# Sugars

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At the University of Leicester

by

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# Other Work

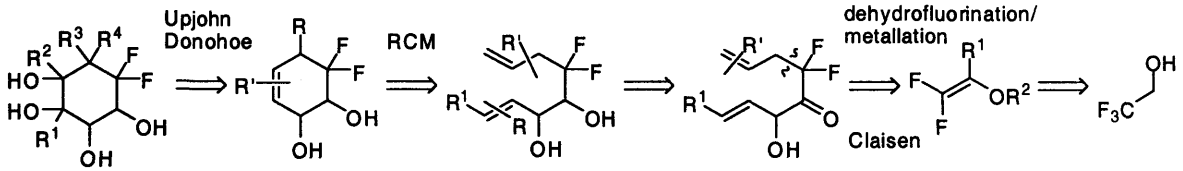
Some of the results described in this thesis have been presented as Oral Communication at national and international conferences:

- "6$^{e}$ Colloque Francophone sur la Chimie Organique du Fluor", Avignon (France) Mai 2005
- "17$^{TH}$ International Symposium On Fluorine Chemistry", Shanghai (China) July 2005;
- "5$^{th}$ Annual RSC Fluorine Subject Group Postgraduate Meeting", Oxford (UK) September 2005.

# Abstract


## Concise syntheses of Difluoroanalogues of Cyclitols and Sugars.

The synthesis of (1*R**,2*R**,3*S**,4*S**)-5,5-difluorocyclohexane-1,2,3,4-tetrol was accomplished with an overall yield of 20 % from trifluoroethanol over 8 steps featuring a key dehydrofluorination/metallation followed by trapping of aldehyde (**scheme**).
The route based on a fluorinated building block approach delivered rapidly a small library of difluoroanalogues of carbasugars using readily available and inexpensive starting materials where the use of protecting group chemistry was reduced to its minimum as well as purification.
This chemistry is unique as a method for the rapid syntheses of difluorinated molecules of this level of complexity and relevance to saccharides.




The synthesis in water of a range of trifluoroethanol ethers represents an atom efficient and sustainable solution to the multigram scale syntheses of some trifluoroethyl ethers; 3-(2',2',2'-Trifluoroethoxy)prop-1-ene was obtained on a mole scale with 99 % yield.

Dehydrofluorination/metallation at low temperature (-100 °C) followed by trapping of aldehyde occurred efficiently with a wide variety of substrates allowing a rapid synthesis of dienols on a comfortable scale (up to 75 mmol). After Claisen rearrangement of the dienols, sodium borohydride was found to be the most diastereoselective as well as practical reducing agents tested for the reduction of the hydroketones.

Ring closing metathesis using second generation Grubbs' catalyst afforded rapidly key difluorinated cyclohexenes in high yield and low catalyst loading from free diols such as (1*S**,2*S**)-6,6-Difluorocyclohex-3-ene-1,2-diol which was obtained with an overall yield of 44 % from trifluoroethanol over 5 steps.

The scope and limitations of Upjohn and Donohoe dihydroxylation procedures were identified for our substrates presenting an extensive variety of substitutions. Dihydroxylation under Upjohn conditions exhibited from average to excellent diastereoselectivity depending of the position and level of substitutions. Donohoe-type dihydroxylations delivered the expected outcome for each substrate in very high diastereoselectivity. Indeed (1*S**,2*S**,3*R**,4*S**,6*S**)-5,5-difluoro-2,6-dimethylcyclo hexane-1,2,3,4-tetrol was obtained as a single diastereoisomer with an overall yield of 11 % from trifluoroethanol over 8 steps.

Also, the use of these intermediates as candidate for analogues of NDP sugars was investigated for a limited number of our substrates such as (1*S**,4*R**,5*R**,6*S**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxycyclohexyl dibenzyl phosphate which was synthesised with an overall yield of 27 % from trifluoroethanol over 8 steps.

## Abbreviations

| | |
|---|---|
| °C | degrees Celsius |
| Å | Angstrom(s) |
| Ac | acetyl |
| anhyd. | anhydrous |
| BAST | *Bis*(2-methoxyethyl)aminosulfur trifluoride |
| Bdmim | 1-Butyl-2,3-dimethylimidazolium chloride |
| Bmim | 1-Butyl-3-methylimidazolium |
| Bn | Benzyl |
| CI | Chemical ionisation |
| d | day(s) |
| DAST | Diethylaminosulfur trifluoride |
| Deoxofluor® | *Bis*(2-methoxyethyl)aminosulfur trifluoride |
| DIBAL | Di*iso*butylaluminium hydride |
| DMF | *N,N*-Dimethylformamide |
| dr | Diastereoisomeric ratio |
| EDTA | Ethylenediaminetetraacetic acid |
| ee | Enantiomeric excess |
| EI | Electron Impact |
| eq. | equivalent(s) |
| ES | Electron Spray |
| Et | Ethyl |
| FAB | Fast Atom Bombardment |
| GC | Gas Chromatography |
| HMBC | Heteronuclear Multiple-Bond Correlation |

| | |
|---|---|
| HMPT | Hexamethylphosphorous triamide |
| HRMS | High Resolution Mass Spectrometry |
| *i*-PrOH | *iso*-Propanol |
| IR | infrared |
| *J* | Coupling constant |
| K-selectride | Potassium tri-*sec*-butylborohydride |
| LAH | Lithium aluminium hydride |
| LDA | Lithium di*iso*propylamine |
| L-selectride | Lithium tri-*sec*-butylborohydride |
| m/z | mass-to-charge ratio |
| *m*-CPBA | *meta*-Chloroperbenzoic acid |
| MHz | Megahertz |
| mol | mole(s) |
| mp | melting point |
| NDP | Nucleoside Diphosphate |
| NMO | *N*-Methylmorpholine *N*-oxide |
| NMR | Nuclear Magnetic Resonance |
| NOE | Nuclear Overhauser Effect |
| NOESY | Nuclear Overhauser Effect Correlation Spectroscopy |
| Ns | o-Nitrobenzenesulfonyl |
| Nu | Nucleophile |
| PG | Protecting group(s) |
| Ph | Phenyl |
| ppm | part(s) per million |
| PTC | Phase Transfer-Catalysis |
| Rf | Retention Factor |

| | |
|---|---|
| rt | Room Temperature |
| sat. | saturated |
| TASF | *tris*-(Dimethylamino)sulfur (trimethylsilyl)difluoride |
| TBAB | Tetra-*n*-butyl ammonium bromide |
| TBAF | Tetra-*n*-butyl ammonium fluoride |
| TBA-$HSO_4$ | Tetra-*n*-butyl ammonium hydrogenosulfate |
| TBAI | Tetra-*n*-butyl ammonium iodide |
| TBS | *tert*-Butyldimethylsilyl Ether |
| *t*-BuLi | *tert*-Butyllithium |
| *t*-BuOH | *tert*-Butanol |
| THF | Tetrahydrofuran |
| TIBAL | Tri*iso*butylaluminum |
| TMEDA | N,N,N′,N′-Tetramethylethylenediamine |
| TMS | trimethylsilane |

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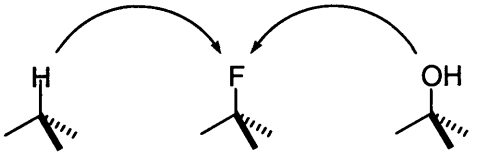
# 1 Introduction

## *1.1 Applications of fluorine in bioorganic chemistry*

The selective introduction of a fluorine atom into a biologically active molecule has been shown to be an effective tool for the modification of its physicochemical properties and consequently its physiological behaviour.[1,2] The high electronegativity of the fluorine atom (4.0 on the Pauling scale as opposed to 2.1 for hydrogen) modifies the behaviour (acidity and basicity) of adjacent functional groups. The Van Der Waals radius of the fluorine atom (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.20 Å),[3] so replacing a hydrogen atom with a fluorine atom creates a minimal steric but a major electronic perturbation. Replacing a hydroxyl group with a fluorine atom creates a minimum electronic perturbation, but results in the loss of hydrogen bonding interactions (**Figure 1**).




minimum steric pertubation

Maximum electronic perturbation

Minimum electronic perturbation

loss of hydrogen bond

**Figure 1.**

Calculations by O'Hagan *et al.*[4,5] have demonstrated that C-F···H-X hydrogen bonds are clearly weaker than C-O···H-X hydrogen bonds. The weaker interaction appears to be due to the higher nuclear charge on the fluorine atom

compacting the surrounding lone pairs. They carried out a survey of organofluorine compounds in the Cambridge Structural Database System (CSDS) which revealed relatively few situations in which a fluorine atom was involved in short contacts (less than 2.3 Å) to an acidic hydrogen atom. The H···F distances recorded in the study ranged between 2.50-2.60 Å, which is close to the sum of the Van Der Waals radii of fluorine and hydrogen whereas the C-F···H-X angles were wider than 100° making the fluorine atom a weak hydrogen bond acceptor but a valuable extra interaction.

Fluorine-containing compounds often exhibit increased thermal stability and resistance to oxidation over their hydrogen counterparts owing to the strength of the carbon-fluorine bond (D=489 kJ $mol^{-1}$). A fluorinated analogue may be able to follow the metabolic pathway of the parent hydrogen compound (*via* enzymes or receptors where stringent steric requirements are imposed) leading to incorporation into the organism. Replacement of hydrogen atoms by fluorine atoms in the molecule results in increased lipid solubility, which aids drug absorption and transport *in vivo*. C-F bonds can alter the lipophilicity of a molecule. In general, fluorination increases lipophilicity with some exceptions. Generally, aromatic $CF_3$ increases lipophilicity. Monofluorinated or trifluorinated alkyl groups have lower lipophilicity than their non-fluorinated counterparts due to the relatively strong dipoles of the CF and $CF_3$ groups.[6] This property has been exploited in drug design, where molecules are required to pass through cell walls and membranes to reach the site at which they are to be active.[2]

## *1.2 Fluoroanalogues of carbasugars and cyclitols*

### 1.2.1 Fluorinated sugars

The literature contains hundreds of fluorinated sugar analogues; some of them have been used to probe interactions at enzyme and substrate levels.[7] Indeed; if an hydroxyl group is believed to act as an hydrogen bond donor to an acceptor group on a receptor, replacement by a fluorine atom will delete that potential interaction while preserving the size and electronic character of the native species as closely as possible and the effect of the deletion could then be seen in reduced binding affinity.

A recent example of this approach used randomised *O*-methylation to prepare a small library of galactose derivatives which were then exposed to a lectin (*Sambucus Nigra* Agglutinin SNA).[8] Good ligands were identified using transferred NOE and saturation transfer difference NMR. The determined outcomes proved consistent with established theories of galactoside recognition by the lectin, thus establishing a rapid NMR screening method for ligand identification.

NMR spectroscopy has been used extensively to probe the conformational consequences of carbohydrate/protein binding,[9] and $^{19}F$ NMR spectra have been reported for many fluorinated carbohydrates.[10] The wide range of vicinal $^{3}J_{H\text{-}F}$ coupling constants makes them highly valuable probes of dihedral angles and thus a rich source of conformational insight. There is current interest in the use of fluorinated ligands for $^{19}F$ NMR studies of the internal space within proteins,[11] and given the current high level of activity in the design and synthesis of partially fluorinated proteins,[12] this area can be expected to

become more active. Heteronuclear NOE methods are particularly useful when fluorinated ligands are available. When magnetisation can be transferred from specific sites on the ligand into the binding protein without any of the problems that arise from overlapping proton signals[13] much valuable information can be obtained. If the SNA/galactoside library binding screen, mentioned previously, had been performed with fluorinated ligands, it would be possible in principle to use the fluorine atom on each ligand as an NOE probe to identify key residues in the binding site of the lectin. The bound conformation could be probed also, using vicinal $^3J_{H\text{-}F}$ coupling constants. Once the array has been characterised and key interactions identified, techniques such as computational fluorine scanning could be used to identify particularly effective ligands.[14]

In the case of the axial anomer, the most common explanation for the anomeric effect (**Figure 2**) is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the σ* orbital associated with the exocyclic C-O bond. The *endo* and *exo* anomeric effects modulate strongly the conformation (and therefore the shape) and chemical reactivity of glycosides.

Axial anomer

Equatorial anomer
No stabilisation from anomeric effect

**Figure 2.** Anomeric effect.

Molecules in which $CF_2$ replaces the ring oxygen could be a possible mode of carbohydrate mimicry; the electron-withdrawing $CF_2$ centre would disrupt the

processes of anomeric equilibration and alter radically the stereoelectronic influences upon, and stability of, the glycosidic linkage.

There has been considerable interest in modified nucleosides such as 5-iodo-2'-deoxyuridine (IDU) **1** (**Figure 3**) and the corresponding carbocyclic compound **2**. Compounds from both series exhibit interesting and useful anti-viral properties. The replacement of the heterocyclic oxygen atom of a sugar is a drastic change in terms of the stereoelectronic effect on the rest of the molecule. Proposing that there is an isosteric relationship between an oxygen atom and a fluoromethylene group, Biggadike *et al.*[15] explored the synthesis of two carbocyclic fluorinated carbocyclic nucleosides **3** and **4**. The fluorination step was realised with DAST (diethylaminosulfur trifluoride) (*cf.* **1.3.**). Interestingly, 6'-α-fluoro-compound **4** was highly active against herpes simplex virus type 1 (HSV-1) infected cells while the 6'-β-fluoro-compound **3** was at least two orders of magnitude less active.

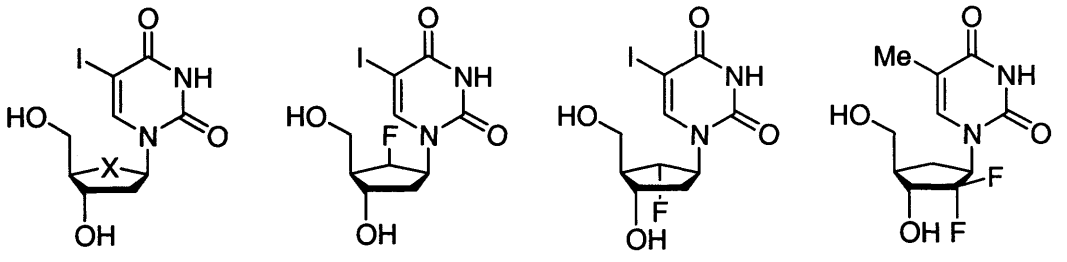


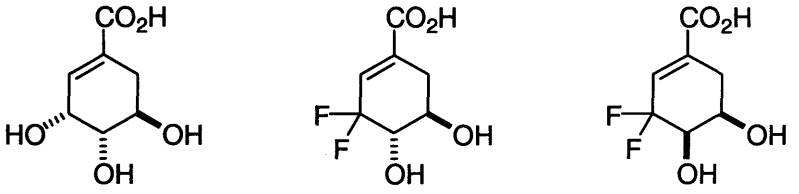

**Figure 3.** Fluoroanalogues of nucleosides.

In contrast, Biggadike *et al.*[16] reported that the 6',6'-difluoro-compound **5** (**Figure 3**) was not active against HSV-1. Nevertheless, Marquez *et al.*[17] have shown that the introduction of one fluorine atom can change the conformer

populations of nucleosides implicating a possible conformational problem in the reactivity of compound such as **5**.

### 1.2.2 Fluorinated cyclitols

Shikimic acid **6** (**Figure 4**) is an important intermediate in the biosynthetic sequence known as the shikimate pathway which converts carbohydrate precursors to essential aromatic α-amino acids (Phe, Tyr, Trp) in plants, fungi and microorganisms.[18] The absence of the shikimate pathway from mammals has spurred an intense search for specific enzyme inhibitors along the pathway as potential herbicides and antimicrobial agents.

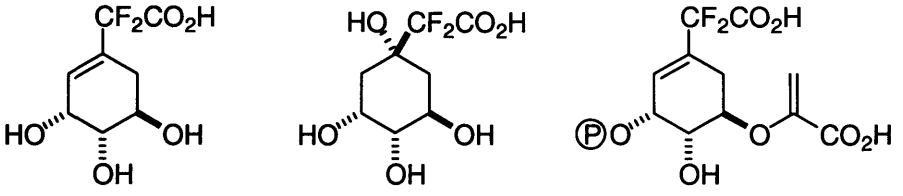



**6** **7** **8**

**Figure 4.**

Recently the existence of a functional shikimate pathway in *apicoplexan* parasites was reported,[19] which thus provides attractive targets for the development of new antiparasite agents. Because of the interest shown in the pathway, increasing effort had been directed toward the synthesis of analogues; Singh *et al.*[20] have reported of difluoro-substituted Shikimic acids **7** and **8** (**Figure 4**) from natural quinic acid *via* a *gem*-difluorination of an α,β-unsaturated ketone with DAST. Hydroxyl group replacement at position 3 obviously prevents progression *via* phosphorylation; these compounds are presumably intended as substrate analogues for the subsequent kinase.

On the other hand, Whitehead *et al.*[18] have reported the synthesis of difluoromethylene homologue **9** (**Figure 5**) of shikimic acid and the corresponding homologue **10** of (-)-quinic acid *via* a building block approach. These compounds were selected as possible prodrugs for the intracellular generation of the difluoromethylene homologue **11** of 5-enolpyruvylshikimic acid-3-phosphate. Compound **11** was targeted as a likely competitive inhibitor of *chorismate synthetase*, the enzyme which catalyses the seventh step of the Shikimic acid pathway. These difluoroanalogues were obtained using the Reformatsky reaction between ethyl bromodifluoroacetate and the appropriate ketone.

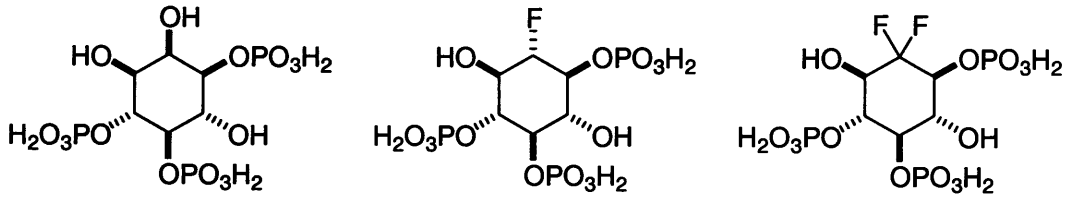



**9** **10** **11**

**Figure 5.**

The discovery that D-myo-Inositol-1,4,5-triphosphate-Ins(1,4,5)$P_3$ **12** is able to act as a second messenger in cells, and can trigger the mobilisation of $Ca^{2+}$ from intramolecular storage[21] has led to widespread interest into the metabolism and effects of inositol phosphates. The isosteric and isoelectronic replacement of a hydroxyl group with a fluorine atom has been adopted as a common strategy in the preparation of analogues of inositol and its phosphates. Potter *et al.*[22] have reported the synthesis of fluorinated analogues of Ins(1,4,5)$P_3$ **13** and **14** (**Figure 6**). They revealed the interaction of **13** and **14** with the $Ca^{2+}$-releasing receptor of SH-SY5Y *neuroblastoma* cells and the metabolic enzymes Ins(1,4,5)$P_3$-3-kinase and 5-phosphatase. The fluorinated analogue

**13** can bind to the Ins(1,4,5)$P_3$ receptor with high affinity and mobilised $Ca^{2+}$ ions; also, L-2-deoxy-2,2-difluoro- Ins(1,4,5)$P_3$ **14** acted as a potent inhibitor of the 3-kinase and 5-phosphatase.




**12** **13** **14**

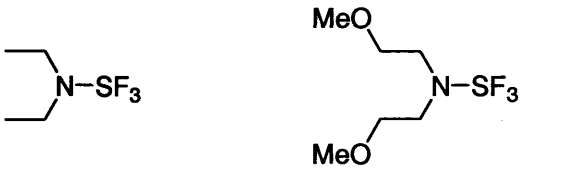
**Figure 6.**

## *1.3 Selective fluorination*

### 1.3.1 Generalities

The continuing discovery of biologically active fluoroorganic compounds has led to the development of numerous selective fluorination methods. Different approaches exist for the synthesis of selectively fluorinated molecules; the classical method involves direct fluorination *via* the use of fluorinating agents. The introduction of the C-F bond can be achieved *via* nucleophilic and electrophilic sources.

The use of elemental fluorine, sulfur tetrafluoride, diethylaminosulfur trifluoride[23] (DAST) **15** (**Figure 7**) and other reagents have been described extensively. Although it is possible to achieve fluorination in high yields, and with selectivity in a limited number of cases, many fluorinating agents are highly toxic and difficult to handle. For example, DAST is reported to be explosive over 60 °C due to an exothermic decomposition.




DAST **15**

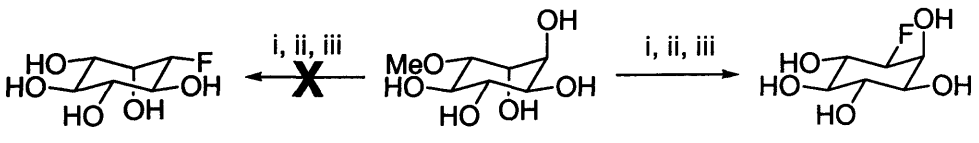
Deoxofluor®(BAST) **16**

**Figure 7.**

In case where functionality is dense, extensive protecting group chemistry is required. DAST and *bis*(2-methoxyethyl)aminosulfur trifluoride[24] (BAST, Deoxofluor®) **16** (**Figure 7**) are effective for the conversion of alcohols and carbonyl groups to CH-F and $CF_2$ groups respectively.[25] BAST has been recently developed; this fluorinating agent presents enhanced thermal stability.[24] The use of fluorinating agents can also lead to side-reaction and fragmentation (**Scheme 1**); unexpected side-reactions with DAST are NPG (neighbouring group participation), elimination and 1,2-group shifts, typical of processes with developed carbenium ion character.

### 1.3.2 Examples

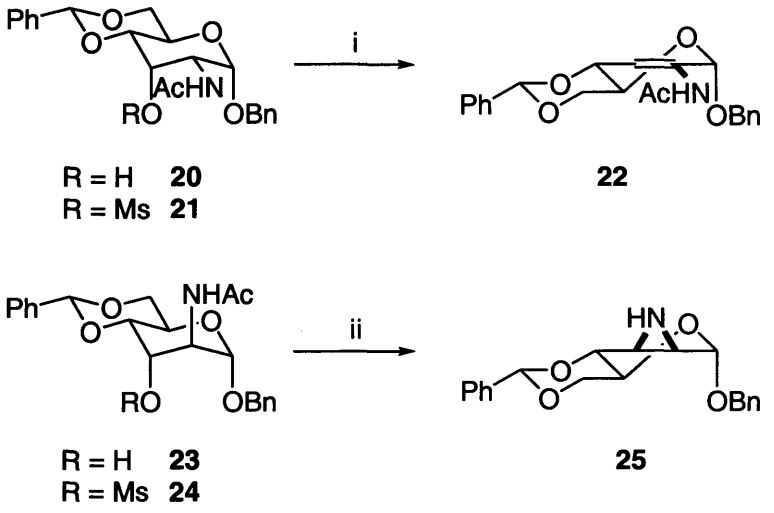
In this unusual synthesis (**Scheme 1**) reported by Kozikowski *et al.*[26] the fluoroanalogue of cyclitol **18** is obtained *via* the fluorinating agent DAST, without protection of the hydroxyl groups.




**19** **17** **18**

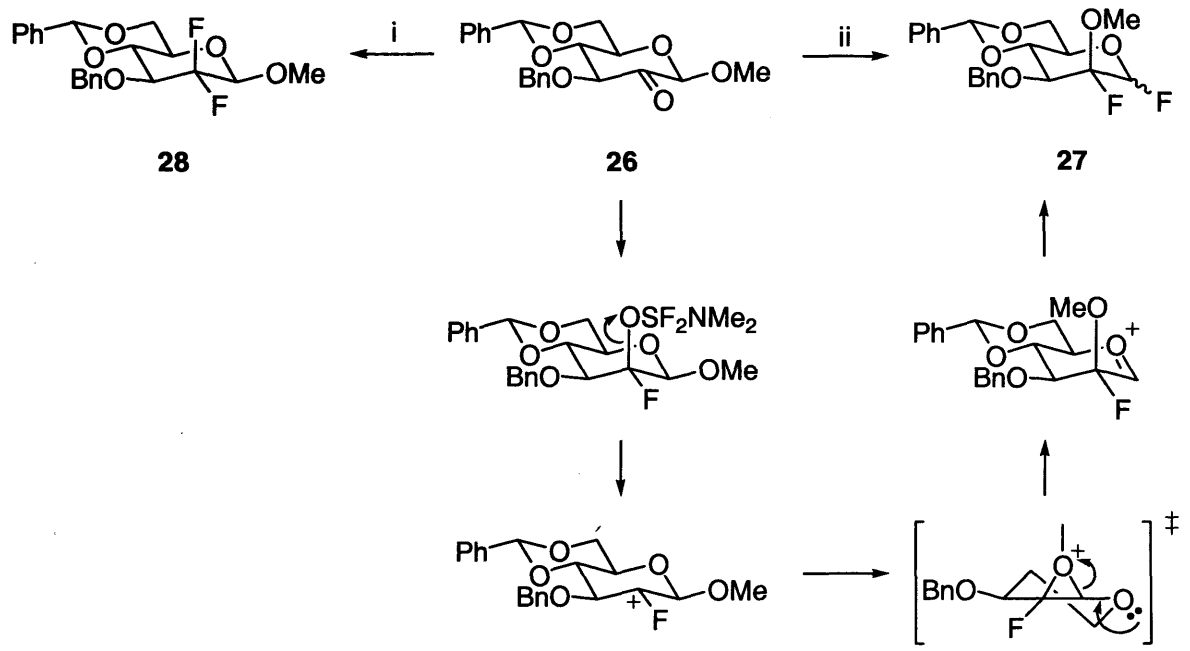
**Scheme 1.** Reagents and conditions: i) DAST, dichloromethane, -40 to -30 °C, 0.5 h; ii) 0 °C, 3 h; iii) $BBr_3$, dichloromethane, -40 °C, 19h.

Significant side reactions involving NGP were observed by Sharma *et al.*[27] in their attempts to substitute fluorine for the 3-OH in 2-acetamido-2-deoxy-D-hexopyranosides (**Scheme 2**). Elimination, to yield enamine **22**, predominated in the reaction of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside **20** (as well as its 3-mesylate **21**) with DAST. The different outcomes from **20** and **23** arise from stereoelectronic control; in **20**, the scissile C-O bond is antiperiplanar to a C-H bond and elimination ensues. However, in **23**, the C-N bond is antiperiplanar to the scissile C-O, a perfect arrangement for neighbouring group participation.



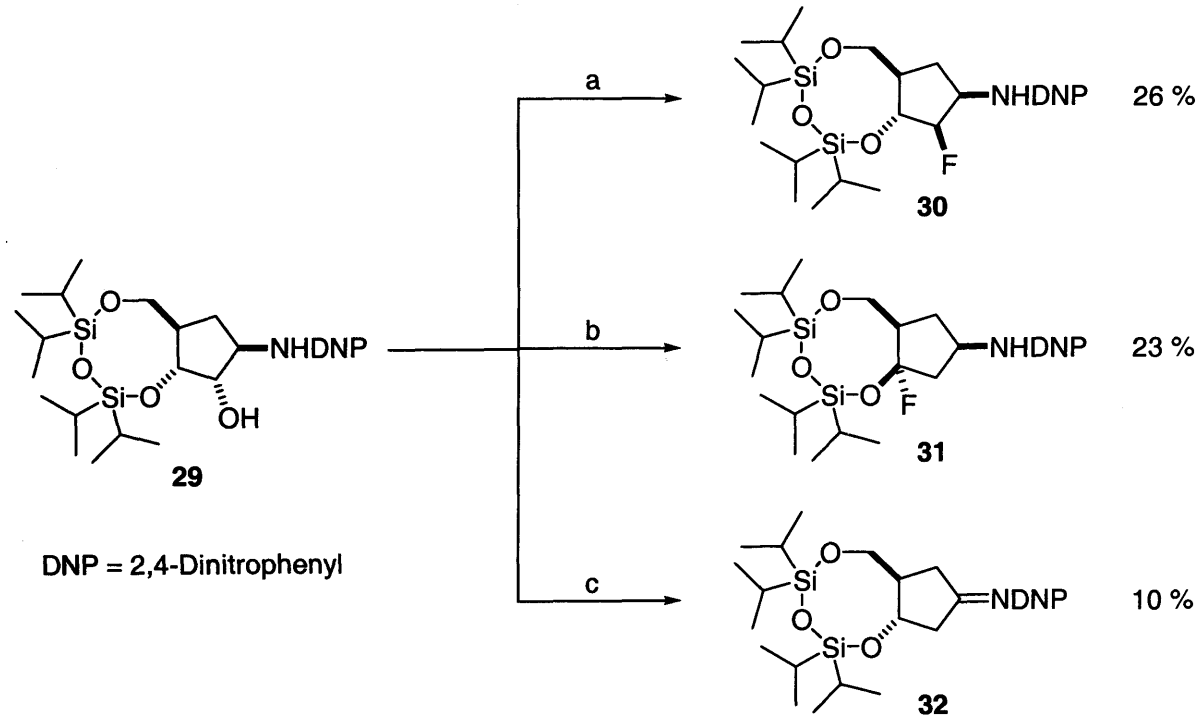

**Scheme 2.** Reagents and conditions: i) DAST, 70 %; ii) DAST, 84 %.

Similarly, Castillon *et al.*[28] reported some limitations in the selectivity of this reagent. Indeed the difluorination by DAST of protected sugar **26** resulted in the formation of two products (**Scheme 3**), the desired difluorinated species **28** and the product of migration **27**. The side product **27** arises from the attack by the equatorial methoxy group at the monofluorinated carbon, resulting in migration of this group and fluorination at the anomeric position.




**Scheme 3.** Reagents and conditions: i) DAST, dichloromethane, 24 h, 0 °C, 80 %; ii) DAST, benzene, reflux (part of the structure of the transition state was omitted for clarity).

Biggadike *et al.*[29] have described elimination and 1,2-shift in carbocyclic nucleoside chemistry (**Scheme 4**).




**Scheme 4.** Reagents and conditions: DAST, py., 0 °C.

Pathway (a) delivered the desired fluoro compound **30** in low yield because of competing side-reactions; a 1,2 hydride shift lead to the fluorination of **31** (path b) in 23 % yield and **32** resulted from elimination and double bond migration (path c) in 10 % yield.

The synthesis of sugar analogues and related species is of constant and current interest. Fluorinated cyclitol analogues have been prepared successfully by many groups including those of Carless,[30] Potter,[22] Kozikowski[26] and Prestwich.[31] Most use fluorination methods in which highly protected cyclitols are transformed *via* a free hydroxyl or carbonyl group (**Figure 8**).

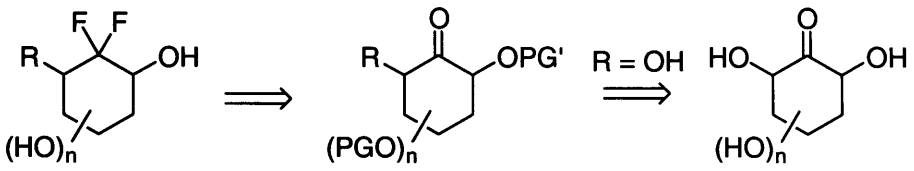
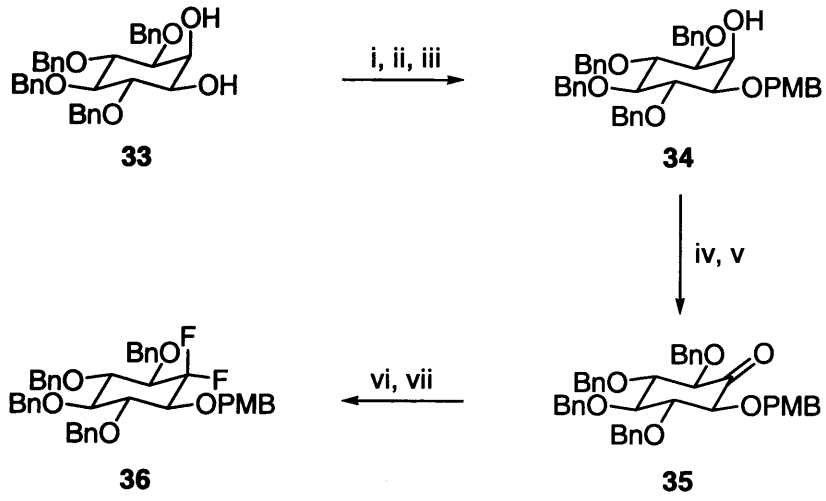



**Figure 8.**

It is worth mentioning a limitation to this particular strategy; there are no obvious and convenient sources of suitable precursors to obtain a substituted analogue (R equal Methyl or hydroxymethyl).

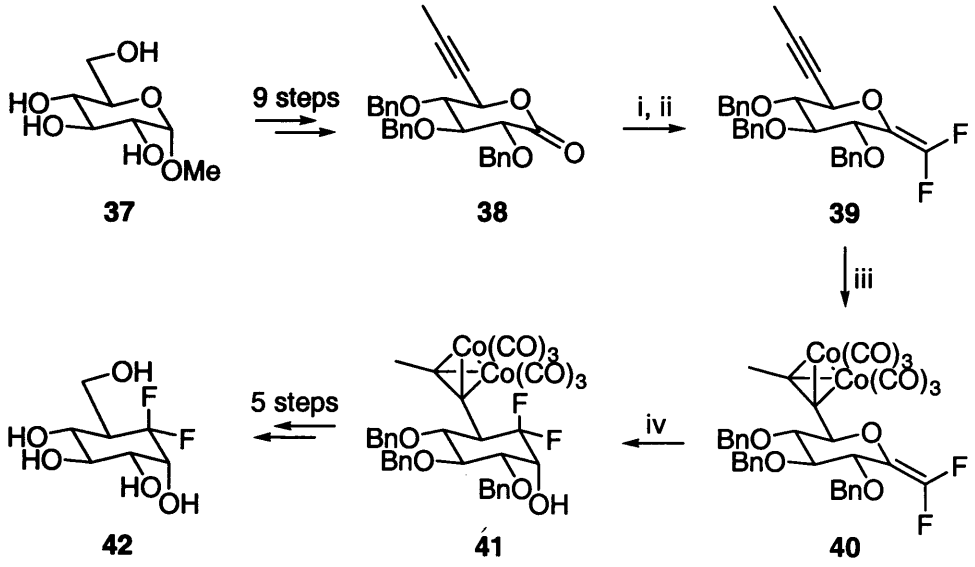
Potter *et al.*[22] have reported (**Scheme 5**) the synthesis of difluoroanalogues **36** *via* direct fluorination of protected ketone **35** using DAST. This route to fluoroanalogues of cyclitols involved protected starting material **33** and many further protection/deprotection steps to achieve this pathway, which lead to a fluoroanalogue of an inositol. In addition, the fluorination step involved twelve equivalents of DAST, which imposes a severe limitation of scale.




**Scheme 5.** Reagents and conditions: i) $Bu_2SnO$, Toluene, reflux, 3h; ii) CsF, KI, *p*-$MeOC_6H_4Cl$, DMF, rt, 24 h; iii) aq, $NaHCO_3$; iv) $Ac_2O$ (24 eq.), DMSO; v) aq. $NaHCO_3$; vi) DAST (12eq.), dichloromethane, rt, 12 h; vii) aq. $NaHCO_3$.

## *1.4 TIBAL-Induced Rearrangement Approach*

In a recent example, Sinaÿ *et al.*[32] obtained a gem-difluoro analogue of carba-glucopyranose **42** (**Scheme 6**). The fluorination step here is a difluoromethylenation using $CBr_2F_2$. The key rearrangement was performed through a two step one pot procedure that involved the initial complexation of the alkyne by dicobalt octacarbonyl followed by the reductive TIBAL-induced rearrangement of the gem-difluoroalkene precursor **40**. The route delivered the difluoro analogue of carba-glucose **42** with an overall yield of 8% over 17 steps from glucose methylated in anomeric position **37**. Furthermore, it is a linear synthesis, so one substrate delivers one product; 7 steps are also required from gem-difluoroalkene **40** to obtain the β anomer only.



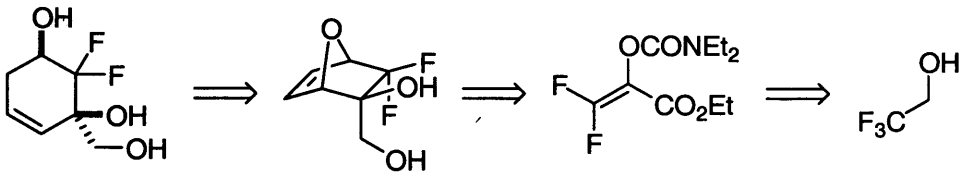

**Scheme 6.** Reagents and conditions: i) HMPT (5 eq.), THF, -40 °C to rt; ii) $CBr_2F_2$ (5 eq.), Zn, HMPT (5 eq.), THF, rt to reflux, 1 h, 95 % (over 2 steps); iii) $[Co_2(CO)_8]$ (1.5 eq.), dichloromethane, rt, 2 h; iv) TIBAL (5 eq.), toluene, rt, 2.5 h.

## *1.5 Building block approach*

An alternative approach consists of the use of building blocks, this has been developed as a more controlled approach to selective fluorination. This building block approach involves the synthesis of fluorine-containing compounds from a fluorinated starting material by carbon-carbon bond formation. The fluorinated starting material should be easy to handle, commercially available and sustainable (many fluorinated starting materials with useful properties are becoming unavailable because of the Montreal and Kyoto Protocol). The advantage of a building block approach is that it could deliver numerous compounds from a single starting material. Indeed direct fluorination affords only one molecule from a given starting material and cannot deliver libraries of target compounds.

Therefore, an attractive approach to highly functionalised fluorinated molecules would involve the use of simple, easily-derived fluorine-containing building block

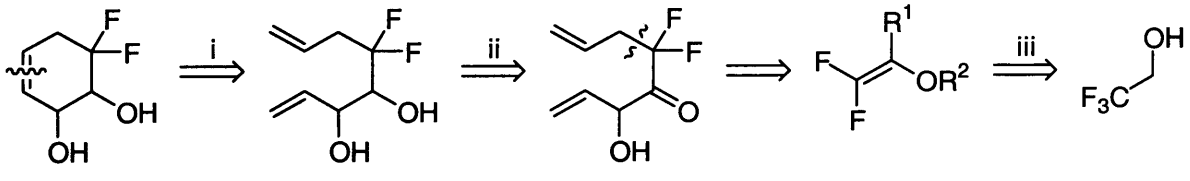
such as trifluoroethanol. A recent paper[33] reported the useful conversion of trifluoroethanol **46** (**Scheme 7**) to fluoroanalogues of cyclitols. Alkenoate **45** prepared on a multigram scale from trifluoroethanol **46** underwent cycloaddition with furan in good yield leading to intermediate **44** after one more step. Ring opening afforded difluoro-cyclitol **43** after deprotection.




**43** **44** **45** **46**

**Scheme 7.**

A building block approach to obtain difluoroanalogues of cyclitols **47** was proposed based on retrosynthetic analysis (**Scheme 8**) indicated by the path i; a ring closing metathesis reaction would convert diols **48** to key cyclohexenes **47**. The corresponding difluoroketones **48** could be synthesised from difluorovinyl ether **49** (path ii) which underwent [3,3]-Claisen rearrangement with appropriate $R_2$. These ethers can be prepared from commercially available trifluoroethanol **46** (path iii).




**47** **48** **49** **46**

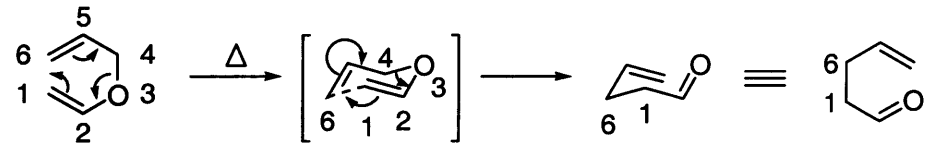
**Scheme 8.**

## *1.6 [3,3]-Claisen sigmatropic rearrangement*

### 1.6.1 Generalities

The Claisen rearrangement is a high-performance method for carbon-carbon bond formation.[34] The first example of a thermal [3,3]-sigmatropic rearrangement of an aliphatic allyl vinyl ether was reported by Ludwig Claisen in 1912.[35] Development of the Claisen rearrangement, which now involves a variety of modified variants, has made this reaction widely applicable to the synthesis of organic molecules, in particular to natural product synthesis.

A sigmatropic rearrangement involves an intramolecular migration of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π system becoming reorganised in the process. In its simplest form, the rearrangement is exemplified by the transformation of an allyl vinyl ether to a γ,δ-unsaturated carbonyl compound (**Scheme 9**).[36]




**50** **51** **52**

**Scheme 9.** Rearrangement of allyl vinyl ether.

The Claisen rearrangement is a unimolecular process with activation parameters that suggest a cyclic transition state. Stereochemical studies have revealed transfer of asymmetry from the double bonds to a newly formed σ bond in a manner that suggests not only a transition state with cyclic delocalisation of the six electrons of the original π bond and the C-O σ bond but a three-dimensional geometry which is chair-like (**Scheme 9**).[37] The

observations could be rationalised by formation of a chair-like oxacyclohexanediyl or zwitterion-like transition state or intermediate resulting from complete C1-C6 bond making (**Figure 9**). Alternatively, dissociation of the C4-O bond into an oxaallyl-allyl radical pair or an enolate ion and an allyl cation pair in chair-like relationship can also account for the stereochemistry provided that tumbling of one or the other of the three heavy atom units does not occur.

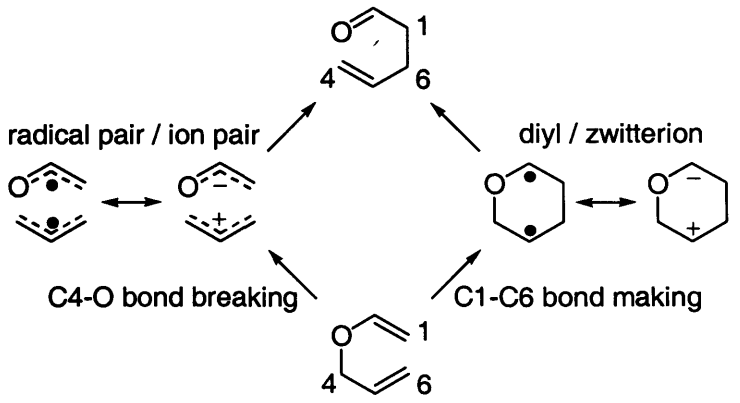



**Figure 9.**

The Claisen rearrangement is defined as a pericyclic process in which, by definition bond breaking and bond making occur through an acyclic array of interacting orbitals. Gajewski *et al.*[38,39] showed that the C4-O bond breaking proceeds somewhat ahead of C1-C6 bond making; this theory has been supported by *ab initio* calculations[40] while Dewar *et al.* argued that bond formation is more advanced than C-O cleavage which implies more diyl character in the transition state.[41] In addition, Gajewski[37] investigated the Claisen rearrangement response to solvents and substituents and established a variation in transition state according to different substituents

### 1.6.2 Substituent effects

The Claisen rearrangement tolerates a very wide range of functional groups and substitution patterns. Donor or acceptor groups at various sites of six-atom backbone can have a rate-accelerating or -retarding effect.[42] Burrows and Carpenter[43] predicted and observed an acceleration of the reaction when an electron acceptor was placed on carbon 2, 4 or 5 (**Figure 10**). The Claisen rearrangement in these cases was more rapid than for the unsubstituted allyl vinyl ether. In contrast, the rate was slowed by the presence of an electron acceptor on carbon 1 or 6.

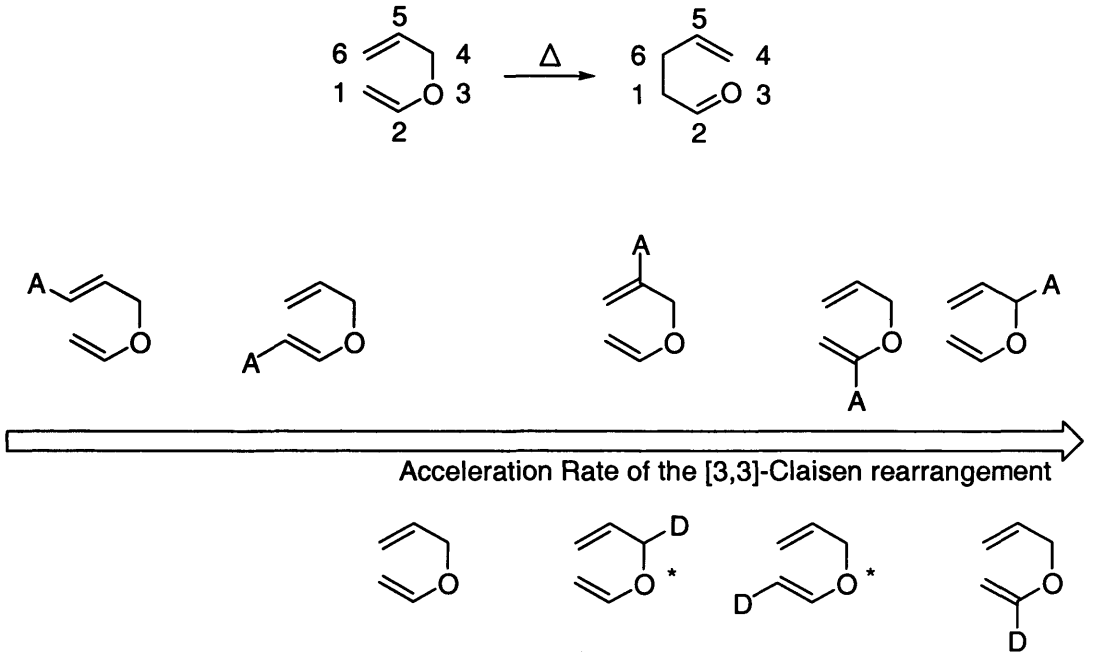
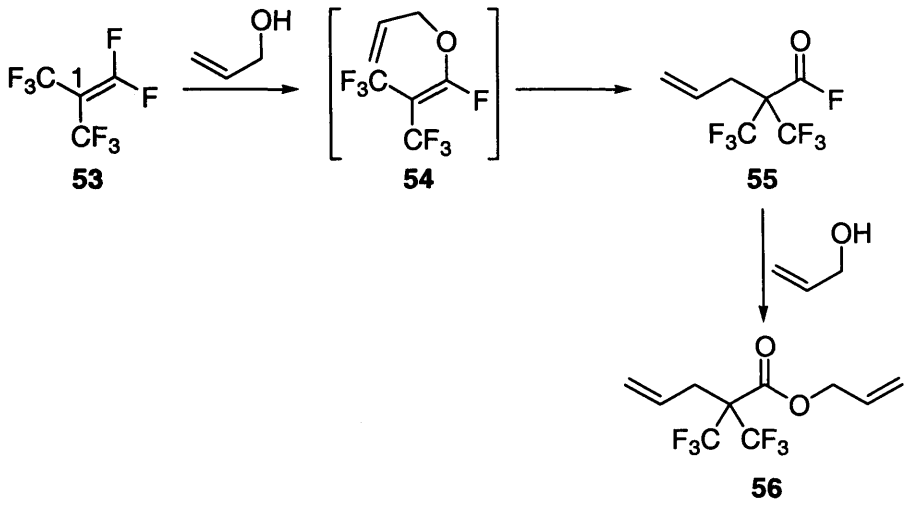



**Figure 10.** A = acceptor; D = donor; *: predicted result

Sigmatropic rearrangement of fluorinated substrates are most attractive reactions for the interconversion of selectively fluorinated substrates and for the elaboration of simple and readily available fluorinated building blocks. With the correct design of the rearrangement system, fluorine atom substituent effects can be exploited to the full, allowing thermal rearrangements to occur at unusually low temperatures or providing a driving force for changes in

equilibrium position. In view of the building block approach, it is of interest to examine the use of [3,3]-sigmatropic rearrangements to introduce fluorine into organic compounds. One of the earliest observations of acceleration of the Claisen rearrangement by fluorine atoms was made by Krespan *et al.*[44] when they attempted to prepare a number of allyl vinyl ethers with fluorine substitution in the vinyl moiety (**Scheme 10**). The reaction of allyl alcohol and octafluoroisobutene **53** lead to vinyl ether **54**, with fluorine bound at C2 position, which rearranges below 50 °C.




**Scheme 10.**

This rearrangement appears to be assisted by the rehybridisation from $sp^2$ to $sp^3$ of the $CF_2$ centre (geminal fluorines on $sp^2$ carbon are destabilised relative to geminal fluorines on $sp^3$ carbon by approximately 5 Kcal $mol^{-1}$). Rearrangement of allyl fluorovinyl ethers with fluorine in the terminal position gives rise to α-fluorocarbonyl compounds. Normant *et al.*[45] found that with increasing fluorine substitution, lower temperatures could be used to accomplish the rearrangement. Thus **57** (**Table 1**) rearranges at -20 °C, while **58** rearranges at -35 °C and **59** rearranges at -50 °C.

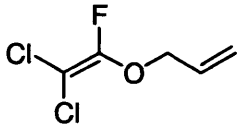
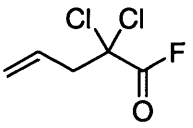
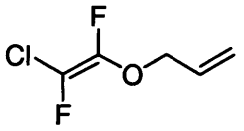
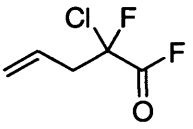
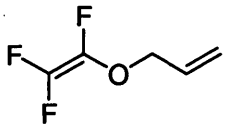
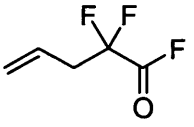
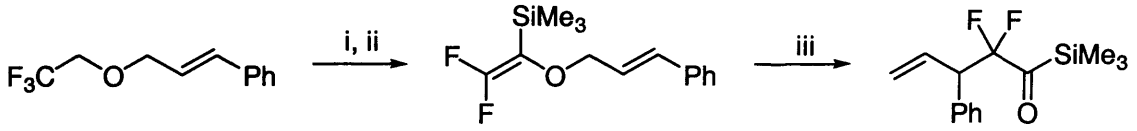
| Allyl Vinyl Ether | Temperature (°C) | Product |
|---|---|---|
|  **57** | -20 |  **60** |
|  **58** | -35 |  **61** |
|  **59** | -50 |  **62** |

**Table 1.**

Metcalfe *et al.*[46] have reported the synthesis of α,α-difluoroacylsilane *via* Claisen rearrangement (**Scheme 11**). Trifluoroether **63** undergoes dehydrofluorination/metallation followed by silicon trapping affording difluoro vinyl silane **64** which rearrange in difluoro ketone **65**. The reactions described by those authors are facile and faster than the non-fluorinated cases.



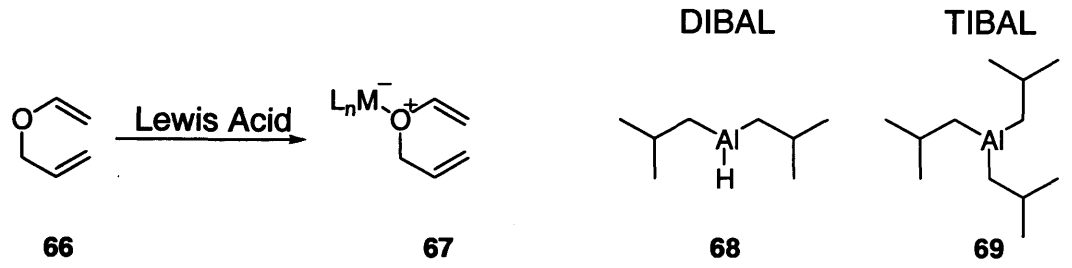
**63** **64** **65**

**Scheme 11.** Reagents and conditions: i) LDA/TMSCl (3.3 eq.) (inverse addition), -100 °C, THF; ii) -100 to -40 °C, 88 %; iii) 80 °C, $CCl_4$.

### 1.6.3 Catalysis

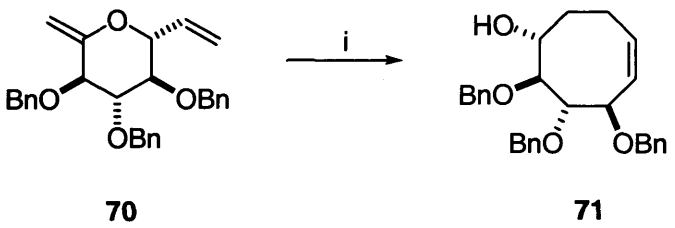
[3,3]-Claisen sigmatropic rearrangement can be catalysed by a number of Brönsted and Lewis acids, and even weak acids like silica gel or Celite. The metal or a proton can coordinate to the oxygen weakening the C-O bond (compound **67**), and leading more easily to rearrangement.[47] Trivalent

organoaluminium reagents give good results for regio- and stereospecific rearrangement. Lewis acids such as DIBAL **68** (**Scheme 12**) can catalyse those sigmatropic rearrangements.




**Scheme 12.**

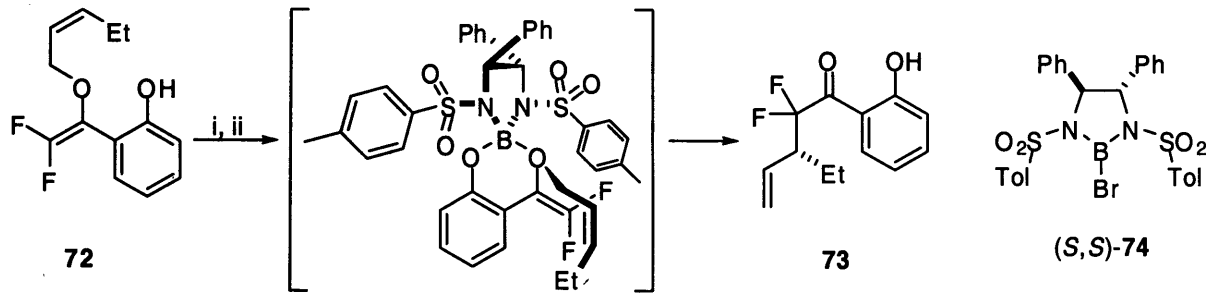
The tri*iso*butylaluminium (TIBAL) **69** promoted Claisen rearrangement of 2-methylene-6-vinyl-pyran derivatives, which afford cyclooctanic compounds by insertion of a $C_2$ unit, has been reported by Sinaÿ *et al.*[48] for the synthesis of carbohydrate mimetics; the cyclooctanol derivative **71** (**Scheme 13**) was smoothly obtained in 96 % yield from the TIBAL-catalysed sigmatropic rearrangement of the gluco derivative **70**. Here, the trialkylaluminium reagent was used as a reducing agents as well as Lewis acid, therefore the sigmatropic rearrangement delivered directly the reduced ketone **71**.




**Scheme 13.** Reagents and conditions: i) TIBAL, toluene, 50 °C, 0.5 h., 96 %.

The development of preparative methods for chiral organofluorine compounds is very important in the field of medicinal chemistry. The enantioselective Claisen rearrangement of difluorovinyl allyl ethers (**Scheme 14**) was achieved,

for the first time by Taguchi *et al.*,[49] in moderate to good enantioselectivity using a chiral boron reagent **74** as the Lewis acid. They obtained difluoroketone **73** with 43 % ee.




72 73 (*S*,*S*)-**74**

**Scheme 14.** Reagents and conditions: i) (*S*,*S*)-**74**, $Et_3N$, dichloromethane, -78 °C; ii) rt., 6 h, 58 %, ee 43 %.

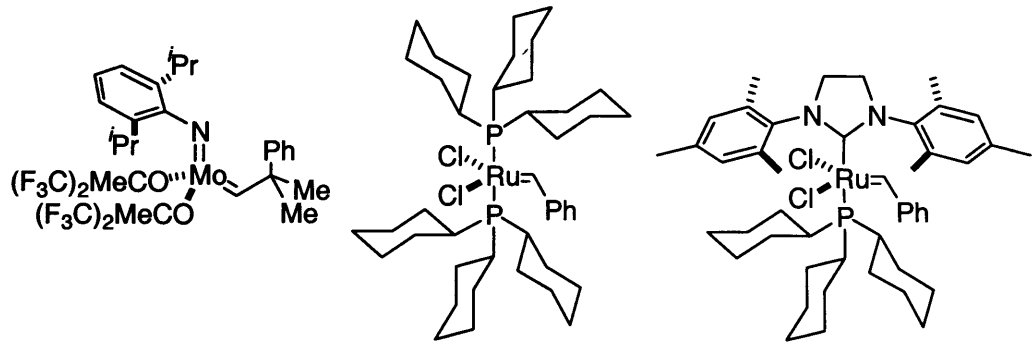
The efficiency of this system is based on the σ-bond formation between the chiral boron reagent **74** and the phenolic hydroxy group in the substrate and the subsequent coordination of the ethereal oxygen to the boron atom to form a rigid environment and to promote the reaction at low temperature. Furthermore, in the chiral boron-mediated Claisen rearrangement, the reaction temperature and enantioselectivity were found to affected by the configuration of the olefin (*E* or *Z*) and the steric bulkiness of the substituent at the γ-position consistent with passage through a highly organised transition state.

## *1.7 Ring closing metathesis*

### 1.7.1 Generalities

Over the past 15 years, the olefin metathesis reaction has attracted increasing attention as a versatile carbon-carbon bond-forming method. [50-53] The success of the alkene-metathesis reaction and the many stunning and ingenious

situations in which it has been applied are largely due to the advent of today's readily available catalyst systems that display high activity, excellent functional group tolerance, an access to a wide range of ring size and mild reaction conditions. The three such catalysts most routinely used by organic chemists (all of which are commercially available) are Schrock's catalyst **75**, first and second generation Grubbs' catalyst **76** and **77** respectively (**Figure 11**).[54]




**75** **76** **77**

**Figure 11.** Commonly used alkene metathesis initiators (catalysts).

The molybdenum-based catalyst **75** was introduced by the Schrock group in 1990.[55] Catalyst **75** displays superb metathesis activity with a wide variety of alkene substrates, and is particular useful for the formation of crowded systems. The singular drawback of catalyst **75** is its pronounced sensitivity to oxygen, moisture, and certain polar or protic functional groups owing to electrophilicity of the high-oxidation-state transition-metal centre.[54]

Grubbs *et al.*[56,57] introduced ruthenium-based carbene complex **76** as a general and practical metathesis catalyst. Grubbs' catalyst is formed through the stabilisation of carbenes as transition metal complexes: decomposition of phenyldiazomethane in the presence of Ruthenium(II) complex gives a carbene complex stable enough to be isolated and stored for months. Although less active than the Schrock molybdenum-based system **75**, the first generation

Grubbs' catalyst **76** exhibits much greater functional group tolerance. Recent developments in catalyst design have focused largely on the specific tailoring of catalyst reactivity through modifications of the ancillary ligands bound to the ruthenium centre. In particular, the replacement of one of the phosphine ligands in **77** with an *N*-heterocyclic carbene ligand as reported independently by several groups,[58-60] increases the catalytic activity, thermal stability, and functional group tolerance of the complex. The second generation Grubbs' catalyst **77** engenders metathesis reactions with particularly high levels of activity.[61]

In any catalyst system, functional groups in the substrate or solvent (including oxygen and water) can interfere with catalytic activity in several ways. They may bind to the active metal centre and deactivate the catalyst, or they may react directly with the metal centre and destroy the active species. Thus, the key to improved functional group tolerance in olefin metathesis is the development of a catalyst that reacts preferentially with olefins in the presence of heteroatomic functionalities.[62] These catalysts were observed to react more selectively with olefins as the metal centres were varied from left to right and bottom to top on periodic table (**Table 2**).[63]

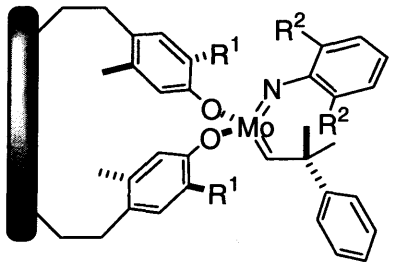
| Titanium | Tungsten | Molybdenum | Ruthenium |
|---|---|---|---|
| Acids | Acids | Acids | *Olefins* |
| alcohols, water | alcohols, water | alcohols, water | Acids |
| Aldehydes | Aldehydes | Aldehydes | alcohols, water |
| Ketones | Ketones | *Olefins* | Aldehydes |
| Esters, amides | *Olefins* | Ketones | Ketones |
| *Olefins* | Esters, amides | Esters, amides | Esters, amides |

**Table 2.** Functional group tolerance of transition metal olefin metathesis catalysts.

In comparison, molybdenum catalysts are more reactive toward olefins, although they also react with alcohols and other polar or protic groups. Ruthenium reacts preferentially with carbon-carbon double bonds over most species, which makes these catalysts unusually tolerant of alcohols, and other polar or protic Lewis basic groups.

### 1.7.2 Supported catalysts

Schrock *et al.*[64] have developed the first polymer-supported chiral and recyclable metathesis catalyst **78** (**Figure 12**). The fact that the molybdenum-based catalyst is supported on polymer allows purification by filtration and therefore a potential scaling-up. Also, they demonstrated in most cases that the polymer-bound catalyst provides similarly high levels of enantioselectivity as the corresponding non supported catalyst; it can also be recycled with significant efficiency (up to 3 times).

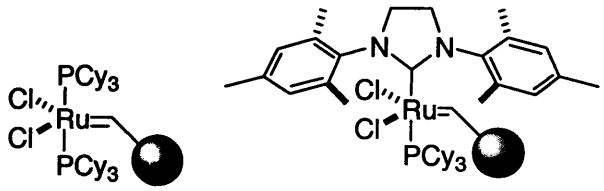



$R^1$ = *tert*-butyl, $R^2$ = isopropyl

**78**

**Figure 12.**

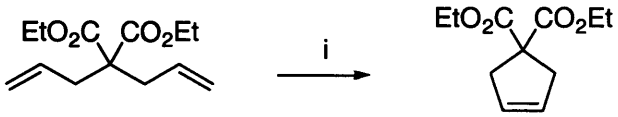
Nolan *et al.*[65] has also investigated polymer-supported olefin metathesis catalysts. The ruthenium catalyst **76** and **77** among others have been grafted to polymer supports to afford catalyst **79** and **80** respectively and found to be effective heterogeneous catalysts for ring closing metathesis (**Figure 13**).



79 80

**Figure 13.**

In some cases, they are recyclable, show comparable reactivity to their homogeneous counterparts (**Table 3**), tolerate functional groups, and perform very well with unsubstituted dienes.



81 82

| Entry | Catalyst | cycle | Yield (%)[a] |
|---|---|---|---|
| 1 | **77** | - | 100 |
| 2 | **80** | 1 | 100 |
| 3 | **80** | 2 | 99 |
| 4 | **80** | 3 | 99 |
| 5 | **80** | 4 | 100 |

**Table 3.** Reagents and conditions: i) catalyst (5 mol%), dichloromethane, 30 min; [a]: GC yield, average of two runs.

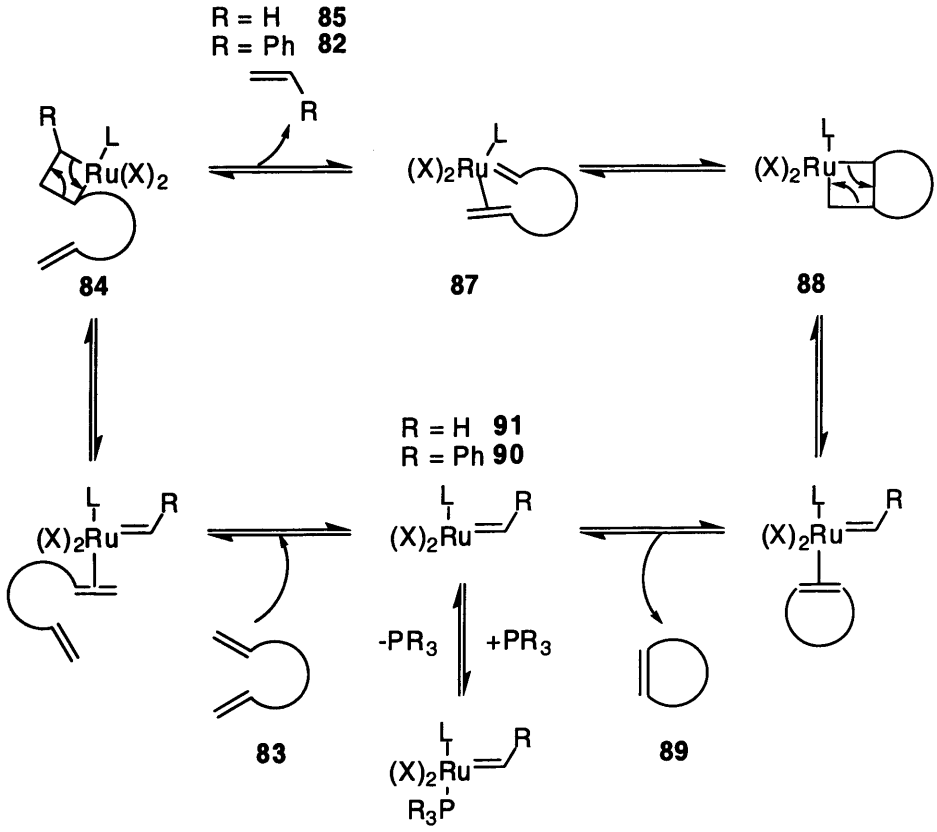
### 1.7.3 Mechanism

The generally accepted mechanism of alkene metathesis was originally proposed by Chauvin in 1971,[66] with key experimental evidence for its validity subsequently being provided by the Casey,[67] Katz,[68] and Grubbs groups,[69,70] and invokes metal carbene intermediates as key propagating species in the catalytic cycle.[71]

First the carbene complex **90** (**Scheme 15**) adds to one of the alkenes **83** in what can be drawn as a [2+2] metallo cycloaddition to give a 4 membered ring **84** with the metal atom in the ring.

Now the same reaction happens in reverse (all cycloadditions are reversible in principle), either to give the starting material or, by cleavage of the other two bonds, a new carbene complex **87** and styrene **85** (in case of Grubbs' catalyst).

Next an intramolecular [2+2] cycloaddition closes the ring and produces a second metallacyclobutane **88**, which decomposes in the same way as the first one to give a third carbene complex **91** and the desired product **89**. This new carbene complex then attacks another molecule of the starting material and the cycle is repeated except that ethylene is now lost instead of styrene in the rest of the cycle.



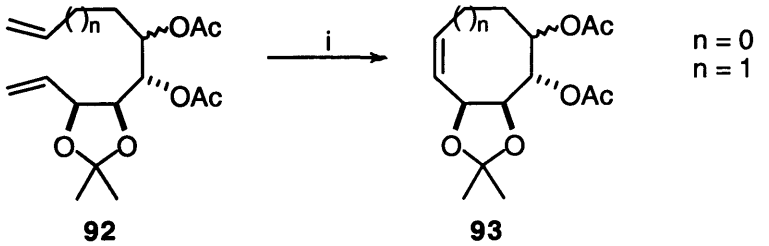

**Scheme 15.** Ring closing metathesis mechanism.

Both "associative" and "dissociative" mechanisms have been proposed for ring closing metathesis reactions. These involve 18e and 14e key species and Grubbs *et al.*[70] (inter alia) have discussed this question extensively. For the purpose of this discussion we will use the dissociative model

Since ring closing metathesis inevitably cuts a molecule into two, the forward reaction is entropically driven. The equilibrium is constantly shifted towards the cycloalkene more strongly still if ethylene or another volatile olefin is formed as the by-product. If the product has more highly substituted double bond than the substrate, the retro reaction is kinetically hindered because most catalysts are sensitive to the substitution pattern of the olefin.[72]

### 1.7.4 Features

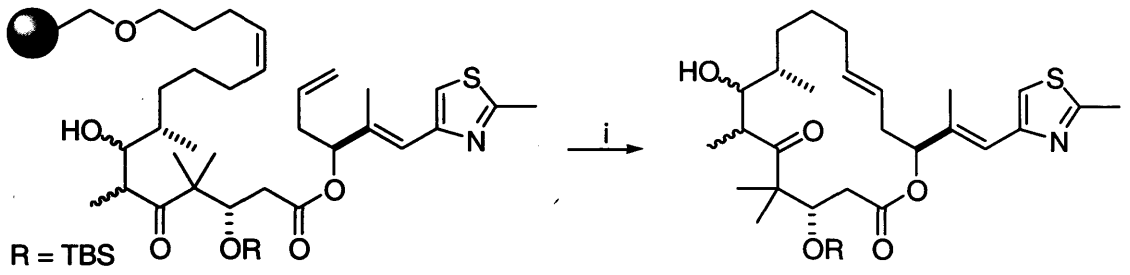
Ring closing metathesis has became a very efficient tool for the formation of carbo and heterocyles of any size ≥ 5, including medium and large ring compounds which are difficult to prepare otherwise.[72] The literature describes many applications of ring closing metathesis for the synthesis of cyclic molecules; for example, Hanna,[73] performed the synthesis of 7- and 8-membered ring **93** with very good yield using the Grubbs' catalyst **76** (**scheme 16**). Further examples (**Scheme 17**, **18**, **19** and **20**) show the diversity of size ring which could be obtained.




**92** **93**

**Scheme 16.** Reagents and conditions: i) Grubbs' catalyst **76** (5 mol%), dichloromethane, reflux, 24 h.

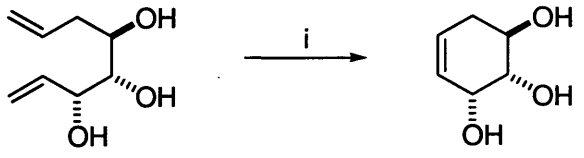
In addition, ring closing metathesis presents a very good tolerance to diverse functional groups; Nicolaou *et al.*[74] reported the synthesis of epothilone **95** from an intermediate containing functional groups such as ester, ketone, alcohol and thiazole (**Scheme 17**).




**94** **95**

**Scheme 17.** Reagents and conditions: i) Grubbs' catalyst **76** (10 mol%), dichloromethane, reflux, 48 h.

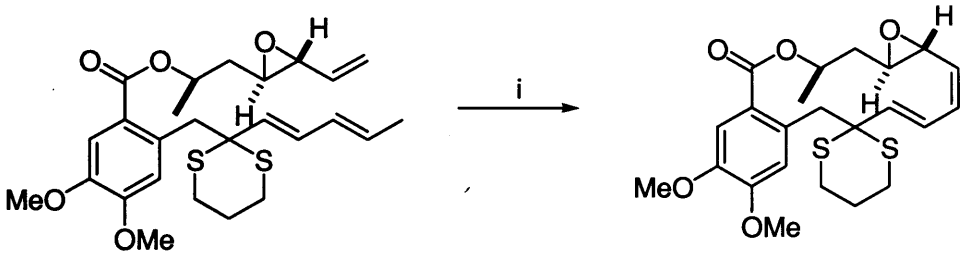
Carbohydrates are densely functionalised molecules, and as result their synthetic application often requires many reaction steps, usually for manipulation of different protecting groups. Ring closing metathesis was revealed to be a transformative tool allowing unprotected materials to be elaborated rapidly; Madsen *et al.*[75] described the synthesis of diverse carbohydrate from substrates with many hydroxyl groups exposed such as **96** with very high yield using the first generation Grubbs' catalyst **76** (**Scheme 18**).




**96** **97**

**Scheme 18.** Reagents and conditions: i) Grubbs' catalyst **76** (10 mol%), dichloromethane, rt, 95 %.

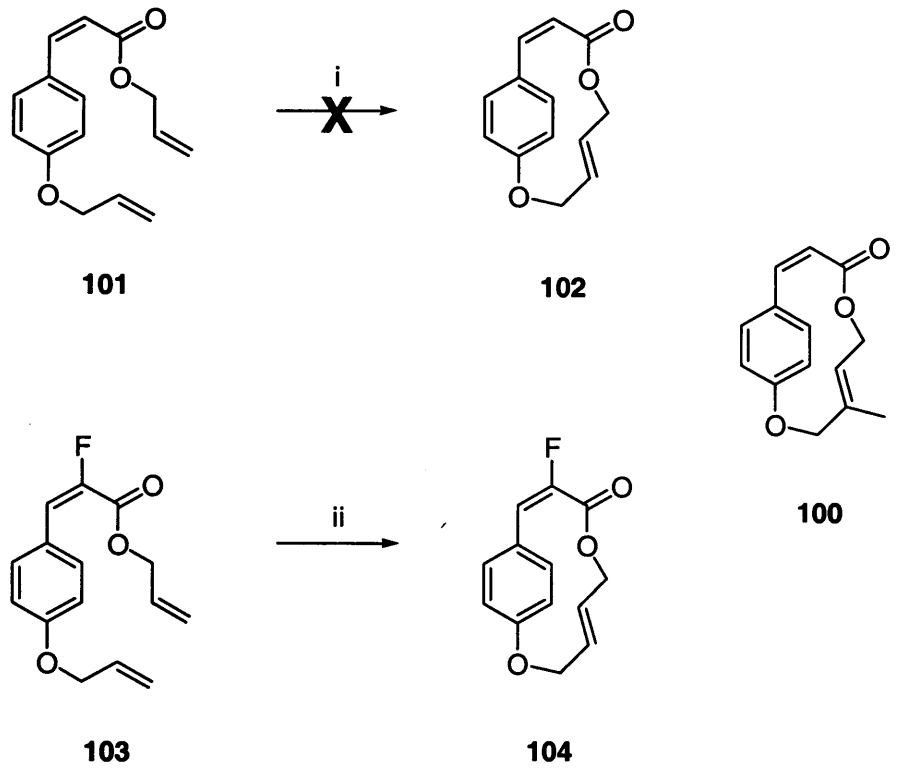
Danishefsky *et al.*[76] reported the synthesis of monocillin I (**Scheme 19**) in which they achieved the formation of macrolide **99** with an unprecedented ring closing metathesis of a diene and a vinyl epoxide using Grubbs catalyst **76**. The initial reaction next to allylic oxygen was reasonably fast.




**98** **99**

**Scheme 19.** Reagents and conditions: i) Grubbs' catalyst **76**, dichloromethane, 45°C, 55 %.

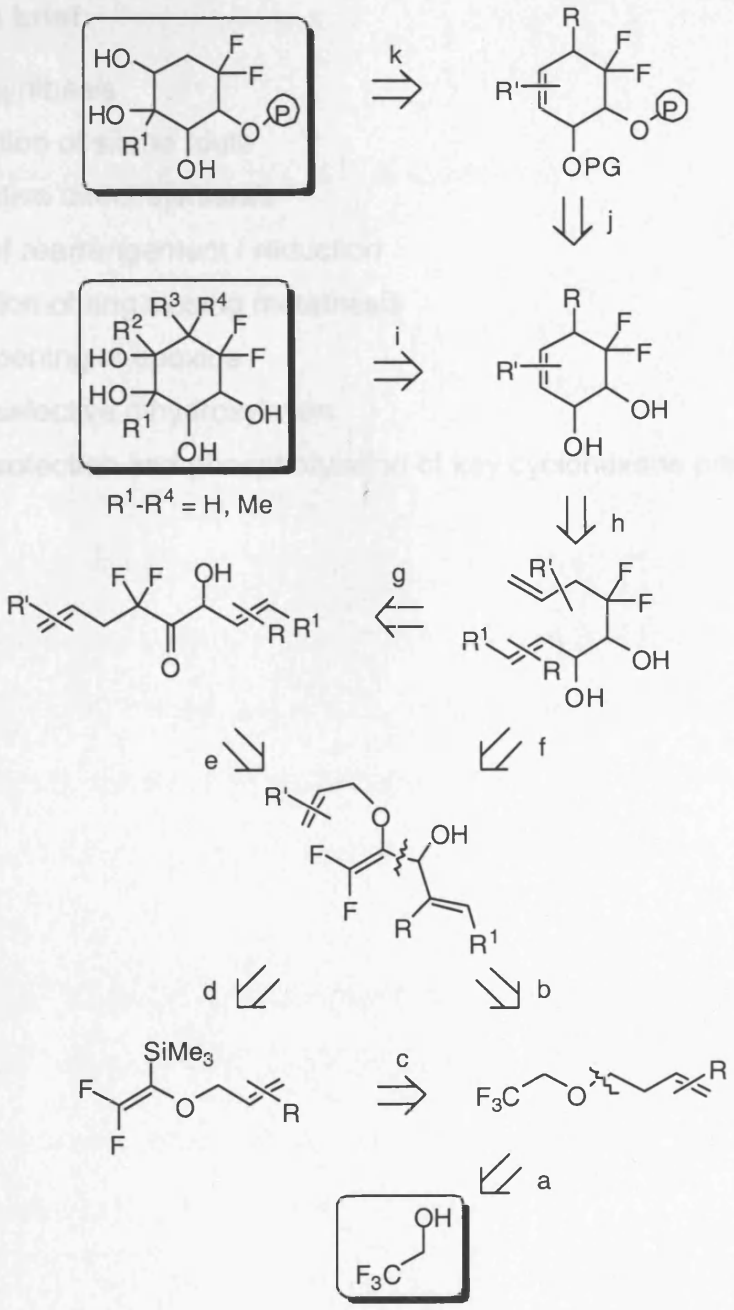
Ring closing metathesis has been applied to the synthesis of extremely rigid macrolactones and macrolactams of various size. Piva *et al.*[77] have reported the synthesis of 13- to 16- membered ansa-bridged macrolactones including pondaplin **100** (**Scheme 20**) using ring closing metathesis. Their substrate **101** was submitted to ring closing metathesis conditions by using Grubbs's catalyst **76**. The reaction led only to complex mixtures of starting material and dimeric structures, while **103** delivered a mixture of desired molecule **104** and dimeric structures. Comparison of the process performed on **101** and **103** indicates clearly that the presence of a fluorine atom has a beneficial role on the cyclisation. It could prevent any metathesis on the conjugated double bond and avoid the formation of polymeric structures.


i
ii
F
O
O
O

## *1.8 Objectives*

Our chemistry seeks to construct generic precursors to a very wide range of mono- and difluoro- analogues of cyclitols and monosaccharides (in which the ring oxygen is replaced) from an inexpensive fluorinated building block. From a generic precursor, small libraries of fluorinated cyclitol analogues can be obtained. The libraries could then be used to probe interactions with receptors as well as providing novel structures for screening and inhibitor synthesis. Unlike any of the methods in the literature, the sequences of the route are short, minimise the use of protecting group chemistry and use readily available and inexpensive starting materials.

Allyl ethers of trifluoroethanol (**Scheme 22**) (path a) undergo dehydrofluorination/metallation and can form vinyl silanes (path c). The latter can be trapped with α,β-unsaturated aldehydes when treated with a fluoride source (e.g. TBAF) to afford this diene ether (path d). A tandem process involving Claisen rearrangement followed by reduction (path f), affords highly functionalised diene diols which can be converted to difluoro cyclohexene *via* ring closing metathesis (path h). Alternatively, after dehydrofluorination/metallation, the ether of trifluoroethanol could be trapped directly with α,β-unsaturated aldehydes (path b) to afford difluorinated hydroxyketones after rearrangement (path e). If the rearrangement is followed by reduction (path g) and ring closing metathesis, it can afford difluorodiols, which can lead diverse analogues of cyclitols, carbasugars and precursor of NDP carbasugars (path l, j and k).




**Scheme 22.**

**Objectives in brief:**

1. Ether synthesis
2. Evaluation of silane route
3. Alternative direct synthesis
4. Proof of rearrangement / reduction
5. Validation of ring closing metathesis
6. Ring opening of epoxide
7. Stereoselective dihydroxylation
8. Monoprotection and phosphorylation of key cyclohexene precursor

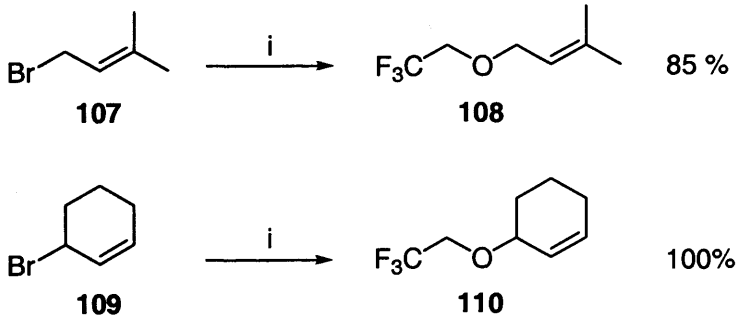
# 2 Results and Discussions

## *2.1 Synthesis of Ethers of Trifluoroethanol*

### 2.1.1 Ionic Liquid Procedure

Typical conditions for the synthesis of trifluoroethyl ethers involve the formation of the sodium salt in tetrahydrofuran using the strong base sodium hydride, followed by treatment with the carbon electrophile. Metcalf[46] used this procedure to prepare a cinnamyl trifluoroethyl ether in moderate yield (63%) on an unspecified scale. We wished to develop chemistry that could be applied at or above the mole scale; we were deterred, by the large volumes of hydrogen that would be produced by using sodium hydride, and decided to avoid it unless absolutely necessary.

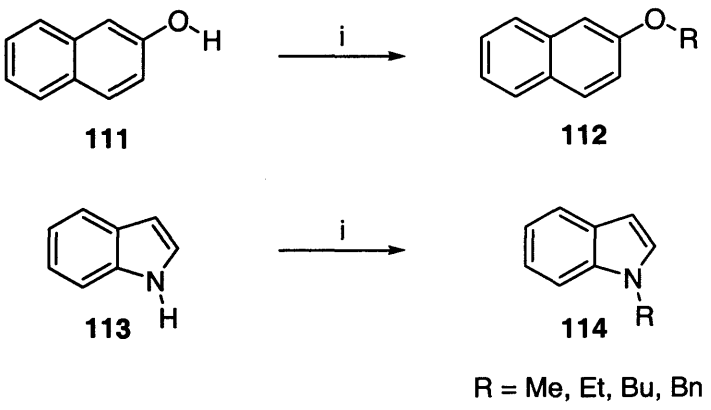
Phase Transfer-Catalysis (PTC) allowed the synthesis of allyl trifluoroethyl ethers; Garayt[80] reported successful preparation ethers **108** and **110** in very high yield. Allylation was carried out under Schlosser conditions using *N*-tetrabutylammonium iodide (**Scheme 23**) as PTC.




**Scheme 23.** Reagents and conditions: i) 50 % NaOH (7 eq), $Bu_4NHSO_4$ (5 %), $Bu_4NI$ (5 %) $CF_3CH_2OH$ **46** (1 eq.), rt, 12 h.

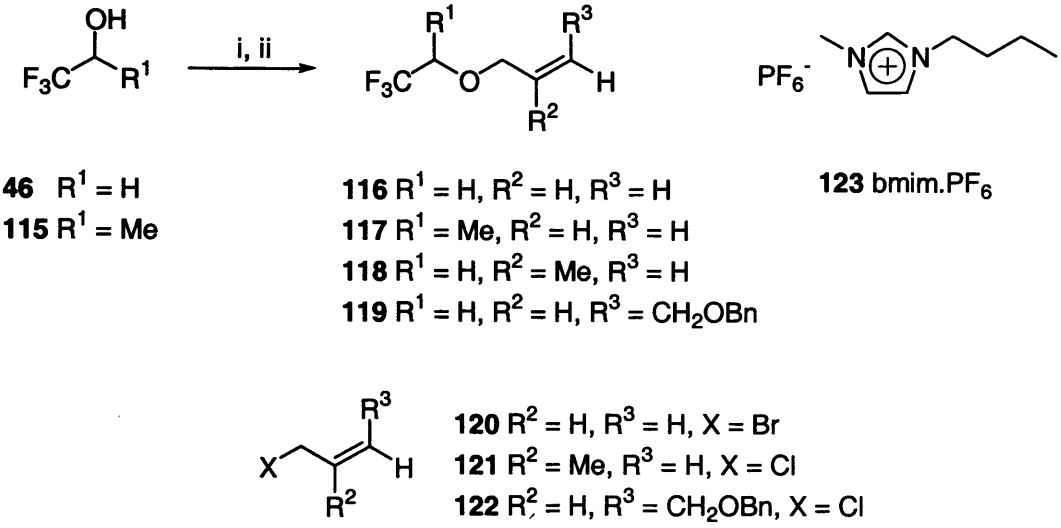
The synthesis of ethers of trifluoroethanol poses some purification problems by classical methods; indeed the small volatile ethers can not be separated from either low or high boiling point organic solvent used to extract the products of the phase transfer procedure.

Seddon *et al.*[81] reported an efficient (**Scheme 24**) and very high yielding alkylation of naphthol **111** or indole **113** in bmim.$PF_6$, which used potassium hydroxide as base. The $pK_a$ of the indole or naphthol proton is 16.7 or 10 respectively, and trifluoroethanol proton $pK_a$ lies in between with a pKa of 12.5,[82] so we estimated that this medium was appropriate for the synthesis of trifluoroethyl ethers.




**Scheme 24.** Reagents and conditions: i) Alkyl halide (R-Br), bmim.$PF_6$, KOH, 91-98 %.

We performed the allylation reaction in room temperature ionic liquid bmim.$PF_6$ and distilled the ether directly from the reaction medium (**Scheme 25**). The readily available ionic liquid bmim.$PF_6$ **123** was chosen for its high polarity and non volatility; furthermore bmim.$PF_6$ is liquid at room temperature, stable to moisture and air, and can be recycled.




**46** $R^1$ = H
**115** $R^1$ = Me

**116** $R^1$ = H, $R^2$ = H, $R^3$ = H
**117** $R^1$ = Me, $R^2$ = H, $R^3$ = H
**118** $R^1$ = H, $R^2$ = Me, $R^3$ = H
**119** $R^1$ = H, $R^2$ = H, $R^3$ = $CH_2OBn$

**123** bmim.$PF_6$




**120** $R^2$ = H, $R^3$ = H, X = Br
**121** $R^2$ = Me, $R^3$ = H, X = Cl
**122** $R^2$ = H, $R^3$ = $CH_2OBn$, X = Cl

**Scheme 25.** Reagents and conditions: i) Base (2.0 eq.), bmim.$PF_6$, 0 °C, 1 h; ii) Allylic halide (**120-122**), 40 °C, overnight then distillation.

Different bases were tested to optimise the reaction (**Table 4**); classic bases such as sodium hydroxide and potassium hydroxide were investigated, along with bases such as potassium fluoride and cesium fluoride. Potassium fluoride gave no product formation and the starting material was retrieved after reaction; cesium fluoride gave poor yield without total conversion of the trifluoroethanol and a fluorinated side-product was formed in significant amounts (1:1) with ether **116**. Sodium hydroxide was less efficient than potassium hydroxide; the latter gave good yield with high purity (no evidence of other compounds by $^1H$ and $^{19}F$ NMR).

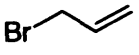
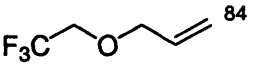
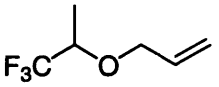
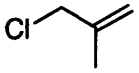
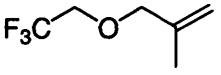
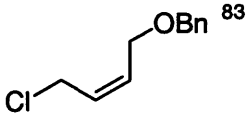
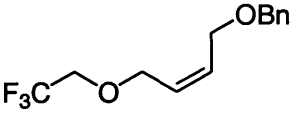
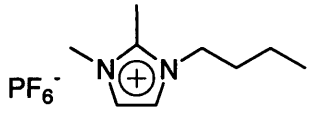
| Halide | | Base | Product | | scale (mmol) | Yield (%) |
|---|---|---|---|---|---|---|
|  | **120** | NaOH |  [84] | **116** | 100 | 60[a] |
| | | CsF | | | 5 | 30[b] |
| | | KOH | | | 50 | 74[a] |
| | | KOH | | | 200 | - |
| | | KOH |  | **117** | 50 | 92[a] |
|  | **121** | NaOH |  | **118** | 200 | 65[a] |
| | | KF | | | 50 | - |
|  [83] | **122** | KOH |  | **119** | 20 | 70[a] |

**Table 4.** [a]: isolated yield; [b]: conversion by $^{19}F$ NMR.

Small trifluoroethyl ethers can be distilled directly from the reaction mixture delivering compounds in high purity and allowing easy scale-up. Trifluoroethyl ethers were prepared very successfully in good yield from various allylic halides after optimisation of the reaction. The very viscous suspension of the finely ground base in ionic liquid was difficult to stir magnetically; causing a significant limitation (we did not try mechanical stirring). Bmim.PF6 is liquid at room temperature but gets more viscous at 0 °C limiting contacts in the reaction mixture.

Expensive bmim.$PF_6$ could be recycled after washing with water being insoluble in this particular solvent,[85] and was ready to re-use without significant loss of

yield (after two uses), but deterioration occurred rapidly as further reactions were attempted probably because of the strongly basic reaction conditions. Rogers *et al.*[86] reported that the degradation of [bmim] type (1-butyl-3-methylimidazolium) ionic liquids is due to proton abstraction at the 2-position with formation of a carbene species. A solution to this problem could be the ionic liquid bdmim.$PF_6$ **124** (**Figure 13**) in which the proton at the 2-position is replaced by a methyl group (1-butyl-2,3-dimethylimidazolium chloride).[87] The limitations in using bdmim.$PF_6$ are its melting point that is above room temperature, thus requiring a slight heating and also its cost which must become significant.

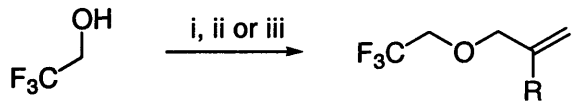



**124**

**Figure 13.** bdmim.$PF_6$.

### 2.1.2 Ether Synthesis in Water: a Sustainable Procedure

Ionic liquids have accrued considerable publicity as environmentally benign solvents but reactions in water would appear to have considerably less impact all round at much lower cost.




**46**

R = H **116**
R = Me **118**

**Scheme 26.** Reagents and conditions: i) KOH (1.0 eq.), water, rt, 1 h; ii) allyl bromide **120**, 40 °C, overnight; iii) methallyl chloride **121**, 40 °C, overnight.

Further investigations have shown that water can be an excellent solvent for the alkylation reaction (**Scheme 26**).[88] Actually a minimum volume of water plus an additional 10 % (which was pre-cooled at 0 °C before use) was used to dissolve the solid base allowing the large scale preparation of ethers in small reactors (typically, a 250 ml flask was used to prepare 1 mole of ether). The reaction did not show a significant exotherm compared to the same reaction carried out in an ionic liquid. At the end of the reaction, phase separation (achieved simply by pouring the mixture into a separating funnel) returned the wet trifluoroethyl ether, which was redistilled from calcium hydride in preparation for the strong base chemistry. Ether **116** was prepared in excellent yield (**Table 5**) after distillation on a mole scale. In the same manner **118** was prepared in very good yield.

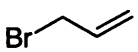
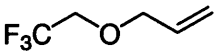
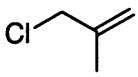
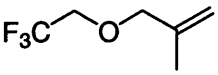
| Halide | | Product | | scale (mmol) | Yield (%)[a] |
|---|---|---|---|---|---|
|  | **120** |  | **116** | 200 | 88 |
| | | | | 300 | 99 |
| | | | | 1000 | 99 |
|  | **121** |  | **118** | 200 | 78 |

**Table 5.** [a]: isolated yield.

Furthermore, this method represents an atom efficient and sustainable solution to the syntheses of some trifluoroethyl ethers, given that the by-products are water and potassium chloride or bromide.

## 2.2 Routes to Acyclic Diol

### 2.2.1 First Generation Route via Vinyl Silane

#### *2.2.1.1 Synthesis of Vinyl Silane via Dehydrofluorination/Metallation*

Under strong base conditions (**Figure 14**) at low temperature, dehydrofluorination occurs with a high $E1_cB$ character for the removal of the first hydrogen. Indeed, the carbanion formed **125** is fairly stable due the strong electronegative effect of the $CF_3$ group. Furthermore, the fluorine atom is a poor leaving group and the proton is quite acidic being α- to an electron withdrawing group ($CF_3$) favoring the stepwise $E1_cB$ mechanism.[89]

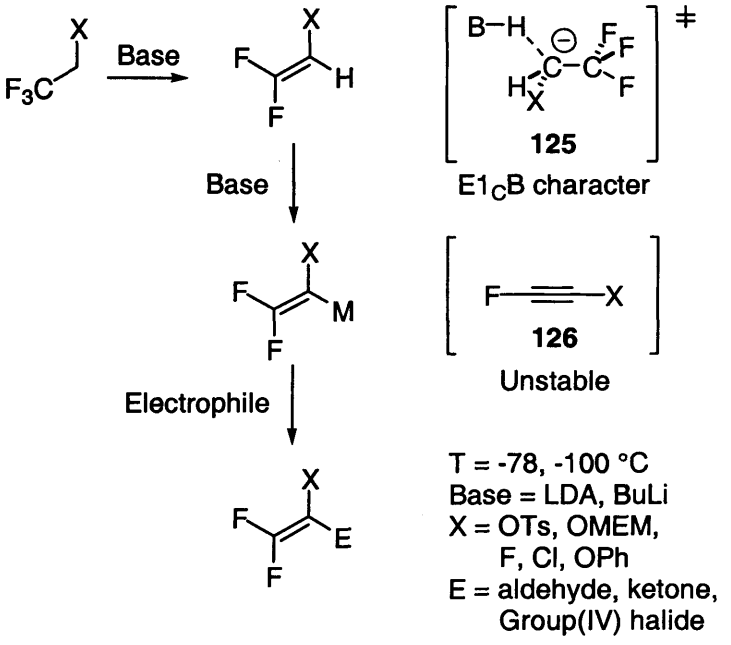
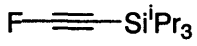



**Figure 14.** Dehydrofluorination/metallation/trapping.

The stability of the metal intermediate is temperature dependent and decomposition can occur *via* an antiperiplanar elimination of M-F if not handled properly[90,91] leading to fluoroacetylene **126**. These types of compound are known to be very unstable and potentially explosive inducing very few reports

on the syntheses of fluoroacetylenes. Hanamoto *et al.*[92] reported the synthesis of an unusually stable fluoroacetylene **127** (**Figure 15**). The TIPS group screens the fluoroacetylene and slows the usually rapid polymerisation.



**127**

**Figure 15.**

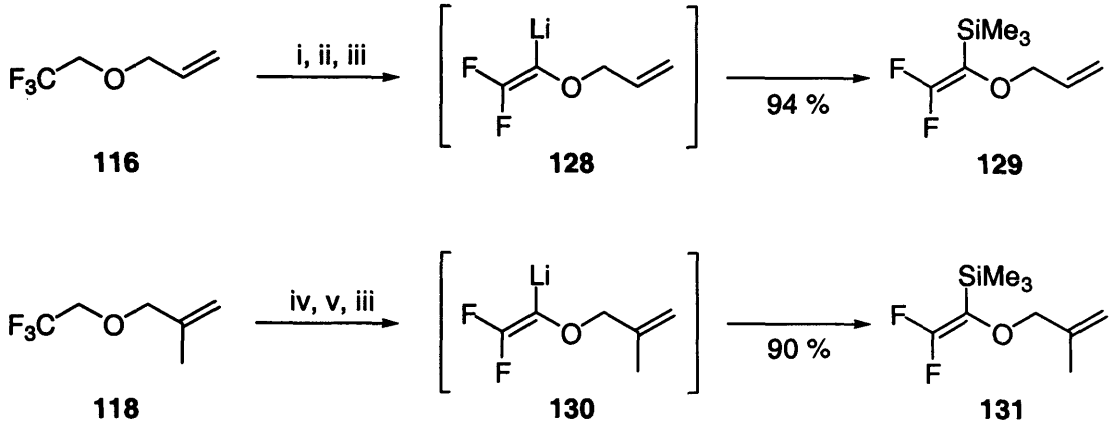
Electrophiles can potentially react with the metallated difluoroenol intermediate to deliver the corresponding product, provided the reaction with the electrophile is sufficiently fast at low temperature.

Metcalfe *et al.*[46] reported the synthesis of difluorovinyl ether based on Corey's observation that LDA is compatible with chlorotrimethyl silane at low temperature (< -80 °C). Dehydrofluorination/metallation reactions required strong base and trapping conditions at low temperature (-100 °C) in some cases. Trapping conditions consist of inverse addition of the starting material to a pre-mixed solution of strong base and trapping reactant. As soon as the lithium intermediate is formed, it reacts with the trapping species (*eg.* chlorotrimethyl silane; silicon electrophiles are particularly effective traps for hard organometallic reagents) to afford the desired compound.

Trifluoroether **116** was therefore submitted to Metcalf conditions.[88] Treatment with LDA afforded lithium species **128** (**Scheme 27**); interception with chlorotrimethyl silane delivered difluorovinyl silane **129**. Allyl ether **116** was most demanding, requiring low temperature and trapping conditions; however, vinyl silane **129** could be obtained in excellent crude yield, and redistilled (Kugelrohr, room temperature) without rearrangement or decomposition

occurring. Under these conditions, this reaction was successfully scaled-up since 94 % of silane was recovered on a 130 mmol scale.

In contrast to the behaviour of **116**, **118** undergoes dehydrofluorination/ metallation smoothly at -78 °C with the normal addition of *n*-butyllithium to deliver methallyl silane **131** with a 90 % yield.

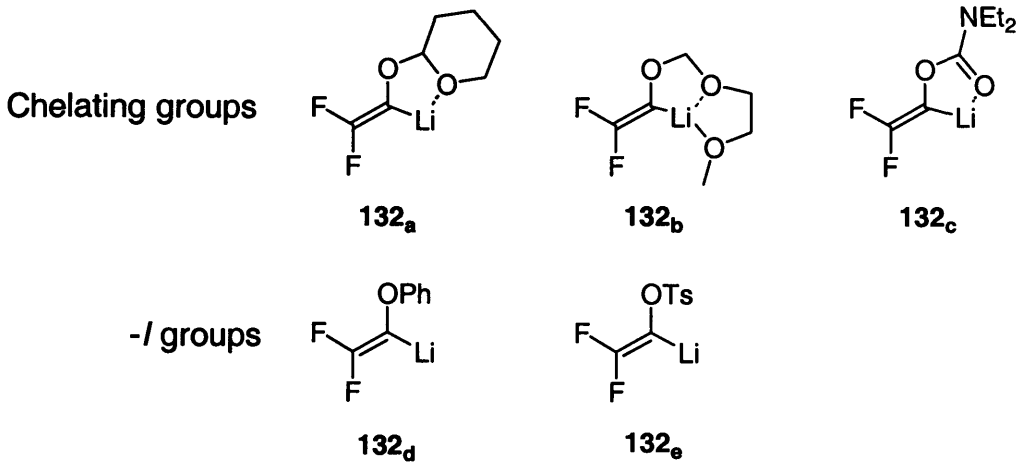



**Scheme 27.** Reagents and conditions: i) LDA (2.2 eq.)/$Me_3SiCl$ (1.2 eq.) (inverse addition), tetrahydrofuran, -100 °C; ii) -100 to -40 °C, 1 h; iii) $NH_4Cl_{sat.}$ at -40 °C; iv) *n*-BuLi (2.0 eq.), tetrahydrofuran, -78 °C; v) -78 to -40 °C, 1h.

The formation of a difluorovinylic species can be confirmed by $^{19}F$ NMR; indeed the starting material presents a typical shift (~ -74 ppm) and coupling constant $^3J_{F\text{-}H}$ (~ 8 Hz) of a trifluoroethyl group and the product of the dehydrofluorination/ metallation presents a pair of doublet with a coupling constant $^2J_{F\text{-}F}$ (~ 60 Hz) typical of a difluorovinylic compound.

Those results indicate that the thermal stability of the simple metallated difluoroenols **128** or **130** is sufficient at -100 or -78 °C for rapid trapping to be achieved even in the absence of inductively electron-withdrawing substituent[93-96] or chelating substituent,[97,98] features we believed necessary to retard the antiperiplanar elimination of lithium fluoride (**Figure 16**) as in $\mathbf{132_{a\text{-}e}}$ to the extent that trapping reactions with electrophiles were possible. The idea is

founded on early observations by Tarrant *et al.*,[99] and Normant *et al.*[100] in which a considerable difference in stability between 1-lithio-2,2-difluoroethene and 1-lithio-1,2,2-tri-fluoroethene was noted. Whereas the former species could be generated and trapped at -100 °C only, the latter could be generated at -78 °C and reacted with a range of electrophiles at that temperature.




**132a** **132b** **132c**

**132d** **132e**

**Figure 16.** Metallated difluoroenol derivatives from the literature.

The higher stability of methyllated lithium intermediate **130** cannot be explained by the presence of an additional methyl group. Indeed the inductive effect would destabilise further the difluoroenol.

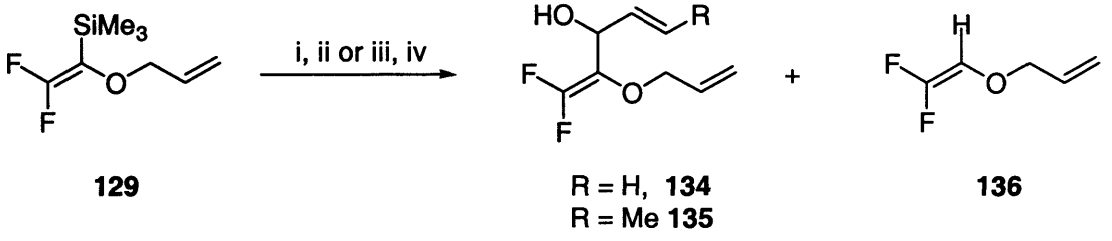
The vinylsilanes can be stored in the freezer but crystals of oxalic acid, the product of hydrolysis, develop in time when stored at room temperature (> 1 month).

Achieving efficient stirring at low temperature represents the main limitation of the reaction. A very low temperature (-100 °C) is very difficult to maintain, especially with highly exothermic reactions such as dehydrofluorination/ metallation. Slow addition was essential to achieve control of the exotherm. The reaction is carried out in tetrahydrofuran which melts at -108.4 °C; thus high

viscosity of the reaction mixture poses stirring difficulties. Despite this, mechanical stirring was not tried and all the results obtained were from magnetically stirred reactions.

### *2.2.1.2 Trapping of α,β-Unsaturated Aldehydes*

The carbon-silicon bond can be cleaved when treated with a fluoride ion source as shown by Percy *et al.*,[98] so silane **129** (**Scheme 28**) was reacted with fluoride sources in the presence of acrolein **133** (R = H) to form the corresponding dienol **134**. The product of protodesilylation **136** was also anticipated.




**129** R = H, **134** R = Me **135** **136**

**Scheme 28.** Reagents and conditions: i) **133** (1.1 eq.), tetrahydrofuran, 0 °C; ii) TBAF or TASF (1-2 eq.), 0 °C, 1 h; iii) TBAX (0.1 eq.), KF (0.5 eq.); (iv) rt, 2 h.

An unwanted side-reaction delivered protonated compound **136** resulting from protodesilylation of **129**. Signals arising from the presence of allylic alcohol **134** and by-product **136** were observed in the $^{19}F$ NMR, which contains an additional coupling ($^{3}J_{F\text{-}H}$ 16.3 Hz) for **136** due to the proton *trans* to one of the fluorine atoms.

In the same manner, we reacted **129** with a different aldehyde **137** (R = Me) to deliver dienol **135**. Different fluoride ion sources were investigated (**Scheme 28**); these included tetra-*n*-butylammonium fluoride (TBAF), *tris*-

(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF), and *in situ* generated quaternary ammonium fluorides [TBAX/KF] (X = Br, I, $HSO_4$). Ooi *et al.*[101] reported catalysed hydrolysis of trimethylsilyl ether by *in situ* generation of quaternary ammonium fluorides under phase-transfer conditions. They employed various tetrabutylammonium salts (TBAX) as precursors and examined the anion exchange under solid-liquid phase-transfer conditions with a catalytic amount of potassium fluoride dihydrate (0.5 eq.). We applied this strategy for the cleavage of carbon-silicon bond with C-C bond formation.

*In situ* generation of quaternary ammonium fluoride was revealed to be inefficient delivering only the protonated compound **136** (**Table 6**), except TBAB/KF which afforded 20 % of the desired dienol **134**. TASF also delivered the protonated compound. However, TBAF delivered only dienol **134** (no evidence of **136** by $^{19}F$ NMR). The dienol could not be obtained in a sufficiently pure state to allow rigorous characterisation.

| Fluorine Source | Ratio[a] 134/136 | Ratio[a] 135/136 | Scale (mmol) |
|---|---|---|---|
| TBAF | 1:0[b] | | 10.0 |
| | 1:0[b] | | 4.0 |
| | 1:0[b] | | 3.0 |
| | 1:0[c] | | 3.0 |
| | 1:2[c] | | 20.0 |
| | 1:2[c] | | 14.0 |
| | 0:1[b] | | 0.3[e] |
| | 0:1[c] | | 42.0 |
| | | 1:4[b] | 0.3 |
| | | 0:1[b] | 0.3 |
| TASF | 0:1 | | 1.8 |
| | | 0:1 | 0.3 |
| TBAB/KF | 1:4 | | 0.2 |
| | -[d] | | 5.0 |
| TBAI/KF | 0:1 | | 0.2 |
| TBA-$HSO_4$/KF | 0:1 | | 0.2[f] |

**Table 6.** [a]: by $^{19}F$ NMR; [b]: 1M TBAF in tetrahydrofuran (TBAF was dried over $P_2O_5$ for 5 days under high vacuum); [c]: Commercial 1M TBAF solution in tetrahydrofuran from Lancaster Synthesis; [d]: complex $^{19}F$ NMR; [e]: this reaction was attempted 3 times; [f]: this reaction was attempted 2 times.

Nevertheless only five attempts delivered dienol **134** successfully; we can argue that small scale reactions failed for this particular reason; indeed traces of water influence the issue of the reaction more importantly on small scale. However, those reactions were repeated several times with different batches of TBAF solution with the same result. The main difficulty involved obtaining consistently dry TBAF even from commercial sources; decomposition occurred over 40 °C,[102] requiring the removal of traces of water to be attempted at room

temperature. TBAF was dried over phosphorus pentoxide under vacuum in a special apparatus (**Figure 17**).[102-104] This procedure required drying for five days and can be achieved on small quantities only; typically a batch of 10 grams. A procedure which was restricted in scale and was difficult to reproduce was clearly an unsatisfactory way to start our synthesis. A direct route from the trifluoroether was therefore attempted.

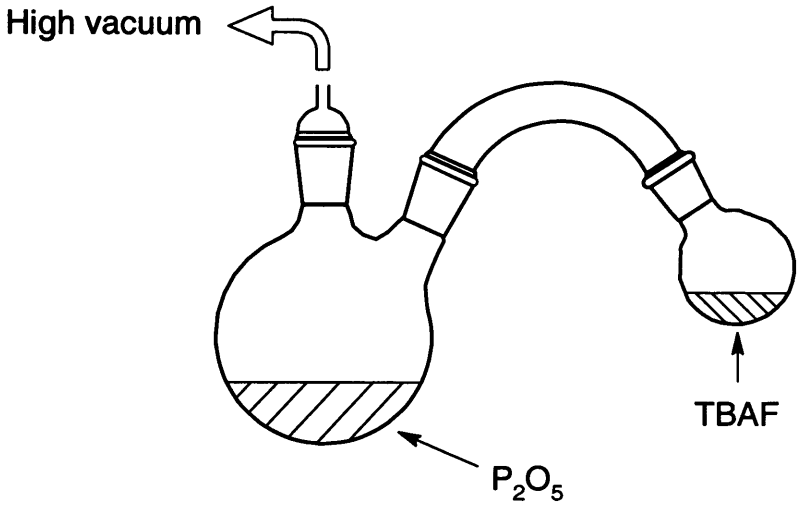
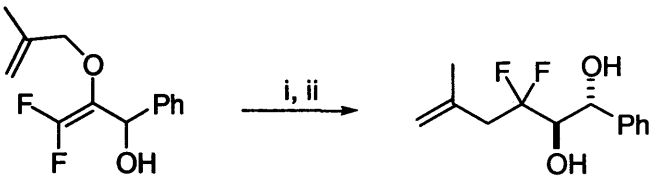



**Figure 17.** Set-up for TBAF drying.

### *2.2.1.3 Tandem Claisen Rearrangement/Reduction*

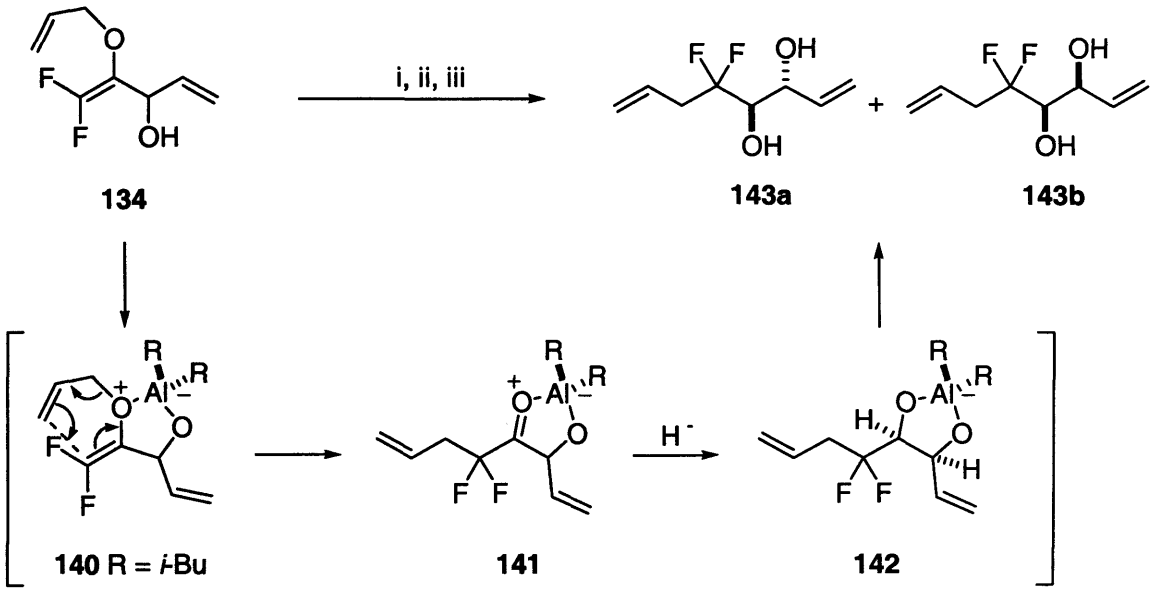
Taguchi *et al.*[49] reported enantioselective rearrangement promoted by a chiral Lewis acid with compounds very similar to our substrate. Also, the use of trialkylaluminium reagents as Lewis acid, then as reducing agents in subsequent steps has recently been used extensively by Sinaÿ *et al.*[48] Furthermore, Garayt[80] has reported tandem rearrangement/reduction (**Scheme 29**). He performed this tandem reaction using dienol **138** and DIBAL to deliver diol **139** stereoselectively.




**138** **139**

**Scheme 29.** Reagents and conditions: i) DIBAL, toluene, -78 °C to rt, 1 h; ii) HCl 1N.

Based on the similarity of our substrate, the tandem rearrangement/reduction was performed using dienol **134** and DIBAL to deliver diol **143** (**Scheme 30**).




**134** **143a** **143b**

**140** R = *i*-Bu **141** **142**

**Scheme 30.** Reagents and conditions: i) DIBAL (3.0 eq.), tetrahydrofuran, -78 °C; ii) -78 °C to rt, 2.5 h; iii) NaOH (1N).

The mechanism is believed to involve the following steps. First, the aluminium reacts with the hydroxyl group and forms an ionic bond with the enolic oxygen, leading to the five-membered ring chelate intermediate **140**. Polarisation accelerates the sigmatropic rearrangement strongly to afford intermediate **141**, then external hydride delivery from the least hindered face of chelated complex gives **142**. Furthermore, the rehybridisation from $sp^2$ to $sp^3$ of the $CF_2$ centre eases the sigmatropic rearrangement (*cf.* **1.6.2.**).

Finally we obtained the racemic *anti*-diol compound **143**. The NMR data did not permit us to confirm the configuration of the two stereogenic centres, but showed a stereoselectivity of 9:1 between diastereoisomers **143a** and **143b**. The DIBAL poses extraction problems (insoluble aluminium salts) with acidic work-up but based on (2*Z*)-4-(4-methoxyphenoxy)but-2-en-1-ol synthesis, a basic work-up was developed allowing an effective extraction. The major diastereoisomer was isolated by column chromatography to afford the pure (racemic) diastereoisomer in very poor yield (10 %). Low yield was explained by the volatility of diol **143** and of the precursor dienol **134**. The 1D and 2D NMR experiments ($^{1}H$, $^{19}F$ and $^{13}C$) allowed us to confirm the structure of diol **143**; every proton and hydroxyl group could be clearly identified from the different spectra.

### 2.2.2 Second Generation Route *via* Direct Procedure from Ether to Dienol

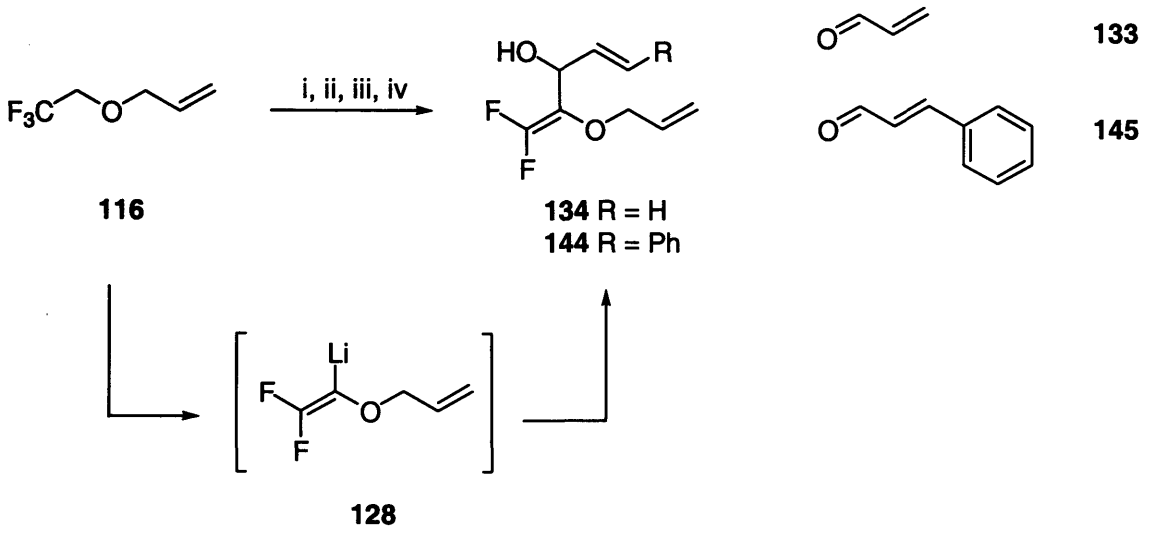
Aldehydes are reactive electrophiles and can potentially trap organolithium species even at low temperature. Through dehydrofluorination/metallation at very low temperature and trapping of α,β-unsaturated aldehydes, the corresponding dienol can be obtained (*cf.* **2.2.1.1**).

#### *2.2.2.1 Dehydrofluorination/Metallation*

##### 2.2.2.1.1 First Attempts

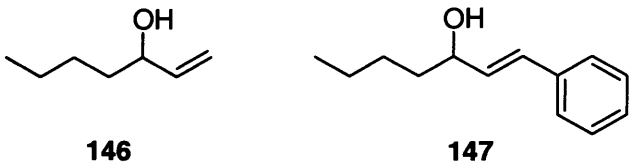
Allyl ethers of trifluoroethanol **116** undergo dehydrofluorination/metallation at -100 °C to afford difluoroalkenylmetal **128** which can be trapped with

α,β-unsaturated aldehydes **133** and **145** to afford **134** and **144** respectively **(Scheme 31)**.




**Scheme 31.** Reagents and conditions: i) *n*-BuLi (2.2 eq.), tetrahydrofuran, -100 °C, 1 h; ii) Acrolein **133** or cinnamaldehyde **145** (1.0 eq.), -100 °C; iii) -100 to -40 °C, 1 h; iv) $NH_4Cl_{sat.}$ at -40 °C.

We were not able to purify dienol **134** obtained from acrolein. This compound was unstable on silica gel and actually rearranged very quickly at room temperature (within 2 hours) (*c.f.* **2.2.2.2.**). Furthermore dienol **134** seemed to be volatile and was thus taken through the subsequent steps as a solution in the extraction solvent. A side-product, **146**, is the adduct of *n*-butyllithium with acrolein **133**, which might be formed due to low reactivity of *n*-butyllithium with the trifluoroethyl ether at -100 °C; instead, it reacts more rapidly with the aldehyde to form **146** (**Figure 18**).




**146** **147**

**Figure 18.**

In the same manner, side-product **147** is the adduct of *n*-butyllithium to cinnamaldehyde (**Figure 18**). The $^{1}H$ and $^{13}C$ NMR of butyllithium adduct **147** was in agreement with that reported in the literature.[107]

The formation of a difluorovinylic species can be confirmed by $^{19}F$ NMR; indeed the starting material presents a typical shift (~ -74 ppm) and coupling constant $^{3}J_{F\text{-}H}$ (~ 8 Hz) of a trifluoroethyl group and the product of the dehydrofluorination/ metallation presents a pair of doublets with a coupling constant $^{2}J_{F\text{-}F}$ (~ 60 Hz) typical of a difluorovinylic compound. Mass spectrometry confirms the formation of **134** and **144**.

The dehydrofluorination/metallation was first conducted at -78 °C leading to decomposition of the reaction mixture which turned from bright yellow to black. Further investigations have shown that difluoroalkenylmetal **128** decomposes very quickly above -80 °C, loss of temperature control or accidentally rapid addition results in almost complete decomposition.

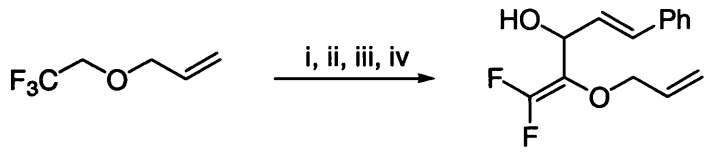
The reaction of the *n*-butyllithium with the ether of trifluoroethanol is highly exothermic. Slow addition (*eg.* rate described a gradient from 10 $mL.h^{-1}$ to 40 $mL.h^{-1}$ during addition for a 10 mmol reaction) was essential to achieve control of the exotherm and to prevent any decomposition of the lithium species from occurring.

2.2.2.1.2 Optimisation

The significant quantities of *n*-butyllithium adduct can be explained by the nucleophilic character of the small butyl group. A more hindered base such as

LDA or *t*-butyllithium was used for the dehydrofluorination/metallation reaction, considering that a much lower nucleophilicity would deliver higher yields despite LDA having a lower pKa than *n*-butyllithium (36 compared to 50).[108]

First attempts were performed with LDA but without any success; indeed we were unable to recover any of the desired product after reaction. When realised with *t*-butyllithium (**Scheme 32**), the dehydrofluorination/metallation reaction delivered cleaner crude material; indeed we did not observe any *tert*-butyllithium adduct with cinnamaldehyde by $^1$H NMR.



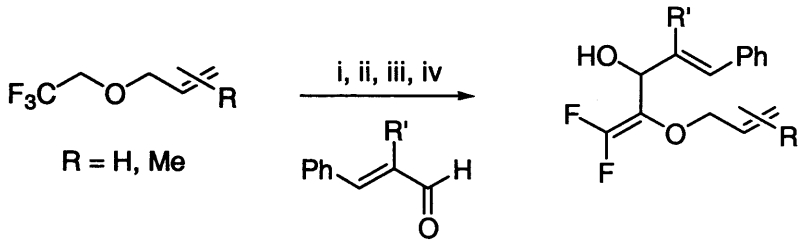

**116** **144**

**Scheme 32.** Reagents and conditions: i) *t*-BuLi (2.2 eq.), tetrahydrofuran, -100 °C, 15 min; ii) cinnamaldehyde **145** (1.0 eq.), -100 °C; iii) -100 to -90 °C, 15 min; iv) $NH_4Cl_{sat.}$ at -90 °C.

The reaction conditions were optimised according to the quality of crude material and obviously the yield of diol **168**, after reduction (*c.f.* **2.2.3.**).

2.2.2.1.3 Versatile Route

The reaction sequence was then explored using a range of ethers and aldehydes with the objective of producing a small library of diols. We assay different ethers of trifluoroethanol and α,β-unsaturated aldehydes against the strong base conditions at low temperature (**Scheme 33**) to deliver a wide variety of racemic dienols (**Table 7**).




**Scheme 33**. Reagents and conditions: i) *t*-BuLi (2.2 eq.), tetrahydrofuran, -100 °C, 15 min; ii) aldehyde (1.0 eq.), -100 °C; iii) -100 to -90 °C, 15 min; iv) $NH_4Cl_{sat.}$ at -90 °C.

The stability of the difluoroalkenylmetal of the substituted substrates **118**, **A**[88] and **108** was in general greater than that of **128**. Decomposition of the lithiated intermediate occurs rapidly above -100 °C; despite the higher stability of the more substituted key intermediate, the reaction was still performed at -100 °C delivering crude material of higher quality and better yield after reduction (*cf.* **2.2.3.**).

The formation of the different difluorovinylic species can be monitored by $^{19}F$ NMR as explained previously (*cf.* **2.2.2.1.1**)

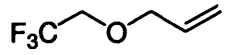
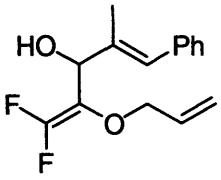
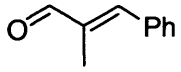
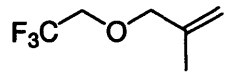
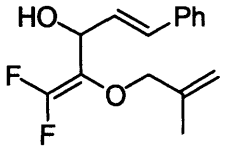
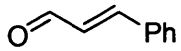
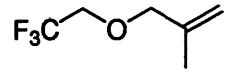
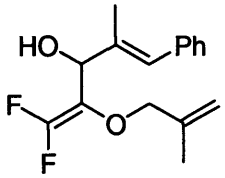
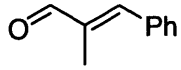
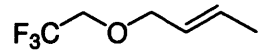
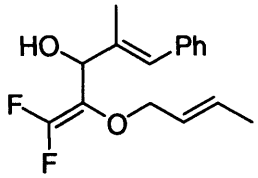
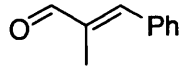
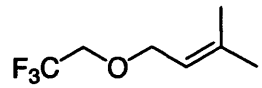
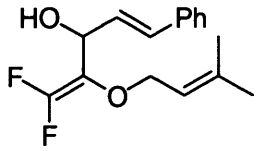
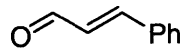
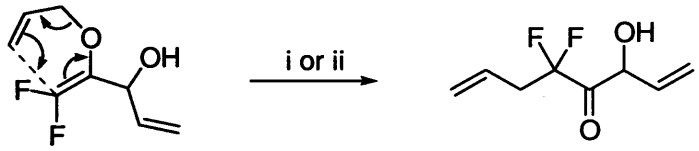
| Ether | | Dienol | | Aldehyde | |
|---|---|---|---|---|---|
|  | **116** |  | **149** |  | **148** |
|  | **118** |  | **150** |  | **145** |
|  | **118** |  | **151** |  | **148** |
|  | **A** |  | **152** |  | **148** |
|  | **108** |  | **153** |  | **145** |

**Table 7.** Generation of diversity *via* the dehydrofluorination/metallation reaction.

### *2.2.2.2 [3,3]-Claisen Rearrangement*

#### 2.2.2.2.1 First Attempts

Dienol **134** rearranged thermally under mild conditions (**Scheme 34**) to deliver hydroxyketones **154**. The sigmatropic rearrangement was first performed while concentrating in *vacuo* at 50 °C delivering the desired compound. However some decomposition occurred and the product seemed to be volatile. We then found that rearrangement occurred on the rotary evaporator close to room temperature. A more reliable procedure was required leading to a reaction in solution in diethyl ether at room temperature.




**134** **154**

**Scheme 34.** Reagents and conditions: i) **134**, rt, $Et_2O$, 2 h; ii) rotary-evaporator, 40 °C, 20 mmHg.

The rearrangement is probably facilitated by two effects. The rehybridisation from $sp^2$ to $sp^3$ of the $CF_2$ centre is known to drive rearrangement. $^{19}F$ NMR showed significant changes characteristic of a rehybridisation from an $sp^2$ or vinylic $CF_2$ to an $sp^3$ $CF_2$. Indeed the dienol exhibits a pair of doublets with a $^2J_{F\text{-}F}$ coupling constant of *ca.* ~ 60 Hz, typical of a difluorovinylic compound while the spectrum of the rearrangement product exhibits an AB system (a pair of doublets of triplets) with a $^2J_{F\text{-}F}$ coupling constant of *ca.* ~ 270 Hz, typical of $sp^3$ $CF_2$ centre α- to a ketone. Furthermore, the $^{13}C$ NMR spectrum shows a carbonyl peak (~ 200 ppm) clearly.

Also, the C-3 hydroxyl group (**Figure 19**) could form an intramolecular hydrogen bond to the enolic oxygen, which should increase the positive charge on the oxygen and weaken the O1'-C2' bond, enhancing the rearrangement rate.

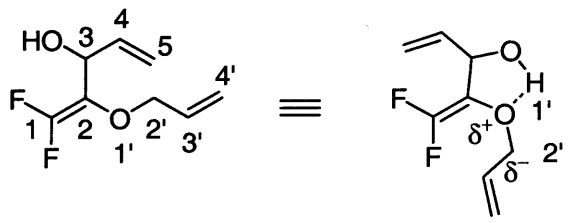


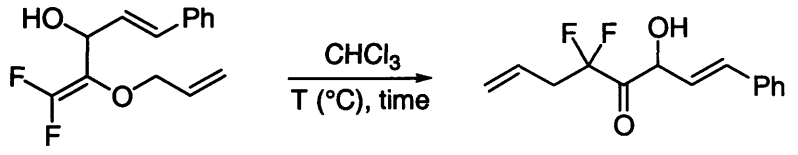

**Figure 19.** Polarisation of C2'-O1' bond by intramolecular hydrogen bonding.

Indeed, polarisation of C2-O1' bond due to solvent effect by hydrogen bonding is a well known phenomenon[37] as well as by intermolecular hydrogen bonding as described by Curran *et al.*[109]

2.2.2.2.2 Solvent and Temperature Influences

Claisen rearrangement was first performed at reflux in chloroform. Due to occasional instability of the temperature control, some decomposition occurred. Indeed, further investigations have shown that the reaction mixture decomposes above 80 °C, turning from yellow-orange solution to dark brown-black. Therefore, the rearrangement was carried out at 60 °C in chloroform.

Decreasing the temperature by 10 °C reduced the kinetic rate of the rearrangement of **144** into **155** five fold with no increase in yield (**Figure 20**).

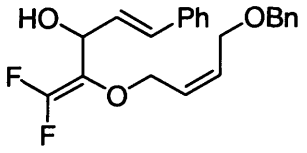



**144** **155**

| T(°C) | Time (min) |
|---|---|
| 50 | 140 |
| 60 | 25 |

**Figure 20.** Temperature influence on Claisen rearrangement.

Different solvents were used for the Claisen rearrangement by Yang[110] for a similar substrate, dienol **156** (**Figure 21**).




**156**

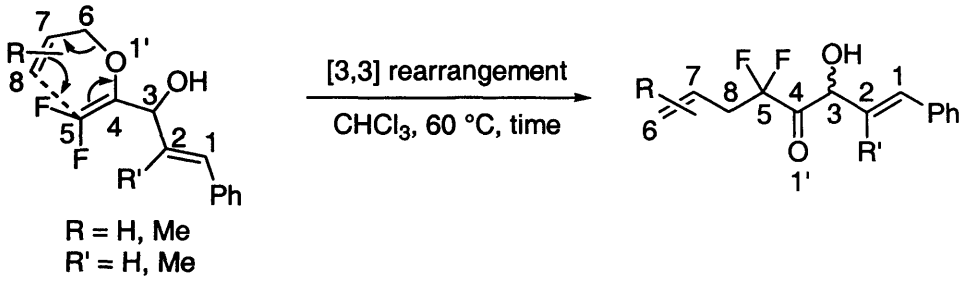
**Figure 21.**

Diethyl ether, dichloromethane and chloroform were used as solvents for the sigmatropic rearrangement at reflux. Chloroform was superior to diethyl ether or

dichloromethane for the reaction, possibly due to the higher boiling point increasing the rate of the Claisen rearrangement as shown previously in the case of dienol **144.**

2.2.2.2.3 Results

The optimised reaction conditions were applied to synthesise a small library of hydroxyketones (**Scheme 35**).




**Scheme 35.** Rearrangement conditions.

The substrates behaved differently under the rearrangement conditions (**Table 8**) according to the level of substitution. While dienol **144** rearranged smoothly at 60 °C in 25 minutes to afford **155**, the mono-substituted or disubstituted species rearranged more slowly (over 120-150 minutes) to deliver the corresponding hydroxyketones with 100 % conversion.

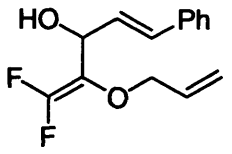
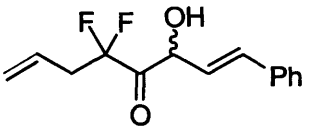
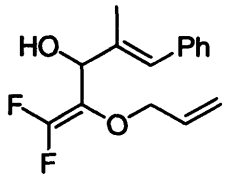
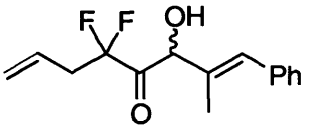
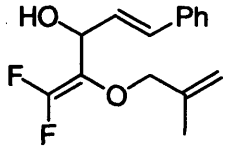
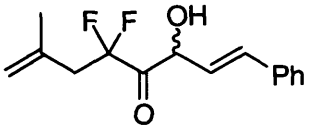
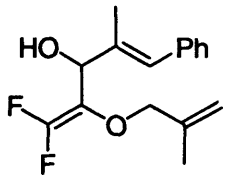
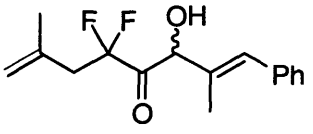
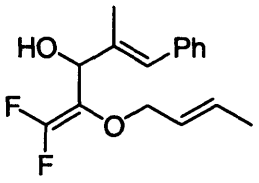
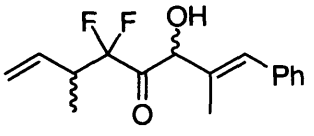
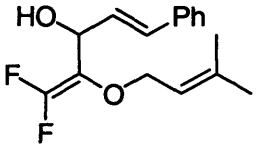
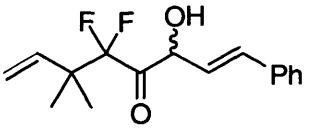
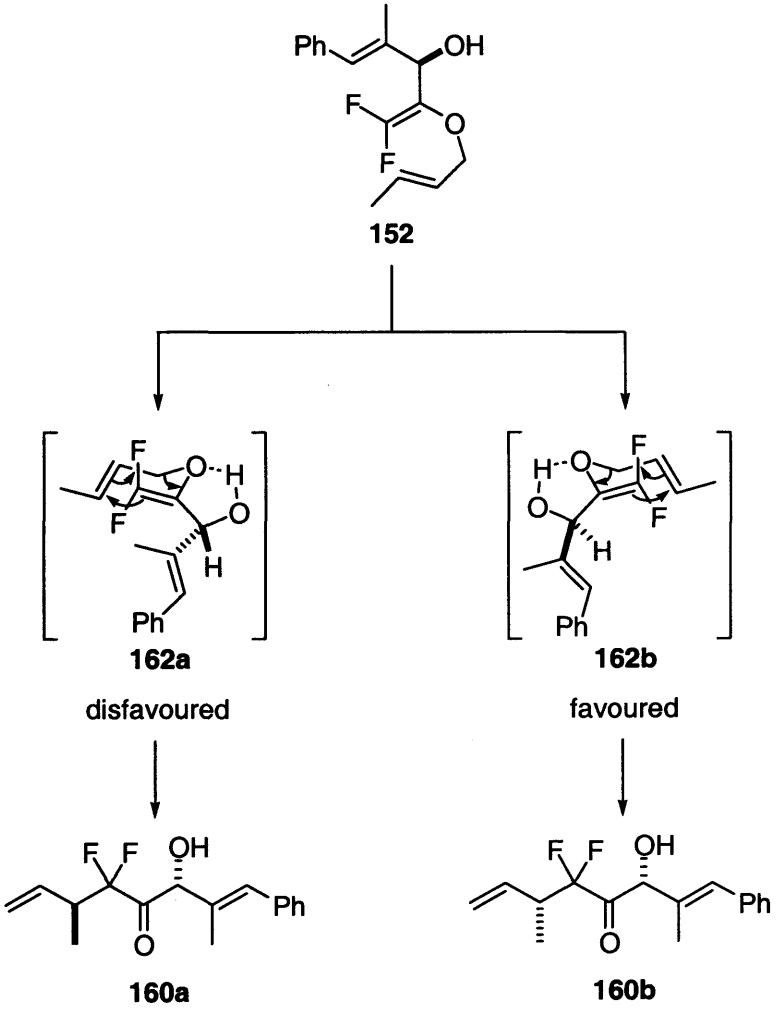
| Dienol | | Hydroxyketone | | Time (min) |
|---|---|---|---|---|
|  | **144** |  | **155** | 25 |
|  | **149** |  | **157** | 120 |
|  | **150** |  | **158** | 150 |
|  | **151** |  | **159** | 150 |
|  | **152** |  | **160** | 150 |
|  | **153** |  | **161** | 150 |

**Table 8.** Claisen rearrangement of substituted analogues

Non-volatile dienol **144** also rearranged while evaporating under vacuum (20 mmHg) at 50 °C but due to uncertain reproducibility as previously mentioned, we preferred a reaction in solution.

The stereochemical outcome of the sigmatropic rearrangement of disubstituted dienol **152** can be explained by the chair-like conformation of the transition state (**Scheme 36**). We will consider for the explanation only one of the enantiomers of the racemic compound. Two different transition states **162a** and **162b** can be

envisaged for dienol **152**. Their energy difference can be explained by the steric effect of cinnamyl moiety disrupting the transition state. Transition state **162a** is disfavored due to steric repulsion between the difluoroalkene and the cinnamyl moieties. In transition state **162b** the repulsion is lower, favoring this particular transition state instead of **162a**. The expected stereochemical outcome is therefore a mixture of two diastereoisomers; the major diastereoisomer **160b** presenting an *anti* relationship between the methyl group and the hydroxyl – the minor diastereoisomer **160a** a *syn* one.




**Scheme 36.** Most likely transition states of the [3,3] sigmatropic rearrangement and stereochemical outcome.

Three-dimensional representation of the transition state of dienol **152** (**Figure 22**) demonstrates the spatial interference between the methyl group of the

α-methyl cinnamyl moiety and the forming bond (C5-C8). Therefore, the decreased reactivity of the [3,3] rearrangement for the different substrates could be explained by a higher level of hindrance of the dienol destabilising the chair-like transition state and therefore slowing the rate of rearrangement.

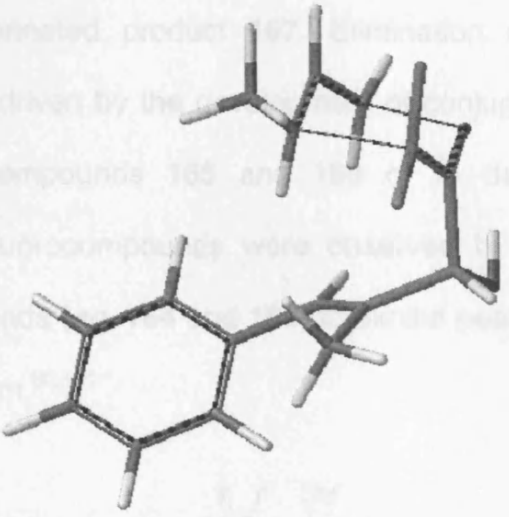


**Figure 22.** Three-dimensional representation of the Claisen rearrangement transition state of dienol **152**.

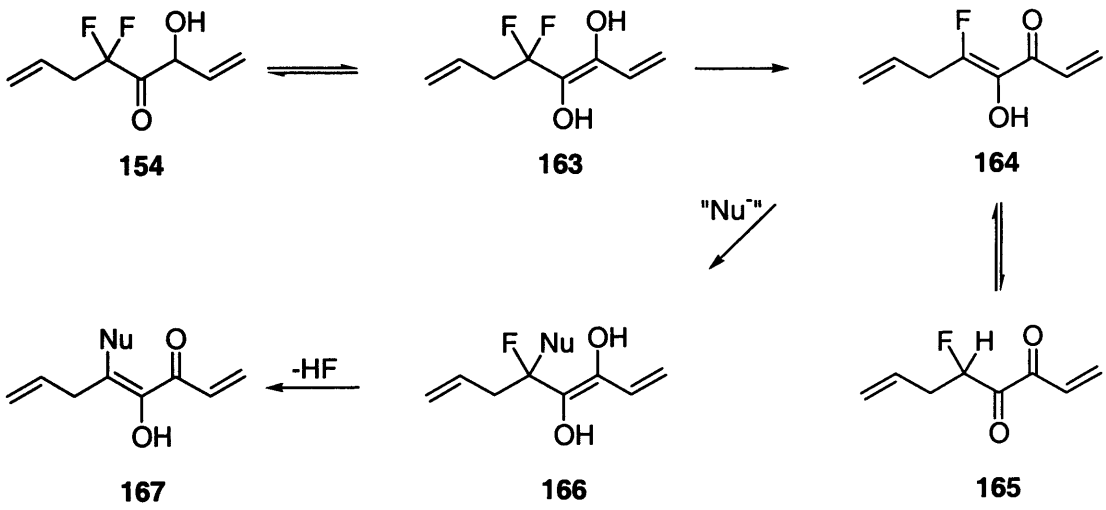
The theoretical sense of selection was in agreement with the coupling constant of the ring closing metathesis product (*cf.* **2.3.3.2**) and confirmed when a crystal structure was obtained after ring closing metathesis and dihydroxylation (*cf.* **2.4.2.2**).

2.2.2.2.4 Stability

Hydroxyketones **154** and **155** were only moderately stable and decomposed during attempted purification by column chromatography, so no attempt at purification were made for the other hydroxyketones. Despite their instability, all the hydroxyketones could be kept overnight in the freezer when in solution in

chloroform or diethyl ether-neat crude materials were very unstable even at -20 °C.

The moderate stability of hydroxyketones **154** and **155** could be explained by their enolisation leading to enediol **163** (**Scheme 37**) from which elimination of HF could occur. Nucleophilic attack on the highly electrophilic centre in **164** can deliver the non-fluorinated product **167**. Elimination of HF should be an irreversible process driven by the development of conjugation and should lead to the monofluorocompounds **165** and **166** or to desfluoro species **167**. However no monofluorocompounds were observed by $^{19}F$ NMR; we would expect such compounds (*eg.* **164** and **165**) to exhibit peaks around -200 ppm in the $^{19}F$ NMR spectrum.[80,111]

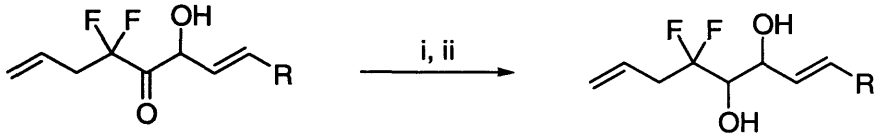



**Scheme 37.**

In order to avoid the stability problem, we decided to reduce those ketones into the corresponding diols *in situ* without purification.

### 2.2.3 Reduction Methods

First, we attempted the reduction of the two simplest hydroxyketones **154** and **155** using sodium borohydride in diethyl ether (**Scheme 38**). Indeed, we obtained volatile intermediate **154** in solution in this particular solvent.




**154** R = H
**155** R = Ph

(3*S**,4*S**)-**143a** R = H
(3*S**,4*R**)-**143b** R = H
(3*S**,4*S**)-**168** R = Ph
(3*S**,4*R**)-**169** R = Ph

**Scheme 38.** Reagents and conditions: i) $NaBH_4$ (3.0 eq.), $Et_2O$, rt, overnight; ii) Water.

The reduction of hydroxyketones **154** and **155** affords racemic diols **143a**, **143b** and **168, 169** respectively as a mixture of diastereoisomers (**Table 9**). The diastereoisomeric ratio was determined by $^{19}F$ NMR. In the case of **154**, the $^{19}F$ NMR showed no relevant differences between sodium borohydride and DIBAL induced tandem rearrangement/reduction in terms of stereochemical outcome; the same ratio was observed (9:1) in each case. For hydroxyketone **155**, a 6:1 ratio of diastereoisomers was observed.

The structure of **168/169** was confirmed by NMR and mass spectroscopy but, at this stage, the stereochemical outcome of the reduction could not be determined (the configurations of **168** and **169** were deduced after the ring closing metathesis step).

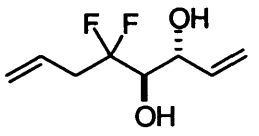
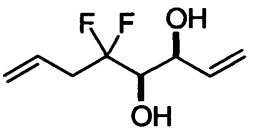
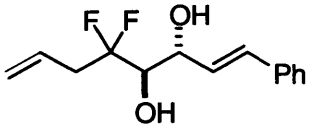
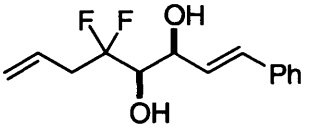
| Ketone | Racemic diastereoisomeric diol | | Yield (%)[a] | Ratio[b] |
|---|---|---|---|---|
| 154 |  **143a** |  **143b** | 11[c] | 9:1 |
| 155 |  **168** |  **169** | 20[c]<br>51[d] | 6:1 |

**Table 9.** [a]: yield from ether **116** (over 3 steps); [b]: by $^{19}F$ NMR; [c]: dehydrofluorination/metallation performed with *n*-BuLi; [d]: dehydrofluorination/metallation performed with *t*-BuLi.

The sense of the borohydride reduction appears to be in broad agreement with the literature describing α-hydroxyketone reduction in which *anti*-products are favored.

Generally speaking, the hydroxyl substituent can influence the reduction in two ways (**Figure 23**):[112]

**A.** by electronic effects (overlap of $\sigma_{C\text{-}O}^*$ with the forming bond) which stabilise a particular rotamer in the transition state, and

**B.** by becoming involved in a chelated complex involving the carbonyl oxygen and a metal ion.

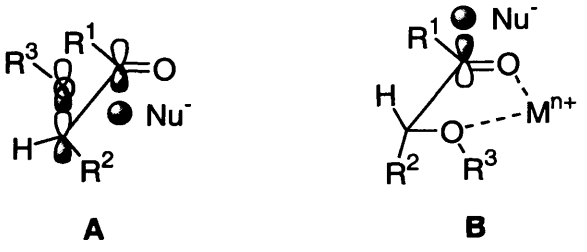
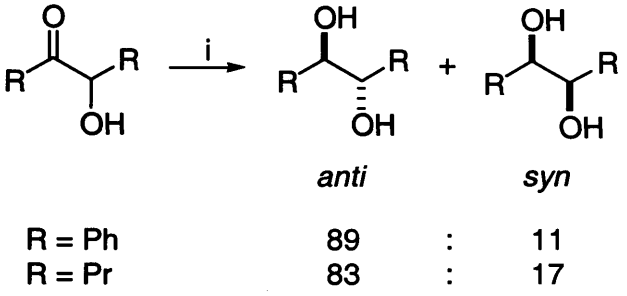



**Figure 23.** 'Felkin-Ahn' model and 'Chelation control' in the addition of nucleophiles to C=O groups.

In many cases, one of the above effects will tend to direct attack to one face of the carbonyl group, while another will promote the alternative mode of reaction. It is worth mentioning that the stereochemical outcome is different in the two cases. The Felkin-Ahn transition state leads to *syn*-products whereas a reaction under chelation control affords the *anti*-products.

Unprotected α-hydroxyketones appear to favor chelation control with most reagents.[112] Araki *et al.*[113] obtained very good *anti* diastereoselectivity using sodium borohydride for the reduction of different α-hydroxyketones (**Scheme 39**).

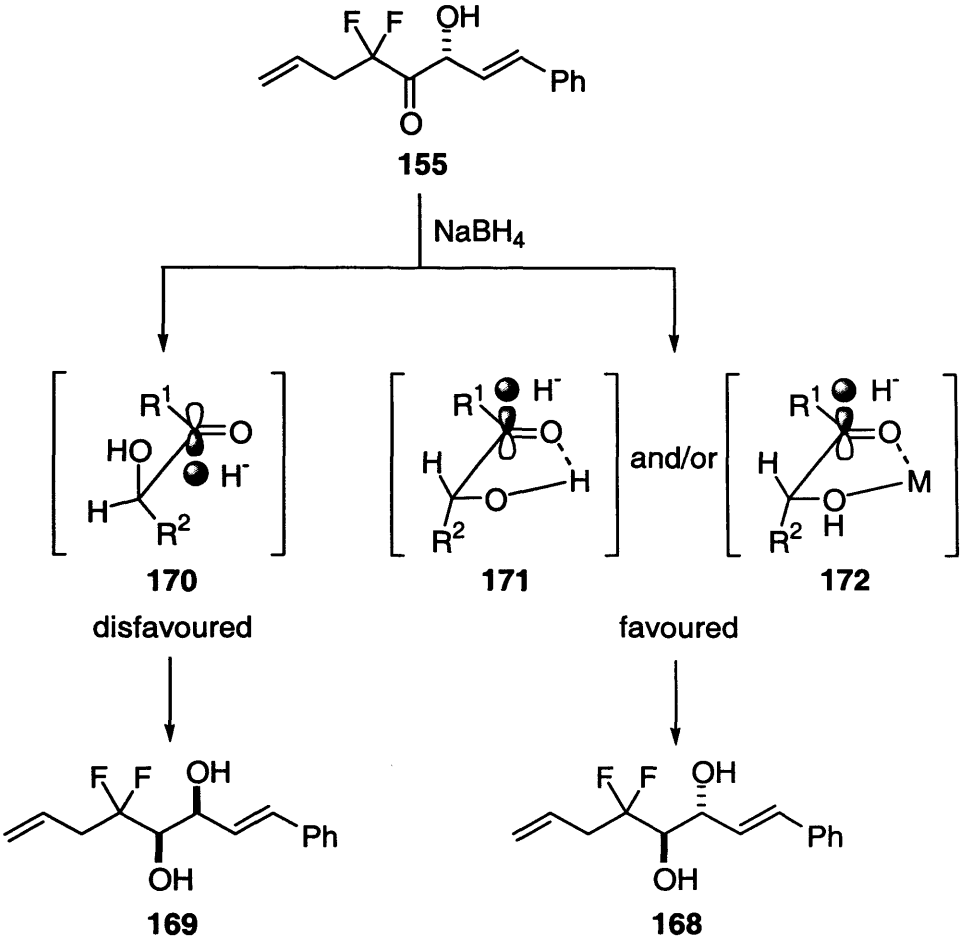



**Scheme 39.** Reagents and conditions: i) $NaBH_4$ (2-5 eq.), $Et_2O$, rt, overnight.

Moreover, we can argue that in a relatively non-polar solvent, here diethyl ether, the hydrogen atom of the hydroxyl group plays the role of the metal ion by bridging the two oxygen atoms; therefore no metal ion is needed to favor transition state **B** compared to **A** (**Figure 23**). However the hydrogen atom is much less effective than a metal ion, resulting in a moderate diastereoisomeric excess of *anti*-product over *syn*-product.

So the principle can be applied to hydroxyketone **155** (**Scheme 40**) to explain the stereochemical outcome of the reduction with sodium borohydride. The two possible transition states can be considered; first **170** resulting from the Felkin-Ahn model and **171/172** from the hydrogen bonding/chelation control. A large

number of empirical studies have shown that reactions of this type of molecule favor 'chelation control' **171/172** resulting in a diastereoisomeric excess of the *anti*-products **168** compared to the *syn*-products **169**.

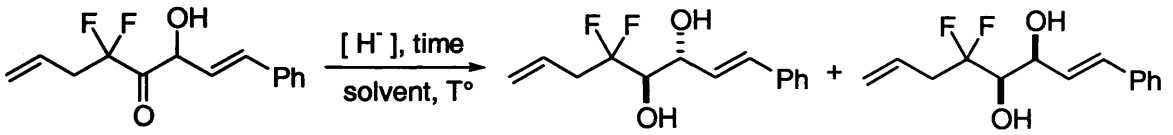



**Scheme 40.** Stereoselective reduction of the α-hydroxyketone.

### *2.2.3.1 Screening Different Reducing Agents*

Due to its ease of handling and mild reactivity, sodium borohydride was initially used for the reduction of hydroxyketones **154** and **155**. Further investigations were necessary to determine if sodium borohydride was offering the best stereoselectivity. Hydroxyketone **155** was reacted mainly with different lithium based reducing agents (**Scheme 41**) (**Table 10**). The reaction conditions were

the ones used commonly for each reducing agent for the reduction of a α-hydroxyketones.[112]




155 168 169

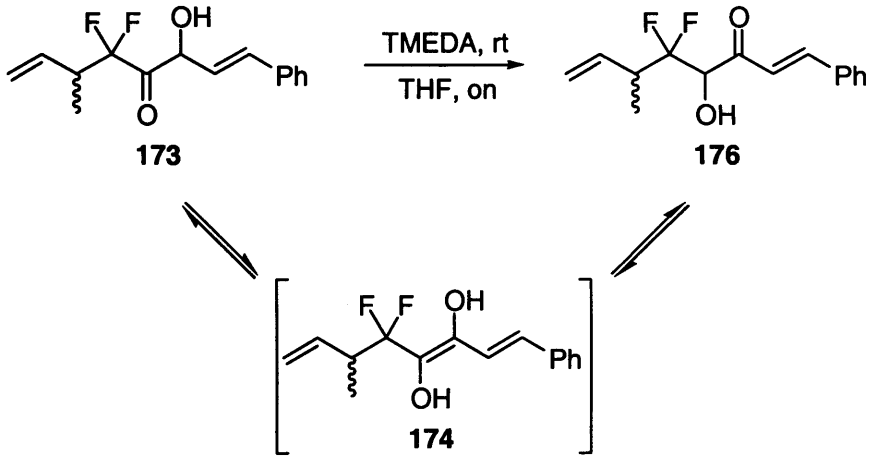
**Scheme 41.** Screening of different reduction conditions.

| Solvent | [H⁻] | T (°C) | Time (h) | Ratio[a] |
|---|---|---|---|---|
| $Et_2O$ | $NaBH_4$ | rt | 20 | 6:1 |
| Dry $Et_2O$ | LAH | -78 | 3.0 | 6:1 |
| Dry $Et_2O$ | DIBAL | -78 | 2.8 | 5.5:1 |
| Dry $Et_2O$ | K-Selectride | -78 | 2.5 | -[b,c] |
| Dry $Et_2O$ | L-Selectride | -78 | 2.5 | -[b,c] |
| Dry $Et_2O$ | $LiBH_4$ | -78 | 2.5 | -[b] |

**Table 10.** [a]: ratio of **168/169** by $^{19}F$ NMR; [b]: complex mixture by $^{19}F$ NMR (no ratio could be determined); [c]: new AB system appears.

The stereoselectivity of the reduction using LAH and DIBAL were very similar or identical to that obtained with sodium borohydride. Indeed, we observed a diastereoisomeric ratio of 6:1. In the case of lithium borohydride, the $^{19}F$ NMR spectrum of the crude material was very complex preventing the determination of the diastereoisomeric ratio.

The $^{19}F$ NMR spectrum of the crude product of the reduction of hydroxyketone **155** using K and L-selectride exhibited a new AB system and was also very complex. Unfortunately, the complexity of the crude material did not allow us to determine the structure of this new product. Nevertheless, K and L-selectride are known to potentially reduce α-enones to the corresponding saturated alcohol[114] and Audouard[115] has demonstrated that under basic conditions hydroxyketone **173** can transpose to form an α-enone (**Scheme 42**). The reduction condition using K and L-selectride are basic and could therefore cause transposition leading to the saturated alcohol.

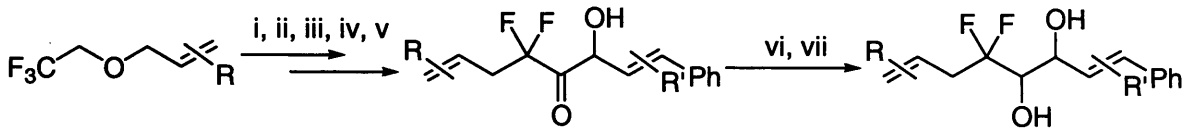



**Scheme 42.** Transposition of hydroxyketone in basic condition.

This transposition was also investigated on hydroxyketone **155** under the same reaction conditions. Unfortunately, due to the lower stability of hydroxyketone **155** compared to **173** (in contrary to **155**, hydroxyketone **173** can be purified by column chromatography on silica gel and is reasonably stable when kept at room temperature), no transposed product could be isolated from the crude material. The $^{1}H$ and $^{19}F$ NMR spectra indicated decomposition of the reaction mixture.

### *2.2.3.2 Solvent Effects on the Reduction*

Sodium borohydride appeared to be the best reducing agent for our substrates delivering a good stereoselectivity at low cost. To complete the optimisation of the reduction (**Scheme 43**), a systematic investigation of different solvents was performed (**Table 11**).




R = H, Me R' = H, Me

**Scheme 43.** Reagents and conditions: i) *t*-BuLi (2.0 eq.), tetrahydrofuran, -100 °C, 15 min ii) *trans*-cinnamaldehyde **145** or α-methyl *trans*-cinnamaldehyde **148**, -100 °C iii) -100 to -90 °C, 15 min; iv) $NH_4Cl_{sat.}$ at -90 °C, v) chloroform, 60 °C, 25-150 min, vi) $NaBH_4$ (3.0 eq.) **solvent**, rt, overnight, vii) $HCl_{conc}$

The different solvents were compared according to the quality of $^1H$ and $^{19}F$ NMR spectra of the crude material (*cf.* **Appendix II - 6.2.1.**) and especially by the yield after purification by flash column chromatography. Three different α-hydroxyketones were investigated. The nature of the substitution of the hydroxyketones seemed not to influence the yield of the reduction. Ethanol was found to be a superior solvent for those reaction conditions giving much cleaner crude product and yielding more of the desired product. Indeed the yields from the reactions in diethyl ether or chloroform were inferior. No yield could be obtained when isopropanol was used, due to complexity of the crude product mixture.

It is worth mentioning that the reaction conditions are now including a polar solvent, therefore the reduction model establish previously (cf. **2.2.3**) involving hydrogen bonding cannot apply under polar conditions. So, the chelation of the weak Lewis acid sodium delivers the *anti*-diastereoisomers in the same ratio.

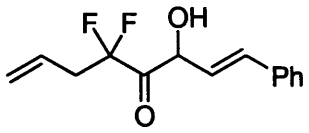
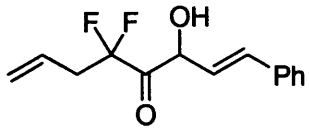
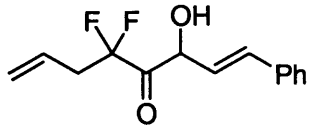
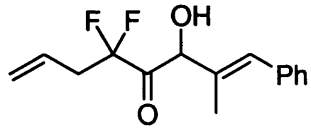
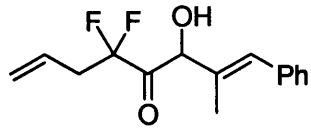
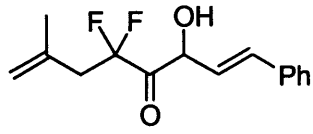
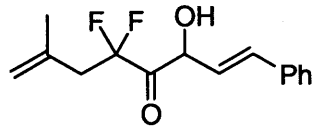
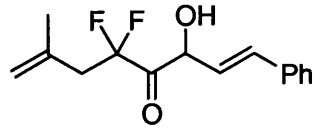
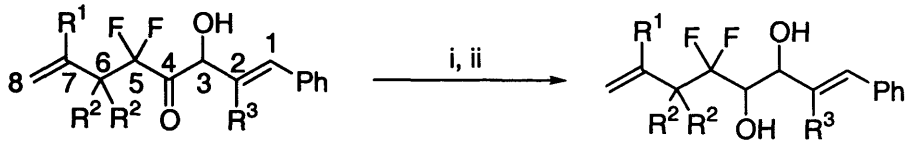
| Entry | ketones | | [H⁻] Solvent | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  | **155** | $Et_2O$ | 51 |
| 2 |  | **155** | EtOH | 68 |
| 3 |  | **155** | *i*-PrOH | -[b] |
| 4 |  | **157** | $Et_2O$ | 41 |
| 5 |  | **157** | EtOH | 56 |
| 6 |  | **158** | $Et_2O$ | 29 |
| 7 |  | **158** | EtOH | 52 |
| 8 |  | **158** | $CHCl_3$ | 40 |

**Table: 11.** [a]: isolated yield from ether (over 3 steps); [b]: complex $^{19}F$ NMR spectrum.

### *2.2.3.3 Application of the Optimised Conditions*

The optimised conditions were then applied to the small library of dienols (**Scheme 44**).




**Scheme 44.** Reagents and conditions: i) $NaBH_4$ (3.0 eq.), EtOH, rt, overnight, ii) $HCl_{conc}$

The different substrates behaved differently under the reduction conditions (**Table 12**) according to the level and the position of the substitution. First, the non-substituted hydroxyketone delivers racemic acyclic diols **168** and **169** with a diastereoisomeric ratio of 6:1 as seen previously.

When the substrate was substituted at C-7, such as hydroxyketone **158**, the diastereoselectivity increased dramatically delivering mainly one diastereoisomer with a ratio of 11:1.

Furthermore, when substituted at C-2 position such as in hydroxyketones **157** and **159**, the diastereoselectivity was very high delivering a single detectable diastereoisomer in a good and excellent yield respectively over three steps; from ether **116** and **117**. Crude diol **180** could be purified directly by recrystallisation from hot hexane.

Furthermore, we obtained the crystal structure of acyclic diol **180** (**Figure 24**) that shows clearly the relationship between the stereogenic centres set in the reduction step. The 1D and 2D NMR experiments allowed us to assign each proton and carbon of the molecule and to confirm clearly the structure of the diol **180**.

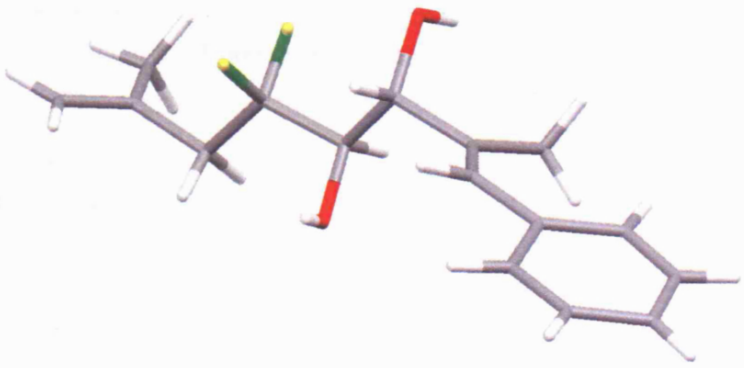


**Figure 24**. Molecular structure of diol **180** in the crystal.

A 3:1 mixture of hydroxyketones **160b** and **160a** (the diastereoselective mixture arises from the Claisen rearrangement (*cf.* **2.2.2.2.3**)) afforded a 3:1 mixture of diols **182** and **183** after reduction. No additional diastereoisomers could be detected.

When the substrate was substituted at C-6, such as in hydroxyketone **161**, the diastereoselectivity decreased leading to *anti*-diol **184** and *syn*-diol **185** in a 7:1 ratio but still a very good yield of 65 % from the allyl ether of trifluoroethanol.

The structure of the acyclic diols was inferred from the crystal structure of the ring closing metathesis products

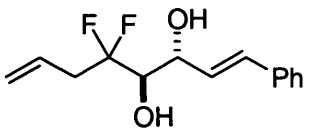
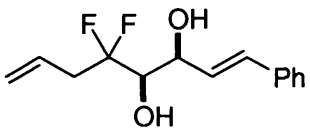
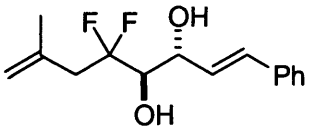
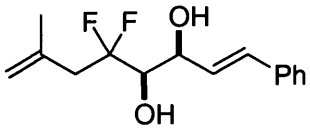
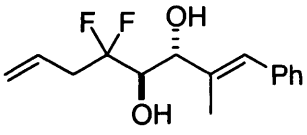
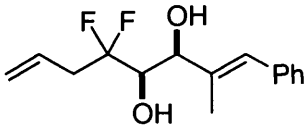
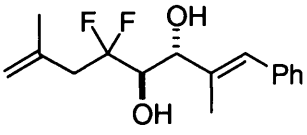
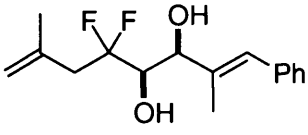
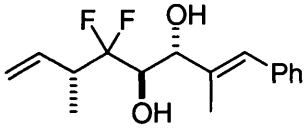
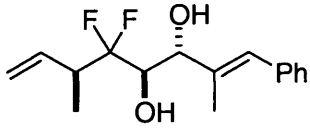
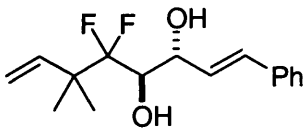
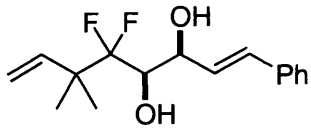
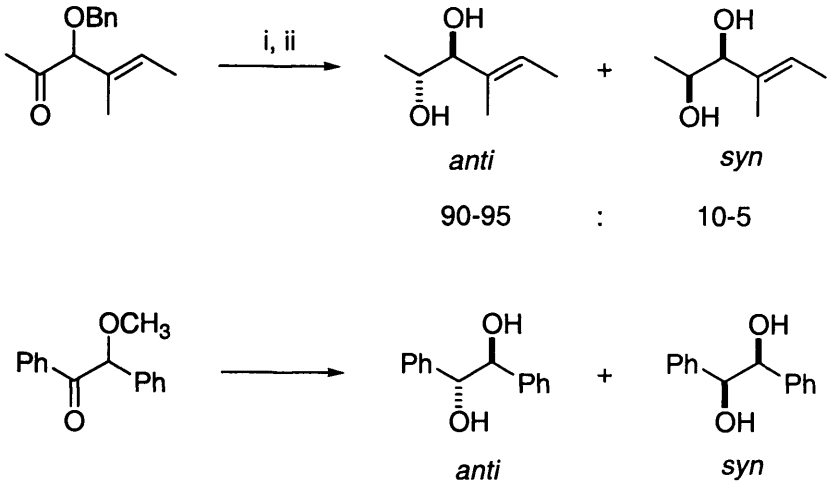
| ketones | Diastereoisomeric diol | | Yield (%)[a] | ratio[c] |
|---|---|---|---|---|
| 155 |  168 |  169 | 68 | 6:1 |
| 158 |  176 |  177 | 52 | 11:1 |
| 157 |  178 |  179 | 56 | 1:0 |
| 159 |  180 |  181 | 86[b] | 1:0 |
| 160a 160b |  182 |  183 | 78 | 3:1 |
| 161 |  184 |  185 | 65 | 7:1 |

**Table 12.** [a]: isolated yield over 3 steps; [b]: purified by recrystallisation in hot hexane; [c]: determined by $^{19}F$ NMR.

A bulky substituent such as methyl group attached *via* an $sp^2$-hybridised carbon seems to promote chelation control, even in presence of reagents which promote Felkin-Ahn transition state (*eg.* K-Selectride is known to promote Felkin-Ahn transition state with non-substituted substrates) (**Scheme 45**), with a very good diastereoselectivity.[116,117]




| Methods | dr (*anti*/*syn*) | Yield (%) |
|---|---|---|
| LAH, $Et_2O$, -78 °C | 98:2 | 83 |
| DIBAL-H, THF, -78 °C | 99:1 | 85 |
| $NaBH_4$, $MeOH/H_2O$, 0 °C | 90:10 | 86 |
| K-Selectride, $Et_2O$, -78 °C | 99:1 | 68 |

**Scheme 45.** Reagents and conditions: i) LAH or $NaBH_4$; ii) Na / liq. $NH_3$.

Furthermore, the level of substitution seemed to have an important influence on the quality of the crude material.

### 2.2.4 Protected Acyclic Diols

We were interested explore the effect of cyclic diol protecting groups on the ring closing metathesis because protecting group will be required later on in the synthesis. We were also interested in the effect exerted on the ring closing metathesis, which would now be annelative rather than annulative (**Figure 25**). Each rotation that must be frozen makes $\Delta S^{\ddagger}$ more negative and therefore ($-T\Delta S^{\ddagger}$) becomes more positive increasing $\Delta G^{\ddagger}$ ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) and decreasing K. So the annelations benefit because the pre-existing ring restricts rotation around one rotor at least.

Cyclic protection of the *anti*-diol would present the chains that form the diene *cis* to each other which would be expected to assist ring closing metathesis.

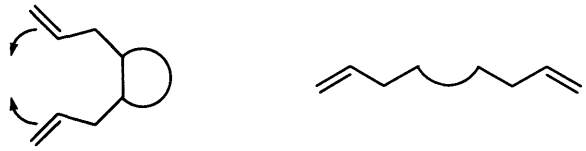
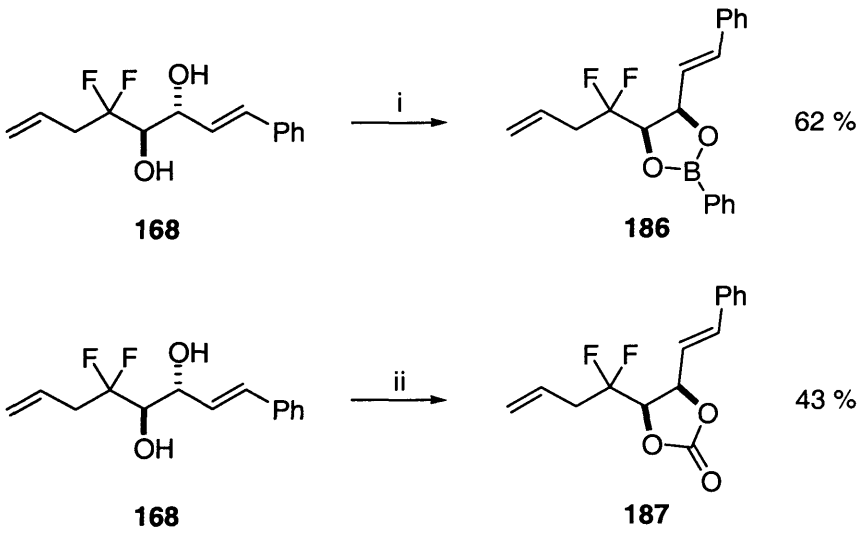



**Figure 25.** Hypothetical advantages of protecting group.

The ability of boron acids to form stable esters reversibly, upon reaction with hydroxyl groups or enolates, has allowed their exploitation as templates to facilitate cyclisation reactions such as pericyclic and macrocyclisation reactions.[118]

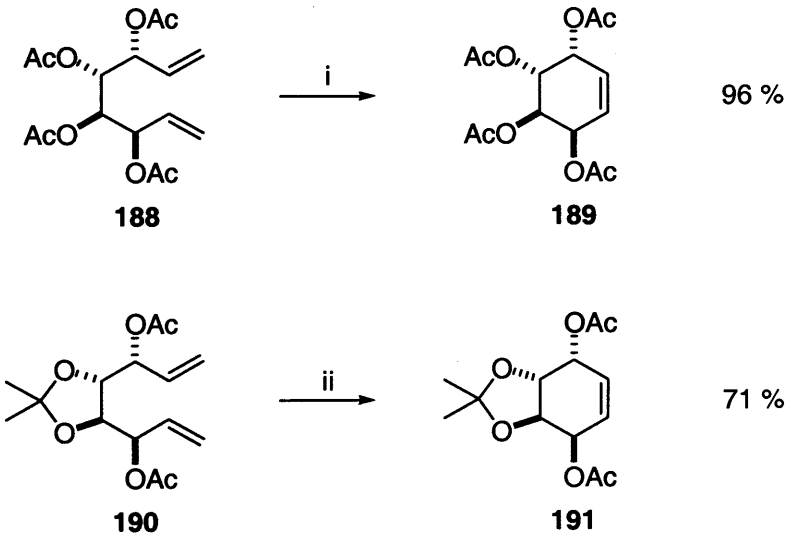
We reacted one of our acyclic diols with two different protecting groups (**Scheme 46**).




**Scheme 46.** Reagents and conditions: i) benzeneboronic acid, tetrahydrofuran, rt, 1.5 h; ii) phosgene, pyridine (6 eq.), tetrahydrofuran, 0 °C, 1.0 h.

The reaction with benzeneboronic acid delivered rapidly dioxaborolane **186** in moderate yield. This compound was of particular interest because of its relationship to a common mode ofprotection.[118] Acyclic diol **168** was reacted with phosgene[119] to afford carbonate **187** in moderate yield. Mass spectrometry and NMR spectra allowed us to confirm the obtention of those cyclic precursors. Unfortunately, the presence of a very small amount of impurities did not allow us to obtain the accurate mass on either of these products.

Examples reported by Fürnster *et al.*[79] and Madsen *et al.*[120] allowed us to compare the influence of an additional ring, here an acetonide to protect a 1,2 diol function (**Scheme 47**). For these particular substrates, **188** and **190**, the presence of an additional ring reduced the amount of catalyst required by 7.5 fold still in good yield (71 %).



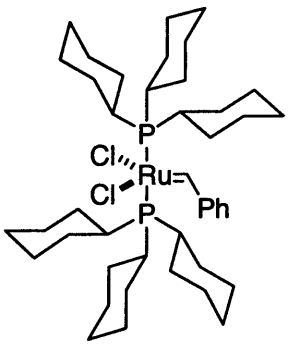

**Scheme 47.** Reagents and conditions: i) **76** (7.5 mol%), dichloromethane, reflux; ii) **76** (1 mol%), dichloromethane, 5 h.

## *2.3 Toward Cyclic Precursors*

The next key step of the synthesis of cyclitols and carbasugars analogues was the ring closing metathesis which would allow us to obtain the cyclohexene precursors to difluoroanalogues of cyclitols and carbasugars.

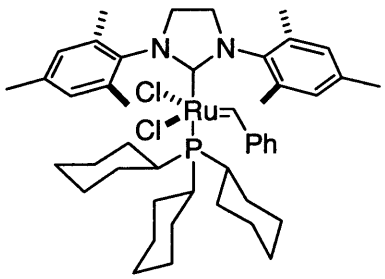
### 2.3.1 First Attempts

First the ring closing metathesis reaction was investigated on non-substituted substrate **168** with the first generation Grubbs' catalyst **76** (**Figure 26**). Unfortunately, the reaction time was long considering the catalyst loading (reagents and conditions: **76** (5 mol%), dichloromethane, 25 hours at reflux to reach 95 % conversion).




**76**

Grubbs I



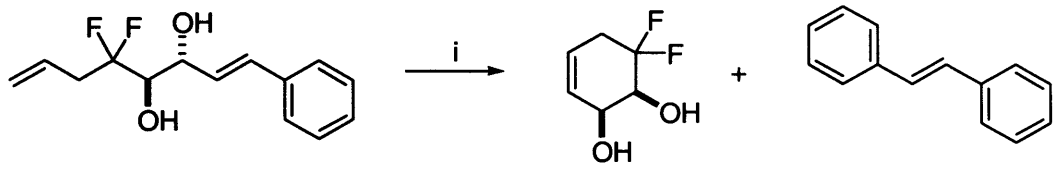

**77**

Grubbs II

**Figure 26.** Grubbs' catalyst **76** and **77**.

Therefore ring closing metathesis was performed on non-substituted acyclic diol **168** (**Scheme 48**) under unoptimised conditions in presence of second generation Grubbs' catalyst **77**, which is known to be more reactive than the first generation catalyst **76** (*cf.* **1.7.1.**). The starting material was consumed

completely within 2.5 hours to afford cyclic diol **192** and stilbene **193** as by-product. The difluoro cyclohexene diol **192** was isolated after column chromatography in modest yield (51 %) in very good purity (97 %), though the reaction was carried out on a small scale (~ 0.5 mmol). The crude material quality was very poor delivering the compound as a black oil due to the presence of significant contaminants of ruthenium oxides.




**168** **192** **193**

**Scheme 48.** Reagents and conditions: i) **77** (5 mol%), dichloromethane, reflux, 2.5 h, C = 0.05 M, 44-51%.

Prior to this stage, the stereochemical outcome of the reduction could not be determined. We could determine the stereochemical relationship looking at the value of $^{3}J_{H\text{-}H}$ coupling constant between the two hydroxyl groups by $^{1}H$ NMR spectroscopy. A $^{3}J_{H\text{-}H}$ coupling constant of 4.7 Hz (**Figure 27**) is characteristic of an axial-equatorial relationship between the two methine protons,[121] whereas an axial-axial relationship would exhibit a coupling constant between 9 and 13 Hz. Both conformers of diol **192** present one equatorial and one axial hydroxyl group and are probably similar in energy.

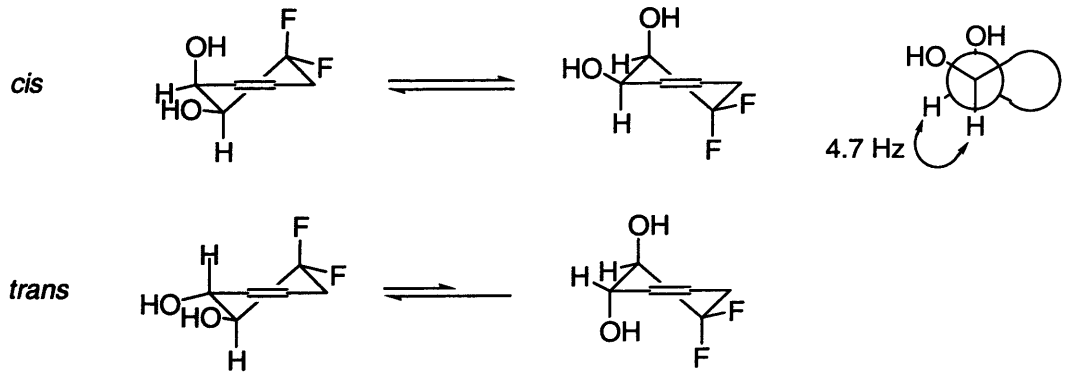
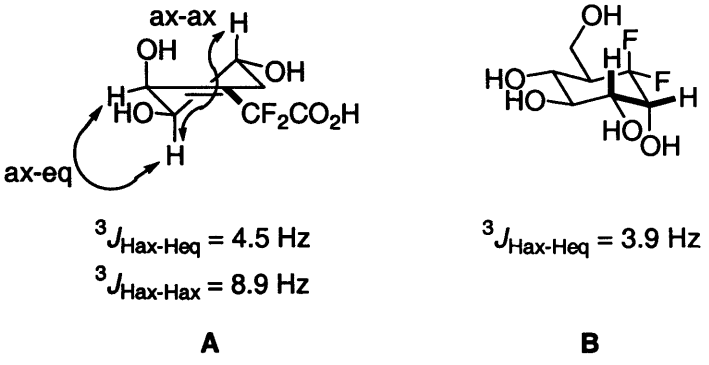


**Figure 27.**

Furthermore, we can compare the value of the coupling constants measured, with value from the literature such as those for **A**[18] (**Figure 28**) and **B**[32] which exhibit similar values for a *cis* relationship between two hydroxyl groups in each case.




$^3J_{Hax-Heq}$ = 4.5 Hz
$^3J_{Hax-Hax}$ = 8.9 Hz

**A**

$^3J_{Hax-Heq}$ = 3.9 Hz

**B**

**Figure 28.** Examples from the literature.

Therefore the *cis* relationship could be assigned identifying the *anti*-1,2-diastereoisomer of diol **168** as the major product from the reduction.

Furthermore, small blocks of diol **192** fortuitously crystallised from the dark oil. These were of sufficient quality for structural determination by x-ray crystallography. The crystal structure (**Figure 29**) shows clearly the relationship between the stereogenic centres set in the reduction step. The 1D and 2D NMR experiments allowed us to assign each proton and carbon of the molecule and to confirm clearly the structure of the diol **192**.

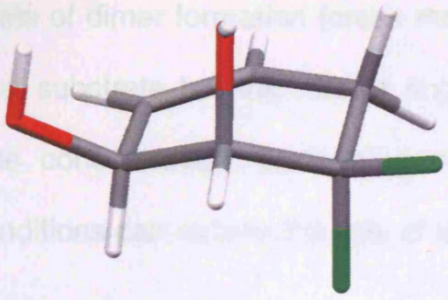


**Figure 29**. Molecular structure of diol **192** in the crystal.

Initially, the usual purification by column chromatography on silica gel did not allow us to obtain pure diol **192**. Further investigations with mass spectrometry have shown that phosphine derivatives were present even after several purifications. The relatively low melting point of our diols (range: 50-80 °C) allowed us to use sublimation at very low pressure (~ 0.05 mmHg) and moderate temperature (50-100 °C) to avoid decomposition. The volatile desired product sublimed away from the non volatile catalyst residues affording microanalytically pure product.

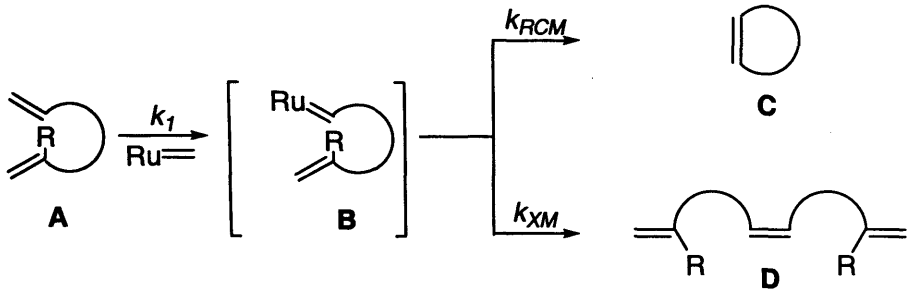
### 2.3.2 Optimisation

In order to obtain a better chemical yield from the ring closing metathesis, we screened the various parameter including concentration and catalyst loading, the key parameters of this particular reaction.

#### *2.3.2.1 Concentration*

The reaction concentration is very important key parameter of ring closing metathesis reactions. It can be seen (**Figure 30**) that the catalyst dependent term for productive ring closing metathesis versus dimer formation is

$k_{RCM}/k_{XM}$.[122] Since the rate of dimer formation (cross metathesis) is dependent upon the concentration of substrate but the rate of ring closing metathesis is independent of substrate concentration, performing ring closing metathesis reactions under dilute conditions can reduce the rate of dimerisation to the point where it is not observed.

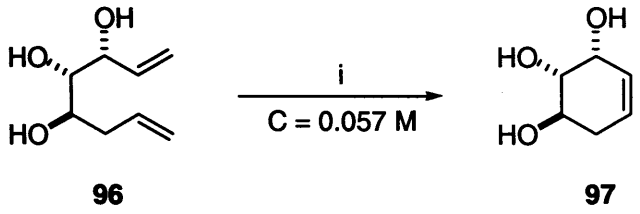



The kinetic ratio of product to dimer at time = t

$$\frac{d[C]}{dt} = k_{RCM}[B] \qquad \frac{d[D]}{dt} = k_{XM}[B]\cdot[A] \qquad \frac{[C]}{[D]} = \frac{k_{RCM}[B]}{k_{XM}[B]\cdot[A]} = \frac{k_{RCM}}{k_{XM}[A]}$$

**Figure 30.** The kinetics of ring closing versus dimerisation.

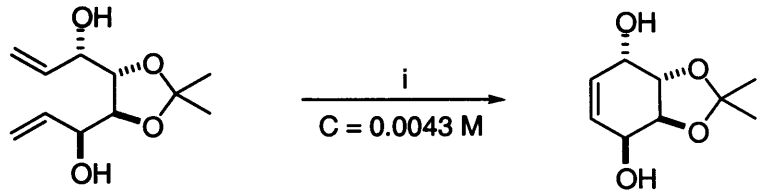
The use of a low concentration in order to avoid cross metathesis is a scale limiting factor of the reaction. The literature gives examples of concentration for substrates similar to ours. Madsen *et al.*[75] reported the ring closing metathesis using Grubbs' catalyst first generation **76** to cyclise triol **96** with a concentration of 0.057 M in substrate (**Scheme 49**). The concentration reported by Madsen *et al.*[75] varied from 0.063 to 0.027 M for the various substrates because it appears to be calculated on the weight of substrate rather than on the number of mole. It is therefore very difficult to measure the effect of concentration on the ring closing metathesis reactions reported and therefore determine if a lower yield is due to a lower reactivity or a result of a different concentration.




**96** **97**

**Scheme 49.** Reagents and conditions: i) Grubbs I **76** (10 mol%), dichloromethane, reflux, 1 h, 95 %.

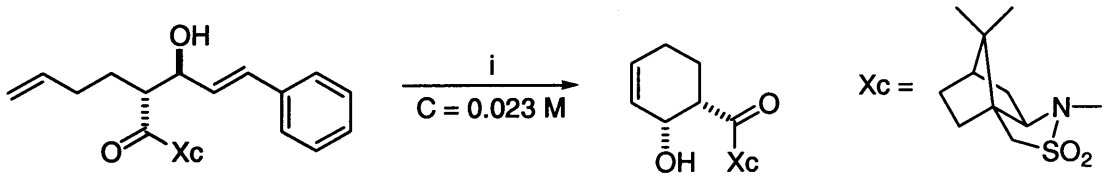
Similarly, Fürstner *et al.*[79] described ring closing metathesis of diols such as **105** (**Scheme 50**) to obtained conduritol derivatives after deprotection with a much more dilute reaction conditions (0.0043 M).




**105** **106**

**Scheme 50.** Reagents and conditions: i) **76** (1.5 mol%), dichloromethane, reflux, 5 h, 69 %.

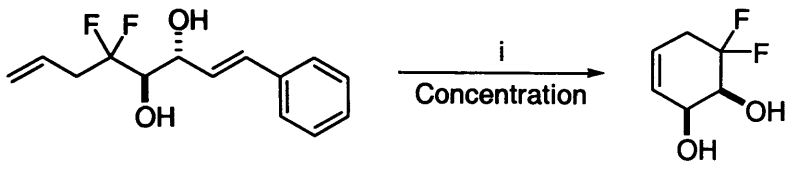
Finally, Perlmutter *et al.*[123] reported the synthesis of precursors to carbasugars (**Scheme 51**) obtained *via* a ring closing metathesis (C = 0.023 M) of a substrate with similar pattern to our substrate.




**194** **195**

**Scheme 51.** Reagents and conditions: i) **76** (10 mol%), dichloromethane, rt, overnight, 74 %.

Diol **168** was tested at three concentrations against ring closing metathesis conditions (**Scheme 52**).




168 192

**Scheme 52.** Reagents and conditions: i) **77** (5 mol%), dichloromethane, reflux, 45 min.

A dramatic loss in yield (**Table 13**) was observed from an average of 80 % at 0.025 and 0.01 M to 50 % when the concentration was doubled to 0.05 M. This drop in the yield might be explained by the competition between ring closing metathesis and dimerisation; new systems were observed in $^{19}F$ NMR in the residue obtained after washing the column with methanol; indeed, they were present in the baseline of the $^{19}F$ NMR spectrum of the crude material. No dimers were isolated and clearly identified due to the poor quality of the residue obtained after washing.

| Entry | Concentration (M) | Yield (%) |
|---|---|---|
| 1 | 0.05 | 44-51 |
| 2 | 0.025 | 77-82 |
| 3 | 0.01 | 78 |

**Table 13.** [a]: determined by $^{19}F$ NMR.

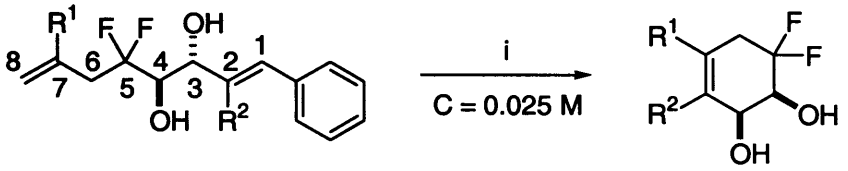
Therefore we performed further reactions at a concentration of 0.025 M.

### *2.3.2.2 Catalyst Loading*

Catalyst loading is also a key parameter in ring closing metathesis. Indeed the loading determines the rate of the reaction and therefore its reaction time and

conversion. A wide range of loadings, from 1 to 10%, can be found in the literature for substrates with similar pattern to our substrates.[75,79]

The reaction was investigated at different catalyst loadings (**Scheme 53**).




| | | | |
|---|---|---|---|
| $R^1 = R^2 = H$ | **168** | $R^1 = R^2 = H$ | **192** |
| $R^1 = H; R^2 = Me$ | **178** | $R^1 = H; R^2 = Me$ | **196** |
| $R^1 = Me; R^2 = H$ | **176** | $R^1 = Me; R^2 = H$ | **197** |

**Scheme 53.** Reagents and conditions: i) **77** (x mol%), dichloromethane, reflux, time.

Rapid full conversion of the non-substituted starting material **168** occurred with 5 mol% of second generation Grubbs' catalyst **77**. We observed (**Table 14**) no significant variation in reactivity and conversion rate when decreasing catalyst loading to 0.5 mol%. The reaction time increased dramatically (from 45 minutes to 48 hours with only 95 % conversion) at still lower loadings.

The subsequent reactions were therefore carried out with 0.5 mol% catalyst.

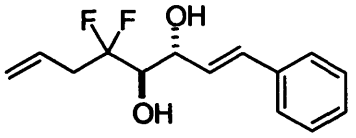
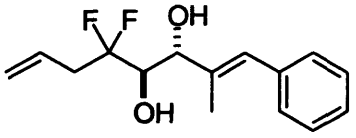
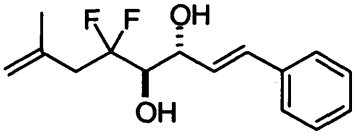
| Entry | Substrate | Catalyst (mol%) | Time (h) | Conversion (%)[a] |
|---|---|---|---|---|
| 1 |  **168** | 5 | 0.25 | 100 |
| 2 | | 1 | 0.25 | 100 |
| 3 | | 0.5 | 0.75 | 100 |
| 4 | | 0.25 | 48 | 95 |
| 5 | | 0.1 | 48 | 90 |
| 6 |  **178** | 5 | 44 | 100 |
| 7 | | 3 | 44 | 100 |
| 8 | | 1 | 44 | 93 |
| 9 | | 0.5 | 44 | 80 |
| 10 |  **176** | 6 | 28 | 100 |
| 11 | | 4 | 30 | 100 |
| 12 | | 2 | 48 | 29 |
| 13 | | 1.5 | 48 | <20 |

**Table 14.** [a]: determined by $^{19}F$ NMR.

A factor limiting the ability of the route diversity is the reactivity of more substituted substrates. Indeed, the types of double bond in the metathesis precursor determine the outcomes of the ring closing metathesis.[124]

We successfully obtained a wide range of substituted acyclic diols. The level of substitution at and around the ethenyl groups affects the ring closing metathesis rate strongly (*cf.* **2.3.3.2**).

We performed the metathesis reaction with diol **178** (**Scheme 53**) with a methylated double bond. We could immediately observe the difference

(**Table 14**) in reactivity compared to the non-substituted substrate. The reaction required a higher catalyst loading to achieve full conversion (3 % compared to 0.5 % - *cf.* **2.3.1**), indeed the metathesis did not reach full conversion when only 1 mol% was used.

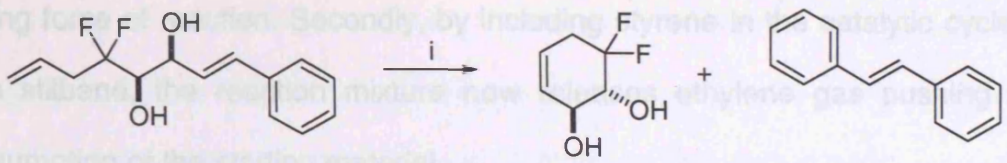
We observed similar behaviour for starting material **176** (**Scheme 53**). Here, 4 mol% was needed to convert acyclic diol **176** fully (**Table 14**).

Comparing entry **1** with entry **6** (**Table 14**) gives the rate difference of 160:1 measuring the effect of the methyl group at C2 position on the cyclisation and comparing entry **1** with entry **10** gives a ratio of 120:1 measuring the effect of the methyl group at C7 position on the initial allylidene exchange as metathesis occurs initially at the terminal olefin.[122]

### 2.3.3 Application of the Optimised Conditions

#### *2.3.3.1 Non-Substituted Substrate*

We performed ring closing metathesis with the minor diastereoisomer obtained from the reduction of hydroxyketone **155** under the reaction conditions previously determined (0.5 mol% of second generation Grubbs' catalyst **77**) for the major diastereoisomer (**Scheme 54**). The volatile desired product sublimed away from the non volatile catalyst residues affording microanalytically pure material after a further purification by column chromatography to remove traces of stilbene. The reaction delivered cyclic diol **198** with good yield (81 %).




169 198 193

**Scheme 54**. Reagents and conditions: i) **77** (0.5 mol%), dichloromethane, reflux, 45 min, C = 0.025 M, 81 %.

The crystal structure (**Figure 31**) shows clearly the relationship between the stereogenic centres set in the reduction step. Indeed we observed a *trans* relationship between the two hydroxyl groups inducing a *syn* relation for acyclic diol **169**.

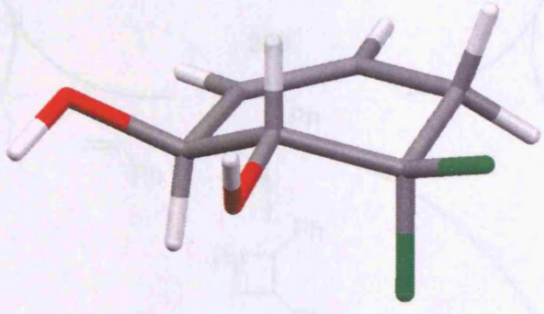


**Figure 31**. Molecular structure of diol **198** in the crystal.

Furthermore, we clearly identified one side product of the ring closing metathesis of acyclic diols **168** and **169** being stilbene **193** (**Scheme 54**). The presence of stilbene after consumption of the starting material could be explained by the pattern of our substrates **168** and **169**. Indeed, traditional ring closing metathesis substrates found in the literature present no substitution on the double bond. Here; the cinnamyl moiety is involved in the proposed catalytic cycle (**Figure 32**).

The formation of stilbene could be explained by two different driving forces. First, the development of extended conjugation (*cf.* **1.7.**) is known to be a

driving force of reaction. Secondly, by including styrene in the catalytic cycle to form stilbene, the reaction mixture now releases ethylene gas pushing the consumption of the starting material.

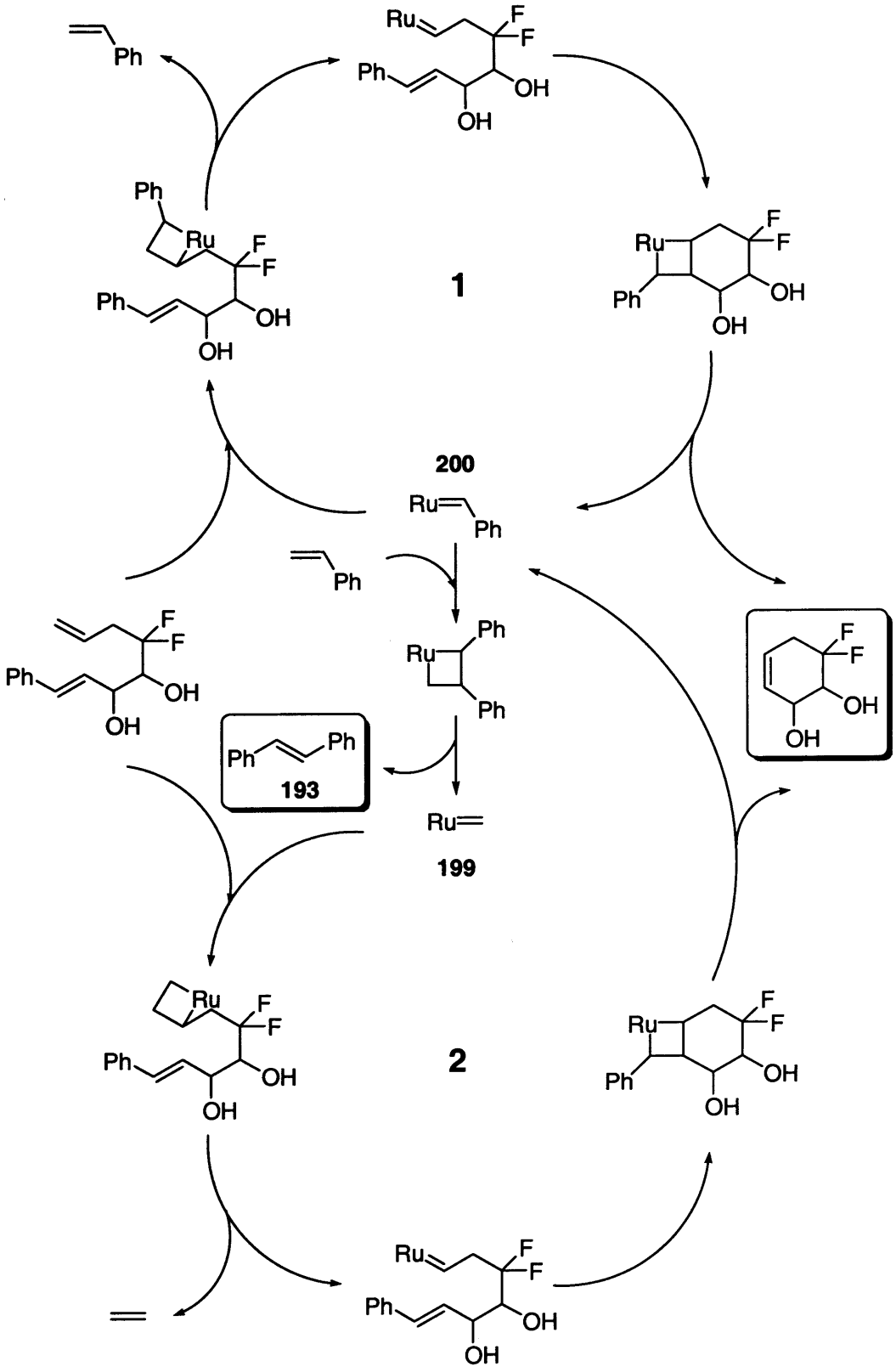
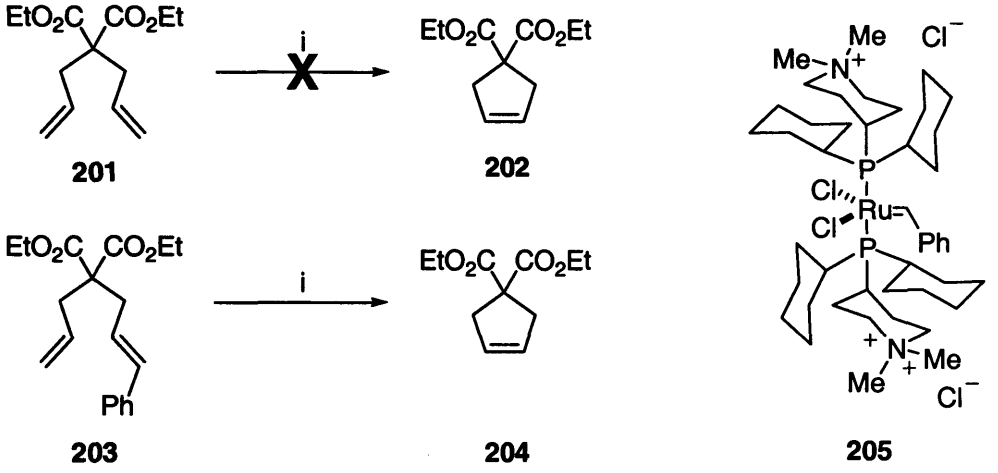



**Figure 32.** Proposed catalytic cycle.

Furthermore, it is worth mentioning that cycle **2** (**Figure 32**) regenerates benzylidene **200**, a more stable and active catalyst upon each turnover. Grubbs *et al.*[125] has investigated the influence of having phenyl-substituted substrates on the reactivity compared with non-substituted ones (**Scheme 55**). They demonstrated that some substrates required a phenyl substituent in order to perform the ring closing metathesis due to the higher stability of the ruthenium benzylidene compared to the ruthenium methylidene.[126]

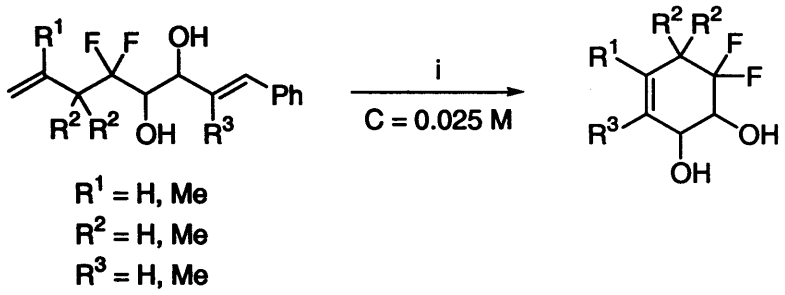



**Scheme 55.** Reagents and conditions: i) **205** (5 mol%), methanol, 45 °C, C = 0.24 M, 95 % conversion.

This particular point will be especially interesting in the case of substituted and therefore sterically hindered substrates (*cf.* **2.3.3.2**).

### *2.3.3.2 Substituted Substrates*

Substrates with different levels of substitution (**Scheme 56**) at various positions were now investigated with between 2.5 % to 8.5 % catalyst loadings.




$R^1$ = H, Me
$R^2$ = H, Me
$R^3$ = H, Me

**Scheme 56.** Reagents and conditions: i) **77** (x mol%), dichloromethane, reflux, time.

The volatile desired product sublimed away from the non volatile catalyst residues in each case affording microanalytically pure material after a further purification by column chromatography to remove traces of stilbene. We obtained the corresponding cyclohexyl difluoroanalogues with very good to moderate yield (**Table 15**). The reaction times are approximate and represent the reflux period required to achieve full conversion of starting material.

As discussed previously (*cf.* **2.3.1**), the phenyl substitution and therefore the regeneration of the benzylidene upon each turnover seemed to play an important role. Even the substrates with bulky substituents (**Table 15**) (methyl or dimethyl groups) undergo ring closing metathesis fairly rapidly with a higher catalyst loading of between 4 and 8.5 mol% than the non-substituted substrates (acyclic diol **168** and **169**).

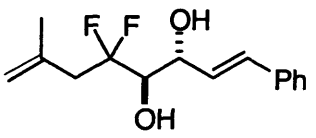
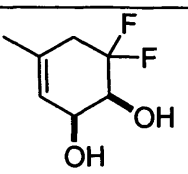
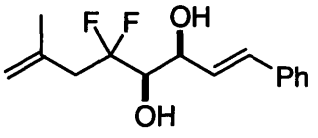
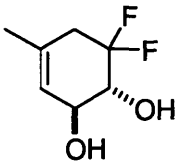
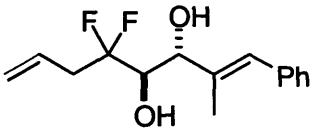
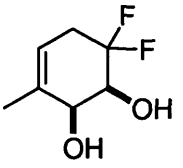
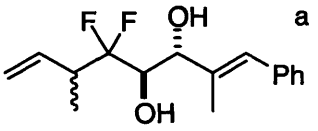
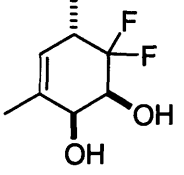
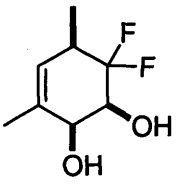
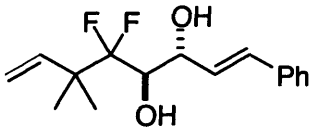
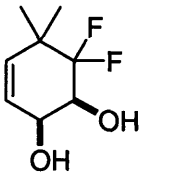
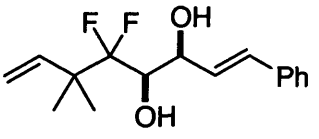
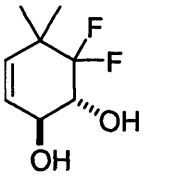
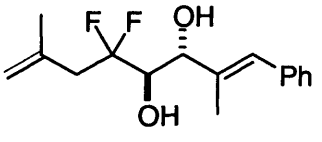
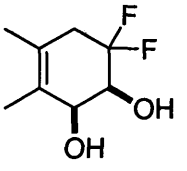
| Entry | Acyclic Diols | | Cyclic Diols | | CL[d] (mol%) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **176** |  | **197** | 4.0 | 30 | 79[b] |
| 2 |  | **177** |  | **206** | 5.0 | 48 | 90[c] |
| 3 |  | **178** |  | **196** | 2.5 | 48 | 77[b] |
| 4 |  dr: 3:1 | **182** **183** |   | **207** **208** | 8.5 | 48 | 81[b] |
| 5 |  | **184** |  | **209** | 5.0 | 5 | 83[b] |
| 6 |  | **185** |  | **210** | 5.0 | 18 | 80[b] |
| 7 |  | **180** |  | **211** | 8.5 | 48 | 81[b] |

**Table 15.** Ring closing metathesis of substituted substrates; [a]: mixture of diastereoisomers **182** and **183**; [b]: sublimed away then purified by column chromatography; [c]: purified by column chromatography; [d]: CL = catalyst loading.

Additionally, by comparing the reaction time for the ring closing metathesis of the *syn* acyclic diols with the *anti* acyclic ones (**Table 15** - entry **1** *vs* entry **2**; entry **5** *vs* entry **6**), we observed that the full consumption of starting material took from 1.5 to 3.5 times longer for the *syn* diols. In the same time, diol **168**

(*cf.* **2.3.2.2.** entry **3**) and diol **169** (*cf.***2.3.3.1.**) exhibited the same reaction time; the difference in reactivity might not show for these particular substrates due to the relatively short reaction time (45 minutes).

Grubbs *et al.*[127] has investigated the substituent effect on ruthenium(II) carbene **76** metathesis (**Table 16**) and demonstrated the important impact of substitution on the reaction rate.

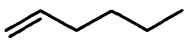
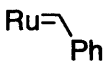
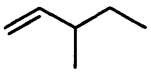
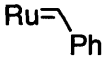
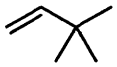
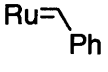
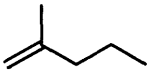
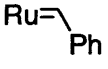
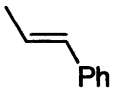
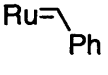
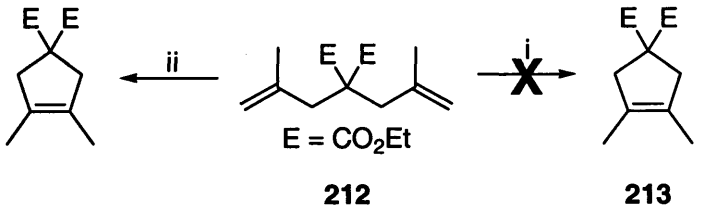
| Entry | Olefin | Initiator | Temperature (°C) | mole.s$^{-1}$ |
|---|---|---|---|---|
| 1 |  |  | 35 | ~$10^{-2}$ |
| 2 |  |  | 35 | 2.5 ± 0.2 x $10^{-4}$ |
| 3 |  |  | 35 | 2 x $10^{-6}$ |
| 4 |  |  | 35 | no reaction |
| 5 |  |  | 35 | no obs. reaction |

**Table 16.**

Comparing entry **1** with entry **2** and entry **1** with entry **3** (**Table 16**) shows the influence of allylic methyl group and allylic dimethyl group respectively, decreasing the reactivity of the substrate 100 and 10000 fold respectively. So, from Grubbs *et al.*[127] data we would expect diols **182/183** (**Table 15** - entry **4**) and diols **184/185** (**Table 15** - entry **5** and **6**) to start slowly and not at all respectively from the free double bond moiety. Also reactivity of the cinnamyl alcohol moiety (presenting an allylic alcohol) is poor from the result of the vinylic

phenyl part (**Table 16** -entry **5**) and Grubbs *et al.*[124] demonstrated that allylic alcohols exhibit slow cross metathesis (Type II when using the second generation Grubbs' catalyst **77**). Therefore, the ring closing metathesis reaction might start on the styrene moiety for these substituted diols instead of the non-substituted end of the olefin as shown by Grubbs *et al.*[122] This conjecture could be supported by the formation of stilbene from this styrene moiety driving the reaction to the full consumption of the starting material (*cf.* **2.3.3.1.**).

In addition, Nolan *et al.*[65] showed the low reactivity of disubstituted olefin substrate (**Scheme 57**). Diene **212** was non-reactive in presence of the first generation of Grubbs' catalyst **76** and required the second generation catalyst **77** to undergo ring closing metathesis.




**212** **213**

**Scheme 57.** Reagents and conditions: i) **76** (5 mol%), toluene, 80 °C, 3 h; ii) **77** (5 mol%), toluene, 80 °C, 1 h.

In order to determine the stereochemical outcome of the reduction step, we compared the coupling constant between the two protons which are α- to the hydroxyl groups with known-configuration non-substituted cyclic diol **192** (**Table 17**). As expected (*cf.* **2.2.3.1**) we observed very similar coupling constants for all the major diastereoisomers **192**, **196**, **197**, **209** and **211** (between 4.3 and 5.0 Hz) characteristic of an axial-equatorial relationship and therefore a configuration *cis* of our substrates (*cf.* **2.3.1**) and a 7.5 Hz coupling

constant for *trans* diol **210**, in the range of a pseudoaxial-pseudoaxial relationship (with a torsion angle smaller than 180°).[121]

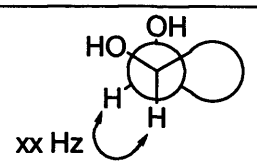
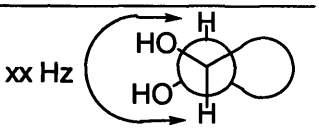
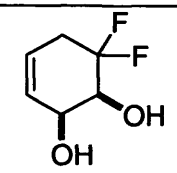
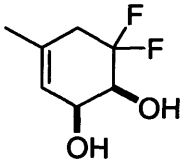
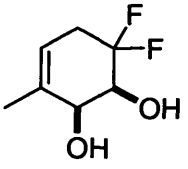
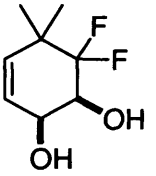
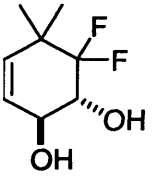
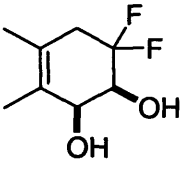
| Diols | |  ax-eq |  ax-ax |
|---|---|---|---|
|  | **192** | 4.7 | |
|  | **197** | 4.3 | |
|  | **196** | 5.3 | |
|  | **209** | 5.0 | |
|  | **210** | | 7.5 |
|  | **211** | 5.0 | |

**Table 17.** Coupling constant between the two protons α- to the hydroxyl groups ($^1$H NMR in $CDCl_3$).

Furthermore, we obtained the crystallographic structure of some of our difluorocyclohexenes. The crystal structure (**Figure 33**) of diol **196** shows clearly the relationship between the stereogenic centres set in the reduction step confirming the coupling constant observed in $^1$H NMR spectrum.

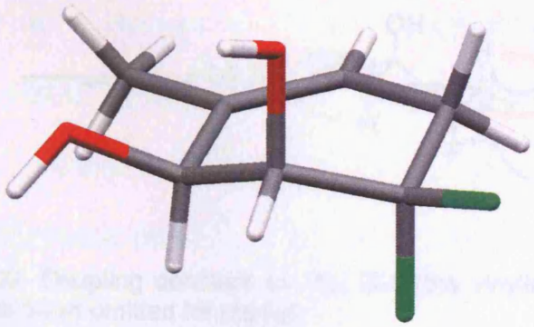


**Figure 33.** Molecular structure of diol **196** in the crystal.

The $^{1}H$ NMR spectrum of minor diastereoisomer **206** did not allow us to determine its configuration. Logically we expected a *trans* relationship as the major diastereoisomer **176** of the reduction step presented a *cis* configuration. Indeed, the crystal structure (**Figure 34**) shows clearly the relationship between the stereogenic centres set in the reduction step.

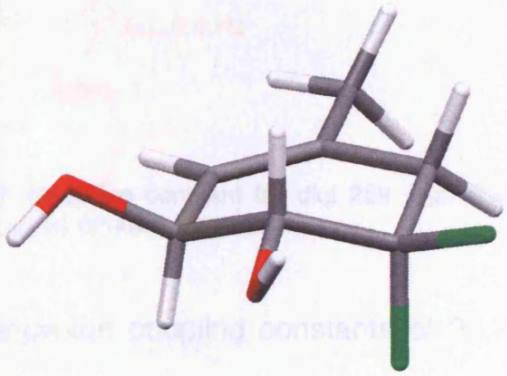


**Figure 34.** Molecular structure of diol **206** in the crystal.

Unfortunately; we did not obtain any crystallographic structure of diols **207** and **208**. So the configuration was determined by NMR spectroscopy. Indeed, we could measure precisely the coupling constants in the $^{1}H$ and $^{19}F$ NMR spectra. First, for **207** the coupling constants measured (**Figure 35**) corresponded to a *cis* relationship between the two hydroxyl groups and a *trans* one between them and the methyl group.

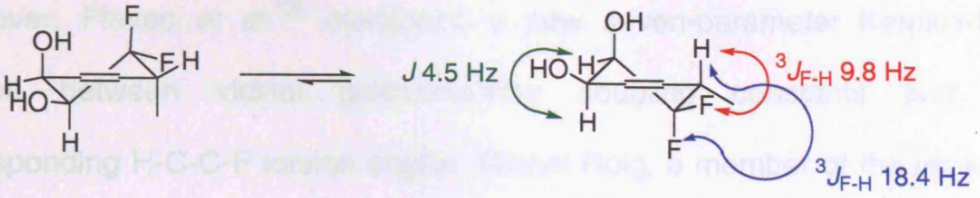



**Figure 35.** Coupling constant for diol **207** (the vinylic methyl group has been omitted for clarity).

Secondly, we determined the coupling constant of the minor diastereoisomer **208** (**Figure 36**). The different values corresponded to a relationship between the stereogenic centres, which placed the methyl group and the two hydroxyl groups all *cis*.

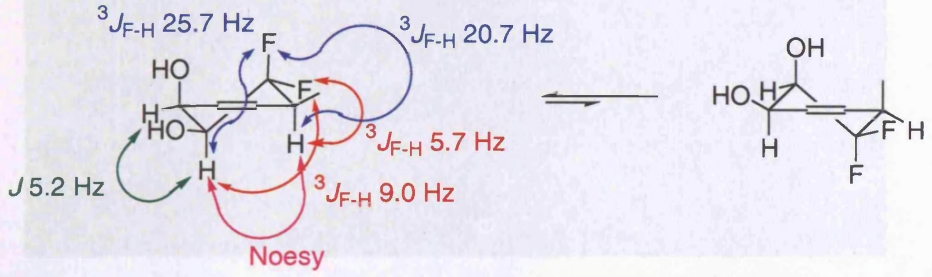
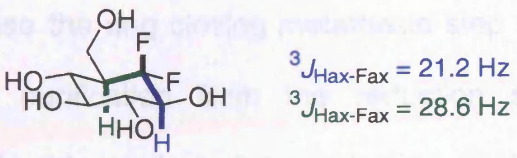



**Figure 36.** Coupling constant for diol **208** (the vinylic methyl group has been omitted for clarity).

The diaxial $^3J$ fluorine-proton coupling constants of 20.7 and 25.7 Hz can be explained by a F-C-C-H dihedral angle close to 180° and therefore giving a maximal value via the Karplus equation. Sinaÿ *et al.*[32] reported similar values for the difluoroanalogue of carba-glucose **42** (**Figure 37**).




**42**

**Figure 37.**

Moreover, Plavec *et al.*[128] developed a new seven-parameter Karplus-type relation between vicinal proton-fluorine coupling constants and the corresponding H-C-C-F torsion angles. Ricard Roig, a member of the research group,[129] established an excel sheet from Plavec *et al.* equations (**Figure 38**).

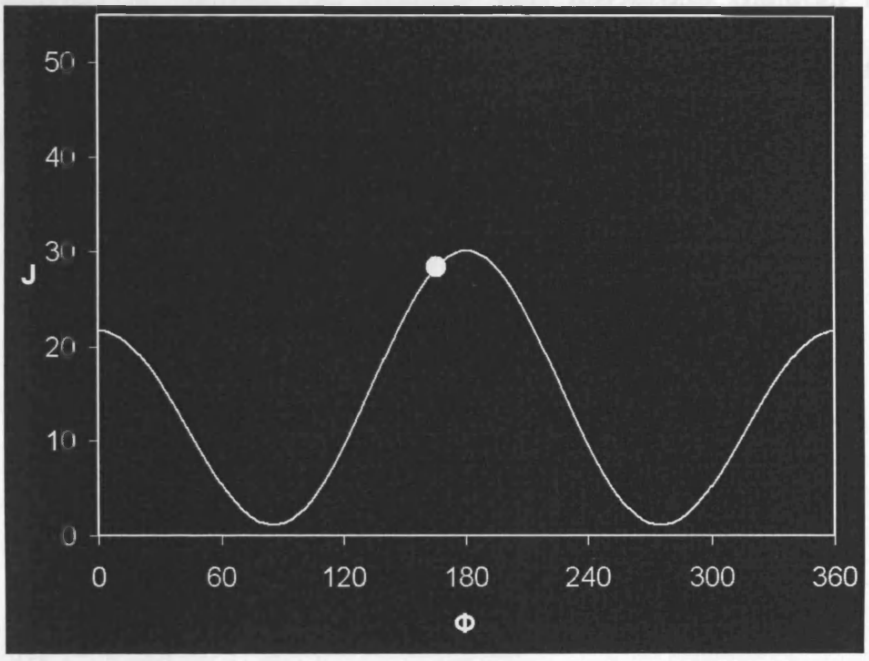
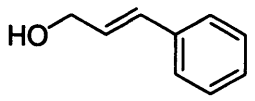



**Figure 38.**

The plot (**Figure 38**) showed a value for the coupling constants around 30 Hz when the dihedral angles get close to 180°.

### 2.3.4 Side Product Influence

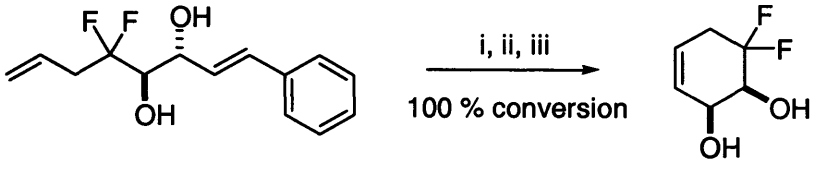
Another way to optimise the ring closing metathesis step would be to perform the reaction without purification from the reduction step. As discussed previously, the possible side product of the reduction would be the butyllithium adduct and some cinnamyl alcohol **214** from the reduction of unreacted cinnamaldehyde (**Figure 39**).



214

**Figure 39.**

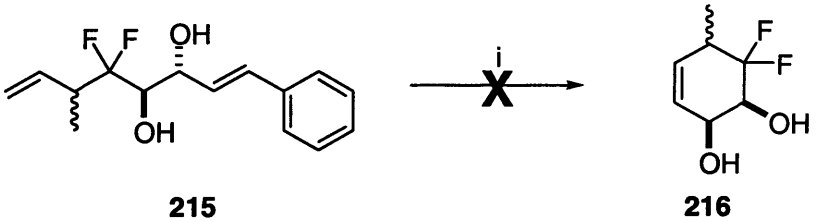
So we decided to perform the reaction with the crude material from the reduction (**Scheme 58**). The metathesis stopped before total conversion of the starting material requiring addition of more catalyst.




**168** **192**

**Scheme 58.** Reagents and conditions: i) **77** (0.5 mol%), dichloromethane, reflux, 1h; ii) **77** additional 0.1 mol%, 1h; iii) **77** additional 0.7 mol%, 1h.

Audouard[115] has shown that cinnamyl alcohol inhibits ring closing metathesis. Indeed, he performed the reaction with a 1:1 stoichiometric ratio between the second generation Grubbs' catalyst **77** and cinnamyl alcohol **214** (**Scheme 59**). Acyclic diol **215** was left unreacted after two days.




**215** **216**

**Scheme 59.** Reagents and conditions: i) **77** (5 mol%), cinnamyl alcohol (5 mol%), dichloromethane, reflux, 48h.

So whenever cinnamyl alcohol **214** is present, its alkene functionality reacts with the ruthenium catalyst to form the metallacyclobutane intermediate, which

breaks down spontaneously to afford metal alkylidene with an hydroxyl group in the allylic position **217** (**Figure 40**) driven by the development of extended conjugation (*cf.* **1.7.**) of stilbene **193**.

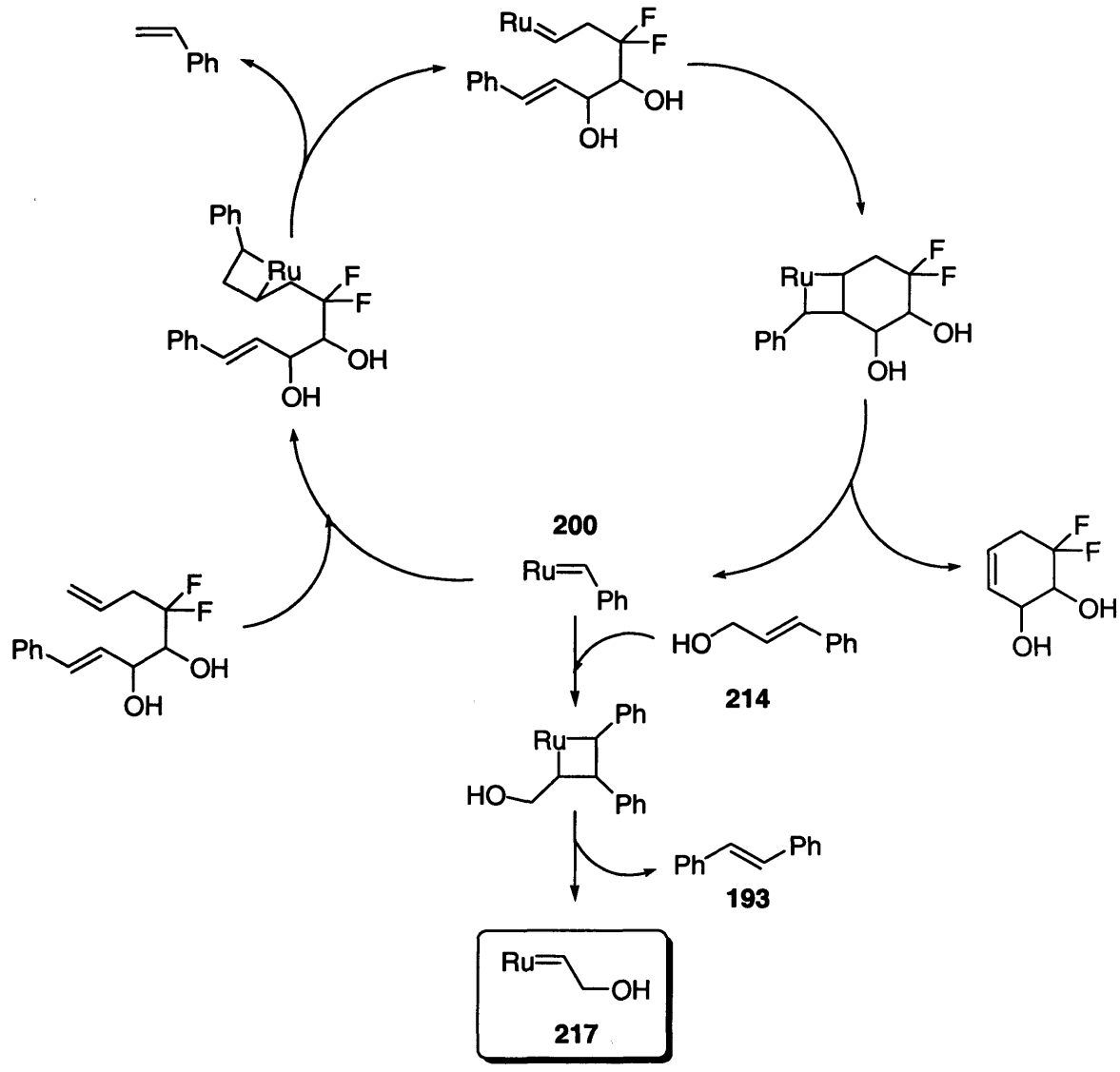
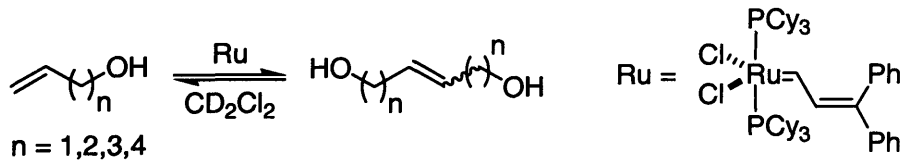



**Figure 40.** Proposed catalytic cycle.

Grubbs *et al.*[130] investigated the efficiency of ruthenium for the metathesis of olefin alcohols (**Scheme 60**).




**Scheme 60.**

They showed that the yield decreased with decreasing separation of the hydroxyl group and the double bond (**Table 18**); the allylic alcohol (entry 1) presenting the lowest yield (21 %).

| entry | olefin alcohols | time (h)[a] | yield (%)[b] |
|---|---|---|---|
| 1 | $CH_2$=$CHCH_2OH$ | 2.5 | 21 |
| 2 | $CH_2$=$CHCH_2CH_2OH$ | 2.5 | 27 |
| 3 | $CH_2$=$CH(CH_2)_2CH_2OH$ | 4.5 | 55 |
| 4 | $CH_2$=$CH(CH_2)_3CH_2OH$ | 4.5 | 55 |

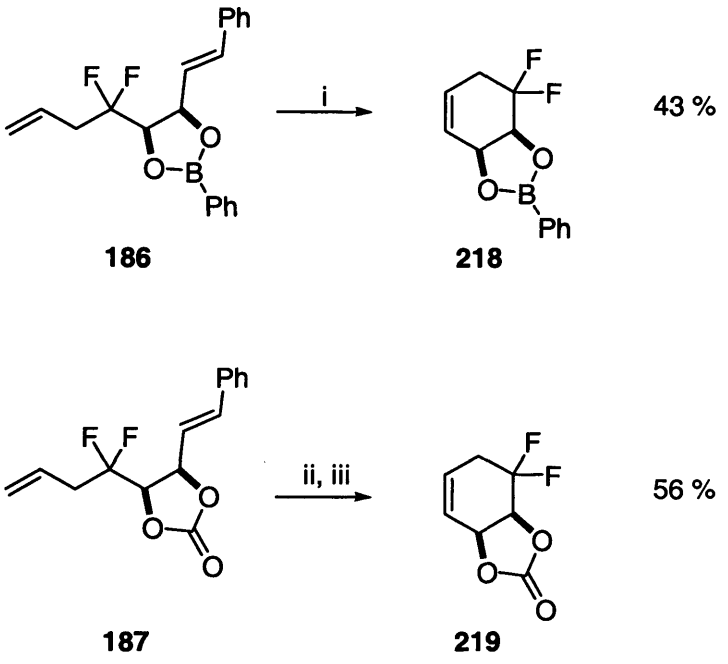
**Table 18.** Metathesis of olefin alcohols by Ru (9.6 mM solution in $CD_2Cl_2$). [a]: at room temperature; [b]: determined by $^1H$ NMR spectroscopy.

They assumed that the isomerisation activity is associated with ruthenium hydrides formed in decomposition side reactions during the normal metathesis cycle and therefore decreasing the catalyst efficiency. It is known that ruthenium alkylidene catalysts can facilitate the migration of alkyl chains (*cf.* **page 31**). The low yields from entries **1** and **2** (**Table 18**) arise because enol formation drives the isomerisation. This reaction is less favourable when the alkene and hydroxyl groups are more remote (entries **3** and **4** - **Table 18**). Also, α-heteroatom substituents will significantly reduce activities of the Ruthenium carbene complexes relative to ordinary carbon substituents.[131]

Our sequence using the second generation Grubbs' catalyst **77** limited the potential isomerisation of the cinnamyl alcohol **214** (**Figure 40**). Its presence implicate ruthenium complex **200** which would be deactivated and therefore would present a much lower activity. Our experiments concord with Grubbs *et al.* observations; the catalytic cycle stops at the allylic alcohol substituted ruthenium complex **217** leaving our substrate unreacted.

### 2.3.5 Boronate and Carbonate

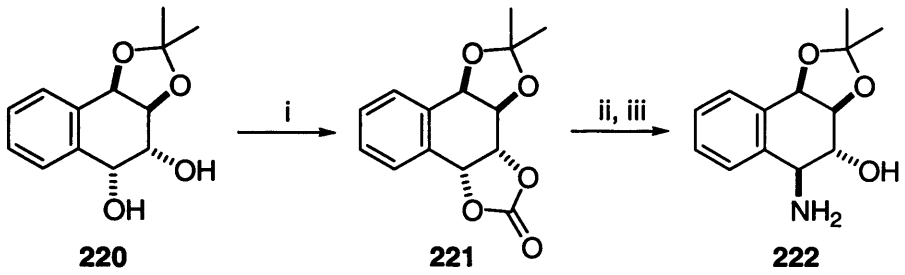
As described previously (*cf.* **2.2.4**), we were very interested to investigate the reactivity of protected diols such as **186** and **187** towards ring closing metathesis. We performed the cyclisation reaction under the conditions used for the unprotected diol **168** (0.5 mol% of second generation Grubbs' catalyst **77**) (**Scheme 61**).




**Scheme 61.** Reagents and conditions: i) **77** (0.5 mol%), dichloromethane, reflux, 150 min; ii) **77** (0.5 mol%), dichloromethane, reflux, 60 min; iii) **77** (0.5 mol%), dichloromethane, reflux, 39 h (97 % conversion).

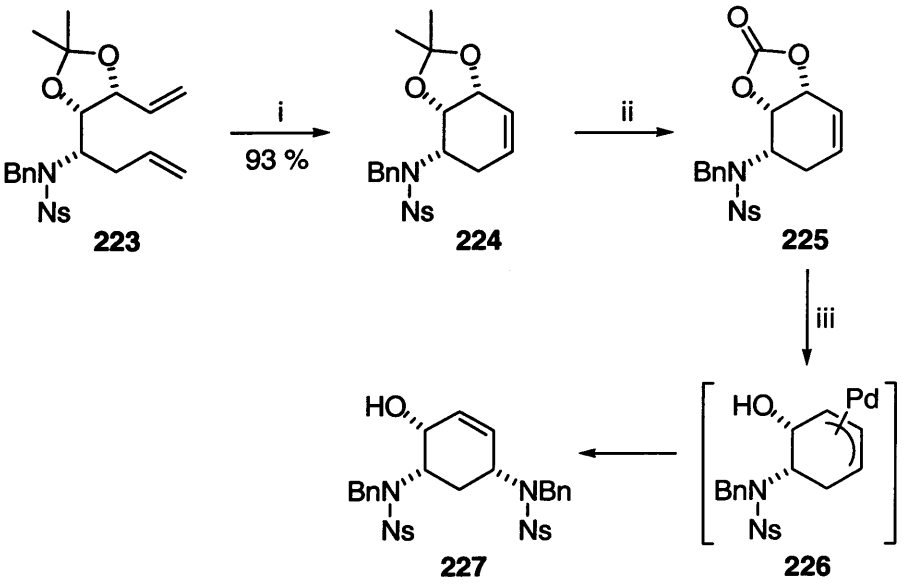
Unfortunately, the reactivity revealed to be inferior compare to the unprotected diol **168** requiring more reaction time to deliver corresponding cyclic boronate **218** and carbonate **219** in moderate yield. Combined with the poor yield for the formation of **218** and **219**, it is clearly better to perform the ring closing metathesis with the unprotected diol. However, bicyclic carbonate **219** could be useful for the introduction of nucleophiles *via* the $S_N2'$ reaction.

Orsini *et al.*[132] used a similar strategy to replace the existing hydroxyl group with an amine group (**Scheme 62**).




**Scheme 62.** Reagents and conditions: i) triphosgene, pyridine, dichloromethane, 0 °C; ii) $NaN_3$, DMF, 110 °C; iii) $H_2$, Pd/C, methanol, rt.

Also, van Boom *et al.*[133,134] introduced an extra functional group *via* a bicyclic carbonate obtained from the ring closing metathesis of acetonide **223** (**Scheme 63**) at low catalyst loading (1.5 mol%). Cyclic carbonate **225** derivative undergoes a palladium catalysed allylic amination, using *N*-benzyl-nosylamide as the nucleophile, resulting in the desired 4,6-diaminocyclohexene **227**.




**Scheme 63.** Reagents and conditions: i) Grubbs' catalyst **76** (1.5 mol%), 93%; ii) a. AcOH/$H_2O$ 8/2, reflux, b. carbonyldiimidazole, DMF, 84% (over two steps); iii) NsNHBn (1.5 eq.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), $PPh_3$ (25 mol%), $Et_3N$ (3 eq.), THF, 80%.

## *2.4 Toward Cyclitol and Difluorosugar Analogues*

Our prime objective was to synthesise cyclitols and carbasugar analogues; having obtained our key cyclohexene intermediate *via* ring closing metathesis, two principal routes were investigated.

First, fully hydroxylated cyclitol analogues might be elaborated *via* epoxidation of the non-substituted cyclohexenes, followed by selenolate ring opening at C-4 and selenoxide elimination to deliver a set of triols which could be further dihydroxylated.

Secondly, the key ring closing metathesis product could be directly dihydroxylated to deliver a wide range of carbasugar analogues.

### 2.4.1 Epoxidation

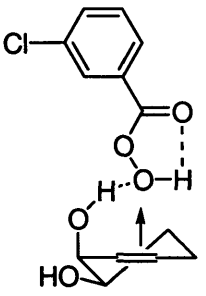
Epoxides can be obtained by oxidising simple intermediates like **192** *via* Henbest epoxidation (**Figure 41**). Non-directed epoxidation could also be explored to increase the diversity set.

**192**

**Figure 41.**

### *2.4.1.1 Henbest - Directed Epoxidation*

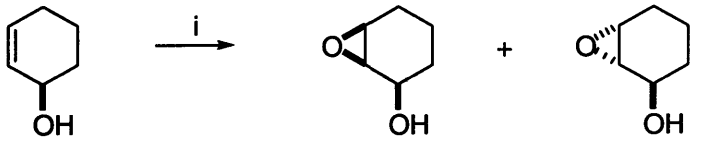
Formation of epoxides from cyclic allylic alcohol in presence of peroxides such as *m*-CPBA occurs on the side *cis* to the hydroxyl group.[135,136] The hydroxyl group in allylic position exerts a promoting effect by hydrogen bonding through a transition state such as **228** (**Figure 42**).



**228**

**Figure 42.** Transition state.

The literature[135,137] gives many examples of Henbest epoxidation of simple allylic alcohols such as **229**, with a similar pattern to our substrate, in presence of *m*-CPBA (**Scheme 64**). The reaction exhibits a diastereoselectivity of 7.5:1.

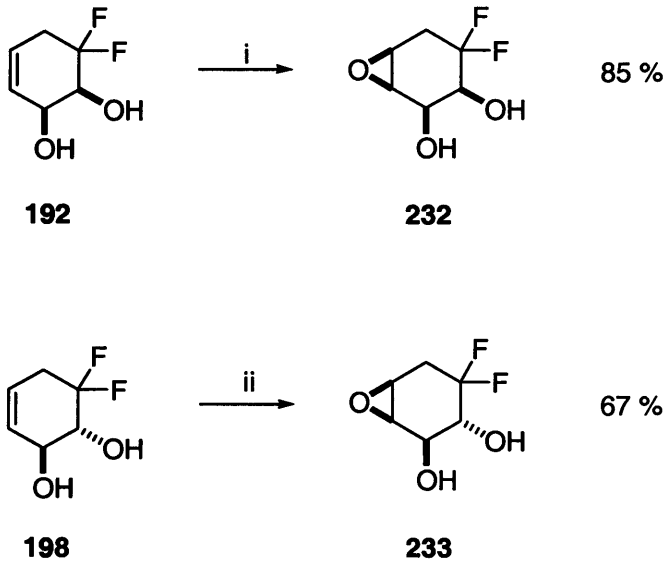


**229** **230** **231**

**Scheme 64.** Reagents and conditions: i) *m*-CPBA, $Na_2CO_3$, dichloromethane, rt, 10 min.

Under those epoxidation conditions, allylic alcohol **192** (**Scheme 65**) was transformed to epoxide **232** as a single diastereoisomer in good yield (85 %). In

the same manner, epoxidation of **198** afforded **233** also as a single diastereoisomer in moderate yield (67 %).




**Scheme 65**. Reagents and conditions: i) *m*-CPBA, $NaH_2PO_4$, dichloromethane, rt, 1 h; ii) *m*-CPBA, $NaH_2PO_4$, acetonitrile, rt, 1 h

Epoxidation of allylic alcohol **198** was initially performed in dichloromethane but the conversion reached only 50 % after 3 days. The very low solubility of the substrate in dichloromethane was resolved by changing the solvent to acetonitrile.

As expected, the epoxidation of allylic alcohols **192** and **198** delivered the *cis* products. Epoxide **233**, from *trans* diol **198**, exhibits two large coupling constants in the $^{19}F$ NMR spectrum (arising from flanking axial protons) (**Figure 43**), while H-1 in the $^{1}H$ NMR spectrum contains a $^{3}J$ coupling constant (8.6 Hz) consistent with a *trans*-pseudodiaxial coupling to H-2. The configuration of epoxide **233** can be further confirmed by the size of the coupling constant (2.0 Hz) between the two protons α- to each other at C-2 and C-3.

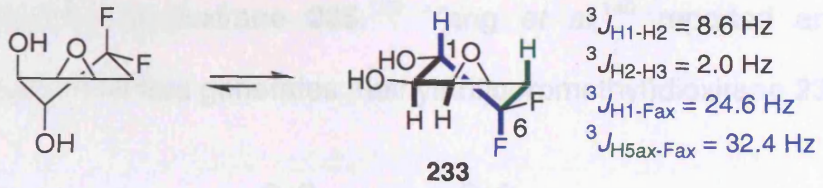



**Figure 43.**

Furthermore, epoxide **232** crystallised from hot hexane. The crystal structure (**Figure 44**) shows clearly the relationship between the stereogenic centres set in the reduction step. The 1D and 2D NMR experiments allowed us to assign each proton and carbon of the molecule and to confirm clearly the structure of the epoxide **232**.

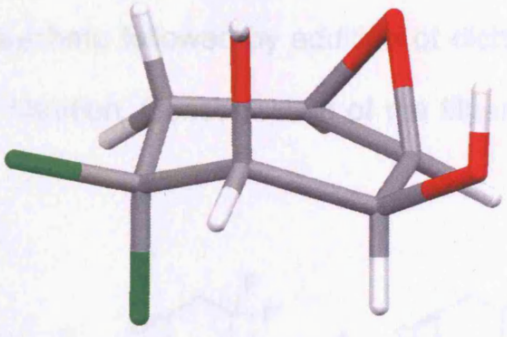


**Figure 44**. Crystallographic structure of epoxide **232**.

### *2.4.1.2 Non-Directed Epoxidation*

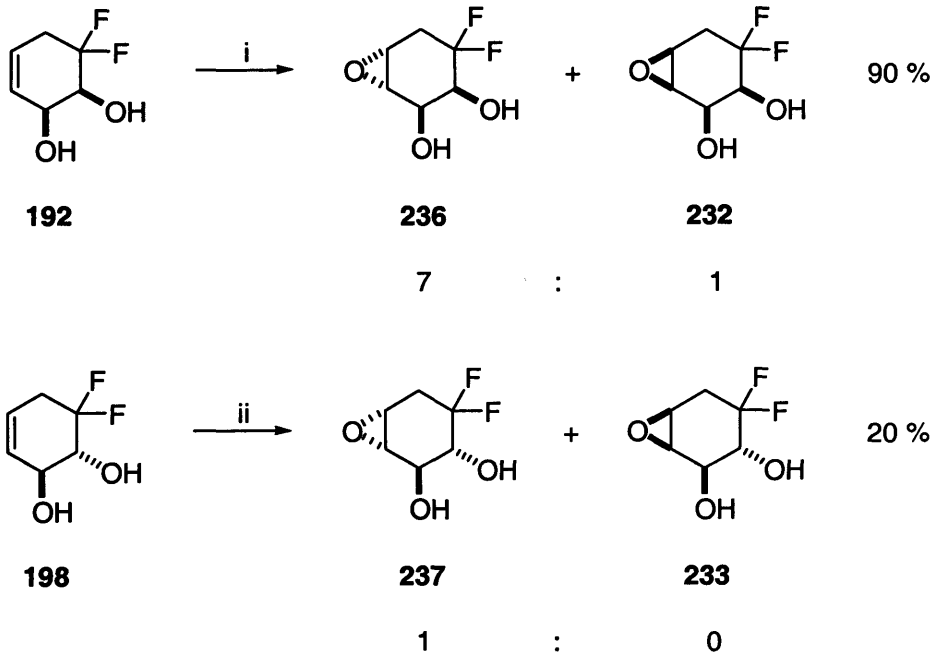
Dioxiranes are powerful epoxidation reagents[138] with high reactivity toward olefins, under neutral conditions. Despite the fact that dioxiranes can be generated from potassium peroxomonosulfate and ketones, their isolation is rather difficult due to their volatility and therefore limits their use. A more convenient approach is to use dioxiranes generated *in situ*. Dioxirane such as dimethyldioxirane **234** (**Figure 45**) presents a low epoxidation rate compared to

methyl(trifluoromethyl)dioxirane **235**.[139] Yang *et al.*[140] reported an efficient epoxidation protocol that generates methyl(trifluoromethyl)dioxirane **235** *in situ*.

**234** **235**

**Figure 45.** Dimethyldioxirane **234** and methyl(trifluoromethyl)dioxirane **235**.

We applied this protocol to our key cyclohexene **192** (**Scheme 66**). The reaction delivered a mixture of epoxides **236** and **237** in very good yield (90 %) and good diastereoselectivity (7:1). The good solubility of the product in dichloromethane allowed facile purification avoiding any chromatography; the water was absorbed by sodium sulphate followed by addition of dichloromethane and the solid was removed by filtration. Concentration of the filtrate delivered epoxides **236** and **237**.



**192** **236** **232**

7 : 1

**198** **237** **233**

1 : 0

**Scheme 66.** Reagents and conditions: i) $Na_2EDTA$, trifluoroacetone, $NaHCO_3$, Oxone®, acetonitrile, 0 °C, 1.5 hours; ii) $Na_2EDTA$, trifluoroacetone, $NaHCO_3$, Oxone®, acetonitrile, 0 °C, 19 hours.

Minor product of the epoxidation of diol **232** was clearly identified as the all *cis* epoxide confirming the *cis/trans* relationship between the epoxide and the hydroxyl groups of the major product of the reaction **236**. Mass spectrometry and NMR spectroscopy allowed the identification of the structure of **236**.

In the same manner, diol **198** was reacted (**Scheme 66**) with the *in situ*-prepared trifluoromethyl dioxirane to deliver epoxide **237** as a single diastereoisomer in poor yield (20 %); the $^{19}F$ NMR spectrum of the crude material presented a very poor quality and exhibited a few other fluorinated compounds which could not be identified after column chromatography.

The Dioxirane is generated from Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_3$) and trifluoroacetone (**Figure 46**).

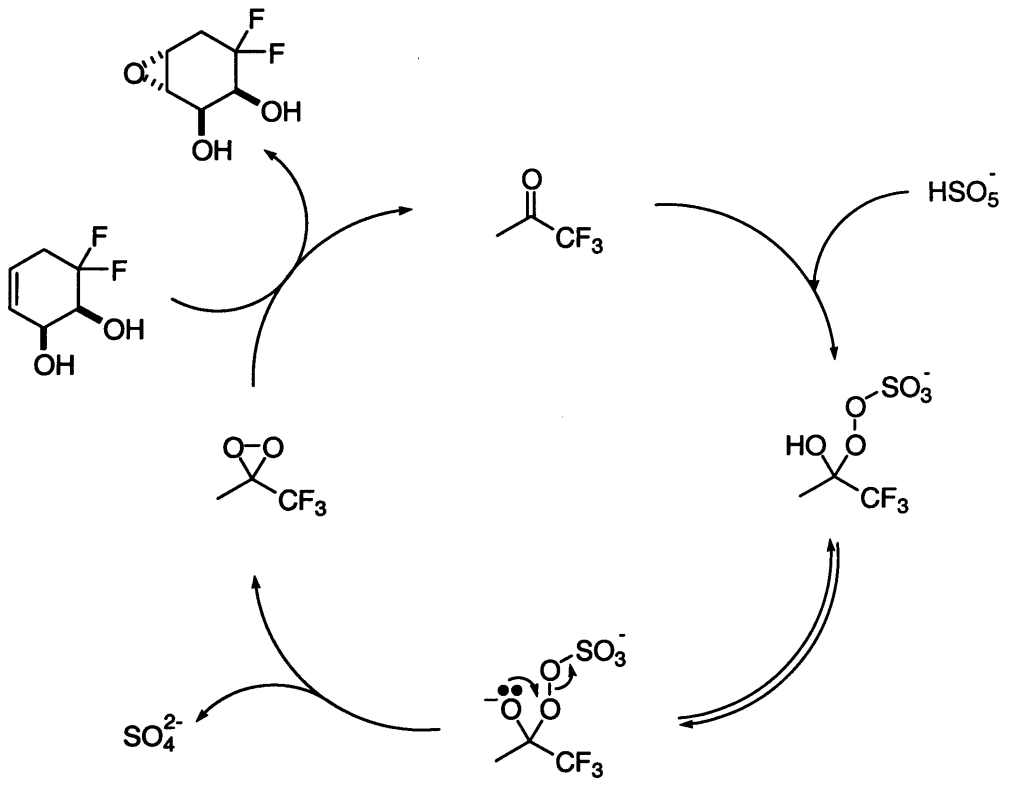
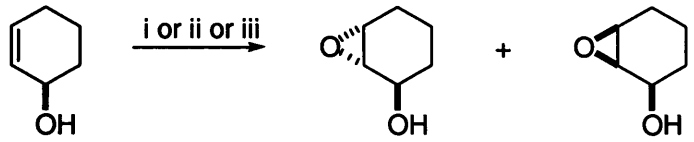



**Figure 46.** Mechanism of epoxidation using dioxirane.

Murray *et al.*[141] investigated the diastereoselectivity in the epoxidation of substituted cyclohexene by dimethyldioxirane (**Scheme 67**).




**229** **231** **230**

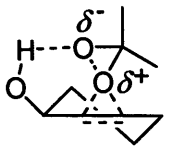
**Scheme 67.** Reagents and conditions: i) dimethyldioxirane **234**, rt, **solvent**, 1 h.; ii) $Na_2EDTA$, trifluoroacetone, $NaHCO_3$, Oxone®, acetonitrile, 0 °C, 10 min; iii) $Na_2EDTA$, acetone, $NaHCO_3$, Oxone®, acetonitrile, 0 °C, 10 min.

Murray *et al.*[141] demonstrated that there is a strong effect of substitution on epoxide stereoisomer ratio. Most of the epoxide ratios appear to be determined primarily by the steric influence of the substituents except when the substituent is an allylic hydroxyl group (*eg.* **229**) (as in our substrate) and the solvent used. So changing the composition of the solvent system by adding non-polar (*eg.* dichloromethane) or polar (*eg.* methanol) solvents influences the diastereoselectivity of the epoxidation (**Table 19**).[137,141]

| Solvent | (%) | dr (231/230) | dioxirane |
|---|---|---|---|
| $CCl_4$/acetone | (95:5) | 1:15.7 | **234** |
| dichloromethane/acetone | (97:3) | 1:4.6 | **234** |
| dichloromethane/acetone | (90:10) | 1:3.5 | **234** |
| acetone | (100) | 1.2:1 | **234** |
| methanol/acetone | (90:10) | 2:1 | **234** |
| acetonitrile/water | (60/40) | 1.2:1 | **234** |
| acetonitrile/water | (60/40) | 3.3:1 | **235** |

**Table 19.**

This effect of solvent on diastereoselectivity can be attributed to the relative ease of attaining a transition state, such as **238** (**Figure 47**), in which hydrogen bonding can occur to the developing negative charge on one oxygen of the dioxirane in the activated complex.




**238**

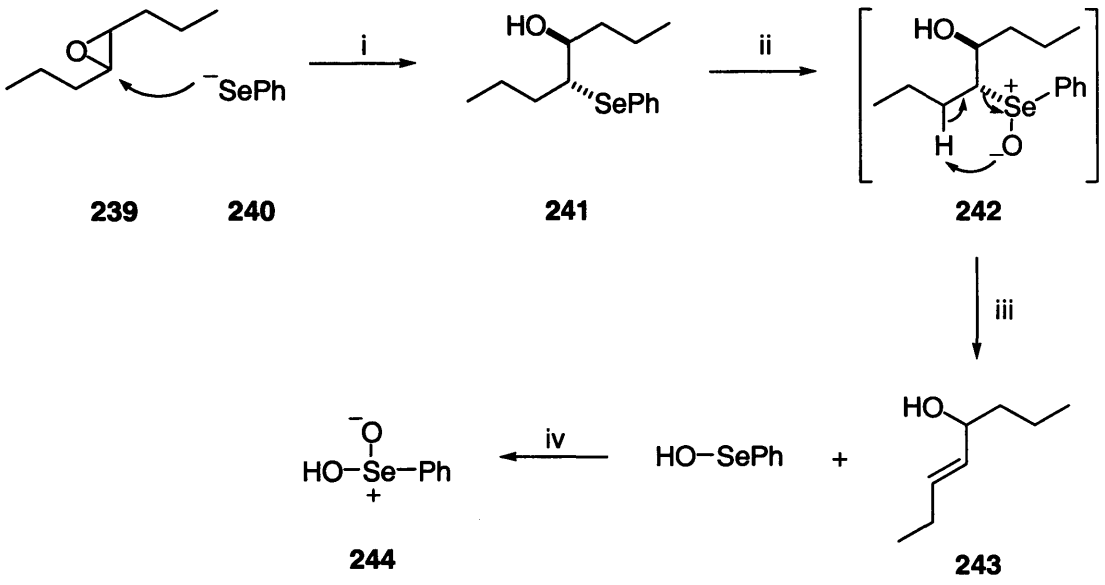
**Figure 47.** transition state.

In the presence of the homogeneous acetonitrile/water solvent system employed in our reaction, which can hydrogen bond strongly with the allylic hydroxyl of the substrate, the epoxidation gives more of the *trans* isomer since such solvent hydrogen bonding will block the *cis* approach of the dioxirane reflecting steric effect of the substrate. The diastereoisomeric ratio of 7:1 is in agreement with the theoretical expectation of the outcome of the reaction. The configuration of the major epoxide (*trans*) was confirmed by the formal identification of the minor diastereoisomer being the *cis* epoxide (*cf.* **2.4.1.1**). Furthermore 1D and 2D NMR spectroscopy experiments and mass spectrometry confirmed the structure of the epoxide.

### *2.4.1.3 Attempted Opening via Selenium Chemistry*

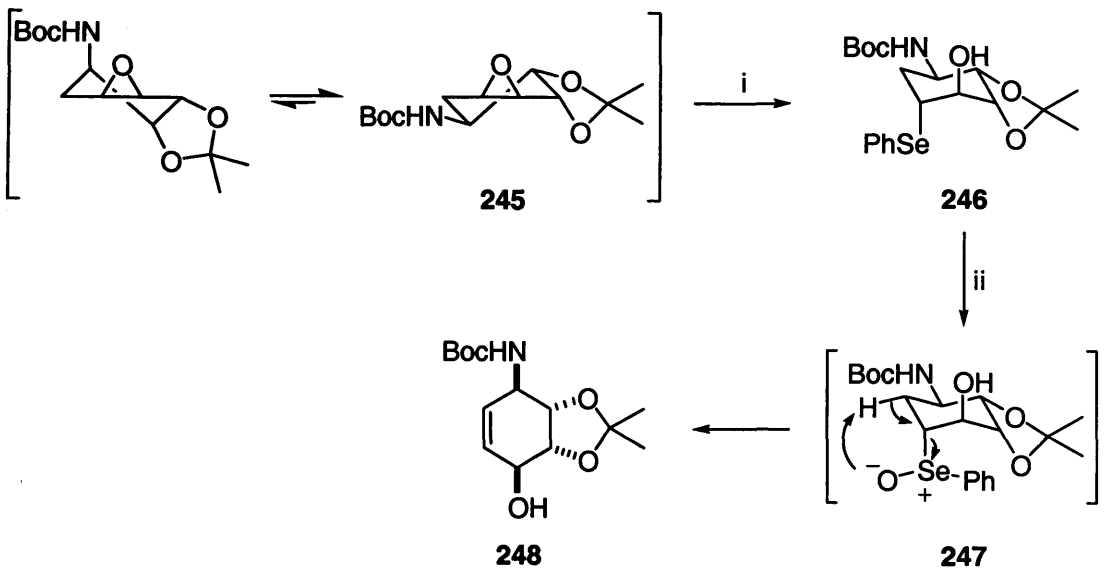
Epoxides can be cleaved by nucleophilic organoselenium reagents, PhSeM (M = H, metal), giving *β*-hydroxyselenides, which are transformed to allylic alcohol by oxidation and *syn* elimination.[142] This mild procedure for the

conversion of epoxides to allylic alcohols was developed by Sharpless *et al.*[143] They opened epoxide **239** (**Scheme 68**) with the selenide anion **240** (obtained from the reaction between diphenyldiselenide and sodium borohydride) to afford the hydroxyselenide **241** (step i). The hydroxyselenide is not isolated, but is oxidised (step ii) by excess hydrogen peroxide to the unstable selenoxide **242**, which decomposes (step iii) to the *E* allylic alcohol **243** in 98 %.



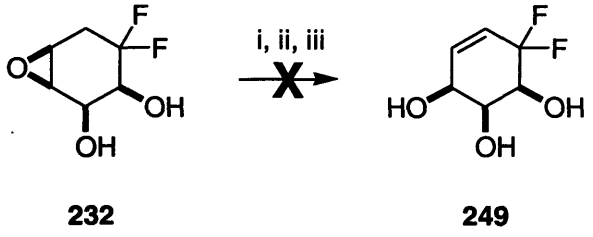

**Scheme 68.** Reagents and conditions: i) EtOH, rt, 2 h; ii) excess $H_2O_2$, 0 °C to rt; iii) 10 h, rt; iv) $H_2O_2$.

Muchowski *et al.*[144] performed the conversion of epoxide **245**, *via* a *trans* diaxial ring opening, to the allylic alcohol using a very similar procedure (**Scheme 69**) to deliver the precursor **248** of their target, (+)-conduramine. The pattern of substrate **245** exhibits some similarity with our epoxide so this is a good precedent.




**Scheme 69.** Reagents and conditions: i) $(PhSe)_2$, n-BuLi, tetrahydrofuran, 84 %; ii) $H_2O_2$, $(i\text{-}Pr)_2NEt$, dichloromethane, 0 °C then tetrahydrofuran, reflux, 90 %.

Initially, the Sharpless procedure was applied to epoxide **232** (**Scheme 70**). Unfortunately, the outcome of the reaction was not as expected, triol **249**; instead, an unidentifiable compound was obtained.

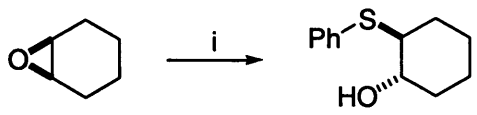



**232** **249**

**Scheme 70.** Reagents and conditions: i) diphenyldiselenide, $NaBH_4$, EtOH, rt, 1 h (inverse addition); ii) reflux, overnight; iii) $H_2O_2$, 20 °C, tetrahydrofuran.

Due to the high toxicity of the selenium derivatives, we performed only the opening (first step) of epoxide **232** using diphenyldisulfide instead of diphenyldiselenide in order to isolate and identify the product of the reaction *via* column chromatography and understand the sense of opening.

Indeed, the conversion of epoxides to allylic alcohol can be performed in the same manner *via* thiolysis (**Scheme 71**).[145]

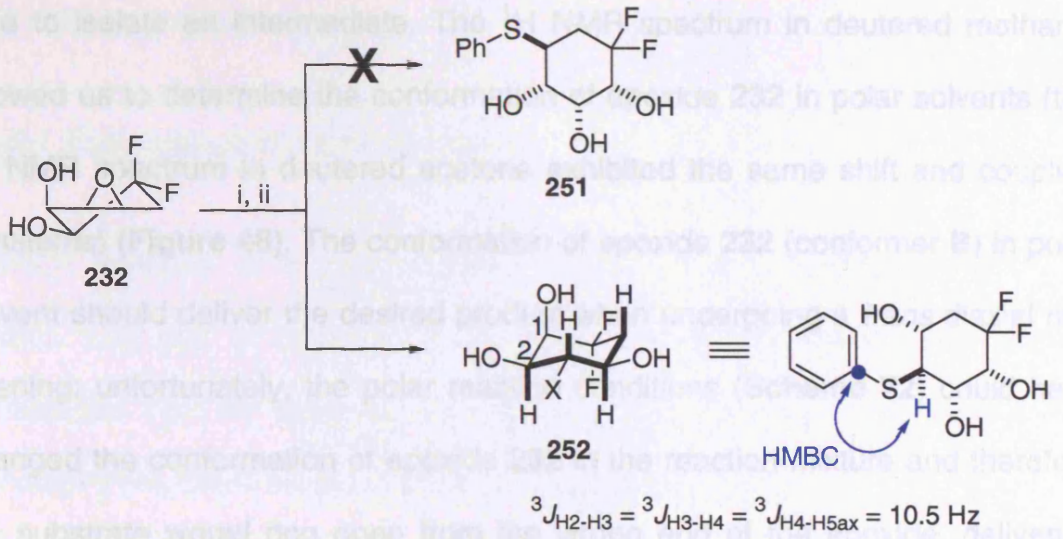



**250**

**Scheme 71.** Reagents and conditions: i) water, pH 4.0, 30 °C, PhSH.

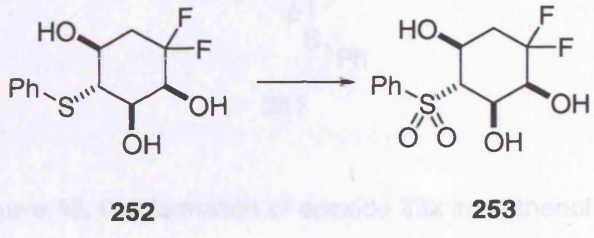
However, thermal rearrangements of allylic organoselenium compound occurred considerably faster than the related sulfur cases.[143]

The reaction, under the same conditions used for the first step, using diphenyldisulfide (**Scheme 72**) exhibited crude material of much lower quality with the presence of several unidentified fluorine-containing molecules. Purification by column chromatography delivered **252** instead of the desired product **251** in very low yield (27 %). The $^{1}H$ NMR spectrum exhibited coupling constants that allowed us to determine the configuration of **252**; in addition, 2D experiments (especially HMBC) and mass spectrometry showed clearly the thiophenyl moiety attached at C3 position and confirmed the rest of the structure.




**Scheme 72.** Reagents and conditions: i) diphenyldisulfide, $NaBH_4$, EtOH, rt, 1 h (inverse addition); ii) reflux, overnight, 27 %; X = SPh.

The thiophenyl moiety was fully oxidised to avoid any decomposition through the sulfoxide and in the hope that the derivative would crystallise; **252** was reacted with peroxide to deliver triol **253** (**Scheme 73**) in moderate yield (74 %). The $^1$H NMR spectrum and mass spectrometry confirmed the sense of opening occurring in the first step.




**Scheme 73.** Reagents and conditions: i) *m*-CPBA, dichloromethane, $NaH_2PO_4$, rt, overnight, 74 %.

Unfortunately, **253** crystallised as fine needles which were not adequate for X-ray analysis.

The reaction using diphenyldisulfide instead of diphenyldiselenide allowed us to understand the outcome of the reaction under Sharpless conditions[143] by being

able to isolate an intermediate. The $^1$H NMR spectrum in deutered methanol allowed us to determine the conformation of epoxide **232** in polar solvents (the $^1$H NMR spectrum in deutered acetone exhibited the same shift and coupling constants) (**Figure 48**). The conformation of epoxide **232** (conformer **B**) in polar solvent should deliver the desired product when undergoing a *trans* diaxial ring opening; unfortunately, the polar reaction conditions (**Scheme 72**) could have changed the conformation of epoxide **232** in the reaction mixture and therefore the substrate would ring open from the wrong end of the epoxide, delivering intermediate **252** on which the *syn* elimination did not occur.

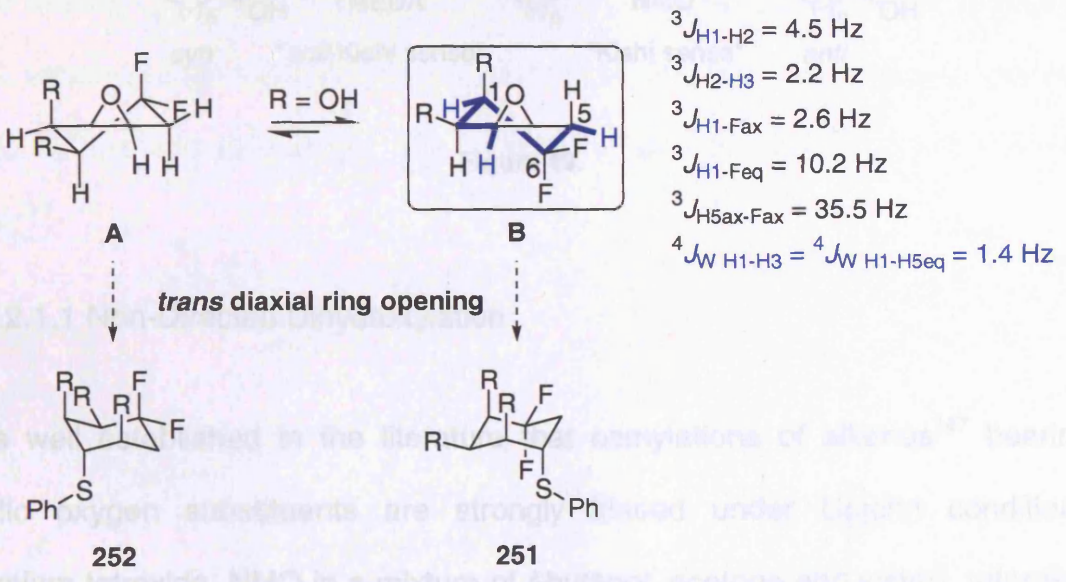



**Figure 48.** Conformation of epoxide **232** in methanol-$d_4$.

The reactions using diphenyldiselenide or diphenyldisulfide were performed on the other epoxides synthesised previously, but unfortunately the quality of the crude material in each case was very poor not allowing us to isolate useful intermediates to identify and understand the opening of our epoxides (*cf.* **Appendix III - 6.3.**).

## 2.4.2 Dihydroxylation

### *2.4.2.1 Reagents and Stereoselectivity*

Osmium tetroxide is a very reliable reagent for the *cis*-dihydroxylation of alkenes. Our aim of obtaining a small library of analogues of cyclitols and carbasugars can be achieved by exploiting the stereoselective possibilities afforded by the dihydroxylation reaction (**Figure 49**).[146]

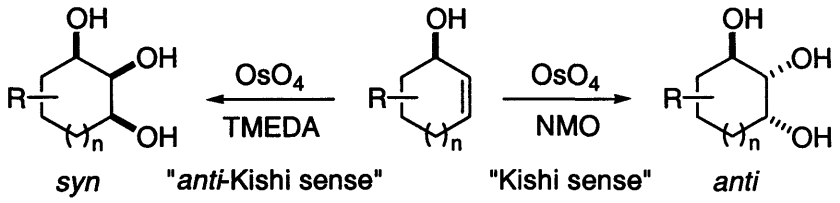



**Figure 49.**

2.4.2.1.1 Non-Directed Dihydroxylation

It is well established in the literature that osmylations of alkenes[147] bearing allylic oxygen substituents are strongly biased under Upjohn conditions (osmium tetroxide, NMO in a mixture of *t*-butanol, acetone and water), affording triol products in which the major diastereoisomer has the newly formed C-O bonds *trans* to the pre-existing C-O bond ("Kishi's empirical rule") (**Figure 50**).[148-150]

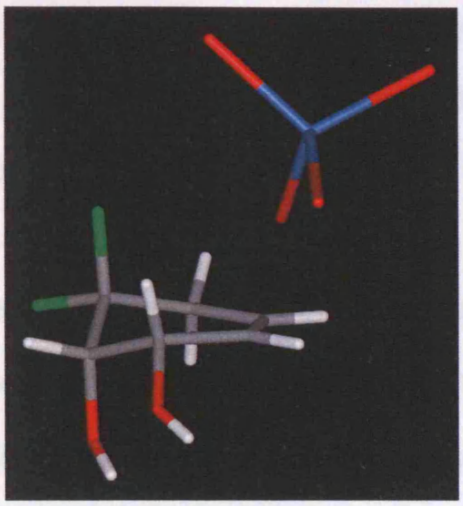


**Figure 50.** Three-dimensional representation of Kishi empirical rule of the *cis* approach under Upjohn-type dihydroxylation.

The reaction proceeds through the formation of cyclic osmate ester **A** (**Figure 51**), which is then hydrolysed to form the *cis* diol **C**. In this process, osmium (VIII) is reduced to osmium (VI) by reaction with an olefin to yield a vicinal diol.[151]

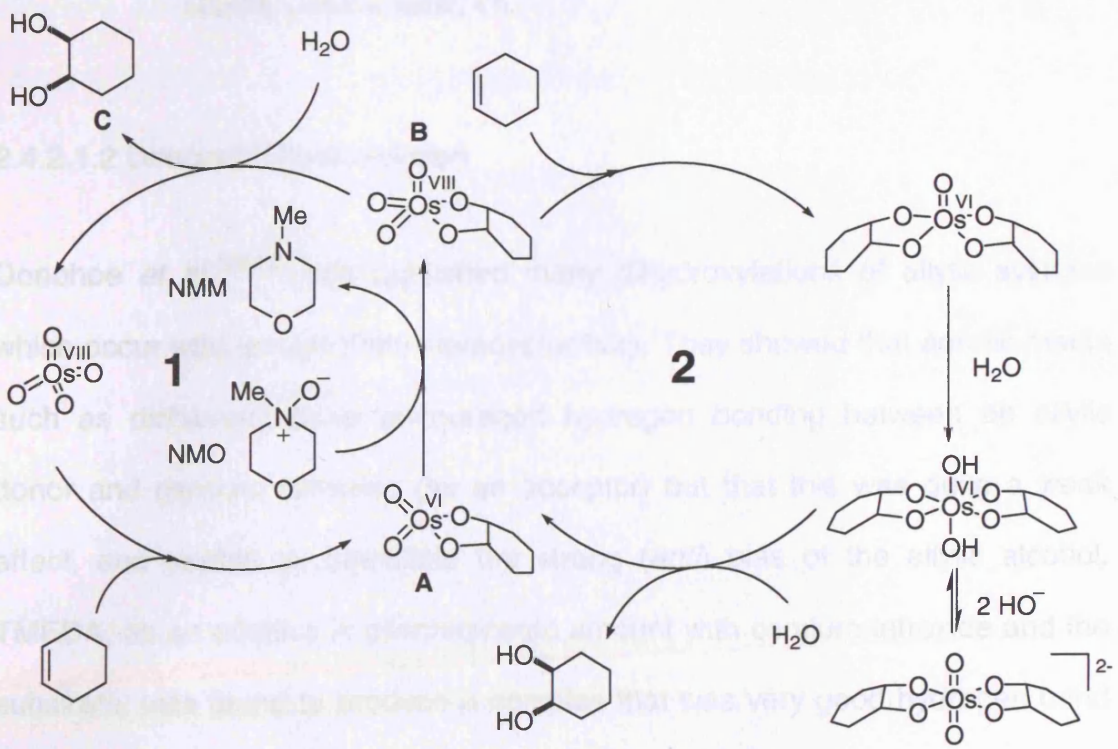
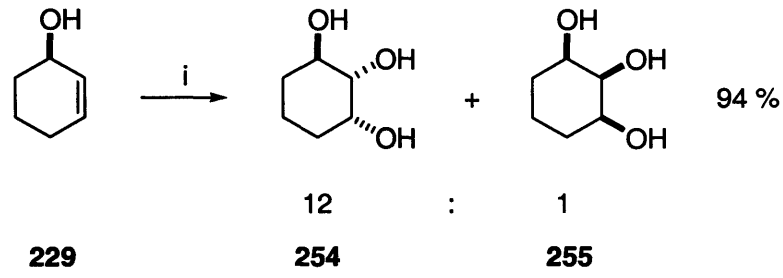



**Figure 51.** Proposed mechanism for the Os(VIII)-catalysed dihydroxylation of olefins with NMO as reoxidant.

NMO is the co-oxidant that enables the use of a catalytic amount of osmium tetroxide, because this reagent is able to reoxidise an osmium (VI) species to an osmium (VIII) species.

Donohoe *et al.*[152] performed the dihydroxylation of cyclohexenol **229** under the Upjohn conditions (**Scheme 74**). They mainly obtained the expected triol **254**, exhibiting a *trans* relationship between the existing hydroxyl group and the newly formed *cis* diol.

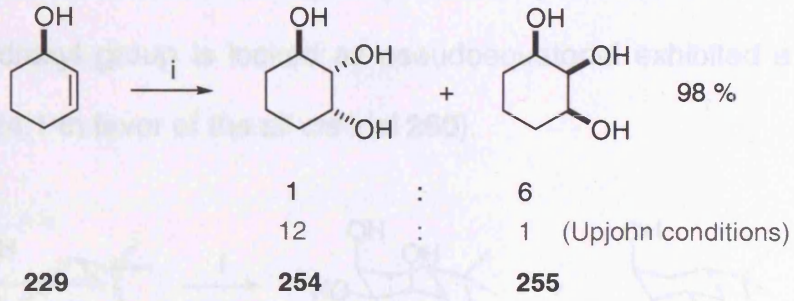



**Scheme 74.** Reagents and conditions: i) 1 mol% $OsO_4$, NMO, *t*-BuOH, acetone, water, 4 h.

2.4.2.1.2 Directed Dihydroxylation

Donohoe *et al.*[152,153] has published many dihydroxylations of allylic systems which occur with an *anti* Kishi stereoselectivity. They showed that aprotic media such as dichloromethane encouraged hydrogen bonding between an allylic donor and osmium tetroxide (as an acceptor) but that this was quite a weak effect, and unable to overcome the strong (*anti*) bias of the allylic alcohol. TMEDA, as an additive in stoichiometric amount with osmium tetroxide and the substrate, was found to produce a complex that was very good hydrogen bond acceptor and that was also capable of dihydroxylating alkene at -78 °C. The dihydroxylation of cyclohexenol **229** performed under those conditions (**Scheme**

**75**) delivered preferentially (6:1) the all *cis* triol **255** in excellent yield (98 %) whereas the dihydroxylation of the same substrate under Upjohn conditions afforded mainly (12:1) triol **254**, presenting a *trans* relationship between the newly *cis* diol formed and the existing hydroxyl group.




**Scheme 75.** Reagents and conditions: i) $OsO_4$ (1 eq.), TMEDA (1 eq.), dichloromethane, -78 °C, 1 h.

TMEDA formed a five membered chelate with osmium tetroxide and this complex was efficient at hydrogen bonding through an oxo ligand (**Figure 52**). Electron donating groups bind to osmium and increase the electron density on the oxo ligands and make them better hydrogen bond acceptors.[154]

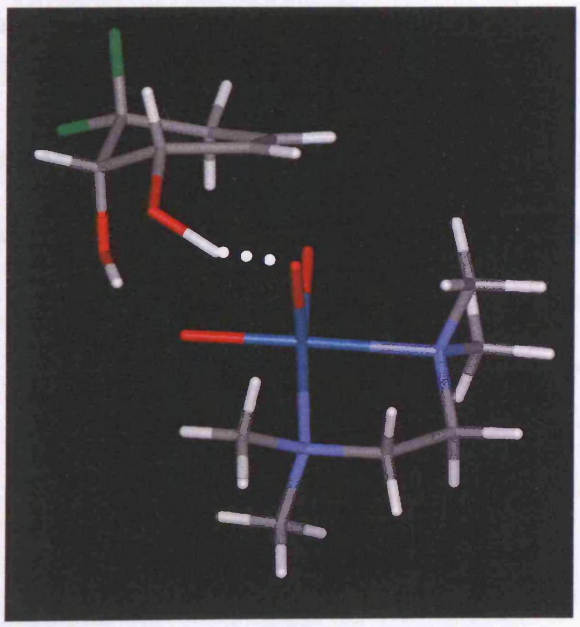
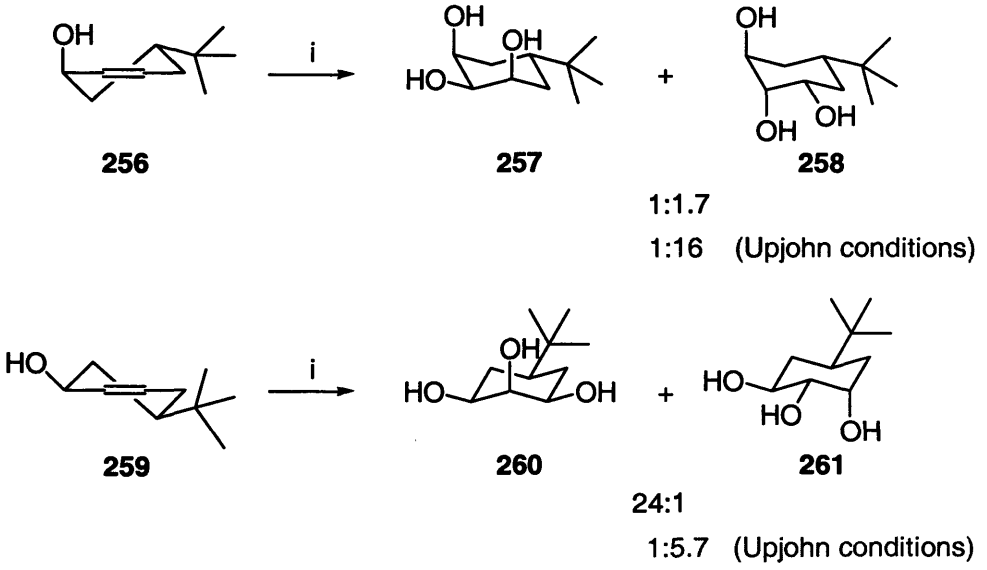


**Figure 52.** Three-dimensional representation of hydrogen bonding between substrate and complex $OsO_4$/TMEDA under Donohoe-type dihydroxylation.

Donohoe *et al.* showed that the directing effect of the allylic alcohol was general for the variety of cyclic compounds tested.[152] Nevertheless, directed dihydroxylation of the pseudoaxially locked cyclohexenol **256** (**Scheme 76**) using the reagent $OSO_4$/TMEDA delivered the products with a very low selectivity. On the other hand, dihydroxylation of cyclohexenol **259** in which this time the hydroxyl group is locked as pseudoequatorial exhibited a very good selectivity (24:1 in favor of the all *cis* triol **260**).




**Scheme 76.** Reagents and conditions: i) $OsO_4$ (1 eq.), TMEDA (1 eq.), dichloromethane, -78 °C, 1 h.

This result was explained by proposing that the cleft between the pseudoaxial directing group and the alkene is too small for the bulky TMEDA based osmylating agent (**A** - **Figure 53**). This situation does not arise with the equatorially locked diastereoisomer **B**, which gives very high levels of *syn* selectivity.[152]

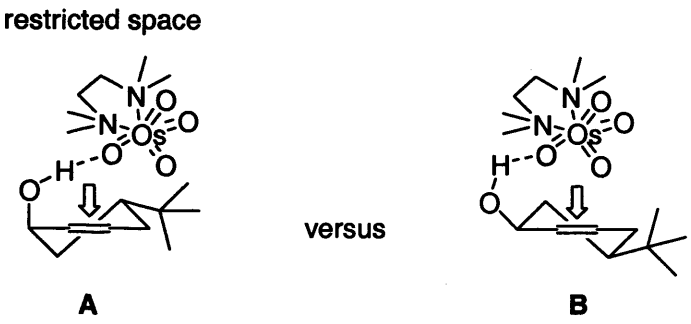
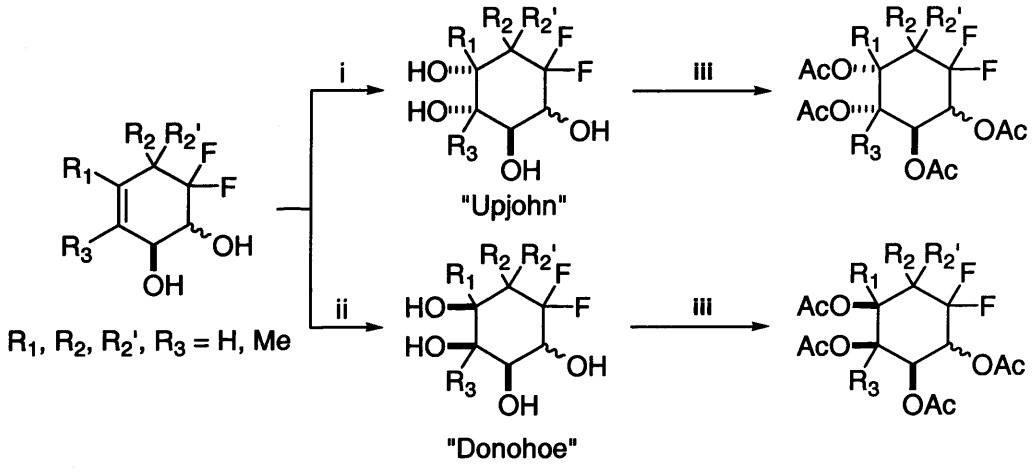



**Figure 53.**

### *2.4.2.2 Results*

Substrates (*cf.* **2.3.**) with different levels of substitution (**Scheme 76**) at various positions were now investigated under both Upjohn and Donohoe-type conditions. Unfortunately, the purification and isolation of the most of the tetrols formed under either Upjohn or Donohoe-type dihydroxylation were very problematic. Due to high water solubility, the osmium residues present in the reaction mixture could not be removed. Instead, we considered the peracetylation of the tetrols as a solution to the purification problem.




**Scheme 76.** Reagents and conditions: i) 2 mol% $OsO_4$, NMO, *t*-BuOH, acetone, water, 7 h-2 d; ii) $OsO_4$ (1.0 eq.), TMEDA (1 eq.), -78 °C, 1-1.5 h; iii) $Ac_2O$, pyridine, rt, overnight.

We therefore obtained the corresponding peracetylated tetrols (**Table 20**). When the substrates were substituted, the hydroxyl group geminal to the methyl group was not acetylated and remained unprotected (entry **3-7**). The dihydroxylation under Upjohn conditions delivered the peracetylated tetrols in poor (entry **2** and **3**) to very good (entry **5** and **7**) and moderate (entry **1** and **6**) *trans*-diastereoselectivity except for diol **207,** which afforded an "*anti*-Kishi" product (entry **4**). The protection step was not necessary for tetrol **268** (entry **7**) which was obtained as a free tetrol in very good yield (92 %).

When the Donohoe-type conditions were applied to the same substrates, we observed a varied diastereoselectivity from 11:1 to 1:0 (entry **1-5**) in favor of the expected "*anti* Kishi" product except for diol **208,** which delivered a "Kishi" product (entry **5**).

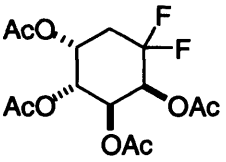
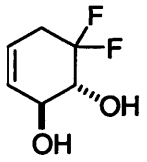
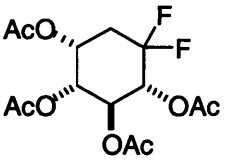
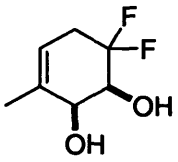
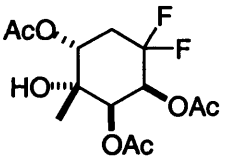
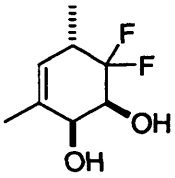
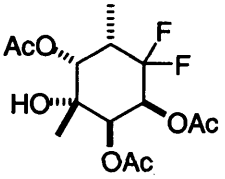
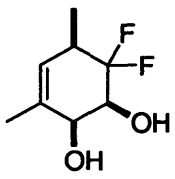
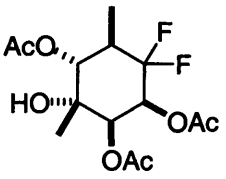
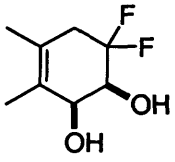
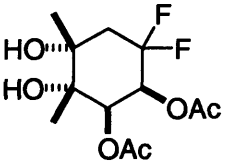
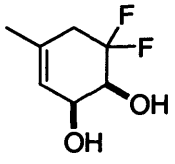
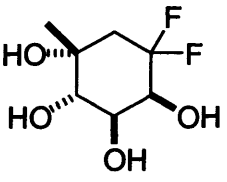
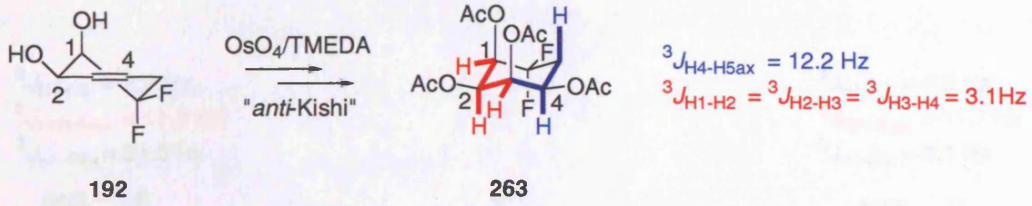
| Entry | substrate | | Product[e] | | Upjohn | | | Donohoe | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | dr | yield (%) | t (h)[d] | dr | yield (%)[a] | t (h)[d] |
| 1 | | **192** |  | **262** | 5:1 | 58[a] | 7.0 | 1:11 | 48 | 1.5 |
| 2 |  | **198** |  | **264** | 2.5:1 | 57[a] | 24 | 1:16 | 52 | 1.5 |
| 3 |  | **196** |  | **266** | 2.2:1 | 23[a] | 48 | 1:11 | 56 | 1.0 |
| 4 |  | **207** |  | **268** | 0:1 | 79[a] | 48 | 0:1 | 42 | 1.5 |
| 5 |  | **208** |  | **270** | 32:1 | 41[a] | 48 | 1:0 | 40 | 1.5 |
| 6 |  | **211** |  | **272** | 5:1 | 33[a] | 48 | -[b] | -[b] | -[b] |
| 7 |  | **197** |  | **274** | 1:0 | 95[c] | 48 | -[b] | -[b] | -[b] |

**Table 20.** [a]: over 2 steps; [b]: Donohoe-type dihydroxylation was not done on this substrate; [c]: over 1 step; [d]: reaction time of the dihydroxylation only; [e]: only the Kishi product is represented.

By comparing diols **192** and **211** (entry **1** and **6**, **Table 20**), we concluded that the level of substitution of the double bond did not seem to interfere under

Upjohn conditions delivering the same level of diastereoselectivity. At the same time, diols **196** and **197** with a similar level of substitution presented different level of selectivity under Upjohn conditions (entry **3** and **7**, **Table 20**).

Unfortunately; we were not able to obtain any crystal structures for acetylated tetrols **262** and **263**, so the configuration was determined by NMR spectroscopy. Indeed, we could measure the coupling constants precisely in the $^1$H NMR spectra. The dihydroxylation of diol **192** under Donohoe conditions delivered protected tetrol **263** with a *cis* relationship between the existing diol and the newly formed diol (**Figure 54**).




**192** **263**

**Figure 54.**

The structure of the product of the dihydroxylation under Upjohn conditions could be deduced from the previous result as being acetylated tetrol **262** (with a *trans* relationship between the existing diol and the newly formed one); furthermore the structure was confirmed by mass spectrometry, 1D and 2D NMR experiments.

The relative configuration of protected tetrols **264** and **265** (obtained under Upjohn and Donohoe conditions respectively) could be determined from the coupling constant between each proton of the ring (**Figure 55**).

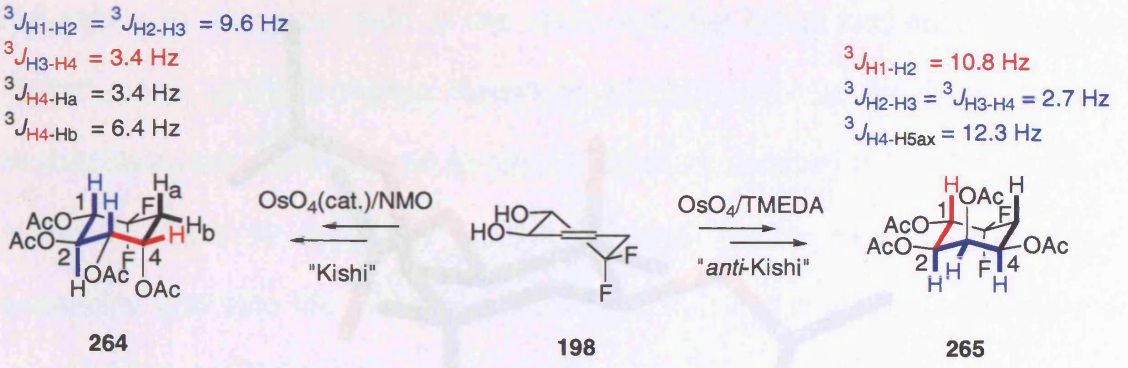



**Figure 55.**

Measurement of the coupling of each of the protected tetrols **266** and **267** allowed us to confirm the structure of the products (**Figure 56**). Indeed, the set of coupling constants obtained corresponded to the expected stereochemical outcome under either dihydroxylation conditions.

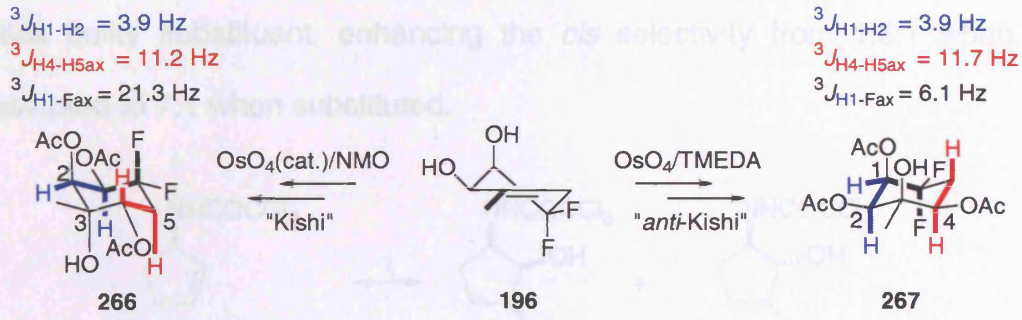



**Figure 56.**

In addition, the crystallographic structure of protected tetrol **267** allowed us to confirm the stereochemical outcome of the dihydroxylation of diol **196** under Donohoe conditions (**Figure 57**) unequivocally.

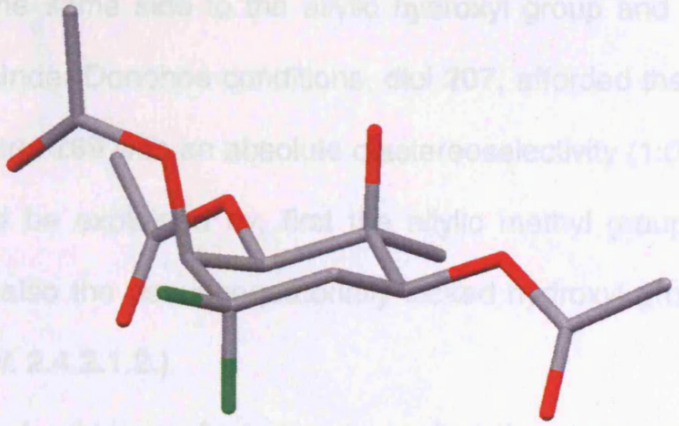
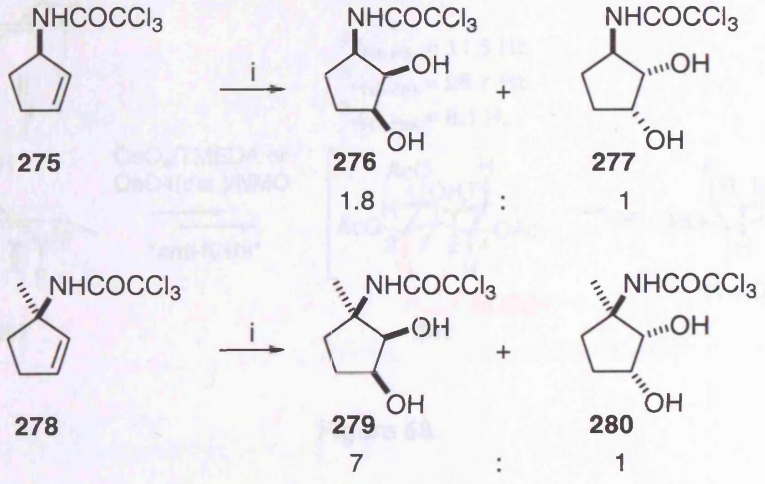


**Figure 57**. Crystallographic structure of **267** (hydrogens were omitted for clarity).

Donohoe *et al.*[152] explored the effect of allylic substitution on dihydroxylation of protected allylic amines **275** and **278** under Upjohn conditions (**Scheme 77**). The presence of an allylic methyl group directed the attack to the face opposite to this bulky substituent, enhancing the *cis* selectivity from 1.8:1 when not substituted to 7:1 when substituted.




**Scheme 77.** Reagents and conditions: i) 1 mol% $OsO_4$, NMO, *t*-BuOH, acetone, water, 4 h.

Under Upjohn conditions; diol **207** delivered the protected tetrol **269** exhibiting an "*anti*-Kishi" selectivity (entry **4**, **Table 20**). This result could be explained by the steric hindrance of the methyl in allylic position to the reaction site forcing

the attack on the same side to the allylic hydroxyl group and opposite to the methyl group. Under Donohoe conditions, diol **207**, afforded the same product, tri-acetylated tetrol **269** with an absolute diastereoselectivity (1:0). The excellent selectivity could be explained by, first the allylic methyl group as mentioned previously and also the pseudoequatorially locked hydroxyl group favoring the *cis* selectivity (*cf.* **2.4.2.1.2.**).

Several pieces of evidence allowed us to confirm the stereochemical outcome of the dihydroxylation of diol **207** under either Upjohn or Donohoe conditions (delivering the same product) (**Figure 58**). Indeed, the coupling constant between the axial fluorine atom and the two α-protons are 6.1 and 28.7 Hz characteristic of respectively an axial-equatorial and axial-axial relationship. Furthermore, the H4-H5 coupling constant (11.5 Hz) agrees with the assignment along with the NOESY peak between H2 and H4.

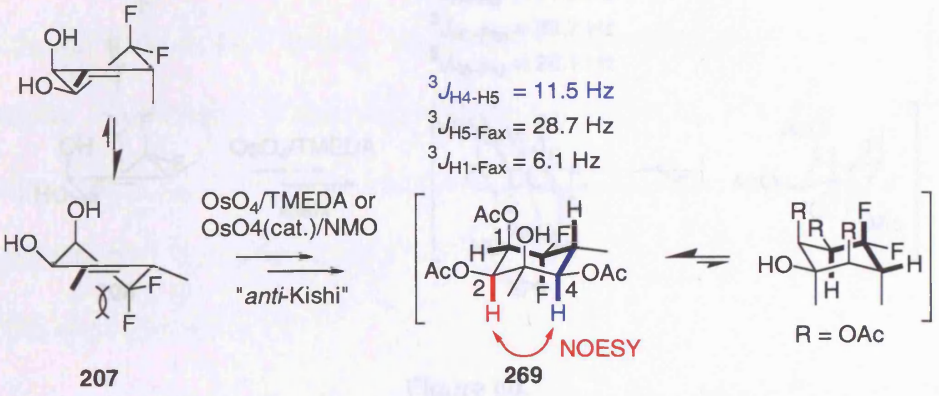



**Figure 58.**

In addition, an X-ray structure of **269**, obtained by recrystallisation from hot hexane, proved the relative stereochemistry unambiguously (**Figure 59**).

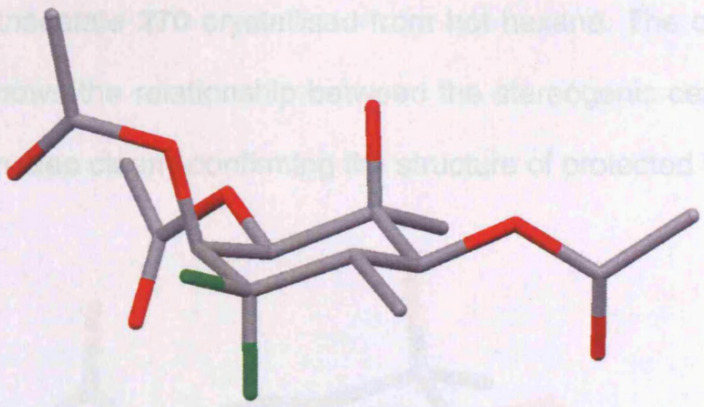


**Figure 59.** Crystallographic structure of **269** (hydrogens were omitted for clarity).

The different values (**Figure 60**) correspond to a relationship between the stereogenic centres which placed the two methyl group, the two existing hydroxyl group and the two newly formed hydroxyl groups in *trans* relationship.

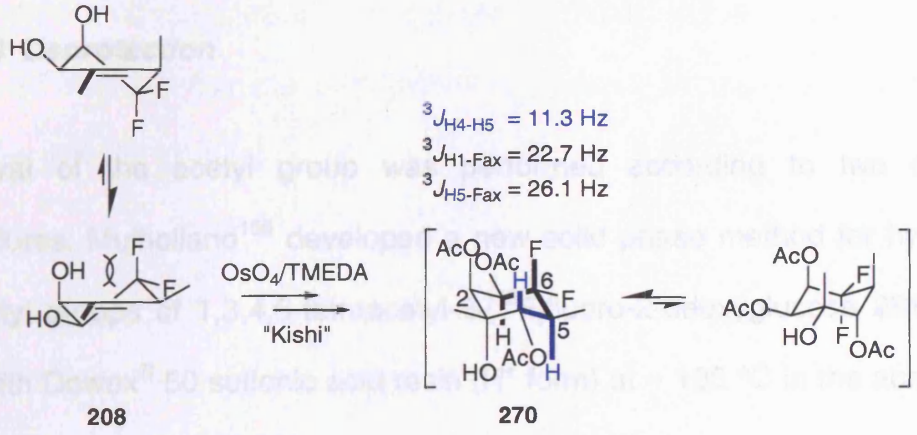



**Figure 60.**

The excellent diastereoselectivity (1:0), delivering only the Kishi product, could be explained by, first the influence of the methyl group, forcing the attack on the opposite side to the allylic alcohol function and also the pseudoaxially locked hydroxyl group favoring the *trans* selectivity (*cf.* **2.4.2.1.2.**).

Furthermore, triacetate **270** crystallised from hot hexane. The crystal structure (**Figure 61**) shows the relationship between the stereogenic centres set in the dihydroxylation step clearly confirming the structure of protected tetrol **270**.

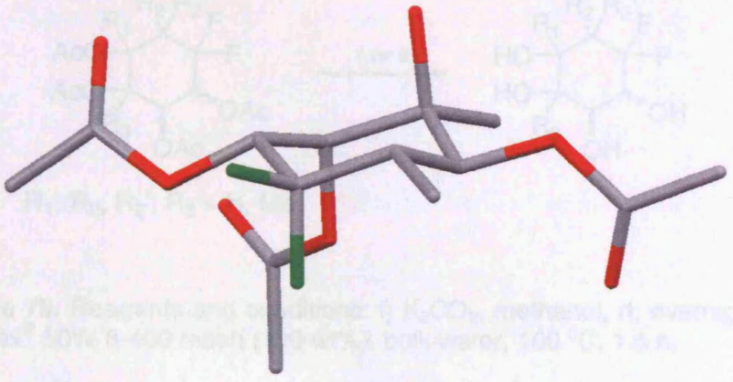


**Figure 61**. Crystallographic structure of **270** (hydrogens were omitted for clarity).

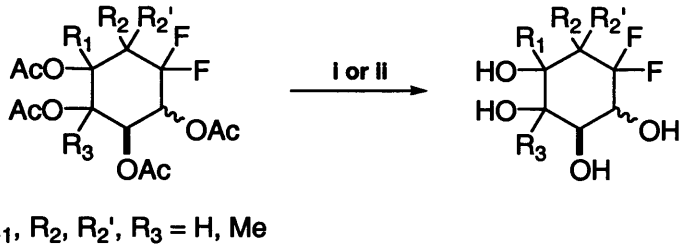
### *2.4.2.3 Deprotection*

Removal of the acetyl group was performed according to two different procedures. Mulholland[155] developed a new solid phase method for hydrolysis of acetyl groups of 1,3,4,6-tetraacetyl-2-[$^{18}$F]fluoro-2-deoxyglucose **281** (FDG-$Ac_4$) with Dowex® 50 sulfonic acid resin ($H^+$ form) at ~ 100 °C in the absence of the bulk water (**Scheme 78**).

**281** **282**

**Scheme 78.** Reagents and conditions: i) Dowex® 50W 8-400 mesh, 100 °C, 10 min.

We considered it very interesting to investigate this solid phase procedure for the deprotection of our substrates (**Scheme 79**). We also used a basic hydrolysis with potassium carbonate in methanol.[156,157]




$R_1$, $R_2$, $R_2'$, $R_3$ = H, Me

**Scheme 79.** Reagents and conditions: i) $K_2CO_3$, methanol, rt, overnight; ii) Dowex® 50W 8-400 mesh (100 wt%), bulk water, 100 °C, 1.5 h.

Both methods delivered the corresponding free tetrol in good yield (**Table 21**). The main advantage of the use of this solid phase resin in the hydrolysis step consists in the absence of residual salt after filtration and concentration of the solvent. In contrast, the use of potassium carbonate in methanol required an additional filtration on silica.

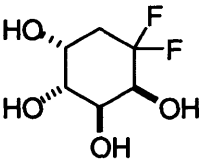
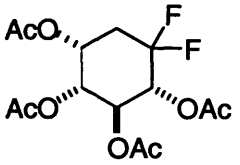
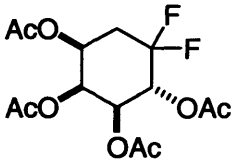
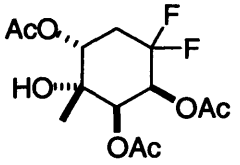
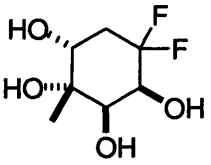
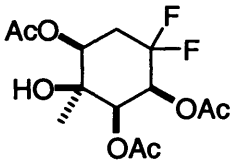
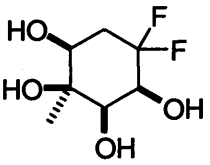
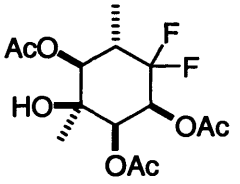
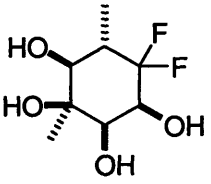
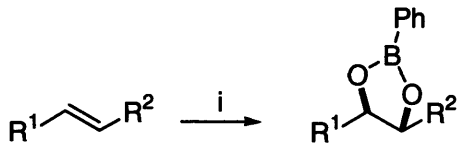
| substrate | | Product | | Yield (%) Dowex | Yield (%) $K_2CO_3$ |
|---|---|---|---|---|---|
| | **262** |  | **283** | 93 | -[a] |
|  | **264** | | **284** | -[a] | 88 |
|  | **265** | | **285** | 91 | -[a] |
|  | **266** |  | **286** | 95 | -[a] |
|  | **267** |  | **287** | 96 | -[a] |
|  | **269** |  | **288** | 75 | -[a] |

**Table 21.** [a]: not effected on the substrate.

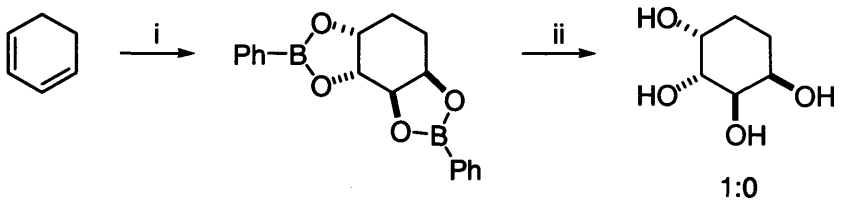
### *2.4.2.4 Narasaka's Modification of Upjohn Procedure*

Narasaka *et al.*[158] used benzeneboronic acid to replace water as the agent which removed the diolate from the osmium in the NMO/$OsO_4$ dihydroxylation cycle. This modified Upjohn procedure resulted *in situ* protection of the newly formed diol as cyclic boronate esters (**Scheme 80**). By removing the product of the reaction, the formation of this new structure allows a low loading of catalyst.




**Scheme 80.** Reagents and conditions: i) benzeneboronic acid (1.0-1.5 eq.), osmium tetroxide (2 mol%), anhyd. NMO, rt, dichloromethane.

Use of this procedure carries a number of advantages, including faster reaction times and a lower osmium catalyst loadings. Sharpless *et al.*[159] investigated this catalytic osmylation process for the bisdihydroxylation of cyclic dienes (**Scheme 81**). The deprotection of boronates step is an oxidative cleavage with aqueous hydrogen peroxide.[118]




**Scheme 81.** Reagents and conditions: i) benzeneboronic acid (1.0-1.5 eq.), osmium tetroxide (2 mol%), anhyd. NMO, rt, dichloromethane; ii) H2O2, ethyl acetate/acetone (1:1), rt, overnight.

Based on Sharpless *et al.*[159] results, we performed the dihydroxylation of some of our substrates using this Narasaka's modification of the Upjohn procedure. Our starting materials present a diol function already, so a simple modification of Sharpless' procedure was necessary. The existing diol was therefore protected beforehand (*cf.* **2.2.4.**) using two equivalents of benzeneboronic acid. We were hoping to increase the diastereoselectivity by introducing this additional ring to the substrate. Indeed the first equivalent of the boronic acid first reacts with the diol to form a bicyclic structure which curves the molecule (**Figure 62**) probably increasing the proportion of attack from the open face and

thus the diastereoselectivity. The second equivalent of phenyl boronic acid reacts with the new formed diol to form a third ring.

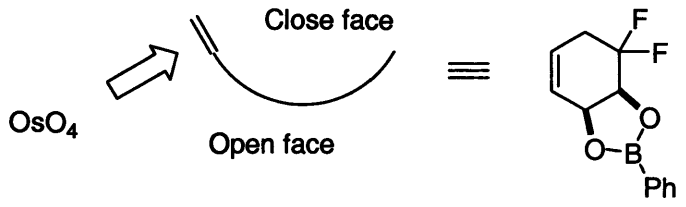
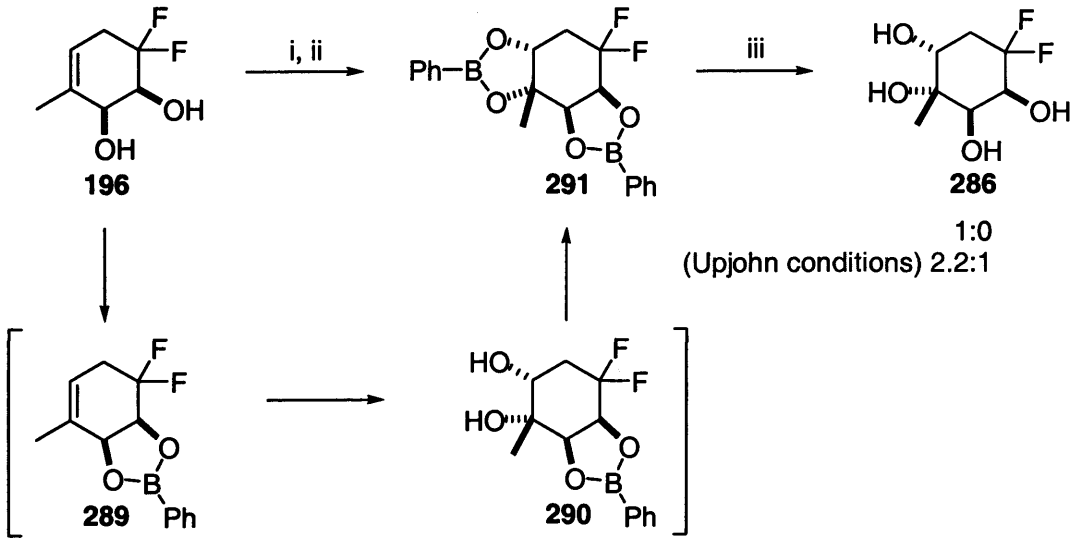



**Figure 62.**

The dihydroxylation of diol **196** under the new conditions (**Scheme 82**) delivered free tetrol **286** in moderate yield (37 % from diol **196**) and excellent diastereoselectivity (1:0) compared to the one obtained under Upjohn conditions (2.2:1) demonstrating clearly the *trans* directing effect of the topology of the bicyclic boronate ester.



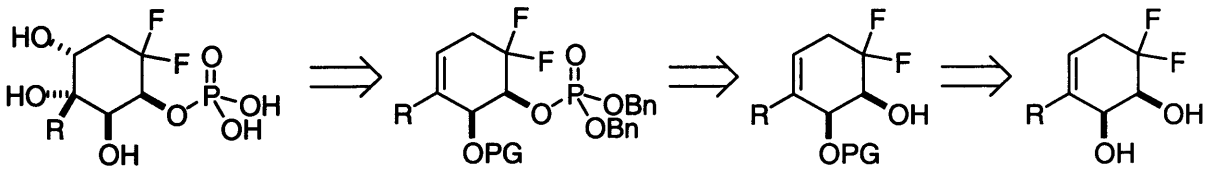

**Scheme 82.** Reagents and conditions: i) benzeneboronic acid (2 eq.), dichloromethane, rt, 1 h; ii) osmium tetroxide (0.2 mol%), NMO, rt, overnight; iii) hydrogen peroxide, ethyl acetate-acetone (1:1), rt, overnight, 37 % over 2 steps).

The main disadvantage of this procedure was the purification step which was extremely difficult. Indeed, in addition to the high water solubility of the free tetrol (*cf.* **2.4.2.2.**), a number of boron species were present after several

purifications by column chromatography. Furthermore, we performed the dihydroxylation of a couple of other substrates under these conditions, but unfortunately we obtained complex mixtures by $^{19}F$ NMR and struggled to isolate any desired product.

## *2.5 Toward Analogues of NDP Sugar Precursors*

The planned route to precursors for NDP sugar analogues such as **292** (**Figure 63**) from our substrate involved first the regioselective monoprotection of a diol followed by phosphorylation. The dihydroxylation under Upjohn conditions could be highly diastereoselective because of the bulky protecting group. Deprotection would afford the precursor of NDP sugars such as **292** or as its more stable salt form.




**292** R = H
**293** R = Me

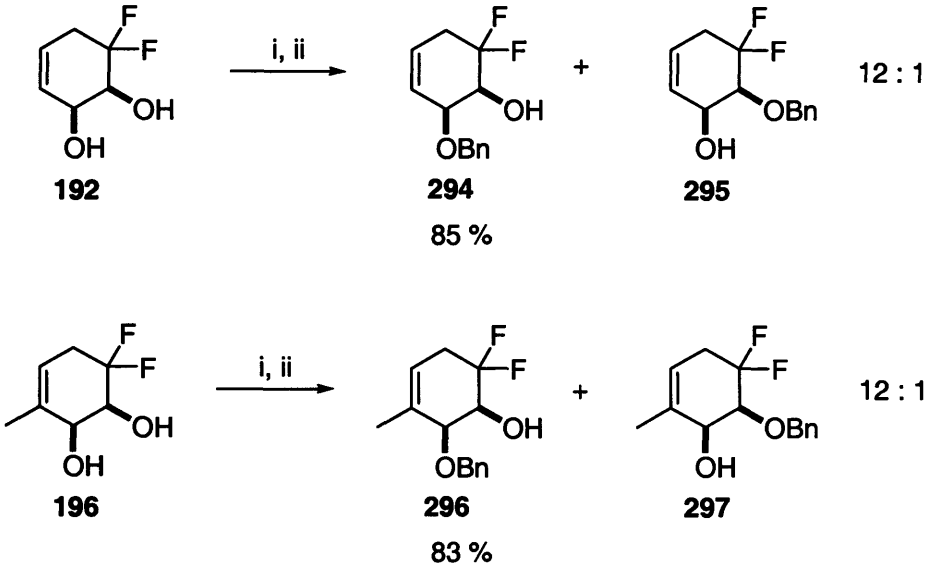
R = H, Me

**Figure 63.**

### 2.5.1 Monoprotection

First, diol **192** was protected. The monoprotection was achieved *via* an intermediate stannylene formed by refluxing diol **192** in toluene (distillation process - *cf.* **Experimental - 4.3.**) in the presence of dibutyltin dimethoxide (**Scheme 83**).[160] The stannylene formed was then opened with an electrophile. Because the next step introduces two benzyl groups *via* the phosphorylation

using tetrabenzyl pyrophosphate, benzyl bromide was used as electrophile to protect the hydroxyl at C2 position (*cf.* **2.5.2.**). The tetrabutylammonium iodide was added in order to form benzyl iodide which is much more electrophilic than benzyl bromide.

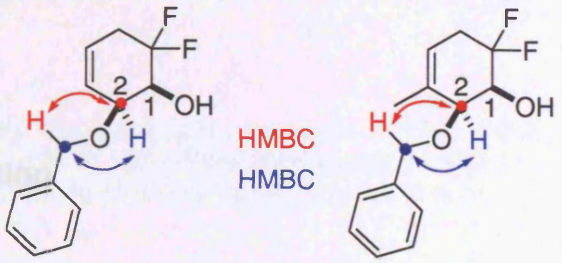



**Scheme 83.** Reagents and conditions: i) Dibutyltin methoxide, toluene, reflux (distillation); ii) benzyl bromide, TBAI, reflux, overnight.

The reaction of protection of diol **192** occurred with a good regioselectivity (12:1) in favor of the desired product. The two regioisomers could be separated by recrystallisation affording pure monoprotected diol **294** in very good yield (85 %). In the same manner, diol **196** was regioselectively protected to deliver **296** (**Scheme 83**) in also very good yield (83 %) after recrystallisation.

Disappointingly, only one of the regioisomers formed could be isolated. The major product of each of the protection reaction was clearly identified by NMR spectroscopy and in particular by HMBC (**Figure 64**). A cross peak between the benzylic proton and the carbon at C2 position for each of the monoprotected

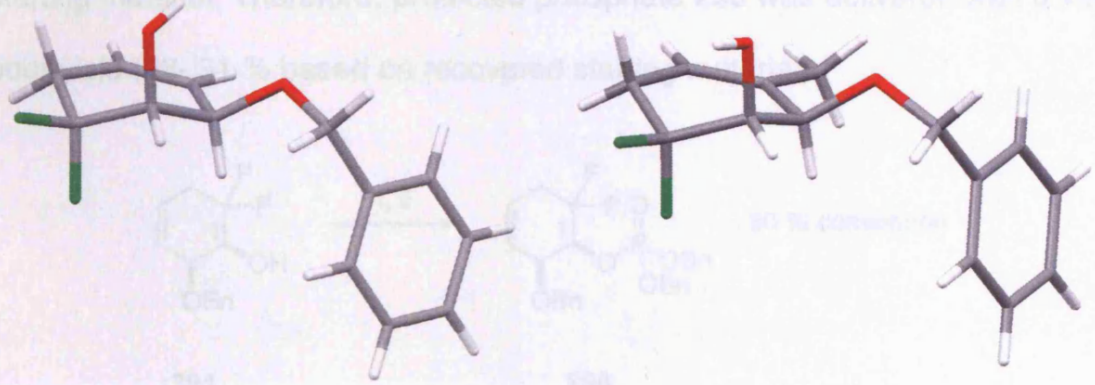
diols, proved the regioselectivity of the benzylation. Also a clear cross peak can be observed between the proton at C2 position and the benzylic carbon.




**294** **296**

**Figure 64.**

Furthermore, **294** and **296** were crystallised from hot hexane. The crystal structure (**Figure 65**) shows clearly the regioselectivity of the monoprotection of diols **192** and **196**.



**294** **296**

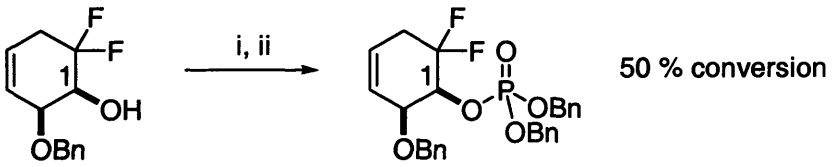
**Figure 65**. Molecular structure of **294** and **296** in the crystal.

It is well-established that the difference in reactivity of the equatorial and axial hydroxyl group could be utilised for regioselective introduction of a protective group. For example, the use of organotin derivatives in alkylations is a well-known method to discriminate between equatorial and axial hydroxyl groups.[161] But here, our system does not present any preferential conformation and therefore the main effect to consider could be that the OH function α- to the $CF_2$

centre is strongly deactivated; indeed the electron withdrawing effect of the $CF_2$ centre decreases considerably the nucleophilicity of the oxygen atom favoring the attack of the oxygen atom at C2 position on the benzyl iodide.

### 2.5.2 Phosphorylation

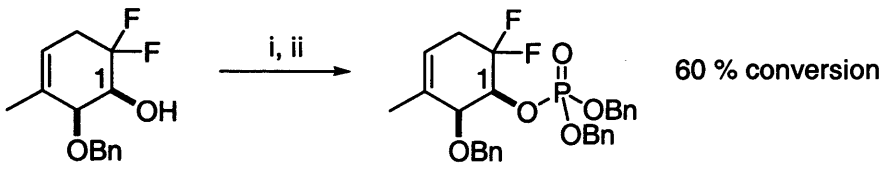
The next step toward NDP sugar precursors was the phosphorylation of the hydroxyl group at the C1 position of monoprotected diols **294** and **296**. Initially, the phosphorylation of **294** was attempted by treatment with LDA[162] in tetrahydrofuran, followed by addition of tetrabenzyl pyrophosphate[163] at 0 °C (**Scheme 84**). Unfortunately, the reaction did not reach completion; the $^{19}F$ NMR spectrum of the crude material showed only 50 % conversion of the starting material. Therefore, protected phosphate **298** was delivered with a very poor yield (23- 31 % based on recovered starting material).




**294** **298**

**Scheme 84.** Reagents and conditions: i) LDA, tetrahydrofuran, -78 °C, 15 min ii) tetrabenzyl pyrophosphate, -78 to 0 °C, 2 h, 23 % (31 % based on recovered starting material).

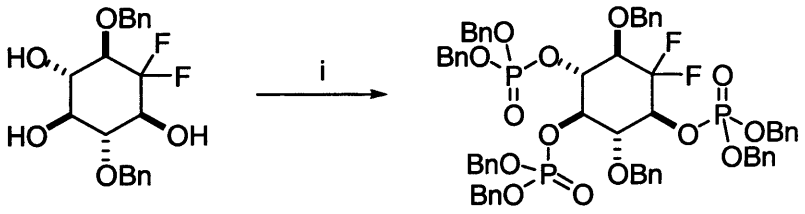
The same reaction conditions were applied to monoprotected diol **296** (**Scheme 85**) with a similar outcome. Indeed, the reaction delivered phosphate **299** in poor yield (37-63 % based on recovered starting material) and a similar low conversion (60 %).




**296** **299**

**Scheme 85.** Reagents and conditions: i) LDA, tetrahydrofuran, -78 °C, 15 min; ii) tetrabenzyl pyrophosphate, -78 to 0 °C, 2 h, 37 % (63 % based on recovered starting material).

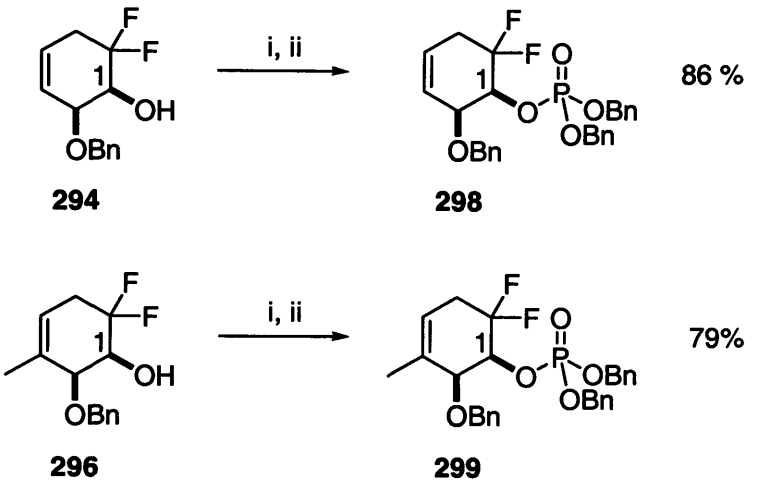
Considering the ease of the deprotonation of such substrates, the limiting factor must be nucleophilic attack of the newly formed lithium alkoxide on the phosphorus of the tetrabenzyl reagent. The enhancement of the nucleophilicity might be achieved by choosing a different counter ion. Sodium hydride would generate a sodium alkoxide intermediate which is expected to be more nucleophilic. Prestwich *et al.*[21] used these set of conditions for the phosphorylation of intermediate **300** (**Scheme 86**) presenting very similar pattern to our substrate. No yield was quoted.




**300** **301**

**Scheme 86.** Reagents and conditions: i) NaH (inverse addition), DMF, 0 °C, 30 min; ii) tetrabenzyl pyrophosphate, rt.

Monoprotected diol **294** was added to sodium hydride dissolved in tetrahydrofuran at room temperature, followed by addition of tetrabenzyl pyrophosphate (**Scheme 87**). Under these conditions, we obtained intermediate **298** in very good yield (86 %). In the same manner, the phosphorylation of **296** afforded **299** with a similar yield (79 %).

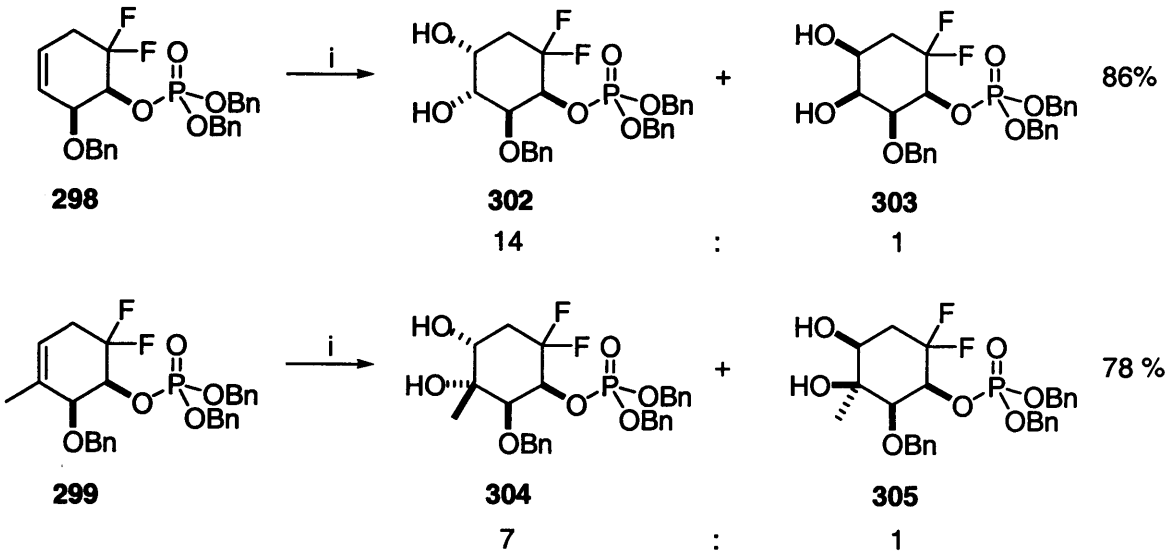



**Scheme 87**. Reagents and conditions: i) NaH (inverse addition), tetrahydrofuran, rt, 30 min; ii) tetrabenzyl pyrophosphate, rt, 19 h.

These two products exhibited characteristic single peak in their $^{31}P$ NMR spectra (-1.5 ppm). Additionally, the $^{13}C$ NMR spectra of each product of the phosphorylation showed a coupling constant between the carbon atom at C1 position and the phosphorus atom (*eg.* $^{2}J_{C\text{-}P}$ 5.6) confirming the formation of the carbon-phosphorus bond. Complemented by mass spectrometry and elemental analysis, the structure of these two intermediates can be confirmed unambiguously.

### 2.5.3 Dihydroxylation

The dihydroxylation of the phosphoric acid triesters obtained previously was accomplished under Upjohn conditions (**Scheme 88**). The reaction of precursor **298** in presence of a catalytic amount of osmium tetroxide delivered the desired product **302** with a very good diastereoselectivity (14:1) in excellent yield (86 %). In the same manner, **299** afforded intermediate **304** with a lower selectivity (7:1) and yield (78 %) than the non-substituted substrate **298**.




**Scheme 88.** Reagents and conditions: i) 2 mol% $OsO_4$, NMO, *t*-BuOH, acetone, water, 3 d.

The phosphorylated compounds were stable on silica, and no decomposition was observed during purification. Unfortunately, neither of the products obtained could be separated and therefore were treated as a mixture of diastereoisomers and characterised as so. Mass spectrometry allowed us to confirm the structure of the products as well as coupling constant between the phosphorus atom and the carbon atom β- to it ($^2J_{C\text{-}P}$ 6.4) confirmed the stability of the phosphorus-carbon bond through dihydroxylation conditions.

The dihydroxylation under Upjohn conditions of precursors **298** and **299** delivered the expected stereochemical outcome; favoring the *trans* product as the major diastereoisomer (the newly formed diol presenting a *trans* relationship with the existing protected diol). Indeed, the NOESY spectrum exhibits clear correlation peaks between H-$3_{ax}$, H-5 and the benzylic protons (**Figure 66**) of **302.**

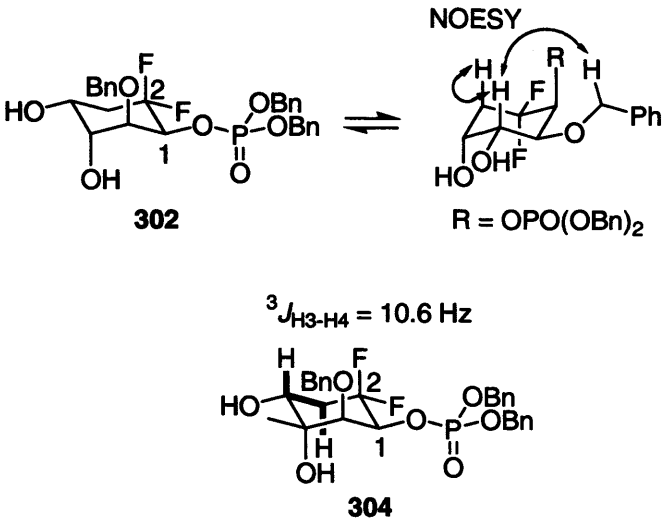



**Figure 66.**

### 2.5.4 Potential Route to NDP Sugar Analogues

Considering the small library of dilfuorocyclohexenediol obtained previously (*cf.* **2.3.**), different precursors could be considered; global debenzylation *via* hydrogenation of these phosphates would afford the deprotected sodium salts (**Figure 67**).

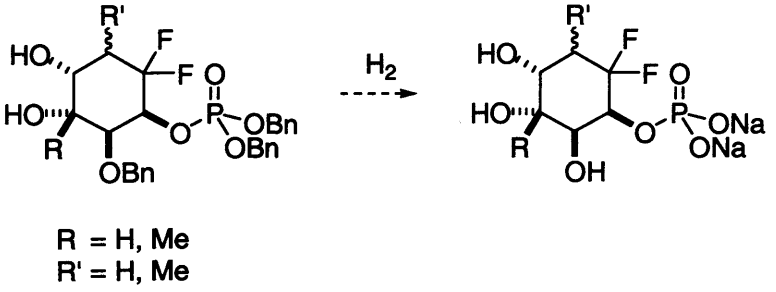
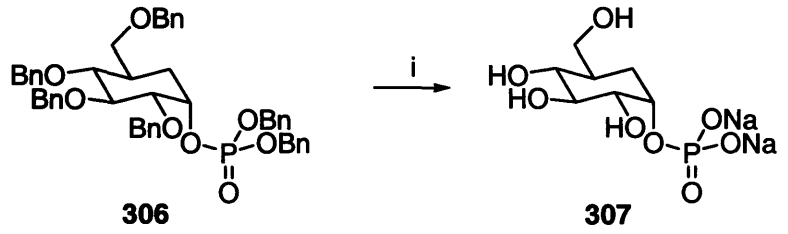



**Figure 67.**

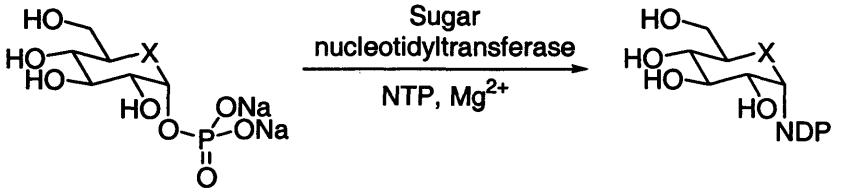
Pohl *et al.*[164] obtained the deprotection of the benzyl group of carbasugar **306** exhibiting a similar pattern to our substrates (**Scheme 89**).




306 307

**Scheme 89.** Reagents and conditions: i) $Pd(OH)_2$, $H_2$, methanol, 99 %.

Pohl *et al.*[164] showed that sugar nucleotidyltransferases provide an easy chemoenzymatic synthesis of activated sugars from their sodium salt precursors such as **307** (**Scheme 90**). These types of analogues would be part of studies of the effects of the replacement of the ring oxygen by a $CH_2$ centre on the conformations and properties of carbasugars and for co-crystallisation studies with glycosyltransferases and their respective glycosyl acceptors.

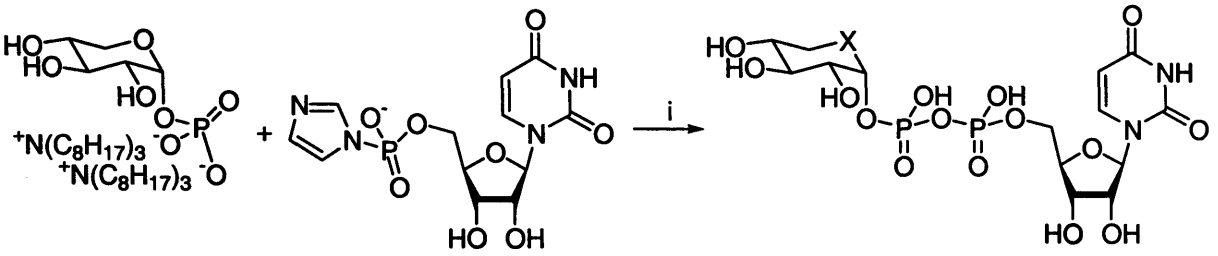



**307** X = $CH_2$
**308** X = O

**309** X = $CH_2$
**310** X = O

**Scheme 90.**

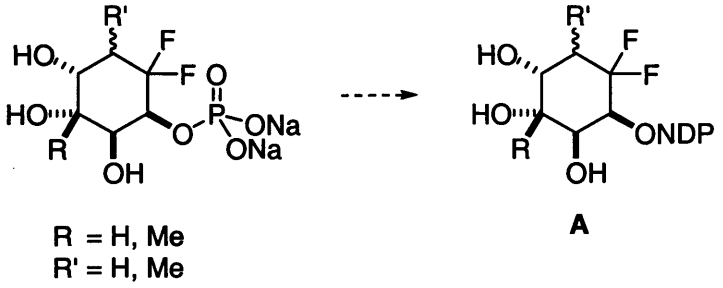
Hase *et al.*[165] performed the chemical synthesis of uridine 5'-diphospho-α-D-xylopyranose **313** from the tri-*n*-octylammonium salt of D-xylopyranose 1-phosphate **311** and uridine 5'-monophosphoimidazolide **312** (**Scheme 91**). The synthetic preparation of compounds such as **313** would allow glycoconjugate biosynthetic studies and structural, functional, and kinetic studies of xylosyltransferases.



311 312 313

**Scheme 91.** Reagents and conditions: i) DMF/pyridine (35:8, *v/v*), 5days, rt, 35 %.

Similarly, our compound could be a potential substrate to obtain activated sugars such as **A** (**Figure 68**).



R = H, Me
R' = H, Me

**A**

**Figure 68.**

Ring closing metathesis using second generation Grubbs' catalyst afforded rapidly key difluorinated cyclohexenes in high yield from free diols. We were able to optimised the concentration as well as the catalyst loadings for a wide range of level of substitution of the acyclic diols. The presence of reduced unreacted cinnamaldehyde inhibiting the activity of the catalyst, was revealed as being an important factor.

These key intermediates opened two paths, toward carbasugar analogues and precursors of analogues of NDP sugars. The fully hydroxylated cyclitols analogues were envisaged *via* epoxidation of the difluorocyclohexenes intermediates followed by their opening using selenium chemistry. Unfortunately, the conversion of our epoxides, obtained in high diastereoselectivity in either Henbest or non-directed conditions, to allylic alcohols failed.

Therefore, the dihydroxylation of the difluorocyclohexenes themselves was investigated. The scope and limitations of different methods of dihydroxylation were identified for our substrates presenting an extensive variety of substitutions. Dihydroxylation under Upjohn conditions exhibited from average to excellent diastereoselectivity depending of the position and level of substitutions. Donohoe-type dihydroxylations delivered the expected outcome for each substrates in very high diastereoselectivity . The only concern of this method arises from the use of a stoichiometric amount of highly toxic osmium tetroxide. Narasaka's modifications of Upjohn procedure were disappointing considering the purifications difficulties we encountered.

Also, the use of these intermediates as candidate for analogues of NDP sugars was investigated for a limited number of our substrates. The monobenzylation

# 3 Conclusion

The route based on a fluorinated building block approach delivered rapidly a small library of difluoroanalogues of carbasugars using readily available and inexpensive starting materials where the use of protecting group chemistry was reduced to its minimum as well as purification.
This chemistry is unique as a method for the rapid syntheses of difluorinated molecules of this level of complexity and relevance to saccharides.

The synthesis of a wide range of trifluoroethanol ethers was first performed in an ionic liquid which we were able to recycle (up to 3 times) for further reactions but this process was not suitable for large scale reactions and also was not cost efficient. In contrary, the synthesis in water represents an atom efficient and sustainable solution to the multigram scale syntheses of some trifluoroethyl ethers, given that the by-products are water and potassium chloride or bromide.

Dehydrofluorination/metallation at low temperature (-100 °C) followed by trapping of aldehyde occurred efficiently with a wide variety of substrates allowing a rapid synthesis of allylic alcohols on a comfortable scale (up to 75 mmol). This process was developed as a second generation route after non-reproducibility of the first generation route based on vinyl silanes.

After Claisen rearrangement of the dienols obtained after dehydrofluorination/ metallation, sodium borohydride was found to be the most diastereoselective as well as practical reducing agents tested for the reduction of the acyclic diols.

of the key difluorocyclohexenes presented very good regioselectivity. Once phosphorylated, these monoprotected intermediates underwent dihydroxylation under Upjohn conditions in very good diastereoselectivity to deliver precursor of analogues of NDP sugars after global debenzylation.

# 4 Experimental

## *4.1 General Procedures*

NMR spectra were recorded on a Bruker ARX 250 ($^1$H, 250.13 MHz; $^{13}$C, 62.90 MHz; $^{19}$F, 235.36 MHz) spectrometer, a Bruker DPX 300 ($^1$H, 300.13 MHz; $^{13}$C, 75.47 MHz; $^{19}$F, 282.40 MHz, COSY, HMQC, HMBC) spectrometer and a Bruker DRX 400 ($^1$H, 400.13 MHz; $^{13}$C, 100.62 MHz; $^{19}$F, 376.45 MHz, COSY, HMQC, HMBC, NOESY) spectrometer. Chemical shifts for $^1$H and $^{13}$C NMR spectra were recorded using deuterated solvent as the lock and residual solvent as the internal standard. $^{19}$F NMR spectra were referenced to fluorotrichloromethane as the external standard. They are reported consecutively as chemical shift ($\delta_H$, $\delta_C$, or $\delta_F$), relative integral, multiplicity (s = singlet, br s = broad singulet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quadruplet, app. = apparent), coupling constant *J* refers to $^3J_{H\text{-}H}$; all other homo- and Heteronuclear couplings are defined fully and assignment. Electron Impact (EI) mass spectra were recorded on Kratos Concept 1H. Chemical Ionization (CI) mass spectra were recorded on a Kratos Concept 1H using ammonia as the reagent gas. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC spectrometer. High Resolution Mass Spectrometry (HRMS) was measured on a Kratos Concept 1H spectrometer using peak matching to stable reference peaks, depending on the technique used. Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40-63μ) and HPFC Biotage Horizon system with

Biotage silica prepacked Flash+ purification cartridges and Samplet sample-loading cartridges (12+M, 12+S, 25+M, 40+Mand 40+S). Column fractions were collected and monitored by Thin Layer Chromatography (TLC) and carried out on precoated aluminium backed silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 $F_{254}$, thickness 0.2 mm) or on precoated glass plates supplied by Merck (Silica gel 60 $F_{254}$). The compounds were visualized using UV light, potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenolhydrazine (DNP) or phosphomolybdic acid (PMA). Gas Chromatography was measured on a Perkin Elmer Autosystem Gas Chromatograph linked to a Perkin Elmer Turbomass mass spectrometer. The chromatograph was fitted with a PE5 MS (5 % phenyl, 95 % dimethylpolysiloxane phase column (30 m)), experiments were carried out between 45 C- 250 ºC with a 10 ºC $min^{-1}$ ramp. Infra-red (IR) spectra were obtained on a Perkin Elmer 1600 series FTIR in the region 4000-500 $cm^{-1}$. The samples were run as solutions in dry dichloromethane (DCM) in a NaCl cell, or as neat samples in a Perkin Elmer SpectrumOne FT-IR spectrometer.

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, and was distilled and collected by syringe as required. Dichloromethane, diethyl ether, toluene and acetonitrile were dried by refluxing with calcium hydride. They were then distilled and collected by dry syringe as required. *n*-Butyllithium was titrated immediately before use according to the method described by Duhamel *et al.*[166] using 4-phenylbenzylidene benzylamine. All other chemicals and solvents were used as received without any further purification.

# 4 Experimental

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Biotage silica prepacked Flash+ purification cartridges and Samplet sample-loading cartridges (12+M, 12+S, 25+M, 40+Mand 40+S). Column fractions were collected and monitored by Thin Layer Chromatography (TLC) and carried out on precoated aluminium backed silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 $F_{254}$, thickness 0.2 mm) or on precoated glass plates supplied by Merck (Silica gel 60 $F_{254}$). The compounds were visualized using UV light, potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenolhydrazine (DNP) or phosphomolybdic acid (PMA). Gas Chromatography was measured on a Perkin Elmer Autosystem Gas Chromatograph linked to a Perkin Elmer Turbomass mass spectrometer. The chromatograph was fitted with a PE5 MS (5 % phenyl, 95 % dimethylpolysiloxane phase column (30 m)), experiments were carried out between 45 C- 250 ºC with a 10 ºC $min^{-1}$ ramp. Infra-red (IR) spectra were obtained on a Perkin Elmer 1600 series FTIR in the region 4000-500 $cm^{-1}$. The samples were run as solutions in dry dichloromethane (DCM) in a NaCl cell, or as neat samples in a Perkin Elmer SpectrumOne FT-IR spectrometer.

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, and was distilled and collected by syringe as required. Dichloromethane, diethyl ether, toluene and acetonitrile were dried by refluxing with calcium hydride. They were then distilled and collected by dry syringe as required. *n*-Butyllithium was titrated immediately before use according to the method described by Duhamel *et al.*[166] using 4-phenylbenzylidene benzylamine. All other chemicals and solvents were used as received without any further purification.

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(1*S**,2*S**)-6,6-Difluoro-5,5-dimethyl-cyclohex-3-ene-1,2-diol **209** ..... 202

(1*R**,2*S**)-6,6-Difluoro-5,5-dimethyl-cyclohex-3-ene-1,2-diol **210** ..... 203

(1*S**,2*S**,5*S**)-6,6-Difluoro-3,5-dimethyl-cyclohex-3-ene-1,2-diol **207** ..... 204

(1*S**,2*S**,5*R**)-6,6-Difluoro-3,5-dimethyl-cyclohex-3-ene-1,2-diol **208** ..... 204

(1*S**,2*S**)-6,6-Difluoro-3,4-dimethyl-cyclohex-3-ene-1,2-diol **211** ..... 206

(1*R**,2*R**,3*S**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol **232** ..... 207

(1*S**,2*R**,3*S**,6*R**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol **236** ..... 208

(1*R**,2*R**,3*S**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol **232** ..... 208

(1*R**,2*R**,3*R**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol **233** ..... 209

(1*S**,2*R**,3*R**,6*R**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol **237** .....210

(1*S**,2*R**,3*R**,4*S**)-6,6-difluoro-3-(phenylthio)cyclohexane-1,2,4-triol **252** .....212

(1*S**,2*R**,3*R**,4*S**)-6,6-difluoro-3-(phenylsulfonyl)cyclohexane-1,2,4-triol **253** .....213

(1*R**,2*R**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **262** ...214

(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **263**....214

(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **263**....216

(1*R**,2*R**,3*S**,4*R**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **264** ...217

(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **265**....217

(1*R**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate **265**....219

(1*R**,2*R**,3*R**,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclo hexyl acetate **266** .....221

(1*S**,2*S**,3*R**,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclo hexyl acetate **267** .....221

(1*S**,2*S**,3*R*,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclohexyl acetate **267** .....223

(1*S**,2*S**,3*R**,4*S**,6*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate **269** .....225

(1*S**,2*S**,3*R**,4*S**,6*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate **269** .....227

(1*R**,2*R**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate **270** .....228

(1*S**,2*S**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate **271** .....228

(1*R**,2*R**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate **270** .....230

(1*R**,2*S**,3*R**,6*S**)-6-(acetyloxy)-5,5-difluoro-2,3-dihydroxy-2,3-dimethyl cyclohexyl acetate **272**.....231

(1*R**,2*R**,3*S**,6*S**)-6-(acetyloxy)-5,5-difluoro-2,3-dihydroxy-2,3-dimethyl cyclohexyl acetate **273**.....231

(1*R**,2*R**,3*S**,4*S**)-5,5-difluorocyclohexane-1,2,3,4-tetrol **283**.....234

(1*R**,2*R**,3*S**,4R*)-5,5-difluorocyclohexane-1,2,3,4-tetrol **284**.....235

(1*S**,2*S**,3*S**,4R*)-5,5-difluorocyclohexane-1,2,3,4-tetrol **285**.....235

(1*S**,2*S**,3*S**,4R*)-5,5-difluorocyclohexane-1,2,3,4-tetrol **285**.....236

(1*R**,2*R**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol **286**.....237

(1*R**,2*R**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol **286**.....238

(1*S**,2*S**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol **287**.....239

(1R*,2S*,3S*,4S*)-5,5-difluoro-1-methylcyclohexane-1,2,3,4-tetrol **274**.....240

(1*S**,2*S**,3*R**,4*S**,6*S**)-5,5-difluoro-2,6-dimethylcyclohexane-1,2,3,4-tetrol **288**.....242

(1*S**,2*S**)-2-(Benzyloxy)-6,6-difluorocyclohex-3-en-1-ol **294**.....243

(1*S**,2*S**)-6-(Benzyloxy)-5,5-difluorocyclohex-2-en-1-ol **295**.....243

(1*S**,2*S**)-2-(Benzyloxy)-6,6-difluoro-3-methylcyclohex-3-en-1-ol **296**.....245

(1*S**,6*S**)-6-(Benzyloxy)-5,5-difluoro-2-methylcyclohex-2-en-1-ol **297**.....245

(1*S**,2*S**)-2-(benzyloxy)-6,6-difluorocyclohex-3-en-1-yl dibenzyl phosphate **298**.....247

(1*S**,2*S**)-2-(benzyloxy)-6,6-difluoro-3-methylcyclohex-3-en-1-yl dibenzyl phosphate **299**.....249

(1*S**,4*R**,5*R**,6*S**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxycyclohexyl dibenzyl phosphate **302**.....251

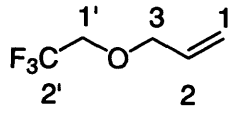
(1*S**,4*S**,5*S**,6*S**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxycyclohexyl dibenzyl phosphate **303**.....251

(1*S**,4*R**,5*R**,6*R**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxy-5-methyl cyclohexyl dibenzyl phosphate **304** ..... 253

(1*S**,4*S**,5*S**,6*R**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxy-5-methyl cyclohexyl dibenzyl phosphate **305** ..... 253

## 4.3 Procedures

### 3-(2',2',2'-Trifluoroethoxy)prop-1-ene 116

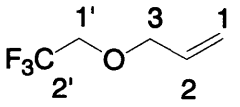



**116**

Trifluoroethanol (3.6 mL, 50.0 mmol) was added to a suspension of potassium hydroxide (6.6 g, 100.0 mmol) in bmim.$PF_6^-$ (10.0 mL) and the suspension was stirred for 30 minutes at 0 °C. Allyl bromide (4.8 mL, 55.0 mmol) was added and the mixture was stirred overnight at 40 °C, then distilled to afford ether **116** (5.2 g, 74 %, 99 % by GC); bp 78 °C; $\upsilon_{max}$(film)/$cm^{-1}$ 1277s, 1154s, 989w; $\delta_H$ (300 MHz, $CDCl_3$) 5.89 (1H, ddt, *J* 17.2, 10.4, 5.6, *HC*=$CH_2$), 5.35-5.25 (2H, m, HC=C*H*$_2$), 4.13 (2H, d, *J* 5.6, C*H*$_2$CH=$CH_2$), 3.80 (2H, q, $^3J_{H\text{-}F}$ 8.5, $CF_3CH_2$); $\delta_C$ (75 MHz, $CDCl_3$) 133.1 (C-2), 124.1 (q, $^1J_{C\text{-}F}$ 279.2, C-2'), 118.5 (C-1), 73.0 (C-3), 67.0 (q, $^2J_{C\text{-}F}$ 33.9, C-1'); $\delta_F$ (282 MHz, $CDCl_3$) -74.3 (t, $^3J_{F\text{-}H}$ 8.5); [HRMS (EI, $M^+$) Found: 140.04488. Calc. for $C_6H_9OF_3$ 140.04490]; *m/z* (EI) 140 (35 %, $M^+$), 83 (80, M-$C_3H_5O$), 71 (64), 55 (100).

The remaining ionic liquid was washed with water (2 x 200 mL) and brine (200 mL) then dried by heating at 70 °C under vacuum (<1mmHg) for 6 hours, the ionic liquid bmim.$PF_6$ was then ready to re-use.

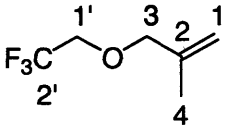
### 3-(2',2',2'-Trifluoroethoxy)prop-1-ene 116




**116**

Trifluoroethanol (1.00 mol, 72.7 mL) was added slowly over 5 minutes to a solution of potassium hydroxide (1.10 mol, 73.0 g) in water (80 mL) at 0 °C. The mixture was stirred for one hour at room temperature. Allyl bromide (1.05 mol, 91.8 mL) was added slowly at room temperature. The mixture was stirred overnight at 40 °C, then allowed to cool and the organic layer was separated from the aqueous layer and distilled from calcium hydride to afford trifluoroether **116** as a colourless liquid (139.0 g, 99 %). Data were in agreement with those reported under ionic liquid conditions.

### 2-Methyl-3-(2',2',2'-trifluoro-ethoxy)prop-1-ene 118



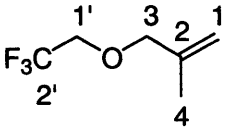

**118**

Sodium hydroxide (400.0 mmol, 16.0 g) was ground finely and suspended in bmim.$PF_6$ (50.0 mL) and the suspension was stirred for 1 hour at room temperature. Trifluoroethanol (200.0 mmol, 14.7 mL) was added to this suspension at 0 °C and stirred for 1 hour at 0 °C. Methallyl chloride **121** (220.0 mmol, 21.7 mL) was added at 0 °C and the mixture was stirred overnight at 40

°C then distilled to afford ether **118** (20.0 g, 65 %); bp 92 °C, $\upsilon_{max}$(film)/cm$^{-1}$ 3022 w, 2944 w, 1277s, 1156s, 989w; $\delta_H$ (300 MHz, $CDCl_3$) 5.12-5.08 (2H, m, $CH_3C{=}CH_2$), 4.15 (2H, s, $H_2C{=}CCH_3CH_2$), 3.88 (2H, q, $^3J_{H\text{-}F}$ 8.9, $CF_3CH_2$), 1.86 (3H, s, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 141.1 (C-2), 124.1 (q, $^1J_{C\text{-}F}$ 279.2, C-2'), 114.2 (C-1), 76.4 (C-3), 67.1 (q, $^2J_{C\text{-}F}$ 34.0, C-1'), 19.4 (C-4); $\delta_F$ (282 MHz, $CDCl_3$) -74.8 (t, $^3J_{F\text{-}H}$ 8.9); [HRMS (EI, $M^+$) Found: 154.06057. Calc. for $C_6H_9OF_3$ 154.06055]; *m/z* (EI) 154 (38 %, $M^+$), 139 (66), 113 (9), 55 (100).

The remaining ionic liquid was washed with water (2 x 200 mL) and brine (200 mL) then dried by heating at 70 °C under vacuum (<1mmHg) for 6 hours, the ionic liquid bmim.$PF_6$ was then ready to re-use.

**2-Methyl-3-(2',2',2'-trifluoroethoxy)prop-1-ene 118**

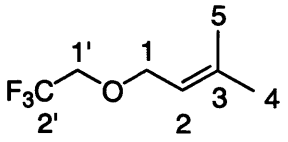



**118**

Trifluoroethanol (200 mmol, 14.7 mL) was added slowly to a solution of potassium hydroxide (220 mmol, 14.5 g) in water (20 mL) at 0 °C. The mixture was stirred for one hour at room temperature. Methallyl chloride **121** (210 mmol, 20.7 mL) was added slowly at room temperature. The mixture was stirred for 48 hours at 40 °C, then allowed to cool and the organic layer was separated from the aqueous layer and distilled from calcium hydride to afford trifluoroether **118**

as a colourless liquid (20.0 g, 78 %, 100 % by GC). Data were in agreement with those reported in ionic liquid conditions.

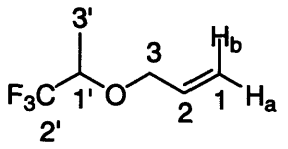
### 3-Methyl-1-(2',2',2'-trifluoroethoxy)but-2-ene 108




**108**

Trifluoroethanol (30 mmol, 3.0 g) was added slowly to a solution of potassium hydroxide (33 mmol, 2.2 g) in water (5 mL) at 0 °C. The mixture was stirred for one hour at room temperature. Prenyl bromide (30 mmol, 4.7 g) was added slowly at room temperature. The mixture was stirred for 48 hours at 40 °C, then allowed to cool and the organic layer was separated from the aqueous layer and distilled from calcium hydride to afford trifluoroether **108** as a colourless liquid (2.36 g, 47 %, 89 % by GC); $\upsilon_{max}$ (film)/cm$^{-1}$: 3029m, 2918s, 1472s, 1148s; $\delta_H$ (300 MHz; $CDCl_3$) 5.31 (1H, t, *J* 7.0, $(CH_3)_2C{=}CHCH_2$), 4.11 (2H, d, *J* 7.0, $CHCH_2$), 3.76 (2H, q, $^3J_{H\text{-}F}$ 8.8, $CF_3CH_2$), 1.75 (3H, s, $CH_3$), 1.67 (3H, s, $CH_3$); $\delta_C$ (75 MHz; $CDCl_3$) 139.1 (C-3), 124.2 (q, $^1J_{C\text{-}F}$ 279.2, C-2'), 119.5 (C-2), 68.4 (C-1), 66.7 (q, $^2J_{C\text{-}F}$ 33.9, C-1'), 25.6 (C-4), 17.8 (C-5); $\delta_F$ (282 MHz; $CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8.8); [HRMS (EI, M) Found: 168.07619. Calc. for ($C_6H_9OF_2$) 168.07620]; *m/z* (EI) 168 (60 %, M), 85 (100, M-$C_2H_2F_3$).

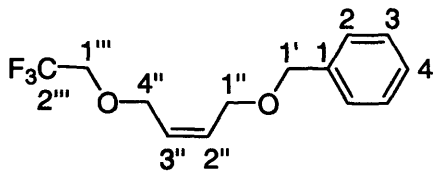
## 3-(2',2',2'-Trifluoro-1-methylethoxy)prop-1-ene 117




**117**

Potassium hydroxide (100.0 mmol, 6.6 g) was ground finely and suspended in bmim.$PF_6$ (10.0 mL) and the suspension was stirred for 0.5 hour at room temperature. Trifluoropropanol (50.0 mmol, 4.5 mL) was added to this suspension at 0 °C and stirred for 1 hour at 0 °C. Allyl bromide (55.0 mmol, 4.8 mL) was slowly added at 0 °C and the mixture was stirred overnight at 40 °C then distilled to afford ether **117** (5.2 g, 92 %, 99 % by GC); bp 79 °C; $\delta_H$ (300 MHz, $CDCl_3$) 5.89 (1H, ddt, *J* 17.2, 10.4, 5.7, *HC*=$CH_2$), 5.31 (1H, ddt, *J* 17.2, $^2J$ 1.6, $^4J$ 1.2, HC=C*H*$_a$H$_b$), 5.23 (1H, ddt, *J* 10.4, $^2J$ 1.6, $^4J$ 1.2, HC=CH$_a$*H*$_b$), 4.19 (1H, dd, $^2J$ 12.7, *J* 5.7, C*H*$_2$CH=$CH_2$), 4.11 (1H, dd, $^2J$ 12.7, *J* 5.7, C*H*$_2$CH=$CH_2$), 3.80 (1H, heptet, *J* 6.6, $CF_3CHCH_3$), 1.32 (3H, d, *J* 6.6, C*H*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 133.8 (C-2), 125.3 (q, $^1J_{C\text{-}F}$ 282.7, C-2'), 118.0 (C-1), 72.7 (q, $^2J_{C\text{-}F}$ 30.5, C-1'), 72.0 (C-3), 14.2 (q, $^3J_{C\text{-}F}$ 2.4, C-3'); $\delta_F$ (282 MHz, $CDCl_3$) -78.6 (d, $^3J_{F\text{-}H}$ 6.6).

## 1-Benzyloxy-4-(2',2',2'-trifluoroethoxy)but-2Z-ene 119

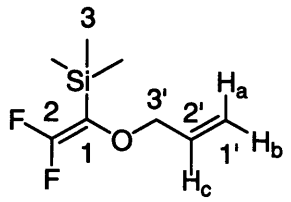



**119**

Potassium hydroxide (40.0 mmol, 2.3 g) was ground finely and suspended in bmim.$PF_6$ (5.0 mL) and the suspension was stirred for 1 hour at room temperature. Trifluoroethanol (20.0 mmol, 3.6 mL) was added to this suspension at 0 °C and stirred for 1 hour at 0 °C. 1-Chloro-4-benzyloxy-but-2Z-ene **122** (55.0 mmol, 4.5 g) was added at 0 °C and the mixture was stirred overnight at 40 °C then distilled (bp 70 °C/0.04 mmHg) to afford ether **119** (9.1 g, 70 %, 98 % by GC); $R_f$ (5 % diethyl ether in hexane) 0.35; $\delta_H$ (300 MHz, $CDCl_3$) 7.38-7.35 (5H, m, $CH_2C_6H_5$), 5.93-5.83 (1H, m, HC=C*H*), 5.78-5.68 (1H, m, *HC*=CH), 4.53 (2H, s, C$H_2$Ar), 4.20 (2H, d, *J* 6.4, HC=CHC$H_2$O), 4.10 (2H, d, *J* 6.4, HC=CHC$H_2$O), 3.79 (2H, q, $^3J_{H\text{-}F}$ 8.8, C$H_2CF_3$); $\delta_C$ (75 MHz, $CDCl_3$) 138.1 (C-1), 131.0 (C-2", C-3"), 128.5 (C-3), 127.9 (C-2, C-4), 124.1 (q, $^1J_{C\text{-}F}$ 279.5, C-2'''), 72.5 (C-1'), 67.8 (C-1"), 67.3 (q, $^2J_{C\text{-}F}$ 34.0, C-1'''), 65.6 (C-4"); $\delta_F$ (282 MHz, $CDCl_3$) -74.0 (t, $^3J_{F\text{-}H}$ 8.8). Data were in agreement with those reported by Garayt.[80]

The remaining ionic liquid was washed with water (2 x 200 mL) and brine (200 mL) then dried by heating at 70 °C under vacuum (<1mmHg) for 6 hours, the ionic liquid bmim.$PF_6$ was then ready to re-use.

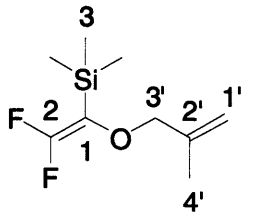
## 2,2-Difluoro-1-(allyl)oxy-1-trimethylsilyl ethene 129




**129**

Chlorotrimethylsilane (154.2 mmol, 20.0 mL) was added to a freshly prepared solution of LDA (282.6 mmol, 2.2 eq.) in tetrahydrofuran (250 mL) [prepared from *n*-butyllithium (118 mL of a 2.4 M solution in hexane, 282.6 mmol) and di*iso*propylamine (282.6 mmol, 40.0 mL) in dry tetrahydrofuran (250 mL)] at -100 °C under an atmosphere of nitrogen. Ether **116** (128.5 mmol, 18.0 g) was added dropwise at -100 °C and the temperature was allowed to warm to -40 °C over 1.5 hours. The mixture was quenched at -40 °C with ammonium chloride (40 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil which was distilled (Kugelrohr) to afford silane **129** (23.2 g, 94 %, 95 % by GC) as a colourless liquid; bp 30 °C/0.025 mmHg; $R_f$ (100 % hexane) 0.62; $\upsilon_{max}$(film)/$cm^{-1}$ 1687m, 1250m, 1155w, 839s, 759w; $\delta_H$ (300 MHz, $CDCl_3$) 5.96-5.82 (1H, m, *HC*=$CH_2$), 5.26 (1H, d, *J* 17.3, HC=C*H*$_a$H$_b$), 5.17 (1H, d, *J* 10.3, HC=CH$_a$*H*$_b$), 4.12 (2H, d, *J* 5.5, HC=CHC*H*$_2$), 0.13 (9H, s, Si(C*H*$_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 160.8 (dd, $^1J_{C\text{-}F}$ 283.0, 282.6, C-2), 133.9 (C-2'), 117.6 (C-1'), 117.4 (dd, $^2J_{C\text{-}F}$ 7.2, 7.0, C-1), 73.8 (dd, $^4J_{C\text{-}F}$ 2.8, 2.3, C-3'), 1.5 (C-3); $\delta_F$ (282 MHz, $CDCl_3$) -81.7 (1F, d, $^2J_{F\text{-}F}$ 58.5), -105.3 (1F, d, $^2J_{F\text{-}F}$ 58.5); [HRMS (EI, $M^+$) Found: 192.07825. Calc. for $C_8H_{14}OF_2$ 192.07820]; *m/z* (EI) 192 (35 %, $M^+$), 101 (38), 77 (71), 73 (100).

## 2,2-Difluoro-1-(methallyl)oxy-1-trimethylsilyl ethene 131




**131**

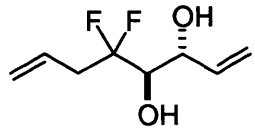
*n*-Butyllithium (10 mmol, 5 mL of a 2 M solution in hexane) was added dropwise to a solution of trifluoroether **118** (0.77 g, 5 mmol) in dry tetrahydrofuran (20 mL) at -78 °C under an atmosphere of nitrogen. The mixture was stirred a further 20 min at -78 °C and chlorotrimethylsilane (0.69 mL, 5.5 mmol) was added in one portion. The temperature was allowed to rise to -40 °C over one hour. The mixture was quenched at -40 °C with ammonium chloride (20 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil (1.35 g) which was purified by flash column chromatography on silica gel to afford silane **131** (0.93 g, 90 %, 98 % by GC) as a clear oil; $R_f$ (100 % hexane) 0.67; $\upsilon_{max}$ (KBr)/$cm^{-1}$: 3081w, 2959w, 2863w, 1689w, 844w; $\delta_H$ ($CDCl_3$, 300 MHz) 5.01-4.96 (1H, m, $CH_3C{=}CH_aH_b$), 4.92-4.88 (1H, m, $CH_3C{=}CH_aH_b$), 4.04 (2H, s, $OCH_2$), 1.77 (2H, s, $CH_3$), 0.19 (9H, s, $Si(CH_3)_3$); $\delta_C$ ($CDCl_3$, 75 MHz) 160.7 (dd, $^1J_{C\text{-}F}$ 282.6, 282.0, C-2), 141.5 (C-2'), 112.8 (C-1'), 76.8 (dd, $^4J_{C\text{-}F}$ 2.8, 2.3, C-3'), 19.5 (C-4'), -0.9 (C-3); $\delta_F$ ($CDCl_3$, 282 MHz) -82.0 (1F, d, $^2J_{F\text{-}F}$ 59.8), -105.5 (1F, d, $^2J_{F\text{-}F}$ 59.8); [HRMS (CI, M) Found: 224.093818. Calc. for $C_9H_{20}ONF_2Si$ 224.093854]; *m/z* (CI) 224 (10 %, $M+NH_4^+$), 207 (7, $M+H^+$), 90 (100).

The C-1 signal could not be observed in the $^{13}C$ NMR spectrum.

**Procedure for drying TBAF**

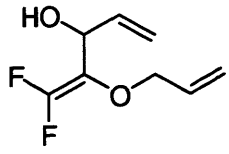
TBAF (38 mmol, 10 g) was dried over phosphorus pentoxide in a desiccator under high *vacuum* for 5 days at room temperature. The dried material was taken up in tetrahydrofuran (38 mL) under an atmosphere of nitrogen to afford a 1M solution which was stored in a suba-sealed bottle and transferred via dry syringe.

**Preparation of (3*S**,4*S**)-5,5-Difluoroocta-1,7-diene-3,4-diol 143a *via* Vinyl Silane**

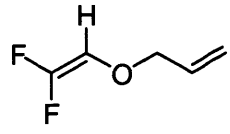



**143a**

**i) Fluoride-ion mediated vinyl addition: 2-(Allyloxy)-1,1-difluoro-penta-1,4-dien-3-ol 134 and 1-(Allyloxy)-2,2-difluoro-ethene 136**




**134**

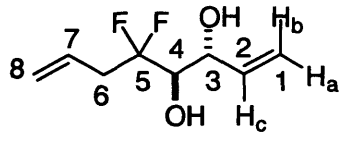



**136**

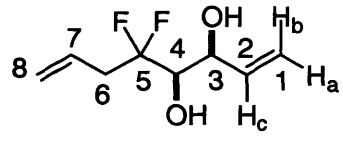
Dry tetra-*n*-butylammonium fluoride (50.0 mmol, 50 mL of a 1 M solution in tetrahydrofuran) was added dropwise to a solution of vinyl silane **129** (41.6 mmol, 8.0 g) and acrolein **133** (47.8 mmol, 3.3 mL) in tetrahydrofuran (120 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred for 3 hours, quenched with water (10 mL) and extracted with diethyl ether (3 x 30 mL). The

combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture (9:1) of dienol **134** and difluoro alkene **136** as an orange oil (3.20 g); data for **134**: $R_f$ (40 % ethyl acetate in hexane) 0.75; $\delta_H$ (300 MHz, $CDCl_3$) 6.03-5.85 (2H, m, *HC*=$CH_2$), 5.42-5.19 (4H, m, HC=C$H_2$), 4.86-4.76 (1H, m, C*H*OH), 4.35 (2H, ddd, *J* 6.0, $^4J$ 1.1, 0.5, OC$H_2$); $\delta_F$ (282 MHz, $CDCl_3$) -99.9 (1F, d, $^2J_{F\text{-}F}$ 70.3), -111.6 (1F, dd, $^2J_{F\text{-}F}$ 70.3, $^4J_{F\text{-}H}$ 2.6). Data for **136**: $R_f$ (40 % ethyl acetate in hexane) 0.80; $\delta_H$ (300 MHz, $CDCl_3$) 5.93-5.66 (1H, m, *HC*=$CH_2$), 5.54 (1H, dd, $^3J_{H\text{-}F}$ 16.3, 2.6, $CF_2$=C*H*O), 5.30-5.04 (2H, m, HC=C$H_2$), 4.08 (2H, ddd, *J* 6.0, $^4J$ 1.1, 0.5, C$H_2$CH=$CH_2$); $\delta_F$ (282 MHz, $CDCl_3$) -101.1 (1F, dd, $^2J_{F\text{-}F}$ 80.2, $^3J_{F\text{-}H}$ 16.3), -121.6 (1F, dd, $^2J_{F\text{-}F}$ 80.2, $^3J_{F\text{-}H}$ 2.6).

### ii) Tandem Claisen Rearrangement/Reduction: (3*S**,4*S**)-5,5-Difluoroocta-1,7-diene-3,4-diol 143a




**143a**



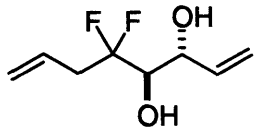

**143b**

Di*iso*butylaluminium hydride (54.5 mmol, 54.5 mL of a 1 M solution in toluene) was added slowly to a crude solution of dienol **134** (18.1 mmol, 3.2 g) in tetrahydrofuran (50 mL) at -78 °C. The mixture was allowed to warm to room temperature over two hours and stirred for a one hour at room temperature. The mixture was quenched at 0 °C with sodium hydroxide (10 mL of a 1M solution) until the complete dissolution of the salts and extracted with dichloromethane

(3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil as a (9:1) mixture of two diastereoisomers **143a** and **143b** which was separated by column chromatography (10 % ethyl acetate in hexane) to afford diastereoisomers **143a** and **143b** (0.3 g, 10 % over 3 steps, 94 % by GC) as white solids; data for **143a**: mp: 47-49 °C; $R_f$ (40 % ethyl acetate in hexane) 0.47; $\delta_H$ (300 MHz, $CDCl_3$) 6.00-5.90 (1H, m, $H_2C=CHCH_2$), 5.86-5.78 (1H, m, $H_c$), 5.43 (1H, dt, *J* 17.1, $^2J$ 1.4, $^4J$ 1.4, $H_b$), 5.32-5.25 (2H, m, $H_2C=CHCH_2$), 5.30 (1H, dt, *J* 10.3, $^2J$ 1.4, $^4J$ 1.4, $H_a$), 4.60-5.90 (1H, m, $CHOHCH=CH_2$), 3.66 (1H, d, $^3J_{H-F}$ 19.3, $CF_2CHOH$), 2.95-2.75 (2H, m, $CH_2CF_2$), 2.88 (1H, br s, OH), 2.11 (1H, br s, OH); $\delta_C$ (75 MHz, $CDCl_3$) 136.6 (C-2), 128.7 (dd, $^3J_{C-F}$ 7.8, 3.4, C-7), 123.4 (dd, $^1J_{C-F}$ 247.8, 245.7, C-5), 120.8 (C-1), 117.1 (C-8), 73.2 (dd, $^2J_{C-F}$ 30.6, 25.5, C-4), 68.4 (dd, $^3J_{C-F}$ 3.6, 2.1, C-3), 38.1 (dd, $^2J_{C-F}$ 25.5, 23.3, C-6); $\delta_F$ (282 MHz, $CDCl_3$) -107.3 (1F, ddd, $^2J_{F-F}$ 250.9, $^3J_{F-H}$ 19.3, 4.6), -111.7 (1F, dtd, $^2J_{F-F}$ 250.9, $^3J_{F-H}$ 18.4, 12.0); data for **143b**: mp: 58-59 °C; $R_f$ (40 % ethyl acetate in hexane) 0.34; $\delta_H$ (300 MHz, $CDCl_3$) 6.04-5.90 (1H, m, $H_c$), 5.85-5.68 (1H, m, $H_2C=CHCH_2$), 5.36 (1H, dt, *J* 17.2, $^2J$ 1.5, $^4J$ 1.5, $H_b$), 5.31 (1H, dt, *J* 10.5, $^2J$ 1.5, $^4J$ 1.5, $H_a$), 5.23-5.14 (2H, m, $H_2C=CHCH_2$), 4.43-4.36 (1H, m, $CF_2CHOHCHOH$), 3.80 (1H, ddd, $^3J_{H-F}$ 17.5, 6.6, *J* 4.2, $CF_2CHOH$), 2.79-2.60 (2H, m, $CH_2CF_2$), 2.55 (1H, br s, OH), 2.26 (1H, br s, OH); $\delta_C$ (75 MHz, $CDCl_3$) 135.5 (t, $^4J_{C-F}$ 1.2, C-2), 128.6 (dd, $^3J_{C-F}$ 7.2, 4.2, C-7), 122.8 (dd, $^1J_{C-F}$ 247.7, 245.3, C-5), 120.8 (C-1), 117.9 (C-8), 73.9 (dd, $^2J_{C-F}$ 28.7, 25.1, C-4), 71.6 (dd, $^3J_{C-F}$ 2.4, 1.2, C-3), 38.6 (dd, $^2J_{C-F}$ 25.1, 23.9, C-6); $\delta_F$ (282 MHz, $CDCl_3$) -106.8 (1F, dtd, $^2J_{F-F}$ 252.6, $^3J_{F-H}$ 19.4, 6.6), -108.5 (1F, ddt, $^2J_{F-F}$ 252.6, $^3J_{F-H}$ 17.5, 13.7)

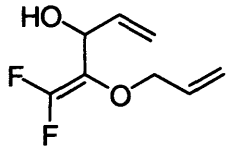
A molecular ion could not be obtained under a range of conditions (ES-MS, EI, CI, FAB) for neither of the products.

**Preparation of (3*S**,4*S**)-5,5-Difluoroocta-1,7-diene-3,4-diol 143a *via* Direct Addition**

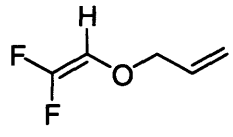



**143a**

**i) Dehydrofluorination/Metallation: 2-(Allyloxy)-1,1-difluoro-penta-1,4-dien-3-ol 134 and 1-(Allyloxy)-2,2-difluoro-ethene 136**




**134**



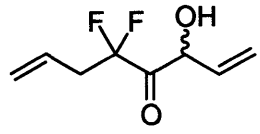

**136**

*n*-Butyllithium (110 mmol, 45.8 mL of a 2.4 M solution in hexane) was added dropwise over 25 minutes to a solution of ether **116** (50.0 mmol, 7.0 g) in tetrahydrofuran (100 mL) at -100°C under an atmosphere of nitrogen and the mixture was maintained at -100°C for one hour. Acrolein (47.5 mmol, 3.3 mL) was added dropwise at -100°C. The mixture was allowed to warm to -40°C over one hour and a half. The mixture was quenched at -40°C with ammonium chloride (40 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) to afford a (9:1) mixture of dienol **134** and difluoro ethene

**136**; this mixture was used directly in solution in the extraction solvent for the next step without further purification.

The data were in agreement with those reported previously.

### ii) Claisen Rearrangement: 5,5-Difluoro-3-hydroxyocta-1,7-dien-4-one 154

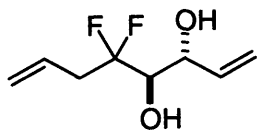


**154**

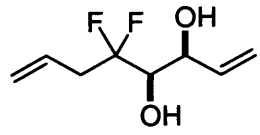
The solution of dienol **134** (50 mmol) in diethyl ether (150 mL) obtained previously was stirred at room temperature for 2 hours to afford hydroxy ketone **154**; Significant peaks for **154**: $\delta_F$ (282 MHz, $CDCl_3$) -105.1 (1F, dt, $^2J_{F\text{-}F}$ 273.5, $^3J_{F\text{-}H}$ 16.1), -106.8 (1F, dt, $^2J_{F\text{-}F}$ 273.5, $^3J_{F\text{-}H}$ 18.0).

The crude hydroxy ketone was used directly for the next step without further purification.

### iii) Reduction: (3*S**,4*S**)-5,5-Difluoroocta-1,7-diene-3,4-diol 143a



**143a**

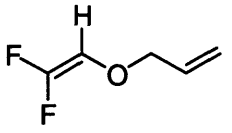


**143b**

Sodium borohydride (150 mmol, 5.7 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of hydroxy ketone **154** (50.0 mmol)

obtained previously in diethyl ether (350 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with water (40 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange oil as a mixture of diastereoisomers **143a** and **143b** (dr: 9:1) which were separated by column chromatography (10 % ethyl acetate in hexane) to afford diols **143a** and **143b** (1.8 g, 20 % over 3 steps / from ether **116**, 94 % by GC) as white solids. Data were in agreement with those reported previously.

**1-(Allyloxy)-2,2-difluoro-ethene 136**

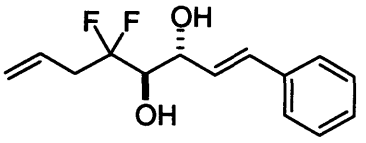



**136**

*n*-Butyllithium (22 mmol, 9.2 mL of a 2.4 M solution in hexane) was added dropwise to a solution of ether **116** in tetrahydrofuran (20 mL) at 0 °C under an atmosphere of nitrogen and the mixture was maintained at 0 °C for 1 hour. The mixture was quenched at 0 °C with ammonium chloride (20 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and kept in solution due to its high volatility.

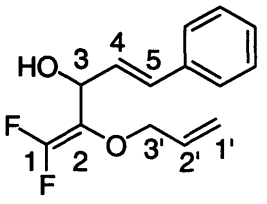
The $^{19}F$ NMR was in agreement with the one reported previously.

**Preparation of (1*E*,3*S**,4*S**)-5,5-difluoro-1-phenyl-octa-1,7-diene-3,4-diol 168**




**168**

**i) Dehydrofluorination/Metallation: 2-(Allyloxy)-1,1-difluoro-5-phenyl-penta-1,4-dien-3-ol 144**



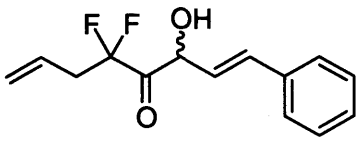

**144**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of ether **116** (11 mmol, 1.54 g) in tetrahydrofuran (22 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. *Trans*-cinnamaldehyde (10 mmol, 1.34 g) as a solution in tetrahydrofuran (2 mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave dienol **144** as an orange oil; $R_f$ (40 % ethyl acetate in hexane) 0.70; $\upsilon_{max}$(neat)/$cm^{-1}$ 3390br, 1748s, 1670m, 1239s, 1067s; 966s; $\delta_H$ (300 MHz, $CDCl_3$) 7.34-7.09 (5H, m, *Ar*), 6.58 (1H, dd, *J* 15.9, $^4J$ 1.4,

HC=C*H*Ar), 6.21 (1H, ddd, *J* 15.9, 6.3, $^{5}J_{H\text{-}F}$ 0.9, *H*C=CHAr), 5.87 (1H, ddtd, *J* 17.2, 10.4, 5.8, $^{6}J_{H\text{-}F}$ 0.9, *H*C=$CH_2$), 5.23 (1H, dq, *J* 17.2, 1.6, HC=C$H_a$$H_b$), 5.14 (1H, ddt, *J* 10.4, $^{2}J$ 1.6, $^{4}J$ 1.2, HC=$CH_a$$H_b$), 4.91 (1H, ddt, *J* 6.3, $^{4}J_{H\text{-}F}$ 3.5, $^{4}J$ 1.4, $^{4}J_{H\text{-}F}$ 1.4, C*H*OH), 4.37-4.23 (1H, m, $H_2$CCH=$CH_2$); $\delta_C$ (75 MHz, $CDCl_3$) 154.1 (dd, $^{1}J_{C\text{-}F}$ 292.6, 285.4, C-1), 136.4 (C-2'), 133.4 (Ar), 129.1 (Ar), 128.7 (Ar), 128.0 (Ar), 127.3 (t, $^{4}J_{C\text{-}F}$ 2.4, C-4), 126.7 (C-5), 118.5 (C-1'), 118.0 (dd, $^{2}J_{C\text{-}F}$ 35.3, 10.8, C-2), 74.8 (dd, $^{4}J_{C\text{-}F}$ 4.8, 2.3, C-3'), 68.6 (dd, $^{3}J_{C\text{-}F}$ 4.8, 1.8, C-3); $\delta_F$ (282 MHz, $CDCl_3$) -99.3 (1F, d, $^{2}J_{F\text{-}F}$ 69.2), -110.7 (1F, dd, $^{2}J_{F\text{-}F}$ 69.3, $^{4}J_{F\text{-}H}$ 3.3); *m/z* (EI) 252 (2 %, $M^+$), 232 (2, M-HF), 214 (1, M-HF-$H_2O$), 131 (100, $C_9H_7O$).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: 5,5-Difluoro-3-hydroxy-1-phenyl-octa-1,7-dien-4-one 155**



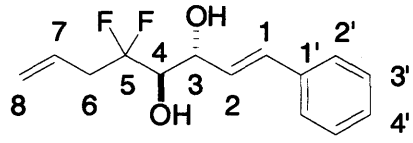

**155**

Crude dienol **144** (10 mmol) was taken up in chloroform (30 mL). The solution was stirred at 60 °C for 25 minutes to afford hydroxy ketone **155**; significant data for **155**: $R_f$ (40 % ethyl acetate in hexane) 0.64; $\upsilon_{max}$(neat)/$cm^{-1}$ 3405br, 1746m, 1670m, 1249s, 1163m, 1124m, 1071s; 969s; $\delta_H$ (300 MHz, $CDCl_3$) 7.43-7.21 (5H, m, *Ar*), 6.84 (1H, dd, *J* 15.8, $^{4}J$ 1.5, HC=C*H*Ar), 6.17 (1H, dddd, *J* 15.8, 6.4, $^{5}J_{H\text{-}F}$ 1.3, $^{5}J_{H\text{-}F}$ 0.9, *H*C=CHAr), 5.69 (1H, ddt, *J* 16.8, 10.4, 7.2,

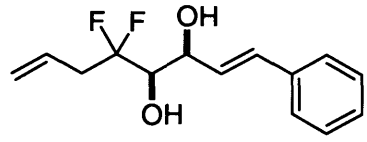
*H*C=$CH_2$), 5.30-5.26 (1H, m, C*H*OH), 5.26-5.17 (2H, m, C$H_2$=CH), 2.91-2.76 (1H, m, $CH_2$=CHC$H_2$), 2.28 (1H, br s, O*H*); $\delta_F$ (282 MHz, $CDCl_3$) -104.3 (1F, dt, $^2J_{F\text{-}F}$ 273.9, $^3J_{F\text{-}H}$ 16.1), -105.5 (1F, dt, $^2J_{F\text{-}F}$ 273.9, $^3J_{F\text{-}H}$ 18.0); *m/z* (EI) 252 (1 %, $M^+$), 234 (1, M-$H_2O$), 232 (1, M-HF), 214 (1, M-HF-$H_2O$), 131 (100, O=CCH=CHPh).

The crude hydroxy ketone was used directly for the next step without further purification.

### iii) Reduction: (1*E*,3*S**,4*S**)-5,5-difluoro-1-phenyl-octa-1,7-diene-3,4-diol 168




**168**



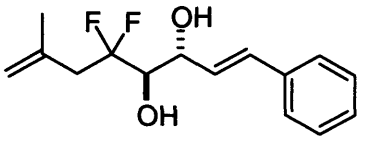

**169**

Sodium borohydride (30.0 mmol, 1.13 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **155** (*ca.* 10 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a mixture of diastereoisomers **168** and **169** (5.1:1) as a pale yellow solid which was purified by column chromatography (10 % ethyl acetate in hexane) to afford diols **168** and **169** as a white solid (1.72 g,

68 % over 3 steps); data for **168**: mp 59-60 °C; $R_f$ (40 % ethyl acetate in hexane) 0.40; (Found: C, 66.32; H, 6.51; $C_{14}H_{16}O_2F_2$ requires: C, 66.13; H, 6.34 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3346br, 3245br, 1066s, 972s; $\delta_H$ (300 MHz, $CDCl_3$) 7.34-7.15 (5H, m, Ar*H*), 6.71 (1H, d, *J* 16.0, HC=C*H*Ar), 6.37 (1H, dddd, *J* 16.0, 6.6, $^4J$ 2.0, $^5J$ 1.3, *H*C=CHAr), 5.93-5.70 (1H, m, $CH_2$=C*H*$CH_2$), 5.30-5.20 (2H, m, HC=C$H_2$), 4.55 (1H, dd, *J* 6.6, 4.3, HC=CHC*H*OH), 3.87 (1H, ddd, $^3J_{H\text{-}F}$ 16.5, 6.6, *J* 4.3, $CF_2$C*H*OH), 2.80-2.60 (2H, m, C$H_2$$CF_2$), 2.47 (1H, br s, O*H*), 2.20 (1H, br s, O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 136.2 (C-1'), 133.1 (C-1), 128.7 (C-7), 128.6 (C-2'), 128.1 (C-4'), 126.7 (C-3'), 126.5 (C-2), 122.9 (dd, $^1J_{C\text{-}F}$ 247.7, 245.3, C-5), 120.8 (C-8), 74.3 (dd, $^2J_{C\text{-}F}$ 28.6, 25.0, C-4), 71.7 (dd, $^3J_{C\text{-}F}$ 3.0, 1.2, C-3), 38.7 (dd, $^2J_{C\text{-}F}$ 25.1, 23.3, C-6); $\delta_F$ ($CDCl_3$, 282 MHz) -106.6 (1F, dtd, $^2J_{F\text{-}F}$ 252.1, $^3J_{F\text{-}H}$ 19.9, 6.6), -108.5 (1F, ddt, $^2J_{F\text{-}F}$ 252.1, $^3J_{F\text{-}H}$ 16.5, 13.4); [HRMS (EI, $M^+$) Found: 254.11186. Calc. for $C_{14}H_{16}F_2O_2$ 254.11184]; *m/z* (EI) 254 (30 %, $M^+$), 234 (33, M-HF), 216 (5, M-HF-$H_2O$), 145 (8), 133 (100). Data for **169**: mp 75-77 °C; $R_f$ (40 % ethyl acetate in hexane) 0.56; (Found: C, 66.26; H, 6.27; $C_{14}H_{16}O_2F_2$ requires: C, 66.13; H, 6.34 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3405br, 3220br, 1119s, 966s; $\delta_H$ (300 MHz, $CDCl_3$) 7.39-7.18 (5H, m, Ar*H*), 6.65 (1H, d, *J* 15.9, HC=C*H*Ar), 6.25 (1H, dd, *J* 15.9, 6.6, *H*C=CHAr), 5.81 (1H, ddt, *J* 17.0, 10.4, 7.0, $CH_2$=C*H*$CH_2$), 5.28-5.18 (2H, m, $H_2$C=CH), 4.68-4.59 (1H, m, HC=CHC*H*OH), 3.69 (1H, ddd, $^3J_{H\text{-}F}$ 18.0, 10.0, *J* 5.4, $CF_2$C*H*OH), 3.42 (1H, br s, O*H*), 2.87-2.68 (3H, m, C$H_2$$CF_2$, O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 136.2 (C-1'), 132.4 (C-1), 128.8 (dd, $^3J_{C\text{-}F}$ 7.8, 3.6, C-7), 128.7 (C-2'), 128.1 (C-4'), 127.7 (C-2), 126.7 (C-3'), 123.3 (dd, $^1J_{C\text{-}F}$ 247.7, 245.9, C-5), 120.8 (C-8), 73.3 (dd, $^2J_{C\text{-}F}$ 29.9, 25.7, C-4), 69.8 (dd, $^3J_{C\text{-}F}$ 3.6, 2.0, C-3), 38.2 (dd, $^2J_{C\text{-}F}$ 25.7, 23.3, C-6); $\delta_F$ ($CDCl_3$, 282 MHz) -106.3 (1F, dddd, $^2J_{F\text{-}F}$ 251.1, $^3J_{F\text{-}H}$ 21.8, 19.0, 5.2), -110.4 (1F, dtd, $^2J_{F\text{-}F}$ 251.1, $^3J_{F\text{-}H}$ 18.0, 12.3); [HRMS (EI, $M^+$) Found: 254.11186. Calc.

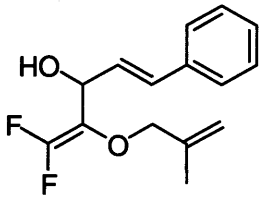
for $C_{14}H_{16}F_2O_2$ 254.11184]; *m/z* (EI) 254 (40 %, $M^+$), 234 (53, M-HF), 216 (2, M-HF-$H_2O$), 145 (18), 133 (100, HOCHCH=CHPh).

**Preparation of (1*E*,3*S**,4*S**)-5,5-Difluoro-7-methyl-1-phenyl-octa-1,7-diene-3,4-diol 176**




**176**

**i) Dehydrofluorination/Metallation: 1,1-Difluoro-2-(2-methyl-allyloxy)-5-phenyl-penta-1,4-dien-3-ol 150**



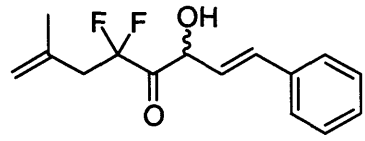

**150**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of ether **118** (11 mmol, 1.75 g) in tetrahydrofuran (22 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. *Trans*-cinnamaldehyde (10 mmol, 1.34 g) as a solution in tetrahydrofuran (2 mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and

concentrated *in vacuo* to leave dienol **150** as an orange oil (2.34 g); significant peaks for **150**: $\delta_F$ (282 MHz, $CDCl_3$) -99.4 (1F, dt, $^2J_{F\text{-}F}$ 69.7, $^4J_{F\text{-}H}$ 0.9), -110.7 (1F, dd, $^2J_{F\text{-}F}$ 69.7, $^4J_{F\text{-}H}$ 3.3).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: 5,5-Difluoro-3-hydroxy-2,7-dimethyl-1-phenyl-octa-1,7-dien-4-one 158**

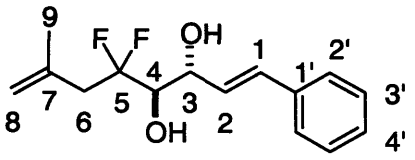



**158**

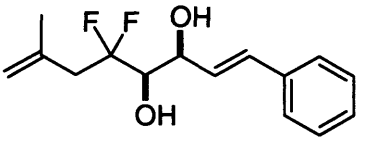
Crude dienol **150** (10 mmol) was taken up in chloroform (30 mL). The solution was stirred at 60 °C for 150 minutes to afford hydroxy ketone **158**; significant peaks for **158**: $\delta_F$ (282 MHz, $CDCl_3$) -102.6 (1F, dt, $^2J_{F\text{-}F}$ 272.0, $^3J_{F\text{-}H}$ 16.6), -10.3.6 (1F, dt, $^2J_{F\text{-}F}$ 272.0, $^3J_{F\text{-}H}$ 18.5).

The crude hydroxy ketone was used directly for the next step without further purification.

**iii) Reduction: (1*E*,3*S**,4*S**)-5,5-Difluoro-7-methyl-1-phenyl-octa-1,7-diene-3,4-diol 176**




**176**

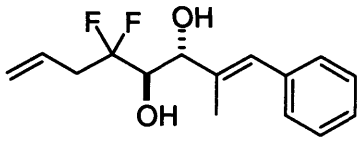



**177**

Sodium borohydride (30.0 mmol, 1.13 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **158** (10 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a mixture of diastereoisomers **176** and **177** (11:1) as a pale yellow solid which was purified by column chromatography (20 % ethyl acetate in hexane) to afford diols **176** and **177** as a white solid (1.45 g, 52 % over 3 steps); data for **176**: mp 86-87 °C; $R_f$ (40 % ethyl acetate in hexane) 0.44; (Found: C, 67.27; H, 6.65; $C_{15}H_{18}O_2F_2$ Requires: C, 67.15; H, 6.76 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3364br, 3279br, 1449m, 1193m, 1059s; $\delta_H$ (400 MHz, $CDCl_3$) 7.42-7.23 (5H, m, Ar*H*), 6.73 (1H, dd, *J* 16.0, $^4J$ 0.8, HC=C*H*Ar), 6.37 (1H, dddd, *J* 16.0, 6.5, $^5J_{H\text{-}F}$ 2.0, $^5J_{H\text{-}F}$ 1.2, *H*C=CHAr), 5.02-4.99 (1H, m, $H_aH_bC$=$CCH_3$), 4.93-4.91 (1H, m, $H_aH_bC$=$CCH_3$), 4.65 (1H, dddd, *J* 6.5, 4.3, $^4J_{H\text{-}F}$ 1.2, $^4J_{H\text{-}F}$ 0.5, HC=CHC*H*OH), 3.96 (1H, dt, $^3J_{H\text{-}F}$ 17.6, *J* 4.3, $CF_2CHOH$), 2.84-2.63 (2H, m, $CH_2CF_2$), 2.48 (1H, br s, O*H*), 2.23 (1H, br s, O*H*), 1.84 (3H, s, $H_2C$=$CCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 137.6 (dd, $^3J_{C\text{-}F}$ 5.6, 1.6, C-7), 136.2 (C-

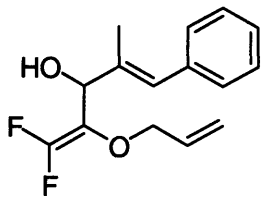
1'), 133.1 (C-1), 128.7 (C-2'), 128.1 (C-4'), 126.7 (C-3'), 126.5 (d, $^4J_{C\text{-}F}$ 2.4, C-2), 123.3 (dd, $^1J_{C\text{-}F}$ 248.5, 246.9, C-5), 117.1 (C-8), 74.3 (dd, $^2J_{C\text{-}F}$ 28.8, 24.8, C-4), 71.7 (dd, $^3J_{C\text{-}F}$ 3.2, 0.8, C-3), 41.8 (dd, $^2J_{C\text{-}F}$ 24.8, 23.2, C-6), 23.6 (t, $^4J_{C\text{-}F}$ 1.6, C-9); $\delta_F$ ($CDCl_3$, 376.5 MHz) -105.0 (1F, dddd, $^2J_{F\text{-}F}$ 252.6, $^3J_{F\text{-}H}$ 22.7, 18.7, 5.6), -107.5 (1F, dtd, $^2J_{F\text{-}F}$ 252.6, $^3J_{F\text{-}H}$ 18.7, 11.6); [HRMS (EI, $M^+$) Found: 268.12750. Calc. for $C_{15}H_{18}F_2O_2$ 268.12749]; *m/z* (EI) 268 (2 %, $M^+$), 250 (2, M-$H_2O$), 133 (100, $C_9H_9O$). Data for **177**: mp 87-89 °C; $R_f$ (40 % ethyl acetate in hexane) 0.60; $\upsilon_{max}$(neat)/$cm^{-1}$ 3408br, 3215br, 1449m, 1118s, 1062s; $\delta_H$ (400 MHz, $CDCl_3$) 7.41-7.23 (5H, m, Ar*H*), 6.72 (1H, dd, *J* 15.8, $^4J$ 0.8, HC=C*H*Ar), 6.27 (1H, dd, *J* 15.8, 6.5, *H*C=CHAr), 5.03-5.00 (1H, m, $H_aH_bC$=$CCH_3$), 4.96-4.93 (1H, m, $H_aH_bC$=$CCH_3$), 4.73 (1H, ddd, *J* 6.5, 2.0, $^4J_{H\text{-}F}$ 1.2, HC=CHC*H*OH), 3.70 (1H, d, $^3J_{H\text{-}F}$ 19.2, $CF_2CH$OH), 2.99 (1H, br s, O*H*), 2.87-2.66 (2H, m, $CH_2CF_2$), 2.21 (1H, br s, O*H*), 1.85 (3H, s, $H_2C$=$CCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 137.5 (d, $^3J_{C\text{-}F}$ 6.4, C-7), 136.2 (C-1'), 132.4 (C-1), 128.6 (C-2'), 128.0 (C-4'), 127.7 (C-2), 126.6 (C-3'), 123.8 (t, $^1J_{C\text{-}F}$ 248.5, C-5), 117.0 (C-8), 73.4 (dd, $^2J_{C\text{-}F}$ 31.2, 24.8, C-4), 69.6 (dd, $^3J_{C\text{-}F}$ 4.0, 1.6, C-3), 41.3 (dd, $^2J_{C\text{-}F}$ 24.8, 22.4, C-6), 23.6 (dd, $^4J_{C\text{-}F}$ 2.4, 1.6, C-9); $\delta_F$ ($CDCl_3$, 376.5 MHz) -105.3 (1F, dddd, $^2J_{F\text{-}F}$ 250.7, $^3J_{F\text{-}H}$ 23.3, 19.1, 3.6), -109.9 (1F, dtd, $^2J_{F\text{-}F}$ 250.7, $^3J_{F\text{-}H}$ 19.1, 10.8); [HRMS (EI, $M^+$) Found: 268.12756. Calc. for $C_{15}H_{18}F_2O_2$ 268.12749]; *m/z* (EI) 268 (5 %, $M^+$), 250 (1, M-$H_2O$), 248 (3, M-$H_2O$), 133 (100, HOCHCH=CHPh).

**Preparation of (1*E*,3*S**,4*S**)-5,5-Difluoro-2-methyl-1-phenyl-octa-1,7-diene-3,4-diol 178**




**178**

**i) Dehydrofluorination/Metallation: 2-Allyloxy-1,1-difluoro-4-methyl-5-phenyl-penta-1,4-dien-3-ol 149**

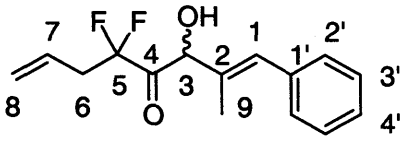



**149**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of ether **116** (11 mmol, 1.54 g) in tetrahydrofuran (22 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. α-Methyl-*trans*-cinnamaldehyde (10 mmol, 1.49 g) as a solution in tetrahydrofuran (2 mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave dienol **149** as an orange oil (2.6 g); significant peaks for **149**: $\delta_F$ (282 MHz, $CDCl_3$) -99.1 (1F, dt, $^2J_{F\text{-}F}$ 69.0, $^4J_{F\text{-}H}$ 1.6), -109.9 (1F, dd, $^2J_{F\text{-}F}$ 69.0, $^4J_{F\text{-}H}$ 3.3).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: 5,5-Difluoro-3-hydroxy-2-methyl-1-phenyl-octa-1,7-dien-4-one 157**

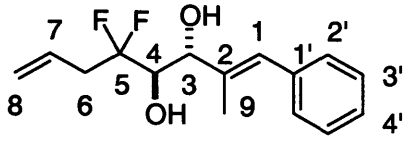



**157**

Crude dienol **149** (10 mmol) was taken up in chloroform (30 mL). The solution was stirred at 60 °C for 120 minutes to afford hydroxy ketone **157**; significant data for **157**: $\delta_H$ (300 MHz, $CDCl_3$) 7.39-7.22 (5H, m, *Ar*), 6.70 (1H, s, HC=C*H*Ar), 5.71 (1H, ddt, *J* 16.8, 10.5, 7.2, *H*C=$CH_2$), 5.28-5.19 (2H, m, HC=C$H_2$), 5.20-5.18 (1H, m, C*H*OH), 2.89-2.74 (2H, m, C$H_2$CH=$CH_2$) 1.77 (1H, d, $^4J$ 1.4, C$H_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 200.6 (dd, $^2J_{C\text{-}F}$ 32.3, 29.9, C-4), 136.4 (C-2), 132.8 (C-1), 132.3 (C-1'), 128.8 (C-2'), 126.5 (dd, $^3J_{C\text{-}F}$ 7.2, 4.8, C-7), 128.1 (C-4'), 127.1 (C-3'), 122.0 (C-8), 120.8 (t, $^1J_{C\text{-}F}$ 253.7, C-5), 79.9 (C-3), 38.3 (t, $^2J_{C\text{-}F}$ 23.9, C-6), 13.0 (C-9); $\delta_F$ (282 MHz, $CDCl_3$) -103.3 (1F, dt, $^2J_{F\text{-}F}$ 274.4, $^3J_{F\text{-}H}$ 15.6), -105.5 (1F, dt, $^2J_{F\text{-}F}$ 274.4, $^3J_{F\text{-}H}$ 18.5, $^4J_{F\text{-}H}$ 1.5).

The crude hydroxy ketone was used directly for the next step without further purification.

**iii) Reduction: (1*E*,3*S**,4*S**)-5,5-Difluoro-2-methyl-1-phenyl-octa-1,7-diene-3,4-diol 178**

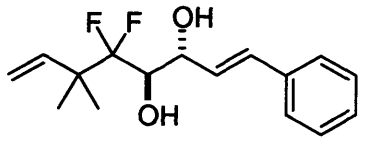



**178**

Sodium borohydride (30.0 mmol, 1.13 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **157** (10 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave diol **178** as a single diastereoisomer as a pale yellow solid which was purified by column chromatography (20 % ethyl acetate in hexane) to afford diol **178** (1.5 g, 56 % over 3 steps) as a white solid; mp 63-64 °C; $R_f$ (40 % ethyl acetate in hexane) 0.55; (Found: C, 67.25; H, 6.59; $C_{15}H_{18}O_2F_2$ Requires: C, 67.15; H, 6.76 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3422br, 3309br, 1083s, 1115s, 990s; $\delta_H$ (400 MHz, $CDCl_3$) 7.37-7.21 (5H, m, Ar*H*), 6.60 (1H, s, $CH_3C$=C*H*Ar), 5.88 (1H, ddt, *J* 16.8, 10.4, 7.1, $H_2C$=C*H*$CH_2$), 5.31-5.23 (2H, m, *H*$_2$C=CH), 4.47 (1H, dd, *J* 7.0, 0.8, HC=C$CH_3$C*H*OH), 3.90 (1H, dt, $^3J_{H\text{-}F}$ 14.7, *J* 7.0, $CF_2$C*H*OH), 2.95-2.74 (2H, m, C*H*$_2$$CF_2$), 2.22 (2H, br s, O*H*), 1.95 (3H, d, $^4J$ 1.4, C*H*$_3$C=CHAr); $\delta_C$ (100.6 MHz, $CDCl_3$) 136.8 (C-1'), 136.5 (C-2), 129.6 (C-1), 129.2 (C-2'), 129.0 (dd, $^3J_{C\text{-}F}$ 6.4, 4.8, C-7), 128.3 (C-4'), 127.1 (C-3'), 123.7 (dd, $^1J_{C\text{-}F}$ 247.7, 245.3, C-5), 120.9 (C-8), 77.0 (t, $^3J_{C\text{-}F}$ 2.4 C-3), 72.3 (dd, $^2J_{C\text{-}F}$

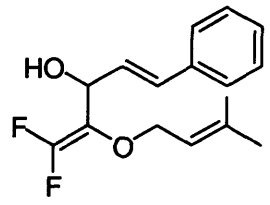
27.2, 25.6, C-4), 38.7 (t, $^2J_{C\text{-}F}$ 24.4, C-6), 13.7 (C-9); $\delta_F$ ($CDCl_3$, 376.5 MHz) -106.5 (1F, dddd, $^2J_{F\text{-}F}$ 251.6, $^3J_{F\text{-}H}$ 21.3, 18.6, 6.9), -109.0 (1F, dddd, $^2J_{F\text{-}F}$ 251.6, $^3J_{F\text{-}H}$ 19.2, 14.4, 12.4); [HRMS (EI, $M^+$) Found: 268.12753. Calc. for $C_{15}H_{18}F_2O_2$ 268.12749]; *m/z* (EI) 268 (3 %, $M^+$), 248 (7, M-HF), 230 (1, M-HF-$H_2O$), 147 (100, $HOCHC(CH_3)$=CHPh), 129 (74), 115 (34), 91 (71).

**Preparation of (1*E*,3*S**,4*S**)-5,5-Difluoro-6,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 184**




**184**

**i) Dehydrofluorination/Metallation: 1,1-Difluoro-2-(3-methyl-but-2-enyloxy)-5-phenyl-penta-1,4-dien-3-ol 153**



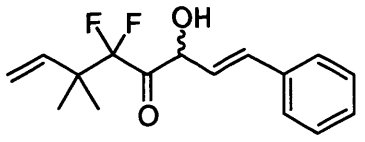

**153**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of 3-methyl-1-trifluoroethoxy-but-2-ene **108** (5.8 mmol, 1.0 g) in tetrahydrofuran (12 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. *Trans*-cinnamaldehyde (5.55 mmol, 0.74 g) as a solution in tetrahydrofuran (1

mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave dienol **153** as an orange oil; significant peaks for **153**: $\delta_F$ (282 MHz, $CDCl_3$) -100.4 (1F, d, $^2J_{F\text{-}F}$ 70.1), -111.6 (1F, dd, $^2J_{F\text{-}F}$ 70.1, $^4J_{F\text{-}H}$ 3.3).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: 5,5-Difluoro-3-hydroxy-6,6-dimethyl-1-phenyl-octa-1,7-dien-4-one 161**

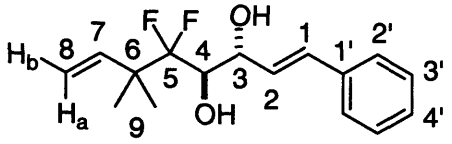



**161**

Crude dienol **153** (5.55 mmol) was taken up in chloroform (20 mL). The solution was stirred at 60 °C for 150 minutes to afford hydroxy ketone **161**; significant peaks for **161**: $\delta_F$ (282 MHz, $CDCl_3$) -111.6 (1F, d, $^2J_{F\text{-}F}$ 264.0), -115.2 (1F, dt, $^2J_{F\text{-}F}$ 264.0).

The crude hydroxy ketone was used directly for the next step without further purification.

**iii) Reduction: (1*E*,3*S**,4*S**)-5,5-Difluoro-6,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 184**



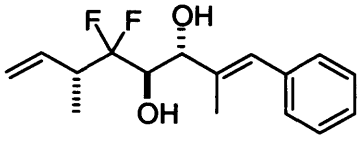

**184**

Sodium borohydride (16.7 mmol, 0.63 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **161** (5.55 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a mixture of diastereoisomers **184** and **185** (7:1) which were separated by column chromatography (15 % ethyl acetate in hexane) to afford diols **184** and **185** as a white solid (1.02 g, 65 % over 3 steps); data for **184**: mp: 61-62 °C; $R_f$ (40 % ethyl acetate in hexane) 0.49; (Found: C, 68.17; H, 7.01; $C_{16}H_{20}O_2F_2$ requires: C, 68.07; H, 7.14 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3453br, 3389br, 1066s, 966s; $\delta_H$ (300 MHz, $CDCl_3$) 7.42-7.21 (5H, m, Ar*H*), 6.71 (1H, dd, *J* 16.1, $^4J$ 0.9, HC=C*H*Ar), 6.38 (1H, dddd, *J* 16.1, 5.6, $^4J$ 2.8, $^5J$ 1.3, *H*C=CHAr), 6.01 (1H, dd, *J* 17.5, 10.7, $H_2C$=C*H*), 5.20 (1H, d, *J* 17.5, $H_aH_bC$=CH), 5.17 (1H, dd, *J* 10.7, $^2J$ 0.9, $H_aH_bC$=CH), 4.65 (1H, s, HC=CHC*H*OH), 4.15 (1H, ddd, $^3J_{H\text{-}F}$ 22.1, 5.4, *J* 2.2, $CF_2$C*H*OH), 2.39 (2H, br s, O*H*), 1.23 (3H, s, $CF_2CCH_3$), 1.21 (3H, s, $CF_2CCH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 141.2 (t, $^3J_{C\text{-}F}$ 4.2, C-7), 136.6 (C-1'), 132.6 (C-1), 128.7 (C-2'), 128.0 (C-4'), 126.8 (C-

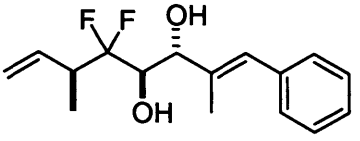
3'), 126.6 (dd, $^4J_{C\text{-}F}$ 2.4, 1.2, C-2), 123.7 (dd, $^1J_{C\text{-}F}$ 257.9, 251.3, C-5), 115.1 (C-8), 73.1 (dd, $^2J_{C\text{-}F}$ 31.7, 22.1, C-4), 71.6 (d, $^3J_{C\text{-}F}$ 5.4, C-3), 44.4 (t, $^2J_{C\text{-}F}$ 22.3, C-6), 21.5 (t, $^3J_{C\text{-}F}$ 4.8, C-9), 21.0 (dd, $^3J_{C\text{-}F}$ 5.4, 3.6, C-9); $\delta_F$ ($CDCl_3$, 282 MHz) -113.3 (1F, d, $^2J_{F\text{-}F}$ 256.8), -121.9 (1F, dd, $^2J_{F\text{-}F}$ 256.8, $^3J_{F\text{-}H}$ 22.1); [HRMS (EI, $M^+$) Found: 282.14315. Calc. for $C_{16}H_{20}F_2O_2$ 282.14314]; *m/z* (EI) 282 (6 %, $M^+$), 262 (21, M-HF), 133 (100, HOCHCH=CHPh). Data for **185**: mp 68-70 °C; $R_f$ (40 % ethyl acetate in hexane) 0.67; (Found: C, 68.21; H, 7.11; $C_{16}H_{20}O_2F_2$ requires: C, 68.07; H, 7.14 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3562br, 3409br, 1064s, 967s; $\delta_H$ (300 MHz, $CDCl_3$) 7.42-7.21 (5H, m, Ar*H*), 6.70 (1H, dd, *J* 15.9, $^4J$ 0.7, HC=C*H*Ar), 6.27 (1H, ddd, *J* 15.9, 6.4, $^4J$ 0.9, *HC*=CHAr), 6.06 (1H, dd, *J* 17.5, 10.8, $H_2C$=C*H*), 5.18 (1H, d, *J* 17.5, C$H_a$$H_b$=CH), 5.17 (1H, d, *J* 10.8, C$H_a$$H_b$=CH), 4.78 (1H, d, *J* 6.4, HC=CHC*H*OH), 3.86 (1H, dd, $^3J_{H\text{-}F}$ 23.5, 9.4, $CF_2$C*H*OH), 2.93 (1H, br s, O*H*), 2.24 (1H, br s, O*H*), 1.26 (3H, s, $CF_2$CC$H_3$), 1.23 (3H, s, $CF_2$CC$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 141.4 (t, $^3J_{C\text{-}F}$ 4.2, C-7), 136.4 (C-1'), 132.3 (C-1), 128.7 (C-2'), 128.1 (C-4'), 127.9 (C-2), 126.7 (C-3'), 124.5 (dd, $^1J_{C\text{-}F}$ 258.5, 251.3, C-5), 114.8 (C-8), 72.7 (dd, $^2J_{C\text{-}F}$ 33.5, 22.7, C-4), 70.3 (dd, $^3J_{C\text{-}F}$ 5.4, 1.2, C-3), 44.3 (t, $^2J_{C\text{-}F}$ 22.3, C-6), 21.7 (t, $^3J_{C\text{-}F}$ 4.8, C-9), 21.0 (dd, $^3J_{C\text{-}F}$ 4.8, 3.6, C-9); $\delta_F$ ($CDCl_3$, 282 MHz) -111.6 (1F, d, $^2J_{F\text{-}F}$ 253.5), -123.8 (1F, dd, $^2J_{F\text{-}F}$ 253.5, $^3J_{F\text{-}H}$ 23.7); [HRMS (EI, $M^+$) Found: 282.14309. Calc. for $C_{16}H_{20}F_2O_2$ 282.14314]; *m/z* (EI) 282 (31 %, $M^+$), 262 (64, M-HF), 133 (100, HOCHCCH=CHPh).

No $H^3$-$H^4$ coupling constant was visible in the $^1$H NMR spectrum.

**Preparation of (1*E*,3*S**,4*S**,6*S**)-5,5-Difluoro-2,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 182 and (1*E*,3*S**,4*S**,6*R**)-5,5-Difluoro-2,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 183**

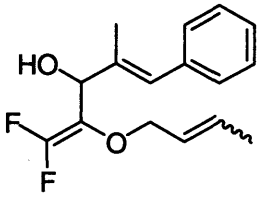



**182**




**183**

**i) Dehydrofluorination/Metallation: 1,1-Difluoro-4-methyl-2-(1-methyl-allyloxy)-5-phenyl-penta-1,4-dien-3-ol 152**



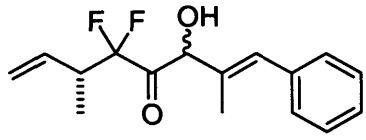

**152**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of 1-trifluoro-ethoxy-but-2-ene **A**[88] (11 mmol, 1.71 g) in tetrahydrofuran (22 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. α-Methyl-*trans*-cinnamaldehyde (10 mmol, 1.49 g) in solution in tetrahydrofuran (2 mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave dienol **152** as an orange oil;

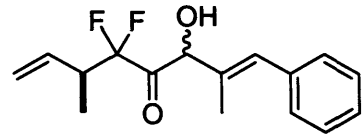
significant peaks for **152**: $\delta_F$ (282 MHz, $CDCl_3$) -99.4 (1F, d, $^2J_{F-F}$ 69.0), -111.2 (1F, dd, $^2J_{F-F}$ 69.0, $^4J_{F-H}$ 3.8).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: (6*S**)-5,5-Difluoro-3-hydroxy-2,6-dimethyl-1-phenyl-octa-1,7-dien-4-one 160a and(6*R**)-5,5-Difluoro-3-hydroxy-2,6-dimethyl-1-phenyl-octa-1,7-dien-4-one 160b**




**160a**

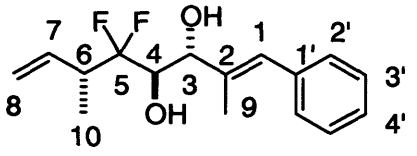



**160b**

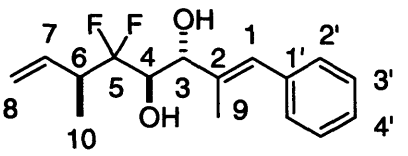
Crude dienol **152** (10 mmol) was taken up in chloroform (30 mL). The solution was stirred at 60 °C for 150 minutes to afford hydroxy ketones **160a** and **160b**; significant peaks for **160a**: $\delta_F$ (282 MHz, $CDCl_3$) -110.5 (1F, dd, $^2J_{F-F}$ 272.5, $^3J_{F-H}$ 15.3), -111.9 (1F, dd, $^2J_{F-F}$ 272.5, $^3J_{F-H}$ 16.6). Significant peaks for **160b**: $\delta_F$ (282 MHz, $CDCl_3$) -106.6 (1F, dt, $^2J_{F-F}$ 268.7, $^3J_{F-H}$ 10.0), -118.6 (1F, dd, $^2J_{F-F}$ 268.7, $^3J_{F-H}$ 25.2).

The crude hydroxy ketone was used directly for the next step without further purification.

**iii) Reduction: (1*E*,3*S**,4*S**,6*S**)-5,5-Difluoro-2,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 182 and (1*E*,3*S**,4*S**,6*R**)-5,5-Difluoro-2,6-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 183**




**182**

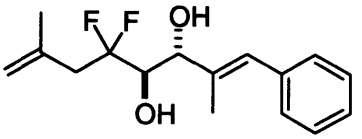



**183**

Sodium borohydride (30.0 mmol, 1.13 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **160** (10 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a mixture of diastereoisomers **182** and **183** (4:1) as a pale yellow solid which was purified by column chromatography (15 % ethyl acetate in hexane) to afford an inseparable pure mixture of diols **182** and **183** as a white solid (2.2 g, 78 % over 3 steps). mp 71-73 °C; $R_f$ (40 % ethyl acetate in hexane) 0.62; (Found: C, 68.17; H, 7.15; $C_{16}H_{20}O_2F_2$ Requires: C, 68.07; H, 7.14 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3587br, 3404br, 1183m, 1017s, 977s; [HRMS (EI, $M^+$) Found: 282.14320. Calc. for $C_{16}H_{20}F_2O_2$ 282.14314]; *m/z* (EI) 282 (5 %, $M^+$), 262 (20, M-HF), 244 (2, M-HF-$H_2O$), 147 (100, $HOCHC(CH_3)$=CHPh), 129 (82); data for **182**: $\delta_H$ (300 MHz, $CDCl_3$) 7.38-7.19 (5H, m, Ar*H*), 6.58 (1H, br s, $CH_3C$=C*H*Ar), 5.90 (1H, ddd, *J* 17.1, 10.5, 8.0, $H_2C$=C*H*$CHCH_3$), 5.31-5.17 (2H, m, $H_2C$=CH), 4.49 (1H, dd, *J* 7.2, 0.9,

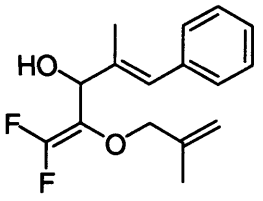
HC=CCH$_3$C*H*OH), 4.05-3.88 (1H, m, CF$_2$C*H*OH), 3.18-2.96 (1H, m, C*H*CH$_3$CF$_2$), 1.95 (3H, d, $^4J$ 1.4, C*H*$_3$C=CHAr), 2.12 (2H, br s, O*H*), 1.21 (3H, d, *J* 7.2, CHC*H*$_3$CF$_2$); $\delta_C$ (75.5 MHz, $CDCl_3$) 136.7 (C-2), 136.7 (C-1'), 135.7 (dd, $^3J_{C\text{-}F}$ 5.4, 4.2, C-7), 129.7 (C-1), 129.2 (C-2'), 128.3 (C-4'), 127.1 (C-3'), 124.6 (t, $^1J_{C\text{-}F}$ 250.1, C-5), 118.1 (C-8), 77.15 (m, C-3), 71.2 (dd, $^2J_{C\text{-}F}$ 28.1, 24.5, C-4), 42.1 (t, $^2J_{C\text{-}F}$ 23.0, C-6), 13.7 (dd, $^3J_{C\text{-}F}$ 6.0, 4.8, C-10), 13.5 (C-9); $\delta_F$ ($CDCl_3$, 282.4 MHz) -115.6 (1F, dt, $^2J_{F\text{-}F}$ 251.2, $^3J_{F\text{-}H}$ 14.7), -116.4 (1F, ddd, $^2J_{F\text{-}F}$ 251.2, $^3J_{F\text{-}H}$ 18.0, 8.5). Data for **183**: $\delta_H$ (300 MHz, $CDCl_3$) 7.38-7.19 (5H, m, Ar*H*), 6.58 (1H, br s, CH$_3$C=C*H*Ar), 5.82 (1H, ddd, *J* 17.2, 10.2, 8.8, H$_2$C=C*H*CHCH$_3$), 5.31-5.17 (2H, m, *H*$_2$C=CH), 4.51 (1H, dd, *J* 7.0, 0.7, HC=CCH$_3$C*H*OH), 4.05-3.88 (1H, m, CF$_2$C*H*OH), 3.18-2.96 (1H, m, C*H*CH$_3$CF$_2$), 1.99 (2H, br s, O*H*), 1.94 (3H, d, $^4J$ 1.4, C*H*$_3$C=CHAr), 1.18 (3H, d, *J* 7.2, CHC*H*$_3$CF$_2$); $\delta_C$ (75.5 MHz, $CDCl_3$) 136.8 (C-2), 136.6 (C-1'), 136.4 (dd, $^3J_{C\text{-}F}$ 6.6, 4.2, C-7), 129.5 (C-1), 129.2 (C-2'), 128.3 (C-4'), 127.0 (C-3'), 124.7 (dd, $^1J_{C\text{-}F}$ 252.5, 250.1, C-5), 118.4 (C-8), 77.15 (t, $^3J_{C\text{-}F}$ 2.4 C-3), 71.0 (dd, $^2J_{C\text{-}F}$ 28.1, 25.7, C-4), 42.2 (dd, $^2J_{C\text{-}F}$ 23.9, 22.7, C-6), 13.7 (C-9), 12.6 (t, $^3J_{C\text{-}F}$ 5.4, C-10); $\delta_F$ ($CDCl_3$, 282.4 MHz) -118.0 (1F, ddd, $^2J_{F\text{-}F}$ 251.2, $^3J_{F\text{-}H}$ 16.1, 10.4), -118.7 (1F, ddd, $^2J_{F\text{-}F}$ 251.2, $^3J_{F\text{-}H}$ 20.9, 7.6).

**Preparation of (1*E*,3*S**,4*S**)-5,5-Difluoro-2,7-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 180**




**180**

**i) Dehydrofluorination/Metallation1,1-Difluoro-4-methyl-2-(2-methyl-allyloxy)-5-phenyl-penta-1,4-dien-3-ol 151**

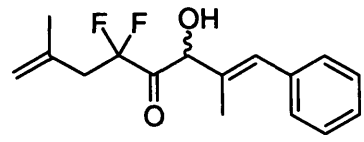



**151**

*t*-Butyllithium (22 mmol, 13.3 mL of a 1.65 M solution in pentane) was added dropwise over 25 minutes to a solution of ether **000$_{CA}$** (11 mmol, 1.75 g) in tetrahydrofuran (22 mL) at -100 °C under an atmosphere of nitrogen and the mixture was maintained at -100 °C for 15 min. α-Methyl-*trans*-cinnamaldehyde (10 mmol, 1.49 g) as a solution in tetrahydrofuran (2 mL) was added dropwise at -100 °C and the mixture was maintained at -100 °C for 15 min. The mixture was quenched at -90 °C with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave dienol **151** as an orange oil; significant peaks for **151**: $\delta_F$ (282 MHz, $CDCl_3$) -98.8 (1F, dt, $^2J_{F-F}$ 69.7, $^4J_{F-H}$ 1.4), -110.7 (1F, dd, $^2J_{F-F}$ 69.7, $^4J_{F-H}$ 3.3).

The crude dienol was used directly for the next step without further purification.

**ii) Rearrangement: 5,5-Difluoro-3-hydroxy-2,7-dimethyl-1-phenyl-octa-1,7-dien-4-one 159**

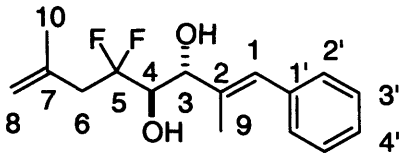



**159**

Crude dienol **151** (10 mmol) was taken up in chloroform (30 mL). The solution was stirred at 60 °C for 150 minutes to afford hydroxy ketone **159**; significant peaks for **159**: $\delta_F$ (282 MHz, $CDCl_3$) -101.5 (1F, dt, $^2J_{F\text{-}F}$ 273.0, $^3J_{F\text{-}H}$ 16.1), -104.5 (1F, dt, $^2J_{F\text{-}F}$ 273.0, $^3J_{F\text{-}H}$ 19.0).

The crude hydroxy ketone was used directly for the next step without further purification.

**iii) Reduction: (1*E*,3*S**,4*S**)-5,5-Difluoro-2,7-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 180**

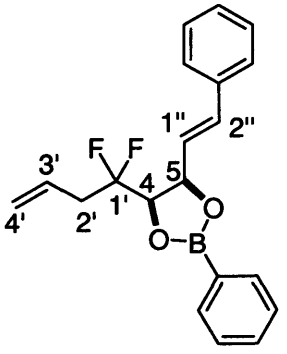



**180**

Sodium borohydride (30.0 mmol, 1.13 g) was added in 3 portions over 30 minutes at room temperature to a crude solution of the hydroxy ketone **159** (10 mmol) in ethanol (30.0 mL). The suspension was stirred overnight at room temperature. The reaction mixture was quenched with concentrated hydrochloric acid (4 mL) and concentrated *in vacuo*. The residue was dissolved in brine (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave diol **180** as a single diastereoisomer as a pale yellow solid which was purified by recrystallisation in hot hexane to afford diol **180** as colourless plates (2.42 g, 86 % over 3 steps). mp 97-99 °C; $R_f$ (20 % ethyl acetate in hexane) 0.28; (Found: C, 67.85; H, 7.10; $C_{16}H_{20}O_2F_2$ Requires: C, 68.07; H, 7.14 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3374br, 3321br, 1490m, 1358m, 1083s, 1032s; $\delta_H$ (300 MHz, $CDCl_3$) 7.38-7.20 (5H, m, Ar*H*), 6.59 (1H, br s, $CH_3C$=C*H*Ar), 5.05-5.00 (1H, m, C$H_a$$H_b$=$CCH_3$), 4.96-4.92 (1H, m, $CH_a$$H_b$=$CCH_3$), 4.45 (1H, d, *J* 7.0, HC=$CCH_3$C*H*OH), 3.90 (1H, dt, $^3J_{H\text{-}F}$ 15.3, *J* 6.5, $CF_2$C*H*OH), 2.92-2.66 (2H, m, C$H_2$$CF_2$), 2.29 (2H, br s, O*H*), 1.95 (3H, d, $^4J$ 1.3, C$H_3$C=CHAr), 1.86 (3H, s, $H_2C$=CC$H_3$); $\delta_C$ (75.5 MHz, $CDCl_3$) 137.7 (dd, $^3J_{C\text{-}F}$ 5.4, 1.8, C-7), 136.8 (C-1'), 136.5 (C-2), 129.5 (C-1), 129.2 (C-2'), 128.3 (C-4'), 127.1 (C-3'), 124.1 (dd, $^1J_{C\text{-}F}$ 248.9, 246.5, C-5), 117.1 (C-8), 77.0 (t, $^3J_{C\text{-}}$

$_F$ 2.1 C-3), 72.4 (dd, $^2J_{C\text{-}F}$ 28.1, 25.1, C-4), 41.7 (dd, $^2J_{C\text{-}F}$ 24.5, 23.3, C-6), 23.9 (t, $^4J_{C\text{-}F}$ 1.8, C-10), 13.7 (C-9); $\delta_F$ ($CDCl_3$, 376.5 MHz) -105.0 (1F, dddd, $^2J_{F\text{-}F}$ 251.6, $^3J_{F\text{-}H}$ 23.2, 18.0, 6.0), -107.9 (1F, dddd, $^2J_{F\text{-}F}$ 251.6, $^3J_{F\text{-}H}$ 21.3, 15.2, 11.4); [HRMS (EI, $M^+$) Found: 282.14316. Calc. for $C_{16}H_{20}F_2O_2$ 282.14314]; *m/z* (EI) 282 (3 %, $M^+$), 262 (9, M-HF), 147 (100, $HOCHC(CH_3)$=CHPh), 129 (61). The stereochemistry and identity of this product were confirmed by XRD analysis; $C_{16}H_{20}F_2O_2$, crystal size 0.25 x 0.21 x 0.10 $mm^3$, $M$ = 282.32, crystal system monoclinic, unit cell dimensions a = 29.670(6), b = 5.2359(11), c = 9.158(2) Å, $\alpha$ = 90°, $\beta$ = 95.393(4)°, $\gamma$ = 90°, U = 1416.4(5) $Å^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.103 $mm^{-1}$, 8200 reflections collected 2030 unique [R(int) = 0.0332], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0409, wR2 = 0.0997; R indices (all data) R1 = 0.0463, wR2 = 0.1032.

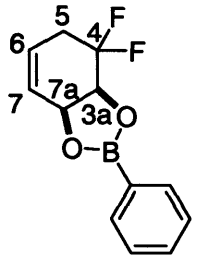
**(4*S**,5*S**)-4-(1,1-difluorobut-3-enyl)-2-phenyl-5-[(*E*)-2-phenylvinyl]-1,3,2-dioxaborolane 186**




**186**

Benzeneboronic acid (0.15 mmol, 18.3 mg) was added to a solution of diol **168** in tetrahydrofuran (3 mL). The reaction mixture was stirred at room temperature for 90 minutes and concentrated *in vacuo* to leave a white solid which was purified by column chromatography (20 % ethyl acetate in hexane) to afford dioxaborolane **186** as a colourless oil (21 mg, 62 %, 95 % by GC). $R_f$ (40 % ethyl acetate in hexane) 0.46; $\delta_H$ (300 MHz, $CDCl_3$) 7.91-7.86 (1H, m, Ar*H*), 7.54-7.20 (9H, m, Ar*H*), 6.75 (1H, d, *J* 15.8, HC=C*H*Ar), 6.48 (1H, ddt, *J* 15.8, 7.9, $^5J_{H\text{-}F}$ 3.1, *HC*=CHAr), 5.85 (1H, ddt, *J* 16.8, 10.5, 7.2, $H_2C$=C*H*), 5.35-5.22 (3H, m, $H_2C$=CH, HC=CHC*H*OB), 4.69 (1H, ddd, $^3J_{H\text{-}F}$ 21.2, *J* 8.2, $^3J_{H\text{-}F}$ 4.1, $CF_2CH$OB), 2.89-2.74 (2H, m, $CH_2CF_2$); $\delta_C$ (75.5 MHz, $CDCl_3$) 136.4 (C-Ar), 135.2 (C-Ar), 133.8 (dd, $^5J_{C\text{-}F}$ 1.8, 1.2, C-2''), 132.1 (C-Ar), 128.7 (C-Ar), 128.6 (dd, $^3J_{C\text{-}F}$ 3.6, 1.2, C-3'), 128.1 (C-Ar), 127.0 (C-Ar), 124.6 (dd, $^4J_{C\text{-}F}$ 3.0, 1.8, C-1''), 122.2 (dd, $^1J_{C\text{-}F}$ 250.1  244.7, C-1'), 121.2 (C-4'), 80.0 (C-5), 78.7 (dd, $^2J_{C\text{-}F}$ 32.9, 25.7, C-4), 39.1 (dd, $^2J_{C\text{-}F}$ 25.1, 23.3, C-2'); $\delta_F$ ($CDCl_3$, 282.4 MHz) -106.9 (1F, dt, $^2J_{F\text{-}F}$ 254.9, $^3J_{F\text{-}H}$ 20.4), -109.7 (1F, dttd, $^2J_{F\text{-}F}$ 254.9, $^3J_{F\text{-}H}$ 21.2, 15.1, 2.8); [HRMS (EI, $M^+$) Found: 340.14470. Calc. for $C_{20}H_{19}F_2O_2B$ 340.14462]; *m/z* (EI) 340 (22 %, $M^+$), 264 (3, M-Ph), 218 (7, M-PhB$(OH)_2$), 181 (21, M-PhB$(OH)_2$-HF-$H_2O$), 131 (33), 55 (100).

**(3a*S**,7a*S**)-4,4-Difluoro-2-phenyl-3a,4,5,7a-tetrahydro-1,3,2-benzodioxaborole 218**

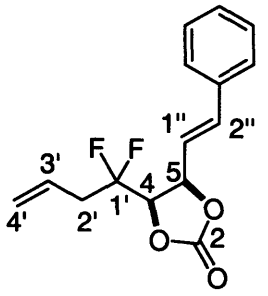



**218**

Second generation Grubbs' catalyst (0.6 μmol, 0.5 mg) was added to a solution of dioxaborolane **186** (0.12 mmol, 41 mg) in dry degassed dichloromethane (4.8 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 3 hours then concentrated *in vacuo* to leave a black oil which was purified by column chromatography (20 % ethyl acetate in hexane) to afford dioxaborole **218** (12 mg, 43 %) as colourless oil; $R_f$ (40 % ethyl acetate in hexane) 0.45; (Found: C, 61.16; H, 4.66; $C_{12}H_{11}F_2O_2B$ requires: C, 61.07; H, 4.70 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 1815m, 1359s, 1213m, 1084s; $\delta_H$ (300 MHz, $CDCl_3$) 7.87-7.82 (2H, m, Ar-*H*), 7.53-7.47 (1H, m, Ar-*H*), 7.42-7.36 (2H, m, Ar-*H*), 5.97-5.89 (1H, m, incl. app. d, *J* 10.5, $CH_2CH$=C*H*), 5.85-5.76 (1H, m, $CH_2CH$=CH), 5.15 (1H, ddd, *J* 7.3, 2.5, $^4J_{H\text{-}F}$ 1.0, HC=CHC*H*OB), 4.73 (1H, dddd, $^3J_{H\text{-}F}$ 10.0, *J* 7.3, $^3J_{H\text{-}F}$ 6.5, $^4J$ 1.5, $CF_2CH$OB), 2.76 (1H, dddddd, $^3J_{H\text{-}F}$ 21.0, $^2J$ 19.2, $^3J_{H\text{-}F}$ 9.6, *J* 3.4, $^4J$ 2.3, $^4J$ 1.6, C*H*$_a$H$_b$CH=CH), 2.63-2.47 (1H, m, CH$_a$*H*$_b$CH=CH); $\delta_C$ (75.5 MHz, $CDCl_3$) 135.2 (C-Ar), 132.1 (C-Ar), 128.0 (C-Ar), 125.7 (t, $^4J_{C\text{-}F}$ 1.2, C-7), 124.8 (dd, $^3J_{C\text{-}F}$ 7.2, 3.6, C-6), 120.6 (dd, $^1J_{C\text{-}F}$ 247.1, 238.8, C-4), 75.7 (dd, $^2J_{C\text{-}F}$ 34.7, 23.9, C-3a), 75.3 (dd, $^3J_{C\text{-}F}$ 3.6, 2.4, C-7a), 30.2 (t, $^2J_{C\text{-}F}$ 25.1, C-5); $\delta_F$ (376.5 MHz, $CDCl_3$) -105.7 (1F, dddddd, $^2J_{F\text{-}F}$ 256.8, $^3J_{F\text{-}H}$ 11.8, 10.0, 9.6, $^4J_{F\text{-}H}$ 3.8, 1.9), -106.7 (1F, ddddd, $^2J_{F\text{-}F}$ 256.8, $^3J_{F\text{-}H}$ 21.0, 10.9, 6.5, $^4J_{F\text{-}H}$ 1.0); [HRMS

(EI, $M^+$) Found 236.08210. Calc. for $C_{12}H_{11}F_2O_2B$ 236.08202]; *m/z* (EI) 236 (37 %, $M^+$), 172 (100).

**(4*S**,5*S**)-4-(1,1-Difluorobut-3-enyl)-5-[(*E*)-2-phenylvinyl]-1,3-dioxolan-2-one 187**

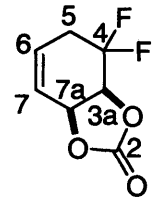



**187**

Phosgene (6.5 mmol, 3.25 mL of a 2.0 M solution in toluene) was added at 0 °C to a solution of diol **168** (4.3 mmol, 1.1 g) and pyridine (26.0 mmol, 2.1 mL) in toluene (40 mL). The reaction mixture was stirred at 0 °C 60 minutes. The whole was washed successively with water (20 mL), citric acid (20 mL of a 5 % aqueous solution), sodium carbonate (20 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated in *vacuo* to leave the crude carbonate **187** as a orange-brown oil. The washings were combined, brought to pH 4 by addition of 10 % aqueous hydrochloric acid, saturated with sodium chloride and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (100 % dichloromethane) to afford a second crop of the carbonate (total crude: 0.88 g). The combined were purified by column chromatography (8 % ethyl acetate in hexane) to afford carbonate **187** (0.52 g,

43 %, 98 % by GC) as a colourless oil. $R_f$ (20 % ethyl acetate in hexane) 0.54; $\delta_H$ (300 MHz, $CDCl_3$) 7.45-7.29 (5H, m, Ar*H*), 6.80 (1H, d, *J* 15.8, HC=C*H*Ar), 6.39 (1H, ddt, *J* 15.8, 8.3, $^5J_{H\text{-}F}$ 3.1, *H*C=CHAr), 5.76 (1H, ddt, *J* 18.0, 9.2, 7.2, $H_2C$=C*H*), 5.43 (1H, t, *J* 8.3, HC=CHC*H*OC(O)), 5.35-5.26 (2H, m, $H_2$C=CH), 4.77 (1H, ddd, $^3J_{H\text{-}F}$ 21.0, *J* 8.3, $^3J_{H\text{-}F}$ 3.3, $CF_2$C*H*OC(O)), 2.88-2.74 (2H, m, C$H_2$C$F_2$); $\delta_C$ (75.5 MHz, $CDCl_3$) 153.0 (C-2), 138.0 (t, $^5J_{C\text{-}F}$ 1.8, C-2"), 135.1 (C-Ar), 129.2 (C-Ar), 128.9 (C-Ar), 127.3 (dd, $^3J_{C\text{-}F}$ 7.8, 3.6, C-3'), 127.2 (C-Ar), 122.5 (C-4'), 120.9 (dd, $^1J_{C\text{-}F}$ 251.3, 246.5, C-1'), 119.0 (dd, $^4J_{C\text{-}F}$ 3.6, 2.4, C-1"), 79.8 (C-5), 76.1 (dd, $^2J_{C\text{-}F}$ 34.7, 25.7, C-4), 38.8 (dd, $^2J_{C\text{-}F}$ 25.1, 22.7, C-2'); $\delta_F$ ($CDCl_3$, 282.4 MHz) -108.2 (1F, dtt, $^2J_{F\text{-}F}$ 260.2, $^3J_{F\text{-}H}$ 20.3, 3.3, $^4J_{F\text{-}H}$ 3.3), -109.6 (1F, ddt, $^2J_{F\text{-}F}$ 260.2, $^3J_{F\text{-}H}$ 21.0, 13.8); [HRMS (EI, $M^+$) Found: 280.09101. Calc. for $C_{15}H_{14}F_2O_3$ 280.09110]; *m/z* (EI) 280 (22 %, $M^+$), 252 (3, M-CO), 236 (5, M-$CO_2$), 218 (7, M-CO-$H_2O$-$H_2O$), 147 (63), 131 (31), 104 (100).

**(3a*S**,7a*S**)-4,4-difluoro-3a,4,5,7a-tetrahydro-1,3-benzodioxol-2-one 219**

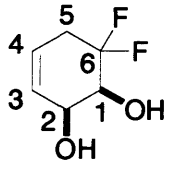



**219**

Second generation Grubbs' catalyst (77 µmol, 65 mg) was added to a solution of carbonate **187** (1.54 mmol, 0.43 g) in dry degassed dichloromethane (62 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 1 hour then concentrated *in vacuo* to leave a black oil which was purified by

column chromatography (20 % ethyl acetate in hexane) to afford cyclic carbonate **219** (150 mg, 55 %, 57 % based on recovered starting material, 98 % by GC) as pale yellow oil; $R_f$ (40 % ethyl acetate in hexane) 0.44; (Found: C, 47.60; H, 3.38; $C_7H_6F_2O_3$ requires: C, 47.74; H, 3.43 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 1796s, 1347m, 1074s; $\delta_H$ (300 MHz, $CDCl_3$) 6.11-6.02 (1H, m, $CH_2CH$=CH), 5.91 (1H, d, *J* 10.2, $CH_2CH$=C*H*), 5.30 (1H, ddd, *J* 6.8, 2.3, $^4J_{H-F}$ 1.2, HC=CHC*H*OC(O)), 4.89 (1H, ddd, $^3J_{H-F}$ 10.4, *J* 6.8, $^3J_{H-F}$ 4.7, $CF_2CH$OC(O)), 2.93-2.57 (2H, m, $CH_2$CH=CH); $\delta_C$ (75.5 MHz, $CDCl_3$) 153.2 (C-2), 125.8 (dd, $^3J_{C-F}$ 7.2, 3.6, C-6), 121.3 (t, $^4J_{C-F}$ 1.2, C-7), 118.6 (dd, $^1J_{C-F}$ 248.9, 238.8, C-4), 74.3 (dd, $^3J_{C-F}$ 3.6, 1.8, C-7a), 73.6 (dd, $^2J_{C-F}$ 38.3, 23.9, C-3a), 30.2 (t, $^2J_{C-F}$ 25.1, C-5); $\delta_F$ (376.5 MHz, $CDCl_3$) -105.6 (1F, ddtdd, $^2J_{F-F}$ 263.9, $^3J_{F-H}$ 14.2, 10.4, $^4J_{F-H}$ 3.8), -107.8 (1F, ddd, $^2J_{F-F}$ 263.9, $^3J_{F-H}$ 21.3, 11.4, 4.7); [HRMS (EI, $M^+$) Found 176.02849. Calc. for $C_7H_6F_2O_3$176.02850]; *m/z* (EI) 176 (7 %, $M^+$), 132 (3, M-$CO_2$), 112 (4, M-$CO_2$-HF), 91 (100).

### (1*S**,2*S**)-6,6-Difluorocyclohex-3-ene-1,2-diol 192



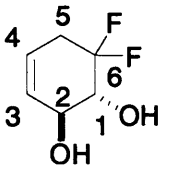

**192**

Second generation Grubbs' catalyst (0.177 mmol, 0.150 g) was added to a solution of diol **168** (35.4 mmol, 9.0 g) in dry degassed dichloromethane (1.41 L, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 0.75 hours then concentrated *in vacuo* to leave a black oil which was purified

by Kugelrohr distillation (bp 90 °C/0.07 mmHg) to afford cyclic diol **192** (4.1 g, 76 %) as colourless plates; mp 53°C; $R_f$ (40 % ethyl acetate in hexane) 0.19; (Found: C, 48.21; H, 5.18; $C_6H_8F_2O_2$ requires: C, 48.00; H, 5.37 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3371br, 1070s, 1023s, 880s, 866s; $\delta_H$ (300 MHz, $CDCl_3$) 5.75-5.66 (2H, m, *HC=CH*), 4.47-4.37 (1H, m, HC=CHC*H*OH), 4.01 (1H, dt, $^3J_{H-F}$ 13.7, *J* 4.7, $CF_2CHOH$), 2.80-2.66 (1H, m, $CF_2CH_aH_b$), 2.55-2.41 (1H, m, $CF_2CH_aH_b$), 2.85 (1H, br s, O*H*), 1.99 (1H, br s, O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 127.3 (C-3), 123.9 (dd, $^3J_{C-F}$ 7.2, 3.6, C-4), 122.0 (dd, $^1J_{C-F}$ 246.2, 242.0, C-6), 69.3 (dd, $^2J_{C-F}$ 29.3, 21.9, C-1), 67.8 (dd, $^3J_{C-F}$ 4.1, 1.4, C-2), 31.8 (t, $^2J_{C-F}$ 25.1, C-5); $\delta_F$ (282 MHz, $CDCl_3$) -106.3 (1F, dd, $^2J_{F-F}$ 251.8, $^3J_{F-H}$ 11.0), -107.4 (1F, ddd, $^2J_{F-F}$ 251.8, $^3J_{F-H}$ 21.3, 13.7); [HRMS (EI, $M^+$) Found 150.04920. Calc. for $C_6H_8O_2F_2$ 150.04924]; *m/z* (EI) 150 (96 %, $M^+$), 132 (61, M-$H_2O$), 122 (22), 112 (14, M-$H_2O$-HF), 101 (45), 84 (74, M-$H_2O$-CO-HF), 70 (100).

The stereochemistry and identity of this product were confirmed by XRD analysis; $C_6H_8F_2O_2$, crystal size 0.15 x 0.08 x 0.05 mm$^3$, *M* = 150.12, crystal system triclinic, unit cell dimensions a = 6.0189(19), b = 10.381(3), c = 11.590(4) Å, $\alpha$ = 72.114(5)°, $\beta$ = 80.734(5)°, $\gamma$ = 78.330(5)°, U = 671.1(4) Å$^3$, T = 150(2) K, space group P-1, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.144 mm$^{-1}$, 3104 reflections collected 2206 unique [R(int) = 0.1489], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0579, wR2 = 0.1344; R indices (all data) R1 = 0.0818, wR2 = 0.1454.

**(1*R**,2*S**)-6,6-difluorocyclohex-3-ene-1,2-diol 198**

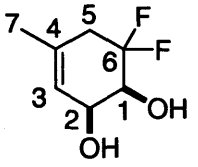



**198**

Second generation Grubbs' catalyst (79 μmol, 67 mg) was added to a solution of diol **169** (15.7 mmol, 4.0 g) in dry degassed dichloromethane (0.63 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 0.75 hours then concentrated *in vacuo* to leave a black oil (3.74 g) which was purified by Kugelrohr distillation (bp 50 °C/0.07 mmHg) to remove the catalyst residues, then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **198** (1.88 g, 81 %) as colourless plates; mp 80-82 °C; $R_f$ (40 % ethyl acetate in hexane) 0.12; (Found: C, 48.18; H, 5.23; $C_6H_8F_2O_2$ requires: C, 48.00; H, 5.37 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3248br, 3183br, 1355m, 1290m, 1080s, 1023s, 967s, 902s, 840s, 801s; $\delta_H$ (300 MHz, acetone-$d_6$) 5.70-5.52 (2H, m, HC=C*H*), 4.75 (1H, d, *J* 5.4, $CF_2CHOH$), 4.26-4.18 (1H, m, HC=CHC*H*OH), 3.79 (1H, ddd, $^3J_{H\text{-}F}$ 22.8, *J* 5.4, $^3J_{H\text{-}F}$ 2.8, $CF_2CHOH$), 2.67-2.60 (1H, m, $CF_2CH_aH_b$), 2.60-2.52 (1H, m, $CF_2CH_aH_b$); $\delta_C$ (75 MHz, acetone-$d_6$) 131.7 (d, $^4J_{C\text{-}F}$ 2.4, C-3), 123.8 (dd, $^1J_{C\text{-}F}$ 244.7, 242.9, C-6), 123.3 (dd, $^3J_{C\text{-}F}$ 10.2, 1.2, C-4), 75.9 (t, $^2J_{C\text{-}F}$ 20.7, C-1), 75.3 (dd, $^3J_{C\text{-}F}$ 5.4, 3.0, C-2), 36.0 (dd, $^2J_{C\text{-}F}$ 26.3, 25.1, C-5); $\delta_F$ (282 MHz, acetone-$d_6$) -107.0 (1F, ddddd, $^2J_{F\text{-}F}$ 243.1, $^3J_{F\text{-}H}$ 10.9, 6.2, 2.8, $^4J_{F\text{-}H}$ 1.4), -115.7 (1F, dtdd, $^2J_{F\text{-}F}$ 243.1, $^3J_{F\text{-}H}$ 22.8, 18.4, $^4J_{F\text{-}H}$ 2.3); [HRMS (EI, $M^+$) Found 150.04927. Calc. for $C_6H_8O_2F_2$ 150.04924]; *m/z* (EI) 150 (39 %, $M^+$), 132 (24, M-$H_2O$), 122 (6), 112 (7, M-$H_2O$-HF), 101 (18), 86 (42), 84 (33, M-$H_2O$-CO-HF), 70 (100).

The stereochemistry and identity of this product were confirmed by XRD analysis; $C_6H_8F_2O_2$, crystal size 0.30 x 0.13 x 0.08 $mm^3$, $M$ = 150.12, monoclinic, $a$ = 10.368(3), $b$ = 7.1164(17), $c$ = 9.045(2) Å, $\alpha$ = 90(5), $\beta$ = 102.157(4), $\gamma$ = 90 deg, $U$ = 652.4(3) $Å^3$, $T$ = 150(2) K, space group $P2(1)/c$, $Z$ = 4, $\mu$ (Mo-K$\alpha$) = 0.148 $mm^{-1}$, 4165 reflections collected, 1148 unique, ($R_{int}$ = 0.0909), which were used in all calculations. Final R indices [$F^2 > 2\sigma F^2$] $R1$ = 0.0458, $wR2$ = 0.1060; R indices (all data) $R1$ = 0.0624, $wR2$ = 0.1140.

**(1*S**,2*S**)-6,6-Difluoro-4-methyl-cyclohex-3-ene-1,2-diol 197**

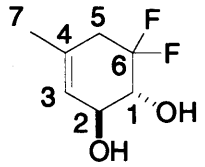



**197**

Second generation Grubbs' catalyst (92 µmol, 79 mg) was added to a solution of diol **176** (2.3 mmol, 0.62 g) in dry degassed dichloromethane (93 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 30 hours then concentrated *in vacuo* to leave a black oil which was purified by Kugelrohr distillation (bp 60 °C/0.01 mmHg) to remove the catalyst residue then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **197** (296 mg, 79 %) as a white solid; mp 45-47 °C; $R_f$ (40 % ethyl acetate in hexane) 0.13; (Found: C, 51.15; H, 6.02; $C_7H_{10}F_2O_2$ requires: C, 51.22; H, 6.14 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3416br, 3294br, 1372m, 1208m, 1084s, 1035s, 884s, 859s; $\delta_H$ (400 MHz, $CDCl_3$) 5.51-5.46 (1H, m, *H*C=CCH$_3$), 4.38-4.32 (1H, m, H$_3$CC=CHC*H*OH), 3.95 (1H, dt, $^3J_{H\text{-}F}$ 15.2, $J$ 4.3, CF$_2$C*H*OH), 2.66 (1H, td, $^2J$

18.0, $^{3}J_{H\text{-}F}$ 12.1, $CF_2CH_aH_b$), 2.43 (1H, dt, $^{2}J$ 18.0, $^{3}J_{H\text{-}F}$ 13.8, $CF_2CH_aH_b$), 1.77 (3H, s, HC=CC$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 133.2 (t, $^{3}J_{C\text{-}F}$ 5.6, C-4), 122.2 (dd, $^{1}J_{C\text{-}F}$ 244.5, 242.1, C-6), 121.9 (C-3), 69.1 (dd, $^{2}J_{C\text{-}F}$ 27.2, 21.6, C-1), 67.8 (t, $^{3}J_{C\text{-}F}$ 3.9, C-2), 36.9 (t, $^{2}J_{C\text{-}F}$ 25.2, C-5), 22.8 (C-7); $\delta_F$ (376 MHz, $CDCl_3$) -106.8 (1F, dddt, $^{2}J_{F\text{-}F}$ 251.0, $^{3}J_{F\text{-}H}$ 18.2, 13.8, $^{4}J_{F\text{-}H}$ 3.8), (-107.5)-(-108.5) (1F, m, incl. d, $^{2}J_{F\text{-}F}$ 251.0); [HRMS (EI, $M^+$) Found 164.06482. Calc. for $C_7H_{10}O_2F_2$ 164.06489]; *m/z* (EI) 164 (49 %, $M^+$), 149 (100, M-Me), 146 (12, M-$H_2O$), 131 (19, M-Me-$H_2O$), 126 (12, M-$H_2O$-HF), 103 (33), 98 (46, M-$H_2O$-CO-HF), 84 (98).

**(1*R**,2*S**)-6,6-Difluoro-4-methyl-cyclohex-3-ene-1,2-diol 206**




**206**

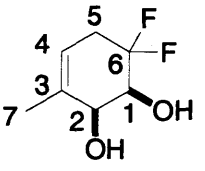
Second generation Grubbs' catalyst (1.70 µmol, 1.4 mg) was added to a solution of diol **177** (3.4 µmol, 9.1 mg) in dry degassed dichloromethane (1.4 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 48 hours then concentrated *in vacuo* to leave a black oil which was purified by column chromatography (100 % diethyl ether) to afford cyclic diol **206** (5.0 mg, 90 %) as colourless plates; mp 135-136 °C; $R_f$ (40 % ethyl acetate in hexane) 0.15; $\delta_H$ (400 MHz, $CDCl_3$) 5.45 (1H, s, $CH_3C$=C*H*), 4.36-4.26 (1H, m, $CH_3C$=CHC*H*OH), 3.85 (1H, ddd, $^{3}J_{H\text{-}F}$ 20.3, 6.5, *J* 2.3, $CF_2CH$OH), 2.62 (1H, dd, $^{2}J$ 18.0, $^{3}J_{F\text{-}H}$ 8.2, $CF_2CH_aH_b$), 2.59-2.50 (1H, m, $CF_2CH_aH_b$); 1.76 (3H, s, HC=C$CH_3$); $\delta_F$ (376 MHz, $CDCl_3$), -107.3 (1F, ddd, $^{2}J_{F\text{-}F}$ 246.0, $^{3}J_{F\text{-}H}$ 8.2, 6.5),

-113.9 (1F, ddd, $^2J_{F-F}$ 246.0, $^3J_{F-H}$ 20.3, 17.8); [HRMS (EI, $M^+$) Found 164.06496. Calc. for $C_7H_{10}O_2F_2$ 164.06489]; *m/z* (EI) 164 (47 %, $M^+$), 149 (100, M-Me), 146 (30, M-$H_2O$), 131 (20, M-Me-$H_2O$), 126 (25, M-$H_2O$-HF), 103 (34), 98 (55, M-$H_2O$-CO-HF), 84 (88).

The stereochemistry and identity of this product were confirmed by XRD analysis; $C_7H_{10}F_2O_2$, crystal size 0.30 x 0.28 x 0.14 $mm^3$, $M$ = 164.15, crystal system monoclinic, unit cell dimensions a = 10.989(4), b = 7.855(3), c = 9.098(3) Å, $\alpha$ = 90°, $\beta$ = 108.042(5)°, $\gamma$ = 90°, U = 746.8(3) $Å^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.136 $mm^{-1}$, 5059 reflections collected 1316 unique [R(int) = 0.0793], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0535, wR2 = 0.1342; R indices (all data) R1 = 0.0590, wR2 = 0.1381.

An insufficient quantity was available for $^{13}C$ NMR.

**(1*S**,2*S**)-6,6-difluoro-3-methylcyclohex-3-ene-1,2-diol 196**



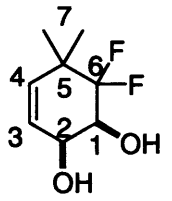

**196**

Second generation Grubbs' catalyst (69 µmol, 59 mg) was added to a solution of diol **178** (2.8 mmol, 745 mg) in dry degassed dichloromethane (111 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 2 days then concentrated *in vacuo* to leave a black oil which was purified by distillation under reduced pressure in a Kugelrohr (bp: 80 °C / 0.035 mmHg) to

remove the catalyst residue then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **196** ( 351 g, 77 %) as colourless plates; $R_f$ (40 % ethyl acetate in hexane) 0.37; (Found: C, 51.44; H, 6.32; $C_7H_{10}F_2O_2$ Requires: C, 51.22; H, 6.14 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3418br, 3307br, 1673w, 1372m, 1210m, 1081s, 1037s, 890s, 861s; $\delta_H$ (300 MHz, $CDCl_3$) 5.43-5.35 (1H, m, *HC*=CCH$_3$), 4.24-4.14 (1H, m, HC=CCH$_3$C*H*OH), 4.00 (1H, dt, $^3J_{H-F}$ 14.7, *J* 5.3, $CF_2CHOH$), 3.33 (1H, br s, O*H*), 2.83-2.62 (1H, m, $CF_2CH_aCH_b$), 2.58-2.36 (1H, m, $CF_2CH_aCH_b$), 2.34 (1H, br s, O*H*), 1.85-1.82 (3H, m, HC=C*CH*$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 134.2 (C-3), 122.1 (t, $^1J_{C-F}$ 244.1, C-6), 118.6 (t, $^3J_{C-F}$ 6.0, C-4), 70.7 (t, $^3J_{C-F}$ 3.6, C-2), 69.6 (t, $^2J_{C-F}$ 25.1, C-1), 32.4 (t, $^2J_{C-F}$ 25.1, C-5), 19.6 (C-7); $\delta_F$ (282 MHz, $CDCl_3$) -107.4 (1F, dtdd, $^2J_{F-F}$ 248.3, $^3J_{F-H}$ 14.7, 12.3, $^4J_{F-H}$ 2.3), -108.0 (1F, dddddd, $^2J_{F-F}$ 248.3, $^3J_{F-H}$ 16.1, 14.2, 5.7, $^4J_{F-H}$ 2.8, 2.7); [HRMS (EI, $M^+$) Found 164.06486. Calc. for $C_7H_{10}O_2F_2$ 164.06489]; *m/z* (EI) 164 (95 %, $M^+$), 149 (10, M-Me), 146 (22, M-$H_2O$), 131 (13, M-Me-$H_2O$), 126 (12, M-$H_2O$-HF), 115 (14), 100 (24), 98 (20, M-$H_2O$-CO-HF), 84 (100).

The stereochemistry and identity of this product were confirmed by XRD analysis; $C_7H_{10}F_2O_2$, crystal size 0.22 x 0.14 x 0.08 mm$^3$, *M* = 164.15, crystal system monoclinic, unit cell dimensions a = 9.8701(16), b = 10.9641(18), c = 21.172(4) Å, $\alpha = 90°$, $\beta = 99.186(3)°$, $\gamma = 90°$, U = 2261.7(6) Å$^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.135 mm$^{-1}$, 15931 reflections collected 3978 unique [R(int) = 0.0562], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0456, wR2 = 0.0798; R indices (all data) R1 = 0.0704, wR2 = 0.0872.

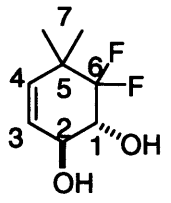
**(1*S**,2*S**)-6,6-Difluoro-5,5-dimethyl-cyclohex-3-ene-1,2-diol 209**




**209**

Second generation Grubbs' catalyst (35 μmol, 30 mg) was added to a solution of diol **184** (0.7 mmol, 199 mg) in dry degassed dichloromethane (28 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 5 hours then concentrated *in vacuo* to leave a black oil which was purified by Kugelrohr distillation (bp 50 °C/0.01 mmHg) to remove the catalyst residue then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **209** (103 mg, 83 %) as white solid; mp 70-71 °C; $R_f$ (40 % ethyl acetate in hexane) 0.34; (Found: C, 54.10; H, 6.73; $C_8H_{12}F_2O_2$ requires: C, 53.93; H, 6.79 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3368br, 3271br, 1474m, 1068s, 1043s; $\delta_H$ (400 MHz, $CDCl_3$) 5.76 (1H, ddd, *J* 10.0, 4.5, $^5J_{H\text{-}F}$ 0.5, *H*$^3$), 5.58 (1H, ddddd, *J* 10.0, $^4J_{H\text{-}F}$ 5.5, $^4J_{H\text{-}F}$ 1.7, $^4J$ 0.6, $^4J$ 0.2, *H*$^4$), 4.30 (1H, dt, $^4J_{H\text{-}F}$ 5.0, *J* 4.5, HC=CHC*H*OH), 4.10 (1H, dt, $^3J_{H\text{-}F}$ 22.1, *J* 5.0, $CF_2CHOH$), 3.14 (1H, br s, O*H*), 1.92 (1H, br s, O*H*), 1.21 (3H, d, $^4J_{H\text{-}F}$ 2.0, $CF_2CCH_3$), 1.15 (3H, d, $^4J_{H\text{-}F}$ 1.5, $CF_2CCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 138.3 (dd, $^4J_{C\text{-}F}$ 4.8, 1.6, C-4), 123.7 (dd, $^1J_{C\text{-}F}$ 251.7, 246.9, C-6), 123.6 (d, $^3J_{C\text{-}F}$ 1.6, C-3), 67.6 (dd, $^3J_{C\text{-}F}$ 4.0, 1.6, C-2), 67.5 (t, $^2J_{C\text{-}F}$ 21.2, C-1), 41.0 (t, $^2J_{C\text{-}F}$ 22.4, C-5), 24.9 (dd, $^3J_{C\text{-}F}$ 5.4, 4.2, C-7), 21.5 (dd, $^3J_{C\text{-}F}$ 6.6, 2.4, C-7) ; $\delta_F$ (376.5 MHz, $CDCl_3$) -121.6 (1F, d, $^2J_{F\text{-}F}$ 250.3), -122.3 (1F, dd, $^2J_{F\text{-}F}$ 250.3, $^3J_{F\text{-}H}$ 22.1); [HRMS (EI, $M^+$) Found 178.0856. Calc. for $C_8H_{12}O_2F_2$ 178.08054]; *m/z* (EI) 178 (2 %, $M^+$), 163 (4, M-Me), 160 (2, M-$H_2O$), 143 (4, M-Me-HF), 97 (13, M-Me-$H_2O$-CO-HF), 86 (100).

**(1*R**,2*S**)-6,6-Difluoro-5,5-dimethyl-cyclohex-3-ene-1,2-diol 210**

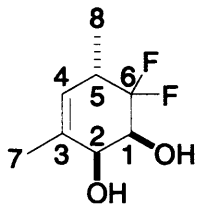



**210**

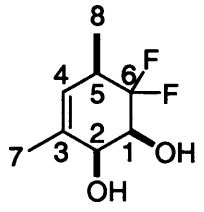
Second generation Grubbs' catalyst (62 μmol, 52 mg) was added to a solution of diol **185** (1.2 mmol, 350 mg) in dry degassed dichloromethane (49 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 18 hours then concentrated *in vacuo* to leave a black oil which was first purified by Kugelrohr distillation (bp 70 °C/0.03 mmHg) to remove the catalyst residues, then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **210** (177 mg, 80 %) as white solid; mp 108 °C; $R_f$ (40 % ethyl acetate in hexane) 0.12; (Found: C, 54.11; H, 6.73; $C_8H_{12}F_2O_2$ requires: C, 53.93; H, 6.79 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3351br, 3233br, 1475m, 1083s, 1044s, 1026s; $\delta_H$ (300 MHz, $CDCl_3$) 5.53 (1H, ddd, *J* 10.2, $^5J_{H\text{-}F}$ 2.0, 0.6, *H*$^3$), 5.40 (1H, ddd, *J* 10.2, $^4J_{H\text{-}F}$ 7.0, 2.0, *H*$^4$ ), 4.36 (1H, ddd, *J* 7.5, $^4J_{H\text{-}F}$ 4.6, $^4J$ 0.3, HC=CHC*H*OH), 4.01 (1H, dd, $^3J_{H\text{-}F}$ 24.2, *J* 7.5, $CF_2CHOH$), 2.69 (2H, br s, O*H*), 1.17 (3H, d, $^4J_{H\text{-}F}$ 2.1, $CF_2CCH_3$), 1.16 (3H, d, $^4J_{H\text{-}F}$ 2.6, $CF_2CCH_3$); $\delta_C$ (75.5 MHz, $CDCl_3$) 135.1 (d, $^4J_{C\text{-}F}$ 6.6, C-4), 124.9 (d, $^3J_{C\text{-}F}$ 2.1, C-3), 123.2 (dd, $^1J_{C\text{-}F}$ 251.3, 247.1, C-6), 73.1 (dd, $^2J_{C\text{-}F}$ 22.7, 19.7, C-1), 72.4 (dd, $^3J_{C\text{-}F}$ 5.4, 3.6, C-2), 41.2 (t, $^2J_{C\text{-}F}$ 22.7, C-5), 26.0 (t, $^3J_{C\text{-}F}$ 4.2, C-7), 20.5 (d, $^3J_{C\text{-}F}$ 9.6, C-7) ; $\delta_F$ (376.5 MHz, $CDCl_3$) (-122.5)-(-123.5) (1F, m, incl. app. ddt, $^2J_{F\text{-}F}$ 244.0, $^3J_{F\text{-}H}$ 7.1, $^4J_{F\text{-}H}$ 1.9), -125.6 (1F, ddt, $^2J_{F\text{-}F}$ 244.0, $^3J_{F\text{-}H}$ 24.2, $^4J_{F\text{-}H}$ 2.0); [HRMS (EI, $M^+$) Found 178.0850. Calc. for $C_8H_{12}O_2F_2$ 178.08054]; *m/z* (EI) 178 (31 %, $M^+$), 163 (4, M-Me), 160 (1, M-$H_2O$), 143 (6, M-Me-HF), 143 (6, M-Me-HF), 97 (14, M-Me-$H_2O$-CO-HF), 86 (100).

**(1*S**,2*S**,5*S**)-6,6-Difluoro-3,5-dimethyl-cyclohex-3-ene-1,2-diol 207**

**(1*S**,2*S**,5*R**)-6,6-Difluoro-3,5-dimethyl-cyclohex-3-ene-1,2-diol 208**




**207**

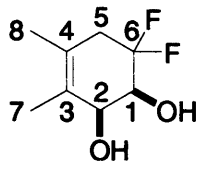



**208**

Second generation Grubbs' catalyst (0.3 mmol, 257 mg) was added to a solution of diols **182** and **183** (3.5 mmol, 0.99 g) in dry degassed dichloromethane (140 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 2 days then concentrated *in vacuo* to leave a black oil as a mixture of diastereoisomers (4:1) which was purified by Kugelrohr distillation (bp: 65 °C / 0.025 mmHg) to remove the catalyst residue then separated by column chromatography (15 % ethyl acetate in hexane) to afford cyclic diols **207** and **208** (505 mg, 81 %) as a white solid; data for **207**: mp 51-53 °C; $R_f$ (40 % ethyl acetate in hexane) 0.42; (Found: C, 54.01; H, 6.78; $C_8H_{12}F_2O_2$ Requires: C, 53.93; H, 6.79 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3452br, 3329br, 1673w, 1403m, 1225m, 1109s, 1024s, 866s; $\delta_H$ (400 MHz, $CDCl_3$) 5.27-5.22 (1H, m, *H*$^4$), 4.24-4.18 (1H, m, *H*$^2$), 4.08 (1H, ddd, $^3J_{H\text{-}F}$ 15.0, *J* 4.5, $^3J_{H\text{-}F}$ 2.0 $CF_2CHOH$), 2.84 (1H, ddddq, $^3J_{H\text{-}F}$ 18.4, 9.8, *J* 7.2, 4.8, $^4J$ 2.4, $CF_2CHCH_3$), 1.81 (3H, ddd, $^4J$ 2.2, $^4J$ 1.5, $^5J$ 1.0, $HC{=}CCH_3$), 1.10 (3H, dd, *J* 7.2, $^4J_{H\text{-}F}$ 1.2, $CF_2CHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 132.8 (C-3), 125.5 (dd, $^3J_{C\text{-}F}$ 8.0, 2.4, C-4), 123.2 (dd, $^1J_{C\text{-}F}$ 247.7, 245.3, C-6), 70.7 (dd, $^3J_{C\text{-}F}$ 5.2, 2.0, C-2), 69.2 (dd, $^2J_{C\text{-}F}$ 31.2, 22.3, C-1), 35.0 (dd, $^2J_{C\text{-}F}$ 24.8, 22.3, C-5), 19.3 (C-7), 12.7 (dd, $^3J_{C\text{-}F}$ 7.2, 2.4, C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) -110.2 (1F, dddd, $^2J_{F\text{-}F}$ 250.6, $^3J_{F\text{-}H}$ 15.0, 9.8,

$^4J_{F\text{-}H}$ 5.7), -121.6 (1F, dd, $^2J_{F\text{-}F}$ 250.6, $^3J_{F\text{-}H}$ 18.4); [HRMS (EI, $M^+$) Found 178.08042 Calc. for $C_8H_{12}O_2F_2$ 178.08054]; *m/z* (EI) 178 (100 %, $M^+$), 163 (10, M-Me), 160 (48, M-$H_2O$), 145 (36, M-Me-$H_2O$), 140 (25, M-$H_2O$-HF), 125 (15, M-Me-$H_2O$-HF), 100 (84), 98 (76), 97 (69, M-Me-$H_2O$-CO-HF). Data for **208**: mp 89-90 °C; $R_f$ (40 % ethyl acetate in hexane) 0.38; (Found: C, 54.09; H, 6.80; $C_8H_{12}F_2O_2$ Requires: C, 53.93; H, 6.79 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3420br, 3302br, 1456m, 1227m, 1120s, 1077s, 1025s, 992s; $\delta_H$ (300 MHz, $CDCl_3$) 5.29-5.24 (1H, m, *H*$^4$), 4.08 (1H, ddd, *J* 10.7, 5.2, 4.7, *H*$^2$), 3.88 (1H, dddd, $^3J_{H\text{-}F}$ 25.7, 9.0, *J* 5.2, $^4J$ 2.3 $CF_2CHOH$), 3.03 (1H, br s, O*H*), 2.69-2.53 (1H, m, $CF_2CHCH_3$), 1.87 (3H, ddd, $^4J$ 2.4, $^4J$ 1.5, $^5J$ 0.5, HC=CC*H*$_3$), 1.60 (1H, br s, O*H*), 1.18 (3H, dd, *J* 7.2, $^4J_{H\text{-}F}$ 1.2, $CF_2CHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 133.5 (d, $^4J_{C\text{-}F}$ 2.0, C-3), 127.0 (d, $^3J_{C\text{-}F}$ 9.0, C-4), 122.2 (dd, $^1J_{C\text{-}F}$ 247.7, 243.5, C-6), 71.3 (d, $^3J_{C\text{-}F}$ 4.8, C-2), 70.0 (t, $^2J_{C\text{-}F}$ 20.0, C-1), 37.6 (t, $^2J_{C\text{-}F}$ 23.9, C-5), 20.4 (d, $^5J_{C\text{-}F}$ 1.2, C-7), 12.3 (dd, $^3J_{C\text{-}F}$ 7.2, 1.2, C-8); $\delta_F$ (282.4 MHz, $CDCl_3$) -114.2 (1F, ddtd, $^2J_{F\text{-}F}$ 244.5, $^3J_{F\text{-}H}$ 9.0, 5.7, $^4J_{F\text{-}H}$ 2.4), -130.1 (1F, ddddd, $^2J_{F\text{-}F}$ 244.5, $^3J_{F\text{-}H}$ 25.7, 20.9, $^4J_{F\text{-}H}$ 4.2, 0.9); [HRMS (EI, $M^+$) Found 178.08059 Calc. for $C_8H_{12}O_2F_2$ 178.08054]; *m/z* (EI) 178 (100 %, $M^+$), 163 (11, M-Me), 160 (26, M-$H_2O$), 145 (23, M-Me-$H_2O$), 140 (17, M-$H_2O$-HF), 125 (14, M-Me-$H_2O$-HF), 100 (92), 98 (99), 97 (65, M-Me-$H_2O$-CO-HF).

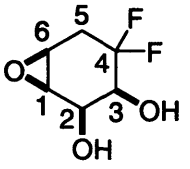
**(1*S**,2*S**)-6,6-Difluoro-3,4-dimethyl-cyclohex-3-ene-1,2-diol 211**




**211**

Second generation Grubbs' catalyst (0.17 mmol, 143 mg) was added to a solution of diol **180** (2.0 mmol, 565 mg) in dry degassed dichloromethane (80 mL, C = 0.025 M) under an atmosphere of argon. The mixture was heated at reflux for 2 days then concentrated *in vacuo* to leave a black oil which was purified by Kugelrohr distillation (bp 65 °C/0.03 mmHg) to remove the catalyst residues, then by column chromatography (40 % ethyl acetate in hexane) to afford cyclic diol **211** (289 mg, 81 %) as an oil; $R_f$ (20 % ethyl acetate in hexane) 0.11; (Found: C, 53.92; H, 6.93; $C_8H_{12}F_2O_2$ requires: C, 53.93; H, 6.79 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3383br, 1382m, 1209m, 1069s, 1032m; $\delta_H$ (300 MHz, $CDCl_3$) 4.12 (1H, t, *J* 5.0, *H*$^2$ ), 3.92 (1H, dddt, $^3J_{H\text{-}F}$ 20.8, *J* 5.0, $^3J_{H\text{-}F}$ 3.0, $^4J$ 0.6, $CF_2CHOH$), 2.66 (1H, dt, $^2J$ 18.0, $^3J_{H\text{-}F}$ 12.7, $CF_2CH_aH_b$), 2.45 (1H, ddd, $^3J_{H\text{-}F}$ 20.8, $^2J$ 18.0, $^3J_{H\text{-}F}$ 12.3, $CF_2CH_aH_b$), 2.41 (2H, br s, O*H*), 1.80 (3H, s, $CH_3C{=}CCH_3$), 1.69 (3H, s, $CH_3C{=}CCH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 126.7 (C-3), 125.6 (dd, $^3J_{C\text{-}F}$ 6.6, 4.2, C-4), 121.9 (dd, $^1J_{C\text{-}F}$ 243.5, 242.3, C-6), 72.1 (dd, $^3J_{C\text{-}F}$ 4.2, 2.4, C-2), 69.4 (dd, $^2J_{C\text{-}F}$ 24.5, 20.3, C-1), 38.9 (dd, $^2J_{C\text{-}F}$ 25.1, 23.9, C-5), 19.0 (C-8), 15.8 (C-7); $\delta_F$ (282 MHz, $CDCl_3$), -107.0 (1F, dtdd, $^2J_{F\text{-}F}$ 246.9, $^3J_{F\text{-}H}$ 12.3, 4.2, $^4J_{F\text{-}H}$ 3.0), -110.5 (1F, dtd, $^2J_{F\text{-}F}$ 246.9, $^3J_{F\text{-}H}$ 20.8, 12.7); [HRMS (EI, $M^+$) Found 178.08048. Calc. for $C_8H_{12}O_2F_2$ 178.08054]; *m/z* (EI) 178 (84 %, $M^+$), 163 (100, M-Me), 160 (10, M-$H_2O$), 145 (40, M-Me-$H_2O$), 140 (5, M-HF-$H_2O$), 125 (8, M-HF-Me-$H_2O$), 117 (40, M-$H_2O$-Me-CO), 97 (54, M-$H_2O$-Me-CO-HF).

**(1*R**,2*R**,3*S**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol 232**



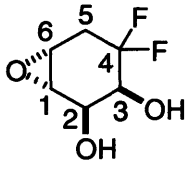

**232**

*m*-CPBA (1.5 mmol, 0.26 g) was added at 0 °C to a suspension of diol **192** (1.0 mmol, 0.15 g) and $NaH_2PO_4$ (1.5 mmol, 0.18g) in dichloromethane (10 mL, C = 0.05 M). The reaction mixture was stirred at room temperature for 1 hour then concentrated *in vacuo* to leave crude epoxide **232** as a single diastereoisomer which was purified by column chromatography (30 % ethyl acetate in hexane) to afford epoxide **232** (0.18 g, 85 %) as colourless plates; mp 107-108 °C; $R_f$ (40 % ethyl acetate in hexane) 0.12; (Found: C, 43.48; H, 4.87; $C_6H_8F_2O_3$ requires: C, 43.38; H, 4.85 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3467br, 3407br, 1417m, 1257m, 1074s, 1051s; $\delta_H$ (400 MHz, methanol-$d_4$) 4.12 (1H, dddd, *J* 4.5, $^4J_{H\text{-}F}$ 3.9, *J* 2.2, $^4J_{H\text{-}F}$ 1.9, $H^2$), 3.85 (1H, dddd, $^3J_{H\text{-}F}$ 10.2, *J* 4.5, $^3J_{H\text{-}F}$ 2.6, $^4J$ 1.4, $CF_2CHOH$), 3.40 (1H, dddd, $^4J_{H\text{-}F}$ 7.5, *J* 4.9, 3.9, $^4J$0.6, $CH_2CH(O)CH$), 3.39 (1H, dddd, *J* 3.9, 2.2, $^4J$ 1.4, $^4J$0.6, $CH_2CH(O)CH$), 2.56 (1H, dddt, $^3J_{H\text{-}F}$ 33.5, $^2J$ 16.1, $^3J_{H\text{-}F}$ 7.5, $^4J$0.6, $CF_2CH_aH_b$), 2.42 (1H, ddddd, $^3J_{H\text{-}F}$ 19.0, $^2J$ 16.1, *J* 4.9, $^3J_{H\text{-}F}$ 2.2, $^4J$ 1.4, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.7 (dd, $^1J_{C\text{-}F}$ 251.7, 238.1, C-4), 71.8 (dd, $^2J_{C\text{-}F}$ 32.8, 22.4, C-3), 67.7 (d, $^4J_{C\text{-}F}$ 8.0, C-2), 56.0 (C-1), 50.9 (d, $^3J_{C\text{-}F}$ 12.0, C-6), 30.4 (t, $^2J_{C\text{-}F}$ 26.0, C-5); $\delta_F$ (376.5 MHz, methanol-$d_4$) (-100.9)-(-101.7) (1F, ddt, $^2J_{F\text{-}F}$ 254.6, $^3J_{F\text{-}H}$ 10.2, $^3J_{F\text{-}H}$ 7.5, $^4J_{F\text{-}H}$ 7.5), -105.4 (1F, ddddd, $^2J_{F\text{-}F}$ 254.6, $^3J_{F\text{-}H}$ 33.5, 19.0, $^4J_{F\text{-}H}$ 3.9, $^3J_{F\text{-}H}$ 2.6); [HRMS (EI, $M^+$) Found 166.04415. Calc. for $C_6H_8O_3F_2$ 166.04415]; *m/z* (EI) 148 (2 %, M-$H_2O$), 128 (5, M-$H_2O$-HF), 73 (100).

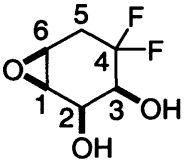
The stereochemistry and identity of this product were confirmed by XRD analysis; $C_6H_8F_2O_3$, crystal size 0.39 x 0.22 x 0.06 $mm^3$, *M* = 166.12, crystal system monoclinic, unit cell dimensions a = 11.166(3), b = 5.7258(16), c = 10.978(3) Å, $\alpha$ = 90°, $\beta$ = 111.988(4)°, $\gamma$ = 90°, U = 650.8(3) $Å^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.169 $mm^{-1}$, 4399 reflections collected 1141 unique [R(int) = 0.0578], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0502, wR2 = 0.1101; R indices (all data) R1 = 0.0651, wR2 = 0.1161.

**(1*S**,2*R**,3*S**,6*R**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol 236**

**(1*R**,2*R**,3*S**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol 232**




**236**

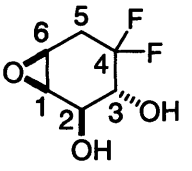



**232**

$Na_2EDTA$ (2.0 mmol, 5.0 mL of a 0.4 mM aqueous solution) was added to a solution of diol **192** (1.0 mmol, 0.15 g) in acetonitrile (10 mL). The solution was cooled to 0 °C then trifluoroacetone (10.0 mmol, 1.9 mL of a 60 wt/v aqueous solution) was added. A mixture of $NaHCO_3$ (7.75 mmol, 0.65 g) and Oxone (5.0 mmol, 3.07 g) was added in one portion. The reaction mixture was stirred at 0 °C for 1.5 hours; then $Na_2SO_4$ (*ca.* 10g) was added followed by dichloromethane (20 mL). The solid was removed by filtration and the filtrate was concentrated *in vacuo* to afford epoxides **236** and **232** as an inseparable mixtures of diastereoisomers (7:1) (149 mg, 90 %); mp 101-102 °C; $R_f$ (40 %

ethyl acetate in hexane) 0.12; (Found: C, 43.50; H, 4.76; $C_6H_8F_2O_3$ requires: C, 43.38; H, 4.85 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3347br, 1371m, 1275m, 1061s; [HRMS (EI, M$^+$) Found 166.04413. Calc. for $C_6H_8O_3F_2$ 166.04415]; *m/z* (EI) 166 (2 %, M$^+$), 148 (4, M-$H_2O$), 146 (8, M-HF), 128 (6, M-$H_2O$-HF), 73 (100); data for **236**: $\delta_H$ (300 MHz, methanol-$d_4$) 4.06 (1H, t, *J* 3.8, *H-2*), 3.80 (1H, dt, $^3J_{H-F}$ 13.5, *J* 3.8, $CF_2CHOH$), 3.39-3.32 (1H, m, $CH_2CH(O)CH$), 3.15 (1H, d, *J* 3.8, $CH_2CH(O)CH$), 2.54 (1H, dddd, $^3J_{H-F}$ 21.8, $^2J$ 16.0, $^3J_{H-F}$ 13.5, *J* 3.4, $CF_2CH_aH_b$), 2.40 (1H, td, $^2J$ 16.0, $^3J_{H-F}$ 9.5, $CF_2CH_aH_b$); $\delta_C$ (75.5 MHz, methanol-$d_4$) 123.0 (dd, $^1J_{C-F}$ 245.9, 243.0, C-4), 69.8 (dd, $^2J_{C-F}$ 28.7, 22.7, C-3), 68.4 (dd, $^4J_{C-F}$ 6.0, 1.8, C-2), 55.6 (C-1), 53.0 (dd, $^3J_{C-F}$ 9.8, 3.0, C-6), 31.7 (dd, $^2J_{C-F}$ 26.3, 22.7, C-5); $\delta_F$ (282.4 MHz, methanol-$d_4$) -101.8 (1F, ddddt, $^2J_{F-F}$ 254.5, $^3J_{F-H}$ 21.8, 15.2, 3.8, $^4J_{F-H}$ 2.4), -103.1 (1F, dtdd, $^2J_{F-F}$ 254.5, $^3J_{F-H}$ 13.5, 9.5, $^4J_{F-H}$ 3.8). Data for **232**: data were in agreement with those reported previously.

**(1*R**,2*R**,3*R**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol 233**

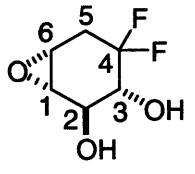



**233**

*m*-CPBA (0.73 mmol, 126 mg) was added at 0 °C to a suspension of diol **198** (0.36 mmol, 55 mg) and $NaH_2PO_4$ (0.73 mmol, 87 mg) in acetonitrile (4 mL, C = 0.1 M). The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was filtered through Celite then concentrated *in vacuo* to leave a white residue which was taken up in dichloromethane. The suspension was

filtered then concentrated *in vacuo* to afford single diastereoisomer epoxide **233** (40 mg, 67 %) as a white solid; mp 130 °C; $R_f$ (60 % ethyl acetate in hexane) 0.2; (Found: C, 43.50; H, 4.96; $C_6H_8F_2O_3$ requires: C, 43.38; H, 4.85 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3344br, 3234br, 1421m, 1085s; $\delta_H$ (300 MHz, methanol-$d_4$) 3.98 (1H, dt, *J* 8.6, 2.0, $H^2$), 3.70 (1H, ddd, $^3J_{H\text{-}F}$ 24.6, *J* 8.6, $^3J_{H\text{-}F}$ 1.6, $CF_2CHOH$), 3.40 (1H, dd, *J* 4.0, 2.0, $H^1$), 3.35-3.29 (1H, m, $H^6$), 2.56 (1H, dddd, $^3J_{H\text{-}F}$ 19.7, $^2J$ 16.2, *J* 4.8, $^3J_{H\text{-}F}$ 1.3, $CF_2CH_aH_b$), 2.36 (1H, ddd, $^3J_{H\text{-}F}$ 32.4, $^2J$ 16.2, $^3J_{H\text{-}F}$ 8.9, $CF_2CH_aH_b$); $\delta_C$ (75.5 MHz, methanol-$d_4$) 122.3 (dd, $^1J_{C\text{-}F}$ 246.5, 242.3, C-4), 72.2 (dd, $^2J_{C\text{-}F}$ 20.9, 19.1, C-3), 71.5 (dd, $^3J_{C\text{-}F}$ 7.2, 3.0, C-2), 57.3 (d, $^4J_{C\text{-}F}$ 1.2, C-1), 50.5 (d, $^3J_{C\text{-}F}$ 12.6, C-6), 34.7 (t, $^2J_{C\text{-}F}$ 26.0, C-5); $\delta_F$ (282.4 MHz, methanol-$d_4$) (-104.9)-(-105.9) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 246.4), -115.3 (1F, ddddd, $^2J_{F\text{-}F}$ 246.4, $^3J_{F\text{-}H}$ 32.4, 24.6, 19.7, $^4J_{F\text{-}H}$ 1.9); [HRMS (EI, $M^+$) Found 166.04423. Calc. for $C_6H_8O_3F_2$ 166.04415]; *m/z* (EI) 166 (2 %, $M^+$), 148 (20, M-$H_2O$), 146 (57, M-HF), 128 (24, M-$H_2O$-HF), 73 (100).

**(1*S**,2*R**,3*R**,6*R**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol 237**

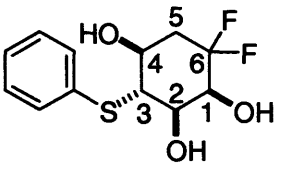



**237**

$Na_2EDTA$ (2.0 mmol, 5.0 mL of a 0.4 mM aqueous solution) was added to a solution of diol **198** (1.0 mmol, 0.15 g) in acetonitrile (10 mL). The solution was cooled to 0 °C, then trifluoroacetone (10.0 mmol, 1.9 mL of a 60 wt/v aqueous solution) was added. A mixture of $NaHCO_3$ (7.75 mmol, 0.65 g) and Oxone (5.0

mmol, 3.07 g) was added in one portion. The reaction mixture was stirred at 0 °C for 2 hours; then $Na_2SO_4$ (*ca.* 10g) was added followed by dichloromethane (20 mL). The solid was removed by filtration and the filtrate was concentrated *in vacuo*. The crude epoxide **237**, obtained as a single diastereoisomer was purified by column chromatography (20 % methanol in dichloromethane) to afford epoxide **237** (33 mg, 20 %, 99 % by GC) as a colourless oil; $R_f$ (20 % methanol in dichloromethane) 0.25; $\upsilon_{max}$(neat)/$cm^{-1}$ 3355br, 1372m, 1275m, 1062s; $\delta_H$ (400 MHz, methanol-$d_4$) 3.93 (1H, tdd, *J* 5.4, 4.2, $^4J_{H\text{-}F}$ 3.2, $CH_2CH$(O)CH), 3.91-3.88 (1H, m, incl. app. dd, *J* 7.9, 2.9, $H^2$), 3.89-3.82 (1H, m, incl. app. d, *J* 7.9, $CF_2CH$OH), 3.85-3.81 (1H, m, incl. app. dd, *J*5.4, 2.8, $CH_2CH$(O)C*H*), 2.19 (1H, dddd, $^3J_{H\text{-}F}$ 21.4, $^2J$ 14.5, $^3J_{H\text{-}F}$ 7.6, *J* 4.2, $CF_2CH_aH_b$), 2.18-2.05 (1H, m, incl. app. ddd, $^2J$ 14.5, $^3J_{H\text{-}F}$ 10.5, *J* 5.4, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.5 (dd, $^1J_{C\text{-}F}$ 246.9, 242.9, C-4), 73.9 (C-1), 72.4 (dd, $^2J_{C\text{-}F}$ 23.2, 20.8, C-3), 71.9 (dd, $^4J_{C\text{-}F}$ 5.6, 1.6, C-2), 68.6 (dd, $^3J_{C\text{-}F}$ 8.0, 3.2, C-6), 36.2 (t, $^2J_{C\text{-}F}$ 22.0, C-5); $\delta_F$ (376.5 MHz, $CDCl_3$, 193K) major conformer: -99.4 (1F, d, $^2J_{F\text{-}F}$ 246.3), (-111.0)-(-112.0) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 246.3); minor conformer: -101.0 (1F, d, $^2J_{F\text{-}F}$ 257.4), (-101.9)-(-103.1) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 257.4); [HRMS (EI, $M^+$) Found 166.04422. Calc. for $C_6H_8O_3F_2$ 166.04415]; *m/z* (EI) 166 (1 %, $M^+$), 148 (4, M-$H_2O$), 146 (7, M-HF), 128 (5, M-$H_2O$-HF), 73 (100).

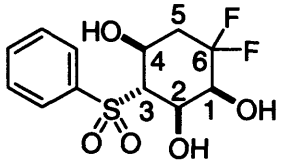
**(1*S**,2*R**,3*R**,4*S**)-6,6-difluoro-3-(phenylthio)cyclohexane-1,2,4-triol 252**




**252**

Diphenyl disulfide (0.13 mmol, 29 mg) was dissolved in absolute ethanol (5 mL) then sodium borohydride (0.27 mmol, 10 mg) was added in 3 portions over 30 minutes at room temperature under an atmosphere of argon. The solution was stirred at room temperature until the bright yellow solution turned colourless. Epoxide **232** (0.23 mmol, 39 mg) was added then the reaction mixture was refluxed overnight. The solution was concentrated *in vacuo* then the residue was purified by column chromatography (35 % ethyl acetate in hexane) to afford triol **252** (17 mg, 27 %, 99 % by GC) as an oil; $R_f$ (60 % ethyl acetate in hexane) 0.67; $\delta_H$ (300 MHz, methanol-$d_4$) 7.69-7.64 (2H, m, Ar*H*), 7.35-7.29 (3H, m, Ar*H*), 3.91-3.85 (1H, m, $CF_2CHOH$), 3.42 (1H, td, *J* 10.5, 6.4, $CH_2CHOH$), 3.41-3.34 (1H, m, $H^2$), 3.06 (1H, t, *J* 10.5, *CH*SPh), 2.34-2.10 (2H, m, $CF_2CH_2$); $\delta_C$ (75.5 MHz, methanol-$d_4$) 135.6 (C-Ar), 133.9 (C-Ar), 129.8 (C-Ar), 128.9 (C-Ar), 122.8 (dd, $^1J_{C\text{-}F}$ 250.1, 237.6, C-6), 72.4 (dd, $^2J_{C\text{-}F}$ 32.3, 22.1, C-1), 69.8 (d, $^4J_{C\text{-}F}$ 8.4, C-2), 66.8 (d, $^3J_{C\text{-}F}$ 13.8, C-4), 57.7 (C-3), 37.8 (t, $^2J_{C\text{-}F}$ 22.1, C-5); $\delta_F$ (282.4 MHz, methanol-$d_4$) -104.4 (1F, dq, $^2J_{F\text{-}F}$ 257.8, $^3J_{F\text{-}H}$ 5.7), (-106.5)-(-107.6) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 257.8); *m/z* (EI) 276 (15 %, $M^+$), 258 (2, M-$H_2O$), 165 (19, M-PhSH), 147 (9, M-PhSH-$H_2O$), 110 (100, PhSH).

**(1*S**,2*R**,3*R**,4*S**)-6,6-difluoro-3-(phenylsulfonyl)cyclohexane-1,2,4-triol 253**

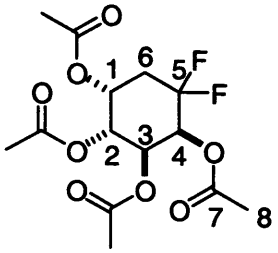



**253**

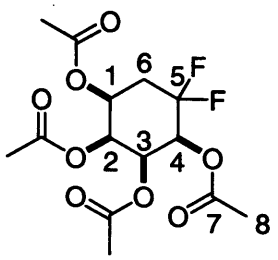
*m*-CPBA (0.12 mmol, 20 mg) was added at 0 °C to a suspension of triol **252** (0.06 mmol, 16 mg) and $NaH_2PO_4$ (0.12 mmol, 14 mg) in dichloromethane (5 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* to leave a white residue which was taken up in ethyl acetate. After filtration through filter paper, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (35% ethyl acetate in hexane) to afford triol **253** (13 mg, 74 %, 86 % by GC) as a white solid; mp: 146-147 °C; $R_f$ (60 % ethyl acetate in hexane) 0.48; $\delta_H$ (400 MHz, methanol-$d_4$) 8.00-7.92 (2H, m, Ar*H*), 7.74-7.44 (3H, m, Ar*H*), 4.12 (1H, td, *J* 10.3, 7.1, $CH_2CHOH$), 3.98 (1H, dddd, *J* 10.3, $^4J_{H\text{-}F}$ 3.7, *J* 3.1, $^4J_{H\text{-}F}$ 1.9, $H^2$), 3.85-3.79 (1H, m, $CF_2CHOH$), 3.53 (1H, t, *J* 10.3, $CHSO_2Ph$), 2.33-2.15 (2H, m, $CF_2CH_2$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 142.3 (C-Ar), 134.9 (C-Ar), 130.0 (C-Ar), 129.8 (C-Ar), 122.1 (dd, $^1J_{C\text{-}F}$ 250.1, 236.5, C-6), 72.4 (dd, $^2J_{C\text{-}F}$ 32.0, 22.4, C-1), 71.2 (C-3), 68.1 (d, $^4J_{C\text{-}F}$ 8.8, C-2), 64.4 (d, $^3J_{C\text{-}F}$ 13.6, C-4), 37.0 (t, $^2J_{C\text{-}F}$ 22.4, C-5); $\delta_F$ (376.5 MHz, methanol-$d_4$) -105.1 (1F, dq, $^2J_{F\text{-}F}$ 258.8, $^3J_{F\text{-}H}$ 5.9), (-107.4)-(-108.4) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 258.8); [HRMS (FAB+, $MH^+$) Found 309.06088. Calc. for $C_{12}H_{15}O_5F_2S$ 309.06083]; *m/z* (EI) 308 (1 %, $M^+$), 280 (38, M-$H_2O$), 156 (90), 141 (53, $PhSO_2$), 139 (78), 104 (100).

**(1*R**,2*R**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 262**

**(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 263**



**262**



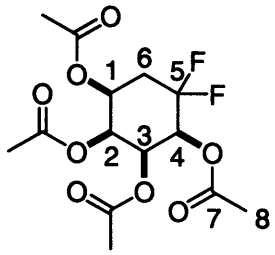
**263**

Osmium tetroxide (68 µL of a 2.5 wt. % solution in *tert*-butanol, 6.7 µmol, 2 mol%) was added to a solution of diol **192** (0.33 mmol, 50.0 mg) and NMO.$H_2O$ (0.67 mmol, 92.8 mg, 2.0 eq.) in a mixture of acetone (0.3 mL), water (0.3 mL) and *tert*-butanol (0.15 mL) precooled to 0 °C. The reaction mixture was stirred at room temperature for 7 hours. The reaction was quenched with sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite; the residue was rinsed with methanol (15 mL) and concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (2 mL) and acetic anhydride (2.0 mmol, 0.2 mL) was added. The mixture was stirred at room temperature overnight. The solution was concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with potassium carbonate (15 mL of a saturated aqueous solution), and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **262** and **263** (5:1) which were separated by flash chromatography (30 % ethyl acetate in hexane) to afford tetraacetates **262** as a white solid and **263** as an colourless oil (67 mg, 58 % over 2 steps); data for **262**: mp 121-122 °C; $R_f$ (40 % ethyl

acetate in hexane) 0.39; (Found: C, 47.80; H, 5.03; $C_{14}H_{18}F_2O_8$ requires: C, 47.73; H, 5.15 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 1740s, 1372m, 1208s, 1181s, 1021s; $\delta_H$ (400 MHz, $CDCl_3$) 5.53 (1H, dd, $^3J_{H\text{-}F}$ 7.6, *J* 3.2, $CF_2CHOAc$), 5.47-5.40 (2H, m, *H*$^2$, *H*$^3$), 5.22 (1H, dd, *J* 9.2, 3.3, $CH_2CHOAc$), 2.45-2.35 (2H, m, $CF_2CH_2$), 2.15 (3H, s, $C(O)CH_3$), 2.09 (3H, s, $C(O)CH_3$), 2.07 (3H, s, $C(O)CH_3$), 2.05 (3H, s, $C(O)CH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.1 (C-7), 169.9 (C-7), 169.5 (C-7), 169.1 (C-7), 118.7 (t, $^1J_{C\text{-}F}$ 248.5, C-5), 68.9 (t, $^2J_{C\text{-}F}$ 28.3, C-4), 67.9 (C-2), 67.0 (t, $^3J_{C\text{-}F}$ 3.0, C-3), 65.3 (t, $^3J_{C\text{-}F}$ 5.4, C-1), 32.8 (t, $^2J_{C\text{-}F}$ 23.5, C-6), 20.9 (C-8), 20.7 (C-8), 20.6 (C-8); $\delta_F$ (376.5 MHz, $CDCl_3$, 328 K) -100.1 (1F, dt, $^2J_{F\text{-}F}$ 266.8, $^3J_{F\text{-}H}$ 17.8), (-102.9)-(-104.5) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 266.8); [HRMS (EI, M$^+$) Found 352.09671. Calc. for $C_{14}H_{18}F_2O_8$ 352.09697]; *m/z* (EI) 352 (10 %, M$^+$), 310 (18, M-Ac), 293 (4, M-OAc), 268 (7, M-Ac-Ac), 250 (21, M-OAc-Ac), 232 (70, M-OAc-OAc), 190 (100, M-OAc-OAc-Ac). Data for **263**: $R_f$ (40 % ethyl acetate in hexane) 0.32; $\upsilon_{max}$(neat)/cm$^{-1}$ 1739s, 1368m, 1215s, 1182s, 1031s; $\delta_H$ (400 MHz, $CDCl_3$) 5.55 (1H, t, *J* 3.1, *H-2*), 5.48-5.43 (1H, m, $CF_2CHOAc$), 5.15 (1H, td, *J* 3.1, $^4J_{H\text{-}F}$ 1.3, *H*$^3$), 5.09 (1H, dddd, *J* 12.2, 4.8, 3.1, $^4J_{H\text{-}F}$ 0.4, $CH_2CHOAc$), 2.54 (1H, dddd, $^3J_{H\text{-}F}$ 30.8, $^2J$ 13.2, *J* 12.2, $^3J_{H\text{-}F}$ 5.3, $CF_2CH_aH_b$), 2.35-2.25 (1H, m, $CF_2CH_aH_b$), 2.16 (3H, s, $CH_3$), 2.10 (3H, s, $CH_3$), 2.07 (3H, s, $CH_3$), 2.05 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.0 (C-7), 169.5 (C-7), 169.2 (C-7), 169.1 (C-7), 119.1 (dd, $^1J_{C\text{-}F}$ 255.6, 240.5, C-5), 68.9 (dd, $^2J_{C\text{-}F}$ 36.8, 24.1, C-4), 67.6 (C-2), 66.3 (dd, $^3J_{C\text{-}F}$ 9.6, 1.8, C-3), 65.6 (dd, $^3J_{C\text{-}F}$ 13.2, 5.4, C-1), 30.8 (t, $^2J_{C\text{-}F}$ 23.2, C-6), 20.8 (C-8), 20.7 (C-8), 20.6 (C-8), 20.5 (C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) -102.9 (1F, ddddd, $^2J_{F\text{-}F}$ 266.8, $^3J_{F\text{-}H}$ 30.8, 9.5, 5.3, $^4J_{F\text{-}H}$ 1.3), -110.9 (1F, ddd, $^2J_{F\text{-}F}$ 266.8, $^3J_{F\text{-}H}$ 12.3, 6.6); [HRMS (EI, M$^+$) Found 352.09694. Calc. for $C_{14}H_{18}F_2O_8$ 352.09697]; *m/z* (EI) 352 (3 %, M$^+$), 310 (36, M-Ac), 293 (7,

M-OAc), 268 (8, M-Ac-Ac), 250 (45, M-OAc-Ac), 232 (41, M-OAc-OAc), 190 (84, M-OAc-OAc-Ac), 103 (100).

**(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 263**



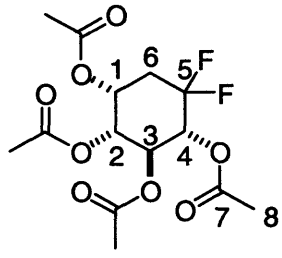

**263**

A solution of osmium tetroxide (0.44 mmol, 113 mg, 1.05 eq.) in dichloromethane (1 mL) was added to a solution of diol **192** (0.42 mmol, 63.4 mg) and TMEDA (0.465 mmol, 70 µL, 1.1 eq.) in dichloromethane (42.2 mL, 0.01 M) precooled to -78 °C. The solution turned deep red and then brown-black. The solution was stirred until the starting material was consumed (TLC analysis, 1.25 h) before being allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was taken up in tetrahydrofuran (15 mL) and aqueous sodium sulfite (15 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite. The filter bed was washed with methanol (40 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (2 mL) and acetic anhydride (4.2 mmol, 0.4 mL) was added, then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5% aqueous solution) then extracted with dichloromethane (3 x 15 mL). The

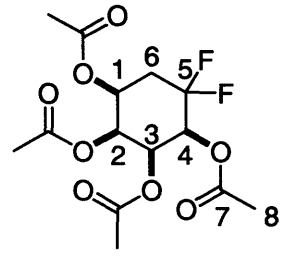
combined organic extracts were washed with potassium carbonate (20 mL of a saturated aqueous solution), and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **263** and **262** (11:1) which were separated by flash chromatography (30% ethyl acetate in hexane) to afford tetraacetates **263** and **262** as a colourless oil (72 mg, 48 % over 2 steps). Data for **263**and **262** were in agreement with those reported previously.

**(1*R**,2*R**,3*S**,4*R**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 264**

**(1*S**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 265**



**264**



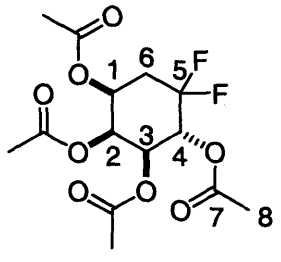
**265**

Osmium tetroxide (38 µL of a 2.5 wt. % solution in *tert*-butanol, 3.7 µmol, 2 mol%) was added to a solution of diol **198** (0.19 mmol, 28 mg) and $NMO.H_2O$ (0.37 mmol, 52 mg, 2.0 eq.) in a mixture of acetone (0.2 mL), water (0.2 mL) and *tert*-butanol (0.1 mL) precooled to 0 °C. The reaction mixture was stirred at room temperature for 24 hours. The reaction was quenched with sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite; the residue was rinsed with methanol (15 mL) and concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (1 mL) and acetic anhydride (1.1 mmol, 0.1 mL) was added. The mixture was stirred at room

temperature overnight. The solution was concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with potassium carbonate (10 mL of a saturated aqueous solution), and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **264** and **265** (2.5:1) which were purified by flash chromatography (30 % ethyl acetate in hexane) to afford a mixture of tetraacetates **264** and **265** as a white solid (35.6 mg, 57 % over 2 steps); data for **264**: mp 99-101 °C; $R_f$ (40 % ethyl acetate in hexane) 0.47; (Found: C, 47.84; H, 5.03; $C_{14}H_{18}F_2O_8$ requires: C, 47.73; H, 5.15 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 1743s, 1370m, 1210s, 1185s, 1028s; $\delta_H$ (300 MHz, $CDCl_3$) 5.56 (1H, td, *J* 9.6, $^4J_{H\text{-}F}$ 1.3, $H^3$), 5.40 (1H, dt, *J* 6.4, 3.4, $CH_2CHOAc$), 5.30 (1H, ddd, $^3J_{H\text{-}F}$ 18.4, *J* 9.6, $^3J_{H\text{-}F}$ 5.1, $CF_2CHOAc$), 5.08 (1H, dd, *J* 9.6, 3.4, $H^2$), 2.58 (1H, dddd, $^2J$ 15.5, $^3J_{H\text{-}F}$ 11.4, *J* 6.4, $^3J_{H\text{-}F}$ 3.8, $CF_2CH_aH_b$), 2.51-2.21 (1H, m, $CF_2CH_aH_b$), 2.14 (3H, s, $C(O)CH_3$), 2.13 (3H, s, $C(O)CH_3$), 2.04 (3H, s, $C(O)CH_3$), 2.03 (3H, s, $C(O)CH_3$); $\delta_C$ (75.5 MHz, $CDCl_3$) 170.1 (C-7), 169.8 (C-7), 169.4 (C-7), 119.0 (t, $^1J_{C\text{-}F}$ 251.3, C-5), 70.8 (dd, $^2J_{C\text{-}F}$ 23.9, 19.1, C-4), 70.5 (C-2), 68.2 (d, $^3J_{C\text{-}F}$ 8.4, C-3), 65.5 (d, $^3J_{C\text{-}F}$ 10.8, C-1), 33.8 (dd, $^2J_{C\text{-}F}$ 23.9, 22.7, C-6), 20.9 (C-8), 20.6 (C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) -101.2 (1F, dddd, $^2J_{F\text{-}F}$ 253.0, $^3J_{F\text{-}H}$ 6.2, 5.1, 3.8), -106.9 (1F, dddd, $^2J_{F\text{-}F}$ 253.0, $^3J_{F\text{-}H}$ 30.8, 18.4, 11.4); [HRMS (FAB, $MH^+$) Found 353.10484. Calc. for $C_{14}H_{19}F_2O_8$ 353.10480]; *m/z* (FAB+) 353 (37 %, $MH^+$), 293 (88, $MH^+$-OAc), 269 (2, $MH^+$-Ac-Ac), 251 (17, $MH^+$-OAc-Ac), 154 (100). Data for **265**: mp 142-144 °C; $R_f$ (40 % ethyl acetate in hexane) 0.47; (Found: C, 47.77; H, 5.10; $C_{14}H_{18}F_2O_8$ requires: C, 47.73; H, 5.15 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 1741s, 1373m, 1216s, 1192s; $\delta_H$ (400 MHz, $CDCl_3$) 5.66-5.63 (1H, td, *J* 2.7, $^4J$ 1.4, $H^2$), 5.53 (1H, ddd, $^3J_{H\text{-}F}$ 19.9, *J* 10.8, $^3J_{H\text{-}F}$ 4.1,

$CF_2CHOAc$), 5.13 (1H, ddd, *J* 10.8, 2.7, $^4J_{H\text{-}F}$ 1.0, $H^3$), 5.11 (1H, dddd, *J* 12.3, 5.1, 2.7, $^4J_{H\text{-}F}$ 1.3, $CH_2CHOAc$), 2.55-2.29 (2H, m, $CF_2CH_2$), 2.19 (3H, s, $C(O)CH_3$), 2.14 (3H, s, $C(O)CH_3$), 2.03 (3H, s, $C(O)CH_3$), 2.01 (3H, s, $C(O)CH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.9 (C-7), 169.8 (C-7), 169.5 (C-7), 169.4 (C-7), 118.4 (dd, $^1J_{C\text{-}F}$ 250.9, 243.7, C-5), 69.0 (C-2), 68.6 (d, $^2J_{C\text{-}F}$ 22.7, C-4), 68.3 (d, $^3J_{C\text{-}F}$ 9.6, C-3), 65.3 (d, $^3J_{C\text{-}F}$ 12.8, C-1), 33.6 (dd, $^2J_{C\text{-}F}$ 23.9, 23.6, C-6), 20.8 (C-8), 20.7 (C-8), 20.6 (C-8), 20.5 (C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) (-103.6)-(-104.3) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 253.0), -110.9 (1F, dddd, $^2J_{F\text{-}F}$ 253.0, $^3J_{F\text{-}H}$ 33.2, 19.9, 11.4); [HRMS (FAB+, $MH^+$) Found 353.10478. Calc. for $C_{14}H_{19}F_2O_8$ 353.10480]; *m/z* (EI) 353 (1 %, $MH^+$), 310 (4, $MH^+$-Ac), 293 (3, $MH^+$-OAc), 268 (9, $MH^+$-Ac-Ac), 250 (15, $MH^+$-OAc-Ac), 233 (2, $MH^+$-OAc-OAc), 190 (100, $MH^+$-OAc-OAc-Ac).

**(1*R**,2*S**,3*S**,4*S**)-2,3,4-tris(acetyloxy)-5,5-difluorocyclohexyl acetate 265**



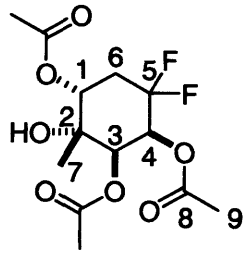

**265**

Osmium tetroxide (0.20 mmol, 49.8 mg, 1.05 eq.) in solution in dichloromethane (1 mL) was added to a solution of diol **198** (0.19 mmol, 28.0 mg) and TMEDA (0.21 mmol, 31µL, 1.1 eq.) in dichloromethane (18.7 mL, 0.01 M) precooled to -78 °C. The solution turned deep red and then brown-black. The solution was stirred until the starting material was consumed (TLC analysis, 1.5 h) before

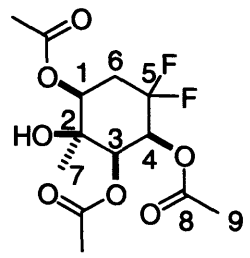
being allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was taken up in tetrahydrofuran (10 mL) and aqueous sodium sulfite (10 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite, the residue was rinsed with methanol (30 mL) and concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (2 mL) and acetic anhydride (1.08 mmol, 0.1 mL) was added. The mixture was stirred at room temperature overnight. The solution was concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with potassium carbonate (15 mL of a saturated aqueous solution), and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **265** and **264** (16:1) which were separated by flash chromatography (30 % ethyl acetate in hexane) to afford tetraacetates **265** and **264** as a white solid (33 mg, 52 % over 2 steps). Data were in agreement with those reported previously.

**(1*R**,2*R**,3*R**,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclo hexyl acetate 266**

**(1*S**,2*S**,3*R**,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclo hexyl acetate 267**




**266**




**267**

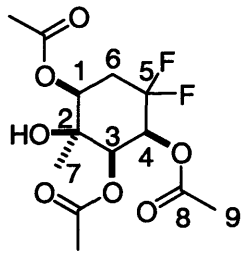
Osmium tetroxide (78 µL of a 2.5 wt. % solution in *tert*-butanol, 7.7 µmol, 2 mol%) was added to a solution of diol **196** (0.38 mmol, 63.5 mg) and NMO.$H_2O$ (0.77 mmol, 107 mg, 2.0 eq.) in a mixture of acetone (0.4 mL), water (0.4 mL) and *tert*-butanol (0.2 mL) precooled to 0 °C . The reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite; the residue was rinsed with methanol (20 mL) and concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (2 mL) and acetic anhydride (2.3 mmol, 0.25 mL) was added. The mixture was stirred at room temperature overnight. The solution was concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (20 mL of a saturated aqueous solution), and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **266** and **267** (2.2:1) which were separated by flash chromatography (40 % ethyl acetate in

hexane) to afford tetraacetates **266** and **267** (27.7 mg, 23 % over 2 steps) as white solids; data for **266**: mp 134-136 °C; $R_f$ (40 % ethyl acetate in hexane) 0.32; (Found: C, 48.10; H, 5.70; $C_{13}H_{18}F_2O_7$ requires: C, 48.15; H, 5.59 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3468br, 1732s, 1335m, 1223s, 1029s; $\delta_H$ (400 MHz, $CDCl_3$) 5.53 (1H, ddd, $^3J_{H\text{-}F}$ 21.3, 5.3, *J* 3.9, $CF_2CHOAc$), 5.30 (1H, ddd, $^4J_{H\text{-}F}$ 5.3, *J* 3.9, $^4J_{H\text{-}F}$ 0.8, $H^3$ ), 5.11 (1H, dd, *J* 11.2, 5.1, $CH_2CHOAc$), 2.53-2.28 (3H, m, $CF_2CH_2$, *OH*), 2.14 (3H, s, C(O)C$H_3$), 2.13 (3H, s, C(O)C$H_3$), 2.09 (3H, s, C(O)C$H_3$), 1.24 (3H, s, $CHOHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.1 (C-8), 169.9 (C-8), 168.8 (C-8), 119.1 (dd, $^1J_{C\text{-}F}$ 250.1, 246.1, C-5), 72.7 (C-2), 72.7 (d, $^3J_{C\text{-}F}$ 8.0, C-3), 70.6 (d, $^3J_{C\text{-}F}$ 11.2, C-1), 68.3 (dd, $^2J_{C\text{-}F}$ 24.0, 17.6, C-4), 34.0 (t, $^2J_{C\text{-}F}$ 23.2, C-6), 22.3 (C-7), 20.8 (C-9), 20.7 (C-9), 20.5 (C-9); $\delta_F$ (376.5 MHz, $CDCl_3$) -99.3 (1F, ddt, $^2J_{F\text{-}F}$ 248.2, $^3J_{F\text{-}H}$ 11.0, 5.3), (-107.8)-(-109.5) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 248.2); [HRMS (FAB+, $MH^+$) Found 325.10984. Calc. for $C_{13}H_{19}F_2O_7$ 325.10988]; *m/z* (FAB+) 325 (7 %, $MH^+$), 307 (100, $MH^+$-$H_2O$), 265 (5, $MH^+$-OAc), 247 (6, $MH^+$-OAc-$H_2O$), 223 (5, $MH^+$-OAc-Ac), 205 (20, $MH^+$-OAc-OAc), 185 (15, $MH^+$-OAc-OAc-HF), 163 (20, $MH^+$-OAc-OAc-Ac), 154 (25). Data for **267**: mp 110-111 °C; $R_f$ (40 % ethyl acetate in hexane) 0.10; (Found: C, 48.09; H, 5.56; $C_{13}H_{18}F_2O_7$ requires: C, 48.15; H, 5.59 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3551br, 1732s, 1371m, 1215s, 1026s; $\delta_H$ (400 MHz, $CDCl_3$) 5.42 (1H, ddd, $^3J_{H\text{-}F}$ 6.1, *J* 3.9, $^4J$ 1.7, $CF_2CHOAc$), 4.96 (1H, ddd, *J* 3.9, $^4J_{H\text{-}F}$ 2.3, $^4J_{H\text{-}F}$ 1.2, $H^3$ ), 4.92 (1H, ddd, *J* 11.7, 4.7, $^4J_{H\text{-}F}$ 0.8, $CH_2CHOAc$), 2.54 (2H, dddd, $^3J_{H\text{-}F}$ 32.4, $^2J$ 13.3, *J* 11.7, $^3J_{H\text{-}F}$ 6.2, $CF_2CH_aH_b$, *OH*), 2.40-2.30 (1H, m, $CF_2CH_aH_b$), 2.16 (6H, s, C(O)C$H_3$), 2.13 (3H, s, C(O)C$H_3$), 1.20 (3H, s, $CHOHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.9 (C-8), 169.4 (C-8), 168.9 (C-8), 118.6 (dd, $^1J_{C\text{-}F}$ 254.0, 239.7, C-5), 72.8 (C-2), 70.9 (dd, $^3J_{C\text{-}F}$ 12.0, 2.4, C-1), 70.3 (d, $^3J_{C\text{-}F}$ 6.4, C-3), 68.7 (dd, $^2J_{C\text{-}F}$ 36.7, 24.0, C-4), 31.3 (t, $^2J_{C\text{-}F}$ 23.2, C-6), 22.2 (C-7), 20.9 (C-9), 20.7 (C-9),

20.6 (C-9); $\delta_F$ (376.5 MHz, $CDCl_3$) -103.2 (1F, ddddd, $^2J_{F-F}$ 266.8, $^3J_{F-H}$ 32.4, 9.6, 6.1, $^4J_{F-H}$ 2.3), -104.1 (1F, ddd, $^2J_{F-F}$ 266.8, $^3J_{F-H}$ 33.2, 12.5, 6.2); [HRMS (FAB+, $MH^+$) Found 325.10981. Calc. for $C_{13}H_{19}F_2O_7$ 325.10988]; *m/z* (FAB+) 325 (50 %, $MH^+$), 307 (34, $MH^+$-$H_2O$), 265 (13, $MH^+$-OAc), 247 (4, $MH^+$-OAc-$H_2O$), 223 (10, $MH^+$-OAc-Ac), 205 (28, $MH^+$-OAc-OAc), 185 (7, $MH^+$-OAc-OAc-HF), 163 (11, $MH^+$-OAc-OAc-Ac), 154 (100).

The stereochemistry and identity of **267** were confirmed by XRD analysis; $C_{13}H_{18}F_2O_7$, crystal size 0.33 x 0.29 x 0.13 $mm^3$, *M* = 324.27, crystal system monoclinic, unit cell dimensions a = 5.6676(19), b = 13.376(5), c = 19.932(7) Å, $\alpha$ = 90°, $\beta$ = 92.670(6)°, $\gamma$ = 90°, U = 1509.4(9) $Å^3$, T = 150(2) K, space group P2(1)/n, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.130 $mm^{-1}$, 10531 reflections collected 2656 unique [R(int) = 0.0766], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0548, wR2 = 0.1289; R indices (all data) R1 = 0.0608, wR2 = 0.1330.

**(1*S**,2*S**,3*R*,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclohexyl acetate 267**

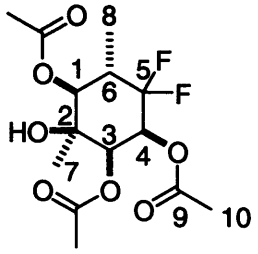



**267**

Osmium tetroxide (0.38 mmol, 97.0 mg, 1.05 eq.) in solution in dry dichloromethane (1 mL) was added to a solution of diol **196** (0.36 mmol, 60.0

mg) and TMEDA (0.40 mmol, 62μL, 1.1 eq.) in dichloromethane (36.0 mL, 0.01 M) precooled to -78 °C. The solution turned deep red and then brown-black. The solution was stirred until the starting material was consumed (TLC analysis, 1.0 h) before being allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was taken up in tetrahydrofuran (20 mL) and aqueous sodium sulfite (20 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite, the residue was rinsed with methanol (45 mL) and concentrate *in vacuo* to leave a black oil. The residue was taken up in pyridine (3 mL) and acetic anhydride (2.2 mmol, 0.2 mL) was added. The mixture was stirred at room temperature overnight. The solution was concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (20 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (20 mL of a saturated aqueous solution), and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude tetraacetates as a mixture of diastereoisomers **267** and **266** (10.6:1) which were separated by flash chromatography (30 % ethyl acetate in hexane) to afford tetraacetates **267** and **266** as a white solid (61 mg, 56 % over 2 steps); data were in agreement with those reported previously.

**(1*S**,2*S**,3*R**,4*S**,6*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 269**



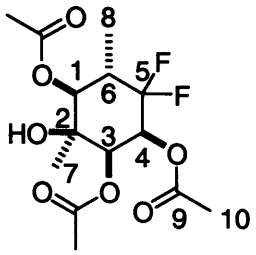

**269**

Osmium tetroxide (60 µL of a 2.5 wt. % solution in *tert*-butanol, 5.9 µmol, 2 mol%) was added to a solution of diol **207** (0.30 mmol, 52.8 mg) and NMO.$H_2O$ (0.59 mmol, 83 mg, 2.0 eq.) in a mixture of acetone (0.3 mL), water (0.3 mL) and *tert*-butanol (0.15 mL) precooled to 0 °C . The reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite. The filter bed was washed with methanol (15 mL) and the combined initial filtrate and washings concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (1.3 mmol, 0.11 mL) and acetic anhydride (1.0 mL) was added, then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (15 mL of a saturated aqueous solution), and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude triacetate as a single diastereoisomer **269** which was purified by flash chromatography (70 % ethyl acetate in hexane) to afford triacetate **269** as a white solid (72 mg, 79 % over 2 steps); mp 108-110 °C; $R_f$ (80 % ethyl

acetate in hexane) 0.46; (Found: C, 49.63; H, 5.88; $C_{14}H_{20}F_2O_7$ requires: C, 49.70; H, 5.96 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3534br, 1739s, 1370m, 1210s, 1039s; $\delta_H$ (400 MHz, $CDCl_3$) 5.52 (1H, td, $^3J_{H-F}$ 6.1, *J* 3.9, $CF_2CHOAc$), 4.96 (1H, ddd, *J* 3.9, $^4J_{H-F}$ 3.0, $^4J_{H-F}$ 1.9, $CF_2CHOAcCHOAc$), 4.87 (1H, dt, *J* 11.5, $^4J_{H-F}$ 1.0, $CH(CH_3)CHOAc$), 2.84-2.63 (1H, m, incl. app. d, $^3J_{H-F}$ 28.7, $CF_2CHCH_3$), 2.47 (1H, br s, O*H*), 2.20 (3H, s, C(O)C*H*$_3$), 2.16 (3H, s, C(O)C*H*$_3$), 2.12 (3H, s, C(O)C*H*$_3$), 1.13 (3H, s, CHOHC*H*$_3$), 1.06 (3H, d, *J* 6.7, $CF_2CHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.2 (C-9), 169.4 (C-9), 168.9 (C-9), 119.4 (dd, $^1J_{C-F}$ 257.2, 241.3, C-5), 74.8 (d, $^3J_{C-F}$ 11.2, C-1), 73.5 (C-2), 69.9 (d, $^3J_{C-F}$ 8.0, C-3), 69.0 (dd, $^2J_{C-F}$ 39.1, 24.0, C-4), 35.0 (t, $^2J_{C-F}$ 21.6, C-6), 22.6 (C-7), 20.8 (C-10), 20.7 (C-10), 20.6 (C-10), 7.4 (C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) (-110.0)-(-111.1) (1F, m, incl. app. d, $^2J_{F-F}$ 266.3), -116.7 (1F, dddd, $^2J_{F-F}$ 266.3, $^3J_{F-H}$ 28.7, 6.1, $^4J_{F-H}$ 3.0); [HRMS (FAB+, $MH^+$) Found 339.12542. Calc. for $C_{14}H_{21}F_2O_7$ 339.12553]; *m/z* (FAB+) 339 (36 %, $MH^+$), 321 (38, $MH^+$-$H_2O$), 279 (22, $MH^+$-OAc), 261 (7, $MH^+$-OAc-$H_2O$), 235 (6, $MH^+$-OAc-Ac), 219 (31, $MH^+$-OAc-OAc), 199 (17, $MH^+$-OAc-OAc-HF), 177 (25, $MH^+$-OAc-OAc-Ac), 137 (100).

The stereochemistry and identity of **269** were confirmed by XRD analysis; $C_{14}H_{20}F_2O_7$, crystal size 0.26 x 0.20 x 0.10 mm$^3$, *M* = 338.30, crystal system monoclinic, unit cell dimensions a = 20.454(5), b = 8.329(2), c = 9.502(3) Å, $\alpha$ = 90°, $\beta$ = 101.455(4)°, $\gamma$ = 90°, U = 1586.4(7) Å$^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.127 mm$^{-1}$, 11017 reflections collected 2787 unique [R(int) = 0.0588], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0488, wR2 = 0.1086; R indices (all data) R1 = 0.0685, wR2 = 0.1172.

**(1*S**,2*S**,3*R**,4*S**,6*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 269**



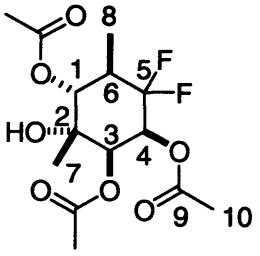

**269**

A solution of osmium tetroxide (0.35 mmol, 89.2 mg, 1.05 eq.) in dichloromethane (1 mL) was added to a solution of diol **207** (0.33 mmol, 60.8 mg) and TMEDA (0.37 mmol, 55 µL, 1.1 eq.) in dichloromethane (33.4 mL, 0.01 M) precooled to -78 °C. The solution turned deep red and then brown-black. The solution was stirred until the starting material was consumed (TLC analysis, 1.5 h) before being allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was taken up in tetrahydrofuran (15 mL) and aqueous sodium sulfite (15 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite. The filter bed was washed with methanol (40 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (2 mL) and acetic anhydride (0.63 mmol, 60 µL) was added, then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (15 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (20 mL of a saturated aqueous solution), and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude triacetate as a single diastereoisomer **269** which was purified

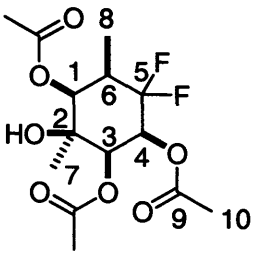
by flash chromatography (70 % ethyl acetate in hexane) to afford triacetate **269** as a white solid (48 mg, 42 % over 2 steps). Data were in agreement with those reported previously.

**(1*R**,2*R**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 270**

**(1*S**,2*S**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 271**




**270**




**271**

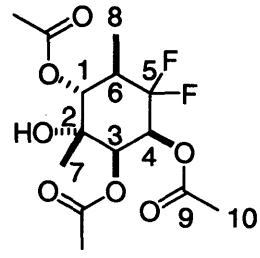
Osmium tetroxide (33 µL of a 2.5 wt. % solution in *tert*-butanol, 3.3 µmol, 2 mol%) was added to a solution of diol **208** (0.16 mmol, 29 mg) and NMO.$H_2O$ (0.73 mmol, 45.4 mg, 2.0 eq.) in a mixture of acetone (0.15 mL), water (0.15 mL) and *tert*-butanol (0.08 mL) precooled to 0 °C. The reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with sodium sulfite (70 mg) and stirred for a further 3 hours. The product was filtered through Celite. The filter bed was washed with methanol (15 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (0.72 mmol, 58 µL) and acetic anhydride (1.0 mL) was added, then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in

hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (15 mL of a saturated aqueous solution), and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude mixture of triacetate as a mixture of diastereoisomers **270** and **271** (32:1) which were separated by flash chromatography (40 % ethyl acetate in hexane) to afford triacetate **270** as colourless plates (22 mg, 41 % over 2 steps); mp 124-125 °C; $R_f$ (40 % ethyl acetate in hexane) 0.35; (Found: C, 49.78; H, 5.92; $C_{14}H_{20}F_2O_7$ requires: C, 49.70; H, 5.96 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3500br, 1753s, 1726s, 1364m, 1220s, 1038s; $\delta_H$ (400 MHz, $CDCl_3$) 5.55 (1H, ddd, $^3J_{H-F}$ 22.7, 5.1, *J* 3.9, $CF_2CHOAc$), 5.30 (1H, dd, $^4J_{H-F}$ 5.1, *J* 3.9, $CF_2CHOAcCHOAc$), 5.08 (1H, dd, *J* 11.3, $^4J_{H-F}$ 0.8, $CH(CH_3)CHOAc$), 2.56 (1H, ddqd, $^3J_{H-F}$ 26.1, *J* 11.3, 6.8, $^3J_{H-F}$ 4.3, $CF_2CHCH_3$), 2.20 (3H, s, $C(O)CH_3$), 2.16 (3H, s, $C(O)CH_3$), 2.11 (3H, s, $C(O)CH_3$), 1.84 (1H, br s, OH), 1.19 (3H, s, $CHOHCH_3$), 1.11 (3H, d, *J* 6.8, $CF_2CHCH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.1 (C-9), 170.0 (C-9), 169.8 (C-9), 119.9 (dd, $^1J_{C-F}$ 253.2, 246.9, C-5), 74.6 (d, $^3J_{C-F}$ 10.4, C-1), 72.9 (d, $^4J_{C-F}$ 1.6, C-2), 72.7 (dd, $^3J_{C-F}$ 8.0, 1.6, C-3), 68.4 (dd, $^2J_{C-F}$ 23.2, 17.6, C-4), 38.1 (t, $^2J_{C-F}$ 21.6, C-6), 23.1 (C-7), 20.9 (C-10), 20.8 (C-10), 20.7 (C-10), 7.8 (dd, $^3J_{C-F}$ 5.6, 3.2, C-8); $\delta_F$ (376.5 MHz, $CDCl_3$) -106.6 (1F, dtd, $^2J_{F-F}$ 246.8, $^3J_{F-H}$ 5.1, 4.3), -123.0 (1F, ddd, $^2J_{F-F}$ 246.8, $^3J_{F-H}$ 26.1, 22.7); [HRMS (FAB+, $MH^+$) Found 339.12551. Calc. for $C_{14}H_{21}F_2O_7$ 339.12553]; *m/z* (FAB+) 339 (4 %, $MH^+$), 321 (100, $MH^+$-$H_2O$), 279 (36, $MH^+$-OAc), 261 (5, $MH^+$-OAc-$H_2O$), 235 (3, $MH^+$-OAc-Ac), 219 (26, $MH^+$-OAc-OAc), 199 (12, $MH^+$-OAc-OAc-HF), 177 (27, $MH^+$-OAc-OAc-Ac), 137 (34).

The stereochemistry and identity of **270** were confirmed by XRD analysis; $C_{14}H_{20}F_2O_7$, crystal size 0.26 x 0.16 x 0.12 $mm^3$, *M* = 338.30, crystal system

monoclinic, unit cell dimensions a = 8.418(5), b = 10.252(7), c = 18.904(12) Å, α = 90°, β = 101.992(10)°, γ = 90°, U = 1595.9(18) $Å^3$, T = 150(2) K, space group P2(1)/c, absorption coefficient μ (Mo-Kα) = 0.126 $mm^{-1}$, 9148 reflections collected 2796 unique [R(int) = 0.1916], which were used in all calculations. Final R indices [I>2σ(I)] R1 = 0.0840, wR2 = 0.1489; R indices (all data) R1 = 0.1227, wR2 = 0.1626.

**(1*R**,2*R**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 270**



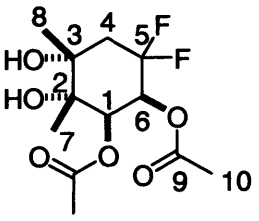

**270**

A solution of osmium tetroxide (67 μmol, 17 mg, 1.05 eq.) in dichloromethane (1 mL) was added to a solution of diol **208** (63 μmol, 11.3 mg) and TMEDA (70 μmol, 11 μL, 1.1 eq.) in dichloromethane (6.3 mL, 0.01 M) precooled to -78 °C. The solution turned deep red and then brown-black. The solution was stirred until the starting material was consumed (TLC analysis, 1.5 h) before being allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was taken up in tetrahydrofuran (5 mL) and aqueous sodium sulfite (5 mL). This mixture was heated at reflux for 3 h and the product filtered through Celite. The filtered bed was washed with methanol (20 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to leave a black oil. The

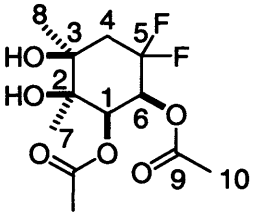
residue was taken up in pyridine (4 mL) and acetic anhydride (0.6 mmol, 59 µL) was added, Then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (5 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with potassium carbonate (10 mL of a saturated aqueous solution), and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude triacetate as a single diastereoisomer **270** which was purified by flash chromatography (30 % ethyl acetate in hexane) to afford triacetate **270** as a white solid (8.5 mg, 40 % over 2 steps). Data were in agreement with those reported previously.

**(1*R**,2*S**,3*R**,6*S**)-6-(acetyloxy)-5,5-difluoro-2,3-dihydroxy-2,3-dimethyl cyclohexyl acetate 272**

**(1*R**,2*R**,3*S**,6*S**)-6-(acetyloxy)-5,5-difluoro-2,3-dihydroxy-2,3-dimethyl cyclohexyl acetate 273**




**272**



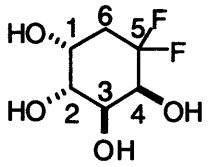

**273**

Osmium tetroxide (57 µL of a 2.5 wt. % solution in *tert*-butanol, 5.6 µmol, 2 mol%) was added to a solution of diol **211** (0.28 mmol, 49.8 mg) and $NMO.H_2O$ (0.56 mmol, 78 mg, 2.0 eq.) in a mixture of acetone (0.3 mL), water (0.3 mL) and *tert*-butanol (0.15 mL) precooled to 0 °C. The reaction mixture was

stirred at room temperature for 2 days. The reaction was quenched with sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite. The filter bed was washed with methanol (20 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to leave a black oil. The residue was taken up in pyridine (1 mL) and acetic anhydride (2.7 mmol, 0.26 mL) was added, then the mixture was stirred at room temperature overnight then concentrated *in vacuo* to leave a black solid. The residue was taken up in hydrochloric acid (10 mL of a 5 % aqueous solution) then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with potassium carbonate (15 mL of a saturated aqueous solution), and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver the crude bis-acetates as a mixture of diastereoisomers **272** and **273** (5:1) which were separated by flash chromatography (40 % ethyl acetate in hexane) to afford bis-acetates **272** and **273** as a white solid (26 mg, 33 % over 2 steps); data for **272**: mp 116-118 °C; $R_f$ (40 % ethyl acetate in hexane) 0.19; (Found: C, 48.58; H, 5.89; $C_{12}H_{18}F_2O_6$ requires: C, 48.65; H, 6.12 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3502br, 3457br, 1740s, 1325m, 1217s, 1021s; $\delta_H$ (400 MHz, $CDCl_3$) 5.56-5.48 (1H, m, incl. app. dd, *J* 3.9, $^4J$ 1.3, $CF_2CHOAc$), 5.38 (1H, t, $^4J_{H\text{-}F}$ 3.9, *J* 3.9, $CF_2CHOAcCHOAc$), 2.90 (1H, br s, O*H*), 2.57 (1H, br s, O*H*), 2.41-2.18 (2H, m, $CF_2CH_2$), 2.11 (3H, s, $C(O)CH_3$), 2.10 (3H, s, $C(O)CH_3$), 1.38 (3H, s, $CH_3$), 1.28 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.4 (C-9), 169.5 (C-9), 119.2 (dd, $^1J_{C\text{-}F}$ 250.1, 245.3, C-5), 75.2 (C-2), 73.3 (t, $^3J_{C\text{-}F}$ 4.8, C-3), 72.5 (t, $^3J_{C\text{-}F}$ 3.2, C-1), 69.0 (dd, $^2J_{C\text{-}F}$ 29.6, 21.6, C-6), 41.6 (t, $^2J_{C\text{-}F}$ 21.6, C-4), 24.0 (d, $^4J_{C\text{-}F}$ 2.4, C-8), 20.9 (C-10), 20.7 (C-10), 19.4 (C-7); $\delta_F$ (376.5 MHz, $CDCl_3$, 213K) major conformer: -96.9 (1F, d, $^2J_{F\text{-}F}$ 246.1), (-109.1)-(-110.0) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 246.1); minor conformer: -98.9 (1F, dd, $^2J_{F\text{-}F}$ 265.3, $^3J_{F\text{-}H}$ 23.3), -

100.1 (1F, d, $^{2}J_{F\text{-}F}$ 265.3); [HRMS (EI, $M^{+}$) Found 296.10714. Calc. for $C_{12}H_{18}F_2O_6$ 296.10715]; *m/z* (EI) 296 (1 %, $M^{+}$), 281 (1, $M^{+}$-Me), 278 (1, M-$H_2O$), 263 (1, M-Me-$H_2O$), 254 (3, M-Ac), 236 (4, M-OAc), 216 (8, M-OAc-HF), 194 (17, M-OAc-Ac), 176 (25, M-OAc-OAc), 156 (72, M-OAc-OAc-HF), 113 (78), 87 (100). Data for **273**: mp 142-144 °C; $R_f$ (40 % ethyl acetate in hexane) 0.10; (Found: C, 48.74; H, 5.99; $C_{12}H_{18}F_2O_6$ requires: C, 48.65; H, 6.12 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3478br, 3387br, 1743s, 1318m, 1225s, 1017s; $\delta_H$ (400 MHz, $CDCl_3$) 5.40-5.32 (1H, m, incl. app. dd, *J* 3.7, $^{4}J$ 1.2, $CF_2CHOAc$), 5.21 (1H, dt, *J* 3.9, $^{4}J_{H\text{-}F}$ 1.6, $CF_2CHOAcCHOAc$), 3.02 (2H, br s, O*H*), 2.48 (1H, dd, $^{3}J_{H\text{-}F}$ 31.3, $^{2}J$ 14.9, $CF_2CH_aH_b$), 2.22-2.08 (1H, m, $CF_2CH_aH_b$), 2.14 (6H, m, $C(O)CH_3$), 1.28 (6H, m, $CH_3$); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.4 (C-9), 169.1 (C-9), 119.2 (dd, $^{1}J_{C\text{-}F}$ 247.7, 246.1, C-5), 77.4 (C-2), 74.4 (C-3), 73.8 (C-1), 69.0 (dd, $^{2}J_{C\text{-}F}$ 26.4, 24.8, C-6), 41.4 (t, $^{2}J_{C\text{-}F}$ 20.8, C-4), 31.0 (C-7), 23.4 (dd, $^{4}J_{C\text{-}F}$ 2.4, $^{4}J_{C\text{-}F}$ 1.6, C-8), 20.8 (C-10), 20.7 (C-10); $\delta_F$ (376.5 MHz, $CDCl_3$, 213K) major conformer: -99.0 (1F, d, $^{2}J_{F\text{-}F}$ 254.6), (-104.2)-(-105.1) (1F, m, incl. app. d, $^{2}J_{F\text{-}F}$ 254.6); minor conformer: -101.3 (1F, d, $^{2}J_{F\text{-}F}$ 265.3), (-101.7)- (-102.6) (1F, m, incl. app. dd, $^{2}J_{F\text{-}F}$ 265.3, $^{3}J_{F\text{-}H}$ 31.3); [HRMS (EI, $M^{+}$) Found 296.10721. Calc. for $C_{12}H_{18}F_2O_6$ 296.10715]; *m/z* (EI) 296 (1 %, $M^{+}$), 281 (1, $M^{+}$-Me), 278 (1, M-$H_2O$), 263 (2, M-Me-$H_2O$), 254 (3, M-Ac), 236 (4, M-OAc), 216 (7, M-OAc-HF), 194 (16, M-OAc-Ac), 176 (24, M-OAc-OAc), 156 (70, M-OAc-OAc-HF), 113 (77), 87 (100).

**(1*R**,2*R**,3*S**,4*S**)-5,5-difluorocyclohexane-1,2,3,4-tetrol 283**



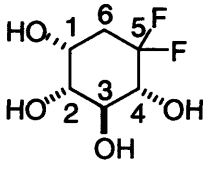

**283**

A solution of tetraacetate **262** (0.13 mmol, 44 mg) in dichloromethane (1 mL) was added to a vessel containing wet, freshly washed Dowex® 50w x 8-400 mesh (4.4 g, 100 eq. by weight). The organic solvent was driven off by evaporation under a stream of $N_2$. The gas flow was discontinued after solvent was removed after 5-10 min, and the open vessel was heated at 100 °C without stirring or agitation for 3 hours. The reaction mixture was allowed to cool to room temperature, filtered and rinsed with methanol (15 mL) through a filter. The filtrate was concentrated *in vacuo* to afford tetrol **283** (21.5 mg, 93 %, 98 % by GC) as a colourless oil; $R_f$ (10 % methanol in dichloromethane) 0.1; $\upsilon_{max}$(neat)/cm$^{-1}$ 3436br, 3306br, 3212br, 1213m, 1061s, 1045s ; $\delta_H$ (400 MHz, methanol-$d_4$) 4.06 (1H, dddd, *J* 7.3, 4.6, 3.1, $^4J_{H\text{-}F}$ 2.0, $CH_2CHOH$), 3.93 (1H, dd, *J* 6.4, 3.5, $H^3$), 3.91 (1H, ddd, $^3J_{H\text{-}F}$ 15.2, *J* 3.5, $^4J$ 1.0, $CF_2CHOH$), 3.84 (1H, dd, *J* 6.4, 3.1, $H^2$ ), 2.26-2.17 (1H, m, incl. app. ddd, $^2J$ 14.1, *J* 4.6, $^4J$ 0.6, $CF_2CH_aH_b$), 2.17-2.07 (1H, m, incl. app. ddd, $^2J$ 14.1, *J* 7.3, $^4J$ 1.0, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.2 (t, $^1J_{C\text{-}F}$ 241.1, C-5), 72.4 (C-2), 71.6 (t, $^3J_{C\text{-}F}$ 3.2, C-3), 71.2 (d, $^2J_{C\text{-}F}$ 27.2, C-4), 66.9 (dd, $^3J_{C\text{-}F}$ 6.4, 4.8, C-1), 35.6 (t, $^2J_{C\text{-}F}$ 22.4, C-6); $\delta_F$ (376.5 MHz, methanol-$d_4$, 213 K) major conformer: -101.1 (1F, d, $^2J_{F\text{-}F}$ 255.2), -101.9 (1F, dd, $^2J_{F\text{-}F}$ 255.2, $^3J_{F\text{-}H}$ 29.9); minor conformer: -98.0 (1F, d, $^2J_{F\text{-}F}$ 244.8), (-112.0)-(-112.8) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 244.8, $^3J_{F\text{-}H}$ 21.8); [HRMS (FAB, $MNa^+$) Found 207.04457. Calc. for $C_6H_{10}F_2O_4Na$ 207.04452];

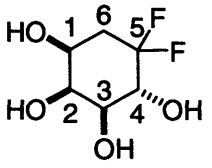
*m/z* (EI) 166 (2 %, M-$H_2O$), 148 (5, M-$H_2O$-$H_2O$), 146 (6, M-$H_2O$-HF), 128 (12, M-$H_2O$-$H_2O$-HF), 73 (100).

**(1*R**,2*R**,3*S**,4R*)-5,5-difluorocyclohexane-1,2,3,4-tetrol 284**

**(1*S**,2*S**,3*S**,4R*)-5,5-difluorocyclohexane-1,2,3,4-tetrol 285**




**284**

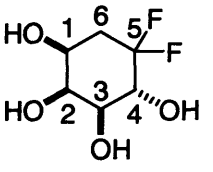



**285**

Potassium carbonate (0.38 mmol, 53 mg, 5 eq.) was added to a solution of tetraacetates **264** and **265** (77 μmol, 27 mg) in methanol (2 mL). The suspension was stirred at room temperature for 2 days. The reaction was filtered through silica, the filter bed was rinsed with methanol (20 mL) and the combined filtrate and washings were concentrated *in vacuo* to afford a mixture of tetrols **284** and **285** (12.5 mg, 88 %, 97 % by GC) as a colourless oil; $\upsilon_{max}$(neat)/$cm^{-1}$ 3431br, 3324br, 3257br, 1290m, 1038s, 1024s ; data for **284**: $R_f$ (20 % methanol in dichloromethane) 0.30; $\delta_H$ (400 MHz, methanol-$d_4$) 4.06-4.02 (1H, m, $CH_2CHOH$), 3.79 (1H, td, *J* 9.0, $^4J_{H\text{-}F}$ 2.0, $H^3$), 3.56 (1H, ddd, $^3J_{H\text{-}F}$ 18.8, *J* 9.0, $^3J_{H\text{-}F}$ 3.9, $CF_2CHOH$), 3.50 (1H, dd, *J* 9.0, 3.3, $H^2$), 2.36-2.26 (1H, m, incl. app. ddd, $^2J$ 15.1, $^3J_{H\text{-}F}$ 7.2, *J* 3.9, $CF_2CH_aH_b$), 2.02 (1H, dddd, $^3J_{H\text{-}F}$ 32.1, $^2J$ 15.1, $^3J_{H\text{-}F}$ 6.1, *J* 3.5, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.0 (dd, $^1J_{C\text{-}F}$ 247.7, 242.9, C-5), 75.1 (t, $^2J_{C\text{-}F}$ 20.8, C-4), 74.7 (d, $^4J_{C\text{-}F}$ 2.4, C-2), 72.3 (d, $^3J_{C\text{-}F}$ 8.8, C-3), 68.1 (d, $^3J_{C\text{-}F}$ 11.2, C-1), 36.7 (t, $^2J_{C\text{-}F}$ 22.4, C-6); $\delta_F$ (376.5 MHz, methanol-$d_4$, 328 K) -101.2 (1F, ddtd, $^2J_{F\text{-}F}$ 248.2, $^3J_{F\text{-}H}$ 8.2, 6.1, $^4J_{F\text{-}H}$ 3.4),

(-109.6)-(-110.5) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 248.2, $^3J_{F\text{-}H}$ 32.1, 18.8); [HRMS (FAB, $MNa^+$) Found 207.04447. Calc. for $C_6H_{10}F_2O_4Na$ 207.04452]; *m/z* (EI) 166 (1 %, M-$H_2O$), 148 (2, M-$H_2O$-$H_2O$), 146 (1, M-$H_2O$-HF), 128 (8, M-$H_2O$-$H_2O$-HF), 73 (100). Data for **285**: $R_f$ (20 % methanol in dichloromethane) 0.30; $\delta_H$ (400 MHz, methanol-$d_4$) 3.98-3.96 (1H, m, $H^2$), 3.86 (1H, ddd, $^3J_{H\text{-}F}$ 21.0, *J* 9.9, $^3J_{H\text{-}F}$ 5.6, $CF_2CHOH$), 3.74 (1H, dddd, *J* 11.8, 5.0, 2.6, $^4J_{H\text{-}F}$ 1.5, $CH_2CHOH$), 3.48 (1H, ddd, *J* 9.9, 2.6, $^4J_{H\text{-}F}$ 1.9, $H^3$), 2.21 (1H, dddd, $^3J_{H\text{-}F}$ 35.1, $^2J$ 13.2, *J* 11.8, $^3J_{H\text{-}F}$ 3.8, $CF_2CH_aH_b$), 2.18-2.06 (1H, m, incl. app. ddd, $^2J$ 13.2, *J* 5.0, $^4J$ 1.2, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 122.2 (dd, $^1J_{C\text{-}F}$ 246.1, 241.3, C-5), 74.0 (d, $^4J_{C\text{-}F}$ 2.4, C-2), 72.3 (d, $^3J_{C\text{-}F}$ 9.6, C-3), 72.2 (t, $^2J_{C\text{-}F}$ 20.8, C-4), 67.1 (d, $^3J_{C\text{-}F}$ 12.8, C-1), 36.5 (dd, $^2J_{C\text{-}F}$ 23.2, 20.8, C-6); $\delta_F$ (376.5 MHz, methanol-$d_4$) (-104.1)-(-104.9) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 248.2), -116.8 (1F, ddd, $^2J_{F\text{-}F}$ 248.2, $^3J_{F\text{-}H}$ 21.0, 11.0); [HRMS (FAB, $MH^+$) Found 185.06260. Calc. for $C_6H_{11}F_2O_4$ 185.06254]; *m/z* (EI) 166 (1 %, M-$H_2O$), 148 (3, M-$H_2O$-$H_2O$), 146 (6, M-$H_2O$-HF), 144 (12, M-HF-HF), 128 (7, M-$H_2O$-$H_2O$-HF), 73 (100).

**(1*S**,2*S**,3*S**,4*R**)-5,5-difluorocyclohexane-1,2,3,4-tetrol 285**

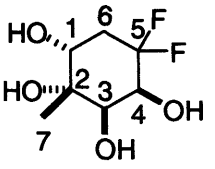



**285**

A solution of tetraacetate **265** (57 µmol, 20 mg) in dichloromethane (1 mL) was added to a vessel containing wet, freshly washed Dowex® 50w x 8-400 mesh (2.0 g, 100 eq. by weight). The organic solvent was driven off by evaporation

under a stream of $N_2$. The gas flow was discontinued after solvent was removed after 5-10 min, and the open vessel was heated at 100 °C without stirring or agitation for 3 hours. The reaction mixture was allowed to cool to room temperature, filtered and rinsed with methanol (15 mL) through a filter. The filtrate was concentrated *in vacuo* to afford tetrol **285** (9.3 mg, 91 %, 99 % by GC) as a colourless oil. Data were in agreement with those reported previously.

**(1*R**,2*R**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol 286**

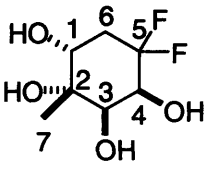



**286**

A solution of triacetate **266** (48 µmol, 17 mg) in dichloromethane (1 mL) was added to a vessel containing wet, freshly washed Dowex® 50w x 8-400 mesh (1.7 g, 100 eq. by weight). The organic solvent was driven off by evaporation under a stream of $N_2$. The gas flow was discontinued after solvent was removed after 5-10 min, and the open vessel was heated at 100 °C without stirring or agitation for 1.25 hours. The reaction mixture was allowed to cool to room temperature, filtered and rinsed with methanol (15 mL) through a filter. The filtrate was concentrated *in vacuo* to afford tetrol **286** (9.9 mg, 95 %, 100 % by GC) as a white solid; mp 57-59 °C; $R_f$ (100 % ethyl acetate) 0.32; $\upsilon_{max}$(neat)/cm$^{-1}$ 3501br, 3372br, 3307br, 3246br, 1289m, 1187m, 1046s, 1020s; $\delta_H$ (400 MHz, methanol-$d_4$) 4.02 (1H, ddd, $^3J_{H\text{-}F}$ 22.4, 6.6, *J* 4.0, $CF_2CHOH$), 3.77 (1H, ddd, *J* 8.7, 8.0, $^4J_{H\text{-}F}$ 0.9, $CH_2CHOH$), 3.66 (1H, ddd, $^4J_{H\text{-}F}$ 6.2, *J* 4.0, $^4J_{H\text{-}F}$ 1.6, $H^3$),

2.21-2.08 (1H, m, $CF_2CH_2$), 1.34 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.0 (dd, $^1J_{C\text{-}F}$ 246.9, 242.9, C-5), 77.6 (d, $^3J_{C\text{-}F}$ 8.8, C-3), 74.8 (C-2), 69.8 (dd, $^2J_{C\text{-}F}$ 21.6, 18.4, C-4), 68.9 (d, $^3J_{C\text{-}F}$ 11.2, C-1), 37.9 (dd, $^2J_{C\text{-}F}$ 23.2, 20.8, C-6), 22.9 (C-7); $\delta_F$ (376.5 MHz, methanol-$d_4$) (-98.1)-(-98.8) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 245.5, $^3J_{F\text{-}H}$ 6.6), (-111.5)-(-112.5) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 245.5, $^3J_{F\text{-}H}$ 22.4); [HRMS (FAB, $MNa^+$) Found 221.06025. Calc. for $C_7H_{12}F_2O_4Na$ 221.06017]; *m/z* (EI) 180 (5 %, M-$H_2O$), 163 (2, M-HF-Me), 162 (18, M-$H_2O$-$H_2O$), 160 (3, M-$H_2O$-HF), 145 (2, M-HF-Me-$H_2O$), 142 (11, M-$H_2O$-$H_2O$-HF), 140 (3, M-HF-HF-$H_2O$), 125 (5, M-Me-$H_2O$-HF-HF), 122 (3, M-HF-HF-$H_2O$-$H_2O$), 117 (100).

**(1*R**,2*R**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol 286**

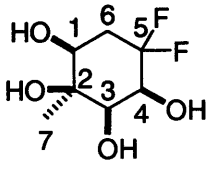



**286**

Benzeneboronic acid (0.75 mmol, 91.4 mg, 2 eq.) was added to a solution of diol **196** (0.375 mmol, 62 mg) in dichloromethane (4 mL) under a $N_2$ atmosphere. The reaction was stirred at room temperature for 1 hour. Osmium tetroxide (0.75 mL of a 1 mM solution in dichloromethane, 0.75 µmol, 0.2 mol%) and NMO (0.41 mmol, 56 mg, 2.0 eq.) were added to the reaction mixture and stirred overnight at room temperature. The reaction was quenched with sodium sulfite (1 mL of a saturated aqueous solution) and the mixture was stirred for 1 hour. The aqueous layer was extracted with dichloromethane (3 x 10 mL), and

the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was taken up in a 1:1 mixture of ethyl acetate-acetone (2 mL). Hydrogen peroxide (0.43 mL of a 30 % solution in water, 3.75 mmol, 10 eq.) was then added and the mixture stirred overnight at room temperature. $NaSO_4$ (*ca.* 5g) was added and the mixture was filtered through silica, and the filter rinsed with ethyl acetate (30 mL). The combined initial filtrate and washings were concentrated *in vacuo* then purified by column chromatography (50 % ethyl acetate in hexane) to afford tetrol **286** (27 mg, 37 % over 2 steps, 100 % by GC) as a white solid. Data were in agreement with those reported previously.

**(1*S**,2*S**,3*R**,4*S**)-5,5-difluoro-2-methylcyclohexane-1,2,3,4-tetrol 287**

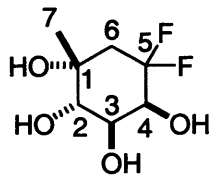



**287**

A solution of triacetate **267** (0.216 mmol, 70 mg) in dichloromethane (1 mL) was added to a vessel containing wet, freshly washed Dowex® 50w x 8-400 mesh (7.0 g, 100 eq. by weight). The organic solvent was driven off by evaporation under a stream of $N_2$. The gas flow was discontinued after solvent was removed after 5-10 min, and the open vessel was heated at 100 °C without stirring or agitation for 1.5 hours. The reaction mixture was allowed to cool to room temperature, filtered and rinsed with methanol (15 mL) through a filter. The filtrate was concentrated *in vacuo* to afford tetrol **287** (41 mg, 96 %, 99 % by

GC) as white solids; mp 154-156 °C; $R_f$ (100 % ethyl acetate) 0.32; $\upsilon_{max}$(neat)/cm$^{-1}$ 3480br, 3395br, 3323br, 3236br, 1289m, 1039s, 1018s; $\delta_H$ (400 MHz, methanol-$d_4$) 3.82 (1H, dddd, $^3J_{H\text{-}F}$ 7.0, 4.3, $J$ 3.2, $^4J$ 1.9, $CF_2CHOH$), 3.47 (1H, dddd, $J$ 12.0, 4.8, $^4J_{H\text{-}F}$ 1.4, 0.5, $CH_2CHOH$), 3.37 (1H, td, $^4J_{H\text{-}F}$ 3.2, $J$ 3.2, $^4J_{H\text{-}F}$ 2.0, $H^3$), 2.33 (1H, dddd, $^3J_{H\text{-}F}$ 36.5, $^2J$ 13.5, $J$ 12.0, $^3J_{H\text{-}F}$ 4.3, $CF_2CH_aH_b$), 2.06 (1H, ddddd, $^2J$ 13.5, $^3J_{H\text{-}F}$ 10.4, 5.9, $J$ 4.8, $^4J$ 1.9, $CF_2CH_aH_b$), 1.30 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 122.7 (dd, $^1J_{C\text{-}F}$ 251.7, 237.3, C-5), 77.1 (C-2), 74.2 (dd, $^2J_{C\text{-}F}$ 32.8, 21.6, C-4), 70.9 (dd, $^3J_{C\text{-}F}$ 8.8, C-3), 70.8 (d, $^3J_{C\text{-}F}$ 11.2, C-1), 34.3 (t, $^2J_{C\text{-}F}$ 22.4, C-6), 21.7 (C-7); $\delta_F$ (376.5 MHz, methanol-$d_4$) (-104.2)-(-105.0) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 257.5, $^3J_{F\text{-}H}$ 6.6), (-106.4)-(-107.3) (1F, m, incl. app. ddd, $^2J_{F\text{-}F}$ 257.5, $^3J_{F\text{-}H}$ 36.5, 10.4); [HRMS (EI, $M^+$) Found 198.07042. Calc. for $C_7H_{12}F_2O_4$ 198.07037]; *m/z* (EI) 180 (10 %, M-$H_2O$), 163 (2, M-HF-Me), 162 (22, M-$H_2O$-$H_2O$), 160 (3, M-$H_2O$-HF), 158 (1, M-HF-HF), 145 (1, M-HF-Me-$H_2O$), 142 (10, M-$H_2O$-$H_2O$-HF), 140 (4, M-HF-HF-$H_2O$), 125 (7, M-Me-$H_2O$-HF-HF), 122 (5, M-HF-HF-$H_2O$- $H_2O$), 117 (100).

**(1R*,2S*,3S*,4S*)-5,5-difluoro-1-methylcyclohexane-1,2,3,4-tetrol 274**

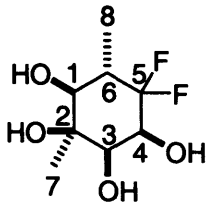



**274**

Osmium tetroxide (61 µL of a 2.5 wt. % solution in *tert*-butanol, 6.1 µmol, 2 mol%) was added to a cool (0 °C) solution of diol **197** (0.30 mmol, 50 mg) and NMO.$H_2O$ (0.61 mmol, 84 mg, 2.0 eq.) in a mixture of acetone (0.3 mL), water

(0.3 mL) and *tert*-butanol (0.15 mL). The reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with solid sodium sulfite (100 mg) and stirred overnight. Solid $Na_2SO_4$ (*ca.* 10g) was added followed by ethyl acetate (5 mL). The mixture was filtered through silica, and the filter rinsed with ethyl acetate (30 mL). The combined initial filtrate and washings were concentrated *in vacuo* then freeze-dried to afford tetrol **274** (57 mg, 95 %, 100 % by GC) as a single diastereoisomer as a white solid ; mp 90-92 °C; $R_f$ (10 % methanol in dichloromethane) 0.55; (Found: C, 42.31; H, 6.00; $C_7H_{12}F_2O_4$ requires: C, 42.43; H, 6.10 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3487br, 3356br, 3297br, 3221br, 1289m, 1191m, 1048s, 1031s ; $\delta_H$ (400 MHz, methanol-$d_4$) 3.93-3.85 (1H, m, $CF_2CHOH$), 3.85-3.76 (1H, m, incl. app. d, *J* 9.8, $H^3$), 3.56 (1H, d, *J* 9.8, $H^2$), 2.15 (1H, ddd, $^3J_{H\text{-}F}$ 33.6, $^2J$ 14.9, $^3J_{H\text{-}F}$ 6.6, $CF_2CH_aH_b$), 2.11-1.96 (1H, m, $CF_2CH_aH_b$), 1.28 (s, $CH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.1 (dd, $^1J_{C\text{-}F}$ 245.9, 244.1, C-5), 74.5 (C-2), 73.5 (dd, $^2J_{C\text{-}F}$ 32.9, 22.1, C-4), 71.2 (d, $^3J_{C\text{-}F}$ 11.4, C-1), 70.9 (d, $^3J_{C\text{-}F}$ 7.3, C-3), 40.5 (t, $^2J_{C\text{-}F}$ 21.5, C-6), 27.7 (C-7); $\delta_F$ (282 MHz, methanol-$d_4$) -102.9 (1F, d, $^2J_{F\text{-}F}$ 255.0), -105.2 (1F, ddd, $^2J_{F\text{-}F}$ 255.0, $^3J_{F\text{-}H}$ 33.6, 11.4); [HRMS (FAB, $[M\text{-}H]^-$) Found 197.060252. Calc. for $C_7H_{11}F_2O_4$ 197.06254]; *m/z* (ES-) 197 (15 %, $[M\text{-}H]^-$), 177 (10, $[M\text{-}H]^-$-HF), 114 (100).

**(1*S**,2*S**,3*R**,4*S**,6*S**)-5,5-difluoro-2,6-dimethylcyclohexane-1,2,3,4-tetrol 288**



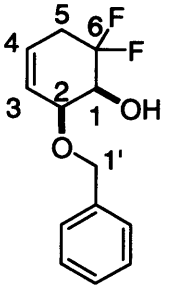

**288**

A solution of triacetate **269** (0.115 mmol, 39 mg) in dichloromethane (1 mL) was added to a vessel containing wet, freshly washed Dowex® 50w x 8-400 mesh (3.9 g, 100 eq. by weight). The organic solvent was driven off by evaporation under a stream of $N_2$. The gas flow was discontinued after solvent was removed after 5-10 min, and the open vessel was heated at 100 °C without stirring or agitation for 1.75 hours. The reaction mixture was allowed to cool to room temperature, filtered and rinsed with methanol (15 mL) through a filter. The filtrate was concentrated *in vacuo* to afford tetrol **288** (18 mg, 75 %, 100 % by GC) as a colourless oil; $R_f$ (20 % methanol in dichloromethane) 0.68; $\upsilon_{max}$(neat)/cm$^{-1}$ 3503br, 3335br, 1289m, 1029s, 1021s; $\delta_H$ (400 MHz, methanol-$d_4$) 3.86 (1H, ddd, $^3J_{H\text{-}F}$ 7.5, 4.4, *J* 3.3, $CF_2CHOH$), 3.37 (1H, td, $^4J_{H\text{-}F}$ 3.3, *J* 3.3, $^4J_{H\text{-}F}$ 2.2, *H*$^3$), 3.02 (1H, dt, *J* 11.0, $^4J_{H\text{-}F}$ 1.0, *H*$^1$), 2.37 (1H, ddqd, $^3J_{H\text{-}F}$ 29.5, *J* 11.0, 6.7, $^3J_{H\text{-}F}$ 3.3, $CF_2CHCH_3$), 1.30 (3H, s, $CHOHCH_3$), 1.16 (3H, d, *J* 6.7, $CF_2CHCH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 123.5 (dd, $^1J_{C\text{-}F}$ 253.2, 240.5, C-5), 70.4 (dd, $^3J_{C\text{-}F}$ 8.8, C-3), 76.2 (d, $^3J_{C\text{-}F}$ 10.4, C-1), 77.4 (C-2), 74.6 (dd, $^2J_{C\text{-}F}$ 34.0, 22.0, C-4), 36.8 (t, $^2J_{C\text{-}F}$ 20.8, C-6), 22.2 (C-7), 8.3 (dd, $^3J_{C\text{-}F}$ 4.8, 2.4, C-8); $\delta_F$ (376.5 MHz, methanol-$d_4$) -111.5 (1F, ddt, $^2J_{F\text{-}F}$ 258.0, $^3J_{F\text{-}H}$ 7.5, 3.3, $^4J_{H\text{-}F}$ 3.3,), -120.5 (1F, dddd, $^2J_{F\text{-}F}$ 258.0, $^3J_{F\text{-}H}$ 29.5, 4.4, $^4J_{F\text{-}H}$ 2.2); [HRMS (FAB+,

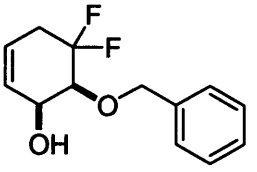
$MH^+$) Found 213.09381. Calc. for $C_8H_{15}F_2O_4$ 213.09384]; *m/z* (EI) 194 (21 %, M-$H_2O$), 179 (2, M-Me-$H_2O$) 176 (12, M-$H_2O$-$H_2O$), 161 (4, M-Me-$H_2O$-$H_2O$), 156 (9, M-$H_2O$-$H_2O$-HF), 141 (5, M-Me-$H_2O$-$H_2O$-HF), 131 (92, M-Me-$H_2O$-HF-CO), 108 (100).

**(1*S**,2*S**)-2-(Benzyloxy)-6,6-difluorocyclohex-3-en-1-ol 294**

**(1*S**,2*S**)-6-(Benzyloxy)-5,5-difluorocyclohex-2-en-1-ol 295**




**294**




**295**

Dibutyltin methoxide (0.55 mmol, 126 µL) was added to a solution of diol **192** (0.5 mmol, 75 mg) in toluene (25 mL). The mixture was heated at reflux and 10 mL of toluene was distilled over to remove the methanol formed. The reaction mixture was allowed to cool to room temperature then benzyl bromide (0.55 mmol, 67 µL) and tetrabutyl ammonium iodide (0.75 mmol, 283 mg) were added in one portion. The mixture was heated at reflux overnight. The reaction was quenched with water (5 mL), extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver a mixture of regioisomers **294** and **295** (12:1) as a yellow solid (640 mg) which was purified by flash chromatography (15 % ethyl acetate in hexane) to afford a mixture (12:1) of regioisomers **294** and **295** as a white solid. The regioisomers

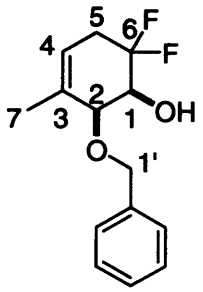
were separated by recrystallisation from hot hexane to deliver pure monobenzyl ether **294** (102 mg, 85 %) as colourless plates; mp 48-50 °C; $R_f$ (40 % ethyl acetate in hexane) 0.19; (Found: C, 65.15; H, 5.79; $C_{13}H_{14}F_2O_2$ requires: C, 64.99; H, 5.87 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3371br, 1322m, 1032s; $\delta_H$ (300 MHz, $CDCl_3$) 7.39-7.29 (5H, m, Ar*H*), 5.74-5.59 (2H, m, *HC*=C*H*), 4.67 (1H, d, $^2J$ 11.4, C$H_a$H$_b$Ph), 4.65 (1H, d, $^2J$ 11.4, CH$_a$$H_b$Ph), 4.28-4.22 (1H, m, HC=CHC*H*OH), 4.18-4.10 (1H, m, incl. app. d, $^3J_{H\text{-}F}$ 11.8, $CF_2$C*H*OH), 2.89-2.67 (2H, m, incl. app. d, $^3J_{H\text{-}F}$ 29.9, $CF_2$C$H_a$H$_b$, O*H*), 2.54-2.38 (1H, m, incl. app. d, $^3J_{H\text{-}F}$ 15.6, $CF_2$CH$_a$$H_b$); $\delta_C$ (75 MHz, $CDCl_3$) 137.2 (Ar), 128.7 (Ar), 128.2 (Ar), 127.9 (Ar), 124.8 (d, $^4J_{C\text{-}F}$ 1.8, C-3), 124.1 (d, 122.1, $^3J_{C\text{-}F}$ 10.8, C-4), (dd, $^1J_{C\text{-}F}$ 250.7, 237.0, C-6), 74.9 (dd, $^3J_{C\text{-}F}$ 6.0, 1.8, C-2), 71.4 (C-1'), 67.3 (dd, $^2J_{C\text{-}F}$ 33.5, 22.1, C-1), 31.1 (dd, $^2J_{C\text{-}F}$ 26.3, 24.5, C-5); $\delta_F$ (282 MHz, $CDCl_3$) (-102.4)-(-103.5) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 254.5), -107.9 (1F, dddt, $^2J_{F\text{-}F}$ 254.5, $^3J_{F\text{-}H}$ 29.9, 15.6, $^4J_{F\text{-}H}$ 2.4); [HRMS (EI, M$^+$) Found 240.09623. Calc. for $C_{13}H_{14}F_2O_2$ 240.09619]; *m/z* (EI) 240 (13 %, M$^+$), 222 (1, M-$H_2O$), 149 (21, M-$CH_2$Ph), 91 (100, $CH_2$Ph).

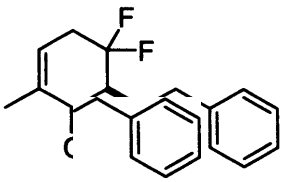
The stereochemistry and identity of this product were confirmed by XRD analysis; $C_{13}H_{14}F_2O_2$, crystal size 0.07 x 0.15 x 0.24 mm$^3$, *M* = 240.24, crystal system triclinic, unit cell dimensions a = 6.4573(16), b = 8.499(2), c = 11.186(3) Å, $\alpha$ = 77.975(5)°, $\beta$ = 76.852(5)°, $\gamma$ = 87.668(5)°, U = 584.7(3) Å$^3$, T = 150(2) K, space group P-1, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.112 mm$^{-1}$, 4258 reflections collected 2036 unique [R(int) = 0.0508], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0778, wR2 = 0.1917; R indices (all data) R1 = 0.1121, wR2 = 0.2124.

The minor regioisomer **295** could not be obtained pure. Significant peaks at: $\delta_F$ (282 MHz, $CDCl_3$) (-99.8)-(-100.8) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 254.9), -105.2 (1F, dddd, $^2J_{F\text{-}F}$ 254.9, $^3J_{F\text{-}H}$ 30.2, 15.2, $^4J_{F\text{-}H}$ 2.8)

**(1*S**,2*S**)-2-(Benzyloxy)-6,6-difluoro-3-methylcyclohex-3-en-1-ol 296**

**(1*S**,6*S**)-6-(Benzyloxy)-5,5-difluoro-2-methylcyclohex-2-en-1-ol 297**




**296** **297**

Dibutyltin methoxide (2.2 mmol, 505 μL) was added to a solution of diol **196** (2.0 mmol, 330 mg) in toluene (100 mL). The mixture was heated at reflux and 50 mL of toluene was distilled over to remove the methanol formed. The reaction mixture was allowed to cool to room temperature then benzyl bromide (2.2 mmol, 267 μL) and tetrabutyl ammonium iodide (3.0 mmol, 1.13 g) were added in one portion. The mixture was heated at reflux overnight. The reaction was quenched with water (15 mL), extracted with ethyl acetate (3 x 15 mL), washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver a mixture of regioisomers **296** and **297** (12:1) as a yellow oil which was purified by flash chromatography (15 % ethyl acetate in hexane) to afford a mixture (12:1) of regioisomers **296** and **297** as a white solid. The regioisomers were separated by recrystallisation from hot hexane to deliver pure monobenzyl ether **296** (419 mg, 83 %) as colourless plates; mp 50-51 °C; $R_f$ (20 % ethyl acetate in hexane) 0.50; (Found: C, 66.27; H, 6.28; $C_{14}H_{16}F_2O_2$ Requires: C, 66.13; H, 6.34 %); $\upsilon_{max}$(neat)/cm$^{-1}$ 3416br, 1318m, 1120m, 1041s; $\delta_H$ (300 MHz, $CDCl_3$) 5.42-5.35 (1H, m, *H*C=C($CH_3$)), 4.74 (1H, d, $^2J$ 11.4, OC*H*$_a$H$_b$Ph), 4.62 (1H, d, $^2J$ 11.4, OCH$_a$*H*$_b$Ph), 4.20-4.08 (2H, m, $CF_2$C*H*OH, $CF_2$CHOHC*H*OH), 2.89-2.66

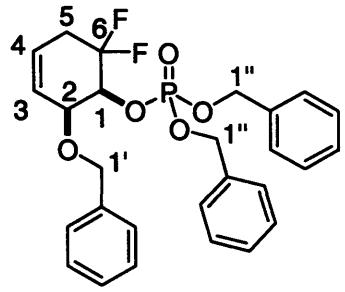
(2H, m, $CF_2CH_aCH_b$, O*H*), 2.50-2.32 (1H, m, $CF_2CH_aCH_b$), 1.85-1.75 (3H, m, HC=C$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 137.3 (Ar), 132.0 (d, $^4J_{C\text{-}F}$ 1.8, C-3), 128.7 (Ar), 128.4 (Ar), 128.2 (Ar), 122.5 (dd, $^1J_{C\text{-}F}$ 250.7, 235.8, C-6), 118.8 (d, $^3J_{C\text{-}F}$ 11.4, C-4), 77.7 (dd, $^3J_{C\text{-}F}$ 6.6, 1.2, C-2), 72.4 (C-1'), 66.9 (dd, $^2J_{C\text{-}F}$ 34.7, 21.5, C-1), 30.9 (dd, $^2J_{C\text{-}F}$ 25.7, 24.5, C-5), 19.4 (C-7); $\delta_F$ (282 MHz, $CDCl_3$) (-102.2)-(-103.2) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 253.0), -108.9 (1F, dddt, $^2J_{F\text{-}F}$ 253.0, $^3J_{F\text{-}H}$ 30.8, 15.6, $^4J_{F\text{-}H}$ 2.4); [HRMS (FAB+, $MH^+$) Found 255.11956. Calc. for $C_{14}H_{17}F_2O_2$ 255.11966]; *m/z* (EI) 254 (1 %, $M^+$), 236 (1, M-$H_2O$), 163 (16, M-$CH_2Ph$), 107 (13, $PhCH_2O$), 91 (100, $PhCH_2$).

The stereochemistry and identity of this product were confirmed by XRD analysis; $C_{14}H_{16}F_2O_2$, crystal size 0.32 x 0.28 x 0.11 $mm^3$, *M* = 254.27, crystal system triclinic, unit cell dimensions a = 6.5179(17), b = 9.224(2), c = 11.151(3) Å, $\alpha$ = 73.533(4)°, $\beta$ = 76.994(4)°, $\gamma$ = 89.422(4)°, U = 625.4(3) $Å^3$, T = 150(2) K, space group P-1, absorption coefficient $\mu$ (Mo-K$\alpha$) = 0.108 $mm^{-1}$, 4514 reflections collected 2180 unique [R(int) = 0.0597], which were used in all calculations. Final R indices [I>2$\sigma$(I)] R1 = 0.0408, wR2 = 0.1035; R indices (all data) R1 = 0.0487, wR2 = 0.1083.

The minor regioisomer **297** could not be obtained pure. Significant peaks at: $\delta_F$ (282 MHz, $CDCl_3$) (-100.5)-(-101.5) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 252.6), -105.8 (1F, ddddd, $^2J_{F\text{-}F}$ 252.6, $^3J_{F\text{-}H}$ 29.4, 15.2, 3.3, $^4J_{F\text{-}H}$ 1.2).

**(1*S**,2*S**)-2-(benzyloxy)-6,6-difluorocyclohex-3-en-1-yl dibenzyl phosphate**

**298**

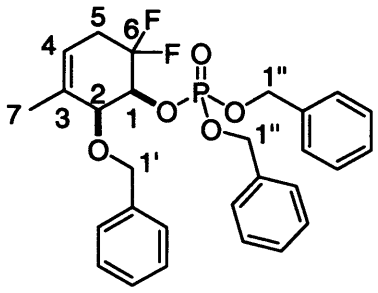



**298**

Sodium hydride (0.96 mmol, 23 mg of a 60 % w/w dispersion in paraffin oil) was washed with dry hexane (3 x 5 mL) under an atmosphere of argon. Monoprotected diol **294** (0.19 mmol, 46 mg) was added as a solution in dry tetrahydrofuran (4 mL) to a suspension of the washed sodium hydride in tetrahydrofuran (4 mL) under an atmosphere of argon. The reaction mixture was stirred for 30 minutes at room temperature then the suspension was cooled to 0 °C and tetrabenzyl pyrophosphate (0.23 mmol, 12.4 mg) was added as a solution in tetrahydrofuran (4 mL). The suspension was then stirred for 19 hours at room temperature. The reaction mixture was poured into a buffer solution (10 mL, PH 7) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and filtered through silica gel. The filtered bed was washed with dichloromethane (2 x 5 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to deliver crude phosphate **298** (100 mg) which was purified by column chromatography (20 % ethyl acetate in hexane) to afford phosphate **298** (83 mg, 86 %) as a colourless oil; $R_f$ (20 % ethyl acetate in hexane) 0.28; (Found: C, 64.84; H, 5.52; $C_{27}H_{27}F_2O_5P$ requires: C, 64.80; H, 5.44 %);

$\upsilon_{max}$(neat)/cm$^{-1}$ 1215m, 1140m, 999s; $\delta_H$ (400 MHz, $CDCl_3$) 7.40-7.17 (15H, m, Ar*H*), 5.73-5.67 (1H, m, incl. app. d, *J* 10.4, $CH_2CH{=}CH$), 5.67-5.60 (1H, m, $CH_2CH{=}CH$), 5.16-5.09 (1H, m, $CF_2CHOP$), 5.08 (1H, dd, $^2J$ 11.9, $^3J_{H\text{-}P}$ 7.1, P(O)OC$H_a$H$_b$Ph), 5.04 (1H, dd, $^2J$ 11.9, $^3J_{H\text{-}P}$ 7.8, P(O)OCH$_a$$H_b$Ph), 5.00 (1H, dd, $^2J$ 11.9, $^3J_{H\text{-}P}$ 7.2, P(O)OC$H_a$H$_b$Ph), 4.98 (1H, dd, $^2J$ 11.9, $^3J_{H\text{-}P}$ 7.0, P(O)OCH$_a$$H_b$Ph), 4.86 (1H, d, $^2J$ 11.6, CHOC$H_a$H$_b$Ph), 4.58 (1H, d, $^2J$ 11.6, CHOCH$_a$$H_b$Ph), 4.34-4.28 (1H, m, $CHOCH_2Ph$), 2.74-2.57 (1H, m, incl. app. ddd, $^3J_{H\text{-}F}$ 31.7, $^2J$ 18.0, $^3J_{H\text{-}F}$ 8.0, $CF_2CH_aH_b$), 2.57-2.45 (1H, m, incl. app. t, $^3J_{H\text{-}F}$ 18.0, $^2J$ 18.0, $CF_2CH_a$$H_b$); $\delta_C$ (100.6 MHz, $CDCl_3$) 137.6, 136.0, 135.9, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8 (all Ar), 126.1 (d, $^4J_{C\text{-}F}$ 1.6, C-3), 122.6 (d, $^3J_{C\text{-}F}$ 11.2, C-4), 120.7 (ddd, $^1J_{C\text{-}F}$ 254.0, 238.9, $^3J_{C\text{-}P}$ 6.4, C-6), 74.4 (dd, $^3J_{C\text{-}F}$ 6.0, 2.7, C-2), 72.5 (ddd, $^2J_{C\text{-}F}$ 36.0, 22.4, $^2J_{C\text{-}P}$ 5.6, C-1), 71.7 (C-1'), 69.7 (d, $^2J_{C\text{-}P}$ 5.6, C-1"), 69.2 (d, $^2J_{C\text{-}P}$ 5.6, C-1"), 31.6 (t, $^2J_{C\text{-}F}$ 25.2, C-5); $\delta_F$ (376.5 MHz, $CDCl_3$) -101.5 (1F, ddtd, $^2J_{F\text{-}F}$ 255.1, $^3J_{F\text{-}H}$ 8.4, 8.0, $^4J_{F\text{-}H}$ 8.0, 2.2), -106.3 (1F, dddd, $^2J_{F\text{-}F}$ 255.1, $^3J_{F\text{-}H}$ 31.7, $^3J_{F\text{-}H}$ 18.0, $^4J_{F\text{-}H}$ 3.7); $\delta_P$ (162 MHz, $CDCl_3$) -1.46; [HRMS (FAB+, $MH^+$) Found 501.16435. Calc. for $C_{27}H_{28}O_5F_2P$ 501.16424]; *m/z* (FAB+) 501 (86 %, $MH^+$), 423 (1, $MH^+$-Ph), 409 (2, $MH^+$-$CH_2Ph$), 321 (3, $MH^+$-$CH_2Ph$-$CH_2Ph$), 181 (100).

**(1*S**,2*S**)-2-(benzyloxy)-6,6-difluoro-3-methylcyclohex-3-en-1-yl dibenzyl phosphate 299**



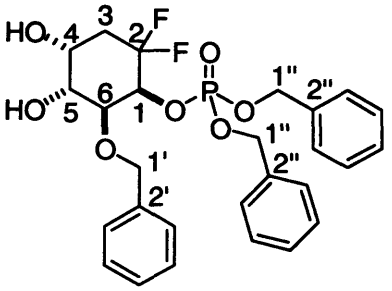

**299**

Sodium hydride (2.53 mmol, 101 mg of a 60 % w/w dispersion in paraffin oil) was washed with dry hexane (3 x 8 mL) under an atmosphere of argon. Monoprotected diol **296** (0.51 mmol, 128 mg) was added as a solution in dry tetrahydrofuran (1 mL) to a suspension of the washed sodium hydride in tetrahydrofuran (10 mL) under an atmosphere of argon. The reaction mixture was stirred for 30 minutes at room temperature then the suspension was cooled to 0 °C and tetrabenzyl pyrophosphate (0.56 mmol, 300 mg) was added as a solution in tetrahydrofuran (1 mL). The suspension was then stirred for 19 hours at room temperature. The reaction mixture was poured into a buffer solution (15 mL, PH 7) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered through silica gel. The filter bed was washed with dichloromethane (2 x 10 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to deliver crude phosphate **299** (271 mg) which was purified by column chromatography (20 % ethyl acetate in hexane) to afford phosphate **299** (205 mg, 79 %) as a colourless oil; $R_f$ (20 % ethyl acetate in hexane) 0.43; (Found: C, 65.36; H, 5.55; $C_{28}H_{29}F_2O_5P$ requires: C, 65.36; H, 5.68 %); $\upsilon_{max}$(neat)/$cm^{-1}$

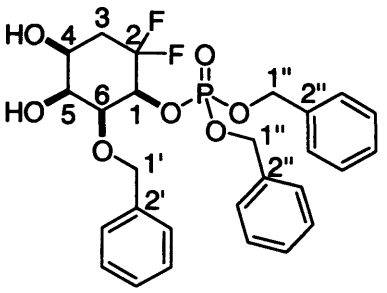
1216m, 1001s; $\delta_H$ (400 MHz, $CDCl_3$) 7.42-7.38 (2H, m, Ar*H*), 7.34-7.23 (11H, m, Ar*H*), 7.18-7.13 (2H, m, Ar*H*), 5.34-5.29 (1H, m, $CH_2CH$=$CCH_3$), 5.13 (1H, dddt, $^3J_{H\text{-}F}$ 10.6, *J* 9.5, $^4J_{H\text{-}P}$ 3.7, $^4J$ 1.2, $^3J_{H\text{-}F}$ 1.2, $CF_2CHOP$), 5.08 (1H, dd, $^2J$ 11.8, $^3J_{H\text{-}P}$ 7.2, P(O)OC$H_a$$H_b$Ph), 5.03 (1H, dd, $^2J$ 11.8, $^3J_{H\text{-}P}$ 7.8, P(O)OC$H_a$$H_b$Ph), 4.96 (1H, dd, $^2J$ 11.8, $^3J_{H\text{-}P}$ 7.2, P(O)OC$H_a$$H_b$Ph), 4.95 (1H, d, $^2J$ 11.3, CHOC$H_a$$H_b$Ph), 4.92 (1H, dd, $^2J$ 11.8, $^3J_{H\text{-}P}$ 6.8, P(O)OC$H_a$$H_b$Ph), 4.54 (1H, d, $^2J$ 11.3, CHOC$H_a$$H_b$Ph), 4.18-4.13 (1H, m, HC=$CCH_3$C*H*O$CH_2$Ph), 2.74-2.57 (1H, m, incl. app. ddd, $^3J_{H\text{-}F}$ 31.2, $^2J$ 18.0, $^3J_{H\text{-}F}$ 8.1, $CF_2CH_aH_b$), 2.53-2.39 (1H, m, incl. app. t, $^3J_{H\text{-}F}$ 18.0, $^2J$ 18.0, $CF_2CH_aH_b$); $\delta_C$ (100.6 MHz, $CDCl_3$) 137.7 (Ar), 136.0 (Ar), 135.9 (Ar), 133.1 (d, $^4J_{C\text{-}F}$ 1.6, C-3), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 120.8 (ddd, $^1J_{C\text{-}F}$ 253.2, 238.9, $^3J_{C\text{-}P}$ 6.4, C-6), 117.2 (d, $^3J_{C\text{-}F}$ 10.4, C-4), 76.6 (dd, $^3J_{C\text{-}F}$ 5.6, 2.4, C-2), 72.5 (ddd, $^2J_{C\text{-}F}$ 35.2, 22.4, $^2J_{C\text{-}P}$ 5.6, C-1), 72.5 (C-1'), 69.6 (d, $^2J_{C\text{-}P}$ 5.6, C-1"), 69.2 (d, $^2J_{C\text{-}P}$ 5.6, C-1"), 31.8 (t, $^2J_{C\text{-}F}$ 24.8, C-5), 19.4 (C-7); $\delta_F$ (376.5 MHz, $CDCl_3$) (-101.3)-(-102.1) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 252.8), -106.8 (1F, dddd, $^2J_{F\text{-}F}$ 252.8, $^3J_{F\text{-}H}$ 31.2, $^3J_{F\text{-}H}$ 18.0, $^4J_{F\text{-}H}$ 3.7); $\delta_P$ (162 MHz, $CDCl_3$) -1.47; [HRMS (FAB+, $MH^+$) Found 515.17981. Calc. for $C_{28}H_{30}O_5F_2P$ 515.17989]; *m/z* (FAB+) 515 (43 %, $MH^+$), 425 (4, $MH^+$-$CH_2Ph$), 281 (18, $MH^+$-HF-$H_2O$-Me-$CH_2Ph$-$CH_2Ph$), 207 (29, $MH^+$-HF-$H_2O$-$CH_2Ph$-$CH_2Ph$), 181 (100).

**(1*S**,4*R**,5*R**,6*S**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxycyclohexyl dibenzyl phosphate 302**

**(1*S**,4*S**,5*S**,6*S**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxycyclohexyl dibenzyl phosphate 303**



**302**



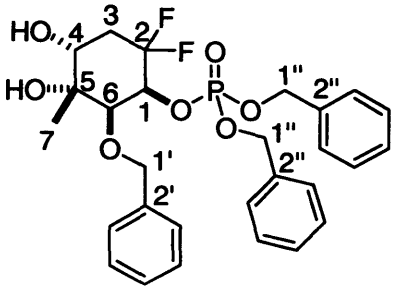
**303**

Osmium tetroxide (19 µL of a 2.5 wt. % solution in *tert*-butanol, 1.9 µmol, 2 mol%) was added to a cool (0 °C) solution of **298** (0.094 mmol, 47 mg) and NMO.$H_2O$ (0.19 mmol, 26 mg, 2.0 eq.) in a mixture of acetone (0.1 mL), water (0.1 mL) and *tert*-butanol (0.05 mL). The reaction mixture was stirred at room temperature for 3 days. The reaction was quenched with solid sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite. The filter bed was washed with methanol (20 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to deliver the crude phosphate esters as a mixture of diastereoisomers **302** and **303** (14:1) which were purified by flash chromatography (70 % ethyl acetate in hexane) to afford phosphate esters **302** and **303** as a mixture of diastereoisomers as a colourless oil (43 mg, 86 %); $\upsilon_{max}$(neat)/$cm^{-1}$ 3401br, 1605w, 1223m, 1092s, 1034s; [HRMS (FAB+, $MH^+$) Found 535.16967. Calc. for $C_{27}H_{30}O_7F_2P$ 535.16972]; *m/z* (FAB+) 557 (22 %, $MNa^+$), 535 (100, $MH^+$); data for **302**: $R_f$ (100 % ethyl acetate) 0.53; $\delta_H$ (400 MHz, methanol-$d_4$) 7.39-7.21 (15H, m, Ar*H*), 5.05 (2H,

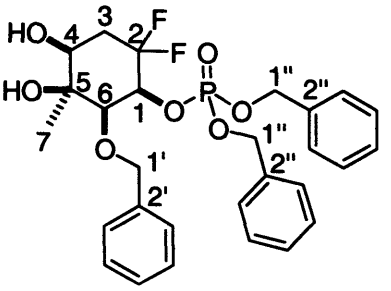
dd, $^{2}J$ 7.9, $^{3}J_{H\text{-}P}$ 2.9, P(O)OC$H_2$Ph), 5.04 (2H, dd, $^{2}J$ 7.9, $^{3}J_{H\text{-}P}$ 1.7, P(O)OC$H_2$Ph), 4.97-4.88 (1H, m, incl. app. d, $J$ 3.2, $CF_2CH$OP), 4.72 (1H, d, $^{2}J$ 11.5, CHOC$H_a$H$_b$Ph), 4.65 (1H, d, $^{2}J$ 11.5, CHOCH$_a$$H_b$Ph), 4.08 (1H, dddd, $J$ 6.7, 4.5, 3.1, $^{4}J_{H\text{-}F}$ 2.4, $CH_2CH$OH), 4.00-3.96 (1H, m, incl. app. dd, $J$ 7.3, 3.2, $CH$OCH$_2$Ph), 3.92 (1H, dd, $J$ 7.3, 3.1, $H^5$), 2.31-2.21 (1H, m, incl. app. dd, $^{2}J$ 14.3, $J$ 6.7, $CF_2CH_a$H$_b$), 2.21-2.13 (1H, m, incl. app. dd, $^{2}J$ 14.3, $J$ 4.5, $CF_2$CH$_a$$H_b$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 139.4 (C-2'), 137.0 (d, $^{3}J_{C\text{-}P}$ 3.2, C-2"), 136.9 (d, $^{3}J_{C\text{-}P}$ 3.2, C-2"), 129.7, 129.6, 129.6, 129.6, 129.3, 129.1, 129.1, 129.0, 128.8 (all Ar), 121.3 (td, $^{1}J_{C\text{-}F}$ 247.7, $^{3}J_{C\text{-}P}$ 6.4, C-2), 78.0 (t, $^{3}J_{C\text{-}F}$ 3.2, C-6), 76.7 (ddd, $^{2}J_{C\text{-}F}$ 30.4, 24.8, $^{2}J_{C\text{-}P}$ 6.4, C-1), 74.4 (C-1'), 70.9 (C-5), 69.7 (d, $^{2}J_{C\text{-}P}$ 6.4, C-1"), 69.6 (d, $^{2}J_{C\text{-}P}$ 6.4, C-1"), 66.8 (t, $^{3}J_{C\text{-}F}$ 5.2, C-4), 35.8 (t, $^{2}J_{C\text{-}F}$ 21.2, C-3); $\delta_F$ (376.5 MHz, methanol-$d_4$, 333 K) -98.9 (1F, d, $^{2}J_{F\text{-}F}$ 254.0), (-104.2)-(-105.5) (1F, m, incl. app. d, $^{2}J_{F\text{-}F}$ 254.0); $\delta_P$ (162 MHz, $CDCl_3$) -2.2. Significant peaks for **303**: $\delta_F$ (376.5 MHz, methanol-$d_4$, 333 K) -103.0 (1F, d, $^{2}J_{F\text{-}F}$ 261.5), -104.6 (1F, dd, $^{2}J_{F\text{-}F}$ 261.5, $^{3}J_{F\text{-}H}$ 31.6); $\delta_P$ (162 MHz, $CDCl_3$) -2.8.

**(1*S**,4*R**,5*R**,6*R**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxy-5-methyl cyclohexyl dibenzyl phosphate 304**

**(1*S**,4*S**,5*S**,6*R**)-6-(benzyloxy)-2,2-difluoro-4,5-dihydroxy-5-methyl cyclohexyl dibenzyl phosphate 305**



**304**



**305**

Osmium tetroxide (63 µL of a 2.5 wt. % solution in *tert*-butanol, 6.2 µmol, 2 mol%) was added to a cool (0 °C) solution of **299** (0.31 mmol, 159 mg) and NMO.$H_2O$ (0.62 mmol, 86 mg, 2.0 eq.) in a mixture of acetone (0.2 mL), water (0.4 mL) and *tert*-butanol (0.4 mL). The reaction mixture was stirred at room temperature for 3 days. The reaction was quenched with solid sodium sulfite (100 mg) and stirred for a further 3 hours. The product was filtered through Celite. The filter bed was washed with methanol (30 mL) and the combined initial filtrate and washings were concentrated *in vacuo* to deliver the crude phosphate esters as a mixture of diastereoisomers **304** and **305** (7:1) which were purified by flash chromatography (5 % methanol in dichloromethane) to afford phosphate esters **304** and **305** as a mixture of diastereoisomers as a white solid (132 mg, 78 %, 95 % by GC); mp 113-114 °C; $\upsilon_{max}$(neat)/$cm^{-1}$ 3321br, 1602w, 1455m, 1212m, 1100s, 1013s; [HRMS (FAB+, $MH^+$) Found 449.18544. Calc. for $C_{28}H_{32}O_7F_2P$ 549.18537]; *m/z* (FAB+) 571 (5 %, $MNa^+$), 549 (20, $MH^+$), 458 (6, $MH^+$-$CH_2Ph$), 368 (2, $MH^+$-$CH_2Ph$-$CH_2Ph$), 181 (100);

data for **304**: $R_f$ (10 % methanol in dichloromethane) 0.54; $\delta_H$ (400 MHz, methanol-$d_4$) 7.35-7.24 (15H, m, Ar*H*), 5.07 (2H, d, $^2J$ 8.2, P(O)OC$H_2$Ph), 5.04 (2H, dd, $^2J$ 8.2, $^3J_{H\text{-}P}$ 1.2, P(O)OC$H_2$Ph), 5.12-4.98 (1H, m, $CF_2CHOP$), 4.74 (1H, d, $^2J$ 11.3, CHOC$H_a$H$_b$Ph), 4.53 (1H, d, $^2J$ 11.3, CHOCH$_a$$H_b$Ph), 3.80 (1H, dd, $J$ 10.6, 5.9, $CH_2CHOH$), 3.78 (1H, m, incl. app. d, $J$ 3.5, $CHOCH_2Ph$), 2.33-2.21 (1H, m, incl. app. dd, $^2J$ 13.3, $J$ 5.9, $CF_2CH_aH_b$), 2.26-2.16 (1H, m, incl. app. dd, $^2J$ 13.3, $J$ 10.6, $CF_2CH_aH_b$), 1.29 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 139.6 (C-2'), 136.9 (d, $^3J_{C\text{-}P}$ 3.2, C-2"), 136.8 (d, $^3J_{C\text{-}P}$ 3.2, C-2"), 129.8, 129.7, 129.7, 129.6, 129.2, 129.1, 128.6, 128.5 (all Ar), 121.3 (ddd, $^1J_{C\text{-}F}$ 251.7, 242.9, $^3J_{C\text{-}P}$ 4.8, C-2), 84.2 (t, $^3J_{C\text{-}F}$ 3.2, C-6), 77.2 (ddd, $^2J_{C\text{-}F}$ 20.8, 18.4, $^2J_{C\text{-}P}$ 6.4, C-1), 76.7 (C-1'), 75.0 (C-5), 71.2 (d, $^2J_{C\text{-}P}$ 6.4, C-1"), 71.0 (d, $^2J_{C\text{-}P}$ 6.4, C-1"), 68.9 (dd, $^3J_{C\text{-}F}$ 8.0, 3.2, C-4), 37.9 (t, $^2J_{C\text{-}F}$ 21.6, C-3), 22.6 (C-7); $\delta_F$ (376.5 MHz, methanol-$d_4$, 233 K) (-96.3)-(-97.0) (1F, m, incl. app. d, $^2J_{F\text{-}F}$ 243.3), -110.6 (1F, ddt, $^2J_{F\text{-}F}$ 243.3, $^3J_{F\text{-}H}$ 28.7, 19.9); $\delta_P$ (162 MHz, $CDCl_3$) -1.8. Significant data for **305**: $R_f$ (10 % methanol in dichloromethane) 0.57; $\delta_H$ (400 MHz, methanol-$d_4$) 7.46-7.17 (15H, m, Ar*H*), 5.04-4.96 (1H, m, $CF_2CHOP$), 4.87 (1H, d, $^2J$ 11.0, CHOC$H_a$H$_b$Ph), 4.53 (1H, d, $^2J$ 11.0, CHOCH$_a$$H_b$Ph), 3.50 (1H, dd, $J$ 13.3, 4.5, $CH_2CHOH$), 3.42-3.38 (1H, m, incl. app. d, $J$ 3.5, $CHOCH_2Ph$), 2.50 (1H, dtd, $^3J_{H\text{-}F}$ 37.6, $^2J$ 13.3, $J$ 13.3, $^3J_{H\text{-}F}$ 3.1, $CF_2CH_aH_b$), 2.24-2.13 (1H, m, incl. app. dd, $^2J$ 13.3, $J$ 4.5, $CF_2CH_aH_b$), 1.35 (3H, s, $CH_3$); $\delta_C$ (100.6 MHz, methanol-$d_4$) 138.6 (C-2'), 129.9, 129.5, 129.5, 129.4, 129.3, 129.2, 129.1, 129.1, 128.9 (all Ar), 78.7 (m, C-1), 74.7 (C-5), 71.3 (d, $^2J_{C\text{-}P}$ 6.4, C-1"), 70.6 (d, $^2J_{C\text{-}P}$ 6.4, C-1"), 34.6 (t, $^2J_{C\text{-}F}$ 21.6, C-3), 23.0 (C-7); $\delta_F$ (376.5 MHz, methanol-$d_4$, 233 K) -102.0 (1F, d, $^2J_{F\text{-}F}$ 262.1), (-104.8)-(-105.7) (1F, m, incl. app. dd, $^2J_{F\text{-}F}$ 262.1, $^3J_{F\text{-}H}$ 37.6); $\delta_P$ (162 MHz, $CDCl_3$) -2.6.

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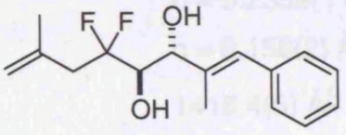
# 6 Appendix

## 6.1 Appendix I: Crystal Structure

### 6.1.1 (1*E*,3*S**,4*S**)-5,5-Difluoro-2,7-dimethyl-1-phenyl-octa-1,7-diene-3,4-diol 180



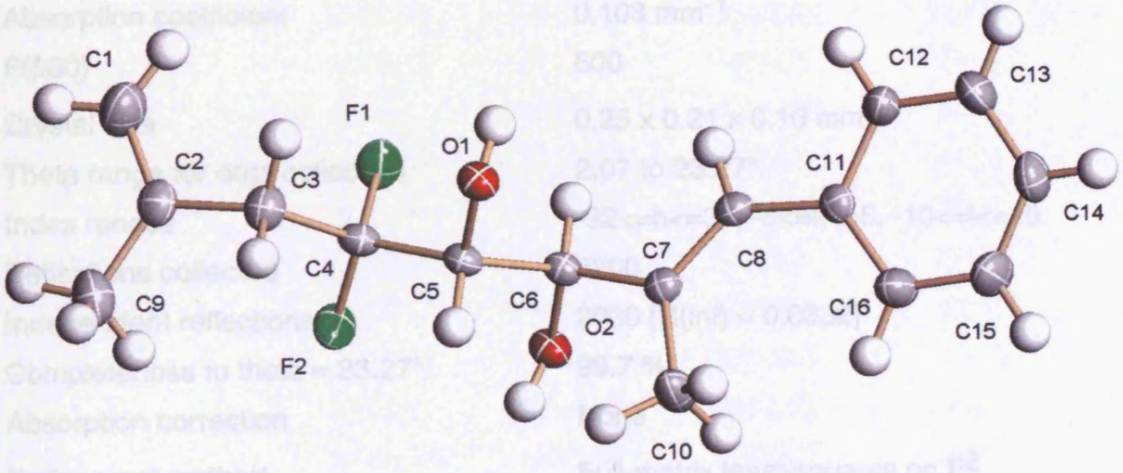



Table 1. Crystal data and structure refinement for 04116.

| | | |
|---|---|---|
| Identification code | 04116 | |
| Empirical formula | C16 H20 F2 O2 | |
| Formula weight | 282.32 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 29.670(6) Å | □= 90°. |
| | b = 5.2359(11) Å | □= 95.393(4)°. |
| | c = 9.158(2) Å | □ = 90°. |
| Volume | 1416.4(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.324 $Mg/m^3$ | |
| Absorption coefficient | 0.103 $mm^{-1}$ | |
| F(000) | 600 | |
| Crystal size | 0.25 x 0.21 x 0.10 $mm^3$ | |
| Theta range for data collection | 2.07 to 23.27°. | |
| Index ranges | -32<=h<=32, -5<=k<=5, -10<=l<=10 | |
| Reflections collected | 8200 | |
| Independent reflections | 2030 [R(int) = 0.0332] | |
| Completeness to theta = 23.27° | 99.7 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2030 / 0 / 185 | |
| Goodness-of-fit on $F^2$ | 1.093 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0409, wR2 = 0.0997 | |
| R indices (all data) | R1 = 0.0463, wR2 = 0.1032 | |
| Largest diff. peak and hole | 0.235 and -0.165 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 04116. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 1617(1) | 12953(2) | 4118(1) | 37(1) |
| F(2) | 1487(1) | 10039(2) | 2441(1) | 37(1) |
| O(1) | 2176(1) | 9050(2) | 5817(1) | 26(1) |
| O(2) | 2375(1) | 11090(2) | 2075(1) | 27(1) |
| C(1) | 578(1) | 11915(5) | 4976(3) | 47(1) |
| C(2) | 770(1) | 9949(4) | 4284(2) | 30(1) |
| C(3) | 1250(1) | 9191(4) | 4778(2) | 31(1) |
| C(4) | 1606(1) | 10349(3) | 3909(2) | 23(1) |
| C(5) | 2083(1) | 9279(3) | 4273(2) | 22(1) |
| C(6) | 2460(1) | 10840(3) | 3640(2) | 22(1) |
| C(7) | 2928(1) | 9775(3) | 4059(2) | 22(1) |
| C(8) | 3210(1) | 11028(4) | 5031(2) | 24(1) |
| C(9) | 527(1) | 8457(5) | 3135(2) | 44(1) |
| C(10) | 3040(1) | 7346(4) | 3302(2) | 36(1) |
| C(11) | 3678(1) | 10487(3) | 5620(2) | 23(1) |
| C(12) | 3848(1) | 11822(4) | 6867(2) | 31(1) |
| C(13) | 4282(1) | 11449(4) | 7510(2) | 38(1) |
| C(14) | 4565(1) | 9743(4) | 6905(2) | 36(1) |
| C(15) | 4409(1) | 8421(4) | 5669(2) | 38(1) |
| C(16) | 3974(1) | 8786(4) | 5020(2) | 35(1) |

Table 3. Bond lengths [Å] and angles [°] for 04116.

| | | | |
|---|---|---|---|
| F(1)-C(4) | 1.377(2) | F(2)-C(4)-F(1) | 104.77(14) |
| F(2)-C(4) | 1.367(2) | F(2)-C(4)-C(3) | 109.99(15) |
| O(1)-C(5) | 1.420(2) | F(1)-C(4)-C(3) | 109.50(15) |
| O(2)-C(6) | 1.437(2) | F(2)-C(4)-C(5) | 108.64(14) |
| C(1)-C(2) | 1.361(3) | F(1)-C(4)-C(5) | 108.80(15) |
| C(2)-C(9) | 1.447(3) | C(3)-C(4)-C(5) | 114.67(15) |
| C(2)-C(3) | 1.507(3) | O(1)-C(5)-C(4) | 109.65(14) |
| C(3)-C(4) | 1.507(3) | O(1)-C(5)-C(6) | 109.87(14) |

| | | | |
|---|---|---|---|
| C(4)-C(5) | 1.530(3) | C(4)-C(5)-C(6) | 114.39(15) |
| C(5)-C(6) | 1.541(2) | O(2)-C(6)-C(7) | 110.96(14) |
| C(6)-C(7) | 1.512(3) | O(2)-C(6)-C(5) | 110.97(14) |
| C(7)-C(8) | 1.335(3) | C(7)-C(6)-C(5) | 112.94(15) |
| C(7)-C(10) | 1.500(3) | C(8)-C(7)-C(10) | 124.96(17) |
| C(8)-C(11) | 1.469(3) | C(8)-C(7)-C(6) | 119.39(17) |
| C(11)-C(12) | 1.393(3) | C(10)-C(7)-C(6) | 115.64(16) |
| C(11)-C(16) | 1.399(3) | C(7)-C(8)-C(11) | 131.39(18) |
| C(12)-C(13) | 1.377(3) | C(12)-C(11)-C(16) | 116.65(17) |
| C(13)-C(14) | 1.378(3) | C(12)-C(11)-C(8) | 117.50(17) |
| C(14)-C(15) | 1.370(3) | C(16)-C(11)-C(8) | 125.83(17) |
| C(15)-C(16) | 1.381(3) | C(13)-C(12)-C(11) | 122.10(19) |
| | | C(12)-C(13)-C(14) | 120.03(19) |
| C(1)-C(2)-C(9) | 123.1(2) | C(15)-C(14)-C(13) | 119.23(19) |
| C(1)-C(2)-C(3) | 118.9(2) | C(14)-C(15)-C(16) | 121.0(2) |
| C(9)-C(2)-C(3) | 117.95(19) | C(15)-C(16)-C(11) | 120.98(19) |
| C(2)-C(3)-C(4) | 115.13(16) | | |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04116. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

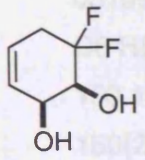
| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 34(1) | 20(1) | 57(1) | 1(1) | 6(1) | 3(1) |
| F(2) | 28(1) | 60(1) | 22(1) | 1(1) | -3(1) | 1(1) |
| O(1) | 30(1) | 27(1) | 20(1) | 4(1) | 0(1) | -1(1) |
| O(2) | 33(1) | 28(1) | 20(1) | 3(1) | 0(1) | -4(1) |
| C(1) | 36(1) | 44(1) | 61(2) | -1(1) | 8(1) | 6(1) |
| C(2) | 26(1) | 33(1) | 32(1) | 7(1) | 5(1) | -2(1) |
| C(3) | 29(1) | 32(1) | 33(1) | 7(1) | 4(1) | 1(1) |
| C(4) | 30(1) | 20(1) | 20(1) | -1(1) | -1(1) | 1(1) |
| C(5) | 27(1) | 20(1) | 19(1) | -1(1) | 0(1) | -2(1) |
| C(6) | 26(1) | 20(1) | 19(1) | 1(1) | 0(1) | -2(1) |
| C(7) | 25(1) | 21(1) | 21(1) | 3(1) | 5(1) | -1(1) |
| C(8) | 27(1) | 22(1) | 23(1) | 0(1) | 6(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(9) | 32(1) | 49(2) | 49(1) | 6(1) | -1(1) | -8(1) |
| C(10) | 29(1) | 29(1) | 49(1) | -9(1) | -3(1) | 3(1) |
| C(11) | 23(1) | 22(1) | 24(1) | 3(1) | 4(1) | -4(1) |
| C(12) | 25(1) | 31(1) | 37(1) | -6(1) | 4(1) | -1(1) |
| C(13) | 31(1) | 42(1) | 39(1) | -9(1) | -3(1) | -5(1) |
| C(14) | 23(1) | 39(1) | 44(1) | 2(1) | -5(1) | 0(1) |
| C(15) | 28(1) | 39(1) | 47(1) | -6(1) | 1(1) | 11(1) |
| C(16) | 32(1) | 35(1) | 35(1) | -8(1) | 0(1) | 4(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 04116.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 2212 | 10510 | 6189 | 39 |
| H(2) | 2301 | 9663 | 1707 | 41 |
| H(1A) | 271 | 12363 | 4712 | 56 |
| H(1B) | 752 | 12839 | 5725 | 56 |
| H(3A) | 1274 | 7308 | 4724 | 37 |
| H(3B) | 1316 | 9688 | 5819 | 37 |
| H(5) | 2089 | 7522 | 3847 | 26 |
| H(6) | 2452 | 12597 | 4065 | 26 |
| H(8) | 3086 | 12537 | 5408 | 28 |
| H(9A) | 219 | 9128 | 2936 | 65 |
| H(9B) | 513 | 6671 | 3448 | 65 |
| H(9C) | 684 | 8561 | 2242 | 65 |
| H(10A) | 3213 | 7744 | 2472 | 54 |
| H(10B) | 2759 | 6470 | 2944 | 54 |
| H(10C) | 3219 | 6237 | 3994 | 54 |
| H(12) | 3659 | 13030 | 7288 | 37 |
| H(13) | 4386 | 12368 | 8371 | 45 |
| H(14) | 4865 | 9486 | 7339 | 43 |
| H(15) | 4602 | 7235 | 5251 | 46 |
| H(16) | 3875 | 7869 | 4154 | 41 |

### 6.1.2 (1*S**,2*S**)-6,6-Difluorocyclohex-3-ene-1,2-diol 192



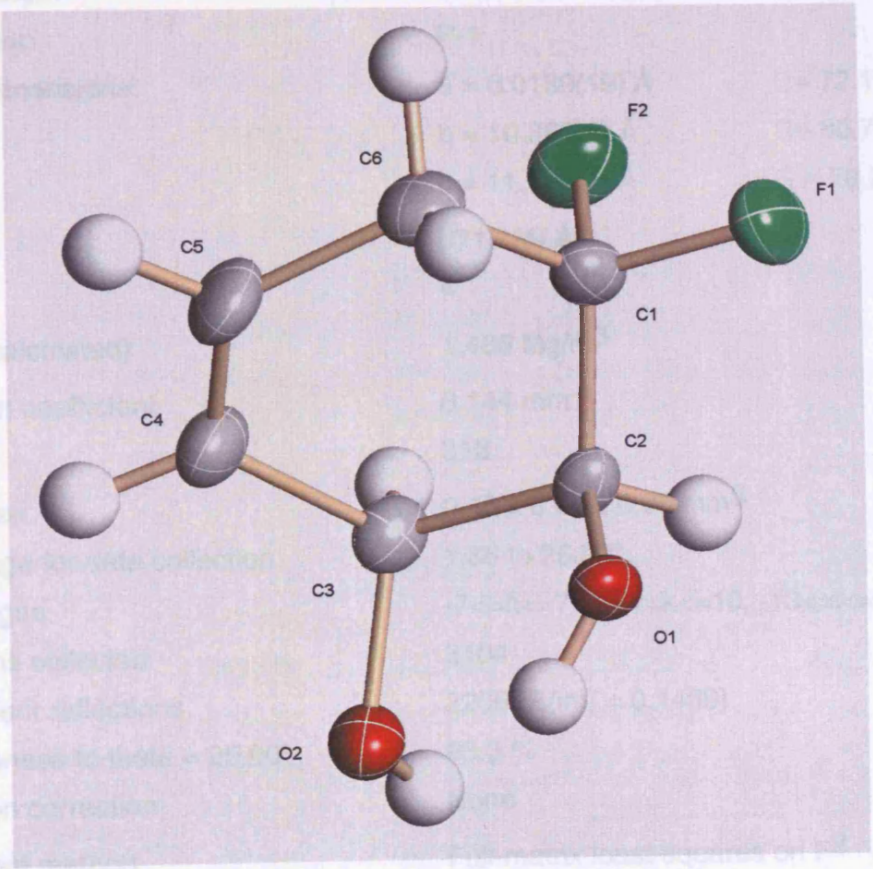



Table 1. Crystal data and structure refinement for 03159.

| | | |
|---|---|---|
| Identification code | 03159 | |
| Empirical formula | C6 H8 F2 O2 | |
| Formula weight | 150.12 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 6.0189(19) Å | □= 72.114(5)°. |
| | b = 10.381(3) Å | □= 80.734(5)°. |
| | c = 11.590(4) Å | □ = 78.330(5)°. |
| Volume | 671.1(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.486 $Mg/m^3$ | |
| Absorption coefficient | 0.144 $mm^{-1}$ | |
| F(000) | 312 | |
| Crystal size | 0.15 x 0.08 x 0.05 $mm^3$ | |
| Theta range for data collection | 1.86 to 25.00°. | |
| Index ranges | -7<=h<=7, -12<=k<=10, -13<=l<=13 | |
| Reflections collected | 3104 | |
| Independent reflections | 2206 [R(int) = 0.1489] | |
| Completeness to theta = 25.00° | 93.3 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2206 / 0 / 185 | |
| Goodness-of-fit on $F^2$ | 0.979 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0579, wR2 = 0.1343 | |
| R indices (all data) | R1 = 0.0818, wR2 = 0.1453 | |
| Largest diff. peak and hole | 0.298 and -0.251 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 03159P-1. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 3808(3) | 3949(2) | 977(2) | 41(1) |
| F(2) | 143(3) | 4496(2) | 1417(2) | 41(1) |
| O(2) | -966(4) | 833(2) | 948(2) | 28(1) |
| O(1) | 3266(3) | 1386(2) | 921(2) | 24(1) |
| C(3) | -827(5) | 1950(3) | 1391(3) | 27(1) |
| C(2) | 1403(5) | 2488(3) | 835(3) | 22(1) |
| C(1) | 1893(5) | 3382(3) | 1525(3) | 26(1) |
| C(6) | 2119(6) | 2692(4) | 2851(3) | 34(1) |
| C(5) | 334(6) | 1795(4) | 3400(3) | 38(1) |
| C(4) | -930(6) | 1450(4) | 2761(3) | 34(1) |
| F(1A) | 7915(4) | 7781(2) | 4247(2) | 52(1) |
| F(2A) | 4448(4) | 7318(2) | 4676(2) | 46(1) |
| O(2A) | 3371(4) | 8642(2) | 987(2) | 26(1) |
| O(1A) | 7579(4) | 8328(2) | 1756(2) | 28(1) |
| C(3A) | 3736(5) | 7861(3) | 2219(3) | 25(1) |
| C(2A) | 5628(5) | 8328(3) | 2633(3) | 25(1) |
| C(1A) | 6334(6) | 7313(4) | 3810(3) | 34(1) |
| C(6A) | 7207(6) | 5893(3) | 3715(3) | 36(1) |
| C(5A) | 5760(6) | 5482(3) | 2998(3) | 32(1) |
| C(4A) | 4221(6) | 6364(3) | 2320(3) | 28(1) |

Table 3. Bond lengths [Å] and angles [°] for 03159P-1.

| | | | |
|---|---|---|---|
| F(1)-C(1) | 1.374(3) | O(1)-C(2)-C(3) | 110.7(2) |
| F(2)-C(1) | 1.387(3) | C(1)-C(2)-C(3) | 110.0(2) |
| O(2)-C(3) | 1.427(4) | F(1)-C(1)-F(2) | 104.4(2) |
| O(1)-C(2) | 1.422(3) | F(1)-C(1)-C(2) | 110.3(2) |
| C(3)-C(4) | 1.506(4) | F(2)-C(1)-C(2) | 108.0(3) |
| C(3)-C(2) | 1.527(4) | F(1)-C(1)-C(6) | 110.0(3) |
| C(2)-C(1) | 1.492(5) | F(2)-C(1)-C(6) | 108.8(3) |

| | | | |
|---|---|---|---|
| C(1)-C(6) | 1.498(5) | C(2)-C(1)-C(6) | 114.9(3) |
| C(6)-C(5) | 1.499(5) | C(1)-C(6)-C(5) | 110.7(3) |
| C(5)-C(4) | 1.307(5) | C(4)-C(5)-C(6) | 123.9(3) |
| F(1A)-C(1A) | 1.376(4) | C(5)-C(4)-C(3) | 124.0(3) |
| F(2A)-C(1A) | 1.389(4) | O(2A)-C(3A)-C(4A) | 110.0(3) |
| O(2A)-C(3A) | 1.436(4) | O(2A)-C(3A)-C(2A) | 110.1(2) |
| O(1A)-C(2A) | 1.424(3) | C(4A)-C(3A)-C(2A) | 112.3(3) |
| C(3A)-C(4A) | 1.494(4) | O(1A)-C(2A)-C(1A) | 106.8(3) |
| C(3A)-C(2A) | 1.518(5) | O(1A)-C(2A)-C(3A) | 109.4(3) |
| C(2A)-C(1A) | 1.508(4) | C(1A)-C(2A)-C(3A) | 109.3(3) |
| C(1A)-C(6A) | 1.492(5) | F(1A)-C(1A)-F(2A) | 104.1(3) |
| C(6A)-C(5A) | 1.494(5) | F(1A)-C(1A)-C(6A) | 110.6(3) |
| C(5A)-C(4A) | 1.328(5) | F(2A)-C(1A)-C(6A) | 110.5(3) |
| | | F(1A)-C(1A)-C(2A) | 109.9(3) |
| O(2)-C(3)-C(4) | 108.6(3) | F(2A)-C(1A)-C(2A) | 107.2(3) |
| O(2)-C(3)-C(2) | 109.1(2) | C(6A)-C(1A)-C(2A) | 114.0(3) |
| C(4)-C(3)-C(2) | 110.9(3) | C(1A)-C(6A)-C(5A) | 111.3(3) |
| O(1)-C(2)-C(1) | 106.8(3) | C(4A)-C(5A)-C(6A) | 123.4(3) |
| | | C(5A)-C(4A)-C(3A) | 123.2(3) |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03159P-1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

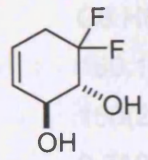
| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 38(1) | 41(1) | 47(1) | -16(1) | 8(1) | -17(1) |
| F(2) | 43(1) | 34(1) | 44(1) | -17(1) | -2(1) | 7(1) |
| O(2) | 26(1) | 34(1) | 25(1) | -8(1) | -5(1) | -7(1) |
| O(1) | 20(1) | 23(1) | 28(1) | -10(1) | -1(1) | -2(1) |
| C(3) | 20(2) | 33(2) | 27(2) | -9(1) | -3(1) | -2(1) |
| C(2) | 21(2) | 21(2) | 21(2) | -6(1) | 0(1) | 3(1) |
| C(1) | 24(2) | 23(2) | 32(2) | -12(1) | 1(1) | -2(1) |
| C(6) | 37(2) | 42(2) | 28(2) | -15(2) | -6(2) | -9(2) |
| C(5) | 43(2) | 50(2) | 20(2) | -12(2) | 4(2) | -14(2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(4) | 33(2) | 45(2) | 27(2) | -14(2) | 7(2) | -12(2) |
| F(1A) | 64(2) | 69(2) | 31(1) | -10(1) | -19(1) | -22(1) |
| F(2A) | 56(2) | 56(1) | 19(1) | -7(1) | 12(1) | -9(1) |
| O(2A) | 21(1) | 31(1) | 23(1) | -6(1) | 0(1) | -2(1) |
| O(1A) | 26(1) | 35(1) | 23(1) | -7(1) | 4(1) | -12(1) |
| C(3A) | 25(2) | 26(2) | 19(2) | -4(1) | 1(1) | -2(1) |
| C(2A) | 26(2) | 26(2) | 22(2) | -8(1) | 2(1) | -4(1) |
| C(1A) | 35(2) | 44(2) | 20(2) | -6(2) | 1(2) | -11(2) |
| C(6A) | 32(2) | 37(2) | 27(2) | 3(2) | 0(2) | 0(2) |
| C(5A) | 34(2) | 26(2) | 33(2) | -5(2) | 6(2) | -8(2) |
| C(4A) | 31(2) | 31(2) | 23(2) | -9(1) | 4(1) | -12(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 03159P-1.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | -1559 | 1135 | 288 | 41 |
| H(1) | 2811 | 688 | 884 | 35 |
| H(3A) | -2144 | 2700 | 1150 | 32 |
| H(2A) | 1289 | 3022 | -38 | 26 |
| H(6A) | 1959 | 3396 | 3287 | 41 |
| H(6B) | 3653 | 2130 | 2947 | 41 |
| H(5) | 107 | 1457 | 4263 | 45 |
| H(4) | -1978 | 848 | 3187 | 41 |
| H(2B) | 4615 | 8608 | 541 | 39 |
| H(1B) | 8034 | 9087 | 1568 | 42 |
| H(3B) | 2300 | 8041 | 2754 | 30 |
| H(2C) | 5106 | 9264 | 2744 | 30 |
| H(6D) | 7225 | 5243 | 4544 | 43 |
| H(6C) | 8793 | 5846 | 3317 | 43 |
| H(5B) | 5950 | 4541 | 3029 | 39 |
| H(4B) | 3388 | 6026 | 1877 | 33 |

### 6.1.3 (1*R**,2*S**)-6,6-difluorocyclohex-3-ene-1,2-diol 198



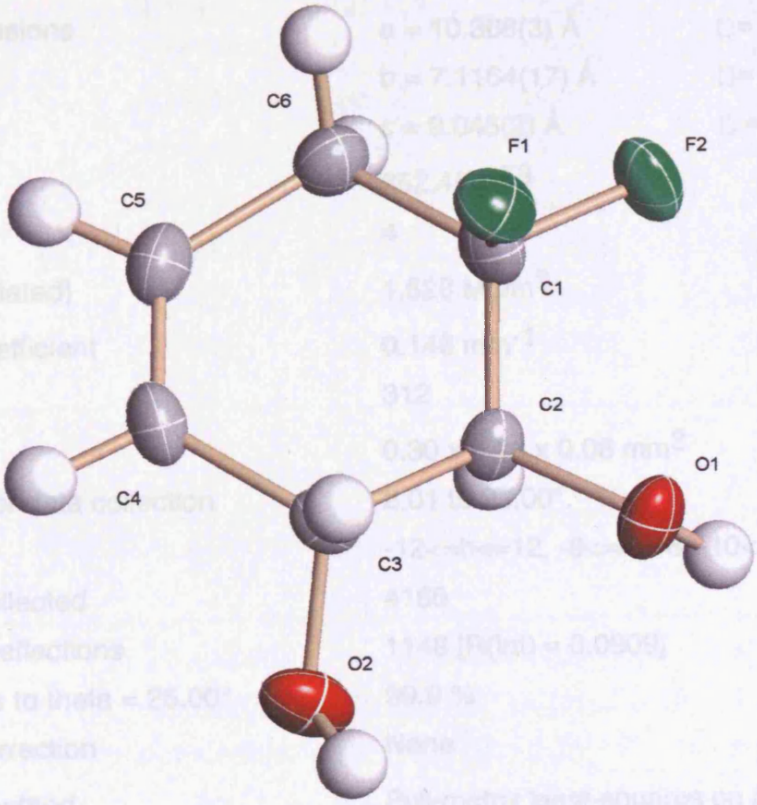



Table 1. Crystal data and structure refinement for 04079.

| | | |
|---|---|---|
| Identification code | 04079 | |
| Empirical formula | C6 H8 F2 O2 | |
| Formula weight | 150.12 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 10.368(3) Å | □= 90°. |
| | b = 7.1164(17) Å | □= 102.157(4)°. |
| | c = 9.045(2) Å | □ = 90°. |
| Volume | 652.4(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.528 $Mg/m^3$ | |
| Absorption coefficient | 0.148 $mm^{-1}$ | |
| F(000) | 312 | |
| Crystal size | 0.30 x 0.13 x 0.08 $mm^3$ | |
| Theta range for data collection | 2.01 to 25.00°. | |
| Index ranges | -12<=h<=12, -8<=k<=8, -10<=l<=10 | |
| Reflections collected | 4165 | |
| Independent reflections | 1148 [R(int) = 0.0909] | |
| Completeness to theta = 25.00° | 99.9 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1148 / 0 / 93 | |
| Goodness-of-fit on $F^2$ | 0.983 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0458, wR2 = 0.1060 | |
| R indices (all data) | R1 = 0.0624, wR2 = 0.1140 | |
| Largest diff. peak and hole | 0.326 and -0.208 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 04079. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 8637(1) | 9997(2) | 1442(1) | 36(1) |
| F(2) | 8586(1) | 11193(2) | 3640(1) | 42(1) |
| O(1) | 6161(2) | 11264(2) | 1730(2) | 32(1) |
| O(2) | 4907(1) | 7625(2) | 1085(2) | 36(1) |
| C(1) | 8192(2) | 9661(3) | 2751(2) | 29(1) |
| C(2) | 6710(2) | 9556(3) | 2355(2) | 25(1) |
| C(3) | 6284(2) | 7956(3) | 1251(2) | 26(1) |
| C(4) | 7029(2) | 6205(3) | 1796(2) | 32(1) |
| C(5) | 8161(2) | 6183(3) | 2799(3) | 34(1) |
| C(6) | 8835(2) | 7920(3) | 3507(3) | 34(1) |

Table 3. Bond lengths [Å] and angles [°] for 04079.

| | | | |
|---|---|---|---|
| F(1)-C(1) | 1.380(2) | F(1)-C(1)-C(6) | 109.65(17) |
| F(2)-C(1) | 1.365(2) | F(2)-C(1)-C(2) | 110.13(16) |
| O(1)-C(2) | 1.408(2) | F(1)-C(1)-C(2) | 108.28(16) |
| O(2)-C(3) | 1.423(2) | C(6)-C(1)-C(2) | 113.66(17) |
| C(1)-C(6) | 1.501(3) | O(1)-C(2)-C(1) | 111.02(16) |
| C(1)-C(2) | 1.505(3) | O(1)-C(2)-C(3) | 110.29(16) |
| C(2)-C(3) | 1.517(3) | C(1)-C(2)-C(3) | 109.59(16) |
| C(3)-C(4) | 1.494(3) | O(2)-C(3)-C(4) | 109.55(17) |
| C(4)-C(5) | 1.323(3) | O(2)-C(3)-C(2) | 109.89(16) |
| C(5)-C(6) | 1.497(3) | C(4)-C(3)-C(2) | 110.50(17) |
| | | C(5)-C(4)-C(3) | 123.97(19) |
| F(2)-C(1)-F(1) | 104.74(16) | C(4)-C(5)-C(6) | 123.4(2) |
| F(2)-C(1)-C(6) | 109.98(16) | C(5)-C(6)-C(1) | 111.35(18) |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04079. 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) | 35(1) | 37(1) | 36(1) | 4(1) | 7(1) | -7(1) |
| F(2) | 48(1) | 29(1) | 40(1) | -9(1) | -11(1) | -6(1) |
| O(1) | 43(1) | 27(1) | 23(1) | 4(1) | 3(1) | 11(1) |
| O(2) | 32(1) | 47(1) | 26(1) | 11(1) | -5(1) | -9(1) |
| C(1) | 36(1) | 27(1) | 22(1) | -5(1) | 1(1) | -4(1) |
| C(2) | 32(1) | 23(1) | 19(1) | 2(1) | 3(1) | 4(1) |
| C(3) | 29(1) | 28(1) | 21(1) | 1(1) | 3(1) | -5(1) |
| C(4) | 44(1) | 21(1) | 29(1) | -3(1) | 8(1) | -5(1) |
| C(5) | 40(1) | 25(1) | 37(1) | 3(1) | 10(1) | 5(1) |
| C(6) | 32(1) | 33(1) | 34(1) | 2(1) | 1(1) | 5(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 04079.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 5793 | 11811 | 2353 | 48 |
| H(2) | 4494 | 8188 | 313 | 55 |
| H(2A) | 6381 | 9298 | 3298 | 30 |
| H(3) | 6468 | 8309 | 246 | 31 |
| H(4) | 6669 | 5038 | 1398 | 38 |
| H(5) | 8566 | 5003 | 3084 | 40 |
| H(6A) | 9773 | 7895 | 3427 | 41 |
| H(6B) | 8805 | 7948 | 4593 | 41 |

### 6.1.4 (1*R**,2*S**)-6,6-Difluoro-4-methyl-cyclohex-3-ene-1,2-diol 206

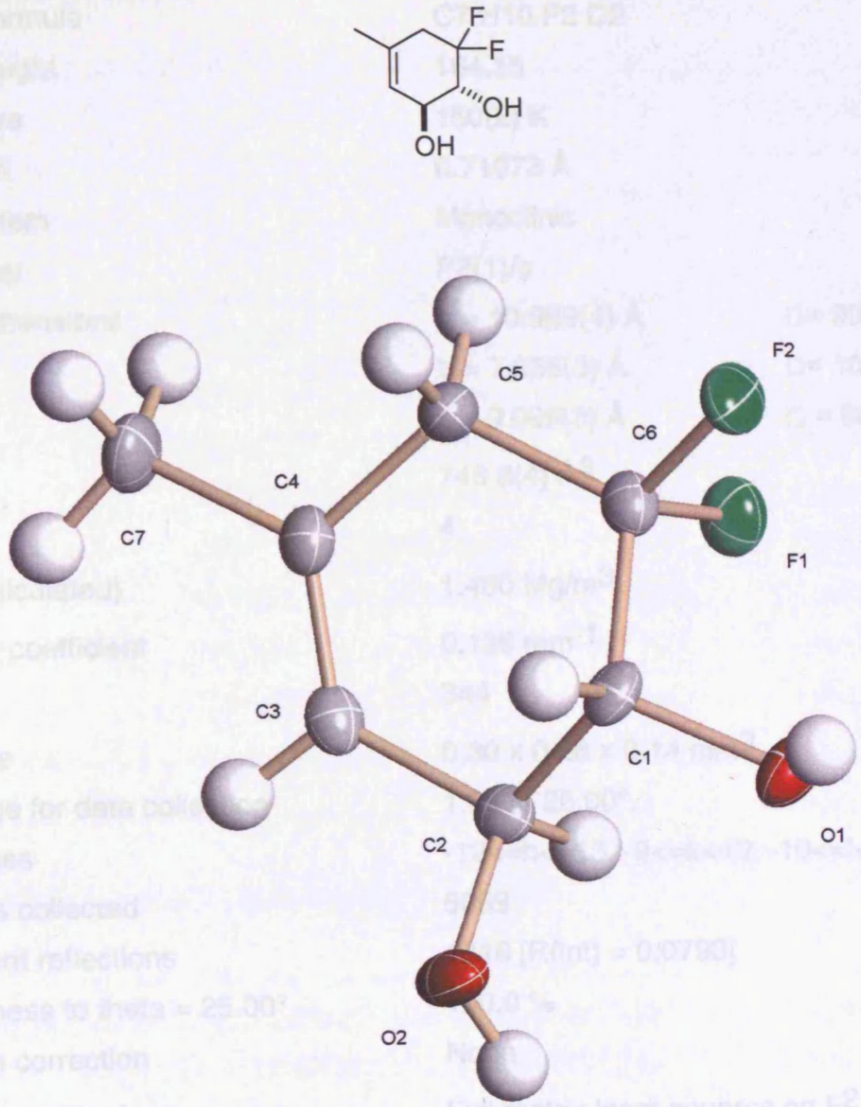


Table 1. Crystal data and structure refinement for 05021.

| | | |
|---|---|---|
| Identification code | 05021 | |
| Empirical formula | C7 H10 F2 O2 | |
| Formula weight | 164.15 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 10.989(4) Å | □= 90°. |
| | b = 7.855(3) Å | □= 108.042(5)°. |
| | c = 9.098(3) Å | □ = 90°. |
| Volume | 746.8(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.460 $Mg/m^3$ | |
| Absorption coefficient | 0.136 $mm^{-1}$ | |
| F(000) | 344 | |
| Crystal size | 0.30 x 0.28 x 0.14 $mm^3$ | |
| Theta range for data collection | 1.95 to 25.00°. | |
| Index ranges | -12<=h<=13, -9<=k<=9, -10<=l<=10 | |
| Reflections collected | 5059 | |
| Independent reflections | 1316 [R(int) = 0.0793] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1316 / 0 / 103 | |
| Goodness-of-fit on $F^2$ | 1.137 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0535, wR2 = 0.1342 | |
| R indices (all data) | R1 = 0.0590, wR2 = 0.1381 | |
| Largest diff. peak and hole | 0.616 and -0.228 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05021. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 1578(1) | 180(2) | 7933(2) | 31(1) |
| F(2) | 1675(1) | -558(2) | 5663(2) | 32(1) |
| O(1) | 3952(2) | -984(2) | 8011(2) | 26(1) |
| O(2) | 5305(1) | 2213(2) | 9069(2) | 29(1) |
| C(1) | 3510(2) | 648(3) | 7428(2) | 21(1) |
| C(2) | 3955(2) | 1963(3) | 8702(2) | 21(1) |
| C(3) | 3284(2) | 3631(3) | 8238(2) | 23(1) |
| C(4) | 2186(2) | 3836(3) | 7113(2) | 23(1) |
| C(5) | 1511(2) | 2367(3) | 6141(3) | 26(1) |
| C(6) | 2065(2) | 673(3) | 6771(2) | 22(1) |
| C(7) | 1554(2) | 5539(3) | 6700(3) | 32(1) |

Table 3. Bond lengths [Å] and angles [°] for 05021.

| | | | |
|---|---|---|---|
| F(1)-C(6) | 1.380(2) | O(2)-C(2)-C(3) | 109.30(17) |
| F(2)-C(6) | 1.366(3) | O(2)-C(2)-C(1) | 109.77(17) |
| O(1)-C(1) | 1.414(3) | C(3)-C(2)-C(1) | 111.46(17) |
| O(2)-C(2) | 1.429(3) | C(4)-C(3)-C(2) | 125.0(2) |
| C(1)-C(6) | 1.513(3) | C(3)-C(4)-C(7) | 122.8(2) |
| C(1)-C(2) | 1.516(3) | C(3)-C(4)-C(5) | 121.7(2) |
| C(2)-C(3) | 1.498(3) | C(7)-C(4)-C(5) | 115.55(19) |
| C(3)-C(4) | 1.328(3) | C(6)-C(5)-C(4) | 112.85(18) |
| C(4)-C(7) | 1.501(3) | F(2)-C(6)-F(1) | 105.00(16) |
| C(4)-C(5) | 1.503(3) | F(2)-C(6)-C(5) | 110.39(17) |
| C(5)-C(6) | 1.501(3) | F(1)-C(6)-C(5) | 109.44(18) |
| | | F(2)-C(6)-C(1) | 109.51(17) |
| O(1)-C(1)-C(6) | 110.88(18) | F(1)-C(6)-C(1) | 107.58(16) |
| O(1)-C(1)-C(2) | 109.79(16) | C(5)-C(6)-C(1) | 114.46(18) |
| C(6)-C(1)-C(2) | 110.15(17) | | |

Symmetry transformations used to generate equivalent atoms:

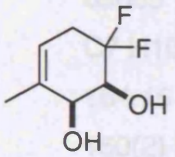
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05021. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

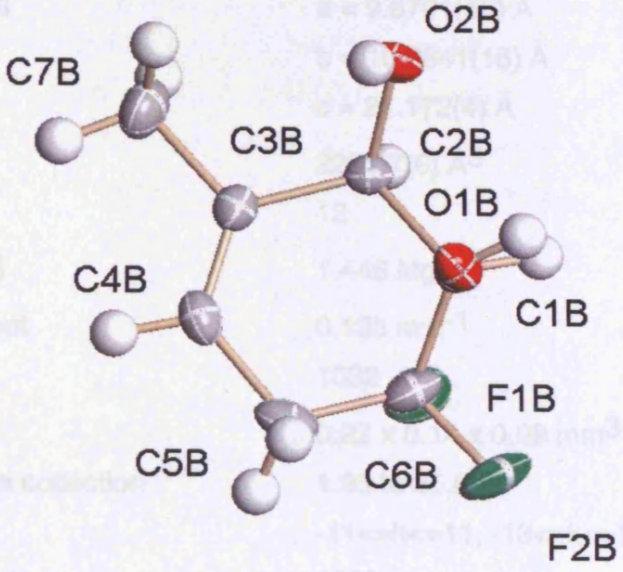
| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 30(1) | 31(1) | 36(1) | 7(1) | 17(1) | -2(1) |
| F(2) | 39(1) | 21(1) | 30(1) | -4(1) | 2(1) | -3(1) |
| O(1) | 36(1) | 23(1) | 21(1) | 2(1) | 10(1) | 10(1) |
| O(2) | 22(1) | 38(1) | 24(1) | 12(1) | 2(1) | -3(1) |
| C(1) | 28(1) | 20(1) | 16(1) | 6(1) | 9(1) | 5(1) |
| C(2) | 22(1) | 24(1) | 18(1) | 2(1) | 6(1) | -2(1) |
| C(3) | 29(1) | 20(1) | 22(1) | -3(1) | 11(1) | -3(1) |
| C(4) | 28(1) | 19(1) | 23(1) | 2(1) | 11(1) | -1(1) |
| C(5) | 23(1) | 22(1) | 28(1) | 3(1) | 3(1) | 0(1) |
| C(6) | 27(1) | 20(1) | 20(1) | 1(1) | 8(1) | -3(1) |
| C(7) | 34(1) | 17(1) | 44(1) | 4(1) | 12(1) | 5(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x$ $10^3$) for 05021.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 4134 | -1549 | 7324 | 39 |
| H(2) | 5676 | 1810 | 9950 | 44 |
| H(1A) | 3880 | 938 | 6584 | 25 |
| H(2A) | 3767 | 1534 | 9643 | 25 |
| H(3) | 3674 | 4616 | 8790 | 27 |
| H(5A) | 595 | 2393 | 6078 | 31 |
| H(5B) | 1563 | 2499 | 5080 | 31 |
| H(7A) | 2066 | 6411 | 7389 | 48 |
| H(7B) | 697 | 5503 | 6816 | 48 |
| H(7C) | 1485 | 5815 | 5627 | 48 |

### 6.1.5 (1*S**,2*S**)-6,6-difluoro-3-methylcyclohex-3-ene-1,2-diol 196



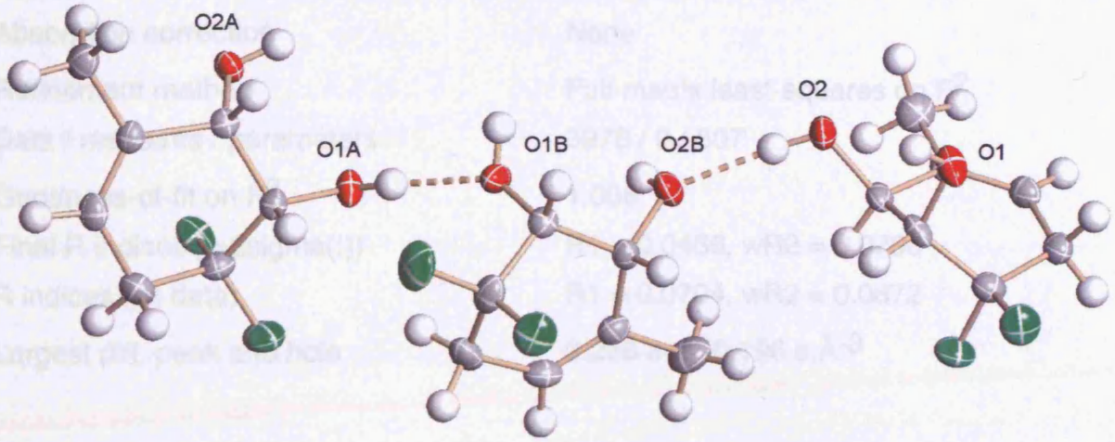



Table 1. Crystal data and structure refinement for 05095.

| | | |
|---|---|---|
| Identification code | 05095 | |
| Empirical formula | C7 H10 F2 O2 | |
| Formula weight | 164.15 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 9.8701(16) Å | □= 90°. |
| | b = 10.9641(18) Å | □= 99.186(3)°. |
| | c = 21.172(4) Å | □ = 90°. |
| Volume | 2261.7(6) $Å^3$ | |
| Z | 12 | |
| Density (calculated) | 1.446 $Mg/m^3$ | |
| Absorption coefficient | 0.135 $mm^{-1}$ | |
| F(000) | 1032 | |
| Crystal size | 0.22 x 0.14 x 0.08 $mm^3$ | |
| Theta range for data collection | 1.95 to 25.00°. | |
| Index ranges | -11<=h<=11, -13<=k<=13, -25<=l<=25 | |
| Reflections collected | 15931 | |
| Independent reflections | 3978 [R(int) = 0.0562] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3978 / 0 / 307 | |
| Goodness-of-fit on $F^2$ | 1.008 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0456, wR2 = 0.0798 | |
| R indices (all data) | R1 = 0.0704, wR2 = 0.0872 | |
| Largest diff. peak and hole | 0.236 and -0.196 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05095. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 462(1) | 1583(2) | 9187(1) | 36(1) |
| O(2) | 3053(1) | 708(1) | 9130(1) | 38(1) |
| F(1) | -265(1) | 3868(1) | 8643(1) | 43(1) |
| F(2) | 1550(1) | 3850(1) | 8181(1) | 40(1) |
| C(1) | 1414(2) | 2340(2) | 8935(1) | 28(1) |
| C(2) | 2475(2) | 1568(2) | 8660(1) | 28(1) |
| C(3) | 1868(2) | 933(2) | 8044(1) | 27(1) |
| C(4) | 716(2) | 1318(2) | 7691(1) | 28(1) |
| C(5) | -137(2) | 2362(2) | 7866(1) | 29(1) |
| C(6) | 619(2) | 3086(2) | 8405(1) | 29(1) |
| C(7) | 2699(2) | -99(2) | 7839(1) | 42(1) |
| O(1B) | 7980(1) | 1270(1) | 10407(1) | 29(1) |
| O(2B) | 5620(1) | 1383(1) | 9527(1) | 31(1) |
| F(1B) | 6649(1) | 4034(1) | 10934(1) | 45(1) |
| F(2B) | 8384(1) | 2952(1) | 11402(1) | 54(1) |
| C(1B) | 6953(2) | 2119(2) | 10507(1) | 25(1) |
| C(2B) | 6066(2) | 2463(2) | 9873(1) | 24(1) |
| C(3B) | 6756(2) | 3353(2) | 9482(1) | 26(1) |
| C(4B) | 7856(2) | 3970(2) | 9732(1) | 31(1) |
| C(5B) | 8567(2) | 3856(2) | 10409(1) | 37(1) |
| C(6B) | 7655(2) | 3240(2) | 10810(1) | 33(1) |
| C(7B) | 6055(2) | 3547(2) | 8804(1) | 43(1) |

Table 3. Bond lengths [Å] and angles [°] for 05095.

| | | | |
|---|---|---|---|
| O(1)-C(1) | 1.419(2) | C(2)-O(2)-H(2) | 109.5 |
| O(1)-H(1) | 0.8400 | O(1)-C(1)-C(6) | 107.49(16) |
| O(2)-C(2) | 1.424(2) | O(1)-C(1)-C(2) | 110.72(17) |
| O(2)-H(2) | 0.8400 | C(6)-C(1)-C(2) | 108.91(17) |
| F(1)-C(6) | 1.375(2) | H(5A)-C(5)-H(5B) | 108.0 |
| F(2)-C(6) | 1.383(2) | F(1)-C(6)-F(2) | 104.10(16) |

| | | | |
|---|---|---|---|
| C(1)-C(6) | 1.504(3) | F(1)-C(6)-C(5) | 110.13(17) |
| C(1)-C(2) | 1.532(3) | F(2)-C(6)-C(5) | 109.81(17) |
| C(2)-C(3) | 1.516(3) | F(1)-C(6)-C(1) | 110.60(17) |
| C(3)-C(4) | 1.325(3) | F(2)-C(6)-C(1) | 106.83(16) |
| C(3)-C(7) | 1.501(3) | C(5)-C(6)-C(1) | 114.78(18) |
| C(4)-C(5) | 1.502(3) | C(3)-C(7)-H(7B) | 109.5 |
| C(4)-H(4) | 0.9500 | H(7A)-C(7)-H(7B) | 109.5 |
| C(5)-C(6) | 1.488(3) | C(1B)-O(1B)-H(1B) | 109.5 |
| C(5)-H(5B) | 0.9900 | C(2B)-O(2B)-H(2B) | 109.5 |
| C(7)-H(7B) | 0.9800 | O(1B)-C(1B)-C(6B) | 107.95(16) |
| O(1B)-C(1B) | 1.417(2) | O(1B)-C(1B)-C(2B) | 110.69(16) |
| O(1B)-H(1B) | 0.8400 | C(6B)-C(1B)-C(2B) | 109.45(17) |
| O(2B)-C(2B) | 1.425(2) | O(1B)-C(1B)-H(1B1) | 109.6 |
| O(2B)-H(2B) | 0.8400 | C(6B)-C(1B)-H(1B1) | 109.6 |
| F(1B)-C(6B) | 1.378(2) | C(2B)-C(1B)-H(1B1) | 109.6 |
| F(2B)-C(6B) | 1.379(2) | O(2B)-C(2B)-C(3B) | 112.61(16) |
| C(1B)-C(6B) | 1.502(3) | O(2B)-C(2B)-C(1B) | 109.48(16) |
| C(1B)-C(2B) | 1.529(3) | C(3B)-C(2B)-C(1B) | 113.34(17) |
| C(1B)-H(1B1) | 1.0000 | O(2B)-C(2B)-H(2B1) | 107.0 |
| C(2B)-C(3B) | 1.510(3) | C(3B)-C(2B)-H(2B1) | 107.0 |
| C(2B)-H(2B1) | 1.0000 | C(1B)-C(2B)-H(2B1) | 107.0 |
| C(3B)-C(4B) | 1.317(3) | C(4B)-C(3B)-C(7B) | 122.3(2) |
| C(3B)-C(7B) | 1.506(3) | C(4B)-C(3B)-C(2B) | 121.77(19) |
| C(4B)-C(5B) | 1.498(3) | C(7B)-C(3B)-C(2B) | 115.80(19) |
| C(4B)-H(4B) | 0.9500 | C(3B)-C(4B)-C(5B) | 124.9(2) |
| C(5B)-C(6B) | 1.492(3) | C(3B)-C(4B)-H(4B) | 117.6 |
| C(5B)-H(5B1) | 0.9900 | C(5B)-C(4B)-H(4B) | 117.6 |
| C(5B)-H(5B2) | 0.9900 | C(6B)-C(5B)-C(4B) | 110.44(18) |
| C(7B)-H(7B1) | 0.9800 | C(6B)-C(5B)-H(5B1) | 109.6 |
| C(7B)-H(7B2) | 0.9800 | C(4B)-C(5B)-H(5B1) | 109.6 |
| C(7B)-H(7B3) | 0.9800 | C(6B)-C(5B)-H(5B2) | 109.6 |
| | | C(4B)-C(5B)-H(5B2) | 109.6 |
| C(1)-O(1)-H(1) | 109.5 | H(5B1)-C(5B)-H(5B2) | 108.1 |
| O(2)-C(2)-C(3) | 110.91(17) | F(1B)-C(6B)-F(2B) | 104.95(16) |
| O(2)-C(2)-C(1) | 108.76(17) | F(1B)-C(6B)-C(5B) | 109.93(19) |
| C(3)-C(2)-C(1) | 112.36(17) | F(2B)-C(6B)-C(5B) | 110.21(18) |
| C(4)-C(3)-C(7) | 122.5(2) | F(1B)-C(6B)-C(1B) | 107.49(17) |
| C(4)-C(3)-C(2) | 121.57(19) | F(2B)-C(6B)-C(1B) | 109.80(18) |

| | | | |
|---|---|---|---|
| C(7)-C(3)-C(2) | 115.82(18) | C(5B)-C(6B)-C(1B) | 114.02(18) |
| C(3)-C(4)-C(5) | 124.6(2) | C(3B)-C(7B)-H(7B1) | 109.5 |
| C(3)-C(4)-H(4) | 117.7 | C(3B)-C(7B)-H(7B2) | 109.5 |
| C(5)-C(4)-H(4) | 117.7 | H(7B1)-C(7B)-H(7B2) | 109.5 |
| C(6)-C(5)-C(4) | 111.31(17) | C(3B)-C(7B)-H(7B3) | 109.5 |
| C(6)-C(5)-H(5B) | 109.4 | H(7B1)-C(7B)-H(7B3) | 109.5 |
| C(4)-C(5)-H(5B) | 109.4 | H(7B2)-C(7B)-H(7B3) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05095. 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) | 29(1) | 57(1) | 21(1) | 5(1) | 3(1) | -15(1) |
| O(2) | 26(1) | 42(1) | 40(1) | 15(1) | -9(1) | -10(1) |
| F(1) | 44(1) | 41(1) | 45(1) | -12(1) | 9(1) | 7(1) |
| F(2) | 44(1) | 32(1) | 47(1) | 7(1) | 9(1) | -10(1) |
| C(1) | 25(1) | 35(1) | 22(1) | -3(1) | 2(1) | -13(1) |
| C(2) | 22(1) | 31(1) | 29(1) | 6(1) | 0(1) | -8(1) |
| C(3) | 28(1) | 30(1) | 25(1) | 2(1) | 7(1) | -5(1) |
| C(4) | 34(1) | 30(1) | 20(1) | -3(1) | 1(1) | -5(1) |
| C(5) | 30(1) | 31(1) | 25(1) | 2(1) | -1(1) | -3(1) |
| C(6) | 28(1) | 26(1) | 34(1) | -2(1) | 9(1) | -3(1) |
| C(7) | 40(1) | 44(2) | 43(2) | -1(1) | 11(1) | 4(1) |
| O(1A) | 21(1) | 42(1) | 23(1) | 3(1) | 0(1) | -2(1) |
| O(2A) | 24(1) | 26(1) | 26(1) | -6(1) | 0(1) | -3(1) |
| F(1A) | 33(1) | 41(1) | 32(1) | -7(1) | 14(1) | -10(1) |
| F(2A) | 56(1) | 35(1) | 39(1) | 13(1) | 0(1) | -7(1) |
| C(1A) | 22(1) | 27(1) | 21(1) | -1(1) | 2(1) | 2(1) |
| C(2A) | 20(1) | 25(1) | 21(1) | -2(1) | 6(1) | 1(1) |
| C(3A) | 23(1) | 28(1) | 19(1) | -3(1) | 3(1) | 3(1) |
| C(4A) | 27(1) | 38(1) | 23(1) | -7(1) | 0(1) | 1(1) |
| C(5A) | 33(1) | 29(1) | 33(1) | -4(1) | 7(1) | -6(1) |
| C(6A) | 32(1) | 25(1) | 26(1) | 3(1) | 6(1) | 2(1) |
| C(7A) | 36(1) | 34(1) | 25(1) | -3(1) | -2(1) | 3(1) |
| O(1B) | 23(1) | 25(1) | 39(1) | 5(1) | 3(1) | 2(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O(2B) | 22(1) | 32(1) | 38(1) | -8(1) | 2(1) | -4(1) |
| F(1B) | 54(1) | 45(1) | 38(1) | -14(1) | 8(1) | 10(1) |
| F(2B) | 61(1) | 66(1) | 27(1) | -8(1) | -16(1) | 3(1) |
| C(1B) | 23(1) | 28(1) | 25(1) | 2(1) | 6(1) | 2(1) |
| C(2B) | 21(1) | 25(1) | 26(1) | -4(1) | 2(1) | 2(1) |
| C(3B) | 29(1) | 24(1) | 25(1) | 1(1) | 5(1) | 5(1) |
| C(4B) | 36(1) | 23(1) | 37(1) | 3(1) | 14(1) | 0(1) |
| C(5B) | 30(1) | 26(1) | 52(2) | -9(1) | 0(1) | -4(1) |
| C(6B) | 36(1) | 36(1) | 24(1) | -7(1) | -5(1) | 7(1) |
| C(7B) | 58(2) | 41(2) | 30(1) | 8(1) | 4(1) | 4(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x 10 $^3$) for 05095.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 738 | 1462 | 9578 | 54 |
| H(2) | 3873 | 894 | 9265 | 57 |
| H(1A) | 1887 | 2890 | 9277 | 33 |
| H(2A) | 3225 | 2121 | 8567 | 33 |
| H(4) | 408 | 905 | 7300 | 34 |
| H(5A) | -389 | 2898 | 7489 | 35 |
| H(5B) | -995 | 2042 | 7990 | 35 |
| H(7A) | 2309 | -352 | 7404 | 63 |
| H(7B) | 2681 | -789 | 8132 | 63 |
| H(7C) | 3649 | 169 | 7848 | 63 |
| H(1A1) | -105 | 1132 | 493 | 44 |
| H(2A1) | 1546 | -1020 | 950 | 39 |
| H(1A2) | 948 | 1989 | 1279 | 28 |
| H(2A2) | 1164 | 121 | 1711 | 26 |
| H(4A) | 4601 | 1746 | 2364 | 35 |
| H(5A1) | 3114 | 3303 | 1701 | 38 |
| H(5A2) | 4483 | 2938 | 1428 | 38 |
| H(7A1) | 4291 | -138 | 2812 | 49 |
| H(7A2) | 3784 | -1139 | 2276 | 49 |
| H(7A3) | 2724 | -576 | 2696 | 49 |
| H(1B) | 7768 | 574 | 10525 | 44 |

| | | | | |
|---|---|---|---|---|
| H(2B) | 6284 | 1066 | 9384 | 46 |
| H(1B1) | 6362 | 1757 | 10801 | 30 |
| H(2B1) | 5228 | 2876 | 9979 | 29 |
| H(4B) | 8227 | 4530 | 9462 | 38 |
| H(5B1) | 9421 | 3378 | 10421 | 44 |
| H(5B2) | 8817 | 4676 | 10585 | 44 |
| H(7B1) | 6554 | 4167 | 8599 | 65 |
| H(7B2) | 5111 | 3821 | 8805 | 65 |
| H(7B3) | 6045 | 2779 | 8566 | 65 |

Table 6. Torsion angles [°] for 05095.

| | | | |
|---|---|---|---|
| O(1)-C(1)-C(2)-O(2) | -51.7(2) | O(1B)-C(1B)-C(2B)-O(2B) | 49.7(2) |
| C(6)-C(1)-C(2)-O(2) | -169.65(15) | C(6B)-C(1B)-C(2B)-O(2B) | 168.56(16) |
| O(1)-C(1)-C(2)-C(3) | 71.5(2) | O(1B)-C(1B)-C(2B)-C(3B) | -76.9(2) |
| C(6)-C(1)-C(2)-C(3) | -46.5(2) | C(6B)-C(1B)-C(2B)-C(3B) | 41.9(2) |
| O(2)-C(2)-C(3)-C(4) | 142.34(19) | O(2B)-C(2B)-C(3B)-C(4B) | -139.77(19) |
| C(1)-C(2)-C(3)-C(4) | 20.4(3) | C(1B)-C(2B)-C(3B)-C(4B) | -14.8(3) |
| O(2)-C(2)-C(3)-C(7) | -41.5(2) | O(2B)-C(2B)-C(3B)-C(7B) | 44.1(2) |
| C(1)-C(2)-C(3)-C(7) | -163.52(17) | C(1B)-C(2B)-C(3B)-C(7B) | 169.05(17) |
| C(7)-C(3)-C(4)-C(5) | -178.64(19) | C(7B)-C(3B)-C(4B)-C(5B) | 177.4(2) |
| C(2)-C(3)-C(4)-C(5) | -2.8(3) | C(2B)-C(3B)-C(4B)-C(5B) | 1.5(3) |
| C(3)-C(4)-C(5)-C(6) | 12.8(3) | C(3B)-C(4B)-C(5B)-C(6B) | -16.5(3) |
| C(4)-C(5)-C(6)-F(1) | -167.52(16) | C(4B)-C(5B)-C(6B)-F(1B) | -74.8(2) |
| C(4)-C(5)-C(6)-F(2) | 78.4(2) | C(4B)-C(5B)-C(6B)-F(2B) | 169.94(17) |
| C(4)-C(5)-C(6)-C(1) | -41.9(2) | C(4B)-C(5B)-C(6B)-C(1B) | 45.9(2) |
| O(1)-C(1)-C(6)-F(1) | 65.1(2) | O(1B)-C(1B)-C(6B)-F(1B) | -177.06(15) |
| C(2)-C(1)-C(6)-F(1) | -174.87(16) | C(2B)-C(1B)-C(6B)-F(1B) | 62.4(2) |
| O(1)-C(1)-C(6)-F(2) | 177.80(15) | O(1B)-C(1B)-C(6B)-F(2B) | -63.4(2) |
| C(2)-C(1)-C(6)-F(2) | -62.2(2) | C(2B)-C(1B)-C(6B)-F(2B) | 176.02(16) |
| O(1)-C(1)-C(6)-C(5) | -60.2(2) | O(1B)-C(1B)-C(6B)-C(5B) | 60.8(2) |
| C(2)-C(1)-C(6)-C(5) | 59.8(2) | C(2B)-C(1B)-C(6B)-C(5B) | -59.8(2) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 05095 [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(1)-H(1)...O(1A)#1 | 0.84 | 1.93 | 2.7412(19) | 160.9 |
| O(1A)-H(1A1)...O(1B)#2 | 0.84 | 1.88 | 2.7077(19) | 170.9 |
| O(2A)-H(2A1)...O(1)#3 | 0.84 | 2.05 | 2.8479(19) | 157.9 |
| O(1B)-H(1B)...O(2)#4 | 0.84 | 1.83 | 2.6496(19) | 164.4 |
| O(2B)-H(2B)...O(2A)#5 | 0.84 | 1.98 | 2.7897(19) | 163.2 |
| O(2)-H(2)...O(2B) | 0.84 | 1.81 | 2.6440(19) | 176.4 |

Symmetry transformations used to generate equivalent atoms:

### 6.1.6 (1*R**,2*R**,3*S**,6*S**)-4,4-difluoro-7-oxabicyclo[4.1.0]heptane-2,3-diol

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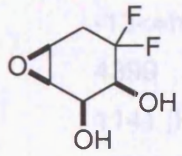


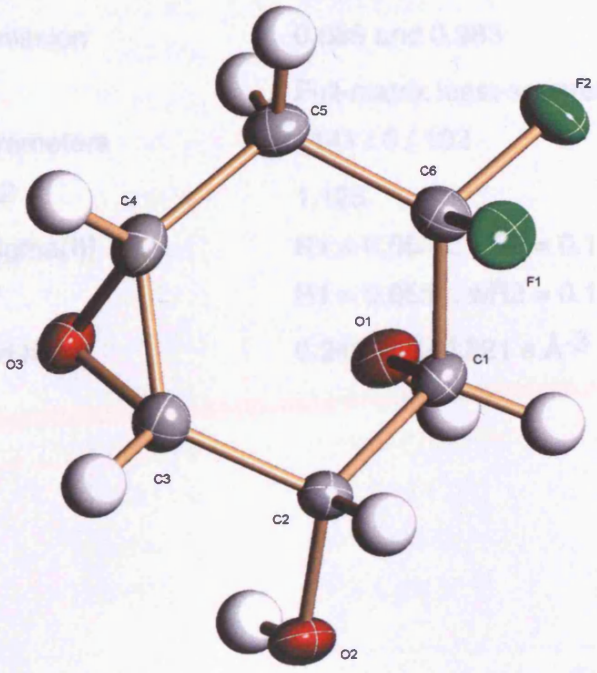



Table 1. Crystal data and structure refinement for 04170.

| | | |
|---|---|---|
| Identification code | 04170 | |
| Empirical formula | C6 H8 F2 O3 | |
| Formula weight | 166.12 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 11.166(3) Å | □= 90°. |
| | b = 5.7258(16) Å | □= 111.988(4)°. |
| | c = 10.978(3) Å | □ = 90°. |
| Volume | 650.8(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.695 $Mg/m^3$ | |
| Absorption coefficient | 0.169 $mm^{-1}$ | |
| F(000) | 344 | |
| Crystal size | 0.39 x 0.22 x 0.06 $mm^3$ | |
| Theta range for data collection | 1.97 to 25.00°. | |
| Index ranges | -13<=h<=13, -6<=k<=6, -13<=l<=13 | |
| Reflections collected | 4399 | |
| Independent reflections | 1141 [R(int) = 0.0578] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.689 and 0.983 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1141 / 0 / 102 | |
| Goodness-of-fit on $F^2$ | 1.125 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0502, wR2 = 0.1101 | |
| R indices (all data) | R1 = 0.0651, wR2 = 0.1161 | |
| Largest diff. peak and hole | 0.248 and -0.221 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 04170. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 4050(1) | 660(3) | 8626(1) | 32(1) |
| F(2) | 3656(2) | -3063(3) | 8339(2) | 36(1) |
| O(1) | 1128(2) | -2135(3) | 6673(2) | 26(1) |
| O(2) | 201(2) | 2389(3) | 6605(2) | 25(1) |
| O(3) | 1693(2) | 994(3) | 4822(2) | 26(1) |
| C(1) | 1909(2) | -435(4) | 7534(2) | 21(1) |
| C(2) | 1541(2) | 2033(4) | 6983(2) | 20(1) |
| C(3) | 1998(2) | 2621(4) | 5898(2) | 24(1) |
| C(4) | 3019(2) | 1262(5) | 5693(2) | 25(1) |
| C(5) | 3611(2) | -847(4) | 6524(3) | 25(1) |
| C(6) | 3294(2) | -938(4) | 7734(2) | 24(1) |

Table 3. Bond lengths [Å] and angles [°] for 04170.

| | | | |
|---|---|---|---|
| F(1)-C(6) | 1.374(3) | O(2)-C(2)-C(3) | 111.9(2) |
| F(2)-C(6) | 1.373(3) | O(2)-C(2)-C(1) | 110.33(19) |
| O(1)-C(1) | 1.409(3) | C(3)-C(2)-C(1) | 113.6(2) |
| O(2)-C(2) | 1.411(3) | O(3)-C(3)-C(4) | 59.31(15) |
| O(3)-C(4) | 1.438(3) | O(3)-C(3)-C(2) | 117.4(2) |
| O(3)-C(3) | 1.441(3) | C(4)-C(3)-C(2) | 121.2(2) |
| C(1)-C(6) | 1.507(3) | O(3)-C(4)-C(3) | 59.48(15) |
| C(1)-C(2) | 1.531(3) | O(3)-C(4)-C(5) | 115.2(2) |
| C(2)-C(3) | 1.498(3) | C(3)-C(4)-C(5) | 121.5(2) |
| C(3)-C(4) | 1.466(4) | C(6)-C(5)-C(4) | 111.6(2) |
| C(4)-C(5) | 1.509(4) | F(2)-C(6)-F(1) | 104.74(18) |
| C(5)-C(6) | 1.498(4) | F(2)-C(6)-C(5) | 109.6(2) |
| C(4)-O(3)-C(3) | 61.21(16) | F(1)-C(6)-C(5) | 108.8(2) |
| O(1)-C(1)-C(6) | 108.02(19) | F(2)-C(6)-C(1) | 109.9(2) |
| O(1)-C(1)-C(2) | 111.45(19) | F(1)-C(6)-C(1) | 107.4(2) |
| C(6)-C(1)-C(2) | 110.0(2) | C(5)-C(6)-C(1) | 115.8(2) |

Symmetry transformations used to generate equivalent atoms:

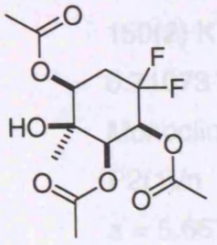
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04170. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 25(1) | 40(1) | 28(1) | -6(1) | 5(1) | -6(1) |
| F(2) | 33(1) | 31(1) | 45(1) | 16(1) | 16(1) | 11(1) |
| O(1) | 25(1) | 22(1) | 37(1) | -4(1) | 17(1) | -6(1) |
| O(2) | 23(1) | 26(1) | 28(1) | -6(1) | 10(1) | 3(1) |
| O(3) | 27(1) | 32(1) | 22(1) | -3(1) | 11(1) | -2(1) |
| C(1) | 23(1) | 22(1) | 21(1) | -3(1) | 11(1) | -3(1) |
| C(2) | 19(1) | 19(1) | 21(1) | -2(1) | 8(1) | 0(1) |
| C(3) | 29(1) | 19(1) | 24(1) | -1(1) | 10(1) | -3(1) |
| C(4) | 25(1) | 29(1) | 24(1) | -1(1) | 13(1) | -5(1) |
| C(5) | 22(1) | 24(1) | 31(2) | -3(1) | 14(1) | -2(1) |
| C(6) | 23(1) | 21(1) | 26(1) | 2(1) | 7(1) | 0(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 04170.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 599 | -2669 | 6981 | 39 |
| H(2) | -200 | 1489 | 5981 | 38 |
| H(1A) | 1804 | -551 | 8397 | 25 |
| H(2A) | 1979 | 3143 | 7718 | 24 |
| H(3) | 1956 | 4310 | 5655 | 29 |
| H(4) | 3589 | 2139 | 5334 | 30 |
| H(5A) | 3288 | -2281 | 6000 | 30 |
| H(5B) | 4561 | -799 | 6782 | 30 |

### 6.1.7 (1*S**,2*S**,3*R**,4*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2-methylcyclohexyl acetate 267



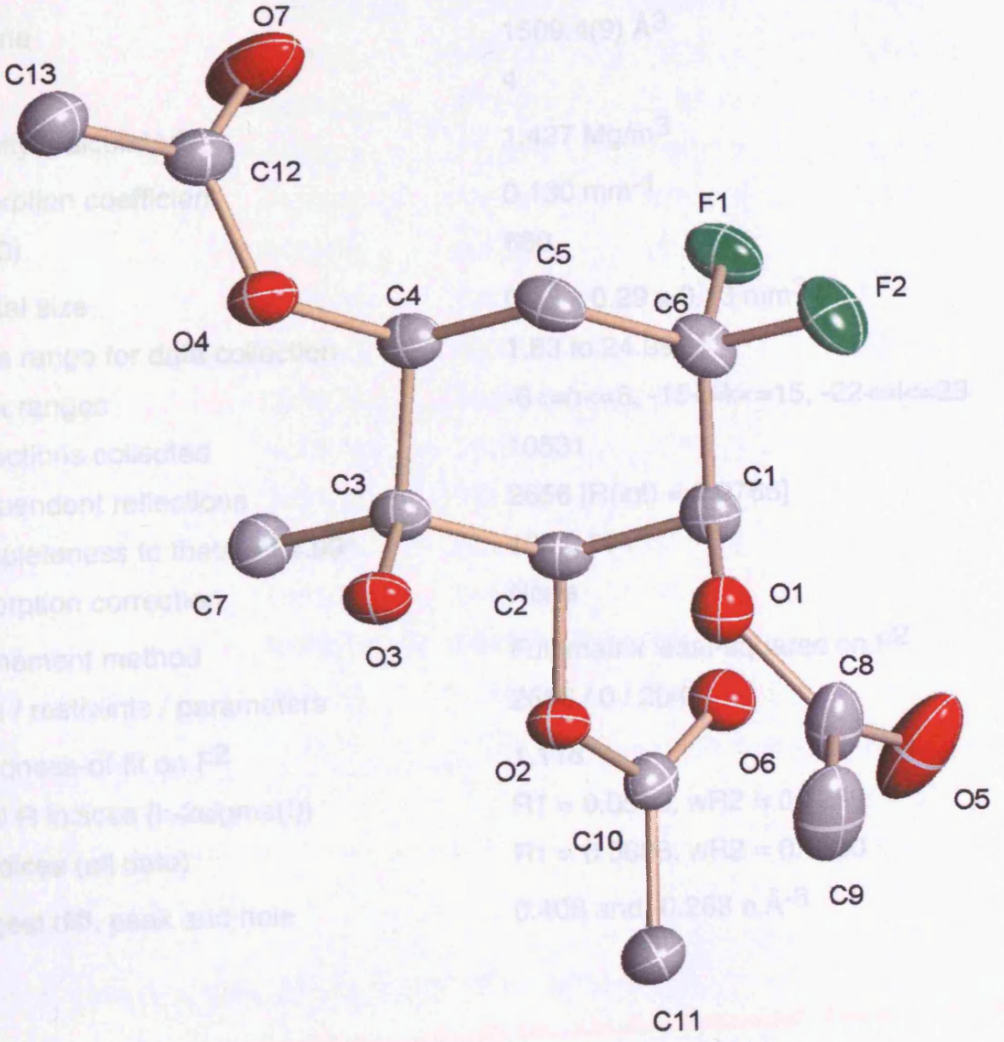



Table 1. Crystal data and structure refinement for 05111.

| | | |
|---|---|---|
| Identification code | 05111 | |
| Empirical formula | C13 H18 F2 O7 | |
| Formula weight | 324.27 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 5.6676(19) Å | □= 90°. |
| | b = 13.376(5) Å | □= 92.670(6)°. |
| | c = 19.932(7) Å | □ = 90°. |
| Volume | 1509.4(9) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.427 $Mg/m^3$ | |
| Absorption coefficient | 0.130 $mm^{-1}$ | |
| F(000) | 680 | |
| Crystal size | 0.33 x 0.29 x 0.13 $mm^3$ | |
| Theta range for data collection | 1.83 to 24.99°. | |
| Index ranges | -6<=h<=6, -15<=k<=15, -22<=l<=23 | |
| Reflections collected | 10531 | |
| Independent reflections | 2656 [R(int) = 0.0766] | |
| Completeness to theta = 24.99° | 100.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2656 / 0 / 204 | |
| Goodness-of-fit on $F^2$ | 1.118 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0548, wR2 = 0.1289 | |
| R indices (all data) | R1 = 0.0608, wR2 = 0.1330 | |
| Largest diff. peak and hole | 0.408 and -0.268 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05111. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 6669(3) | 8728(1) | 3382(1) | 30(1) |
| O(2) | 5086(2) | 10634(1) | 3109(1) | 25(1) |
| O(3) | 8519(2) | 9862(1) | 2292(1) | 26(1) |
| O(4) | 7286(3) | 9067(1) | 1061(1) | 30(1) |
| O(5) | 4882(3) | 9013(2) | 4342(1) | 66(1) |
| O(6) | 1362(3) | 10724(1) | 3452(1) | 30(1) |
| O(7) | 4446(3) | 8595(2) | 312(1) | 59(1) |
| F(1) | 1948(2) | 8005(1) | 2249(1) | 35(1) |
| F(2) | 4461(2) | 7115(1) | 2855(1) | 40(1) |
| C(1) | 4459(4) | 8859(2) | 3006(1) | 26(1) |
| C(2) | 4413(4) | 9856(2) | 2633(1) | 24(1) |
| C(3) | 6122(3) | 9943(2) | 2056(1) | 24(1) |
| C(4) | 5625(4) | 9042(2) | 1593(1) | 26(1) |
| C(5) | 5928(4) | 8049(2) | 1957(1) | 29(1) |
| C(6) | 4239(4) | 7998(2) | 2513(1) | 29(1) |
| C(7) | 5691(4) | 10922(2) | 1677(1) | 31(1) |
| C(8) | 6636(4) | 8822(2) | 4055(1) | 38(1) |
| C(9) | 9051(5) | 8685(3) | 4371(1) | 53(1) |
| C(10) | 3399(4) | 10970(2) | 3512(1) | 25(1) |
| C(11) | 4430(4) | 11663(2) | 4033(1) | 34(1) |
| C(12) | 6469(4) | 8802(2) | 443(1) | 29(1) |
| C(13) | 8378(4) | 8790(2) | -47(1) | 36(1) |

Table 3. Bond lengths [Å] and angles [°] for 05111.

| | | | |
|---|---|---|---|
| O(1)-C(8) | 1.349(3) | O(2)-C(2)-C(1) | 108.01(16) |
| O(1)-C(1) | 1.440(2) | O(2)-C(2)-C(3) | 106.23(16) |
| O(2)-C(10) | 1.354(3) | C(1)-C(2)-C(3) | 115.66(17) |
| O(2)-C(2) | 1.447(2) | O(2)-C(2)-H(2) | 108.9 |
| O(3)-C(3) | 1.421(2) | C(1)-C(2)-H(2) | 108.9 |

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05111. 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) | 22(1) | 35(1) | 32(1) | 5(1) | 0(1) | 2(1) |
| O(2) | 23(1) | 27(1) | 26(1) | -5(1) | -1(1) | -1(1) |
| O(3) | 19(1) | 31(1) | 28(1) | -6(1) | -3(1) | 0(1) |
| O(4) | 24(1) | 39(1) | 27(1) | -9(1) | 1(1) | -2(1) |
| O(5) | 37(1) | 131(2) | 31(1) | 10(1) | 2(1) | 9(1) |
| O(6) | 26(1) | 31(1) | 34(1) | -4(1) | 4(1) | 1(1) |
| O(7) | 32(1) | 109(2) | 37(1) | -19(1) | -3(1) | -13(1) |
| F(1) | 21(1) | 35(1) | 48(1) | -9(1) | 1(1) | -4(1) |
| F(2) | 40(1) | 24(1) | 56(1) | 4(1) | 8(1) | 1(1) |
| C(1) | 18(1) | 30(1) | 30(1) | 1(1) | 1(1) | 1(1) |
| C(2) | 21(1) | 25(1) | 26(1) | -5(1) | -3(1) | 0(1) |
| C(3) | 18(1) | 26(1) | 26(1) | -2(1) | -2(1) | 0(1) |
| C(4) | 19(1) | 32(1) | 28(1) | -5(1) | 0(1) | 1(1) |
| C(5) | 23(1) | 25(1) | 40(1) | -8(1) | 2(1) | 0(1) |
| C(6) | 23(1) | 24(1) | 40(1) | 1(1) | 1(1) | 2(1) |
| C(7) | 34(1) | 28(1) | 30(1) | 2(1) | 1(1) | 3(1) |
| C(8) | 31(1) | 49(2) | 33(1) | 14(1) | 1(1) | -2(1) |
| C(9) | 36(2) | 78(2) | 43(2) | 23(2) | -8(1) | -2(1) |
| C(10) | 30(1) | 21(1) | 23(1) | 3(1) | 1(1) | 3(1) |
| C(11) | 40(1) | 35(1) | 26(1) | -5(1) | 3(1) | -5(1) |
| C(12) | 29(1) | 30(1) | 27(1) | -2(1) | -5(1) | 1(1) |
| C(13) | 37(1) | 42(2) | 28(1) | -2(1) | 0(1) | -2(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x$ $10^3$) for 05111.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3) | 8736 | 10207 | 2641 | 39 |
| H(1) | 3128 | 8834 | 3318 | 31 |
| H(2) | 2768 | 9987 | 2451 | 29 |

| | | | |
|---|---|---|---|
| O(3)-H(3) | 0.8400 | C(3)-C(2)-H(2) | 108.9 |
| O(4)-C(12) | 1.342(3) | O(3)-C(3)-C(7) | 110.99(17) |
| O(4)-C(4) | 1.451(3) | O(3)-C(3)-C(4) | 106.51(16) |
| O(5)-C(8) | 1.197(3) | C(7)-C(3)-C(4) | 110.87(18) |
| O(6)-C(10) | 1.201(3) | O(3)-C(3)-C(2) | 111.81(16) |
| O(7)-C(12) | 1.197(3) | C(7)-C(3)-C(2) | 110.01(17) |
| F(1)-C(6) | 1.378(3) | C(4)-C(3)-C(2) | 106.52(17) |
| F(2)-C(6) | 1.367(3) | O(4)-C(4)-C(5) | 107.85(17) |
| C(1)-C(6) | 1.516(3) | O(4)-C(4)-C(3) | 108.33(17) |
| C(1)-C(2) | 1.528(3) | C(5)-C(4)-C(3) | 112.69(18) |
| C(1)-H(1) | 1.0000 | O(4)-C(4)-H(4) | 109.3 |
| C(2)-C(3) | 1.541(3) | C(5)-C(4)-H(4) | 109.3 |
| C(2)-H(2) | 1.0000 | C(3)-C(4)-H(4) | 109.3 |
| C(3)-C(7) | 1.525(3) | C(6)-C(5)-C(4) | 109.35(18) |
| C(3)-C(4) | 1.535(3) | C(6)-C(5)-H(5A) | 109.8 |
| C(4)-C(5) | 1.520(3) | C(4)-C(5)-H(5A) | 109.8 |
| C(4)-H(4) | 1.0000 | F(2)-C(6)-F(1) | 105.08(17) |
| C(5)-C(6) | 1.499(3) | F(2)-C(6)-C(5) | 111.18(18) |
| C(5)-H(5A) | 0.9900 | F(1)-C(6)-C(5) | 109.91(19) |
| C(7)-H(7A) | 0.9800 | F(2)-C(6)-C(1) | 109.26(19) |
| C(8)-C(9) | 1.491(3) | F(1)-C(6)-C(1) | 106.85(17) |
| C(9)-H(9A) | 0.9800 | C(5)-C(6)-C(1) | 114.09(19) |
| C(10)-C(11) | 1.491(3) | C(3)-C(7)-H(7A) | 109.5 |
| C(11)-H(11A) | 0.9800 | O(5)-C(8)-O(1) | 123.0(2) |
| C(12)-C(13) | 1.491(3) | O(5)-C(8)-C(9) | 126.3(2) |
| C(13)-H(13A) | 0.9800 | O(1)-C(8)-C(9) | 110.7(2) |
| C(8)-O(1)-C(1) | 116.98(18) | C(8)-C(9)-H(9A) | 109.5 |
| C(10)-O(2)-C(2) | 117.19(16) | O(6)-C(10)-O(2) | 123.4(2) |
| C(3)-O(3)-H(3) | 109.5 | O(6)-C(10)-C(11) | 125.7(2) |
| C(12)-O(4)-C(4) | 117.18(17) | O(2)-C(10)-C(11) | 110.86(19) |
| O(1)-C(1)-C(6) | 106.75(17) | C(10)-C(11)-H(11A) | 109.5 |
| O(1)-C(1)-C(2) | 110.75(17) | H(11A)-C(11)-H(11B) | 109.5 |
| C(6)-C(1)-C(2) | 110.36(18) | O(7)-C(12)-O(4) | 123.2(2) |
| O(1)-C(1)-H(1) | 109.6 | O(7)-C(12)-C(13) | 124.8(2) |
| C(6)-C(1)-H(1) | 109.6 | O(4)-C(12)-C(13) | 111.94(19) |
| C(2)-C(1)-H(1) | 109.6 | C(12)-C(13)-H(13A) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

| | | | | |
|---|---|---|---|---|
| H(4) | 3979 | 9091 | 1393 | 31 |
| H(5A) | 5617 | 7492 | 1639 | 35 |
| H(5B) | 7570 | 7985 | 2145 | 35 |
| H(7A) | 6008 | 11486 | 1982 | 46 |
| H(7B) | 4045 | 10949 | 1505 | 46 |
| H(7C) | 6744 | 10960 | 1302 | 46 |
| H(9A) | 10117 | 9188 | 4195 | 79 |
| H(9B) | 9631 | 8015 | 4267 | 79 |
| H(9C) | 8994 | 8762 | 4859 | 79 |
| H(11A) | 3202 | 12121 | 4178 | 50 |
| H(11B) | 5712 | 12049 | 3845 | 50 |
| H(11C) | 5052 | 11276 | 4420 | 50 |
| H(13A) | 8251 | 8179 | -318 | 54 |
| H(13B) | 9921 | 8807 | 197 | 54 |
| H(13C) | 8218 | 9375 | -341 | 54 |

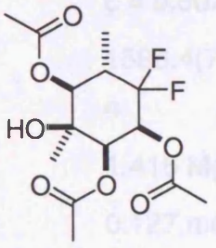
Table 6. Torsion angles [°] for 05111.

| | | | |
|---|---|---|---|
| C(8)-O(1)-C(1)-C(6) | -132.9(2) | C(7)-C(3)-C(4)-C(5) | -177.48(18) |
| C(8)-O(1)-C(1)-C(2) | 106.9(2) | C(2)-C(3)-C(4)-C(5) | -57.8(2) |
| C(10)-O(2)-C(2)-C(1) | -80.2(2) | O(4)-C(4)-C(5)-C(6) | 179.92(16) |
| C(10)-O(2)-C(2)-C(3) | 155.14(17) | C(3)-C(4)-C(5)-C(6) | 60.4(2) |
| O(1)-C(1)-C(2)-O(2) | -51.0(2) | C(4)-C(5)-C(6)-F(2) | -179.80(17) |
| C(6)-C(1)-C(2)-O(2) | -169.01(16) | C(4)-C(5)-C(6)-F(1) | 64.3(2) |
| O(1)-C(1)-C(2)-C(3) | 67.8(2) | C(4)-C(5)-C(6)-C(1) | -55.7(2) |
| C(6)-C(1)-C(2)-C(3) | -50.2(2) | O(1)-C(1)-C(6)-F(2) | 55.1(2) |
| O(2)-C(2)-C(3)-O(3) | 57.1(2) | C(2)-C(1)-C(6)-F(2) | 175.51(16) |
| C(1)-C(2)-C(3)-O(3) | -62.7(2) | O(1)-C(1)-C(6)-F(1) | 168.28(16) |
| O(2)-C(2)-C(3)-C(7) | -66.7(2) | C(2)-C(1)-C(6)-F(1) | -71.3(2) |
| C(1)-C(2)-C(3)-C(7) | 173.48(17) | O(1)-C(1)-C(6)-C(5) | -70.0(2) |
| O(2)-C(2)-C(3)-C(4) | 173.07(15) | C(2)-C(1)-C(6)-C(5) | 50.4(2) |
| C(1)-C(2)-C(3)-C(4) | 53.3(2) | C(1)-O(1)-C(8)-O(5) | -0.6(4) |
| C(12)-O(4)-C(4)-C(5) | 96.3(2) | C(1)-O(1)-C(8)-C(9) | -179.0(2) |
| C(12)-O(4)-C(4)-C(3) | -141.41(19) | C(2)-O(2)-C(10)-O(6) | -7.0(3) |
| O(3)-C(3)-C(4)-O(4) | -57.6(2) | C(2)-O(2)-C(10)-C(11) | 172.35(18) |
| C(7)-C(3)-C(4)-O(4) | 63.3(2) | C(4)-O(4)-C(12)-O(7) | 3.4(3) |

| | | | |
|---|---|---|---|
| C(2)-C(3)-C(4)-O(4) | -177.05(16) | C(4)-O(4)-C(12)-C(13) | -176.02(19) |
| O(3)-C(3)-C(4)-C(5) | 61.7(2) | | |

Symmetry transformations used to generate equivalent atoms:

### 6.1.8 (1*S**,2*S**,3*R**,4*S**,6*S**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 269



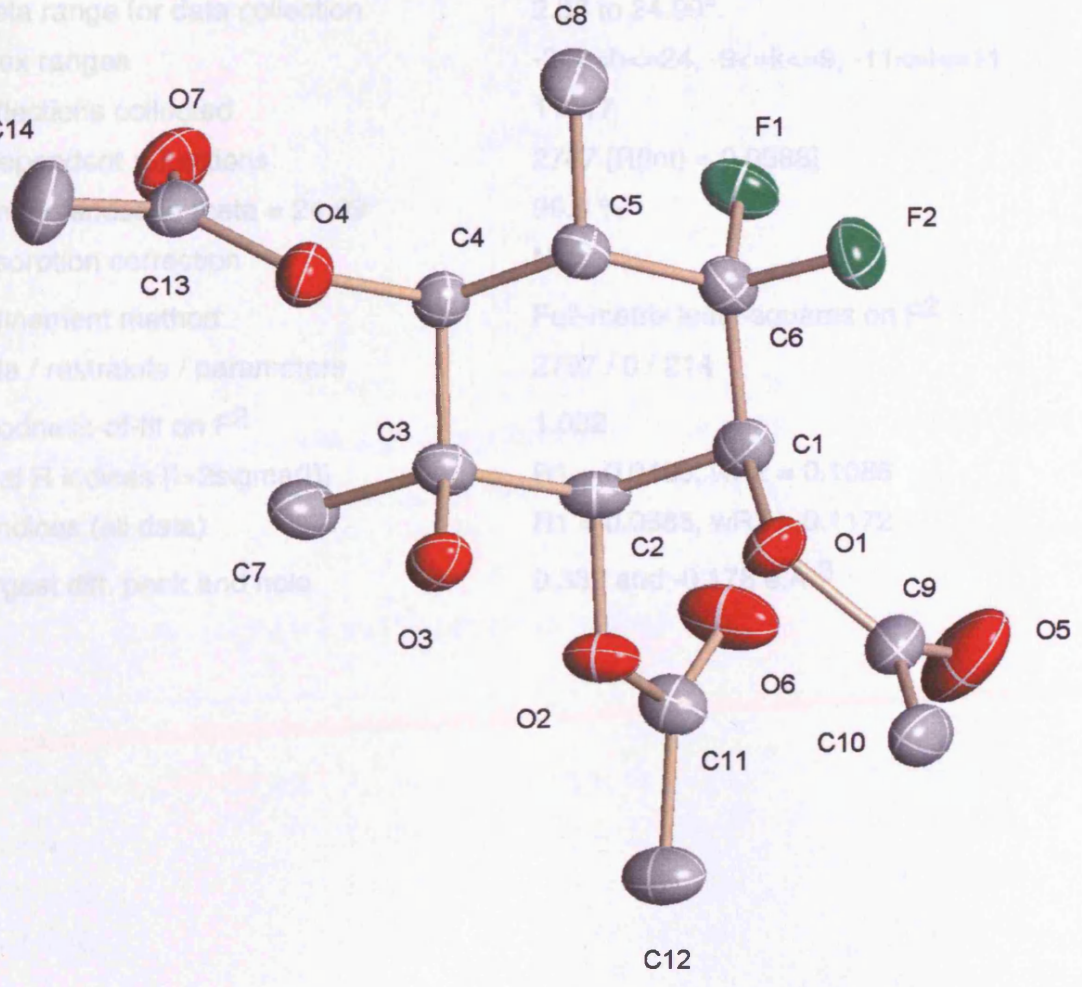



Table 1. Crystal data and structure refinement for 05110a.

| | | |
|---|---|---|
| Identification code | 05110a | |
| Empirical formula | C14 H20 F2 O7 | |
| Formula weight | 338.30 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 20.454(5) Å | □= 90°. |
| | b = 8.329(2) Å | □= 101.455(4)°. |
| | c = 9.502(3) Å | □ = 90°. |
| Volume | 1586.4(7) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.416 $Mg/m^3$ | |
| Absorption coefficient | 0.127 $mm^{-1}$ | |
| F(000) | 712 | |
| Crystal size | 0.26 x 0.20 x 0.10 $mm^3$ | |
| Theta range for data collection | 2.03 to 24.99°. | |
| Index ranges | -24<=h<=24, -9<=k<=9, -11<=l<=11 | |
| Reflections collected | 11017 | |
| Independent reflections | 2787 [R(int) = 0.0588] | |
| Completeness to theta = 24.99° | 99.9 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2787 / 0 / 214 | |
| Goodness-of-fit on $F^2$ | 1.032 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0488, wR2 = 0.1086 | |
| R indices (all data) | R1 = 0.0685, wR2 = 0.1172 | |
| Largest diff. peak and hole | 0.332 and -0.178 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05110a. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 1609(1) | 5822(2) | 6965(2) | 30(1) |
| O(2) | 1795(1) | 2556(2) | 7292(1) | 31(1) |
| O(3) | 2717(1) | 4223(2) | 6090(1) | 32(1) |
| O(4) | 3924(1) | 5083(2) | 7747(2) | 31(1) |
| O(5) | 609(1) | 5195(3) | 7405(2) | 67(1) |
| O(6) | 1365(1) | 1692(2) | 9138(2) | 50(1) |
| O(7) | 4559(1) | 3500(2) | 9406(2) | 46(1) |
| F(1) | 2578(1) | 6020(2) | 10481(1) | 36(1) |
| F(2) | 2115(1) | 7894(2) | 9012(1) | 38(1) |
| C(1) | 1916(1) | 5197(3) | 8345(2) | 28(1) |
| C(2) | 2256(1) | 3593(2) | 8207(2) | 27(1) |
| C(3) | 2876(1) | 3681(2) | 7540(2) | 26(1) |
| C(4) | 3354(1) | 4900(2) | 8409(2) | 26(1) |
| C(5) | 3051(1) | 6572(2) | 8460(2) | 25(1) |
| C(6) | 2423(1) | 6432(2) | 9049(2) | 27(1) |
| C(7) | 3201(1) | 2035(3) | 7573(3) | 38(1) |
| C(8) | 3539(1) | 7758(3) | 9326(3) | 39(1) |
| C(9) | 933(1) | 5800(3) | 6635(3) | 34(1) |
| C(10) | 672(1) | 6553(3) | 5229(3) | 39(1) |
| C(11) | 1368(1) | 1674(3) | 7882(2) | 31(1) |
| C(12) | 945(1) | 657(3) | 6775(2) | 41(1) |
| C(13) | 4494(1) | 4299(3) | 8339(3) | 37(1) |
| C(14) | 5005(1) | 4563(4) | 7442(3) | 53(1) |

Table 3. Bond lengths [Å] and angles [°] for 05110a.

| | | | |
|---|---|---|---|
| O(1)-C(9) | 1.355(3) | C(7)-C(3)-C(2) | 110.07(18) |
| O(1)-C(1) | 1.434(2) | O(3)-C(3)-C(4) | 108.06(16) |
| O(2)-C(11) | 1.345(3) | C(7)-C(3)-C(4) | 110.93(17) |
| O(2)-C(2) | 1.437(2) | C(2)-C(3)-C(4) | 107.56(16) |
| O(3)-C(3) | 1.425(2) | O(4)-C(4)-C(5) | 106.62(16) |

| | | | |
|---|---|---|---|
| O(3)-H(3) | 0.8400 | O(4)-C(4)-C(3) | 108.66(16) |
| O(4)-C(13) | 1.358(3) | C(5)-C(4)-C(3) | 113.70(17) |
| O(4)-C(4) | 1.438(2) | O(4)-C(4)-H(4) | 109.3 |
| O(5)-C(9) | 1.193(3) | C(5)-C(4)-H(4) | 109.3 |
| O(6)-C(11) | 1.195(3) | C(3)-C(4)-H(4) | 109.3 |
| O(7)-C(13) | 1.198(3) | C(6)-C(5)-C(8) | 111.43(18) |
| F(1)-C(6) | 1.378(2) | C(6)-C(5)-C(4) | 108.78(16) |
| F(2)-C(6) | 1.369(2) | C(8)-C(5)-C(4) | 112.44(17) |
| C(1)-C(6) | 1.518(3) | C(6)-C(5)-H(5) | 108.0 |
| C(1)-C(2) | 1.523(3) | C(8)-C(5)-H(5) | 108.0 |
| C(1)-H(1) | 1.0000 | C(4)-C(5)-H(5) | 108.0 |
| C(2)-C(3) | 1.529(3) | F(2)-C(6)-F(1) | 105.11(15) |
| C(2)-H(2) | 1.0000 | F(2)-C(6)-C(5) | 110.14(17) |
| C(3)-C(7) | 1.521(3) | F(1)-C(6)-C(5) | 109.96(16) |
| C(3)-C(4) | 1.532(3) | F(2)-C(6)-C(1) | 108.71(17) |
| C(4)-C(5) | 1.529(3) | F(1)-C(6)-C(1) | 105.62(16) |
| C(4)-H(4) | 1.0000 | C(5)-C(6)-C(1) | 116.61(17) |
| C(5)-C(6) | 1.504(3) | C(3)-C(7)-H(7A) | 109.5 |
| C(5)-C(8) | 1.524(3) | C(3)-C(7)-H(7B) | 109.5 |
| C(5)-H(5) | 1.0000 | H(7A)-C(7)-H(7B) | 109.5 |
| C(7)-H(7A) | 0.9800 | C(3)-C(7)-H(7C) | 109.5 |
| C(7)-H(7B) | 0.9800 | H(7A)-C(7)-H(7C) | 109.5 |
| C(7)-H(7C) | 0.9800 | H(7B)-C(7)-H(7C) | 109.5 |
| C(8)-H(8A) | 0.9800 | C(5)-C(8)-H(8A) | 109.5 |
| C(8)-H(8B) | 0.9800 | C(5)-C(8)-H(8B) | 109.5 |
| C(8)-H(8C) | 0.9800 | H(8A)-C(8)-H(8B) | 109.5 |
| C(9)-C(10) | 1.477(3) | C(5)-C(8)-H(8C) | 109.5 |
| C(10)-H(10A) | 0.9800 | H(8A)-C(8)-H(8C) | 109.5 |
| C(10)-H(10B) | 0.9800 | H(8B)-C(8)-H(8C) | 109.5 |
| C(10)-H(10C) | 0.9800 | O(5)-C(9)-O(1) | 122.0(2) |
| C(11)-C(12) | 1.488(3) | O(5)-C(9)-C(10) | 126.1(2) |
| C(12)-H(12A) | 0.9800 | O(1)-C(9)-C(10) | 111.9(2) |
| C(12)-H(12B) | 0.9800 | C(9)-C(10)-H(10A) | 109.5 |
| C(12)-H(12C) | 0.9800 | C(9)-C(10)-H(10B) | 109.5 |
| C(13)-C(14) | 1.490(4) | H(10A)-C(10)-H(10B) | 109.5 |
| C(14)-H(14A) | 0.9800 | C(9)-C(10)-H(10C) | 109.5 |
| C(14)-H(14B) | 0.9800 | H(10A)-C(10)-H(10C) | 109.5 |
| C(14)-H(14C) | 0.9800 | H(10B)-C(10)-H(10C) | 109.5 |

| | | | |
|---|---|---|---|
| C(9)-O(1)-C(1) | 116.70(17) | O(6)-C(11)-O(2) | 122.8(2) |
| C(11)-O(2)-C(2) | 118.58(16) | O(6)-C(11)-C(12) | 126.5(2) |
| C(3)-O(3)-H(3) | 109.5 | O(2)-C(11)-C(12) | 110.54(18) |
| C(13)-O(4)-C(4) | 118.20(17) | C(11)-C(12)-H(12A) | 109.5 |
| O(1)-C(1)-C(6) | 107.12(16) | C(11)-C(12)-H(12B) | 109.5 |
| O(1)-C(1)-C(2) | 111.36(17) | H(12A)-C(12)-H(12B) | 109.5 |
| C(6)-C(1)-C(2) | 110.45(17) | C(11)-C(12)-H(12C) | 109.5 |
| O(1)-C(1)-H(1) | 109.3 | H(12A)-C(12)-H(12C) | 109.5 |
| C(6)-C(1)-H(1) | 109.3 | H(12B)-C(12)-H(12C) | 109.5 |
| C(2)-C(1)-H(1) | 109.3 | O(7)-C(13)-O(4) | 124.0(2) |
| O(2)-C(2)-C(1) | 108.89(17) | O(7)-C(13)-C(14) | 126.4(2) |
| O(2)-C(2)-C(3) | 106.13(16) | O(4)-C(13)-C(14) | 109.6(2) |
| C(1)-C(2)-C(3) | 115.05(17) | C(13)-C(14)-H(14A) | 109.5 |
| O(2)-C(2)-H(2) | 108.9 | C(13)-C(14)-H(14B) | 109.5 |
| C(1)-C(2)-H(2) | 108.9 | H(14A)-C(14)-H(14B) | 109.5 |
| C(3)-C(2)-H(2) | 108.9 | C(13)-C(14)-H(14C) | 109.5 |
| O(3)-C(3)-C(7) | 108.70(17) | H(14A)-C(14)-H(14C) | 109.5 |
| O(3)-C(3)-C(2) | 111.52(16) | H(14B)-C(14)-H(14C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05110a. 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) | 23(1) | 39(1) | 27(1) | 5(1) | 2(1) | -1(1) |
| O(2) | 37(1) | 35(1) | 21(1) | -1(1) | 4(1) | -14(1) |
| O(3) | 29(1) | 43(1) | 22(1) | 1(1) | 3(1) | -1(1) |
| O(4) | 25(1) | 34(1) | 35(1) | 0(1) | 6(1) | 3(1) |
| O(5) | 30(1) | 114(2) | 57(1) | 15(1) | 10(1) | -8(1) |
| O(6) | 71(1) | 55(1) | 26(1) | -5(1) | 17(1) | -29(1) |
| O(7) | 34(1) | 44(1) | 53(1) | 6(1) | -6(1) | 8(1) |
| F(1) | 49(1) | 38(1) | 21(1) | -2(1) | 7(1) | -5(1) |
| F(2) | 38(1) | 31(1) | 45(1) | -5(1) | 12(1) | 7(1) |
| C(1) | 28(1) | 34(1) | 21(1) | 2(1) | 5(1) | -1(1) |
| C(2) | 33(1) | 27(1) | 20(1) | 0(1) | -1(1) | -7(1) |
| C(3) | 31(1) | 25(1) | 20(1) | 1(1) | 1(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(4) | 25(1) | 28(1) | 23(1) | 1(1) | 4(1) | 1(1) |
| C(5) | 29(1) | 22(1) | 25(1) | 1(1) | 5(1) | 1(1) |
| C(6) | 32(1) | 26(1) | 22(1) | 1(1) | 4(1) | 5(1) |
| C(7) | 41(1) | 28(1) | 41(1) | -6(1) | -3(1) | 4(1) |
| C(8) | 36(1) | 27(1) | 53(2) | -6(1) | 8(1) | -4(1) |
| C(9) | 25(1) | 38(1) | 39(1) | -6(1) | 5(1) | -2(1) |
| C(10) | 32(1) | 36(1) | 44(1) | -6(1) | -4(1) | 6(1) |
| C(11) | 38(1) | 29(1) | 28(1) | 1(1) | 8(1) | -5(1) |
| C(12) | 42(2) | 47(2) | 34(1) | -5(1) | 5(1) | -17(1) |
| C(13) | 28(1) | 32(1) | 46(2) | -10(1) | -2(1) | 1(1) |
| C(14) | 31(1) | 60(2) | 72(2) | -9(2) | 15(1) | 6(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 05110a.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3) | 2303 | 4163 | 5787 | 47 |
| H(1) | 1570 | 5053 | 8943 | 33 |
| H(2) | 2380 | 3091 | 9179 | 33 |
| H(4) | 3504 | 4492 | 9410 | 31 |
| H(5) | 2927 | 6984 | 7453 | 30 |
| H(7A) | 2870 | 1247 | 7119 | 57 |
| H(7B) | 3375 | 1721 | 8571 | 57 |
| H(7C) | 3568 | 2076 | 7050 | 57 |
| H(8A) | 3316 | 8792 | 9376 | 58 |
| H(8B) | 3922 | 7906 | 8861 | 58 |
| H(8C) | 3694 | 7340 | 10299 | 58 |
| H(10A) | 539 | 5715 | 4504 | 58 |
| H(10B) | 1019 | 7225 | 4952 | 58 |
| H(10C) | 284 | 7218 | 5296 | 58 |
| H(12A) | 1172 | -364 | 6689 | 62 |
| H(12B) | 866 | 1215 | 5849 | 62 |
| H(12C) | 517 | 448 | 7057 | 62 |
| H(14A) | 5449 | 4327 | 8011 | 80 |
| H(14B) | 4989 | 5684 | 7122 | 80 |
| H(14C) | 4914 | 3852 | 6604 | 80 |

Table 6. Torsion angles [°] for 05110a.

| | | | |
|---|---|---|---|
| C(9)-O(1)-C(1)-C(6) | -130.53(19) | O(4)-C(4)-C(5)-C(6) | 176.02(15) |
| C(9)-O(1)-C(1)-C(2) | 108.6(2) | C(3)-C(4)-C(5)-C(6) | 56.3(2) |
| C(11)-O(2)-C(2)-C(1) | -86.1(2) | O(4)-C(4)-C(5)-C(8) | -60.1(2) |
| C(11)-O(2)-C(2)-C(3) | 149.47(18) | C(3)-C(4)-C(5)-C(8) | -179.78(18) |
| O(1)-C(1)-C(2)-O(2) | -49.8(2) | C(8)-C(5)-C(6)-F(2) | 59.8(2) |
| C(6)-C(1)-C(2)-O(2) | -168.69(16) | C(4)-C(5)-C(6)-F(2) | -175.72(16) |
| O(1)-C(1)-C(2)-C(3) | 69.1(2) | C(8)-C(5)-C(6)-F(1) | -55.6(2) |
| C(6)-C(1)-C(2)-C(3) | -49.7(2) | C(4)-C(5)-C(6)-F(1) | 68.9(2) |
| O(2)-C(2)-C(3)-O(3) | 56.5(2) | C(8)-C(5)-C(6)-C(1) | -175.76(18) |
| C(1)-C(2)-C(3)-O(3) | -63.9(2) | C(4)-C(5)-C(6)-C(1) | -51.3(2) |
| O(2)-C(2)-C(3)-C(7) | -64.2(2) | O(1)-C(1)-C(6)-F(2) | 52.0(2) |
| C(1)-C(2)-C(3)-C(7) | 175.35(17) | C(2)-C(1)-C(6)-F(2) | 173.48(16) |
| O(2)-C(2)-C(3)-C(4) | 174.86(15) | O(1)-C(1)-C(6)-F(1) | 164.41(15) |
| C(1)-C(2)-C(3)-C(4) | 54.4(2) | C(2)-C(1)-C(6)-F(1) | -74.2(2) |
| C(13)-O(4)-C(4)-C(5) | 136.23(18) | O(1)-C(1)-C(6)-C(5) | -73.1(2) |
| C(13)-O(4)-C(4)-C(3) | -100.9(2) | C(2)-C(1)-C(6)-C(5) | 48.3(2) |
| O(3)-C(3)-C(4)-O(4) | -55.8(2) | C(1)-O(1)-C(9)-O(5) | -5.0(3) |
| C(7)-C(3)-C(4)-O(4) | 63.2(2) | C(1)-O(1)-C(9)-C(10) | 176.79(18) |
| C(2)-C(3)-C(4)-O(4) | -176.34(15) | C(2)-O(2)-C(11)-O(6) | -1.5(3) |
| O(3)-C(3)-C(4)-C(5) | 62.7(2) | C(2)-O(2)-C(11)-C(12) | -178.71(18) |
| C(7)-C(3)-C(4)-C(5) | -178.22(18) | C(4)-O(4)-C(13)-O(7) | -2.3(3) |
| C(2)-C(3)-C(4)-C(5) | -57.8(2) | C(4)-O(4)-C(13)-C(14) | 176.40(19) |

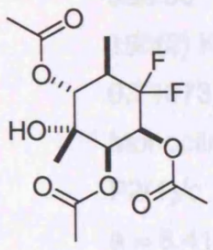
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 05110a [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(3)-H(3)...O(6)#1 | 0.84 | 2.33 | 3.104(2) | 152.4 |
| O(3)-H(3)...O(2) | 0.84 | 2.35 | 2.766(2) | 111.4 |
| O(3)-H(3)...O(1) | 0.84 | 2.41 | 2.890(2) | 117.0 |

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z-1/2

### 6.1.9 (1*R**,2*R**,3*R**,4*S**,6*R**)-3,4-bis(acetyloxy)-5,5-difluoro-2-hydroxy-2,6-dimethylcyclohexyl acetate 270



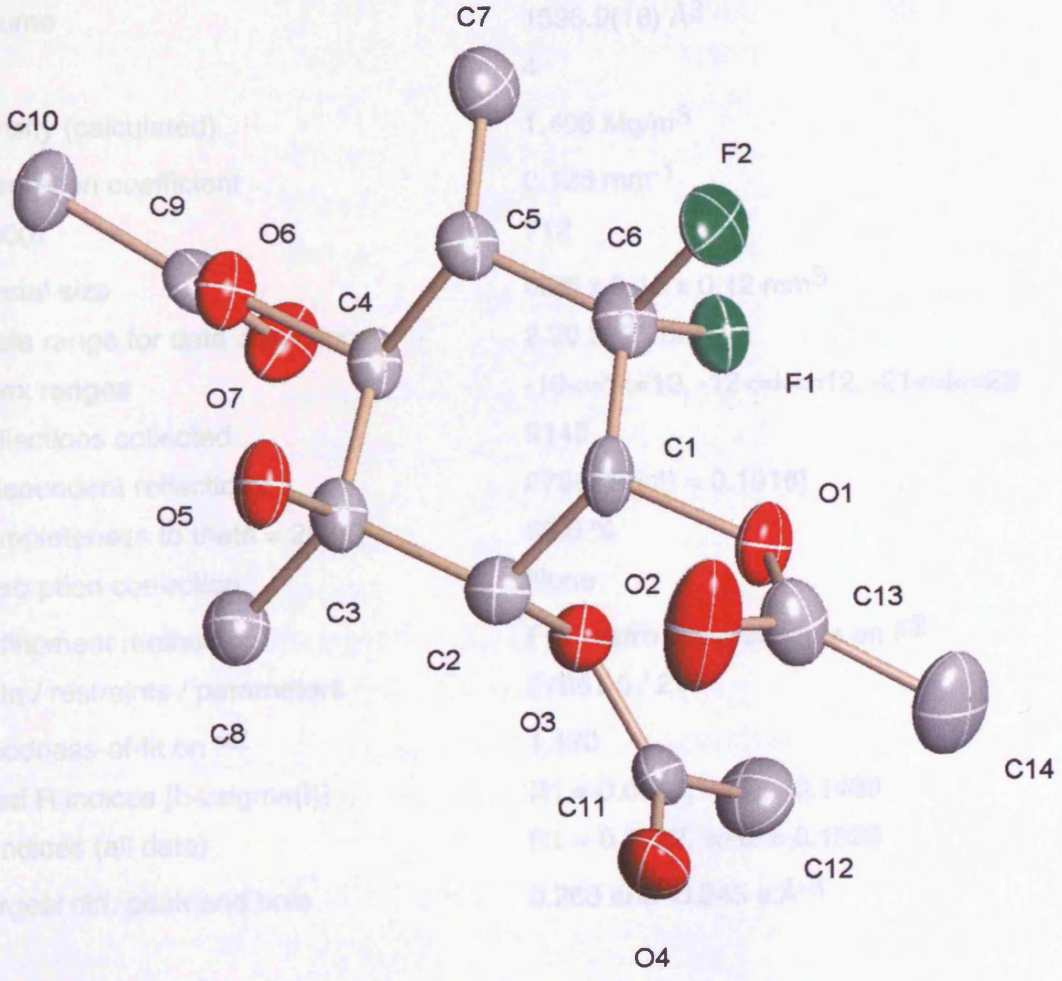



Table 1. Crystal data and structure refinement for 05105.

| | | |
|---|---|---|
| Identification code | 05105 | |
| Empirical formula | C14 H20 F2 O7 | |
| Formula weight | 338.30 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 8.418(5) Å | □= 90°. |
| | b = 10.252(7) Å | □= 101.992(10)°. |
| | c = 18.904(12) Å | □ = 90°. |
| Volume | 1595.9(18) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.408 $Mg/m^3$ | |
| Absorption coefficient | 0.126 $mm^{-1}$ | |
| F(000) | 712 | |
| Crystal size | 0.26 x 0.16 x 0.12 $mm^3$ | |
| Theta range for data collection | 2.20 to 25.00°. | |
| Index ranges | -10<=h<=10, -12<=k<=12, -21<=l<=22 | |
| Reflections collected | 9148 | |
| Independent reflections | 2796 [R(int) = 0.1916] | |
| Completeness to theta = 25.00° | 99.6 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2796 / 0 / 214 | |
| Goodness-of-fit on $F^2$ | 1.170 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0840, wR2 = 0.1489 | |
| R indices (all data) | R1 = 0.1227, wR2 = 0.1626 | |
| Largest diff. peak and hole | 0.263 and -0.243 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05105. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 283(3) | 9414(3) | 1331(1) | 34(1) |
| O(2) | -1(4) | 9911(4) | 2444(2) | 73(1) |
| O(3) | 3275(3) | 9443(3) | 1011(1) | 30(1) |
| O(4) | 3035(3) | 11443(3) | 1459(2) | 45(1) |
| O(5) | 4185(3) | 7306(3) | 2555(1) | 36(1) |
| O(6) | 4998(2) | 5622(3) | 1446(1) | 30(1) |
| O(7) | 5894(3) | 6112(3) | 438(2) | 36(1) |
| F(1) | 865(2) | 7587(2) | 413(1) | 35(1) |
| F(2) | -567(2) | 6816(2) | 1143(1) | 43(1) |
| C(1) | 1367(4) | 8377(4) | 1609(2) | 32(1) |
| C(2) | 3125(4) | 8858(4) | 1691(2) | 30(1) |
| C(3) | 4349(4) | 7745(4) | 1860(2) | 30(1) |
| C(4) | 3851(4) | 6682(4) | 1301(2) | 26(1) |
| C(5) | 2161(4) | 6122(4) | 1314(2) | 29(1) |
| C(6) | 975(4) | 7220(4) | 1120(2) | 33(1) |
| C(7) | 1738(4) | 4938(4) | 835(2) | 41(1) |
| C(8) | 6063(4) | 8231(4) | 1887(2) | 37(1) |
| C(9) | 5915(4) | 5406(4) | 944(2) | 28(1) |
| C(10) | 6914(4) | 4221(4) | 1123(2) | 35(1) |
| C(11) | 3138(4) | 10743(4) | 962(2) | 31(1) |
| C(12) | 3104(5) | 11180(5) | 207(2) | 47(1) |
| C(13) | -271(4) | 10156(5) | 1814(2) | 42(1) |
| C(14) | -1209(5) | 11279(5) | 1456(3) | 57(1) |

Table 3. Bond lengths [Å] and angles [°] for 05105.

| | | | |
|---|---|---|---|
| O(1)-C(13) | 1.344(5) | O(3)-C(2)-C(3) | 108.4(3) |
| O(1)-C(1) | 1.428(5) | O(3)-C(2)-C(1) | 107.7(3) |
| O(2)-C(13) | 1.191(5) | C(3)-C(2)-C(1) | 112.0(3) |
| O(3)-C(11) | 1.339(5) | O(3)-C(2)-H(2) | 109.5 |
| O(3)-C(2) | 1.446(4) | C(3)-C(2)-H(2) | 109.5 |
| O(4)-C(11) | 1.200(5) | C(1)-C(2)-H(2) | 109.5 |
| O(5)-C(3) | 1.423(4) | O(5)-C(3)-C(4) | 110.5(3) |

| | | | |
|---|---|---|---|
| O(5)-H(5) | 0.8400 | O(5)-C(3)-C(8) | 110.3(3) |
| O(6)-C(9) | 1.360(4) | C(4)-C(3)-C(8) | 112.5(3) |
| O(6)-C(4) | 1.442(4) | O(5)-C(3)-C(2) | 103.8(3) |
| O(7)-C(9) | 1.197(4) | C(4)-C(3)-C(2) | 108.4(3) |
| F(1)-C(6) | 1.372(4) | C(8)-C(3)-C(2) | 110.9(3) |
| F(2)-C(6) | 1.372(4) | O(6)-C(4)-C(3) | 109.4(3) |
| C(1)-C(6) | 1.498(6) | O(6)-C(4)-C(5) | 107.5(3) |
| C(1)-C(2) | 1.537(5) | C(3)-C(4)-C(5) | 112.3(3) |
| C(1)-H(1) | 1.0000 | O(6)-C(4)-H(4) | 109.2 |
| C(2)-C(3) | 1.526(5) | C(3)-C(4)-H(4) | 109.2 |
| C(2)-H(2) | 1.0000 | C(5)-C(4)-H(4) | 109.2 |
| C(3)-C(4) | 1.514(6) | C(6)-C(5)-C(7) | 113.2(3) |
| C(3)-C(8) | 1.518(5) | C(6)-C(5)-C(4) | 106.7(3) |
| C(4)-C(5) | 1.539(4) | C(7)-C(5)-C(4) | 113.1(3) |
| C(4)-H(4) | 1.0000 | C(6)-C(5)-H(5A) | 107.9 |
| C(5)-C(6) | 1.499(6) | C(7)-C(5)-H(5A) | 107.9 |
| C(5)-C(7) | 1.512(6) | C(4)-C(5)-H(5A) | 107.9 |
| C(5)-H(5A) | 1.0000 | F(2)-C(6)-F(1) | 104.0(3) |
| C(7)-H(7A) | 0.9800 | F(2)-C(6)-C(1) | 107.9(3) |
| C(8)-H(8A) | 0.9800 | F(1)-C(6)-C(1) | 110.2(3) |
| C(9)-C(10) | 1.476(6) | F(2)-C(6)-C(5) | 110.6(3) |
| C(10)-H(10A) | 0.9800 | F(1)-C(6)-C(5) | 110.6(3) |
| C(11)-C(12) | 1.490(6) | C(1)-C(6)-C(5) | 113.1(3) |
| C(12)-H(12A) | 0.9800 | C(5)-C(7)-H(7A) | 109.5 |
| C(13)-C(14) | 1.479(7) | C(3)-C(8)-H(8A) | 109.5 |
| C(14)-H(14A) | 0.9800 | O(7)-C(9)-O(6) | 122.9(3) |
| | | O(7)-C(9)-C(10) | 126.4(3) |
| C(13)-O(1)-C(1) | 117.1(3) | O(6)-C(9)-C(10) | 110.7(3) |
| C(11)-O(3)-C(2) | 116.9(3) | C(9)-C(10)-H(10A) | 109.5 |
| C(3)-O(5)-H(5) | 109.5 | O(4)-C(11)-O(3) | 124.0(4) |
| C(9)-O(6)-C(4) | 116.4(3) | O(4)-C(11)-C(12) | 125.4(4) |
| O(1)-C(1)-C(6) | 108.7(3) | O(3)-C(11)-C(12) | 110.5(4) |
| O(1)-C(1)-C(2) | 109.0(3) | C(11)-C(12)-H(12A) | 109.5 |
| C(6)-C(1)-C(2) | 113.6(3) | O(2)-C(13)-O(1) | 122.6(4) |
| O(1)-C(1)-H(1) | 108.5 | O(2)-C(13)-C(14) | 126.5(4) |
| C(6)-C(1)-H(1) | 108.5 | O(1)-C(13)-C(14) | 110.9(4) |
| C(2)-C(1)-H(1) | 108.5 | C(13)-C(14)-H(14A) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05105. 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) | 28(1) | 45(2) | 31(2) | 4(1) | 12(1) | 16(1) |
| O(2) | 79(2) | 105(3) | 36(2) | -1(2) | 16(2) | 53(2) |
| O(3) | 31(1) | 34(2) | 28(2) | 1(1) | 8(1) | 2(1) |
| O(4) | 44(2) | 42(2) | 44(2) | -11(2) | -3(1) | 1(1) |
| O(5) | 30(1) | 53(2) | 26(2) | 11(1) | 9(1) | 14(1) |
| O(6) | 24(1) | 42(2) | 29(1) | 6(1) | 14(1) | 9(1) |
| O(7) | 32(1) | 42(2) | 43(2) | 11(2) | 24(1) | 6(1) |
| F(1) | 30(1) | 46(2) | 29(1) | 5(1) | 4(1) | 5(1) |
| F(2) | 19(1) | 51(2) | 62(2) | 6(1) | 14(1) | 3(1) |
| C(1) | 22(2) | 44(3) | 29(2) | 5(2) | 8(2) | 13(2) |
| C(2) | 32(2) | 36(2) | 23(2) | 1(2) | 11(2) | 1(2) |
| C(3) | 22(2) | 42(3) | 27(2) | 7(2) | 9(2) | 3(2) |
| C(4) | 19(2) | 38(2) | 25(2) | 4(2) | 9(2) | 4(2) |
| C(5) | 23(2) | 38(2) | 29(2) | 2(2) | 12(2) | 1(2) |
| C(6) | 23(2) | 46(3) | 34(2) | 6(2) | 13(2) | 0(2) |
| C(7) | 28(2) | 49(3) | 47(3) | -2(2) | 11(2) | 3(2) |
| C(8) | 30(2) | 43(3) | 38(3) | 3(2) | 9(2) | 3(2) |
| C(9) | 18(2) | 39(2) | 30(2) | 1(2) | 13(2) | -4(2) |
| C(10) | 28(2) | 43(3) | 37(2) | 6(2) | 15(2) | 13(2) |
| C(11) | 19(2) | 31(2) | 39(2) | -1(2) | 0(2) | -1(2) |
| C(12) | 50(2) | 45(3) | 48(3) | 11(2) | 13(2) | -1(2) |
| C(13) | 31(2) | 58(3) | 38(3) | -7(2) | 9(2) | 12(2) |
| C(14) | 53(3) | 64(4) | 56(3) | -6(3) | 16(2) | 30(3) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 05105.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(5) | 5085 | 7029 | 2784 | 53 |
| H(1) | 1184 | 8134 | 2098 | 38 |
| H(2) | 3363 | 9527 | 2084 | 35 |
| H(4) | 3847 | 7043 | 809 | 32 |

| | | | | |
|---|---|---|---|---|
| H(5A) | 2156 | 5854 | 1822 | 35 |
| H(7A) | 622 | 4667 | 836 | 61 |
| H(7B) | 2486 | 4225 | 1018 | 61 |
| H(7C) | 1833 | 5156 | 341 | 61 |
| H(8A) | 6280 | 8987 | 2210 | 55 |
| H(8B) | 6178 | 8485 | 1400 | 55 |
| H(8C) | 6840 | 7535 | 2068 | 55 |
| H(10A) | 7180 | 3863 | 681 | 52 |
| H(10B) | 6307 | 3571 | 1340 | 52 |
| H(10C) | 7919 | 4443 | 1467 | 52 |
| H(12A) | 2010 | 11058 | -87 | 71 |
| H(12B) | 3881 | 10665 | 3 | 71 |
| H(12C) | 3400 | 12105 | 209 | 71 |
| H(14A) | -2122 | 11458 | 1690 | 86 |
| H(14B) | -1623 | 11077 | 944 | 86 |
| H(14C) | -504 | 12048 | 1497 | 86 |

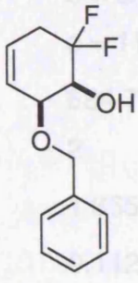
Table 6. Torsion angles [°] for 05105.

| | | | |
|---|---|---|---|
| C(13)-O(1)-C(1)-C(6) | 141.3(3) | O(6)-C(4)-C(5)-C(6) | -176.7(3) |
| C(13)-O(1)-C(1)-C(2) | -94.4(4) | C(3)-C(4)-C(5)-C(6) | 62.9(4) |
| C(11)-O(3)-C(2)-C(3) | -141.3(3) | O(6)-C(4)-C(5)-C(7) | -51.6(4) |
| C(11)-O(3)-C(2)-C(1) | 97.3(4) | C(3)-C(4)-C(5)-C(7) | -172.0(3) |
| O(1)-C(1)-C(2)-O(3) | -50.9(4) | O(1)-C(1)-C(6)-F(2) | -63.8(4) |
| C(6)-C(1)-C(2)-O(3) | 70.4(4) | C(2)-C(1)-C(6)-F(2) | 174.6(3) |
| O(1)-C(1)-C(2)-C(3) | -170.1(3) | O(1)-C(1)-C(6)-F(1) | 49.1(3) |
| C(6)-C(1)-C(2)-C(3) | -48.7(4) | C(2)-C(1)-C(6)-F(1) | -72.4(4) |
| O(3)-C(2)-C(3)-O(5) | 175.9(3) | O(1)-C(1)-C(6)-C(5) | 173.5(3) |
| C(1)-C(2)-C(3)-O(5) | -65.4(4) | C(2)-C(1)-C(6)-C(5) | 51.9(4) |
| O(3)-C(2)-C(3)-C(4) | -66.6(4) | C(7)-C(5)-C(6)-F(2) | 57.1(4) |
| C(1)-C(2)-C(3)-C(4) | 52.1(4) | C(4)-C(5)-C(6)-F(2) | -177.9(3) |
| O(3)-C(2)-C(3)-C(8) | 57.4(4) | C(7)-C(5)-C(6)-F(1) | -57.6(4) |
| C(1)-C(2)-C(3)-C(8) | 176.1(3) | C(4)-C(5)-C(6)-F(1) | 67.5(4) |
| C(9)-O(6)-C(4)-C(3) | -113.8(3) | C(7)-C(5)-C(6)-C(1) | 178.3(3) |
| C(9)-O(6)-C(4)-C(5) | 124.0(3) | C(4)-C(5)-C(6)-C(1) | -56.7(4) |
| O(5)-C(3)-C(4)-O(6) | -67.3(3) | C(4)-O(6)-C(9)-O(7) | 6.3(5) |
| C(8)-C(3)-C(4)-O(6) | 56.5(4) | C(4)-O(6)-C(9)-C(10) | -174.5(3) |

| | | | |
|---|---|---|---|
| C(2)-C(3)-C(4)-O(6) | 179.6(2) | C(2)-O(3)-C(11)-O(4) | 6.4(5) |
| O(5)-C(3)-C(4)-C(5) | 52.0(4) | C(2)-O(3)-C(11)-C(12) | -172.7(3) |
| C(8)-C(3)-C(4)-C(5) | 175.8(3) | C(1)-O(1)-C(13)-O(2) | -6.3(6) |
| C(2)-C(3)-C(4)-C(5) | -61.2(4) | C(1)-O(1)-C(13)-C(14) | 173.0(4) |

Symmetry transformations used to generate equivalent atoms:

### 6.1.10 (1*S**,2*S**)-2-(Benzyloxy)-6,6-difluorocyclohex-3-en-1-ol 294



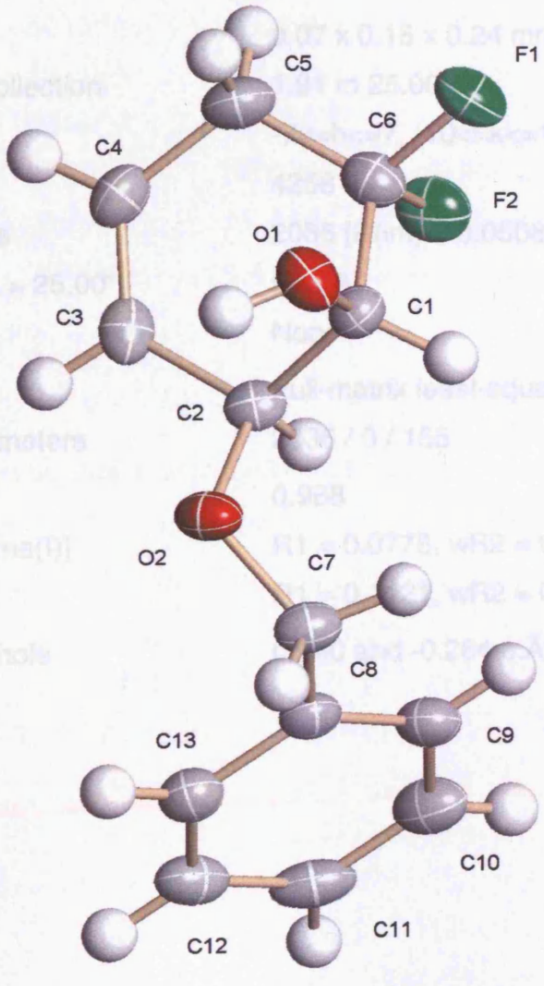



Table 1. Crystal data and structure refinement for 04186.

| | | |
|---|---|---|
| Identification code | 04186 | |
| Empirical formula | C13 H14 F2 O2 | |
| Formula weight | 240.24 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 6.4573(16) Å | □= 77.975(5)°. |
| | b = 8.499(2) Å | □= 76.852(5)°. |
| | c = 11.186(3) Å | □ = 87.668(5)°. |
| Volume | 584.7(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.365 $Mg/m^3$ | |
| Absorption coefficient | 0.112 $mm^{-1}$ | |
| F(000) | 252 | |
| Crystal size | 0.07 x 0.15 x 0.24 $mm^3$ | |
| Theta range for data collection | 1.91 to 25.00°. | |
| Index ranges | -7<=h<=7, -10<=k<=10, -13<=l<=13 | |
| Reflections collected | 4258 | |
| Independent reflections | 2036 [R(int) = 0.0508] | |
| Completeness to theta = 25.00° | 99.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2036 / 0 / 155 | |
| Goodness-of-fit on $F^2$ | 0.988 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0778, wR2 = 0.1917 | |
| R indices (all data) | R1 = 0.1121, wR2 = 0.2124 | |
| Largest diff. peak and hole | 0.540 and -0.264 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 04186. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 10975(3) | 8236(3) | -2597(2) | 46(1) |
| F(2) | 9564(3) | 9715(2) | -1253(2) | 45(1) |
| O(1) | 8206(4) | 5741(3) | -1349(2) | 35(1) |
| O(2) | 5540(4) | 5933(3) | 941(2) | 33(1) |
| C(1) | 8486(6) | 7030(4) | -769(3) | 29(1) |
| C(2) | 6471(6) | 7393(4) | 152(3) | 28(1) |
| C(3) | 4840(6) | 8222(4) | -506(4) | 33(1) |
| C(4) | 5278(6) | 8969(5) | -1697(4) | 38(1) |
| C(5) | 7440(7) | 9022(5) | -2526(4) | 43(1) |
| C(6) | 9102(6) | 8496(4) | -1797(3) | 34(1) |
| C(7) | 6527(6) | 5297(4) | 1975(3) | 32(1) |
| C(8) | 5918(6) | 6234(4) | 3006(3) | 30(1) |
| C(9) | 7411(6) | 7117(4) | 3297(3) | 35(1) |
| C(10) | 6845(7) | 7952(5) | 4263(4) | 41(1) |
| C(11) | 4776(7) | 7888(4) | 4943(4) | 41(1) |
| C(12) | 3258(7) | 7006(5) | 4670(3) | 39(1) |
| C(13) | 3834(6) | 6184(4) | 3697(3) | 35(1) |

Table 3. Bond lengths [Å] and angles [°] for 04186.

| | | | |
|---|---|---|---|
| F(1)-C(6) | 1.372(4) | C(6)-C(1)-C(2) | 109.0(3) |
| F(2)-C(6) | 1.379(4) | O(2)-C(2)-C(3) | 107.7(3) |
| O(1)-C(1) | 1.421(4) | O(2)-C(2)-C(1) | 110.2(3) |
| O(2)-C(2) | 1.429(4) | C(3)-C(2)-C(1) | 111.9(3) |
| O(2)-C(7) | 1.443(4) | C(4)-C(3)-C(2) | 123.6(3) |
| C(1)-C(6) | 1.506(5) | C(3)-C(4)-C(5) | 123.3(4) |
| C(1)-C(2) | 1.530(5) | C(4)-C(5)-C(6) | 111.9(3) |
| C(2)-C(3) | 1.492(5) | F(1)-C(6)-F(2) | 104.7(3) |
| C(3)-C(4) | 1.322(5) | F(1)-C(6)-C(5) | 109.7(3) |
| C(4)-C(5) | 1.487(5) | F(2)-C(6)-C(5) | 110.4(3) |

| | | | |
|---|---|---|---|
| C(5)-C(6) | 1.491(5) | F(1)-C(6)-C(1) | 110.2(3) |
| C(7)-C(8) | 1.507(5) | F(2)-C(6)-C(1) | 107.6(3) |
| C(8)-C(9) | 1.379(5) | C(5)-C(6)-C(1) | 113.9(3) |
| C(8)-C(13) | 1.389(5) | O(2)-C(7)-C(8) | 111.8(3) |
| C(9)-C(10) | 1.387(5) | C(9)-C(8)-C(13) | 119.2(3) |
| C(10)-C(11) | 1.375(6) | C(9)-C(8)-C(7) | 121.0(3) |
| C(11)-C(12) | 1.381(6) | C(13)-C(8)-C(7) | 119.8(3) |
| C(12)-C(13) | 1.387(5) | C(8)-C(9)-C(10) | 120.6(4) |
| | | C(11)-C(10)-C(9) | 119.6(4) |
| C(2)-O(2)-C(7) | 114.7(3) | C(10)-C(11)-C(12) | 120.7(4) |
| O(1)-C(1)-C(6) | 107.3(3) | C(11)-C(12)-C(13) | 119.4(4) |
| O(1)-C(1)-C(2) | 112.8(3) | C(12)-C(13)-C(8) | 120.5(4) |

Symmetry transformations used to generate equivalent atoms:

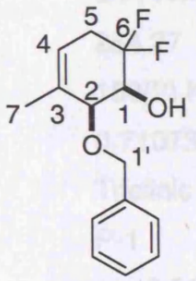
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04186. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| F(1) | 41(1) | 49(1) | 39(1) | -6(1) | 5(1) | -5(1) |
| F(2) | 55(2) | 33(1) | 46(1) | -8(1) | -8(1) | -11(1) |
| O(1) | 35(2) | 31(1) | 41(2) | -17(1) | -1(1) | -1(1) |
| O(2) | 45(2) | 29(1) | 24(1) | -6(1) | -5(1) | -7(1) |
| C(1) | 33(2) | 29(2) | 28(2) | -6(2) | -10(2) | 0(2) |
| C(2) | 38(2) | 23(2) | 26(2) | -8(2) | -7(2) | 2(2) |
| C(3) | 30(2) | 31(2) | 42(2) | -19(2) | -9(2) | 7(2) |
| C(4) | 40(2) | 36(2) | 40(2) | -7(2) | -18(2) | 8(2) |
| C(5) | 55(3) | 41(2) | 30(2) | 1(2) | -12(2) | 1(2) |
| C(6) | 37(2) | 32(2) | 32(2) | -9(2) | -2(2) | -3(2) |
| C(7) | 44(2) | 26(2) | 26(2) | -6(2) | -8(2) | 4(2) |
| C(8) | 37(2) | 27(2) | 24(2) | 1(2) | -8(2) | 2(2) |
| C(9) | 43(2) | 34(2) | 26(2) | -1(2) | -6(2) | -4(2) |
| C(10) | 59(3) | 32(2) | 33(2) | -4(2) | -14(2) | -9(2) |
| C(11) | 73(3) | 26(2) | 24(2) | -4(2) | -11(2) | 6(2) |
| C(12) | 47(3) | 35(2) | 27(2) | -1(2) | -2(2) | 11(2) |
| C(13) | 41(2) | 32(2) | 30(2) | -4(2) | -10(2) | 1(2) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 04186.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 6928 | 5441 | -1130 | 53 |
| H(1A) | 9664 | 6763 | -316 | 35 |
| H(2) | 6852 | 8095 | 686 | 34 |
| H(3) | 3409 | 8213 | -45 | 39 |
| H(4) | 4156 | 9498 | -2039 | 45 |
| H(5A) | 7761 | 10134 | -3010 | 51 |
| H(5B) | 7472 | 8315 | -3129 | 51 |
| H(7A) | 8092 | 5331 | 1668 | 39 |
| H(7B) | 6092 | 4158 | 2316 | 39 |
| H(9) | 8842 | 7154 | 2831 | 42 |
| H(10) | 7879 | 8564 | 4455 | 49 |
| H(11) | 4388 | 8456 | 5607 | 50 |
| H(12) | 1833 | 6963 | 5145 | 46 |
| H(13) | 2794 | 5582 | 3501 | 41 |

### 6.1.11 (1*S**,2*S**)-2-(Benzyloxy)-6,6-difluoro-3-methylcyclohex-3-en-1-ol 296



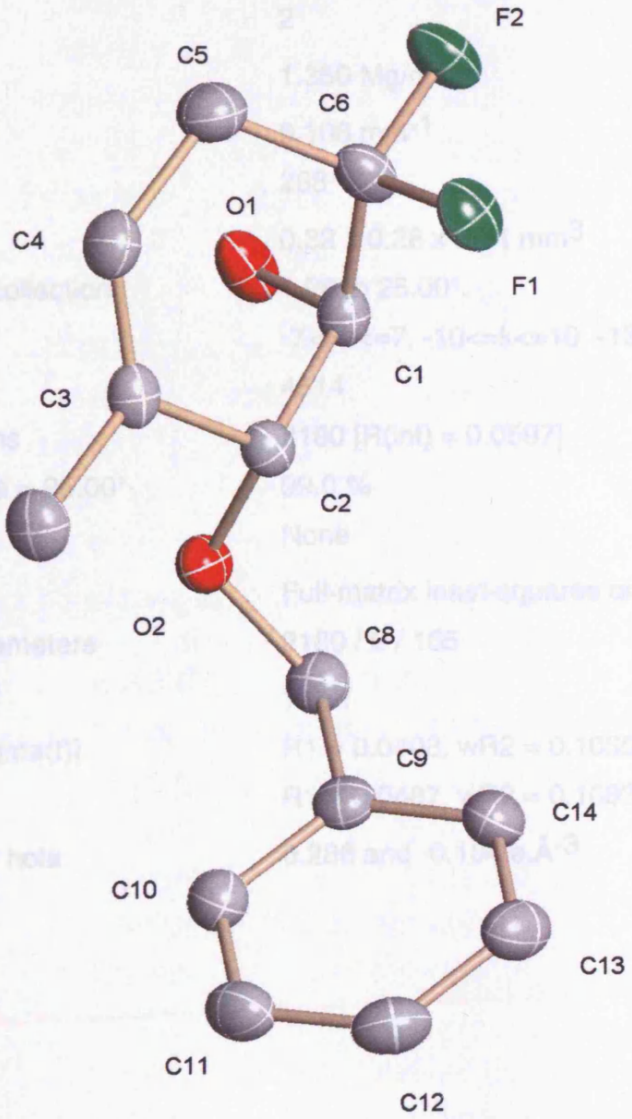



Table 1. Crystal data and structure refinement for 05088.

| | | |
|---|---|---|
| Identification code | 05088 | |
| Empirical formula | C14 H16 F2 O2 | |
| Formula weight | 254.27 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 6.5179(17) Å | □= 73.533(4)°. |
| | b = 9.224(2) Å | □= 76.994(4)°. |
| | c = 11.151(3) Å | □ = 89.422(4)°. |
| Volume | 625.4(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.350 $Mg/m^3$ | |
| Absorption coefficient | 0.108 $mm^{-1}$ | |
| F(000) | 268 | |
| Crystal size | 0.32 x 0.28 x 0.11 $mm^3$ | |
| Theta range for data collection | 1.96 to 25.00°. | |
| Index ranges | -7<=h<=7, -10<=k<=10, -13<=l<=13 | |
| Reflections collected | 4514 | |
| Independent reflections | 2180 [R(int) = 0.0597] | |
| Completeness to theta = 25.00° | 99.0 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2180 / 0 / 165 | |
| Goodness-of-fit on $F^2$ | 1.031 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0408, wR2 = 0.1035 | |
| R indices (all data) | R1 = 0.0487, wR2 = 0.1083 | |
| Largest diff. peak and hole | 0.286 and -0.184 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 05088. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| F(1) | 4737(1) | 4488(1) | -1798(1) | 33(1) |
| F(2) | 5853(2) | 3093(1) | -3069(1) | 38(1) |
| O(1) | 3069(2) | 729(1) | -1504(1) | 32(1) |
| O(2) | 805(2) | 860(1) | 848(1) | 25(1) |
| C(1) | 3560(2) | 1938(2) | -1051(2) | 24(1) |
| C(2) | 1720(2) | 2269(2) | -53(1) | 22(1) |
| C(3) | 8(2) | 3109(2) | -626(2) | 24(1) |
| C(4) | 323(3) | 3790(2) | -1876(2) | 30(1) |
| C(5) | 2331(3) | 3773(2) | -2846(2) | 34(1) |
| C(6) | 4104(2) | 3317(2) | -2201(2) | 27(1) |
| C(7) | -1973(3) | 3233(2) | 322(2) | 31(1) |
| C(8) | 1771(3) | 337(2) | 1925(2) | 28(1) |
| C(9) | 1101(2) | 1199(2) | 2896(1) | 25(1) |
| C(10) | -998(3) | 1110(2) | 3556(2) | 30(1) |
| C(11) | -1633(3) | 1890(2) | 4453(2) | 33(1) |
| C(12) | -163(3) | 2780(2) | 4703(2) | 35(1) |
| C(13) | 1917(3) | 2879(2) | 4053(2) | 35(1) |
| C(14) | 2557(3) | 2092(2) | 3154(2) | 31(1) |

Table 3. Bond lengths [Å] and angles [°] for 05088.

| | | | |
|---|---|---|---|
| F(1)-C(6) | 1.3816(18) | C(1)-C(2)-H(2) | 108.6 |
| F(2)-C(6) | 1.3750(18) | C(4)-C(3)-C(7) | 122.83(15) |
| O(1)-C(1) | 1.4142(17) | C(4)-C(3)-C(2) | 121.45(15) |
| O(1)-H(1) | 0.8400 | C(7)-C(3)-C(2) | 115.50(13) |
| O(2)-C(2) | 1.4344(17) | C(3)-C(4)-C(5) | 124.54(15) |
| O(2)-C(8) | 1.4415(19) | C(3)-C(4)-H(4) | 117.7 |
| C(1)-C(6) | 1.506(2) | C(5)-C(4)-H(4) | 117.7 |
| C(1)-C(2) | 1.535(2) | C(6)-C(5)-C(4) | 110.69(14) |
| C(1)-H(1A) | 1.0000 | C(6)-C(5)-H(5A) | 109.5 |
| C(2)-C(3) | 1.509(2) | C(4)-C(5)-H(5A) | 109.5 |
| C(2)-H(2) | 1.0000 | C(6)-C(5)-H(5B) | 109.5 |
| C(3)-C(4) | 1.326(2) | C(4)-C(5)-H(5B) | 109.5 |

| | | | |
|---|---|---|---|
| C(3)-C(7) | 1.500(2) | H(5A)-C(5)-H(5B) | 108.1 |
| C(4)-C(5) | 1.502(2) | F(2)-C(6)-F(1) | 104.42(12) |
| C(4)-H(4) | 0.9500 | F(2)-C(6)-C(5) | 110.20(14) |
| C(5)-C(6) | 1.491(2) | F(1)-C(6)-C(5) | 110.09(13) |
| C(5)-H(5A) | 0.9900 | F(2)-C(6)-C(1) | 110.23(13) |
| C(5)-H(5B) | 0.9900 | F(1)-C(6)-C(1) | 107.87(13) |
| C(7)-H(7A) | 0.9800 | C(5)-C(6)-C(1) | 113.60(13) |
| C(7)-H(7B) | 0.9800 | C(3)-C(7)-H(7A) | 109.5 |
| C(7)-H(7C) | 0.9800 | C(3)-C(7)-H(7B) | 109.5 |
| C(8)-C(9) | 1.504(2) | H(7A)-C(7)-H(7B) | 109.5 |
| C(8)-H(8A) | 0.9900 | C(3)-C(7)-H(7C) | 109.5 |
| C(8)-H(8B) | 0.9900 | H(7A)-C(7)-H(7C) | 109.5 |
| C(9)-C(10) | 1.391(2) | H(7B)-C(7)-H(7C) | 109.5 |
| C(9)-C(14) | 1.391(2) | O(2)-C(8)-C(9) | 111.86(12) |
| C(10)-C(11) | 1.380(2) | O(2)-C(8)-H(8A) | 109.2 |
| C(10)-H(10) | 0.9500 | C(9)-C(8)-H(8A) | 109.2 |
| C(11)-C(12) | 1.391(2) | O(2)-C(8)-H(8B) | 109.2 |
| C(11)-H(11) | 0.9500 | C(9)-C(8)-H(8B) | 109.2 |
| C(12)-C(13) | 1.376(3) | H(8A)-C(8)-H(8B) | 107.9 |
| C(12)-H(12) | 0.9500 | C(10)-C(9)-C(14) | 118.77(15) |
| C(13)-C(14) | 1.387(2) | C(10)-C(9)-C(8) | 120.23(14) |
| C(13)-H(13) | 0.9500 | C(14)-C(9)-C(8) | 120.99(14) |
| C(14)-H(14) | 0.9500 | C(11)-C(10)-C(9) | 120.86(16) |
| | | C(11)-C(10)-H(10) | 119.6 |
| C(1)-O(1)-H(1) | 109.5 | C(9)-C(10)-H(10) | 119.6 |
| C(2)-O(2)-C(8) | 114.40(11) | C(10)-C(11)-C(12) | 119.83(16) |
| O(1)-C(1)-C(6) | 106.84(13) | C(10)-C(11)-H(11) | 120.1 |
| O(1)-C(1)-C(2) | 112.89(12) | C(12)-C(11)-H(11) | 120.1 |
| C(6)-C(1)-C(2) | 109.06(12) | C(13)-C(12)-C(11) | 119.82(17) |
| O(1)-C(1)-H(1A) | 109.3 | C(13)-C(12)-H(12) | 120.1 |
| C(6)-C(1)-H(1A) | 109.3 | C(11)-C(12)-H(12) | 120.1 |
| C(2)-C(1)-H(1A) | 109.3 | C(12)-C(13)-C(14) | 120.37(16) |
| O(2)-C(2)-C(3) | 108.44(12) | C(12)-C(13)-H(13) | 119.8 |
| O(2)-C(2)-C(1) | 108.74(11) | C(14)-C(13)-H(13) | 119.8 |
| C(3)-C(2)-C(1) | 113.74(13) | C(13)-C(14)-C(9) | 120.35(16) |
| O(2)-C(2)-H(2) | 108.6 | C(13)-C(14)-H(14) | 119.8 |
| C(3)-C(2)-H(2) | 108.6 | C(9)-C(14)-H(14) | 119.8 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05088. 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) | 32(1) | 25(1) | 43(1) | -13(1) | -3(1) | -5(1) |
| F(2) | 29(1) | 41(1) | 37(1) | -14(1) | 7(1) | 0(1) |
| O(1) | 27(1) | 28(1) | 43(1) | -22(1) | 3(1) | -4(1) |
| O(2) | 26(1) | 22(1) | 26(1) | -7(1) | -6(1) | -2(1) |
| C(1) | 22(1) | 23(1) | 31(1) | -12(1) | -7(1) | 2(1) |
| C(2) | 23(1) | 20(1) | 25(1) | -9(1) | -5(1) | -1(1) |
| C(3) | 22(1) | 20(1) | 34(1) | -13(1) | -7(1) | 2(1) |
| C(4) | 26(1) | 29(1) | 36(1) | -10(1) | -12(1) | 4(1) |
| C(5) | 37(1) | 36(1) | 27(1) | -6(1) | -7(1) | 2(1) |
| C(6) | 26(1) | 26(1) | 29(1) | -13(1) | 2(1) | -1(1) |
| C(7) | 27(1) | 29(1) | 40(1) | -15(1) | -7(1) | 6(1) |
| C(8) | 28(1) | 25(1) | 29(1) | -7(1) | -8(1) | 6(1) |
| C(9) | 29(1) | 22(1) | 22(1) | -3(1) | -7(1) | 4(1) |
| C(10) | 28(1) | 32(1) | 29(1) | -8(1) | -8(1) | 2(1) |
| C(11) | 30(1) | 39(1) | 28(1) | -8(1) | -3(1) | 6(1) |
| C(12) | 47(1) | 31(1) | 25(1) | -9(1) | -7(1) | 5(1) |
| C(13) | 43(1) | 34(1) | 28(1) | -9(1) | -7(1) | -9(1) |
| C(14) | 29(1) | 35(1) | 26(1) | -7(1) | -3(1) | -3(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 05088.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 1937 | 268 | -1033 | 48 |
| H(1A) | 4813 | 1699 | -667 | 29 |
| H(2) | 2283 | 2887 | 420 | 27 |
| H(4) | -799 | 4326 | -2179 | 36 |
| H(5A) | 2137 | 3054 | -3329 | 41 |
| H(5B) | 2676 | 4794 | -3467 | 41 |
| H(7A) | -2881 | 3941 | -121 | 46 |
| H(7B) | -1614 | 3605 | 994 | 46 |
| H(7C) | -2720 | 2235 | 712 | 46 |

| | | | | |
|---|---|---|---|---|
| H(8A) | 3324 | 453 | 1612 | 33 |
| H(8B) | 1377 | -753 | 2344 | 33 |
| H(10) | -2007 | 505 | 3387 | 36 |
| H(11) | -3070 | 1818 | 4899 | 40 |
| H(12) | -594 | 3318 | 5320 | 41 |
| H(13) | 2920 | 3489 | 4222 | 42 |
| H(14) | 3997 | 2164 | 2712 | 37 |

Table 6. Torsion angles [°] for 05088.

| | | | |
|---|---|---|---|
| C(8)-O(2)-C(2)-C(3) | -147.82(12) | O(1)-C(1)-C(6)-F(2) | -62.31(16) |
| C(8)-O(2)-C(2)-C(1) | 88.04(14) | C(2)-C(1)-C(6)-F(2) | 175.38(12) |
| O(1)-C(1)-C(2)-O(2) | 44.55(16) | O(1)-C(1)-C(6)-F(1) | -175.75(11) |
| C(6)-C(1)-C(2)-O(2) | 163.13(12) | C(2)-C(1)-C(6)-F(1) | 61.94(15) |
| O(1)-C(1)-C(2)-C(3) | -76.38(16) | O(1)-C(1)-C(6)-C(5) | 61.93(17) |
| C(6)-C(1)-C(2)-C(3) | 42.21(17) | C(2)-C(1)-C(6)-C(5) | -60.38(17) |
| O(2)-C(2)-C(3)-C(4) | -135.90(15) | C(2)-O(2)-C(8)-C(9) | 76.25(15) |
| C(1)-C(2)-C(3)-C(4) | -14.8(2) | O(2)-C(8)-C(9)-C(10) | 64.16(18) |
| O(2)-C(2)-C(3)-C(7) | 49.33(16) | O(2)-C(8)-C(9)-C(14) | -116.02(15) |
| C(1)-C(2)-C(3)-C(7) | 170.43(12) | C(14)-C(9)-C(10)-C(11) | -0.1(2) |
| C(7)-C(3)-C(4)-C(5) | 176.10(15) | C(8)-C(9)-C(10)-C(11) | 179.71(14) |
| C(2)-C(3)-C(4)-C(5) | 1.7(2) | C(9)-C(10)-C(11)-C(12) | 0.1(2) |
| C(3)-C(4)-C(5)-C(6) | -17.3(2) | C(10)-C(11)-C(12)-C(13) | 0.0(2) |
| C(4)-C(5)-C(6)-F(2) | 171.33(12) | C(11)-C(12)-C(13)-C(14) | -0.2(3) |
| C(4)-C(5)-C(6)-F(1) | -74.01(17) | C(12)-C(13)-C(14)-C(9) | 0.2(2) |
| C(4)-C(5)-C(6)-C(1) | 47.08(18) | C(10)-C(9)-C(14)-C(13) | -0.1(2) |
| | | C(8)-C(9)-C(14)-C(13) | -179.89(14) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 05088 [Å and °].

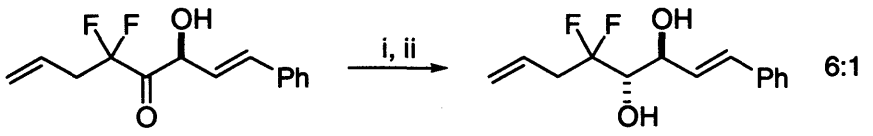
| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(1)-H(1)...O(2)#1 | 0.84 | 2.02 | 2.7742(16) | 149.5 |

Symmetry transformations used to generate equivalent atoms: #1 -x,-y,-z

## 6.2 Appendix II: NMR Spectra of Crude Materials

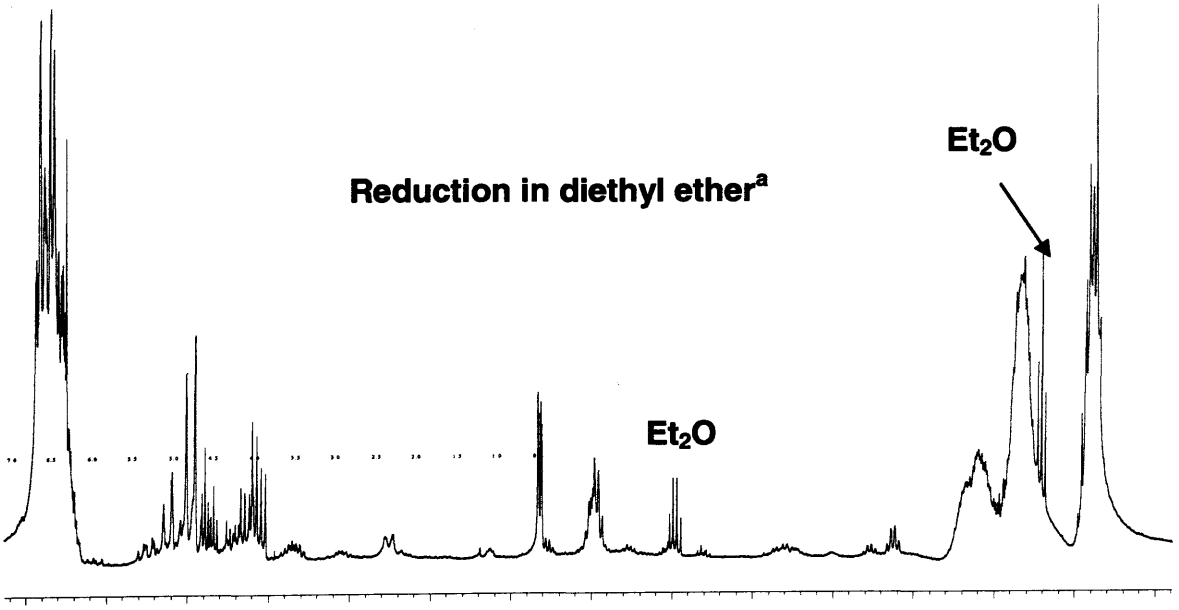
We reported here $^{1}H$ and $^{19}F$ NMR spectra to illustrate the solvent effects on the reduction and therefore and the quality of the NMR spectra of the crude material.

The reduction of hydroxyketone **155** using sodium borohydride as reducing agent (**Scheme 92**) exhibited obvious difference in the quality of the crude material as illustrated by their $^{1}H$ NMR spectra (**Figure 69**).




**155** **168**

**Scheme 92.** Reagents and conditions: i) $NaBH_4$ (3.0 eq.), solvent, rt, overnight; ii) $HCl_{conc}$.



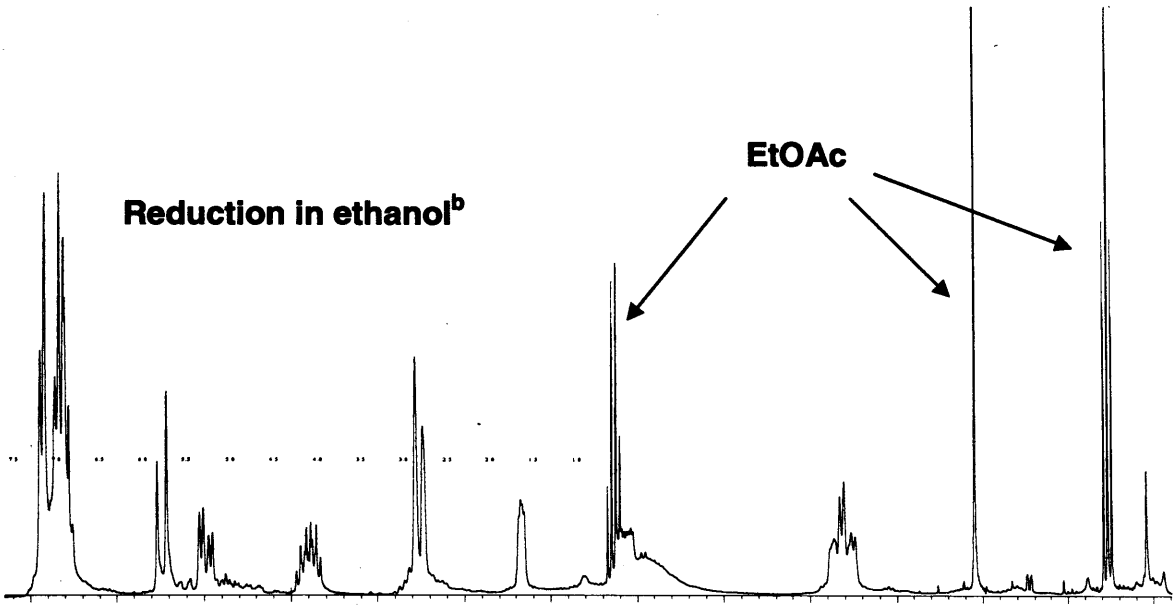
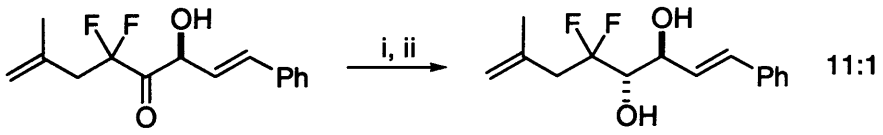


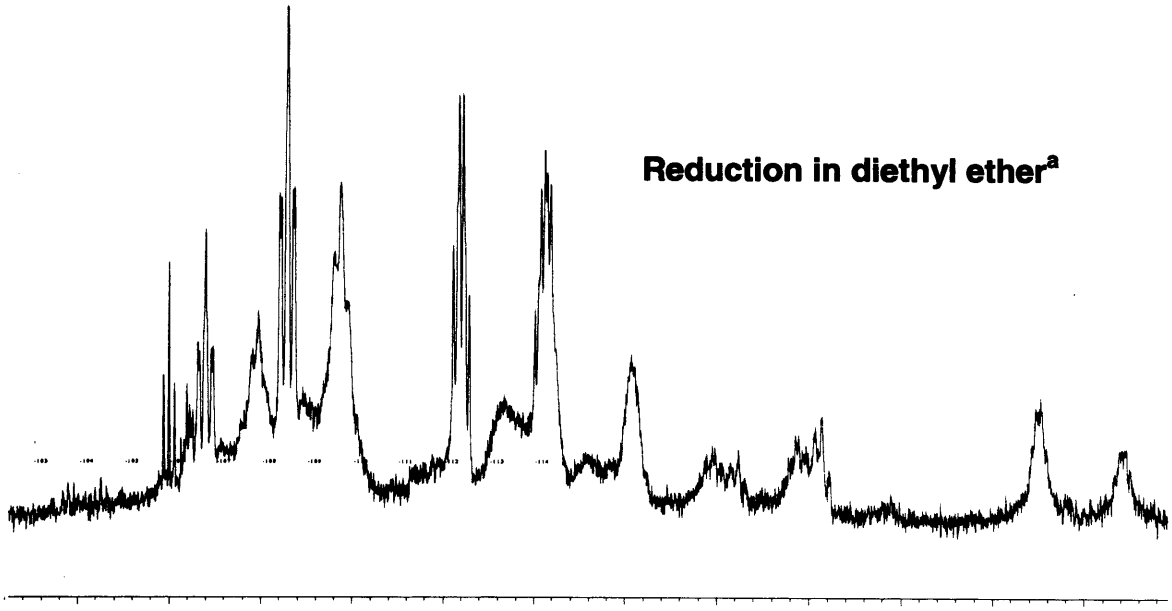

**Figure 69.** [a]: dehydrofluorination performed with *n*-BuLi; [b]: dehydrofluorination performed with *t*-BuLi.

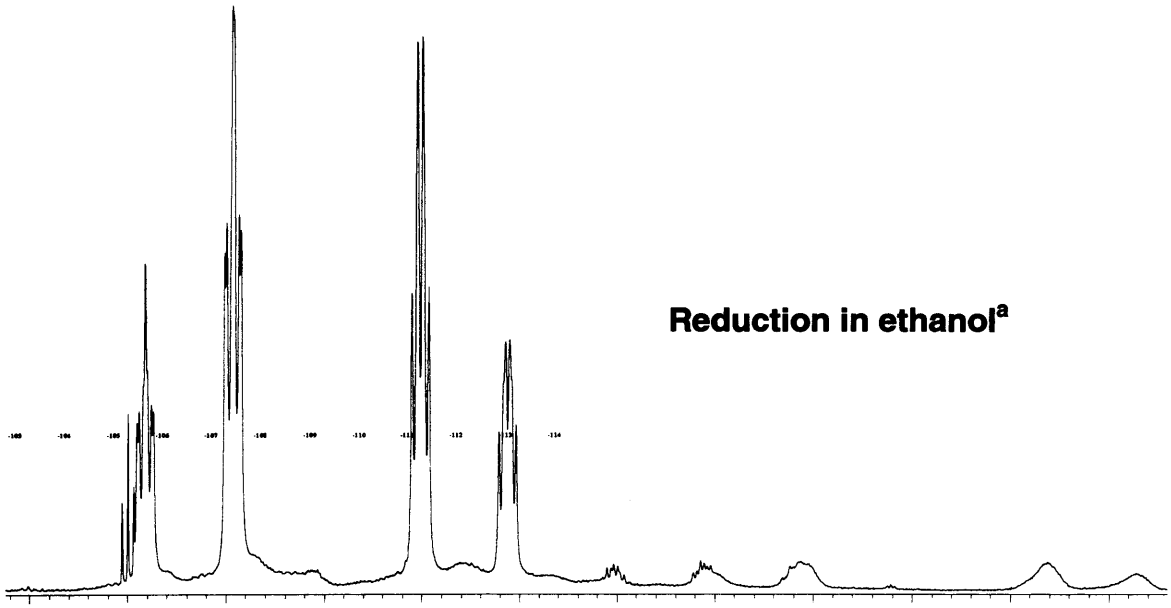
The reduction of hydroxyketone **158** using sodium borohydride as reducing agent (**Scheme 93**) exhibited obvious difference in the quality of the crude material as illustrated by their $^1$H NMR spectra (**Figure 70**).




**158** **176**

**Scheme 93.** Reagents and conditions: i) $NaBH_4$ (3.0 eq.), solvent, rt, overnight; ii) $HCl_{conc}$.


Reduction in diethyl ether[a]


Reduction in ethanol[a]

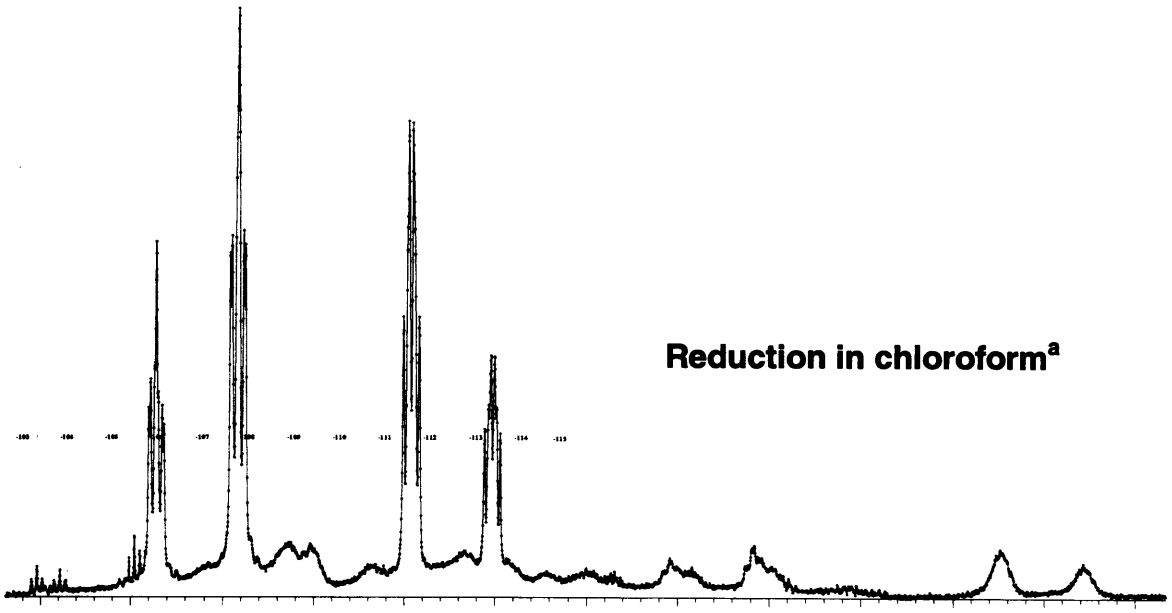
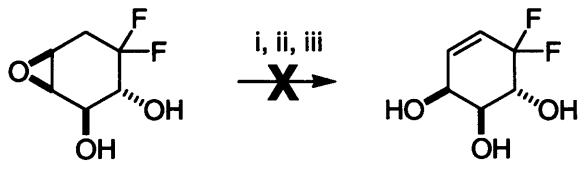



**Figure 70.** [a]: dehydrofluorination performed with *t*-BuLi.

## *6.3 Appendix III: Attempted Opening via Selenium Chemistry*

The reactions using diphenyldiselenide or diphenyldisulfide were performed on the other epoxides synthesised previously, but unfortunately the quality of the crude material in each case was very poor not allowing us to isolate useful intermediates to identify and understand the opening of our epoxides.

The Sharpless procedure was applied to epoxide **233** (**Scheme 94**). Unfortunately, the outcome of the reaction could not be determined due the very poor quality of the crude material (by $^{1}H$ and $^{19}F$ NMR spectroscopy).




**233** **314**

**Scheme 94.** Reagents and conditions: i) diphenyldiselenide, $NaBH_4$, EtOH, rt, 1 h (inverse addition); ii) reflux, overnight; iii) $H_2O_2$, 20 °C, tetrahydrofuran.

Anyhow, we could identify two new set of peaks arising from the baseline around 6.1 and 5.8 ppm (**Figure 71**) of the $^{1}H$ NMR spectrum being potentially due the formation of some of the desired product **314** (**Scheme 94**) but in minority among other unknown products of the reaction (more than 6 difluoro-species can be observed in the $^{19}F$ NMR spectrum).

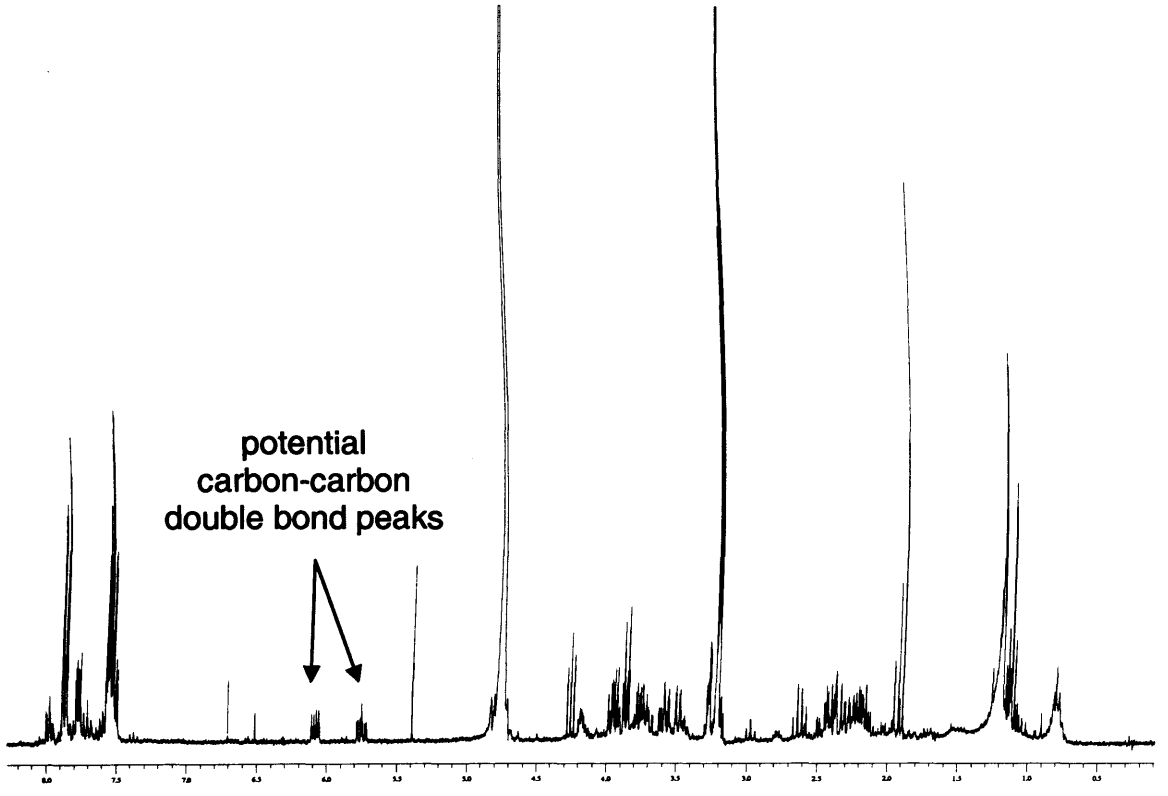
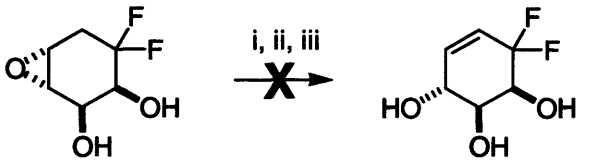



**Figure 71.** $^{1}H$ NMR spectrum of the crude material

The same reaction using diphenyldisulfide instead of diphenyldiselenide exhibited a similar complex mixture by $^{19}F$ NMR without presenting the two new set of peak in the double bond region on the $^{1}H$ NMR spectrum. It is worth mentioning that the sulfide anion is a poorer nucleophile than the selenide equivalent.

The Sharpless procedure was applied to epoxide **236** (**Scheme 95**). Unfortunately, the outcome of the reaction could not be determined due the very poor quality of the crude material (by $^{1}H$ and $^{19}F$ NMR spectroscopy).




**236** **315**

**Scheme 95.** Reagents and conditions: i) diphenyldiselenide, $NaBH_4$, EtOH, rt, 1 h (inverse addition); ii) reflux, overnight; iii) $H_2O_2$, 20 °C, tetrahydrofuran.

Before the addition of hydrogen peroxide to the reaction mixture, an aliquot was taken and analyse by electrospray spectrometry. The substrate with an thiophenyl moiety attached could identify among many other unidentified peaks.