Total Synthesis of Conformationally-locked Difluorinated Pento- and Hexopyranose Analogues, and Pentopyranosyl Phosphate Mimetics

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By

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Other Work

Sections of this thesis have been presented at the following meetings.

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"Difluorinated Cyclooctenones as Templates for the Synthesis of Conformationally-locked Analogues of Sugars" (poster 2) presented as a poster at The 16th International Symposium on Olefin Metathesis and Related Chemistry, Poznan, Poland, 7-12th August 2005

"Difluorinated Cyclooctenones as Templates for the Synthesis of Conformationally-locked Analogues of Sugars" (poster 1) presented as a poster at Loughbrough Organic Chemistry Symposium 20th October 2004

"Difluorinated Cyclooctenones as Templates for the Synthesis of Conformationally-locked Analogues of Sugars" (poster 2) was further presented at RSC Fluorine Subject Group post graduate meeting at Oxford on the 1-2nd of September 2005

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Total Synthesis of Conformationally-locked Difluorinated Pento- and Hexopyranose Analogues, and Pentopyranosyl Phosphate Mimetics.
## Jonathan A. L. Miles
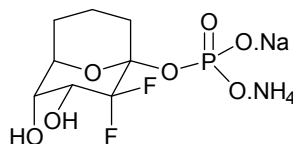
A range of pentopyranosyl phosphate mimetics including 2,2-difluoro-3R*,4R*-dihydroxy-9-oxa-1S*,5R*-bicyclo[3.3.1]nonanyl-1S*-phosphate ammonium sodium salt have been prepared concisely from trifluoroethanol. Such species once activated to full NDP sugars are intended as probes for the glycosyl transferase class of enzymes.

Trifluoroethanol was elaborated, *via* a telescoped sequence involving a metallated difluoroenol, a difluoroallylic alcohol, [2,3]-Wittig rearrangement and ultimately a ring closing metathesis (RCM) reaction, and requiring minimal intermediate purification, to a number of cyclooctenone intermediates including 3-benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one. Studies on the RCM reaction with alternate metathesis catalysts including Neolyst resulted in the unexpected isolation and full characterisation of a number of unusual homodimeric species.

From 3-benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one a divergent approach delivers novel bicyclic analogues of pentopyranoses, either *via* epoxidation followed by transannular ring-opening, or dihydroxylation followed by transannular hemiacetalisation. These species were further elaborated with an emphasis on minimal protecting group manipulation to analogues of glycosyl phosphates.

Furthermore the library of non natural sugars has been expanded with the initial steps toward a range of hexoses based on the 6-deoxy class of sugars being elucidated. 3-benzyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-enone was synthesised *via* a relay RCM after initial attempts with a traditional RCM precursor (3-benzoyloxy-4-4-difluoro-9-methyl-deca-1,9-diene-5-one) failed to deliver satisfactory quantities of material. In both cases RCM precursors were synthesised *via* chemistry analogous to that used in the construction of 3-benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one.
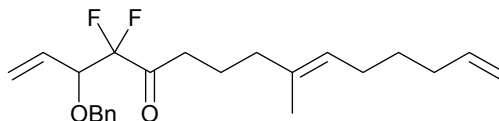
The epoxide transanular ring opening has been further investigated with a range of neutral and anionic nucleophiles which has allowed the mechanism of initial nucleophilic attack at the ketone to be proven and a new class of nitrogen bridged azasugar analogues to be characterised.

R = H, Bn
X = NH, NMe, NCH$_2$CH=CH$_2$
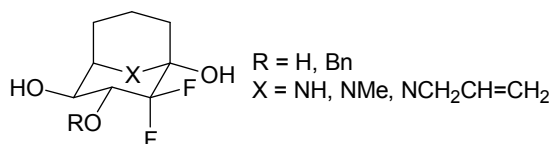
List of Abbreviations

Å	Angstrom
ADMET	acyclic diene metathesis polymerisation
ATP	adenosine tri-phosphate
Bn	benzyl
BOC	t-butyloxycarbonyl
Bp.	boiling point
Bs	brosylate
Bz	benzoyl
CAN	cerium ammonium nitrate
CI	chemical ionisation
CHN	carbon/hydrogen/nitrogen elemental analysis
COSY	homonuclear correlation spectrometry
CSDS	Cambridge structural database system
DABCO	1,4-diazobicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano benzo quinone
DEAD	diethylazo dicarboxylate
DEC	diethylcarbamoyl
Dia	diastereoisomer

DIOS	2-deoxy-*scyllo*-inosose synthase
DIPA	di*iso*propylamine
DMAP	4-dimethylamino pyridine
DMF	*N,N*-dimethylformamide
DNP	2,4-dinitrophenol
EI	electron impact
ENYRCM	enyne ring closing metathesis
ES	electrospray
FAB	fast atom bombardment
FTIR	fourier transform infra-red
Fuc	fucose
Gal	galactose
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
GDP	guanosine di-phosphate
Glu	glucose
GT	glycosyl transferase
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
HMQC	hertonuclear multipel-quantum coherence
HPLC	high pressure liquid chromatography
Hr	hour(s)

HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infra-red
LAH	lithium aluminium hydride
LDA	lithium di*iso*propylamide
LC-MS	liquid chromatography, mass spectrometry
m-CPBA	m-Chloroperbenzoic acid
Mes	mesityl
MHz	megahertz
Mol	mole
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilazide
*n*BuLi	n-butyllithium
NDP	nucleotide diphosphate
NHC	N-heterocyclic carbene
NMI	*N*-methyl imidazole
NMM	*N*-methyl morpholine
NMO	*N*-methyl morpholine oxide
NMR	nuclear magnetic resonance
MTFMDO	methyl trifluoromethyl dioxirane
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect correlation spectroscopy
ON	overnight

PMA	phosphomolybdic acid
ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
PVP	poly (vinylpyridine)
Py	pyridine
RCM	ring closing metathesis
R_f	retention factor
ROM	ring opening metathesis
ROMP	ring opening metathesis polymerisation
Sat.	saturated
SM	starting material
SPE	solid phase extraction
STM	scanning tunnelling microscopy
TBAF	tetrabutylammonium fluoride
TBAHSO$_4$	*tetra-n*-butylammonium hydrogen sulphate
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBPP	tetrabenzylpyrophosphate
TBS	tributylsilyl
t-BuLi	*tert*-butyllithium
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIBAL	triisobutylalluminium
TLC	Thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylene diamine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
Ts	tosylate
UTP	uridine triphosphate

Table Of Contents

1.0 Introduction

1.1 The Use and Effect of the Fluorine Atom in Modifying the Physical Properties and Chemical Behaviour of Organic Molecules

It is well known that the fluorine atom with its unique properties offers many interesting possibilities when used as a replacement for common functional groups in organic chemistry. Fluorine has been most commonly used to replace hydrogen atoms and hydroxyl groups, especially in biologically important compounds. At first appearances, this may seem counter-productive as the number of natural products which contain a fluorine atom is exceedingly small, with just over a dozen known to science.[1] In contrast, those containing bromine and chlorine provide many thousands of examples.

Despite this, fluorine is a good choice as a replacement for either an hydrogen atom or an hydroxyl group. The Van der Waals radius of fluorine falls between those of hydrogen and oxygen; F (1.47 Å), compared to H (1.20 Å), and O (1.57 Å).[2] Indeed the relationship to oxygen is almost isosteric. As a corollary of this fluorine is an appropriate mimic for both as the effects of its incorporation into a molecule should cause minimum disruption of the overall steric requirements of the molecule. This has been demonstrated by O'Hagan[3] by STM of monofluorinated analogues of stearic acid on graphite which showed an approximately 1% increase in surface area demand over the natural product. The effect of replacing the methylene (CH_2) functional group with a *gem*-difluoro methylene group (CF_2) can have a more pronounced effect on the physical properties of a

molecule and its conformation, possibly due to the increase in C-CX$_2$-C angle from 109.5° to 115-119°.[2]

A second very important property of the fluorine atom is its electronegativity; fluorine is the most electronegative of the elements. Measured on the Pauling scale fluorine has an electronegativity of 4.0, compared to 3.4 for oxygen, and 2.2 for hydrogen,[4] so the incorporation of fluorine into a molecule should have a profound effect on the electronic characteristics of the species, and will affect the reactivity of neighbouring functional groups. Of particular interest in biological systems is the effect of fluorine on the acid/base characteristics of a molecule. For example the pK$_a$ of 1,1,1-trifluoroethanol is 12.5 compared to 16 for ethanol itself.[5]

The replacement of an hydroxyl group by fluorine is a more complex case than that for replacement of hydrogen because of the ability of hydroxyl groups to form hydrogen bond arrays (Figure 1) with other substrates, a process which is of key importance in enzymic pathways. Clearly the lack of an acidic proton precludes fluorine from acting as a hydrogen bond donor; however it's acceptor characteristics are less clear cut.
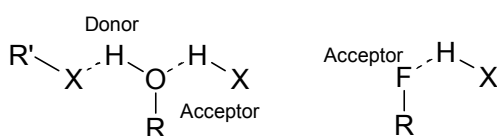
Figure 1

Howard and O'Hagan have studied the hydrogen bonding ability of fluorine,[6] by analyzing the known organofluorine compounds on the Cambridge Structural Database System (CSDS). In parallel, they modelled the interaction of 1-fluoromethane and 1-

fluoroethene with water to calculate the interaction energy at optimum bond length. The structural database study looked for short contacts ((C-F···H-X) ≤ 2.35Å) only as these are the length of interactions required if fluorine is to replace oxygen in a highly organized binding situation such as in an enzyme substrate complexes. The results showed that C-F···H-X interactions (worth 2.38 kcal mol^{-1} in the model system) were rare, and the majority (when present) were between fluorine and non acidic carbon bound hydrogen's. It was also observed that C(sp^3)-F contacts to OH and NH were statistically more frequent than C(sp^2)-F interactions. In the solid phase, there are very few compounds which possess both an acceptable X-H···F–C distance and angle required for an interaction. In the parallel computational study it was found that C-F···H-O interactions (worth 2.38 kcal mol^{-1}) are significantly weaker than C-O···H-O interactions which are conservatively estimated at 5-10 kcal mol^{-1}, and the C(sp^2)-F···H-O (1.48 kcal mol^{-1}) are weaker than their C(sp^3)-F···H-O (2.38 kcal mol^{-1}) counterparts. O'Hagan states that these weak "hydrogen bonds" may form to allow other stronger reactions to occur.

This is supported by elegant work from Eguchi[7] who used monofluorinated sugars to study the effect of hydrogen bonding at C-2 and C-3 of D-glucose 6-phosphate on the recognition and binding of this substrate by the enzyme 2-deoxy-*scyllo*-inosose synthase (DOIS). A range of mimics (Figure 2) were synthesised with substitution of the hydroxyl group at C-2 or C-3 with either a fluorine atom or an amino group. The fluorine substituent was intended to act as an hydrogen bond acceptor only, for reasons already discussed, whereas an amino group will act only as a donor, being protonated and therfore present as an ammonium cation at physiological pH. Therefore when a hydroxyl

group is involved as a donor in a key recognition interaction with the enzyme the amino sugars should be accepted by the enzyme. The deoxyfluoro sugar should be recognised less well and bound less tightly in the binding pocket; the converse is also true. Where the hydroxyl group is of limited importance substitution by either group should have a limited effect.
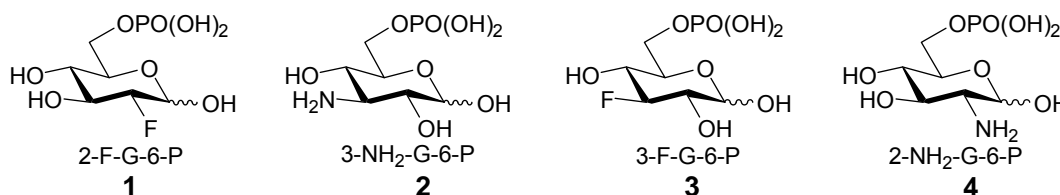
Figure 2

In incubation studies with recombinant DIOS, it was found that both 2-deoxy 2-fluoro (2-F-G-6-P) **1,** and 3-amino 3-deoxy (3-NH$_2$-G-6-P) **2** were recognised as substrates and turned over by the enzyme whereas no trace of enzymatic products were detected from the reaction of 3-deoxy 3-fluoro (3-F-G-6-P) **3,** and 2-amino 2-deoxy (2-NH$_2$-G-6-P) **4**. Furthermore neither **3** nor **4** showed any inhibitory activity against DIOS suggesting that neither **3** or **4** were bound to the enzyme even as a ligand. The corollary of these results is that the hydroxyl group at C-2 is a crucial hydrogen bond acceptor whereas its neighbour at C-3 is a key donor. Clearly the affinity of **1** for the enzyme suggests that the fluorine is undertaking a role as an hydrogen bond acceptor. The strength of these interactions can be inferred from the kinetic data obtained for the reaction; k_{cat}/K_m was 24 M^{-1} s^{-1} for **1** and 10 M^{-1} s^{-1} for **2**. These values are two orders of magnitude lower than the value for natural D-glucose 6-phosphate (4800 M^{-1} s^{-1}) and show that the analogues are much

poorer substrates for the enzyme. Thus although fluorine has been shown to act as an acceptor it is clearly much less effective than an authentic hydroxyl group.

It is generally thought that fluorine cannot act very effectively as an hydrogen bond acceptor, because of it's extreme electronegativity, which makes polarisation of the non-bonding electrons very difficult. It follows that the replacement of an hydroxyl group with the fluorine atom may disrupt any molecular recognition processes which rely on *strong* hydrogen bonding interactions.

Another consideration concerns the most important property of C-F bonds; these are the strongest single bonds known (D = 489 kJ mol^{-1}),[8] and therefore the thermal stability and resistance to oxidation of the fluorine-containing analogue is increased, if an hydrogen atom that is removed in metabolism is replaced. Carbon-fluorine bonds also increase the lipophilicity of a molecule thus greatly aiding transport in *vivo* and passage through cellular membranes. These properties make fluorine-containing species desirable targets in the pharmaceutical industry.

Another advantage of incorporating fluorine into biological systems is that fluorine serves as an efficient reporter group for the study of biological systems by NMR.[9],[10] Because fluorine is a spin ½ nucleus and has an isotopic abundance composition of 100%, ^{19}F can be easily located and causes both large couplings and changes in chemical shifts in near neighbour protons.

The AFP-07 prostacyclin analogue **5** (Figure 3) developed by Asahi Glass[11] illustrates the remarkable ability of fluorine to modify the reactivity of a functional group in a useful way. Prostacyclin **6** is a potent platelet aggregation inhibitor and vasodilator which contains a very reactive enol ether moiety. The half life of **6** is 76.2s under physiological

conditions due to the reactive enol ether; however modification of an allylic methylene to a *gem*-difluoro methylene group provides an analogue **5** which has a half life of greater than 30 days. The *gem*-difluoro methylene group greatly stabilises the enol ether moiety by inductively destabilising the oxacarbenium intermediate formed upon its protonation through which the hydrolysis of **5** occurs.
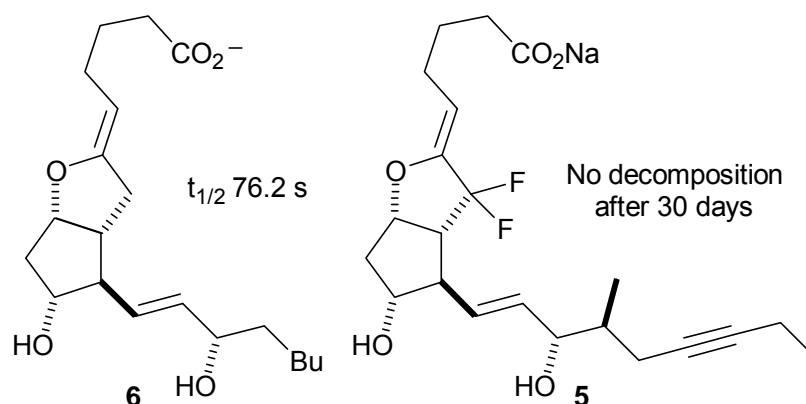
Figure 3

1.2 Carbohydrates; Key Components in Biological Systems

The macromolecules that make up all living things can be divided in to four broad classes: these are proteins, lipids, polysaccharides, and nucleic acids, which themselves are constructed from three types of building blocks, amino acids, fatty acids, and monosaccharides, the latter often in the form of activated nucleotide diphosphate (NDP) sugars. Monosaccharides themselves may also appear as components in other classes either as post-translational modifications on proteins, and crucially as part of the backbone of DNA and RNA in the form of D-ribose, and 3-deoxy-D-ribose respectively.

Carbohydrates serve as energy stores, components of cell walls, and now are being discovered to be crucial to many recognition processes.

A vast range of monosaccharides exist, with variation in chain length (pentoses and hexoses), and form (pyranose, furanose, open chain). Different types of functionality (hydroxyl, amino), levels of deoxygenation, alkylation, relative and absolute configuration add further complexity (Figure 4).

Crucial to the chemistry of carbohydrates is the anomeric centre and the glycosidic bond formed to it; this is an acetal linkage which joins saccharides together to form the di, tri, and higher oligomers found in nature. These linkages can be either axial or equatorial and are classified according to the configuration at C1. The glycosidic bond can be readily cleaved and synthesised by enzymes under the right conditions.

Pentoses

Ring Form → Chain Form

CHO
— OH
— OH
— OH
CH$_2$OH

D-ribose

CHO
HO —
— OH
— OH
CH$_2$OH

D-arabinose

CHO
— OH
HO —
— OH
CH$_2$OH

D-xylose

CHO
HO —
HO —
— OH
CH$_2$OH

D-lyxose

Hexoses

CHO
H — OH
H — OH
H — OH
H — OH
CH$_2$OH

D-allose

CHO
HO — H
H — OH
H — OH
H — OH
CH$_2$OH

D-altrose

CHO
H — OH
HO — H
H — OH
H — OH
CH$_2$OH

D-glucose

CHO
HO — H
HO — H
H — OH
H — OH
CH$_2$OH

D-mannose

CHO
H — OH
H — OH
HO — H
H — OH
CH$_2$OH

D-gulose

CHO
HO — H
H — OH
HO — H
H — OH
CH$_2$OH

D-idose

CHO
H — OH
HO — H
HO — H
H — OH
CH$_2$OH

D-galactose

CHO
HO — H
HO — H
HO — H
H — OH
CH$_2$OH

D-talose

Pyranose Form

Furanose Form
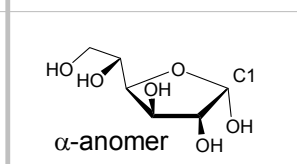
Functionality/Deoxygenation

α-anomer

β-anomer

L-Form

D-Form

6-deoxy-D-glucose

6-amino-6-deoxy-D-glucose
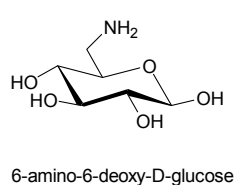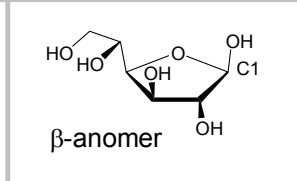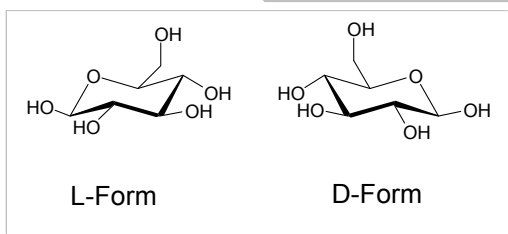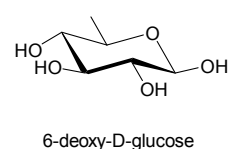
Figure 4

1.3 The Effect of Fluorine on the Rate of Glycoside Hydrolysis

Hydrolysis of the glycosidic bond occurs in a concerted mechanism *via* an oxacarbenium ion-like transition state **7** (Scheme 1); oxacarbenium ions themselves are thought to be too unstable to exist as intermediates in water.[12] It has been shown that incorporation of a fluorine atom into a saccharide will affect the stability of the glycoside linkages due to the unique electronic properties of fluorine; significant differences in hydrolysis rates under acidic conditions have been observed for substituted glucose[13] (Table 1). The order of reactivity, parent (DNPglc) > 6-deoxy-6-fluoro > 3-deoxy-3-fluoro > 4-deoxy-4-fluoro > 2-deoxy-2-fluoro was observed.

DNP glycoside	*Pseudo* first order rate constant at 37°C (sec^{-1})	k_{rel}
DNPglc	5.58 x 10^{-6}	1
2FDNPglc	1.45 x 10^{-7}	0.026
3FDNPglc	8.23 x 10^{-7}	0.15
4FDNPglc	3.74 x 10^{-7}	0.067
6FDNPglc	1.99 x 10^{-6}	0.36

Table 1

Scheme 1
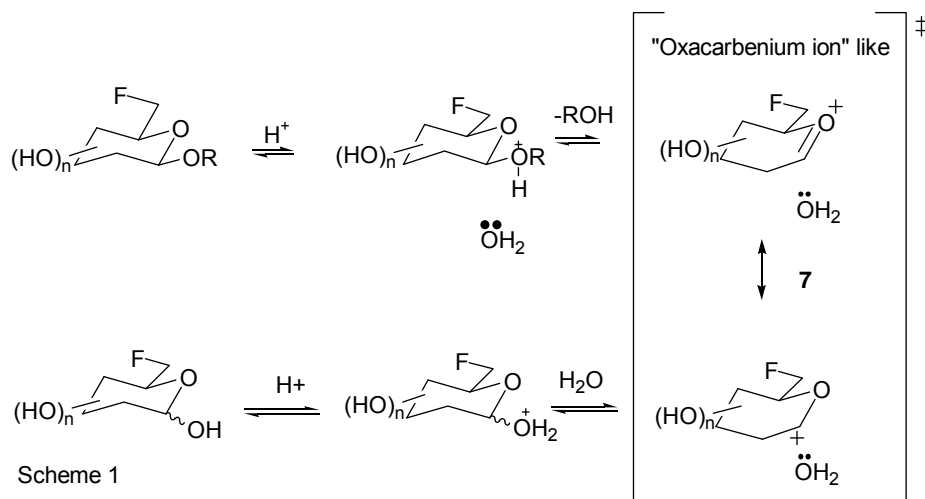
A similar order of reactivity is seen for the galactose series (not in table); parent (DNPgal) > 3-deoxy-3-fluoro > 6-deoxy-6-fluoro > 4-deoxy-4-fluoro > 2-deoxy-2-fluoro, although the rate of species substituted at C3 and C6 are reversed. Fluorine atom substitutents affect the rate of hydrolysis by inductively destabilising the oxacarbenium ion-like transition state **7** through which hydrolysis takes place. The high electronegativity of fluorine pulls charge away from the anomeric centre and therefore opposes the development of the positive charge in **7** retarding its formation. This effect is strongest in 2-deoxy-2-fluorosugars where the fluorine substituent is closest to the anomeric centre; here, the rate of hydrolysis is shown to be two orders of magnitude slower than for the parent species. The differences in rate however should not be merely attributed to the distance of the substituent from C1 as this correlation is not obeyed by C3 and C4. Therfore although the effect of electronegativity is important in rationalising these observations it is not the only effect as steric factors and solvation may also play a part.

1.4 Transportation, Construction, and Cleavage; Glycosyl Transferases and Glycosidases

The task of processing the glycosidic bonds of saccharides in *vivo* is accomplished by two classes of enzymes. Glycosyl transferases (GT's)[14] are responsible for the construction of glycosidic bonds to saccharides. The cleavage of these linkages is catalysed by a separate class of enzymes, the glycosidases.

Glycosyl transferase (GT) enzymes catalyse the transfer of activated nucleotide di-phosphate or NDP sugars, onto the relevant acceptor which is usually an hydroxyl (alcohol or phenol), carboxyl, or amino functionality. They mediate fundamentally important biotransformations and are essential in the formation of cellulose, the storage of energy as starch, in the encoding of bio-information as nucleic acids, and the synthesis of many antibiotic natural products. In terms of mass processed they may be the most important enzymes on earth. Currently there are about seventy families of GT's classified according to their amino acid sequence on the carbohydrate-active enzymes server "CAZY".[15] Glycosyl transferases show varying degrees of sugar substrate flexibility, ranging from the highly flexible GT's found in simple soil bacteria to highly substrate specific enzymes found in more complex biological systems. The GT's involved in the synthesis of human blood group determinant glycoproteins for example, are exquisitely selective. GT's are becoming increasingly important synthetic tools in the construction of complex natural products by combinatorial biosynthetic pathways.[16]

Natural product in *vitro* glycorandomization[17] (IVG) is an emerging technique which takes advantage of the flexibility of chemical synthesis to deliver a wide range of non-natural sugars (Scheme 2). By combining this synthetic flexibility with the inherent or tailored promiscuity of enzymes to activate (sugar kinases and nucleotidyltransferases), and attach (GT's) these carbohydrates to various natural product aglycones, the flexibility can be transferred from the monosaccharide to the final glycorandomised natural product library. Crucial to the success of the technique is the selection of flexible enzymes which will process the diverse library of chemically synthesised sugars. Access to such enzymes is becoming easier as techniques improve. Thorson has reported a cultured GalK mutant

(Y371H) which has shown remarkable flexibility in its kinase activity toward both D and L sugars (which had failed as substrates for wild-type GalK). Another example is the nucleotidylyltransferase α-D-glucopyranosyl phosphate thymidylyltransferase (E_p) from *Salmonella enterica* LT2. Uniquely E_p was found to be promiscuous toward both its nucleotide triphosphate, and the sugar phosphate substrates. In IVG the diversity of the final products stems from the upstream chemical synthesis rather than many downstream modifications of a substrate by many separate enzymes. The transformations take place in a single pot three enzyme process. Current problems with the technique include difficulties of scale up with expensive substrates and cofactors, and secondly establishing generality of the *in vitro* conditions which allow both enzyme function and substrate solubility. IVG may become a key tool in the synthesis of glycorandomised libraries of non-natural sugars.
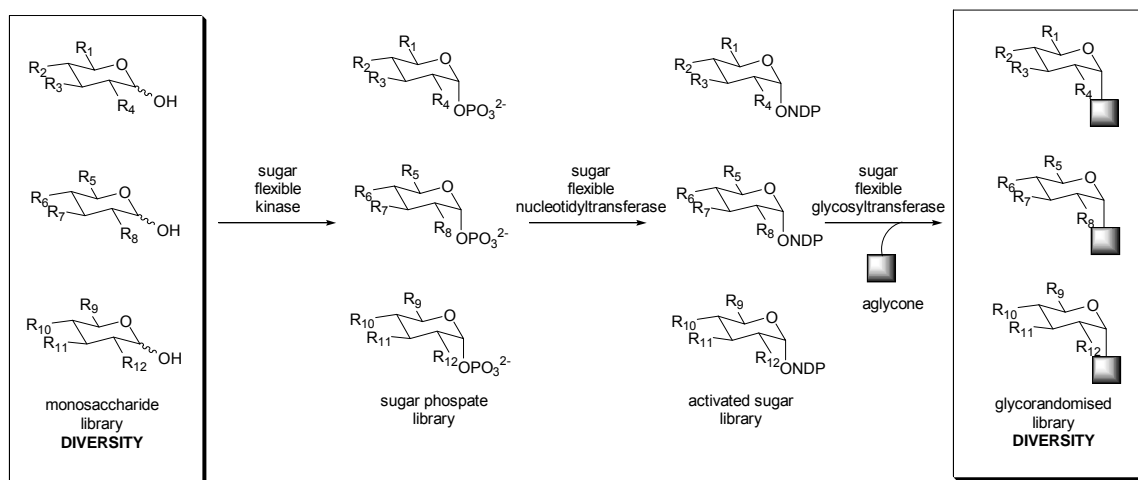
Scheme 2

Combinatorial biosynthesis is a strategy for producing complex "unnatural" or hybrid natural products using the machinery of nature in the form of enzymes tailored to

complete most of the transformations. This is achieved using substrate flexible enzymes or through targeted modification of selected biosynthetic genes.

The search for sugar flexible GT's that are able to transfer a range of sugars and are therefore useful for combinatorial biosynthesis is an area attracting considerable interest. Rohr[18] has synthesised a range of novel hybrid tetracenomycins (Figure 5) using a GT encoded for by the *elm* genes in cosmid 16F4 of the elloramycin biosynthetic pathway of *Streptomyces olivaceus* Tü2353. By modifying cosmid 16F4, the workers were able to alter post-polyketide behaviour. The modified enzyme proved able to transfer a range of 6-deoxysugars including D-olivose **8**, L-rhodinose **9**, D-mycarose **10**, and a disaccharide containing two 1,3-linked D-olivoses **11**, onto the phenolic 8-OH group of the aglycone of tetracenomycin, (8-dimethyltetracenomycin) **12**. The sugar substrates processed showed varying degrees of deoxygenation and stereochemistry.
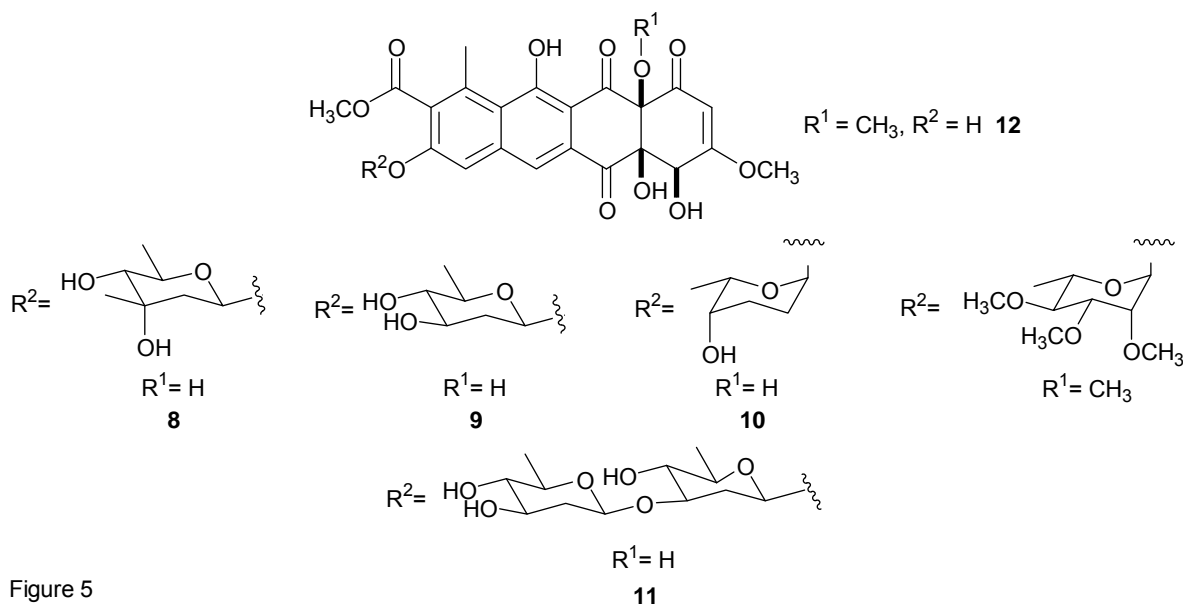
Figure 5

The cosmid was hosted by the urdamycin **(12)** producer *Streptomyces fradiae* Tü2717; experiments conducted with only the host present showed no glycosylation upon incubation proving that the GT was encoded for by cosmid 16F4, and that the novel tetracenomycins were not synthesised by the GT indigenous to the host. It should be noted that the GT showed only flexibility towards the deoxysugar transferred, and not toward either the aglycone itself or the acceptor hydroxyl. This work with the transfer of deoxysugars is important as deoxysugar moieties are increasingly being recognised as important structural elements in many antibiotics and anti-cancer agents.

Glycosyl transferases recognise the NDP sugar substrates through recognition arrays of hydrogen bonding interactions between hydroxyl groups and other residues. There are thought to be two binding sites; one binds to the sugar whilst the other binds the nucleotide (Figure 6). The binding domain is thought to be quite close to the surface of the enzyme with the enzyme itself membrane bound on the cell. The diphosphate spacer with divalent cation is critical in establishing the correct separation between the two pockets by holding the phosphate linker in a rigid orientation. A number of glycosyl transferases have been isolated which have shown considerable flexibility towards NDP sugars, suggesting high tolerance in the sugar binding site towards variations in the number and orientation of hydroxyl groups in the substrate sugars. These GT's rely on a few key interactions with the recognition array to achieve binding.

Glycosyl Transferase

Sugar Binding Pocket

BASE

Nucleotide Binding Pocket
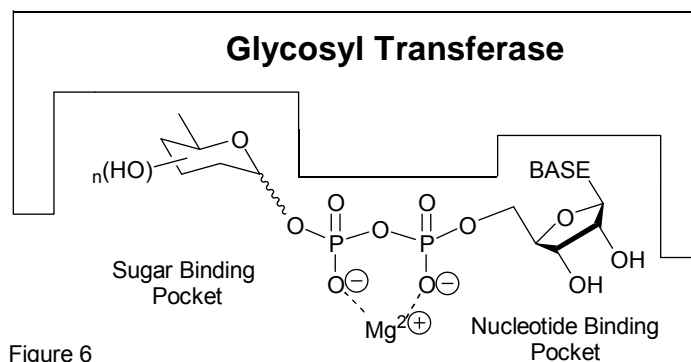
Figure 6

Glycosyl transferases occur in two classes; these are inverting and retaining GT's depending on whether the configuration at the anomeric centre of the NDP-glycosyl donor, either axial (a) or equatorial (e) is retained or inverted in the resulting glycoside. Thus enzymes can be grouped into four classes dependant on the stereochemical outcome of the turnover e → e, a → a, e → a, and a → e. In most cases, and assuming D-sugar configuration, the donor will be an α-linked species, so retention will give an α-D-linkage in the final product, whereas inversion will produce a β-D-linked species. The mechanism of inverting GT's is relatively well understood[19] and is thought to proceed *via* an "exploded" S_N2 transition state (Scheme 3) with considerable oxacarbenium ion character in which the key features are held in alignment by the enzyme. An active site residue acts as a general base catalyst whilst another amino acid functions as a general acid; attack occurs at the anomeric carbon centre of the NDP sugar in a concerted one step process. It is thought that the transition state conformation is a flattened half chair with considerable oxacarbenium ion character at the anomeric position of the glycosyl donor.
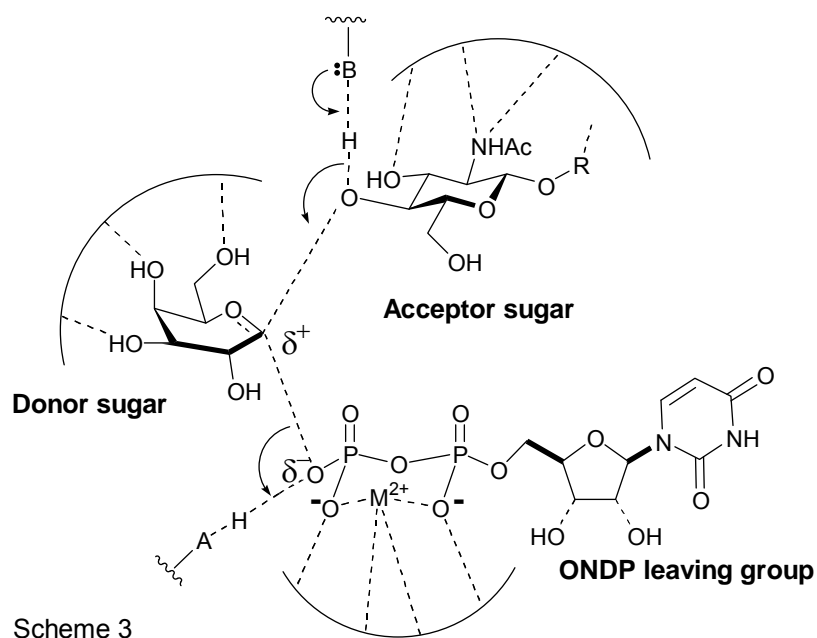
Scheme 3

Retaining GT enzymes are much less well understood[20] but may function through a double-displacement mechanism *via* a glycosyl-enzyme intermediate and two oxacarbenium-like transition states (Pathway A, Scheme 4). An alternative mechanism which involves a single step "internal return" $S_{N}i$ transition state (Pathway B, Scheme 4) has been postulated, where the nucleophile and leaving group exist on the same side of the sugar ring. This mechanism would be highly unusual in terms of the way we think about concerted nucleophilic displacements.

Scheme 4 $S_N i$ transition state
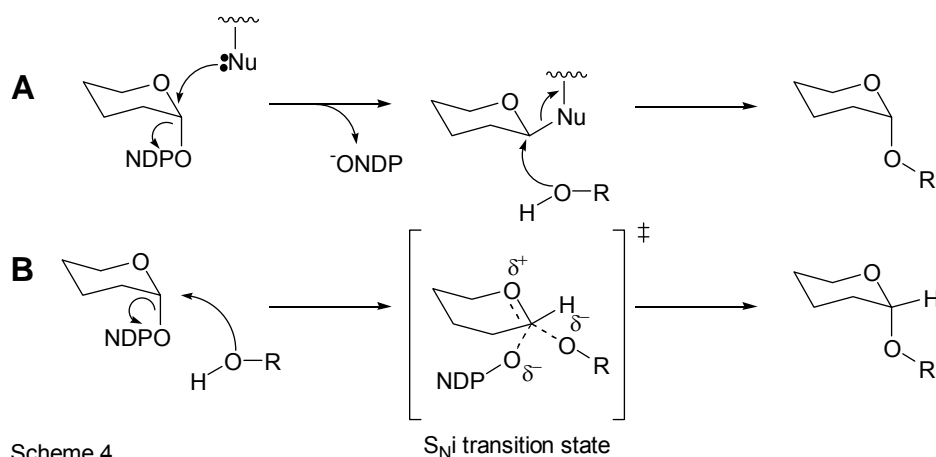
1.5 Understanding Enzyme Active Sites by Inhibition studies

The need to understand the structure and function of GT's is becoming more important, particularly for retaining enzymes as enzyme-catalysed glycosylation becomes a more viable synthetic tool. Crystallographic studies[21] are a convenient analytical tool for observing the active site. However it is still a challenge to access systems with a substrate bound in the enzyme active site (recognition array, donor, acceptor, NDP leaving group) due to rapid turnover by the enzyme. One method of allowing access to relevant structures is to present all the features within an array with a substrate mimic that cannot be processed further through cleavage of the fragile glycosidic bond. It would be hoped that presenting a sugar-flexible GT with a non-natural NDP sugar that can bind as a ligand but not react, will allow access to stable complexes whose structure can be successfully studied to yield valuable information about the active site.

A related strategy of using non-natural sugars to study the active site of enzymes is an established and powerful technique known as active site labelling. The technique does

not aim to present a substrate bound as a ligand in the active site but allows initial progression by the enzyme. In identifying or "labelling" active site residues the methodology has shown considerable promise in the study of retaining enzymes. Davies has used 2-deoxy-2-fluoro substituted sugars to trap the covalent glycosyl-enzyme intermediate on the pathway catalysed by Endoglucanase CalB2 from *Streptomyces lividans*.[22]

13
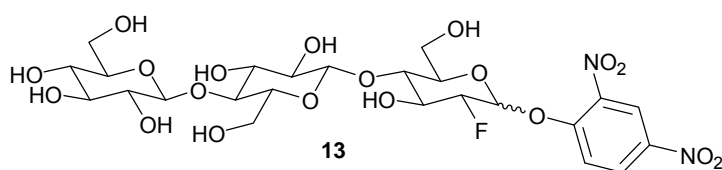
The enzyme was fed DNP-2-F-cellotrioside **13**; after binding and reaction to give the covalently bound glycosyl-enzyme intermediate, further progression *via* glycosidic bond cleavage was prevented by inductive destabilisation of the oxacarbenium ion "like" transition state by fluorine at C-2, and also by the loss of key transition state stabilisation interactions through hydrogen bonding. Clearly fluorine will also destabilise the initial binding and transition state of the substrate too by removing or reducing hydrogen bonding; however the use of a very good leaving group such as 2,4-dinitrophenolate can compensate for this. The labelled glycosyl-enzyme intermediate was available for analysis with the substrate bound covalently allowing identification of key residues at the active site. Davies[23] has also used UDP-2-deoxy-2-fluoro-glucose to crystallise Trehalose-6-phosphate synthase, a key enzyme in the biosynthesis of Trehalose. Such work has provided strong supporting evidence for the double displacement mechanism for retaining enzymes.

The retaining mechanism of glycosidases are better understood than those for GT's but active site labelling can still prove a powerful tool. In his elegant study of the axial-axial retaining enzyme *Phanerochaete chryrosporium* α-galactosidase, Withers[24] used a mechanism based inhibitor strategy based on a 2-deoxy-2,2-difluorosugar as an affinity label to identify the amino acid nucleophile at the active site. The enzyme acts through a double displacement mechanism (Scheme 5) where one of the active site carboxylates acts as a nucleophile **(14)** generating a glycosyl enzyme intermediate **15**. A second carboxylate then functions sequentially as a general acid, then a general base, to promote the formation and then breakdown of the intermediate.
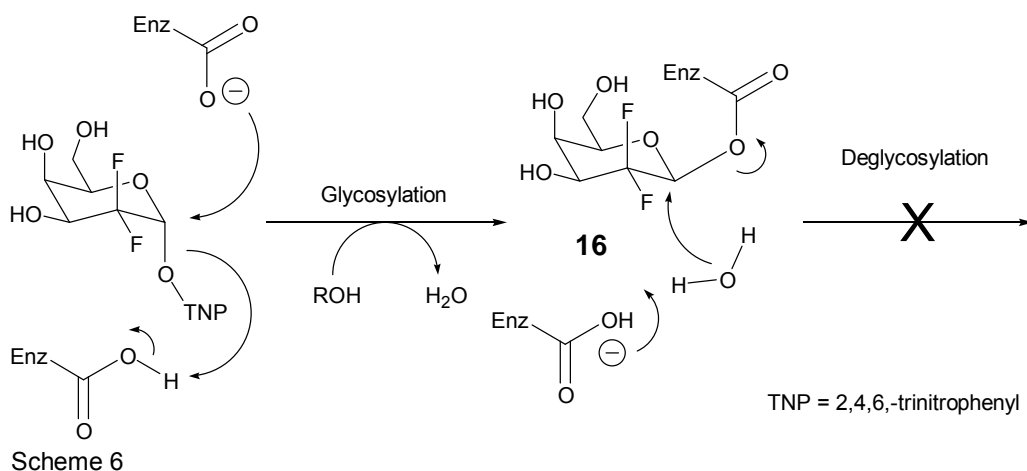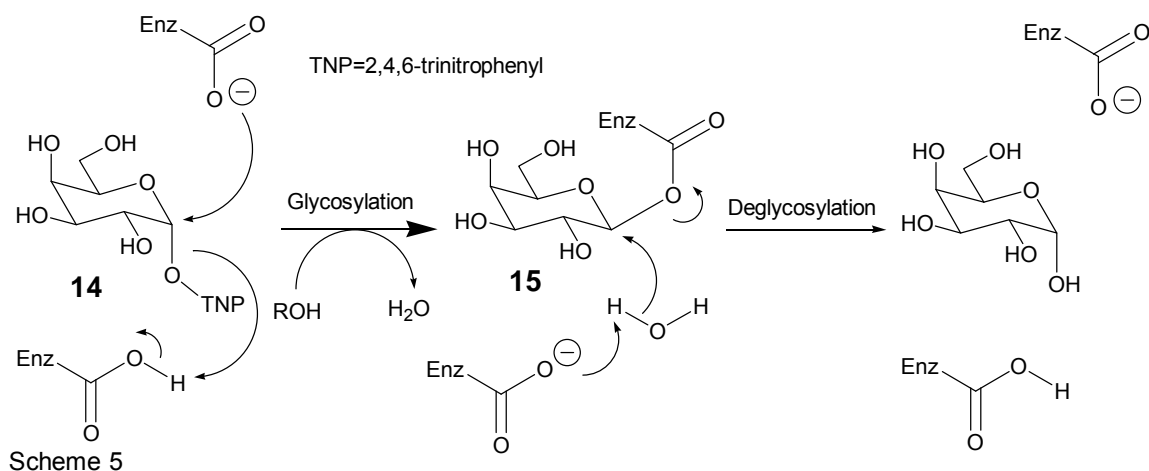
Scheme 5

Scheme 6

Feeding the non-natural fluorosugar to the enzyme successfully caused inhibition after the initial glycosylation **(16)**, the *gem*-difluoro group preventing passage through the transition state required for the second step (Scheme 6). Following a complex enzyme catalysed cleavage of the labelled protein, the active site nucleophile was identified as Asp-130. This approach using 2-deoxy-2,2-fluoroglycosides is often required for a → a retaining enzymes which are often not inhibited by the 2-deoxy-2-fluoroglycosides used so successfully with e → e retaining enzymes.

The design of inhibitors for GT's is more challenging as considerably less is known about their detailed 3D structure, which makes it more difficult to design effective structure-based inhibitors. However Wong[25] has published excellent work on the inhibition of various GT's with a range of fluorosugars. The inhibition of four important human fucosyltransferases (fuct-III, V, VI, and VII) with GDP-2F-Fuc **17**, GDP-6F-Fuc **18**, GDP-α-2F-Fuc **19** (Table 2, Figure 8) showed some interesting results. Mammalian fucosyltransferases transfer a fucose moiety from the donor guanosine 5'-diphospho-β-D-fucose to a carbohydrate acceptor in enzyme, with inversion of anomeric configuration.
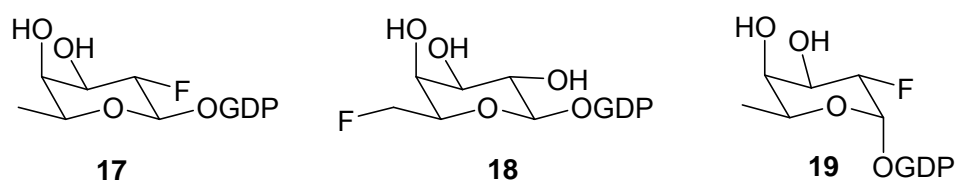
GT	17	18	19
	K_i (µM)	K_i (µM)	K_i (µM)
FucT-III	38±4	22±10	
FucT-V	4.0±0.6	3.4±1.0	36±4
FucT-VI	10±2.4	1.0±0.5	2±1
FucT-VIII	21±2	11±2	

Table 2; Figure 8

Both **17** and **18** show similar levels of inhibition toward all four GT's suggesting that decoration with fluorine at the 2 or 6 position of the glycosyl donor has a similar electronic effect on the reactivity of the species, although substitution at the 6 position gives slightly better inhibition in all cases. This is not altogether unexpected as the substitutions in each case are about equidistant from the ring oxygen. These results are in contrast to the previously discussed examples from Withers where 2-deoxy-2-fluorosugars were used exclusively despite being less accessible synthetically than 6-deoxy-6-fluorosugars. Significant inhibition of fucT-V, and fucT-VI is observed with **19**, although the other enzymes are unaffected; this substrate contains the non-natural configuration at the anomeric carbon and therefore demonstrates that some fucT enzymes contain a binding domain which is flexible with respect to sugar stereochemistry. The authors concede that it is unknown whether the substrates are acting as non-reacting analogues which merely bind in the active site and don't react, or as slow substrates for some of the enzymes.

Schengrund[26] has studied the effect of UDP-6-deoxy-6fluoro-α-D-galactose **20** (Figure 9) on the retaining GT's α-(1→3)-galactotransferase, and β-(1→4)-galactotransferase, both of which successfully transfer UDP-α-D-Gal **21** to the appropriate acceptor.
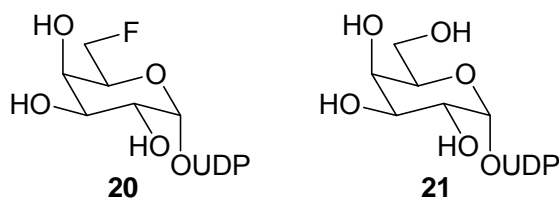
Figure 9

Inhibition studies showed that when a five–fold excess of **20** was used relative to **21** the amount of transferred galactose detected fell by 55 ±16 % for the β-(1→4) transferase and 76 ±4 for α-(1→3)-galactotransferase. Furthermore, no product indicative of the transfer of **20** was detected either in competition with **21**, or when used as the sole substrate. The inhibition studies indicated that although **20** could be successfully recognised and bound by the enzyme as a slowly dissociating ligand, it could not react successfully and catalyse transfer from the UDP to the acceptor sugar.

1.6 Conformationally Locked Acetals Show Strong Resistance to Hydrolysis

Kirby[27] has investigated stereoelectronic effects at oxygen in tetrahydropyrans extensively and has shown that conformationally locked acetal **22** shows remarkable stability towards hydrolysis when compared to **23** which is similarly substituted at the anomeric carbon (Scheme 7). The acetal C-O bond of conformationally locked **22** is hydrolysed 10^{13} times more slowly than that in **23**, corresponding to a difference in free energy of activation of $\Delta G^{\neq}$ 18.4 kcal (77 kJ) mol^{-1}. This effect is observed despite a very good leaving group being used.

Scheme 7   Hydrolysis **23** 10^{13} > **22**
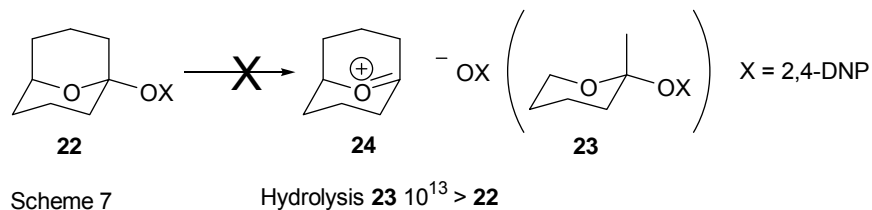
The crucial difference between these two systems is that in bicycle **22** the "oxacarbenium ion" like transition state **24** is forced to adopt a perpendicular geometry across the $C=O^+$ bond. This provides a significant stereoelectronic barrier to acetal cleavage as calculations have shown that the difference in energy between the planar **25** and perpendicular **26** conformations of the methoxymethyl cation is as much as 20.8 kcal (87 kJ mol^{-1}).

25   **26**

27   **28**   **29**
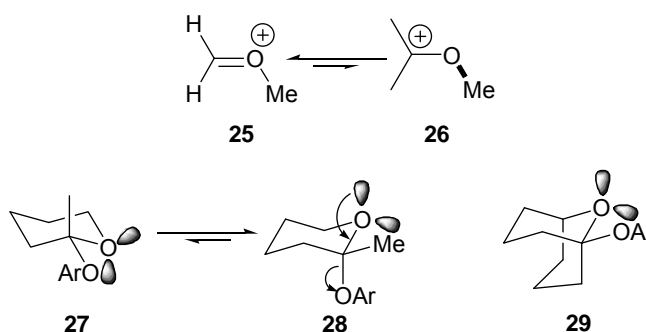
Scheme 8

This effect can be rationalised by considering the two lone pairs on the ring oxygen; they adopt a geometry where one is axial and one equatorial (Scheme 8). Conformational flexibility in **23/27** allows the ring to flip thus enabling one of these lone pairs to move antiperiplanar to the breaking C-O bond and donate electron density into the C-O σ* **28**. This planar overlap stabilises the transition state. In **22/29** the conformational lock prevents either of the lone pairs of the bridgehead oxygen overlapping with the C-O σ* of the breaking bond. This leads to a transition state with a perpendicular geometry the instability of which prevents it's formation. Kirby also argues that the dominant effect from the bridgehead oxygen is therefore destabilising σ-electron withdrawal and the energy difference between the two transition states of **22** and **23** is 19.1 kcal (80 kJ) mol^{-1},

and hydrolysis by the traditional mechanism is effectively suppressed. Despite the lock **22** does still undergo hydrolysis but the reaction is forced to proceed *via* two possible unfavourable solvolysis (Scheme 9) to give ketone **30**.
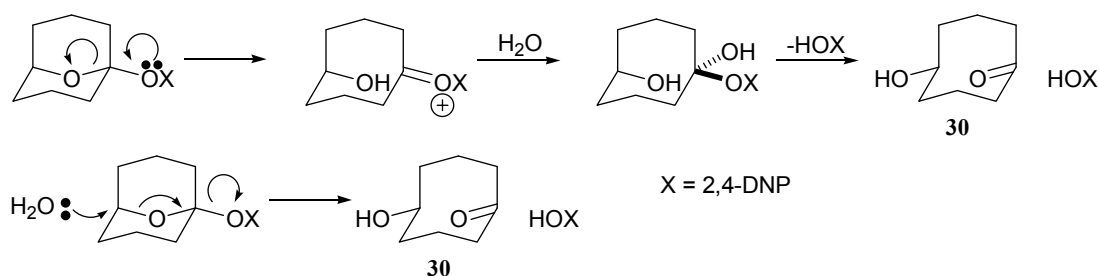
Scheme 9

These observations suggest that glycosidic bonds can be almost completely deactivated towards hydrolysis by restricting the flexibility of the hemiacetal ring system with the incorporation of a conformational lock. Clearly a class of non-natural β-glycosides synthesised with this bicyclic framework should show remarkable resistance towards hydrolysis.

1.7 Chemo-enzymatic Synthesis of Activated NDP Sugars

Sugars are carried and transferred by GTs as their nucleotide diphosphate (NDP) derivatives. The traditional chemical synthetic routes to activated NDP sugars are difficult and often proceed in very low yield;[28] much of the difficulty in the synthesis arises from the decomposition of the diphosphate linker. Recently, new chemo-enzymatic methods which allow the chemically synthesised phosphorylated sugar to be transferred

to the nucleotide using cultured enzymes have been developed. Pyrophosphorylases are the enzymes responsible for the construction of the diphosphate bond of sugar nucleotides, and are responsible for the biosynthetic pathway to natural NDP sugars.

Scheme 10
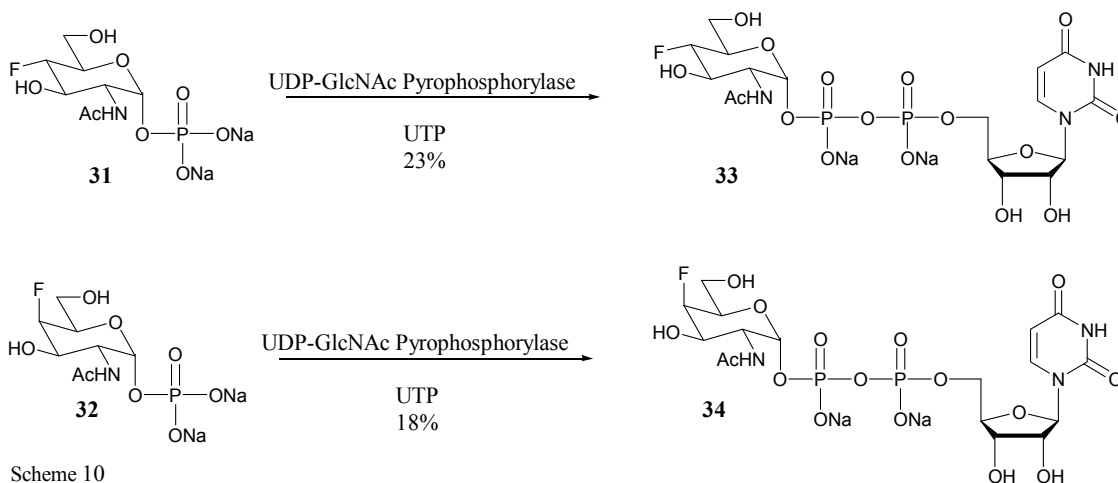
Recently Nishimura[29] successfully demonstrated the transfer of two non-natural fluorinated 2-*N*-acetamidosugars donors, 2-acetamido-2,4-dideoxy-4-fluoro-α-D-glucopyranose 1-phosphate (4-FGlcNAc-1-P) **31** and 2-acetamido-2,4-dideoxy-4-fluoro-α-D-galactopyranose 1-phosphate (4-FGalNAc-1-P) **32** using the enzyme UDP-GlcNAc pyrophosphorylase to give the corresponding fluorinated 2-*N*-acetamidosugar nucleotides in acceptable yields of 23% for (UDP-4-FGlcNAc) **33** and 18% for (UDP-4-FGalNAc) **34** (Scheme 10). The enzyme UDP-GlcNAc pyrophosphorylase was produced in *E. coli* JM 109 and incubated with the sugars, the product being isolated by HPLC after an hour. The transfer of **31** by the enzyme was expected as **31** is a mimic for the enzymes natural substrate (GlcNAc-1-P). More surprisingly it was also found that galactose **32** was successfully accepted as a substrate by the enzyme and transferred despite the axial configuration at the C-4 position. This suggests that this enzyme may show broad

specificity towards substrates for transfer. A weakness in the methodology is the synthesis of the substrates themselves; both **31** and **32** were synthesised from commercially available D-GalNAc and D-GlcNAc respectively. Each reaction sequence required nine synthetic steps most involving the application or removal of protecting groups. Fluorination was achieved directly using TBAF or DAST giving inversion of the C-4 stereocentre. It would clearly be desirable to synthesise both substrates *via* a divergent route and introduce the fluorine in such a way as to reduce the need for protecting group manipulation.

Wong[25] has incorporated this chemoenzymatic approach into a one-pot synthesis of UDP-2-deoxy-2-fluoro galactose (UDP-2F-gal) **35** at 100mg scale (Scheme 11). The fluorination, phosphorylation, and chemoenzymatic activation from galactal **36** to (UDP-2F-gal) **35** all occur without isolation and in an excellent overall yield of 60 %.
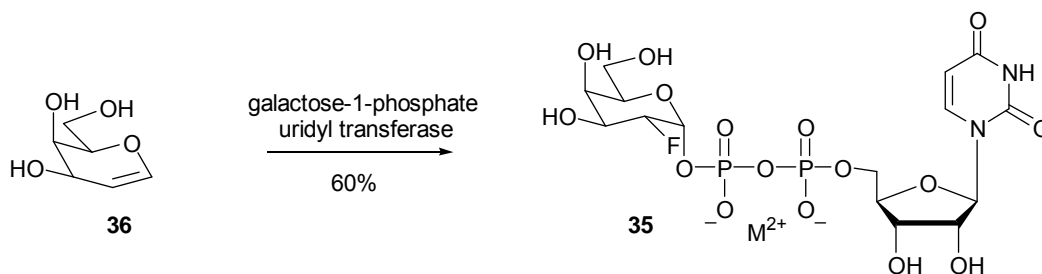
Scheme 11; Reagents and conditions; i)F-TEDA-CH$_2$Cl·OTf, 3 mL H$_2$O, 3h; 100mM Tris-HCl pH 7.4; galactokinase, acetate kinase, ATP, AcOP, ß-mercaptoethanol, Bovine Serum Albumin, MgCl$_2$, 4 days. Galactose-1-phosphate uridyl transferase, UDP-glucose, Pyrophosphorylase, Pyrophosphatase, UTP, pH 8.4, 3 days.

These enzymes, a pyrophosphorylase and a nucleotidyl transferase, appear tolerant of non-natural NDP sugars with fluorine substituent in the 2'-position or the 4'-position in both axial and equatorial configuration. The considerable flexibility observed suggest that

the hydroxyl groups found in these positions in the normal sugar are not involved in the recognition array between the substrate and the enzyme.

1.8 Exploring Conformational Space; Non-natural Analogues of Sugars

There has been much recent interest in the design of sugar analogues that contain non-natural structures and adopt unusual conformations. Sinaÿ has developed a synthesis of cyclooctanoic carbocycle **44** as a potential mimic of D-Glucose (Scheme 12).[30] It is argued that the cyclooctanoic species may offer new and interesting distributions of hydroxyl groups within conformational space. The key transformation in the synthesis is a tri*iso*butylaluminium (TIBAL) promoted Claisen rearrangement of 2-methylene-6-vinyl-tetrahydropyran **38** synthesised in a traditional manner from methyl α-D-glucopyranoside **39**. This elegant reaction originally developed by Paquette[31] affords a cyclooctanic derivative by insertion of a C2 unit. From cyclooctenone **40** methylation and subsequent hydroboration gives **41** in good yield. Oxidation and treatment with Tebbe reagent gives **42** which is hydroborated to give diastereomers **37** and **43**, which are deprotected to give **44** and **45** in excellent yield. The structural similarity between precursor **37** and **46** is immediately apparent. Compound **37** is thought to occupy a boat chair conformation based on ^3J couplings in the proton NMR and an H1-H5 NOE interaction.
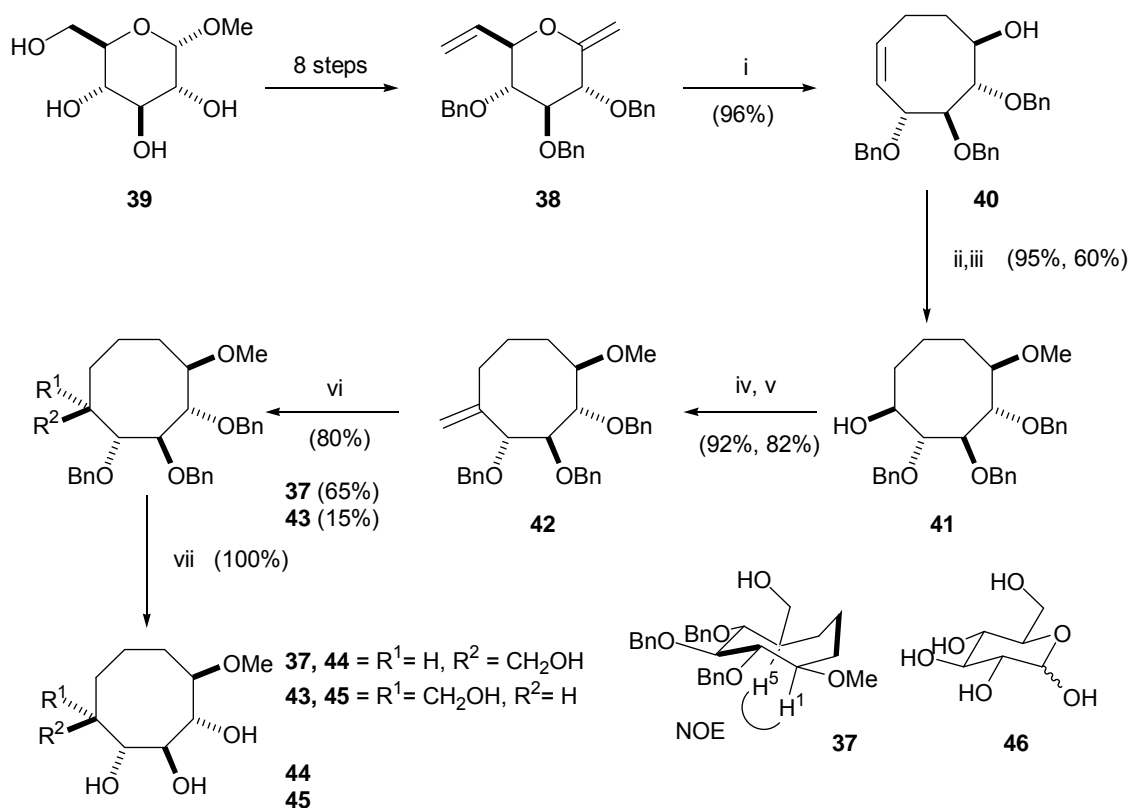
Scheme 12; Reagents and conditions; i. iBu_3Al, toluene, $50^{o}C$, 30 min; ii. NaH, MeI 2.8 eq, DMF, RT, 2 h; iii. BH_3·THF 2eq, THF, RT, 2h, then NaOH aq, H_2O_2, $0^{o}C$ to RT, 1.5 h; iv. PCC 3eq, DCM, $0^{o}C$, 2h; v. Tebbe 2eq, py/THF (1:1), $-78^{o}C$ to RT, 20 min; vi. BH_3·THF 2eq, THF, RT, 1h, then NaOH $_{aq}$, H_2O_2, $0^{o}C$ to RT, 2 h; vii. H_2, Pd/C, EtOAc, MeOH, RT, 2h.

Van Boom[32] has used a Paquette rearrangement of similar pyran **47** to give protected cyclooctenone **48** (Scheme 13). Under acid catalysed conditions the eight membered ring collapses to the [3.3.1] bicyclic acetal **49**. This compound is interesting as it's relationship to Kirby's conformationally locked bicycle **22** is clear. However **49** is much more sugar-like than **22** and therefore **49** offers the possibility of a new class of sugars that will show tremendous resistance to hydrolysis.

Pyran **47** can also undergo a thermally induced [3,3]-Claisen rearrangement to give cyclooctenone **50**. Treatment with ammonium formate and reduction of the product imine

in situ gave amine **51** in poor yield. Reaction with a catalytic amount of acid furnished

bicyclic compound **52** which could be easily deprotected to give azasugar **53**.

Both **49** and **53** can be thought of as analogues of sugars; they contain an anomeric

carbon and oxygen and a *pseudo* glycosidic bond which should show increased resistance

towards hydrolysis. Secondly, key hydroxyl groups required for recognition are in their

correct orientations. Azasugar **53** is a close structural mimic to Calystegine B$_2$ **54**, a

naturally occurring micromolar inhibitor of both β-glucosidase and α-galactosidase.

Preliminary experiments have shown that **53** does not show any ability to inhibit these

enzymes suggesting a key recognition component is absent in **53**.
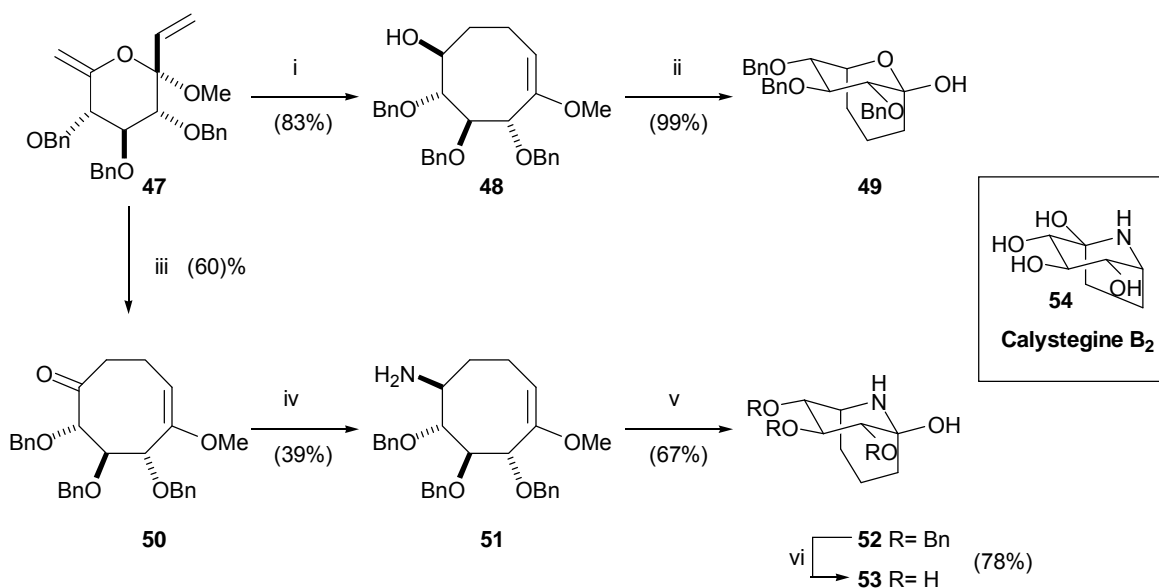
Scheme 13; Reagents and Conditions; i. TIBAL (4 equiv), toluene, 20°C; ii. TBDMSiCl, imidazole, DMF; iii. Δ, xylene, reflux, 12 h; iv. NH$_4^+$HCO$_2^-$, NaCNBH$_3$, 3 A sieves, MeOH/CH$_2$Cl$_2$, 24h; v. *p*-TsOH, aqueous THF, 20°C, 2 h; vi. Pd/C, H$_2$, EtOH, 48 h, (78°C).

Mehta[33] has synthesised a range of ring expanded carbasugar analogues. By replacement

of the anomeric ring oxygen with a methylene group it is argued that the core structure

and hydroxyl receptor array can be retained whilst making the molecules resistant to glycosidases by removing the pathway through which the enzymes hydrolyse their substrates. The molecules are constructed rapidly from lactone **55** which is easily prepared in large quantities (Scheme 14). From **55** an divergent syntheis is used to rapidly construct a range of polyols (Scheme 15).
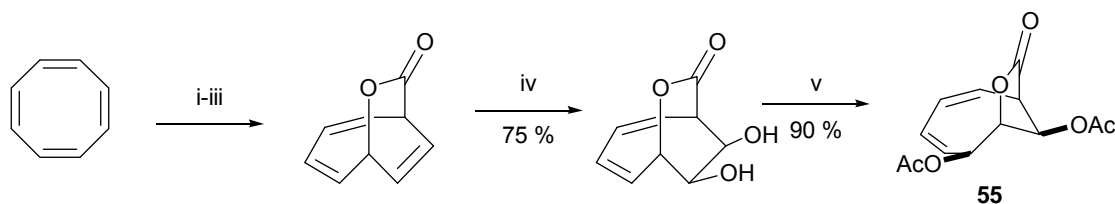
Scheme 14; Reagents and conditions; i, Li, Et$_2$O, -78°C; ii, (CH$_3$)$_2$NC(O)Cl, Et$_2$O, -78 to 15°C then H$_2$SO$_4$; iii, m-CPBA, DCM (60 %); iv, OsO$_4$, NMO; V. Ac$_2$O, py.
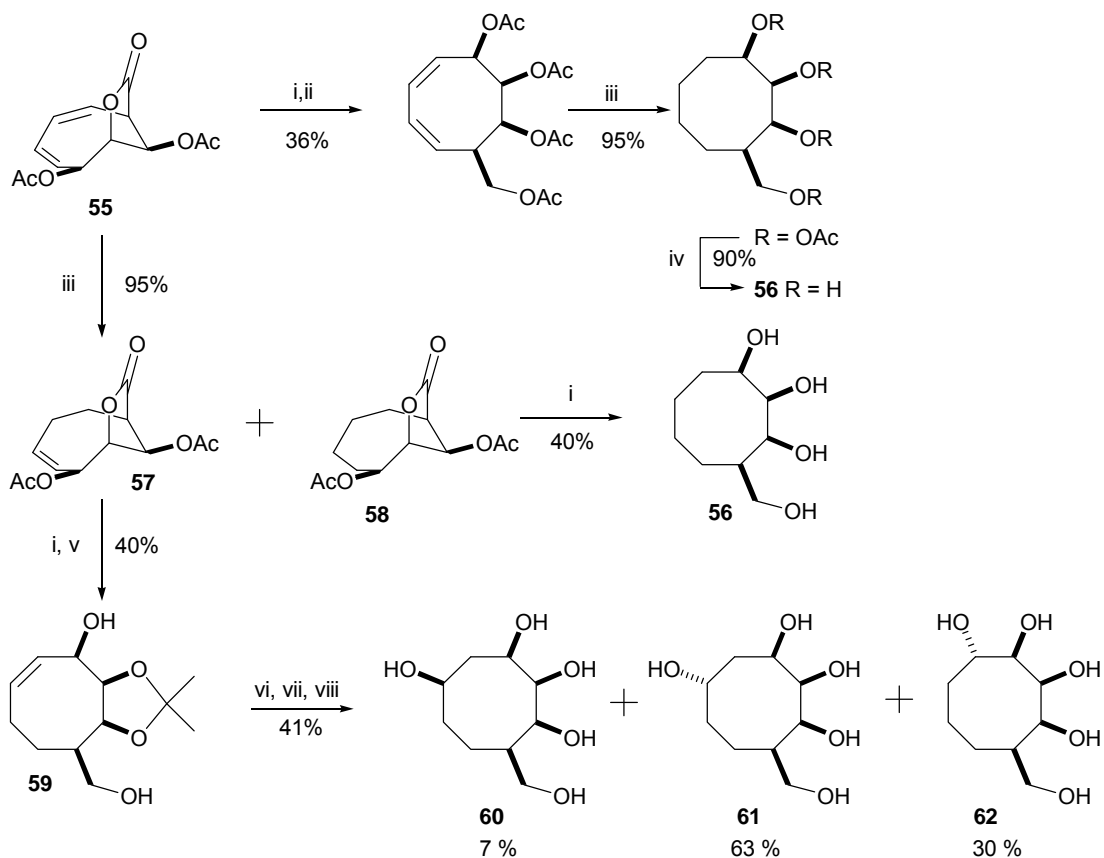
Scheme 15; Reagents and conditions; i, LAH, THF; ii, Ac$_2$O, py; iii, 10% Pd/C, H$_2$, EtOAc; iv, K$_2$CO$_3$, MeOH; v, (CH$_3$)$_2$CO, Amberlyst-15 MS 4A; vi, BH$_3$·THF, NaOH, H$_2$O$_2$; vii, Ac$_2$O, py, DMAP; viii, 2N HCl.

Firstly opening the lactone with LiAlH$_4$, followed by hydrogenation and removal of the protecting groups gave cyclooctane polyol **56**. Alternatively hydrogenation of **55** leads to a 1:1 mixture of the partially and fully reduced lactones **57** and **58**. The fully reduced lactone is converted to **56**, whereas the partially reduced product is converted into acetal **59**. Following hydroboration and removal of protecting groups pentahydroxy-cyclooctanoids **60, 61,** and **62** are isolated in a 7:63:30 % ratio.

Recently Paquette[34] has synthesised a range of enantiopure cyclooctane polyols. Vinyl cyclobutane **63** (Scheme 16) is available from a chiral pool starting material. Dess-Martin oxidation and reaction with alkynyl Grignard gives **64** without loss of stereochemical integrity. Mild basic desilylation was followed by thermally induced rearrangement to cyclooctenone **65**, with the driving force being provided by the relief of ring strain.
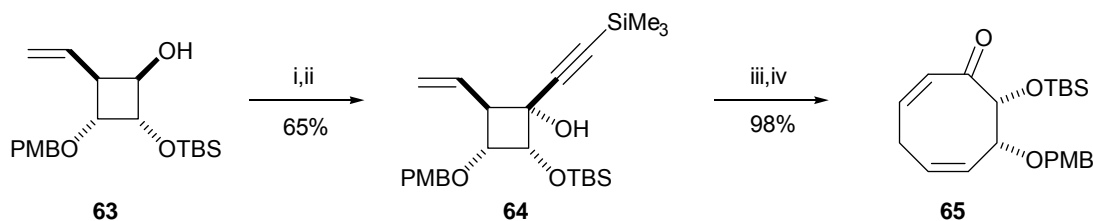
Scheme 16; Reagents and conditions; i, Dess-Martin periodinane, NaHCO$_3$, CH$_2$Cl$_2$; ii, BrMgCCSiMe$_3$, THF, 0°C; iii, K$_2$CO$_3$, CH$_3$OH, rt; iv, C$_6$H$_6$, reflux.

Luche reduction of **65** with sodium borohydride in the presence of cerium (III) chloride and methanol gave **66** as the sole product (Scheme 17). The choice of solvent and the presence of lanthanide were crucial in achieving selectivity. Standard deprotection procedures were used to obtain **67** in good yield. Alternatively sequential reductions with L-Selectride gave **68** then **69** and **70** in excellent yield. The initial reduction at -78°C selectively reduces the conjugated double bond. The second reaction conducted at room

temperature reduces the ketone with complete stereocontrol to give the all *cis* product **69**, although significant migration of the silyl protecting group was observed in **70**. From **69** Upjohn dihydroxylation and stepwise deprotection gave enantiomerically pure polyol **71** in good yield. The optical rotation and presence of eight distinct signals in the ^{13}C NMR spectrum indicated that dihydroxylation had occurred selectively *trans* to the existing functionality (*cis* attack would lead to a *meso* compound, where symmetry would show only five environments in the NMR).
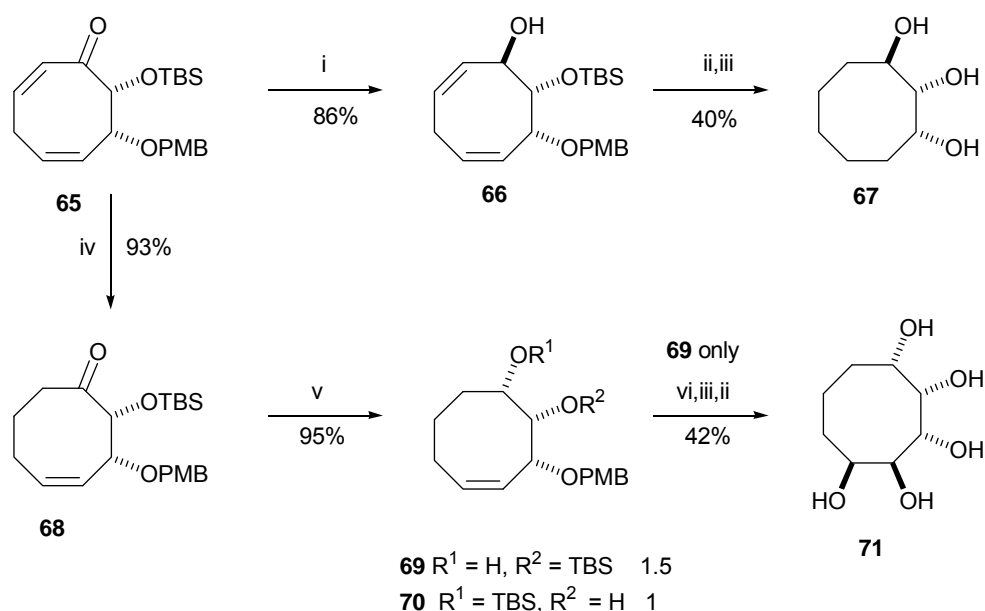
Scheme 17; Reagents and conditions; i, NaBH$_4$, CeCl$_3$, CH$_3$OH; ii, H$_2$, Pd/C, CH$_3$OH; iii, TBAF, THF; iv, L-Selectride, THF, -78°C; v, L-Selectride, THF, rt; vi, OsO$_4$, NMO, 8:1 acetone/water.

Dihydroxylation before reduction of the carbonyl group in **68** gave three 6,6 bicycles **72, 73,** and **74** (no cyclooctanic product was isolated) as products (Scheme 18). These result from transanular hemiacetal formation *via* attack of an hydroxyl from the product diols on the ketone. The results show that the dihydroxylation was non-stereoselective with

attack of osmate on both faces of the olefin. There is a slight bias towards attack *trans* to the existing functionality to give **72** (56%) as opposed to *cis* attack which results in **73** (38%) and a small amount of **74** (4%), where protecting group migration has occurred. The hemiacetal bridge in **72** was removed by acid catalysed reaction with 2,2-dimethoxypropane resulting in **75** with the carbonyl group unmasked. A Wittig reaction proceeds in good yield to give **76**. Hydroboration is not totally stereoselective with small amounts of **77** (9%) being formed in addition to **78** (76%) although the acetonide does significantly restrict approach of the reagent to one face. Both these compound could be rapidly progressed to fully deprotected pentose mimetics **79** and **80** as pentopyranose mimics in good yield.
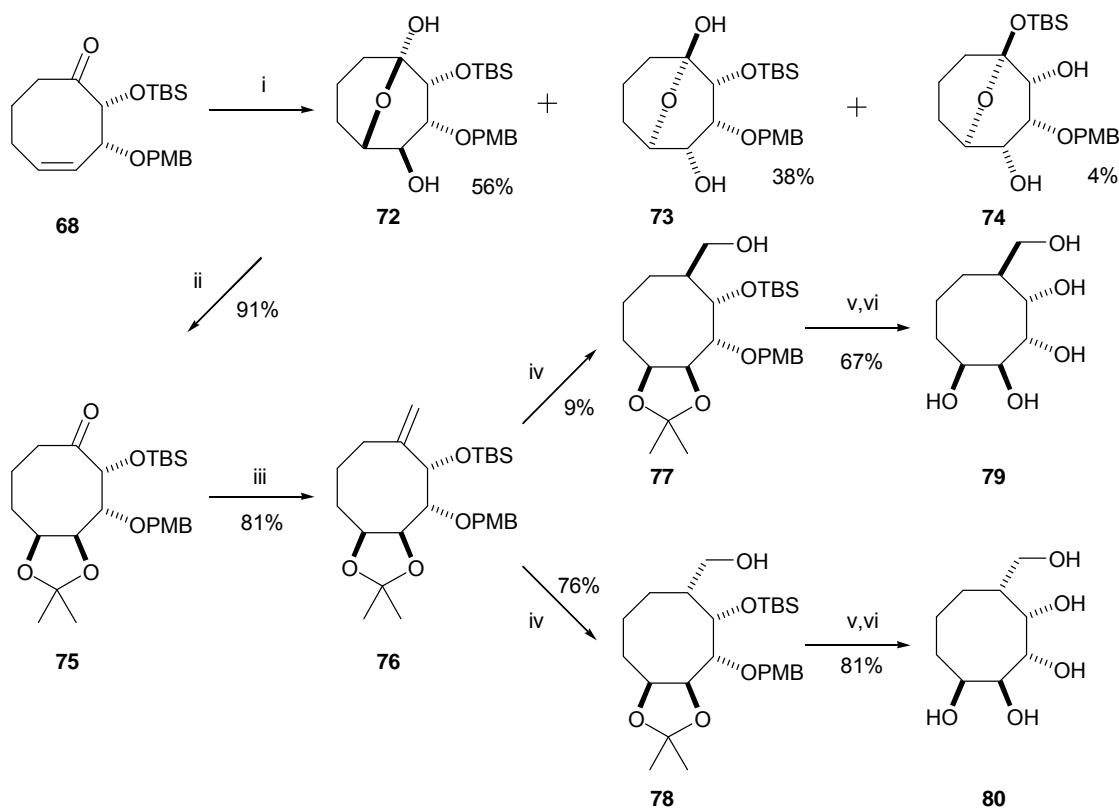
Scheme 18; Reagents and conditions; i, OsO$_4$, NMO, 1:1 acetone/water; ii, Me$_2$C(OMe)$_2$, PPTS; iii, PPh$_3$=CH$_2$, THF; iv, BH$_3$.THF, H$_2$O$_2$, NaOH; v, DDQ, CH$_2$Cl$_2$, H$_2$O, rt; vi, 1M, HCl, CH$_3$OH.

49

1.9 Synthetic Strategies Towards the Synthesis of Eight Membered Rings

Synthesis of medium ring compounds has long posed a significant challenge for the synthetic chemist with the construction of eight-membered rings being particularly problematic. In an enlightening paper on the ring closure of bifunctional chain molecules Illuminati and Mandolini[35] show that the rate constant for lactonisation (Figure 11) increases from the value for three membered ring formation to a global maximum for the formation of the five membered ring. The rate constants then drop until a global minimum is reached for eight membered rings before becoming more facile again although never again reaching anything like the former values.
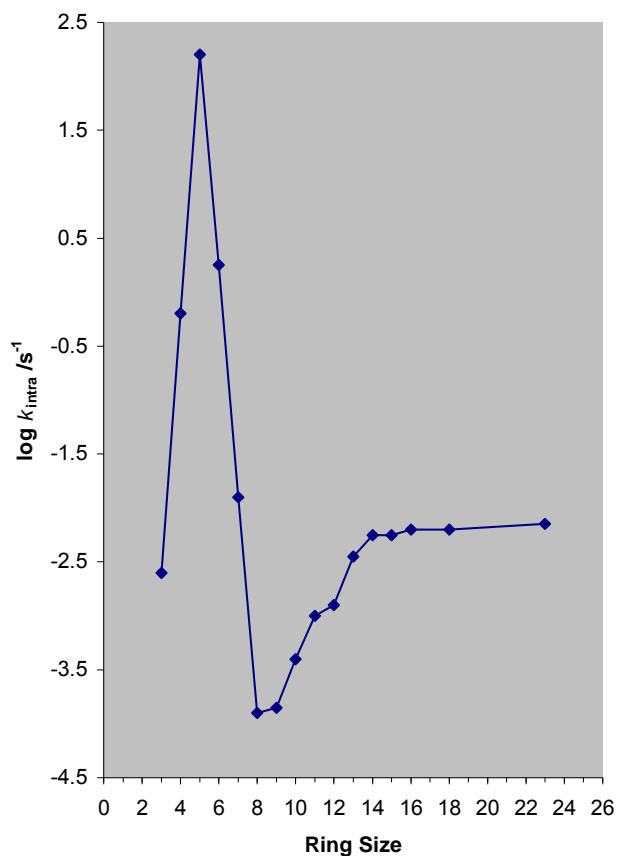
Figure 11

The difficulties arise due to particular properties of both the transition state leading to the cyclic product; in the form of a combination of Baeyer, Pitzer, and transannular strain, and the high conformational flexibility of the acyclic precursor. These effects result in unfavourable enthalpic and entropic contributions to the free energy of activation for the cyclisation reaction, especially when compared to the alternative dimerisation reaction which is bimolecular. As a consequence of this medium ring cyclisations also show low effective molarities. Effective molarity (EM) is defined as k_{intra}/k_{inter} (where k_{inter} is the rate of the intermolecular reaction and k_{intra} the rate of the intramolecular reaction) and has the units moles per litre (mol/L). Effective synthesis must be run at significantly lower concentrations than the EM. A consequence of this is that dimerisation and polymerisation become competitive side reactions unless the cyclisations are run at high dilution.

A range of metal catalysed techniques[36] have been developed along with other strategies for the synthesis of medium rings (Scheme 19).[37] The free radical conversion of **81** into **82** is promoted by samarium(II); *via* a 8-*endo*-trig cyclisation, similar examples using manganese, iron, cobalt, and copper exist in the literature. Alternative strategies using palladium(II) such as the ring closure of ω-bromoallene **83** to **84** can be used. In all cases methodology must be chosen were the precursors are relatively easy to synthesise.
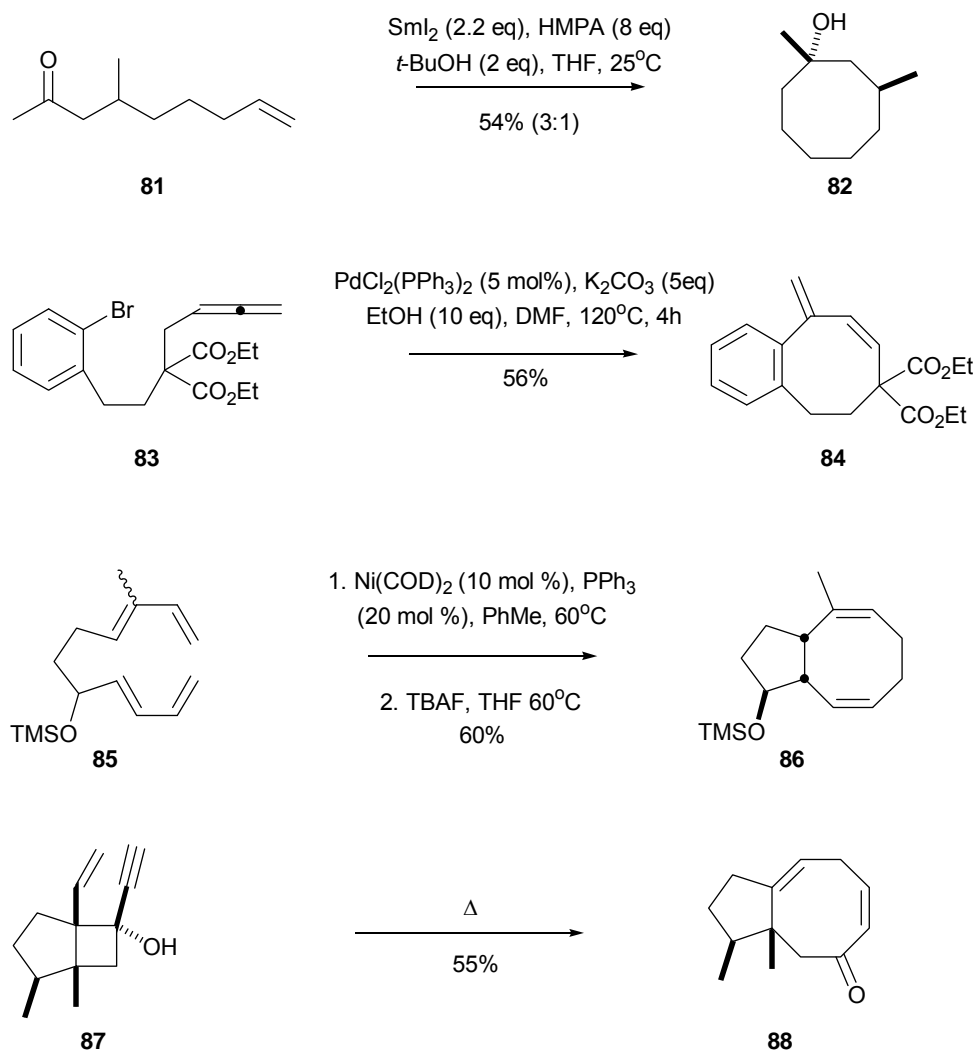
Scheme 19

There are many examples of eight ring synthesis *via* metallo-cycloadditions and sigmatropic rearrangements, such as the nickel catalysed [4 + 4] cycloaddition of **85** into **86**, and the thermally promoted [3,3] sigmatropic rearrangement of **87** to **88,** which has the advantage of containing no metallic reagent that must be removed post cyclisation. As seen in section **1.8** both van Boom and Sinaÿ have successfully taken advantage of this type of approach.

1.10 Facile Cyclisations to Eight Membered Rings *Via* Olefin Metathesis

In the last decade olefin metathesis has emerged as an extremely important and powerful technique for the construction of unsaturated carbon-carbon bonds. This has been due to the development of a range of well-characterised and relatively stable catalysts based on metal carbenes. These catalysts can be used under mild conditions, on a wide range of functionalised substrates requiring little use of protecting groups, and have led to the award of the 2005 Nobel Prize in chemistry to the three main explorers Grubbs, Schrock, and Chauvin. The panoply of applications of metathesis has recently been reviewed comprehensively by Nicolaou[38] and can be divided into five general types of reaction (Scheme 20).

Scheme 20
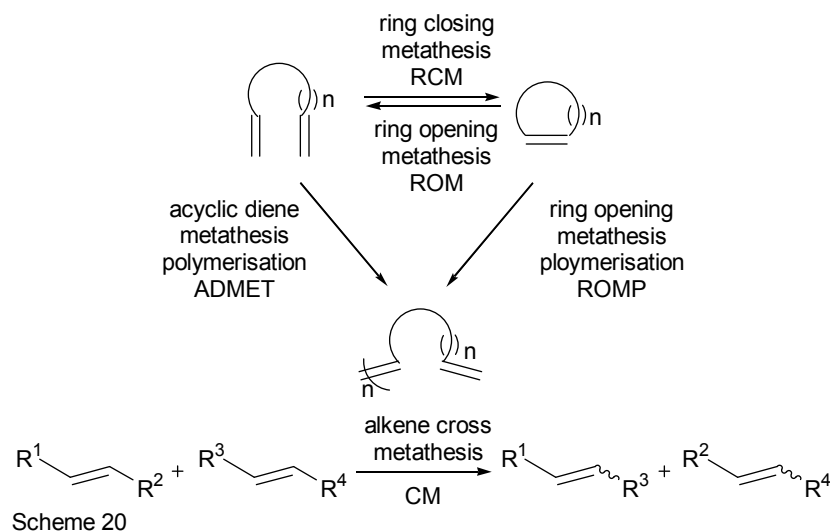
RCM, ROM, and cross metathesis are commonly used in total synthesis whereas ROMP and ADMET are germane to the polymer chemist. The design of catalysts is currently attracting much interest[39] and a number are available commercially. Catalysts are

usually designed based on one of two metal systems (either ruthenium (Grubbs)[40][41] or molybdenum (Schrock)).[42] Initially the molybdenum systems such as **89** (Figure 12) showed higher activity toward a broad range of substrates with variation in steric and electronic properties, but suffered from incompatibility with aldehydes and alcohols. The molybdenum systems are also much less moisture and oxygen stable than the ruthenium systems, and decompose readily upon storage.
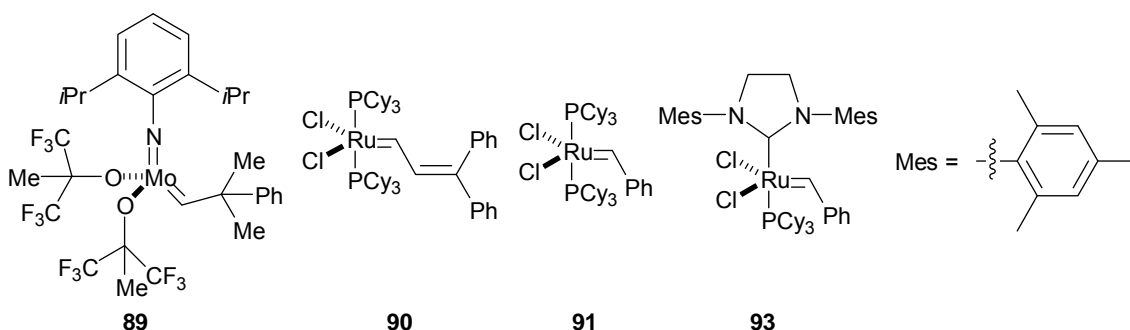
Figure 12

Grubbs' initial discoveries lead to the development of **90** and **91**[43] as first generation catalysts. These complexes, especially **91,** showed significant activity in the RCM of functionalised olefins. Technically the complexes discussed here are catalyst precursors or precatalysts, as phosphine dissociation has been shown to be a crucial step along the olefin metathesis reaction coordinate.[44]

The bulky, Lewis basic PCy_3 ligands were demonstrated to be crucial in increasing activity over precatalysts containing other phosphines such as PPh_3. This observation was rationalised by suggesting that the greater electron donating properties and steric bulk of PCy_3 increased the *trans*-effect in the complex, and consequently led to a more facile dissociation of phosphine to form the active catalyst. Such an effect would also

subsequently aid the stabilisation of the electron-deficient intermediate formed. The mechanistic detail will be discussed later, but the catalyst is thought to propagate through a 14e methylidine species, and react *via* the formation of metallocyclobutane intermediates.

R—N⏜N—R   Mes—N⏜N—Mes   Mes =

R =Ar **92**   **94**
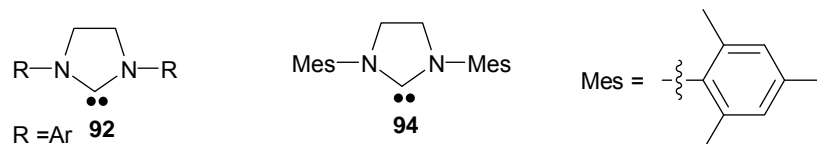
Figure 13

The replacement of one of the phosphine ligands with a *N*-heterocyclic carbene (NHC) ligand of the imidazolinylidene class **92** (Figure 13) led to the synthesis of catalyst **93**[45] derivatised with 1,3-dimesityl-imidazolin-2-ylidene carbene **94**. This catalyst showed much increased activity, especially toward sterically demanding olefins including those with allylic substituents; indeed activity is comparable with that of the more active molybdenum-based systems. However some di- and tri-substituted olefins often still react slowly, if at all, with the catalyst. Initially the axiom behind this increase in activity was thought to be the significantly higher Lewis basicity and steric bulk of the ligands. However ^{31}P NMR studies of the phosphine exchange rate between free and bound phosphine have shown that moving from the PCy_3 ligand in catalyst **91** to an NHC ligand in **93** results in a *decrease* in the phosphine exchange rate by 2 orders of magnitude (k_B 9.6 ± 0.2 (s^{-1}) for **91** and 0.13 ± 0.01 for **93** (80$^{\text{o}}$C)), corresponding to a difference in the Gibbs energy of activation at 298K of 3.12 ± 0.46 kcal/mol^{-1}. These results also suggested that the first step in the mechanism was the dissociation of phosphine to give a

14e species **95**, followed by olefin association, rather than olefin association to form 18e complex **96** followed by phosphine dissociation (Scheme 21).

$$1/k_{obs} = k_{-1}[PPh_3]/k_1 k_2[\text{olefin}] + 1/k_1 \quad (1)$$
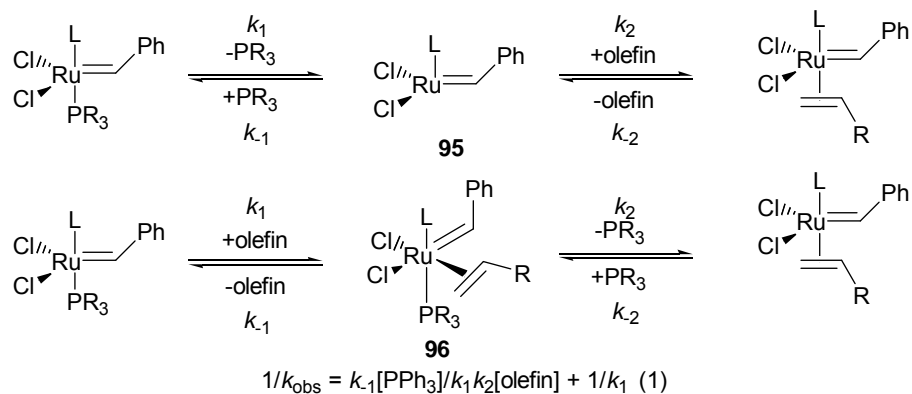
Scheme 21

This pathway is governed by two important factors; the first is the rate of phosphine dissociation ($k_1=k_B$) to produce 14e intermediate **95**. The second is the rate at which **95** either rebinds PR_3 (k_{-1}) or binds the olefin (k_2). Grubbs' has argued that it is possible (with a number of caveats) to see the k_{-1}/k_2 ratio obtainable from equation **(1)** as a measure of catalyst activity. These caveats are firstly, that olefin binding is essentially irreversible (although olefin dissociation must be allowed for catalytic turnover this assumption holds for allyl vinyl ether which reacts rapidly and irreversibly to form a stable carbene after the initial metathesis event), and secondly, all subsequent steps in the mechanism are fast. The rate constants were measured under saturation conditions of free phosphorous (PCy_3) by ^1H NMR for the reaction of the complexes with ethyl vinyl ether. Importantly the values measured for k_1 are close to those measured for k_B in the phosphine exchange experiments. For complex **93**, k_{-1}/k_2 is only 1.25 whereas for **91**, k_{-1}/k_2 is 1.3 x 10^4. These data show that although phosphine dissociation from **93** is two

orders of magnitude less facile than from **91**, preferential binding of olefin over phosphine reassociation is four orders of magnitude higher giving the catalyst higher metathesis activity.

Complexes such as **91** are synthesised easily (Scheme 22) [46][43] from RuCl$_2$(PPh$_3$)$_3$ and a diazoalkane; derivatisation to **91**, and **93** is by ligand exchange. Alternatively **91** and **93** are available commercially under licence.
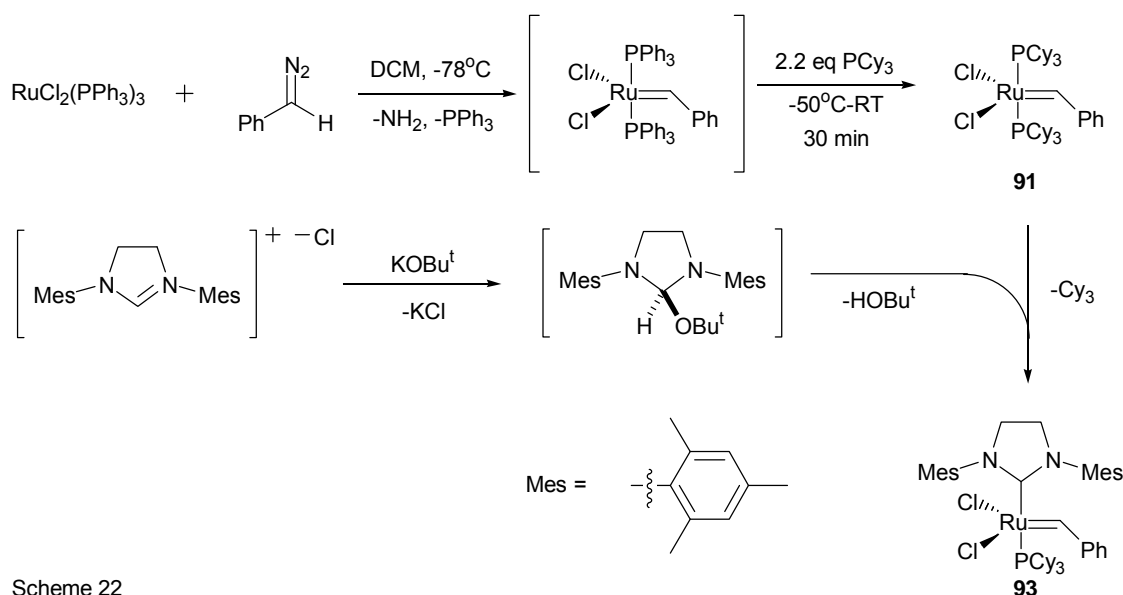
Scheme 22

The first use of olefin metathesis in the synthesis of eight membered rings came from the laboratories of Grubbs[47] where the efficiency of catalyst **90** towards a range of precursors was investigated (Scheme 23). Exposure of **97** and **98** towards metathesis conditions failed to result in the formation of eight membered ring products **99** or **100**. The reaction was found to proceed smoothly upon the introduction of a conformational tether in moderate yield. These annelative ring closures are more facile due to the reduction of the entropic contribution to the free energy of activation. Metathesis of **101**

and **102** proceeded in good yield to give bicycles **103** (75 %) and **104** (60 %). However, the *cis* diastereoisomer of **102**, **105** underwent RCM in poor yield **106** (20 %), with significant oligomeric side products and recovered starting material being detected. It is suggested that the conformation of the cyclohexane ring in **105** forces one of the allylic alcohols into an axial orientation and away from it's intramolecular metathesis partner alkene.
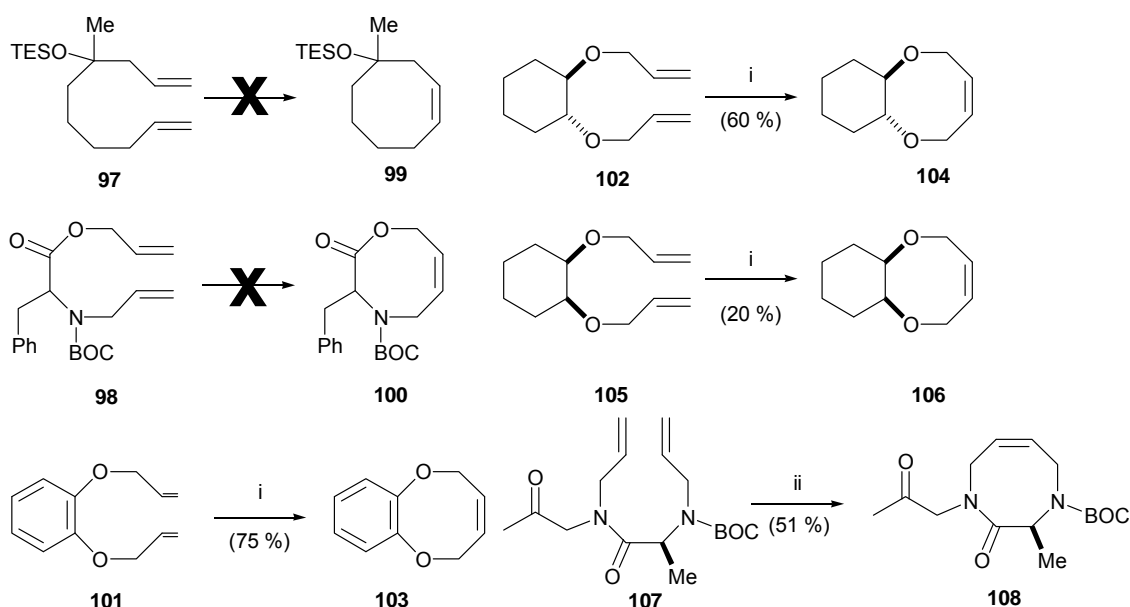
Scheme 23; Reagents and Conditions; i. 8 mol % **90** , 55°C, benzene, 2-3 h, (0.015 M); ii. 10 mol % **90**, 60°C, benzene, 24 h, (0.005 M)

In the same paper the first non-annelative eight ring synthesis *via* RCM is reported with the successful conversion of **107** into **108**; a significant dilution (0.015 to 0.005 M) and increase in reaction time is required to facilitate reaction. This successful cyclisation, where the similar precursor **98** failed, is thought to be because the rotamer required for cyclisation is favoured in **107** and disfavoured in **98** possibly due do the presence of a amide in **107** rather than and ester in **98**.

Little use was made of these findings until both Taylor[48] and Crimmins[49][50] independently used RCM to construct an eight membered ring in their approaches to the total synthesis of Prelaureatin (Scheme 24). Both cyclisations are non-annelative and proceed in high yield, although high dilution (0.005 M in the example from Crimmins) is required. The cyclisation is aided by a favourable *gauche* effect[51] between the C-6 and C-7 C-O bonds in precursors **109** and **110** which help to reduce the entropic contribution towards the free energy of activation by biasing the rotamer population toward those with a favourable conformation for RCM. In both cases excellent yields of cyclised product were obtained 99 % for **111**, and 95 % for **112**.
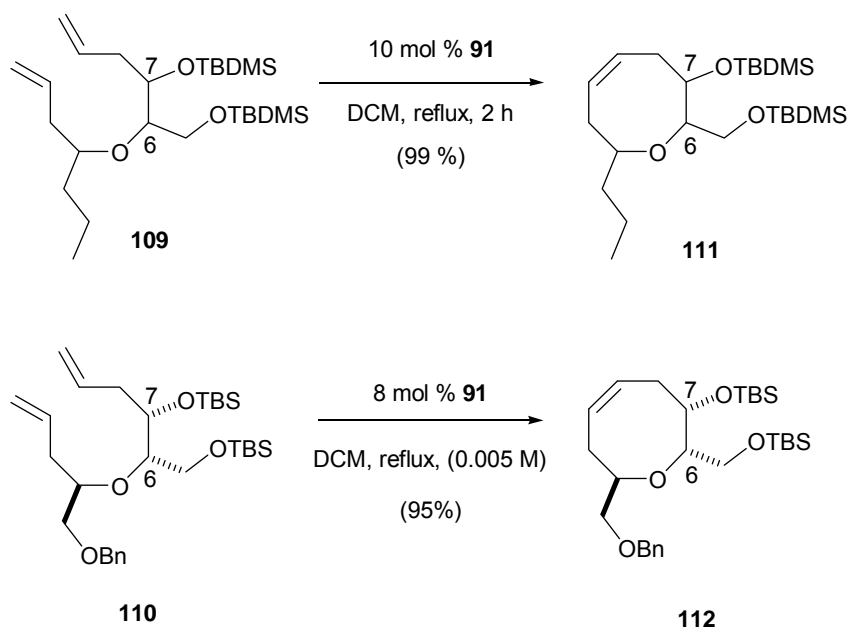
Scheme 24

Substituents on the carbon backbone have been shown to have a large effect on the efficiency of RCM. Sibi[52] synthesised a range of dienes with methyl substituents at various positions along the carbon backbone **113-116** (Scheme 25).
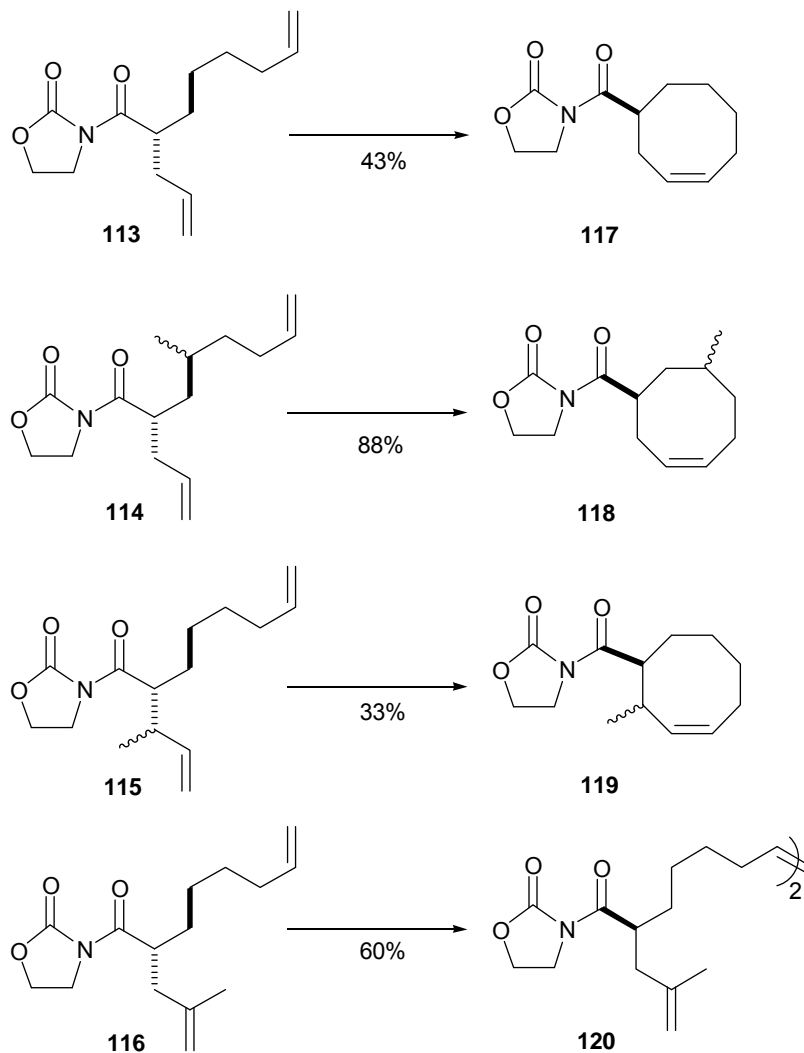
Scheme 25; Reagents and conditions; 10 mol% **93**, DCM (1mM), reflux, 18 h.

The minimally substituted **113** undergoes RCM to afford **117** in moderate yield (43%). However, the introduction of a methyl group remote from the olefin as in **114**, vastly improves the yield (88%) of eight membered ring product **118**. This is possibly because the extra group reduces the conformational flexibility of the system and therefore lowers the entropic contribution to the Gibbs energy of activation. The insertion of a methyl group in an allylic position of the olefin **115** leads to a drastic reduction in reaction

efficiency with a poor yield **119** (33%) of cyclised product although no study of rate is made. Diene **116** with a substituent at C-2 fails to undergo RCM and instead dimer **120** is isolated in reasonable yield (60%). This low reactivity is due to the steric bulk of the methyl group crowding the alkylidene moiety *via* which RCM proceeds and making formation of the metallocyclobutane intermediate energetically difficult. This effect will be discussed in detail in a later chapter.

Since these results were published, RCM has become an increasingly popular technique[53] for the synthesis of eight-membered rings due to it's applicability to a wide range of substrates. This is despite the significant limitations still associated with the technique, including the high dilution required to prevent competitive dimer formation, dependence on substrate structure, and the high cost of the catalyst.

1.11 Synthetic Strategies for Introducing a *gem*-Difluoro Group

A number of synthetic strategies have been developed for the introduction of fluorine into highly functionalised molecules. These strategies can be broadly grouped into two approaches. The first approach is direct fluorination, which involves direct carbon-fluorine bond formation and is often carried out in the later stages of a synthetic route by transformation of a suitable functional group with a fluorinating agent.[54][55][56]

Fluorinating agents are often costly but late introduction can minimise yield loss in subsequent transformations. Both electrophillic Selectfluor (F-TEDA) **121** and

nucleophilic fluorine sources such as SF$_4$, anhydrous TBAF **122**, Deoxofluor **123,** and DAST **124** (Figure 14) have been used.

| 121 | 122 | 123 | 124 |
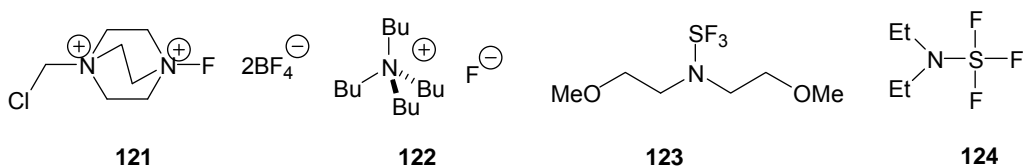
Figure 14

This direct fluorination approach presents a number of problems. Many fluorinating agents are toxic, difficult to handle, and costly. DAST (diethylaminosulfur trifluoride) **124** is commonly used to introduce fluorine into molecules; it transforms hydroxyl groups to produce a C-F bond, and reacts with aldehydes and ketones to form *gem*-difluorides. DAST is thought to react by an S$_N$2 or S$_N$1 contact ion pair mechanism and therefore inversion of configuration takes place at the reaction centre when displacing hydroxyl groups (Scheme 26). Ketones are converted to *gem*-difluoro groups *via* α-fluoro alcohols **125**, which then react with a second equivalent of **124** to give the product.
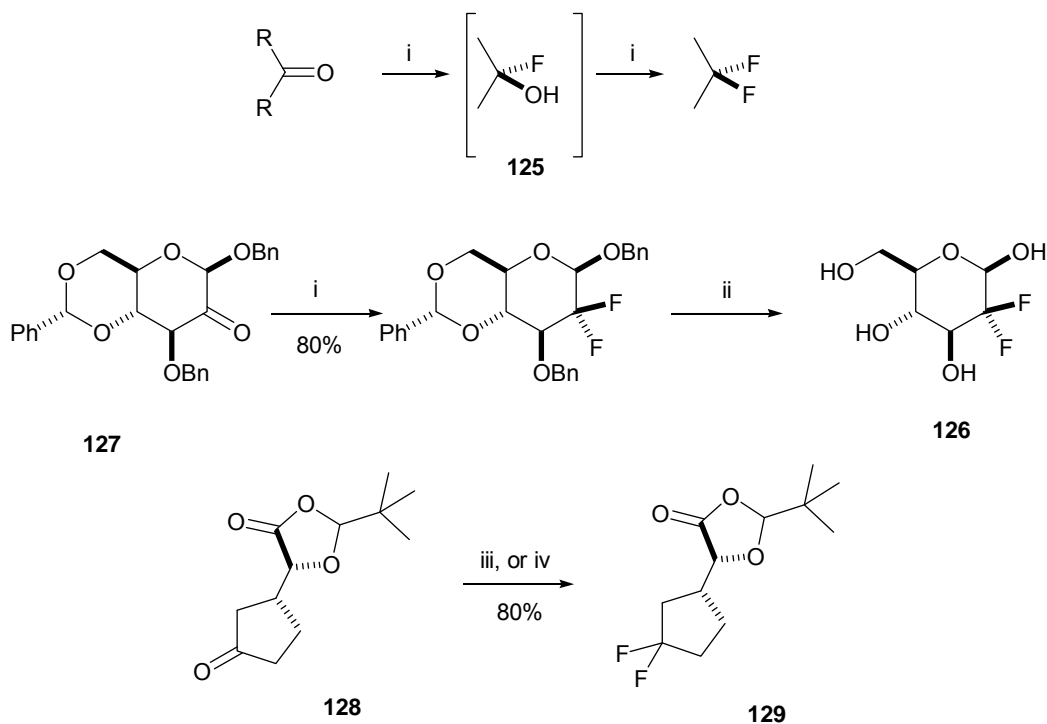
Scheme 26; Reagents and conditions; i, **124**, toluene, 5 min reflux; ii, H$_2$, Pd/C; iii, **123**, DCE, 40°C; iv, **124**, DCE, reflux.

2-Deoxy-2,2-difluoro glucose **126** is easily synthesised from **127** in good yield.[57] Protection of the remaining hydroxyl groups in the sugar is required to prevent unwanted side reactions because of the high reactivity of **124**. This adds to the complexity of the total synthesis and lowers the overall yield of the procedure by adding additional synthetic steps protecting and deprotecting the compound. The transformation of **128** into **129** can be achieved using both **124** and **123** in comparable yield. However the reaction using **124** required considerably more forcing conditions, with important practical consequences. A practical limitation arises because **124** undergoes highly exothermic decomposition at relatively low temperatures and thermal runaways and explosions are therefore a major risk. Deoxofluor **123** is a new reagent that shows similar chemistry to **124** with respect to alcohols and carbonyls, but will also convert carboxylic acids to their

trifluoromethyl derivatives over two steps. The great advantage of **123** over **124** is much greater thermal stability. However **123** has yet to be tested against a wide range of substrates.

Perhaps the most crucial limitation with the whole direct fluorination approach is that for most target substrates a specific precursor must be used. In many cases this precursor may be expensive, or only available, if at all, after a complex synthesis. This severely limits the use of direct fluorination to quickly synthesise a library of related compounds.

The second approach is known as the "building block" approach[58] and involves taking a small fluorinated starting material and elaborating to the complex final product using carbon-carbon bond formation and traditional transformations. The advantage of this strategy is that the building block can be chosen so as to be commercially available or easily synthesised, and easy to handle. More importantly synthesis can be designed to be divergent and a number of related compounds can be synthesised from one product stream. The challenge in the approach is in learning how to apply conventional synthetic chemistry to the building blocks; this has been demonstrated by Percy[59][60][61] and co-workers (Scheme 27).

Scheme 27

OH
CF$_3$ **130**

i. NaH, THF, 0°C
ii. DECCl

i. NaH, THF, 0°C
ii. MEMCl

i. KOH, H$_2$O
ii. RCH=CHCH$_2$Cl

ODEC
CF$_3$ **132**

OMEM
CF$_3$ **131**

i.LDA, THF, -78°C, then SnBu$_3$Cl
ii. EtOCOCl, 2.5 % Pd(OAc)$_2$
PPh$_3$, CuI, THF, 60°C

O CF$_3$ **133**

i. LDA, THF, -78°C
ii

F F
EtO$_2$C ODEC

i. t-BuLi, -100°C, then cinnamaldehyde
ii. [3,3], chloroform
iii. NaBH$_4$, ethanol

OMEM
F F OH

R^1 O R^2

Diels Alder

HO Ph
F F OH

Red-Al, hexane

O F ODEC
R^2 R^1 CO$_2$Et + exo

RCM

OMEM
F OH

PhSCl, CHCl$_3$

PhS O F ODEC
R^2 R^1 F O

OH
HO
F F

i. HCl, THF
ii. NaBH$_4$

OH
F OH + anti

UpJohn

i. O$_3$, TMSCl, MeOH
ii Me$_2$S

F F
R^2 OH
HO R^1 OH OH

OH OH
HO OH
F F OH **134**

33

OH
F O OMe **135**

R^1,R^2 = H, Me

A range of strikingly different fluorinated compounds has been synthesised from the cheap and available trifluoroethanol **130**. This is elaborated into a range of simple building blocks, such as the methoxyethoxymethoxy (MEM) ether[62] **131**, diethyl carbamate (DEC) **132**,[63] or fluorinated allyl ether **133**.[64] The group uses traditional synthetic chemistry such as Diels Alder[65], Claisen, RCM, and Suzuki couplings to give a range of highly functionalised end products including cyclitols[60] **134** and methyl furanoside[61] **135** with scope for elaboration throughout the synthesis. Such an approach

often shows greater tolerance of functional groups than the direct fluorination approach, and allows highly functionalised molecules to be assembled quickly. However the unique electronegativity of fluorine atoms can often affect the reactivity of fluorinated intermediates in common reactions.

Sinaÿ and co workers have developed an elegant method in their synthesis of gem-difluorocarba-D-glucose **136** (Scheme 28)[66]. using CF_2Br_2 as the fluorinated building block. The crucial step is a TIBAL induced reductive rearrangement of **137** into **138**. Firstly the alkyne is protected as a cobalt hexacarbonyl complex **139**. Coordination of TIBAL to the anomeric oxygen causes cleavage of the C-O bond and the formation of a carbocation at C5. The carbocation is stabilised by the cobalt hexacarbonyl complex[67][68] allowing rearrangement and insertion of the CF_2 centre and subsequent sterically controlled stereoselective reduction *in situ* of the resultant carbonyl to give **140**. Simple decomplexation furnishes **138** in 65% yield over three steps; standard chemistry completes the synthesis. The β anomer could be obtained by using the Lewis acid Cl₃TiO*i*Pr to promote the rearrangement instead of TIBAL, with subsequent addition of LiHBEt₃ to reduce the ketone under electronic control.
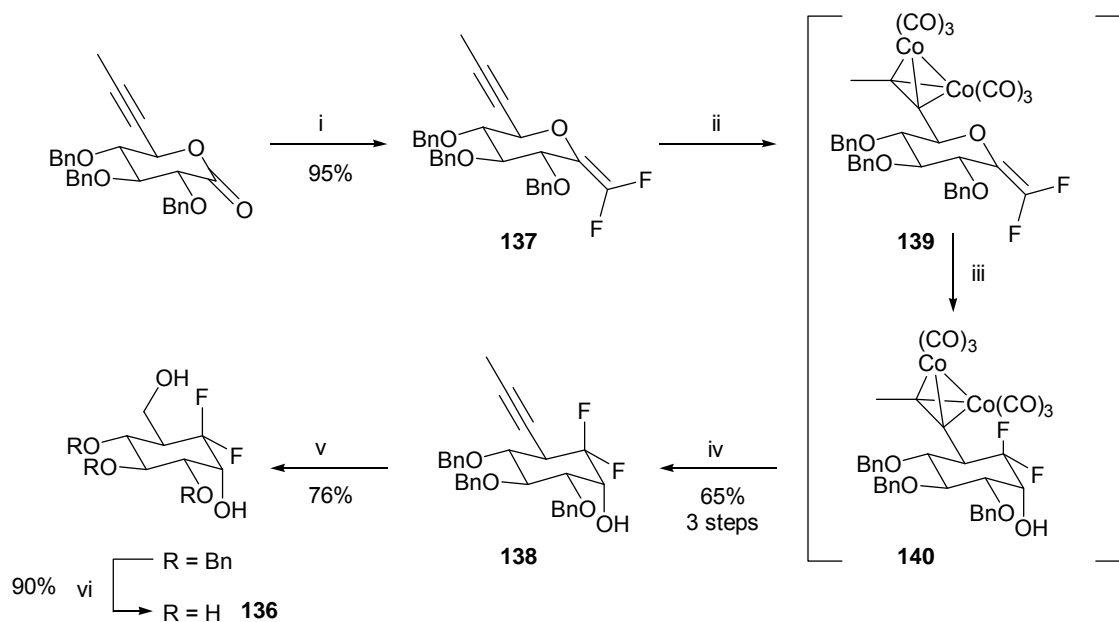
Scheme 28; Reagents and conditions; i, a) HMPT (5 equiv), THF, -40°C to rt, , 4 h; b) CBrF$_2$ (5 equiv), HMPT (5 equiv), THF, rt to reflux, 1 h; ii, [Co$_2$(CO)$_8$] (1.5 equiv), DCM, rt, 2h; iii, TIBAL (5 equiv), toluene, rt, 2.5 h; iv, CAN (5 equiv), NEt$_3$ (1 equiv), acetone, 30 min; v, a) Pd/CaCO$_3$, H$_2$, MeOH, rt, 4 h; b) O$_3$, DCM, -78°C, 5 min; c) NaBH$_4$, DCM, rt, 1h; vi, Pd/C, H$_2$, MeOH, rt, 1 h.

The authors suggest that the final compounds could be useful as substrates for probing the role of the endocyclic oxygen in sugar-protein interactions as the *gem*-difluoro group may allow the retention of hydrogen bond interactions with fluorine acting as a weak acceptor. Deletion of the endocyclic oxygen prevents hydrolysis as there is no glycosidic bond.

1.12 Difluorinated Cyclooctenones; Towards a New Class of Conformationally Locked Sugar Analogues

Previous work within the Percy group has established methodology delivering a new class of *gem*-difluorinated sugar analogues (Scheme 29).[69] Treatment of ether **131** with strong base[62] and trapping of the metallated intermediate with an aldehyde electrophile gives access to allylic alcohol **141** (90%). Allylation under phase transfer conditions (91%) and subsequent [2,3]-Wittig rearrangement afforded β-hydroxy ketone **143** in acceptable yield (55%). Removal of the MEM protecting group under acidic conditions gave **143** (65%), which can be cyclised *via* RCM to cyclooctenone **144** in good yield (78%).
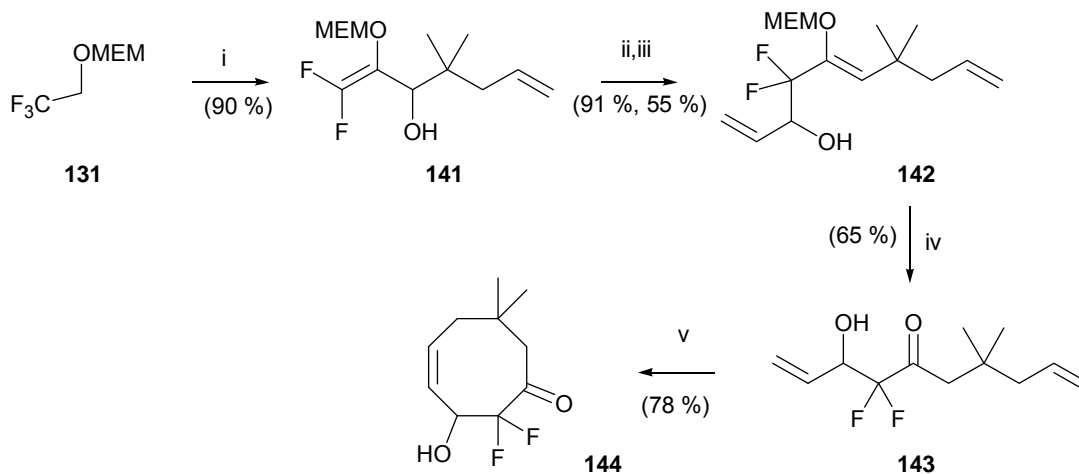
Scheme 29; Reagents and conditions: i. LDA, THF, -78°C, then CHOC(CH$_3$)$_2$CH$_2$CHCH$_2$; ii. allyl bromide, NaOH, Bu$_4$NHSO$_4$; iii. LDA, THF, -78°C to -30°C; iv SOCl$_2$, MeOH, 0°C; v. 5% **93**, Ti(O*i*Pr)$_4$, DCM, reflux;

An alternate synthetic[70] route to functionalised eight membered rings is also available from **132** (Scheme 30). Treatment with base and trapping of the metallated intermediate

with either **145** or **146** proceeds smoothly in the presence of boron trifluoride etherate to

afford allylic alcohols **147a** (79 %) and **147b** (66 %) in good yield and on a large scale

(up to 0.33 mole for **147b**). Subsequent treatment with base affords an allylic alkoxide

which undergoes a transcarbamoylation releasing a difluoroenolate. This can be trapped

with acrolein in an aldol reaction to give **148a** and **148b** in 58 % and **148c** and **d** 64 %

yields respectively. Diastereomers **148c** and **148d** were successfully separated and

exposed to catalyst **93** along with unseparated **148a** and **148b** to give eight membered

rings **149c** (69%) and **149d** (77%) along with **149a** and **149b** (63%) respectively which

could be separated by column chromatography (Biotage). The difference in efficiency of

the two Grubbs' catalysts was noticeable in the RCM to give **149d**; 5mol % of first

generation catalyst **91** gave a 77 % yield after 144 hours whereas 2.5 mol % **93** with the

NHC ligand catalysed the same conversion in 18 hours in almost identical yield (75 %).

149a R = H, X = ODEC, Y = H (63 % combined)
149b R = H, X = H, Y = ODEC
149c R = Me, X = ODEC, Y = H (69 %)
149d R = Me, X = H, Y = ODEC (77 % **91**, 75 % **93**)

148a (58 % combined)
148b
148c (64 % combined)
148d
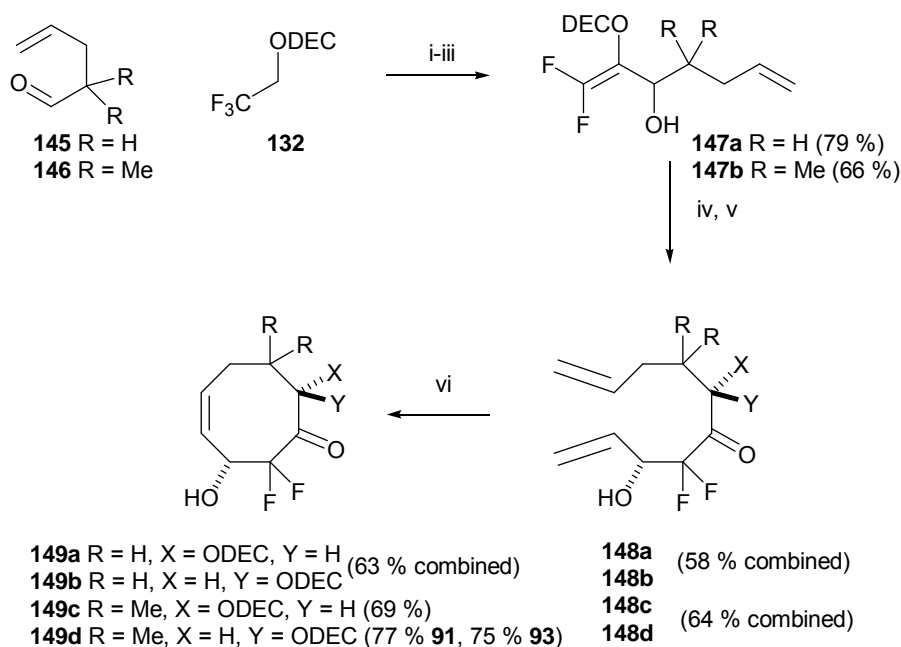
Scheme 1.29; Reagents and conditions; i, LDA, THF, -78°C; ii, **145** or **146**; iii,
F$_3$B.OEt$_2$; iv, n-BuLi, THF, -78 to -10°C; v, acrolein then NH$_4$Cl; vi, 5 mol % **91** or
2.5 mol % **93**, Ti(OiPr$_4$), DCM, reflux.

From this intermediate, the group developed two oxidation strategies for **144** and **149** (Scheme 31); firstly dioxirane epoxidation[71] and microwave promoted hydrolytic ring opening gave bicycle **150a-e**. Secondly dihydroxylation[72] gave bicyclic triols **151a-e** and **152a-e**. The microwave reaction under slightly basic conditions removes the DEC protecting group to expose a sugar motif. These are interesting compounds as they are structurally analogous to Kirby's previously discussed conformationally locked acetal. This along with the presence of the *gem*-difluoro group, this should make the glycosidic bond very resistant indeed to hydrolysis. If they could be incorporated into larger structural motifs such as NDP sugars they offer possibilities as a new class of non-reacting substrate mimics for sugar processing enzymes. Clearly this specific class of compounds is of little use as sugar mimics as they contain the distinctly unnatural *gem*-dimethyl group on the bridging backbone.

149a, 150a, 151a, 152a, R = H, X = OH, Y = H
149b, 150b, 151b, 152b, R = H, X = H, Y = OH
149c, 150c, 151c, 152d R = Me, X = OH, Y = H
149d, 150d, 151d, 152d, R = Me, X = H, Y = OH
144, 150e, 151e, 152e, R = Me, X = Y = H
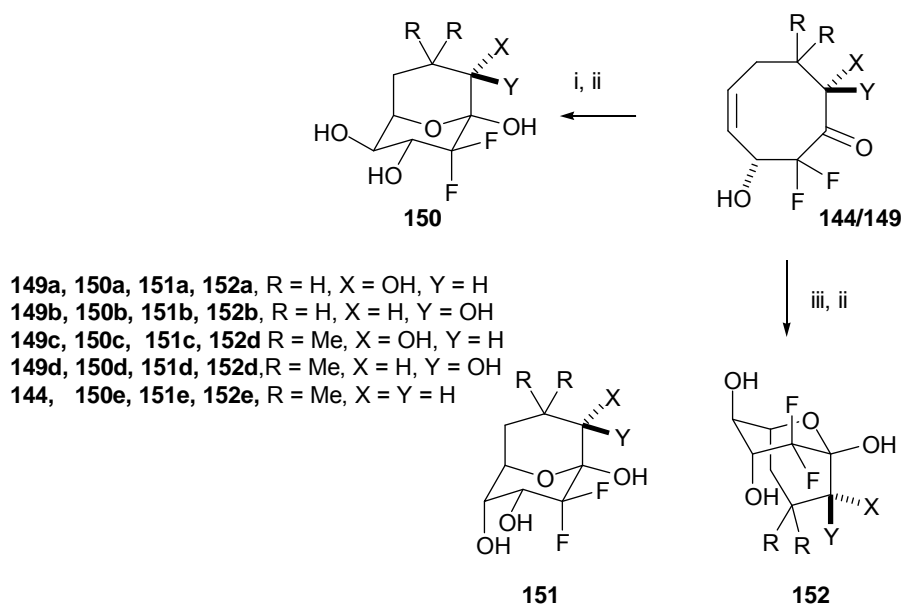
Scheme 31; i. EDTA, MeCOCF$_3$, NaHCO$_3$, Oxone, MeCN, H$_2$O; ii. HONa/H$_2$O, microwave; iii. 2% OsO$_4$, NMO, *t*BuOH/acetone/H$_2$O, 0°C.

1.13 The Project

We hope to synthesise a range of non-natural NDP sugars **153** (Scheme 32) as substrate mimics for the glycosyl transferase class of enzymes. There is sufficient evidence described above that these compounds should be accepted as substrates by the more sugar flexible GT's. The examples from the Withers group discussed above suggest that the *gem*-difluorogroup at C-2 should not affect the recognition characteristics of the species. The *gem*-difluoro group will also provide a useful NMR assay once incorporated. The $^3J_{H-F}$ coupling constants should also give crucial information about the conformation of the ring in the binding pocket as they are extremely sensitive to changes in conformation. We suggest that once bound as a ligand in the active site our substrate will not be able to react with the enzyme due to the prohibitive energy barrier in forming an oxacarbenium ion "like" transition state caused by the incorporation of the conformational lock.

The synthesis of compounds of type **153** will be split into two distinct parts; phosphates **154** will be synthesised chemically using a building block approach from cheap easily available starting materials including ether **131** and aldehyde **145**, easily available from the Claisen rearrangement of ethyl vinyl ether.

Scheme 32
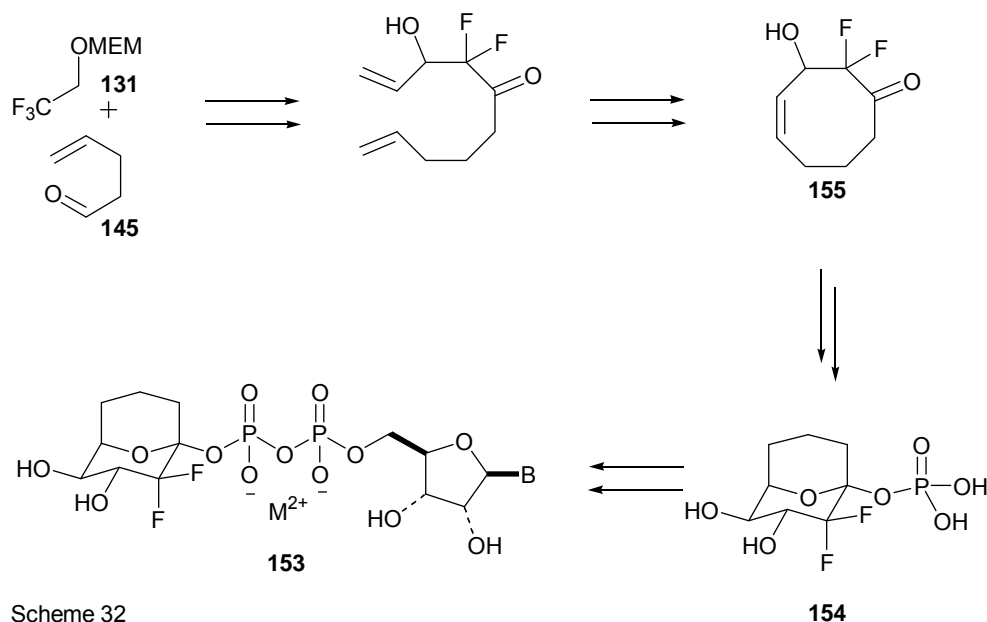
The crucial synthesis of eight membered carbocycle **155** will be attempted *via* the established MEM protocol already discussed, with the cyclisation being performed using the well precedented RCM. The original chemistry described above contains the distinctly unnatural *gem*-dimethyl group in the conformational lock. We hope to synthesise the CH_2 analogue of this class of compounds by reacting MEM ether **131** with aldehyde **145** currently used in the carbamate based route.

Eight membered ring **155** is similar to species previously prepared by the Percy group and we therefore expect similar reactivity to the existing species upon oxidation to give the [3.3.1]-oxa-bicycles which are true non-natural sugars with the removal of the *gem*-dimethyl group. Strategies for the advancement to the phosphates **154** will be developed and these compounds will be handed over to collaborators for chemoenzymatic activation into the final products.
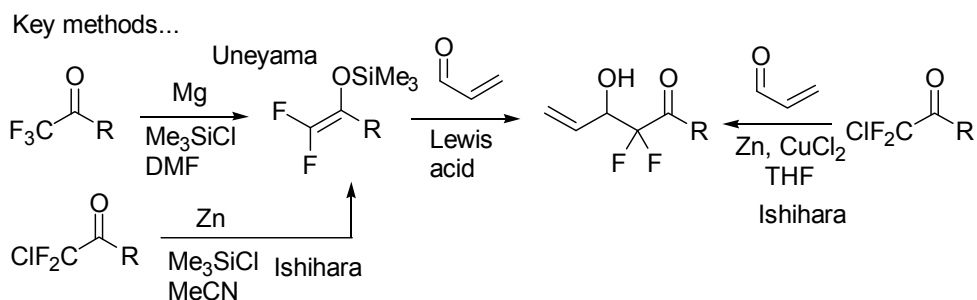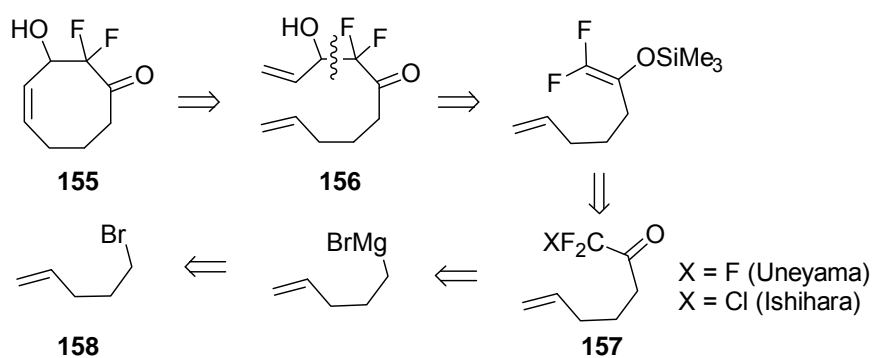
Scheme 33

Attempts will be made to develop a shorter chemical synthesis of RCM precursor **156** (Scheme 33) that does not rely on strong base low temperature chemistry and is therefore more ameable to scale up. It is hoped that a range of trihaloketones **157** can be prepared from bromide **158** *via* Grignard chemistry. It is then expected that reductive dehalogenation using either Uneyama's[73] magnesium or Ishihara's[74] zinc promoted chemistry and trapping of the subsequent enolate with acrolein in an aldol reaction will lead to RCM precoursor **156** and hence to a new class of bicyclic compounds.

2.0 Results and Discussion

2.1 Preparation of 1,1,1-Trifluoro-hept-6-en-2-one 159
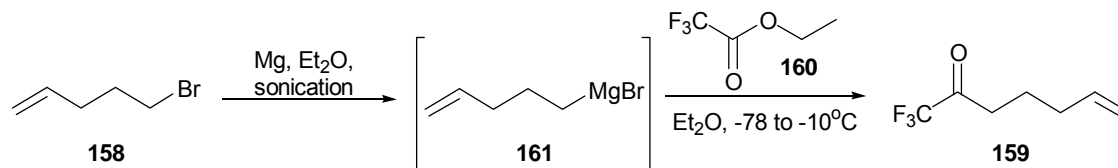
Scheme 34

Trifluoromethyl ketone **159** previously synthesised by Laurent[75] was successfully prepared (Scheme 34) from ethyl trifluoroacetate **160** and Grignard reagent **161** (prepared from 5-bromopent-1-en **158**) in 36% yield. Though modest this yield is an improvement over the existing literature preparation (29%). Initiation of the Grignard reaction was found to be challenging, and considerable difficulty was experienced in achieving self reflux despite the use of freshly acid washed magnesium, prolonged sonication, and external heating. Indeed an appreciable amount of magnesium was observed at the bottom of the reaction flask after attempted formation of the characteristic black Grignard solution; this difficulty is suggested as a contributory factor towards the poor yield. Upon formation **161** was added to electrophillic trifluoroacetate **160** and reacted smoothly *via* nucleophilic substitution at the carbonyl group.

Grignard reagents, which exist as organometallic clusters in ether, react *via* a cyclic 6-membered transition state[76] **162** to form an unstable tetrahedral intermediate (Scheme

35); **163** which breaks down to give the ketone **164**. Usually the ketone is then subject to further nucleophilic attack by the Grignard to give a tertiary alcohol due to it's higher reactivity than the original ester. The survival of the ketone in this case is thought to be due to either inductive stabilisation of **163** by the trifluoromethyl group only releasing the ketone on aqueous work up, or alternatively enolisation of the resultant ketone may protect the functionality from further nucleophilic attack giving the tertiary alcohol.
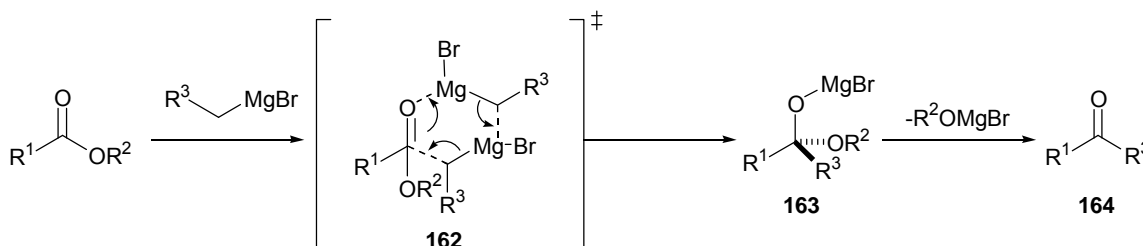
Scheme 35

The most likely side reaction in a Grignard reaction is a Wurtz coupling[77] delivering deca-1,9-diene in this case. Although this could not be positively identified as a side product after distillation, significant amounts of a product with resonances in the alkyl region of the NMR spectrum were observed as a contaminant in the product fractions. Deca-1,9-diene has a boiling point of 162-163°C[78] compared to that of 95-100°C for **159**; the difference in boiling points suggests that any contamination must be in the form of an azeotrope. Although small amounts of unidentified CF_3 compounds were observed in the ^{19}F NMR spectrum they could not be identified.

2.2 Attempted Reductive Defluorination of 159 Under Uneyama Conditions

Uneyama[73] has shown that magnesium can promote selective cleavage of a C-F bond in trifluoromethyl ketones **165** before trapping with TMS-Cl to give 2,2-difluoroenol silanes **166**. These are enolate equivalents which can be reacted with electrophiles to give β-hydroxyketones **167** (Scheme 36). The scope of the reaction has been shown to encompass aromatic, hetroaromatic, and aliphatic trifluoromethyl ketones.

R= Aryl, Cy, C₆H₁₃
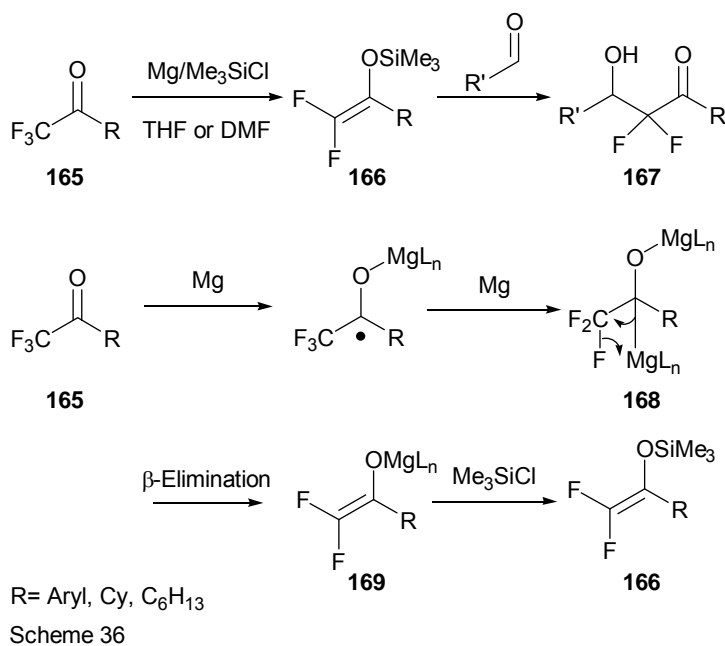
Scheme 36

The reaction is thought to proceed through the following mechanism (Scheme 36); **165** undergoes two successive magnesium promoted 1 electron reductions to give **168**. Species **168** then readily undergoes a facile β-elimination of fluoride to give metal enolate **169**, which is then is trapped with TMS chloride to give **166**.

A considerable barrier to bond cleavage is the large bond energy associated with the C-F bond (*ca*. 489 kJ mol^{-1}). The reaction is much easier when the CF$_3$ group is attached to a π system; Uneyama has proposed that this is due to the increased ability of the carbonyl group to accept an electron; the subsequent extrusion of fluoride ion is highly exothermic and may provide an additional driving force to the reaction.

The attempts made to extend this chemistry to **159** proved disappointing (Scheme 37, Table 3). Following the original procedure (entry 1) led to decomposition by NMR, and some protonated compound **170,** indicative of protodesilylation. Extending the reaction time to 18 hours over molecular sieves (entry 2) allowed detection of a small amount of the intermediate **171** which was assigned by a characteristic $^2J_{H-F}$ coupling (53.7 Hz), along with significant amounts of decomposition products; no aldol product **156** from trapping with acrolein **172** was observed in either case. Initially the reactions had been conducted in DMF, the preferred solvent for aliphatic ketones. A change in solvent to THF, the usual solvent for aromatic and hetroaromatic ketones (entry 3) also gave no intermediate enol silane by NMR.

R = (CH$_2$)$_3$CH=CH$_2$ = **171**   **156**   **170**
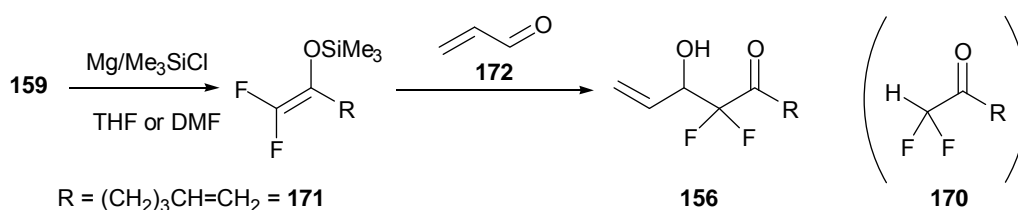
Entry[a]	Solvent	Temperature (°C)	Time (hr)	Yield (%)	Comments
1	DMF	rt	0.5	No aldol	-
2	DMF	rt	18	No aldol	4Å molecular sieve
3	THF	rt, Acrolein added at -78	18	No aldol	-

Scheme 37; Table 3, a) **159** 1eq, Mg 2eq, TMSCl 4eq, **172** 2eq.

The results suggest that the enol silane intermediate is forming slowly and that decomposition reactions are successfully competing with **172** for **171**. This is not altogether unexpected, as this chemistry has been primarily applied to aromatic trifluoromethyl ketones. Aromatic ketones are easier to reduce than aliphatic ones and it may be more energetically favourable for them to undergo the two-electron reduction with magnesium to form the ketyl anion species.

2.3 Synthesis of 1-Chloro-1,1-difluoro-hept-6-en-2-one 173

Scheme 38

Novel chlorodifluoromethyl ketone **173** was prepared from the previously described Grignard **161** and a range of electrophiles **174** (Scheme 38, Table 4); after optimisation **173** was obtained in a yield of 33% from the methyl ester (R = Me). Synthesis from chlorodifluoroacetic acid sodium salt (entry 1, R = Na) was limited by the poor solubility of the sodium salt in THF. The reaction gave material of good purity by ^{19}F NMR, but the proton NMR showed evidence of the previously discussed Wurtz product. Synthesis from the acid (entry 2, R = H) was also problematic, requiring two equivalents of Grignard reagent. To avoid wasting expensive starting material, the initial deprotonation was attempted with an equivalent of *i*PrMgCl, with Grignard **161** being added later. The yields obtained using this methodology were however disappointing (18%), and the

material obtained after distillation again showed significant contamination in the high field alkyl region, possibly indicating Wurtz coupled product, especially as the ^{19}F NMR showed good purity. The most successful synthesis followed a procedure developed by Kitazume[79] (entry 3, R = Me). Again the purity of the distilled product was disappointing (74 % GC) with evidence for possible Wurtz product and unidentified CF_3 products visible in the ^{19}F NMR spectrum. Furthermore the GCMS showed a peak (16 %) with a characteristic fragmentation pattern of 14 mass units probably due to CH_2 loss from the Wurtz product although no molecular ion was found. A third major GC peak (9 %) had characteristic chlorine signals with strong ions at 85 and 87 mass units in a 3:1 ratio and very little at higher mass. This could correspond to a ClF_2C^+ fragment of an unknown type.

Entry	**174** R=	Conditions	Yield (%)
1	Na	i. Mg, Sonication. ii. Add to NaO_2CCF_2Cl, -20°C, 18hr	28
2	H	i(a). Mg, Sonication. i(b). ClF_2CCO_2H + iPrMgCl, -10°C. ii. [i(a) + i(b)], -10°C to rt, 18hr.	18[a]
3	Me	i. Mg, Sonication. ii. Add to MeO_2CCF_2Cl, -70°C, 50 hr	33

Table 4 [a] material of poor purity obtained after distillation

The low yields obtained for this procedure, taken with the results for trifluoromethyl ketone **159**, suggest that firstly Grignard **161** is either particularly unstable or difficult to form, as demonstrated by the initiation difficulties, and secondly the yield is less affected by the nature of the electrophile. In both the trifluoro- and chlorodifluoro- cases, a major side reaction is probably a Wurtz coupling to give deca-1, 9-diene.

2.4 Attempted Reformatsky-type Aldol Reactions with Chlorodifluoromethyl Ketone 173

Ishihara[74][79] has shown that chlorodifluoromethyl ketones react with carbonyl compounds in the presence of zinc dust and a copper salt. This Reformatsky-type reaction is an efficient method of preparing α,α-difluoro-β-hydroxy ketones. It was hoped that **173** would react smoothly with acrolein **172** to afford β-hydroxy ketone **156** (Scheme 39).

Scheme 39
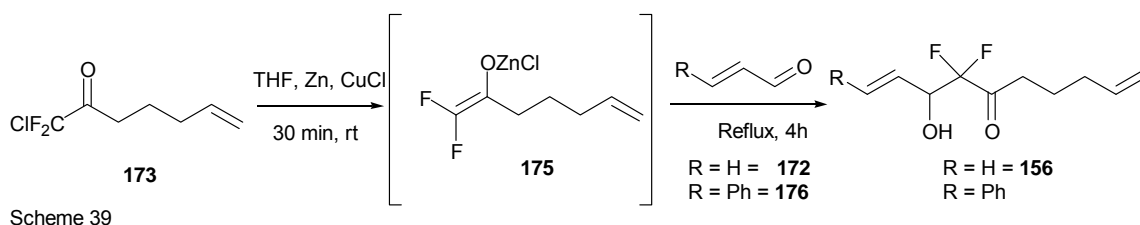
The reaction proceeds *via* a zinc enolate **175** which is then trapped by the aldehyde electrophile. The reaction was easily monitored using ^{19}F NMR, as the environment of the fluorine atoms changes from enantiotopic sp^3, to sp^2, and then to diastereotopic sp^3. Results of the attempted transformation are summarized (Table 5). Using Ishihara's conditions (entry 1) the aldol product was observed by ^{19}F NMR, though conversion was only about 20%. It is known that many reactions involving zinc dust can be greatly accelerated using a small amount of silver. Using this "activated zinc"[80] (entry 2) appeared to have little effect on the reaction however with the conversion remaining around 20 %.

Entry	R	Conditions	Conversion[a] (%)
1	H	Acid washed Zn dust, CuCl, rt, 30 min then acrolein, reflux, 18 hr	~20
2	H	Zn/Ag, CuCl, rt, 30 min then acrolein, reflux, 18 hr	~20
3	H	Zn/Ag, CuI, rt, 30 min then acrolein, reflux, 18 hr	~20
4	H	Zn/Ag, CuI, rt, 30 min then acrolein, reflux, sonicate, 18 hr	~20
5	H	Acid washed Zn dust, CuCl, rt, 30 min then acrolein, Ti(O^{i}Pr)$_4$, reflux, 18 hr	-
6	Ph	Zn, CuCl, rt 30 min then cinnamaldehyde, reflux 24hr	~50

Table 5; a) Conversion by ^{19}F NMR.

The use of copper iodide in place of copper chloride (entry 3), and of activation by sonication (entry 4) also gave similarly disappointing yields. Lewis acids can be used to accelerate aldol reactions as they can coordinate to the reacting species holding them in proximity and stabilizing the transition state. However using an equivalent of titanium isopropoxide as a Lewis acid catalyst led only to the decomposition of the starting material (entry 5). It was found that changing the electrophile to cinnamaldehyde **176** had a beneficial effect on the conversion (entry 6) increasing it to 50%. The effect of changing the reagent proportions was investigated and can be seen in (Table 6).

Entry[a]	Zn (mmol)	CuCl (mmol)	Electrophile (mmol)		Time (h)	Conversion (%)[c]
			172	**176**		
1	3	0.6	-	1.1	50	~50
2	3	1.2	-	1.1	50	~50
3	6	0.6	-	1.1	50	~50
4	6	1.2	-	1.1	50	~50
5	3	0.6	1.1	-	24	~20
6	3	0.6	2	-	24	~20
7	3	0.6[b]	6	-	24	~20
8	3	1[b]	9	-	96	~20

Table 6; a) all reactions 1 mmol **173**, b) CuI, c) by ^{19}F NMR.

Using Ishihara's original molar ratios (entry 1) gave a conversion of about 50 % with aldehyde **176**. However increasing the loading of CuCl and Zn, individually and in concert (entry 2-4) showed no measurable effect on the overall conversion. Increasing the number of equivalents of the electrophile (entry 5-7) similarly showed no effect on the overall conversion. When the reaction was left to run at high loading for an extended period of time (entry 8) the same conversion was observed. These results were disappointing as Ishihara has shown the reaction works well with alkyl ketones, and acrolein was shown to be an effective aldehyde.

The most interesting observation taken from the above examples is the homogeneity between the results observed with a common electrophile. The percentage conversion changes markedly when the electrophile is switched from acrolein to cinnamaldehyde. The phenyl group is moderately electron withdrawing and may slightly increase the electrophilicity of the carbonyl carbon, lowering the activation barrier for the reaction. It is suggested that the reaction with cinnamaldehyde is therefore kinetically faster, driving the conversion further before the reaction is poisoned by an unknown deactivating species. An alternate suggestion is the initial aldol reaction my result in a more effective alkoxide nucleophile than the zinc enolate leading to ploymerisation of all subsequent electrophile. All attempts to isolate the addition product proved impossible on silica gel chromatography.

A number of alternative methods were explored following the failure of the one pot reduction/aldol methodology (Table 7). An attempt to synthesise and isolate the intermediate enol as a silyl enol ether using Ishihara's older zinc-promoted reductive protocol[81] failed to consume the starting material (entry 1). A second strategy[82] using

tetrakis(dimethylamino)ethylene (TDAE) mediated reduction led only to the decomposition of the starting material (entry 2). Indium is known to mediate Reformatsky type reactions[83] when the reagents are shaken as a biphasic mixture. Disappointingly, attempts with both aldehydes (entries 3, 4) using this methodology failed to convert the starting material. It should be noted that the Indium and TDAE procedures appear to have been used exclusively with aromatic, or hetroaromatic ketones.

Entry	Conditions	Yield (%)
1	Zn (1.2eq), TMS-Cl (1.2eq), MeCN, 60°C, 20 hr	starting material
2	TEDA, (1.2eq), Cinnamaldehyde (5eq), DMF, -20°C, 1 hr	decomposition
3	In (1.2eq), acrolein (1 eq), THF/H$_2$O (1/4), shake, 24 hr	starting material
4	In (1.2 eq), cinnamaldehyde (1.2eq), THF/H$_2$O (1/4), shake, 24 hr	starting material

Table 7

2.5 Preparation of 1,1,1-Trifluoro-2-(2-methoxy-ethoxymethoxy)-ethane 131
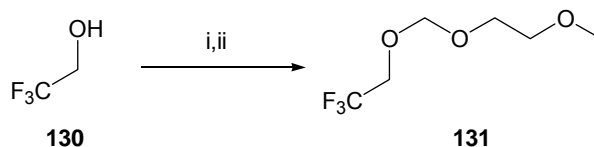
Scheme 40; Reagents and conditions; i. NaH, THF
ii. MEM-Cl

MEM-ether **131** was successfully prepared from trifluoroethanol **130** according to the procedure of Percy and Patel[62] (Scheme 40). The reaction was conducted on a large (1.05 mole) scale and gave a good yield (72 %, lit. 80 %) of pure **131** after distillation.

2.6 Preparation of Pent-4-enal 145
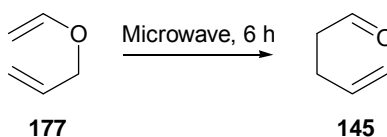
Scheme 41; Reagents and conditions;
Microwave, 300-40W, 150°C, 6 hr

Pent-4-enal **145** (Scheme 41) was prepared from ethyl vinyl ether **177** *via* a microwave induced Claisen rearrangement at 150°C (microwave power (ca. 40 watts after an initial burst of 300W to reach temperature) was used to maintain this temperature for 6 hours after which a conversion of over 95 % was observed by proton NMR). Little evidence of polymerisation was observed and the material was used without further purification. The purely thermal reaction[84] was attempted in an Ace^{TM} tube; however this required higher temperatures and longer reaction times (160°C, and over 18 hours) to drive the reaction to completion. Additionally the material from the thermal reaction showed more evidence of polymerisation and therefore had to be distilled in disappointing yield (45%).

2.7 Preparation of 1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-hepta-1,6-dien-3-ol 178
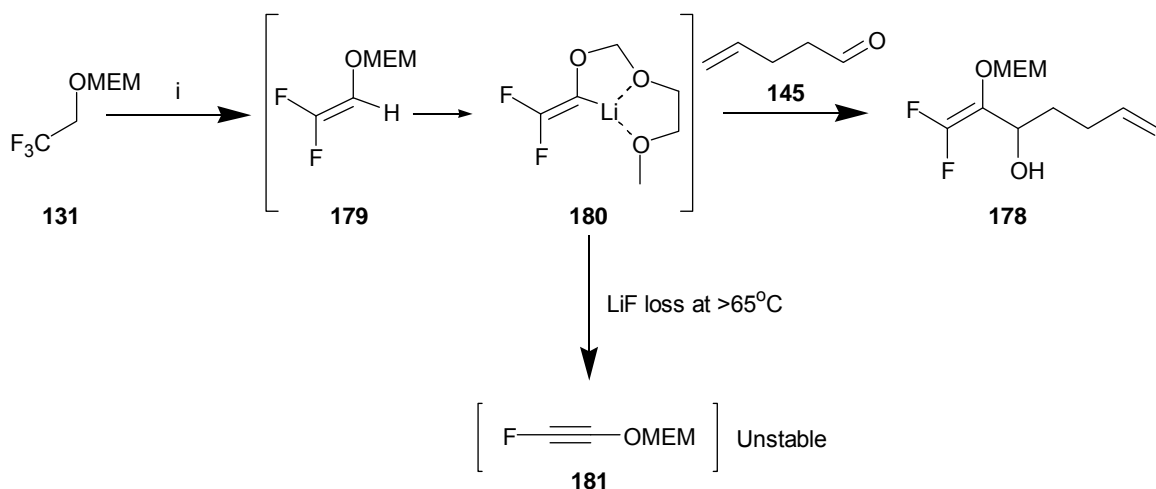
Scheme 42; Reagents and conditions; i, 2.0 LDA, THF, -78°C, 30min, then **145** -78 to -40°C, then NH$_4$Cl/MeOH

Allylic alcohol **178** was prepared from MEM ether **131** and aldehyde **145** in good yield (82 %, 95 % conversion by ^{19}F NMR of crude material) on a 0.1 mol scale according to the procedure published by Percy and co-workers (Scheme 42).[62] This procedure has been shown to be effective in the synthesis of a range of allylic alcohols.[85] Slow addition of the substrate was required to control the strongly exothermic reaction. The first dehydrofluorination step is thought to have E2 character resulting in enol acetal **179**; this species is then rapidly metallated. It is known that the metallalation of **179** is rapid compared to its formation as the treatment of **131** with 1 equivalent of base results in a mixture of **179** and recovered starting material. The resulting lithiated intermediate **180** is stable at -78°C due to chelation of the lithium with each of the oxygen atoms in the MEM protecting group. Above -65°C however **180** decomposes *via* LiF loss resulting in the formation of unstable **181** which goes on to form a viscous black mixture.

In a modification to the published procedure the reaction mixture was only stirred for 30 min at -78°C subsequent to addition of **131** and not 2 hours. Upon stirring for longer periods the solution was observed to get progressively darker and give a poorer yield upon quench and work up. After quenching with **145** and extractive work up material of excellent quality was obtained that could be used crude but was usually distilled as a clear liquid.

2.8 Preparation of 3-Allyloxy-1,1-difluoro-hepta-1,6-dien-2-ol 182
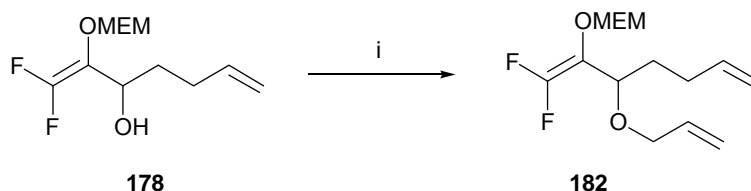
Scheme 43; Reagents and conditions; i, 1.2 allyl bromide, 50 % NaOH(aq), TBAHSO$_4$ 0°C to rt 18 hr

Allylic alcohol **178** was allylated successfully (91%) under phase transfer conditions with tetrabutylammonium hydrogen sulphate (TBAHSO$_4$) as the phase transfer catalyst to give ether **182** in good yield (Scheme 43). No purification was required after extractive work up. Deprotonation in the aqueous layer is followed by phase transfer and nucleophilic attack of the resulting alkoxide on allyl bromide to give the desired product.

2.9 Preparation of 4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-deca-1,5,9-trien-3-ol 183
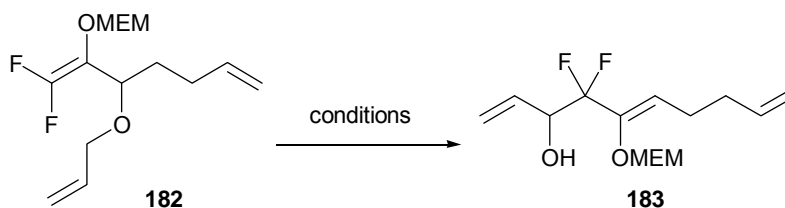
Scheme 44

Allylic alcohol **183** is obtained via a [2,3]-Wittig rearrangement of allyl ether **182** (Scheme 44). The [2,3]-Wittig rearrangement is a sigmatropic process involving the conjugate base of allylic ethers and results in the lengthening of the carbon chain by three units, from seven to ten atoms.

Entry	Base	Base Equivalents	Temperature / Time	Purification	Yield (%)
1	LDA	2.2	-78°C (2 hr), -30°C (18 hr)	Silica column	55
2	*t*-BuLi	2.2	-100°C (2 hr), -30°C (18 hr)	Flash silica column	26
3	LDA	2.2	-100°C (2 hr), -30°C (18 hr)	Flash silica column	24
4	*t*-BuLi	2.2	-90°C (2 hr), -30°C (72 hr)	Flash silica column	26
5	LDA	2.2	-90°C (2 hr), -30°C (72 hr)	Flash silica column	38
6	*t*-BuLi	2.2	-85°C (2 hr), -30°C (18 hr)	Flash silica column	26
7	LDA	2.2	-85°C (2 hr), -30°C (18 hr)	Flash silica column	24
8	*t*-BuLi	2.2	-90°C (2 hr), -30°C (48 hr)	None	85
9	*t*-BuLi	1.1	-90°C (2 hr), -30°C (72 hr)	None	SM
10	*t*-BuLi	2.2	-90°C (2 hr), -30°C (96 hr)	None	92
11	*t*-BuLi	2.2	-90°C (2 hr), -30°C (4 hr)	None	97
12	LDA	2.2	-100°C to -30°C (7 hr)	None	92

Table 8;

The initial published[86] conditions which used LDA at -78°C gave a yield of 55% (Table 8, entry 1). As the organolithium intermediate may be decomposing, the reaction was run at a range of lower temperatures (entry 2-7), using LDA or *t*-BuLi as the base. This had a

detrimental effect on the yields obtained, although the results showed good homogeneity. Varying the temperatures and bases, (with the exception of entry 5) suggested that these variables have little effect on the reaction outcome.

It was noted that TLC of the fractions after chromatography appeared to show more decomposition products than TLC of the crude mixture. Additionally the crude NMR spectra did not suggest large amounts of by-products. It was also noted that the isolated yield was lower when purification (entries 2-7) had been conducted on flash columns, than (entry 1) when the product was purified on a normal silica column. It was suggested that the product was unstable on silica and therefore using the packed flash columns may have led to the observed decrease in yield.

With these observations in hand the reaction was run at -90°C without purification and yielded an excellent 85% after 50 hours with t-BuLi as the base (entry 8). Attempts to reduce the molar ratio of base to 1.1 equivalents gave only recovered starting material (entry 9). Initially extending the reaction time to 98 hours appeared to increase the yield (entry 10); however it was later discovered that the reaction was complete after 6 hours in an almost quantitative yield of 97% (entry 11). Using t-BuLi as the base also led to the formation of significant amounts of t-BuLi adduct **184** being observed by ^{19}F NMR ($\geq$5%). Additionally there was significant contamination in the alkyl region of the proton NMR spectrum.

184
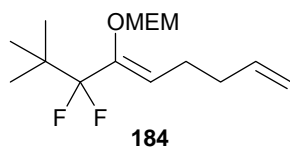
Switching back to LDA and adding the substrate at -100°C removed the adduct contamination and gave very pure material by proton NMR (Figure 15) and GC. Using these conditions the reaction could be conducted efficiently on a large scale (up to 30 mmol) in good yield (87 %).
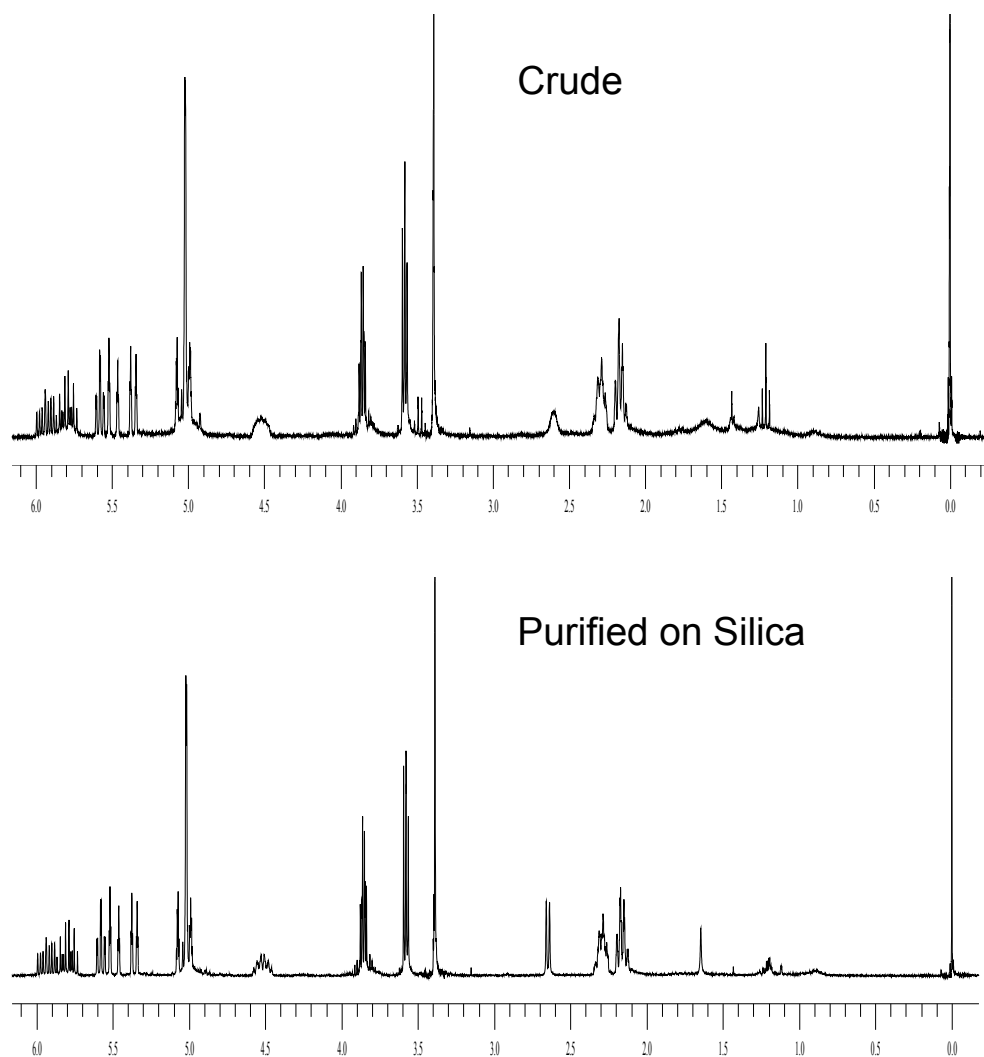
Figure 15

There are two sites for deprotonation upon treatment with base; these are the allylic methylene protons H_a or the methine H_b (Scheme 45). Only deprotonation at H_a can lead to rearrangement.

Scheme 45
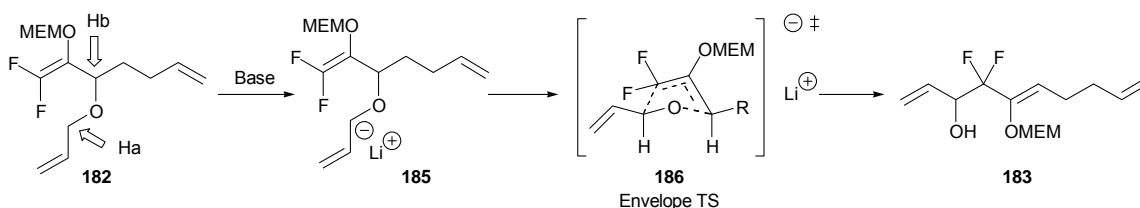
Attempts to identify the site of deprotonation by quenching at $-100^{\circ}C$ with d_4-methanol resulted in return of starting material with no incorporation of deuterium. Quenching at higher temperature $-78^{\circ}C$ after 20 min also gave only starting material with no sign of deuterium incorporation. These results suggest that rearrangement is rapid once deprotonation occurs. From **182,** the allylic position α-to oxygen is deprotonated to give **185**; the system then rearranges giving **183** on workup. The reaction passes through an envelope transition state **186**, which allows the σ overlap to develop head on whilst the π overlap develops side on. All the orbitals involved are conjugated in the transition state and the reaction is therefore pericyclic. The vinylic di-fluorogroup helps to accelerate the rate of the sp^2 to sp^3 rearrangement as the electron withdrawing effect makes C1 highly electron deficient and therefore electrophillic towards the organolithium nucleophile. The major driving force for the reaction is the conversion of a carbon bound lithium anion into a more stable alkoxide anion.

2.10 Preparation of 4,4-Difluoro-3-hydroxy-deca-1,9-dien-5-one 172
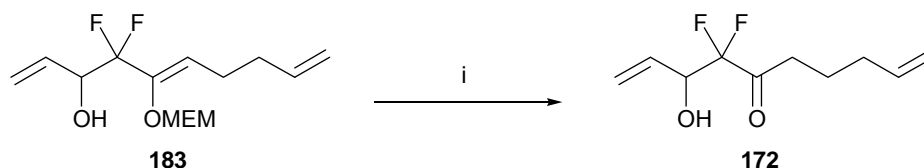
Scheme 46; Reagents and conditions; i, SOCl$_2$, MeOH, 0°C to rt, 18 hr

β-Hydroxy ketone **172** could be prepared from **183** by removal of the MEM protecting group under mild acidic conditions[85][87] (Scheme 46). The reaction gave the crude product as a brown liquid usually in above 90% yield. Pure material could be obtained as a clear oil by distillation under reduced pressure, although this significantly reduced the yield to a maximum of 48%. The quality of the purified material was not significantly better than the crude and both were used in subsequent transformations. Although the reaction was usually left overnight for an extended reaction time of 18 hours, the reaction was in fact much quicker. Studies on an NMR scale showed conversion to the cleaved product was complete after 90 min. The thionyl chloride reacts with the methanol to create an acidic medium in which deprotection occurs.
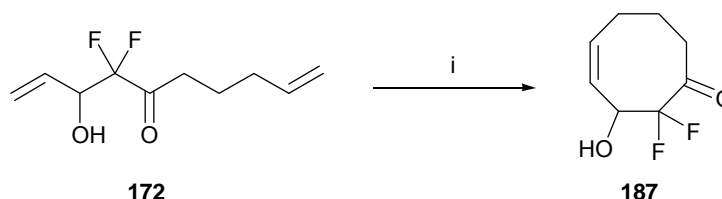
Scheme 47; Reagents and conditions; i, Grubbs' cat **93,** Ti(O^{i}Pr$_4$), DCM

Attempts by co-workers to synthesise eight membered ring **187** from **172** by RCM initially failed due to the high volatility of product which was removed accidentally on the rotary evaporator (Scheme 47). Later, **187** was successfully isolated by removal of DCM at atmospheric pressure and careful chromatography of the residue in low boiling solvents.[88] Due to the difficulties in isolating the product, **172** was abandoned as an RCM precursor and it was decided to protect the allylic alcohol.

2.11 Preparation of 3-benzyloxy-4,4-difluoro-5-(-2-methoxy-ethoxymethoxy)-deca-1,5,9-trienyl ether 188
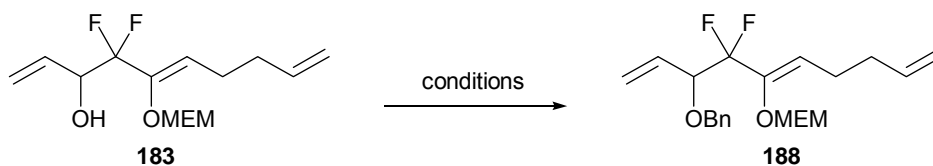
Scheme 48

Benzyl ethers are useful protecting groups for alcohols; they are generally stable to both acidic and basic conditions and can be removed cleanly by hydrogenolysis. Three approaches toward the synthesis of **188** (Scheme 48) were assessed.

Entry	Conditions	Yield (%)
1	1.5eq nBuLi, THF, -78°C, 1 hr; then 1.5eq BnCl, to -30°C 1 hr.	SM
2	50% NaOH, 1eq allyl bromide, TBAHSO$_4$, 0°C to rt, 18 h	SM
3	3 eq NaH, THF, 0°C, 45 min; then 0.99eq BnBr, TBAI, 0°C to rt, 18 hr	92

Table 9

Initial attempts to use *n*-butyllithium to form the alkoxide of **183** and trap with benzyl chloride (Table 9, entry 1) failed to return anything but starting material despite the use of

an excess of base and electrophile. Purifying the benzyl chloride to remove water and benzyl alcohol contaminants failed to affect the outcome of the reaction. A test reaction was conducted with allyl bromide (entry 2) to see if the benzyl group could be introduced under our phase transfer conditions; after following our established procedure only starting material could be isolated after the reaction. Switching to sodium hydride as the base and benzyl bromide as the electrophile with a catalytic amount of TBAI (which forms reactive benzyl iodide *in situ*) resulted in a clean reaction with an excellent yield (entry 3, 92 %). These conditions are fairly standard for introducing the benzyl group.[89] It was found that by using a slight excess of **183** the crude product could be taken forward without purification as no column was needed to remove excess benzyl bromide. The amount of base could be reduced to 3 equivalents without a significant effect on the yield.

2.12 Preparation of 3-Benzoic acid 4,4-difluoro-5-(2-methoxy-ethoxymethoxy)-deca-1,5,9-trienyl ester 189
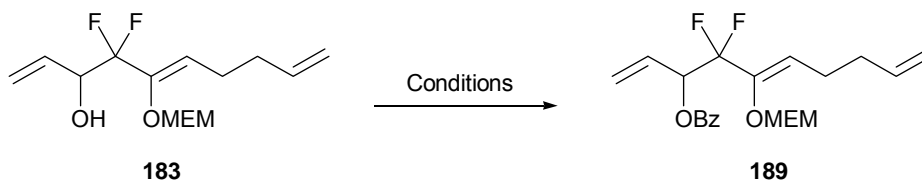
Scheme 49

Allylic alcohol **183** was also protected as a benzoate ester **189** (Scheme 49). Initial attempts with alkyllithium bases were disappointing. With *t*-butyllithium (Table 10, entry 1) the reaction failed to go to completion with conversion ca. 74 % by ^{19}F NMR and gave very contaminated spectra. With *n*-butyllithium a conversion of 93 % by ^{19}F NMR was

obtained, which gave a disappointing yield of **189** of 30 % upon purification due to the instability of the MEM group on silica.

Entry	Conditions	Yield (%)[a]
1	1eq tBuLi, -78°C, 30 min, then 1eq BzCl, 30 min	(74)
2	1eq nBuLi, -78°C, 30 min, then 1eq BzCl, to -30°C, 2 hr	30[b]
3	Py, 1eq Bz$_2$O, DMAP, rt, 24 hr	64[c]

Table 10; [a] ^{19}F NMR yields in parenthesis; [b] Isolated yield; [c] Crude yield.

Switching to more traditional conditions[90] (entry 3) gave very high quality crude material in reasonable yield with 100% conversion by fluorine NMR. It is expected that the repeated washes with cold dilute 10% HCl to remove the pyridine will have affected the yield, as the MEM group is not highly acid stable. Latterly co-workers have developed a new approach to **189** using polymer supported base PVP;[88] this produces material of a high crude quality and negates the problems of removing the base. The procedure will be discussed later with reference to other compounds.

DMAP (4-dimethylaminopyridine) **190** is used in the reaction as a nucleophilic catalyst (Scheme 50). The dialkylamino group at the 4-position reinforces the nucleophilic nature of the nitrogen atom by reacting with the anhydride **191** then acting as an electron sink to promote the reaction with the alcohol **192**, giving the product whilst regenerating the catalyst.

190 **191** **192**
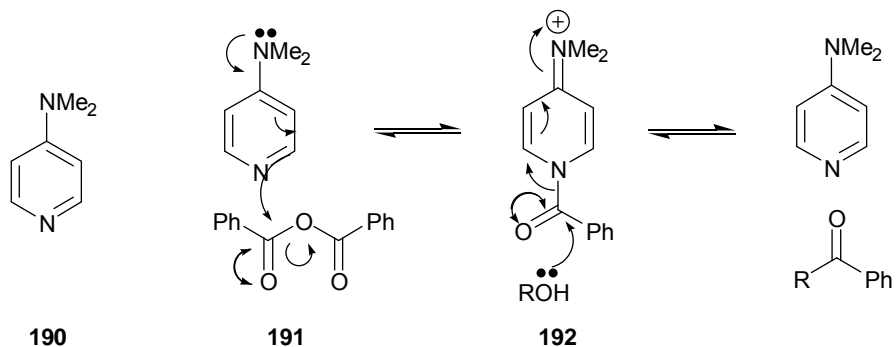
Scheme 50

2.13 Preparation of 3-(4'-Bromobenzene-sulfonyloxy)-4,4-difluoro-5-(2-methoxy-ethoxymethoxy)-deca-1,5,9-trienyl ester 193 and 3-Toluene-sulfonyloxy-4,4-difluoro-5-(2-methoxy-ethoxymethoxy)-deca-1,5,9-trienyl ester 194

183

R = Bs **193**
R = Ts **194**
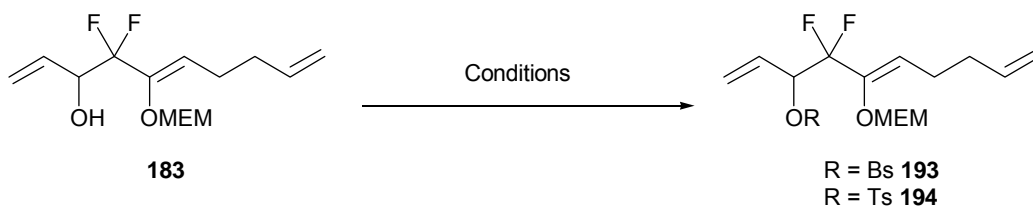
Scheme 51

Allylic alcohol **183** was also successfully protected as a brosylate **193** (Scheme 51, Table 11, entry 1) using a modification of the sodium hydride strategy used in the synthesis of **188**. The reaction proceeded smoothly with a lower loading of base and without the use of TBAI compared to the above procedure. The reasons for the choice of the brosylate protecting group were twofold. Firstly it was hoped that it would form a crystalline product after RCM, and secondly brosylates are good leaving groups and may be useful for introducing additional functionality after RCM. Similar reasoning was behind the

synthesis of tosylate **194**, by chemistry analogous to that used to produce benzoyl ester **189** (entry 2). In neither case was purification attempted.

Entry	R	Conditions	Yield (%)
1	Bs	2.7eq NaH, THF, 0°C, 2 hr; then 1.2eq BsCl, 0°C to rt, 18hr	69
2	Ts	Py, 1.1eq TsCl, DMAP, 0°C to rt, 18 hr	55

Table 11

2.14 Synthesis of a range of RCM precursors

A range of RCM precursors were synthesised with the secondary allylic alcohol protected. The simplest preparation was from fully protected compounds **188, 189, 193, 194,** and **183** by removal of the MEM protecting group in an acid catalysed methanolysis using thionyl chloride and previously discussed conditions (Scheme 52, Table 12). In all cases the resultant ketone was the sole product by TLC and ^{19}F NMR. Any unconverted [2,3]-Wittig precursor simply evaporated from the crude material being volatile after removal of the MEM group.

R = Bn	**188**
R = Bz	**189**
R = Bs	**193**
R = Ts	**194**
R = H	**183**

R = Bn	**195**
R = Bz	**196**
R = Bs	**167**
R = Ts	**198**
R = H	**172**
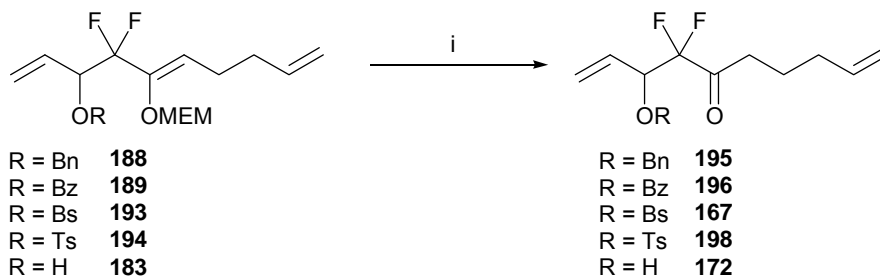
Scheme 52; Reagents and conditions; i, SOCl$_2$, MeOH, 0°C to rt, 18 hr

Entry	Starting Material	R	Product	Yield (%)[a]
1	**188**	Bn	**195**	94
2	**189**	Bz	**196**	84 (56)
3	**193**	Bs	**197**	88
4	**194**	Ts	**198**	96 (66)
5	**183**	OH	**172**	90 (48)

Table 12; [a] Purified yield in parenthesis.

In the case of benzyl protected compound **188**, the MEM group could be removed easily and in good yield to give **195** (Table 12 entry 1) without purification. It should be noted that this represents a 59% yield from MEM ether **131** with only one intermediate purification (the distillation of **178**) being required.

The benzoyl system (entry 2) also gave an excellent crude yield of **196** (84 %) as the sole product, however an appreciable loss of yield (56 %) was obtained if the material was purified on silica.

For the series protected as a brosylate (entry 3) the MEM group could be removed from **193** to give **197** in excellent crude yield (88 %). Similar behaviour was observed for the tosylate system (entry 4) **194**, a considerable reduction in yield of **198** (96 to 66 %) being observed upon chromatography. It should be noted that these yields are comparable to those of the free hydroxyl compound **172**.

Attempts were also made to prepare **197** and **198** from hydroxy ketone **172**, in order to evaluate the most efficient order of the protection and deprotection steps. Tosylate **198** proved difficult to synthesise from **172** (Table 13). In all cases purified **172** was used.
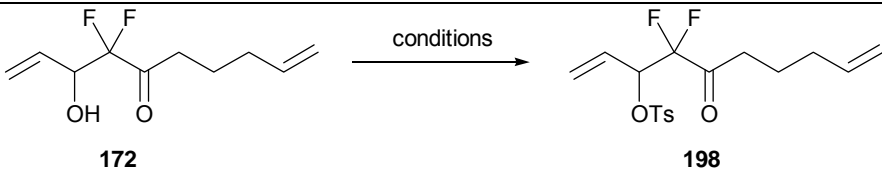
Entry		Yield (%)
1	1.125eq TsCl, py, 0°C to rt, ON	33
2	1.5eq TsCl, py, DMAP, rt, ON	51
3	1.2eq TsCl, PVP, DMAP, DCM, shake, rt, ON	SM
4	1.5eq TsCl, 4eq py, DMAP, CHCl$_3$, 0°C to rt, 60 hr	54
5	1.5eq TsCl, 2eq DABCO, DMAP, DCM, 0°C to rt, 60 hr	31[a]

Table 13; [a] after purification on silica

Initially protection was attempted using the standard literature conditions[91] of tosyl chloride in pyridine (entry 1). This proved disappointing returning **198** in a poor 33 % yield. This is possibly due to compound being washed out with the pyridine, as ^{19}F NMR analysis of the reaction mixture had showed complete conversion of the starting material. Two exposures to the conditions were required to drive the reaction to completion. The addition of DMAP as a nucleophilic catalyst (entry 2) improved the yield to 51 % but still gave disappointing results.

The reaction was attempted with a solid supported base to try and solve an apparent problem of product being washed out with the pyridine upon workup. Shaking **172** with polyvinylpyridine (PVP) in DCM failed to produce any conversion of starting material (entry 3). In an attempt to reduce the amount of pyridine present, the reaction was conducted in chloroform as the solvent[92] (entry 4). This gave comparable yields to the pyridine/DMAP procedure, but unfortunately the crude product was contaminated with an inseparable by-product tentatively identified as diarylsulphone **199** by proton NMR.[93]
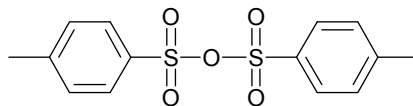
199

It is known that DABCO can be used in place of pyridine in tosylation reactions.[94] Primarily this had been to remove the requirement for toxic pyridine and DMAP. However we were interested in this reagent as a possible more effective base. DABCO is more basic than pyridine (pK_a = 8.9 compared to 3.4 for pyridine in DMSO).[5] Results proved disappointing, with the crude material requiring purification and giving a poor isolated yield (31 %). Brosylate **197** was synthesised from **172** *via* the standard pyridine procedure in disappointing yield (32%).

These generally disappointing results for the protection of hydroxy ketone **197** coupled with the low yield after distillation of **197** itself, suggest that the most efficient route to all the above RCM precursors is to protect post [2,3]-Wittig rearrangement then remove the MEM group.

2.15 Synthesis of Cyclooctenones by Ring Closing Metathesis
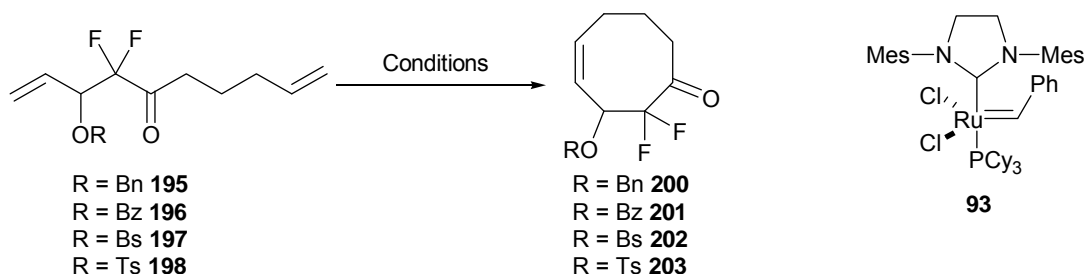
Scheme 53

Ring closing metathesis reactions using Grubbs' 2nd generation catalyst **93** were carried out on all four protected substrates each of which cyclised successfully to give cyclooctenones **200-203** in poor to good yields (Scheme 53, Table 14). The *cis* geometry about the double bond was confirmed by analysis of the ^3J coupling constant between the olefinic protons which was found to be ca. 11 Hz for all the systems synthesised. It should be noted that only **200** (Table 14, entry 1, R=Bn) represents an optimised yield (75%). The other three systems were run using initial reaction conditions of 5% catalyst loading, 0.33% Ti(O^{i}Pr)$_4$ Lewis acid, and 0.01M concentration in DCM which were the optimised conditions for the RCM of the first generation *gem*-dimethyl and DEC species **144** and **149a-d** discussed in the introduction, and previously prepared by our group.[70]

Entry	R	Product	Conditions	Yield (%)
1	Bn	**200**	5 mol% **93**, 0.33 mol% Ti(O^{i}Pr)$_4$, 0.0022M DCM, reflux, 18 hr	75
2	Bz	**201**	5 mol% **93**, 0.33 mol% Ti(O^{i}Pr)$_4$, 0.01M DCM, reflux, 18 hr	46
3	Bs	**202**	5 mol% **93**, 0.33 mol% Ti(O^{i}Pr)$_4$, 0.01M DCM, reflux, 18 hr	49
4	Ts	**203**	5 mol% **93**, 0.33 mol% Ti(O^{i}Pr)$_4$, 0.01M DCM, reflux, 18 hr	38

Table 14

A modified purification procedure was developed to remove catalyst and Lewis acid residues. After removal of the DCM, the residue was taken up in ether and filtered through celite which removed the insoluble catalyst residues before column chromatography. Despite this, disappointing yields of cyclooctenones were obtained after column chromatography for the unoptimised systems (entry 2-4) although complete consumption of starting material was observed by NMR, and mass recovery post-reaction was always close to 100%. The poor yields may be the result of loss during purification. Alternatively, based on the optimisation work for **200** (R = Bn, see below), it may be that significant amounts of dimeric and oligomeric material may have been produced at this concentration, visible as small signals in the baseline of the crude ^{19}F NMR. For the benzoyl system a homodimer, has been identified by NMR and the sixteen ring cyclised product isolated and characterised by a co-worker within the group.[95] Their work has shown that the optimum synthetic concentration for the RCM of **201** is 0.02M in DCM making it considerably more efficient than that for **200** where the maximum synthetic concentration was 0.0025M. No optimisation work was carried out on either of the aryl sulphonates.

2.16 Optimisation of the Ring Closing Metathesis of 195

The ring closing metathesis of **195** (R = Bn) was optimised at a range of concentrations and catalyst loadings, crude **195** was used in all reactions. An easy method of removing the ruthenium and Lewis acid residues was found serendipitously and applied to all

reactions. Both were found to be almost insoluble in ether and could therefore be removed by simple filtration through celite. After this procedure the mass yield was always very close to the theoretical yield although a very strong ion was often observed in the MS corresponding to the mesitylene ligand from the catalyst.

Crude material always showed evidence of dimers and higher ring systems in the ES-MS and ^{19}F NMR spectra. Despite this, crude GC traces were very pure, but when the benzyl homodimer was later prepared *via* a different procedure (see below) it was found to not travel through the GC, so this technique is unreliable in judging product purity in this case. A homodimeric species was later positively identified (see below) from these RCM's by comparison of the crude NMR spectra with the purified spectra of a known dimer isolated from a reaction using a different catalyst.

The literature reaction conditions[70] (Table 15, entry 1) gave average yields after purification. Reducing the catalyst loading slightly (entry 2) improved the yield although this may be just the effect of a particularly efficient column. Dropping the catalyst loading to 4 mol% failed to result in complete conversion of starting material (entry 3). Using a 2.5 mol% catalyst loading and adding the substrate to the catalyst over 1 hour gave only a 36 % yield from a 50 % conversion (entry 4). This lower conversion is possibly due to the inverse mode of addition as the catalyst will be thermally degraded before the full amount of substrate has been added. At these concentrations significant amounts of material assigned as mixtures of dimers and larger rings (by ES-MS) was isolated and still seen in the purified cyclooctenones.

Entry	Catalyst[a] (mol %)	Concentration (M)	Purification Method	Yield (%)
1	5	0.01	C	56
2	4.5	0.01	C	68
3	4	0.01	n/a	70 conversion[c]
4[b]	2.5	0.01	C	36 (50 conversion)[c]
5	4	0.005	A	94
6	5	0.005	B	87
7	4	0.005	C	72
8	4	0.0025	D	89
9	5	0.0022	E	75

Table 15; All reactions were concentrated then dissolved in ether and filtered through Celite. Additional purification methods: A; None. B; Silica plug. C; Silica column. D; SPE column. E; SPE then silica column. [a] All reactions 0.33 mol% Ti(O^{i}Pr)$_4$ in dry degassed DCM, reflux, 18 hours; [b] Inverse addition of substrate, final concentration 0.01M; [c] by ^{19}F NMR.

In order to try and reduce the amount of dimeric material present in the crude product the concentration was reduced to 0.005M (entry 5). Here, in contrast to earlier observations, 4 mol% of catalyst proved sufficient to drive the reaction to 100 % conversion. A good crude yield (94 %) was obtained although this material was not pure enough to give good yields in some subsequent transformations. Purification through a silica plug or silica column (entry 6, and 7 respectively) gave progressively better quality material by ^{19}F NMR albeit at slightly lower yield but failed to completely remove dimeric species.

Again with the aim of reducing the amount of cross metathesis products the concentration of the reaction was reduced further. For these reactions the purification was augmented by Stratosphere solid phase extraction (SPE) columns from Polymer Labs Inc. which are specifically designed to remove ruthenium residues. At 0.0025M concentration material of a better crude quality was obtained and filtered through the SPE column (entry 8). The filtration resulted in a definite reduction in colour from the crude material and gave a

good yield (89 %) but failed to remove any dimeric material. The addition of a chromatographic step (entry 9) gave the only material to crystallise (75 %) after purification; this was analysed to give acceptable CHN results.

In all the examples outlined above and indeed, almost exclusively in cyclooctenone synthesis by RCM, the eight membered ring product had a *cis* geometry about the newly formed double-bond. There is however one example in the literature of the formation of the *trans*-cyclooctene kinetic product (Scheme 54).[96] When exposed to either ruthenium catalyst **91** or molybdenum catalyst **89**, carbonate **204** was found to give *trans* cyclooctenone **205** in 34 % and 41 % yield respectively. Interestingly the carbonate group was crucial to the outcome of the reaction as isopropylidene **206** gave only *cis* cyclooctenone **207** with **89** and showed only traces of product with **91**. Clearly it is expected that **205** should be significantly less stable than the corresponding *cis* cyclooctene due to increased strain, and therefore this example represents a reaction completely under kinetic rather than the thermodynamic control usual in olefin metathesis.[97],[98]
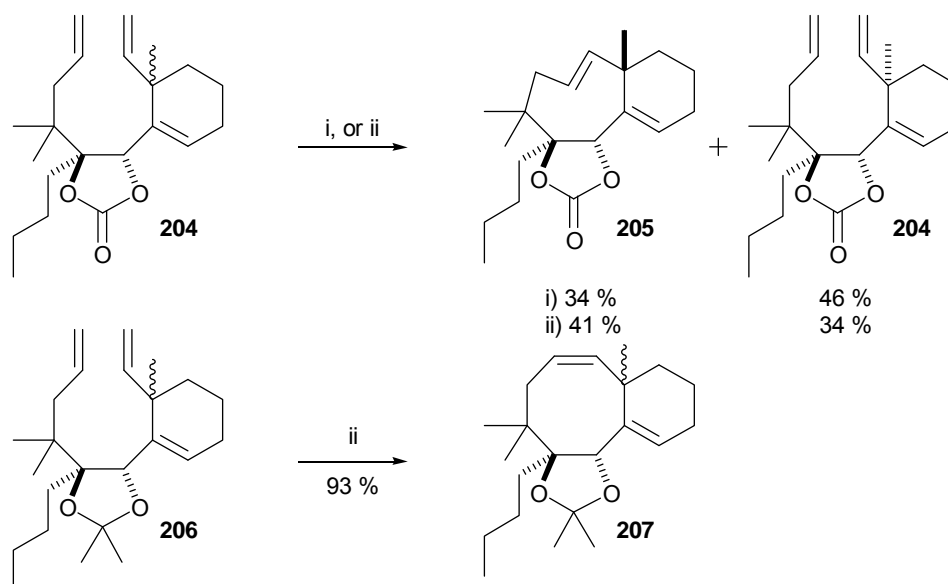
Scheme 54; Reagents and conditions; i, 10 mol% **91**, 0.02M benzene, 80°C, 8 d; ii, 10 mol% **89**, 0.02M benzene, 80°C, 3 d.

2.17 The Mechanism of Alkene Metathesis

The mechanism of ring closing metathesis has received much attention from Grubbs[44],[99],[100] and others.[101] The generally accepted mechanism is shown in Scheme 55. The initial step is dissociation of phosphine from pre-catalyst **208** to give 14-electron alkylidene **209a**. This is thought to be the rate limiting step for the reaction as it has been shown that the initiation rate constant is independent of olefin concentration and saturation kinetics are achieved even at low olefin concentrations for **93** (5 equivalents).
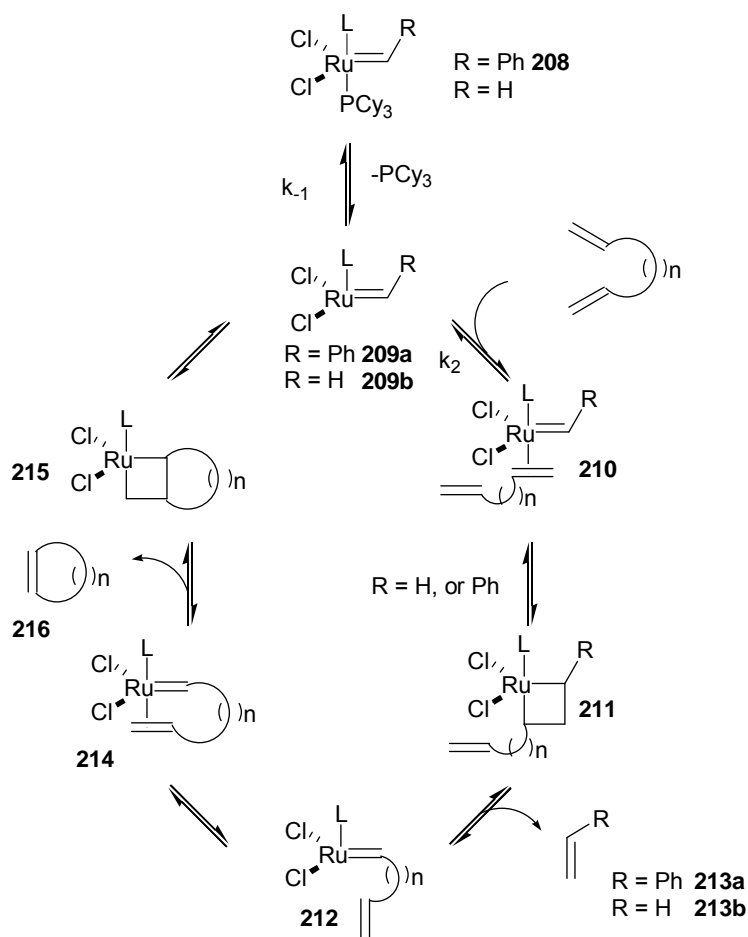
Scheme 55

From **209a** olefin binding competes with phosphine reassociation, although the former is kinetically favourable by 4 orders of magnitude for **93** ($k_{-1}/k_2 \sim 10^4$ for **91**, and ~1 for **93**). Due to the Lewis acidity of **209a** electron rich olefins react much more efficiently than electron deficient examples. Olefin coordination reforms a 16-electron species **210** which can undergo a [2+2] cycloaddition to give metallocyclobutane **211**. Opening of **211** gives a new 14-electron substrate alkylidene **212**, with the elimination of styrene **213a**. Intramolecular coordination of the second olefin of the diene reforms a 16-electron species **214** which again can react through a metallocyclobutane **215** to eliminate the ring closed product **216** and generate a new 14-electron methylidene **209b** which then

catalyses all subsequent turnovers; in subsequent turnovers ethene **213b** is eliminated on the formation of **212**. Although all the steps are reversible, the loss of ethene into an open system drives the reaction to the right.

Straub[101] has shown that there are four possible conformations in which the alkene can bind to the metal centre in relation to the carbene (Scheme 56). In three of these conformations the orientation of the olefin and carbene molecular orbitals precludes [2+2] cycloaddition; these are therefore inactive whilst the fourth is active and is the conformation through which the reaction proceeds.

INACTIVE
active alkene,
inactive carbene
orientation

INACTIVE
inactive alkene,
active carbene
orientation

INACTIVE
inactive alkene,
inactive carbene
orientation

ACTIVE
active alkene,
active carbene
orientation

L = NHC

NHC strong σ-donor

decrease of NHC-Ru-alkene angle

active carbene conformation

weak alkene σ-donor

antibonding interaction

increased backbonding

Scheme 56

Furthermore the model provides a possible explanation for the increased activity of the 2nd generation Grubbs catalyst over the 1st and the k_{-1}/k_2 data. The NHC ligand is a better σ donor than phosphine. A pronounced antibonding interaction is observed with a decrease of the NHC-Ru-alkene angle. Straub states that "With the increasing antibonding interaction the back bonding of the ruthenium fragment to the carbene acceptor orbital increases and the active carbene conformation is stabilised". This

stabilisation of the active conformation over the inactive conformations is greater in the second generation catalysts hence their higher activity.

The importance of the titanium *iso*-propoxide to the RCM had been illustrated previously in the Percy group and by others[70][102]. Precursor **148d** (Scheme 57) fails to undergo RCM in the absence of the Lewis acid (Table 16, entry 1 and 2) using the first generation catalyst **91**. The more active second generation catalyst **93** gives a good yield of cyclooctenone **149d** in the absence of the Lewis acid though the reaction time is extended at 72 hours (entry 3). The addition of the Lewis acid co-catalyst significantly reduces the reaction time (entry 4).
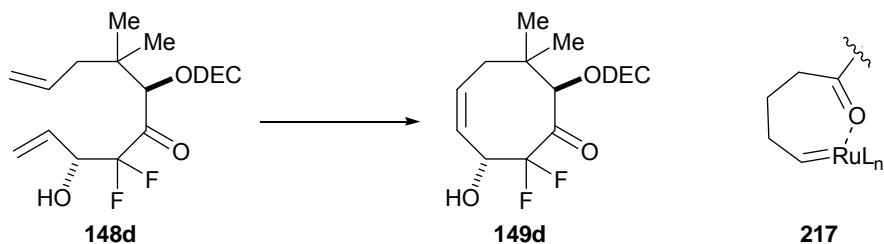
Scheme 57; Reagents and conditions; cat., DCM, reflux.

Entry	Catalyst	Ti(O^{i}Pr)$_4$	Time (hr)	Yield (%)
1	5% **91**	No	144	0
2	5% **91**	Yes	144	77
3	2.5% **93**	No	72	82
4	2.5% **93**	Yes	18	72

Table 16

The Lewis acid prevents the chelation of the lone pairs of the ketone oxygen to the catalyst **217**. Such coordination would lead to deactivation of the catalyst. The Lewis acid binds preferentially to the ketone preventing its participation in the reaction.

2.18 Ring Closing Versus Cross Metathesis
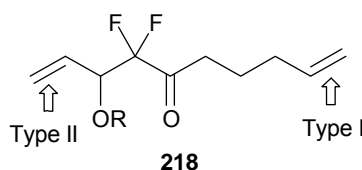
Figure 16

In the ring closing metathesis of non-symmetrical dienes the regioselectivity of olefin coordination should be considered. Olefins can be grouped according to their reactivity with a particular catalyst (Figure 16).[103] Substrates of type **218** contain an unsubstituted terminal olefin and a secondary allylic alcohol (protected); these are classified as a type I and type II olefin respectively in terms of their reactivity with catalyst **93**. This classification is based on the rate of homodimerisation which in turn depends on the ease of formation of the metallocyclobutane intermediate and will be discussed in a future section. Therefore it is expected that the first olefin to coordinate to the catalyst is the unsubstituted terminal olefin with the allylic substituted olefin only coordinating intramolecularly during RCM.

The RCM of dienes presents further considerations (Scheme 58). After the collapse of the initial metallocyclobutane the alkylidene is left coordinated to the more reactive olefin **219**. From this position three possible pathways can occur; firstly intramolecular binding of the second olefin (k_C) leads to formation of the cyclised product **220**. Although theoretically reversible, in an open system loss of ethene essentially makes the reaction irreversible. There is no evidence that ROM/ROMP is taking place, as a purified sample

of cyclooctenone **200** was exposed to the benzyl metathesis conditions and remained

unchanged after 18 hours at reflux.
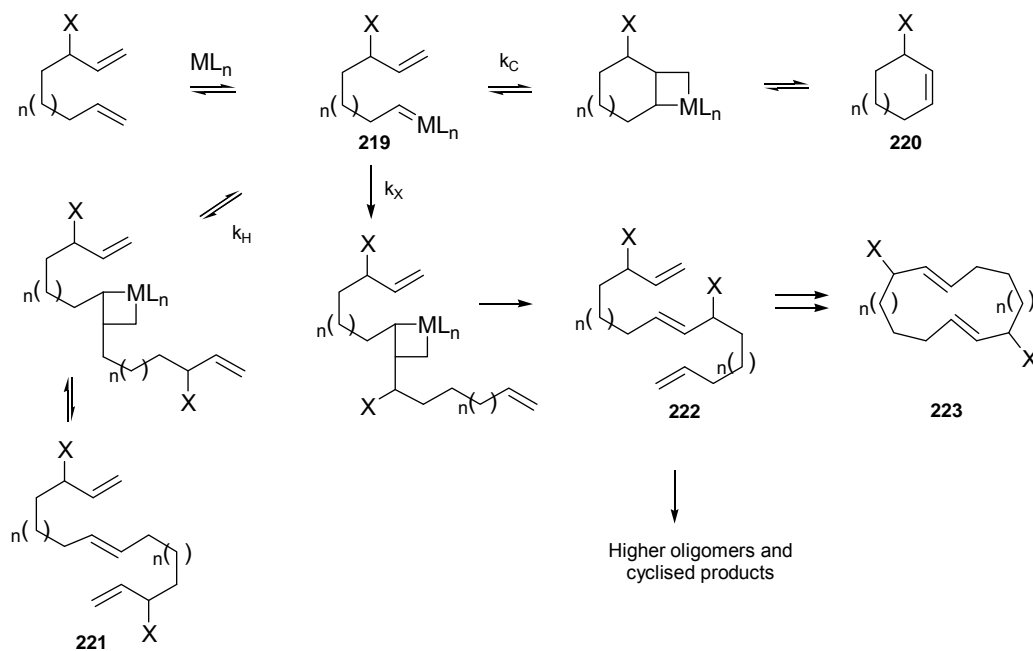
Scheme 58

Alternatively the system can react intermolecularly with the more reactive unsubstituted

olefin of a second diene (k_H). This leads to a homodimer cross metathesis product **221**. It

is thought that type I/type I homodimers are unstable in the presence of **93** and the

reaction is reversible with little or no **221** being present in solution. The third possibility

is a cross metathesis reaction with the less reactive olefin of a second diene (k_X). This

leads to a heterodimer **222** where the resulting internal double bond is unreactive towards

the metathesis catalyst. Hetrodimers can cyclise to give 16-membered ring **223** or

undergo further cross metathesis reactions to give higher open chain and cyclised

analogues.

2.19 The Effect of Concentration on the Outcome of a Metathesis Reaction

The kinetics of the inter- and intra- molecular reactions allow the system to be tuned to favour cyclisation over cross metathesis. It has been shown that catalyst **93** reaches saturation kinetics at very low loading of olefin (5eq).[99] The rate constant for the formation of the new alkylidene **219** is first order in substrate and first order in 14-electron alkylidene **209a/b**, giving second order kinetics overall (Scheme 59).
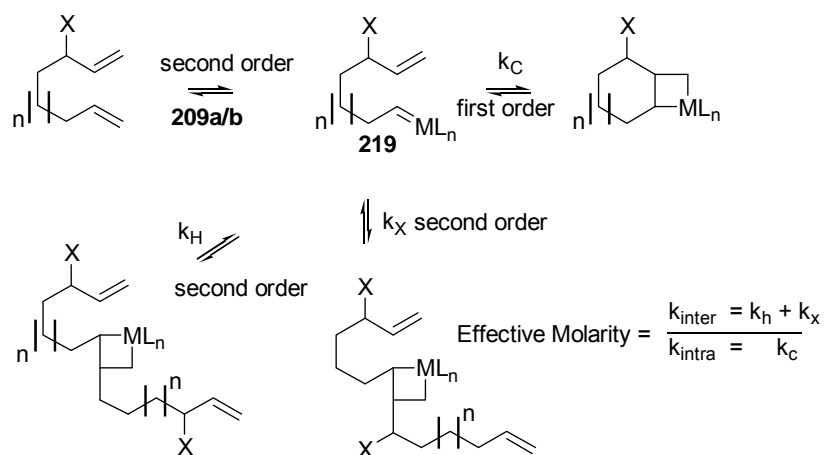
Scheme 59

The rate constant for cyclisation (k_C) is first order in **219** and therefore in olefin whereas homo and hetro dimer formation (k_H and k_X) are second order in olefin. It is therefore possible to disfavour the intermolecular reaction with respect to the intramolecular one by running the RCM at low concentration. The concentration at which the rate of the intra and intermolecular reactions are equal is known as the effective molarity. For efficient cyclisation, reactions must be run considerably lower concentration than the effective molarity. High dilution has drawbacks however; firstly it will decrease the rate of

formation of **219** *via* a second order reaction. More importantly it reduces the scale that the RCM can be run through the purely practical issue of solvent volume required.

2.20 Effect of Alternative Metathesis Catalysts

Grubbs' 2nd generation complex **93** is not the only metathesis catalyst available commercially (Figure 17). Although the first and second generation Grubbs' catalysts **91** and **93** are by far the most popular in organic synthesis, they are not a panacea for all systems.

91   **93**   **224**   **225**   **226**

Figure 17
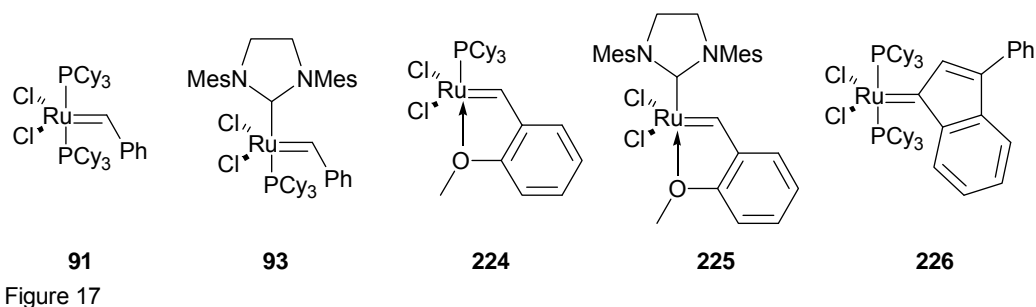
Hoveyda has developed catalysts **224**[104] and **225**[105],[106] based on Grubbs' first and second generation complexes respectively, but with a isopropoxybenzylidene as the dissociating ligand. Catalyst **225** has been shown to be particularly useful in cross metathesis or with electron deficient alkenes. It is very robust, and recoverable in good yield by column chromatography and can be reused to catalyse subsequent transformations with similar efficiency. Alternatively the Neolyst catalyst[107] **226** contains a traditional phosphine dissociating ligand whilst modifying the carbene to an

indenylidene, and is thought to be roughly equivalent to **91** in level of activity. Catalysts **93, 225,** and **226** were screened for activity towards diene **195** (Scheme 60).

Scheme 60
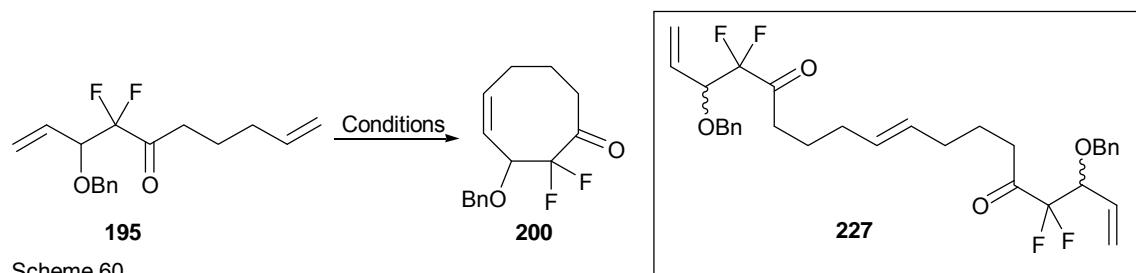
Entry	Catalyst	Conditions	Yield (%)[a,b]		
			200	227	195
1	**93**	5 mol% **93**, 0.33% Ti(O^{i}Pr)$_4$, 0.0022M DCM	75	-	-
2	**93**	5 mol% **93**, 0.33% Ti(O^{i}Pr)$_4$, 0.005M DCM	50 (90)	(8)	(2)
3	**226**	10 mol% **226**, 0.33% Ti(O^{i}Pr)$_4$, 0.008M	4	38	36
4	**226**	5 mol% **226**, 0.33% Ti(O^{i}Pr)$_4$, 0.008M	(24)	(53)	(21)
5	**226**	5 mol% **226**, 0.008M DCM	29 (32)	13 (57)	19 (11)[c]
6	**225**	5 mol % **225**, 0.33% Ti(O^{i}Pr)$_4$, 0.008M DCM	10 (63)	2 (19)	(13)[c]
7	**225**	5 mol% **225**, 0.008M DCM,	26 (81)	(9.5)	7 (9.5)

Table 17; [a] ^{19}F NMR yields in parenthesis, NMR and isolated yields from different experiments in entry 5; [b] The integration measures 2 fluorine environments in Dimer **227** and one in the other products; [c] Remaining % of material of an unknown species visible in the NMR

The standard synthetic metathesis conditions (Table 17, entry 1) gave good yields of cyclooctenone **200**. At higher concentrations (entry 2) ES-MS and ^{19}F NMR evidence was observed for a compound later identified as homodimeric species **227** (8 %) but this was never isolated after purification. Initially when Neolyst was used as a catalyst (entry 3) small amounts of cyclooctenone were observed by ^{19}F NMR with the remainder being apparently unconverted SM by GC. Initial analysis of the ^{19}F NMR data confirmed this. However, a molecular ion for the dimer was noticed and the ^{19}F NMR was analysed more

carefully, showing a tiny observable change in the chemical shift from that of the starting material and a definite change in splitting. A third product was isolated upon purification, along with **200** (4 %), and **159** (36 %). Analysis of the proton NMR showed loss of the internal methine and terminal methylenes corresponding to the unsubstituted terminal olefin (a type I). A new olefinic signal was observed with an integration equal to that of the second internal methine (Figure 18). This compound gave a good molecular ion for the dimer (Figure 19) and was assigned as the symmetrical homodimer **227** (38% of a possible 50% maximum yield) based on the simple proton NMR. The type I/type I connectivity was conclusively proved by a COSY experiment. It was the isolation of this compound that then allowed its identification in the earlier synthetic RCM reactions (entry 2). The isolation of this dimer was somewhat surprising as it was thought that type I/type I dimers would be consumed readily by the active catalyst. Creighton[108] identified by MS an open chain dimer by LC-MS as part of a mixture of products generated during a cyclooctannulation reaction but was unable to isolate or characterise the species.

Figure 18

Type 1-Type 1 homodimer (observed)

Type 2-Type 2 homodimer (not seen)

Hetrodimer (not seen)
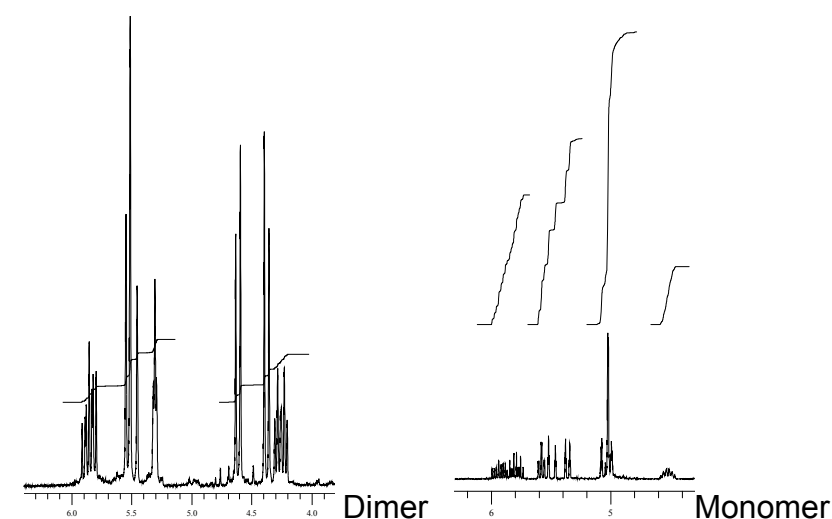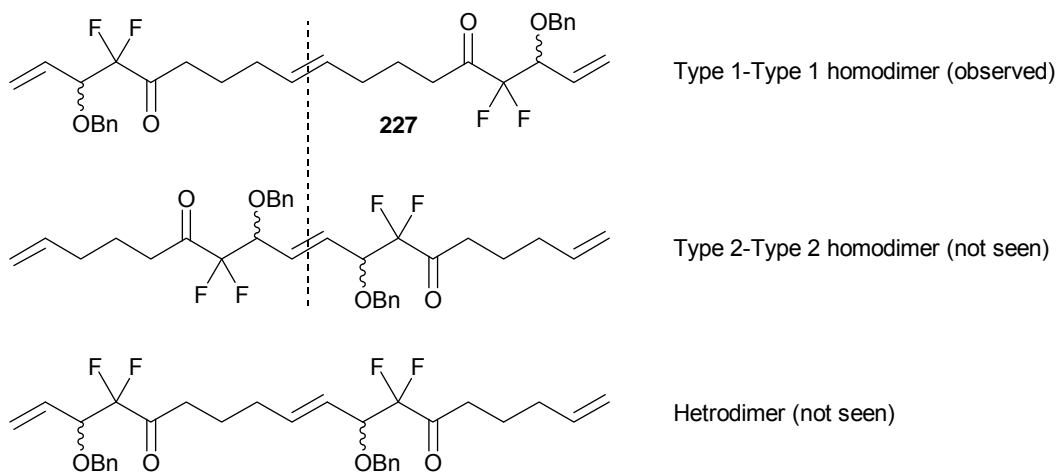
Figure 19

Cross metathesis is not normally E/Z selective although the E stereoisomer is normally favoured[103]. Compound **227** had been assigned as the E stereoisomer due to ^{19}F NMR evidence discussed below.

To investigate the effect of catalyst and Lewis acid on the reaction a number of RCM's were run under identical conditions. Yields were calculated by ^{19}F NMR as well as from isolated material. Interestingly the metathesis using **226** without the Lewis acid co-catalyst (entry 5) is slightly more efficient by ^{19}F NMR both for **200** and **227**, compared to the reaction with the co-catalyst (entry 4), although for the dimer the difference is close to the 5% error associated with NMR integrations. Comparison of the NMR and isolated yields for entry 5 also illustrates the considerable loss of material upon purification, although this must be qualified with the caveat that the yields come from different reactions. The effect of increasing catalyst loading (entry 3 and 5) appears to drive the reaction further toward dimer formation at the expense of **200**. Also of interest is the large amount of **195** recovered at the higher catalyst loading. Unfortunately an accurate

conclusion cannot be drawn as no crude NMR was run for one reaction (entry 3) and its comparator (entry 4) failed to survive purification.

Using Grubbs-Hoveyda 2nd generation catalyst **225** (entry 6) limited amounts of **200** (10 %) were isolated along with traces of **227** (2 %) although more was visible in the NMR (19 %). This was slightly surprising as **225** is known to be an efficient cross metathesis catalyst. The increase in the amount of **200** formed and decrease in the amount of **227** seen when the Lewis acid was excluded (entry 7) was also surprising

A pure sample of **227** was exposed to the standard RCM conditions with **93**. About 50 % of the dimer was shown (by ^{19}F NMR) to be consumed and converted to cyclooctenone **200**. Analysis by GC of the reaction mixture showed an identical retention time to an authentic sample of **200**. This was confirmed by spiking the reaction mixture with a known sample of **200**; GC analysis of the resulting mixture gave only one peak.

2.21 Dimerisation, Cyclisation, and Catalyst Activity

The possible pathways in the metathesis reaction must be considered to explain the formation of homodimer **227** (Scheme 61).
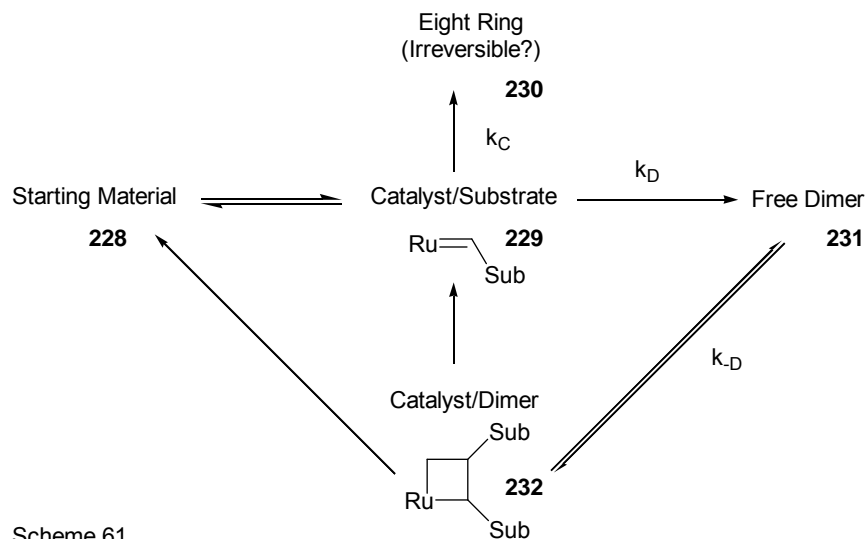
Scheme 61

Starting material **228** reacts with catalyst and forms a new alkylidene **229**. At this point it should be noted that the catalytic intermediate generated after the initial turnover of Neolyst **226** is identical to that generated by Grubbs' 1st generation catalyst **91**. Carbene **229** can either form the cyclised product **230** or a CM dimer **231**. It is assumed at this point that RCM is irreversible; this has been shown to be true with our system by re-exposing the cyclooctenone to the more active **93**, and analogous behaviour is expected for the less active **226**. Although three dimers are possible, only the homodimer **227** was seen, this is perfectly understandable according to Grubbs' own rules where type I homodimerisation is much faster than either type II homodimerisation or type I/type II CM.

The free dimer **231** can then react reversibly with the catalyst (either Neolyst **226**, or the common intermediate) generating **232** which fragments to reform **228** and carbene **229**, returning to the beginning of the cycle. Theoretically, granted infinite catalyst lifetime all material should be sequestered as **230**. It is suggested that the homollylic fluorine atoms make the type II olefin electron deficient to such an extent that it reacts exceedingly slowly if at all in cross metathesis, so no type II dimers are found. It is observed to react to give **200** only because the intramolecular tether removes the requirement for the external translational and rotational entropy to be lost before reaction, although internal rotations do need to be lost before reaction. Therefore if k_C is small (expected due to low type II activity) and k_D is greater than k_{-D} then significant build up of dimer should be seen.

The reaction with Grubbs-Hoveyda catalyst **225** showed much more material sequestered as **200** and little as **227** (up to 19 %) compared to catalyst **226**. Catalyst **225** shares the same propagating species as **93** which has been shown to produce small amounts (8%) of **227** in synthetic reactions run at similar concentration (0.005M). These results follow from the fact that **93** is known to react better with electron deficient olefins, increasing k_C and therefore reducing (but not eliminating) homodimer formation.

2.22 Dimer Structure and NMR

The structural assignment advanced in the thesis is based on the assumption that the alkene configuration is E and that the stereoisomers arise from the sp^3 stereogenic centres.

However there is an alternative explanation; alkene cross metathesis is known to produce E/Z mixtures, and it may be that the additional peaks arise from the presence of the E/Z diastereoisomers. We are not able to distinguish between these possibilities on the basis of the evidence available.

As the diene monomer contains a chiral centre, four dimers are possible. Cross metathesis between two R or two S enantiomers gives rise to either an R,R **233a** or an S,S **233b** dimer (Figure 20). These dimers are C_2 symmetric and enantiomeric, and hence indistinguishable in the NMR spectra; they contain two fluorine environments as each fluorine is paired with a chemically and magnetically equivalent nucleus on the second metathesis partner. Alternatively coupling between an R and an S enantiomer gives the same compound **234** (the R,S and S,R dimers being interconvertible with a simple 180° rotation) with meso symmetry. In **234** all four fluorines are magnetically different and should appear separately in the fluorine spectra.
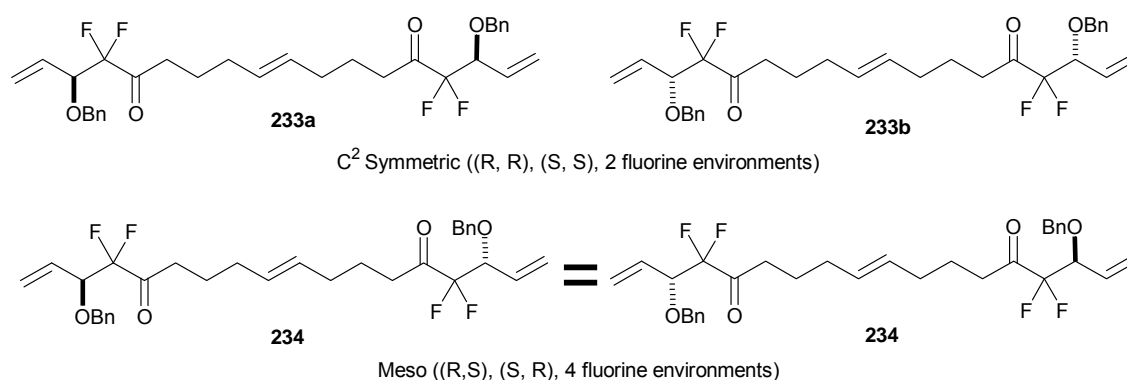
Figure 20

These dimers are practically coincident in the proton NMR but are easily seen differentiated in the ^{19}F spectrum after proton decoupling (Figure 21). Ignoring the duplication from large fluorine-fluorine couplings; in the high field end of the spectra

three environments are visible. One corresponds to the C_2 dimer and two to the *meso*; the integration is approximately 2:1:1 moving upfield. This pattern suggests that the two signals from the C_2 species are coincident, with the two signals from the *meso* compound appearing alongside.
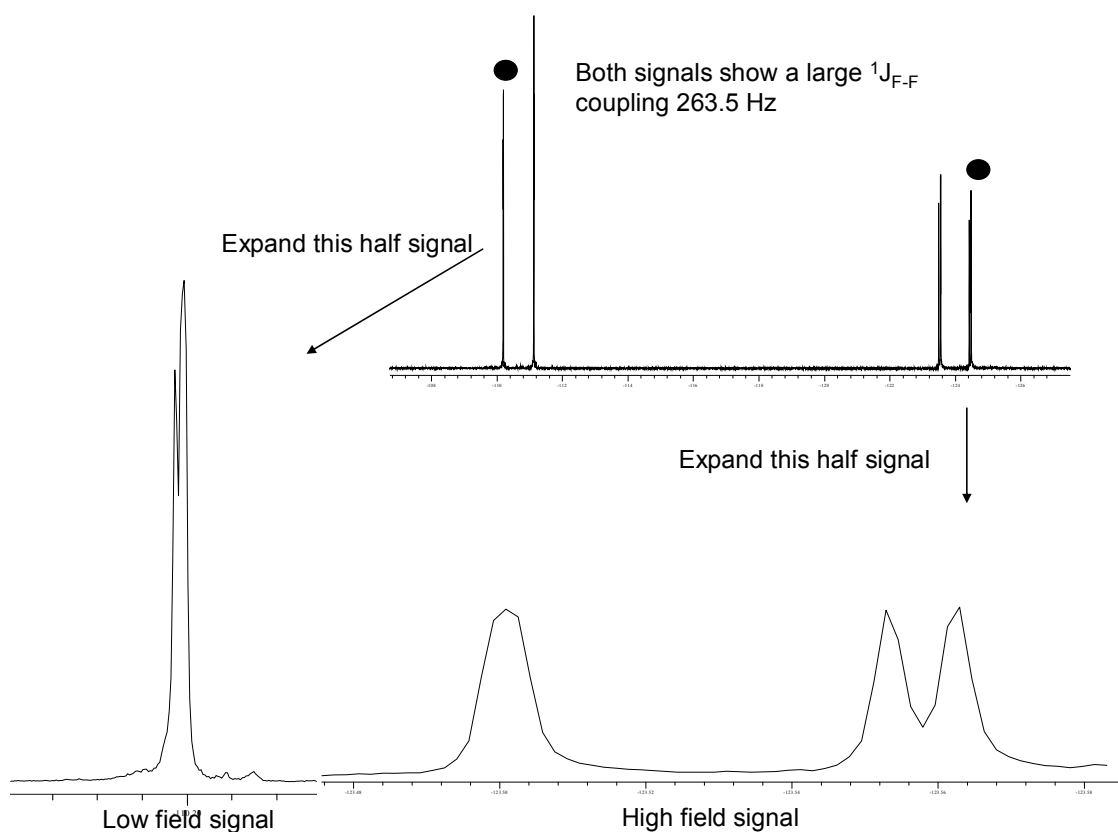
Figure 21

The low field end is less clear with signal overlap; however there is one resonance slightly separated from the rest. The integration is 1:3, which suggests the separate resonance belongs to the meso compound with the second resonance from the meso species being coincident with the signal from the C_2 symmetric species.

Most of the resonances are also coincident in the carbon spectra. However considerable differences can be seen with the alkyl region of the spectrum where six methylene signals can be observed (figure 22).
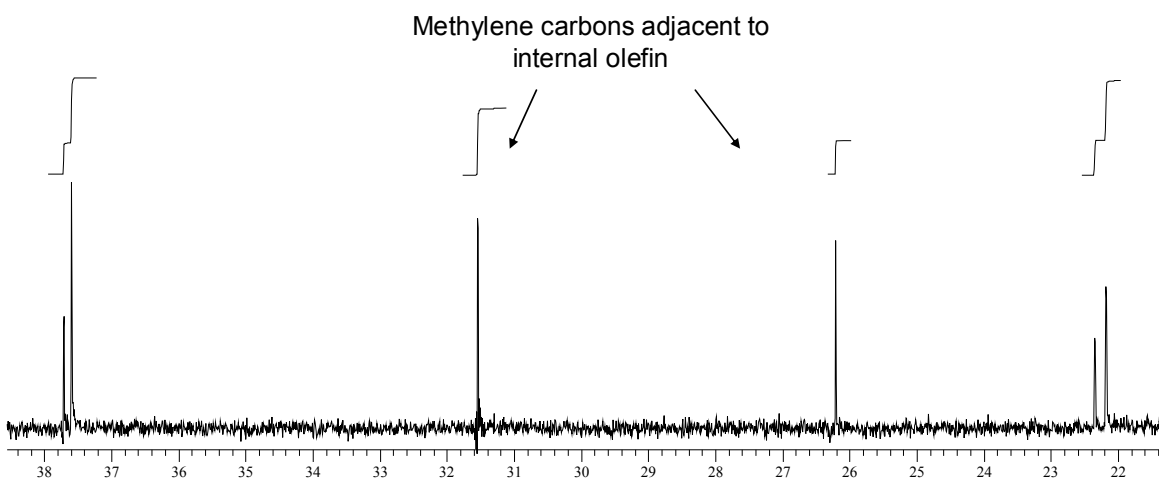
Figure 22

The carbon nuclei allylic to the internal olefin show the biggest difference in chemical shift appearing at 26.2 and 31.5 ppm. An inverse gated experiment[109] gave rough integration for the resonances of 3:1. The same behaviour is observed with the pairs of signals observed at 22.3, and 22.1 ppm, plus 37.7, and 37.6 ppm. The rationalisation of these results also requires a consideration of symmetry. The carbons in analogous positions on opposite sides of the double bond in the symmetric molecule should be magnetically equivalent and therefore coincident. For the meso compound, the nuclei cannot be interconnected *via* a simple symmetry operation and appear as separate resonances in the ^{13}C NMR. One of these resonances is coincident with the symmetric compound whereas the other is seen distinctly for all three carbons. The ^{19}F and ^{13}C NMR data suggest the ratio of **223a/b** to **234** is 1:1

2.23 Synthesis of Further Dimers with Neolyst

With dimer formation appearing to be the preferred reaction pathway with Neolyst and diene **195** (Table 18, entry 1) the scope of the reaction against **196** and **172** was investigated. The benzoyl series tolerates higher substrate concentrations; (0.02M in the synthesis of cyclooctenone **201**). This concentration was therefore chosen to run the Neolyst reaction (entry 2). Homodimer **235** was isolated in good yield (34 % of a possible 50 %) after chromatography, along with recovered starting material (42 % (the percentage yields are calculated on a different number of moles for the monomeric and dimeric species and therefore do not have to add up to 100%)). The structure of the dimer was assigned by a COSY experiment and also proved to be a type I/type I homodimer. It was found that **235** showed analogous NMR behaviour to benzyl dimers **233**, and **234**.
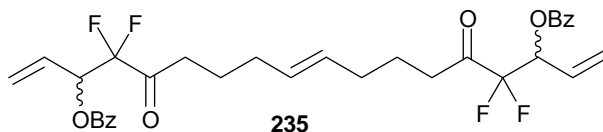
The attempted cross metathesis of unprotected allylic alcohol **172** proved difficult. The solvent was removed carefully after reaction (maximum vacumn 250 torr) due to the known volatility of cyclooctenone **187**. Following chromatography starting material (5 %) was isolated pure in addition to a mixture of material that looked identical to cyclooctenone **187** by chemical shift and $^2J_{F\text{-}F}$ coupling constant analysis of the ^{19}F NMR spectrum. The second component of the mixture had similar signal NMR characteristics to known dimers **233, 234**, and **235** and this was therefore tentatively assigned as

homodimer. Despite a range of solvent systems these two components could not be isolated pure. No MS evidence for either species could be obtained.
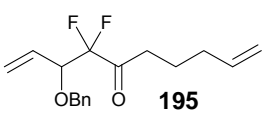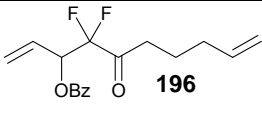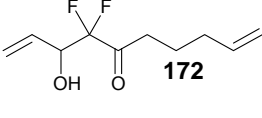
Entry	Substrate	Conditions	Outcome
1	F F OBn O **195**	10 mol% **226**, 0.33% Ti(O^{i}Pr)$_4$, 0.008M	**200** 4% **233, 234** 38% **195** 36%
2	F F OBz O **196**	5 mol% **226**, 0.33% Ti(O^{i}Pr)$_4$, 0.02M	**235** 34% **196** 42%
3	F F OH O **172**	10 mol% **226**, 0.33% Ti(O^{i}Pr)$_4$, 0.008M	**172** 5% Possible 8 ring, Dimers

Table 18

Existing syntheses of eight membered rings using **226** include two examples from the laboratories of Fürstner (Scheme 62).[107] Initial activity was measured with diene **236** which was cyclised to **237** in 70% yield, comparable to that obtained with **91**. Fürstner also used **226** to synthesize the ADE-ring system of Nakadomarin A **238**. The annelative ring closure of **239** was achieved with 5 mol% catalyst loading at high dilution to afford tricycle **240** in almost quantitative yield (98 %, catalyst **91** gave 82 %).
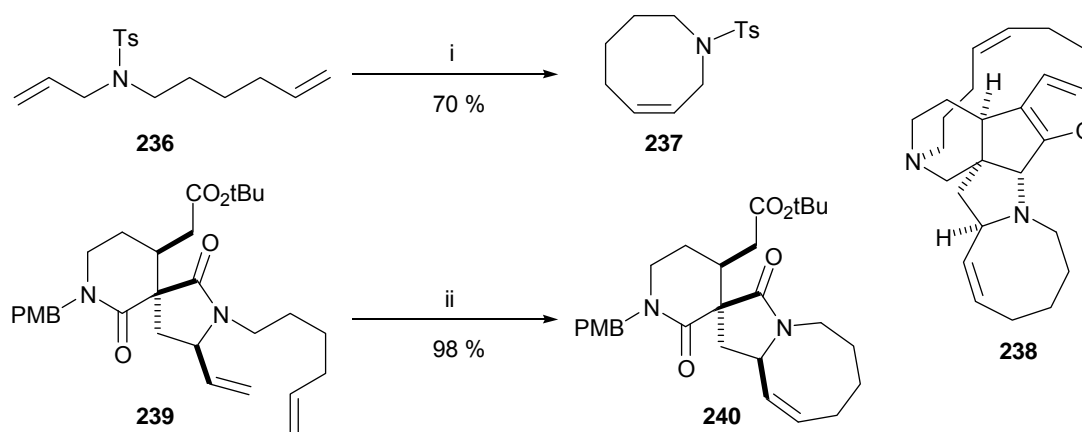
Scheme 62; Reagents and conditions; i, 1 mol% **226**, 0.019M DCM; ii, 5 mol% **226**, 0.002M DCM

Dimer formation is not reported in either of the above examples. The presence of the pyrrolidine ring results in a reduction of the entropic contribution toward the Gibbs energy of activation for the metathesis reaction by making the entropy loss required to form the $\acute{\eta}^2$–complex less negative and intramolecular coordination of the second olefin more favourable.

2.24 Catalyst Longevity and Decomposition and the Effect on Difficult RCM Reactions

It is not merely the pre-catalyst initiation rate or the rate of catalyst turnover that controls the final outcome of a metathesis reaction. The longevity of both pre-catalyst and active catalytic species are equally important in contributing toward a good chemical yield. For example a catalyst that is slow to activate but stable in solution undergoing many turnovers, may be more effective than a fast activating complex that undergoes few

turnovers before decomposing. Indeed Grubbs has shown that where the concentration of the propagating methylidene is high (a fast initiating pre-catalyst) the rate of decomposition of the catalyst is also increased.[110]

It is therefore important to have an understanding of the factors that effect the longevity of the pre- and active catalytic species and the pathways *via* which they decompose. Many factors can effect the catalyst lifetime including solvent and temperature[111], an increase in the latter often causing faster catalyst decomposition. The simplest form of catalyst deactivation is the re-coordination of the phosphine ligand to the metal centre. This can occur with either the benzylidene **241** or the propagating methylidene **242** forming **93** or **243** (Figure 23) before any catalysis has occurred or after a number of turnovers, terminating the reaction in the case of **243**. The active **241** can be re-formed from **93** but limited evidence[44] suggests that **243** (once formed) loses phosphine extremely reluctantly.
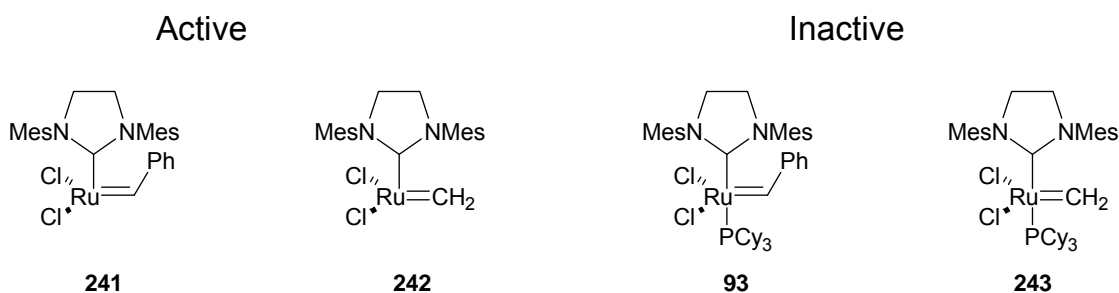
Figure 23

Clearly methylidene **242** is more important to the overall metathesis scenario, yet Grubbs' has been unable calculate the phosphine dissociation constant for **243**, making the effect of re-coordination difficult to quantify[44]. Phosphine scavengers such as HCl

125

and CuCl have been used[100] to try and prevent phosphine re-association but these can have a detrimental effect on catalyst lifetime and as such were not used in our case. In fact the half life of benzylidene pre-catalyst **93** in refluxing solvent is increased by the addition of excess phosphine whereas that of complex **243** is not. This suggests that methylidene species **243** decomposes *via* a different pathway to benzylidene **93**.

Until recently no decomposition products had been observed from catalysts under typical metathesis conditions. The first such compound to be identified is dinuclear ruthenium complex **244**[112] along with methyltrichlorohexylphosphonium chloride **245** (Scheme 63). The formation of **244** and **245** is initiated by attack of dissociated phosphine on 14-electron methylidene species **242** at the carbene carbon. The identification of this species helps explain the above observation of catalytic systems with high methylidene concentrations decomposing at faster rates
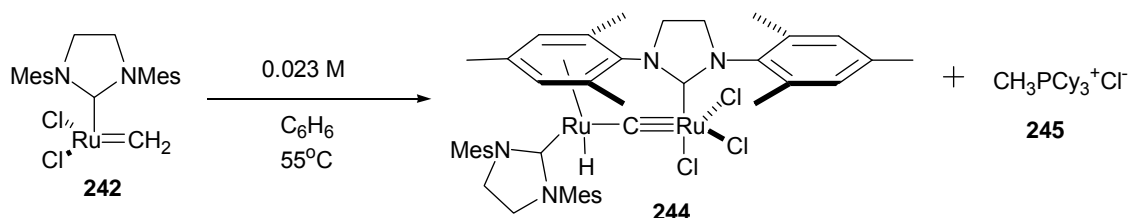
Scheme 63

A good measure of the reactivity and stability of a catalyst is turnover number (TON) or the average number of catalytic cycles undertaken per catalyst molecule, which can be thought of as the catalytic activity lifetime. For the metathesis reaction this can be seen as the number of cyclisations per catalytic molecule. The TON does not give any information about the longevity of either the pre-catalyst or the active catalyst but the

stability of the combined system. Neither does it give any information about the efficiency of the catalyst; a separate quantity, the turnover frequency (TOF) records the efficiency of the catalyst; giving the number of turnovers per molecule, per hour. Blechert[113] has measured the TON of eight membered ring formation for catalysts **91, 93, 224,** and **225** (Scheme 64, Table 19)

R = H **246**
R = CO$_2$Me **248**

R = H **247**
R = CO$_2$Me **249**

Scheme 64
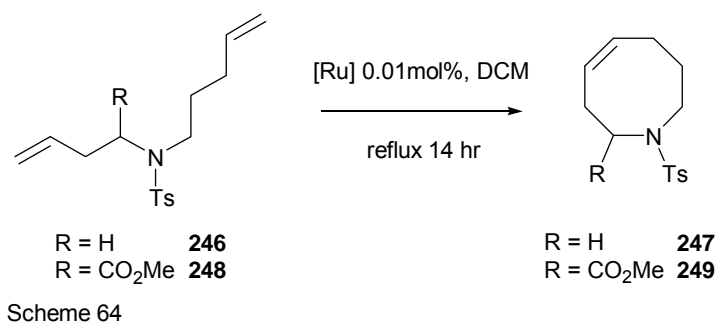
Entry	Substrate	Catalyst	Conversion[a]	TON
1	**246**	**91**	46	4600
2	**246**	**93**	12	1200
3	**246**	**224**	87	8700
4	**246**	**225**	24	2400
5	**248**	**91**	39	3600
6	**248**	**93**	49	4900
7	**248**	**224**	46	4600
8	**248**	**225**	54	5400

Table 19; [a] Measured by HPLC

For **246** (R = H) interesting results are obtained. Both the first generation catalysts showed much higher TON and gave better conversions to **247** than the NHC complexes.

Indeed the first generation Grubbs-Hoveyda catalyst **224** is almost twice as active as the next best catalyst. With the more difficult RCM of **248** to **249** (where the ester carbonyl can coordinate to the metal centre causing deactivation) an almost complete reversal in performance is observed. Both NHC complexes outperform their rivals in both TON and conversion albeit by a small margin. Clearly the first generation systems are more stable in solution and hence show high overall activity with simple substrates. When confronted with a more challenging system the greater efficiency of the second generation catalysts **93** and **225** allow them to outperform **91** and **224**.

2.25 Cyclooctenone Oxidation and Progression to Bicyclic Systems

Two oxidation strategies could be applied to cyclooctenones **200** and **201** in a divergent synthesis. Firstly epoxidation with methyl trifluoromethyldioxirane[114] (MTFMDO) generated *in situ* gave good yields of the trans epoxides **250** and **251** as crystalline solids and single (racemic) stereoisomers (Scheme 65, Table 20). Dioxiranes are excellent epoxidation reagents reacting with both electron rich and electron poor olefins under neutral conditions.
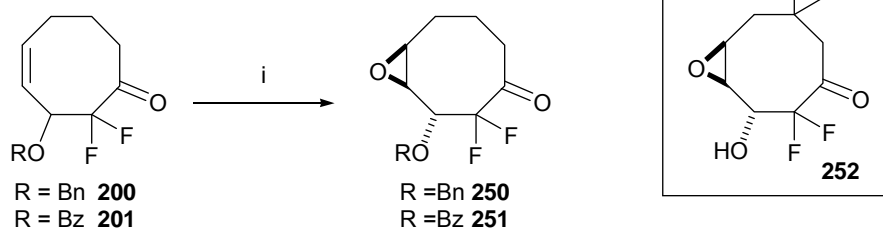
Scheme 65; Reagents and conditions; NaHCO$_3$, Oxone, Na$_2$EDTA, CF$_3$COMe, MeCN, 0°C to rt, ON
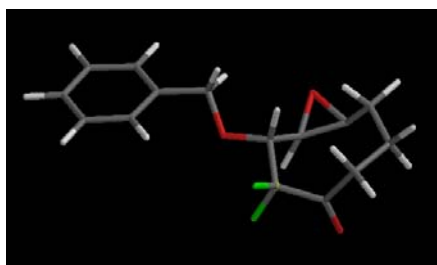
Figure 24

Entry	R	Yield (%)
1	Bz	64
2	Bn	75

Table 20

The stereochemistry was proved from an X-ray crystal structure[115] for **250** (Figure 24, *R* value unacceptable for publication) and it's origin is discussed below. This epoxidation gives the same diastereofacial selection as observed in our earlier systems[71] illustrated by **252** and to that demonstrated by Curci[116] and co-workers. Although the maximum yield achieved for **250** exceeds that for **251** the yield for this system was less reproducible and was usually between 40 and 50 % whereas **251** was consistently around 60 %. The epoxidation of **200** also resulted in a small amount of **251** (up to 10%) being formed through oxidation of the benzylic methylene. Dimethyldioxirane oxidation of benzylic ethers is known[117], efforts to suppress this reaction by reducing the amount of oxone present in the system failed. It was important to use good quality purified cyclooctenone in the reaction otherwise poor yields were obtained. Difficulties were encountered removing trifluoroacetone hydrate after the reaction; in the case of **251** this

could sometimes be achieved after prolonged exposure to high vacuum. However for **250** a chromatographic step was unfortunately always required.

It was found that significantly longer reaction times were required for the epoxidation of **250** and **251** compared to those for the systems tested by Yang when developing the protocol. He found the reactions took between 15 min and 2 hours, (although no cyclooctenes were tested). In contrast with **250** and **251** 6 hours was required to effect complete conversion. A suggested reason for the extended reaction time is that the reaction is trying to install a strained three membered ring onto an already strained cyclooctenone.

The benzyl system alone was also dihydroxylated. The benzoyl protecting group was abandoned due to problems encountered by co-workers with lability under aqueous basic conditions. As expected from our previous experience on the dihydroxylation of cyclooctenones[72] the reaction proved to be non-stereoselective and no cyclooctenone diols **253**, and **254** were isolated following the reactions. In all but one case (see below) [3.3.1] oxabicyclic diols **255** and **256** were isolated as the sole products (Scheme 66). It is argued that ring strain in the cyclooctanic products **253** and **254** is relieved by intramolecular transanular nucleophilic attack of the C-5 hydroxyl on the ketone, to give the two bicyclic products. The oxygen bridge was confirmed for both structures by an HMBC experiment which showed a crosspeak between the proton on C-5 and the C-1 carbon on the acetates prepared subsequently from these compounds (see below).[118]
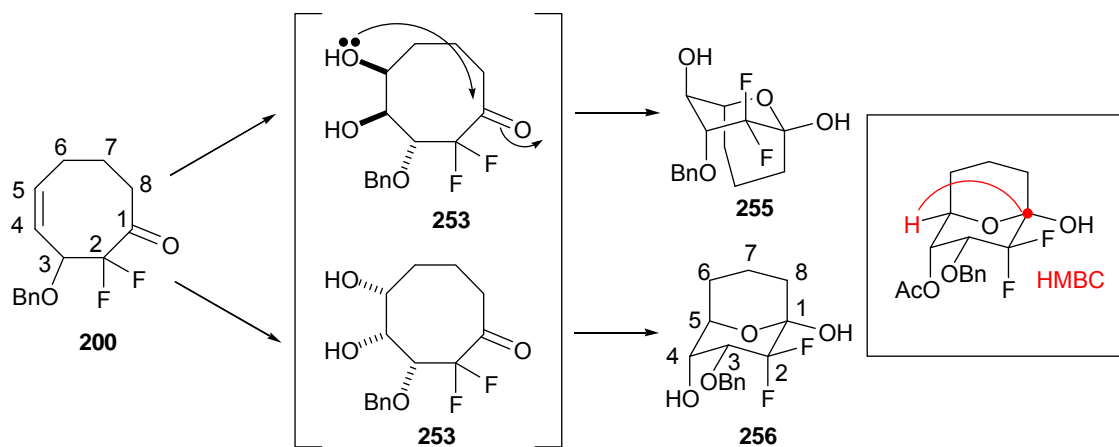
Scheme 66

The structures of both **255** and **256** were proven from X ray crystallographic analysis[119] and good supporting evidence was obtained by NMR (Figure 25). The $^3J_{H-F}$ coupling constant is exquisitely sensitive to changes in the conformation of the pyran ring. The size of the coupling constant is directly related to the dihedral angle between the proton on C-3 and either of the fluorines on C-2. The Karplus equation tells us that the coupling constant shall be at a maximum when the dihedral angle tends toward 0 or 180°. Conversely at 90° the coupling constant should tend to zero.[10]
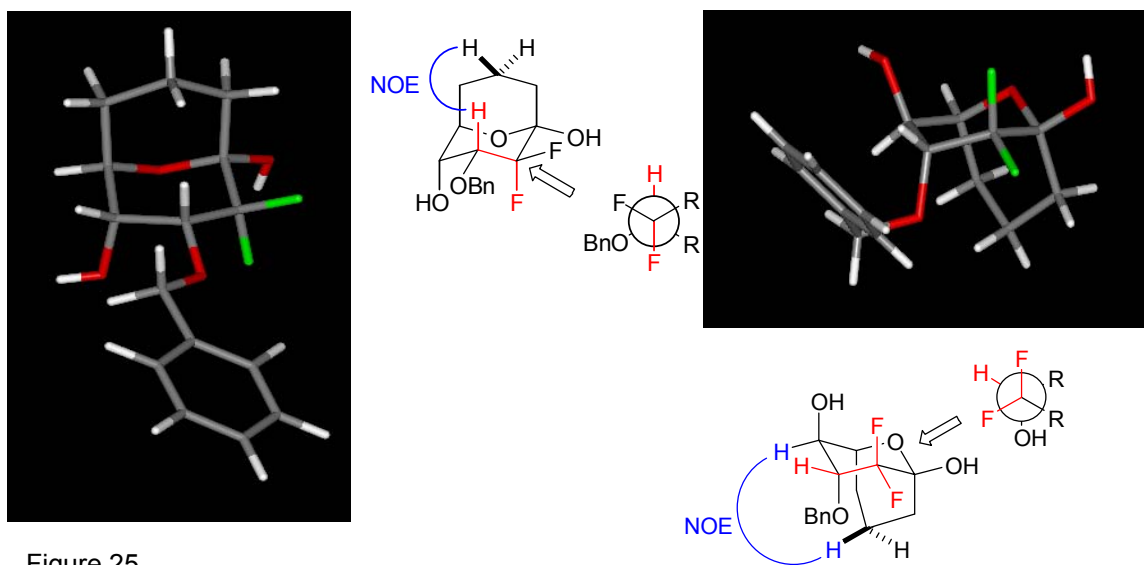
Figure 25

Based on knowledge of previous systems $^3J_{\text{H-F}}$ coupling constants of around 20-22 Hz suggest a close to antiperiplanar relationship between the proton and one of the fluorine atoms. For compound **256** the $^3J_{\text{H-F}}$ coupling constants were measured as 20.1, and 4.8 Hz this suggests a close to antiperiplanar relationship to one of the fluorines and a much smaller angle toward the second. These couplings corroborate the measured H-C-C-F dihedral angles from the single crystal of 161.0 and 46.3°. Further evidence[120] for the structure of **256** is provided by a NOESY experiment showing a strong crosspeak between the C-3 proton and a proton on C-7 of the carbon backbone (1.896 Å)[121]. These two pieces of evidence suggest the solution conformation of **256** is very similar to the crystal structure with the CF_2-containing pyran adopting a $^1C_4$ chair configuration, the conformation also adopted by the second pyran ring. For **255** the $^3J_{\text{H-F}}$ coupling constants were measured as 13.2 and 4.4 Hz; neither of these are close to the values expected for an antiperiplanar relationship and suggest that the C-H bond sits inside the F-C-F angle as seen in the crystal structure, where the H-C-C-F dihedral angles are calculated as 80.8 and -32.7°. The NOESY[122] experiment produced a crosspeak between the C-4 proton

132

and a C-7 proton (3.022 Å).[121] Thus the solution conformation of **255** appears to also be similar to that found in the single crystal, with both rings adopting chair configurations and the CF_2 containing pyran in a $^4C_1$ conformation.

The initial dihydroxylation method chosen is known as the UpJohn procedure and was the same at that used on our earlier systems.[72] This methodology resulted in **256** being formed as the major product in a 3.1:1 ratio (Table 21, entry 1). Conducting the reaction at 0°C led to a big improvement in yield (72 %) but no significant change in product ratio (entry 2).

Entry	Conditions	Temperature ($^{\circ}$C)	Yield (%)	**255/256** Ratio[b]
1	5% OsO$_4$, NMO, Acetone, H$_2$O, tBuOH, (4:2:1), 6 hr	rt	43	1:3.1
2	5% OsO$_4$, NMO, Acetone, H$_2$O, tBuOH, (4:2:1), 6 hr	0	73	1:2.9
3	5% OsO$_4$, NMO, Acetone, H$_2$O, tBuOH, (4:2:1), 6 hr	0	61[a]	-
4	4% OsO$_4$, NMO, Acetone, H$_2$O, tBuOH, (4:2:1), 6 hr	0	48[a]	-
5	2.5% OsO$_4$, NMO, Acetone, H$_2$O, tBuOH, (4:2:1), 6 hr	0	45[a]	1:2.6
7	1.12 eq OsO$_4$, TMEDA, DCM, 18 hr	-78	89[c,d]	1:1
8	1.4 eq NaIO$_4$, 10% CeCl$_3$.7H$_2$O, 2.5% RuCl$_3$.H$_2$O, EtOAc, MeCN, H$_2$O, 3:3:1, 20 hr	0 to rt	45	1:1.7

Table 21; [a] crude **200** used, yield over two steps; [b] by ^{19}F NMR; [c] crude material acetylated before isolation; [d] starting material recovered 9 %.

The dihydroxylation was attempted using crude cyclooctenone **200** (entry 3); this initially returned an excellent yield over 2 steps (61 %). This was better than the stepwise total yield (54 %) but unfortunately this high figure could not be reproduced, the normal yield being ca. 45 %. Dropping the amount of catalyst to 4 % and then to 2.5 % (entries 4, and

5) reduced the yield from the maximum achieved but not from the average. Indeed catalyst loading appeared to have very little effect on the reaction.

Donohoe's[123],[124] OsO$_4$/TMEDA dihydroxylation (entry 7) and subsequent acetylation gave **257** and **258** (plus small amounts of unacetylated **256**) unselectively in excellent yield (89 %) along with recovered **200** (9 %). No product was initially detected upon work up of the reaction in this case. Two unknown compounds, one with very broad resonances, were visible in the ^{19}F NMR spectrum. The mass spectrum gave a very strong molecular ion for osmate ester **259** (Scheme 67), which was easily hydrolysed with 2M HCl to liberate diols **255** and **256** in a 1:1 ratio. Indeed Donohoe has noted that these TMEDA/osmate complexes are very stable, and cannot be hydrolysed in *situ* by an oxidising agent, thus preventing the reaction being made catalytic.
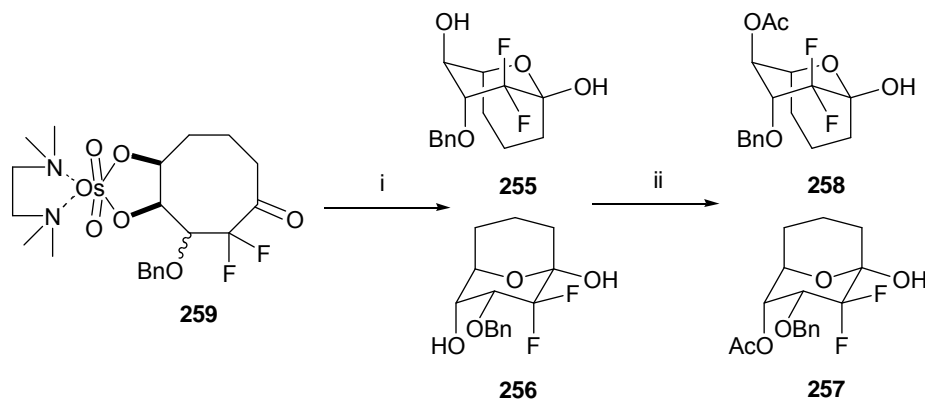
Scheme 67; reagents and conditions i. 2M HCl; ii. PVP, Ac$_2$O DMAP, DCM

Usually the OsO$_4$/TMEDA procedure is significantly faster than the UpJohn methodology; indeed it has been suggested that the rate of reaction may by up to 10 000 timers quicker. This did not appear to be the case with **200**, where starting material was still detected after 18 hours and a small amount (9 %, therefore a 98 % yield of useable

material) isolated upon purification, despite the use of an excess of OsO₄/TMEDA. Along with the Donohoe dihydroxylation being slower than expected, the UpJohn methodology was fast compared to results obtained for dihydroxylation of cyclohexanes by others in the group (Scheme 68).[125] Cylohexene **260** was dihydroxylated using 2 mol % osmium tetroxide and gave **261** in 51 % yield after 24 hours. At a similar catalyst loading (2.5 mol %) the dihydroxylation of **200** was complete after six hours in higher yield (71 %).

260   **261**
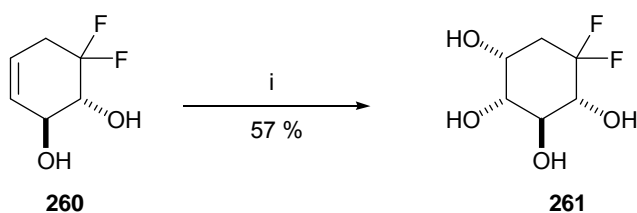
Scheme 68; Reagents and Conditions; i, 2 mol% OsO₄, NMO Acetone/water/tBuOH, 4/2/1, 24 hr.

This is probably due to the higher strain present in the eight membered ring which is relieved by the transannular reaction. A possible reason for the Donohoe reaction being slower than the UpJohn procedure is that in the UpJohn methodology the transannular reaction can act as a product sink removing hydrolysed diol post osmate hydrolysis thus driving the hydrolysis equilibrium toward the product and increasing the rate of reaction (with the caveat that osmate hydrolysis is reversible). The dihydroxylation itself actually introduces strain to the system as the two sp^2 centres reduce the transanular repulsions. In the Donohoe reaction the osmates are stable to hydrolysis under the reaction conditions and therefore no rate acceleration from transannular collapse is possible.

An alternative strategy using RuO₄ generated in *situ* as the dihydroxylating agent[126] was attempted (entry 8) due to the high toxicity of osmium. Although this was the easiest

reaction to carry out, the yield proved disappointing (45 %). The reaction was stereoselective but less so than the osmium tetroxide procedure; **256** was again found to be the major diastereoisomer although only by a 1:1.7 ratio. Due to the excellent yield and since both diastereoisomers are required for later stages, the Donohoe dihydroxylation would be the method of choice for the dihydroxylation on a small scale. However the large amount of toxic reagents would preclude it's use on a large scale, furthermore its use is limited by the cost of the stoichiometric reagent.

2.26 Understanding the Stereochemical Outcome 1; Solution Conformation of the Cyclooctenones

In order to understand the origin of the stereochemistry observed in the oxidation reactions on cyclooctenones **200** and **201** one must consider the conformations that they adopt in solution. A number of techniques were used, contributing information to this conformational analysis. Molecular modelling using PC Spartan Pro was carried out by Percy[127] on the free hydroxyl ring system **187**. This system was chosen for it's simplicity as the large number of atoms in the protecting groups used would make calculations on the true systems much slower. The calculations involved Monte Carlo conformational searching (MMFF94 forcefield) in Spartan04.[128] The geometries of all the conformers generated in this way were optimised by *ab initio* calculations (RHF 6-31G*) and energies were also calculated using the 6-311+G** basis set.

The molecular modelling provided four low energy conformations within 1.5 kcal mol^{-1} of the lowest energy conformation (Figure 26, structures A-D). Structures A and C were shown to have the lowest predicted energy (Table 22) and could be analysed with respect to experimental evidence. Firstly as has been discussed above the $^3J_{H-F}$ coupling is exceptionally responsive to changes in the conformation of the ring. The measured couplings for **200** and **201** are 19.5 (323 K) and 21.3 Hz (300 K) respectively. These couplings fit well with what is already known about these systems with large $\geq$ 20Hz H-F couplings being visible between a fluorine atom and the allylix methine in earlier *gem*-dimethyl species, and also visible in the brosylate **202** (19.5 Hz, 300 K) and tosylate **203** (20.6 Hz, 300 K) cyclooctenones discussed earlier. These results suggest that one of the fluorine atoms is in a close to antiperiplanar (180°) orientation with the methine proton on C-3.
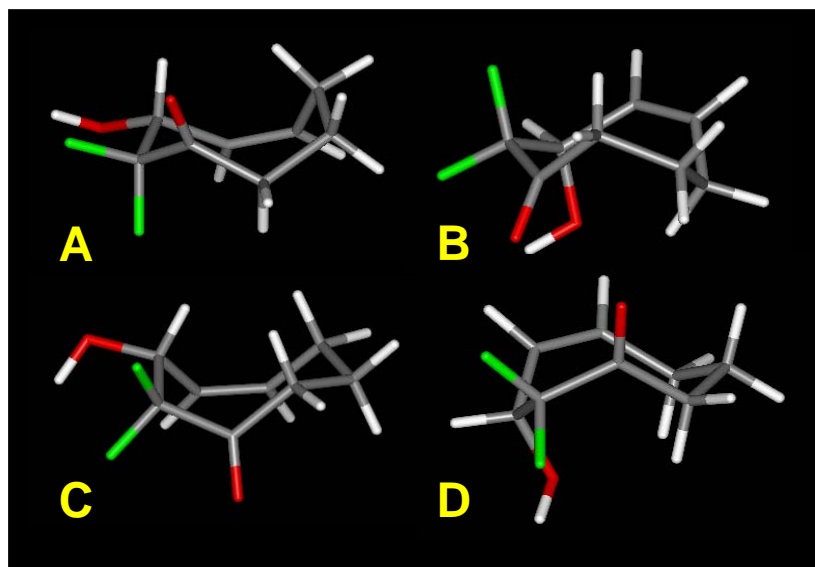
Figure 26

This arrangement is visible in conformations A and C where the H-C-C-F dihedral angles are -175.39°, and 68.46° in conformer A, and 164.76°, and 48.11° in conformer C. No

such orientation is visible for conformations B (55.60°, -59.70°) and D (75.83°, and -40.17°). It should also be noted that conformers A and C are interconverted by an in-out flipping of the ketone, the same relationship holds for B and D.

Structure	E_{rel} (kcal mol^{-1})[a]	$^3J_{H\text{-}F}$ coupling > ~20 Hz	NOESY	Calculated Proton Contact Distances (Å)
A	0.000	Yes	Yes	C3-H – C6-H 2.265
B	+1.015	No	No	-
C	+0.440	Yes	Yes	C3-H – C6-H 2.232
				C6-H – C8-H 2.554
				C3-H – C8-H 2.475
D	+1.514	No	Yes	C6-H – C8-H 2.563

Table 22; [a] calculated energies of the conformations.

Further information about the solution conformation of the cyclooctenones came from NOESY experiments[129]. The experiment is designed to pick up contacts of up to 3Å, and upon analysis of both **200** and **201** cross peaks were detected between the proton on C-3 and one proton each on C-6 and C-8. Such a characteristic set of peaks is also visible in brosylate **202** (tosylate **203** was not run) and in previous first generation examples. Again looking at the four calculated conformations one can see that a close proximity relationship between these three protons is visible in conformation C, and also between C3-H and C6-H but not C8-H in conformation A. There is also a NOE relationship in D but this is between C6-H and C8-H and not the C3-H interaction clearly visible in the spectra. It is therefore possible to suggest with some confidence that conformations A and C both exist is solution and are occupied by the majority of the material. This statement is made with a number of caveats. Firstly crystal structures need not bear any resemblance to solution conformations. Secondly although in this case the crystal structure is backed by the NMR solution analysis the detection level of the NMR is only about 95 % and

therefore one of the other conformations or indeed any other conformation may be present in up to 5 % in the solution. Finally there is the unknown effect of the protecting group upon conformation.

2.27 Understanding the Stereochemical Outcome 2; Stereochemistry of the Epoxidation

As the cyclooctenones appear to adopt conformations A and C in solution this leads to a view of the molecule as having a curved topology with one convex (open) and one concave (closed) face 262 (Scheme 69). The *trans* epoxide (relative to the allylic C-O bond) formed is indicative of attack of the dioxirane 263 on to the more sterically available open face of the molecule. This is the same diastereofacial selection to that observed by Curci[116] and co-workers in the acetone/potassium caroate epoxidation of cyclooctenol. Attack at the closed face is hindered by the concave topology.

Scheme 69
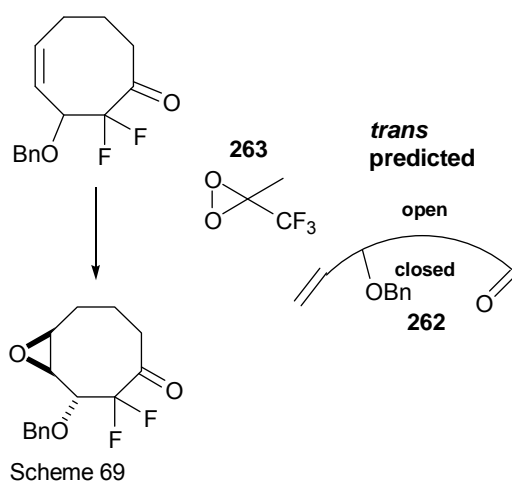
This observed selectivity is contrary to that observed by Adam[130] who found that MTFMDO epoxidation of allylic alcohols proceeded with *cis* selectivity although not to the exclusion of the *trans*-pathway. Adam rationalised his results by proposing that MTFMDO was delivered to the same face of the olefin by hydrogen bonding to the allylic hydroxyl and defined the delivery trajectory by a specified C=C-C-O angle of 130° present in the transition state. For comparison the corresponding dihedral angles in conformers A-D are 163.02°, -49.68°, 148.58°, -38.06° respectively; only conformer C has a dihedral angle remotely close to that suggested. This rational however is not applicable to **200** or **201** as there is no allylic hydroxyl proton to participate in a hydrogen bond. Secondly, the aqueous acetonitrile used as a solvent would reduce the importance of hydrogen bond interactions.

2.28 The Dihydroxylation Mechanism

In the UpJohn mechanism[131] (Scheme 70) osmium tetroxide **264** coordinates to the olefin reducing it to an Os (VI) complex **265**, which is then reoxidised to Os (VIII) **266** by *N*-methyl morphline oxide (NMO) which itself is reduced to *N*-methyl morpholine (NMM). The product diol **267** is then hydrolysed regenerating **264**, or alternatively **266** can enter a second catalytic cycle binding a second olefin to form a new Os (VI) complex **268**. Hydrolysis of this complex results in the formation of aforementioned **265** and the re-entry to the first catalytic cycle.
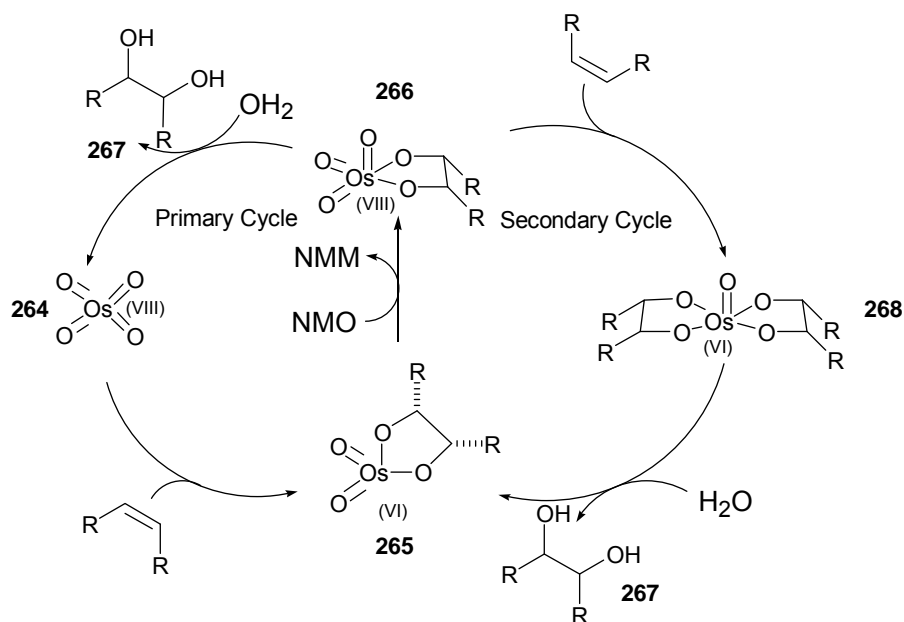
Scheme 70

There has been some discussion[132] as to the true identity of the reaction between **264** and the olefin. It has been suggested that the step could be either a [3+2] cycloaddition directly forming **265** (Scheme 71) or a stepwise reaction with an initial [2+2] cycloaddition to give intermediate **269** followed by a ring expansion to give **265**.
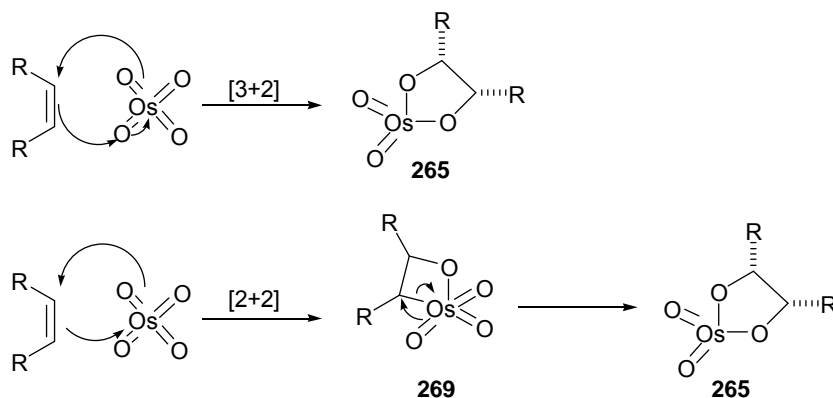
Scheme 71

The same mechanistic arguments can be applied to the ruthenium mediated dihydroxylation as both Ru and Os are group (VIII) transition metals. In the Ru methodology, NaIO$_4$ acts as the reoxidant and the CeCl$_3$ is believed to activate the ruthenate ester towards hydrolysis.

Following on from the "open face attack" argument regarding the stereocontrol of the epoxidation, it was initially easy to think that the same would be true for the dihydroxylation. This is especially so as attack by OsO$_4$ *anti* to the pre-existing alkoxy group has been shown by Kishi to be favoured according to his empirical rule.[133][134]
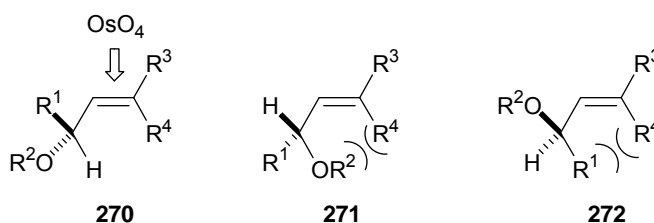
Figure 27

Kishi argues that conformation **270** (Figure 27) is the most populated conformation due to being least sterically compressed especially for *cis* olefins where R^4 is large and **271**, and **272** energetically unfavourable. However **270** is not available to cyclic olefins if R^1 and R^4 are connected by a tether and such systems are forced to react through **272**. With the caveat that this conformational preference is present in the transition state then attack of the osmium reagent should be onto the face of the olefin opposite to the pre-existing alkoxy group. Choice of protecting group for the allylic alcohol has little effect on the stereochemical outcome with the exception of acyl groups which give poor results.

However attack of the osmium reagent onto the more open face of the cyclooctenone **273** (Scheme 72) should give rise to the *trans*, *cis* triol **274**, which gives **255** after the transannular reaction, the minor product from the dihydroxylation for both the osmium and ruthenium methodology.

Scheme 72
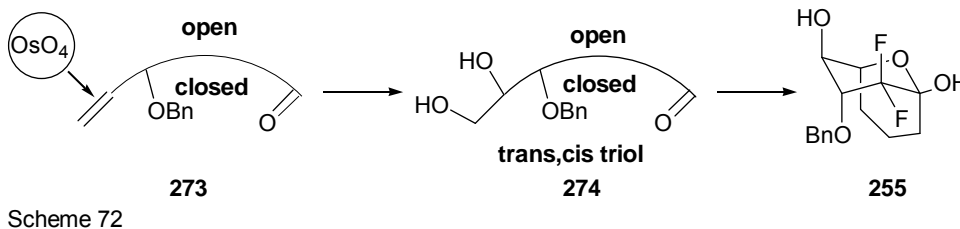
The major product in both these cases is **256**, and its formation was initially rationalised as follows. Bicycle **256** must be formed *via cis,cis* triol **275** which in turn is the result of attack by the osmium reagent on the closed face of the cyclooctenone **276**. This at first appears counter intuitive, but in a C type conformation the C-1 ketone is in a position to act as a Lewis base firstly to coordinate the osmium tetroxide and then to deliver the reagent to the closed face of the olefin (Scheme 73).
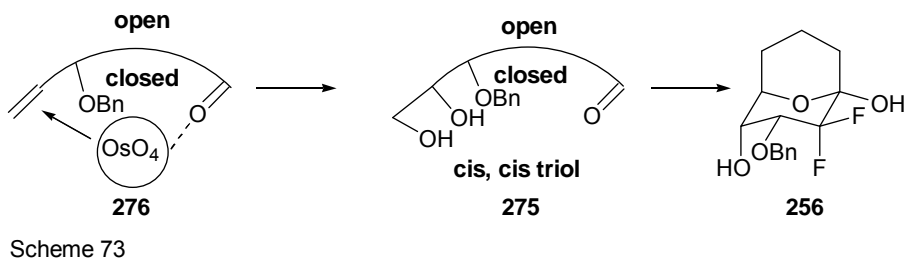
Scheme 73

Precedence for ketonic delivery of OsO$_4$ (Scheme 74) has been claimed, [3.3.0] oxabicyclic lactone **277** has a clearly defined *exo* (open) and *endo* (closed) face. Upon

dihydroxylation and protection, it was found that *endo* acetonide **278** was the major product rather than the expected *exo* adduct **279**[135]. The role of the ketone was highlighted by the contrasting results seen for methyl ether **280**. In this case osmylation gave three acetonides **281**, **282**, and **283** in a 4:1 ratio, favouring attack on the open *exo* face.
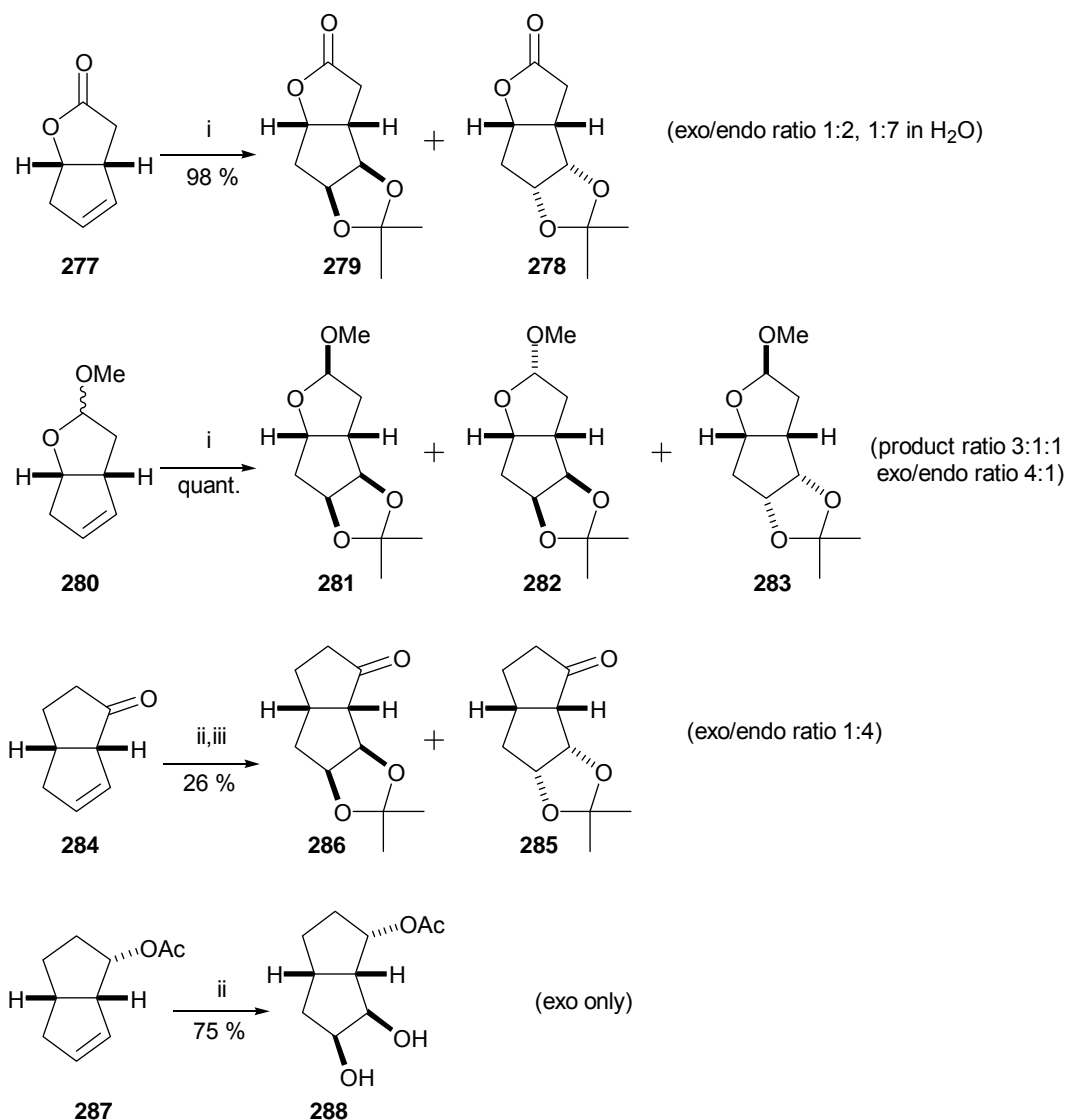
Scheme 2.41; i, OsO$_4$, NMO, acetone, then H$^+$, Me$_2$C(OMe)$_2$; ii, OsO$_4$, NMO, THF tBuOH, H$_2$O; iii, Me$_2$C(OMe)$_2$, DCM, TSOH

Similar behaviour was observed for [3.3.0] bicycleic ketone **284**[136] which has similar topology; here osmylation proceeded to favour the *endo* adduct **285** over the *exo* **286** in a 4:1 ratio. Again the *endo* selectivity was lost when acetate **287** was dihydroxylated with only the *exo* product **288** being formed. The endo selectivity is observed only when the ketone is present in both cases and both authors conclude that this functionality plays a crucial role in the "delivery" of the osmylation reagent to the closed *endo* face however neither specify how the delivery might be achieved. Certainly, the direction of the lone pairs does not suggest delivery, though this does not rule out an electrostatic effect

This mechanistic proposal appeared to fit the UpJohn and Ru dihydroxylation well. However significant problems develope when attempts are made to rationalise the results of the Donohoe directed dihydroxylation. The reaction uses a stoichiometric amount of Osmium coordinated with TMEDA to give a bulky octahedral complex **289**. Donohoe had developed the OsO_4/TMEDA methodology to allow the dihydroxylation of allylic alcohols to proceed with *syn* selectivity **290** as opposed to the *anti* selectivity **291** seen with traditional UpJohn protocol according to Kishi's empirical rule. The reaction is designed with the sense of dihydroxylation being directed by hydrogen bonding of the OsO_4/TMEDA complex to the allylic alcohol **292** which can then deliver the reagent *cis* to the existing C-O bond (Scheme 75).

Scheme 75
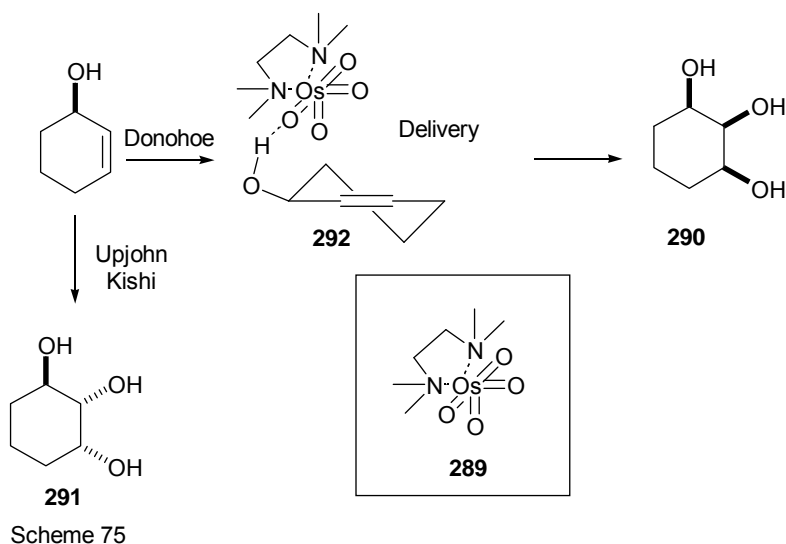
Clearly with the allylic alcohol in **200** protected, no hydrogen bonding was expected and consequently the reaction was not expected to be *syn* selective. It was firstly hoped that the coordinatevly saturated **289** (a 20e complex) would be unable to interact with the cyclooctanic ketone. Secondly is was thought that the bulky **289** would be too large to react on the closed face of **200** and consequently that the stereoselectivity of the reaction would be the inverse of that of the UpJohn methodology, delivering **255** through (close to) exclusive reaction on the open face.

The outcome of the reaction was unexpected, proceeding unselectively and delivering equal amounts of both products. It is difficult to rationalise the large amount of **256** formed with the reaction proceeding through either a type A or a type C conformation for the cyclooctenone.

The evidence for conformers A and C being present in solution is primarily based on NOESY and coupling constant analysis. There are two obvious problems with this; firstly the NMR's are run in a different solvent to both reactions, and the low energy conformations are the result of gas phase calculations. The true identity of the

conformations present in both reaction solvent systems is inferred rather than known. The second effect is the detection threshold of the NMR. This detection level is about $\geq 5\%$ of the total composition of the sample. One can therefore argue that conformers B and D may be present in solution below this threshold level. Assuming A-D are the lowest energy conformers in all solvents and that B and D are present in small amounts along with A and C, a new reactivity relationship can be imagined (Scheme 76).
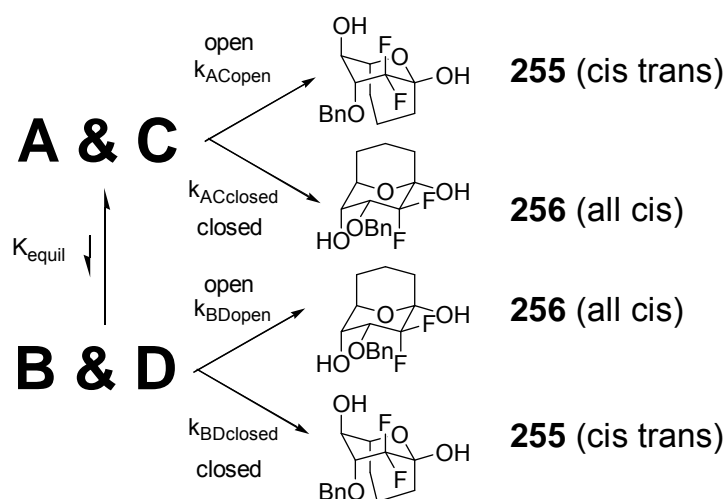
Scheme 76

As already described above, from A and C, **255** and **256** are delivered by attack on the open and closed face respectively. The situation is reversed if conformations B and D are considered. It should be noted that the ketone in D is positioned to deliver the reagent to the closed face as in C. For OsO_4 and RuO_4 the product ratio could be a result of both open face direct attack and chelation delivery on the closed face from A and C, with B and D taking little part in the reaction (or a small part with the stereochemical outcome reversed). Alternately if chelation does not occur and assuming the metal tetroxides are too bulky to easily access the closed face ($k_{ACclosed}$ and $k_{BDclosed}$ small), then the same

147

outcome could be achieved *via* open face attack on A and C delivering **255**, and open face attack on B and D delivering **256**. For this second pathway open face attack on B and D (k_{BDopen}) would need to be faster than the corresponding attack on A and C (k_{ACopen}) in order to give the correct product distribution. Rapid reaction of B and D would drive the equilibrium (K_{equil}) toward their formation. A third possibility is of both pathways operating simultaneously.

The OsO_4/TMEDA result could be the result of material reacting *via* the open faces of both sets of conformers. If $k_{ACopen} = k_{BDopen}$ then this would lead to an equal mixture of **255** and **256** as long as the equilibration between the two sets of conformers is more rapid than the consumption of B and D. Alternativly from an NMR sensitivity of 5% we can estimate that $K_{equil} < 1/20$ and therefore k_{BD} must be quite a bit larger than k_{AC}.

These UpJohn dihydroxylation results show a complete difference in stereochemical outcome to those obtained on a similar system by Paquette.[34] In his synthesis of a range of cyclooctanne polyols the dihydroxylation of **68** (Scheme 77, for full context see introduction **1.8**) was a key step. The structure of **68** is a mimic of **200** with respect to the ketone and the olefin, plus a similar protecting group on the allylic alcohol.
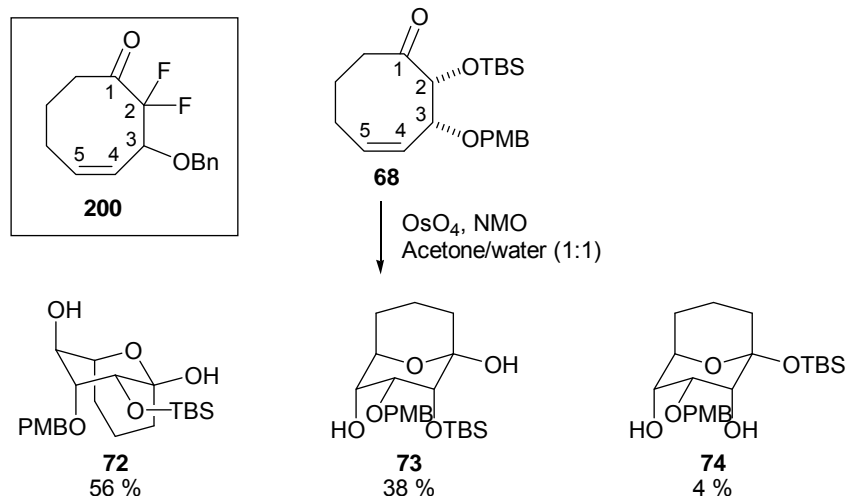
Scheme 77

The dihydroxylation resulted in the formation three compounds. The major product **72** comes from normal Kishi attack *trans-* to the allylic alcohol giving the *cis-trans-* cyclooctenone which as observed with **255** undergoes a transannular reaction to give **72**. Both **73** and **74** come from the same sense of dihydroxylation with a protecting group migration accounting for the difference. Dihydroxylation occurs *cis* to the allylic alcohol giving an all *cis* cyclooctenone before transannular reaction.

The stereochemical outcome of this reaction is the opposite to that observed with **200**, with **72** being formed as the major product in a 1.3:1 ratio. Not only is the outcome of the reaction reversed but the excess of the major stereoisomer is smaller than that observed with **200**. This difference in outcome could be due to cyclooctenone **68** adopting a totally different solution conformation to **200**. This is a distinct possibility as the bulky OTBS group at C-2 in **68** should have a much larger effect on conformation then the small CF_2 group at C-2 in **200**.

2.29 Microwave Mediated Epoxide Opening
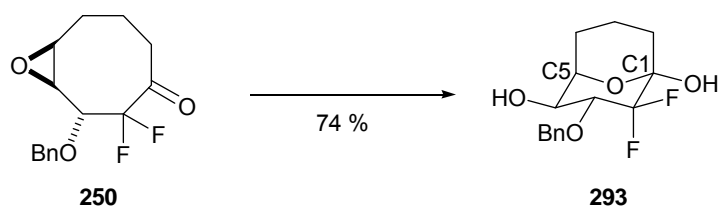
Scheme 78; Reagents and conditions; 0.5% NaOH(aq), μW, 100°C, 30 min
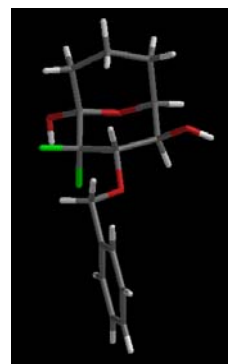
Figure 28

Epoxide **250** was opened under microwave mediated conditions catalysed by a trace amount of base to afford **293** in good yield (Scheme 78). As with the dihydroxylation the product was a [3.3.1] bicyclic system. The location of the oxygen bridge was proved as for the previous examples by an HMBC experiment with a cross peak being found between the C-5 proton and C-1 in the acetate derivative (see below), and an X-ray crystal structure[137] (Figure 28). The structure with equatorial C-O bonds at C-3 and C-4 was expected from the outcome of previous hydrolysis reactions on cyclooctenone epoxides[71]. Attempts to use crude epoxide in the reaction failed to give any **293** upon work up and chromatography. On a single occasion one of the by-products of the reaction was isolated by column chromatography. Initially this product could not be identified but appeared to be a bicyclic system and have the same molecular ion as **293**. It is suggested that the structure of the by-product is [4.2.1] bicycle **294**. This assignment could be proven by an HMBC NMR experiment but unfortunately, enough material was not available to obtain a good carbon spectrum. Subsequently a [4.2.1] bicyclic system was obtained and fully characterised from a related opening of **250** (see below). It is argued that this later structure provides good supporting evidence for the nature of **294.**

294
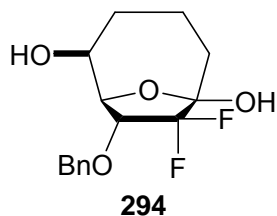
Attempts by a co-worker[95] to repeat the reaction with epoxide **251** found that the hydrolysis conditions removed the benzoyl protecting group along with the desired reaction giving a very difficult isolation problem. It was for this reason that the benzoate-protected intermediate was dropped from the synthesis at this point.

2.30 Mechanism of Epoxide Opening

Based on previous studies within the group a mechanism for the opening of the epoxides and the transannular reaction had been proposed[71][138] (Scheme 79). Initial nucleophilic attack on **250** with a generic nucleophile occurs on the ketone carbon to form hemiacetal's **295** and **296** which are degenerate in the case of Nu = ⁻OH. These can be deprotonated easily by the trace amount of base (perhaps due to a low pK_a) to give the conjugate bases **297** and **298**. From **298** the alkoxide can perform a transannular nucleophilic attack on the epoxide to give **299**, the protonation of which gives the product **293**. The stereoisomer **297** cannot perform the transannular reaction, because **297** cannot present the alkoxide for approach along the back projection of the epoxide C-O bond.
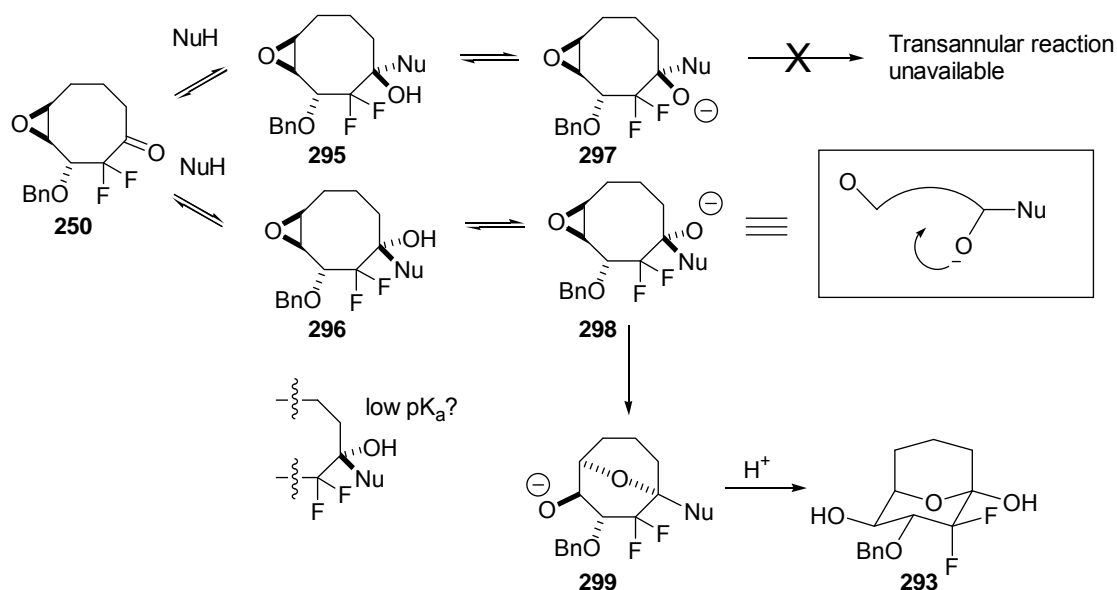
Scheme 79

A major question about the reaction mechanism was whether the initial nucleophilic attack was on the ketone or on the epoxide directly; both pathways could deliver the same product. Attack at the ketone was expected firstly as fluorination next to a ketonic carbonyl favours the addition of nucleophiles.[139] This suggests that addition should occur despite the increase in transanular strain which developes when a nucleophile is added to the carbonyl group of a cyclooctenone[140]. In order to answer this key question the epoxide was opened with a solution of 0.5 % NaOMe in methanol. Somewhat surprisingly two products were observed by ^{19}F NMR in a 4:1 ratio. These compounds could not be separated by chromatography so they were acetylated using established conditions (see below). The acetylated compounds separated upon chromatography and one was quickly identified as [3.3.1] bicycle **300** (Scheme 80).
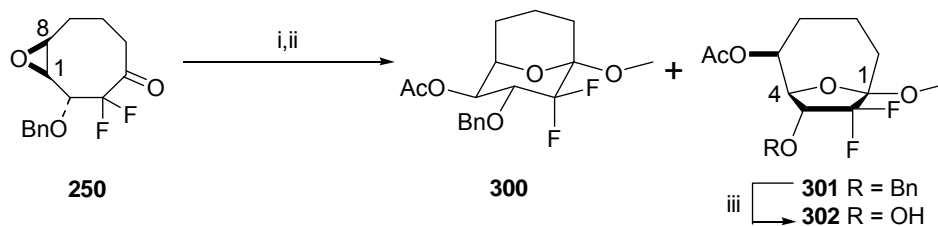
Scheme 80; reagents and conditions; i) 0.5% MeONa/MeOH, 100°C, 30min, microwave; ii) PVP, Ac$_2$O, DMAP, DCM; iii. 10% Pd/C, H$_2$, EtOH

Importantly a HMBC experiment[141] proved conclusively that the nucleophile was located on the anomeric carbon C-1. The assignment was later also corroborated by a crystal structure (Figure 29).
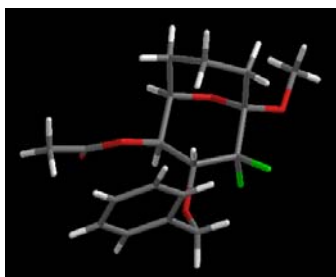
Figure 29

The second compound was later identified as [4.2.1] bicycle **301** formed from transannular nucleophilic ring opening of the epoxide at C-1 and also showed a clear HMBC crosspeak locating the methoxy group on C-1 of the product.[142] The only way that the methoxy group can end up on the C-1 carbon is if the initial nucleophilic attack is on the ketone and the result provides excellent corroborative evidence that both compounds are formed *via* the mechanism outlined above. The structure of **301** was proven by an HMBC experiment which showed a crosspeak between the C-4 proton and

the C-1 carbon. This was visible in both **301**, and deprotected **302**.[143] Attempts to grow a

crystal of **301** or its hydrogenated product **302** failed.

The presence of **301** was surprising as it was thought that the [3.3.1] bicycle should be

considerably more stable thermodynamically than the [4.2.1]. A [4.2.1] system had been

isolated once in the hydrolysis of **250** but **294** was only visible in trace amounts in the ^{19}F

NMR spectrum along with other unidentified by-products. In the methanolysis reaction

301 is present at 20 % by ^{19}F NMR before acetylation, and can clearly not be described a

minor by-product. The formation of **301** and consequently the hydrolysis by-product **294**

is easily explained (Scheme 81).
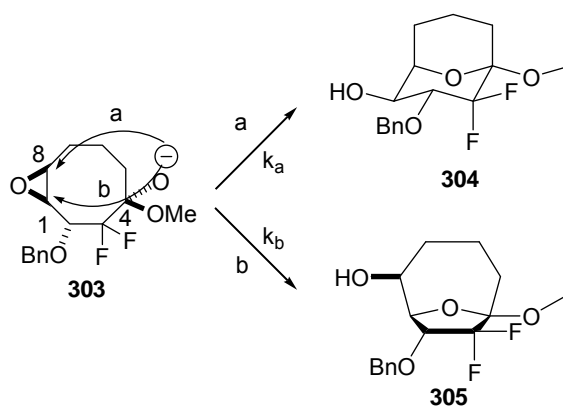
Scheme 81

According to the proposed mechanism **303** is formed after attack of the nucleophile

alkoxide. In the methanolysis the crucial stereochemistry around C-4 is obvious with **303**

being the only stereoisomer through which further reaction can occur. Two possible

transannular pathways are open; attack at C-8, pathway (a) leads to the major product **304**

whereas attack at C-1 (b) gives minor product **305**. If it is assumed that the reaction is

essentially irreversible after the transannular ring closure, then the product distribution is

under kinetic control. Therefore for the observed outcome $k_a > k_b$ and the much lower ratio of **304** to **305** compared with **293** to **294** suggests that the rate constants for the methanolysis are closer together than for the hydrolysis. If the reaction were reversible, and consequently under thermodynamic control; one would expect conversion of all material to the more stable stereoisomer which we would expect to be [3.3.1] bicycle **300**. Both **300** and **301** appeared to show coupling between the methoxy protons and one of the fluorine atoms. The methoxy CH_3 resonance is clearly split into a doublet and the fluorine resonance is much more complex than usual. The proton signal collapses to a singlet and the fluorine to a doublet when the corresponding nucleus is decoupled (Figure 30). The interaction which has been seen in rigid systems before[59]; is almost certainly a through space interaction rather than a $^5J_{H-F}$ through bond interaction; the coupling constants were measured at 1.5 and 1.8 Hz for **300** and **301** respectively.
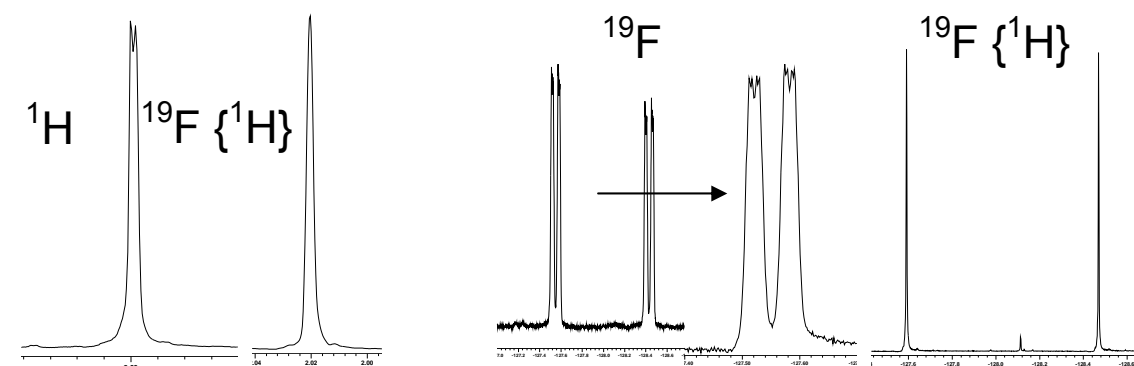
Figure 30

2.31 Attempts to Access the Fourth Stereoisomer *via* Mitsunobu Chemistry

Three of the four possible stereoisomers of the [3.3.1] bicycles had been obtained from the epoxide hydrolysis and dihydroxylation reactions. It was hoped that the final isomer **306** would be accessible *via* the inversion of the secondary alcohol on **255** using a modified Mitsunobu protocol (Scheme 82).[144]
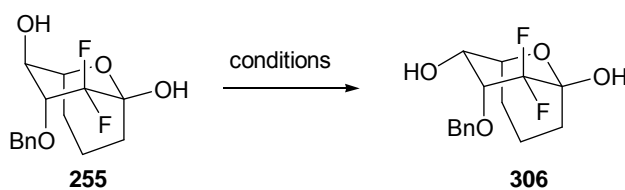
Scheme 82

The Mitsunobu[145] reaction is a powerful methodology for the inversion of alcohol configuration under mild conditions. However difficulties can be experienced with hindered secondary alcohols. Martin[144] suggests using *p*-nitrobenzoic acid as the nucleophile in place of benzoic acid. The resultant esters are more easily hydrolysed to the inverted alcohol than the parent benzoyl systems.

Entry	Conditions	Outcome[a]
1	5eq PPh$_3$, 5eq DEAD (polymer supported), 4.4eq p-NO$_2$C$_6$H$_4$CO$_2$H, toluene, shake, rt, 96 h	SM
2	5eq PPh$_3$, 5eq DEAD (polymer supported), 4.4eq p-NO$_2$C$_6$H$_4$CO$_2$H, Benzene, shake, rt, 140 h	SM

Table 23; [a] By TLC and ^{19}F NMR.

Because of previous problems with the removal of diethyl azodicarboxylate (DEAD) residues,[146] polymer supported DEAD was used. The reaction was attempted in toluene (Table 23, entry 1) and benzene (entry 2), both common solvents for the reaction. However no conversion of starting material was observed in either case. A suggested reason for the poor reactivity is (as Martin concedes) that little conversion may be achieved on substrates with large α-substituents. Thus the benzyloxy group on C-3 or the rigid carbon backbone from C-5 may be hindering the reaction, both are disposed axially and may therefore lie close to the trajectory of the incoming nucleophile.

2.32 The First Sugar Analogues

With compounds **255**, **256**, and **293** in hand, hydrogenolysis under standard conditions[147] furnished a set of non-natural sugar analogues **307**, **308**, and **309** in good yield (Scheme 83). The only purification required upon isolation of the sugars was the removal of the palladium on carbon by filtration through celite. After this step analyliticaly pure material was obtained in each case.
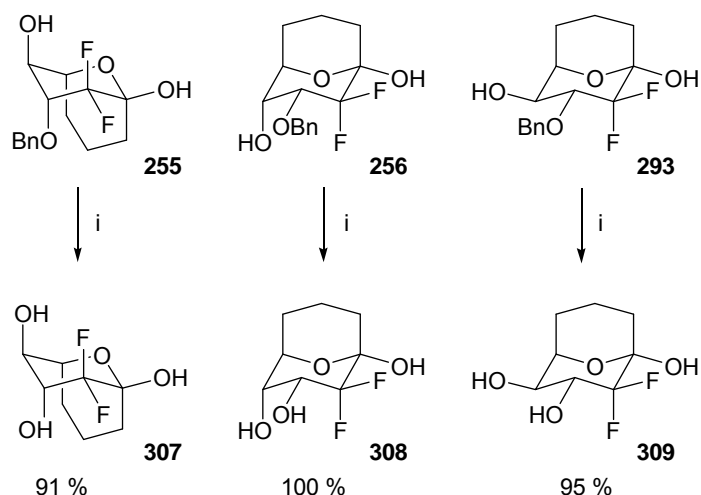
Scheme 83; Reagents and conditions; i, 10 % Pd/C, H$_2$, EtOH, 48 h.

2.33 Attempted Phosphorylation of 255 and 256

It was initially hoped that a protocol could be developed to selectively phosphorylate the anomeric hydroxyl at C-1 of **255**, **256**, and **293** whilst leaving the secondary hydroxyl at C-4 unprotected. Such a strategy was based of the suspected pK$_a$ difference between the two hydroxyl groups (Figure 31). As illustrated for **256** the secondary hydroxyl group at C-4 was expected to have a pK$_a$ close to 16 based on known systems (*i*-PrOH pK$_a$ = 16.5[5]). The pK$_a$ of the pseudo anomeric hydroxyl was slightly harder to predict with two functionalities affecting the value. The *gem*-difluorogroup should have a similar effect to that of the three fluorine atoms in trifluoroethanol which has a pK$_a$ of 12.5[5] although the lack of a third fluorine may increase the value by a small amount. Secondly the hemiacetal functionality should affect the values for example glucose has a pK$_a$ of 12.3

for the anomeric hydroxyl reflecting the inductive effect of the pyran oxygen. Taking

these two effects together a pK$_a$ of about 10 is predicted for the anomeric hydroxyl.
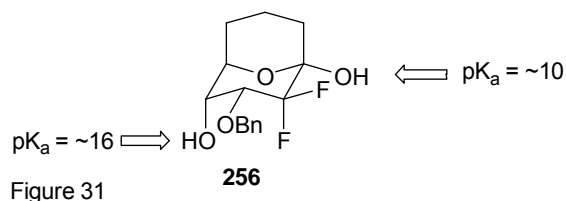
Figure 31

It was hoped to exploit this difference by attempting deprotonation using one equivalent

of base followed by a long equilibration time to preferentially form the alkoxide at the C-

1 position. The phosphorylation would then be achieved by addition of a phosphorus

electrophile in the form of tetrabenzyl pyrophosphate (TBPP) which we had experience

of within the group.[125] It should be noted that although deprotonation at C-1 is expected

to be favoured over that at C-4, the alkoxide formed from deprotonation at C-4 is more

nucleophilic than the one formed at C-1. Several experiments were conducted to try and

ascertain the optimum conditions for selective monophosphorylation (Table 24).

Entry	Substrate	Conditions	SM (%)	**310** (%)	**311** (%)	**312** (%)
1	**256**	i. 1 eq nBuLi, THF, -78 to 0°C, 5 hr ii. 1eq TBPP, THF, -78 to -30 to 0°C, ON	(35)	(14)	(3)	-
2	**255**	i. 1 eq nBuLi, THF, -78 to 0°C, 5 hr ii. 1eq TBPP, THF, -78 to -30 to 0°C, ON	88	12, **313**	-	-
3	**256**	i. 1eq NaHMDS, THF, -78°C to rt, 6 hr ii. 1eq TBPP, rt, 64 hr	40	40	16	4
4	**256**	i. 1eq NaHMDS, THF, 0 °C, 24 hr ii. 1eq TBPP, rt, 24 hr	44	37	15	4
5	**256**	i. 1.1eq NaHMDS, THF, 0 °C, 24 hr ii. 1eq TBPP, rt, 20 hr	48	34.5	14	3.5
6	**256**	i. 1eq NaHMDS, 1eq 15-crown-5, THF, 0 to -20 °C, 96 hr ii. 1eq TBPP, THF,-20°C, 27 hr	44	40	16	-
7	**255**	i. 1eq NaHMDS, 1eq 15-crown-5, THF, -78 °C, 24 hr ii. 1eq TBPP, THF,-20°C, 24 h	37	42, **313**	17, **314**	4, **315**
8	**256**	i. 1.1eq NaHMDS, 1.1eq 15-crown-5, 4 Å mol. Sieves, THF, 0 to -78 °C, 24 hr ii. 1.1eq TBPP,-78°C to rt, 24 hr	49	16	25	10

Table 24; Isolated yields in parenthesis; products from **255** in bold

Initial conditions used *n*-BuLi as the base (entry 1) and an equilibration period of 5 hours at 0°C before the electrophile was added. Three compounds were isolated upon workup (Figure 32); they were the desired monophosphorylated product **310** (14 %), the *bis*-phosphorylated species **311** (3 %), and recovered **256** (35 %). The chemoselectivity of phosphorylation was assigned as the expected **310** rather than the alternative **312** by comparison of the C-4 proton chemical shift which was practically unchanged between **256** and **311**. Attempts to use the same methodology with **255** (entry 2) gave mostly unconverted **255** (88 %) by ^{19}F NMR and a small amount of what is probably **313** (12 %).

310   **311**   **312**

313   **314**   **315**
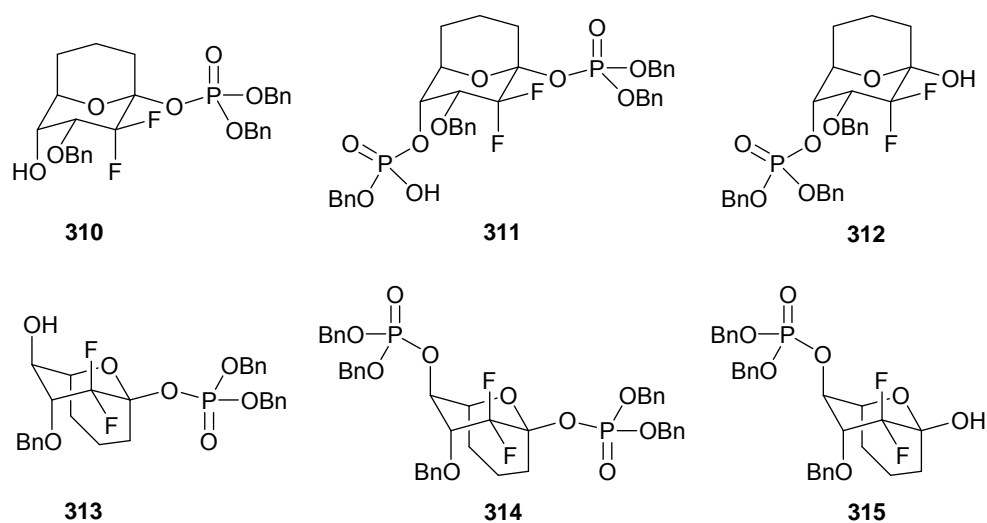
Figure 32

The base was changed to sodium hexamethyldisilazide (NaHMDS) in the hope that the sodium counterion (being more diffuse than the lithium cation) would form a looser ion pair with the alkoxide and thus increase it's nucleophilicity. Conversions to **310** of 40% were observed using this methodology (entry 3) along with a small amount of **312** where phosphorylation has occurred exclusively on the secondary hydroxyl. These conversions were little affected (entry 4) by increasing the equilibration temperature (to 0°C) and time (to 24 hours), or using a slight excess of base (entry 5). Further attempts were made to increase the nucleophilicity of the alkoxide by adding 15-crown-5 which binds sodium and could help to further dissociate it from the alkoxide. This appeared to have little effect on the conversions or the amount of *bis* phosphate **311** (entry 6) even at extended equilibration times. When **255** was phosphorylated using this methodology (entry 7) conversions appeared much the same as for **256**. Although no products from the phosphorylation of **255** were ever isolated their identities are proposed due to the similarity of the conversion percentages with those for **256**. The amount of

phosphorylated material did not appear to account for the amount of base in the reaction (eg. entry 3; 40 % **310**, 32 % **311** (ie. 2 x 16%), and 4 % **312**, accounts for 76 % of base). This suggested that some of the alkoxide may be becoming quenched during the long equilibrations. To try and combat this 4Å molecular sieves (activated for 1 hour at 300°C under vacumn) were added (entry 8) and stirred with the substrate solvent mix for an hour before the base was added. The sieves had the effect of increasing the amount of **311** (25 %) so it was present in greater amounts than **310** (16 %) whilst still leaving unconverted **256** (49 %). The origin of this product inversion is unknown. The addition of the sieves also did not prevent the apparent quenching of alkoxide with 76 % of base accounted for in entry 8.

Although the initial hypothesis that the hydroxyl at C-1 should prove more reactive than that at C-4 due to it's lower pK_a proved correct, the difference between the reactivity of the two groups did not prove sufficient to tune the reactivity of either **255** or **256** toward good yields of **310** or **313** respectively. Even at apogee only a 40 % conversion to **310** was obtained and this problem along with the not insignificant amount of bis phosphates produced by the procedure precluded it from use as a synthetic procedure.

2.34 Protection of the C-4 Hydroxyl with Acetate

With the failure of the direct phosphorylation strategy it was decided to protect the C-4 secondary hydroxyl as an acetate. The procedure was based on one developed within the group[95] using poly(vinylpyridine) (PVP) as the base. It was hoped that the use of

polymer supported reagents would aid purification and prevent the problem of removal of pyridine. Acetate was chosen because it could be attached under very mild conditions using our PVP procedure and should only react with the C-4 hydroxyl due to the anticipated low nucleophilicity of the C-1 hydroxyl. All three systems were acetylated successfully (Scheme 84) and the acetylation at C-4 was proved in each case by an HMBC NMR experiment.[118],[137] These results were used to confirm the bridging structure of the previous diols **255, 256**, and **293**. An X-ray structure was also obtained for **316** (Figure 33).[148]
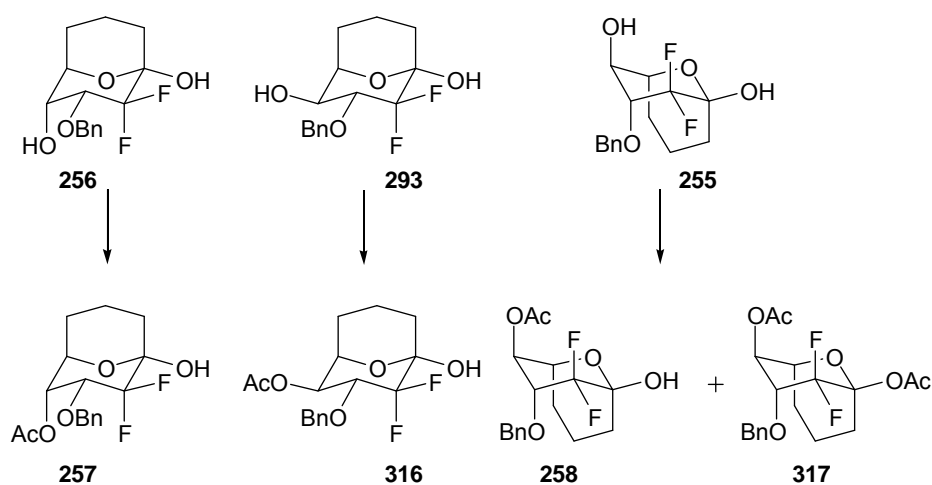
Scheme 84
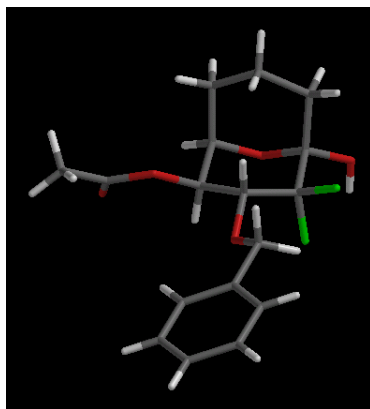
Figure 33

Entry	Substrate	Conditions	Yield (%)
1	**256**	5eq Ac$_2$O, 0.3eq DMAP, PVP (1 g/mmol), DCM, shake, rt, 75 hr, then 4.7eq Ac$_2$O, 0.4eq DMAP, PVP (0.7 g/mmol), shake, 48 hr	89
2	**293**	3eq Ac$_2$O, 0.3eq DMAP, PVP (1 g/mmol), DCM, shake, rt, 18 hr	89
3	**255**	5eq Ac$_2$O, 0.25eq DMAP, PVP (1 g/mmol), DCM, shake, rt, 18 hr	58[a]
4	**255**	5eq Ac$_2$O, 0.25eq DMAP, PVP (1 g/mmol), DCM, shake, rt, 18 hr	88

Table 25; [a] 13% of **317** also formed

There was a striking difference in reactivity between the three systems. With **256** (Table 25, entry 1) significantly higher loadings of reagents were required to drive the reaction to completion by TLC. Indeed it was usual for the reaction to be so slow that a second addition of reagent was required. Despite this, good yields (89 %) of **257** were obtained. In contrast **293** acetylated to give **316** much more rapidly, and at lower loading of reagent, yet in identical yield (89 %). The acetylation of **255** also proceeded rapidly compared to **256** and at loadings of reagent in between the other two systems and in a poorer yield (58 % of **258**). One reason for this lower yield was that in all but one case **258** was not the sole product isolated from the reaction. A minor product which was identified as *bis*-acetate **317** was isolated as up to 13 % of the reaction mixture. In one unexplained case **258** was isolated as the sole product in (88 %) yield from apparently identical conditions. It is suggested that the more rapid reaction times and lower loadings of reagent required for the acetylation of **255** and **293** over **256** arises from variations in the accessibility of the C-4 hydroxyl group. In **256** the benzyl and hydroxyl groups are *cis* and therefore the benzyl group shields the hydroxyl much more than in **293** where they are *trans*, and in **255** where they are on opposite sides of the molecule. The reason for the *bis* acetate being only seen for **255** is unknown.

2.35 Phosphorylation of Protected Systems

Protected species **257**, **258**, and **316** where successfully phosphorylated to give benzyl phosphates **318**, **319**, and **320** respectively in moderate to good yields (Scheme 85, Table 26). In all three cases small amounts of acetate cleaved species **310**, **313**, and **321**, were sometimes isolated after chromatography.

Entry	Substrate	Conditions	Yield (%)
1	**257**	1.1eq NaHMDS, THF, 0°C, 1 hr, then 1.1eq TBPP, 0°C to rt, 20 hr	64
2	**258**	1.1eq NaHMDS, THF, 0°C, 1 hr, then 1.1eq TBPP, 0°C to rt, 20 hr	84
3	**316**	1.1eq NaHMDS, THF, 0°C, 1 hr, then 1.1eq TBPP, 0°C to rt, 16 hr	49

Table 26
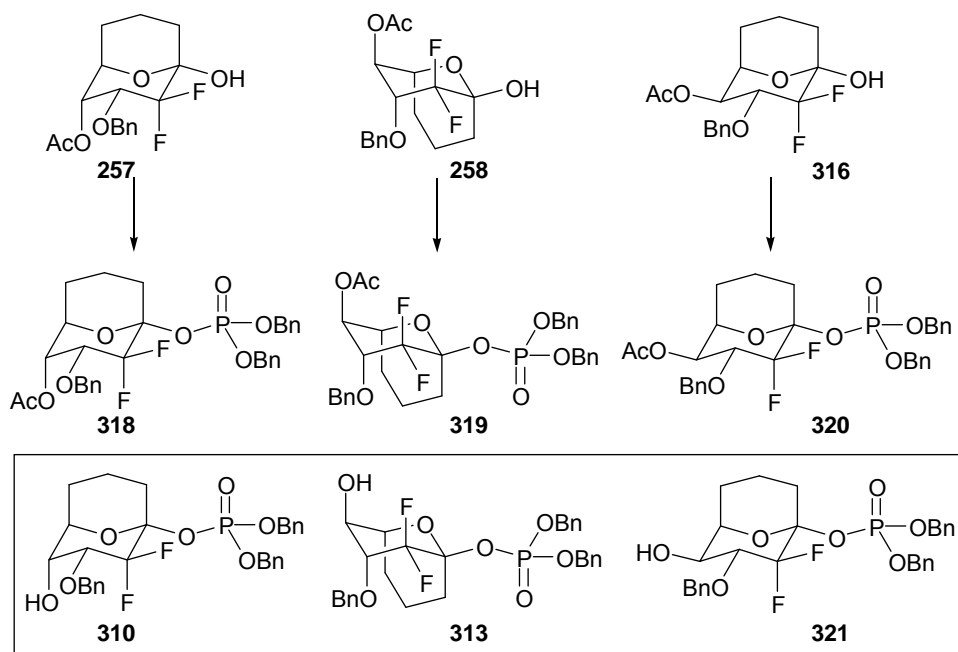
Scheme 85

It is not clear for **310** or **313** whether the cleavage of the acetate takes place under the basic reaction conditions or the mildly acidic column used for chromatography. Small

amounts (ca. ~7%) of the deprotected products are visible in the crude ^{19}F NMR spectrum. However in some (but not all) cases, the amount of material isolated appears too large by a few percentage points to correspond to the NMR integration, though this discrepancy may be explained by the detection threshold of the NMR experiment.

Phosphate **320** with an equatorial acetate group appeared to be by far the most susceptible to this cleavage reaction to the extent that in one case, **321** was isolated as the sole product. In this case deprotection post-reaction but prior to chromatography is clearly visible in both the ^{19}F NMR spectrum and more importantly as **320** and **321** have similar ^{19}F chemical shifts, in the ^{1}H NMR spectrum. In all cases the origin of the deprotection is thought to be in the reaction itself rather than the work up, as the reaction is quenched with pH 7 buffer solution. This was chosen to prevent hydrolysis of the fragile benzyl phosphates but should also protect the acetate functionalities.

In order to cleave the acetate a nucleophile must be available during the reaction. Of the species present during the reaction NaHMDS is expected to be too bulky to attack at the acetate carbonyl. However as the reaction occurs in strong base it is feasible that enolisation of the acetate and subsequent fragmentation to give a ketene and alkoxide is a possible pathway by which the deprotected compounds may be produced (Scheme 86). Seebach and Dunitz[149] have obtained crystal structures of lithium ester enolates as intermediates in the cleavage pathway of esters when exposed to strong base.
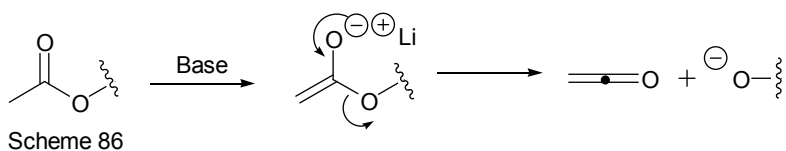
Scheme 86

2.36 Deprotection to Give Final Target Compounds

Fully protected phosphates **318**, **313**, and **320** were successfully deprotected over three steps to give the target activated non-natural sugar phosphates **322**, **323**, and **324** (Scheme 87). It was decided to remove the benzyl groups first due to the stability of the acetate toward hydrogenolysis. It was feared that any attempts to remove the acetate in the presence of the phosphate ester would lead to it's cleavage. However simple phosphate monoester dianions are known to have hydrolysis half-lives (in H_2O at 25^oC, pH 7) on the geological timescale[150] (1.1×10^{12} years), and should therefore be stable toward deacetylation conditions which are basic, thus allowing the phosphates to exist as dianions. This assumption is corroborated by work from Kirby[151] that shows dianion hydrolysis rate decreases with increasing pK_a of the leaving group and that the rate for $pK_a > 7$ can often be too slow to measure. As outlined above, the pK_a of the anomeric hydroxyl is suggested to be around 10.

This indeed proved to be the case with **325**, **326**, and **327** being obtained under our standard hydrogenolysis conditions.[147] The reaction gave clean, sharp ^{19}F spectrum but very broad, ^1H, and ^{31}P NMR spectra, although the completion of the reaction could be seen by the empty aromatic region of the proton spectra. All attempts to purify these products failed to improve these spectra, so full characterisation was not attempted, although a molecular ion was obtained for each series. It was therefore decided to progress the unpurified compounds.
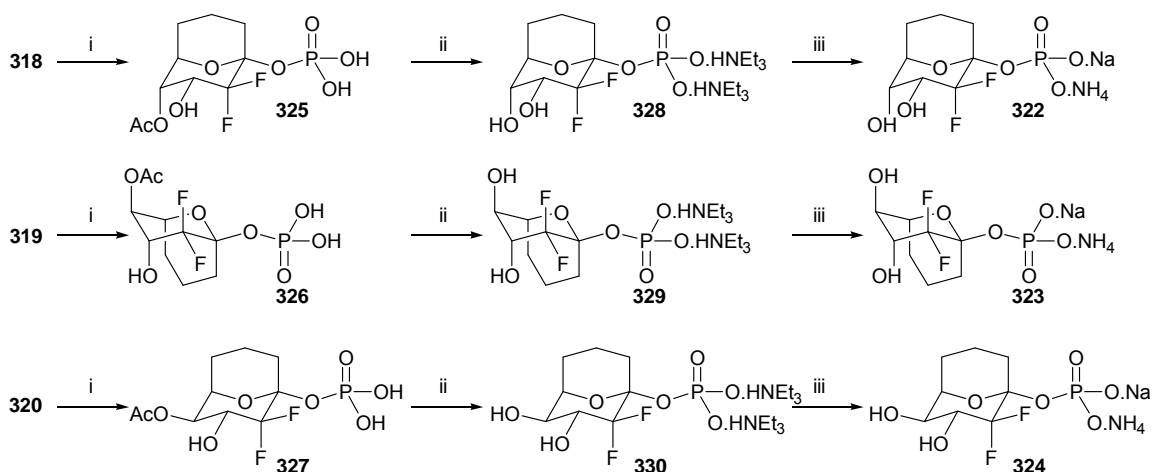
Scheme 87; i, H$_2$, 10% Pd/C, EtOH; ii, MeOH, H$_2$O, NEt$_3$; iii, Silica, EtOH, H$_2$O, NH$_3$.

The acetate groups were removed under very mild conditions by stirring overnight in a solvent of methanol, water, and triethylamine (5:2:1).[152] After removal of the volatile solvents the products were isolated by freeze drying; removal of the acetate functionality was confirmed by ^{1}H NMR, although the spectra remained broad. The species were isolated as triethylamine salts **328**, **329**, and **330** which gave good ^{19}F, and ^{31}P NMR spectra and a strong molecular ion. Again the decision was made to progress the compounds without full characterisation and the three products were purified somewhat surprisingly on normal phase silica gel, eluted with a solvent mixture of ethanol, water, and 35% aqueous ammonia (5:3:1) to give sugar phosphates **322**, **323**, and **324**, all of which gave sharp NMR spectra. Initially the nature of the final salts was in doubt but an elemental analysis of **322** suggested they were present as a mixed sodium ammonium salt. Yields over the three steps were good for **322** (66 %), **323** (50 %), and **324** (61 %).

Phosphates **322, 323,** and **324** are valuble highly functionalised compounds which should be seen as a new class of activated non-natural sugar with a unique conformational lock. These compounds are now available for further study toward their full activation to NDP

glycosides either enzymatically or *via* traditional chemical techniques. Once activated they can be screened for activity against a range of GT enzymes in the hope they display usefull binding behaviour.

2.37 A New Series of Analogues of the 6-Deoxy Class of Sugars

With the success of the initial series of non-natural sugars, it was hoped that the same chemistry could be used to synthesise a range of non-natural analogues to the important 6-deoxy class **330** (Scheme 88) that appears in nature. It was hoped that the chemistry would be virtually analogous to that described above. The 6-deoxy class is one of the more crucial classes of sugars in nature and is found in many complex antibiotics. The GT's that process these substrates are therefore of vital importance.
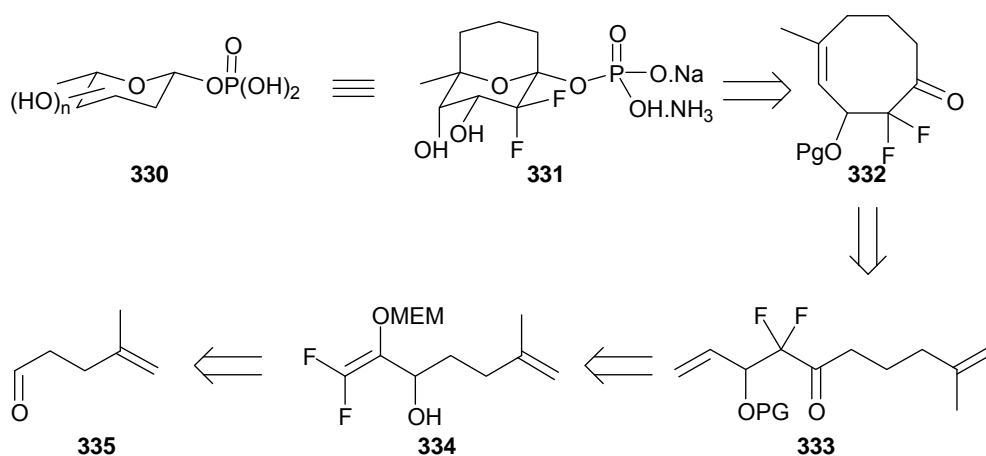
Scheme 88

A familiar retrosynthetic analysis can be imagined. The final activated sugar **331** and its stereoisomers could be available from cyclooctenone **332** *via* established oxidation, protection, phosphorylation, and deprotection procedures. The assembly of **332** would again utilise RCM, from diene **333** which should be available from allylic alcohol **334** which in turn could be synthesised from aldehyde **335** which, although not commercial, is a known compound.[153]

The crucial step in the synthesis is expected to be the synthesis of **332** *via* RCM. This may prove problematic as the reactive unsubstituted type I olefin present in the previous series has been replaced with a much less reactive type III system with a vinylic methyl group. It is expected that the RCM therefore will be more challenging than the example in the existing synthesis, because it will have to initiate on a type II alkene.

2.38 Synthesis of Aldehyde 335
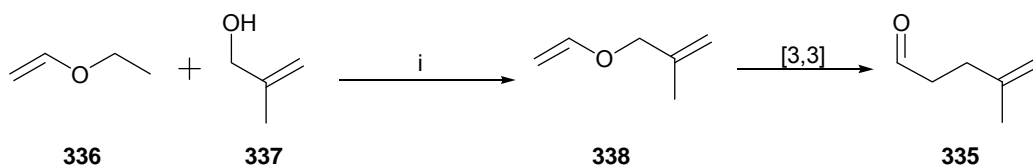
Scheme 89; Reagents and conditions; i, Hg(CO$_2$CF$_3$)$_2$, reflux

The crucial aldehyde **335** was prepared according to the procedure established by Baker[153] from ethyl vinyl ether **336** and methallyl alcohol **337** *via* a transvinylation reaction catalysed by mercury(II) trifluoroacetate (Scheme 89). The resultant ether **338** was rearranged in a microwave-mediated Claisen rearrangement to give **335**.

Unexpectedly it proved impossible to purify **338** after the transesterification with the product always distilling (as an approximately 50 % mixture by NMR) with 1,1-diethoxy ethane. The acetal contamination did not effect the Claisen rearrangement which proceeded smoothly under the established conditions in 6 hours as opposed to the 24 required for the thermal rearrangement. No attempt was made to purify **335** post-rearrangement and the material was used crude with the stoichiometry for the reagent being calculated in accordance with the 50 % NMR purity. The microwave-mediated rearrangement was a modification to the thermal literature procedure and was included due to the success of the synthesis of pentenal **145** in the earlier series.

The transvinylation reaction may proceed through the mechanism[154] suggested below (Scheme 90). The equilibrium of the system is driven toward the ether R' = CH_2CMeCH_2 due to the large excess of ethyl vinyl ether present in the reaction. Nucleophilic attack of the olefin on mercury(II) trifluoroacetete gives mercurium ion **339** which is then attacked at the more substituted end by the alcohol R' = CH_2CMeCH_2 which after proton transfer delivers intermediate **340**. A second proton transfer then loss of ethanol R = CH_3CH_2 generates a second mercurium ion **141** which undergoes ligand exchange reforming **339.**
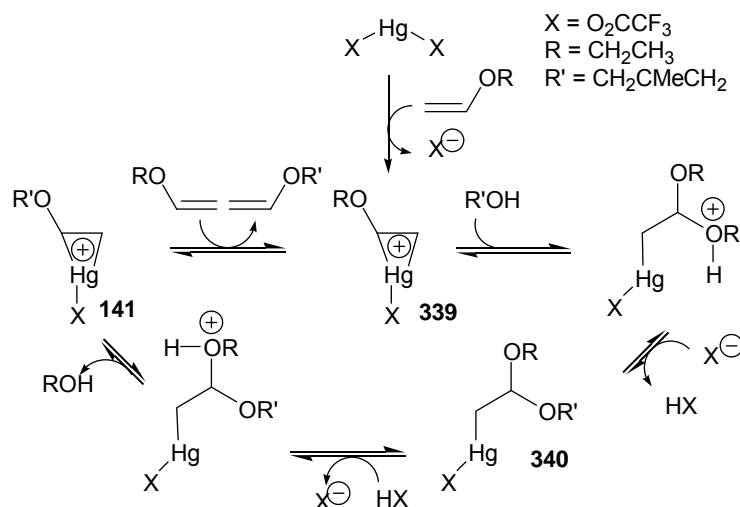
Scheme 90

2.39 Assembly of Precursor 345 *via* Established Chemistry

Novel allylic alcohol **329** (Scheme 91) was synthesised from **131** and **335** in good yield (73 %, cf. **178** 82 %). The reaction was conducted using our established methodology. The only major difference in procedure was that the reaction to form **329** was warmed to -40°C over 3 and not 4 hours as with **178**. The yield for **329** is slightly poorer than that for **178**, possibly due to the difficulties of working out the exact amount of impure electrophile to add. This suggestion is corroborated by the fact that the conversion of **329** is 86% by ^{19}F NMR of the crude material, compared to 95 % for **178**. Interestingly **329** shows a much higher bp. than **178** , distilling at 115°C compared to 75°C for **178** (both at 0.05 mm Hg).
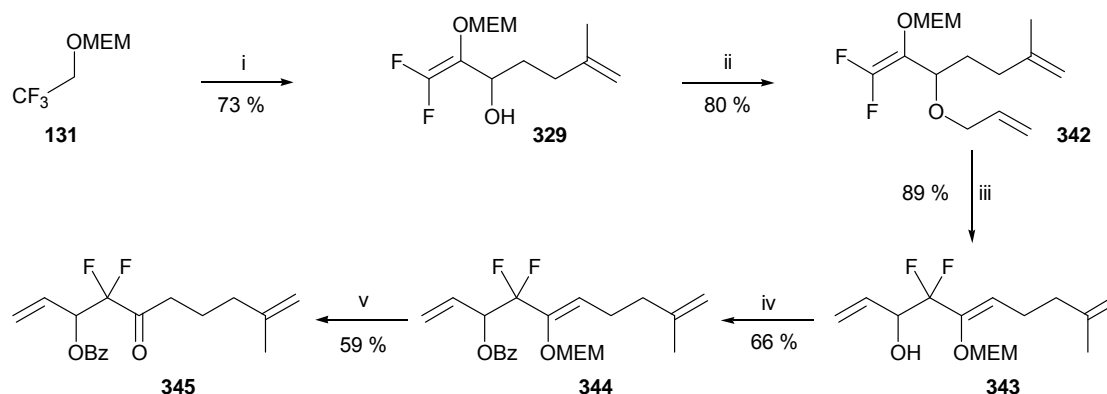
Scheme 91; Reagents and Conditions

i, 2eq LDA, THF, -78°C, 40 min, then **335**, -78 to -40°C, 3 h; ii, 1.2eq allyl bromide, 50% NaOH, TBAHSO$_4$, 0°C to rt, ON; iii, 2eq LDA, -100 to -40°C, 4h; iv, PVP, 1 eq Bz$_2$O, 0.3eq DMAP, DCM, shake, rt, ON; v, 1eq SOCl$_2$, MeOH, 0°C to rt, ON.

The allylation of **329** to **342** again proved trivial proceeding in good yield (80%) although this was poorer than in the previous system (91 % for **182**), and the product was (as before) used without further purification.

The [2,3]-Wittig rearrangement of **342** to **343** was conducted at the lower temperature (-100°C) conditions that had been developed for **183**. This methodology delivered **343** (89 %, 95 % conversion by ^{19}F NMR, and GC) material of a sufficiently good quality to be used crude. The yield is almost identical to that obtained for **183** (87 %, at 30mmol scale).

When the protecting group was chosen for **343** the problems of the lability of the benzoyl group under hydrolysis condition was not yet known, so the benzoyl group was selected due to its easy application under mild conditions using PVP. Indeed this protection did proceed very smoothly with only one equivalent of benzoic anhydride being required to furnish **344** in 66 % yield. The yield is comparable to that obtained from the pyridine procedure used for **189** (64 %). Due to the high quality of the material obtained from the reaction (100 % by GC), the sequence was progressed without purification.

The MEM group was removed as previously using SOCl$_2$ in MeOH. As the RCM was expected to be challenging it was decided to purify the unmasked ketone on silica. This gave **345** as a clear oil in 59 % yield, very similar to that achieved for **196** after purification (56 %). With the isolation of **345,** the total yield over five steps was 20 % from **131** with only two intermediate purifications. This further illustrates the robustness and flexibility of the route.

2.40 Ring Closing Metathesis of 345

345

Scheme 92

346
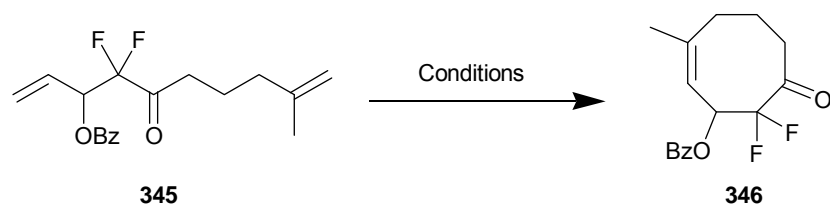
It was found that **345** would indeed undergo ring closing metathesis (Scheme 92) to give cyclooctenone **346** although only at sacrificial catalyst loading, and giving low isolated yields. Initially (Table 27, entry 1) no change was seen in the ^{19}F NMR after the addition of the first 5 mol% of catalyst; however characteristic cyclooctenone signals began to grow in upon subsequent additions of catalyst. Once the conversion reached ca. 40 % by ^{19}F NMR the reaction was stopped and product isolated (30 %, along with 12 % recovered **345**). Moving to a larger scale (entry 2) had little effect on the reaction, with a slightly lower yield being obtained on a slightly lower loading of catalyst.

174

Entry	Scale (mmol)	Conditions	Yield (%)[a]
1	0.18	25 mol%[b] **93**, 0.6 eq Ti(O^{i}Pr)$_4$, 0.01M DCM, reflux, 216 hr	30 (40)[f]
2	1.05	20 mol%[c] **93**, 1 eq Ti(O^{i}Pr)$_4$, 0.01M DCM, reflux, 288 hr	24[g]
3	0.35	33 mol%[d] **93**, 1.86 eq eq Ti(O^{i}Pr)$_4$, 0.005M DCM, reflux, 114 hr	22
4	1	20 mol%[e] **93**, 0.6 eq Ti(O^{i}Pr)$_4$, 0.01M toluene, reflux, 96 hr	- (29)

Table 27; [a] ^{19}F NMR conversion in parenthesis; [b] initially 5% then additional 5% T = 18 hr, then 73, 146, and 192 hr; [c] 10 % at T = 0, then 5 % T = 55, 134 hr; [d] 13 % T = 0, then 5 % T = 24, 48, 72, 96 hr; [e] 5 % T= 0, then 5 % T = 18 hr, 10 % T = 48 hr; [f] 12 % starting material recovered; [g] 11 % starting material recovered.

In the light of the experience with dimerisation in **195** the reaction was run at a lower concentration of 0.005M (entry 3) this however delivered a lower isolated yield at higher catalyst loading.

Carrying out the reaction in toluene (entry 4) in an attempt to speed up the reaction, failed to give any isolated material although there was consumption of **345** by ^{19}F NMR (ca. 29 %). The higher reaction temperature had a larger effect on catalyst decomposition than on RCM rate. The recovery of **345** from entries 1 and 2 and the lack of any sign of a molecular ion for either dimeric or 16 ring material suggests none was formed during the reaction.

Conformational analysis of **346** revealed that it occupied a similar solution conformation to **200**. The $^3J_{H\text{-}F}$ coupling constant (H3) was found to be 21.1 at 323 K, and a NOESY experiment showed close contacts between the protons on C-3, C-6, and C-8[155]. This interaction was important as it proved that the **346** was in fact the cyclooctenone and not the symmetrical sixteen membered dimeric ring product. A good molecular ion for the monomer was also obtained.

As Hoye and Zhao[156] had shown that an allylic alcohol can affect the efficiency of the RCM reaction, it was decided to attempt the metathesis with the allylic alcohol

deprotected. This was in full knowledge of Hoye and Zhao's warning of the tendency of

these species to rearrange to the methyl ketone, and also the known volatility of **187**.
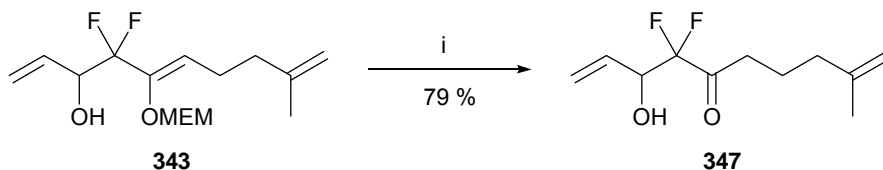
Scheme 93; Reagents and conditions; SOCl$_2$, MeOH, 0°C, ON

Allylic alcohol **347** was synthesised from **343** using the standard conditions for the

removal of the MEM group, and distilled as a clear liquid (79 %) (Scheme 93). With **347**

in hand the RCM was attempted (Scheme 94) with a catalyst loading of 10 mol%.

Complete consumption of starting material was observed by TLC after 3 days.
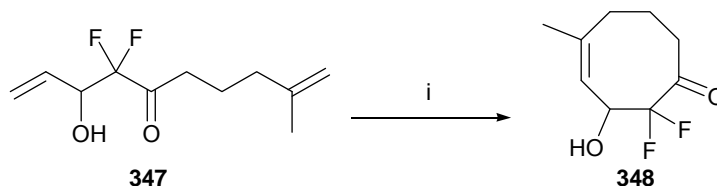
Scheme 94; Reagents and conditions; i, 10 mol% **93**, 0.33eq
Ti(O^{i}Pr)$_4$ 0.01M DCM, reflux, 72 hr

The solvent was distilled away at atmospheric pressure and the ^{19}F NMR spectrum of the

crude mixture showed at least two products. A weak [M+NH$_4$]$^+$ ion was detected in the

electrospray for the dimeric species and the GC of the reaction mixture appeared to show

a product with a similar retention time (20.33 min) to that of **346** (20.15 min). The true

identity of these products could not be established as no pure compounds were isolated

after attempted chromatography in low boiling solvents. It is possible from the evidence

that both a dimeric species and a cyclooctenone were present in the crude reaction mixture. However the difficulty in isolation of the volatile products reinforces our belief that the secondary hydroxyl group of these systems must be protected in order to make isolation of the RCM products viable.

Clearly Hoye and Zhao are correct to say allylic alcohols can greatly increase the rate of reaction of allylic alcohols towards RCM when compared to their protected analogues. Unprotected **347** is completely consumed by **93** at only 10 % loading whereas with **345** a 25 % loading only gives a 40 % conversion.

2.41 Explaining the Low Metathesis Activity of 345

The drastic drop in metathesis activity between **196** and **345** is caused by the positioning of the methyl group at the internal position of the double bond (Scheme 95). This converts what had been a type I olefin in **196** into a type III in **345**, and forces the metathesis catalyst to initiate on a type II olefin. This presents problems in the metallocyclobutane intermediate where the allylic benzoyl group in **349** is sterically much more demanding than the proton in **350**; the greater size of the benzoyl group causes unwanted steric interactions with the other ligands on the metal centre.
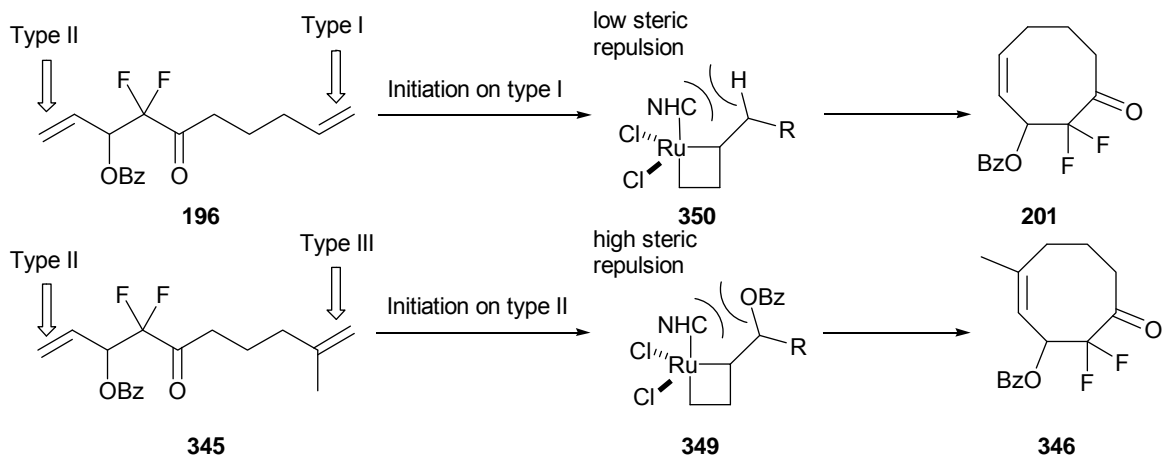
Scheme 95

This obviously slows down the initial metathesis reaction and the formation of the substrate alkylidene by increasing the enthalpic contribution to the Gibbs free energy of activation. The same problem is present in the second intramolecular metathesis reaction. In the cyclisation to **201**, a type II olefin is reacting intramolecularly and some of the problems caused by poor steric interactions are somewhat offset by the better entropic contribution to the Gibbs energy of activation due to the loss of some degrees of roatation. The same entropic contribution does also benefit the intramolecular cyclisation to **346**, however the vinylic methyl group is now directly substituted onto the metallocyclobutane and thus the steric and consequently enthalpic contributions are again considerably worse than in **196**. The corollary of both these effects is that the cyclisation is much slower for **345** than with **196** and therefore each molecule of catalyst can accomplish fewer turnovers before it decomposes. The lack of evidence for dimeric material in the reaction is not unexpected either as even the easier type II homodimer is disadvantaged enthalpically as well as entropically.

There is evidence in the literature for successful type II/type III cyclisation *via* RCM. Macrocycle **351**[157] was successfully formed in acceptable yield from **352** by RCM with **93** (Scheme 96). The authors found that only the 19R diastereoisomer of **352** reacted weras the 19S did not, and comment that they suspect that this is due to an hydrogen bond between the C-19 hydroxyl and the C-1 methoxy group positioning the two reacting side chains in close proximity. It should also be noted that an olefin with an allylic methyl group is towards the top end of type II reactivity.
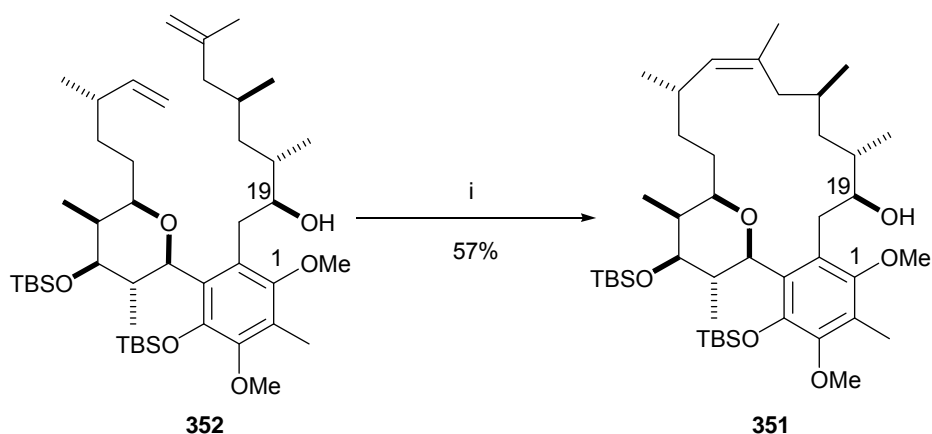
Scheme 96; Reagents and Conditions; **i, 93** 10 mol%, 0.002M DCM, reflux.

In our system, the fact that any cyclised product was obtained at all (this is to our knowledge the first type II, type III cyclooctanic cyclisation) illustrates the increased efficiency of Grubbs' second generation catalyst **93** for cyclooctenone formation. Whilst looking at the effect of olefin substitution on RCM efficiency, Grubbs attempted the cyclisation of **353** with his first generation catalyst **91** (Scheme 97).[158]
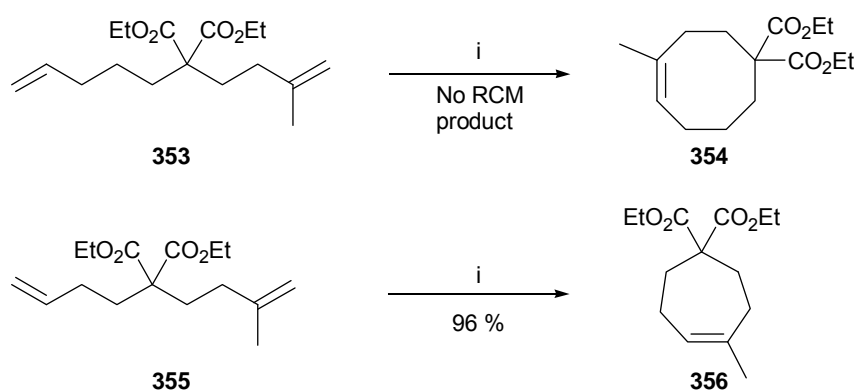
Scheme 97; Reagents and Conditions; i, 5 mol% **91**, DCM.

No **354** was isolated after exposure to metathesis conditions although unidentified dimeric material was detected. This is in stark contrast to **355** which was successfully cyclised to seven membered ring **356** in excellent yield. This illustrates the particular difficulties in the synthesis of eight membered rings. It should also be noted that both these species contain an unsubstituted type I olefin for the reaction to initiate on and may also be aided by a Thorpe-Ingold effect[159] from the malonate substitution and are therefore considerably easier than the cyclisation of **345**.

2.42 Increasing Metathesis Efficiency Through the Incorporation of a Reactive Tether; Relay RCM

An elegant strategy for the RCM of sterically hindered olefins has been developed by Hoye[160] and has become known as relay ring closing metathesis (RRCM).[161] The strategy relies on the fact that although catalyst initiation onto sterically demanding olefins is difficult, the intramolecular reaction of a ruthenium alkylidene onto such an

alkene is attainable. The approach is illustrated in the synthesis of tetrasubstituted olefin

357, usually a recalcitrant cyclisation (Scheme 98). Attempts to form **357** from a standard

RCM precursor **358** were unsuccessful as **91** could not initiate on either olefin of the

substrate due to their hindered nature (type III). However precursor **359** with the addition

of a "relay" moiety in the form of a more reactive, unhindered (type I) olefin at the end of

a carbon tether makes the intramolecular initiation metathesis more facile. The length of

the relay tether is chosen as a five carbon unit so as to allow the easy cyclisation and

elimination of cyclopentene **360** (believed to be a very efficient RCM). This initial RCM

delivers the alkylidene moiety onto the less reactive vinylic system **361** (thus the desired

alkylidene from **358** has been obtained in an intramolecular reaction) which can then

undergo the easier cyclisation to give **357** .
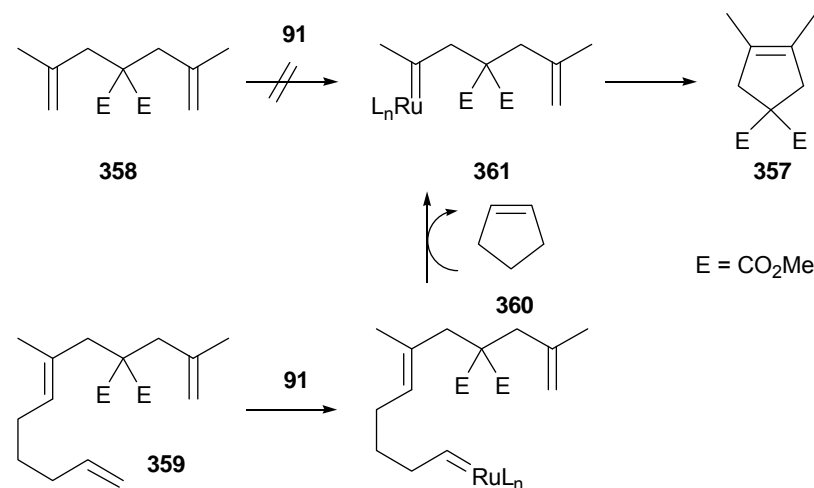
Scheme 98

Porco[162] has used this relay technique in the total synthesis of oximidine III (Scheme 99).

When exposed to the Grubbs-Hoveyda metathesis catalyst **225**, precursor **362** gives only

a 15 % isolated yield of macrocycle **363**. After the incorporation of a relay tether **364** the cyclisation proceeds in much improved yield of 58 % of **365** (71 % in refluxing DCE).

362 R = H
364 R = (CH₂)₃CH=CH₂

363 R = H 15 %
365 R = (CH₂)₃CH=CH₂ 58 %

Scheme 99; i, 10 mol% **225**, DCM 0.002M, reflux.
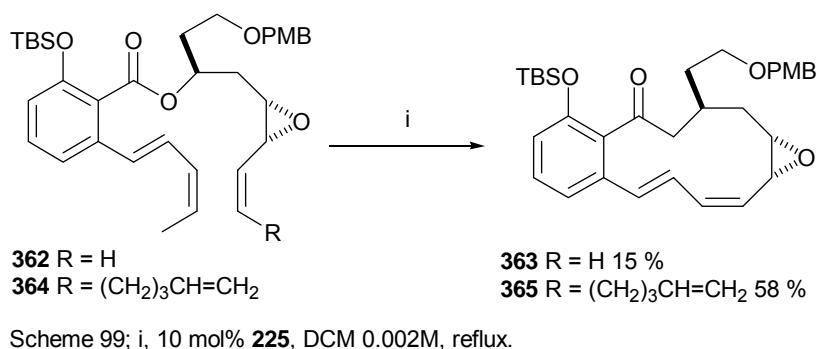
It was hoped that this powerful approach could be adapted and used in the synthesis of cyclooctenone **366**. The retrosynthetic analysis (Scheme 100) gives a new RCM precursor **367** which is synthesised from allylic alcohol **368** *via* established chemistry. Allylic alcohol **368** is obtained from the reaction of aldehyde **369** with MEM ether **131**. This aldehyde can be prepared by [3,3]-Claisen rearrangement from ether **370** which itself is synthesised from bromide **371**.

366   **367**   **368**

371   **370**   **369**   **131**
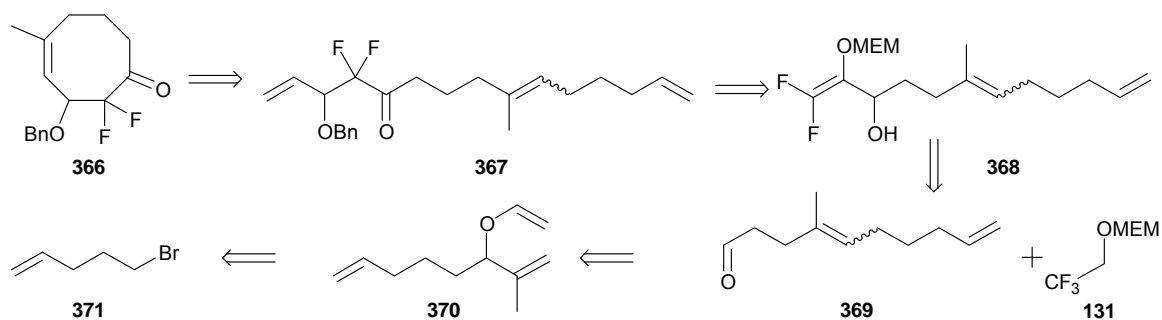
Scheme 100

It should be noted that the stereochemistry about the internal olefin is (formally) irrelevant to the overall outcome of the relay reaction, as this moiety is destroyed by the primary metathesis event giving the same propagating species. However Porco has noted that the Z isomer of such systems is often more the more reactive species. For example the isomer of **364** with *E* configuration on the relay internal olefin does not give any macrocycle **365** upon cyclisation. The generality of this effect is unknown and it was decided to attempt RRCM on a mixture of stereoisomers initially, then focus on the *Z* stereoisomer if required.

2.43 Synthesis of Aldehyde 369

The initial step in the route toward aldehyde **369** was the synthesis of allylic alcohol **372** from bromide **371** *via* a Grignard reaction (Scheme 101). However it was remembered that this Grignard had given low yields in the synthesis of ketones **159** and **173** (see section **2.1**, and **2.3**). In the intervening period, analysis of the literature had provided a modified proceedure based on one described by Hudlicky[163] for the related compound **373**.
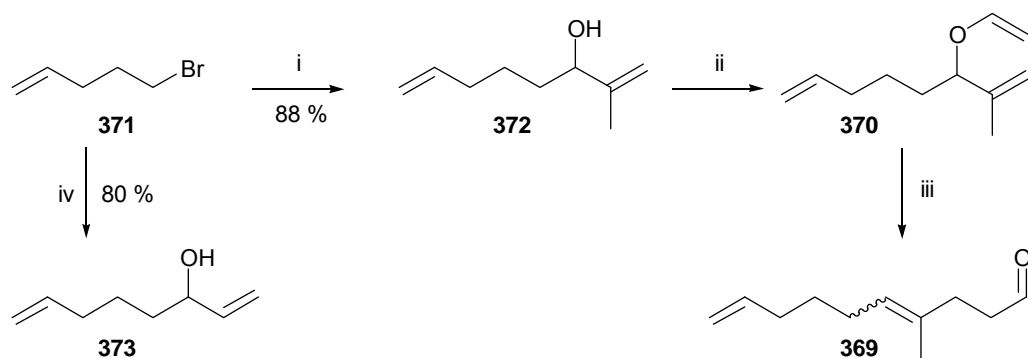
Scheme 101; Reagents and conditions; i, Mg, ether, rt, 1 h then methacrolein 0°C, 1 hr; ii, ethyl vinyl ether, Hg(O$_2$CCF$_3$)$_2$, reflux, 22 hr; ii, mω, 150°C, 10 min; iv, Mg, ether, rt, 1 hr then acrolein -10°C, 1 hr

The procedure was unusual as it called for the reaction to be stirred during the formation of the Grignard reagent. When the procedure was followed, the reaction initiated extremely strongly with a powerful self-reflux. This was in stark contrast to the behaviour seen with the previous attempts using the old unstirred methodology. Upon reaction with methacrolein, quenching and work up, allylic alcohol **372** was delivered in excellent yield (88 %) at up to a 0.17 mol scale.

Vinylation proceeded well using the previously discussed mercury(II) trifluoroacetate procedure giving ether **370** at 98 % conversion by GC. Again acetal contamination was observed but was removed by distillation from **370** to give a crude yield of 94 %. Due to the sensitive nature of the ether no further purification was attempted although minor contaminants could be seen in the ^{1}H NMR spectrum at chemical shifts between 3.85 and 3.35, characteristic of acetal contaminants.

Crude **370** underwent [3,3]-Claisen rearrangement using our microwave-mediated procedure. Initially, exposure to the established conditions used for **145** of 150°C and a reaction time of 6 hours gave material of dubious quality by both ^{1}H NMR and GC.

Significant amounts of material of a significantly higher retention time (22.67 min) were observed along with contamination in the alkyl region of the NMR spectrum. A range of experiments (Figure 34) showed that the Claisen rearrangement was significantly faster for **370** than had been the case for either of the previous examples and was in fact complete after only 10 min. Attempts to reduce the reaction time to 5 min lead to incomplete conversion (93 % by NMR).
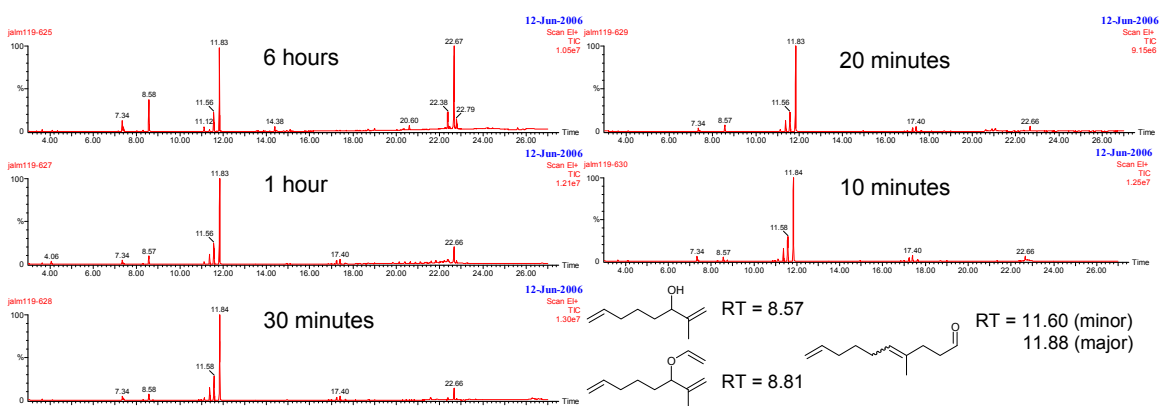
Figure 34

It is expected that the rearrangement of **370** should be faster than that of **177** and **338** as the reaction produces a trisubstituted olefin from a disubstituted system which is thermodynamically more stable than either the di- or mono- substituted olefins retained in **335** and **145** (Scheme 102). Although in all three cases it is the formation of the strong CO double bond of the aldehyde which is the major driving force to the reaction, this increased stability from higher substitution provides an extra driving force. A Thorpe – Ingold effect from the additional alkyl chain in **370** may also be in operation[159].
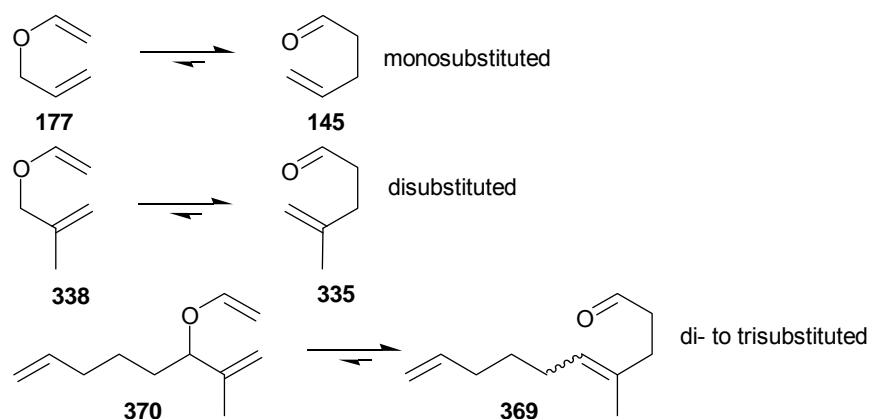
Scheme 102

With the rearrangement of **370** to **369** there is an issue about the geometry about the new internal olefin. The pure thermal rearrangement is known to give an *E* to *Z* ratio of 69:31.[164] The *E* geometry in the final bond is favoured because the alkyl substituent on the saturated carbon atom next to the oxygen prefers to adopt an equatorial arrangement in the chair transition state. The ratio of the two stereoisomers of **369** was measured and found to be 86:14 by ^{1}H NMR and 76:24 by GCMS, the discrepancy between these results suggests that one of the stereoisomers is less responsive to GCMS analysis (either on the column or in the detector) than the other and it is suggested the ratio taken from the NMR integration is the more accurate. It was assumed that the major product is the *E* stereoisomer. No further attempt to purify **369**, which was analysed as 77 % pure by GC was attempted.

2.44 Progression to a Relay RCM Precursor

A relay RCM precursor was quickly synthesised from **131** (Scheme 103) using the chemistry established for previous systems. The initial allylic alcohol synthesis proceeded smoothly on a 30 mmol scale to give **368** in a good yield of 84 %. Aldehyde **369** was used at 77 % purity and no purification was carried out on the crude material obtained after the reaction, as the NMR data showed a product of good purity.
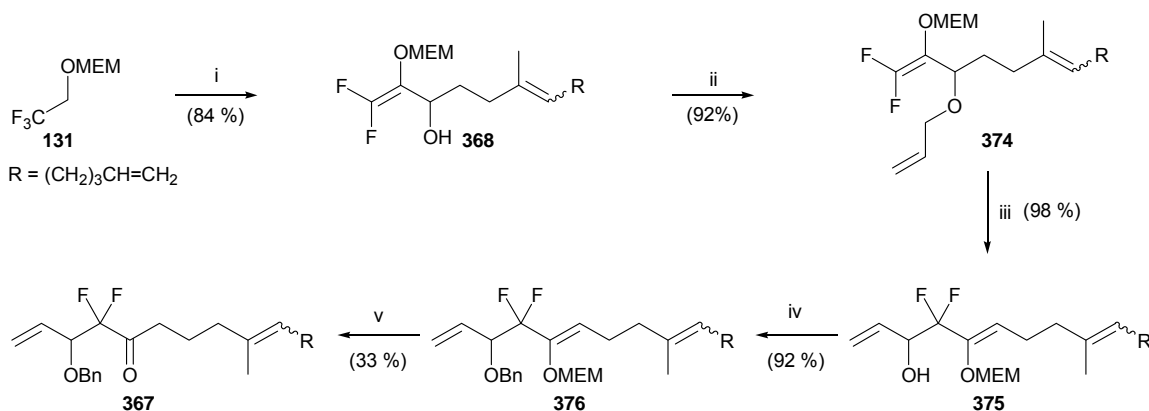
Scheme 103; Reagents and conditions, i, 2 eq LDA, THF, -78°C, then 1.2 eq **369** @ 77 % purity, -78 to -30°C, 2hr; ii, 1.2 eq allyl bromide, 50 % NaOH(aq), 10 % TBAHSO$_4$, 0°C to rt, ON; iii, 2 eq LDA, THF, -100 to -40°C, 4 h; iv, 3 eq NaH, THF, 0°C, 1 hr, then 1.1 eq BnBr, 10 % TBAI, 0°C to rt, ON; v, 1 eq SOCl$_2$, MeOH, 0°C to rt, ON.

Allylation under phase transfer conditions was trivial delivering ether **374** in excellent yield (92 %). This was followed by the crucial-[2,3] Wittig rearrangement which also proceeded well, delivering **375** almost quantitative yield (98%). Both these procedures delivered material which was not purified.

The allylic hydroxyl of **375** was then protected as the now preferred benzyl ether **376** (92 %) using the procedure developed for **188**. Although the material now obtained

showed significant contamination from being progressed un-purified through a number of stages it was decided to attempt to cleave off the MEM ether using standard conditions and then purify the material. This would limit the number of purifications from **131** to one and supply pure material for the relay RCM. After purification by flash column chromatography **367** was isolated as in 33 % yield from **375**. This represents an excellent 23 % from **131** over five steps. The ratio of the two stereoisomers in **367** was calculated to be 84:16 by ^{19}F NMR which is very similar to that calculated by ^{1}H NMR for **369** (86:14). Indeed they are within the 5 % sensitivity error of the NMR integration suggesting that both stereoisomers progress equally well through the reaction sequence.

2.45 Relay Ring Closing Metathesis of 367

It was found that **367** would undergo relay RCM with Grubbs' second generation catalyst **93** (Scheme 104). With an initial catalyst loading of 15 mol %, a new spot was observed by TLC, and when measured by ^{19}F NMR a conversion of around 40 % to a new product was observed after 22 hours. A further addition of catalyst (15 mol %) was required to drive the reaction to completion and desired cyclooctenone **366** was isolated after column chromatography in acceptable yield (57 %, Table 28, entry 1). Although this yield is only mediocre, especially given the high catalyst loading, it should be noted that firstly it is the un-optimised yield of a single reaction, and secondly the conversion of **367** by ^{19}F NMR was 100% suggesting that the main issue is one of purification. Indeed this is not a total surprise as the mass ratio of substrate to catalyst and co-catalyst is practically 1:1.

Optimisation could either come *via* modification of the purification procedure and/or attempts to reduce the catalyst loading required. It should also be noted that the 100% conversion recorded suggests both diastereoisomers react *via* the relay methodology unlike the behaviour observed by Porco with **364**[162].
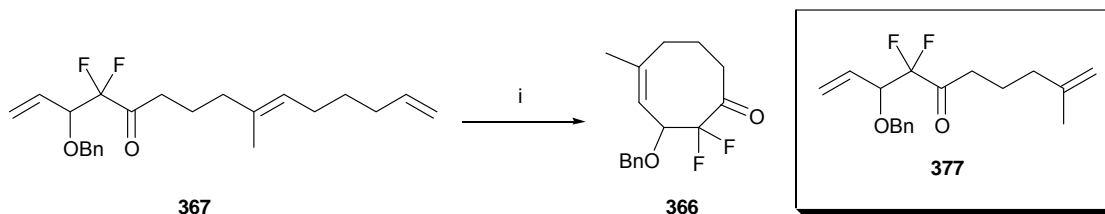
Scheme 104; Reagents and conditions; i, 30 mol% **93**, 30 mol% Ti(O^{i}Pr)$_4$, 0.0025M DCM, reflux, 45 hr.

Due to the extended reaction time it was anticipated that moving to a higher boiling solvent would speed up the reaction and improve the yield. Small scale reactions were conducted in DCE and chloroform (entry 2, and 3) and analysed by ^{19}F NMR. Initially it was thought that only starting material had been recovered as both chemical shift and coupling constant analysis suggested that the material was unchanged. However subsequently it was noticed that the minor diastereoisomer of **367** (only distinguished in the low field fluorine resonance) was not visible in the NMR.

Entry	Conditions	Yield^a
1	30 mol% **93**^{b}, 30 mol% Ti(O^{i}Pr)$_4$, 0.0025M DCM, reflux, 45 hr	57 % **366**
2	10 mol% **93**, 30 mol% Ti(O^{i}Pr)$_4$, 0.0025M DCE, reflux, 17 hr	(100 %) **377**
3	10 mol% **93**, 30 mol% Ti(O^{i}Pr)$_4$, 0.0025M chloroform, reflux, 28 hr	85 % **377**

Table 28; ^{a} ^{19}F NMR conversions in parenthesis; ^{b} Two additions of 15 mol % at T = 0 and 22 hr.

The reaction in chloroform was therefore re-run on a larger scale (entry 3) and the product isolated. Again this looked identical to the major diastereoisomer by ^{19}F NMR. However upon analysis of the ^{1}H NMR the loss of all protons associated with the relay tether was observed along with a new olefinic methylene signal (Figure 35). It is suggested that this product is diene **377** which being almost analogous to **345** is expected to react very slowly in RCM. It is assumed that this is the same product that was detected but not isolated in the DCE reaction.

Figure 35
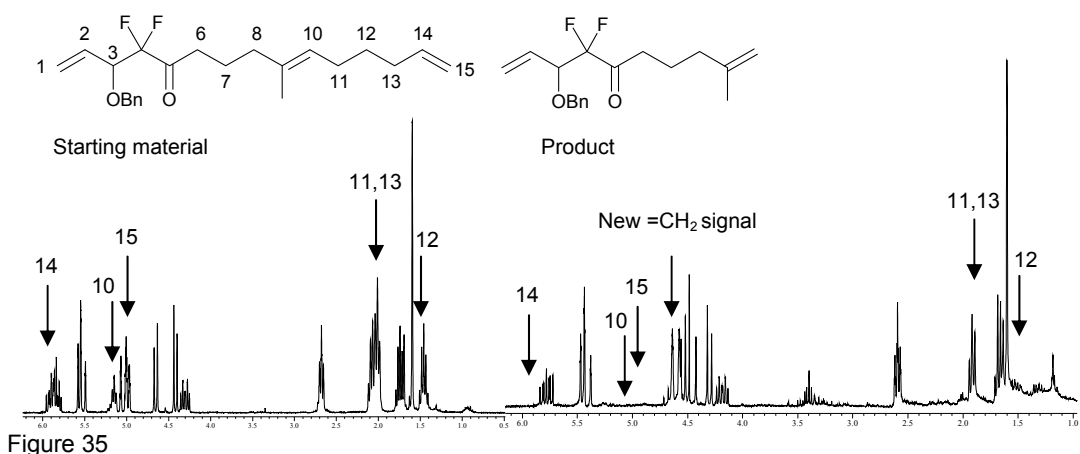
The formation of **377** is possible by the following route (Scheme 105). Firstly the catalyst initiates on the unsubstituted olefin of the relay moiety giving substrate alkylidene **378**. The initial cyclisation occurs to liberate cyclopentene and give a new alkylidene **379**. This species instead of undergoing the expected RCM to give **366** reacts in a cross metathesis with **367** to give **377** and regenerate **378**.

367

93

F F

RuLₙ

OBn O

378

377

Cross metathesis

367

F F

RuLₙ

OBn O

379
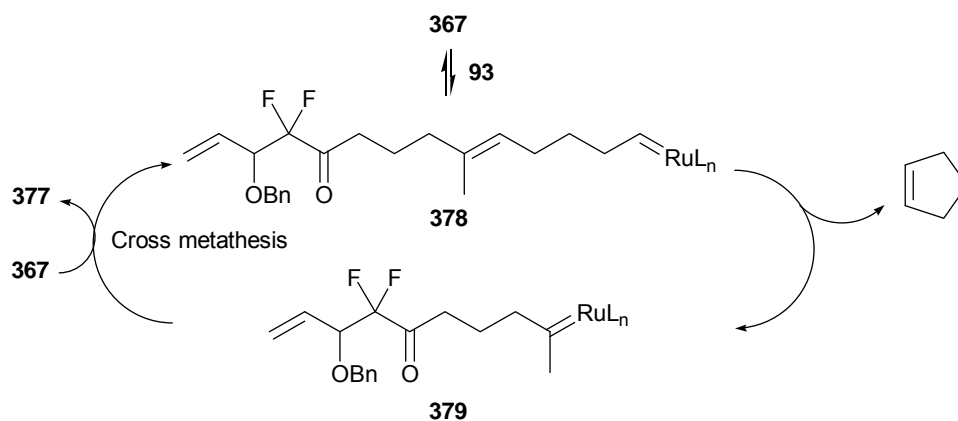
Scheme 105

No **377** was ever indicated by the NMR spectra for the reaction in DCM. The cross metathesis and RCM have different entropic requirements and therefore elicit different responses to a change in temperature.

2.46 Solution Conformation of 366 and Reactivity in Dihydroxylation

The solution conformation of **366** was again analysed by NMR and the results corresponded well to the structure obtained from X-ray crystallographic analysis[165] (Figure 36).

C6-H
C3-H
C8-H

C3-H – C8-H = 2.407 Å
C3-H – C6-H = 2.108 Å
C6-H – C8-H = 2.460 Å

Figure 36

191
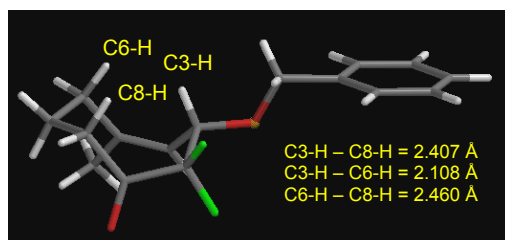
The $^3J_{\text{H-F}}$ coupling constant analysis (H3) gave a value of 19.2 at 363K suggestive of

aclose to antiperiplanar arrangement of one of the fluorine atoms and the C-3 methine

proton as seen in the other cyclooctenones synthesised during the project. A close to

antiperiplanar arrangement is visible from the x-ray crystal structure with a dihedral angle

of -168.34° being observed, the second dihedral angle being -51.66°.

The NOESY experiment showed crosspeaks between C3-H, C6-H, and C8-H[166] as

observed in previous systems such as **200**. The X-ray revealed that these protons were

well within the 3Å contact distance required for a nOe contact when measured from the

pdb file using PC Spartan Pro. It is therefore assumed that **366** adopts a similar

conformation in solution to **200** (with the caveats as discussed above about what that

solution conformation actually is) and therefore may show similar behaviour in the

dihydroxylation.
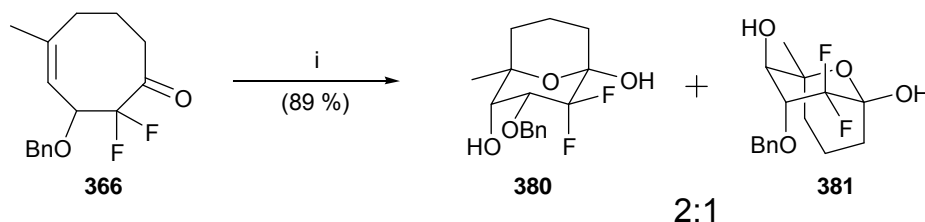
Scheme 106; Reagents and conditions; i, 5 mol% OsO_4, NMO, H_2O, acetone tBuOH
(4:2:1), 0°C, 6h

Unfortunately, time restrictions allowed the dihydroxylation of **366** to be investigated

under UpJohn conditions only (Scheme 106). This showed similar behaviour to that of

200, with **380** (the result of attack of OsO_4 onto the "closed" face) being isolated as the

major product although in a less diastereoselective manner than with **200**. Although only

on the basis of a single experiment, **366** appears to dihydroxylate more efficiently than

200. This can be explained by the slightly more electron rich olefin in **366** which reacts more rapidly with the Lewis acidic OsO_4. It proved much more difficult to separate diastereoisomers **380** and **381** than those in the existing series although good separation could be accomplished by preparative HPLC.

2.47 Progression of the 6-Deoxy Route to Target Compounds

Unfortunately time constraints made it impossible to progress any further towards the final target sugar phosphates. However the route as developed so far suggests that they are practical target compounds. Firstly aldehyde **369** can be synthesised on a large scale and used crude in the synthesis of **368**. Secondly relay RCM precursor **367** is obtainable in 23 % yield over 5 steps. Although the RCM is still running at high catalyst loading the conversions are 100 % by ^{19}F NMR and therefore it is expected that the yield of 57 % may be increased by improving the isolation of **366**. Even if the isolated yield cannot be improved by optimisation it is high enough to allow a useable amount of material to be processed through the step, albeit at high cost in catalyst. As **366** has shown the same behaviour as **200** in the dihydroxylation reaction it is expected that it will behave in a similar manner to **200** in the epoxidation and hopefully other subsequent transformations. It is envisaged that the 6-deoxy class of sugar phosphates could be obtained *via* this route.

2.48 Generalisation of the Ring Opening of Epoxides 250 and 251 With Other Nucleophiles

The scope of the microwave-mediated epoxide opening reaction with both **250** and **251** was investigated using a range of neutral and ionic nucleophiles based on different heteroatoms. Initial attempts used neutral nitrogen nucleophiles as they offered an interesting chemoselectivity issue upon reaction. If the suggested mechanism (illustrated for **250** in Scheme 107) for the opening is correct and the nucleophile adds to the ketone then it is possible for the transanular ring closure to be accomplished with either the nitrogen acting as the nucleophile (giving an N-bridged species **382**), or the oxygen acting as the nucleophile (giving an exocyclic amino group **383**).
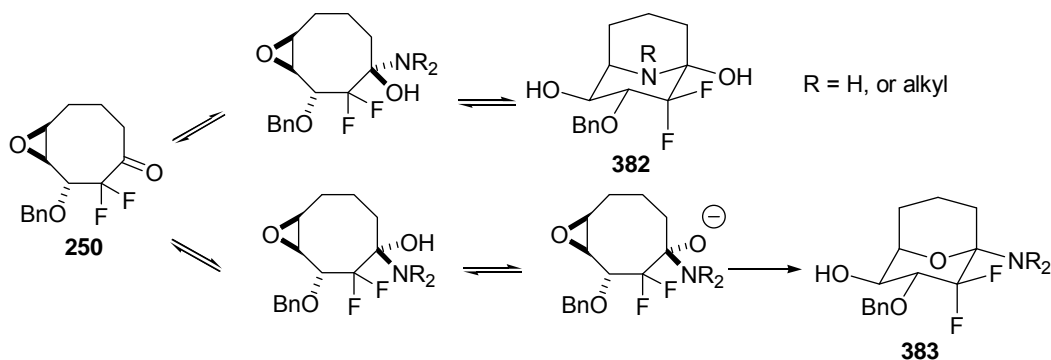
Scheme 107

Initial experiments were conducted in 35% ammonia solution (Scheme 108, Table 29, entry 1) which gave a white solid product in moderate yield (43 %). The same product was obtained when the reaction was conducted in methanol, but in an improved yield (74 %, entry 2). Attempts to assign the structure of the compound proved challenging as analysing the nature of the bridging atom could not be done by NMR. In the end the

compound was assigned as N bridged species **384** due to an x-ray crystal structure (Figure 37)[167] although as nitrogen and oxygen are close to isosteric, the reliability of this assignment is questionable.

The reaction was repeated with methylamine as the nucleophile in both water and methanol (entries 3, and 4). The same product was isolated from both reactions, with the reaction conducted in methanol again providing the better yield (67 compared to 53 %). More importantly the methyl group of methylamine was easily locatable by NMR and showed an HMBC crosspeak between the protons on the methyl group and the C5 carbon[168], thus positively identifying nitrogen as the bridging atom in **385**. This was further corroborated by an X-ray crystal structure[169] (Figure 37). On the basis of analogous reactivity, this supports the assignment of a nitrogen bridge in **384**. Later hydrogenolysis was used to remove the benzyl group from **384** to deliver the free aza sugar **386** (35 %). The conventional hydrogenolysis condition were modified with a methanol co-solvent required in order to dissolve **384**.

Figure 37

Scheme 108; Reagents and conditions; i, 10 % Pd/C, EtOH, H_2

Entry	R	R'	X	Conditions[a]	Yield (%)
1	Bn	Bn	NH	35 % NH_3 in H_2O	43
2	Bn	Bn	NH	Sat. NH_3 in MeOH	74
3	Bn	Bn	NMe	2M NH_2Me in MeOH	67
4	Bn	Bn	NMe	40 % NH_2Me in H_2O	53
5	Bn	Bn	$NCH_2CH=CH_2$	2M allyl amine in MeOH	77
6	Bn	H	NMe	2M NH_2Me in MeOH	87
7	Bn	H	$NCH_2CH=CH_2$	2M allyl amine in MeOH	77
8	Bn	-	-	2M (R) methylbenzyl amine	-
9	Bn	Bn	O	2M Na_2S, 0.5M $NaHCO_3$, H_2O	(100) **293**
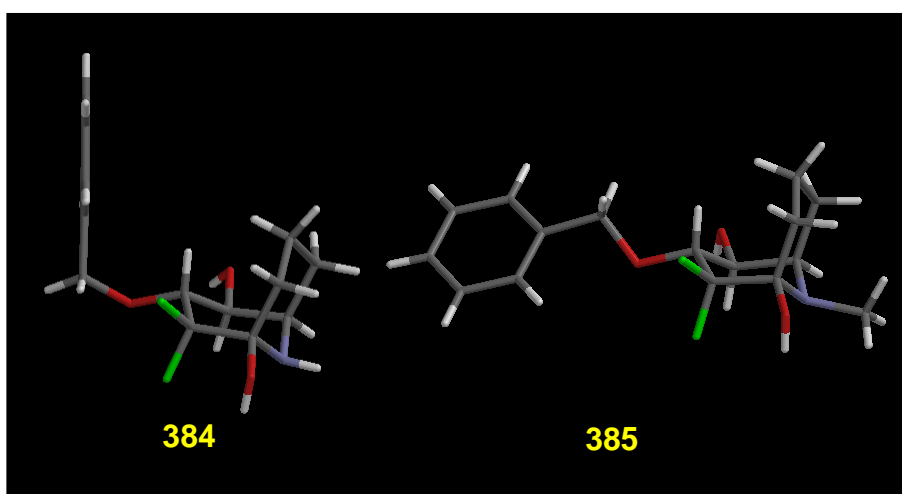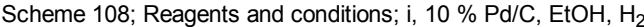
Table 29; [a] All reactions carried out in the microwave (30 W, 100°C, 30 min)

The generality of the epoxide opening was further explored using allylamine as the nucleophile (entry 5). The white solid isolated was identified as nitrogen bridged species **287** again by analysis of the HMBC spectra.[170] The methylamine and allylamine reactions were repeated for benzoate **251** (entry 6, and 7) but in methanol only, due to the difficulties experienced in the hydrolysis reaction of this compound. In this case the benzoyl group was cleaved off by the reaction conditions but good yields of **288** (87 %) and **289** (77 %) respectively were achieved. Both compounds were shown to have nitrogen bridges by HMBC NMR analysis.[171] Interest now turned to the use of a chiral amine is it was hoped that the diastereomeric products would be easily separated and allow access to enantiomerically pure material. When the reaction was conducted with (R)-methyl benzylamine as the nucleophile (entry 8) two major products were indeed obtained. However purification proved impossible due to the extremely low solubility of

the compounds. Unfortunately time constraints prevented the analysis of other chiral amines. With the success with both oxygen and nitrogen nucleophiles an attempt was made to open **250** with Na$_2$S in the hope of obtaining a sulfur bridged species. Disappointingly only **293** the conventional hydrolysis product was detected by ^{19}F NMR and MS after the reaction. It should be noted that unlike the hydrolysis or methanolysis reactions in none of the above experiments was any product other than the [3.3.1] bicycle formed, therefore there is no evidence for attack at C-1.

390
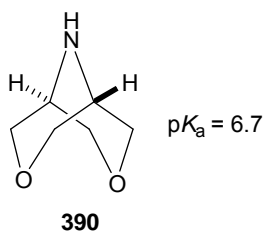
Figure 38

It is expected that this class of amines should have a low pK_a. The structurally similar [3.3.1] bicycle **390** has a pK_a of 6.7[172] (Figure 38). The basicity of nitrogen was used to provide further evidence for the nitrogen bridge. Treatment of **284** and **285** with d-TFA lead to deuteration of the bridging nitrogen and this effect was visible in the ^{1}H NMR as a shift downfield for all the methine resonances. In both cases the H-5 proton was observed to undergo the largest change in chemical shift (ca. 0.5 ppm) suggesting it was close to the site of deuteration.[173]
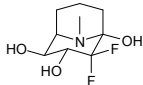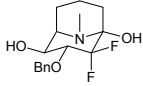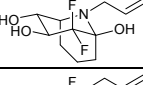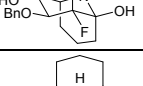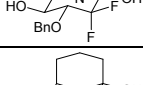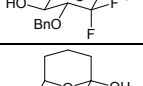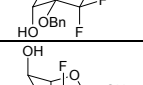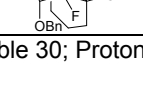
Compound	H-3 (ppm)	H-4 (ppm)	H-5 (ppm)
	3.9	3.75	3.0
	4.05	3.95	3.1
	3.95	3.7	3.1
	4.05	3.9	3.2
	4.0	3.9	3.2
	4.0	3.4	4.2
	3.9	3.75	4.0
	3.9	3.8	4.1

Table 30; Proton chemical shifts

With all these compounds in hand an interesting pattern was observed in the ordering of the chemical shift values for the methine protons (Table 30). In all the nitrogen bridged systems H-3 appeared the furthest down field (yellow), followed by H-4 (green), with H-5 always occurring as the highest field resonance (blue). This was in stark contrast to the oxygen bridged species where H-5 appears at lowfield with H-4 at highfield for all the diastereoisomers. It was this ordering of signals in **384** provides additional evidence for the bridging structure.

A number of conclusions can be drawn from the above results. Firstly the reaction gives better yields and slightly better quality crude material when conducted in methanol rather than water, but the general reactivity appears to be neither substrate nor solvent dependent. That reaction is also completely chemoselective with only the nitrogen

bridged species being detected in each case, is perhaps not a complete surprise if one considers the mechanism (Scheme 109).
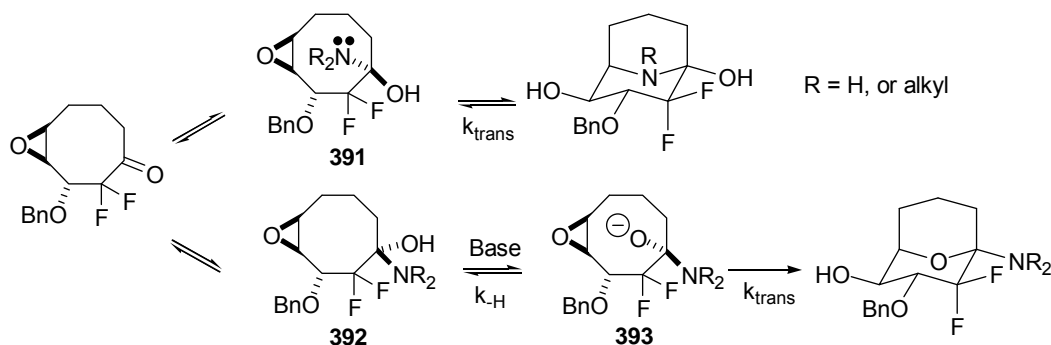
Scheme 109

After the initial nucleophilic attack, intermediate **391** can proceed immediately with the transannular reaction (k_{trans}) as the amine acts as a neutral nucleophile for a second time. For the oxygen to act as a nucleophile **392** must first be deprotonated (k_{-H}) to **393** then react (k_{trans}). Although the transannular reaction with an alkoxide pKa 16 should certainly be faster than that with a neutral amine pKa 9.21 (NH_4^+ conjugate acid of NH_3), if the nitrogen base is not strong enough to catalyse the initial deprotonation then all the material will react through the pathway resulting in the nitrogen bridged species. It is suggested that the three bases used above must therefore not be sufficiently strong to deprotonate **392**.

It was hoped that after the success of these reactions it would prove possible to open the epoxide **250** with a more exotic nucleophile such as alcohol **394**. This would hopefully give access to glycosylated species **395** (Scheme 110). If successful, the procedure could be extended to include protected sugars and lead to the synthesis of a library of disaccharide analogues.
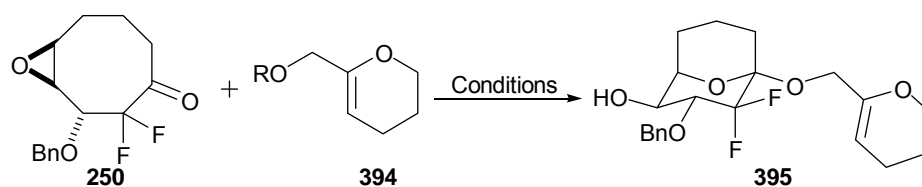
Scheme 110

Entry	R	Conditions	Yield
1	H	**250**, 4 eq pyran, 30W, 100°C, 30 min	SM
2	H	**250**, 4 eq pyran, CF$_3$CH$_2$OH, 30W, 100°C, 30 min	SM
3	Na	**250**, 2.2 eq pyran, THF, 30W, 100°C, 30 min	-
4	-	**250** 0.1M MeONa, THF, 30W, 100°C, 30 min	Mainly **293**
5	Na	**250**, 2 eq pyran, 2 eq NaHMDS, 2 eq 15-crown 5, 0°C, 1 h	-

Table 31

An initial experiment attempted to use the nucleophile as the solvent (Table 31, entry 1). This returned mainly starting material and traces of conventional hydrolysis product **293**. There was no evidence for **395** by either NMR or ES. Very similar results were obtained when trifluoroethanol was used as the solvent (entry 2).

With the success of the methanolysis reaction a similar strategy was developed using pre-prepared sodium salt **294** (R = Na) in a carrier solvent (THF). This was then carefully transferred to a microwave tube containing a solution of **250** in THF (entry 3). After irradiation in the microwave, a very complex ^{19}F spectra was obtained along with a weak molecular ion for **395** in the ES, but no characteriasble product was isolated. This disappointing result led to an attempt to try and recreate the methanolysis result in THF rather than methanol (entry 4). A 0.1M solution of NaOMe was added to a microwave tube containing **250** in THF, which was then sealed and irradiated. Analysis by ^{19}F NMR showed mainly hydrolysis product **293** plus an unknown CF$_2$ species and only traces of

the methanolysis products **304**, and **305**. With the failure of the microwave mediated attempts a reaction was conducted in a more classical manner (entry 5). The alkoxide was generated in *situ* by addition of base to a solution of **250** and **394** (R = H) in THF with a crown ether additive to aid nucleophilicity. Again the crude NMR showed a large number of signals including conventional hydrolysis product **293**. Attempts to purify on column chromatography lead to the isolation of a small amount (2 mg) of one of the unknown signals in poor purity. This fraction gave a strong molecular ion for **395** and appeared to show elements of both partners in **395**. It however was only one of many products from the reaction and could not be obtained pure in any case.

These results demonstrate the expoxides **250** and **251** appear to react cleanly, and in good yield with a range of nucleophiles. Neutral nitrogen nucleophiles react to give the *N*-bridged species exclusively, irrespective of the carrier solvent used. This should offer a powerful methodology access a new class of novel aza sugars especially if a suitable chiral amine can be found to allow separation of the products into enantiomerically pure streams after the transanular reaction.

The results also demonstrate that the neutral alcohols cannot act as effective nucleophiles as they appear unable to add to the ketone of **250** or if added act as nucleophiles. Increasing the nucleophilicity of the oxygen by conversion to the alkoxide using a trace amount of base allows a facile reaction to occur. Extension of the methodology to complex oxygen nucleophiles where the nucleophile cannot be used as the solvent necessitated the use of a carrier solvent. However the reaction of the pyran **394** (R = H) by conversion to the sodium salt **394** (R = Na) proved problematic as THF proved a poor carrier solvent giving low control of reactivity. The failure of the methanolysis reaction is

testament to this; clearly enough water was present to produce the hydrolysis product rather than and coupled product.

Further unsucessful related work can be found in appendix 1 on the accompanying CD

3.0 Conclusions

A range of locked difluorinated pentopyranoside analogues have been synthesised using a concise synthesis from commercially available trifluoroethanol *via* a crucial RCM to furnish key intermediate cyclooctenone 3-benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one **200**. It was found that a range of cyclooctenones could be constructed rapidly *via* a telescoped synthesis requiring minimal purification. Initial reactions including metallated difluoroenol acetal chemistry and a [2,3]-Wittig rearrangement; which proceeded in good yield and on a large scale (100 and 30 mmol respectively) as long as careful control of temperature was achieved. This was especially important in the [2,3]-Wittig rearrangement to **183** where optimisation studies showed a temperature of -100°C was required to afford material which required no purification post-isolation. An alternative route to the synthesis of **200** without resorting to two low temperature/strong base transformations was investigated using α,α,α-trihaloketones. The synthesis of trifluoroketone **159** and chlorodifluoroketone **173** proceeded in poor yield, and subsequent attempts to advance these species to **156** by magnesium- and zinc-promoted reductive defluorination/aldol methodology failed to give any isolable product and only poor conversions of starting material by ^{19}F NMR.

Allylic alcohol **183** could be rapidly advanced to an RCM precursor; however post RCM it was found that product volatility necessitated the protection of the secondary hydroxyl group. A range of protecting groups was explored with the benzyl ether proving the most suitable in terms of yield and stability in future synthetic transformations. Unfortunately a relatively low concentration of 0.0025M was required in order to prevent competitive

cross metathesis reactions reducing the yield of the RCM reaction. Despite this practical limitation, multi gram quantities (9 mmol) of **200** could be easily prepared *via* this methodology.

During optimisation studies of **200** homodimeric species *syn* **233** and *meso* **234** were prepared in good yield using the Neolyst catalyst. Analogous dimers **235** were then synthesised from the benzoyl protected series. These results were surprising as it had been thought that type I/type I homodimers were too reactive towards metathesis catalysts to exist in isolable amounts. Indeed even the more active Grubbs' second generation catalyst only gave a conversion to **200** of ca. 50% when exposed to purified **233/234.**

From 3-benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one **200** oxidation of the substrate allows a divergent synthesis to be established. Dihydroxylation and subsequent transannular hemiacetalisation is achievable *via* a number of methodologies with varying degrees of selectivity. A ruthenium tetroxide dihydroxylation and traditional UpJohn methodology deliver a stereoselective mixture of [3.3.1] bicyclic hemiacetals **255** and **256**, with **256** as the major product. In contrast a very efficient Donohoe OsO_4/TMEDA dihydroxylation delivers **255** and **256** non-stereoselectively. Alternatively, epoxidation to give the *trans* epoxide and subsequent hydrolysis leading to transannular ring opening allows access to a third diastereoisomer **293**.

Attempts to rationalise these findings in terms of the solution conformation of cyclooctenone **200** has proved challenging. The major conformer in solution is thought to be type C and thus epoxidation proceeds as expected onto the open face of **200.** In the stereoselective dihydroxylation reactions the major product is a result of osmium

tetroxide attack on the closed face. This observation has led to the proposition of ketonic delivery of OsO$_4$ to the closed face although the mechanism of the delivery is unknown. This approach does not however adequately explain the outcome of the Donohoe dihydroxylation. Alternate approaches involving reaction through minor conformers have been discussed but as yet no firm conclusions can be drawn. Although it will prove impossible to get good NMR data for **200** in the solvent mixtures used for the UpJohn and ruthenium reactions it is suggested that a NOESY experiment of **200** in d^2 DCM should provide information about the true conformer present in the Donohoe reaction.

Attempts to selectively phosphorylate the pseudo-anomeric hydroxyl of **255, 256**, and **293** by exploiting the pK$_a$ difference between the groups proved successful but not to a useful synthetic extent. Having protected the competing secondary hydroxyl phosphorylation occurred in good yield. These fully protected species were rapidly deprotected in good yield to give the final pentopyranosyl phosphates **322**, **323**, and **324** as mixed salts.

The flexibility of the initial stages of the synthetic route has been further demonstrated with two further systems brought through to the RCM precursor stage. With the aim of repeating the above synthesis toward a class of 6-deoxyhexopyranose analogues, cyclooctenones of type **332** a *tris*-substituted olefin were required. Toward this diene **345** was isolated in 20% yield from MEM ether **131** with only two intermediate purifications. The RCM of **345** proved a challenging synthetic step with high catalyst loadings (20-33 mol %) delivering isolated yields consistent with a stoichiometric reaction. The RCM of **345** is a challenging type II/type III cyclisation and it is pleasing that any conversion to the traditionally difficult eight membered ring occurred at all. Steric congestion in the

transition state leading to the formation of the metallocyclobutane intermediate is proposed as the major cause for the poor reaction efficiency. This effect is especially important in the initial metathesis initiation onto the type II olefin.

A relay approach was adopted in an attempt to negate these difficulties by giving the metathesis catalyst an easy olefin upon which to initiate. Again the existing synthetic route proved robust with RRCM precursor **367** being isolated from **131** in excellent 23 % yield over five steps, with only one intermediate purification. In initial metathesis experiments the relay approach was successful with **366** being isolated in 57% yield and although the catalyst loading is still high (30 %) conversion by ^{19}F NMR is 100% suggesting the problem is now one of isolation. It is expected that optimisation of this reaction should lead to an increased isolated yield and/or a reduction in catalyst loading. Unfortunately limited time was available for the progression of **366** although similar behaviour to **200** was observed in the UpJohn dihydroxylation and this strongly suggests analogous behaviour to the pyranose series should be expected. Indeed were more time available this would be the primary research goal.

Lastly further studies were made on the transannular epoxide opening reaction. The mechanism had been proposed as attack of the nucleophile on the ketone of the cyclooctenone followed by transannular epoxide opening rather than the alternative of the nucleophile opening the epoxide then alkoxide collapse onto the ketone. When conducted in 0.5% MeONa/MeOH the resultant compounds were shown to have the methoxy group incorporated exclusively on the anomeric carbon thus proving the proposed mechanism. Interestingly and unexpectedly this reaction also demonstrated that the transannular reaction is non-selective opening the epoxide at either end to give both a [3.3.1] **300** and

[4.2.1] **301** bicycle. It was also observed that both the benzyl and benzoyl epoxides **250** and **251** can be opened with a range of neutral nitrogen nucleophiles including methylamine and allylamine. These reactions were found to be very clean and gave exclusively nitrogen bridged bicyclic products offering access to a new class of azasugar analogues. This reaction also allows the possibility for separation of the enantiomers of **250** by reaction with a chiral amine and separation of the resultant diastereoisomers. Disappointingly although reaction with (R)-methylbenzylamine did give two major products solubility problems prevented separation or characterisation. It is hoped that further work in this direction will allow access to a valuable class of enantiomerically pure compounds.

4.0 Experimental

4.1 General Experimental

NMR spectra where recorded on a Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{19}F, 282.40 MHz; ^{31}P, 121 MHz; COSY; HMQC) spectrometer or on a Bruker DRX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz; ^{19}F, 376.45 MHz; ^{14}N, 29 MHz; COSY; HMQC; HMBC; NOESY; VT NMR) spectrometer using Norell 507-HP NMR tubes. Chemical shifts for ^{1}H and ^{13}C were recorded using deuterated solvent as the lock and residual solvent as the internal standard. ^{19}F NMR spectra were referenced to CCl_3F as the external standard. Spectra are recorded consecutively as follows; chemical shift in parts per million (δ_H, δ_C, δ_F, δ_P, or δ_N), relative integral, multiplicity (m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, and multiples there of eg. dd = double doublet; also, inc. = including, env. = envelope, app. = apparent, br. = broad), coupling constant (J/Hz), and assignment.

Electron Impact (EI) mass spectra were recorded on a Kratos Concent 1H mass spectrometer in house, or a Quattro II mass spectrometer at the EPSRC National Mass Spectrometry Service Centre. Chemical Ionisation (CI) mass spectra were recorded on a Kratos Concent 1H mass spectrometer using ammonia as the reagent gas in house, or a Quattro II mass spectrometer at the EPSRC National Mass Spectrometry Service Centre. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H mass spectrometer using xeon and *m*-nitrobenzyl alcohol as the matrix in house, or on a

MAT95 mass spectrometer using *m*-nitrobenzyl alcohol as the matrix at the EPSRC National Mass Spectrometry Service Centre. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC mass spectrometer in house, or on one of a ZQ4000, Quattro, or MAT9x mass spectrometers at the EPSRC National Mass Spectrometry Service Centre. High Resolution Mass Spectrometry (HMRS) were recorded on the above mass spectrometers using peak matching to stable reference peaks, depending on the technique used. Gas chromatograms were recorded on a Perkin Elmer Autosystem Gas Chromatograph fitted with a PE5 MS (5% phenyl, 95% dimethylpolysiloxane phase column (30 m)); experiments were carried out between 45-250°C with a 10°C min^{-1} ramp. Column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40-63μ) or using a Biotage Horizon flash chromatography system. Thin layer chromatography (TLC) was conducted on precoated aluminium backed silicagel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F$_{254}$, thickness 0.2 mm). Compound were visulised using UV light, potassium permanganate, *p*-anisaldehyde, iodine, 2,4-dinitrophenylhydrazine (DNP), phosphomolybdic acid (PMA), or sulfuric acid. Preprative HPLC was conducted on a PerkinElmer Quaternary LC Pump Modle 200Q/410 with Series 200 Autosampler using a Waters Sterisorb S5 ODS2 colunm (20 x 250 mm).

Crystals for X ray crystallographic analysis were grown by the vapour diffusion of pantane into ethyl acetate.

Light petroleum refers to the fraction boiling between 40-60°C. Tetrahydrofuran (THF) was dried by refluxing with benzophenone over sodium wire under an atmosphere of nitrogen. Dichloromethane (DCM), and chloroform were dried by refluxing over calcium

hydride under an atmosphere of nitrogen. Ether, and toluene were obtained dry from an Innovative Technology Pure Solve system. Diisopropylamine (DIPA) and other chemicals where stated as purified, were done so according to the procedures of Perrin,[185] all other compounds were used as supplied. Alkyllithiums, and NaHMDS were titrated according to the procedures of Duhamel[186]. Common impurities in NMR spectra were identified using tables provided by Gottlieb[187]

4.2 Experimental procedures

Preparation Of 1,1,1-Trifluoro-hept-6-en-2-one 159
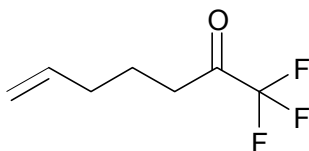
5-bromoprop-1-ene (50.7 mmol, 6.0 cm^3) in diethyl ether (30 cm^3) was added to a sonicated three necked flask containing magnesium turnings (49 mmol, 1.2 g) in diethyl ether (20 cm^3) dropwise so as to maintain a reflux. The black Grignard solution was sonicated at rt for 150 min.

The black Grignard solution was then added *via* cannulation into an addition funnel and added cautiously dropwise to a stirred solution of ethyl chlorodifluoroacetate (75 mmol, 9.0 cm^3) in diethyl ether (30 cm^3) at -78°C under an atmosphere of N$_2$. The solution was warmed to -30°C and stirred for 90 min, then warmed to -10°C and stirred for a further 90 min, upon which a white precipitate was observed. The reaction was quenched with 20%

aqueous HCl solution (20 cm^3), and the aqueous phase saturated with NaCl, then extracted with diethyl ether (1 x 100 cm^3, 2 x 50 cm^3). The combined extracts were washed with NaHCO$_3$ (2 x 20 cm^3), brine (20 cm^3), dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give a yellow oil, which was purified by distillation (Kugelrohr bp. 95-100°C/760 mm Hg) to give the known ketone **159** (2.94 g, 36%) as a clear oil. R$_f$ (50 % ethyl acetate/hexane) 0.45; υ_{max}(film)/cm^{-1} 2940w, 1764s, 1643w, 1204s, 1145s; δ_H (300 MHz, CDCl$_3$) 5.85-5.65 (1H, m, CH$_2$=C*H*), 5.12-5.01 (2H, m, C*H*$_2$=CH), 2.72 (2H, t, *J* 7.2, C*H*$_2$CO), 2.12 (2H, q, *J* 7.2, =CHC*H*$_2$), 1.79 (2H, quint., *J* 7.2, CH$_2$C*H*$_2$CH$_2$,); δ_C (75MHz, CDCl$_3$) 191.3 (q, $^2J_{C-F}$ 34.7), 137.0, 116.2, 115.7 (q, $^1J_{C-F}$ 292.0), 35.5, 32.6, 21.4; δ_F (282MHz, CDCl$_3$) -79.4 (3F, s); [HRMS (EI$^+$, [M]$^+$) Found: 166.06047. Calc. for C$_7$H$_9$F$_3$O: 166.06055]; *m/z* (EI$^+$) 166 (8%, [M$^+$]), 165 (100), 145 (33), 124 (15), 113 (96), 95 (38), 59 (29). The data were in agreement with Felix and Laurent[75] previously reported at a lower level of characterization.

Modified Uneyama[73] Reductive Defluorination Protocol.

Trifluoromethyl ketone **159** (3 mmol, 0.5 g) was added to a stirred suspension of magnesium (6 mmol, 0.145 g), TMSCl (12 mmol, 1.52 cm^3) and dry DMF (12 cm^3) at 0°C under an argon atmosphere. The suspension was stirred for 30 min, cooled to -78°C then freshly distilled acrolein (6 mmol, 0.36 cm^3), and a trace of TiCl$_4$ were added. The solution was allowed to warm to room temperature. No product was detected by NMR and no extraction was attempted.

Preparation of 1-Chloro-1,1-difluoro-hept-6-en-2-one 173
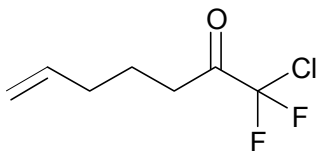
5-bromoprop-1-ene (134 mmol, 15.8 cm^3) in diethyl ether (25 cm^3) was added to a three necked flask containing magnesium turnings (160 mmol, 3.84 g) in diethyl ether (15 cm^3) dropwise so as to maintain a reflux (brief sonication 20 sec was used to initiate reflux). The black Grignard solution was then added *via* cannula into an addition funnel and added cautiously dropwise to a stirred solution of methyl chlorodifluoroacetate (145 mmol, 15.3 cm^3) in diethyl ether (140 cm^3) at -70°C under an atmosphere of N$_2$ then was allowed to warm to rt and stirred for 48 hours. The solution was quenched with saturated aqueous ammonium chloride (30 cm^3), extracted with diethyl ether (2 x 100 cm^3), washed with brine (2 x 50 cm^3), dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give a yellow oil, which was purified by distillation (Kugelrohr bp. 32°C/10 mmHg) to give the ketone **173** (8.12 g, 33%, 74%GC); R$_f$ (30% ethyl acetate/hexane) 0.58; GC retention time 5.95min; υ_{max}(film)/cm^{-1} 2930w, 1760s, 1115s, 1148s, 911s; δ_H (300 MHz, CDCl$_3$) 5.77 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, *J* 6.7, CH$_2$=C*H*CH$_2$), 5.10-5.02 (2H, m, C*H$_2$*CH), 2.77 (2H, t, *J* 7.2, C*H$_2$*CO), 2.17-2.13 (2H, m, CHC*H$_2$*CH$_2$), 1.80 (2H, quint, *J* 7.2, CH$_2$C*H$_2$*CH$_2$); δ_C (75MHz, CDCl$_3$) 191.7 (t, $^2J_{C\text{-}F}$ 29.3), 137.0, 119.8 (t, $^1J_{C\text{-}F}$ 306), 116.0, 34.1, 32.5, 21.8; δ_F (282MHz, CDCl$_3$) -68.2 (2F, s); [HRMS (EI$^+$, [M]$^+$) Found: 182.03100. Calc. for C$_7$H$_9$F$_2$O^{35}Cl: 182.03111]; *m/z* (EI$^+$) 182 (10%, M$^+$), 135 (5), 97 (100), 85 (22), 79 (12), 69 (87), 55 (40), 54 (46).

Ishihara[74] Protocol for the Synthesis of α,α-Difluoro-β-hydroxy Ketones.

Powdered zinc (3 mmol, 0.196 g), and CuCl (0.3 mmol, 0.030 g) in THF (5 cm^3) was stirred for 30 min under an argon atmosphere, then freshly distilled acrolein (1.1 mmol, 0.06 cm^3) and **173** (1 mmol, 0.182 g) were added by syringe and the mixture was stirred at reflux for 4 hours. Conversion of starting material was observed to be approximately 20 % by NMR. After cooling to room temperature the reaction mixture was filtered through a pad of celite and the filtrate concentrated under reduced pressure. Purification on silica gel eluted with (30 % ethyl acetate/hexane) gave no identifiable product.

Preparation of 1,1,1-trifluoro-2-(2'methoxy-ethoxymethoxy) ethane 131
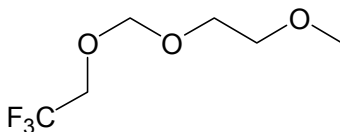
1,1,1-trifluoroethanol (1.054 mol, 76.6 cm^3) in THF (100 cm^3) was added dropwise over 1 hour to sodium hydride (1.054 mol, 42.16 g, at 60 % dispersion from which the oil had been removed by washing repeatedly with hexane) in THF (100 cm^3) at 0°C. The olive green suspension was stirred for 1 hour, then MEMCl (1.405 mol, 175 cm^3) in dry THF (166 cm^3) was added dropwise over 2 hours at 0°C. The white suspension was allowed to warm to room temperature, and stirred overnight. Cautious addition of water (600 cm^3) and extractive workup with diethyl ether (4 x 300 cm^3) followed. The combined ether extracts were washed with brine (2 x 100 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give a yellow oil which was distilled (Kugelrohr bp. 68-72°C, 35 mmHg) to

give the known ether **131** as a clear liquid (142.6 g, 72 %); R_f (30% ethyl acetate/hexane) 0.47; δ_H (300 MHz, CDCl$_3$) 4.75 (2H, s, OCH_2O), 3.88 (2H, q, $^3J_{\text{H-F}}$ 8.7, CF$_3$CH_2O), 3.67-3.62 (2H, m, OCH_2CH$_2$OCH$_3$), 3.54-3.49 (2H, m, OCH$_2$CH_2OCH$_3$), 3.34 (3H, s, OCH_3); δ_C (75 MHz, CDCl$_3$) 123.9 (q, $^1J_{\text{C-F}}$ 278.0), 95.4, 71.4, 67.3, 64.3 (q, $^2J_{\text{C-F}}$ 34.6), 58.7; δ_F (282 MHz, CDCl$_3$) -74.5 (3F, t, $^3J_{\text{H-F}}$ 8.7). The data are in agreement with Patel and Percy[62]

Preparation of Pent-4-enal 145
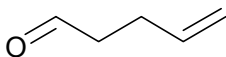
Allyl vinyl ether (64.15 mmol, 5.40 g) was sealed in a crimp-capped microwave vial and irradiated in the cavity of a CEM Discover microwave instrument at 150°C for 6 hours, until analysis of the proton NMR showed conversion at greater than 95%. Aldehyde **145** was used without purification; δ_H (300 MHz, CDCl$_3$) 9.99 (1H, t, J 1.5, HCO), 5.83 (1H, ddt, $^3J_{\text{trans}}$ 17.1, $^3J_{\text{cis}}$ 10.3, J 6.4, CH$_2$=CH), 5.10-4.99 (2H, m, $^3J_{\text{trans}}$ 17.1, $^3J_{\text{cis}}$ 10.3, CH_2=CH), 2.58-2.51 (2H, m, OCCH_2), 2.44-2.35 (2H, m, CH_2CH); δ_c (75 MHz, CDCl$_3$) 202.1, 136.8, 115.9, 43.0, 26.4; spectral data were in agreement with those reported by *Murphy et al.*[84]

Preparation of 1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-dien-3-ol 178
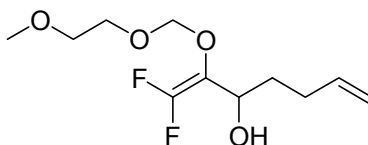
Acetal **131** (100 mmol, 16.79 cm^3) was added dropwise over 10 min to a cold (-78°C) solution of LDA (prepared by the slow addition of *n*BuLi (200 mmol, 86.95 cm^3, of a 2.3 M solution in hexane) to a cold (-78 °C) stirred solution of diisopropylamine (240 mmol, 33.73 cm^3) in THF (100 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -78°C). The orange/brown solution was stirred at this temperature for 40 minutes and pent-4-enal **145** (180 mmol, 17.77 cm^3) was added in one portion over 1 min. The mixture was allowed to warm to -40 °C over 4 hours and quenched with ammonium chloride (10 cm^3 of a saturated methanolic solution). Water (200 cm^3) was added and the mixture was extracted with diethyl ether (3 x 100 cm^3). The combined organic extracts were washed with brine (2 x 50 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to leave a red/brown oil. Distillation (Kugelrohr, bp. 75°C/0.05 mmHg) afforded the desired difluoroallylic alcohol **178** (20.97 g, 82 %, 100% GC) as a colourless oil. R$_f$ (20% ethyl acetate/hexane) 0.34; υ$_{max}$(film)/cm^{-1} 3432br, 2932s, 1751s, 1641s, 1455w, 1245s, 1111s, 914s, 850s; δ$_H$ (300 MHz, CDCl$_3$) 5.81 (1H, ddt, $^3J_{trans}$ 16.8, $^3J_{cis}$ 10.2, J 6.6, CH$_2$=C*H*), 5.04 (1H, ddt, $^3J_{trans}$ 16.8, ^2J 3.3, ^4J 1.6, C*H*$_a$H$_b$=CH), 5.00 (1H, d, AB, ^2J 6.5, OC*H*$_a$H$_b$O), 4.98 (1H, ddt, $^3J_{cis}$ 10.2, ^2J 3.3, ^4J 1.2, CH$_a$*H*$_b$=CH), 4.88, (1H, d, AB, ^2J 6.5, OCH$_a$*H*$_b$O), 4.26 (1H, broad s, C*H*(OH)CH$_2$), 3.96 (1H, ddd, AB, ^2J 10.8, J 6.2, 3.6, C*H*$_a$H$_b$CH$_2$OCH$_3$), 3.78 (1H, ddd, AB, ^2J 10.8, J 4.8, 3.1, CH$_a$*H*$_b$CH$_2$OCH$_3$), 3.61-3.56 (2H, m, CH$_2$C*H*$_2$OCH$_3$), 3.39 (3H, s,

OCH$_3$), 2.10 (2H, q, *J* 7.6, CH(OH)C*H*$_2$), 1.90-1.65 (2H, m, C*H*$_2$CH=); δ$_C$ (75 MHz, CDCl$_3$) 154.6 (dd, $^1J_{F-F}$ 292.0, 186.0), 137.7, 118.1 (dd, $^2J_{C-F}$ 36.5, 10.0), 115.1, 98.2, 71.5, 68.5, 66.5, 59.0, 33.1, 29.8; δ$_F$ (282 MHz, CDCl$_3$) -100.2 (1F, d, $^2J_{F-F}$ 64.5), -109.8 (1F, dd, $^2J_{F-F}$ 64.5, $^4J_{H-F}$ 3.8), [HRMS (EI, [M$^+$]) Found: 252.11729. Calc. for C$_{11}$H$_{18}$O$_4$F$_2$: 252.11732]; *m/z* (CI$^+$) 270 (52 %, [M+NH$_4$]$^+$), 215 (10), 137 (10), 89 (100), 59 (99).

Preparation of 3-allyloxy-1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-diene 182
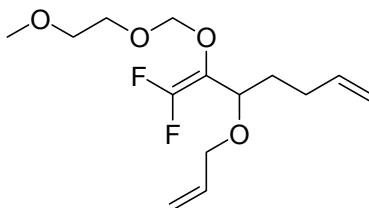
A mixture of difluoroallylic alcohol **178** (68.24 mmol, 17.40 g), and allyl bromide (81.90 mmol, 6.87 cm^3) was added over 1 min to a vigorously stirred solution of tetra-*n*-butylammonium hydrogensulphate (3.45 mmol, 1.16 g) and sodium hydroxide (488.39 mmol, 24.28 cm^3 of a 50% aqueous solution) at 0°C. The mixture was stirred at this temperature for 30 min then allowed to warm to room temperature, and stirred for a further 16 hours. The yellow white solution was diluted with water (40 cm^3) and the layers separated, the aqueous phase was then extracted with diethyl ether (4 x 100 cm^3). The combined organic extracts were washed with brine (2 x 30 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to afford the desired difluoroallylic ether **182** as a pale

yellow oil as the sole product by GC (18.24 g, 91 %, 100 %), which was used without any further purification; R_f (10 % diethyl ether in hexane) 0.42; υ_{max}(film)/cm^{-1} 2931s, 1748m, 1642w, 1453s, 1230s, 1114s; δ_H (300 MHz, CDCl$_3$) 5.96-5.83 (1H, m, =CHCH$_2$O), 5.81(1H, ddt, $^3J_{trans}$ 16.8, $^3J_{cis}$ 10.1, J 6.6, CH$_2$CH$_2$CH=), 5.28 (1H, d of AB dd, $^3J_{trans}$ 17.2, ^2J 3.0, ^4J 1.2, CH_aH$_b$=CHCH$_2$O), 5.19 (1H, d of AB dd, $^3J_{cis}$ 10.2, ^2J 3.0, ^4J 1.2, CH$_a$$H_b$=CHCH$_2$O), 5.09-4.94 (4H, env. containing 5.09-4.94 (2H, m, CH$_2$CH$_2$CH=CH_2) and 5.05 (1H, d, AB, ^2J 6.3 OCH_aH$_b$O), and 4.95 (1H, d, AB, ^2J 6.3, OCH$_a$$H_b$O), 4.10 (1H, ddt, ^2J 12.7, J 5.1, ^4J 1.2, OCH_aH$_b$CH=), 4.02 (1H, tdd, J 7.2, $^4J_{H-F}$ 3.8, 2.2, CCHO), 3.94-3.74 (3H, m, OCH$_a$$H_b$CH=, and OC$H_2CH_2$O), 3.61-3.57 (2H, m, OCH$_2$CH_2O), 3.41 (3H, s, CH_3), 2.13-2.06 (2H, m, CH$_2$CH_2CH=), 1.95-1.70 (2H, m, OCHCH_2); δ_C (75 MHz, CDCl$_3$) 156.0 (dd, $^1J_{C-F}$ 291.8, 282.8), 137.7, 134.3, 117.3, 115.1, 112.4 (dd, $^2J_{C-F}$ 36.8, 9.8), 97.1, 73.8, 71.6, 69.3, 68.3, 59.0, 31.0, 29.6; δ_F (282 MHz, CDCl$_3$) -97.7 (1F, dd, $^2J_{F-F}$ 63.5, $^4J_{F-H}$ 2.2), -109.5 (1F, dd, $^2J_{F-F}$ 63.5, $^4J_{F-H}$ 3.8); [HRMS (FAB, [M+H]$^+$) Found: 293.15634. Calc. for C$_{14}$H$_{23}$O$_4$F$_2$ 293.15634]; m/z (FAB) 293 (20 %, [M+H]$^+$), 215 (24), 165 (74), 137 (100), 89 (100), 59 (84).

Preparation of 4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-deca-1,5,9-trien-3-ol 183

Difluoroallylic ether **182** (34.25 mmol, 10.00 g) in THF (60 cm^3) was added dropwise over 15 min to a stirred solution of LDA (prepared by the slow addition of nBuLi (68.50 mmol, 28.30 cm^3, of a 2.42 M solution in hexane) to a cold (-78 ^{o}C) stirred solution of

diisopropylamine (75.30 mmol, 10.58 cm^3) in THF (342 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -100°C). The pale pink solution was stirred at this temperature for 30 min before being allowed to warm to -30°C over four hours and stirred for a further 3 hours at this temperature. During warming the solution was observed to change colour to yellow then through orange to brown and finally black. The reaction was quenched with ammonium chloride (10 cm^3 of a saturated methanolic solution) whereupon which the black colour disappeared and an orange/red solution was observed. The layers were separated and the aqueous phase extracted with diethyl ether (3 x 150 cm^3). The combined organic extracts were washed with brine (2 x 50 cm^3), dried with (MgSO$_4$), filtered, and concentrated under reduced pressure to give the product allylic alcohol **183** (8.71 g, 87%) as an red brown oil, 95% conversion by NMR and GC which was used without further purification. These data are obtained from a sample purified by flash chromatography on silica gel eluted with 30% diethyl ether/hexane; R$_f$ (30% ether/hexane) 0.12; υ_{max}(film)/cm^{-1} 3434br, 2928w, 1682w, 1641w, 1452w, 1252w, 1170s, 1112s, 1006s, 933s; δ_H (300 MHz, CDCl$_3$) 5.93 (1H, ddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.5, J 5.6, CHCH(OH)), 5.80 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.1, J 6.4, CH$_2$CH=CH$_2$), 5.57 (1H, td, J 7.3, ^4J 1.3, C(OMEM)=CHCH$_2$), 5.47 (1H, dt, $^3J_{trans}$ 17.2, ^2J 1.5, ^4J 1.5, CH_aH$_b$=CHCH), 5.35 (1H, dt, $^3J_{cis}$ 10.5, ^2J 1.5, ^4J 1.5, CH$_a$$H_b$=CHCH), 5.07-4.95 (4H, m, OCH_2O, and CH$_2$CH=CH_2), 4.50 (1H, broad s, =CHCH(OH)), 3.86 (1H, t, J 4.6, OCH_aH$_b$CH$_2$O), 3.85 (1H, t, J 4.6, OCH$_a$$H_bCH_2$O), 3.58 (2H, t, J 4.6, OCH$_2$CH_2O), 3.38 (3H, s, OCH_3), 2.92 (1H, broad s, OH), 2.35-2.25 (2H, m, C=CHCH_2), 2.20-2.08 (2H, m, CH$_2$CH_2CH=); δ_C (75 MHz, CDCl$_3$) 145.4 (dd, $^2J_{C-F}$ 27.5, $^2J_{C-F}$ 25.2), 135.5, 131.5, 119.8

(t, $^3J_{C-F}$ 5.43), 118.8, 118.2 (dd, $^1J_{C-F}$ 250.1, $^1J_{C-F}$ 247.1), 115.4, 97.2, 72.4 (dd, $^2J_{C-F}$ 30.5, $^2J_{C-F}$ 27.5), 70.5, 67.9, 58.0, 32.0, 23.6; δ_F (282 MHz, CDCl$_3$) -109.5 (1F, dd, $^2J_{F-F}$ 253.2, $^3J_{H-F}$ 8.3), 115.9 (1F, dd, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 14.7); [HRMS (FAB, MH$^+$) Found: 293.15648. Calc. For C$_{14}$H$_{23}$O$_4$F$_2$ 293.15648]; *m/z* (FAB) 293 (44 %, [M+H]$^+$), 137 (100), 89 (90), 59 (100).

Preparation Of 4,4-Difluoro-3-hydroxy-deca-1,9-dien-5-one 172

Thionyl chloride (3.54 mmol, 259 cm^3) was added to a stirred solution of enol ether **183** (3.54 mmol, 1.04 g) in methanol (35.4 cm^3) at 0 ^{o}C. The solution was allowed to warm to room temperature and stirred for 18 hours after which the solvent was removed in *vacuo*. The resulting paste was diluted with water (20 cm^3) and extracted with diethyl ether (3 x 30 cm^3). The combined organic extracts were washed with NaHCO$_3$ (20 cm^3), brine (50 cm^3), dried (MgSO$_4$), filtered and concentrated in v*acuo* to give ketone **172** (706 mg, 98%) as a brown oil, which could be used crude or purified by distillation (Kugelrohr bp.75-80°C/0.1 mmHg) to give ketone **172** as a clear oil (48 %, 100% GC); bp. 75-80 ^{o}C/0.098 mmHg; R$_f$ (10 % diethyl ether/hexane) 0.22; υ_{max}(film)/cm^{-1} 3380br, 3060w, 2994w, 1740w; δ_H (300 MHz, CDCl$_3$) 5.92 (1H, dddt, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.5, *J* 5.8, $^4J_{H-F}$ 0.6, =C*H*CH), 5.76 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, *J* 6.7, CH$_2$C*H*=), 5.50 (1H, dt, $^3J_{trans}$ 17.2, ^2J 1.3, ^4J 1.3, C*H*$_a$H$_b$=CHCH), 5.42 (1H, dt, $^3J_{cis}$ 10.5, ^2J 1.3, ^4J 1.3, CH$_a$*H*$_b$=CHCH), 5.07-4.97 (2H, m, CH$_2$CH=C*H*$_2$), 4.56-4.43 (1H, m, =CHC*H*), 2.72 (2H,

t, *J* 7.2, (O)CC*H₂*), 2.37 (1H, br s, O*H*), 2.18 (2H, q, *J* 7.2, C*H₂*CH=), 1.73 (2H, pent., *J* 7.2, CH₂C*H₂*CH₂); δ$_C$ (75 MHz, CDCl₃) 201.8 (dd, $^2J_{C-F}$ 30.9, 25.5), 137.5, 131.1, 120.4, 114.8 (dd, $^1J_{C-F}$ 258.8, 255.0), 115.6, 72.1 (dd, $^2J_{C-F}$ 28.1, 25.1), 37.1, 32.6, 21.4; δ$_F$ (282 MHz, CDCl₃) −113.7 (1F, dd, $^2J_{F-F}$ 273.0, $^3J_{F-H}$ 7.1), -123.3 (1F, dd, $^2J_{F-F}$ 273.0, $^3J_{F-H}$ 15.2); [HRMS (EI, M+H⁺) Found: 204.09621. Calc. for C₁₀H₁₄O₂F₂ 204.09621]; *m/z* (CI) 222 (100%, [M+NH₄]⁺), 204 (9).

Preparation of 3-benzyloxy-4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-deca-1,5Z,9-triene 188

Allylic alcohol (20.2 mmol, 5.9 g) **183** in THF (50 cm³) was cautiously added to a suspension of NaH (101 mmol, 4.04 g, of a 60% suspension in mineral oil, pre-washed with hexane 3 x 30 cm³) in THF at 0°C under a nitrogen atmosphere. The mixture was stirred at this temperature for 45 min and a gas was observed to evolve. TBAI (2.86 mmol, 1.05 g) and benzyl bromide (19.19 mmol, 2.28 cm³) were added, and the reaction allowed to warm to room temperature over 1 hour, and then stirred for a further 12 hours. The reaction was quenched by the cautious addition of water (150 cm³) and the layers separated. The aqueous layer was extracted by ethyl acetate (3 x 150 cm³) and the combined organic layers washed with brine (100 cm³), dried (MgSO₄), filtered, and

concentrated in *vacuo* to give benzyl ether **188** as a brown oil (7.10 g, 92%, 98% GC) which was used without any further purification. These data are from a small sample purified by flash chromatography on silica gel eluted with 20% diethyl ether/hexane; R_f (30% diethyl ether/hexane) 0.38; GC retention time 18.88 min; υ_{max}(film)/cm^{-1} 2923s, 1743w, 1678w, 1637w, 1454s, 1113s, 938s, 850w, 732w, 699s; δ_H (400 MHz, CDCl$_3$) 7.25-7.17 (5H, m, 5 x Ph-*H*), 5.77 (1H, ddd, $^3J_{trans}$ 17.5, $^3J_{cis}$ 10.1, *J* 7.4, =C*H*CH(OBn)), 5.72 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, *J* 6.5, CH$_2$C*H*=), 5.50 (1H, td, *J* 7.4, $^4J_{H-F}$ 1.4, C=C*H*), 5.38-5.36 (1H, m, C*H*$_a$H$_b$=CHCH), 5.35-5.32 (1H, m, CH$_a$*H*$_b$=CHCH), 4.98-4.92 (1H, apparent dq, $^3J_{trans}$ 17.1, ^2J 1.7, ^4J 1.7 CH$_2$CH=C*H*$_a$H$_b$), 4.89-4.87 (1H, apparent dq, $^3J_{cis}$ 10.2, ^2J 1.9, ^4J 1.9, CH$_2$CH=CH$_a$*H*$_b$), 4.87 (1H, d, AB, ^2J 5.9, OC*H*$_a$H$_b$O), 4.86 (1H, d, AB, ^2J 5.9, OCH$_a$*H*$_b$O), 4.58 (1H, AB, ^2J 11.9, PhC*H*$_a$H$_b$), 4.44 (1H, AB, ^2J 11.9, PhCH$_a$*H*$_b$), 4.14 (1H, dddt, $^3J_{H-F}$ 14.2, 8.5, *J* 7.4, ^4J 0.9 C*H*CF$_2$), 3.71 (1H, t, *J* 4.9, OC*H*$_a$H$_b$CH$_2$O), 3.69 (1H, t, *J* 4.4, OCH$_a$*H*$_b$CH$_2$O), 3.46 (2H, dd, *J* 4.4, 4.9, OCH$_2$C*H*$_2$O), 3.29 (3H, s, OC*H*$_3$), 2.26-2.18 (2H, m, OC=CHC*H*$_2$), 2.09-2.03 (2H, m, C*H*$_2$CH=CH$_2$); δ_c (100 MHz, CDCl$_3$) 145.4 (dd, $^2J_{C-F}$ 27.2, 24.8), 137.6, 137.5, 131.1 (dd, $^3J_{C-F}$ 3.6, 1.8), 128.3, 127.8, 127.7, 121.5, 119.7 (t, $^3J_{C-F}$ 5.1), 118.1 (dd, $^1J_{C-F}$ 251.0, 246.0), 115.3, 98.2, 79.0 (dd, $^2J_{C-F}$ 31.7, 25.7), 71.6, 71.4, 68.8, 59.0, 33.1, 24.6; δ_F (282 MHz, CDCl$_3$) -108.1 (1F, dd, $^2J_{F-F}$ 254.8, $^3J_{H-F}$ 8.5), -114.7 (1F, dd, $^2J_{F-F}$ 154.8, $^3J_{H-F}$ 14.2); No satisfactory ion could be obtained for this compound (ES, EI, CI, FAB).

Preparation of 3-Benzoyloxy-4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-deca-1,5Z,9-triene 189

Benzoic anhydride (7.93 mmol, 1.79 g), and DMAP (1.58 mmol, 0.194 g) were added to a solution of allylic alcohol **183** (7.93 mmol, 2.32 g) in pyridine (8 cm^3). The resulting solution was stirred for 24 hours at rt before being diluted with water (30 cm^3). The aqueous was extracted with diethyl ether (3 x 50 cm^3) and the combined organic extracts washed with cold HCl (2 x 30 cm^3 of a 10% solution), NaHCO$_3$ (2 x 30 cm^3), and brine (2 x 30 cm^3), then dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give benzoate **189** as a brown oil (2.02 g, 64 %, 100% GC) which was used without further purification. These data are obtained from a sample purified by flash chromatography on silica gel eluted with 20% diethyl ether/hexane; R$_f$ (30% diethyl ether/hexane) 0.27; GC retention time 23.17 min; υ_{max}(film)/cm^{-1} 2887w, 1730s, 1602w, 1452w, 1264s, 1096s, 988s, 709s; δ_H (300 MHz, CDCl$_3$) 8.09-8.05 (2H, m, Ph-*H*), 7.58 (1H, apparent tt, *J* 7.4, ^4J 1.4, Ph-*H*), 7.48-7.42 (2H, m, Ph-*H*), 6.01-5.89 (2H, m, =C*H*C*H*), 5.73 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, *J* 6.4, CH$_2$C*H*=CH$_2$), 5.62 (1H, t, *J* 7.5, C=C*H*), 5.53 (1H, dd, $^3J_{trans}$ 16.0, ^2J 1.3, C*H*$_a$H$_b$=CHCH), 5.43 (1H, dd, $^3J_{cis}$ 10.3, ^2J 1.3, CH$_a$*H*$_b$=CHCH), 5.00 (2H, s, OC*H*$_2$O), 5.00-4.90 (2H, m, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, CH$_2$CH=C*H*$_2$), 3.94-3.80 (2H, m, OC*H*$_2$CH$_2$O), 3.60-3.55 (2H, m, OCH$_2$C*H*$_2$O), 3.38 (3H, s, OC*H*$_3$), 2.33-2.23 (2H, m, CCHC*H*$_2$), 2.13-2.04 (2H, m, C*H*$_2$CH=CH$_2$); δ_C (75 MHz, CDCl$_3$) 164.8, 144.8 (t, $^2J_{C-F}$ 25.7), 137.3,

133.4, 129.9, 129.5, 128.9 (dd, $^3J_{C-F}$ 3.6, 1.8), 128.4, 121.4, 120.2 (t, $^3J_{C-F}$ 5.1), 117.3 (dd, $^1J_{C-F}$ 251.2, 247.4), 115.4, 98.3, 72.8 (dd, $^2J_{C-F}$ 31.7, 26.9), 71.6, 68.9, 59.0, 33.9, 24.5; δ_F (282 MHz, CDCl$_3$) -110.8 (1F, dd, AB, $^2J_{F-F}$ 253.2, $^3J_{H-F}$ 10.9), -112.4 (1F, dd, AB, $^2J_{F-F}$ 253.2, $^3J_{H-F}$ 12.3); [HRMS (EI, [M$^+$]) Found: 396.17473. Calc. for C$_{21}$H$_{26}$O$_5$F$_2$ 396.17473]); *m/z* (EI) 396 (3 %, [M+]$^+$), 355 (7), 220 (39), 205 (100), 145 (21), 106 (68).

Preparation of 3-Bromobenzene-sulfonyloxy-4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-deca-1,5Z,9-triene 193

Sodium hydride (2.24 mmol, 97 mg of a 60% suspension in mineral oil) was washed successively with hexane (3 x 2 cm^3) and suspended in THF (20 cm^3). The suspension was cooled to 0°C and allylic alcohol **183** (0.808 mmol, 236 mg) was added dropwise in THF (3.6 cm^3); the resulting solution stirred at this temperature for 2 hours. 4-Bromobenzenesulphonylchloride (0.97 mmol, 248 cm^3) was added in one portion and the solution allowed to warm to room temperature over two hours then stirred for 16 hours. TLC analysis showed incomplete conversion of starting material, the reaction was cooled to 0°C and pre washed sodium hydride (1.25 mmol, 50 mg), and 4-

bromobenzenesulphonyl chloride (0.587 mmol, 150 mg) were added then warmed to room temperature and stirred for 18 hours. The reaction was quenched with pH 7 buffer (30 cm^3), the layers separated and the aqueous extracted with ethyl acetate (2 x 20 cm^3). The combined organic layers were washed with brine (30 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to sulphone **193** as a brown oil (277 mg, 69%); R$_f$ (30% ether/hexane) 0.43; υ_{max}(film)/cm^{-1} 2923s, 1637w, 1576s, 1472m, 1377s, 1189s, 1067s, 1014s, 932s, 856s, 743s; δ_H (400 MHz, CDCl$_3$) 7.74 (2H, dt, AB, J 8.6, ^4J 2.1, Ph-*H*), 7.65 (2H, dt, AB, J 8.6, ^4J 2.1, Ph-*H*), 5.80-5.65 (env. containing, 5.80-5.65 (1H, m, CHC*H*=CH$_2$) and 5.68 (1H, dd, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, H$_2$C=C*H*CH$_2$), 5.49 (1H, t, J 7.3, C(O)=C*H*CH$_2$), 5.48 (1H, d, $^3J_{trans}$ 16.8, *H*$_a$H$_b$C=CHCH), 5.38 (1H, d, $^3J_{cis}$ 10.4, H$_a$*H*$_b$C=CHCH), 5.34 (1H td, $^3J_{H-F}$ 10.7, J 7.3, (O)C*H*CF$_2$), 5.00 (1H, m, inc. $^3J_{trans}$ 17.1, CH$_2$CH=C*H*$_a$H$_b$), 4.97 (1H, m, inc. $^3J_{cis}$ 10.2, CH$_2$CH=CH$_a$*H*$_b$), 4.90 (1H, s, OC*H*$_2$O), 3.81 (1H, dt, ^2J 10.6, J 4.3, OC*H*$_a$H$_b$CH$_2$O), 3.79 (1H, td, ^2J 10.6, J 4.3, OCH$_a$*H*$_b$CH$_2$O), 3.58-3.55 (2H, m, OCH$_2$C*H*$_2$O), 3.38 (3H, s, OC*H*$_3$), 2.27-2.12 (2H, m, C*H*$_2$CH=CH$_2$), 2.10-2.04 (2H, m, C=CHC*H*$_2$); δ_c (75MHz, CDCl$_3$) 143.6 (t, $^2J_{C-F}$ 25.7), 137.2, 136.0, 132.3, 129.4, 129.0, 127.8 (dd, $^3J_{C-F}$ 2.7, 2.7), 123.5, 121.0 (t, $^3J_{C-F}$ 5.1), 116.2 (dd, $^1J_{C-F}$ 251.9, 249.5), 115.5, 98.3, 79.9 (dd, $^2J_{C-F}$ 31.1, 28.1), 71.5, 68.9, 59.0, 32.8, 24.5; δ_F (282 MHz, CDCl$_3$) -111.3 (1F, dd, AB, $^1J_{F-F}$ 252.6, $^3J_{H-F}$ 10.7), -112.5 (1F, dd, AB, $^1J_{F-F}$ 252.6, $^3J_{H-F}$ 11.4); [HRMS (EI$^+$, [M]$^+$) Found: 510.05253. Calc. for C$_{20}$H$_{25}$F$_2$O$_6$^{79}BrS: 510.05233]; *m/z* (EI$^+$) 512 (1%, [M]$^+$), 435 (3), 376 (4), 254 (18), 221 (26), 220 (24), 157 (42), 155 (43), 109 (10), 89 (100), 59 (97).

Preparation of 3-Toluene-sulfonyloxy-4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-deca-1,5Z,9-triene 194

4-Methylbenzylsulphonyl chloride (1.1 mmol, 209 mg) and DMAP (0.4 mmol, 49 mg) were added in one portion to a stirred solution of enol ether **183** (1 mmol, 292 mg) in pyridine (1 cm^3) at 0$^\mathrm{o}$C. The solution was warmed to rt over 1 hour and then stirred for 18 hours. TLC analysis showed incomplete conversion of starting material and additional 4-methylbenzylsulphonyl chloride (0.9 mmol, 171 mg) was added at 0$^\mathrm{o}$C, the solution was warmed to rt over 1 hour and stirred for 8 hours until TLC showed consumption of starting material. The reaction mixture was diluted with water (15 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The combined organic layers were washed with 5% HCL solution (30 cm^3), NaHCO$_3$ (30 cm^3), and brine (30 cm^3), then dried (MgSO$_4$), filtered, then concentrated in *vacuo* to give tosylate **194** as a yellow oil (237 mg, 55%) which was used without further purification. R$_f$ (30% ether/hexane) 0.47; υ_{max}(film)/cm^{-1} 2926br, 1748w, 1677w, 1636w, 1595w, 1448w, 1373s, 1178s, 990s, 931s, 854s, 667s; δ_H (300 MHz, CDCl$_3$) 7.76-7.74 (2H, m, inc. *J* 8.4, Ph-*H*), 7.35-7.31 (2H, m, inc. *J* 8.4, Ph-*H*), 5.82-5.68 (2H, m, 2 x C*H*=CH$_2$), 5.50 (1H, t, *J* 7.2, =C*H*CH$_2$), 5.45 (1H, d, $^3J_{trans}$ 17.0, H$_a$H$_b$C=CHC*H*), 5.35 (1H, d, $^3J_{cis}$ 10.2, H$_a$*H$_b$*C=CHCH), 5.37-5.35 (1H, m, C*H*CF$_2$), 5.05-4.95 (2H, m, C*H$_2$*=CHCH$_2$), 4.92 (2H, s, OC*H$_2$*O), 3.85-3.79 (2H, m, OC*H$_2$*CH$_2$O),

3.58 (2H, t, J 4.5, OCH$_2$CH_2O), 3.39 (3H, s, OCH_3), 2.43 (3H, s, CCH_3), 2.25-2.13 (2H, m, C=CHCH_2), 2.11-2.02 (2H, m, CH_2CH=CH$_2$); δ_c (75 MHz, CDCl$_3$) 144.8, 143.8 (t, $^2J_{C-F}$ 25.7), 137.3, 134.1, 129.6, 128.1, (dd, $^3J_{C-F}$ 3.0, 2.4), 128.0, 123.0, 120.8 (t, $^3J_{C-F}$ 5.1), 116.3 (dd, $^1J_{C-F}$ 251.9, 248.9), 115.4, 98.2, 79.4 (dd, $^2J_{C-F}$ 31.1, 28.1), 71.5, 68.8, 59.0, 33.8, 24.5, 21.6; δ_F (282 MHz, CDCl$_3$) -111.2 (1F, dd, AB, $^2J_{F-F}$ 252.6, $^3J_{H-F}$ 10.4), -112.5 (1F, dd, AB, $^2J_{F-F}$ 252.6, $^3J_{H-F}$ 11.4); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 464.1913. Calc. for C$_{21}$H$_{28}$F$_2$O$_6$SN: 464.1913]; m/z (CI$^+$) 464 (94%, [M+NH$_4$]$^+$), 310 (62), 274 (73), 186 (38), 108 (72), 94 (100).

Preparation of 3-Benzyloxy-4,4-difluoro-deca-1,9-dien-5-one 195

Thionyl chloride (18.6 mmol, 1.34 cm^3) was added to a stirred solution of enol ether **188** (18.6 mmol, 7.10 g) in methanol (180 cm^3) at 0°C. The solution was allowed to warm to room temperature over 1 hour and stirred for 15 hours. The methanol was removed in *vacuo*, and the resulting paste dissolved in water (40 cm^3), and extracted with ethyl acetate (3 x 150 cm^3). The combined organic extracts were washed with NaHCO$_3$ (70 cm^3), brine (2 x 100 cm^3), dried (MgSO$_4$), filtered, and concentrated in vacuo to give ketone **195** as a yellow oil (5.13 g, 94%, 99% GC) which was used in the next step without purification. The following data were obtained from a sample purified by Flash

chromatography on silica gel eluted with 10% ether/hexane; R_f (30% ether/hexane) 0.68; GC retention time 17.73 min; (Found: C, 69.49; H, 6.98; $C_{17}H_{20}F_2O_2$ requires: C, 69.37; H, 6.85 %); υ_{max}(film)/cm^{-1} 1941w, 1740s, 1642w, 1455w, 1372w, 1217s, 1091s, 913s, 736s, 698s; δ_H (400 MHz, CDCl$_3$) 7.37-7.21 (5H, m, 5 x Ph-H), 5.85 (1H, ddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.5, J 7.6, =CHCH(O)), 5.72 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, J 6.7, =CHCH$_2$), 5.53 (1H, ddd, $^3J_{cis}$ 10.5, ^2J 1.4, ^4J 0.9, H_aH_bC=CHCH(O)), 5.48 (1H, ddd, $^3J_{trans}$ 17.2, ^2J 1.4, ^4J 0.9, H$_a$$H_b$C=CHCH(O)), 4.99 (1H, ddd, $^3J_{trans}$ 17.1, ^2J 3.4, ^4J 1.6, H_aH$_b$C=CHCH$_2$), 4.96 (1H, dddd, $^3J_{cis}$ 10.2, ^2J 3.4, ^4J 2.0, 1.2, H$_a$$H_b$C=CHCH$_2$), 4.61 (1H, AB, ^2J 11.5, PhCH_aH$_b$), 4.38 (1H, AB, ^2J 11.5, PhCH$_a$$H_b$), 4.26 (1H, dddt, $^3J_{H-F}$ 16.6, 6.6, J 7.6, ^4J 0.9, CH(O)CF$_2$), 2.68 (2H, tt, J 7.3, ^4J 1.7, C(O)CH_2), 2.03 (2H, tdd, J 7.3, 6.7, ^4J 1.2, CH$_2$CH_2=), 1.69 (2H, pent., J 7.3, CH$_2$CH_2CH$_2$); δ_c (75 MHz, CDCl$_3$) 201.7 (dd, $^2J_{C-F}$ 31.1, 25.1), 137.6, 136.8, 129.6 (dd, $^3J_{C-F}$ 3.6, 1.2), 128.4, 128.1, 128.0, 123.2, 115.4, 115.0 (dd, $^1J_{C-F}$ 261.5, 253.7), 79.4 (dd, $^2J_{C-F}$ 30.5, 23.9), 71.4, 37.6, 32.7, 21.5; δ_F (282 MHz, CDCl$_3$) -110.6 (1F, dd, $^2J_{F-F}$ 263.0, $^3J_{H-F}$ 6.6), -124.1 (1F, dd, $^2J_{F-F}$ 263.0, $^3J_{H-F}$ 16.6) [HRMS (CI$^+$, [M+NH$_4$]$^+$) Found: 312.1769. Calc. for $C_{17}H_{24}F_2O_2N$: 312.1770]; m/z (CI$^+$) 312 (100%, [M+NH$_4$]$^+$), 294 (4), 216 (33), 186 (20), 170 (9), 126 (8), 108 (11), 84 (8).

Preparation of 3-benzoyloxy-4-4-difluoro-deca-1,9-diene-5-one 196
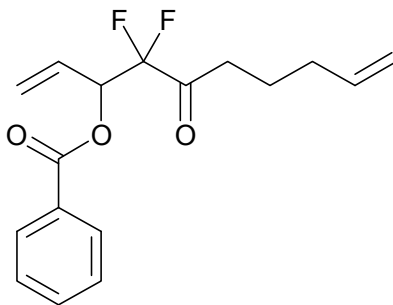
Thionyl chloride (0.39 mmol, 0.028 cm^3) was added to a stirred solution of enol ether **189** (0.39 mmol, 0.154 g) in methanol (3.9 cm^3) at 0 °C. The solution was allowed to warm to room temperature and stirred for 18 hours after which the solvent was removed in *vacuo*. The resulting paste was diluted with water (3 cm^3) and extracted with diethyl ether (3 x 10 cm^3). The combined organic extracts were washed with NaHCO$_3$ (10 cm^3), brine (15 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give ketone **196** (100 mg, 84%, 88% GC) as a brown oil, which could be used crude or purified by flash chromatography on silica gel eluted with 10 % ethyl acetate/hexane to give ketone **196** as a clear oil (67 mg, 56 %, 97 % GC); R$_f$ (10 % diethyl ether in hexane) 0.56; GC retention time 18.37 min; υ_{max}(film)/cm^{-1} 3076w, 2937w, 1733s, 1642w; δ_H (300 MHz, CDCl$_3$) 8.06-8.01 (2H, m, Ph-*H*), 7.60 (1H, apparent tt, *J* 7.5, ^{4}*J* 1.3, Ph-*H*), 7.49-7.42 (2H, m, Ph-*H*), 6.05-5.88 (2H, m, CH$_2$=C*H*(O)C*H*), 5.71 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, *J* 7.3, CH$_2$C*H*=CH$_2$), 5.57 (1H, dd, $^3J_{trans}$ 16.0, ^2J 0.9, C*H*$_a$H$_b$=CHCH), 5.50 (1H, dd, $^3J_{cis}$ 9.4, ^2J 0.9, CH$_a$*H*$_b$=CHCH), 5.02-4.94 (2H, m, inc. $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, CH$_2$CH=C*H*$_2$), 2.74 (2H, t, *J* 7.3, (O)=CC*H*$_2$), 2.05 (2H, q, *J* 7.3, C*H*$_2$CH=), 1.71 (2H, pent, *J* 7.3, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz, CDCl$_3$) 199.7 (dd, $^2J_{C\text{-}F}$ 28.7, 28.7), 164.4, 137.3, 133.7, 129.9, 128.9, 128.6, 127.7, 122.8, 115.7, 114.1 (dd, $^1J_{C\text{-}F}$ 260.9, 256.1), 72.4 (dd, $^2J_{C\text{-}F}$ 29.9, 25.1), 36.7, 32.6, 21.5; δ_F (282 MHz, CDCl$_3$) −113.7 (1F, dd, $^2J_{F\text{-}F}$ 274.4, $^3J_{F\text{-}H}$ 9.0),

-118.9 (1F, dd, $^2J_{F\text{-}F}$ 274.4, $^3J_{F\text{-}H}$ 14.2); [HRMS (EI, [M$^+$]) Found: 308.12240. Calc. for C$_{13}$H$_{18}$O$_2$F$_2$ 308.12242]); m/z (EI) 308 (37 %, [M+]$^+$), 105 (85).

Preparation of 3-Bromobenzene-sulfonyloxy-4,4-difluoro-deca-1,9-dien-5-one

197
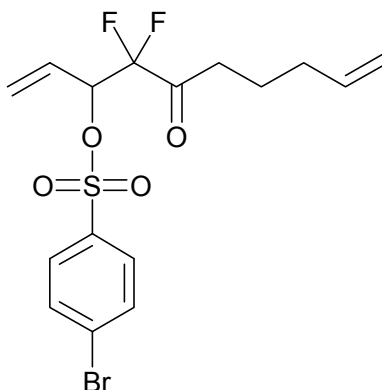
Thionyl chloride (0.561 mmol, 0.041 cm^3) was added to a stirred solution of enol ether **193** (0.561 mmol, 279 mg) in methanol (5.6 cm^3) at 0 ^{o}C. The solution was allowed to warm to room temperature and stirred for 18 hours after which the solvent was removed in *vacuo*. The resulting paste was diluted with water (10 cm^3) and extracted with diethyl ether (4 x 20 cm^3). The combined organic extracts were washed with NaHCO$_3$ (20 cm^3), brine (20 cm^3), dried (MgSO$_4$), filtered and concentrated in v*acuo* to give ketone **197** (210 mg, 88%) as a brown oil, which was used without further purification; R$_f$ (30% ether/hexane) 0.55; υ_{max}(film)/cm^{-1} 2928s, 1744s, 1576s, 1380s, 1191s, 1070s, 989s, 822s, 743s; δ_H (300 MHz, CDCl$_3$) 7.73 (2H, d, AB, J 8.8, Ph-H), 7.69 (2H, d, AB, J 8.8, Ph-H), 5.77 (1H, ddd, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.4, J 7.5, =CHCH(OH) 5.72 (1H, ddt, $^3J_{trans}$ 16.4, $^3J_{cis}$ 10.8, J 6.7, CH$_2$CH=), 5.52 (1H, d, $^3J_{trans}$ 17.0, H_aH$_b$C=CHCH), 5.47 (1H, d, $^3J_{cis}$ 10.4, H$_a$$H_b$C=CHCH), 5.38 (1H, ddd, $^3J_{H\text{-}F}$ 12.4, 9.0, J 7.5, CHCH(OH), 5.05-5.97 (2H, m,

CH$_2$CH=CH$_2$), 2.62 (2H, t, J 7.2, C(O)CH_2), 2.03 (2H, qt, J 7.2, ^4J 1.3, CH_2CH=), 1.65 (1H, pent., J 7.2 CH$_2$CH_aH$_b$CH$_2$), 1.64 (1H, pent., J 7.2, CH$_2$CH$_a$$H_bCH_2$); δ_c (75 MHz, CDCl$_3$) 199.4 (dd, $^2J_{C\text{-}F}$ 29.6, 27.8), 137.2, 135.5, 132.6, 129.5, 129.4, 126.6 (dd, $^3J_{C\text{-}F}$ 3.3, 2.1), 124.9, 115.8, 112.9 (dd, $^1J_{C\text{-}F}$ 263.3, 257.9), 79.2 (dd, $^2J_{C\text{-}F}$ 30.5, 25.7), 36.9, 32.6, 21.3; δ_F (282 MHz, CDCl$_3$) -113.8 (1F, dd, AB, $^2J_{F\text{-}F}$ 276.3, $^3J_{H\text{-}F}$ 9.0), -118.2 (1F, dd, AB, $^2J_{F\text{-}F}$ 276.3, $^3J_{H\text{-}F}$ 12.4); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 440.0340. Calc. for C$_{16}$H$_{21}$F$_2$O$_4$^{79}BrSN: 440.0340]; m/z (CI$^+$) 442 (100%, [M+NH$_4$]$^+$), 440 (93), 362 (18), 320 (9), 222 (22), 204 (21), 186 (84), 168 (30), 136 (29), 94 (63), 80 (47).

Preparation of 3-Toluene-sulfonyloxy-4,4-difluoro-deca-1,9-dien-5-one 198
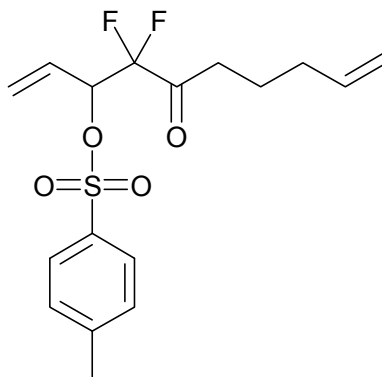
Thionyl chloride (0.307 mmol, 0.022 cm^3) was added to a stirred solution of enol ether **194** (0.307 mmol, 137 mg) in methanol (3.0 cm^3) at 0 ^{o}C. The solution was allowed to warm to room temperature and stirred for 18 hours after which the solvent was removed in *vacuo*. The resulting paste was diluted with water (15 cm^3) and extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts were washed with NaHCO$_3$ (20 cm^3), brine (20 cm^3), dried (MgSO$_4$), filtered and concentrated in v*acuo* to give ketone **198** (106 mg, 96%) as a brown oil, which could be used crude or purified by flash

chromatography on silica gel eluted with 10% ether/hexane to give **198** as a yellow oil (43 mg, 66%); R_f (30% ether/hexane) 0.48; υ_{max}(film)/cm^{-1} 2931br, 2355w, 1744s, 1637w, 1596w, 1376s, 1179s, 1095s, 992s, 815s, 674s; δ_H (300 MHz, CDCl$_3$) 7.76-7.74 (2H, m, J 8.4, Ph-H), 7.35-7.31 (2H, m, J 8.4, Ph-H), 5.76 (1H, ddd, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.4, J 7.4, =CHCH), 5.71 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.4, J 6.6, CH$_2$CH=), 5.48 (1H, dt, $^3J_{trans}$ 17.1, ^2J 0.9, ^4J 0.9 H_aH$_b$C=CHCH), 5.43 (1H, dt, $^3J_{cis}$ 10.4, ^2J 0.9, ^4J 0.9 H$_a$$H_b$C=CHCH), 5.33 (1H, dddt, $^3J_{H\text{-}F}$ 12.9, 8.9, J 7.4, ^4J 0.9, CHCF$_2$), 5.04-4.96 (2H, m, CH$_2$CH=CH_2), 2.61 (2H, td, J 7.2, ^4J 2.6, C(O)CH_2), 2.44 (3H, s, CH_3), 2.20 (2H, qt, J 7.2, ^4J 1.3, CH_2CH=), 1.68-1.59 (2H, m, inc. J 7.2, CH$_2$CH_2CH$_2$); δ_c (75 MHz, CDCl$_3$) 199.6 (dd, $^2J_{C\text{-}F}$ 29.3, 27.5), 145.4, 137.3, 133.4, 129.8, 128.0, 126.9 (dd, $^3J_{C\text{-}F}$ 3.3, 1.5), 124.4, 115.7, 113.1 (dd, $^1J_{C\text{-}F}$ 263.0, 257.6), 78.8, (dd, $^2J_{C\text{-}F}$ 31.1, 25.7), 37.0, 32.5, 21.7, 21.3; δ_F (282 MHz, CDCl$_3$) -113.4 (1F, dd, AB, $^2J_{F\text{-}F}$ 273.0, $^3J_{H\text{-}F}$ 8.9), -118.8 (1F, dd, AB, $^2J_{H\text{-}F}$ 273.0, $^3J_{H\text{-}F}$ 12.9); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 376.1387. Calc. for C$_{17}$H$_{24}$F$_2$O$_4$SN: 376.1389]; m/z (CI$^+$) 376 (100%, [M+NH$_4$]$^+$), 204 (7), 188 (17), 186 (62), 168 (39), 151 (31), 108 (35).

Preparation of 3-Benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one 200

Difluoroketone **195** (2.21 mmol, 0.650 g), and Ti(O^{i}Pr)$_4$ (0.66 mmol, 0.198 cm^3) were dissolved in freshly degassed DCM (1000 cm^3) under an atmosphere of nitrogen. The solution was refluxed for 30 min then 2nd Generation Grubbs catalyst (0.11 mmol, 94 mg, 5 mol%) was added via syringe in DCM (5 cm^3). Reflux was maintained for 18h upon which consumption of starting material was observed by ^{19}F NMR. The solvent was removed in *vacuo* and the residue taken up in diethyl ether (50 cm^3) then filtered through celite and concentrated to give crude cyclooctenone **200** as a brown oil. The oil was then taken up in methanol and filtered through a stratosphere SPE column concentrated in *vacuo* and purified by flash column chromatography on silica gel eluted with 10% ether/hexane to give cyclooctenone **200** as a yellow solid (440 mg, 75%, 96% GC); R$_f$ (30% diethyl ether/hexane) 0.40; Mp. 32-35°C; GC retention time 18.83 min.; (Found: C, 67.59; H, 6.15; C$_{15}$H$_{16}$F$_2$O$_2$ requires: C, 67.66; H, 6.06 %); υ_{max}(solid)/cm^{-1} 2866s, 1743s, 1648w, 1497w, 1455s, 1185s, 1100s, 1070s, 992w, 845s, 812s, 737s, 698s; δ_H (300 MHz, CDCl$_3$) 7.40-4.22 (5H, m, 5 x Ph-*H*), 5.99-5.88 (1H, m, inc $^3J_{cis}$ 11.1, CH$_2$C*H*=), 5.60 (1H, ddd, $^3J_{cis}$ 11.1, *J* 8.0, ^4J 2.6, =C*H*CH(O)), 4.76 (1H, AB, ^2J 12.0, PhC*H*$_a$H$_b$), 4.66 (1H, AB, ^2J 12.0, PhCH$_a$*H*$_b$), 4.66 (1H, dddd, $^3J_{H-F}$ 20.0, 4.7, *J* 8.0, ^4J 1.3, CHC*H*(O)), 2.60-2.48 (2H, m, C*H*$_2$CO) 2.28 (1H, dddd, *J* 13.7 11.1, 5.6, ^4J 2.7 ,=CHC*H*$_a$H$_b$), 2.04-

1.86 (2H, m, =CCH$_a$H$_b$CH$_a$H$_b$), 1.80-1.46 (1H, m, =CCH$_2$CH$_a$H$_b$); δ_c (75 MHz, CDCl$_3$) 200.4 (dd, $^2J_{\text{C-F}}$ 26.6, 24.8), 137.0, 135.4, 128.6, 128.1, 128.0, 127.7 (d, $^3J_{\text{C-F}}$ 6.0), 117.8 (dd, $^1J_{\text{C-F}}$ 263.9, 258.5), 73.0 (dd, $^2J_{\text{C-F}}$ 23.3, 19.7), 72.1, 36.7, 27.4, 27.1; δ_F (376 MHz, 323K, CDCl$_3$) -110.9 (1F, d, $^2J_{\text{F-F}}$ 240.4), -130.8 (1F, dd, $^2J_{\text{F-F}}$ 240.4, $^3J_{\text{H-F}}$ 19.5); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 284.1457. Calc. for C$_{15}$H$_{20}$F$_2$O$_2$N: 284.1456]; *m/z* (CI$^+$) 284 (100%, [M+NH$_4$]$^+$), 270 (5), 220 (3), 158 (7), 140 (11), 123 (6), 90 (8).

Preparation of 3-Benzoyloxy-2,2-difluoro-cyclooct-4Z-en-1-one 201

Difluoroketone **196** (4.07 mmol, 1.26 g), and Ti(O^{i}Pr)$_4$ (1.21 mmol, 0.365 cm^3) were dissolved in freshly degassed DCM (407 cm^3) under an atmosphere of nitrogen. The solution was refluxed for 30 min then 2nd Generation Grubbs catalyst (0.203 mmol, 173 mg, 5 mol%) was added *via* syringe in DCM (5 cm^3). Reflux was maintained for 18 hours upon which consumption of starting material was observed by ^{19}F NMR. The solvent was removed *in vacuo* and the residue taken up in diethyl ether (30 cm^3) then filtered and concentrated to give crude cyclooctenone **201** as a brown oil which was purified by flash column chromatography on silica gel eluted with 10% ether/hexane to give

cyclooctenone **201** as a white solid; (0.531 mg, 46%, 96% GC); R_f (10 % diethyl ether in hexane) 0.20; Mp. 91-90°C; (Found C, 64.31%; H, 5.16%; $C_{15}H_{14}F_2O_3$ requires: C, 64.28 %; H, 5.03 %); υ_{max} (solid)/cm^{-1} 2968m, 2919m, 1725w, 1743w; δ_H (300MHz, CDCl$_3$) 8.14-8.10 (2H, m, Ph-H), 7.64-7.58 (1H, m, Ph-H), 7.52-7.45 (2H, m, Ph-H), 6.36 (dddd, 1H, $^3J_{H\text{-}F}$ 21.3, J 7.8, ^4J 3.8, ^5J 1.5, CHCF$_2$), 6.07-5.96 (1H, m, =CHCH$_2$), 5.65 (1H, ddd, ^3J 11.0, 7.8, ^4J 2.5, =CHCH), 2.82 (1H, dddd, ^2J 12.6, J 10.4, 3.9, ^4J 2.0, (O)CCH_aH_b), 2.68 (1H, ddt, ^2J 12.6, ^3J 7.2, ^4J 3.7, (O)CCH$_a$$H_b$), 2.44-2.27 (2H, m, =CHCH_2), 2.13-2.02 (1H, m, CH$_2$CH_aH$_b$CH$_2$), 1.89-1.74 (1H, m, CH$_2$CH$_a$$H_bCH_2$); δ_C (75 MHz, CDCl$_3$) 199.5 (t, $^2J_{C\text{-}F}$ 25.5), 165.2, 135.6, 133.7, 130.0, 129.0, 128.6, 125.3, 116.6 (dd, $^1J_{C\text{-}F}$ 262.6, 260.0), 68.2 (dd, $^2J_{C\text{-}F}$ 24.2, 18.9), 36.8, 27.5, 27.1; δ_F (282MHz, CDCl$_3$) −111.0 (1F, d, $^2J_{F\text{-}F}$ 239.8), -130.9 (1F, dd, $^2J_{F\text{-}F}$ 239.8, $^3J_{F\text{-}H}$ 21.3); m/z (ES$^+$) 281 (M+H$^+$, 42%), 121 (PhCOO, 100%).

Preparation of 4-Bromo-benzenesulfonic acid 8,8-difluoro-7-oxo-cyclooct-2-enyl ester 202

Difluoroketone **197** (0.425 mmol, 0.180 g), and Ti(O^{i}Pr)$_4$ (0.222 mmol, 0.063 cm^3) were dissolved in freshly degassed DCM (148 cm^3) under an atmosphere of nitrogen. The solution was refluxed for 30 min then 2nd Generation Grubbs catalyst (0.037 mmol, 31 mg, 8.7 mol%) was added in one portion. Reflux was maintained for 18h upon which

consumption of starting material was observed by ^{19}F NMR. The solvent was removed in *vacuo* and the residue taken up in diethyl ether then filtered and concentrated to give crude cyclooctenone **202** as a brown oil which was purified by flash column chromatography on silica gel eluted with 20% then 30% ether/hexane to give cyclooctenone **202** as a brown solid (0.082 g, 41%, 91% GC); R_f (50% ether/hexane) 0.18; Mp. 113-115°C; GC retention time 24.75 min.; (Found: C, 42.37; H, 3.40; $C_{14}H_{13}F_2O_4BrS$ requires: C, 42.55; H, 3.32 %); υ_{max}(solid)/cm^{-1} 2966s, 1747s, 1575s, 1471w, 1374s, 1184s, 1086s, 980s, 908s, 859s 737s; δ_H (400 MHz, CDCl$_3$) 7.81 (2H, ddd, AB, J 8.8, ^4J 2.2, ^5J 2.1, Ph-*H*), 7.72 (2H, ddd, AB, J 8.8, ^4J 2.2, ^5J 2.1, Ph-*H*), 5.96 (1H, dddd, J 11.0, 9.3, 7.9, ^4J 1.3, =C*H*CH$_2$), 5.74 (1H, dddd, $^3J_{H-F}$ 19.5, J 8.0, $^3J_{H-F}$ 3.7, ^4J 1.3, =CHC*H*(O)), 5.52 (1H, ddddd, J 11.0, 8.0, $^4J_{H-F}$ 2.4, ^4J 1.3, $^4J_{H-F}$ 1.2, CHC*H*=), 2.67 (2H, env. containing 2.67 (1H, dddd, ^2J 12.7, J 12.8, ^4J 4.0, $^3J_{H-F}$ 1.9, C(O)C*H*$_a$H$_b$), and 2.67-2.60 (1H, m, ^4J 4.2, C(O)CH$_a$*H*$_b$)), 2.38 (1H, dddd, J 13.2, 7.9, ^4J 5.1, 3.1, =CHC*H*$_a$H$_b$), 2.17 (1H, ddddd, J 13.2, 9.3, ^4J 3.1, 1.3, =CHCH$_a$*H*$_b$), 2.10-2.01 (1H, m, CH$_2$C*H*$_a$H$_b$CH$_2$), 1.76 (1H, ddddd, ^2J 14.1, J 12.8, 9.8, ^4J 4.2, 3.1, CH$_2$CH$_a$*H*$_b$CH$_2$); δ_c (75 MHz, CDCl$_3$) 198.2 (dd, $^2J_{C-F}$ 25.7, 24.5), 136.3, 135.4, 132.6, 129.6, 129.3, 124.1 (d, $^3J_{C-F}$ 4.2), 115.5 (dd, $^1J_{C-F}$ 264.2, 261.8), 74.5 (dd, $^3J_{C-F}$ 24.5, 19.7), 36.8, 27.5, 27.0; δ_F (282 MHz, CDCl$_3$) -109.6 (1F, d, $^2J_{F-F}$ 239.8), -131.7 (1F, dd, $^2J_{F-F}$ 239.8, $^3J_{H-F}$ 19.5); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 412.0027. Calc. for $C_{14}H_{17}F_2O_4{}^{79}BrSN$: 412.0024]; *m/z* (CI$^+$) 414 (23%, [M+NH$_4$]$^+$), 412 (22), 234 (5), 194 (9), 178 (23), 176 (24), 158 (100), 140 (31), 112 (28), 94 (50), 84 (30), 72 (28).

Preparation of Toluene-4-sulfonic acid 8,8-difluoro-7-oxo-cyclooct-2-enyl ester 203

Difluoroketone **198** (0.789 mmol, 0.283 g), and Ti(O^{i}Pr)$_4$ (0.236 mmol, 0.071 cm^3) were dissolved in freshly degassed DCM (80 cm^3) under an atmosphere of nitrogen. The solution was refluxed for 30 min then 2nd Generation Grubbs catalyst (0.039 mmol, 33 mg, 5 mol%) was added in one portion. Reflux was maintained for 18 hours upon which consumption of starting material was observed by ^{19}F NMR. The solvent was removed in *vacuo* and the residue taken up in diethyl ether then filtered and concentrated to give crude cyclooctenone **203** as a brown oil which was purified by Flash column chromatography on silica gel eluted with 30% ether/hexane to give cyclooctenone **203** as a white solid (0.100 g, 38%, 96% GC); R$_f$ (30% ether/hexane) 0.09; Mp. 67-70°C; GC retention time 22.80; (Found: C, 54.36; H, 4.70; C$_{15}$H$_{16}$F$_2$O$_4$S requires: C, 54.54; H, 4.88 %); υ_{max}(solid)/cm^{-1} 2958w, 1739s, 1598w, 1439w, 1376s, 1177s, 1079s, 986s, 906s, 858s, 713s, 669s; δ_H (300 MHz, CDCl$_3$) 7.82 (2H, d, *J* 8.1, Ph-*H*), 7.35 (2H, d, *J* 8.1, Ph-*H*), 5.91 (1H, dt, $^3J_{cis}$ 11.0, *J* 9.0, CH$_2$C*H*=), 5.70 (1H, ddd, $^3J_{H-F}$ 20.6, *J* 8.6, ^4J 3.9, C*H*CF$_2$), 5.51 (1H, dd, $^3J_{cis}$ 11.0, *J* 8.6, CHC*H*=), 2.72-2.58 (2H, m, C(O)C*H$_2$*), 2.43 (3H, s, CC*H$_3$*), 2.41-2.30 (1H, m, =CHC*H$_a$*H$_b$), 2.22-2.08 (1H, m, =CHCH$_a$*H$_b$*), 2.08-1.98 (1H, m, CH$_2$C*H$_a$*H$_b$CH$_2$), 1.83-1.71 (1H, m, CH$_2$CH$_a$*H$_b$*CH$_2$); δ_c (75 MHz, CDCl$_3$) 198.4 (dd, $^2J_{C-F}$ 26.0, 24.2), 145.5, 135.9, 133.3, 129.9, 127.9, 124.5 (d, $^3J_{C-F}$ 4.8), 115.5 (dd, $^1J_{C-F}$ 264.2, 261.8), 73.8 (dd, $^2J_{C-F}$ 24.5, 19.7), 36.8, 27.5, 27.1, 21.7; δ_F (282 MHz, CDCl$_3$) -

109.8 (1F, d, $^2J_{F-F}$ 240.3), -131.8 (1F, dd, $^2J_{F-F}$ 240.3, $^3J_{H-F}$ 20.6); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 348.1077. Calc. for C$_{15}$H$_{20}$F$_2$O$_4$SN: 348.1076]; m/z (CI$^+$) 348 (70%, [M+NH$_4$]$^+$), 176 (21), 158 (100), 140 (35), 124 (24), 108 (60), 95 (29).

Preparation of (±)-*Syn* and achiral and *meso* 3,16-dibenzyloxy-4,4,15,15-tetrafluoro-octadeca-1,9*E*,17-trien-5,14-diones 233 and 234

A solution of difluoroketone **200** (0.190 mmol, 56 mg), Ti(O^{i}Pr)$_4$ (0.063 mmol, 0.019 cm^3), and Neolyst catalyst (0.0095 mmol, 9 mg, 10%) in freshly degassed DCM (25 cm^3) was refluxed under a nitrogen atmosphere for 18 hours. The solvent was removed in *vacuo* and the residue dissolved in diethyl ether, the solids were removed by filtration through celite and the filtrate concentrated in *vacuo* to leave a black oil which was purified by Flash chromatography on silica gel eluted with 20% diethyl ether/hexane to give dimers **233** and **234** as an inseparable yellow oil (20 mg, 38%); R$_f$ (10% diethyl ether/hexane) 0.40; υ_{max}(film)/cm^{-1} 2933s, 1730s, 1455w, 1402w, 1208w, 1098s, 738s, 699s; δ_H (300MHz, CDCl$_3$) 7.39-7.28 (10H, m, 10 x Ph-*H*), 5.85 (2H, ddd, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.5, *J* 7.4, 2 x CH$_2$=C*H*), 5.53 (2H, d, $^3J_{cis}$ 10.5, 2 x C*H*$_a$H$_b$=CH), 5.48 (2H, d, $^3J_{trans}$ 17.1, 2 x CH$_a$*H*$_b$=CH), 5.30 (2H, t, ^3J 3.8, C*H*=C*H*), 4.61 (2H, d, AB, ^2J 11.6, 2 x

PhCH_aH$_b$), 4.38 (2H, d, AB, ^2J 11.6, 2 x PhCH$_a$$H_b$), 4.25 (2H, dt, $^3J_{H-F}$ 16.4, J 7.4, 2 x
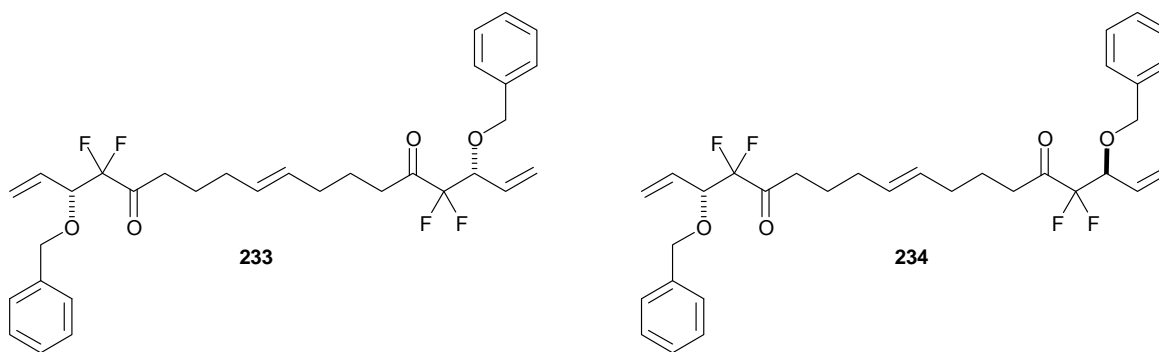
CHCF$_2$), 2.69-2.61 (4H, m, 2 x C(O)CH_2), 2.00-1.90 (4H, m, 2 x CH$_2$CH=), 1.63 (4H,

quintet, ^3J 7.3, 2 x CH$_2$CH_2CH$_2$); δ_C (100MHz, CDCl$_3$) 201.7 (dd, $^2J_{C-F}$ 31.2, 25.6), 201.6

(dd, $^2J_{C-F}$ 32.0, 24.8), 136.8, 130.2, 129.6, 128.4, 128.1, 128.0, 128.0, 123.2, 115.0 (dd,

$^1J_{C-F}$ 262.0, 254.0), 79.3 (dd, $^2J_{C-F}$ 31.2, 24.0), 71.4, 37.7, 37.6, 31.5, 26.2, 22.3, 22.1; δ_F

{^{1}H} (282 MHz, CDCl$_3$) −110.7 (4F, d, $^2J_{F-F}$ 263.5), -124.0 (2F, d, $^2J_{F-F}$ 263.5), -124.1

(1F, d, $^2J_{F-F}$ 263.5), -124.1 (1F, d, $^2J_{F-F}$ 263.5); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found:

578.2899. Calc. for C$_{32}$H$_{40}$F$_4$O$_4$N: 578.2888]; m/z (CI$^+$) 578 (24%, [M+NH$_4$]$^+$), 358 (13),

172 (38), 106 (100); and cyclooctenone **200** (2 mg, 4%) as a yellow oil; characterised

above, and recovered starting material **195** (20 mg, 36%).

The structural assignment advanced in the thesis is based on the assumption that the

alkene configuration is E and that the stereoisomers arise from the sp^3 stereogenic centres.

However there is an alternative explanation; alkene cross metathesis is known to produce

E/Z mixtures, and it may be that the additional peaks arise from the presence of the E/Z

diastereoisomers. We are not able to distinguish between these possibilities on the basis

of the evidence available.

Preparation of (±)-*Syn* and achiral and *meso* 3,16-dibenzoyloxy-4,4,15,15-tetrafluoro-octadeca-1,9*E*,17-trien-5,14-diones 235a and 235b
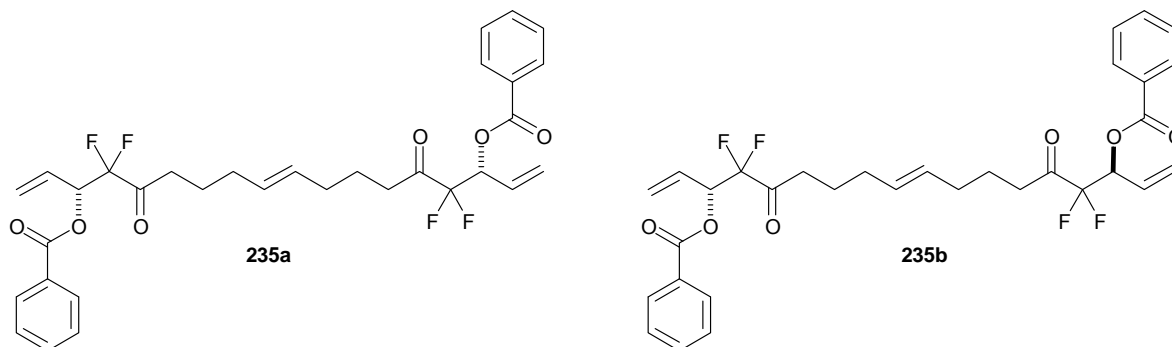
Titanium *iso*-propoxide (0.051 mmol, 15.2 μl) was added to a solution of difluoroketone **196** (0.17 mmol, 52 mg) in freshly degassed DCM (8.5 cm^3) and refluxed under a nitrogen atmosphere for 20 min. Neolyst catalyst (0.0084 mmol, 8 mg, 5 mol%) was added and the resulting solution refluxed for 18 hours. The solvent was removed in *vacuo* and the residue dissolved in diethyl ether, the solids were removed by filtration through celite and the filtrate concentrated in *vacuo* to leave a black oil which was purified by Flash chromatography on silica gel eluted with 10% diethyl ether/hexane to give dimers **235a** and **235b** as an inseparable yellow oil (14 mg, 34%); R$_f$ (30% diethyl ether/hexane) 0.24; υ_{max}(film)/cm^{-1} 2935s, 1742s, 1601w, 1452s, 1264s, 1108s, 987w, 711s; δ$_H$ (300MHz, CDCl$_3$) 8.06-8.01 (4H, m, 4 x Ph-*H*), 7.63-7.56 (2H, m, 2 x Ph-*H*), 7.49-7.42 (4H, m, 4 x Ph-*H*), 6.05-5.87 (4H, m, 2 x =C*H*C*H*CF$_2$), 5.57 (2H, d, $^3J_{trans}$ 16.0, 2 x C*H*$_a$H$_b$=), 5.50 (2H, d, $^3J_{cis}$ 9.4, 2 x CH$_a$*H*$_b$=), 5.32-5.27 (2H, m, C*H*=C*H*), 2.65 (4H, t, *J* 7.2, (O)CC*H*$_2$), 2.00-1.91 (4H, m, 2 x C*H*$_2$CH=), 1.65 (2H, quintet, *J* 7.2, diastereomer a CH$_2$C*H*$_2$CH$_2$), 1.65 (2H, quintet, *J* 7.3, diastereomer b CH$_2$C*H*$_2$CH$_2$); δ$_C$ (100MHz, CDCl$_3$) 199.7 (dd, $^2J_{C-F}$ 29.6, 28.0), 164.3 (d, $^4J_{C-F}$ 1.6), 133.7, 130.1, 129.8, 129.5, 129.0 (d, $^5J_{C-F}$ 2.4), 128.6, 127.7-127.6 (m), 122.8, 114.1 (dd, $^1J_{C-F}$ 262.0, 255.6), 72.34 (dd,

$^2J_{C-F}$ 30.0, 25.2), 72.31 (dd, $^2J_{C-F}$ 30.0, 25.2), 36.9, 36.7, 31.4, 26.1, 22.3, 22.1; δ_F {^{1}H}

(282 MHz, CDCl$_3$) –113.6 (1F, d, $^2J_{F-F}$ 274.4), -113.6 (1F, d, $^3J_{F-F}$ 274.4), -113.7 (2F, d,

$^2J_{F-F}$ 274.9), -118.8 (1F, d, $^2J_{F-F}$ 274.9), -118.8 (1F, d, $^2J_{F-F}$ 274.9), -118.9 (1F, d, $^2J_{F-F}$

274.4), -118.9 (1F, d, $^2J_{F-F}$ 274.4); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 606.2470. Calc. for

C$_{32}$H$_{36}$F$_4$O$_6$N: 606.2473]; m/z (ES$^+$) 611 (100%, [M+Na]$^+$), 419 (14), and recovered

starting material **196** (22mg, 42%) as a yellow oil; characterised above

The structural assignment advanced in the thesis is based on the assumption that the

alkene configuration is E and that the stereoisomers arise from the sp^3 stereogenic centres.

However there is an alternative explanation; alkene cross metathesis is known to produce

E/Z mixtures, and it may be that the additional peaks arise from the presence of the E/Z

diastereoisomers. We are not able to distinguish between these possibilities on the basis

of the evidence available.

Preparation of 2*R**-Benzyloxy-3,3-difluoro-9-oxa-(1*S**,8*S**)-bicyclo[6.1.0]nonan-4-
one 250**
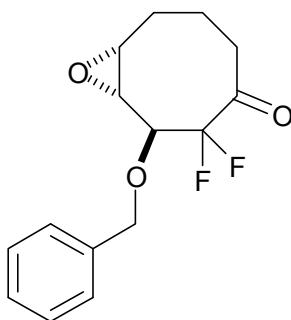
Cyclooctenone **200** (2.33 mmol, 0.620 g) was dissolved in a biphasic solution of

Na$_2$EDTA (9.3 cm^3 of a 4 x 10^{-4} mol l^{-1} aqueous solution) and acetonitrile (23.3 cm^3).

The mixture was cooled to 0°C and trifluoroacetone (4.7 cm^3 of a 60% aqueous solution) was added *via* a pre-cooled syringe to the stirred solution, then NaHCO$_3$ (34.95 mmol, 2.94 g) and oxone (11.65 mmol, 7.16 g) were added in one portion and the reaction mixture was stirred for 6 hours at 0°C. The solid residues removed by filtration through celite, chloroform (150 cm^3) and water (30 cm^3) were added and the layers separated, the aqueous layer was extracted with chloroform (2 x 50 cm^3); the combined organic layers were washed with brine (50 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give a brown oil. Purification on silica column eluted with 20% ether/hexane gave the product epoxide **250** as a white solid (495 mg, 75 %, 98% GC); R$_f$ (30% diethyl ether/hexane) 0.20; Mp. 70-73°C; GC retention time 20.05 min.; (Found: C, 63.77; H, 5.78; C$_{15}$H$_{16}$F$_2$O$_3$ requires: C, 63.82; H, 5.71 %); υ_{max}(solid)/cm^{-1} 3465w, 2923w, 1744s, 1499w, 1452s, 1340w, 1236w, 1193s, 1105s, 1083s, 1019s, 1028s, 969s, 862s, 830s, 755s, 702s; δ_H (400 MHz, CDCl$_3$) 7.44-7.29 (5H, m, 5 x Ph-*H*), 4.89 (1H, d, AB, ^2J 11.9, PhC*H*$_a$H$_b$), 4.85 (1H, d, AB, ^2J 11.9, PhCH$_a$*H*$_b$), 3.68 (1H, ddd, $^3J_{H-F}$ 20.3, *J* 8.6, ^4J 4.7, CF$_2$C*H*(O)), 3.07 (1H, ddt, *J* 8.6, 4.7, ^4J 1.6, C*H*CH(O)CF$_2$), 2.90 (1H, dt, *J* 10.7, 4.7, ^4J 4.7 CH$_2$C*H*(O)CH), 2.76-2.68 (1H, m, C(=O)C*H*$_a$H$_b$CH$_2$), 2.48 (1H, dddd, ^2J 13.4, *J* 9.4, *J* 4.4, ^4J 2.2, C(=O)CH$_a$*H*$_b$CH$_2$), 2.36 (1H, dtd, ^2J 14.5, *J* 4.5, 4.5, 3.1, CHC*H*$_a$H$_b$), 2.09-1.99 (1H, m, CH$_2$C*H*$_a$H$_b$CH$_2$), 1.97-1.85 (1H, m, CH$_2$CH$_a$*H*$_b$CH$_2$), 1.02 (1H, dddd, ^2J 14.5, *J* 13.7, 10.7, 3.3, CHCH$_a$*H*$_b$); δ_c (75 MHz, CDCl$_3$) 201.1 (t, $^2J_{C-F}$ 25.7), 136.8, 128.5, 128.2, 128.1, 115.6 (dd, $^1J_{C-F}$ 161.5, 157.9), 75.3 (dd, $^2J_{C-F}$ 22.4, 18.7), 73.2 (d, $^4J_{C-F}$ 1.2), 54.6 (d, $^3J_{C-F}$ 10.8), 53.8, 35.8, 28.3, 24.0; δ_F (282 MHz, CDCl$_3$) -113.6 (1F, d, $^2J_{F-F}$ 245.9), -128.8 (1F, dd, $^2J_{F-F}$ 245.9, $^3J_{H-F}$ 20.3); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found:

300.1409. Calc. for $C_{15}H_{20}F_2O_3N$: 300.1406]; m/z (CI$^+$) 300 (100%, [M+NH$_4$]$^+$), 282 (6), 262 (2), 174 (3), 125 (3), 108 (3).

Crystal data: $C_{15}H_{16}F_2O_3$, crystal size 0.17 x 0.15 x 0.08 mm^3, M = 282.28, monoclinic, a = 7.9759(19) Å, b = 11.944(3) Å, c = 14.467(3) Å, α= 90°, β= 96.970(4)°, γ = 90°, U = 1368.0(6) Å^3, T = 150(2) K, space group P2(1)/c, Z = 4, μ(Mo-Kα) = 0.112 mm^{-1}, 9474 reflections measured, 2406 [R(int) = 0.0778] which were used in all calculations. Final R indices [F^2>σ(F^2)] R1 = 0.1209, wR2 = 0.2973; R indices (all data) R1 = 0.1403, wR2 = 0.3116.

Preparation of 2R*-Benzoyloxy-3,3-difluoro-9-oxa-(1S*,8S*)-bicyclo[6.1.0]nonan-4-one 251
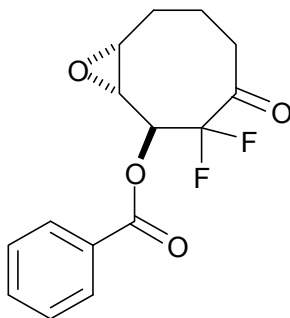
Cyclooctenone **201** (1.21 mmol, 0.338 mg) was dissolved in a biphasic solution of Na$_2$EDTA (4.84 cm^3 of a 4 x 10^{-4} mol l^{-1} aqueous solution) and acetonitrile (12.1 cm^3). The mixture was cooled to 0°C and trifluoroacetone (2.42 cm^3 of a 60% aqueous solution) was added *via* a pre-cooled syringe. The reaction mixture was stirred and NaHCO$_3$ (18.76 mmol, 1.38 g) and oxone (6.05 mmol, 3.72 g) were added in one portion. The reaction mixture was stirred for 18 hours at 0°C and the solid residues removed by

filtration through celite. DCM (100 cm^3) and water (10 cm^3) were added and the layers separated, the aqueous layer extracted by DCM (2 x 50 cm^3), the combined organic layers were washed with brine (50 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give **251** as a white solid (228 mg, 64%) which required no further purification; R$_f$ (50% Ethyl acetate/ hexane) 0.34; Mp. 75-78°C ; (Found; C, 60.9; H, 4.8. C$_{15}$H$_{14}$F$_2$O$_4$ requires C, 60.8; H, 4.8%); ν$_{max}$ (solid)/cm^{-1} 2954w, 1736, 1602w, 1453w, 1249s, 1080s, 973s, 707s; δ$_H$ (300MHz, CDCl$_3$) 8.18-8.13 (2H, m, Ph-*H*), 7.65-7.59 (1H, m, Ph-*H*), 7.52-7.43 (1H, m, Ph-*H*), 5.59 (1H, ddd, $^3J_{H-F}$ 20.9, *J* 8.9, $^3J_{H-F}$ 4.4, CF$_2$C*H*), 3.24 (1H, ddt, *J* 8.9, *J* 4.4, $^3J_{H-F}$ 1.2, CH(O)C*H*CH(O)), 3.04 (1H, dt, *J* 10.6, 4.4, ^4J 4.4 (O)C*H*CH$_2$), 2.85-2.65 (2H, m, C*H$_2$*C(O)), 2.48 (1H, dddd, ^2J 14.7, *J* 4.5, 4.3 2.9, CHC*H*$_a$H$_b$), 2.20-2.09 (1H, m, CH$_2$C*H*$_a$H$_b$CH$_2$), 2.05-1.90 (1H, m, CH$_2$CH$_a$*H*$_b$CH$_2$), 1.37 (1H, dddd, ^2J 14.7, *J* 13.6, 10.6, 3.4, CHCH$_a$*H*$_b$); δ$_C$ (75 MHz, CDCl$_3$) 200.0 (t, $^2J_{C-F}$ 25.4), 165.0, 133.9, 130.2, 128.6, 128.6, 114.3 (dd, $^1J_{C-F}$ 260.3, 259.1), 69.9 (dd, $^2J_{C-F}$ 23.3, 18.6), 54.9, 52.9 (dd, $^3J_{C-F}$ 9.6, 1.2), 36.0, 28.4, 24.2; δ$_F$ (282MHz, CDCl$_3$) -113.7 (1F, dd, $^2J_{F-F}$ 247.4, $^3J_{H-F}$ 4.4), -127.3 (1F, dd, $^2J_{F-F}$ 246.9, $^3J_{H-F}$ 20.9); [HRMS (ES, [M+H]$^+$) found: 279.0932. Calc for C$_{15}$H$_{15}$F$_2$O$_4$ 297.0933].

Preparation of 3R*-Benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,4S*-diol 256 and 3R*-benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nona-1R*,4R*-diol 255

256   **255**
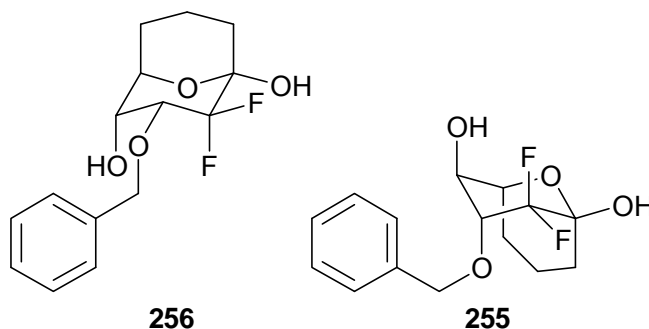
NMO (2.52 mmol, 295 mg) was added to a solution of cyclooctenone **200** (1.26 mmol, 336 mg) in acetone (3.16 cm^3) and H$_2$O (1.58 cm^3) at 0°C. Osmium tetroxide (0.063 mmol, 0.79 cm^3, of a 2.5 % by wt. solution in *t*-BuOH), and the resulting solution stirred at 0°C for 6 hours. The reaction was quenched by the addition of Na$_2$SO$_3$ (0.4 g) and the suspension stirred for 1hour, then diluted with water (3 cm^3) and extracted with ethyl acetate (3 x 30 cm^3). The combined organic layers were washed with brine (30 cm^3), dried (MgSO$_4$), filtered and concentrated in *vacuo*. Purification on a flash silica column eluted with 50-70% ethyl acetate gave minor diastereoisomer **255** (38 mg, 11%); R$_f$ (50% ethyl acetate/hexane) 0.24; Mp. 128-131°C; GC retention time 20.92 min.; (Found: C, 59.86; H, 5.90; C$_{15}$H$_{18}$F$_2$O$_4$ requires: C, 59.99; H, 6.04 %); υ_{max}(solid)/cm^{-1} 3364br, 3166br, 2913s, 1470m, 1351s, 1210s, 1150s, 1072s, 1034s, 943s, 915s, 882m, 819w, 750s, 699s; δ_H (300 MHz, CDCl$_3$) 7.40-7.29 (5H, m, 5 x Ph-*H*), 4.89 (1H, d, AB, ^2J 11.5, PhC*H*$_a$H$_b$), 4.66 (1H, d, AB, ^2J 11.5, PhCH$_a$*H*$_b$), 4.21 (1H, d, *J* 6.7, CH$_2$C*H*O), 3.97 (1H, dddd, $^3J_{H-F}$ 13.2, *J* 6.4, $^3J_{H-F}$ 4.4, ^4J 0.9 C*H*CF$_2$), 3.78-3.71 (1H, m, C*H*OH), 3.44 (1H, d, $^4J_{H-F}$ 6.3, OCO*H*), 2.46 (1H, dd, *J* 7.9, ^4J 1.2, CHO*H*), 2.24-2.06 (2H, m, C(OH)C*H*$_a$H$_b$,

$CH_2CH_aH_bCH_2$), 1.92-1.81 (1H, m, $CHCH_aH_b$), 1.78-1.68 (3H, m, $CHCH_aH_b$, $CH_2CH_aH_bCH_2$, $C(OH)CH_aH_b$); δ_C (75 MHz, $CDCl_3$) 137.2, 128.6, 128.2, 127.9, 118.2 (dd, $^1J_{C-F}$ 268.1, 251.9), 94.7 (dd, $^2J_{C-F}$ 29.9, 20.3), 80.2 (dd, $^2J_{C-F}$ 30.4, 18.0), 77.0, 75.0 (d, $^4J_{C-F}$ 1.8), 71.5 (dd, ^3J 3.0, 3.0), 29.6, 24.4, 15.9; δ_F (282 MHz, $CDCl_3$) -109.5 (1F, ddd, $^2J_{F-F}$ 259.6, $^3J_{H-F}$ 13.2, 5.5), (-121.9)-(-122.8) (1F, m inc. app. d, $^2J_{F-F}$ 159.6); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 318.1512. Calc. for $C_{15}H_{18}F_2O_4N$: 318.1511]; m/z (CI$^+$) 318 (100%, [M+NH$_4$]$^+$), 288 (8), 258 (3), 241 (14), 228 (5), 212 (4), 192 (5), 163 (10), 108 (3);

Crystal data: $C_{15}H_{18}F_2O_4$, crystal size 0.16 x 0.13 x 0.08 mm^3, M = 300.29, monoclinic, a = 10.3624(14) Å, b = 6.6363(9) Å, c = 11.0444(15)) Å, α = 90°, β = 112.613(2) °, γ = 90°, U = 701.11(16) Å^3, T = 150(2) K, space group P2(1), Z = 2, μ(Mo-Kα) = 0.119 mm^{-1}, 5059 reflections measured, 2397 [R(int) = 0.0672] which were used in all calculations. Final R indices [F^2>2σ(F^2)] R1 = 0.0465, wR2 = 0.0618; R indices (all data) R1 = 0.0684, wR2 = 0.0683, followed by a mixture of **255** and **256** (92 mg, 25%); and major diastereoisomer **256** as a white solid (138 mg, 37%); R$_f$ (50% ethyl acetate/hexane) 0.12; Mp. 112-109°C; GC Retention time 21.67 min; (Found: C, 59.86; H, 5.95; $C_{15}H_{18}F_2O_4$ requires: C, 59.99; H, 6.04 %); υ_{max}(solid)/cm^{-1} 3364br, 3180br, 2902w, 1737s, 1453w, 1343w, 1155s, 1089s, 933s, 867w, 728s, 693s; δ_H (300 MHz, $CDCl_3$) 7.41-7.33 (5H, m, 5 x Ph-H), 4.91 (1H, d, AB, ^2J 11.7, PhCH_aH$_b$), 4.78 (1H, d, AB, ^2J 11.7, PhCH$_a$$H_b$), 4.32 (1H, d, J 6.6, CH$_2$CHO), 4.01 (1H, ddd, $^3J_{H-F}$ 20.1, J 7.8, $^3J_{H-F}$ 4.8, CF$_2$CH), 3.86-3.80 (1H, m, CH(OH)), 3.64 (1H, d, ^4J 5.5, OCOH), 2.95 (1H, s, CHOH), 2.08-2.00 (1H, m, OCCH_aH$_b$), 1.96-1.70 (3H, m, OCCH$_a$$H_b$, and OCHC$H_2$), 1.50-1.37 (2H, m, CH$_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 136.6, 128.6, 128.5, 128.2, 118.0 (dd, $^1J_{C-F}$ 258.8,

254.6). 94.1 (dd, $^2J_{C-F}$ 26.9, 20.3), 74.8, 74.6 (dd, $^2J_{C-F}$ 20.0 17.6), 73.3 (d, $^4J_{C-F}$ 1.8), 71.0 (dd, $^3J_{C-F}$ 7.8, 1.2) 27.9 (d, $^3J_{C-F}$ 1.8), 23.0, 18.3; δ_F (282 MHz, CDCl$_3$) (-114.0)-(-114.9) (1F, m inc. app. d, $^2J_{F-F}$ 287.8), -124.1 (dddd, $^2J_{F-F}$ 287.8, $^3J_{H-F}$ 20.1, $^4J_{H-F}$ 5.5, 2.4); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 318.1515. Calc. for C$_{15}$H$_{22}$F$_2$O$_4$N: 318.1511]; m/z (CI$^+$) 318 (100%, [M+NH$_4$]$^+$), 302 (4), 228 (17), 212 (3), 121 (6), 52 (10);

Crystal data: C$_{15}$H$_{18}$F$_2$O$_4$, crystal size 0.14 x 0.09 x 0.06 mm^3, M = 300.29, monoclinic, a = 15.5415(19) Å, b = 6.6332(8) Å, c = 13.9404(17) Å, α = 90°, β = 106.126(2) °, γ = 90°, U = 1380.6(3) Å^3, T = 150(2) K, space group P2(1)/c, Z = 4, μ(Mo-Kα) = 0.121 mm^{-1}, 9657 reflections measured, 2430 [R(int) = 0.0967] which were used in all calculations. Final R indices [F^2>2σ(F^2)] R1 = 0.0514, wR2 = 0.0661; R indices (all data) R1 = 0.1050, wR2 = 0.0785. Crude **200** could be used in the reaction to give product in 61% yield over two steps from RCM precursor **195**.

Alternatively the Diols Could be Prepared by a Donohoe Procedure.

TMEDA (1.1 mmol, 0.166 cm^3) was added to a solution of cyclooctenone **200** (0.87 mmol, 0.232 g) in dry DCM (100 cm^3). The solution was cooled to −78 °C and osmium tetroxide (0.98 mmol, 250 mg) was added in one portion. The solution was stirred at this temperature for 12 hours then Na$_2$SO$_3$ (1 g) was added in one portion and stirred as the reaction warmed to rt over 3 hours. Water was added (30 cm^3) and the layers separated, then the aqueous layer was extracted with DCM (2 x 20 cm^3). The combined organic

extracts were washed with brine and concentrated in *vacuo*. The ^{19}F NMR spectrum ($\{^1H\}\delta_F$ (282 MHz, CDCl$_3$) -108.6 (1F, d, $^2J_{F-F}$ 265.8), (-111.8)-(-116.0) (2F, m), -131.2 (d, $^2J_{F-F}$ 265.8, 1F) was not consistent with the formation of **255** and **256**, and electrospray MS showed the product still bound as the osmate ester (*m/z*, (ES-MS, ES$^+$) 637 (44%, [M-H]$^+$, 635 (62)) therefore the crude material was taken up in CD$_3$OD (0.5 cm^3) and conc. HCl (3 drops, 0.3 cm^3) was added. The ^{19}F NMR spectrum then showed the presence of **255** and **256** (1:1) alone. The crude material was taken up in ethyl acetate (50 cm^3) and shaken with 2M HCl (10 cm^3). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 10 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give **257** and **258** as a grey paste. The crude material was dissolved in DCM (16 cm^3), PVP (800 mg, at 1g per mmol loading), and acetic anhydride (4.80 mmol, 0.454 cm^3) were added and the suspension shaken for 48 hours at rt. The PVP was removed by filtration and the solution concentrated in *vacuo*. Flash chromatography of the residue on silica eluted with 0 to 20% (linier increase) ethyl acetate/hexane for 10 column volumes then 20% ethyl acetate/hexane gave acetate **257** (67mg, 25%), a mixture of **257**, and **258** and diol **256** (108 mg, 43%), acetate **258** (54 mg, 21%), and cyclooctenone starting material **200** (21 mg, 9%).

Diols 255 and 256 Were Also Prepared *via* a Ru Dihydroxylation.

NaIO$_4$ (1.4 mmol, 300 mg) and CeCl$_3$.7H$_2$O (0.1 mmol, 38 mg) were dissolved in H$_2$O (2 cm^3) and stirred at rt for 10 min. The Solution was cooled to 0°C and ethyl acetate (3

cm^3), acetonitrile (6 cm^3) and RuCl$_3$.H$_2$O (0.025 mmol, 5.2 mg) were added sequentially and the solution stirred for a further 3 min. Cyclooctenone **200** (0.98 mmol, 261 mg) was added in ethyl acetate (3 cm^3) the solution stirred vigorously and allowed to warm to room temperature over 2 hours then stirred at this temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (80 cm^3), washed with NaHCO$_3$ (10 cm^3), and brine (10 cm^3), then dried (MgSO$_4$), filtered and concentrated in vacuo go give a thick red oil. Flash chromatography on silica gel eluted with 30-50% ethyl acetate/hexane (linier increase) for 4 column volumes then 50% ethyl acetate/hexane to give **255** (62 mg, 21%) and **256** (71 mg, 24%).

Preparation of 3R*-Benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,4R*-diol 293 and 3R*-Benzyloxy-2,2-difluoro-9-oxa-1S*,4R*-bicyclo[4.2.1]nona-1S*-5S*-diol 294
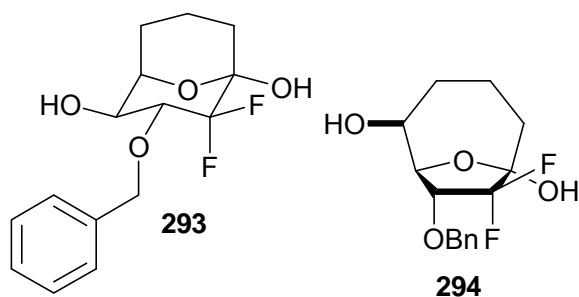
Epoxide **250** (0.44 mmol, 125 mg) and NaOH (2.2 cm^3 of an 0.5% aqueous solution) were sealed in a microwave vial equipped with a stirrer bead. The solution was irradiated in the cavity of a CEM Discover microwave at 30W power to maintain a temperature of 100°C for 10 min, with a 10 min ramp. The solution was made just acidic by the addition of a few drops of an aqueous solution of 10% HC1, (0.3 mL of a 3M aqueous solution)

upon which a white solid was observed to precipitate. The aqueous solution was extracted by ethyl acetate (3 x 20 cm^3) and the combined organic layers washed with NaHCO$_3$ (20 cm^3), and brine (30 cm^3), dried (MgSO$_4$), then filtered. The solvent was removed *in vacuo* to give a white solid which was purified on a Flash silica column eluted with 50% ethyl acetate/hexane to give **293** as a white solid (98 mg, 74 %); R$_f$ (50% ethyl acetate/hexane) 0.28; Mp. 127-130°C; (Found: C, 60.13; H, 6.1; C$_{15}$H$_{18}$F$_2$O$_4$ requires: C, 59.99; H, 6.04 %); υ_{max}(solid)/cm^{-1} 3364br, 2949w, 1350w, 1213w, 1080s, 1022s, 907s, 735s, 695s; δ_H (300 MHz, CDCl$_3$) 7.45-7.32 (5H, m, 5 x Ph-*H*), 5.01 (1H, dd, AB, ^2J 11.3, ^4J 1.1, PhC*H*$_a$H$_b$), 4.67 (1H, d, AB, ^2J 11.3, PhCH$_a$*H*$_b$), 4.22 (1H, t, J 5.1, CH$_2$C*H*), 4.06-3.98 (2H, m, C*H*CF$_2$, C*H*OH), 3.39 (1H, d, J 5.4, CHO*H*), 2.23 (1H, br. s, CO*H*), 2.11-2.02 (1H, m, C*H*$_a$H$_b$COH), 1.95-1.52 (5H, m, CHC*H*$_2$C*H*$_2$CH$_a$*H*$_b$); δ_C (75 MHz, CD$_3$OD) 138.0, 127.9, 127.8, 127.4, 118.7 (dd, $^1J_{C\text{-}F}$ 257.6, 252.8), 93.6 (dd, $^2J_{C\text{-}F}$ 26.9, 20.3), 80.2 (dd, $^2J_{C\text{-}F}$ 19.1, 19.1), 74.4 (d, $^4J_{C\text{-}F}$ 2.4), 73.0, 71.4 (d, $^3J_{C\text{-}F}$ 8.4), 28.7 (d, $^3J_{C\text{-}F}$ 2.4), 20.0, 17.9; δ_F (282 MHz, CDCl$_3$) -113.8 (1F, dd, $^2J_{F\text{-}F}$ 248.3, $^3J_{H\text{-}F}$ 7.6), (-128.7)-(129.8) (1F, m inc. app. d, $^2J_{F\text{-}F}$ 248.3); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 318.1510. Calc. for C$_{15}$H$_{22}$F$_2$O$_4$N: 318.1511]; *m/z* (CI$^+$) 318 (100%, [M+NH$_4$]$^+$), 228 (3), 210 (3), 108 (10), 91 (5), 52 (52).

Crystal data: C$_{15}$H$_{18}$F$_2$O$_4$, crystal size 0.19 x 0.10 x 0.04 mm^3, M = 300.29, triclinic, a = 9.9359(15) Å, b = 11.1641(17) Å, c = 13.130(2) Å, α = 78.181(3)°, β = 86.925(3)°, γ = 88.750(3)°, U = 1423.4(4) Å^3, T = 150(2) K, space group P-1, Z = 4, μ(Mo-Kα) = 0.117 mm^{-1}, 10395 reflections measured, 4966 [R(int) = 0.0818] which were used in all calculations. Final R indices [F^2>2σ(F^2)] R1 = 0.0571, wR2 = 0.0924; R indices (all data) R1 = 0.1002, wR2 = 0.1055.

On one occasion the main impurity 3*R**-Benzyloxy-2,2-difluoro-9-oxa-1*S**,4*R**-bicyclo[4.2.1]nona-1S*-5S*-diol **294** was isolated after chromatography, R$_f$ (50% ethyl acetate/hexane) 0.30; υ_{max}(solid)/cm^{-1} 3305br, 2932w, 1686w, 1443w, 1358m, 1156m, 1025s, 908s, 731s; δ_H (300 MHz, CDCl$_3$) 7.43-7.31 (5H, m, 5 x Ph-*H*), 4.98 (1H, d, AB, ^2J 11.4, PhC*H*$_a$H$_b$), 4.75 (1H, d, AB, ^2J 11.4, PhCH$_a$*H*$_b$), 4.24 (1H, dd, *J* 14.1, 5.8, C*H*CH$_2$), 4.04 (1H, ddd, $^3J_{H-F}$ 17.0, *J* 9.5, $^3J_{H-F}$ 8.7, C*H*CF$_2$), 3.75 (1H, apparent dt, *J* 9.5, ^4J 1.3, C*H*(OH)), 2.34 (1H, dd, *J* 13.4, 4.5, CC*H*$_a$H$_b$), 1.85-1.37 (5H, m, CCH$_a$*H*$_b$C*H*$_2$C*H*$_2$); δ_F (282 MHz, CDCl$_3$) -111.0 (1F, dd, $^2J_{F-F}$ 254.5, $^3J_{H-F}$ 8.7), -112.8 (1F, app. dt, $^2J_{F-F}$ 254.5, $^3J_{H-F}$ 17.0); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 318.1509. Calc. for C$_{15}$H$_{22}$F$_2$O$_4$N: 318.1511]; *m/z* (CI$^+$) 318 (100%, [M+NH$_4$]$^+$), 278 (7), 228 (7), 122 (16), 108 (38), 91 (17), 52 (84).

Preparation of 4*R**-Acetoxy-3*R**-benzyloxy-2,2-difluoro-1*S**-methoxy-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nonane 300 and 5*S**-acetoxy-3*R**-benzyloxy-2,2-difluoro-1*S**-methoxy-9-oxa-1*S**,4*R**-bicyclo[4.2.1]nonane 301

300   **301**
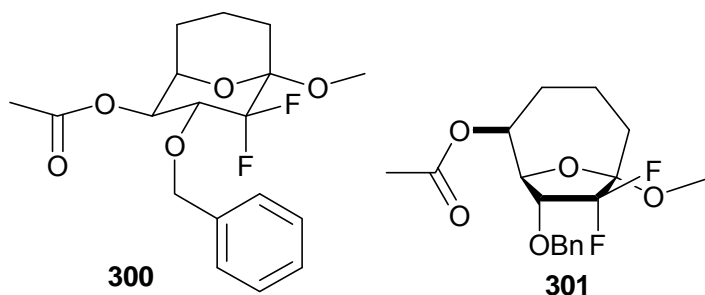
Epoxide **250** (0.32 mmol, 90 mg) was dissolved in methoxide solution (3.2 cm^3 of a 0.5 % solution in methanol) and placed in a microwave tube equipped with a stirrer bead. The tube was sealed and irradiated with 30 watts in the cavity of a CEM Explorer

microwave so as to maintain a temperature of 100°C for 20 min, with a 10 min ramp. The solvent was removed in *vacuo* and the residue taken up in DCM (70 cm^3) and washed with cold dilute HCl (10 cm^3 of a 1M solution), brine (20 cm^3), dried MgSO$_4$, then filtered into a round bottom flask. PVP (340 mg), and acetic anhydride (1.17 mmol, 0.160 cm^3) were added and shaken at room temperature for 64 hours. The PVP was removed by filtration and washed with DCM (70 cm^3). The combined organic extracts were washed with NaHCO$_3$ (10 cm^3), brine (20 cm^3), dried MgSO$_4$, filtered and concentrated in *vacuo* to give a grey paste which was purified by flash chromatography on silica gel eluted with 20% ethyl acetate/hexane to give **301** as a grey paste (20 mg, 18 %, 83% of a mixture with **300** ^{19}F NMR); R$_f$ (20% Ethyl acetate/hexane) 0.30; υ_{max}(film)/cm^{-1} 2948s, 2359s, 1742s, 1454m, 1372m, 1238s, 1062s, 739w, 699w; δ_H (400 MHz, CDCl$_3$) 7.38-7.30 (5H, m, 5 x PhH), 5.15 (1H, dd, J 5.7, 5.3, CH(OAc)), 4.84 (1F, d, AB, ^2J 11.9, PhCH_aH$_b$), 4.57 (1F, d, AB, ^2J 11.9, PhCH$_a$$H_b$), 4.42-4.33 (2H, env. containing, 4.42-4.33 (1H, m, {^{19}F} dd, J 6.5, 3.9, CH(OC)), and 4.33 (1H, ddd, $^3J_{H\text{-}F}$ 9.9, 8.5, J 3.9, CHCF$_2$)), 3.49 (3H, d, $^5J_{H\text{-}F}$ 1.8, OCH_3), 2.11-1.96 (2H, m, CHCH_aH$_b$, CH_aH$_b$), 1.92 (3H, s, CCH_3), 170-1.28 (4H, m, CHCH$_a$$H_b$, CH$_a$$H_b$, C$H_2$); δ_C (100 MHz, CDCl$_3$) 169.6, 136.9, 128.5, 128.1, 128.1, 123.7 (dd, $^1J_{C\text{-}F}$ 267.2, 261.6), 105.8 (dd, $^2J_{C\text{-}F}$ 29.2, 18.0), 77.9 (d, $^3J_{C\text{-}F}$ 9.6), 77.3 (dd, $^2J_{C\text{-}F}$ 16.0, 10.4), 72.4 (d, $^4J_{C\text{-}F}$ 2.4), 71.0, 51.8 (d, $^4J_{C\text{-}F}$ 5.6), 34.3, 30.1, 20.9, 18.0; δ_F (282 MHz, CDCl$_3$) -114.3 (1F, dd, $^2J_{F\text{-}F}$ 235.0, $^3J_{H\text{-}F}$ 9.9), (-126.0)-(-126.9) (1F, m inc. app. d, $^2J_{F\text{-}F}$ 235.0); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 374.1773. Calc. for C$_{18}$H$_{26}$F$_2$O$_5$N: 374.1774]; *m/z* (CI$^+$) 374 (100%, [M+NH$_4$]$^+$), 284 (5), 208 (6), 106 (9), 77 (18), 52 (79).

 And acetate **300** (45 mg, 39%); R$_f$ (20% ethyl acetate/hexane) 0.16; Mp. 92-93°C; (Found: C, 60.76; H, 6.3; C$_{18}$H$_{22}$F$_2$O$_5$ requires: C, 60.67; H, 6.22 %); υ_{max}(solid)/cm^{-1}

2955w, 1737s, 1440w, 1363s, 1239s, 1029s, 892s, 758s; δ_H (400 MHz, CDCl$_3$) 7.41-7.32 (5H, m, 5 x PhH), 5.21 (1H, ddd, J 9.9, 6.5, ^4J 1.2, CH(OAc)), 4.96 (1H, d, AB, ^2J 12.0, PhCH_aH$_b$), 4.70 (1H, d, AB, ^2J 12.0, PhCH$_a$$H_b$), 4.46-4.42 (1H, m, C$HCH_2$), 4.16 (1H, ddd, $^3J_{H-F}$ 17.5, 7.3, J 9.9, CHCF$_2$), 3.51 (3H, d, $^5J_{H-F}$ 1.5, OCH_3), 2.02 (3H, s, CCH_3), 1.96-1.60 (6H, m, 3 x CH_2); δ_C (100 MHz, CDCl$_3$) 169.5, 137.4, 128.4, 128.4, 128.0, 119.2 (dd, $^1J_{C-F}$ 259.2, 257.6), 95.8 (dd, $^2J_{C-F}$ 25.6, 17.6), 77.2 (dd, $^2J_{C-F}$ 21.6, 19.2), 74.1 (d, $^4J_{C-F}$ 2.4), 72.5 (d, $^3J_{C-F}$ 8.8), 69.6, 50.7 (d, $^4J_{C-F}$ 4.0), 25.9 (d, $^3J_{C-F}$ 2.4), 21.1, 20.7, 18.1; δ_F (282 MHz, CDCl$_3$) $-$114.8 (1F, dd, AB, $^2J_{F-F}$ 248.3, $^3J_{H-F}$ 7.3), -128.0 (1F, dddd, AB, $^2J_{F-F}$ 248.3, $^3J_{H-F}$ 17.5, $^4J_{H-F}$ 3.8, $^5J_{H-F}$ 1.5); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 374.1777. Calc. for C$_{18}$H$_{26}$F$_2$O$_5$N: 374.1774]; m/z (CI$^+$) 374 (100%, [M+NH$_4$]$^+$), 284 (13), 208 (9), 108 (21), 77 (19). In the $\{^{19}F\}^1$H NMR spectrum, the signal at 3.51 simplified to 3.51 (s, 3H).

Crystal data: C$_{18}$H$_{22}$F$_2$O$_5$, crystal size 0.35 x 0.24 x 0.20 mm^3, M = 356.36, triclinic, a = 7.240(2) Å, b = 9.607(3) Å, c = 13.226(4) Å, α = 98.732(5) °, β = 102.590(5) °, γ = 100.713(5) °, U = 864.2(4) Å^3, T = 150(2) K, space group P-1, Z = 2, μ(Mo-Kα) = 0.113 mm^{-1}, 6306 reflections measured, 3024 [R(int) = 0.0485] which were used in all calculations. Final R indices [F^2>2σ(F^2)] R1 = 0.0455, wR2 = 0.1179; R indices (all data) R1 = 0.0554, wR2 = 0.1240.

Preparation of 5S*-Acetoxy-2,2-difluoro-1S*-methoxy-9-oxa-1S*,4R*-bicyclo[4.2.1]nonan-3R*-ol 302
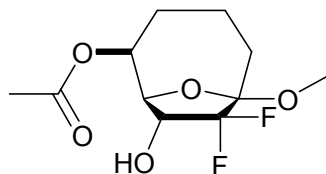
Bicyclic acetal **301** (0.07 mmol, 25 mg) was dissolved in a suspension of 10% palladium on activated carbon (10 mg) in ethanol (1 cm^3). The atmosphere was removed and replaced with hydrogen pressure from a balloon. The solution was stirred at room temperature for 72 hours then the hydrogen atmosphere removed and replaced with air. The solution was filtered through celite then concentrated in *vacuo* and purified by flash chromatography on silica gel eluted with 10-30% ethyl acetate/hexane to give bicyclic acetal **302** as a grey paste (10 mg, 59 %); R_f (30% ethyl acetate/hexane) 0.25; υ_{max}(film)/cm^{-1} 3447br, 2952w, 1736s, 1441w, 1374w, 1232s, 1036s, 973w, 787w; δ_H (400 MHz, CDCl$_3$) 5.20-5.15 (1H, m, C*H*(OAc)), 4.54 (1H, ddd, $^3J_{H-F}$ 11.0, 8.1, *J* 3.5, C*H*CF$_2$), 4.32 (1H, ddd, *J* 6.4, 3.5, $^4J_{H-F}$ 1.7, C*H*CH(OH)), 3.49 (3H, d, $^5J_{H-F}$ 1.4, OC*H$_3$*), 2.12-1.94 (6H, env. containing, 2.12-1.94 (3H, m, CHC*H*$_a$H$_b$, C*H$_2$*), and 2.10 (3H, s, CC*H$_3$*)), 1.74-1.60 (3H, m, CHCH$_a$*H*$_b$, C*H$_2$*); δ_C (376 MHz, CDCl$_3$) 170.0, 122.8 (t, $^1J_{C-F}$ 262.8), 105.5 (dd, $^2J_{C-F}$ 28.8, 18.4), 80.0 (d, $^3J_{C-F}$ 9.6), 72.0 (dd, $^2J_{C-F}$ 28.0, 17.6), 71.2, 51.6 (d, $^4J_{C-F}$ 4.8), 33.7-33.6 (m), 29.75-29.70 (m), 21.0, 18.1; δ_F (282 MHz, CDCl$_3$) − 119.6 (1F, dd, $^2J_{F-F}$ 236.5, $^3J_{H-F}$ 11.0), -126.6- (-127.5) (1F, m, $^2J_{F-F}$ 236.5, $^3J_{H-F}$ 8.1); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 284.1306. Calc. for C$_{11}$H$_{20}$F$_2$O$_5$N: 374.1774]; *m/z* (ES$^+$) 289 (33%, [M+Na]$^+$), 155 (5), 136 (6), 73 (22), 51 (100). In the {^{19}F}^{1}H NMR spectrum, the signal at 4.32 collapses to 4.32 (dd , *J* 6.4, 3.5, 1H) and the signal at 3.49 to

3.49 (s, 3H). The signals reported as multiplets in the ^{13}C NMR spectrum are weak and significantly broadened.

Preparation of 2,2-Difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nona-1R*,3R*,4R*-triol 307
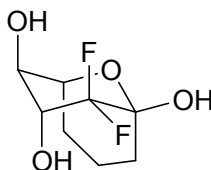
Bicyclic acetal **255** (0.133 mmol, 40 mg) was dissolved in a suspension of 10 % palladium on activated carbon (10 mg) in ethanol (1.3 cm^3). The atmosphere was removed and replaced by hydrogen pressure from a balloon. The reaction was stirred at room temperature for 23 hours. The hydrogen atmosphere was removed in *vacuo* and replaced with air, the carbon was then removed by filtration through celite. Concentration in vacuo gave the bicyclic triol **307** (25 mg, 91%); R$_f$ (100% ethyl acetate) 0.29; Mp. 60-57°C; (Found: C, 45.84; H, 5.88; C$_8$H$_{12}$F$_2$O$_4$ requires: C, 45.72; H, 5.75 %); υ_{max}(solid)/cm^{-1} 3289br, 2963w, 1351m, 1205m, 1092s, 1000s, 958s, 894s; δ_H (300MHz, MeOD) 3.97 (1H, broad s, C*H*CH$_2$), 3.86 (1H, ddd, $^3J_{H-F}$ 13.4, 12.5, ^3J 6.9, C*H*CF$_2$), 3.53 (1H, dt, ^3J 6.9, 2.7, CHC*H*(OH)), 2.00-1.90 (1H, m, C*H$_a$*H$_b$COH), 1.72-1.38 (5H, m, CHC*H$_2$CH$_2$CH$_a$H$_b$*); δ_C (400MHz, MeOD) 118.1 (dd, $^1J_{C-F}$ 258.0, 258.0), 94.2 (dd, $^2J_{C-F}$ 31.2, 20.0), 77.0, 72.2 (dd, $^2J_{C-F}$ 28.8, 19.2), 70.6 (dd, $^3J_{C-F}$ 6.0, 2.0), 30.2, 24.8, 15.4; δ_F (282MHz, MeOD) -112.7 (1F, ddd, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 12.5, $^4J_{H-F}$ 3.8), -125.1 (1F, dd, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 13.4); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 228.1038. Calc. for C$_8$H$_{16}$F$_2$O$_4$N: 228.1042]; *m/z* (CI$^+$) 228 (100%, [M+NH$_4$]$^+$).

Preparation of 2,2-Difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,3R*,4S*-triol 308
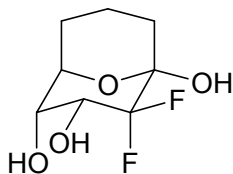
Bicyclic acetal **256** (0.173 mmol, 52 mg) was dissolved in a suspension of 10% palladium on activated carbon (17 mg) in ethanol (1.7 cm^3). The atmosphere was removed and replaced by hydrogen pressure from a balloon. The reaction was stirred at room temperature for 72 hours. The hydrogen atmosphere was removed in *vacuo* and replaced with air, the carbon was then removed by filtration through celite. Concentration in *vacuo* gave the bicyclic triol **308** (36 mg, 100%); R$_f$ (100% ethyl acetate) 0.15; Mp. 153-155°C; (Found: C, 45.79; H, 5.80; C$_8$H$_{12}$F$_2$O$_4$ requires: C, 45.72; H, 5.75 %); υ_{max}(solid)/cm^{-1} 3346br, 2951w, 1647w, 1444w, 1353w, 1204s, 1076s, 1037s, 928s; δ_H (300MHz, MeOD) 4.17-4.04 (2H, env. containing 4.10 (1H, ddd, $^3J_{H-F}$ 21.4, 8.6, J 4.8, (OH)C*H*CF$_2$) and 4.11-4.09 (1H, m, CHC*H*(OH)), 3.72 (1H. broad s, C*H*CH$_2$), 1.90 (1H, broad d, J 9.6, CC*H*$_a$H$_b$), 1.80-1.44 (5H, m, CHC*H*$_2$C*H*$_2$ and CCH$_a$*H*$_b$); δ_C (100MHz, MeOD) 117.9 (dd, $^1J_{C-F}$ 254.0, 254.0), 93.8 (dd, $^2J_{C-F}$ 26.8, 20.4), 75.9, 72.0 (dd, $^3J_{C-F}$ 8.0, 1.6), 68.8 (dd, $^2J_{C-F}$ 21.6, 19.2), 29.0 (d, $^3J_{C-F}$ 2.4), 23.0, 17.7; δ_F (282 MHz, MeOD) (-119.2)-(-120.24) (1F, m inc. app. d, $^2J_{F-F}$ 247.4), -127.3 (1F, ddd, $^2J_{F-F}$ 247.4, $^3J_{H-F}$ 21.4, $^4J_{H-F}$ 3.8); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 228.1038. Calc. for C$_8$H$_{16}$F$_2$O$_4$N: 228.1042]; *m/z* (CI$^+$) 228 (100%, [M+NH$_4$]$^+$), 123 (6).

Preparation of 2,2-Difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,3R*,4R*-triol 309
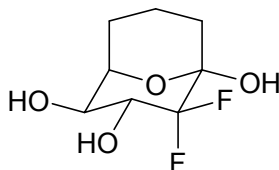
Bicyclic acetal **293** (0.080 mmol, 24 mg) was dissolved in a suspension of 10% palladium on activated carbon (5 mg) in ethanol (1 cm^3). The atmosphere was removed and replaced by hydrogen pressure from a balloon. The reaction was stirred at room temperature for 23 hours. The hydrogen atmosphere was removed in *vacuo* and replaced with air, the carbon was then removed by filtration through celite. Concentration in *vacuo* gave the bicyclic triol **309** (16 mg, 95%); R$_f$ (100% ethyl acetate) 0.31; Mp. 156-158°C; (Found: C, 45.68; H, 5.70; C$_8$H$_{12}$F$_2$O$_4$ requires: C, 45.72; H, 5.75 %); υ_{max}(solid)/cm^{-1} 3296br, 2964w, 1440w, 1345w, 1207m, 1116m, 1034s, 996s, 929s, 823s; δ_H (300MHz, MeOD) 4.06-3.92 (2H, m, C*H*CF$_2$, and C*H*CH$_2$), 3.76 (1H, dd, *J* 9.5, 6.4, C*H*CH(OH)CF$_2$), 1.92-1.48 (6H, m, C*H$_2$*CH$_2$CH$_2$); δ_C (100MHz, MeOD) 117.9 (dd, $^1J_{C-F}$ 156.4, 150.9), 93.5 (dd, $^2J_{C-F}$ 26.8, 20.4), 73.0, 72.9 (dd, $^2J_{C-F}$ 20.4, 20.4), 72.0 (d, $^3J_{C-F}$ 8.0), 28.7 (d, $^3J_{C-F}$ 2.4), 20.0, 18.9; δ_F (282MHz, MeOD) -118.20 (1F, dd, $^3J_{F-F}$ 246.7, $^3J_{H-F}$ 8.2), -129.4 (1F, ddd, $^2J_{F-F}$ 246.7, $^3J_{H-F}$ 19.4, $^4J_{H-F}$ 4.3); [HRMS (CI$^-$, [M-H]$^-$) Found: 209.0630. Calc. for C$_8$H$_{11}$F$_2$O$_4$N: 209.0631]; *m/z* (CI$^-$) 209 (30%, [M-H]$^-$), 191 (11), 170 (18), 152 (15), 79 (22).

Preparation of 3*R**-Benzyloxy-1*R**-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1*R**,5*S**-bicyclo[3.3.1]nona-4*R**-ol 310 and 3*R**-Benzyloxy-1*R**,4*R**-bis(dibenzylphosphoryloxy)- 2,2-difluoro-9-oxa-1*R**,5*S**-bicyclo[3.3.1]nonane 311
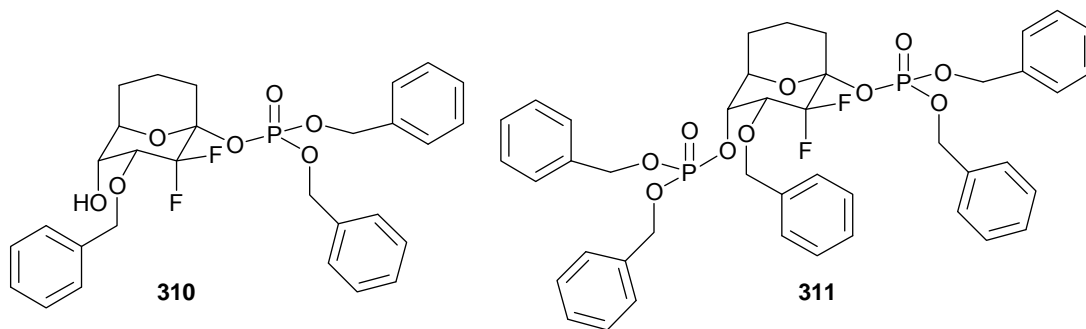
nButyl lithium (0.035 mmol, 15.2 mm^3, of a 2.03M solution in hexanes) was added to a stirred solution of bicyclic diol **256** (0.035 mmol, 10.5 mg) in dry THF (1.5 cm^3) under an atmosphere of nitrogen at -78°C. The solution was allowed to warm to 0°C and stirred for 5 hr. The solution was re-cooled to -78°C then tetrabenzylpyrophosphate (0.035 mmol, 19 mg) was added in THF (0.5 cm^3) in one portion then stirred over night at -30°C. The solution was allowed to warm to 0°C then the reaction was quenched with pH buffer solution (5 cm^3) and the aqueous layer extracted with ethyl acetate (3 x 20 cm^3). The combined organic layers were washed with brine (10 cm^3), dried (MgSO$_4$), and concentrated in vacuo to give a grey paste which was purified on a Flash silica gel column eluted with (70% ethyl acetate/hexane) to give mono phosphate **310** (15 mg, 14 %) as a grey paste; R$_f$ (70% ethyl acetate/hexane) 0.21; υ_{max}(film)/cm^{-1} 3425br, 2943s, 1490w, 1455s, 1279w, 1214s, 1108s, 1038s, 744s, 697s; δ_H (400 MHz, CDCl$_3$) 7.41-7.28 (15H, m, 15 x Ph-*H*), 5.14 (1H, dd, AB, ^2J 11.8, $^3J_{H-P}$ 7.3, PhC*H*$_{a1}$H$_{b1}$), 5.11 (1H, dd, AB, ^2J 11.8, $^3J_{H-P}$ 7.3, PhCH$_{a1}$*H*$_{b1}$), 5.09 (1H, s, PhC*H*$_{a2}$H$_{b2}$), 5.06 (1H, s, PhCH$_{a2}$*H*$_{b2}$), 4.91 (1H, AB, d, ^2J 11.7, PhC*H*$_{a3}$H$_{b3}$), 4.78 (1H, AB, d, ^2J 11.7, PhCH$_{a3}$*H*$_{b3}$), 4.43 (1H, d, *J*

6.6, CHCH$_2$), 4.01 (1H, ddd, $^3J_{\text{H-F}}$ 19.4, J 7.0, $^3J_{\text{H-F}}$ 4.4, CHCF$_2$), 3.83 (1H, br. s, CH(OH)CH(O)), 2.54-2.40 (1H, m, CCH_aH$_b$), 2.18-2.06 (1H, m, CCH$_a$$H_b$) 2.03-1.75 (2H, m, CHC$H_2$) , 1.51-1.35 (2H, m, CH$_2CH_2CH_2$); δ_C (100 MHz, CD$_3$OD) 136.5, 136.0 (d, $^2J_{\text{C-P}}$ 8.8), 135.8 (d, $^2J_{\text{C-P}}$ 8.0), 128.7, 128.5, 128.5, 128.4, 128.4, 128.2, 128.2, 128.0, 127.9, 116.6 (dd, $^1J_{\text{C-F}}$ 258.0, 251.7), 99.7 (ddd, $^2J_{\text{C-F}}$ 27.2, 17.6, $^2J_{\text{C-P}}$ 7.2), 74.3 (ddd, $^2J_{\text{C-F}}$ 20.0, 16.8, $^4J_{\text{C-P}}$ 1.6), 73.2 (d, $^4J_{\text{C-F}}$ 1.6), 70.8 (d, $^3J_{\text{C-F}}$ 8.0), 69.7 (d, $^2J_{\text{C-P}}$ 6.4), 69.4 (d, $^2J_{\text{C-P}}$ 6.4) 28.0, 22.7, 18.4; δ_F (282 MHz, CDCl$_3$) (-114.9)-(-115.8) (1F, m inc. app. d, $^2J_{\text{F-F}}$ 246.7), -121.6 (1F, AB, ddd, $^2J_{\text{F-F}}$ 246.7, $^3J_{\text{H-F}}$ 19.4, $^4J_{\text{H-F}}$ 4.3); δ_P (121 MHz, CDCl$_3$) -8.50 (quintet, $^3J_{\text{P-H}}$ 7.3); [HRMS (ES$^+$, [M+H]$^+$) Found: 561.1845. Calc. for C$_{29}$H$_{32}$F$_2$O$_7$P: 561.1848]; m/z (ES$^+$) 561 (97%, [M+H]$^+$), 404 (4), 381 (4), 228 (100), 158 (13); and diphosphate **311** (7 mg, 3 %) as a grey paste; R$_f$ (70% ethyl acetate/hexane) 0.15; δ_H (300 MHz, CDCl$_3$) 7.44-7.17 (20H, m, 20 x Ph-H), 5.15-5.02 (2H, m, 2 x PhCH_2), 5.02 (1H, d, AB, ^2J 10.4, PhCH$_{a1}$H$_{b1}$), 4.97 (1H, d, AB, ^2J 10.4, PhCH$_{a1}$$H_{b1}$), 4.96 (1H, d, AB, ^2J 11.8, PhCH_{a2}H$_{b2}$), 4.91 (1H, d, AB, ^2J 11.8, PhCH$_{a2}$$H_{b2}$), 4.86 (1H, d, AB, ^2J 11.5, PhCH_{a3}H$_3$), 4.81 (1H, d, AB, ^2J 11.5, PhCH$_{a3}$$H_{b3}$), 4.76- 4.69 (1H, m, CHCH(OBn)), 4.38 (1H, d, ^3J 6.1, CHCH$_2$), 4.03 (1H, broad d, $^3J_{\text{H-F}}$ 19.9, CHCF$_2$), 2.48-2.41 (1H, m, CH_aH$_b$C(O)), 2.48-1.78 (3H, m, CH$_a$$H_b$C(O), CHC$H_2$), 1.48-1.32 (2H, m, CH$_2CH_2CH_2$); δ_F (282 MHz, CDCl$_3$) -117.5 (1F, d, $^2J_{\text{F-F}}$ 146.4), -123.4 (1F, ddd, $^2J_{\text{F-F}}$ 246.4, $^3J_{\text{H-F}}$ 19.9, $^4J_{\text{H-F}}$ 5.2); δ_P (121 MHz, CDCl$_3$) -1.86 (1P, quintet, $^3J_{\text{P-H}}$ 7.3), -8.68 (1P, quintet, $^3J_{\text{P-H}}$ 7.3); [HRMS (ES$^+$, [M+H]$^+$) Found: 821.2448. Calc. for C$_{43}$H$_{45}$F$_2$O$_{10}$P$_2$: 821.2451]; m/z (ES$^+$) 821 (79%, [M+H]$^+$), 583 (19), 561 (23), 404 (6), 228 (100), 158 (32). Insufficient material was obtained for a carbon spectra. Starting material was also recovered (21 mg, 35%).

Alternate Procedure Using Sodium-Hexamethyldisilazane

Sodium-Hexamethyldisilazane (0.041 mmol, 0.0234 cm^3) was added to a stirred solution of bicyclic diol **256** (0.041 mmol, 12.2 mg) in dry THF (0.5 cm^3) at 0°C. 15-Crown-5 (0.041mmol, 0.0081 cm^3) was added and the solution cooled to -20°C for 24 hours. Benzyl pyrophosphate (0.041 mmol, 22.1 mg) was added in dry THF (0.2 cm^3) and the solution stirred at -20°C for a further 27 hours. The reaction was quenched with pH 7 buffer solution (5 cm^3) and extracted with ethyl acetate (3 x 20 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried (MgSO$_4$), filtered and concentrated in *vacuo* to give a grey paste. Analysis by ^{19}F NMR gave yields for mono-phosphate **310** (40%), bis-phosphate **311** (16%), recovered starting material **256** (44%), and traces of an unknown compound probably the product of mono-phosphorylation of the secondary alcohol of the starting material.

Preparation of 4S*-Acetoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nonan-1S*-ol 257

Acetic anhydride (2.26 mmol, 0.214 cm^3), DMAP (0.14 mmol, 16.5 mg), and PVP (450 mg at 1g per mmol loading) were added so a solution of bicyclic diol **256** (136 mg, 0.45

mmol) in DCM (4.5 cm^3). The suspension was shaken at room temperature for 75 hours

TLC analysis showed the reaction was incomplete so further acetic anhydride (0.200 cm^3,

2.11 mmol), DMAP (20 mg, 0.17 mmol), and PVP (320 mg) were added and the reaction

shaken at rt for a further 48 hours until consumption of starting material was observed by

TLC. The PVP was removed by filtration and washed with DCM (30 cm^3). Then the

filtrate was washed with NaHCO$_3$ (2 x 15 cm^3), and brine (20 cm^3), then dried (MgSO$_4$),

and concentrated in vacuo to give a yellow oil which was purified a flash silica gel

column eluted with 50% ethyl acetate/hexane to give acetate **257** (138 mg, 89 %) as a

white solid Mp. 28-30°C; R$_f$ (50% ethyl acetate/hexane) 0.34; (Found: C, 59.50; H, 5.73;

C$_{17}$H$_{20}$F$_2$O$_5$ requires: C, 59.64; H, 5.89 %); υ_{max}(film)/cm^{-1} 3434br, 2951s, 1730s, 1367s,

1074s, 908s, 733s; δ_H (300 MHz, CDCl$_3$) 7.39-7.30 (5H, m, 5 x PhH), 5.20 (1H, ddd, J

4.9 $^4J_{H-F}$ 3.8, ^4J 1.5, CH(OAc)), 4.76 (1H, d, AB, ^2J 12.4, PhCH_aH_b), 4.73 (1H, d, AB, ^2J

12.4, PhCH$_aH_b$), 4.22 (1H, d, J 6.7, CHCH$_2$), 4.04 (1H, ddd, $^3J_{H-F}$ 21.8, 7.3, J 4.9,

CH(O)CF$_2$), 3.61 (1H, d, ^4J 6.4, OH), 2.15 (3H, s, CH_3), 2.06-1.38 (6H, m, CH_2CH_2CH_2);

δ_C (100 MHz, CDCl$_3$) 170.6, 136.7, 128.6, 128.3, 128, 117.4 (dd, $^1J_{C-F}$ 256.4, 255.6),

94.3 (dd, $^2J_{C-F}$ 26.8, 20.4), 73.8, 73.2, 73.2, 70.8 (dd, $^3J_{C-F}$ 9.2, 1.6), 27.8 (d, $^3J_{C-F}$ 1.6),

23.0, 21.0, 18.2; δ_F (282 MHz, CDCl$_3$) (-116.8)-(-117.8) (1F, m inc. app. d, $^2J_{F-F}$ 245.9), -

127.0 (1F, ddt, $^2J_{F-F}$ 245.8, $^3J_{H-F}$ 21.8, ^4J 5.2); [HRMS (ES$^+$, [M+H]$^+$) Found: 343.1356.

Calc. for C$_{17}$H$_{21}$F$_2$O$_5$: 343.1352]; m/z (EI$^+$) 342 (2%, [M+H]$^+$), 176 (13), 116 (83), 91

(100), 43 (61).

Preparation of 4R*-Acetoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nonan-1S*-ol 316

Acetic anhydride (2.08 mmol, 0.197cm^3), DMAP (0.208 mmol, 25 mg), and PVP (346 mg, at 0.5g per mmol loading) were added so a solution of bicyclic diol **293** (0.69 mmol, 208 mg) in DCM (14 cm^3). The suspension was shaken at room temperature for 18 hours, then the PVP was removed by filtration. The filtrate was diluted with DCM (70 cm^3), washed with NaHCO$_3$ (30 cm^3), and brine (30 cm^3), then dried (MgSO$_4$), and concentrated in vacuo to give **316** as white solid which was used without further purification (212 mg, 89 %, 100% GC) as a white solid Mp. 118-120°C; R$_f$ (50% ethyl acetate/hexane) 0.34; (Found: C, 59.59; H, 5.99; C$_{17}$H$_{20}$F$_2$O$_5$ requires: C, 59.64; H, 5.89 %); GC retention time 22.19 min; υ_{max}(film)/cm^{-1} 3468br, 2940s, 1739s, 1455w, 1367s, 1242s, 1072s, 1029s, 909s, 733s; δ_H (300 MHz, CDCl$_3$) 7.40-7.30 (5H, m, 5 x PhH), 5.17 (1H, dd, J 9.8, 6.6, CH(OAc), 4.94 (1H, d, AB, ^2J 12.0, PhCH_aH$_b$), 4.68 (1H, d, AB, ^2J 12.0, PhCH$_a$H$_b$), 4.36 (1H, br. t, J 5.7, CH$_2$CH), 4.15 (1H, ddd, $^3J_{H-F}$ 18.2, 7.7, J 9.8, CHCF$_2$), 3.68 (1H, br. s, OH), 2.12-1.50 (9H, env. containing, 2.12-1.50 (6H, m, 3 x CH$_2$), and 2.00 (3H, s, CH_3)); δ_C (100 MHz, CDCl$_3$) 169.6, 137.3, 128.4, 128.1, 128.0, 118.3 (dd, $^1J_{C-F}$ 259.7, 251.3), 93.8 (dd, $^2J_{C-F}$ 26.5, 20.5), 77.2 (m), 74.5, (d, $^4J_{C-F}$ 2.4), 72.5 (dd, $^3J_{C-F}$ 9.0, 1.2), 69.6, 27.7 (d, $^3J_{C-F}$ 1.8), 20.8, 20.7, 18.1; δ_F (282 MHz, CDCl$_3$) -114.5 (1F, dd, $^2J_{F-F}$ 247.6, $^3J_{H-F}$ 7.7), -128.4 (ddd, $^2J_{F-F}$ 247.6, $^3J_{H-F}$ 18.2, $^4J_{H-F}$ 5.7);

[HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 360.1615. Calc. for C$_{17}$H$_{25}$F$_2$O$_5$N: 360.1617]; m/z (EI$^+$) 360 (100%, [M+NH$_4$]$^+$), 343 (3), 270 (6), 108 (9), 52 (12).

Preparation of 4S*-Aceteoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nona-1R*-ol 258 and 1R*,4S*-Aceteoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nonane 317

258   **317**

Acetic anhydride (3.48 mmol, 0.329 cm^3), DMAP (0.18 mmol, 22 mg), and PVP (690 mg at 1g per mmol loading) were added so a solution of bicyclic diol **255** (0.69 mmol, 209 mg) in DCM (12.2 cm^3). The suspension was shaken at room temperature for 18 hours, then the PVP was removed by filtration. The filtrate was diluted with DCM (200 cm^3), washed with NaHCO$_3$ (50 cm^3), and brine (100 cm^3), then dried (MgSO$_4$), and concentrated in vacuo to give a yellow oil which was purified on silica gel column eluted with 50% ethyl acetate/hexane to give **258** as a white solid (136 mg, 58%); Mp. 110-112°C; R$_f$ (50% ethyl acetate/hexane) 0.52; (Found: C, 59.48; H, 5.97; C$_{17}$H$_{20}$F$_2$O$_5$ requires: C, 59.64; H, 5.89 %); υ_{max}(film)/cm^{-1} 3486br, 2949s, 1720s, 1455w, 1370s, 1247s, 1101s, , 909s, 700s; δ_H (300 MHz, CDCl$_3$) 7.40-7.28 (5H, m, 5 x PhH), 4.87 (1H, m, CH(OAc)), 4.86, (1H, d, AB, ^2J 11.5, PhCH_aH$_b$), 4.75 (1H, d, AB, ^2J 11.5, PhCH$_a$$H_b$), 4.22 (1H, d, J 6.4, CHCH$_2$), 3.96 (1H, dddd, $^3J_{H-F}$ 14.6, J 5.6, ^4J 3.7, 1.2, CHCF$_2$), 3.60
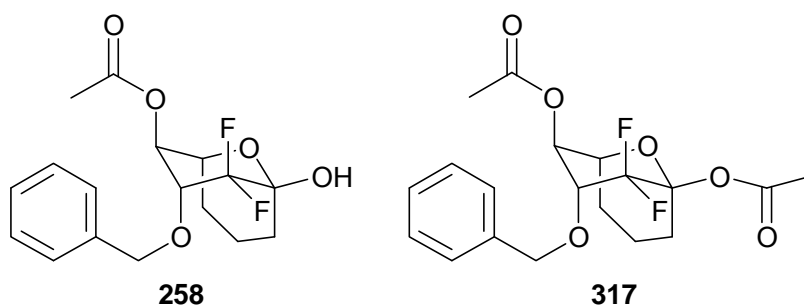
(1H, br. s, OH), 2.34-1.60 (env. containing, 2.34-1.60 (6H, m, 3 x CH_2), and 2.08 (3H, s, CH_3)); δ_C (100 MHz, CDCl$_3$) 170.3, 137.0, 128.5, 128.1, 127.9, 117.0 (dd, $^1J_{\text{C-F}}$ 266.3, 250.1), 94.1 (dd, $^2J_{\text{C-F}}$ 29.3, 20.9), 77.9 (dd, $^2J_{\text{C-F}}$ 35.3, 18.6), 75.3, 74.9 (d, $^4J_{\text{C-F}}$ 1.8), 73.6 (dd, $^3J_{\text{C-F}}$ 3.6, 3.6), 29.3 (d, $^3J_{\text{C-F}}$ 1.8), 24.7, 21.0, 15.8 (d, $^4J_{\text{C-F}}$ 1.2); δ_F (282 MHz, CDCl$_3$) -111.3 (1F, ddd, $^2J_{\text{F-F}}$ 258.7, $^3J_{\text{H-F}}$ 14.6, $^4J_{\text{H-F}}$ 4.7), -123.1 (1F, d, $^2J_{\text{F-F}}$ 258.7); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 360.1620. Calc. for C$_{17}$H$_{25}$F$_2$O$_5$N: 360.1617]; m/z (CI$^+$) 360 (100%, [M+NH$_4$]$^+$), 318 (7), 270 (8), 194 (9).

And bis acetate **317** (34 mg, 13%) as a grey paste; R$_f$ (70% ethyl acetate/hexane) 0.48; υ_{max}(film)/cm^{-1} 2954s, 1747s, 1449w, 1369s, 1237s, 1030s, 740s, 699s; δ_H (300 MHz, CDCl$_3$) 7.37-7.28 (5H, m, 5 x PhH), 4.91 (1H, d, AB, ^2J 11.7, PhCH_aH$_b$), 4.86 (1H, d, J 8.1, CH(OAc)), 4.72 (1H, d, ^2J 11.7, PhCH$_a$$H_b$), 4.33 (1H, ddd, $^3J_{\text{H-F}}$ 15.2, 9.5, J 8.1, CHCF$_2$), 4.24-4.19 (1H, m, CHCH$_2$), 2.60-2.54 (1H, m, OCCH_aH$_b$), 2.11 (3H, s, CH$_3$), 2.02 (3H, s, CH_3), 1.95-1.74 (5H, m, OCCH$_a$$H_b$, and CHC$H_2CH_2$); δ_C (100 MHz, CDCl$_3$) 170.3, 167.6, 137.4, 128.4, 128.0, 128.0, 118.3 (dd, $^1J_{\text{C-F}}$ 264.4, 259.6), 100.9 (dd, $^2J_{\text{C-F}}$ 32.0, 19.2), 77.5 (dd, $^3J_{\text{C-F}}$ 25.6, 19.2), 77.2, 75.3 (d, $^4J_{\text{C-F}}$ 2.4), 72.8 (dd, $^4J_{\text{C-F}}$ 7.2, 3.2), 29.5, 25.5, 21.6, 20.8, 16.9 (d, $^3J_{\text{C-F}}$ 4.8); δ_F (282 MHz, CDCl$_3$) -107.9 (1F, ddd, $^2J_{\text{F-F}}$ 255.4, $^3J_{\text{H-F}}$ 9.5, $^4J_{\text{H-F}}$ 1.9), -119.8 (1F, dd, $^2J_{\text{F-F}}$ 255.4, $^3J_{\text{H-F}}$ 15.2); [HRMS (ES$^+$, [M+H]$^+$) Found: 385.1459. Calc. for C$_{19}$H$_{22}$F$_2$O$_6$: 385.1457]; m/z (EI$^+$) 384 (36%, [M]$^+$), 342 (75), 278 (19), 250 (27), 232 (100), 218 (70), 201 (93).

Preparation of 4R*-Acetoxy-3R*-benzyloxy-1R*-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nonane 318 and 3R*-benzyloxy-1R*-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nonan-4R*-ol 310

318   310
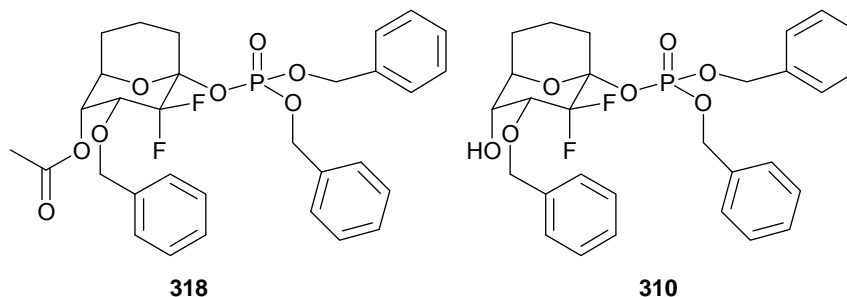
NaHDMS (0.54 mmol, 317 µl of a 1.7 molar solution in THF) was added dropwise to diol **257** (0.49 mmol, 168 mg) in THF (10 cm^3) at 0°C and stirred at this temperature for 1 hour. Tetrabenzyl pyrophosphate (0.54 mmol, 290 mg) was added and the reaction allowed to warm to room temperature over 2 hours, then stirred for 18 hours after which a white precipitate was observed. The reaction was quenched with pH 7 buffer (10 cm3) and extracted into ethyl acetate (2 x 50 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried (MgSO$_4$), filtered and concentrated in vacuo to give a grey paste which was purified on flash silica column eluted with 50% ethyl acetate in hexane to give phosphate **318** (188 mg 64%); R$_f$ (100% ethyl acetate) 0.60; υ_{max}(film)/cm^{-1} 3472w, 2955s, 1738s, 1496s, 1455s, 1371s, 1243s, 1017s, 873w, 738s; δ_H (300 MHz, CDCl$_3$) 7.38-7.28 (15H, m, 15 x Ph*H*), 5.22-5.18 (1H, m, C*H*(OAc)), 5.17-5.05 (4H, m, 2 x PhC*H$_2$*), 4.75 (2H, s, PhC*H$_2$*), 4.35 (1H, d, *J* 6.6, CHC*H$_2$*), 4.05 (1H, ddd, $^3J_{H-F}$ 20.5, *J* 7.0, $^3J_{H-F}$ 5.0, C*H*CF$_2$), 2.56-2.40 (1H, m, CC*H$_a$H$_b$*), 2.16-1.79 (env. containing 2.16-1.79 (3H, m, CHC*H$_2$* and CC*H$_a$H$_b$*) and 2.06 (3H, s, C*H$_3$*)), 1.52-1.36 (2H, m, CH$_2$C*H$_2$*CH$_2$); δ_C (100 MHz, CDCl$_3$) 170.5, 136.6, 136.0 (d, $^3J_{C-P}$ 8.8), 135.7 (d, $^3J_{C-P}$ 8.0), 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 116.0 (ddd, $^2J_{F-F}$ 264.7, 256.9, $^3J_{C-P}$ 6.8),

99.8 (ddd, $^2J_{\text{C-F}}$ 27.2, 18.4, $^2J_{\text{C-P}}$ 7.2), 75.8, 73.3, 73.0 (ddd, $^2J_{\text{C-F}}$ 21.6, 17.6, $^4J_{\text{C-P}}$ 1.6), 70.4 (d, $^3J_{\text{C-F}}$ 9.6), 69.7 (dd, $^2J_{\text{C-P}}$ 6.4, $^6J_{\text{C-F}}$ 1.6), 69.4 (d, $^2J_{\text{C-P}}$ 6.4), 27.8, 22.6, 20.9, 18.4; δ_{F} (282 MHz, CDCl$_3$) (-117.7)-(-118.5) (1F, m inc. app. d, $^2J_{\text{H-F}}$ 245.9), -124.3 (1F, ddd, $^2J_{\text{F-F}}$ 245.9, $^3J_{\text{H-F}}$ 20.5, $^4J_{\text{H-F}}$ 5.2); δ_{P} (121 MHz, CDCl$_3$) -8.8 (1P, quintet, $^3J_{\text{H-P}}$ 7.3); [HRMS (ES$^+$, [M+H]$^+$) Found: 603.1955. Calc. for C$_{31}$H$_{34}$F$_2$O$_8$P: 603.1954]; m/z (CI$^+$) 603 (28%, [M+H]$^+$), 513 (5), 360 (7), 125 (13), 108 (51), 106 (100). Occasionally deprotection of the acetate protecting group was observed to give small amounts of alcohol **310** reported previously.

Preparation of 4*S**-Acetoxy-3*R**-benzyloxy-1*S**-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nonane 319 and 3*R**-benzyloxy-1*S**-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nonan-4*S**-ol 313

319   **313**
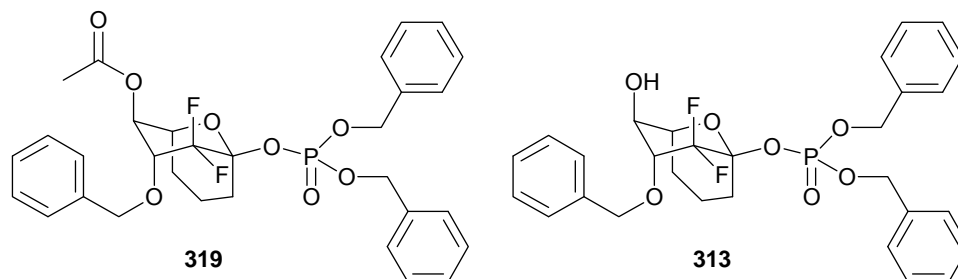
NaHDMS (0.45 mmol, 265 μl of a 1.7 molar solution in THF) was added dropwise to Diol **258** (0.41 mmol, 140 mg) in THF (8.2 cm^3) at 0°C and stirred at this temperature for 1 hour. Tetrabenzyl pyrophosphate (0.45 mmol, 243 mg) was added and the reaction allowed to warm to room temperature over 2 hours, then stirred for 18 hours after which a white precipitate was observed. The reaction was quenched with pH 7 buffer (10 cm^3) and extracted into ethyl acetate (2 x 40 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried (MgSO$_4$), filtered and concentrated in vacuo to give a grey paste which was purified on flash silica column eluted with 50% ethyl acetate in hexane to give phosphate **319** (208 mg 84%); R$_f$ (50% ethyl Acetate/Hexane) 0.43; υ$_{max}$(film)/cm^{-1} 3460br, 2956s, 1745s, 1497s, 1455s, 1396s, 1238s, 1108s, 1024s, 740s, 698s; δ$_H$ (300 MHz, CDCl$_3$) 7.37-7.28 (15H, m, 15 x Ph*H*), 5.10 (2H, dd, $^3J_{\text{H-P}}$ 7.3, ^2J 1.9, PhC*H*$_2$OP), 5.09 (2H, d, $^3J_{\text{H-P}}$ 7.3, PhC*H*$_2$OP), 4.88 (1H, d, AB, ^2J 11.5, PhC*H*$_a$H$_b$OC), 4.82 (1H, dt, *J* 6.1, $^4J_{\text{H-F}}$ 1.9, C*H*(OAc)), 4.70 (1H, d, ^2J 11.5, PhCH$_a$*H*$_b$OC), 4.30-4.25 (1H, m, C*H*CH$_2$), 4.15 (1H, dt, $^3J_{\text{H-F}}$ 11.4, *J* 6.1, C*H*CF$_2$), 2.30-2.23 (1H, m, OCC*H*$_a$H$_b$), 2.14-2.05 (2H, m, OCCH$_a$*H*$_b$, CHCH$_2$C*H*$_a$H$_b$), 2.01 (3H, s, C*H*$_3$), 1.84-1.71 (3H, m, CHC*H*$_2$, CHCH$_2$CH$_a$*H*$_b$); δ$_C$ (100 MHz, CDCl$_3$) 170.2, 137.2, 136.0 (d, $^3J_{\text{C-P}}$ 8.0), 135.9

(d, $^3J_{C-P}$ 7.2), 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 116.9 (dt, $^1J_{C-F}$ 262.0, $^3J_{C-P}$ 4.8), 100.5 (ddd, $^2J_{C-F}$ 26.4, 18.4, $^2J_{C-P}$ 7.2), 77.6 (dd, $^2J_{C-F}$ 30.4, 19.2), 77.0, 75.3, 72.9 (dd, $^3J_{C-F}$ 5.6, 2.4), 69.5 (d, $^2J_{C-P}$ 5.6), 69.3 (d, $^2J_{C-P}$ 5.6), 30.2, 24.9, 20.8, 16.3 (d, $^3J_{C-F}$ 3.2); δ_F (282 MHz, CDCl$_3$) -108.3 (1F, dd, $^2J_{F-F}$ 255.2, $^3J_{H-F}$ 11.4), -121.9 (1F, dd, $^2J_{F-F}$ 255.2, $^3J_{H-F}$ 11.4); δ_P (121 MHz, CDCl$_3$) -8.1 (1P, quintet, $^3J_{H-P}$ 7.3); [HRMS (ES$^+$, [M+H]$^+$) Found: 603.1960. Calc. for C$_{31}$H$_{34}$F$_2$O$_8$P: 603.1954]; m/z (CI$^+$) 603 (30%, [M+H]$^+$), 530 (8), 360 (9), 270 (11), 125 (14), 106 (100). Occasionally deprotection of the acetate protecting group was to give small amounts of alcohol **313**; R$_f$ (50% ethyl Acetate/Hexane) 0.13; υ_{max}(film)/cm^{-1} 3392br, 3032s, 2955s, 1743w, 1497s. 1455s, 1267s, 1020s, 738s, 670s; δ_H (300 MHz, CDCl$_3$) 7.38-7.28 (15H, m, PhH), 5.10 (2H, d, $^3J_{H-P}$ 7.6, PhCH_2OP), 5.09 (2H, d, $^3J_{H-P}$ 7.6, PhCH_2OP), 4.91 (1H, d, AB, ^2J 11.4, PhCH_aH$_b$OC), 4.61 (1H, d, AB, ^2J 11.4, PhCH$_a$$H_b$OC), 4.31-4.26 (1H, m, C$HCH_2$), 4.04 (1H, ddd, $^3J_{H-F}$ 10.7, 10.7, J 5.8, CHCF$_2$), 3.70 (1H, dt, J 5.8, $^3J_{H-F}$ 2.7, CH(OH)), 2.32-1.43 (6H, m, CH_2CH_2CH_2); δ_C (300 MHz, CDCl$_3$) 137.3, 136.0 (d, $^2J_{C-P}$ 11.2), 135.9 (d, $^2J_{C-P}$ 11.2), 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.8, 127.7, 117.5, td, $^1J_{C-F}$ 262.8, $^3J_{C-P}$ 4.8), 101.0-100.4 (m), 80.1 (dd, $^2J_{C-F}$ 27.2, 17.6), 78.2, 75.3, 70.9 (t, $^3J_{C-F}$ 3.5), 69.4, 69.3, 30.2, 24.5, 16.2 (d, $^3J_{C-F}$ 2.4); δ_F (282 MHz, CDCl$_3$) -107.0 (1F, ddd, $^2J_{F-F}$ 255.9, $^3J_{H-F}$ 10.7, $^3J_{H-F}$ 2.7), -122.1 (1F, d, $^2J_{F-F}$ 255.9, $^3J_{H-F}$ 10.7); δ_P (121 MHz, CDCl$_3$) -7.8 (1P, quintet, $^3J_{H-P}$ 7.6); [HRMS (ES$^+$, [M+H]$^+$) Found: 561.18498 Calc. for C$_{29}$H$_{32}$F$_2$O$_7$P: 561.1852]; m/z (ES$^+$) 561 (100%, [M+H]$^+$), 543 (8), 341 (12), 242 (21), 181 (16), 91 (20).

Preparation of 4S*-Acetoxy-3R*-benzyloxy-1R*-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nonane 320 and 3R*-benzyloxy-1R*-(dibenzylphosphoryloxy)-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nonan-4S*-ol 321

320   **321**

NaHDMS (0.48 mmol, 286 µl of a 1.7 molar solution in THF) was added dropwise to Diol **316** (0.44 mmol, 152 mg) in THF (8.8 cm^3) at 0°C and stirred at this temperature for 1 hour. Tetrabenzyl pyrophosphate (0.48 mmol, 258 mg) was added and the reaction allowed to warm to room temperature, then stirred for 16 hours after which a white precipitate was observed. The reaction was quenched with pH 7 buffer (10 cm3) and extracted into ethyl acetate (2 x 40 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried (MgSO$_4$), filtered and concentrated in vacuo to give a grey paste which was purified on flash silica column eluted with 50% ethyl acetate in hexane to give phosphate **320** (119 mg 49%); R$_f$ (50% ethyl Acetate/Hexane) 0.14; υ_{max}(film)/cm^{-1} 2951s, 1749s, 1455s, 1365s, 1213s, 1018s, 737s, 697s; δ_H (300 MHz, CDCl$_3$) 7.36-7.28 (15H, m, 15 x Ph*H*), 5.20 (dd, *J* 9.7, $^4J_{\text{H-F}}$ 6.4, C*H*(OAc)), 5.10 (2H, dd, $^3J_{\text{H-P}}$ 7.5, ^2J 3.5, PhC*H*$_2$OP), 5.07 (2H, d, $^3J_{\text{H-P}}$ 7.5, PhC*H*$_2$OP), 4.94 (1H, d, AB, ^2J 12.0, PhC*H*$_a$H$_b$OC), 4.68 (1H, d, AB, ^2J 12.0, PhCH$_a$*H*$_b$OC), 4.45 (1H, t, broad, *J* 5.7, CH$_2$C*H*), 4.14 (1H, ddd, $^3J_{\text{H-F}}$ 17.3, 7.0, *J* 9.7, C*H*CF$_2$), 2.58-2.42 (1H, m, CC*H*$_a$H$_b$), 2.18-2.08 (1H, m, CCH$_a$*H*$_b$), 1.99 (3H, s, C*H*$_3$), 1.90-1.70 (2H, m, CHC*H*$_2$), 1.67-1.50 (2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (100 MHz, CDCl$_3$) 169.4, 137.1, 135.9 (d, $^2J_{\text{C-P}}$ 15.0) 135.7 (d, $^2J_{\text{C-P}}$

14.4), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 117.3 (ddd, $^1J_{C-F}$ 259.4, 259.4, $^3J_{C-P}$ 6.8), 99.4 (ddd, $^3J_{C-F}$ 25.7, 18.0, $^2J_{C-P}$ 7.2), 77.1 (t, $^3J_{C-F}$ $^2J_{C-F}$ 19.4), 74.5 (d, $^4J_{C-F}$ 2.4), 71.8 (d, $^3J_{C-F}$ 9.0), 71.0, 69.7 (d, $^2J_{C-P}$ 7.2), 69.4 (d, $^2J_{C-P}$ 6.0), 27.5, 20.7, 20.4, 18.2; δ_F (282 MHz, CDCl$_3$) -115.7 (1F, dd, $^2J_{F-F}$ 246.9, $^3J_{H-F}$ 7.0), -126.1 (1F, ddd, $^2J_{F-F}$ 246.9, $^3J_{H-F}$ 17.3, $^4J_{H-F}$ 6.4); δ_P (121 MHz, CDCl$_3$) -8.6 (1P, quintet, $^3J_{H-P}$ 7.5); [HRMS (ES$^+$, [M+H]$^+$) Found: 603.1959. Calc. for C$_{31}$H$_{34}$F$_2$O$_8$P: 603.1954]; m/z (CI$^+$) 603 (22%, [M+H]$^+$), 360 (50), 270 (48), 212 (10), 156 (10), 106 (100). Occasionally deprotection of the acetate protecting group was observed to give small amounts of alcohol **321**; R$_f$ (50% ethyl Acetate/Hexane) 0.15; υ_{max}(film)/cm^{-1} 3359br, 2916s, 1751w, 1455s, 1267s, 1016br, 740s, 697s; δ_H (300 MHz, CDCl$_3$) 7.40-7.29 (15H, m, 15 x PhH), 5.10 (1H, d, $^3J_{H-P}$ 7.3, PhCH_aH$_b$OP), 5.08 (1H, d, $^3J_{H-P}$ 7.3, PhCH$_a$H$_b$OP), 5.07 (2H, d, $^3J_{H-P}$ 7.3, PhCH_2OP), 5.01 (1H, d, AB, ^2J 11.3, PhCH_aH$_b$OC), 4.69 (1H, d, AB, ^2J 11.3, PhCH$_a$H$_b$OC), 4.31 (1H, t, broad, J 5.3, CH$_2$CH), 4.11-3.94 (env. containing 4.11-4.04 (1H, m, CH(OH)) and 4.02 (1H, ddd, $^3J_{H-F}$ 17.1 J 9.5, $^3J_{H-F}$ 7.0, CHCF$_2$)), 2.50-2.32 (1H, m, CCH_aH$_b$), 2.18-2.08 (1H, m, CCH$_a$H$_b$), 1.93-1.52 (4H, m, CHCH_2CH_2)); δ_F (282 MHz, CDCl$_3$) (-114.5)-(-115.4) (1F, m inc. app. d, $^2J_{F-F}$ 247.1), (-125.7)-(-126.7) (1F, m inc. app. d $^2J_{F-F}$ 247.1); δ_P (121 MHz, CDCl$_3$) -8.4 (1P, quintet, $^3J_{H-P}$ 7.3); [HRMS (ES$^+$, [M+H]$^+$) Found: 561.1845. Calc. for C$_{29}$H$_{32}$F$_2$O$_7$P: 561.1849]; m/z (ES$^+$) 561 (100%, [M+H]$^+$), 381 (10), 181 (36), 118 (47), 105 (84).

Preparation of 2,2-Difluoro-3R*,4S*-dihydroxy-9-oxa-1S*,5R*-bicyclo[3.3.1]nonanyl-1S*-phosphate ammonium sodium salt 322

Phosphate di-ester **318** (0.28 mmol, 170 mg) was dissolved in a suspension of palladium activated carbon (64 mg) and ethanol (5.6 cm^3). The atmosphere was removed and replaced with a balloon of hydrogen, and the reaction stirred at rt for 90 hours. The solution was filtered through celite and concentrated in *vacuo* to give phosphate di-acid **325** (98 mg, 100%); δ_F {^{1}H} (282 MHz, MeOD) −116.3 (1F, d, $^2J_{F\text{-}F}$ 243.2), -121.2 (1F, d, $^2J_{F\text{-}F}$ 243.2); δ_P (121 MHz, MeOD) +8-(-12) (1P, m, broad); [HRMS (ES$^-$, [M-H]$^-$) Found: 331.0396. Calc. for $C_{10}H_{14}F_2O_8$: 331.0400]; *m/z* (ES$^-$) 331 (100%, [M-H]$^-$), 289 (15), 167 (17), 89 (46), 75 (44). The crude di-acid (0.28 mmol, 98 mg) was dissolved in a solution of methanol, water, and triethylamine (5.9 cm^3, of a 5:2:1 solution) and stirred at rt for 22 hours. The organic solvents were removed in vacuo, then the water was freeze dried to give the triethylamine salt **328**; δ_F (282 MHz, MeOD) −119.7 (1F, d, $^2J_{F\text{-}F}$ 245.0), -124.2 (1F, dd, $^2J_{F\text{-}F}$ 245.0, $^3J_{H\text{-}F}$ 20.8); δ_P (121 MHz, MeOD) −3.9 (1P, s); [HRMS (ES$^+$, [M+H]$^+$) Found: 493.2851. Calc. for $C_{20}H_{43}F_2O_7P$: 493.2849]; *m/z* (ES$^+$) 493 (58%, [M+H]$^+$), 392 (97), 242 (5), 102 (100), 74 (35). Purification on silica eluted with ethanol, water, aqueous ammonia (5:3:1) gave phosphate **322** as the mixed sodium/ammonia salt (60 mg, 66 %); R_f (ethanol, water, aqueous ammonia (5:3:1)) 0.13; Mp. 137-139°C; υ_{max}(film)/cm^{-1} 2952br, 1444w, 1361w, 1167m, 1078s, 1040s, 910s, 808s, 751s, 685w; δ_H (400 MHz, D$_2$O) 4.35 (1H, ddd, $^3J_{H\text{-}F}$ 21.5, 8.1, *J* 4.8, C*H*CF$_2$), 4.33-4.31 (1H, m, C*H*CH$_2$), 3.98-3.92 (1H, m, (O)CHC*H*), 2.28 (1H, ddd, ^2J 14.2, *J* 14.0, 7.3,

C*H*aHbC(OH)), 2.06 (1H, dd, ^2J 14.2, J 5.4, CHa*H*bC(OH)), 1.95-1.75 (2H, m, CHC*H*aHbC*H*aHb), 1.71-1.60 (1H, m, CH2CHa*H*b), 1.57-1.50 (1H, dd, J 14.0, 5.3, CHCHa*H*b); δ_C (100 MHz, D2O) 117.4 (dd, $^1J_{C-F}$ 256.4, 250.1), 97.2 (ddd, $^2J_{C-F}$ 25.6, 18.4, $^2J_{C-P}$ 7.2), 76.8, 71.4 (dd, $^3J_{C-F}$ 8.0, 1.6), 68.4 (dd, $^2J_{C-F}$ 20.8, 18.4), 27.6, 22.3, 17.5; δ_F (282 MHz, D2O) (−118.4)-(-119.4) (1F, m inc. app. d, $^2J_{F-F}$ 243.1), -123.7 (1F, ddd, $^2J_{F-F}$ 243.1, $^3J_{H-F}$ 21.5, $^4J_{H-F}$ 5.9); δ_P (121 MHz, D2O), -4.1 (1P, s); [HRMS (ES⁻, [M-H]⁻) Found: 289.0297. Calc. for C8H12F2O7P: 289.0294]; *m/z* (ES⁻) 289 (4%, [M-H]⁻), 273 (5), 183 (3), 125 (56), 97 (100).

Preparation of 2,2-Difluoro-3R*,4R*-dihydroxy-9-oxa-1S*,5R*-bicyclo[3.3.1]nonanyl-1S*-phosphate ammonium sodium salt 323

Phosphate di-ester **319** (0.15 mmol, 89 mg) was dissolved in a suspension of palladium activated carbon (35 mg) and ethanol (3 cm³). The atmosphere was removed and replaced with a balloon of hydrogen, and the reaction stirred at rt for 90 hours. The solution was filtered through celite and concentrated in vacuo to give phosphate di-acid **326** (50 mg, 100%); δ_F (282 MHz, MeOD) −121.7 (1F, dd, AB, $^2J_{F-F}$ 245.9, $^3J_{H-F}$ 7.6), -130.1 (1F, dd, AB, $^2J_{F-F}$ 245.9, $^3J_{H-F}$ 17.5); δ_P (121 MHz, MeOD) (−5)-(-8) (1P, broad m); [HRMS (ES⁻, [M-H]⁻) Found: 331.0400. Calc. for C10H14F2O8P: 331.0400]; *m/z* (ES⁻) 331 (5%, [M-H]⁻), 227 (8), 113 (100), 59 (20). The crude di-acid (0.14 mmol, 48 mg) was dissolved in a solution of methanol, water, and triethylamine (2.8 cm³, of a 5:2:1 solution) and stirred at

rt for 65 hours. The organic solvents were removed in vacuo, then the water was freeze dried to give the triethylamine salt **329**; δ_F (282 MHz, MeOD) −120.7 (1F, dd, AB, $^2J_{F-F}$ 244.0, $^3J_{H-F}$ 7.1), -129.7 (1F, ddd, AB, $^2J_{F-F}$ 244.0, $^3J_{H-F}$ 19.0, $^4J_{H-F}$ 4.7); δ_P (121 MHz, MeOD) −3.6 (1P, s); [HRMS (ES$^+$, [M+H]$^+$) Found: 493.2853. Calc. for $C_{20}H_{43}F_2O_7P$: 493.2849]; *m/z* (ES$^+$) 493 (2%, [M+H]$^+$), 392 (2), 143 (3), 102 (100), 74 (14).

Purification on silica eluted with ethanol, water, aqueous ammonia (5:3:1) gave phosphate **323** as the mixed sodium/ammonium salt (30 mg, 61%); R_f (ethanol, water, aqueous ammonia (5:3:1)) 0.29; Mp. 135-137°C; υ_{max}(solid)/cm^{-1} 2945w,br, 2339w,br, 1443w, 1028s, 948s, 801w; δ_F (400 MHz, D$_2$O) 4.29-4.18 (2H, env. containing 4.11 (1H, ddd, $^3J_{H-F}$ 19.2, *J* 9.8, $^3J_{H-F}$ 8.0, C*H*CF$_2$), and 4.25-4.21 (1H, m, C*H*CH$_2$)), 3.93 (1H, dd, *J* 9.8, 6.4, CH$_2$CHC*H*), 2.34-2.26 (1H, m, C*H*$_a$H$_b$C(OH)), 2.08 (1H, d, br, *J* 14.5, CH$_a$*H*$_b$C(OH)), 1.84-1.54 (4H, m, CHC*H*$_2$C*H*$_2$); δ_C (100 MHz, D$_2$O) 117.6 (ddd, $^1J_{C-F}$ 258.0, 252.4, $^3J_{C-P}$ 5.9), 96.8 (ddd, $^2J_{C-F}$ 26.4, 18.4, $^2J_{C-P}$ 6.4), 73.3, 72.2 (t, $^2J_{C-F}$ 20.0), 71.4 (d, $^3J_{C-F}$ 8.0), 26.8, 19.5, 17.7; δ_F (282 MHz, D$_2$O) −119.9 (1F, dd, AB, $^2J_{F-F}$ 243.3, $^3J_{H-F}$ 8.0), -128.5 (1F, ddd, AB, $^2J_{F-F}$ 243.3, $^3J_{H-F}$ 19.2, $^4J_{H-F}$ 5.7); δ_P (121 MHz, D$_2$O) −2.6 (1P, s); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 308.0705. Calc. for $C_8H_{17}F_2O_7PN$: 308.0705]; *m/z* (ES$^-$) 289 (38%, [M-H]$^-$), 97 (21), 79 (100).

Preparation of 2,2-Difluoro-3R*,4R*-dihydroxy-9-oxa-1R*,5S*-bicyclo[3.3.1]nonanyl-1R*-phosphate ammonium sodium salt 324

Phosphate di-ester **320** (0.35 mmol, 208 mg) was dissolved in a suspension of palladium activated carbon (79 mg) and ethanol (6.8 cm^3). The atmosphere was removed and replaced with a balloon of hydrogen, and the reaction stirred at rt for 84 hours. The solution was filtered through celite and concentrated in vacuo to give phosphate di-acid **327** (110 mg, 96%); δ_F (282 MHz, MeOD) –110.3 (1F, dd, AB, $^2J_{F-F}$ 151.2, $^3J_{H-F}$ 10.9), -123.9 (1F, dd, AB, $^2J_{F-F}$ 251.2, $^3J_{H-F}$ 14.7); δ_P (121 MHz, MeOD) (–5)-(-8) (1P, broad m); A suitable molecular ion could not be obtained. The crude phosphate di-acid (0.33 mmol, 110 mg) was dissolved in a solution of methanol, water, and triethylamine (6.6 cm^3, of a 5:3:1 solution) and stirred at rt for 48 hours. The organic solvents were removed in vacuo, then the water was freeze dried to give the triethylamine salt **330**; δ_F (282 MHz, D$_2$O) –109.6 (1F, ddd, $^2J_{F-F}$ 249.7, $^3J_{H-F}$ 11.8, $^4J_{H-F}$ 3.3), -124.3 (1F, dd, $^3J_{F-F}$ 249.7, $^3J_{H-F}$ 13.3); δ_P (121 MHz, D$_2$O) –4.2 (1P, s); [HRMS (ES$^+$, [M+H]$^+$) Found: 493.2847. Calc. for C$_{20}$H$_{44}$F$_2$O$_7$P: 493.2849]; m/z (ES$^-$) 143 (10%), 102 (100). Purification on silica eluted with ethanol, water, aqueous ammonia (5:3:1) gave phosphate **324** as the mixed sodium/ammonia salt (58 mg, 50 %); R$_f$ (ethanol, water, aqueous ammonia (5:3:1)) 0.28; Mp. 142-144°C; υ_{max}(solid)/cm^{-1} 2954br, 1446w, 1066m, 1023m, 951s, 820w; δ_H (300 MHz, D$_2$O) 4.08-4.03 (1H, m, CHCH$_2$), 3.97 (1H, ddd, $^3J_{H-F}$ 16.8, 11.0, J 8.6, CHCF$_2$), 3.61 (1H, dd, J 8.6, $^4J_{H-F}$ 3.0, CHCHCH$_2$), 2.21-2.12 (1H, m, CCH_aH_b), 2.03-1.90 (1H, m, CCH_aH_b), 1.76-1.59 (3H, m, CHC$H_aH_bCH_2$), 1.50-1.44 (1H, m, CCH_aH_b); δ_C (100 MHz,

D$_2$O) 119.2 (ddd, $^1J_{\text{C-F}}$ 262.1, 257.3, $^4J_{\text{C-P}}$ 3.4), 98.3 (ddd, $^2J_{\text{C-F}}$ 32.9, 18.6, $^2J_{\text{C-P}}$ 5.4), 78.2, 72.1 (dd, $^2J_{\text{C-F}}$ 27.0, 19.1), 70.3 (dd, $^3J_{\text{C-F}}$ 6.8, 1.4), 29.9 (t, $^3J_{\text{C-F}}$ 2.4), 25.5, 16.0 (d, $^4J_{\text{C-F}}$ 4.8); δ_{F} (282 MHz, D$_2$O) −107.5 (1F, ddd, $^2J_{\text{F-F}}$ 246.9, $^3J_{\text{H-F}}$ 11.0, $^4J_{\text{H-F}}$ 3.0), -122.8 (1F, dd, $^2J_{\text{F-F}}$ 246.9, $^3J_{\text{H-F}}$ 16.8); δ_{P} (121 MHz, D$_2$O) −2.9 (1P, s); [HRMS (ES$^-$, [M-H]$^-$) Found: 289.0295. Calc. for C$_8$H$_{12}$F$_2$O$_7$P: 289.0294]; *m/z* (ES$^-$) 289 (10%, [M-H]$^-$), 145 (5), 97 (50), 79 (100).

Preparation of 2-Methyl-3-vinyloxy-propene 338

Mercury trifluoroacetate (0.85 mmol, 365 mg) was added to a stirred solution of 2-methyl-2-propen-1-ol (140 mmol, 11.67 cm^3) in ethyl vinyl ether (75 cm^3). The solution was refluxed for 4hr under an atmosphere of nitrogen then allowed to cool. The solution was washed with NaHCO$_3$ (50 cm^3), water (2 x 50 cm^3), and brine (50 cm^3), dried (MgSO$_4$), and filtered. Distillation (Kugelrohr, bp. 88-96$^{\text{o}}$C/760 mmHg) gave ether **338** as an inseparable 50% (^{1}H NMR) azeotrope with acetal (8.11g, 30%); δ_{H} (300 MHz, CDCl$_3$) 6.43 (1H, dd, $^3J_{\text{trans}}$ 14.3, $^3J_{\text{cis}}$ 6.7, OC*H*=), 5.00-4.98 (1H, m, C=C*H*$_a$H$_b$), 4.92-4.90 (1H, m, C=CH$_a$*H*$_b$), 4.21 (1H, dd, $^3J_{\text{trans}}$ 14.3, ^2J 2.0, CH=C*H*$_a$H$_b$), 3.98 (1H, dd, $^3J_{\text{cis}}$ 6.7, ^2J 2.0, CH=CH$_a$*H*$_b$), 4.10 (2H, s, broad, OC*H*$_2$), 1.76-1.73 (3H, m, CC*H*$_3$), compound previously peported but not characterised by Baker.[153]

Preparation of 4-Methyl-pent-4-enal 335

Ether **338** (21.0 mmol, 4.12 g of a 1:1 solution in acetal) was sealed in a microwave tube fitted with a stirrer bead and irradiated in the cavity of a CEM Explorer microwave. A power rating of up to 300W was used to maintain a temperature of 150°C for a period of 6hr upon which conversion to aldehyde **335** was observed to be ≥95% by proton NMR. Aldehyde **335** was used without any further purification; δ_H (300 MHz, CDCl$_3$) 9.77 (1H, t, J 1.8, CHO), 4.78-4.76 (1H, m, C(Me)=CH$_a$H$_b$), 4.71-4.68 (1H, m, C(Me)=CH$_a$H$_b$), 2.61-2.54 (2H, m, C(O)CH_2), 2.35 (2H, t, J 7.3, CH_2CH=), 1.76-1.74 (3H, m, CH_3); Compound previously reported but not characterised by Baker.[153]

Preparation of 1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-6-methyl-hepta-1,6-diene-3-ol 329

Acetal **131** (25 mmol, 4.7 g) was added dropwise over 20 min to a cold (-78°C) solution of LDA (prepared by the slow addition of nBuLi (50 mmol, 21.01 cm^3 of a 2.38 M solution in hexane) to a cold (-78 °C) stirred solution of diisopropylamine (55 mmol, 7.73 cm^3) in THF (25 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -78°C). The orange/brown

solution was stirred at this temperature for 40 min and 4-methyl-pent-4-enal **335** (37.5 mmol, 3.68 g, as a 1:1 solution in acetal) was added in one portion over 1 min. The mixture was allowed to warm to -40 °C over 3 hours and quenched with ammonium chloride (3 cm^3 of a saturated aqueous solution). Water (50 cm^3) was added and the mixture was extracted with diethyl ether (3 x 50 cm^3). The combined organic extracts were dried (MgSO$_4$), filtered, and concentrated in *vacuo* to leave a yellow oil. Distillation (Kugelrohr, bp 115°C/0.05 mmHg) afforded difluoroallylic alcohol **329** (4.85 g, 73 %, 93 % by GC) as a colourless oil; R_f (30% ethyl acetate/hexane) 0.16; GC retention time 15.01 min.; υ_{max}(film)/cm^{-1} 3434br, 2937br, 1751s, 1648w, 1451w, 1279s, 1236s, 1111w, 1138w, 889s; δ_H (300 MHz, CDCl$_3$) 5.01 (1H, d, ^2J 6.6, OCH_aH$_b$O), 4.88 (1H, d, ^2J 6.6, OCH$_a$$H_b$O), 4.72 (1H, s, C$H_aH_b$=C), 4.70 (1H, s, CH$_a$$H_b$=C), 4.30-4.19 (1H, m, C$H$OH), 3.97 (1H, ddd, ^2J 10.7, J 6.3, 3.6, OCH_aH$_b$CH$_2$O), 3.77 (1H, ddd, ^2J 10.7, J 5.4, 3.1, OCH$_a$$H_bCH_2$O), 3.64-3.55 (2H, m, OCH$_2$CH_2O), 3.40 (3H, s, OCH_3), 3.29 (1H, d, J 8.5, CHOH), 2.06 (2H, q, J 7.6, CH_2(CMe)), 1.92-1.70 (2H, m, CHCH_2), 1.73 (3H, s, C(CH_3)); δ_c (75 MHz, CDCl$_3$) 154.6 (dd, $^1J_{C-F}$ 292.0, 285.9), 144.7, 117.8 (dd, $^2J_{C-F}$ 36.9, 9.8), 110.1, 97.8 (t, $^3J_{C-F}$ 3.4), 71.4, 68.3, 66.7 (t, $^3J_{C-F}$ 2.6), 58.8, 33.5, 31.6, 21.2; δ_F (282 MHz, CDCl$_3$) -100.4 (1F, d, $^2J_{F-F}$ 64.0), -110. (1F, d, $^2J_{F-F}$ 64.0); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 284.16702. Calc. for C$_{12}$H$_{24}$F$_2$O$_4$N: 284.1668]; *m/z* (CI$^+$) 284 (66%, [M+NH$_4$]$^+$), 277 (22), 268 (24), 229 (21), 214 (61), 196 (43), 181 (100), 179 (92), 167 (83), 142 (43), 99 (92), 94 (84).

Preparation of 3-Allyloxy-1,1-difluoro-2-(2-methoxy-ethoxymethoxy)-6-methyl-hepta-1,6-diene 342
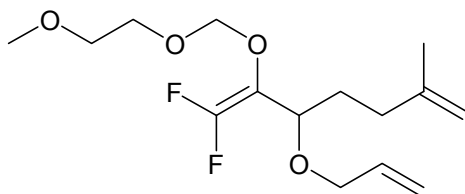
A mixture of difluoroallylic alcohol **329** (17.5 mmol, 4.65 g), and allyl bromide (21.0 mmol, 1.76 cm^3), was added to vigorously stirred sodium hydroxide (122.4 mmol, 6.48 cm^3 of a 50 % aqueous solution), and tetra-*n*-butylammonium hydrogensulfate (0.87 mmol, 0.30 g) at 0 ^{o}C in one portion over 1 min. The mixture was stirred at this temperature for 1 hour, (a white suspension was formed after 10 min) then allowed to warm to room temperature overnight. The yellow white suspension was quenched with ammonium chloride (5 cm^3 of a saturated aqueous solution), and extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to afford the desired ether **342** as a pale yellow oil (4.28 g, 80 %, 97% by GC), which was used without further purification. R$_f$ (30% ethyl acetate/hexane) 0.46; GC retention time 15.26 min.; υ_{max}(film)/cm^{-1} 3077w, 2932s, 2359w, 1749s, 1648s, 1451s, 1375w, 1280s, 1235s, 1117s, 1042s, 952s, 890s; δ_H (300 MHz, CDCl$_3$) 5.88 (1H, dddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.4, 6.2, 5.1, CH$_2$C*H*=), 5.31-5.22 (1H, m inc. app. d, $^3J_{trans}$ 17.2, CH=C*H$_a$*H$_b$), 5.19-5.14 (1H, m inc. app. d, $^3J_{cis}$ 10.4, CH=CH$_a$*H$_b$*), 5.03 (1H, d, ^2J 6.1, OC*H$_a$*H$_b$O), 4.94 (1H, d, ^2J 6.1, OCH$_a$*H$_b$*O), 4.71 (1H, s, C=C*H$_a$*H$_b$), 4.70 (1H, s, C=CH$_a$*H$_b$*) 4.09 (1H, ddt, ^2J 12.5, J 5.1, ^4J 1.4, OC*H$_a$*H$_b$CH), 4.00 (1H, tdd, J 7.0, $^4J_{H-F}$ 3.7, 2.3, OC*H*CH$_2$), 3.93-3.74 (3H, m, OC*H$_2$*CH$_2$, OCH$_a$*H$_b$*CH=), 3.56 (2H, t, J 5.3, CH$_2$C*H$_2$*O), 3.38 (3H, s, OC*H$_3$*), 2.10-2.00 (2H, m,

CCH_2), 1.97-1.66 (2H, m, OCHCH_2), 1.72 (3H, s, CCH_3); δ_C (75MHz, CDCl$_3$) 156.0 (dd, $^1J_{C-F}$ 293.8, 284.7), 144.8, 134.3, 117.2, 112.3 (dd, $^2J_{C-F}$ 36.7, 10.1), 110.3, 97.0 (dd, $^4J_{C-F}$ 4.1, 2.5), 74.0 (t, $^3J_{C-F}$ 3.2), 71.5, 69.2, 68.2 (d, $^6J_{C-F}$ 1.8), 58.9, 33.4, 29.7 (t, $^4J_{C-F}$ 1.9), 22.2; δ_F (282 MHz, CDCl$_3$), -97.9 (1F, dd, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 2.3), -109.6 (1F, dd, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.7); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 324.1979. Calc. for C$_{15}$H$_{27}$F$_2$O$_4$N: 324.1981]; *m/z* (CI$^+$)]; 324 (100%, [M+NH$_4$]$^+$), 286 (12), 277 (26), 236 (15), 219 (26), 196 (19), 181 (23), 179 (34), 165 (34), 94 (24), 52 (81).

Preparation of 4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-deca-1,5,9-trien-3-ol 343
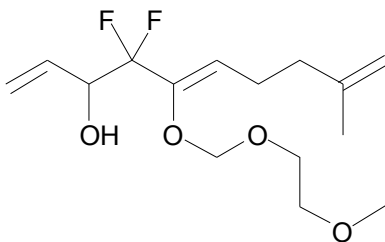
Difluoroallylic ether **342** (13.35 mmol, 4.09 g) in dry THF (26 cm^3) was added dropwise over 20 min to a stirred solution of LDA (prepared by the slow addition of *n*BuLi (26.70 mmol, 11.56 cm^3, of a 2.31 M solution in hexane) to a cold (-78 ^{o}C) stirred solution of diisopropylamine (29.37 mmol, 4.13 cm^3) in THF (133 cm^3)) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -100°C). The pale pink solution was stirred at this temperature for 30 min before being allowed to warm to -40 ^{o}C over four hours. During warming the solution was observed to change colour to yellow then through orange to brown and finally black. The reaction was quenched with ammonium chloride (2 cm^3 of a saturated

methanolic solution); the black colour disappeared and an orange/red solution was observed. The layers were separated and the aqueous phase extracted with diethyl ether (3 x 50 cm^3). The combined organic extracts were washed with brine (2 x 25 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give the product allylic alcohol **343** (3.64 g, 89%, 90% by GC) as an red brown oil, (95% conversion by NMR and GC) which was used without further purification. The following data were obtained from a small sample purified by flash chromatography on silica gel (30% diethyl ether/hexane); R$_f$ (30 % diethyl ether/hexane) 0.20; GC retention time 17.54 min.; υ_{max}(film)/cm^{-1} 3436br, 2919s, 1749w, 1643w, 1443s, 1167w, 1114w, 1038s, 938w, 885w; δ_H (300 MHz, CDCl$_3$) 5.91 (1H, ddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.6, J 5.5, CH$_2$=CH), 5.56 (1H, td, J 7.4, ^4J 1.3, =CHCH$_2$), 5.48 (1H, apparent dt, $^3J_{trans}$ 17.2, ^4J 1.5, ^2J 1.5, HC=CH$_a$$H_b$), 5.33 (1H, aparent dt, $^3J_{cis}$ 10.6, ^4J 1.5, ^2J 1.5, HC=CH$_a$$H_b$), 5.03 (1H, d, ^2J 5.9, OCH_aH$_b$O), 5.01 (1H, d, ^2J 5.9, OCH$_a$$H_b$O) 4.76-4.74 (1H, m, C(Me)=CH_aH$_b$), 4.71-4.68 (1H, m, C(Me)=CH$_a$$H_b$), 4.50 (1H, dddt, $^3J_{H-F}$ 14.2, 8.8, J 5.5, ^4J 1.5, CHCF$_2$), 3.88-3.84 (2H, m, OCH_2CH$_2$O), 3.60-3.56 (2H, m, OCH$_2$CH_2O), 3.38 (3H, s, OCH_3), 2.39-2.29 (2H, m, =CHCH_2), 2.10 (2H, t, J 7.5, CH$_2$CH_2C), 1.72 (3H, s, CCH_3); δ_C (75MHz, CDCl$_3$) 155.2 (dd, $^2J_{C-F}$ 27.5, 25.2), 144.6, 132.5 (dd, $^3J_{C-F}$ 3.6, 2.3), 120.0 (t, $^3J_{C-F}$ 5.0), 118.8, 118.2 (dd, $^1J_{C-F}$ 250.2, 249.2), 110.6, 98.2, 72.4 (dd, $^3J_{C-F}$ 30.4, 27.6), 71.5, 68.8, 59.0, 36.9, 23.4, 22.3; δ_F (282 MHz, CDCl$_3$), -110.1 (1F, dd, $^2J_{F-F}$ 253.1, $^3J_{H-F}$ 8.8), -115.6 (1F, dd, $^2J_{F-F}$ 253.1, $^3J_{H-F}$ 14.2); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 324.1979. Calc. for C$_{15}$H$_{28}$F$_2$O$_4$N: 324.1981] *m/z* (CI$^+$) 324 (33%, [M+NH$_4$]$^+$), 268 (5), 200 (8), 184 (10), 167 (10), 149 (7), 122 (14), 108 (47), 94 (100), 89 (13), 72 (11), 58 (25).

Preparation of 3-benzoic acid 4,4-difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-deca-1,5,9-trienyl ester 344
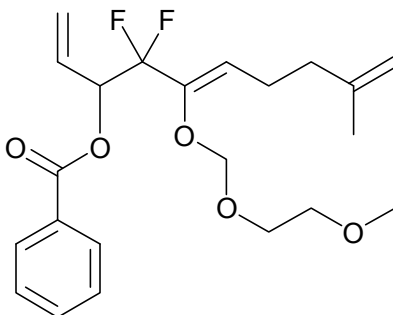
Polyvinylpyridine (9.96 g, 9.96 mmol at 1 mmol equiv g^{-1}), benzoic anhydride (9.66 mmol, 2.57 g), and DMAP (3.86 mmol, 0.47 g) were added to a solution of allylic alcohol **343** (9.66 mmol, 2.96 g) in DCM (100 cm^3), and resulting suspension was shaken for 18 hours at room temperature. The polyvinylpyridine was removed by filtration and washed with DCM (2 x 20 cm^2), then the organics were washed with NaHCO$_3$ (30 cm^3), then brine (50 cm^3), dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give the benzoate **344** as an orange brown oil (2.63 g, 66%, 100% by GC) which was used without further purification; R$_f$ (50 % diethyl ether/hexane) 0.43; GC retention time 23.28 min.; υ_{max}(film)/cm^{-1} 2919s, 1730s, 1449m, 1265s, 1114s, 1032w, 944w, 890w, 712s; δ_H (300 MHz, CDCl$_3$) 8.07 (2H, dd, *J* 8.4, ^4J 1.4, Ph*H*), 7.58 (1H, t, *J* 7.5, Ph*H*), 7.44 (2H, t, *J* 7.5, Ph*H*), 6.02-5.89 (2H, m, =C*H*C*H*), 5.61 (1H, t, *J* 7.6, =C*H*CH$_2$), 5.53 (1H, dd, $^3J_{trans}$ 15.9, ^2J 1.2, *H$_a$*H$_b$C=CH), 5.42 (1H, dd, $^3J_{cis}$ 9.5, ^2J 1.2, H$_a$*H$_b$*C=CH), 5.01 (2H, s, OC*H$_2$*O), 4.68-4.66 (1H, m, *H$_a$*H$_b$C=C), 4.64-4.63 (1H, m, H$_a$*H$_b$*C=C), 3.87 (1H, t, *J* 4.9 OC*H$_a$*H$_b$CH$_2$O), 3.86 (1H, t, *J* 4.5, OCH$_a$*H$_b$*CH$_2$O), 3.57 (2H, dd, *J* 4.9, 4.5, OCH$_2$C*H$_2$*O), 3.38 (3H, s, OC*H$_3$*), 2.37-2.27 (2H, m, =CHC*H$_2$*), 2.02 (2H, t, *J* 7.5, CH$_2$C*H$_2$*C), 1.65 (3H, s, CC*H$_3$*); δ_C (75MHz, CDCl$_3$) 164.8, 144.6 (t, $^2J_{C-F}$ 25.4), 144.3, 133.4, 129.9, 129.5,

128.9, 128.4, 121.4, 120.5 (t, $^3J_{C-F}$ 5.1), 117.3 (dd, $^1J_{C-F}$ 251.1, 249.5), 110.6, 98.2, 72.8 (dd, $^2J_{C-F}$ 31.7, 27.0), 71.6, 69.8, 59.0, 36.8, 32.2, 22.3; δ_F (282 MHz, CDCl$_3$) -110.8 (1F, dd, $^2J_{F-F}$ 253.4, $^3J_{H-F}$ 11.2), -112.4 (1F, dd, $^2J_{F-F}$ 253.4, $^3J_{H-F}$ 12.6); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 428.2243. Calc. for C$_{22}$H$_{32}$F$_2$O$_5$N: 428.2243]; m/z (CI$^+$) 428 (100%, [M+NH$_4$]$^+$), 374 (3), 340 (5), 308 (7), 288 (12), 228 (12), 139 (23), 122 (10), 94 (22), 52 (68).

Preparation of 3-Benzoic acid 4,4-difluoro-9-methyl-5-oxo-deca-1,9-dienyl ester 345
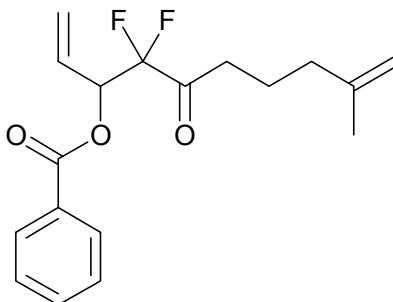
Thionyl chloride (6.41 mmol, 0.470 cm^3) was added to a stirred solution of enol ether **344** (6.41 mmol, 2.63 g) in methanol (65 cm^3) at 0 °C. The solution was allowed to warm to room temperature and stirred for 18 hours after which the solvent was removed in *vacuo*. The resulting paste was suspended in water (50 cm^3) and extracted with diethyl ether (4 x 40 cm^3). The combined organic extracts were washed with NaHCO$_3$ (30 cm^3), brine (30 cm^3), dried (MgSO$_4$), filtered and concentrated in *vacuo* to give an orange oil, which was purified by flash chromatography on silica gel eluted with 5% ether/hexane to give ketone **345** as a clear oil (1.22 g, 59%, 94% by GC); R$_f$ (30% diethyl ether/hexane) 0.54; GC retention time 19.23 min.; υ_{max}(film)/cm^{-1} 3459br, 2935s, 1742s, 1649m, 1602m,

1452s, 1263s, 1107s, 891m, 712s; δ_H (300 MHz, CDCl$_3$) 8.04 (2H, dd, J 8.4, ^4J 1.4, Ph*H*),

7.61 (1H, t, J 7.5, Ph*H*), 7.46 (2H, t, J 7.5, Ph*H*), 6.05-5.88 (2H, m, H$_2$C=C*H*, and

C*H*OBz), 5.58 (1H, dd, $^3J_{trans}$ 16.0, ^2J 1.0, C*H*$_a$H$_b$=CH), 5.52 (1H, dd, $^3J_{cis}$ 9.3, ^2J 1.0,

CH$_a$*H*$_b$=CH), 4.71 (1H, td, ^4J 1.4, ^2J 0.9, C(Me)=C*H*$_a$H$_b$), 4.64 (1H, dd, ^4J 2.2, ^2J 0.9,

C(Me)=CH$_a$*H*$_b$), 2.72 (2H, t, J 7.2, COC*H*$_2$), 2.00 (2H, t, J 7.2, C*H*$_2$C=), 1.76 (2H, pent.,

J 7.2, CH$_2$C*H*$_2$CH$_2$), 1.66 (3H, s, CC*H*$_3$); δ_C (75MHz, CDCl$_3$) 199.8 (dd, $^2J_{C-F}$ 29.9, 28.1),

164.3, 144.3, 133.7, 129.8, 128.9, 128.6, 127.6, 122.7 (dd, $^3J_{C-F}$ 3.1, 2.3), 114.2 (dd, $^1J_{C-F}$

261.6, 256.1), 111.0, 72.4 (dd, $^2J_{C-F}$ 29.7, 25.1), 36.9, 36.5, 22.0, 20.1; δ_F (282 MHz,

CDCl$_3$) -113.7 (1F, dd, $^2J_{F-F}$ 274.0, $^3J_{H-F}$ 8.9), -118.8 (1F, dd, $^2J_{F-F}$ 274.0, $^3J_{H-F}$ 14.6);

[HRMS (ES$^+$, [M+H]$^+$) Found: 323.1454. Calc. for C$_{18}$H$_{21}$F$_2$O$_3$: 323.1453]; *m/z* (CI$^+$) 340

(100%, [M+H$^+$]), 323 (13), 200 (22), 183 (22), 139 (10), 105 (9), 52 (80).

Preparation of 3-Benzoyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-en-1-one 346
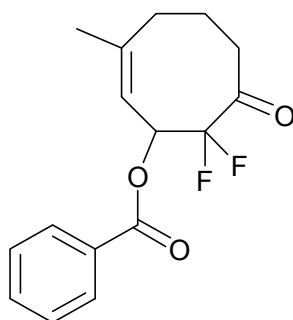
Freshly purified **345** (1.00 mmol, 323 mg), and Ti(O^{i}Pr)$_4$ (0.33 mmol, 0.100 cm^3) were

dissolved in freshly degassed DCM (100 cm^3) under an atmosphere of nitrogen. The

solution was refluxed for 30 min then Grubbs 2nd Generation catalyst (0.1 mmol, 85 mg,

10 mol %) was added. The solution was refluxed for 12 days with two further additions

of catalyst (each 0.05 mmol, 42 mg, 5 mol %) and Ti(O^{i}Pr)$_4$ (each 0.3 mmol, 90 cm^3) after 55, and 134 hours until a conversion of approximately 50% was observed by ^{19}F NMR of aliquots. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel, eluted with 10% ether/hexane, to give cyclooctenone **346** as a yellow oil (70 mg 24%, 99% by GC); GC retention time 20.15 min.; υ_{max}(film)/cm^{-1} 2937s, 2361s, 1731s, 1601w, 1452s, 1271s, 1095s, 1027w, 968w, 710s; δ_H (300 MHz, CDCl$_3$) 8.06-8.02 (2H, m, Ph-*H*), 7.56-7.49 (1H, m, *J* 7.5, Ph-*H*), 7.43-7.36 (2H, m, Ph-*H*), 6.21 (1H, ddd, $^3J_{H\text{-}F}$ 19.8, *J* 8.3, ^4J 3.5, C*H*CF$_2$), 5.28 (1H, d, *J* 8.3, C*H*=CCH$_3$), 2.71 (1H, dddd, *J* 12.6, 10.7, ^2J 3.6, ^4J 2.1, CH$_a$H$_b$C(O)), 2.60-2.50 (1H, m, CH$_a$H$_b$C(O)), 2.45 (1H, td, ^3J 13.3, ^2J 5.2, (Me)CCH$_a$H$_b$), 2.11 (1H, ddd, *J* 13.3, ^2J 5.2, ^4J 2.7, (Me)CCH$_a$H$_b$), 2.07-1.95 (1H, m, CH$_2$CH$_a$H$_b$), 1.86-1.74 (1H, m, CH$_2$CH$_a$H$_b$), 1.70 (3H, s, CC*H*$_3$); δ_c (100 MHz, CDCl$_3$) 199.6 (dd, $^2J_{C\text{-}F}$ 26.2, 24.6), 165.3, 144.6, 133.6, 130.0, 129.1, 128.5, 118.9 (d, $^3J_{C\text{-}F}$ 5.1), 116.5 (dd, $^1J_{C\text{-}F}$ 263.1, 260.3), 68.9 (dd, $^2J_{C\text{-}F}$ 23.9, 18.6), 37.0, 32.9, 26.6, 24.2; δ_F (282 MHz, CDCl$_3$, 323K) -111.1 (1F, d, $^2J_{F\text{-}F}$ 238.8), -132.0 (1F, $^2J_{F\text{-}F}$ 238.8, $^3J_{H\text{-}F}$ 21.1); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 312.1403. Calc. for C$_{16}$H$_{20}$F$_2$O$_3$N: 312.1406]; *m/z* (CI$^+$) 312 (100%, [M+NH$_4$]$^+$), 294 (5), 174 (23), 172 (88), 154 (39), 137 (19), 105 (21), 52 (94).

Preparation of 4,4-Difluoro-3-hydroxy-9-methyl-deca-1,9-dien-5-one 347
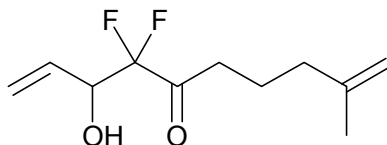
Thionyl chloride (6.41 mmol, 0.47 cm^3) was added to a stirred solution of enol ether **343** (6.41 mmol, 2.63 g) in methanol (65 cm^3) at 0°C. The solution was allowed to warm to room temperature over 1 hour and stirred for 15 hours. The methanol was removed *in vacuo*, and the resulting paste dissolved in water (50 cm^3), and extracted with ether (4 x 40 cm^3). The combined organic extracts were washed with NaHCO$_3$ (30 cm^3), brine (30 cm^3), dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give ketone **347** as an orange oil (1.86g, 90%, 93% GC); which was used crude or purified by distillation (Kugelrohr, bp. 60-65°C 0.025 mmHg) to give **347** a clear oil (76%); R$_f$ (30% ether/hexane) 0.50; GC retention time 11.88 min; υ_{max}(film)/cm^{-1} 3418br, 2940s, 1741s, 1651w, 1456w, 1375w, 1070s, 992m, 938m, 892m, 814w; δ_H (300 MHz, CDCl$_3$) 5.98-5.86 (1H, ddd, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.5, J 5.8, CH$_2$=C*H*), 5.50 (1H, apparent dt, $^3J_{trans}$ 17.1, ^2J 1.2, *H*$_a$H$_b$C=CH), 5.42 (1H, apparent dt, $^3J_{cis}$ 10.5, ^2J 1.2, H$_a$*H*$_b$C=CH), 4.76-4.73 (1H, m, C(Me)=C*H*$_a$H$_b$), 4.70-4.67 (1H, m, C(Me)=CH$_a$*H*$_b$), 4.62-4.50 (1H, m, C*H*(OH)), 2.71 (2H, t, J 7.4, COC*H*$_2$), 2.04 (2H, t, J 7.4, C*H*$_2$C(Me), 1.77 (2H, pent, J 7.4, CH$_2$C*H*$_2$CH$_2$), 1.70 (3H, s, C(C*H*$_3$)); δ_c (75 MHz, CDCl$_3$) 202.0 (dd, $^2J_{C-F}$ 31.0, 27.5), 144.5, 131.2 (t, $^3J_{C-F}$ 3.0), 120.4, 114.9 (dd, $^1J_{C-F}$ 260.2, 256.1), 110.8, 72.1 (dd, $^2J_{C-F}$ 28.6, 25.5), 37.3, 36.6, 22.1, 20.1; δ_F (282 MHz, CDCl$_3$) -113.6 (1F, dd, $^2J_{F-F}$ 271.1, $^3J_{H-F}$ 7.1), -123.4 (1F, dd, $^2J_{F-F}$ 271.1, $^3J_{H-F}$ 15.6); [HRMS (CI$^+$, [M+NH$_4$]$^+$) Found: 236.1457. Calc. for C$_{11}$H$_{20}$F$_2$O$_2$N: 236.1457]; *m/z* (CI$^+$) 236 (100%, [M+NH$_4$]$^+$), 219 (21), 200 (19), 183 (17), 167 (13), 99 (10), 73 (12).

Preparation of 2-Methyl-octa-1,7-dien-3-ol 372
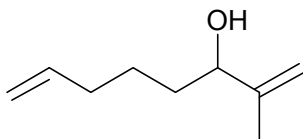
A three neck flask was equipped with a dropping funnel, condenser and nitrogen line. The flask was charged with magnesium turnings (209.6 mmol, 5.09 g) and ether (17 cm^3). 5-Bromopent-1-en **371** (167.7 mmol, 25 g) in diethyl ether (85 cm^3) was added dropwise over 1 hour *via* the dropping funnel; the reaction mixture was stirred during the addition and refluxed without external heating. The black Grignard solution was cooled to 0°C and methacrolein (192.9 mmol, 15.88 cm^3) was added dropwise over 30 min, then the solution was stirred for a further 30 min at this temperature. The reaction was quenched with water (50 cm^3) and a solid was precipitated; the solution was then diluted with water. The liquids were removed and the solids washed with diethyl ether (500 cm^3). The layers were separated and the aqueous was extracted with diethyl ether (2 x 50 cm^3). The combined organic layers were washed with NaHCO$_3$ (30 cm^3), brine (50 cm^3), dried (MgSO$_4$), filtered and the solvent removed in *vacuo*. Distillation of the impurities away from the residue (20°C/0.5 mmHg) gave alcohol **372** as a pale yellow oil (20.80 g, 88 %, 98% by GC) which was used without further purification. R$_f$ (30% ether /hexane) 0.45; bp. 40-42°C 0.075/mmHg; GC retention time 8.61 min; υ_{max}(film)/cm^{-1} 3348br, 2936s, 1641m, 1441m, 994s, 908s; δ_H (300MHz, CDCl$_3$) 5.81 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, J 6.6, =CH), 5.06-4.93 (3H, m, CH=CH_2, C(Me)=CH_aH_b), 4.85-4.83 (1H, m, C(Me)=CH$_a$$H_b$), 4.07 (1H, t, J 6.5, CH(OH)), 2.09 (2H, dt, ^3J 7.1, 6.6, =CHCH_2), 1.72 (3H, s, CH_3), 1.61-1.33 (5H, m, 2 x CH_2, OH); δ_C (75MHz, CDCl$_3$) 147.5, 138.6, 114.5, 110.9, 75.6, 33.9, 33.5, 25.0 17.3; [HRMS (EI$^+$, [M-H]$^+$) Found: 139.1115. Calc. for

C$_9$H$_{15}$O: 139.1117]; *m/z* (EI$^+$) 139 (1%, [M-H]$^+$), 125 (8), 96 (15), 71 (94), 43 (100).

Previously prepared to a lower level of charicterisation by Pattenden[188]

Preparation of 2-Methyl-3-vinyloxy-octa-1,7-diene 370

Mercury(II) trifluoroacetate (1.44 mmol, 633 mg) was added to a solution of alcohol **372** (148.3 mmol, 20.8 g) in ethyl vinyl ether (250 cm^3). The solution was refluxed for 22.5 hours, then the solvent removed in *vacuo* to give a pale yellow oil. Acetal was removed by distillation (bp 15°C/0.5 mmHg) to give ether **370** a pale yellow oil (23.07 g, 94 % 98% conversion by GC) which was used without further purification. For analysis a small sample was purified by Flash chromatography on silica gel eluted with 5% ether/hexane; R$_f$ (5% ether/hexane) 0.66; GC retention time 8.81 min; υ_{max}(film)/cm^{-1} 2935s, 2360w, 1639s, 1443w, 1377w, 1195s, 909s; δ_H (300MHz, CDCl$_3$) 6.29 (1H, dd, $^3J_{trans}$ 14.0, $^3J_{cis}$ 6.6, OC*H*=), 5.80 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, *J* 6.9, =C*H*CH$_2$), 5.06-4.90 (4H, m, C*H$_2$*=CHCH$_2$, C=C*H$_2$*), 4.30 (1H, dd, $^3J_{trans}$ 14.0, ^2J 1.3, OCH=C*H$_a$*H$_b$), 4.09 (1H, dd, *J* 7.0, 6.1, C*H*(O)), 3.99 (1H, dd, $^3J_{cis}$ 6.6, ^2J 1.3, OCH=CH$_a$*H$_b$*), 2.13-2.04 (2H, m, =CHC*H$_2$*), 1.78-1.30 (envelope containing 1.68 (3H, s, CH$_3$) and (4H, m, C*H$_2$*C*H$_2$*CH(O))); δ_C (75MHz, CDCl$_3$) 150.5, 144.2, 138.5, 114.7, 113.2, 88.6, 83.6, 33.5, 32.7, 24.8, 16.9; No suitable molecular ion could be obtained (ES, EI, CI, FAB).

Preparation of 4-Methyl-deca-4,9-dienal 369

Ether **370** (118.0 mmol, 19.57 g) was equally divided into microwave tubes equipped with a stirrer beads. The tubes were sealed and irradiated in the cavity of a CEM Explorer microwave at 150°C for 10 min, until conversion to aldehyde **369** (19.57 g, 100 %, 77 % GC) was observed to be complete by proton NMR. The aldehyde was used without further purification; R_f (10% ether/hexane) 0.41; GC retention time 11.60 (minor diastereoisomer) and 11.88 min (major diastereoisomer); δ_H (400MHz, CDCl$_3$) 9.78 (minor diastereoisomer, 1H, t, J 1.8, CHO), 9.76 (major diastereoisomer, 1H, t, J 2.0), 5.80 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, J 6.7, CH$_2$=CH), 5.16 (1H, tq, J 7.2, ^4J 1.4, CH=C), 5.00 (1H, m inc. app. d, $^3J_{trans}$ 17.1, CH_aH$_b$=CH), 4.94 (1H, ddt, $^3J_{cis}$ 10.2, ^4J 2.2, ^2J 1.4, CH$_a$$H_b$=CH), 2.54-2.46 (2H, m, =C(CH$_3$)CH_2), 3.33 (2H, t, J 7.6, CH_2CHO), 2.08-1.96 (4H, m, 2 x =CHCH_2), 1.69 (minor diastereoisomer, 3H, m, CH_3), 1.61 (major diastereoisomer, 3H, m, CH_3), 1.42 (2H, quintet, J 7.6, CH$_2$CH_2CH$_2$); δ_C (100MHz, CDCl$_3$) 202.6, 202.2, 138.8, 138.7, 133.1, 133.0, 126.6, 125.5, 114.5, 114.4, 42.3, 42.1, 33.4, 33.3, 31.8, 29.1, 28.9, 27.3, 27.2, 24.3, 23.0, 16.1; [HRMS (ES$^+$, [M+H]$^+$) Found: 167.1431. Calc. for C$_{11}$H$_{19}$O: 167.1430]; m/z (CI$^+$) 167 (23%, [M+H]$^+$), 149 (14), 122 (13), 81 (15), 52 (50).
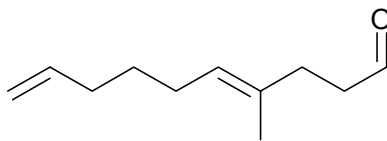
Preparation of 1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-6-methyl-dodeca-1,6,11-trien-3-ol 368
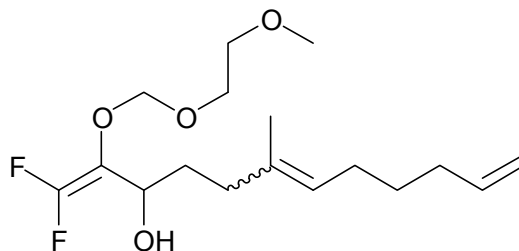
Acetal **131** (30.00 mmol, 5.03 cm^3) was added dropwise over 20 min to a cold (-78°C) solution of LDA (prepared by the slow addition of *n*-BuLi (60.00 mmol, 20.69 cm^3, of a 2.90 M solution in hexane) to a cold (-78°C) stirred solution of diisopropylamine (66.00 mmol, 9.28 cm^3) in THF (35 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -78°C). The orange/brown solution was stirred at this temperature for 45 minutes hours and aldehyde **369** (36.00 mmol, 6.55 g, @ 77 % purity by GC) was added in one portion over 1 min. The mixture was stirred at this temperature for 1 hour then allowed to warm to -30 $^{\circ}$C over 2 hours and quenched with ammonium chloride (10 cm^3 of a saturated methanolic solution). Water (50 cm^3) was added and the mixture was extracted with diethyl ether (3 x 120 cm^3). The combined organic extracts were washed with brine (2 x 50 cm^3), dried (MgSO$_4$), filtered and concentrated *in vacuo* to leave a red/brown oil (8.42 g, 84 %) which was used without any further purification. These data were obtained from a sample purified by flash chromatography on silica gel eluted with a gradient (0-20%) of ethyl acetate in hexane to give the desired difluoroallylic alcohol **368** as a yellow oil; R$_f$ (20% ethyl acetate/hexane) 0.16; GC retention time, minor diastereoisomer. 19.36 min; major diastereoisomer. 19.80 min; υ_{max}(film)/cm^{-1}3437br, 2930s, 1752m, 1637w, 1443w, 1237w, 1112s, 732m; δ_H (300MHz, CDCl$_3$) 5.77 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.2, *J* 6.6,

C*H*=CH₂), 5.12 (1H, t, *J* 6.9, C(Me)=C*H*), 5.01-4.74 (4H, m, =C*H*₂, OC*H*₂O), 4.19 (1H, br. s, C*H*(OH)), 3.97-3.53 (4H, m, OC*H*₂C*H*₂O), 3.36 (3H, s, OC*H*₃), 2.07-1.93 (6H, m, 3 x C*H*₂), 1.85-1.60 (2H, m, C*H*₂) 1.60 (3H, s, CC*H*₃), 1.44-1.34 (2H, quintet, *J* 7.4, CH₂C*H*₂CH₂); δ_C (75MHz, CDCl₃) 154.6 (dd, $^1J_{C-F}$ 292.0, 286.0), 138.9, 134.1, 124.9, 118.1 (dd, $^2J_{C-F}$ 36.8, 9.9), 114.3, 97.9 (dd, $^4J_{C-F}$ 4.2, 3.0), 71.4, 68.4, 66.8 (dd, $^3J_{C-F}$ 3.0, 1.8), 59.0, 35.5, 33.3, 32.0, 28.9, 27.3, 15.8; δ_F (282MHz, CDCl₃) −100.2 (minor diastereoisomer, d, $^2J_{F-F}$ 63.5), −100.3 (major diastereoisomer, 1F, d, $^2J_{F-F}$ 63.5), -109.6 (minor diastereoisomer, dd, $^2J_{F-F}$ 63.5, $^4J_{H-F}$ 3.3), -109.7 (major diastereoisomer, 1F dd, $^2J_{F-F}$ 63.5, $^4J_{H-F}$ 3.0); [HRMS (ES⁺, [M+H]⁺) Found: 335.2027. Calc. for C₁₇H₂₉F₂O₄: 335.2028]; *m/z* (ES⁺) 335 (5%, [M+H]⁺), 321 (8), 280 (11), 229 (6), 188 (100), 115 (15), 89 (12).

Preparation of 3-Allyloxy-1,1-difluoro-2-(2-methoxy-ethoxymethoxy)-6-methyl-dodeca-1,6,11-triene 374
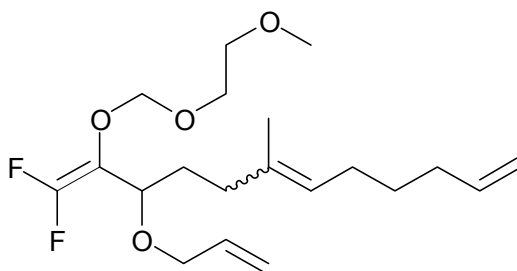
A mixture of difluoroallylic alcohol **368** (25.2 mmol, 8.42 g), allyl bromide (30.2 mmol, 2.63 cm³), was added to stirred sodium hydroxide (140.0 mmol, 7.4 cm³) of a 50 % aqueous solution, and tetra-*n*-butylammonium hydrogensulfate (2.5 mmol, 0.85 g) at 0 °C in one portion over 1 min. The mixture was stirred at this temperature for 1 hour, (a white

suspension was formed after 10 min) then allowed to warm to room temperature and stirred for 40 hours. The yellow white suspension was quenched with water (20 cm^3) and extracted with diethyl ether (2 x 150 cm^3). The combined organic extracts were washed with brine (50 cm^3), dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the desired ether **374** as a pale yellow oil (8.662 g, 92 %), which was used without further purification. For analysis a sample (0.512 mg) was purified by flash chromatography on silica gel eluted with 10% diethyl ether/hexane to give **374** as a yellow oil (230 mg, 36%, 84% GC); R$_f$ (10% diethyl ether/hexane) 0.39; GC retention time minor 20.00 min; major 22.44 min; v_{max}(film)/cm^{-1} 2929s, 1749m, 1640m, 1452w, 1231w, 1131s, 914w; δ_H (300MHz, CDCl$_3$) 5.94-5.74 (env. containing 5.94-5.81 (1H, m, OCH$_2$C*H*=), and 5.81 (1H, ddt, $^3J_{trans}$ 16.8, $^3J_{cis}$ 10.1, J 6.6, CH$_2$CH$_2$C*H*=)), 5.31-5.24 (1H, m inc. app. d, $^3J_{trans}$ 17.1, OCH$_2$CH=C*H*$_a$H$_b$), 5.20-5.10 (env. containing 5.20-5.14 (1H, m, $^3J_{cis}$ 10.2, OCH$_2$CH=CH$_a$*H*$_b$), and 5.16 (1H, t, J 7.0, C(Me)=C*H*)), 5.04-4.91 (4H, m, OC*H*$_2$O, (CH$_2$)$_2$CH=C*H*$_2$), 4.08 (1H, ddt, ^2J 12.6, J 5.0, 1.5, OC*H*$_a$H$_b$CH$_2$O), 4.00-3.74 (4H, m, OCH$_a$*H*$_b$CH$_2$O, C*H*(O), OC*H*$_2$CH), 3.59-3.55 (2H, m, OCH$_a$H$_b$C*H*$_2$O), 3.39 (3H, s, OCH$_3$), 2.09-1.66 (8H, m, C*H*$_2$CH$_2$C(Me), C*H*$_2$CH$_2$C*H*$_2$), 1.59 (3H, s, CCH$_3$), 1.47-1.36 (2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75MHz, CDCl$_3$) * Both diastereoisomer, 155.0* (dd, $^1J_{C-F}$ 293.8, 284.8), 138.9*, 134.4*, 134.0*, 125.8 (minor diastereoisomer), 125.1 (major diastereoisomer), 117.1*, 114.3*, 112.4* (dd, $^2J_{C-F}$ 36.5, 9.6), 97.1* (dd, $^4J_{C-F}$ 3.8, 2.6), 74.3 (t, $^3J_{C-F}$ 3.0, minor diastereoisomer), 74.0 (t, $^3J_{C-F}$ 3.3, major diastereoisomer), 71.6*, 69.2*, 68.2* (d, $^5J_{C-F}$ 1.8), 59.0*, 35.3 (major diastereoisomer), 33.3 (minor diastereoisomer), 33.3 (major diastereoisomer), 30.1 (m, minor diastereoisomer), 30.0 (major diastereoisomer), 29.2 (minor diastereoisomer), 29.0 (major diastereoisomer),

27.5 (minor diastereoisomer), 27.3 (major diastereoisomer), 27.1 (minor diastereoisomer), 23.2 (minor diastereoisomer), 15.8 (major diastereoisomer); δ_F (282MHz, CDCl$_3$) −97.6 (minor diastereoisomer, 1F, dd, $^2J_{F-F}$ 36.3, $^4J_{H-F}$ 3.5), -97.7 (major diastereoisomer, 1F, dd, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5), -109.3 (minor diastereoisomer, 1F, dd, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5), -109.5 (major diastereoisomer, 1F, dd, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 392.2611. Calc. for C$_{20}$H$_{36}$F$_2$O$_4$N: 392.2607]; m/z (CI$^+$) 392 (97%, [M+NH$_4$]$^+$), 251 (19), 233 (21), 182 (20), 122 (64), 94 (100).

Preparation of 4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-pentadeca-1,5,9,14-tetraen-3-ol 375
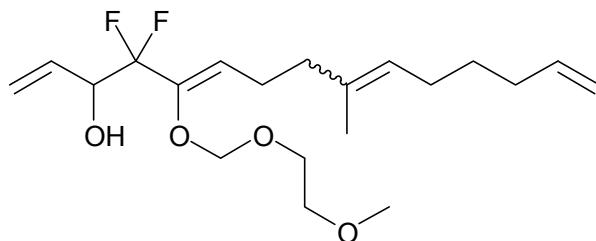
Difluoroallylic ether **374** (23.04 mmol, 8.662 g) in THF (23 cm^3) was added dropwise over 15 min to a stirred solution of LDA (prepared by the slow addition of nBuLi (46.07 mmol, 15.89 cm^3, of a 1.9 M solution in hexane) to a cold (-78 ^{o}C) stirred solution of diisopropylamine (50.69 mmol, 7.12 cm^3) in THF (230 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -100°C). The pale pink solution was stirred and allowed to warm to -70°C over 1.5 hours before being allowed to warm to -40°C over 3 hours. The reaction was quenched with ammonium chloride (10 cm^3 of a saturated methanolic solution) whereupon the black colour disappeared and an orange/red solution was observed. Water

(50 cm^3) was added, the layers separated and the aqueous phase extracted with diethyl ether (3 x 100 cm^3). The combined organic extracts were washed with NaHCO$_3$ (20 cm^3), brine (2 x 100 cm^3), dried (MgSO$_4$), and concentrated in *vacuo* to afford allylic alcohol **375** (8.53 g, 98 %, at >95 % conversion from **374** by ^{19}F NMR) as an red brown oil, which was used without further purification. For analysis a sample (250 mg) was purified by flash chromatography on silica eluted with 30% diethyl ether/ hexane (pre-washed with 5% triethylamine in 30% diethyl ether/ hexane) to give **375** as a yellow oil (110 mg, 44%); R$_f$ (30% ether/hexane) 0.11; GC retention time minor 21.85 min, major 22.13 min; ν_{max}(film)/cm^{-1} 3420br, 2922s, 1640w, 1458w, 1116s, 910s, 733s; δ_H (300MHz, CDCl$_3$) 5.92 (1H, ddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.5, J 5.6, =C*H*CH), 5.80 (1H, ddt, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.1, J 6.6, CH$_2$C*H*=CH$_2$), 5.55 (1H, td, J 7.4, ^4J 1.3, (O)C=C*H*), 5.48 (1H, app. dt, $^3J_{trans}$ 17.2, ^2J 1.5, *H*$_a$H$_b$C=CHCH), 5.34 (1H, app. dt, $^3J_{cis}$ 10.5, ^2J 1.5, H$_a$*H*$_b$C=CHCH), 5.15 (1H, td, J 7.2, ^4J 1.0, (Me)C=C*H*), 5.04-4.91 (4H, m, OC*H*$_2$O, CH$_2$CH=C*H*$_2$), 5.56-5.44 (1H, m, C*H*(OH)), 3.90-3.80 (2H, m, OC*H*$_2$CH$_2$O), 3.59-3.56 (2H, m, OCH$_2$C*H*$_2$O), 3.38 (3H, s, OC*H*$_3$), 2.79 (1H, d, J 6.0, O*H*), 2.34-2.23 (2H, m, (O)C=CHC*H*$_2$), 2.12-1.95 (6H, m, C*H*$_2$C(Me), C(Me)=CHC*H*$_2$, and, C*H*$_2$CH=CH$_2$), 1.68 (3H, d, ^4J 1.0, minor diastereoisomer CC*H*$_3$), 1.59 (3H, s, major diastereoisomer, CC*H*$_3$), 1.42 (2H, quintet, J 7.4, CH$_2$C*H*$_2$CH$_2$); δ_C (100MHz, CDCl$_3$) * both diastereoisomer, 145.2* (dd, $^2J_{C-F}$ 27.6, 25.2), 139.0 (major diastereoisomer), 139.0 (minor diastereoisomer), 133.9 (major diastereoisomer), 133.9 (minor diastereoisomer), 132.5* (dd, $^3J_{C-F}$ 3.2, 2.4), 126.3 (minor diastereoisomer), 125.4 (major diastereoisomer), 120.2 (t, $^3J_{C-F}$ 5.2, major diastereoisomer), 120.0 (t, $^3J_{C-F}$ 5.1, minor diastereoisomer), 118.8*, 118.2* (dd, $^1J_{C-F}$ 250.4, 247.2), 114.44 (major diastereoisomer), 114.43 (minor diastereoisomer), 98.3

(minor diastereoisomer), 98.2 (major diastereoisomer), 72.4* (dd, $^2J_{C-F}$ 30.8, 27.5), 71.5*,

68.8*, 59.0*, 38.8 (major diastereoisomer), 33.4 (minor diastereoisomer), 33.3 (major

diastereoisomer), 31.0 (minor diastereoisomer), 29.2 (minor diastereoisomer), 28.9

(major diastereoisomer), 27.3 (major diastereoisomer), 27.3 (minor diastereoisomer),

23.8 (major diastereoisomer), 23.7 (minor diastereoisomer), 23.1 (minor diastereoisomer),

15.8 (major diastereoisomer); δ_F (282MHz, CDCl$_3$) −109.7 (minor diastereoisomer, 1F,

dd, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 9.0), -109.8 (major diastereoisomer, 1F, dd, $^2J_{F-F}$ 253.0, $^3J_{H-F}$ 8.5), -

115.7 (major diastereoisomer, 1F, dd, $^2J_{F-F}$ 253.0, $^3J_{H-F}$ 14.2), -115.9 (minor

diastereoisomer, 1F, dd, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 14.7); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found:

392.2606. Calc. for C$_{20}$H$_{36}$F$_2$O$_4$N: 392.2607]; m/z (CI$^+$) 392 (100%, [M+NH$_4$]$^+$), 299 (9),

142 (38), 122 (31), 94 (92).

**Preparation of 3- benzyloxy-4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-
pentadeca-1,5,9,14-tetraene 376**
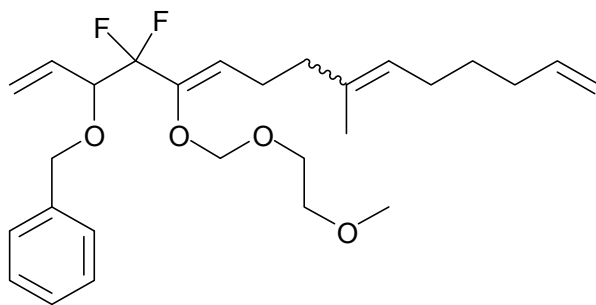
Allylic alcohol (22.67 mmol, 8.53 g) **375** in THF (70 cm^3) was added cautiously to a

suspension of NaH (68.05 mmol, 2.72 g, of a 60% suspension in mineral oil, pre-washed

with hexane (3 x 50 cm^3) in THF at 0°C under a nitrogen atmosphere. The mixture was

stirred at this temperature for 45 min while a gas was evolved. TBAI (2.27 mmol, 0.837

g) and benzyl bromide (24.94 mmol, 2.96 cm^3) were added, and the reaction was allowed to warm to room temperature over 3 hours, and then stirred overnight. The reaction was quenched by the cautious addition of water (150 cm^3) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 150 cm^3) and the combined organic extracts were washed with brine (2 x 100 cm^3), dried (MgSO$_4$), and concentrated in *vacuo* to give benzyl ether **376** as a brown oil (9.719 g, 92%), which was used without any further purification. For characterisation a small sample (181 mg) was purified by flash chromatography on silica gel eluted with 10% diethyl ether/hexane to give **376** as a yellow oil; R$_f$ (10% diethyl ether/hexane) 0.11; ν_{max}(film)/cm^{-1} 2927s, 2358m, 1682w, 1640w, 1454, 1116, 938m, 853s, 736s, 699s; δ_H (300MHz, CDCl$_3$) 7.36-7.26 (5H, m, 5 x Ph*H*), 5.94-5.75 (2H, env. containing, 5.85 (1H, ddd, $^3J_{trans}$ 15.5, $^3J_{cis}$ 9.4, J 7.3, =C*H*CH), and 5.84 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, J 6.7, CH$_2$C*H*=CH$_2$)), 5.58 (1H, td, J 7.3, ^4J 1.2 C(O)=C*H*), 5.50-5.41 (2H, m, C*H$_2$*=CHCH), 5.16 (1H, td, J 7.2, ^4J 1.2, C=C*H*), 5.06-4.93 (4H, env. containing, 5.06-4.93 (2H, m, CH$_2$CH=C*H$_2$*) and 4.96 (2H, s, OC*H$_2$*O)), 4.68 (1H, d, ^2J 11.8, PhC*H$_a$*H$_b$), 4.54 (1H, d, ^2J 11.8, PhCH$_a$*H$_b$*), 4.28-4.17 (1H, m, C*H*CF$_2$), 3.82-3.77 (2H, m, OC*H$_2$*CH$_2$O), 3.55 (2H, dd, J 5.1, 4.2, OCH$_2$C*H$_2$*O), 3.39 (3H, s, OC*H$_3$*), 2.36-2.25 (2H, m, C(O)CHC*H$_2$*), 2.11-1.95 (6H, m, C*H$_2$*C, C*H$_2$*CH$_2$C*H$_2$*), 1.70 (minor diastereoisomer, 3H, d, ^4J 1.2, CC*H$_3$*), 1.61 (major diastereoisomer, 3H, s, CC*H$_3$*), 1.49-1.38 (2H, m, CH$_2$C*H$_2$*CH$_2$); δ_C (75MHz, CDCl$_3$) * both diastereomers, 145.0* (dd, $^2J_{C-F}$ 26.9, 25.1), 138.9 (major diastereoisomer), 138.9 (minor diastereoisomer), 137.6*, 134.1*, 131.1* (dd, $^3J_{C-F}$ 3.6, 1.8), 128.3*, 127.8*, 127.7*, 126.1 (minor diastereoisomer), 125.2 (major diastereoisomer), 121.4 (minor diastereoisomer), 121.4 (major diastereoisomer), 120.1 (t, $^3J_{C-F}$ 5.4, major diastereoisomer), 120.0 (t, $^3J_{C-F}$ 5.4, minor

diastereoisomer), 118.1* (dd, $^1J_{C\text{-}F}$ 250.7, 245.3), 114.4*, 98.2 (minor diastereoisomer), 98.2 (major diastereoisomer), 79.0* (dd, $^2J_{C\text{-}F}$ 31.4, 26.0), 71.6*, 71.4*, 68.7*, 59.0*, 38.9*, 33.4*, 31.1 (minor diastereoisomer), 29.2 (minor diastereoisomer), 29.0 (major diastereoisomer), 27.3 (major diastereoisomer), 23.8*, 23.2 (minor diastereoisomer), 15.9 (major diastereoisomer); δ_F (282MHz, CDCl$_3$) −108.3 (both diastereoisomer, 2F, $^2J_{F\text{-}F}$ 254.5, $^3J_{H\text{-}F}$ 9.0), -114.3 (major diastereoisomer, 1F, $^2J_{F\text{-}F}$ 254.5, $^3J_{H\text{-}F}$ 13.7), -114.6 (minor diastereoisomer, 1F, $^2J_{F\text{-}F}$ 254.5, $^3J_{H\text{-}F}$ 14.2); [HRMS (ES$^+$, [M+Na]$^+$) Found: 487.2632. Calc. for C$_{27}$H$_{38}$F$_2$O$_4$: 487.2630]; m/z (ES$^+$) 487 (31%, [M+Na]$^+$), 482 (52), 389 (12), 123 (26), 91 (100).

Preparation of 3-Benzyloxy-4,4-difluoro-9-methyl-pentadeca-1,8,13-trien-5-one 367
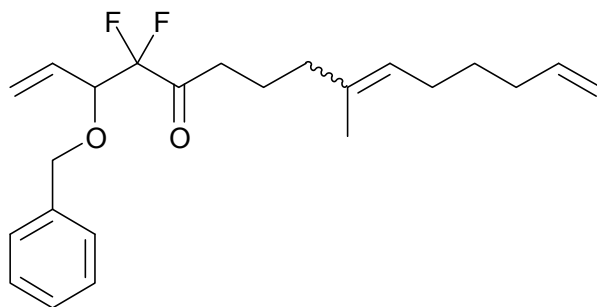
Thionyl chloride (20.95 mmol, 1.52 cm^3) was added to a stirred solution of enol ether **376** (20.95 mmol, 9.719 g) in methanol (200 cm^3) at 0°C. The solution was allowed to warm to room temperature over 2 hours and stirred for 18 hours. The methanol was removed in *vacuo,* and the resulting paste dissolved in water (100 cm^3), and extracted with diethyl ether (3 x 100 cm^3). The combined organic extracts were washed with NaHCO$_3$ (30 cm^3), brine (100 cm^3), dried (MgSO$_4$), and concentrated in vacuo to give a yellow oil which was purified by flash chromatography on silica gel eluted with 5% ether/hexane to give

ketone **367** as a pale yellow oil (2.588 g, 33%); R_f (5 % diethyl ether/hexane) 0.23; ν_{max}(film)/cm^{-1} 2929s, 2359m, 1741s, 1640w, 1454m, 1101s, 910m, 736s, 698s; δ_H (300MHz, CDCl$_3$) 7.40-7.24 (5H, m, Ph*H*), 5.96-5.77 (2H, env. containing 5.90 (1H, ddd, $^3J_{trans}$ 17.1, $^3J_{cis}$ 10.3, J 7.6, CH$_2$C*H*=CH$_2$), and 5.85 (1H, ddt, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.2, J 6.7, CH$_2$=CHC*H*)), 5.59-5.48 (2H, m, C*H$_2$*=CHCH), 5.15 (1H, t, J 7.2, C(Me)=C*H*), 5.08-5.00 (1H, m inc. app. d, $^3J_{trans}$ 17.1, CH$_2$CH=CH$_a$H$_b$), 5.00-4.96 (1H, m inc. app. d, $^3J_{cis}$ 10.3, CH$_2$CH=CH$_a$*H$_b$*), 4.65 (1H, d, ^2J 11.5, PhCH$_a$H$_b$), 4.42 (1H, d, ^2J 11.5, PhCH$_a$*H$_b$*), 4.30 (1H, dt, $^3J_{H-F}$ 16.6, 6.7, J 6.7, C*H*CF$_2$), 2.67 (2H, t, J 7.3, C(O)C*H$_2$*), 2.12-1.97 (6H, m, C*H$_2$*C(Me), C(Me)=CC*H$_2$*, and C*H$_2$*CH=CH$_2$), 1.75-1.68 (5H, env. containing, 1.75 (2H, pentet, J 7.4, C*H$_2$*CH$_2$CH=), and 1.70-1.68 (minor diastereoisomer, 3H, m, CC*H$_3$*)), 1.59 (major diastereoisomer, 3H, s, CC*H$_3$*), 1.45 (2H, pentet, J 7.6, C*H$_2$*CH$_2$CH); δ_C (75MHz, CDCl$_3$) * both diasteriomers, 208.9* (dd, $^2J_{C-F}$ 31.7, 25.1), 239.9 (major diastereoisomer), 238.8 (minor diastereoisomer), 236.8*, 234.2 (minor diastereoisomer), 234.1 (major diastereoisomer), 129.6* (dd, $^3J_{C-F}$ 3.6, 1.2), 128.3*, 128.0*, 128.0*, 126.2 (minor diastereoisomer), 125.5 (major diastereoisomer), 123.2*, 115.0* (dd, $^1J_{C-F}$ 262.1, 253.7), 114.4*, 79.3* (dd, $^2J_{C-F}$ 31.1, 23.9), 71.4*, 38.7*, 38.0 (minor diastereoisomer), 37.7 (major diastereoisomer), 33.4 (major diastereoisomer), 30.7 (minor diastereoisomer), 29.3 (minor diastereoisomer), 29.0 (major diastereoisomer), 27.4 (major diastereoisomer), 27.3 (minor diastereoisomer), 23.1 (minor diastereoisomer), 20.7 (minor diastereoisomer), 20.6 (major diastereoisomer), 15.7 (major diastereoisomer); δ_F (282MHz, CDCl$_3$) (−110.1)-(111.1) (both diastereoisomer, 2F, m, $^2J_{F-F}$ 263.5), -124.0 (both diastereoisomer, 2F, dd, $^2J_{F-F}$ 263.5, $^3J_{H-F}$ 16.6); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 394.2549. Calc. for

$C_{23}H_{34}F_2O_3N$: 394.2552]; *m/z* (CI$^+$) 394 (100%, [M+NH$_4$]$^+$), 268 (10), 216 (8), 142 (12), 108 (17).

Preparation of 3-Benzyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-enone 366
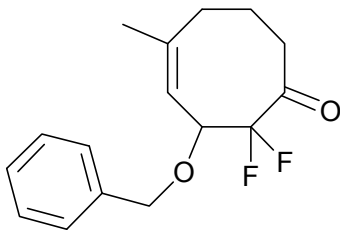
Titanium iso-propoxide (0.422 mmol, 0.126 cm^3) was added to a solution of ketone **367** (1.28 mmol, 482 mg) in freshly degassed DCM (512 cm^3). The solution was refluxed for 20 min then Grubbs' 2nd generation catalyst (0.192 mmol, 163 mg, 15 %) was added and reflux maintained for 18 hours. Fluorine NMR of an aliquot of the reaction showed conversion was incomplete and a further portion of catalyst was added (0.192 mmol, 163 mg, 15 %) and the solution refluxed for a further 24 hours. The solvent was removed in *vacuo* and the residue taken up in ether (50 cm^3) filtered through a plug of celite and concentrated in vacuo, then filtered through an Stratosphere SPE tube eluting with methanol (25 cm^3). The solution was concentrated in *vacuo* to give a brown oil which was purified by flash chromatography on silica gel eluted with 20 % diethyl ether/hexane to give cyclooctenone **366** as clear crystals (203 mg, 57 %, 92% by GC); R$_f$ (20% diethyl ether/hexane) 0.28; Mp. 69-71°C; GC retention time 19.56 min; (Found: C, 68.54; H, 6.55; $C_{18}H_{23}F_2O_3N$ requires: C, 68.56; H, 6.47; %); ν_{max}(solid)/cm^{-1} 2936w, 1742s, 1667w, 1448m, 1060s, 864m, 730s, 697s; δ_H (400MHz, CDCl$_3$) 7.40-7.31 (5H, m, Ph-*H*), 5.33 (1H, d, *J* 8.0, C*H*=C), 4.79 (1H, d, ^{2}*J* 12.0, PhC*H*$_a$H$_b$), 4.67 (1H, d, ^{2}*J* 12.0,

PhCH$_a$H$_b$), 4.59 (1H, ddd, $^3J_{\text{H-F}}$ 20.1, J 8.0, $^3J_{\text{H-F}}$ 4.3, CHCF$_2$), 2.61 (1H, dddd, ^2J 12.5, J 10.5, 4.0, ^4J 2.2, CH_aH$_b$C(O)), 2.58-2.49 (1H, m inc. app. d, ^2J 12.5, CH$_a$$H_b$C(O)), 2.15-2.11 (2H, m, =C(Me)CH_2), 2.01-1.92 (1H, m, CH$_2$CH_aH$_b$CH$_2$), 1.86-1.76 (1H, m, CH$_2$CH$_a$$H_bCH_2$), 1.78 (3H, s, CC$H_3$); δ_C (100MHz, CDCl$_3$) 200.4 (dd, $^2J_{\text{C-F}}$ 27.2, 24.8), 144.0, 137.1, 128.5, 128.1, 128.0, 121.4 (d, $^3J_{\text{C-F}}$ 5.6), 117.7 (dd, $^1J_{\text{C-F}}$ 263.6, 258.8), 73.5 (dd, $^2J_{\text{C-F}}$ 23.2, 19.2), 71.8, 36.8, 32.6, 26.4, 24.3; δ_F (376MHz, 363K, toluene) −111.0 (1F, d, $^2J_{\text{F-F}}$ 240.3), -129.6 (1F, dd, $^2J_{\text{F-F}}$ 240.3, $^3J_{\text{H-F}}$ 19.2); [HRMS (ES$^+$, [M+Na]$^+$) Found: 303.1168. Calc. for C$_{16}$H$_{18}$F$_2$O$_2$: 303.1167]; m/z (ES$^+$) 281 (50%, [M+NH$_4$]$^+$), 132 (13), 91 (61).

Crystal data: C$_{16}$H$_{18}$F$_2$O$_2$, crystal size 0.33 x 0.29 x 0.25 mm^3, M = 280.31, monoclinic, a = 12.837(4) Å, b = 7.615(3) Å, c = 15.535(5) Å, α= 90°, β= 112.153(6)°, γ = 90°, U = 1406.5(8) Å^3, T = 150(2) K, space group P2(1)/n, Z = 4, μ(Mo-Kα) = 0.103 mm^{-1}, 9739 reflections measured, 2473 [R(int) = 0.1222] which were used in all calculations. Final R indices [F^2>σ(F^2)] R1 = 0.0609, wR2 = 0.1387; R indices (all data) R1 = 0.0752, wR2 = 0.1468.

Preparation of 3R*-Benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-methyl-5S*-bicyclo[3.3.1]nona-1R*,4R*-diol 380 and 3R*-Benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-methyl-5R*-bicyclo[3.3.1]nona-1S*,4S*-diol 381

380   **381**
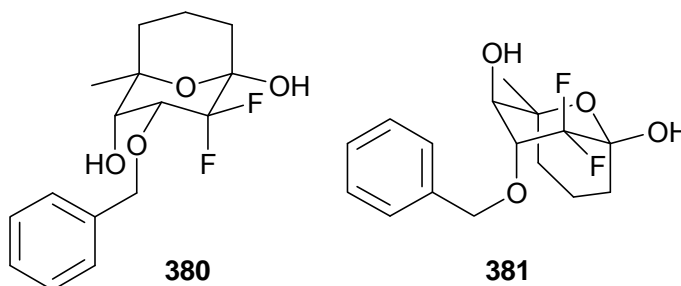
Osmium tetroxide (0.03 mmol, 0.406 cm^3 of a 2.5% solution in tBuOH) was added to a solution of cyclooctenone **366** (0.649 mmol, 182 mg) and NMO (1.198 mmol, 152 mg) in a ‚ixture of water (0.813 cm^3) and acetone (1.6 cm^3) at 0°C. The reaction was stirred at this temperature for 6 hours until consumption of starting material was observed by TLC. The reaction was quenched by the addition of Na$_2$S$_2$O$_5$ and then stirred for 18 hours. Water (15 cm^3) was added and the reaction extracted with ethyl acetate (2 x 50 cm^3); the combined organic extracts were washed with brine (15 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give a grey paste which was purified on Flash silica eluted with 70% ethyl acetate/hexane to give **381** as a white solid (5 mg, 2%); R$_f$ (50% ethyl acetate/hexane) 0.25; Mp. 56-58°C; (Found C, 61.31%; H, 6.57%; C$_{16}$H$_{20}$F$_2$O$_4$ requires: C, 61.14 %; H, 6.41 %); v_{max}(solid)/cm^{-1} 3422br, 2937w, 1456w, 1338w, 1217w, 1129m, 1083s, 1019s, 985s, 911m, 753s, 699s; δ_H (400MHz, CDCl$_3$) 7.45-7.33 (5H, m, Ph-H), 4.93 (1H, d, ^2J 11.5, PhCH_aH_b), 4.69 (1H, d, ^2J 11.5, PhCH$_a$$H_b$), 3.98 (1H, ddd, $^3J_{H-F}$ 12.8, 6.7, J 4.4, CHCF$_2$), 3.67-3.65 (1H, m, {^{19}F} simplifies to dd, J 7.2, ^4J 4.4, CH(OH)), 3.33 (1H, br. s, OH), 2.22-2.14 (1H, m, CCH_aH_b), 2.07-1.97 (1H, m, CCH$_a$$H_b$), 1.88-1.83 (1H, m, CHC$H_aH_b$), 1.75-1.55 (3H, m, CHCH$_a$$H_b$, CH$_2CH_2CH_2$), 1.34 (3H, s, C$H_3$); δ_C

(100MHz, CDCl$_3$) 137.2, 128.6, 128.2, 127.9, 118.3 (dd, $^1J_{C\text{-}F}$ 268.4, 250.8), 95.8 (dd, $^2J_{C\text{-}F}$ 29.2, 19.9), 80.5 (dd, $^2J_{C\text{-}F}$ 29.8, 17.5), 77.6, 75.1 (d, $^4J_{C\text{-}F}$ 2.3), 72.6 (t, $^3J_{C\text{-}F}$ 3.5), 31.4, 28.9 (d, $^3J_{C\text{-}F}$ 1.8), 25.5, 16.3; δ_C (376MHz, CDCl$_3$) −110.2 (1F, dd, $^2J_{F\text{-}F}$ 258.6, $^3J_{H\text{-}F}$ 12.8), (-123.5)-(-124.3) (1F, m inc. app. d, $^2J_{F\text{-}F}$ 258.6); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 332.1666. Calc. for C$_{16}$H$_{24}$F$_2$O$_4$N: 332.1668]; m/z (ES$^-$) 313 (29%, [M-H]$^-$), 293 (20), 205 (18), 185 (100), 182 (34), 123 (15), 59 (91).

A mixture of **381** and **380** (141 mg, 69%), and **380** as a white solid (36 mg, 18%); R$_f$ (50% ethyl acetate/hexane) 0.35; Mp. 125-127°C; (Found C, 61.25%; H, 6.38%; C$_{16}$H$_{20}$F$_2$O$_4$ requires: C, 61.14 %; H, 6.41 %); ν_{max}(solid)/cm^{-1} 3421br, 2937w, 1454w, 1340w, 1218w, 1132m, 1083s, 1015s, 982s, 913m, 754s, 701s; δ_H (400MHz, CDCl$_3$) 7.42-7.34 (5H, m, Ph*H*), 4.91 (1H, d, ^2J 11.7, PhC*H*$_a$H$_b$), 4.80 (1H, d, ^2J 11.7, PhCH$_a$*H*$_b$), 4.10 (1H, ddd, $^3J_{H\text{-}F}$ 20.5, 7.6, J 4.4, C*H*CF$_2$), 3.63 (1H, ddd, J 4.4, $^3J_{H\text{-}F}$ 4.3, ^4J 2.8, C*H*(OH)), 2.06-1.99 (1H, m, C*H*$_a$H$_b$C(OH)), 1.87-1.79 (1H, m, (Me)CC*H*$_a$H$_b$), 1.75-1.61 (2H, m, CH$_a$*H*$_b$C(OH), Me)CCH$_a$*H*$_b$), 1.56-1.45 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.39 (3H, s, C*H*$_3$); δ_C (100MHz, CDCl$_3$) 136.6, 128.7, 128.5, 128.2, 117.7 (dd, $^1J_{C\text{-}F}$ 258.4, 254.9), 94.7 (dd, $^2J_{C\text{-}F}$ 26.6, 20.1), 76.6, 74.5 (dd, $^2J_{C\text{-}F}$ 19.9, 17.5), 73.1 (d, $^4J_{C\text{-}F}$ 1.8), 72.8 (dd, $^3J_{C\text{-}F}$ 7.6, 1.8), 30.7, 27.4 (d, $^3J_{C\text{-}F}$ 1.8), 25.6, 18.8; δ_F (376MHz, CDCl$_3$) (−116.4)-(-117.1) (1F, m inc. app. d, $^2J_{F\text{-}F}$ 248.8), -124.0 (1F, ddd, $^2J_{F\text{-}F}$ 248.8, $^3J_{H\text{-}F}$ 20.5, $^4J_{H\text{-}F}$ 6.1, 2.8); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 332.1672. Calc. for C$_{16}$H$_{24}$F$_2$O$_4$N: 332.1668]; m/z (CI$^+$) 332 (100%, [M+NH$_4$]$^+$), 242 (47), 206 (6), 108 (20), 91 (11), 52 (28). The mixture of **381** and **380** was then purified by HPLC (Waters Spherisorb S5 ODS2 column, 20 x 250mm, eluted with 40% water/methanol) to give sufficient pure **381** for analysis.

Preparation of 3*R**-Benzyloxy-2,2-difluoro-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,4*R**-diol 384
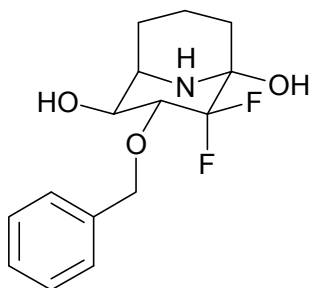
Epoxide **250** (0.44 mmol, 129 mg) was dissolved in a saturated solution of ammonia in methanol (5 cm^3) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM Explorer microwave at 30W power to hold a temperature of 100$^{\text{o}}$C, for 30 min with a 10 min ramp to 100$^{\text{o}}$C. The solution was concentrated in vacuo to give a sticky yellow solid which was purified on flash silica chromatography eluted with 100% ethyl acetate to give amide **284** as a white solid (101 mg, 74%); Mp. 165-170 $^{\text{o}}$C; R$_f$ (100% ethyl acetate) 0.24; (Found: C, 60.06; H, 6.31; N, 4.56; C$_{15}$H$_{19}$F$_2$O$_3$N requires: C, 60.19; H, 6.40; N, 4.68 %); υ_{max}(solid)/cm^{-1} 3416br, 2945s, 1737s, 1455w, 1367s, 1198s, 1144s, 1037s, 905s, 751s, 695s; δ_H (300 MHz, CD$_3$OD) 7.45-7.26 (5H, m, Ph*H*), 4.91 (1H, d, ^2J 11.3, PhC*H*$_a$H$_b$) 4.81 (1H, d, ^2J 11.3 PhCH$_a$*H*$_b$), 4.02 (1H, ddd, $^3J_{\text{H-F}}$ 18.0, 7.4, *J* 9.4, C*H*CF$_2$), 3.94-3.87 (1H, m, C*H*(OH)), 3.22-3.15 (1H, m, CH$_2$C*H*), 2.05-1.48 (6H, m, C*H$_2$*C*H$_2$*C*H$_2$*); δ_C (100 MHz, CD$_3$OD) 138.2, 127.9, 127.8, 127.3, 120.4 (dd, $^1J_{\text{C-F}}$ 159.6, 149.3), 81.1 (t, $^2J_{\text{C-F}}$ 19.2), 80.8 (d, $^2J_{\text{C-F}}$ 20.0), 74.5 (d, $^4J_{\text{C-F}}$ 2.4), 73.5 (d, $^3J_{\text{C-F}}$ 7.2), 52.8, 30.3 (d, $^3J_{\text{C-F}}$ 2.4), 20.6, 19.0; δ_F (282 MHz, CD$_3$OD) -117.1 (1F, dd, $^2J_{\text{F-F}}$ 245.5, $^3J_{\text{H-F}}$ 7.4), -128.1 (1F, ddd, $^2J_{\text{F-F}}$ 245.5, $^3J_{\text{H-F}}$ 18.0, $^4J_{\text{H-F}}$ 3.8); δ_N (29MHz, CDCl$_3$) -70.1 (s); [HRMS (ES$^+$, [M+H]$^+$) Found:

300.1409. Calc. for $C_{15}H_{20}F_2O_3N$: 300.1406]; *m/z* (ES$^+$) 300 (50%, [M+H]$^+$), 297 (59), 242 (47), 163 (14), 91 (100), 72 (95).

Alternatively Epoxide **250** (0.56 mmol, 157 mg) was dissolved in a solution of aqueous ammonia (5.6 cm^3 of a 35% solution by wt.) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM Explorer microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 100% ethyl acetate to give amide **284** as a white solid (72 mg, 43%).

Crystal data: $C_{15}H_{19}F_2O_3N$, crystal 0.33 x 0.20 x 0.10 mm^3, M = 299.31, Orthorhombic, a = 11.428(3) Å, b = 24.352(6) Å, c = 10.474(2) Å, α = 90°, β = 90 °, γ = 90°, U = 2915.0(12) Å^3, T = 150(2) K, space group Pccn, Z = 8, μ(Mo-Kα) = 0.111 mm^{-1}, 19696 reflections measured, 2576 [R(int) = 0.0528] which were used in all calculations. Final R indices [$F^2 > 2\sigma(F^2)$] R1 = 0.0498, wR2 = 0.1134; R indices (all data) R1 = 0.0658, wR2 = 0.1194.

Preparation of 3R*-Benzyloxy-2,2-difluoro-9-methyl-9-aza-1S*,5R*-bicyclo[3.3.1]nona-1S*,4R*-diol 385
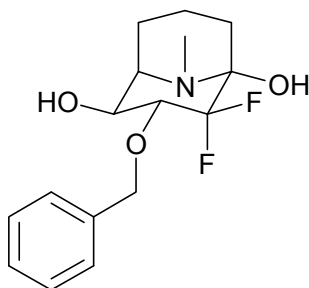
Epoxide **250** (0.2 mmol, 55 mg) was dissolved in a solution of methyl amine in methanol (2 cm^3 of a 2M solution) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM discover microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 70 % ethyl acetate/hexane to give amine **385** as a white solid (41mg, 67%); R_f (50% ethyl acetate/hexane) 0.31; Mp. 182-184 ^{o}C; (Found: C, 61.40; H, 6.70; N, 4.39; $C_{16}H_{21}F_2O_3N$ requires: C, 61.33; H, 6.76; N, 4.47 %); υ_{max}(solid)/cm^{-1} 3401br, 2956s, 2524w, 2454w, 1459w, 1332w, 1220w, 1105s, 1009s, 912s, 753s, 697s; δ_H (400 MHz, CD$_3$OD) 7.46-7.27 (5H, m, Ph*H*), 4.91 (1H, d, ^2J 11.3, PhC*H*$_a$H$_b$), 4.80 (1H, d, ^2J 11.3, PhCH$_a$*H*$_b$), 4.03 (1H, dt, $^3J_{H-F}$ 17.5, 9.2, *J* 9.4, C*H*CF$_2$), 3.96 (1H, dd, *J* 9.4, 5.8, C*H*(OH)), 3.07 (1H, t, *J* 4.8, C*H*CH$_2$), 1.85-1.55 (6H, m, C*H$_2$*C*H$_2$*C*H$_2$*); δ_C (100 MHz, CD$_3$OD) 138.2, 128.8, 128.7, 127.4, 119.9 (dd, $^1J_{C-F}$ 253.2, 251.7), 91.4 (t, $^2J_{C-F}$ 19.4), 84.0 (dd, $^2J_{C-F}$ 25.6, 19.2), 74.2 (d, $^4J_{C-F}$ 2.4), 71.3 (d, $^3J_{C-F}$ 11.2), 60.0, 32.4 (d, $^4J_{C-F}$ 2.4), 22.6, 19.2, 13.3; δ_F (282 MHz, CD$_3$OD) -114.7 (1F, dd, $^2J_{F-F}$ 244.6, $^3J_{H-F}$ 9.2), -124.3 (1F, dd, $^2J_{F-F}$ 244.6, $^3J_{H-F}$ 17.5); δ_N (29 MHz, CD$_3$OD) -140.8 (s); [HRMS (ES$^+$,

[M+H]$^+$) Found: 314.1563. Calc. for C$_{16}$H$_{21}$F$_2$O$_3$N: 314.1562]; *m/z* (ES$^+$) 314 (100%, [M]$^+$).

Alternately **385** could be prepared with aqueous methylamine using the following procedure; epoxide **250** (0.13 mmol, 38 mg) was dissolved in a solution of methyl amine (1.3 cm^3 of a 40 % aqueous solution) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM discover microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 70 % ethyl acetate/hexane to give amide **385** as a white solid (22mg, 53 %).

Crystal data: C$_{16}$H$_{21}$F$_2$NO$_3$, crystal size 0.20 x 0.14 x 0.07 mm^3, *M* = 313.34, monoclinic, a = 6.7020(18) Å, b = 16.936(4) Å, c = 13.275(4) Å, α= 90°, β= 90.508(6)°, γ = 90°, U = 1506.7(7) Å^3, T = 150(2) K, space group P2(1)/c, Z = 4, μ(Mo-Kα) = 0.111 mm^{-1}, 10673 reflections measured, 2644 [R(int) = 0.1284] which were used in all calculations. Final *R* indices [F^2>σ(F^2)] R1 = 0.0584, wR2 = 0.0899; R indices (all data) R1 = 0.1157, wR2 = 0.1049.

Preparation Of 2,2-Difluoro-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,3*R**,4*R**-triol 386
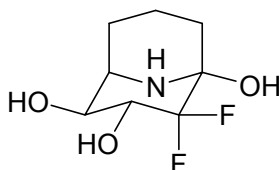
Bicyclic amine **384** (0.247 mmol, 74 mg) was dissolved in a suspension of 10 % palladium on activated carbon (24 mg) in ethanol (2.4 cm^3), and methanol (1 cm^3). The atmosphere was removed and replaced with hydrogen from a balloon. The solution was stirred at room temperature for 48 hours, then the hydrogen atmosphere was removed and replaced with air. The solution was filtered through celite and concentrated in *vacuo* then purified by flash chromatography on silica gel eluted with 100% ethyl acetate to give bicyclic amine **386** as a white solid (18 mg, 35%); R$_f$ (100% ethyl acetate) 0.19; Mp. 222-224°C; δ_H (400 MHz, CD$_3$OD) 4.06 (1H, ddd, $^3J_{\text{H-F}}$ 19.4, 8.5, *J* 9.6, C*H*CF$_2$), 3.82-3.77 (1H, m, NCHC*H*(OH))$^{\neq}$, 3.22-3.17 (1H, m, C*H*N), 2.04-1.96 (2H, m, CHC*H*$_a$H$_b$, C*H*$_a$H$_b$C(OH)), 1.83-1.75 (1H, m, CH$_2$C*H*$_a$H$_b$CH$_2$), 1.67-1.51 (3H, m, CHCH$_a$*H*$_b$, CH$_a$*H*$_b$C(OH), CH$_2$CH$_a$*H*$_b$CH$_2$); δ_C (100 MHz, CD$_3$OD) 119.7 (dd, $^1J_{\text{C-F}}$ 258.8, 246.9), 80.7 (dd, $^2J_{\text{C-F}}$ 24.0, 20.0), 74.2 (d, $^3J_{\text{C-F}}$ 8.0), 73.5 (t, $^2J_{\text{C-F}}$ 20.8), 52.7, 30.2 (d, $^3J_{\text{C-F}}$ 3.2), 20.5, 19.1; δ_F (282 MHz, CD$_3$OD) −121.8 (1F, dd, $^2J_{\text{F-F}}$ 243.7, $^3J_{\text{H-F}}$ 8.5), -130.6 (1F, ddd, $^2J_{\text{H-F}}$ 243.7, $^3J_{\text{H-F}}$ 19.4, $^4J_{\text{H-F}}$ 4.0); [HRMS (ES$^+$, [M+H]$^+$) Found: 210.0937 Calc. for C$_8$H$_{14}$F$_2$O$_3$N: 210.0936]; *m/z* (CI$^+$) 210 (100%, [M+H]$^+$), 292 (3), 172 (4), 156 (5), 115 (4), 98 (6), 52 (13). $^{\neq}$ In the {^{19}F} ^{1}H NMR spectrum, this signal simplifies to (1H, dd, *J* 9.6, 5.9).

Preparation of 3R*-Benzyloxy-2,2-difluoro-9-allyl-9-aza-1S*,5R*-bicyclo[3.3.1]nona-1S*,4R*-diol 387
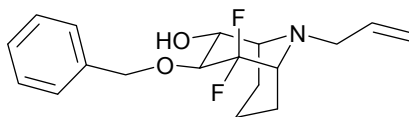
Epoxide **250** (0.2 mmol, 56 mg) was dissolved in a solution of allylamine in methanol (2 cm^3 of a 2M solution) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM Explorer microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 70% ethyl acetate/hexane to give amine **387** as a white solid (52 mg, 77%); R$_f$ (70% ethyl acetate/hexane) 0.32; Mp. 111-113°C; (Found: C, 63.62; H, 6.77; N, 4.11; C$_{18}$H$_{23}$F$_2$O$_3$N requires: C, 63.70; H, 6.83; N, 4.13; %); υ_{max}(solid)/cm^{-1} 3503br, 3374br, 2943w, 1456w, 1335m, 1200s, 1123s, 1022s, 924s, 852s, 746s; δ_H (400 MHz, CD$_3$OD) 7.47-7.27 (5H, m, Ph*H*), 5.79 (1H, dddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.1, *J* 7.6, 4.6, C*H*=CH$_2$), 5.27-5.20 (1H, m, $^3J_{trans}$ 17.2, =CH$_a$H$_b$), 5.14-5.08 (1H, m inc. app. d, $^3J_{cis}$ 10.1, =CH$_a$H$_b$), 4.92 (1H, d, ^2J 11.3, PhC*H*$_a$H$_b$), 4.80 (1H, d, ^2J 11.3, PhCH$_a$*H*$_b$), 4.05 (1H, dt, $^3J_{H-F}$ 17.4, 9.5, *J* 9.5, C*H*CF$_2$), 3.89 (1H, dd, *J* 9.5, 6.0, C*H*(OH)), 3.63-3.57 (1H, m, NC*H*$_a$H$_b$), 3.30 (1H, dd, ^2J 14.3, *J* 7.6, NCH$_a$*H*$_b$), 3.21-3.16 (1H, m, C*H*CH$_2$), 1.81-1.60 (6H, m, C*H$_2$*C*H$_2$*C*H$_2$*); δ_C (100 MHz, CD$_3$OD) 138.2, 137.0, 127.9, 127.8, 127.4, 120.1 (dd, $^1J_{C-F}$ 154.4, 152.0), 115.4, 84.0 (dd, $^2J_{C-F}$ 25.6, 19.2), 81.6 (t, $^2J_{C-F}$ 20.0), 74.3 (d, $^4J_{C-F}$ 2.4), 71.5 (d, $^3J_{C-F}$ 9.6), 54.5, 46.0 (d, $^4J_{C-F}$ 1.6), 24.7, 19.3, 13.6; δ_F (282 MHz, CD$_3$OD) -113.4 (1F, dd, $^2J_{F-F}$ 241.7, $^3J_{H-F}$ 9.5), -124.7 (1F, dd, $^2J_{F-F}$ 241.7, $^3J_{H-F}$ 17.4); δ_N (29 MHz,

CD$_3$OD) -274.9; [HRMS (ES$^+$, [M+H]$^+$) Found: 340.1716. Calc. for C$_{18}$H$_{24}$F$_2$O$_3$N: 340.1719]; m/z (ES$^+$) 340 (100%, [M+H]$^+$), 214 (15), 106 (29).

Preparation of 2,2-difluoro-9-methyl-9-aza-1S*,5R*-bicyclo[3.3.1]nona-1S*,3R*,4R*-triol 388

Epoxide **251** (0.135 mmol, 40 mg) was dissolved in a solution of methyl amine in methanol (1.3 cm^3 of a 2M solution) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM Explorer microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 100% ethyl acetate/hexane to give amide **388** as a white solid (37mg, 87%); R$_f$ (50% ethyl acetate/hexane) 0.07; Mp. 95-97°C; υ_{max}(film)/cm^{-1} 3375br,w, 2964w, 2508w, 2321br, 1444w, 1341w, 1128s, 999s, 850m, 780s; δ_H (300 MHz, CD$_3$OD) 3.95 (1H, dt, $^3J_{H-F}$ 18.8, 9.7, J 9.7, CHCF$_2$), 3.74 (1H, dd, J 9.7, $^4J_{H-F}$ 5.5, CHCHCF$_2$), 2.95 (1H, t, broad, J 4.6, CHCH$_2$), 1.72-1.46 (6H, m, 2 x CH_2); δ_C (100 MHz, CD$_3$OD) 119.2 (dd, $^1J_{C-F}$ 252.4, 249.3), 83.8 (dd, $^2J_{C-F}$ 25.6, 18.4), 73.9 (dd, $^2J_{C-F}$ 22.4, 20.0), 72.1 (dd, $^3J_{C-F}$ 10.4, 1.6), 60.0, 32.4 (d, $^4J_{C-F}$ 2.4), 22.5 (d, $^3J_{C-F}$ 1.6), 19.3, 13.1; δ_F (282 MHz, CD$_3$OD) −119.9 (1F, dd, $^2J_{F-F}$ 243.6, $^3J_{H-F}$ 9.7) −126.8 (1F, ddd, $^2J_{F-F}$ 243.6, $^3J_{H-F}$ 18.8, $^4J_{H-F}$ 5.5); δ_N (29 MHz, CD$_3$OD) −138.2 (s); [HRMS (ES$^+$,

[M+H]$^+$) Found: 224.1095. Calc. for C$_9$H$_{16}$F$_2$O$_3$N: 224.1093]; *m/z* (ES$^+$) 224 (1%, [M]$^+$), 223 (11), 206 (12), 142 (18), 112 (100), 73 (60).

Preparation of 2,2-difluoro-9-allyl-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,3*R**,4*R**-triol 398
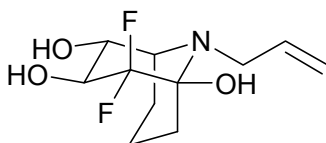
Epoxide **251** (0.15 mmol, 44 mg) was dissolved in a solution of allyl amine in methanol (1.5 cm^3 of a 2M solution) and sealed in a microwave vial equipped with a stirrer bead. The solution was stirred and irradiated in the cavity of a CEM Explorer microwave at 30W power to hold a temperature of 100°C, for 30 min with a 10 min ramp. The solution was concentrated in *vacuo* to give a sticky yellow solid which was purified on flash silica chromatography eluted with 100% ethyl acetate to give amide **389** as a white solid (29 mg, 77%); R$_f$ (50% ethyl acetate) 0.23; Mp. 119-121°C; (Found: C, 52.98; H, 6.94; N, 5.59; C$_{11}$H$_{17}$F$_2$O$_3$N requires: C, 53.01; H, 6.87; N, 5.62; %); υ_{max}(soild)/cm^{-1} 3406br.s, 2944s, 1400w, 1342m, 1155m, 1015s, 932s, 852s, 783m; δ_H (400 MHz, CD$_3$OD) 5.79 (1H, dddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.2, *J* 7.5, 4.7, C*H*=), 5.12 (1H, ddd, $^3J_{trans}$ 17.2, ^4J 1.9, ^2J 1.1, =C*H*$_a$H$_b$), 4.98 (1H, ddd, $^3J_{cis}$ 10.2, ^4J 1.9, ^2J 1.1, =CH$_a$*H*$_b$), 3.93 (1H, ddd, $^3J_{H-F}$ 18.6, 9.8, *J* 9.7, C*H*CF$_2$), 3.78 (1H, ddt, *J* 9.7, 5.8, $^4J_{H-F}$ 1.5, ^4J 1.5, C*H*(OH)CHN), 3.60 (1H, ddt, ^2J 14.5, *J* 4.7, ^4J 1.9, NC*H*$_a$H$_b$), 3.30 (1H, dd, ^2J 14.5, *J* 7.5, NCH$_a$*H*$_b$), 3.21-3.16 (1H, m, C*H*CH$_2$), 1.82-1.59 (6H, m, 3 x C*H*$_2$); δ_C (100 MHz, CD$_3$OD) 137.0, 119.3 (dd, $^1J_{C-F}$ 254.0, 250.1), 115.4, 83.8 (dd, $^2J_{C-F}$ 26.4, 20.0), 74.0 (dd, $^2J_{C-F}$ 22.4, 20.0), 72.3 (d, $^3J_{C-F}$

8.8), 54.5, 46.0, 24.6 (d, $^3J_{C\text{-}F}$ 2.4), 19.3, 13.4; δ_F (282 MHz, CD$_3$OD) -119.6 (1F, dd, AB, $^2J_{F\text{-}F}$ 243.1, $^3J_{H\text{-}F}$ 9.8), -126.8 (1F, ddd, AB, $^2J_{F\text{-}F}$ 243.1, $^3J_{H\text{-}F}$ 18.6, $^4J_{H\text{-}F}$ 1.5); δ_N (29 MHz, CD$_3$OD) $-$138.4 (s); [HRMS (ES$^+$, [M+H]$^+$) Found: 250.1250. Calc. for C$_{11}$H$_{18}$F$_2$O$_3$N: 250.1249]; m/z (ES$^+$) 250 (100%, [M+H]$^+$), 132 (15).

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[168] See appendix section 6.3.14

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6.1 Appendix 1: Unsuccessful Projects of Interest

6.1.1 Access to 6-Deoxy Route *via* Enyne Metathesis

An alternative approach to the construction of the key cyclooctenone intermediate for the 6-deoxy series is ring closing enyne metathesis[174] (ENYRCM), rather than alkene metathesis. ENYRCM is the cyclisation of an enyne and an alkene and is catalysed by the same alkylidene catalysts as RCM under similar conditions. Unlike RCM, ENYRCM reactions are often conducted under an atmosphere of ethene which in many cases leads to better yields and a decrease in reaction times. Clearly there is an important mechanistic issue about the starting location of the metathesis. It is thought that this depends acutely on the substitution pattern of both the alkene and alkyne. The procedure is used less often than alkene metathesis but a limited number of cyclooctanic species have been prepared in this manner. Methylene cyclooctadiene **396** was prepared rapidly from enyne **397** in good yield[175] (Scheme 111). Interestingly the reaction was found to be chemoselective forming only **397** and exhibiting no reactivity on the disubstituted (less reactive) olefin to form **398**.
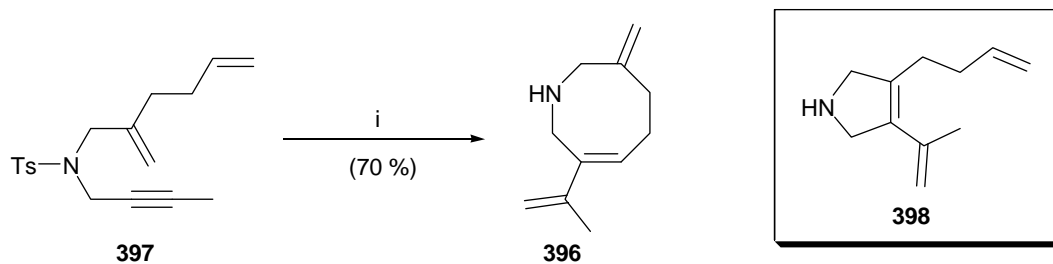
Scheme 111; Reagents and conditions; i, 5 mol% **93**, 0.1 M DCM, reflux, 50 min

There is a crucial difference between ENYRCM and conventional alkene RCM. In alkene RCM the olefins cyclise to give a compound two units smaller then the length of the initial diene with the outstanding carbon units being lost as ethene. In ENYRCM however these residual carbon units remain incorporated (hence the non detrimental effect of the ethene atmosphere) as an additional olefinic substituent on the newly formed double bond (in effect a 1,3 diene). If a non-terminal enyne is used, it's pendant functionality on the terminus remote from the alkene will end up as a substituent on the internal vinylic position of the exocyclic olefin.
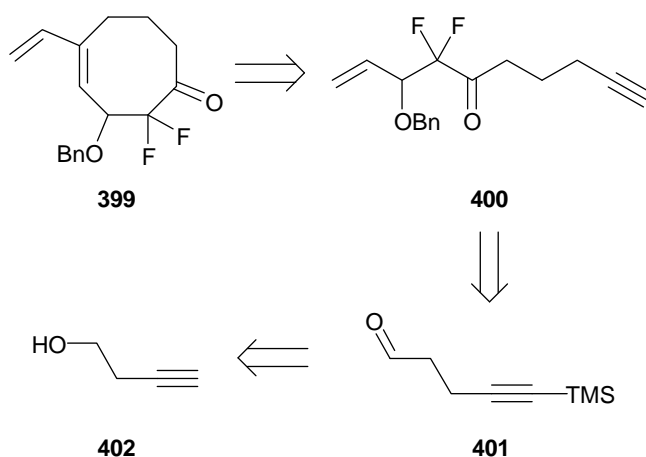
Scheme 112

The closest corresponding product available *via* enyne metathesis to **346/366** is cyclooctenone **399** (Scheme 112). This compound should be available by ENYRCM from precursor **400** which can be synthesised using our existing chemistry from **131** and known aldehyde[176] **401** which is available from commercial pent-4-yn-1-ol **402**. The protection of the alkynyl proton with TMS is necessary as it's pK_a should be around 24[5] and is therefore vulnerable to the strong base procedures involved in the synthesis of **400**.

The TMS group may have to be removed prior to RCM as is it has been shown to be detrimental to metathesis efficiency in some cases.
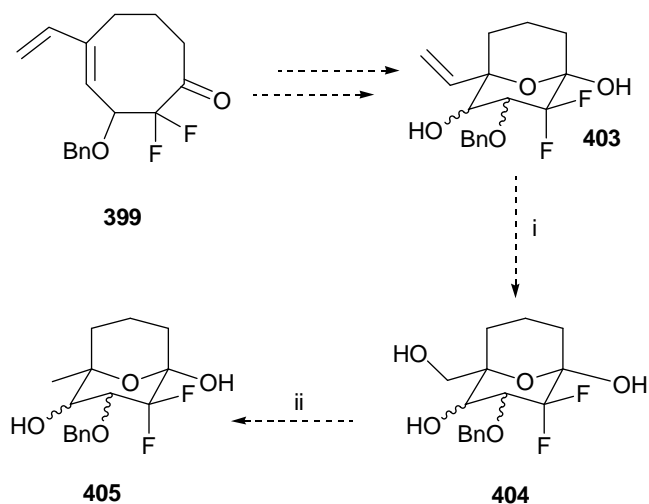
Scheme 113; Reagents and conditions, i, O₃, DCM, -78°C, then NaBH₄; ii, Et₃SiCl, TFA, DCM.

One benefit of this approach is that it will offer access not only to the 6-deoxy class of compounds but a second class of hexose analogues with an hydroxyl group at the position analogous to C6 in the natural product (Scheme 113). From **399**, oxidation and ring closure by established chemistry leads to the formation of bicycle **403**. This compound offers access to compounds type **404** baring an hydroxyl group by ozonolysis, and subsequently selective dehydration leads to **405** and access to the 6-deoxy class.

Protected alkyne **406** was easily prepared from **401** (Scheme 114) (78 %) and then converted to aldehyde **401** by Swern oxidation[177] in good yield (86 %) although the proton NMR showed some additional alkyl signals indicating contamination by unknown material. It was decided not to attempt to purify **401** as it was thought that the aldehyde functionality may not be stable on silica. The formation of allylic alcohol **407** proceeded

in disappointing yield (38 %, 88 % purity by ^{19}F NMR) after distillation (bp. 120°C/0.05 mmHg).
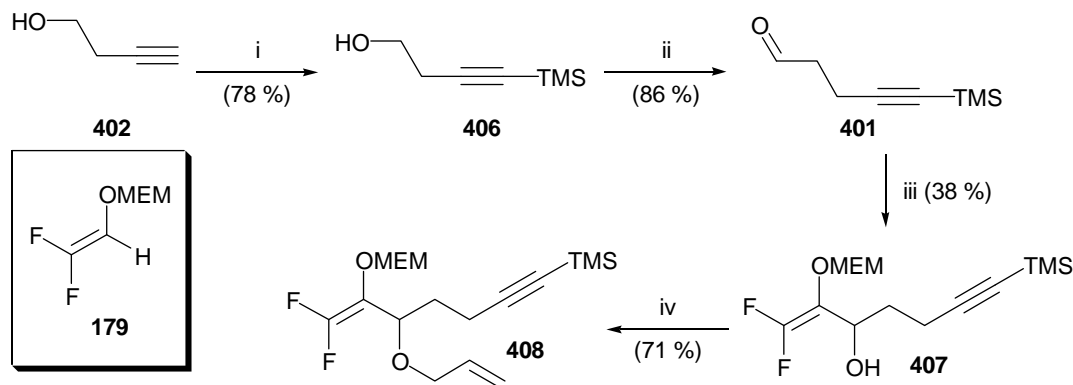
Scheme 114; Reagents and conditions; i, 2 eq *n*BuLi, THF, -78 to 0°C, then TMS-Cl, -78°C to reflux 12hr, then 10 % HCl; ii, 2.3 eq DMSO, 1.2 eq Oxyal chloride, THF, -78°C, then **406**, Et$_3$N; iii, **131**, 2eq LDA, THF, -78°C, 40 min, then 1.2 eq **401**, -78 to -40°C, 4 hr; iv, 1.2 eq allyl bromide, 5 mol% TBAHSO$_4$, 50% NaOH, 0°C to RT 72 hr.

The crude yield of **407** after this procedure was (89 %) this material was estimated to be 70 % pure by ^{19}F NMR along with 10 % of an unknown CF$_3$ species and 15 % of protiolysis product **179**, and small amounts of other species. This suggests that the purification was at fault for the poor yield, because of the complete conversion of **131** and relatively high purity of the crude material. The presence of **179** suggests that either the reaction was not completely dry or an insufficient amount of **401** was used. The latter is the more probable explanation as **401** was definitely impure by proton NMR. The allylation again proceeded smoothly to give **408** in good yield (71 %) although the purity by ^{19}F NMR was shown to be only 63 %.

The next step in the sequence would have been the [2,3]-Wittig rearrangement. However due to the low purity of the material obtained after allylation the viability of this synthetic route was questioned. Clearly **408** could be purified at some cost in material and after a

process that had never required purification before. More importantly doubts were raised about how **408** would behave in the [2,3]-Wittig reaction.[178]

408
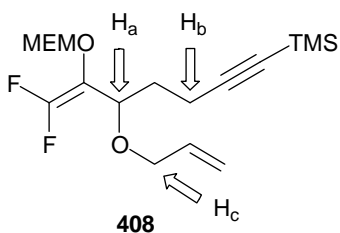
Figure 38

The crucial point was that **408** has five potentially acidic protons (Figure 38), and which of the allylic methine (H_a), or propargylic methylene protons (H_b), or one of the desired allylic methylene's (H_c) would be deprotonated by base in the initial step of the [2,3]-Wittig was uncertain. Deprotonation at any position other than H_c would not lead to a [2,3]-Wittig rearrangement and could lead to decomposition or unwanted by-products. It was decided on the basis of this uncertainty and with the additional concern about the poor purity that would exacerbate the situation, not to progress any further with the sequence.

This sequence is the first investigated where the established conditions do not allow a facile telescopic synthesis to be established. This is not to say the methodology is a failure with this system; as the reactivity of **408** towards the [2,3]-Wittig reaction remains unknown. The failure to distil **407** in good purity led to similar poor purity being observed in the synthesis of **408**. It was primarily this pure purity especially when expressed alongside that of material in the other approaches that lead to the decision to

abandon the route. Theses results defiantly show that terminal alkynes are not as conducive to this methodology as the terminal olefins studied.

6.1.2 Access to α-Haloketones, as Remote Groups to Facilitate RCM and add Functionality

The ring closing metathesis of cyclooctenones such as **200** shows considerable concentration dependence. In order to prevent dimerization, the reaction must be run at the very low concentration of 0.025M; this presents a practical problem in synthesizing our bicyclic systems on a large scale, due to the prohibitive amount of solvent required. Murphy[179] has suggested that difficult RCM substrates may be modified preferentially towards metathesis by the introduction of a temporary atom such as a chlorine or bromine atom) onto the carbon chain. This effect has been demonstrated in principle by Linderman who conducted some of the first non-annelative RCM reactions by including the very bulky tributylstannane group remote from the reaction centre.[180] The effect is rationalised with the argument that in RCM the metal alkylidene group with associated ligands represents a considerably sterically bulky unit. Even a small substituent remote from the reaction centre may therefore have a considerable effect on the solution conformer population of a compound.
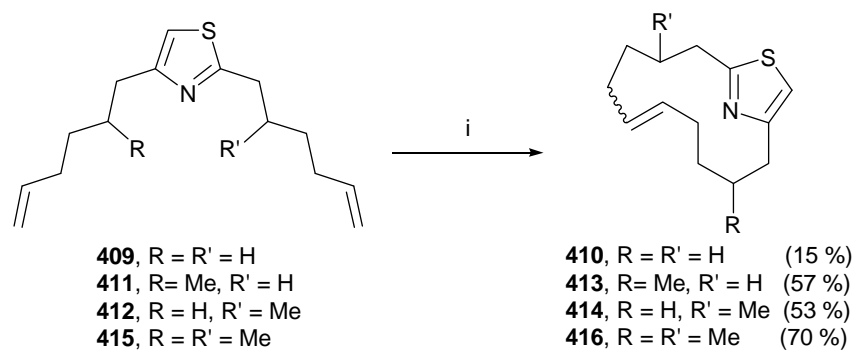
Scheme 115; Reagents and conditions; i, 2 mol% **91**, DCM, reflux, 4 h

409, R = R' = H	**410**, R = R' = H (15 %)
411, R= Me, R' = H	**413**, R= Me, R' = H (57 %)
412, R = H, R' = Me	**414**, R = H, R' = Me (53 %)
415, R = R' = Me	**416**, R = R' = Me (70 %)

Murphy[179] illustrates this idea in his synthesis of Muscothiazoles A and B (Scheme 115). Diene **409** undergoes a poor RCM to give **410** in only 15 % yield. The introduction of a single methyl group at either R **411** or R' **412** dramatically increases the yield of **413** (57 %) and **414** (53 %) respectively and the introduction of two methyl groups in **415** increases the yield of **416** further (70 %). This would be similar to the Thope-Ingold/reactive rotamer effect,[159] where a remote *gem*-dialkyl substituent in an alkyl chain is observed to increase the rate of cyclisation over that of related species where the group is absent.

A striking example of the power of the effect of remote functionality is illustrated in Scheme 116. RCM attempts on unsubstituted ketone **417** produced only a complex mixture of oligomers and no detectable cyclised product. Ketone **418** with two *gem*-dialkyl groups underwent RCM smoothly to afford **419** in excellent yield (95 %) in the absence of solvent.[181]
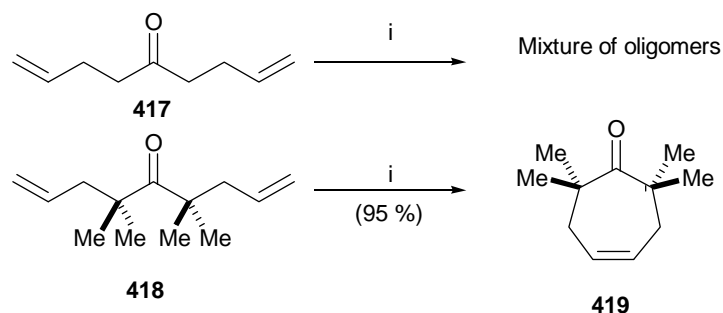
Scheme 116; Reagents and conditions; i, **89**, neat, 25°C

If the MEM group could be removed and an α-haloketone **420** formed, the new carbon-halogen bond would be synthetically very useful, as α-haloketones are usually extremely reactive towards nucleophiles. It should therefore be possible to remove the halogen easily after it has facilitated the RCM, or to introduce a wide range of functional groups. This would allow us to greatly expand the library of conformationally locked sugar analogues (Scheme 117).

Scheme 117
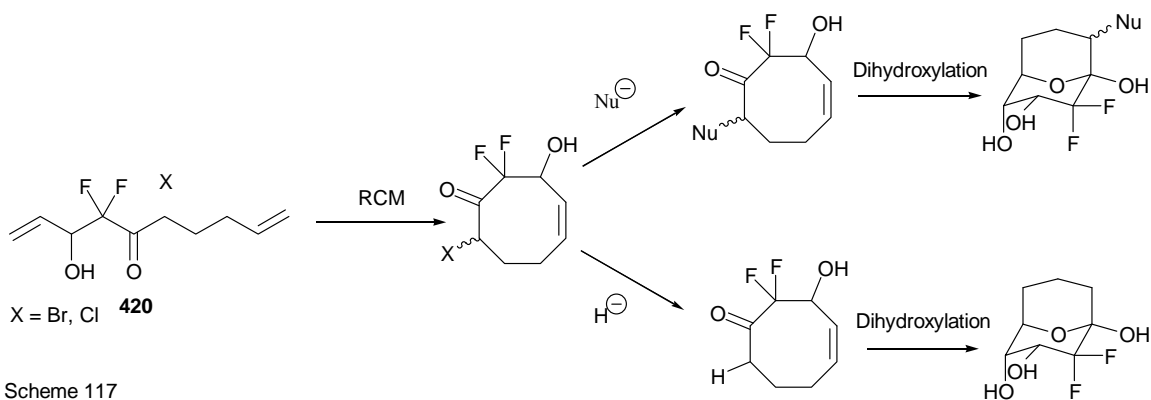
An attempt was made to introduce a bromine into the system from intermediate **183**. Clearly exposing **183** to a brominating agent presents possible regioselectivity problems; however it was hoped that the enol ether would react more rapidly than the less reactive

terminal double bonds. Cleavage of the MEM group would occur to give an α-bromoketone.

Cupric bromide is a little known brominating agent but has been demonstrated by Castro[182] to halogenate olefins at reflux in methanol. Exposing **183** to the literature conditions (Scheme 118) gave **421** as two inseparable diastereoisomers in good yield (96 %), and good purity (92 %, GCMS). Purification proved difficult as both diastereoisomers proved unstable to both Kugelrohr distillation and column chromatography with most of the compound decomposing in both cases. They were therefore progressed without further purification.
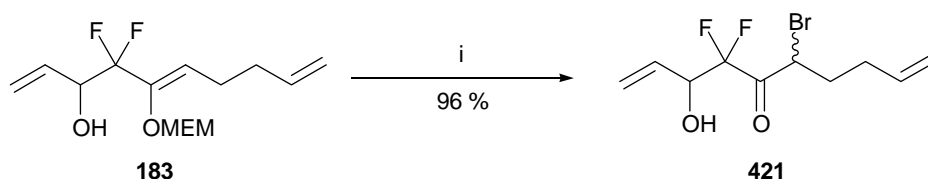
Scheme 118; Reagents and conditions; i, CuBr$_2$, MeOH, reflux

Mechanistically (Scheme 119) it is suggested that the first step in the reaction is the cleavage of the MEM group by the Lewis acid. This may result in the formation of a copper enolate **422**, a species considerably more reactive than the terminal double bonds present in the molecule. Kinetic studies by Castro on allylic alcohols showed that the rate of reaction was independent of olefin concentration, thus suggesting that a second brominating agent is present in the solution. The most likely candidate for this is molecular bromine produced from the disproportionation of cupric bromide. Either molecular bromine, cupric bromide or both could act as the bromine electrophile completing the bromination **423**. Although cupric bromide does not decompose readily in

methanol any trace of molecular bromine would be rapidly trapped by the copper enolate driving further dissociation.
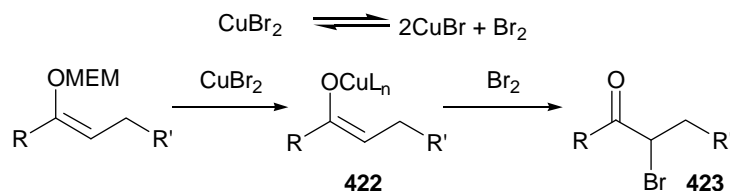
Scheme 119

In the same paper Castro also describes the corresponding reaction with cupric chloride as the halogenating agent under the same conditions. Attempts were made to synthesise the corresponding α-chloroketone from **183** due to the expected increased stability of the carbon-chlorine bond over the carbon-bromine bond (Scheme 120). The reaction again gave a compound that was identified as the chloroketone by NMR and gave a good ion in the ES.
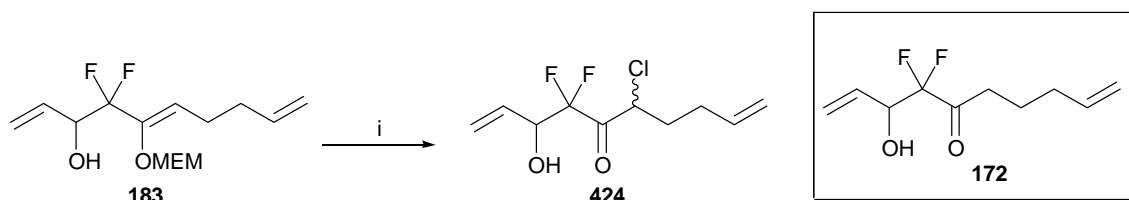
Scheme 120; Reagents and conditions; i, CuCl$_2$, MeOH, reflux

The crude reaction mixture showed a third major component that was identified as the conventional MEM cleavage product **172**. This compound was present in subsequent attempts to repeat the reaction and appeared to occur in unpredictable amounts 24-63 % and furthermore could not be removed by column chromatography as **424** proved unstable on silica.

Castro noted that Cu(II)Cl$_2$ was much less likely than Cu(II)Br$_2$ to dissociate to the molecular diatomic species upon moderate heating and indeed found no evidence for its intermediary in halogenations. Indeed molecular bromine was distilled from refluxing cupric bromide in acetonitrile but not from the corresponding cupric chloride reaction. This suggests that there is little if any molecular chlorine for the copper enolate formed in the initial step to react with. The discrepancy between the two halogenation results would suggest that the above statement is true and that molecular bromine is the major brominating agent in the cupric bromide procedure.
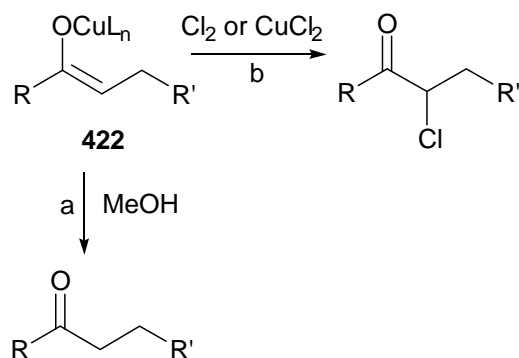
Scheme 121

The by-product **172** almost certainly comes from **422** reacting with the protic solvent (pathway a, Scheme 121) rather than a chlorine electrophile (pathway b). This is not observed with cupric bromide as there is enough molecular bromine in solution to trap **422** rapidly as it is formed. The reaction may become competitive however due to the lack of molecular chlorine present in solution either slowing down the chlorination reaction or forcing it to proceed *via* cupric chloride as the major chlorinating agent.

6.1.3 The Effect of Bromination On Ring Closing Metathesis

α-Bromoketone **421** was successfully cyclised to give cyclooctenones **425** and **426** (Scheme 122). An initial catalyst loading of 5 mol% proved insufficient and an additional 2.5 mol % was added after 6 hours to drive the reaction to completion. On one occasion a catalyst loading of 5 mol% gave complete conversion of starting material; however in this case the isolated yield was disappointing (36 %). The two diastereomeric products could be separated by column chromatography on silica gel to give an acceptable combined isolated yield of 58 %. The first diastereoisomer to be eluted (a brown oil), was unstable on silica and was thus difficult to obtain pure (maximum 91 % by ^{19}F NMR). No molecular ion could be found for the compound nor could a GC purity be obtained as the compound appeared to decompose on the column. The second diastereoisomer was eluted as a white solid that returned much stronger characterisation data including a good elemental analysis.
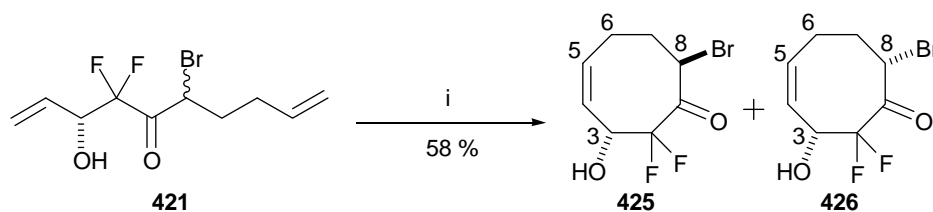
Scheme 122; Reagents and conditions; i, 7.5 mol% **93**, 0.001M DCM, reflux

Which diastereoisomer corresponded to the *trans* **425** and which to *cis* **426** was assigned from the NOESY spectra of the second diastereoisomer. A cross peak was observed between C3-H and C8-H[183] proving that the methine protons must be on the same side of the molecule and suggesting the second diastereoisomer is the *cis* species **426**.

Attempts to confirm this assignment through growing a single crystal of the second diastereoisomer failed. The solution conformations of the two species where however shown to be very different by analysis of the $^3J_{\text{H-F}}$ coupling constant. A value of 24.1 (323 K) Hz was obtained for the first diastereoisomer, suggesting similar behaviour to previous species with an antiperiplanar arrangement of one of the fluorine's and the methane next to the hydroxyl. The second diastereoisomer showed a much smaller than usual coupling constant of 16.0 Hz (323 K) suggesting the methine proton lies somewhere between the two fluorine atoms. Further analysis of the NOESY spectra showed for **426** in addition to the C3-H to C8-H interaction a second cross peak was observed between C3-H and C6-H. This set of cross peaks suggests that **426** has a similar conformation in solution to the other cyclooctenones discussed above despite the slightly smaller than expected $^3J_{\text{H-F}}$ coupling constant. In the case of **425** a cross peak was observed between C3-H and C6-H suggesting that both diastereoisomers adopt similar solution conformations.

It should not be assumed that either **425** or **426** will occupy one of the four solution conformations suggested by molecular modelling for **187**. The large bromine substituent is likely to have a considerable effect on the solution conformation of the molecule and may want to adopt an equatorial orientation in any structure, although this effect is slightly less clear in medium rings.

Attempts were made to study the effect of concentration on the reaction. However no suitable assay was available at the time and all attempts to monitor the reaction by GC failed due to the incompatibility of dimeric and larger species with the GC column. With hindsight an NMR assay such as that later developed in the group[95] would have been

usefully in analysing the outcome of the reaction. Therefore no useful information about the presence or absence of a Thorpe-Ingold type effect was obtained.

6.1.4 Displacement of Bromine with Charged Nucleophiles

The major reason for the insertion of the bromine functionality was with the intention of using the high reactivity of α-haloketones in the S_N2 reaction[184] (Scheme 123), to insert nucleophiles of interest into the C8 position of the cyclooctenone framework.

Scheme 123
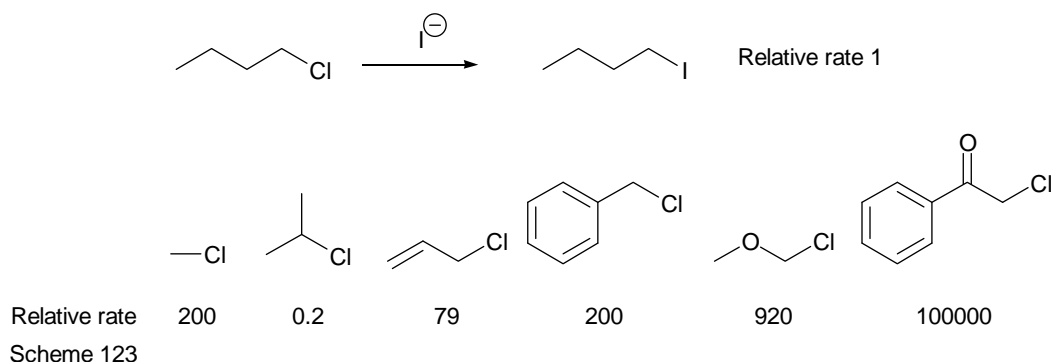
It was decided that initial experiments would be conducted on acyclic bromide **421** as it should be more reactive toward nucleophiles than cyclooctenones. It was expected that in **425**, and **426**, the constraints of the ring may hinder the approach of the nucleophile onto the rear lobe of the empty σ*-orbital associated with the carbon halogen bond.
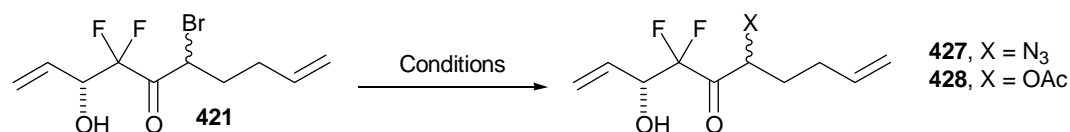
Scheme 124

Entry	Conditions	Yield
1	6 eq AcOH, THF/H$_2$O (50/1), reflux, ON	**421** 18 %
2	1 eq NaN$_3$, acetone, rt, 24 h	-
3	2.2 eq NaN$_3$, EtOH/AcOH (10/1), 0°C, 48 h	**421** 22 %

Table 32

Initial attempts to displace bromine by acetate solvolysis (Scheme 124, Table 32, entry 1) returned mainly starting material by ^{19}F NMR although little was isolated after chromatography (18 %). Small amounts of decomposition products were also isolated but could not be separated or identified. A further attempt with azide anion in acetone (entry 2) gave decomposition to a number of products that could not be isolated by column chromatography. Conducting the azide reaction in a mixed solvent system of ethanol and acetic acid and at a lower temperature (entry 3) appeared give an interesting result. Two new compounds were seen in the ^{19}F NMR but only in small amounts (ca. 10 %). No molecular ion was detected for azide and no new product was isolated after chromatography along with recovered starting material (22 %).

These results suggest that the α-haloketone moiety in **421** is reactive but difficult to displace cleanly or efficiently. The conditions in entry three gave the best results with a reasonably clean reaction but at a poor conversion and with no positive identification of the final product. It was decided that the difficulties experience with the acyclic system did not bode well for displacement from the cyclic system. This, along with the

disappointing yield of **425**, and **246** from the RCM, especially when only one of the diastereoisomers was fit for further study, led to the bromination chemistry being put on one side. The bromination reaction itself represented a useful conversion and it was hoped the series could be returned to at a future date. Unfortunately no further time was available for it's prosecution.

6.2.5 Experimental Data for Appendix Compounds

Preparation of 4-Trimethylsilanyl-but-3-yn-1-ol 406
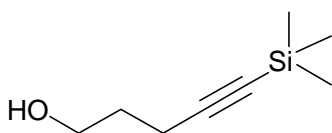
n-Butyllithium (40 mmol, 17.24 cm^3 of a 2.32M solution in hexane) was added dropwise over 20 min to a solution of pent-4-yn-1-ol **402** (20 mmol, 1.86 cm^3), in THF (40 cm^3) at -78°C. The solution was stirred at this temperature for 30 min before being warmed to 0°C and stirred for 2 hours. After re-cooling to -78°C, TMSCl (5.37 cm^3) was added dropwise over 5 min and the yellow colour of the solution faded, and a white precipitate was observed. The solution was refluxed for 12 hours, before being allowed to cool, diluted with 10% HCl (22 cm^3) and stirred for 30 min, before being extracted with diethyl ether (3 x 40 cm^3). The combing organic extracts were washed with NaHCO$_3$ (2 x 20 cm^3), brine (30 cm^3), dried (MgSO$_4$), then filtered and concentrated in vacuo to give a yellow oil which was purified on silica eluted with 50% diethyl ether in hexane to give **406** (2.43 mg, 78%) as a pale yellow oil (2.44 g, 78%); R$_f$ (30% diethyl ether/hexane)

0.37; δ_H (300MHz, CDCl$_3$) 3.61 (2H, t, J 6.5, HOCH_2), 2.21 (2H, t, J 6.5, CH_2C≡), 2.63 (2H, quintet, J 6.5, CH$_2$CH_2CH$_2$), 0.00 (9H, s, Si(CH_3)$_3$). The data were in agreement with those of Hiroi.[176]

Preparation of 5-Trimethylsilanyl-pent-4-yn-1-ol 401
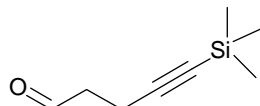
Dry DMSO (34.5 mmol, 2.45 cm^3) in THF (8 cm^3) was added dropwise over 10 min to oxalyl chloride (18 mmol, 1.55 cm^3) in THF (32 cm^3) at -78°C and a gas was observed to evolve. The solution was stirred for 5 min, then alcohol **406** (15 mmol, 2.34 g) was added dropwise over 10 min, and the solution was stirred for a further 15 min. Triethylamine (75 mmol, 10.45 cm^3) was added and the reaction allowed to warm to room temperature, then diluted with diethyl ether (250 cm^3). The resulting solution was washed with ammonium chloride (100 cm^3 of a saturated aqueous solution), CuSO$_4$ (2 x 100 cm^3 of a saturated aqueous solution), brine (2 x 100 cm^3), dried (MgSO$_4$), then filtered and concentrated in vacuo to give a aldehyde **401** as a yellow oil (2.00 g, 86%) which was used without further purification. δ_H (300MHz, CDCl$_3$) 9.66 (1H, t, J 1.2, CHO), 2.57-2.37 (4H, m, CH$_2$CH$_2$), 0.00 (9H, s, Si(CH$_3$). The data were in agreement with those of Hiroi.[176]

Preparation of 1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-7-trimethylsilylanyl-hept-1-en-6-yn-3-ol 407
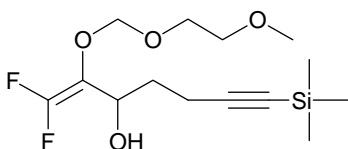
Acetal **131** (10 mmol, 1.68 cm^3) was added dropwise over 10 min to a cold (-78°C) solution of LDA (prepared by the slow addition of *n*BuLi (20 mmol, 8.77 cm^3, of a 2.28 M solution in hexane) to a cold (-78 ^{o}C) stirred solution of diisopropylamine (22 mmol, 3.09 cm^3) in THF (10 cm^3) under a nitrogen atmosphere. The solution was then warmed to rt for 15 min giving a pale yellow solution, then re-cooled to -78°C). The orange/brown solution was stirred at this temperature for 40 minutes hours and aldehyde **401** (12 mmol, 1.85 cm^3) was added in one portion over 1 min. The mixture was allowed to warm to -40 ^{o}C over 4 hours and quenched with ammonium chloride (2 cm^3 of a saturated aqueous solution). Water (30 cm^3) was added and the mixture was extracted with diethyl ether (3 x 70 cm^3). The combined organic extracts were washed with brine (2 x 40 cm^3), dried (MgSO$_4$), then filtered and concentrated under reduced pressure to leave a orange oil (2.87 mg). Distillation (Kugelrohr, bp. 120°C/0.05 mmHg) afforded difluoroallylic alcohol **407** (1.22 g, 38 %, 88 % by ^{19}F NMR); R$_f$ (30% ethyl acetate /hexane) 0.45; υ_{max}(film)/cm^{-1} 3435br, 2959w, 2175w, 1750s, 1249s, 1024s, 840s; δ_H (300MHz, CDCl$_3$) 4.85 (1H, d, ^2J 6.6, OC*H*$_a$H$_b$O), 4.74 (1H, d, ^2J 6.6, OCH$_a$*H*$_b$O), 4.35-4.25 (1H, m, broad, CC*H*), 3.81 (1H, ddd, ^2J 10.8, ^3J 6.3, 3.6, OC*H*$_a$H$_b$CH$_2$O), 3.64 (1H, ddd, ^2J 10.8, ^3J 4.7, 3.1, OCH$_a$*H*$_b$CH$_2$O), 3.47-3.42 (2H, m, OCH$_a$H$_b$C*H*$_2$O), 3.25 (3H, s, OCH$_3$), 2.17 (2H, m, CH$_2$C), 1.87-1.75 (1H, m, CHC*H*$_a$H$_b$), 1.71-1.59 (1H, m, CHCH$_a$*H*$_b$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75MHz, CDCl$_3$) 154.7 (dd, $^1J_{C-F}$ 292.3, 286.3),

117.9 (dd, $^2J_{\text{C-F}}$ 36.5, 10.7), 105.9, 98.0 (dd, $^4J_{\text{C-F}}$ 4.2, 3.0), 85.3, 71.4, 68.4, 65.9 (dd, $^3J_{\text{C-F}}$ 3.0, 1.8), 59.0, 32.7 (t, $^4J_{\text{C-F}}$ 2.4), 16.2, 0.0; δ_F (282MHz, CDCl$_3$) -99.6 (1F, dd, $^2J_{\text{F-F}}$ 62.1, $^4J_{\text{H-F}}$ 0.9), -109.0 (1F, dd, $^2J_{\text{F-F}}$ 62.1, $^4J_{\text{H-F}}$ 3.3); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 340.1752. Calc. for C$_{14}$H$_{28}$F$_2$O$_4$N: 340.1750]; m/z (CI$^+$) 340 (33%, [M+NH$_4$]$^+$), 305 (12), 218 (11), 108 (21), 90 (100).

Preparation of [5-Allyloxy-7,7-difluoro-6-(2-methoxy-ethoxymethoxy)-hept-6-en-1-ynyl]-trimethyl-silane 408
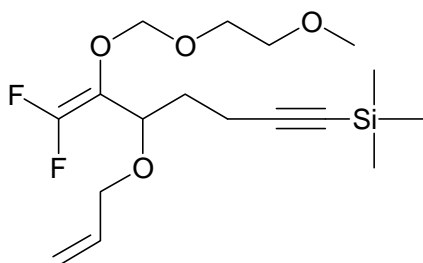
A mixture of difluoroallylic alcohol **407** (3.38 mmol, 1.09 g), and allyl bromide (4.06 mmol, 0.341 cm^3) was added over 1 min to a vigorously stirred solution of tetra-*n*-butylammonium hydrogensulfate (0.17 mmol, 57 mg) and sodium hydroxide (23.66 mmol, 1.52 cm^3) of a 50% aqueous solution at 0°C. The mixture was stirred at this temperature for 30 min then allowed to warm to room temperature, and stirred for a further 72 hours. The pale yellow solution was diluted with water (15 cm^3) and the layers separated. The aqueous phase was extracted with diethyl ether (3 x 20 cm^3). The combined organic extracts were washed with brine (2 x 10 cm^3), dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the desired difluoroallylic ether **408** as a pale yellow oil (0.870 mg, 71 %, 63 % purity by ^{19}F NMR); R$_f$ (30 % diethyl ether in

hexane) 0.27; υ_{max}(film)/cm^{-1} 2959s, 2361s, 2174s, 1749s, 1647w, 1455w, 1250s, 1117s, 844s, 760m; δ_H (300MHz, CDCl$_3$) 5.75 (1H, dddd, $^3J_{trans}$ 17.2, $^3J_{cis}$ 10.4, J 6.1, 5.1, CHC=CH$_2$), 5.13 (1H, d of AB dd, $^3J_{trans}$ 17.2, ^2J 1.6, ^4J 1.4, CH$_a$H$_b$=CH), 5.04 (1H, d of AB dd, $^3J_{cis}$ 10.4, ^2J 1.6, ^4J 1.2, CH$_a$H$_b$=CH), 4.88 (1H, d, AB, ^2J 6.0, OCH$_a$H$_b$O), 4.79 (1H, d, AB, ^2J 6.0, OCH$_a$H$_b$O), 4.15-4.05 (1H, m, CCH), 3.96 (1H, dd, ^2J 12.7, 5.1, =CHCH$_a$H$_b$), 3.79-3.70 (1H, m, =CHCH$_a$H$_b$), 3.69-3.59 (1H, m, OCH$_2$CH$_2$O), 3.43 (1H, m, OCH$_2$CH$_2$O), 3.25 (3H, s, OCH$_3$), 2.29-2.08 (2H, m, CH$_2$C≡), 1.91-1.80 (1H, m, CHCH$_a$H$_b$), 1.71-1.59 (1H, m, CHCH$_a$H$_b$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75MHz, CDCl$_3$) 156.0 (dd, $^1J_{C-F}$ 295.6, 285.4), 134.2, 117.2, 112.1 (dd, $^2J_{C-F}$ 36.5, 10.2), 105.9, 97.0 (dd, $^4J_{C-F}$ 4.2, 2.4), 85.3, 72.7 (dd, $^3J_{C-F}$ 3.0, 3.0), 71.5, 69.3, 68.2, 58.9, 30.7-30.6 (m), 16.0, -0.1; δ_F (282MHz, CDCl$_3$) -97.3 (1F, dd, $^2J_{F-F}$ 62.1, $^4J_{H-F}$ 4.3), -119.1 (1F, dd, $^2J_{F-F}$ 62.1, $^4J_{H-F}$ 3.8); [HRMS (ES$^+$, [M+NH$_4$]$^+$) Found: 380.2061. Calc. for C$_{17}$H$_{32}$F$_2$O$_4$SiN: 380.2063]; m/z (CI$^+$) 380 (62%, [M+NH$_4$]$^+$), 308 (17), 241 (35), 223 (22), 122 (28), 90 (100).

Preparation of 6-Bromo-4,4-difluoro-3-hydroxy-deca-1,9-dien-5-one 421
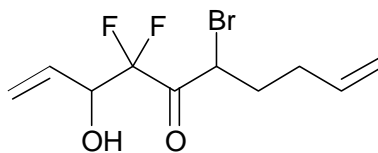
Allylic alcohol **183** (4.1 mmol, 1.2 g) was added to a stirred solution of cupric bromide (13.5 mmol, 3.02 g) in methanol (20 cm^3) at rt. The solution was stirred at reflux for 4 hours before being allowed to cool to rt, diluted with water (20 cm^3) and filtered through celite. The aqueous solution was extracted with ethyl acetate (3 x 100 cm^3) and the

combined organic extracts were washed with brine (20 cm^3), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give bromoketone **421** as a brown oil (1.12 g, 96%, 92% by GC) as an iseparablea mixture of diastereoisomers which was used without further purification. For analysis a small sample was purified my column chromatography on silica eluted with 20% diethyl ether/hexane which gave **421** as a brown oil; R$_f$ (10% ethyl acetate/hexane) 0.19; GC retention time 13.89 and 14.00 min; bp. 50°C 1.8 mmHg; υ_{max}(film)/cm^{-1} 3410br, 2955s, 1741s, 1444m, 1367m, 1075s, 991s, 916s; δ_H (300MHz, CDCl$_3$) 6.04-5.87 (1H, m, CH$_2$=CHCH), 5.83-5.68 (1H, m, CH$_2$CH=CH$_2$), 5.58-5.43 (2H env. containing, 5.53 (1H, ddt, $^3J_{trans}$ 17.2, ^2J 7.2, J 1.3, CH$_a$H$_b$CHCH$_2$), and 5.53-5.43 (1H, m, CH$_a$H$_b$CHCH$_2$)), 5.15-5.03 (2H, m, CH$_2$CH=CH$_2$), 4.73-4.69 (1H, m, COCHBr), 4.69-4.59 (1H, br. m, CH(OH)CF$_2$), 2.28-2.01 (4H, m, CH$_2$CH$_2$); δ_C (75MHz, CDCl$_3$) 195.1 (dd, $^2J_{C-F}$ 32.9, 25.1), 194.4 (t, $^2J_{C-F}$ 29.3), 135.0, 134.9, 130.9, 130.8, 120.1, 119.9, 115.6, 115.5, 115.2 (dd, $^1J_{C-F}$ 261.7, 257.6), 115.0 (dd, $^1J_{C-F}$ 262.6, 258.2), 72.8 (dd, $^2J_{C-F}$ 29.9, 24.6), 72.4 (dd, $^2J_{C-F}$ 26.9, 25.7), 44.0, 43.6, 30.7, 30.4, 29.9, 29.8; δ_F (282 MHz, CDCl$_3$) −109.0 (1F, dd, $^2J_{F-F}$ 268.6, $^3J_{H-F}$ 5.7), -112.7 (1F, dd, $^2J_{F-F}$ 272.6, $^3J_{H-F}$ 9.2), -118.6 (1F, dd, $^2J_{F-F}$ 272.6, $^3J_{H-F}$ 12.8), 125.3 (1F, dd, $^2J_{F-F}$ 268.6, $^3J_{H-F}$ 18.0); [HRMS (ES$^+$, [M-H]$^+$) Found: 280.9992, Calc. for C$_{10}$H$_{12}$F$_2$O$_2$^{79}Br: 280.9994]; *m/z* (EI$^+$) 203 (10%, [M$^+$-^{79}Br]), 177 (10), 175 (10), 165 (20), 149 (37), 147 (54), 129 (29), 106 (42), 95 (61), 79 (60), 67 (95), 57 (100).

Preparation of 8*S**-Bromo-2,2-difluoro-3*S**-hydroxy-cyclooct-4*Z*-enone 425 and 8*R**-Bromo-2,2-difluoro-3*S**-hydroxy-cyclooct-4*Z*-enone 426
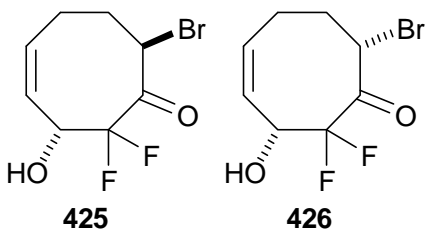
Grubbs 2nd generation catalyst (60mg, 5 mol%) was added to a stirred solution of α-bromoketone **421** (1.41 mmol, 400 mg) in freshly degassed DCM (1400 cm^3), the solution was refluxed for 6 hours after which TLC analysis showed incomplete conversion of starting material. A second loading of Grubbs 2nd generation catalyst (30 mg, 2.5 mol%) was added and reflux continued for 6 hours. Solvent was removed in *vacuo* and the residue purified on silica eluted with 20% ethyl acetate/hexane to give cyclooctenone **425** as a brown oil (100 mg, 28 %, 91 % by ^{19}F NMR); R$_f$ (ethyl acetate/hexane) 0.22; υ_{max}(solution)/cm^{-1} 3399br, 2934s, 1732s, 1448s, 1378w, 1208s, 1109s, 828s; δ_H (300MHz, CDCl$_3$) 5.82 (1H, ddd, *J* 11.3, 7.3, ^{4}*J* 1.8, =C*H*CH$_2$), 5.72-5.63 (1H, m, CHC*H*=), 4.74 (1H, ddd, *J* 11.0, 5.70, ^{3}*J*$_{H-F}$ 2.5, C*H*Br), 4.65 (1H, dd, ^{3}*J*$_{H-F}$ 23.8, *J* 5.3, C*H*(OH)), 2.36-2.08 (3H, m, CHBrC*H$_2$*C*H*$_a$H$_b$), 2.85-2.01 (1H, m, =CHCH$_a$*H$_b$*); δ_C (75MHz, CDCl$_3$) 197.4 (dd, ^{2}*J*$_{C-F}$ 31.4, 22.4), 130.1, 129.2 (d, ^{3}*J*$_{C-F}$ 3.6), 117.3 (dd, ^{1}*J*$_{C-F}$ 260.9, 259.1), 68.5 (t, ^{2}*J*$_{C-F}$ 22.7), 41.5, 33.3, 25.8; δ_F (376 MHz, 323 K, CDCl$_3$) -113.9 (1F, d, ^{2}*J*$_{F-F}$ 242.5), -130.8 (1F, dd, ^{2}*J*$_{F-F}$ 242.5, ^{3}*J*$_{H-F}$ 24.1); No suitable molecular ion could be obtained; and cyclooctenone **426** as a white solid (89mg, 25%, 100% GC); R$_f$ (20% ethyl acetate/hexane) 0.11; Mp. 87-90°C ; GC retention time 26.94 min; (Found: C, 37.97; H, 3.46; C$_8$H$_9$F$_2$O$_2$Br requires: C, 37.67; H, 3.56 %); υ_{max}(solution)/cm^{-1} 3401br, 2937s, 1732s, 1443s, 1373w, 1243s, 1099s, 955w, 819s; δ_H

(300MHz, CDCl$_3$) 5.95-5.84 (1H, m, J 8.1, =CHCH$_2$) 5.67-5.57 (1H, m, J 8.1 CHCH=), 4.96 (1H, ddd, $^3J_{\text{H-F}}$ 14.1, 6.9, J 6.9, CHCF$_2$), 4.66 (1H, ddd, J 11.4, 4.0, ^4J 1.6, CHBr), 2.55-2.18 (4H, m, CH$_2$CH$_2$); δ_{C} (75MHz, CDCl$_3$) 194.5 (dd, $^2J_{\text{C-F}}$ 29.6, 23.6), 133.7, 128.2 (d, $^3J_{\text{C-F}}$ 4.8), 116.9 (dd, $^1J_{\text{C-F}}$ 264.1, 258.2), 68.1 (dd, $^2J_{\text{C-F}}$ 26.0, 21.2), 44.1 (dd, $^3J_{\text{C-F}}$ 2.4, 1.8) 37.4, 26.9; δ_{F} (376 MHz, 323 K, CDCl$_3$) -112.1 (1F, d, $^2J_{\text{F-F}}$ 240.6), -130.0 (dd, $^2J_{\text{F-F}}$ 240.6, $^3J_{\text{H-F}}$ 16.0); [HRMS (ES$^+$, [M-NH$_4$]$^+$) Found: 272.0091, Calc. for C$_8$H$_{13}$F$_2$O$_2$^{79}BrN: 272.0092]; m/z (CI$^+$) 274 (M$^+$, 4%), 272 (4%, [M$^+$]), 227 (5), 194 (48), 158 (100), 140 (56), 123 (25); and a mixture of both diastereoisomers (19 mg, 5%).

6.2 Appendix 2: Crystal Structure Data
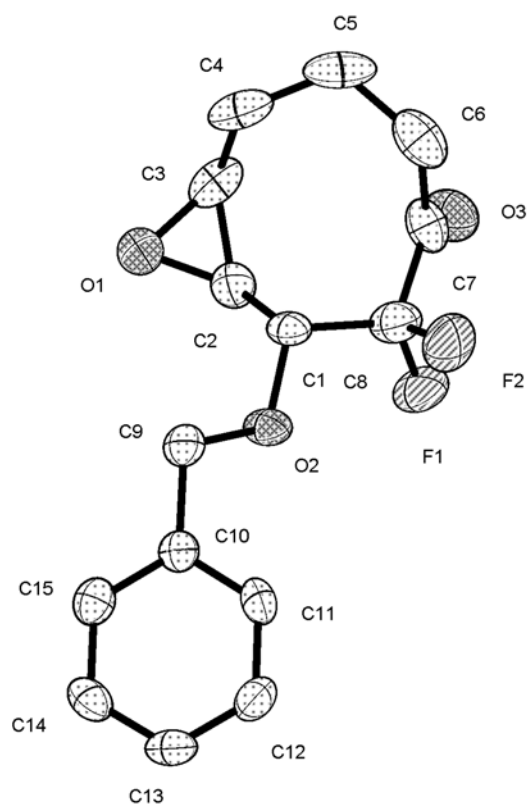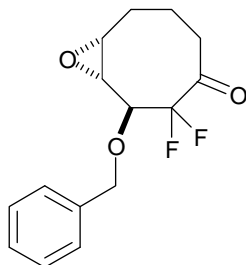
Table 1. Crystal data and structure refinement for 05085.

Identification code	05085
Empirical formula	C15 H16 F2 O3
Formula weight	282.28
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 7.9759(19) Å α= 90°.
	b = 11.944(3) Å β= 96.970(4)°.
	c = 14.467(3) Å γ = 90°.
Volume	1368.0(6) Å^3
Z	4
Density (calculated)	1.371 Mg/m^3
Absorption coefficient	0.112 mm^{-1}
F(000)	592
Crystal size	0.17 x 0.15 x 0.08 mm^3
Theta range for data collection	2.22 to 25.00°.
Index ranges	-9<=h<=9, -14<=k<=14, -17<=l<=17
Reflections collected	9474
Independent reflections	2406 [R(int) = 0.0778]
Completeness to theta = 25.00°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2406 / 0 / 181
Goodness-of-fit on F^2	1.122
Final R indices [I>2sigma(I)]	R1 = 0.1209, wR2 = 0.2973
R indices (all data)	R1 = 0.1403, wR2 = 0.3116
Largest diff. peak and hole	1.109 and -0.279 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 05085. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5497(6)	8623(4)	2196(3)	61(1)
O(2)	3029(4)	6856(4)	1074(3)	40(1)
O(3)	5829(6)	8768(4)	-894(3)	52(1)
F(1)	3200(4)	7642(4)	-595(2)	59(1)
F(2)	4772(5)	6168(3)	-445(3)	60(1)
C(1)	4608(6)	7290(4)	906(3)	30(1)
C(2)	4874(8)	8458(5)	1251(4)	41(1)
C(3)	6554(8)	8928(5)	1471(4)	47(2)
C(4)	8185(7)	8299(6)	1487(5)	53(2)
C(5)	8850(7)	8278(6)	560(6)	57(2)
C(6)	7897(8)	7502(6)	-161(5)	52(2)
C(7)	6087(8)	7914(5)	-469(4)	40(1)
C(8)	4651(7)	7265(5)	-146(4)	44(2)
C(9)	2967(7)	6450(5)	1984(4)	36(1)
C(10)	1299(6)	5881(4)	2011(3)	28(1)
C(11)	674(7)	5151(5)	1311(4)	40(1)
C(12)	-869(7)	4634(5)	1318(4)	43(2)
C(13)	-1790(7)	4818(5)	2041(4)	37(1)
C(14)	-1179(7)	5521(5)	2759(4)	36(1)
C(15)	353(7)	6062(5)	2738(4)	35(1)

Table 3. Bond lengths [Å] and angles [°] for 05085.

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O(1)-C(2)	1.411(7)
O(1)-C(3)	1.469(8)
O(2)-C(9)	1.410(6)
O(2)-C(1)	1.410(6)
O(3)-C(7)	1.196(7)
F(1)-C(8)	1.335(7)
F(2)-C(8)	1.386(8)
C(1)-C(2)	1.488(8)
C(1)-C(8)	1.526(8)
C(1)-H(1)	1.0000
C(2)-C(3)	1.453(8)
C(2)-H(2)	1.0000
C(3)-C(4)	1.500(9)
C(3)-H(3)	1.0000
C(4)-C(5)	1.502(10)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.527(10)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.538(9)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.504(8)
C(9)-C(10)	1.498(7)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(15)	1.383(7)
C(10)-C(11)	1.383(8)
C(11)-C(12)	1.378(8)
C(11)-H(11)	0.9500
C(12)-C(13)	1.367(8)
C(12)-H(12)	0.9500
C(13)-C(14)	1.377(8)

C(13)-H(13)	0.9500
C(14)-C(15)	1.387(8)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(2)-O(1)-C(3)	60.5(4)
C(9)-O(2)-C(1)	114.9(4)
O(2)-C(1)-C(2)	112.3(4)
O(2)-C(1)-C(8)	107.0(4)
C(2)-C(1)-C(8)	109.5(5)
O(2)-C(1)-H(1)	109.3
C(2)-C(1)-H(1)	109.3
C(8)-C(1)-H(1)	109.3
O(1)-C(2)-C(3)	61.7(4)
O(1)-C(2)-C(1)	118.4(5)
C(3)-C(2)-C(1)	121.7(5)
O(1)-C(2)-H(2)	114.9
C(3)-C(2)-H(2)	114.9
C(1)-C(2)-H(2)	114.9
C(2)-C(3)-O(1)	57.7(4)
C(2)-C(3)-C(4)	125.8(6)
O(1)-C(3)-C(4)	115.9(5)
C(2)-C(3)-H(3)	114.8
O(1)-C(3)-H(3)	114.8
C(4)-C(3)-H(3)	114.8
C(3)-C(4)-C(5)	113.2(5)
C(3)-C(4)-H(4A)	108.9
C(5)-C(4)-H(4A)	108.9
C(3)-C(4)-H(4B)	108.9
C(5)-C(4)-H(4B)	108.9
H(4A)-C(4)-H(4B)	107.8
C(4)-C(5)-C(6)	114.8(5)
C(4)-C(5)-H(5A)	108.6
C(6)-C(5)-H(5A)	108.6
C(4)-C(5)-H(5B)	108.6
C(6)-C(5)-H(5B)	108.6

H(5A)-C(5)-H(5B)	107.5
C(5)-C(6)-C(7)	112.1(5)
C(5)-C(6)-H(6A)	109.2
C(7)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6B)	109.2
C(7)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
O(3)-C(7)-C(8)	120.6(5)
O(3)-C(7)-C(6)	121.3(5)
C(8)-C(7)-C(6)	117.9(5)
F(1)-C(8)-F(2)	104.8(5)
F(1)-C(8)-C(7)	108.8(5)
F(2)-C(8)-C(7)	107.8(5)
F(1)-C(8)-C(1)	110.8(5)
F(2)-C(8)-C(1)	109.9(5)
C(7)-C(8)-C(1)	114.2(5)
O(2)-C(9)-C(10)	108.2(4)
O(2)-C(9)-H(9A)	110.1
C(10)-C(9)-H(9A)	110.1
O(2)-C(9)-H(9B)	110.1
C(10)-C(9)-H(9B)	110.1
H(9A)-C(9)-H(9B)	108.4
C(15)-C(10)-C(11)	118.3(5)
C(15)-C(10)-C(9)	121.1(5)
C(11)-C(10)-C(9)	120.6(5)
C(12)-C(11)-C(10)	121.3(5)
C(12)-C(11)-H(11)	119.4
C(10)-C(11)-H(11)	119.4
C(13)-C(12)-C(11)	119.8(5)
C(13)-C(12)-H(12)	120.1
C(11)-C(12)-H(12)	120.1
C(12)-C(13)-C(14)	120.1(5)
C(12)-C(13)-H(13)	120.0
C(14)-C(13)-H(13)	120.0
C(13)-C(14)-C(15)	119.9(5)
C(13)-C(14)-H(14)	120.0

C(15)-C(14)-H(14)	120.0
C(10)-C(15)-C(14)	120.5(5)
C(10)-C(15)-H(15)	119.7
C(14)-C(15)-H(15)	119.7

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Symmetry transformations used to generate equivalent atoms:

Table 4.　Anisotropic displacement parameters　($\text{Å}^2 \times 10^3$) for 05085. The anisotropic displacement factor exponent takes the form:　$-2\pi^2[\, h^2\, a^{*2}U^{11} + ... + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	56(3)	80(3)	50(3)	-22(2)	16(2)	-28(2)
O(2)	25(2)	62(3)	33(2)	17(2)	-3(2)	-7(2)
O(3)	50(3)	53(3)	54(3)	15(2)	9(2)	0(2)
F(1)	45(2)	84(3)	42(2)	18(2)	-12(2)	-18(2)
F(2)	76(3)	47(2)	56(2)	-11(2)	8(2)	-18(2)
C(1)	19(2)	37(3)	32(3)	7(2)	-1(2)	0(2)
C(2)	42(3)	43(3)	41(3)	-6(3)	10(2)	-7(3)
C(3)	48(4)	38(3)	52(4)	-5(3)	-12(3)	-4(3)
C(4)	33(3)	50(4)	69(4)	10(3)	-16(3)	-9(3)
C(5)	19(3)	50(4)	99(6)	6(4)	-3(3)	4(3)
C(6)	57(4)	45(4)	59(4)	10(3)	26(3)	17(3)
C(7)	51(4)	38(3)	33(3)	8(3)	14(2)	6(3)
C(8)	34(3)	53(4)	44(3)	8(3)	-3(3)	-7(3)
C(9)	34(3)	46(3)	26(3)	7(2)	-1(2)	-6(2)
C(10)	30(3)	30(3)	24(2)	9(2)	0(2)	0(2)
C(11)	44(3)	51(3)	26(3)	-4(2)	13(2)	-8(3)
C(12)	45(3)	52(4)	30(3)	-3(3)	-2(2)	-18(3)
C(13)	25(3)	42(3)	44(3)	10(3)	-1(2)	-6(2)
C(14)	29(3)	44(3)	38(3)	4(2)	11(2)	8(2)
C(15)	38(3)	33(3)	31(3)	-1(2)	0(2)	4(2)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\mathring{A}^2$x 10 ^{3}) for 05085.

	x	y	z	U(eq)
H(1)	5529	6801	1215	36
H(2)	3988	9004	992	50
H(3)	6636	9750	1353	57
H(4A)	8013	7519	1689	63
H(4B)	9041	8648	1952	63
H(5A)	10050	8045	656	68
H(5B)	8810	9048	305	68
H(6A)	7851	6741	106	62
H(6B)	8518	7454	-712	62
H(9A)	3089	7077	2435	43
H(9B)	3900	5913	2154	43
H(11)	1321	5003	815	48
H(12)	-1292	4152	822	52
H(13)	-2852	4461	2049	45
H(14)	-1808	5635	3269	44
H(15)	757	6561	3226	41

Table 6. Torsion angles [°] for 05085.

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C(9)-O(2)-C(1)-C(2)	-81.0(6)
C(9)-O(2)-C(1)-C(8)	158.8(5)
C(3)-O(1)-C(2)-C(1)	112.8(6)
O(2)-C(1)-C(2)-O(1)	84.4(6)
C(8)-C(1)-C(2)-O(1)	-156.8(5)
O(2)-C(1)-C(2)-C(3)	157.0(5)
C(8)-C(1)-C(2)-C(3)	-84.2(6)
C(1)-C(2)-C(3)-O(1)	-107.6(6)
O(1)-C(2)-C(3)-C(4)	100.4(7)
C(1)-C(2)-C(3)-C(4)	-7.2(9)
C(2)-O(1)-C(3)-C(4)	-117.6(6)
C(2)-C(3)-C(4)-C(5)	88.8(8)
O(1)-C(3)-C(4)-C(5)	156.4(5)
C(3)-C(4)-C(5)-C(6)	-73.9(7)
C(4)-C(5)-C(6)-C(7)	67.3(7)
C(5)-C(6)-C(7)-O(3)	66.1(8)
C(5)-C(6)-C(7)-C(8)	-108.5(7)
O(3)-C(7)-C(8)-F(1)	14.8(8)
C(6)-C(7)-C(8)-F(1)	-170.6(5)
O(3)-C(7)-C(8)-F(2)	128.0(6)
C(6)-C(7)-C(8)-F(2)	-57.4(7)
O(3)-C(7)-C(8)-C(1)	-109.6(6)
C(6)-C(7)-C(8)-C(1)	65.0(7)
O(2)-C(1)-C(8)-F(1)	44.6(6)
C(2)-C(1)-C(8)-F(1)	-77.4(6)
O(2)-C(1)-C(8)-F(2)	-70.8(5)
C(2)-C(1)-C(8)-F(2)	167.2(4)
O(2)-C(1)-C(8)-C(7)	168.0(5)
C(2)-C(1)-C(8)-C(7)	45.9(6)
C(1)-O(2)-C(9)-C(10)	-172.3(4)
O(2)-C(9)-C(10)-C(15)	-135.4(5)
O(2)-C(9)-C(10)-C(11)	45.2(7)
C(15)-C(10)-C(11)-C(12)	1.6(8)
C(9)-C(10)-C(11)-C(12)	-179.0(5)

C(10)-C(11)-C(12)-C(13)	-1.8(9)
C(11)-C(12)-C(13)-C(14)	0.2(9)
C(12)-C(13)-C(14)-C(15)	1.5(8)
C(11)-C(10)-C(15)-C(14)	0.1(8)
C(9)-C(10)-C(15)-C(14)	-179.3(5)
C(13)-C(14)-C(15)-C(10)	-1.6(8)

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Symmetry transformations used to generate equivalent atoms:

6.2.2 3R*-Benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nona-1R*,4R*-diol 255
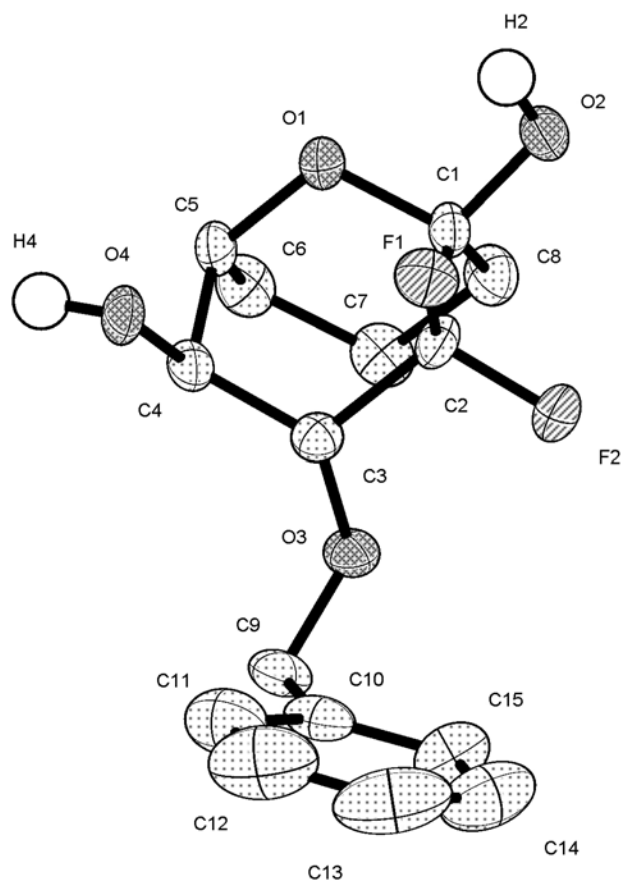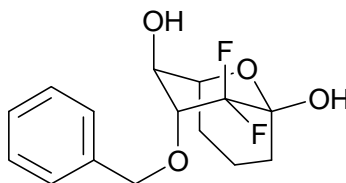
Table 1. Crystal data and structure refinement for 05081.

Identification code	05081
Empirical formula	C15 H18 F2 O4
Formula weight	300.29
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 10.3624(14) Å α= 90°.
	b = 6.6363(9) Å β= 112.613(2)°.
	c = 11.0444(15) Å γ = 90°.
Volume	701.11(16) Å^3
Z	2
Density (calculated)	1.422 Mg/m^3
Absorption coefficient	0.119 mm^{-1}
F(000)	316
Crystal size	0.16 x 0.13 x 0.08 mm^3
Theta range for data collection	2.00 to 25.00°.
Index ranges	-12<=h<=12, -7<=k<=7, -13<=l<=13
Reflections collected	5059
Independent reflections	2397 [R(int) = 0.0672]
Completeness to theta = 25.00°	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2397 / 1 / 192
Goodness-of-fit on F^2	0.826
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.0618
R indices (all data)	R1 = 0.0684, wR2 = 0.0683
Absolute structure parameter	0.6(10)
Largest diff. peak and hole	0.164 and -0.159 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 05081. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	9494(2)	5095(3)	8297(2)	32(1)
F(2)	7595(2)	6610(3)	7000(2)	34(1)
O(1)	8209(2)	3799(3)	9924(2)	25(1)
O(2)	8500(2)	7143(3)	9767(2)	28(1)
O(3)	6261(2)	3212(3)	6180(2)	28(1)
O(4)	9054(2)	528(3)	8558(2)	28(1)
C(1)	7711(3)	5488(5)	9085(3)	24(1)
C(2)	8059(3)	5051(5)	7879(3)	25(1)
C(3)	7604(3)	3034(4)	7195(3)	23(1)
C(4)	7682(3)	1351(5)	8161(3)	25(1)
C(5)	7419(3)	2004(5)	9379(3)	25(1)
C(6)	5899(3)	2291(5)	9216(3)	32(1)
C(7)	5229(3)	4112(5)	8363(3)	34(1)
C(8)	6197(3)	5938(5)	8814(3)	31(1)
C(9)	6067(3)	1864(5)	5098(3)	34(1)
C(10)	7006(3)	2363(5)	4385(3)	34(1)
C(11)	7985(4)	1017(6)	4338(3)	53(1)
C(12)	8856(4)	1492(8)	3686(4)	72(2)
C(13)	8740(4)	3291(9)	3070(4)	74(2)
C(14)	7767(4)	4660(7)	3118(3)	63(1)
C(15)	6900(4)	4213(6)	3776(3)	46(1)

Table 3. Bond lengths [Å] and angles [°] for 05081.

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F(1)-C(2)	1.377(3)
F(2)-C(2)	1.372(3)
O(1)-C(1)	1.419(3)
O(1)-C(5)	1.440(3)
O(2)-C(1)	1.403(3)
O(2)-H(2)	0.8400
O(3)-C(3)	1.417(3)
O(3)-C(9)	1.443(3)
O(4)-C(4)	1.425(3)
O(4)-H(4)	0.8400
C(1)-C(8)	1.510(4)
C(1)-C(2)	1.536(4)
C(2)-C(3)	1.521(4)
C(3)-C(4)	1.526(4)
C(3)-H(3)	1.0000
C(4)-C(5)	1.533(4)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.527(4)
C(5)-H(5)	1.0000
C(6)-C(7)	1.525(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.529(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.505(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.367(4)
C(10)-C(15)	1.383(5)
C(11)-C(12)	1.390(5)
C(11)-H(11)	0.9500

C(12)-C(13)	1.357(6)
C(12)-H(12)	0.9500
C(13)-C(14)	1.373(5)
C(13)-H(13)	0.9500
C(14)-C(15)	1.388(5)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(1)-O(1)-C(5)	112.0(2)
C(1)-O(2)-H(2)	109.5
C(3)-O(3)-C(9)	112.6(2)
C(4)-O(4)-H(4)	109.5
O(2)-C(1)-O(1)	106.1(2)
O(2)-C(1)-C(8)	107.3(3)
O(1)-C(1)-C(8)	112.0(3)
O(2)-C(1)-C(2)	109.3(2)
O(1)-C(1)-C(2)	105.6(2)
C(8)-C(1)-C(2)	116.0(3)
F(2)-C(2)-F(1)	105.1(2)
F(2)-C(2)-C(3)	110.8(2)
F(1)-C(2)-C(3)	105.9(2)
F(2)-C(2)-C(1)	109.6(2)
F(1)-C(2)-C(1)	106.8(2)
C(3)-C(2)-C(1)	117.8(3)
O(3)-C(3)-C(2)	110.0(2)
O(3)-C(3)-C(4)	112.7(3)
C(2)-C(3)-C(4)	112.0(3)
O(3)-C(3)-H(3)	107.3
C(2)-C(3)-H(3)	107.3
C(4)-C(3)-H(3)	107.3
O(4)-C(4)-C(3)	105.9(2)
O(4)-C(4)-C(5)	109.3(2)
C(3)-C(4)-C(5)	115.3(3)
O(4)-C(4)-H(4A)	108.7
C(3)-C(4)-H(4A)	108.7
C(5)-C(4)-H(4A)	108.7

O(1)-C(5)-C(6)	109.9(3)
O(1)-C(5)-C(4)	109.6(2)
C(6)-C(5)-C(4)	117.1(3)
O(1)-C(5)-H(5)	106.5
C(6)-C(5)-H(5)	106.5
C(4)-C(5)-H(5)	106.5
C(7)-C(6)-C(5)	112.1(3)
C(7)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6A)	109.2
C(7)-C(6)-H(6B)	109.2
C(5)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
C(6)-C(7)-C(8)	109.9(2)
C(6)-C(7)-H(7A)	109.7
C(8)-C(7)-H(7A)	109.7
C(6)-C(7)-H(7B)	109.7
C(8)-C(7)-H(7B)	109.7
H(7A)-C(7)-H(7B)	108.2
C(1)-C(8)-C(7)	114.2(3)
C(1)-C(8)-H(8A)	108.7
C(7)-C(8)-H(8A)	108.7
C(1)-C(8)-H(8B)	108.7
C(7)-C(8)-H(8B)	108.7
H(8A)-C(8)-H(8B)	107.6
O(3)-C(9)-C(10)	112.6(3)
O(3)-C(9)-H(9A)	109.1
C(10)-C(9)-H(9A)	109.1
O(3)-C(9)-H(9B)	109.1
C(10)-C(9)-H(9B)	109.1
H(9A)-C(9)-H(9B)	107.8
C(11)-C(10)-C(15)	118.9(4)
C(11)-C(10)-C(9)	120.9(3)
C(15)-C(10)-C(9)	120.2(3)
C(10)-C(11)-C(12)	120.7(4)
C(10)-C(11)-H(11)	119.6
C(12)-C(11)-H(11)	119.6

C(13)-C(12)-C(11)	120.6(5)
C(13)-C(12)-H(12)	119.7
C(11)-C(12)-H(12)	119.7
C(12)-C(13)-C(14)	119.2(4)
C(12)-C(13)-H(13)	120.4
C(14)-C(13)-H(13)	120.4
C(13)-C(14)-C(15)	120.8(4)
C(13)-C(14)-H(14)	119.6
C(15)-C(14)-H(14)	119.6
C(10)-C(15)-C(14)	119.8(4)
C(10)-C(15)-H(15)	120.1
C(14)-C(15)-H(15)	120.1

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Symmetry transformations used to generate equivalent atoms:

6.2.3 3R*-benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,4S*-diol 256
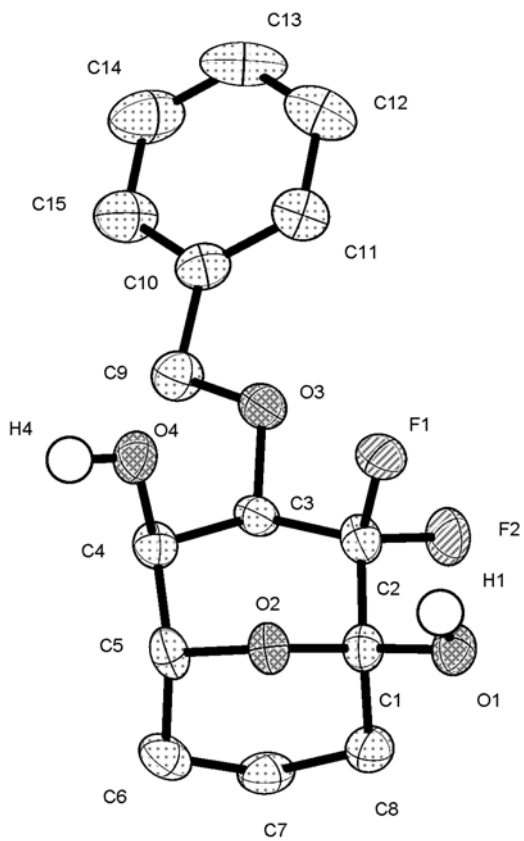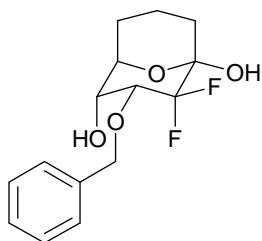
Table 1. Crystal data and structure refinement for 05077.

Identification code	05077
Empirical formula	C15 H18 F2 O4
Formula weight	300.29
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 15.5415(19) Å $\alpha= 90°$.
	b = 6.6332(8) Å $\beta= 106.126(2)°$.
	c = 13.9404(17) Å $\gamma = 90°$.
Volume	1380.6(3) Å^3
Z	4
Density (calculated)	1.445 Mg/m^3
Absorption coefficient	0.121 mm^{-1}
F(000)	632
Crystal size	0.14 x 0.09 x 0.06 mm^3
Theta range for data collection	2.73 to 25.00°.
Index ranges	-18<=h<=18, -7<=k<=7, -16<=l<=16
Reflections collected	9657
Independent reflections	2430 [R(int) = 0.0967]
Completeness to theta = 25.00°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2430 / 0 / 192
Goodness-of-fit on F^2	0.844
Final R indices [I>2sigma(I)]	R1 = 0.0514, wR2 = 0.0661
R indices (all data)	R1 = 0.1050, wR2 = 0.0785
Largest diff. peak and hole	0.198 and -0.184 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 05077. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	466(1)	1298(2)	3533(1)	32(1)
O(2)	473(1)	4619(3)	3899(1)	30(1)
O(3)	2521(1)	5676(3)	2684(1)	34(1)
O(4)	1040(1)	7803(3)	2766(1)	34(1)
F(1)	1104(1)	3399(2)	2292(1)	37(1)
F(2)	2217(1)	1817(2)	3301(1)	40(1)
C(1)	1031(2)	2909(4)	3935(2)	28(1)
C(2)	1629(2)	3389(4)	3255(2)	29(1)
C(3)	2147(2)	5329(4)	3479(2)	27(1)
C(4)	1578(2)	7047(4)	3700(2)	28(1)
C(5)	985(2)	6356(4)	4351(2)	31(1)
C(6)	1457(2)	5972(4)	5442(2)	36(1)
C(7)	2031(2)	4076(4)	5616(2)	37(1)
C(8)	1522(2)	2345(4)	4992(2)	34(1)
C(9)	3131(2)	7305(4)	2848(2)	36(1)
C(10)	3637(2)	7293(4)	2068(2)	34(1)
C(11)	3544(2)	5769(5)	1388(2)	39(1)
C(12)	3998(2)	5827(5)	665(2)	54(1)
C(13)	4562(2)	7390(6)	635(2)	60(1)
C(14)	4668(2)	8897(6)	1329(3)	61(1)
C(15)	4206(2)	8864(5)	2031(2)	48(1)

Table 3. Bond lengths [Å] and angles [°] for 05077.

_____

O(1)-C(1)	1.398(3)
O(1)-H(1)	0.8400
O(2)-C(1)	1.420(3)
O(2)-C(5)	1.442(3)
O(3)-C(3)	1.407(3)
O(3)-C(9)	1.414(3)
O(4)-C(4)	1.429(3)
O(4)-H(4)	0.8400
F(1)-C(2)	1.364(3)
F(2)-C(2)	1.376(3)
C(1)-C(8)	1.506(3)
C(1)-C(2)	1.535(4)
C(2)-C(3)	1.504(3)
C(3)-C(4)	1.525(3)
C(3)-H(3)	1.0000
C(4)-C(5)	1.531(4)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.516(4)
C(5)-H(5)	1.0000
C(6)-C(7)	1.522(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.523(3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.509(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.366(4)
C(10)-C(15)	1.377(4)
C(11)-C(12)	1.382(4)
C(11)-H(11)	0.9500

C(12)-C(13)	1.366(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.368(4)
C(13)-H(13)	0.9500
C(14)-C(15)	1.366(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(1)-O(1)-H(1)	109.5
C(1)-O(2)-C(5)	111.4(2)
C(3)-O(3)-C(9)	113.8(2)
C(4)-O(4)-H(4)	109.5
O(1)-C(1)-O(2)	106.7(2)
O(1)-C(1)-C(8)	107.1(2)
O(2)-C(1)-C(8)	111.8(2)
O(1)-C(1)-C(2)	109.3(2)
O(2)-C(1)-C(2)	106.3(2)
C(8)-C(1)-C(2)	115.3(2)
F(1)-C(2)-F(2)	105.0(2)
F(1)-C(2)-C(3)	109.8(2)
F(2)-C(2)-C(3)	109.2(2)
F(1)-C(2)-C(1)	108.1(2)
F(2)-C(2)-C(1)	108.8(2)
C(3)-C(2)-C(1)	115.4(2)
O(3)-C(3)-C(2)	106.9(2)
O(3)-C(3)-C(4)	115.3(2)
C(2)-C(3)-C(4)	112.0(2)
O(3)-C(3)-H(3)	107.4
C(2)-C(3)-H(3)	107.4
C(4)-C(3)-H(3)	107.4
O(4)-C(4)-C(3)	107.7(2)
O(4)-C(4)-C(5)	110.4(2)
C(3)-C(4)-C(5)	112.0(2)
O(4)-C(4)-H(4A)	108.9
C(3)-C(4)-H(4A)	108.9
C(5)-C(4)-H(4A)	108.9

O(2)-C(5)-C(6)	111.0(2)
O(2)-C(5)-C(4)	109.3(2)
C(6)-C(5)-C(4)	116.2(2)
O(2)-C(5)-H(5)	106.6
C(6)-C(5)-H(5)	106.6
C(4)-C(5)-H(5)	106.6
C(5)-C(6)-C(7)	113.4(2)
C(5)-C(6)-H(6A)	108.9
C(7)-C(6)-H(6A)	108.9
C(5)-C(6)-H(6B)	108.9
C(7)-C(6)-H(6B)	108.9
H(6A)-C(6)-H(6B)	107.7
C(6)-C(7)-C(8)	110.1(2)
C(6)-C(7)-H(7A)	109.6
C(8)-C(7)-H(7A)	109.6
C(6)-C(7)-H(7B)	109.6
C(8)-C(7)-H(7B)	109.6
H(7A)-C(7)-H(7B)	108.2
C(1)-C(8)-C(7)	114.4(2)
C(1)-C(8)-H(8A)	108.7
C(7)-C(8)-H(8A)	108.7
C(1)-C(8)-H(8B)	108.7
C(7)-C(8)-H(8B)	108.7
H(8A)-C(8)-H(8B)	107.6
O(3)-C(9)-C(10)	109.8(2)
O(3)-C(9)-H(9A)	109.7
C(10)-C(9)-H(9A)	109.7
O(3)-C(9)-H(9B)	109.7
C(10)-C(9)-H(9B)	109.7
H(9A)-C(9)-H(9B)	108.2
C(11)-C(10)-C(15)	118.7(3)
C(11)-C(10)-C(9)	121.9(3)
C(15)-C(10)-C(9)	119.4(3)
C(10)-C(11)-C(12)	120.5(3)
C(10)-C(11)-H(11)	119.7
C(12)-C(11)-H(11)	119.7

C(13)-C(12)-C(11)	120.4(3)
C(13)-C(12)-H(12)	119.8
C(11)-C(12)-H(12)	119.8
C(12)-C(13)-C(14)	119.0(3)
C(12)-C(13)-H(13)	120.5
C(14)-C(13)-H(13)	120.5
C(15)-C(14)-C(13)	120.7(3)
C(15)-C(14)-H(14)	119.6
C(13)-C(14)-H(14)	119.6
C(14)-C(15)-C(10)	120.7(3)
C(14)-C(15)-H(15)	119.7
C(10)-C(15)-H(15)	119.7

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Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters ($Å^2$x 10^3) for 05077. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	33(1)	27(1)	32(1)	-1(1)	2(1)	-2(1)
O(2)	30(1)	25(1)	34(1)	-5(1)	7(1)	-1(1)
O(3)	39(1)	34(1)	31(1)	-4(1)	14(1)	-6(1)
O(4)	38(1)	26(1)	33(1)	1(1)	4(1)	4(1)
F(1)	45(1)	37(1)	26(1)	-3(1)	8(1)	-6(1)
F(2)	44(1)	29(1)	52(1)	-2(1)	20(1)	9(1)
C(1)	30(2)	23(2)	30(2)	-2(1)	7(2)	-1(2)
C(2)	30(2)	26(2)	25(2)	-3(1)	0(2)	7(2)
C(3)	31(2)	30(2)	24(2)	-3(1)	11(2)	-1(2)
C(4)	28(2)	28(2)	24(2)	-2(1)	1(2)	1(2)
C(5)	32(2)	26(2)	36(2)	-10(2)	11(2)	-3(2)
C(6)	38(2)	44(2)	29(2)	-11(2)	12(2)	-12(2)
C(7)	40(2)	44(2)	23(2)	4(2)	5(2)	-7(2)
C(8)	40(2)	33(2)	29(2)	1(2)	7(2)	-4(2)
C(9)	34(2)	37(2)	36(2)	-1(2)	11(2)	-6(2)
C(10)	28(2)	41(2)	30(2)	5(2)	4(2)	0(2)
C(11)	33(2)	47(2)	36(2)	-1(2)	9(2)	-1(2)
C(12)	44(2)	81(3)	39(2)	-7(2)	15(2)	5(2)
C(13)	42(3)	108(4)	34(2)	14(2)	15(2)	-2(2)
C(14)	55(3)	80(3)	49(2)	8(2)	16(2)	-24(2)
C(15)	46(2)	59(2)	38(2)	-2(2)	11(2)	-15(2)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10 ^{3})
for 05077.

	x	y	z	U(eq)
H(1)	36	1717	3067	48
H(4)	866	8974	2846	51
H(3)	2653	5106	4093	33
H(4A)	1983	8146	4056	34
H(5)	545	7465	4333	37
H(6A)	1002	5854	5815	43
H(6B)	1841	7145	5714	43
H(7A)	2191	3709	6333	44
H(7B)	2592	4333	5431	44
H(8A)	1951	1252	4975	41
H(8B)	1084	1807	5325	41
H(9A)	3557	7190	3521	43
H(9B)	2802	8593	2815	43
H(11)	3163	4660	1411	47
H(12)	3918	4773	187	65
H(13)	4876	7431	140	72
H(14)	5068	9977	1322	73
H(15)	4278	9935	2499	57

Table 6. Torsion angles [°] for 05077.

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C(5)-O(2)-C(1)-O(1)	176.7(2)
C(5)-O(2)-C(1)-C(8)	59.9(3)
C(5)-O(2)-C(1)-C(2)	-66.7(3)
O(1)-C(1)-C(2)-F(1)	45.3(3)
O(2)-C(1)-C(2)-F(1)	-69.5(3)
C(8)-C(1)-C(2)-F(1)	165.9(2)
O(1)-C(1)-C(2)-F(2)	-68.1(3)
O(2)-C(1)-C(2)-F(2)	177.0(2)
C(8)-C(1)-C(2)-F(2)	52.5(3)
O(1)-C(1)-C(2)-C(3)	168.7(2)
O(2)-C(1)-C(2)-C(3)	53.9(3)
C(8)-C(1)-C(2)-C(3)	-70.7(3)
C(9)-O(3)-C(3)-C(2)	-171.8(2)
C(9)-O(3)-C(3)-C(4)	63.0(3)
F(1)-C(2)-C(3)-O(3)	-47.3(3)
F(2)-C(2)-C(3)-O(3)	67.2(3)
C(1)-C(2)-C(3)-O(3)	-169.8(2)
F(1)-C(2)-C(3)-C(4)	79.8(3)
F(2)-C(2)-C(3)-C(4)	-165.6(2)
C(1)-C(2)-C(3)-C(4)	-42.6(3)
O(3)-C(3)-C(4)-O(4)	42.1(3)
C(2)-C(3)-C(4)-O(4)	-80.4(3)
O(3)-C(3)-C(4)-C(5)	163.6(2)
C(2)-C(3)-C(4)-C(5)	41.1(3)
C(1)-O(2)-C(5)-C(6)	-61.0(3)
C(1)-O(2)-C(5)-C(4)	68.5(3)
O(4)-C(4)-C(5)-O(2)	67.0(3)
C(3)-C(4)-C(5)-O(2)	-52.9(3)
O(4)-C(4)-C(5)-C(6)	-166.4(2)
C(3)-C(4)-C(5)-C(6)	73.7(3)
O(2)-C(5)-C(6)-C(7)	53.9(3)
C(4)-C(5)-C(6)-C(7)	-71.8(3)
C(5)-C(6)-C(7)-C(8)	-44.7(3)
O(1)-C(1)-C(8)-C(7)	-168.5(2)

O(2)-C(1)-C(8)-C(7)	-52.0(3)
C(2)-C(1)-C(8)-C(7)	69.6(3)
C(6)-C(7)-C(8)-C(1)	43.7(3)
C(3)-O(3)-C(9)-C(10)	168.3(2)
O(3)-C(9)-C(10)-C(11)	-5.7(4)
O(3)-C(9)-C(10)-C(15)	173.8(3)
C(15)-C(10)-C(11)-C(12)	-1.3(4)
C(9)-C(10)-C(11)-C(12)	178.3(3)
C(10)-C(11)-C(12)-C(13)	1.4(5)
C(11)-C(12)-C(13)-C(14)	-0.2(5)
C(12)-C(13)-C(14)-C(15)	-1.2(5)
C(13)-C(14)-C(15)-C(10)	1.3(5)
C(11)-C(10)-C(15)-C(14)	0.0(5)
C(9)-C(10)-C(15)-C(14)	-179.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters (Å^2x 10^3) for 05081. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	23(1)	37(1)	35(1)	-3(1)	11(1)	-7(1)
F(2)	43(1)	25(1)	29(1)	8(1)	8(1)	0(1)
O(1)	28(1)	19(1)	26(1)	1(1)	8(1)	-1(1)
O(2)	26(1)	21(1)	32(1)	-3(1)	6(1)	0(1)
O(3)	22(1)	29(1)	25(1)	-3(1)	3(1)	3(1)
O(4)	27(1)	19(1)	34(1)	4(1)	7(1)	6(1)
C(1)	24(2)	16(2)	29(2)	1(2)	8(2)	2(2)
C(2)	21(2)	21(2)	27(2)	8(2)	3(2)	1(2)
C(3)	20(2)	25(2)	23(2)	0(2)	6(2)	-1(2)
C(4)	19(2)	20(2)	29(2)	-2(2)	1(2)	-1(1)
C(5)	28(2)	16(2)	29(2)	2(2)	8(2)	-3(2)
C(6)	32(2)	32(2)	37(2)	-3(2)	18(2)	-8(2)
C(7)	26(2)	37(2)	40(2)	-4(2)	15(2)	-2(2)
C(8)	27(2)	27(2)	37(2)	-1(2)	11(2)	4(2)
C(9)	32(2)	35(2)	26(2)	-9(2)	2(2)	-5(2)
C(10)	27(2)	45(3)	25(2)	-11(2)	4(2)	-3(2)
C(11)	49(2)	64(3)	44(3)	-10(2)	17(2)	5(2)
C(12)	54(3)	118(5)	52(3)	-12(3)	28(3)	15(3)
C(13)	45(3)	142(6)	39(3)	-2(3)	22(2)	-2(4)
C(14)	50(3)	94(4)	42(3)	15(3)	14(2)	-10(3)
C(15)	40(2)	57(3)	37(2)	8(2)	12(2)	4(2)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10 ^{3}) for 05081.

	x	y	z	U(eq)
H(2)	9295	6749	10272	42
H(4)	9063	-638	8857	42
H(3)	8274	2685	6773	28
H(4A)	6989	284	7691	30
H(5)	7811	916	10047	30
H(6A)	5360	1066	8813	39
H(6B)	5859	2468	10091	39
H(7A)	4322	4416	8427	40
H(7B)	5052	3807	7435	40
H(8A)	5865	6994	8131	37
H(8B)	6130	6485	9622	37
H(9A)	5081	1931	4473	41
H(9B)	6257	466	5433	41
H(11)	8070	-255	4756	63
H(12)	9539	548	3672	87
H(13)	9324	3600	2611	88
H(14)	7687	5928	2696	76
H(15)	6235	5175	3809	55

Table 6. Torsion angles [°] for 05081.

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C(5)-O(1)-C(1)-O(2)	176.0(2)
C(5)-O(1)-C(1)-C(8)	59.2(3)
C(5)-O(1)-C(1)-C(2)	-68.0(3)
O(2)-C(1)-C(2)-F(2)	-66.9(3)
O(1)-C(1)-C(2)-F(2)	179.3(2)
C(8)-C(1)-C(2)-F(2)	54.5(3)
O(2)-C(1)-C(2)-F(1)	46.5(3)
O(1)-C(1)-C(2)-F(1)	-67.4(3)
C(8)-C(1)-C(2)-F(1)	167.9(3)
O(2)-C(1)-C(2)-C(3)	165.2(2)
O(1)-C(1)-C(2)-C(3)	51.4(3)
C(8)-C(1)-C(2)-C(3)	-73.3(3)
C(9)-O(3)-C(3)-C(2)	149.0(3)
C(9)-O(3)-C(3)-C(4)	-85.3(3)
F(2)-C(2)-C(3)-O(3)	-35.6(3)
F(1)-C(2)-C(3)-O(3)	-149.1(2)
C(1)-C(2)-C(3)-O(3)	91.7(3)
F(2)-C(2)-C(3)-C(4)	-161.8(2)
F(1)-C(2)-C(3)-C(4)	84.8(3)
C(1)-C(2)-C(3)-C(4)	-34.5(3)
O(3)-C(3)-C(4)-O(4)	145.3(2)
C(2)-C(3)-C(4)-O(4)	-90.0(3)
O(3)-C(3)-C(4)-C(5)	-93.7(3)
C(2)-C(3)-C(4)-C(5)	31.0(3)
C(1)-O(1)-C(5)-C(6)	-62.4(3)
C(1)-O(1)-C(5)-C(4)	67.6(3)
O(4)-C(4)-C(5)-O(1)	72.8(3)
C(3)-C(4)-C(5)-O(1)	-46.3(3)
O(4)-C(4)-C(5)-C(6)	-161.1(3)
C(3)-C(4)-C(5)-C(6)	79.8(4)
O(1)-C(5)-C(6)-C(7)	57.0(3)
C(4)-C(5)-C(6)-C(7)	-68.9(4)
C(5)-C(6)-C(7)-C(8)	-47.8(4)
O(2)-C(1)-C(8)-C(7)	-166.6(3)

O(1)-C(1)-C(8)-C(7)	-50.5(4)
C(2)-C(1)-C(8)-C(7)	70.9(4)
C(6)-C(7)-C(8)-C(1)	44.7(4)
C(3)-O(3)-C(9)-C(10)	-65.7(3)
O(3)-C(9)-C(10)-C(11)	117.8(3)
O(3)-C(9)-C(10)-C(15)	-61.4(4)
C(15)-C(10)-C(11)-C(12)	-0.3(5)
C(9)-C(10)-C(11)-C(12)	-179.5(3)
C(10)-C(11)-C(12)-C(13)	-0.8(6)
C(11)-C(12)-C(13)-C(14)	1.3(7)
C(12)-C(13)-C(14)-C(15)	-0.6(7)
C(11)-C(10)-C(15)-C(14)	0.9(5)
C(9)-C(10)-C(15)-C(14)	-179.9(3)
C(13)-C(14)-C(15)-C(10)	-0.4(6)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 05081 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(4)#1	0.84	1.88	2.718(3)	171.7
O(4)-H(4)...O(2)#2	0.84	1.99	2.783(3)	156.6

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+2   #2 x,y-1,z

6.2.4 3R*-Benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nona-1S*,4R*-diol 293
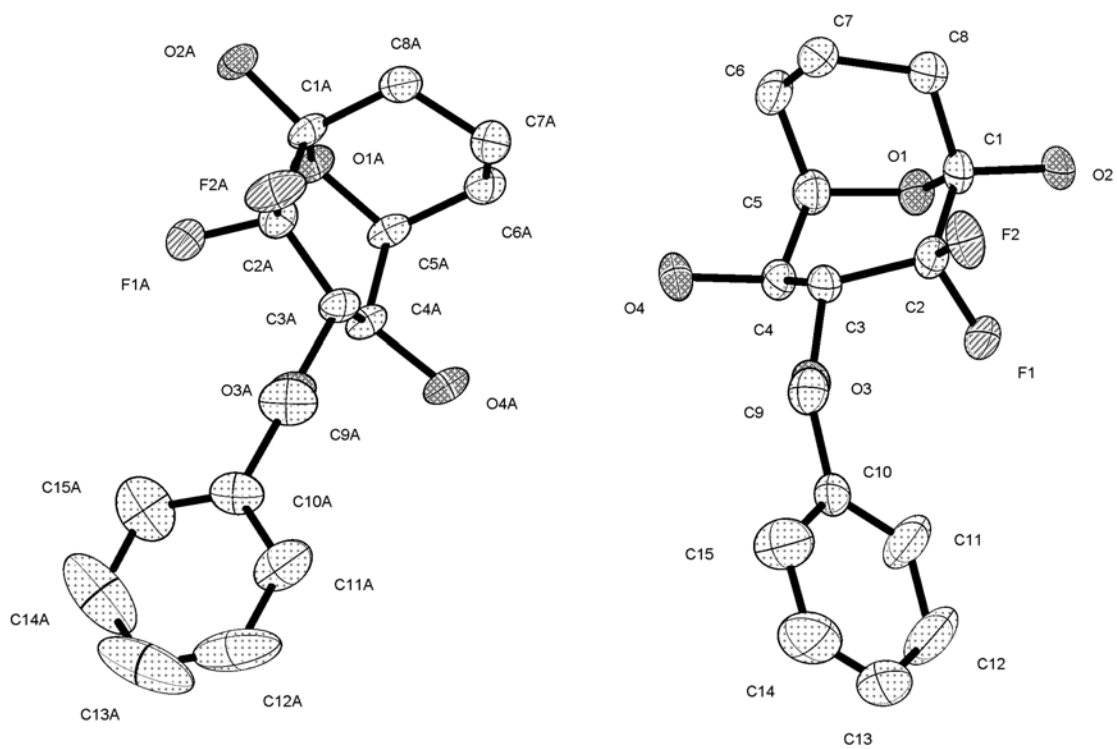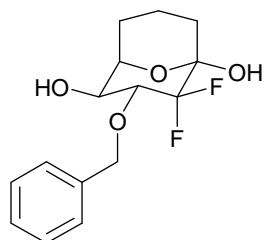
Table 1. Crystal data and structure refinement for 05089.

Identification code	05089
Empirical formula	C15 H18 F2 O4
Formula weight	300.29
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.9359(15) Å α= 78.181(3)°.
	b = 11.1641(17) Å β= 86.925(3)°.
	c = 13.130(2) Å γ = 88.750(3)°.
Volume	1423.4(4) Å^3
Z	4
Density (calculated)	1.401 Mg/m^3
Absorption coefficient	0.117 mm^{-1}
F(000)	632
Crystal size	0.19 x 0.10 x 0.04 mm^3
Theta range for data collection	1.59 to 25.00°.
Index ranges	-11<=h<=11, -13<=k<=13, -15<=l<=15
Reflections collected	10395
Independent reflections	4966 [R(int) = 0.0818]
Completeness to theta = 25.00°	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4966 / 0 / 383
Goodness-of-fit on F^2	0.959
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.0924
R indices (all data)	R1 = 0.1002, wR2 = 0.1055
Largest diff. peak and hole	0.203 and -0.208 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 05089. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5764(2)	2939(2)	3066(1)	33(1)
O(2)	7493(2)	3266(2)	4032(1)	40(1)
O(3)	7021(2)	5428(2)	534(1)	27(1)
O(4)	5290(2)	3475(2)	262(1)	31(1)
F(1)	7060(2)	5203(1)	2565(1)	40(1)
F(2)	8919(2)	4326(2)	2132(1)	43(1)
C(1)	7186(3)	3066(3)	3062(2)	31(1)
C(2)	7545(3)	4187(3)	2218(2)	30(1)
C(3)	7024(3)	4218(2)	1146(2)	25(1)
C(4)	5589(3)	3768(3)	1233(2)	27(1)
C(5)	5344(3)	2653(3)	2108(2)	32(1)
C(6)	5976(3)	1447(3)	1944(2)	43(1)
C(7)	7492(3)	1406(3)	1994(2)	44(1)
C(8)	7907(3)	1898(3)	2936(2)	40(1)
C(9)	8263(3)	5825(2)	-28(2)	32(1)
C(10)	8265(3)	7196(3)	-275(2)	30(1)
C(11)	8728(4)	7838(3)	-1213(3)	56(1)
C(12)	8792(4)	9102(3)	-1418(3)	68(1)
C(13)	8371(4)	9727(3)	-674(3)	69(1)
C(14)	7856(5)	9094(4)	256(3)	95(2)
C(15)	7819(4)	7838(3)	469(3)	68(1)
O(1A)	7229(2)	4864(2)	7730(1)	29(1)
O(2A)	7536(2)	3213(2)	9034(1)	33(1)
O(3A)	5114(2)	3027(2)	6022(1)	29(1)
O(4A)	6591(2)	5156(2)	4963(1)	29(1)
F(1A)	5359(2)	2982(2)	8025(1)	42(1)
F(2A)	6901(2)	1709(1)	7647(1)	45(1)
C(1A)	7611(3)	3600(3)	7965(2)	27(1)
C(2A)	6560(3)	2927(2)	7479(2)	28(1)
C(3A)	6358(3)	3406(2)	6333(2)	26(1)
C(4A)	6356(3)	4795(2)	6063(2)	26(1)

C(5A)	7382(3)	5389(2)	6629(2)	27(1)
C(6A)	8835(3)	5331(3)	6244(2)	33(1)
C(7A)	9425(3)	4047(3)	6481(2)	36(1)
C(8A)	9058(3)	3413(3)	7603(2)	32(1)
C(9A)	5087(3)	1782(3)	5896(3)	42(1)
C(10A)	3714(3)	1551(3)	5563(2)	37(1)
C(11A)	3579(4)	1203(3)	4621(3)	56(1)
C(12A)	2324(6)	1011(4)	4299(4)	88(2)
C(13A)	1191(6)	1162(4)	4895(5)	105(2)
C(14A)	1323(4)	1503(3)	5829(5)	90(2)
C(15A)	2575(4)	1702(3)	6157(3)	59(1)

Table 3.　Bond lengths [Å] and angles [°] for 05089.

_____

O(1)-C(1)	1.422(3)
O(1)-C(5)	1.445(3)
O(2)-C(1)	1.388(3)
O(2)-H(2)	0.8400
O(3)-C(3)	1.424(3)
O(3)-C(9)	1.434(3)
O(4)-C(4)	1.426(3)
O(4)-H(4)	0.8400
F(1)-C(2)	1.374(3)
F(2)-C(2)	1.373(3)
C(1)-C(8)	1.509(4)
C(1)-C(2)	1.527(4)
C(2)-C(3)	1.519(3)
C(3)-C(4)	1.513(4)
C(3)-H(3)	1.0000
C(4)-C(5)	1.525(4)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.523(4)
C(5)-H(5)	1.0000
C(6)-C(7)	1.511(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.531(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.498(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.355(4)
C(10)-C(15)	1.376(4)
C(11)-C(12)	1.383(5)
C(11)-H(11)	0.9500

C(12)-C(13)	1.356(5)
C(12)-H(12)	0.9500
C(13)-C(14)	1.359(5)
C(13)-H(13)	0.9500
C(14)-C(15)	1.373(5)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
O(1A)-C(1A)	1.430(3)
O(1A)-C(5A)	1.446(3)
O(2A)-C(1A)	1.380(3)
O(2A)-H(2A)	0.8400
O(3A)-C(3A)	1.423(3)
O(3A)-C(9A)	1.434(3)
O(4A)-C(4A)	1.425(3)
O(4A)-H(4A1)	0.8400
F(1A)-C(2A)	1.365(3)
F(2A)-C(2A)	1.370(3)
C(1A)-C(8A)	1.513(4)
C(1A)-C(2A)	1.538(4)
C(2A)-C(3A)	1.512(4)
C(3A)-C(4A)	1.519(4)
C(3A)-H(3A)	1.0000
C(4A)-C(5A)	1.531(3)
C(4A)-H(4A2)	1.0000
C(5A)-C(6A)	1.508(4)
C(5A)-H(5A)	1.0000
C(6A)-C(7A)	1.516(4)
C(6A)-H(6A1)	0.9900
C(6A)-H(6A2)	0.9900
C(7A)-C(8A)	1.526(4)
C(7A)-H(7A1)	0.9900
C(7A)-H(7A2)	0.9900
C(8A)-H(8A1)	0.9900
C(8A)-H(8A2)	0.9900
C(9A)-C(10A)	1.498(4)
C(9A)-H(9A1)	0.9900

C(9A)-H(9A2)	0.9900
C(10A)-C(15A)	1.367(4)
C(10A)-C(11A)	1.384(4)
C(11A)-C(12A)	1.373(5)
C(11A)-H(11A)	0.9500
C(12A)-C(13A)	1.364(7)
C(12A)-H(12A)	0.9500
C(13A)-C(14A)	1.370(6)
C(13A)-H(13A)	0.9500
C(14A)-C(15A)	1.376(5)
C(14A)-H(14A)	0.9500
C(15A)-H(15A)	0.9500
C(1)-O(1)-C(5)	112.1(2)
C(1)-O(2)-H(2)	109.5
C(3)-O(3)-C(9)	116.0(2)
C(4)-O(4)-H(4)	109.5
O(2)-C(1)-O(1)	107.6(2)
O(2)-C(1)-C(8)	106.4(2)
O(1)-C(1)-C(8)	111.1(2)
O(2)-C(1)-C(2)	110.1(2)
O(1)-C(1)-C(2)	106.3(2)
C(8)-C(1)-C(2)	115.1(2)
F(2)-C(2)-F(1)	104.6(2)
F(2)-C(2)-C(3)	109.2(2)
F(1)-C(2)-C(3)	108.6(2)
F(2)-C(2)-C(1)	109.4(2)
F(1)-C(2)-C(1)	107.6(2)
C(3)-C(2)-C(1)	116.6(2)
O(3)-C(3)-C(4)	107.0(2)
O(3)-C(3)-C(2)	111.5(2)
C(4)-C(3)-C(2)	110.8(2)
O(3)-C(3)-H(3)	109.2
C(4)-C(3)-H(3)	109.2
C(2)-C(3)-H(3)	109.2
O(4)-C(4)-C(3)	108.3(2)

O(4)-C(4)-C(5)	109.6(2)
C(3)-C(4)-C(5)	113.2(2)
O(4)-C(4)-H(4A)	108.6
C(3)-C(4)-H(4A)	108.6
C(5)-C(4)-H(4A)	108.6
O(1)-C(5)-C(6)	110.5(2)
O(1)-C(5)-C(4)	108.5(2)
C(6)-C(5)-C(4)	116.7(2)
O(1)-C(5)-H(5)	106.9
C(6)-C(5)-H(5)	106.9
C(4)-C(5)-H(5)	106.9
C(7)-C(6)-C(5)	113.5(2)
C(7)-C(6)-H(6A)	108.9
C(5)-C(6)-H(6A)	108.9
C(7)-C(6)-H(6B)	108.9
C(5)-C(6)-H(6B)	108.9
H(6A)-C(6)-H(6B)	107.7
C(6)-C(7)-C(8)	110.0(2)
C(6)-C(7)-H(7A)	109.7
C(8)-C(7)-H(7A)	109.7
C(6)-C(7)-H(7B)	109.7
C(8)-C(7)-H(7B)	109.7
H(7A)-C(7)-H(7B)	108.2
C(1)-C(8)-C(7)	113.8(2)
C(1)-C(8)-H(8A)	108.8
C(7)-C(8)-H(8A)	108.8
C(1)-C(8)-H(8B)	108.8
C(7)-C(8)-H(8B)	108.8
H(8A)-C(8)-H(8B)	107.7
O(3)-C(9)-C(10)	108.4(2)
O(3)-C(9)-H(9A)	110.0
C(10)-C(9)-H(9A)	110.0
O(3)-C(9)-H(9B)	110.0
C(10)-C(9)-H(9B)	110.0
H(9A)-C(9)-H(9B)	108.4
C(11)-C(10)-C(15)	118.1(3)

C(11)-C(10)-C(9)	121.9(3)
C(15)-C(10)-C(9)	120.0(3)
C(10)-C(11)-C(12)	121.5(3)
C(10)-C(11)-H(11)	119.2
C(12)-C(11)-H(11)	119.2
C(13)-C(12)-C(11)	120.0(4)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
C(12)-C(13)-C(14)	118.9(4)
C(12)-C(13)-H(13)	120.6
C(14)-C(13)-H(13)	120.6
C(13)-C(14)-C(15)	121.2(4)
C(13)-C(14)-H(14)	119.4
C(15)-C(14)-H(14)	119.4
C(14)-C(15)-C(10)	120.2(4)
C(14)-C(15)-H(15)	119.9
C(10)-C(15)-H(15)	119.9
C(1A)-O(1A)-C(5A)	112.37(18)
C(1A)-O(2A)-H(2A)	109.5
C(3A)-O(3A)-C(9A)	115.2(2)
C(4A)-O(4A)-H(4A1)	109.5
O(2A)-C(1A)-O(1A)	107.88(19)
O(2A)-C(1A)-C(8A)	106.9(2)
O(1A)-C(1A)-C(8A)	111.3(2)
O(2A)-C(1A)-C(2A)	109.8(2)
O(1A)-C(1A)-C(2A)	105.8(2)
C(8A)-C(1A)-C(2A)	115.0(2)
F(1A)-C(2A)-F(2A)	105.2(2)
F(1A)-C(2A)-C(3A)	109.0(2)
F(2A)-C(2A)-C(3A)	109.8(2)
F(1A)-C(2A)-C(1A)	107.9(2)
F(2A)-C(2A)-C(1A)	108.6(2)
C(3A)-C(2A)-C(1A)	115.8(2)
O(3A)-C(3A)-C(2A)	112.3(2)
O(3A)-C(3A)-C(4A)	106.8(2)
C(2A)-C(3A)-C(4A)	111.5(2)

O(3A)-C(3A)-H(3A)	108.7
C(2A)-C(3A)-H(3A)	108.7
C(4A)-C(3A)-H(3A)	108.7
O(4A)-C(4A)-C(3A)	107.54(19)
O(4A)-C(4A)-C(5A)	110.4(2)
C(3A)-C(4A)-C(5A)	114.5(2)
O(4A)-C(4A)-H(4A2)	108.1
C(3A)-C(4A)-H(4A2)	108.1
C(5A)-C(4A)-H(4A2)	108.1
O(1A)-C(5A)-C(6A)	110.7(2)
O(1A)-C(5A)-C(4A)	108.3(2)
C(6A)-C(5A)-C(4A)	116.3(2)
O(1A)-C(5A)-H(5A)	107.0
C(6A)-C(5A)-H(5A)	107.0
C(4A)-C(5A)-H(5A)	107.0
C(5A)-C(6A)-C(7A)	112.9(2)
C(5A)-C(6A)-H(6A1)	109.0
C(7A)-C(6A)-H(6A1)	109.0
C(5A)-C(6A)-H(6A2)	109.0
C(7A)-C(6A)-H(6A2)	109.0
H(6A1)-C(6A)-H(6A2)	107.8
C(6A)-C(7A)-C(8A)	110.8(2)
C(6A)-C(7A)-H(7A1)	109.5
C(8A)-C(7A)-H(7A1)	109.5
C(6A)-C(7A)-H(7A2)	109.5
C(8A)-C(7A)-H(7A2)	109.5
H(7A1)-C(7A)-H(7A2)	108.1
C(1A)-C(8A)-C(7A)	114.8(2)
C(1A)-C(8A)-H(8A1)	108.6
C(7A)-C(8A)-H(8A1)	108.6
C(1A)-C(8A)-H(8A2)	108.6
C(7A)-C(8A)-H(8A2)	108.6
H(8A1)-C(8A)-H(8A2)	107.5
O(3A)-C(9A)-C(10A)	107.7(2)
O(3A)-C(9A)-H(9A1)	110.2
C(10A)-C(9A)-H(9A1)	110.2

O(3A)-C(9A)-H(9A2)	110.2
C(10A)-C(9A)-H(9A2)	110.2
H(9A1)-C(9A)-H(9A2)	108.5
C(15A)-C(10A)-C(11A)	118.6(3)
C(15A)-C(10A)-C(9A)	121.6(3)
C(11A)-C(10A)-C(9A)	119.8(3)
C(12A)-C(11A)-C(10A)	120.3(4)
C(12A)-C(11A)-H(11A)	119.9
C(10A)-C(11A)-H(11A)	119.9
C(13A)-C(12A)-C(11A)	120.9(5)
C(13A)-C(12A)-H(12A)	119.5
C(11A)-C(12A)-H(12A)	119.5
C(12A)-C(13A)-C(14A)	118.9(5)
C(12A)-C(13A)-H(13A)	120.6
C(14A)-C(13A)-H(13A)	120.6
C(13A)-C(14A)-C(15A)	120.7(5)
C(13A)-C(14A)-H(14A)	119.7
C(15A)-C(14A)-H(14A)	119.7
C(10A)-C(15A)-C(14A)	120.6(4)
C(10A)-C(15A)-H(15A)	119.7
C(14A)-C(15A)-H(15A)	119.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \text{x } 10^3$) for 05089. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\text{ }h^2\text{ }a^{*2}U^{11} + ... + 2\text{ }h\text{ }k\text{ }a^*\text{ }b^*\text{ }U^{12}\text{ }]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	42(1)	36(1)	22(1)	-10(1)	0(1)	0(1)
O(2)	64(2)	40(1)	19(1)	-12(1)	-11(1)	15(1)
O(3)	26(1)	31(1)	23(1)	-5(1)	0(1)	1(1)
O(4)	28(1)	44(1)	23(1)	-11(1)	-6(1)	3(1)
F(1)	67(1)	32(1)	25(1)	-12(1)	-6(1)	4(1)
F(2)	36(1)	61(1)	33(1)	-10(1)	-11(1)	-6(1)
C(1)	42(2)	36(2)	19(2)	-12(1)	-7(1)	5(2)
C(2)	34(2)	32(2)	27(2)	-14(1)	-5(1)	3(1)
C(3)	30(2)	26(2)	19(2)	-5(1)	-2(1)	3(1)
C(4)	30(2)	31(2)	21(2)	-10(1)	-2(1)	5(1)
C(5)	39(2)	34(2)	25(2)	-8(1)	-3(1)	-3(2)
C(6)	74(3)	30(2)	26(2)	-10(2)	-6(2)	-4(2)
C(7)	68(3)	34(2)	33(2)	-14(2)	-11(2)	16(2)
C(8)	57(2)	35(2)	29(2)	-11(2)	-9(2)	11(2)
C(9)	30(2)	39(2)	28(2)	-11(1)	3(1)	0(1)
C(10)	33(2)	31(2)	28(2)	-6(1)	-8(1)	-3(1)
C(11)	73(3)	47(2)	45(2)	-5(2)	17(2)	2(2)
C(12)	96(3)	47(2)	51(3)	9(2)	6(2)	-5(2)
C(13)	101(3)	32(2)	74(3)	-5(2)	-31(3)	-5(2)
C(14)	196(6)	42(3)	56(3)	-26(2)	-8(3)	-8(3)
C(15)	133(4)	36(2)	39(2)	-18(2)	1(2)	-11(2)
O(1A)	39(1)	29(1)	21(1)	-11(1)	-4(1)	4(1)
O(2A)	35(1)	48(1)	16(1)	-8(1)	-3(1)	6(1)
O(3A)	39(1)	21(1)	29(1)	-9(1)	-10(1)	-1(1)
O(4A)	44(1)	26(1)	18(1)	-4(1)	-7(1)	5(1)
F(1A)	36(1)	63(1)	25(1)	-7(1)	0(1)	-10(1)
F(2A)	73(1)	27(1)	35(1)	-1(1)	-21(1)	1(1)
C(1A)	36(2)	33(2)	14(2)	-9(1)	-3(1)	2(1)
C(2A)	33(2)	24(2)	26(2)	-3(1)	0(1)	1(1)
C(3A)	30(2)	28(2)	22(2)	-11(1)	-6(1)	1(1)
C(4A)	35(2)	26(2)	17(2)	-6(1)	-5(1)	4(1)

C(5A)	38(2)	25(2)	19(2)	-5(1)	-7(1)	-1(1)
C(6A)	34(2)	41(2)	25(2)	-6(1)	-4(1)	-8(2)
C(7A)	32(2)	45(2)	30(2)	-10(2)	2(1)	1(2)
C(8A)	31(2)	38(2)	26(2)	-7(1)	-6(1)	3(2)
C(9A)	54(2)	23(2)	54(2)	-11(2)	-14(2)	0(2)
C(10A)	44(2)	21(2)	47(2)	-7(2)	-14(2)	-5(2)
C(11A)	82(3)	45(2)	39(2)	-3(2)	-11(2)	-28(2)
C(12A)	129(4)	53(3)	79(3)	12(2)	-68(3)	-41(3)
C(13A)	74(4)	39(3)	193(7)	18(3)	-75(4)	-20(3)
C(14A)	46(3)	35(2)	187(6)	-21(3)	0(3)	3(2)
C(15A)	57(3)	33(2)	89(3)	-20(2)	2(2)	-4(2)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for 05089.

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	x	y	z	U(eq)
H(2)	7140	3930	4122	60
H(4)	4537	3778	82	47
H(3)	7611	3681	781	30
H(4A)	4971	4444	1364	32
H(5)	4347	2530	2191	39
H(6A)	5589	772	2482	51
H(6B)	5736	1307	1255	51
H(7A)	7905	1907	1348	52
H(7B)	7821	553	2051	52
H(8A)	7725	1265	3575	47
H(8B)	8889	2045	2868	47
H(9A)	8349	5508	-679	38
H(9B)	9035	5510	400	38
H(11)	9015	7410	-1744	68
H(12)	9131	9531	-2079	81
H(13)	8434	10593	-801	83
H(14)	7515	9528	768	114
H(15)	7484	7412	1133	82
H(2A)	6731	3249	9258	50
H(4A1)	6108	5769	4737	44
H(3A)	7111	3092	5919	31
H(4A2)	5437	5093	6249	31
H(5A)	7128	6275	6540	32
H(6A1)	9375	5870	6573	40
H(6A2)	8901	5646	5482	40
H(7A1)	10418	4084	6371	43
H(7A2)	9078	3566	5998	43
H(8A1)	9234	2525	7675	38
H(8A2)	9659	3718	8069	38
H(9A1)	5272	1219	6562	51

H(9A2)	5783	1644	5362	51
H(11A)	4359	1096	4195	67
H(12A)	2244	770	3652	106
H(13A)	325	1032	4666	126
H(14A)	541	1603	6254	108
H(15A)	2649	1947	6803	70

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Table 6. Torsion angles [°] for 05089.
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C(5)-O(1)-C(1)-O(2)	-176.5(2)
C(5)-O(1)-C(1)-C(8)	-60.4(3)
C(5)-O(1)-C(1)-C(2)	65.5(3)
O(2)-C(1)-C(2)-F(2)	67.0(3)
O(1)-C(1)-C(2)-F(2)	-176.70(18)
C(8)-C(1)-C(2)-F(2)	-53.2(3)
O(2)-C(1)-C(2)-F(1)	-46.2(3)
O(1)-C(1)-C(2)-F(1)	70.1(3)
C(8)-C(1)-C(2)-F(1)	-166.4(2)
O(2)-C(1)-C(2)-C(3)	-168.5(2)
O(1)-C(1)-C(2)-C(3)	-52.2(3)
C(8)-C(1)-C(2)-C(3)	71.3(3)
C(9)-O(3)-C(3)-C(4)	-153.3(2)
C(9)-O(3)-C(3)-C(2)	85.4(3)
F(2)-C(2)-C(3)-O(3)	-74.6(3)
F(1)-C(2)-C(3)-O(3)	38.9(3)
C(1)-C(2)-C(3)-O(3)	160.7(2)
F(2)-C(2)-C(3)-C(4)	166.3(2)
F(1)-C(2)-C(3)-C(4)	-80.1(3)
C(1)-C(2)-C(3)-C(4)	41.6(3)
O(3)-C(3)-C(4)-O(4)	75.0(2)
C(2)-C(3)-C(4)-O(4)	-163.3(2)
O(3)-C(3)-C(4)-C(5)	-163.3(2)
C(2)-C(3)-C(4)-C(5)	-41.6(3)
C(1)-O(1)-C(5)-C(6)	60.7(3)
C(1)-O(1)-C(5)-C(4)	-68.4(3)
O(4)-C(4)-C(5)-O(1)	175.1(2)
C(3)-C(4)-C(5)-O(1)	54.2(3)
O(4)-C(4)-C(5)-C(6)	49.6(3)
C(3)-C(4)-C(5)-C(6)	-71.3(3)
O(1)-C(5)-C(6)-C(7)	-53.8(3)
C(4)-C(5)-C(6)-C(7)	70.7(3)
C(5)-C(6)-C(7)-C(8)	45.9(3)
O(2)-C(1)-C(8)-C(7)	169.9(3)

O(1)-C(1)-C(8)-C(7)	53.0(3)
C(2)-C(1)-C(8)-C(7)	-67.9(3)
C(6)-C(7)-C(8)-C(1)	-45.5(4)
C(3)-O(3)-C(9)-C(10)	-158.4(2)
O(3)-C(9)-C(10)-C(11)	-138.6(3)
O(3)-C(9)-C(10)-C(15)	43.1(4)
C(15)-C(10)-C(11)-C(12)	1.8(5)
C(9)-C(10)-C(11)-C(12)	-176.6(3)
C(10)-C(11)-C(12)-C(13)	-0.8(6)
C(11)-C(12)-C(13)-C(14)	-1.7(7)
C(12)-C(13)-C(14)-C(15)	3.2(7)
C(13)-C(14)-C(15)-C(10)	-2.2(7)
C(11)-C(10)-C(15)-C(14)	-0.4(6)
C(9)-C(10)-C(15)-C(14)	178.1(4)
C(5A)-O(1A)-C(1A)-O(2A)	175.12(19)
C(5A)-O(1A)-C(1A)-C(8A)	58.2(3)
C(5A)-O(1A)-C(1A)-C(2A)	-67.4(3)
O(2A)-C(1A)-C(2A)-F(1A)	47.6(3)
O(1A)-C(1A)-C(2A)-F(1A)	-68.5(3)
C(8A)-C(1A)-C(2A)-F(1A)	168.2(2)
O(2A)-C(1A)-C(2A)-F(2A)	-65.9(3)
O(1A)-C(1A)-C(2A)-F(2A)	177.9(2)
C(8A)-C(1A)-C(2A)-F(2A)	54.6(3)
O(2A)-C(1A)-C(2A)-C(3A)	170.0(2)
O(1A)-C(1A)-C(2A)-C(3A)	53.9(3)
C(8A)-C(1A)-C(2A)-C(3A)	-69.4(3)
C(9A)-O(3A)-C(3A)-C(2A)	-76.7(3)
C(9A)-O(3A)-C(3A)-C(4A)	160.8(2)
F(1A)-C(2A)-C(3A)-O(3A)	-39.2(3)
F(2A)-C(2A)-C(3A)-O(3A)	75.6(3)
C(1A)-C(2A)-C(3A)-O(3A)	-161.0(2)
F(1A)-C(2A)-C(3A)-C(4A)	80.6(3)
F(2A)-C(2A)-C(3A)-C(4A)	-164.6(2)
C(1A)-C(2A)-C(3A)-C(4A)	-41.2(3)
O(3A)-C(3A)-C(4A)-O(4A)	-75.0(3)
C(2A)-C(3A)-C(4A)-O(4A)	161.9(2)

O(3A)-C(3A)-C(4A)-C(5A)	161.9(2)
C(2A)-C(3A)-C(4A)-C(5A)	38.9(3)
C(1A)-O(1A)-C(5A)-C(6A)	-61.6(3)
C(1A)-O(1A)-C(5A)-C(4A)	67.1(3)
O(4A)-C(4A)-C(5A)-O(1A)	-171.9(2)
C(3A)-C(4A)-C(5A)-O(1A)	-50.4(3)
O(4A)-C(4A)-C(5A)-C(6A)	-46.5(3)
C(3A)-C(4A)-C(5A)-C(6A)	75.1(3)
O(1A)-C(5A)-C(6A)-C(7A)	55.1(3)
C(4A)-C(5A)-C(6A)-C(7A)	-69.2(3)
C(5A)-C(6A)-C(7A)-C(8A)	-45.6(3)
O(2A)-C(1A)-C(8A)-C(7A)	-166.8(2)
O(1A)-C(1A)-C(8A)-C(7A)	-49.2(3)
C(2A)-C(1A)-C(8A)-C(7A)	71.1(3)
C(6A)-C(7A)-C(8A)-C(1A)	43.0(3)
C(3A)-O(3A)-C(9A)-C(10A)	-179.7(2)
O(3A)-C(9A)-C(10A)-C(15A)	-58.5(4)
O(3A)-C(9A)-C(10A)-C(11A)	120.0(3)
C(15A)-C(10A)-C(11A)-C(12A)	-0.2(5)
C(9A)-C(10A)-C(11A)-C(12A)	-178.8(3)
C(10A)-C(11A)-C(12A)-C(13A)	0.2(6)
C(11A)-C(12A)-C(13A)-C(14A)	-0.4(7)
C(12A)-C(13A)-C(14A)-C(15A)	0.6(7)
C(11A)-C(10A)-C(15A)-C(14A)	0.5(5)
C(9A)-C(10A)-C(15A)-C(14A)	179.0(3)
C(13A)-C(14A)-C(15A)-C(10A)	-0.7(6)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 05089 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4A)-H(4A1)...O(3A)#1	0.84	1.94	2.769(2)	166.9
O(2A)-H(2A)...O(4)#2	0.84	1.94	2.729(3)	155.5
O(4)-H(4)...O(3)#3	0.84	1.90	2.734(3)	170.8
O(2)-H(2)...O(4A)	0.84	1.98	2.758(2)	153.9

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1   #2 x,y,z+1   #3 -x+1,-y+1,-z

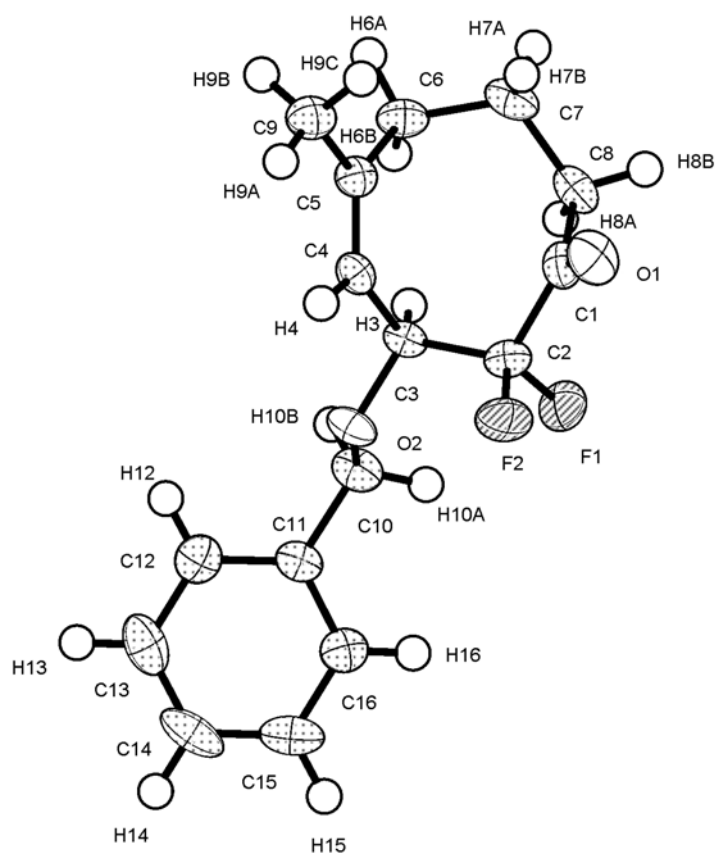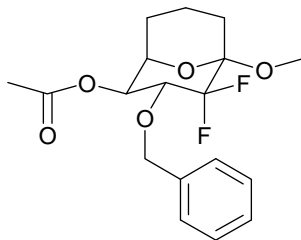### 6.2.5 4*R**-Acetoxy-3*R**-benzyloxy-2,2-difluoro-1*S**-methoxy-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nonane 300

Table 1. Crystal data and structure refinement for 06036.

Identification code	06036
Empirical formula	C16 H18 F2 O2
Formula weight	280.30
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 12.837(4) Å $\alpha= 90°$.
	b = 7.615(3) Å $\beta= 112.153(6)°$.
	c = 15.535(5) Å $\gamma = 90°$.
Volume	1406.5(8) Å^3
Z	4
Density (calculated)	1.324 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	592
Crystal size	0.33 x 0.29 x 0.25 mm^3
Theta range for data collection	1.76 to 25.00°.
Index ranges	-15<=h<=15, -9<=k<=9, -18<=l<=18
Reflections collected	9739
Independent reflections	2473 [R(int) = 0.1222]
Completeness to theta = 25.00°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2473 / 0 / 182
Goodness-of-fit on F^2	1.121
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1387
R indices (all data)	R1 = 0.0752, wR2 = 0.1468
Largest diff. peak and hole	0.359 and -0.244 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 06036. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4430(1)	5522(2)	692(1)	44(1)
F(2)	4116(1)	3901(2)	1719(1)	44(1)
O(1)	3945(2)	6848(2)	2481(1)	45(1)
O(2)	2579(1)	2981(2)	41(1)	32(1)
C(1)	3618(2)	6903(3)	1646(2)	33(1)
C(2)	3675(2)	5223(3)	1109(2)	31(1)
C(3)	2530(2)	4677(3)	399(2)	27(1)
C(4)	1709(2)	4671(3)	875(1)	26(1)
C(5)	1081(2)	6032(3)	918(1)	28(1)
C(6)	1061(2)	7768(3)	450(2)	35(1)
C(7)	1994(2)	9044(3)	1028(2)	41(1)
C(8)	3171(2)	8531(3)	1080(2)	37(1)
C(9)	356(2)	5935(3)	1476(2)	37(1)
C(10)	2811(2)	2988(3)	-799(2)	36(1)
C(11)	2851(2)	1127(3)	-1090(1)	28(1)
C(12)	1884(2)	106(3)	-1427(2)	36(1)
C(13)	1935(2)	-1601(4)	-1709(2)	45(1)
C(14)	2940(3)	-2304(3)	-1658(2)	47(1)
C(15)	3901(3)	-1301(4)	-1326(2)	48(1)
C(16)	3849(2)	398(3)	-1045(2)	35(1)

Table 3.   Bond lengths [Å] and angles [°] for 06036.

_____

F(1)-C(2)	1.373(3)
F(2)-C(2)	1.352(3)
O(1)-C(1)	1.205(3)
O(2)-C(3)	1.417(3)
O(2)-C(10)	1.443(3)
C(1)-C(8)	1.503(3)
C(1)-C(2)	1.544(3)
C(2)-C(3)	1.525(3)
C(3)-C(4)	1.499(3)
C(3)-H(3)	1.0000
C(4)-C(5)	1.330(3)
C(4)-H(4)	0.9500
C(5)-C(9)	1.495(3)
C(5)-C(6)	1.505(3)
C(6)-C(7)	1.541(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.534(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.495(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(16)	1.374(3)
C(11)-C(12)	1.389(3)
C(12)-C(13)	1.382(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.370(4)
C(13)-H(13)	0.9500

C(14)-C(15)	1.376(4)
C(14)-H(14)	0.9500
C(15)-C(16)	1.375(4)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(3)-O(2)-C(10)	113.97(16)
O(1)-C(1)-C(8)	124.0(2)
O(1)-C(1)-C(2)	119.0(2)
C(8)-C(1)-C(2)	116.9(2)
F(2)-C(2)-F(1)	105.73(17)
F(2)-C(2)-C(3)	109.78(19)
F(1)-C(2)-C(3)	111.29(18)
F(2)-C(2)-C(1)	109.31(19)
F(1)-C(2)-C(1)	107.65(18)
C(3)-C(2)-C(1)	112.80(18)
O(2)-C(3)-C(4)	109.54(17)
O(2)-C(3)-C(2)	111.08(17)
C(4)-C(3)-C(2)	108.01(17)
O(2)-C(3)-H(3)	109.4
C(4)-C(3)-H(3)	109.4
C(2)-C(3)-H(3)	109.4
C(5)-C(4)-C(3)	125.1(2)
C(5)-C(4)-H(4)	117.5
C(3)-C(4)-H(4)	117.5
C(4)-C(5)-C(9)	120.9(2)
C(4)-C(5)-C(6)	124.1(2)
C(9)-C(5)-C(6)	115.03(19)
C(5)-C(6)-C(7)	113.85(19)
C(5)-C(6)-H(6A)	108.8
C(7)-C(6)-H(6A)	108.8
C(5)-C(6)-H(6B)	108.8
C(7)-C(6)-H(6B)	108.8
H(6A)-C(6)-H(6B)	107.7
C(8)-C(7)-C(6)	113.8(2)
C(8)-C(7)-H(7A)	108.8

C(6)-C(7)-H(7A)	108.8
C(8)-C(7)-H(7B)	108.8
C(6)-C(7)-H(7B)	108.8
H(7A)-C(7)-H(7B)	107.7
C(1)-C(8)-C(7)	113.1(2)
C(1)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8A)	109.0
C(1)-C(8)-H(8B)	109.0
C(7)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(5)-C(9)-H(9A)	109.5
C(5)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(5)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(2)-C(10)-C(11)	108.19(18)
O(2)-C(10)-H(10A)	110.1
C(11)-C(10)-H(10A)	110.1
O(2)-C(10)-H(10B)	110.1
C(11)-C(10)-H(10B)	110.1
H(10A)-C(10)-H(10B)	108.4
C(16)-C(11)-C(12)	118.5(2)
C(16)-C(11)-C(10)	120.4(2)
C(12)-C(11)-C(10)	121.2(2)
C(13)-C(12)-C(11)	120.2(2)
C(13)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
C(14)-C(13)-C(12)	120.4(3)
C(14)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8
C(13)-C(14)-C(15)	119.7(2)
C(13)-C(14)-H(14)	120.1
C(15)-C(14)-H(14)	120.1
C(16)-C(15)-C(14)	119.8(3)
C(16)-C(15)-H(15)	120.1

C(14)-C(15)-H(15)	120.1
C(11)-C(16)-C(15)	121.4(2)
C(11)-C(16)-H(16)	119.3
C(15)-C(16)-H(16)	119.3

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Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters ($Å^2$x 10^3) for 06036. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\,h^2\,a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	39(1)	54(1)	47(1)	-8(1)	25(1)	-5(1)
F(2)	49(1)	40(1)	36(1)	8(1)	9(1)	16(1)
O(1)	55(1)	50(1)	25(1)	-7(1)	9(1)	-3(1)
O(2)	51(1)	22(1)	30(1)	-1(1)	23(1)	2(1)
C(1)	32(1)	36(1)	30(1)	-5(1)	12(1)	-7(1)
C(2)	33(1)	30(1)	31(1)	5(1)	15(1)	7(1)
C(3)	34(1)	22(1)	26(1)	0(1)	13(1)	3(1)
C(4)	33(1)	24(1)	22(1)	-1(1)	9(1)	-3(1)
C(5)	30(1)	32(1)	21(1)	-3(1)	8(1)	2(1)
C(6)	40(1)	32(1)	33(1)	6(1)	14(1)	12(1)
C(7)	58(2)	24(1)	45(2)	2(1)	25(1)	5(1)
C(8)	50(2)	27(1)	36(1)	-6(1)	19(1)	-8(1)
C(9)	41(1)	40(1)	32(1)	-3(1)	16(1)	5(1)
C(10)	50(2)	32(1)	33(1)	1(1)	26(1)	1(1)
C(11)	39(1)	28(1)	17(1)	2(1)	12(1)	4(1)
C(12)	36(1)	40(2)	31(1)	7(1)	10(1)	2(1)
C(13)	61(2)	40(2)	24(1)	-1(1)	6(1)	-15(1)
C(14)	93(2)	25(1)	28(1)	-2(1)	27(1)	4(2)
C(15)	65(2)	41(2)	47(2)	5(1)	31(1)	20(1)
C(16)	37(1)	38(1)	30(1)	1(1)	13(1)	4(1)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10 ^{3}) for 06036.

_____

	x	y	z	U(eq)
H(3)	2281	5545	-122	32
H(4)	1631	3613	1169	32
H(6A)	321	8331	316	42
H(6B)	1138	7554	-152	42
H(7A)	1813	10234	755	49
H(7B)	2000	9099	1667	49
H(8A)	3146	8339	442	44
H(8B)	3695	9516	1356	44
H(9A)	402	4754	1739	55
H(9B)	-426	6189	1075	55
H(9C)	615	6798	1981	55
H(10A)	3540	3573	-684	43
H(10B)	2215	3639	-1295	43
H(12)	1185	584	-1464	44
H(13)	1271	-2292	-1940	54
H(14)	2972	-3480	-1851	57
H(15)	4599	-1780	-1292	58
H(16)	4517	1081	-815	42

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Table 6. Torsion angles [°] for 06036.

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O(1)-C(1)-C(2)-F(2)	-0.1(3)
C(8)-C(1)-C(2)-F(2)	178.67(19)
O(1)-C(1)-C(2)-F(1)	-114.5(2)
C(8)-C(1)-C(2)-F(1)	64.3(2)
O(1)-C(1)-C(2)-C(3)	122.3(2)
C(8)-C(1)-C(2)-C(3)	-58.9(3)
C(10)-O(2)-C(3)-C(4)	148.41(18)
C(10)-O(2)-C(3)-C(2)	-92.4(2)
F(2)-C(2)-C(3)-O(2)	-47.5(2)
F(1)-C(2)-C(3)-O(2)	69.2(2)
C(1)-C(2)-C(3)-O(2)	-169.64(18)
F(2)-C(2)-C(3)-C(4)	72.7(2)
F(1)-C(2)-C(3)-C(4)	-170.62(17)
C(1)-C(2)-C(3)-C(4)	-49.5(2)
O(2)-C(3)-C(4)-C(5)	-148.1(2)
C(2)-C(3)-C(4)-C(5)	90.8(3)
C(3)-C(4)-C(5)-C(9)	-174.97(19)
C(3)-C(4)-C(5)-C(6)	3.2(3)
C(4)-C(5)-C(6)-C(7)	-85.6(3)
C(9)-C(5)-C(6)-C(7)	92.7(2)
C(5)-C(6)-C(7)-C(8)	72.7(3)
O(1)-C(1)-C(8)-C(7)	-73.4(3)
C(2)-C(1)-C(8)-C(7)	107.9(2)
C(6)-C(7)-C(8)-C(1)	-69.4(3)
C(3)-O(2)-C(10)-C(11)	179.36(18)
O(2)-C(10)-C(11)-C(16)	-111.6(2)
O(2)-C(10)-C(11)-C(12)	69.6(3)
C(16)-C(11)-C(12)-C(13)	-0.1(3)
C(10)-C(11)-C(12)-C(13)	178.8(2)
C(11)-C(12)-C(13)-C(14)	0.1(4)
C(12)-C(13)-C(14)-C(15)	-0.2(4)
C(13)-C(14)-C(15)-C(16)	0.3(4)
C(12)-C(11)-C(16)-C(15)	0.1(3)
C(10)-C(11)-C(16)-C(15)	-178.7(2)

C(14)-C(15)-C(16)-C(11)   -0.2(4)

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Symmetry transformations used to generate equivalent atoms:

6.2.6 4*R**-Acetoxy-3*R**-benzyloxy-2,2-difluoro-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nonan-1*S**-ol 316
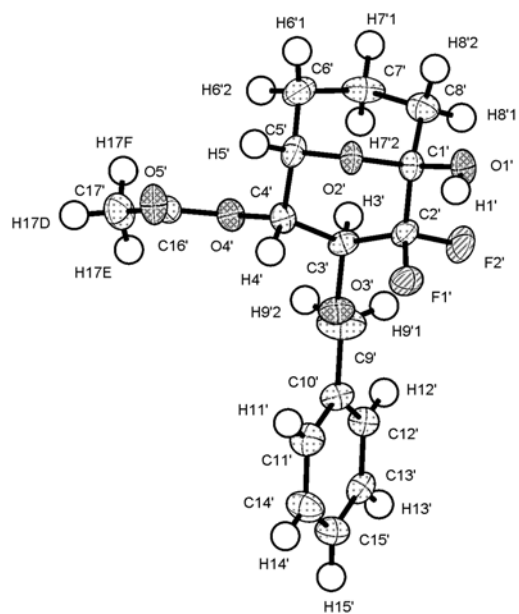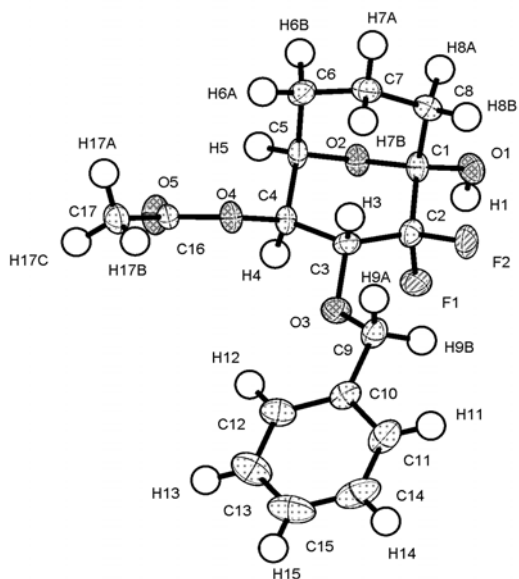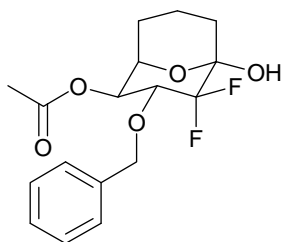
Table 1. Crystal data and structure refinement for 06014a.

Identification code	06014a	
Empirical formula	C17 H20 F2 O5	
Formula weight	342.33	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6331(14) Å	α= 93.604(4)°.
	b = 7.7551(14) Å	β= 97.580(4)°.
	c = 27.749(5) Å	γ = 96.179(3)°.
Volume	1613.9(5) Å^3	
Z	4	
Density (calculated)	1.409 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	720	
Crystal size	0.22 x 0.21 x 0.10 mm^3	
Theta range for data collection	2.23 to 25.00°.	
Index ranges	-9<=h<=8, -9<=k<=9, -32<=l<=32	
Reflections collected	11759	
Independent reflections	5631 [R(int) = 0.0731]	
Completeness to theta = 25.00°	99.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5631 / 0 / 437	
Goodness-of-fit on F^2	0.869	
Final R indices [I>2sigma(I)]	R1 = 0.0546, wR2 = 0.0980	
R indices (all data)	R1 = 0.1196, wR2 = 0.1175	
Largest diff. peak and hole	0.301 and -0.195 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3)
for 06014a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

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	x	y	z	U(eq)
F(1)	7791(2)	6113(2)	752(1)	35(1)
F(2)	7839(2)	8151(2)	1332(1)	36(1)
O(1)	7463(3)	9082(3)	353(1)	29(1)
O(2)	4858(3)	7295(2)	214(1)	26(1)
O(3)	5978(3)	4671(2)	1415(1)	27(1)
O(4)	2385(3)	4591(2)	1008(1)	25(1)
O(5)	1145(3)	2957(3)	332(1)	38(1)
C(1)	6055(4)	8384(4)	577(1)	24(1)
C(2)	6725(4)	7180(4)	959(1)	25(1)
C(3)	5303(4)	6050(4)	1169(1)	23(1)
C(4)	3848(4)	5263(4)	762(1)	22(1)
C(5)	3277(4)	6581(4)	400(1)	25(1)
C(6)	2253(4)	8012(4)	574(1)	29(1)
C(7)	3391(4)	9369(4)	943(1)	28(1)
C(8)	5180(4)	9893(4)	773(1)	25(1)
C(9)	6853(4)	5149(4)	1898(1)	29(1)
C(10)	7021(4)	3582(4)	2178(1)	28(1)
C(11)	8288(4)	3654(5)	2588(1)	41(1)
C(12)	5878(4)	2051(4)	2059(1)	34(1)
C(13)	6015(5)	643(4)	2334(1)	47(1)
C(14)	8420(5)	2236(6)	2863(1)	52(1)
C(15)	7281(5)	739(5)	2735(1)	54(1)
C(16)	1143(4)	3396(4)	754(1)	25(1)
C(17)	-204(4)	2717(4)	1058(1)	33(1)
F(1')	2150(2)	3854(2)	4221(1)	37(1)
F(2')	2136(2)	1746(2)	3665(1)	43(1)
O(1')	2509(3)	936(3)	4653(1)	35(1)
O(2')	5051(3)	2809(2)	4785(1)	28(1)
O(3')	3854(3)	5102(3)	3521(1)	33(1)
O(4')	7512(3)	5392(3)	3962(1)	31(1)
O(5')	8773(3)	7054(3)	4634(1)	42(1)

C(1')	3911(4)	1638(4)	4429(1)	26(1)
C(2')	3231(4)	2775(4)	4030(1)	28(1)
C(3')	4636(4)	3864(4)	3806(1)	27(1)
C(4')	6048(4)	4742(4)	4212(1)	26(1)
C(5')	6634(4)	3542(4)	4604(1)	31(1)
C(6')	7725(4)	2131(4)	4460(1)	43(1)
C(7')	6668(4)	700(4)	4102(1)	42(1)
C(8')	4859(4)	146(4)	4262(1)	36(1)
C(9')	4002(5)	4877(5)	3020(1)	53(1)
C(10')	3058(4)	6174(4)	2738(1)	29(1)
C(11')	2731(4)	7728(4)	2960(1)	37(1)
C(12')	2489(4)	5826(4)	2245(1)	29(1)
C(13')	1609(4)	6985(4)	1983(1)	30(1)
C(14')	1822(5)	8888(4)	2694(1)	43(1)
C(15')	1257(4)	8516(4)	2206(1)	38(1)
C(16')	8783(4)	6586(4)	4216(1)	32(1)
C(17')	10121(4)	7219(4)	3906(1)	44(1)

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Table 3.   Bond lengths [Å] and angles [°] for 06014a.

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F(1)-C(2)	1.374(3)
F(2)-C(2)	1.375(3)
O(1)-C(1)	1.388(3)
O(1)-H(1)	0.8741
O(2)-C(1)	1.432(3)
O(2)-C(5)	1.444(3)
O(3)-C(3)	1.412(3)
O(3)-C(9)	1.426(3)
O(4)-C(16)	1.344(3)
O(4)-C(4)	1.452(3)
O(5)-C(16)	1.200(3)
C(1)-C(8)	1.515(4)
C(1)-C(2)	1.531(4)
C(2)-C(3)	1.519(4)
C(3)-C(4)	1.523(4)
C(3)-H(3)	1.0000
C(4)-C(5)	1.534(4)
C(4)-H(4)	1.0000
C(5)-C(6)	1.515(4)
C(5)-H(5)	1.0000
C(6)-C(7)	1.530(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.525(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.491(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.386(4)
C(10)-C(12)	1.390(4)
C(11)-C(14)	1.382(5)

C(11)-H(11)	0.9500
C(12)-C(13)	1.376(4)
C(12)-H(12)	0.9500
C(13)-C(15)	1.368(5)
C(13)-H(13)	0.9500
C(14)-C(15)	1.371(5)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.487(4)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
F(1')-C(2')	1.368(3)
F(2')-C(2')	1.376(3)
O(1')-C(1')	1.385(3)
O(1')-H(1')	0.8725
O(2')-C(1')	1.432(3)
O(2')-C(5')	1.444(3)
O(3')-C(9')	1.413(3)
O(3')-C(3')	1.414(3)
O(4')-C(16')	1.357(3)
O(4')-C(4')	1.455(3)
O(5')-C(16')	1.195(3)
C(1')-C(8')	1.509(4)
C(1')-C(2')	1.532(4)
C(2')-C(3')	1.514(4)
C(3')-C(4')	1.523(4)
C(3')-H(3')	1.0000
C(4')-C(5')	1.528(4)
C(4')-H(4')	1.0000
C(5')-C(6')	1.510(4)
C(5')-H(5')	1.0000
C(6')-C(7')	1.526(4)
C(6')-H(6'1)	0.9900
C(6')-H(6'2)	0.9900
C(7')-C(8')	1.533(4)

C(7')-H(7'1)	0.9900
C(7')-H(7'2)	0.9900
C(8')-H(8'1)	0.9900
C(8')-H(8'2)	0.9900
C(9')-C(10')	1.499(4)
C(9')-H(9'1)	0.9900
C(9')-H(9'2)	0.9900
C(10')-C(12')	1.379(4)
C(10')-C(11')	1.381(4)
C(11')-C(14')	1.386(4)
C(11')-H(11')	0.9500
C(12')-C(13')	1.369(4)
C(12')-H(12')	0.9500
C(13')-C(15')	1.374(4)
C(13')-H(13')	0.9500
C(14')-C(15')	1.367(4)
C(14')-H(14')	0.9500
C(15')-H(15')	0.9500
C(16')-C(17')	1.484(4)
C(17')-H(17D)	0.9800
C(17')-H(17E)	0.9800
C(17')-H(17F)	0.9800
C(1)-O(1)-H(1)	112.9
C(1)-O(2)-C(5)	112.1(2)
C(3)-O(3)-C(9)	114.7(2)
C(16)-O(4)-C(4)	117.2(2)
O(1)-C(1)-O(2)	107.4(2)
O(1)-C(1)-C(8)	107.2(2)
O(2)-C(1)-C(8)	111.4(2)
O(1)-C(1)-C(2)	109.8(2)
O(2)-C(1)-C(2)	105.9(2)
C(8)-C(1)-C(2)	114.9(2)
F(1)-C(2)-F(2)	104.8(2)
F(1)-C(2)-C(3)	108.4(2)
F(2)-C(2)-C(3)	109.6(2)

F(1)-C(2)-C(1)	108.0(2)
F(2)-C(2)-C(1)	109.2(2)
C(3)-C(2)-C(1)	116.1(2)
O(3)-C(3)-C(2)	112.9(2)
O(3)-C(3)-C(4)	107.8(2)
C(2)-C(3)-C(4)	110.0(2)
O(3)-C(3)-H(3)	108.7
C(2)-C(3)-H(3)	108.7
C(4)-C(3)-H(3)	108.7
O(4)-C(4)-C(3)	105.0(2)
O(4)-C(4)-C(5)	111.6(2)
C(3)-C(4)-C(5)	112.9(2)
O(4)-C(4)-H(4)	109.0
C(3)-C(4)-H(4)	109.0
C(5)-C(4)-H(4)	109.0
O(2)-C(5)-C(6)	111.1(2)
O(2)-C(5)-C(4)	107.0(2)
C(6)-C(5)-C(4)	118.0(3)
O(2)-C(5)-H(5)	106.7
C(6)-C(5)-H(5)	106.7
C(4)-C(5)-H(5)	106.7
C(5)-C(6)-C(7)	113.2(2)
C(5)-C(6)-H(6A)	108.9
C(7)-C(6)-H(6A)	108.9
C(5)-C(6)-H(6B)	108.9
C(7)-C(6)-H(6B)	108.9
H(6A)-C(6)-H(6B)	107.7
C(8)-C(7)-C(6)	110.4(2)
C(8)-C(7)-H(7A)	109.6
C(6)-C(7)-H(7A)	109.6
C(8)-C(7)-H(7B)	109.6
C(6)-C(7)-H(7B)	109.6
H(7A)-C(7)-H(7B)	108.1
C(1)-C(8)-C(7)	114.4(2)
C(1)-C(8)-H(8A)	108.7
C(7)-C(8)-H(8A)	108.7

C(1)-C(8)-H(8B)	108.7
C(7)-C(8)-H(8B)	108.7
H(8A)-C(8)-H(8B)	107.6
O(3)-C(9)-C(10)	110.8(2)
O(3)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9A)	109.5
O(3)-C(9)-H(9B)	109.5
C(10)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.1
C(11)-C(10)-C(12)	117.8(3)
C(11)-C(10)-C(9)	119.9(3)
C(12)-C(10)-C(9)	122.2(3)
C(14)-C(11)-C(10)	120.8(3)
C(14)-C(11)-H(11)	119.6
C(10)-C(11)-H(11)	119.6
C(13)-C(12)-C(10)	121.2(3)
C(13)-C(12)-H(12)	119.4
C(10)-C(12)-H(12)	119.4
C(15)-C(13)-C(12)	120.1(3)
C(15)-C(13)-H(13)	120.0
C(12)-C(13)-H(13)	120.0
C(15)-C(14)-C(11)	120.2(4)
C(15)-C(14)-H(14)	119.9
C(11)-C(14)-H(14)	119.9
C(13)-C(15)-C(14)	120.0(4)
C(13)-C(15)-H(15)	120.0
C(14)-C(15)-H(15)	120.0
O(5)-C(16)-O(4)	122.9(3)
O(5)-C(16)-C(17)	125.1(3)
O(4)-C(16)-C(17)	112.0(3)
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

C(1')-O(1')-H(1')	114.8
C(1')-O(2')-C(5')	112.5(2)
C(9')-O(3')-C(3')	114.2(2)
C(16')-O(4')-C(4')	117.1(2)
O(1')-C(1')-O(2')	107.3(2)
O(1')-C(1')-C(8')	107.2(3)
O(2')-C(1')-C(8')	111.3(2)
O(1')-C(1')-C(2')	110.1(3)
O(2')-C(1')-C(2')	105.2(2)
C(8')-C(1')-C(2')	115.6(3)
F(1')-C(2')-F(2')	104.9(2)
F(1')-C(2')-C(3')	108.8(3)
F(2')-C(2')-C(3')	109.0(2)
F(1')-C(2')-C(1')	108.0(2)
F(2')-C(2')-C(1')	109.3(2)
C(3')-C(2')-C(1')	116.3(3)
O(3')-C(3')-C(2')	110.4(2)
O(3')-C(3')-C(4')	111.2(3)
C(2')-C(3')-C(4')	109.0(2)
O(3')-C(3')-H(3')	108.7
C(2')-C(3')-H(3')	108.7
C(4')-C(3')-H(3')	108.7
O(4')-C(4')-C(3')	104.4(2)
O(4')-C(4')-C(5')	112.0(2)
C(3')-C(4')-C(5')	114.0(3)
O(4')-C(4')-H(4')	108.8
C(3')-C(4')-H(4')	108.8
C(5')-C(4')-H(4')	108.8
O(2')-C(5')-C(6')	110.9(3)
O(2')-C(5')-C(4')	107.2(2)
C(6')-C(5')-C(4')	117.0(3)
O(2')-C(5')-H(5')	107.1
C(6')-C(5')-H(5')	107.1
C(4')-C(5')-H(5')	107.1
C(5')-C(6')-C(7')	113.4(3)
C(5')-C(6')-H(6'1)	108.9

C(7')-C(6')-H(6'1)	108.9
C(5')-C(6')-H(6'2)	108.9
C(7')-C(6')-H(6'2)	108.9
H(6'1)-C(6')-H(6'2)	107.7
C(6')-C(7')-C(8')	110.4(3)
C(6')-C(7')-H(7'1)	109.6
C(8')-C(7')-H(7'1)	109.6
C(6')-C(7')-H(7'2)	109.6
C(8')-C(7')-H(7'2)	109.6
H(7'1)-C(7')-H(7'2)	108.1
C(1')-C(8')-C(7')	114.3(3)
C(1')-C(8')-H(8'1)	108.7
C(7')-C(8')-H(8'1)	108.7
C(1')-C(8')-H(8'2)	108.7
C(7')-C(8')-H(8'2)	108.7
H(8'1)-C(8')-H(8'2)	107.6
O(3')-C(9')-C(10')	111.1(3)
O(3')-C(9')-H(9'1)	109.4
C(10')-C(9')-H(9'1)	109.4
O(3')-C(9')-H(9'2)	109.4
C(10')-C(9')-H(9'2)	109.4
H(9'1)-C(9')-H(9'2)	108.0
C(12')-C(10')-C(11')	118.4(3)
C(12')-C(10')-C(9')	120.0(3)
C(11')-C(10')-C(9')	121.6(3)
C(10')-C(11')-C(14')	120.4(3)
C(10')-C(11')-H(11')	119.8
C(14')-C(11')-H(11')	119.8
C(13')-C(12')-C(10')	120.9(3)
C(13')-C(12')-H(12')	119.6
C(10')-C(12')-H(12')	119.6
C(12')-C(13')-C(15')	120.6(3)
C(12')-C(13')-H(13')	119.7
C(15')-C(13')-H(13')	119.7
C(15')-C(14')-C(11')	120.3(3)
C(15')-C(14')-H(14')	119.8

C(11')-C(14')-H(14')	119.8
C(14')-C(15')-C(13')	119.3(3)
C(14')-C(15')-H(15')	120.3
C(13')-C(15')-H(15')	120.3
O(5')-C(16')-O(4')	122.8(3)
O(5')-C(16')-C(17')	126.0(3)
O(4')-C(16')-C(17')	111.2(3)
C(16')-C(17')-H(17D)	109.5
C(16')-C(17')-H(17E)	109.5
H(17D)-C(17')-H(17E)	109.5
C(16')-C(17')-H(17F)	109.5
H(17D)-C(17')-H(17F)	109.5
H(17E)-C(17')-H(17F)	109.5

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Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters ($Å^2$x 10^3) for 06014a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	29(1)	33(1)	46(1)	9(1)	14(1)	9(1)
F(2)	32(1)	35(1)	35(1)	6(1)	-9(1)	-11(1)
O(1)	29(1)	27(1)	32(1)	4(1)	12(1)	-2(1)
O(2)	28(1)	30(1)	19(1)	3(1)	2(1)	-6(1)
O(3)	32(1)	27(1)	22(1)	4(1)	0(1)	5(1)
O(4)	25(1)	26(1)	23(1)	0(1)	6(1)	-6(1)
O(5)	37(2)	42(2)	29(1)	-11(1)	7(1)	-8(1)
C(1)	20(2)	26(2)	25(2)	3(2)	7(2)	-4(2)
C(2)	21(2)	26(2)	24(2)	-4(2)	1(2)	1(2)
C(3)	22(2)	24(2)	23(2)	6(1)	2(1)	6(1)
C(4)	19(2)	23(2)	23(2)	0(1)	5(1)	-3(1)
C(5)	19(2)	27(2)	26(2)	4(1)	1(1)	-8(1)
C(6)	21(2)	35(2)	35(2)	14(2)	5(2)	5(2)
C(7)	29(2)	26(2)	32(2)	7(2)	9(2)	8(2)
C(8)	31(2)	22(2)	24(2)	4(1)	4(2)	4(2)
C(9)	24(2)	36(2)	26(2)	4(2)	-2(2)	-1(2)
C(10)	25(2)	38(2)	22(2)	5(2)	7(2)	8(2)
C(11)	27(2)	60(3)	37(2)	17(2)	3(2)	4(2)
C(12)	44(2)	34(2)	26(2)	7(2)	5(2)	12(2)
C(13)	67(3)	37(2)	39(2)	10(2)	12(2)	10(2)
C(14)	46(3)	79(3)	36(2)	24(2)	2(2)	26(2)
C(15)	76(3)	49(3)	48(3)	26(2)	17(2)	29(2)
C(16)	19(2)	18(2)	36(2)	1(2)	4(2)	0(1)
C(17)	27(2)	26(2)	46(2)	2(2)	11(2)	-1(2)
F(1')	31(1)	42(1)	42(1)	8(1)	11(1)	10(1)
F(2')	37(1)	49(1)	35(1)	0(1)	-11(1)	-8(1)
O(1')	30(1)	34(1)	39(1)	3(1)	12(1)	-7(1)
O(2')	27(1)	30(1)	23(1)	-1(1)	3(1)	-8(1)
O(3')	39(2)	40(1)	22(1)	7(1)	6(1)	14(1)
O(4')	32(1)	32(1)	30(1)	5(1)	10(1)	-2(1)
O(5')	40(2)	41(2)	42(2)	-5(1)	11(1)	-10(1)

C(1')	26(2)	27(2)	24(2)	-2(2)	2(2)	-2(2)
C(2')	22(2)	31(2)	28(2)	-1(2)	-3(2)	4(2)
C(3')	27(2)	34(2)	19(2)	3(2)	-1(2)	8(2)
C(4')	26(2)	29(2)	26(2)	6(2)	11(2)	-1(2)
C(5')	24(2)	41(2)	25(2)	7(2)	-1(2)	-6(2)
C(6')	27(2)	55(3)	49(2)	25(2)	5(2)	6(2)
C(7')	51(3)	48(2)	36(2)	17(2)	19(2)	28(2)
C(8')	43(2)	34(2)	30(2)	2(2)	1(2)	8(2)
C(9')	77(3)	66(3)	23(2)	12(2)	13(2)	32(2)
C(10')	30(2)	41(2)	20(2)	8(2)	10(2)	11(2)
C(11')	45(2)	43(2)	20(2)	-2(2)	-1(2)	6(2)
C(12')	31(2)	32(2)	26(2)	2(2)	9(2)	7(2)
C(13')	24(2)	43(2)	22(2)	5(2)	4(2)	0(2)
C(14')	60(3)	33(2)	36(2)	-2(2)	3(2)	14(2)
C(15')	41(2)	37(2)	37(2)	10(2)	4(2)	9(2)
C(16')	27(2)	27(2)	44(2)	7(2)	9(2)	4(2)
C(17')	40(2)	39(2)	57(3)	6(2)	22(2)	0(2)

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Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3})
for 06014a.

	x	y	z	U(eq)
H(1)	7918	8298	184	66(13)
H(3)	4764	6794	1403	27
H(4)	4284	4274	581	26
H(5)	2491	5904	119	30
H(6A)	1241	7485	726	35
H(6B)	1759	8601	289	35
H(7A)	2758	10408	980	34
H(7B)	3587	8883	1264	34
H(8A)	5006	10709	515	30
H(8B)	5996	10522	1051	30
H(9A)	6167	5956	2066	35
H(9B)	8051	5761	1886	35
H(11)	9075	4690	2681	49
H(12)	4986	1976	1783	40
H(13)	5229	-396	2245	56
H(14)	9301	2300	3141	62
H(15)	7372	-233	2925	65
H(17A)	-1201	3419	1028	49
H(17B)	340	2782	1399	49
H(17C)	-639	1504	945	49
H(1')	2080	1677	4842	62(13)
H(3')	5210	3079	3591	32
H(4')	5572	5753	4370	31
H(5')	7373	4291	4879	37
H(6'1)	8214	1604	4757	51
H(6'2)	8742	2663	4311	51
H(7'1)	7347	-316	4085	51
H(7'2)	6486	1128	3772	51
H(8'1)	4085	-543	3987	43
H(8'2)	5036	-622	4532	43

H(9'1)	3484	3685	2891	63
H(9'2)	5274	5014	2976	63
H(11')	3132	8003	3298	44
H(12')	2711	4767	2086	35
H(13')	1237	6728	1643	36
H(14')	1589	9948	2851	51
H(15')	629	9309	2024	45
H(17D)	10898	8217	4079	66
H(17E)	9512	7573	3601	66
H(17F)	10837	6285	3833	66

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Table 6. Torsion angles [°] for 06014a.

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C(5)-O(2)-C(1)-O(1)	-176.3(2)
C(5)-O(2)-C(1)-C(8)	-59.2(3)
C(5)-O(2)-C(1)-C(2)	66.4(3)
O(1)-C(1)-C(2)-F(1)	-46.8(3)
O(2)-C(1)-C(2)-F(1)	68.8(3)
C(8)-C(1)-C(2)-F(1)	-167.8(2)
O(1)-C(1)-C(2)-F(2)	66.6(3)
O(2)-C(1)-C(2)-F(2)	-177.8(2)
C(8)-C(1)-C(2)-F(2)	-54.3(3)
O(1)-C(1)-C(2)-C(3)	-168.8(2)
O(2)-C(1)-C(2)-C(3)	-53.2(3)
C(8)-C(1)-C(2)-C(3)	70.2(3)
C(9)-O(3)-C(3)-C(2)	80.0(3)
C(9)-O(3)-C(3)-C(4)	-158.3(2)
F(1)-C(2)-C(3)-O(3)	42.4(3)
F(2)-C(2)-C(3)-O(3)	-71.4(3)
C(1)-C(2)-C(3)-O(3)	164.2(2)
F(1)-C(2)-C(3)-C(4)	-78.0(3)
F(2)-C(2)-C(3)-C(4)	168.2(2)
C(1)-C(2)-C(3)-C(4)	43.8(3)
C(16)-O(4)-C(4)-C(3)	-161.0(2)
C(16)-O(4)-C(4)-C(5)	76.3(3)
O(3)-C(3)-C(4)-O(4)	70.3(3)
C(2)-C(3)-C(4)-O(4)	-166.3(2)
O(3)-C(3)-C(4)-C(5)	-167.8(2)
C(2)-C(3)-C(4)-C(5)	-44.4(3)
C(1)-O(2)-C(5)-C(6)	60.7(3)
C(1)-O(2)-C(5)-C(4)	-69.4(3)
O(4)-C(4)-C(5)-O(2)	174.3(2)
C(3)-C(4)-C(5)-O(2)	56.2(3)
O(4)-C(4)-C(5)-C(6)	48.2(3)
C(3)-C(4)-C(5)-C(6)	-69.9(3)
O(2)-C(5)-C(6)-C(7)	-53.7(3)
C(4)-C(5)-C(6)-C(7)	70.5(3)

C(5)-C(6)-C(7)-C(8)	45.0(3)
O(1)-C(1)-C(8)-C(7)	168.5(2)
O(2)-C(1)-C(8)-C(7)	51.3(3)
C(2)-C(1)-C(8)-C(7)	-69.1(3)
C(6)-C(7)-C(8)-C(1)	-44.0(3)
C(3)-O(3)-C(9)-C(10)	162.7(2)
O(3)-C(9)-C(10)-C(11)	159.3(3)
O(3)-C(9)-C(10)-C(12)	-24.3(4)
C(12)-C(10)-C(11)-C(14)	0.9(5)
C(9)-C(10)-C(11)-C(14)	177.5(3)
C(11)-C(10)-C(12)-C(13)	-1.0(5)
C(9)-C(10)-C(12)-C(13)	-177.4(3)
C(10)-C(12)-C(13)-C(15)	0.6(5)
C(10)-C(11)-C(14)-C(15)	-0.6(5)
C(12)-C(13)-C(15)-C(14)	-0.2(5)
C(11)-C(14)-C(15)-C(13)	0.2(6)
C(4)-O(4)-C(16)-O(5)	-4.6(4)
C(4)-O(4)-C(16)-C(17)	175.8(2)
C(5')-O(2')-C(1')-O(1')	176.1(2)
C(5')-O(2')-C(1')-C(8')	59.2(3)
C(5')-O(2')-C(1')-C(2')	-66.7(3)
O(1')-C(1')-C(2')-F(1')	47.9(3)
O(2')-C(1')-C(2')-F(1')	-67.4(3)
C(8')-C(1')-C(2')-F(1')	169.5(2)
O(1')-C(1')-C(2')-F(2')	-65.6(3)
O(2')-C(1')-C(2')-F(2')	179.1(2)
C(8')-C(1')-C(2')-F(2')	55.9(3)
O(1')-C(1')-C(2')-C(3')	170.5(2)
O(2')-C(1')-C(2')-C(3')	55.2(3)
C(8')-C(1')-C(2')-C(3')	-67.9(3)
C(9')-O(3')-C(3')-C(2')	-116.4(3)
C(9')-O(3')-C(3')-C(4')	122.4(3)
F(1')-C(2')-C(3')-O(3')	-45.7(3)
F(2')-C(2')-C(3')-O(3')	68.1(3)
C(1')-C(2')-C(3')-O(3')	-167.9(2)
F(1')-C(2')-C(3')-C(4')	76.8(3)

F(2')-C(2')-C(3')-C(4')	-169.4(2)
C(1')-C(2')-C(3')-C(4')	-45.4(3)
C(16')-O(4')-C(4')-C(3')	164.7(2)
C(16')-O(4')-C(4')-C(5')	-71.5(3)
O(3')-C(3')-C(4')-O(4')	-71.2(3)
C(2')-C(3')-C(4')-O(4')	166.8(2)
O(3')-C(3')-C(4')-C(5')	166.3(3)
C(2')-C(3')-C(4')-C(5')	44.3(3)
C(1')-O(2')-C(5')-C(6')	-60.8(3)
C(1')-O(2')-C(5')-C(4')	68.0(3)
O(4')-C(4')-C(5')-O(2')	-173.1(2)
C(3')-C(4')-C(5')-O(2')	-54.8(3)
O(4')-C(4')-C(5')-C(6')	-47.8(4)
C(3')-C(4')-C(5')-C(6')	70.4(4)
O(2')-C(5')-C(6')-C(7')	53.7(4)
C(4')-C(5')-C(6')-C(7')	-69.6(4)
C(5')-C(6')-C(7')-C(8')	-45.1(4)
O(1')-C(1')-C(8')-C(7')	-168.0(2)
O(2')-C(1')-C(8')-C(7')	-51.0(4)
C(2')-C(1')-C(8')-C(7')	68.9(3)
C(6')-C(7')-C(8')-C(1')	43.8(4)
C(3')-O(3')-C(9')-C(10')	176.9(3)
O(3')-C(9')-C(10')-C(12')	-156.8(3)
O(3')-C(9')-C(10')-C(11')	23.0(5)
C(12')-C(10')-C(11')-C(14')	1.2(5)
C(9')-C(10')-C(11')-C(14')	-178.6(3)
C(11')-C(10')-C(12')-C(13')	-0.5(5)
C(9')-C(10')-C(12')-C(13')	179.3(3)
C(10')-C(12')-C(13')-C(15')	-0.6(5)
C(10')-C(11')-C(14')-C(15')	-0.8(5)
C(11')-C(14')-C(15')-C(13')	-0.3(5)
C(12')-C(13')-C(15')-C(14')	1.0(5)
C(4')-O(4')-C(16')-O(5')	3.0(5)
C(4')-O(4')-C(16')-C(17')	-176.1(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 06014a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1')-H(1')...O(5')#1	0.87	1.93	2.785(3)	167.3
O(1)-H(1)...O(5)#2	0.87	1.94	2.785(3)	163.4

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1   #2 -x+1,-y+1,-z

6.2.7 3-Benzyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-enone 366

Table 1. Crystal data and structure refinement for 06036.

Identification code	06036
Empirical formula	C16 H18 F2 O2
Formula weight	280.30
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 12.837(4) Å α= 90°.
	b = 7.615(3) Å β= 112.153(6)°.
	c = 15.535(5) Å γ = 90°.
Volume	1406.5(8) Å^3
Z	4
Density (calculated)	1.324 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	592
Crystal size	0.33 x 0.29 x 0.25 mm^3
Theta range for data collection	1.76 to 25.00°.
Index ranges	-15<=h<=15, -9<=k<=9, -18<=l<=18
Reflections collected	9739
Independent reflections	2473 [R(int) = 0.1222]
Completeness to theta = 25.00°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2473 / 0 / 182
Goodness-of-fit on F^2	1.121
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1387
R indices (all data)	R1 = 0.0752, wR2 = 0.1468
Largest diff. peak and hole	0.359 and -0.244 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 06036. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4430(1)	5522(2)	692(1)	44(1)
F(2)	4116(1)	3901(2)	1719(1)	44(1)
O(1)	3945(2)	6848(2)	2481(1)	45(1)
O(2)	2579(1)	2981(2)	41(1)	32(1)
C(1)	3618(2)	6903(3)	1646(2)	33(1)
C(2)	3675(2)	5223(3)	1109(2)	31(1)
C(3)	2530(2)	4677(3)	399(2)	27(1)
C(4)	1709(2)	4671(3)	875(1)	26(1)
C(5)	1081(2)	6032(3)	918(1)	28(1)
C(6)	1061(2)	7768(3)	450(2)	35(1)
C(7)	1994(2)	9044(3)	1028(2)	41(1)
C(8)	3171(2)	8531(3)	1080(2)	37(1)
C(9)	356(2)	5935(3)	1476(2)	37(1)
C(10)	2811(2)	2988(3)	-799(2)	36(1)
C(11)	2851(2)	1127(3)	-1090(1)	28(1)
C(12)	1884(2)	106(3)	-1427(2)	36(1)
C(13)	1935(2)	-1601(4)	-1709(2)	45(1)
C(14)	2940(3)	-2304(3)	-1658(2)	47(1)
C(15)	3901(3)	-1301(4)	-1326(2)	48(1)
C(16)	3849(2)	398(3)	-1045(2)	35(1)

Table 3.   Bond lengths [Å] and angles [°] for 06036.

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F(1)-C(2)	1.373(3)
F(2)-C(2)	1.352(3)
O(1)-C(1)	1.205(3)
O(2)-C(3)	1.417(3)
O(2)-C(10)	1.443(3)
C(1)-C(8)	1.503(3)
C(1)-C(2)	1.544(3)
C(2)-C(3)	1.525(3)
C(3)-C(4)	1.499(3)
C(3)-H(3)	1.0000
C(4)-C(5)	1.330(3)
C(4)-H(4)	0.9500
C(5)-C(9)	1.495(3)
C(5)-C(6)	1.505(3)
C(6)-C(7)	1.541(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.534(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.495(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(16)	1.374(3)
C(11)-C(12)	1.389(3)
C(12)-C(13)	1.382(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.370(4)
C(13)-H(13)	0.9500

C(14)-C(15)	1.376(4)
C(14)-H(14)	0.9500
C(15)-C(16)	1.375(4)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(3)-O(2)-C(10)	113.97(16)
O(1)-C(1)-C(8)	124.0(2)
O(1)-C(1)-C(2)	119.0(2)
C(8)-C(1)-C(2)	116.9(2)
F(2)-C(2)-F(1)	105.73(17)
F(2)-C(2)-C(3)	109.78(19)
F(1)-C(2)-C(3)	111.29(18)
F(2)-C(2)-C(1)	109.31(19)
F(1)-C(2)-C(1)	107.65(18)
C(3)-C(2)-C(1)	112.80(18)
O(2)-C(3)-C(4)	109.54(17)
O(2)-C(3)-C(2)	111.08(17)
C(4)-C(3)-C(2)	108.01(17)
O(2)-C(3)-H(3)	109.4
C(4)-C(3)-H(3)	109.4
C(2)-C(3)-H(3)	109.4
C(5)-C(4)-C(3)	125.1(2)
C(5)-C(4)-H(4)	117.5
C(3)-C(4)-H(4)	117.5
C(4)-C(5)-C(9)	120.9(2)
C(4)-C(5)-C(6)	124.1(2)
C(9)-C(5)-C(6)	115.03(19)
C(5)-C(6)-C(7)	113.85(19)
C(5)-C(6)-H(6A)	108.8
C(7)-C(6)-H(6A)	108.8
C(5)-C(6)-H(6B)	108.8
C(7)-C(6)-H(6B)	108.8
H(6A)-C(6)-H(6B)	107.7
C(8)-C(7)-C(6)	113.8(2)
C(8)-C(7)-H(7A)	108.8

C(6)-C(7)-H(7A)	108.8
C(8)-C(7)-H(7B)	108.8
C(6)-C(7)-H(7B)	108.8
H(7A)-C(7)-H(7B)	107.7
C(1)-C(8)-C(7)	113.1(2)
C(1)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8A)	109.0
C(1)-C(8)-H(8B)	109.0
C(7)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(5)-C(9)-H(9A)	109.5
C(5)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(5)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(2)-C(10)-C(11)	108.19(18)
O(2)-C(10)-H(10A)	110.1
C(11)-C(10)-H(10A)	110.1
O(2)-C(10)-H(10B)	110.1
C(11)-C(10)-H(10B)	110.1
H(10A)-C(10)-H(10B)	108.4
C(16)-C(11)-C(12)	118.5(2)
C(16)-C(11)-C(10)	120.4(2)
C(12)-C(11)-C(10)	121.2(2)
C(13)-C(12)-C(11)	120.2(2)
C(13)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
C(14)-C(13)-C(12)	120.4(3)
C(14)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8
C(13)-C(14)-C(15)	119.7(2)
C(13)-C(14)-H(14)	120.1
C(15)-C(14)-H(14)	120.1
C(16)-C(15)-C(14)	119.8(3)
C(16)-C(15)-H(15)	120.1

C(14)-C(15)-H(15)   120.1

C(11)-C(16)-C(15)   121.4(2)

C(11)-C(16)-H(16)   119.3

C(15)-C(16)-H(16)   119.3

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Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters (Å^2x 10^3) for 06036. The anisotropic
displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	39(1)	54(1)	47(1)	-8(1)	25(1)	-5(1)
F(2)	49(1)	40(1)	36(1)	8(1)	9(1)	16(1)
O(1)	55(1)	50(1)	25(1)	-7(1)	9(1)	-3(1)
O(2)	51(1)	22(1)	30(1)	-1(1)	23(1)	2(1)
C(1)	32(1)	36(1)	30(1)	-5(1)	12(1)	-7(1)
C(2)	33(1)	30(1)	31(1)	5(1)	15(1)	7(1)
C(3)	34(1)	22(1)	26(1)	0(1)	13(1)	3(1)
C(4)	33(1)	24(1)	22(1)	-1(1)	9(1)	-3(1)
C(5)	30(1)	32(1)	21(1)	-3(1)	8(1)	2(1)
C(6)	40(1)	32(1)	33(1)	6(1)	14(1)	12(1)
C(7)	58(2)	24(1)	45(2)	2(1)	25(1)	5(1)
C(8)	50(2)	27(1)	36(1)	-6(1)	19(1)	-8(1)
C(9)	41(1)	40(1)	32(1)	-3(1)	16(1)	5(1)
C(10)	50(2)	32(1)	33(1)	1(1)	26(1)	1(1)
C(11)	39(1)	28(1)	17(1)	2(1)	12(1)	4(1)
C(12)	36(1)	40(2)	31(1)	7(1)	10(1)	2(1)
C(13)	61(2)	40(2)	24(1)	-1(1)	6(1)	-15(1)
C(14)	93(2)	25(1)	28(1)	-2(1)	27(1)	4(2)
C(15)	65(2)	41(2)	47(2)	5(1)	31(1)	20(1)
C(16)	37(1)	38(1)	30(1)	1(1)	13(1)	4(1)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for 06036.

	x	y	z	U(eq)
H(3)	2281	5545	-122	32
H(4)	1631	3613	1169	32
H(6A)	321	8331	316	42
H(6B)	1138	7554	-152	42
H(7A)	1813	10234	755	49
H(7B)	2000	9099	1667	49
H(8A)	3146	8339	442	44
H(8B)	3695	9516	1356	44
H(9A)	402	4754	1739	55
H(9B)	-426	6189	1075	55
H(9C)	615	6798	1981	55
H(10A)	3540	3573	-684	43
H(10B)	2215	3639	-1295	43
H(12)	1185	584	-1464	44
H(13)	1271	-2292	-1940	54
H(14)	2972	-3480	-1851	57
H(15)	4599	-1780	-1292	58
H(16)	4517	1081	-815	42

Table 6. Torsion angles [°] for 06036.

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O(1)-C(1)-C(2)-F(2)	-0.1(3)
C(8)-C(1)-C(2)-F(2)	178.67(19)
O(1)-C(1)-C(2)-F(1)	-114.5(2)
C(8)-C(1)-C(2)-F(1)	64.3(2)
O(1)-C(1)-C(2)-C(3)	122.3(2)
C(8)-C(1)-C(2)-C(3)	-58.9(3)
C(10)-O(2)-C(3)-C(4)	148.41(18)
C(10)-O(2)-C(3)-C(2)	-92.4(2)
F(2)-C(2)-C(3)-O(2)	-47.5(2)
F(1)-C(2)-C(3)-O(2)	69.2(2)
C(1)-C(2)-C(3)-O(2)	-169.64(18)
F(2)-C(2)-C(3)-C(4)	72.7(2)
F(1)-C(2)-C(3)-C(4)	-170.62(17)
C(1)-C(2)-C(3)-C(4)	-49.5(2)
O(2)-C(3)-C(4)-C(5)	-148.1(2)
C(2)-C(3)-C(4)-C(5)	90.8(3)
C(3)-C(4)-C(5)-C(9)	-174.97(19)
C(3)-C(4)-C(5)-C(6)	3.2(3)
C(4)-C(5)-C(6)-C(7)	-85.6(3)
C(9)-C(5)-C(6)-C(7)	92.7(2)
C(5)-C(6)-C(7)-C(8)	72.7(3)
O(1)-C(1)-C(8)-C(7)	-73.4(3)
C(2)-C(1)-C(8)-C(7)	107.9(2)
C(6)-C(7)-C(8)-C(1)	-69.4(3)
C(3)-O(2)-C(10)-C(11)	179.36(18)
O(2)-C(10)-C(11)-C(16)	-111.6(2)
O(2)-C(10)-C(11)-C(12)	69.6(3)
C(16)-C(11)-C(12)-C(13)	-0.1(3)
C(10)-C(11)-C(12)-C(13)	178.8(2)
C(11)-C(12)-C(13)-C(14)	0.1(4)
C(12)-C(13)-C(14)-C(15)	-0.2(4)
C(13)-C(14)-C(15)-C(16)	0.3(4)
C(12)-C(11)-C(16)-C(15)	0.1(3)
C(10)-C(11)-C(16)-C(15)	-178.7(2)

C(14)-C(15)-C(16)-C(11)   -0.2(4)

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Symmetry transformations used to generate equivalent atoms:

### 6.2.8 3*R**-Benzyloxy-2,2-difluoro-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,4*R**-diol 384
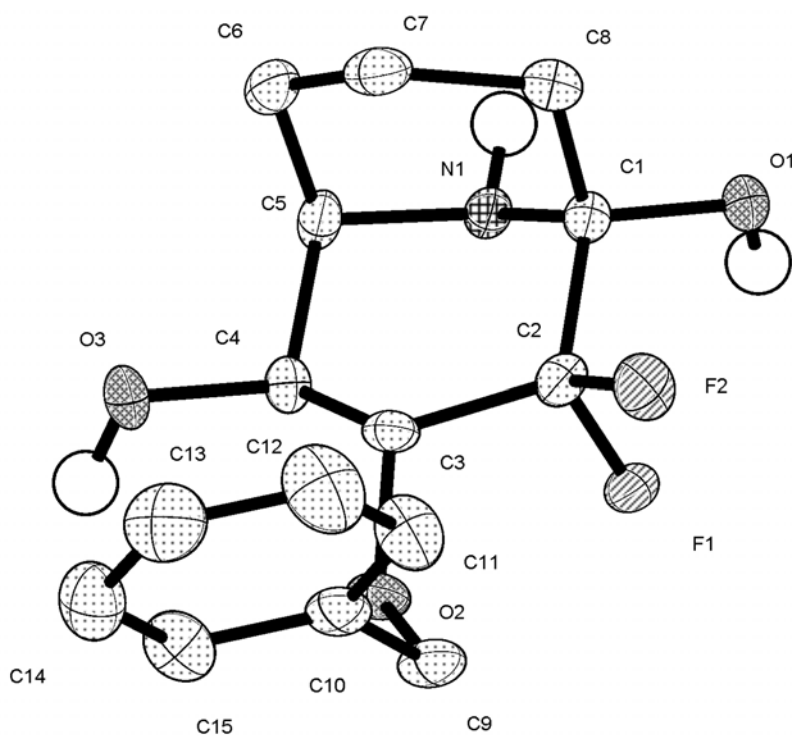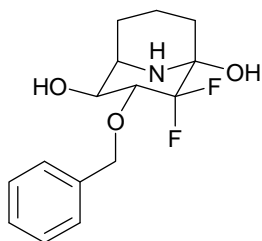
Table 1. Crystal data and structure refinement for 05086.

Identification code	05086
Empirical formula	C15 H19 F2 N O3
Formula weight	299.31
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pccn
Unit cell dimensions	a = 11.428(3) Å $\alpha= 90°$.
	b = 24.352(6) Å $\beta= 90°$.
	c = 10.474(2) Å $\gamma = 90°$.
Volume	2915.0(12) Å^3
Z	8
Density (calculated)	1.364 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	1264
Crystal size	0.33 x 0.20 x 0.10 mm^3
Theta range for data collection	1.67 to 25.00°.
Index ranges	-13<=h<=13, -28<=k<=28, -12<=l<=12
Reflections collected	19696
Independent reflections	2576 [R(int) = 0.0528]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.981 and 0.792
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2576 / 0 / 202
Goodness-of-fit on F^2	1.149
Final R indices [I>2sigma(I)]	R1 = 0.0498, wR2 = 0.1134
R indices (all data)	R1 = 0.0658, wR2 = 0.1194
Largest diff. peak and hole	0.577 and -0.247 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for 05086. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	11265(1)	5429(1)	1455(1)	25(1)
F(2)	11021(1)	6313(1)	1628(1)	29(1)
N(1)	8846(1)	5283(1)	937(2)	19(1)
O(1)	10013(1)	5773(1)	-498(1)	22(1)
O(2)	11019(1)	5576(1)	3921(1)	23(1)
O(3)	8608(1)	5294(1)	4434(1)	27(1)
C(1)	9482(2)	5794(1)	708(2)	19(1)
C(2)	10444(2)	5822(1)	1744(2)	19(1)
C(3)	10063(2)	5736(1)	3132(2)	19(1)
C(4)	9162(2)	5277(1)	3217(2)	20(1)
C(5)	8228(2)	5303(1)	2176(2)	21(1)
C(6)	7373(2)	5785(1)	2254(2)	27(1)
C(7)	7917(2)	6339(1)	1916(2)	28(1)
C(8)	8685(2)	6296(1)	722(2)	25(1)
C(9)	11844(2)	6002(1)	4261(2)	26(1)
C(10)	11318(2)	6453(1)	5051(2)	24(1)
C(11)	11303(2)	6987(1)	4617(2)	37(1)
C(12)	10849(3)	7404(1)	5363(3)	48(1)
C(13)	10390(2)	7287(1)	6545(2)	42(1)
C(14)	10391(2)	6756(1)	6996(2)	37(1)
C(15)	10862(2)	6343(1)	6251(2)	33(1)

Table 3.   Bond lengths [Å] and angles [°] for 05086.

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F(1)-C(2)	1.373(2)
F(2)-C(2)	1.371(2)
N(1)-C(1)	1.462(3)
N(1)-C(5)	1.478(2)
N(1)-H(1)	0.88(2)
O(1)-C(1)	1.402(2)
O(1)-H(1A)	0.88(3)
O(2)-C(3)	1.425(2)
O(2)-C(9)	1.447(2)
O(3)-C(4)	1.424(2)
O(3)-H(3)	0.88(3)
C(1)-C(8)	1.523(3)
C(1)-C(2)	1.547(3)
C(2)-C(3)	1.532(3)
C(3)-C(4)	1.522(3)
C(3)-H(3A)	1.0000
C(4)-C(5)	1.528(3)
C(4)-H(4)	1.0000
C(5)-C(6)	1.529(3)
C(5)-H(5)	1.0000
C(6)-C(7)	1.528(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.531(3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.501(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.376(3)
C(10)-C(15)	1.388(3)
C(11)-C(12)	1.383(3)

C(11)-H(11)	0.9500
C(12)-C(13)	1.374(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.377(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.383(3)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(1)-N(1)-C(5)	110.68(15)
C(1)-N(1)-H(1)	108.4(14)
C(5)-N(1)-H(1)	107.6(14)
C(1)-O(1)-H(1A)	106.5(16)
C(3)-O(2)-C(9)	116.50(15)
C(4)-O(3)-H(3)	109.8(18)
O(1)-C(1)-N(1)	109.39(15)
O(1)-C(1)-C(8)	107.26(16)
N(1)-C(1)-C(8)	112.59(16)
O(1)-C(1)-C(2)	109.01(16)
N(1)-C(1)-C(2)	106.00(15)
C(8)-C(1)-C(2)	112.54(16)
F(2)-C(2)-F(1)	105.04(15)
F(2)-C(2)-C(3)	109.93(15)
F(1)-C(2)-C(3)	107.92(15)
F(2)-C(2)-C(1)	108.53(15)
F(1)-C(2)-C(1)	107.50(15)
C(3)-C(2)-C(1)	117.21(16)
O(2)-C(3)-C(4)	106.49(15)
O(2)-C(3)-C(2)	111.71(16)
C(4)-C(3)-C(2)	110.44(15)
O(2)-C(3)-H(3A)	109.4
C(4)-C(3)-H(3A)	109.4
C(2)-C(3)-H(3A)	109.4
O(3)-C(4)-C(3)	109.37(15)
O(3)-C(4)-C(5)	109.07(16)
C(3)-C(4)-C(5)	113.58(16)

O(3)-C(4)-H(4)	108.2
C(3)-C(4)-H(4)	108.2
C(5)-C(4)-H(4)	108.2
N(1)-C(5)-C(4)	106.93(15)
N(1)-C(5)-C(6)	112.23(16)
C(4)-C(5)-C(6)	116.15(16)
N(1)-C(5)-H(5)	107.0
C(4)-C(5)-H(5)	107.0
C(6)-C(5)-H(5)	107.0
C(7)-C(6)-C(5)	113.90(17)
C(7)-C(6)-H(6A)	108.8
C(5)-C(6)-H(6A)	108.8
C(7)-C(6)-H(6B)	108.8
C(5)-C(6)-H(6B)	108.8
H(6A)-C(6)-H(6B)	107.7
C(6)-C(7)-C(8)	111.18(17)
C(6)-C(7)-H(7A)	109.4
C(8)-C(7)-H(7A)	109.4
C(6)-C(7)-H(7B)	109.4
C(8)-C(7)-H(7B)	109.4
H(7A)-C(7)-H(7B)	108.0
C(1)-C(8)-C(7)	113.96(17)
C(1)-C(8)-H(8A)	108.8
C(7)-C(8)-H(8A)	108.8
C(1)-C(8)-H(8B)	108.8
C(7)-C(8)-H(8B)	108.8
H(8A)-C(8)-H(8B)	107.7
O(2)-C(9)-C(10)	113.60(17)
O(2)-C(9)-H(9A)	108.8
C(10)-C(9)-H(9A)	108.8
O(2)-C(9)-H(9B)	108.8
C(10)-C(9)-H(9B)	108.8
H(9A)-C(9)-H(9B)	107.7
C(11)-C(10)-C(15)	118.6(2)
C(11)-C(10)-C(9)	120.9(2)
C(15)-C(10)-C(9)	120.5(2)

C(10)-C(11)-C(12)	120.7(2)
C(10)-C(11)-H(11)	119.6
C(12)-C(11)-H(11)	119.6
C(13)-C(12)-C(11)	120.1(2)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
C(12)-C(13)-C(14)	120.2(2)
C(12)-C(13)-H(13)	119.9
C(14)-C(13)-H(13)	119.9
C(13)-C(14)-C(15)	119.4(2)
C(13)-C(14)-H(14)	120.3
C(15)-C(14)-H(14)	120.3
C(14)-C(15)-C(10)	121.1(2)
C(14)-C(15)-H(15)	119.5
C(10)-C(15)-H(15)	119.5

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Symmetry transformations used to generate equivalent atoms:

Table 4.   Anisotropic displacement parameters (Å^2x 10^3) for 05086. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2\, a^{*2}U^{11} + ... \; + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	17(1)	37(1)	20(1)	-1(1)	0(1)	6(1)
F(2)	27(1)	31(1)	29(1)	4(1)	-3(1)	-13(1)
N(1)	15(1)	27(1)	15(1)	-3(1)	0(1)	-3(1)
O(1)	21(1)	30(1)	16(1)	2(1)	3(1)	0(1)
O(2)	22(1)	26(1)	20(1)	-1(1)	-7(1)	3(1)
O(3)	29(1)	36(1)	16(1)	4(1)	6(1)	3(1)
C(1)	16(1)	25(1)	17(1)	0(1)	1(1)	0(1)
C(2)	16(1)	19(1)	23(1)	0(1)	2(1)	0(1)
C(3)	17(1)	23(1)	17(1)	-1(1)	-5(1)	4(1)
C(4)	20(1)	24(1)	15(1)	-1(1)	4(1)	1(1)
C(5)	17(1)	29(1)	17(1)	-3(1)	4(1)	-5(1)
C(6)	19(1)	44(1)	18(1)	-6(1)	0(1)	3(1)
C(7)	23(1)	35(1)	25(1)	-6(1)	-5(1)	11(1)
C(8)	23(1)	29(1)	23(1)	2(1)	-4(1)	2(1)
C(9)	19(1)	32(1)	27(1)	-3(1)	-8(1)	1(1)
C(10)	19(1)	30(1)	24(1)	-3(1)	-8(1)	-2(1)
C(11)	46(2)	35(1)	30(1)	1(1)	2(1)	1(1)
C(12)	69(2)	29(1)	46(2)	2(1)	4(1)	6(1)
C(13)	48(2)	38(1)	41(2)	-14(1)	1(1)	9(1)
C(14)	41(1)	42(1)	28(1)	-6(1)	3(1)	-4(1)
C(15)	41(1)	29(1)	29(1)	-1(1)	-5(1)	-4(1)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3}) for 05086.

	x	y	z	U(eq)
H(1)	8315(19)	5244(8)	330(20)	24(6)
H(1A)	10310(20)	5444(11)	-570(20)	39(7)
H(3)	8890(20)	5032(11)	4930(30)	53(8)
H(3A)	9715	6083	3469	23
H(4)	9582	4918	3139	24
H(5)	7754	4959	2243	25
H(6A)	6710	5713	1668	32
H(6B)	7055	5804	3132	32
H(7A)	8397	6470	2641	33
H(7B)	7288	6611	1765	33
H(8A)	8173	6283	-40	30
H(8B)	9173	6630	658	30
H(9A)	12170	6163	3470	31
H(9B)	12499	5835	4743	31
H(11)	11609	7069	3796	44
H(12)	10854	7771	5059	57
H(13)	10072	7574	7053	51
H(14)	10070	6674	7811	45
H(15)	10875	5977	6567	39

Table 6. Torsion angles [°] for 05086.

_____

C(5)-N(1)-C(1)-O(1)	-177.22(15)
C(5)-N(1)-C(1)-C(8)	-58.1(2)
C(5)-N(1)-C(1)-C(2)	65.38(19)
O(1)-C(1)-C(2)-F(2)	66.34(19)
N(1)-C(1)-C(2)-F(2)	-176.01(14)
C(8)-C(1)-C(2)-F(2)	-52.5(2)
O(1)-C(1)-C(2)-F(1)	-46.8(2)
N(1)-C(1)-C(2)-F(1)	70.87(18)
C(8)-C(1)-C(2)-F(1)	-165.64(15)
O(1)-C(1)-C(2)-C(3)	-168.45(16)
N(1)-C(1)-C(2)-C(3)	-50.8(2)
C(8)-C(1)-C(2)-C(3)	72.7(2)
C(9)-O(2)-C(3)-C(4)	-164.36(15)
C(9)-O(2)-C(3)-C(2)	75.0(2)
F(2)-C(2)-C(3)-O(2)	-76.45(19)
F(1)-C(2)-C(3)-O(2)	37.6(2)
C(1)-C(2)-C(3)-O(2)	159.04(16)
F(2)-C(2)-C(3)-C(4)	165.22(15)
F(1)-C(2)-C(3)-C(4)	-80.73(18)
C(1)-C(2)-C(3)-C(4)	40.7(2)
O(2)-C(3)-C(4)-O(3)	73.04(19)
C(2)-C(3)-C(4)-O(3)	-165.50(15)
O(2)-C(3)-C(4)-C(5)	-164.87(15)
C(2)-C(3)-C(4)-C(5)	-43.4(2)
C(1)-N(1)-C(5)-C(4)	-70.60(19)
C(1)-N(1)-C(5)-C(6)	57.9(2)
O(3)-C(4)-C(5)-N(1)	-179.91(15)
C(3)-C(4)-C(5)-N(1)	57.8(2)
O(3)-C(4)-C(5)-C(6)	53.9(2)
C(3)-C(4)-C(5)-C(6)	-68.3(2)
N(1)-C(5)-C(6)-C(7)	-51.9(2)
C(4)-C(5)-C(6)-C(7)	71.5(2)
C(5)-C(6)-C(7)-C(8)	44.3(2)
O(1)-C(1)-C(8)-C(7)	172.70(16)

N(1)-C(1)-C(8)-C(7)	52.3(2)
C(2)-C(1)-C(8)-C(7)	-67.4(2)
C(6)-C(7)-C(8)-C(1)	-44.4(2)
C(3)-O(2)-C(9)-C(10)	63.5(2)
O(2)-C(9)-C(10)-C(11)	-119.1(2)
O(2)-C(9)-C(10)-C(15)	62.6(3)
C(15)-C(10)-C(11)-C(12)	0.3(3)
C(9)-C(10)-C(11)-C(12)	-178.1(2)
C(10)-C(11)-C(12)-C(13)	-0.9(4)
C(11)-C(12)-C(13)-C(14)	0.6(4)
C(12)-C(13)-C(14)-C(15)	0.4(4)
C(13)-C(14)-C(15)-C(10)	-1.0(4)
C(11)-C(10)-C(15)-C(14)	0.7(3)
C(9)-C(10)-C(15)-C(14)	179.0(2)

Symmetry transformations used to generate equivalent atoms:

6.2.9 3*R**-Benzyloxy-2,2-difluoro-9-methyl-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,4*R**-diol 385
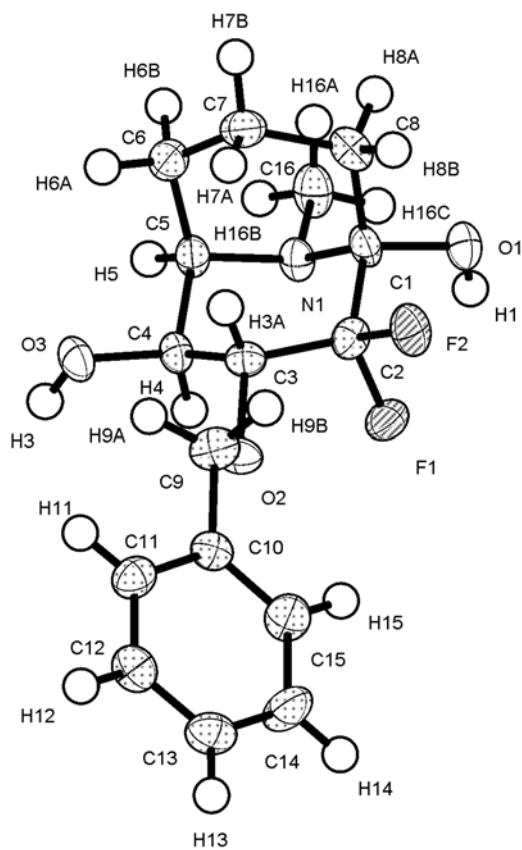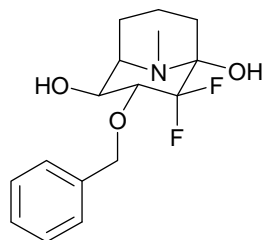
Table 1. Crystal data and structure refinement for 06018a.

Identification code	06018a
Empirical formula	C16 H21 F2 N O3
Formula weight	313.34
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c

Unit cell dimensions

a = 6.7020(18) Å	α= 90°.
b = 16.936(4) Å	β= 90.508(6)°.
c = 13.275(4) Å	γ = 90°.

Volume	1506.7(7) Å^3
Z	4
Density (calculated)	1.381 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	664
Crystal size	0.20 x 0.14 x 0.07 mm^3
Theta range for data collection	1.95 to 25.00°.
Index ranges	-7<=h<=7, -19<=k<=20, -15<=l<=15
Reflections collected	10673
Independent reflections	2644 [R(int) = 0.1284]
Completeness to theta = 25.00°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2644 / 0 / 202
Goodness-of-fit on F^2	0.930
Final R indices [I>2sigma(I)]	R1 = 0.0584, wR2 = 0.0899
R indices (all data)	R1 = 0.1157, wR2 = 0.1049
Largest diff. peak and hole	0.198 and -0.252 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 06018a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4980(2)	4429(1)	8966(1)	32(1)
F(2)	5808(2)	3740(1)	7650(1)	35(1)
O(1)	3116(3)	4988(1)	7347(2)	30(1)
O(2)	8813(3)	4013(1)	9153(1)	27(1)
O(3)	10738(3)	5512(1)	8847(2)	29(1)
N(1)	5605(3)	5862(1)	7927(2)	24(1)
C(1)	5184(4)	5114(2)	7409(2)	25(1)
C(2)	6077(5)	4472(2)	8101(2)	25(1)
C(3)	8252(4)	4567(2)	8381(2)	24(1)
C(4)	8637(4)	5408(2)	8724(2)	24(1)
C(5)	7789(4)	6004(2)	7965(2)	25(1)
C(6)	8721(5)	6010(2)	6920(2)	32(1)
C(7)	8146(4)	5318(2)	6240(2)	33(1)
C(8)	5953(4)	5080(2)	6339(2)	31(1)
C(9)	10233(5)	3437(2)	8801(2)	32(1)
C(10)	10706(5)	2871(2)	9631(2)	25(1)
C(11)	12677(5)	2661(2)	9821(2)	31(1)
C(12)	13134(5)	2085(2)	10533(2)	33(1)
C(13)	11656(5)	1721(2)	11058(2)	36(1)
C(14)	9692(5)	1939(2)	10893(3)	41(1)
C(15)	9237(5)	2508(2)	10177(2)	35(1)
C(16)	4515(4)	6547(2)	7512(2)	35(1)

Table 3.   Bond lengths [Å] and angles [°] for 06018a.

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F(1)-C(2)	1.370(3)
F(2)-C(2)	1.388(3)
O(1)-C(1)	1.404(3)
O(1)-H(1)	0.8400
O(2)-C(3)	1.438(3)
O(2)-C(9)	1.443(3)
O(3)-C(4)	1.427(3)
O(3)-H(3)	0.8400
N(1)-C(1)	1.467(4)
N(1)-C(16)	1.476(3)
N(1)-C(5)	1.484(3)
C(1)-C(8)	1.516(4)
C(1)-C(2)	1.540(4)
C(2)-C(3)	1.510(4)
C(3)-C(4)	1.517(4)
C(3)-H(3A)	1.0000
C(4)-C(5)	1.532(4)
C(4)-H(4)	1.0000
C(5)-C(6)	1.526(4)
C(5)-H(5)	1.0000
C(6)-C(7)	1.526(4)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.531(4)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.493(4)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(15)	1.373(4)
C(10)-C(11)	1.390(4)
C(11)-C(12)	1.390(4)

C(11)-H(11)	0.9500
C(12)-C(13)	1.363(4)
C(12)-H(12)	0.9500
C(13)-C(14)	1.383(4)
C(13)-H(13)	0.9500
C(14)-C(15)	1.385(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(1)-O(1)-H(1)	109.5
C(3)-O(2)-C(9)	112.2(2)
C(4)-O(3)-H(3)	109.5
C(1)-N(1)-C(16)	114.3(2)
C(1)-N(1)-C(5)	110.0(2)
C(16)-N(1)-C(5)	111.7(2)
O(1)-C(1)-N(1)	110.1(2)
O(1)-C(1)-C(8)	106.4(2)
N(1)-C(1)-C(8)	114.0(2)
O(1)-C(1)-C(2)	107.8(2)
N(1)-C(1)-C(2)	104.9(2)
C(8)-C(1)-C(2)	113.4(3)
F(1)-C(2)-F(2)	104.2(2)
F(1)-C(2)-C(3)	108.9(2)
F(2)-C(2)-C(3)	108.8(2)
F(1)-C(2)-C(1)	109.2(2)
F(2)-C(2)-C(1)	109.0(2)
C(3)-C(2)-C(1)	116.2(2)
O(2)-C(3)-C(2)	110.6(2)
O(2)-C(3)-C(4)	110.8(2)
C(2)-C(3)-C(4)	109.6(2)
O(2)-C(3)-H(3A)	108.6
C(2)-C(3)-H(3A)	108.6
C(4)-C(3)-H(3A)	108.6

O(3)-C(4)-C(3)	108.4(2)
O(3)-C(4)-C(5)	110.7(2)
C(3)-C(4)-C(5)	111.1(2)
O(3)-C(4)-H(4)	108.9
C(3)-C(4)-H(4)	108.9
C(5)-C(4)-H(4)	108.9
N(1)-C(5)-C(6)	112.4(2)
N(1)-C(5)-C(4)	106.0(2)
C(6)-C(5)-C(4)	116.7(3)
N(1)-C(5)-H(5)	107.1
C(6)-C(5)-H(5)	107.1
C(4)-C(5)-H(5)	107.1
C(5)-C(6)-C(7)	115.5(3)
C(5)-C(6)-H(6A)	108.4
C(7)-C(6)-H(6A)	108.4
C(5)-C(6)-H(6B)	108.4
C(7)-C(6)-H(6B)	108.4
H(6A)-C(6)-H(6B)	107.5
C(6)-C(7)-C(8)	112.9(3)
C(6)-C(7)-H(7A)	109.0
C(8)-C(7)-H(7A)	109.0
C(6)-C(7)-H(7B)	109.0
C(8)-C(7)-H(7B)	109.0
H(7A)-C(7)-H(7B)	107.8
C(1)-C(8)-C(7)	113.9(3)
C(1)-C(8)-H(8A)	108.8
C(7)-C(8)-H(8A)	108.8
C(1)-C(8)-H(8B)	108.8
C(7)-C(8)-H(8B)	108.8
H(8A)-C(8)-H(8B)	107.7
O(2)-C(9)-C(10)	109.3(3)
O(2)-C(9)-H(9A)	109.8
C(10)-C(9)-H(9A)	109.8
O(2)-C(9)-H(9B)	109.8
C(10)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.3

C(15)-C(10)-C(11)	118.3(3)
C(15)-C(10)-C(9)	121.9(3)
C(11)-C(10)-C(9)	119.6(3)
C(10)-C(11)-C(12)	120.4(3)
C(10)-C(11)-H(11)	119.8
C(12)-C(11)-H(11)	119.8
C(13)-C(12)-C(11)	120.5(3)
C(13)-C(12)-H(12)	119.7
C(11)-C(12)-H(12)	119.7
C(12)-C(13)-C(14)	119.6(3)
C(12)-C(13)-H(13)	120.2
C(14)-C(13)-H(13)	120.2
C(13)-C(14)-C(15)	119.8(3)
C(13)-C(14)-H(14)	120.1
C(15)-C(14)-H(14)	120.1
C(10)-C(15)-C(14)	121.3(3)
C(10)-C(15)-H(15)	119.4
C(14)-C(15)-H(15)	119.4
N(1)-C(16)-H(16A)	109.5
N(1)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
N(1)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\mathring{A}^2$x 10^3) for 06018a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\,h^2\,a^{*2}U^{11} + ... \ + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	29(1)	36(1)	30(1)	5(1)	6(1)	-2(1)
F(2)	35(1)	23(1)	45(1)	-7(1)	-8(1)	-2(1)
O(1)	19(1)	34(1)	36(1)	-5(1)	-1(1)	-1(1)
O(2)	28(1)	28(1)	24(1)	3(1)	1(1)	10(1)
O(3)	19(1)	38(1)	31(1)	-4(1)	-4(1)	1(1)
N(1)	19(2)	19(1)	34(2)	2(1)	-5(1)	3(1)
C(1)	19(2)	29(2)	28(2)	-1(2)	-7(2)	-2(1)
C(2)	28(2)	20(2)	26(2)	-6(2)	4(2)	-3(1)
C(3)	26(2)	23(2)	22(2)	3(2)	0(1)	2(1)
C(4)	18(2)	27(2)	26(2)	-2(2)	-2(1)	-1(1)
C(5)	22(2)	22(2)	33(2)	3(2)	-5(2)	-2(1)
C(6)	25(2)	35(2)	37(2)	11(2)	-3(2)	-1(2)
C(7)	28(2)	42(2)	28(2)	9(2)	3(2)	4(2)
C(8)	30(2)	34(2)	29(2)	-4(2)	-6(2)	4(2)
C(9)	33(2)	29(2)	33(2)	4(2)	6(2)	10(2)
C(10)	30(2)	21(2)	23(2)	-3(2)	-1(2)	2(2)
C(11)	36(2)	27(2)	30(2)	-1(2)	4(2)	-3(2)
C(12)	29(2)	32(2)	37(2)	-1(2)	-3(2)	8(2)
C(13)	45(2)	29(2)	35(2)	6(2)	-4(2)	5(2)
C(14)	39(2)	38(2)	48(2)	18(2)	7(2)	-1(2)
C(15)	31(2)	30(2)	44(2)	7(2)	-2(2)	5(2)
C(16)	23(2)	32(2)	51(2)	-2(2)	-4(2)	4(2)

Table 5.   Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for 06018a.

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	x	y	z	U(eq)
H(1)	2581	5140	7883	44
H(3)	10977	5719	9411	44
H(3A)	9073	4461	7770	29
H(4)	7980	5492	9389	28
H(5)	7994	6542	8259	30
H(6A)	10190	6014	7001	39
H(6B)	8334	6506	6577	39
H(7A)	8999	4859	6410	39
H(7B)	8407	5464	5531	39
H(8A)	5129	5433	5911	37
H(8B)	5786	4535	6081	37
H(9A)	11467	3706	8583	38
H(9B)	9667	3148	8216	38
H(11)	13720	2912	9462	37
H(12)	14486	1944	10655	39
H(13)	11974	1320	11533	43
H(14)	8656	1700	11270	50
H(15)	7883	2648	10060	42
H(16A)	4731	6579	6784	53
H(16B)	5004	7032	7835	53
H(16C)	3086	6487	7643	53

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Table 6. Torsion angles [°] for 06018a.

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C(16)-N(1)-C(1)-O(1)	-51.8(3)
C(5)-N(1)-C(1)-O(1)	-178.4(2)
C(16)-N(1)-C(1)-C(8)	67.8(3)
C(5)-N(1)-C(1)-C(8)	-58.8(3)
C(16)-N(1)-C(1)-C(2)	-167.5(2)
C(5)-N(1)-C(1)-C(2)	65.9(3)
O(1)-C(1)-C(2)-F(1)	-48.5(3)
N(1)-C(1)-C(2)-F(1)	68.9(3)
C(8)-C(1)-C(2)-F(1)	-166.1(2)
O(1)-C(1)-C(2)-F(2)	64.7(3)
N(1)-C(1)-C(2)-F(2)	-177.9(2)
C(8)-C(1)-C(2)-F(2)	-52.9(3)
O(1)-C(1)-C(2)-C(3)	-172.0(3)
N(1)-C(1)-C(2)-C(3)	-54.6(3)
C(8)-C(1)-C(2)-C(3)	70.4(3)
C(9)-O(2)-C(3)-C(2)	114.1(3)
C(9)-O(2)-C(3)-C(4)	-124.2(3)
F(1)-C(2)-C(3)-O(2)	46.7(3)
F(2)-C(2)-C(3)-O(2)	-66.2(3)
C(1)-C(2)-C(3)-O(2)	170.4(2)
F(1)-C(2)-C(3)-C(4)	-75.8(3)
F(2)-C(2)-C(3)-C(4)	171.3(2)
C(1)-C(2)-C(3)-C(4)	47.9(3)
O(2)-C(3)-C(4)-O(3)	65.7(3)
C(2)-C(3)-C(4)-O(3)	-171.9(2)
O(2)-C(3)-C(4)-C(5)	-172.4(2)
C(2)-C(3)-C(4)-C(5)	-50.1(3)
C(1)-N(1)-C(5)-C(6)	57.1(3)
C(16)-N(1)-C(5)-C(6)	-71.0(3)
C(1)-N(1)-C(5)-C(4)	-71.6(3)
C(16)-N(1)-C(5)-C(4)	160.4(2)
O(3)-C(4)-C(5)-N(1)	-178.0(2)
C(3)-C(4)-C(5)-N(1)	61.6(3)
O(3)-C(4)-C(5)-C(6)	56.0(3)

C(3)-C(4)-C(5)-C(6)	-64.5(3)
N(1)-C(5)-C(6)-C(7)	-48.5(4)
C(4)-C(5)-C(6)-C(7)	74.2(3)
C(5)-C(6)-C(7)-C(8)	38.8(4)
O(1)-C(1)-C(8)-C(7)	171.9(2)
N(1)-C(1)-C(8)-C(7)	50.4(3)
C(2)-C(1)-C(8)-C(7)	-69.6(3)
C(6)-C(7)-C(8)-C(1)	-38.9(4)
C(3)-O(2)-C(9)-C(10)	-178.6(2)
O(2)-C(9)-C(10)-C(15)	49.4(4)
O(2)-C(9)-C(10)-C(11)	-135.0(3)
C(15)-C(10)-C(11)-C(12)	1.2(4)
C(9)-C(10)-C(11)-C(12)	-174.5(3)
C(10)-C(11)-C(12)-C(13)	-0.2(5)
C(11)-C(12)-C(13)-C(14)	-1.3(5)
C(12)-C(13)-C(14)-C(15)	1.9(5)
C(11)-C(10)-C(15)-C(14)	-0.6(5)
C(9)-C(10)-C(15)-C(14)	175.0(3)
C(13)-C(14)-C(15)-C(10)	-1.0(5)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 06018a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(3)#1	0.84	1.89	2.711(3)	163.8
O(3)-H(3)...O(2)#2	0.84	1.96	2.787(3)	166.5

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z   #2 -x+2,-y+1,-z+2

6.3 Appendix 3 NMR data

6.3.1 3-Benzyloxy-2,2-difluoro-cyclooct-4Z-en-1-one 200
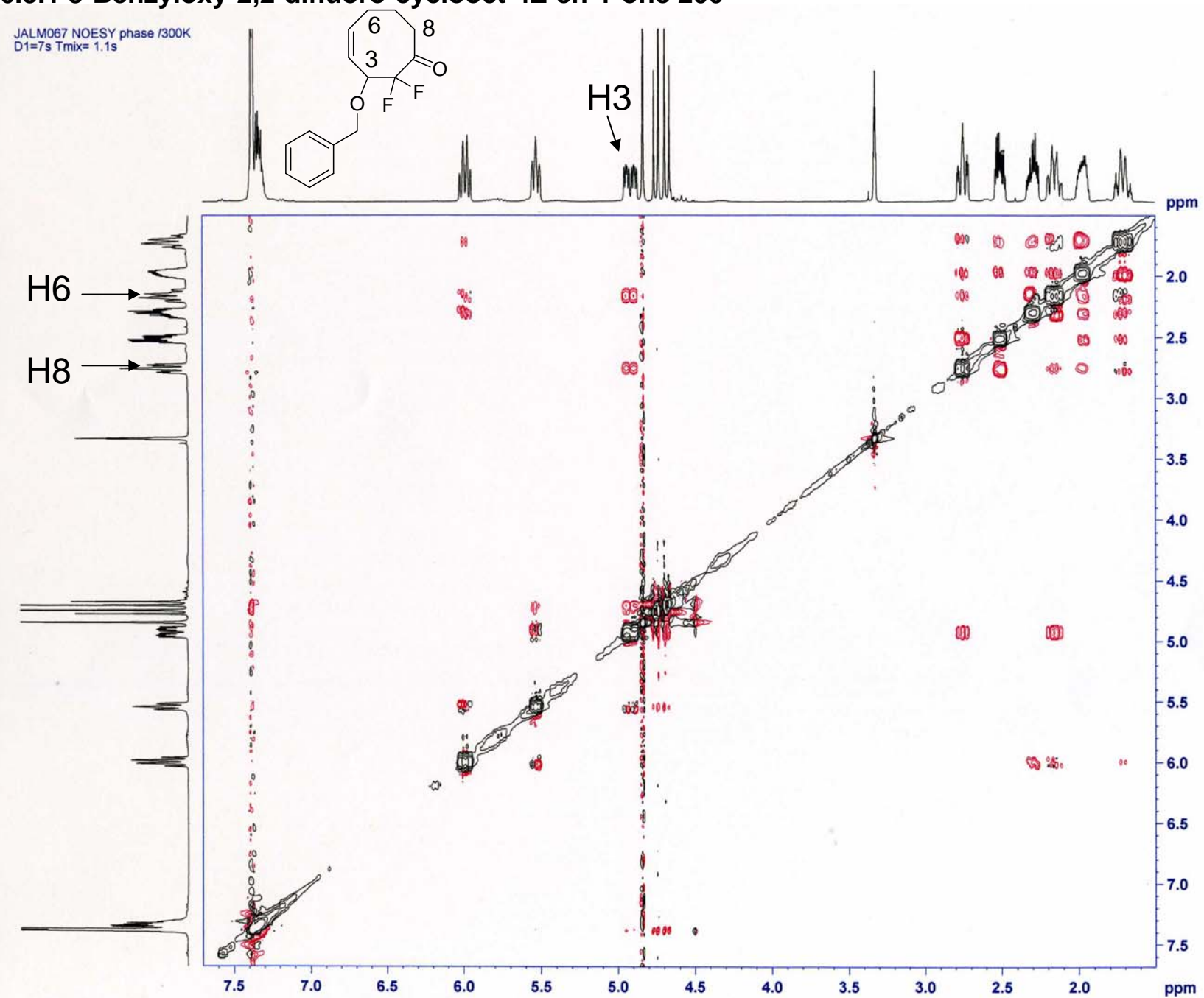
6.3.2 3-Benzoyloxy-2,2-difluoro-cyclooct-4Z-en-1-one 201

EU2383 NOESY phase /300K
D1=5s Tmix= 850ms
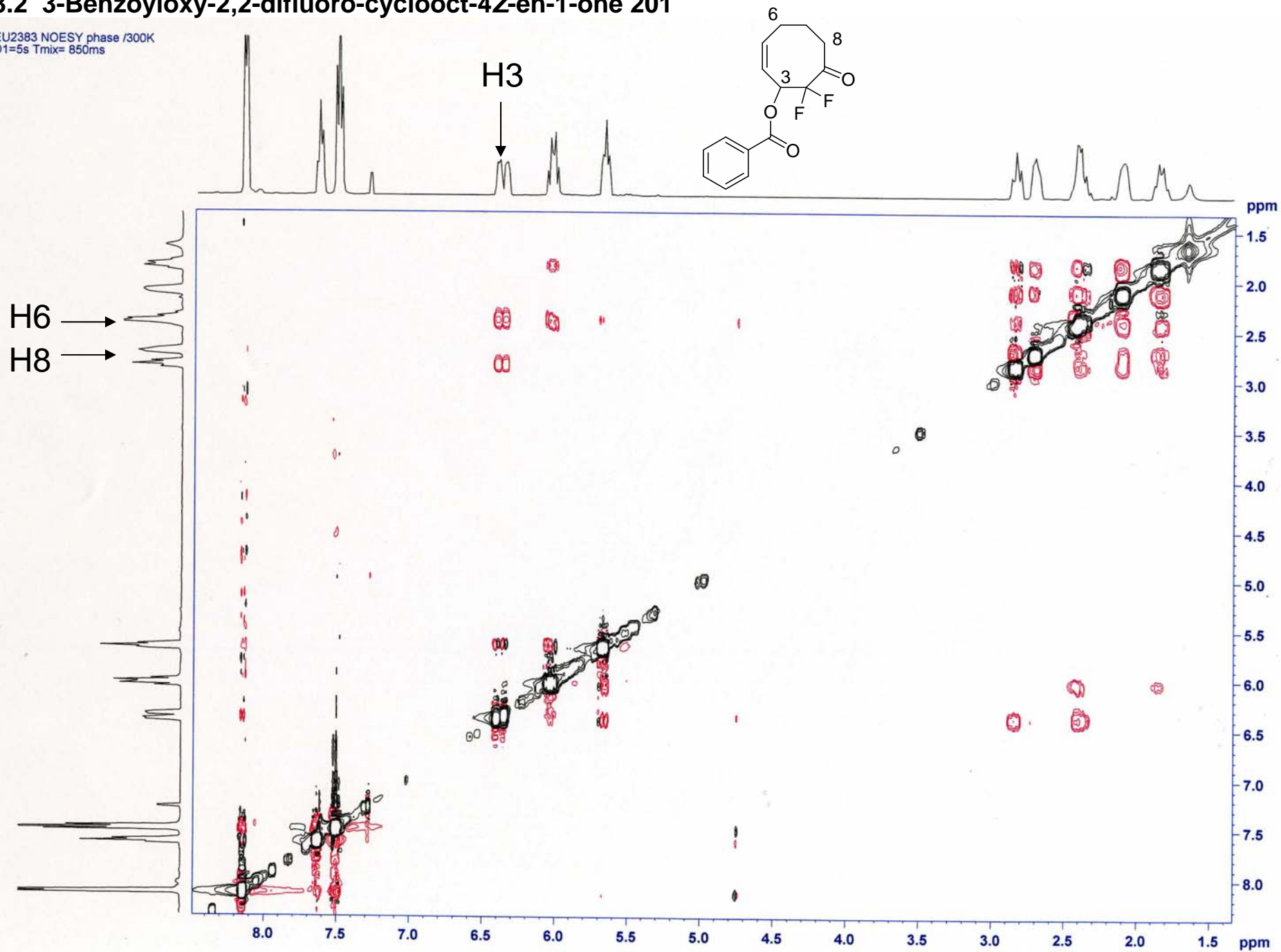
6.3.3 4-Bromo-benzenesulfonic acid 8,8-difluoro-7-oxo-cyclooct-2-enyl ester 202

6.3.4 3*R**-Benzyloxy-2,2-difluoro-9-oxa-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,4*S**-diol 256

JALM070MAJOR NOESY phase /300K
D1=4s Tmix= 850ms
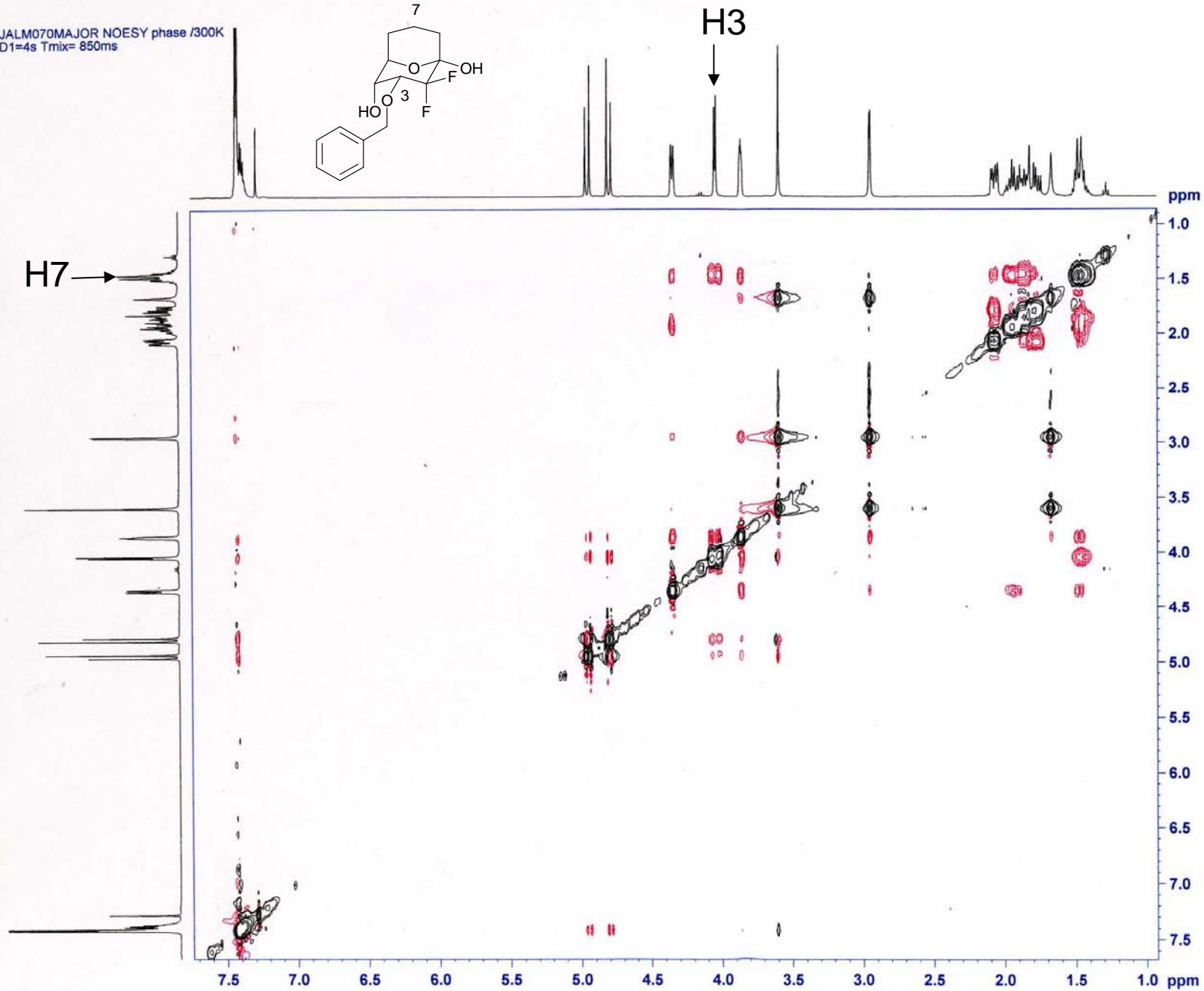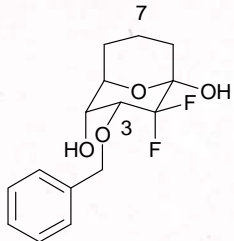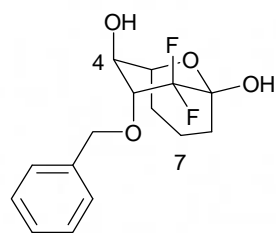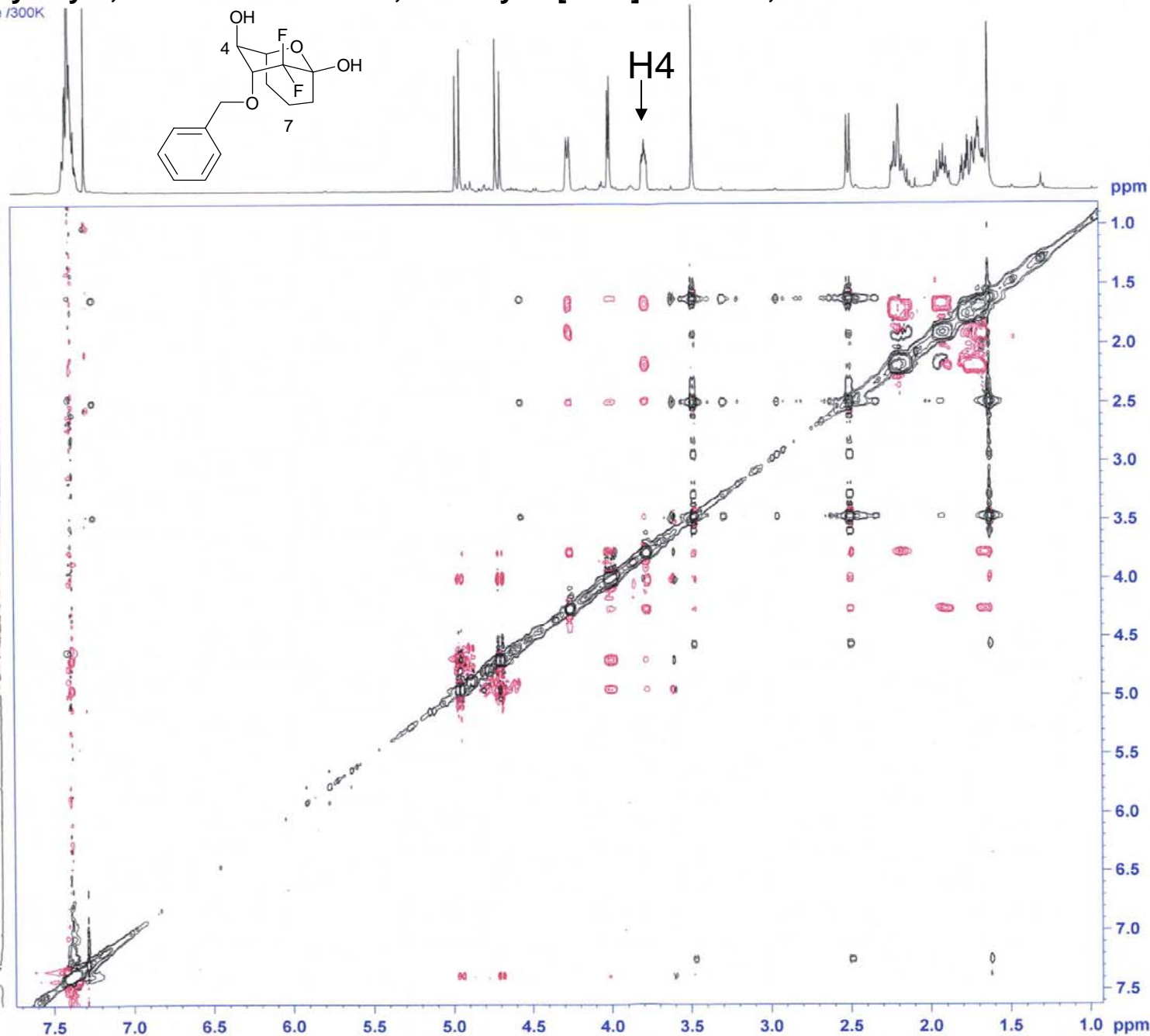
Current Data Parameters
NAME   jalm070major
EXPNO   3
PROCNO   1

F2 - Acquisition Parameters
Date_   20050616
Time   10.44
INSTRUM   drx400
PROBHD 5 mm QNP 1H/1
PULPROG   noesyph
TD   2048
SOLVENT   CDCl3
NS   16
DS   16
SWH   3810.976 Hz
FIDRES   1.860828 Hz
AQ   0.2687476 sec
RG   90
DW   131.200 usec
DE   6.00 usec
TE   300.0 K
d0   0.00011465 sec
D1   4.00000000 sec
D8   0.85000002 sec
IN0   0.00026240 sec
MCREST   0.00000000 sec
MCWRK   2.00000000 sec
ST1CNT   64

======== CHANNEL f1 ========
NUC1   1H
P1   13.00 usec
PL1   0.00 dB
SFO1   400.1314405 MHz

F1 - Acquisition parameters
ND0   1
TD   128
SFO1   400.1314 MHz
FIDRES   29.773247 Hz
SW   9.524 ppm
FnMODE   States-TPPI

F2 - Processing parameters
SI   1024
SF   400.1300000 MHz
WDW   QSINE
SSB   2
LB   0.00 Hz
GB   0
PC   1.00

F1 - Processing parameters
SI   1024
MC2   States-TPPI
SF   400.1300000 MHz
WDW   QSINE
SSB   2
LB   0.00 Hz
GB   0

6.3.7 5S*-acetoxy-3R*-benzyloxy-2,2-difluoro-1S*-methoxy-9-oxa-1S*,4R*-bicyclo[4.2.1]nonane 301
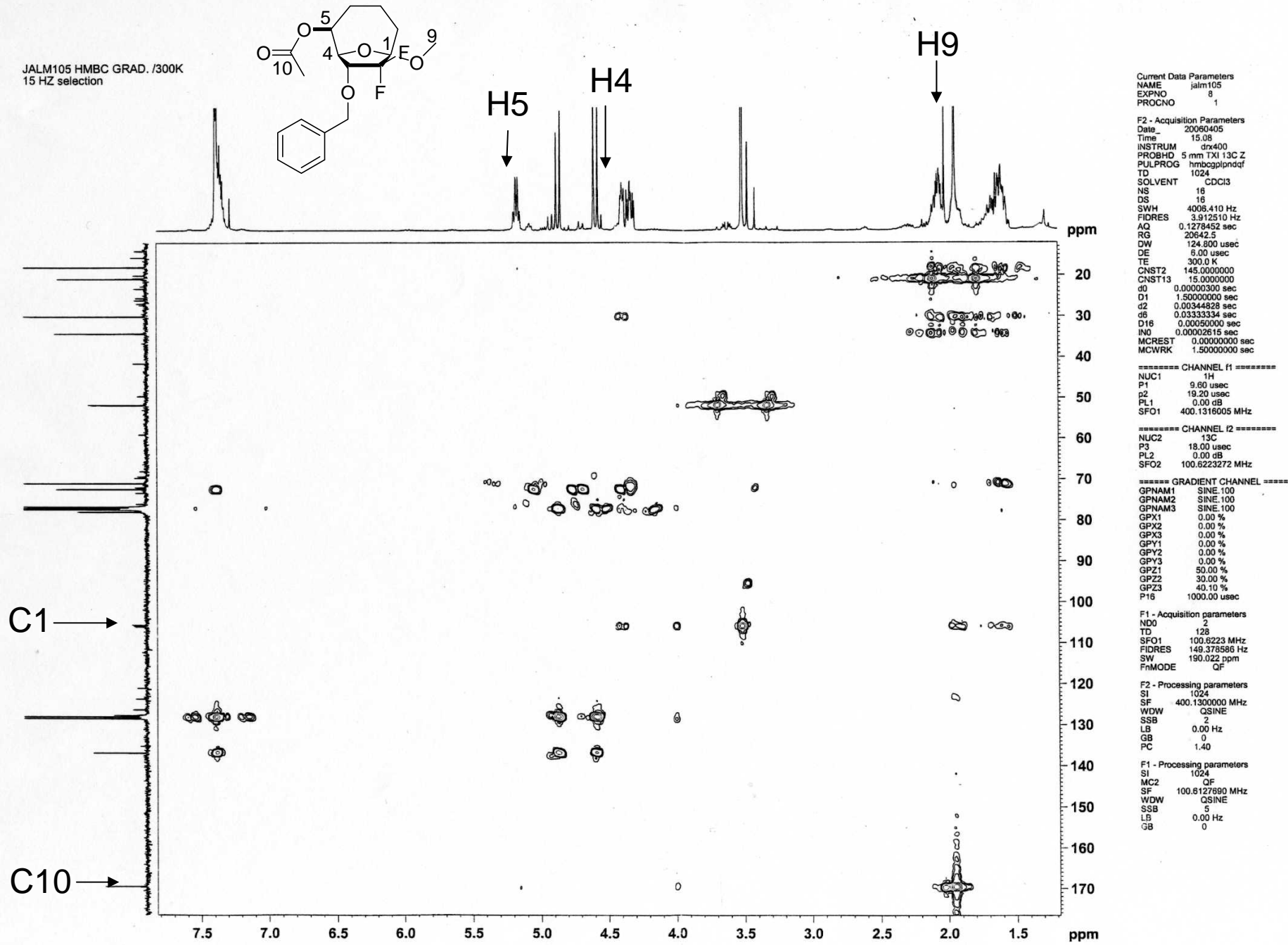
6.3.8 5S*-Acetoxy-2,2-difluoro-1S*-methoxy-9-oxa-1S*,4R*-bicyclo[4.2.1]nonan-3R*-ol 302

JALM121_1 HMBC grad. /300K
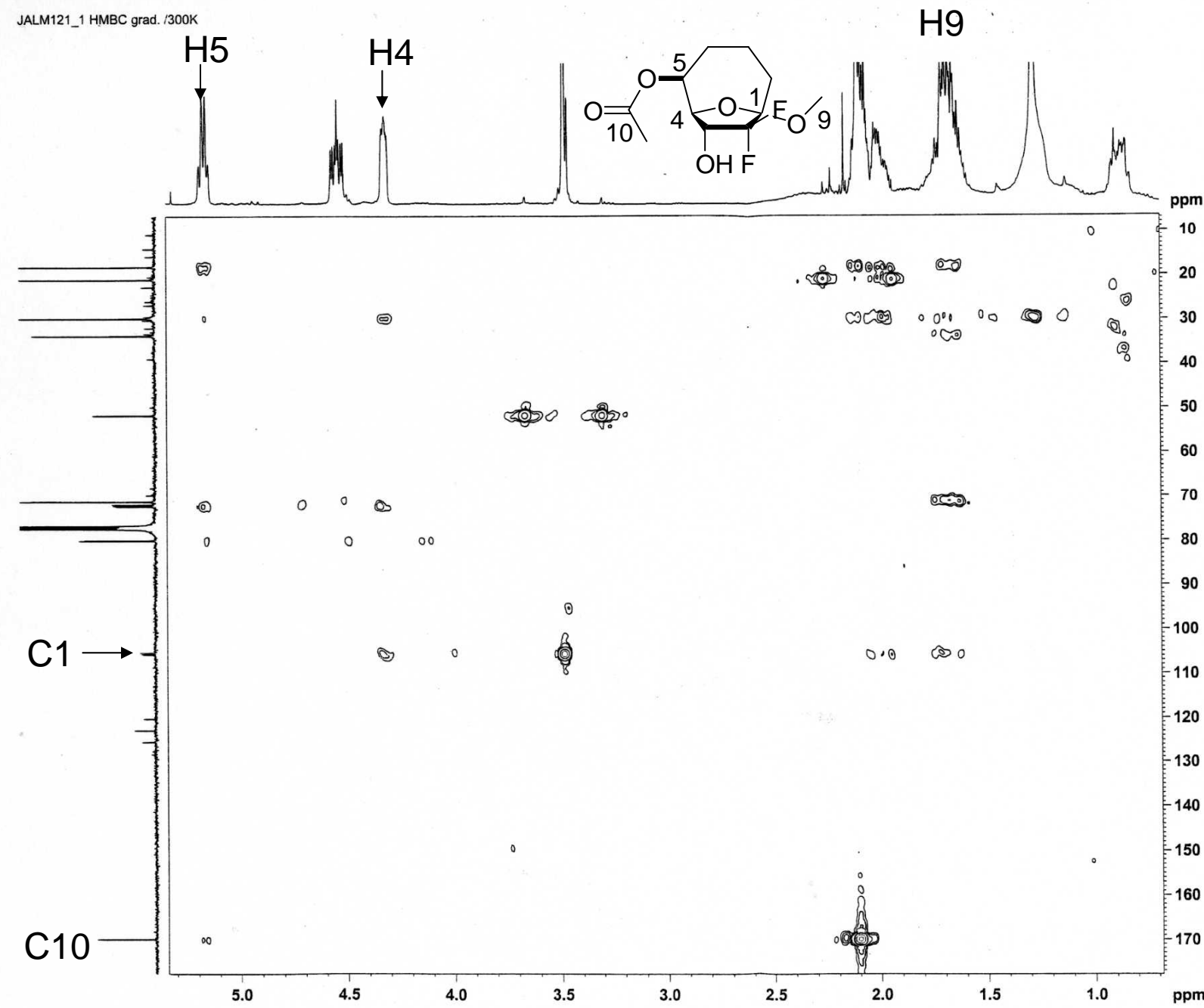
Current Data Parameters
NAME   jalm121_1
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20060620
Time   14.15
INSTRUM   drx400
PROBHD 5 mm TXI 13C Z
PULPROG hmbcgplpndqf
TD   1024
SOLVENT   CDCl3
NS   16
DS   16
SWH   3396.739 Hz
FIDRES   3.317128 Hz
AQ   0.1507828 sec
RG   20642.5
DW   147.200 usec
DE   6.00 usec
TE   300.0 K
CNST2   145.0000000
CNST13   10.0000000
d0   0.00000300 sec
D1   1.50000000 sec
d2   0.00344828 sec
d6   0.05000000 sec
D16   0.00050000 sec
IN0   0.00001910 sec
MCREST 0.00000000 sec
MCWRK   1.50000000 sec

======== CHANNEL f1 ========
NUC1   1H
P1   9.60 usec
p2   19.20 usec
PL1   0.00 dB
SFO1   400.1316005 MHz

======== CHANNEL f2 ========
NUC2   13C
P3   18.00 usec
PL2   0.00 dB
SFO2   100.6238364 MHz

====== GRADIENT CHANNEL =====
GPNAM1   SINE.100
GPNAM2   SINE.100
GPNAM3   SINE.100
GPX1   0.00 %
GPX2   0.00 %
GPX3   0.00 %
GPY1   0.00 %
GPY2   0.00 %
GPY3   0.00 %
GPZ1   50.00 %
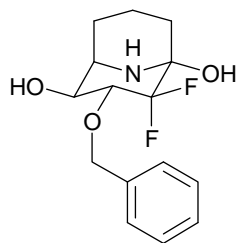GPZ2   30.00 %
GPZ3   40.10 %
P16   1000.00 usec

F1 - Acquisition parameters
ND0   2
TD   128
SFO1   100.6238 MHz
FIDRES 204.515701 Hz
SW   260.157 ppm
FnMODE   QF

F2 - Processing parameters
SI   1024
SF   400.1300000 MHz
WDW   QSINE
SSB   2
LB   0.00 Hz
GB   0
PC   1.00

F1 - Processing parameters
SI   1024
MC2   QF
SF   100.6127690 MHz
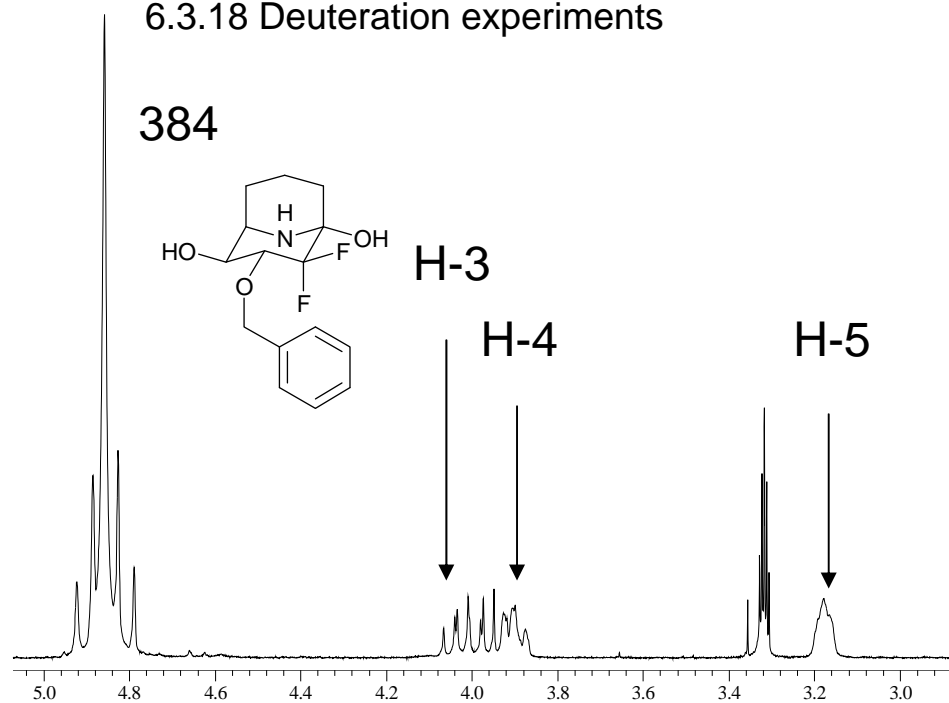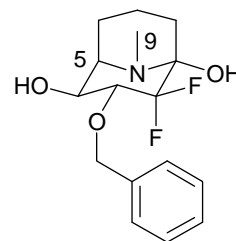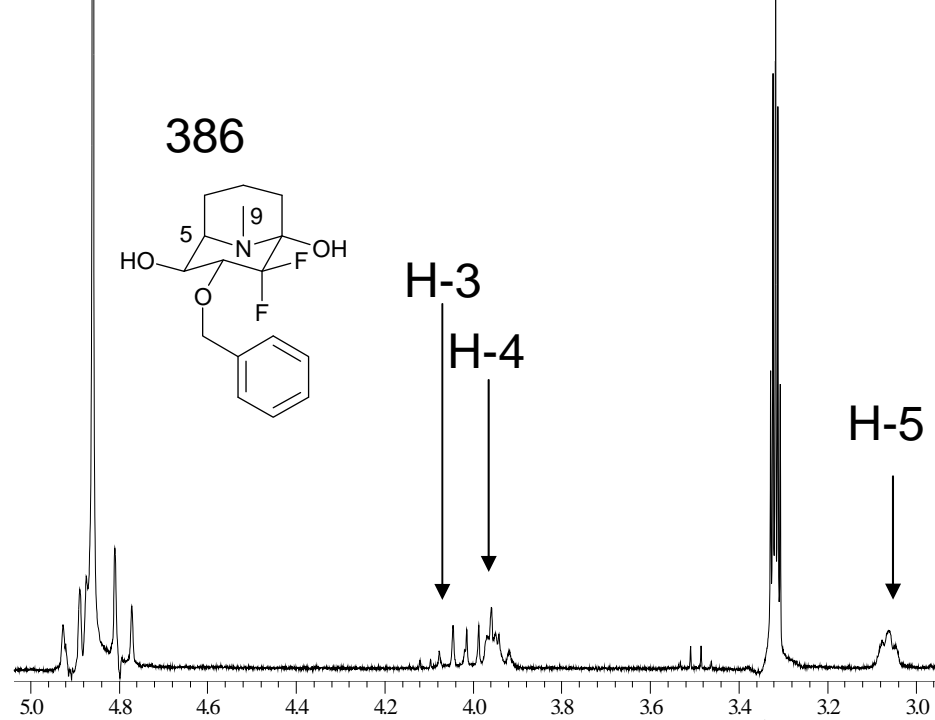WDW   QSINE
SSB   5
LB   0.00 Hz
GB   0

6.3.10 4R*-Acetoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-bicyclo[3.3.1]nonan-1S*-ol 316

JALM078 HMBC grad. /300K

H4   H5

C1

C9

6.3.11 4S*-Aceteoxy-3R*-benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-bicyclo[3.3.1]nona-1R*-ol 258

6.3.12 3-Benzoyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-en-1-one 346

6.3.13 3-Benzyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-enone 366

6.3.14 3R*-Benzyloxy-2,2-difluoro-9-methyl-9-aza-1S*,5R*-bicyclo[3.3.1]nona-1S*,4R*-diol 385

JALM101 HMBC grad. /300K

6.3.16 2,2-difluoro-9-methyl-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,3*R**,4*R**-triol 388

6.3.17 2,2-difluoro-9-allyl-9-aza-1*S**,5*R**-bicyclo[3.3.1]nona-1*S**,3*R**,4*R**-triol 389

JALM112 HMBC grad. /300K

6.3.18 Deuteration experiments
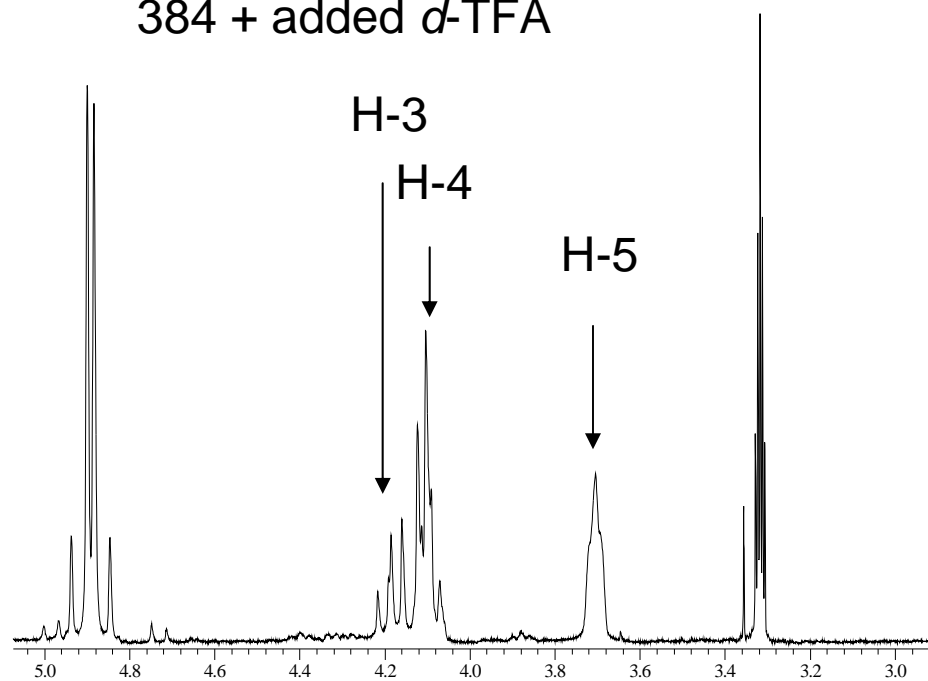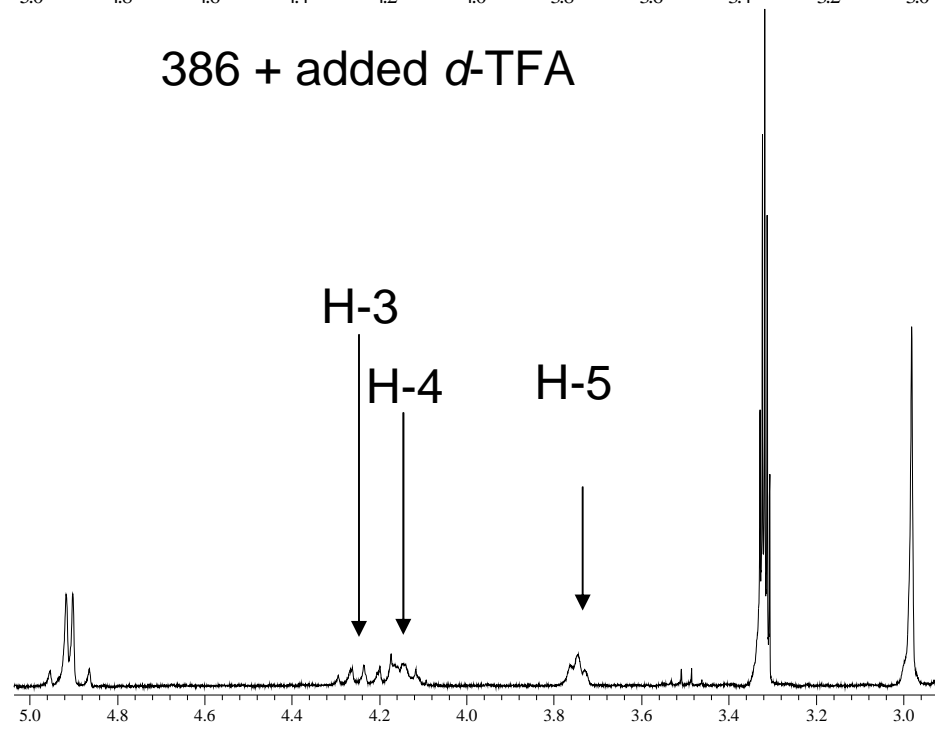
JALM038A NOESY phase /300K
D1=8s Tmix= 1s

H8

H3
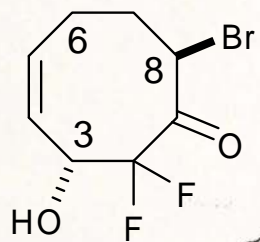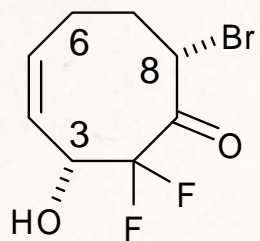
H6 →

Current Data Parameters
NAME   jalm038a
EXPNO   9
PROCNO   1

F2 - Acquisition Parameters
Date_   20040910
Time   15.42
INSTRUM   drx400
PROBHD   5 mm TXI 13C Z
PULPROG   noesyph
TD   2048
SOLVENT   CDCl3
NS   16
DS   16
SWH   6410.256 Hz
FIDRES   3.130008 Hz
AQ   0.1597940 sec
RG   57
DW   78.000 usec
DE   6.00 usec
TE   300.0 K
d0   0.00006578 sec
D1   8.00000000 sec
D8   1.00000000 sec
IN0   0.00015600 sec
MCREST   0.00000000 sec
MCWRK   4.00000000 sec
ST1CNT   128

======== CHANNEL f1 ========
NUC1   1H
P1   9.60 usec
PL1   0.00 dB
SFO1   400.1324008 MHz

F1 - Acquisition parameters
ND0   1
TD   256
SFO1   400.1324 MHz
FIDRES   25.040064 Hz
SW   16.020 ppm
FnMODE   States-TPPI

F2 - Processing parameters
SI   1024
SF   400.1300000 MHz
WDW   QSINE
SSB   2
LB   0.00 Hz
GB   0
PC   1.00

F1 - Processing parameters
SI   1024
MC2   States-TPPI
SF   400.1300000 MHz
WDW   QSINE
SSB   2
LB   0.00 Hz
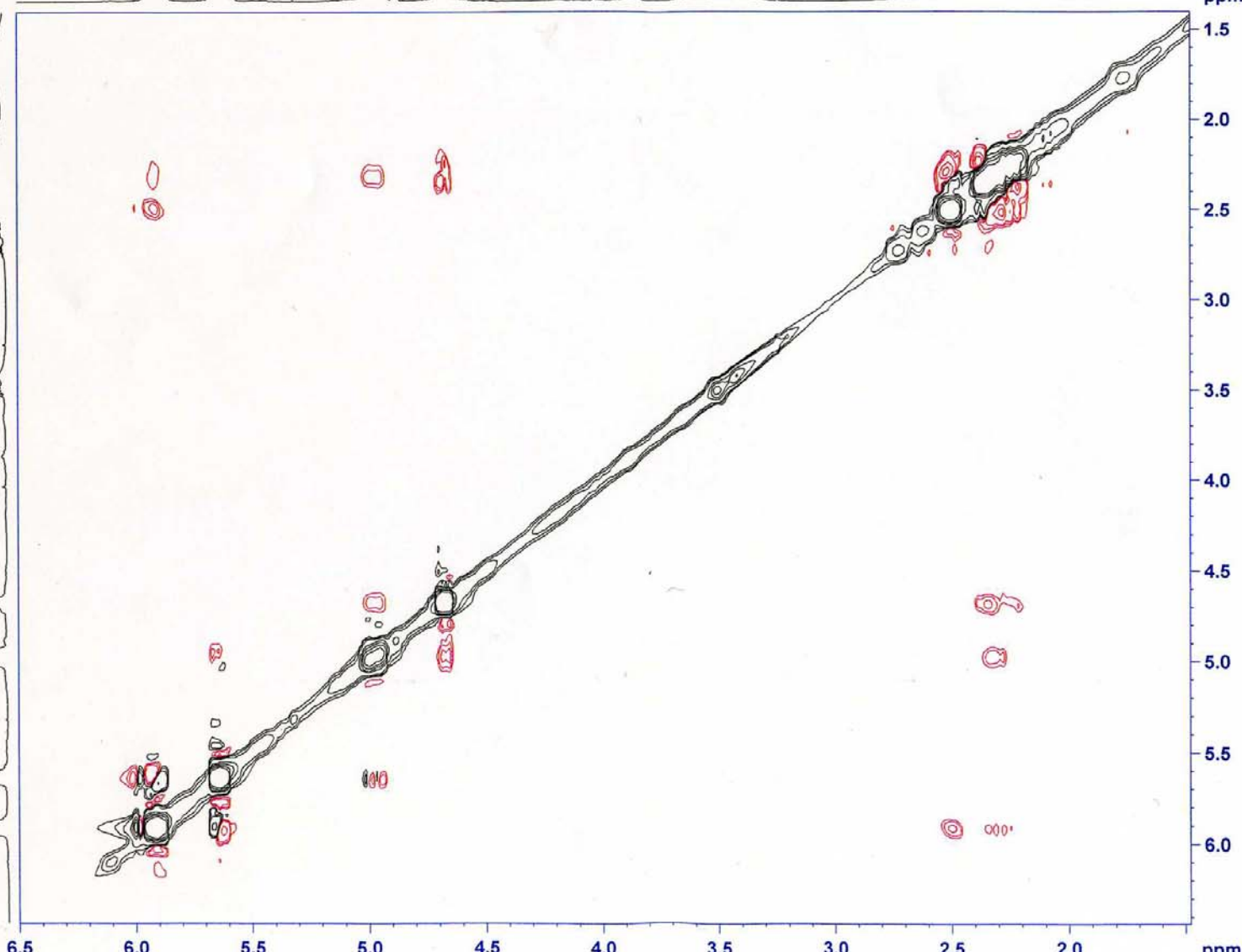GB   0

6.3.20 8*R**-Bromo-2,2-difluoro-3*S**-hydroxy-cyclooct-4*Z*-enone 426

H8

H6

H3