Allyl Fluorides: New Syntheses and Enantioselective Manipulations

by

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Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date:

Acknowledgements

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Finally, I would like to sincerely thank all my friends and family for their support over the years.

Abbreviations

^{o}C	Degrees Celsius
$(DHQ)_2$	1,4-Bis(9-O-dihydroquinine)
$(DHQD)_2$	1,4-Bis(9-O-dihydroquinidine)
Å	Angstrom(s)
Ac	Acetate
AD	Asymmetric dihydroxylation
AQN	Anthraquinone
B	Base
Bu	Butyl
Bn	Benzyl
cf.	*Confer*
Cbz	Carboxybenzyl
$CDCl_3$	Deuterated chloroform
CD_2Cl_2	Deuterated dichloromethane
COSY	Correlation spectroscopy
CM	Cross metathesis
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
de	Diastereoisomeric excess
dr	Diastereoisomeric ratio
DET	Diethyl tartrate

DIPT	Di*iso*propyl tartrate
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
eq	Equivalents
et al.	*et alli*
Et	Ethyl
h	Hour(s)
IR	Infrared
J	Coupling constant
K	Kelvin
K_{222}	Kryptofix 222
L	Litre(s)
M	Molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	Methyl
min	Minute(s)
MeOD	Deuterated methanol
MHz	Megahertz
Mol	Mole(s)
m.p.	Melting point
NMO	*N*-Methylmorpholine *N*-oxide

NMR	Nuclear magnetic resonance
Ph	Phenyl
PHAL	Phthalazine
PHT	Pyrrolidone hydrotribromide
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	Parts per million
Pr	Propyl
Red-Al®	Bis(2-methoxyethoxy)aluminium hydride
Rf	Retention factor
RCM	Ring closing metathesis
RI	Refractive index
ROMP	Ring opening metathesis polymerisation
RT	Room temperature
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
SM	Starting material
S_N2	Bimolecular nucleophilic substitution
t-BuOH	2-Methyl-2-propanol
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

TMS	Trimethylsilyl
TREAT.HF	Triethylamine trishydrogen fluoride
Ts	Tosylate

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Abstract

Selectively mono-fluorinated sugars have been acknowledged as useful molecular tools for the study of sugar processing enzymes.[1] The small steric size of the fluorine atom coupled with its high electronegativity make fluorinated sugars ideal candidates to study structure relationships in carbohydrate architecture. We have identified the, as yet, under researched *de novo* route to fluorinated sugars, whereby the modern tools of asymmetric synthesis are applied to small highly functionalised fluorinated building blocks allowing the possibility of entire libraries of fluorinated sugar analogues to be generated in high enantiomeric excess from a single versatile fluorinated building block.[2]

We believe the allylic fluoride moiety represents one of the most versatile and useful functional groups for fluorinated building blocks of this nature. As such, ready access to compounds of this nature is required.

Firstly, this work describes the comparison of a new nucleophilic fluorination methodology developed within our laboratory using TBAF.$3H_2O$ and KHF_2,[3] against a recently reported fluorination reaction by Hou[4] on a small selection of simple allylic bromides. A potential fluorinated building block is then prepared and its compatability with a number of asymmetric dihydroxylation techniques assessed.

Secondly, the stereodivergent and stereoselective synthesis of all four diastereoisomers of a versatile C4 fluorinated building block is described. The development and optimisation of a new and facile method for the determination of ee's for these and other fluorinated substrates is also described.

Thirdly, a stereodivergent route to an analogous C4 fluorinated building block, *via* an unusual alkene inversion, developed within our laboratory, is examined in detail.[5]

Finally, the development, scope and limitations of a novel methodology for the generation of allylic fluorides using cross metathesis is described. A potentially versatile fluorinated building block is prepared *via* this method and its suitability as a fluorinated pentose precursor explored.

1. Introduction

1.1. Fluorine

Fluorine is not a rare element, ranking 13th in the order of most abundant elements in the Earth's crust, making it by far the most common of the halogens. The other halogens are rarer with chlorine 20th, bromine 46th and iodine 60th. Astatine is the rarest naturally occurring element with less than 30 g believed to be present in the Earth's crust.[6,7] Though fluorine is abundant in minerals (e.g. fluorite-CaF_2, cryolite-Na_3AlF_6 and fluorapatite-$Ca_5(PO_4)_3F$), naturally occurring organic fluorides are extremely rare; the first example of such a compound was not discovered until 1943 in a sample of *Dichapetalum cymosum*, a poisonous South African plant. The toxicity of this plant was later attributed to the presence of fluoroacetic acid, a metabolite in the organism.[8,9] Since then fluorine has been discovered as a component of only 13 secondary metabolites, of which eight are ω-fluorinated homologues of long-chain fatty acids found as co-metabolites in the seeds of the same plant. So effectively, only six discrete fluorinated natural products have been isolated excluding these fatty acids[10] and most of the metabolites discovered so far have been attributed to the metabolism of fluoroacetate.

However there are a few examples of more complex species, one being nucleocidin **1**, which contains a ribose moiety with a fluorine at C4 and is biosynthesised by *Streptomyces Calvus*, an organism obtained from an Indian soil sample.[11,12]

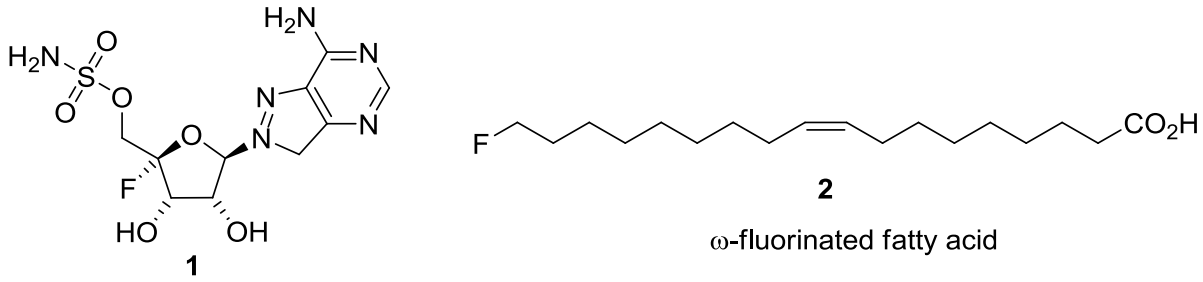
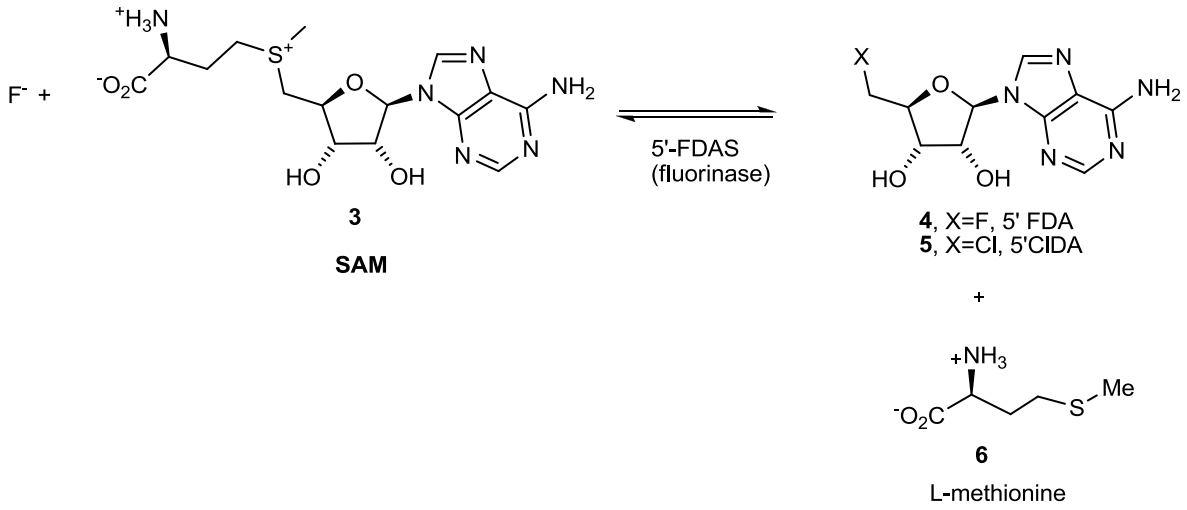


Figure 1

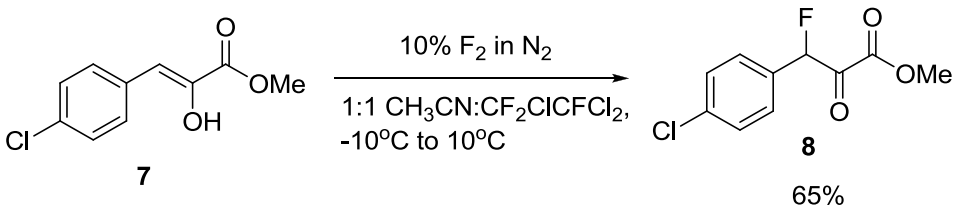
Recently a fluorination enzyme, 5′-fluoro-5′-deoxyadenosine synthetase (FDAS), was identified and isolated[13] from *Streptomyces Cattleya*. The enzyme catalyses the reaction between *S*-adenosyl-L-methionine (SAM) and fluoride ions to form L-methionine and 5′-fluoro-5′-deoxyadenosine (5′-FDA) (Scheme 1). As the k_{cat} is small, the reaction is slow, but the equilibrium products are favoured thermodynamically due to the formation of the strong C-F bond. The enzyme has been crystallized and its structure determined.[14] The enzyme works with the chloride as well as the fluoride ion.[15] Interestingly, there is no sequence match between the genome of the plant that produces FDAS and genomes from elsewhere in the plant kingdom, despite the fact that several plants have been reported to accumulate high concentrations of fluoroacetate and in some cases fluorocitrate and fluorooleic acid. This raises the possibility that biology may have evolved more than one catalytic strategy for F^- incorporation.



Scheme 1

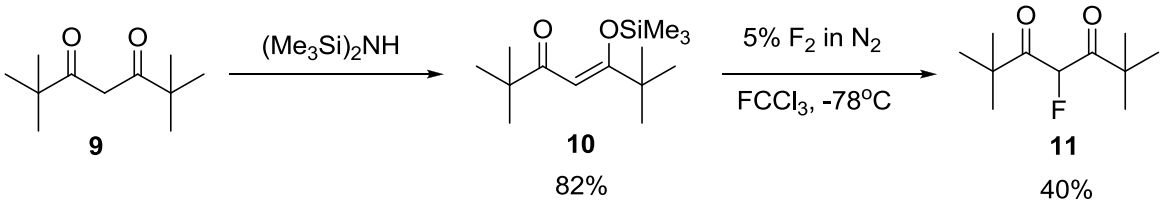
Although the mechanism of this fluorinase has been elucidated,[16] nature has provided little inspiration for fluorination methods in the laboratory, nor have complex inorganic fluorides found in the Earth's crust been useful as direct sources of fluorine for C-F bond formation.

Fluorine is the most electronegative element in the periodic table with a Pauling value of 4.0 (*cf.* O 3.4, Cl 3.2, H 2.2) and is by far the most reactive element.[17] Elemental fluorine is a powerful oxidant and is therefore extremely difficult to handle, although it has been used successfully as a reagent for the fluorination of a number of organic molecules. Tsushima and co-workers were successfully able to perform the direct fluorination of a number of pyruvic acid derivatives utilising fluorine gas, generating a number of compounds exhibiting activity towards pyridoxal dependent enzymes (Scheme 2).[18,19]



Scheme 2

Purrington and Bumgardner were able to perform similar reactions with fluorine gas to perform the monofluorination of β-diketones.[20] It was found that trimethylsilyl enol ethers can be selectively monofluorinated to form α-fluoroketones using dilute fluorine (Scheme 3).

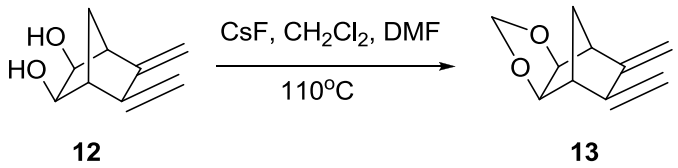


Scheme 3

Unfortunately, the extreme reactivity of fluorine also means it is often difficult to control the violence with which it reacts, and heavy dilution of the elemental fluorine with inert gases such as N_2 or He is required to "tame" the reagent. Nonetheless the practical difficulties and specialised equipment needed ensure elemental fluorine is seldom utilised as a reagent for direct fluorination; instead indirect methods are preferred.

The introduction of fluorine into molecules *via* nucleophilic substitution with the fluoride ion represents a difficult and yet intriguing research topic which will form the main focus of this thesis. The small size of F^- and its low polarisability contribute to make it more basic than nucleophilic. The fluoride ion has frequently been successfully

used as a base in organic synthesis,[21] for example in the synthesis of 1,3-dioxolanes from 1,2-cycloalkane diols.[22] The use of DMF as the solvent in this carbene reaction results in a "naked fluoride" ion acting as the base. These conditions can be successfully applied to even sensitive diols such as 5,6-dimethylidene-*exo,exo*-norbornanediol **12** (Scheme 4).



12 **13**

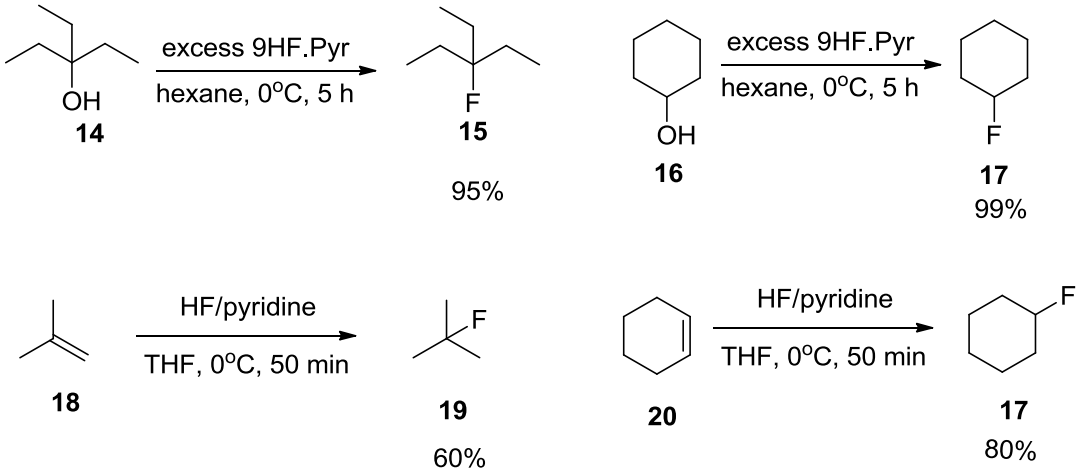
Scheme 4

1.2. Hydrogen fluoride

Hydrogen fluoride (HF) is a cheap and effective source of fluoride, and remains the reagent on which the vast majority of fluorination chemistry is based. HF both in its anhydrous form (and in concentrated solution) is extremely dangerous to work with; it is extremely toxic, corrosive to standard glassware and volatile (bp<20^{o}C), requiring reactions to be carried out under pressure. As a result amine complexes of HF, such as Olah's reagent (pyridine.9HF) or TREAT.HF (Et_3N.3HF), are often preferred due to their superior ease of handling.

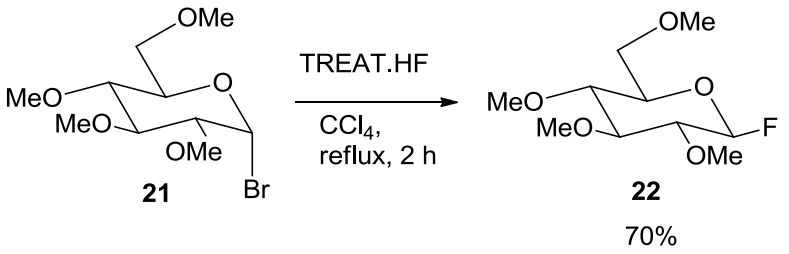
The first reported use of an HF complex with lower volatility than that of the parent anhydrous hydrogen fluoride was Hirschman's use of the tetrahydrofuran-hydrogen fluoride complex.[23] This led the way for a number of stable HF solutions with amines,[24] amides,[25] carbamic esters and acids,[26] trialkylphosphines[27] and alcohols[28] although these reagents proved to be very substrate specific. Pyridinium hydrofluoride is difficult to

prepare in contrast to other pyridinium halides; however the reaction of pyridine with anhydrous hydrogen fluoride gives rise to remarkably stable poly(hydrogen fluoride) solutions. The solution contains approximately 9 equivalents of HF to 1 equivalent of pyridine and is stable up to 55^{o}C, the poly(hydrogen fluoride) being in equilibrium with a small amount of free HF. Solutions with lower concentrations of HF can also be used when required. In the seminal paper published by Olah in 1979, the wide range of reactions achievable through the use of this reagent were outlined (Scheme 5).[29]



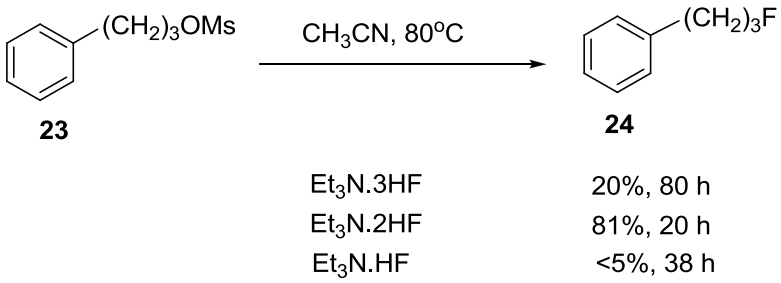
Schemes 5

In comparison to the pyridine based complexes TREAT.HF is significantly easier to use in the synthetic chemistry laboratory environment. It is a colourless liquid (bp 78^{o}C), weakly acidic and is compatible with standard borosilicate glassware. Although TREAT.HF is less nucleophilic than a number of other fluoride sources, it can be used successfully with reactive substrates (possessing particularly labile leaving groups), as demonstrated by Picq and co-workers in the synthesis of protected 1-deoxy-1-fluoro sugar **22** (Scheme 6).[30]



Scheme 6

The nucleophilicity of the reagent can be altered by varying the ratio of hydrogen fluoride to triethylamine; the variation in fluorinating ability appearing to be linked to the stability of the complexes (Scheme 7).[31]



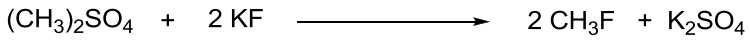
Scheme 7

Although HF remains the life blood of the fluorochemicals industry, the use of HF and its stable complexes on the laboratory scale is diminishing in favour of easier to handle and often more selective sources of fluoride.

1.3. Inorganic sources of fluoride

1.3.1. Alkali metal fluorides

Fluorinating agents based on alkali metal fluorides have been used for centuries, and were involved in some of the first syntheses of aliphatic fluorides; Dumas and Peligot formed methyl fluoride in 1835 by heating dimethyl sulfate with potassium fluoride (Scheme 8).[32]

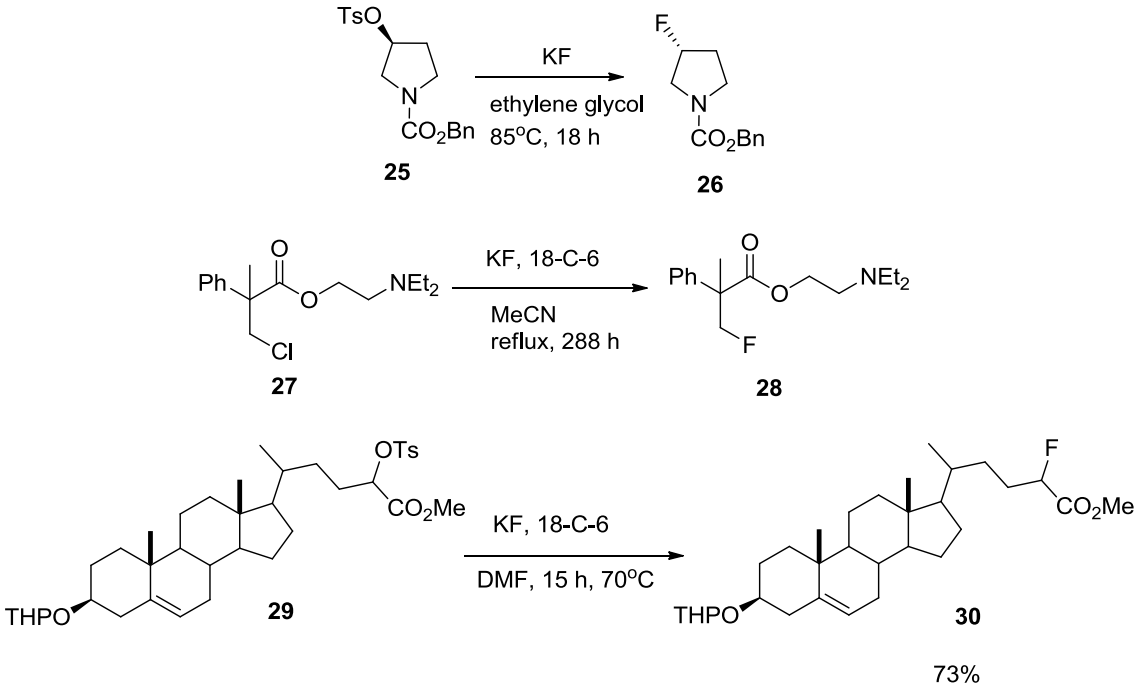


Scheme 8

These reagents are most commonly used for the substitution of a halogen with fluorine; this has been carried out for a wide range of such compounds including alkyl halides, aromatic halides and α-halo esters, amides and nitriles. The formation of the thermodynamically strong C-F bond (448 kJ/mol) is the main driving force of these reactions. The reactions are often performed in refluxing high boiling solvents which assists in the solubilisation of the inorganic fluorides. Anhydrous solvents are usually required as under these conditions, stray hydrogen bond formation to traces of water, caused by the high hydration energy of fluoride (515 kJ/mol), are minimised. This encourages the formation of what Liotta described as "naked fluoride."[33] Crown ethers are often used to assist in the solvation of inorganic fluoride by complexation in less polar solvents. The most popular and widely used alkali metal fluorides in carbon-fluorine bond forming reactions are KF and CsF.

1.3.1.1. Potassium fluoride

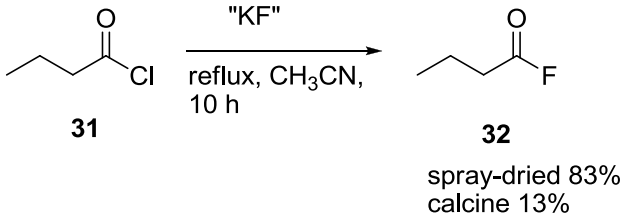
Potassium fluoride is only sparingly soluble in organic media and is usually employed in anhydrous, polar solvents (acetonitrile, DMF, glycols) when used without complexing agents. Despite this insolubility KF has been successfully used to achieve a diverse range of fluorination reactions (Scheme 9).[34,35]



Scheme 9

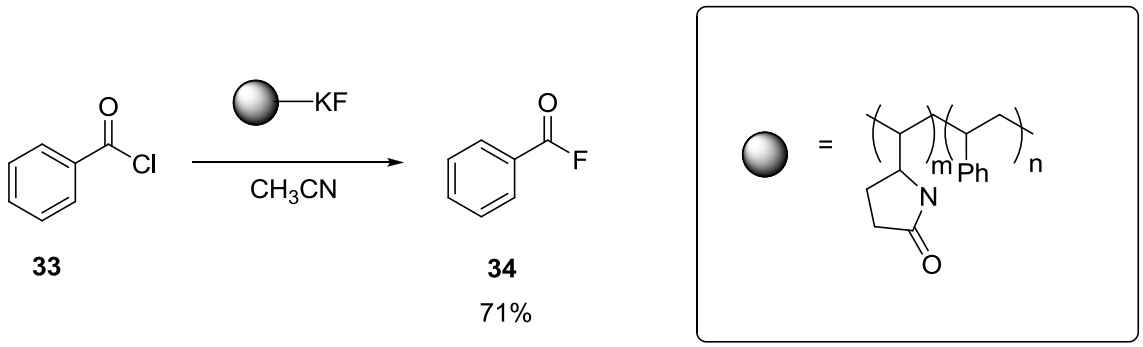
There are reports of modifications that improve the effectiveness of potassium fluoride as a reagent. 'Spray-dried' KF has been described which is reported to be less hygroscopic and more effective in fluorinations than calcine dried KF.[36] The advantage of spray-dried KF compared to calcine-dried material is attributed to the difference in particle size or surface area. Spray-dried KF was prepared using a stainless steel spray

drier; a 30% w/w solution of KF was sprayed and dried by a stream of heated air (300-500^{o}C) yielding KF with a particle size of 10-50 μm and a specific suface area of 1.3 m^2/g. Calcine-dried KF was produced by grinding commercial KF and baking at 250-300^{o}C yielding KF with a particle size of 200-300 μm and a specific surface area of 0.1 m^2/g. Ishikawa and co-workers observed considerably superior results with KF fluorinations using spray-dried material (Scheme 10).[36]



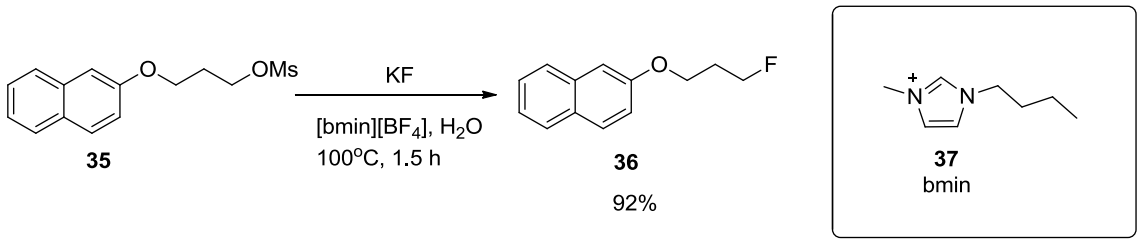
Scheme 10

The combination of potassium fluoride and calcium fluoride has been shown to be an effective heterogeneous fluorinating agent, showing superior activity than KF powder alone in certain reactions.[37] Benzyl bromide was converted to the corresponding fluoride in good yield (81%) using the KF/CaF_2 mixture (1:2 or 1:4 w/w) in acetonitrile at room temperature whereas CaF_2 or KF alone yielded only traces of product. A further benefit is the ability to remove the fluorinating reagent by filtration, as is the case with polymer supported KF. Liu has shown that KF supported on an organic polymer support shows comparable reactivity to KF supported on CaF_2 and superior fluorinating power to KF alone (Scheme 11).[38]



Scheme 11

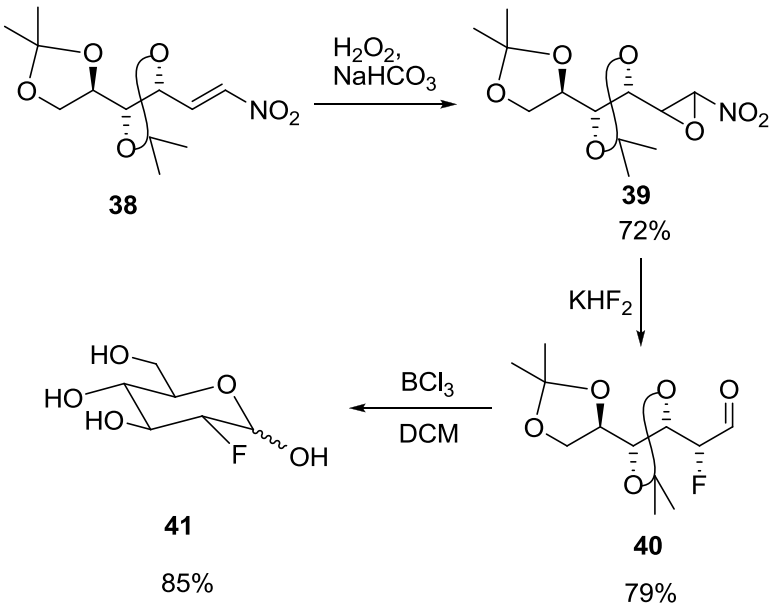
In addition, facile fluorination of some alkyl halides and mesylates was demonstrated using KF in the presence of an ionic liquid and water. The ionic liquid-water system was able not only to enhance the observed reactivity significantly (92% yield *cf.* trace of product) but reduce the formation of by-products (Scheme 12).[39] Although these results seem impressive at first sight, repetition of this methodology within our laboratory found that the ionic liquid system degrades rapidly (producing black tar like material) and work-up of the desired material was difficult.[3]



Scheme 12

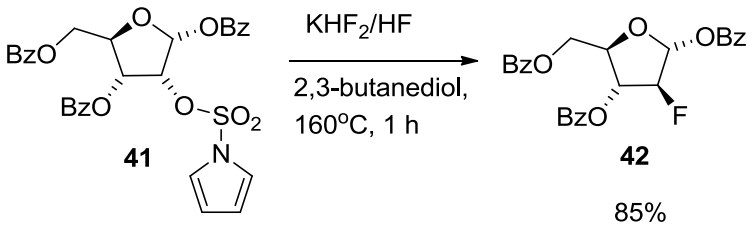
1.3.1.2. Potassium hydrogen difluoride

Commercially-available KHF_2, is another commonly used fluorinating agent consisting of the bifluoride anion (HF_2^-) and the potassium cation. This reagent has been used on its own as a fluorinating agent; Szarek used KHF_2 in a rapid and stereospecific synthesis of 2-deoxy-2-fluoro-D-glucose **41** (Scheme 13).[40]



Scheme 13

Potassium hydrogen difluoride can also be used effectively in combination with other reagents; for example Howell and co-workers were able to prepare the protected 2-deoxy-2-fluoro arabinofuranose **42** on a 1 mole scale using a mixture of KHF_2 and HF solution (Scheme 14).[41]



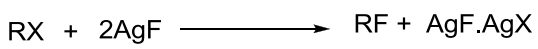
Scheme 14

1.3.1.3. Cesium fluoride

A more soluble yet expensive source of fluoride is CsF, which can be used as a reactive source of fluoride, or as a catalyst to enhance the reactivity of other fluoride sources. Benzyl fluoride was formed by heating the corresponding bromide in refluxing acetonitrile with CsF for 1.5 hours.[42] However, Clark and co-workers were able to show that the activity of CsF can be significantly enhanced by supporting it on calcium fluoride. With this reagent, the reaction time for benzyl fluoride formation was halved under these conditions.[42] In addition the nucleophilicity of CsF can be enhanced by "capping" with 18-crown-6 or dibenzo-24-crown-8 as shown by Harpp.[43]

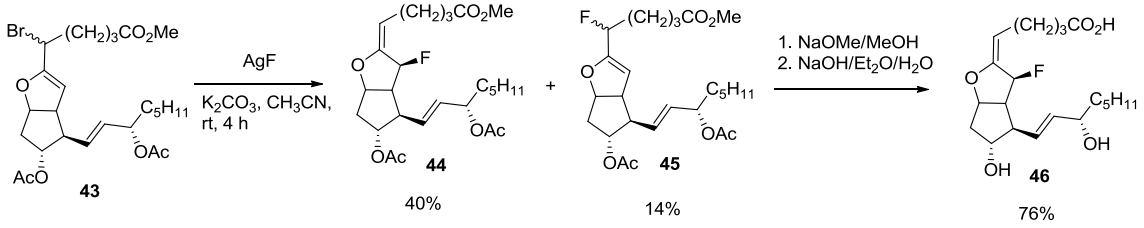
1.3.2. Silver fluoride

Silver (I) fluoride, having been first used by Moissan in the formation of organic fluorides in 1897 represents one of the 'classical' fluorinating reagents.[44] The reagent is much less basic than the alkali metal fluorides and is generally more selective as competing elimination reactions are minimised during nucleophilic substitution transformations. The obvious disadvantage of this reagent is the high cost; silver is a precious metal and two moles of silver fluoride are required to make one mole of product (Scheme 15).



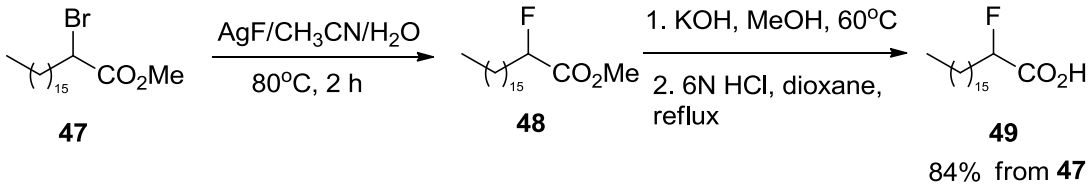
Scheme 15

Silver fluoride is often employed when displacement reactions on delicate systems are required, for example in Kurozumi's synthesis of chemically stable fluorinated PGI_2 analogues (Scheme **16**).[45]



Scheme 16

Much recent work has sought to modify the nucleophilicity of silver fluoride through various additives, in particular inorganic salts, or even water. Although water is believed to lower the nucleophilicity of F^- through hydrogen bonding, high yielding fluorinations have been achieved using "wet" silver fluoride.[46] Jensen was able to synthesise 2-fluorostearic acid **49** in an impressive 84% yield over two steps by modifying a previous procedure with water (Scheme 17); the same reaction gives a very poor 10-15% yield of the product under anhydrous conditions.

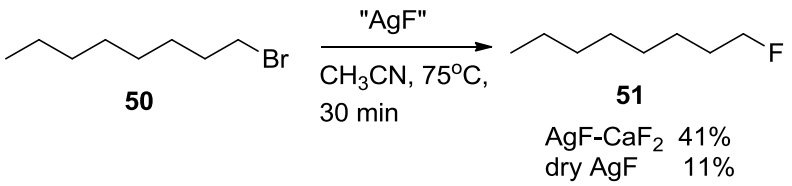


Scheme 17

The mechanism by which the presence of small quantities of water enhances the reactivity of silver fluoride is unknown, but similar results have been observed for other

fluorinating reagents. Clark and co-workers reported that incomplete drying of KF supported on CaF_2 results in an increase in reactivity. KF-CaF_2 dried at a temperature of 80^{o}C for 1 hour was more reactive than either undried material or KF-CaF_2 dried thoroughly at 280^{o}C for 16 hours.[42] However, it is worth noting that these observations lack detail (especially regarding the effectiveness of the drying techniques employed), and repetition with more vigorous quantification of the actual water content within the reagents is required before firm conclusions can be reached.

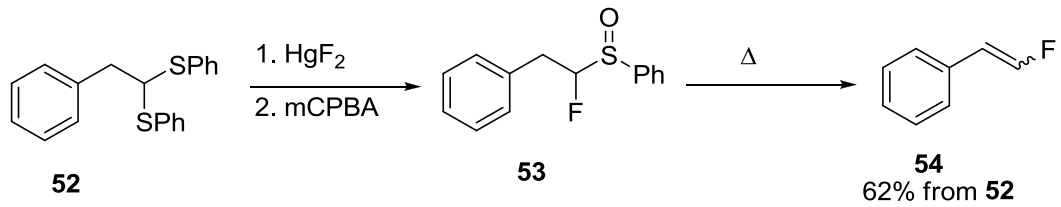
Indeed as appears to be common with most metal fluorides, the activity of silver fluoride as a fluorinating agent appears to be enhanced by combination with a solid support such as calcium fluoride (Scheme 18).[47] The rationale for this enhanced activity has been attributed to calcium fluoride's ability to act as an inert non-hydroxylated surface over which the metal fluoride could disperse without the loss of nucleophilicity observed with alumina or silica supports. The reagent was also observed to be significantly less hygroscopic; fluoride salts are often hygroscopic which poses practical difficulties. However, it should be noted that the increased yields achieved with this reagent are probably negated by the high cost of silver fluoride, especially on the industrial scale.



Scheme 18

1.3.3. Other inorganic fluorides

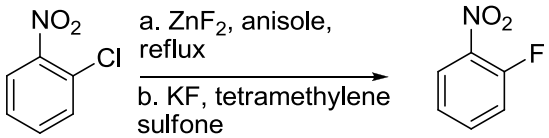
Although mercury (II) fluoride is a stable crystalline ionic solid its insolubility in most organic solvents has limited its use as a nucleophilic fluoride source in carbon-fluorine bond forming reactions. However, HgF_2 has been shown to be effective in the formation of α-fluoro sulfoxide **53**, precursors to vinyl fluorides (Scheme 19).[48,49]



52 **53** **54**
62% from **52**

Scheme 19

Another commercially available fluoride salt, ZnF_2 has also been explored as a nucleophilic source of the fluoride ion. Like mercury difluoride the high toxicity of zinc difluoride has limited its use in synthesis. However it has been shown to be effective in the fluorination of aromatic compounds where other more ubiquitous fluorination reagents have produced disappointing results (Scheme 20).[50-52]



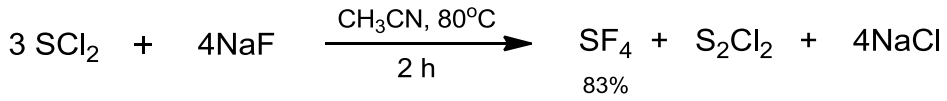
55 **56**
a. 49%
b. 7%

Scheme 20

1.4. Organic fluoride sources

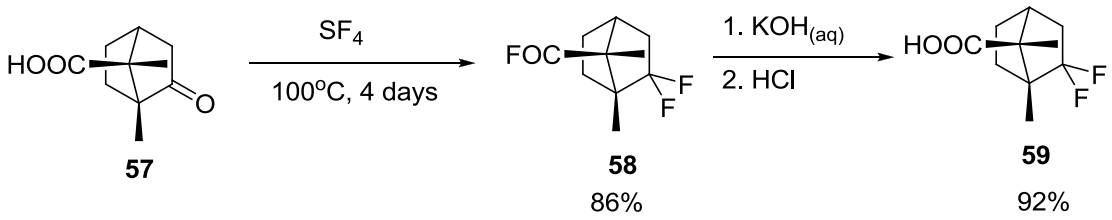
1.4.1. Sulfur-based species[53]

Sulfur fluorides have proved extremely effective sources of the fluoride ion, particularly for the replacement of oxygen functions with fluorine. Sulfur tetrafluoride (SF_4) is the simplest sulfur fluoride compound (SF_2 is unstable and disproportionates to form SF_4 and SSF_2) and is most commonly used to prepare *gem*-difluorinated compounds by the fluorination of ketones and aldehydes.[54] SF_4 can be prepared effectively by reacting sulfur chloride with sodium fluoride (Scheme 21).



Scheme 21

A number of useful mono- and difluorinated molecules have been prepared successfully using SF_4 in varying yield depending on the particular transformation. Dmowski was able to prepare a series of fluorinated derivatives of camphor carboxylic acid in good yields using SF_4 under forcing conditions (Scheme 22).[55]

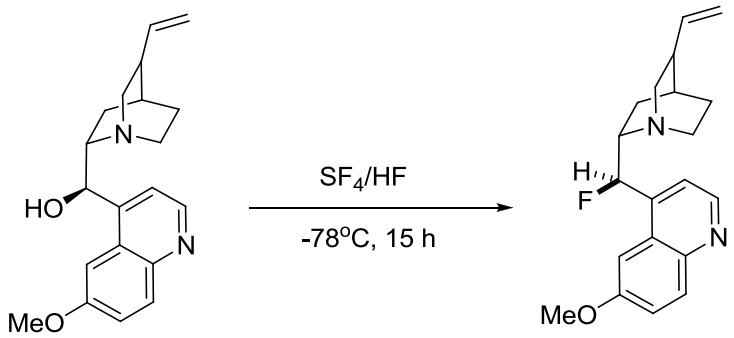


57 **58** 86% **59** 92%

Scheme 22

Sulfur tetrafluoride can also be used in conjunction with Lewis acids or, more commonly, liquid HF allowing, in most cases, a lowering of the reaction time and

temperature (although their use creates new practical disadvantages such as vessel choice). Kollonitsch and others were able to synthesise a deoxyfluoro quinine **61** from quinine **60** in good yield (84%); the ^{1}H NMR spectrum suggested a single diastereoisomer had been formed, although as both S_N1 and S_N2 mechanisms were reported, the identity of the product diastereoisomer is unclear (Scheme 23).[56]



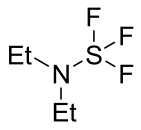
60 **61**

84%

Scheme 23

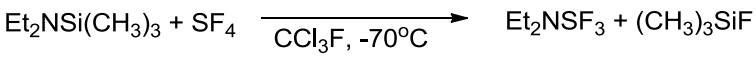
However, this reagent has several drawbacks; it is difficult to handle, highly toxic, has a boiling point close to -40°C, hydrolyses readily to HF and SOF_2, and must be used in metal autoclaves. The use of SF_4 has therefore diminished in recent times and its use tends to be limited to the industrial scale where it is handled only by specialists.

1.4.1.1. DAST



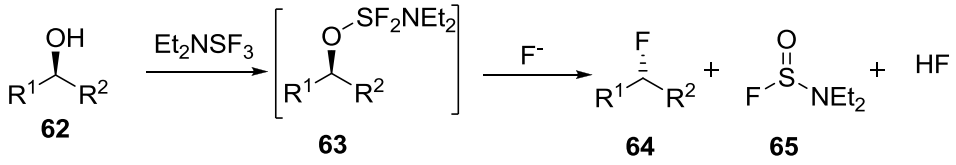
DAST

Diethylaminosulfur trifluoride (DAST) has become one of the most widely used nucleophilic fluorination reagents as it can perform much of the chemistry of SF_4 with more moderate toxicity and without the need for high pressure and autoclaves.[57] The widespread use of these reagents in fluorine chemistry is mainly due to the pioneering work of Middleton and his research group at Du Pont.[58] DAST can be prepared by reacting (diethylamino)trimethylsilane with SF_4 in trichlorofluoromethane yielding the product in high yield. The volatile trimethylfluorosilane can be easily removed by distillation (Scheme 24).



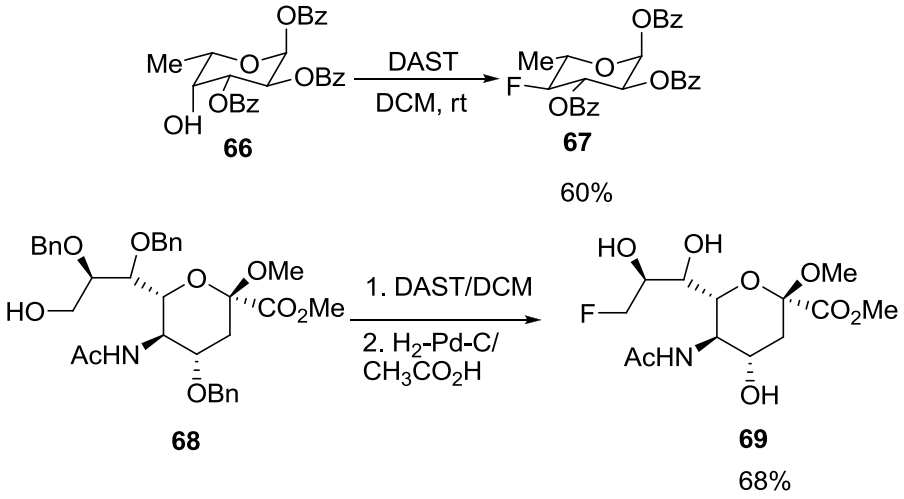
Scheme 24

DAST is commercially available as a low boiling (30-33^{o}C), moderately stable liquid and is compatible with standard laboratory glassware. By far the most common use for DAST is the conversion of alcohols into fluorides *via* an S_N2 mechanism, with inversion of alcohol configuration (Scheme 25).[59]



Scheme 25

DAST is compatible with a wide range of structures and moderate to good yields are obtained with primary, secondary and tertiary alcohols under relatively mild conditions; attributes which have seen the reagent used extensively in carbohydrate syntheses (Scheme 26).[60,61]

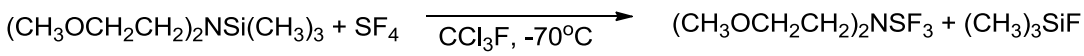


Scheme 26

DAST has several unattractive features, the main one being its stability; the reagent is susceptible to spontaneous decomposition and has been reported to undergo detonation upon heating above 90^{o}C.

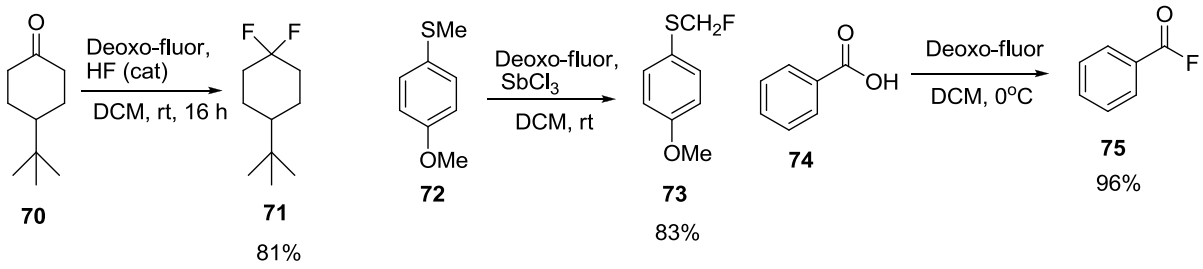
1.4.1.2. Deoxo-fluor™

Deoxo-fluor™ (bis(2-methoxyethyl)aminosulfur trifluoride) is synthesised in a manner similar to DAST (Scheme 27) although, unlike DAST, it doesn't self-heat during decomposition (so thermal runaway is not an issue). As such it is safer to use than DAST and performs much of the same chemistry, occasionally with better reactivity.[61]



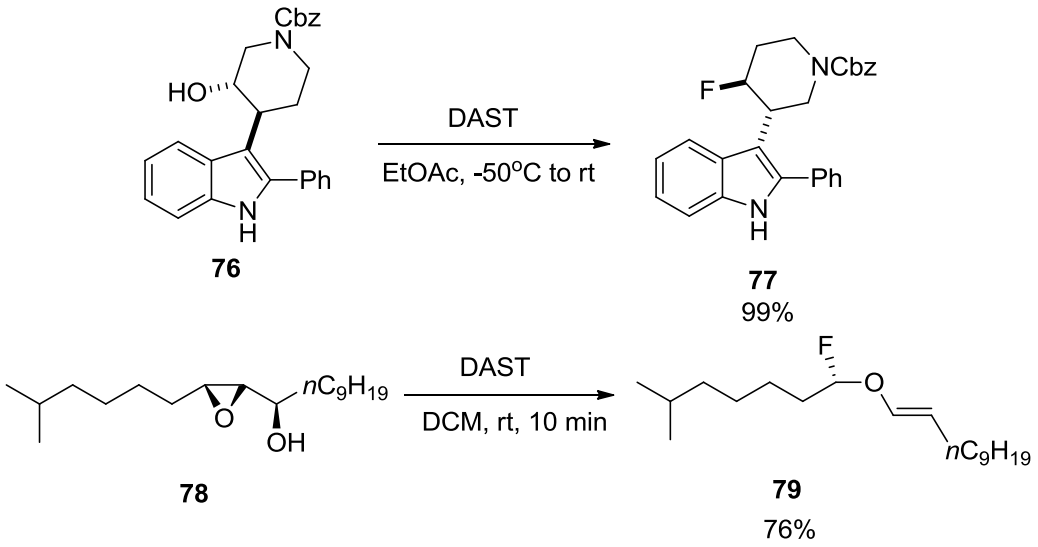
Scheme 27

As well as performing S_N2 reactions with alcohols DAST and Deoxo-fluor™ have also been used on a wide range of other functional groups including ketones, aldehydes, carboxylic acids and sulfides (Scheme 28).[53,62,63]



Scheme 28

Unfortunately a number of problems can be encountered when using DAST and Deoxo-fluor™ for fluorinations. As well as the need for extensive protecting group chemistry, a number of side-reactions, such as rearrangement, elimination and neighbouring group participation, can compete with the desired reaction lowering yields significantly (Scheme 29).[64-66]

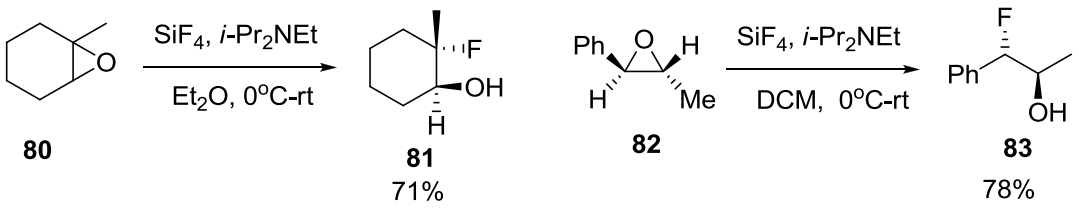


Scheme 29

1.4.2. Silicon

1.4.2.1. Silicon tetrafluoride

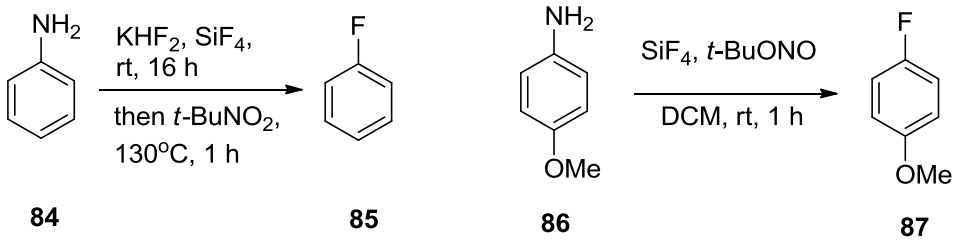
Silicon tetrafluoride (SiF_4) is obtained as a by-product in the manufacture of hydrogen fluoride (HF) from fluorite, and in the wet-processing of phosphoric acid and phosphate fertilizers from phosphate rock.[67] Despite some initial investigation into the chemical properties of this compound, there have been few reports about the utility of SiF_4 as a fluoride source. The reagent has been shown to ring open epoxides by Shimizu and co-workers (Scheme 30).[68]



80 **81** 71% **82** **83** 78%

Schemes 30

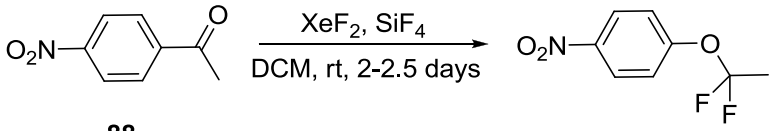
More recently Tamura found that a mixture of KHF_2 and SiF_4 with *t*-butyl nitrite was an efficient reagent for the synthesis of fluoroarenes from anilines (Scheme 31).[69] Where milder conditions are required, for example if acid sensitive groups are present, the same transformation can be effected by using SiF_4 (as a sole fluorine source) and *t*-butyl nitrite in DCM (Scheme 31).[70]



84 **85** **86** **87**

Schemes 31

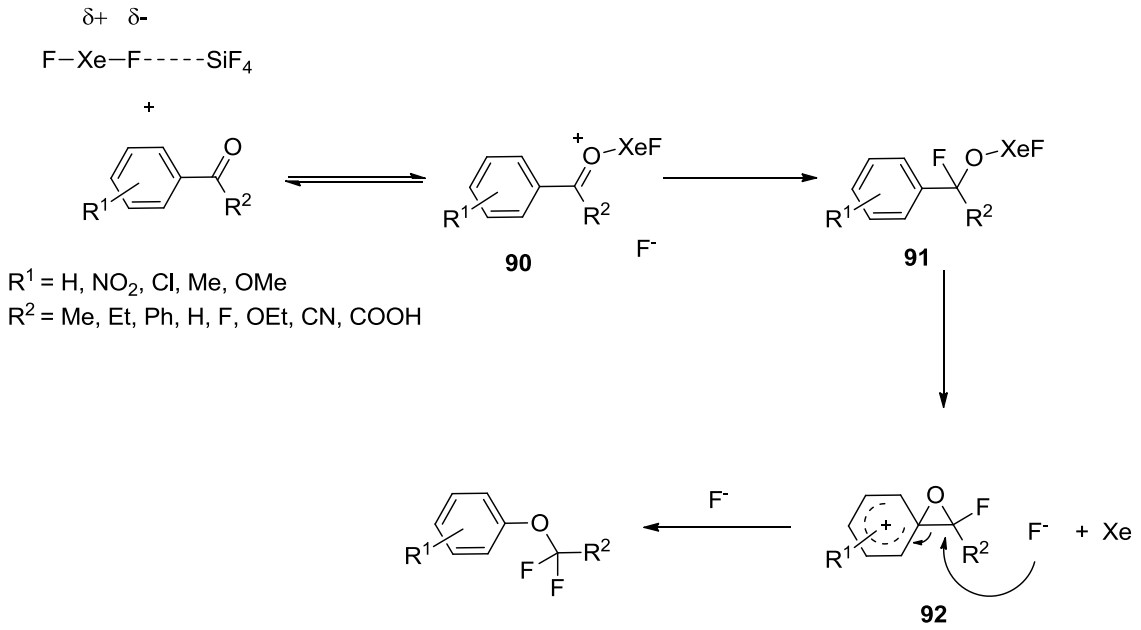
Silicon tetrafluoride has also been shown to promote the reaction of carbonyl compounds with the (usually electrophilic) fluorinating reagent XeF_2 to yield difluoroalkylethers (Scheme 32).[71]



88 **89** 91%

Scheme 32

Xenon difluoride has been utilised in the fluorination of alkenes, thioethers, aromatic and aliphatic compounds and is usually used in conjunction with Lewis Acids to enhance its electrophilicity.[72] However, when activated with SiF_4 the reagent reacts with aromatic carbonyl compounds to form α,α-difluoroalkyl phenyl ethers *via* an unusual mechanism that involves phenonium participation (Scheme 33).[71] The reaction is remarkably tolerant of variation in electron availability in the arene and carbonyl functional group.

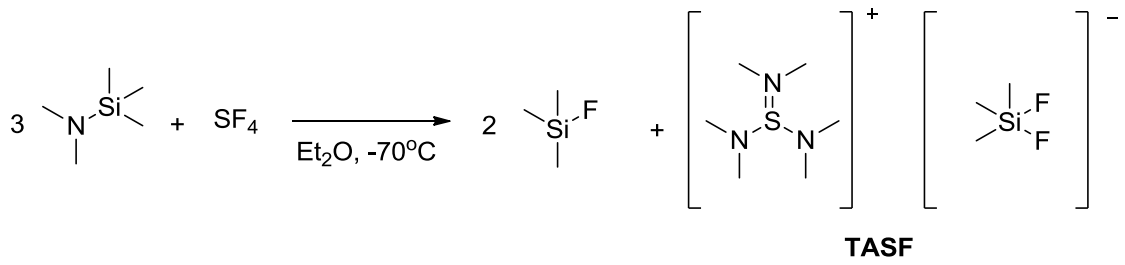


Scheme 33

1.4.2.2. TASF

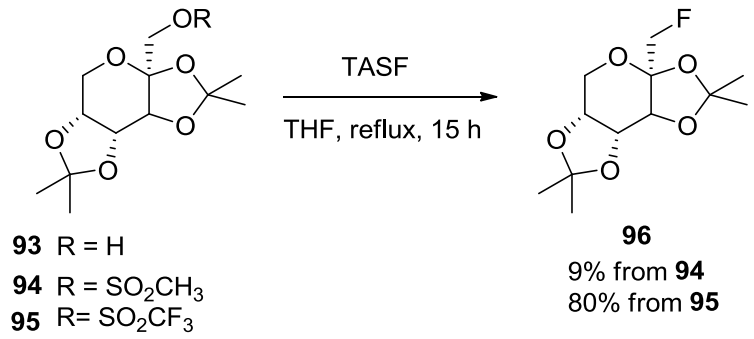
Tris(diethylamino)sulfonium difluorotrimethylsiliconate (TASF) is another nucleophilic fluorinating reagent.[73] It is a soluble organic fluoride, and weakly basic as the extraordinary basicity of "naked" fluoride is tamed through formation of an adduct with

the weak Lewis Acid trimethylsilylfluoride ($Si(CH_3)_3F$). It is most commonly prepared from *N*,*N*-dimethylaminotrimethylsilane and sulphur tetrafluoride.[74,75]



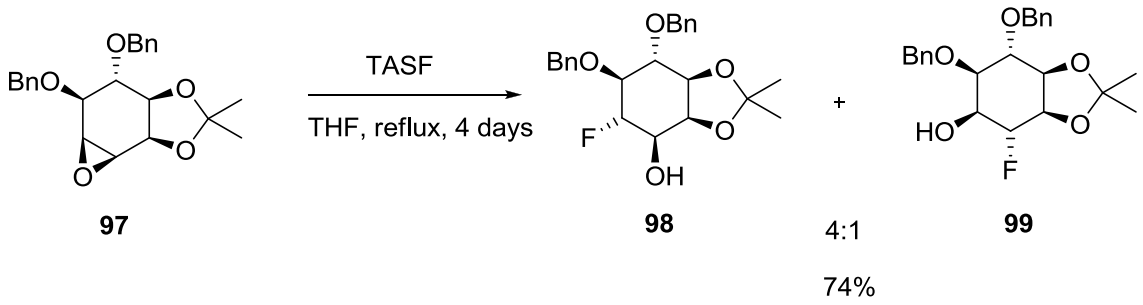
Scheme 34

During the synthesis of a 1-deoxy-1-fluorosucrose Card and Hitz were unable to fluorinate the mesylate **94** with TBAF, or the alcohol **93** with DAST. However, performing the fluorination on the analogous triflate **95** with 1.1.eq of TASF in refluxing THF afforded the desired product in an excellent 80% yield (Scheme 35).[76]



Scheme 35

In Ley's synthesis of 6-deoxy cyclitol analogues, a 4:1 mixture of regioisomeric fluorohydrins **98** and **99** was obtained by treating a highly functionalized six-membered epoxide with TASF (Scheme 36).[77,78]



97 **98** 4:1 **99**

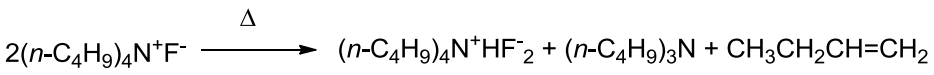
74%

Scheme 36

1.4.3. Nitrogen

1.4.3.1. Tetraalkylammonium fluorides

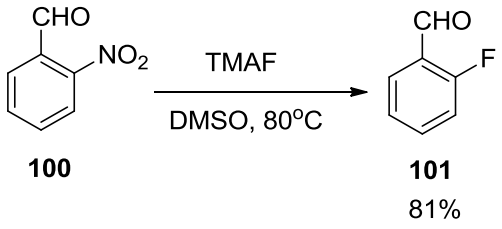
Tetraalkylammonium fluorides were designed to overcome some of the more common drawbacks of using alkali metal fluorides by providing a soluble source of F^- and replacing the M^+ ion with a bulky organic cation. The bulky cation decreases ion pairing and enhances the nucleophilicity (and the basicity) of fluoride (in a similar manner to the previously mentioned TASF reagent).[50] These organic fluoride salts are highly hygroscopic[79] and need to be dried thermally before use, as the hydration level of the system can have a profound effect on the nucleophilicity of the fluoride ion. Unfortunately, many of these salts can undergo decomposition reactions during the drying process (Scheme 37).[80]



Scheme 37

1.4.3.1.1. TMAF

Tetramethylammonium fluoride is the simplest of the tetraalkyl ammonium fluorides structurally and as such has some distinct advantages. The elimination reactions leading to decomposition of the fluoride salts require the presence of β-hydrogens in the quaternary ammonium cation, which tetramethylammonium fluoride (TMAF) does not have. TMAF has been found to be stable to elevated temperatures. While being commercially available as the tetrahydrate, it is unique in that it can be dried completely to the anhydrous salt.[79] Elsewhere it has been dried by the azeotropic removal of water using cyclohexane or toluene,[81] although recent work has highlighted difficulties with this method.[82] Later re-examination of simple fluorination reactions revealed that analysis of the reactions *via* standard GC protocols was misleading due to the formation of a number of involatile products which were not detected. The incorporation of an internal standard revealed the actual yields were lower than those reported previously.[83] In addition it was found that higher yields were obtained with TMAF.4/3H_2O in DMAc, rather than the azeotropically dried TMAF/DMSO system with an internal standard. Despite this TMAF has been used to fluorodenitrate many nitroaromatics (Scheme 38) often in moderate yield.[84,85]

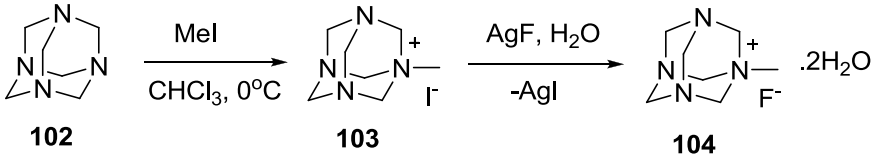


Scheme 38

Reaction times are also much shorter than those reported with KF, even at lower temperatures. Perhaps most importantly, it has been reported that fluorodenitration with TMAF results in the absence of the hydrolysis by-products in these systems. Although there are more widely used quaternary onium fluorides than TMAF, it has been described as the only reliable nitrogen based truly "naked" fluoride salt.[86]

1.4.3.1.2. MHAF

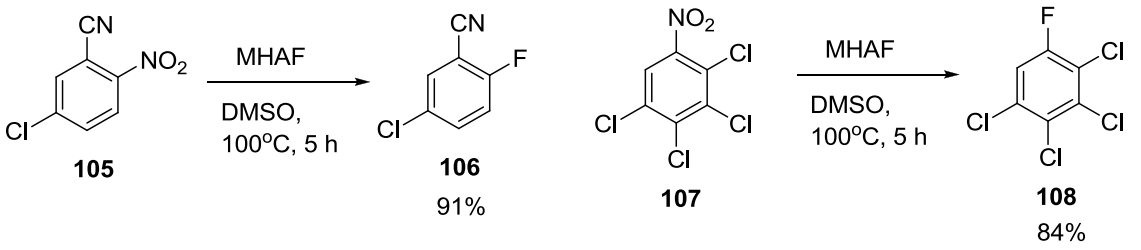
1-Methylhexamethylenetetramine (MHAF) has been shown to be a source of "naked" fluoride ions.[87] As MHAF has no β-hydrogen atoms, it is not susceptible to Hofmann (E2) elimination and possesses relatively high thermal stability. Furthermore, the large size and steric bulk of the cation renders it a potentially useful fluoride ion source. The reagent can be prepared by quaternising urotropine **102** with methyl iodide to form 1-methylhexamethylenetetramine iodide **103**. This can then be converted into the corresponding fluoride **104** by a metathesis reaction with AgF in aqueous solution (Scheme 39).



102 **103** **104**

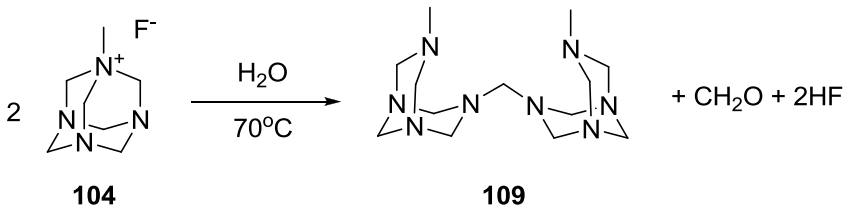
Scheme 39

Clark and Nightingale were able to perform a number of fluorodenitration reactions in high conversions (GCMS) using MHAF as the source of fluoride (Scheme 40).[88]



Scheme 40

Unfortunately, MHAF suffers from a number of drawbacks that limit its synthetic use severely including insolubility in most common solvents and a propensity towards ring opening and aminal formation or formation of symmetrical aminals under aqueous conditions (Scheme 41).[87]



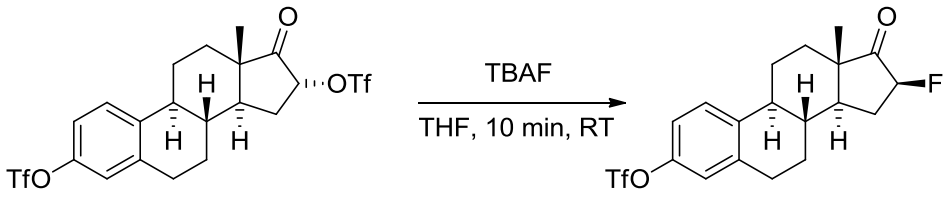
Scheme 41

The condensation of two 1-methylhexamethylenetetramine fluoride molecules in the presence of some water results in the formation **109** a neutral, methylene-bridged structure containing two symmetric groups of bicyclic *N*,*N*-bridged triazine rings. Not surprisingly MHAF is rarely used as a fluoride source in the synthesis of fluorinated organic compounds.

1.4.3.1.3. TBAF

Tetra-*N*-butylammonium fluoride (TBAF) is by far the most commonly used organic fluoride salt. The reagent is prepared by neutralisation of tetrabutylammonium hydroxide with HF to yield TBAF.3H_2O; this stable but hygroscopic form is a

commercial product.[50] Nucleophilic substitution of halides and sulfonates using TBAF as the source of fluoride is one of the most widely employed methods of fluorine introduction into aliphatic molecules. For example Kiesewetter and co-workers were able to introduce fluorine into analogues of estrogens in a facile and convenient manner using TBAF under mild conditions (Scheme 42).[89]

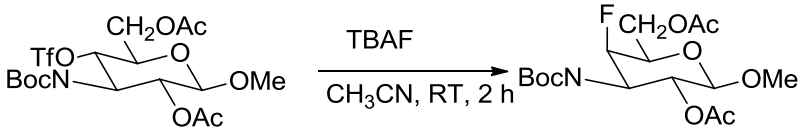


110 **111**

82%

Scheme 42

Similarly in Dax's synthesis of fluorinated analogues of the aminoglycoside, Kanamycin, TBAF was used to great effect as a fluoride source for fluorine introduction (Scheme 43).[90]



112 **113**

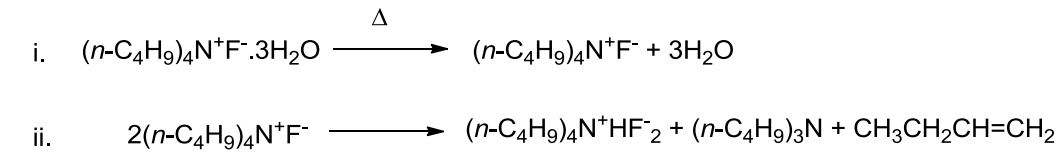
70%

Scheme 43

The popularity of TBAF as a source of fluoride is most likely a result of the relatively mild nature of the reagent, reasonable cost, tolerance of a wide range of functional groups and general solubility in most commonly used solvent systems.

Unfortunately, one of the main disadvantages of TBAF is its high hygroscopicity which has ensured a great deal of debate has taken place over the actual water content or nature of various commercial and "anhydrous" TBAF complexes, and the effect that water content has on the fluorination chemistry performed.

The instability of TBAF and other quaternary ammonium fluoride sources was examined by Fry; it was found that hydrated TBAF can be dehydrated at 70°C under reduced pressure, but when the last of the water molecules solvating the fluoride ion are removed, fluoride's strongly basic nature dominates and a rapid E2 elimination results leading to the formation of the thermodynamically stable bifluoride ion (Scheme 44).[91]

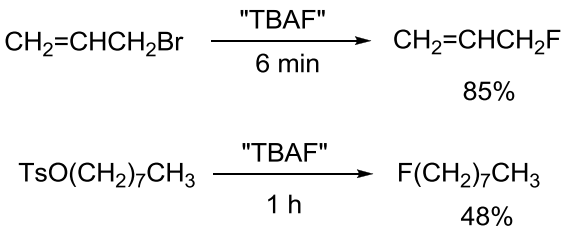


Scheme 44

The mass loss by water represented in equation i, corresponds to 17.1% of the original mass. By subjecting samples of TBAF trihydrate to a vacuum of at least 2 torr and a lower temperature of 40°C, water loss levels close to this value were reached without generating the decomposition products. For example after 147 hours, a sample had lost 16.5% of its original mass. Solutions of this "almost anhydrous" TBAF in CD_2Cl_2 were found to be quite unstable with only the decomposition products present after 12 hours. It was concluded after this study that previous examples of "naked" fluoride from sources susceptible to β-elimination were actually likely to have been a result of the hydrated fluoride ion or the bifluoride ion.

The “almost anhydrous” TBAF described by Fry was examined more closely by Cox and co-workers and was found to have somewhat unpredictable reactivity when exposed to a number of simple substrates.[92] The material, which contains 0.1-0.3 molar equivalents of water is an oil at room temperature and could be used without solvent.

A number of simple alkyl halides and tosylates were found to give the corresponding fluoro compounds in good yields, comparable to other sources of fluoride but at lower temperature and reaction time (Scheme 45).

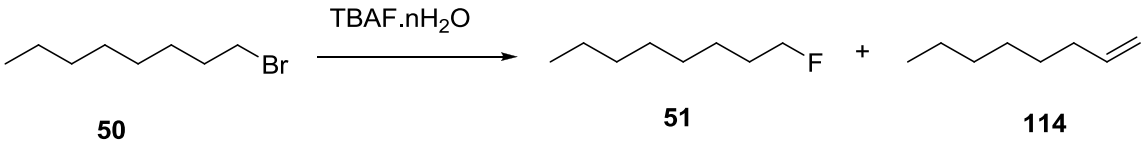


Scheme 45

However, “anhydrous TBAF” can also behave as a potent base as well as a powerful source of fluoride. Elimination of HBr is the dominant reaction upon treatment of 2-bromooctane with TBAF, and the elimination of HOTf is the main side reaction with 2-octyltosylate. In addition, hydrolysis of the starting halide or tosylate to the corresponding alcohol is a significant side reaction on treatment of benzyl bromide or 1-bromooctane with “anhydrous TBAF”. Presumably this is a result of the remaining traces of moisture in the reagent, which are rendered highly nucleophilic by the fluoride ion.

The influence of varying quantities of water in TBAF, ranging from 0.5-10 molar equivalents, was examined in detail by Landini and co-workers.[93] Previously they had

reported that in the same hydration range ($1.5 < n < 6$) of $R_4N^+F^-.nH_2O$, the basicity of F^- decreases more significantly than the nucleophilicity when *n* is increased.[94] On the basis of these results, it was hypothesised that hydrated TBAF.nH_2O would behave as an efficient, nonbasic, nucleophilic fluorinating agent. Accordingly the nucleophilic fluorination of alkyl halides and sulfonates with TBAF of varying hydration states (0.5-10 molar equivalents) was investigated. Commercially available TBAF was found to contain 3.5 molar equivalents of water. The water content was decreased by heating commercial TBAF under sonication and high vacuum (4×10^{-4}) at 40°C (12 hours for n =1.2, 30 hours for n = 0.5) while monitoring the mass loss. Higher values of water content were obtained by stirring commercial TBAF in 2-methoxynaphthalene with the quantity of water required for the desired hydration state. As expected it was found that the product distribution from the nucleophilic fluorination reaction depended heavily on the molar ratio of water present (*n*). In particular, the ratio of fluorination/elimination products greatly increased by increasing *n* (Scheme 46, Table 1).



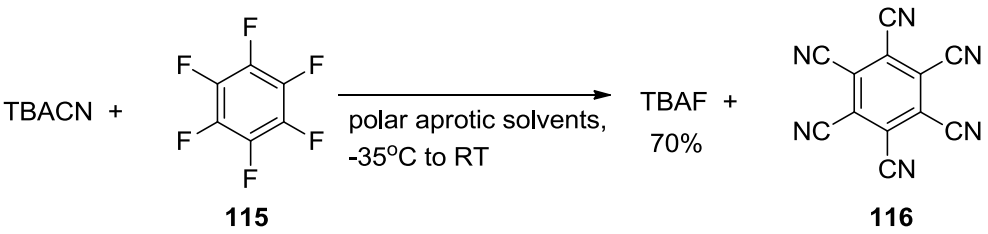
Scheme 46

n	Reaction time (h)	T°C	%51	%114
0.5	0.25	80	63	37
1.2	0.25	80	70	30
3.5	0.25	80	91	9
5	0.5	80	94	6
10	4	80	93	7

Table 1

Also, in contradiction with the earlier findings of Cox *et al.*,[92] Landini's group observed no detectable amounts of the corresponding alcohols when the fluorinations were performed on a small selection of alkyl halides and mesylates using TBAF.nH_2O (n = 0.5-10).[94] It was concluded from their investigation that hydrated TBAF, in particular the commercially available species (n = 3.5) and the pentahydrate, are powerful, non-basic and nucleophilic fluorinating agents particularly suitable for conversion of alkyl bromides, chlorides and methyl sulfonates to the corresponding fluorides.

As complete dehydration of commercially available TBAF appears to be impossible without experiencing significant levels of decomposition via E2 elimination reactions,[95] DiMagno decided the solution to truly anhydrous TBAF was to generate the reagent *in situ* in the absence of water.[96] DiMagno and co-workers utilised a low-temperature nucleophilic aromatic substitution (S_NAr) to generate anhydrous TBAF directly in aprotic solvents (Scheme 47).

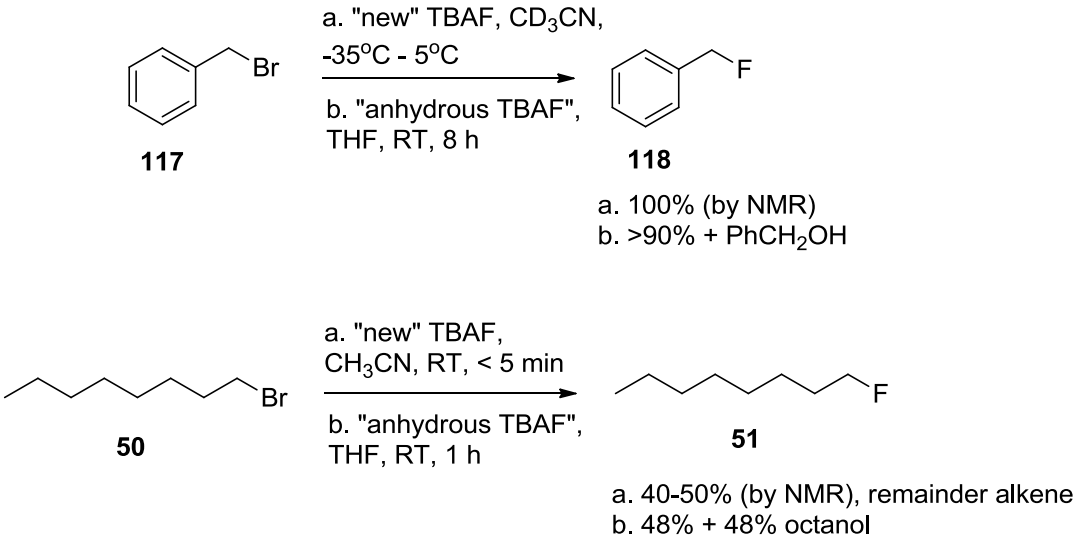


Scheme 47

The demands of an *in situ* generation of TBAF based on the S_NAr reaction are quite severe and a careful choice of nucleophile is necessary. As the enthalpic driving force for the liberation of fluorine in the S_NAr reaction derives almost exclusively from ion-pairing and ΔBDE terms, and because the C-F bond in aromatics is strong (126 kcal/mol), only diffusely charged anionic nucleophiles capable of forming extremely strong bonds to carbon are capable of performing a S_NAr reaction at low temperature. The cyanide ion is a potent, weakly basic nucleophile that forms strong bonds to sp^2-hybridized carbon (BDE 133 kcal/mol),[97] and therefore is an excellent choice. Reaction of hexafluorobenzene and tetrabutylammonium cyanide (TBACN) (in 1:1 to 1:6 molar ratios) in the polar aprotic solvents THF, acetonitrile, or DMSO at or below room temperature gave good yields of anhydrous TBAF (70% isolated). ^{19}F NMR spectroscopy confirmed that the overall yield of TBAF in solution in all cases was >95%. Another benefit of the choice of cyanide as the anion is cyano substitution dramatically increases the susceptibility of the perfluoroaryl ring to further nucleophilic attack, as shown by the observation of pentacyanofluorobenzene and hexafluorobenzene as the principal fluorinated aromatic species in the reaction solution, even if 1:1 TBACN/C_6F_6 stoichiometry is utilised.

It was found that this anhydrous TBAF was stable under nitrogen at -35^{o}C for weeks but decomposes slowly in the solid state or as a THF solution if warmed above 0^{o}C. However, the anhydrous TBAF can be prepared and used *in situ* without isolation or purification, being stable in acetonitrile for hours and for more than 24 hours in DMSO at room temperature. Only small quantities (<4%) of the bifluoride by-product were observed.

This "new" anhydrous TBAF displayed reactivity comparable to other fluoride sources in nucleophilic fluorination reactions, and in head-to-head comparisons, DiMagno reported significantly enhanced rates of fluorination in comparison to vacuum dried TBAF (Scheme 48).[96]

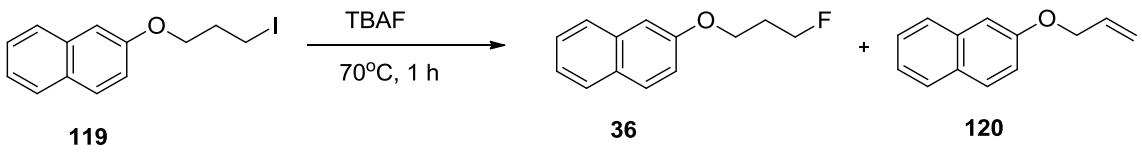


Scheme 48

However, it is worth noting that these reactions are of simple substrates and the yields quoted are NMR yields (not isolated yields as the examples from standard TBAF reagents are). In addition, the "naked" fluoride anion can still cause base-catalysed

elimination reactions and the reaction of tetrabutylammonium cyanide and hexafluorobenzene is highly exothermic, so care must be taken for reactions on a larger scale. Therefore the supposed advantages of this reagent almost certainly do not outweigh the increased cost and associated practical disadvantages.

Recently Kim and co-workers have shown non-polar, protic tertiary alcohol solvents show unexpected good performance in the nucleophilic fluorination reactions of sulfonate ester and alkyl halide substrates with TBAF (Scheme 49).[98] The protic environment of the *tert*-alcohol reduces the basicity of the TBAF, but maintains the high nucleophilicity. Fluorination of the haloalkanes showed a reasonable reaction rate under mild conditions, but the competing base-catalyzed eliminations are inhibited, enhancing the selectivity of the fluorination reactions.[99] Once again it is worth noting that these conditions have only been examined for a small set of simple substrates and the wider applicability of TBAF in protic tertiary alcohol solvents remains to be seen.

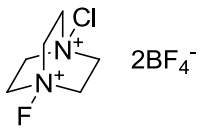


119 **36** **120**

CH_3CN:	38%	57%
t-amyl alcohol:	72%	19%

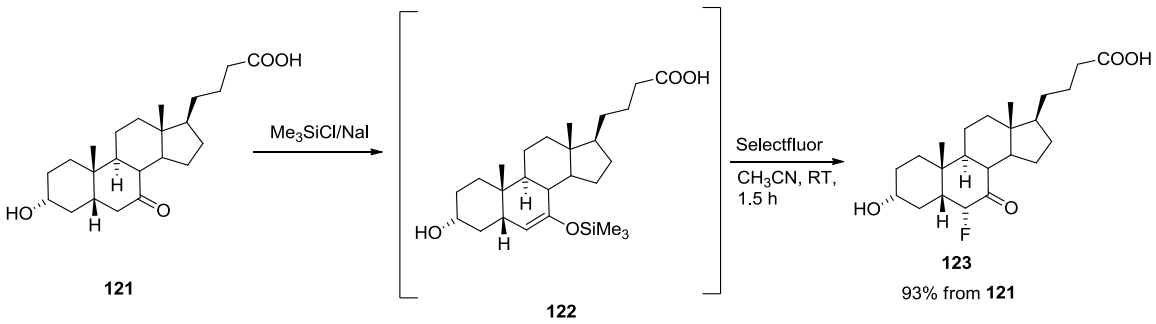
Scheme 49

1.4.3.2. Selectfluor™



Selectfluor™

Although Selectfluor™ is an electrophilic reagent and falls out with the scope of this mini-review on nucleophilic fluorination sources, as one of the most popular and widely used fluorination reagents available it is worthwhile briefly discussing this reagent. Selectfluor™ or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) is a versatile electrophilic source of fluorine. The reagent acts essentially as a stoichiometric source of F^+ and can be used to fluorinate specific positions in a range of substrates. For example 6-α-fluoroursodeoxycholic acid **123**, a potential agent for the prevention and treatment of colorectal cancer, was prepared using a route where the key transformation is an electrophilic fluorination with Selectfluor™ *via* silyl enol ether intermediate **122** (Scheme 50).[100]



Scheme 50

More information on Selectfluor™ as a reagent and the versatility of its applications in synthesis can be found in an in depth review by Pez.[101]

In conclusion, nucleophilic fluorination is a diverse topic encompassing a vast number of inorganic and organic reagents. As this review has shown, there is no universal nucleophilic fluorination reagent available. Most of these reagents have their own associated advantages and drawbacks and their performance in reactions is incredibly

substrate specific. A number of factors must be taken into account when choosing a fluorination agent; these include scale, cost, substrate functionality and by-product formation. It can be also be seen that there is still ample opportunity for the development of new nucleophilic fluorination reagents and the in depth assessment of their scope and limitations.

1.5. Fluorinated carbohydrates

The substantial differences between fluorine and the other halogens lends fluorinated carbohydrates, and their derivatives, interesting and appealing properties. Fluorinated saccharides are becoming increasingly important molecules for the study of enzymatic reactions, for use as mechanistic probes and as reagents for enzymatic glycosylations. Interest in these molecules arises from their relative stability in aqueous solutions and continued improvements in the ease of their synthetic preparation.[102]

1.5.1. Biological uses of fluorinated sugars

1.5.1.1. ^{18}F labelled carbohydrates

One of the oldest and most common uses of fluorinated sugar-like molecules is as radiotracers for biomedical applications through the introduction of ^{18}F. This radioactive isotope of fluorine was first produced by Snell[103] and is now widely used in the development of radiopharmaceuticals for Positron Emission Tomography (PET), a technique that affords much insight in modern medicine. The widespread use of Fluorine-18 is related to the nuclear and physical properties of this radioisotope: its half-life of 109 minutes, positron decay (97%) and positron weak energy (635 keV maximum, 2.3 mm range in matter), are particularly advantageous in terms of resolution and dosimetry.[104] Additionally, Fluorine-18 can be produced reliably on a large scale (several GBq), and its sufficiently long half-life ensures radiopharmaceutical drugs can be prepared using well established short synthetic routes.

PET is a non-invasive functional and metabolic imaging technique; its good spatial resolution and excellent sensitivity make it possible to quantify specific biological and pharmacological processes in man and animal.[105] Fluorine-18 has the following decay mode:

$$_{9}F^{18} \rightarrow {}_{8}O^{18} + {}_{+1}e^{0} \quad (1.656 \text{ MeV})$$

The positron travels only a few millimetres in tissue before it meets an electron, resulting in an annihilation, producing two gamma ray photons of equal energy (511 MeV), and emitted at 180^{0} from each other. PET is based on the detection of these two coincident emissions.

In its simplest form, ^{18}F is an excellent tracer for bone imaging, accurately defining the anatomic location and extent of lesions, and assessing changes in bone metabolism.[106] However nine out of every ten PET examinations use FDG (2-deoxy-2-fluoro-D-glucose, **128**). This glucose analogue is taken up by body cells that are high users of glucose such as brain and cancer cells. The presence of fluorine in position 2 causes FDG to remain unmetabolized and it accumulates in the cell at a rate proportional to the need for glucose. The intracellular concentration of FDG will therefore reflect the energetic metabolism of the cell, in particular all cells presenting a variation of the glucidic metabolism, for example cancer cells. Once the ^{18}F has decayed to the stable ^{18}O the normal metabolic process is restored.

However there are limitations to the effectiveness of ^{18}F-FDG for cancer studies, as success is dependent on the location and homogeneity of the tumour. Labelled amino acids which are incorporated in proteins are sometimes preferred (see Figure 2), although ^{14}C labelled compounds are often more useful.[107]

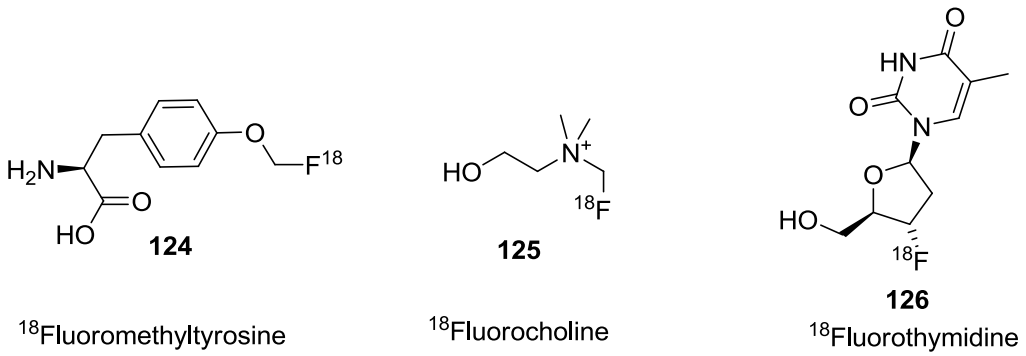
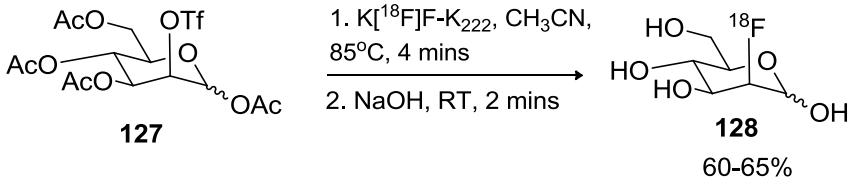


Figure 2

Radiosyntheses are subject to heavy constraints arising from radioactivity; these include the need for radiation protection, work in hot-cells, short half-life of radioisotope requiring "fast chemistry'' and the need to obtain the radiopharmaceutical with a high specific radioactivity. As a direct consequence total preparation time for the substrates including synthesis, final purification (usually by HPLC), formulation and quality control must be as short as possible, necessitating the incorporation of the radioactive isotope as late as possible in the reaction pathway.

Therefore most radioactive syntheses do not involve more than two steps and often involve simple nucleophilic fluorination reactions, as illustrated in the synthesis of FDG (Scheme 51).[108]



Scheme 51

1.5.1.2. Fluorinated sugars as molecular probes

Glycosyltransferases are enzymes involved in a wide variety of biological processes ranging from the processing of *N*-linked glycan structures, signal transduction, bacterial cell wall and natural product synthesis.[109-111] A thorough understanding of these enzyme-catalyzed reactions is important for the rational design of molecular therapeutics targeting these enzymes. Glycosyltransferase-catalyzed reactions fall into two distinct categories: retaining, where the product glycoside has the same stereochemistry as the activated leaving group, and inverting, where the reaction proceeds with inversion of stereochemistry at C-1. It is believed that the inverting type enzymes proceed *via* electrophilic activation and the formation of an oxocarbenium ion-like intermediate.

Hen egg-white lysozyme (HEWL), a β-retaining enzyme, was the first to have its three-dimensional structure determined by the X-ray diffraction technique. Despite the catalytic mechanism of the HEWL enzyme being the subject of many studies, certain aspects of the mechanism long-remained contentious until very recently.[112] Two mechanistic pathways for this enzyme were believed to be viable (Figure 3).[113] Based on model building studies, and the three-dimensional structure determined by X-ray diffraction, Phillips suggested that the intermediate structure **130** was a long-lived metastable ion pair formed between the oxocarbenium ion and the enzymic carboxylate Asp-52.[114] However, other data, including α-deuterium kinetic isotope effects (KIE) measured using substrates for which the rate-determining step is breakdown of the intermediate, pointed towards a covalent intermediate **131**.

NAG = 2-acetamido-2-deoxy-glucopyranoside

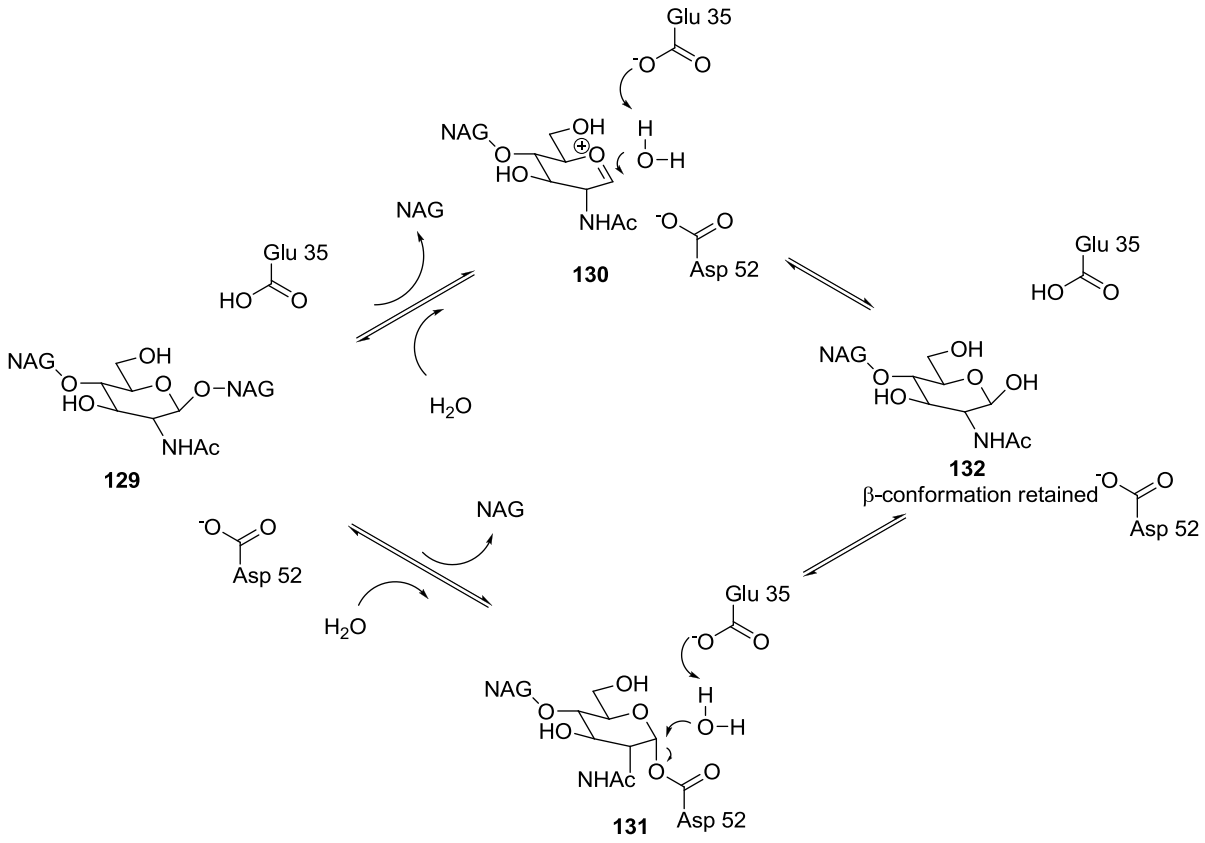
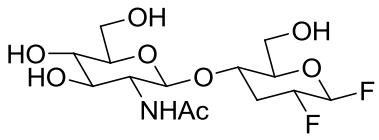


Figure 3

Possible mechanisms for hen egg white lysozyme. The upper path shows a mechanism involving a metastable oxocarbenium ion as proposed by Phillips[114] and the lower path shows a covalent glycosyl-enzyme intermediate as first proposed by Koshland.[115]

The sizes of the α-deuterium kinetic isotope effects are not decisive with HEWL as no substrate for this enzyme has been found for which the rate-determining step is deglycosylation. In the absence of other suitable substrates for KIE experiments, 2-deoxy-2-fluorodisaccharides were synthesised as mechanism-based inhibitors of HEWL that function by accumulation of a stabilized intermediate.[113]



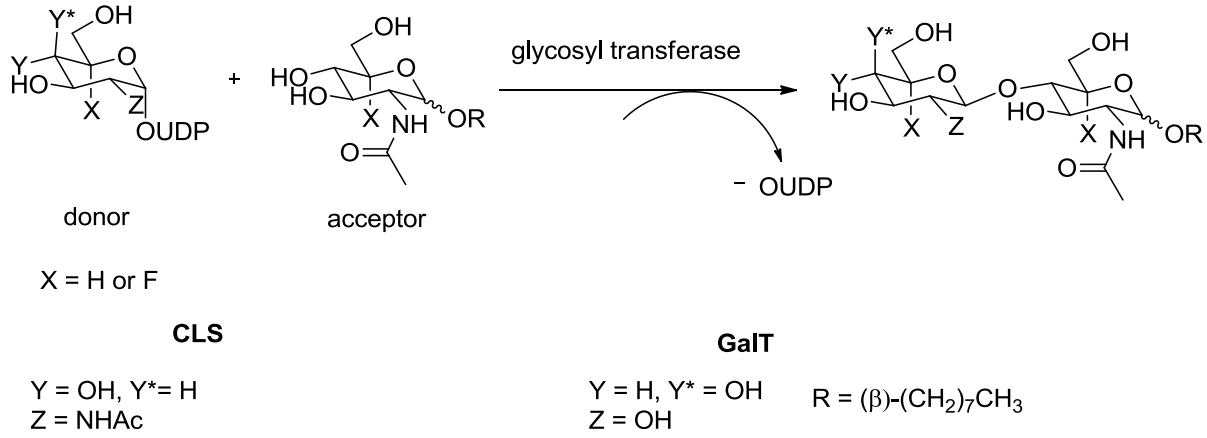
133

inactivator of HEWL

The substitution of electronegative fluorine at the 2 position inductively destabilizes the oxocarbenium transition state leading to the formation and hydrolysis of the intermediate, slowing both steps. When a good leaving group (2,4-dinitrophenolate or fluoride) is also incorporated, acceleration of the first step occurs. The net result is breakdown of the intermediate is slowed to a greater extent than its formation, which leads to accumulation of the now kinetically accessible intermediate. Through this approach, the covalent glycosyl-enzyme intermediate formed on lysozyme could be characterised by X-ray crystallography. From this data it was concluded that HEWL, in common with all other β-retaining glycosides, performs catalysis by the formation and subsequent breakdown of a covalent intermediate species and not by the formation of a long-lived ion pair.

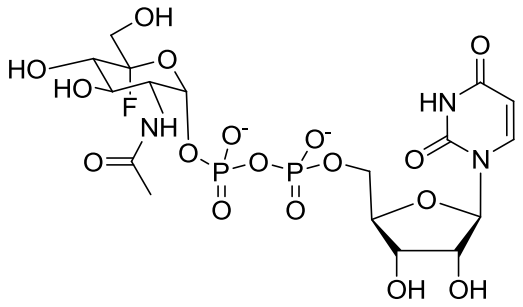
Similarly, in an effort to better understand the mechanism of glycosyl-transferase catalysed reactions, Hartman *et al.* employed selectively fluorinated saccharide structures. Fluorine was introduced at C-5 in both donor and acceptor substrates in order to explore its effect on UDP-GlcNAc:GlcNAc-P-P-Dol *N*-acetylglucosaminyl transferase (chitobiosyl-PP-lipid synthase, CLS) and *β-N*-acetylglucosaminyl-*â*-1,4 galactosyltransferase (GalT).[116]

It was rationalised that this substitution of electronegative fluorine at C-5 would exert an electronic effect on both the developing oxocarbenium ion, if incorporated into the donor, and the C-4 or C-6 hydroxyl group, if incorporated into the glycosyl acceptor.

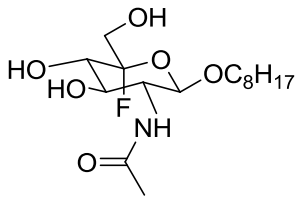


Scheme 52

It was shown that the processing of UDPGlcNAc by CLS is competitively inhibited by UDP-(5-F)-GlcNAc **135**. Thus, a very strong inactivating effect is exerted simply by addition of the sterically small but powerfully electron-withdrawing fluorine at C5. This evidence supports a mechanism whereby an oxocarbenium ion-like transition state is destabilized by the presence of the electron-withdrawing fluorine at the neighboring 5-position. This type of mechanism is consistent with other studies of glycosyltransferases.[117,118]



134



135

The (5-F)-GlcNAc *β*-octyl glycoside acceptor analogue **134** was found to be a competent acceptor substrate for both the CLS and GalT enzymes. With the data from the C5 fluorinated donor and acceptor substrates it was concluded that the glycosyl transferases (which proceed with inversion) operate through a mechanism involving a transition state with significant bond breaking of the anomeric sugar-UDP bond yet little bond formation with the GlcNAc acceptor.

In an effort to quantify the effect of the location of fluorine substitution, Withers and co-workers prepared 1-phosphates of deoxyfluoro sugars with fluorine inserted at various points in the hexose ring.[119] 2-Deoxy-2-fluoro- (**136**), 3-deoxy-3-fluoro- (**137**), 4-deoxy-4-fluoro- (**138**) and 6-deoxy-6-fluoro-α-D-glucopyranosyl phosphate (**139**) were prepared, and their acid catalysed hydrolysis reactions were studied. The first and second ionisation constants (pK_a1 and pK_a2) of these compounds were determined *via* potentiometry, as well as by ^{19}F NMR chemical shifts at a series of pH values. The rate constants of hydrolysis for neutral (**142**) and monoanion (**143**) were then calculated. It was found that the location of fluorine in the hexose ring had a profound effect on the first-order rate constants (see *k* values in Figure 4).

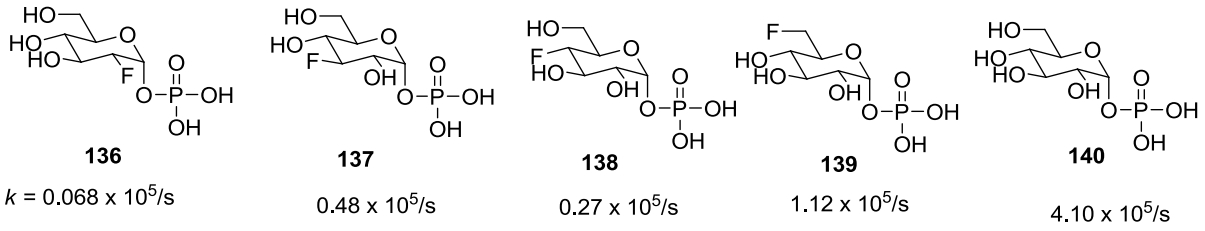
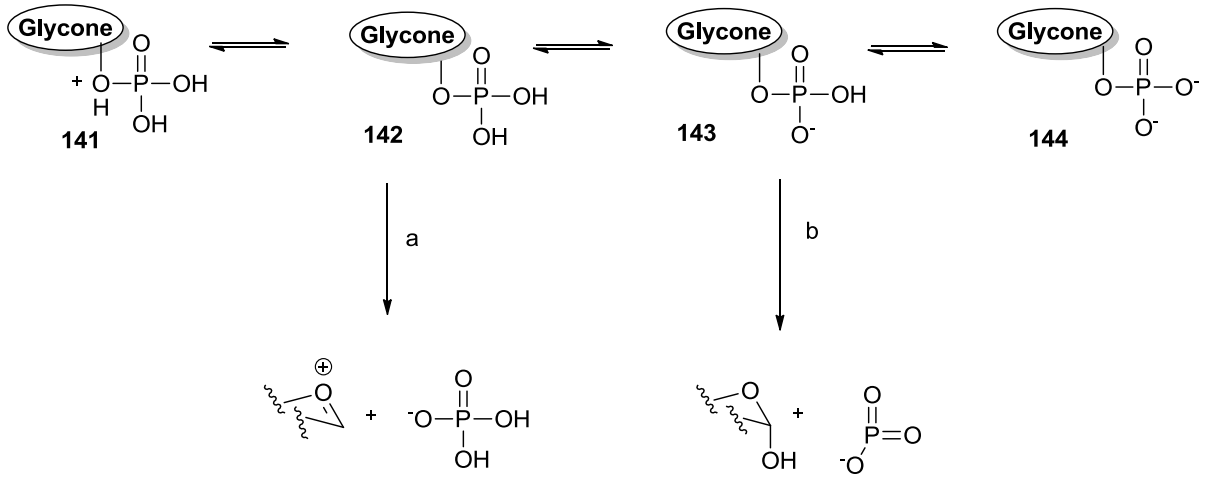


Figure 4



Scheme 53

These rate constants were also found to be highly dependent on temperature and the pH of the solution. These results were explained by a mechanism involving 3 species; conjugated acid (**141** - present principally at pH < l), neutral (**142** - pH 2 - 5), and monoanion (**143** - pH > 5), which cleave in 3 distinct manners. In these hydrolyses, the position of the fluorine atom exerts a large influence on the strength of the glycosidic bond, with fluorine insertion at C-2 found to have the greatest stabilising effect on glycosidic bond strength.

As such, regioselective fluorine substitution into substrates can be a useful tool for discriminating between enzymes. For example, enzymes engaged in route *a* (such as

glycogen phosphorylase) are unable to catalyze the hydrolysis of **136 (**because of the stabilisation of the glycosidic bond exerted by the fluorine at C-2) whereas the enzymes engaged in route *b* (such as phosphoglucomutase) can catalyze the hydrolysis.

1.5.2. 6-Deoxy-6-fluoro sugars

Of all the known modifications of the monosaccharides with fluorine, the 6-deoxy-6-fluoro sugars are particularly interesting. The reasons lie in the interactions by which different sugars are recognised in nature, for example hexoses and deoxyhexoses. Deoxygenation at C-6 in saccharide structures is a common biosynthetic modification, representing a characteristic feature of many macrolide antibiotics (Figure 5).[120,121]

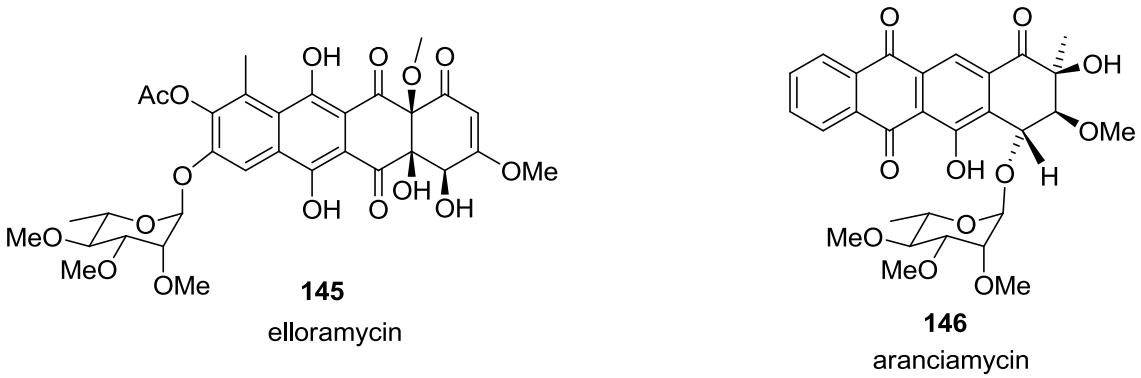


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Figure 5

The most generally accepted model of saccharide recognition involves a combination of hydrogen bond networks and the accommodation of lipophilic moieties in substrates within hydrophobic ‘pockets’ in the enzyme. Significant differences in the ways in which hexoses and their 6-deoxy analogues are processed by enzymes would be expected.

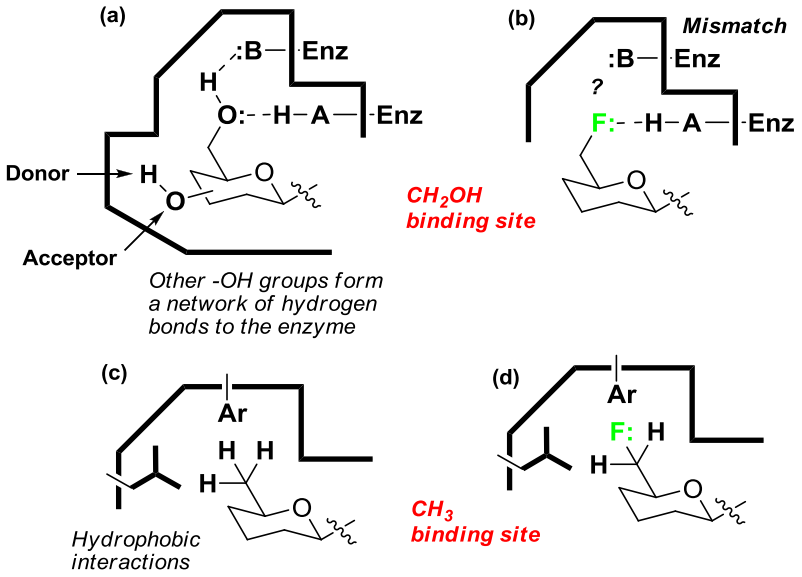


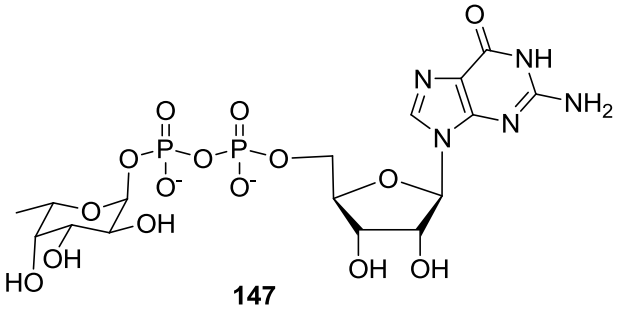
Figure 6 Cartoon representations of features within the binding site of a sugar processing enzyme. (a) The C-6 hydroxyl group makes classical hydrogen bonding interations with the protein; (b) a weakly attractive interaction and a potential repulsive interaction with proximal basic broups on the enzyme arise when F replaces OH; (c) shows the likely arrangement within the CH_3 binding site for a 6-deoxysugar; (d) shows how F for H replacement may be less deleterious within the CH_3 binding site.

As Figure 6 illustrates, the binding model for a hexose in the binding site of a sugar processing enzyme is quite different from that of a 6-deoxyhexose. The hexose, possessing a -CH_2OH group, occupies a region within the enzyme that maximises the opportunity for hydrogen bonding donor and acceptor interactions with the protein wall. In contrast, the 6-deoxyhexose, with its comparatively greasy –CH_3 functionality occupies a region that can accommodate the methyl group within a hydrophobic pocket. As the CH_3 and CH_2OH moieties are also sterically different, high selectivities for hexoses over 6-deoxyhexoses could expected for enzymes in higher organisms.

However, the binding model is much more ambiguous for 6-deoxy-6-fluoro hexoses. As figure 6 shows, replacement of $–CH_2OH$ with $–CH_2F$ is likely to diminish the hydrogen bonding capacity of the substrate within a binding pocket. A hydrogen bonding donor interaction is lost completely and fluorine acts as a much weaker hydrogen bonding acceptor than oxygen. Replacement of $-CH_3$ with $–CH_2F$ is likely to have a less dramatic effect on the hydrophobic interactions seen with 6-deoxy-sugars. Accordingly, 6-deoxy-6-fluoro sugars represent potentially useful tools for probing the importance of functionality at C-6 in the recognition and binding mechanisms between enzymes and hexoses and their 6-deoxy analogues.

In addition to effects on binding interactions insertion of fluorine at the 6-position has a profound effect on the ability of the substrates to participate in glycosylation; electronegative fluorine destabilising the developing positive charge on the oxocarbenium intermediate.

Wong[122] used fluorinated fucose analogues to study fucosyltransferases III, V, VI and VII.

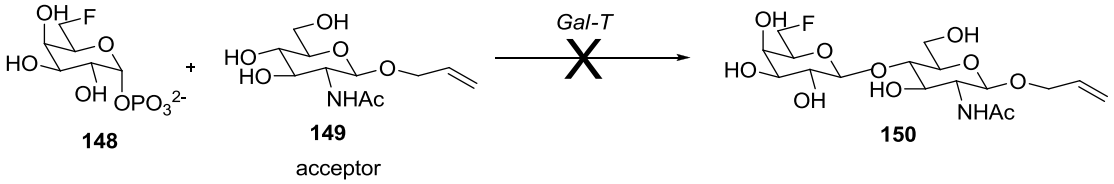


147

GDP-fucose

Fucosyltransferases catalyse the transfer of fucose from a nucleoside diphosphate fucose to an acceptor molecule, usually another carbohydrate, a glycoprotein, or a glycolipid

molecule. If the binding interactions described in Figure 6 are correct, fucosyl transferases would be expected to bind 6-deoxy-6-fluoro analogues of GDP-fucose **147**. Wong and his colleagues prepared 2-deoxy-2-fluoro and 6-fluoro analogues of GDP-fucose and found that in general, introduction of fluorine into the sugar nucleotides resulted in the molecules becoming competitive inhibitors for the enzymes rather than substrates. As the fluoro sugar nucleotides formed stable tight complexes with the enzyme, it can be concluded that the 6-deoxy-6-fluoro analogues are good binding mimics for the original substrates as Figure 6 suggests.



Scheme 54: Interaction of a 6-deoxy-6-fluoro sugar and a Galactosyltransferase

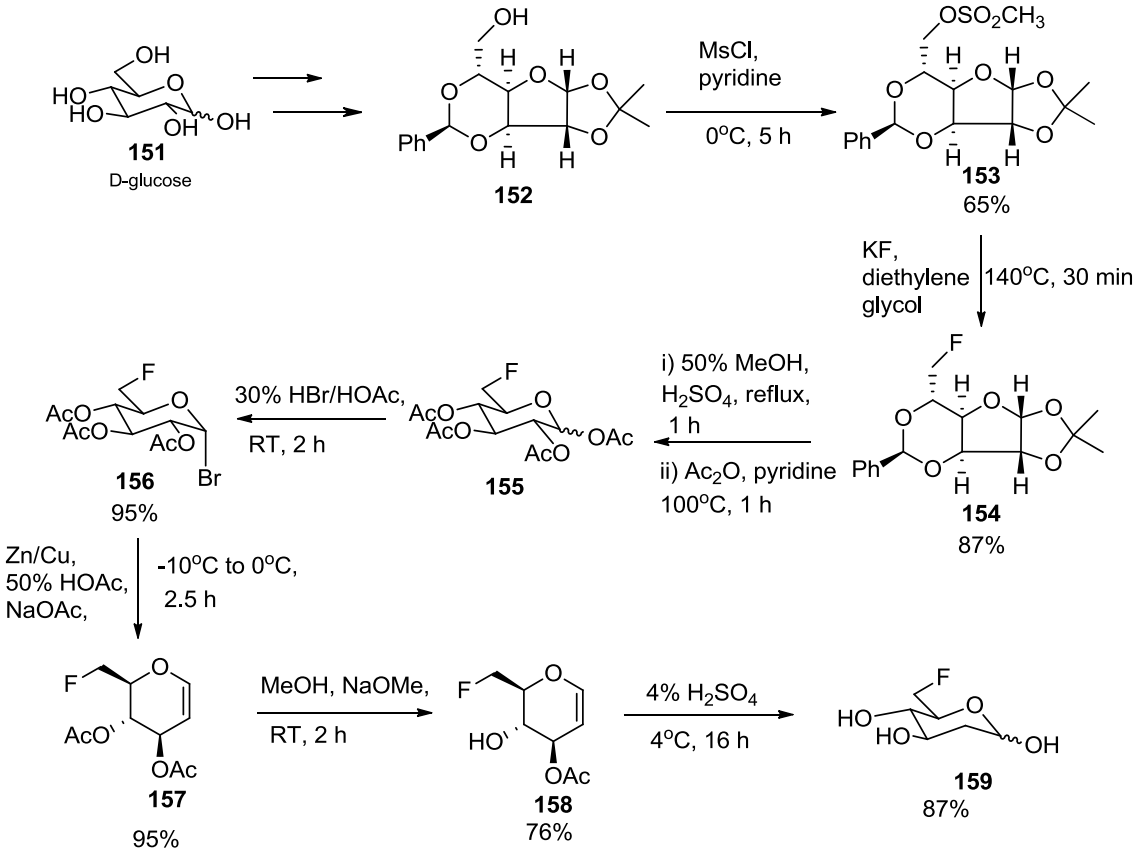
Kovác showed that although the presence of fluorine at C-6 in **148** had little effect on the ability of galactosyltransferases to bind to **148**, it does negate the enzymes ability to catalyse the transfer of the 6-deoxy-6-fluoro sugar moiety from UDP to the acceptor sugar **149** (Scheme 54).[123,124] This result would suggest that, for this enzyme at least, hydrogen bonding recognition at C-6 is probably not the most significant interaction factor in the binding mechanism.

To summarise a large number of fluorine containing mono-, di- and oligosaccharides have been prepared for a variety of uses;[102] the main use is to probe the binding mechanisms between target enzymes and the parent substrates. Fluorine insertion into carbohydrate type molecules is particularly beneficial in this regard because of the close

isosteric relationship of fluorine and oxygen (Pauling van der Waals radius of fluorine being 1.35 Å compared to 1.40 Å for oxygen). The replacement of a hydroxyl group in the parent substrate with a fluorine atom usually causes minimal steric perturbation. However, the high electronegativity of fluorine can have a profound effect on the electron distribution, and hence behaviour of the molecule in biological systems (for example glycosyltransferases). This has led to the discovery of useful inhibitors for enzymes in many instances.

1.5.3. Synthesis of 6-deoxy-6-fluorosugars from the chiral pool

Over the years a number of elegant syntheses of 6-deoxy-6-fluoro sugar analogues have been developed. O'Hagan and Nieschalk were able to achieve the synthesis of 6-fluoro-D-olivose **159** in an impressive 23% overall yield from optically pure D-glucose **151**.[125]



Scheme 55

The sequence delivers the target compound in good yield from cheap and readily available starting materials but the approach, of modifying chiral precursors, can be restrictive if a more diverse range of fluorinated structures are required. Though there

are a very limited number of selective monofluorinations of unprotected sugars,[126] polyols can be problematic in fluorination reactions and isolation of a single hydroxyl group via protecting group chemistry is usually required;[30,60,127] In addition, side reactions such as rearrangement or cyclic sulfonate formation can occur competitively when the most commonly used deoxyfluorination reagents such as DAST or Deoxo-fluor® are used (see review of nucleophilic fluorination chemistry earlier).[64,128-130]

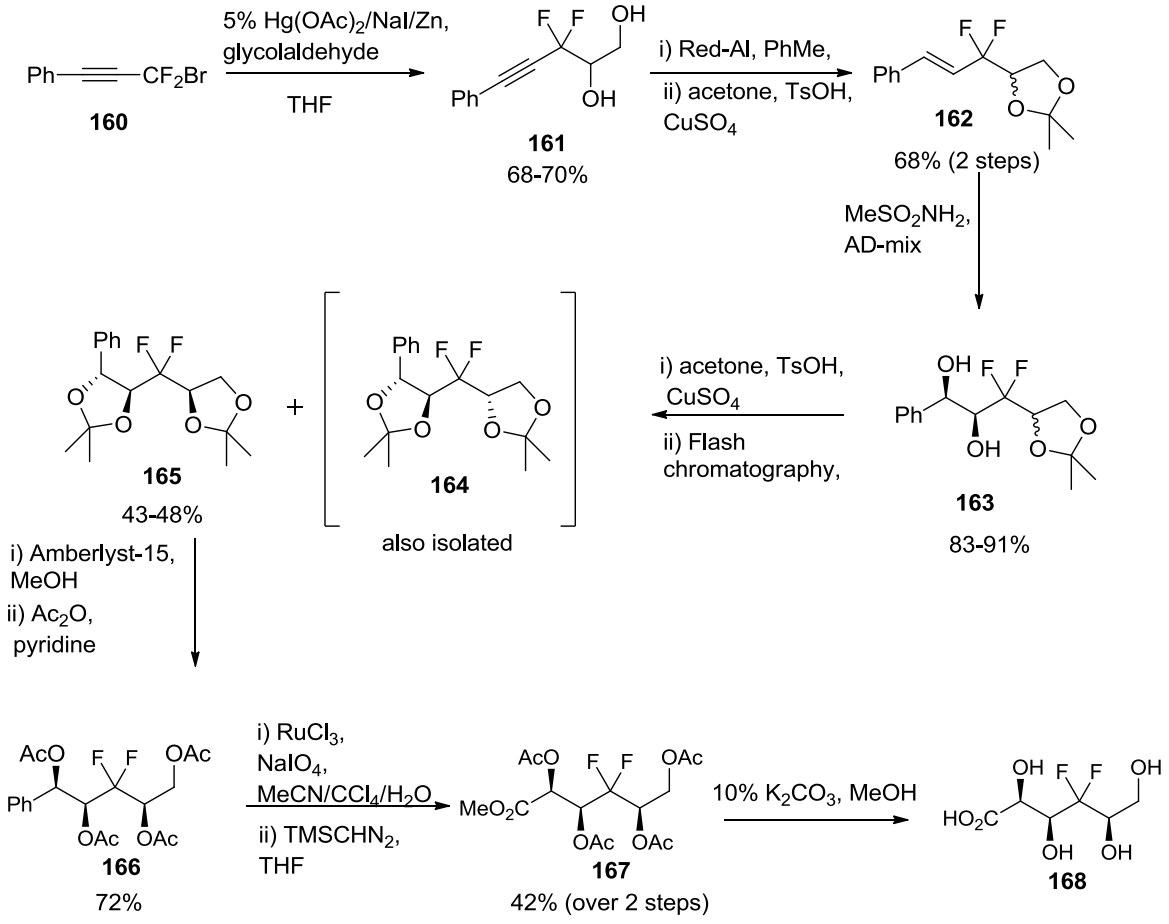
These limitations and the extensive protecting group chemistry required to overcome the lack of selectivity when using these fluorination reagents, produce a unique synthetic challenge towards each potential target molecule.[60,131]

1.5.4. *De Novo* methods towards fluorinated saccharides

An attractive and, as of yet, underused alternative is to utilise inexpensive and readily available (and, perhaps more importantly, fluorinated) general building blocks as a start point to enable potentially stereodivergent *de novo* syntheses.[132] In this way, by applying the modern methodology of asymmetric synthesis, entire libraries of related sugar analogues could be generated in high enantiomeric excess from a single versatile fluorinated building block. This is in stark contrast to the existing methodology, whereby specific chiral molecules are manipulated to deliver unique targets.

One of the first examples of a direct and stereodivergent route to highly enantiomerically enriched fluorinated products was performed within our laboratory.[2] Aldonic acid analogue **168** was synthesized in a stereoselective fashion from the achiral starting material, (bromodifluoromethyl)alkyne **160** (Scheme 56). The alkyne **160** was prepared in good yield (85%) by adding lithioalkyne to the dibromodifluoromethane electrophile

at -78°C. Addition of the resulting alkyne **160** to commercial glycolaldehyde *via* zinc-mediated addition in the presence of a Hg(II) catalyst (either $Hg(OAc)_2$/NaI in THF or $Hg(OCOCF_3)_2$ in DMF) yielded the desired product **161** in a reproducible 70% yield.



Scheme 56

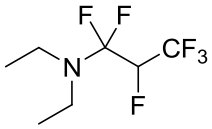
Reduction of the alkynyl group with Red-Al and protection of the racemic diol as the acetonide **162** occurred in 68% yield over the two steps. Sharpless asymmetric dihydroxylation was then carried out in high yield (91% with AD-mix β). The inseparable diastereoisomeric diol **163** were protected as the *bis*-acetonides, which were separated successfully by column chromatography to afford *bis*-acetonides **165** and **164**.

Methanolysis of the *bis*-acetonide **165** and *per*-acetylation to **166** set the stage for a successful oxidative cleavage and **167** was isolated after work-up with TMS diazomethane. Exposure to catalytic potassium carbonate in methanol delivered aldonic acid **168**.

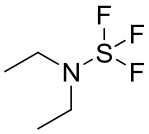
Our aim is to explore new methods in nucleophilic fluorination chemistry to assist in the generation of 6-deoxy-6-fluorosugar derivatives *via de novo* synthetic strategies such as the aldonic acid synthesis. As this strategy differs from the chiral pool method in that the fluorine atom is usually introduced near the beginning of the synthesis, rather than the end, the building block approach is generally unsuitable for synthesising ^{18}F labelled fluorosugars. However, the stereodivergent syntheses that are possible with this route potentially allow rapid access to families of fluorinated molecular probes which may be used for analysis of enzyme mechanistic pathways.

2. Evaluation of a new nucleophilic fluorination method

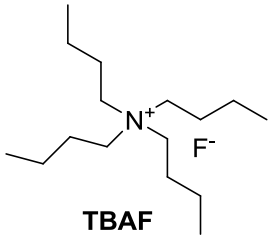
Nucleophilic fluorination involving displacement of a good leaving group by the fluoride anion, is a widely used reaction but still proves to be a surprisingly difficult transformation to achieve generally and reliably.[133,134] Reagents capable of performing nucleophilic fluorination chemistry are often costly, hazardous or both.[29,96] In addition fluorinating agents such as DAST, TBAF or the Ishikawa reagent **169** can be effective but competing side reactions are prevalent even for simple substrates and yields can suffer dramatically as a result.[135-137]



169



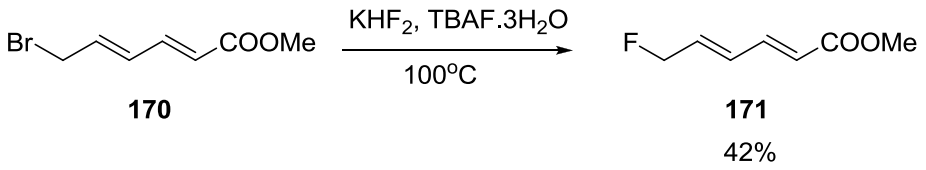
DAST



TBAF

We were therefore very interested in exploring the scope and limitations of a promising new solvent-free melt fluorination reaction developed within the laboratory.[5] Many nucleophilic fluorination reactions are carried out in acetonitrile,[138] and given the current global shortage, a solvent free fluorination method would be highly desirable. It had been found that certain allyl bromides could undergo successful monofluorination upon exposure to a mixture of tetrabutylammonium fluoride (TBAF.3H_2O) and potassium hydrogen fluoride (KHF_2) heated to melting (>60^oC) in the absence of solvent.[3] This

method had proved quite successful with a limited number of substrates; for example the fluorination of bromohexadienoate (Scheme 57), had proceeded in moderate yield.[1]

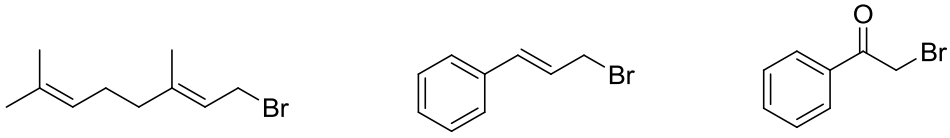


170 **171**

42%

Scheme 57

To explore the scope of this reaction, three structurally simple, commercially available bromides were chosen as substrates for the reaction (Figure 7).



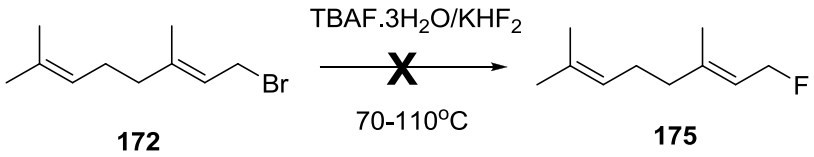
172 **173** **174**

Figure 7

Reproducible results were not easy to obtain for these solvent free reactions. Upon heating, TBAF.$3H_2O$ begins to melt to form a clear viscous liquid, presumably as a result of partial dissolution of the salts as the water content is liberated. Insoluble solid material, assumed to be KHF_2, usually remained at the bottom of the reaction vessel, or fused with the glass walls. The liquid reaction mixture was found to be corrosive to standard glassware, causing etching on the glass surface. This may suggest that the reaction generates hydrogen fluoride *in situ* although, as the mechanistic detail for this fluorination reaction is poorly understood, we are unable to comment on this further.

Nonetheless, these reactions were treated as if HF generation was a possibility, and careful quenching of the reactions with sodium hydrogen carbonate was performed before work-up.

2.1. Fluorination of geranyl bromide 172



Scheme 58

The fluorination of bromides **172**, **173** and **174** using the solvent-free TBAF.$3H_2O$/KHF_2 method delivered mixed results with erratic yields. Geranyl bromide, **172**, proved to be the poorest substrate under these conditions; even trace quantities of the desired product could not be observed in ^{19}F NMR of crude products.

Exposure of geranyl bromide to a mixture of TBAF.$3H_2O$/KHF_2 at 100^{o}C for 30 minutes yielded a viscous brown gum, that resembled neither starting material **172** nor the desired product **175** by ^{1}H NMR upon work-up. The lack of any sign of definable structure and the complex series of multiplets produced suggested the fluorination conditions had caused complete degradation of the starting material. Although much of the initial exploration of this fluorination methodology was performed without the availability of ^{19}F NMR, this was of only minor importance as the $^2J_{H\text{-}F}$ splitting is very distinctive (between 40-50Hz) and can be used as an excellent diagnostic of the success of any reactions in crude ^{1}H NMR spectra. Later analysis of the crude reaction mixtures by ^{19}F NMR confirmed that no fluorination had occurred.

In an effort to address the apparent complete decomposition of the substrate, a number of modifications to the reaction temperature and length were investigated. As the melting of the TBAF.$3H_2O$/KHF_2 mixture occurs between 60-70^oC, 70^oC represents the lowest temperature at which the reaction can be performed. Additionally the majority of these experiments were performed in pressure resistant microwave vessels (due to their consumable nature and ease of stirring) allowing temperatures above 100^oC to be achieved while maintaining the water content in the reaction. The water content was perceived to be important, assisting the mobilisation of the reaction media and success of the fluorine introduction. For example the Hou[4] fluorination methodology, discussed in more detail later, proceeds with KF.$2H_2O$, but no reaction occurs when anhydrous KF is used. It was found that neither shorter reactions (10 minutes) at higher temperatures (110-125^oC) nor longer reactions (1 hour) at lower temperatures (70^oC) had any beneficial effect on the fluorination reaction and the resulting level of degradation of starting material.

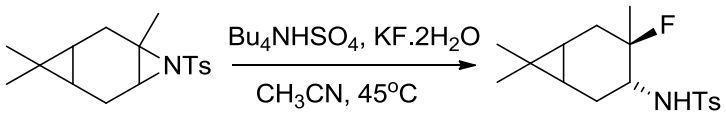
The synthesis of geranyl fluoride has been achieved previously in the literature, by Guijaro and Yus,[139] using commercial TBAF.$3H_2O$ in acetonitrile under the fluorination conditions reported by Albanese.[93] They reported that the desired pure product was recovered in good yield upon evaporation of the solvent media after aqueous work-up. For comparison, this reaction was repeated in our laboratory and we were unable to find any trace of the desired product in the crude mixture; the ^{19}F NMR spectrum suggested that fluorination had most likely occurred internally (Scheme 59) (absence of the distinctive $^2J_{H\text{-}F}$ splitting and a multiplet (δ_F -140.1 to -140.7), including repeating splitting $^3J_{H\text{-}F}$ 11.4, consistent with a tertiary fluorine). This is an unusual

finding and it is unclear why we were unable to replicate Guijaro and Yus's results. As the reaction is a relatively simple one involving only two reagents and a reaction solvent we can only speculate that the contradicting outcomes may be a result of differing qualities of commercial TBAF.$3H_2O$ used (possibly arising from different batches, suppliers or reagent grade).

172 **176**

Scheme 59

Around the time of this investigation of the TBAF.$3H_2O$/KHF_2 method, an independent study concerned with adapting an alternative nucleophilic fluorination method reported by Hou, was underway within our laboratory.[4] This method, which used potassium fluoride (KF.$2H_2O$) and tetrabutylammonium sulfate (Bu_4NHSO_4) in refluxing acetonitrile, had been used to convert a range of aziridines to β-fluoro amine derivatives (Scheme 60).



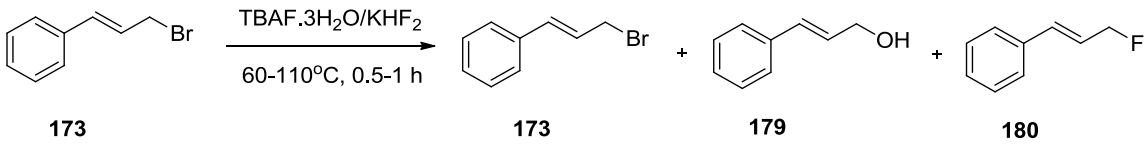
177 **178**
76%

Scheme 60

The presence of solvent meant that the reaction was practically easier to perform, and significantly less etching of the glassware was observed due to the improved dispersion

of solid material in the reaction mixture. Geranyl bromide was exposed to the Hou fluorination conditions and the repeated failure to observe any fluorinated product allowed us to conclude that geranyl bromide was a very poor substrate for nucleophilic fluorination.

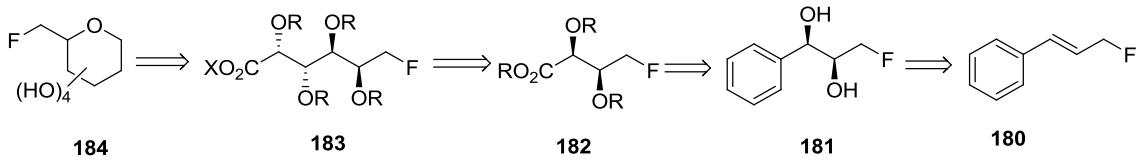
2.2. Fluorination of cinnamyl bromide 173



Scheme 61

Cinnamyl bromide **173** proved to be only marginally better than geranyl bromide **172** as a substrate for fluorination using the $TBAF.3H_2O/KHF_2$ method. Once again we found it difficult to obtain reproducible results, and complex mixtures containing cinnamyl bromide **173**, cinnamyl alcohol **179** and cinnamyl fluoride **180** were obtained (Scheme 61). Purification of these mixtures proved to be problematic due to their similar elution times on silica and decomposition upon attempted distillation. Despite these erratic results, a small quantity of the desired cinnamyl fluoride **180** was successfully synthesised and obtained in pure form using this procedure, albeit in low yield (9%).

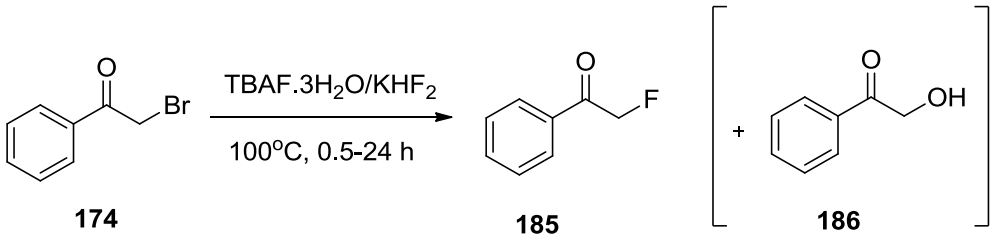
The difficulty encountered in synthesising cinnamyl fluoride was disappointing as this substrate could be a useful building block in syntheses of fluorinated sugars (Scheme 62), a key interest of our research group.



Scheme 62

The alkenyl group could be used for the introduction of stereogenic centres with control of absolute configuration *via* a Sharpless Asymmetric Dihydroxylation. The phenyl group could be converted to the carboxylic acid *via* ruthenium catalysed oxidation,[140,141] affording a C4 fluorinated building block. The carboxylic acid could be reduced to the aldehyde oxidation level and the carbon chain extended using Wittig chemistry. Dihydroxylation of the new olefin bond and subsequent lactonisation and reduction would have allowed the generation of fluorinated hexose analogues. Unfortunately the low yield of cinnamyl fluoride, and the difficulties encountered in its purification, meant the quantities we were able to synthesise were prohibitively small to use in a multi-step synthetic sequence of the type shown in Scheme 62.

2.3. Fluorination of bromoacetophenone 174



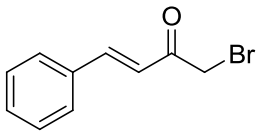
Scheme 63

The substrate found to be most compatible with this fluorination chemistry was 2-bromoacetophenone **174**; the desired fluorinated product **185** was obtained in good yield (73%) reproducibly. It was also observed that longer reaction times favoured the formation of the by-product 2-hydroxyacetophenone **186**, (from ~50% after 1 h to ~100% after 24 hr by ^{1}H NMR). This observation is somewhat surprising as it is difficult to envisage the desired fluorinated product once formed participating in a nucleophilic substitution reaction with hydroxide (or water) as the nucleophile and fluoride as the leaving group. It seems more likely that longer reaction times allow a greater level of decomposition of the fluorinated product to take place under the harsh reaction conditions leaving only the unwanted by-products observable by ^{1}H NMR.

A reaction time of 30 minutes was found to give the optimal balance between conversion of starting material to product and the unwanted by-product formation. Comparable yields for the formation of 2-fluoroacetophenone **185** were also achieved using Hou's conditions and, as this chemistry was more amenable to scale-up (homogeneous stirring is more easily achieved with solvent), it was used as the primary fluorination method for the formation of allyl fluorides and α-fluoroketones.

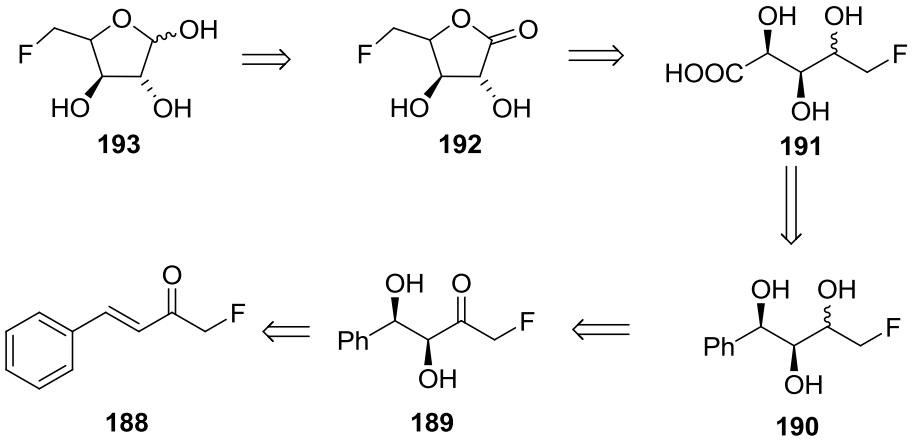
2.4. Preparation and fluorination of α-bromoketone 187

Carbonyl groups next to substitution centres activate them more strongly than alkenyl groups so α,β-unsaturated bromoketone **187** was prepared and examined.



187

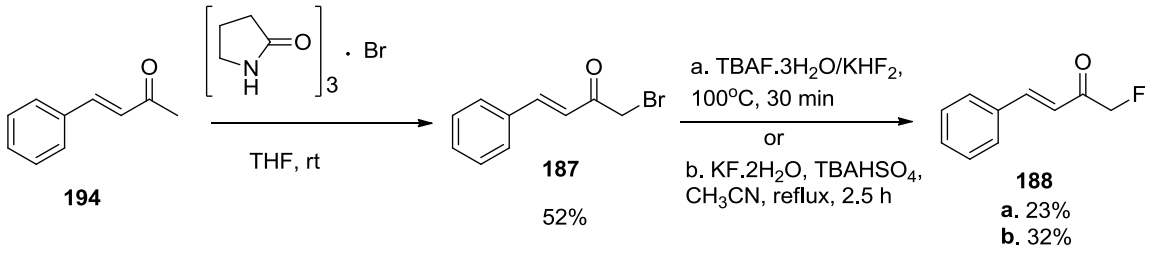
This target molecule was also structurally similar to 2-bromoacetophenone **185**, and therefore we were confident the nucleophilic fluorination would proceed well. More importantly however, the molecule has functionality to be an achiral precursor for fluorinated sugars (Scheme 64). Once again we proposed to utilise the double bond present to introduce stereogenic centres with control of absolute configuration *via* the Sharpless Asymmetric Dihydroxylation reaction. Subsequent reduction of the ketone to the corresponding alcohol and ruthenium-catalysed oxidation (after triol protection) of the phenyl group to the carboxylic acid[140,141] would promote lactonisation to form the fluorinated furanone **192**; the final targets here would be 5-deoxy-5-fluoro pentoses **193**.



Scheme 64

Although the synthesis of 4-phenyl-3-but-2-one **194** can be quickly and easily achieved *via* the condensation of benzaldehyde with acetone,[142] we preferred to use the commercially available material as the subsequent bromination step benefits greatly from a high level of purity in the starting material. The pyrrolidone hydrotribromide (PHT),[143] reagent selectivity brominates ketones.[144] Methyl ketone **194** was stirred with PHT in THF under nitrogen to afford the desired bromide **187** in moderate yield (52%)

as a pale green solid, which slowly assumed a dark green colour upon storage in the fridge. Despite the significant change in appearance of the compound, no change in the purity of the material was observable by ^{1}H NMR or GC-MS. Unfortunately the fluorination step progressed in a disappointingly low yield with both the TBAF.3H_2O/KHF_2 (23%) and KF.2H_2O (32%) methods. The low yield of this reaction was attributed to the tedious purification of the material; flash chromatography followed by distillation under reduced pressure was required to achieve an acceptable level of purity (removal of yellow colour and high field peaks in the ^{1}H NMR spectrum).



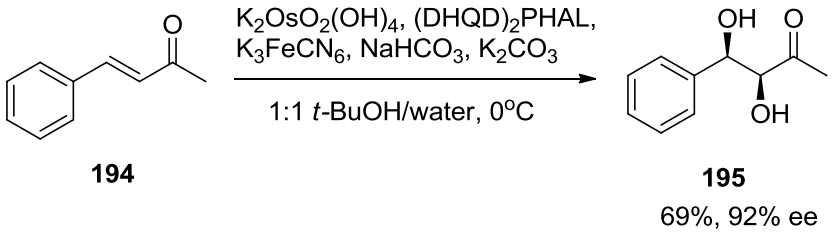
Scheme 65

2.5. SAD of α-fluoroketone 188

We began to examine the Sharpless Asymmetric Dihydroxylation step on the small amounts of available material. Although the asymmetric epoxidation reaction remains a significant and powerful synthetic tool[145] the reaction is limited by the need for a directing functional group in the substrate (allylic alcohol).[146-148] The Sharpless asymmetric dihydroxylation is a more versatile reaction in terms of substrate tolerance, and is a practical synthetic tool for our purposes. The standard conditions for this reaction utilise a relatively complex mixture of; potassium osmate, potassium ferricyanide, potassium carbonate and a chiral ligand (either $(DHQ)_2$PHAL or

$(DHQD)_2PHAL$) in a mixed *t*-BuOH/water solvent. One of the main advantages of the SAD is the absence of air or moisture sensitivity (in contrast to the Sharpless Asymmetric epoxidation which is extremely moisture sensitive and requires the use of molecular sieves). Pleasingly the solid reagents are commercially available in a pre-mix in the most commonly used stoichiometry, which significantly reduces the complexity of the reaction even further.

The conjugated double bond in unsaturated ketones is relatively electron-deficient and reacts slowly with osmium tetroxide to give ketodiol products.[149] However, Sharpless has shown that the so-called "improved" conditions[150] (1 mol% $K_2OsO_2(OH)_4$ *cf.* 0.2 mol%) effected the dihydroxylation of the non-fluorinated enone **194** (Scheme 66) in good yield and excellent enantiomeric excess (69% and 92% respectively using AD-mix β).[151] The sodium hydrogen carbonate was present to act as a buffer and maintain the pH at the desired level; dihydroxylation reactions operate best at high pH (<10).

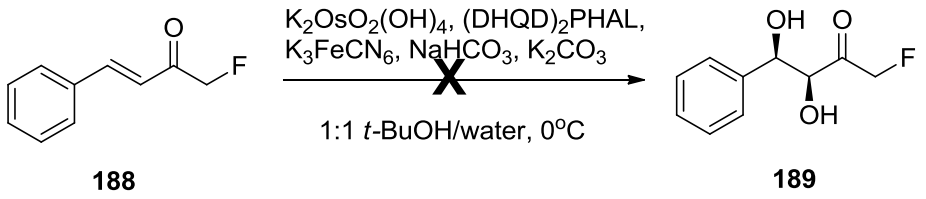


194 **195**

69%, 92% ee

Scheme 66

The remote fluorine atom on our substrate **188** was expected to have minimal influence on the outcome of the dihydroxylation reaction so we subjected **188** to the same buffered AD conditions described in the literature for **194** (Scheme 67).[151,152]



188 **189**

Scheme 67

An aliquot was taken after the mixture had been allowed to stir at 0°C overnight, and was analysed by ^{1}H NMR, revealing that almost no conversion of the starting material **188** had taken place. The reaction was allowed to continue stirring for a further 2 days, and then quenched with saturated sodium sulfite solution, worked up and analysed. Both ^{1}H and ^{19}F NMR spectra suggested that the majority of the crude product was starting material **188**, although the presence of a strong aldehyde signal ~10 ppm in the ^{1}H NMR was of most concern (Figure 8).

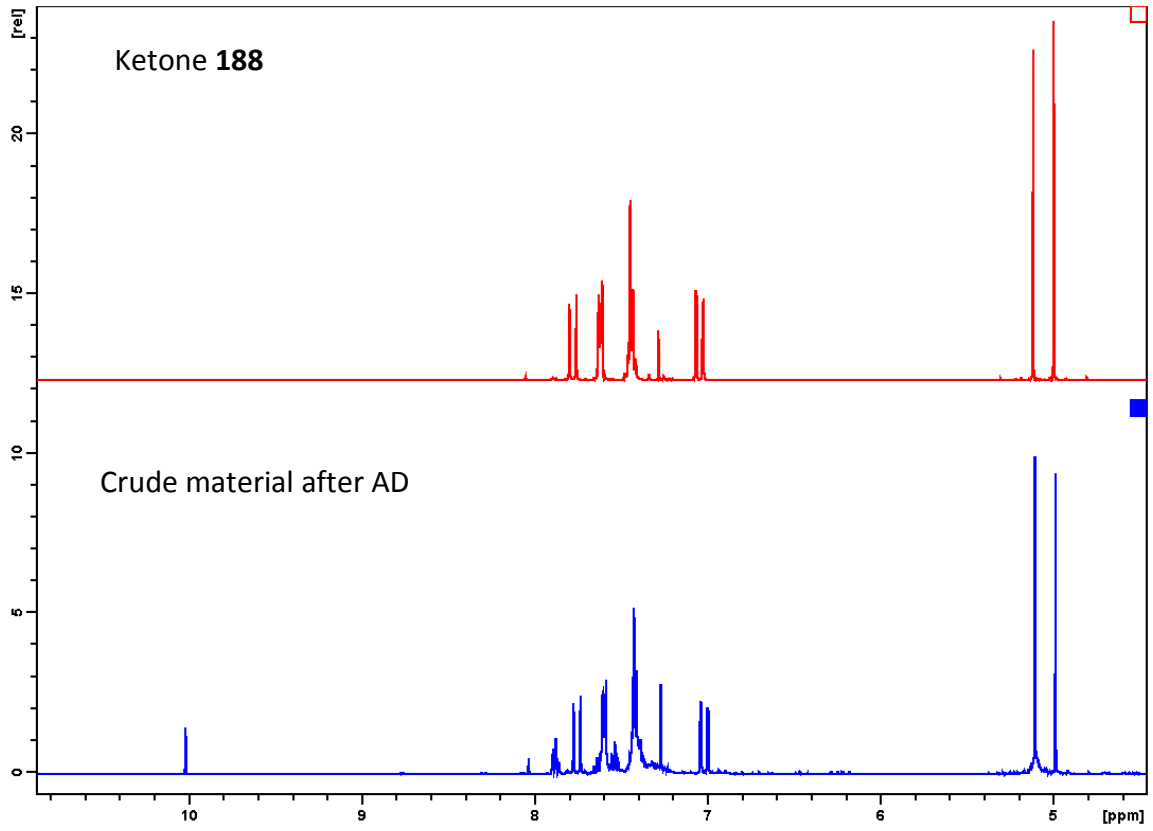
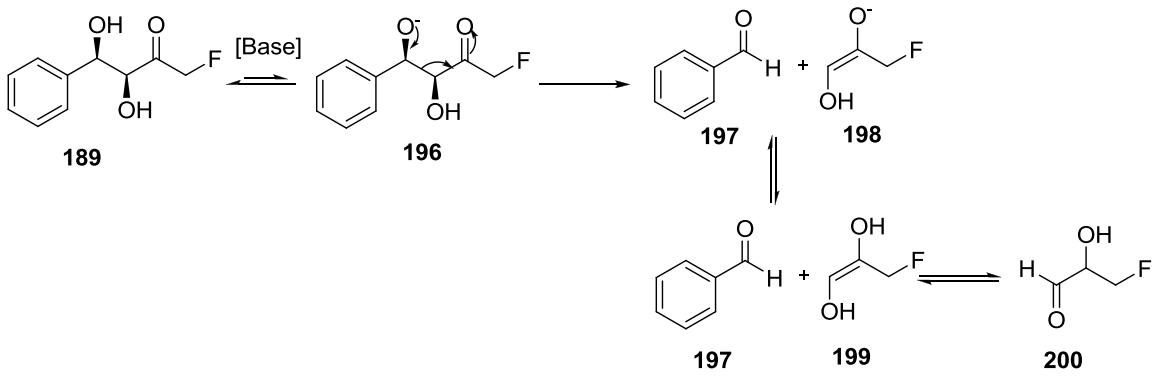


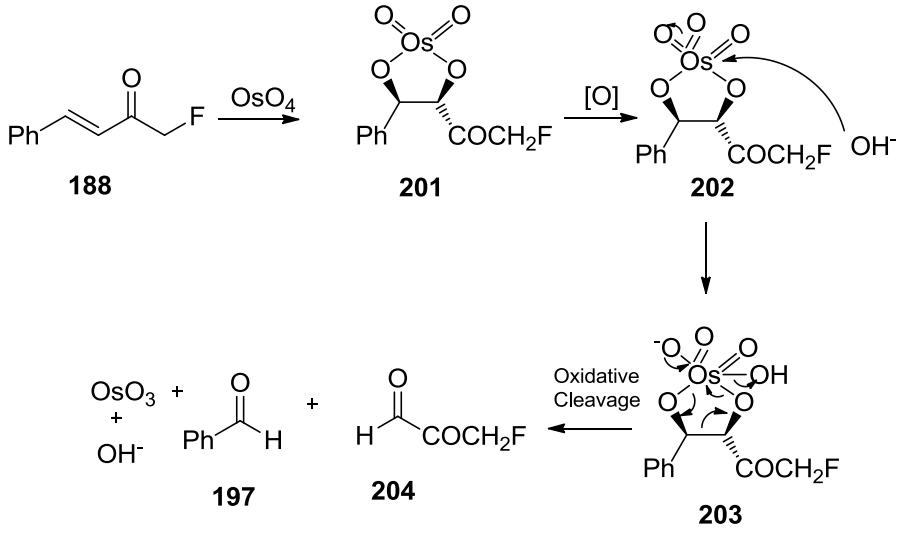
Figure 8. Partial ^{1}H NMR (400 MHz) spectra comparing SM and the crude product from the SAD of α-fluoroketone **188**

The presence of the aldehyde signal suggested that oxidative cleavage of the double bond was occurring instead of the desired dihydroxylation reaction. Although there is literature precedent for the oxidative cleavage of olefins in the presence of osmium tetroxide,[153] strong co-oxidants such as hydrogen peroxide or Oxone™ are usually required. There is very little evidence of this oxidative cleavage occurring using the oxidatively milder Sharpless AD conditions, and this is only described as "an undesired retro-aldol reaction" when observed, with no further detail given.[151,154] If oxidative cleavage of the double bond does occur, it is likely that low molecular weight, volatile

fluorinated molecules would be produced as well as benzaldehyde. Schemes 68 and 69 show two postulated mechanisms for two possible pathways for generation of aldehydes from the AD; a retro-aldol reaction (Scheme 68) and an osmium tetroxide catalysed oxidative cleavage of the double bond (the osmium catalysed mechanism is likely to be more complex in the asymmetric reaction) (Scheme 69).



Scheme 68



Scheme 69

2.6. SAD of methyl ketone 194

As a control experiment, the literature procedure for the Sharpless asymmetric dihydroxlylation of **194** was carried out in order to determine if the cleavage problem was inherent to the fluorinated substrate, or was caused by the experimental technique or reagents used. Although the desired product **195** was synthesised and isolated successfully, the product was obtained in significantly lower yield than that quoted in the literature (47% *cf.* 77%) and benzaldehyde was isolated as a by-product from the flash chromatography, indicating scission of the double bond had occurred (Figure 9).

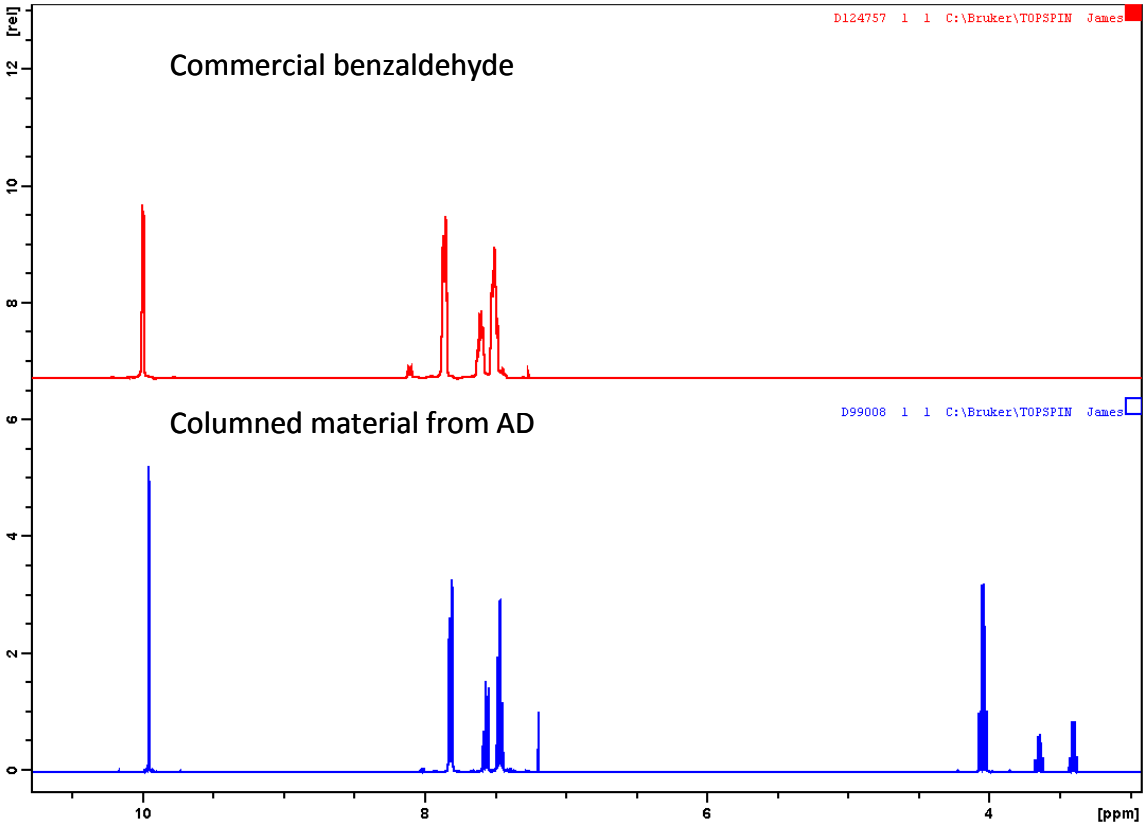
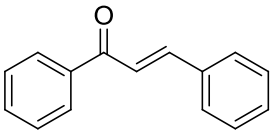


Figure 9. Partial ^{1}H NMR (400 MHz) spectra of benzaldehyde (commercially available and isolated from the SAD of **194**)

These findings contradict those of a paper by Sharpless and co-workers[151] which stated that although the retro-aldol reaction was observed during AD of chalcone (1,3-diphenyl-2-propen-1-one, **205**), other α,β-unsaturated ketones, including **194**, were successfully dihydroxylated under buffered conditions with no evidence of the retro-aldol cleavage.



205

In an effort to assess the stability of the product to the reaction conditions, the isolated diol **195** was exposed to the Sharpless AD conditions and monitored by ^{1}H NMR over a period of 2 days. Again, oxidative cleavage occurred, with the aldehyde peak growing in slowly with time (Figure 10).

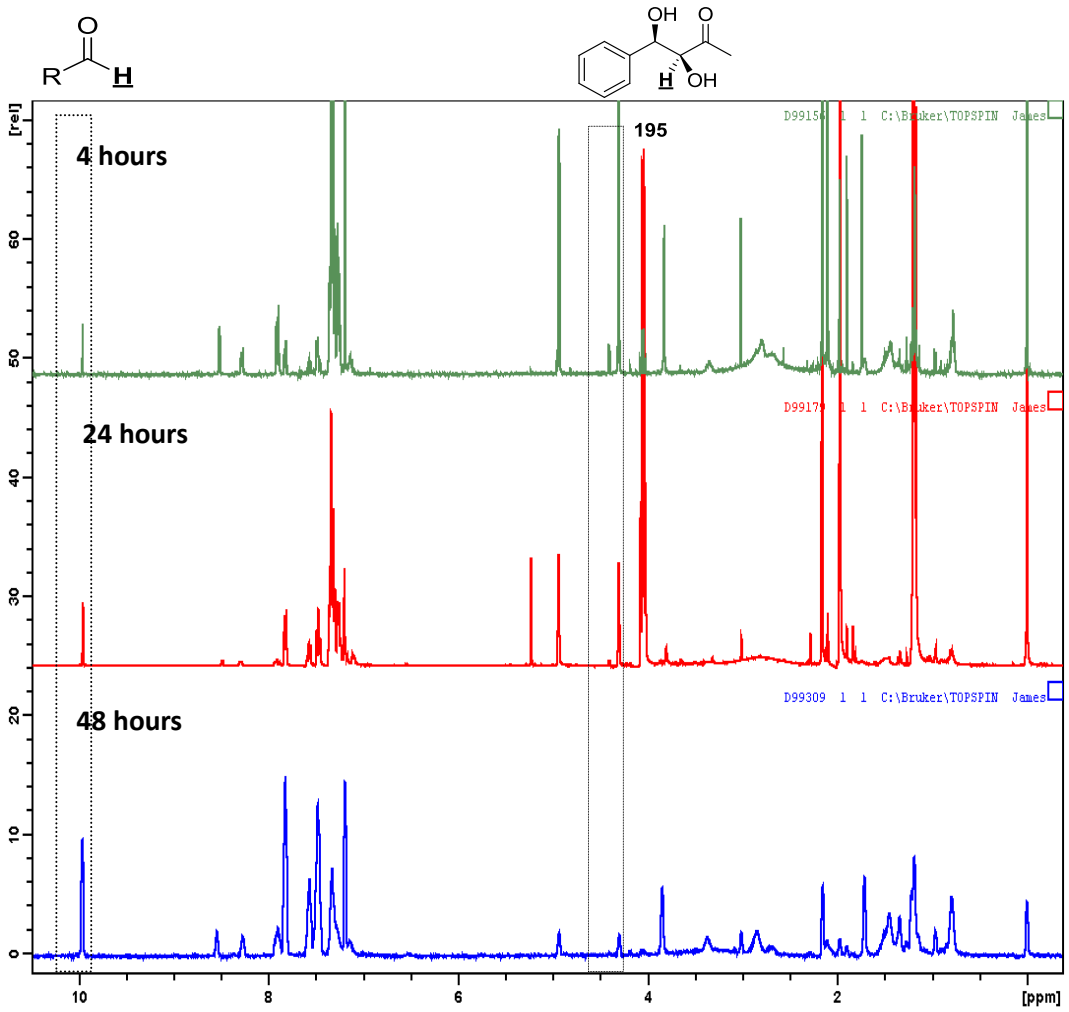


Figure 10. Partial ^{1}H NMR (400 MHz) spectra showing growth of scission products and consumption of diol **195** under SAD conditions

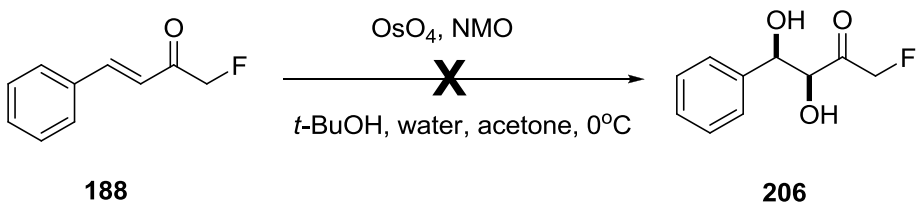
2.7. SAD of olefin 194 at high pH

We speculated that the pH of the reaction may be the source of the cleavage problems we had encountered. As previously mentioned Sharpless Asymmetric Dihydroxylations of internal olefins are said to work best at high pH's (around 12)[155] while osmium catalysed cleavage of double bonds have been shown to be sensitive to the acidity of the

reaction media.[153] It had been noted that the reactions performed as part of this programme of study had been carried out at around pH 8 (to pH paper), significantly lower than the recommended value. In order to establish whether the low pH had a significant influence on the outcome of the reaction, the AD of **194** was carried out as before and the pH adjusted to pH 12 by dropwise addition of a 50% $KOH_{(aq)}$ solution. However, once again significant quantities of benzaldehyde were visible in the crude ^1H NMR spectrum with no visible improvement over previous experiments.

2.8. Dihydroxylation of olefin 188 under UpJohn conditions

As attempts to dihydroxylate the olefin enantioselectively had failed, we wanted to establish whether a racemic dihydroxylation using UpJohn conditions would be more successful.



188 **206**

Scheme 70

Ketone **188** was stirred with NMO and a catalytic quantity of osmium tetroxide in a mixture of *t*-BuOH, water and acetone at 0°C (Scheme 70). Although analysis of the crude mixture after work-up showed that the starting material had been consumed, the ^1H NMR spectrum revealed that a significant quantity of benzaldehyde was present with no evidence of the desired product. Fragmentation of the substrate under these conditions was also supported by at least 6 distinct signals in the ^{19}F NMR, the largest of which is neither starting material **188** nor diol **206**. The starting material **188** appears as

a triplet of doublets in the ^{19}F NMR at -228.8 ppm, whereas the fragments appear as triplets from ~(-227.5)-(241.0) ppm.

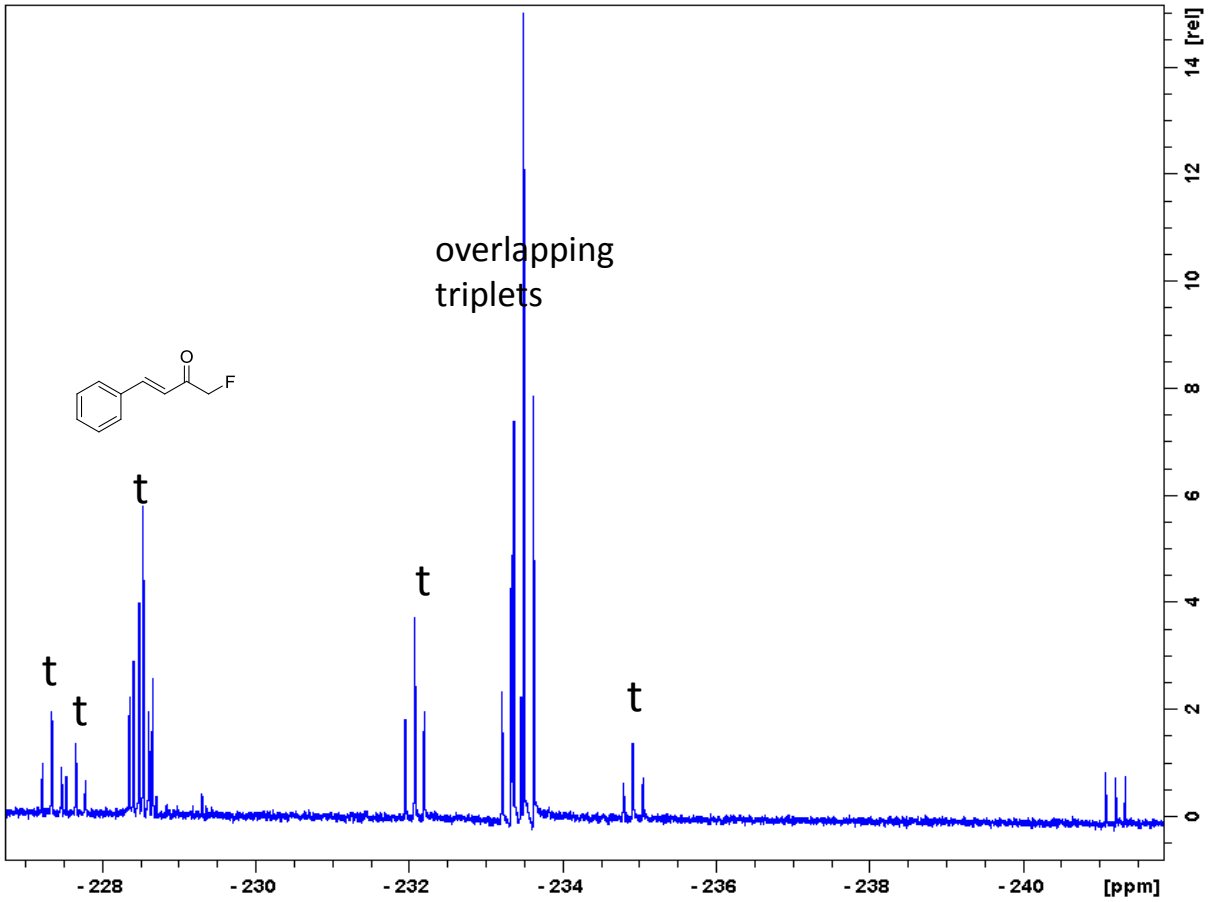
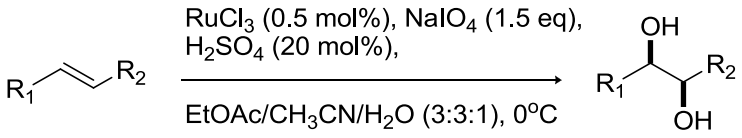


Figure 11. Partial ^{19}F NMR (376 MHz) spectrum showing evidence of the fragmentation of **188** under UpJohn conditions

2.9. Ruthenium-catalysed dihydroxylation of allyl fluoride 188

Ruthenium-catalysed hydroxylation reactions have been reported to provide easy access to *syn*-diols,[156,157] although some of the associated drawbacks have limited their use. Over-oxidation is a common side reaction and the high catalyst loadings can offset the lower price of ruthenium compared to osmium. Recently however, Plietker and

Niggemann published an improved protocol using low catalyst loading (0.5 mol%) under acidic conditions, affording the diols in good to excellent yields with only minor formation of side products (Scheme 71, Table 2).[158] Further, in a control experiment in the same article the rate of formation of scission products was shown to be slow in comparison to the timescale of the dihydroxylation. This suggested a possible solution to the problem of oxidative cleavage within our dihydroxylation reactions.



Scheme 71

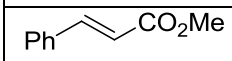
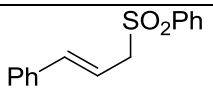
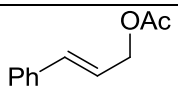
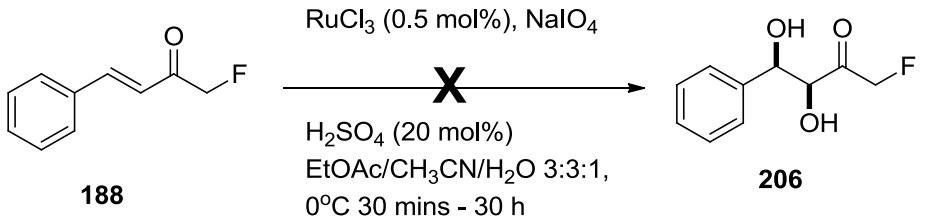
Substrate	Reaction time (mins)	Yield
	2	84
	5	94
	3	78

Table 2

The α,β-unsaturated ketone of interest **188** was reacted with ruthenium chloride at 0°C in the presence of sodium periodate in a mixture of water, ethyl acetate, acetone and sulfuric acid. Upon work-up the material was found to be predominantly starting material, with benzaldehyde clearly visible in the ^{1}H NMR, suggesting that the retro-aldol reaction was still competing with dihydroxylation.

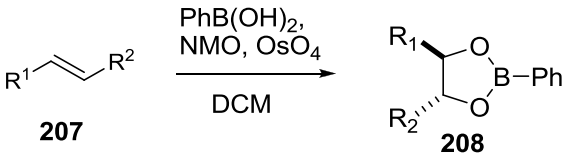


Scheme 72

Increasing the temperature of the ruthenium-catalysed reaction had been shown previously to favour the formation of the scission products,[158] so in an effort to drive the conversion we significantly extended the reaction time at lower temperature. The reaction was allowed to stir at 0^{o}C overnight with aliquots taken and analysed by NMR after 2, 24 and 28 hours. After 30 hours the reaction was worked up fully and analysis by both ^{1}H and ^{19}F NMR revealed that the longer reaction time had little, if any, effect on the degree of conversion of starting material. With no indication that the desired product had been formed the ruthenium-catalysed method offered no advantages and was therefore abandoned.

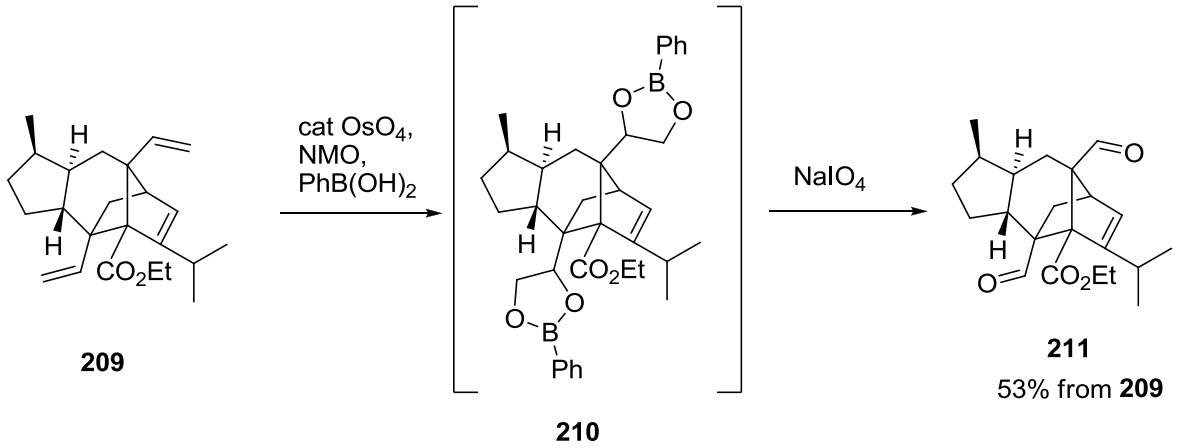
2.10. Narasaka modification

As our substrate of interest, **188**, had decomposed under all the dihydroxylation conditions assessed so far (Sharpless, UpJohn and ruthenium-catalysed) and as the product was obviously prone to fragmentation *via* a retro-aldol reaction, we wondered if protection of the diol *in situ* would be advantageous. We decided to investigate the interesting modification to the catalytic osmylation reaction made by Narasaka[159,160] in which phenylboronic acid replaces water as the agent which facilitates the release of the diolate from the osmium in the NMO/OsO_4 dihydroxylation cycle (Scheme 73).



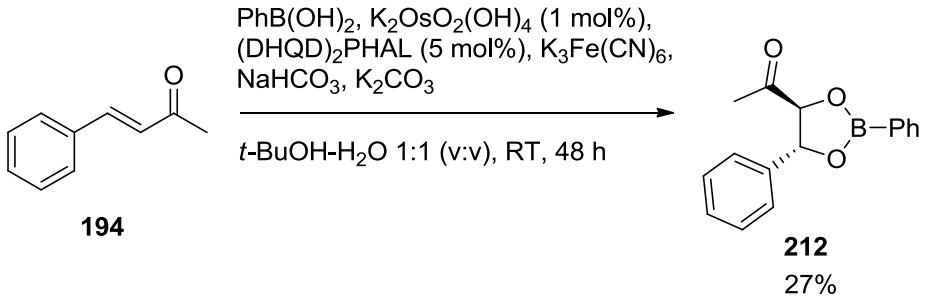
Scheme 73

This procedure elegantly achieves the *in situ* protection of the diols as cyclic boronate esters, which are highly soluble in organic solvents. Other reported advantages of this method over the standard UpJohn procedure include faster reaction times, even at lower osmium loadings, and fewer by-products from overoxidation.[161] For example in Narasaka's synthesis of (-)-Sordarin, selective oxidative cleavage of the two vinyl groups in **209** is one of the final steps. The two vinyl groups were converted into bulky cyclic boronate esters to prevent overoxidation of the highly reactive norborene unit, and after successful oxidative cleavage with $NaIO_4$, the desired dialdehyde **211** was synthesised in a reasonable 53% yield over 2 steps.[162]



Scheme 74

Recently, Muniz and co-workers reported the development of an asymmetric phenylboronic acid promoted dihydroxylation that gives rise to enantiomerically pure boronic esters from olefins.[163] It was found that upon addition of 1.2 equivalents of $PhB(OH)_2$ to the otherwise unchanged conditions for enantioselective AD reaction, completely selective olefin oxidation and concomitant formation of cyclic boronic esters took place. These were the only detectable products at quantitative olefin conversion and importantly, free diols were never observed. As this sequence formed boronic acids in good yield and high enantioselectivity for a diverse range of substrates, we decided to apply this to the fluorinated ketone **188**. However, it was decided to validate the Narasaka chemistry on commercially available benzylidene acetone **194** in the first instance (Scheme 75).



194

212
27%

Scheme 75

4-Phenyl-3-buten-2-one **194** was reacted under the 'improved' Sharpless AD conditions, as described previously with 1.2 equivalents of phenyl boronic acid present and ambient temperature. Upon work up and purification by flash chromatography the desired boronate ester **212** was isolated as a white solid in a disappointing (27%) yield.

Although we experienced difficulty in detecting a strong ion in either the GCMS or electrospray, the substantial difference in chemical shifts and splitting pattern observed between the pure diol and boronate product for the protons attached to C-3 and 4 in ^{1}H NMR confirm a new product has indeed been formed.

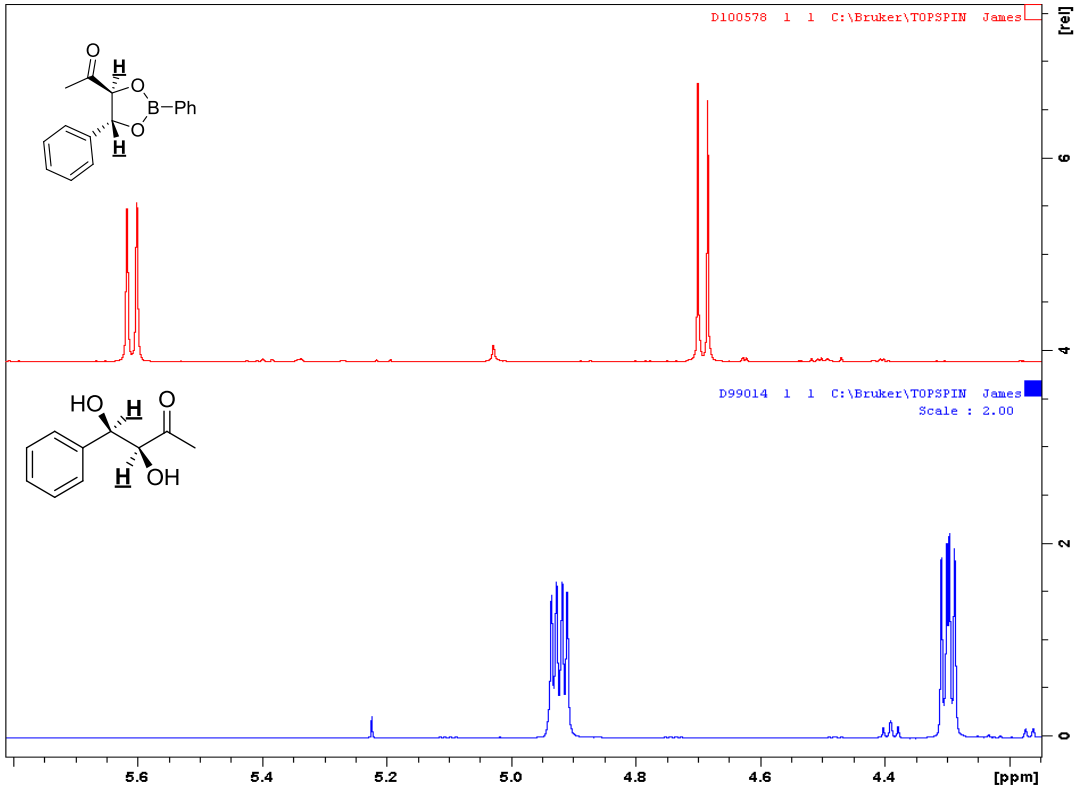


Figure 12: Partial ^{1}H NMR (400 MHz) spectra of diol **195** and boronate ester **212** showing change in chemical shift and splitting for protons on C3 and C4

Accurate mass analysis of **212** was only possible *via* EI analysis (with probe insertion). The sample yielded a molecular ion envelope by EI, and accurate mass measurement of the monoisotopic ^{10}B isotope ion was attempted. Although the m/z of this ion correlates with the expected m/z, it is not fully resolved from an isotopic ion of the reference compound FC43. The sample's ^{11}B isotope, (which is a mixture of isotopologues) was therefore also measured.

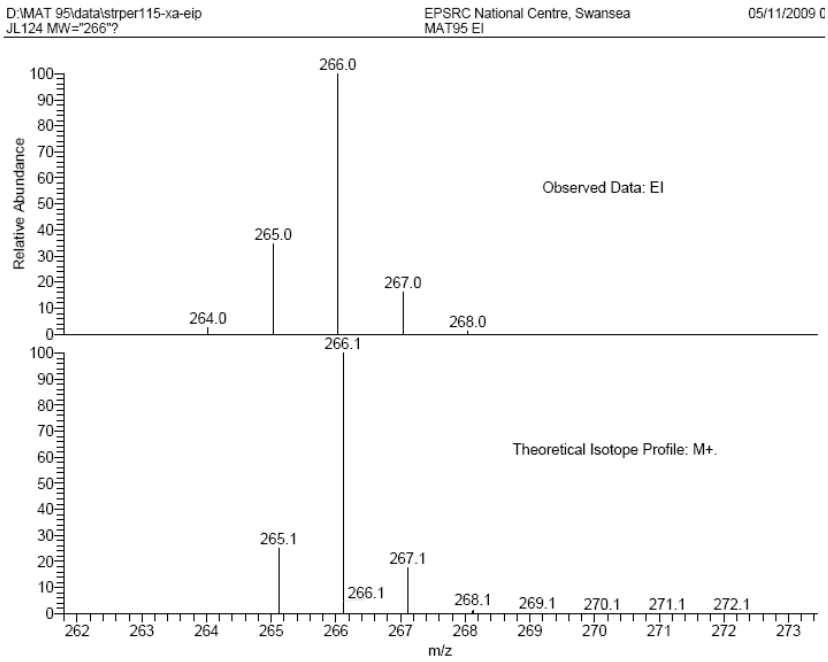


Figure 13

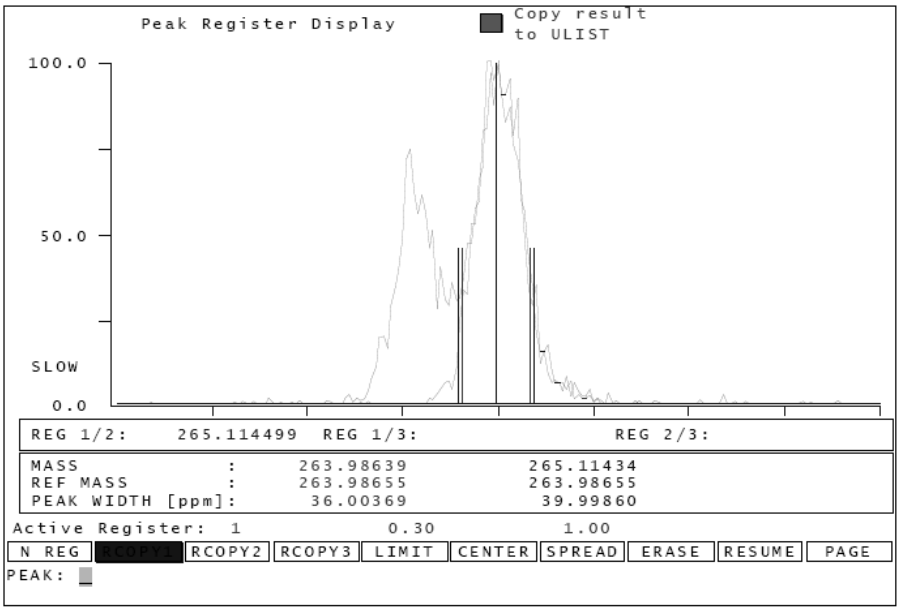
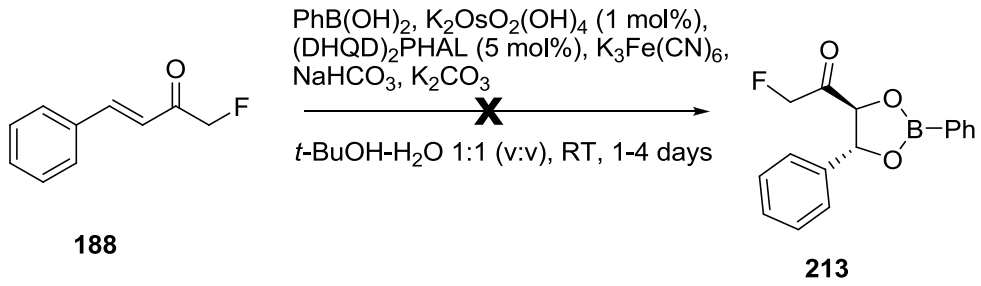


Figure 14: Accurate mass analysis of boronate ester **212**

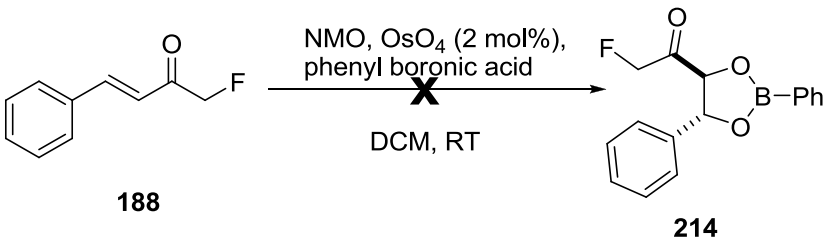
Fluorinated olefin **188** was exposed to identical conditions to **194** and periodically sampled and analysed by ^{1}H NMR to monitor the progress of the reaction. The reaction seemed to proceed much slower than that of the non-fluorinated analogue **194** as starting material could still be observed after 24 and 48 hours in the crude ^{1}H NMR spectrum. The reaction was allowed to continue in an effort to push the conversion of the starting material; upon work-up after 96 hours, the crude product was observed to contain trace starting material and a disappointingly large aldehyde peak, presumably as a result of scission. The ^{19}F NMR spectrum contained only weak signals, perhaps due to the fluorine atom of **188** being lost as volatile small molecules after fragmentation.



188 **213**

Scheme 76

Narasaka *et al.* also published a variant procedure in DCM,[159] as opposed to the usual partly aqueous environment of a *t*-BuOH/water mixture (Scheme 77). Unfortunately, this reaction also proved unsuccessful with large quantities of benzaldehyde present suggesting scission of the double bond had occurred.



188 214

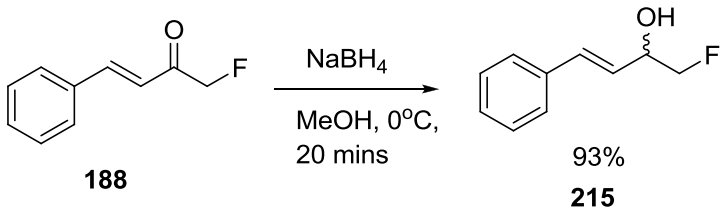
Scheme 77

It is clear from these data that the fluorinated α,β-unsaturated ketone **188** could not be dihydroxylated under any of the well known conditions. Although disappointing, this finding suggests that the influence of even a remote fluorine atom on the chemical properties and reactivity of a molecule can be considerable. Although the difference in ketones **188** and **194** is minimal (a hydrogen α to the carbonyl group is replaced by a fluorine) the ability of the substrate to undergo dihydroxylation changes dramatically. This is particularly surprising as one would expect the carbonyl functionality to exert a much stronger influence on the double bond (the point of action for dihydroxylation chemistry) than the electronegative fluorine atom. However even unfluorinated ketone **194** decomposes to some extent and the introduction of fluorine into this molecule obviously drives the outcome of the dihydroxylation reaction completely to the scission products.

2.11. Synthesis and attempted dihydroxylations of allylic alcohol 215

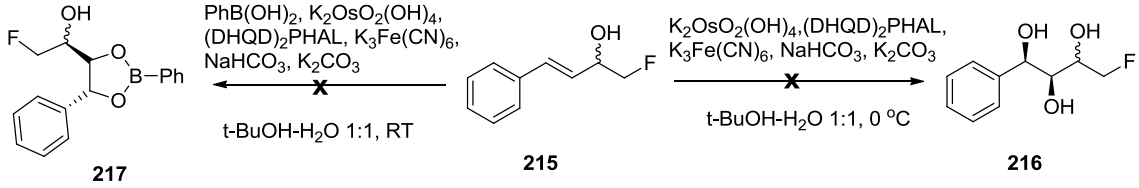
As various attempts to dihydroxylate the α,β-unsaturated ketones had failed, racemic alcohol **215** was prepared *via* reduction. It was expected that the alcohol would react more rapidly under the Asymmetric Dihydroxylation conditions.[164] The resulting

diasteroisomeric triols could be separated in due course. Our proposed route to monofluorinated sugar like compounds from structure **188** would have involved reduction of the ketone functionality at a later stage anyway; (see retrosynthetic pathway Scheme 64). This modification would however deplete the amount of enantiomerically pure material available by 50% at the triol stage.



Scheme 78

Ketone **188** was stirred with sodium borohydride in methanol at 0°C; upon workup alcohol **215** was obtained in close to quantitative yield (93%). This is believed to be the first synthesis of fluorinated alcohol **215**; unfortunately attempts to dihydroxylate the allyl alcohol **215** under Sharpless AD and Narasaka modification conditions were unsuccessful (Scheme 79), the reactions giving poor conversion of starting material and/or visible scission of the olefin bond into benzaldehyde.



Scheme 79

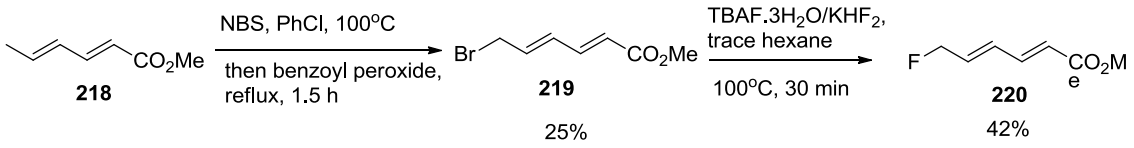
2.12. Conclusions

The effectiveness of the TBAF.$3H_2O$/KHF_2 solvent free fluorination method was evaluated against three commercially available allyl bromides, and found to give comparable results to the recently reported Hou methodology.[4] However, significant etching of the glassware used and difficulties in achieving uniform stirring on a larger scale mean the TBAF/KHF_2 methodolgy is better suited to smaller scale reactions.

Although the phenyl group vinylic to the olefin bond and the terminal fluorine in **188** are ideal structural features for the purposes of a building block towards fluorinated pentoses, their presence unfortunately prevents the success of the key dihydroxylation reaction. Although no traces of dihydroxylated material were observed for any of the related fluorinated substrates, it is worth noting that oxidative cleavage was also observed under Sharpless and Narasaka dihydroxylation conditions for the non-fluorinated olefin **194**. Although similar cleavage reactions have been observed in the literature for structurally similar compounds such as chalcone **205**, no cleavage reactions have previously been reported for olefin **194**. This would suggest that electron-deficient α,β-unsaturated ketones of this type may be poorer substrates for dihydroxylation reactions than previously reported.

3. *De Novo* route to a versatile fluorinated building block from crotonic acid

An asymmetric, stereodivergent route to selected 6-deoxy-6-fluorohexoses had been developed from methyl sorbate *via* fluorinated dienoate **220**.[1] Methyl sorbate **218** was converted into allylic bromide **219** using the method previously described by Green and co-workers,[165] although the high yields and levels of selectivity described by Green were never reproducible. The by-products were identified as **221**, which is the *Z, E* isomer of *E, E* allyl bromide **219**, and dibromohexenoate **222**.



Scheme 80

Nucleophilic fluorination was attempted using a range of conditions; it was found that a fluorination using a mixture of TBAF trihydrate and KHF_2 mobilised in hexane afforded **220** in useful yield, after numerous attempts to employ various forms of TBAF (commercial "anhydrous" or the trihydrate) had resulted in decomposition. The fluorinated dienoate was obtained as a crystalline solid which sublimed close to 30°C. The molecular structure of the solid was confirmed by X-ray crystallographic analysis. Only extremely pure bromide could undergo fluorination successfully (crude material or material purified by Kugelrohr yielding complex mixtures of products) and attempts to scale the reaction beyond 12 mmol led to significant reductions in yield. Hydrolysis of

bromide **219** to alcohol **223** was identified as one of the main competing pathways, and ratios of product to **223** were typically as low as 2:1 or 3:1.

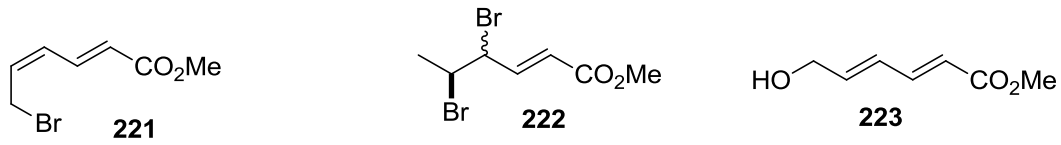
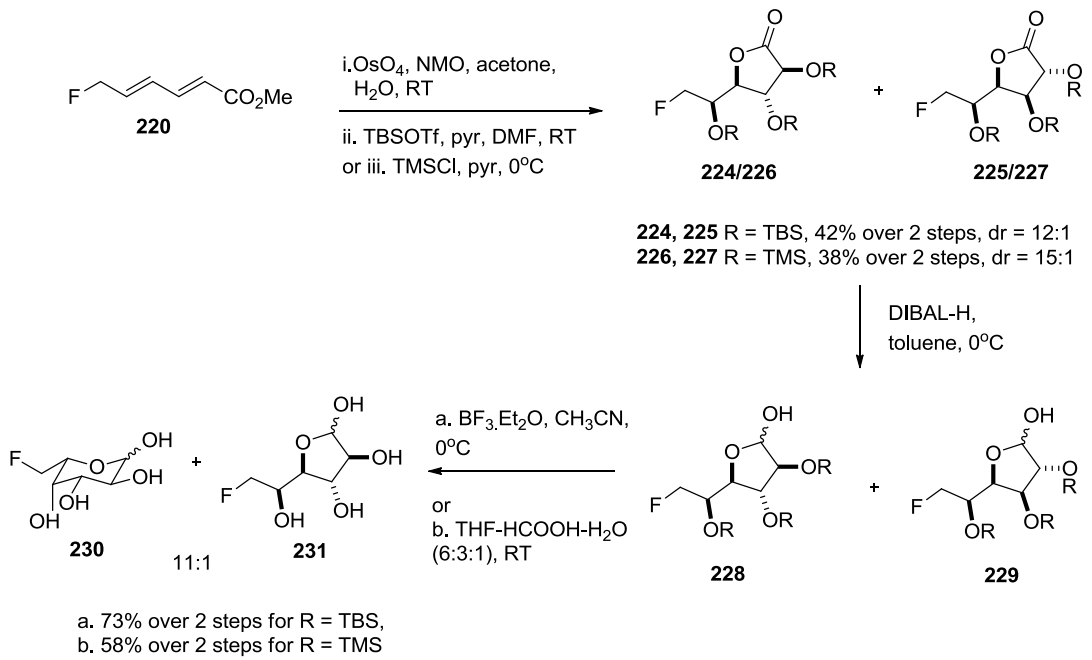


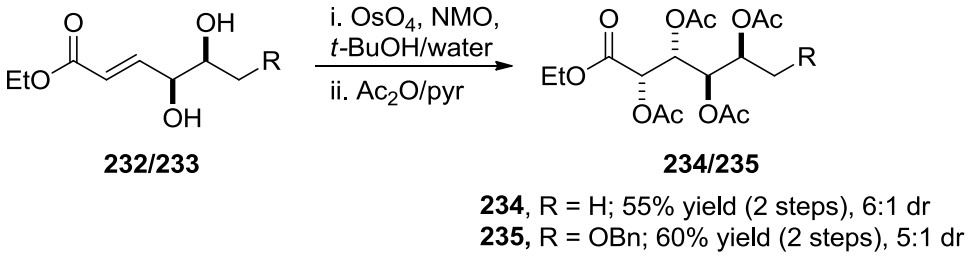
Figure 15: By-products identified in bromination **221** and **222**; by-product identified in fluorination **223**.

Fluorohexadienoate **220** was subjected to two sequential UpJohn dihydroxylations and the crude tetrol was pertrialkylsilylated to yield the inseparable **224/226** (major) and **225/227** (minor) furanolactones after purification (confirmation of the lactone ring formation was achieved by the HMBC spectrum). The level of diastereomeric purity was determined by [^{1}H] ^{19}F NMR, with R = $SiMe_3$ resulting in a slightly higher dr (15:1, 38% yield over 2 steps) than R = $SiMe_2$*t*Bu (12:1, 42% yield over 2 steps). Reduction with DIBAL-H to the hemi-acetal, and global deprotection of the silyl groups yielded 6-deoxy-6-fluorogalactose as an 11:1 mixture of pyranose **230** and furanose **231** (58% over 2 steps). The data were identical with those reported by Schengrund and Kovac.[166]



Scheme 81

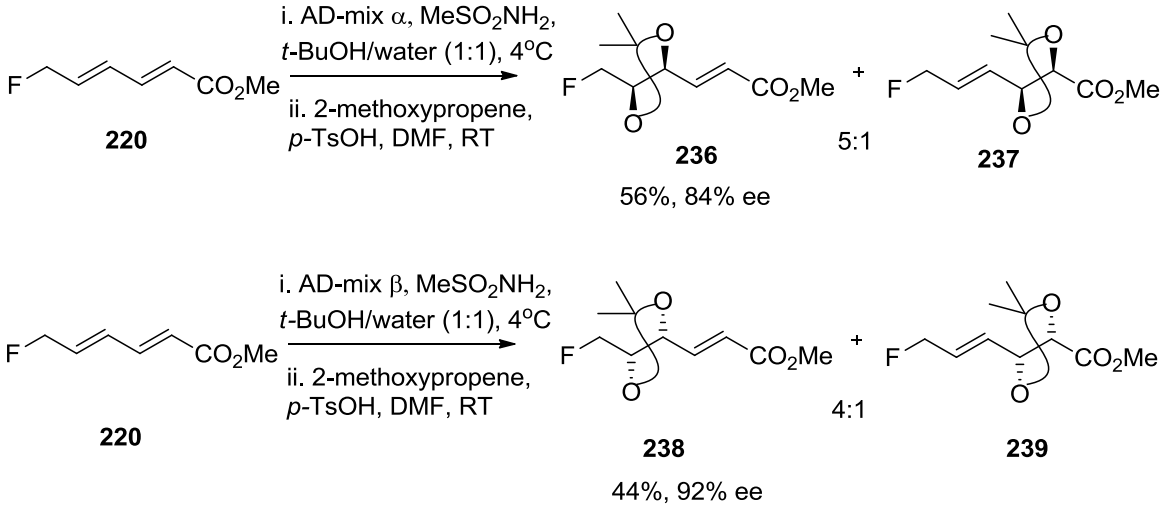
Although the yields are slightly higher when TBS protection is used, the use of TMS protection allows facile deprotection after which no further product purification is required. Based on previous results (*vide infra*) and those of Sharpless[167] and O'Doherty,[168] the initial dihydroxylation is most likely across the more electron rich C4/C5 olefin bond. If this is the case the second dihydroxylation proceeds in higher stereoselectivity than the substrate controlled dihydroxylations on analogous substrates by O'Doherty and co-workers (12:1 *c.a.* 6:1, see Scheme 82).



Scheme 82

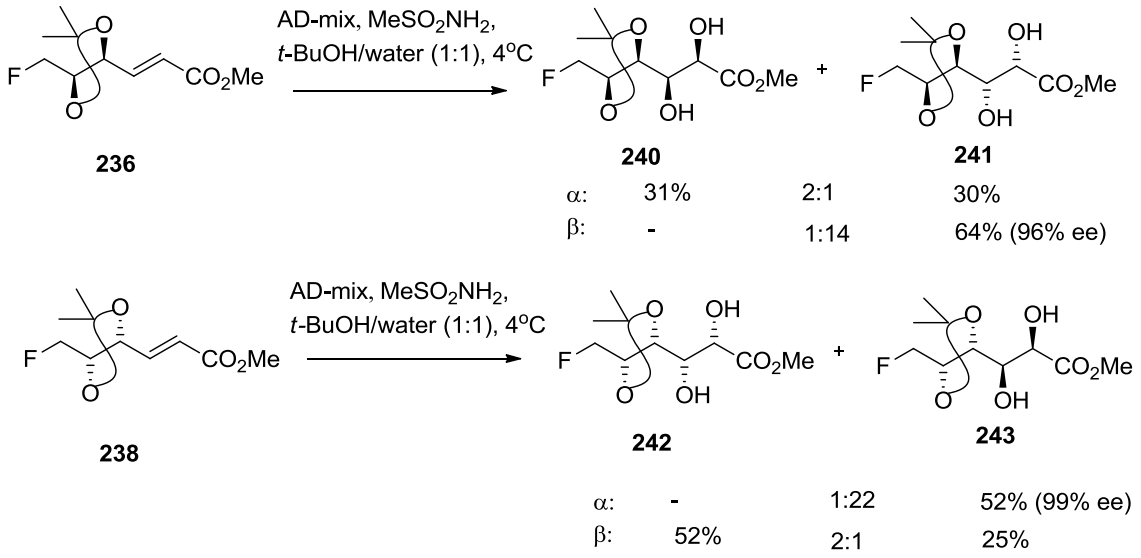
This result would suggest the remote fluorine increases the level of diastereofacial control exerted by the γ-hydroxyl group, further emphasising the profound chemical effects often exerted by a remote fluorine atom.

When fluoro-hexadienoate **220** was subjected to sequential asymmetric dihydroxylations and acetonide protection (Scheme 83), the regioselectivity of the reactions was found to be only moderate, yielding 5:1 or 4:1 mixtures of acetonides (**236** and **237**) and (**238** and **239**).[1]



Scheme 83

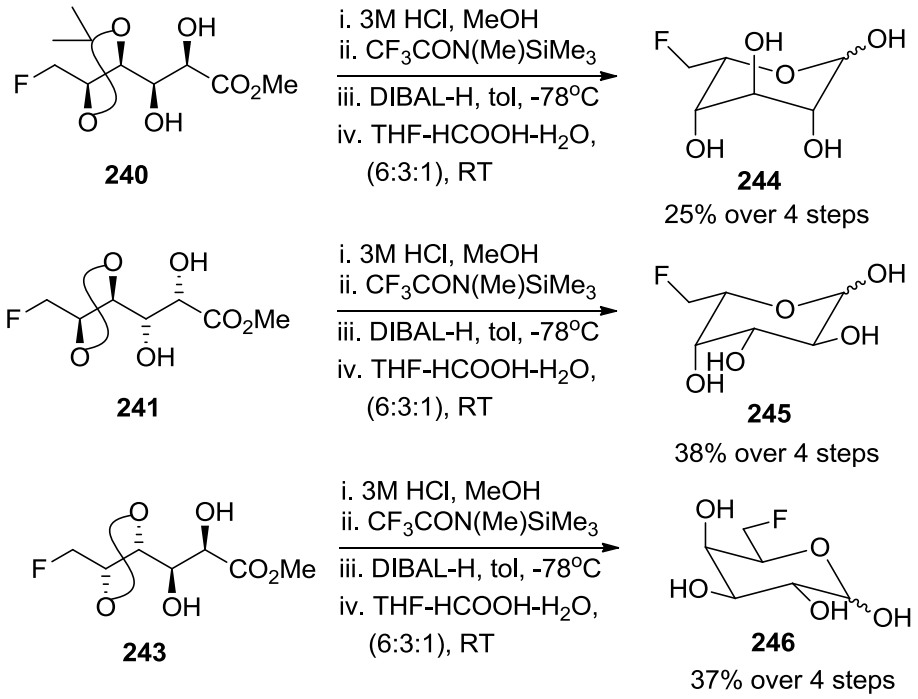
The high regioselectivity experienced in the AD reactions of substrates **232** and **233** is rationalised by O'Doherty as the effect of deactivation of the α,β-olefin by the alkoxycarbonyl group. Unfortunately, the introduction of fluorine deactivates the γ,δ-olefin enough for it to react competitively with α,β-olefin under AD conditions although the regioisomers could be separated.



Ratios were determined by ^{19}F NMR of crude product mixtures

Scheme 84

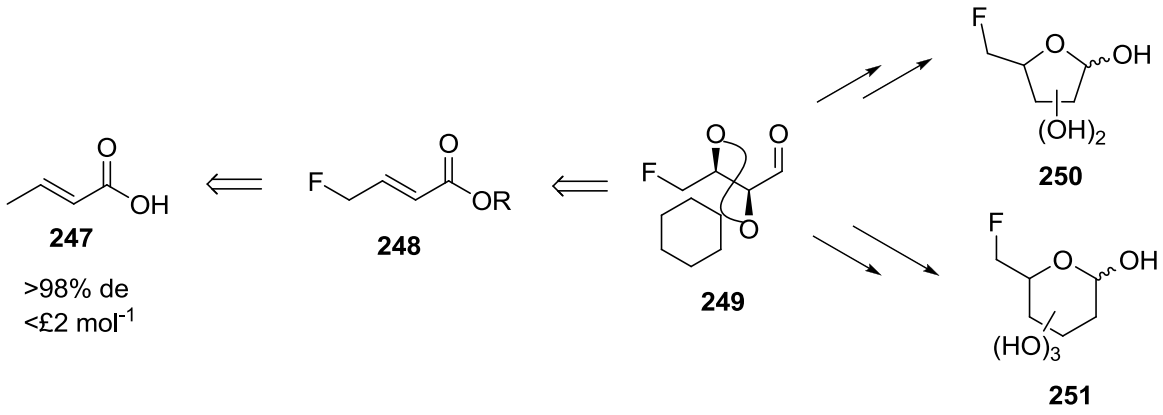
Strong matched/mismatched interactions were observed for the second dihydroxylation (Scheme 84); the matched reactions proceeding in excellent diasteroselectivities (14:1 and 22:1).[1]



Scheme 85

Removal of the acetonide groups was followed by per-trimethylsilylation and finally DIBAL-H reduction (Scheme 85). The final sugars were characterised by NMR and their rotations compared to literature values. The overall yields of sugars from these sequences from our laboratory (calculated from fluoro hexadienoate **220**) are 4% for L-idose analogue **244**, 6% for L-fucose analogue **245** and 8% for D-galactose analogue **246**. The idose **244** is a new compound but **245** and **246** have been synthesised before. Although the *de novo* syntheses of a carbohydrate are less efficient and attractive than a transformative method from a readily available precursor, the potential for fully asymmetric and divergent methodology from an achiral precursor was effectively demonstrated.

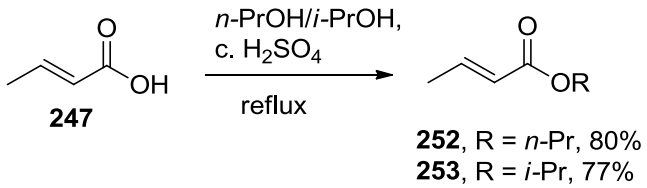
Although this sequence did successfully deliver the desired fluorinated sugar analogues, the chemistry is moderate yielding, not least because of the extremely difficult fluorination reaction. We planned to synthesise a structurally similar allyl fluoride building block in an analogous fashion, although we hoped that with our increased experience and knowledge of nucleophilic fluorination reagents a more reliable fluorination reaction could be achieved. Crotonic acid **247** was selected as the initial starting material as it is commercially available cheaply and diastereomerically pure (>98%). Diastereomeric purity is particularly important as the *de novo* syntheses must deliver the highest enantiomeric purity possible to be competitive with syntheses from enantiomerically pure natural products. As diastereomeric impurities are often difficult or impossible to remove and can have adverse effects on the outcomes of asymmetric reactions, we hoped to maintain a high diastereomeric purity from the very beginning of the projected synthesis.



Scheme 86

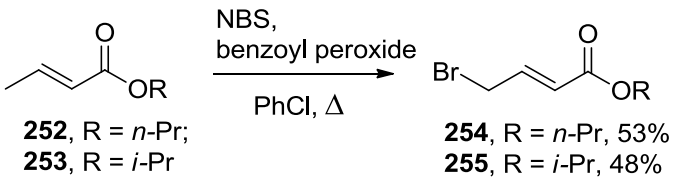
3.1. Esterification and bromination of crotonic acid

The first step in our approach from crotonic acid was the esterification of the carboxylic acid moiety. The formation of the ester was carried out in order to both protect the carboxylic acid group and to add molecular weight to the substrate. It was known from the work on the methyl substrate analogue that the products from this scheme of work were likely to be extremely volatile.[1] Therefore, we hoped to increase the molecular weight enough for the manipulation of the substrates to be manageable, but keep the molecular weight low enough for purification by distillation to still be a viable option due to the large scale of the syntheses planned. The *iso*- and *n*-propyl alcohols were used in the esterification as they were both very cheap; the effect of the ester structure on the subsequent synthetic steps was also of interest (Scheme 87).



Scheme 87

The esters **252** and **253** were easily generated by refluxing commercial crotonic acid in either *n*- or *iso*-propyl alcohol with a catalyltic quantity of sulfuric acid. Purification was kept at a minimum due to the large scale (>500 mmol) and volatile nature of the products. Accordingly, the concentrated organic layers after aqueous work-up (with saturated sodium hydrogen carbonate solution) were taken forward with no further purification.



252, R = *n*-Pr;
253, R = *i*-Pr

254, R = *n*-Pr, 53%
255, R = *i*-Pr, 48%

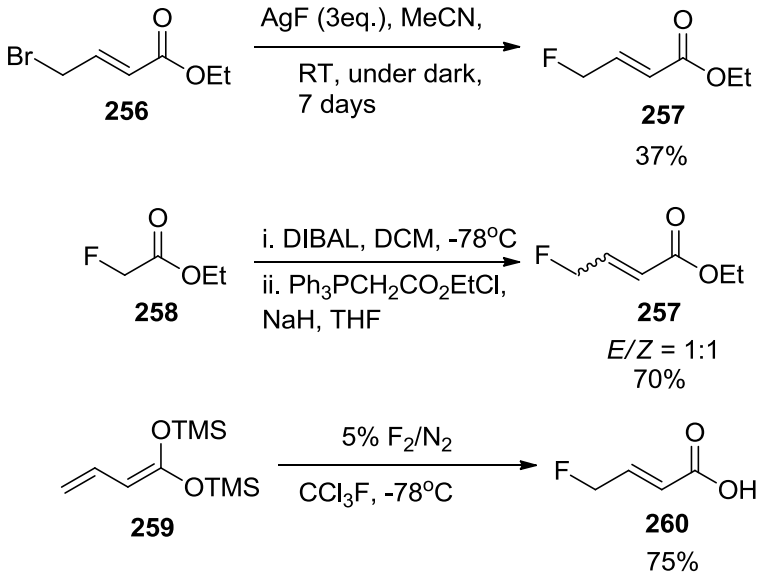
Scheme 88

In order to install a fluorine atom into molecules using nucleophilic fluorination chemistry, a suitable leaving group has to be introduced into the substrate. We decided to employ a radical bromination reaction, as radical bromination chemistry is robust[169] and had worked well with the analogous substrate derived from methyl sorbate.[1] Employing the methodology used to effect the bromination of ethyl sorbate with *N*-bromosuccinimide and benzoyl peroxide, as described by Lester *et al.*,[165] produced good results on a small scale with the *i*-propyl ester **253** (72% crude yield). However, the reaction was more problematic when carried out at scale (>150 mmol) resulting in violent discharge of the reaction mixture through the top of the condenser, despite careful addition of the benzoyl peroxide in portions over several hours. This was particularly problematic as this early and important substrate was required in bulk. A search of the literature uncovered an analogous procedure for the bromination of butyl crotonate.[170] This procedure differed to the one described by Lester and co-workers in that all the solid reagents, including benzoyl peroxide (although in this instance a much reduced quantity), were present at the start of the reaction and the solvent, carbon tetrachloride, was slowly brought to the reflux temperature. This procedure was used for substrates **252** and **253**, but less toxic chlorobenzene was used as the solvent for the reaction. As the boiling point of chlorobenzene is significantly higher than that of carbon tetrachloride (131^{o}C *cf.* 85^{o}C) the reaction was heated to the boiling point of carbon

tetrachloride, a much lower temperature. Pleasingly, these conditions, although requiring much longer reaction times, yielded comparable crude product to the Lester methodology without producing the violent exotherms that had been experienced previously. The bromination of the propyl esters was carried out safely and reproducibly at scale (>300 mmol) using this new methodology in moderate yield (48-53%).

3.2. Fluorination of allyl bromides 254 and 255

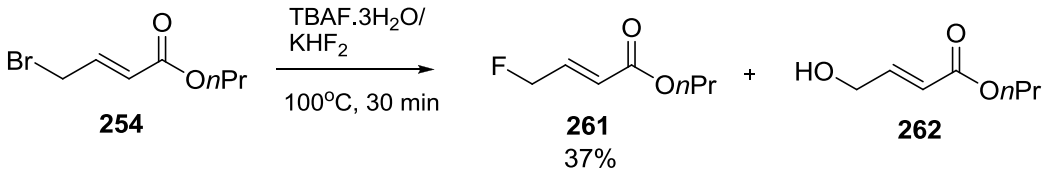
With bromoesters **254** and **255** in hand, the nucleophilic fluorination reaction was explored. An examination of the preparations of analogous substrates in the literature revealed existing methodologies towards this substrate were unappealing. Inomata and his group synthesized the unsaturated fluoro ester **257** from the corresponding bromide in a 37% yield, although stoichiometric quantities of expensive silver fluoride were required (Scheme 89).[171] Li had previously synthesized the same ester as a 1:1 mixture of *Z*- and *E*-isomers in 70% yield from ethyl fluoroacetate **258** *via* a DIBAL reduction and Wittig reaction (Scheme 89).[172] Despite the relatively high yield this route suffers from poor diastereoselectivity and involves manipulation of highly toxic fluoroacetate. 4-Fluorocrotonic acid **260** was synthesized from **259** in an impressive 75% yield by Purrington and co-workers,[173] although our laboratory is unequipped to handle elemental fluorine and the starting material is not commercially available, and would require preparation.



Scheme 89

We concluded that we needed a new route to fluoro crotonate **248**, as none of the known literature preparations were deemed to be viable options, especially for syntheses on a larger scale. It was also known from our earlier work on the fluorohexadienoate substrate that commercial TBAF (TBAF.3H_2O) and so called 'anhydrous' TBAF (obtained by heating the commercial material under reduced pressure) were likely to cause decomposition of our substrates **254** and **255** (this had occurred with the structurally related bromohexadienoate **219**). The first nucleophilic conditions we examined for the fluorination of allyl bromide **254**, was the solvent free reaction developed within our laboratory using commercial TBAF and KHF_2. There were a number of associated drawbacks with this reaction. The yield of the product was moderate (37%), but the purification of the material was extremely difficult due to the complex mixture of products. Allyl alcohol **262** and the initial starting material **254** were

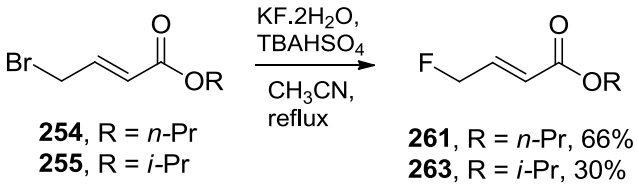
present and difficult to separate. Further, the significant etching of glassware and lack of solvent ensured scale up of the synthesis was problematic.



Scheme 90

During the course of this project, TBAF.(*t*BuOH)$_4$ was reported to be more effective than other fluoride sources.[174] Over the past several decades a number of phase transfer based protocols and reagents have been developed. The most widespread reagents are those based on tetraalkylammonium salts, due to their good solubility and nucleophilicity in common organic solvents[175] and of these, TBAF is the most popular. Unfortunately their hygroscopicity ensures that they are only available in the form of their hydrates, allowing the hydroxide ion to compete with fluoride in any hydrophilic reactions. Attempts to produce anhydrous versions of these reagents by heating under a dynamic vacuum[92] or by generating the reagent *in situ* through the S_NAr reaction of hexafluorobenzene and tetrabutylammonium cyanide (TBACN) in polar aprotic solvent[96,176] are generally unsatisfactory due to the strong basicity of the reagents produced (see introduction for a more in depth discussion of these reagents). However Kim *et al.* have reported that TBAF.(*t*BuOH)$_4$ was obtained as a non-hygroscopic crystalline white solid after refluxing commercial TBAF in a mixture of hexane and *t*-BuOH, and which can be considered as a truly anhydrous source of the TBAF reagent.[174] Unfortunately, this reagent caused complete and utter decomposition of our substrate with a black colour forming almost immediately after addition of the

fluorinating reagent, even at room temperature. In our hands, this novel system behaved differently to the way it was described in the literature. Although a white solid was obtained after filtration, the material could not be described as completely non-hygroscopic, with the white crystals formed possessing a sticky texture. When a spatula (approximately 250 mg) of the material was left exposed to the atmosphere for 2-3 hours, only a colourless liquid remained, almost certainly as a result of absorption of moisture from the atmosphere. The appearance and quality of the white crystals obtained was extremely variable, and appeared to be dependent on the method and duration of filtration. If the precipitate was washed with a 7:3 *t*-BuOH/hexane mixture and dried under reduced pressure for 20 minutes as described in the publication, a glossy white solid was obtained which left droplets of liquid on a metal spatula during transfer. Washing the solid with pure hexane and allowing it to dry under reduced pressure for 30 minutes produced finer white crystals which appeared drier than previous precipitates formed; although significant clumping of the crystals was observed suggesting that liquid was still present. Crystals of the size and texture shown in photograph in the publication by Kim and co-workers could not be produced. In addition to these disparities in appearance and texture, the ratio of the tetrabutylammonium cation to *t*-BuOH was variable in the ^{1}H NMR although examination of the crystals by X-ray crystallography always confirmed the literature formula. Further investigations revealed that the *t*-BuOH ligands are likely to be extremely loosely bound, perhaps explaining the unusual discrepancies in the ^{1}H NMR integrations for the material.[177]



254, R = *n*-Pr
255, R = *i*-Pr

261, R = *n*-Pr, 66%
263, R = *i*-Pr, 30%

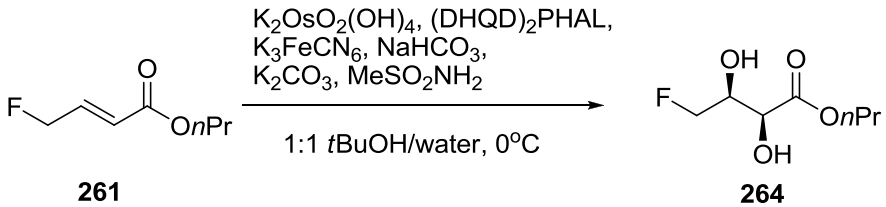
Scheme 91

Fortunately, the phase transfer conditions described by Hou[4] utilising $TBAHSO_4$ and $KF.2H_2O$ in refluxing acetonitrile successfully effected the fluorination of allyl bromides **254** and **255** on both a small and large scale (>150 mmol). Due to the quantities of crude material produced in the larger scale reactions, purification by chromatography was impractical. Rapid Kugelrohr distillation under reduced pressure was attempted initially but the quality of the distilled material was unsatisfactory. Fractional distillation using a Vigreux condenser at reduced pressure yielded the desired fluoride in an acceptable level of purity (>95% by ^{1}H NMR) although the quoted yields show a rather large variation (30-66%). However this is likely to be a result of the volatility of the fluorinated product resulting in significant depreciation during solvent evaporation on the rotary evaporator, rather than a reflection on the fluorination chemistry itself. For the most part however, this chemistry could be performed reproducibly on a large scale (up to ~200 mmol), with yields commonly between 35-40%.

3.3. Optimisation of the SAD of fluoro crotonate 261

From this point, the *n*-propyl ester compounds became the focus of the synthetic route with only a limited number of reactions also performed on the *iso*-propyl analogues. With fluoro crotonate **261** synthesised, introduction of the desired stereochemical

information into the molecule *via* a Sharpless Asymmetric Dihydroxylation of the double bond could now be considered. Although the commercial AD-mixes (0.4 mol% osmium/1 mol% ligand) are sufficient for most standard substrates, osmium tetroxide is an electrophilic reagent,[178] and electron deficient olefins, such as unsaturated amides and esters, have been found to react relatively slowly.[151,178] Once again it was thought that modified conditions, such as the so-called "improved procedure",[179] in which higher ligand/oxidant loadings (1 mol% osmium/5 mol% ligand), would be required to allow the reactions to proceed in acceptable yields and enantioselectivities.[152,179] Therefore, the asymmetric dihydroxylation conditions were subject to some optimization, with regard to the osmium and chiral ligand content. In addition to the commercial AD-mix, we carried out the dihydroxylations with 2 mol% osmium/2 mol% ligand, the so-called "improved procedure" and 1 mol% osmium/10 mol% ligand (results summarised in Table 3). Methyl sulfonamide which can speed up hydrolysis and catalytic turnover was also added to the reaction mixtures.[180] Yields for the dihydroxylation chemistry were variable (44-80%). However, the lower yields were obtained on the first run through of the chemistry and higher yields (>55%) were reproducibly achieved through careful removal of solvent from the relatively volatile products on the rotary evaporator.



Scheme 92

The "improved conditions" (1 mol% Os, 5 mol% ligand) were found to give comparable results (within experimental error) to the 2 mol% osmium/2 mol% and 1 mol% osmium/10 mol% ligand conditions suggesting the ee could not be indefinitely improved by increasing the ligand or osmium concentrations.

Despite the significant improvement achieved using the improved conditions for the asymmetric dihydroxylation, the ee's were still somewhat disappointing and we wondered if a new ligand class could improve the ee's further. Sharpless has reported that the $(DHQ)_2AQN$ and $(DHQD)_2AQN$ ligands based on the anthraquinone core, (Figure 16), are superior ligands for olefins bearing heteroatoms in the allylic position.[181]

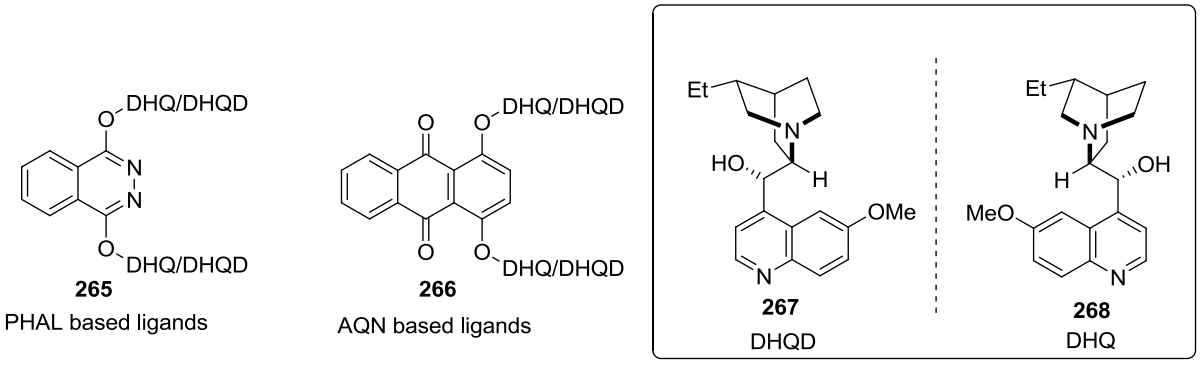


Figure 16. SAD ligand structures

As substrate **261** has heteroatoms in both allylic positions (a fluorine on one side and a carbonyl oxygen from the ester moiety on the other) alkene **261** was considered to be an ideal substrate for the AQN based ligands. An asymmetric dihydroxylation reaction was performed using the improved Sharpless conditions with the new AQN based ligands, producing excellent ee's for both enantiomers of the diol; 95% for the enantiomer derived from AD mix α , 97% for the enantiomer from AD-mix β (Table 3).

Ligand	Loading	α	β
PHAL	Standard (0.4 mol % Os, 1 mol % ligand)	66% ee	72% ee
PHAL	2 mol % Os, 2 mol % ligand	80% ee	89% ee
PHAL	Improved (1 mol% Os, 5 mol % ligand)	83% ee	91% ee
PHAL	1 mol % Os, 10 mol % ligand	82% ee	90% ee
AQN	1 mol% Os, 5 mol % ligand	95% ee	97% ee

Table 3 Optimisation of SAD reaction

3.4. Development and optimisation of two methods for the determination of ee

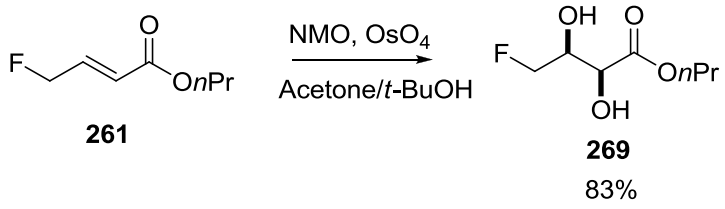
As asymmetric chemistry requires accurate and practical measurement of ee, discussion of the method of ee determination used for these compounds is now required. Because these molecules are novel, optical rotations cannot be used to measure the ee's of the diols. As diols **264** and **270** do not contain chromophores, ee determination by chiral HPLC is difficult. Despite the lack of a chromophore, attempts were made within our laboratory to measure the ee's by chiral HPLC (Chiralcel OD-H, 10% IPA in hexane, 235nm). Although good approximations of the ee's for the diols could be obtained from the chromatograms produced, the very low absorbance of light at 235 nm ensured that the data was not definitive; the small peak areas for the desired compound and comparatively large peak areas for the background and trace impurities (as judged by ^{1}H and ^{13}C NMR) meant the accuracy of the data obtained was probably low. Attempts to

use RI detection in conjunction with the Chiral HPLC were also unsuccessful, failing to give accurate and definitive data.

In order to overcome the lack of a chromophore for these diols, we developed two solutions, one synthetic and one involving a new technique.

3.4.1. Synthesis and analysis of dibenzoates

In the first approach the diols were derivatised as the dibenzoates, installing a strong chromophore and thus allowing much more accurate quantification by UV detection. In order to define the peaks for each enantiomer, unambiguously racemic material is required, as well as the enantiomerically enriched diols. Although, *pseudo*-racemate can be quickly produced by mixing the diols produced from the α and β dihydroxylation reactions, genuine racemate synthesised using the UpJohn oxidation procedure avoids any ambiguity. Treatment of fluoro alkene **261** with osmium tetroxide (2.5% w/w solution in *t*-BuOH) and NMO in a mixture of *t*-BuOH and water (Scheme 93) afforded the desired racemate **269** in good yield (83%).

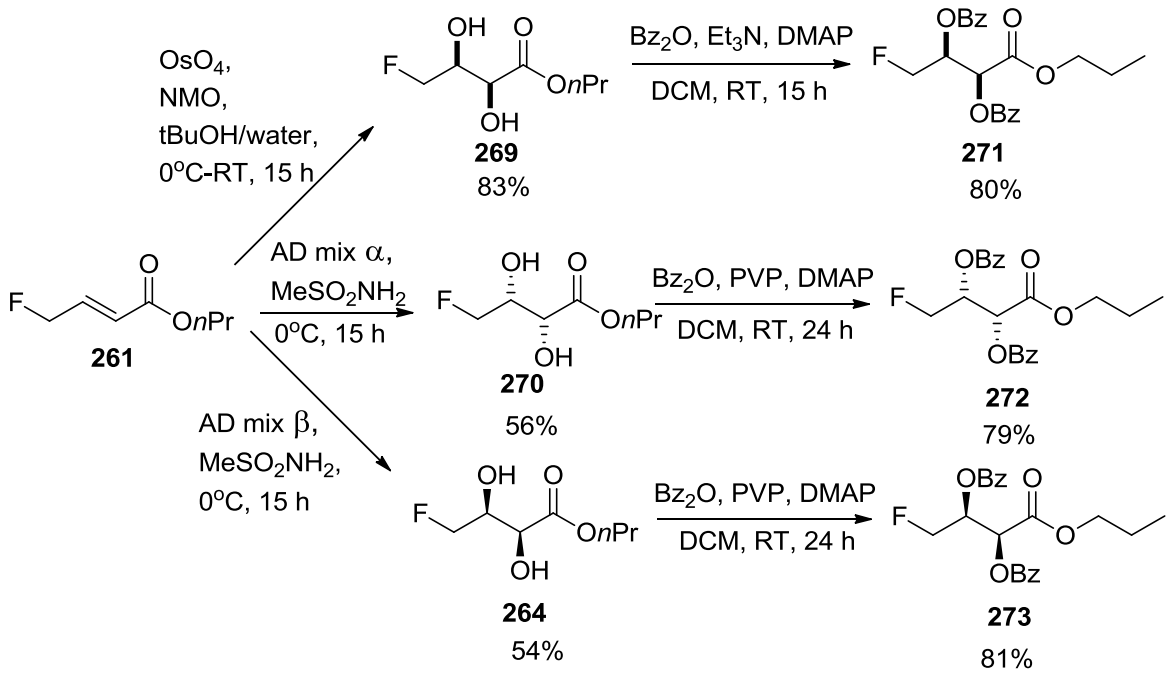


261 **269** 83%

Scheme 93

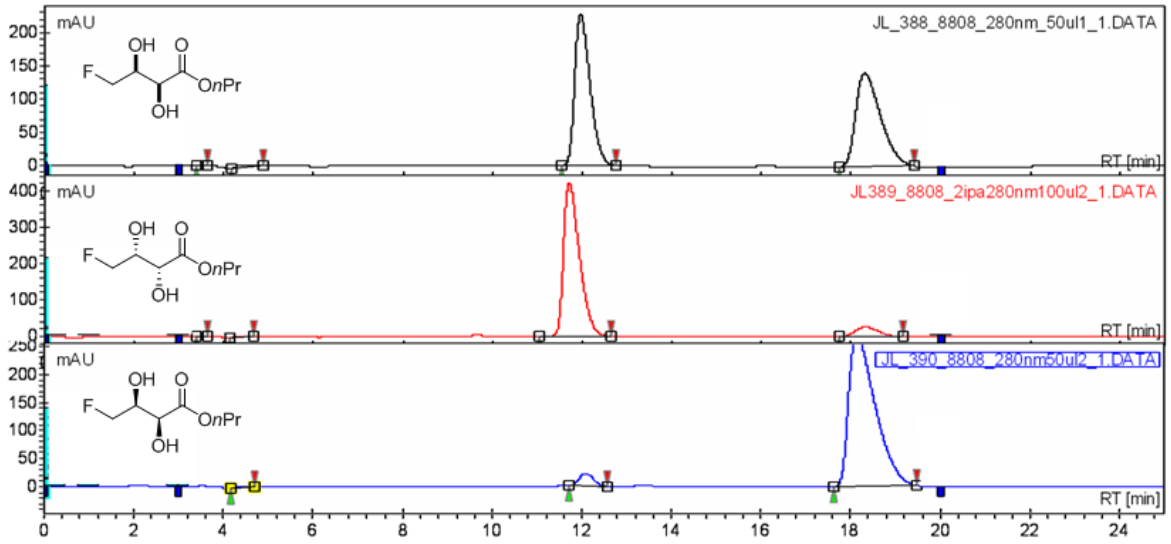
Transformation of the racemate **269** into the corresponding dibenzoate was effected by strirring the diol overnight with benzoic anhydride, triethylamine and DMAP at room temperature. For the enantiomerically enriched diols, polyvinylpyridine (PVP) was used

as the base in the reaction, as its removal after reaction is easily achieved *via* filtration (Scheme 94).



Scheme 94

The dibenzoates were purified by Flash Chromatography then examined by chiral HPLC (Chiralcel OD, 2% *i*PrOH in hexane). The separation of the enantiomers **272** and **273** was excellent with over 6 minutes separating the stereoisomers in the chromatograms. Due to the robust nature of the dibenzoylation chemistry and the excellent chromatograms produced, the derivatisation/Chiral HPLC assay was used routinely.



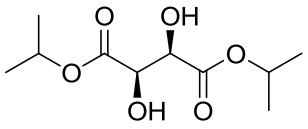
Chromatogram 1. HPLC Analysis of dibenzoates **271**, **272** and **273** (Chiralcel OD, 2% *i*PrOH in hexane)

However, despite the excellent results achieved using chiral HPLC on the dibenzoates, direct measurement of the ee of the fluorinated diols **264** and **270** could not be achieved by the same method. In order to measure the ee of any enantiomerically enriched diol material synthesised by Chiral HPLC, an additional synthetic step is required which is both time consuming and wasteful of a high value compound. A new analytical method was therefore sought which would allow the ee's of the diols to be measured quickly and directly using ^{19}F [^{1}H] NMR.

3.4.2. Development and optimisation of a novel ee determination method based on [^{1}H]^{19}F NMR

Although the determination of enantiomeric excesses using NMR is not a new technique,[182] *in situ* derivatisation,[183] very specific functionality[184] or expensive and/or structurally complex shift reagents are usually required.[182,185] The necessity of these reagents arises from the need to examine a single peak in a high level of detail despite the often cluttered nature of ^{1}H (and ^{13}C) NMR's, especially with complex or high MW structures. NMR determination of enantiomeric purity using chiral solvents though less well known has been described in the literature[186] and is particularly effective when heteroatomic NMR techniques are used.[187] For example, α-methylbenzylamine was used to resolve the components of the racemate of 2,2,2-trifluoro-1-phenylethanol in the ^{19}F NMR ($\Delta\delta_F$ = 0.04 ppm) spectrum[188] and in another a case, a chiral liquid crystalline medium was used to resolve racemic mixtures of fluoroalkanes.[189]

NMR experiments cannot normally distinguish between enantiomers, due to their identical magnetic properties. However, if the enantiomers are solubilised in a chiral environment, like di*iso*propyl L-tartrate **274**, the formation of diastereoisomeric solvation complexes results in magnetic non-equivalence and hence the appearance of separate signals for the complexes in the NMR experiment.



274

We preferred to use [^{1}H]^{19}F NMR to establish the ee of the diols as any splitting of the strong singlet produced could be easily detected, and subsequent integration was easier.

Initially, the NMR experiment was performed by diluting the substrate in an NMR tube with a 1:1 w/w mixture of di*iso*propyl L-tartrate and HPLC grade chloroform, and then adding a sealed capillary containing $CDCl_3$ to provide the instrument with a 'lock' signal. Unfortunately this method produced inconsistent results with the NMR spectrometer often failing to establish a 'lock' on the sample. This difficulty was overcome by replacing the HPLC grade chloroform with $CDCl_3$, ensuring the instrument could establish a consistent 'lock' on the samples. Pleasingly the racemic diol **269** analysed under these conditions by $^{19}F[^{1}H]$ NMR showed a good separation of the two enantiomers ($\Delta\delta_F$ = 0.02 ppm). By performing the same experiment on **264** and **270** integration of the signals for each enantiomer could be used to calculate the enantiomeric excesses. The results matched the chiral HPLC analysis of the derivatised dibenzoates closely; for example the ee's for **264** and **270**, from the 1 mol% Os, 5 mol% PHAL conditions, were 82% and 91% by NMR respectively and 83% and 91% by HPLC for the corresponding dibenzoates **272** and **273**.

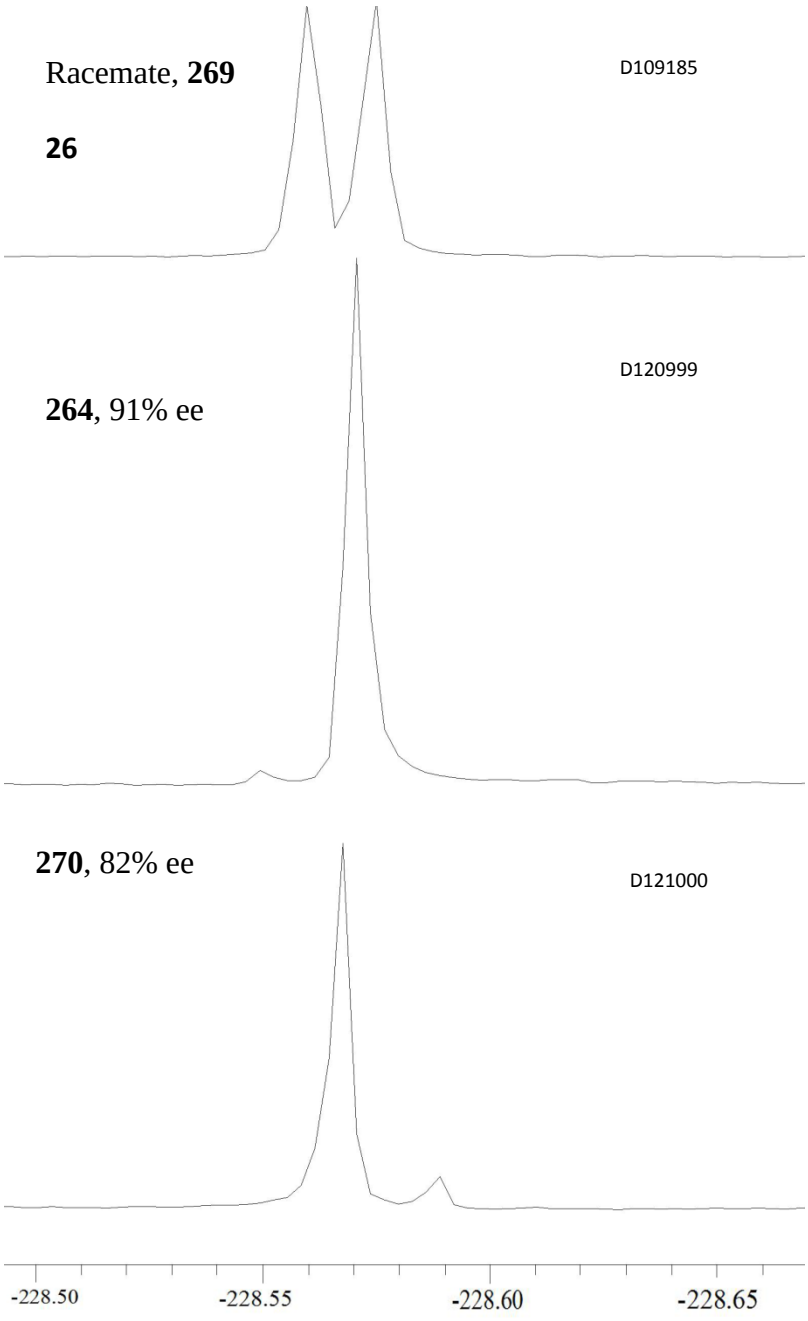


Figure 17: Partial [^{1}H]^{19}F NMR (376 MHz, L-(+)-DIPT/$CDCl_3$, 300K) spectra of racemate **269**, diol **264** and **270** under standard acquisition parameters.

Unfortunately, upon very close examination it is revealed that the separation of the enantiomer peaks is not perfect in the NMR spectra and some ambiguity exists in where to begin and end peak integrations (Figure 18).

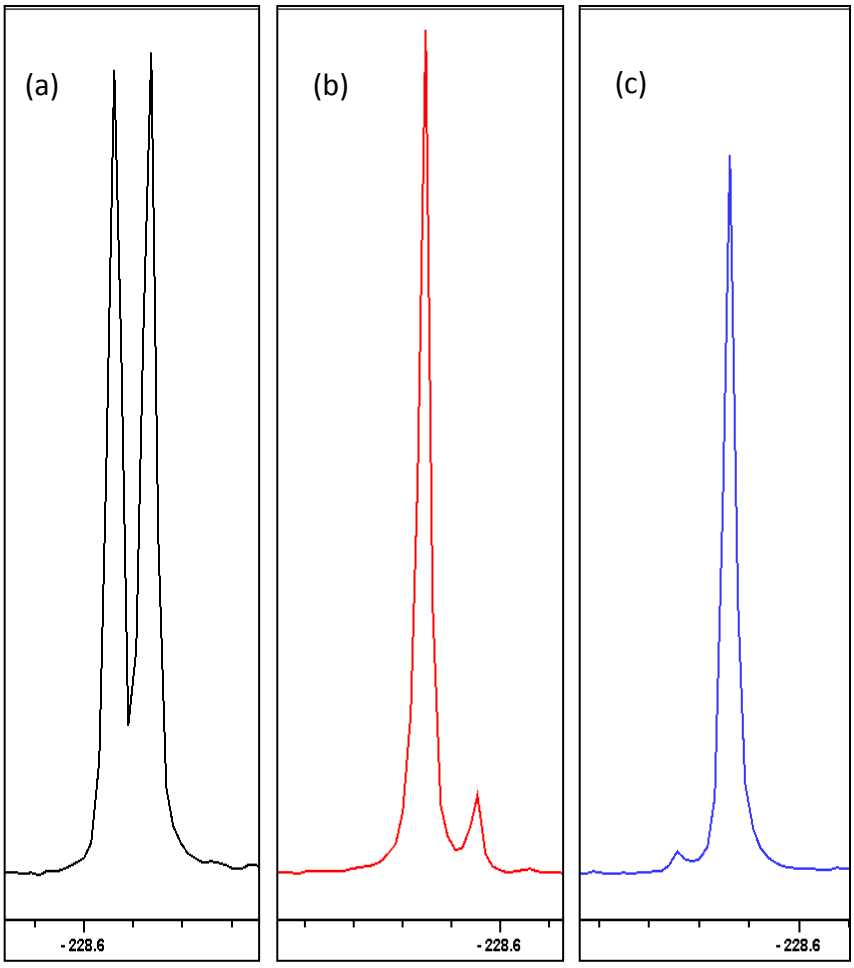


Figure 18 Partial [^{1}H] ^{19}F NMR(376 MHz, L-(+)-DIPT/$CDCl_3$, 300K) spectra of (a) racemate **269**, (b) diol **264** and (c) **270** under standard acquisition parameters revealing the partial enantiomer overlap.

In an effort to improve the baseline resolution, alterations to the acquisition parameters on the NMR instrument were examined. Initially it was assumed that focusing the sweep width around the signal of interest and increasing the number of scans for the

experiment would increase the resolution of the spectra, giving a lower peak width and and sharper baseline resolution.

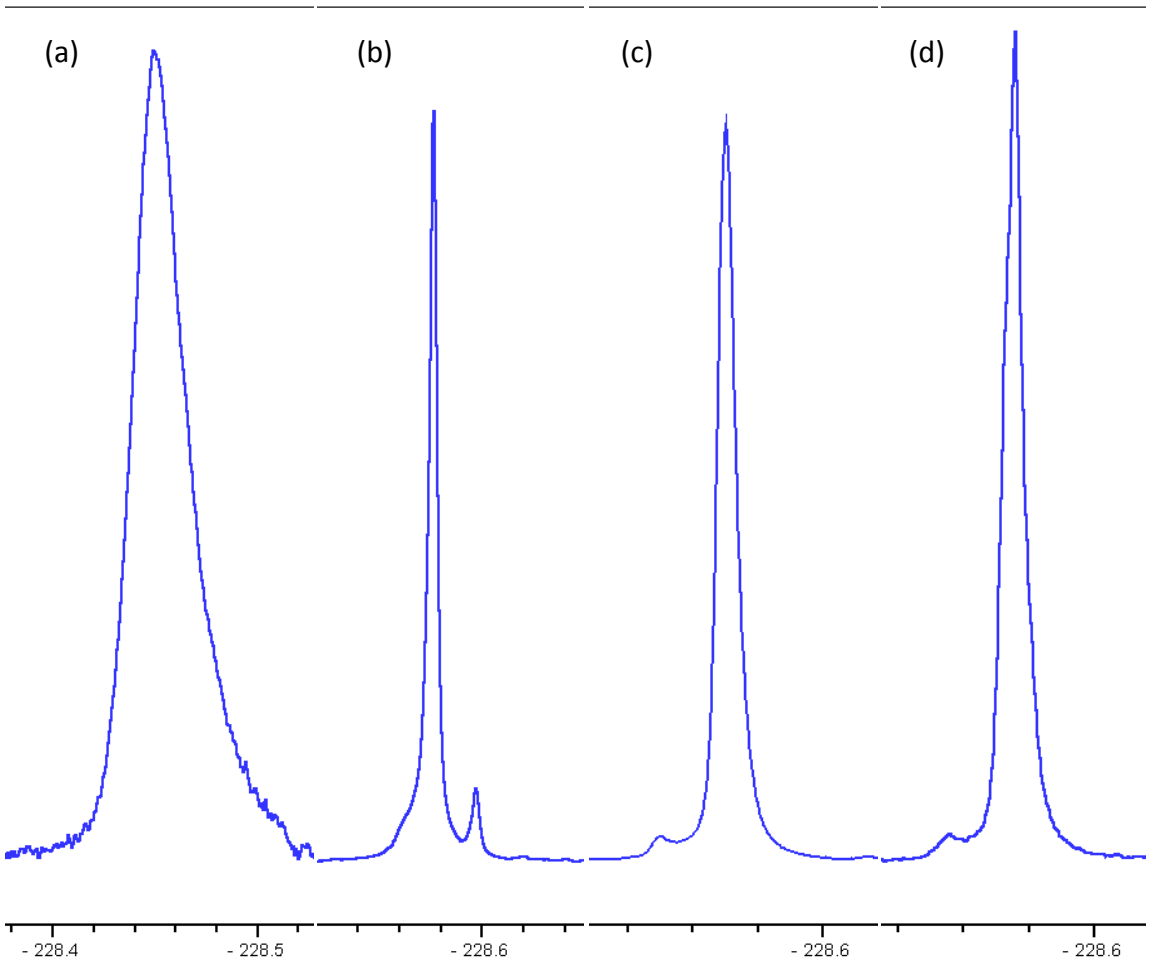


Figure 19 Partial [^{1}H]^{19}F NMR (400 MHz, L-(+)-DIPT/$CDCl_3$, 300K) spectra of (a) diol **270**, SW 40, 256 scans (b) diol **270** SW 40, O1P -230, 64 scans (c) diol **264**, SW20, 64 scans (d) diol 128, SW40, 128 scans,

Our first attempts to optimise the peak shape actually caused a decrease in the quality of the spectra produced, with -broadening of the signals and a reduction in the peak

separation observed (Figure 19). This was caused by heating of the reaction sample within the NMR instrument as a result of the lengthening of the acquisition time (decoupling produces heating of the sample). As the NMR experiment in question is proton decoupled, a degree of heating of the sample occurs throughout the length of the acquisition. If the acquisition lengths are kept short the effect of this sample heating is minimal. However, narrowing the sweep width (or spectral window) and increasing the number of scans both increase the acquisition length significantly (from around 1.5 minutes to ~4-6.5 minutes). This results in a much more pronounced heating of the sample solution. As the signal shift changes slightly with temperature, an averaging of the signal position occurs over the course of the experiment, causing a broadening of the signal and a reduction in peak separation. Following further refinement, a set of experimental parameters that would allow a narrowing of the sweep width (SW), but keep the acquisition (AQ) and relaxation times short, hence minimising sample heating was established.[190]

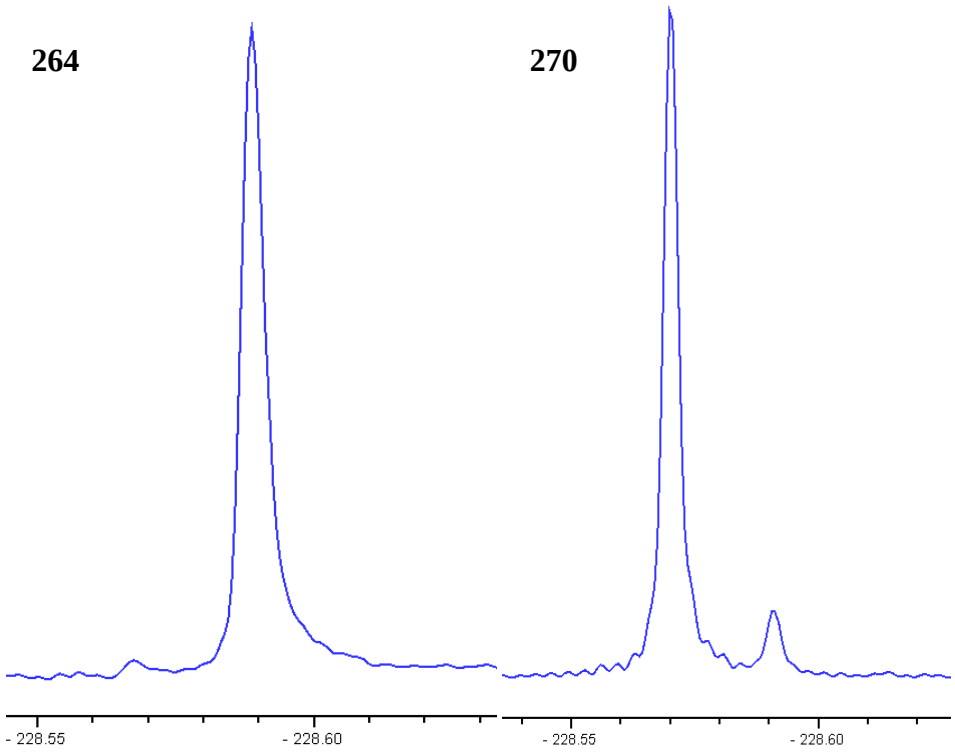


Figure 20: Partial ^{19}F [^{1}H] NMR (400 MHz, L-(+)-DIPT/$CDCl_3$, 300K) spectra of **264** and **270** using optimised conditions; SW 40, AQ = 0.8, O1P -230, d1 = 5, 32 or 64 scans.

Although some initial optimisation of the sweep width was required, these new acquisition parameters for the ^{19}F [^{1}H] NMR ee determination experiment soon gave vastly improved spectra (Figure 20).

With the improved peak shapes observed in the spectra our method now represented a truly superior method for the ee determination of the fluorinated diols **264** and **270**. The ^{19}F [^{1}H] NMR technique benefits from using a cheap readily available chiral solvating agent and is quick (2 minutes per sample) and simple to perform, being no more complicated than a standard NMR experiment. Although the technique is sacrificial in

the sample, the quantities required (<2 mg) make this of negligible concern. This is in stark contrast to the chiral HPLC method which obviously requires expensive equipment and chiral columns, but is also a much more lengthy process with accurate values usually requiring several hours of HPLC runs. A further advantage of the NMR technique is that it is more tolerant of functionality within the fluorinated substrates. Although the dibenzoates used for the HPLC work performed poorly using the NMR technique, most probably as a result of diminished binding with the chiral solvating agent due to the loss of the hydroxyl groups, a number of chiral substrates synthesised later in the project did produce good results.

3.5. Route to *anti*-diastereoisomers

The Sharpless Asymmetric Dihydroxylation of olefin **261** had successfully delivered both *syn* diol enantiomers with excellent ee's. However, as ours was a *de novo* strategy we were also interested in synthesising the remaining two *anti* diastereoisomers (Figure 21). Access to all 4 possible diastereoisomers from one common precursor would establish our route as truly stereodivergent.

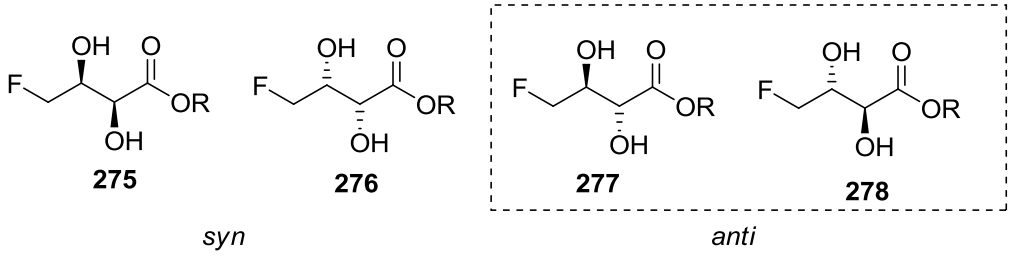
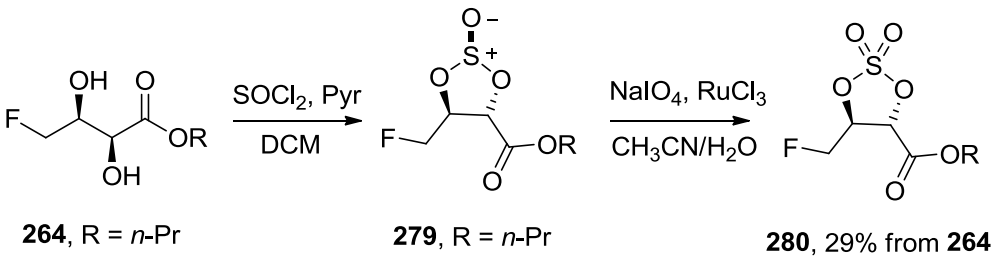


Figure 21

3.5.1. Synthesis of cyclic sulfates

Conversion of vicinal diols into cyclic sulfates and subsequent regio- and stereoselective nucleophilic ring opening has been utilized previously in the literature to install new *anti* relationships into molecules with control of absolute configuration, diversifying synthetic routes.[191,192] The significant role of cyclic sulfates in synthesis originates from several inherent properties of these molecules. First, they have high reactivity towards various nucleophiles, and are generally more reactive than their analogous epoxides. Secondly, they can promote nucleophilic attack at one position almost exclusively. Finally, an additional advantage arises because the hydroxyl group released upon ring opening is temporarily protected as the sulfate ester.[193]



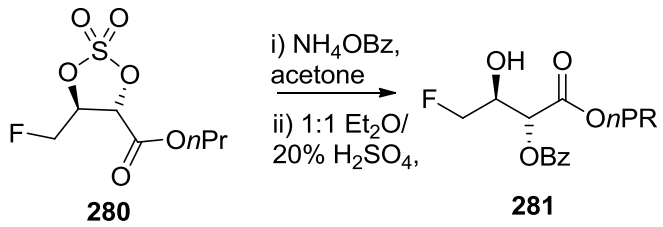
264, R = *n*-Pr **279**, R = *n*-Pr **280**, 29% from **264**

Scheme 95

Cyclic sulfate **280** was synthesised by treating (enantiomerically enriched) diol **264** with thionyl chloride in the presence of pyridine, and oxidizing the resulting cyclic sulfite **279** with sodium metaperiodate and catalytic ruthenium trichloride (Scheme 95). The progression of this synthetic sequence, from diol to cyclic sulfite to cyclic sulfate was monitored by ^{19}F [^{1}H] NMR. Upon completion of the reaction of **264** with thionyl chloride, the signal from **264** at -225.5 ppm split into two new signals (δ_F -225.8 and -234.0 ppm) as a result of the formation of both diastereoisomers of the cyclic sulfite **279**.

Completion of the oxidation of the cyclic sulfite **279** to the cyclic sulfate **280** is indicated by the appearance of one new singlet at δ_F -223.3 ppm. At this stage C3 is primed for nucleophilic attack; cyclic sulfates with ester functionality in the α position yielding almost exclusively the products of nucleophilic attack at this position. This regioselectivity is attributed to the overlap between the 2p orbital at the substitution centre with the carbonyl π^* antibonding orbital.[193]

3.5.2. Ring opening of cyclic sulfates with ammonium benzoate



280 **281**

60% from **280**

Scheme 96

The first nucleophile used to validate this chemistry was ammonium benzoate. Crude cyclic sulfate **280** was dissolved in acetone, treated with solid ammonium benzoate and allowed to stir at room temperature overnight. Nucleophilic ring opening reactions were performed on the crude cyclic sulfate mixtures as the avoidance of column chromatography at this point in the sequence led to a vast improvement in the overall yields. After ring opening, sulfate ester cleavage was achieved by stirring the concentrated residue in acid (20% H_2SO_4) and ether, yielding the desired mono-benzoate in moderate yield (60%) after purification (Scheme 96). The regiochemistry of the ring opening was revealed in the HMBC spectrum of mono-benzoate **281** (see Figure 22**)**. The ^{1}H NMR signal corresponding to the methine proton at C-2, couples to both

carbonyl signals in the ^{13}C spectrum ($^{3}J_{C\text{-}H}$). This indicates that both carbonyl groups (belonging to the propyloxy and benzoate moieties) are within 3 bonds of the hydrogen on C-2. However, the signal from the hydrogen on C-3 only couples to the *n*-propyl ester carbonyl, proving that the benzoate carbonyl is more than 3 bonds away, and confirming the expected regiochemistry for structure **281**.

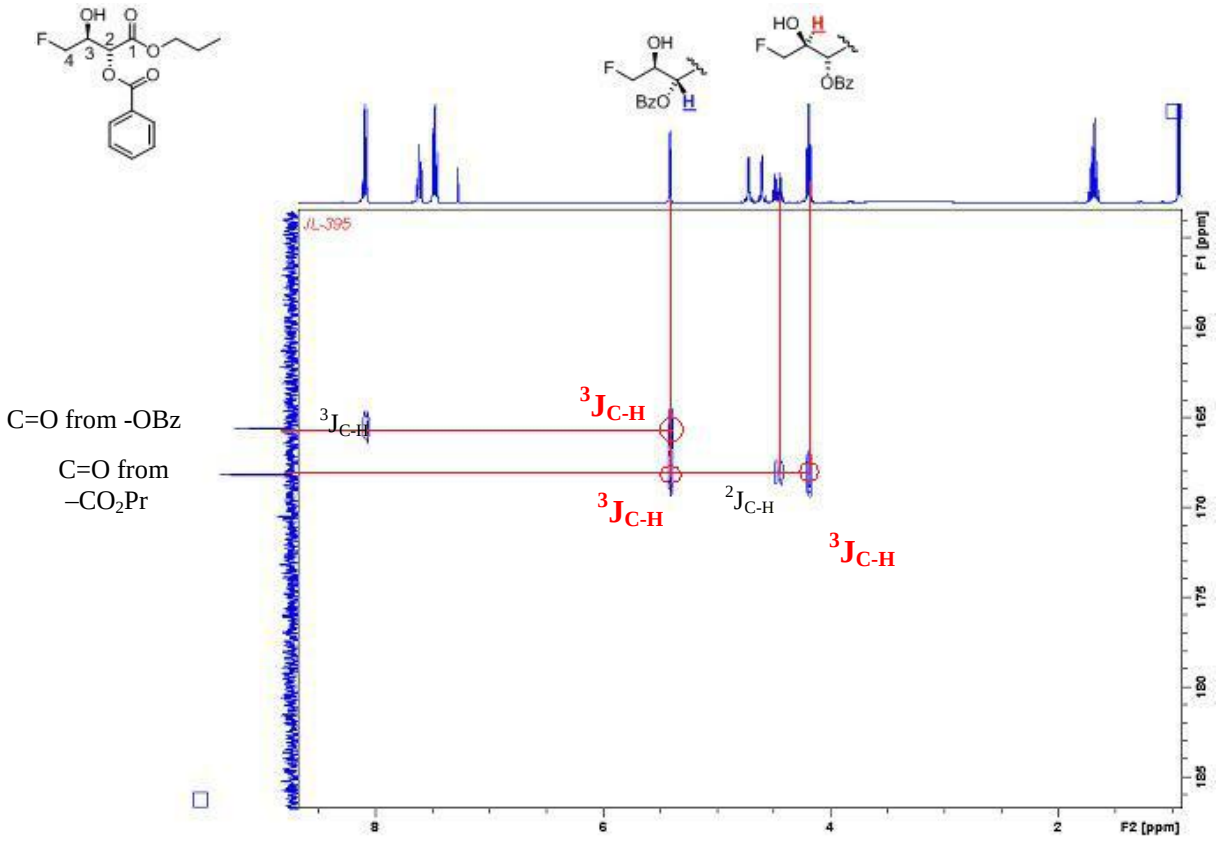


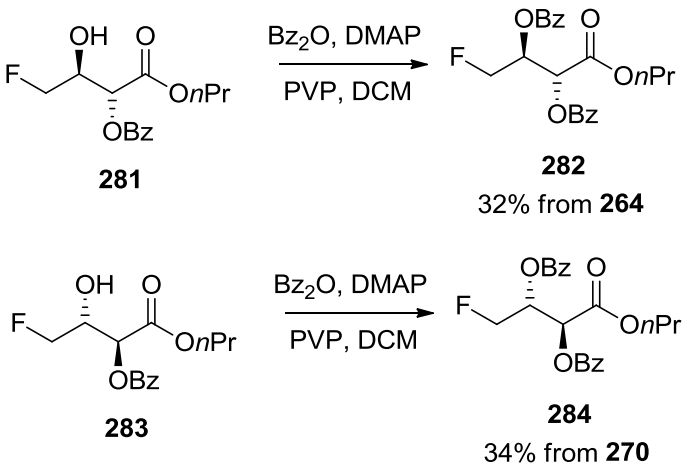
Figure 22: Partial HSQC spectrum of **281** confirming regiochemistry

This chemistry was robust and the material could be carried forward without purification until after the ring opening step. However, removal of impurities, with aromatic signals, presumably benzoic acid, proved difficult by chromatography purification required two

columns. In subsequent reactions, removal of these impurities was attempted at the work-up stage by filtering the material through a DSC-NH_2 SPE tube. Unfortunately, the quality of the material deteriorated during this treatment with new signals appearing in both the ^{1}H and ^{19}F NMR spectra. This may be a result of benzoyl group migration onto the C-3 free hydroxyl group. This result was also observed when a basic wash (5% NaOH) was introduced into the work-up procedure.

3.5.3. Synthesis of *anti*-dibenzoates

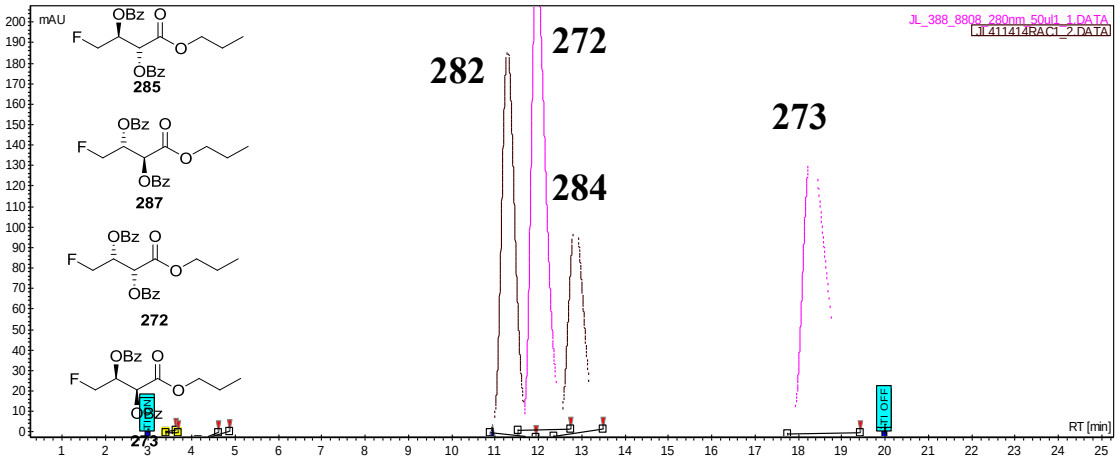
In an effort to eliminate the problem of protecting group migration the dibenzoates **282** and **284** were synthesised directly from the crude reaction mixture (Scheme 97).



Scheme 97

Treatment of the crude mono-benzoate **281** and **283** with benzoic anhydride in the presence of DMAP and PVP afforded the desired dibenzoates **282** and **284** in a satisfactory 32-34% yield from the unprotected *syn*-diols **264** and **270**. The *syn* and *anti* di-benzoates have distinct signals in the ^{19}F NMR spectra (-230.3 and -231.0 ppm

respectively), so we can be confident that the ring-opening of the *syn*-cyclic sulfates does not produce *syn*-dibenzoate, and that competitive epimerisation is not an issue with this chemistry. This is further supported by the HPLC analyses of the dibenzoates which also suggests clean 1:1 conversion occurs, again without epimerisation.



Chromatogram 2. HPLC Analysis of *syn* (**272**/**273**) and *anti* (**282**/**284**) dibenzoates revealing distinct retention times (Chiralcel OD-H column, hexane/*i*PrOH 98/2, 1 mL min^{-1}, 280 nm)

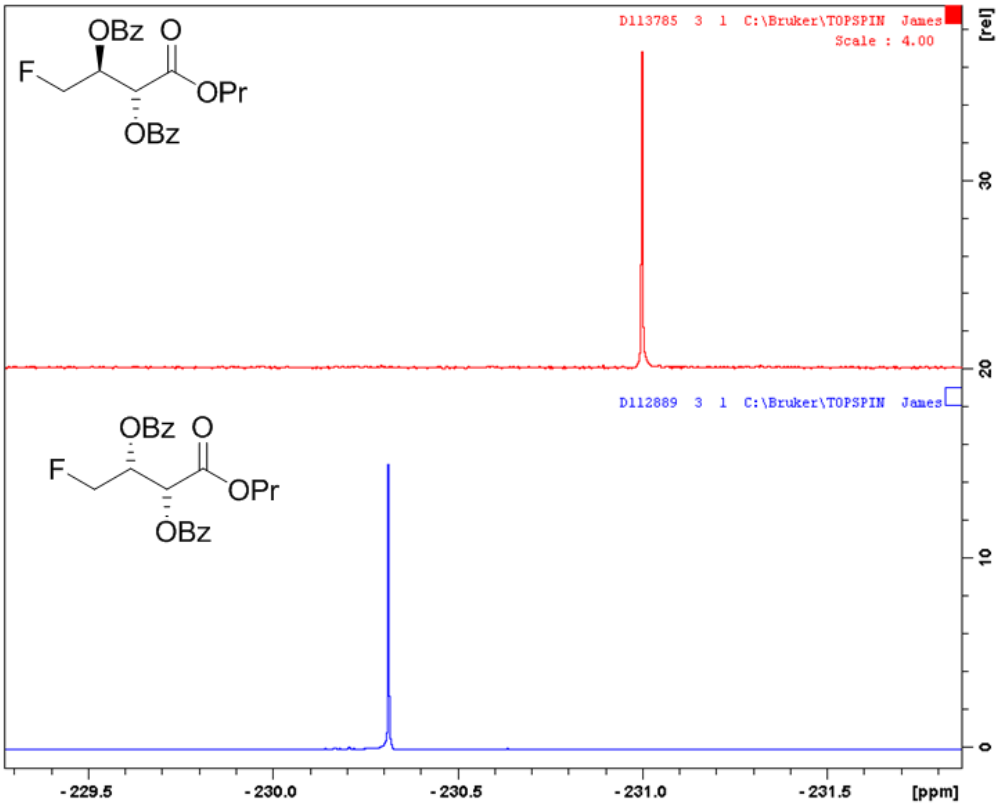
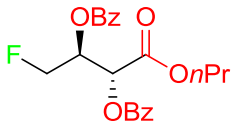


Figure 23: Partial [^{1}H]^{19}F NMR spectra showing the different chemical shifts of *syn* (**282**) and *anti* (**272**) dibenzoates

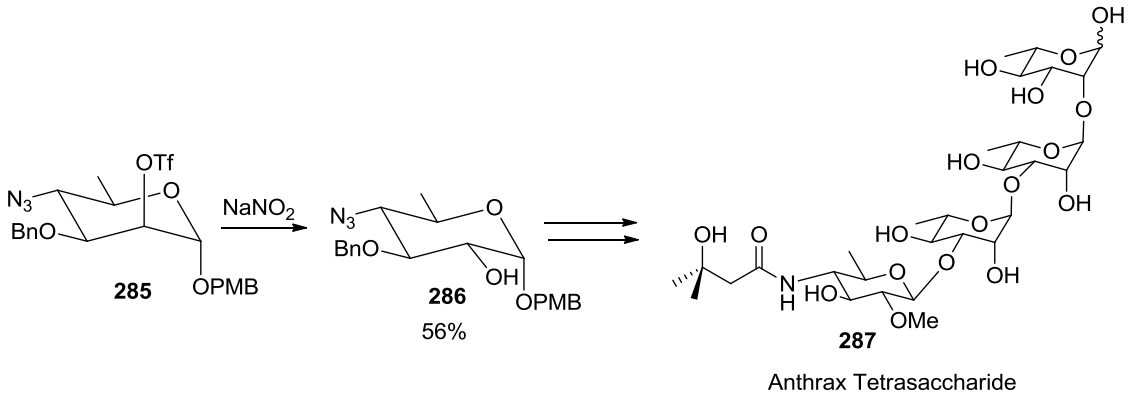
3.5.4. Ring opening of cyclic sulfates with a nucleophilic hydroxyl equivalent

Although the formation of the *anti* di-benzoates was the ideal choice for HPLC analysis, **282** utilises the ester moiety as a protecting group for three separate hydroxyl groups in the molecule, and differentiation of these at a later stage could prove problematic.



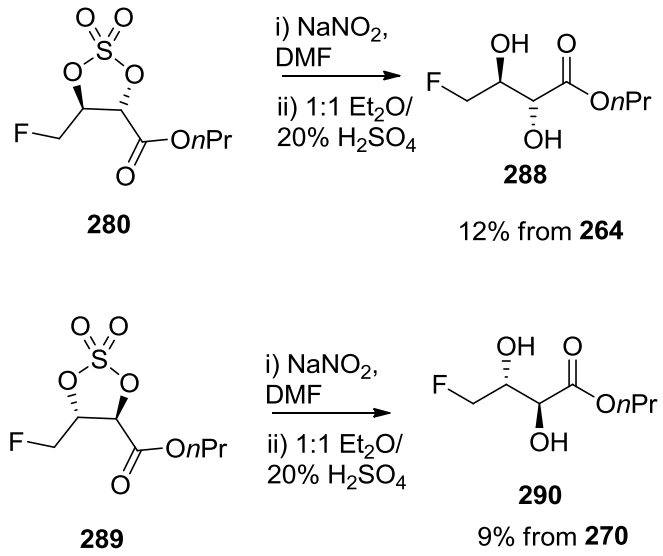
282

For the inversion of the diol stereochemistry to be synthetically useful a nucleophile that could act as a more direct hydroxyl equivalent was required. In the *de novo* asymmetric synthesis of Anthrax tetrasaccharide **287** and related tetrasaccharides published by O'Doherty and co-workers, Mitsunobu chemistry failed to facilitate an axial inversion of the alcohol at C-2. This synthetic challenge was overcome by converting the free alcohol to the triflate **285** and performing an S_N2 displacement using sodium nitrite as the nucleophile to afford the equatorial alcohol **286** in 56% yield (Scheme 98).[194]



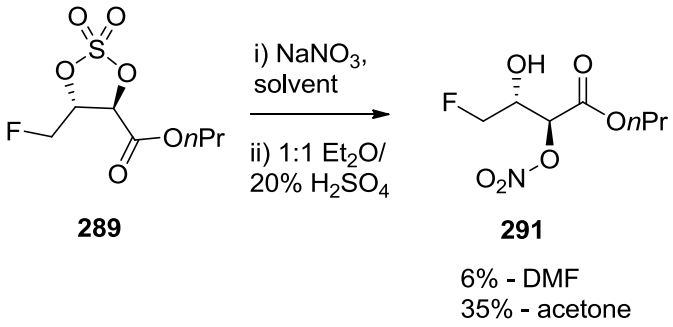
Scheme 98

Sulfate esters **280** and **289** were exposed to sodium nitrite in DMF; the mixture was heated at reflux until completion of the reaction was confirmed by ^{19}F NMR. Subsequent acid cleavage of the sulfate esters afforded the desired *anti* diols in a disappointing yield (9-12%) after purification over 4 steps (Scheme 99).



Scheme 99

The low yield was attributed, at least partially, to the small scale and difficulty of the work-up caused by the presence of DMF, the reaction solvent for the ring-opening reaction. Unfortunately, attempts to carry out the reaction in acetone, the solvent used for the ammonium benzoate reaction, led to complete decomposition of the substrate, most likely a result of the strong oxidising properties of sodium nitrite. Due to an error with the reagents used the initial reactions were carried out using sodium nitrate resulting in the formation of **291** (Scheme 100)**.**



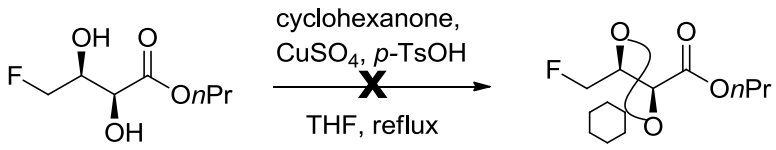
Scheme 100

This outcome was not immediately spotted as the NMR spectra and ESI-MS were consistent with the desired product. Only careful analysis of the mass spectrum revealed that the nitrate ester was present.

With the successful synthesis of the *anti*-diols, we have shown that all four possible diastereisomers are available from a common intermediate. Although the diols with *anti*-stereochemistry are afforded in low yield, we have successfully demonstrated that this methodology is both stereodivergent and stereocontrolled.

3.6. Acetal protection and ester reduction

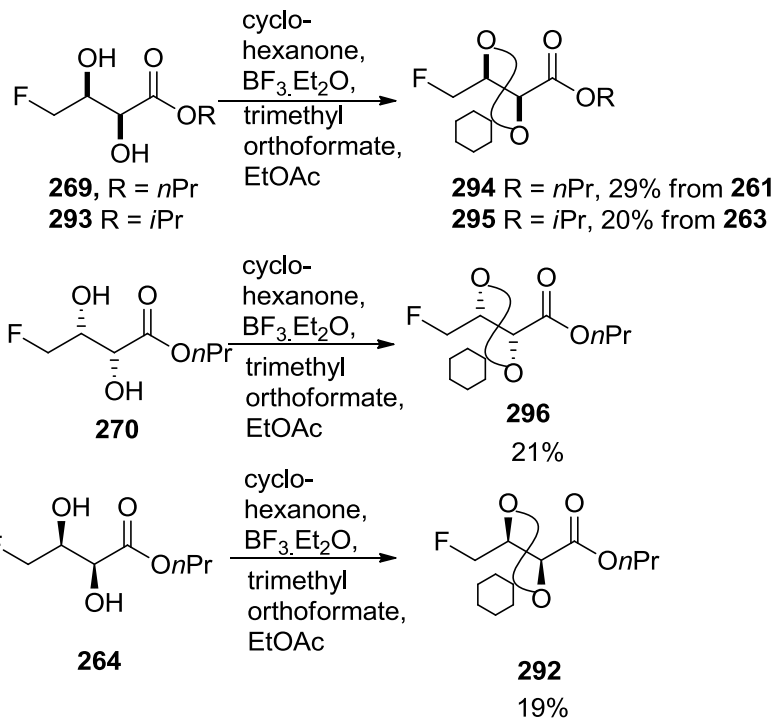
Although the *syn*- and *anti*- diols were protected as the dibenzoates previously for chiral HPLC analysis, a protecting group compatible with the planned subsequent chemistry was required. Cyclohexylidene protection was chosen for three reasons; firstly, the acetal functionality was likely to be stable enough for subsequent processing, secondly, the addition of a significant amount of molecular mass to the molecule, knowing subsequent saponification would yield a volatile four carbon based unit, would be advantageous and finally, it was possible that the cyclohexylidene group may encourage crystallisation of the products. Enantiomeric purity of the product could be improved by recrystallisation and chromatographic separations could be avoided.



264 **292**

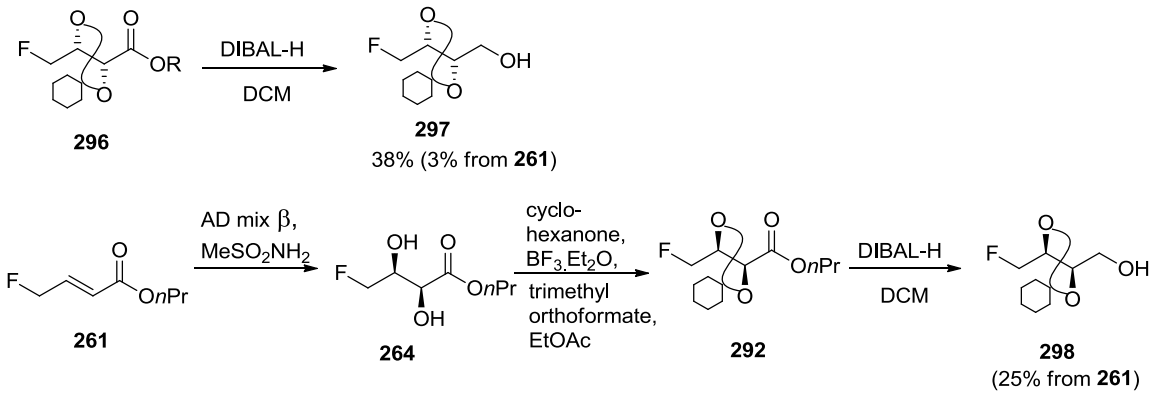
Scheme 101

Initial attempts to protect the diol with cyclohexanone using catalytic tosic acid in refluxing THF were unsuccessful (Scheme 101).



Scheme 102

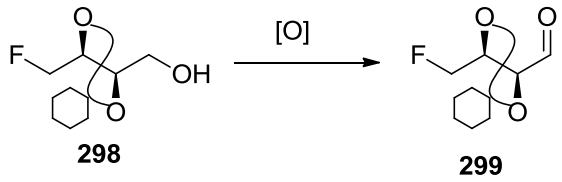
Fortunately it was discovered that using $BF_3.Et_2O$ as a Lewis acid in ethyl acetate solvent promoted the desired cyclohexylidene formation effectively,[195] although the yields obtained were very low after purification (19-29%). Subsequent reduction of the ester functionality with DIBAL-H (Scheme 103) afforded fluoro-alcohol **297** in a disappointing 38% yield. However, delaying purification of the products until after the reduction step increased the overall yield from the unsaturated fluoroester to 25% over 3 steps (*cf.* ~3% with column chromatography after each synthetic step). This method delivers the protected fluoro butanetriol **298** from crotonic acid in a disappointing 7% overall yield, although in excellent diastereomeric purity, a key goal of this route.



Scheme 103

3.7. Oxidation of primary alcohol

As the DIBAL-H reaction failed to deliver any aldehyde directly (only starting ester and alcohol were detected in reaction mixtures), oxidation of the primary alcohols to the corresponding aldehyde was necessary (Scheme 104).



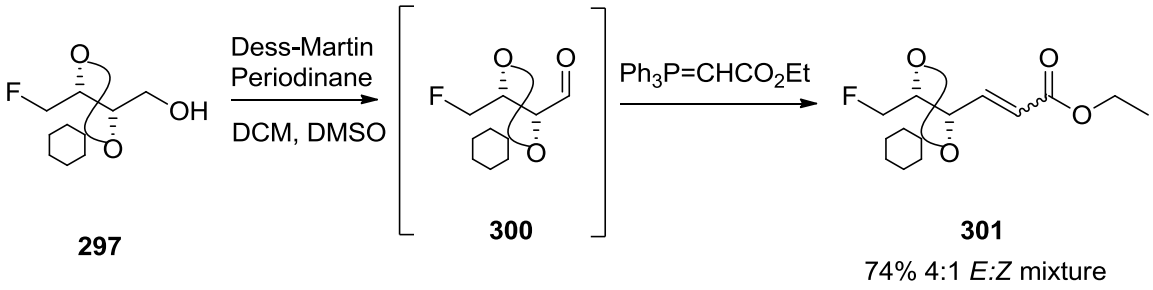
Scheme 104

Our initial attempts to generate the aldehyde **299** were unsuccessful; pyridinium chlorochromate (buffered[196] and unbuffered[197]), Dess-Martin periodinane[198] and Swern[199] conditions all resulted in varying degrees of decomposition of the substrate (indicated by the appearance of numerous signals in the ^{19}F NMR spectra of the crude products). Further experimentation with the Swern conditions revealed the desired intermediate aldehyde **299** could be worked up, and was sufficiently long lived to be

observable by NMR. However, the presence of a number of small signals in the ^{19}F NMR spectrum suggested that decomposition had begun, with the quality of the crude product deteriorating over time (by ^{1}H and ^{19}F NMR). Our eventual success with the Swern oxidation methodology and the perceived sensitivity of the target aldehyde meant alternative routes to **299**, such as oxidation of the primary alcohol with the Ley-Griffith reagent (TPAP) were not explored.[200]

Reaction of the aldehyde *in situ*, or as soon as possible after isolation was therefore necessary. Consistent results with the Swern method were only obtained when freshly opened oxalyl chloride was used. Rigorous efforts to keep the temperature of the reaction as low as possible through slower addition of reagents to the vessel were rewarded, a possible rationale for the disparity of these results with those of the earlier Swern oxidations.

3.8. Two carbon extension of chain *via* a one pot oxidation/Wittig reaction

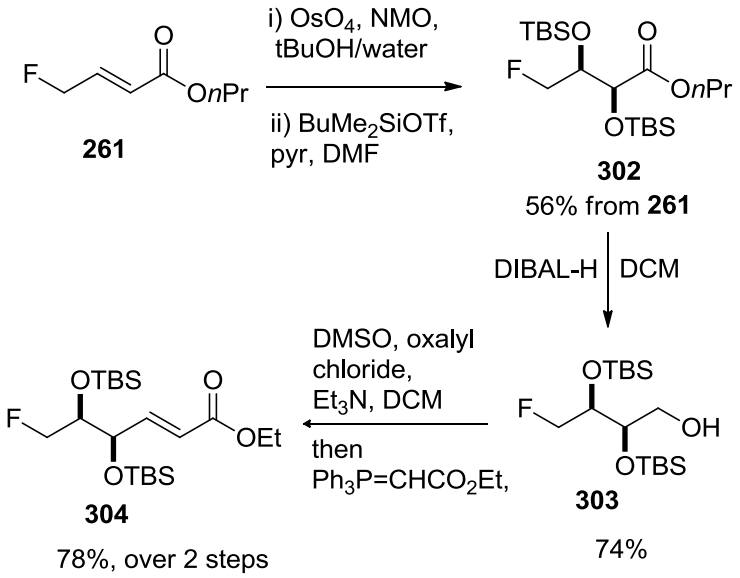


Scheme 105

The short-lived nature of the aldehyde suggested that one-pot oxidation/Wittig procedures would be worthwhile. Dess-Martin periodinane,[201] PCC[202] and Swern[203]

conditions were explored for the oxidation step in the presence of (carbethoxymethylene)triphenylphosphorane. The Dess-Martin periodinane reagent was found to be the most effective, affording a 4:1 *E:Z* mixture of the product alkene in good yield (74%, Scheme 105). A second purification by column chromatography isolated the *E*-isomer of **301** in 37% yield and a mixed fraction of the *E*- and *Z*-alkenes (*E*-isomer identified by the alkene vicinal coupling values in the ^{1}H NMR spectrum, *E:Z* ratios by integration of the distinct signals in the ^{19}F[^{1}H] NMR spectra). Analysis of the pure *E*-alkene using the chiral ^{19}F NMR method revealed that the ee was unchanged from the diol **270**, confirming epimerisation was not occurring during the subsequent reactions.

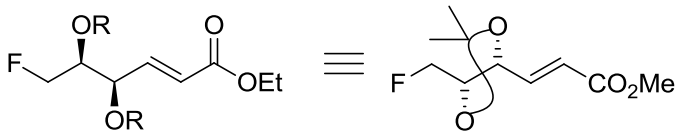
Alternative protecting group strategies were explored; for example the exposure of the racemic diol to *t*-butyldimethylsilyl triflate in the presence of base (pyridine) afforded the bis TBS ether **302** in good yield (56 % from **261**).



Scheme 106

Subsequent DIBAL-H reduction to the primary alcohol **303** and a one-pot oxidation/Wittig reaction afforded the desired unsaturated ester **304** in good yield (78 %, Scheme 106). Although this route afforded the protected Wittig product in a higher yield than the analogous cyclohexylidene protection method (32% yield from **261** *cf.* 18 %), the cost of the silyl protection is far greater (*tert*-Butyldimethylsilyl trifluoromethanesulfonate ~ £1/mmol, cyclohexanone < £0.01/mmol, Sigma Aldrich) and silyl ether cleavage can be notoriously problematic, especially for bulkier substrates.[204,205]

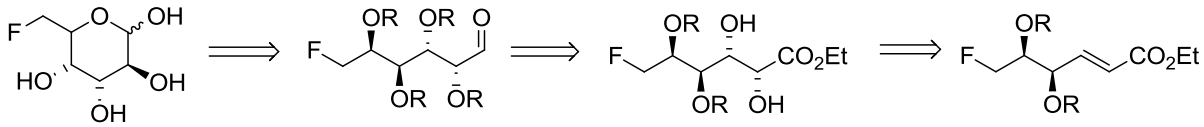
The synthesis of alkenes **301** and **304** is particularly significant, as at this stage the crotonic acid route overlaps with the published syntheses of 6-deoxy-6-fluorohexoses from methyl sorbate (see Figure 24).[1]



305 **238**

Figure 24

As such they represent important potential intermediates in the synthesis of fluorinated hexoses (see Scheme **81**-**86** and **107**).



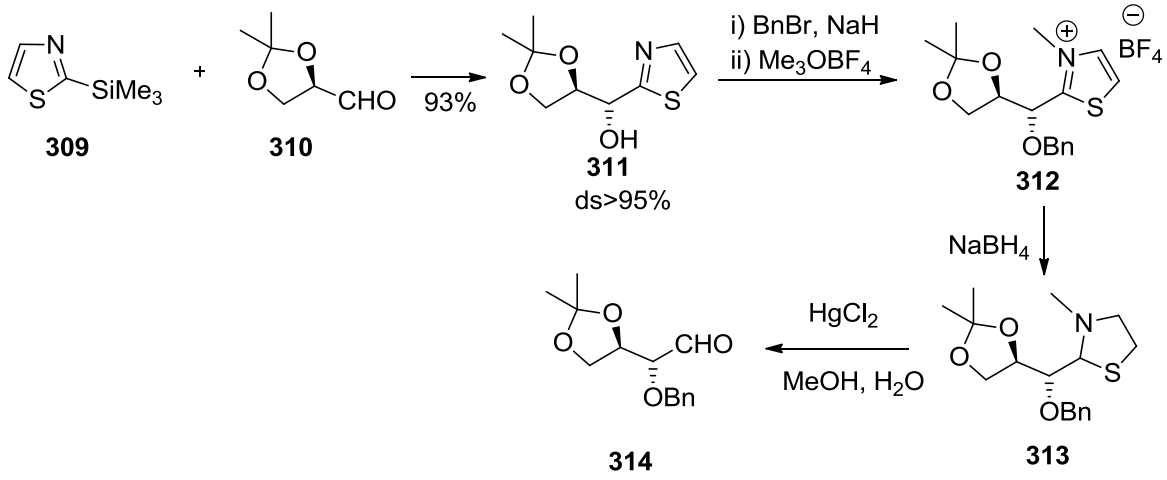
308 **307** **306** **305**

Scheme 107

One of the benefits of the crotonic acid route to **305** is the absence of regioisomers as the double bond is installed after the asymmetric oxidation (regioselectivity is not complete during the AD of the dienoate due to the influence of the fluorine atom). In addition, the crotonic acid route has the potential to deliver all of the 6-deoxy-6-fluorohexose isomers, as the cyclic sulfate chemistry can generate the previously inaccessibly *anti* diol relationships, either at C2-C3, C4-C5 or both.

3.9. One carbon extension of chain *via* Dondoni thiazole chemistry

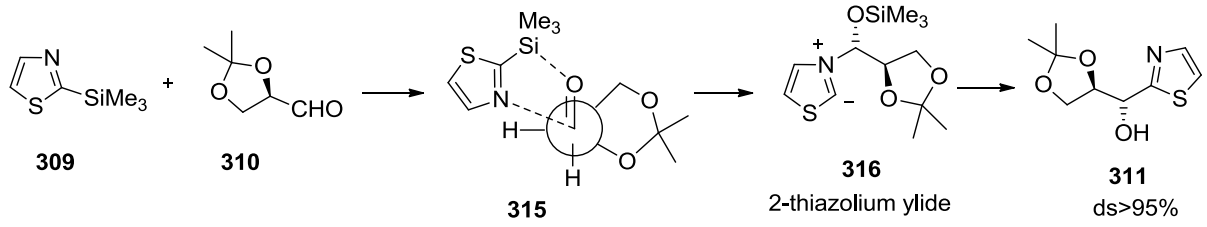
As well as a useful intermediate towards fluorinated hexoses, **299** has some potential as a possible precursor to fluorinated pentoses. Dondoni has shown that the thiazolyl group can be thought of as a latent formyl group (see Scheme 108).[206,207]



Scheme 108

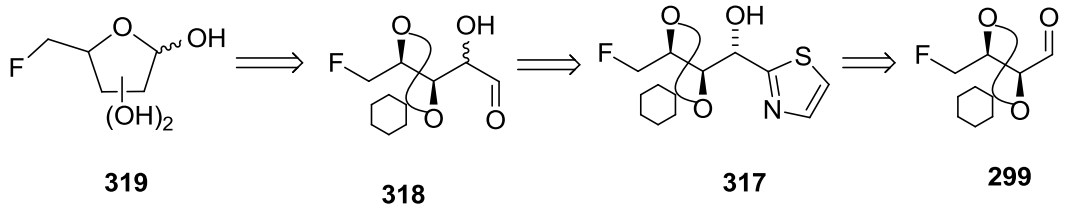
Further, it has been shown that the sequence proceeds with excellent diastereoselectivity for many substrates. For example, the addition of 2-trimethylsilylthiazole **309** to *D*-

glyceraldehyde acetonide **310** gave the *anti*-isomer **311** in >95% diastereomeric purity. Dondoni proposes a 4-centre transition state (**315**) where bonding between the nitrogen of the thiazole ring and the carbon of the carbonyl occurs in concert with transfer of the silyl group from C-2 to oxygen to explain the high selectivity. This leads to a 2-thiazolium ylide **316** which by 1,2-shift of the *N*-silyloxy moiety gives the final adduct **311** (Scheme 109).[206]



Scheme 109

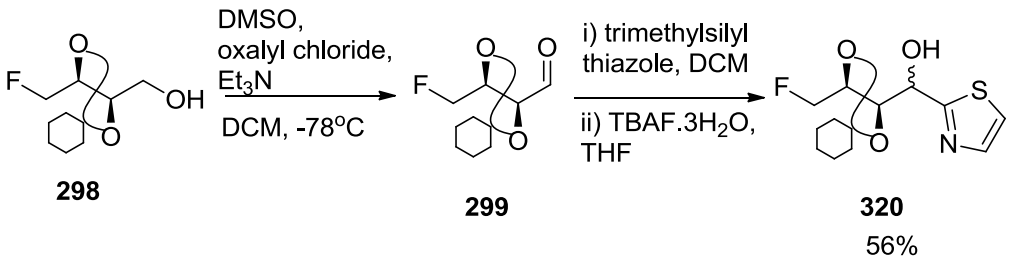
Dondoni's thiazole chemistry would allow extension of the carbon chain of the intermediate **299** by one carbon, while installing the terminal aldehyde moiety, allowing cyclisation to a fluorinated pentose (Scheme 110).



Scheme 110

3.9.1. Synthesis of Dondoni product 325

The silyl ether was formed successfully, via aldehyde **299**, and deprotected (TBAF.3H_2O) to afford alcohol **320** in reasonable yield (56%).



Scheme 111

Unfortunately, due to the attrition in yield over a number of steps in the synthetic sequence to the Dondoni compound this chemistry was carried out on a very small scale and we were unable to cleave the thiazole group successfully.

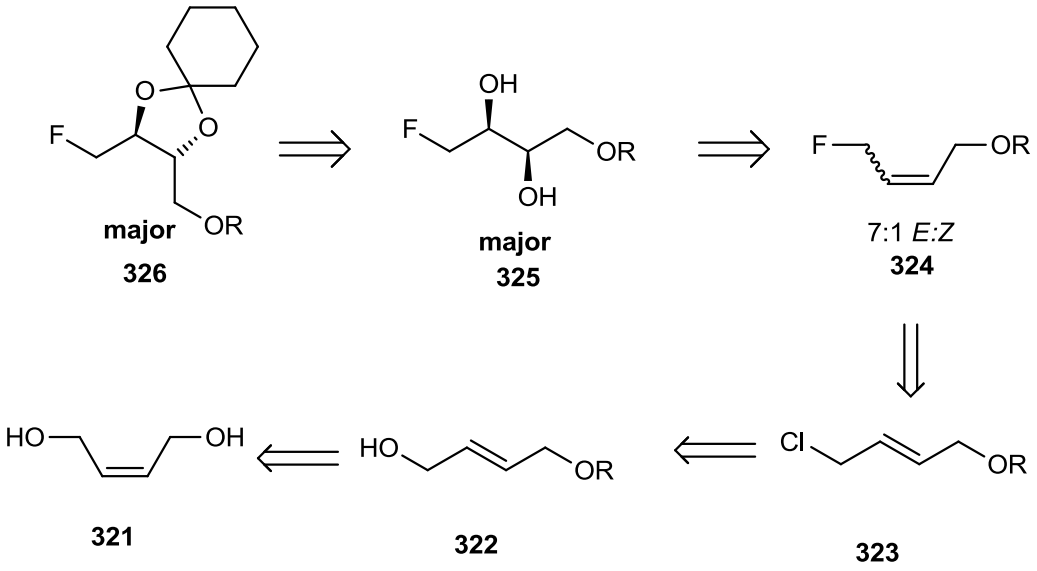
3.10. Conclusion

In summary, we have explored a *de novo* stereocontrolled route to a potentially versatile C4 building block from commercially available, and achiral, crotonic acid. Further, we have shown, that although moderate yielding, the route is completely stereodivergent, with all four possible diastereoisomers accessible in good to excellent enatiomeric purity (>93%) a key goal of this route. Elaboration of the sequence to deliver the final saccharide products through Wittig and Dondoni type chemistry was not completed, although it was shown that extension of the chain and addition of functional groups was possible without loss of enantio enrichment. Indeed, as the products of the Wittig chemistry overlap with a previous (and complete) *de novo* synthesis of fluorinated hexoses developed within our laboratory,[1] we are confident that this route represents a viable stereodivergent and stereocontrolled synthesis of fluorinated hexoses. Finally a new and facile method for the determination of ee for fluorinated molecules

using [^{1}H]^{19}F NMR was developed. The main advantages of this method are that it is quick and simple to perform. The sample preparation, running of the NMR experiment and analysis of the data can all be performed within minutes. Further the process is no more complicated to perform than a standard NMR, once the experimental parameters have been set. Although the method is sacrificial in sample, such small quantities are required (between 2-3 mg) that this will rarely be an issue.

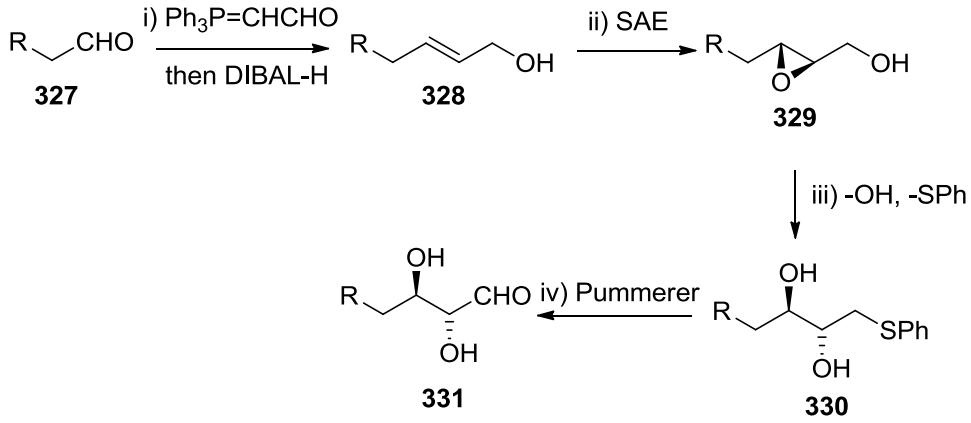
4. Optimisation of a route to fluorinated building block 333 from *Z*-1,4-butenediol

The availability of fluoride sources suggested that a re-examination of other allyl halide substrates could be productive, in particular allyl fluoride **324** as a building block for fluorinated sugar construction. Roig had shown that allyl fluoride **324** could be successfully generated from commercially available *Z*-1,4-butenediol *via* an unusual alkene isomerisation reaction.[3,5] Subsequent SAD and cyclohexylidene protection yielded a useful C4 building block **326** (Scheme 112). We believed that the application of newer nucleophilic fluorination reagents, alternative SAD ligands and the development of a NMR based ee determination method for fluorinated substrates warranted a thorough re-examination of the route in an effort to improve the yields as well as assess the scope and limitations of a number of key steps.



Scheme 112

The versatility of a 4 carbon aldehyde unit such as **299** had already been shown in the seminal Masamune and Sharpless synthesis of all eight L-hexoses.[145] The cycle consists of four key transformations; (i) conversion of an aldehyde to a two carbon extended allylic alcohol; (ii) asymmetric epoxidation directed by the allylic alcohol; (iii) regioselective and stereospecific opening of the epoxy alcohol; (iv) oxidation of the primary alcohol to the corresponding aldehyde. Upon completion of this cycle the stage is set for the next cycle (Scheme 113).



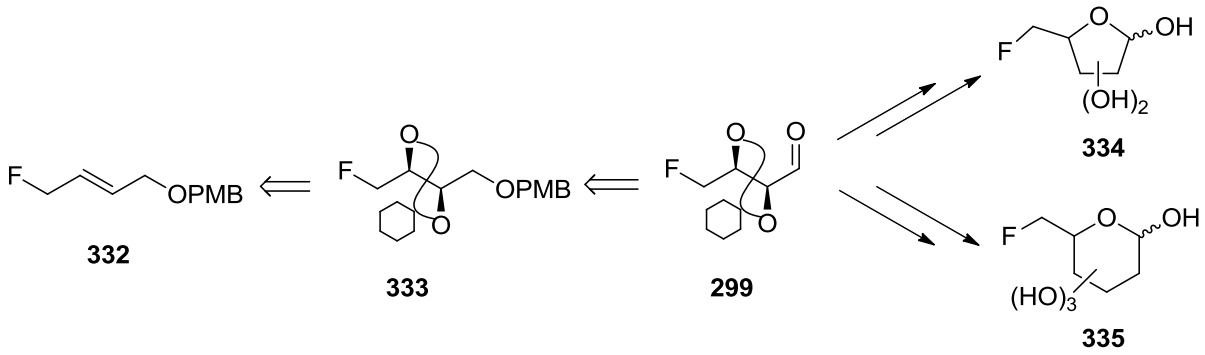
327 **328** **329** **330** **331**

Scheme 113

The Masamune chemistry relies on the Sharpless Asymmetric Epoxidation reaction; we hoped to achieve a similar outcome utilising the more direct Asymmetric Dihydroxylation reaction. Our preference for the dihydroxylation reaction in this instance mainly arises from its tolerance of a diverse range of functionality, and its ease of execution. The SAE reaction requires the presence of an allylic hydroxyl group to direct the chemistry,[208] as well as necessitating an extra synthetic step to open the epoxide.

With the desired allyl fluoride functionality installed at one end of the olefin, a directing allylic hydroxyl group at the other side would produce an extremely small and volatile molecule, which would ensure manipulation of the substrate would be difficult, if not impossible. The Sharpless Asymmetric Dihydroxylation reaction, as well as benefiting from ease of execution and high ee's, tolerates protection of the allyl hydroxyl, allowing us to modify the volatility of the substrate. Further, the stereochemistry of the resulting *syn*-diol can be controlled explicitly through the choice of directing ligand.

Acetal protection of the diol would yield versatile fluorinated building block **333** for the synthesis of sugar analogues, similar to the building block **292** derived from crotonic acid (Scheme 114).

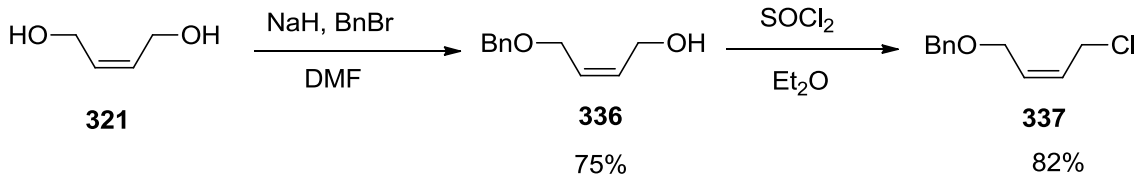


Scheme 114

Successful optimisation of this chemistry had the potential to produce a superior synthetic route to aldehyde **299** as it would avoid the difficult DIBAL-H reduction required by the other sequence. The need to reduce the propyl ester of **292** to the primary alcohol oxidation level only to re-oxidise the substrate to the aldehyde **299** immediately afterwards was extremely inefficient and detrimental to the overall yield of the sequence.

4.1. Synthesis of allyl chloride 337

The synthesis of **337** was carried out according to the literature procedure from commercially available *Z*-but-2-ene.[209,210]



321 **336** 75% **337** 82%

Scheme 115

Allyl alcohol **336** was obtained in good yield (75%) by treating butene diol with sodium hydride and benzyl bromide in DMF, followed by Kugelrohr distillation. Subsequent conversion to the allyl chloride **337** was achieved by simple addition of thionyl chloride to an ethereal solution of the allyl alcohol **336** (Scheme 115). The desired product was isolated in good yield (82%) as a clear, colourless oil after Kugelrohr distillation.

4.2. Fluorination of allyl chloride 337

Allyl chloride **337** was exposed to a number of nucleophilic fluorination sources; however the target fluoride was not a product of any of the reactions (Table 4).[39,93,211]

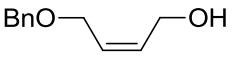
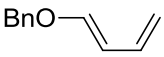
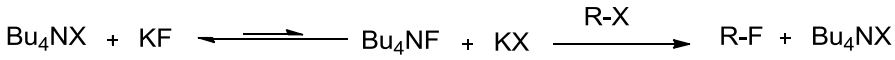
Reaction Conditions	Outcome
KF, CH_3CN, reflux	No reaction
KF, THF, reflux	No reaction
TBAF.$3H_2O$, CH_3CN, reflux	Elimination and hydrolysis products  **336**  **338**
KF, $BminBF_4$, H_2O, CH_3CN, 90°C	No reaction
KF, $BminPF_6$, H_2O, CH_3CN, 90°C	No reaction

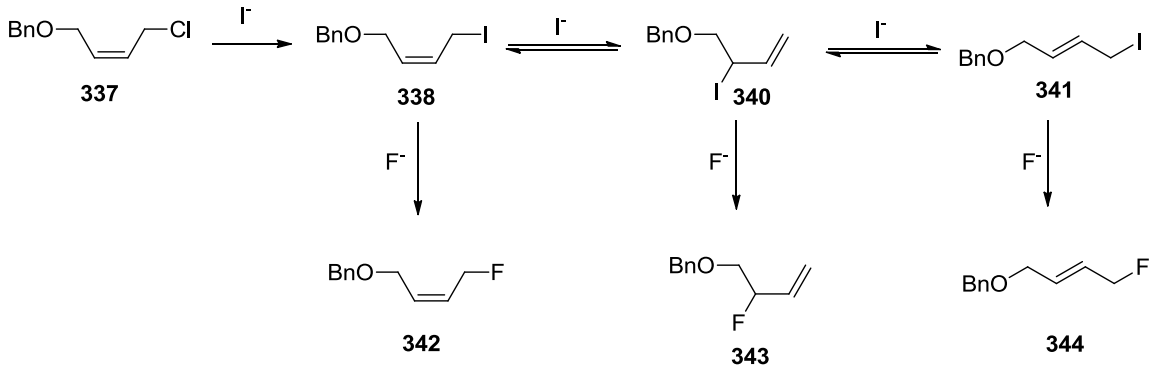
Table 4: Nucleophilic fluorination reactions with allyl chloride **337** performed by R. Roig[3]

Roig proposed[3] that a solid liquid phase mixture of potassium fluoride and tetrabutyl ammonium iodide would generate catalytic amounts of TBAF *in situ* and lead to fluorination (Scheme 116).[212,213]



Scheme 116

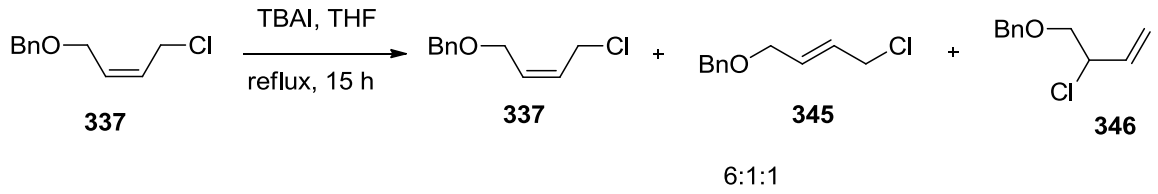
Roig followed the reaction by GC-MS and ^{1}H NMR and unexpected yet extremely interesting results were observed.[3] In the resulting chromatogram of the reaction mixture another peak which possessed a similar retention time to the *Z*-allyl fluoride and exactly the same molecular weight was present. The two other structures consistent with the GCMS are **343** and **344**, and **343** was inconsistent with the ^{1}H NMR spectrum. It was proposed that during the reaction two sequential S_N2' reactions were taking place to yield the *E*-allyl fluoride as the major component (Scheme 117). As iodide is both a good nucleophile and excellent leaving group it was proposed that the TBAI was promoting this isomerisation reaction.



Scheme 117

4.3. Investigation of the unexpected alkene isomerisation

Refluxing *Z*-allyl chloride with TBAI in THF yielded 3 distinct allyl chlorides; the *E* **341**, the *Z* **337** and the internal chloride **346** as a 6:1:1 mixture (Scheme 118). The isomerisation of the *Z*-chloride could be monitored by GC-MS and doing so revealed that an equilibrium appeared to be established relatively quickly (Figure 25).



Scheme 118

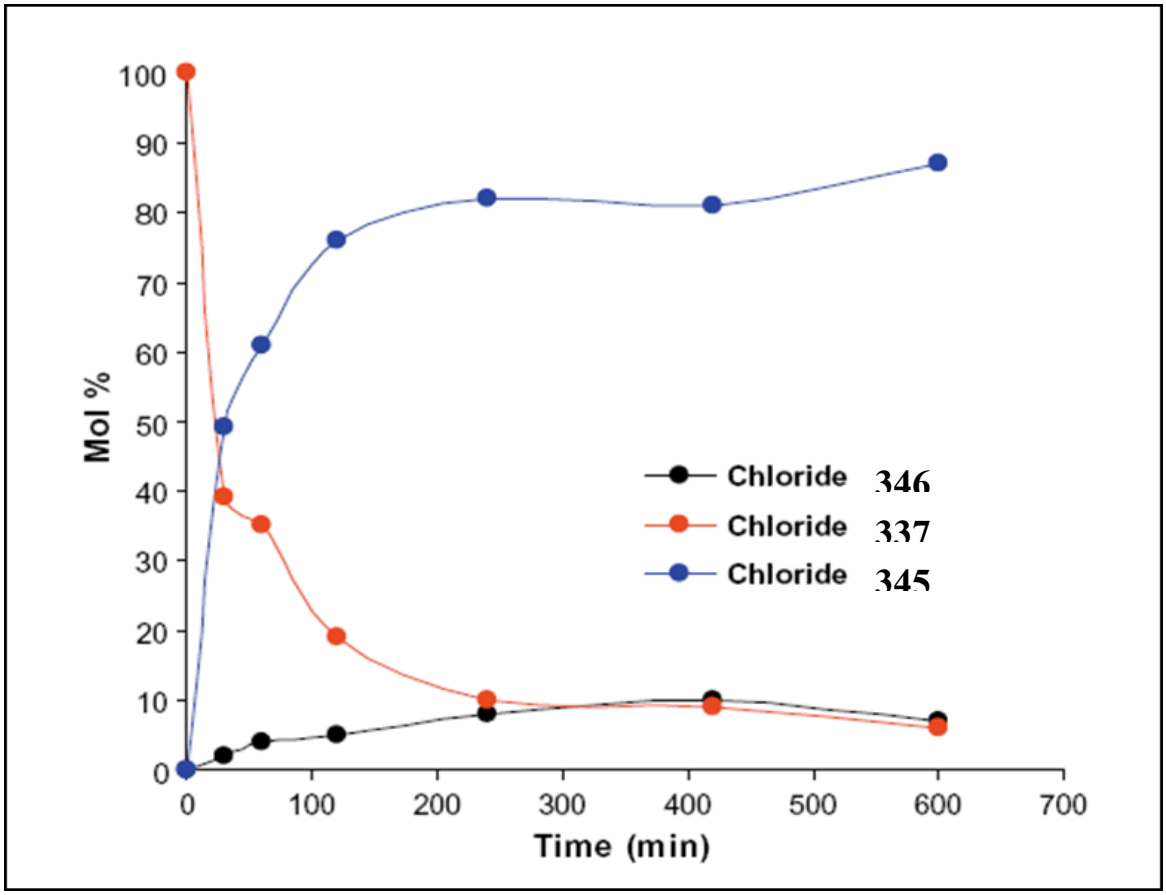
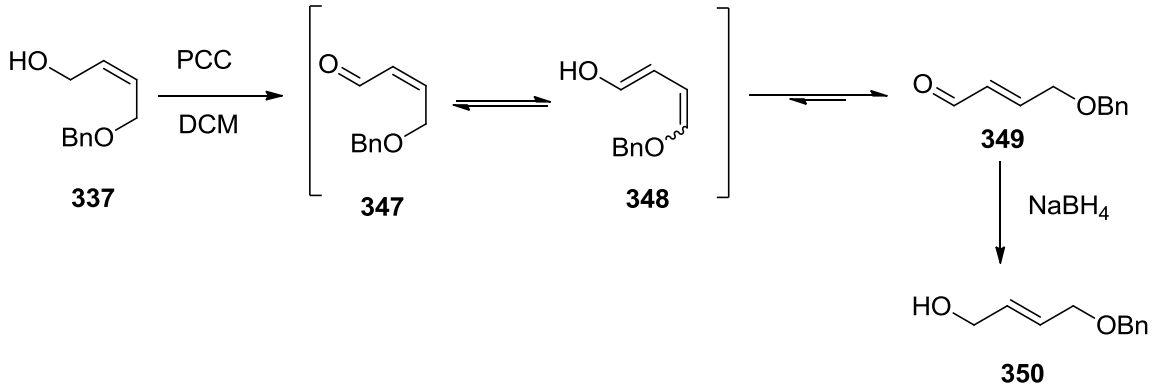


Figure 25. Following the course of the *Z*-chloride isomerisation

This unexpected alkene inversion is particularly interesting as we found little evidence of similar reactions in the literature, and no examples which operate under this proposed

mechanism. Danishefsky and Regan prepared allylic alcohol **350** *via E*-butenal **349** by PCC oxidation of **337**; in this case, it is more likely that the isomerisation proceeds through acid-catalysed enolisation and reprotonation (Scheme 119).[214] *Z*-Enal **347** is the immediate product formed but it is less stable than *E*-enal **349**, so there is a driving force for this isomerisation.



Scheme 119

Although the synthetically more useful *E*-alkene **345** is the major product of the isomerisation reaction a more stereoselective reaction would be advantageous. Roig had reported that the alkene isomerisation yielded a 6:1 mixture of the *E*- and *Z*-isomers, but it was unclear if the reactions conditions reported were optimised.[3] Repetition of these results was initially problematic with the isomerisation reaction yielding 1:1 mixtures of the *E*- and *Z*-alkenes. It was found that between 2.5-3 molar equivalents of TBAI and heating at reflux for ~2 days was required before *E:Z* ratios as high as 7:1 were obtained. Unfortunately, neither increasing the quantity of TBAI in the reaction (up to 5 eq. *cf.* 2 eq.) nor significantly increasing the reaction time to (5 days) showed any noticeable

improvement in the quantity of *E*-alkene present (from the integration of the alkene signals in the crude ^{1}H NMR spectrum). The persistence of species **337** and **346** was interesting and in an attempt to understand these findings further the lowest energy conformations of **337**, **345** and **346** were determined using the equilibrium conformer search algorithm within SPARTAN'06 v1.1.0 (MMFF94).[215] Geometries were optimised, with full frequency calculations (B3LYP/6-31G*), allowing free energies (gas phase, 298 K) to be determined relative to **345**; **337** (+6.75 kJ mol^{-1}) and **346** (+8.44 kJ mol^{-1}) are less stable, but the free energy differences would suggest that **345** should be favoured more decisively at equilibrium. Of course, these are gas phase energies and it is possible that they may converge once solvent polarity is taken into account in the calculations. Further, **346** is more hindered than **337** and may therefore react quite slowly once formed, so it would not be expected to be present in significant amounts at equilibrium.

4.4. Synthesis of the *para*-methoxybenzyl protected analogues

Para-methoxybenzyl protected allyl fluoride **359** was considered as a superior substrate for the deployment of Sharpless Asymmetric Dihydroxylation chemistry. Corey and co-workers have shown that allylic 4-methoxybenzoates and allylic 4-methoxybenzyl ethers undergo SAD reactions in higher yield and enantiomeric purity than species with other allylic protecting groups. The increased enantiomeric purities arising from the inclusion of these functional groups is a result of favourable hydrophobic and aryl-aryl

interactions within the U-shaped binding pocket of the chiral ligand/osmium tetroxide complex (Figure 26).[216-220]

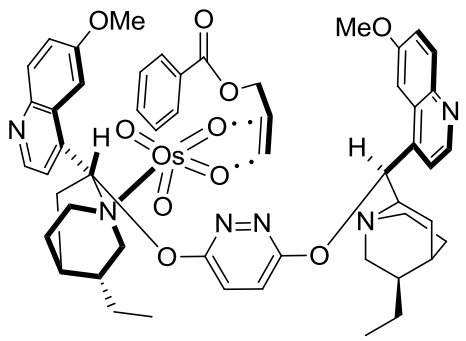
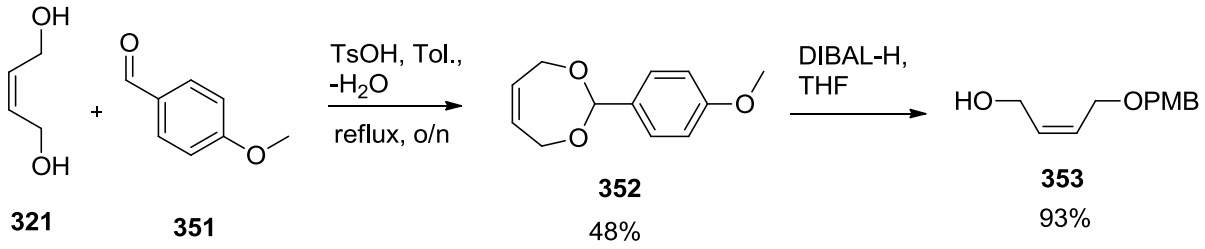


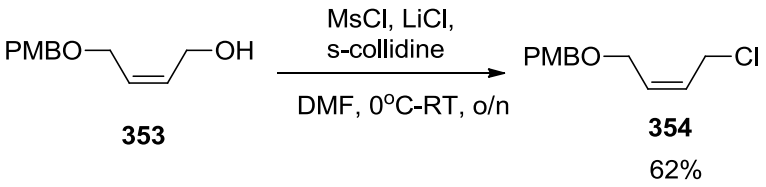
Figure 26

The cyclic ketal **352** was synthesized from the reaction between cheap and commercially available *cis*-2-butene-1,4-diol **321** and *p*-anisaldehyde **351** in the presence of *p*-toluenesulfonic acid (acid catalyst) to generate cyclic 1,3-dioxepin **352**, according to a procedure by Williams *et al.*.[221,222]



Scheme 120

The material was carried on to the next step without purification; cleavage of the acetal with DIBAL-H, afforded the corresponding mono protected *Z*-allyl alcohol **353** in good yield (93%, Scheme 120).



353 **354** 62%

Scheme 121

Surprisingly the subsequent halogen displacement of the allylic alcohol **353** proved difficult to effect, with only a procedure utilizing mesyl chloride and *s*-collidine as the base proving effective (Scheme 121).[223] The method using thionyl chloride (see Scheme 115) afforded a complex crude product mixture. This may be a result of the low stability of the *para*-methoxybenzyl ether under acidic conditions.[224] Modification of the conditions by adding pyridine as a hydrogen chloride scavenger (the Darzen procedure)[225,226] produced only a moderate improvement. The superiority of *s*-collidine **355** as a base in this reaction can be explained by its poorer nucleophilic properties (with respect to pyridine) preventing further substitution on the allylic chloride once it has formed. When pyridine is used, a large quantity of the desired product is lost in the aqueous work-up, possibly as the *N*-allylic pyridinium salt **357**.

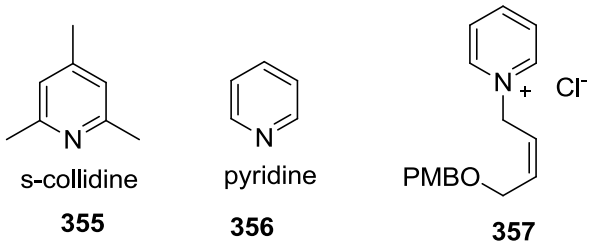
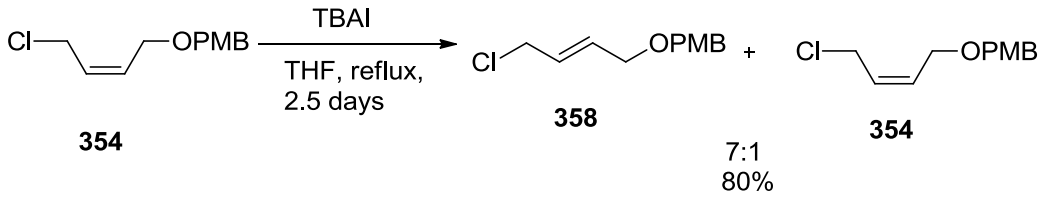


Figure 27

Conversion of *Z*-allyl chloride **354** to the *E*-allyl chloride **358** *via* the TBAI induced inversion once again required quite forcing conditions (2.6 molar equilvalents of TBAI and heating at reflux for >48 hours). However **358** was obtained as the major product of a 7:1 mixture of **358** and **354** in good yield (80%, Scheme 122).

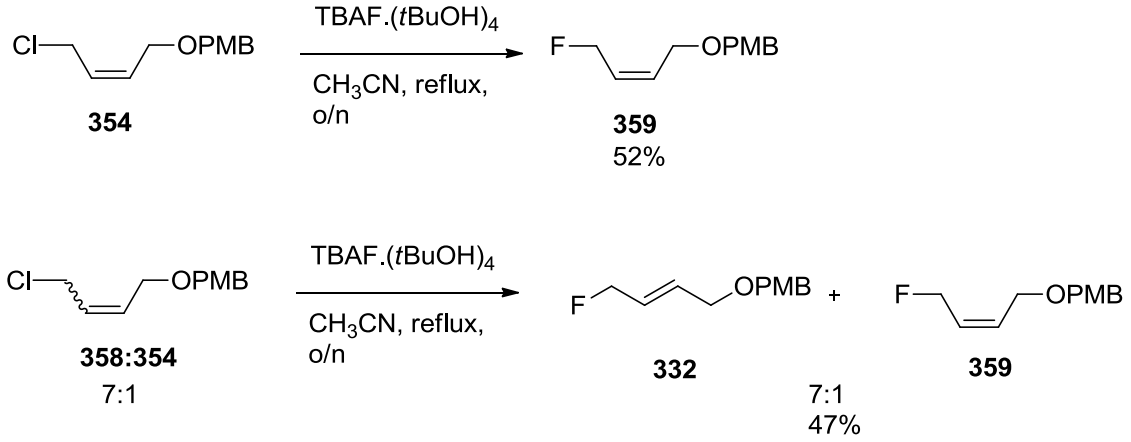


Scheme 122

4.5. Optimisation of the fluorination of allyl chlorides 354 and 358

Fluorination of the allylic chlorides was subject to some optimization. The preparation of allyl fluoride **359** had previously been achieved with commercial TBAF.3H_2O in refluxing THF (65% yield).[3] However, this method also produced inferior results with erratic yields (26-88%) and complex mixtures of compounds formed (as shown by GC-MS). The Hou method using KF.2H_2O and $TBAHSO_4$ produced higher yields and cleaner material (by GC-MS) but a vast excess of the fluoride source (over 12 eq.) were

required in conjuction with long reaction times (up to a week at reflux) to force the fluorination to completion, meaning this method was far from being cost or time effective. This reaction requires the fluorination to go as near to completion as possible as the physical and chemical similarities of the respective allyl chlorides and fluorides ensure that removal of unreacted starting material is difficult.



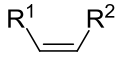
Scheme 123

Recently Kim *et. al*. reported that TBAF.(*t*BuOH)$_4$ was an effective fluorinating agent.[174] Our attempts to use TBAF.(*t*BuOH)$_4$ in the fluorination of butenoate **254** had proved unsuccessful, causing decomposition of the substrate, and suggesting that this fluoride source was more basic than other fluoride reagents in our repertoire (for example potassium fluoride dihydrate). However, exposure of allyl chlorides **358** and **354** to TBAF.(*t*BuOH)$_4$ in refluxing acetonitrile yielded the desired allyl fluorides **332** and **359** in moderate yield, with little visible evidence of unwanted side-products in the GC-MS (Scheme 123). Further, the stoichiometry of the fluoride source (2 eq. *cf.* 12 eq. KF.2H$_2$O) was acceptable and significantly shorter reaction times (overnight at reflux

compared to 1 week) could be used. It remains unclear why this seemingly clean reaction delivers isolated product in only moderate yield as ^{1}H NMR and GC-MS of the crude mixture reveal little evidence of side product formation.

4.6. Optimisation of the SAD of allyl fluorides 332 and 359

With the desired allyl fluorides (*Z* - **359** and 7:1 mixture of **332:359**) performance in the Sharpless Asymmetric Dihydroxylation reaction was examined. *Z*- alkenes are classically very poor substrates for the SAD reaction.[227]



cis-olefin

Figure 28

One limitation involves the “meso problem". When $R^1 = R^2$, AD of this symmetrical *cis*-disubstituted olefin leads to formation of the meso diol. As R^1 approaches R^2 in size, the vanishing prochiral asymmetry of the olefin renders enantiofacial selection increasingly more difficult, resulting in the low levels of enantio-enrichment.[227] *β*-Substituted styrenes therefore yield products in the range of 70-80% ee, while aliphatic substrates give even lower selectivities, with even cyclic *cis*-olefins yielding poor ee results (Table 5).

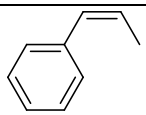
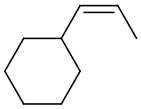
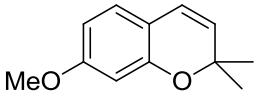
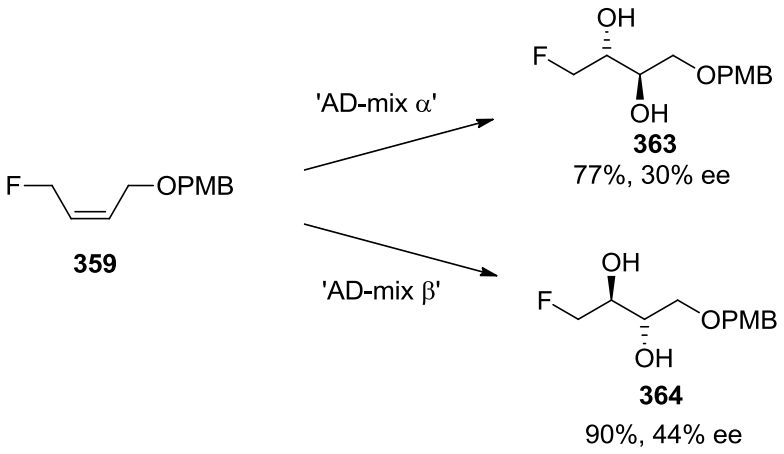
	ee%	
	DHQD-IND	DHQ-IND
 **360**	72	59
 **361**	56	44
 **362**	32	67

Table 5

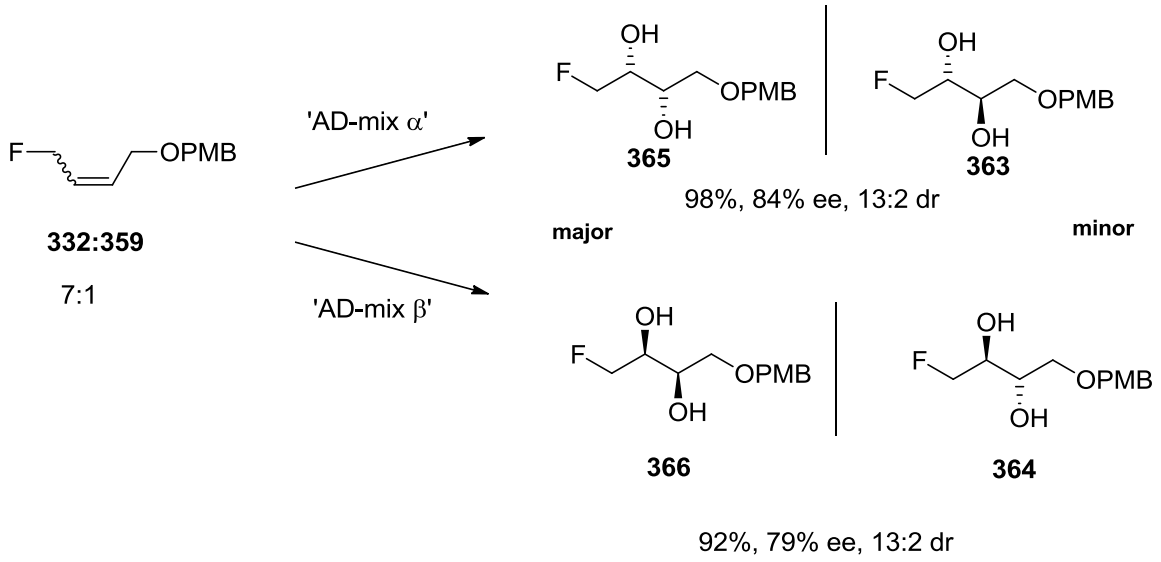
As well as the standard PHAL based ligands, the stereoselectivity of the AD reactions was explored with AQN ligands, which display improved selectivity for substrates with allylic heteroatoms. This would be particularly useful if successful, as the *Z*-olefin **359** can be accessed entirely diastereomerically pure (the *E*-alkene **332** can be synthesised as a 7:1 mixture of **332**:**359** respectively at best).



AD-mix-α : $K_2OsO_4.2H_2O$, $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0°C;
AD-mix-β : $K_2OsO_4.2H_2O$, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0°C

Scheme 124

Under the 'improved' AD conditions, with higher osmium and ligand content, and using the standard PHAL based ligands, *Z*-olefin **359** was converted into diols **363** and **364** in good yield (77 and 90%) but with a poor ee (30% from the α-mix, 44% from the β-mix) (Scheme 124). Under the same conditions *E*-allyl chloride **332** was converted into diols **365** and **366** in good yield (98% and 92%) and ee (84% and 79%) (acceptable and consistent values compared to analogous substrates in the literature)[178] but the presence of the *Z*-allyl chloride **359** as an impurity in the substrate resulted in a low dr (13:2) for the diol products (Scheme 125).



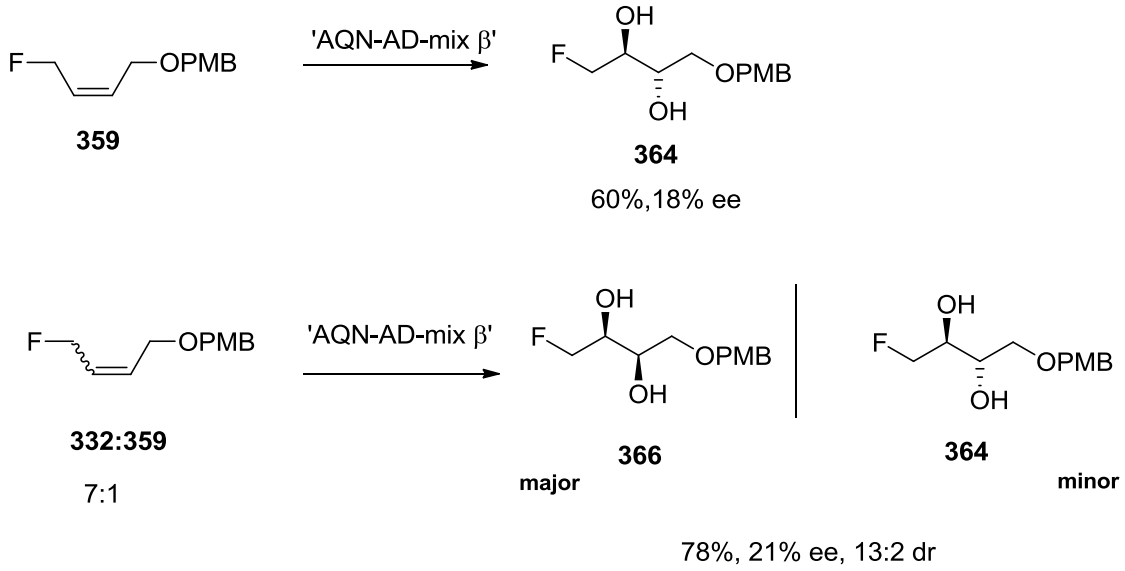
AD-mix-α : $K_2OsO_4.2H_2O$, $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0°C;
AD-mix-β : $K_2OsO_4.2H_2O$, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0°C

Scheme 125

Despite the presence of hetero-atoms in both allylic positions for substrate **359** (as was the case for buteneoate **261**) exposure of the *Z*-alkene **359** to SAD conditions with the $(DHQD)_2AQN$ ligand gave no enhancement of the ee obtained for diol **364** (18%). $(DHQD)_2AQN$ was chosen over $(DHQ)_2AQN$ to validate the effect of the AQN core as the DHQD ligands tend to give slightly higher levels of enantioenrichment.[178] This can be explained by the diastereomeric rather than enantiomeric nature of the DHQD and DHQ (Figure 16).

More surprisingly however, exposure of the 7:1 **332:359** mixture to these conditions also resulted in a decrease in the ee obtained (21% compared to 44% from the analogous PHAL ligand). This result is unexpected as allylic OPMB ethers are reported to be

excellent substrates for the SAD reaction due to favourable interactions between the benzyl ether aromatic ring of the substrate and the chiral ligand/osmium complex.[218] As the only structural difference between *E*-alkene **332** and butenoate **261** is the replacement of the OPMB group by a propyl ester, it can be assumed that the favourable interactions between the OPMB aromatic ring of the substrate and the chiral ligand/osmium complex are absent or even unfavourable when the chiral ligand possesses the AQN core.

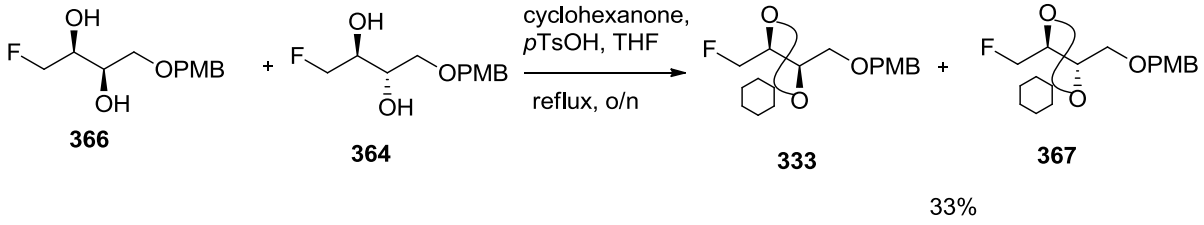


AQN AD-mix β : $K_2OsO_4.2H_2O$, $(DHQD)_2AQN$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0°C

Scheme 126

4.7. Cyclohexylidene formation

As the diastereomers of the free diols were inseparable *via* flash chromatography, they were protected as the corresponding cyclohexylidene acetals. Due to our earlier success of using $BF_3.Et_2O$ as a Lewis Acid for cyclohexylidene acetal formation in the route from crotonic acid, diols **366** and **364** were exposed to the same reaction conditions. However, neither NMR (^1H and ^{19}F) or mass spectrometry revealed any evidence of the presence of the desired product and the poor quality of the crude NMR spectra suggested this substrate was not compatible with these acetal forming conditions. Acetals **333** and **367** were formed in moderate yield (33%)[3] by refluxing the diols **366** and **364** with cyclohexanone and catalytic *p*-toluenesulfonic acid in THF.



Scheme 127

Although the products did not crystallize, it was found that the diastereomeric acetals could now be separated on silica, albeit *via* a difficult separation requiring two or more columns. After a second purification this method delivered the major diastereoisomers (*syn)* of the cyclohexylidene diastereomerically pure (to the detection levels of ^{19}F [^1H] NMR) and an enriched mixture of the cyclohexylidene **333** and **367** (8:1 respectively).

4.8. Conclusion

In conclusion, the *Z* to *E* isomerisation of allylic chloride **354** afforded a very convenient way of making mixtures enriched in the *E*-diastereoisomer **332**. These are effective substrates in Sharpless AD reactions, delivering highly enantiomerically-enriched fluorinated butene triol building blocks. Although this method does not deliver the minor *anti* diastereoisomers it may benefit from a potentially superior protecting group in the allylic position compared to the crotonic acid route (PMB ether *cf.* propyl ester). Removal of the propyl ester requires a DIBAL-H reduction followed by a difficult work-up and purification, leading to a significant attrition in yield. The PMB ether can be removed by a hydrogenation or by using a variety of oxidising agents (e.g. CAN, DDQ), possibly avoiding the work-up issues inherent with the other method. Re-examination of this route has led to more reproducible conditions for the fluorination of allyl chloride **360** using the new reagent TBAF.(tBuOH)$_4$.

The limits of the alkene isomerisation have been defined further, with mixtures no higher than 7:1 *E:Z* able to be obtained despite forcing conditions. The asymmetric dihydroxylations of the alkenes **359** and the **332:359** mixture have been explored in depth with both PHAL and AQN ligands, revealing the AQN ligand is incompatible with the OPMB protected substrates **332** and **359** in SAD reactions.

However, the route from crotonic acid would be the preferred method for the generation of fluorinated building blocks. The diastereomeric impurities arising from the alkene inversion chemistry require a difficult separation (at least 2 columns) resulting in very

poor yields and the compatibility of the butenoate substrates with the AQN ligands means higher ee's are achievable with the crotonic acid route.

5. Discovery of a novel method for the preparation of allyl fluorides *via* a direct cross metathesis reaction

While allyl fluorides are synthetically useful, their synthesis can be challenging. Fluorinating reagents can be expensive, difficult to handle[7] and unselective, resulting in unwanted byproducts, especially if particularly sensitive functional groups are present.[64,128-130] The fluorination methods used in this work, for example that which uses a neat TBAF/KHF_2 mixture, are limited to certain substrates.[1] Further, synthesis of an analogous allyl halide or tosylate is necessary before exposure to the fluorinating reagents, resulting in a lengthening of the synthetic route.[60] An alternative and more direct route to allyl fluorides would be highly desirable and was explored as a potential method for the generation of allyl fluorides.

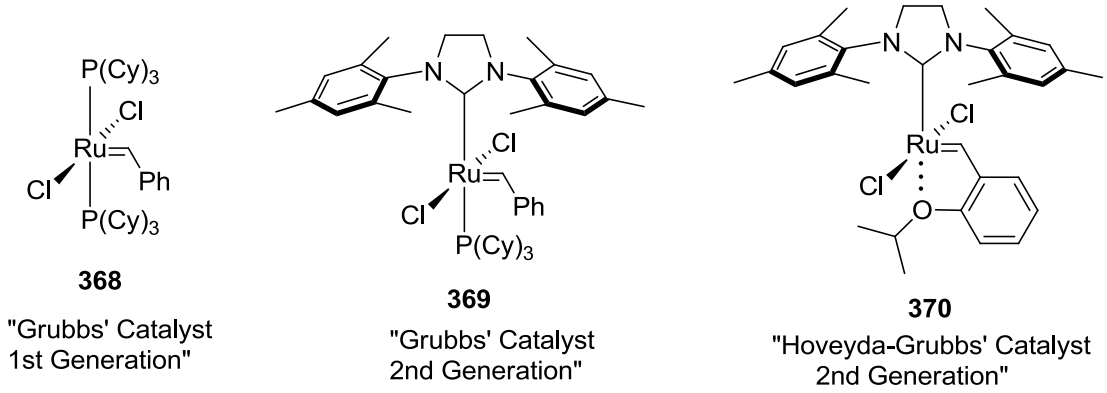
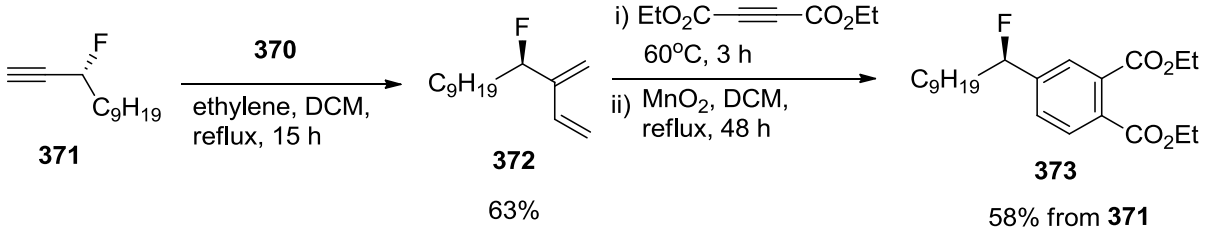


Figure 27: Commonly used olefin metathesis catalysts

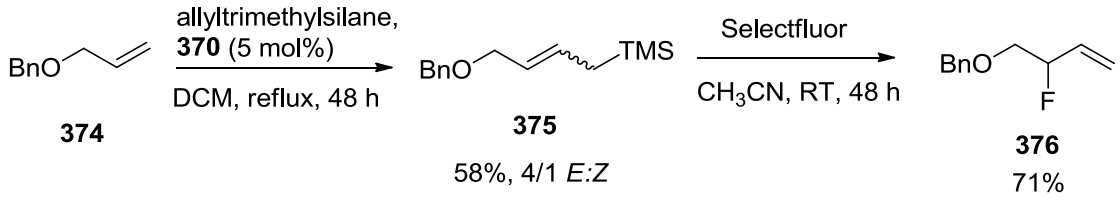
Although some elegant examples of fluorine introduction into molecules by cross metathesis do exist in the literature, this method remains limited and rarely used, especially in the synthesis of allylic fluorides. Kaliappian and Gree achieved the

synthesis of benzylic fluorides using an ene-yne metathesis-aromatization strategy.[228] This work utilized the propargylic fluoride[229] **371** to readily afford the diene **372** (Scheme 128). Subsequent reaction of **372** with diethyl acetylenedicarboxylate in a Diels-Alder reaction then afforded the corresponding 1,4-cyclohexadienes which were then readily oxidized to the respective benzylic fluoride **373**.



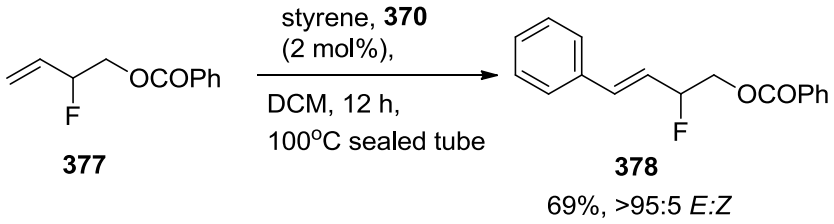
Scheme 128

The Gouverneur group has shown that electrophilic fluorodesilylation of vinylsilanes and allylsilanes is a useful entry to internal allyl fluorides.[230] A novel two-step procedure for the preparation of a variety of allylic fluorides has been developed by combining the electrophilic fluorodesilylation reaction with the cross metathesis reaction. Readily available functionalized alkenes underwent cross metathesis with allyltrimethylsilane, followed by the electrophilic fluorodesilylation of the corresponding allyl silanes in the presence of Selectfluor™ (Scheme 129).[231]



Scheme 129

So far only internal allyl fluorides (with terminal alkenyl groups) have been prepared using this new reaction. The Gouverneur group has gone on to show these terminal allyl fluorides are able to participate in further intermolecular cross metathesis reactions with a variety of olefinic partners to yield a variety of functionalised disubstituted allylic monofluorides.[232] Of note are the extremely forcing conditions used to react alkene **377** with styrene; the reaction requiring heating at high temperature and under pressure for over 12 hours (Scheme 130).

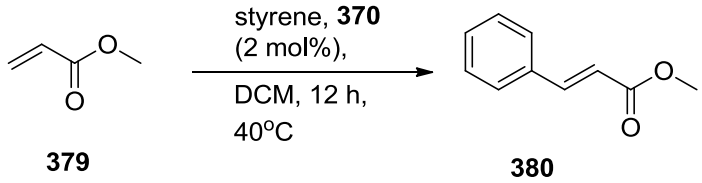


377 **378**

69%, >95:5 *E:Z*

Scheme 130

This contrasts sharply with standard cross metathesis reaction conditions which usually take place between room temperature and reflux (40°C for DCM) at standard pressure for a few hours.[233] The deactivating effect of fluorine on the olefin is obviously large, as the analogous reaction (Scheme 131) between styrene and electron-deficient methyl acryalte **379** proceeds in good yield without forcing conditions.[234,235]



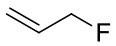
379 **380**

Scheme 131

In conclusion, although a number of synthetically useful monofluorinated allyl fluorides have been synthesised using cross metathesis, the fluorine atom is always positioned internally. Further, the fluorinated cross metathesis substrate is either operationally relatively complex requiring a difficult fluorination in its own preparation, or the fluorine atom is introduced indirectly later *via* a fluorodesilylation.

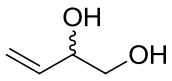
5.1. 1-Fluoroprop-2-ene 381

1-Fluoroprop-2-ene **381** (allyl fluoride) is a commercial product; it is not inexpensive and is volatile (bp – 10^{o}C) but it offers the prospect of the availability of a very new way of synthesising allyl fluorides, in a single step.

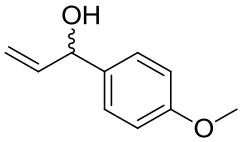


381

In addition, the fluorine atom is located terminally in the resulting allyl fluoride; molecules of this type are significantly more difficult to access *via* the fluorodesilylation route.



382

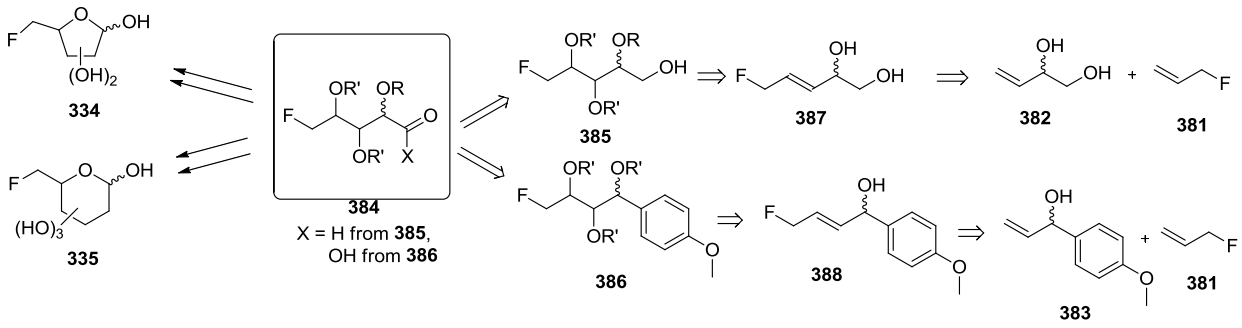


383

Figure 28

Two olefin cross metathesis partners (Figure 28) were chosen to explore the compatibility of allyl fluoride **381** with cross metathesis chemistry. These would lead to synthetically useful fluorinated building blocks and would react efficiently with allyl

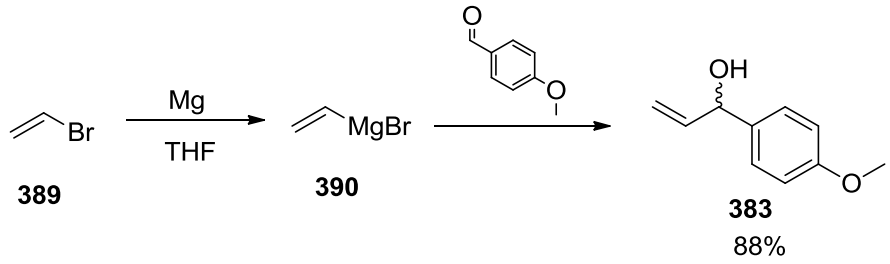
fluoride according to the general model for selectivity in olefin cross metathesis as outlined by Grubbs.[233] Using Grubbs' classification of olefin types with **370** (the metathesis catalyst utilised in all previous metathesis reactions with allyl fluorides), **382** and **383** are Type II olefins undergoing slow homodimerisation whereas allyl fluoride **381** was expected to behave as Type I, displaying fast and reversible homodimerisation. Combining Type I and II alkenes usually discourages the formation of unwanted homodimerisation products. Both **382** and **383** possess manipulable functional groups (the primary alcohol in **382** and the aromatic ring in **383** *via* oxidative cleavage) that once the substrate has been fluorinated, could be used to expand the molecules into versatile building blocks (of the type **384**) for fluorinated sugar analogues.[2]



Scheme 132

5.2. Synthesis of allyl alcohol 383

3-Butene-1,2-diol, **382**, is commercially available. Alcohol **383** was synthesised by the reaction between the Grignard reagent **390** (prepared from vinyl bromide) and *p*-anisaldehyde (Scheme 133).



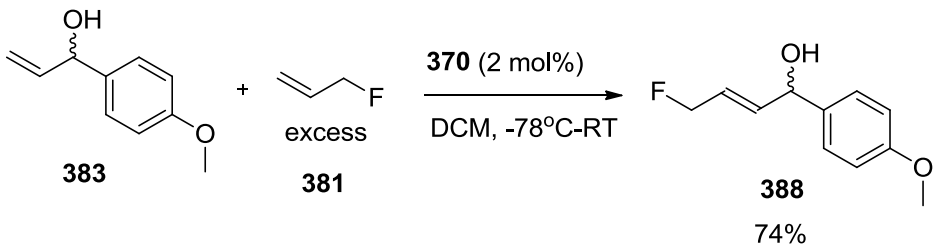
Scheme 133

The Grignard reagent **390** was formed by condensing gaseous vinyl bromide **389** into a cooled (-78^{o}C) solution of THF using a dry ice condenser and subsequent dropwise addition of the mixture onto activated magnesium under an inert atmosphere. "Dry Stir" activation of the magnesium (stirring the turnings under an atmosphere of nitrogen for several hours)[236] produced superior results to acid washing or iodine activation of the metal. Although the formation of olefin **383** was initially low yielding (17%, iodine activation, ~70 mmol), subsequent attempts on a larger scale (~140 mmol) with "Dry Stir" activation were significantly more efficient, yielding the alcohol **383** in good yield (88%) after flash chromatography.

5.3. Cross metathesis of olefins 382 and 382 with allyl fluoride

Allyl fluoride **381** is a gas at room temperature (b.p. -10^{o}C) so the addition of reagents and initial stages of the reaction must be performed at low temperature. **370** was weighed into a Radley's carousel tube under an atmosphere of nitrogen and cooled to -78^{o}C in a dry ice/acetone bath. A balloon was filled with allyl fluoride and the contents condensed into the bottom of the carousel tube using a long needle. The quantity of allyl fluoride was calculated approximately using the mass loss from the allyl fluoride gas canister. The mixture was then warmed to -18^{o}C (ice/salt bath) and the coupling partner

olefin added dropwise as a solution in degassed DCM. Both reactions were accompanied by a pronounced colour change (pale green to greenish yellow for **388** and pale green to a dark green black for **387**).



Scheme 134

Olefin **383** underwent cross metathesis with allyl fluoride **381** remarkably cleanly on the basis of ^{1}H and ^{19}F NMR spectra of the crude product (Figures 29 and 30); the spectra were consistent with the formation of the desired allyl fluoride **388** as the major component in a good yield (74%, Scheme 134).

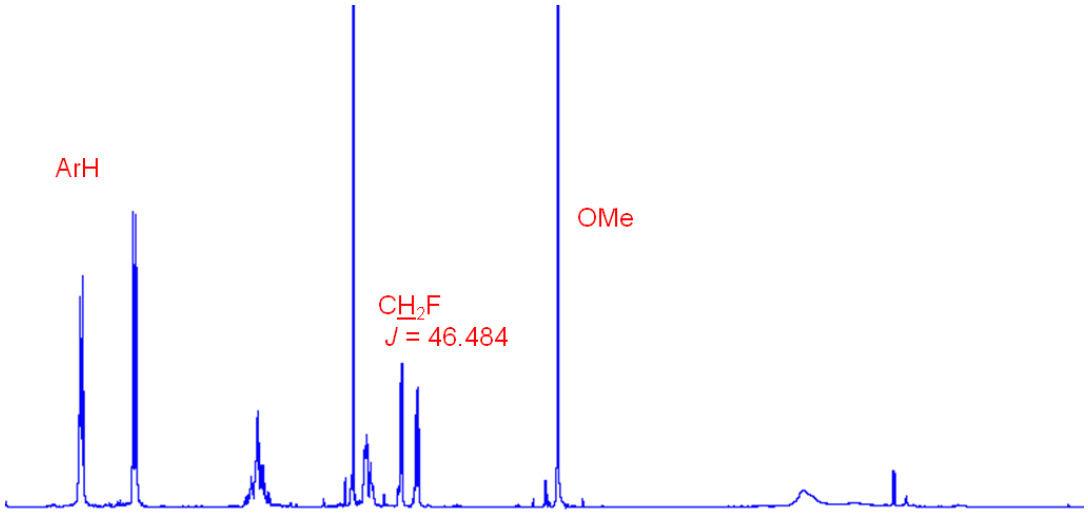


Figure 29: Partial ^{1}H (400 MHz) spectrum of crude product **388**

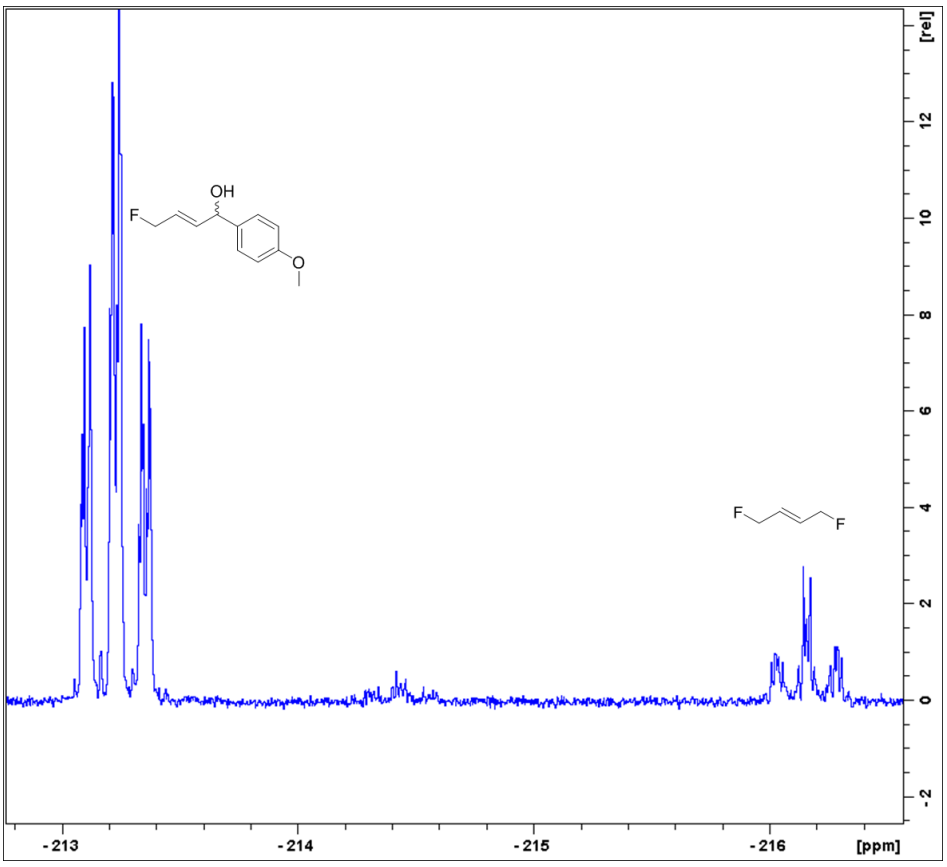
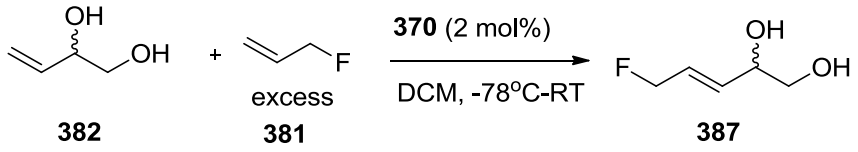


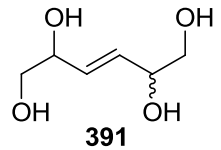
Figure 30: Partial ^{19}F NMR (376 MHz) spectrum of crude product **388**



Scheme 135

Olefin **382** underwent a significantly less clean reaction and it was observed that a gummy insoluble material had precipitated from the reaction. This was confirmed as

tetrol **391**, the product of homodimerisation of diol **382**, by the ^{1}H NMR spectrum in deuterated MeOH.



391

However both the crude ^{1}H and ^{19}F NMR spectra displayed evidence of the formation of a small quantity of the desired product **387** (Figures 31 and 32).

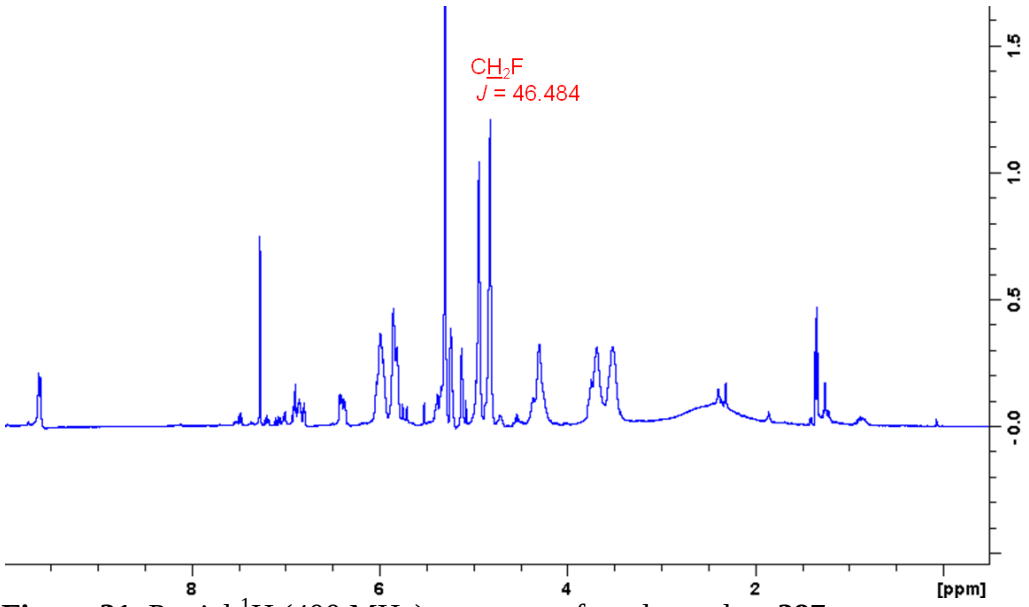


Figure 31: Partial ^{1}H (400 MHz) spectrum of crude product **387**

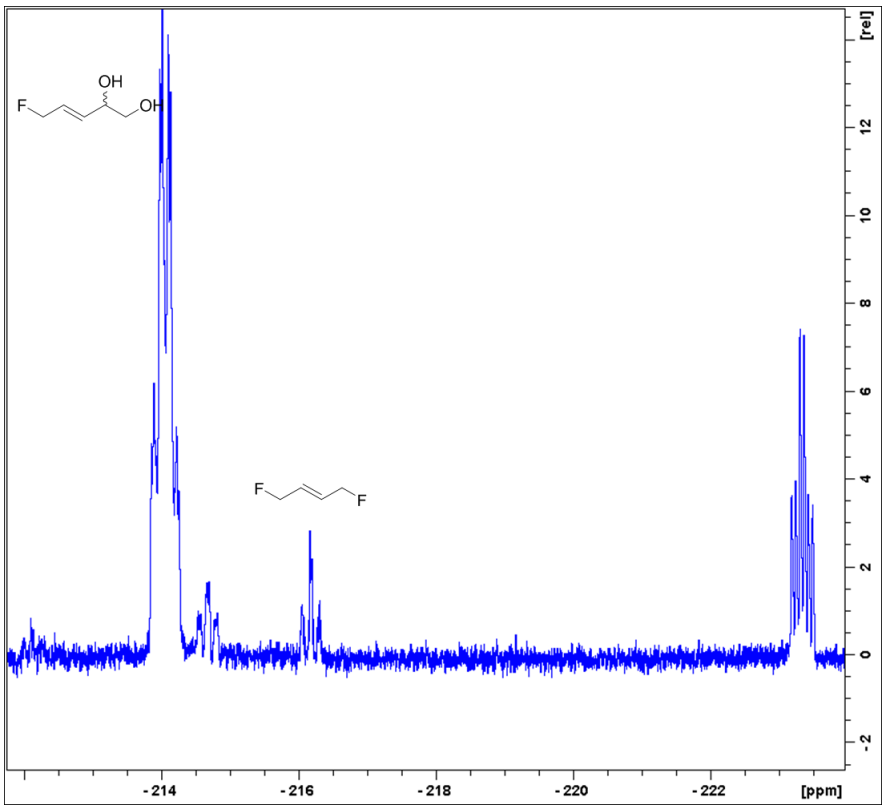
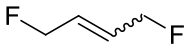


Figure 32: Partial ^{19}F (376 MHz) spectrum of crude product **387**

Although the NMR spectra for crude product **387** are significantly less clean than the crude product spectra of **388**, a distinctive CH_2F signal is clearly visible in the ^{1}H NMR spectrum. The ^{19}F NMR spectrum reveals a strong signal from difluorobutene **392** (at ~ -216 ppm) as well as what can be assumed to be the product **387** signal at -214 ppm. Purification of **388** was achieved using flash chromatography to yield the allyl fluoride in good yield based upon the limiting olefin **383** (74%). It should be noted however that despite the appearance of a relatively clean crude compound in the NMR spectra of **388**, the corresponding TLCs display a large number of close running spots resulting in a difficult separation. The purification of **387** proved even more problematic; flash

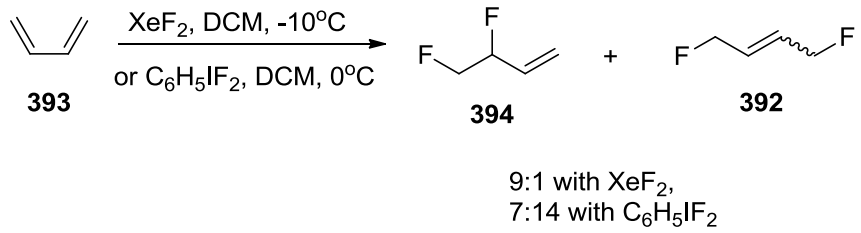
chromatography did not remove all of the impurities and the significantly lower yield and associated small quantities of material meant further purification was not a viable option. Accurate yields or clean NMR spectra could not be obtained for this compound although the spectroscopic evidence that the desired cross metathesis reaction had proceeded was strong.

5.4. Investigation of homodimerisation of allyl fluoride 392



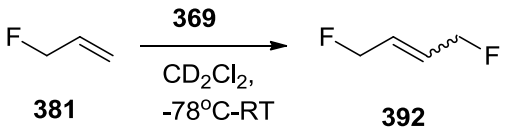
392

The product of homodimerisation of allyl fluoride **381** is 1,4-difluorobut-2-ene **392**. A common signal in the ^{19}F NMR spectrum was observed in both the cross metathesis reactions of **382** and **383** with allyl fluoride **381**. Although **392** was expected to be a relatively volatile molecule (its structure differing only from the gas but-2-ene, b.p. 3.7^{o}C, by two fluorine atoms) we observed what we believed to be this compound in the crude reaction mixture even after concentration under reduced pressure on a rotary evaporator. The boiling point quoted in the literature for this compound is 74-75^{o}C which may go some way to explaining its persistence. However, the level of characterization in the literature for this compound is relatively poor. In Shellhamer's fluorination of 1,3-dienes with xenon difluoride and (difluoroiodo)benzene, difluorobutene **392** was produced and characterized by ^{19}F NMR ((δ_F neat 254 MHz -159.1 (tm J = 45 Hz) as well as ^{1}H NMR (CCl_4), IR and *m/e* (Scheme 136).[237]



Scheme 136

In Meurs' research into the oxidative fluorination in amine.HF mixtures, **392** was produced and only characterised by ^{19}F NMR ((δ_F $CDCl_3$ -216.7 (td, J = 51.0, 11.2)).[238] Our own initial characterisation of the difluorobuteneoate **392** in crude reaction mixtures consisted entirely of ^{19}F NMR data ((δ_F 376.4 MHz $CDCl_3$ -216.2 (m. incl. app. t, J = 50.4)). We decided to prepare 1,4-difluorobut-2-ene **392** unambiguously by cross metathesis homodimerisation and then characterise the compound by NMR (^1H, ^{19}F and ^{13}C if possible) and mass spectrometry (Scheme 137).



Scheme 137

Allyl fluoride was condensed into a carousel tube at -78°C under an atmosphere of nitrogen, and **369** was then added dropwise in CD_2Cl_2. The mixture was then allowed to warm to room temperature slowly overnight and the resulting crude mixture was then analysed by ^1H and ^{19}F NMR. The NMR spectrum showed evidence of a high concentration of a second fluorinated species and the presence of a terminal alkene; even though the temperature of the NMR solution was substantially higher than the boiling point of **381** (25°C *cf.* -10°C) the second species was most likely unreacted allyl fluoride

381. The persistence of the allyl fluoride solution after distillation was surprising; the catalyst was removed (for purposes of mass spectrometry) by slow Kugelrohr distillation of the volatile species at atmospheric pressure. Even after the solution had been heated above 40°C during distillation, the distillate still contained an approximately 2:1 mixture of the allyl fluoride:1.4-difluorobut-2-ene as judged by ^{1}H NMR. The spectra for pure allyl fluoride were obtained by bubbling the gas through cooled CD_2Cl_2 in an NMR tube and analysing the resulting solution by ^{1}H and ^{19}F NMR (Figure 33).

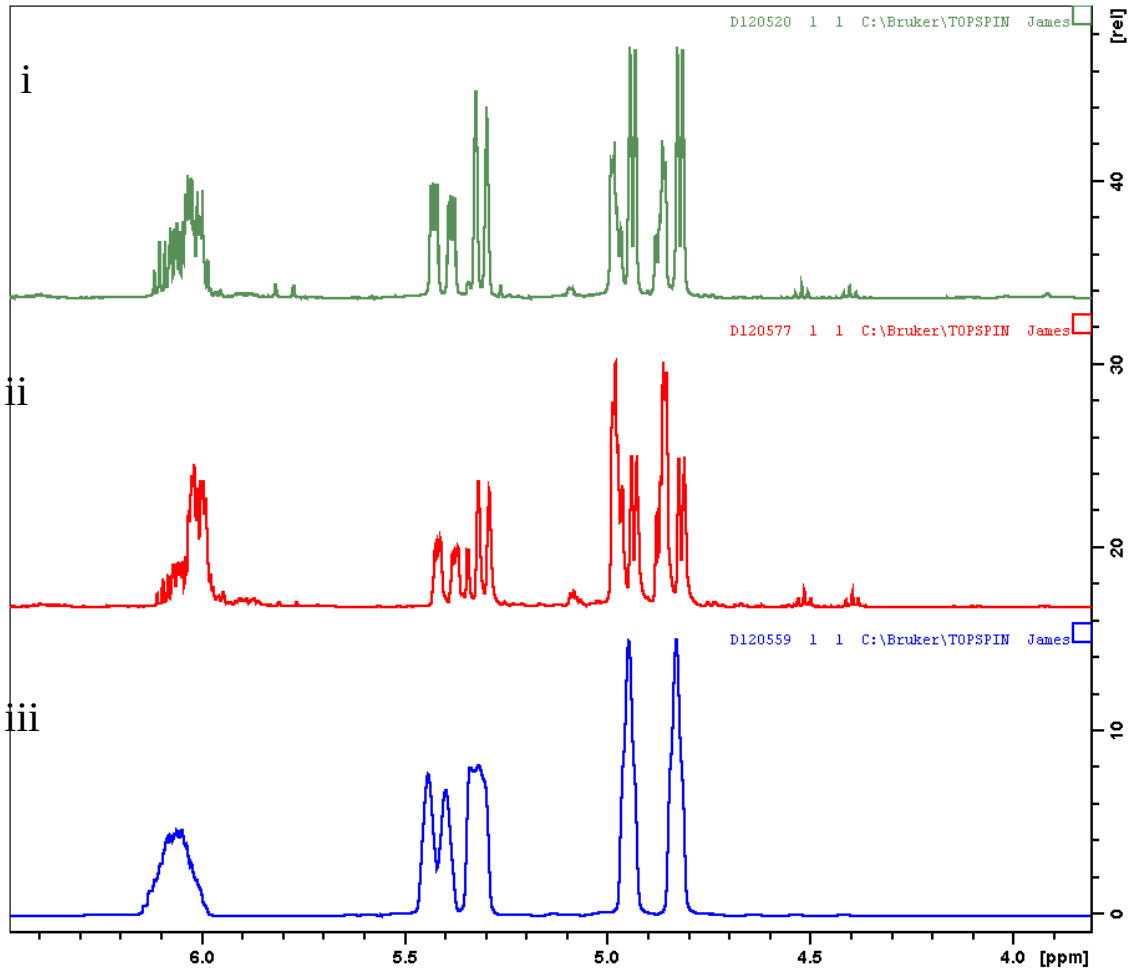


Figure 33: Partial ^{1}H (400 MHz, CD_2Cl_2) spectrum of: (i) crude product **392**, (ii) distilled product **392** (iii) allyl fluoride **381**

The ^{1}H NMR spectra of the crude and distilled products were well resolved, with the corresponding signals from the allyl fluoride **381** and 1,4-difluorobut-2-ene **392** clearly visible with limited overlap. The broadness of the allyl fluoride ^{1}H NMR spectrum is most likely a result of saturation of the CD_2Cl_2 solution.

Conclusive GC-MS investigation of the reaction distillate used a cold on-column split injection (holding the temperature at 40^{o}C for 10 minutes); this allowed the detection of both the allyl fluoride **381** starting material and the difluorobutene **392** (Figure 34 and Table 6). The distilled NMR sample was diluted with $CHCl_3$ for the GCMS injection, explaining its presence in the resulting chromatogram.

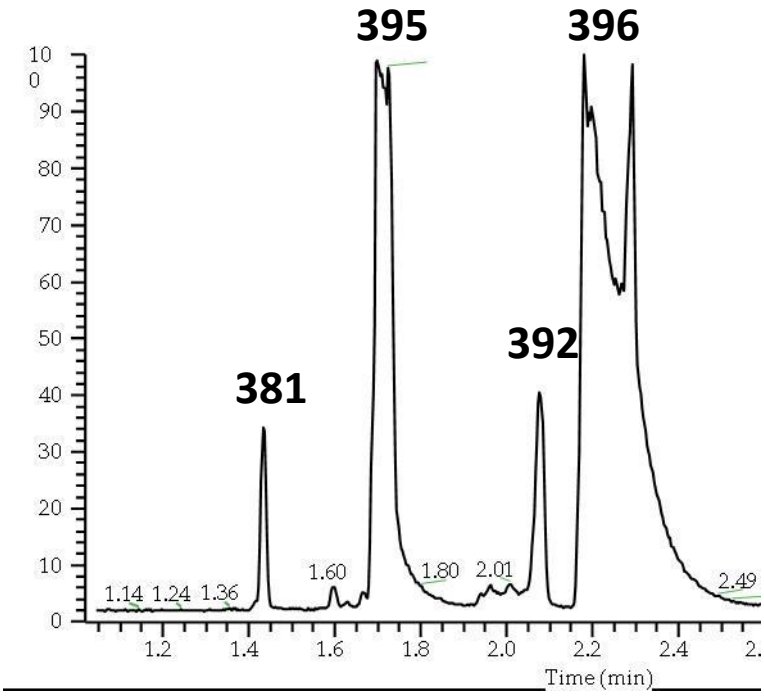


Figure 34

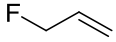
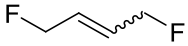
		M^+
395	CD_2Cl_2	85
396	$CHCl_3$	118
381		60
392		92

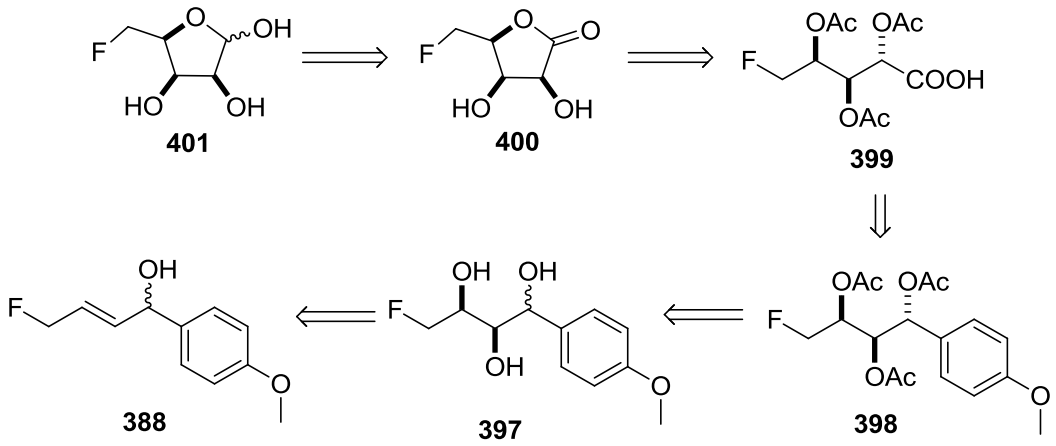
Table 6

It can be concluded this investigation that these small fluorinated molecules are significantly less volatile than would be expected, especially when compared with their non-fluorinated analogues, propene and but-2-ene. This lack of volatitly may be a result

of strong dipole-dipole interactions arising from the extreme electronegativity of the fluorine atom. However, this effect does not appear to be universal for all molecules containing the allyl fluoride motif; many substrates previously synthesised within this research project such as fluoro butenoate **261**, and fluoro hexadienoate **220** (which sublimes close to 30^{o}C) are volatile enough to require great care when concentrating reaction mixtures *in vacuo*.

5.5. Towards mono-fluorinated pentoses from cross-metathesis with allyl fluoride

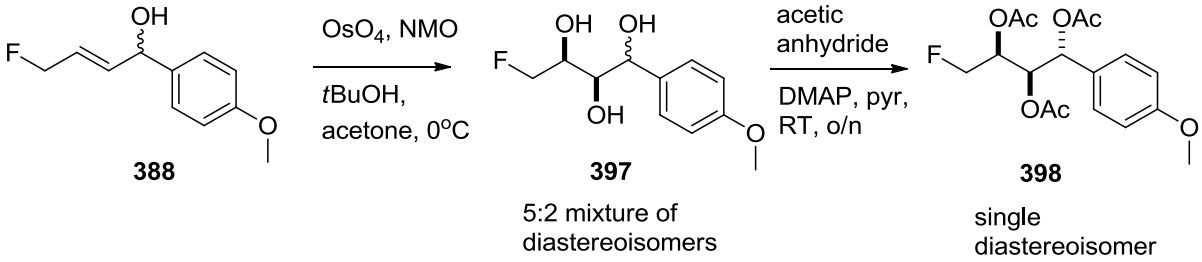
Cross metathesis product **388** was taken into a synthetic route according to Scheme 138. The route was attempted on a small scale because very limited amounts of material were available from the cross metathesis. A feature of this set of compounds was the difficulty in obtaining M^+ in the *m/z*.



Scheme 138

UpJohn dihydroxylation of allyl fluoride **394** afforded triol **397** as 5:2 mixture of diastereoisomers (by ^{19}F NMR) which was used in the next step without any further

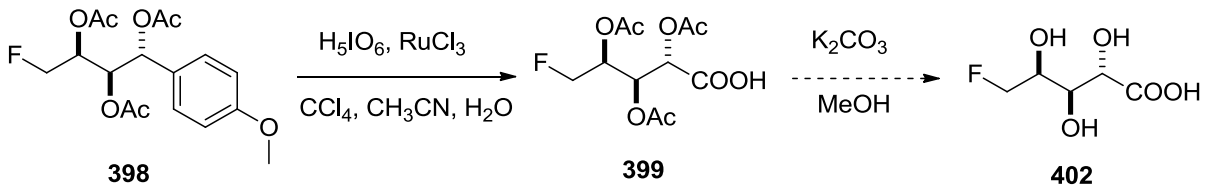
purification. Peracetylation of the triol was performed using acetic anhydride and catalytic DMAP in pyridine. Purification using flash chromatography yielded a single diastereoisomer **398** as a white solid (Scheme 139), which failed to afford a satisfactory mass spectrum. However, we were confident from the ^{1}H and ^{19}F NMR spectra that the protected triol **398** had been synthesised and the material was carried forward to the next step in the synthetic sequence. Presumably the 2 diasteroisomeric peracetylated products are separable *via* flash chromatography, and the major diasteroisomer was isolated from the purification. Repetition on a larger scale may allow recovery of the minor diasteriosomer in addition to the major diastereoisomer from purification by flash chromatography. Although we were unable to conclusively determine the stereochemistry of **398** by NMR anlysis, it can be assumed from previous examples dihydroxylations on a variety of allylic alcohols,[239,240] that the major product from the dihydroxylation of **388** under UpJohn conditions is the *anti* diastereoisomer.



Scheme 139

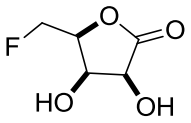
Oxidative cleavage of the aromatic ring was performed following the procedure described by Martin and co-workers[140] using catalytic ruthenium trichloride in conjunction with excess (>14 eq) periodic acid (Scheme 140). An ion was obtained for **399**, allowing measurement of the accurate mass (the first one in the synthetic sequence)

although by now, due to the small amount of substrate at the beginning of the synthetic route, attrition of material had left very little of the carboxylic acid to continue the sequence with (~30 mg).



Scheme 140

Global removal of the acetyl protecting groups was performed with potassium carbonate solution in methanol to generate triol **402**. The resulting ^{1}H NMR spectrum showed a clear change in the CH_2F signal observed. Mass spectrometric analysis (electrospray) showed a mass corresponding to lactone **401** in the positive ion spectrum, and the deprotonated and deprotected carboxylic acid **402** in the negative ion spectrum.



401

Unfortunately, when the material was refluxed overnight in methanol containing a catalytic quantity of *p*-toluene sulfonic acid, decomposition of the material occurred with NMR and electrospray failing to detect any product or starting material.

5.6. Attempt to improve efficiency of cross metathesis reaction of 383 with allyl fluoride

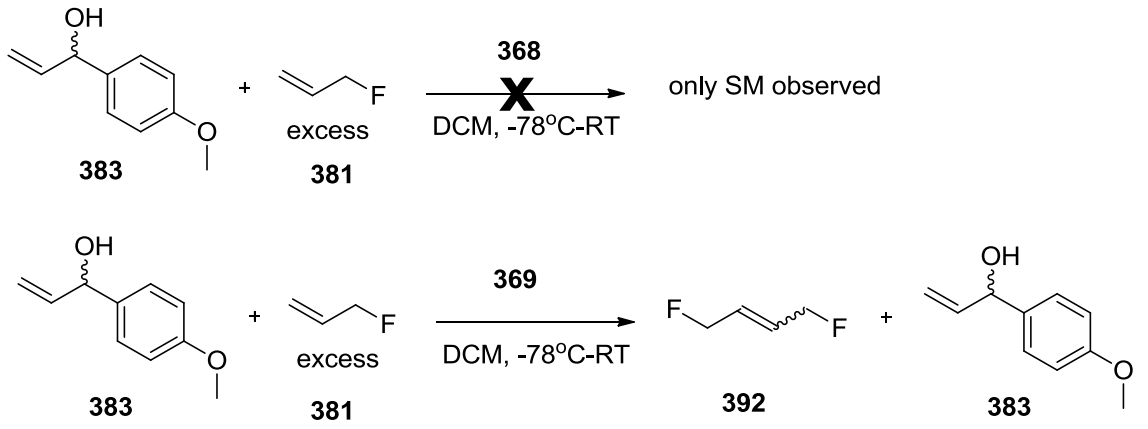
To obtain a greater quantity of starting material **388** the cross metathesis reaction with allyl fluoride **381** was explored further in an attempt to improve the efficiency. Although

the cross metathesis between allyl fluoride and **383** proceeded in good yield with respect to the limiting reagent using the initial reaction conditions, extremely large excesses of allyl fluoride were used (>14 eq). The addition of gaseous allyl fluoride *via* a balloon also lacked precision and lowered the efficiency of useage of this material.

It was found that addition of the gaseous allyl fluoride **381** to the cooled reaction vessel could be achieved more efficiently and precisely using a gas tight syringe; knowledge of the temperature and atmospheric pressure in the laboratory allowed the quantity of gas to be calculated easily. The greater degree of control in this addition also allowed closer to stoichiometric quantities of the allyl fluoride to be used. Although the isolated yield of **388** dropped from 74% to 21% using a lower stoichiometry of the allyl fluoride, the reaction was substantially less wasteful of the excess reagent (1 mmol product from 9.8 mmol of **381** *cf.* 1 mmol from 25.7 mmol).

5.7. The effect of metathesis pre-catalyst structure on outcome of cross metathesis reaction of 383 with allyl fluoride

As olefin **383** had performed well in the cross metathesis with allyl fluoride, the reaction was used to screen some of the other less expensive metathesis pre-catalysts. It was found that pre-catalyst **368** was ineffective in this reaction. The crude ^{1}H and ^{19}F NMR spectra suggesting a mixture of predominantly unreacted allyl alcohol **383** and allyl fluoride **381**.



Scheme 141

369 performed only marginally better, effecting the homodimerisation of allyl fluoride to difluorobutene **392**. However no product of cross metathesis with **383** was observed.

As allyl fluoride **381** is expected to behave as a Type I substrate for cross metathesis (rapid formation of homodimers, homodimers consumable) one would expect this alkene to undergo metathesis with itself preferentially to cross metathesis with **383**, explaining the observed products from the reaction with **369**. The ineffectiveness of **368** for allyl fluoride cross metathesis is probably due to the inferior metathesis activity of **368** *cf.* **369**. The superior activity of **369** is a result of the higher basicity of the saturated dihydroimidazole ylidene ligand (*cf.* tricyclohexyl phosphine ligand).[241] Hoveyda designed and synthesised pre-catalyst **370** with a styrenyl ether ligand attached in an effort improve the ease in which the ruthenium catalyst could be recovered and reused after the desired catalytic cycle had been completed.[242] However, it was found that the

installation of the styrenyl ether ligand also improved the metathesis activity of **370** due to the ready release and recapture of the active Ru species. The relative activities of the previously mentioned metathesis pre-catalysts (**370** > **369** > **368**) correlate with the outcomes of the reactions in Scheme 141 and 134. Only the most active catalyst **370** is able to effect the cross metathesis reaction of hypothesised Type I olefin **381** and Type II olefin **383** successfully.

5.8. Attempt to recycle difluorobutene

If allyl fluoride behaves as a Type I substrate, the homodimer product, 1,4-difluorobutene **392**, would also be consumable in the cross metathesis reaction. In an effort to reuse the large quantities of difluorobutene generated by the rapid homodimerisation (allyl fluoride is a relatively expensive reagent) an attempt was made to isolate the difluorobutene **392** from a cross metathesis reaction between allyl fluoride **381** and **383** and assess its reactivity in a cross metathesis reaction with fresh **383** and **370**. A cross-metathesis reaction between **383** and excess allyl fluoride **381** was performed as described previously. During the work up the reaction mixture was concentrated under reduced pressure using a Kugelrohr and a liquid N_2 trap rather than a rotary evaporator. The remaining crude residue contained the desired cross metathesis product (obtained in 62% yield after column chromatography based on the limiting reagent **383**) as well as traces of difluorobutene **392**. The material which collected in the trap was analysed by ^{19}F NMR, confirming the presence of the homodimerisation product **392**. The liquid was then dried ($MgSO_4$), filtered, degassed with N_2 and cooled

to -15^{o}C. The cross-metathesis reaction was then attempted with olefin **383**. The desired cross metathesis product **388** was obtained as a mixture with unreacted **383** (the R_fs of **383** and **388** are identical) in a yield of 37%. This result confirms that the product of homodimerisation **392** is consumable in the cross metathesis reaction, although is clearly a less active substrate than **381** as the conversion of **383** was incomplete.

5.9. Conclusion

In conclusion, an entirely novel method for the synthesis of allylic fluorides which negates the need for any fluorination agents by utilising the cross metathesis of commercially available allyl fluoride **381** has been discovered and investigated. We have shown that the main by-product of this chemistry, homodimerisation product **392** is also an active substrate for the introduction of the allylic fluoride moiety, although to a much lesser degree than allyl fluoride **381**. Although potentially synthetically useful fluorinated building blocks were prepared (olefin **388**) the low efficiency of the chemistry and purification difficulties (starting material and cross metathesis product co-elute on silica) coupled with the relatively high costs of metathesis pre-catalyst **370** and allyl fluoride **381** limit the synthetic use of this chemistry.

6. Conclusions

A number of conclusions can be drawn from this body of work. Firstly, it is clear that although the *de novo* approach to fluorinated saccharide structures from small highly functionalised fluorinated building blocks is a viable one, the synthetic routes required are lengthy. The inevitable attriton of yields *via* these routes is an obvious disadvantage. However it has also been shown that these routes are truly stereodivergent and stereoselective, an advantage over syntheses from the chiral pool. Therefore, it would appear the choice of a *de novo* or chiral pool route is very dependent on the needs and requirements of a particular synthesis.

Secondly, it is obvious that nucleophilic fluorination chemistry is difficult and generally moderate yielding with by-product formation ubiquitous. Additionally, there appears to be no superior nucleophilic fluorination agent, nor a method of predicting which reagents will react best with particular substrates.

Finally, it has become clear that fluorine incorporation has larger than expected effects on reactivity and the physical properties of molecules. In particular the effect of the fluorine atom on alkene reactivity in allylic fluorides appears to be profound, with metathesis and osmylation reactions effected significantly.

7. Experimental

General Synthetic Procedures

NMR spectra were recorded on a Bruker AV400 spectrometer (^{1}H 400.03 MHz; ^{13}C 100.59 MHz; ^{19}F 376.40 MHz) or a Bruker DPX400 spectrometer (^{1}H 400.13 MHz; ^{13}C 100.59 MHz; ^{19}F 376.50 MHz). ^{1}H and ^{13}C NMR spectra were recorded using deuterated solvent as the lock and residual solvent as the internal reference. ^{19}F NMR spectra were recorded relative to chlorotrifluoromethane as the external standard. The multiplicities of the spectroscopic data are presented in the following manner: app. = apparent, s = singlet, d = doublet, t = triplet, dd = double doublet, td = triplet doublets, br = broad, m = multiplet. The appearance of complex signals is indicated by app.. Homocouplings (H-H) are given in Hertz and specified by *J*; the nuclei involved in heteronuclear couplings are defined with the observed nucleus given first. Unless stated otherwise, all refer to ^{3}J couplings. Low resolution ESI analyses were performed on a Finnigan LC Q Duo mass spectrometer. GC-MS analyses were performed on a Finnigan Polaris Q spectrometer carried on a 30 m x 0.25 μm PE-5 column running a 40-320^{o}C ramp over 25 minutes (unless otherwise stated). High resolution mass spectrometry measurements were carried out at the EPSRC National Mass Spectrometry Service Centre in Swansea using peak matching to suitable reference peaks, depending on the technique used. Thin Layer Chromatography (TLC) was performed on precoated aluminium backed silica gel plates (Merck, silica gel 60 F_{254}). The compounds were visualized using UV light (λ = 254 and 386 nm), potassium permanganate or *p*-anisaldehyde stains. Flash chromatography was performed using silica gel (33-70 μm)

and a Buchi Sepacore system. Infra-red (IR) spectra were obtained on a Perkin Elmer, Spectrum One, FT-IR spectrometer. Melting points were obtained using a Reichert hot stage melting point apparatus. Optical rotations were performed on a Perkin Elmer Polarimeter 341 using an optical cell (path length 10 cm) maintained at 298 K with a continuous flow water bath. Solvents were dried (when required) using a Pure Solv apparatus (Innovative Technologies Inc.). Where required, solvents were degassed by bubbling nitrogen through for at least 30 minutes. All other chemicals and solvents were used as received without any further purification.

Determination of ee by [^{1}H]^{19}F NMR procedure

The sample to be analysed was dissolved (~2-3 mg/mL) in a mixture of $CDCl_3$ and diisopropyl L-tartrate (1:1 w/w) and 0.75 mL transferred to an NMR tube. The NMR instrument's acquisition parameters were then set to:

SW = 40, (sweep width controls size of spectral window)

AQ = 0.8, (acquisition time is lowed to keep the experiment short)

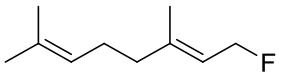
O1P = -230, (defines the location of the spectral window centre)

d1 = 5 seconds, (adjusts length of relaxation delay).

Upon completion of the NMR experiment the signals for each enantiomer in the resulting spectrum were integrated to determine the ee of the sample.

Attempted Preparation of Geranyl Fluoride 175

TBAF.3H_2O/KHF_2 method



General Procedure

Tetrabutylammonium fluoride trihydrate (1.45 g, 4.6 mmol) and potassium hydrogen difluoride (1.44 g, 18.4 mmol) were heated with stirring until melting occurred. Geranyl bromide **172** (1 g, 4.6 mmol) was then added and the resulting brown viscous suspension was stirred vigorously for 30 minutes. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (15 mL) and water (15 mL) to solubilise all the salts. The organic layer was separated and solid $NaHCO_3$ (~1 - 1.5 g) was added to the aqueous layer until it was found to be neutral (to pH paper) at which point it was extracted further with Et_2O (3 x 15 mL). The combined organic extracts and the original organic layer were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil which was taken up in $CDCl_3$ for NMR analysis.

Reagents and Conditions	Outcome
172 (4.6 mmol, 1 g), TBAF (4.6 mmol, 1.45 g), KHF_2 (18.4 mmol, 1.44 g), 100°C, 30 mins	No product[a]
172 (4.6 mmol, 1 g), TBAF (4.6 mmol, 1.45 g), KHF_2 (18.4 mmol, 1.44 g), 110°C, 30 mins	No product[a]
172 (4.6 mmol, 1 g), TBAF (4.6 mmol, 1.45 g), KHF_2 (18.4 mmol, 1.44 g), 110°C, 1 hour	No product[a]
172 (4.6 mmol, 1 g), TBAF (4.6 mmol, 1.45 g), KHF_2 (18.4 mmol, 1.44 g), 125°C, 30 mins	No product[a]
172 (4.6 mmol, 1 g), TBAF (4.6 mmol, 1.45 g), KHF_2 (18.4 mmol, 1.44 g), 125°C, 10 mins	No product[a]
172 (3.2 mmol, 700 mg), TBAF (4.9 mmol, 1.53 g), KHF_2 (12.8 mmol, 1 g), 70°C, 30 mins	No product[a]
172 (3.2 mmol, 700 mg), TBAF (4.9 mmol, 1.53 g), KHF_2 (12.8 mmol, 1 g), 70°C, 60 mins	No product[a]

[a] by crude ^{1}H NMR spectra

TBAF.3H_2O in acetonitrile method[139]

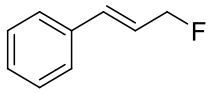
Geranyl bromide **172** (1 g, 4.6 mmol) and tetrabutylammonium fluoride trihydrate (2.9 g, 9.2 mmol) were dissolved in acetonitrile (10 mL) and the mixture was allowed to stir at room temperature for 30 minutes. Water (2.5 mL) was then added and the mixture extracted with *n*-pentane (5 x 5 mL). The organic extracts were then combined, dried ($MgSO_4$), filtered and dried *in vacuo* to afford a brown gum. No product (**175**) was detected. The following significant peaks were detected in the ^{19}F

NMR spectrum; δ_F (376 MHz, $CDCl_3$) (-140.1) – (-140.7) (m, including a repeating splitting of $J_{H\text{-}F}$ 11.4) suggested internal fluorination.

$TBAHSO_4$ and $KF.2H_2O$ method[4]

Geranyl bromide **172** (700 mg, 3.2 mmol) was added to a solution of $KF.2H_2O$ (1.21 g, 12.8 mmol) and Bu_4NHSO_4 (1.22 g, 3.5 mmol) in acetonitrile (16 mL) and the mixture was heated at reflux overnight. The mixture was then diluted with water (20 mL) and extracted with diethyl ether (1 x 20 mL and 2 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale brown gum. No product (**175**) was detected.

Preparation of Cinnamyl Fluoride 180



General Procedure

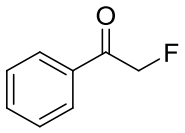
Tetrabutylammonium fluoride trihydrate (1.68 g, 5.3 mmol) and potassium hydrogen difluoride (1.11 g, 14.2 mmol) were heated with stirring in a round bottomed flask or microwave tube (depending on the scale) until melting occurred. Cinnamyl bromide **173** (1.04 g, 5.3 mmol) was then added and the resulting brown viscous suspension was stirred vigorously for 30 minutes. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (10 mL) and water (10 mL) to solubilise all the salts. The organic layer was separated and solid $NaHCO_3$ (~1 – 1.5 g) was added to the aqueous layer until it was found to be neutral (to pH paper) at which

point it was extracted with Et_2O (3 x 10 mL). The combined organic extracts and the original organic layer were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown gum. Purification by flash chromatography (Buchi Sepacore, 5% EtOAc in petroleum ether 40-60^oC) and then distillation by Kugelrohr at reduced pressure (80^oC/0.75 mmHg) afforded cinnamyl fluoride **180** as a colourless oil (see table for yield); R_f (10% EtOAc in pet. ether 40-60^oC) 0.52; δ_H (400 MHz, $CDCl_3$) 7.46-7.29 (m, 5H), 6.73 (dd, J = 15.9, $^4J_{H-F}$ = 5.4, 1H), 6.40 (ddt, J = 15.9, J_{H-F} = 12.4, J = 6.0, 1H), 5.10 (ddd, $^2J_{H-F}$ = 46.9, J = 6.0, ^4J = 1.2, 2H); δ_C (100 MHz, $CDCl_3$) 136.0, 134.2 (d, $^3J_{C-F}$ = 11.7), 128.7, 128.3, 126.8, 123.6 (d, $^2J_{C-F}$ = 16.1), 83.5 (d, $^1J_{C-F}$ = 162.5); δ_F (376 MHz, $CDCl_3$) -210.4 (tdd, $^2J_{F-H}$ = 47.0, J_{F-H} = 12.4, $^4J_{F-H}$ = 5.4). The data were in agreement with those reported by Boukerb *et al.*.[243]

Reagents and Conditions	**Outcome**
173 (3.6 mmol, 700 mg), TBAF (5.3 mmol, 1.68 g), KHF_2 (14.2 mmol, 1.11 g), 110^oC, 30 mins	14:5:1 mixture of **180**:**179**:**173** respectively[a]
173 (3.6 mmol, 700 mg), TBAF (4.3 mmol, 1.35 g), KHF_2 (14.2 mmol, 1.11 g), 110^oC, 30 mins	6:4 mixture of **179**:**173** respectively[a]
173 (3.6 mmol, 700 mg), TBAF (5.3 mmol, 1.68 g), KHF_2 (14.2 mmol, 1.11 g), 100^oC, 1 hr	Decomposition[a]
173 (10 mmol, 1.97 g), TBAF (15 mmol, 4.73 g), KHF_2 (40 mmol, 3.12 g), 120^oC, 30 mins	Decomposition[a]
173 (3.6 mmol, 700 mg), TBAF (5.3 mmol, 1.68 g), KHF_2 (14.2 mmol, 1.11 g), 65^oC, 30 mins	7:2:1 mixture of **180**:**179**:**173** respectively[a]
173 (3.6 mmol, 700 mg), TBAF (5.3 mmol, 1.68 g), KHF_2 (14.2 mmol, 1.11 g), 65^oC, 10 mins	4:5:1 mixture of **180**:**179**:**173** respectively[a]
173 (3.6 mmol, 700 mg), TBAF (5.3 mmol, 1.68 g), KHF_2 (14.2 mmol, 1.11 g), 100^oC, 30 mins	**180**, 12 mg, 9%[b]

[a] by crude ^1H NMR spectra; [b] Isolated purified yield

Preparation of 2-Fluoroacetophenone 185



General Procedure

Tetrabutylammonium fluoride trihydrate (1.59 g, 5 mmol) and potassium hydrogen difluoride (1.56 g, 20 mmol) were heated with stirring until melting occurred. 2-Bromoacetophenone **174** (1 g, 5 mmol) was then added and the resulting brown viscous suspension was stirred vigorously for 30 minutes. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (15 mL) and water (15 mL) to solubilise all the salts. The organic layer was separated and solid $NaHCO_3$ was added to the aqueous layer until it was found to be neutral (to pH paper) at which point it was extracted with Et_2O (3 x 15 mL). The combined organic extracts and the original organic layer were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown gum. Distillation by Kugelrohr at reduced pressure (90^{o}C/0.65 mmHg) afforded 2-fluoroacetophenone **185** as a white solid (503 mg, 73%); m.p. 26-27^{o}C (lit. 26-27^{o}C);[244] R_f (10% EtOAC in pet. ether 40-60^{o}C) 0.38; δ_H (400 MHz, $CDCl_3$) 7.92-7.88 (m, 2H), 7.66-7.61 (m, 1H), 7.53-7.48 (m, 2H), 5.55 (d, $^{2}J_{H-F}$ 47.0, 2H); δ_C (100 MHz, $CDCl_3$) 193.5 (d, $^{2}J_{C-F}$ 16.1), 134.2, 133.7, 128.9, 127.9, 83.5 (d, $^{1}J_{C-F}$ 183.0); δ_F (376 MHz, $CDCl_3$) -230.7 (t, $^{2}J_{F-H}$ 47.0); $\nu_{max}(CDCl_3)/cm^{-1}$ 3044s, 2937s, 1707br, 1598, 1450, 1234, 1088br, 968, 757, 690. The data were in agreement with those reported by Olah and co-workers.[245]

Reagents and Conditions	Outcome
174 (5 mmol, 1 g), TBAF (5 mmol, 1.59 g), KHF_2 (20 mmol, 1.56 g), 100°C, 1 h	1:1 mixture of **185** and **186**[a]
174 (5 mmol, 1 g), TBAF (5 mmol, 1.59 g), KHF_2 (20 mmol, 1.56 g), 100°C, 3 h	Trace product[a]
174 (5 mmol, 1 g), TBAF (5 mmol, 1.59 g), KHF_2 (20 mmol, 1.56 g), 100°C, 24 h	Decomposition[a]
174 (11 mmol, 2.2 g), TBAF (16.6 mmol, 5.23 g), KHF_2 (44.2 mmol, 3.45 g), 100°C, 30 min	**185,** 1.1 g, 73%[b]
174 (30 mmol, 5.97 g), TBAF (45 mmol, 14.2 g), KHF_2 (120 mmol, 9.36 g), 100°C, 30 min	**185,** 2.8 g, 68%[b]

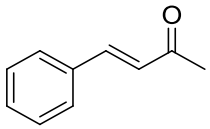
[a] by crude ^{1}H NMR spectra; [b] Isolated purified yield

Preparation of 2-Fluoroacetophenone 185

$TBAHSO_4$ and $KF.2H_2O$ method[4]

2-Bromoacetophenone **174** (1 g, 5 mmol) was added to a solution of $KF.2H_2O$ (1.89 g, 20 mmol) and Bu_4NHSO_4 (1.92 g, 5.5 mmol) in acetonitrile (20 mL) and the mixture was heated at reflux overnight. The mixture was then cooled to room temperature, diluted with water (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale brown gum. Kugelrohr distillation at reduced pressure (90°C/0.65 mmHg) afforded 2-fluoroacetophenone **185** as a white solid (490 mg, 71% yield).

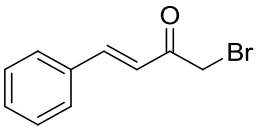
Preparation of 4-Phenyl-3-buten-2-one 194



Sodium hydroxide (3.75 mL of a 2.5 M aqueous solution) was added to a solution of benzaldehyde (15.9 g, 150 mmol) in acetone (23.9 g, 412.5 mmol) and the mixture was allowed to stir at room temperature for 90 minutes. The reaction mixture was then acidified (to pH 5 by pH paper) by the dropwise addition of dilute hydrochloric acid, causing a colour change from orange to yellow. The reaction mixture was then extracted with diethyl ether (2 x 30 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Kugelrohr distillation at reduced pressure (105^oC/0.08 mmHg) afforded **194** as an off white solid (13.3 g, 61% yield); m.p. 37-39^oC (lit. 39-42^oC);[246] δ_H (400 MHz, $CDCl_3$) 7.58-7.52 (m, 3H), 7.44-7.41 (m, 3H), 6.74 (d, ^3J = 16.2, 1H), 2.41 (s, 3H); δ_C (100 MHz, $CDCl_3$) 198.0, 143.4, 134.4, 130.5, 128.9, 127.1, 125.7, 27.5; ν_{max}(film)/cm^{-1} 3005, 2900, 1610, 975, 690; The data were in agreement with those reported by Jung.[247]

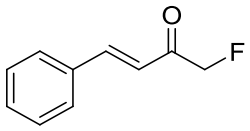
Note: This material was not utilised in any of the chemistry described in this work due to the superior diastereomeric purity and low cost of commercially available **194**.

Preparation of 1-bromo-4-phenyl-3-buten-2-one 187



A solution of pyrrolidone hydrotribromide (38 g, 76.6 mmol) in dry THF (240 mL) was slowly added to a solution of **194** (9.3 g, 64 mmol) in dry THF (150 mL) at room temperature under nitrogen *via* cannula. The mixture was allowed to stir at room temperature for 24 hours and excess pyrrolidone hydrotribromide was then removed by filtration (as a white solid). The orange filtrate was concentrated *in vacuo*, then re-dissolved in ether (100 mL), washed with brine (2 x 100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a crude brown gum. Purification by flash chromatography (Buchi Sepacore), 5%-15% Et_2O in pet. ether 40-60^oC gradient afforded **187** as a brown/green solid (7.5 g, 52% yield); m.p. 42-44^oC (lit. 44-45^oC)[248]; R_f (1:6 Et_2O in hexane) 0.16; δ_H (400 MHz, $CDCl_3$) 7.63-7.59 (m, 2H), 7.47-7.42 (m, 3H), 7.25 (d, *J* = 16.2, 1H), 6.98 (d, *J* = 16.2, 1H), 4.15 (s, 2H); δ_C (100 MHz, $CDCl_3$) 190.7, 145.0, 133.7, 130.9, 128.8, 128.4, 122.1, 33.0; ν_{max}(film)/cm^{-1} 3065, 2940, 1685, 1612, 1490, 1330, 970; The data were in agreement with those reported by Clark *et al.*.[249]

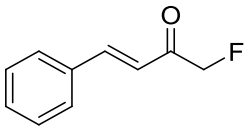
Preparation of 1-fluoro-4-phenyl-3-buten-2-one 188



TBAF/KHF_2 method

Tetrabutylammonium fluoride trihydrate (18.1 mmol, 5.7 g) and potassium hydrogen difluoride (47.4 mmol, 3.7 g) were heated with stirring in a round bottomed flask until melting occurred. Bromide **187** (11.56 mmol, 2.6 g) was then added and the resulting brown viscous suspension was stirred vigorously for 30 minutes. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (25 mL) and water (15 mL) to solubilise all the salts. The organic layer was separated and solid $NaHCO_3$ was added to the aqueous layer until it was neutral (to pH paper). The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts and the original organic layer were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown gum. Purification by Flash Chromatography (Buchi Sepacore), 5%-15% EtOAc in petroleum ether 40-60^oC gradient and then Kugelrohr distillation at reduced pressure (110^oC/0.073 mmHg) afforded **188** as a white solid (436 mg, 23%).

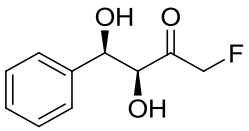
Preparation of 1-fluoro-4-phenyl-3-buten-2-one 188



KF.2H$_2$O General Method

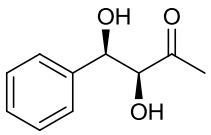
A solution of bromide **187** (9.68mmol, 2.18 g) in degassed acetonitrile (44 mL) was added via cannula to a mixture of potassium fluoride hydrate (34.7 mmol, 3.26 g) and tetrabutylammonium sulfate (9.53 mmol, 3.24 g) under nitrogen. The resulting reaction mixture was maintained at reflux for 2.5 hours under nitrogen. The mixture was then allowed to cool to room temperature, diluted with diethyl ether (40 mL) and washed with water (40 mL). The organic layer was then isolated, dried ($MgSO_4$), and concentrated *in vacuo* to afford a brown gum. Purification by Flash Chromatography (Buchi Sepacore), 5%-15% EtOAc in petroleum ether 40-60^{o}C gradient and then Kugelrohr distillation at reduced pressure (110^{o}C/0.073 mmHg) afforded **188** as an off white solid (1.34 g, 32%); m.p. 33-36^{o}C; R_f (10% Et_2O in pet. ether 40-60^{o}C) 0.18; δ_H (400 MHz, $CDCl_3$) 7.78 (d, *J* = 16.2, 1H), 7.63-7.61 (m, 2H), 7.46-7.41 (m, 3H), 7.05 (dd, *J* = 16.2, $^4J_{H-F}$ = 3.2, 1H), 5.06 (d, $^2J_{H-F}$ = 47.4, 2H); δ_C (100 MHz, $CDCl_3$) 194.8 (d, $^2J_{C-F}$ = 17.6), 145.1 (d, $^4J_{C-F}$ = 5.9), 134.1, 131.2, 129.1, 128.7, 119.8, 84.7 (d, $^1J_{C-F}$ = 184.4); δ_F (376 MHz, $CDCl_3$) -228.8 (td, $^2J_{F-H}$ = 47.4, $^4J_{F-H}$ = 3.2); $\nu_{max}(CDCl_3)/cm^{-1}$ 3055, 2986, 2305, 1710, 1691, 1608, 1265s, 1040, 738; *m/z* (EI^+) 205 (84), 175 (44), 161 (100), 99 (18), 81 (22), 69 (24), 55 (56); HRMS (ES^+, $[M + H]^+$) calcd. for $C_{10}H_{10}FO$ 165.0708, found 165.0709. The data were in agreement with those reported by Chung.[250]

Attempted preparation of 189 *via* Sharpless Asymmetric Conditions



A solution of potassium osmate dehydrate (0.0061 mmol, 2.2 mg), $(DHQD)_2PHAL$ (0.031 mmol, 24 mg), potassium ferricyanide (1.83 mmol, 603 mg), sodium hydrogen carbonate (1.82 mmol, 153 mg) and potassium carbonate (1.83 mmol, 252 mg) in a mixture of *tert*-butanol and water (3.5 mL of a 1:1 mixture) was allowed to stir at room temperature for 15 minutes. Fluoride **188** (0.61 mmol, 100 mg) was added and the reaction was allowed to stir at 0^oC for 24 hours. Analysis of a reaction aliquot by ^{19}F NMR revealed that no conversion had occurred; so the reaction was allowed to stir at 0^oC for a further 48 hours. Upon warming to room temperature, the reaction was quenched with saturated sodium sulfite solution (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were then washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (82 mg). Analysis by ^1H and ^{19}F nmr spectra revealed the majority of the crude to be starting material **188** with evidence of scission having occurred. Significant peaks; δ_H (400 MHz, $CDCl_3$) 10.02 (s), 8.50 (br), 8.37 (br), 8.03 (br), 7.91-7.86 (m), 7.78 (d, J = 16.2, SM), 7.65-7.50 (m), 7.45-7.11 (m), 7.05 (dd, J = 16.2, $^4J_{H\text{-}F}$ = 3.2, SM), 5.12-5.00 (d, $^2J_{H\text{-}F}$ = 47.4, SM); δ_F (376 MHz, $CDCl_3$) -227.1 (td, $^2J_{F\text{-}H}$ = 47.4, $^4J_{F\text{-}H}$ = 3.2), -228.8 (td, $^2J_{F\text{-}H}$ = 47.4, $^4J_{F\text{-}H}$ = 3.2, SM), -233.8 (t, $^2J_{F\text{-}H}$ = 47.4).

Preparation of 195 *via* Sharpless Asymmetric Conditions



A solution of potassium osmate dihydrate (0.025 mmol, 9 mg), $(DHQD)_2PHAL$ (0.13 mmol, 98 mg), potassium ferricyanide (7.5 mmol, 2470 mg), sodium hydrogen carbonate (7.5 mmol, 630 mg) and potassium carbonate (7.5 mmol, 1035 mg) was allowed to stir in *tert*-butanol and water (25 mL of a 1:1 mixture) at room temperature for 15 minutes. Olefin **194** (2.5 mmol, 365 mg) was added and the reaction was allowed to stir at 0^oC for 24 hours. Analysis of an aliquot revealed that no conversion had occurred and so the reaction was allowed to stir at 0^oC for a further 48 hours. Upon warming to room temperature, the reaction was quenched with sodium sulfite (25 mL of a saturated solution), and extracted with EtOAc (4 x 15 mL). The combined organic extracts were then washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange gum (422 mg). Purification by flash chromatography (Buchi Sepacore), EtOAc in petroleum ether 40-60^oC (5%-15% gradient), then MeOH in DCM (0%-50% gradient) afforded **195** as a white solid (224 mg, 47%); m.p. 64-66^oC; δ_H (400 MHz, $CDCl_3$) 7.36-7.24 (m, 5H), 4.92 (dd, *J* = 6.8, J = 3.3, 1H), 4.30 (dd, *J* = 5.1, *J* = 3.3, 1H), 3.60 (dd, *J* = 6.8, 1H), 2.75 (dd, *J* = 5.3, 1H), 2.15 (s, 3H); δ_C (100 MHz, $CDCl_3$) 208.3, 140.0, 128.5, 128.1, 126.3, 80.7, 73.9, 26.4; $\nu_{max}(CDCl_3)/cm^{-1}$ 3425 (br), 2916 (w), 1713, 1355, 1054; the data were in agreement with those reported by Sharpless[151] (however the hydroxyl

protons appear to be misassigned in the associated reference; supported by coupling between H-3 and H-4 in COSY spectra).

Exposure of diol 195 to SAD conditions

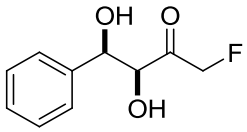
A solution of potassium osmate dihydrate (0.012 mmol, 5 mg), $(DHQD)_2PHAL$ (0.06 mmol, 48 mg), potassium ferricyanide (3.72 mmol, 1.3 g), sodium hydrogen carbonate (3.72 mmol, 312 mg) and potassium carbonate (3.72 mmol, 513 mg) was allowed to stir in *tert*-butanol and water (12 mL of a 1:1 mixture) at room temperature for 15 minutes. Diol **195** (1.24 mmol, 224 mg) was then added and the reaction allowed to stir at 0^oC. Aliquots (1 mL) of the reaction mixture were taken after 4, 24 and 48 hours, quenched with saturated sodium sulfite solution (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extracts were then dried ($MgSO_4$), concentrated *in vacuo* and analysed by ^1H NMR; significant peaks; δ_H (400 MHz, $CDCl_3$) 10.01 (s, intensity increased with time (4-48 h)), 4.92 (dd, J = 6.8, J = 3.3, intensity decreased with time (4-48 h)), 4.30 (dd, J = 5.1, J = 3.3, intensity decreased with time (4-48 h)).

Investigation of effect of pH on dihydroxylation reaction

A solution of potassium osmate dihydrate (0.05 mmol, 18 mg), $(DHQD)_2PHAL$ (0.25 mmol, 195 mg), potassium ferricyanide (15 mmol, 4939 mg), sodium hydrogen carbonate (15 mmol, 1260 mg) and potassium carbonate (15 mmol, 2070 mg) was allowed to stir in *tert*-butanol and water (50 mL of a 1:1 mixture) at room temperature for 15 minutes. Olefin **194** (5 mmol, 731 mg) was then added and the

reaction allowed to stir at 0°C for 30 minutes. The pH was then analysed by Fisherbrand indicator paper and found to be pH 8. A solution of potassium hydroxide (50 mL of a 50% w/w solution) was then added dropwise until the pH reached approximately pH 12. The reaction mixture was then allowed to stir at 0°C for 48 hours. Upon warming to room temperature, the reaction was quenched with saturated sodium sulfite solution (50 mL), and extracted with EtOAc (4 x 30 mL). The combined organic extracts were then washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange gum (789 mg) which was analysed by ^1H NMR. Crude material appears to contain benzaldehyde. Significant peaks; δ_H (400 MHz, $CDCl_3$) 10.02 (s), 7.91-7.86 (m), 7.65-7.50 (m), 7.45-7.11 (m), 5.12-5.00 (d, $^2J_{H\text{-}F}$ = 47.4, SM), 4.92 (dd, J = 6.8, J = 3.3), 4.30 (dd, *J* = 5.1, *J* = 3.3).

Attempted Dihydroxylation of 188 under UpJohn conditions to 206

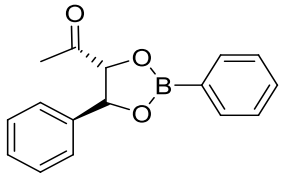


General Procedure

A solution of 4-methylmorpholine *N*-oxide (1.22 mmol, 143 mg) in water (0.3 mL) was added to a stirred solution of olefin **188** (0.61 mmol, 100 mg) in a mixture of acetone and *tert*-butanol (1.4 mL of a 1:1 mixture). After 10 minutes the solution was cooled to 0°C and osmium tetroxide (124 μL of a 2.5 wt% solution in *t*-butanol) was added as a dropwise, and the mixture allowed to stir vigorously at 0°C. The reaction

was then quenched with solid sodium sulfite, filtered through cotton wool and celite and washed with ethyl acetate and methanol (10 mL of a 1:1 mixture). The filtrate was then concentrated *in vacuo*, diluted with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. Purification by flash chromatography (Buchi Sepacore), 10% EtOAc in pet. ether 40-60^oC failed to isolate any desired product **206**. δ_H (400 MHz, $CDCl_3$) significant peaks, 10.01 (s) intense signal; δ_F (376 MHz, $CDCl_3$) -227.1 (td, $^2J_{F-H}$ = 47.4, $^4J_{F-H}$ = 3.2), -228.8 (td, $^2J_{F-H}$ = 47.4, $^4J_{F-H}$ = 3.2), -233.8 (t, $^2J_{F-H}$ = 47.4, largest signal).

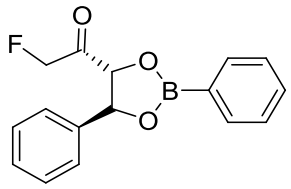
Preparation of boronate ester 212



A solution of potassium osmate dihydrate (0.025 mmol, 9 mg), potassium carbonate (7.51 mmol, 1.03 g), potassium hexacyanoferrate (7.50 mmol, 2.5 g), phenyl boronic acid (3.02 mmol, 366 mg), $(DHQD)_2PHAL$ (0.125 mmol, 97 mg) was allowed to stir in *tert*-butanol and water (25 mL of a 1:1 mixture) at room temperature for 30 minutes. Olefin **194** (2.5 mmol, 365 mg) was then added in one portion and the mixture allowed to stir at room temperature for 48 hours. The reaction was then quenched with sodium sulfite (4 g) causing a colour change from yellow to grey. The mixture was then diluted with water (25 mL) and extracted with DCM (2 x 25 mL).

The combined organic layers were then washed with saturated sodium sulfite solution, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by Flash Chromatography (Buchi Sepacore), 3%-13% EtOAc in petroleum ether 40-60^oC gradient afforded the pure product **212** (181 mg, 27%); m.p. 46-48^oC; R_f (10% EtOAC in pet. ether 40-60^oC) 0.14; δ_H (400 MHz, $CDCl_3$) 8.00-7.96 (m, 2H), 7.60-7.55 (m, 1H), 7.47-7.32 (m, 7H), 5.61 (d, *J* = 6.3, 1H), 4.69 (d, *J* = 6.1, 1H), 2.42 (s, 3H); δ_C (100 MHz, $CDCl_3$) 207.9, 140.6, 135.2, 132.4, 129.6, 128.8, 128.4, 128.1, 125.4, 88.7, 80.8, 26.6; $\nu_{max}(CDCl_3)/cm^{-1}$ 3155, 3060 and 3035d, 2253, 1719, 1604, 1358, 1200br, 1098, 908br, 721br, 650; HRMS (EI^+, $[M]^+$) calcd. for ^{10}B isotope $C_{16}H_{15}BO_3$ 265.1145, found 265.1145, (EI^+, $[M + H]^+$) calcd. for ^{11}B isotope $C_{16}H_{15}BO_3$ 266.1111, found 266.1109 (Note: peak is poorly resolved from standard).

Attempted preparation of boronate ester 213



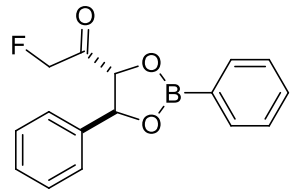
A solution of either potassium osmate dihydrate (0.025 mmol, 1 mg), potassium carbonate (0.9 mmol, 124 mg), potassium hexacynaoferrate (0.9 mmol, 296 mg) and $(DHQD)_2PHAL$ (0.125 mmol, 12 mg) or AD-mix β (433 mg) was allowed to stir in 1:1 *tert*-butanol and water (3 mL) at room temperature for 30 minutes with methyl sulfonamide (0 or 0.3 mmol) and phenyl boronic acid (0.36 mmol, 44 mg). Olefin **188** (2.5 mmol, 365 mg) was then added in one portion and the mixture allowed to

stir at room temperature for 96 hours (with aliquots taken and analysed[a] every 24 hours). The reaction was then quenched with sodium sulfite (700 mg). The mixture was then diluted with water (5 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were then washed with saturated sodium sulfite solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange gum which was taken up in $CDCl_3$ for NMR analysis.

Reagents and Conditions	**Outcome**
188 (0.3 mmol, 50 mg), $K_2[OsO_2(OH)_4]$ (1 mol%, 1 mg), K_2CO_3 (0.9 mmol, 124 mg), $K_3Fe(CN)_6$ (0.9 mmol, 296 mg), $PhB(OH)_2$ (0.36 mmol, 44 mg), $(DHQH)_2PHAL$ (5mol%, 12 mg), 1:1 *t*-BuOH/H_2O (3 mL), RT, 96 h	Evidence of scission and unconverted starting material, 10.01 (s) [a]
188 (0.3 mmol, 50 mg), AD-mix β (433 mg), $PhB(OH)_2$ (0.36 mmol, 44 mg), 1:1 *t*-BuOH/H_2O (3 mL), RT, 96 h	Consumption of starting material and evidence of scission, 10.01 (s)[a]

[a]by ^1H NMR and ^{19}F NMR spectra

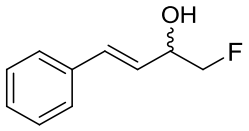
Attempted preparation of 214 *via* Narasaka modification with organic solvent



General Procedure

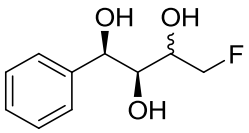
A solution of 4-methylmorpholine *N*-oxide (1.2 mmol, 140 mg), phenyl boronic acid (1.2 mmol, 143mg) and osmium tetroxide (203 μL of a 2.5 wt% solution in *t*-BuOH) in DCM (1 mL) was allowed to stir at room temperature for 15 minutes. A colour change from off white to yellow was observed. A solution of olefin **188** (1 mmol, 164 mg) in DCM (2 mL) was added and the reaction was allowed to stir at room temperature overnight. A colour change from yellow to black was observed. The reaction was then quenched with solid sodium sulfite (1.5 g), filtered through cotton wool and celite and washed with ethyl acetate and methanol (35 mL of a 1:1 mixture). The filtrate was then concentrated under reduced pressure, diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated under reduced pressure to afford a pale brown oil (266 mg). Purification by flash chromatography (Buchi Sepacore), 10% EtOAc in pet. ether 40-60^oC failed to isolate any boronate ester **214**; δ_H (400 MHz, $CDCl_3$) 10.01 (s), no evidence of fluorinated material (no ^2J splitting visible); δ_F (376 MHz, $CDCl_3$) no signal. The significant peaks were indicative of oxidative cleavage

Preparation of racemic 1-fluoro-4-phenyl-3-buten-2-ol 215



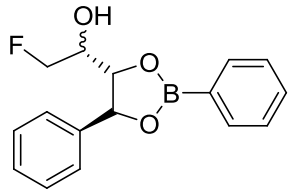
A solution of ketone **188** (1.2 mmol, 200 mg) was dissolved in methanol (3 mL) was cooled to 0^oC in an ice bath. Sodium borohydride (1.7 mmol, 51 mg) was then added in one portion with vigorous stirring. The mixture was then allowed to stir at 0^oC for 20 minutes. The methanol was then evaporated under reduced pressure and, the residue was taken up in diethyl ether (5 mL) and washed with ammonium chloride solution (5 mL), water (5 mL) then brine (5 mL) in that order. The organic phases were separated and then dried ($MgSO_4$) and concentrated under reduced pressure to afford crude **215** as a white solid. Kugelrohr distillation under reduced pressure (150^0C/0.07 mmHg) afforded alcohol **215** as a white solid (190 mg, 93%); m.p. 40-42^oC; R_f (2:3 Et_2O in pet. ether 40-60^oC) 0.31; δ_H (400 MHz, $CDCl_3$) 7.32-7.16 (m, 5H), 6.66 (dd, J = 16.2, ^4J = 1.3, 1H), 6.08 (dd, J = 15.9, J = 6.3, 1H), 4.58-4.47 (m, 1H), 4.50-4.22 (m, 2H), 2.35 (br, 1H); δ_C (100 MHz, $CDCl_3$) 136.1, 133.1, 128.7, 128.1, 126.6, 125.3 (d, $^3J_{C\text{-}F}$ = 8.8), 86.2 (d, $^1J_{C\text{-}F}$ = 172.7), 71.5 (d, $^2J_{C\text{-}F}$ = 20.5); δ_F (376 MHz, $CDCl_3$) -225.6 (td, $^2J_{F\text{-}H}$ = 47.0, J = 17.2); $\nu_{max}(CDCl_3)/cm^{-1}$ 3388br, 3059d, 2980d, 2889, 1494, 1449, 1266, 1072, 1009, 969, 711, 694; *m/z* (EI^+) 166 (19), 1495 (22), 133 (100), 115 (70), 105 (45), 91 (32), 55 (46); HRMS (ES^+, $[M]^+$) calcd. for $C_{10}H_{11}FO$ 166.0788, found 166.0789.

Attempted preparation of triol 216



A solution of potassium osmate (0.006 mmol, 2 mg), $(DHQD)_2PHAL$ (0.03 mmol, 23 mg), potassium ferricyanide (1.8 mmol, 592 mg), sodium hydrogen carbonate (1.8 mmol, 151 mg) and potassium carbonate (1.8 mmol, 248 mg) was allowed to stir in *tert*-butanol and water (3 mL of a 1:1 mixture) at room temperature for 15 minutes. Allylic alcohol **215** (0.6 mmol, 90 mg) was then added and the reaction was allowed to stir at 0^oC for 24 hours. Upon warming to room temperature, the reaction was quenched with sodium sulfite (10 mL of a saturated solution), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were then washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (64 mg). The ^1H and ^{19}F NMR spectra of the crude product showed that none of the triol **216** had formed.

Attempted preparation of boronate ester 217



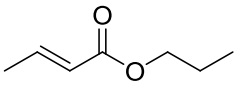
A solution of potassium osmate dihydrate (0.003 mmol, 1 mg), potassium carbonate (0.90 mmol, 124 mg), potassium hexacyanoferrate (0.90 mmol, 296 mg), phenyl boronic acid (0.36 mmol, 44 mg) and $(DHQD)_2PHAL$ (0.015 mmol, 12 mg) was allowed to stir in *tert*-butanol and water (3 mL of a 1:1 mixture) at room temperature for 30 minutes. Allylic alcohol **215** (0.30 mmol, 50 mg) was then added in one portion and the mixture allowed to stir at room temperature for 48 hours. The

reaction was then quenched with solid sodium sulfite (4 g). The mixture was then diluted with water (5 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were then washed with saturated sodium sulfite solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (84 mg). The ^{1}H and ^{19}F NMR spectra of the crude product showed that none of the desired boronate ester **217** had formed.

Preparation of TBAF.(*t*-BuOH)$_4$

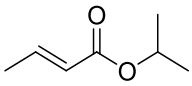
Commercially available TBAF.3H$_2$O was added to a mixture of *t*-BuOH (440 mL) and hexane (110 mL), warmed to 90^{o}C and maintained at this temperature for 30 minutes. During this time the TBAF dissolved completely. The solution was cooled to room temperature, and a white crystalline solid separated. The solid was collected by filtration and washed rapidly with a 7:3 mixture of *t*-BuOH/hexane. The precipitate was kept under reduced pressure for 15-20 minutes to remove residual solvent and TBAF.(*t*-BuOH)$_4$ was afforded as a white crystalline solid (5.2g, 59%): m.p 27-29^{o}C δ_H (400 MHz, $CDCl_3$) 3.32 (t, *J* = 9.1, 8H), 1.70-1.58 (m, 8H), 1.50-1.38 (m, 8H), 1.25 (s, 24-36H (integrals varied)), 0.98 (*t*, *J* = 9.1, 12H). The chemical shifts were in agreement with those reported by Kim.[174]

Preparation of *n*-propyl but-2-*E*-enoate 252



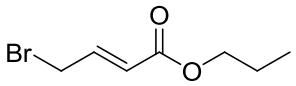
A solution of crotonic acid **247** (581 mmol, 50 g) in *n*-propanol (225 mL) containing concentrated sulfuric acid (6.9 mL) was heated at reflux overnight. The reaction mixture was then diluted with diethyl ether (100 mL) and washed with aqueous $NaHCO_3$ (ca. 3 x 75 mL of a saturated aqueous solution) until no more gas was evolved. The combined aqueous washings were back extracted with diethyl ether (2 x 100 mL) and the combined organic extracts and original layer were dried ($MgSO_4$) and concentrated *in vacuo* to afford ester **252** as a colourless oil which was used in the next step without purification (59.7 g, ca. 80%). The following data were obtained from a small purified sample (flash chromatography, 10% diethyl ether in petroleum ether 40-60^{o}C): R_f (12.5% diethyl ether in pet. ether 40-60^{o}C) 0.66; δ_H (400 MHz, $CDCl_3$) 6.97 (dq, J = 15.7, 7.0, 1H), 5.84 (dq, J = 15.7, 1.8, 1H), 4.1 (t, J = 7.0, 2H), 1.87 (dd, J = 7.0, 1.8, 3H), 1.72-1.63 (m, 2H), 0.95 (t, J = 7.0, 3H); δ_C (100 MHz, $CDCl_3$) 166.6, 144.3, 122.7, 65.7, 22.0, 17.8, 10.3; *m/z* (EI) 129 (15%), 87 (35), 69 (100); HRMS (EI^+, $[M]^+$) calcd. for $C_7H_{12}O_2$ 128.0831, found 128.0832. The compound was reported previously[251] but at lower level of characterisation.

Preparation of *iso*-propyl but-2-*E*-enoate 253



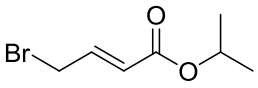
From crotonic acid **247** (872 mmol, 75 g), *i*-propanol (365 mL) and concentrated sulfuric acid (8.8 mL) according to the previous procedure, work-up and isolation. The ester **253** was obtained (86.5 g ca. 77%) and used in the next step without purification. The following data were obtained from a small purified sample (flash chromatography, 10% diethyl ether in petroleum ether 40-60^{o}C): R_f (20% diethyl ether in petroleum ether 40-60^{o}C) 0.59; δ_H (400 MHz, $CDCl_3$) 7.00-6.89 (m, 1H), 5.82 (d, J = 15.7, 1H), 5.10-5.02 (m incl. app. septet, J = 6.3, 1H), 1.86 (d, J = 6.3, 3H), 1.25 (d, J = 6.3, 6H); δ_C(100 MHz, $CDCl_3$) 166.1, 144.0, 123.3, 67.3, 21.9, 17.8; ν_{max}(film)/cm^{-1} 3539, 3422, 2981, 2878, 1720, 1660, 1446, 1375, 1293, 1191, 1110, 1002, 834, 690; HRMS (EI^+, $[M]^+$) calcd. for $C_7H_{12}O_2$ 128.0832, found 128.0830. The data were in agreement with those reported by Jonczyk *et al*..[252]

Preparation of *n*-propyl 4-bromobut-2-*E*-enoate 254



A solution of *N*-bromosuccinimide (41.7 g, 234 mmol), benzoyl peroxide (283 mg, 1.17 mmol) and ester **252** (30 g, 234 mmol) in chlorobenzene (300 mL) was warmed slowly to 85^{o}C over ca. 45 minutes. The reaction mixture was then allowed to stir at this temperature for 2.5 days. The cooled reaction mixture was then filtered and the precipitate washed with diethyl ether (200 mL). The combined filtrate and washings were then washed with NaOH (4 x 200 mL of a 5% aqueous solution) until the washings were almost colourless, then with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Kugelrohr distillation (80^{o}C/0.38 mmHg) afforded the bromide **254** as a pale yellow oil (25.97 g, ca. 53% yield) which was used in the next step without further purification (estimated to be ~90% pure by ^{1}H NMR). The following data were obtained from a small purified sample (flash chromatography, 10% diethyl ether in petroleum ether 40-60^{o}C): R_f (20% diethyl ether in petroleum ether 40-60^{o}C) 0.59; δ_H (400 MHz, $CDCl_3$) 7.00 (dt, J = 15.4, J = 7.3, 1H), 6.04 (dt, J = 15.4, J = 1.3, 1H), 4.11 (t, J = 6.8, 2H), 4.01 (dd, J = 7.3, J = 1.3, 2H), 1.75-1.64 (m, 2H), 0.96 (t, J = 7.3, 3H); δ_C (100 MHz, $CDCl_3$) 165.4, 141.5, 124.6, 66.2, 29.1, 21.9, 10.3; ν_{max}(film)/cm^{-1} 2969, 2879, 1722 (C=O), 1655 (C=C); *m/z* (EI^{+}) 207 (100%), 147 (50), 68 (30); HRMS (EI^{+}, [M]$^{+}$) calcd for $C_7H_{11}BrO_2$ 205.9934, found 205.9931; Anal. Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35; Br, 38.59. Found: C, 40.51; H, 5.12; Br, 38.41.

Preparation of *iso*-propyl 4-bromobut-2-*E*-enoate 255



From a solution of *N*-bromosuccinimide (60.7 g, 341 mmol), benzoyl peroxide (362 mg, 1.5 mmol) and ester **253** (39.7 g, 310 mmol) in chlorobenzene (200 mL) and according to the previous procedure, work-up and isolation the bromide **255** was obtained (33.8 g, ca 48%). The following data were obtained from a small purified sample (Flash chromatography, 0-25% diethyl ether in petroleum ether 40-60^{o}C): R_f (10% diethyl ether in petroleum ether 40-60^{o}C) 0.28; δ_H (400 MHz, $CDCl_3$) 7.02-6.94 (m, 1H), 6.06-6.01 (m incl. app. dt, J = 15.2, J = 1.1, 1H), 5.12-5.04 (sept., J = 6.3, 1H), 4.01 (dd, J = 7.3, 1.1, 2H), 1.27 (d, J = 6.3, 6H); δ_C (100 MHz, $CDCl_3$) 165.0, 141.3, 125.2, 68.2, 29.2, 21.8; ν_{max}(film)/cm^{-1} 3419, 2982, 2939, 1718, 1654, 1468, 1313, 1280, 1197, 1108, 976, 909, 823, 722, 584; *m/z* (EI$^+$) 209 (85), 207 (100), 149 (24), 109 (7), 81 (14), 68 (21); HRMS (EI$^+$, [M]$^+$) calcd. for $C_7H_{11}BrO_2$ 205.9937, found 205.9936.

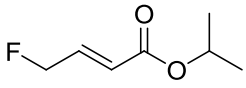
Lester method

Benzoyl peroxide (47 mg, 0.2 mmol) was added to a refluxing mixture of ester **253** (5 g, 39 mmol) and *N*-bromosuccinimide (6.95 g, 39 mmol) in chlorobenzene (50 mL) over 2 hours. The mixture was then maintained at reflux for a further 3 hours. The cooled reaction mixture was then filtered and the precipitate washed with diethyl ether (100 mL). The combined filtrate and washings were then washed with NaOH (4 x 50 mL of a 5% aqueous solution) until the washings were almost colourless, then with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to

afford an orange oil. Kugelrohr distillation (80°C/0.38 mmHg) afforded the bromide **255** as a pale yellow oil (5.75 g, ca. 72% yield).

Scale-up (15 g of ester **253**) under these conditions led to violent discharge of the reaction mixture out the top of the condenser.

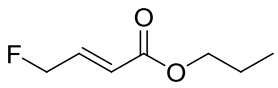
Preparation of *iso*-propyl 4-fluorobut-2-*E*-enoate 263



Bromoester **255** (34.5 g, 167 mmol) was added to a solution of $KF.2H_2O$ (62.1 g, 668 mmol) and Bu_4NHSO_4 (67.22 g, 200 mmol) in acetonitrile (650 mL) and the mixture was heated at reflux overnight. The mixture was then diluted with water (400 mL) and extracted with diethyl ether (1 x 400 mL and 2 x 150 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Fractional distillation under reduced pressure (55-70°C/0.08 mmHg) afforded ester **263** as a pale yellow oil (7.34 g ca. 30%) which was used in the next step without any further purification (estimated to be ~95% pure by ^{1}H NMR). The following data were obtained from a small purified sample (flash chromatography, 10% diethyl ether in petroleum ether 40-60°C): R_f (10% diethyl ether in petroleum ether 40-60°C) 0.22; δ_H (400 MHz, $CDCl_3$) 6.99-6.86 (m, 1H), 6.11-6.04 (m incl. app. d, J = 15.7, 1H), 5.11-4.96 (m, 3H), 1.26 (d, J = 6.7, 6H); δ_C (100 MHz, $CDCl_3$) 165.2, 141.0 (d, $^2J_{C\text{-}F}$ = 17.6), 122.0 (d, $^3J_{C\text{-}F}$ = 11.4), 81.1 (d, $^1J_{C\text{-}F}$ = 172.7), 68.1, 21.8; δ_F (376 MHz, $CDCl_3$) -230.1 (tdd, $^2J_{F\text{-}H}$ = 46.5, $^3J_{F\text{-}H}$ = 22.4, $^4J_{F\text{-}H}$ = 1.7); ν_{max}(film)/cm^{-1} 3430, 2983, 2878, 1721, 1667, 1469, 1376, 1305, 1279, 1182, 1108, 999, 912, 836, 680, 587; *m/z* (EI$^+$) 233 (10%), 147 (100), 87 (80), 59

(10); HRMS (EI^+, $[M]^+$) calcd. for $C_7H_{11}FO_2$ 146.0738, found 146.0738, (EI^+, $[M + H]^+$) calcd. for $C_7H_{12}FO_2$ 147.0816, found 147.0815.

Preparation of *n*-propyl 4-fluorobut-2-*E*-enoate 261



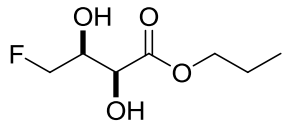
$KF.2H_2O$/ Bu_4NHSO_4 method

From bromoester **254** (22.05 g, 106 mmol), $KF.2H_2O$ (39.9 g, 424 mmol), Bu_4NHSO_4 (43.2 g, 127 mmol) and acetonitrile (500 mL) according to the procedure, work-up and isolation described previously. Fluoride **261** was prepared (10.2 g ca. 66%) and used in the next step without purification (estimated to be ~90% pure by ^{1}H NMR). The following data were obtained from a small purified sample (Flash chromatography, 10% Et_2O in petroleum ether 40-60^{o}C): R_f (20% diethyl ether in petroleum ether 40-60^{o}C) 0.55; δ_H (400 MHz, $CDCl_3$) 6.96 (ddt, $^3J_{H-F}$ = 22.7, J = 15.9, 3.8, 1H), 6.12 (dq, J = 15.9, $^4J_{H-F}$ = 2.0, 1H), 5.06 (ddd, $^2J_{H-F}$ = 46.2, J = 3.8, 2.0, 2H), 4.12 (t, J = 6.7, 2H), 1.75-1.65 (m, 2H), 0.96 (t, J = 7.3, 3H); δ_C (100 MHz, $CDCl_3$) 165.8, 141.3 (d, $^2J_{C-F}$ 16.0), 121.4 (d, $^3J_{C-F}$ 11.4), 81.1 (d, $^1J_{C-F}$ 171.3), 66.2, 21.9, 10.3; δ_F (376 MHz, $CDCl_3$) -223.3 (tdd, $^2J_{F-H}$ 46.2, $^3J_{F-H}$ 22.7, $^4J_{F-H}$ 2.0); ν_{max}(film)/cm^{-1} 2971, 2882, 1722 (C=O), 1669 (C=C); *m/z* (EI^+) 163 (8%), 147 (80), 87 (100), 59 (19); HRMS (EI^+, $[M]^+$) calcd. for $C_7H_{11}FO_2$ 146.0738, found 146.0736, (EI^+, $[M + H]^+$) calcd. for $C_7H_{12}FO_2$ 147.0816, found 147.0815.

TBAF.3H_2O/KHF_2 method

Tetrabutylammonium fluoride trihydrate (4.1 g, 4.88 mmol) and potassium hydrogen difluoride (2.7 g, 11.7 mmol) were heated with stirring in a round bottomed flask until melting occurred. Bromoester **254** (1.0 g, 4.88 mmol) was then added and the resulting brown viscous suspension was stirred vigorously for 30 minutes. The reaction mixture was then cooled to room temperature and diluted with diethyl ether (15 mL) and water (15mL) to solubilise all the salts. The organic layer was separated and solid $NaHCO_3$ (~1 – 1.5 g) was added to the aqueous layer until it was found to be neutral (to pH paper) at which point it was extracted with Et_2O (3 x 15 mL). The combined organic extracts and the original organic layer were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown gum. Fractional distillation under reduced pressure (55-70^oC/0.08 mmHg) afforded the fluoride **261** as a pale yellow oil (263 mg ca. 37%).

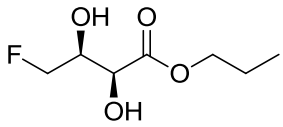
Preparation of (2*S,3*S**)-*n*-propyl 4-fluoro-2,3-dihydroxybutanoate 269 (±)**



A solution of NMO (1.4 g, 11.4 mmol) in water (1 mL) was added to a mixture of *t*-BuOH and acetone (10 mL of a 1:1 mixture) at 0^oC. Fluorinated ester **261** (836 mg, 5.7 mmol) was then added in one portion, the mixture allowed to stir for 15 minutes and then OsO_4 (1.4 mL of a 2.5% wt solution in *t*-BuOH) was added dropwise by syringe over 20 minutes. The mixture was allowed to continue stirring and warm slowly to room temperature overnight. The reaction was quenched by the addition of

sodium sulfite (8 g) and diluted with water (30 mL). The aqueous solution was then extracted with EtOAc (2 x 30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford diol **269** as an orange gum that was used without purification (855 mg, ca. 83%). The following data were obtained from a small purified sample (flash chromatography, 1% methanol in 1:1 ethyl acetate/hexane): R_f (50% ethyl acetate in petroleum ether 40-60^{o}C) 0.47; δ_H (400 MHz, $CDCl_3$) 4.50 (ddd, $^2J_{H\text{-}F}$ = 46.6, J = 9.4, 6.1, 2H), 4.27 (br s, 1H), 4.25-4.13 (m, 3H), 3.33 (br s, 1H), 2.85 (br s, 1H), 1.70 (sextet, J = 7.2, 2H), 0.95 (t, J = 7.2, 3H); δ_C (100 MHz, $CDCl_3$) 172.8, 83.0 (d, $^1J_{C\text{-}F}$ = 170.6), 70.5 (d, $^2J_{C\text{-}F}$ = 21.0), 70.0 (d, $^3J_{C\text{-}F}$ = 5.1), 68.0, 21.8, 10.2; δ_F (376 MHz, $CDCl_3$) -225.5 (td, $^2J_{F\text{-}H}$ = 46.9, $^3J_{F\text{-}H}$ = 13.4); ν_{max}(film)/cm^{-1} 3454, 2982, 2865, 1756, 1451, 1375, 1287, 1220, 1105, 927; HRMS (ES$^+$, [M + H]$^+$) calcd. for $C_7H_{14}FO_4$ 181.0871, found 181.0871; Anal. Calcd.: C, 46.66; H, 7.27; Found C, 46.34; H, 7.30.

Preparation of (2*S*,3*S*)-*n*-propyl 4-fluoro-2,3-dihydroxybutanoate 264



Sharpless AD with 2 mol% osmium/2 mol% ligand

A solution of $K_3Fe(CN)_6$ (2 g, 6.09 mmol), K_2CO_3 (840 mg, 6.09 mmol), $MeSO_2NH_2$ (195 mg, 2.03 mmol), $(DHQD)_2PHAL$, (2 mol%), $K_2OsO_4.2H_2O$ (2 mol%) in a mixture of *t*-BuOH and water (14 mL, 1:1 v/v) was cooled to 0^oC and allowed to stir for ca. 30 mins until a homogenous solution with a deep orange colour was observed. Fluoroester **261** (300 mg, 2.03 mmol) was then added in one portion and the mixture was allowed to stir at 0^oC for 15 hours (reaction completion was confirmed by micro work-up of an aliquot and analysis by ^{19}F NMR). The reaction was quenched by the addition of solid sodium sulfite (2 g) and allowed to warm to room temperature. A colour change from yellow to grey was observed. Water (30 mL) was then added and the suspension was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were then washed with brine (30 mL), KOH (30 mL of a 1M solution), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 1% methanol in 1:1 ethyl acetate/hexane) afforded diol **264** as a colourless oil (163 mg, 44%). Data were identical to those described previously for **269** apart from; $[\alpha]_D$ -13.2 (*c* 1.0, $CDCl_3$), 89% ee by ^{19}F [^1H] NMR, L-(+)-DIPT/$CDCl_3$.

General Procedure for AD-mix β standard conditions

Crude diol **264** was prepared from a solution of fluoroester **261** (1.04 g, 7.1 mmol), AD-mix β (9.94 g) and methyl sulfonamide (675 mg, 7.1 mmol) in 1:1 *t*-BuOH/water (70 mL) according to the procedure and work-up described previously. Purification

by flash chromatography (Buchi Sepacore, 50% diethyl ether in petroleum ether 40-60^{o}C) afforded the diol **264** as a colourless oil (700 mg, 54%, 72% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

1 mol% osmium/10 mol% ligand

Crude diol **264** was prepared from a solution of fluoroester **261** (73 mg, 0.5 mmol), AD-mix β (700 mg), methyl sulfonamide (48 mg, 0.5 mmol), $(DHQD)_2PHAL$ (9 mol%), $K_2OsO_2(OH)_4$ (0.6 mol%) and $NaHCO_3$ (1.5 mmol) in *t*-BuOH/water (5 mL, 1:1 v/v) according to the procedure and work-up described previously to afford diol **264** (71 mg, ca. 79%, 90% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

General Procedure for modified AD-mix β conditions

1 mol% osmium/5 mol% ligand

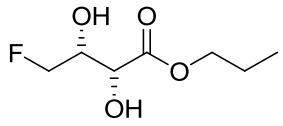
Crude diol **264** was prepared from a solution of fluoroester **261** (2.19 g, 15 mmol), AD-mix β (21 g), methyl sulfonamide (1425 mg, 15 mmol), $(DHQD)_2PHAL$ (4 mol%), $K_2OsO_2(OH)_4$ (0.6 mol%) and $NaHCO_3$ (45 mmol) in 1:1 *t*-BuOH/water (150 mL) according to the procedure and work-up described previously to afford diol **264** (1.87 g, 78%, 91% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

1 mol% osmium/5 mol% $(DHQD)_2AQN$ ligand

Crude diol **264** was prepared from a solution of fluoroester **261** (3 g, 20.3 mmol), $K_3Fe(CN)_6$ (20 g, 60.9 mmol), K_2CO_3 (8.4 g, 60.9 mmol), $MeSO_2NH_2$ (1.95 g, 20.3 mmol), $(DHQD)_2AQN$, (5 mol%, 870 mg), $K_2OsO_4.2H_2O$ (2 mol%, 74 mg) in a mixture of *t*-BuOH and water (140 mL, 1:1 v/v) according to the procedure and

work-up described previously to afford diol **264** (2.63 g, 72%, 97% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

Preparation of (2*R*,3*R*)-*n*-propyl 4-fluoro-2,3-dihydroxybutanoate 270



General Procedure for AD-mix α standard conditions

Crude diol **270** was prepared from a solution of fluoroester **261** (1.04 g, 7.1 mmol), AD-mix α (9.94 g) and methyl sulfonamide (675 mg, 7.1 mmol) in 1:1 *t*-BuOH/water (70 mL) according to the procedure and work-up described previously. Purification by flash chromatography (Buchi Sepacore, 50% diethyl ether in petroleum ether 40-60^{o}C) afforded the desired product **270** as a colourless oil (712 mg, 56%, 66% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

Sharpless AD with 2 mol% osmium/2 mol% ligand

Crude diol **270** was prepared from a solution of fluoroester **261** (302 mg, 2.07 mmol), $K_3Fe(CN)_6$ (2.04 g, 6.21 mmol), K_2CO_3 (858 mg, 6.21 mmol), $MeSO_2NH_2$ (198 mg, 2.07 mmol), $(DHQ)_2PHAL$, (2 mol%), $K_2OsO_4.2H_2O$ (2 mol%) in *t*-BuOH/water (14 mL, 1:1 v/v) according to the procedure and work-up described previously. Purification by flash chromatography (Buchi Sepacore, 2% methanol in 1:1 ethyl acetate/hexane) afforded the desired product **261** as a colourless oil (163 mg, 45%). Data were identical to those described previously for **269** apart from; $[\alpha]_D$ +12.8 (*c* 1.0, $CDCl_3$), 80% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$.

General Procedure for modified AD-mix α conditions:

1 mol% osmium/10 mol% ligand

Crude diol **270** was prepared from a solution of fluoroester **261** (73 mg, 0.5 mmol), AD-mix α (700 mg), methyl sulfonamide (48 mg, 0.5 mmol), $(DHQ)_2PHAL$ (9 mol%), $K_2OsO_2(OH)_4$ (0.6 mol%) and $NaHCO_3$ (1.5 mmol) in *t*-BuOH/water (5 mL, 1:1 v/v) according to the procedure and work-up described previously to afford the desired diol **270** (54 mg, ca. 60%, 82% ee by ^{19}F [^1H] NMR, L-(+)-DIPT/$CDCl_3$).

General Procedure for modified AD-mix α conditions:

1 mol% osmium/5 mol% ligand

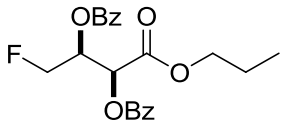
Crude diol **270** was prepared from a solution of fluoroester **261** (1.6g, 10.8 mmol), AD-mix α (15.1 g), methyl sulfonamide (1027 mg, 10.8 mmol), $(DHQ)_2PHAL$ (4 mol%), $K_2OsO_2(OH)_4$ (0.6 mol%) and $NaHCO_3$ (32.4 mmol) in a mixture of *t*-BuOH/water (110 mL, 1:1 v/v) according to the procedure and work-up described previously to afford the desired diol **270** (1.56 g ca. 80%, 83% ee by ^{19}F [^1H] NMR, L-(+)-DIPT/$CDCl_3$).

1 mol% osmium/5 mol% $(DHQ)_2AQN$ ligand

Crude diol **264** was prepared from a solution of fluoroester **261** (1.5 g, 10.2 mmol), $K_3Fe(CN)_6$ (10 g, 30.6 mmol), K_2CO_3 (4.2 g, 30.6 mmol), $MeSO_2NH_2$ (975 mg, 10.2 mmol), $(DHQ)_2AQN$, (5 mol%, 435 mg), $K_2OsO_4.2H_2O$ (2 mol%, 37 mg) in a mixture of *t*-BuOH and water (70 mL, 1:1 v/v) according to the procedure and work-

up described previously to afford diol **264** (640 mg, 59%, 95% ee by ^{19}F [^{1}H] NMR, L-(+)-DIPT/$CDCl_3$).

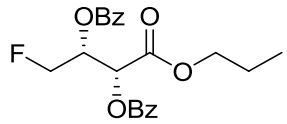
Preparation of (*2S*,3S)-4-Dibenzyloxy-4-fluorobutanoate 271 (±)**



Benzoic anhydride (1.13 g, 5 mmol) and DMAP (49 mg, 0.4 mmol) were added to a solution of crude racemic diol **269** (360 mg, 2 mmol) in DCM (20 mL) at room temperature. Triethylamine (700 µL) was then added dropwise over ca. 30 minutes and the resulting mixture was allowed to stir at room temperature overnight. Analysis of a sample of the reaction by ^{19}F NMR confirmed that the reaction had gone to completion. The mixture was diluted with DCM (20 mL) and washed with $NaHCO_3$ (2 x 20 mL of a saturated aqueous solution), brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil (700 mg, 90% (crude)). Purification by Flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^{o}C) afforded the dibenzoate **271** as a white syrup (622 mg, 80%): R_f (10% diethyl ether in petroleum ether 40-60^{o}C) 0.29; δ_H (400 MHz, $CDCl_3$) 8.11 (m incl. app. d, J = 17.7, 2H), 8.09 (m incl. app. d, J = 17.7, 2H), 7.64-7.56 (m, 2H), 7.50-7.42 (m, 4H), 5.96-5.86 (dq, J = 13.7, J = 3.7, 1H), 5.70 (d, J = 3.7, 1H), 4.78 (dqd, $^{2}J_{H\text{-}F}$ = 46.5, J = 9.7, J = 5.6, 2H) , 4.14 (t, J = 6.7, 2H), 1.66-1.56 (m, 2H), 0.87 (t, J = 7.8, 3H); δ_C (100 MHz, $CDCl_3$) 166.8, 165.4, 165.2, 133.7, 133.6, 130.0, 129.9, 128.6, 128.5, 80.2 (d, $^{1}J_{C\text{-}F}$ = 174.2), 70.6 (d, $^{3}J_{C\text{-}F}$ = 4.4), 70.3 (d, $^{2}J_{C\text{-}F}$ = 23.4), 67.7, 21.8, 10.2; δ_F (376 MHz, $CDCl_3$) -230.3 (td, $^{2}J_{F\text{-}H}$ = 47.0, $^{3}J_{F\text{-}H}$ = 12.6); ν_{max}(film)/cm^{-1} 3070, 2970, 2674, 1971, 1915, 1729, 1602, 1452, 1289, 1104, 1026, 935, 804, 712;

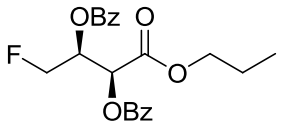
HRMS (ES^+, $[M + NH_4]^+$) calcd. for $C_{21}H_{21}FO_6NH_4$ 406.1660, found 406.1663, (ES^+, $[2M + NH_4]^+$) calcd. for $C_{42}H_{42}F_2O_{12}NH_4$ 794.2983, found 794.2990.

Preparation of (2*R*,3*R*)- 4-Dibenzyloxy-4-fluorobutanoate 272



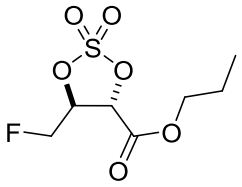
Benzoic anhydride (127 mg, 0.56 mmol), DMAP (7 mg, 0.056 mmol) and poly(vinylpyridine) (280mg, 0.28mmol) were added to a solution of diol **270** (50 mg, 0.28 mmol) in DCM (3 mL) at room temperature. The mixture was then shaken at room temperature overnight. Analysis of the crude mixture by ^{19}F NMR showed the reaction had not gone to completion. Benzoic anhydride (63 mg, 0.28 mmol) was added and the mixture shaken at room temperature for a further 4 hours. Analysis of an aliquot by ^{19}F NMR confirmed the reaction had gone to completion. The mixture was diluted with diethyl ether (10 mL), filtered, and the precipitate washed with Et_2O (10 mL). The combined filtrate and washings were washed with $NaHCO_3$ (3 x 15 mL of a saturated aqueous solution), brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 10% Et_2O in petroleum ether 40-60^oC) afforded dibenzoate **272** as a colourless oil (86 mg, 79%). Data were identical to those for **271** apart from; $[\alpha]_D$ -50.4 (*c* 0.5, $CHCl_3$); HPLC (Chiralcel OD-H column, hexane/*i*PrOH 98/2, 1mL min^{-1}, 280 nm): t_R (major) 11.7 min, 83% ee.

Preparation of (2*S*,3*S*)- 4-Dibenzyloxy-4-fluorobutanoate 273



Benzoic anhydride (127 mg, 0.56 mmol), DMAP (7 mg, 0.056 mmol) and poly(vinylpyridine) (280 mg, 0.28 mmol) were added to a solution of diol **264** (50 mg, 0.28 mmol) in DCM (3 mL) at room temperature. The mixture was then shaken at room temperature overnight. Analysis of the crude mixture by ^{19}F NMR showed the reaction had not gone to completion. Benzoic anhydride (63 mg, 0.28 mmol) was added and the mixture allowed to stir at room temperature for a further 4 hours. Analysis of an aliquot by ^{19}F NMR confirmed full conversion of the starting material had taken place. The mixture was diluted with diethyl ether (10 mL), filtered, and the precipitate washed with Et_2O (10 mL). The filtrate was then washed with $NaHCO_3$ (3 x 15 mL of a saturated aqueous solution), brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^oC) afforded the dibenzoate **273** as a colourless oil (88 mg, 81%). Data were identical to those for **271** apart from; $[\alpha]_D$ +47.6 (*c* 0.55, $CHCl_3$); HPLC (Chiralcel OD-H column, hexane/*i*PrOH 98/2, 1mL min^{-1}, 280nm): t_R (major) 18.1 min, 91% ee.

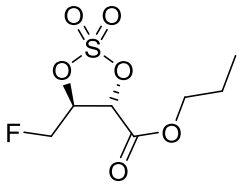
Preparation of (4*S,5*S**)-*n*propyl-5-fluoromethyl-[1,3,2]-dioxathiolane-4-carboxylate-2,2-dioxide 280(±)**



A solution of NMO (384 mg, 3.3 mmol) in water (0.5 mL) was added to a 1:1 mixture of *t*-BuOH/acetone (4 mL) at 0^{o}C. Fluoroester **261** (239 mg, 1.64 mmol) was then added and the mixture was allowed to stir for 15 minutes, and then OsO_4 (330 µL of a 2.5% wt solution in *t*-BuOH) was added dropwise by syringe over 20 minutes. The mixture was allowed to continue stirring and slowly warmed to room temperature overnight. The progress of this reaction was monitored by the ^{19}F NMR spectra. The reaction was quenched by the addition of sodium sulfite (1.7 g), stirred for 30 minutes and eluted through a pad of Celite with EtOAc/MeOH (30 mL a 1:1 mixture). The filtrate was then concentrated *in vacuo* to afford the diol **269** (δ_F [^{1}H] ^{19}F -223.3). The crude diol was then taken up in dry DCM (6 mL), cooled to 0^{o}C and treated with pyridine (370 µL, 4.6 mmol) and $SOCl_2$ (170 µL, 3.3 mmol). After stirring for 15 minutes, the reaction was quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford crude **279(±)** (δ_F [^{1}H] ^{19}F -225.8 and -234.0). The crude material was then taken up in a mixture of acetonitile (8 mL) and water (1.5 mL), cooled to 0^{o}C and solid $NaIO_4$ (491 mg, 2.3 mmol) followed by $RuCl_3$ (catalytic ~ 1 drop from a capillary) were added. After stirring for 10 minutes the reaction mixture was diluted with Et_2O (10 mL) and filtered through a pad of celite. The organic filtrate was then washed with water (10

mL), $NaHCO_3$ (10 mL of a saturated aqueous solution), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired product (δ_F [^{1}H] -223.4). Purification by flash chromatography (Buchi Sepacore, 30% ethyl acetate in petroleum ether 40-60^{o}C) afforded cyclic sulfate **280(±)** as an oil (117 mg, 29% yield): R_f (30% ethyl acetate in petroleum ether 40-60^{o}C) 0.42; δ_H (400 MHz, $CDCl_3$) 5.21 (d, J = 7.3, 1H), 5.14 (dddd $^3J_{H\text{-}F}$ = 21.7, J = 7.3, = 3.3, 2.2, 1H), 4.9–4.66 (m, 2H) 4.25-4.21 (m, 2H), 1.78-1.73 (m, 2H), 0.98 (t, J = 7.4, 3H); δ_C (100 MHz, $CDCl_3$) 164.7, 79.2 (d, $^1J_{C\text{-}F}$ = 181.3), 74.7 (d, $^3J_{C\text{-}F}$ = 6.8), 80.5 (d, $^2J_{C\text{-}F}$ = 19.9), 69.1, 21.7, 10.1; δ_F (376 MHz, $CDCl_3$) -223.4 (ddd, $^2J_{F\text{-}H}$ = 47.3, $^2J_{F\text{-}H}$ = 45.9, $^3J_{F\text{-}H}$ = 21.7); ν_{max}(film)/cm^{-1} 3670, 3527, 2975, 2885, 1771, 1745; HRMS (EI, [M + H]$^+$) calcd. for $C_7H_{12}FO_6S$ 243.0333, found 243.0341; Anal. Calcd. for $C_7H_{11}FO_6S$: C, 34.71; H, 4.58; S, 13.24. Found: C, 35.05; H, 4.69; S, 13.25.

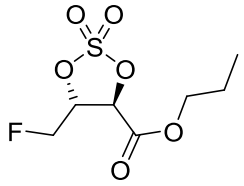
Preparation of (4*S*,5*S*)-*n*-propyl-5-fluoromethyl-[1,3,2]-dioxathiolane-4-carboxylate 2,2-dioxide 280(+)



From enriched diol **264** (792 mg, 4.4 mmol), dry DCM (20 mL), pyridine (1.36 µL, 17.6 mmol), $SOCl_2$ (615 µL, 8.8 mmol) then $NaIO_4$ (1.3 g, 6.2 mmol), $RuCl_3$ (catalytic ~ 2-3 drops from a capillary), acetonitrile (25 mL) and water (5 mL) and according to the procedure and work-up described previously cyclic sulfate **280(+)** was prepared. Purification by flash chromatography (Buchi Sepacore), 30% ethyl acetate in hexane afforded **280(+)** (340 mg, 29% yield). Data were identical to those

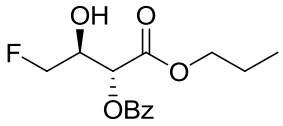
described previously for **280(±)** apart from; $[\alpha]_D$ +23.4 (*c* 1.0, $CDCl_3$); HPLC (Chiralcel OD-H column, hexane/*i*PrOH 85/15, 1mL min^{-1}, 280 nm): t_R (major) 14.5 min, 92% ee.

Preparation of (4*R*,5*R*)-*n*-propyl-5-fluoromethyl-[1,3,2]-dioxathiolane-4-carboxylate 2,2-dioxide 289(-)



From enriched diol **270** (792 mg, 4.4 mmol), dry DCM (20 mL), pyridine (1.36 μL, 17.6 mmol), $SOCl_2$ (615 μL, 8.8 mmol) then $NaIO_4$ (1.3 g, 6.2 mmol), $RuCl_3$ (catalytic ~ 2-3 drops from a capillary), acetonitrile (25 mL) and water (5 mL) and according to the procedure and work-up described previously cyclic sulfate **289** was prepared. Purification by flash chromatography (Buchi Sepacore), 30% ethyl acetate in hexane afforded **289(-)** (553 mg, 38% yield). Data were identical to those described previously for **280(±)** apart from; $[\alpha]_D$ -20.5 (*c* 1.0, $CDCl_3$); HPLC (Chiralcel OD-H column, hexane/*i*PrOH 85/15, 1mL min^{-1}, 280 nm): t_R (major) 13.2 min, 80% ee.

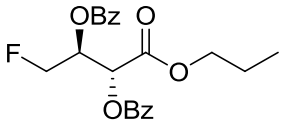
Preparation of *n*-Propyl (2*R*)-benzyloxy-4-fluoro-(3*S*)-hydroxybutanoate 281



Crude cyclic sulfate **280** was prepared from enriched diol **264** (90 mg, 0.5 mmol), dry DCM (1.5 mL), pyridine (180 μL, 2.3 mmol), $SOCl_2$ (75 μL, 1 mmol), $NaIO_4$ (149 mg, 0.75 mmol), $RuCl_3$ (catalytic ~ 1 drop from a capillary), acetonitrile (3 mL) and water (1 mL) and according to the procedure and work-up described previously for **280(±)**. Ammonium benzoate (119 mg, 1 mmol) was added to a solution of **280** in acetone (2 mL) and allowed to stir at room temperature overnight. After confirmation that the reaction was complete by ^{19}F NMR, the reaction was concentrated *in vacuo* and taken up in Et_2O (2.5 mL). A solution of sulfuric acid (2.5mL of a 20% v/v aqueous solution) was then added dropwise and the resulting mixture allowed to stir at room temperature overnight. After the consumption of the starting material had been confirmed by ^{19}F NMR, the mixture was partitioned between ether (10 mL) and water (10 mL). The aqueous layer was separated, neutralized with solid $NaHCO_3$ and extracted with ether (2 x 5 mL). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude material as an off white semi-solid (222 mg). Purification by Flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^oC then 0-8% methanol in dichloromethane) afforded the benzoate **281** as a colourless oil (85mg, 60% yield): R_f (10% methanol in dichloromethane) 0.39; $[\alpha]_D$ +2.9 (*c* 1.25, $CDCl_3$); δ_H (400 MHz, $CDCl_3$) 8.12-8.06 (m, 2H), 7.64-7.59 (m, 1H), 7.50-7.45 (m, 2H), 5.40 (d, J = 5.6, 1H), 4.64 (ddd, $^2J_{H\text{-}F}$ = 47.0, J = 4.5, J = 1.5, 1H), 4.63 (ddd, $^2J_{H\text{-}F}$ = 47.0, J = 5.0, J = 2.0, 1H), 4.50-4.42

(dq, J = 18.7, J = 4.8, 1H), 4.19 (t, J = 6.6, 2H), 1.73-1.64 (m incl. J = 6.6, J = 7.6, 2H), 0.93 (t, J = 7.6, 3H); δ_C (100 MHz, $CDCl_3$) 168.1, 165.5, 133.7, 130.2, 129.9, 128.8, 128.6, 128.4, 82.9 ($^1J_{C\text{-}F}$ = 171.3), 72.6 ($^3J_{C\text{-}F}$ = 5.9), 70.1 ($^2J_{C\text{-}F}$ = 20.5), 67.6, 21.8, 10.2; δ_F (376 MHz, $CDCl_3$) -232.0 (td, $^2J_{F\text{-}H}$ = 47.0, $^3J_{F\text{-}H}$ = 18.4); ν_{max}(film)/cm^{-1} 3482 (br), 2964, 1973, 1725, 1604, 1451, 1263, 1107, 709; HRMS (ES$^+$, [M + H]$^+$) calcd. for $C_{14}H_{17}FO_5NH_4$ 302.1398, found 302.1403, (ES$^+$, [2M + NH_4]$^+$) calcd. for $C_{28}H_{34}F_2O_{10}NH_4$ 591.2012, found 591.2013.

Preparation of (2*R*,3*S*)-4-fluoro-1-oxo-1-propoxybutane-2,3-diyl dibenzoate 282



Cyclic Sulfate preparation

Cyclic sulfate **280** was prepared from diol **264** (245 mg, 1.36 mmol), dry DCM (4 mL), pyridine (487 μL, 6.1 mmol), $SOCl_2$ (204 μL, 2.7 mmol) then $NaIO_4$ (435 mg, 2.8 mmol), $RuCl_3$ (catalytic couple of drops from a capillary) acetonitrile (9 mL) and water (3 mL) according to the procedure and work-up procedures described previously.

Nucleophilic ring opening

Ammonium benzoate (323 mg, 2.7 mmol) was added to a solution of **280** (~ 1.36 mmol) in acetone (2 mL) and allowed to stir at room temperature overnight. After confirmation that the reaction was complete by ^{19}F NMR, the reaction was concentrated *in vacuo* and taken up in Et_2O (2.5 mL). A solution of sulfuric acid (2.5mL, of a 20% v/v aqueous solution) was then added dropwise and the resulting mixture allowed to stir at room temperature overnight. After consumption of the

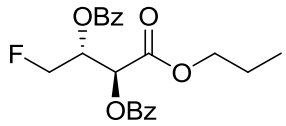
starting material had been confirmed by ^{19}F NMR, the mixture was diluted with ether (10 mL) and water (10 mL). The aqueous layer was separated, neutralized with solid $NaHCO_3$ and extracted with ether (2 x 5 mL). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude alcohol **281**.

Hydroxyl protection

The alcohol **281** was taken up in DCM (14 mL), treated with benzoic anhydride (370mg, 1.63 mmol), DMAP (33 mg, 20 mol%) and PVP (1.4 g) and allowed to shake overnight at room temperature. Analysis of an aliquot by ^{19}F NMR confirmed that the reaction had gone to completion. The mixture was diluted with Et_2O (25 mL), filtered, and the precipitate washed with Et_2O (20 mL). The filtrate and washings were combined and washed with $NaHCO_3$ (3 x 20 mL of a saturated aqueous solution), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^oC) afforded dibenzoate **282** as a colourless oil (170 mg, 32% over 3 steps. R_f (10% diethyl ether in pet. ether 40-60^oC) 0.21; $[\alpha]_D$ -4.5 (*c* 1.1, $CDCl_3$), δ_H (400 MHz, $CDCl_3$) 8.10-8.03 (m, 4H), 7.64-7.52 (m, 2H), 7.50-7.43 (m, 4H), 5.92-5.88 (m, 1H), 5.69 (dd, J = 4.6, J = 1.1, 1H), 4.94-4.80 (m incl. app. d, $^2J_{H\text{-}F}$ = 46.7, 1H), 4.24-4.14 (m, 2H), 1.71-1.62 (m, 2H), 0.92 (t, J = 7.3, 3H); δ_C (100 MHz, $CDCl_3$) 167.9, 165.3, 165.25, 133.7, 133.6, 130.0, 129.9, 129.1, 128.8, 128.6, 128.4, 80.5 ($^1J_{C\text{-}F}$ = 175.6), 70.8 ($^3J_{C\text{-}F}$ = 5.8), 70.9 ($^2J_{C\text{-}F}$ = 22.0), 67.7, 21.8, 10.2; δ_F (376 MHz, $CDCl_3$) -231.0 (td, $^2J_{F\text{-}H}$ = 46.7, $^3J_{F\text{-}H}$ = 16.7); ν_{max}(film)/cm^{-1} 3056, 2948, 1733, 1602, 1454, 1263, 1099, 712; HRMS (ES$^+$, $[M + NH_4]^+$) calcd. for

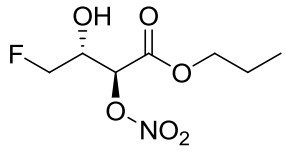
$C_{21}H_{21}FO_6NH_4$ 406.1667, found 406.1660; HPLC (Chiralcel OD-H column, hexane/*i*PrOH 98/2, 1mL min^{-1}, 280 nm): t_R (major) 11.2 min, 95% ee.

Preparation of (2*S*,3*R*)-4-fluoro-1-oxo-1-propoxybutane-2,3-diyl dibenzoate 284



Dibenzoate **284** was prepared from diol **270** (86 mg, 0.48 mmol), dry DCM (1.4 mL), pyridine (175 μL, 2.2 mmol), $SOCl_2$ (75 μL, 1 mmol) then $NaIO_4$ (155 mg, 1 mmol) catalytic $RuCl_3$ (couple of drops from a capillary ~5-10 mg), acetonitrile (3 mL), water (1 mL) then ammonium benzoate (119 mg, 1 mmol), benzoic anhydride (136 mg, 0.6 mmol), DMAP (12 mg, 20 mol%), PVP (0.5 g) and DCM (5 mL) according to the procedure described previously to afford dibenzoate **284** (65 mg, 34% over 3 steps). Data were identical to those described previously for **282** apart from; $[\alpha]_D$ +4.4 (*c* 1.3, $CDCl_3$); HPLC (Chiralcel OD-H column, hexane/*i*PrOH 98/2, 1mL min^{-1}, 280 nm): t_R (major) 12.7 min, 78% ee.

Preparation of (2*S*,3*R*)-propyl 4-fluoro-3-hydroxy-2-(nitrooxy)butanoate 291(-) (DMF)



Cyclic Sulfate preparation

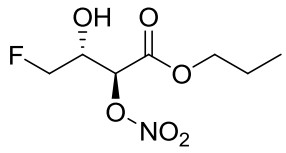
Cyclic sulfate **289** was prepared from diol **276** (137 mg, 0.76 mmol), dry DCM (2 mL), pyridine (272 μL, 3.4 mmol), $SOCl_2$ (110 μL, 1.7 mmol), $NaIO_4$ (244 mg, 1.14

mmol) and catalytic $RuCl_3$ (couple of drops from a capillary ~5-15mg) according to the procedure and work-up procedures described previously.

Nucleophilic ring opening

Sodium nitrate (157mg, 2.28 mmol) was added in one portion to a solution of cyclic sulfate **289** (~0.76 mmol) in DMF (2.5 mL) at room temperature and the mixture allowed to stir overnight. After confirmation of consumption of the starting materials by ^{19}F NMR the reaction was diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated under reduced pressure. The resulting yellow oil was then taken up in diethyl ether (4 mL) and sulfuric acid added dropwise (4 mL of a 20% v/v aqueous solution). The reaction mixture was diluted with diethyl ether (5 mL) and washed with $NaHCO_3$ (5 mL of a saturated solution) then brine (5 mL). The organic layer was then isolated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 0-50% diethyl ether in pet. ether 40-60^oC) afforded **291(-)** as a colourless oil (10 mg, 6%): R_f (50% diethyl ether in pet. ether 40-60^oC) 0.34; δ_H (400 MHz, $CDCl_3$) 5.35 (d, J = 4.5, 1H), 4.68-4.48 (m incl. app. dd, J = 47.0, J = 5.1, 2H), 4.42-4.30 (m incl. app. d, J = 17.2), 4.23 (t, J = 6.6, 2H), 2.80 (d (br), 1H), 1.78-1.64 (m, 2H), 1.26 (s (br), 1H), 0.96 (t, J = 7.6, 3H); δ_C (100 MHz, $CDCl_3$) 165.3, 81.1 (d, $^1J_{C\text{-}F}$ = 172.8), 77.8 (d, $^3J_{C\text{-}F}$ = 5.2), 67.8 (d, $^2J_{C\text{-}F}$ = 22.6), 67.2, 20.8, 9.2; δ_F (376 MHz, $CDCl_3$) -231.4 (td, $^2J_{F\text{-}H}$ = 47.0, $^3J_{F\text{-}H}$ = 17.2); ν_{max}(film)/cm^{-1} 3477 (br), 2974, 1748, 1720, 1296, 1026,; HRMS (CI, $[M+NH_4]^+$) calcd. for $C_7H_{16}O_6N_2F$ 243.0985, found 243.0987.

Preparation of (2*S*,3*R*)-propyl 4-fluoro-3-hydroxy-2-(nitrooxy)butanoate 291(-) (Acetone)



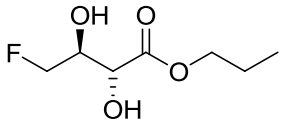
Cyclic Sulfate preparation

Cyclic sulfate **289** was prepared from diol **276** (486 mg, 2.7 mmol), dry DCM (7.5 mL), pyridine (895 μL, 11.1 mmol), $SOCl_2$ (395 μL, 5.4 mmol), $NaIO_4$ (873 mg, 4.1 mmol) and catalytic $RuCl_3$ (couple of drops from a capillary ~5-15mg) according to the procedure and work-up procedures described previously. Crude cyclic sulfate **289** isolated as a yellow oil (317 mg, ~1.3 mmol).

Nucleophilic ring opening

Sodium nitrate (157mg, 2.28 mmol) was added in one portion to a solution of cyclic sulfate **289** (~1.3 mmol) in acetone (6 mL) at room temperature and the mixture allowed to stir overnight. Analysis of a reaction aliquot by ^{19}F NMR showed the starting material had only been partially consumed. Another portion of $NaNO_3$ (1.95 mmol) was added and the reaction left to reflux for 24 hours. After confirmation of consumption of the starting materials by ^{19}F NMR the reaction the reaction was concentrated under reduced pressure. The resulting yellow oil was then taken up in diethyl ether (6 mL) and sulfuric acid added dropwise (6 mL of a 20% v/v aqueous solution). The reaction mixture was diluted with diethyl ether (10 mL) and washed with $NaHCO_3$ (10 mL of a saturated solution) then brine (5 mL). The organic layer was then isolated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 0-50% diethyl ether in pet. ether 40-60^oC) afforded **291(-)** as a colourless oil (185 mg, 35%).

Preparation of (2*R*,3*S*)-propyl 4-fluoro-2,3-dihydroxybutanoate 288



Cyclic Sulfate preparation

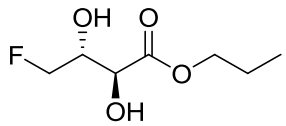
Cyclic sulfate **280** was prepared from diol **275** (432 mg, 2.4 mmol), dry DCM (7.5 mL), pyridine (895 μL, 11.1 mmol), $SOCl_2$ (357 μL, 4.8 mmol), $NaIO_4$ (770 mg, 3.6 mmol) and catalytic $RuCl_3$ (couple of drops from a capillary ~5-15mg) according to the procedure and work-up procedures described previously.

Nucleophilic ring opening

Sodium nitrite (828 mg, 12 mmol) was added in one portion to a solution of cyclic sulfate **280** (2.4 mmol) in DMF (10 mL) at room temperature and the mixture allowed to stir overnight. After confirmation of consumption of the starting materials by ^{19}F NMR the reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated under reduced pressure. The resulting yellow oil was then taken up in diethyl ether (4 mL) and sulfuric acid added dropwise (4 mL of a 20% v/v aqueous solution). The reaction mixture was diluted with diethyl ether (10 mL) and washed with $NaHCO_3$ (10 mL of a saturated solution) then brine (10 mL). The organic layer was then isolated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 0-50% diethyl ether in pet. ether 40-60^oC) afforded **288** as a colourless oil (52 mg, 12% from **264**): R_f (100% diethyl ether in pet. ether 40-60^oC) 0.49; δ_H (400 MHz, $CDCl_3$) 4.64-4.45 (m incl. app. dd, J = 47.0, J = 5.1, 2H), 4.32 (d, J = 4.0, 1H), 4.22-4.18 (m incl. app. t, J = 6.6, 2H), 4.18-4.12 (m, 1H), 3.32 (br s, 1H), 2.85 (br s, 1H), 1.76-1.67 (m, 2H), 0.97

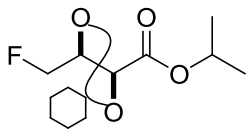
(t, J = 7.3, 3H); δ_C (100 MHz, $CDCl_3$) 172.2, 82.7 (d, $^1J_{C\text{-}F}$ = 169.8), 71.7 (d, $^2J_{C\text{-}F}$ = 20.5), 69.9 (d, $^3J_{C\text{-}F}$ = 5.9), 68.0, 21.8, 10.2; δ_F (376 MHz, $CDCl_3$) -230.2 (td, $^2J_{F\text{-}H}$ = 47.0, $^3J_{F\text{-}H}$ = 16.1); ν_{max}(film)/cm^{-1} 3478, 2974, 2556, 1748, 1652, 1296, 1057, 850; HRMS (FAB, $[M+NH_4]^+$) calcd. for $C_7H_{17}O_4NF$ 198.1136, found 198.1134; $[^1H]^{19}F$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 94% ee; $[\alpha]_D$ +33.4 (*c* 1.04, $CDCl_3$).

Preparation of (2*S*,3*R*)-propyl 4-fluoro-2,3-dihydroxybutanoate 290



Diol **290** was prepared from diol **276** (432 mg, 2.4 mmol), dry DCM (7.5 mL), pyridine (895 μL, 11.1 mmol), $SOCl_2$ (357 μL, 4.8 mmol), $NaIO_4$ (770 mg, 3.6 mmol), catalytic $RuCl_3$ (couple of drops from a capillary ~5-15mg) then sodium nitrite (828 mg, 12 mmol) and DMF (10 mL) and according to the procedure described previously to afford *anti*-diol **290** as a colourless oil (41 mg, 9% from **264**). The data were identical to those obtained for **288** apart from; $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 95% ee; $[\alpha]_D$ -34.0 (*c* 0.99, $CDCl_3$).

Preparation of (2*S,3*S**)-*Iso*propyl 4-fluoro-2,3-*O*-cyclohexylidene butanoate 295**



Dihydroxylation

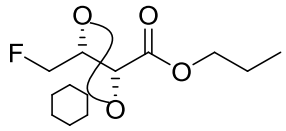
A solution of NMO (1.5 g, 12.8 mmol) in water (1 mL) was added to *t*-BuOH/acetone (13 mL, 1:1 v/v) at 0^{o}C. Fluorinated ester **261** (939 mg, 6.4 mmol) was then added, the mixture allowed to stir for 15 minutes and then OsO_4 (1.6 mL of a 2.5% wt solution in *t*-BuOH) was added dropwise by syringe over ca. 20 minutes. The mixture was allowed to continue stirring and warm slowly to room temperature overnight. The reaction was quenched by addition of solid sodium sulfite (9.6 g) and then washed through a bed of Celite with MeOH/EtOAc (120 mL, 1:1 v/v). The filtrate was concentrated *in vacuo*, taken up in ethyl acetate (20mL) and washed with brine (2 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude racemic diol **269** as an orange oil.

Protection of diol

The crude diol **269** was taken up in a mixture of cyclohexanone (522 mg, 5.3 mmol) and trimethyl orthoformate (565 mg, 5.3 mmol) in ethyl acetate (5 mL) and stirred for 15 minutes at room temperature. The yellow solution was then treated with boron trifluoride diethyl etherate (0.67 mL, 5.3 mmol). A colour change to dark orange was observed and the mixture was stirred at room temperature for 48 hours. The mixture was then diluted with ethyl acetate (30 mL) and the organic phase was washed with $NaHCO_3$ (30 mL of a saturated aqueous solution), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification by flash

chromatography (Buchi Sepacore, 0-20% gradient of Et_2O in petroleum ether 40-60^oC) afforded the acetal **295** as a colourless oil (335mg, 20% over 2 steps): R_f (20% diethyl ether in petroleum ether 40-60^oC) 0.36; δ_H (400 MHz, $CDCl_3$) 5.12 (septet, J = 6.2, 1H), 4.74-4.45 (m, 2H), 4.39-4.31 (m, 2H), 1.78-1.58 (envelope, 8H), 1.46-1.37 (br, 2H), 1.29 (d, J = 6.2, 6H); δ_C (100 MHz, $CDCl_3$) 170.2, 112.8, 82.3 (d, $^1J_{C\text{-}F}$ = 175.6), 77.4 (d, $^2J_{C\text{-}F}$ = 19.0), 74.3 (d, $^3J_{C\text{-}F}$ = 7.3), 69.3, 36.3, 35.1, 25.0, 23.8, 23.6, 21.2, 21.1; δ_F (376 MHz, $CDCl_3$) (-230.1)-(-230.4) (m incl. app. td, $^2J_{F\text{-}H}$ = 47.3, $^3J_{F\text{-}H}$ = 20.6); ν_{max}(film)/cm^{-1} 2939, 1754, 1728, 1446, 1367, 1285, 1106, 1032, 845, 637; *m/z* (EI$^+$) 261 (100), 231 (42), 189 (8), 175 (70); HRMS (EI, [M]$^+$) calcd. for $C_{13}H_{21}FO_4$ 260.1418, found 260.1420.

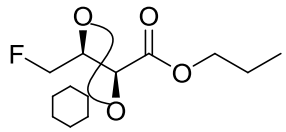
Preparation of (2*R*,3*R*)- Propyl 4-fluoro-2,3-*O*-cyclohexylidene butanoate 296



Crude acetal **296** was prepared from a solution of diol **270** (314 mg, 1.7 mmol), boron trifluoride diethyl etherate (260 µL, 2.04 mmol) and cyclohexanone (200 mg, 2.0 mmol) in ethyl acetate (1.7 mL) according to the procedure and work-up described previously for **295**. Purification by flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^oC) afforded **296** as a colourless oil (96 mg, 21%): R_f (10% diethyl ether in petroleum ether 40-60^oC) 0.37; $[\alpha]_D$ +26.8 (*c* 1.2, $CDCl_3$); δ_H (400 MHz, $CDCl_3$) 4.76-4.32 (m, 4H), 4.21-4.10 (m, 2H), 1.75-1.55 (br m, 10H), 1.45-1.37 (br m, 2H), 0.96 (t, J = 7.1, 3H); δ_C (100 MHz, $CDCl_3$) 170.7, 112.8, 82.1 (d, $^1J_{C\text{-}F}$ = 175.6), 77.3 (d, $^2J_{C\text{-}F}$ = 20.5) 74.1 (d, $^3J_{C\text{-}F}$ = 7.3), 67.2, 36.2, 35.0, 25.0, 23.8, 23.6, 21.9, 10.3; δ_F (376 MHz, $CDCl_3$) -230.45 (td, $^2J_{F\text{-}H}$ = 47.0, J =

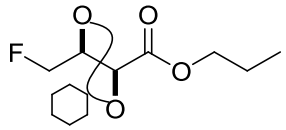
21.2); ν_{max}(film)/cm^{-1} 2944, 1760, 1728, 1449, 1362, 1288, 1240, 1159, 1066, 1021, 908, 842, 829, 792, 652; *m/z* (EI$^+$) 261 (7), 231 (43), 217 (100), 175 (24); HRMS (ES$^+$, [M + H]$^+$) calcd. for $C_{13}H_{22}FO_4$ 261.1497, found 261.1497.

Preparation of (2*S*,3*S*)-Propyl 4-fluoro-2,3-*O*-cyclohexylidene butanoate 292



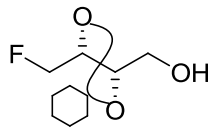
From diol **264** (1.09 g, 6.1 mmol), cyclohexanone (598 mg, 6.1 mmol), boron trifluoride diethyl etherate (927 μL, 7.3 mmol) and ethyl acetate (5 mL) and according to the procedure described previously for **295** crude acetal **264** was afforded (393 mg, 19%). The data were identical to those obtained for **296** apart from; $[\alpha]_D$ -30.0 (*c* 0.8, $CDCl_3$).

Preparation of (2*S,3*S**)-propyl-4-fluoro-2,3-*O*-cyclohexylidene butanoate 294**



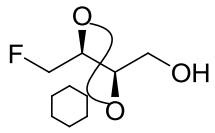
From racemic diol **269** (855 mg, 4.75 mmol), cyclohexanone (559 mg, 5.7 mmol), boron trifluoride diethyl etherate (720 μL, 5.7 mmol) and ethyl acetate (5 mL) and according to the procedure described previously crude acetal **294** was prepared (366 mg, 29% crude yield). The data were identical to those obtained for **296**.

Preparation of (2*R*,3*R*)-*4*-fluoro-2,3-*O*-cyclohexylidenebutan-1-ol 297



A solution of cyclohexylidene **296** (1.02 g, 3.9 mmol) in dry DCM (40 mL) was cooled to -78°C under an atmosphere of nitrogen. DIBAL-H (9.75 mmol, 8.9 mL of a 1.1 M solution in cyclohexane) was then added dropwise over 20 minutes and the reaction was allowed to warm slowly to room temperature overnight under a nitrogen atmosphere. The mixture was diluted with EtOAc (60 mL) and brine (60 mL) forming a viscous emulsion which was filtered through a pad of wet Celite. The organic layer in the filtrate was isolated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts and the original layer were then dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (Buchi Sepacore, 0-40% ethyl acetate in petroleum ether 40-60°C) afforded the desired product **297** as a pale yellow oil (300 mg, 38% yield): R_f (50% ethyl acetate in petroleum ether 40-60°C) 0.65; $[\alpha]_D$ -3.2 (*c* 0.9, $CDCl_3$), δ_H (400 MHz, $CDCl_3$) 4.65-4.43 (ddd, $^2J_{H\text{-}F}$ = 47.5, *J* = 4.1, *J* = 3.5, 2H), 4.20-4.10 (m, 1H), 4.08-4.04 (m, 1H), 3.90-3.83 (m incl. app. d, *J* = 12.1, 1H), 3.70-3.63 (m, 1H), 1.96-1.89 (m, 1H), 1.69-1.56 (envelope, 8H), 1.45-1.37 (m, 2H); δ_C (100 MHz, $CDCl_3$) 110.5, 82.4 (d, $^1J_{C\text{-}F}$ = 172.7), 77.8 (d, $^3J_{C\text{-}F}$ = 5.9), 75.2 (d, $^2J_{C\text{-}F}$ = 20.5), 61.9, 36.7, 36.3, 25.0, 23.85, 23.75; δ_F (376 MHz, $CDCl_3$) -230.8 (td, $^2J_{F\text{-}H}$ = 47.0, $^3J_{F\text{-}H}$ = 20.7); ν_{max}(film)/cm^{-1} 3446br, 2938, 2863, 1450, 1366, 1282, 1117, 940, 845; *m/z* (EI^+) 205 (84), 175 (44), 161 (100), 99 (18), 81 (22), 69 (24), 55 (56); HRMS (ES^+, $[M + H]^+$) calcd. for $C_{10}H_{18}FO_3$ 205.1234, found 205.1233.

Preparation of (2*S*,3*S*)-*4*-fluoro-2,3-*O*-cyclohexylidenebutan-1-ol 298



Asymmetric Dihydroxylation

Crude diol **264** was prepared from a solution of fluoroester **261** (2.19 g, 15 mmol), AD-mix β (21 g), methyl sulfonamide (1425 mg, 15 mmol), $(DHQD)_2PHAL$ (4 mol%), $K_2OsO_2(OH)_4$ (0.6 mol%) and $NaHCO_3$ (45 mmol) in 1:1 *t*-BuOH/water (150 mL) according to the procedure and work-up described previously to afford crude diol **264** (2.43 g, ~89%).

Acetal Protection

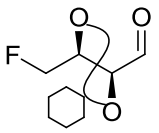
From diol **264** (2.43 g, 13.5 mmol), cyclohexanone (1.6 g, 16.2 mmol), boron trifluoride diethyl etherate (2.3 mL, 16.2 mmol) and ethyl acetate (10 mL) and according to the procedure described previously crude acetal **292** was afforded (2.1 g, ~59%).

DIBAL-H reduction

A solution of ester **292** (2.1 g, 8.1 mmol) in dry DCM (140 mL) was cooled to -78^{o}C under an atmosphere of nitrogen. DIBAL-H (20.3 mmol, 18.4 mL of a 1.1 M solution in cyclohexane) was then added dropwise over 20 minutes and the reaction was allowed to warm slowly to room temperature overnight under a nitrogen atmosphere. The mixture was diluted with EtOAc (100 mL) and brine (100 mL) forming a viscous emulsion which was filtered through a pad of wet Celite. The organic layer in the filtrate was isolated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts and the original layer were then

dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (Buchi Sepacore, 0-40% ethyl acetate in petroleum ether 40-60^oC) afforded the desired alcohol **298** as a pale yellow oil (758 mg, 25% over 3 steps); The data were identical to those obtained for **297** apart from; $[\alpha]_D$ +2.9 (*c* 0.9, $CDCl_3$).

Attempted preparations of (2*S*,3*S*)-4-fluoro-2,3-*O*-cyclohexylidenebutanal 299



Attempted oxidation with PCC

A solution of alcohol **298** (20 mg, 0.1 mmol) in DCM (0.2 mL) was added to a solution of PCC (26 mg, 0.12 mmol) in DCM (0.3 mL). The reaction mixture was then allowed to stir at room temperature overnight. A colour change from orange to brown to black was observed. The mixture was then eluted through (a small glass pipette column of) silica with DCM (15 mL). The filtrate was then concentrated *in vacuo* to afford a colourless oil. Analysis by ^{19}F NMR suggested decomposition had occurred (large number of td signals visible in ^{19}F NMR).

Attempted oxidation with buffered PCC

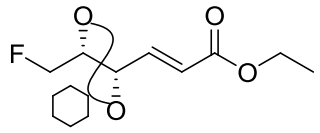
A solution of alcohol **298** (20 mg, 0.1 mmol) in dry DCM (0.5 mL) was added to a stirred solution of PCC (54 mg, 0.25 mmol), sodium acetate (2 mg, 25 mol%) and 4Å molecular sieves (24 mg) in DCM (1.0 mL) under N_2 at 0^oC. The reaction was then allowed to stir at 0^oC for 2 hours. The mixture was then eluted through (a small glass

pipette column of) silica with DCM (15 mL). The filtrate was then concentrated *in vacuo* to afford a colourless oil. Analysis by ^{19}F NMR suggested decomposition had occurred (large number of td signals visible in ^{19}F NMR).

Attempted oxidation with Dess-Martin Periodinane

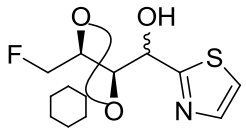
A cooled solution (0^oC) of Dess-Martin periodinane in DCM (1 mL) was added to a solution of the alcohol **298** in DCM (1.5 mL) at 0^oC. The reaction mixture was then allowed to stir at 0^oC for 2 hours. The reaction mixture was diluted with $NaHCO_3$ (5 mL of a 0.1 M aqueous solution) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Analysis by ^{19}F NMR suggested decomposition had occurred (large number of td signals visible in ^{19}F NMR).

Preparation of (4*R*,5*R*)-ethyl 6-fluoro-4,5-*O*-cyclohexylidenehex-2-enoate 301



Alcohol **297** and (carbethoxymethylene)triphenylphosphorane (780 mg, 2.24 mmol) were taken up in a mixture of DCM (4.2 mL) and DMSO (0.7 mL) at room temperature and allowed to stir at room temperature for 5 minutes. Solid Dess-Martin Periodinane (93 mg, 1.23 mmol) was added causing an instant colour change to yellow. The reaction was stirred for 30 minutes then diluted with Et_2O (50 mL) and the organic phase washed with $NaHCO_3$ (3 x 50 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to afford alkenoate **301** as a mixture of *E:Z* isomers (4:1) and as a viscous orange gum. Purification by flash chromatography (Buchi Sepacore, 0-50% ethyl acetate in petroleum ether 40-60^oC) afforded the alkene **301** as a clear oil (114 mg, 74%, 57 mg *E* isomer (37%), 57 mg mixed fraction): R_f (50% diethyl ether in petroleum ether 40-60^oC) 0.56; $[\alpha]_D$ +6.5 (*c* 1.2, $CDCl_3$), δ_H (400 MHz, $CDCl_3$) 6.91 (dd, J = 15.7, J = 5.6, 1H), 6.17 (dd, J =15.7, J = 1.5, 1H), 4.68-4.43 (m, 3H), 4.22 (q, J = 7.3, 2H), 3.98 (m, 1H), 1.70-1.58 (envelope, 8H), 1.57-1.45 (br, 2H), 1.30 (t, J = 7.1, 3H); δ_C (100 MHz, $CDCl_3$) 165.8, 143.4, 123.2, 111.4, 81.3 (d, $^1J_{C\text{-}F}$ = 174.2), 78.7 (d, $^2J_{C\text{-}F}$ = 20.5), 75.6 (d, $^3J_{C\text{-}F}$ = 7.3), 60.7, 36.3, 36.2, 25.0, 23.8, 23.75, 14.2; δ_F (376 MHz, $CDCl_3$) -231.0 (td, $^2J_{F\text{-}H}$ = 47.0, $^3J_{F\text{-}H}$ = 20.7); ν_{max}(film)/cm^{-1} 3425, 2939, 2863, 1723, 1664, 1450, 1368, 1303, 1278, 1178, 1130, 1034, 976, 908, 847; *m/z* (EI^+) 273 (26), 243 (26), 229 (56), 199 (10), 175 (11), 129 (20), 81 (22); HRMS (EI^+, $[M]^+$) calcd. for $C_{14}H_{21}FO_4$ 272.1418, found 272.1419; 82% ee by ^{19}F [^1H] NMR, L-(+)-DIPT/$CDCl_3$.

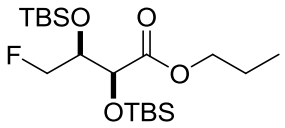
(2*R*,3*R*)-4-Fluoro-2,3-*O*-cyclohexylidene-1-(thiazol-2-yl)butan-1-ol 320



A solution of DMSO (31 mg, 0.4 mmol) in DCM (0.3 mL) was added slowly (ca. 20 minutes) to a solution of oxalyl chloride (30 mg, 0.24 mmol) in DCM (0.5 mL) at -78^{o}C under an atmosphere of nitrogen. The mixture was stirred for 20 mins and then a solution of alcohol **298** (40 mg, 0.2 mmol) in DCM (0.15 mL) was added. The mixture was stirred for 15 minutes and then Et_3N (131 μL) was added dropwise (the clear solution became opaque (white) immediately). The mixture was stirred for ca. 20 minutes at -78^{o}C and then allowed to warm to room temperature over ca. 30 minutes. The reaction was then diluted with water (1 mL), stirred for 25 minutes and extracted with DCM (2 x 1 mL). The combined organic extracts were washed with brine (2 x 1 mL), dried ($MgSO_4$), concentrated *in vacuo* and taken up in $CDCl_3$ for analysis by NMR. The ^{1}H and ^{19}F NMR spectra (δ_F (376 MHz, $CDCl_3$) -230.40 (td, $^{2}J_{F\text{-}H}$ = 47.0, $^{3}J_{F\text{-}H}$ = 22.9) Δ 0.4ppm) confirmed consumption of starting material but complete assignment of the product ^{1}H peaks within the crude mixture was not possible. After confirmation of the aldehyde formation by ^{1}H NMR the sample was concentrated *in vacuo*, taken up in dry DCM (1 mL), treated with trimethylsilyl thiazole (0.3 mmol) and stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure, redissolved in $CDCl_3$ and analysed by NMR, confirming the disappearance of the aldehyde signal. The sample was then concentrated under reduced pressure, redissolved in THF (1 mL) and treated with TBAF.3H_2O (0.3 mmol). A colour change from pale yellow to pale orange was

observed. After 3 hours the solvent was removed under reduced pressure, the residue diluted with water (1 mL) and extracted with DCM (2 x 1 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. Elution through a pipette of silica with 50% diethyl ether in petroleum ether 40-60^oC afforded the product **320** as a colorless oil (32 mg, 56%): R_f (50% diethyl ether in petroleum ether 40-60^oC) 0.29 ; δ_H (400 MHz, $CDCl_3$) 7.78 (d, J = 3.3, 1H), 7.37 (d, J = 3.3, 1H), 5.18 (d, J = 5.1, 1H), 4.44-4.05 (m, 4H), 1.71-1.56 (envelope m, 8H), 1.48-1.38 (m, 2H); δ_C (100 MHz, $CDCl_3$) 168.7, 141.1, 119.7, 110.1, 81.8 (d, $^1J_{C\text{-}F}$ = 172.7), 77.5 (d, J = 8.8), 75.2 (d, J = 17.6), 70.5, 35.6, 35.2, 24.0, 22.9, 22.7; δ_F (376 MHz, $CDCl_3$) -228.9 (td, J = 47.0, 22.9); ν_{max}(film)/cm^{-1} 3215 br, 2937, 2249, 1703, 1626, 1503, 1449, 1118, 1056, 941, 733; HRMS (ES^+, $[M + H]^+$) calcd. for $C_{13}H_{19}FNO_3S$ 288.1064, found 288.1067.

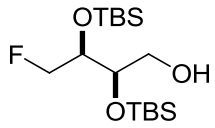
Preparation of (2*S,3*S**)-*n*Propyl 2,3-bis(tert-butyldimethylsilyloxy)-4-fluorobutanoate 302**



A solution of NMO (1.01 g, 8.6 mmol) in water (2.2 mL) was added to a mixture of *t*-BuOH (5 mL) and acetone (5 mL) at 0^oC. Fluorinated ester **261** (625 mg, 4.28 mmol) was then added, the mixture was allowed to stir for 15 minutes and then OsO_4 (0.87 mL of a 2.5%wt solution in *t*-BuOH) was added dropwise by syringe over 20 minutes. The mixture was allowed to continue stirring and warm slowly to room

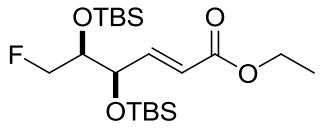
temperature overnight. The reaction was quenched by addition of solid sodium sulfite (4.3 g) and then washed through a pad of Celite with MeOH/EtOAc (90 mL 1:1 v/v). The filtrate was concentrated under reduced pressure to afford the diol. Crude diol was then taken up in dry DMF (28 mL) and cooled to 0^{o}C, then pyridine (14.3 mL), followed by $BuMe_2SiOTf$ (3.45g, 12.8 mmol) were added under an atmosphere of nitrogen. The solution was allowed to warm to room temperature and stirred ca. 24 hours. The mixture was then concentrated under reduced pressure, and the residue was taken up in DCM (30 mL), washed with water (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60^{o}C) afforded the bis silyl ether **302** as a colourless oil (970mg, 56% yield): R_f (10% diethyl ether in petroleum ether 40-60^{o}C) 0.17; δ_H (400 MHz, $CDCl_3$) 4.58 (ddd, $^2J_{H\text{-}F}$ = 46.7, J = 9.3, 4.6, 1H), 4.37 (ddd, $^2J_{H\text{-}F}$ = 48.1, J = 9.3, 6.8, 1H), 4.25 (dd, J = 3.7, 1.6, 1H), 4.23-4.13 (m, 1H), 4.15-3.99 (m, 2H), 1.76-1.64 (m, 2H), 0.95 (t, J = 7.4, 3H), 0.91 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H) 0.04 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.4, 83.8 (d, $^1J_{C\text{-}F}$ = 168.6), 73.0, 72.9 (d, $^2J_{C\text{-}F}$ = 16.7), 66.5, 25.6, 21.9, 18.2, 18.0, 10.4, -4.6, -5.0, -5.1, -5.4; δ_F (376 MHz, $CDCl_3$) -226.6 (td, $^2J_{F\text{-}H}$ = 47.4, $^3J_{F\text{-}H}$ = 13.8); ν_{max}(film)/cm^{-1} 2957, 2930, 2887, 2858, 1762, 1730; Anal. Calcd. for $C_{19}H_{41}FO_4Si_2$: C, 55.84; H, 10.11. Found: C, 55.73; H, 10.27.

Preparation of (2*S,3*S**)-2,3-Bis(tert-butyldimethylsilyloxy)-4-fluorobutan-1-ol 303**



A solution of **302** (517 mg, 1.26 mmol) in dry DCM (10 mL) was cooled to -78°C under an atmosphere of nitrogen. DiBAL-H (3.15 mmol, 2.9 mL of a 1.1 M solution in cyclohexane) was then added dropwise over 20 minutes and the reaction allowed to stir at -40°C for 2.5 hours. The mixture was warmed to room temperature, diluted with DCM (60 mL) and water (20 mL) forming a viscous emulsion which was filtered through a pad of wet Celite. The organic layer in the filtrate was isolated and the aqueous layer was extracted with DCM (2 x 40 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 10% diethyl ether in petroleum ether 40-60°C) afforded the alcohol **303** as a colourless oil (331 mg, 74%): R_f (10% diethyl ether in petroleum ether 40-60°C) 0.37; δ_H (400 MHz, $CDCl_3$) 4.68-4.37 (m, 2H), 3.96 (dddd, $^3J_{H\text{-}F}$ = 21.0, J = 7.6, J = 4.8, J = 2.3, 1H), 3.79-3.73 (m, 1H), 3.70-3.56 (m, 2H), 2.0 (dd, J = 7.6, J = 5.0, 1H), 0.90 (9H, s), 0.89 (9H), 0.11 (3H, s), 0.10 (6H, s), 0.9 (3H, s); δ_C (100 MHz, $CDCl_3$) 84.6 (d, $^1J_{C\text{-}F}$ = 165.9), 74.2 (d, $^2J_{C\text{-}F}$ = 17.3), 72.9, 62.6, 25.6, 17.9, -4.83, -5.21; δ_F (376 MHz, $CDCl_3$) -226.4 (td, $^2J_{F\text{-}H}$ = 48.2, $^3J_{F\text{-}H}$ = 21.0); Anal. Calcd. for $C_{16}H_{37}FO_3Si_2$: C, 54.50; H, 10.58. Found: C, 54.20; H 10.58.

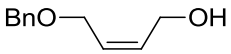
Preparation of (4*S,5*S**)-Ethyl 4,5-bis(tert-butyldimethylsilyloxy)-6-fluorohex-2-*E*-enoate 304**



A solution of DMSO (98mg, 1.25 mmol) in DCM (0.5 mL) was added slowly (ca. 20 minutes) to a solution of oxalyl chloride (82mg, 0.62mmol) in DCM (1 mL) at -78°C under an atmosphere of nitrogen. The mixture was stirred for 20 mins and then a solution of alcohol **303** (200mg, 0.57mmol) in DCM (0.5 mL) was added. The mixture was stirred for 15 minutes and then Et_3N (0.4 mL) was added dropwise over ca. 20 minutes. The solution became opaque and the mixture was stirred for 1 hour at -78°C and then $Ph_3P{=}CHCO_2Et$ (297mg, 0.85mmol) was added. The mixture was stirred at -78°C for 1 hour and then allowed to warm to room temperature over 15 minutes. The reaction mixture was diluted with Et_2O (5 mL), washed with $NaHCO_3$ (3 x 5 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude alkenoate. Purification by flash chromatography (Buchi Sepacore, 3% diethyl ether in petroleum ether 40-60°C) afforded the alkenoate **304** (187mg, 78%): R_f (3% diethyl ether in petroleum ether 40-60°C) 0.38; δ_H (400 MHz, $CDCl_3$) 7.08 (dd, J = 15.7, 3.8, 1H), 6.02 (dd, J = 15.7, ^4J = 2.0, 1H), 4.48 (ddd, $^2J_{H\text{-}F}$ = 47.6, J = 9.5, J 2.4, 1H), 4.31-4.26 (m, 1H), 4.27-4.05 (m, 3H), 4.02-3.91 (m, 1H), 1.29 (t, J = 7.1, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.10-0.07 (m, 9H), 0.06 (s, 3H); δ_C (100 MHz, $CDCl_3$) 166.3, 146.5, 121.1, 84.7 (d, $^1J_{C\text{-}F}$ 168.7), 74.2 (d, $^2J_{C\text{-}F}$ 18.6), 72.5 (d, $^3J_{C\text{-}F}$ 9.8), 60.4, 25.7, 18.1, 18.0, 14.2, -4.8, -4.9, -5.1, -5.2; δ_F (376 MHz, $CDCl_3$) -230.2 (m. ind. app. td, $^2J_{F\text{-}H}$ = 47.6, $^3J_{F\text{-}H}$ = 17.2); ν_{max}(film)/cm^{-1} 2957, 2932, 2889,

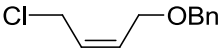
2860, 1725, 1659; HRMS (ES^+, $[M + NH_4]^+$) calcd. for $C_{20}H_{41}FO_4Si_2NH_4$ 438.2866, found 438.2866.

Preparation of 4-(benzyloxy)-*Z*-but-2-en-1-ol 336



Sodium hydride (60% mineral dispersion, 2.024 g, 50.6 mmol) was added to a solution of *Z*-butene diol **321** (4.05 g, 46 mmol) in DMF (250 mL) at 0^{o}C and the resulting mixture allowed to stir at this temperature for 30 minutes. Benzyl bromide (8.6 g, 50.6 mmol) was then added and the mixture allowed to warm to room temperature overnight. The reaction mixture was poured into water (300 mL) and extracted with ether (2 x 200 mL). The combined organic extracts were washed with brine (300 mL), concentrated under vacuum to yield a yellow oil. Kugelrohr distillation (130-135^{o}C/0.25 mmHg) afforded the benzyl ether **336** as a clear oil (6.1 g, 75% yield); R_f (50% diethyl ether in pet. ether 40-60^{o}C) 0.28; δ_H (400 MHz, $CDCl_3$) 7.40-7.25 (m, 5H), 5.75 (m, 2H), 4.50 (s, 2H), 4.10 (d, J = 5.6, 2H), 4.07 (d, J = 5.6, 2H), 2.35 (brs, 1H). The data were in agreement with those reported by Thurner *et al.*.[253]

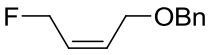
Preparation of 4-Benzyloxy-1-chloro-*Z*-butene-2-diol 337



Allyl alcohol **336** (34 mmol, 6.1 g) was added dropwise to a stirred solution of thionyl chloride (51 mmol, 6.1 g) in diethyl ether (850 mL) at room temperature and allowed to stir for 24 hours. The solution was diluted with water (300 mL), the phases were separated and the aqueous phase was extracted with diethyl ether (2 x 200 mL). The combined organic extracts and original organic phase were then washed with brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a

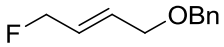
clear oil. Kugelrohr distillation (134-136^{o}C/0.25 mmHg) afforded the allyl chloride **337** as a clear oil (5.6 g, 82% yield); R_f (50% diethyl ether in pet. ether 40-60^{o}C) 0.28; δ_H (400 MHz, $CDCl_3$) 7.40-7.24 (m, 5H), 5.83-5.77 (m, 2H), 4.52 (s, 2H), 4.13-4.00 (m, 4H); δ_C (100 MHz, $CDCl_3$) 138.4, 131.2, 128.9, 128.8, 128.3, 128.2, 72.9, 65.6, 39.6; *m/z* (EI$^+$) 161 (2), 105 (6), 91 (100). The data were in agreement with those reported by Yadav *et al.*[254]

Preparation of *Z*-1-fluoro-4-benzyloxy-but-2-ene 342



Allyl chloride **337** (1 mmol, 197 mg) was added to a stirred solution of commercial TBAF.3H_2O (2.1 mmol, 670 mg) in THF (5 mL) at reflux. After 6 h, the solution was diluted with water (2 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* to afford a pale brown oil. Purification by flash chromatography (Buchi Sepacore, 0-20% diethyl ether in pet. ether 40-60^{o}C) afforded **342** as a colourless oil (47 mg, 26%); R_f (20% diethyl ether in pet. ether 40-60^{o}C) 0.83; δ_H (400 MHz, $CDCl_3$) 7.39-7.23 (m, 5H), 5.89-5.73 (m, 2H), 5.05-4.83 (m incl. app. d, $^2J_{H\text{-}F}$ = 46.0, 2H), 4.51 (s, 2H), 4.13-4.05 (m, 2H); δ_C (100 MHz, $CDCl_3$) 137.9, 131.0 (d, $^3J_{C\text{-}F}$ = 10.2), 128.5, 127.9, 127.8, 127.2 (d, $^2J_{C\text{-}F}$ = 19.4), 78.9 (d, $^1J_{C\text{-}F}$ = 159.4), 72.5, 65.7; δ_F (376 MHz, $CDCl_3$) (-212.7)-(-213.2) (m incl. app. t, $^2J_{F\text{-}H}$ = 46.0); ν_{max}(film)/cm^{-1} 2858, 1454, 1073, 973; *m/z* (EI) 180 (21), 136 (56), 105 (73), 91 (100); HRMS (EI, [M]$^+$) calcd. for $C_{11}H_{13}OF$ 180.0950, found 180.0950.

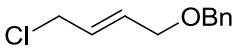
Preparation of *E*-1-fluoro-4-benzyloxy-but-2-ene 344 (major)



Allyl chloride **337** (2.1 mmol, 410 mg) was added to a stirred solution of TBAI (2 mmol, 750 mg) in dry THF and heated to and maintained at reflux for 4 hours. Commercial TBAF.$3H_2O$ was then added to the mixture and the solution heated to and maintained at reflux for a further 5 hours. The solution was then diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were then concentrated *in vacuo* to leave a clear a orange/brown oil. Purification by flash chromatography (Buchi Sepacore, 0-20% EtOAc in pet. ether 40-60^{o}C) afforded **344** as the major component (6:1, **344:342**) of a colourless oil (103mg, 28%); R_f (20% EtOAc in pet. ether 40-60^{o}C) 0.83; δ_H (400 MHz, $CDCl_3$) 7.36-7.22 (m, 5H), 5.94-5.86 (m, 2H), 4.92-4.73 (m incl. app. d. $^2J_{H-F}$ = 46.7, 2H), 4.50 (s, 2H), 4.07-4.00 (m, 2H); δ_C (100 MHz, $CDCl_3$) 138.1, 131.3 (d, $^3J_{C-F}$ =11.6), 128.4, 127.75, 127.7, 126.9 (d, $^2J_{C-F}$ =17.0), 82.7 (d, $^1J_{C-F}$ = 163.1), 72.4, 69.5; δ_F (376 MHz, $CDCl_3$) (-212.7)-(-213.2) (m incl. app. t, $^2J_{F-H}$ = 46.7); ν_{max}(film)/cm^{-1} 2855, 1454, 1360, 1103, 968; *m/z* (EI) 180 (1), 136 (3), 105 (10), 91 (100); HRMS (EI, $[M]^+$) calcd. for $C_{11}H_{13}OF$ 180.0950, found 180.0950; and allyl alcohol as colourless oil (105mg, 29%); R_f (20% EtOAc in pet. ether 40-60^{o}C) 0.22; δ_H (400 MHz, $CDCl_3$) 7.36-7.23 (m, 5H), 5.92-5.71 (m, 2H), 4.50 (s, 2H), 4.12-3.98 (m, 4H); δ_C (100 MHz, $CDCl_3$) 138.2, 132.5, 128.4, 127.8, 127.7, 127.5, 72.3, 70.2, 62.7; ν_{max}(film)/cm^{-1} 3372 (br), 2856, 1454, 1361, 1092, 969; *m/z* (EI) 178 (1), 160 (1), 134 (2), 107 (12); HRMS (EI, $[M]^+$) calcd. for $C_{11}H_{14}O_2$ 178.0994, found 178.0994.

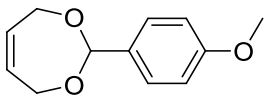
Preparation of 4-benzyloxy-1-chloro-*E*-but-2-ene 345 (major)

[Reaction of with TBAI]



Allyl chloride **337** (6.6 mmol, 1.29 g) was added to a solution of TBAI (4.8 g ,13 mmol) in dry THF (80 mL) and heated to and maintained at reflux for 12 hours. A colour change form colourless to orange was observed. The mixture was then diluted with diethyl ether (20 mL), filtered and concentrated *in vacuo* to afford a pale orange oil. Kugelrohr distillation (62-65^{o}C/0.09 mmHg) afforded the allyl chloride **345** as the major product of an inseparable mixture of isomers (**345**:**337**:**346** = 6:1:1) (1.23 g, 95% yield); R_f (20% EtOAc in pet. ether 40-60^{o}C) 0.83; δ_H (400 MHz, $CDCl_3$) 7.40-7.24 (m, 5H), 5.95-5.77 (m, 2H), 4.52 (s, 2H), 4.13-3.99 (m, 4H); δ_C (100 MHz, $CDCl_3$) 138.1, 131.2, 128.5, 128.4, 127.8, 127.7, 72.9, 65.5, 44.4; ν_{max}(film)/cm^{-1} 1454, 1361, 1111; *m/z* (EI) 196 (1), 161 (2), 126 (4), 105 (8); HRMS (EI, $[M]^+$) calcd. for $C_{11}H_{13}OCl$ 196.0655, found 196.0654.

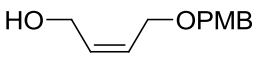
Preparation of 2-(4-methoxyphenyl)-4,7-dihydro-1,3-dioxepine 352



A mixture of *p*-anisaldehyde (95 mmol, 12.9 g), *cis*-2-butene-1,4-diol **321** (113 mmol, 21.6 g) and TsOH (0.22 mmol, 42 mg) in toluene was refluxed with azeotropic (Dean-Stark) removal of water overnight. The resulting dark brown mixture was then cooled and washed with water (3 x 100 mL) and then brine (100 mL). The organic layer was then isolated, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting orange oil **352** (9.5 g, 48%) was used in the next step

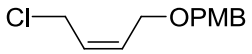
without further purification. The following data were obtained from a small purified sample; R_f (20% EtOAc in pet. ether 40-60^{o}C) 0.59; δ_H (400 MHz, $CDCl_3$) 7.45 (d, *J* = 8.6, 2H), 6.90 (d, *J* = 8.6, 2H), 5.83 (s, 1H), 5.76 (t, *J* = 1.8, 2H), 4.43-4.20 (m, 4H), 3.81 (s, 3H); δ_C (100 MHz, $CDCl_3$) 160.1, 131.6, 130.3, 128.1, 113.9, 102.4, 64.8, 55.6; ν_{max}(film)/cm^{-1} 1513, 1445, 1034; *m/z* (EI) 206 (3), 160 (27), 147 (18), 136 (46) 135 (100); the data were in agreement with those reported by Williams *et al.*[221]

Preparation of (Z)-4-(4-methoxybenzyloxy)but-2-en-1-ol 353



DIBAL-H (4.6 mL of a 1.1M solution in cyclohexane) was added dropwise to a solution of dioxepin **352** (1.0 g, 4.9 mmol) at 0^{o}C. The mixture was then allowed to slowly warm to room temperature with stirring overnight. The solution was then diluted with methanol (10 mL) and NaOH (20 mL of a 5% aqueous solution) and extracted with ether (3 x 15 mL). The combined organic extracts were then washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford **353** as a pale yellow oil (948 mg, 93%) which was used in the next step without any further purification; R_f (20% EtOAc in pet. ether 40-60^{o}C) 0.10; δ_H (400 MHz, $CDCl_3$) 7.23 (d, *J* = 8.8, 2H), 6.85 (d, *J* = 8.8, 2H), 5.86-5.62 (m, 2H), 4.46 (s, 2H), 4.12-4.03 (m, 4H), 3.80 (s, 3H), 2.01 (s (br), 1H); δ_C (100 MHz, $CDCl_3$) 159.7, 132.7, 130.3, 129.9, 128.7, 114.2, 72.6, 65.7, 59.1, 56.7; ν_{max}(film)/cm^{-1} 3446 (br), 2956, 2838, 1612, 1514, 1464, 1034; *m/z* (EI) 207 (1), 138 (38), 136 (19), 122 (14), 121 (100), 77 (24); The data were in agreement with those reported by Williams *et al.*[221]

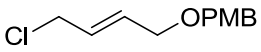
Preparation of (*Z*)-chloro-4-(*p*-methoxybenzyloxy)but-2-ene 354



Mesyl chloride (4.8 mmol, 373 μL) was added at 0°C to a stirred solution of allyl alcohol **353** (2 mmol, 416 mg), 2,4,6-trimethylpyridine (2 mmol, 265 μL) and dry LiCl (4 mmol, 170 mg) in dry DMF and the mixture allowed to stir overnight. The mixture was then quenched with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were then washed with $NaHCO_3$ (5 mL of a saturated solution), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60°C) afforded **354** as a colourless oil (279mg, 62%); R_f (20% EtOAc in pet. ether 40-60°C) 0.62; δ_H (400 MHz, $CDCl_3$) 7.26 (d, J = 8.8, 2H), 6.88 (d, J = 8.8), 5.82-5.72 (m, 2H), 4.44 (s, 2H), 4.14-4.06 (m, 4H), 3.80 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.3, 130.9, 130.3, 129.5, 128.4, 114.2, 72.1, 64.8, 55.6, 39.6; ν_{max}(film)/cm^{-1} 2935, 2837, 1611, 1511, 1245, 1033; *m/z* (EI) 191 (10), 161 (5), 136 (13), 121 (100); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{15}O_2Cl$ 226.0761, found 226.0761.

Preparation of (*E*)-chloro-4-(*p*-methoxybenzyloxy)but-2-ene 358 (major)

TBAI Inversion

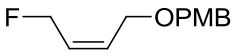


A solution of allyl chloride **354** (3.5 mmol, 793 mg) in dry THF (40 mL) was added to TBAI (7.4 mmol, 2.7 g) under an atmosphere of nitrogen and the mixture heated to and maintained at reflux overnight. Analysis (^1H NMR) of a reaction aliquot revealed the **358:354** ratio to be approximately 1:1. More TBAI (1.87 mmol, 675 mg) was added and the mixture heated to and maintained at reflux overnight once

again. Analysis (^{1}H NMR) of a reaction aliquot revealed the **358:354** ratio to be approximately 7:1. The reaction mixture was then cooled, diluted with Et_2O (40 mL) filtered and the precipitate washed with EtOAc (30 mL). The filtrate was then concentrated *in vacuo* to yield an orange oil. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^{o}C) afforded allyl chlorides **358** as the major component of an inseparable mixture of isomers (**358:354** = 7:1) as a colourless oil (635 mg, 80%); R_f (25% Et_2O in pet. ether 40-60^{o}C) 0.61; δ_H (400 MHz, $CDCl_3$) 7.26 (d, J = 8.7, 2H), 6.88 (d, J = 8.7, 2H), 5.91-5.86 (m, 2H), 4.45 (s, 2H), 4.08-4.05 (m, 2H), 3.80 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.3, 131.4, 130.1, 129.4, 128.3, 113.8, 72.1, 69.2, 55.3, 44.4; ν_{max}(film)/cm^{-1} 2954, 2837, 1612, 1512, 1033; *m/z* (EI) 191 (12), 136 (16), 135 (14), 121 (100), 109 (10); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{15}O_2Cl$ $C_{12}H_{15}O_2Cl$ 226.0761, found 226.0761.

Preparation of (*Z*)-fluoro-4-(*p*-methoxybenzyloxy)but-2-ene 359

TBAF.3H$_2$O/KHF$_2$ method



Allyl chloride **354** (2.5 mmol, 557 mg) was added to a stirred solution of commercial TBAF.3H_2O (5 mmol, 1.58 g) in THF (20 mL) and heated to and maintained at reflux for 6 hours with stirring. The cooled solution was then diluted with water (20 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were concentrated *in vacuo* to leave a pale brown oil. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^{o}C) afforded **359** as a colourless oil (267 mg, 51%). Note: yields and quality of product varied greatly using TBAF.3H_2O in the preparation of **359**; R_f (20% Et_2O in pet. ether 40-60^{o}C)

0.61; δ_H (400 MHz, $CDCl_3$) 7.26 (d, J = 8.7, 2H), 6.88 (d, J = 8.7, 2H), 5.88-5.73 (m, 2H), 5.04-4.84 (m incl. app. d, $^2J_{H\text{-}F}$ = 46.0, 2H) 4.43 (s, 2H), 4.11-4.01 (m, 2H), 3.79 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.3, 131.1 (d, $J_{C\text{-}F}$ = 10.2), 130.0, 129.5, 127.1 (d, $^2J_{C\text{-}F}$ = 19.4), 113.9, 78.9 (d, $^1J_{C\text{-}F}$ = 159.3), 72.1, 65.3, 55.3; δ_F (376 MHz, $CDCl_3$) (-212.7)-(-213.2) (m incl. app. t, $^2J_{F\text{-}H}$ = 46.0); ν_{max}(film)/cm^{-1} 2838, 1612, 1512, 1464, 1245, 1033; *m/z* (EI) 210 (5), 179 (4), 136 (19), 135 (17), 122 (21), 121 (100), 77 (25); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{15}O_2F$ 210.1056, found 210.1056.

Preparation of (*Z*)-fluoro-4-(*p*-methoxybenzyloxy)but-2-ene 359

$KF.2H_2O$, Bu_4NHSO_4 method

A solution of allyl chloride **354** (3.5 mmol, 800 mg) in acetonitrile (35 mL) was added to a mixture of $KF.2H_2O$ (14 mmol, 1.3 g) and Bu_4NHSO_4 (4.2 mmol, 1.4 g) and the resulting mixture heated to and maintained at reflux for 15 hours. Analysis (GCMS) of a reaction aliquot showed conversion was incomplete, product:starting material = 1:1. $KF.2H_2O$ (14 mmol, 1.3 g) and Bu_4NHSO_4 (4.2 mmol, 1.4 g) were added to the mixture and the reaction heated to and maintained at reflux for 24 hours. Analysis (GCMS) of a reaction aliquot showed conversion was incomplete, product:starting material = 3:1. $KF.2H_2O$ (14 mmol, 1.3 g) and Bu_4NHSO_4 (4.2 mmol, 1.4 g) were added to the mixture and the reaction heated to and maintained at reflux for a further 24 hours. Analysis (GCMS) of a reaction aliquot showed conversion was complete. The cooled solution was then diluted with water (20 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were concentrated *in vacuo* to leave a pale brown oil. Purification by flash

chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^oC) afforded **359** as a colourless oil (542 mg, 74%).

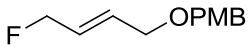
Preparation of (*Z*)-fluoro-4-(*p*-methoxybenzyloxy)but-2-ene 359

TBAF.*t*BuOH$_4$ method

TBAF. *t*BuOH$_4$ (1.68 mmol, 908 mg) was added to a solution of allyl chloride **354** (0.66 mmol, 150 mg) in acetonitrile (3 mL) and the mixture allowed to stir at 70^oC for 1 hour. An instant colour change from colourless to orange/brown was observed. The cooled mixture was then diluted with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^oC) afforded **359** as a colourless oil (72 mg, 52%).

Preparation of (*E*)-fluoro-4-(*p*-methoxybenzyloxy)but-2-ene 332 (major)

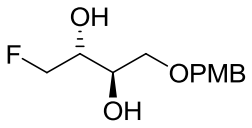
TBAF.*t*BuOH$_4$ method



TBAF.*t*BuOH$_4$ (7.4 mmol, 4 g) was added to a 7:1 solution of allyl chlorides **358:354** (3.5 mmol, 791 mg) in acetonitrile (15 mL) and the mixture allowed to stir at 70^oC for 1 hour. An instant colour change from colourless to orange/brown was observed. The cooled mixture was then diluted with water (15 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^oC) afforded **332** as

the major component (**332:359**, 7:1) of a colourless oil (346 mg, 47%); R_f (20% Et_2O in pet. ether 40-60^oC) 0.61; δ_H (400 MHz, $CDCl_3$) 7.25 (d, J = 8.8, 2H), 6.85 (d, J = 8.8, 2H), 5.96-5.84 (m, 2H), 4.82 (m incl. app. d, J = 46.0, 2H), 4.43 (s, 2H), 4.04-3.97 (m, 2H), 3.74 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.3, 131.5 (d, $^3J_{C-F}$ = 11.6), 130.2, 129.4, 126.9 (d, $^2J_{C-F}$ = 16.9), 113.8, 82.8 (d, $^1J_{C-F}$ = 162.9), 72.1, 69.3, 55.3; δ_F (376 MHz, $CDCl_3$) (-212.7)-(-213.1) (m, incl. app. t, $^2J_{F-H}$ = 46.0); ν_{max}(film)/cm^{-1} 2937, 2838, 1612, 1512, 1245, 1033; *m/z* (EI) 210 (8), 179 (6), 136 (30), 135 (27), 122 (22), 121 (100), 77 (29); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{15}O_2F$ 210.1056, found 210.1058.

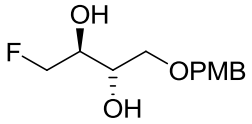
Preparation of (2*R*,3*R*)-1-Fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 363



A solution of AD-mix α (1.34 g), $(DHQ)_2PHAL$, (0.04 mmol, 30 mg), $K_2OsO_4.2H_2O$ (0.006 mmol, 2 mg), $NaHCO_3$ (2.88 mmol, 242 mg) in a mixture of *t*-BuOH and water (14 mL, 1:1 v/v) was cooled to 0^oC and allowed to stir for ca. 30 mins until a homogenous deep orange colour was observed. Allyl fluoride **359** (0.96 mmol, 200 mg) was then added in one portion and the mixture was allowed to stir at 0^oC for 15 hours (reaction completion was confirmed by micro work-up and analysis by ^{19}F NMR). A colour change from orange to brilliant yellow was observed. The reaction was quenched by the addition of solid sodium sulfite (1.5 g) and allowed to warm to room temperature. Water (10 mL) was then added and the suspension extracted with ethyl acetate (3 x 10mL). The combined organic extracts were then

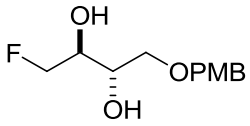
washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 100% Et_2O) afforded diol **363** as a colourless oil (181 mg, 77%); R_f (100% Et_2O in pet. ether 40-60^oC) 0.47; δ_H (400 MHz, $CDCl_3$) 7.24 (d, J = 8.8, 2H), 6.88 (d, J = 8.8, 2H), 4.67-4.48 (m, 4H), 3.94-3.55 (m, 4H), 3.79 (s, 3H), 2.55 (br.s, 2H); δ_C (100 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.5 (d, $^1J_{C\text{-}F}$ = 167.3), 73.3, 71.4 (d, $^2J_{C\text{-}F}$ = 18.8), 70.8, 69.9 (d, $^3J_{C\text{-}F}$ = 6.2), 55.3; δ_F (376 MHz, $CDCl_3$) (-233.9)-(-233.4) (m); ν_{max}(film)/cm^{-1} 3413 (br), 2911, 1612, 1513, 1245, 1075, 1030; *m/z* (EI) 244 (4), 159 (2), 78 (22), 121 (100); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{17}O_4F$ 244.1110, found 244.1110; $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 30% ee.

(2*S*,3*S*)-1-Fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 364



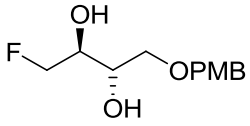
Diol **364** was prepared from allyl fluoride **359** (0.96 mmol, 200 mg), AD-mix β (1.34 g), $(DHQD)_2PHAL$, (0.04 mmol, 30 mg), $K_2OsO_4.2H_2O$ (0.006 mmol, 2 mg), $NaHCO_3$ (2.88 mmol, 242 mg) in a mixture of *t*-BuOH and water (14 mL, 1:1 v/v) according to the procedure described previously. Purification by flash chromatography (Buchi Sepacore, 100% Et_2O) afforded the desired product **364** as a colourless oil (210 mg, 90%); Data were identical to those described previously for **363** apart from $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 44% ee.

Preparation of 1-Fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 364(±)



A solution of NMO (0.6 mmol, 70 mg) in water (0.3 mL) was added to a solution of *t*-BuOH and acetone (1 mL of a 1:1 mixture) at 0°C. Allyl fluoride **359** (0.3 mmol, 63 mg) was then added in one portion, the mixture allowed to stir for 15 minutes and then OsO_4 (61 μL of a 2.5% wt solution in *t*-BuOH) was added dropwise by syringe. The mixture was allowed to continue stirring and slowly warm to room temperature overnight. The reaction was quenched by the addition of sodium sulfite (500 mg) and diluted with water (4 mL). The aqueous solution was then extracted with EtOAc (2 x 4 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford racemate **364(±)** as an orange gum that was used without purification (69 mg, 94%).

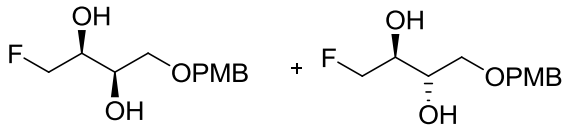
Preparation of (2*S*,3*S*)-1-Fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 364 (AQN ligand)



A solution of $K_3Fe(CN)_6$ (1.05 mmol, 342 mg), K_2CO_3 (1.05 mmol, 143 mg), $MeSO_2NH_2$ (0.35 mmol, 33 mg), $(DHQD)_2AQN$, (0.018 mmol, 15 mg), $K_2OsO_4.2H_2O$ (0.0035 mmol, 1.5 mg) in a mixture of *t*-BuOH and water (4 mL, 1:1 v/v) was cooled to 0°C and allowed to stir for ca. 30 mins until a homogenous deep orange colour was observed. Allyl fluoirde **359** (0.35 mmol, 72 mg) was then added

in one portion and the mixture was allowed to stir at 0°C for 15 hours (reaction completion was confirmed by micro work-up and analysis by ^{19}F NMR). The reaction was quenched by the addition of solid sodium sulfite (500 mg) and allowed to warm to room temperature. A colour change from yellow to grey was observed. Water (10 mL) was then added and the suspension extracted with ethyl acetate (3 x 10mL). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 1% methanol in 1:1 ethyl acetate/hexane) afforded the diol **364** as a colourless oil (51 mg, 60%); $\delta_{F[1H]}$ (376 MHz, 3:1 diisopropyl L-tartrate:$CDCl_3$) 18% ee.

Preparation of (2*S*,3*R*)-1-fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 366 (major)

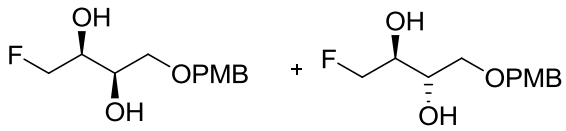


13:2

A solution of AD mix β (1.11 g), $(DHQD)_2PHAL$ (0.032 mmol, 25 mg), $K_2OsO_4.2H_2O$ (0.005 mmol, 2 mg), $NaHCO_3$ (2.4 mmol, 201 mg) and $MeSO_2NH_2$ (0.8 mmol, 75 mg) in a mixture of *t*-BuOH and water (10 mL, 1:1 v/v) was cooled to 0°C and allowed to stir for ca. 30 mins until a homogenous deep orange colour was observed. A 7:1 mixture of allyl fluorides **332:359** (0.8 mmol, 170 mg) was then added in one portion and the mixture allowed to stir at 0°C for 15 hours (reaction completion was confirmed by micro work-up and analysis by ^{19}F NMR). The

reaction was quenched by the addition of solid sodium sulfite (1.5 g) and allowed to warm to room temperature. Water (10 mL) was then added and the suspension was extracted with ethyl acetate (3 x 10mL). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Buchi Sepacore, 1% methanol in 1:1 ethyl acetate/hexane) afforded diol **366** (as the major component of a 13:2 mixture of **366** and **364**) as a colourless oil (141 mg, 98%); R_f (35% EtOAc in pet. ether 40-60^{o}C) 0.17; δ_H (400 MHz, $CDCl_3$) 7.24 (d, J = 8.8, 2H), 6.88 (d, J = 8.8, 2H), 4.47 (s, 2H), 4.46 (ddd, $^2J_{H-F}$ = 47.2, J = 9.6, J = 4.9, 1H), 4.42 (ddd, $^2J_{H-F}$ = 47.2, J = 9.6, J = 5.7, 1H), 3.94-3.74 (m, 2H), 3.79 (s, 3H), 3.62-3.53 (m, 2H), 2.88 (br d, 1H), 2.81 (br d, 1H); δ_C (100 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.0 (d, $^1J_{C-F}$ = 168.9), 73.3, 71.5, 70.7 (d, $^2J_{C-F}$ = 20.0), 69.3 (d, $^3J_{C-F}$ = 5.8), 55.3; δ_F (376 MHz, $CDCl_3$) – 230.4 (td, $^2J_{F-H}$ = 47.2, J = 16.6); ν_{max}(film)/cm^{-1} 3455 (br), 2928, 2878, 1610, 1514, 1247, 1088, 1028; *m/z* (EI) 244 (4), 121 (100), 77 (13); HRMS (EI, $[M]^+$) calcd. for $C_{12}H_{17}O_4F$ 244.1110, found 244.1110; $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 84% ee, 13:2 dr.

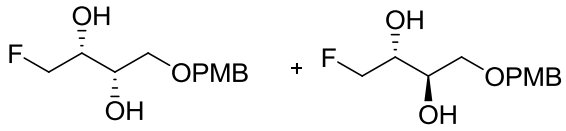
Preparation of (2*S*,3*R*)-1-Fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 366 (major) AQN ligand



13:2

Diol **366** was prepared from a 7:1 mixture of olefins **332:359** (168 mg, 0.8 mmol), $K_3Fe(CN)_6$ (2.4 mmol, 790 mg), K_2CO_3 (2.4 mmol, 331 mg), $(DHQD)_2AQN$, (0.08 mmol, 7 mg), $K_2OsO_4.2H_2O$ (0.032 mmol, 1 mg) in a mixture of *t*-BuOH and water (10 mL, 1:1 v/v) according to the procedure described previously. Purification by flash chromatography (Buchi Sepacore, 1% methanol in 1:1 ethyl acetate/hexane) afforded diol **366** (as the major component of a 13:2 mixture of **366** and **364**) (152 mg, 78%); Data were identical to those described previously for **366** apart from $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) ~21% ee, 13:2 dr.

Preparation of (2*R*,3*S*)-1-fluoro-4-(4-methoxybenzyloxy)butane-2,3-diol 365 (major)

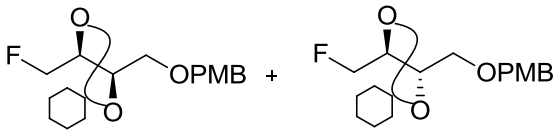


13:2

Diol **365** was prepared from a 7:1 mixture of olefins **332:359** (567 mg, 2.7 mmol), AD mix α (3.78 g), $(DHQ)_2PHAL$ (0.11 mmol, 84 mg), $K_2OsO_4.2H_2O$ (0.02 mmol, 6 mg), $NaHCO_3$ (8.1 mmol, 680 mg) and $MeSO_2NH_2$ (2.7 mmol, 253 mg) in a mixture of *t*-BuOH and water (30 mL, 1:1 v/v) according to the procedure described

previously. Purification by flash chromatography (Buchi Sepacore, 1% methanol in 1:1 ethyl acetate/hexane) afforded diol **365** (as the major component of a 13:2 mixture of **365** and **363**) as a colourless oil (606 mg, 92%); Data were identical to those described previously for **363** apart from $\delta_{F[1H]}$ (376 MHz, 1:1 diisopropyl L-tartrate:$CDCl_3$) 79% ee, 13:2 dr.

Preparation of cyclohexylidenes 333 and 367



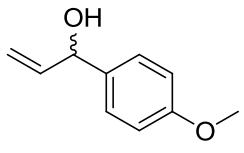
333 **367**

A 13:2 mixture of diols **366** and **364** (0.67 mmol, 161 mg) was added to a solution of copper sulfate (0.8 mmol, 130 mg), cyclohexanone (1.7 mmol, 165 mg) and *p*-toluenesulfonic acid (0.034 mmol, 6 mg) in THF (4 mL) and the mixture heated to and maintained at reflux overnight. The reaction mixture was then cooled, washed through a plug of silica with EtOAc (10 mL) and DCM (15 mL) and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^oC) afforded a colourless oil (72 mg, 33%, 6:1 **333:367** by ^{19}F NMR). A second purification by flash chromatography (Buchi Sepacore, 0-30% EtOAc in pet. ether 40-60^oC) afforded the *syn* isomer **333** (12 mg) as a colourless oil and an enriched mixture (51 mg) of the *syn* **333** and *anti* **367** (8:1); R_f (35% EtOAc in pet. ether 40-60^oC) 0.63; δ_H (400 MHz, $CDCl_3$) 7.29-7.21 (m, 2H), 6.88 (m incl. app. d, J = 8.6, 2H), 4.56 (ddd, $^2J_{H\text{-}F}$ = 47.3, J = 10.1, J = 2.8, 1H), 4.51

(s, 2H), 4.44 (ddd, $^{2}J_{H\text{-}F}$ = 47.3, J = 10.1, J = 4.5, 1H), 4.11-3.97 (m, 2H), 3.80 (s, 3H), 3.65 (dd, J = 10.1, J = 4.5, 1H), 3.54 (dd, J = 10.1, J = 5.1, 1H), 1.67-1.33 (env., 10H); δ_C (100 MHz, $CDCl_3$) 159.3, 130.0, 129.3, 113.8, 110.6, 82.8 (d, $^{1}J_{C\text{-}F}$ = 173.0), 77.5 (d, $^{2}J_{C\text{-}F}$ = 19.5), 75.0 (d, $^{3}J_{C\text{-}F}$ = 6.7), 73.3, 70.3, 55.3, 36.6, 36.3, 25.1, 23.9, 23.8; δ_F (376 MHz, $CDCl_3$) – 228.9 (tdd, $^{2}J_{F\text{-}H}$ = 47.3, J = 16.6, J = 3.0); ν_{max}(film)/cm^{-1} 2935, 2861, 1612, 1513, 1246, 1087, 1033; HRMS (EI, $[M]^{+}$) calcd. for $C_{18}H_{25}O_4F$ 324.1737, found 324.1737; *m/z* (EI) 175 (7), 136 (12), 121 (100).

Preparation of 1-(4-methoxyphenyl)prop-2-en-1-ol 383

(Iodine activation)

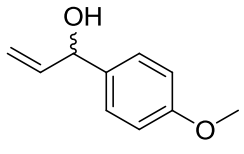


Vinyl bromide (78 mmol, 8.31 g) was condensed into a cooled (-78^{o}C) solution of THF (75 mL) using a dry ice condenser. A portion of the resulting vinyl bromide solution (~30 mL) was then cannulated onto magnesium turnings (93.6 mmol, 2.28 g). Iodine (2-3 pellets) was then added and the resulting mixture was heated with a heat gun until initiation of the reaction. The temperature of the reaction was balanced at reflux by the addition of more vinyl bromide solution and the periodic application of an ice bath. Upon completion of the addition of the vinyl bromide solution, the reaction was allowed to reflux under its own heat until it reached room temperature again. The reaction mixture was then cooled to 0^{o}C and anisaldehyde (86 mmol, 10.2 mL) was added dropwise over 20 minutes. The solution was then allowed to stir for 2.5 hours while slowly warming to room temperature. The reaction was quenched with ammonium chloride (100 mL of a saturated solution) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were then washed with NH_4Cl (2 x 100 mL) then brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 0-30% Et_2O in pet. ether 40-60^{o}C) afforded alcohol **383** as a pale yellow oil (2.19 g, 17%); R_f (25% EtOAc in pet. ether 40-60^{o}C) 0.27; δ_H (400 MHz, $CDCl_3$) 7.31 (d, J = 8.6, 2H), 6.90 (d, J = 8.6, 2H), 6.10-6.02 (m, 1H), 5.34 (dt, J = 17.2, J = 1.5, 1H), 5.20 (dt, J = 10.6, J = 1.5,

1H), 5.19-5.15 (br, 1H), 3.81 (s, 3H). The data were in agreement with those reported by Liu *et al*.[255]

Preparation of 1-(4-methoxyphenyl)prop-2-en-1-ol 383

(Stirring under nitrogen atmosphere activation)

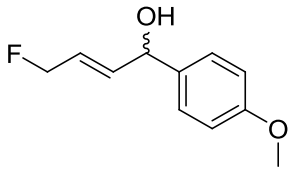


Vinyl bromide (140 mmol, 14.79 g) was condensed into a cooled (-78^{o}C) solution of THF (100 mL) using a dry ice condenser. A portion of the resulting vinyl bromide solution (~30 mL) was then cannulated on to magnesium turnings (154 mmol, 4.0 g) that had been allowed to stir under an atmosphere of nitrogen for 5 hours (black coating on metal observed). The resulting mixture was carefully heated with a heat gun until initiation of the reaction. . The temperature of the reaction was balanced at reflux by the addition of more vinyl bromide solution and the periodic application of an ice bath. Upon completion of the addition of the vinyl bromide solution, the reaction was allowed to reflux under its own heat until it reached room temperature again. The reaction mixture was then cooled to 0^{o}C and anisaldehyde (154 mmol, 18.3 mL) added dropwise. The solution was then allowed to stir for 2.5 hours while slowly warming to room temperature. The reaction was quenched with ammonium chloride (150 mL of a saturated solution) and extracted with Et_2O (2 x 150 mL). The combined organic extracts were then washed with NH_4Cl (2 x 150 mL) then brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by

flash chromatography (Buchi Sepacore, 0-30% Et_2O in pet. ether 40-60^oC) afforded alcohol **383** as a pale yellow oil (20.41 g, 88%).

Preparation of (*E*)-4-fluoro-1-(4-methoxyphenyl)but-2-en-1-ol 388

Initial Exploration Conditions



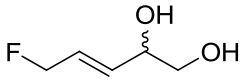
370 (0.02 mmol, 12 mg) was weighed into a carousel tube under nitrogen and the carousel tube cooled to -78^oC (dry ice/acetone bath). Allyl fluoride **381** (~19 mmol, 1.14 g) was then condensed into the base of the vessel from a balloon *via* a long needle. The mixture was allowed to stir at -78^oC for one hour and the vessel was then warmed to -20^oC (ice/salt bath). A solution of terminal alkene **383** (1 mmol, 164 mg) in degassed DCM (5 mL) was then added dropwise over 2 hours. The reaction mixture was then allowed to warm to room temperature overnight while stirring under an atmosphere of nitrogen (colour change from pale green to dark green/black observed). The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 20-50% Et_2O in pet. ether 40-60^oC) afforded **388** as a pale orange oil (145 mg, 74%); R_f (25% EtOAc in pet. ether 40-60^oC) 0.29; δ_H (400 MHz, $CDCl_3$) 7.31 (d, J = 8.6, 2H), 6.90 (d, J = 8.6, 2H), 6.10-5.90 (m, 2H), 5.22 (br s, 1H), 4.90 (dd, J = 47.0, J = 4.0, 1H), 4.89 (dd, J = 47.0, J = 5.6, 1H), 3.80 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.4, 136.7 (d, $^3J_{C\text{-}F}$ = 10.2), 127.7, 124.9 (d, $^2J_{C\text{-}F}$ = 17.6), 114.1, 113.9, 82.7 (d, $^1J_{C\text{-}F}$ = 163.9), 73.6, 55.3; δ_F (376 MHz, $CDCl_3$) (–213.0)-(-213.5) (m incl. app. t, $^2J_{F\text{-}H}$ = 47.0); ν_{max}(film)/cm^{-1} 3309 (br), 2957, 2838, 1610, 1512, 1303, 1175, 1075, 832. A satisfactory mass spectrum

(containing M^+) could not be acquired for this compound (by standard GC-MS, GC-MS with cold injection and EI).

Syringe method

370 (0.02 mmol, 12 mg) was weighed into a carousel tube under nitrogen and the carousel tube cooled to -78^{o}C (dry ice/acetone bath). Allyl fluoride **381** (48 mL, 2 mmol) was then condensed into the base of the vessel from a gas tight syringe *via* a long needle. The mixture was allowed to stir at -78^{o}C for one hour and the vessel was then warmed to -20^{o}C (ice/salt bath). A solution of terminal alkene **383** (1 mmol, 164 mg) in degassed DCM (5 mL) was then added dropwise over 2 hours. The reaction mixture was then allowed to warm to room temperature overnight while stirring under an atmosphere of nitrogen (colour change from pale green to dark green/black observed). The reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 20-50% Et_2O in pet. ether 40-60^{o}C) afforded **388** as a pale orange oil (38 mg, 21%).

Preparation of (*E*)-5-fluoropent-3-ene-1,2-diol 387

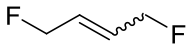


370 (0.02 mmol, 13 mg) was weighed into a carousel tube under nitrogen and the carousel tube cooled to -78^{o}C (dry ice/acetone bath). Allyl fluoride **381** (~22 mmol, 1.32 g) was then condensed into the base of the vessel from a balloon *via* a long needle. The mixture was allowed to stir at -78^{o}C for one hour and the vessel was then warmed to -20^{o}C (ice/salt bath). A solution of terminal alkene **382** (1 mmol, 88 mg) in degassed DCM (5 mL) was then added dropwise over 2 hours. The reaction

mixture was then allowed to warm to room temperature overnight while stirring under an atmosphere of nitrogen (colour change from pale green to yellow/green observed and a white gum observed at the bottom of the vessel). The liquid reaction mixture was separated from the insoluble gum and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 100% Et_2O in pet. ether 40-60^oC) afforded a pale yellow oil **387** (68 mg, ~56% impurities still present); δ_H (400 MHz, $CDCl_3$) main peaks: 6.04-5.92 (m, 1H), 5.86-5.78 (m, 1H), 4.86 (dd, *J* = 47.0, *J* = 5.3), 4.28 (s, 1H), 3.70-3.64 (m, 1H), 3.50 (s, 1H), 3.10 (br s, 1H), 2.80 (br s, 1H); δ_F (376 MHz, $CDCl_3$) (-213.8)-(-214.2) (m incl. app. t, *J* = $^2J_{F-H}$ = 47.0). A satisfactory mass spectrum (containing M^+) could not be acquired for this compound (by standard GC-MS, GC-MS with cold injection and ESI).

The remaining white gum was washed with DCM and dried under reduced pressure. Analysis by NMR (^1H) confirmed this material to be the known tetrol **391**; δ_H (400 MHz, MeOD) 5.79-5.75 (m, 2H), 4.16-4.10 (m, 2H), 3.54-3.44 (m, 4H). Data in agreement with those reported by Belanger *et al.*[256]

Preparation of 1,4-difluorobut-2-ene 392



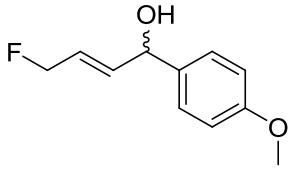
Allyl fluoride **381** (~14.1 mmol, 850 mg) was condensed into a carousel tube at -78^oC under an atmosphere of nitrogen. **369** (40 mg, 0.07 mmol) was then added in CD_2Cl_2 (0.75 mL) and the mixture allowed to stir under an atmosphere of nitrogen and warm to room temperature overnight. The reaction mixture was then analysed by NMR (^1H and ^{19}F) revealing a mixture of allyl fluoride **381** and difluorobutene **392**.

The NMR solution was then carefully distilled (Kugelrohr) to remove the catalyst, diluted with $CHCl_3$ and analysed by GCMS (split injection, 40^{o}C for 10 minutes).

Allyl fluoride; δ_H (400 MHz, CD_2Cl_2) 6.16-5.98 (m, 1H), 5.42 (br d, J = 17.4, 1H), 5.35-5.28 (m, 1H), 4.98-4.80 (m incl. app. d, J = 46.5, 2H); δ_C (100 MHz, CD_2Cl_2) 133.4 (d, $^2J_{C\text{-}F}$ = 17.4), 117.8 (d, $^3J_{C\text{-}F}$ = 11.7), 83.6 (d, $^1J_{C\text{-}F}$ = 162.5); δ_F (376 MHz, CD_2Cl_2) (-216.6)-(-217.2) (m); *m/z* 60 (30), 59 (78), 57 (15), 41 (12), 39 (42).

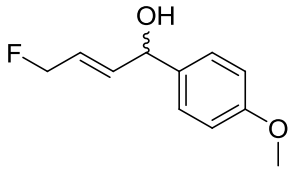
Difluorobutene; δ_H (400 MHz, CD_2Cl_2) 6.05-5.98 (m, 2H), 4.99-4.85 (m incl. app. d, J = 47.0, 4H), δ_F (376 MHz, CD_2Cl_2) -216.2 (tdd, $^2J_{F\text{-}H}$ = 47.0, J = 14.9, J = 4.6); *m/z* 92 (22), 77 (64), 59 (100), 46 (34), 39 (58).

Attempted synthesis of 388 using 368



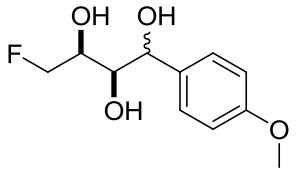
Allyl fluoride **381** (~1 g, 16.7 mmol) was condensed into a Radley's carousel tube at -78^{o}C. A solution of terminal alkene **383** (164 mg, 1 mmol) in degassed DCM (5 mL) was then added dropwise under an atmosphere of nitrogen. The reaction mixture was allowed to stir at this temperature for 15 minutes and then allowed to warm to -18 ^{o}C in an ice/salt bath. A solution of **368** (28 mg, 0.034 mmol) in degassed DCM (1 mL) was then added dropwise and the reaction mixture allowed to warm to room temperature overnight with stirring. The reaction mixture was then concentrated under reduced pressure and the residue analysed by ^{1}H and ^{19}F NMR. Analysis of the spectra revealed only unreacted SM **383**.

Attempted synthesis of 388 using 369



Allyl fluoride **381** (~1 g, 16.7 mmol) was condensed into a Radley's carousel tube at -78^{o}C. A solution of the terminal alkene **383** (164 mg, 1 mmol) in degassed DCM (5 mL) was then added dropwise under an atmosphere of nitrogen. The reaction mixture was allowed to stir at this temperature for 15 minutes and then allowed to warm to -18 ^{o}C in an ice/salt bath. A solution of **368** (28 mg, 0.034 mmol) in degassed DCM (1 mL) was then added dropwise and the reaction mixture allowed to warm to room temperature overnight with stirring. The reaction mixture was then concentrated under reduced pressure and the residue analysed by ^{1}H and ^{19}F NMR. Analysis of the spectra revealed difluorobutene **392** and unreacted SM **383**.

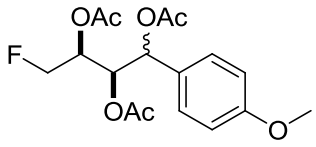
Preparation of triol 397



NMO (210 mg, 1.78 mmol) was added to a solution of alcohol **388** in *t*-BuOH and acetone (2 mL of a 1:1 mixture) at 0^{o}C. OsO_4 (180 μL of a 2.5% wt solution in *t*-BuOH) was added dropwise by syringe over 20 minutes. The mixture was allowed to continue stirring and slowly warm to room temperature overnight. The reaction was quenched by the addition of sodium sulfite (1 g) and filtered through a pad of celite

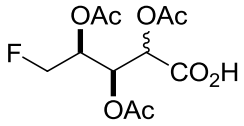
with MeOH/EtOAc (20 mL of a 1:1 mixture). The filtrate was concentrated under reduced pressure to yield **397** (5:2 mixture of diasteroisomers) as an orange oil (330 mg) which was used in the next step without further purification; δ_F (376 MHz, $CDCl_3$) (-225.9) (td, $^2J_{F\text{-}H}$ = 47.0, J = 10.3) and (-228.0)-(-228.4) (m).

Preparation of (1*R*,2*R*,3*S*)-4-fluoro-1-(4-methoxyphenyl)butane-1,2,3-triyl triacetate 398



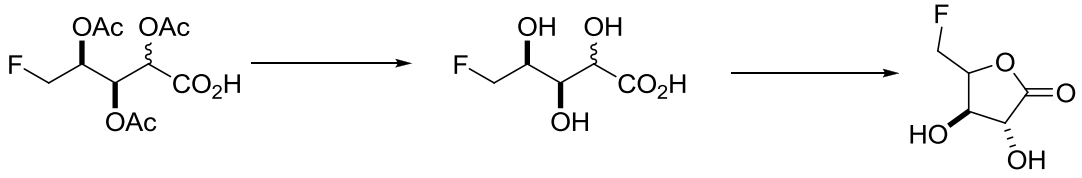
DMAP (6 mg, 0.047 mmol) and acetic anhydride (100 μL, 1.03 mmol) were added to a solution of triol **397** (109 mg, 0.47 mmol) in pyridine (1 mL) and the mixture was allowed to stir ar room temperature overnight. The reaction mixture was then diluted with water (5 mL) amd extracted with EtOAc (5 mL) and Et_2O (5 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (Buchi Sepacore, 20% Et_2O in pet. ether 40-60^{o}C) afforded **398** as a white solid (63mg, 38% yield); m.p. 93-95; δ_H (400 MHz, $CDCl_3$) 7.30 (d, J =8.6, 2H), 6.9 (d, J =8.6, 2H), 5.75 (d, J = 9.0, 1H), 5.60-5.50 (m, 2H), 4.45-4.30 (m, 2H), 3.80 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H), 1.88 (s, 3H); δ_C (100 MHz, $CDCl_3$) 170.1, 169.4, 169.35, 129.0, 128.2, 113.8, 81.6 (d, $^1J_{C\text{-}F}$ = 175.6), 71.4, 68.8, 68.6, 55.2, 21.0, 20.8, 20.4; δ_F (376 MHz, $CDCl_3$) -213.1 (td, $^2J_{F\text{-}H}$ = 47.0, J = 16.1) $\nu_{max}(CDCl_3)/cm^{-1}$ 2948 (br), 2846, 1747, 1180, 1055; A satisfactory mass spectrum (containing M^+) could not be acquired for this compound.

Preparation of (2*S*,3*R*,4*S*)-2,3,4-triacetoxy-5-fluoropentanoic acid 399



Periodic acid (550 mg, 2.41 mmol) was added to a solution of **398** (60 mg, 0.17 mmol) in CCl_4/CH_3CN/water (1.5 mL of a 1:1:1 mixture) at 0°C. A drop of $RuCl_3$ was then added and the mixture allowed to stir at this temperature for 4 hours. The reaction mixture was then diluted with water (5 mL) and extracted with ether (3 x 5 mL). Combined organic extracts were then washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield **399** (31 mg, 62%) as a purple oil; δ_H (400 MHz, $CDCl_3$) 5.62 (t, *J* = 5.3, 1H), 5.51-5.42 (m, 1H), 5.26 (d, *J* = 5.3, 1H), 4.70-4.48 (m, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H); δ_F (376 MHz, $CDCl_3$) (-231.27)-(-231.33) (m); *m/z* (EI^+) 611 (50), 408 (15), 331 (8), 312 (100), 280 (10); HRMS (ES^+, $[M + NH_4]^+$) calcd. for $C_{11}H_{15}FO_8NH_4$ 312.1089, found 312.1094.

Attempted deactylation of 399 and lactonisation to 401



Solid K_2CO_3 (2 mg, 0.01 mmol) was added to a solution of **399** (30 mg, 0.1 mmol) in MeOH (3 mL) at 0°C. The mixture was allowed to stir overnight while warming to room temperature. The reaction mixture was then concentrated under reduced

pressure and the residue analysed electrospray; *m/z* (EI^+) 237 (30%), 219 (100), 151 (40); (EI^-) 167 (20).

The residue was then diluted with MeOH and the mixture allowed to reach reflux. A catalytic quantity (tip of a spatula) of *p*TsOH was then added and the mixture allowed to stir at reflux overnight. The reaction mixture was then concentrated under reduced pressure. NMR analysis suggested decomposition (several peaks in ^{19}F NMR) and a satisfactory mass spectrum (containing M^+) could not be acquired.

Synthesis of 388 with recycled 392

370 (0.02 mmol, 12 mg) was weighed into a carousel tube under nitrogen and the carousel tube cooled to -78^{o}C (dry ice/acetone bath). Allyl fluoride **381** (~19 mmol, 1.14 g) was then condensed into the base of the vessel from a balloon *via* a long needle. The mixture was allowed to stir at -78^{o}C for one hour and the vessel was then warmed to -20^{o}C (ice/salt bath). A solution of terminal alkene **383** (1 mmol, 164 mg) in degassed DCM (5 mL) was then added dropwise over 2 hours. The reaction mixture was then allowed to warm to room temperature overnight while stirring under an atmosphere of nitrogen (colour change from pale green to dark green/black observed). The reaction mixture was then evaporated *via* Kugelrohr at reduced pressure (20^{o}C/ 23 mmHg). Purification of the resulting residue by flash chromatography (Buchi Sepacore, 20-50% Et_2O in pet. ether 40-60^{o}C) afforded **388** as a pale orange oil (121 mg, 62%).

The distillate (a solution of difluorobutene **392** in DCM) was dried ($MgSO_4$), filtered through cotton wool and added to **370** (0.02 mmol, 12 mg) in a carousel tube under nitrogen at -78^{o}C (dry ice/acetone bath). A solution of terminal alkene **383** (1 mmol,

164 mg) in degassed DCM (5 mL) was then added dropwise over 2 hours. The reaction mixture was then allowed to warm to room temperature overnight while stirring under an atmosphere of nitrogen. The reaction mixture was then concentrated under vacuum. Purification by flash chromatography (Buchi Sepacore, 20-50% Et_2O in pet. ether 40-60^oC) afforded **388** and **383** as an inseparable mixture (72 mg, 37%).

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