp 91-92 °C; $[\alpha]_D^{23}$ +15 (*c* 1 in $CHCl_3$), lit.[264] $[\alpha]_D^{20}$ +11.6 (*c* 1 in $CHCl_3$); ν_{max}(ATR)/cm^{-1} 2946, 2909, 2868, 2841, 1631, 1546, 1447; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (3H, d, *J* 6.4, C*H*$_3$), 0.93 (3H, d, *J* 6.6, C*H*$_3$), 0.95 (3H, d, *J* 6.6, C*H*$_3$), 1.14 (1H, dt, J 3.4 and 12.9, C*H*H), 1.25 (1H, ddd, *J* 26.3, 13.4 and 3.4, CH*H*), 1.50-1.41 [1H, m, C*H*$(CH_3)_2$], 1.81-1.60 (4H, m, 2 x C*H*$_2$), 2.80-2.00 (2H, br s, N*H*$_2$), 3.33-3.28 (1H, m, C*H*NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.7 (C*H*$_3$), 21.3 (C*H*$_3$), 22.5 (C*H*$_3$), 23.8 (*C*H_2), 25.6 (*C*H), 29.1 (*C*H), 35.2 (*C*H_2), 42.5 (*C*H_2), 47.7 (2 x *C*H_2); *m*/*z* (ESI^+) 156.1746 (100%, MH^+. $C_{10}H_{22}N$ requires 156.1747), 139 (15, -NH_2).

(*S*)-Benzyl 2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate [265] 214



Solution of Cbz-Pro-OH **213** (2.0 g, 8.02 mmol) and Et_3N (0.9 g, 1.23 mL, 8.83 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C; isobutyl chloroformate (1.21 g, 1.14 mL, 8.83 mmol) was added dropwise under stirring. After 15 min, pyrolidine (0.57 g, 0.67 mL, 8.02 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1 M $KHSO_4$ (30 mL), saturated $NaHCO_3$ (30 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacuo*. Then recrystallised from ethyl acetate to yield product **214** as a white, crystalline solid (2.4 g, 75%); mp 125-128 °C, (lit.[266] 130-131 °C); $[\alpha]_D^{25}$ -13.8 (*c* 1.6 in MeOH), lit.[266] $[\alpha]_D^{22}$ -14.1 (*c* 1.61 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (mixture of rotamers) 1.57-2.22 (8H, m, 4 × C*H*$_2$), 3.25-3.81 (6H, m, 3 × C*H*$_3$), 4.48 (1H, ddd, *J* 49.6, 6.64 and 5.1, C*H*N), 5.11 (2H, ddd, *J* 53.7, 27.9 and 12.3, C*H*$_2$Ph), 7.28-7.39 (5H, m, ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (mixture of rotamers) 23.8, 23.9 (*C*H$_2$), 24.1, 24.4 (*C*H$_2$), 26.0, 26.3 (*C*H$_2$), 29.5, 30.5 (*C*H$_2$), 45.9, 46.0 (*C*H$_2$), 46.0, 46.2 (*C*H$_2$), 46.7, 47.3 (*C*H$_2$), 57.7, 58.2 (*C*H), 66.9, 67.1 (*C*H$_2$), 127.7 (2 × Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.4 (2 × Ar*C*H), 136.7, 136.8 (Ar*C*), 154.2, 154.9 (*C*=O), 170.7, 170.9 (C=O).

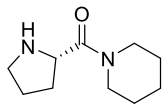
(*S*)-Pyrrolidin-1-yl(pyrrolidin-2-yl)methanone[267] 216a



Solution of Boc-Pro-OH **215** (3.01 g, 14.0 mmol) and Et_3N (2.14 mL, 15.4 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, isobutyl chloroformate (2.0 mL, 15.4 mmol) was added dropwise under stirring. After 15 min, pyrrolidine (1.16 mL, 14.0 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1M $KHSO_4$ (50 mL), saturated $NaHCO_3$ (50 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacue*. To the residue in CH_2Cl_2 (14 mL) was added TFA (14 mL) and stirred overnight at RT. Then, solvent and excess TFA were removed under vacuum and H_2O (100 mL) was added. The mixture was extracted with ether (2 × 50 mL). The ether phase was washed with 50 mL water and the ether phase was given

up. The pH value of combined 3 aqueous phases were brought into the range of 10-11 by the addition of 1M NaOH, and then extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and removed the solvent under reduced pressure to yield the title compound as a light yellow oil **216a** (1.2 g, overall yield 51%); $[\alpha]_D^{23}$ -60.0, (*c* 1, $CHCl_3$), lit.[268] $[\alpha]_D^{25}$ -63.4 (*c* 1, $CHCl_3$), lit.[269] $[\alpha]_D^{25}$ -72.3 (*c* 1, MeOH); ν_{max} (ATR)/cm^{-1} 3391, 2969, 2879, 1611, 1535, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.63-1.77 (2H, m, C*H*$_2$), 179-183 (1H, m, C*H*H), 1.87 (1H, q, *J* 6.7, CH*H*), 1.98 (2H, q, *J* 6.7, C*H*$_2$), 2.07-2.16 (1H, m, C*H*H), 2.82-2.89 (1H, m, CH*H*), 2.99-3.02 (1H, m, C*H*H), 3.18-3.23 (1H, m, CH*H*), 3.37-3.57 (4H, m, 2 x C*H*$_2$), 3.77-3.82 (1H, m, C*H*NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.1 (*C*H$_2$), 26.1 (*C*H$_2$), 26.5 (*C*H$_2$), 30.5 (*C*H$_2$), 46.0 (*C*H$_2$), 46.1 (*C*H$_2$), 47.8 (*C*H$_2$), 59.6 (*C*H), 172.6 (*C*=O).

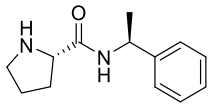
(*S*)-Piperidin-1-yl(pyrrolidin-2-yl)methanone [267] 216b



Solution of Boc-Pro-OH **215** (3.01 g, 14.0 mmol) and Et_3N (2.14 mL, 15.4 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, isobutyl chloroformate (2.0 mL, 15.4 mmol) was added dropwise under stirring. After 15 min, pyrrolidine (1.38 mL, 14.0 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1M $KHSO_4$ (50 mL), saturated $NaHCO_3$ (50 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacuo*. To the residue in CH_2Cl_2 (14 mL) was added TFA (14 mL) and stirred overnight at RT. Then, solvent and excess TFA were removed under vacuum and H_2O (100 mL) was added. The mixture was extracted with ether (2 × 50 mL). The ether phase was washed with 50 mL water and the ether phase was given up. The PH value of combined 3 aqueous phases were brought into the range of 10-11 by the addition of 1M NaOH, and then extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and removed the solvent under reduced pressure to yield the title compound as a clear oil **216b** (1.5 g, overall yield 59%); $[\alpha]_D^{23}$ -52.0, (*c* 1, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3390, 2938, 2860, 1616, 1534, 1444; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.52-1.62 (4H, m, 2 x C*H*$_2$), 162-171 (4H, m, 2 x C*H*$_2$), 1.77-1.85 (1H, m, C*H*H), 2.01-2.10 (1H, m, CH*H*), 2.81-2.89 (1H, m, C*H*H), 3.08-3.22 (2H, m, C*H*$_2$), 3.40-3.45 (2H, m, C*H*$_2$), 3.55-3.61 (2H, m, C*H*$_2$), 3.89-3.94 (1H, m, N*H*);

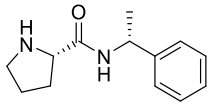
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.5 (*C*H_2), 25.6 (*C*H_2), 26.3 (*C*H_2), 26.5 (*C*H_2), 31.1 (*C*H_2), 43.3 (*C*H_2), 46.0 (*C*H_2), 47.7 (*C*H_2), 58.1 (*C*H), 172.2 (*C*=O).

(*S*)-*N*-((*S*)-1-Phenylethyl)pyrrolidine-2-carboxamide[267,270,271] 216c



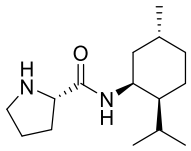
Solution of Boc-Pro-OH **215** (3.0 g, 13.94 mmol) and Et_3N (2.14 mL, 15.33 mmol) in CH_2Cl_2 (75 mL) was cooled to 0 °C, isobutyl chloroformate (2.00 mL, 15.33 mmol) was added dropwise under stirring. After 15 min, (*S)*-(-)-*α*-Methylbenzylamine (1.80 mL, 13.94 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1 M $KHSO_4$ (50 mL), saturated $NaHCO_3$ (50 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacue*. To the residue in CH_2Cl_2 (13 mL) was added TFA (13 mL) and stirred overnight at RT. Then, solvent and excess TFA were removed under vacuum and H_2O (50 mL) was added. The mixture was extracted with ether (2 × 50 mL). The ether phase was washed with water (50 mL) and the ether phase was given up. The PH value of combined 3 aqueous phases were brought into the range of 10-11 by the addition of 1M NaOH, and then extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and removed the solvent under reduced pressure to yield the title compound **216c** as a white solid (2.6 g, overall yield 85%); $[\alpha]_D^{23}$ - 88.0 (*c* 0.5 in CH_2Cl_2), lit.[272] $[\alpha]_D^{25}$ - 91.8 (*c* 0.5 in CH_2Cl_2); mp 143-148 °C, lit.[272] 145–147 °C; ν_{max} (ATR)/cm^{-1} 3270, 3186, 3024, 2977, 2866, 1669, 1559, 1489; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.49 (3H, d, *J* 6.9, C*H*$_3$), 1.66-1.81 (2H, m, C*H*$_2$), 1.92-2.00 (1H, m, C*H*H), 2.04 (1H, s, N*H*), 2.11-2.21 (1H, m, CH*H*), 2.92 (1H, dt, *J* 10.2 and 6.3, C*H*H), 3.03 (1H, dt, *J* 10.2 and 6.8, CH*H*), 3.73 (1H, dd, *J* 9.1 and 5.4, C*H*CH$_3$), 5.11 (1H, dd, *J* 15.5 and 6.9, C*H*NH), 7.24-7.30 (1H, m, ArH), 7.32-7.37 (4H, m, 4 x ArH), 7.93 (1H, d, *J* 6.9, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 22.1 (*C*H$_3$), 26.2 (*C*H$_2$), 30.7 (*C*H$_2$), 47.2 (*C*H$_2$), 48.0 (*C*H), 60.6 (*C*H), 126.1 (2 x Ar*C*H), 127.2 (Ar*C*H), 128.6 (2 x Ar*C*H), 143.5 (Ar*C*), 174.1 (*C*=O).

(*S*)-*N*-((*R*)-1-Phenylethyl)pyrrolidine-2-carboxamide[267,270] 216d



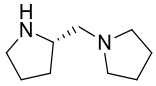
Solution of Boc-Pro-OH **215** (4.0 g, 18.58 mmol) and Et_3N (2.85 mL, 20.44 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C, isobutyl chloroformate (2.65 mL, 20.44 mmol) was added dropwise under stirring. After 15 min, (*R)*-(+)-*α*-Methylbenzylamine (2.36 mL, 18.58 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1 M $KHSO_4$ (100 mL), saturated $NaHCO_3$ (100 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacue*. To the residue in CH_2Cl_2 (18 mL) was added TFA (18 mL) and stirred overnight at RT. Then, solvent and excess TFA were removed under vacuum and H_2O (100 mL) was added. The mixture was extracted with ether (2 × 50 mL). The ether phase was washed with 50 mL water and the ether phase was given up. The PH value of combined 3 aqueous phases were brought into the range of 10-11 by the addition of 1M NaOH, and then extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and removed the solvent under reduced pressure to yield the title compound **216d** as a white solid (2.8 g, overall yield 70%); $[\alpha]_D^{23}$ +20.0 (*c* 1 in MeOH), lit.[273] $[\alpha]_D^{25}$ +21.5 (*c* 1 in MeOH); mp 75-79 °C; ν_{max} (ATR)/cm^{-1} 3266, 3175, 3018, 2966, 2861, 1672, 1548, 1474; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.49 (3H, d, *J* 6.9, C*H*$_3$), 1.68 (2H, app pent, *J* 6.9, C*H*$_2$), 1.90(1H, dt, *J* 19.4 and 6.2, C*H*H), 2.06 (1H, s, N*H*), 2.07-2.18 (1H, m, CH*H*), 2.88 (1H, dt, *J* 10.2 and 6.3, C*H*H), 3.01 (1H, dt, *J* 10.2 and 6.8, CH*H*), 3.76 (1H, dd, *J* 9.1 and 5.2, C*H*CH$_3$), 5.10 (1H, dd, *J* 15.3 and 7.0, C*H*NH), 7.23-7.36 (5H, m, 5 x ArH), 7.96 (1H, d, *J* 7.9, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 22.3 (*C*H$_3$), 26.2 (*C*H$_2$), 30.7 (*C*H$_2$), 47.3 (*C*H$_2$), 47.8 (*C*H), 60.6 (*C*H), 126.0 (2 x Ar*C*H), 127.0 (Ar*C*H), 128.6 (2 x Ar*C*H), 143.8 (Ar*C*), 174.2 (*C*=O).

(*S*)-*N*-((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)pyrrolidine-2-carboxamide[267] 216e



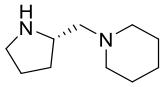
Solution of Boc-Pro-OH **215** (1.38 g, 6.44 mmol) and Et_3N (1.0 mL, 7.08 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C; isobutyl chloroformate (0.92 mL, 7.08 mmol) was added dropwise under stirring. After 15 min, (1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexan amine (1.00 g, 6.44 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature overnight. The mixture was washed with 1 M $KHSO_4$ (30 mL), saturated $NaHCO_3$ (30 mL), and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under *vacuo*. To the residue was dissolved in CH_2Cl_2 (7 mL) was added TFA (7 mL) and stirred overnight at RT. Then, solvent and excess TFA were removed under vacuum and H_2O (30 mL) was added. The mixture was extracted with ether (2 × 20 mL). The ether phase was washed with water (30 mL) and the ether phase was given up. The PH value of combined 3 aqueous phases were brought into the range of 10-11 by the addition of 1M NaOH, and then extracted with CH_2Cl_2 (5 × 40 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and removed the solvent under reduced pressure to yield the title compound as a light yellow oil **216e** (1.3 g, overall yield 80%) as a white solid; $[\alpha]_D^{25}$ = +16.4 (*c* 1.3, EtOH), lit.[274] $[\alpha]_D^{25}$ +16.8 (*c* 1.3, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.87 (2H, s, C*H*$_2$), 0.89 (6H, d, *J* 1.8, 2 × C*H*$_3$), 0.90 (3H, d, *J* 1.8, C*H*$_3$), 0.92-1.10 (2H, m, C*H*$_2$), 1.28-1.49 (2H, m, C*H*$_2$), 1.69-1.86 (6H, m, 3 × C*H*$_2$), 1.91-1.1.98 (1H, m, C*H*CH$_3$), 2.11-2.20 (1H, m, C*H*CHCH$_3$), 2.93 (1H, dt, *J* 10.3 and 6.6, CHC*H*CH$_3$), 3.06 (1H, dt, *J* 10.3 and 6.6, C*H*NH), 3.80 (1H, dd, *J* 9.0 and 5.2,), 4.27 (1H, dd, *J* 9.4 and 3.0, NH), 7.90 (1H, d, *J* 8.4, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.8 (*C*H$_3$), 21.0 (*C*H$_3$), 22.3 (*C*H$_3$), 25.4(*C*H$_2$), 26.2 (*C*H$_2$), 27.0 (*C*H), 29.7 (*C*H), 30.9 (*C*H$_2$), 34.9 (*C*H$_2$), 40.4 (*C*H$_2$), 45.5 (*C*H), 46.4 (*C*H), 47.3 (*C*H$_2$), 60.8 (*C*H), 173.6 (*C*=O).

(*S*)-1-(Pyrrolidin-2-ylmethyl)pyrrolidine [270] 217a



Finely powdered $LiAlH_4$ (0.7 g, 17.83 mmol) in dry THF (5 mL) at 0 °C was placed in a dry round bottom flask equipped with a reflux condenser. The solution of amide **216a** (1.0 g, 5.94 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. Then the reaction mixture was heated under reflux for 6h. After cooling to 0°C the excess of $LiAlH_4$ was decomposed by the successive addition of water (2 mL), 15% NaOH solution (2 mL), and water (5 mL). The white precipitate thus obtained were filtered off under *vacuo* and washed thoroughly with methanol (3 × 15 mL). The filtrate was concentrated under *vacuo* and residual mass was dissolved in $CHCl_3$ (25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent to give the title compound **217a** as yellow oil (0.6 g, 65%); $[\alpha]_D^{23}$ +7.9 (*c* 2.4 in EtOH), lit.[275] $[\alpha]_D^{20}$ +8.5 (*c* 2.4 in EtOH), lit.[276] +8.9 (c 2.4 in EtOH), lit.[277] $[\alpha]_D^{25}$ +8.3 (*c* 2.4 in EtOH), lit.[278] $[\alpha]_D^{29}$ +8.2 (*c* 2.38 in EtOH); ν_{max} (ATR)/cm^{-1} 2958, 2873, 2777, 1671, 1458; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.32–1.40 (1H, m, C*H*H), 1.71-1.80 (6H, m, 3 x CH_2), 1.87-1.95 (1H, m, CH*H*), 2.34-2.40 (1H, m, CH_2), 2.47-2.61 (4H, m, 2 x CH_2), 2.85-2.91 (1H, m, C*H*H), 2.97-3.03 (1H, m, CH*H*), 3.21-3.28 (1H, m, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 23.5 (2 x *C*H_2), 25.0 (*C*H_2), 30.1 (*C*H_2), 46.1 (*C*H_2), 54.6 (2 x *C*H_2), 57.5 (*C*H), 62.0 (*C*H_2).

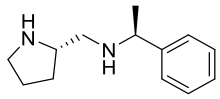
(*S*)-1-(Pyrrolidin-2-ylmethyl)piperidine[270] 217b



Finely powdered $LiAlH_4$ (0.7 g, 17.83 mmol) in dry THF (5 mL) at 0 °C was placed in a dry round bottom flask equipped reflux condenser. The solution of amide **216b** (1.0 g, 5.94 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. Then the reaction mixture was heated under reflux for 6h. After cooling to 0°C the excess of $LiAlH_4$ was decomposed by the successive addition of water (2 mL), 15% NaOH solution (2 mL), and water (5 mL). The white precipitate thus obtained were filtered off under *vacuo* and washed thoroughly with methanol (3 × 15 mL). The filtrate was concentrated under *vacuo* and residual mass was dissolved in $CHCl_3$ (25

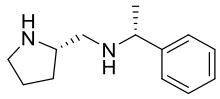
mL), washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the title compound **217b** as a yellow oil (0.6 g, 70%); $[\alpha]_D^{23}$ +16.5 (*c* 0.5 in EtOH), lit.[279] $[\alpha]_D^{17}$ +15.8 (*c* 0.5 in EtOH); ν_{max} (ATR)/cm^{-1} 2932, 2853, 2791, 1442; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28-1.36 (1H, m, C*H*H), 1.41-1.45 (2H, m, CH_2), 1.51-1.62 (4H, m, 2 X CH_2), 1.70-1.77 (2H, m, CH_2), 1.83-1.92 (1H, m, CH*H*), 2.27 (2H, d, *J* 7.3, CH_2), 2.31-2.34 (2H, m, CH_2), 2.45-2.55 (2H, m, CH_2), 2.83-2.89 (1H, m, C*H*H), 2.97-3.03 (1H, m, CH*H*), 3.24-3.31 (1H, m, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.5 (*C*H_2), 25.0 (*C*H_2), 26.0 (2 x *C*H_2), 30.0 (*C*H_2),46.0 (*C*H_2), 55.0 (2 x *C*H_2), 55.6 (*C*H) , 64.8 (*C*H_2).

(*S*)-1-Phenyl-*N*-((*S*)-pyrrolidin-2-ylmethyl)ethanamine[270] 217c



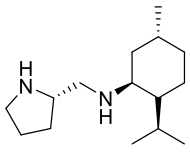
Finely powdered $LiAlH_4$ (1.14 g, 30 mmol) in dry THF (30 mL) at 0 °C was placed in a dry round bottom flask equipped reflux condenser. The solution of amide **216c** (2.18 g, 10 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. Then the reaction mixture was heated under reflux for 6h. After cooling to 0°C the excess of $LiAlH_4$ was decomposed by the successive addition of water (5 mL), 15% NaOH solution (5 mL), and water (10 mL). The white precipitate thus obtained were filtered off under *vacuo* and washed thoroughly with methanol (3 × 15 mL). The filtrate was concentrated under *vacuo* and residual mass was dissolved in $CHCl_3$ (40 mL), washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the title compound **217c** as a yellow oil (1.4 g, 68%); $[\alpha]_D^{23}$ -40.1 (*c* 1.1 in EtOH), lit.[280] $[\alpha]_D^{24}$ -43.0 (*c* 1.1 in EtOH), ν_{max} (ATR)/cm^{-1} 3291, 3024, 2958, 2868, 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.15-1.24 (1H, m, C*H*H), 1.30 (3H, d, *J* 6.6, CH_3), 1.54-1.67 (2H, m, CH_2), 1.69-1.78 (1H, m, CH*H*), 2.31-2.39 (4H, m, CH_2 and 2 x N*H*), 2.78-2.85 (2H, m, CH_2), 3.10 (1H, dt, *J* 14.3 and 6.5, C*H*CH_3), 3.68 (1H, dd, *J* 13.2 and 6.5, C*H*NH), 7.13-7.17 (1H, m, Ar*H*), 7.22-7.28 (4H, m, 4 x Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.5 (*C*H_3), 25.5 (*C*H_2), 29.7 (*C*H_2), 46.4 (*C*H_2), 53.0 (*C*H_2), 58.5 (*C*HCH_3), 58.7 (*C*HNH), 126.6 (2 x Ar*C*H), 126.8 (Ar*C*H), 128.3 (2 x Ar*C*H), 145.8 (Ar*C*).

(*R*)-1-Phenyl-*N*-((*S*)-pyrrolidin-2-ylmethyl)ethanamine[270] 217d



Finely powdered $LiAlH_4$ (1.04 g, 27.48 mmol) in dry THF (10 mL) at 0 °C was placed in a dry round bottom flask equipped reflux condenser. The solution of amide **216d** (2.00 g, 9.16 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. Then the reaction mixture was heated under reflux for 6h. After cooling to 0°C the excess of $LiAlH_4$ was decomposed by the successive addition of water (1 mL), 15% NaOH solution (1 mL), and water (3 mL). The white precipitate thus obtained were filtered off under *vacuo* and washed thoroughly with methanol (3 × 10 mL). The filtrate was concentrated under *vacuo* and residual mass was dissolved in $CHCl_3$ (25 mL), washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent to give the title compound **217d** as yellow oil (1.4 g, 75%); $[\alpha]_D^{23}$ +47.1 (*c* 1.02 in EtOH). lit.[280] $[\alpha]_D^{24}$ +53.5 (*c* 1.02 in EtOH), ν_{max} (ATR)/cm^{-1} 3291, 2959, 2869, 1663, 1602, 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.24-1.33 (1H, m, C*H*H), 1.37 (3H, d, *J* 6.6, CH_3), 1.67-1.74 (2H, m, CH_2), 1.79-1.86 (1H, m, CH*H*), 1.9 (2H, bro s, 2 x N*H*), 2.32 (1H, dd, *J* 11.6 and 8.5, C*H*H), 2.55 (1H, dd, *J* 11.6 and 4.5, C*H*H), 2.87 (2H, t, *J* 6.7, CH_2), 3.23 (1H, ddd, *J* 15.2, 7.3 and 4.5, C*H*CH_3), 3.78 (1H, dd, *J* 13.2 and 6.7, C*H*NH), 7.22-7.28 (1H, m, Ar*H*) 7.31-7.35 (4H, m, 4 x Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.5 (*C*H_3), 25.6 (*C*H_2), 29.6 (*C*H_2), 46.4 (*C*H_2), 52.5 (*C*H_2), 58.3 (*C*HCH_3), 58.5 (*C*HNH), 126.6 (2 x Ar*C*H), 126.8 (Ar*C*H), 128.4 (2 x Ar*C*H), 145.9 (Ar*C*).

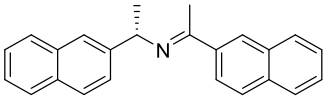
(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-N-((*S*)-pyrrolidin-2-ylmethyl)cyclohexanamine[270] 217e



Finely powdered $LiAlH_4$ (0.54 g, 14.26 mmol) in dry THF (15 mL) at 0 °C was placed in a dry round bottom flask equipped reflux condenser. The solution of amide **216e** (1.20 g, 4.75 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. Then the reaction mixture was heated under reflux

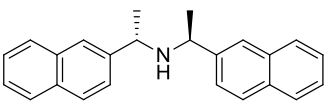
for 6h. After cooling to 0°C the excess of $LiAlH_4$ was decomposed by the successive addition of water (3 mL), 15% NaOH solution (3 mL), and water (3 mL). The white precipitate thus obtained were filtered off under *vacuo* and washed thoroughly with methanol (3 × 10 mL). The filtrate was concentrated under *vacuo* and residual mass was dissolved in $CHCl_3$ (40 mL), washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent to give the title compound **217e** as yellow oil (0.6 g, 62%); $[\alpha]_D^{25}$ +11.4 (c 1 in MeOH), lit.[274] $[\alpha]_D^{25}$ +11.1 (*c* 1 in EtOH),; ν_{max} (ATR)/cm^{-1} 2955, 2870, 2779, 1668, 1455; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.86 (2H, d, *J* 6.5, CH_2), 0.90 (3H, d, *J* 2.5, CH_3), 0.91 (6H, d, *J* 2.5, 2 × CH_3), 1.00-1.10 (2H, m, CH_2), 1.28-1.41 (2H, m, CH_2), 1.50-1.61 (2H, m, CH_2), 1.62-1.90 (4H, m, 2 × CH_2), 2.48 (1H, dd, *J* 11.6 and 4.9, C*H*), 2.67 (1H, dd, *J* 11.6 and 7.6, C*H*), 2.8-2.85 (1H, m, C*H*), 2.86-3.3.05 (2H, m, CH_2), 3.21 (1H, dt, *J* 12.2 and 7.2, C*H*), 3.73 (1H, dd, *J* 9.1 and 5.2, C*H*), 4.27 (1H, dd, *J* 9.3 and 2.6, N*H*), 7.9 (1H, d, *J* 8.3, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.8 (*C*H_3), 21.5 (*C*H_3), 22.6 (*C*H_3), 24.3 (*C*H_2), 25.4 (*C*H_2), 25.6 (*C*H), 28.9 (*C*H), 29.4 (*C*H_2), 35.4 (*C*H_2), 38.2 (*C*H_2), 46.3 (*C*H_2), 48.4 (*C*H), 52.1 (*C*H_2), 53.7 (*C*H), 58.8 (*C*H).

(*S*)-α-Methyl-*N*-[1-(2-naphthalenyl)ethylidene] 220



Amine (*S*)-**218** (1.70 g, 10 mmol) and ketone **219** (1.71, 10 mmol), was added to Titanium (IV) propoxide (8.5 g, 30 mmol) and stirred at room temperature overnight. Cooled to 0 °C and then added H_2O (10 mL). Filtered through celite, washed with EtOAc (3× 20 mL) and washed the organic phase with H_2O (30 mL) Dried over $MgSO_4$, filtered and concentrated under vacuum, followed by washing with petroleum ether (3 × 20 mL). This crude product was used in the next reaction without further purification.

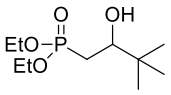
(*S*)-Bis((*S*)-1-(naphthalen-2-yl)ethyl)amine[230] 221



Solution of the imine **220** (1 g, 3.09 mmol) in CH_2Cl_2 (8 mL), DMF (1.44 mL, 18.55 mmol) was added. The mixture was then cooled to 0 °C and $HSiCl_3$ (0.94 mL, 9.27 mmol) was

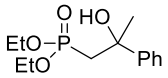
added dropwise by means of a syringe. The reaction mixture was stirred at 0 °C for 4 h, and then quenched by the addition of $NaHCO_3$ saturated solution (8 mL). The mixture was allowed to warm up to room temperature and H_2O (8 mL) and CH_2Cl_2 (15 mL) were added. The organic phase was separated and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product which was then purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether (1:4) to afford the amine **221** (0.4 g, 57%) as a pale yellow oil; (1.4 g, 68%); $[\alpha]_D^{20}$ -347 (*c* 1.15 in $CHCl_3$), lit.[281] $[\alpha]_D^{25}$ 335 [(*c* 1.15 in $CHCl_3$) (isomer *R*,*R*)]; ν_{max} (ATR)/cm^{-1} 3051, 3015, 2958, 2922, 2861, 1599, 1506,1445; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41 (6H, d, *J* 6.7, 2 × C*H*$_3$), 1.78 (1H, s br, N*H*), 3.74 (2H, q, *J* 6.7, 2 × NHC*H*), 7.46-7.54 (6H, m, Ar*H*), 7.62 (2H, s br, Ar*H*), 7.82-7.85 (2H, m, Ar*H*), 7.89 (4H, d, *J* 8.7, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 24.9 (2 × *C*H$_3$), 55.3 (2 × *C*H), 124.9 (2 x Ar*C*H), 125.5 (4 x Ar*C*H), 126.0 (2 x Ar*C*H), 127.7 (2 x Ar*C*H), 127.8 (2 x Ar*C*H), 128.3 (2 x Ar*C*H), 132.8 (2 x Ar*C*), 133.5 (2 x Ar*C*), 143.1 (2 x Ar*C*).

Diethyl (2-hydroxy-3,3-dimethylbutyl)phosphonate[231] 227g



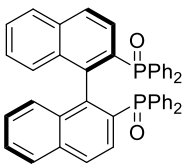
A solution of diethyl iodomethylphosphonate **225** (0.14 g, 0.5 mmol) and pivalaldehyde **226g** (0.04 g, 0.5 mmol) in THF (2 mL) was added dropwise over a 10 min period at room temperature to a stirred solution of SmI_2 in tetrahydrofuran (0.1 M, 12 mL). Soon after the addition, the original blue solution turned to a yellow suspension. The reaction was monitored by TLC (EtOAc). The reaction mixture was treated with aqueous HCl (0.1M solution, 3 mL) and extracted with ethyl acetate (3 × 4 mL); the organic layer was washed with a saturated Na_2SO_3 aqueous solution (6 mL), dried with sodium sulfate, filtered, the solvent evaporated under reduced pressure and the crude purified by flash chromatography on silica gel using ethyl acetate as eluent yielded the desired compound **227g** (0.07 g, 58%) as a pale yellow oil; ν_{max} (ATR)/cm^{-1} 3389, 2959, 2908, 2871, 1480, 1444; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.93 (9H, s, 3 × C*H*$_3$), 1.36 (6H, ddd, *J* 7.1 and 2.7, 2 × C*H*$_3$), 1.80 (1H, td, *J* 15.5 and 11.2, C*H*HP), 1.99 (1H, dd, *J* 20.5 and 15.0, CH*H*P), 3.68 (1H, t, *J* 10.3, C*H*OH), 4.22-4.10 (4H, m, 2 × C*H*$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.3 (*C*H$_3$), 16.4 (*C*H$_3$), 16.5 (*C*H$_3$), 25.4 (2 x *C*H$_3$), 28.5 (d, $J_{C\text{-}P}$ 139.6, *C*H$_2$P), 61.9 (d, $J_{C\text{-}P}$ 5.1, O*C*H$_2$CH$_3$), 62.0 (d, $J_{C\text{-}P}$ 5.1, O*C*H$_2$CH$_3$), 73.8 (d, $J_{C\text{-}P}$ 6.2, *C*HOH); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 32.65.

Diethyl (2-hydroxy-2-phenylpropyl)phosphonate[231] 227h



A solution of THF (2 mL), diethyl iodomethylphosphonate **225** (0.14 g, 0.5 mmol) and acetophenone **226h** (0.06 g, 0.5 mmol) was added dropwise over a 10 min period at room temperature to a stirred solution of SmI_2 in tetrahydrofuran (0.1 M, 12 mL). Soon after the addition, the original blue solution turned to a yellow suspension. The reaction was monitored by TLC (EtOAc). The reaction mixture was treated with aqueous HCl (0.1M solution, 3 mL) and extracted with ethyl acetate (3 × 4 mL); the organic layer was washed with a saturated Na_2SO_3 aqueous solution (6 mL), dried with sodium sulfate, filtered, the solvent evaporated under reduced pressure and the crude purified by flash chromatography on silica gel using ethyl acetate as eluent yielded the desired compound **227h** (0.09 g, 66%) as a pale yellow oil; ν_{max} (ATR)/cm^{-1} 3399, 3086, 3059, 3026, 2980, 2932, 2907, 1492, 1446, 1391; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.02 (3H, t, *J* 7.1 C*H*$_3$), 1.33 (3H, t, *J* 7.1 C*H*$_3$), 1.64 (3H, d, *J* 2.4, C*H*$_3$), 2.42 (2H, ddd, *J* 52.5, 17.2 and 15.4, C*H*$_2$P), 3.45-3.35 (1H, m, C*H*HCH$_3$), 3.76-3.67 (1H, m, CH*H*CH$_3$), 4.14-4.00 (2H, m, C*H*$_2$CH$_3$), 5.02 (1H, s br, O*H*), 7.25-6.63 (1H, tt, *J* 2.1, Ar*H*), 7.36 (2H, t, *J* 7.7, Ar*H*), 7.52-7.49 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.1 (d, $J_{C\text{-}P}$ 6.2, *C*H$_3$), 16.3 (d, $J_{C\text{-}P}$ 6.2, *C*H$_3$), 32.5 (d, $J_{C\text{-}P}$ 14.44, *C*H$_3$), 39.7 (d, $J_{C\text{-}P}$ 135.55, *C*H$_2$P), 61.4 (d, $J_{C\text{-}P}$ 6.5, O*C*H$_2$CH$_3$), 61.7 (d, $J_{C\text{-}P}$ 6.5, O*C*H$_2$CH$_3$), 72.0 (d, $J_{C\text{-}P}$ 5.9, *C*-OH), 124.8 (2 × Ar*C*H), 126.7 (Ar*C*H), 128.1 (2 × Ar*C*H), 147.2 (d, $J_{C\text{-}P}$ 7.1, Ar*C*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.93.

(*R*)-2,2'-*Bis*-(Diphenylphosphinoyl)-1,1'-binaphthyl [282] 229



(*R*)-2,2'-*bis*-(Diphenylphosphino)-1,1'-binaphthyl **228** (0.5 g, 0.8 mmol) was added to dichloromethane (15 mL) and the solution cooled to 0 °C. Hydrogen peroxide (35 wt.%, 1 mL) was added dropwise and the mixture stirred for 18 hours. The solution was poured into water (15 mL) and the organic phase separated. The aqueous layer was extracted with diethylether (3 × 75 mL) and the combined organic phases washed with a saturated aqueous solution of sodium sulfite (20 mL) and dried over magnesium sulfate. Removal of the solvent

in vacuo afforded a white crystalline solid that required no further purification (0.48 g, 95%). m.p. 259 °C; $[\alpha]_D^{25}$ +386 (*c* 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.77-6.86 (4H, m, Ar*H*), 7.25-7.53 (20H, m, Ar*H*), 7.70-7.78 (4H, m, Ar*H*), 7.80-7.90 (4H, m, Ar*H*); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 28.3. All data is in accordance with the literature.

References

1. I. Abubakar, L. Irvine, C. F. Aldus, G. M. Wyatt, R. Fordham, S. Schelenz, L. Shepstone, A. Howe, M. Peck and P. R. Hunter, *Health Technol Assess*, 2007, **11**, 1-216.
2. G. McDonnell and A. D. Russell, *Clin. Microbiol. Rev.*, 1999, **12**, 147-179.
3. H. W. Boucher, G. H. Talbot, J. S. Bradley, J. E. Edwards, D. Gilbert, L. B. Rice, M. Scheld, B. Spellberg and J. Bartlett, *Clin Infect Dis*, 2009, **48**, 1-12.
4. A. K. Mukerjee and A. K. Singh, *Tetrahedron*, 1978, **34**, 1731-1767.
5. S. L. Kaplan and E. O. Mason, Jr., *Clin. Microbiol. Rev.*, 1998, **11**, 628-644.
6. R. Pallares, P. F. Viladrich, J. Linares, C. Cabellos and F. Gudiol, *Microb. Drug Resist. (Larchmont, N. Y.)*, 1998, **4**, 339-347.
7. S. Singh, G. N. Phillips, Jr. and J. S. Thorson, *Nat. Prod. Rep.*, 2012, **29**, 1201-1237.
8. H. C. Neu, *Science (Washington, D. C., 1883-)*, 1992, **257**, 1064-1072.
9. B. E. Lacy and J. Rosemore, *J Nutr*, 2001, **131**, 2789S-2793S.
10. R. Gavin, A. A. Rabaan, S. Merino, J. M. Tomas, I. Gryllos and J. G. Shaw, *Mol. Microbiol.*, 2002, **43**, 383-397.
11. H. Yoshiyama and T. Nakazawa, *Microbes Infect*, 2000, **2**, 55-60.
12. S. Tarahomjoo, *Antonie van Leeuwenhoek*, 2014, **105**, 275-288.
13. E. Andersen-Nissen, K. D. Smith, K. L. Strobe, S. L. R. Barrett, B. T. Cookson, S. M. Logan and A. Aderem, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 9247-9252.
14. H. P. Zhang, A. Be'er, E. L. Florin and H. L. Swinney, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 13626-13630, S13626/13621-S13626/13628.
15. T. Kohler, L. K. Curty, F. Barja, C. Van Delden and J.-C. Pechere, *J. Bacteriol.*, 2000, **182**, 5990-5996.
16. G. M. Fraser and C. Hughes, *Curr Opin Microbiol*, 1999, **2**, 630-635.
17. E. M. F. Mauriello, T. Mignot, Z. Yang and D. R. Zusman, *Microbiol. Mol. Biol. Rev.*, 2010, **74**, 229-249.
18. H. C. Berg, *Annu. Rev. Biochem.*, 2003, **72**, 19-54.
19. M. Meister, G. Lowe and H. C. Berg, *Cell (Cambridge, Mass.)*, 1987, **49**, 643-650.
20. E. Mizraji, *Biosystems*, 1985, **18**, 193-195.
21. P. M. Power and M. P. Jennings, *FEMS Microbiol Lett*, 2003, **218**, 211-222.
22. P. Lertsethtakarn, K. M. Ottemann and D. R. Hendrixson, *Annu. Rev. Microbiol.*, 2011, **65**, 389-410.
23. Y. V. Morimoto and T. Minamino, *Biomolecules*, 2014, **4**, 217-234, 218 pp.
24. P. Guerry, *Trends Microbiol.*, 2007, **15**, 456-461.
25. Q. Duan, M. Zhou, L. Zhu and G. Zhu, *J Basic Microbiol*, 2013, **53**, 1-8.
26. W. Shi and D. R. Zusman, *Proc Natl Acad Sci U S A*, 1993, **90**, 3378-3382.
27. M. J. McBride, *Annu. Rev. Microbiol.*, 2001, **55**, 49-75.
28. Y. Li, H. Sun, X. Ma, A. Lu, R. Lux, D. Zusman and W. Shi, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 5443-5448.
29. D. E. Bradley, *J. Gen. Microbiol.*, 1972, **72**, 303-319.
30. H. Sun, D. R. Zusman and W. Shi, *Curr. Biol.*, 2000, **10**, 1143-1146.
31. J. Hodgkin and D. Kaiser, *Molecular and General Genetics MGG*, 1979, **171**, 177-191.
32. R. Yu and D. Kaiser, *Mol. Microbiol.*, 2007, **63**, 454-467.
33. C. Wolgemuth, E. Hoiczyk, D. Kaiser and G. Oster, *Curr. Biol.*, 2002, **12**, 369-377.
34. E. Hoiczyk and W. Baumeister, *Curr. Biol.*, 1998, **8**, 1161-1168.
35. R. P. Burchard, *Annu. Rev. Microbiol.*, 1981, **35**, 497-529.
36. G. A. O'Toole and R. Kolter, *Mol. Microbiol.*, 1998, **30**, 295-304.
37. T. Tolker-Nielsen, U. C. Brinch, P. C. Ragas, J. B. Andersen, C. S. Jacobsen and S. Molin, *J. Bacteriol.*, 2000, **182**, 6482-6489.
38. J. M. Skerker and H. C. Berg, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 6901-6904.

39. I. Scheuerpflug, T. Rudel, R. Ryll, J. Pandit and T. F. Meyer, *Infect. Immun.*, 1999, **67**, 834-843.
40. R. C. Johnson, D. M. Ferber and B. Ely, *J. Bacteriol.*, 1983, **154**, 1137-1144.
41. P. M. Power and M. P. Jennings, *FEMS Microbiol. Lett.*, 2003, **218**, 211-222.
42. S. M. Logan, J. F. Kelly, P. Thibault, C. P. Ewing and P. Guerry, *Mol. Microbiol.*, 2002, **46**, 587-597.
43. P. R. Erickson and M. C. Herzberg, *J. Biol. Chem.*, 1993, **268**, 23780-23783.
44. T. Garbe, D. Harris, M. Vordermeier, R. Lathigra, J. Ivanyi and D. Young, *Infect. Immun.*, 1993, **61**, 260-267.
45. E. Stimson, M. Virji, K. Makepeace, A. Dell, H. R. Morris, G. Payne, J. R. Saunders, M. P. Jennings, S. Barker and a. et, *Mol. Microbiol.*, 1995, **17**, 1201-1214.
46. K. M. Dobos, K.-H. Khoo, K. M. Swiderek, P. J. Brennan and J. T. Belisle, *J. Bacteriol.*, 1996, **178**, 2498-2506.
47. P. Doig, N. Kinsella, P. Guerry and T. J. Trust, *Mol. Microbiol.*, 1996, **19**, 379-387.
48. C. D. Brimer and T. C. Montie, *J. Bacteriol.*, 1998, **180**, 3209-3217.
49. G. Leclerc, S. P. Wang and B. Ely, *J. Bacteriol.*, 1998, **180**, 5010-5019.
50. C. Lindenthal and E. A. Elsinghorst, *Infect. Immun.*, 1999, **67**, 4084-4091.
51. C. M. Szymanski, R. Yao, C. P. Ewing, T. J. Trust and P. Guerry, *Mol. Microbiol.*, 1999, **32**, 1022-1030.
52. I. Benz and M. A. Schmidt, *Mol. Microbiol.*, 2001, **40**, 1403-1413.
53. C. Moormann, I. Benz and M. A. Schmidt, *Infect. Immun.*, 2002, **70**, 2264-2270.
54. M. Wacker, D. Linton, P. G. Hitchen, M. Nita-Lazar, S. M. Haslam, S. J. North, M. Panico, H. R. Morris, A. Dell, B. W. Wren and M. Aebi, *Science (Washington, DC, U. S.)*, 2002, **298**, 1790-1793.
55. N. M. Young, J.-R. Brisson, J. Kelly, D. C. Watson, L. Tessier, P. H. Lanthier, H. C. Jarrell, N. Cadotte, F. St. Michael, E. Aberg and C. M. Szymanski, *J. Biol. Chem.*, 2002, **277**, 42530-42539.
56. P. Thibaul, S. M. Logan, J. F. Kelly, J.-R. Brisson, C. P. Ewing, T. J. Trust and P. Guerry, *J. Biol. Chem.*, 2001, **276**, 34862-34870.
57. T. Angata and A. Varki, *Chem. Rev. (Washington, D. C.)*, 2002, **102**, 439-469.
58. A. K. Sundaram, L. Pitts, K. Muhammad, J. Wu, M. Betenbaugh, R. W. Woodard and W. F. Vann, *Biochem. J.*, 2004, **383**, 83-89.
59. M. E. Tanner, *Bioorg. Chem.*, 2005, **33**, 216-228.
60. W. F. Vann, D. A. Daines, A. S. Murkin, M. E. Tanner, D. O. Chaffin, C. E. Rubens, J. Vionnet and R. P. Silver, *J. Bacteriol.*, 2004, **186**, 706-712.
61. J. Gunawan, D. Simard, M. Gilbert, A. L. Lovering, W. W. Wakarchuk, M. E. Tanner and N. C. J. Strynadka, *J. Biol. Chem.*, 2005, **280**, 3555-3563.
62. J. Hao, W. F. Vann, S. Hinderlich and M. Sundaramoorthy, *Biochem. J.*, 2006, **397**, 195-201.
63. F. Liu, H. J. Lee, N. C. J. Strynadka and M. E. Tanner, *Biochemistry*, 2009, **48**, 9194-9201.
64. D. J. Weitz and M. D. Bednarski, *J. Org. Chem.*, 1989, **54**, 4957-4959.
65. S. Vorwerk and A. Vasella, *Angew. Chem., Int. Ed.*, 1998, **37**, 1732-1734.
66. L. A. Paquette, T. M. Mitzel, M. B. Isaac, C. F. Crasto and W. W. Schomer, *J. Org. Chem.*, 1997, **62**, 4293-4301.
67. T.-H. Chan and M.-C. Lee, *J. Org. Chem.*, 1995, **60**, 4228-4232.
68. W. K. Chou, S. Dick, W. W. Wakarchuk and M. E. Tanner, *J. Biol. Chem.*, 2005, **280**, 35922-35928.
69. M. R. Webb, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 4884-4887.
70. A. M. Gil-Serrano, M. A. Rodriguez-Carvajal, P. Tejero-Mateo, J. L. Espartero, M. Menendez, J. Corzo, J. E. Ruiz-Sainz and A. M. Buendia-Claveria, *Biochem. J.*, 1999, **342**, 527-535.
71. S. M. Logan, *Microbiology (Reading, U. K.)*, 2006, **152**, 1249-1262.

72. M. Zunk and M. J. Kiefel, *RSC Adv.*, 2014, **4**, 3413-3421.
73. J. L. Parker, M. J. Day-Williams, J. M. Tomas, G. P. Stafford and J. G. Shaw, *MicrobiologyOpen*, 2012, **1**, 149-160.
74. I. C. Schoenhofen, E. Vinogradov, D. M. Whitfield, J.-R. Brisson and S. M. Logan, *Glycobiology*, 2009, **19**, 715-725.
75. D. J. McNally, A. J. Aubry, J. P. M. Hui, N. H. Khieu, D. Whitfield, C. P. Ewing, P. Guerry, J.-R. Brisson, S. M. Logan and E. C. Soo, *J. Biol. Chem.*, 2007, **282**, 14463-14475.
76. D. J. McNally, J. P. M. Hui, A. J. Aubry, K. K. K. Mui, P. Guerry, J.-R. Brisson, S. M. Logan and E. C. Soo, *J. Biol. Chem.*, 2006, **281**, 18489-18498.
77. I. C. Schoenhofen, D. J. McNally, E. Vinogradov, D. Whitfield, N. M. Young, S. Dick, W. W. Wakarchuk, J.-R. Brisson and S. M. Logan, *J. Biol. Chem.*, 2006, **281**, 723-732.
78. I. C. Schoenhofen, D. J. McNally, J.-R. Brisson and S. M. Logan, *Glycobiology*, 2006, **16**, 8C-14C.
79. D. J. McNally, I. C. Schoenhofen, R. S. Houliston, N. H. Khieu, D. M. Whitfield, S. M. Logan, H. C. Jarrell and J.-R. Brisson, *ChemMedChem*, 2008, **3**, 55-59.
80. P. Guerry, C. P. Ewing, M. Schirm, M. Lorenzo, J. Kelly, D. Pattarini, G. Majam, P. Thibault and S. Logan, *Mol. Microbiol.*, 2006, **60**, 299-311.
81. J. P. Morrison, I. C. Schoenhofen and M. E. Tanner, *Bioorg. Chem.*, 2008, **36**, 312-320.
82. I. C. Schoenhofen, V. V. Lunin, J.-P. Julien, Y. Li, E. Ajamian, A. Matte, M. Cygler, J.-R. Brisson, A. Aubry, S. M. Logan, S. Bhatia, W. W. Wakarchuk and N. M. Young, *J. Biol. Chem.*, 2006, **281**, 8907-8916.
83. F. Liu and M. E. Tanner, *J. Biol. Chem.*, 2006, **281**, 20902-20909.
84. E. S. Rangarajan, A. Proteau, Q. Cui, S. M. Logan, Z. Potetinova, D. Whitfield, E. O. Purisima, M. Cygler, A. Matte, T. Sulea and I. C. Schoenhofen, *J. Biol. Chem.*, 2009, **284**, 20989-21000.
85. G. M. Blackburn, *Chem. Ind. (London)*, 1981, 134-138.
86. T. C. Myers, K. Nakamura and J. W. Flesher, *J. Am. Chem. Soc.*, 1963, **85**, 3292-3295.
87. N. R. Glover and A. S. Tracey, *Biochemistry*, 1999, **38**, 5256-5271.
88. T. R. Burke, Jr., B. Ye, X. Yan, S. Wang, Z. Jia, L. Chen, Z.-Y. Zhang and D. Barford, *Biochemistry*, 1996, **35**, 15989-15996.
89. D. B. Berkowitz and M. Bose, *J. Fluorine Chem.*, 2001, **112**, 13-33.
90. R. Engel, *Chem. Rev.*, 1977, **77**, 349-367.
91. G. A. Patani and E. J. LaVoie, *Chem. Rev. (Washington, D. C.)*, 1996, **96**, 3147-3176.
92. D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609-16644.
93. R. Waschbuesch, J. Carran, A. Marinetti and P. Savignac, *Chem. Rev. (Washington, D. C.)*, 1997, **97**, 3401-3423.
94. K. Moonen, I. Laureyn and C. V. Stevens, *Chem. Rev. (Washington, DC, U. S.)*, 2004, **104**, 6177-6215.
95. F. Palacios, C. Alonso and J. M. De los Santos, *Chem. Rev. (Washington, DC, U. S.)*, 2005, **105**, 899-931.
96. D. O'Hagan and H. S. Rzepa, *Chem. Commun. (Cambridge)*, 1997, DOI: 10.1039/a604140j, 645-652.
97. K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev. (Washington, DC, U. S.)*, 2004, **104**, 1-16.
98. D. M. Lemal, *J. Org. Chem.*, 2004, **69**, 1-11.
99. P. Jeschke, *ChemBioChem*, 2004, **5**, 570-589.
100. C. M. Timperley and W. E. White, *J. Fluorine Chem.*, 2003, **123**, 65-70.
101. M. Hoffmann and J. Rychlewski, *Int. J. Quantum Chem.*, 2002, **89**, 419-427.
102. C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303-319.
103. C. E. McKenna and P.-D. Shen, *J. Org. Chem.*, 1981, **46**, 4573-4576.
104. G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1119-1125.

105. R. D. Chambers, D. O'Hagan, R. B. Lamont and S. C. Jain, *J. Chem. Soc., Chem. Commun.*, 1990, DOI: 10.1039/c39900001053, 1053-1054.
106. J. Nieschalk and D. O'Hagan, *J. Chem. Soc., Chem. Commun.*, 1995, DOI: 10.1039/c39950000719, 719-720.
107. G. R. J. Thatcher and A. S. Campbell, *J. Org. Chem.*, 1993, **58**, 2272-2281.
108. D. R. Budman, *Semin. Oncol.*, 1996, **23**, 8-14.
109. D. L. Jakeman, A. J. Ivory, M. P. Williamson and G. M. Blackburn, *J. Med. Chem.*, 1998, **41**, 4439-4452.
110. J. D. Dunitz and R. Taylor, *Chem. - Eur. J.*, 1997, **3**, 89-98.
111. H. Plenio and R. Diodone, *Chem. Ber./Recl.*, 1997, **130**, 633-640.
112. J. A. K. Howard, V. J. Hoy, D. O'Hagan and G. T. Smith, *Tetrahedron*, 1996, **52**, 12613-12622.
113. D. P. Phillion and D. G. Cleary, *J. Org. Chem.*, 1992, **57**, 2763-2764.
114. T. R. Burke, Jr., H. K. Kole and P. P. Roller, *Biochem. Biophys. Res. Commun.*, 1994, **204**, 129-134.
115. H. Chen, L.-N. Cong, Y. Li, Z.-J. Yao, L. Wu, Z.-Y. Zhang, T. R. Burke, Jr. and M. J. Quon, *Biochemistry*, 1999, **38**, 384-389.
116. D. B. Berkowitz, Q. Shen and J.-H. Maeng, *Tetrahedron Lett.*, 1994, **35**, 6445-6448.
117. D. B. Berkowitz, M. Eggen, Q. Shen and R. K. Shoemaker, *J. Org. Chem.*, 1996, **61**, 4666-4675.
118. Y. Higashimoto, S. i. Saito, X.-H. Tong, A. Hong, K. Sakaguchi, E. Appella and C. W. Anderson, *J. Biol. Chem.*, 2000, **275**, 23199-23203.
119. S. Halazy, A. Ehrhard and C. Danzin, *J. Am. Chem. Soc.*, 1991, **113**, 315-317.
120. S. Halazy, A. Ehrhard, A. Eggenspiller, V. Bergess-Gross and C. Danzin, *Tetrahedron*, 1996, **52**, 177-184.
121. N. A. Caplan, C. I. Pogson, D. J. Hayes and G. M. Blackburn, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 515-520.
122. E. P. Garvey, G. T. Lowen and M. R. Almond, *Biochemistry*, 1998, **37**, 9043-9051.
123. S. F. Wnuk and M. J. Robins, *J. Am. Chem. Soc.*, 1996, **118**, 2519-2520.
124. W. Chen, M. T. Flavin, R. Filler and Z.-Q. Xu, *Tetrahedron Lett.*, 1996, **37**, 8975-8978.
125. T. Yokomatsu, T. Yamagishi, K. Matsumoto and S. Shibuya, *Tetrahedron*, 1996, **52**, 11725-11738.
126. T. R. Burke, Jr., M. S. Smyth, M. Nomizu, A. Otaka and P. R. Roller, *J. Org. Chem.*, 1993, **58**, 1336-1340.
127. G. M. Blackburn and S. P. Langston, *Tetrahedron Lett.*, 1991, **32**, 6425-6428.
128. A. S. Campbell and G. R. J. Thatcher, *Tetrahedron Lett.*, 1991, **32**, 2207-2210.
129. G. M. Blackburn, M. J. Guo, S. P. Langston and G. E. Taylor, *Tetrahedron Lett.*, 1990, **31**, 5637-5640.
130. G. M. Blackburn and A. Rashid, *J. Chem. Soc., Chem. Commun.*, 1988, DOI: 10.1039/C39880000317, 317-319.
131. G. M. Blackburn, T. D. Perree, A. Rashid, C. Bisbal and B. Lebleu, *Chem. Scr.*, 1986, **26**, 21-24.
132. G. M. Blackburn, F. Eckstein, D. E. Kent and T. D. Perree, *Nucleosides Nucleotides*, 1985, **4**, 165-167.
133. R. E. Parks, Jr. and R. P. Agarwal, 1972.
134. I. S. Kazmers, B. S. Mitchell, P. E. Dadonna, L. L. Wotring, L. B. Townsend and W. N. Kelley, *Science (Washington, D. C., 1883-)*, 1981, **214**, 1137-1139.
135. R. B. Gilbertsen and J. C. Sircar, 1990.
136. J. D. Stoeckler, R. P. Agarwal, K. C. Agarwal, K. Schmid and R. E. Parks, Jr., *Biochemistry*, 1978, **17**, 278-283.

137. J. D. Stoeckler, J. B. Ryden, R. E. Parks, Jr., M. Y. Chu, M. I. Lim, W. Y. Ren and R. S. Klein, *Cancer Res*, 1986, **46**, 1774-1778.
138. P. E. Daddona, W. P. Wiesmann, W. Milhouse, J. W. Chern, L. B. Townsend, M. S. Hershfield and H. K. Webster, *J. Biol. Chem.*, 1986, **261**, 11667-11673.
139. J. V. Tuttle and T. A. Krenitsky, *J. Biol. Chem.*, 1984, **259**, 4065-4069.
140. T. A. Krenitsky, J. V. Tuttle, W. H. Miller, A. R. Moorman, G. F. Orr and L. Beauchamp, *J. Biol. Chem.*, 1990, **265**, 3066-3069.
141. C. E. Nakamura, S. H. Chu, J. D. Stoeckler and R. E. Parks, Jr., *Biochem. Pharmacol.*, 1986, **35**, 133-136.
142. G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Perkin Trans. 1*, 1986, 913-917.
143. K. E. Stremler and C. D. Poulter, *J. Am. Chem. Soc.*, 1987, **109**, 5542-5544.
144. S. A. Biller, C. Forster, E. M. Gordon, T. Harrity, W. A. Scott and C. P. Ciosek, Jr., *J. Med. Chem.*, 1988, **31**, 1869-1871.
145. R. D. Chambers, R. Jaouhari and D. O'Hagan, *Tetrahedron*, 1989, **45**, 5101-5108.
146. E. Differding, R. O. Duthaler, A. Krieger, G. M. Rueegg and C. Schmit, *Synlett*, 1991, DOI: 10.1055/s-1991-20739, 395-396.
147. G. S. Lal, *J. Org. Chem.*, 1993, **58**, 2791-2796.
148. S. D. Taylor, A. N. Dinaut, A. N. Thadani and Z. Huang, *Tetrahedron Lett.*, 1996, **37**, 8089-8092.
149. B. Iorga, F. Eymery and P. Savignac, *Synthesis*, 2000, DOI: 10.1055/s-2000-6375, 576-580.
150. B. Iorga, F. Eymery and P. Savignac, *Tetrahedron*, 1999, **55**, 2671-2686.
151. C. C. Kotoris, W. Wen, A. Lough and S. D. Taylor, *Perkin 1*, 2000, 1271-1281.
152. G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Chem. Commun.*, 1981, DOI: 10.1039/C39810000511, 511-513.
153. T. C. Sanders and G. B. Hammond, *J. Org. Chem.*, 1993, **58**, 5598-5599.
154. F. Benayoud, D. J. deMendonca, C. A. Digits, G. A. Moniz, T. C. Sanders and G. B. Hammond, *J. Org. Chem.*, 1996, **61**, 5159-5164.
155. F. Benayoud, L. Chen, G. A. Moniz, A. J. Zapata and G. B. Hammond, *Tetrahedron*, 1998, **54**, 15541-15554.
156. G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1982, DOI: 10.1039/C39820001270, 1270-1271.
157. G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1417-1424.
158. G. M. Blackburn and A. Rashid, *J. Chem. Soc., Chem. Commun.*, 1989, DOI: 10.1039/C39890000040, 40-41.
159. R. Waschbusch, J. Carran and P. Savignac, *Tetrahedron*, 1996, **52**, 14199-14216.
160. A. Keeney, J. Nieschalk and D. O'Hagan, *J. Fluorine Chem.*, 1996, **80**, 59-62.
161. G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1983, DOI: 10.1039/C39830000886, 886-888.
162. T. Tatsuoka, K. Imao and K. Suzuki, *Heterocycles*, 1986, **24**, 2133-2136.
163. J. J. Kulagowski, *Tetrahedron Lett.*, 1989, **30**, 3869-3872.
164. H. Tanaka, M. Fukui, K. Haraguchi, M. Masaki and T. Miyasaka, *Tetrahedron Lett.*, 1989, **30**, 2567-2570.
165. J. R. Falck, A. Abdali and S. J. Wittenberger, *J. Chem. Soc., Chem. Commun.*, 1990, DOI: 10.1039/c39900000953, 953-955.
166. Y.-H. Zhang, C.-F. Xu, J.-F. Li and C.-Y. Yuan, *Chin. J. Chem.*, 2003, **21**, 883-892.
167. Y. Gao, J. Wu, J. Xu, P. Zhang, G. Tang and Y. Zhao, *RSC Adv.*, 2014, **4**, 51776-51779.
168. A. Moriyama, S. Matsumura, M. Kuriyama and O. Onomura, *Tetrahedron: Asymmetry*, 2010, **21**, 810-824.
169. O. I. Kolodiazhnyi, *Russ. Chem. Rev.*, 2006, **75**, 227-253.
170. A. R. Sardarian and Z. Shahsavari-Fard, *Synth. Commun.*, 2007, **37**, 289-295.
171. O. Pamies and J. E. Baeckvall, *J. Org. Chem.*, 2003, **68**, 4815-4818.

172. A. Woschek, W. Lindner and F. Hammerschmidt, *Adv. Synth. Catal.*, 2003, **345**, 1287-1298.
173. F. Orsini and E. M. Lucci, *Tetrahedron Lett.*, 2005, **46**, 1909-1911.
174. T. Taniguchi, A. Idota, S.-i. Yokoyama and H. Ishibashi, *Tetrahedron Lett.*, 2011, **52**, 4768-4770.
175. Y. Zhang, J.-f. Li and C.-y. Yuan, *Tetrahedron*, 2003, **59**, 473-479.
176. P. G. Devitt and T. P. Kee, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3169-3182.
177. T. Yokomatsu, T. Yamagishi and S. Shibuya, *Tetrahedron: Asymmetry*, 1993, **4**, 1401-1404.
178. X. Wang, J. Zhang, Y. Liu and Y. Cui, *Bull. Chem. Soc. Jpn.*, 2014, **87**, 435-440.
179. E. V. Gryshkun, V. Nesterov and O. I. Kolodyazhnyi, *ARKIVOC (Gainesville, FL, U. S.)*, 2012, DOI: 10.3998/ark.5550190.0013.409, 100-117.
180. V. V. Nesterov and O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 2006, **17**, 1023-1026.
181. C. Meier and W. H. G. Laux, *Tetrahedron: Asymmetry*, 1995, **6**, 1089-1092.
182. C. Meier and W. H. G. Laux, *Tetrahedron*, 1996, **52**, 589-598.
183. M. Kitamura, M. Tokunaga, T. Pham, W. D. Lubell and R. Noyori, *Tetrahedron Lett.*, 1995, **36**, 5769-5772.
184. M. Kitamura, M. Tokunaga and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 2931-2932.
185. K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y. D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science (Washington, D. C., 1883-)*, 1986, **231**, 1108-1117.
186. T. A. Nguyen, *Top. Curr. Chem.*, 1980, **88**, 145-162.
187. R. Noyori, M. Tokunaga and M. Kitamura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 36-56.
188. R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475-1490.
189. V. Ratovelomanana-Vidal and J.-P. Genet, *Can. J. Chem.*, 2000, **78**, 846-851.
190. K. Faber, *Chem. - Eur. J.*, 2001, **7**, 5004-5010.
191. H. Pellissier, *Tetrahedron*, 2003, **59**, 8291-8327.
192. R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito and a. et, *J. Am. Chem. Soc.*, 1989, **111**, 9134-9135.
193. J. P. Genet, C. Pinel, S. Mallart, S. Juge, S. Thorimbert and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1991, **2**, 555-567.
194. I. Gautier, V. Ratavelomanana-Vidal, P. Savignac and J.-P. Genet, *Tetrahedron Lett.*, 1996, **37**, 7721-7724.
195. J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal and J. P. Genet, *Tetrahedron*, 2001, **57**, 2563-2568.
196. X. Tao, W. Li, X. Li, X. Xie and Z. Zhang, *Org. Lett.*, 2013, **15**, 72-75.
197. X. Tao, W. Li, X. Ma, X. Li, W. Fan, L. Zhu, X. Xie and Z. Zhang, *J. Org. Chem.*, 2012, **77**, 8401-8409.
198. S.-M. Son and H.-K. Lee, *J. Org. Chem.*, 2014, **79**, 2666-2681.
199. P. Merino, *Org. React. (Hoboken, NJ, U. S.)*, 2015, **87**, 1-256.
200. T. Yokomatsu, K. Suemune, T. Yamagishi and S. Shibuya, *Synlett*, 1995, DOI: 10.1055/s-1995-5103, 847-849.
201. G. Borg, M. Chino and J. A. Ellman, *Tetrahedron Lett.*, 2001, **42**, 1433-1435.
202. P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1-26.
203. J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581-1590.
204. G. Snatzke, *Berichte der Bunsengesellschaft für physikalische Chemie*, 1982, **86**, 1087-1087.
205. E. M. Vogl, H. Groger and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1570-1577.
206. S. Arrasate, E. Lete and N. Sotomayor, *Tetrahedron: Asymmetry*, 2001, **12**, 2077-2082.
207. D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580-2627.
208. J. E. Clifton, I. Collins, P. Hallett, D. Hartley, L. H. C. Lunts and P. D. Wicks, *J. Med. Chem.*, 1982, **25**, 670-679.
209. R. M. Barmore, S. R. Logan and B. C. Van Wagenen, *Tetrahedron Lett.*, 1998, **39**, 3451-3454.

210. J. W. Canary, C. S. Allen, J. M. Castagnetto and Y. Wang, *J. Am. Chem. Soc.*, 1995, **117**, 8484-8485.
211. C. M. Cain, R. P. C. Cousins, G. Coumbarides and N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523-544.
212. R. Shirai, M. Tanaka and K. Koga, *J. Am. Chem. Soc.*, 1986, **108**, 543-545.
213. R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki and K. Koga, *Tetrahedron*, 1997, **53**, 5963-5972.
214. R. Shirai, K. Aoki, D. Sato, H.-D. Kim, M. Murakata, T. Yasukata and K. Koga, *Chem. Pharm. Bull.*, 1994, **42**, 690-693.
215. E. Curthbertson, P. O'Brien and T. D. Towers, *Synthesis*, 2001, DOI: 10.1055/s-2001-12768, 693-695.
216. N. S. Simpkins, *Pure Appl. Chem.*, 1996, **68**, 691-694.
217. T. P. Yoon and E. N. Jacobsen, *Science (Washington, DC, U. S.)*, 2003, **299**, 1691-1693.
218. I. Atodiresei, I. Schiffers and C. Bolm, *Tetrahedron: Asymmetry*, 2006, **17**, 620-633.
219. C. Mazet, *Angew. Chem., Int. Ed.*, 2012, **51**, 305.
220. Y. L. Bennani and S. Hanessian, *Chem. Rev. (Washington, D. C.)*, 1997, **97**, 3161-3195.
221. D. Stead, P. O'Brien and A. Sanderson, *Org. Lett.*, 2008, **10**, 1409-1412.
222. V. M. Foley, R. Cano and G. P. McGlacken, *Tetrahedron: Asymmetry*, 2016, **27**, 1160-1167.
223. Y. Zhang, C. Yuan and Z. Li, *Tetrahedron*, 2002, **58**, 2973-2978.
224. P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 2001, DOI: 10.1039/a907926b, 95-113.
225. P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439-1458.
226. M. J. Bassindale, J. J. Crawford, K. W. Henderson and W. J. Kerr, *Tetrahedron Lett.*, 2004, **45**, 4175-4179.
227. K. W. Henderson, W. J. Kerr and J. H. Moir, *Tetrahedron*, 2002, **58**, 4573-4587.
228. D. Mueller, L. Guenee and A. Alexakis, *Eur. J. Org. Chem.*, 2013, **2013**, 6335-6343.
229. A. Alexakis, S. Gille, F. Prian, S. Rosset and K. Ditrich, *Tetrahedron Lett.*, 2004, **45**, 1449-1451.
230. S. Guizzetti, M. Benaglia, C. Biaggi and G. Celentano, *Synlett*, 2010, DOI: 10.1055/s-0029-1218541, 134-136.
231. F. Orsini and A. Caselli, *Tetrahedron Lett.*, 2002, **43**, 7255-7257.
232. K. Mikami and M. Yamaoka, *Tetrahedron Lett.*, 1998, **39**, 4501-4504.
233. J. A. Buonomo, C. G. Eiden and C. C. Aldrich, *Chem. - Eur. J.*, 2017, **23**, 14434-14438.
234. E. A. Mash, K. A. Nelson, S. Van Deusen and S. B. Hemperly, *Org. Synth.*, 1990, **68**, 92-103.
235. F. Toda and K. Tanaka, *Tetrahedron Lett.*, 1988, **29**, 551-554.
236. X. Gao, J. Han and L. Wang, *Org. Lett.*, 2015, **17**, 4596-4599.
237. T. Steinbach, C. Wahlen and F. R. Wurm, *Polym. Chem.*, 2015, **6**, 1192-1202.
238. A. Pichota, V. Gramlich, H.-U. Bichsel, T. Styner, T. Knoepfel, R. Wuensch, T. Hintermann, W. B. Schweizer, A. K. Beck and D. Seebach, *Helv. Chim. Acta*, 2012, **95**, 1273-1302.
239. *Organic Syntheses*, 1999, **76**, 12.
240. G. T. Giuffredi, S. Purser, M. Sawicki, A. L. Thompson and V. Gouverneur, *Tetrahedron: Asymmetry*, 2009, **20**, 910-920.
241. J. E. D. Kirkham, T. D. L. Courtney, V. Lee and J. E. Baldwin, *Tetrahedron*, 2005, **61**, 7219-7232.
242. R. R. Milburn, K. McRae, J. Chan, J. Tedrow, R. Larsen and M. Faul, *Tetrahedron Lett.*, 2009, **50**, 870-872.
243. M. Zhou, Y. Zhou and Q. Song, *Chem. - Eur. J.*, 2015, **21**, 10654-10659.
244. G. P. Luke, C. K. Seekamp, Z.-Q. Wang and B. L. Chenard, *J. Org. Chem.*, 2008, **73**, 6397-6400.
245. M. Zhou, M. Chen, Y. Zhou, K. Yang, J. Su, J. Du and Q. Song, *Org. Lett.*, 2015, **17**, 1786-1789.

246. X. Li, A. Bhandari, C. P. Holmes and A. K. Szardenings, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4301-4306.
247. P. Zhou, B. Hu, L. Li, K. Rao, J. Yang and F. Yu, *J. Org. Chem.*, 2017, **82**, 13268-13276.
248. W. Liang, Z. Zhang, D. Yi, Q. Fu, S. Chen, L. Yang, F. Du, J. Ji and W. Wei, *Chin. J. Chem.*, 2017, **35**, 1378-1382.
249. Y. Zhou, C. Rao, S. Mai and Q. Song, *J. Org. Chem.*, 2016, **81**, 2027-2034.
250. V. Gutierrez, E. Mascaro, F. Alonso, Y. Moglie and G. Radivoy, *RSC Adv.*, 2015, **5**, 65739-65744.
251. N. Yi, R. Wang, H. Zou, W. He, W. Fu and W. He, *J. Org. Chem.*, 2015, **80**, 5023-5029.
252. P. Beier, A. V. Alexandrova, M. Zibinsky and G. K. Surya Prakash, *Tetrahedron*, 2008, **64**, 10977-10985.
253. M. Obayashi, E. Ito, K. Matsui and K. Kondo, *Tetrahedron Letters*, 1982, **23**, 2323-2326.
254. T. Jeanmaire, Y. Hervaud and B. Boutevin, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1137-1145.
255. Y. Xu, S. A. Lee, T. G. Kutateladze, D. Sbrissa, A. Shisheva and G. D. Prestwich, *J. Am. Chem. Soc.*, 2006, **128**, 885-897.
256. M. P. Teulade, P. Savignac, E. E. Aboujaoude and N. Collignon, *J. Organomet. Chem.*, 1986, **312**, 283-295.
257. W. Gruber, *Can. J. Chem.*, 1953, **31**, 564-568.
258. C. J. Cooper, M. D. Jones, S. K. Brayshaw, B. Sonnex, M. L. Russell, M. F. Mahon and D. R. Allan, *Dalton Trans.*, 2011, **40**, 3677-3682.
259. J.-C. Kizirian, N. Cabello, L. Pinchard, J.-C. Caille and A. Alexakis, *Tetrahedron*, 2005, **61**, 8939-8946.
260. E. A. Wappes, S. C. Fosu, T. C. Chopko and D. A. Nagib, *Angew. Chem., Int. Ed.*, 2016, **55**, 9974-9978.
261. A. Mohan, V. Ramkumar and S. Sankararaman, *J. Organomet. Chem.*, 2015, **799-800**, 115-121.
262. M. Yamashita, Y. Soeda, N. Suzuki, M. Yamada, K. Tsunekawa, T. Oshikawa and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1871-1872.
263. P. Jumaryatno, K. Rands-Trevor, J. T. Blanchfield and M. J. Garson, *ARKIVOC (Gainesville, FL, U. S.)*, 2007, DOI: 10.3998/ark.5550190.0008.713, 157-166.
264. J. Kulisch, M. Nieger, F. Stecker, A. Fischer and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2011, **50**, 5564-5567, S5564/5561-S5564/5534.
265. A. Chardon, T. Mohy El Dine, R. Legay, M. De Paolis, J. Rouden and J. Blanchet, *Chem. - Eur. J.*, 2017, **23**, 2005-2009.
266. G. Otani and S. Yamada, *Chem. Pharm. Bull.*, 1973, **21**, 2112-2118.
267. J. Xin, L. Chang, Z. Hou, D. Shang, X. Liu and X. Feng, *Chem. - Eur. J.*, 2008, **14**, 3177-3181.
268. D. Lu, Y. Gong and W. Wang, *Adv. Synth. Catal.*, 2010, **352**, 644-650.
269. R. M. Lanigan, V. Karaluka, M. T. Sabatini, P. Starkov, M. Badland, L. Boulton and T. D. Sheppard, *Chem. Commun. (Cambridge, U. K.)*, 2016, **52**, 8846-8849.
270. K. N. Singh, P. Singh, P. Singh, N. Lal and S. K. Sharma, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4225-4228.
271. M. E. Due-Hansen, S. K. Pandey, E. Christiansen, R. Andersen, S. V. F. Hansen and T. Ulven, *Org. Biomol. Chem.*, 2016, **14**, 430-433.
272. X.-M. Hu, D.-X. Zhang, S.-Y. Zhang and P.-A. Wang, *RSC Adv.*, 2015, **5**, 39557-39564.
273. F. Kelleher, S. Kelly, J. Watts and V. McKee, *Tetrahedron*, 2010, **66**, 3525-3536.
274. Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588-600.
275. T. Sone, K. Hiroi and S. Yamada, *Chem. Pharm. Bull.*, 1973, **21**, 2331-2335.
276. K. Nagasawa, H. Takahashi, K. Hiroi and S. Yamada, *Yakugaku Zasshi*, 1975, **95**, 33-45.
277. U. Koehn, M. Klopfleisch, H. Goerls and E. Anders, *Tetrahedron: Asymmetry*, 2006, **17**, 811-818.

278. M. Asami, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 721-727.
279. T. Mukaiyama, S. Kobayashi and T. Sano, *Tetrahedron*, 1990, **46**, 4653-4662.
280. M. Asami, H. Ohno, S. Kobayashi and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1869-1873.
281. V. N. Wakchaure and B. List, *Angew. Chem., Int. Ed.*, 2016, **55**, 15775-15778.
282. S. Kotani, S. Hashimoto and M. Nakajima, *Tetrahedron*, 2007, **63**, 3122-3132.