Synthesis of Bicyclic Difluorinated Analogues of Sugars

Thesis submitted for the degree of Doctor of Philosophy
at the University of Leicester

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Statement

The accompany thesis submitted for the degree of Ph.D entitled "Synthesis of Bicyclic Difluorinated Analogues of Sugars" is based upon work conducted by the author in the Department of Chemistry at the University of Leicester during the period between September 2001 and September 2004.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed..... Date.....

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2007

ABSTRACT

This thesis describes the synthesis of *gem*-difluorinated cyclooctenone analogues using building block approaches based on the RCM with Grubbs' catalysts.

Des- and *gem*-dialkyl-substituted difluorodienes were synthesised from commercially available trifluoroethanol by dehydrofluorination/metalation, trapping, allylation and [2,3]-Wittig rearrangement successfully.

The *gem*-difluorinated dienes produced the corresponding difluorinated cyclooctenones smoothly and in good yields. However, a dithioketal-containing diene did not afford any cyclic product. Thorpe-Ingold effect was also observed from the concentration study of *des*- and *gem*-dimethyl dienes in the RCM reaction. The *gem*-dimethyl diene cyclised faster than *des*-dimethyl diene, and the *des*-dimethyl diene could cyclise only at low concentration (0.001 M).

The cyclooctenone analogues have interesting topological conformations, which were studied by NMR experiments and computational calculations.

The dihydroxylation and stero-controlled epoxidation were developed on unique 8-membered ring molecules. Dihydroxylation reactions gave mixtures of diastereomeric triol products, which underwent transannular collapse to afford bicyclic products. The stereo-controlled epoxidation with methyl(trifluoromethyl) dioxirane gave the corresponding *trans*-epoxyalcohol in good yields. The epoxides were very stable under acid conditions however, in basic aqueous solution with microwave irradiation, they afforded bicyclic molecules by a transannular reaction *via* hemiaminal formation next to fluorine atoms. The newly synthesised conformationally locked difluorinated bicyclic molecules are hydrolytically resistant sugar mimics.

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Chapter 1 : Introduction

Chapter 2 : Results and Discussion

Abbreviations

Asn	Asparagine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bppb	1,4-bis(Diphenylphosphino)butane
Bz	Benzoyl
Cat	Catalyst
CBz	Benzyloxycarbonyl
CDA	Cyclohexane1,2-diacetal
CI	Chemical ionization
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEC	*N,N*-Diethylcarbamoyl
Deoxo-Fluor™	bis-(2-Methoxyethyl)aminosulfur trifluoride
DCM	Dichloromethane
DIBAL-H	Di*iso*butylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMB	2,4-Dimethoxybenzyl
DMSO	Dimethylsulfoxide
DNP	2,4-Dinitrophenyl
DOIS	2-deoxy-*scyllo*-inosose synthase
EI	Electron impact
ES	Electrospray
Eq.	Equivalent
FAB	Fast atom bombardment
GC	Gas chromatography
h	Hour
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIV	Human immunodeficiency virus
HOAt	1-Hydroxy-7-azabenzotriazole
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared

LDA	Lithium di*iso*propylamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MEM	Methoxyethoxymethyl
Mes	Mesityl(2,4,6-trimethylphenyl)
MHz	Megahertz
min	Minute(s)
MM	Molecular Mechanics
MMFF	Merck Molecular Force Field
MS	Mass spectrometry
Ms	Methanesulfonyl
MTO	Methyltrioxorhenium
MW	Microwave
NGP	Neighbouring group participation
NMO	4-Methylmorpholine-*N*-oxide
NMI	*N*-methyl imidazole
NMR	Nuclear magnetic resonance
PCC	pyridinium chlorochromate
PPTS	Pyridinium *para*-toluene sulfonate
Pv	Pivaloate (trimethyl acetate)
Py	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
Selectfluor™	1-(Chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate)
TBDPS	*tert*-Butyldiphenylsilyl
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIBAL	Tri*iso*butylaluminum
TMEDA	*N,N,N',N'*-tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

Chapter 1 : Introduction

1. The role of sugars in Nature

Carbohydrates fulfill a range of important roles in Nature and synthesis and breakdown play an important part in human health. Sugars modify proteins and lipids on cell surfaces and participate in fundamental biological processes such as immunity and cell-to-cell communication.[1] They also play a part in a range of diseases from viral infections to cancer. Many scientists study and synthesise sugars for use in research and as drugs because of these facts.

Sugars are recognised through the formation of hydrogen bond networks to donor and acceptor groups on receptors. An example is provided by the enzyme-oligosaccharide hydrogen bond network between β-1, 3-1, 4-cellotriose (CLTR) and TFsβ-glucanase residues (Figure 1).[2]

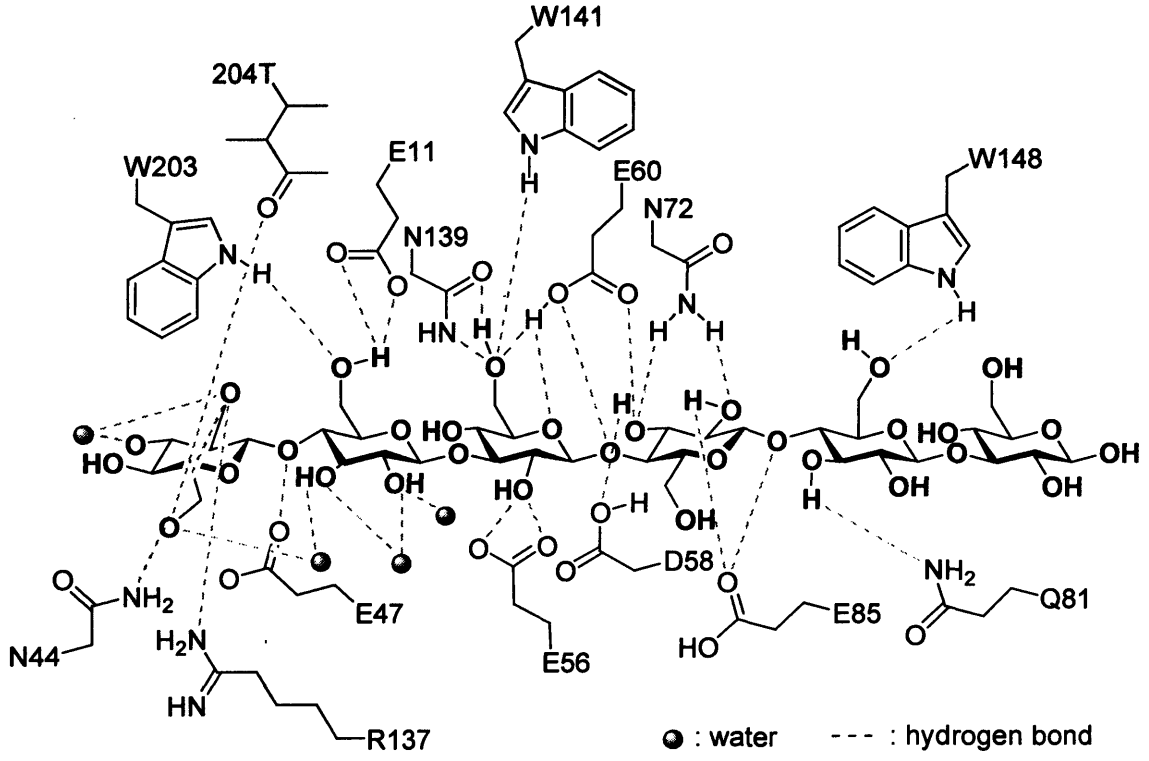


Figure 1

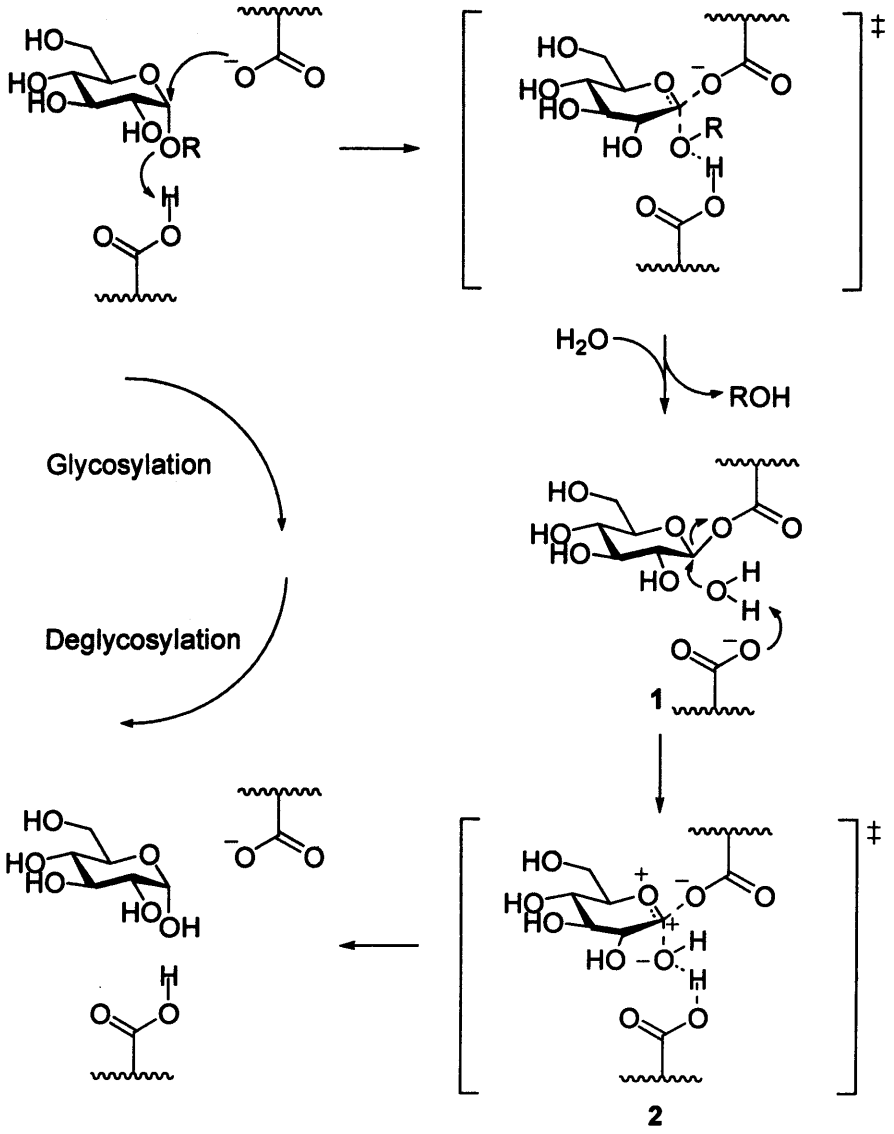
All the individual sugar unit in the hexaose ligand are D-glucosyl configuration. The bond angles deviate significantly in the drawing from those which represent glucose accurately; this is so that the image of the complex can be rendered in two

dimensions. Proton locations are not specified in the source paper. The dotted lines indicate the approach of heteroatoms within the distance which would normally suggest that a hydrogen bond would be formed. We are not able to locate the protons from the information available.

Hydrogen bonding to hydroxyl groups effects recognition at cell surfaces. Each of these hydrogen bonds is relatively weak (5-10 kcal mol^{-1}), however a multi hydrogen bonding network results in a strong interaction. The correct number and location of hydroxyl groups are required to maximize the binding energy.

Sugars also occur as linear and branched chains in oligosaccharides, which are held together by glycosidic linkages. Antibiotics and proteins are also modified (glycosylated) with sugars. If they are to stay modified or if glycosylation patterns are to be preserved, the glycosidic bonds must remain intact.

Glycoside hydrolysis is slow in water at pH 7 alone but fast when catalysed by enzymes (glycosidases). There are many ways for enzymes to break a glycosidic bond, the most common being the hydrolytic process adopted by glycosidases. Withers *et al.* proposed a mechanism of action for retaining glycosidases, in which one carboxyl group acts as a nucleophile, forming a covalent glycosyl-enzyme intermediate **1**. While the other acts as a general acid catalyst in the first step, donating a proton to the aglycone leaving group (Scheme 1).[4,35] The transition state for this reaction is an exploded S_N2 with high S_N1 character, and in which formation of an energetic oxacarbenium ion is avoided.[3] In the second step, a carboxylate group acts as a general base, removing a proton from incoming water in the oxacarbenium ion-like transition state **2**. There is a second major class of glycosidase known as the inverting glycosidases, both classes share highly oxacarbenium ion-like transition states.[4]



Scheme 1

Non-enzymic hydrolysis of sugars also occurs *via* an oxacarbenium ion-like transition state. The anomeric effect, which controls and exerts a strong effect on conformation, is related to the ability to form this type of transition state. It follows that the replacement of hydroxyl groups with more electronegative substituents, like fluorine atoms, will affect both molecular recognition and the ability to sustain oxacarbenium ion character. Withers has provided many good examples of these effects.[5]

A series of monosubstituted n-deoxy and n-deoxy-n-fluoro 2,4-dinitrophenyl (DNP) β-D-glycopyranosides were synthesised and used to probe the uncatalysed mechanism of β-glycoside hydrolysis.[5] Generally, the rate of hydrolysis follows the relative stability of the oxacarbenium ion-like transition states; thus the order of rate of

hydrolysis of monodeoxygenated glycosides and α-glucosyl phosphates is 2-deoxy > 4-deoxy > 3-deoxy > 6-deoxy > hexose. When a hydroxyl group is replaced by a more electronegative fluorine atom, the rate of glycoside hydrolysis decreases, and in the order, 6-deoxy-6-fluoro > 3-deoxy-3-fluoro > 4-deoxy-4-fluoro > 2-deoxy-2-fluoro (Table 1).[5]

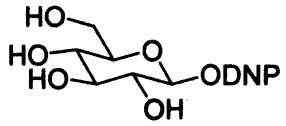
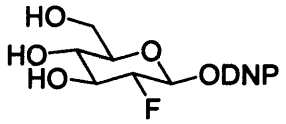
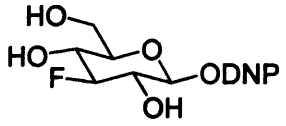
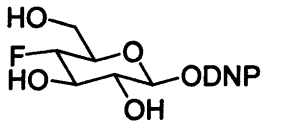
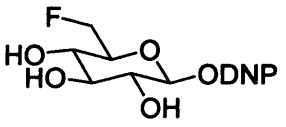
DNP glycoside		$k_0 37°C/s^{-1}$	k_{rel}
DNPglc		5.58×10^{-6}	(1.0)
2FDNPglc		1.45×10^{-7}	0.026
3FDNPglc		8.23×10^{-7}	0.147
4FDNPglc		3.73×10^{-7}	0.067
6FDNPglc		1.99×10^{-6}	0.357

Table 1

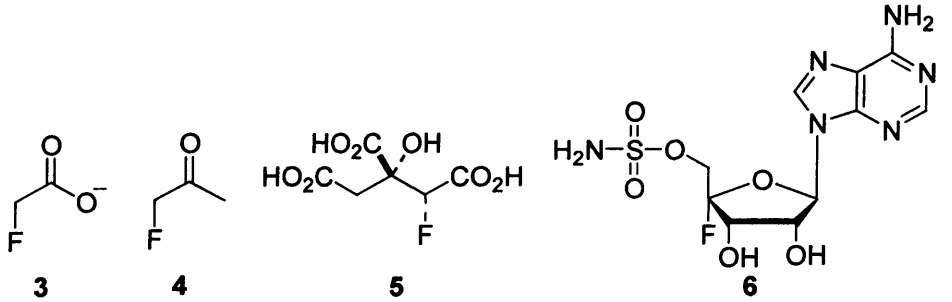
Both acid catalysed and uncatalysed pathways involve the development of full or high partial positive charge. The presence of the strongly inductive electron withdrawing fluorine atom will oppose this charge development and make exocyclic C-O bond cleavage occur more slowly. The nearer the site of fluorination is to the site of cleavage, the bigger the effect. The least reactive compound has a fluorine atom at C-2 and this makes the modified glucoside nearly 40 times less reactive than the glucoside. The effect at C-4 is also significant indicating that there is build up of partial positive charge on the pyranose oxygen at the transition state.

These substituent effects can be used to modulate the rates of spontaneous and enzymatic hydrolysis and to control the kinetic stability of glycosidic bonds made between sugars and proteins, antibiotics and other sugars. Potentially, a fluorinated

sugar analogue, which is still recognised, could fill a sugar binding site but resist the attempts of glycosidases to cleave it. Moreover, it may be able to heighten the biological activity. Another way to alter the stability of the glycosidic bond involves the removal of the endocyclic oxygen atom from the molecule. The removal of the oxygen atom will remove the anomeric effect and stabilise the bond at the C-1 position which becomes an ether rather than an acetal. For this purpose, several methods for the synthesis of carbasugars and highly functionalised cyclohexane derivatives have been developed. The replacement of the exocyclic oxygen in C-glycosides has also been explored extensively. For example, Kishi prepared a C-glycoside analogue of lactose and looked at the ligand both in the free state and bound to peanut lectin. The C-glycoside was able to bind in essentially the same conformation as lactose itself.[6] Similar approaches have been successful with trisaccharides.[7,8]

2. Effect of introducing one, two or more fluorine atoms on mono-saccharides.

Although there are only about twelve known naturally occurring fluorinated molecules, Figure 2 shows a selection,[9] more and more fluorinated compounds are appearing in the literature [10] and fluorine is increasingly present in bioactive compounds such as pharmaceuticals and agrochemicals.[11] A large proportion of these compounds contain a single fluorine atom or a trifluoromethyl or a perfluoroalkyl group on an aryl or heteroaryl ring to increase lipophilicity and resist metabolic oxidation.[9]



3 4 5 6

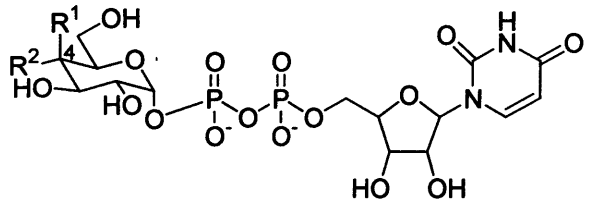
Figure 2

The van der Waals radius of the fluorine atom (1.47 Å) is fairly similar to that of oxygen (1.57 Å),[12] so replacement of a hydroxyl group with a fluorine atom should change the steric environment of the molecule minimally. However, the fluorine atom cannot mimic a hydroxyl group fully. Potentially, the fluorine atom can act as a hydrogen bond acceptor using one of its three lone pairs, but obviously not as a hydrogen bond donor.[13] From calculations, the C-F...H hydrogen bond is much weaker than C-O...H hydrogen bonds.[13] The fluorine atom is strongly electronegative and therefore functions less effectively as an electron donor than an oxygen atom and a weaker hydrogen bond results. Calculations estimate the strength of a C-F...H bond to be between 2.0 and 3.2 kcal mol^{-1} and that of an C-O...H hydrogen bond to be between 5 to 10 kcal mol^{-1}.[13] Calculated H...F distances emerged between 2.5 and 2.6 Å, which is close to the sum of the van der Waals radii of hydrogen and fluorine.[13] If fluorine is to replace the oxygen atom directly in the spatially demanding situation in an enzyme active site, a short F...H contact of about 2.0 to 2.3 Å is required.[13] The replacement of a hydroxyl group with one or two fluorine atoms therefore can alter both molecular recognition arrays based on hydroxyl groups, and the reactivity of the modified substrate.

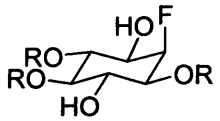
However, some studies have shown that the fluorine atom can act as a hydrogen bond acceptor successfully. UDP-4-Deoxy-4-fluoroglucose (UDP-FGlc) **7** and UDP-4-deoxy-4-fluorogalactose (UDP-Fgal) **8** were tested as substrates for UDP-D-glucose dehydrogenase, an enzyme which oxidises the C-6 hydroxyl group of UDP-D-glucose,[14] and distinguishes between glucose and galactose derivatives (Figure 3). The two 4-deoxy-4-fluoro analogues behave rather differently in the presence of the enzyme. Only **7** is a substrate for the enzyme (K_m = 30.2 mM compared to 9.6 mM for the natural substrate). However, the diastereoisomeric C-4 epimer, UDP-Fgal **8** was not a substrate but a competitive inhibitor; K_i = 20 mM. This implies that the C-4

OH group is a hydrogen bond acceptor, and that the fluorine atom in **7** can also fulfill this role to some extent. The fact that **8** is not a substrate but **7** is clearly demonstrates that the configuration of the fluorine at C-4 is crucial in securing a reactive conformation of the substrate on the enzyme surface for the reaction at the remote C-6 centre.[13] The difference in reactivity between the natural substrate and fluorinated substrate is based on the binding ability; the fluoro-analogue is bound less strongly because of the high electronegativity of the fluorine atom. The highly electronegative fluorine atom will make all the neighbouring hydroxyl groups less basic but more acidic.[18] The lower binding affinity suggested for the fluorinated compounds of the hydroxyl group oxygens with acidic groups on the receptor is very important.

Inositol phosphates, which are extremely important as secondary messengers, are also recognised by networks of hydrogen bonds.[15,16] D-*myo*-Inositol-1,4,5-triphosphate and its fluorodeoxy analogue **9** were nearly equipotent in their ability to mobilise sequestered Ca^{2+} ions from intracellular stores, consistent with the fluorine atom of **9** accepting a hydrogen bond from the receptor.[13] It is also possible that the C-4 position is not involved in binding at all. In this case, a compound with two hydrogens at C-4 might be expected to behave in the same way as the natural and fluorinated ligands. However, the unsubstituted compound is not reported in the literature.[15,16]



R^1 = H, R^2 = F UDP-FGlc **7**
R^1 = F, R^2 = H UDP-FGal **8**



R = PO_2^{2-} **9**

Figure 3

Eguchi *et al.* have also succeeded in revealing the different roles of C-2 and C-3 hydroxyl groups in **10-13** in certain biochemical transformations by using mono-fluorinated sugars as analogues.[17] They replaced one of the hydroxyl groups in D-glucose 6-phosphate with a fluorine atom as a potential hydrogen bond acceptor, and with an amino group as a hydrogen bond donor. The 2-deoxy-2-fluoro (2-F-G-6-P) **10** and 3-amino-3-deoxy (3-NH_2-G-6-P) **13** analogues were accepted as substrates by 2-deoxy-*scyllo*-inosose synthase (DOIS). However, 3-deoxy-3-fluoro (3-F-G-6-P) **11** and 2-amino-2-deoxy (2-NH_2-G-6-P) **12** were not accepted. This experiment showed that the hydroxyl group at C-2 has a role as a hydrogen bond acceptor and that the hydroxyl group at C-3 has a role as a hydrogen bond donor in the enzyme substrate complex. The fluorine at the C-2 position clearly worked as an acceptor; however, the amino group could not, because it is protonated. On the other hand, the protonated amino group at C-3 could work as an excellent donor, whereas the fluorine atom at C-3 could not act as a donor. (Figure 4) The kinetic parameters of the analogues with DOIS are interesting; k_{cat}/K_m is 24 $M^{-1}s^{-1}$ for **10** and 10 $M^{-1}s^{-1}$ for **13** compared to 4800 $M^{-1}s^{-1}$ for the natural substrate **14**. Analogues **11** and **12** were clearly poorer substrates than the natural substrate **14**. However, while distinguishing between the hydrogen bond donor and acceptor roles by using an ammonium substituent is an interesting idea, the introduction of a full charge into the molecule is a major structural perturbation. These results should therefore be treated with some caution.

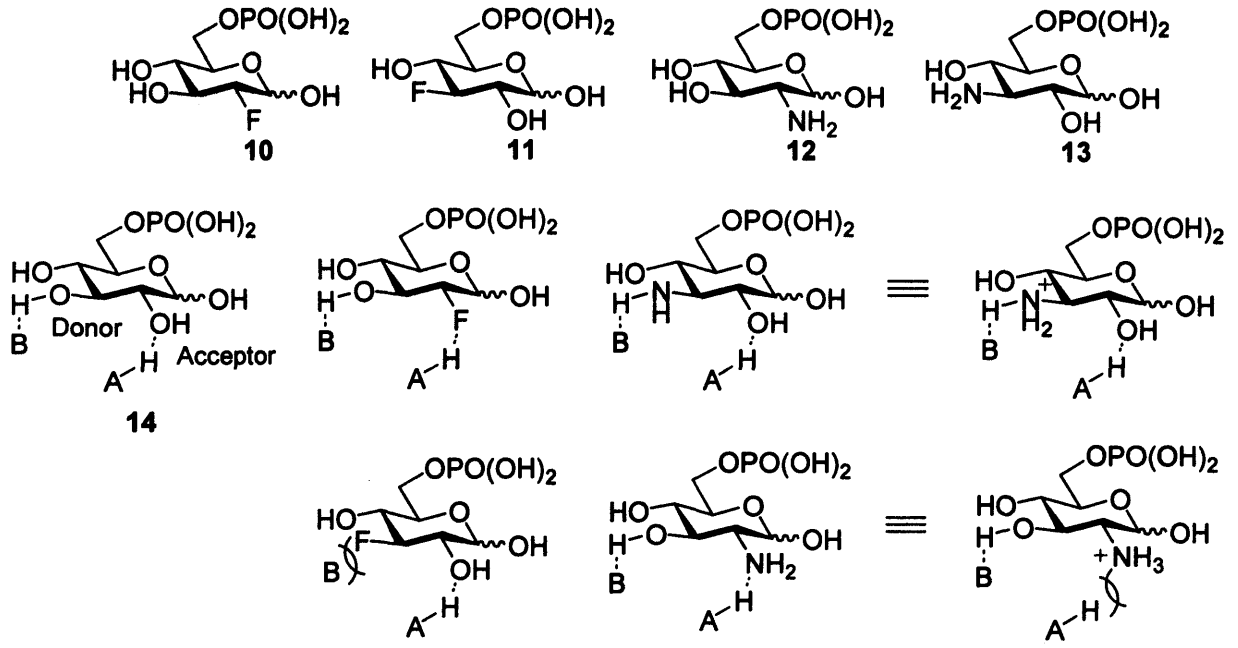


Figure 4

Fluorine is the most electronegative element and will therefore also have a significant effect on neighbouring functional groups, such as changing their basicity or acidity.[18] Conformational changes may also be introduced because of dipole-dipole interactions.[18] Finally, the presence of fluorine atoms in molecules may increase their lipophilicity, an important parameter in medicinal chemistry, because effective lipophilicity is related to solubility in fats and the ability to cross lipid membranes.[18]

The anomeric effect in carbohydrates increases the preference for axial over equatorial locations at O-C-X anomeric carbon. The explanation of this effect is that the lone pair on oxygen which lies anti periplaner to the C-X bond donates electrons into the $\sigma^*_{c\text{-}x}$ orbital in a stabilising hyperconjugative interaction. (Figure 5) This stabilisation enhances C-X bond cleavage and the formation of the oxacarbenium ion intermediate **15**. The stability of **15** is affected strongly by the nature of the substituent Y. Hexoses have a hydroxyl group at C-2, but many important sugars found in antibiotics and other bioactives are 2-deoxy sugars. Withers has shown that anomeric hydroxyl group in 2-deoxy-sugar is cleaved ca. 5 times more rapidly than

their non-deoxy counterparts.[5] This higher reactivity results in relatively facile deglycosylation of important species and loss of their activity.

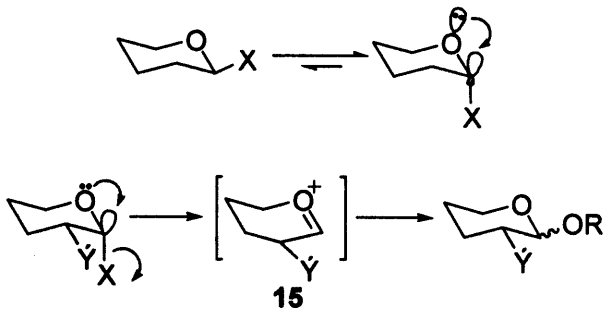
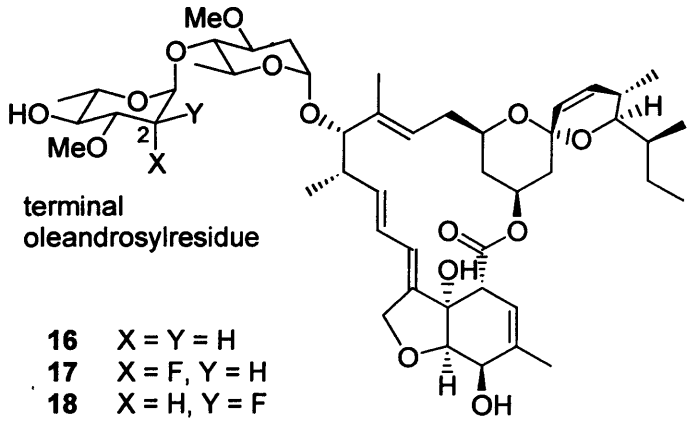


Figure 5

Avermectins[19] are polycyclic macrolides from the milbemycin family that have potent antiparasitic activity.[37] The disaccharide di-α-L-oleandrose and especially the terminal oleandrose unit, are essential for activity.[20] Avermectin B_{1a} **16** loses the terminal oleandrosyl unit readily, and its activity with it.[20] As the C-2 position cannot be involved in any process of hydrogen bond donation, replacement of the hydrogen atom by the fluorine atom looked like a reasonable way to stabilise the agent against hydrolysis (Figure 6).[21]

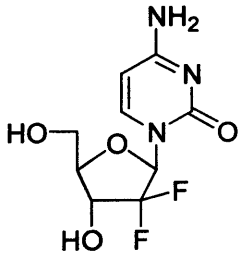


16 X = Y = H
17 X = F, Y = H
18 X = H, Y = F

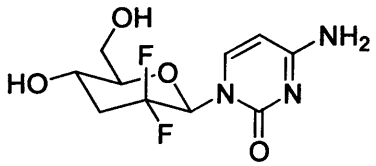
Figure 6

To increase the stability of the glycosidic bond, Lukacs *et al.* introduced a fluorine atom at position 2 of the oleandrose to slow the hydrolytic process by destabilising the oxacarbenium cation intermediate during the glycosidic cleavage.[22] 2-α- and 2-β-Fluorooleandroses were synthesised and introduced in the terminal unit of

avermectin B_{1a} **16** to afford analogues **17** and **18**. Biological tests showed **17** was as active as avermectin B_{1a} **16** against the two spotted spider mite and both **17** and **18** were at least as active as the parent compound against gastrointestinal helminths.[22] Among fluorinated sugar-type molecules, sugar nucleoside analogues have attracted a lot of interest in recent years as potential antiviral and anticancer agents.[23] Introducing fluorine atoms onto these molecules may increase their lifetime under the highly acidic conditions in the stomach, which is important for oral administration. To modify the biological activity of compounds, introduction of fluorine into positions 2β, 3α and 5 in nucleosides has been useful method. The most successful compound of this kind is probably gemcitabine **19**, which is highly active against certain types of refractory solid tumours and has been approved for treating several types of cancer.[24] The success of this compound has stimulated other groups to prepare further analogues of gemcitabine using this idea. Unfortunately, none has proved to be usefully biologically active. In this context, Castillón *et al.* prepared dideoxy-difluoropyranosyls **20** and **21** as pyranosyl analogues of gemcitabine **19** where the C-2 or C-3 position is *gem*-difluorinated, respectively.[25] Unfortunately, biological tests on difluorinated pyranosyls **20** and **21** did not show any activity against the HIV virus or any toxicity in MT-4 cells (Figure 7).



19



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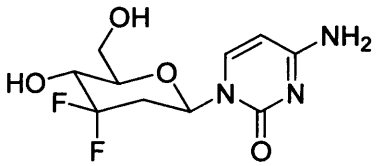

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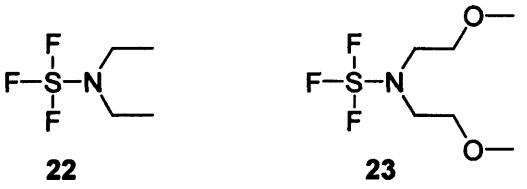
Figure 7

3. Methods for the synthesis of difluorinated monosaccharide analogues

There are two strategically different ways to introduce fluorine into molecules. The first method involves direct fluorination of non-fluorinated substrates with fluorinating agents (Figure 8). Diethylaminosulfur trifluoride (DAST) **22** and derivatives such as bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor^{TM}) **23** are example of nucleophilic fluorinating reagents and commonly used for replacement of hydroxyl groups with fluorine atoms.[26] The second method exploit the building-block approach which uses fluorine-containing synthetic blocks as starting materials. The latter method allows the synthesis to start from readily available and easy-to-handle fluorine-containing molecules and builds them up into a desired target molecule. Both of these methods have some limitations in terms of the range of synthetic chemistry available.



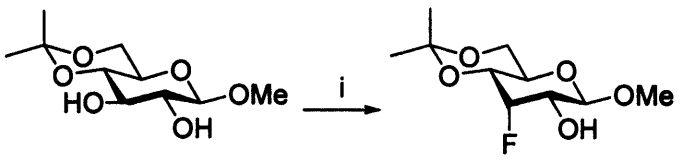
22 **23**

Figure 8

3-1. Direct fluorination method using fluorinating reagents

DAST is one of most popular and widely used fluorinating reagents for the synthesis of fluorinated oligosaccharides, however DAST is a very toxic, potentially explosive and expensive reagent.[27] It can react with a wide range of functional groups, including alcohols, hemiacetals, aldehydes and ketones. Furthermore, many examples require a large excess of DAST, because of its slow reaction and high moisture sensitivity. DAST has limited thermal stability and undergoes strongly exothermic reaction, therefore a reaction requiring an excess of DAST risks the possibility of an explosion. The synthesis of fluorinated monosaccharides with DAST

usually requires extensive protection, because DAST usually shows no chemoselectivity in its reactions (Scheme 2).[28]

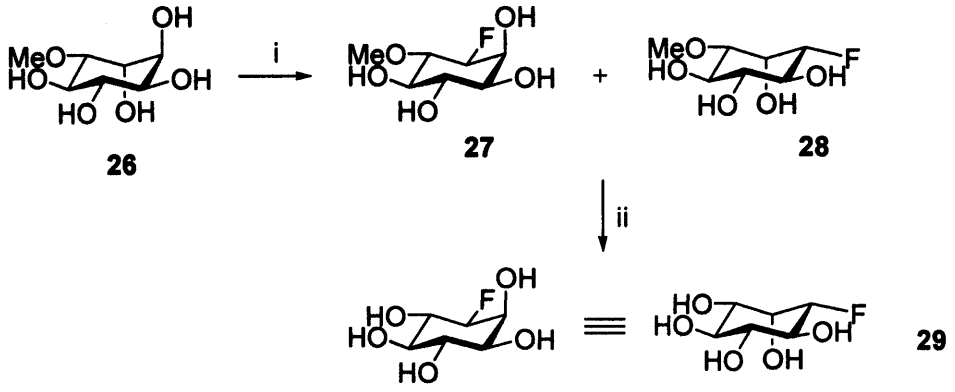


24 **25**

Reagents and conditions : i, DAST (4.5 eq.), CH_2Cl_2, -40°C to rt, overnight, 45%.

Scheme 2

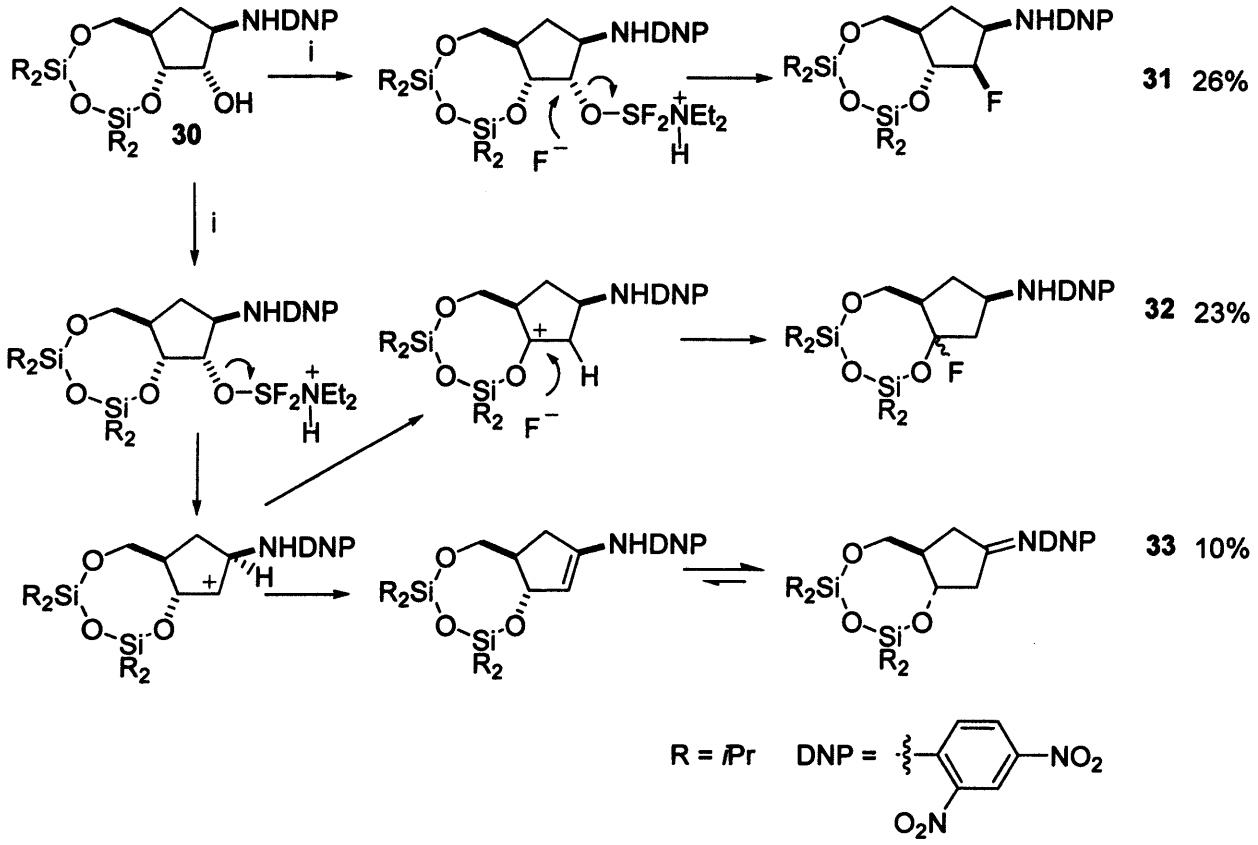
There are few examples of fluorination of lightly protected and unprotected substrates. Quebrachitol **26** is one of them; Kozikowski *et al.* have synthesised fluoro-*myo*-inositol **29** in two steps by reacting DAST with quebrachitol **26** which can be isolated from waste rubber solids.[29] Fluorinated inositol analogue **29** was investigated for its effect on cellular growth in PC12 cells, and found to markedly inhibit cellular replication in a dose-dependent manner. Quebrachitol **26** was treated with DAST in the absence of solvent at 20 °C and fluorinated products **27** and **28** were deprotected with BBr_3 to afford **29** in 35-50% overall yield. Evidently, the mixture of isomers **27** and **28** is formed by selective replacement of either of the axial hydroxyl groups by a fluorine atom. Because of the latent symmetry, demethylation converges these two products in **29**. This result suggested that the more favoured pathway involved attack by fluoride of the axial hydroxyl group (Scheme 3).[30] The only products isolated from the reaction arise from the reactions of the axial hydroxyl group with DAST. Both could react equally well; however as the products converge after demethylation, it is impossible to say if either or both have reacted. As the total yield is only 50%, we could not tell the equatorial hydroxyls have reacted, but have formed unstable products or not.



Reagents and conditions : i, DAST, ii, BBr_3

Scheme 3

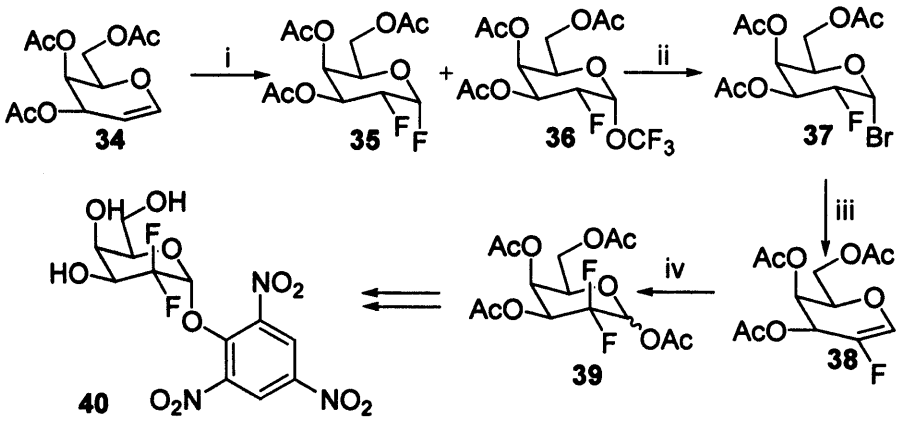
Another significant limitation of DAST is the occurrence of side reactions. A number of reactions which involve neighbouring group participation (NGP), elimination and 1,2-group shifts have been reported.[31] These reactions occur because the C-O cleavage step in the DAST reaction involves the development of significant oxacarbenium ion character, hence the occurrence of these S_N1-related side reactions. Biggadike *et al.* have described an example of each of these side reactions (Scheme 4).[32] Monofluorinated compound **31** was produced in 26% yield, side product **32** was produced by 1,2-hydride migration in 23% yield, and **33** was produced in 10% yield by tautomerisation of enamine.[32]



Reagents and conditions: i, DAST, DCM.

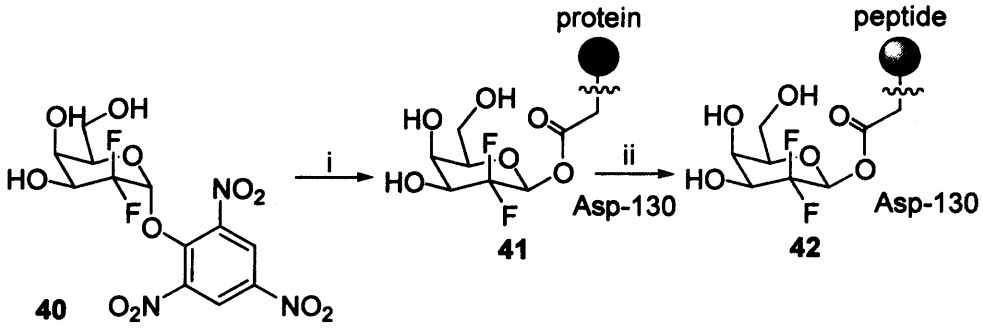
Scheme 4

Introducing two fluorine atoms into carbohydrate analogues can be more difficult; however, even larger electronic effects can be expected in the products. For example, Withers *et al.* synthesised 2,2-difluorosugars *via* electrophilic fluorination of a glycal **38** with acetyl hypofluorite (Scheme 5) and demonstrated that the difluorinated glycoside **40** with a very good leaving group undergoes reaction with glycosidases to label an active site nucleophile (an aspartate) with the difluorosugar residue as shown in Scheme 6.[33,34] The labelled protein underwent peptic digest to prepare degradation fragments suitable for MS-MS sequencing of the glycosidase.[34] In the synthesis, the glycal **34** has attacked the fluorinating agent through its less hindered face; the nucleophile can the presumably attack either face but the axial anomers are favoured with good leaving groups. Fluoride anion is formed *in situ* upon break down of trifluoromethoxide. The regioselectivity is controlled by the formation of an oxacarbenium ion.



Reagents and conditions: i, CF_3OF, $CFCl_3$; ii, HBr, AcOH; iii, NEt_3; iv, AcOF

Scheme 5

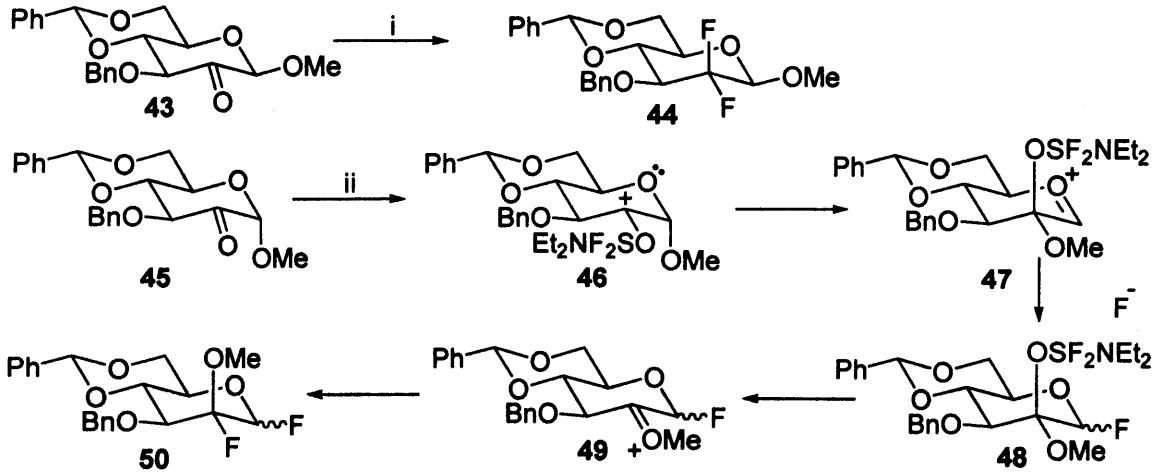


Reagents and conditions: i, *P. chrysosporium α-galactosidase*; ii, peptic digest

Scheme 6

Castillón *et al.* have also synthesised 2-deoxy-2,2-difluorosugars and reported an interesting relationship between the fluorination outcome and the orientation of the functional group at the anomeric centre. (Scheme 7).[36]

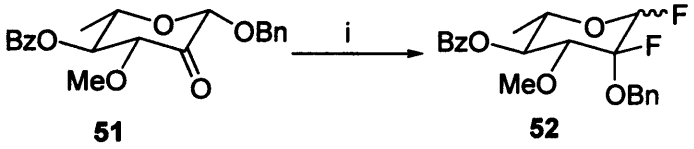
When the alkoxy group at the anomeric center was equatorial **43**, fluorination occurred successfully to produce the desired difluorinated products **44**. However, when the alkoxy group was axial **45**, 1,2-migration *via* the oxonium cation intermediate occurred to produce the by-product **46**.



Reagents and conditions: i, DAST (4.2 eq.), DCM, rt, 24 h, **44**, 80%; ii, DAST (10 eq.), benzene, reflux, 24 h, **50**, 43%.

Scheme 7

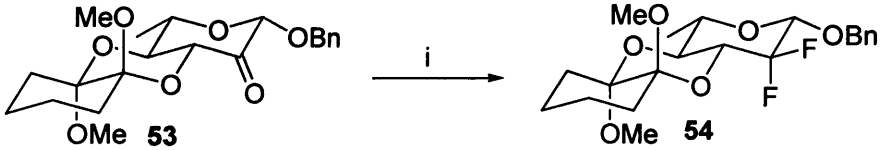
When the authors attempted fluorinate rhamnose-derived ulose **51**, the product **52** was one of neighbouring group participation by axial OBn group, indicating that ring-flipping had occurred in the starting ketone (Scheme 8). [37]



Reagents and conditions: i, DAST, CH_2Cl_2.

Scheme 8

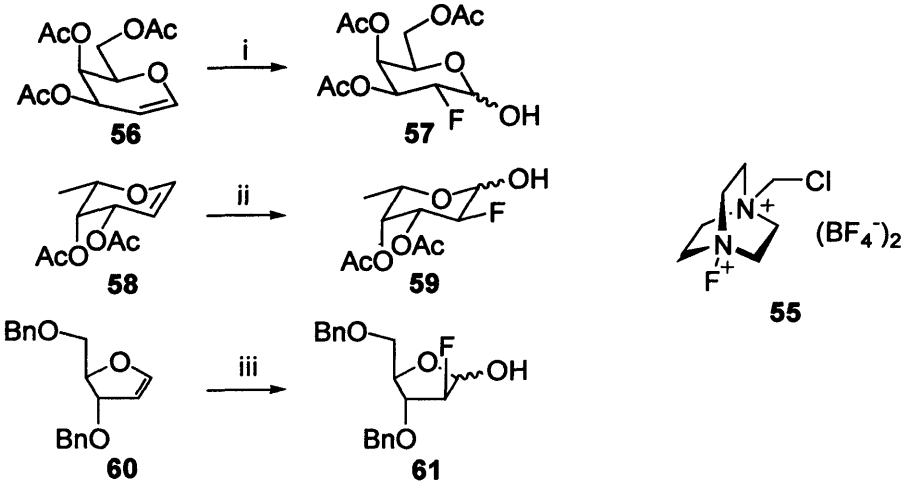
The authors solved this problem by using cyclohexane 1,2-diacetal (CDA) protection in **53**. A combination of the trans-decalin formation and favourable n to δ* stereoelectronic interacts holds this molecule in the conformation shown and delivers the desired 2,2-difluoroulanose. The control experiment describing the fate of the axial anomer of **53** was not reported in the literature.[37]



Reagents and conditions: i, DAST (7.8 eq.), DCM, rt, 6 h, **54**, 69%.

Scheme 9

It is an alternative fluorination strategy to use 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F-TEDA) **55**, which is a mild electrophilic fluorinating reagent and is useful for fluorinating carbon-carbon double bonds and active methylene protons.[38,39] The reagent is relatively inexpensive, safe and easy to handle. However, relatively few examples have been reported in carbohydrate chemistry. Wong *et al.* have reported the one-pot synthesis of 2-deoxy-2-fluoro glycosides and glycosylation reaction with Selectfluor **55**.[39] Selectfluor reacts with glycals in the presence of a nucleophile to give 2-deoxy-2-fluoro derivatives, which provides a new route to various 2-deoxy-2-fluoro monosaccharides, glycosides and disaccharides in high yields. Selectfluor transforms glycals cleanly to 2-deoxy-2-fluoro sugars in good yields (Scheme 10). [39] All these reaction involve addition of the fluorine to the less hindered face to the alkene.



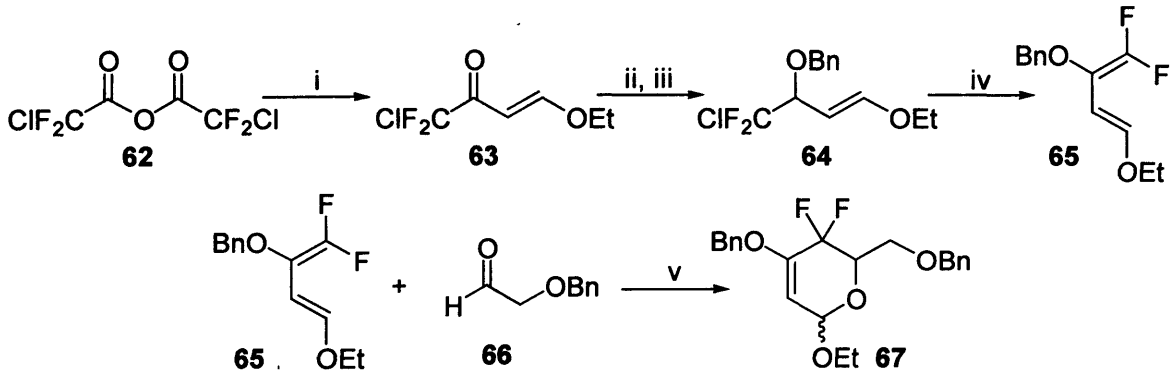
Reagents and conditions: i, 1.5eq. **55**, DMF/H_2O (3/1), rt, 79%; ii, 1.5eq. **55**, DMF/H_2O (3/1), rt, 97%; iii, 1.5 eq **55**, DMF/H_2O (3/1), rt, 73%.

Scheme 10

3-2. The building block approach

Fluorinated sugars are attractive targets but their synthesis by fluorination strategies can be very difficult. Many groups have reported that reactions involving DAST

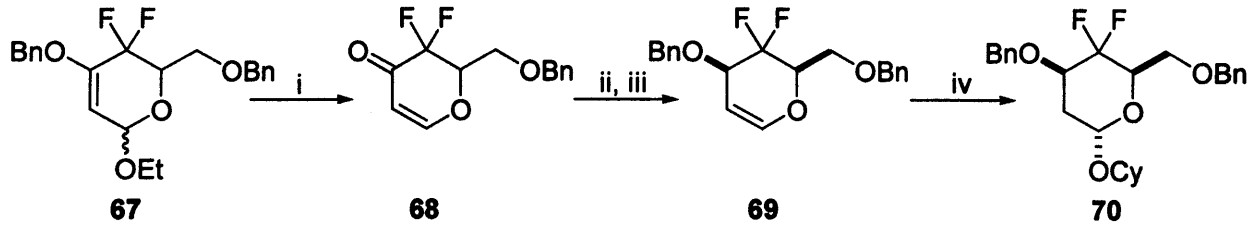
encounter problems including low yield, lack of chemoselectivity, requirement of extensive protection steps, and in particular, problems associated with difluorination. The alternative method for the introduction of one (or two) fluorine atom(s) into a molecule is the building block approach, which starts from inexpensive and readily available fluorinated chemicals. Among a large number of fluorinated building blocks, mono and difluoroalkenes and dienes have been employed as a starting substrate for sugars. In particular, the hetero Diels-Alder reaction is a useful method for sugar synthesis, especially the reaction with oxygenated 1,3-dienes containing fluorine atoms and aldehydes. Taguchi *et al.* reported a synthesis of 4-deoxy-4,4-difluoropyranosides using a hetero-Diels Alder reaction between difluorinated diene **65** and benzyloxyacetaldehyde. Diene **65** was synthesised from commercially available chlorodifluoroacetic anhydride, which was reacted with ethylvinyl ether to afford enone **63**.[40] Lithium aluminium hydride reduction followed by protection afforded enol ether **64**. The reducing agent attacks in a 1,2-sense, reacting with the hardest (carbonyl) carbon of the vinylogous ester **63**. Treatment with strong base afforded the desired diene **65** in good yield (Scheme 11).[40]



Reagents and conditions: i, CH_2=CHOEt, Py., DCM, 12 h, rt, **63**, 60%; ii, $LiAlH_4$, Et_2O, -78 °C; iii, NaH, BnBr, THF/DMF, 0 °C, 1h, **64**, 64% over 2 steps; iv, ^tBuOK, THF, -50 °C, **65**, 90%; v, cat. $ZnCl_2$, -50 °C to rt, 12 h, **67**, 79%.

Scheme 11

Adduct **67** was converted to enone **68** by treatment with *p*-toluenesulfonic acid in DCM at room temperature.[40] Luche reduction with sodium borohydride and cerium(III) chloride heptahydrate was followed by protection. Then, treatment with cyclohexyl alcohol under *p*-TsOH-catalytic conditions afforded cyclohexyl pyranoside **70** with high 2,6-*trans*-selectivity (1:13) (Scheme 12).[40]

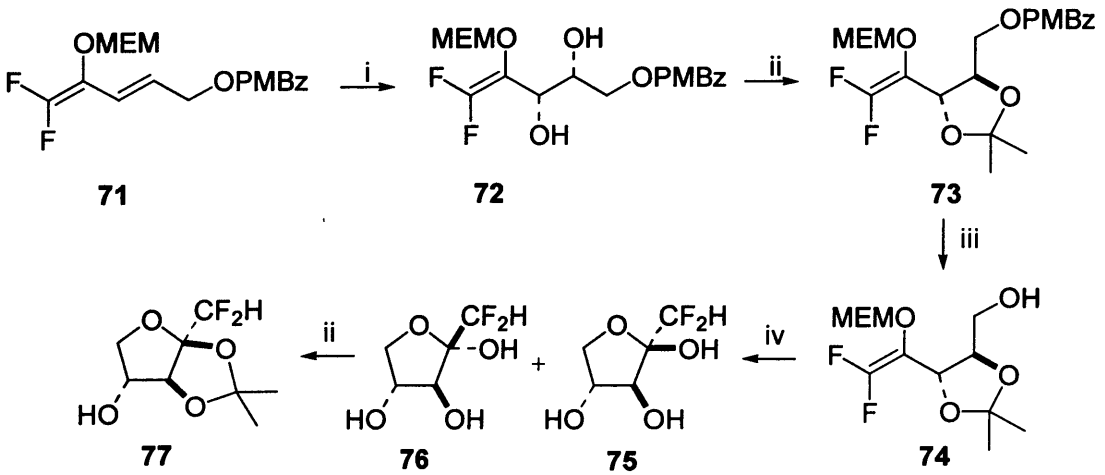


67 **68** **69** **70**

Reagents and conditions: i, *p*TsOH, DCM, rt, 2 h, **68**, 82%; ii, $NaBH_4$, $CeCl_3.7H_2O$, DCM/EtOH, -78 °C to rt, 16 h; iii, NaH, BnBr, THF/DMF, 0 °C, 1 h, **69**, 86% (2 steps); iv, *p*TsOH, CyOH, DCM, rt, 24 h, **70**, 79%.

Scheme 12

Percy *et al.* suggested attractive methods to difluorinated sugar analogues starting from inexpensive starting materials *via* Sharpless asymmetric dihydroxylations.[41] The key reaction is AD reaction of diene **71** with control of pH (11-12).[41] Diol **72** was protected in acetonide **73**. Then hydrolysis of the ester moiety of **73** followed by removal of both acetals afforded deoxy difluorosugars **75** and **76**. Exposure to acid conditions converged **75** and **76** to **77** (Scheme 13).



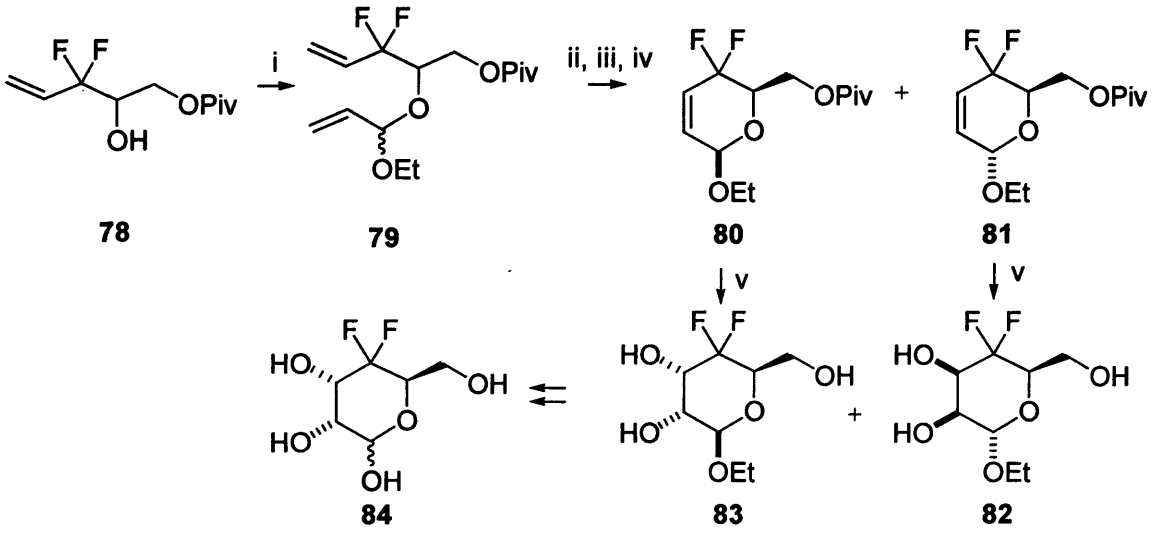
71 **72** **73** **74** **75** **76** **77**

Reagents and conditions: i, $K_2OsO_4.2H_2O$ (2 mol %), $(DHQD)_2PHAL$ (4 mol %), $K_3Fe(CN)_6$(3 eq.), t-BuOH/H_2O (1:1), pH 11.0-12.0, rt, 54%; ii, anhydrous $CuSO_4$ (2 eq.), PTSA (1 mol %), acetone, rt,

68%; iii, 30% H_2O_2 (4.2 eq.), $LiOH.H_2O$ (2.2 eq.), THF/H_2O (3:1), 0 °C, 61%; iv, Me_3SiCl (1.2 eq.), MeOH, rt, 88%.

Scheme 13

Another useful method to approach sugars is ring closing metathesis which is recently becoming popular.[42-44] Audouard and co-workers have suggested that 4,4-difluoroglycosides could be made using ring-closing metathesis (Scheme 14).[42] The reaction started from 1-bromo-1,1-difluoropropene and various aldehydes to give key difluoro alcohol **78**. The transacetalisation of **78** afforded diene **79** as a 1:1 mixture of diastereomeric acetals. Ring closing metathesis took place with Grubbs' catalyst to form cyclic products **80** and **81**. Dihydroxylation produced difluorinated glycosides **82** and **83**, both of which underwent hydrolysis to afford fluorinated sugar **84** as a final product. The dihydroxylation occus trans to the allylic (and also anomeric) C-O bond.[45]



Reagents and conditions: i. acrolein diethyl acetal, PhMe, heat, 60 mmHg; ii, 5% Grubbs' catalyst **86**, DCM, reflux; iii, separation; iv, DIBAL-H, -78 °C to 0 °C; v, OsO_4, NMO, *t*-BuOH, acetone, water, 0 °C to rt, **82**, 62% and **83**, 62%

Scheme 14

The building block approach is very attractive method for the synthesis of fluorinated analogues, however there are some disadvantages. The main disadvantage arises

from the fact that few methods which connect readily-available fluorinated starting materials with the powerful asymmetric reaction of modern organic synthesis have been discovered to date. It is clear that more and more sophisticated chemistry is required.

4. Ring closing metathesis for sugar analogues

Hexoses normally occupy chair conformations; for example, α-D-glucose adopts a $^4C_1$ conformation. α-D-altro pyranose can exist in a number of different conformaion, including $^1C_4$ conformaion which conformer is populated depends on a balance between the demands of substituents for equatorial environments. Polyhydroxylated cyclooctane derivatives can adopt conformations similar to that of a hexose and thus can be potential non hydrolysable sugar mimetics.[46] One of the promising methods for medium ring size construction is ring closing metathesis.[47-49] Olefin metathesis in the presence of metal carbene complex catalysts is a very powerful carbon-carbon bond-forming reaction.[50] When the reaction is carried out intramolecularly, a ring is formed and the reaction is called ring-closing metathesis (RCM). Recently, RCM has become a popular method for the synthesis of medium- to large-sized rings from acyclic dienes, and well defined and stable metal catalysts have been developed.[54-57] The first well defined molybdenum catalyst **85** was developed by Schrock *et al.*[51] This metal complex was very active, but also very sensitive to air and moisture. The longer lifetime of the catalysts is essential to give high yields of products with reasonable catalyst loading. Grubbs *et al.* and other groups developed several ruthenium-based catalysts such as **86-88**.[49] These are tolerant to many functional groups such as alcohol, ketone, ester and amide.[53] and are much less sensitive to air and moisture than Schrock's catalyst **85**. Catalysts **87** and **88** have increased activity and lifetimes, achieved by the introduction of *N,N*-disubstituted imidazolidine ligands

instead of tricyclohexylphosphine (Figure 9).[52] Catalyst **86**, known as 1st generation Grubbs' catalyst and catalyst **87** known as 2nd generation Grubbs' catalyst show high activity and stability.

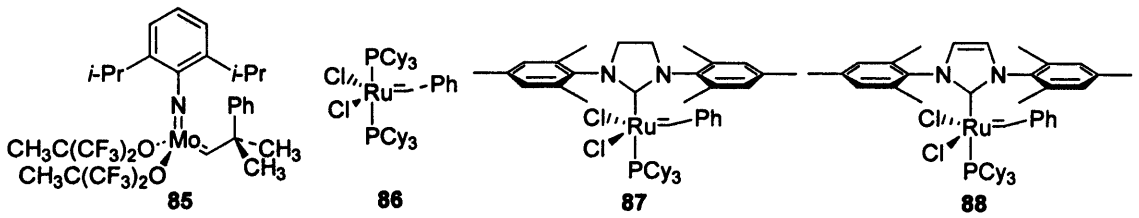
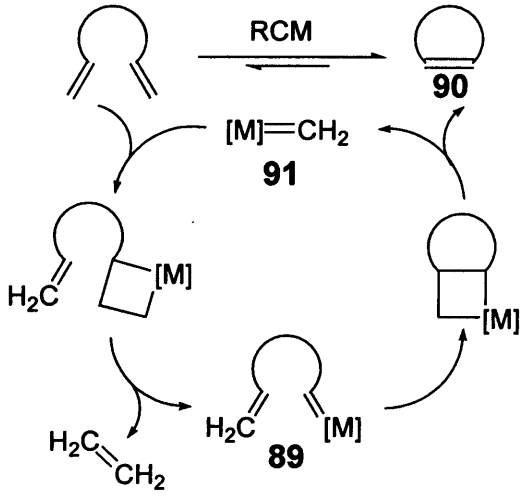


Figure 9

The generally accepted mechanism for RCM with Grubbs' catalyst **86** is shown in Scheme 15.[54] The reaction proceeds *via* a sequence of formal [2+2] cycloaddition/cycloreversions to afford ruthenium carbene **89**. The ruthenium carbene **89** goes through the same sequence intramolecularly to deliver the RCM product **90**. The reaction is mainly driven by release of ethylene or a volatile by-product and the newly produced alkylidene **91** enters the catalytic cycle again.[54]

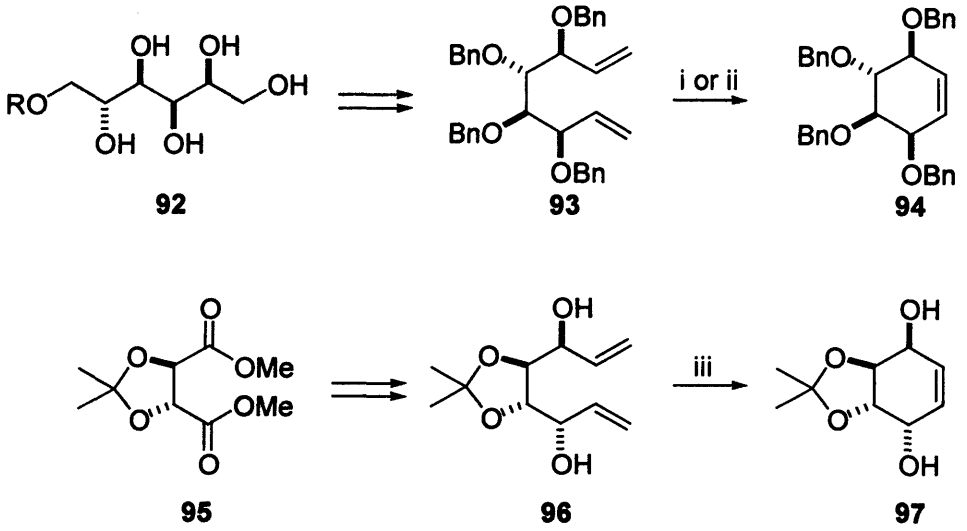


Scheme 15

4-1. Application of RCM for small ring compounds

Effective and easy-to-handle metathesis catalysts have been widely used in the synthesis of various sizes of rings. Stable and easily formed 5-and 6-membered ring compounds were synthesised in the first studies. Fürstner *et al.* succeeded in

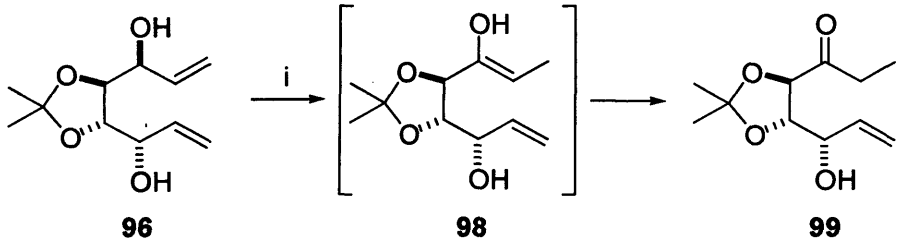
producing conduritols from commercially available monosaccharide building blocks in short sequences and also showed the difference in the reactivities of the various catalysts.[54] RCM precursor **93** can be synthesised from D-glucose in 5 steps. With catalyst **88**, RCM products were formed in much better yields and a shorter time than with catalyst **86**, even in the presence of two-unprotected hydroxyl groups in the substrate (Scheme 16). [54]



Reagents and conditions: i, catalyst **86**, DCM, reflux, 60 h, 32%; ii, catalyst **88**, DCM, reflux, 2 h, 89%; iii, catalyst **88**, DCM, reflux, 2 h, 69%.

Scheme 16

In the same reaction, however, catalyst **86** also effected slow isomerisation of one of the double bonds rather than RCM to form intermediate **98** and delivered hydroxyketone **99** as the only product (Scheme 17).[54]

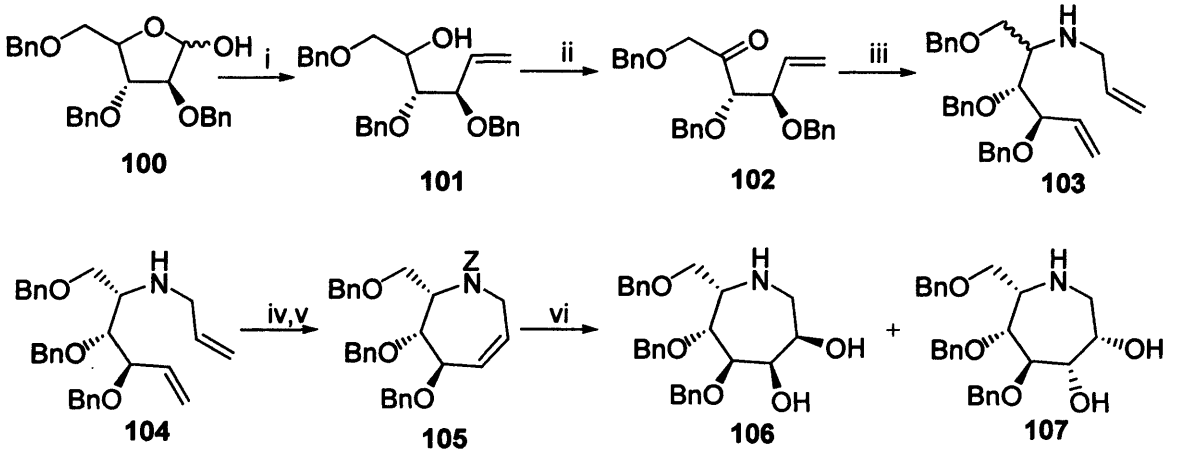


Reagents and conditions: i, catalyst **86** (20 mol %), DCM, reflux, 20 h, 29%.

Scheme 17

Sinaÿ *et al.* synthesised substituted azepanes mimicking monosaccharides.[58] RCM precursors **103** was easily prepared from D-arabinose in a short synthesis.[59] The

alcohol **101** was prepared through Wittig olefination of tribenzyl-D-arabinose **100**, then oxidised with PCC to give ketone **102** in 90% yield. Reductive amination of ketone **102** with allylamine and acetic acid in the presence of $NaBH_3CN$ gave aminohexenitols **103** in 58% yield (syn/anti = 2/3). The amine moieties can decrease the reactivity of the ruthenium catalyst,[60] therefore the amines were protected with a benzyloxycarbonyl group (Cbz or Z) to afford the corresponding carbamate and the RCM was carried out to afford dihydroazepanes **105** in good yield. Dihydroxylation proceeded smoothly to give *cis* diols **106** and **107** in a 4:1 ratio (Scheme18).[58]



Reagents and conditions: i, $CH_2=PPh_3$; ii, PCC, molecular sieves, DCM, ether, 90%; iii, allylamine, AcOH, $NaBH_3CN$, CH_2Cl_2, 30 °C, 58%; iv, ZCl, $KHCO_3$, 90%; v, catalyst **86**, DCM, 45 °C, 3 days, 84%; vi, OsO_4, NMO, acetone/water, 89%.

Scheme 18

4-2. Application of RCM for medium to large ring compounds

RCM can also be used to form medium-sized carbo- and heterocycles and there are several interesting examples.[61-63] However, medium rings (8-10) are more difficult to form than small rings (5-6) because eight-membered species pose particular problems. The combination of Baeyer(bond angle), Pitzer (torsional) and transannular strain in the cyclic products, and high conformational flexibility in the

acyclic precursors, results in unfavourable enthalpic and entropic contributions to the free energy of activation for the cyclisation reaction.[64] Low effective molarities and disappointing synthetic yields for eight-membered ring formation are the inevitable consequence when reversible reactions are attempted.

Reitz *et al.* have used RCM to synthesise the 7-amino-8-oxoazocane-2-carboxylic acid scaffolds **109-111** which mimic *ox*-[Cys-Cys] **108**.[65] The *ox*-[Cys-Cys] **108** is an unusual dipeptide found in the catalytic domain of mercuric ion reductase, malformin and in the *N*-terminal extracellular domain of most nicotinic acetylcholine receptor (nAChR) protein subunits. Closely related compounds may be useful for studying the structure activity relationships of a variety of biologically relevant peptides including somatostatin, malformin and the enkephalins (Figure 10).[65]

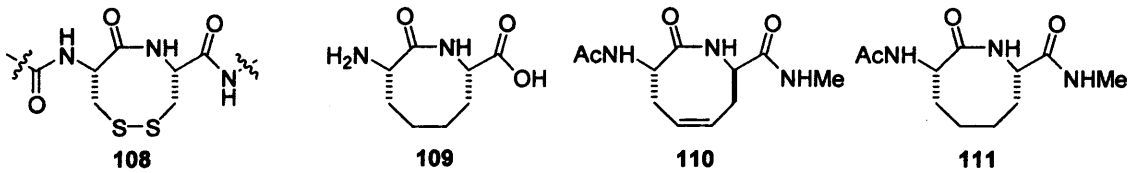
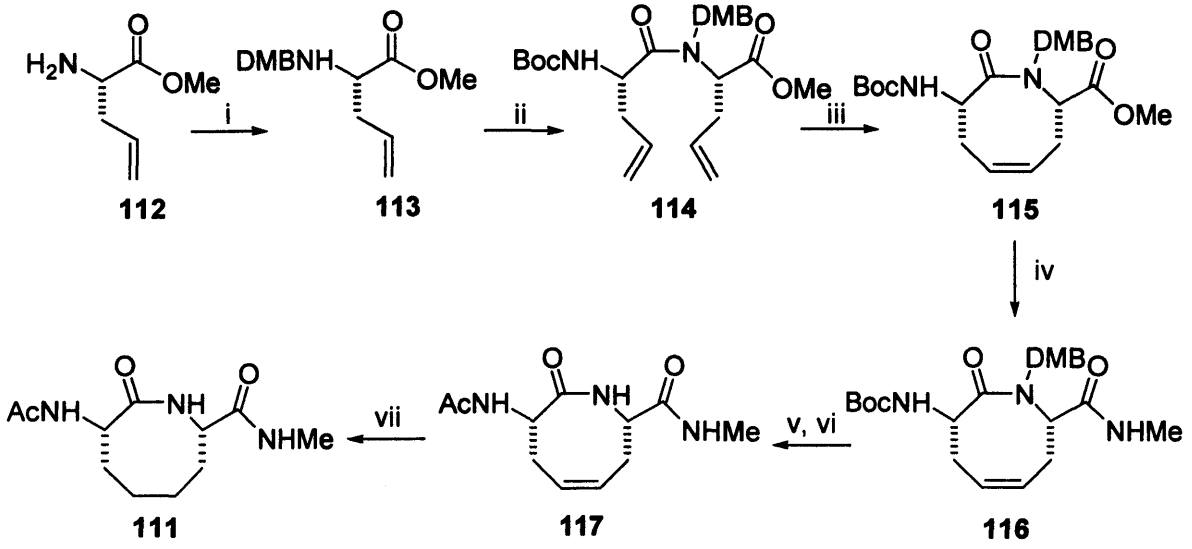


Figure 10

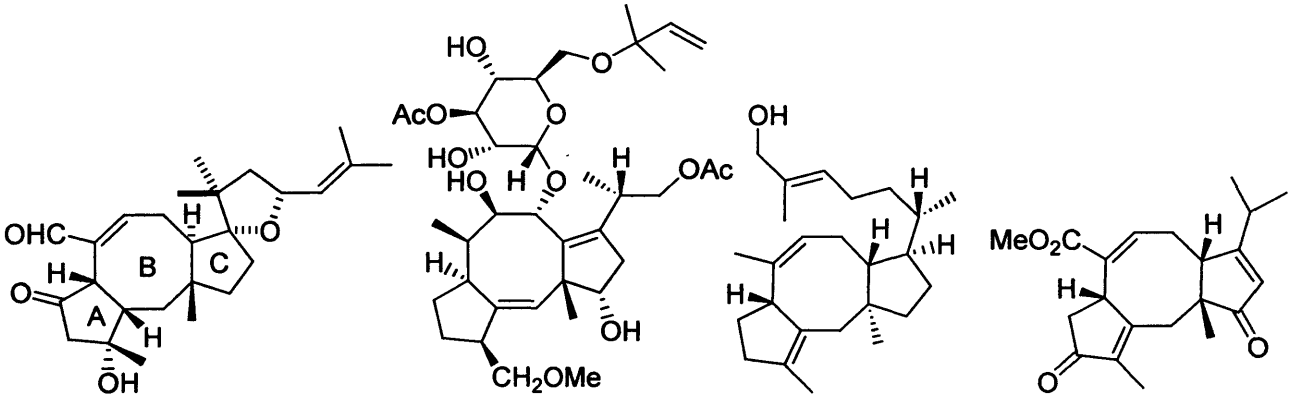
The key 8-membered ring compound **115** was prepared by RCM starting from two adjacent allylglycine (Agy) residues. L-Allylglycine methyl ester **112** was reductively alkylated with 2,4-dimethoxybenzaldehyde to give **113**, which was coupled with *N*-(Boc)-L-allylglycine to afford dipeptide **114**. RCM of **114** with Grubbs' 1st generation catalyst **86** at relatively high dilution produced protected product **115** in high yield. Methyl ester **115** was treated with methylamine to form amide **116**, followed by removal of the Boc group and protection as an acetamide to afford **117**. Finally, hydrogenation delivered the target product **111** (Scheme 19).[66]



Reagents and conditions: i, 2,4-dimethoxybenzaldehyde, $Na(AcO)_3BH$; ii, Boc-L-Allylglycine, HOAt/HATU, *N*-ethyl morpholine; iii, Grubbs' catalyst **86**, DCM, reflux (0.003 M substrate), 1 day; iv, 2 M $MeNH_2$/MeOH; v, TFA, Et_3SiH; vi, acetic anhydride; vii, H_2, Pd/C. DMB = 2,4-$(MeO)_2PhCH_2$-

Scheme 19

Ring closing metathesis is also useful for the synthesis of natural products containing medium rings such as ophiobolin A **118**, fusicoccin A **119**, ceroplastol II **120** and serpendione **121** (Figure 11).[67]

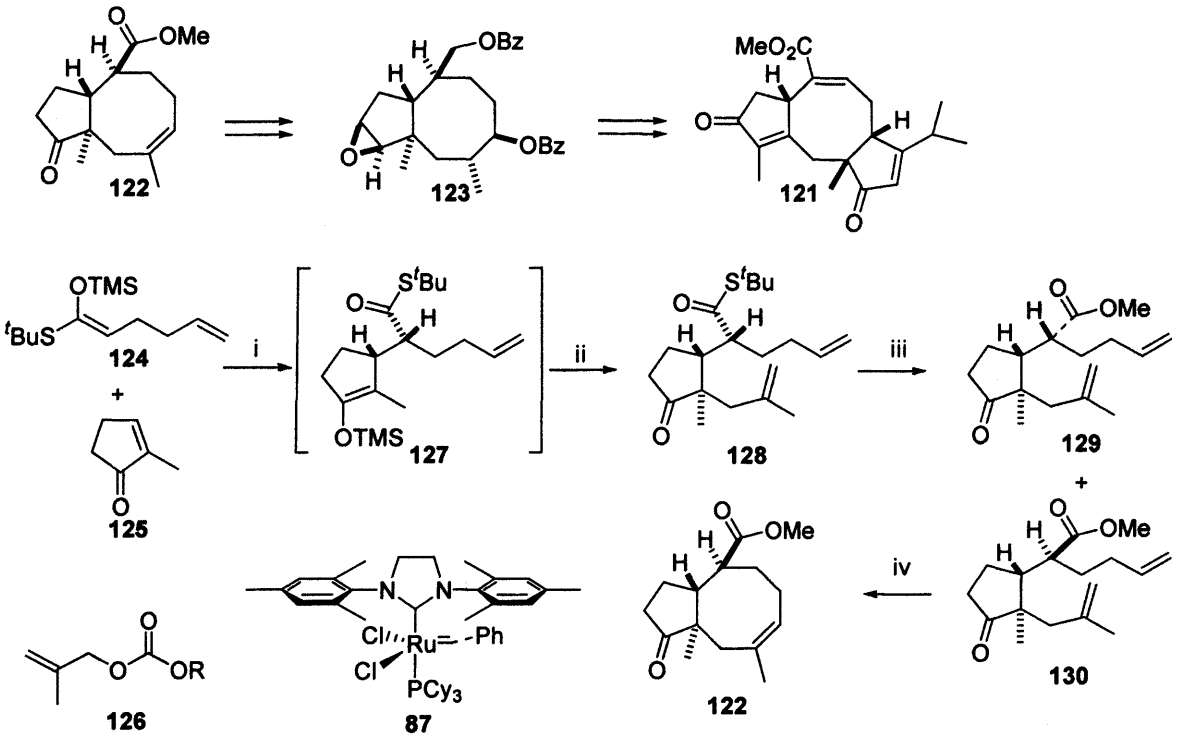


118 **119** **120** **121**

Figure 11

For the synthesis of sependione **121** and ceroplastol **119**, Wicha *et al.* prepared cyclooctapentane **122** as an advanced intermediate.[67] The Mukaiyama-Michael reaction of **124** with enone **125** in the presence of trimethylsilyl triflate afforded an adduct **127**. The adduct **127** was alkylated with carbonate **126** and $Pd(OAc)_2$-bppb as the catalyst in 82% yield. The electrophile added from less hindered face of the

silylenol ether. After ester exchange to methyl ester and epimerisation, the diene **130** was subjected to RCM using Grubbs' 2nd generation catalyst **87** to afford 8-membered ring product **122** (Scheme 20).

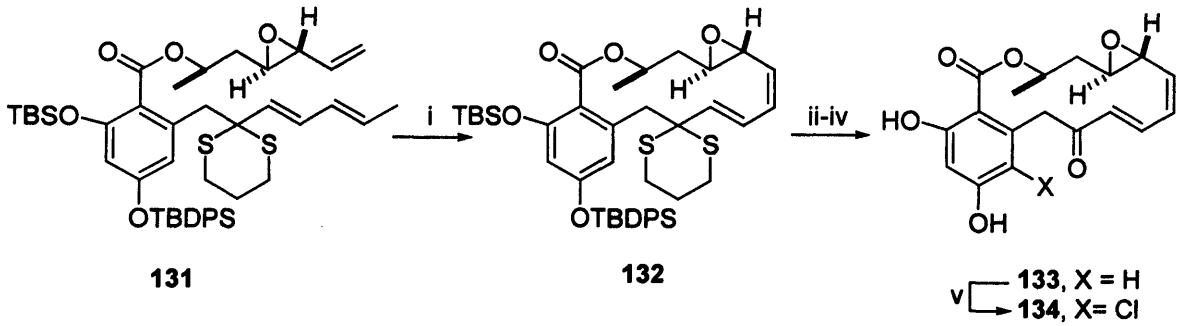


Reagents and conditions: i, TMSOTf, DCM, -78 °C; ii, **126**, 3 mol % $Pd(OAc)_2$-dppb, THF, 30 °C, 120h, 82%; iii, MeOK/MeOH, reflux, >90% (**129/130** =1/1); iv, 3 mol % catalyst **87**, DCM, reflux, 6h, 95%.

Scheme 20

RCM was found to be useful for the synthesis of medium to large ring products, such as macrolides radicicol **134**.[68] This example also shows the tolerance of Grubbs' catalyst **87** towards various functional groups as the substrate includes an ester, an additional carbon-carbon double bond, a vinyl epoxide and a dithiane. The reaction produced the 14-membered ring **132** in 60% yield (Scheme 21). This is a remarkable example; there are three alkenyl groups with which a ruthenium alkylidene can react. The least hindered alkene would appear to be part of a vinyl oxirane; presumably, forming 14-membered ring is faster than forming the 12-membered ring. When the *ortho*-hydroxyl group was unprotected, the yield and rate of the ring closure decreased. It may be caused by the formation of the intramolecular hydrogen

bonding. Danishefsky also reported that the new alkene is formed only as the *Z*-diastereoisomer. It is difficult to anticipate the conformation of **132** but the *Z*-alkene can be accommodated with less strain than the *E*-diasteroisomer.



131 **132**

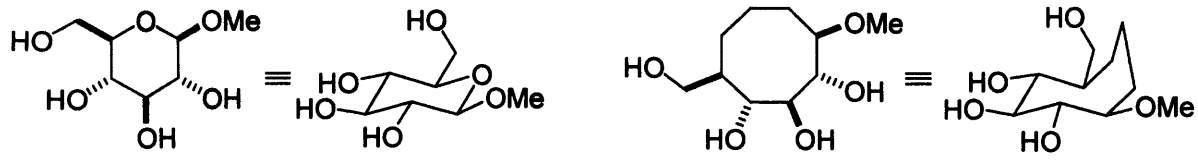
v → **133**, X = H; **134**, X= Cl

Reagents and conditions: i, catalyst **87**, 42 °C. 60%; ii, *m*CPBA; iii, Ac_2O, NEt_3, H_2O, 60 °C; iv, $NaHCO_3$, MeOH, 60%; v, SO_2Cl_2, 58%.

Scheme 21

5. The development of non-hydrolysable oligosaccharide analogues

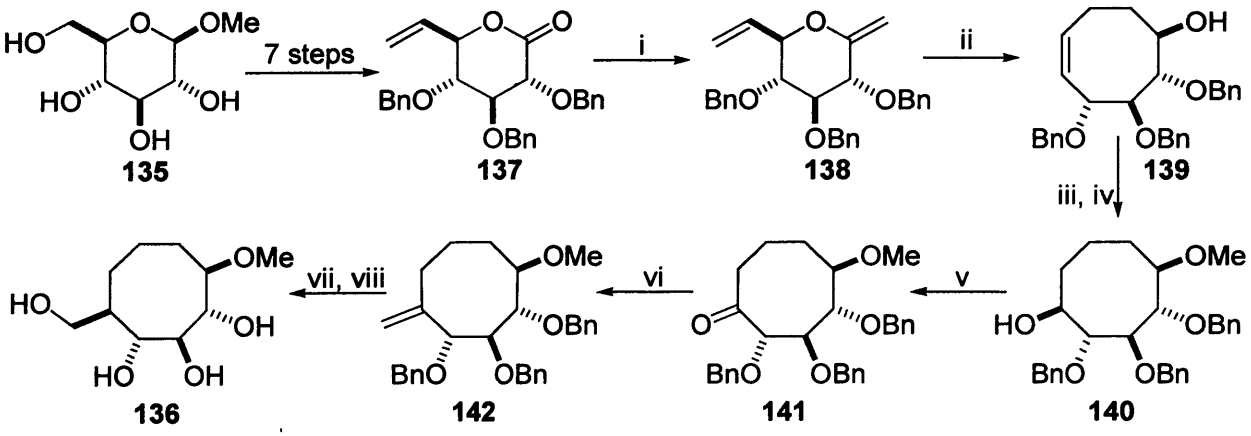
Synthetic oligosaccharides have recently emerged as potential therapeutic agents,[69,70] and useful approaches to the synthesis of nonhydrolysable oligosaccharide mimetics are becoming important.[69,73] One idea is to replace the endocyclic oxygen atom by a methylene group. Recently, several examples of carbasugars and derivatives have been reported in the literature as a new class of potential glycosidase inhibitors.[58,59] Sinaÿ *et al.* have confirmed that cyclooctane derivative **136** can adopt a conformation similar to that of a hexose **135** with respect to the orientations of the hydroxyl groups in space.[46] These cyclooctane polyols may be recognised like the native sugars by sugar processing enzymes or other carbohydrate receptors. However, because they lack the endocyclic oxygen, their linkages to other molecules are more stable ether linkages rather than acetals and will not be substrate for glycosidases (Figure 12).



135 136

Figure 12

Sinaÿ *et al.* have prepared the key intermediate **137** in seven steps starting from pyranoside **135**.[46] Reaction with Tebbe reagent afforded the corresponding enol ether, which was treated with tri(*iso*butyl)aluminium (TIBAL) to trigger a [3,3] Claisen rearrangement followed by stereoselective reduction of the ketone to afford cyclooctene **139**.[71] Protection of the newly formed hydroxyl group, hydroboration followed by oxidation and treatment with Tebbe reagent afforded methylene derivative **142**. Regioselective hydroboration and final deprotection afforded the desired cyclooctanic monosaccharide analogue **136** (Scheme 22).[46] Both reactions achieve hydroboration with the same regioselectivity in each case. C-B bond formation occurs to generate positive charge character at the centre where it is least distabilised.

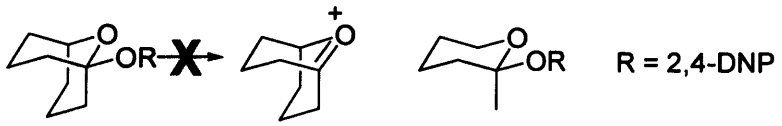


Reagents and conditions: i, Tebbe reagent, Py/THF (1:1), -78 °C to rt, 84%; ii, TIBAL, toluene, 50 °C, 30 min, 98%; iii, NaH, MeI, DMF, rt, 2 h; iv, BH_3.THF, THF, Ar, rt, 1 h then NaOH (11%), H_2O_2 (35%), 0 °C to rt, 1.5 h, 58% over 2 steps; v, PCC, 4 Å molecular sieves, dry DCM, Ar, 0 °C, 2 h, 92%; vi, Tebbe reagent, Py/THF (1:1), -78 °C to rt, 82%; vii, BH_3.THF, THF, Ar, rt, 1 h then NaOH (11%), H_2O_2 (35%), 0 °C to rt, 2 h; viii, H_2, 10% Pd/C, EtOAc/MeOH (1:1), rt, 2 h, 65% over 2 steps.

Scheme 22

6 Stereoelectronic effects at oxygen on acetal hydrolysis

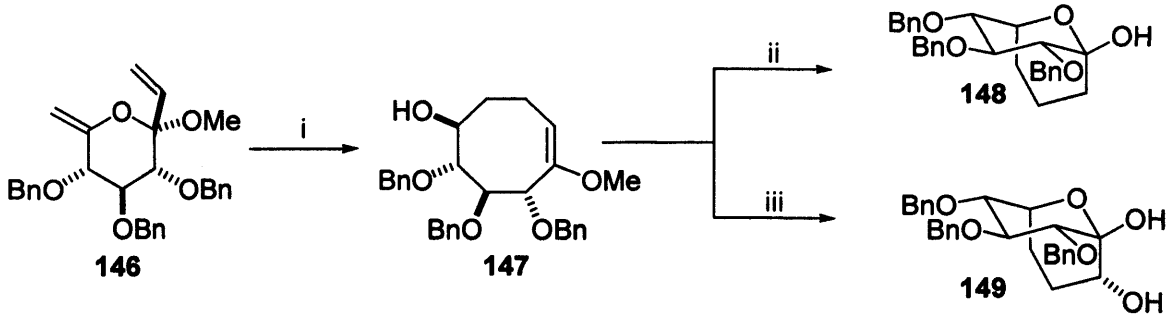
Kirby *et al.* have reported that the cleavage of an acetal C-O bond occurs smoothly when it can be antiperiplanar to one of the non bonding lone pairs on the remaining oxygen atom.[72] When the acetal C-O bond is locked equatorial, the reactivity towards hydrolysis decreases considerably. The rigid acetal derivative **143** gave low reactivity by minimum overlap and destabilisation of carbocation intermediate. The fixed conformation prevented conversion into the oxacarbenium ion **144** which has a bridge-head alkene. The regid bicyclic acetal **143** reacts 10^{13} times more slowly than monocyclic analogue **145**; the slow hydrolysis makes the glycosidic bond inert, so bicyclic sugar analogues of this type could be interesting target molecules (Figure 13).[72]



143 **144** **145**

Figure 13

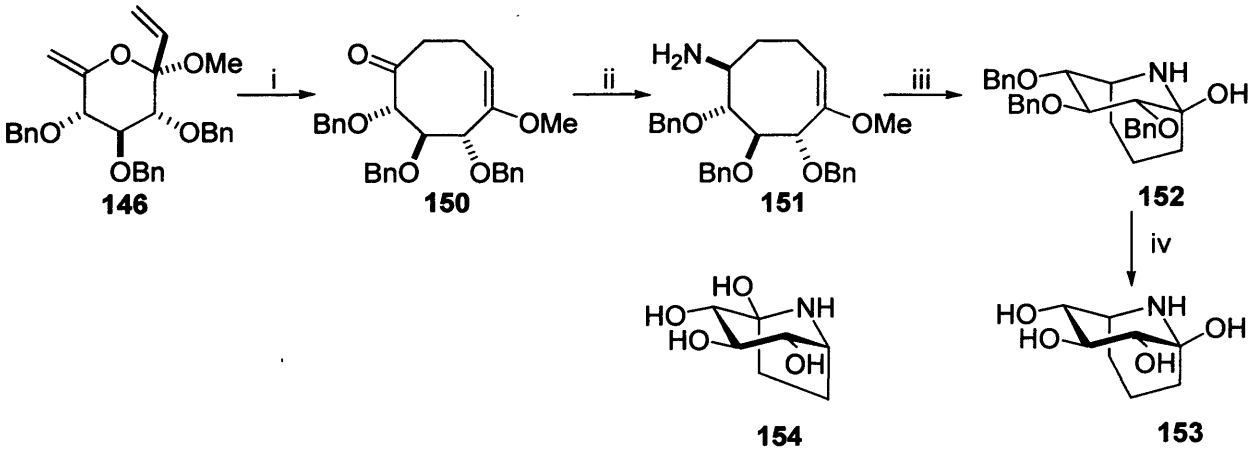
Van Boom *et al.* synthesised cyclooctane precursors to access conformationally locked bicyclic monosaccharide analogues.[73] Allyl vinyl ether **146** was subjected to the [3,3]-Claisen rearrangement-reduction sequence promoted by TIBAL to afford cyclooctene **147**. Treatment of **147** with *p*-toluenesulfonic acid in aqueous THF led to cyclisation to afford bicyclic system **148**. Alternatively, the double bond of cyclooctene **147** was epoxidised and the epoxide reacted intramolecularly with the free hydroxyl group to afford conformationally locked monosaccharide analogue **149** (Scheme 23).



Reagents and conditions: i, TIBAL (4 eq.), toluene, 20 °C, 83%; ii, *p*-TsOH, aq. THF, 20 °C, 86%; iii, *m*-CPBA, DCM, 20 °C, 51%.

Scheme 23

Van Boom *et al.* also converted **146** to the ketone **150** *via* a thermally induced [3,3]-sigmatropic Claisen rearrangement.[73] Reductive amination with ammonium formate afforded amine **151**, which cyclised by treatment with acid in aqueous THF to afford conformationally locked azasugar **152**. After deprotection, **153** is structurally related to calystegine B_2 **154** (Scheme 24).[73] The reductive amination is stereoselective; 8-membered rings have distinct topologies which may be responsible for the outcome observed. Preliminary experiments showed that azasugar **153** did not exhibit any glucosidase or galactosidase inhibition.

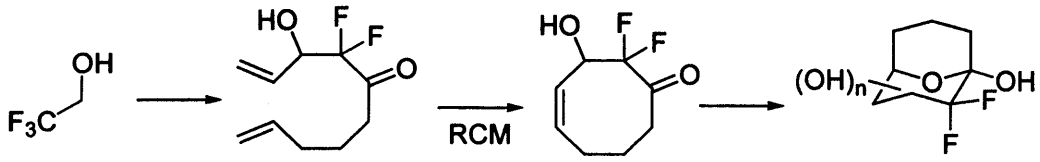


Reagents and conditions: i, heat; ii, $NH_4^+HCO_2^-$, $NaCNBH_3$, 3 Å molecular sieves, MeOH/DCM, 24 h, 39%; iii, *p*-TsOH, aq. THF, 20 °C, 2 h, 67%; iv, Pd/C, H_2, EtOH, 48h, 78%.

Scheme 24

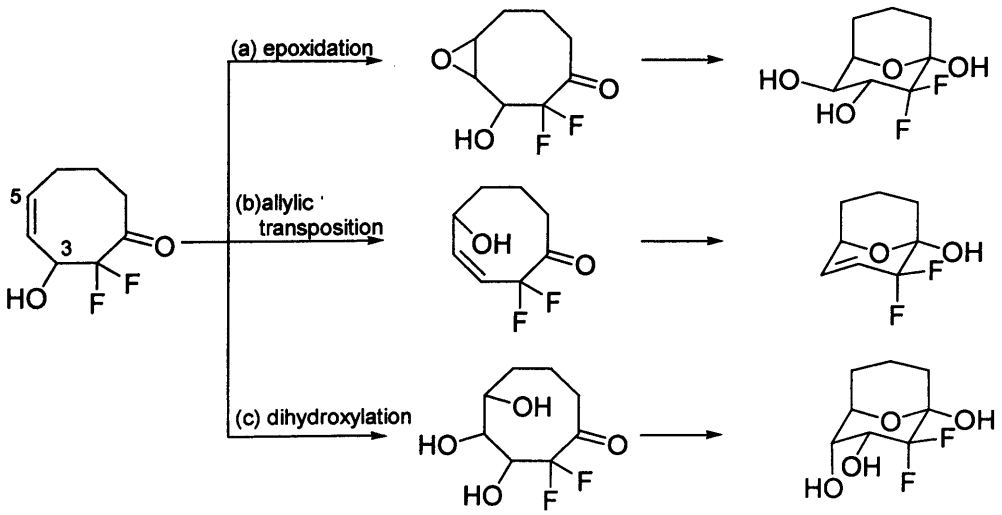
7. Objectives

The RCM reaction is becoming a popular and attractive method to access various ring size products. Grubbs' catalysts **86** and **87** are commonly used and these are easy to handle, commercially available and tolerant to a wide range of functional groups. The RCM reaction proposed in Scheme 25 will allow access to difluorinated sugar molecules from commercially available fluorinated building blocks (Scheme 25).



Scheme 25

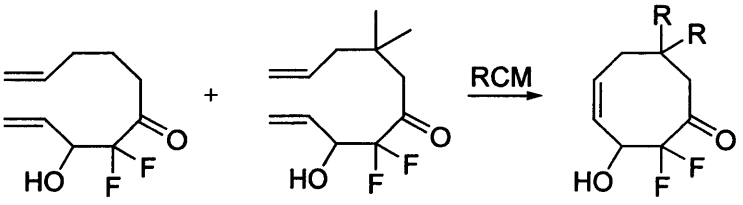
The objective of the project is to synthesise difluorinated bicyclic sugar analogues by using RCM and oxidation reactions controlled by the ring topology will allow a number of different stereochemical relationships between hydroxyl groups to be explored. RCM will be used as a key reaction for a range of difluorinated cyclooctenes which will be used in a number of reactions, including allylic transpositions, dihydroxylations and epoxidations. To rationalise the stereo-chemical outcomes of these transformations, development of understanding of topology will be attempted. The key reaction types are shown below (Scheme 26).



Scheme 26

Stereoselective epoxidation (a), followed by ring opening reaction under acidic or basic conditions could also trigger transannular attack and give stereochemically different bicyclic hemiacetals. An allylic transposition reaction (b) might switch the hydroxyl group position from C-3 to C-5 with transannular attack of a hydroxyl group at the C=O group, or dihydroxylation would also induce a possible transannular attack (c). These ideas are all based on the ease of transannular attack on the C=O triggered by the release of high ring strain, to form stereoelectronically stable bicyclic hemiacetals. A different order of events may give more possibilities.

The second objective is a study of the Thorpe-Ingold effect on the RCM reaction. It is known that the presence of a *gem*-dimethyl group can facilitate cyclisation reactions, though the size of the effect is not clear, especially for eight-membered rings (Scheme 27). Using difluorinated des-methyl and difluorinated *gem*-dimethyl compounds as a comparison may allow to estimate the effect.



R= H or Me

Scheme 27

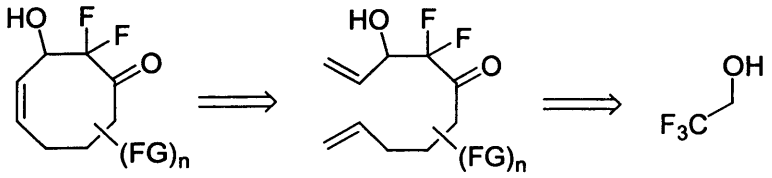
Chapter 2 : Results and discussion

1. Synthesis of difluorocyclooctenones and derivatives

1-1. Introduction

Medium ring compounds have attracted the interests of many chemists and are potential candidates for medicinal chemistry.[58,67] Cyclooctanes and related species are especially attractive; they may be potential inhibitors of glycosidases and can be used as key molecules to access conformationally constrained monosaccharide analogues.[46,58,59] They can mimic sugars but due to the absence of an endocyclic oxygen, they are much more stable towards hydrolysis.[69,73] The eight-membered ring gives access to a range of different conformations and may offer advantages in further reactions such as stereoselective oxidation reactions.[73-75]

By introducing a difluoromethylene moiety into these molecules, the chemical nature of hydroxyl groups would change and the molecules would be altered electronically. In this context, some highly functionalised difluorinated cyclooctenone analogues were synthesised by Percy and co-worker using RCM as a key reaction[48,78] and cheap and commercially available trifluoroethanol was used as a fluorinated building block (Scheme 28).[77]

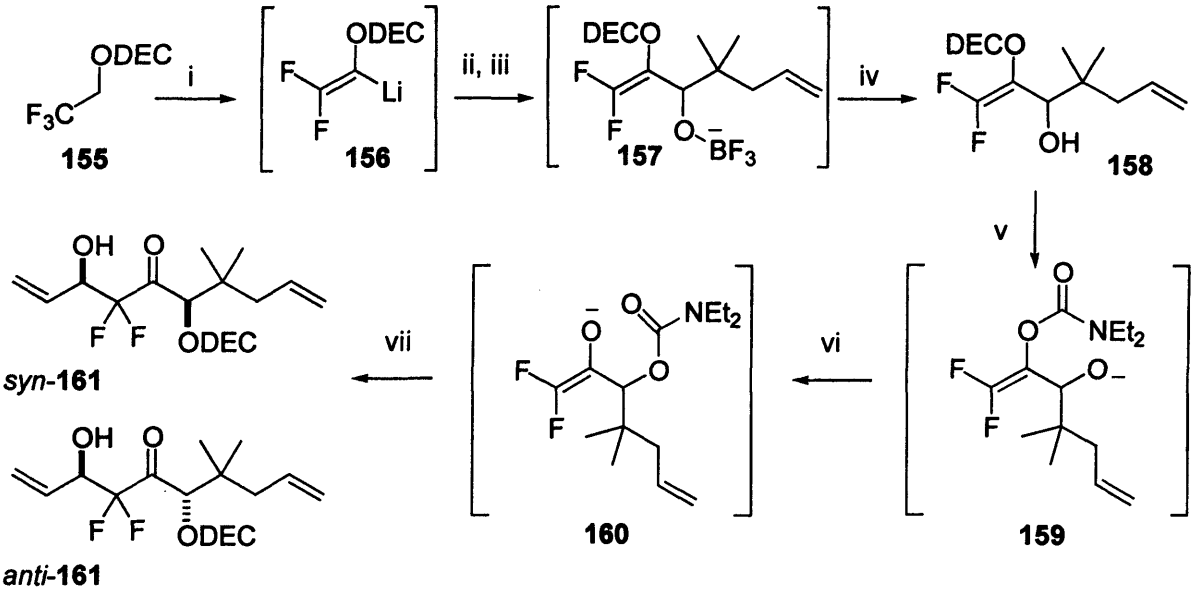


Scheme 28

1-2. Synthesis of difluorinated cyclooctenones *via* a short route

Thomas developed a short route towards difluorocyclooctenones from carbamate **155**.[48] Carbamate **155** was dehydrofluorinated and deprotonated to form lithiated intermediate **156** [78] which was trapped with 2,2-dimethylpent-4-enal to afford allylic

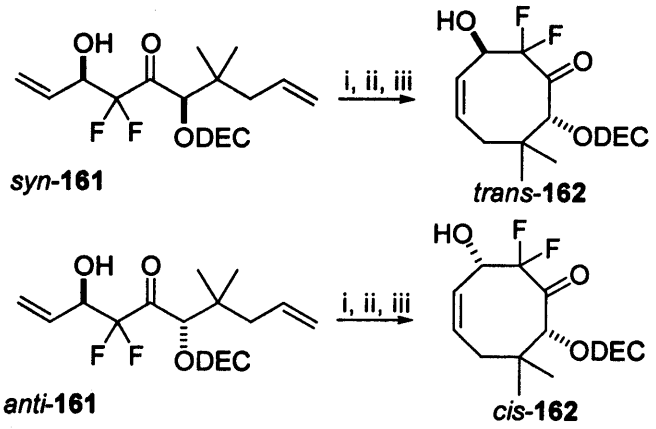
alcohol **158**.[48] In this reaction, one equivalent of boron trifluoride etherate has a very important role in preventing the migration of the *N,N*-diethylcarbamoyl (DEC) group.[78] After treating **158** with *n*-butyllithium and warming the reaction mixture, a transacylation took place from **159** to **160** due to the higher stability of enolate **168** than alkoxide **159**. The enolate **160** was trapped with acrolein to afford aldol products **161** as a 1:1 mixture of diastereoisomers (Scheme 29).[48, 76]



Reagents and conditions: i, LDA (2.0 eq.), THF/hexane. –78 °C, inverse addition; ii, 2,2-dimethylpent-4-enal (1.1 eq.); iii, $BF_3.Et_2O$ (2.0 eq.); iv, -78 °C to –30 °C then NH_4Cl, **158**, 64%; v, *n*-BuLi (1.0 eq.), THF/hexane, -78 °C to –10 °C; vii, acrolein (1.1 eq.), *syn*-**161** 33% and *anti*-**161**, 31%.

Scheme 29

These diastereoisomeric products *syn*-**161** and *anti*-**161** were separated by column chromatography. The *syn*- and *anti*-dienes **161** was allowed to react with 5 mol % Grubbs' catalyst **86** in the presence of titanium(IV) isopropoxide co-catalyst; the reaction took place smoothly but slowly (Scheme 30).[48,76] The possible role of the co-catalyst is discussed on page 39.[76]



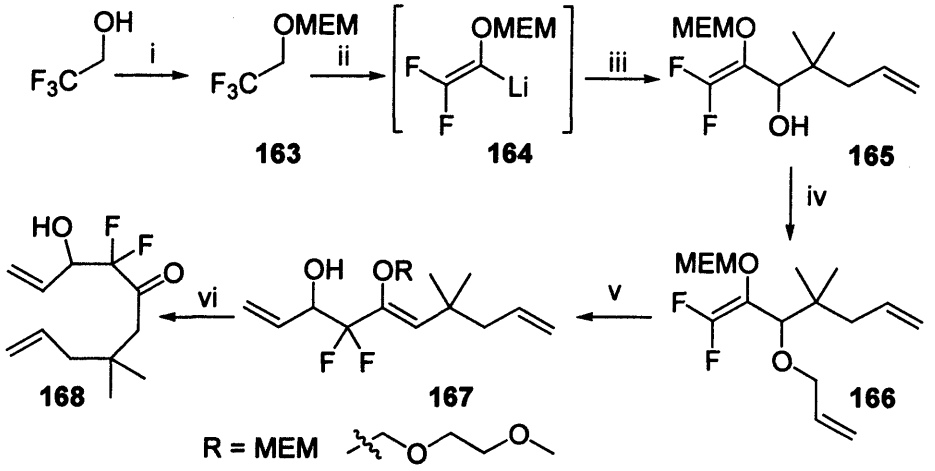
Reagents and conditions: i, 5 mol % Grubbs' cat. **86**, DCM, $Ti(^{i}OPr)_4$ (0.3 eq), reflux, 7 days; ii, short column; iii, recrystallisation, *trans*-**162,** 77% and *cis*-**162**, 69%.

Scheme 30

1-3. Synthesis of difluorinated cyclooctenone from trifluoro MEM-ether

The short synthesis from carbamate **155** was successful.[48] However, it gave products which included the unnecessary and bulky DEC group. For approaches towards more natural-looking carbohydrate analogues, the synthesis of difluorocyclooctenone **171** which started from the methoxyethoxymethyl (MEM-) ether of trifluoroethanol **163** was proposed by Percy *et al.*[77] Ether **163** was synthesised by the reaction between sodium trifluoroethoxide and 2-methoxyethoxymethyl chloride. Dehydrofluorination and subsequent deprotonation were carried out by the addition of two equivalents of LDA at low temperature to afford lithiated intermediate **164**, which was trapped with 2,2-dimethylpent-4-enal.[77] The difluorinated allylic alcohol **165** was purified by distillation and then was subjected to allylation to ether **166** under phase-transfer-catalysed conditions. Allyl ether **166** was subjected to a [2,3]-Wittig rearrangement reaction without purification; the [2,3]-Wittig rearrangement was triggered by the addition of two equivalents of LDA at –78 °C, followed by slow warming to finish the reaction.[79] The [2,3]-Wittig rearrangement step formally requires only one equivalent of LDA, however very low conversions arise unless two equivalent are used. The reason for this is not known.

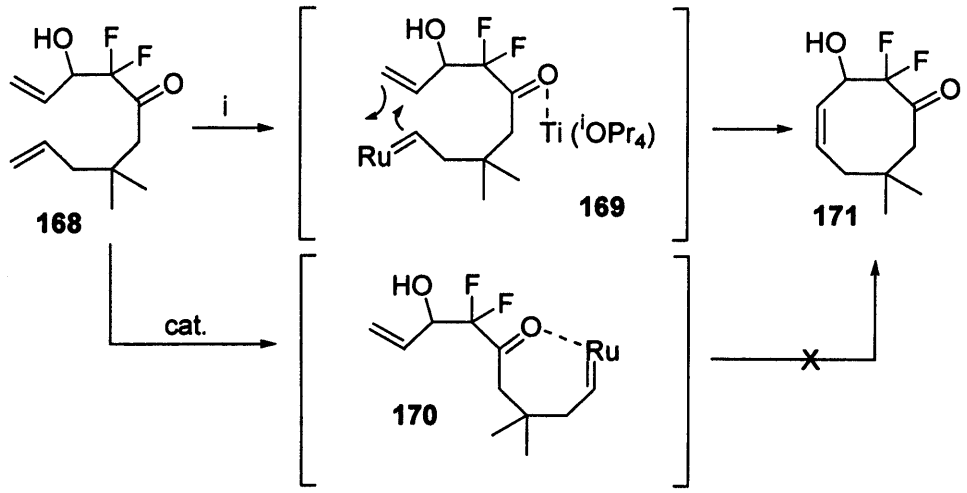
Unfortunately, the enol acetal **167** was unstable to column chromatography and also undistillable because of its large molecular weight. Therefore, the crude product **167** was subjected without purification to the cleavage of enol acetal functionality with hydrochloric acid, which was generated *in situ* from trimethylsilyl chloride and methanol (Scheme 31).



Reagents and conditions: i, NaH (1.0 eq.), MEMCl (1.1 eq.), THF, 0 °C to rt, 18 h, **163**, 76%; ii, LDA (2.0 eq.), inverse addition, THF/hexane, -78 °C; iii, 2,2-dimethylpent-4-enal (1.2 eq.), -78 °C to –30 °C, 2 h, **165**, 77%; iv, allyl bromide (1.2 eq.), 50 wt% aq. NaOH (7.0 eq.), cat. *n*-Bu_4NHSO_4, cat. TBAI, **166**, 92%; v, LDA (2.2 eq.), inverse addition, THF/hexane, -78 °C, 2 h, then –30 °C, 18 h; vi, TMSCl (1.0 eq.), MeOH, 0 °C then rt., 3 h, **168**, 50%.

Scheme 31

The ring closing metathesis on 1,9-diene **168** was carried out with 5 mol % Grubbs' catalyst **86** and 0.3 equivalents of titanium(IV) isopropoxide (Scheme 32). In the reaction, the titanium(IV) isopropoxide can coordinate to the carbonyl group forming **169** and prevent coordination between the carbonyl group and ruthenium as in **170**, which would slow the RCM.[76,80] Under the influence of the co-catalyst, the ruthenium carbene can easily react with diene **168**, and the rate of the RCM reaction is dramatically increased. With Grubbs' 2nd generation catalyst, the reaction requires a longer time to reach completion without the co-catalyst, though it is still successful.

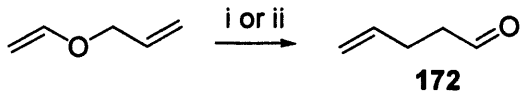


Reagents and conditions: i, 5 mol % Grubbs' cat. **86**, Ti(^{i}OPr)$_4$ (0.3 eq.), DCM, reflux, 24 h, **171**, 70%.

Scheme 32

1-4. Synthesis of difluorinated cyclooctenone from ether 163

Compared with the short synthesis *via* the carbamate route[48], the synthesis from MEM ether **163** is longer, but still efficient for the less substituted cyclooctenone analogues. However, the difluorocyclooctenone **171** still has two methyl groups at the C-7 position. These *gem*-dimethyl groups may facilitate the reaction by accelerating the ring closing metathesis step by a Thorpe-Ingold effect, but are not wanted in the final products. To study this effect and achieve the metathesis of less functionalised cyclooctenone analogues, pent-4-enal **172** was used in place of 2,2-dimethylpent-4-enal in the synthesis. The aldehyde **172** was easily prepared by thermal [3,3]-Claisen rearrangement of commercially available allyl vinyl ether. The allyl vinyl ether was placed in a sealed tube and heated at 150 °C with stirring.[81] The aldehyde **172** was used for the next synthetic step without distillation in order to avoid polymerisation during distillation (Scheme 33).

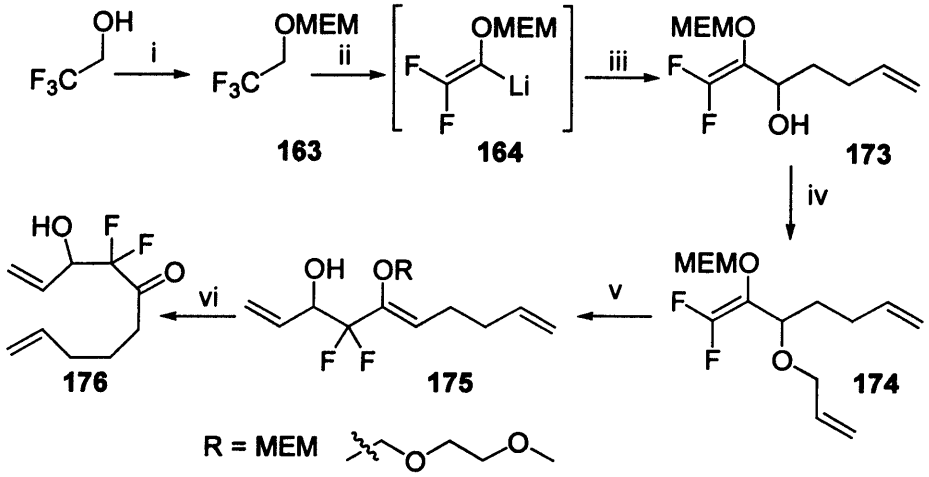


172

Reagents and conditions: i, Neat, sealed tube, 150 °C, 16 h; ii, Neat, sealed tube, microwave irradiation, 150 °C, 5 h, 78%.

Scheme 33

The synthesis of RCM precursor **176** with freshly-made aldehyde **172** followed the same steps described previously.

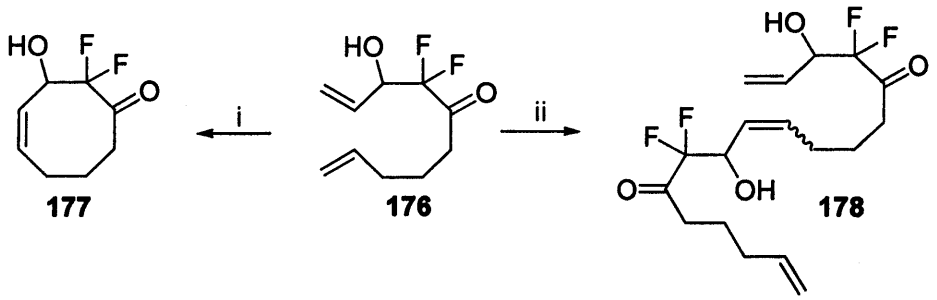


Reagents and conditions: i, NaH (1.0 eq.), MEMCl (1.1 eq.), THF, 0 °C to rt, 18 h, **163**, 76%; ii, LDA (2.0 eq.), inverse addition, THF/hexane, -78 °C; iii, pent-4-enal (1.2 eq.), -78 °C to -30 °C, 2 h, **173**, 78%; iv, allyl bromide (1.2 eq.), 50 wt% aq. NaOH (7.0 eq.), cat. *n*-Bu_4NHSO_4, cat. TBAI, **174** 96%; v, LDA (2.2 eq.), inverse addition, THF/hexane, -78 °C, 2 h, then -30 °C, 18 h; vi, TMSCl (1.0 eq.), MeOH, 0 °C then rt., 3 h, **176**, 55%.

Scheme 34

All of the reaction steps leading to RCM precursor occurred smoothly and in reasonable yields. However, the ring closing metathesis of diene **176** raised several problems. One of the problems was the extremely low concentration required for the RCM reaction. For *gem*-dimethyl diene **168**, the concentration of the reaction was 0.01 M which could allow a large scale reaction. On the other hand, the des-methyl diene **176** required a lower concentration of 0.001 M, ten times higher dilution which was much less practical. In fact, higher concentrations triggered intermolecular olefin metathesis and by-product dimer product **178** was observed by electrospray mass

spectrometry (Scheme 35). Unfortunately the dimer product **178** was not separable from the ring closing metathesis reaction mixtures. Hetero cross methathesis product was more likely formed (scheme 35). We were only able to identify the dimmer from the ES-MS; it was not isolated and characterised by ^{1}H NMR.

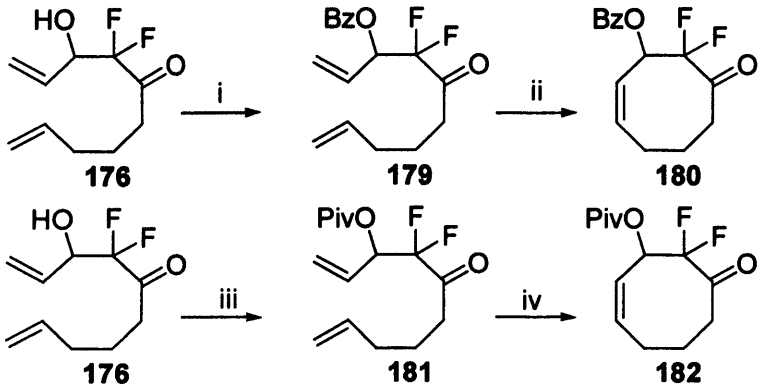


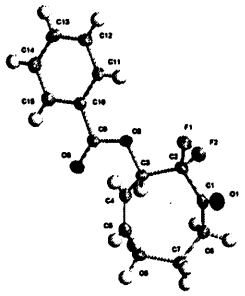
177 **176** **178**

Reagents and conditions: i, 5 mol % 2nd Generation Grubbs' cat. **87**, Ti(^{i}OPr)$_4$ (0.3 eq.), DCM [0.001 M], reflux, 2 h; ii, 5 mol % 2nd Generation Grubbs' cat. **87**, Ti(^{i}OPr)$_4$ (0.3 eq.), DCM [0.01 M], reflux, 2 h.

Scheme 35

Another problem was the volatility of the RCM product **177**. Usually, purification with column chromatography was needed to remove the ruthenium complex after the ring closing metathesis reaction. However, after removal of solvent such as ether, distilled light petroleum ether and even DCM, the RCM product **177** was lost. As a solution to these problems, the hydroxyl group of **176** was first protected (Scheme 36). Benzoate ester **179** was synthesised under mildly basic conditions. The ring closing metathesis of the benzoate **179** afforded solid cyclooctenone benzoate **180** in good yield without any problems; fortunately, a simple recrystallisation gave crystalline benzoate **180** suitable for x-ray analysis. Likewise, pivaloyl ester **181** was prepared. The structure of **180** in the crystals shows the ring occupying a boat-chair conformer with the benzoate in a pseudo-equatorial environment.





X-ray structure of **180**

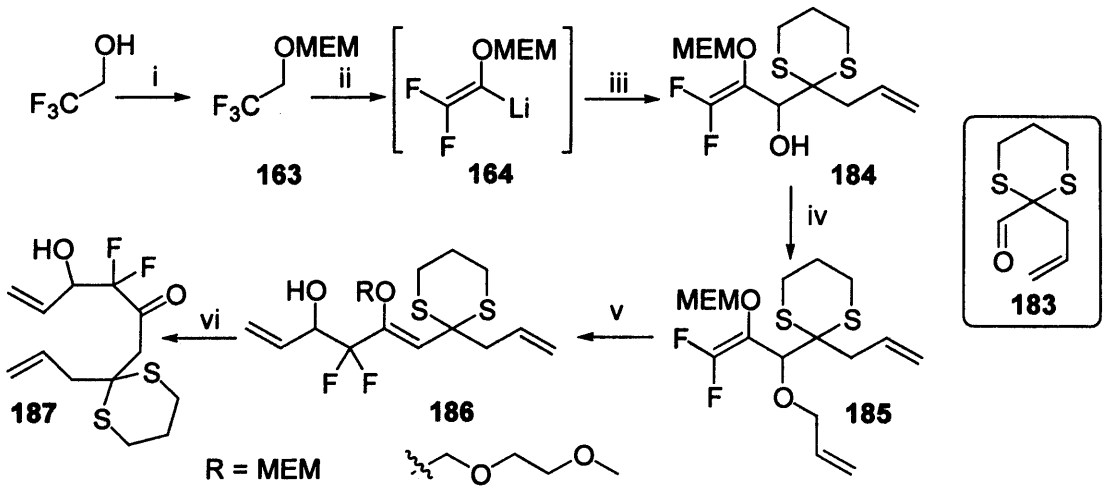
Reagents and conditions: i, benzoic anhydride (1.0 eq), DMAP (0.2 eq.), pyridine, rt, 4 h, **179**, 87%; ii, 5 mol % 2nd Generation Grubbs' cat. **87**, Ti(ⁱOPr)$_4$ (0.3 eq.), DCM [0.001 M], reflux, 2 h, **180**, 81%; iii, *n*-BuLi (1.0 eq.), THF, -78 °C, 30 min., then PivCl (1.1eq.), -78 °C, NH_4Cl, **181**, 87%; iv, 5 mol % 2nd generation Grubbs' cat. **87**, Ti(ⁱOPr)$_4$ (0.3 eq.), DCM [0.001 M], reflux, 2 h, **182**, 70%.

Scheme 36

1-5. Synthesis of difluorinated cyclooctenone with dithiane moiety

An alternative way to moderate the volatility of **176** was to introduce a dithianyl group, which could increase the molecular weight of the RCM product and also introduce further functionality. The dithianyl group could be removed easily by oxidation or reduction, thereafter.[68] It is also possible that a geminal substitution at the C-7 position may help the ring closing metathesis by a Thorpe–Ingold effect. The RCM of the gem-dimethyl substrates was noticeably faster than the less substituted species. The synthesis of **187** was successful, providing the desired RCM precursor in reasonable yield (Scheme 37).[76] The aldehyde **183** [82] trapped lithiated intermediate **164** to form difluoroallylic alcohol **184**. The allylation under phase-transfer-catalysed conditions afforded ether **185** in a reasonable yield. Then, the [2,3]-Wittig reaction was carried out by the action of 2.0 equivalents of LDA at – 78 °C and warming to – 30 °C. The isolated yield of **186** after purification by column chromatography was 30%. The low yield might arise from the decomposition during column chromatography. The clean Wittig product **186** was treated with trimethylsilyl chloride

in methanol which produced hydrochloric acid *in situ* to cleave the enol acetal to provide the corresponding ketone **187**, as in the previous synthesis, which was used for RCM reaction under a range of conditions.

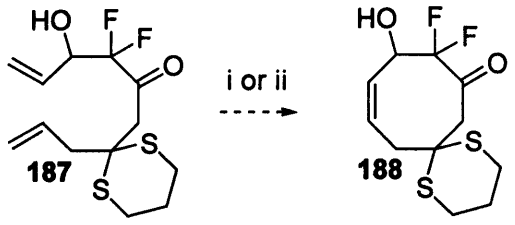


Reagents and conditions: i, NaH (1.0 eq.), MEMCl (1.1 eq.), THF, 0 °C to rt, 18 h, **187**, 76%; ii, LDA (2.0 eq.), inverse addition, THF/hexane, -78 °C; iii, aldehyde **183** (1.2 eq.), -78 °C to -30 °C, 2 h, **184**, 71%; iv, allyl bromide (1.2 eq.), 50 wt% aq. NaOH (7.0 eq.), cat. n-Bu_4NHSO_4, cat. TBAI, **185**, 70%; v, LDA (2.2 eq.), inverse addition, THF/hexane, -78 °C, 2 h, then -30 °C, 18 h, **186**, 30%; vi, $SOCl_2$ (1.0 eq.), MeOH, 0 °C then rt., 3 h, **187**, 76%.

Scheme 37

The ring closing metathesis reaction of diene **187** was examined under normal conditions (DCM under reflux conditions with 5 mol% catalyst **87** for 24 hours), however the ring closing metathesis was not achieved. Additional catalyst (5 mol%) was added to the reaction, but no cyclised product was observed by the TLC. Different solvents, with higher boiling points, such as toluene or benzene were examined. A higher loading (10 mol%) of catalyst **87** was used in toluene and the reaction was run at reflux for 2 days. To compensate for decomposition of the catalyst, 2nd generation Grubbs' catalyst **87** was added in two portions (5 mol% initially, then an additional 5 mol% was after 24 hours). Unfortunately even under the higher temperature conditions in refluxing toluene and with a larger amount of

catalyst **87**, no cyclised product was formed. The reaction was followed by TLC and most of the starting material was recovered unchanged (Scheme 38).



Reagents and conditions: i, 10 mol % 2nd Generation Grubbs' cat. **87**, Ti(OPr)$_4$ (0.3 eq.), DCM, reflux 24 h; ii, 10 mol % 2nd Generation Grubbs' cat. **87**, Ti(OPr)$_4$ (0.3 eq.), toluene, reflux 2 days.

Scheme 38

In conclusion, the synthesis of cyclooctenones **168**, **177**, **180** and **182** from MEM ether **163** was successful with the key RCM reaction proceeding with catalyst **86** and **87**. However, RCM reaction with thioketal diene **187** did not afford the expected cyclised product **188**. We cannot say if Thorpe-Ingold effect arises from the presence of this dithianyl group because the reaction didn't work. Taft's steric factors (Es value)[83] suggest that the thiomethyl group is bulkier than the methyl group so the dithianyl group should be at least comparable or more effective for RCM on the basis of the Thorpe-Ingold effect. However, this is not the case. There are no clear reasons for this failure; however some additional electronic factors may be operating. The possible coordination between divalent sulfur in **187** and ruthenium catalyst might affect and reduce the rate of the first metaloaddition step. There have been some reports where difficulties have been encountered during attempts to RCM with sulfides, disulfides and dithio ketals.[84,85] In each case, only 2nd generation Grubbs' catalyst **87** was effective under refluxing conditions at higher temperature, however, in these cases, the yields were very poor or not determined.

2. Conformational analysis of the cyclooctenone analogues

2-1. NMR studies

Cyclooctenone analogues **162** and **171** showed broad peaks in their ^{19}F NMR spectra at room temperature.[80] The broad peaks suggest that the molecules are fluxional on the NMR timescale and that there is interconversion between different conformers. To understand the conformational behaviour, several NMR experiments were carried out at various temperatures below ambient temperature. At low temperature (223 K), the ^{19}F NMR spectrum of **162** and **171** showed sharp signals and different conformers were apparent. For *trans*-**162**, two sets of signals (ratio 1:1.5) were obtained, suggesting that there were two conformers in roughly equal quantities. For *cis*-**162**, there were also two sets of signals with very different intensities (ratio1:13) suggesting that one of the conformers is more thermally stable than the other and dominates the equilibrium. For *gem*-dimethyl cyclooctenone **171**, two sets of signals (ratio 1.5:1) were obtained.[76,80]

On the basis of many accumulated crystal structures containing fluorine atoms, the diaxial $^3J_{H\text{-}F}$ coupling constants in cyclohexene diols are *ca.* 25-26 Hz in maximum.[42,86] The dihedral angles of 163° and 169° in the solid state are associated with $^3J_{H\text{-}F}$ values of 21.4 and 20.0 Hz in solution. A Much smaller $^3J_{H\text{-}F}$ value suggests that a C-H bond bisects the CF_2 angle, which means that the dihedral H-C-C-F angle is 45-70°. Observed large $^3J_{H\text{-}F}$ coupling constants of *trans*-**162** were 21.9 Hz and 25.8 Hz at 223 K, major conformer of *cis*-**162** was 21.5 Hz (Table 2).[76] For **171**, the observed large $^3J_{H\text{-}F}$ coupling constants were 20.4 Hz and 26.1 Hz, which could suggest that one of H-C-C-F dihedral angles is close to 180° in both conformers (Figure 14).

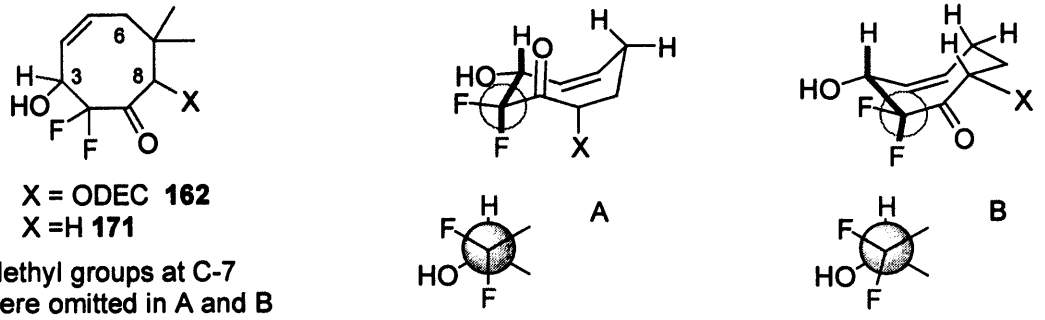


Figure 14

Compound	Major conformer $^3J_{H-F}$	Minor conformer $^3J_{H-F}$
trans-**162**	*21.9*	*25.8*
cis-**162**	*21.5*	-[a]
171	*20.4*	*26.1*

a The coupling constant could not be measured

Table 2

The similarities between the $^3J_{H-F}$ coupling constants for major and minor conformers of all three cyclooctenones suggest that very similar conformations are populated in each case. Unfortunately, the des-methyl system is too flexible to be obtained, even at the lowest temperature available with our spectrometer.

A 400 MHz gradient ROESY was run for *gem*-dimethyl cyclooctenone **171** at 223 K. The spectrum gave complicated signals due to the similar population of two conformers. However, strong cross peaks connecting H-3, one of the H-6 protons and one of the H-8 protons in the major conformer, and H-3 and one of the H-6 protons in the minor conformer were observed (Figure 15).

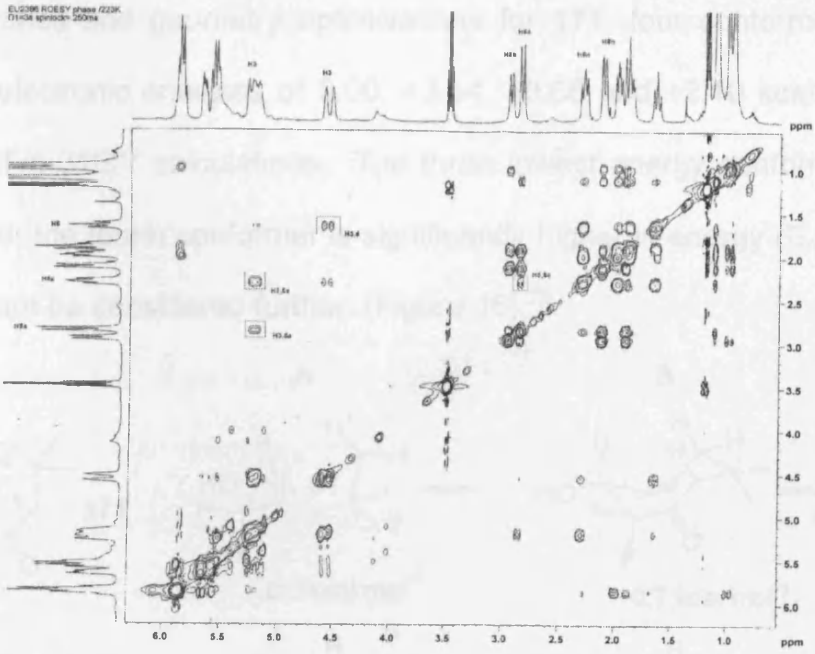


Figure 15

The results suggested that compound **171** have two stable conformers, which have three protons, H-3, H-6 and H-8, in close contact and a large dihedral angle between a fluorine atom and the methine proton. The 2D NMR experiment and coupling constant analysis suggested clear features of these molecules; however, molecular modeling was required to identify the most favourable conformations.

2-2. Conformational searching by electronic structure calculations

To identify the stable conformations for these molecules, conformational searching was carried out using the MacSpartan Pro 1.0.5 programs [87] (MMFF94 force field [88]). At the first stage of conformational searching, all possible conformers were retained, then geometry optimisations were performed for the resulting conformers at the AM1 level, then *ab initio* method (RHF, restricted Hartree Fock) was followed with 6-31G* or 6-31G** basis sets in Spartan. The basis set chosen (6-31G*) was a minimal basis set, selected to achieve an acceptable level of accuracy in Hartree-Fock calculations. The calculations were carried out by Percy.[76] Conformers within 2.5 kcal mol^{-1} of the lowest energy species were selected for further investigation. From

the searches and geometry optimisations for **171**, four conformers were found at relative electronic energies of 0.00, +3.64, +0.66 and +2.10 kcal mol^{-1} respectively from RHF/6-31G** calculations. The three lowest energy conformers are shown in Figure 16; the fourth conformer is significantly higher in energy (E_{rel} +3.64 kcal mol^{-1}) and will not be considered further. (Figure 16).[76]

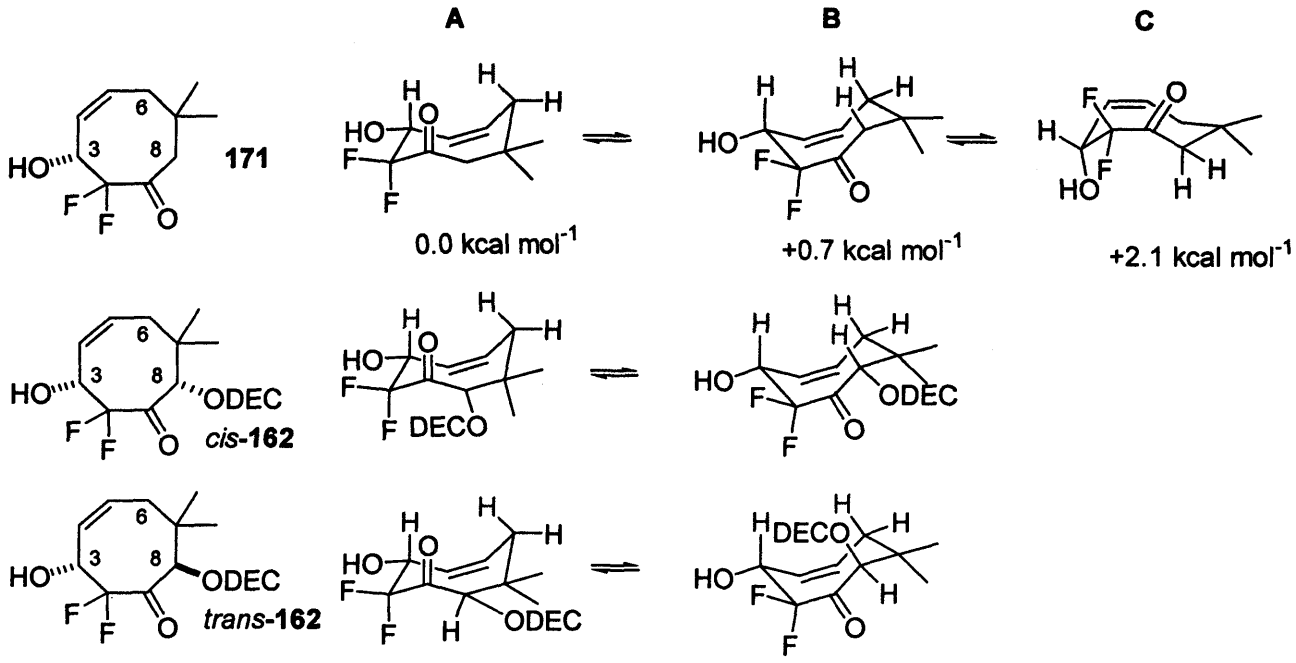
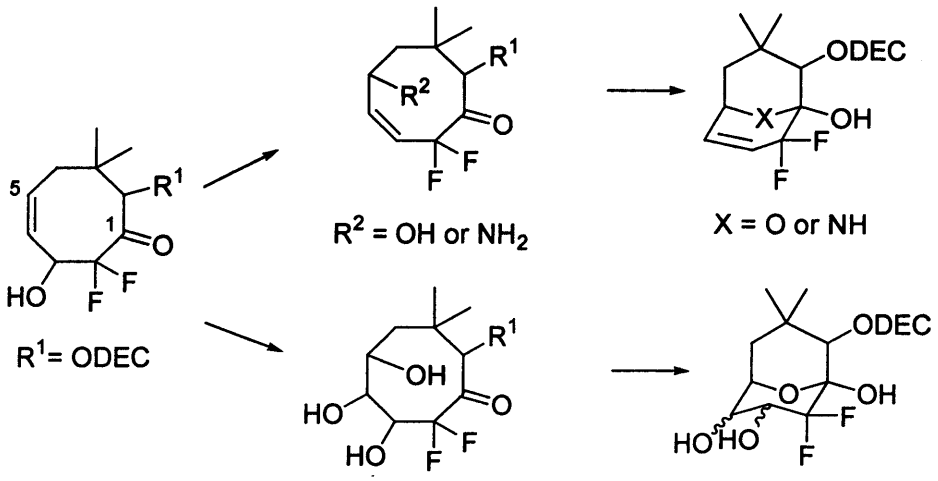


Figure 16

Calculated conformations were sifted by the value of the $^3J_{H\text{-}F}$ coupling constants. The observed values for the $^3J_{H\text{-}F}$ coupling constants argued against the presence of conformer **C** in solution, because the H-3 methine proton is bisecting the CF_2 angle in both conformers and would be expected to produce low $^3J_{H\text{-}F}$ values. However, the conformers **A** and **B** are supported by the measured $^3J_{H\text{-}F}$ coupling constants. The H-3 and one of protons of H-8 and H-6 have close contact for conformer **B** and the H-3 and one of the proton of H-6 are also in close contact for conformer **A**. Similar behaviour for *trans*-and *cis*-**162** was observed in the conformational analysis by NMR, molecular modelling and crystal structures (Figure 16). *Trans*- and *cis*-**162** were made by Pintat and NMR works were carried out by Griffiths.[76] The results were used to try to interpret the outcomes of subsequent oxidation reactions.

3. The synthesis of bicyclic molecules *via* transannular collapse of cyclooctenone analogues

Medium ring compounds have a higher ring strain compared with 6-membered rings and macrocyclic compounds. For example, cyclohexane has the lowest strain energy, *ca.* 0.13 kcal/mol, whereas the strain energy in cyclooctane is much higher at *ca.* 9.68 kcal/mol. Releasing high strain energy provides a strong driving force to trigger transannular reactions across the molecule for example by a hydroxyl or amino group attacking an appropriately positioned carbonyl group (Scheme 39).

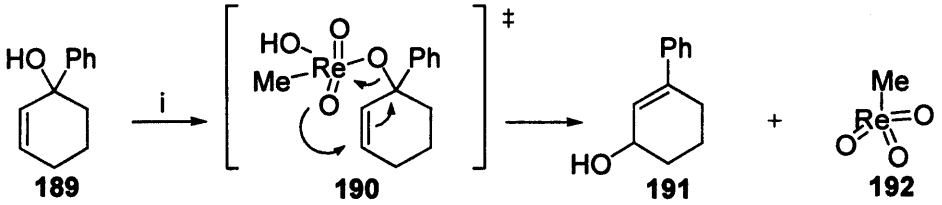


Scheme 39

3-1. Attempted allylic transposition on cyclooctenone analogues

Allylic transposition of allylic alcohols is catalysed or mediated by methyltrioxorhenium (MTO);[89] the reaction can generate the more stable regioisomer of two possibilities. The suggested mechanism is shown in Scheme 40. MTO **192** reacts with the hydroxyl group of allylic alcohol **189** and forms rhenate ester **190**, which can undergo to re-introduce the hydroxyl group at a new position. In the final step, the catalyst is released and a new allylic alcohol **191** is produced. With acyclic substrates, mixtures of alkene diastereoisomers can be formed. With cyclic

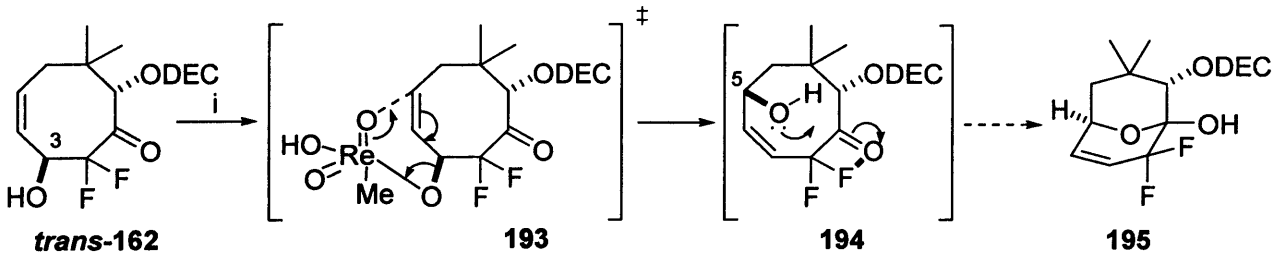
substrates, the reaction is believed to proceed suprafacially, but this has not been proved.



Reagents and conditions: i, 5 % MTO catalyst, benzene, rt, 10h, 98%.

Scheme 40

This idea can be applied to the difluorinated cyclooctenone systems. The cyclooctenone *trans*-**162** has a hydroxyl group at C-3, which would be relocated to C-5 *via* allylic transposition. The movement of the hydroxyl group to the C-5 position may allow subsequent transannular reaction to form bicyclic product **195** (Scheme 41) resulting in release of strain. However, there was no sign of the reaction and only starting material was recovered. There was no obvious source of steric hindrance or additional barriers, which might suppress the coordination to the allylic hydroxyl group in the first step. Therefore, the failure must arise from the rearrangement step.



Reagents and conditions: i, 5 % MTO, benzene, 3 days, rt.

Scheme 41

Forming the 6-membered ring transition state **193** is a key step in this rearrangement process. Once transposition of the hydroxyl group had occurred, the newly formed hydroxyl group at C-5 could trigger transannular reaction to form a more stable and less steric strained bicyclic molecule **195**. However, the rearrangement reaction did

not occur. The inspection of a model of the calculate most favoured conformer of **162** suggested that the allylic alcohol the C-O bond was parallel to the alken δ-plane, orthogonal to the π-plane, which would make rearrangement very difficult. Only two possible low energy conformations (0 and 0.8 kcal mol $^{-1}$) for cyclooctenone **162** were found from molecular modeling based on electronic structure calculations and which satisfied the data from the NOESY spectrum at 243 K. Each of the conformers had the same relationship between the hydroxyl group at C-3 position and double bond, which was not favour a smooth rearrangement. This relationship kept the catalyst far away and prevented rearrangement in the reaction (Figure 17). The same relationship would also explain the failure of the rearrangement step of the attempted Overman transposition (Scheme 42).

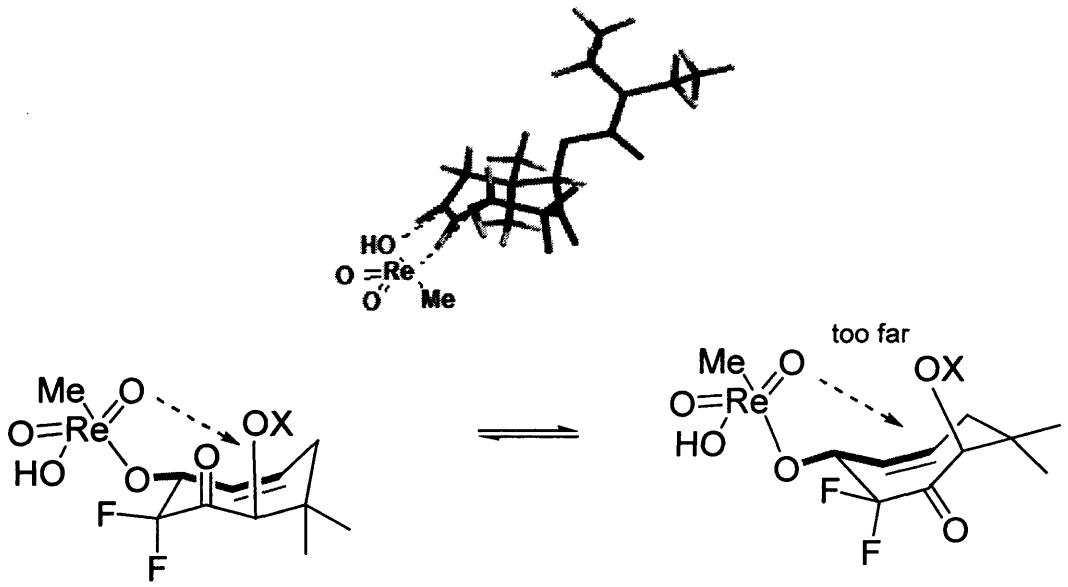
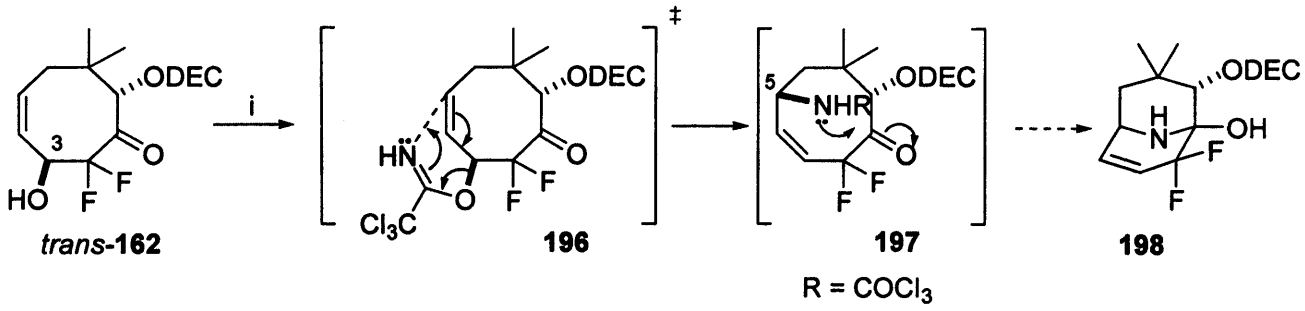


Figure 17

Overman rearrangement [90] was also attempted but without success (Scheme 42). The idea was based on introducing the hydroxyl group of imidate group at C-3 position, which would rearrange to form a new carbon-nitrogen bond at C-5, driven by the formation of a carbonyl group. The transannular reaction could then lead to bicyclic aza-sugar analogue **198**. *Trans*-cyclooctenone **162** was allowed to react with

trichloroacetonitrile under mildly basic conditions, to form an imidate; the formation of imidate **196** was proved by ES-MS. However, the imidate was too unstable to be purified. In the rearrangement step, the crude imidate **196** decomposed so that no identifiable materials were recovered.



Reagents and conditions: i, DBU, Cl_3CCN (6.0 eq.), DCM, rt, 6 h.

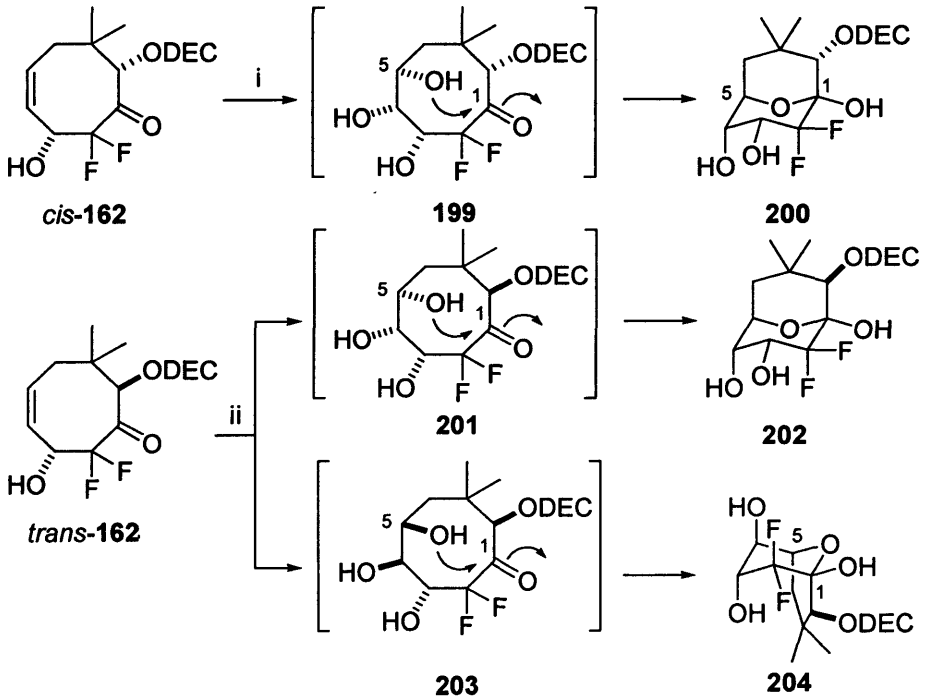
Scheme 42

This reaction also depends on the formation of a 6-membered cyclic transition state from **196**. The unfavourable conformation of the eight-membered cyclooctenone possibly meant that the ring conformation required for Overman rearrangement could not be reached. While the ring can interconvert between conformers, there is no guarantee that the arrangement required for the MTO and Overman transposition is accessible. So proof of this idea would require further computational work.

Two methods of allylic transposition were unsuccessful, possibly due to the unfavourable conformation of *trans*-cyclooctenone **162**. And geometrical problems of hydroxyl group may exist on the molecule after rearrangement process. If successful, the transpositions would have introduced either a hydroxyl or an amido function across the ring from the ketone carbonyl and transannular ring closure would have been expected to proceed. However, as transpositions failed, alternative methods of alkene functionalisation were explored.

3-2. Access to bicyclic molecules *via* dihydroxylation

Cis- and *trans*- cyclooctenones **162** were dihydroxylated under Upjohn conditions [91] (Scheme 43) in an attempt to synthesise polyhydroxylated difluorinated cyclooctanes which may mimic monosaccharides. From previous work,[74] the triol intermediates **199** and **201** triggered a transannular reaction to form the corresponding bicyclic hemiacetals **200, 202** and **204**. The triol intermediates **199,201** and **203** could not be seen during the reaction because one of the newly-made hydroxyl groups reacted rapidly with the ketonic carbonyl group.[74,80] The formation of the conformationally locked 6-membered ring molecules would be driven both by addition of a hydroxyl group to the electrophilic carbonyl group and by the favourable release of eight-membered ring strain. In contrast to the fluxionality in the NMR of cyclooctenone, these bicyclic hemiacetals are not fluxional on the NMR timescale and give sharp signals in their NMR spectra at room temperature.[74,75,80]



Reagents and conditions: i, NMO (2.0 eq.), 2.0 mol % OsO_4, acetone/H_2O/^{t}BuOH, 0 °C, 24 h, **200**, 81%; ii, NMO (2.0 eq.), 2.0 mol % OsO_4, acetone/H_2O/^{t}BuOH, 0 °C, 48 h, **204**, 16%, **202**, 72%.

Scheme 43

The dihydroxylation reaction of *cis*-**162** proceeded stereoselectively to give triol **199** which had all *cis* hydroxyl groups at C-3, C-4 and C-5 positions, affording only one bicyclic analogue **200**. In contrast, *trans*-cyclooctenone **162** gave two products (ratio 4.5:1.0). These stereoselectivities were unexpected so that the results lead to an interesting idea about coordination chemistry. The production of single stereoisomer **200** (as a racemate) might arise from the approach of osmium tetroxide from the concave face instead of the more open face of the molecule. The result suggests that osmium tetroxide could be delivered by coordination to the ketonic carbonyl oxygen.[74]

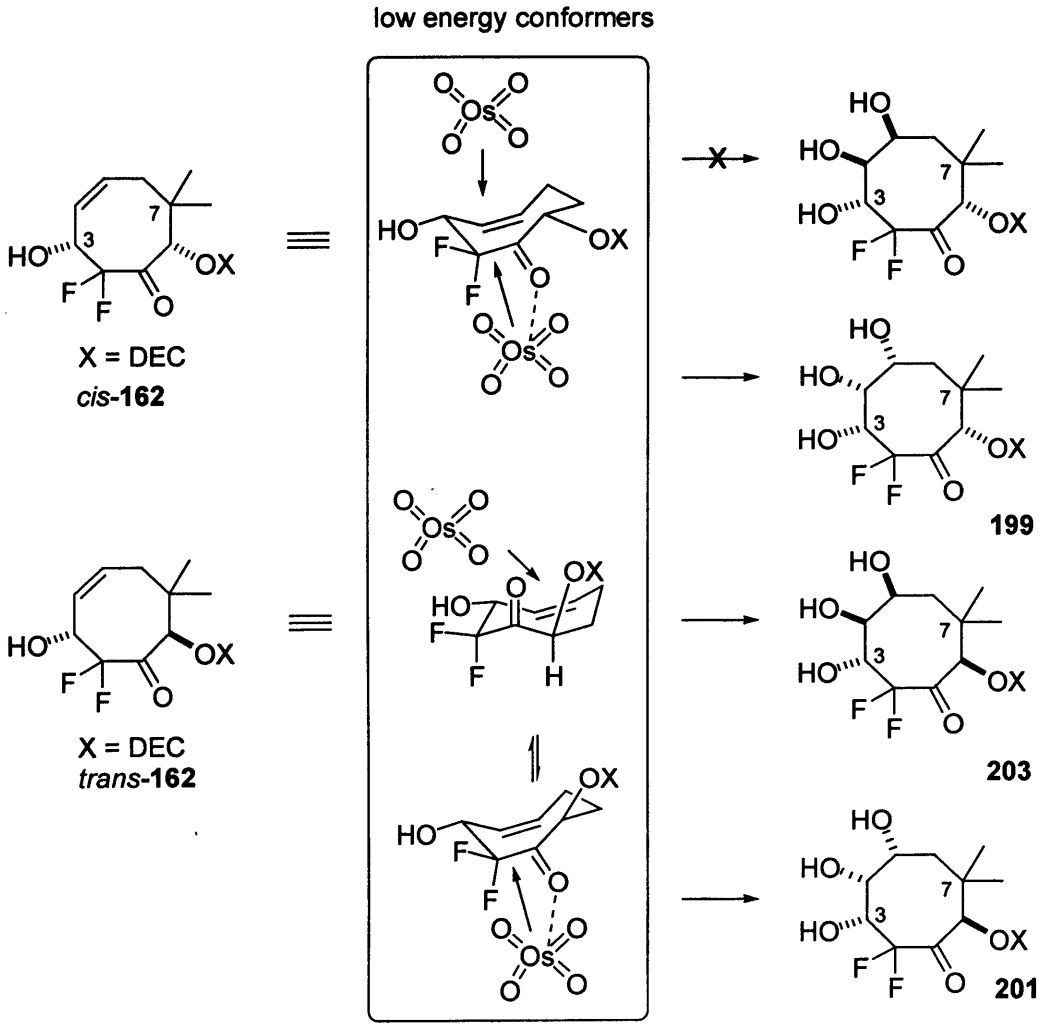
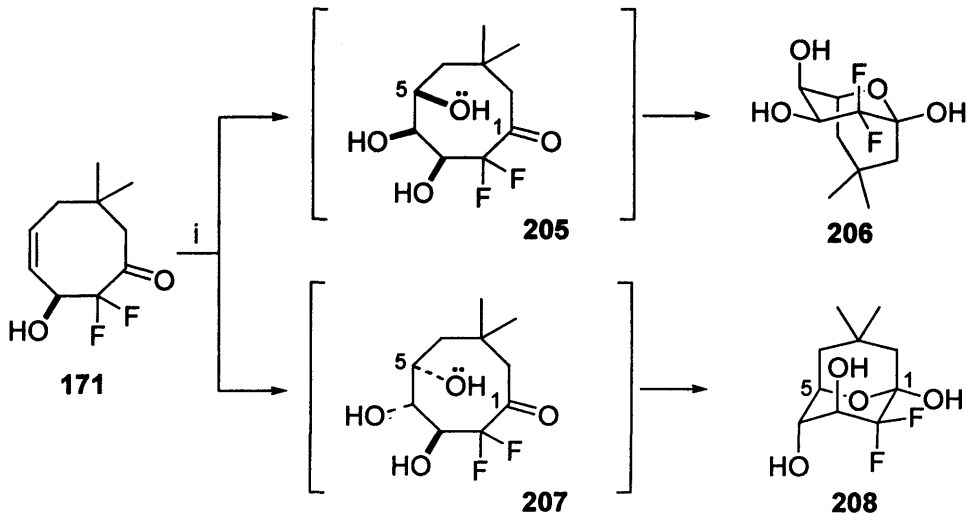


Figure 18

Figure 18 attempts to explain the coordination of the osmium catalyst to the carbonyl oxygen. The conformation of the cyclooctenones may affect the stereoselectivity of the dihydroxylation process. Whereas *cis*-**162** populates mostly one conformer (1:13 ratio), the *trans*-**162** has two different conformers in 1:1.5 ratio at low temperature.[76] To test this idea, *gem*-dimethyl cyclooctenone **171** was used for dihydroxylation under the same conditions. According to the conformational analysis[75,76], the *gem*-dimethyl cyclooctenone **171** has two different conformers and their ratio is 1:1. Therefore, if the idea is correct, the mixture of bicyclic product would be expected. The reaction of **171** produced a 1:1 mixture of two different hemiacetals **206** and **208** in good yield.



Reagents and conditions: i, NMO (2.0 eq.), 2.0 mol % OsO_4, acetone/H_2O/^{t}BuOH, 0 °C, 24 h, **206** and **208**, 81%

Scheme 44

The two favoured conformers of **171** are shown in Figure 19. The ketonic carbonyl group in one conformer orients down towards concave face which may deliver the osmium tetroxide from the more crowded face. In the other conformer, the carbonyl group points outwards on the open face and cannot deliver the reagent, so osmium tetroxide approaches from the more open face (Figure 19). The result of

dihydroxylation with *gem*-dimethyl cyclooctenone **171** leads to the same conclusion which supports the osmium delivery mechanism by ketonic carbonyl group.

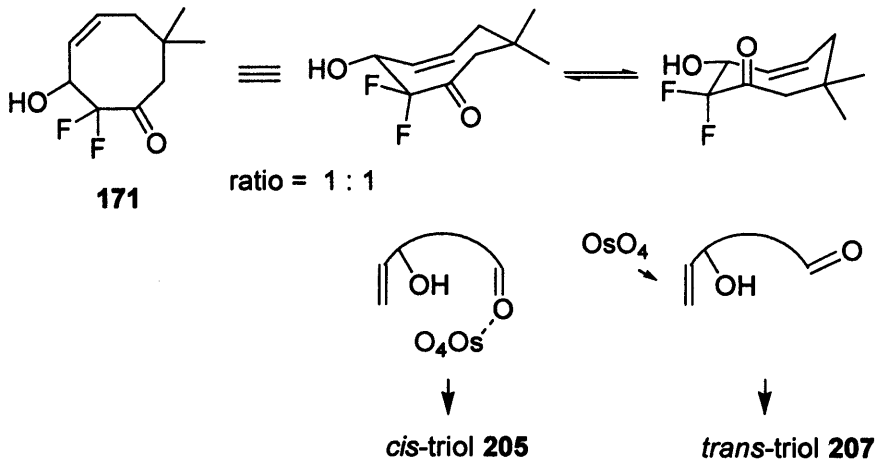
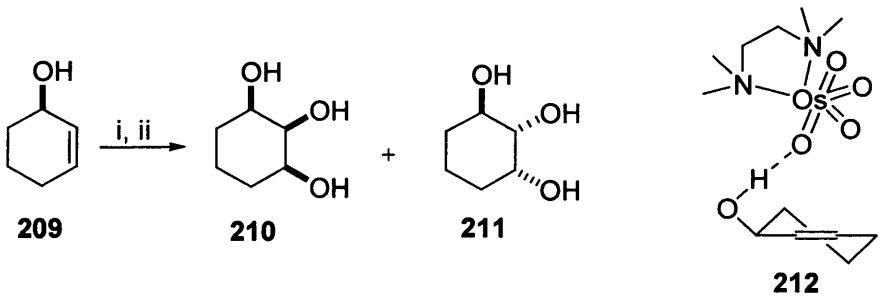


Figure 19

Though methods for directed dihydroxylation are rare, Donohoe has described a procedure which uses OsO_4 modified with TMEDA. The complex forms a hydrogen bond to the proton of the allylic hydroxyl group **212**, delivering the reagent onto the same face. There are a number of stereoselective transformations in the literature, Scheme 45 shows an example.[92] We did not attempt to use this method because it required stoichiometric amounts of OsO_4.[92,93]



Reagents and conditions: i, OsO_4 (1 eq.), TMEDA (1 eq.), CH_2Cl_2, -78°C; ii, Na_2SO_3, aq THF, 98% (**210/211** = 90/10).

Scheme 45

Kishi developed a model which could be used to predict the identity of the major product of dihydroxylation reactions of acyclic allylic alcohols.[45,94,95] However, with cyclic allylic alcohols, the normal selectivity involves attack from anti to the C-O bond, unless there are steric barriers, in which case mixture of products are obtained.[45]

Figure 20 shows the Kishi model for dihydroxylation of allylic alcohols,[95] which minimises 1,3-allylic strain. The osmium reagent then attacks from anti to the C-O bond.

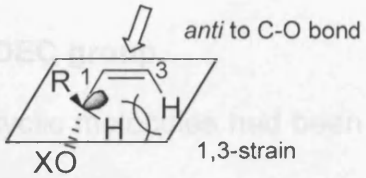


Figure 20

In the more populated conformer of *cis*-**162**, the C-O bond is close to aligned with the alkene δ-plane (close to orthogonal to the π-plane). It seems unlikely that a strong stereoelectronic effect would arise under these circumstances. If the reaction was sterically controlled, attack of the osmium reagent would occur on the more open face of the cyclooctenol, delivering the *cis*, *trans* triol. We observed the exclusive formation of the all-*cis* triol from *cis*-**162** in good yield. The all-*cis* triol is formed by the attack on the less accessible face of the alkene; this trajectory is anti to the C-O bond but is sterically impeded by the carbonyl oxygen and one proton and one fluorine atom (Figure 21).

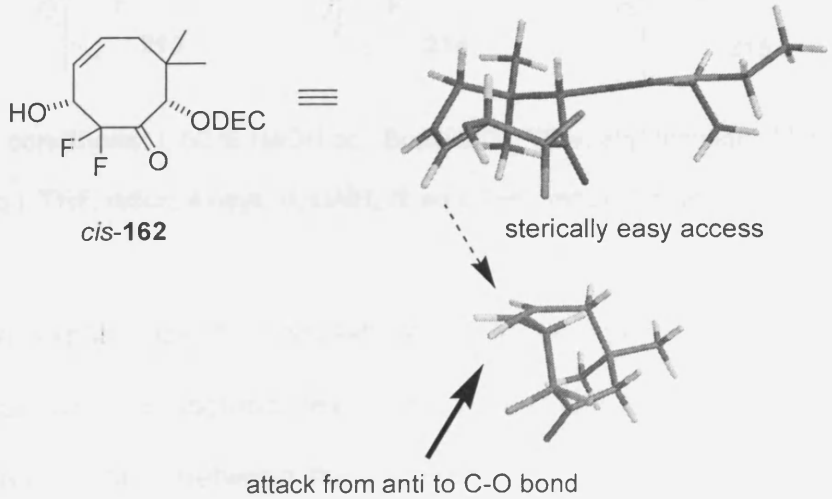


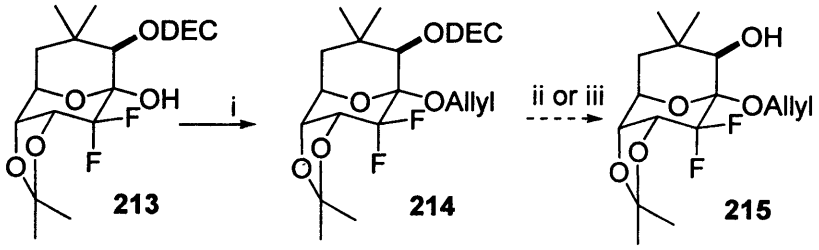
Figure 21

Direction by the carbonyl group has been invoked before by Willis and co-workers [96] and by Leonard and Hussain.[97] The basis of the effect is not clear and computational work will be required to understand it fully.

3-3. Attempted removal of DEC group

Since hydrolytically stable bicyclic molecules had been synthesised successfully, the reduction of the DEC group was attempted to make more sugar-like molecules.

To prevent ring opening and possible retroaldol produces **213** [80] was converted to allyl ether **214** under phase-transfer conditions in good yield.[74] Removal of the DEC group under treatment with DIBAL-H or $LiAlH_4$ was then attempted. The bicyclic allyl ether **214** was treated with 4 equivalents of di*iso*butylaluminium hydride (DIBAL-H) in THF at reflux over 4 days. Unfortunately, the DEC group was not removed. Then, **214** was exposed to 6 equivalents of lithium aluminium hydride ($LiAlH_4$) under reflux conditions for 7 days. However, no sign of deprotection was observed (Scheme 46).



Reagents and conditions: I, 50 % NaOH aq., Bu_4NHSO_4, TBAI, allyl bromide, 72 h, rt, **214**, 100%, ii, DIBAL-H (4.0eq.), THF, reflux, 4 days; iii, $LiAlH_4$ (6 eq.), THF, reflux, 7 days.

Scheme 46

The possible explanation for this failure could be steric hindrance by the *gem*-dimethyl group which is located next to the carbamate functionality. To get a clear view of the relationship between the *gem*-dimethyl group and the carbamate, CPK models of bicyclic product are shown in Figure 22. The left model is a model of the bicyclic product **214** with the dimethyl group and right is a model without the dimethyl group. The view from the carbamoyloxy group side showed severe steric hindrance

of approach to the carbonyl group. The bulky *gem*-dimethyl group could prevent reducing reagents like DIBAL-H or $LiAlH_4$ from attacking the carbonyl carbon of the carbamate. Recovery of the starting material **214** was the result, after even long periods at reflux.

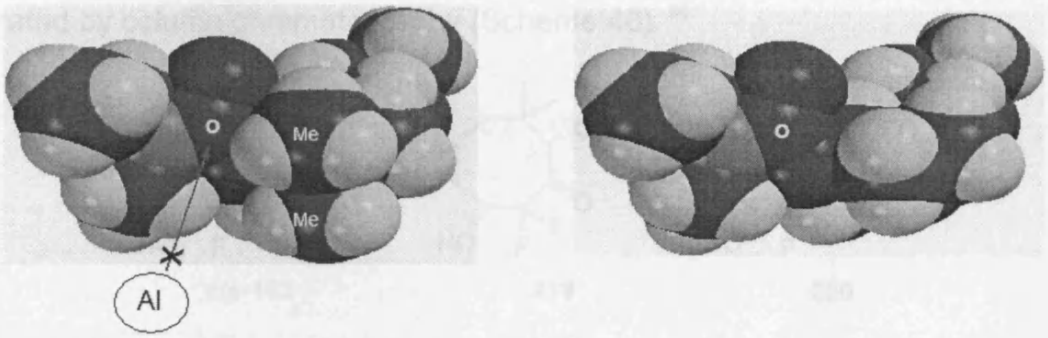
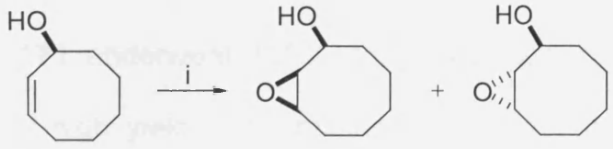


Figure 22

4. The synthesis of difluorinated epoxy alcohols *via* stereocontrolled epoxidation

The epoxidation of the double bond of cyclooctenone analogues would offer an interesting strategy to approach bicyclic molecules. The key is how to control the stereoselectivity of the reaction. Usually hydrogen bonding between the terminal peroxide oxygen and the proton of the hydroxyl group is expected leading to the formation of *cis*-products (Henbest oxidation).[98] However, there are reports of the apparently anomalous epoxidation of medium ring allylic alcohols with *m*-chloroperbenzoic acid (mCPBA).[98] For example, the epoxidation of cyclooct-2-en-1-ol **216** led to *trans* epoxy alcohol **218** instead of *cis* epoxy alcohol **217** (Scheme 47).

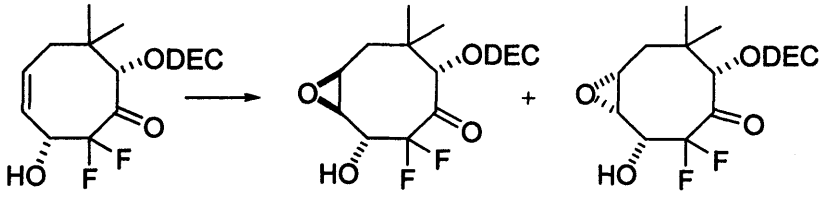


216 **217** **218**

Reagents and conditions: i, *m*CPBA, DCM, 0 °C, 24 h, 81% (ratio *trans*:*cis* = 100:1)

Scheme 47

This example is rationalised on the basis of the unusual topology of the cyclooctene ring which results in the ability of the lower face hydroxyl group to deliver peracid to the upper face of the alkene through the familiar hydrogen bonded mechanism.[102] Pintat tried epoxidation of *cis*-**162** with *m*CPBA at reflux in DCM over 16 hours. A 1:1 mixture of diastereoisomers **219** and **220** was obtained, which could be easily separated by column chromatography (Scheme 48). [80]



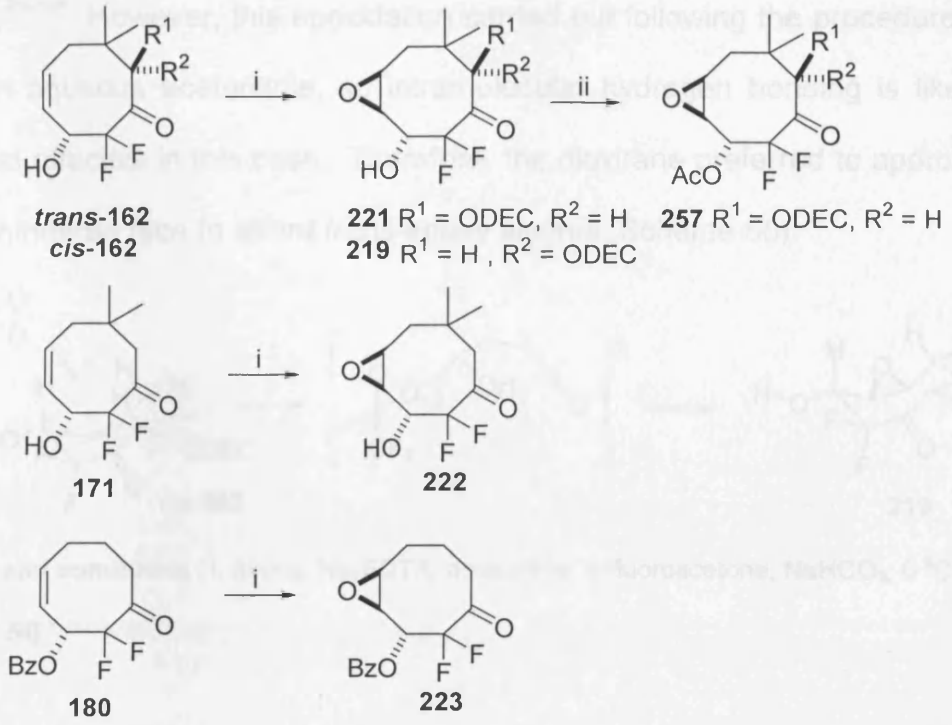
***cis*-162** **219** **220**

Reagents and conditions: i, *m*CPBA (2.0 eq.), DCM, reflux, 16 h, **219**, 41% and **220** 36%.

Scheme 48

The conformation of cyclooctenone *cis*-**162** may explain the much more modest trans selectivity in this case. Eight-membered ring compounds have a curved topology, which restricts the space available on the concave face and favours reagent approach from the less hindered face. Also the reaction temperature was higher than that reported in the literature,[98] allowing more flexibility of the cyclooctenone and potentially decreasing the stereoselectivity.

To improve the stereoselectivity, the reaction should be carried out at a lower temperature (0 °C) and with different reagents such as dioxirane. An alternative oxidant, methyl trifluoromethyldioxirane, was prepared *in situ* [99] from oxone and trifluoroacetone under mildly basic conditions and epoxidation was carried out at 0 °C. Substrates **162** and **171** underwent 100% conversion within 6-12 hours to afford crystalline epoxides in high yields. Surprisingly, the reactions occurred with high stereoselectivity (Scheme 49). The *cis*- and *trans*-**162** and *gem*- and *des*-dimethyl cyclooctenone **171** and **180** produced single epoxides **219**, **221-223** in which the epoxide is *anti* to the OH.



Reagents and conditions: i, oxone, Na_2EDTA, acetonitrile, trifluoroacetone, $NaHCO_3$, 0 °C, 18 h, **219**, 90%, **221**, 98%, **222**, 82%, **223**, 80%; ii, Ac_2O, DMAP, DCM, overnight, **257**, 64%.

Scheme 49

Structures were characterised by X-ray crystallographic analysis. X-ray structure of epoxide **219** is shown in Figure 23. The trans relationship between the epoxide and the hydroxyl group is clearly observed.

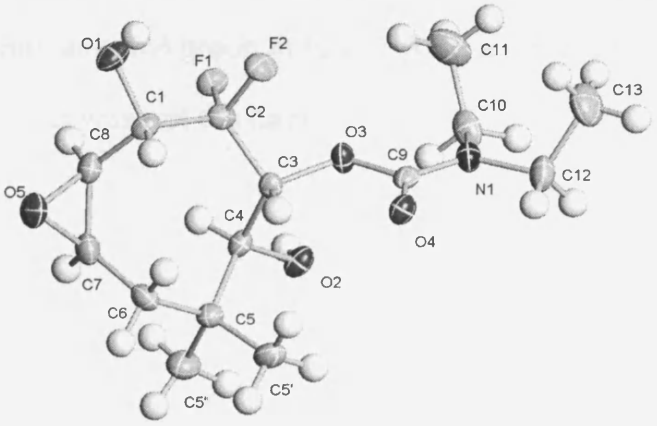
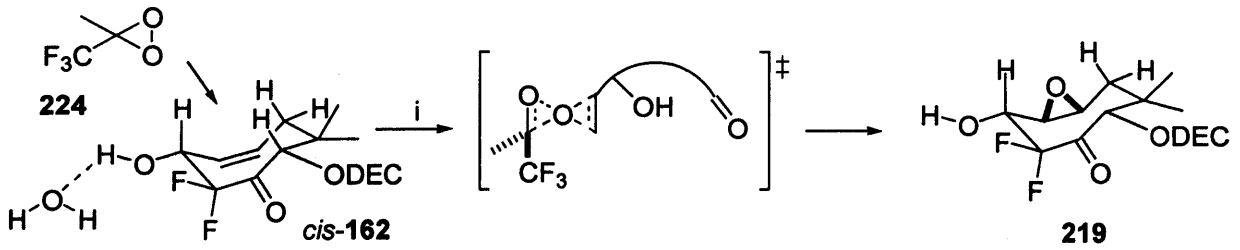


Figure 23

Intramolecular hydrogen bonding is also involved in dioxirane oxidation in non-polar solvents.[99-101] However, this epoxidation carried out following the procedure of Yang occurs in aqueous acetonitrile, so intramolecular hydrogen bonding is likely to be much less effective in this case. Therefore, the dioxirane preferred to approach from the less hindered face to afford *trans*-epoxy alcohol (Scheme 50).

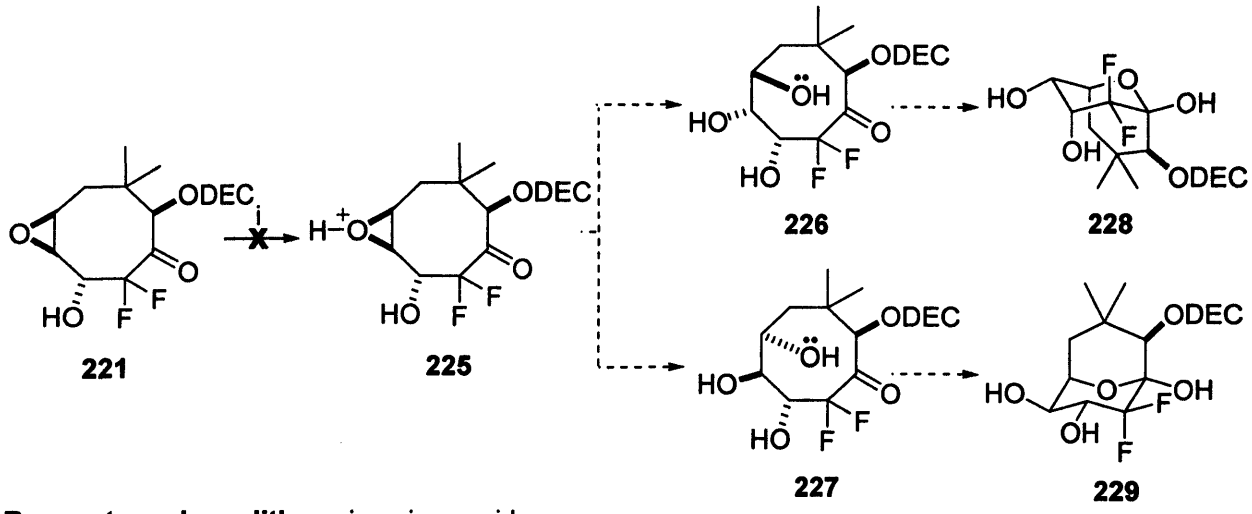


Reagents and conditions : i, oxone, Na_2EDTA, acetonitrile, trifluoroacetone, $NaHCO_3$, 0 °C

Scheme 50

4-1. Attemped ring-opening reaction of epoxide under acidic conditions

Epoxidation reactions with trifluorodioxirane **224** were sterically controlled and gave high yields. To approach conformationally locked bicyclic compounds, epoxide ring opening reaction was attempted under various acid conditions. However, the epoxides were remarkably resistant to hydrolysis in the presence of Brønsted acid and water-stable Lewis acids (Table 3). It is expected that the epoxide would be protonated to undergo solvolysis with release of the strain, forming a diol which would attack the ketonic carbonyl group in turn to form a more stable bicyclic product **228** or **229**. However, this was not the case.



Reagents and conditions; i, various acids

Scheme 51

Entry	Acid [a]	Solvent (1 mL)	Temp.	Time	Result [b]
1	2 M HCl aq	THF	reflux	3 days	No reaction
2	conc. H_2SO_4	THF	reflux	3 days	No reaction
3	$BF_3.Et_2O$	THF	reflux	overnight	No reaction
4	*p*-TsOH	CH_3CN/H_2O	MW, 100 °C	240 min.	No reaction

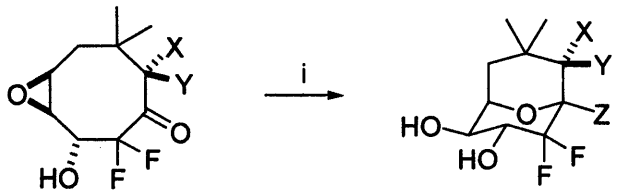
[a] 2.2 eq. of acid was used
[b] Reaction was followed by TLC

Table 3

4-2. Approaches toward conformationally locked bicyclic compounds

Due to the failure of the acid-catalysed hydrolysis, the hydrolysis was attempted under various basic aqueous conditions (Table 4). It is expected that a base opens the epoxide to release the strain, then the newly formed hydroxyl group or amino group attacks the ketonic carbonyl group to afford a more stable bicyclic compound. Concentrated ammonia solution was used as the reaction solvent and the mixture was irradiated in the microwave instrument.[102] The reaction led to the formation of bicyclic molecules **230-232** rapidly. Imidazole and azide allow potential access toward nucleoside analogues which are very interesting targets especially with

fluorine atoms.[23] However, when the ring opening was attempted with imidazole and azide under the same conditions in the microwave instrument, we failed to observe the expected products of ring-opening. The use of aqueous *N*-methylimidazole led to the formation of bicyclic molecules **233-235** unexpectedly.



222 X = Y= H
219 X = ODEC, Y = H,
221 X = H, Y = ODEC
222 X = Y= H
219 X = ODEC, Y = H,
221 X = H, Y = ODEC

230 X = Y= H, Z = NH_2
231 X = ODEC, Y = H, Z =NH_2
232 X = H, Y = ODEC, Z =NH_2
233 X = Y= H, Z = OH
234 X = ODEC, Y = H, Z =OH
235 X = H, Y = ODEC, Z =OH

Reagents and conditions : i, various aqueous base, microwave irradiation, 30 W, 100 °C, cooling, **230**, 60%, **231**, 70%, **232**, 78%, **233**, 71%, **234**, 75% and **235**, 72%.

Scheme 52

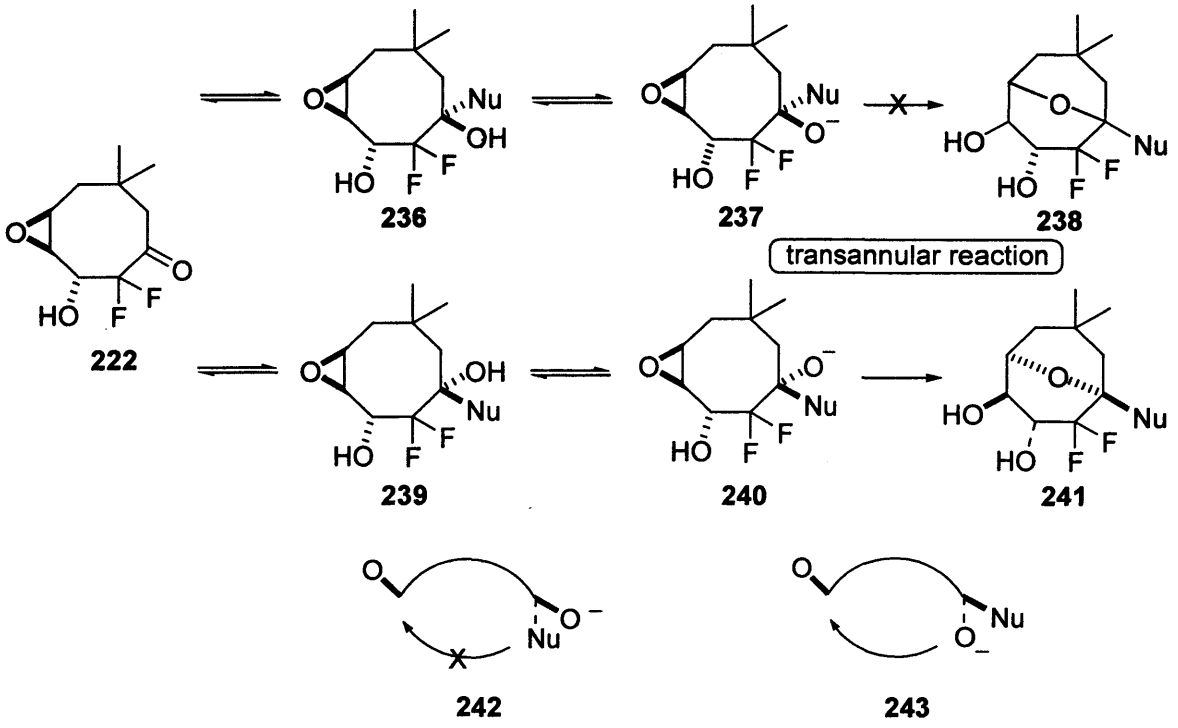
Entry	Base[a]	Temp.	Time (min)	Result
1	NH_4OH	MW, 100 °C	5	60-78 % [b]
2	sat. Imidazole aq.	MW, 100 °C	240	No reaction [c]
3	NaN_3	MW, 100 °C	240	No reaction [c]
4	NMI[a]	MW, 100 °C	5	71-75 % [b]

[a] aqueous NMI
[b] see each yields in the Scheme 52
[c] Reaction was followed by TLC

Table 4

The highly selective transformation was most unexpected. The expected mechanism was shown in scheme 53.[75] The reaction was started by formation of a hemiaminal, followed by transannular reaction. The formation of a new C-O bond is thermodynamically more favourable than the formation of a C-N bond; hemiaminal formation from ketonic carbonyl group is reversible so that the hemiaminal would interconvert between the two possible diastereoisomeric configurations. When the

correct stereochemistry like **240** is formed, the transannular reaction would occur rapidly to release the strain in the eight-membered ring and the epoxide. Once the bicyclic product has formed, the reaction becomes irreversible to terminate the overall transformation. Actually, *N*-methyl imidazole acts as a general base and not as a nucleophile, assisting the attack of water at the carbonyl group to form the hemiacetal, then transannular reaction proceeds. It has to form an anionic nucleophile to be reactive enough and the pK_a for proton loss from NH_2 is too high for it to occur in this reaction. It is surprising that the amino group of the hemiaminal is not sufficiently nucleophilic to undergo the transannular reaction.



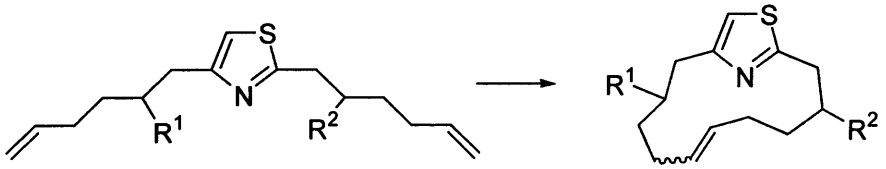
Scheme 53

5. Measuring the Thorpe–Ingold effect on cyclisation

"The Thorpe-Ingold effect" is an apparent acceleration or facilitation of cyclisation which arises especially from the presence of a geminally-disubstituted (typically dialkylated) centre in the precursor. [103]

Figure 24

One explanation of the Thorpe-Ingold effect is based on the idea that *gem*-disubstitution causes compression of the internal angle *b* and brings the X and Y groups closer together; this favours intramolecular cyclisation. The effect is well established in the formation of small (5-6) rings, but has been less well documented in the formation of medium and large rings. There are alternative explanations, including one which suggests that the kinetic effect of the *gem*-dialkyl substitution increases the population of reactive rotamers with the two ends predisposed for the cyclisation. Several examples describe the effect in cyclisations which form medium rings,[104] though few examples describe the effect on the RCM reaction. Murphy *et al.* described a possible effect on the RCM in the formation of a large ring. A single methyl group appeared to favour cyclisation in a study; higher cyclisation yields were observed for methylated **249** and **250**, compared to *des*-methyl **248**. (Scheme 54). [105]



244 $R^1 = R^2 = H$
245 R^1 = Me, R^2 = H
246 R^1 = H, R^2 = Me
247 $R^1 = R^2$ = Me

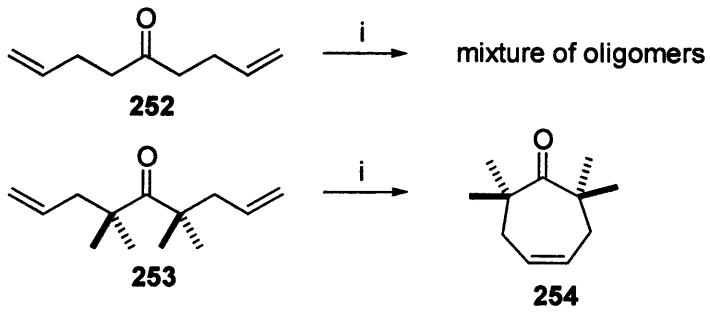
248 $R^1 = R^2$ = H, 15%
249 R^1 = Me, R^2 = H, 53%
250 R^1 = H, R^2 = Me, 57%
251 $R^1 = R^2$ = Me, 70%

Reagents and conditions: 2 % Grubbs' cat., DCM, reflux.

Scheme 54

The cyclisation of thiazole **244** gave a poor result; **248** was obtained in only 15% yield while dimers accounted for 30% of the product. When the thiazole was substituted by methyl groups, the cyclisation was more efficient and gave target macrocycles **249-251** in better yields. Disubstituted **247** gave cyclic product **251** in

70% yield. It is interesting that even a single allyl group appears to improve cyclisation, however this is not a classical *gem*-dialkyl or Thorpe-Ingold effect. A more dramatic example was reported by Forbes *et al.*[106] They investigated the effect based on the reactions of unsubstituted diene **252** and disubstituted diene **253** when exposed to Schrock's catalyst **85**. Unsubstitued diene **252** did not cyclise, giving instead a complex mixture of oligomers, whereas tetrasubstituted diene **253** cyclised easily and gave the desired seven-membered cyclic product **254** in 95% yield (Scheme 55).

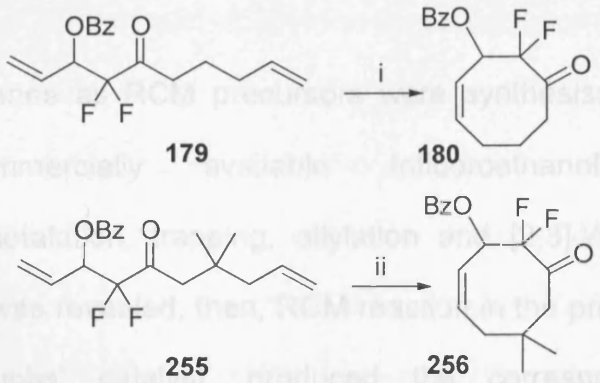


Reagents and conditions: i, cat **85**, neat, 25 °C.

Scheme 55

5-1. The Thorpe-Ingold effect observed in the difluorinated cyclooctenone systems

As reported previously, the difluorinated diene **179** and difluorinated *gem*-dimethyl diene **255** were successfully cyclised by RCM, which could allow us to quantify the Thorpe-Ingold effect in terms of relative rate of the reaction. The RCM experiment involving **179** was carried out under high dilution [0.001 M] in order to avoid the formation of the dimer of **179**; the reaction was followed by sampling every 5 min and using GC-MS to identify and quantify the reaction products (Scheme 56).



Reagents and conditions: i, catalyst **87**, DCM, 2 h, reflux; ii, 5 mol % catalyst **87**, DCM, 2 h, reflux.

Scheme 56

Graph in Figure 25 shows the result of ring closing metathesis of **179** and **255** analysed by the GC-MS. The concentration/time profiles showed clearly that the *gem*-dimethyl diene **255** was forming cyclic product **256** nearly twice as fast as the *des*methyl diene **179**. The half life of each reaction was calculated yielding values of **256** for the *gem*-dimethyl species and **180** for its *des*methyl congener. The rate of cyclisation of *gem*-dimethyl diene **255** was therefore 3 times faster than unsubstituted diene **179**. This preliminary experiment shows for the first time that the *gem*-dialkyl effect increases the *rate* of eight-membered ring-closure by RCM. Considerable further study will be required to measure reaction rate constants and understand their significance.

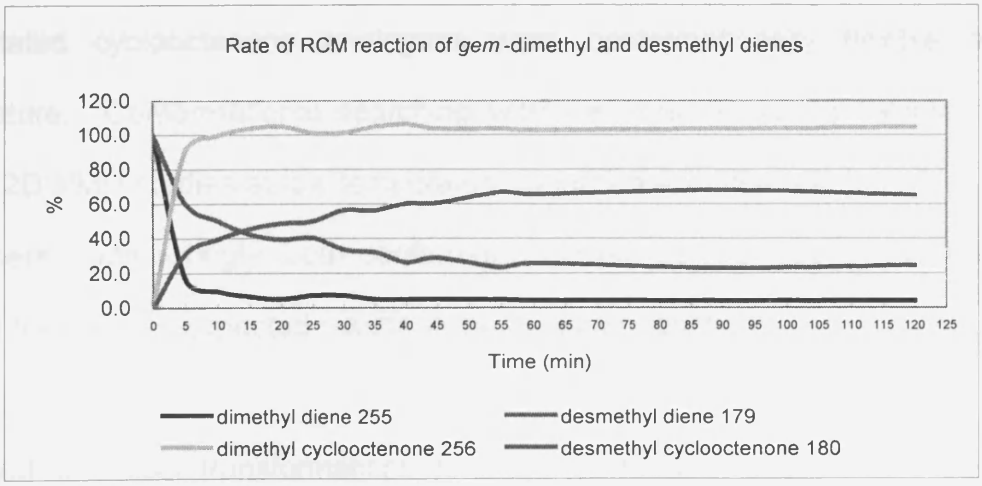


Figure 25

6. Conclusions

gem-Difluorinated dienes as RCM precursors were synthesised successfully from cheap and commercially available trifluoroethanol by sequential dehydrofluorination/metalation, trapping, allylation and [2,3]-Wittig rearrangement. The masked ketone was revealed, then, RCM reaction in the presence of 5 mol % of 2nd generation Grubbs' catalyst, produced the corresponding *gem*-difluoro cyclooctenones **171**, **180** and **182** successfully in good yields. However, dithioketal-containing precursor **187** could not be cyclised, even at higher temperatures.

The effect of substrate concentration in RCM reaction was studied. *gem*-Dimethyl precursor **168** cyclised smoothly at relatively high (0.01 M) concentration, whereas, *des*methyl precursor **176** oligomerised and did not give the desired cyclic product under these conditions. Protected diene precursors **179** and **181** gave the desired products **180** and **182** in good yields only at high dilution only (0.001 M). On the basis of further studies of RCM with dimethyl precursor **255** and desmethyl precursor **179**, it was found that a *gem*-dialkyl or Thorpe-Ingold effect played an important role in assisting cyclooctannulation.

Difluorinated cyclooctenone analogues were conformationally flexible at room temperature. Conformational searching with electronic structure calculations and various 2D NMR studies at low temperature identified a limited number of low energy conformers. Interestingly, both conformers showed curved topologies, which may account for some unexpected results in the oxidation reaction.

Attempted chemical transformations to bicyclic products gave some unexpected results. Stereoselective epoxidation of *gem*-difluorinated cyclooctenones **162**, **171**

and **180** with methyl trifluoromethyldioxirane proceeded smoothly at 0 °C and produced *trans* epoxy alcohols as the sole products. On the other hand, the epoxidation of *cis*-**162** with *m*CPBA under reflux conditions in DCM gave a mixture of *cis*- and *trans*- products. These results suggest the stereoselectivity depends on the flexibility of the eight-membered ring with the less selective oxidation occurring under conditions where the starting ring is interconverting between several conformers more freely.

Attempted allylic transposition reactions were unsuccessful. To create a new hydroxyl group at C-6 position, MTO and trichloroacetonitrile were used under reflux conditions, however, ring conformations avoided the reactive conformation in rearrangement step and the intermediate was decomposed during reaction. Even allylic transposition reactions could possibly introduce a hydroxyl group at C-5 position, however the geometry of it might be opposite to ketone and not be possible to trigger transannular reaction.

Dihydroxylation reactions of the difluorocyclooctenones gave mixtures of diastereomeric triol products, which underwent transannular collapse to afford bicyclic products. These products were separable and were subjected to x-ray crystallographic analysis.

The epoxides of difluoro cyclooctenones are very stable under acid conditions. However, microwave reaction in basic aqueous solution afforded unique bicyclic molecules which were derived by transannular reaction. Hemiaminal formation in conc. ammonia solution or hydration of ketonic carbonyl group next to *gem*-difluoro group in wet *N*-methylimidazole occurred and it triggered transannular reaction to

form stable oxabicyclic molecules. Favourable release of ring strain in the eight-membered ring would be a driving force for the easy transannular reaction of keto-epoxide.

It follows that the cyclooctenone templates can be synthesised readily and can then be transformed into a range of sugar-like highly functionalised templates. The interplay of topology and oxidation stereoselectivity is not yet understood fully, suggesting that further work could be carried out profitably. The control of absolute configuration and the full potential of the reaction products of this study also remain to be addressed.

The primary purpose of this study was not the preparation of enantiomerically pure materials. However, it may be possible to achieve this by resolving either the acyclic or cyclic allylic alcohols *via* an enzyme catalysed acylation or deacylation, or by derivatising with an enantiomerically enriched reagent and then separating diastereoisomers.

Chapter 3: Experimental

General procedures

Nuclear magnetic resonance spectroscopy

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 or a Bruker DRX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz; ^{19}F, 376.45 MHz, COSY, HMQC, HMBC, NOESY) spectrometer using Norell 507-HP NMR tubes. 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 CCl_3F as the external standard. They are reported consecutively as chemical shift (δ_H, δ_C, or δ_F), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, td = triplet of doublets, m = multiplet, env. = envelope, app. = apparent and br.s = broad singlet), coupling constant (J / Hz) and assignment. Carbohydrate numbering is used for the products of dihydroxylation reactions to simplify the reading of the NMR data.

Mass spectrometry and Infrared

Electron Impact (EI) mass spectra were recorded on Kratos Concept 1H mass spectrometer. Chemical Ionization (CI) mass spectra were recorded on a Kratos Concept 1H mass spectrometer using ammonia as the reagent gas. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H mass spectrometer using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC mass spectrometer. High Resolution Mass Spectrometry (HRMS) was measured on a Kratos Concept 1H mass spectrometer using peak matching to stable reference peaks, depending on the technique used. GC-MS was carried out on a Perkin Elmer Turbo Mass spectrometer

fitted with a Zebron ZB-5 column (30 m × 0.25 m) running a 20-350 °C ramp over 27 minutes.

Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum one FT-IR with ATR attachment and were measured in units of cm^{-1}. The data are presented in the following manner: s = strong, m = medium, w = weak.

Chromatography

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+M and 40+S). Column fractions were collected and monitored by Thin Layer Chromatography (TLC) 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 (λ = 254 nm), potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenylhydrazine or phosphomolybdic acid (PMA) stains.

Reagents and solvents

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, or from Pure-Solv Solvent Purification Systems from Innovative Technology, Inc. Dry DMF was used supplied by Aldrich. Acetone was used as reagent grade. Di*iso*propylamine was dried by distillation from calcium hydride powder and stored

over calcium hydride lumps. *n*-Butyllithium was titrated immediately before use according to the method described by Duhamel *et al.* [107]using 4-phenylbenzylidene benzylamine as the indicator. 4 Å Molecular sieves, silica gel, lithium chloride and copper sulfate were dried by heating to 100 °C under reduced pressure (below 50 mmHg) and handled under nitrogen. All other chemicals and solvents were used as received without any further purification.

Where required, solvents were degassed by bubbling argon ornitrogen through them for at least 30 minutes.

Calculations

Calculations were performed using PC Spartan Pro 1.0.5 running on an Intel Pentium 4 (2.66 GHz with 1.28 MB RAM) or MOLPRO on a cluster of dual Opteron PCs running Linux.

Microwave experiments

Microwave experiments were carried in a CEM Discovery instrument (variable power, max. 300W).

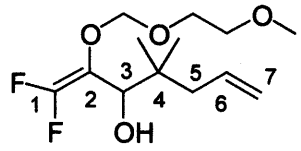
Compounds

1,1,1-Trifluoro-2-{(methoxyethoxy)-methoxy}-methoxyethane **163** was synthesised using the method described by Percy *et al.* [77]

Trans- and cis-8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooctan-1-one **162** was synthesised by Pintat. [80]

9-(*N,N*-diethylcarbamoyloxy)-7,7-difluoro-4,4,10,10-tetramethyl-3,5,12-trioxa-tricyclo[6.3.1.02,6]dodecan-8-ol **213** was synthesised by Pintat.[80]

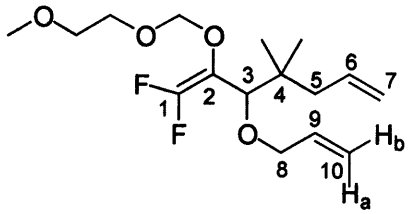
Preparation of 1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-dien-3-ol 165



n-Butyllithium (26 mL of 2.45 M solution in hexane, 63 mmol) was added dropwise to a cold (-78 °C) solution of di*iso*propylamine (9.3 mL, 66 mmol) in dry THF (60 mL) under nitrogen. The solution was allowed to warm to -30 °C and then cooled again to -78 °C. Ether **163** (5.6 g, 30 mmol) was added dropwise over 30 min to this freshly-made LDA solution. The reaction mixture was stirred at this temperature for 40 min and then 2,2-dimethylpent-4-enal (4.9 mL, 33 mmol) was added in one portion. The mixture was allowed to warm to -30 °C over 2 h, then quenched with NH_4Cl (40 mL of a saturated aqueous solution). Water (40 mL) was added to the mixture which was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Kugelrohr distillation afforded allylic alcohol **173** (6.5 g, 77%, 100% by GC-MS) as a clear, colourless oil; bp 90-95 °C/0.1 mmHg; ν_{max}(film)/cm^{-1} 3401m br, 2934m br, 2932s, 2891s, 1639m; R_f (20% ethyl acetate in hexane) 0.40; δ_H (300 MHz, $CDCl_3$) 5.78 (1H, ddt, *J* 16.7, 10.2, 6.7, H-6), 5.05-4.85 (4H, m, H-7 and OCH_2OCH_3), 3.96-3.89 (2H, m, OCH_2CH_2O), 3.79-3.72 (1H, m, H-3), 3.57-3.54 (2H, m, OCH_2CH_2O), 3.36 (3H, s, CH_3), 3.18 (1H, br s, OH), 2.12 (1H, dd, ^2J 13.2, *J* 7.3, H-5_a), 2.00 (1H, dd, ^2J 13.2, *J* 7.3, H-5_b), 0.96 (3H, s, CH_3), 0.90 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 155.0 (dd, $^1J_{C-F}$ 291.3, 285.3), 135.0, 118.2, 98.0 (dd, $^2J_{C-F}$ 36.4, 9.8), 71.4, 68.5, 66.5, 59.0, 55.8, 43.6, 39.0, 23.1, 22.9; δ_F (282 MHz, $CDCl_3$) -100.3 (1F, d, $^2J_{F-F}$ 65.0), -110.0 (1F, dd, $^2J_{F-F}$ 65.0, $^4J_{F-H}$ 4.0,); [HRMS EI, $[M+Na]^+$] Found: 303.1382. Calc. For $C_{13}H_{22}O_4F_2Na$ 303.1384]; *m/z* (EI) 303 (100 %, $[M+Na]^+$), 89 (100, MEM^+), 59 (99, $MeOCH_2CH_2^+$).

Spectral data were in agreement with those reported by Pintat.[80]

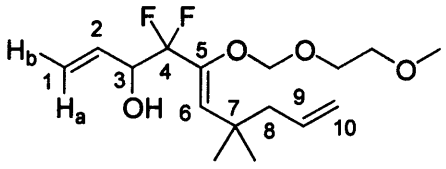
Preparation of 3-allyloxy-1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-diene 166



Allyl bromide (3.6 mL, 42.8 mmol) and tetrabutylammonium iodide (396 mg, 1.1 mmol) were added to vigorously stirred cold (0 °C) NaOH (13.2 mL of a 50% w/v aqueous solution, 249.9 mmol). Allyl alcohol **165** (9.9 g, 35.6 mmol) and tetrabutylammonium hydrogensulfate (606 mg, 1.8 mmol) were added to the solution at this temperature. The reaction mixture was stirred at 0 °C for 18 h, then the mixture was diluted with water (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave allylic ester **166** (10.5 g, 92%, 100% by GC-MS) as a pale yellow oil; R_f (8% diethyl ether in hexane) 0.20; ν_{max}(film)/cm^{-1} 2957s, 2930s, 1638m; δ_H (300 MHz, $CDCl_3$) 5.93-5.71 (2H, m, H-9 and H-6), 5.25 (1H, ddd, *J* 17.2, ^4J 1.6, ^2J 1.6, H-10_a), 5.15 (1H, ddd, *J* 10.2, ^4J 1.6, ^4J 1.6, H-10_b), 5.05-4.97 (4H, m, H-7 and OCH_2OCH_2), 4.13-3.71 (4H, m, OCH_2CH_2O), 3.62 (1H, dd, $^4J_{H\text{-}F}$ 4.1, 2.2, H-3), 3.57-3.51 (2H, m, H-8), 3.38 (3H, s, CH_3), 2.16 (1H, dd, ^2J 13.6, *J* 7.7, H-5_a), 2.04 (1H, dd, ^2J 13.6, *J* 7.7, H-5_b), 0.99 (3H, s, CH_3), 0.91 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 156.9 (dd, $^1J_{C\text{-}F}$ 293.8, 285.8), 135.0, 134.4, 117.4, 117.0, 112.1 (dd, $^2J_{C\text{-}F}$ 33.8, 10.2), 97.1 (dd, $^3J_{C\text{-}F}$ 4.0, 2.8), 80.1 (t, $^4J_{C\text{-}F}$ 2.8), 71.6, 69.3, 68.3, 59.0, 44.0, 38.5 (t, $^4J_{C\text{-}F}$ 1.7), 23.5, 23.0; δ_F (282 MHz, $CDCl_3$) -97.4 (1F, dd, $^2J_{F\text{-}F}$ 61.5), -109.5 (1F, d, $^2J_{F\text{-}F}$ 61.5, $^4J_{H\text{-}F}$ 4.0); [HRMS EI, $[M+Na]^+$] Found: 343.1698. Calc. For $C_{16}H_{26}O_4F_2Na$ 343.1697]; *m/z* (EI) 343 (100%, $[M+Na]^+$).

Spectral data were in agreement with those reported by Pintat.[80]

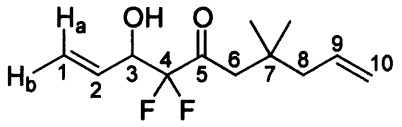
Preparation of 4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-7,7-dimethyl-deca-1,5,9-trien-3-ol 167



A solution of allyl ether **166** (3.4 g, 10.7 mmol) in THF (10 mL) was added dropwise to a cold (-78 °C) solution of LDA (prepared from *n*-BuLi (9.6 mL of a 2.45 M solution in hexanes, 23.5 mmol), di*iso*propylamine (3.6 mL, 25.8 mmol) and THF (20 mL)) under a nitrogen atmosphere. After stirring for 2 h at -78 °C, the solution was warmed to -30 °C over 2 h and stirred at this temperature for 18 h. The reaction mixture was quenched with NH_4Cl (30 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (30 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave allylic alcohol **167** (2.8 g, 80%) as a brown oil; R_f (30% diethyl ether in light petroleum) 0.30; ν_{max}(film)/cm^{-1} 3434m br, 2959s, 2929s, 1681w, 1668w, 1639m; δ_H (300 MHz, $CDCl_3$); 5.93 (1H, ddd, *J* 17.0, 10.6, 5.6, H-2), 5.73 (1H, ddt, *J* 16.7, 10.2, 6.5, H-9), 5.45 (1H, d, *J* 17.0, H-1_a), 5.39 (1H, s, H-6), 5.33 (1H, d, *J* 10.6, H-1_b), 5.05-4.95 (4H, m, H-10 and O*C*H_2O), 4.56-4.40 (1H, m, H-3), 3.88-3.81 (2H, m, O*C*H_2CH_2O), 3.56-3.53 (2H, m, OCH_2*C*H_2O), 3.36 (3H, s, *C*H_3), 2.71 (1H, br s, O*H*), 2.15 (2H, d, *J* 6.5, H-8), 1.13 (3H, s, CH_3), 1.12 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 142.4 (t, $^2J_{C\text{-}F}$ 25.0), 135.2, 132.4 (t, $^3J_{C\text{-}F}$ 3.1), 128.4 (t, $^3J_{C\text{-}F}$ 4.9), 118.7,118.4 (t, $^1J_{C\text{-}F}$ 250.1), 117.1, 98.2, 72.6 (dd, $^2J_{C\text{-}F}$ 30.4, 27.4), 70.5, 68.0, 58.0, 47.4, 35.0, 27.6 (C x 2); δ_F (282 MHz, $CDCl_3$) -110.0 (dd, $^2J_{F\text{-}F}$ 251.5, $^3J_{F\text{-}H}$ 10.3), -115.7 (dd, $^2J_{F\text{-}F}$ 251.5, $^3J_{F\text{-}H}$ 13.0); [HRMS (EI, $[M+Na]^+$) Found: 343.1697. Calc. For $C_{16}H_{26}O_4F_2Na$ 343.1697]; *m/z* (EI) 343 (100%, $[M+Na]^+$).

Spectral data were in agreement with those reported by Pintat. [80]

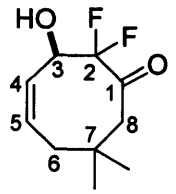
Preparation of 4,4-difluoro-3-hydroxy-7,7-dimethyl-deca-1,9-diene-5-one 168



Thionyl chloride (0.27 mL, 3.7 mmol) was added dropwise to a solution of crude allylic alcohol **167** (1.2 g, 3.7 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred at this temperature for 18 h. The mixture was concentrated *in vacuo*, diluted with water (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Kugelrohr distillation afforded diene **168** (418 mg, 50%) as a clear, colourless oil; bp 85-90 °C/0.098 mmHg; ν_{max}(film)/cm^{-1} 3453m br, 2961s, 1740s, 1639m; R_f (10% ethyl diethyl ether in hexane) 0.33; δ_H (300 MHz, $CDCl_3$) 5.93 (1H, ddd, *J* 17.0, 10.3, 6.4, H-2), 5.76 (1H, ddt, *J* 17.0, 10.2, 6.7, H-9), 5.50 (1H, dt, *J* 17.0, ^2J 1.5, ^4J 1.5, H-1_a), 5.43 (1H, dt, *J* 10.3, ^2J 1.5, ^4J 1.5, H-1_b), 5.07-4.98 (2H, m, H-10), 4.59 (1H, dt, $^3J_{H\text{-}F}$ 15.2, 7.6, H-3), 2.59 (2H, s, H-6), 2.37 (1H, br s, O*H*), 2.15-2.12 (2H, m, H-8), 1.03 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 201.8 (dd, $^2J_{C\text{-}F}$ 30.0, 27.1, C-5), 134.5, 131.1, 120.4, 117.9, 114.8 (dd, $^1J_{C\text{-}F}$ 261.8, 257.8, C-4), 72.1, 47.1, 46.0, 33.5, 26.9 (C x 2); δ_F (282 MHz, $CDCl_3$) -113.7 (1F, dd, $^2J_{F\text{-}F}$ 274.0, $^3J_{F\text{-}H}$ 7.6), -123.3 (1F, dd, $^2J_{F\text{-}F}$ 274.0, $^3J_{F\text{-}H}$ 15.2); [HRMS (EI, $[M+NH_4]^+$) Found: 250.161786. Calc. For $C_{12}H_{22}NO_2F_2$ 250.161864]; *m/z* (CI) 250 (100%, $[M+NH_4]^+$).

Spectral data were in agreement with those reported by Pintat. [80]

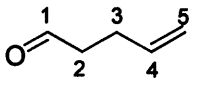
Preparation of 2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooct-4-enone 171



A solution of diene **168** (2.3 g, 10 mmol) and titanium(IV) *iso*propoxide (0.83 mL, 2.8 mmol) in degassed DCM (1 L) was refluxed for 30 min. Grubbs' catalyst **86** (412 mg, 0.5 mmol) was added as a solution in degassed DCM (10 mL) and the reaction mixture was refluxed for 24 h under a positive pressure of nitrogen. The mixture was concentrated *in vacuo* to leave a brown oil (2.5 g). Purification by column chromatography (40% ether in hexane) afforded cyclooctenone **171** (1.8 g, 70%) as a light brown oil; R_f (30% diethyl ether in hexane) 0.20; ν_{max} (film)/cm^{-1} 3444s, 3033w. 2963m, 2928m, 2870m, 1738s, 1652w; δ_H (300 MHz, $CDCl_3$, 323 K) 5.90-5.81 (1H, m, H-5), 5.62-5.57 (1H, m, H-4), 4.84-4.72 (1H, m, H-3), 2.78 (1H, br s, OH), 2.50 (1H, dd, ^2J 12.5, $^4J_{H\text{-}F}$ 2.7, H-8$_a$), 2.35 (1H, d, ^2J 12.5, H-8$_b$), 1.97 (2H, d, J 7.9, H-6), 1.10 (3H, s, CH_3), 0.98 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$, 323 K) 198.4 (t, $^2J_{C\text{-}F}$ 25.7, C-1), 131.8, 129.3 (d, $^3J_{C\text{-}F}$ 3.3), 117.3 (t, $^1J_{C\text{-}F}$ 258.2, C-2), 68.1 (t, $^2J_{C\text{-}F}$ 23.2, C-3), 47.6, 40.2, 37.7, 30.6, 26.9; δ_F (375 MHz, $CDCl_3$, 223 K) major conformer: -108.3 (d, $^2J_{F\text{-}F}$ 240.4), -136.1 (dd, $^2J_{F\text{-}F}$ 240.4, $^3J_{F\text{-}H}$ 20.3), minor conformer: -115.4 (1F, d, $^2J_{F\text{-}F}$ 229.3), -129.1 (1F, dd, $^2J_{F\text{-}F}$ 229.3, $^3J_{F\text{-}H}$ 26.1); [HRMS (EI, [M + Na]$^+$) Found 227.0860. calc. For $C_{10}H_{14}O_2F_2Na$: 227.0860]; *m/z* (ES) 227 ([M+Na]$^+$, 100%).

Spectral data were in agreement with those reported by Pintat. [80]

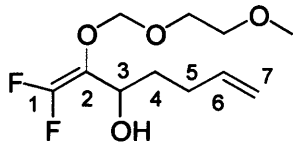
Preparation of pent-4-enal 172



Allyl vinyl ether (3.75 g, 45 mmol) was sealed in a crimp-capped microwave vial and irradiated in the cavity of a CEM Discovery microwave instrument at 150 °C for 5 h. The aldehyde was used without purification; δ_H (300 MHz, $CDCl_3$) 9.99 (1H, t, *J* 1.5, H-1), 6.10-5.97 (1H, m, H-4), 5.32-5.21 (2H, m, H-5), 2.80-2.73 (2H, m, H-2), 2.65-2.56 (2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 202.1, 136.8, 115.9, 43.0, 26.4.

Spectral data were in agreement with those reported by Murphy *et al.*.[81]

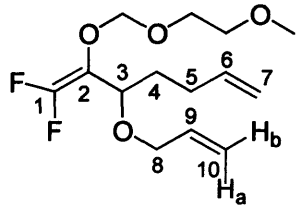
Preparation of 1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-hepta-1,6-diene- 3-ol 173



n-BuLi (32 mL of 2.40 M solution in hexane, 75 mmol) was added dropwise to a cold (-78 °C) solution of di*iso*propylamine (9.8 mL, 78 mmol) in dry THF (36 mL) under nitrogen. The solution was allowed to warm up to -30 °C and then cooled again to -78 °C. Ether **163** (6.6 g, 36 mmol) was added dropwise over 30 min to this freshly-made LDA solution. The reaction was stirred at this temperature for 40 min, then aldehyde **172** (3.6 g, 42 mmol) was added in one portion. The mixture was allowed to warm to -30 °C over 2 h, then quenched with NH_4Cl (30 mL of a saturated aqueous solution). Water (30 mL) was added to the mixture which was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Kugelrohr distillation afforded allylic alcohol **173** (6.9 g, 78 %, 100% by GC-MS) as a clear, colourless oil; bp 80-85 °C/0.25 mmHg; ν_{max}(film)/cm^{-1} 3475m, 2932s, 1751m, 1641s; R_f (20% ethyl acetate in hexane) 0.34; δ_H (300 MHz, $CDCl_3$)

5.80 (1H, ddt, *J* 16.7, 10.2, 6.7, H-6), 5.06-4.85 (4H, m, H-7 and OCH_2O), 4.24 (1H, m, H-3), 3.96 (1H, ddd, ^2J 10.7, *J* 6.3, 3.5, $OCH_aH_bCH_2O$), 3.77 (1H, ddd, ^2J 10.7, *J* 5.5, 3.2, $OCH_aH_bCH_2O$), 3.59-3.55 (2H, m, OCH_2CH_2O), 3.36 (4H, br s, OH, CH_3), 2.14-2.05 (2H, m, H-5), 1.87-1.64 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 154.6 (dd, $^1J_{C-F}$ 290.3, 284.3), 137.7, 118.2 (dd, $^2J_{C-F}$ 36.4, 9.8), 115.1, 98.0, 71.4, 68.5, 66.5, 59.0, 33.1, 29.7; δ_F (282 MHz, $CDCl_3$) -100.2 (1F, d, $^2J_{F-F}$ 64.0), -110.0 (1F, dd, $^2J_{F-F}$ 64.0, $^4J_{F-H}$ 3.8); [HRMS (EI, M^+) Found: 252.11729. Calc. For $C_{11}H_{18}O_4F_2$ 252.11732]; *m/z* (CI) 270 (52%, $[M+NH_4]^+$), 215 (10), 137 (10), 89 (100, MEM^+), 59 (99, $MeOCH_2CH_2^+$).

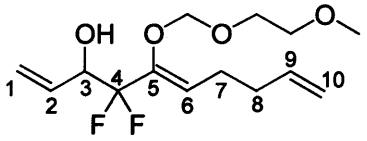
Preparation of 3-allyloxy-1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-hepta-1,6-diene 174



Allyl bromide (1.9 mL, 21.8 mmol) and tetrabutylammonium iodide (220 mg, 0.60 mmol) were added to stirred cold (0 °C) NaOH solution (7.3 mL of a 50 %w/v of solution, 138.9 mmol). Allyl alcohol **173** (6.6 g, 26.3 mmol) and tetrabutylammonium hydrogensulfate (337 mg, 1.0 mmol) were added to the solution at this temperature. The reaction mixture was stirred at 0 °C for 18 h, then the mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave allylic ether **174** (5.6 g, 96%, 100% by GC-MS) as a pale yellow oil; R_f (10% diethyl ether in hexane) 0.42; ν_{max}(film)/cm^{-1} 3080s, 2880s, 1748m, 1642s, 1452s, 1279w; δ_H (300 MHz, $CDCl_3$) 5.87-5.65 (2H, m, H-9 and H-6), 5.19 (1H, dq, *J* 17.2, ^2J 1.6, ^4J 1.6, H-10_a), 5.10 (1H, dq, *J* 10.2, ^2J 1.6, ^4J 1.6, H-10_b), 4.99-4.85 (4H, m, H-7 and OCH_2OCH_2), 4.03 (1H,

ddt, *J* 12.5, 5.0, 1.5, H-3), 4.04-3.92 (1H, m, H-8_a), 3.85-3.67 (3H, m, H-8_b, OCH_2CH_2O), 3.56 (2H, m, OCH_2CH_2O), 3.38 (3H, s, CH_3), 2.13-2.06 (2H, m, H-5), 1.92-1.67 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 156.0 (dd, $^1J_{C\text{-}F}$ 291.8, 282.8), 137.7, 134.3, 117.3, 115.1, 112.4 (dd, $^2J_{C\text{-}F}$ 36.8, 9.8), 97.1, 73.8, 71.6, 69.3, 68.3, 59.0, 31.0, 29.6; δ_F (282 MHz, $CDCl_3$) -97.7 (1F, dd, $^2J_{F\text{-}F}$ 63.5, $^4J_{F\text{-}H}$ 1.9), -109.5 (1F, dd, $^2J_{F\text{-}F}$ 63.5, $^4J_{F\text{-}H}$ 3.8); [HRMS (FAB, $[M+H]^+$) Found: 293.15634. Calc. For $C_{14}H_{23}O_4F_2$ 293.15644]; *m/z* (FAB) 293 (20%, $[M+H]^+$), 215 (24), 165 (74), 137 (100), 89 (100, MEM^+), 59 (84, $MeOCH_2CH_2^+$).

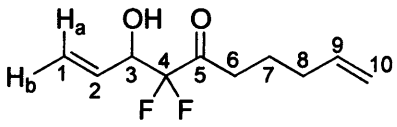
Preparation of 4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-deca-1,5,9-trien-3-ol 175



A solution of allyl ether **174** (5.0 g, 17.1 mmol) in THF (17 mL) was added dropwise to a cold (-78 °C) solution of LDA (prepared by the slow addition of *n*-BuLi (14.7 mL of a 2.45 M solution in hexanes, 35.9 mmol) to a cold (-78 °C) solution of di*iso*propylamine (5.3 mL, 37.6 mmol) in THF (36 mL)) under a nitrogen atmosphere. After stirring for 2 h at -78 °C, the solution was warmed slowly to -30 °C over 3h and stirred at this temperature for 19 h. The reaction mixture was quenched with NH_4Cl (50 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (50 mL) was added and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave allylic alcohol **175** (4.4 g, 89%, 100% by GC-MS) as a brown oil. R_f (30% diethyl ether in light petroleum) 0.26; ν_{max} (film)/cm^{-1} 3434s br., 3080s, 2928s, 1751s, 1681s, 1641s; δ_H (300 MHz, $CDCl_3$) 5.90 (1H, ddd, *J* 16.9, 10.5, 5.6, H-2), 5.77 (1H, ddt, *J* 16.9, 10.2, 6.4, H-9), 5.54 (1H, dt, *J* 7.6, ^2J 1.5, H-6), 5.45

(1H, dt, *J* 17.0, ^2J 1.5, H-1$_a$), 5.32 (1H, dt, *J* 10.5, ^2J 1.5, H-1$_b$), 5.05-4.95 (4H, m, H-10 and OCH_2O), 4.56-4.40 (1H, m, H-3), 3.88-3.77 (2H, m, OCH_2CH_2O), 3.56-3.53 (2H, m, OCH_2CH_2O), 3.36 (3H, s, CH_3), 2.90 (1H, br s, O*H*), 2.31-2.22 (2H, m, H-7), 2.17-2.09 (2H, m, H-8); δ_C (75 MHz, $CDCl_3$) 144.4 (app. t, $^2J_{C\text{-}F}$ 26.3), 136.4, 131.5, 118.9 (app. t, $^3J_{C\text{-}F}$ 4.9), 117.9, 117.2 (app. t, $^1J_{C\text{-}F}$ 247.5), 114.4, 97.2, 71.4 (dd, $^2J_{C\text{-}F}$ 30.4, 27.4), 70.5, 67.9, 58.0, 32.0, 23.6; δ_F (282 MHz, $CDCl_3$) -110.0 (1F, dd, $^2J_{F\text{-}F}$ 252.5, $^3J_{F\text{-}H}$ 8.3), -115.7 (1F, d, $^2J_{F\text{-}F}$ 252.5, $^3J_{F\text{-}H}$ 14.3); [HRMS (FAB, MH^+) Found: 293.15648. Calc. For $C_{14}H_{23}O_4F_2$ 293.15644]; *m/z* (FAB) 293 (44%, $[M+H]^+$), 137 (100), 89 (90, MEM^+), 59 (100, $MeOCH_2CH_2^+$).

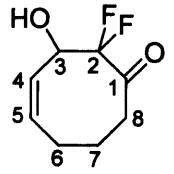
Preparation of 4,4-difluoro-3-hydroxy-deca-1,9-diene-5-one 176



Thionyl chloride (121 µL, 1.4 mmol) was added dropwise to a solution of crude enol ether **175** (404 mg, 1.4 mmol) in MeOH (14 mL) at 0 °C. The reaction mixture was stirred at this temperature for 18 h. The mixture was concentrated *in vacuo*, diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Kugelrohr distillation afforded dienol **176** (155 mg, 55%, 100% by GC-MS) as a clear, colourless oil; bp 75-80 °C/0.098 mmHg; ν_{max}(film)/cm^{-1} 3380s br, 3060s br, 2994s, 1740m, 1621m, 1529m; R_f (10% diethyl ether in hexane) 0.22; δ_H (300 MHz, $CDCl_3$) 5.93 (1H, ddd, *J* 17.1, 10.5, 6.4, H-2), 5.76 (1H, ddt, *J* 16.9, 10.4, 6.7, H-9), 5.50 (1H, dt, *J* 17.1, ^2J 1.5, H-1$_a$), 5.43 (1H, dt, *J* 10.5, ^2J 1.5, H-1$_b$), 5.07-4.98 (2H, m, H-10), 4.63-4.54 (1H, m, H-3), 2.72 (2H, t, *J* 7.3, H-6), 2.37 (1H, br s, O*H*), 2.09 (2H, q, *J* 7.2, H-8), 1.73 (2H, p, *J* 7.2, H-7); δ_C (75 MHz, $CDCl_3$) 201.8 (dd, $^2J_{C\text{-}F}$ 30.9, 25.5, C-5), 137.5, 131.1, 120.4, 115.6, 114.8 (dd, $^1J_{C\text{-}F}$ 258.8, 255.0, C-4), 72.1 (dd, $^2J_{C\text{-}F}$ 27.8,

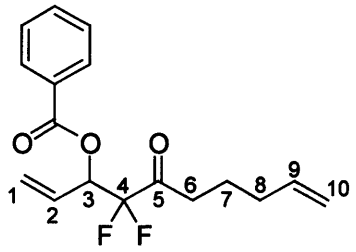
25.5, C-3), 37.1, 32.6, 21.4; δ_F (282 MHz, $CDCl_3$) -113.7 (1F, dd, $^2J_{F-F}$ 273.0, $^3J_{F-H}$ 7.1), -123.3 (1F, dd, $^2J_{F-F}$ 273.0, $^3J_{F-H}$ 15.2); [HRMS (EI, M+H$^+$) Found: 204.09621. Calc. For $C_{10}H_{14}O_2F_2$ 204.09621]; *m/z* (CI) 222 (100%, $[M+NH_4]^+$), 204 (9, M^+).

Preparation of 2,2-difluoro-3-hydroxy-cyclooct-4-enone 177



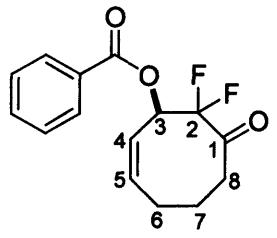
A solution of diene **176** (60 mg, 0.29 mmol) and titanium(IV) *iso*propoxide (27 µL, 0.09 mmol) in DCM (300 mL) was refluxed for 30 min. 2nd Generation Grubbs' catalyst **87** (12 mg, 0.015 mmol) was added as a solution in DCM (5 mL) and the reaction mixture was refluxed for 2 h. The DCM was distilled off at atmospheric pressure to leave a brown oil (54 mg). Purification by column chromatography (40% diethyl ether in light petroleum ether) afforded cyclooctenone **177** (32 mg, 60%, 100% by GC-MS); R_f (40% diethyl ether in light petroleum ether) 0.33; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, dddd, *J* 11.0, 9.4, 7.4, ^4J 1.2, H-5), 5.57 (1H, dddt, *J* 11.0, 7.2, $^4J_{H-F}$ 3.1, ^4J 1.2, H-4), 4.88 (1H, dddd, $^3J_{H-F}$ 21.0, *J* 7.2, $^3J_{H-F}$ 3.5 ^4J 1.2, H-3), 2.69-2.59 (1H, m, H-7_a), 2.57-2.48 (1H, m, H-8_a), 2.30-2.20 (1H, m, H-6_a), 2.06-1.88 (2H, m, H-6_b and H-8_b), 1.74-1.61 (1H, m, H-7_b); δ_C (100 MHz, 300 K, $CDCl_3$) 200.9 (t, $^2J_{C-F}$ 25.6, C-1), 133.3, 128.5 (d, $^3J_{C-F}$ 6.4, C-4), 117.7 (t, $^1J_{C-F}$ 258.8, C-2), 68.1 (t, $^2J_{C-F}$ 23.2, C-3), 36.2, 27.2, 26.2; δ_F (282 MHz, $CDCl_3$) -113.2 (1F, d, $^2J_{F-F}$ 236.0), -123.8 (1F, dd, $^2J_{F-F}$ 236.0, $^3J_{F-H}$ 21.0); *m/z* (EI) 83 ($COCH_2CH_2CH_2CH$, 100%), 175 (42 %, [M-H]).

Preparation of 4,4-difluoro-3-benzoyloxy-deca-1,9-dien-5-one 179



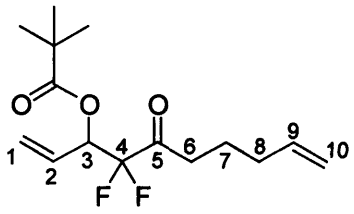
Benzoic anhydride (226 mg, 1.00 mmol) and DMAP (24 mg, 0.20 mmol) were added to a solution of dienol **176** (1.00 mmol, 204 mg) in pyridine (1.0 mL). The mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil. Purification by column chromatography (10% diethyl ether in light petroleum) afforded the benzoate ester **179** (319 mg, 87%) as a yellow oil; R_f (10% diethyl ether in hexane) 0.56; ν_{max}(film)/cm^{-1} 3076s, 2937s, 1733w, 1642s, 1602s; δ_H (300 MHz, $CDCl_3$) 7.99-7.94 (2H, m, Ph-H), 7.56-7.50 (1H, m, Ph-H), 7.42-7.36 (2H, m, Ph-H), 5.97-5.81 (2H, m, H-2 and H-3), 5.64 (1H, ddt, *J* 16.8, 10.2, 6.8, H-9), 5.50 (1H, dd, *J* 16.1, ^2J 0.9, H-1$_a$), 5.43 (1H, dd, *J* 10.2, ^2J 0.9, H-1$_b$), 4.95-4.87 (2H, m, H-10), 2.67 (2H, t, *J* 7.2, H-6), 2.00 (2H, q, *J* 7.2, H-8), 1.64 (2H, p, *J* 7.2, H-7); δ_C (75 MHz, $CDCl_3$) 199.7 (t, $^2J_{C\text{-}F}$ 28.7, C-5), 164.4, 137.3, 133.7, 129.9 (C x 2), 128.9, 128.6 (C x 2), 127.7, 122.8, 115.7, 114.1 (dd, $^1J_{C\text{-}F}$ 260.9. 256.1, C-4), 72.4 (dd, $^2J_{C\text{-}F}$ 29.9, 25.1, C-3), 36.7, 32.6, 21.5; δ_F (282 MHz, $CDCl_3$) -113.7 (1F, dd, $^2J_{F\text{-}F}$ 293.9, $^3J_{F\text{-}H}$ 9.0), -118.9 (1F, dd, $^2J_{F\text{-}F}$ 273.9, $^3J_{F\text{-}H}$ 14.2); [HRMS (EI, M$^+$) Found: 308.12242. Calc. For $C_{17}H_{18}O_3F_2$ 308.12240]); *m/z* (EI) 308 (37 %, [M+]$^+$), 105 (85, [C_6H_5C=O]$^+$).

Preparation of 2,2-difluoro-3-benzoyloxy-cyclooct-4-enone 180



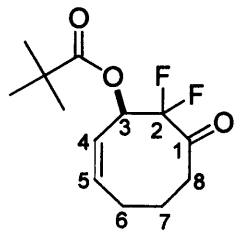
A solution of diene **179** (286 mg, 0.93 mmol) and titanium(IV) *iso*propoxide (83 μL, 0.28 mmol) in degassed DCM (930 mL) was refluxed for 30 min. 2nd Generation Grubbs' catalyst **87** (39 mg, 0.05 mmol) was added as a solution in degassed DCM (10 mL) and the reaction mixture was refluxed for 2 h. The mixture was concentrated *in vacuo* to leave a brown oil (275 mg). Purification by column chromatography (10% diethyl ether in hexane) afforded cyclooctenone **180** (227 mg, 81%) as a white solid which recrystallised from diethyl ether/hexane to afford colourless needles; mp 91-92 °C; R_f (10 % diethyl ether in hexane) 0.20; (Found C, 64.31; H, 5.16; $C_{15}H_{14}F_2O_3$ requires: C, 64.28; H, 5.03%); ν_{max} (solid)/cm^{-1} 2968s, 2919s, 1725w, 1743m; δ_H (300 MHz, $CDCl_3$) 8.14-8.10 (2H, m, Ph-H), 7.64-7.58 (1H, m, Ph-H), 7.51-7.45 (2H, m, Ph-H), 6.36 (1H, dddd, $^3J_{H\text{-}F}$ 21.3, *J* 8.2, $^3J_{H\text{-}F}$ 3.8, ^4J 1.5, H-3), 6.06-5.96 (1H, m, H-5), 5.68-5.60 (1H, m, H-4), 2.82 (1H, dddd, ^2J 12.6, *J* 10.2, *J* 3.8, ^4J 2.0, H-8_a), 2.68 (1H, ddt, ^2J 12.6, *J* 7.2, *J* 3.5, ^4J 3.5, H-8_b), 2.44-2.27 (2H, m, H-6), 2.13-2.02 (1H, m, H-7_a), 1.89-1.74 (1H, m, H-7_b); δ_C (75 MHz, $CDCl_3$) 199.5 (t, $^2J_{C\text{-}F}$ 25.5, C-1), 165.2, 135.6, 133.7, 130.0 (C x 2), 129.0, 128.6 (C x 2), 125.3, 116.6 (dd, $^1J_{C\text{-}F}$ 262.6. 260.0. C-2), 68.2 (dd, $^2J_{C\text{-}F}$ 24.2, 18.9, C-3), 36.8, 27.5, 27.1; δ_F (282MHz, $CDCl_3$) -111.0 (1F, d, $^2J_{F\text{-}F}$ 239.8), -130.9 (1F, dd, $^2J_{F\text{-}F}$ 239.8, $^3J_{F\text{-}H}$ 21.3); *m/z* (ES) 281 ($M+H^+$, 42%), 121 (PhCOO, 100%).

Preparation of 4,4-difluoro-3-(dimethylpropionyloxy)-deca-1,9-dien-5-one 181



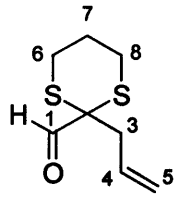
n-BuLi (292 μL of a 2.40 M solution in hexanes, 0.7 mmol) was added dropwise to a solution of diene **176** (143 mg, 0.7 mmol) in THF (8 mL) at -78 °C. The reaction mixture was stirred at this temperature for 30 min and pivaloyl chloride (0.103 mL, 0.84 mmol) was added. The reaction was stirred for 40 min at this temperature and quenched with NH_4Cl (15 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (15 mL) was added and the mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave yellow oil. Purification by column chromatography (10% diethyl ether in light petroleum) afforded pivaloyl ester **181** (131 mg, 87%) as a pale yellow oil; R_f (10% diethyl ether in light petroleum) 0.30; ν_{max}(film)/cm^{-1} 2978s, 2938s, 2875m, 1745m, 1643s; δ_H (300 MHz, $CDCl_3$) 5.89-5.65 (3H, m, H-2, H-3 and H-9), 5.50-5.43 (2H, m, H-1), 5.07-5.00 (2H, m, H-10), 2.69 (2H, t, *J* 7.3, H-6), 2.09 (2H, q, *J* 7.3, H-8), 1.71 (2H, p, *J* 7.3, H-7), 1.20 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 199.6 (t, $^2J_{C\text{-}F}$ 27.2, C-5), 176.1, 137.3, 127.8, 122.2, 115.7, 114.1 (t, $^1J_{C\text{-}F}$ 259.2, C-4), 71.5 (dd, $^2J_{C\text{-}F}$ 30.0, 25.5, C-3), 38.8, 36.7, 32.7, 26.9 (C x 3), 21.5; δ_F (282 MHz, $CDCl_3$) -113.4 (1F, dd, $^2J_{F\text{-}F}$ 274.9, $^3J_{F\text{-}H}$ 8.5), -119.3 (1F, dd, $^2J_{F\text{-}F}$ 274.9, $^3J_{F\text{-}H}$ 14.2); [HRMS (EI, M^+) Found: 288.15371. Calc. For $C_{15}H_{22}O_3F_2$ 288.15370]; *m/z* (EI) 69 (100%, $(CH_3)_3CC$), 288 (12 , [M^+]), 186 (25, [M-$OCO(CH_3)_3$]$^+$).

Preparation of 2,2-difluoro-3-(dimethylpropionyloxy)-cycloct-4-en-1-one 182



A solution of diene **181** (50 mg, 0.17 mmol) and titanium(IV) *iso*propoxide (15 μL, 0.05 mmol) in degassed DCM (170 mL) was refluxed for 30 min. 2nd Generation Grubbs' catalyst **87** (7.2 mg, 8.5 x 10^{-3} mmol) was added as a solution in degassed DCM (1 mL) and the reaction mixture was refluxed for 2 h. The mixture was concentrated *in vacuo* to leave a brown oil (65 mg). Purification by column chromatography (40% diethyl ether in hexane) afforded cyclooctenone **182** (30.7 mg, 70%, 100% by GC-MS) as a clear oil; R_f (30% diethyl ether in hexane) 0.33; ν_{max} (film)/cm^{-1} 2968m, 2919m, 1729s; δ_H (400 MHz, $CDCl_3$, 323 K) 5.83-5.76 (1H, m, H-5), 5.63-5.57 (1H, m, H-4), 4.83 (1H, dddd, $^3J_{H-F}$ 19.3, *J* 7.4, $^3J_{H-F}$ 4.7, ^4J 1.2, H-3), 2.64-2.60 (2H, m, H-7), 2.36-2.42 (1H, m, H-6_a), 2.10-1.90 (2H, m, H-6_a and H-8_a), 1.81-1.70 (1H, m, H-8_b), 0.93 (9H, s, CH_3); δ_C (100 MHz, $CDCl_3$, 323 K) 201.3 (t, $^2J_{C-F}$ 25.5, C-1), 132.6, 130.5, 130.4, 117.5, (t, $^1J_{C-F}$ 255.0, C-2), 68.6 (dd, $^2J_{C-F}$ 24.0, 20.3, C-3), 36.5, 27.2, 26.7, 25.6 (C x 3), 18.3; δ_F (376 MHz, $CDCl_3$, 323 K) -111.9 (1F, d, $^2J_{F-F}$ 237.7), -132.9 (1F, dd, $^2J_{F-F}$ 237.7, $^3J_{F-H}$ 19.3).

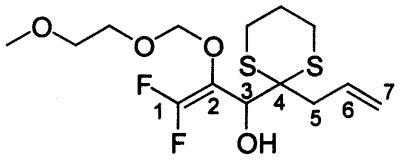
Preparation of 5-allyl-1,3-dithiane-5-carbaldehyde 183



n-BuLi (41.7 mL of 2.4 M solution in hexane, 0.1 mol) was added dropwise to a cold (-30 °C) solution of 1,3-ethanedithiol (12 g, 0.1 mol) in THF (200 mL) over 30 min under nitrogen. The solution was stirred at this temperature for 1 h. Then, dry DMF (31.0 mL, 0.4 mol) in THF (50 mL) was added to the reaction at -30 °C. The reaction mixture was stirred at 0 °C for 8 h. Allyl bromide was added in one portion to the resulting white suspension at 0 °C and stirred at the same temperature for over night. The reaction mixture was poured into ice-cold water (250 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic extracts were washed with 2 M HCl (2 x 200 mL), 10% NaOH aq (2 x 200 mL) and water (2 x 200 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to leave a pale yellow oil. Distillation afforded aldehyde **183** (4.3 g, 23%); δ_H (300 MHz, $CDCl_3$) 9.02 (1H, s, H-1), 5.81-5.67 (1H, m, H-4), 5.17-5.11 (2H, m, H-5), 3.01-2.91 (2H, m, H-3), 2.58-2.50 (4H, m, H-6, H-8), 2.01-1.99 (1H, m, H-7_a), 1.81-1.65 (1H, m, H-7_b).

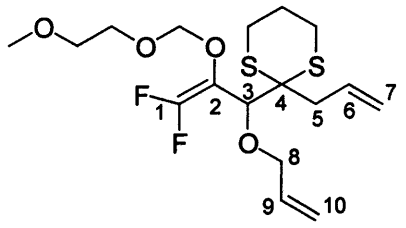
Spectral data were in agreement with those reported by Mathew *et al.*[82]

Preparation of 1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-[1,3]dithian-2-yl-hepta-1,6-dien-3-ol 184



n-BuLi (3.9 mL of 2.4 M solution in hexane, 9.3 mmol) was added dropwise to a cold (-78 °C) solution of di*iso*propylamine (1.4 mL, 9.7 mmol) in THF (10 mL) under nitrogen. The solution was allowed to warm to -30 °C and cooled again to -78 °C. Ether **163** (830 mg, 4.4 mmol) was added dropwise over 3 min to this freshly-made LDA solution. The reaction was stirred at this temperature for 15 min and then aldehyde **183** (1.0 g, 5.3 mmol) was added in one portion. The mixture was allowed to warm to -30 °C over 40 min, then quenched with NH_4Cl (10 mL of a saturated aqueous solution). Water (10 mL was added to the mixture which was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Purification by column chromatography (30% ethyl acetate in hexane) afforded alcohol **183** (1.1 g, 71%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.33; ν_{max}(film)/cm^{-1} 3436s, 2922s, 1750m, 1637w; δ_H (300 MHz, $CDCl_3$) 6.00 (1H, ddt, *J* 16.4, 9.7, 7.2, H-6), 5.20-5.09 (4H, m, OCH_2O, OH and H-7$_a$), 4.96-4.94 (1H, m, H-7$_b$), 4.68 (1H, dd, $^4J_{H\text{-}F}$ 3.8, 2.4, H-3), 3.94-3.81 (2H, m, OCH_2CH_2O), 3.59-3.56 (2H, m, OCH$_2$CH_2O), 3.39 (3H, s, CH_3), 3.04-2.84 (2H, m, SCH_aH$_b$), 2.77-2.50 (4H, m, SCH$_a$$H_b$ and H-5), 2.14-2.01 (1H, m, CH$_2$CH_aH$_b$CH$_2$), 1.91-1.74 (1H, m, CH$_2$CH$_a$$H_bCH_2$); δ_C (75 MHz, $CDCl_3$) 156.4 (t, $^1J_{C\text{-}F}$ 287.3, C-1), 133.1, 118.5, 113.5 (dd, $^2J_{C\text{-}F}$ 33.0, 14.3, C-2), 98.9, 71.6, 68.8, 68.3, 59.1, 53.7, 40.5, 26.3, 25.7, 24.1; δ_F (282 MHz, $CDCl_3$) -96.1 (d, $^2J_{F\text{-}F}$ 57.8), -104.4 (dd, $^2J_{F\text{-}F}$ 57.8, $^4J_{F\text{-}H}$ 3.8); [HRMS EI, [M]$^+$] Found: 356.09276. Calc. For $C_{14}H_{22}O_4F_2S_2$ 356.09280); *m/z* (ES) 379 (30, [M+Na]$^+$), 251 (100%, [M-OMEM]$^+$).

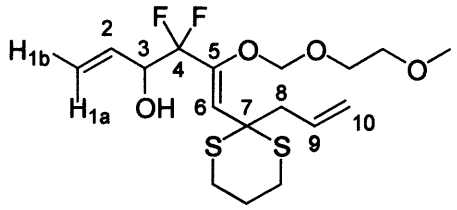
Preparation of 3-allyloxy-1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-[1,3]-dithian-2-yl-hepta-1,6-diene 185



Allyl bromide (130 μL, 1.5 mmol) and tetrabutylammonium iodide (14.1 mg, 0.04 mmol,) were added to stirred cold (0 °C) NaOH (0.5 mL of a 50% w/v of aqueous solution, 9.6 mmol). Allyl alcohol **184** (500 mg, 1.4 mmol) and tetrabutylammonium hydrogensulfate (23.8 mg, 0.07 mmol) were added to the solution at this temperature. The reaction mixture was stirred at 0 °C for 20 h, then the mixture was diluted with water (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave allyl ether **185** (386 mg, 70%, 100% by GC-MS) as a pale yellow oil. Material is taken on without purification; R_f (20% diethyl ether in hexane) 0.36; ν_{max}(film)/cm^{-1} 2920w, 1742m, 1637w; δ_H (300 MHz, $CDCl_3$) 6.08-5.86 (2H, m, H-6 and H-9), 5.39 (1H, dq, *J* 17.2, ^2J 1.4, ^4J 1.4, H-10_a), 5.22 (1H, br. dq, *J* 10.5, ^2J 1.4, ^4J 1.4, H-10_b), 5.15-5.11 (1H, m, H7_a), 5.10-5.05 (2H, m [including 5.06, (1H, d, ^2J 6.0, OC$H_a$$H_b$O), H$7_b$]), 4.95 (1H, br d, ^2J 6.0, OC$H_a$$H_b$O), 4.37 (1H, dd, $^4J_{H\text{-}F}$ 3.2, 2.0, H-3), 4.20 (1H, ddt, ^2J 12.6, *J* 5.1, ^4J 1.2, OC$H_a$$H_b$), 3.96-3.87 (2H, m, OCH_2CH_2O), 3.77 (1H, ddd, ^2J 12.6, 5.4, ^4J 3.9, OCH_aH_b), 3.57-3.56 (2H, m, OCH_2CH_2O), 3.38 (3H, s, CH_3), 3.00-2.84 (2H, m, SC$H_a$$CH_b$), 2.82-2.78 (1H, br d, ^2J 7.2, H-8_a), 2.76-2.64 (3H, m, SCH_aH_b and H-8_b), 2.07-1.79 (2H, m, H-5); δ_c (75 MHz, $CDCl_3$) 157.1 (dd, $^1J_{C\text{-}F}$ 293.3, 285.0, C-1), 133.9, 133.5, 118.5, 118.1, 111.3 (dd, $^2J_{C\text{-}F}$ 33.8, 12.0, C-2), 97.7, 77.9 (t, $^3J_{C\text{-}F}$ 3.0, C-3), 71.6, 70.7, 68.5, 59.7, 55.4, 40.7, 26.6, 26.5, 24.4; δ_F (282 MHz, $CDCl_3$) -95.1 (dd, $^2J_{F\text{-}F}$ 58.3, $^4J_{F\text{-}H}$ 1.9), -106.0 (d, $^2J_{F\text{-}F}$ 58.3); [HRMS EI, M^+] Found: 396.12406. Calc.

For $C_{17}H_{26}O_4F_2S_2$ 396.12408); *m/z* (EI) 159 (100%, $[C(SCH_2CH_2CH_2S)CH_2CHCH_2]^+$)396 (5, $[M]^+$).

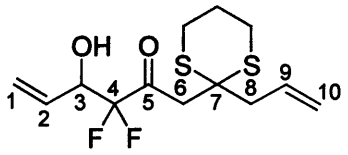
Preparation of 4,4-difluoro-7-([1.3]dithian-2-yl)-5-(2'-methoxy-ethoxymethoxy)-deca-1,5,9-trien-3-ol 186



A solution of allyl ether **185** (2.0 g, 5.1 mmol) in THF (5 mL) was added dropwise to a cold (-78 °C) solution of LDA (prepared from *n*-BuLi (5.6 mL of a 1.9 M solution in hexane, 10.6 mmol), di*iso*propylamine (1.6 mL, 11.1 mol) and THF (10 mL) under a nitrogen atmosphere). After stirring for 2 at –78 °C, the solution was warmed to -30 °C over 1.5 h and stirred at this temperature for 20 h. The reaction mixture was quenched with NH_4Cl (20 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (20 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave allylic alcohol **194** (1.3 g) as a yellow oil. Purification by column chromatography (20% ethyl acetate in hexane) afforded allylic alcohol **186** (519 mg, 30%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.20; ν_{max}(film)/cm^{-1} 3405 br. w, 2920w, 1658w; δ_H (300 MHz, $CDCl_3$) 6.07-5.87 (2H, m, H-2 and H-9), 5.30 (1H, dt, *J* 17.2, *J* 1.5, H-1_a), 5.22 (1H, dt, *J* 10.2, *J* 1.2, H-1_b), 5.15-5.06 (3H, m, OCH_2O and H-10_a), 4.96-4.94 (1H, m, H-10_b), 4.36 (1H, dd, $^4J_{H\text{-}F}$ 3.4, 2.0, H-6), 4.19 (1H, ddt, *J* 12.6, $^3J_{H\text{-}F}$ 5.0, ^4J 1.5, H-3), 3.97-3.86 (2H, m, $OCH_aH_bCH_2O$ and OH), 3.81-3.74 (1H, m, $OCH_2CH_aH_bO$), 3.57-3.54 (2H, m, OCH_2CH_2O), 3.37 (3H, s, CH_3), 3.00-2.65 (6H, m, H-8 and $SCH_2CH_2CH_2S$), 2.05-1.78 (2H, m, $SCH_2CH_2CH_2S$); δ_C (75 MHz, $CDCl_3$) 157.1 (dd, $^1J_{C\text{-}F}$ 292.5, 285.0,

C-4), 134.0, 133.5, 118.4, 118.0, 111.4 (dd, $^2J_{C\text{-}F}$ 33.0, 11.3, C-5), 96.7, 78.2 (t, $^2J_{C\text{-}F}$ 3.5, C-3), 71.6, 70.8, 68.5, 59.1, 55.5, 40.8, 26.6, 26.5, 24.3; δ_C (75 MHz, $CDCl_3$) -95.3 (dd, $^2J_{F\text{-}F}$ 57.8, $^4J_{F\text{-}H}$ 1.9), -106.0 (d, $^2J_{F\text{-}F}$ 57.8); [HRMS EI, $[M]^+$] Found: 396.12406. Calc. For $C_{17}H_{26}O_4F_2S_2$ 396.12412); *m/z* (EI) 159 (100%, $[C(SCH_2CH_2CH_2S)CH_2CHCH_2]^+$), 396 (1, $[M]^+$).

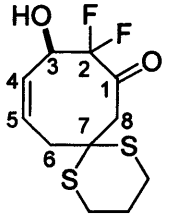
Preparation of 4,4-difluoro-7-([1,3]dithian-2-yl)-3-hydroxy-deca-1,9-diene-5-one 187



Thionyl chloride (18 µL, 0.25 mmol) was added dropwise to a solution of enol ether **186** (100 mg, 0.25 mmol) in MeOH (2.5 mL) at 0 °C. The reaction mixture was stirred at this temperature for 20 h. The mixture was concentrated *in vacuo*, diluted with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Purification by column chromatography (20% ethyl acetate in hexane) afforded diene **187** (60 mg, 76%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.29; ν_{max}(film)/cm^{-1} 3400 br. w, 2922w, 1659w; δ_H (300 MHz, $CDCl_3$) 5.96-5.78 (2H, m, H-2 and H-9), 5.50 (1H, dt, *J* 17.2, ^2J 1.5, ^4J 1.5, H-1_a), 5.42 (1H, dt, *J* 10.5, ^2J 1.5, ^4J 1.5, H-1_b), 5.18-5.01 (2H, m, H-10), 4.61-4.52 (1H, m, H-3), 3.42-3.38 (2H, m, H-6), 2.97-2.86 (4H, m, H-8 and SCH_aCH_b), 2.82-2.73 (2H, m, SCH_aCH_b), 2.64 (1H, br s, OH), 2.09-1.98 (1H, m, $CH_2CH_aH_bCH_2$), 1.96-1.83 (1H, m, $CH_2CH_aH_bCH_2$); δ_C (75 MHz, $CDCl_3$) 197.2 (dd, $^2J_{C\text{-}F}$ 30.8, 27.8, C-5), 131.8, 130.9, 120.6, 119.8, 114.4 (dd, $^1J_{C\text{-}F}$ 260.3, 256.5, C-4), 72.0 (dd, $^2J_{C\text{-}F}$ 28.5, 25.5, C-3), 49.0, 43.9, 42.6, 26.3 (C x 2), 24.8; δ_F (75 MHz, $CDCl_3$) -113.1 ($^2J_{F\text{-}F}$ 273.0, $^3J_{F\text{-}H}$ 7.1),

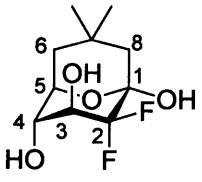
-123.0 ($^2J_{F-F}$ 273.0, $^3J_{F-H}$15.6); [HRMS EI, $[M]^+$] Found: 308.12240. Calc. For $C_{13}H_{18}O_2F_2S_2$ 308.12242); *m/z* (EI) 308 (37%, $[M]^+$), 267 (100, $[M-CH_2CHCH_2]$).

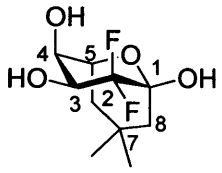
Attempted preparation of 2,2-difluoro-7-[1,3]dithian-3-hydroxy-cyclooct-4-enone 188



A solution of diene **187** (75 mg, 0.24 mmol) and titanium(IV) *iso*propoxide (21 µL, 0.072 mmol) in toluene (24 mL) was refluxed for 30 min. 2nd Generation Grubbs' catalyst **87** (10 mg, 0.012 mmol) was added as a solution in toluene (1 mL) and the reaction mixture was refluxed for 24 h. Additional 2nd Generation Grubbs' catalyst **87** (10 mg, 0.012 mmol) was added and refluxed for 48 h. However the desired product was not obtained.

Preparation of 2,2-difluoro-7,7-dimethyl-9-oxa-bicyclo[3.3.1]nona-1,3,4-triols 206 and 208

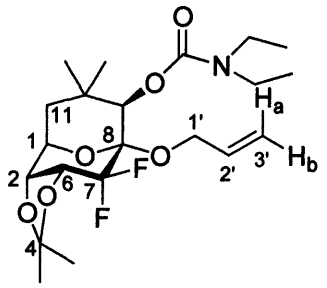




A solution of *N*-methylmorpholine-*N*-oxide (231 mg, 1.5 mmol) in water (0.1 mL) was added to a cold (0 °C) solution of dimethyl alkene **171** (154 mg, 0.75 mmol) in acetone (1.5 mL) and *tert*-butanol (1.5 mL). The mixture was stirred for 10 min and a 2.5 wt. % solution of osmium tetroxide in *tert*-butanol (188 µL, 0.02 mmol) was added. The reaction mixture was stirred at 0 °C for 48 h, quenched with sodium sulfite (400 mg, 3.75 mmol), allowed to warm up to room temperature and stirred at this

temperature for 30 min. The resulting mixture was dissolved in water (2 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave triols **206** and **208** as a diastereoisomeric mixture (1:1) as a white solid (98.2 mg). Purification by column chromatography (50% ethyl acetate in light petroleum) allowed the separation of the two diastereoisomers, however the some diastereoisomers were still remained as a mixture. Diastereoisomer **208**; R_f (40% ethyl acetate in light petroleum) 0.16; Mp 143-145 °C; (Found C, 50.24, H, 6.75; $C_{10}H_{16}F_2O_4$ requires: 50.42, H, 6.77%); ν_{max} (solid)/cm^{-1} 3453s br, 3286s, 3196s br, 2954s; δ_H (300 MHz, DMSO-d_6) 6.46 (1H, br s, OH), 6.15 (1H, d, *J* 5.3, OH), 4.95 (1H, d, *J* 3.5, OH), 4.18-4.10 (1H, m, H-5), 3.99-3.81 (1H, m, H-3), 3.51 (1H, br. s, H-4), 2.55-2.51 (1H, m, H-8), 2.24-2.14 (1H, m, H-8), 1.72-1.50 (2H, m, H-6), 1.01 (3H, s, CH_3), 0.82 (3H, s, CH_3); δ_c (75 MHz, DMSO-d_6) 116.3 (t, $^1J_{C\text{-}F}$ 258.0), 92.3 (dd, $^2J_{C\text{-}F}$ 27.0, 20.3), 73.4 (t, $^2J_{C\text{-}F}$ 17.3), 73.2, 41.1, 34.1, 32.2, 29.9, 29.1; δ_F (282 MHz, DMSO-d_6) -115.2 (dd, $J_{F\text{-}F}$ 245.7, $^3J_{F\text{-}H}$ 12.3), -123.1 (d, $^2J_{F\text{-}F}$ 245.7); *m/z* (ES) 237 (63%, M-H). Diastereoisomer **206**; R_f (40% ethyl acetate in light petroleum) 0.22; Mp 123-125 °C; (Found C, 50.43; H, 6.61; $C_{10}H_{16}F_2O_4$ requires: C, 50.42; H, 6.77%); ν_{max} (solid)/cm^{-1} 3454s br., 2954s; δ_H (300 MHz, DMSO-d_6) 6.53 (1H, br s, OH), 5.05 (1H, d, *J* 8.7, OH), 4.75 (1H, d, *J* 4.1, OH), 4.24-4.10 (2H, m, H-5, H-3), 3.57-3.53 (1H, m, H-4), 1.73 (1H, dd ^2J 12.5, *J* 2.6, H-6), 1.66-1.50 (2H, m, H-8), 1.01 (3H, s, CH_3), 1.10 (1H, dd, ^2J 12.5, ^4J 5.6, H-6), 0.82 (3H, s, CH_3); δ_c (75 MHz, Acetone-d_6) 119.4 (t, $^1J_{C\text{-}F}$ 252.8), 94.8 (dd, $^2J_{C\text{-}F}$ 24.8, 21.0), 73.9, 72.6, 66.4 (t, $^2J_{C\text{-}F}$ 18.8), 42.9, 35.4, 32.5, 29.4(C x 2); δ_F (282 MHz, DMSO-d_6) -123.4 (d, $J_{F\text{-}F}$ 234.1), -130.5 (dd, $J_{F\text{-}F}$ 234.1, $^3J_{H\text{-}F}$ 22.6); *m/z* (ES) 238 (100%, M^+).

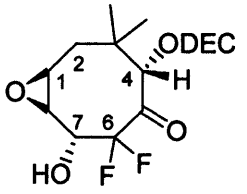
Preparation of 9-(*N,N*-diethylcarbamoyloxy)-8-allyloxy-7,7-difluoro-4,4,10,10-tetramethyl-3,5,12-trioxa-tricyclo[6.3.1.$0^{2,6}$]dodec-9-yl-ester 214



Allyl bromide (27 μL, 0.3 mmol) and tetrabutylammonium iodide (43 mg, 0.01 mmol) were added to stirred cold (0 °C) NaOH (1 mL of a 50 %w/v of solution, 1.8 mmol). Allyl alcohol **213** (100 mg, 0.25 mmol) and tetrabutylammonium hydrogensulfate (337 mg, 1.0 mmol) were added to the solution at this temperature. The reaction mixture was stirred at 0 °C for 72hours, then the mixture was diluted with water (2 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave allylic ether **214** (108 mg, 100%, 100% by GC-MS) as a white sold; R_f (15% ethyl acetate in light petroleum) 0.27; Mp 106–107 °C; (Found C, 58.09; H, 7.73; N, 3.17. $C_{21}H_{33}F_2NO_6$ requires: C, 58.19; H, 7.67; N, 3.23%); ν_{max} (solid)/cm^{-1} 2969m, 2938m, 2887m, 1687s, 1650m; δ_H (300 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 17.3, 10.5, 5.1, H-2'), 5.22 (1H, dq, *J* 17.3, 1.8, H-3'$_a$), 5.01 (1H, dq, *J* 10.5,1.8, H-3'$_b$), 4.75 (1H, d, $^4J_{H-F}$ 1.2, H-9), 4.61 (1H, ddd, $^3J_{H-F}$ 12.3, 10.5, *J* 5.4, H-6), 4.53 (1H, br. dd, *J* 11.5, 4.2, H-1), 4.42 (1H, ddq, ^2J 13.2, *J* 5.0, $^4J_{H-F}$ 1.8, H-1'$_a$), 4.33 (1H, ddq, ^2J 13.2, *J* 5.0, $^4J_{H-F}$ 1.8, H-1'$_b$), 4.02–3.99 (1H, m, H-2), 3.42–3.12 (4H, m, –NCH_2), 2.11 (1H, dd, ^2J 14.3, *J* 11.5, H-11$_a$), 1.50 (3H, s, CH_3), 1.30–1.22 (4H, env., CH_3 and H-11$_b$), 1.17 (3H, s, CH_3), 1.08-1.04 (6H, m, NCH_2CH_3), 0.88 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 154.0, 134.1, 115.9 (dd, $^1J_{C-F}$ 262.0, 257.3), 115.2, 109.9, 95.0 (dd, $^2J_{C-F}$ 26.3, 19.1), 79.2 (d, $^3J_{C-F}$ 6.8), 73.0 (dd, $^2J_{C-F}$ 23.5, 19.8), 74.0, 66.5, 64.3, 41.2, 40.3, 38.3, 33.7, 28.9, 25.8, 25.7, 22.9, 14.2,

13.4 ; δ_F (282 MHz, $CDCl_3$) -117.2 (1F, dd, ^2J 246.3, $^3J_{F-H}$ 10.5), -119.5 (1F, dd, ^2J 246.3, $^3J_{F-H}$ 12.3) ; *m/z* (EI) 434 (100%, [M+H]).

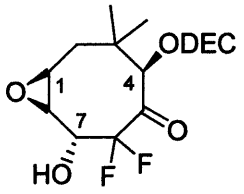
Preparation of 4-(*N,N*-diethylcarbamoyloxy)-6,6-difluoro-7-hydroxy-3,3-dimethyl-9-oxa-bicyclo[6.1.0]non-5-ones 219



Aqueous Na_2.EDTA (22.8 mL of a 4 x 10^{-4} M aqueous solution) was added to a solution of *cis*-cyclooctenone **162** (1.8 g, 5.7 mmol) in acetonitrile (57 mL). The solution was cooled with an ice bath and trifluoroacetone (11.4 mL of a 60% aqueous solution) was added *via* pre-cooled syringe. Sodium bicarbonate (7.4 g, 88.4 mmol) and oxone (17.5 g, 28.5 mmol) were added together in a single portion and the reaction was stirred at 0 °C for 6 h. The solid was removed by filtration and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford epoxide **219** (1.9 g, 98%) as a white solid which required no further purification: R_f (10% ethyl acetate in light petroleum) 0.16; Mp 140-142 °C; (Found C, 53.88; H, 6.78; N, 4.25; $C_{15}H_{23}F_2NO_5$ requires: C, 53.72; H, 6.91; N, 4.18%) ν_{max} (solid)/cm^{-1} 3328s br, 2981s, 2934m, 1746s, 1682s; δ_H (376 MHz, $CDCl_3$, 323 K) 5.04 (1H, d, $^4J_{H-F}$ 1.8, H-4), 4.00 (1H, dt, $^3J_{H-F}$ 19.2, *J* 7.7, H-7), 3.35-3.30 (4H, m, -N(CH_2CH_3)$_2$), 3.12-3.02 (3H, m, H-1, H-8, OH), 2.22 (1H, dd, ^2J 15.0, *J* 4.2, H-2_a), 1.38-1.30 (1H, m, H-2_b), 1.26-1.12 (12H, m, -N(CH_2CH_3)$_2$, CH_3 x 2); δ_C (63 MHz, $CDCl_3$) 196.5 (t, $^2J_{C-F}$ 21.9), 154.9, 115.9 (t, $^1J_{C-F}$ 259.4), 70.0 (dd, $^2J_{C-F}$ 21.6, 16.5), 55.6, 55.4, 52.9, 42.7, 42.0, 39.9, 39.3, 39.2, 30.0, 14.4, 13.6; δ_F (235 MHz, $CDCl_3$, 223 K) major conformer: -106.2 (1F, dd, $^2J_{F-F}$ 247.6, $^3J_{F-H}$ 5.3), -129.1 (1F, dd, $^2J_{F-F}$ 247.6, $^3J_{F-H}$19.1), minor

conformer: -108.4 (1F, d, $^2J_{F-F}$ 252.7), -123.1 (1F, dd, $^2J_{F-F}$ 252.7, $^3J_{F-H}$ 26.4); coalescence was achieved at 323 K. *m/z* (ES) 336 (100%, $[M+H]^+$).

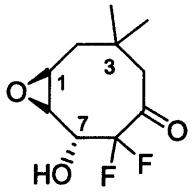
Preparation of 4-(*N,N*-diethylcarbamoyloxy)-6,6-difluoro-7-hydroxy-3,3-dimethyl-9-oxa-bicyclo[6.1.0]non-5-ones 221



Aqueous Na_2.EDTA (12.3 mL of a 4 x 10^{-4} M aqueous solution) was added to a solution of *trans*-cyclooctenone **163** (1.0 g, 3.1 mmol) in acetonitrile (30 mL). The solution was cooled with an ice bath and trifluoroacetone (6.3 mL of a 60% aqueous solution) was added *via* pre-cooled syringe. Sodium bicarbonate (4.1 g, 48.6 mmol) and oxone (9.6 g, 15.7 mmol) were added together in a single portion and the reaction mixture was stirred at 0°C for 3 hours. The solid was removed by filtration and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford epoxide **221** (93 mg, 90%) as a white solid which required no further purification; R_f (40% ethyl acetate in light petroleum) 0.16; Mp 129-132 °C; (Found C, 53.82; H, 6.84; N, 4.10; $C_{15}H_{23}F_2NO_5$ requires: C, 53.72; H, 6.91; N, 4.18%); ν_{max} (solid)/cm-1 3328s br, 2981s, 2934m, 1746s, 1682s; δ_H (400 MHz, Acetone-d_6, 256 K) major conformer 5.04 (1H, br d, *J* 2.3, H-4), 4.22 (1H, ddd, $^3J_{H-F}$ 20.7, $^3J_{H-F}$ 16.0, *J* 8.0, H-7), 3.34 (4H, m, $N(CH_2CH_3)_2$), 3.07 (1H, ddd, *J* 10.2, *J* 9.3, *J* 4.6, H-1), 2.87 (1H, dd, *J* 9.3, *J* 8.0, H-8), 2.08 (1H, m, H-2_a), 1.59 (1H, dd, *J* 14.5, *J* 4.6, H-2_b), 1.06 (12H, m, $N(CH_2CH_3)_2$ and 2 x CH_3); δ_F (376.5 MHz, Acetone-d_6, 256 K) major conformer -113.6 (d, $^2J_{F-F}$ 247.4), -122.9 (dd, $^2J_{F-F}$ 247.4, $^3J_{H-F}$ 28.2), minor conformer -107.3 (d, $^2J_{F-F}$ 259.8), -126.1 (dd, $^2J_{F-F}$ 259.8, $^3J_{H-F}$ 20.1); δ_C (100 MHz, Acetone-d_6, 256 K) major conformer 196.0 (t, $^2J_{C-F}$ 23.9), 153.9, 115.6 (t, $^1J_{C-F}$ 257.2), 82.8, 70.0, 56.8,

52.4, 41.9, 41.5, 39.8, 37.7, 25.8, 22.1, 13.8, 13.1; minor conformer 198.6 (dd, $^{2}J_{C\text{-}F}$ 27.8, $^{2}J_{C\text{-}F}$ 5.6), 153.9, 116.3 (t, $^{1}J_{C\text{-}F}$ 260.5), 75.7, 68.9, 54.7, 50.8, 41.9, 41.0, 38.0, 35.9, 22.8, 13.9, 13.0, 12.6;*m/z* (ES) 336 (100 %, $[M+H]^{+}$).

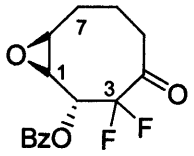
Preparation of 6,6-difluoro-7-hydroxy-3,3-dimethyl-9-oxa-bicyclo[6.1.0]non-5-ones 222



Aqueous Na_2.EDTA (9.4 mL of a 4 x 10^{-4} M aqueous solution) was added to a solution of cyclooctenone **171** (478.5 mg, 2.35 mmol) in acetonitrile (24 mL). The solution was cooled with an ice bath and trifluoroacetone (4.6 mL of a 60% aqueous solution) was added *via* pre-cooled syringe. Sodium bicarbonate (3.1 g, 35.4 mmol) and Oxone (7.2 g, 11.7 mmol) were added together in a single portion and the reaction mixture was stirred at 0 °C for 18 h. The solid was removed by filtration and the aqueous phase was extracted with dichloromethane (3 x 30mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford epoxide **222** (325.4 mg, 63%) as a white solid which required no further purification: R_f (20% ethyl acetate in light petroleum) 0.33; Mp 75-76 °C; (Found C, 54.76; H, 6.62; $C_{10}H_{14}F_2O_3$ requires: C, 54.54; H, 6.41%); ν_{max} (solid)/cm^{-1} 3328s br, 2981s, 2934m, 1746s; δ_H (300 MHz, $CDCl_3$) 5.95-5.85 (1H, m, H-1), 5.67-5.59 (1H, m, H-8), 4.86-4.76 (1H, m, H-7), 2.66-2.59 (1H, m, H-2_a), 2.37-2.33 (1H, m, H-2_b), 2.04-1.92 (2H, m, H-4), 1.14 (3H, s, CH_3), 1.04 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 198.5 (t, $^{2}J_{C\text{-}F}$ 25.7), 131.8, 129.3 (d, $^{3}J_{C\text{-}F}$ 3.3), 117.3 (t, $^{1}J_{C\text{-}F}$ 258.2), 68.1 (t, $^{2}J_{C\text{-}F}$ 21.6, 16.5), 47.6, 40.2, 37.7, 30.7, 26.9; δ_F (376 MHz, $CDCl_3$, 223 K) major conformer: -115.3 (1F, d, $^{2}J_{F\text{-}F}$ 228.9), -128.7 (1F, dd, $^{2}J_{F\text{-}F}$ 228.9, $^{3}J_{F\text{-}H}$ 26.9), minor conformer: -107.9 (1F, d,

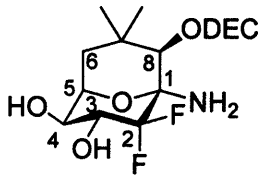
$^2J_{F\text{-}F}$ 240.2), -135.8 (1F, dd, $^2J_{F\text{-}F}$ 240.2, $^3J_{F\text{-}H}$18.6); [HRMS EI, $[M]^+$] Found: 220.09115. Calc. For $C_{10}H_{14}O_3F_2$ 220.09110); *m/z* (EI) 219 (20%, $[M]^-$).

Preparation of 3,3-difluoro-2-benzoyloxy-9-oxa-bicyclo[6.1.0]non-4-ones 223



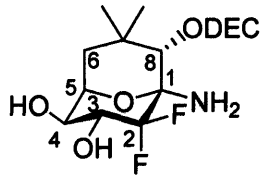
Aqueous Na_2.EDTA (9.4 mL of a 4 x 10^{-4} M aqueous solution) was added to a solution of cyclooctenone **180** (28.7 mg, 0.1 mmol) in acetonitrile (1 mL). The solution was cooled with an ice bath and trifluoroacetone (0.4 mL of a 60% aqueous solution) was added *via* pre-cooled syringe. Sodium bicarbonate (134 mg, 1.6 mmol) and Oxone (315 mg, 0.5 mmol) were added together in a single portion and the reaction mixture was stirred at 0 °C for 2 h. The solid was removed by filtration and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford epoxide **223** (30.2 mg) as a white solid. Purification by column chromatography (30% diethyl ether in light petroleum) afforded the epoxide **223** (24.4 mg, 80%) as a white solid ; Mp 74-76 °C; R_f (30 % diethyl ether in light petroleum) 0.35; ν_{max}(film)/cm^{-1} 2868s, 1736m; δ_H (300 MHz, $CDCl_3$) 8.12-8.02 (2H, m, Ph-H), 7.53-7.47 (1H, m, Ph-H), 7.45-7.37 (2H, m, Ph-H), 5.52 (1H, ddd, $^3J_{H\text{-}F}$ 21.0, *J* 9.0, $^3J_{H\text{-}F}$ 4.5, H-2), 3.17 (1H, ddt, *J* 9.0, 4.2, ^4J 1.2, H-8), 2.98 (1H, dt, *J* 10.5, 4.2, H-1), 2.82-2.64 (2H, m, H-5), 2.44-2.40 (1H, m, H-7_a), 2.18-2.02 (2H, m, H-7_b, H-6_a), 1.38-1.22 (1H, m, H-6_b); δ_C (75 MHz, $CDCl_3$) 199.9 (t, $^2J_{C\text{-}F}$ 24.8, C-1), 165.0, 133.8, 130.0 (C x 2), 128.7 (C x 2), 114.3 (t, $^1J_{C\text{-}F}$ 258.8, C-2), 69.9 (dd, $^2J_{C\text{-}F}$ 23.3, 18.8, C-3), 54.8, 53.0, 36.1, 28.5, 24.3; δ_F (282 MHz, $CDCl_3$) -113.6 (1F, d, $^2J_{F\text{-}F}$ 247.0), -127.8 (1F, dd, $^2J_{F\text{-}F}$ 247.0, $^3J_{F\text{-}H}$ 21.0); [HRMS (EI, $[M+H]^+$) Found: 296.08602. Calc. For $C_{15}H_{14}O_4F_2$ 296.08601]; *m/z* (EI) 296 (4%, $[M]^+$).

Preparation of Diethyl carbamic acid 1-amino-2,2-difluoro-3,4-dihydroxy-7,7-dimethyl-9-oxa-bicyclo[3.3.1]non-2-yl ester 232



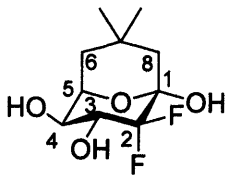
A solution of epoxide **221** (0.2 mmol, 67 mg) in ammonia (2 mL of a 35% aqueous solution) was irradiated for 10min at 30 W microwave power and 100 °C in a sealed vial within the cavity of a CEM Discovery instrument. The solution was evaporated to dryness *in vacuo* to afford a yellow solid which was purified by column chromatography to yield **232** (52.8 mg, 78%) as a white solid; mp 154-155 °C, R_f (80% ethyl acetate in hexane) 0.26; (Found C, 51.19, H, 7.30, N, 7.88%; $C_{15}H_{26}F_2N_2O_5$ requires: C, 51.13; H, 7.44; N, 7.95 %); ν_{max} (solid)/cm^{-1} 3316s br, 2937s, 2979s, 1698s, 1427m, 1271m, 1165m, 1063s, 1034s; δ_H (300 MHz, MeOD) 4.74 (1H, br s, H-8), 4.10-3.97 (1H, m, H-5), 3.96-3.80 (1H, m, H-4), 3.59-3.55 (1H, m, H-3), 3.31-3.22 (4H, m, (CON(CH_2CH_3)$_2$), 1.68-1.51 (2H, m, H-6), 1.21 (3H, s, CH_3), 1.10-1.00 (6H, m, (CON(CH_2CH_3)$_2$), 0.86 (3H, s, CH_3); δ_C (75 MHz, MeOD) 156.3, 86.4, 73.2 (d, $^3J_{C\text{-}F}$ 6.8), 70.6 (t, $^2J_{C\text{-}F}$ 19.5), 69.4, 49.9, 43.3, 42.4, 35.1, 29.8, 23.2, 14.7, 13.6; δ_F (282 MHz, MeOD) –122.4 (1F, dd, $^2J_{F\text{-}F}$ 243.7, $^3J_{F\text{-}H}$ 5.7), –139.1 (1F, dd, $^2J_{F\text{-}F}$ 243.7, $^3J_{F\text{-}H}$ 20.9); [HRMS (FAB, M^+) Found: 353.18880. Calc. For $C_{15}H_{27}N_2O_5F_2$ 353.18880]; *m/z* (FAB) 353 (70% M^+); *m/z* (ES) 353 (100% M^+).

Preparation of diethyl carbamic acid 1-amino-2,2-difluoro-3,4-dihydroxy-7,7-dimethyl-9-oxa-bicyclo[3.3.1]non-2-yl ester 231



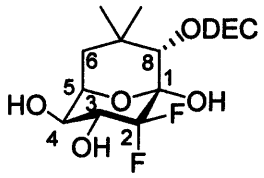
A solution of the epoxide **219** (34 mg, 0.1 mmol) in ammonia (1 mL of a 35% aqueous solution) was irradiated for 10 min at 30 W microwave power and 100 °C in a sealed vial within the cavity of a CEM Discovery instrument. The solution was evaporated to dryness *in vacuo* to afford a yellow solid which was purified by column chromatography to yield **231** (49.2 mg, 70%) as a white solid; mp 146-148 °C, R_f 0.26 (80% ethyl acetate in hexane); (Found C, 50.99, H, 7.47, N, 7.82%; $C_{15}H_{26}F_2N_2O_5$ requires: C, 51.13; H, 7.44; N, 7.95%); ν_{max} (solid)/cm^{-1} 3376m, 3288m, 3117w br, 2963m, 2938m, 2880m, 1685s, 1596m, 1429m, 1277s, 1165s, 117m, 1062, 1037s, 1005s, 986s; δ_H (300 MHz, MeOD) 4.74 (1H, br s, H-8), 4.19-3.97 (2H, m, H-5, H-4), 3.76-3.65 (1H, m, H-3), 3.36-3.15 (4H, m, (CON(CH_2CH$_3$)$_2$), 1.69-1.48 (2H, m, H-6), 1.27 (3H, s, CH$_3$), 1.12-1.00 (6H, m, (CON(CH$_2$CH_3)$_2$), 0.86 (3H, s, CH$_3$); δ_C (75 MHz, $CDCl_3$) 156.7, 119.8 (dd, $^1J_{C\text{-}F}$ 263.3, 244.1), 86.4 (t, $^2J_{C\text{-}F}$ 20.9), 81.0, 73.2 (d, $^3J_{C\text{-}F}$ 6.0), 71.6 (dd, $^2J_{C\text{-}F}$ 20.3, 18.0), 70.4, 43.3, 42.2, 35.1, 29.8, 28.7, 27.2, 14.5, 13.5; δ_F (282 MHz, MeOD) –119.5 (1F, d, $^2J_{F\text{-}F}$ 249.3), –129.1 (1F, d, $^2J_{F\text{-}F}$ 249.3, $^3J_{F\text{-}H}$ 22.8); [HRMS (EI, [M]$^+$) Found: 353.18883. Calc. For $C_{15}H_{27}N_2O_5F_2$ 353.18880]; *m/z* (ES) 353 (100%, [M]$^+$).

Preparation of 2,2-Difluoro-7,7-dimethyl-9-oxo-bicyclo[3.3.1]nonane-1,3,4 –triol 233



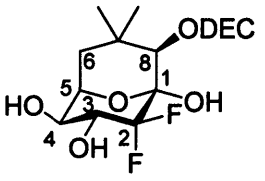
The epoxide **222** (44 mg, 0.2 mmol) in a solution of *N*-methylimidazole (0.4 mL) and water (3.6 mL) was irradiated for 10 min at 30 W microwave power and 100 °C in a sealed vial within the cavity of a CEM Discovery instrument. The solution was washed with cold 2 M HCl solution (2 x 4 mL). The acid solution was extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (38mg) which was purified by column chromatography to yield **233** (33.7 mg, 71%) as a white solid; mp 147-149 °C; R_f (60% ethyl acetate in hexane) 0.36; (Found C, 50.46; H, 6.90%; $C_{10}H_{16}F_2O_4$ requires: C, 50.42; H, 6.77%); ν_{max} (solid)/cm^{-1} 3405s br, 2993m, 2966m, 2931m; δ_H (300 MHz, Acetone-d_6) 4.26 (1H, ddt, *J* 11.7, 5.5, 1.5, H-5), 3.94 (1H, ddd, $^3J_{H\text{-}F}$ 20.4, *J* 9.6, $^3J_{H\text{-}F}$ 5.5, H-3), 3.75 (1H, ddd, *J* 9.1, 5.8, 1.8, H-4), 1.63-1.49 (4H, m, H-6 and H-8), 1.19 (3H, s, CH_3), 0.98 (3H, s, CH_3); δ_C (75 MHz, DMSO-d_6) 118.6 (dd, $^1J_{C\text{-}F}$ 254.3, 250.5, C-2), 93.1 (t, $^2J_{C\text{-}F}$ 24.8, C-1), 70.6 (d, $^3J_{C\text{-}F}$ 6.8, C-5), 68.8 (t, $^2J_{C\text{-}F}$ 18.8, C-3), 68.4, 42.4, 32.2, 31.8, 29.7, 28.4; δ_F (282MHz, Acetone-d_6) -126.2 (1F, dd, $J_{F\text{-}F}$ 237.5, $^3J_{F\text{-}H}$ 5.5), -139.1 (1F, dd, $J_{F\text{-}F}$ 237.5, $^3J_{F\text{-}H}$ 20.4); *m/z* (ES) 237 (100% M^-).

Preparation of Diethyl-carbamic acid 2,2-difluoro-1,3,4-trihydroxy-7,7-dimethyl-1-oxo-bicyclo[3.3.1]non-8-yl ester 234



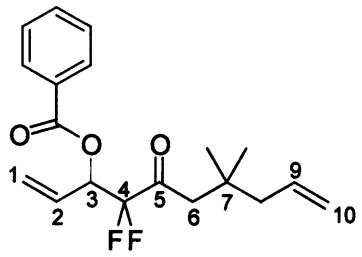
The epoxide **219** (34 mg, 0.1 mmol) in a solution of *N*-methylimidazole (0.2 mL) and water (1.8 mL) was irradiated for 10 min at 30 W microwave power and 100 °C in a sealed vial within the cavity of a CEM Discovery instrument. The solution was washed with cold 2 M HCl solution (2 x 4 mL). The acid solution was extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (38mg) which was purified by column chromatography to yield **234** (26.7 mg, 75%) as a white solid; Mp 149-150 °C; R_f (80% ethyl acetate in hexane) 0.33; (Found C, 50.85; H, 7.24; N, 3.92%; $C_{15}H_{25}F_2NO_6$ requires: C, 50.99; H, 7.13; N, 3.96%); ν_{max} (solid)/cm^{-1} 3289s br, 2923m, 1664s, 1429m, 1286m, 1061s, 1031s, 819m, 763m, 703m; δ_H (400 MHz, Acetone-d_6) 5.18 (1H, t, ^4J 2.4, H-8), 4.42-4.28 (2H, m, H-5, H-3), 3.93 (1H, ddd, *J* 9.0, 5.9, ^4J 1.6, H-4), 3.58-3.27 (4H, m, ($CON(CH_2CH_3)_2$), 1.81 (1H, dd, ^2J 14.3, *J* 5.7, H-6_a), 1.66 (1H, ddd, ^2J 14.4, *J* 11.0, ^4J 2.4, H-6_b), 1.37 (3H, s, CH_3), 1.28-1.15 (6H, m, ($CON(CH_2CH_3)_2$), 0.97 (3H, s, CH_3); δ_C (100 MHz, Acetone-d_6) 154.3, 118.1 (dd, $^1J_{C\text{-}F}$ 262.0 243.0), 95.8 (t, $^2J_{C\text{-}F}$ 21.5), 79.0, 72.1, 70.5 (d, $^2J_{C\text{-}F}$ 18.5), 68.9, 41.8, 40.6, 34.1, 28.8, 27.3, 25.9, 13.6, 12.7; δ_F (282 MHz, Acetone-d_6, 300 K) -121.8 (1F, d, $J_{F\text{-}F}$ 246.4), -129.4 (1F, dd, $J_{F\text{-}F}$ 246.4, $^3J_{F\text{-}H}$ 22.7); *m/z* (ES) 354 (100 % M^+).

Preparation of Diethyl-carbamic acid 2,2-difluoro-1,3,4-trihydroxy-7,7-dimethyl-1-oxo-bicyclo[3.3.1]non-8-yl ester 235



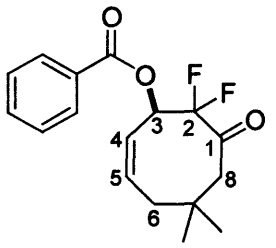
The epoxide **221** (34 mg, 0.1 mmol) in a solution of *N*-methylimidazole (0.2 mL) and water (1.8 mL) was irradiated for 10 min at 30 W microwave power and 100 °C in a sealed vial within the cavity of a CEM Discovery instrument. The solution was washed with cold 2M HCl solution (2 x 4 mL). The acid solution was extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (38 mg) which was purified by column chromatograpy to yield **235** (25.7mg, 72%) as a white solid; ν_{max} (solid)/cm^{-1} 3534s br , 3291s br, 2923m, 1662s, 1426m, 1284m, 1060s, 1029s, 816m, 761m, 700m; δ_H (400 MHz, Acetone-d_6) 4.99 (1H, d, ^4J 1.6, H-8), 4.27-4.21 (1H, m, H-5), 4.05 (1H, ddd, $^3J_{F\text{-}H}$ 20.5, J 9.6, $^3J_{F\text{-}H}$ 5.6, H-3), 3.79 (1H, ddd, J 9.6, 5.9, ^4J 1.6, H-4), 3.43-3.35 (4H, m, ($CON(CH_2CH_3)_2$), 1.93-1.78 (2H, m, H-6), 1.34 (3H, s, CH_3), 1.30-1.13 (6H, m, ($CON(CH_2CH_3)_2$), 1.02 (3H, s, CH_3); δ_C (100 MHz, Acetone-d_6, 300 K) 154.4, 117.7 (dd, $^1J_{C\text{-}F}$ 257.0, 251.0), 94.6 (t, $^2J_{C\text{-}F}$ 20.0), 73.8, 71.1, 69.8 (t, $^2J_{C\text{-}F}$ 19.0), 67.8, 41.7, 41.0, 33.6, 33.0, 28.9, 22.4, 13.8, 12.9; δ_F (282 MHz, Acetone-d_6) –125.2 (1F, dd, $J_{F\text{-}F}$ 239.8, $^3J_{F\text{-}H}$ 5.6), –138.1 (1F, dd, $J_{F\text{-}F}$ 239.8, $^3J_{F\text{-}H}$ 20.5); [HRMS (M^+) Found: 354.17275. Calc. For $C_{15}H_{26}N_1O_6F_2$ 354.17282]; *m/z* (ES) 354 (100% M^+).

Preparation of benzoic acid 2,2-difluoro-5,5-dimethyl-3-oxo-1-vinyl-oct-7- enyl ester 255



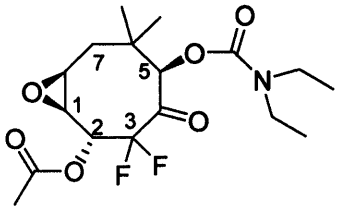
Benzoic anhydride (203 mg, 0.90 mmol) and DMAP (21.9 mg, 0.18 mmol) were added to a solution of diene **168** (208 mg, 0.90 mmol) in pyridine (0.9 mL). The mixture was stirred for 4 h at room temperature. The reaction mixture was washed with water (2 x 5 mL) and extracted with diethyl ether (4 x 6 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by column chromatography (10% diethyl ether in light petroleum) afforded benzoate ester **255** as a yellow oil (247 mg, 84%, 100% by GC-MS); R_f (10 % diethyl ether in light petroleum) 0.52; ν_{max} (film)/cm^{-1} 2961w, 1740s, 1639w; δ_H (300 MHz, $CDCl_3$) 7.99-7.95 (2H, m, Ph-H), 7.58-7.51 (1H, m, Ph-H), 7.48-7.44 (2H, m, Ph-H), 5.96-5.81 (2H, m, H-2 and H-3), 5.72 (1H, ddt, *J* 15.2, *J* 10.5, *J* 8.0, H-9), 5.57 (1H, dd, *J* 16.4, ^4J 0.9, H-1_a), 5.50 (1H, dd, *J* 9.6, ^4J 1.2, H-1_b), 4.95-4.85 (2H, m, H-10), 2.55-2.52 (2H, m, H-6), 2.06-2.02 (2H, m, H-8), 0.99 (6H, s, -CH_3); δ_C (75 MHz, $CDCl_3$) 198.9 (t, $^2J_{C\text{-}F}$ 28.0, C-5), 164.2, 134.4, 133.7, 129.9 (C x 2), 129.2, 128.6 (C x 2), 127.8, 122.6, 118.0, 113.8 (dd, $^1J_{C\text{-}F}$ 262.6, 257.3, C-4), 72.3 (dd, $^2J_{C\text{-}F}$ 30.2, 24.9, C-3), 46.7, 46.0, 33.4, 26.9, 26.8; δ_F (282 MHz, $CDCl_3$) -112.9 (1F, dd, $^2J_{F\text{-}F}$ 273.9, $^3J_{F\text{-}H}$ 8.5), -118.9 (1F, dd, $^2J_{F\text{-}F}$273.9, $^3J_{F\text{-}H}$ 15.2); [HRMS (EI, $[M]^+$) Found 368.18483. calc. For $C_{19}H_{22}O_5F_2$: 368.18481; *m/z* (EI) 368 ($[M]^+$, 5%), 205 (C_6H_5C, 100).

Preparation of 2,2-difluoro-3-benzoyloxy-7,7-dimethyl-cyclooct-4-enone 256



A solution of diene **255** (36.8 mg, 0.1 mmol) and titanium(IV) *iso*propoxide (8.3 μL, 0.03 mmol) in degassed DCM (100 mL) was refluxed for 30 min. 2nd Generation Grubbs' catalyst **87** (4 mg, 0.005 mmol) was added as a solution in degassed DCM (5 mL) and the reaction mixture was refluxed for 2 h. The mixture was concentrated *in vacuo* to leave a brown oil. Purification by column chromatography (10% diethyl ether in hexane) afforded cyclooctenone **256** as a white solid; m.p 84-86 °C; R_f (10 % diethyl ether in hexane) 0.20; (Found C, 66.11; H, 5.81; $C_{17}H_{18}F_2O_3$ requires: C, 66.22; H, 5.88%); ν_{max} (solid)/cm^{-1} 2982s, 2941s, 2878s, 1729w; δ_H (300 MHz, $CDCl_3$) 8.12-8.10 (2H, m, Ph-H), 7.62-7.58 (1H, m, Ph-H), 7.50-7.45 (2H, m, Ph-H), 6.31-6.23 (1H, m, H-3), 6.05-6.00 (1H, m, H-5), 5.73-5.68 (1H, m, H-4), 2.64 (1H, d, ^2J 12.3, H-8_a), 2.48 (1H, dd, ^2J 12.3, $^4J_{H\text{-}F}$ 2.4,H-8_b), 2.30 (1H, dd, ^2J 12.5, J 9.8, H-6_a), 2.12 (1H, dd, ^2J 12.5, J7.8, H-6_b); δ_C (100 MHz, $CDCl_3$, 323 K) 196.6 (t, $^2J_{C\text{-}F}$ 25.5, C-1), 165.1, 134.0, 133.5, 130.0 (C x 2), 129.1, 128.5 (C x 2), 126.1, 116.0 (t, $^1J_{C\text{-}F}$ 259.0, C-2), 68.3 (t, $^2J_{C\text{-}F}$ 22.0, C-3), 48.2, 40.5, 38.5, 31.2, 26.3; δ_F (282MHz, $CDCl_3$, 223 K) major conformer -110.6 (1F, d, $^2J_{F\text{-}F}$ 242.7), -132.6 (1F, dd, $^2J_{F\text{-}F}$ 242.7, $^3J_{F\text{-}H}$ 21.1); minor conformer -114.5 (1F, d, $^2J_{F\text{-}F}$ 229.8), -124.1 (1F, dd, $^2J_{F\text{-}F}$ 229.8, $^3J_{F\text{-}H}$ 25.7).

Preparation of Acetic acid 5-diethylcarbamoyloxy-3,3-difluoro-6,6-dimethyl-4-oxo-9-oxa-bicyclo[6.1.0]non-2-yl ester 257



Acetic anhydride (63 µL, 0.68 mmol) was added to a solution of epoxide **221** (0.15 g, 0.45 mmol) and catalytic DMAP (11 mg, 0.09 mmol) in CH_2Cl_2 (4.5 mL), followed by PVP (0.45 g, 0.45 mmol), and the solution swirled gently overnight. The solids were filtered off and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and washed CH_2Cl_2 (20 mL) for reuse. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers washed with brine (10 mL) and dried ($MgSO_4$) before concentrating *in vacuo* to yield a slightly oily colourless solid. The product was purified by elution with CH_2Cl_2 (1 mL) through Supelco DSC-NH_2 aminopropyl SPE tubes preconditioned with CH_2Cl_2 (3 mL) and the eluted solution concentrated once more *in vacuo* to yield a clear, colourless solid (0.11 g, 64 %); mp 140-142°C; R_f (10% ethyl acetate in hexane) 0.15; (Found; C, 54.17; H, 6.54; N, 3.63. $C_{17}H_{25}F_2NO_6$ requires C, 54.11; H, 6.68; N, 3.71); δ_H (400 MHz,$CDCl_3$, 212 K) major conformer 5.67 (1H, ddd, $^3J_{H\text{-}F}$ 21.3, $^3J_{H\text{-}F}$ 16.0, *J* 8.7, H-2), 5.20 (1H, br s, H-5), 3.75 (1H, ddd, *J* 14.4, *J* 7.3, H-8), 3.10 (5H, m, H-1 and $N(CH_2CH_3)_2$), 2.29 (3H, s, $OCOCH_3$), 1.34 (2H, s, H-7), 1.16 (12H, m, $N(CH_2CH_3)_2$ and 2 x CH_3); minor conformer 5.01 (1H, br dd *J* 7.09, H-2), 4.98 (1H, s, H-5), 3.48 (1H, dd, *J* 13.9, *J* 6.9, H-8), 3.32 (4H, m, $N(CH_2CH_3)_2$), 3.20 (1H, m, H-1), 2.28 (3H, s, $OCOCH_3$), 2.17 (1H, dd, *J* 13.9, *J* 4.7, H-7_a), 1.75 (1H, dd, *J* 14.3, *J* 4.7, H-7_b), 1.10 (12H, m, $N(CH_2CH_3)_2$ and 2 x CH_3); δ_F (374.5 MHz, $CDCl_3$, 212 K) major conformer -106.3 (d, $^2J_{F\text{-}F}$ 262.2), -122.0 (dd, $^2J_{F\text{-}F}$ 262.2, $^3J_{H\text{-}F}$ 21.3), minor conformer -112.6 (d, $^2J_{F\text{-}F}$ 248.2), -118.7 (dd,

$^{2}J_{F\text{-}F}$ 248.2, $^{3}J_{H\text{-}F}$ 27.8). [HRMS (ES, $[M+H]^{+}$) found: 378.1723. Calc for $C_{17}H_{25}F_{2}O_{6}N$ 377.1650].

References

1. Sears, P.; Wong, C. -H.; *Angew. Chem. Int. Ed.*, **1999**, 38, 2300-2324.
2. Tsai, L. -C.; Shyur, L. -F.; Cheng, Y. -S.; Lee, S. -H.; *J. Mol. Biol.*, **2005**, 354, 642-651.
3. Knier, B.L.; Jencks, W. P.; *J. Am. Chem. Soc.*, **1980**, 102, 6789-6798.
4. Withers, S. G.; *Carbohydr. Polym.*, **2001**, 44, 325-337.
5. Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G.; *J. Am.Chem. Soc.*, **2000**, 122, 1270-1277.
6. Ravishankar, R.; Surolia, A.; Vijayan, M.; Lim, S.; Kishi, Y.; *J. Am. Chem. Soc.*, **1998**, 120, 11297-11303.
7. Wei, A.; Boy, K. M.; Kishi, Y.; *J. Am. Chem. Soc.*, **1995**, 117, 9432-9436.
8. Mikkelsen, L. M.; Hernáiz, M. J.; Martin-Pastor, M.; Skrydstrup, T.; Jiménez-Barbero, J.; *J. Am. Chem. Soc.*, **2002**, 124, 14940-14951.
9. O'Hagan, D.; Harper, D. B.; *J. Fluorine Chem.*, **1999**, 100, 127-133.
10. Schofield, H.; *J. Fluorine Chem.*, **1999**, 100, 7-11.
11. Isanbor, C.; O'Hagan, D.; *J. Fluorine Chem.*, **2006**, 127, 303-319.
12. O'Hagan, D.; Rzepa, H. S.; *Chem. Commun.*, **1997**, 645-652.
13. Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T.; *Tetrahedron*, **1996**, *52*, 12613-12622.
14. Chapeau, M. -C.; Frey, P. A.; *J. Org. Chem.*, **1994**, 59, 6994-6998.
15. Lampe, D. C.; Liu, C.; Mahon, M. F.; Potter, B. V. L.; *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1717-1727.
16. Sawyer, D. A.; Potter, B. V. L.; *J. Chem. Soc., Perkin trans 1*, **1992**, 7, 923-932
17. Eguchi, T.; Sasaki, S.; Huang, Z.; Kakinuma, K.;*J. Org. Chem.*, **2002**, *67*, 3979-3984.

18. Böhm H. -J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M.; *Chem. Bio Chem*, **2004**, 5, 637-643.

19. Burg, R. W.; Miller, B. M.; Baker, E. E.; Birnbaum, J.; Currie, S. A.; Hartman, R.; Kong, Y. -L.; Monagham, R. L.; Olson, G.; Putter, I.; Tunac, J. B.; Wallick, H.; Stapley, E. O.; Oiwa, R.; Omura, S.; *Antimicrob. Agent. Chemother.*, **1979**, 15, 361-367.

20. Fisher, M. H.; Mrozik, H.; in 'Macrolide Antibiotics', ed.; Omura, S.; Academic Press: New York, London, 1984.

21. Fried, J.; Hallinan, E. A.; Szwedo, M. J.; *J. Am. Chem. Soc.*, **1984**, 106, 3871-3872.

22. Bliard, C.; Escribano, F. C.; Lukacs, G.; Olesker, A.; Sarda, P.; *J. Chem. Soc., Chem. Commun.*, **1987**, 368-370.

23. Pankiewicz, K. W.; *Carbohydr. Res.*, **2000**, *327*, 87-105.

24. Hertel,L.; Kroin, J.; Grossman, C.; Grindey, G.; Dorr, A.; Stroniolo, A.; Plunkett, W.; Gandhi, V.; Huang, P.; in 'Biomedical Frontiers of Organofluorine Chemistry', ed., Ojima, I.; McCarthy, J. R.; Welch, J. T.; ACS Symp. Ser., 639, American Chemical Society, **1996**, Chapter 19, p265.

25. Frenández, R.; Castillón, S.; *Tetrahedron*, **1999**, 55, 8497-8508.

26. Singh, R. P.; Shreeve, J. M.; *Synthesis*, **2002**, 17, 2561-2578.

27. Middleton, W. J.; *J. Org. Chem.*, **1975**, 40, 574-578.

28. Card, P. J.; Reddy, G. S.; *J. Org. Chem.*, **1983**, 48, 4734-4743.

29. Kiddle, J. J.; *Chem. Rev.*, **1995**, 95, 2189-2202.

30. Kozikowski, A. P.; Fauq, A. H.; Rusnak, J. M.; *Tetrahedron Lett.*, **1989**, 30, 3365-3368.

31. Dax, K.; Albert, M.; *Top. Curr. Chem.*, **2001**, 215, 193-275.

32. Biggadike,k.; Borthwick, A. D.; Evans,D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds,P.; *J. Chem. Soc., Perkin Trans. 1*, **1988**, 549-554.

33. McCarter, J. D.; Adam, M. J.; Braun, C.; Namchuk, M.; Tull, D.; Withers, S. G.; *Carbohydr. Res.*, **1993**, 249, 77-90.

34. Hart, D. O.; He, S. M.; Chany, C. J.; Withers, S. G.; Sims, P. F. G.; Sinnott, M. L. Brumer, H.; *Biochemistry*, **2000**, 39, 9826-9836.

35. Lee, S. S.; Yu, S.; Withers, S. G.; *Biochemistry*, **2003**, 42, 13081-13090.

36. El-Laghdach, A.; Echarri, R.; Matheu, M. I.; Barrena, M. I.; Castillón, S.; *J. Org. Chem.*, **1991**, 56, 4556-4559.

37. Barrena, M. I.; Matheu, M. I.; Castillón, S.; *J. Org. Chem.*, **1998**, *63*, 2184-2188.

38. Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. -H.; *Angew, Chem, Int, Ed*, **2005**, 44, 192-212.

39. Burkart, M. D.; Zhang, Z.; Hung, S. -C.; Wong, C. -H.; *J. Am. Chem. Soc.*, **1997**, 119, 11743-11746.

40. Taguchi, T.; Kodama, Y.; Kanazawa, M.; *Carbohydr. Res.*, **1993**, 249, 243-252.

41. Cox, L. R.; DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M.; Spencer, N.; *Tetrahedron Asymmetry*, **2005**, *16*, 347-359.

42. Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; *Org. Biomol. Chem.*, **2004**, *2*, 528-541.

43. Percy, J. M.; Pintat, S.; *Chem. Commun.*, **2000**, 607.

44. Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Russell, D R.; Ghosh, S.; *Angew. Chem. Int. Ed.*, **1998**, 37, 3298-3300.

45. Cha, J. K.; Kim, N. S.; *Chem. Rev.*, **1995**, 95, 1761-1795.

46. Wang, W.; Zhang, Y.; Sollogoub, M.; Sinaÿ, P.; *Angew. Chem. Int. Engl. Ed*, **2000**, 39, 2466-2467.

47. Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J.; *Angew. Chem Int. Engl. Ed.*, 39, 726-728.

48. Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *Chem. Commun.* **2002**, 228-229.

49. Boyer, F.-D.; Hanna, I.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 4094-4096.

50. Grubbs, R. H.; Chang, S.; *Tetrahedron*, **1998**, *54*, 4413-4450.

51. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M.; *J. Am. Chem. Soc.,* **1990**, 112, 3875-3886.

52. Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L.; *J. Am. Chem. Soc.* **1999,** *121,* 2674-2678.

53. Trnka, T. M.; Grubbs, R. H.; *Acc. Chem. Res*, **2001**, 34, 18-29.

54. Ackermann, L.; Tom, D. E.; Fürstner, A.; *Tetrahedron*, **2000**, 56, 2195-2202.

55. Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R.; *Chem. Eur. J.*, **2001**, 7, 4811-4820.

56. Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H.; *Tetrahedron Lett.*, **1999**, 40, 2247-2250.

57. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H.; *Org. Lett.*, **1999**, 1, 953-956.

58. Li, H.; Blériot, Y.; Chantereau, C.; Mallet, J.; Sollogoub, M.; Zhang, Y.; Rodriguez-García, E.; Vogel, P.; Jiménez-Brabero, J.; Sinaÿ, P.; *Org. Biomol. Chem.*, **2004,** 2, 1492-1499.

59. Bleriot, Y.; Giroult, A.; Mallet, J. M.; Rodriguez, E.; Vogel, P.; Sinaÿ, P.; *Tetrahedron Asymmetry*, **2002**, 13, 2553-2565.

60. Vernall, A. J.; Abell, A. D.; *Aldrichimica Acta*, **2003**, 36, 93-105.

61. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.

62. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013-3043.

63. Sibi, M. P.; Aasmul, M.; Hasegawa, H.; Subramanian, T.; *Org. Lett.*, 5, 2883-2886

64. Eliel, E. L.; Wilen, S. H.; Mander, L. N.; *'Stereochemistry of Organic Compounds'*, Wiley Interscience, New York, **1994**, 765-767.

65. Creighton, C. J.; Reynolds, C. H.; Lee, D. H. S.; Leo, G. C.; Reitz, A. B.; *J. Am. Chem. Soc.*, **2001**, 123, 12664-12669.

66. Creighton, C. J.; Du, Y. M.; Reitz, A. B.; *Bioorganic & Medicinal Chem.*, **2004**, 12, 4375-4385.

67. Michalak, K.; Michalak, M.; Wicha, J.; *Tetrahedron Lett.*, **2005**, 46, 1149-1153.

68. Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J.; *J. Am. Chem. Soc.*, **2001**, 123, 10903-10908.

69. Sisu, E.; Sollogoub, M.; Mallet, J. M.; Sinaÿ, P.; *Tetrahedron*, **2002**, 58, 10189-10196.

70. Mehta, G.; Ramesh, S. S.; *Tetrahedron Lett.*, **2001**, 42, 1987-1990.

71. Sollogoub, M.; Mallet, J. M.; Sinaÿ, P.; *Angew. Chem., Int. Ed. Engl.*, **2000**, 39, 362–364.

72. Briggs, A. J.; Evans, C. M.; Glenn, R.; Kirby, A. J.; *J. Chem Soc., Perkin Trans. 2*, **1983**, 1637-1640.

73. van Hooft, P. A. V.; Litjens, Rejn; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H.; *Org. Lett.*, **2001**, 3, 731-733.

74. Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Uneyama, E.; *Chem. Commun.*, **2004**, 302-303.

75. Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Uneyama, E.; *Org. Lett.*, **2004**, 6, 1277-1280.

76. Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N.; Uneyama, E.; *Org. Biomol. Chem.*, **2005**, 3, 2701-2712.

77. Patel, S. T.; Percy, J. M.; Wilkes, R. D.; *Tetrahedron*, **1995**, 51, 9201-9216.

78. Balnaves, A. S.; Gelbrich, T.; Hursthouse, M. B.; Light, M. E.; Palmer, M J.; Percy, J. M.; *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2525-2535.

79. Patel, S. T.; Percy, J. M.; Wilkes, R. D.; *J. Org. Chem*, **1996**, 61, 166-173.

80. Pintat, S, 'Approaches Towards the synthesis of *gem*-difluorinated Monosaccharide Analogues', Ph.D Thesis, University of Leicester, Leicester, 2003.

81. Breen, A. P.; Murphy, J. A.; *J. Chem . Soc., Perkin Trans. 1*, **1993**, 2979-2990.

82. Wilson, S. R.; Mathew, J.; *Synthesis*, **1980**, 625-626.

83. Taft, R. W.; Ed. by Newman, M. S., 'Steric Effects in Organic Chemistry'. Wiley, New York, 1956, 556-675.

84. Armstrong, S. K.; Christie, B. A.; *Tetrahedron Lett.*, **1996**, 37, 9373-9376.

85. Spagnol, G.; Heck, M. P.; Nolan, S. P.; Mioskowski, C.; *Org. Lett.*, **2002**, 4, 1767-1770.

86. Audouard, C.; Fawcett, J.; Griffiths, G. A.; Kérourédan, E.; Miah, A.; Percy. J. M.; Yang, H.; *Org. Lett.*, 6, **2004**, 4269-4272.

87. PC Spartan Pro, Version, 1.0.5, Wavefunction Inc., Irvine, California, USA.

88. Halgren, A.; *J. Comput. Chem.*, **1996**, 17, 490-519.

89. Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S.; *Organometallics*, **1998**, 17, 1835-1840.

90. Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G.; *J. Org. Chem.*, **1997**, 62, 1449-1456.

91. VanRheenen, V.; Kelly, R. C.; Cha, D. Y.; *Tetrahedron Lett.*, **1976**, 23, 1973-1976.

92. Donohoe, T. J.; *Synthesis*, **2002**, 8, 1223-1232.

93. Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J.; *Tetrahedron Lett.*, **1997**, 38, 5027-5030.

94. Cha, J. K.; Christ, W. J.; Kishi, Y.; *Tetrahedron Lett.*, **1983**, 24, 3943-3946.

95. Cha, J. K.; Christ, W. J.; Kishi, Y.; *Tetrahedron*, **1984**, 40, 2247-2255.

96. Broom, N.; O'Hanlon, P. J.; Simpson, T. J.; Stephen, R.; Willis, C. L.; *J. Chem . Soc., Perkin Trans. 1*, **1995**, 3067-3072.

97. Leonard, J.; Hussain, N.; *J. Chem . Soc., Perkin Trans. 1*, **1994**, 49-60.

98. Itoh, T.; Jitsukawa, K.; Kadeda, K.; Teranishi, S.; *J. Am. Chem. Soc.*, **1979**, 101-159-159.

99. Yang, D.; Wong, M. -K.; Yip, Y. -C.; *J. Org. Chem.*, **1995**, 60, 3887-3889.

100. Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M.; *J. Org. Chem.*, **1996**, 61, 1830-1841.

101. Adam, W.; Smerz, A. K.; *Tetrahedron*, **1995**, 51, 13039-13044.

102. Favretto, L.; Nugent, W. A.; Licini, G.; *Tetrahedron Lett.*, **2002**, 43, 2581-2584.

103. Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N.; *J. Am. Chem. Soc.*, **1984**, 106, 139-140.

104. Keese, R.; Meyer, M.; *Tetrahedron*, **1993**, 49, 2055-2064.

105. Commeureuc, G. J.; Murphy, J. A.; Dewis, M. L.; *Org. Lett.*, **2003**, 5, 2785-2788.

106. Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith. D. W.; Schulz, G. R.; Wagner, K. B.; *J. Am Chem. Soc.*, **1992**, 114, 10978-10980.

107. Duhamel, L.; Plaquevent, J. C.; *J. Organomet. Chem.*, **1993**, 448, 1-3.

Appendix

X-ray structure of **180**

X-ray structure of **219**

X-ray structure of **257**

X-ray structure of **222**

X-ray structure of **232**

X-ray structure of **233**

X-ray structure of **180**

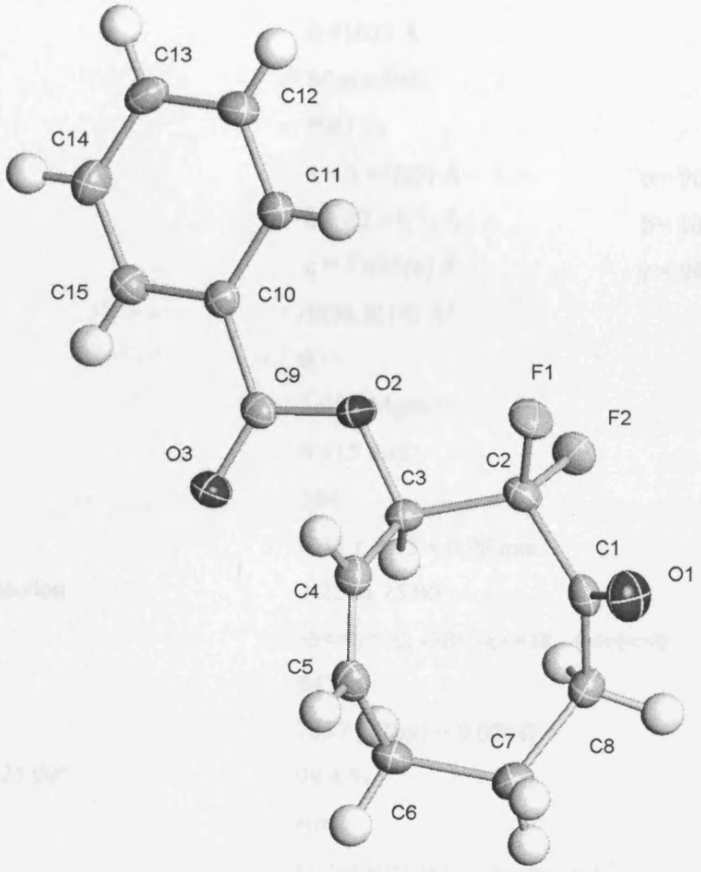


Table 1. Crystal data and structure refinement for 03196.

Identification code	03196	
Empirical formula	C15 H14 F2 O3	
Formula weight	280.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 5.448(5) Å	α= 90°.
	b = 32.61(3) Å	β= 100.705(14)°.
	c = 7.629(6) Å	γ = 90°.
Volume	1331.9(19) $Å^3$	
Z	4	
Density (calculated)	1.398 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	584	
Crystal size	0.32 x 0.13 x 0.08 mm^3	
Theta range for data collection	1.25 to 25.00°.	
Index ranges	-6<=h<=6, -38<=k<=38, -9<=l<=9	
Reflections collected	9476	
Independent reflections	2327 [R(int) = 0.0794]	
Completeness to theta = 25.00°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2327 / 0 / 181	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.1082	
R indices (all data)	R1 = 0.0507, wR2 = 0.1119	
Largest diff. peak and hole	0.280 and -0.208 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03196. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4596(2)	890(1)	8606(1)	33(1)
F(2)	1344(2)	493(1)	8307(1)	32(1)
O(1)	6474(2)	420(1)	11231(2)	35(1)
O(2)	577(2)	1331(1)	8624(1)	27(1)
O(3)	-2115(2)	1643(1)	10072(2)	29(1)
C(1)	4241(3)	458(1)	11021(2)	24(1)
C(2)	2892(3)	736(1)	9505(2)	24(1)
C(3)	1407(3)	1077(1)	10164(2)	23(1)
C(4)	3033(3)	1296(1)	11664(2)	26(1)
C(5)	3203(3)	1189(1)	13350(2)	28(1)
C(6)	1747(3)	856(1)	14049(2)	30(1)
C(7)	2913(4)	430(1)	14020(2)	33(1)
C(8)	2657(3)	244(1)	12148(2)	28(1)
C(9)	-1268(3)	1600(1)	8748(2)	22(1)
C(10)	-2084(3)	1828(1)	7060(2)	22(1)
C(11)	-837(3)	1796(1)	5645(2)	25(1)
C(12)	-1677(3)	2011(1)	4090(2)	30(1)
C(13)	-3763(3)	2261(1)	3952(2)	31(1)
C(14)	-4990(3)	2298(1)	5360(2)	31(1)
C(15)	-4169(3)	2080(1)	6914(2)	26(1)

Table 3. Bond lengths [Å] and angles [°] for 03196.

F(1)-C(2)	1.350(2)
F(2)-C(2)	1.3738(19)
O(1)-C(1)	1.204(2)
O(2)-C(9)	1.350(2)
O(2)-C(3)	1.440(2)
O(3)-C(9)	1.194(2)
C(1)-C(8)	1.497(2)
C(1)-C(2)	1.544(2)
C(2)-C(3)	1.515(2)
C(3)-C(4)	1.493(2)
C(4)-C(5)	1.319(3)
C(5)-C(6)	1.501(2)
C(6)-C(7)	1.530(3)
C(7)-C(8)	1.534(3)
C(9)-C(10)	1.483(2)
C(10)-C(11)	1.382(2)
C(10)-C(15)	1.390(2)
C(11)-C(12)	1.382(2)
C(12)-C(13)	1.386(3)
C(13)-C(14)	1.372(3)
C(14)-C(15)	1.383(2)
C(9)-O(2)-C(3)	116.22(12)
O(1)-C(1)-C(8)	123.51(15)
O(1)-C(1)-C(2)	119.21(15)
C(8)-C(1)-C(2)	117.27(14)
F(1)-C(2)-F(2)	105.83(13)
F(1)-C(2)-C(3)	110.75(14)
F(2)-C(2)-C(3)	110.11(13)
F(1)-C(2)-C(1)	108.89(14)
F(2)-C(2)-C(1)	107.93(13)
C(3)-C(2)-C(1)	113.04(13)
O(2)-C(3)-C(4)	113.69(14)
O(2)-C(3)-C(2)	104.96(13)
C(4)-C(3)-C(2)	109.17(14)
C(5)-C(4)-C(3)	123.11(15)
C(4)-C(5)-C(6)	126.23(15)
C(5)-C(6)-C(7)	113.82(16)

C(6)-C(7)-C(8)	113.95(14)
C(1)-C(8)-C(7)	112.87(15)
O(3)-C(9)-O(2)	123.07(14)
O(3)-C(9)-C(10)	125.09(15)
O(2)-C(9)-C(10)	111.84(13)
C(11)-C(10)-C(15)	119.70(15)
C(11)-C(10)-C(9)	121.91(15)
C(15)-C(10)-C(9)	118.39(14)
C(12)-C(11)-C(10)	119.96(16)
C(11)-C(12)-C(13)	120.00(16)
C(14)-C(13)-C(12)	120.26(15)
C(13)-C(14)-C(15)	119.95(17)
C(14)-C(15)-C(10)	120.13(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03196. 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)	37(1)	35(1)	31(1)	1(1)	18(1)	0(1)
F(2)	39(1)	29(1)	26(1)	-6(1)	-1(1)	-2(1)
O(1)	25(1)	38(1)	42(1)	-2(1)	6(1)	5(1)
O(2)	33(1)	28(1)	21(1)	5(1)	8(1)	8(1)
O(3)	34(1)	33(1)	23(1)	1(1)	10(1)	3(1)
C(1)	25(1)	22(1)	26(1)	-7(1)	3(1)	2(1)
C(2)	27(1)	26(1)	21(1)	-3(1)	6(1)	-2(1)
C(3)	27(1)	24(1)	20(1)	3(1)	6(1)	1(1)
C(4)	29(1)	21(1)	27(1)	-1(1)	7(1)	0(1)
C(5)	32(1)	26(1)	26(1)	-5(1)	2(1)	2(1)
C(6)	40(1)	30(1)	20(1)	1(1)	9(1)	5(1)
C(7)	42(1)	30(1)	26(1)	6(1)	7(1)	5(1)
C(8)	30(1)	23(1)	30(1)	3(1)	6(1)	3(1)
C(9)	24(1)	21(1)	22(1)	-2(1)	6(1)	-3(1)
C(10)	23(1)	19(1)	22(1)	-2(1)	2(1)	-3(1)
C(11)	30(1)	22(1)	23(1)	-1(1)	5(1)	1(1)
C(12)	39(1)	30(1)	23(1)	2(1)	9(1)	0(1)
C(13)	38(1)	28(1)	26(1)	6(1)	1(1)	1(1)
C(14)	30(1)	27(1)	36(1)	2(1)	4(1)	5(1)
C(15)	26(1)	27(1)	26(1)	-2(1)	7(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03196.

	x	y	z	U(eq)
H(3)	-72	958	10587	28
H(4)	3990	1523	11391	31
H(5)	4359	1338	14204	34
H(6A)	39	849	13326	35
H(6B)	1600	923	15291	35
H(7A)	2115	243	14770	39
H(7B)	4709	448	14559	39
H(8A)	3136	-49	12257	33
H(8B)	887	259	11544	33
H(11)	596	1625	5741	30
H(12)	-824	1989	3115	36
H(13)	-4345	2407	2878	37
H(14)	-6404	2473	5267	37
H(15)	-5030	2103	7884	32

X-ray structure of **219**

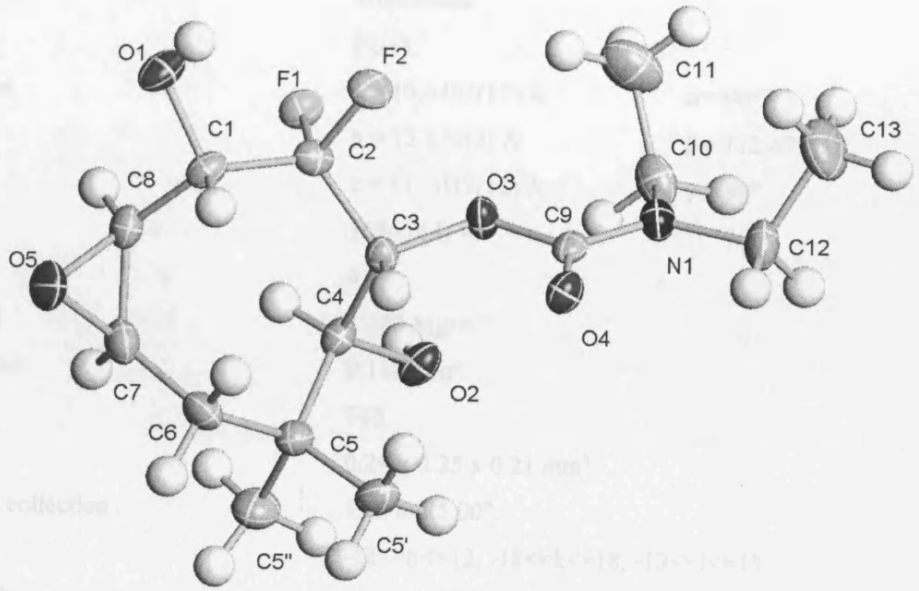


Table 1. Crystal data and structure refinement for 03076.

Identification code	03076	
Empirical formula	C15 H26 F2 N O5.50	
Formula weight	346.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.6401(15) Å	α= 90°.
	b = 15.190(2) Å	β= 112.679(2)°.
	c = 11.1047(15) Å	γ = 90°.
Volume	1656.0(4) $Å^3$	
Z	4	
Density (calculated)	1.389 Mg/m^3	
Absorption coefficient	0.118 mm^{-1}	
F(000)	740	
Crystal size	0.29 x 0.25 x 0.21 mm^3	
Theta range for data collection	1.99 to 25.00°.	
Index ranges	-12<=h<=12, -18<=k<=18, -13<=l<=13	
Reflections collected	11398	
Independent reflections	5801 [R(int) = 0.0264]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5801 / 1 / 443	
Goodness-of-fit on F^2	1.002	
Final R indices [I>2sigma(I)]	R1 = 0.0307, wR2 = 0.0684	
R indices (all data)	R1 = 0.0324, wR2 = 0.0695	
Absolute structure parameter	0.3(4)	
Largest diff. peak and hole	0.163 and -0.163 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03076. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4434(1)	1315(1)	6327(1)	29(1)
F(2)	3941(1)	1768(1)	4342(1)	33(1)
N(1)	1980(1)	-616(1)	2842(1)	28(1)
O(1)	5853(1)	2786(1)	5995(1)	32(1)
O(2)	5194(1)	-1024(1)	5964(1)	28(1)
O(3)	3665(1)	90(1)	4364(1)	27(1)
O(4)	3785(1)	-145(1)	2400(1)	28(1)
O(5)	8654(1)	1824(1)	7165(1)	40(1)
C(1)	6190(2)	1918(1)	5779(2)	25(1)
C(2)	4923(2)	1341(1)	5351(2)	24(1)
C(3)	5026(2)	409(1)	4884(2)	22(1)
C(4)	5927(2)	-235(1)	5978(2)	23(1)
C(5)	7294(2)	-474(1)	5884(2)	27(1)
C(5')	7105(2)	-930(1)	4601(2)	33(1)
C(5")	8048(2)	-1104(1)	7005(2)	39(1)
C(6)	8139(2)	365(1)	5997(2)	30(1)
C(7)	8240(2)	917(1)	7141(2)	31(1)
C(8)	7284(2)	1633(1)	7038(2)	27(1)
C(9)	3176(2)	-226(1)	3127(2)	23(1)
C(10)	1430(2)	-796(1)	3834(2)	37(1)
C(11)	704(2)	-29(2)	4124(2)	55(1)
C(12)	1283(2)	-1006(1)	1553(2)	37(1)
C(13)	-39(2)	-555(2)	776(2)	55(1)
F(1A)	5925(1)	503(1)	-1210(1)	33(1)
F(2A)	6318(1)	-375(1)	443(1)	35(1)
N(1A)	8130(2)	2090(1)	2539(2)	59(1)
O(1A)	4593(1)	-1077(1)	-1763(1)	30(1)
O(2A)	4995(1)	2535(1)	136(1)	33(1)
O(3A)	6601(1)	1253(1)	1059(1)	30(1)
O(4A)	6336(1)	1580(1)	2922(1)	34(1)
O(5A)	1664(1)	-263(1)	-2414(1)	35(1)
C(1A)	4145(2)	-394(1)	-1153(2)	25(1)
C(2A)	5367(2)	185(1)	-374(2)	24(1)
C(3A)	5225(2)	955(1)	459(2)	24(1)
C(4A)	4305(2)	1727(1)	-312(2)	25(1)

C(5A)	2884(2)	1779(1)	-242(2)	29(1)
C(5B)	3007(2)	1970(1)	1152(2)	36(1)
C(5C)	2101(2)	2527(1)	-1134(2)	43(1)
C(6A)	2123(2)	907(1)	-689(2)	30(1)
C(7A)	2015(2)	640(1)	-2020(2)	30(1)
C(8A)	3004(2)	56(1)	-2228(2)	28(1)
C(9A)	6969(2)	1653(1)	2240(2)	26(1)
C(10A)	9082(4)	1909(3)	1847(4)	26(1)
C(11A)	8732(5)	2605(3)	770(4)	38(1)
C(10B)	8407(5)	2509(3)	1338(5)	40(1)
C(11B)	9285(5)	1851(4)	1072(5)	58(1)
C(12A)	8666(2)	2616(1)	3728(2)	39(1)
C(13A)	9939(1)	2242(1)	4744(1)	51(1)
O(6)	5426(1)	3244(1)	8207(1)	48(1)

Table 3. Bond lengths [Å] and angles [°] for 03076.

F(1)-C(2)	1.3716(18)
F(2)-C(2)	1.3654(19)
N(1)-C(9)	1.327(2)
N(1)-C(10)	1.459(2)
N(1)-C(12)	1.460(2)
O(1)-C(1)	1.412(2)
O(2)-C(4)	1.427(2)
O(3)-C(9)	1.356(2)
O(3)-C(3)	1.4216(19)
O(4)-C(9)	1.2201(19)
O(5)-C(8)	1.439(2)
O(5)-C(7)	1.445(2)
C(1)-C(8)	1.498(2)
C(1)-C(2)	1.522(2)
C(2)-C(3)	1.526(2)
C(3)-C(4)	1.566(2)
C(4)-C(5)	1.542(2)
C(5)-C(5')	1.527(2)
C(5)-C(5")	1.530(3)
C(5)-C(6)	1.536(2)
C(6)-C(7)	1.491(3)
C(7)-C(8)	1.463(3)
C(10)-C(11)	1.500(3)
C(12)-C(13)	1.502(3)
F(1A)-C(2A)	1.3682(19)
F(2A)-C(2A)	1.3639(19)
N(1A)-C(9A)	1.327(2)
N(1A)-C(12A)	1.457(2)
N(1A)-C(10A)	1.514(4)
N(1A)-C(10B)	1.605(6)
O(1A)-C(1A)	1.4182(19)
O(2A)-C(4A)	1.418(2)
O(3A)-C(9A)	1.359(2)
O(3A)-C(3A)	1.428(2)
O(4A)-C(9A)	1.1971(19)
O(5A)-C(8A)	1.443(2)
O(5A)-C(7A)	1.445(2)
C(1A)-C(8A)	1.500(2)

C(1A)-C(2A)	1.531(2)
C(2A)-C(3A)	1.535(2)
C(3A)-C(4A)	1.555(2)
C(4A)-C(5A)	1.545(2)
C(5A)-C(5C)	1.526(3)
C(5A)-C(5B)	1.530(2)
C(5A)-C(6A)	1.533(3)
C(6A)-C(7A)	1.493(2)
C(7A)-C(8A)	1.461(3)
C(10A)-C(11A)	1.531(6)
C(10B)-C(11B)	1.474(7)
C(12A)-C(13A)	1.500(2)

C(9)-N(1)-C(10)	122.07(15)
C(9)-N(1)-C(12)	119.51(15)
C(10)-N(1)-C(12)	117.66(15)
C(9)-O(3)-C(3)	117.69(12)
C(8)-O(5)-C(7)	60.96(11)
O(1)-C(1)-C(8)	105.58(13)
O(1)-C(1)-C(2)	109.80(14)
C(8)-C(1)-C(2)	113.64(14)
F(2)-C(2)-F(1)	104.95(12)
F(2)-C(2)-C(1)	106.80(13)
F(1)-C(2)-C(1)	109.27(13)
F(2)-C(2)-C(3)	107.09(13)
F(1)-C(2)-C(3)	109.86(13)
C(1)-C(2)-C(3)	118.01(13)
O(3)-C(3)-C(2)	105.04(12)
O(3)-C(3)-C(4)	108.98(13)
C(2)-C(3)-C(4)	114.74(13)
O(2)-C(4)-C(5)	109.15(13)
O(2)-C(4)-C(3)	110.33(13)
C(5)-C(4)-C(3)	113.93(13)
C(5')-C(5)-C(5")	108.36(15)
C(5')-C(5)-C(6)	108.38(14)
C(5")-C(5)-C(6)	110.22(15)
C(5')-C(5)-C(4)	112.48(14)
C(5")-C(5)-C(4)	107.70(14)
C(6)-C(5)-C(4)	109.69(14)
C(7)-C(6)-C(5)	112.57(15)

O(5)-C(7)-C(8)	59.32(11)
O(5)-C(7)-C(6)	118.27(16)
C(8)-C(7)-C(6)	122.14(16)
O(5)-C(8)-C(7)	59.72(11)
O(5)-C(8)-C(1)	115.23(14)
C(7)-C(8)-C(1)	123.70(15)
O(4)-C(9)-N(1)	126.34(16)
O(4)-C(9)-O(3)	122.74(15)
N(1)-C(9)-O(3)	110.92(14)
N(1)-C(10)-C(11)	113.91(17)
N(1)-C(12)-C(13)	112.76(17)
C(9A)-N(1A)-C(12A)	120.15(16)
C(9A)-N(1A)-C(10A)	121.5(2)
C(12A)-N(1A)-C(10A)	117.0(2)
C(9A)-N(1A)-C(10B)	116.2(2)
C(12A)-N(1A)-C(10B)	113.7(2)
C(10A)-N(1A)-C(10B)	43.7(2)
C(9A)-O(3A)-C(3A)	116.99(13)
C(8A)-O(5A)-C(7A)	60.80(11)
O(1A)-C(1A)-C(8A)	105.75(13)
O(1A)-C(1A)-C(2A)	108.79(13)
C(8A)-C(1A)-C(2A)	116.07(14)
F(2A)-C(2A)-F(1A)	105.43(13)
F(2A)-C(2A)-C(1A)	105.60(13)
F(1A)-C(2A)-C(1A)	108.33(13)
F(2A)-C(2A)-C(3A)	107.17(13)
F(1A)-C(2A)-C(3A)	107.99(13)
C(1A)-C(2A)-C(3A)	121.26(14)
O(3A)-C(3A)-C(2A)	101.60(13)
O(3A)-C(3A)-C(4A)	109.44(13)
C(2A)-C(3A)-C(4A)	115.49(13)
O(2A)-C(4A)-C(5A)	108.79(14)
O(2A)-C(4A)-C(3A)	109.13(14)
C(5A)-C(4A)-C(3A)	115.57(14)
C(5C)-C(5A)-C(5B)	109.14(15)
C(5C)-C(5A)-C(6A)	110.17(15)
C(5B)-C(5A)-C(6A)	108.68(15)
C(5C)-C(5A)-C(4A)	107.80(15)
C(5B)-C(5A)-C(4A)	110.94(15)
C(6A)-C(5A)-C(4A)	110.10(14)

C(7A)-C(6A)-C(5A)	112.63(15)
O(5A)-C(7A)-C(8A)	59.56(11)
O(5A)-C(7A)-C(6A)	117.95(15)
C(8A)-C(7A)-C(6A)	122.38(16)
O(5A)-C(8A)-C(7A)	59.64(11)
O(5A)-C(8A)-C(1A)	114.43(14)
C(7A)-C(8A)-C(1A)	124.23(15)
O(4A)-C(9A)-N(1A)	125.79(16)
O(4A)-C(9A)-O(3A)	123.10(16)
N(1A)-C(9A)-O(3A)	111.05(14)
N(1A)-C(10A)-C(11A)	105.2(3)
C(11B)-C(10B)-N(1A)	103.4(4)
N(1A)-C(12A)-C(13A)	113.48(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03076. 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)	29(1)	28(1)	-1(1)	18(1)	1(1)
F(2)	34(1)	32(1)	28(1)	5(1)	6(1)	9(1)
N(1)	26(1)	27(1)	26(1)	-1(1)	6(1)	-4(1)
O(1)	49(1)	20(1)	26(1)	1(1)	15(1)	3(1)
O(2)	39(1)	22(1)	29(1)	-3(1)	19(1)	-7(1)
O(3)	22(1)	35(1)	22(1)	-6(1)	8(1)	-6(1)
O(4)	34(1)	27(1)	23(1)	-4(1)	12(1)	-4(1)
O(5)	31(1)	33(1)	51(1)	-9(1)	12(1)	-12(1)
C(1)	34(1)	19(1)	24(1)	0(1)	16(1)	0(1)
C(2)	27(1)	28(1)	18(1)	3(1)	9(1)	5(1)
C(3)	20(1)	26(1)	22(1)	-3(1)	9(1)	-3(1)
C(4)	29(1)	19(1)	21(1)	-2(1)	11(1)	-4(1)
C(5)	27(1)	25(1)	28(1)	-1(1)	10(1)	3(1)
C(5')	31(1)	32(1)	40(1)	-6(1)	18(1)	3(1)
C(5")	39(1)	33(1)	40(1)	4(1)	10(1)	8(1)
C(6)	20(1)	34(1)	35(1)	0(1)	9(1)	1(1)
C(7)	25(1)	31(1)	32(1)	-2(1)	6(1)	-6(1)
C(8)	29(1)	26(1)	25(1)	-4(1)	9(1)	-7(1)
C(9)	26(1)	16(1)	23(1)	1(1)	6(1)	4(1)
C(10)	30(1)	41(1)	37(1)	7(1)	9(1)	-10(1)
C(11)	40(1)	78(2)	53(1)	6(1)	25(1)	10(1)
C(12)	35(1)	34(1)	35(1)	-6(1)	4(1)	-10(1)
C(13)	45(1)	64(2)	39(1)	4(1)	-3(1)	-2(1)
F(1A)	41(1)	34(1)	30(1)	-6(1)	23(1)	-8(1)
F(2A)	34(1)	32(1)	32(1)	0(1)	6(1)	7(1)
N(1A)	59(1)	88(2)	43(1)	-38(1)	35(1)	-50(1)
O(1A)	48(1)	19(1)	27(1)	-1(1)	18(1)	0(1)
O(2A)	53(1)	21(1)	29(1)	-4(1)	20(1)	-11(1)
O(3A)	29(1)	38(1)	26(1)	-10(1)	14(1)	-11(1)
O(4A)	35(1)	49(1)	22(1)	-5(1)	14(1)	-11(1)
O(5A)	32(1)	30(1)	37(1)	-5(1)	7(1)	-8(1)
C(1A)	37(1)	20(1)	22(1)	-1(1)	15(1)	-2(1)
C(2A)	30(1)	23(1)	21(1)	2(1)	11(1)	1(1)
C(3A)	27(1)	24(1)	22(1)	-2(1)	11(1)	-6(1)
C(4A)	37(1)	20(1)	21(1)	-3(1)	12(1)	-4(1)

C(5A)	32(1)	25(1)	31(1)	-3(1)	12(1)	2(1)
C(5B)	37(1)	33(1)	45(1)	-10(1)	23(1)	-3(1)
C(5C)	47(1)	28(1)	47(1)	1(1)	10(1)	7(1)
C(6A)	27(1)	29(1)	33(1)	1(1)	11(1)	1(1)
C(7A)	29(1)	25(1)	31(1)	-1(1)	5(1)	-4(1)
C(8A)	35(1)	23(1)	24(1)	-2(1)	8(1)	-6(1)
C(9A)	31(1)	26(1)	21(1)	-2(1)	10(1)	-3(1)
C(10A)	24(2)	33(2)	20(2)	-1(2)	9(2)	-2(2)
C(11A)	37(3)	52(3)	28(2)	8(2)	17(2)	-6(2)
C(10B)	35(2)	39(3)	38(3)	-5(2)	7(2)	-12(2)
C(11B)	38(3)	86(4)	49(3)	5(3)	18(2)	3(3)
C(12A)	45(1)	39(1)	33(1)	-12(1)	16(1)	-16(1)
C(13A)	48(1)	41(1)	64(2)	-10(1)	20(1)	-9(1)
O(6)	88(1)	32(1)	37(1)	0(1)	40(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03076.

	x	y	z	U(eq)
H(1)	5405	3027	5275	48
H(2)	5062	-1063	6661	42
H(1A)	6562	1922	5078	29
H(3)	5383	434	4174	26
H(4)	6134	60	6839	27
H(5'1)	6576	-1471	4516	49
H(5'2)	7999	-1076	4592	49
H(5'3)	6620	-536	3870	49
H(5"1)	8992	-1171	7082	58
H(5"2)	7596	-1679	6831	58
H(5"3)	8039	-866	7822	58
H(6A)	9067	198	6076	36
H(6B)	7717	716	5190	36
H(7)	8606	608	8003	37
H(8)	7089	1741	7837	33
H(10A)	2186	-976	4650	45
H(10B)	788	-1297	3540	45
H(11A)	-107	112	3348	83
H(11B)	1314	482	4366	83
H(11C)	433	-179	4847	83
H(12A)	1102	-1635	1656	45
H(12B)	1888	-975	1064	45
H(13A)	136	65	649	82
H(13B)	-649	-591	1247	82
H(13C)	-466	-843	-75	82
H(1A1)	4821	-1517	-1266	45
H(2A)	5155	2776	-471	49
H(1A2)	3776	-664	-536	30
H(3A)	4903	735	1139	28
H(4A)	4166	1658	-1251	31
H(5B1)	2095	2001	1173	54
H(5B2)	3476	2533	1444	54
H(5B3)	3528	1499	1733	54
H(5C1)	1152	2519	-1209	64

H(5C2)	2127	2450	-2000	64
H(5C3)	2519	3091	-766	64
H(6A1)	2604	439	-59	36
H(6A2)	1196	963	-690	36
H(7A)	1594	1089	-2720	36
H(8A)	3163	163	-3047	34
H(10C)	8933	1309	1469	31
H(10D)	10044	1963	2459	31
H(11D)	8831	3193	1159	56
H(11E)	7791	2522	151	56
H(11F)	9351	2546	311	56
H(10E)	7546	2591	570	47
H(10F)	8877	3084	1580	47
H(11G)	8782	1298	793	86
H(11H)	10097	1749	1867	86
H(11I)	9561	2068	380	86
H(12C)	7960	2663	4100	47
H(12D)	8861	3217	3502	47
H(13D)	10666	2237	4408	77
H(13E)	9763	1639	4953	77
H(13F)	10217	2605	5533	77
H(6C)	5548	3711	8058	72
H(7C)	5512	3040	7568	72

X-ray structure of **257**

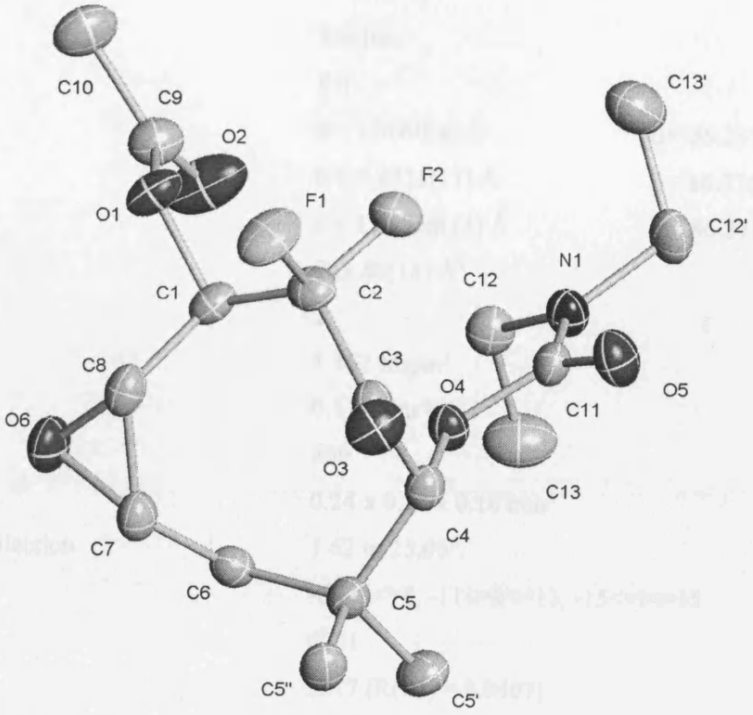


Table 1. Crystal data and structure refinement for 03031.

Identification code	03031	
Empirical formula	C17 H25 F2 N O6	
Formula weight	377.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3660(8) Å	α= 86.297(2)°.
	b = 9.9751(11) Å	β= 80.776(2)°.
	c = 12.7838(14) Å	γ = 86.271(2)°.
Volume	923.80(18) $Å^3$	
Z	2	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	400	
Crystal size	0.24 x 0.18 x 0.16 mm^3	
Theta range for data collection	1.62 to 25.00°.	
Index ranges	-8<=h<=8, -11<=k<=11, -15<=l<=15	
Reflections collected	6701	
Independent reflections	3217 [R(int) = 0.0407]	
Completeness to theta = 25.00°	99.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3217 / 0 / 240	
Goodness-of-fit on F^2	1.013	
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0928	
R indices (all data)	R1 = 0.0514, wR2 = 0.0980	
Largest diff. peak and hole	0.250 and -0.163 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03031. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-1334(1)	1278(1)	7481(1)	44(1)
F(2)	-114(1)	3157(1)	6903(1)	41(1)
N(1)	2711(2)	5678(1)	6992(1)	29(1)
O(1)	1697(2)	794(1)	6079(1)	33(1)
O(2)	3998(2)	2031(2)	5283(1)	59(1)
O(3)	-1297(2)	2047(1)	9327(1)	38(1)
O(4)	2502(2)	3889(1)	8144(1)	26(1)
O(5)	151(2)	5478(1)	8248(1)	37(1)
O(6)	4034(2)	-514(1)	7741(1)	36(1)
C(1)	1883(2)	1251(2)	7097(1)	27(1)
C(2)	124(2)	2025(2)	7527(1)	30(1)
C(3)	-3(2)	2403(2)	8698(1)	27(1)
C(4)	1476(2)	3187(2)	9041(1)	25(1)
C(5)	2881(2)	2355(2)	9638(1)	26(1)
C(5')	4091(3)	3363(2)	10000(1)	37(1)
C(5'')	1856(3)	1624(2)	10621(1)	33(1)
C(6)	4126(2)	1375(2)	8925(1)	27(1)
C(7)	3238(2)	134(2)	8701(1)	29(1)
C(8)	2193(2)	58(2)	7821(1)	29(1)
C(9)	2871(2)	1251(2)	5223(1)	34(1)
C(10)	2551(3)	628(2)	4249(1)	43(1)
C(11)	1660(2)	5083(2)	7817(1)	27(1)
C(12)	4579(2)	5184(2)	6566(1)	32(1)
C(12')	1994(3)	6920(2)	6497(1)	37(1)
C(13)	6006(3)	5615(2)	7176(2)	52(1)
C(13')	1350(3)	6685(2)	5465(2)	50(1)

Table 3. Bond lengths [Å] and angles [°] for 03031.

F(1)-C(2)	1.3571(18)
F(2)-C(2)	1.359(2)
N(1)-C(11)	1.334(2)
N(1)-C(12')	1.461(2)
N(1)-C(12)	1.463(2)
O(1)-C(9)	1.355(2)
O(1)-C(1)	1.4362(18)
O(2)-C(9)	1.188(2)
O(3)-C(3)	1.2011(19)
O(4)-C(11)	1.3792(19)
O(4)-C(4)	1.4363(18)
O(5)-C(11)	1.2121(19)
O(6)-C(8)	1.427(2)
O(6)-C(7)	1.4459(19)
C(1)-C(8)	1.489(2)
C(1)-C(2)	1.508(2)
C(2)-C(3)	1.553(2)
C(3)-C(4)	1.517(2)
C(4)-C(5)	1.550(2)
C(5)-C(5')	1.525(2)
C(5)-C(5'')	1.526(2)
C(5)-C(6)	1.536(2)
C(6)-C(7)	1.501(2)
C(7)-C(8)	1.469(2)
C(9)-C(10)	1.485(2)
C(12)-C(13)	1.505(3)
C(12')-C(13')	1.508(3)
C(11)-N(1)-C(12')	118.78(15)
C(11)-N(1)-C(12)	123.88(14)
C(12')-N(1)-C(12)	117.32(14)
C(9)-O(1)-C(1)	117.71(13)
C(11)-O(4)-C(4)	114.83(12)
C(8)-O(6)-C(7)	61.50(10)
O(1)-C(1)-C(8)	108.67(13)
O(1)-C(1)-C(2)	108.36(13)
C(8)-C(1)-C(2)	109.84(14)
F(1)-C(2)-F(2)	105.83(13)

F(1)-C(2)-C(1)	109.42(14)
F(2)-C(2)-C(1)	110.16(14)
F(1)-C(2)-C(3)	107.13(13)
F(2)-C(2)-C(3)	109.50(14)
C(1)-C(2)-C(3)	114.41(14)
O(3)-C(3)-C(4)	120.77(15)
O(3)-C(3)-C(2)	118.23(15)
C(4)-C(3)-C(2)	120.99(14)
O(4)-C(4)-C(3)	110.69(13)
O(4)-C(4)-C(5)	107.51(13)
C(3)-C(4)-C(5)	115.93(13)
C(5')-C(5)-C(5")	108.36(14)
C(5')-C(5)-C(6)	108.26(14)
C(5")-C(5)-C(6)	111.55(14)
C(5')-C(5)-C(4)	106.47(13)
C(5")-C(5)-C(4)	109.47(14)
C(6)-C(5)-C(4)	112.52(13)
C(7)-C(6)-C(5)	115.25(14)
O(6)-C(7)-C(8)	58.63(10)
O(6)-C(7)-C(6)	116.26(14)
C(8)-C(7)-C(6)	123.89(15)
O(6)-C(8)-C(7)	59.87(10)
O(6)-C(8)-C(1)	116.62(14)
C(7)-C(8)-C(1)	121.45(15)
O(2)-C(9)-O(1)	122.72(16)
O(2)-C(9)-C(10)	126.64(17)
O(1)-C(9)-C(10)	110.63(16)
O(5)-C(11)-N(1)	127.30(16)
O(5)-C(11)-O(4)	121.64(15)
N(1)-C(11)-O(4)	111.05(14)
N(1)-C(12)-C(13)	112.84(15)
N(1)-C(12')-C(13')	112.13(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03031. 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)	57(1)	49(1)	-17(1)	-5(1)	-14(1)
F(2)	49(1)	41(1)	35(1)	-1(1)	-16(1)	6(1)
N(1)	34(1)	24(1)	28(1)	1(1)	-1(1)	-1(1)
O(1)	35(1)	41(1)	23(1)	-7(1)	0(1)	-14(1)
O(2)	61(1)	82(1)	35(1)	-3(1)	2(1)	-42(1)
O(3)	30(1)	47(1)	36(1)	-3(1)	3(1)	-10(1)
O(4)	29(1)	22(1)	25(1)	2(1)	0(1)	-1(1)
O(5)	34(1)	31(1)	40(1)	1(1)	3(1)	6(1)
O(6)	39(1)	32(1)	35(1)	-10(1)	3(1)	5(1)
C(1)	29(1)	30(1)	23(1)	-6(1)	-3(1)	-9(1)
C(2)	29(1)	31(1)	33(1)	-2(1)	-8(1)	-8(1)
C(3)	25(1)	24(1)	30(1)	-2(1)	0(1)	2(1)
C(4)	29(1)	23(1)	23(1)	-2(1)	1(1)	-1(1)
C(5)	29(1)	26(1)	25(1)	-2(1)	-4(1)	-2(1)
C(5')	42(1)	36(1)	35(1)	-4(1)	-13(1)	-6(1)
C(5")	41(1)	31(1)	25(1)	-1(1)	0(1)	0(1)
C(6)	28(1)	29(1)	24(1)	1(1)	-4(1)	1(1)
C(7)	33(1)	24(1)	27(1)	-4(1)	2(1)	2(1)
C(8)	30(1)	25(1)	30(1)	-6(1)	4(1)	-4(1)
C(9)	30(1)	42(1)	29(1)	-2(1)	-1(1)	-5(1)
C(10)	41(1)	59(1)	28(1)	-9(1)	1(1)	-7(1)
C(11)	32(1)	21(1)	28(1)	-5(1)	-5(1)	-1(1)
C(12)	34(1)	33(1)	28(1)	0(1)	1(1)	-4(1)
C(12')	49(1)	23(1)	36(1)	3(1)	-2(1)	-1(1)
C(13)	41(1)	72(2)	45(1)	4(1)	-10(1)	-14(1)
C(13')	56(1)	51(1)	43(1)	2(1)	-13(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03031.

	x	y	z	U(eq)
H(1)	2945	1844	7023	33
H(4)	842	3879	9527	30
H(5'1)	3310	4059	10388	55
H(5'2)	4846	3781	9378	55
H(5'3)	4893	2896	10464	55
H(5"1)	2748	1146	11024	49
H(5"2)	1063	976	10404	49
H(5"3)	1100	2279	11067	49
H(6A)	4568	1860	8241	33
H(6B)	5217	1095	9265	33
H(7)	2865	-489	9333	35
H(8)	1201	-599	7940	34
H(10A)	3203	1111	3623	64
H(10B)	1229	679	4215	64
H(10C)	3010	-316	4266	64
H(12C)	4878	5521	5816	39
H(12D)	4625	4189	6580	39
H(12A)	2969	7575	6362	44
H(12B)	952	7313	6991	44
H(13A)	5911	6597	7207	78
H(13B)	7237	5330	6820	78
H(13C)	5801	5200	7898	78
H(13D)	2370	6277	4979	75
H(13E)	928	7545	5146	75
H(13F)	332	6079	5601	75

X-ray structure of **222**

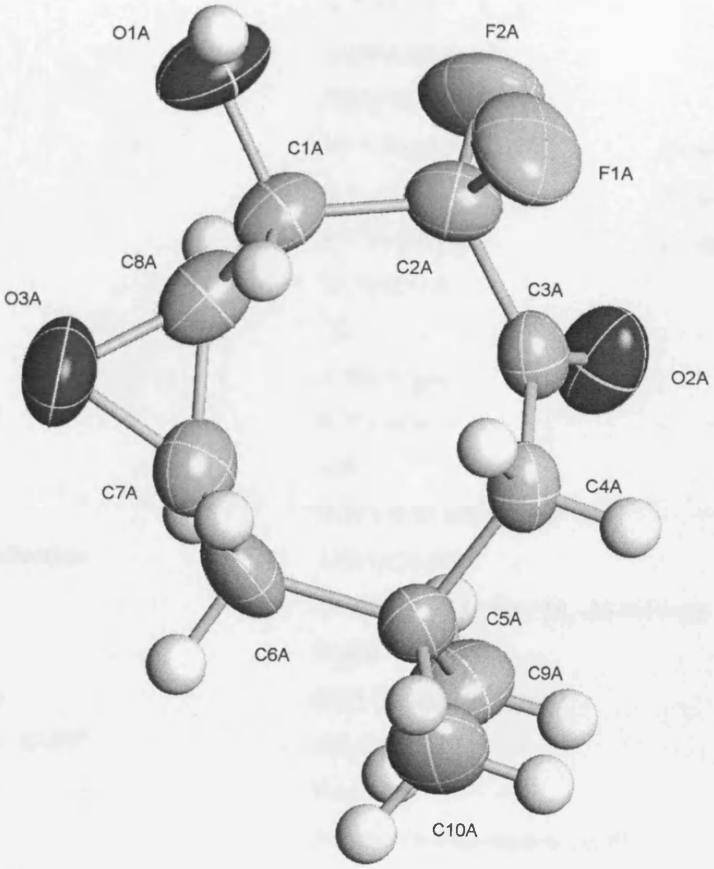


Table 1. Crystal data and structure refinement for 03050.

Identification code	03050	
Empirical formula	C10 H14 F2 O3	
Formula weight	220.21	
Temperature	290(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.6310(8) Å	α= 90°.
	b = 15.8186(19) Å	β= 90°.
	c = 30.694(4) Å	γ = 90°.
Volume	3219.6(7) $Å^3$	
Z	12	
Density (calculated)	1.363 Mg/m^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	1392	
Crystal size	0.24 x 0.13 x 0.13 mm^3	
Theta range for data collection	1.45 to 25.00°.	
Index ranges	-7<=h<=7, -18<=k<=18, -36<=l<=36	
Reflections collected	23604	
Independent reflections	5651 [R(int) = 0.0810]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5651 / 0 / 415	
Goodness-of-fit on F^2	0.717	
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.0515	
R indices (all data)	R1 = 0.1205, wR2 = 0.0636	
Absolute structure parameter	0.00	
Largest diff. peak and hole	0.171 and -0.106 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03050. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1A)	6541(4)	1678(1)	9357(1)	103(1)
F(2A)	9209(4)	1245(1)	9023(1)	102(1)
O(1A)	10326(4)	1719(2)	9824(1)	79(1)
O(2A)	8283(4)	2315(2)	8439(1)	75(1)
O(3A)	12236(4)	3431(2)	9586(1)	83(1)
C(1A)	9592(5)	2339(2)	9534(1)	57(1)
C(2A)	8320(6)	1941(2)	9181(1)	60(1)
C(3A)	7792(5)	2533(2)	8800(1)	52(1)
C(4A)	6700(5)	3332(2)	8895(1)	53(1)
C(5A)	7930(6)	4166(2)	8851(1)	55(1)
C(6A)	9532(6)	4211(2)	9220(1)	70(1)
C(7A)	11211(5)	3648(3)	9174(1)	68(1)
C(8A)	11327(6)	2764(3)	9333(1)	65(1)
C(9A)	8876(6)	4247(2)	8405(1)	80(1)
C(10A)	6449(5)	4877(2)	8921(1)	85(1)
F(1B)	5812(4)	8433(1)	7188(1)	106(1)
F(2B)	8508(4)	8038(1)	7525(1)	104(1)
O(1B)	4742(4)	8049(2)	8006(1)	88(1)
O(2B)	6687(4)	7306(2)	6633(1)	75(1)
O(3B)	2854(4)	6304(2)	7835(1)	89(1)
C(1B)	5467(6)	7399(2)	7735(1)	60(1)
C(2B)	6719(6)	7755(2)	7371(1)	61(1)
C(3B)	7217(5)	7130(2)	6999(1)	55(1)
C(4B)	8307(5)	6341(2)	7110(1)	52(1)
C(5B)	7089(6)	5509(2)	7100(1)	56(1)
C(6B)	5576(5)	5488(2)	7478(1)	65(1)
C(7B)	3847(6)	6049(2)	7425(1)	70(1)
C(8B)	3716(6)	6947(2)	7555(1)	69(1)
C(9B)	6079(5)	5380(2)	6661(1)	79(1)
C(10B)	8622(5)	4800(2)	7180(1)	77(1)
F(1C)	136(3)	6465(1)	9323(1)	93(1)
F(2C)	2870(4)	6420(1)	8945(1)	110(1)
O(1C)	-249(4)	6628(2)	8402(1)	76(1)
O(2C)	4111(4)	7748(2)	9345(1)	92(1)
O(3C)	-2051(4)	8454(2)	8525(1)	84(1)

C(1C)	337(6)	7303(2)	8685(1)	56(1)
C(2C)	1433(6)	6949(2)	9077(1)	63(1)
C(3C)	2356(6)	7615(3)	9382(1)	60(1)
C(4C)	1009(6)	8070(2)	9694(1)	68(1)
C(5C)	710(6)	9015(2)	9581(1)	63(1)
C(6C)	18(6)	9105(2)	9101(1)	67(1)
C(7C)	-1711(6)	8588(2)	8994(1)	66(1)
C(8C)	-1560(6)	7729(3)	8800(1)	67(1)
C(9C)	2611(6)	9539(2)	9640(1)	89(2)
C(10C)	-917(6)	9339(2)	9890(1)	98(2)

Table 3. Bond lengths [Å] and angles [°] for 03050.

F(1A)-C(2A)	1.363(4)
F(2A)-C(2A)	1.340(4)
O(1A)-C(1A)	1.412(3)
O(2A)-C(3A)	1.208(4)
O(3A)-C(8A)	1.441(4)
O(3A)-C(7A)	1.475(4)
C(1A)-C(8A)	1.469(4)
C(1A)-C(2A)	1.511(4)
C(2A)-C(3A)	1.536(4)
C(3A)-C(4A)	1.486(4)
C(4A)-C(5A)	1.557(4)
C(5A)-C(10A)	1.509(4)
C(5A)-C(9A)	1.510(4)
C(5A)-C(6A)	1.556(4)
C(6A)-C(7A)	1.432(4)
C(7A)-C(8A)	1.483(5)
F(1B)-C(2B)	1.351(4)
F(2B)-C(2B)	1.354(4)
O(1B)-C(1B)	1.408(3)
O(2B)-C(3B)	1.211(3)
O(3B)-C(8B)	1.450(4)
O(3B)-C(7B)	1.476(4)
C(1B)-C(8B)	1.471(5)
C(1B)-C(2B)	1.502(5)
C(2B)-C(3B)	1.545(5)
C(3B)-C(4B)	1.482(4)
C(4B)-C(5B)	1.544(4)
C(5B)-C(9B)	1.520(4)
C(5B)-C(10B)	1.533(4)
C(5B)-C(6B)	1.534(4)
C(6B)-C(7B)	1.459(4)
C(7B)-C(8B)	1.478(5)
F(1C)-C(2C)	1.377(4)
F(2C)-C(2C)	1.332(4)
O(1C)-C(1C)	1.432(3)
O(2C)-C(3C)	1.188(4)
O(3C)-C(8C)	1.461(4)
O(3C)-C(7C)	1.474(4)

C(1C)-C(8C)	1.470(4)
C(1C)-C(2C)	1.513(4)
C(2C)-C(3C)	1.535(5)
C(3C)-C(4C)	1.494(4)
C(4C)-C(5C)	1.547(4)
C(5C)-C(9C)	1.519(5)
C(5C)-C(10C)	1.525(4)
C(5C)-C(6C)	1.549(4)
C(6C)-C(7C)	1.445(4)
C(7C)-C(8C)	1.488(5)

C(8A)-O(3A)-C(7A)	61.1(2)
O(1A)-C(1A)-C(8A)	108.2(3)
O(1A)-C(1A)-C(2A)	110.9(3)
C(8A)-C(1A)-C(2A)	109.0(3)
F(2A)-C(2A)-F(1A)	105.8(3)
F(2A)-C(2A)-C(1A)	110.9(3)
F(1A)-C(2A)-C(1A)	109.0(3)
F(2A)-C(2A)-C(3A)	109.0(3)
F(1A)-C(2A)-C(3A)	106.9(3)
C(1A)-C(2A)-C(3A)	114.8(3)
O(2A)-C(3A)-C(4A)	123.6(4)
O(2A)-C(3A)-C(2A)	117.6(4)
C(4A)-C(3A)-C(2A)	118.7(3)
C(3A)-C(4A)-C(5A)	116.6(3)
C(10A)-C(5A)-C(9A)	109.7(3)
C(10A)-C(5A)-C(6A)	107.8(3)
C(9A)-C(5A)-C(6A)	111.9(3)
C(10A)-C(5A)-C(4A)	106.1(3)
C(9A)-C(5A)-C(4A)	111.7(3)
C(6A)-C(5A)-C(4A)	109.4(3)
C(7A)-C(6A)-C(5A)	115.5(3)
C(6A)-C(7A)-O(3A)	114.7(3)
C(6A)-C(7A)-C(8A)	126.4(4)
O(3A)-C(7A)-C(8A)	58.3(2)
O(3A)-C(8A)-C(1A)	115.9(3)
O(3A)-C(8A)-C(7A)	60.6(2)
C(1A)-C(8A)-C(7A)	122.0(3)
C(8B)-O(3B)-C(7B)	60.7(2)
O(1B)-C(1B)-C(8B)	107.9(3)

O(1B)-C(1B)-C(2B)	110.8(3)
C(8B)-C(1B)-C(2B)	109.8(3)
F(1B)-C(2B)-F(2B)	105.9(3)
F(1B)-C(2B)-C(1B)	111.2(3)
F(2B)-C(2B)-C(1B)	110.3(3)
F(1B)-C(2B)-C(3B)	107.2(3)
F(2B)-C(2B)-C(3B)	106.4(3)
C(1B)-C(2B)-C(3B)	115.3(3)
O(2B)-C(3B)-C(4B)	123.3(4)
O(2B)-C(3B)-C(2B)	118.4(4)
C(4B)-C(3B)-C(2B)	118.3(3)
C(3B)-C(4B)-C(5B)	117.3(3)
C(9B)-C(5B)-C(10B)	109.6(3)
C(9B)-C(5B)-C(6B)	112.3(3)
C(10B)-C(5B)-C(6B)	107.3(3)
C(9B)-C(5B)-C(4B)	111.2(3)
C(10B)-C(5B)-C(4B)	105.9(3)
C(6B)-C(5B)-C(4B)	110.2(3)
C(7B)-C(6B)-C(5B)	114.6(3)
C(6B)-C(7B)-O(3B)	114.9(3)
C(6B)-C(7B)-C(8B)	127.0(4)
O(3B)-C(7B)-C(8B)	58.8(2)
O(3B)-C(8B)-C(1B)	115.4(3)
O(3B)-C(8B)-C(7B)	60.5(2)
C(1B)-C(8B)-C(7B)	121.4(4)
C(8C)-O(3C)-C(7C)	60.9(2)
O(1C)-C(1C)-C(8C)	104.8(3)
O(1C)-C(1C)-C(2C)	109.8(3)
C(8C)-C(1C)-C(2C)	113.0(3)
F(2C)-C(2C)-F(1C)	105.3(3)
F(2C)-C(2C)-C(1C)	109.4(3)
F(1C)-C(2C)-C(1C)	109.9(3)
F(2C)-C(2C)-C(3C)	109.4(4)
F(1C)-C(2C)-C(3C)	107.3(3)
C(1C)-C(2C)-C(3C)	115.0(3)
O(2C)-C(3C)-C(4C)	124.2(4)
O(2C)-C(3C)-C(2C)	117.0(4)
C(4C)-C(3C)-C(2C)	118.8(4)
C(3C)-C(4C)-C(5C)	113.6(3)
C(9C)-C(5C)-C(10C)	109.3(3)

C(9C)-C(5C)-C(4C)	113.2(3)
C(10C)-C(5C)-C(4C)	106.0(3)
C(9C)-C(5C)-C(6C)	108.1(3)
C(10C)-C(5C)-C(6C)	110.6(3)
C(4C)-C(5C)-C(6C)	109.8(3)
C(7C)-C(6C)-C(5C)	113.6(3)
C(6C)-C(7C)-O(3C)	115.2(3)
C(6C)-C(7C)-C(8C)	123.6(3)
O(3C)-C(7C)-C(8C)	59.1(2)
O(3C)-C(8C)-C(1C)	114.4(3)
O(3C)-C(8C)-C(7C)	60.0(2)
C(1C)-C(8C)-C(7C)	124.9(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03050. 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(1A)	99(2)	107(2)	102(2)	17(2)	11(2)	-44(2)
F(2A)	154(3)	52(1)	98(2)	-10(1)	-1(2)	27(2)
O(1A)	78(2)	94(2)	66(2)	35(2)	11(2)	14(2)
O(2A)	82(2)	87(2)	55(2)	-24(2)	-6(2)	24(2)
O(3A)	74(2)	101(2)	74(2)	1(2)	-29(2)	-14(2)
C(1A)	53(3)	71(3)	47(3)	16(2)	10(2)	7(2)
C(2A)	64(3)	51(3)	64(3)	1(2)	12(3)	1(3)
C(3A)	43(2)	58(3)	56(3)	-12(2)	-3(2)	-1(2)
C(4A)	41(2)	63(3)	54(2)	-12(2)	-3(2)	6(2)
C(5A)	51(3)	47(2)	67(3)	-3(2)	-12(2)	4(2)
C(6A)	60(3)	50(3)	101(3)	-20(2)	-4(3)	-11(2)
C(7A)	52(3)	84(3)	67(3)	4(3)	-4(2)	-5(3)
C(8A)	56(3)	85(3)	52(3)	7(3)	6(2)	17(3)
C(9A)	83(3)	86(3)	72(3)	25(2)	9(3)	1(3)
C(10A)	80(3)	58(3)	116(4)	-10(2)	-14(3)	15(3)
F(1B)	155(2)	57(2)	105(2)	9(1)	-14(2)	27(2)
F(2B)	97(2)	102(2)	112(2)	-16(2)	-19(2)	-42(2)
O(1B)	76(2)	102(2)	87(2)	-48(2)	-25(2)	30(2)
O(2B)	78(2)	86(2)	61(2)	22(2)	4(2)	16(2)
O(3B)	81(2)	105(2)	80(2)	-8(2)	45(2)	-5(2)
C(1B)	57(3)	69(3)	55(3)	-19(2)	-7(2)	5(2)
C(2B)	57(3)	51(3)	76(3)	3(2)	-21(3)	3(3)
C(3B)	46(3)	56(3)	64(3)	16(2)	10(2)	2(2)
C(4B)	46(3)	58(2)	51(2)	13(2)	7(2)	5(2)
C(5B)	51(3)	55(3)	61(3)	9(2)	11(2)	4(2)
C(6B)	54(3)	57(3)	85(3)	19(2)	11(3)	-3(2)
C(7B)	48(3)	81(3)	82(3)	2(3)	-2(2)	-7(3)
C(8B)	57(3)	84(3)	65(3)	-6(3)	-2(3)	12(3)
C(9B)	68(3)	80(3)	89(3)	-17(2)	3(3)	-5(3)
C(10B)	85(4)	58(3)	87(3)	8(2)	18(3)	20(3)
F(1C)	126(2)	63(2)	92(2)	13(1)	17(2)	-21(2)
F(2C)	106(2)	99(2)	126(2)	-25(2)	7(2)	48(2)
O(1C)	70(2)	78(2)	78(2)	-25(2)	20(2)	-2(2)
O(2C)	60(2)	113(2)	104(2)	8(2)	-2(2)	4(2)
O(3C)	101(2)	71(2)	78(2)	-10(2)	-28(2)	15(2)

C(1C)	52(3)	63(3)	54(3)	-16(2)	5(2)	-6(2)
C(2C)	68(3)	59(3)	64(3)	2(2)	18(3)	6(3)
C(3C)	66(3)	60(3)	53(3)	12(2)	-5(3)	4(3)
C(4C)	85(3)	77(3)	42(2)	1(2)	2(2)	5(3)
C(5C)	83(3)	56(3)	51(3)	-8(2)	4(3)	5(3)
C(6C)	81(3)	41(2)	78(3)	2(2)	-10(3)	-7(2)
C(7C)	60(3)	68(3)	69(3)	-7(2)	-5(2)	6(3)
C(8C)	64(3)	73(3)	64(3)	-19(3)	4(3)	-8(3)
C(9C)	95(4)	72(3)	101(4)	-17(3)	-21(3)	-30(3)
C(10C)	123(4)	83(3)	88(3)	-29(3)	6(3)	2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03050.

	x	y	z	U(eq)
H(1A)	9469	1632	10021	119
H(1A1)	8767	2761	9699	68
H(4A1)	6172	3300	9196	63
H(4A2)	5524	3367	8697	63
H(6A1)	10052	4797	9235	84
H(6A2)	8856	4088	9501	84
H(7A)	12135	3782	8926	81
H(8A)	12288	2388	9174	77
H(9A1)	9611	4783	8386	120
H(9A2)	7818	4233	8182	120
H(9A3)	9812	3776	8358	120
H(10A)	5426	4866	8691	127
H(10B)	7164	5419	8913	127
H(10C)	5794	4808	9205	127
H(1B)	5659	8200	8178	132
H(1B1)	6303	6999	7911	72
H(4B1)	8879	6407	7406	62
H(4B2)	9454	6282	6906	62
H(6B1)	5078	4902	7513	78
H(6B2)	6291	5643	7750	78
H(7B)	2899	5882	7187	84
H(8B)	2730	7300	7388	83
H(9B1)	5061	5821	6616	118
H(9B2)	5429	4824	6654	118
H(9B3)	7094	5413	6429	118
H(10D)	7924	4253	7182	115
H(10E)	9287	4888	7461	115
H(10F)	9633	4803	6947	115
H(1C)	722	6500	8238	113
H(1C1)	1239	7704	8526	68
H(4C1)	1586	8026	9990	81
H(4C2)	-324	7788	9697	81
H(6C1)	-317	9704	9044	80
H(6C2)	1151	8947	8908	80

H(7C)	-2950	8697	9171	79
H(8C)	-2716	7344	8865	81
H(9C1)	3103	9476	9940	133
H(9C2)	2309	10135	9583	133
H(9C3)	3648	9343	9437	133
H(10G)	-1286	9918	9810	147
H(10H)	-403	9332	10189	147
H(10I)	-2108	8974	9870	147

X-ray structure of **232**

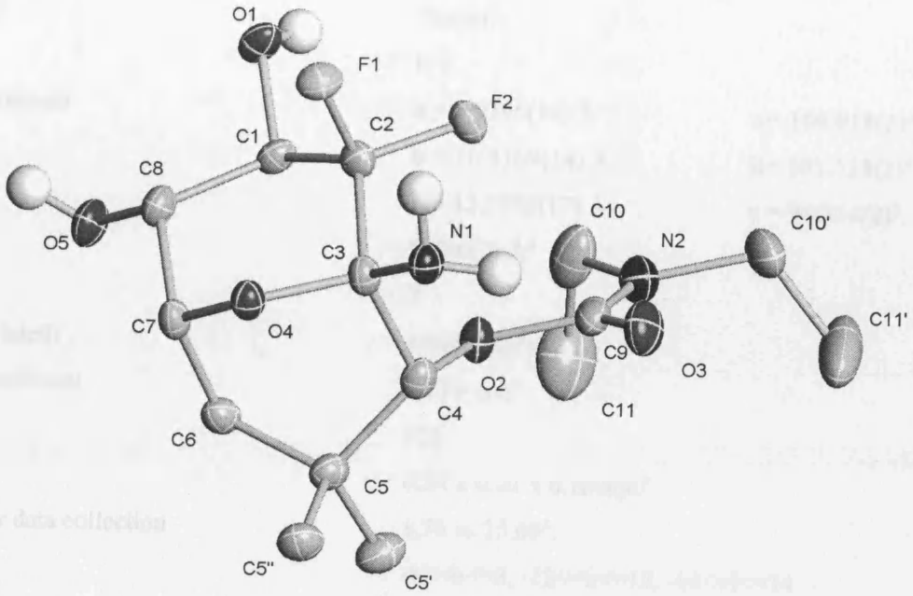


Table 1. Crystal data and structure refinement for 03040.

Identification code	03040	
Empirical formula	C15 H26 F2 N2 O5	
Formula weight	352.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.9296(10) Å	α= 104.018(2)°.
	b = 10.4369(14) Å	β= 103.538(2)°.
	c = 12.3706(17) Å	γ = 96.314(2)°.
Volume	830.6(2) $Å^3$	
Z	2	
Density (calculated)	1.409 Mg/m^3	
Absorption coefficient	0.119 mm^{-1}	
F(000)	376	
Crystal size	0.24 x 0.21 x 0.16 mm^3	
Theta range for data collection	1.76 to 25.00°.	
Index ranges	-8<=h<=8, -12<=k<=12, -14<=l<=14	
Reflections collected	5010	
Independent reflections	2863 [R(int) = 0.0312]	
Completeness to theta = 25.00°	97.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2863 / 0 / 224	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0417, wR2 = 0.1020	
R indices (all data)	R1 = 0.0499, wR2 = 0.1066	
Largest diff. peak and hole	0.310 and -0.185 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03040. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	2721(2)	7126(1)	4216(1)	25(1)
F(2)	2103(2)	5958(1)	5346(1)	25(1)
N(2)	2419(2)	5156(2)	7773(1)	30(1)
O(5)	1617(2)	10547(1)	6412(1)	26(1)
O(1)	-328(2)	7904(1)	5002(1)	24(1)
N(1)	6248(2)	6722(1)	5374(1)	21(1)
O(2)	4103(2)	6989(1)	7579(1)	22(1)
O(3)	5221(2)	5034(1)	7157(1)	33(1)
O(4)	5730(2)	8864(1)	5850(1)	19(1)
C(1)	1607(2)	8209(2)	5768(2)	20(1)
C(2)	2868(3)	7214(2)	5350(2)	20(1)
C(3)	5142(3)	7581(2)	5971(2)	19(1)
C(4)	5756(3)	7599(2)	7261(2)	21(1)
C(5)	6564(3)	9005(2)	8083(2)	22(1)
C(5')	6652(3)	8977(2)	9309(2)	31(1)
C(5'')	8703(3)	9459(2)	8040(2)	29(1)
C(6)	5197(3)	9953(2)	7727(2)	23(1)
C(7)	4796(3)	9866(2)	6444(2)	20(1)
C(8)	2576(3)	9600(2)	5825(2)	21(1)
C(9)	3991(3)	5656(2)	7478(2)	25(1)
C(10)	885(3)	5910(2)	8060(2)	43(1)
C(11)	1299(5)	6566(3)	9324(3)	64(1)
C(10')	2145(3)	3737(2)	7727(2)	37(1)
C(11')	3146(6)	3454(3)	8795(2)	73(1)

Table 3. Bond lengths [Å] and angles [°] for 03040.

F(1)-C(2)	1.362(2)
F(2)-C(2)	1.3569(19)
N(2)-C(9)	1.321(3)
N(2)-C(10)	1.449(3)
N(2)-C(10')	1.458(2)
O(5)-C(8)	1.403(2)
O(1)-C(1)	1.401(2)
N(1)-C(3)	1.425(2)
O(2)-C(9)	1.358(2)
O(2)-C(4)	1.430(2)
O(3)-C(9)	1.209(2)
O(4)-C(3)	1.409(2)
O(4)-C(7)	1.433(2)
C(1)-C(2)	1.503(2)
C(1)-C(8)	1.509(2)
C(2)-C(3)	1.542(2)
C(3)-C(4)	1.548(2)
C(4)-C(5)	1.526(2)
C(5)-C(5')	1.510(3)
C(5)-C(6)	1.514(2)
C(5)-C(5")	1.523(3)
C(6)-C(7)	1.525(2)
C(7)-C(8)	1.511(2)
C(10)-C(11)	1.492(4)
C(10')-C(11')	1.456(3)
C(9)-N(2)-C(10)	123.82(16)
C(9)-N(2)-C(10')	117.75(17)
C(10)-N(2)-C(10')	118.29(17)
C(9)-O(2)-C(4)	115.39(14)
C(3)-O(4)-C(7)	112.83(12)
O(1)-C(1)-C(2)	110.00(14)
O(1)-C(1)-C(8)	108.84(14)
C(2)-C(1)-C(8)	109.43(14)
F(2)-C(2)-F(1)	104.34(13)
F(2)-C(2)-C(1)	111.21(14)
F(1)-C(2)-C(1)	108.16(13)
F(2)-C(2)-C(3)	111.02(13)

F(1)-C(2)-C(3)	105.72(13)
C(1)-C(2)-C(3)	115.58(14)
O(4)-C(3)-N(1)	105.79(13)
O(4)-C(3)-C(2)	104.33(13)
N(1)-C(3)-C(2)	111.11(14)
O(4)-C(3)-C(4)	110.30(13)
N(1)-C(3)-C(4)	108.27(14)
C(2)-C(3)-C(4)	116.50(14)
O(2)-C(4)-C(5)	109.09(14)
O(2)-C(4)-C(3)	111.01(13)
C(5)-C(4)-C(3)	113.38(14)
C(5')-C(5)-C(6)	110.11(15)
C(5')-C(5)-C(5")	107.78(15)
C(6)-C(5)-C(5")	110.82(15)
C(5')-C(5)-C(4)	109.80(15)
C(6)-C(5)-C(4)	109.24(14)
C(5")-C(5)-C(4)	109.07(15)
C(5)-C(6)-C(7)	112.51(14)
O(4)-C(7)-C(8)	108.64(13)
O(4)-C(7)-C(6)	112.32(13)
C(8)-C(7)-C(6)	112.96(15)
O(5)-C(8)-C(1)	109.27(14)
O(5)-C(8)-C(7)	109.64(14)
C(1)-C(8)-C(7)	110.69(14)
O(3)-C(9)-N(2)	125.66(18)
O(3)-C(9)-O(2)	122.17(17)
N(2)-C(9)-O(2)	112.17(16)
N(2)-C(10)-C(11)	113.23(19)
C(11')-C(10')-N(2)	114.36(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03040. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	23(1)	31(1)	20(1)	6(1)	5(1)	6(1)
F(2)	22(1)	18(1)	35(1)	7(1)	6(1)	1(1)
N(2)	33(1)	25(1)	33(1)	14(1)	8(1)	1(1)
O(5)	28(1)	25(1)	32(1)	12(1)	10(1)	14(1)
O(1)	14(1)	32(1)	30(1)	15(1)	4(1)	4(1)
N(1)	21(1)	19(1)	25(1)	7(1)	8(1)	7(1)
O(2)	23(1)	20(1)	29(1)	11(1)	11(1)	7(1)
O(3)	43(1)	24(1)	39(1)	9(1)	16(1)	15(1)
O(4)	18(1)	18(1)	24(1)	8(1)	7(1)	4(1)
C(1)	14(1)	25(1)	20(1)	9(1)	4(1)	6(1)
C(2)	20(1)	18(1)	22(1)	8(1)	6(1)	1(1)
C(3)	18(1)	16(1)	25(1)	7(1)	7(1)	4(1)
C(4)	16(1)	23(1)	27(1)	11(1)	7(1)	7(1)
C(5)	19(1)	24(1)	23(1)	6(1)	3(1)	6(1)
C(5')	30(1)	37(1)	25(1)	8(1)	3(1)	11(1)
C(5")	21(1)	31(1)	31(1)	7(1)	1(1)	3(1)
C(6)	19(1)	21(1)	25(1)	4(1)	3(1)	4(1)
C(7)	20(1)	15(1)	27(1)	7(1)	7(1)	5(1)
C(8)	21(1)	21(1)	23(1)	10(1)	7(1)	9(1)
C(9)	31(1)	21(1)	20(1)	8(1)	3(1)	5(1)
C(10)	32(1)	47(1)	65(2)	35(1)	19(1)	10(1)
C(11)	76(2)	59(2)	80(2)	25(2)	45(2)	35(2)
C(10')	44(1)	23(1)	40(1)	13(1)	5(1)	-5(1)
C(11')	137(3)	35(1)	45(2)	19(1)	11(2)	25(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03040.

	x	y	z	U(eq)
H(5)	1176	11009	5994	56(8)
H(1)	-1120	7531	5276	37
H(1C)	5620	6418	4640	25
H(1B)	6286	6040	5617	25
H(1A)	1509	8179	6539	23
H(4)	6831	7067	7366	25
H(5'1)	7285	9842	9830	47
H(5'2)	7417	8312	9501	47
H(5'3)	5309	8761	9373	47
H(5"1)	9214	10348	8548	44
H(5"2)	8696	9461	7263	44
H(5"3)	9550	8855	8282	44
H(6A)	5813	10865	8178	27
H(6B)	3924	9743	7900	27
H(7)	5384	10735	6382	24
H(8)	2415	9678	5036	25
H(10A)	-407	5310	7794	52
H(10B)	790	6594	7649	52
H(11A)	1377	5895	9736	96
H(11B)	230	7041	9461	96
H(11C)	2554	7184	9588	96
H(10C)	713	3393	7538	44
H(10D)	2651	3258	7107	44
H(11D)	4571	3771	8982	109
H(11E)	2902	2504	8697	109
H(11F)	2626	3900	9412	109

X-ray structure of **233**

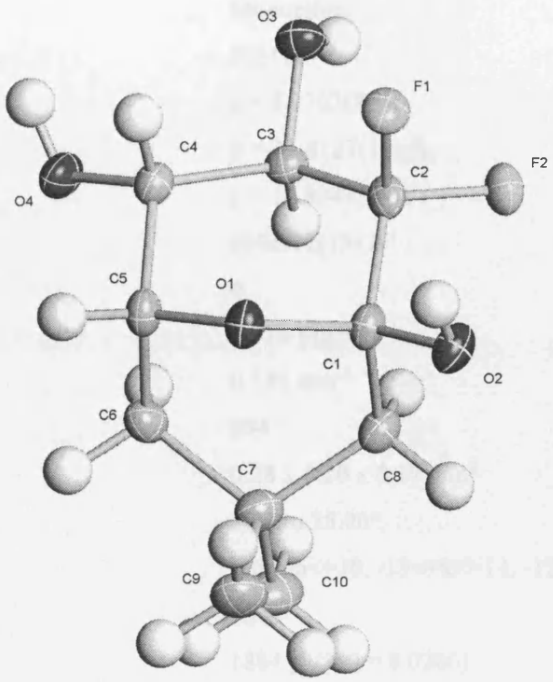


Table 1. Crystal data and structure refinement for 03210.

Identification code	03210	
Empirical formula	C10 H16 F2 O4	
Formula weight	238.23	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.9703(7) Å	α= 90°.
	b = 11.8127(10) Å	β= 111.2200(10)°.
	c = 10.8941(9) Å	γ = 90°.
Volume	1076.11(15) $Å^3$	
Z	4	
Density (calculated)	1.470 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	
F(000)	504	
Crystal size	0.28 x 0.20 x 0.17 mm^3	
Theta range for data collection	2.53 to 25.00°.	
Index ranges	-10<=h<=10, -13<=k<=14, -12<=l<=12	
Reflections collected	7575	
Independent reflections	1884 [R(int) = 0.0286]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1884 / 0 / 150	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0832	
R indices (all data)	R1 = 0.0357, wR2 = 0.0853	
Largest diff. peak and hole	0.265 and -0.217 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03210. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	7054(1)	731(1)	3804(1)	27(1)
F(2)	7143(1)	2551(1)	3504(1)	28(1)
O(1)	9872(1)	378(1)	3418(1)	22(1)
O(2)	10050(1)	1542(1)	5123(1)	25(1)
O(3)	5263(1)	1318(1)	1229(1)	26(1)
O(4)	7213(1)	183(1)	-22(1)	27(1)
C(1)	9473(2)	1478(1)	3749(1)	21(1)
C(2)	7638(2)	1528(1)	3187(1)	21(1)
C(3)	6955(2)	1350(1)	1707(1)	21(1)
C(4)	7618(2)	256(1)	1360(1)	22(1)
C(5)	9449(2)	230(1)	2006(1)	22(1)
C(6)	10309(2)	1103(1)	1446(1)	25(1)
C(7)	11293(2)	1977(1)	2470(1)	26(1)
C(8)	10245(2)	2423(1)	3212(1)	23(1)
C(9)	12851(2)	1454(1)	3420(2)	35(1)
C(10)	11723(2)	2974(1)	1765(2)	36(1)

Table 3. Bond lengths [Å] and angles [°] for 03210.

F(1)-C(2)	1.3664(15)
F(2)-C(2)	1.3734(15)
O(1)-C(1)	1.4288(16)
O(1)-C(5)	1.4554(15)
O(2)-C(1)	1.3971(16)
O(3)-C(3)	1.4159(16)
O(4)-C(4)	1.4172(15)
C(1)-C(2)	1.535(2)
C(1)-C(8)	1.5368(18)
C(2)-C(3)	1.5186(18)
C(3)-C(4)	1.5259(18)
C(4)-C(5)	1.5354(19)
C(5)-C(6)	1.5391(19)
C(6)-C(7)	1.5415(19)
C(7)-C(10)	1.530(2)
C(7)-C(9)	1.536(2)
C(7)-C(8)	1.5375(19)

C(1)-O(1)-C(5)	112.49(9)
O(2)-C(1)-O(1)	106.85(10)
O(2)-C(1)-C(2)	110.67(11)
O(1)-C(1)-C(2)	105.34(10)
O(2)-C(1)-C(8)	108.98(10)
O(1)-C(1)-C(8)	112.09(11)
C(2)-C(1)-C(8)	112.73(11)
F(1)-C(2)-F(2)	105.46(10)
F(1)-C(2)-C(3)	110.33(10)
F(2)-C(2)-C(3)	110.24(10)
F(1)-C(2)-C(1)	108.91(10)
F(2)-C(2)-C(1)	109.33(10)
C(3)-C(2)-C(1)	112.33(11)
O(3)-C(3)-C(2)	111.15(11)
O(3)-C(3)-C(4)	110.39(10)
C(2)-C(3)-C(4)	109.70(10)
O(4)-C(4)-C(3)	109.99(11)
O(4)-C(4)-C(5)	107.79(10)
C(3)-C(4)-C(5)	110.54(11)
O(1)-C(5)-C(4)	107.96(10)

O(1)-C(5)-C(6)	111.24(10)
C(4)-C(5)-C(6)	114.31(11)
C(5)-C(6)-C(7)	113.57(11)
C(10)-C(7)-C(9)	108.31(12)
C(10)-C(7)-C(8)	108.27(12)
C(9)-C(7)-C(8)	111.32(12)
C(10)-C(7)-C(6)	109.58(11)
C(9)-C(7)-C(6)	111.18(12)
C(8)-C(7)-C(6)	108.13(11)
C(1)-C(8)-C(7)	113.38(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03210. 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)	26(1)	26(1)	3(1)	15(1)	-4(1)
F(2)	33(1)	22(1)	31(1)	-4(1)	14(1)	4(1)
O(1)	28(1)	19(1)	18(1)	0(1)	7(1)	3(1)
O(2)	34(1)	21(1)	17(1)	0(1)	7(1)	-3(1)
O(3)	20(1)	25(1)	29(1)	2(1)	6(1)	0(1)
O(4)	28(1)	32(1)	20(1)	-7(1)	7(1)	-6(1)
C(1)	27(1)	19(1)	16(1)	-2(1)	6(1)	0(1)
C(2)	28(1)	15(1)	24(1)	0(1)	13(1)	0(1)
C(3)	19(1)	20(1)	22(1)	1(1)	7(1)	-1(1)
C(4)	24(1)	20(1)	19(1)	-2(1)	7(1)	-2(1)
C(5)	26(1)	22(1)	18(1)	-3(1)	6(1)	3(1)
C(6)	23(1)	32(1)	21(1)	-2(1)	9(1)	0(1)
C(7)	23(1)	31(1)	23(1)	-1(1)	8(1)	-4(1)
C(8)	26(1)	21(1)	20(1)	-1(1)	6(1)	-3(1)
C(9)	23(1)	45(1)	33(1)	-3(1)	6(1)	-2(1)
C(10)	34(1)	44(1)	32(1)	0(1)	14(1)	-12(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03210.

	x	y	z	U(eq)
H(2)	9829	940	5431	37
H(3)	4899	1947	893	38
H(4)	6388	-216	-350	41
H(3A)	7297	1996	1277	25
H(4A)	7157	-407	1671	26
H(5)	9816	-540	1858	27
H(6A)	9502	1508	706	30
H(6B)	11030	697	1090	30
H(8A)	10910	2901	3955	27
H(8B)	9391	2907	2610	27
H(9A)	13481	1162	2919	52
H(9B)	12597	833	3908	52
H(9C)	13469	2033	4040	52
H(10A)	12349	3528	2417	54
H(10B)	10742	3331	1171	54
H(10C)	12356	2701	1256	54