Doctor of Philosophy

at the University of Leicester

by

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Synopsis

This thesis describes the synthesis of *gem*-difluorinated cyclic molecules using building block approaches based mainly on ring-closing metathesis (RCM) using commercially available ruthenium catalysts such as Grubbs' catalyst.

In the first instance, 1-bromo-1,1-difluoroprop-2-ene was used to synthesise difluorinated dihydropyrans in order to demonstrate that the unprecedented RCM of a substrate containing two fluorine atoms in the allylic position could be achieved.

A similar approach allowed the highly diastereoselective synthesis of new 4,4-difluoro-4-deoxyhexoses using a RCM-dihydroxylation sequence. In order to widen the range of available difluorinated monosaccharide analogues, a potentially highly enantioselective, non-RCM based route was developed. This approach relied on the use of (3-bromo-3,3-difluoro-prop-1-ynyl)-benzene as the fluorinated building block and Sharpless asymmetric dihydroxylations to introduce hydroxyl groups enantioselectively. Unfortunately, a poor choice of protecting group prevented access to the desired difluorinated monosaccharide analogues, even if the asymmetric dihydroxylation proved successful and enantioselective.

RCM was also used to synthesise different types of difluorocyclooctenones from trifluoroethanol. These difluorinated 8-membered carbocycles showed interesting and unusual conformational behaviour and were investigated by NMR experiments and a simple computational study. These difluorocyclooctenones were also used to synthesise new bicyclic structures, which are effectively conformationally restrained difluorinated monosaccharide analogues.

Acknowledgments

First of all, I would like to thank Professor Jonathan Percy for his constant help and advice throughout the course of my PhD. I would also like to thank Dr Clive Smith at GlaxoSmithKline for his input into the project, especially during my time at Harlow.

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At last but not least, I would like to thank Christel and my family for their support and encouragement throughout my PhD and particularly through the writing-up of this thesis.

Abbreviations

Asn	Asparagine
Bn	Benzyl
Cat.	Catalyst or catalytic
Cbz	Benzyloxycarbonyl
CI	Chemical ionisation
CM	Cross-metathesis
d.	Day(s)
DAST	Diethylaminosulfur trifluoride
DEAD	Diethyl azodicarboxylate
DEC	*N*,*N*-Diethylcarbamoyl
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL-H	Di*iso*butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DNP	2,4-Dinitrophenyl
EI	Electron impact
ES	Electrospray
Eq.	Equivalents
FAB	Fast atom bombardment
GC	Gas chromatography
h.	Hour(s)
HIV	Human immunodeficiency virus

Hz	Hertz
LDA	Lithium di*iso*proylamide
MEM	Methoxyethoxymethyl
Mes	Mesityl (2,4,6-trimethyl-phenyl)
MHz	Megahertz
min.	Minute(s)
MS	Mass spectrometry
Ms	Methanesulfonyl
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
PPTS	Pyridinium *para*-toluene sulfonate
Pv	Pivaloate (trimethyl acetate)
Py.	Pyridine
RCM	Ring-closing metathesis
ROM	Ring-opening metathesis
Red-Al®	65 wt% solution of sodium *bis*(2-methoxyethoxy)-aluminium hydride in toluene
rt	Room temperature
Selectfluor™	[1-(chloromethyl)-4-fluoro-1,4-daizoniabicyclo[2.2.2]-octane bis(tetrafluoroborate)]
TBDPS	*tert*-Butyl-diphenyl-silyl
TBS	*tert*-Butyl-dimethyl-silyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

Contents

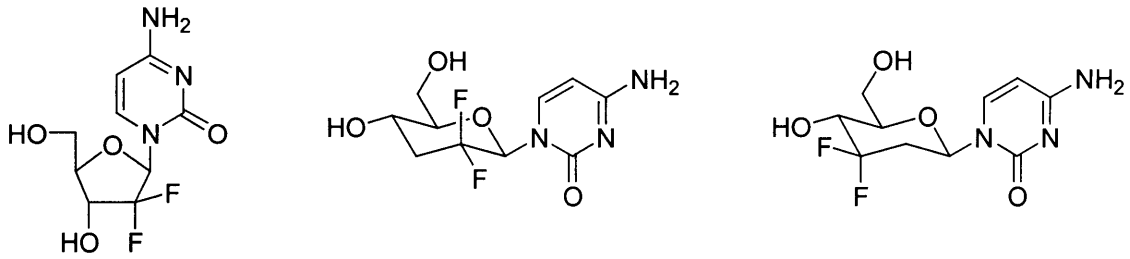
CHAPTER I: Introduction

I - Some effects of introducing fluorines in monosaccharides

Although there are only about twelve known naturally occurring fluorinated molecules,[1] more and more fluorinated compounds appear in the literature[2] and fluorine is increasingly present in bioactive compounds such as pharmaceuticals and agrochemicals. A large proportion of these compounds contains a trifluoromethyl or perfluoroalkyl group on an aryl or heteroaryl ring to increase their lipophilicities. Nevertheless, in some compounds such as fluorinated monosaccharide analogues, one or two fluorines are used to replace hydroxyl groups. The van der Waals radius of the fluorine atom (1.47 Å) is fairly similar to that of oxygen (1.57 Å).[3] Therefore, substitution of a hydroxyl group for a fluorine should not alter significantly the steric environment around the site of substitution. Nevertheless, fluorine is the most electronegative element and therefore may alter dramatically the behaviour of neighbouring functional groups, may change their basicity/acidity if there is such an issue and can also introduce some conformational changes due to dipole-dipole interaction. The introduction of fluorine atoms in molecules also increases their lipophilicities, an important parameter in drug design. Finally, even if this is controversial, fluorine can act as a hydrogen bond acceptor[4] but obviously not as a hydrogen bond donor. Therefore, replacement of a hydroxyl group with one or two fluorine atoms presents a considerable opportunity for modifying both recognition arrays based on hydroxyl groups, and the reactivity of the modified substrate. At the same time, the small change of steric bulk introduced by the fluorine atoms should

not prevent the fluorinated molecule from entering the receptor of the parent compound.

Among fluorinated sugar-type molecules, nucleosides have attracted a lot of interest in recent years as potential antiviral and anticancer agents.[5] The most successful compound of this kind is probably Gemcitabine **1**, which proved to be highly active against certain types of refractory solid tumours and has been approved for treating different types of cancer.[6] Castillón *et al.* prepared dideoxy-difluoropyranosyl **2** and **3** as pyranosyl analogues of Gemcitabine **1** where the C-2 or C-3 position is *gem*-difluorinated respectively.[7] Unfortunately, biological tests on difluorinated pyranosyls **2** and **3** did not show any activity against the HIV virus or any toxicity in MT-4 cells (**Figure 1**).



1 **2** **3**

Figure 1

Avermectins are a group of eight closely related macrocyclic lactones with extremely potent antiparasitic activity.[8] Structure-activity relationship studies for Avermectin B_{1a} **4** have shown that the presence of the disaccharide moiety is essential as the corresponding monosaccharide has about 25 % of the biological activity of the parent compound. The aglycone alone only retains about 5 % of the biological activity of **4**. In order to improve the biological activity of **4**, Lukacs *et al.* attempted to increase the stability of the glycosidic linkage by introducing a fluorine atom at the C-2 position. Indeed, the presence of fluorine at this position slows down the hydrolytic process by inductively destabilising the oxocarbenium cation **8** or oxocarbenium-like transition

state formed during the glycosidic cleavage. 2α- and 2β-Fluorooleandroses were therefore synthesised and introduced in the terminal unit of avermectin B_{1a} **4** to afford analogues **5** and **6** respectively. Biological tests revealed that **5** was as active as avermectin B_{1a} **4** against the two-spotted spider mite and both **5** and **6** were at least as active as the parent compound against gastrointestinal helminths.[9] Castillón *et al.* synthesised 2,2-difluoroleandrose for incorporation into avermectin B_{1a} to afford analogue **7** and further stabilise the glycosidic linkage.[10] Unfortunately, biological tests were not carried out to assess the change of activity introduced by the difluoromethylene group (**Figure 2**).

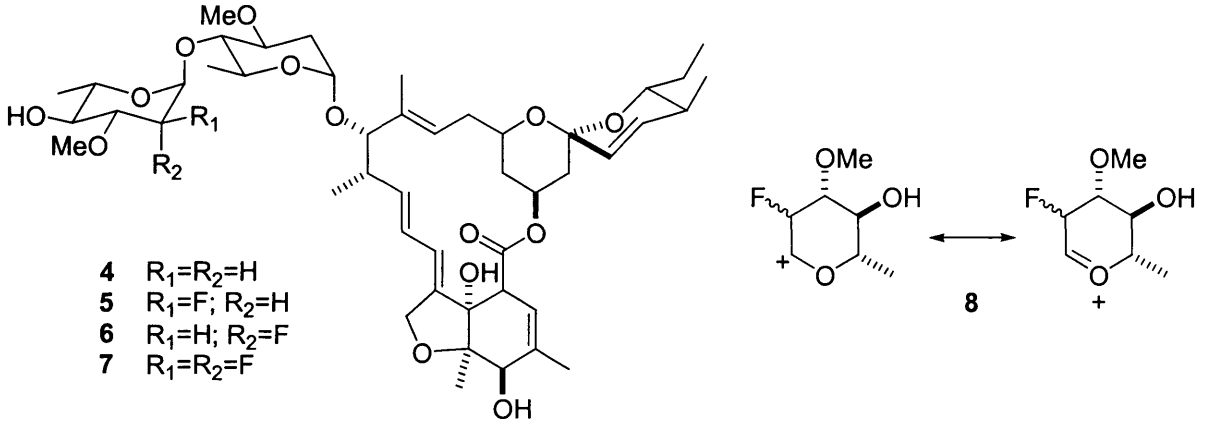
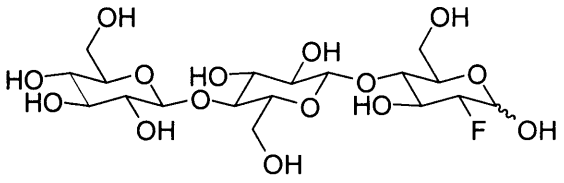


Figure 2

The introduction of a fluorine atom at the C-2 position of a monosaccharide to stabilise the glycosidic linkage has been used to great effect to determine the crystal structures of glycoside hydrolases. As the fluorine at the C-2 position considerably destabilises the oxocarbenium-like transition state, it decreases the rate of breakdown of the glycosyl-enzyme intermediate, which can then be trapped and crystallised. For example, Davies *et al.* managed to obtain the crystal structure of a 2-fluorocellotriosyl complex of the *Streptomyces lividans* endoglucanase CelB2 by using trisaccharide **9**, which bound to the active site but was not hydrolysed as readily as the natural substrate (**Figure 3**).[11]



9

Figure 3

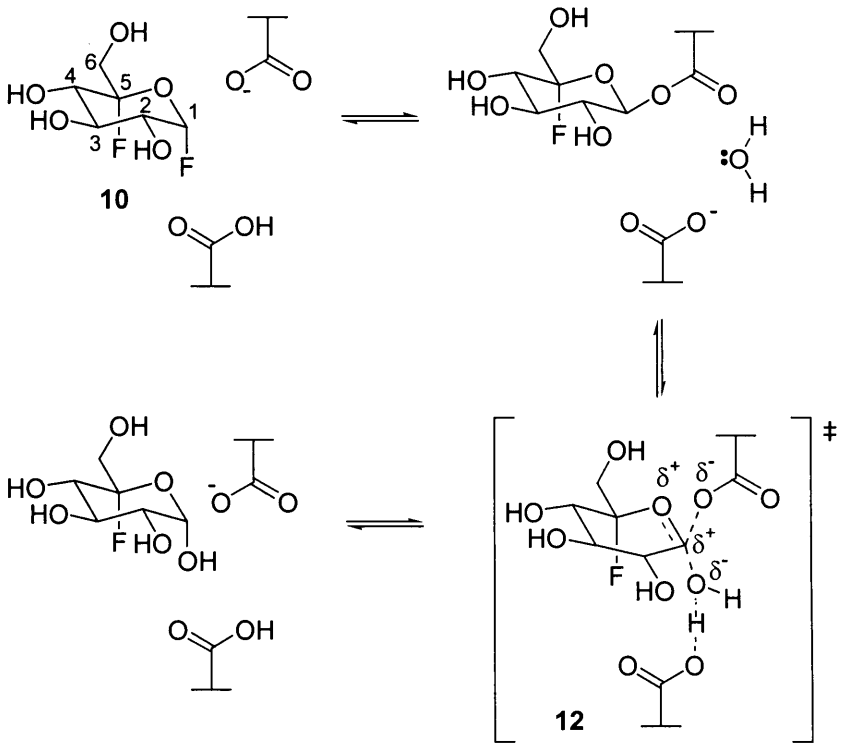
Interestingly, the presence of a fluorine atom at the C-2 position does not prevent binding of the substrate to the enzyme active site even if the natural substrate bears a hydroxyl group, which seems to be involved in a hydrogen-bond with an asparagine residue (Asn 155) of the active site.

Although the introduction of a fluorine at the C-2 position of a monosaccharide is successful for the inhibition of retaining β-glycosidases, the approach has been less suitable for the inhibition and study of α-glycosidases.[12,13] Moreover the presence of the fluorine at the C-2 position may limit the utility of the derivative as some enzymes are intolerant of substitution at this position. To overcome this problem, Withers *et al.* prepared 5-fluoroglycosyl fluorides **10** and **11**, which proved to be potent mechanism-based inhibitors of yeast α-glucosidase and *Agrobacterium faecalis* β-glucosidase respectively (**Figure 4**).[14]

10 **11**

Figure 4

The activity of **10** as an inhibitor can be explained by the slow formation of transition state **12**, where a positive charge has to develop on the oxygen adjacent to the carbon bearing an electron-withdrawing fluorine (**Scheme 1**).



Scheme 1

According to Withers *et al.* the effect of the fluorine at the C-5 position may be greater than at the C-2 position as modeling studies showed that the greatest difference in partial charge between a ground state monosaccharide and the corresponding glycosyl oxocarbenium ion was at the pyranose oxygen rather than the anomeric carbon C-1.[15,16]

Fluorine does not have to be introduced at the C-2 or C-5 positions to decrease the stability of the oxocarbenium ion-like transition state. Indeed, Withers *et al.* studied the hydrolysis of 2,4-dinitrophenyl-β-D-glucoside **13** and deoxyfluoro derivatives **14-17** and showed that the relative rates of hydrolysis of the DNP-glucosides (i.e. 2,4-dinitrophenyl-β-D-glucoside > 6-deoxy-6-fluoro > 3-deoxy-3-fluoro > 4-deoxy-4-fluoro > 2-deoxy-2-fluoro) can be rationalised on the basis of the relative stabilities of the oxocarbenium ion-like transition states, which appear to be principally a function of electronic effects exerted by the ring substituents on O-5, the principal centre of charge development at the transition states (**Figure 5**).[17]

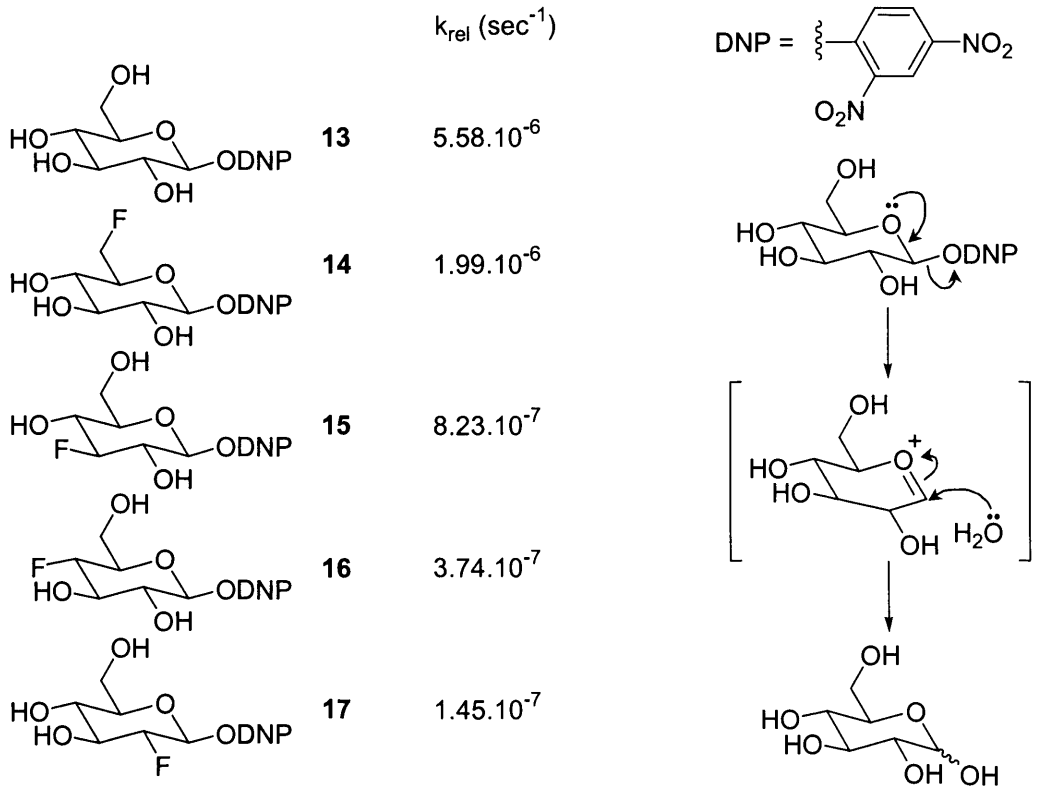


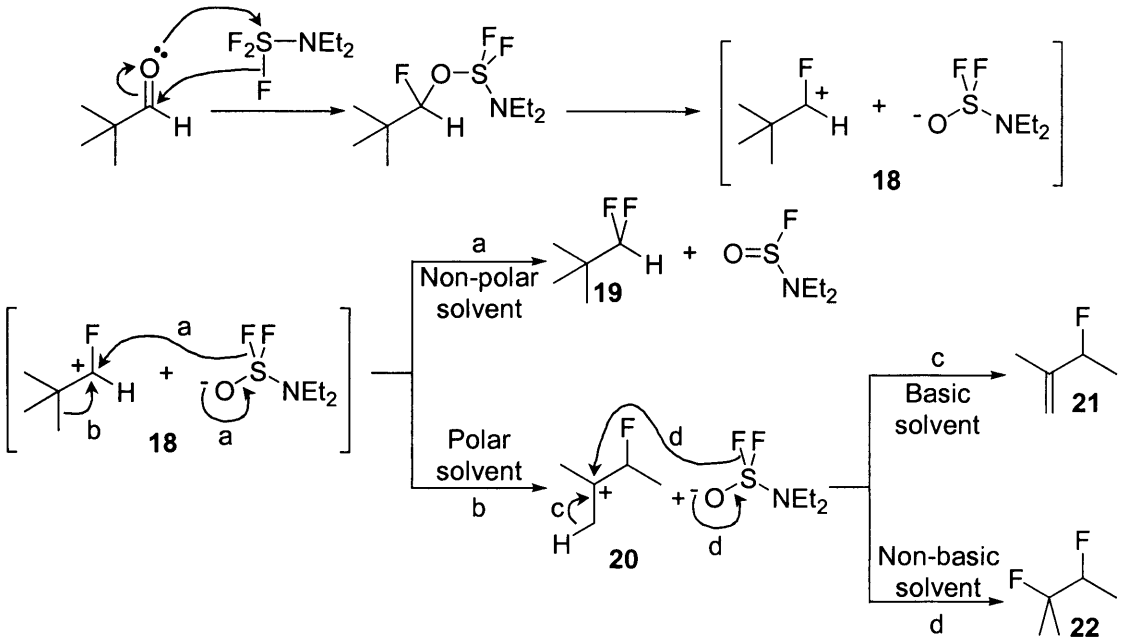
Figure 5

II - Syntheses of difluorinated monosaccharides

There are two general strategies for the synthesis of *gem*-difluorinated compounds in general and difluorinated monosaccharide analogues more specifically. The first one relies on the direct fluorination of a non-fluorinated precursor, commonly using diethylaminosulfur trifluoride (DAST) or derivatives as the fluorinating agent. Alternatively, *gem*-difluorinated molecules can be prepared *via* a building block approach even if examples of such methods are scarce for the synthesis of *gem*-difluorinated monosaccharides. These syntheses involve the use of a small fluorinated starting material (building block), which is processed by successive reactions to the desired target molecule. The scope and limitations of these two methods for the synthesis of fluorinated monosaccharides are described below.

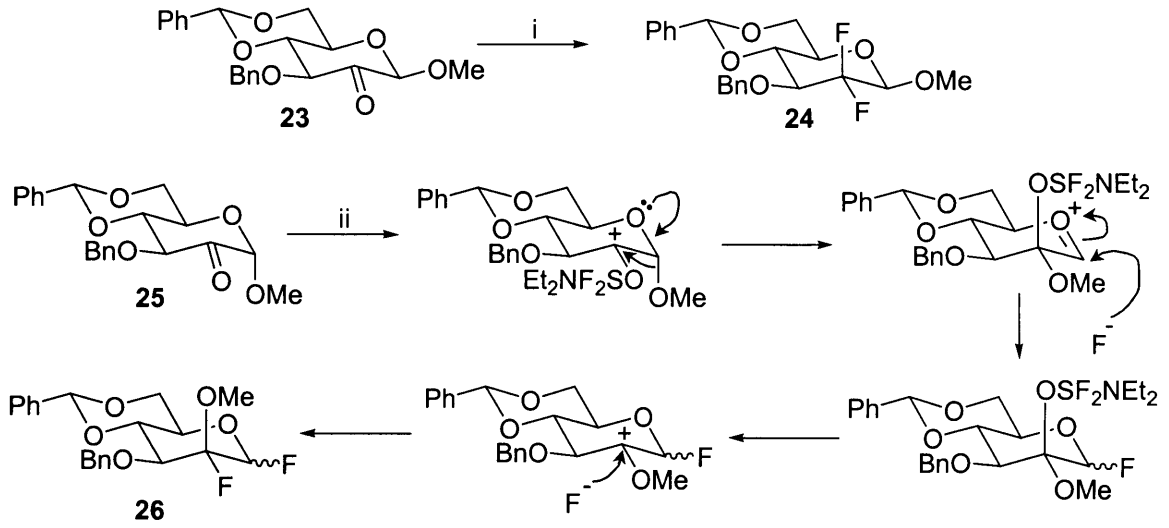
II.a - Direct fluorination

The synthesis of C-2 difluorinated monosaccharides raised a great deal of interest as the presence of the fluorines considerably increase the stability of glycosidic linkage towards acidic hydrolysis. Commonly, the preparation of such molecules is carried out with DAST on a ketonic precursor. This reaction is not necessarily straightforward as DAST is not chemoselective and therefore requires the use of many protecting groups. DAST is also toxic and potentially explosive and very often its low reactivity requires several equivalents to achieve the desired transformation. Moreover, the mechanism proposed by Middleton suggests the formation of a highly reactive intermediate, which may lead to side reactions depending on the substrate. This was exemplified by the difluorination of pivalaldehyde. Upon treatment with DAST monofluoro intermediate **18** is formed and can react along different pathways. In non-polar solvents, the desired *gem*-difluorinated compound **19** is obtained whereas polar solvents promote rearrangement of **18** to a more stable carbocation **20**, which can afford different products such as **21** and **22** (**Scheme 2**).[18]



Scheme 2

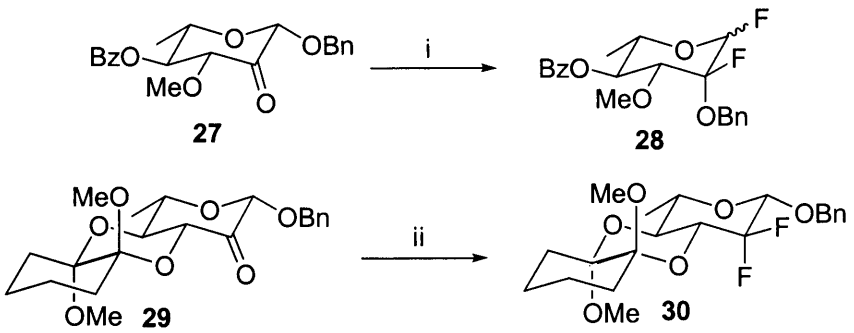
In the field of carbohydrate chemistry, Castillón *et al.* reported different outcomes for the attempted synthesis of 2-deoxy-2,2-difluorohexose derivatives, depending on the orientation of the substituent at the anomeric centre. Where the anomeric substituent was equatorial, the desired *gem*-difluorinated product **24** was obtained, whereas 1,2-difluoro-2-methoxy compound **26** was obtained in the case of an axial anomeric group (**Scheme 3**).[19]



Reagents and conditions: i, DAST (4.2 eq.), DCM, rt, 24 h., **24**, 80 %; ii, DAST (10 eq.), benzene, reflux, 24 h., **26**, 43%.

Scheme 3

Although, the *gem*-difluorination of **23** was successful when the neighbouring groups of the ketone were both equatorial, this cannot be generalised to any substrate. Indeed, when attempting the difluorination of ketone **27**, where both surrounding groups are equatorial, Castillón *et al.* observed a 1,2-migration to form 1,2-difluoro-monosaccharide derivative **28**. It was suggested that the unexpected outcome of this reaction was due to the greater flexibility of **27** compared to **23**. To overcome this difficulty, the more rigid substrate **29** was submitted to DAST fluorination to afford exclusively the desired *gem*-difluorinated product **30** (**Scheme 4**).[10]

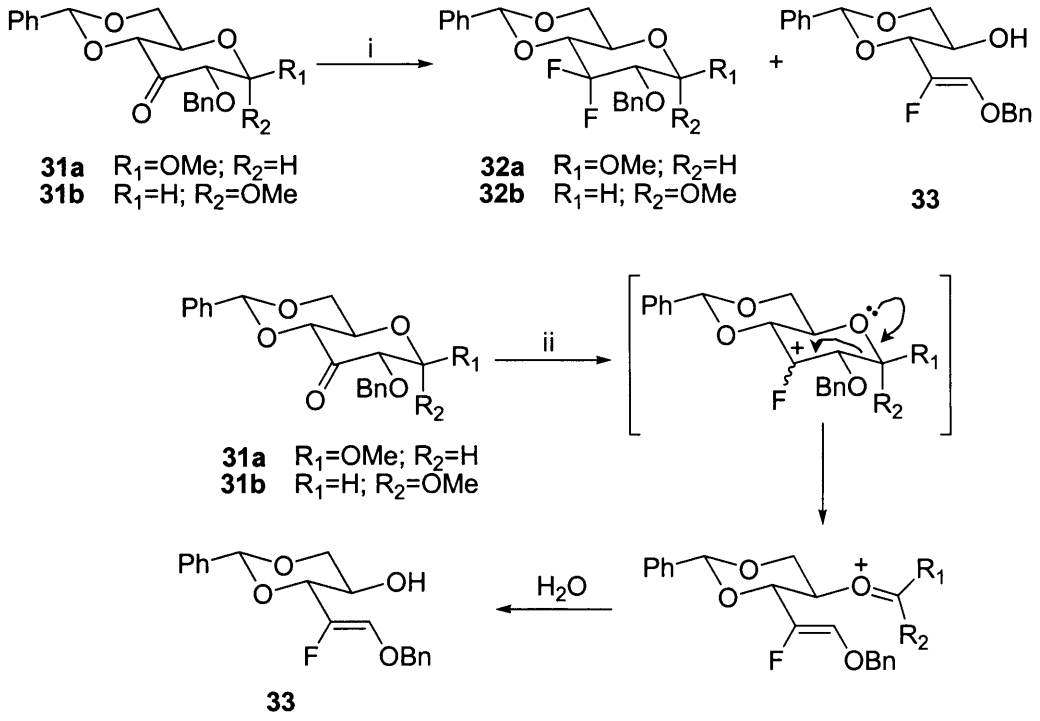


27 28 29 30

Reagents and conditions: i, DAST (6.3 eq.), DCM, rt, 24 h., **28**, 50 %; ii, DAST (7.8 eq.), DCM, rt, 6 h., **30**, 69 %

Scheme 4

DAST fluorination at the C-3 position can also be troublesome. Indeed, Castillón *et al.* attempted such a reaction on both α and β anomers of ketone **31** and isolated low yields of desired compounds **32a** and **32b** due to the competitive formation of by-product **33**, probably formed by a Grob-type fragmentation (**Scheme 5**).[19]



31a R_1=OMe; R_2=H
31b R_1=H; R_2=OMe

32a R_1=OMe; R_2=H
32b R_1=H; R_2=OMe

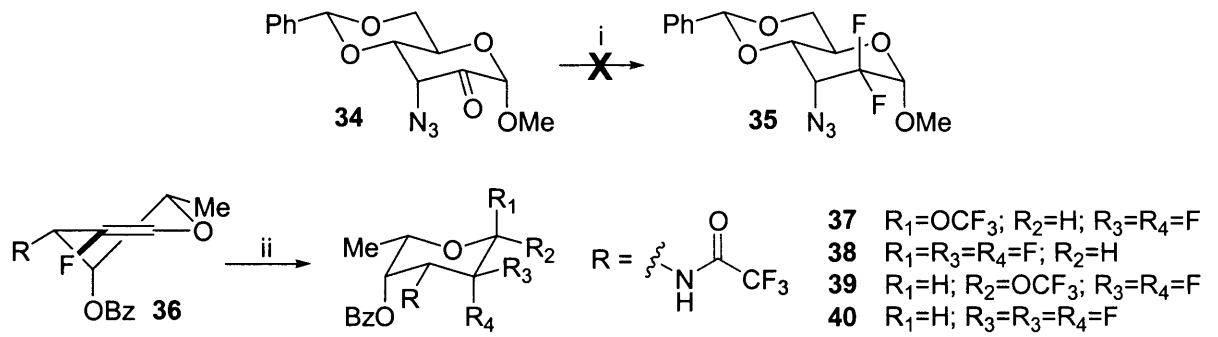
33

Reagents and conditions: i, DAST (10 eq.), benzene, reflux, 10 h., **32a**, 40 % and **33**, 17 % from **31a**, and **32b**, 48 % and **33**, 10 % from **31b**.

Scheme 5

Similarly, Lukacs *et al.* attempted the synthesis of 2,2-difluorodaunosamine **35** by DAST fluorination of ketonic precursor **34** but obtained complex mixtures. Therefore,

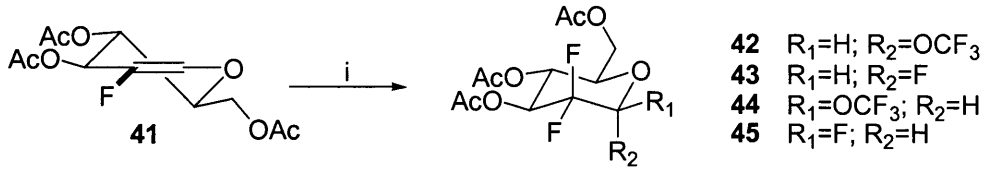
they resorted to the addition of the very reactive trifluorofluoroxymethane to 4-*O*-benzyl-3,6-dideoxy-2-fluoro-3-trifluoroacetmido-L-galactal **36**. This reaction afforded a mixture of compounds, which required careful chromatography to allow the separation of four different protected 2,2-difluorodaunosamine derivatives **37-40** (**Scheme 6**).[20]



Reagents and conditions: i, DAST; ii, CF_3OF (60 eq.), $CFCl_3$, CaO, -70 °C, **37**, 6 %, **38**, 10 %, **39**, 15 % and **40**, 20 %.

Scheme 6

This synthesis is closely related to the work described by Adamson *et al.* who synthesised 2-deoxy-2,2-difluoro-D-*arabino*-hexose derivatives **42-45** from fluoroglucal **41** by addition of trifluorofluoroxymethane (**Scheme 7**).[21]

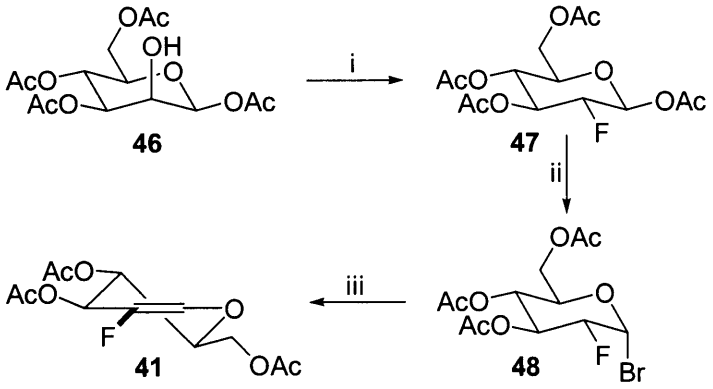


Reagents and conditions: i, CF_3OF, -78 °C, **42**, 8.5 %, **43**, 50 %, **44**, 2 % and **45**, 16 %.

Scheme 7

Obviously these syntheses require an additional fluorination step to prepare monofluoroglycal **36** or **41**. This transformation is usually achieved by treatment of a suitably protected monosaccharide such as **46** with DAST to afford the corresponding monofluoro-sugar **47**,[22,23] which is subsequently treated with hydrogen

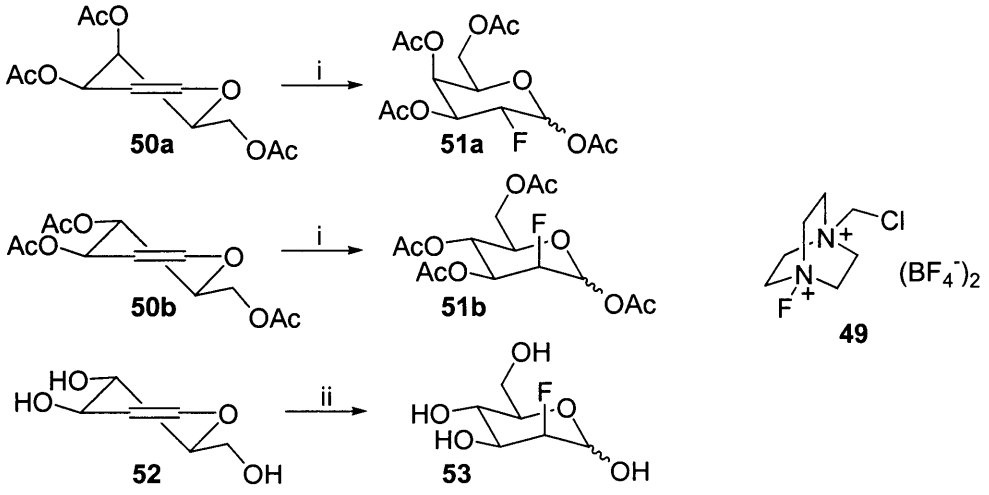
bromide to afford pyranosyl bromide **48**. Elimination promoted by triethylamine then affords the desired fluoro-glycal **41** (**Scheme 8**).[21]



Reagents and conditions: i, DAST, diglyme, **47**, 77 %; ii, HBr; iii, Et_3N, CH_3CN, reflux.

Scheme 8

An alternative synthesis of 2-deoxy-2-fluoro sugars was described by Wong *et al.* using Selectfluor **49** as the fluorinating agent. Although the use of Selectfluor **49** in carbohydrate chemistry remains rare, it allows the clean transformation of glycals such as **50a** and **50b** into the corresponding 2-deoxy-2-fluoro-sugars **51a** and **51b**. Interestingly, the reaction can be carried out in the absence of protecting groups as shown for glycal **52** (**Scheme 9**).[24]

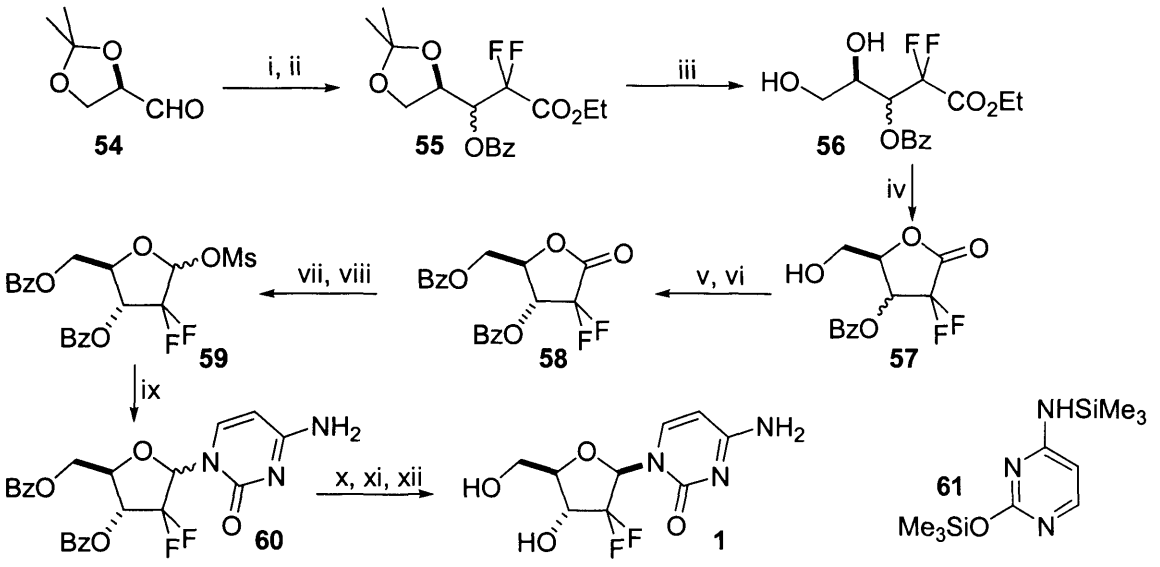


Reagents and conditions: i, Selectfluor (1.5 eq.), DMF/H_2O (3/1), rt, **51a**, 79 % and **51b**, 90 %; ii, Selectfluor (1.5 eq.), H_2O, rt, **53**, 85 %.

Scheme 9

II.b - The building block approach

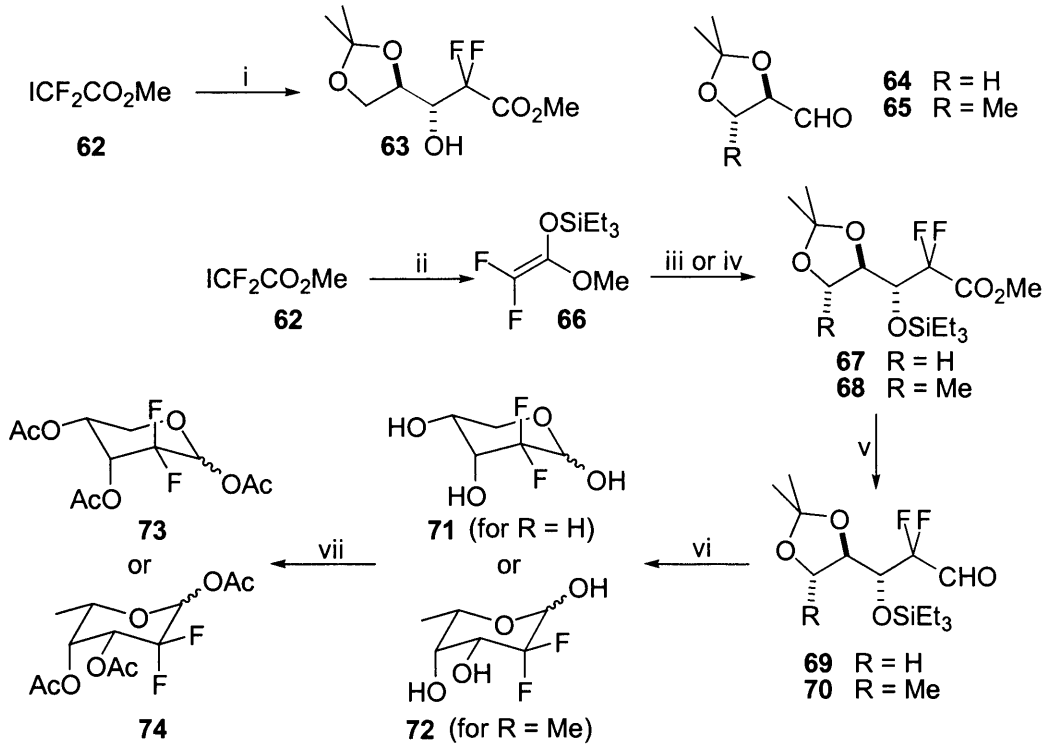
The alternative to direct fluorination is the building block approach, which was successfully applied to a twelve step synthesis of Gemcitabine **1** by Lilly Research Laboratories on a multigram scale. Protected glyceraldehyde **54** was reacted with ethyl bromodifluoroacetate in a Reformatsky reaction and the newly formed hydroxyl group was protected as the corresponding benzoate ester **55**. The acetonide was hydrolysed and subsequent azeotropic distillation with toluene afforded exclusively the 5-membered lactone **57** as a mixture of diastereoisomers. Benzoylation of the primary hydroxyl group allowed selective crystallisation of the desired diastereoisomer **58**. Lactone **58** was then reduced to the lactol and the corresponding mesylates **59** were reacted with silylated pyrimidine derivative **61**. Interestingly, this glycosylation reaction was carried out successfully despite the neighbouring difluoromethylene moiety, suggesting that the positive charge of the oxocarbenium cation-like transition state is predominantly localised on the oxygen rather than the carbon. Deprotection of the hydroxyl groups, acidification and selective crystallisation afforded Gemcitabine **1** as the corresponding hydrochloride salt (**Scheme 10**).[25]



Reagents and conditions: i, $BrCF_2CO_2Et$, Zn, THF/Et_2O; ii, BzCl, 2,6-lutidine, DMAP, DCM, 35 °C; iii, $MeCN/H_2O/CF_3COOH$, reflux, 3 h.; iv, toluene, azeotropic distillation; v, py., DMAP, BzCl, EtOAc, 65 °C, 2h.; vi, selective crystallisation; vii, $LiAl(O^tBu_3)H$, Et_2O/THF, 10 °C, 1.5 h.; viii, Et_3N, MsCl, DCM, rt, 2h.; ix, **61**, 1,1,2-trichloroethane, reflux, 18 h.; x, MeONa, MeOH; xi, HCl, ^{i}PrOH; xii, selective crystallisation.

Scheme 10

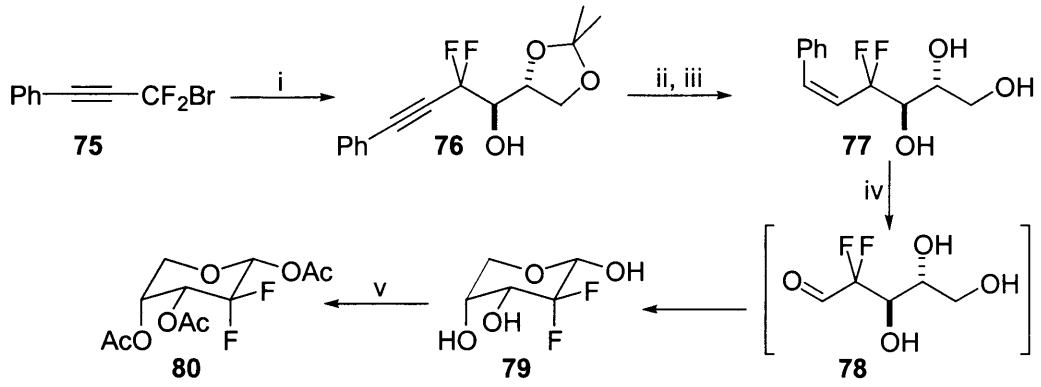
Similarly, Kobaysahi reported a building block synthesis of 2-deoxy-2,2-difluoro-hexose derivatives **73** and **74** also based on a Reformatsky reaction between iodofluoroacetate **62** and aldehydes **64** or **65** respectively. Although the direct Reformatsky reaction of acetate **62** and aldehyde **64** was successful the diastereoselectivity was very low but could be greatly improved by the reaction of silyl ketene acetal **66**, prepared *in situ* by reaction of the Reformatsky reagent with triethylsilyl chloride. Subsequent DIBAL-H reduction of the esters followed by hydrolysis of the acetonides and silyl ethers afforded 2-deoxy-2,2-difluorohexose derivatives **71** and **72**, which were converted to the corresponding tri-acetates **73** and **74** respectively (**Scheme 11**).[26]



Reagents and conditions: i, Zn, **64**, CH_3CN, 0 °C, 2 h., **63**, 45 % (syn/anti = 1/1.8); ii, Zn, Et_3SiCl, CH_3CN, 0 °C; iii, **64**, 0 °C, 20 min., **67**, 74 % (syn/anti = 1/9); iv, **65**, 0 °C, 40 min., **68**, 90 % (syn/anti = 1/17); v, DIBAL-H, Et_2O, -78 °C; vi, CF_3COOH/H_2O, rt, 2.5 h.; vii, Et_3N, Ac_2O, DMAP, 30 min., **73**, 82 % and **74**, 88 % over 3 steps.

Scheme 11

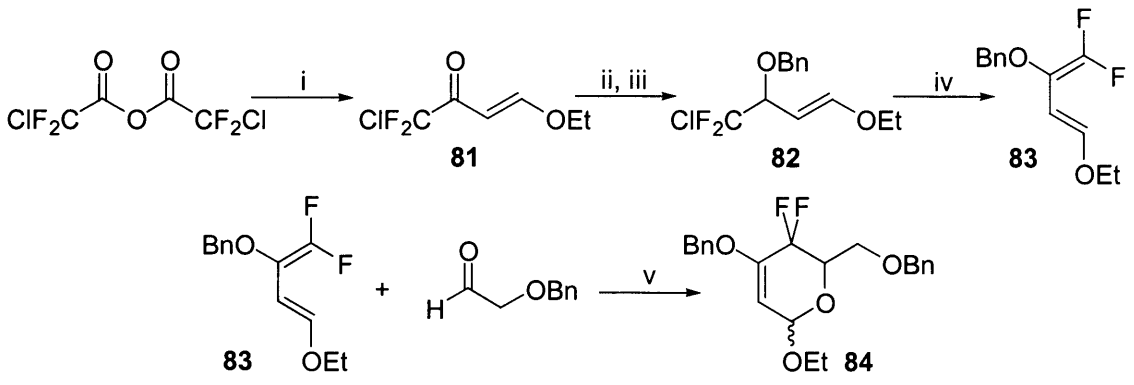
The same group also reported the synthesis of difluorinated monoasaccharide analogue **79** *via* a different route. Bromodifluoromethylacetylene **75** was reacted with adehyde **64** in a Barbier-type reaction to afford difluorinated homopropargylic alcohol **76**, which was reduced to the corresponding homoallylic alcohol **77** with Lindlar's catalyst. Deprotection of the acetonide, followed by ozonolysis of the double bond triggered a cyclisation to form triol **79**, which was acetylated to tri-acetate **80** (**Scheme 12**).[27]



Reagents and conditions: i, **64**, Zn, cat. $HgCl_2$ (5 mol%), THF, 0 °C, **76**, 78 % (syn/anti = 1/2); ii, Pd-$BaSO_4$, H_2; iii, H_3O^+; iv, O_3 then Me_2S; v, Ac_2O, Et_3N, DMAP.

Scheme 12

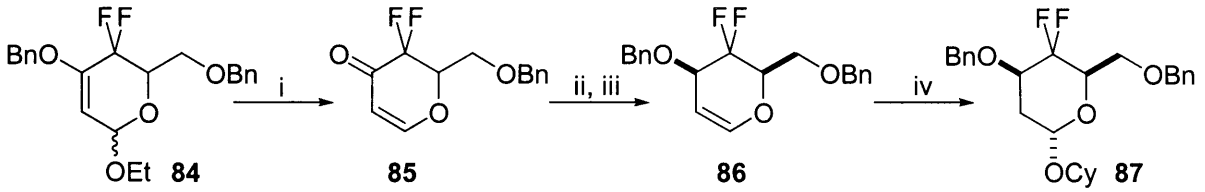
Taguchi *et al.* reported a route towards 4-deoxy-4,4-difluoropyranosides using a building block approach based on a hetero-Diels Alder reaction between difluorinated diene **83** and benzyloxyacetaldehyde. Diene **83** was synthesised from commercially available chlorodifluoroacetic anhydride, which was reacted with ethylvinyl ether to afford enone **81**. Lithium aluminium hydride reduction followed by protection afforded enol ether **82**. Upon treatment with a strong base, hydrochloric acid was eliminated and the desired diene **83** was obtained in good yield but used without purification as it decomposed during attempted chromatography or distillation (**Scheme 13**).[28]



Reagents and conditions: i, CH_2=CHOEt, py., DCM, 12 h., rt, **81**, 60%; ii, $LiAlH_4$, Et_2O, -78 °C; iii, NaH, BnBr, THF/DMF, 0 °C, 1h., **82**, 64 % over 2 steps; iv, ^{t}BuOK, THF, -50 °C, **83**, 90 %; v, cat. $ZnCl_2$, -50 °C to rt, 12 h., **84**, 79 %.

Scheme 13

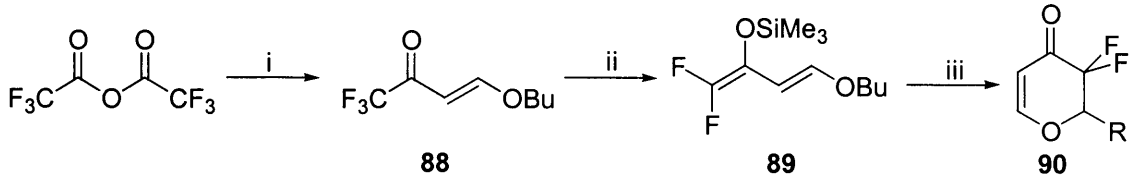
Taguchi *et al.* processed cycloaddition adduct **84** to 2,4-dideoxy-4,4-difluoro-pyranoside derivative **87** but did not report the synthesis of the corresponding 4-deoxy-4,4-difluoro-pyranoside (with a hydroxyl group at the C-2 position). Adduct **84** was converted to enone **85** by treatment with *p*-toluenesulphonic acid in DCM at room temperature. Luche reduction with sodium borohydride and cerium (III) chloride heptahydrate followed by protection and treatment with cyclohexyl alcohol afforded cyclohexyl pyranoside **87** with high 2,6-*trans*-selectivity (1:13) (**Scheme 14**).[28]



Reagents and conditions: i, *p*TsOH, DCM, rt, 2 h., **85**, 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., **86**, 86 % over 2 steps; iv, *p*TsOH, CyOH, DCM, rt, 24 h., **87**, 79%.

Scheme 14

Uneyama *et al.* adopted a similar approach and prepared a similar difluorinated diene **89** by a shorter route. Trifluoromethyl enone **88** was treated with magnesium and trimethylsilyl chloride to afford difluorinated Danishefsky's diene **89** by selective cleavage of a C-F bond of the trifluoroketone. Diene **89** was then reacted with aldehydes in [4+2] Diels-Alder reactions to deliver dihydropyrones **90**, which were not processed any further towards difluorinated monosaccharide analogues (**Scheme 15**).[29]



Reagents and conditions: i, CH_2=CHOBu, py., DCM, 12 h., rt, **88**, 80-90 %; ii, Mg (8.0 eq.), Me_3SiCl (8.0 eq.), DMF, 50 °C, 3 min., **89**, 85 %; iii, RCHO, cat. $ZnBr_2$, DCM then cat. TFA, CCl_4, **90**, 50-64 %.

Scheme 15

In conclusion, direct fluorination has been widely used for the synthesis of *gem*-difluorinated monosaccharide analogues. This approach can be very efficient but the stereochemical outcome of reactions such as DAST difluorinations depend highly on the stereochemistry of the precursor. Moreover, the substrates used in these reactions have to be fully protected as most fluorinating reagents are not chemoselective. Alternatively, the building block approach allows the use of conventional reactions and therefore potentially opens access to a wide range of asymmetric transformations to synthesise difluorinated molecules stereoselectively. Nevertheless, the building block approach is not straightforward as the introduction of fluorines in a substrate may change considerably its reactivity in well established reactions.

III – Ring-closing Metathesis

III.a – Catalysts and mechanism

Olefin metathesis is a unique carbon-carbon bond forming reaction in which unsaturated carbon-carbon bonds react together in the presence of metal carbene complexes to form a new carbon-carbon double bond. The reaction does not usually require additional reagents other that a catalytic amount of metal carbene and the only by-product, in most cases, is a volatile olefin such as ethylene. When the reaction is carried out intramolecularly, a ring is formed and the reaction is then called ring-closing metathesis (RCM).

RCM has received a lot of attention in the past few years as it allows the easy synthesis of medium to large sized rings from acyclic diene precursors.[30-34] The growing interest in RCM was triggered by the development of well defined metal

alkylidene catalysts, which do not require Lewis acidic co-catalysts or promoters, unlike earlier olefin metathesis catalysts. The first effective well defined molybdenum catalyst **91** was developed by Schrock *et al.*.[35] Although, this complex is very active, it is also very sensitive to air and moisture and therefore requires careful handling. Grubbs *et al.* and other groups developed various ruthenium based catalysts such as **92-95**,[36-44] which are tolerant to many functional groups and less sensitive to air and moisture than Schrock's catalyst **91**. The introduction of *N*-heterocycle carbenes as ligands in **94** and **95** instead of a tricyclohexylphosphine increased considerably the activity of these catalysts by increasing their lifetimes (**Figure 6**).

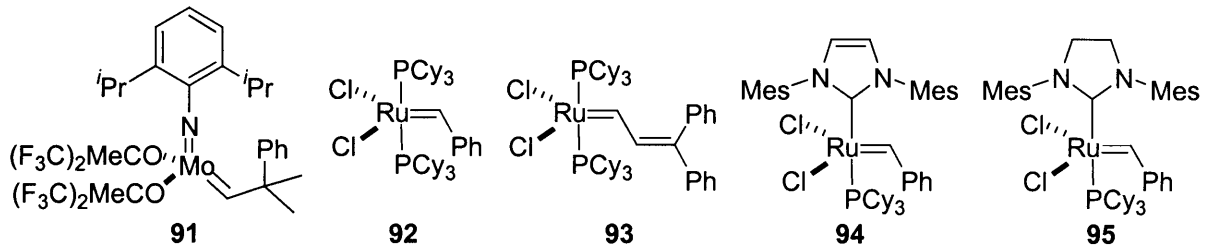
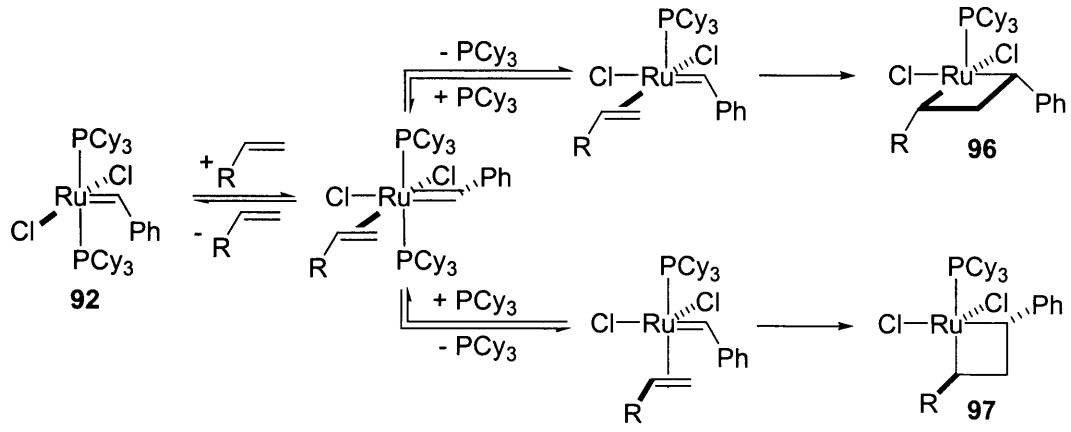


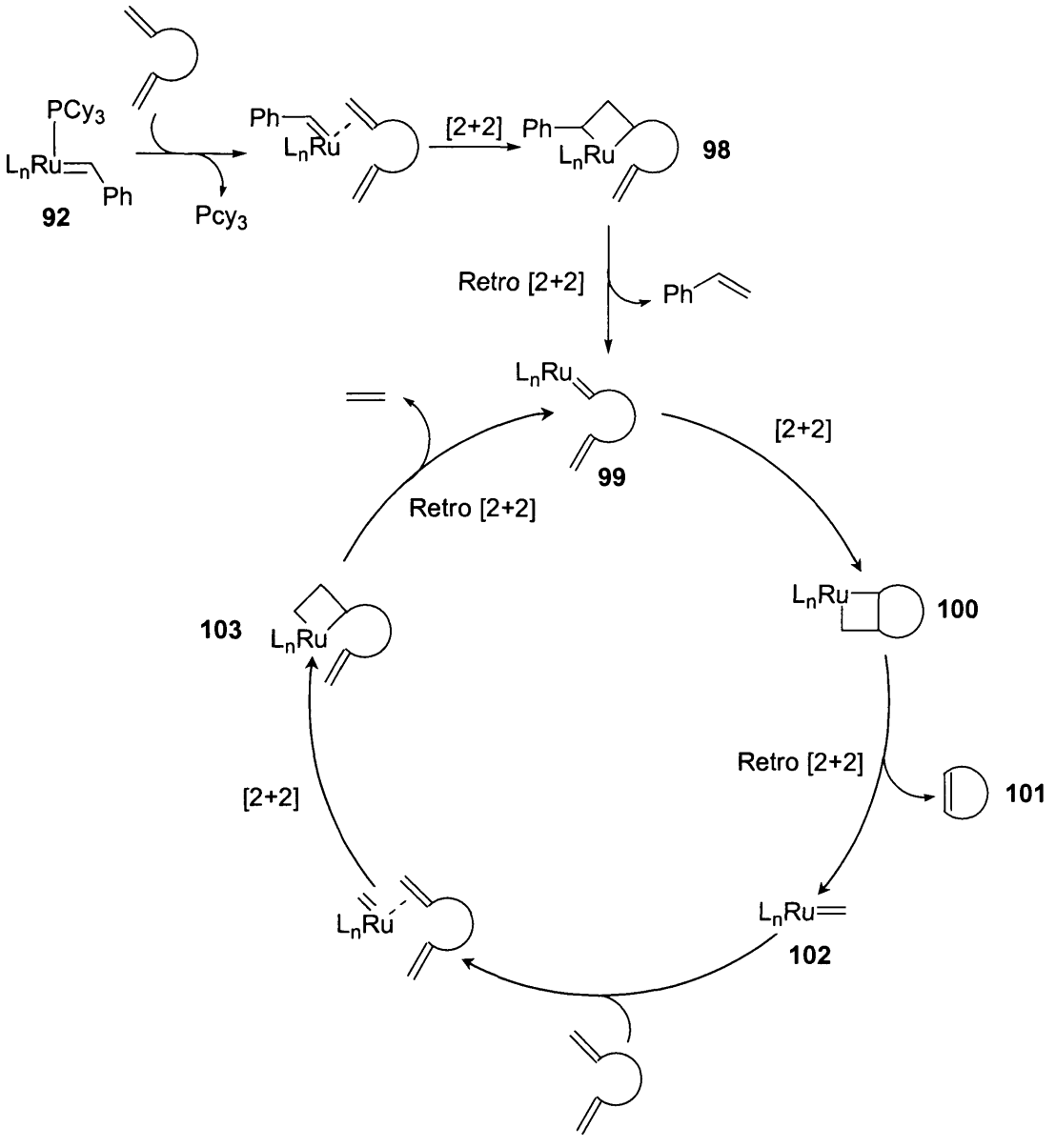
Figure 6

The commonly accepted RCM mechanism for Grubbs' catalyst **92** is shown below. First the catalyst has to lose one of its tricyclohexylphosphine ligands to coordinate with one of the double bonds of the substrate. A formal [2+2] cycloaddition takes place to form metallocyclobutane **96** or **97** (**Scheme 16**).[45]



Scheme 16

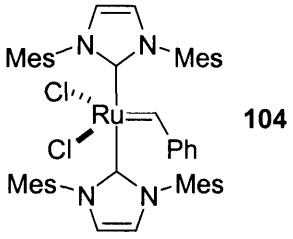
The generic metallocyclobutane **98** then undergoes a formal reverse [2+2] cycloaddition to afford ruthenium carbene **99** and styrene. Ruthenium carbene **99** goes through the same sequence intramolecularly to deliver the RCM product **101**, ethylene and the new catalytic alkylidene **102**, which enters the catalytic cycle again (**Scheme 17**).



Scheme 17

It is noteworthy that Grubbs' catalyst **92** is usually a pre-catalyst as after one turnover, the active catalytic species **102** does not bear any substituent on the alkylidene moiety, at least for the RCM of terminal alkenes.

To be effective the ruthenium catalysts need a loosely binding ligand such as tricyclohexylphosphine to dissociate and allow coordination to the alkene. Grubbs' catalyst **92** bears two of these ligands and tends to decompose relatively quickly in solution by losing both of them. The lifetime of Grubbs' catalyst, and therefore its activity, were considerably improved by replacing one of the tricyclohexylphosphine by a strongly binding ligand such as the *N*-heterocycle carbenes of catalysts **94** and **95**.[36-38,43,44] Interestingly, in catalyst **104**, addition of a second carbene ligand tends to decrease its activity towards RCM as no ligand can dissociate easily from the catalyst to trigger the initial [2+2] cycloaddition (**Figure 7**).[46]

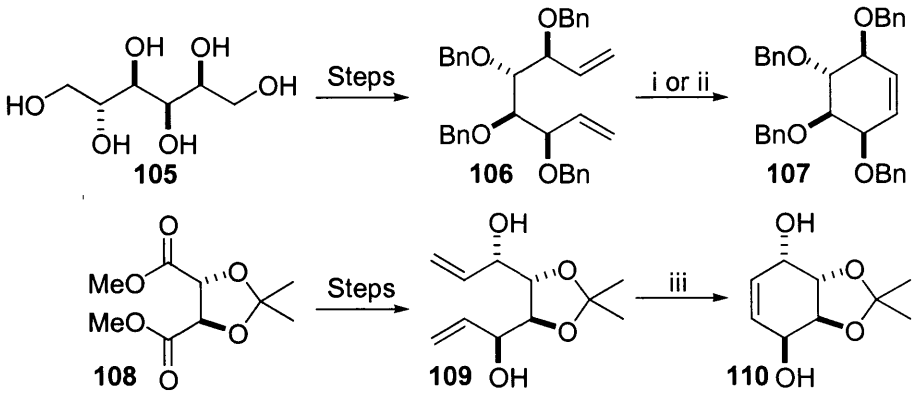


104

Figure 7

III.b – Applications of ring-closing metathesis in synthesis

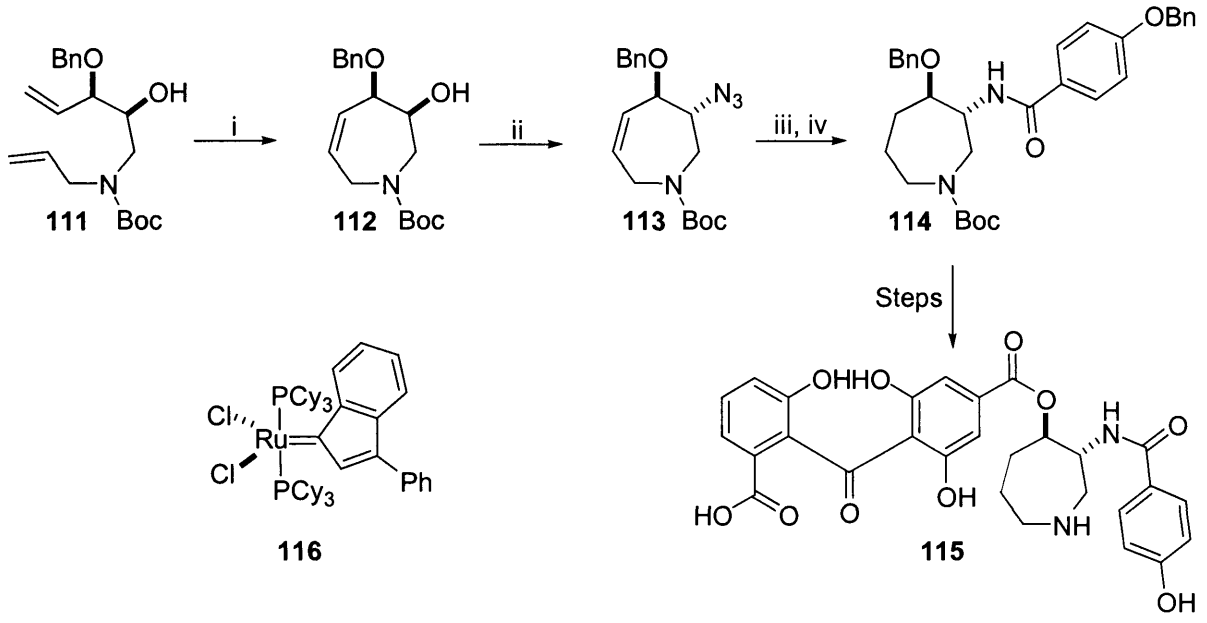
The development of numerous, efficient, easy to handle metathesis catalysts opened a wide field of applications for RCM in the synthesis of various complex molecules, including natural products. The first successful RCM's were reported for the synthesis of 5- and 6-membered rings, which are usually stable and easy to form. For example, RCM was used by Fürstner *et al.* to construct conduritols quickly from commercially available starting materials such as D-glucitol **105**. This example also shows clearly the difference in reactivity between Grubbs' catalyst **92** and Nolan's catalyst **94**. Indeed, a much better yield was achieved in a shorter time with **94** compared to **92**. Interestingly, catalyst **94** achieved RCM of **109** in good yield (69 %) in the presence of two unprotected hydroxyl groups in the substrate (**Scheme 18**).[47]



Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), DCM, reflux, 60 h., **107**, 32 %; ii, Nolan's cat. **94** (5 mol%), DCM, refllux, 2 h., **107**, 89 %; iii, Nolan's cat. **94** (1.5 mol%), DCM, reflux, 2 h., **110**, 69 %.

Scheme 18

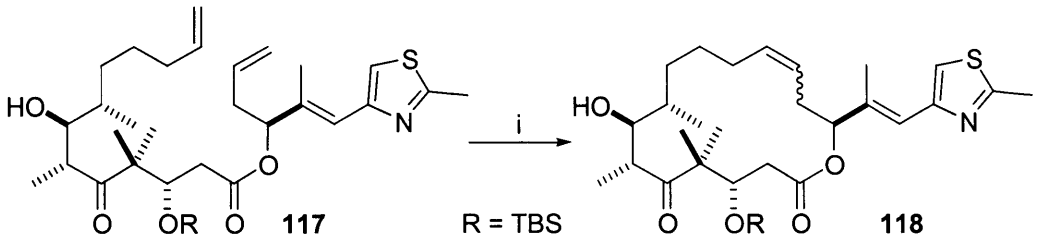
RCM can also be used to form medium-sized carbo- or heterocyles. For example, Fürstner *et al.* used RCM as a key step in the total synthesis of the alkaloid (-)-balanol **115**, thus making its synthesis much shorter compared to the (at least) twelve steps required in previous approaches. The key seven-membered heterocycle was prepared by RCM, followed by hydrogenation to afford saturated amine **114**, which was elaborated to (-)-balanol **115** (**Scheme 19**).[48]



Reagents and conditions: i, cat. **116** (5 mol%), **112**, 87 %; ii, $(PhO)_2P(O)N_3$, PPh_3, DEAD, **113**, 91 %; iii, H_2, Pd/C; iv, *p*-$BnOC_6H_4COCl$, Et_3N, **114**, 55 % over 2 steps.

Scheme 19

RCM was also applied successfully to the synthesis of macrolides by Nicolaou *et al.* for the synthesis of the epothilone skeleton. This example also illustrates the tolerance of Grubbs' catalyst **92** towards various functional groups as the substrate includes an ester, a ketone, a free hydroxyl group and a thiazole. Due to the size of the ring, the desired (*Z*)-isomer (*Z*)-**118** was isolated along with the corresponding (*E*)-16 membered macrocycle (*E*)-**118** (**Scheme 20**).[49,50]

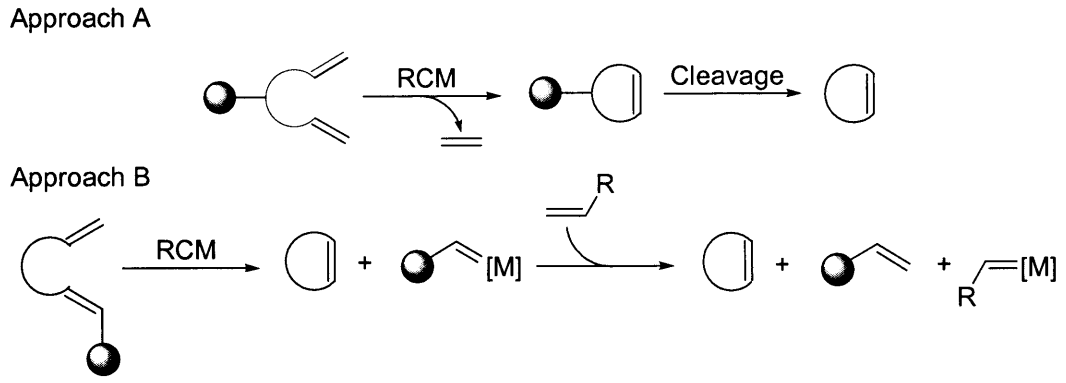


Reagents and conditions: i, Grubbs' cat. **92** (15 mol %), DCM, rt, 8 h., (*Z*)-**118**, 50 % and (*E*)-**118**, 35 %.

Scheme 20

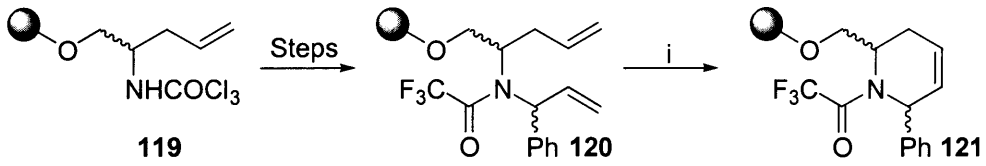
Among recent developments, RCM has been adapted to polymer-supported synthesis using two different strategies. In the first approach (Approach A), the diene substrate is covalently bound to the solid support and the product is cleaved by conventional methodology after RCM. This approach may be used in a sequence of reactions carried out on solid phase and allows easy removal of traces of catalysts by repeated washings. Alternatively, the substrate can be attached to the resin by one of its double bonds (Approach B). During the RCM, the desired cyclic species is formed and released in the solution at the same time. This strategy has the advantage of liberating only compounds with the correct functionality, whereas any by-products or starting material stays covalently bound to the solid support. However, in this approach the catalyst is captured by the polymer matrix during each productive cyclisation/cleavage process, so high loadings of catalyst have to be used to observe good conversions. Alternatively, an auxiliary terminal alkene, such as ethylene or oct-

1-ene, can be used to liberate the catalyst from the bead by cross-metathesis and reconvert it to a soluble species (**Scheme 21**).



Scheme 21

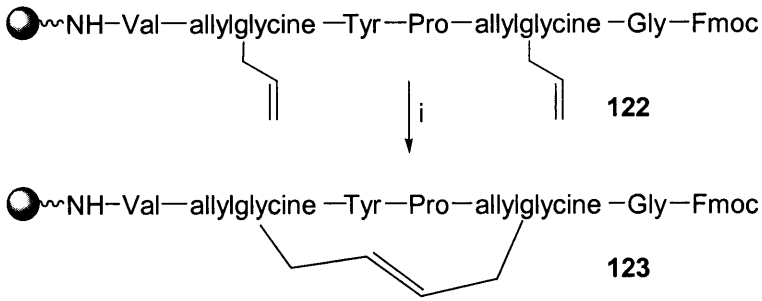
The first approach was used by Blechert *et al.* to prepare cyclic amine **121** as a proof of concept. Substrate **120** was synthesised by a conventional solid phase strategy on a tritylpolystyrol resin. Treatment with Grubbs' catalyst **92** (13 mol%) in refluxing DCM for 12 hours afforded the desired product **121** in 90 % yield (**Scheme 22**).[51]



Reagents and conditions: i, Grubbs' cat. **92** (13 mol%), DCM, reflux, 12 h. **121**, 90 %.

Scheme 22

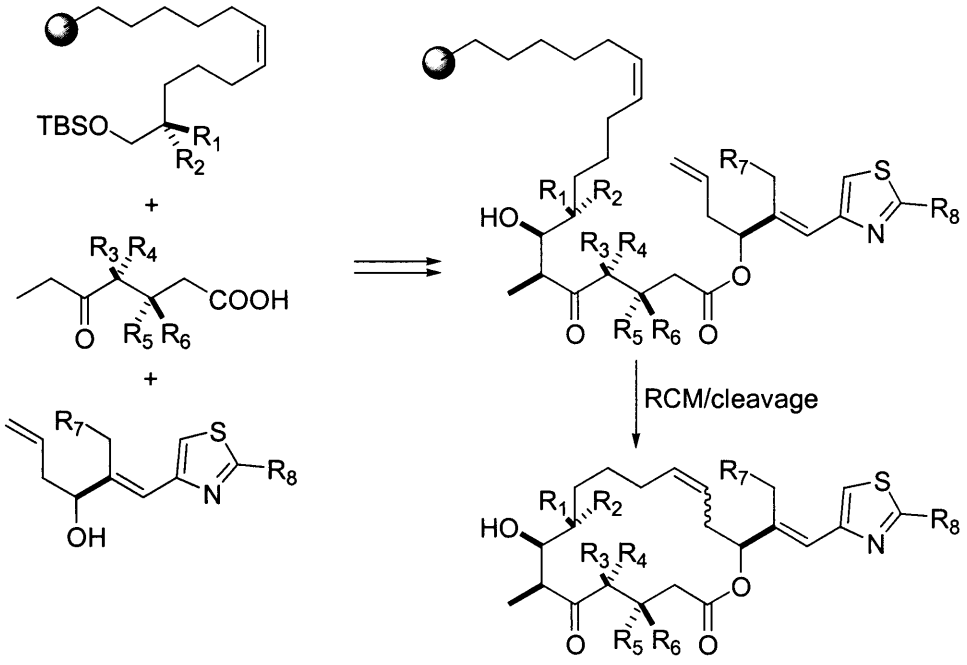
This polymer-supported approach is particularly suited to achieve RCM of a substrate that suffers from poor solubility in the usual non-polar organic solvents in which the metal carbene complexes are usually the most efficient. For example, Grubbs *et al.* prepared peptidic diene **122** by standard solid phase peptide synthesis on a Tentagel resin, and carried out the heterogeneous RCM in refluxing DCM to afford the desired cyclic peptide **123** in 65 % yield after cleavage (**Scheme 23**).[52]



Reagents and conditions: i, Grubbs' cat. **92** (0.5 eq.), DCM, reflux, 22 h., **123**, 65 %.

Scheme 23

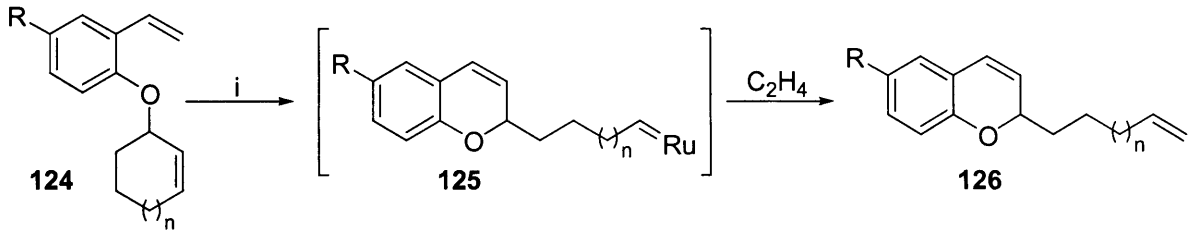
The potential of the second approach to polymer-supported RCM was demonstrated by Nicolaou *et al.*, who prepared a small library of epothilone analogues, which could be promising anti-cancer agents. The diversity was introduced during the polymer-supported synthesis of the RCM precursors. The RCM was carried out to perform the macrocyclisation and release the products into solution. This cyclisation/cleavage strategy is outlined below (**Scheme 24**).[49,50]



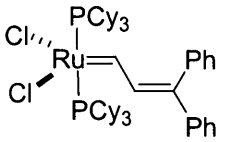
Scheme 24

RCM has also been used as part of more complex cascade-reactions to promote rearrangement *via* a ring-opening metathesis (ROM)/ring-closing metathesis

(RCM)/cross-metathesis (CM) sequence. For example, Hoveyda *et al.* treated ethers **124** with catalyst **93** to carry out the ROM/RCM sequence to produce 2-substituted chromenes **126** after treatment with ethene, which reacts in a cross-metathesis process with ruthenium carbenes **125** (**Scheme 25**).[53]



n	R	Yield
1	H	35 %
2	H	92 %
2	OMe	100 %
2	F	86 %
3	H	90 %
3	NO_2	84 %

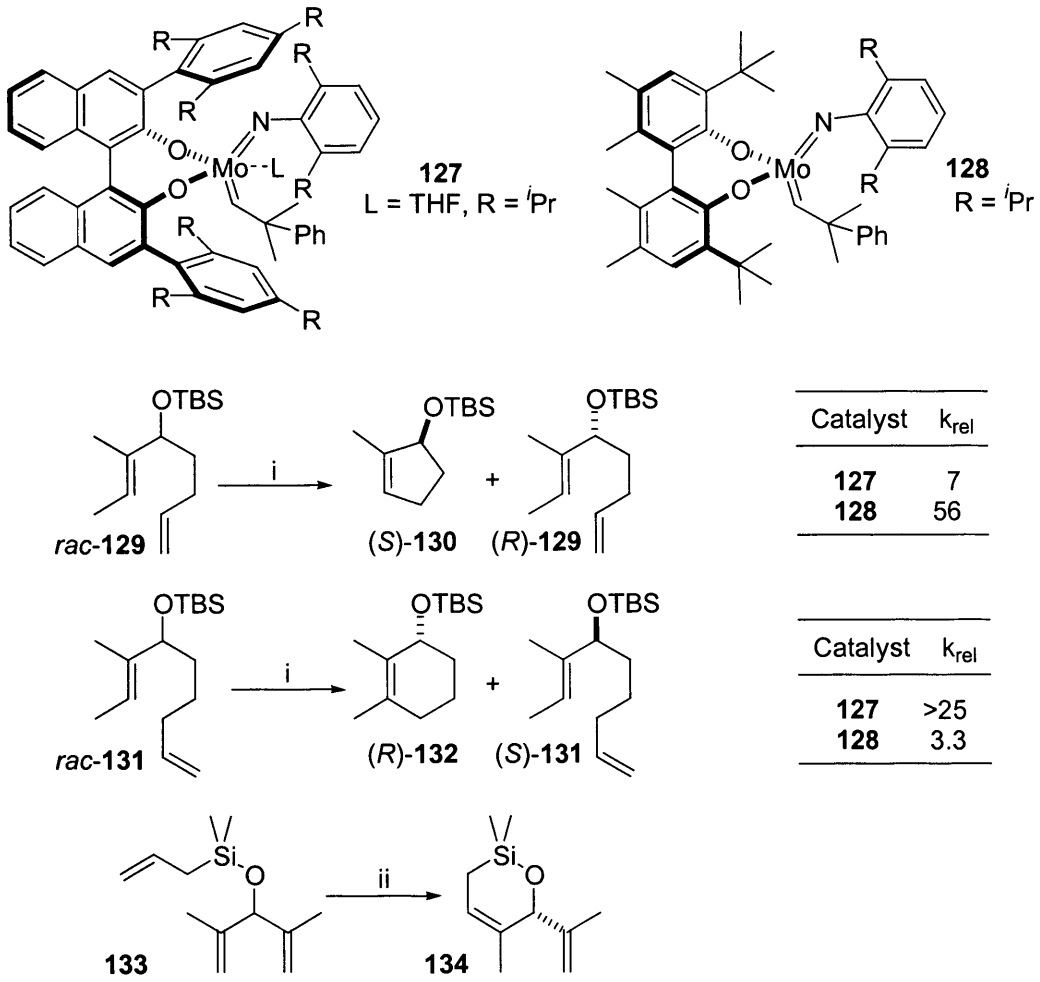


93

Reagents and conditions: i, cat. **93** (5 mol%), DCM, rt, 10-14 h..

Scheme 25

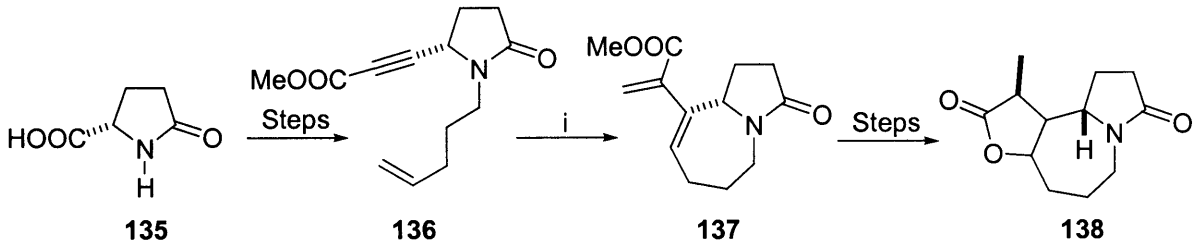
In the context of the syntheses of natural products and complex chiral molecules, the development of an asymmetric RCM has become a challenge for the past few years. So far, Schrock *et al.* are the most successful group in this field and have achieved kinetic resolutions and asymmetric transformations using molybdenum-based catalysts **127** and **128**. Although the reactions were carried out on simple substrates, Schrock *et al.* demonstrated the potential of asymmetric RCM, which will probably be developed further in target-oriented synthesis (**Scheme 26**).[54-57]



Reagents and conditions: i, cat. **127** or **128** (5 mol%), benzene, 25 °C; ii, cat. **127** (2 mol%), **134**, 98 %, ee>99 %.

Scheme 26

Beyond alkene metathesis, ruthenium catalysts such as **92** and **94** were also successfully used for enyne metathesis in which the substrate bears an alkene and an alkyne instead of two alkenes. The ring-closure product is a diene, which can be used for further transformations. For example, Kinoshita *et al.* developed a synthesis of (-)-stemoamide **138** using enyne metathesis as the key step and processing diene **137** to the desired product **138** (**Scheme 27**).[58]



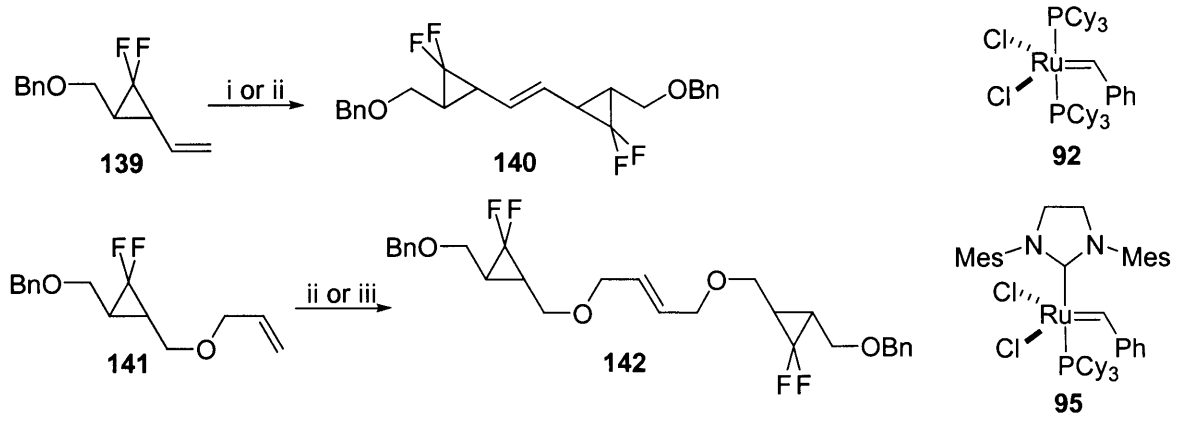
135 136 137 138

Reagents and conditions: i, cat. **93** (4 mol%), **137**, 87 %.

Scheme 27

III.c - Metathesis of fluorinated substrates

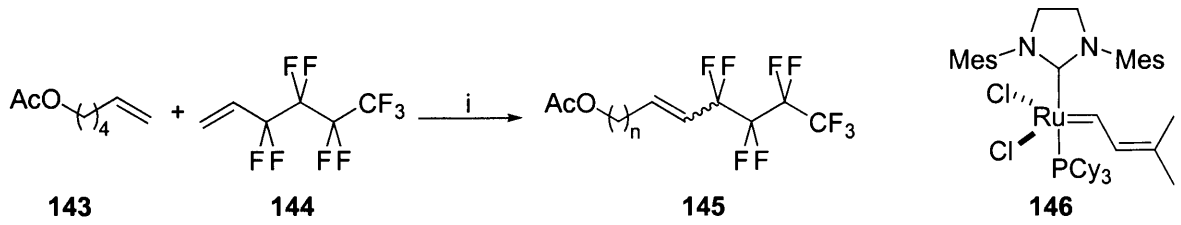
Although metathesis is a powerful tool for carbon-carbon bond formation and has been widely used in synthesis for the past few decades, examples of metathesis involving fluorinated substrates are scarce in the literature. Itoh *et al.* reported the cross-metathesis of difluorinated molecules by using both standard and modified Grubbs' catalysts **92** and **95**. Cross-metathesis of *trans*-1-benzyloxymethyl-2,2-difluoro-3-vinylcyclopropane **139** proved to be very sluggish with **92**, requiring a full equivalent of catalyst to isolate only 35 % of dimer **140**. The more active catalyst **95** achieved the same moderate yield when used in catalytic amount (15 mol%). Cross-metathesis of allylic ether **141**, where the fluorines are farther away from the double bond, proved more effective with both catalysts **92** and **95**. These examples seem to show that the presence of the fluorine atoms in the vicinity of the double bond tend to decrease considerably the rate of the reaction, even if the cyclopropyl ring may also have an adverse effect on the cross-metathesis process. Unfortunately, neither the effects of the fluorine atoms or the cyclopropyl ring have been quantified (**Scheme 28**).[59]



Reagents and conditions: i, Grubbs' cat. **92** (1.0 eq.), DCM, rt, 48 h., **140**, 35 %; ii, cat. **95** (15 mol%), DCM, rt, **140**, 35 % from **139** and **142**, 86 % from **141**; iii, Grubbs' cat. **92** (15 mol%), DCM, rt, 36 h., **142**, 80%.

Scheme 28

More interestingly, Grubbs *et al.* reported a single example of cross-metathesis involving an electron-deficient alkene bearing two fluorine atoms at the allylic position. Cross-metathesis between fluorinated alkene **144** and 6-acetoxy-hex-1-ene **143** proceeded in moderate yield (34 %) despite the use of active catalyst **146**. This poor result was attributed to the very electron deficient nature of the alkene flanked with fluorines (**Scheme 29**).[36]

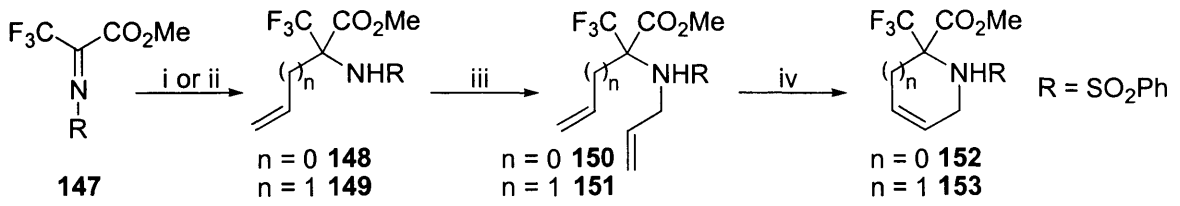


Reagents and conditions: i, cat. **146** (5 mol%), DCM, reflux, 12 h., **145**, 34 %.

Scheme 29

Examples of synthesis of fluorinated cyclic molecules *via* ring-closing metathesis are also very scarce in the literature. Dixneuf *et al.* reported the synthesis of fluorine-containing cyclic amino acid derivatives *via* ring-closing metathesis. Their route started with allylation or vinylation of trifluoromethyl imines **147**, followed by *N*-allylation of the corresponding amines **148** and **149**, to afford the RCM precursors

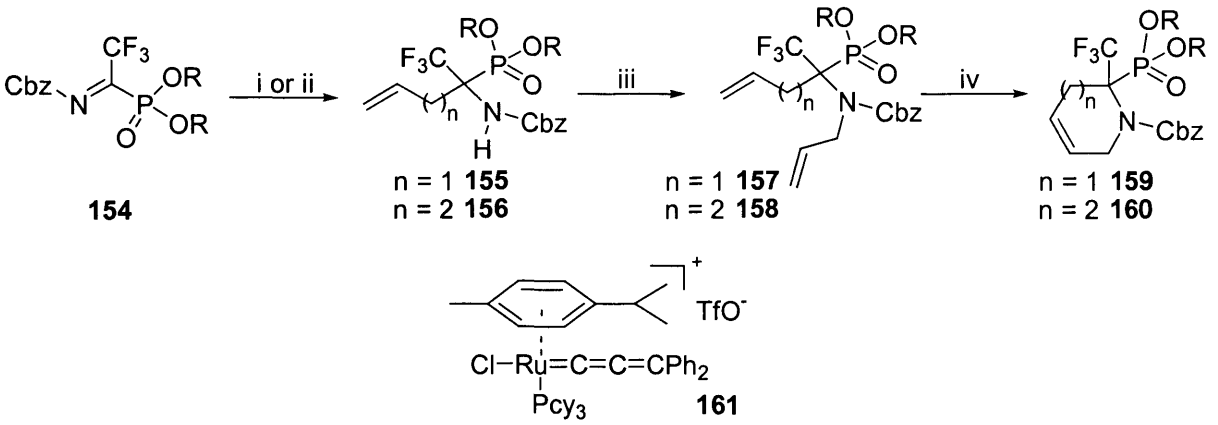
150 and **151**. Ring-closing was carried out with Grubbs' catalyst **92** to yield to 5- or 6-membered fluorinated amino acids derivatives **152** and **153** respectively. In this example, the fluorine atoms probably have little influence on the RCM process as they are remote from both alkenes and they do not exert strong electronic effects on them (**Scheme 30**).[60,61]



Reagents and conditions: i, CH_2=$CHCH_2MgBr$, THF, -100 °C (1 h) to rt (2 h), then aq. HCl (1M); ii, CH_2=$CHMgBr$, THF, -90 °C to rt, then aq. HCl (1 M); iii, NaH, DMF, 0 °C, then allyl bromide, 10 h., rt; iv, Grubbs' cat. **92** (10 mol%), DCM, rt, 3-5 h., **152**, 45 % and **153**, 93 %.

Scheme 30

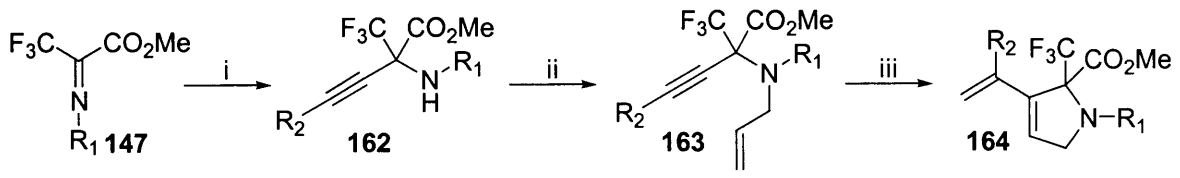
Similarly, the same group described the formation of 6 and 7-membered cyclic α-amino phosphonate derivatives **159** and **160** by alkene metathesis (**Scheme 31**).[60]



Reagents and conditions: i, CH_2=$CHCH_2MgBr$, Et_2O, -78 °C to rt, **155**, 68 %; ii, CH_2=$CH(CH_2)_2MgBr$, Et_2O, -78 °C to rt, **156**, 74 %; iii, NaH, allyl bromide, DMF, -5 °C to rt, 6-8 h., **157**, 69 % from **155** and **158**, 70 % from **156**; iv, cat. **161** (10 mol%), toluene, 80 °C, 6 h., **159**, 69 % from **157** and **160**, 61 % from **158**.

Scheme 31

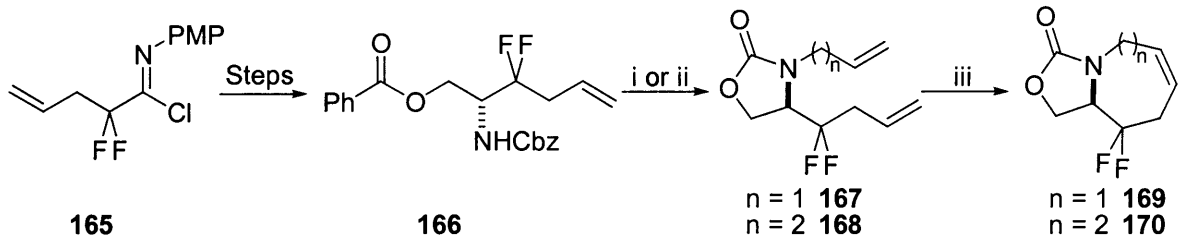
Trifluoromethyl imine was also reacted with lithium acetylides to afford amino esters **162**. Amines **162** were allylated and enynes **163** subsequently submitted to metathesis to afford dienes **164** (**Scheme 32**).[62]



Reagents and conditions: i, $R_2C{\equiv}CLi$, THF; ii, NaH (2 eq.), allyl bromide (3 eq.), DMF; iii, cat. **161** (5-10 mol%), toluene, 80 °C.

Scheme 32

Finally, Fustero *et al.* also reported an enantioselective synthesis of 7- and 8-membered cyclic fluorinated α-amino acids but with fluorines in the homoallylic position using Grubbs' catalyst **92**. The presence of the fluorines in the homoallylic position, and therefore fairly remote from the double bond, does not seem to affect the RCM as cyclic amino acids derivatives **169** and **170** were obtained in good yields with reasonable catalyst loadings (3-10 mol%) (**Scheme 33**).[63]



Reagents and conditions: i, NaH, allyl bromide, DMF, 0 °C, **167**, 84 %; ii, NaH, $Br(CH_2)_2CH{=}CH_2$, DMF, 0 °C, **168**, 45 %; iii, Grubbs' cat. **92** (3-10 mol%), DCM, rt, **169**, 75 % from **167** and **170**, 87 % from **168**.

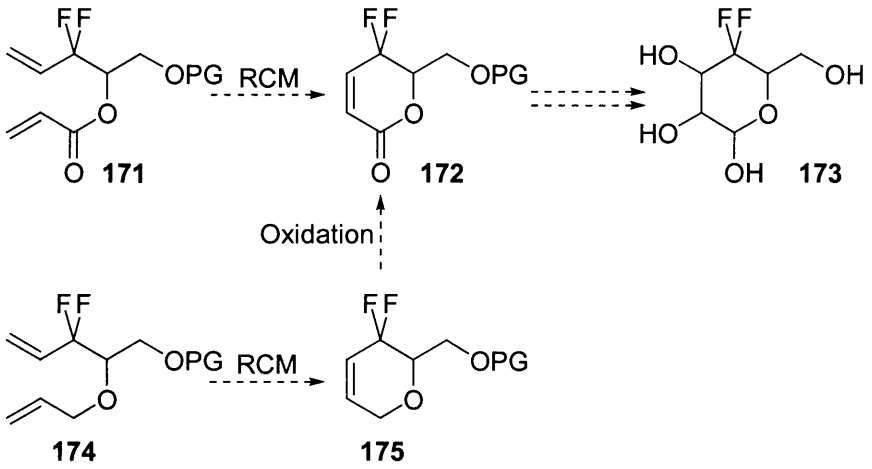
Scheme 33

IV - Objectives

The primary aim of this project was to explore ring-closing metathesis as an efficient alternative to direct difluorination for the preparation of *gem*-difluorinated cyclic molecules. Indeed, commercially available catalysts such as Grubbs' catalyst **92** are tolerant to a wide range of functional groups, easy to handle and allow the access to

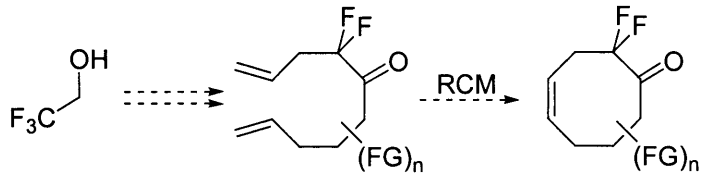
various ring sizes. Therefore, RCM should be ideal to prepare a wide range of highly functionalised difluorinated cyclic molecules from commercially available fluorinated building blocks.

The synthesis of 4-deoxy-4,4-difluorohexoses **173** was of particular interest as direct fluorination methods or building block approaches to such molecules remain scarce and problematic. The first objective was to prepare lactone **172** *via* RCM and process it to the corresponding difluorinated monosaccharide analogue by dihydroxylation followed by reduction of the lactone to the corresponding lactol. Key lactone **172** could be potentially accessed by either the RCM of acrylate **171** or allylic oxidation of dihydropyran **175**, itself synthesised by RCM of ether **174** (**Scheme 34**).



Scheme 34

The objective of this project was also to take advantage of the versatility of commercially available Grubbs' catalyst **92** to explore the synthesis of more complex molecules such as 8-membered carbocycles. Methodologies described by Percy *et al.*,[64,65] would provide a quick entry to the RCM precursors to these medium-sized rings from trifluoroethanol (**Scheme 35**).



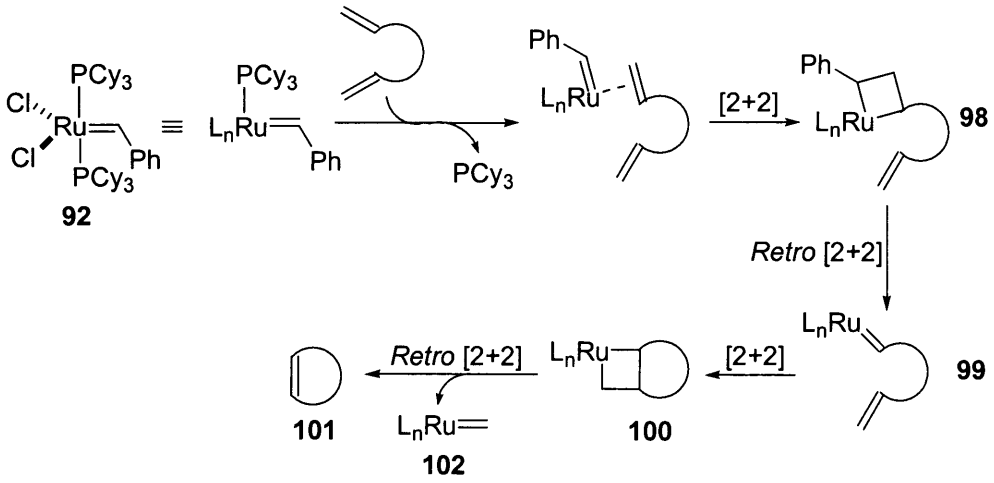
Scheme 35

The ultimate goal would then be to use these 8-membered carbocycles and process them to novel difluorinated molecules, such as unusual monosaccharide analogues by taking advantage of the potential transannular reaction of a hydroxyl group with the ketone.

CHAPTER II: Results and discussion

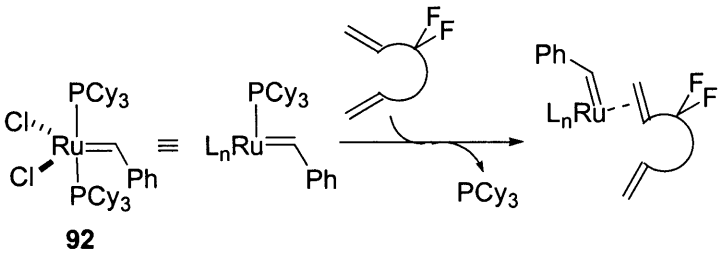
I - Synthesis of difluorinated dihydropyrans *via* RCM – A proof of concept

Ring closing metathesis (RCM) of a substrate containing a double bond with two fluorine atoms in the allylic position was unprecedented and potentially troublesome. Indeed, in the commonly accepted Lemieux mechanism for the RCM,[66] the ruthenium alkylidene catalyst, such as Grubbs' catalyst **92** has to coordinate with one alkene before taking part in a formal [2+2] metallocycloaddition process. A formal retrocycloaddition follows to form a new ruthenium alkylidene **99**, which reacts in the same manner intramolecularly to finally afford the desired cyclic alkene and regenerate the alkylidene catalyst **102** (**Scheme 36**).



Scheme 36

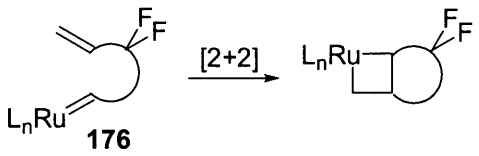
Due to their strong electron-withdrawing properties, the allylic fluorines may decrease the electron density of the alkene to such an extent that it cannot coordinate efficiently to the catalyst, thus preventing the [2+2] cycloaddition between the double bond flanked with the difluoromethylene moiety and the ruthenium alkylidene from taking place (**Scheme 37**).



92

Scheme 37

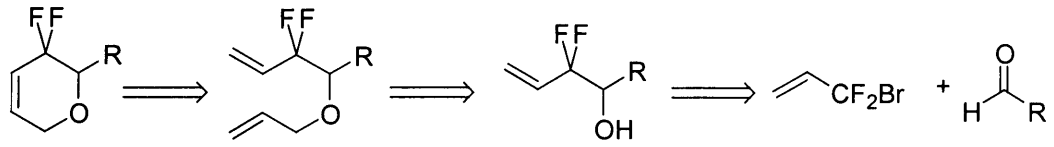
Alternatively, if the alkene flanked with the fluorines is not reactive enough, the ruthenium catalyst can react first with the other double bond to form alkylidene **176**, but once again the electron-withdrawing fluorines may prevent the intramolecular [2+2] cycloaddition from happening (**Scheme 38**).



176

Scheme 38

To show that the unprecedented RCM of substrates containing allylic fluorines was possible, the synthesis of difluorinated dihydropyrans **180** was undertaken from commercially available 1-bromo-1,1-difluoro-prop-2-ene **177**. The key step for the preparation of the RCM precursors **179** was the addition of commercially available bromodifluoropropene **177** to aldehydes to synthesise difluorinated homoallylic alcohols **178** (**Scheme 39**).

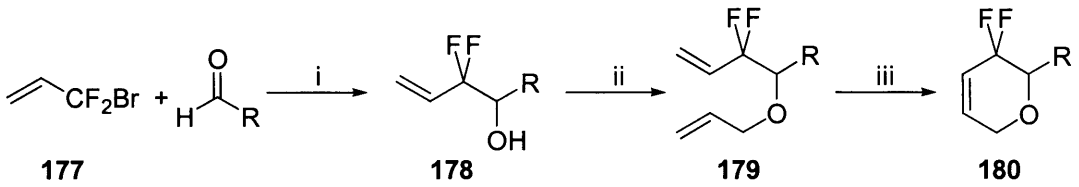


180 **179** **178** **177**

Scheme 39

A few methods are available for the addition of bromodifluoropropene **177** to aldehydes. Addition of *gem*-difluoroallyllithium formed by *in situ* lithium-bromine exchange between *n*-butyllithium and bromodifluoropropene **177** was reported by two

different groups.[67,68] Although this reaction affords difluorinated homoallylic alcohols **178** in good yields for some aldehydes, competitive addition of *n*-butyllithium was observed for more reactive aldehydes such as benzaldehyde or acrolein, dramatically decreasing the yields of desired products. Moreover, this reaction requires low temperature (-95 °C); the *gem*-difluoroallyllithium is unstable in solution even at this temperature.[67] To avoid these drawbacks, Burton *et al.* developed the direct addition of bromodifluoropropene **177** to aldehydes mediated by metals such as acid-washed zinc, cadmium, or a mixture of aluminium and catalytic tin(II) chloride (forming tin metal *in situ*). These reactions proceeded smoothly between 0 and 25 °C with zinc to afford exclusively the product of attack by the CF_2-terminus.[69,70] Alternatively, Kirihara *et al.* reported even better yields by using indium powder in DMF at room temperature. Interestingly, the reaction does not proceed with ketones and acyl chlorides.[71,72] As for Burton *et al.*, the reaction occurred exclusively at the CF_2-terminus and this can be rationalised by the localisation of the negative charge on this carbon, as demonstrated by *ab initio* calculations carried out by Tonachini *et al.*.[73] Therefore, difluorinated homoallyl-allyl ethers **179** were prepared in two steps by the indium mediated addition of bromodifluoropropene **177** to aldehydes,[71,72] followed by allylation under phase transfer catalysed conditions. Crude homoallyl-allyl ethers **179** were subsequently subjected to RCM using 5 mol% of Grubbs' catalyst **92** (**Scheme 40**).[74]



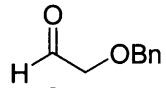
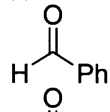
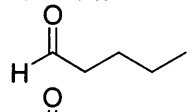
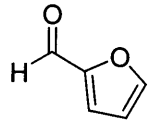
177 178 179 180

Reagents and conditions: i, In (1 eq.), DMF, sonication, 3-5 h., rt; ii, allyl bromide, cat. nBu$_4$NHSO$_4$, 50 wt. % aq. NaOH; iii, Grubbs' cat. **92** (5 mol%), DCM, rt, 24 h..

Scheme 40

Interestingly, reaction mixtures for the synthesis of difluorinated homoallylic alcohols **178** had to be sonicated or vigorously shaken to afford good yields. Under normal stirring as described by Kirihara *et al.*,[71,72] the indium powder tended to form a solid piece of indium metal, which would not react efficiently.

Pleasingly, RCM occurred smoothly under very mild conditions (room temperature in DCM) to afford the difluorinated dihydropyrans **180** in good to excellent yields (**Table 1**).

Entry	Aldehyde	**178**	**179**	**180**
a		80 %	99 %	97 %
b		57 %	98 %	56 %
c		57 %	99 %	81 %
d		77 %	99 %	58 %

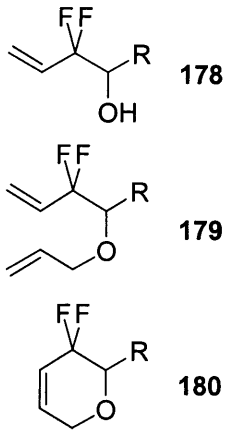
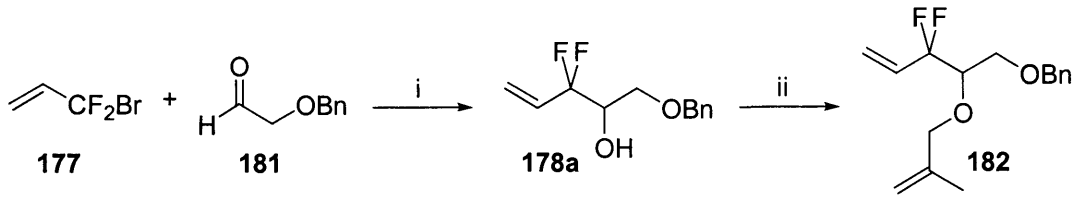


Table 1

To study the tolerance of the RCM reaction of more hindered substrates, methallyl ether **182** was prepared in a similar way as described before. The quantitative methallylation was carried out in the presence of a catalytic amount of tetra-*n*-butylammonium iodide to form the more reactive methallyl iodide *in situ* (**Scheme 41**).

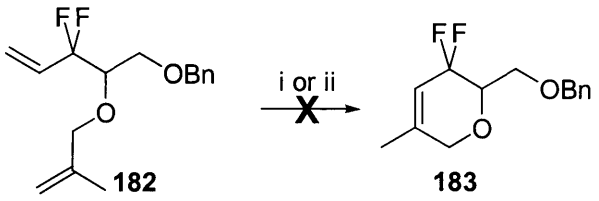


177 181 178a 182

Reagents and conditions: i, In powder (1eq.), sonication, DMF, rt, 4 h., **178a**, 80 %; ii, methallyl chloride, cat. nBu$_4$NHSO$_4$, cat. nBu$_4$NI, 50 wt. % aq. NaOH, 18 h., **182**, 100 %.

Scheme 41

The RCM of methallyl ether **182** was attempted with 5 mol% Grubbs' catalyst **92** in both refluxing DCM and refluxing 1,2-dichloroethane (DCE) but failed even after extended period of time (7 days) and only starting material was recovered (**Scheme 42**).

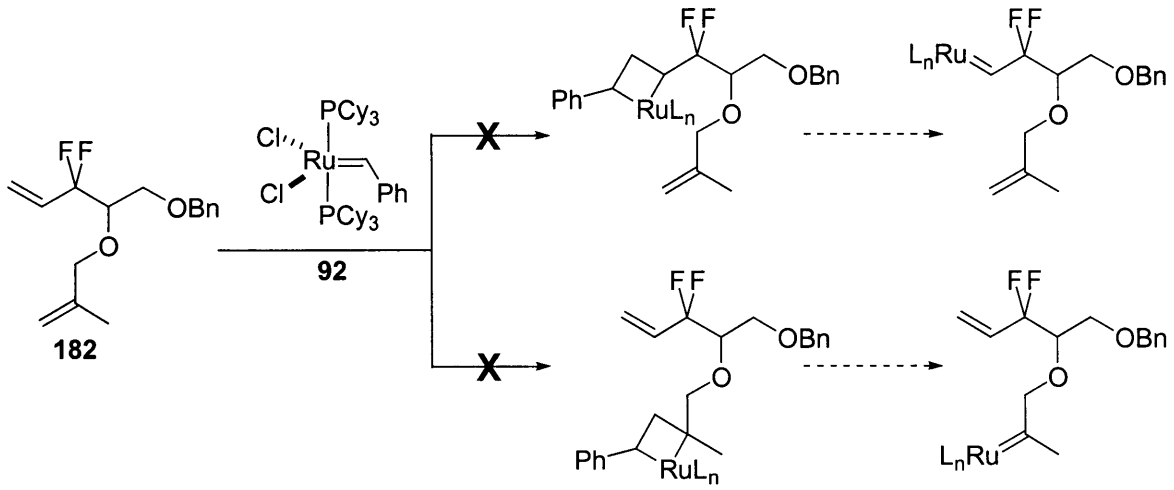


182 183

Regents and conditions: i, 5 mol% Grubbs' cat. **92**, DCM, reflux, 7 d.; ii, 5 mol% Grubbs' cat. **92**, DCE, reflux, 7 d..

Scheme 42

The outcome of this reaction suggests that in the case of allyl ethers **179**, the ruthenium catalyst first reacts with the more electron rich alkene -from the allyl moiety- and that the intramolecularity of the second step of the reaction allows for the RCM to succeed. When a methyl group is introduced on the allyl moiety Grubbs' catalyst **92** cannot react sufficiently rapidly with either of the alkenes; one is too electron deficient because of the allylic fluorines, and the other one is sterically hindered by the methyl group (**Scheme 43**).

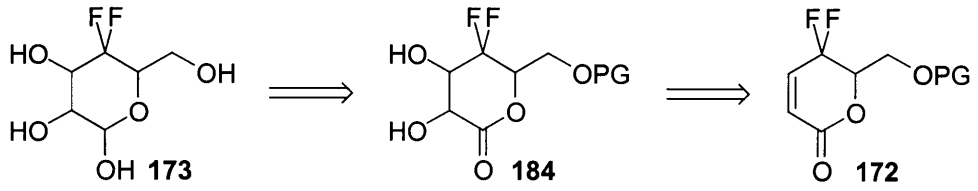


Scheme 43

This unsuccessful reaction indicates strongly that the alkene flanked with the difluoromethylene moiety is very unreactive towards RCM. Successful ring closure requires another reactive alkene (not electron-deficient and not sterically hindered) to initiate the first step of the RCM. Once a ruthenium carbene is formed at the more reactive alkene, the electron-deficient double bond can react intramolecularly to complete the catalytic cycle

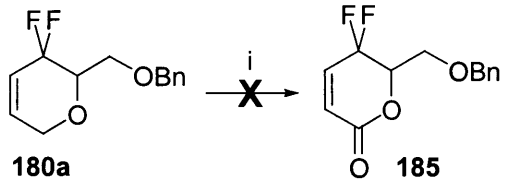
II - Synthesis of 4,4-difluoro-4-deoxyhexoses *via* RCM

The successful synthesis of difluorinated dihydropyrans was encouraging for the unprecedented synthesis of 4,4-difluoro-4-deoxyhexose **173**. Indeed, such fluorinated monosaccharides could be potentially obtained from lactone **172** *via* a dihydroxylation-reduction strategy (**Scheme 44**).



Scheme 44

In the first instance, the synthesis of key lactone **185** was attempted by allylic oxidation of dihydropyran **180a** using chromium trioxide in the presence of 3,5-dimethylpyrazole as described by Salmond *et al.*.[75] Unfortunately, under these strongly oxidising conditions, the substrate decomposed and no fluorinated product was recovered from the reaction mixture (**Scheme 45**).

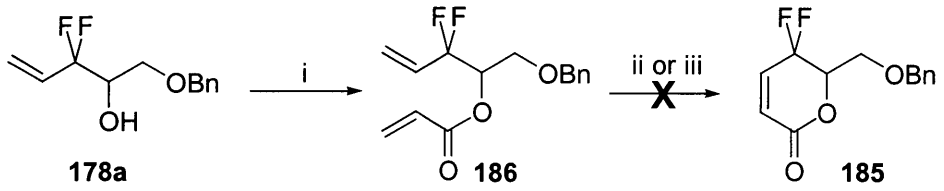


180a **185**

Reagents and conditions: i, CrO_3 (10 eq.), 3,5-dimethylpyrazole (12 eq.), DCM, -20 °C, 4h..

Scheme 45

Alternatively, the oxygen at the C-2 position could be introduced earlier in the synthesis by performing the RCM on acrylate **186** prepared by reaction of difluorinated homoallylic alcohol **178a** and acryloyl chloride (**Scheme 46**).



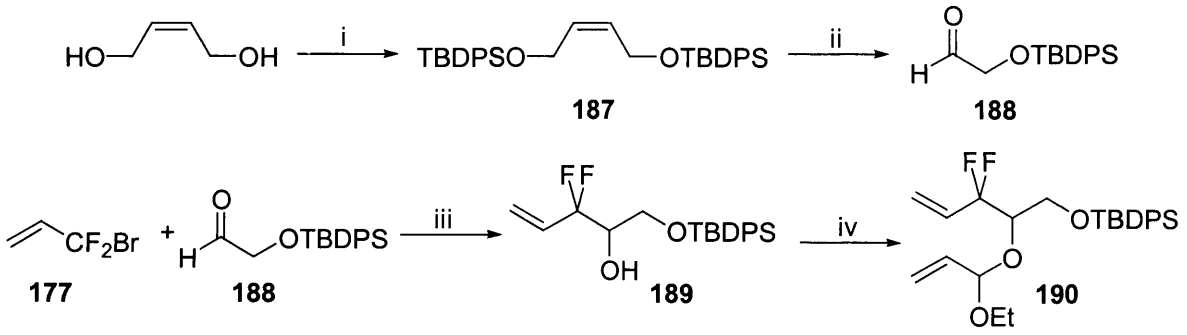
178a **186** **185**

Reagents and conditions: i, acryloyl chloride (1.0 eq.), Et_3N (1.0 eq.), DCM, 0 °C, 2 h. then rt, 16 h., **186**, 50 %; ii, Grubbs' cat. **92** (5 mol%), DCM, reflux, 7 d.; iii, Grubbs' cat. **92** (5 mol%), DCE, reflux, 7 d..

Scheme 46

The RCM of acrylate **186** failed even when refluxing the compound in 1,2-dichloroethane (DCE) in the presence of 5 mol% of Grubbs' catalyst **92** for an extended period of time (7 days). These results can be explained by the presence of one electron-withdrawing moieties -difluoromethylene or carbonyl- next to each alkene. Indeed, the electron poor alkenes cannot coordinate to the ruthenium and therefore the RCM reaction does not take place.

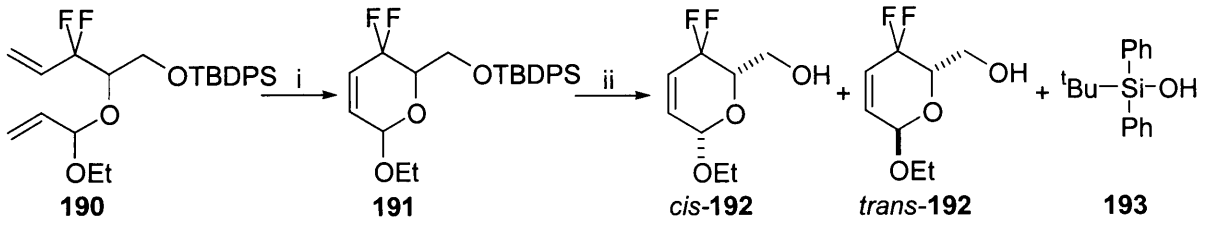
Fortunately, the oxygen functionality at the C-2 position could be introduced at the correct level of oxidation by a transacetalisation reaction described by Crimmins *et al.* [76] and modified by Mulzer *et al.*.[77] This acid-catalysed transacetalisation was performed with acrolein diethyl acetal on difluorinated homoallylic alcohol **189**, prepared by indium mediated addition of bromodifluoropropene **177** to aldehyde **188**. Aldehyde **188** was synthesised in two steps by reaction of (*Z*)-butene-1,4-diol with *tert*-butyl(chloro)diphenyl-silane followed by oxidative cleavage of the alkene with ozone (**Scheme 47**).



Reagents and conditions: i, *tert*-butyl(chloro)diphenylsilane (2 eq.), imidazole (2 eq.), DCM 0 °C to rt, 3h.; ii, O_3, DCM, -78 °C then PPh_3, **188**, 63 % over two steps; iii, In powder (1 eq.), DMF, sonication, rt, 3h., **189**, 61%; iv, acrolein diethyl acetal (5 eq.), cat. PPTS, toluene, 30-40 °C, 60 mmHg, 5 h., **190**, 66%.

Scheme 47

Acetal **190** was afforded as an inseparable mixture of diastereoisomers (1:1) and was subjected to RCM using 5 mol% Grubbs' catalyst **92** in refluxing DCM for two days. The primary hydroxyl group was then deprotected by treatment with tetra-*n*-butylammonium fluoride and the separation of the two diastereoisomers was attempted (**Scheme 48**).

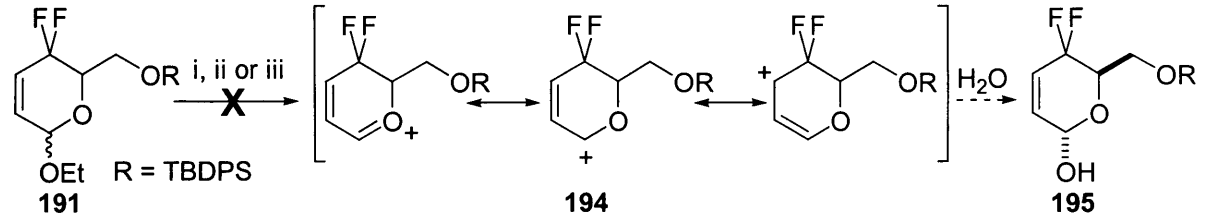


Reagents and conditions: i, 5 mol% Grubbs' cat. **92**, DCM, reflux, 2 d., **191**, 88 %; ii, TBAF (1.5 eq.), THF, rt, 1 h..

Scheme 48

Although the deprotection of the primary hydroxyl using a fluoride source was successful, the two diastereoisomers could not be isolated as pure products by column chromatography as one of them co-eluted with silanol **193** formed during the deprotection reaction.

At this stage, the inseparable mixture of acetals **191** was subjected to acidic aqueous conditions to try to equilibrate the isomers in favour of the more stable *trans*-hemiacetal **195**. Isomerisation failed, probably because oxocarbenium cation **194** or the oxocarbenium cation-like transition state cannot form as it is dramatically destabilised by the strong inductive electron-withdrawing effects of the fluorines (**Scheme 49**).

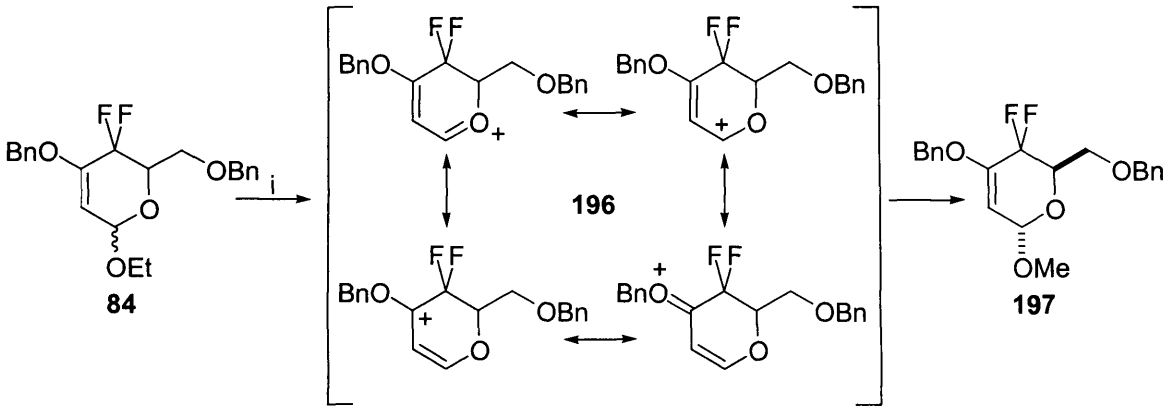


Reagents and conditions: i, Amberlyst 15, aq. CH_3CN, rt, 5 d.; ii, Acetic acid, aq. CH_3CN, reflux, 3d.; iii, cat. *p*-TsOH, aq. CH_3CN, rt, 48 h..

Scheme 49

This observation is in contrast with the results reported by Taguchi *et al.*,[28] who successfully carried out an alcoholysis of acetal **84** under acidic conditions, which probably proceeds *via* an oxocarbenium cation or oxocarbenium cation-like transition state similar to intermediate **196**. The higher reactivity of **84** towards the formation of

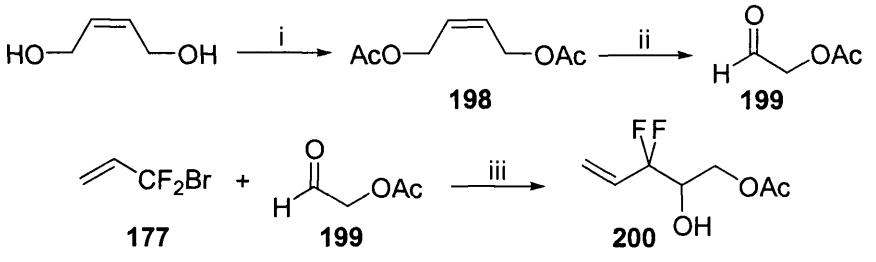
the oxocarbenium cation **196** may be explained by the additional stabilising mesomeric effect introduced by the benzyloxy group at the C-3 position (**Scheme 50**).



Reagents and conditions: i, MeOH, cat. *p*-TsOH, 4 Å molecular sieves, Et_2O, rt, 5h., **197**, 84 %.

Scheme 50

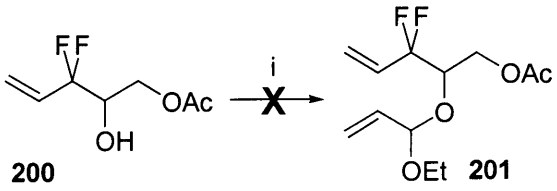
To overcome the problem of purification of acetals **192**, another protecting group was required for the primary hydroxyl group of the RCM precursors. Thus, acetoxyacetaldehyde **199** was prepared from butenediol as described by Leahy *et al.*[78] and subjected to the indium mediated addition of bromodifluoropropene **177** to afford homoallylic alcohol **200** (**Scheme 51**).



Reagents and conditions: i, acetic anhydride (2.5 eq.), cat. DMAP, DCM, 0 °C to rt; ii. O_3, DCM, -78 °C then PPh_3, **199**, 67 % over two steps; iii, In powder (1eq.), sonication, DMF, rt, 4.5 h., **200**, 65 %.

Scheme 51

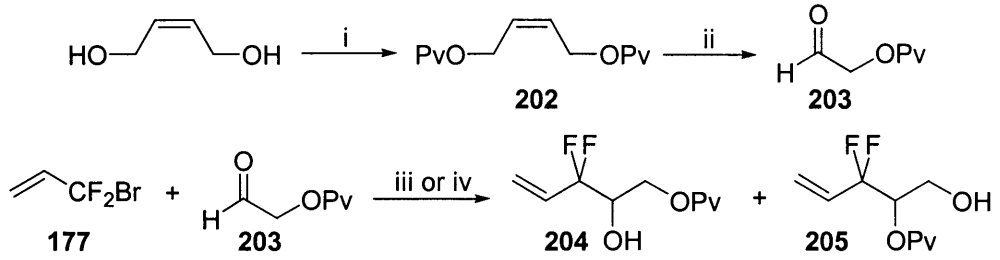
Unfortunately, upon treatment of alcohol **200** with acrolein diethyl acetal in the presence of pyridinium *p*-toluenesulfonate, the acetate hydrolysed and a complex mixture of acetals was recovered (**Scheme 52**)



Reagents and conditions: i, acrolein diethyl acetal (5 eq.), cat. PPTS, toluene, 30-40 °C, 60 mmHg, 5 h..

Scheme 52

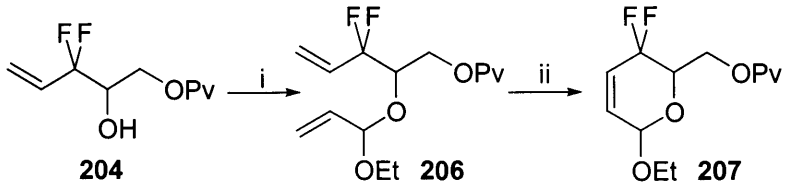
The more robust trimethyl acetate (pivaloate) was therefore used as a protecting group for the primary hydroxyl group and the substrate was prepared in a similar way as described before, by reacting aldehyde **203** with indium powder. Surprisingly, when this reaction was carried out in DMF, a migration of the trimethylacetyl group from the primary hydroxyl group to the more hindered secondary hydroxyl group was observed to afford a mixture of regioisomers **204** and **205**. Fortunately, when carried out in water, the reaction afforded only the desired homoallylic alcohol **204** in very good yield (82 %) (**Scheme 53**).



Reagents and conditions: i, trimethylacetyl chloride (2 eq.), pyridine, 0 °C to rt; ii, O_3, DCM, -78 °C then PPh_3, **203**, 71 % over two steps; iii, In powder, DMF, sonication, rt, 5 h., **204**, 51 % and **205**, 31 %; iv, In powder, water, rt, 18 h., **204**, 82 %.

Scheme 53

Homoallylic alcohol **204** was then reacted as described before with acrolein diethyl acetal to afford a 1:1 diastereoisomeric mixture of acetals **206**, which were subjected to RCM using Grubbs' catalyst **92** in refluxing DCM (**Scheme 54**).

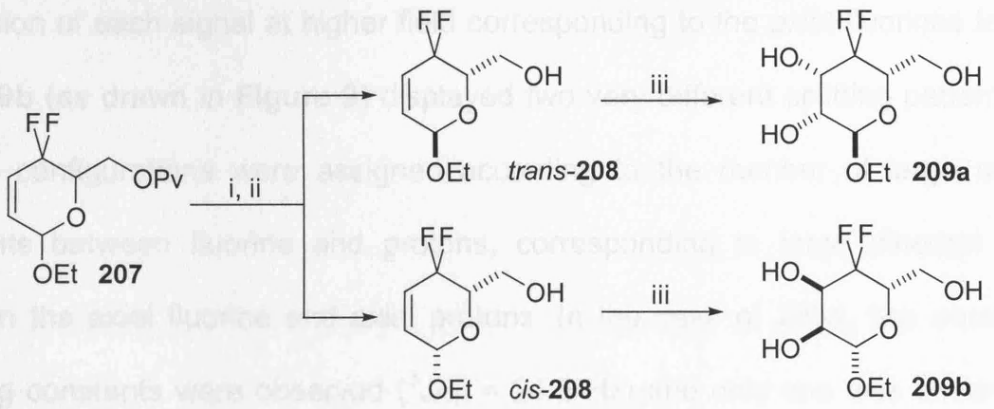


Reagents and conditions: i, acrolein diethyl acetal (5 eq.), cat. PPTS, toluene, 30-40 °C, 60 mmHg, 9h., **206**, 73 %; ii, 5 mol% Grubbs' cat. **92**, DCM, reflux, 5 d., **207**, 66%.

Scheme 54

The RCM of acetal **206** was much slower than the RCM of homoallyl-allyl ethers **179**. This observation is in agreement with the results reported by Hoye *et al.*[79] who estimated that an additional allylic alkoxy group slows RCM for 5-membered ring systems by a factor 8. Similarly, Sarkar *et al.* reported the adverse effect of an allylic methoxy group in cross-metathesis.[80]

The primary hydroxyl group of diastereoisomeric dihydropyrans **207** was revealed by di*iso*butylaluminium hydride (DIBAL-H) reduction of the pivalate ester and the separation of the two diastereoisomers *cis*- and *trans*-**208** was achieved by column chromatography. Each diastereoisomer of dihydropyrans **208** was subjected to dihydroxylation under UpJohn conditions.[81] These reactions took five days to go to completion, probably because of the electron deficient alkene involved, but afforded the desired difluorinated glycosides **209a** and **209b** in reasonable yields (62 % in each case) (**Scheme 55**).



Reagents and conditions: i, DIBAL-H (2.5 eq.), DCM/hexane, -78 to 0 °C; ii, column chromatography, *trans*-**208**, 41 % and *cis*-**208**, 39 %; iii, NMO (2 eq.), cat. OsO_4, water/acetone/^{t}BuOH, 0 °C to rt, 5d., **209a**, 62 % and **209b**, 62 %.

Scheme 55

After completion of the reactions, crude ^{19}F NMR spectra showed a complete diastereoselectivity for each reaction as only one set of signals was observed for **209a** and **209b** (**Figure 8**).

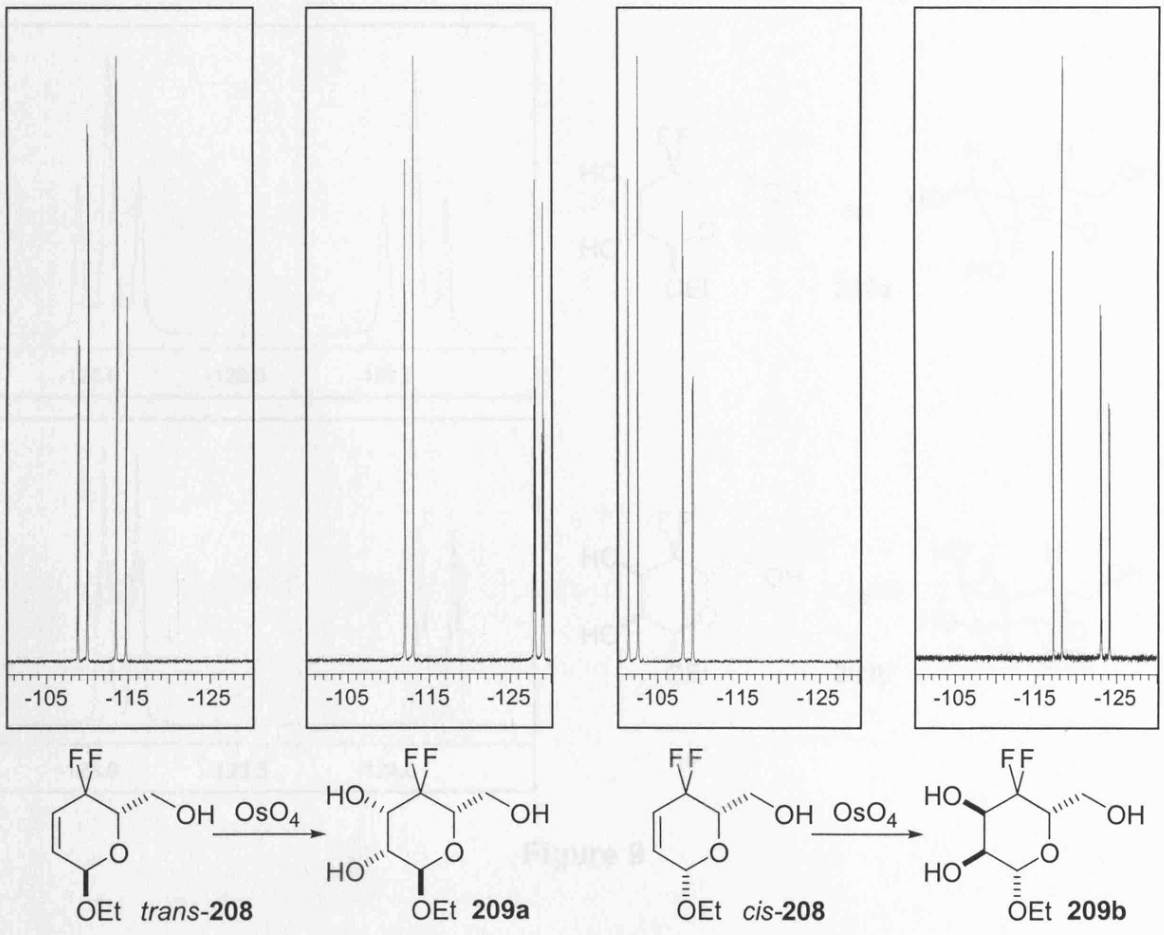
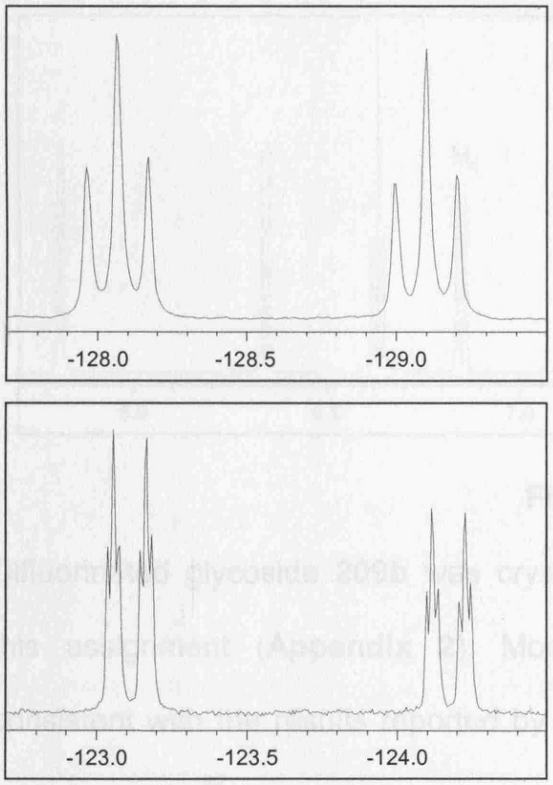
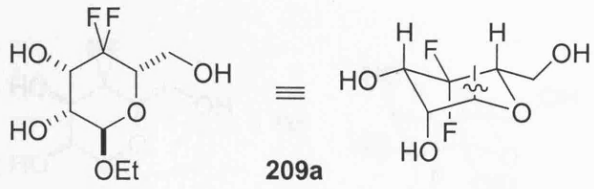


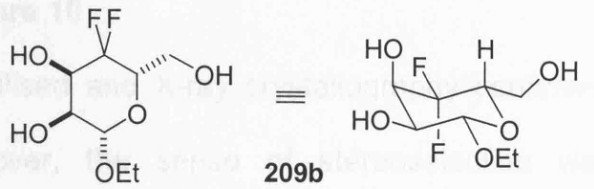
Figure 8

Expansion of each signal at higher field corresponding to the axial fluorines for **209a** and **209b** (as drawn in **Figure 9**) displayed two very different splitting patterns. The relative configurations were assigned according to the number of large coupling constants between fluorine and protons, corresponding to large dihedral angles between the axial fluorine and axial protons. In the case of **209a**, two equal large coupling constants were observed ($^3J_{F\text{-}H}$ = 24.5 Hz) and only one was observed for **209b** ($^3J_{F\text{-}H}$ = 26.5 Hz) in agreement with the structures below. In the case of **209b**, a smaller coupling constant ($^3J_{F\text{-}H}$ = 4.6 Hz) was observed for the coupling between the axial fluorine and the equatorial proton. The ^{19}F NMR spectrum of **209b** also displayed an additional coupling constant of 4.6 Hz, probably corresponding to a four bond coupling with another proton (at C-4 or C-6), although this was not demonstrated by any further experiment (**Figure 9**).





209a



209b

Figure 9

^{1}H NMR also showed a noticeable difference for the coupling pattern of H-1. Indeed, for **209a**, proton H-1 and proton H-2 display a dihedral angle close to 90 ° and only a singlet was observed for proton H-1. For isomer **209b**, the dihedral angle between proton H-1 and proton H-2 is close to 180 ° and a large coupling constant (7.8 Hz) was observed (**Figure 10**). ^{1}H NMR spectra for glycosides **209a** and **209b** were fully assigned by HSQC and HMBC correlations (**Appendix 1**).

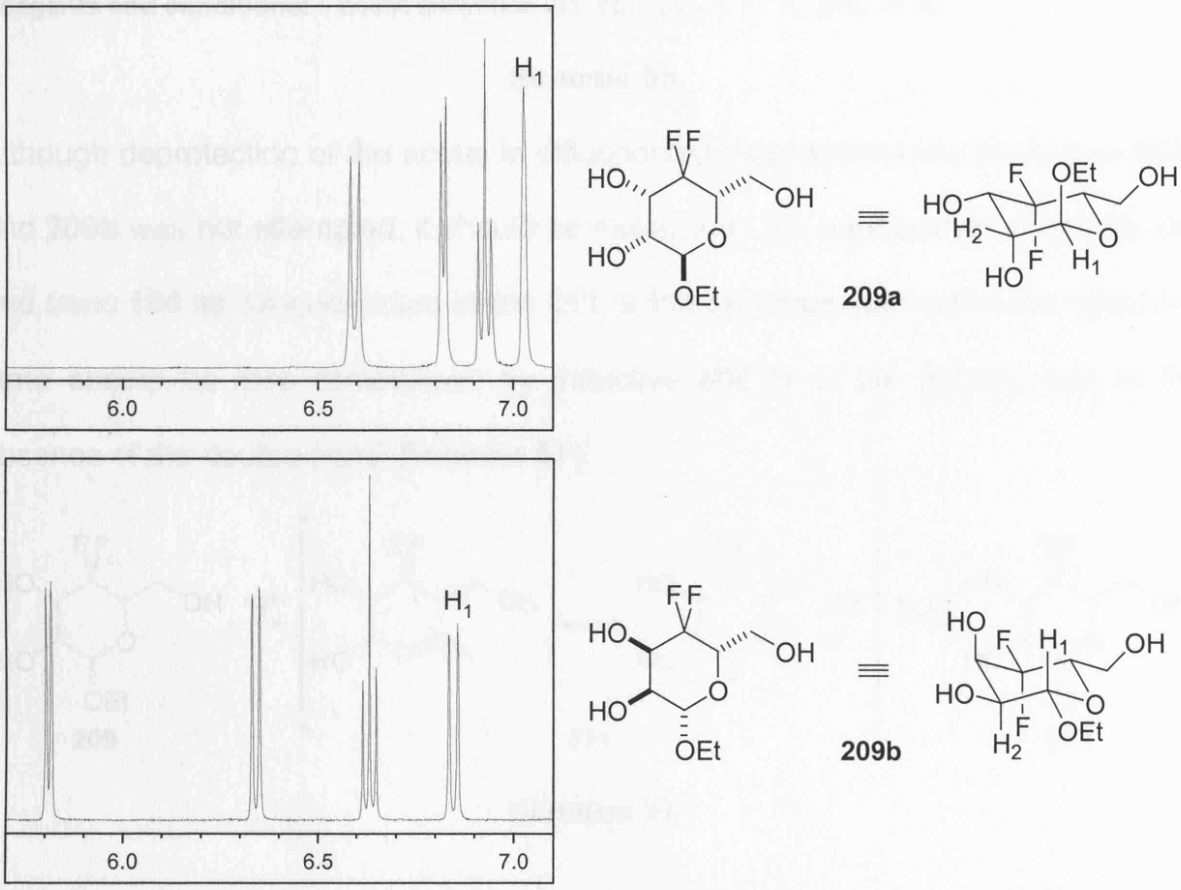
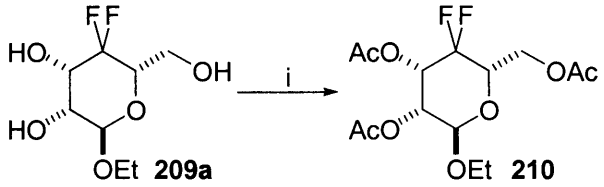


Figure 10

Difluorinated glycoside **209b** was crystallised and X-ray crystallography confirmed this assignment (**Appendix 2**). Moreover, the sense of stereoselection was consistent with the results reported by Cha *et al.*, who rationalised these results on steric grounds.[82]

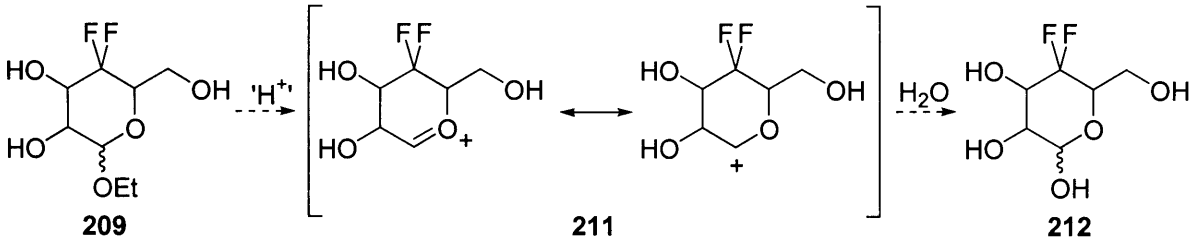
Triol **209a** was recovered as an oil and was converted to the corresponding tri-acetate **210** to obtain a solid, but no crystals good enough for X-ray analysis could be grown (**Scheme 56**).



Reagents and conditions: i, acetic anhydride (5.0 eq.), py., rt, 17 h., **210**, 72 %.

Scheme 56

Although deprotection of the acetal in difluorinated monosaccharide analogues **209a** and **209b** was not attempted, it should be easier than the equilibration of acetals *cis*- and *trans*-**194** as oxocarbenium cation **211** or the oxocarbenium cation-like transition state should be less destabilised by inductive effects of the fluorine due to the absence of the double bond (**Scheme 57**).



Scheme 57

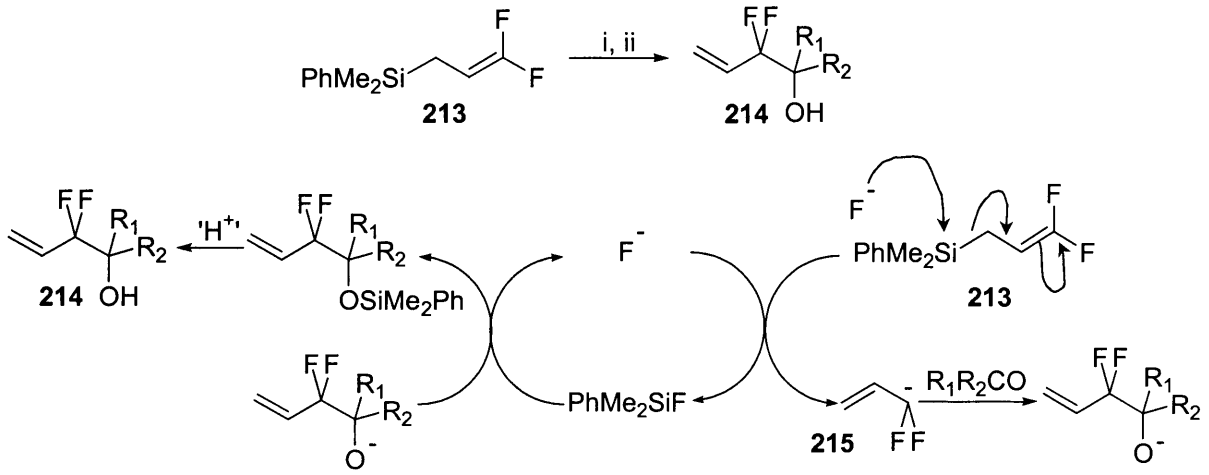
III - An alternative to bromodifluoropropene?

The synthesis of 4,4-difluoro-4-deoxyhexoses **209a** and **209b** described above relied on the use of bromodifluoropropene **177** to prepare key difluorinated homoallylic alcohol **204**. Unfortunately, this material is expensive, not readily available and not easy to make. Indeed, Tarrant *et al.* attempted the synthesis of bromodifluoro-

propene **177** by radical addition of dibromodifluoromethane across ethylene catalysed by benzoyl peroxide, but lost most of the product upon rupture of the safety disc of the autoclave, designed to withstand 85 atmospheres.[83] Therefore, an alternative to bromodifluoropropene **177** was investigated.

III.a – Fluoride-catalysed reaction of 3,3-difluoro-allyl-silanes with aldehydes

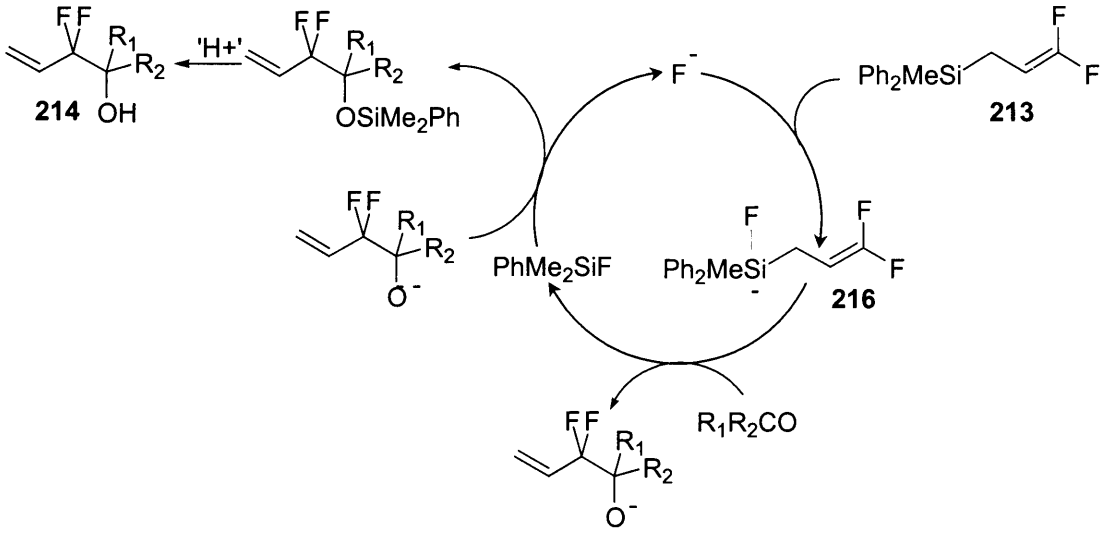
Hiyama *et al.* described an alternative route to homoallylic alcohols **214** by potassium *tert*-butoxide or fluoride catalysed addition of difluoroallylsilane **213** to aldehydes or ketones in polar aprotic solvents, such as DMPU, HMPA and THF.[84,85] According to this work, treatment with tetra-*n*-butylammonium fluoride (TBAF) or tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) generates anion **215**, which reacts with aldehydes or ketones at room temperature. Although the corresponding organolithium species is unstable above -95°C,[67] Hiyama argued that the anion is stabilised by the presence of the counter cation of the fluoride source (TBA^+ or TAS^+) (**Scheme 58**).



Reagents and conditions: i, cat. TBAF or TASF (5-25 mol%), $R_1R_2C{=}O$, HMPA, DMPU or THF, rt.

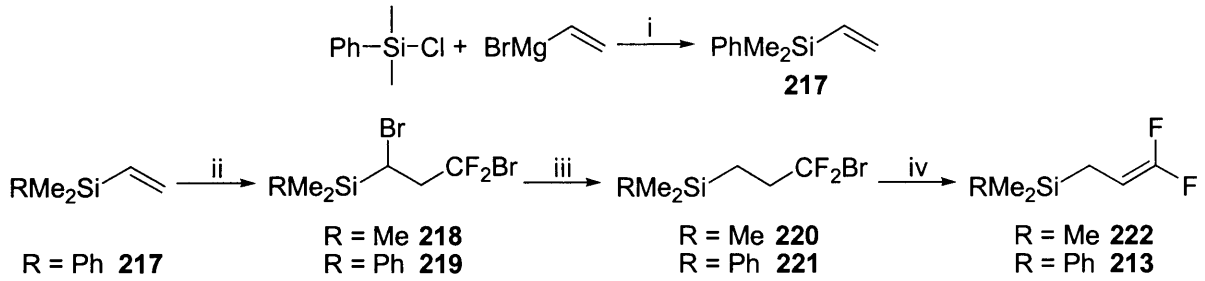
Scheme 58

Alternatively, the fluoride source may react with difluoroallylsilane **213** to form the corresponding ate-complex **216**, which might be the reactive species, rather than anion **215** itself (**Scheme 59**).



Scheme 59

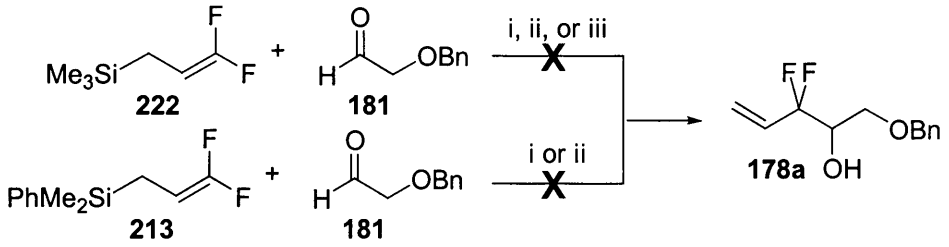
To try to repeat Hiyama's chemistry, two different silanes **213** and **222** were prepared. Dimethylphenylvinylsilane **217** was prepared by reacting vinylmagnesium bromide with chlorodimethylphenylsilane. Both commercially available trimethylvinylsilane and silane **217** were then reacted with dibromodifluoromethane to afford 1,3-dibromo-3,3-difluoro-propyl silanes **218** and **219** respectively, which were subsequently reduced with sodium borohydride in DMSO as described by Elsheimer *et al.*.[86] Desired difluoroallylsilanes **222** and **213** were obtained by treatment of **220** and **221** with DBU to eliminate HBr (**Scheme 60**).



Reagents and conditions: i, THF, 0 °C, 1 h. then rt, 16 h., **217**, 88 %; ii, CF_2Br_2 (2.0 eq.), ethanolamine (0.5 eq.), Cu(I)Cl (1 mol%), *t*-BuOH, Ace tube, 90 °C, 24 h., **218**, 80 % and **219**, 67 %; iii, $NaBH_4$ (1.2 eq.), DMSO, 90 °C, **220**, 52 % and **221**, 61 %; iv, DBU (1.5 eq.), neat, 100 °C, **222**, 94 % and **213**, 94%.

Scheme 60

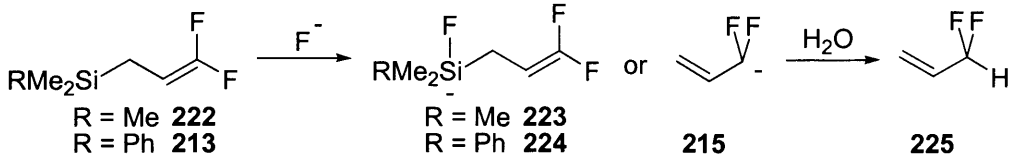
Synthesis of homoallylic alcohol **178a** was attempted using the conditions described by Hiyama *et al.*[84,85] with both silanes **213** and **222** and two different sources of fluoride: tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) or tetra-*n*-butylammonium fluoride difluorotriphenyl-stannate (**Scheme 61**).



Reagents and conditions: i, TASF (10 mol%), DMPU, rt, 18 h.; ii, TASF (10 mol%), THF, rt, 18 h.; iii, $n$$Bu_4NSnPh_3F_2$ (10 mol%), THF, rt, 18 h..

Scheme 61

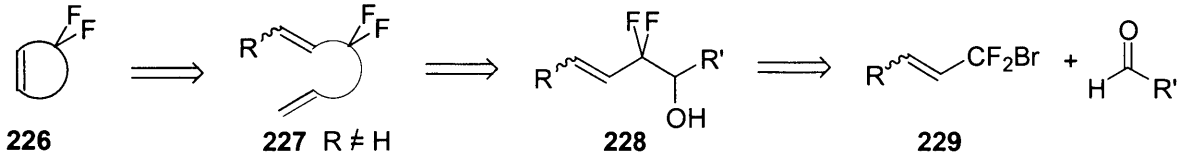
Unfortunately, these reactions failed with both silanes **213** and **222**, possibly because the highly hygroscopic fluoride sources were not dry and ate-complexes **223** and **224** or the corresponding anion **215** reacted with traces of moisture to form volatile difluoropropene **225** (**Scheme 62**).



Scheme 62

III.b - Reaction of (*E*)-(3-bromo-3,3-difluoro-propenyl)-trimethyl-silane with aldehydes

The synthesis of difluorinated cyclic molecules described above and the attempts at finding an alternative to bromodifluoropropene **177** relied on the use of two terminal alkenes in the RCM. However, the same molecules can potentially be obtained from non-terminal alkenes (**Scheme 63**).

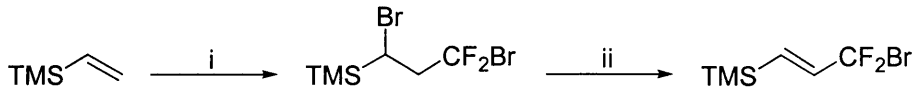


226 **227** R ≠ H **228** **229**

Scheme 63

Therefore any 1-substituted 1-bromo-1,1-difluoro-prop-2-ene such as **229** could be a suitable substitute to 1-bromo-1,1-difluoro-prop-2-ene **177** as starting fluorinated building block.

In the first instance, (*E*)-(3-bromo-3,3-difluoro-propenyl)-trimethylsilane **230** was prepared by radical addition of dibromodifluoromethane to vinyltrimethylsilane followed by elimination of bromine by treatment with DBU as described by Elsheimer *et al.* and Purrington *et al.* (**Scheme 64**).[86,87]



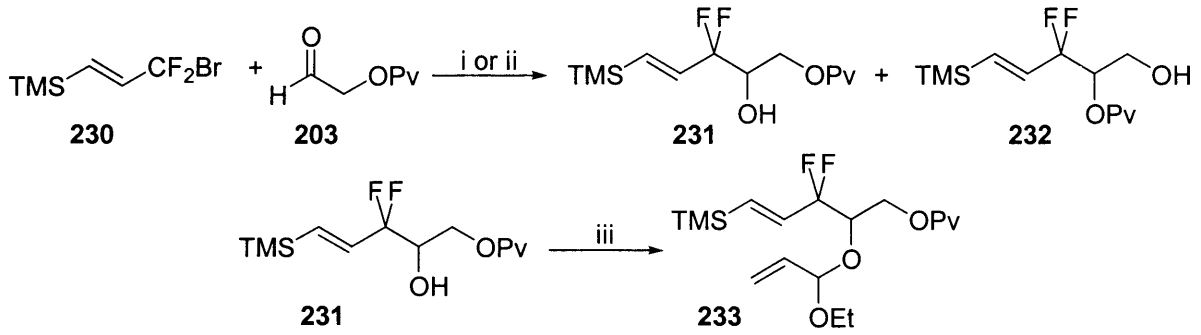
218 **230**

Reagents and conditions: i CF_2Br_2 (2.0 eq.), ethanolamine (0.5 eq.), Cu(I)Cl (1 mol%), *t*-BuOH, Ace tube, 90 °C, 24 h., **218**, 80 %; ii, $NaBH_4$ (1.2 eq.), DMSO, 80-90 °C, 2 h., **230**, 52 %.

Scheme 64

Bromodifluoroalkene **230** was then reacted following the sequence previously described. Indium mediated addition of **230** to aldehyde **203** followed by acid-catalysed transacetalisation afforded the RCM precursor **233** as a mixture of diastereoisomers (1:1). Once again the addition of alkene **230** to aldehyde **203** had

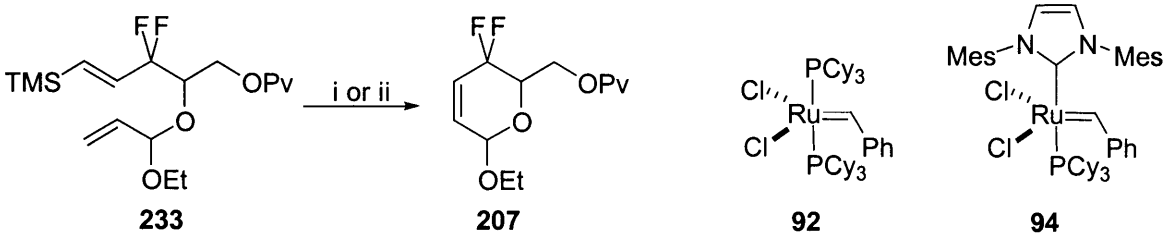
to be carried out in water rather than DMF to avoid migration of the pivaloate from the primary hydroxyl group to the more hindered secondary hydroxyl group (**Scheme 65**).



Reagents and conditions: i, In powder, DMF, sonication, rt, 5 h., **231**, 18 % and **232**, 53 %; ii, In powder, water, rt, 18 h., **231**, 46 %; iii, acrolein diethyl acetal (5 eq.), cat. PPTS, toluene, 30-40 °C, 60 mmHg, 9h., **233**, 86 %.

Scheme 65

The diastereoisomeric mixture of acetals **233** was subjected to RCM using 5 mol% of either Grubbs' catalyst **92** or more active Nolan's catalyst **94** in refluxing DCM for five days, after which time only low yields of dihydropyrans **207** could be obtained (14 % and 24 % respectively) (**Scheme 66**).

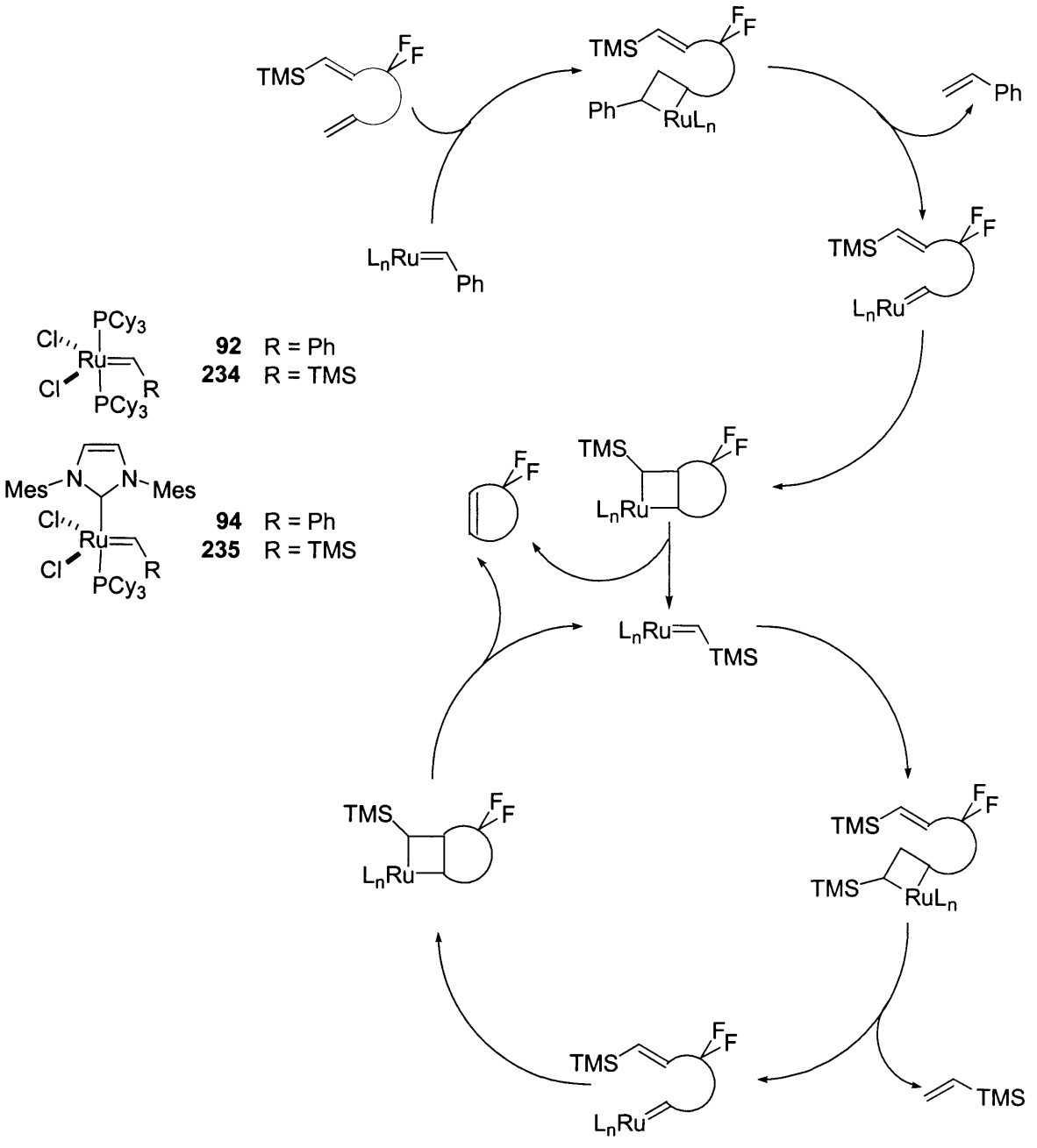


Reagents and conditions: i, Grubbs' Cat. **92** (5 mol%), DCM, reflux, 5 d., **207**, 14 %; ii, Nolan's cat. **94** (5 mol%), DCM, reflux, 5 d., **207**, 24 %.

Scheme 66

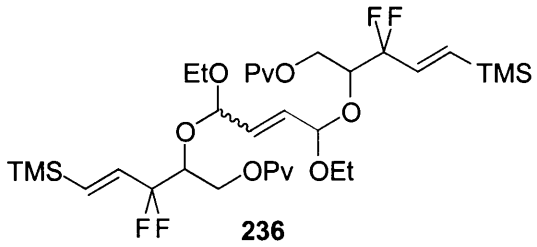
Although the yield is slightly higher with the more active Nolan's catalyst **94**, the trimethylsilyl substituted alkene **233** does not seem to be a suitable substrate for RCM. A closer look at the RCM catalytic cycle may explain these poor results. Indeed, after one turnover catalysts **92** and **94** are converted into the corresponding

ruthenium carbenes **234** and **235** bearing a trimethylsilyl group instead of a phenyl and those species do not seem to be efficient RCM catalysts (**Scheme 67**).



Scheme 67

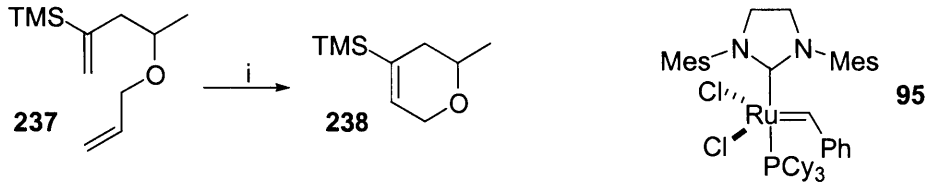
Arguably, the low yields of the RCM can be blamed on the greater steric hindrance introduced by the trimethylsilyl substituent on one of the double bonds. However, in such a case, dimer **236** should probably form by cross-methatesis but was not observed in the crude reaction mixture (**Figure 11**).



236

Figure 11

Moreover, Gouverneur *et al.* reported the successful RCM in excellent yield of trimethylsilyl substituted substrates -albeit in internal position- such as **237** using modified and more reactive Grubbs' catalyst **95** (**Scheme 68**).[88]



237 **238** **95**

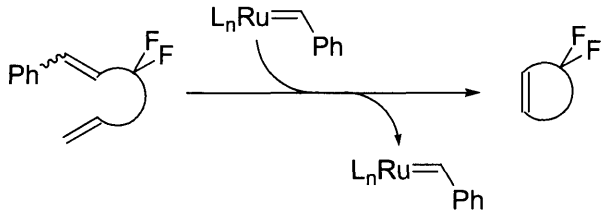
Reagents and conditions: i, cat. **95** (3 mol%), DCM, reflux, 3h., **238**, 93 %.

Scheme 68

In this transformation the catalyst remains active as no trimethylsilyl substituted ruthenium alkylidene such as **234** or **236** is formed and the steric bulk of the trimethylsilyl group does not seem to impede the reaction. Nevertheless, in the case of **237** bearing an internal trimethylsilyl group, the catalyst may approach from a less hindered trajectory than in the case of the terminally substituted alkene of substrate **233**. Moreover, the choice of more active catalyst **95** as used by Gouverneur *et al.* may be critical for the RCM involving a trimethylsilyl substituted alkene.

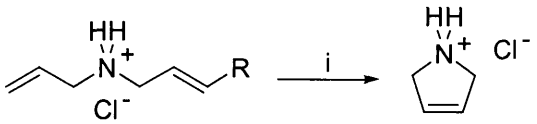
III.c – Attempts to prepare 1-[(*E*)-3-bromo-3,3-difluoro-1-propenyl]-benzene

After the failure for trimethylsilyl substituted alkenes to undergo RCM, it seemed obvious to substitute the trimethylsilyl group with a phenyl group to regenerate the actual Grubbs' or Nolan's catalysts **92** and **94** after each turnover (**Scheme 69**).



Scheme 69

Moreover, a RCM of such a phenyl substituted alkene was reported by Grubbs' *et al.* where the phenyl-substituted substrate afforded a better yield than the non-substituted one. They argued that the higher yield was due to the higher stability of the phenyl-substituted ruthenium catalyst **92** compare to the non-substituted carbene **102** (**Scheme 70**).[89]



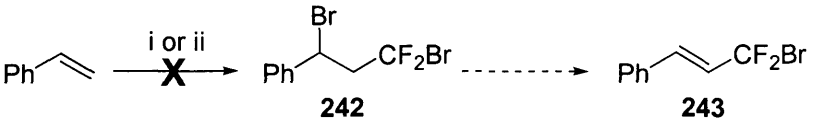
R = H **239**
R = Ph **240**

241

Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), DCM, **241**, 60 % from **239** and **241**, 100 % from **240**.

Scheme 70

To try such an RCM, the preparation of 1-[(*E*)-3-bromo-3,3-difluoro-1-propenyl]benzene **243** was attempted by radical addition of dibromodifluoromethane to styrene using conditions described by Elsheimer *et al.*[86] or Wu *et al.*.[90] Unsurprisingly, these radical reactions produced mainly polystyrene and no desired product could be isolated (**Scheme 71**).

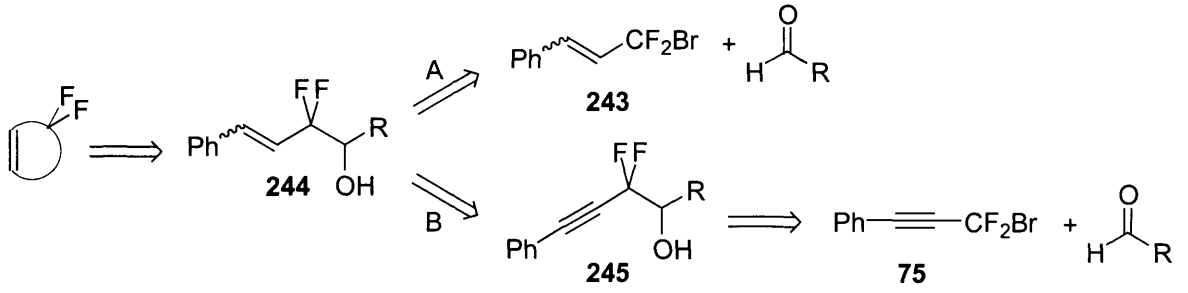


Reagents and conditions: i, CF_2Br_2 (2.0 eq.), ethanolamine (0.5 eq.), Cu(I)Cl (1 mol%), ^tBuOH, Ace tube, 90 °C, 24 h.; ii, CF_2Br_2 (2.0 eq.), $HOCH_2SO_2Na$ (2.0 eq.), Na_2CO_3 (1.5 eq.), CH_3CN/water, rt, 12 h..

Scheme 71

III.d – An alternative fluorinated building block: (3-bromo-3,3-difluoro-prop-1-ynyl)-benzene

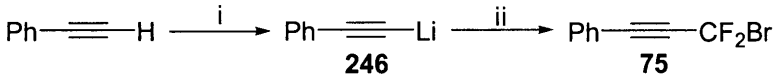
As the key intermediate homoallylic alcohols **244** could not be prepared from alkene **243** as a starting building block (route A), the preparation of homopropargylic alcohols **245** was explored as an alternative (route B). Indeed, reduction of the alkyne to the corresponding alkene should afford the desired homoallylic alcohols **244** and therefore the desired RCM precursors (**Scheme 72**).



Scheme 72

Wakselman *et al.* reported the synthesis of alkyne **75** in 35 % yield by deprotonation of phenylacetylene with *n*-butyllithium followed by addition of dibromodifluoro-methane to trap the lithium acetylide **246**.[91] The yield of this reaction was considerably improved (to 85 %) by pre-cooling the solution of electrophile to -78 °C before addition to lithium acetylide **246**. This reaction was successfully and

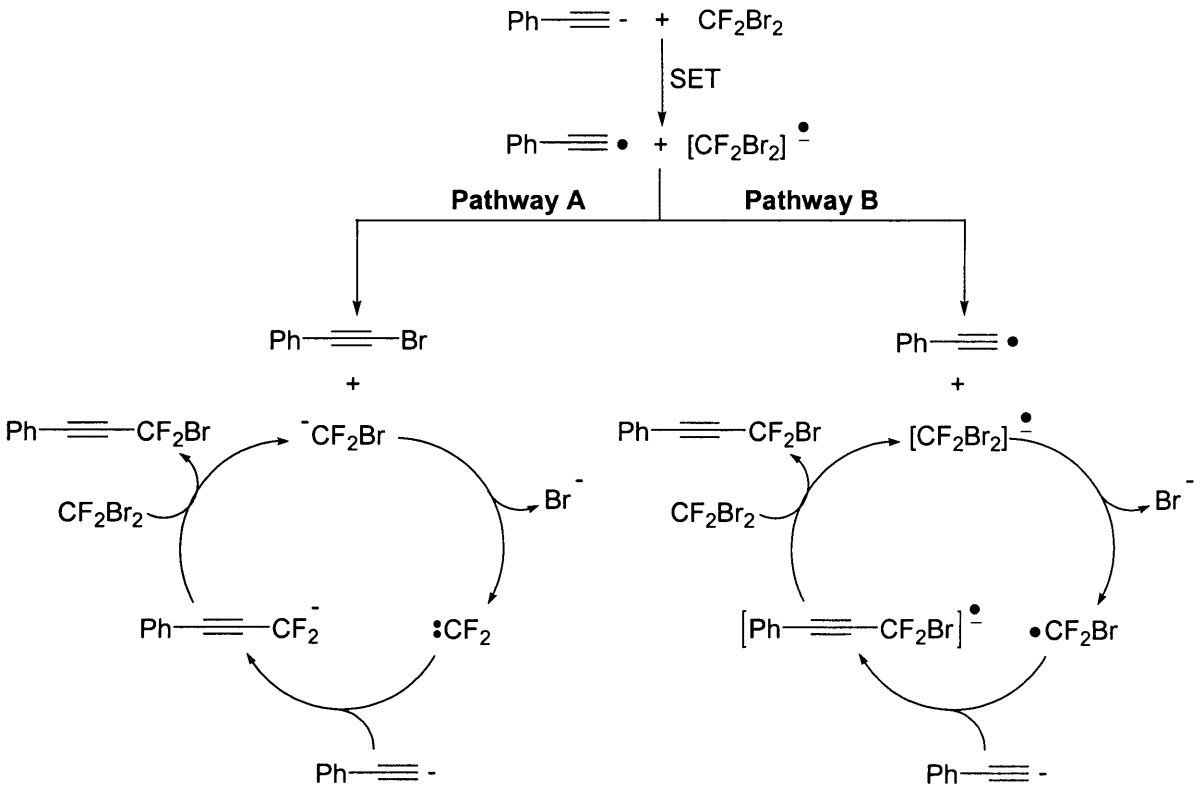
reproducibly scaled up to a 250 mmole scale and the product was easily purified by distillation under reduced pressure (**Scheme 73**).



Reagents and conditions: i, *n*BuLi (1.0 eq.), THF, -78 °C, THF; ii, cold (-78 °C) solution of CF_2Br_2 (1.1 eq.) in THF, **75**, 82 %.

Scheme 73

Although acetylide anion **246** reacts with dibromodifluoromethane in an apparent nucleophilic displacement, the mechanism of the reaction is more complex and can potentially involve two different pathways initiated by single electron transfer (SET) (**Scheme 74**).[91,92]

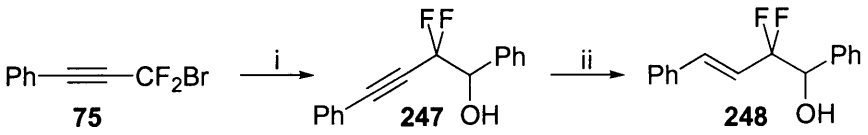


Scheme 74

Wakselman *et al.* ruled out pathway B as they did not observed the formation of the chlorodifluoromethyl-alkyne when carrying out the reaction with bromochloro-difluoromethane (CF_2BrCl) instead of dibromodifluoromethane (CF_2Br_2). Considering

the mechanism of the reaction and the formation of a catalytic amount of highly reactive difluorocarbene, strict control of the temperature and slow addition of the electrophile are essential to achieve good yields for the formation of alkyne **75**.

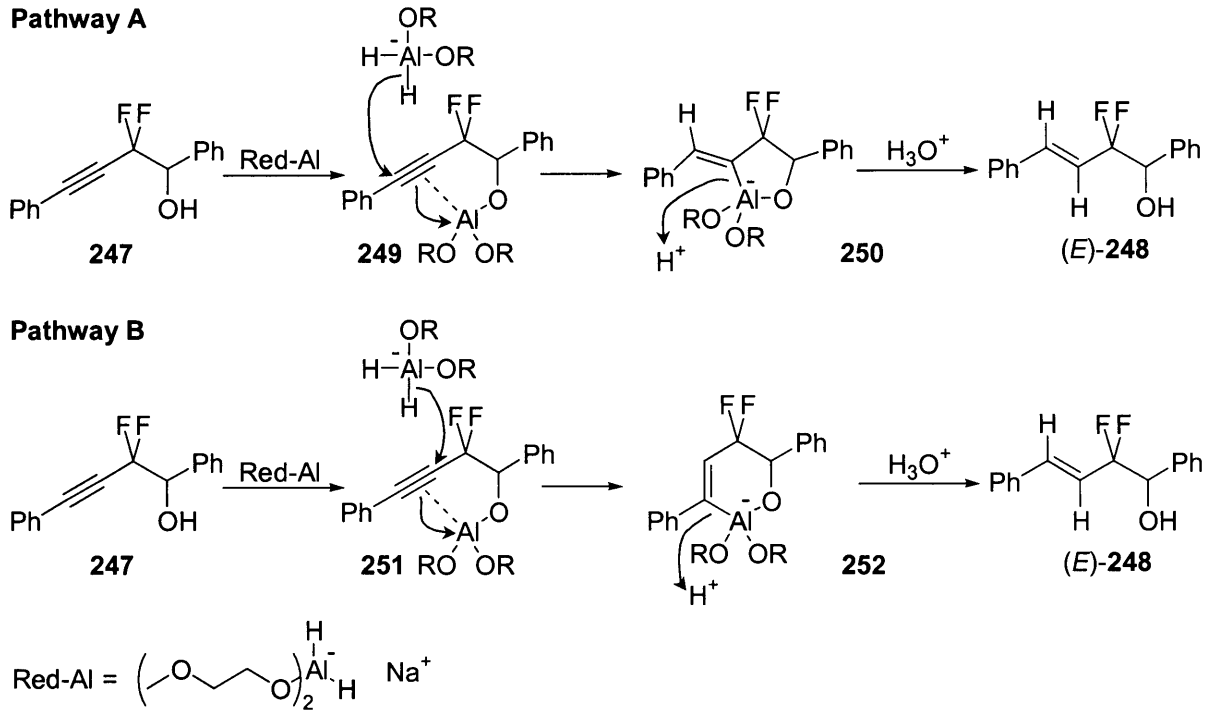
Alkyne **75** was then reacted with benzaldehyde on a small scale (10 mmoles) following a procedure described by Kobayashi *et al.* using three equivalents of zinc and a catalytic amount (5 mol%) of mercury (II) chloride.[27] Homopropargylic alcohol **247** was then reduced to the corresponding alkene **248** using two equivalents of Red-Al to afford exclusively the *trans*-isomer **248** as proved by the coupling constant between the alkenic protons (J_{trans} = 16.2 Hz) (**Scheme 75**).



Reagents and conditions: i, benzaldehyde (1 eq.), Zn powder (3 eq.), $HgCl_2$ (5 mol%), THF, 0 °C to rt, **247**, 73 %; ii, Red-Al (2 eq.), toluene/THF, -20 °C, **248**, 69 %.

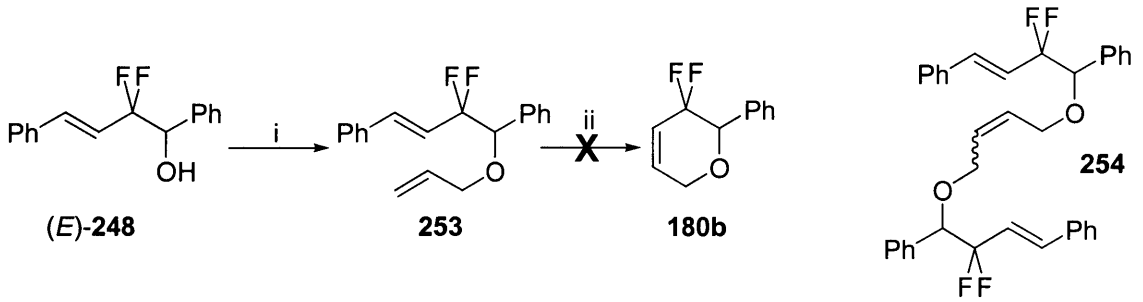
Scheme 75

The stereoselectivity of the Red-Al reduction can be rationalised by a mechanism involving two molecules of Red-Al. The first molecule forms alane **249**, which coordinates to the triple bond and the second molecule delivers an hydride by external nucleophilic attack regioselectively on the more electrophilic carbon next to the phenyl group (pathway A) to form cyclic alane **250**, which is subsequently hydrolysed by acidic aqueous work-up to afford alkene **248**. A mechanism similar to the one described by Alami *et al.*[93] where the hydride reacts at the other end of the alkyne (pathway B) cannot be ruled out as it also delivers the *E*-alkene. (**Scheme 76**).



Scheme 76

Alcohol **248** was allylated under phase transfer catalysed conditions to afford homoallyl-allyl ether **253**. RCM of ether **253** was attempted by using Grubbs' catalyst **92** in DCM at room temperature for 16 hours. The desired dihydropyran **180b** was not observed and only a mixture of *cis*- and *trans*- dimer **254** formed by cross-metathesis was recovered in nearly quantitative yield (**Scheme 77**).



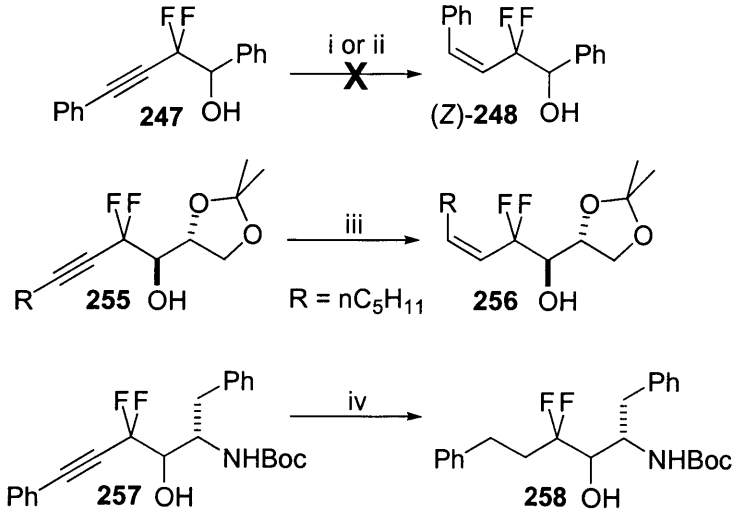
Reagents and conditions: i, allyl bromide (1.1 eq.), cat. nBu$_4$NHSO$_4$, 50 wt. % aq. NaOH (7.0 eq.), rt, 18 h., **253**, 100 %; ii, Grubbs' cat. **92** (5 mol%), DCM, rt, 16h., **254** , 97%.

Scheme 77

The outcome of this reaction suggests that the reactivity of the double bond of the homoallyl moiety of ether **253** is severely attenuated by the steric hindrance of the

phenyl group and by the presence of the electron-withdrawing fluorines. Therefore, the ruthenium carbene reacts on the other double bond and then intermolecularly to form dimer **254** in a cross-metathesis process.

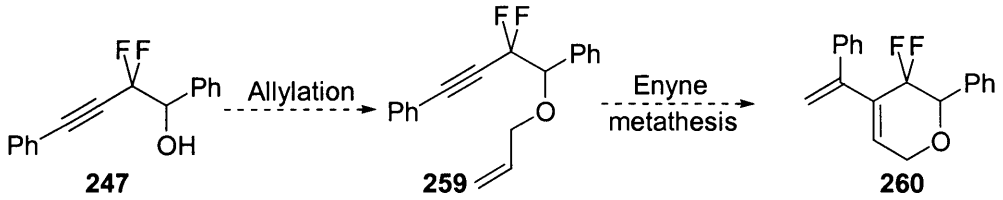
To explore the behaviour of the corresponding *cis*-alkene (*Z*)-**248** in the RCM reaction, alkyne **247** was subjected to catalytic hydrogenation under atmospheric pressure. When both Lindlar's catalyst and palladium on carbon were used, no reduction occurred and only starting material was recovered. This observation is in contrast with results reported by Kobayashi *et al.*[27] and Sham *et al.*[94] who reduced similar alkynes to the corresponding alkene or alkane using Lindlar's catalyst or palladium on carbon respectively (**Scheme 78**).



Reagents and conditions: i, cat. Pd-$BaSO_4$, ethanol, H_2, 1 atm., 48 h.; ii, cat. Pd/C, ethanol, H_2, 1 atm., 48 h.; iii, cat. Pd-$BaSO_4$ poisoned with quinoline, MeOH, H_2, **256**, 73 %; iv, cat. Pd/C, ethanol, H_2, 1 atm., 1 h., **258**, 96 %.

Scheme 78

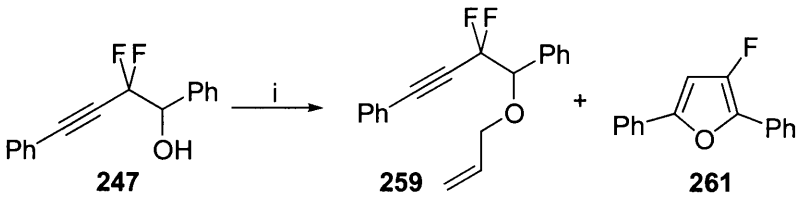
Although alkyne **247** failed to deliver suitable RCM precursors, it was potentially an interesting substrate for enyne metathesis. Indeed, allylation of alcohol **247** would set the stage for enyne metathesis, which would produce novel difluorinated cyclic diene **260** (**Scheme 79**).



247 259 260

Scheme 79

In the first instance allylation of homopropargylic alcohol **247** was attempted under phase transfer catalyst conditions as described previously for allyl alcohols **178**. Under such conditions, the desired ether **259** was afforded in 49 % yield along with 3-fluorofuran **261** (32 %) (**Scheme 80**).

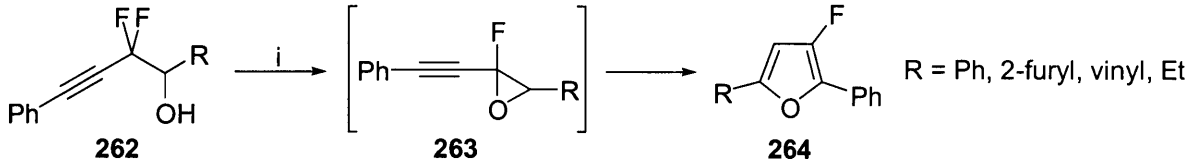


247 259 261

Reagents and conditions: i, allyl bromide (1.1 eq.), cat. nBu$_4$NHSO$_4$, 50 wt. % aq. NaOH (7.0 eq.), DCM, 0°C, 30 min., then rt, 18 h., **259**, 49 % and **261**, 32 %.

Scheme 80

Formation of 3-fluorofuran **261** was not surprising as Sham *et al.* reported the synthesis of 3-fluoro-2,5-disubstituted furans **264** *via* the deprotonation of difluorinated homopropargylic alcohols with potassium *tert*-butoxide in *tert*-butanol.[95] According to this work, the cyclisation may go through an acetylenic epoxide intermediate **263**, which rearranges to the fluorofuran **264** (**Scheme 81**).



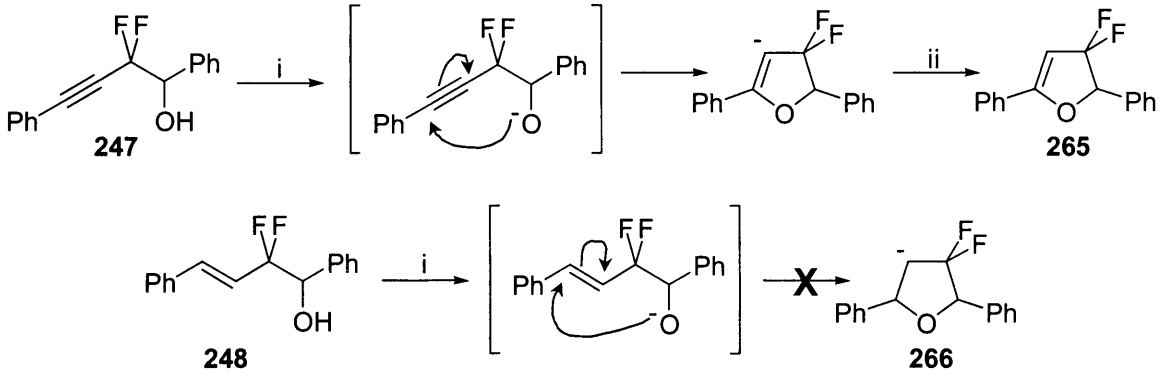
262 263 264

Reagents and conditions: i, ^{t}BuOK, ^{t}BuOH

Scheme 81

Under the phase transfer catalyst conditions used for the allylation, the mechanism may be different for the formation of fluorofuran **261**. Indeed, the crude ^{19}F NMR

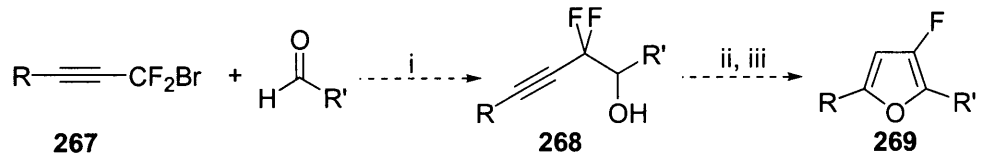
spectrum of the reaction mixture showed a pair of doublets of doublets (-81.6 ppm and -85.7 ppm) along with the signals for allyl ether **259**, suggesting the formation of 3,3-difluoro-2,5-diphenyl-2,3-dihydrofuran **265** *via* a 5-*endo*-dig cyclisation, favoured by Baldwin's rules.[96] After column chromatography, 3-fluorofuran **261** was afforded by elimination of H-F and the ^{19}F NMR spectrum showed only a singlet (-69.4 ppm). Interestingly, a similar reaction was not observed for the allylation of homoalllylic alcohols **248** as it would go through a disfavored 5-*endo*-trig cyclisation (**Scheme 82**).



Reagents and conditions: i, allyl bromide (1.1 eq.), 50 wt. % aq. NaOH (7.0 eq.), cat. nBu$_4$NHSO$_4$, DCM, 0 °C, 30 min., then rt, 18 h.; ii, H_3O^+.

Scheme 82

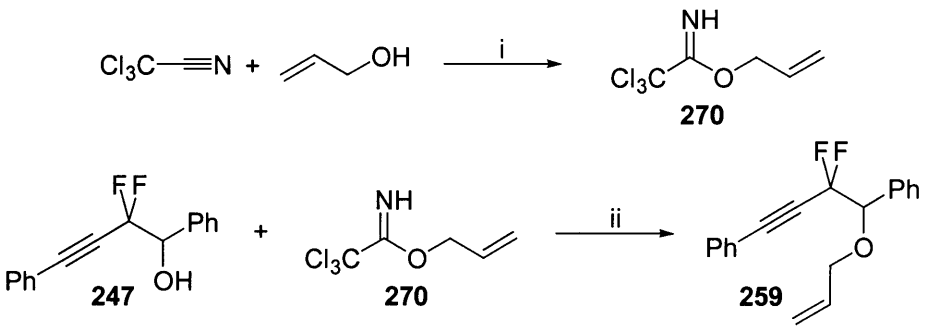
Although this reaction of formation of 3-fluorofurans was not explored any further, it may present some potential for the preparation of a large range of such furans by simply treating the corresponding homoallylic alcohols **268** with an aqueous sodium hydroxide solution in the presence of a phase transfer catalyst. Diversity can be introduced by using different alkynes **267** to change the substituent at the 2-position and various aldehydes to change the substitution pattern at the 5-position (**Scheme 83**).



Reagents and conditions: i, Zn powder, cat. $HgCl_2$, THF; ii, 50% aq. NaOH; iii. chromatography.

Scheme 83

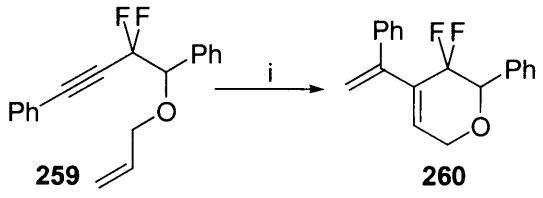
To alleviate the undesired formation of 3-fluorofuran **261** in the synthesis of allyl ether **259**, trichloroacetimidate **270** was prepared and reacted with alcohol **247** as described by Bundle *et al.*,[97] under mildly acidic conditions. Trichloroacetimidate was formed by the reaction of trichloroacetonitrile and allyl alcohol in the presence of a catalytic amount of sodium hydride and reacted with the alcohol in the presence of trifluoromethanesulfonic acid (**Scheme 84**).



Reagents and conditions: i, NaH (0.1 eq.), Et_2O, 0 °C to rt, 1 h., **270**, 88%; ii, cat. TfOH, hexane, rt, 3 d., **259**, 81 %.

Scheme 84

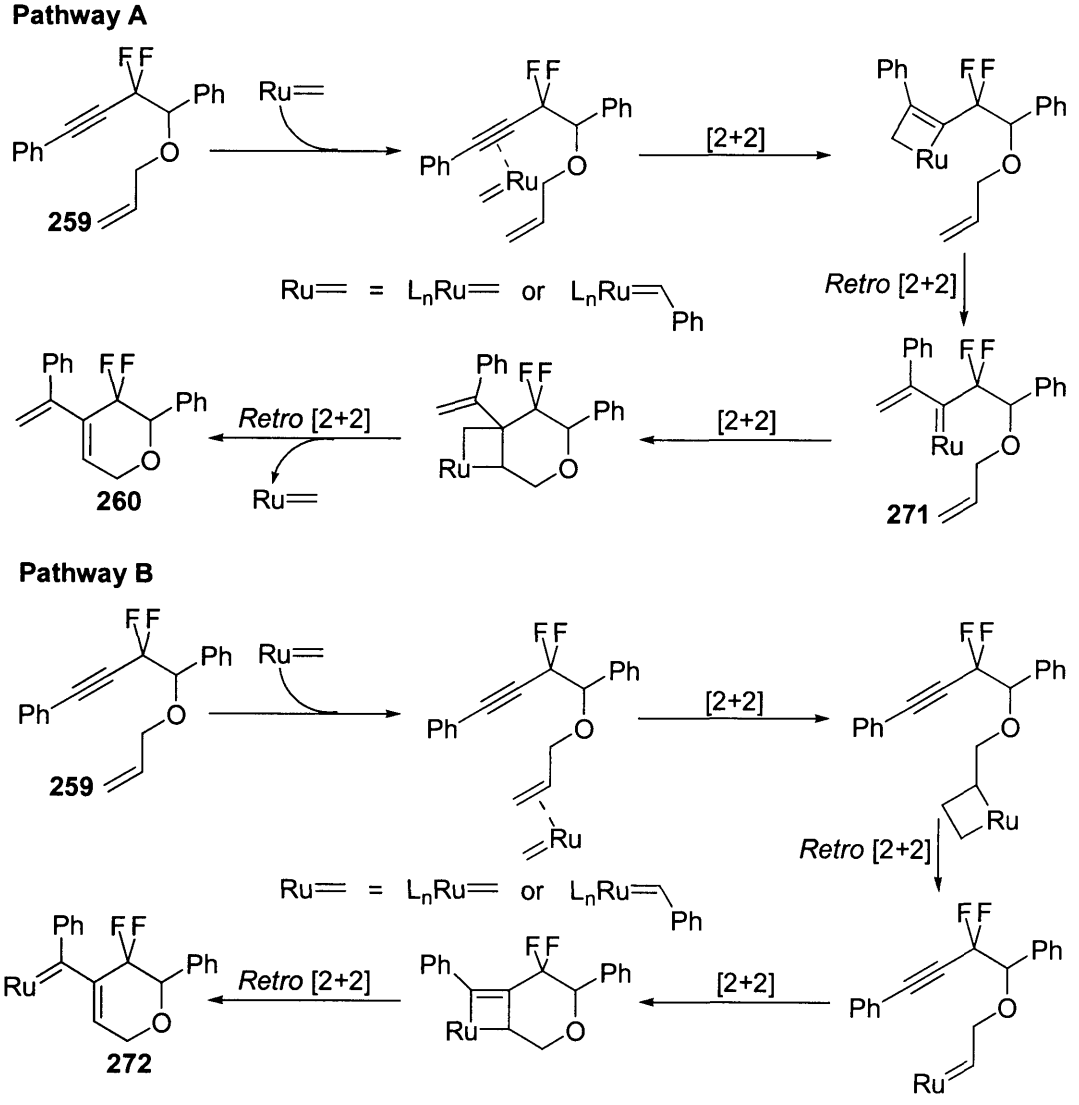
In a non-optimised reaction, ether **259** was reacted with Grubbs' catalyst **92** (5 mol%) for 18 hours in refluxing DCM to afford the desired diene **260** in 43 % yield along with unreacted starting material (**Scheme 85**).



Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), DCM, reflux, 18 h., **260**, 43 %.

Scheme 85

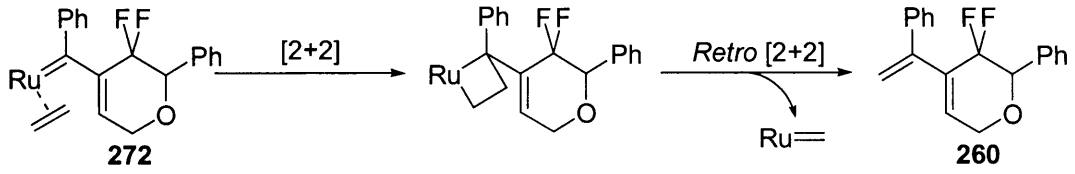
The mechanism of enyne metathesis is different from the normal olefin metathesis as it can possibly adopt two different pathways, depending on whether the ruthenium carbene reacts first with the alkyne or the alkene. In the first case (pathway A), the ruthenium catalyst reacts first with the alkyne to form ruthenium alkylidene **271**. Intramolecular reaction then affords the desired product **260**. On the other hand, when the ruthenium catalyst reacts first with the alkene (pathway B), the intramolecular reaction forms a non-productive complex **272** (**Scheme 86**).



Scheme 86

In the case of substrate **259**, the alkyne is electron-deficient because of the presence of the electron-withdrawing fluorines and the reaction is likely to go down pathway B

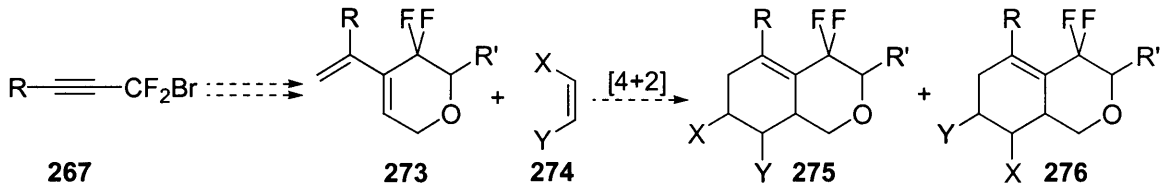
and the formation of non-productive complex **272**. This would explain the low yield of product for this RCM. The yield of this reaction could possibly be increased by carrying out the reaction in an ethylene atmosphere as described by Mori *et al.*[98] Indeed, complex **272** can react with ethylene to afford the desired RCM product **260** by a cross-metathesis process (**Scheme 87**).



272 **260**

Scheme 87

Although optimisation is required, diene **260** could be an interesting starting building block to prepare difluorinated bicyclic molecules such as **275** and **276** by reaction with a wide range of dienophiles in [4+2] Diels-Alder cylcoadditions. These reactions should be regioselective as the fluorines should considerably influence the shape of the HOMO of the diene. Moreover, diversity can also be introduced by using different alkynes and aldehydes (**Scheme 88**).



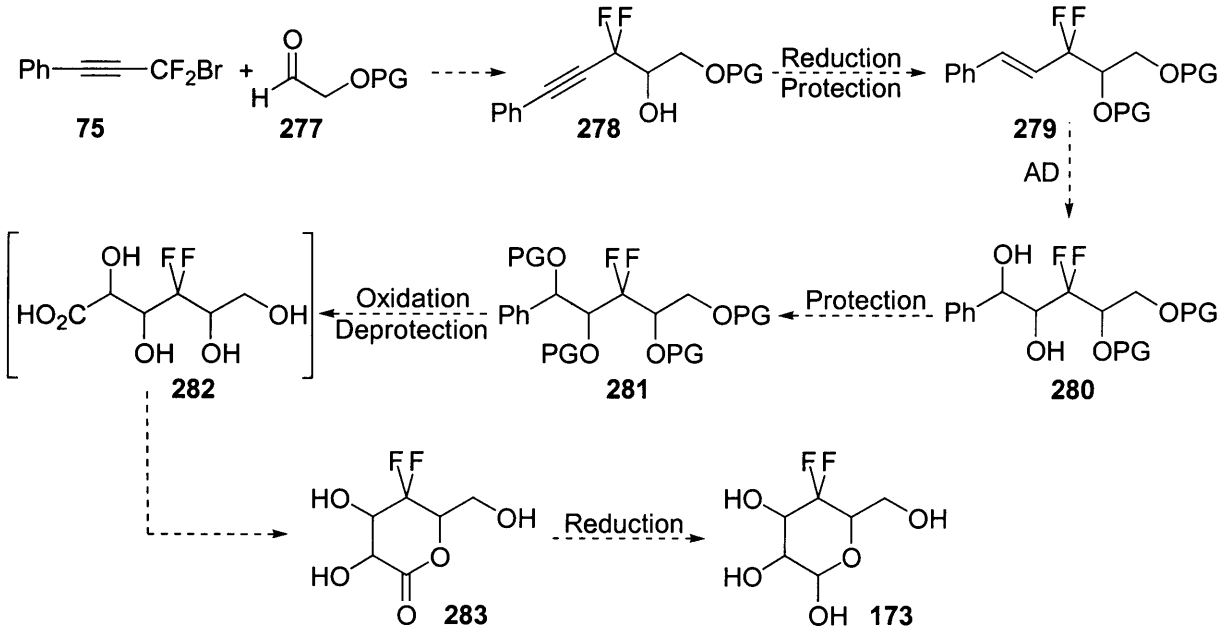
267 **273** **274** **275** **276**

Scheme 88

IV - Towards 4,4-difluoro-4-deoxyhexose *via* a non-RCM based route

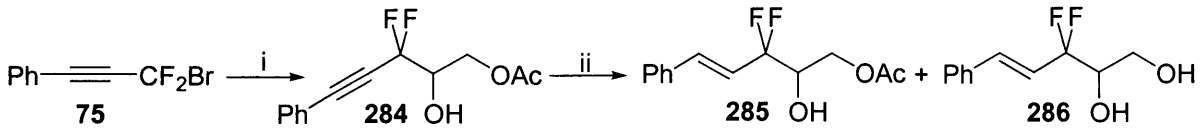
Even if the RCM of a phenyl substituted alkene failed, (3-bromo-3,3-difluoro-prop-1-ynyl)-benzene **75** could be a potential interesting fluorinated starting material for an

asymmetric, non-RCM based synthesis of 4,4-difluoro-4-deoxyhexose. Indeed, addition of alkyne **75** to a protected hydroxyacetaldehyde **277** followed by reduction of the alkyne to the corresponding (*E*)-alkene and protection of the secondary hydroxyl would afford an ideal substrate for asymmetric dihydroxylation. Protection of the newly formed diol **280**, followed by oxidation of the phenyl group to the corresponding carboxylic acid and deprotection of all hydroxyl groups should trigger a lactonisation to afford the key lactone **283**, which would afford difluorinated monosaccharide analogues **173** after reduction (**Scheme 89**).



Scheme 89

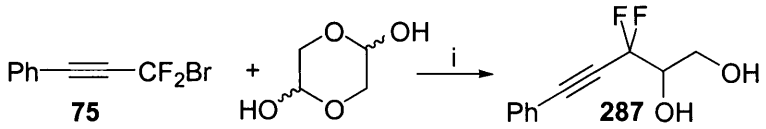
In the first instance, alkyne **75** was reacted with acetoxyacetaldehyde using Kobayashi's method[27] to afford homopropargylic alcohol **284**, which was reduced to the corresponding alkene with two equivalents of Red-Al. Some partial acetate cleavage occurred upon reduction, affording a mixture of diol **286** and acetate **285** (**Scheme 90**).



Reagents and conditions: i, acetoxyacetaldehyde (1 eq.), Zn powder (3 eq.), $HgCl_2$ (5 mol%), THF, 0 °C, 5h., **284**, 56 %; ii, Red-Al (2 eq.), toluene/THF, 0 °C, 3h., **285**, 45 % and **286**, 30 %.

Scheme 90

To alleviate the cleavage of the acetate, an alternative route was explored, by reacting alkyne **75** with glycolaldehyde dimer, a masked hydroxyacetaldehyde, under the same conditions (**Scheme 91**).



Reagents and conditions: i, Zn powder (1 eq.), $HgCl_2$ (5 mol%), THF, rt, 18 h., **287** 73 %.

Scheme 91

Although the reaction of addition to glycolaldehyde dimer afforded the desired diol **287** in good yield (73 %) on a small scale (5 mmoles), any attempt to scale up this reaction failed as it tended to produce mainly dimer **288**, probably *via* a Wurtz type coupling (**Figure 12**).

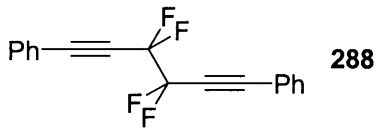
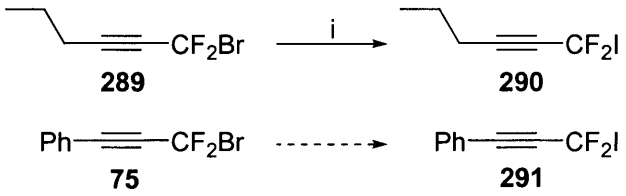


Figure 12

A small screen of other metal mediators (indium, aluminium and magnesium) failed to deliver good yields of product and/or reproducible results. Even the tin/indium (III) chloride mediated reaction described by Kirihara *et al.*[72] or the indium reaction in a mixture of water and THF (80:20) described by Hammond *et al.*[99] failed to produce any useful quantity of material.

As zinc seems to be the metal of choice for the addition of bromodifluoromethylacetylenes to aldehydes,[94,95,100,101] a screen of the reaction with glycolaldehyde dimer using zinc, with different additives and in different solvents was undertaken. Different sources of mercury (II) salts (mercury (II) chloride, mercury (II) acetate, mercury (II) trifluoroacetate) were tried, in the presence or absence of sodium iodide in water, THF or DMF. The presence of one equivalent of sodium iodide may allow the *in situ* formation of the possibly more reactive difluoroiodomethylphenylacetylene **291** as described by Fried *et al.* for a similar substrate **289** (**Scheme 92**).[102]



Reagents and conditions: i, NaI (1.0 eq.), methyl ethyl ketone, reflux, 20 h., **290**, 62 %.

Scheme 92

Initial screening was carried out on a quarter of a millimole scale in one millilitre of solvent. All the reaction components were mixed together in vials, vigorously shaken for eighteen hours, quenched with 1N HCl (2 mL) and extracted with diethyl ether (5 mL). The organic extract was filtered through a short pad of magnesium sulphate and concentrated. A crude ^{19}F NMR for each reaction mixture was recorded and the relative amount of starting material **75**, product **287**, dimer **288** and other impurities were determined by integration. Results are summarised in **Figure 13**.

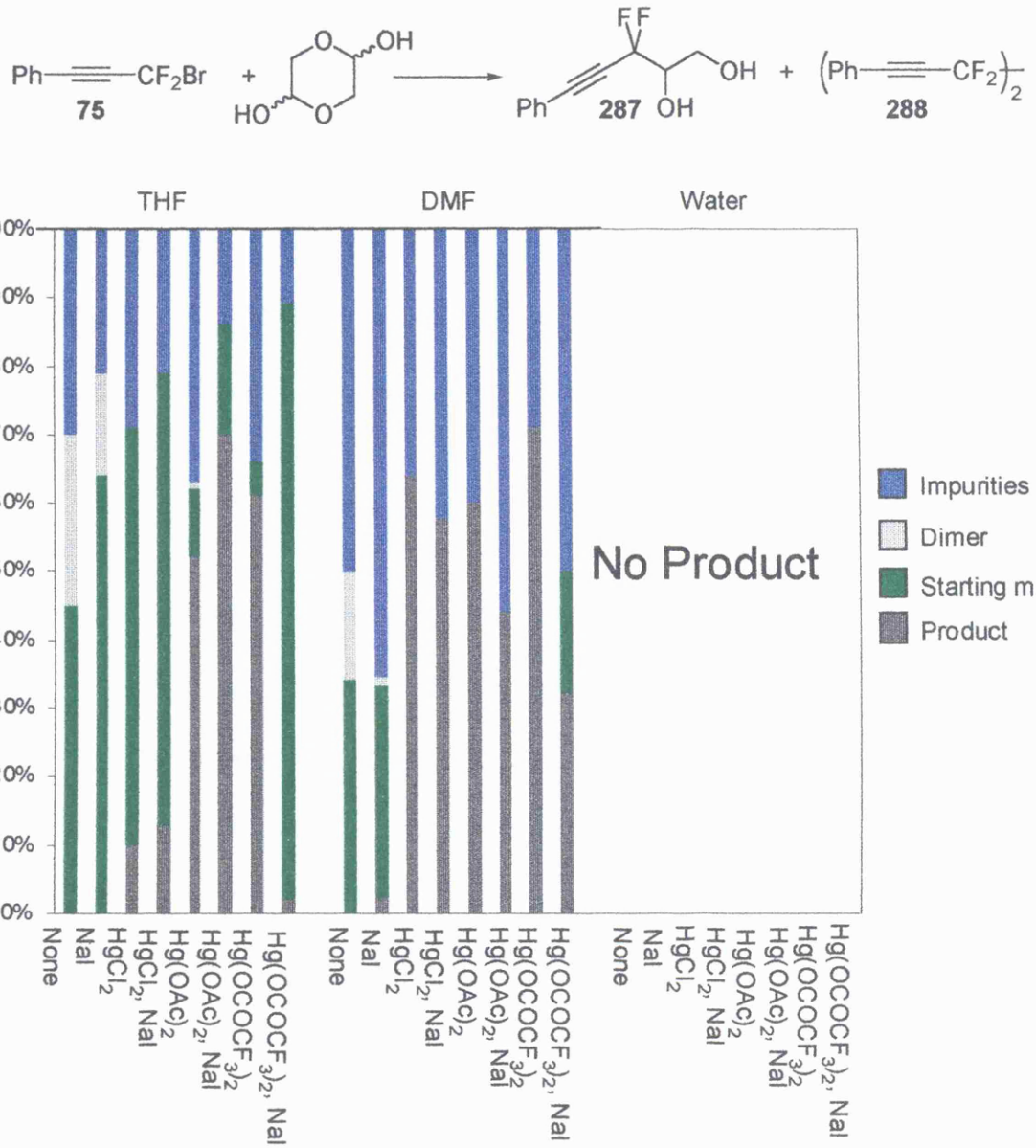
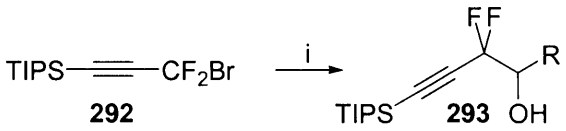


Figure 13

Reactions in water afforded complex mixtures, which did not contain any desired diol **287**. In DMF, the addition of one equivalent of sodium iodide did not seem to have any positive effect on the reaction outcome. The yield of product (as determined by integration of the ^{19}F NMR spectra) for the reaction with mercury (II) trifluoroacetate (71 %) is marginally better than the yield with mercury (II) chloride and mercury (II) acetate (64 % and 60 % respectively). However, in THF, the presence of sodium iodide seemed to increase the yields slightly when mercury (II) chloride or mercury (II) acetate were used but the effect was opposite with mercury (II) trifluoroacetate. In

THF, the best yield (70 %) was observed with the combination of sodium iodide and a catalytic amount of mercury (II) acetate. In both THF and DMF, the reactions *required* the presence of mercury (II) salts. This observation is in contradiction with the results reported by Hammond *et al.*, who reacted TIPS-propynyl **292** with aldehydes in the presence of zinc and without mercury (II) salts to obtain homopropargylic alcohols in good yields **293** (**Scheme 93**).[100,101]

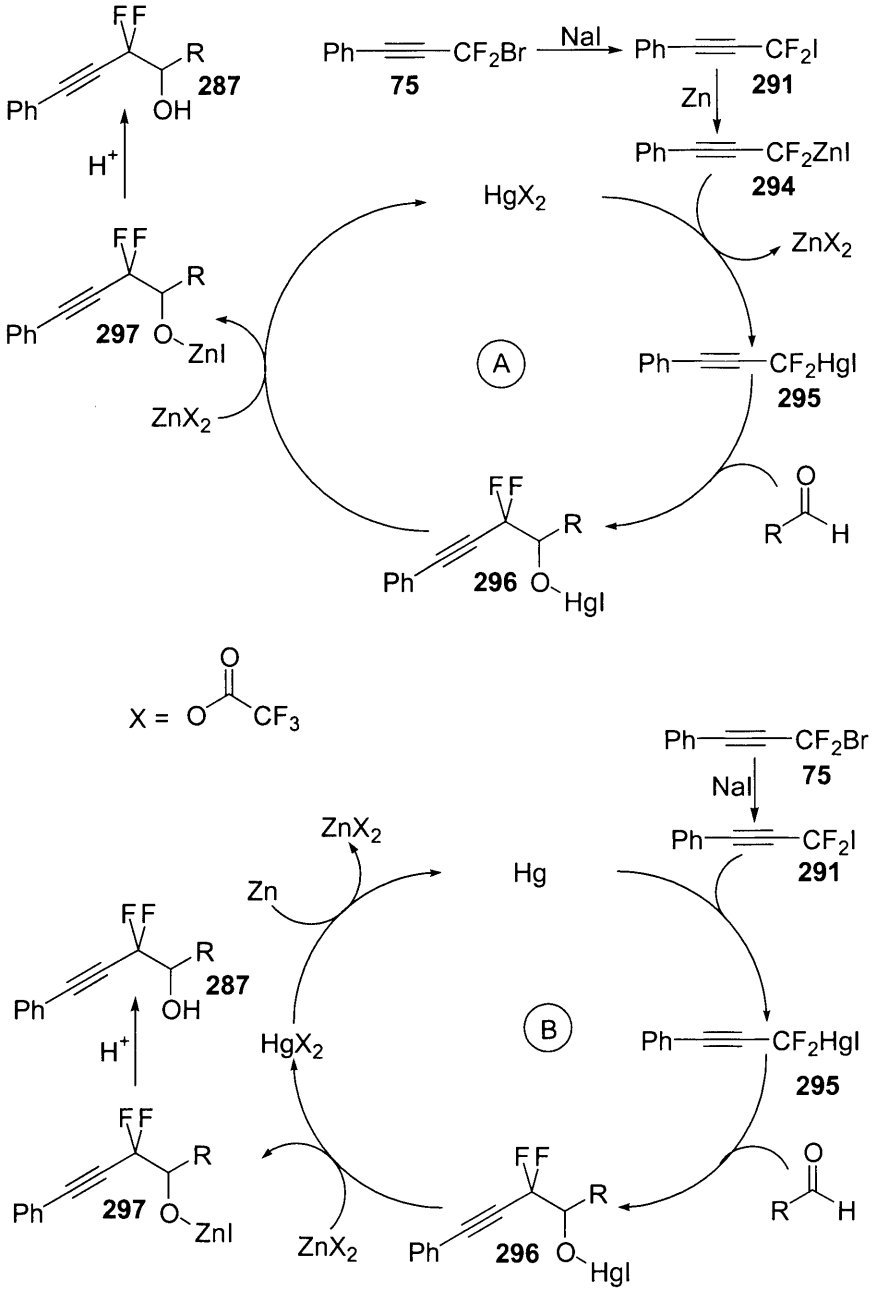


Reagents and conditions: i, Zn powder (1.2 eq.), aldehyde (1.0 eq.), THF, 20 h., rt.

Scheme 93

The best two reactions (mercury (II) trifluoroacetate in DMF and mercury (II) acetate, sodium iodide in THF) were scaled up to 5 millimoles to afford the desired product **287** in 52 % and 69 % isolated yields respectively. Pleasingly, the latter reaction (mercury (II) acetate, sodium iodide in THF) was successfully scaled up to 20 and then to 79 millimoles without any significant yield loss (68 % and 69 % respectively).

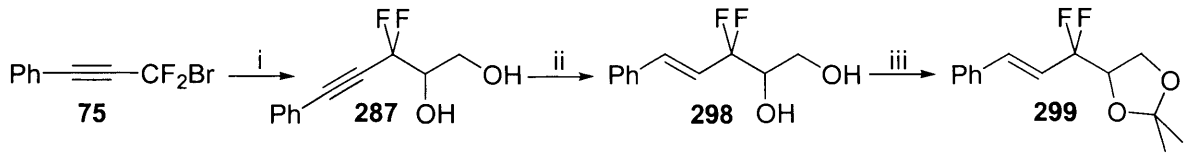
The mechanism of this reaction is unclear, particularly the role of the mercury (II) salt. It is conceivable that sodium iodide reacts with bromoalkyne **75** to afford the more reactive iodo-compound **291**. Zinc would then insert reductively in the carbon-iodine bond (cycle A) and transmetallation with mercury would occur to afford **295**. Organomercury **295** would then react with electrophiles such as aldehydes to regenerate a new mercury (II) salt, which would re-enter the catalytic cycle. Alternatively, reduction potentials of Zn^{2+}/Zn (-0.7618 eV) and Hg^{2+}/Hg (0.851 eV) suggest that the zinc may reduce the mercury (II) salt to mercury metal, which would oxidatively add in the carbon-iodine bond of **291** (cycle B) to enter the catalytic cycle. (**Scheme 94**).



Scheme 94

When the addition of alkyne **75** to glycolaldehyde dimer was carried out on a large scale and after acidic work-up, mercury (0) was observed at the end of the reaction along with iodine, giving a deep red colour to the crude mixture. A sodium sulfite wash was essential to obtain good yields of product and prevent reaction of the remaining iodine with the alkyne.

Alkyne **287** was reduced to the corresponding alkene **298** using two equivalents of Red-Al and the diol was subsequently protected as the acetonide **299** to set the stage for asymmetric dihydroxylation (**Scheme 95**).



Reagents and conditions: i, glycolaldehyde dimer (1 eq.), Zn powder (1 eq.), NaI (1 eq.), $Hg(OAc)_2$ (5 mol%), THF, rt, 18 h., **287**, 69 %; ii, Red-Al (2 eq.), toluene/THF, 0 °C, **298**, 72%, iii, acetone, cat. *p*-TsOH.H_2O, rt, 18 h., **299**, 95 %.

Scheme 95

Dihydroxylation was carried out using AD mixes α and β as formulated by Sharpless *et al.*[103] These pre-mixed reagents are a mixture of potassium osmate dihydrate (a non-volatile source of osmium), potassium ferricyanide (III) (the re-oxidant), potassium carbonate and the chiral ligands *bis*-(dihydroquinine)-phthalazine ($(DHQ)_2PHAL$) and *bis*-(dihydroquinidine)-phthalazine ($(DHQD)_2PHAL$) respectively (**Figure 14**).

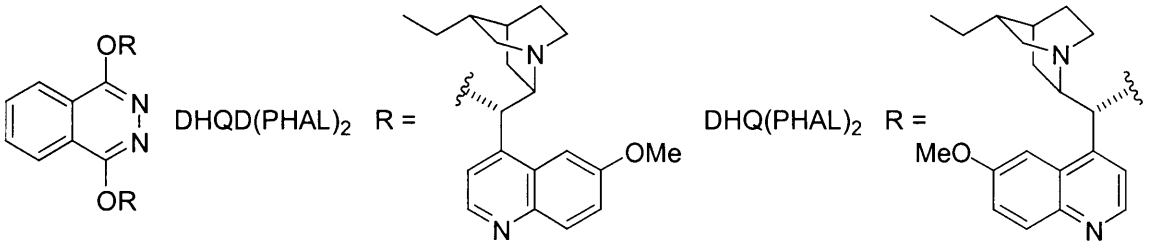
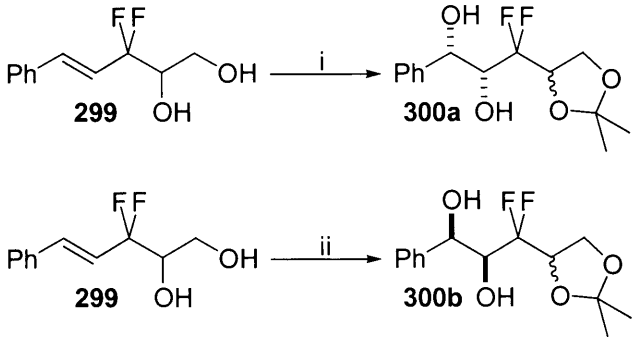


Figure 14

Dihydroxylations of **299** were quite slow and took three days to go to completion despite the use of methanesulfonamide, which usually increases the rate of hydrolysis of the osmate (VI) ester.[104] Nevertheless, each pair of diastereoisomers **300a** and **300b** was afforded in very good yields (83 and 91 % respectively) (**Scheme 96**).



Reagents and conditions: i, AD-mix α, methanesulfonamide (1 eq.), ^{t}BuOH/water, rt, 3 d., **300a**, 83 %; ii, AD-mix β, methanesulfonamide (1 eq.), *t*BuOH/water, rt, 3 d., **300b**, 91 %;

Scheme 96

Attempts to use sodium hydroxide to maintain a constant pH value of 12 to increase the rate of hydrolysis of the osmate esters as described by Beller *et al.*,[105] failed to shorten the reaction times and delivered lower yields of products.

At this stage the stereochemistry of diols **300a** and **300b** could not be determined but was predicted from the model proposed by Sharpless *et al.*.[103,106,107] According to this group, the phthalazine and the dihydroquinidine ring systems of $(DHQD)_2PHAL$ (or dihydroquinine for $(DHQ)_2PHAL$) set up a binding pocket, in which the aromatic group of the substrate undergo parallel stacking with the phthalazine and make attractive edge-to-face interactions with the dihydroquinidine (or dihydroquinine). **Figure 15** explains the stereochemical outcome of the reaction carried out with AD-mix β ($(DHQD)_2PHAL$ ligand). Obviously, the same rationale applies for the reaction with AD-mix α.

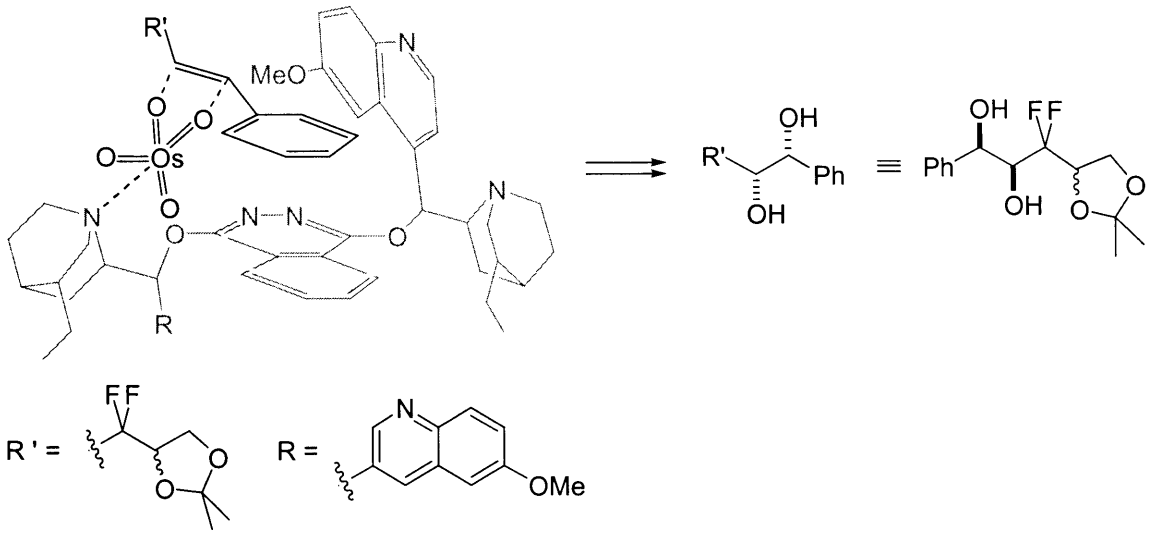


Figure 15

The enantioselectivity of these reactions can also be explained by a different model described by Corey *et al.*.[108] According to this group, the phenyl group only interacts with the ring system of dihydroquinidine by parallel stacking as shown in **Figure 16**.

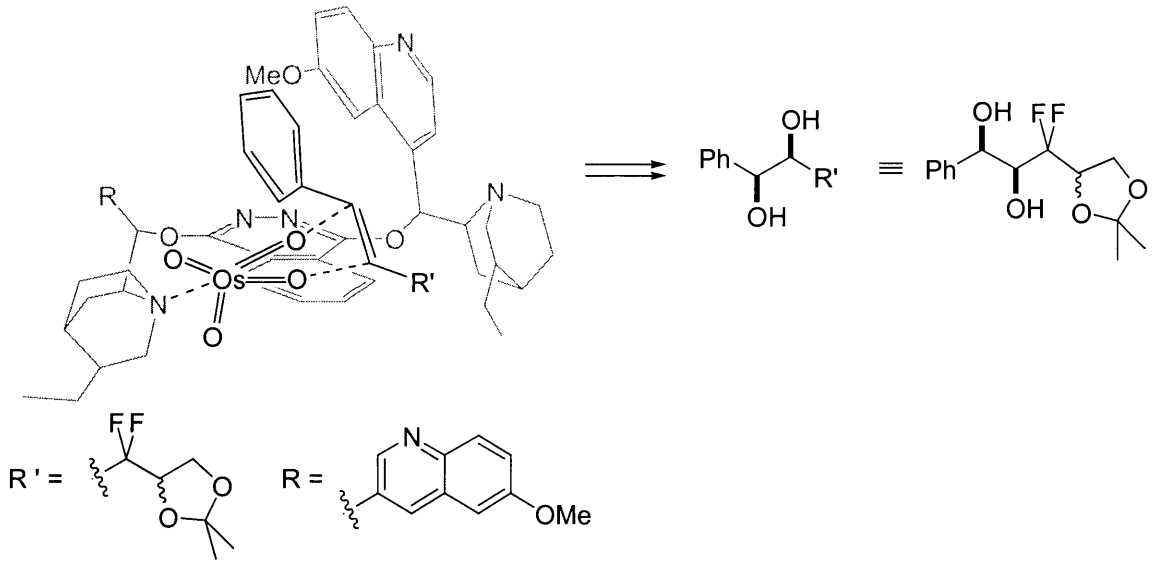
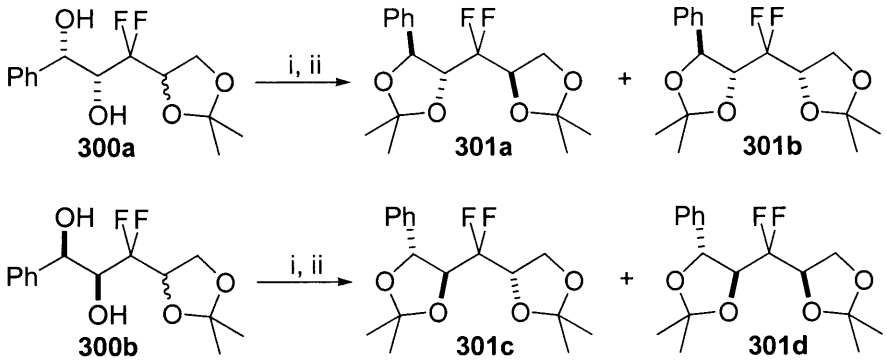


Figure 16

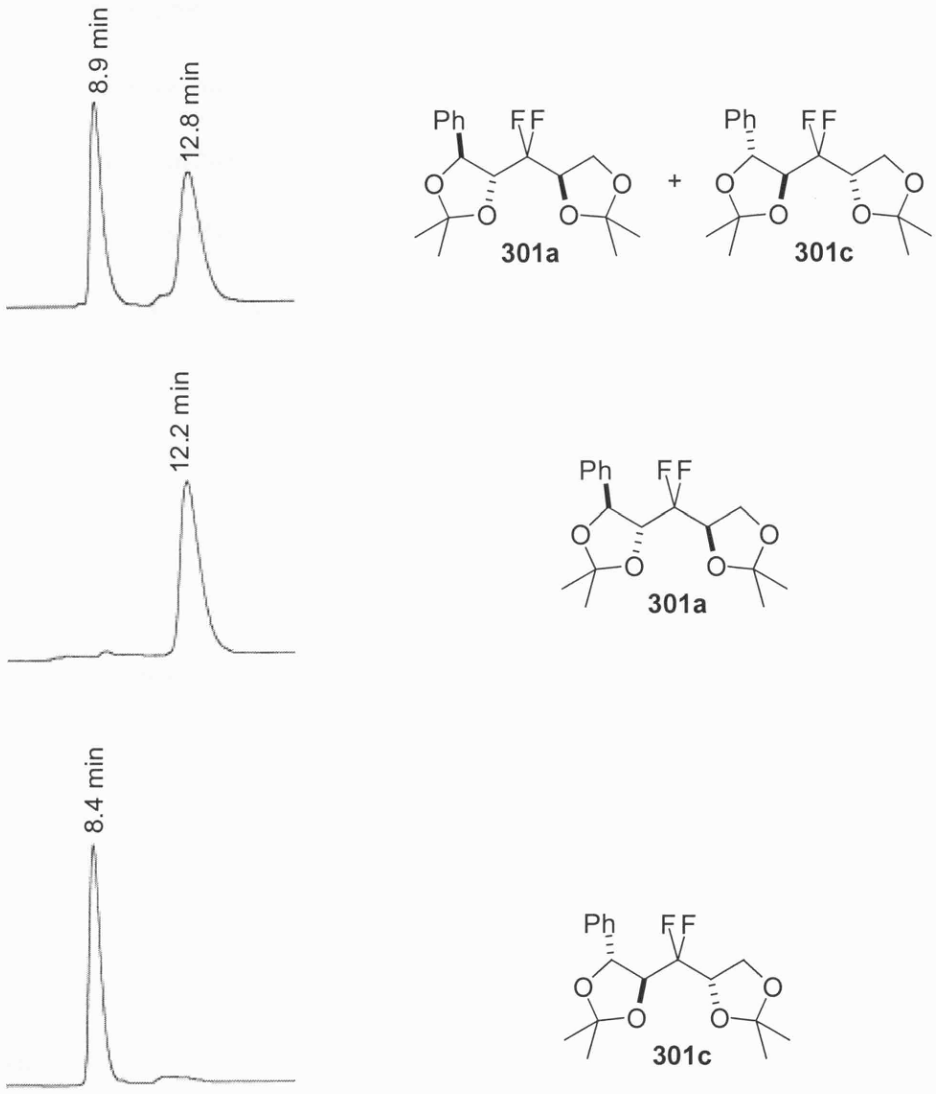
The pair of diols **300a** and **300b** was then protected again as the corresponding acetonides **301a-d**, which allowed for the separation of the two diastereoisomers by column chromatography in each case (**Scheme 97**).



Reagents and conditions: i, acetone, cat. *p*-TsOH.H_2O, anh. $CuSO_4$, rt, 17 h., **301a**, 43 %, **301b**, 46%, **301c**, 41 % and **301d**, 48 %.

Scheme 97

At this stage the determination of the enantiomeric excesses for all four bis-acetonides **301a-d** was attempted by chiral liquid chromatography using polysaccharide-based chiral LC columns (Chiralcel OJ, Chiralcel OD, Chiralpak AD and Chiralpak AS), which were successfully used by Okamoto *et al.* to separate a wide range of enantiomers.[109] With the columns described above, only enantiomers **301a** and **301c** could be separated by using Chiralcel OJ column, hexane/*iso*-propyl alcohol (100:1) as the eluent and a 1mL/min flow rate. Unfortunately, the enantiomeric excesses for **301a** and **301c** could not be calculated accurately. Indeed, the chromatograms for **301a** and **301c** showed the presence of the other enantiomers in small quantities but the corresponding peak could not be integrated as they were too small and too broad (**Figure 17**).



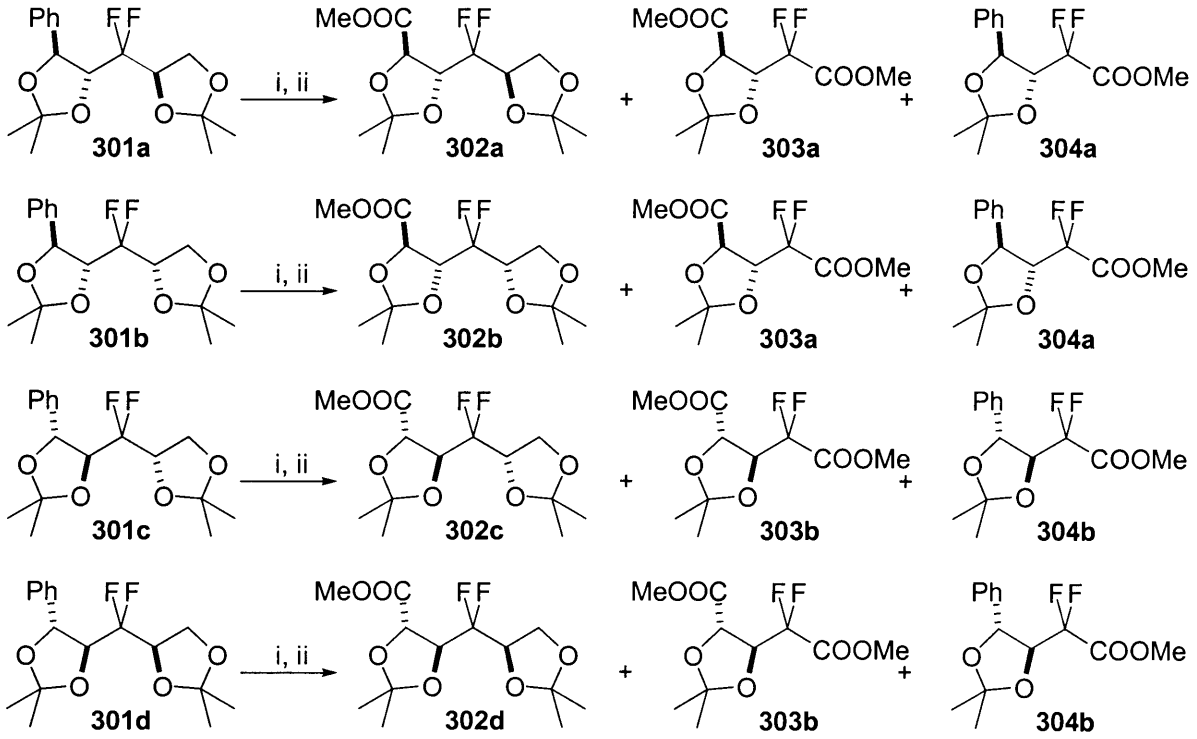
Conditions: Chiralcel OJ, hexane:IPA (100:1), 1.0 mL/min.

Figure 17

Obviously, some more work is required to assess precisely the degree of stereoselection of the dihydroxylations by using different columns and/or different eluents. Nevertheless, the optical rotations for **301a** ($[\alpha]_D$ (*c* 1.08 in MeOH) 10.9), **301b** ($[\alpha]_D$ (*c* 0.91 in MeOH) 3.6), **301c** ($[\alpha]_D$ (*c* 1.11 in MeOH) -11.9) and **301d** ($[\alpha]_D$ (*c* 1.01 in MeOH) -4.6) clearly showed that these compounds are not racemic and that the levels of stereoselection are similar for the AD-mix α and AD-mix β dihydroxylations.

The relative stereochemistry of bis-acetonide **301c**, and therefore those of **301a**, **301b** and **301d**, was assigned by X-ray crystallography (**Appendix 2**). Due to the absence of a heavy atom in the molecule, the absolute stereochemistry could not be determined with certainty.

Each enantiomer was then subjected to an oxidation of the phenyl group to the corresponding carboxylic acids using sodium periodate and a catalytic amount of ruthenium (III) chloride and subsequently esterified with trimethylsilyl-diazomethane. In each case, mixtures of different compounds were obtained (as shown by NMR and GC-MS) and by-products **303a-b** and **304a-b** could not be separated from the desired esters **302a-d** by conventional chromatography methods (**Scheme 98**).

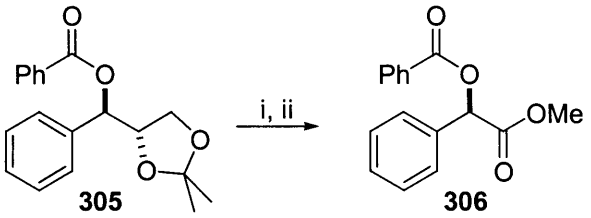


Reagents and conditions: i, $NaIO_4$ (2.0 eq.), $RuCl_3.H_2O$ (10 mol%), $EtOAc/CH_3CN/H_2O$, rt, 18 h.; ii, TMS-CHN_2 (1.5 eq.), MeOH, rt, 15 min..

Scheme 98

The formation of esters **303a-b** and **304a-b** by deprotection of an acetonide and cleavage of the corresponding diol in a Lemieux-type reaction was not unprecedented in the literature. Indeed, Martin *et al.* reported such a reaction when

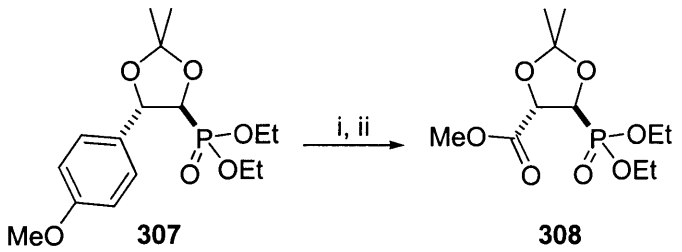
trying to oxidise the phenyl group of acetonide **305** with periodic acid and a catalytic amount of ruthenium (III) chloride (**Scheme 99**).[110]



Reagents and conditions: i, HIO_4 (14.2 eq.), $RuCl_3.H_2O$ (2 mol%), CCl_4/ CH_3CN/ H_2O, 3 h.; ii, CH_2N_2, **306**, 84 % over 2 steps.

Scheme 99

On the other hand, Shibuya *et al.* reported the successful oxidation of the *para*-methoxyphenyl group of acetonide **307** without observing any side reaction when using sodium periodate and ruthenium (III) chloride (**Scheme 100**).[111]

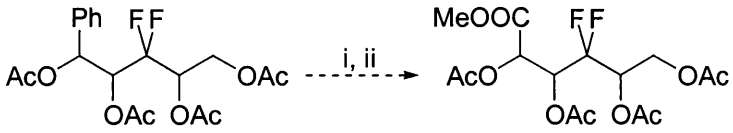


Reagents and conditions: i, $RuCl_3$ (1 mol%), $NaIO_4$ (14.0 eq.), $CH_3CN/CCl_4/H_2O$, rt, 12h.; ii, CH_2N_2, Et_2O, **308**, 95 % over 2 steps.

Scheme 100

The difference of outcomes for these two reactions may be explained by the different oxidants (HIO_4 *vs.* $NaIO_4$) that were used for the oxidation. In the first case, the acidity of the periodic acid is probably responsible for the hydrolysis of the acetonide of **305**. In the case of **301a-d** the pH was measured at the beginning of the reaction and proved to be very low (pH = 2.9) even when sodium periodate was used as opposed to periodic acid. These harshly aqueous acidic conditions explain the hydrolysis of one of the acetonides of **301a-d** followed by oxidation and esterification to afford the undesired esters **303a-b** and **304a-b**. To prevent the cleavage of the acetonides, replacement of the phenyl for a *para*-methoxyphenyl group may improve

the synthesis as oxidation of the latter group is usually faster, but would require the synthesis of a new alkyne. Alternatively and more easily, a change of protecting group would probably solve the oxidation problem. According to Martin *et al.* acetate seems to be a suitable protecting group to withstand the oxidation.[110] Therefore, to improve the synthesis, tetra-acetates **305a-d** would probably make better substrates for the oxidation and could be prepared by a similar route as described before (**Scheme 101**).

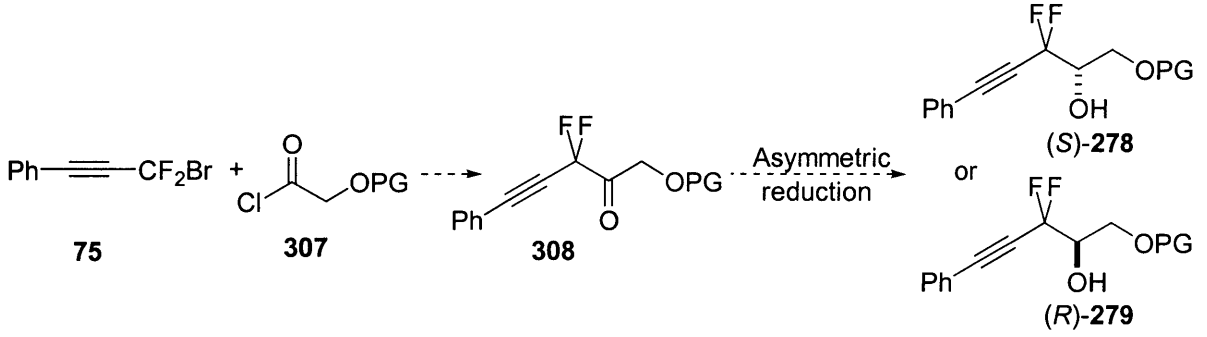


305a-d **306a-d**

Reagents and conditions: i, $NaIO_4$, $RuCl_3.H_2O$, $EtOAc/CH_3CN/H_2O$; ii, $TMS\text{-}CHN_2$, MeOH.

Scheme 101

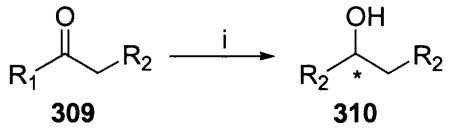
Although the preparation of difluorinated monosaccharide analogues *via* the asymmetric route described above failed because of a poor choice of protecting group, it demonstrated a potential approach to four different enantiomers from a single starting material. This strategy could probably be improved if only one enantiomer was required by avoiding the separation of diastereoisomers. This could probably be achieved by reacting the fluorinated starting building block **75** with an acyl chloride instead of an aldehyde and then reducing the corresponding ketone in an asymmetric fashion (**Scheme 102**).



75 **307** **308**

Scheme 102

There are many examples of asymmetric reduction of prochiral ketones to the corresponding alcohol with high enantioselectivity. These methods are based mainly on two different approaches. In the first one the ketone is hydrogenated in the presence of a chiral catalyst and in the second a chiral reducing agent is used. For instance, Noyori *et al.* developed a ruthenium based catalyst to perform asymmetric reduction of prochiral ketones. The catalyst is easily prepared by heating a mixture of commercially available $[RuCl_2(benzene)]_2$ and (*R*)- or (*S*)-BINAP (Ru:BINAP = 1:1.05) in DMF at 100 °C for 10 minutes followed by evaporation of the solvent under reduced pressure. This crude catalyst was used under 4 atmospheres of hydrogen to reduce various ketones **309** (including β-keto esters) to the corresponding alcohols **310** in high isolated yield (83-97 %) and with high enantioselectivity (ee > 90 %) (**Scheme 103**).[112]



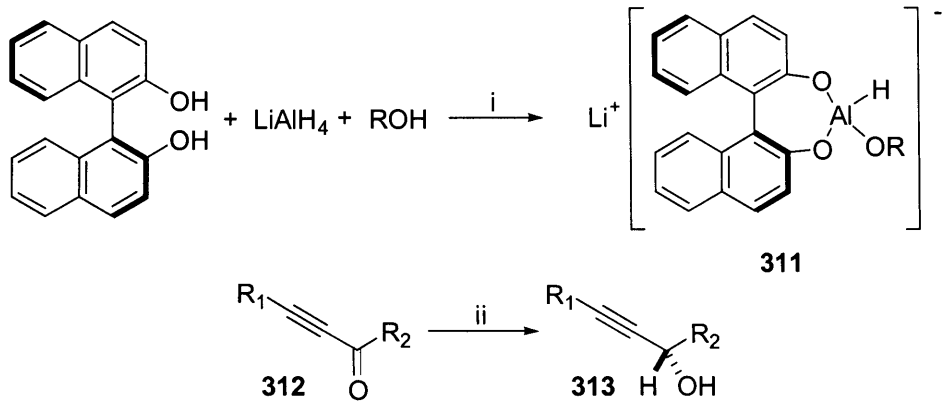
309 **310**

Reagents and conditions: i, Cat. BINAP-Ru(II), H_2, 4 atm., 100 °C, 6 h., **310**, 95-97 %, ee, 93-98 %.

Scheme 103

Although the catalyst previously described is readily prepared, it may not be suitable for the reduction of the ketone of substrates such as **308**, as under hydrogen, the alkyne can also be reduced. Alternatively, Noyori *et al.* used binaphthol-modified aluminium hydride reagent **311** to perform highly enantioselective reductions of alkynyl ketones **312**. The reducing agent is easily prepared by mixing lithium aluminium hydride, an alcohol and optically pure 2,2'-dihydroxy-1,1'-binaphthyl in 1:1:1 ratio in dry THF at room temperature. Ketones **312** were then reduced with 3 equivalents of **311** at -100 °C for 1 hour and then at -78 °C to afford the

corresponding alcohols **313** with high enantiomeric excesses (84 to 96 %) (**Scheme 104**).[113]



Reagents and conditions: i, THF, rt; ii, **311** (3 eq.), THF, -100 °C, 1h. then -78 °C, 2 h., **313**, 71-91 %, ee, 84-96 %.

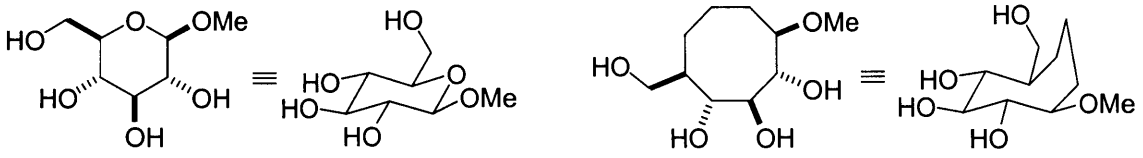
Scheme 104

Although this reaction requires low temperature, it would probably be suitable for the asymmetric reduction of ketone **308**, to afford a single alcohol **278**.

V - Synthesis of difluorocylcooctenones and derivatives

V.a - Introduction

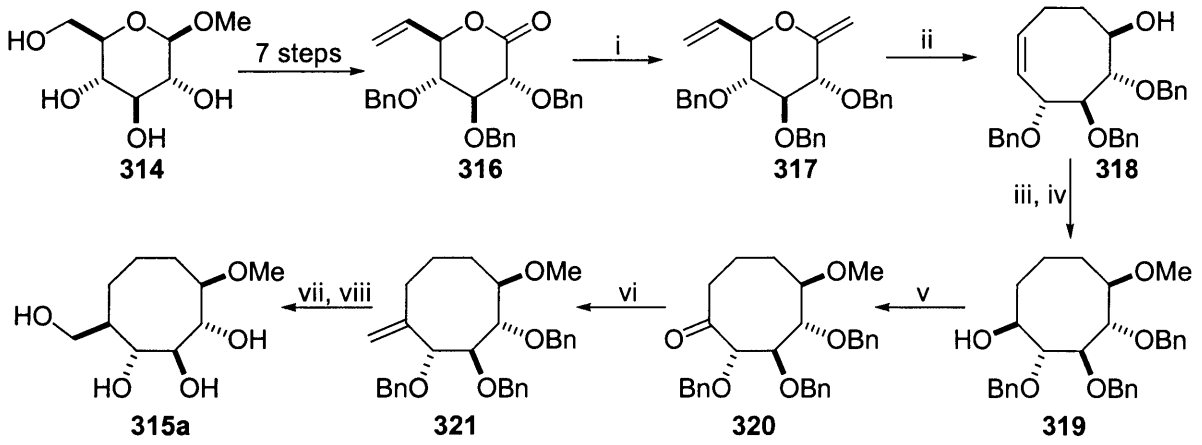
In recent years, several examples of cyclooctanic analogues of monosaccharides appeared in the literature as potential inhibitors of glycosidases. Due to the absence of endocyclic oxygen in these structures, they are hydrolytically stable species and the conformation and conformational equilibration of the cyclooctanic framework may offer potentially interesting and unusual distribution of hydroxyl groups. For example, Sinaÿ *et al.* synthesised cyclooctanic compound **315a** as an analogue of methyl- β-D-glucopyranoside **314** (**Figure 18**).[114]



314 **315a**

Figure 18

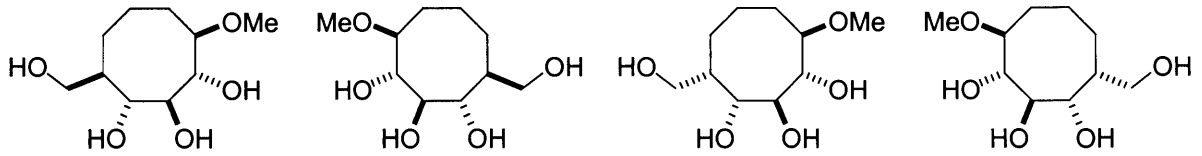
Starting from pyranoside **314**, Sinaÿ *et al.* prepared the key intermediate **316** in seven steps. Reaction with Tebbe reagent afforded the corresponding alkene, which was treated with tri-*iso*-butyl-aluminium (TIBAL) to trigger a [3,3] Claisen rearrangement followed by stereoselective reduction of the ketone to afford cyclooctene **318**. Protection of the newly formed hydroxyl group, hydroboration followed by oxidation and subsequent treatment with Tebbe reagent afforded methylene derivative **321**. Regioselective hydroboration and final deprotection afforded the desired cyclooctanic monosaccharide analogue **315a** (**Scheme 105**).[114]



Reagents and conditions: i, Tebbe reagent, Py./THF (1:1), -78 °C to rt, **317**, 84 %; ii, TIBAL, toluene, 50 °C, 30 min., **318**, 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., **319**, 58 % over 2 steps; v, PCC, 4 Å molecular sieves, dry DCM, Ar, 0 °C, 2 h, **320**, 92 %; vi, Tebbe reagent, Py./THF (1:1), -78 °C to rt, **321**, 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., **315a**, 65 % over 2 steps.

Scheme 105

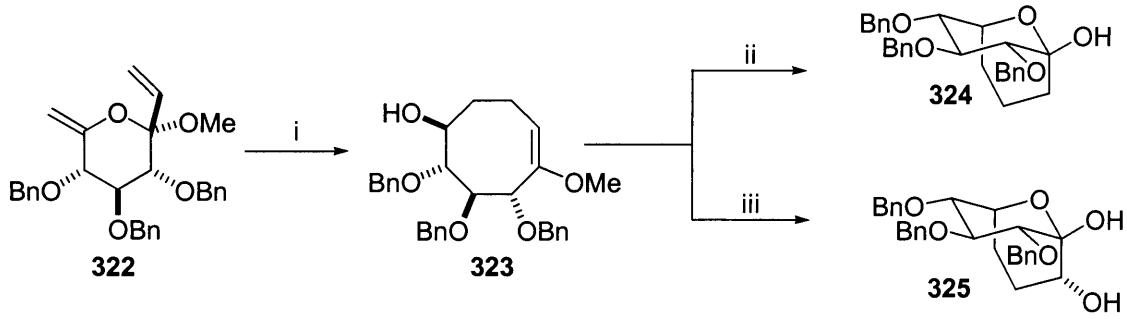
Using similar approaches Sinaÿ *et al.* prepared a total of four different cyclooctanic monosaccharide analogues **315a-d** (**Figure 19**).[115]



315a **315b** **315c** **315d**

Figure 19

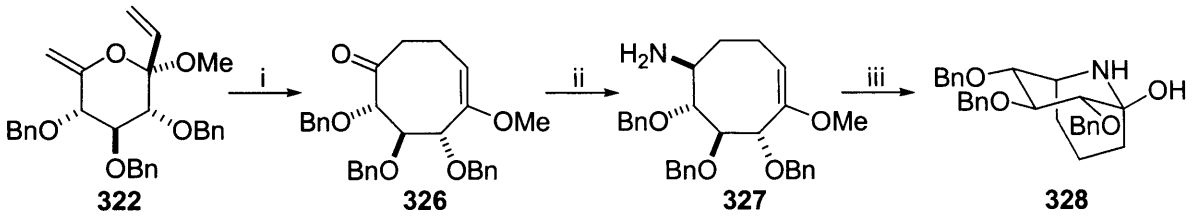
Van Boom *et al.* adopted a similar strategy and synthesised cylcooctanic compounds to access conformationally restrained bicyclic monosaccharide analogues. Allyl vinyl ether **322** was subjected to the previously described [3,3]-Claisen rearrangement-reduction sequence promoted by TIBAL to afford cyclooctene **323**. Treatment of **323** with *p*-toluenesulphonic acid in aqueous THF triggered a cyclisation to afford bicyclic system **324**. Alternatively, the double bond of cyclooctene **323** was epoxidised and the epoxide reacted intramolecularly with the free hydroxyl group to afford conformationally restrained monosaccharide analogue **325** (**Scheme 106**).[116]



Reagents and conditions: i, TIBAL (4 eq.), toluene, 20 °C, **323**, 83 %; ii, *p*-TsOH, aq. THF, 20 °C, **324**, 86 %; iii, *m*-CPBA, DCM, 20 °C, **325**, 51 %.

Scheme 106

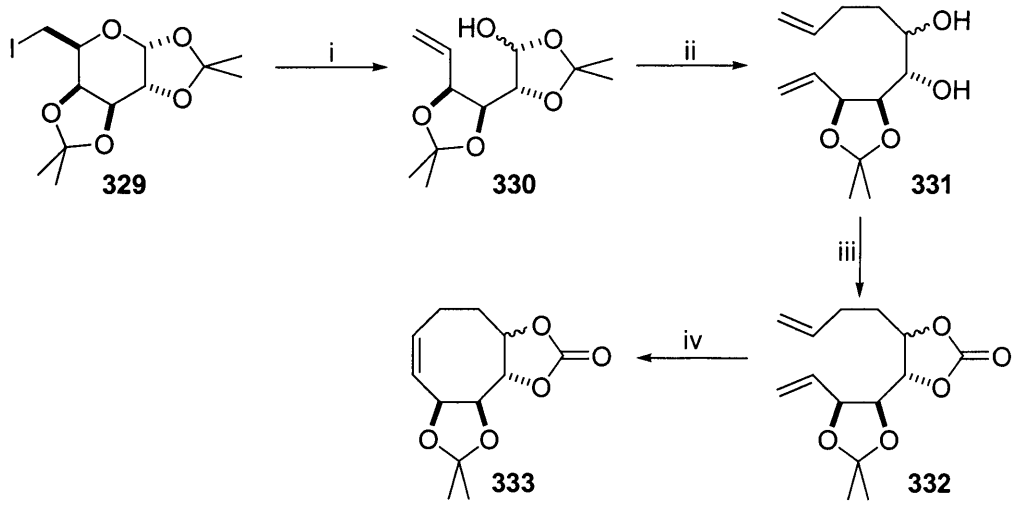
Alternatively, van Boom *et al.* converted **322** to the ketone **326** *via* a thermally induced [3,3]-sigmatropic Claisen rearrangement. Reductive amination with ammonium formate afforded amine **327**, which cyclised upon treatment with acid in aqueous THF to afford conformationally restrained aza-sugar **328** (**Scheme 107**).[117]



Reagents and conditions: i, heat; ii, $NH_4^+HCO_2^-$, $NaCNBH_3$, 3 Å molecular sieves, MeOH/DCM, 24 h. **327**, 39 %; iii, *p*-TsOH, aq. THF, 20 °C, 2 h., **328**, 67 %.

Scheme 107

Finally, Hanna *et al.* also synthesised some highly functionalised eight-membered carbocylces using a strategy based on RCM.[118,119] For example, galactose derivative **329** was converted to hemiacetal **330** by reductive ring-opening triggered by zinc under sonication conditions. Hemiacetal **330** was subsequently reacted with butenylmagnesium bromide to afford diol **331** as a mixture of *cis*- and *trans*-diastereoisomers (1:3). The diol was protected as the corresponding cyclic carbonate **332**, which was subjected to RCM using 5 mol% Grubbs' catalyst **92** to afford cyclooctene **333** (**Scheme 108**).[118]

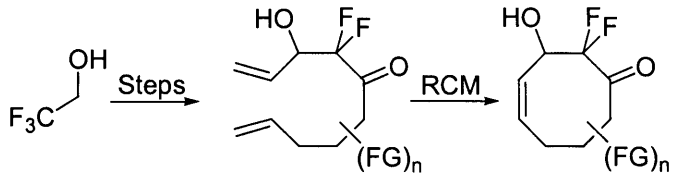


Reagents and conditions: i, Zn powder, sonication, THF/H_2O; ii, butenylmagnesium bromide, 0 °C, **331**, 71 %; iii, 1,1'-carbonyldiimidazole, THF, rt; iv, Grubbs' cat. **92** (5 mol%), reflux, **333**, 96 %.

Scheme 108

These examples show how the cyclooctanic framework can be an interesting surrogate to monosaccharides or a starting point for the synthesis of conformationally

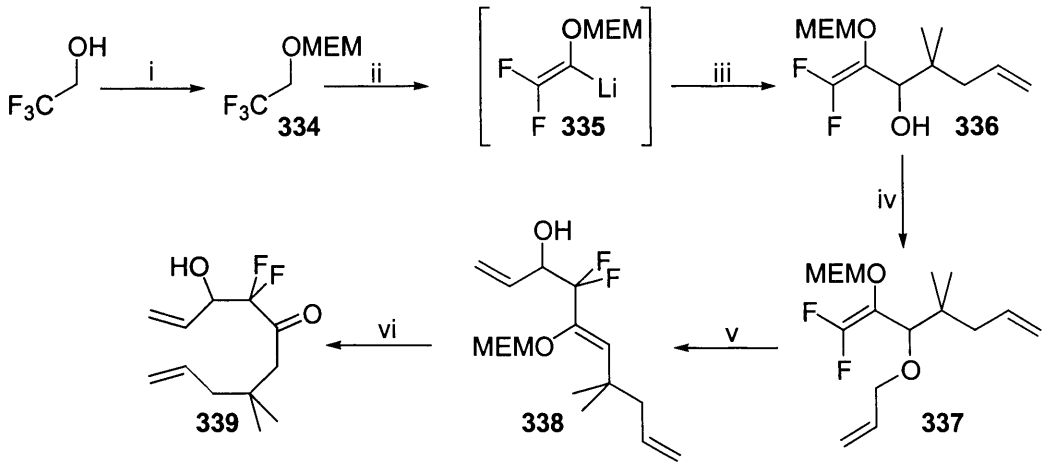
restrained monosaccharide analogues. By introducing a difluoromethylene moiety in such frameworks, not only the distribution of hydroxyl groups would change, but also the electronic properties of these carbohydrate analogues. Therefore the syntheses of highly functionalised difluorinated eight-membered carbocycles were undertaken using RCM as a key-step and commercially available trifluoroethanol as a fluorinated building block (**Scheme 109**).



Scheme 109

V.b - Synthesis of functionalised difluorocyclooctenone from the MEM-ether of trifluoroethanol

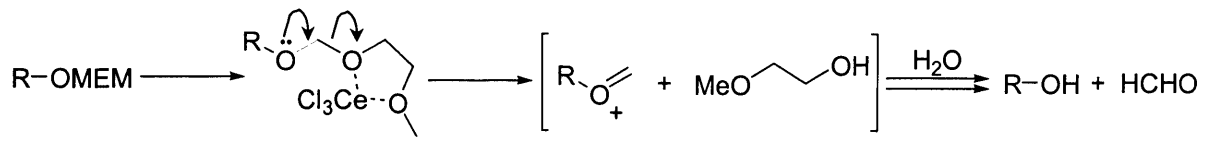
In the first instance, RCM-precursor **339** was prepared starting from MEM-ether of trifluoroethanol **334** using the methodology described by Percy *et al.*.[64,120] Ether **334** was synthesised by reacting sodium trifluoroethoxide with 2-methoxyethoxymethyl chloride. Dehydrofluorination and deprotonation by the addition of two equivalents of LDA afforded lithiated intermediate **335**, which was trapped with 2,2-dimethylpent-4-enal to yield difluorinated allylic alcohol **336** after distillation. Alcohol **336** was subsequently allylated under phase transfer catalyst conditions and crude ether **337** was subjected to a [2,3]-Wittig rearrangement triggered by the addition of 2.2 equivalents of LDA. Enol acetal **338** was then treated with hydrochloric acid (formed *in situ* from thionyl chloride and methanol) to afford ketonic RCM precursor **339** (**Scheme 110**).[121]



Reagents and conditions: i, NaH (1.0 eq.), MEM-Cl (1.1 eq.), THF, 0 °C to rt, 18 h., **334**, 80 %; ii, LDA (2.1 eq.), inverse addition, THF/hexane, -78 °C; iii, 2,2-dimethylpent-4-enal (1.2 eq.), -78 °C to -30 °C, 2h., **336**, 90 %; iv, allyl bromide (1.2 eq.), 50 wt% aq. NaOH (7.0 eq.), cat. nBu$_4$NHSO$_4$, **337**, 91 %; v, LDA (2.2 eq.), inverse addition, THF/hexane, -78 °C, 2h. then -30 °C, 18 h., **338**, 55 %; vi, $SOCl_2$ (1.0 eq.), MeOH, 0 °C then rt, 4h., **339**, 65 %.

Scheme 110

This sequence was not optimised and obviously the deprotection of the masked ketone of enol acetal **338** could be improved as the thionyl chloride used for this reaction probably reacts with the free hydroxyl of **338**. To alleviate this problem, it could be advantageous to try a milder method to carry out the deprotection, such as the use of trimethylsilyl chloride in methanol to generate hydrochloric acid *in situ*. Alternatively, Sabitha *et al.* described a very mild method for the deprotection of MEM-ethers using cerium (III) chloride heptahydrate in acetonitrile (**Scheme 111**).[122]

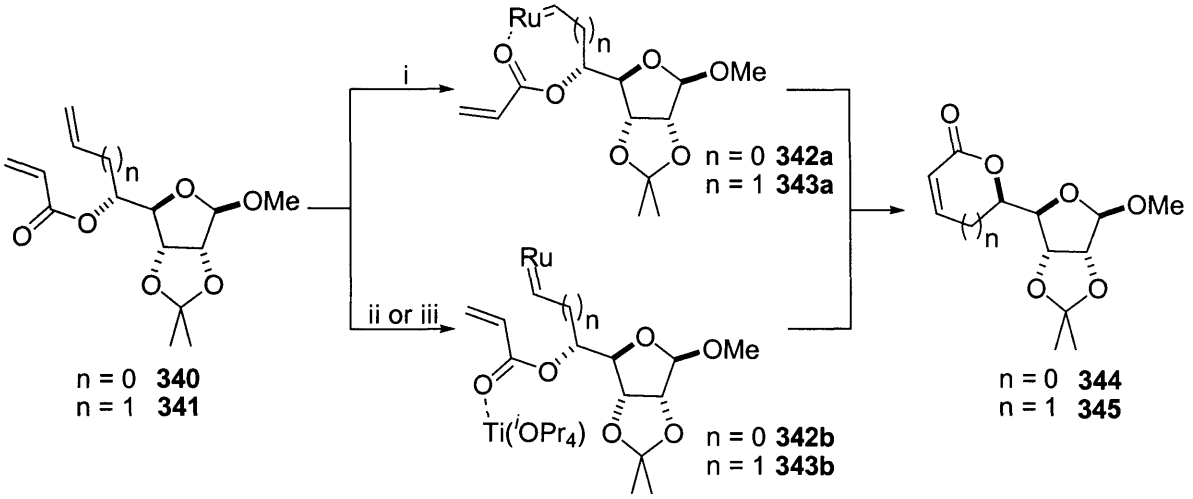


Reagents and conditions: i, $CeCl_3.7H_2O$ (0.5 eq.), CH_3CN, reflux.

Scheme 111

Diene **339** was then subjected to RCM with 5 mol% of Grubbs' catalyst **92** in refluxing DCM. Even after extended periods of time (7 days) under these conditions, no product was formed and only starting material was recovered. Ghosh *et al.*

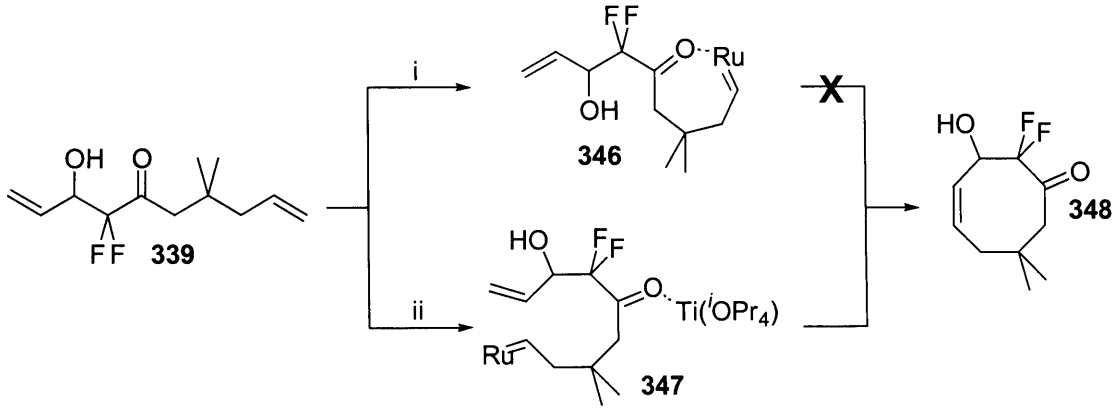
observed similarly sluggish reactions when attempting to synthesise α,β-unsaturated γ- and δ-lactones **344** and **345** by RCM. According to this group, after reaction of Grubbs' catalyst **92** with one alkene, Lewis acidic ruthenium carbenes form non-productive chelates **342a** and **343a** respectively. To solve this problem, Ghosh *et al.* added a Lewis acid ($Ti(^iOPr)_4$) to the reaction mixture, which coordinates to the carbonyl group, allowing the ruthenium carbene to take part in the RCM and therefore increasing the rate of the reaction (**Scheme 112**).[123]



Reagents and conditions: i, Grubbs' cat. **92** (10 mol%), DCM, reflux, for n = 0, 15 h., **344**, 40 %, for n = 1, 10 h., **345**, 88 %; ii, for n = 0, Grubbs' cat. **92** (10 mol%), $Ti(^iOPr)_4$ (3.0 eq.), DCM, reflux, 15 h., **344**, 72 %; iii, for n = 1, Grubbs' cat. **92** (10 mol%), $Ti(^iOPr)_4$ (0.3 eq.), DCM, reflux, 2 h., **345**, 94 %.

Scheme 112

Pleasingly, when 0.3 equivalent of titanium (IV) isopropoxide was added to the reaction mixture for the RCM of diene **339**, the reaction went to completion in 7 days to afford cyclooctenone **348** in good yield (78 %). As for Ghosh *et al.*, a non-productive chelate **346** is probably responsible for the absence of reaction when $Ti(^iOPr)_4$ is omitted (**Scheme 113**).



Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), DCM, reflux, 7d.; ii, Grubbs' cat. **92** (5 mol%), $Ti(^{i}OPr)_4$ (0.3 eq.), DCM, reflux, 7 d., **348**, 78%.

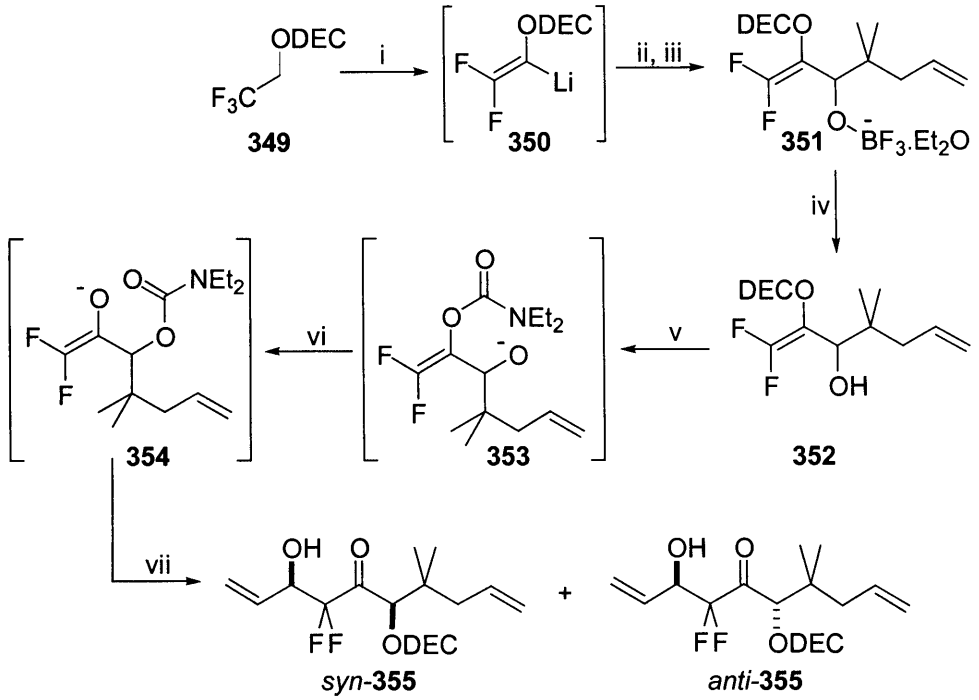
Scheme 113

^{19}F NMR spectrum of the RCM product **348** at room temperature showed a pair of very broad peaks, suggesting that cyclooctenone **348** was interconverting between two conformers at a frequency similar to the frequency of the spectrometer. Indeed, upon cooling the sample to 223 K, two sets of sharp signals appeared, demonstrating the presence of two conformers in a 1.3:1 ratio at this temperature (**Appendix 1**).

V.c - A shorter route to functionalised difluorocyclooctenones from diethylcarbamoyloxy-trifluoroethane

Thomas[124] developed a similar and shorter route towards slightly different difluorocyclooctenones using the chemistry of carbamate **349** described by Percy *et al.* to prepare the RCM precursor.[65] Carbamate **349** was dehydrofluorinated and deprotonated with two equivalents of LDA and the corresponding lithiated species **350** was trapped with 2,2-dimethyl-pent-4-enal to afford alcohol **352**. Before warming up the reaction mixture, one equivalent of boron trifluoride etherate was added to prevent a migration of the carbamoyl group from taking place. Upon treatment of **352** with *n*-butyllithium and after warming up the reaction mixture, a transacylation

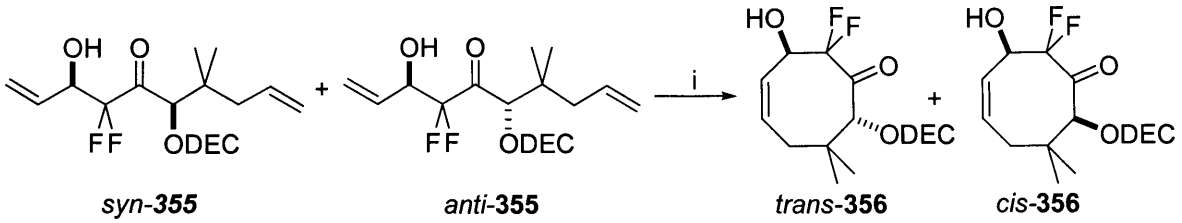
occurred, thus revealing enolate **353**, which could be trapped with acrolein to afford a diastereoisomeric mixture (1:1) of aldol products **355** (**Scheme 114**).[124]



Reagents and conditions: i, LDA (2.0 eq.), THF/hexane, -78 °C, inverse addition; ii, 2,2-dimethyl-pent-4-enal (1.1 eq.); iii, $BF_3.Et_2O$ (2.0 eq.); iv, -78 °C to -30 °C then NH_4Cl, **352**, 64 %; v, *n*BuLi (1.0 eq.), THF/hexane, -78 °C; vi, -78 °C to -10 °C; vii, acrolein (1.1 eq.), *syn*-**355** and *anti*-**355**, 74 %.

Scheme 114

Unfortunately, Thomas did not achieve the separation of diastereoisomers *syn*-**355** and *anti*-**355** and carried out the RCM on the mixture using Grubbs' catalyst and the titanium co-catalyst as described before. According to Thomas, RCM products *trans*-**356** and *cis*-**356** could not be isolated by column chromatography and were purified by vapour-diffusion crystallisation. Crystals showed two discreet forms and were separated by hand for characterisation. Structures and stereochemistries of cyclooctenones *cis*-**356** and *trans*-**356** were determined by X-ray analysis of these two different crystal forms (**Scheme 115**).



syn-**355** *anti*-**355** *trans*-**356** *cis*-**356**

Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), Ti(^{i}OPr)$_4$ (0.3 eq.), DCM, reflux, 5 d., *trans*-**356** and *cis*-**356**, 62 %.

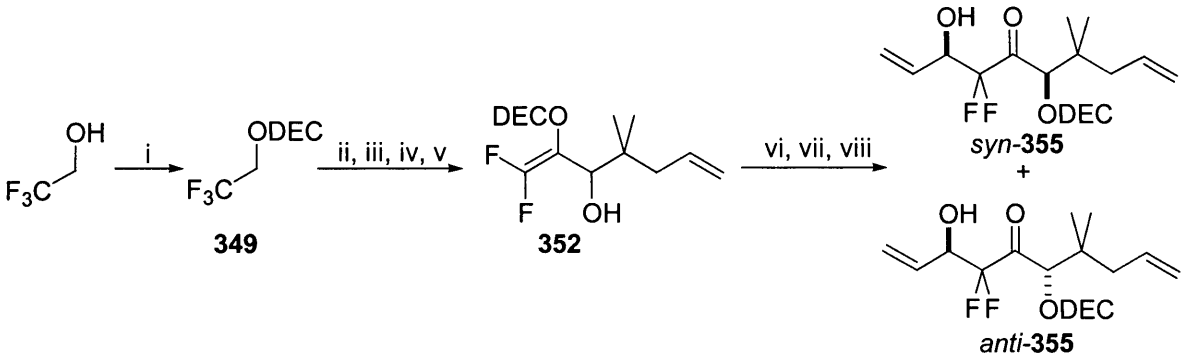
Scheme 115

To make the synthesis of *cis*-**356** and *trans*-**356** viable and useful for the elaboration of derivatives, a few issues had to be addressed:

- The aldol chemistry had to be successfully scaled-up to afford useful quantities of RCM precursors *syn*-**355** and *anti*-**355**.
- The separation of diastereoisomers had to be achieved efficiently before or after RCM.
- RCM products *cis*-**356** and *trans*-**356** had to be purified by simple methods, which should be suitable for a gram-scale synthesis.

The large scale synthesis of RCM precursors *syn*-**355** *anti*-**355** was therefore undertaken from trifluoroethanol, which was deprotonated with sodium hydride and subsequently treated with *N,N*-diethylcarbamoyl chloride on a 1.5 mole scale to afford carbamate **349** in very good yield (88 %) after distillation. Carbamate **349** was then treated with two equivalents of LDA and the lithiated species trapped with 2,2-dimethyl-pent-4-enal. Two batches of 197 millimoles each were combined and difluoroallylic alcohol **352** was afforded in 65 % yield after purification by column chromatography. Treatment with *n*-butyllithium, warming-up and addition of acrolein afforded a mixture of diastereoisomers *syn*-**355** and *anti*-**355**, which were completely separated by column chromatography (using a Biotage chromatography system) on a 240 millimole scale, affording 25.06 g (33 %) of *syn*-**355** and 23.54 g (31 %) of *anti*-

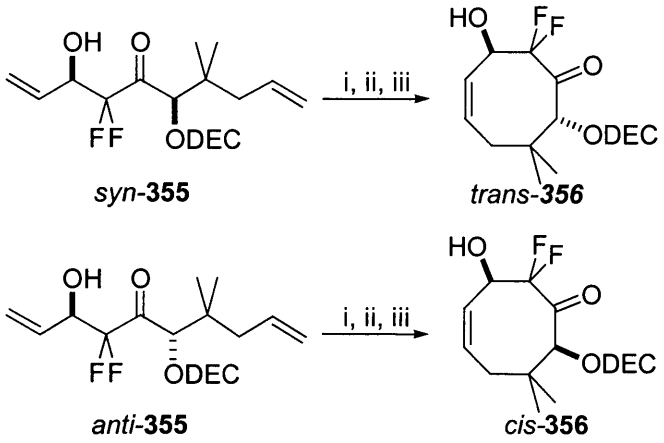
355. Pleasingly, no significant discrepancy of yields was observed through this sequence compared to Thomas' smaller scale synthesis (**Scheme 116**).



Reagents and conditions: i, NaH (1.1 eq.), DEC-Cl (1.1 eq.), THF, 0 °C then rt, 18 h., **349**, 88 %; ii, LDA (2.0 eq.), inverse addition, THF/hexane, -70 °C, iii, 2,2-dimethyl-pent-4-enal (1.1 eq.); iv, $BF_3.Et_2O$ (2.0 eq.), -70 °C to 0 °C, 2h. then 0 °C, 1h.; v, NH_4Cl, **352**, 66 %; vi, *n*BuLi (1.0 eq.), THF/hexane, -70 °C then warm to -10 °C; vii, acrolein (1.1 eq.); viii, column chromatography, *syn*-**355**, 33 % and *anti*-**355**, 31 %.

Scheme 116

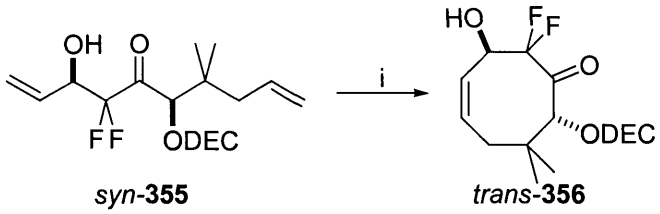
Each diene *syn*-**355** and *anti*-**355** were then subjected separately to RCM using 5 mol% of Grubbs' catalyst **92** and titanium (IV) isopropoxide as the co-catalyst. Purification was easily achieved by a short column with 40 % ethyl acetate in light petroleum to remove highly coloured by-products from catalyst and co-catalyst, followed by recrystallisation (**Scheme 117**).



Reagents and conditions: i, Grubbs' cat. **92** (5 mol%), DCM, reflux, 7 d.; ii, short column; iii, recrystallisation, *trans*-**356**, 77 % and *cis*-**356**, 69 %.

Scheme 117

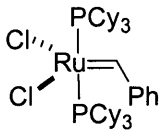
Although cyclooctenones *cis*-**356** and *trans*-**356** were synthesised in good yields, the RCM reactions were quite slow and the presence of titanium (IV) isopropoxide afforded highly coloured crude reaction mixtures. To alleviate these problems, RCM's with two different catalysts (Grubbs' catalyst **92** and the more active Nolan's catalyst **94**) were explored with or without co-catalyst (**Table 2**).



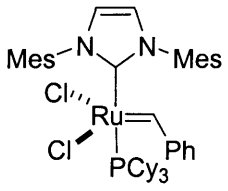
syn-**355** *trans*-**356**

Reagents and conditions: i, see **Table 2** for the amounts of cat. and co-cat. and reaction times, DCM, reflux.

Catalyst	$Ti(^iOPr)_4$ (0.3 eq.)	Time	Yield
5 mol% of **92**	NO	7 days	0 %
5 mol% of **92**	YES	7 days	77 %
2.5 mol% of **94**	NO	3 days	82 %
2.5 mol% of **94**	YES	18 hours	75 %



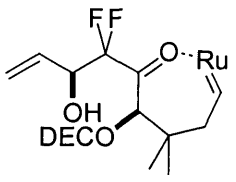
92



94

Table 2

From the results above, Nolan's catalyst **94** is obviously more active than the parent Grubbs' catalyst **92**, as the reaction times are shorter with a lower catalyst loading. Interestingly, the RCM can be carried out without the titanium co-catalyst when catalyst **94** is used. Indeed, **94** is less Lewis acidic than catalyst **92** and therefore the non-productive chelate **357** is probably formed to a lesser extent with **94** than **92** (**Figure 20**).



357

Figure 20

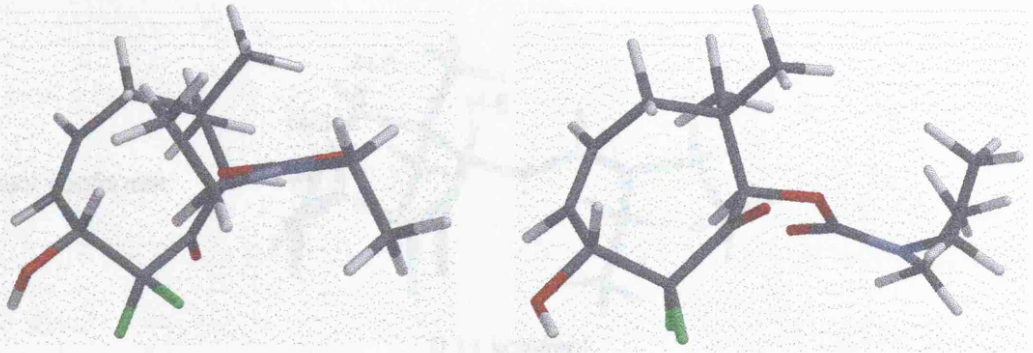
The absence of co-catalyst makes for an easier purification and simple recrystallisation afforded pure products, where column chromatography was required to remove highly coloured by-products when $Ti(^{i}OPr)_4$ was used.

As observed by Thomas,[124] ^{19}F NMR spectra for difluorocycloctenones *cis*-**356** and *trans*-**356** were similar to the spectrum for **348** and displayed broad peaks at room temperature suggesting interconversion between different conformers. To try to understand the conformational behaviour of these molecules, NMR spectra were recorded at different temperatures. At low temperature (223 K), the ^{19}F NMR spectrum for *trans*-**356** showed two sets of sharp signals in a 1:1.5 ratio demonstrating the presence of two different conformers in nearly equal quantity at this temperature (**Appendix 1**). At the same temperature, the ^{19}F NMR spectrum for *cis*-**356** also showed two sets of signals in a 1:13 ratio, suggesting that this isomer prefers to occupy a major conformation. Although the ^{19}F NMR of the major conformer displayed sharp peaks at 223 K, the minor signals showed a pair of broad, unresolved doublets, which may indicate another interconversion between two conformers at 223 K. The possible existence of an additional conformer was not demonstrated as NMR was not carried out at lower temperature to attempt resolution of the broad peaks.

To obtain an insight in the actual geometries of these conformers, some simple computational studies were undertaken. A conformational search was carried out on each diastereoisomer *trans*-**356** and *cis*-**356** using MMFF94 force field in Spartan Pro. Each diastereosiomer afforded a large numbers of conformers, which were classified according to the dihedral angle between the pseudo-axial fluorine and the proton on the adjacent carbon. Remarkably, according to this criterion, a lot of the

conformers were actually very similar as far as the shape of the ring and the dihedral angle were concerned.

Trans-**356** afforded six different groups of conformers according to the above classification. One of each conformer from each group was geometrically optimised using a semi-empirical AM1 method to afford six final conformers (**Appendix 3**). Although the relative energies associated to these conformers may not be accurate, it was assumed that the two lower energy structures gave a fairly good representation of the conformers observed in 1:1.5 ratio in the ^{19}F NMR at 223 K (**Figure 21**).



0.00 kcal/mol
θ_{H-F} =158.0°

1.23 kcal/mol
θ_{H-F} = 174.0°

Figure 21

Interestingly, the H-F coupling constants measured in the ^{19}F NMR spectrum at 223 K (21.8 Hz and 25.8 Hz respectively) are consistent with the H-F dihedral angles observed in the above two conformers. Strikingly, the two conformers display an important difference in the position of the carbonyl, which sits on different sides of the cyclooctenic ring in each.

Similarly, the same process (conformational search, classification of the conformers according to the H-F dihedral angle and geometry optimisation) was carried out for cyclooctenone *cis*-**356** and afforded three different conformers, two of which had very close energy (ΔE = 0.11 kcal/mol) (**Appendix 3**). In addition to this computational

study, a ROESY NMR spectrum was recorded at 223 K and showed cross-peaks between H-3, H-8 and one of the H-6 protons, suggesting that these 3 protons are on the same side of the ring for the major conformer (**Appendix 2**). On this basis, the lowest energy conformer from the conformational search was discarded as a true presentation of the major conformer. Indeed, in this structure H-8 is on the opposite side of the ring compared to H-3 and H-6 and therefore too far from these protons to show a cross-peak in the ROESY NMR spectrum. The geometry of the other conformer(s) might be represented by one or the other or both of the other structures determined with the computational search (**Figure 22**).

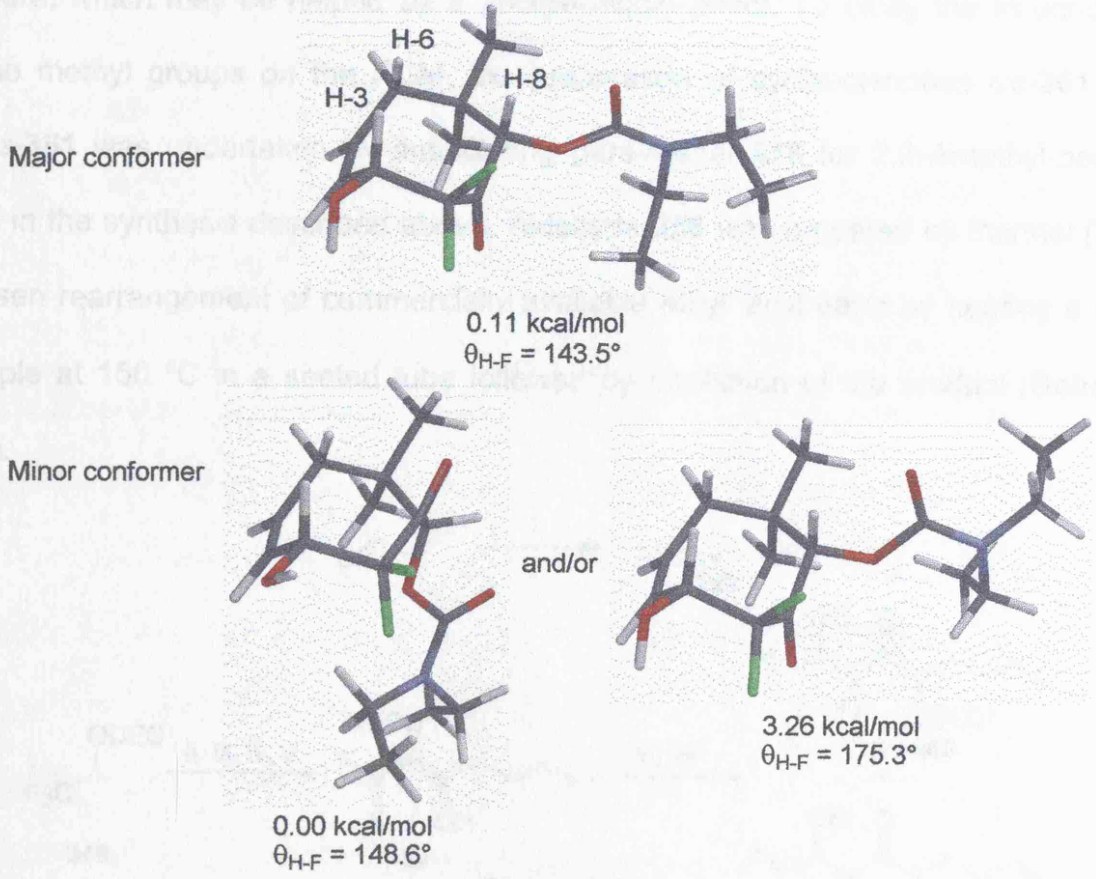


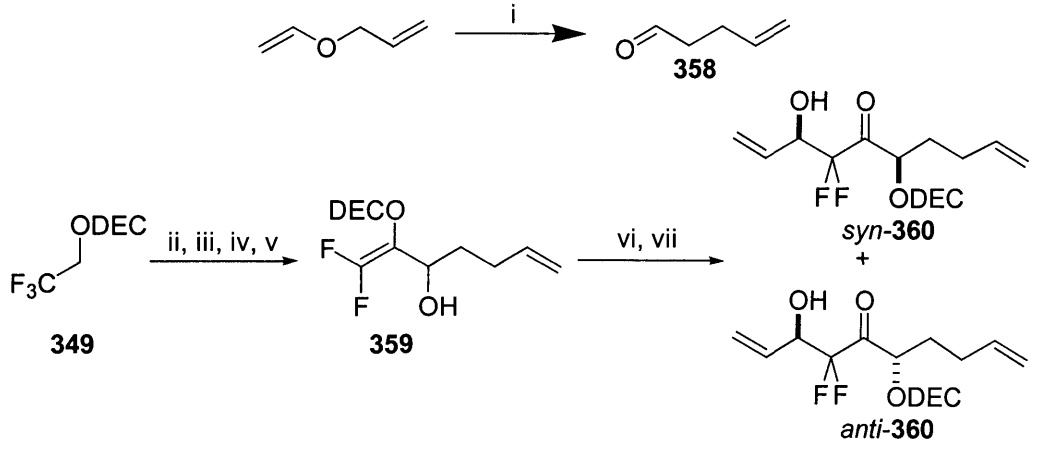
Figure 22

For the major conformer, the dihedral H-F angle is consistent with the H-F coupling constant measured on the ^{19}F NMR spectrum at 223 K (21.5 Hz). Unfortunately, no

coupling constant could be measured on the ^{19}F NMR spectrum at 223 K as the peaks were too broad to observe any splitting.

Clearly, much more modelling work is required to gain accurate insight into the solution conformations. However, the modelling produces ring conformations similar to those observed in the crystal structures of both diastereoisomers (**Appendix 2**).

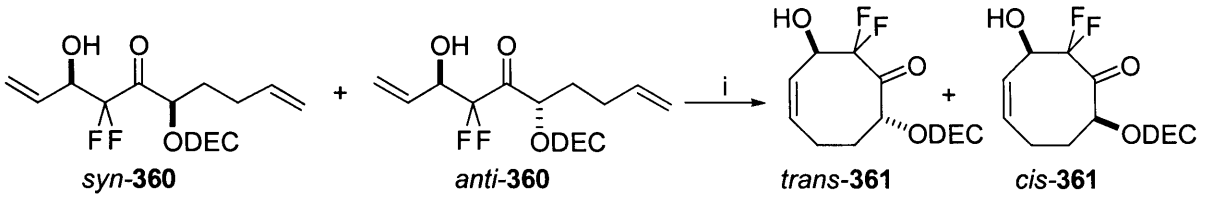
The previous syntheses of difluorocyclooctenones **348**, *cis*-**356** and *trans*-**356** introduced two methyl groups at the C-7 position. These methyls are not necessarily useful in the final products and may arguably be responsible for the successful ring closure, which may be helped by a Thorpe-Ingold effect. To study the influence of these methyl groups on the RCM, the preparation of cyclooctenones *cis*-**361** and *trans*-**361** was undertaken by substituting pent-4-enal **358** for 2,2-dimethyl-pent-4-enal in the synthesis described above. Aldehyde **358** was prepared by thermal [3,3]-Claisen rearrangement of commercially available ethyl vinyl ether by heating a neat sample at 150 °C in a sealed tube followed by distillation of the product (**Scheme 118**).



Reagents and conditions: i, Neat, Ace tube, 150 °C, 16 h., **358**, 90 %; ii, LDA (2.0 eq.), inverse addition, THF/hexane, -70 °C, iii, pent-4-enal **358** (1.1 eq.); iv, $BF_3.Et_2O$ (2.0 eq.), -70 °C to 0 °C, 2h. then 0 °C, 1h.; v, NH_4Cl, **359**, 79 %; vi, *n*BuLi (1.0 eq.), THF/hexane, -70 °C then warm to -10 °C; vii, acrolein (1.1 eq.), *syn*-**360** and *anti*-**360**, 58 %.

Scheme 118

In this sequence, diastereoisomers *syn*-**360** and *anti*-**360** could not be separated by column chromatography and were obtained as a 1:2 mixture. The RCM was attempted on the mixture using Nolan's catalyst **94** and the cyclooctenones *cis*-**361** and *trans*-**361** were separated afterwards by column chromatography and obtained in 63 % combined yield (**Scheme 119**).



Reagents and conditions: i, Nolan's cat. **94** (2 mol%), Ti(^{i}OPr)$_4$ (0.3 eq.), DCM, reflux, 3 d., *trans*-**361**, 20 % and *cis*-**361**, 43 %.

Scheme 119

RCM products were obtained in slightly lower yield and after a longer reaction time compared with *cis*-**356** and *trans*-**356**, suggesting that indeed the methyls may assist the ring closure to some extent, even though they are not required to obtain the eight-membered ring carbocycles. Diastereoisomer *trans*-**361** was recrystallised and an X-Ray crystal structure was obtained to confirm the stereochemistry of *trans*-**361** and *cis*-**361** and their precursors *syn*-**360** and *anti*-**360** (**Appendix 2**).

The absence of methyl groups also altered the dynamic conformational behaviour of *cis*-**361** and *trans*-**361** compared to *cis*-**356** and *trans*-**356**. At 223 K, the ^{19}F NMR spectrum of *trans*-**361** showed two sets of signals in a 1:1.2 ratio. One set of signals consisted of sharp peaks whereas a fluorine atom displayed a broad unresolved doublet in the other set. Although this behaviour was not fully understood and was not explored any further, this may suggest interconversion between two conformers at 223K. *Cis*-**361** also showed an unusual ^{19}F NMR spectrum. At 323 K and at room temperature two sets of signals were observed (in a 1:3.4 ratio), which broadened upon cooling to 223 K. These observations may be explained by two pairs of

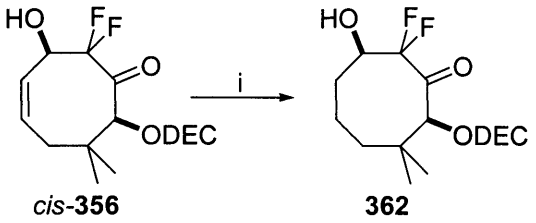
interconverting conformers at a frequency similar to the frequency of the spectrometer at 223 K. Upon warming, average sharp peaks are observed as the rates of interconversion increase. Increasing the temperature further would probably lead to coalescence of the signals, even though such an experiment was not carried out (**Appendix 1**).

VI - Derivatisation of ring-closing metathesis educts

RCM products *cis*-**356**, *anti*-**356**, *cis*-**361** and *anti*-**361** show great potential as they can be prepared on a reasonable scale in a four step sequence from commercially available trifluoroethanol. Moreover, they carry functional groups (alkene, hydroxyls, ketone), which can be used as sites for further modification and derivatisation.

VI.a - Hydrogenation of the double bond

In the first instance, the double bond of cyclooctenone *cis*-**356** was reduced by catalytic hydrogenation. The reaction occurred smoothly under one atmosphere of hydrogen for 2 days in the presence of a catalytic amount of palladium on carbon (**Scheme 120**) and the structure of cyclooctane **362** was confirmed by X-ray crystal structure (**Appendix 2**).



cis-**356** **362**

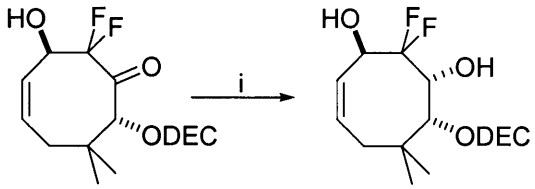
Reagents and conditions: i, 10 % Pd/C, EtOH, 2d., **362**, 100 %.

Scheme 120

It was anticipated that some of the rigidity of cyclooctene *cis*-**356** would arise from the alkenyl group, which would be responsible for the presence of slowly interconverting conformers. However the ^{19}F NMR spectrum of cyclooctane **362** still displayed broad signals at room temperature, clearly showing that the conformational behaviour of *cis*-**356** is not only due to the presence of the double bond in the cyclooctenic framework. Upon cooling to 223 K, two sets of signal appeared but were still significantly broad, suggesting interconversion between at least two pairs of conformers at 223 K, which is consistent with a higher degree of flexibility of the cyclooctanic framework compared to the cyclooctene (**Appendix 1**).

VI.b - Reduction of the ketone

In a simple experiment, the carbonyl group of cyclooctenone *trans*-**356** was reduced with sodium borohydride in ethanol (**Scheme 121**).



trans-**356** **363**

Reagents and conditions: i, $NaBH_4$ (1.0 eq.), EtOH, 0 °C then rt, 2 h., **363**, 72 %.

Scheme 121

As expected, the reaction was chemoselective as sodium borohydride does not usually reduce carbamates. ^{19}F NMR spectra of diol **363** showed only one set of sharp signals at room temperature, clearly demonstrating that the reduction was stereoselective and suggesting that the carbonyl group plays an important part in the conformational behaviour of cyclooctenone *trans*-**356**. The stereochemistry of diol **363** was assigned by X-ray crystallography (**Appendix 2**). Despite the poor quality of the crystal and the unusual shape of the ring in the X-ray crystal structure, the

relative stereochemistry of the newly formed hydroxyl group and the carbamoyloxy moiety was assigned as *cis*. The stereoselective outcome of the reduction can be rationalised by a formal attack of the hydride reagent from the outside of the ring on the carbonyl of only one conformer of *trans*-**356** (open attack trajectory), the other being too hindered by the presence of the carbamoyloxy moiety (**Figure 23**).

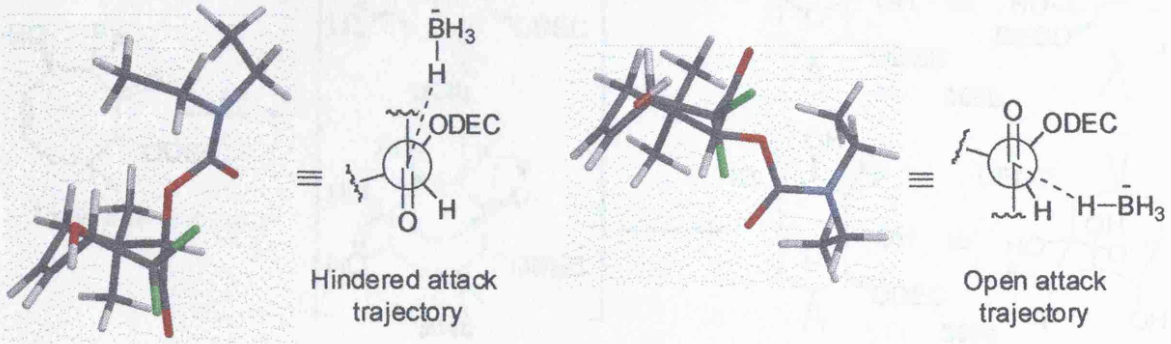
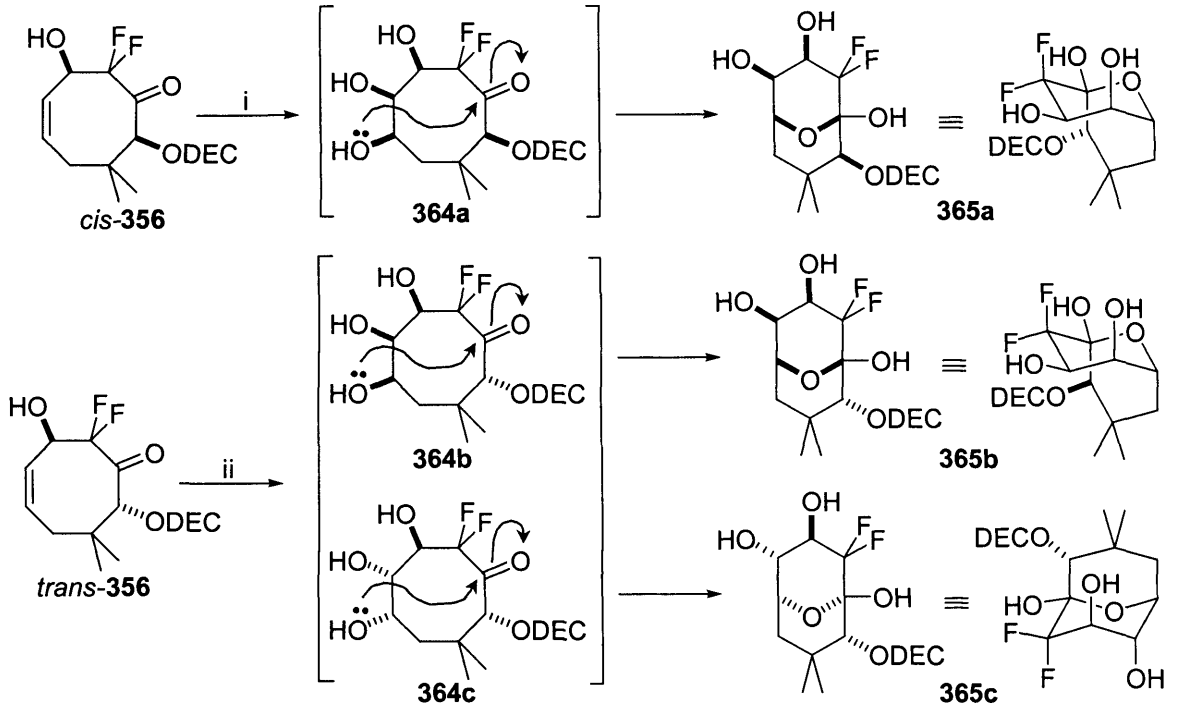


Figure 23

VI.c - Dihydroxylation

In an attempt to synthesise polyhydroxylated cyclooctanic molecules as difluorinated cyclitol or monosaccharide analogues, both cyclooctenone *cis*-**356** and *trans*-**356** were subjected to dihydroxylation under UpJohn conditions,[81] using a catalytic amount of osmium tetraoxide and *N*-methylmorpholine-*N*-oxide as the reoxidant (**Scheme 122**).

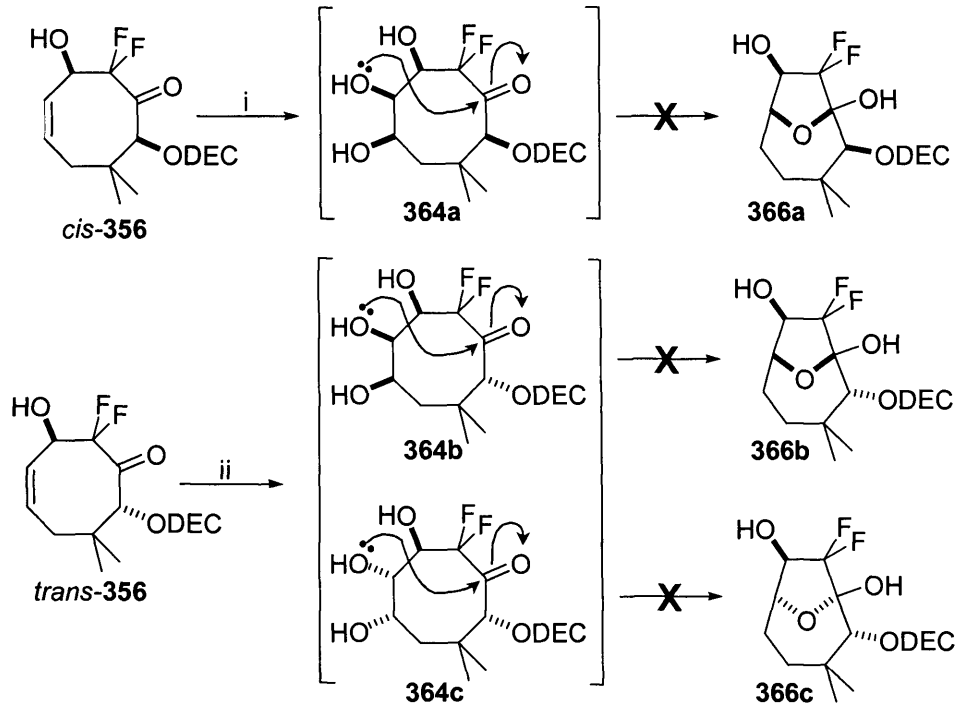


Reagents and conditions: i, NMO (2.0 eq.), OsO_4 (2.0 mol%), acetone/H_2O/^{t}BuOH, 0 °C, 24 h., **365a**, 81 %; ii, NMO (2.0 eq.), OsO_4 (2.0 mol%), acetone/H_2O/^{t}BuOH, 0 °C, 48 h., **365b**, 16 % and **365c**, 72 %.

Scheme 122

During these reactions, triol intermediates **364a-c** are formed but could not be isolated as one of the newly formed hydroxyl groups reacts intramolecularly with the ketone to form the corresponding bicyclic hemiacetals **365a-c** respectively. The cyclisation is likely to be driven by the formation of two stable six-membered rings and by the electrophilicity of the carbonyl, enhanced by the presence of the electron-withdrawing fluorine atoms and carbamate moiety. The formation of these bicyclic systems conferred rigidity upon hemiacetals **365a-c** and their NMR spectra showed sharp peaks at room temperature.

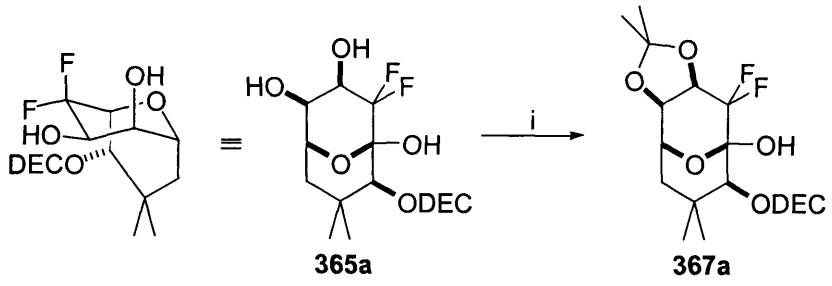
The formation of the less favoured five- and seven-membered ring systems **366a-c** by intramolecular reaction of the other hydroxyl group was not observed (**Scheme 123**).



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

Scheme 123

The stereochemistry of **365a** was determined by X-ray crystallography (**Appendix 2**) of the corresponding acetonide **367a** prepared by treatment of **365a** with acetone in the presence of an acid catalyst (**Scheme 124**).

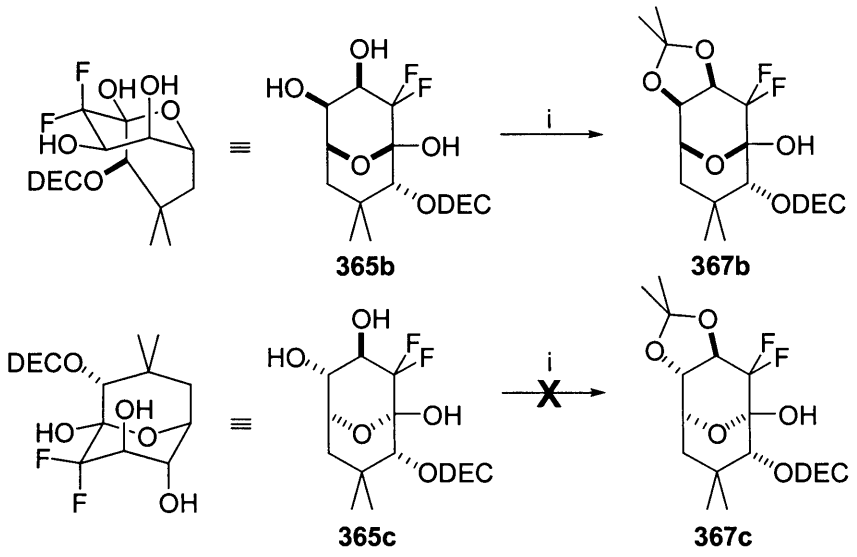


Reagents and conditions: i, acetone, cat. *p*-TsOH, anh. $CuSO_4$ (2.0 eq.), 18 h., **367a**, 100 %.

Scheme 124

Hemiacetals **365b** and **365c** were separated by column chromatography and subjected to the same conditions as before to attempt the formation of the corresponding acetonides **367b** and **367c**. Under these conditions, only diol **365b** reacted. Stereochemistries of **365b** and **365c** were then assigned on the basis that

the acetonide of *cis*-diol **365b** is easier to form than the acetonide of *trans*-diol **365c** (**Scheme 125**).



Reagents and conditions: i, acetone, cat. *p*-TsOH, anh. $CuSO_4$ (2.0 eq.), 18 h., **367b**, 100 %.

Scheme 125

Moreover, this assignment is in agreement with the coupling constants observed for the fluorine atoms to the adjacent proton. Indeed, in the case of diastereoisomer **365b**, the dihedral angle between the axial fluorine and the axial proton is close to 180 ° and therefore a large coupling constant ($^3J_{F\text{-}H}$ = 23.2 Hz) is observed. For **365c**, a smaller coupling constant ($^3J_{F\text{-}H}$ = 11.3 Hz) is observed, which is consistent with the dihedral angle between the equatorial fluorine and equatorial proton.

The stereoselectivities of the dihydroxylation reactions may be explained by a mechanism where the catalytic osmium tetraoxide first coordinates to the carbonyl group. In the case of cyclooctenone *cis*-**356** the major conformer determines the stereochemical outcome of the reaction, and the reagent is therefore delivered to the more hindered concave face of the ring (*cis* to the hydroxyl group of *cis*-**356**) to finally afford a single hemiacetal **365a**. On the other hand, cyclooctenone *trans*-**356** is in

equilibrium between two different conformers where the carbonyl sits on either face of the ring, therefore delivering a mixture of hemiacetals **365b** and **365c** (**Figure 24**).

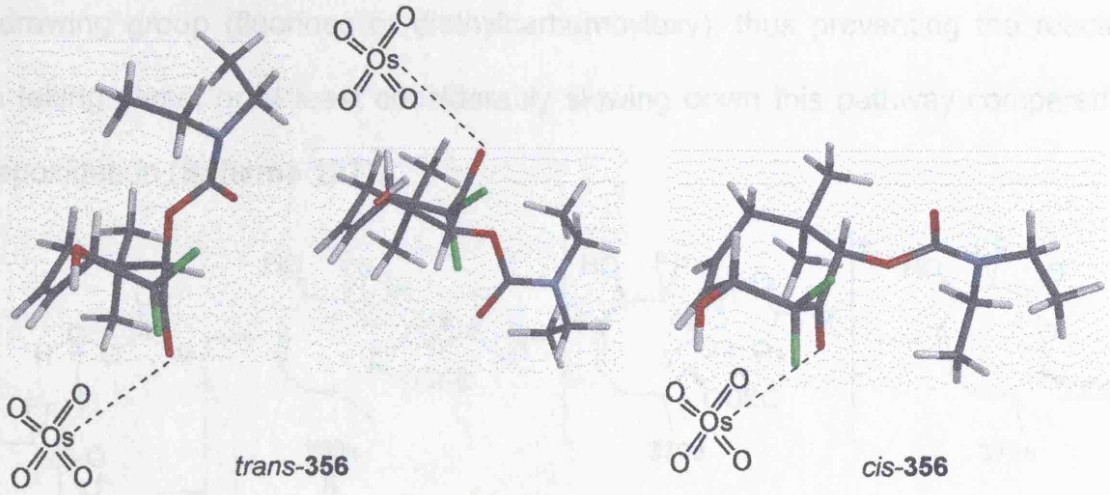
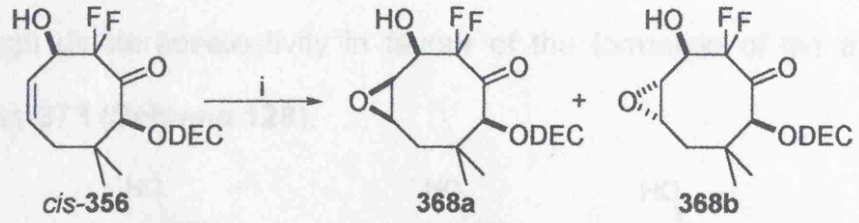


Figure 24

VI.d - Epoxidation

New interesting patterns can also be obtained by epoxidation of the double bond of *cis*-**356** or *trans*-**356**. Cyclooctenone *cis*-**356** was treated with freshly recrystallised *m*-chloroperbenzoic acid in refluxing DCM for 16 hours to obtain a mixture of diastereoisomers, which were successfully separated by column chromatography (**Scheme 126**).

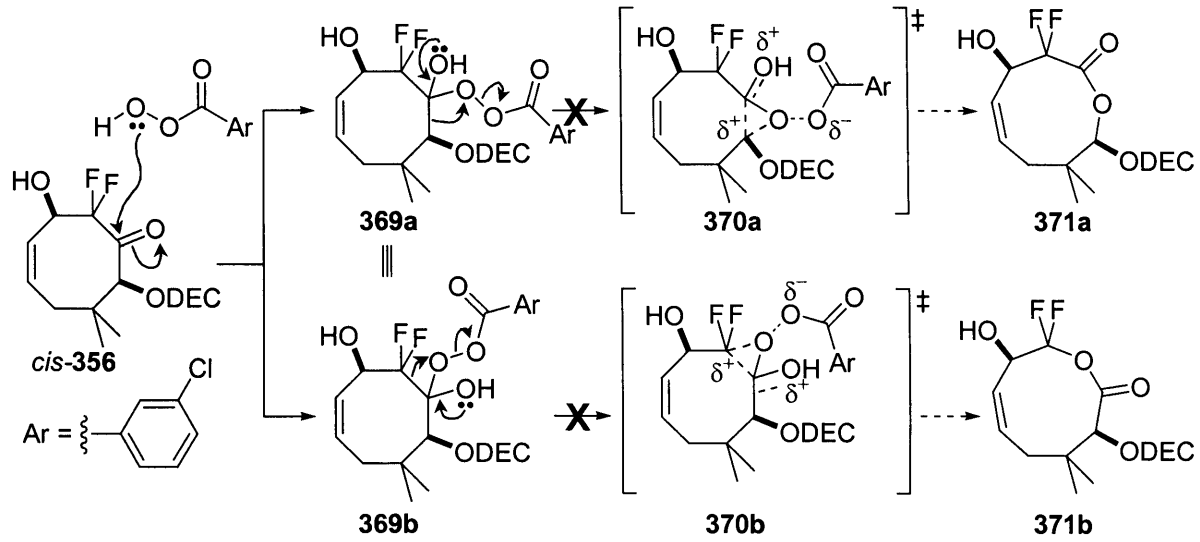


Reagents and conditions: i, *m*CPBA (2.0 eq.), DCM, reflux, 16 h., **368a**, 41 % and **368b**, 36 %.

Scheme 126

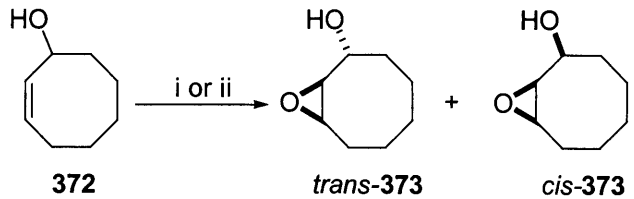
Pleasingly, this reaction was completely chemoselective and no Bayer-Villiger reaction involving the ketone was observed. This selectivity can be explained by the development of a positive charge in the transition-state of the Baeyer-Villiger reaction

on one of the carbon adjacent to the ketone. In substrate *cis*-**356**, this positive charge is destabilised on both carbons next to the ketone due to the presence of electron-withdrawing group (fluorines or diethylcarbamoyloxy), thus preventing the reaction from taking place, or at least considerably slowing down this pathway compared to the epoxidation (**Scheme 127**).



Scheme 127

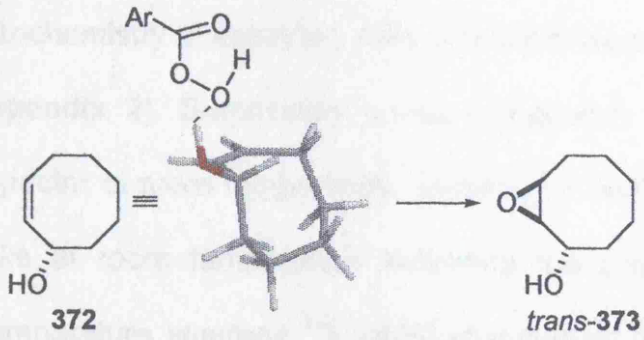
However, the diastereoselectivity of the epoxidation was surprisingly low. Indeed, several groups reported the epoxidation of cyclooct-2-en-1-ol **372** with *m*-chloroperbenzoic acid[125-127] or monoperoxyphthalic acid[128] at room temperature and observed high diastereoselectivity in favour of the formation of the *trans*-hydroxy-epoxide *trans*-**373** (**Scheme 128**).



Reagents and conditions: i, *m*CPBA, DCM, rt, *cis*-**373**:*trans*-**373** < 5:95, 100 %; ii, monoperoxy-phtalic acid, 1M NaOH, rt, *cis*-**373**:*trans*-**373** < 1:100, 90 %

Scheme 128

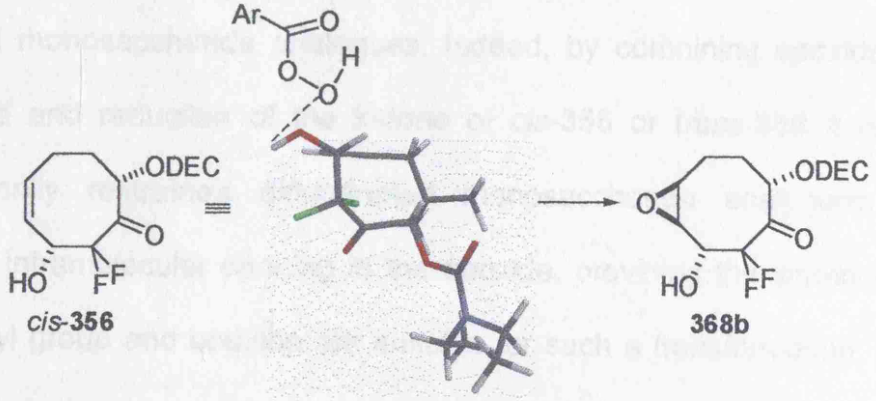
The diastereoselectivity of these reactions is usually rationalised by hydrogen bonding between the hydrogen of the hydroxyl group and an oxygen atom of the per-acid to form a complex in which the epoxidation can only take place on one side of the double bond of cyclooctenone. A structure of the main conformer cyclooctenol (obtained by conformational search with MMFF94 force field in Spartan Pro followed by geometrical optimisation using a semi-empirical AM1 method) clearly shows that the hydroxyl group is associated with the opposite face of the ring for the delivery of the peracid in the epoxidation reaction (**Figure 25**).



372 *trans*-**373**

Figure 25

The low diastereoselectivity for the *m*CPBA epoxidation of *cis*-**356** was surprising as the arrangement of the double bond and the hydroxyl group is similar to cyclooctenol but may be explained by a competition between approach of the reagent to the convex less hindered face of the ring and delivery to the concave face *via* the hydroxyl group (**Figure 26**).



cis-**356** **368b**

Figure 26

Moreover, the reaction was carried out at higher temperature than the literature precedents (refluxing DCM *vs.* room temperature), which may also decrease the level of stereoselection.

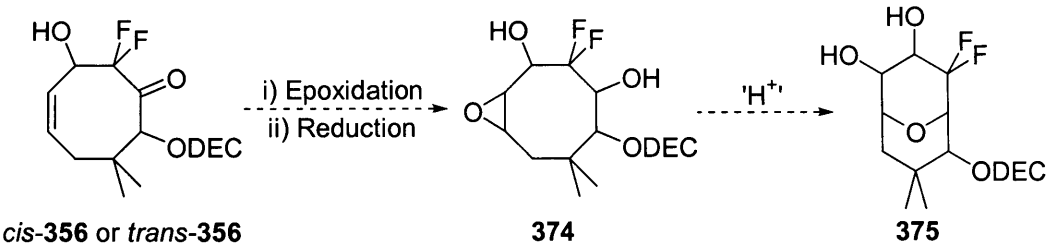
In attempts to improve the diastereoselectivity, the reaction was carried out at lower temperature (0 °C) or with urea hydrogen peroxide but failed to proceed and only starting material was recovered in both cases, presumably because the adjacent electron-withdrawing fluorine atoms considerably decrease the nucleophilicity of the alkene.

Structures and stereochemistry of epoxides **368a** and **368b** were confirmed by X-ray crystallography (**Appendix 2**). Surprisingly, these compounds displayed two very different ^{19}F NMR spectra at room temperature. Indeed, ^{19}F NMR spectrum of **368a** showed sharp peaks at room temperature indicating the presence of only one conformer at this temperature whereas ^{19}F NMR spectrum of **368b** showed broad signals at the same temperature. Upon cooling to 223 K, two sets of sharp signals appeared for two different conformers in a 1:21 ratio (**Appendix 1**).

Vi.e - Further development

Although the number of reactions attempted on cyclooctenones *cis*-**356** and *trans*-**356** is limited, they open up a wide range of transformations to access various difluorinated monosaccharide analogues. Indeed, by combining epoxidation of the double bond and reduction of the ketone of *cis*-**356** or *trans*-**356** a new type of conformationally restrained difluorinated monosaccharide analogues could be obtained by intramolecular opening of the epoxide, providing the stereochemistry of both hydroxyl group and epoxide are suitable for such a transformation. This would

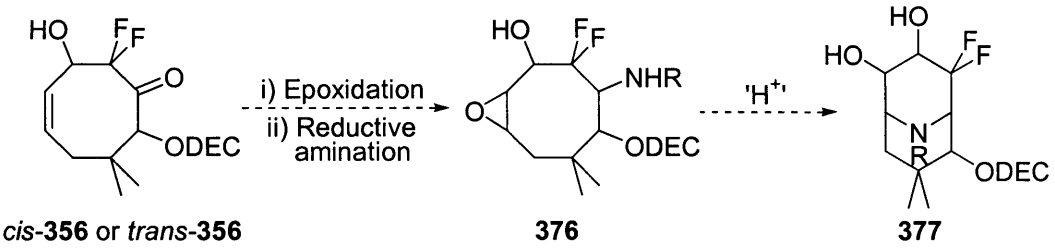
afford compounds similar to **365a-c** but with the hydroxyl groups in different orientations (**Scheme 129**).



cis-**356** or *trans*-**356** **374** **375**

Scheme 129

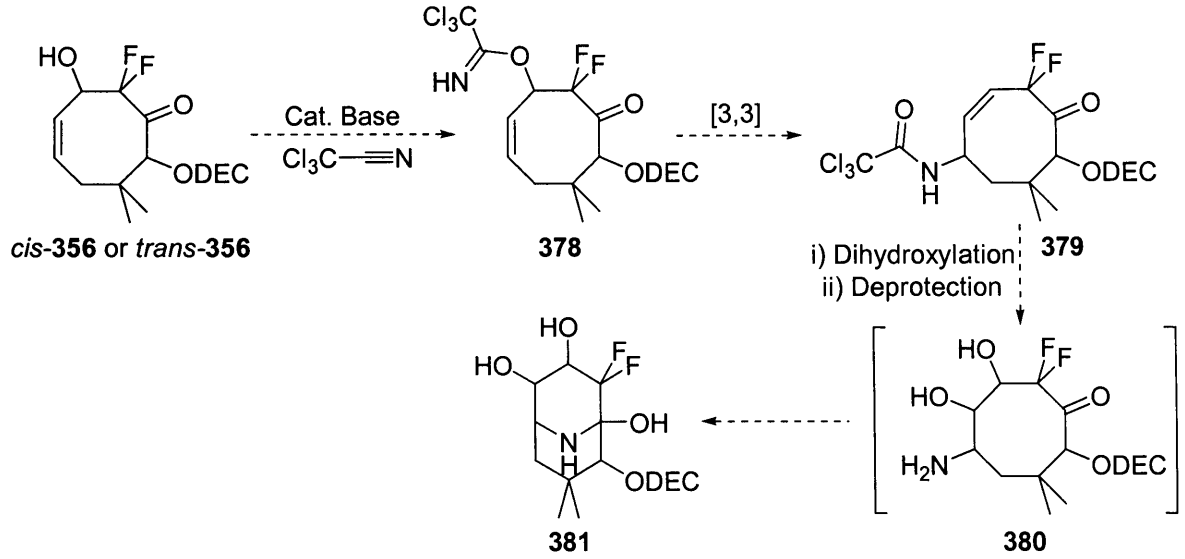
Potentially, similar interesting difluorinated aza-monosaccharide analogues could also be accessed in different ways. For example, epoxidation of the double bond of *cis*-**356** or *trans*-**356** followed by reductive amination of the ketone to afford intermediate **376** could set the stage for an intramolecular opening of the epoxide by reaction with the amine (**Scheme 130**).



cis-**356** or *trans*-**356** **376** **377**

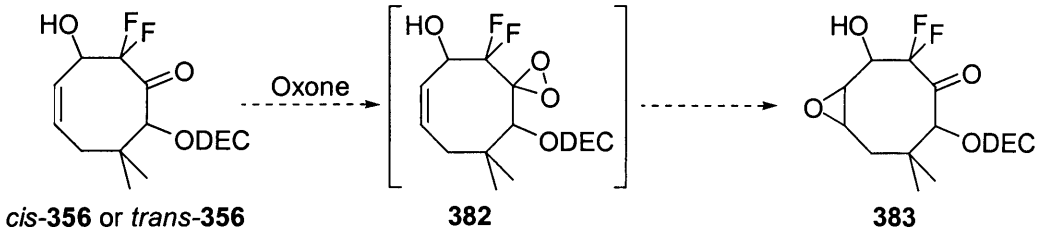
Scheme 130

Alternatively, *cis*-**356** or *trans*-**356** could be reacted with trichloroacetonitrile in the presence of a catalytic amount of sodium hydride to form the corresponding trichloroacetimidate **378**, which can rearrange to form amide **379** *via* a [3,3] sigmatropic rearrangement. Dihydroxylation followed by deprotection of the masked amine would afford reactive intermediate **380**, which should react intramolecularly to form bicyclic system **381** in the same way as observed for **365a-c** (**Scheme 131**).



Scheme 131

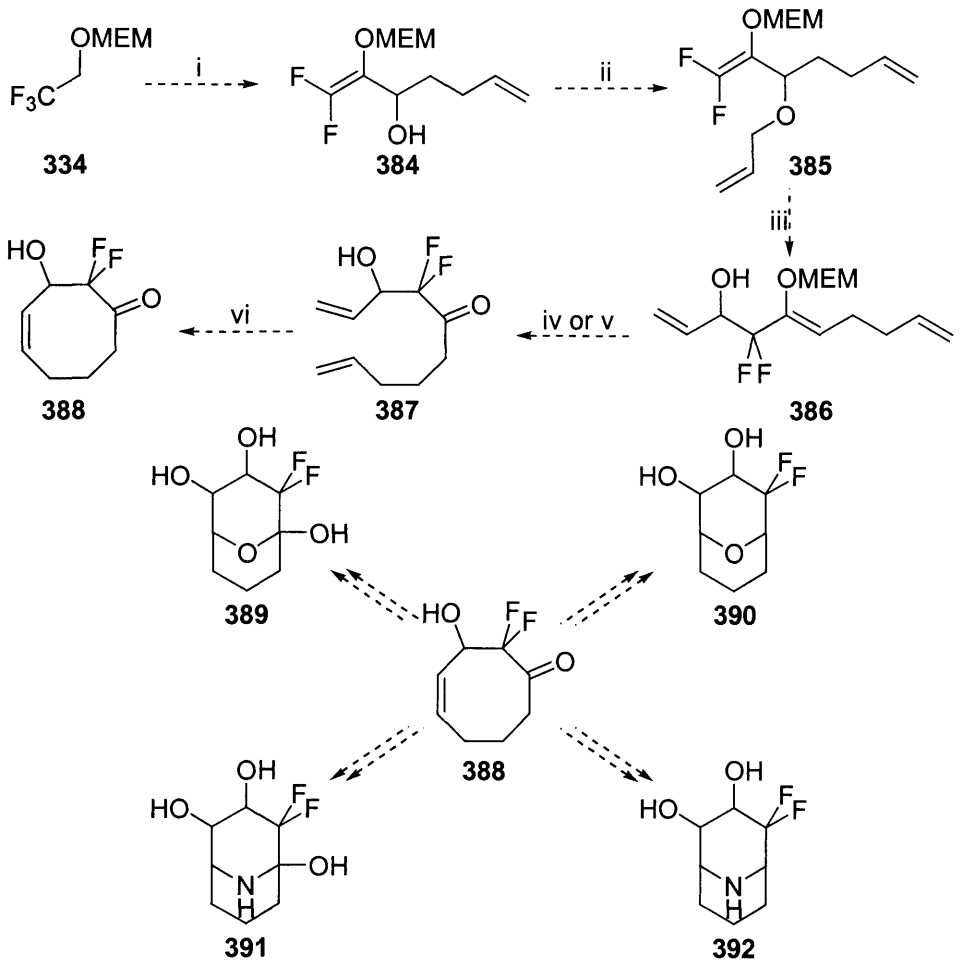
Some of the routes described above relied on the epoxidation of the double bond of cyclooctenes *cis*-**356** or *trans*-**356** and therefore a diastereoselective epoxidation would be highly desirable. Such a transformation seems to be hard to achieve by using per-acids as judged by the formation of two diastereoisomers in the epoxidation of cyclooctenone *cis*-**356**. This problem might be solved by using Oxone to perform the epoxidation. Instead of using an auxiliary ketone to form the active dioxirane, the carbonyl group present in *cis*-**356** or *trans*-**356** could be used to from a dioxirane, which would react intramolecularly, hopefully in a diastereoselective manner depending on the topology of the cyclooctenic framework (**Scheme 132**).



Scheme 132

All the bicyclic systems described so far contained a *gem*-dimethyl and diethylcarbamoyloxy moities in the bridging part of the monosaccharide analogues. Obviously these features are not essential to obtain those conformationally restrained

difluorinated monosccharide analogues. Moreover the carbamoyloxy group, also present in the bridging part of the molecules, introduces an additional stereogenic centre and therefore diastereoisomers have to be separated before or after RCM. This problem could be overcome by using the [2,3]-Wittig rearrangement route described previously starting from the MEM-ether of trifluoroethanol **334** and pentenal **358**. This would afford a single racemic compound after RCM and could be used to prepare bicyclic systems such as **389-392** by following the routes outlined above (**Scheme 133**).



Reagents and conditions: i, LDA (2.0 eq.), inverse addition, THF/hexane, -78 °C, then pent-4-enal **358**, -78 to -30 °C; ii, allyl bromide (1.2 eq.), 50 % aq. NaOH (7 eq.), cat. nBu$_4$NHSO$_4$; iii, LDA (2.2 eq.), inverse addition, THF/hexane -78 to -30 °C; iv $SOCl_2$ (1.0 eq.), MeOH, 0 °C to rt; v, $CeCl_3.7H_2O$ (0.5 eq.), CH_3CN, reflux; vi, RCM.

Scheme 133

VII – Conclusion

Ring-closing metathesis using commercially available ruthenium catalysts and standard conditions (typically refluxing DCM and 5 mol% or less ruthenium catalyst) allowed the preparation of *gem*-difluorinated dihydropyrans despite the potentially troublesome presence of allylic fluorine atoms in the homoallyl-allyl ether RCM-precursors. A similar approach delivered two novel 4-deoxy-4,4-difluoro glycosides in racemic form *via* a highly diastereoselective dihydroxylation of the double bond formed by RCM.

Complementarily, a formal new approach towards four different highly enantiomerically enriched 4-deoxy-4,4-difluoro monosccharide analogues has been developed from (3-bromo-3,3-difluoro-prop-1-ynyl)-benzene **75** as the fluorinated starting building block. This approach relied on the high enantioselectivity of AD-mix dihydroxylations and the ruthenium (III) chloride/sodium periodate oxidation of a phenyl group to the corresponding carboxylic acid. Although the AD-mix dihydroxylations were successful and enantioselective, a poor choice of protecting group did not allow the synthesis of the desired target molecules. Nevertheless, the strategy only probably requires a change of protecting groups to prove successful. Further work is also required to determined accurately the enantiomeric excesses of the dihydroxylation reactions.

Two different types of *gem*-difluorinated cyclooctenones were also prepared by RCM, starting from cheap and commercially available trifluoroethanol. This study delivered unusual templates, which displayed unusual conformational behaviours as judged by NMR at different temperatures. Variable temperature NMR's, H-F coupling constants, computational studies and in some cases ROESY NMR gave an insight of the

structure of the different conformers. Nevertheless, further work is undoubtedly needed to fully understand the dynamic behaviour of these systems and to have a clear representation of the different conformers and a deeper understanding of their conformational behaviours.

The robust chemistry used to prepare these *gem*-difluorinated 8-membered carbocycles was successfully scaled up to produce enough material for further transformations. For instance, dihydroxylation of the double bond formed by RCM afforded novel bicyclic molecules, which are effectively conformationally restrained 2-deoxy-2,2-difluorinated monosaccharide analogues. Similar molecules can potentially be accessed by epoxidation of the double bond and reduction of the ketone to the corresponding hydroxyl. Indeed, intramolecular ring-opening of the epoxide by the hydroxyl would afford bicyclic molecules even if at this stage diastereoselection issues have to be addressed for the epoxidation and ketone-reduction.

The same 8-membered carbocycles also present great potential for the synthesis of conformationally restrained aza-sugar where the pyranose oxygen would be replaced by a nitrogen even if no synthesis was undertaken towards these unusual molecules.

CHAPTER 3: Experimental

General procedures

Nuclear magnetic resonance spectroscopy

NMR spectra were recorded on a Bruker ARX-250, a Bruker DPX-300, a Bruker AC-300 or a Bruker DRX-400 spectrometers. ^{1}H and ^{13}C NMR spectra (250.13 MHz, 301.24 MHz, 300.13 MHz or 400.13 MHz and 62.90 MHz, 75.75 MHz, 75.47 MHz or 100.61 MHz respectively) were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. ^{19}F NMR spectra (235.36 MHz, 283.45 MHz, 282.41 MHz or 376.50 MHz) were recorded relative to chlorotrifluoromethane as the external standard. The multiplicities of the spectroscopic data are presented in the following manner: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, env. = envelope and br = broad.

Mass spectroscopy

Chemical ionisation (CI) mass spectra were recorded on a Micromass Prospec or a Kratos Concept 1H spectrometers using ammonia as the reagent gas. Electron impact (EI) spectra were recorded on a Kratos MS-80, a Micromass Prospec or a Kratos Concept 1H spectrometers. Fast atom bombardment (FAB) spectra were recorded on a Kratos Concept 1H spectrometer using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass LCT or a Micromass Quattro LC spectrometers. High resolution mass spectroscopy measurements were carried out either on the Micromass LCT or the Kratos Concept 1H spectrometers using peak matching to suitable reference peaks, depending on the technique used.

Chromatography

Thin Layer Chromatography (TLC) was performed on precoated aluminium silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F_{254}, thickness 0.2 mm, Art. 1.05554) or on precoated plastic silica gel plates supplied by Macherey-Nagel (Polygram® SIL G/UV_{254}, thickness 0.25 mm, Art. 805 023) or on precoated glass plates supplied by Merck (Silica gel 60 F_{254}, art. 1.05715). Visualisation was achieved by UV light and/or potassium permanganate stain. Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40-63μ, Art. 02050017) or using a Biotage flash chromatography system. Column fractions were collected and monitored by thin layer chromatography. Gas chromatography was carried out on a Carlo Erba 8000 series chromatograph, fitted with a Megabore SGE BPX5 column (15 m x 0.53 mm i.d.) or on a Perkin-Elmer 'Turbomass' chromatograph, fitted with 30 m column 0.25 mm i.d. and designated PE-5 (5 % phenyl, 95 % dimehtylpolysiloxane). The eluent gas was helium with a split of 50:1 at the injector.

Reagents and solvents

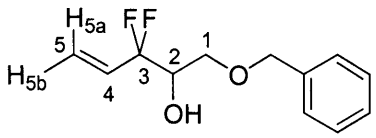
A Transsonic T460/H sonicator was used for sonicated reactions. Ozone was generated by a 500M Fischer Technology ozone generator. THF was dried by refluxing with benzophenone over sodium wire until a deep purple color developed and persisted, then distilled and collected by dry syringe as required. Dichloromethane, diethyl ether, toluene and acetonitrile were dried by refluxing with calcium hydride. They were then distilled and collected by dry syringe as required. All other chemicals were used as received without any further purification. Where required, solvents were degassed by bubbling argon or nitrogen through them for at least 30 minutes. Di*iso*propylamine was dried by distillation from calcium hydride

powder and stored over calcium hydride lumps. *n*-Buthyllithium was titrated immediately before use according to the method described by Duhamel *et al.*.[129] Vinylmagnesium bromide was purchased from Aldrich as a 1.0 M solution in THF and was used as received. 1,1,1-Trifluoro-2-[(methoxyethoxy)-methoxy]ethane **334** was synthesised using the method described by Percy *et al.*.[64]

General procedure for the preparation of difluorohomoallylic alcohols 178a-d

1-Bromo-1,1-difluoro-prop-2-ene **177** (1.5 eq.) and the desired aldehyde (1.0 eq.) were added successively to a sonicated suspension of indium (1.5 eq.) in DMF. The mixture was sonicated for 3 to 5 hours at room temperature. The reaction mixture was then quenched with 1N HCl and extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford pale yellow oils, which were purified by column chromatography.

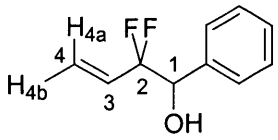
Preparation of 1-benzyloxy-3,3-difluoro-pent-4-en-2-ol 178a



1-Bromo-1,1-difluoro-prop-2-ene **177** (7.5 mmol, 0.76 mL), benzyloxyacetaldehyde (5.0 mmol, 0.70 mL) and indium powder (7.5 mmol, 0.86 g) were treated as described above in DMF (15 mL) for 4 hours. The reaction mixture was quenched with HCl (20 mL of a 1N solution) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil, which was

purified by column chromatography (30 % diethyl ether in light petroleum) to afford the desired difluorohomoallylic alcohol **178a** as a colourless oil (0.99 g, 87 %); R_f (30 % diethyl ether in light petroleum) 0.28; ν_{max} (film)/cm^{-1} 3431s br (O-H), 3064w (Ar-H), 3031w (=C-H), 2872m (C-H), 1652w (C=C); δ_H (300 MHz, $CDCl_3$) 7.40-7.28 (5H, m, -C_6H_5), 6.09-5.91 (1H, m, H-4), 5.72 (1H, dt, J_{trans} 17.6, $^4J_{H-F}$ 2.6, H-5a), 5.52 (1H, d, J_{cis} 11.0, H-5b), 4.57 (2H, s, -OCH_2Ph), 4.10-3.98 (1H, m, H-2), 3.70 (1H, dd, J_{gem} 9.9, J 3.3, H-1a), 3.59 (1H, dd, J_{gem} 9.9, J 7.0, H-1b), 2.76 (1H, d, J 5.2, -OH); δ_C (75 MHz, $CDCl_3$) 137.3, 129.9 (t, $^2J_{C-F}$ 25.5), 128.4, 127.9, 127.7, 120.9 (t, $^3J_{C-F}$ 9.5), 119.1 (t, $^1J_{C-F}$ 243.2), 73.6, 72.2 (t, $^2J_{C-F}$ 29.8), 68.6; δ_F (282 MHz, $CDCl_3$) -107.3 (1F, dt, J_{gem} 252.8, $^3J_{F-H}$ 10.3, 10.3), -111.3 (1F, dt, J_{gem} 252.8, $^3J_{F-H}$ 11.3, 11.3); [HRMS (ES, $[M+Na]^+$) Found: 251.0872, calc. for $C_{12}H_{14}F_2O_2Na$: 251.0860]; *m/z* (ES) 251 (100 %, $[M+Na]^+$).

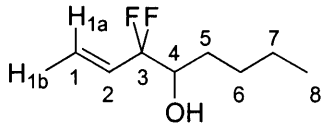
Preparation of 2,2-difluoro-1-phenyl-but-3-en-1-ol 178b



1-Bromo-1,1-difluoro-prop-2-ene **177** (7.5 mmol, 0.76 mL), benzaldehyde (5.0 mmol, 0.51 mL) and indium powder (7.5 mmol, 0.86 g) were treated as described above in DMF (15 mL) for 4 hours. The reaction mixture was quenched with HCl (20 mL of a 1N solution) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil, which was purified by column chromatography (15 % diethyl ether in light petroleum) to afford the desired difluorohomoallylic alcohol **178b** as a colourless oil (0.52 g, 57 %, 100% by GC). R_f (15 % diethyl ether in light petroleum) 0.28; ν_{max} (film)/cm^{-1} 3410s br (O-H), 2980w

(=C-H), 1647w (C=C); δ_H (300 MHz, $CDCl_3$) 7.44-7.35 (5H, m, -C_6H_5), 5.94-5.77 (1H, m, H-3), 5.59 (1H, d, J_{trans} 17.3, H-4a), 5.47 (1H, d, J_{cis} 11.0, H-4b), 4.89 (1H, td, $^3J_{H-F}$ 10.6, J 4.1, H-1), 2.60-2.56 (1H, m, -O*H*); δ_C (63 MHz, $CDCl_3$) 136.4, 129.8 (t, $^2J_{C-F}$ 25.9), 129.1, 128.6, 128.0, 122.0 (t, $^3J_{C-F}$ 9.2), 120.0 (t, $^1J_{C-F}$ 244.4), 76.3 (t, $^2J_{C-F}$ 29.8); δ_F (282 MHz, $CDCl_3$) -107.9 (1F, dt, J_{gem} 246.8, $^3J_{F-H}$ 10.6, 10.6), -109.3 (1F, dt, J_{gem} 246.8, $^3J_{F-H}$ 10.6, 10.6); *m/z* (ES) 207 (100 %, $[M+Na]^+$). Spectral data were in agreement with those reported by Burton *et al.*.[69]

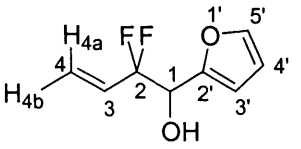
Preparation of 3,3-difluoro-oct-1-en-4-ol 178c



1-Bromo-1,1-difluoro-prop-2-ene **177** (7.5 mmol, 0.76 mL), valeraldehyde (5.0 mmol, 0.53 mL) and indium powder (7.5 mmol, 0.86 g) were treated as described above in DMF (15 mL) for 4 hours. The reaction mixture was quenched with HCl (20 mL of a 1N solution) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil, which was purified by column chromatography (10 % diethyl ether in light petroleum) to afford the desired difluorohomoallylic alcohol **178c** as a colourless oil (0.47 g, 57 %); R_f (10 % diethyl ether in light petroleum) 0.22; ν_{max} (film)/cm^{-1} 3425s br (O-H), 2990w (=C-H), 2915m (C-H), 1650w (C=C); δ_H (300 MHz, $CDCl_3$) 6.02-5.88 (1H, m, H-2), 5.71 (1H, dt, J_{trans} 17.3, $^4J_{H-F}$ 4.8, H-1a), 5.53 (1H, d, J_{cis} 10.7, H-1b), 3.82-3.69 (1H, m, H-4), 1.95 (1H, d, J 5.5, -O*H*), 1.65-1.25 (6H, env., H-5, H-6 and H-7), 0.91 (3H, t, J 7.0, H-8); δ_C (75 MHz, $CDCl_3$) 129.7 (t, $^2J_{C-F}$ 26.0), 121.9 (dd, $^1J_{C-F}$ 246.1, 244.3), 121.5 (t, $^3J_{C-F}$ 9.6), 74.5 (dd, $^2J_{C-F}$ 30.2, 25.6), 28.3 (dd, $^3J_{C-F}$ 4.3, 1.0), 27.7, 22.6, 14.0; δ_F (282 MHz,

$CDCl_3$) -108.7 (1F, dt, J_{gem} 248.7, $^3J_{F\text{-}H}$ 10.5, 10.5), -112.1 (1F, dt, J_{gem} 248.7, $^3J_{F\text{-}H}$ 10.6, 10.6); *m/z* (ES) 187 (100 %, $[M+Na]^+$). Spectral data were in agreement with those reported by Seyferth *et al.*.[68]

Preparation of 2,2-difluoro-1-furan-2'-yl-but-3-en-1-ol 178d

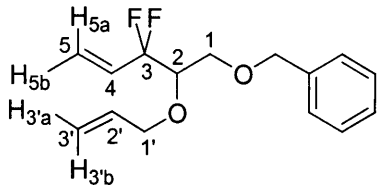


1-Bromo-1,1-difluoro-prop-2-ene **177** (7.5 mmol, 0.76 mL), furfuraldehyde (5.0 mmol, 0.41 mL) and indium powder (7.5 mmol, 0.86 g) were treated as described above in DMF (15 mL) for 4 hours. The reaction mixture was quenched with HCl (20 mL of a 1N solution) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil, which was purified by column chromatography (20 % diethyl ether in light petroleum) to afford the desired difluorohomoallylic alcohol **178d** as a pale yellow oil (1.24 g, 95 %, 100 % by GC); R_f (20 % diethyl ether in light petroleum) 0.27; ν_{max} (film)/cm^{-1} 3415s br (O-H), 2923m (C-H), 1652w (C=C); δ_H (300 MHz, $CDCl_3$) 7.41 (1H, dd, *J* 1.8, ^4J 0.8, H-3'), 6.42 (1H, d, *J* 3.3, H-5'), 6.37 (1H, dd, *J* 3.3, 1.8, H-4'), 6.04-5.87 (1H, m, H-3), 5.70 (1H, dtd, J_{trans} 17.3, $^4J_{H\text{-}F}$ 2.2, J_{gem} 0.7, H-4a), 5.51 (1H, dd, J_{cis} 11.0, J_{gem} 0.7, H-4b), 4.88 (1H, td, $^3J_{H\text{-}F}$ 9.9, *J* 6.6, H-1), 2.98 (1H, d, *J* 6.6, -O*H*); δ_C (75 MHz, $CDCl_3$) 149.5 (t, $^3J_{C\text{-}F}$ 3.1), 142.9, 129.5 (t, $^2J_{C\text{-}F}$ 25.7), 121.8 (t, $^3J_{C\text{-}F}$ 9.3), 118.7 (t, $^1J_{C\text{-}F}$ 244.7), 110.6, 109.5 (t, $^4J_{C\text{-}F}$ 1.7), 70.2 (t, $^2J_{C\text{-}F}$ 31.7); δ_F (282 MHz, $CDCl_3$) -108.8 (t, $^3J_{F\text{-}H}$ 11.4, 11.4); [HRMS (CI, $[M+NH_4]^+$) Found: 192.084434, calc. for $C_8H_{12}NO_2F_2$: 192.083614]; *m/z* (CI) 192 (52 %, $[M+NH_4]^+$), 174 (62), 157 (28), 139 (100).

General procedure for the preparation of difluorohomoallyl-allyl ethers 179a-d

Mixtures of difluorohomoallylic alcohols **178a-d**, allyl bromide (1.2 eq.), 50 wt. % aqueous solution of sodium hydroxide (7 eq.) and tetra-*n*-butylammonium hydrogensulfate (5 mol%) were stirred at 0 °C for 30 minutes, allowed to warm to room temperature and stirred overnight at this temperature. The reaction mixtures were quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford pale yellow oils, which were used for RCM without further purification.

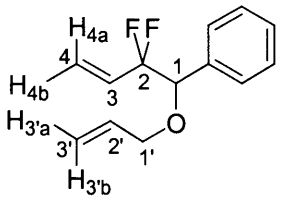
Preparation of (2-allyloxy-3,3-difluoro-pent-4-enyloxymethyl)-benzene 179a



Difluorohomoallylic alcohol **178a** (4.4 mmol, 990 mg), allyl bromide (6.5 mmol, 0.56 mL), sodium hydroxide (30.5 mmol, 1.60 mL of a 50 wt. % aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (220 μmol, 74 mg) were treated as described above. The mixture was quenched with ammonium chloride (25 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with water (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **179a** as a pale yellow oil (1.16 g, 100 %). This compound was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.24; ν_{max} (film)/cm^{-1} 3066w (Ar-H), 3029 m (=C-H), 2920m (C-H); 2870m (C-H), 1649w (C=C); δ_H (300 MHz, $CDCl_3$) 7.40-7.29 (5H,

m, -C_6H_5), 6.10-5.88 (2H, m, H-4 and H-2'), 5.70 (1H, d, J_{trans} 17.3, H-5a), 5.50 (1H, d, J_{cis} 11.0, H-5b), 5.32 (1H, dt, J_{trans} 17.1, ^4J 1.5, H-3'b), 5.22 (1H, d, J_{cis} 10.3, H-3'a), 4.57 (2H, s, -OCH_2Ph), 4.27 (2H, d, J 5.5, H-1'), 3.88-3.79 (1H, m, H-2), 3.73 (1H, dt, J_{gem} 9.9, J 1.5, $^4J_{H\text{-}F}$ 1.5, H-1a), 3.59 (1H, dd, J_{gem} 9.9, J 7.5, H-1b); δ_C (75 MHz, $CDCl_3$) 138.0, 134.5, 130.3 (t, $^2J_{C\text{-}F}$ 25.4), 128.5, 127.7, 127.6, 120.6 (t, $^3J_{C\text{-}F}$ 9.6), 119.5 (t, $^1J_{C\text{-}F}$ 244.7), 117.6, 79.8 (dd, $^2J_{C\text{-}F}$ 29.1, 28.0), 73.6, 73.4, 69.6 (dd, $^3J_{C\text{-}F}$ 5.4, 2.5); δ_F (282 MHz, $CDCl_3$) -103.8 (1F, dt, J_{gem} 254.3, $^3J_{F\text{-}H}$ 10.2, 10.2), -109.1 (1F, dt, J_{gem} 254.3, $^3J_{F\text{-}H}$ 11.1, 11.1); [HRMS (ES, $[M+Na]^+$) Found: 291.1159, calc. for $C_{15}H_{18}O_2F_2Na$: 291.1173]; *m/z* (ES) 291 (100 %, $[M+Na]^+$).

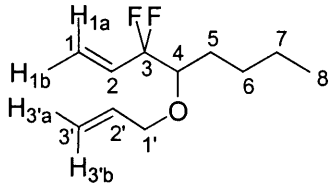
Preparation of (1-allyoxy-2,2-difluoro-but-3-enyl)-benzene 179b



Difluorohomoallylic alcohol **178b** (1.50 mmol, 276 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (11 mmol, 0.55 mL of a 50 wt. % aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **179b** as a pale yellow oil (330 mg, 100 %). This compound was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.49; ν_{max} (film)/cm^{-1} 2985m (=C-H), 2867m (C-H), 1651w (C=C); δ_H (300 MHz, $CDCl_3$) 7.38-7.35 (5H, m, -C_6H_5), 6.07-5.93 (2H, m, H-3 and H-2'), 5.57 (1H, d, J_{trans} 17.3, H-4a), 5.45 (1H, d, J_{cis} 11.0, H-4b), 5.31-5.18 (2H,

m, H-3'a and H-3'b), 4.59 (1H, t, $^{3}J_{H\text{-}F}$ 10.3, H-1), 4.10 (1H, ddd, J_{gem} 13.0, J 6.3, ^{4}J 1.1, H-1'a), 3.92 (1H, ddd, J_{gem} 13.0, J 4.8, ^{4}J 1.1, H-1'b); δ_C (75 MHz, $CDCl_3$) 134.8, 134.0, 130.2 (t, $^{2}J_{C\text{-}F}$ 25.4), 128.8, 128.6 (t, $^{4}J_{C\text{-}F}$ 1.1), 128.2, 120.9 (t, $^{3}J_{C\text{-}F}$ 9.3), 119.0 (t, $^{1}J_{C\text{-}F}$ 244.2), 117.7, 82.1 (t, $^{2}J_{C\text{-}F}$ 30.0), 70.5; δ_F (282 MHz, $CDCl_3$) -104.3 (1F, dt, J_{gem} 248.6, $^{3}J_{F\text{-}H}$ 10.2, 10.2), -109.0 (1F, dt, J_{gem} 248.6, $^{3}J_{F\text{-}H}$ 11.4, 11.4); [HRMS (CI, $[M+NH_4]^+$) Found: 242.135869, calc. for $C_{13}H_{18}N_1O_1F_2$: 242.135646]; *m/z* (CI) 242 (16 %, $[M+NH_4]^+$), 147 (100).

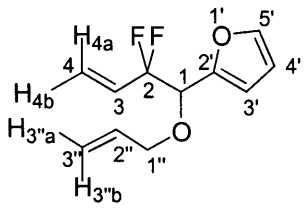
Preparation of 4-allyloxy-3,3-difluoro-oct-1-ene 179c



Difluorohomoallylic alcohol **178c** (1.50 mmol, 246 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (11 mmol, 0.55 mL of a 50 wt. % aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **179c** as a pale yellow oil (301 mg, 98 %). This compound was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.62; ν_{max} (film)/cm^{-1} 2990w (=C-H), 2871s (C-H), 1649w (C=C); δ_H (300 MHz, $CDCl_3$) 6.04-5.81 (2H, m, H-2 and H-2'), 5.65 (1H, ddd, J_{trans} 17.6, $^{4}J_{H\text{-}F}$ 2.9, 1.8, H-1a), 5.47 (1H, dt, J_{cis} 11.0, $^{4}J_{F\text{-}H}$ 2.2, H-1b), 5.28-5.13 (2H, m, H-3'a and H-3'b), 4.24 (1H, dd, J_{gem} 12.4, J 5.0, H-1'a), 4.03 (1H, dd, J_{gem} 12.4, J 6.2, H-1'b), 3.50-3.41 (1H, m, H-4), 1.54-1.22 (6H, env., H-5, H-6 and H-7), 0.87 (3H, t, J

7.7, H-8); δ_C (75 MHz, $CDCl_3$) 134.6, 130.1 (t, $^2J_{C\text{-}F}$ 25.7), 121.0 (dd, $^1J_{C\text{-}F}$ 245.9, 244.2), 120.5 (t, $^3J_{C\text{-}F}$ 9.6), 117.4, 80.6 (dd, $^2J_{C\text{-}F}$ 30.5, 26.0), 73.5, 29.6 (dd, $^3J_{C\text{-}F}$ 4.5, 1.1), 27.8, 22.6, 14.0; δ_F (282 MHz, $CDCl_3$) -102.6 (1F, dt, J_{gem} 250.5, $^3J_{F\text{-}H}$ 10.2, 10.2), -108.8 (1F, ddd, J_{gem} 250.5, $^3J_{F\text{-}H}$ 14.0, 6.4); [HRMS (ES, $[M+Na]^+$) Found: 227.1219, calc. for $C_{11}H_{18}OF_2Na$: 227.1223]; *m/z* (ES) 227 (100 %, $[M+Na]^+$).

Preparation of 2'-(1-allyloxy-2,2-difluoro-but-3-enyl)-furan 179d



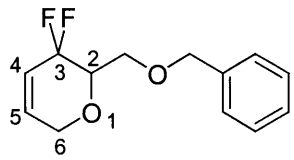
Difluorohomoallylic alcohol **178d** (1.50 mmol, 261 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (11 mmol, 0.55 mL of a 50 wt. % aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether as a pale yellow oil **179d** (319 mg, 99 %, 97 % by GC). This compound was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.43; ν_{max} (film)/cm^{-1} 3085w (=C-H), 2985w (=C-H), 2924m (C-H), 2871m (C-H), 1649w (C=C); δ_H (300 MHz, $CDCl_3$) 7.44 (1H, dd, *J* 1.5, ^4J 0.8, H-3'), 6.44 (1H, d, *J* 2.9, H-5'), 6.39 (1H, dd, *J* 2.9, 1.5, H-4'), 6.13-5.95 (1H, m, H-3), 5.92-5.79 (1H, m, H-2"), 5.67 (1H, ddd, J_{trans} 17.3, $^4J_{H\text{-}F}$ 2.6, 0.8, H-4a), 5.50 (1H, d, J_{cis} 11.0, H-4b), 5.30-5.19 (2H, m, H-3"a and H-3"b), 4.64 (1H, t, $^3J_{H\text{-}F}$ 9.2, H-1), 4.10 (1H, dd, J_{gem} 12.9, *J* 5.1, H-1"a), 3.93 (1H, dd, J_{gem} 12.9, *J* 6.3, H-1"b); δ_C (75 MHz, $CDCl_3$) 148.6 (dd, $^3J_{C\text{-}F}$ 4.8, 1.4), 143.2, 133.6, 130.0 (t, $^2J_{C\text{-}F}$

25.2), 121.0 (t, $^{3}J_{C\text{-}F}$ 9.3), 118.3 (t $^{1}J_{C\text{-}F}$ 244.4), 118.2, 110.7 (t, $^{4}J_{C\text{-}F}$ 1.1), 110.5, 75.9 (t, $^{2}J_{C\text{-}F}$ 31.7), 70.6; δ_F (282 MHz, $CDCl_3$) -107.7 (1F, dt, J_{gem} 250.5, $^{3}J_{F\text{-}H}$ 10.5), -105.0 (1F, dt, J_{gem} 250.5, $^{3}J_{F\text{-}H}$ 9.9); [HRMS (ES, $[M+Na]^+$) Found 237.0709, calc. for $C_{11}H_{12}O_2F_2Na$: 237.0703]; *m/z* (ES) 237 (100 %, $[M+Na]^+$).

General procedure for the preparation of dihydropyrans 180a-d

Solutions of ethers **179a-d** and Grubbs' catalyst (5 mol%) in DCM were stirred for 24 hours at room temperature and oxygen was bubbled through the reaction mixture for 15 minutes. Concentration under reduced pressure left black oils, which were purified by column chromatography to afford the desired difluorinated dihydropyrans **180a-d**.

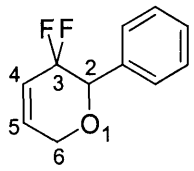
Preparation of 2-benzyloxymethyl-3,3-difluoro-3,6-dihydro-2*H*-pyran 180a



Diene **179a** (1.50 mmol, 403 mg,) and Grubbs' catalyst (75 μmol, 62 mg) were treated as described above in DCM (30 mL). Purification by column chromatography (20 % diethyl ether in light petroleum) afforded the desired dihydropyran **180a** as a colourless oil (350 mg, 97 %). R_f (20 % diethyl ether in light petroleum) 0.30; ν_{max} (film)/cm^{-1} 3058w (Ar-H), 2977m (=C-H), 2865m (C-H), 1641w (C=C); δ_H (300 MHz, $CDCl_3$) 7.33-7.27 (5H, m, -C_6H_5), 6.27 (1H, ddd, *J* 10.7, $^{3}J_{H\text{-}F}$ 3.7, 1.8, H-4), 5.95-5.86 (1H, m, H-5), 4.67 (1H, d, J_{gem} 12.1, -OC$H_a$$H_b$Ph), 4.59 (1H, d, J_{gem} 12.1, -OC$H_a$$H_b$Ph), 4.37-4.18 (2H, m, H-6), 3.98-3.94 (1H, m, H-2), 3.90 (1H, dd, J_{gem} 10.9, *J* 2.4, -C$H_a$$H_b$OBn), 3.71 (1H, dd, J_{gem} 10.9, *J* 7.9, -C$H_a$$H_b$OBn); δ_C (75 MHz, $CDCl_3$)

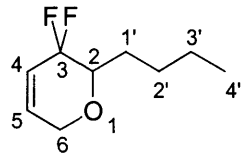
137.8, 135.7 (t, $^{3}J_{C\text{-}F}$ 9.0), 128.5, 127.9, 121.4 (t, $^{2}J_{C\text{-}F}$ 28.0), 113.9 (dd, $^{1}J_{C\text{-}F}$ 243.0, 235.7), 76.8 (t, $^{2}J_{C\text{-}F}$ 30.5), 73.8, 67.2, 65.2, due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (282 MHz, $CDCl_3$) -105.6 (1F, ddt, J_{gem} 273.4, $^{3}J_{F\text{-}H}$ 17.8, 8.9, $^{4}J_{F\text{-}H}$ 8.9), -107.7 (1F, ddd, J_{gem} 273.4, $^{3}J_{F\text{-}H}$ 6.4, 3.8); [HRMS (ES, $[M+Na]^+$) Found: 263.0853, calc. for $C_{13}H_{14}N_1O_2F_2Na$: 263.0860]; *m/z* (ES) 263 (100 %, $[M+Na]^+$).

Preparation of 3,3-difluoro-2-phenyl-3,6-dihydro-2*H*-pyran 180b



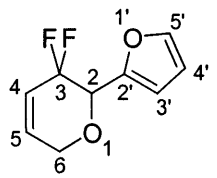
Diene **179b** (0.75 mmol, 170 mg) and Grubbs' catalyst (75 μmol, 62 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded the desired dihydropyran **108b** as a colourless oil (118 mg, 81 %). R_f (5 % diethyl ether in light petroleum) 0.30; ν_{max} (film)/cm^{-1} 2990w (=C-H), 2865m (C-H), 1648w (C=C); δ_H (300 MHz, $CDCl_3$) 7.53-7.38 (5H, m, -C_6H_5), 6.30 (1H, ddd, *J* 10.3, $^{3}J_{H\text{-}F}$ 3.3, 1.5, H-4), 6.09-6.00 (1H, m, H-5), 4.70 (1H, dd, $^{3}J_{H\text{-}F}$ 18.7, 2.6, H-2), 4.52-4.29 (2H, m, H-6); δ_C (75 MHz, $CDCl_3$) 135.2 (dd, $^{3}J_{C\text{-}F}$ 9.6, 8.5), 133.8 (t, $^{3}J_{C\text{-}F}$ 1.1), 128.7, 128.2, 127.8, 122.3 (dd, $^{2}J_{C\text{-}F}$ 30.5, 26.6), 113.7 (dd, $^{1}J_{C\text{-}F}$ 245.6, 234.3), 78.9 (dd, $^{2}J_{C\text{-}F}$ 31.1, 25.4), 65.9 (t, $^{4}J_{C\text{-}F}$ 1.1); δ_F (282 MHz, $CDCl_3$) -102.2 (1F, dddd, J_{gem} 274.3, $^{3}J_{F\text{-}H}$ 17.8, 8.9, $^{4}J_{F\text{-}H}$ 6.4), -106.5 (1F, d, J_{gem} 274.3); [HRMS (ES, $[M+Na]^+$) Found: 219.0596, calc. for $C_{11}H_{10}N_1OF_2Na$: 219.0598]; *m/z* (EI) 196 (30 %, M^+), 105 (74), 90 (100), 77 (40).

Preparation of 2-butyl-3,3-difluoro-3,6-dihydro-2*H*-pyran 180c



Diene **179c** (0.75 mmol, 150 mg) and Grubbs' catalyst (37 μmol, 31 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded the desired dihydropyran **180c** as a colourless oil (73 mg, 56 %). R_f (5 % diethyl ether in light petroleum) 0.43; ν_{max} (film)/cm^{-1} 2980w (=C-H), 2890m (C-H), 1640w (C=C); δ_H (300 MHz, $CDCl_3$) 6.22 (1H, ddd, *J* 10.3, $^3J_{H\text{-}F}$ 3.3, 1.9, H-4), 5.94-5.85 (1H, m, H-5), 4.30-4.07 (2H, m, H-6), 3.52 (1H, ddt, $^3J_{H\text{-}F}$ 16.9, 9.2, *J* 3.6, H-2), 1.82-1.31 (6H, env., H-1', H-2' and H-3'), 0.91 (3H, t, *J* 7.2, H-4'); δ_C (75 MHz, $CDCl_3$) 135.4 (t, $^3J_{C\text{-}F}$ 9.3), 122.0 (dd, $^2J_{C\text{-}F}$ 29.7, 27.4), 114.6 (dd, $^1J_{C\text{-}F}$ 243.6, 234.6), 77.4 (dd, $^2J_{C\text{-}F}$ 31.1, 26.0), 65.2 (t, $^4J_{C\text{-}F}$ 2.0), 27.6, 26.6, 22.6, 14.0; δ_F (282 MHz, $CDCl_3$) -106.4 (1F, ddt, J_{gem} 271.5, $^3J_{F\text{-}H}$ 17.8, 8.9, $^4J_{F\text{-}H}$ 8.9), -108.0 (1F, ddt, J_{gem} 271.5, $^3J_{F\text{-}H}$ 17.8, 8.9, $^4J_{F\text{-}H}$ 8.9); [HRMS (ES, $[M+Na]^+$) Found: 199.0906, calc. for $C_9H_{14}OF_2Na$: 199.0910]; *m/z* (ES) 199 (100 %, $[M+Na]^+$).

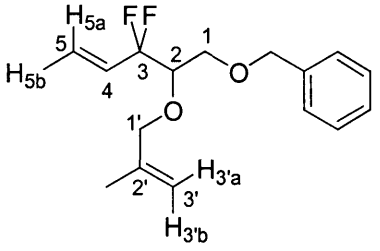
Preparation of 3,3-difiuoro-2-furan-2'-yl-3,6-dihydro-2*H*-pyran 180d



Diene **179d** (0.75 mmol, 160 mg) and Grubbs' catalyst (37 μmol, 31 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded the desired dihydropyran **180d** as a

colourless oil (97 mg, 69 %). R_f (10 % diethyl ether in light petroleum) 0.35; ν_{max} (film)/cm^{-1} 3079w (=C-H), 2986w (=C-H), 2925m (C-H), 1647w (C=C); δ_H (300 MHz, $CDCl_3$) 7.47 (1H, dd, *J* 1.8, ^4J 0.7, H-3'), 6.55 (1H, d, *J* 3.3, H-5'), 6.41 (1H, dd, *J* 3.3, 1.8, H-4'), 6.29 (1H, dt, *J* 10.3, $^3J_{H\text{-}F}$ 2.6, H-4), 6.07-5.98 (1H, m, H-5), 4.84 (1H, dd, $^3J_{H\text{-}F}$ 14.0, 5.9, H-2), 4.37-4.32 (2H, m, H-6); δ_C (75 MHz, $CDCl_3$) 147.1, 143.2, 135.2 (t, $^3J_{C\text{-}F}$ 9.3), 121.8 (dd, $^2J_{C\text{-}F}$ 29.1, 27.4), 113.2 (dd, $^1J_{C\text{-}F}$ 243.3, 237.7), 110.5, 110.4 (t, $^4J_{C\text{-}F}$ 1.7), 73.2 (dd, $^2J_{C\text{-}F}$ 36.6, 31.1), 65.2 (t, $^4J_{C\text{-}F}$ 2.0); δ_F (282 MHz, $CDCl_3$) -102.9 (1F, dddd, first half of an ABX_1X_2 system, J_{gem} 274.5, $^3J_{F\text{-}H}$ 17.6, 7.6, $^4J_{F\text{-}H}$ 3.8), -103.7 (1F, ddt, second half of an ABX_1X_2, J_{gem} 274.5, $^3J_{F\text{-}H}$ 11.4, 5.7, $^4J_{F\text{-}H}$ 5.7); [HRMS (ES, $[M+Na]^+$) Found: 209.0387, calc. for $C_9H_8O_2F_2Na$: 209.0390]; *m/z*(ES) 209 (100 %, $[M+Na]^+$).

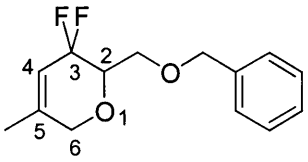
Preparation of [(3,3-difluoro-2-(2'-methyl-allyloxy)-pent-4-enyloxy)methyl]-benzene 182



A mixture of difluorohomoallylic alcohol **178a** (2.00 mmol, 456 mg), methallyl chloride (2.2 mmol, 0.22 mL), 50 wt. % aqueous solution of sodium hydroxide (14 mmol, 0.75 mL), tetra-*n*-butylammonium hydrogensulfate (100 μmol, 34 mg) and tetra-*n*-butylammonium iodide (100 μmol, 37 mg) was stirred at 0 °C for 30 minutes, allowed to warm to room temperature and stirred overnight at this temperature. The reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts

were washed with water (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired methallyl ether **182** as a pale yellow oil (0.56 g, 99%), which was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.57; ν_{max} (film)/cm^{-1} 3065w (Ar-H), 3030m (=C-H), 2916m (C-H), 2808m (C-H), 1654w (C=C); δ_H (300 MHz, $CDCl_3$) 7.41-7.28 (5H, m, -C_6H_5), 6.05 (1H, ddt, J_{trans} 17.3, $^3J_{H\text{-}F}$ 12.9, J_{cis} 11.0, H-4), 5.72 (1H, d, J_{trans} 17.3, H-5a), 5.51 (1H, d, J_{cis} 11.0, H-5b), 5.04 (1H, s, H-3'b), 4.95 (1H, s, H-3'a), 4.58 (2H, s, -OCH_2Ph), 4.18 (2H, s, H-1'), 3.90-3.80 (1H, m, H-2), 3.75 (1H, ddd, J_{gem} 10.5, J 2.9, $^4J_{H\text{-}F}$ 1.8, H-1a), 3.61 (1H, ddd, J_{gem} 10.5, J 7.0, $^4J_{H\text{-}F}$ 1.1, H-1b), 1.79 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 142.3, 138.4, 130.8 (t, $^2J_{C\text{-}F}$ 25.2), 128.8, 128.1, 128.0, 120.8 (t, $^3J_{C\text{-}F}$ 9.7), 119.9 (t, $^1J_{C\text{-}F}$ 244.9), 113.4, 80.3 (t, $^2J_{C\text{-}F}$ 28.7), 76.7, 74.0, 70.0 (dd, $^3J_{C\text{-}F}$ 5.6, 2.5), 19.9; δ_F (282 MHz, $CDCl_3$) -103.3 (1F, dt, J_{gem} 254.3, $^3J_{F\text{-}H}$ 10.2, 10.2), -108.9 (1F, ddd, J_{gem} 254.3, $^3J_{F\text{-}H}$ 12.1, 9.5); [HRMS (ES, $[M+Na]^+$) Found: 305.1326, calc. for $C_{16}H_{20}O_2F_2Na$: 305.1329]; *m/z* (ES) 305 (100 %, $[M+Na]^+$).

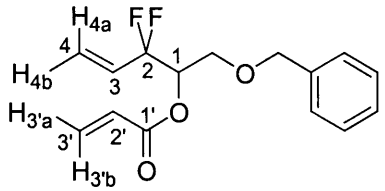
Attempted preparation of 2-[(benzyloxy)methyl]-3,3-difluoro-5-methyl-3,6-dihydro-2*H*-pyran 183



Method A: a solution of diene **182** (0.75 mmol, 160 mg) and Grubbs' catalyst **92** (37 μmol, 31 mg) in DCM (15 mL) was refluxed for 7 days. The reaction mixture was concentrated under reduced pressure to leave a black oil (172 mg). ^{19}F NMR spectrum of the crude reaction mixture only showed diene **182**.

Method B: a solution of diene **182** (0.75 mmol, 159 mg) and Grubbs' catalyst **92** (37 μmol, 31 mg) in DCE (15 mL) was refluxed for 7 days. The reaction mixture was concentrated under reduced pressure to leave a black oil (169 mg). ^{19}F NMR spectrum of the crude reaction mixture only showed diene **182**.

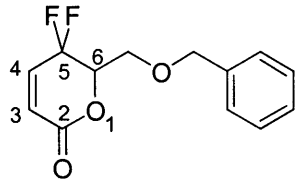
Preparation of acrylic acid 1-benzyloxymethyl-2,2-difluoro-but-3-enyl ester 186



Acryloyl chloride (4.7 mmol, 0.38 mL) was added dropwise to a cold (0 °C) solution of difluorohomoallylic alcohol **178a** (4.70 mmol, 1.06 g) and triethylamine (4.7 mmol, 0.65 mL) in DCM (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 2 hours and at room temperature for 16 hours. The reaction mixture was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (1.33 g). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded the desired acrylate **186** as a colourless oil (0.66 g, 50 %). R_f (10 % diethyl ether in light petroleum) 0.43; ν_{max}(film)/cm^{-1} 3065w (Ar-H), 3032w (Ar-H), 2960m (=C-H), 2932m (C-H), 2872m (C-H), 1738s (C=O); δ_H (300 MHz, $CDCl_3$); 7.37-7.28 (5H, m, -C$_6$*H*$_5$), 6.49 (1H, dd, J_{trans} 17.3, J_{gem} 1.1, H-3'b), 6.18 (1H, dd, J_{trans} 17.3, J_{cis} 10.3, H-2'), 6.01-5.84 (2H, m, H-3'a and H-3), 5.71 (1H, dt, J_{trans} 17.3, $^4J_{H\text{-}F}$ 2.2, H-4a), 5.56-5.45 (2H, m, H-1 and H-4b), 4.58 (1H, d, J_{gem} 12.1, -OC*H*$_a$H$_b$Ph), 4.50 (1H, d, J_{gem} 12.1, -OCH$_a$*H*$_b$Ph), 3.81 (1H, dd, J_{gem} 11.4, *J* 3.1, -C*H*$_a$H$_b$OBn), 3.71 (1H, dd, J_{gem} 11.4, *J* 7.5, -CH$_a$*H*$_b$OBn); δ_C (75 MHz, $CDCl_3$) 164.8, 137.5, 132.3, 129.8 (t, $^2J_{C\text{-}F}$ 25.4), 128.5, 127.8. 127.6,

127.5, 121.6 (t, $^{3}J_{C\text{-}F}$ 9.6), 118.0 (dd, $^{1}J_{C\text{-}F}$ 245.3, 243.6), 73.2, 71.9 (dd, $^{2}J_{C\text{-}F}$ 31.7, 29.4), 66.9 (t, $^{3}J_{C\text{-}F}$ 3.4); δ_F (282 MHz, $CDCl_3$) -105.8 (1F, dt, J_{gem} 254.3, $^{3}J_{F\text{-}H}$ 2.7, 2.7), -110.1 (1F, dt, second half of an AB quartet, J_{gem} 254.3, $^{3}J_{F\text{-}H}$ 3.2, 3.2); [HRMS (FAB, $[M+H]^+$) Found: 283.11459, calc. for $C_{15}H_{17}O_3F_2$: 283.11458; *m/z* (ES) 283 (100 %, $[M+H]^+$).

Attempted preparation of 5,5-difluoro-6-(phenoxymethyl)-5,6-dihydro-2*H*-2-pyranone 185

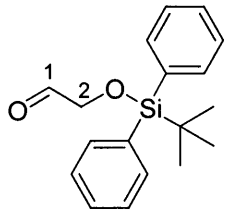


Method A: 3,5-Dimethylpyrazole (20.0 mmol, 1.92 g) was added in one portion to a cold (-20 °C) suspension of chromium trioxide (20.0 mmol, 2.00 g) in dry DCM (8 mL) and the mixture was stirred for 15 minutes. Dihydropyran **180a** (1.0 mmol, 240 mg) was added dropwise as a solution in DCM (2 mL) The mixture was stirred between -15 and -20 °C for 4 hour, quenched with sodium hydroxide (5 mL of a 5N solution). The aqueous phase was separated and further extracted with DCM (3 x 15 mL). The combined organic extracts were washed successively with HCl (20 mL of a 2N solution), water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a dark green oil (253 mg). ^{19}F NMR spectrum of the crude mixture did not show any fluorinated material.

Method B: a solution of acrylate **186** (1.0 mmol, 240 mg) and Grubbs' catalyst **92** (50 μmol, 41 mg) in DCM (15 mL) was refluxed for 7 days. The reaction mixture was concentrated under reduced pressure to leave a black oil (251 mg). ^{19}F NMR spectrum of the crude reaction mixture only showed acrylate **185**.

Method C: a solution of acrylate **186** (1.0 mmol, 240 mg) and Grubbs' catalyst **92** (50 μmol, 41 mg) in DCM (15 mL) was refluxed for 7 days. The reaction mixture was concentrated under reduced pressure to leave a black oil (231 mg). ^{19}F NMR spectrum of the crude reaction mixture only showed acrylate **185**.

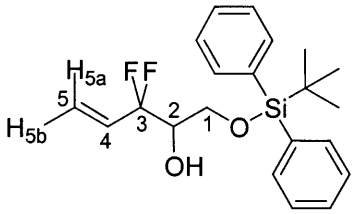
Preparation of (*tert*-butyl-diphenyl-silyloxy-)acetaldehyde 188



tert-Butyl(chloro)diphenylsilane (105 mmol, 27.3 mL) was added dropwise to a cold (0 °C) solution of (*Z*)-2-butene-1,4-diol (50 mmol, 4.1 mL) and imidazole (105 mmol, 7.15 g) in DCM (100 mL). After completion of the addition, the mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was quenched with ammonium chloride (100 mL of a saturated aqueous solution) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil (28.48 g). This crude product was taken up in DCM (1L). The solution was cooled to -78 °C and ozone bubbled through it until complete consumption of the starting alkene, by which time a persistent blue color had developed in the solution. Nitrogen was bubbled through the solution to remove the excess of ozone and the reaction mixture was quenched with triphenylphosphine (55 mmol, 14.54 g), allowed to warm to room temperature and concentrated under reduced pressure to afford a yellow oil (45.20 g), from which part of the triphenylphosphine oxide crystallised. The solid was discarded and the remaining oil was purified by column chromatography (2 to 10 % diethyl ether in light petroleum) to

afford the desired aldehyde **188** as a pale yellow oil (19.09 g, 63 % over two steps). R_f (20 % diethyl ether in light petroleum) 0.36; ν_{max}(film)/cm^{-1} 3070w (Ar-H), 2930m (C-H), 2890m (C-H), 2802w (H-CO), 1735s (C=O); δ_H (300 MHz, $CDCl_3$) 9.72 (1H, s, H-1), 7.73-7.37 (10H, env., 2 x -C_6H_5), 4.22 (2H, s, H-2), 1.11 (9H, -Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 201.8, 135.6, 132.5, 130.1, 128.0, 70.0, 26.8, 19.3. Spectral data were in agreement with those reported by Heissler *et al.*.[130]

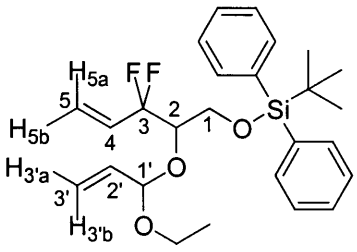
Preparation of 1-(*tert*-butyl-diphenyl-silyloxy)-3,3-difluoro-pent-4-en-2-ol 189



1-Bromo-1,1-difluoro-prop-2-ene **177** (13.7 mmol, 1.40 mL) and aldehyde **188** (13.7 mmol, 4.09 g) were added to a sonicated suspension of indium powder (13.7 mmol, 1.57 g) in DMF (20 mL). The reaction mixture was sonicated for 3 hours, quenched with HCl (25 mL of a 1N solution) and extracted with diethyl ether (3 x 35 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO4), filtered and concentrated under reduced pressure to leave a yellow oil (4.07 g), which was purified by column chromatography (15 % diethyl ether in light petroleum) to afford the desired difluorohomoallylic alcohol **189** as a pale yellow oil (3.14 g, 61 %). R_f (15 % diethyl ether in light petroleum) 0.38; ν_{max}(film)/cm^{-1} 3467m br (O-H), 3072m (Ar-H), 3050m (Ar-H), 2999w (=C-H), 2931s (C-H), 2889s (C-H), 2858s (C-H), 1651w (C=C); δ_H (300 MHz, $CDCl_3$); 7.73-7.38 (10H, m, 2 x -C_6H_5), 6.08-5.90 (1H, m, H-4), 5.69 (1H, d, J_{trans} 17.3, H-5a), 5.49 (1H, d, J_{cis} 11.0, H-5b), 3.94-3.78 (3H, m, H-1 and H-2), 2.81 (1H, d, *J* 5.9, -O*H*), 1.07 (9H, s, -C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 135.8,

132.8, 130.5 (t, $^{3}J_{C\text{-}F}$ 25.4), 130.3, 128.1, 121.1 (t, $^{3}J_{C\text{-}F}$ 19.2), 119.5 (t, $^{1}J_{C\text{-}F}$ 243.3), 73.3 (t, $^{2}J_{C\text{-}F}$ 29.7), 62.4 (dd, $^{3}J_{C\text{-}F}$ 4.8, 3.1), 27.0, 19.5; δ_F (282 MHz, $CDCl_3$) -107.6 (1F, dt, J_{gem} 253.0, $^{3}J_{F\text{-}H}$ 10.2, 10.2), -110.8 (1F, dt, second half of an AB quartet, J_{gem} 253.0, $^{3}J_{F\text{-}H}$ 10.8, 10.8); [HRMS (ES, $[M+Na]^+$) Found: 399.1573, calc. for $C_{21}H_{26}O_2F_2NaSi$: 399.1568]; *m/z* (ES) 400 (30 %, $[M+Na+H]^+$), 399 (100, $[M+Na]^+$).

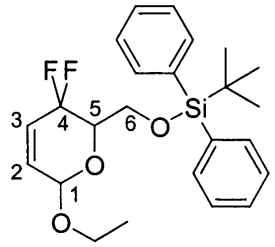
Preparation of *tert*-butyl-[2-(1'-ethoxyallyl)oxy)-3,3-difluoro-pent-4-enyloxy]-diphenylsilane 190



Alcohol **189** (5.0 mmol, 1.88 g), acrolein diethyl acetal (25 mmol, 3.8 mL) and PPTS (0.50 mmol, 0.11 g) were dissolved in dry toluene (30 mL). The mixture was stirred at 30-40 °C under reduced pressure (60 mmHg) for 5 hours to remove ethanol by azeotropic distillation. The reaction mixture was quenched with sodium carbonate (30 mL a saturated aqueous solution), and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (2.02 g). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired acetal **190** as a colourless oil (1.51 g, 66 %). R_f (5 % diethyl ether in light petroleum) 0.35; ν_{max}(film)/cm^{-1} 3071m (Ar-H), 2998m (=C-H), 2931s (C-H), 2890s (C-H), 1652w (C=C); δ_H (300 MHz, $CDCl_3$) **mixture:** 7.73-7.39 (10H, m, 2 x -C_6H_5), 6.15-5.79 (2H, m, H-4 and H-2'), 5.72-5.62 (1H, m, H-5a), 5.47-5.40 (2H, m, H-5b and H-3'a), 5.35-

5.17 (2H, m, H-3'b and H-1'), 4.12-4.01 (1H, m, H-2), 3.89-3.45 (4H, m, H-1 and -OCH_2CH_3), 1.32-1.07 (12H, env., $-OCH_2CH_3$ and $-C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) **mixture:** 135.7, 135.6, 135.1, 135.0, 133.1, 133.0, 132.9, 130.6 (t, $^2J_{C-F}$ 25.2), 130.5 (t, $^2J_{C-F}$ 24.9), 129.9, 129.8, 127.8, 120.3 (t, $^3J_{C-F}$ 9.6), 120.2 (t, $^3J_{C-F}$ 10.5), 119.7 (t, $^1J_{C-F}$ 245.0), 119.3 (t, $^1J_{C-F}$ 244.2), 118.9, 118.7, 102.8, 102.5, 77.7 (dd, $^2J_{C-F}$ 29.7, 26.3), 77.1 (dd, $^2J_{C-F}$ 30.0, 27.1), 63.4 (dd, $^3J_{C-F}$ 12.4, 2.3), 63.3 (dd, $^3J_{C-F}$ 11.9, 2.8), 61.2, 61.0, 26.8, 19.2, 15.2; δ_F (282 MHz, $CDCl_3$) **diastereoisomer 1:** -103.4 (1F, dt, J_{gem} 254.2, $^3J_{F-H}$ 9.9), -107.3 (1F, ddd, J_{gem} 254.2, $^3J_{F-H}$ 12.7, 6.4), **diastereoisomer 2:** -103.5 (1F, dt, first half of an AB quartet, J_{gem} 253.0, $^3J_{F-H}$ 10.8, 10.8), -108.4 (1F, ddd, second half of an AB quartet, J_{gem} 253.0, $^3J_{F-H}$ 13.4, 8.6). Further characterisation could not be obtained for acetal **190** because of its instability.

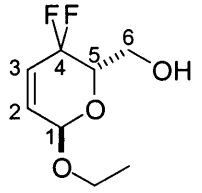
Preparation of ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-(*tert*-butyl-diphenyl-sllyloxy)-DL-*glycero*-hex-2-enopyranoside 191



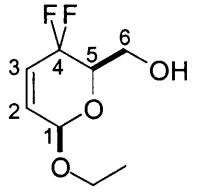
A mixture of acetal **190** (3.0 mmol, 1.38 g) and Grubbs' catalyst **92** (150 μmol, 123 mg) in dry degassed DCM (30 mL) was refluxed for 2 days under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to leave a brown oil (1.33 g). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired dihydropyran **191** as a pale yellow oil (1.14g 88 %). R_f (5% diethyl ether in light petroleum) 0.27; ν_{max}(film)/cm^{-1} 3071w (Ar-H), 2932m (=C-H), 2888m (C-H), 2858m

(C-H); 1472w (C=C); δ_H (300 MHz, $CDCl_3$) ***cis/trans* mixture:** 7.74-7.36 (10H, m, 2 x -C_6H_5), 6.17-5.13 (1H, m, H-3), 5.97-5.90 (1H, m, H-2), 5.17-5.12 (1H, m, H-1), 4.42-3.87 (4H, m, -O$CH_2$$CH_3$ and H-6), 3.66-3.55 (1H, m, H-5), 1.29-1.23 (3H, m, -OCH_2CH_3), 1.07 (9H, s, -C(CH_3)$_3$); δ_c (75 MHz, $CDCl_3$) ***cis/trans* mixture:** 135.8 (t, $^3J_{C\text{-}F}$ 9.6), 135.2, 135.1, 133.0 (t, $^3J_{C\text{-}F}$ 9.3), 132.9, 132.8, 132.7, 129.4, 129.3, 127.3, 127.2, 124.6 (dd, $^2J_{C\text{-}F}$ 29.4, 27.7), 124.0 (dd, $^2J_{C\text{-}F}$ 30.8, 21.2), 113.2 (t, $^1J_{C\text{-}F}$ 239.9), 113.1 (t, $^1J_{C\text{-}F}$ 240.2), 96.5, 92.7, 76.3 (dd, $^2J_{C\text{-}F}$ 29.6, 25.4), 70.9 (dd, $^2J_{C\text{-}F}$ 30.0, 23.7), 63.9, 60.8 (d, $^3J_{C\text{-}F}$ 5.6), 60.4 (d, $^3J_{C\text{-}F}$ 6.8), 26.3, 26.2, 18.8, 18.7, 14.7; δ_F (282 MHz, $CDCl_3$) **diastereoisomer 1:** -107.4 (1F, ddd, J_{gem} 278.5, $^3J_{F\text{-}H}$ 7.7, 5.1), -105.4 (1F, dddd, J_{gem} 278.5, $^3J_{C\text{-}F}$ 19.0, 6.4, $^4J_{F\text{-}H}$ 2.5), **diastereoisomer 2:** -109.8 (1F, J_{gem} 278.8, $^3J_{F\text{-}H}$ 22.7), -113.3 (1F, ddd, J_{gem} 278.8, $^3J_{F\text{-}H}$ 10.2, 3.8). Satisfactory mass spectroscopic data could not be obtained for dihydropyran **191**.

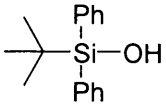
Attempted preparation of ethyl 4,4-difluoro-2,3,4-trideoxy-β-DL-*glycero*-hex-2-enopyranoside *trans*-192 and ethyl 4,4-difluoro-2,3,4-trideoxy-α-DL-*glycero*-hex-2-enopyranoside *cis*-192 from ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-(*tert*-butyl-diphenyl-silyloxy)-DL-*glycero*-hex-2-enopyranoside 191



trans-**192**



cis-**192**

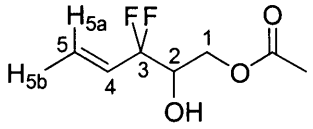


193

Tetrabutylammonium fluoride (0.42 mmol, 0.42 mL of a 1M solution in THF) was added to a solution of silyl ether **191** (0.28 mmol, 120 mg) in THF (5 mL). The reaction mixture was stirred at room temperature for one hour and concentrated under reduced pressure to afford a pale yellow oil (132 mg). Purification by column

chromatography (30 % diethyl ether in light petroleum) afforded 47 mg of an unseparable mixture of alcohol *trans*-**192** and silanol **193** (R_f (30 % diethyl ether in light petroleum) 0.27) and 34 mg of alcohol *cis*-**192** (R_f (30 % diethyl ether in light petroleum) 0.19).

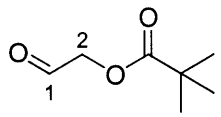
Preparation of acetic acid 3,3-difluoro-2-hydroxy-pent-4-enyl ester 200



1-Bromo-1,1-difluoro-prop-2-ene **177** (2.2 mmol, 0.22 mL) and acetoxyacetaldehyde **199** (2.0 mmol, 200 mg) were added to a sonicated suspension of indium (2.2 mmol, 230 mg) in DMF (4 mL). The mixture was sonicated at room temperature for 4.5 hours, quenched with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO4), filtered and concentrated under reduced pressure to afford a yellow oil (373 mg). Purification by column chromatography (40 % diethyl ether in light petroleum) afforded the desired difluorinated homoallylic alcohol **200** as a colourless oil (233 mg, 65 %, 98 % by GC). R_f (40 % diethyl ether in light petroleum) 0.29; ν_{max} (film)/cm^{-1} 3458s (O-H), 2974s (=C-H), 2875m (C-H), 1718s (C=O), 1654 (C=C); δ_H (300 MHz, $CDCl_3$) 6.01-5.89 (1H, m, H-4), 5.73 (1H, dt, $^3J_{trans}$ 17.3, $^4J_{H-F}$ 2.5, H-5a), 5.55 (1H, d, $^3J_{cis}$ 11.0, H-5b), 4.27 (1H, dd, J_{gem} 12.0, J 3.3, H-1a), 4.17 (1H, dd, J_{gem} 12.0, J 7.4, H-1b), 4.09-3.97 (1H, m, H-2), 3.08 (1H, br s, -O*H*), 2.08 (3H, s, -CH_3); δ_C (75 MHz, $CDCl_3$) 171.4, 129.4 (t, $^2J_{C-F}$ 25.4), 121.6 (t, $^3J_{C-F}$ 9.6), 118.9 (dd, $^1J_{C-F}$ 244.2, 243.0), 71.9 (t, $^2J_{C-F}$ 29.7), 63.5 (tdd, $^3J_{C-F}$ 4.5, 2.8), 20.7; δ_F (282 MHz, $CDCl_3$) -107.6 (1F, dt, J_{gem} 254.3, $^3J_{F-H}$ 8.9, 8.9), -111.8 (1F, dt, J_{gem} 254.3, $^3J_{F-H}$ 11.4, 11.4); [HRMS (ES,

[M+Na]$^+$) Found: 203.0488, calc. for $C_7H_{10}O_3F_2Na$: 203.0496]; *m/z* (ES) 203 (100, [M+Na]$^+$).

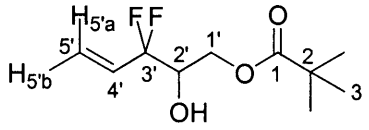
Preparation of pivaloyloxyacetaldehyde 203



Trimethylacetyl chloride (200 mmol, 24.9 mL) was added dropwise to a cold (0 °C) solution of (Z)-2-butene-1,4-diol (100 mmol, 8.2 mL) and pyridine (200 mmol, 16.2 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were washed successively with HCl (50 mL of a 1N solution) and sodium hydrogencarbonate (50 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil (26.03 g). This crude product was taken up in DCM (250 mL). The solution was cooled to -78 °C and ozone was bubbled through it until complete consumption of the starting alkene, by which time a persistent blue color had developed in the solution. Nitrogen was bubbled through the solution to remove the excess of ozone and the reaction mixture was quenched with triphenylphosphine (110 mmol, 28.85 g), allowed to warm to room temperature and concentrated under reduced pressure to afford a yellow oil (55.02 g), from which part of the triphenylphosphine oxide crystallised. The solid was discarded and the remaining oil was purified by short column chromatography (50 % diethyl ether in light petroleum) to afford the desired aldehyde **203** as a colourless oil (10.24 g, 71 % over two steps). R_f (50 % diethyl ether in light petroleum) 0.35; ν_{max} (film)/cm^{-1} 2975s (H-CO), 2874m (C-H), 2719w (H-CO), 1734s (C=O); δ_H (250 MHz, $CDCl_3$) 9.51 (1H, s, H-1), 4.57

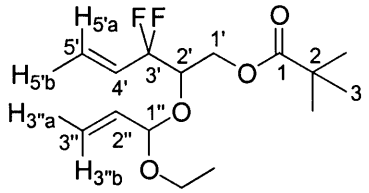
(2H, s, H-2), 1.20 (9H, s, -C(CH_3)$_3$); δ_C (63 MHz, $CDCl_3$) 196.3, 178.3, 68.9, 39.1, 27.5. Spectral data were in agreement with those reported by Grubbs *et al.*.[131]

Preparation of 2,2-dimethyl-propionic acid 3',3'-difluoro-2'-hydroxy-pent-4'-enyl ester 204



A mixture of aldehyde **203** (7.21 g, 50.0 mmol), 1-bromo-1,1-difluoro-prop-2-ene **177** (5.10 mL, 50.0 mmol) and indium powder (5.74 g, 50.0 mmol) in water (100 mL) was sonicated at room temperature for 2 hours and then stirred vigorously overnight. The reaction mixture was quenched with HCl (50 mL of a 1N solution) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil (10.31 g). Purification by column chromatography (20 % diethyl ether in light petroleum) afforded the desired difluorohomoallyllic alcohol **204** as a pale yellow oil (9.09 g, 82 %, 100 % by GC). R_f (20 % diethyl ether in light petroleum) 0.27; ν_{max} (film)/cm^{-1} 3458s br (O-H), 2974s (=C-H), 2875m (C-H), 1718s (C=O), 1651w (C=C); δ_H (300 MHz, $CDCl_3$) 6.07-5.90 (1H, m, H-4'), 5.70 (1H, dtd, $J_{trans,}$ 17.3, $^4J_{H-F}$ 2.2, J_{gem} 0.8, H-5'a), 5.55 (1H, dd, J_{cis} 11.0, J_{gem} 0.8, H-5'b), 4.30-4.18 (2H, m, H-1'), 4.07-3.97 (1H, m, H-2'), 2.85 (1H, br s, -O*H*), 1.19 (9H, s, -C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 179.3, 129.8 (t, $^2J_{C-F}$ 25.4), 121.8 (t, $^3J_{C-F}$ 9.6), 119.2 (t, $^1J_{C-F}$ 243.9), 72.4 (t, $^2J_{C-F}$ 29.7), 63.6 (dd, $^3J_{C-F}$ 4.2, 3.1), 39.1, 27.3; δ_F (282 MHz, $CDCl_3$) -107.8 (1F, dt, J_{gem} 253.0, $^3J_{F-H}$ 10.2, 10.2), -111.6, (1F, dt, J_{gem} 253.0, $^3J_{F-H}$ 12.7, 12.7); [HRMS (FAB, $[M+H]^+$) Found: 223.11454, calc. for $C_{10}H_{17}O_3F_2$: 223.11458]; *m/z* (ES) 245 (100, $[M+Na]^+$).

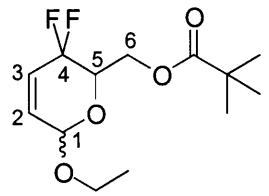
Preparation of 2,2-dimethyl-propionic acid 2'-(1''-ethoxy-allyloxy)-3',3'-difluoro-pent-4'-enyl ester 206



A solution of alcohol **204** (85.0 mmol, 18.9 g), acrolein diethyl acetal (425 mmol, 65.0 mL) and PPTS (8.5 mmol, 2.14 g) in dry toluene (250 mL) was stirred at 30-40 °C under reduced pressure (60 mmHg) for 9 hours to remove ethanol by azeotropic distillation. The reaction mixture was quenched with sodium carbonate (250 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (29.71 g). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired acetals as a colourless oil **206** (14.67 g, 56 %) along with starting alcohol **204** (36.9 mmol, 8.20g), which was reacted with acrolein diethyl acetal (184.4 mmol, 28.0 mL) and PPTS (3.7 mmol, 0.93 g) in toluene (100 mL) as described above. After work-up and purification, products of the two different batches were combined to afford an inseparable diastereoisomeric mixture (1:1) of the desired acetal **206** as a pale yellow oil (18.92 g, 73 %, 100 % by GC). R_f (5 % diethyl ether in light petroleum) 0.25; ν_{max} (film)/cm^{-1} 2977m (=C-H), 2934w (C-H), 1735s (C=O), 1652w (C=C); δ_H (300 MHz, $CDCl_3$) **mixture:** 6.15-5.28 (6H, m, H-5'a, H-5'b, H-3''a, H-3''b, H-4' and H-2''), 5.13-5.08 (1H, m, H-1''), 4.37-4.23 (1H, m, H-2'), 4.18-4.03 (2H, m, H-1'), 3.77-3.47 (2H, m, -OCH_2CH_3), 1.21 (9H, s, -$C(CH_3)_3$), 1.24-1.18 (3H, m, -OCH_2CH_3); δ_C (63 MHz, $CDCl_3$) **mixture:** 178.3, 135.0, 130.3 (t, $^2J_{C-F}$ 25.4), 130.2 (t, $^2J_{C-F}$ 25.7), 121.3, 119.5,

119.1, 103.1, 102.5, 75.0 (t, $^{2}J_{C\text{-}F}$ 28.7), 74.4 (t, $^{2}J_{C\text{-}F}$ 30.3), 63.0, 61.6, 39.0, 27.4, 15.4, 15.3; δ_F (282 MHz, $CDCl_3$) **diastereoisomer 1:** -103.1 (1F, dt, J_{gem} 254.6, $^{3}J_{F\text{-}H}$ 8.9, 8.9), -108.9 (1H, ddd, J_{gem} 254.6, $^{3}J_{F\text{-}H}$ 14.0, 6.4), **diastereoisomer 2:** -103.2 (1F, dt, J_{gem} 252.8, $^{3}J_{F\text{-}H}$ 10.2, 10.2), -109.2 (1F, ddd, J_{gem} 252.8, $^{3}J_{F\text{-}H}$ 14.0, 7.6). Further characterisation could not be obtained for acetal **206** because of its instability.

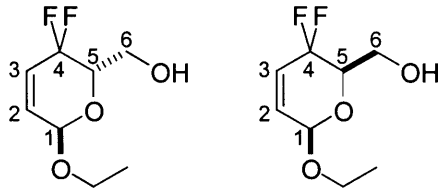
Preparation of ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-pivaloyloxy-DL-*glycero*-hex-2-enopyranoside 207



A mixture of acetal **206** (62.0 mmol, 19.0 g) and Grubbs' catalyst **92** (1.55 mmol, 1.28 g) in dry degassed DCM (1200 mL) was refluxed for 3 days under a nitrogen atmosphere after which time some more Grubbs' catalyst (1.55 mmol, 1.28 g) was added as a solution in dry degassed DCM (10 mL). The reaction mixture was refluxed for an additional 2 days and concentrated under reduced pressure to leave a dark brown oil (20.03 g). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired dihydropyrans **207** as a pale yellow oil (11.47 g, 66 %); R_f (10 % diethyl ether in light petroleum) 0.29; ν_{max} (film)/cm^{-1} 2977m (C-H), 2935w (=C-H), 1735s (C=O), 1657w (C=C); δ_H (250 MHz, $CDCl_3$) ***cis/trans*-mixture** 6.11-6.05 (1H, m, H-3), 5.95-5.85 (1H, m, H-2), 5.10-5.01 (1H, m, H-1), 4.43-3.34 (5H, env., -OC*H*$_2$CH$_3$, H-6 and H-5), 1.20-1.15 (12H, m, -OCH$_2$C*H*$_3$ and -C(C*H*$_3$)$_3$); δ_c (63 MHz, $CDCl_3$) ***cis/trans*-mixture:** 178.0, 136.6 (t, $^{3}J_{C\text{-}F}$ 9.4), 134.0 (t, $^{3}J_{C\text{-}F}$ 9.2), 124.7 (t, $^{2}J_{C\text{-}F}$ 25.9), 124.2 (t,

$^2J_{C\text{-}F}$ 21.9), 113.7 (dd, $^1J_{C\text{-}F}$ 243.6, 236.5), 113.4 (dd, $^1J_{C\text{-}F}$ 245.2, 235.5), 96.8, 93.5, 73.4 (t, $^2J_{C\text{-}F}$ 27.7), 68.6 (t, $^2J_{C\text{-}F}$ 27.0), 64.6, 61.1, 38.9, 27.2, 15.2; δ_F (235 MHz, $CDCl_3$) **diastereoisomer 1:** -104.3 (1F, ddd, J_{gem} 279.0, $^3J_{F\text{-}H}$ 11.9, 5.3), -107.6 (1F, ddt, J_{gem} 279.0, $^3J_{F\text{-}H}$ 14.6, 5.4, $^4J_{F\text{-}H}$ 5.4) **diastereoisomer 2:** -110.1 (1F, dd, J_{gem} 279.3, $^3J_{F\text{-}H}$ 21.2), -113.9 (1F, ddd, J_{gem} 279.3, $^3J_{F\text{-}H}$ 9.3, 2.6). Satisfactory elemental analysis and mass spectroscopic data could not be obtained for pyran **207**

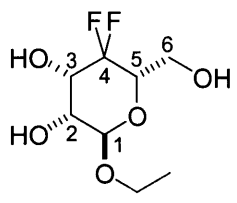
Preparation of ethyl 4,4-difluoro-2,3,4-trideoxy-β-DL-*glycero*-hex-2-enopyranoside *trans*-208 and ethyl 4,4-difluoro-2,3,4-trideoxy-α-DL-*glycero*-hex-2-enopyranoside *cis*-208



DIBAL-H (117.8 mmol, 97.4 mL of a 20 wt. %. solution in hexanes) was added dropwise to a cold (-78 °C) solution of pivaloates **207** (47.10 mmol, 13.12 g) in dry DCM (500 mL). After completion of the addition the mixture was stirred at -78 °C for 1 hour and at 0 °C for an additional hour. The mixture was quenched carefully with water (200 mL) and HCl (150 mL of a 1N solution). The phases were separated and the aqueous layer was extracted with DCM (3 x 230 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude diastereoisomeric mixture (1:1) of alcohols *cis*-**208** and *trans*-**208** as a yellow oil (9.25 g). Purification by column chromatography (30 % diethyl ether in light petroleum) allowed the separation of the two diastereoisomers. **Diastereoisomer 1** (*trans*-**208**) was obtained as a pale yellow oil (3.75 g, 41 %); R_f (30 % diethyl ether in light petroleum) 0.27; ν_{max} (film)/cm^{-1} 3430s br (O-H), 2978m (=C-H), 1664w (C=C);

δ_H (250 MHz, $CDCl_3$) 5.96 (1H, dd, *J* 10.3, $^3J_{H\text{-}F}$ 3.0, H-3), 5.82-5.74 (1H, m, H-2), 4.93 (1H, t, *J* 3.0, ^4J 3.0, H-1), 4.14-4.00 (1H, m, H-6a), 3.83-3.62 (3H, m, H-6b, -OC$H_a$$H_b$$CH_3$ and H-5), 3.47-3.34 (1H, m, -$OCH_aH_bCH_3$), 1.81 (1H, br. s, -O*H*), 1.06 (3H, t, *J* 7.0, -OCH_2CH_3); δ_C (63 MHz, $CDCl_3$) 133.9 (t, $^3J_{C\text{-}F}$ 9.4), 124.6 (dd, $^2J_{C\text{-}F}$ 30.5, 25.9), 114.0 (dd, $^1J_{C\text{-}F}$ 244.1, 235.0), 93.7, 70.8 (dd, $^2J_{C\text{-}F}$ 31.0, 23.9), 65.1, 59.6 (d, $^3J_{C\text{-}F}$ 6.6), 15.4; δ_F (235 MHz, $CDCl_3$) -109.4 (1F, dd, J_{gem} 279.0, $^3J_{F\text{-}H}$ 21.9), -114.0 (1F, ddd, J_{gem} 279.0, $^3J_{F\text{-}H}$ 9.3, 2.7). Satisfactory elemental analysis and mass spectroscopic data could not be obtained for pyran *trans*-**208** . **Diastereoisomer 2** (*cis*-**208**) was obtained as a pale yellow oil (3.56 g, 39 %); R_f (30 % diethyl ether in light petroleum) 0.19; ν_{max} (film)/cm^{-1} 3426s br (O-H), 2979 m (=C-H), 1165w (C=C); δ_H (250 MHz, $CDCl_3$) 5.98 (1H, dd, *J* 10.3, $^3J_{H\text{-}F}$ 1.4, H-3), 5.88-5.79 (1H, m, H-2), 5.05-5.00 (1H, m, H-1), 3.86-3.72 (4H, m, H-6, -OC$H_a$$H_b$$CH_3$ and H-5), 3.56-3.44 (1H, m, -$OCH_aH_bCH_3$), 2.28 (1H, br s, -O*H*), 1.10 (3H, t, *J* 7.1, -OCH_2CH_3); δ_C (63 MHz, $CDCl_3$) 135.9 (t, $^3J_{C\text{-}F}$ 9.7, 9.7), 125.2 (t, $^2J_{C\text{-}F}$ 28.5, 28.5), 114.1 (dd, $^1J_{C\text{-}F}$ 263.0, 242.6), 96.4, 76.3 (dd, $^2J_{C\text{-}F}$ 30.8, 25.7), 64.8, 60.2 (d, $^3J_{C\text{-}F}$ 5.1), 15.4; δ_F (235 MHz, $CDCl_3$) -102.0 (1F, ddd, J_{gem} 279.3, $^3J_{F\text{-}H}$ 11.3, 6.0), -108.7 (1F, ddd, J_{gem} 279.3, $^3J_{F\text{-}H}$ 10.6, 4.0). Satisfactory elemental analysis and mass spectroscopic data could not be obtained for pyran *cis*-**208** .

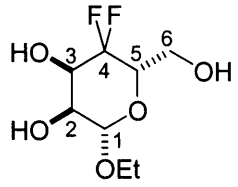
Preparation of ethyl 4,4-difluoro-4-deoxy-α-DL-*lyxo*-pyranoside 209a



A solution of NMO (24.0 mmol, 2.81 g) in water (3 mL) was added to a cold (0 °C) solution of pyran *trans*-**208** (12.0 mmol, 2.33 g) in acetone (12 mL) and *tert*-butanol

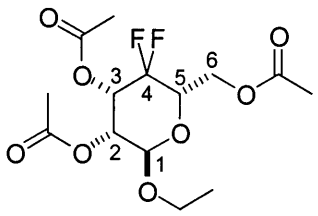
(12 mL). The mixture was stirred for 10 minutes and osmium tetraoxide (0.24 mmol, 2.9 mL of a 2.5 wt. % solution in *tert*-butanol) was added. The reaction mixture was stirred at 0 °C for 2 hours, allowed to warm to room temperature and stirred at this temperature for 5 days. It was then quenched with sodium sulfite (48.0 mmol, 6.05 g), diluted with water (50 mL), stirred for an additional 30 minutes and extracted with ethyl acetate (3 x 50 mL). The aqueous layer was separated and extracted further with diethyl ether in a continuous extractor for 4 days. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil (2.83 g). Purification by column chromatography (80 % ethyl acetate in light petroleum) afforded the desired pyranoside **209a** as a pale yellow oil (1.70 g, 62 %). R_f (80 % ethyl acetate in light petroleum) 0.24; ν_{max}(film)/cm^{-1} 3396s br (O-H), 2978m (C-H), 2934m (C-H); δ_H (250 MHz, DMSO-d_6) 5.50 (1H, d, *J* 8.0, -O*H*), 5.17 (1H, d, *J* 4.4, -O*H*), 5.03 (1H, t, *J* 6.0, -O*H*), 4.89 (1H, s, H-1), 4.02-3.79 (5H, m, H-2, H-3, H-5, H-6a, -OCH_aH$_b$CH$_3$), 3.76-3.56 (2H, m, H-6b, -OCH$_a$$H_bCH_3$), 1.32 (3H, t, *J* 7.1, -OCH$_2$CH_3); δ_C (63 MHz, DMSO-d_6) 118.8 (dd, $^1J_{C\text{-}F}$ 258.1, 244.4), 99.6, 71.5 (dd, $^2J_{C\text{-}F}$ 29.0, 22.9), 70.4 (d, $^3J_{C\text{-}F}$ 7.6), 67.0 (t, $^2J_{C\text{-}F}$ 19.1, 19.1), 62.8, 58.0 (d, $^3J_{C\text{-}F}$ 5.6), 15.0; δ_F (235 MHz, DMSO-d_6) -112.7 (1F, d, J_{gem} 242.8), -128.6 (1F, dt, J_{gem} 242.8, $^3J_{F\text{-}H}$ 24.5, 24.5); [HRMS (FAB, [M-H]$^-$) Found: 227.07300, calc. for $C_8H_{13}O_5F_2$: 227.07311]; *m/z* (ES) 227 (100 %, [M-H]$^-$). ^{1}H and ^{13}C NMR spectra of **209a** were fully assigned by COSY, HMQC and HSBC correlations (**Appendix 1**).

Preparation of ethyl 4,4-difluoro-4-deoxy-β-DL-*ribo*-pyranoside 209b



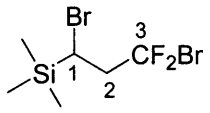
A solution of NMO (24.0 mmol, 2.81 g) in water (3 mL), a solution of pyran *cis*-**208** (12.0 mmol, 2.33 g) in acetone (12 mL) and *tert*-butanol (12 mL) and osmium tetraoxide (0.24 mmol, 2.9 mL of a 2.5 wt. % solution in *tert*-butanol) were treated as described above for the preparation of pyranoside **209a**. Identical work-up afforded a yellow oil (2.85 g). Purification by column chromatography (80 % ethyl acetate in light petroleum) afforded the desired pyranoside **209b** as colourless oil, which solidified on standing (1.71 g, 62 %). R_f (80 % ethyl acetate in light petroleum) 0.27; Mp 92-93 °C; (Found C, 42.28; H, 6.22; $C_8H_{14}F_2O_3$ requires: C, 42.11; H, 6.18 %); ν_{max}(KBr)/cm^{-1} 3392s br (O-H), 2978m (C-H), 2934m (C-H); δ_H (250 MHz, DMSO-d_6) 6.16 (1H, d, *J* 4.8, -O*H*), 5.41 (1H, d, *J* 6.9, -O*H*), 5.01 (1H, t, *J* 6.0, -O*H*), 4.71 (1H, d, *J* 7.8, H-1), 4.11-3.96 (3H, m, H-3, H-5 and -OCH_aH$_b$CH$_3$), 3.91-3.83 (1H, m, H-6a), 3.77-3.63 (2H, m, -OCH$_a$$H_bCH_3$ and H-6b), 3.52-3.43 (1H, m, H-2), 1.33 (3H, t, *J* 7.1 -OCH$_2$C*H*; δ_C (63 MHz, DMSO-d_6) 119.2 (dd, $^1J_{C\text{-}F}$ 256.6, 247.4), 100.2, 72.7 (dd, $^2J_{C\text{-}F}$ 29.0, 21.9), 70.4 (dd, $^2J_{C\text{-}F}$ 32.3, 19.6), 69.6 (d, $^3J_{C\text{-}F}$ 6.1), 64.6, 58.2 (d, $^3J_{C\text{-}F}$ 4.6), 15.4; δ_F (235 MHz, DMSO-d_6) -117.8 (1F, dd, J_{gem} 249.5, $^3J_{F\text{-}H}$ 6.6), -123.6 (1F, ddt, J_{gem} 249.5, $^3J_{F\text{-}H}$ 26.5, 4.6, $^4J_{F\text{-}H}$ 4.6); [HRMS (FAB, [M+H]$^+$) Found: 229.08879, calc. for $C_{15}H_8O_5F_2$: 229.08876]; *m/z* (FAB) 229 (41 %, [M+H]$^+$), 211 (11), 183 (37). An analytical sample was recrystallised by vapour diffusion (diethyl ether/light petroleum) to afford colourless needles, which were used to obtain an X-ray crystal structure of pyranoside **209b** (**Appendix 2**). ^{1}H and ^{13}C NMR spectra of **209b** were fully assigned by COSY, HMQC and HSBC correlations (**Appendix 1**).

Preparation of ethyl 4,4-difluoro-4-deoxy-α-DL-*lyxo*-pyranoside triacetate 210



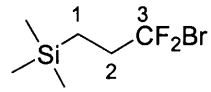
Acetic anhydride (0.5 mL, 5 mmol) was added to a solution of pyranoside **209a** (228 mg, 1.00 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 17 hours, poured over ice/water (~10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were washed successively with sodium hydrogencarbonate (10 mL of a saturated aqueous solution) and water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (262 mg). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded the desired triacetate **210** as a pale yellow solid (251 mg, 72 %). R_f 0.26 (10 % diethyl ether in light petroleum); Mp 52-53 °C; (Found C, 47.59; H, 5.78; $C_{14}H_{20}F_2O_8$ requires: C, 47.46; H, 5.69 %); ν_{max}(KBr)/cm^{-1} 2988m (C-H), 1755s (C=O); δ_H (250 MHz, $CDCl_3$) 5.44 (1H, ddd, $^3J_{H\text{-}F}$ 21.8, 6.2, *J* 3.9, H-3), 5.23 (1H, tt, *J* 3.9, 1.9, $^4J_{H\text{-}F}$ 3.9, 1.9, H-2), 4.83 (1H, d, *J* 1.9, H-1), 4.45 (1H, dd, J_{gem} 11.9, *J* 3.3, H-6a), 4.34 (1H, dd, J_{gem} 11.9, *J* 7.6, H-6b), 4.16 (1H, ddd, $^3J_{H\text{-}F}$ 23.3, *J* 7.6, 3.3, H-5), 3.80-3.49 (2H, m, -OC*H*$_2$CH$_3$), 2.07 (3H, s, -OCOC*H*$_3$), 2.05 (3H, s, -OCOC*H*$_3$), 2.02 (3H, s, -OCOC*H*$_3$), 1.20 (3H, t, *J* 7.1, -OCH$_2$C*H*$_3$); δ_C (63 MHz, $CDCl_3$) 170.9, 170.5, 169.7, 116.3 (dd, $^1J_{C\text{-}F}$ 260.4, 248.7), 97.9, 69.4 (t, $^3J_{C\text{-}F}$ 8.9), 68.9 (dd, $^2J_{C\text{-}F}$ 28.5, 22.9), 66.5 (dd, $^2J_{C\text{-}F}$ 22.1, 17.0), 60.7, 60.6, 21.1, 21.0, 20.8, 15.2; δ_F (235 MHz, $CDCl_3$) -115.9 (1F, d, J_{gem} 248.1), -129.0 (1F, dt, J_{gem} 248.1, $^3J_{F\text{-}H}$ 22.6, 22.6); [HRMS (FAB, $[M+H]^+$) Found: 355.12041, calc. for $C_{14}H_{21}O_8F_2$: 355.12045]; *m/z*(FAB) 355 (50 %, $[M+H]^+$), 309 (65), 249 (100).

Preparation of (1,3-dibromo-3,3-difluoropropyl)-trimethyl-silane 218[86]



A mixture of vinyltrimethylsilane (200 mmol, 30.9 mL), dibromodifluoromethane (400 mmol, 36.5 mL), ethanolamine (100 mmol, 6.10 mL), *tert*-butanol (200 mmol, 19.1 mL) and copper (I) chloride (2.00 mmol, 198 mg) was heated in an Ace tube at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and was taken up in hexane (20 mL). The liquid was separated from the thick brown oil, which formed upon addition of hexane. The brown oil was further extracted with hexane (2 x 20 mL) and the combined hexane extracts were filtered through a short pad of silica and concentrated under reduced pressure to afford a colourless oil (60.32 g). Purification by distillation under reduced pressure afforded the desired silane **218** as a colourless liquid (49.55 g, 80 %, 100 % by GC). Bp 75-76 °C/10 mmHg (Lit[86] 78-79 °C/12 mmHg); ν_{max} (film)/cm^{-1} 2957m (C-H); δ_H (250 MHz, $CDCl_3$) 3.20-3.15 (1H, m, H-1), 2.83-2.53 (2H, m, H-2), 0.00 (9H, s, -Si(C*H*$_3$)$_3$); δ_C (63 MHz, $CDCl_3$) 125.4 (t, $^1J_{C\text{-}F}$ 308.7), 50.7 (t, $^2J_{C\text{-}F}$ 21.6), 34.5, -0.4; δ_F (235 MHz, $CDCl_3$) -41.7 (1F, ddd, J_{gem} 153.8, $^3J_{F\text{-}H}$ 14.1, 8.2), -45.4 (1F, dt, J_{gem} 153.8, $^3J_{F\text{-}H}$ 15.3). Satisfactory mass spectroscopic data could not be obtained for silane **218**. The rest of the spectral data were in agreement with those reported by Elsheimer *et al.*.[86]

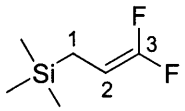
Preparation of (3-bromo-3,3-difluoro-propyl)-trimethyl-silane 220[86]



Sodium borohydride (24.0 mmol, 0.91 g) was added portionwise to a heated (80 °C) solution of silane **218** (20.0 mmol, 6.20 g) in DMSO (40 mL) at such a rate that the

temperature of the reaction mixture remained between 80 and 90 °C. After completion of the addition, the mixture was cooled to 0 °C, diluted with hexane (40 mL) and carefully quenched with 12 N HCl until no further gas evolution was observed. The hexane layer was separated and washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (4.75 g). Distillation under reduced pressure afforded the desired silane **220** as a colourless liquid (2.39 g, 52 %). Bp 74 °C/45 mmHg (Lit.[86] 139-140 °C/760 mmHg); ν_{max} (film)/cm^{-1} 2963m (C-H); δ_H (300 MHz, $CDCl_3$) 2.35-2.20 (2H, m H-2), 0.82-0.76 (2H, m, H-1), 0.04 (9H, s, -Si(CH_3)$_3$); δ_C (63 MHz, $CDCl_3$) 125.2 (t, $^1J_{C\text{-}F}$ 306.3), 40.1 (t, $^2J_{C\text{-}F}$ 22.5), 10.4, -2.9; δ_F (282 MHz, $CDCl_3$) -45.6 (t, $^3J_{F\text{-}H}$ 13.4). Satisfactory mass spectroscopic data could not be obtained for silane **220**. The rest of the spectral data were in agreement with those reported by Elsheimer *et al.*.[86]

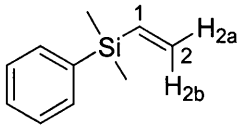
Preparation of (3,3-difluoro-allyl)-trimethyl-silane 222



A mixture of silane **220** (2.15 g, 9.30 mmol) and DBU (2.1 mL, 14.0 mmol) were heated at 100 °C in a Kugelrohr distillation apparatus, during which time the desired allyl silane **222** distilled as a colourless liquid (1.31 g, 94 %). Bp 84-85 °C/760 mmHg (Lit.[132] 83-85 °C/760 mmHg). δ_H (300 MHz, CDCl3) 4.09 (1H, dtd, $^3J_{H\text{-}F}$ 25.4, *J* 8.8, $^3J_{H\text{-}F}$ 2.6, H-2), 1.22 (2H, ddd, *J* 8.8, $^4J_{H\text{-}F}$ 1.8, 1.5, H-1), 0.02 (9H, s, -Si(CH_3)$_3$); δ_C (63 MHz, $CDCl_3$) 156.4 (t, $^1J_{C\text{-}F}$ 284.8), 75.8 (t, $^2J_{C\text{-}F}$ 18.3), 15.6, -3.2; δ_F (282 MHz, $CDCl_3$) -91.3 (1F, d, J_{gem} 54.7), 94.4 (1F, dd, J_{gem} 54.7, $^3J_{F\text{-}H}$ 25.4). Satisfactory mass

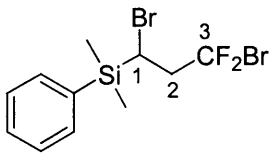
spectroscopic data could not be obtained for silane **222**. The rest of the spectral data were in agreement with those reported by Seyferth *et al.*.[132]

Preparation of dimethyl-phenyl-vinyl-silane 217[133]



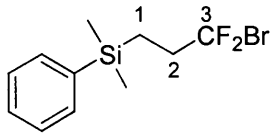
Vinylmagnesium bromide (44.0 mmol, 44.0 mL of 1N solution in THF) was added dropwise to a cold (0 °C) solution of chlorodimethylphenylsilane (40.0 mmol, 6.7 mL) in THF (20 mL). After completion of the addition, the reaction mixture was stirred at 0 °C for 1 hour, at room temperature for 16 hours, quenched with water (25 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (5.83 g). This residue was dissolved in hexane and filtered through a short pad of silica to afford the desired silane **217** as a colourless liquid (5.69 g, 88 %, 100 % by GC). R_f (light petroleum) 0.68; δ_H (300 MHz, $CDCl_3$) 7.57-7.36 (5H, m, -C_6H_5), 6.32 (1H, dd, J_{trans} 20.2, J_{cis} 14.7, H-1), 6.08 (1H, dd, J_{cis} 14.7, J_{gem} 3.7, H_a), 5.78 (1H, dd, J_{trans} 20.2, J_{gem} 3.7, H_b), 0.37 (6H, s, 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 141.3, 140.9, 136.8, 135.7, 131.9, 130.7, 0.0; *m/z* (EI) 162 (12 %, M^+), 147 (100), 135 (20), 121 (73). Spectral data were in agreement with those reported by Fleming *et al.*.[133]

Preparation of (1,3-dibromo-3,3-difluoro-propyl)-dimethyl-phenyl-silane 219



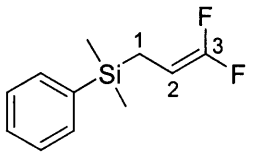
A mixture of vinylsilane **217** (35.1 mmol, 5.69 mL), dibromodifluoromethane (70.2 mmol, 6.4 mL), ethanolamine (61.1 mmol, 1.10 mL), *tert*-butanol (35.1 mmol, 3.4 mL) and copper (I) chloride (350 μmol, 35 mg) was heated in an Ace tube at 90 °C for 20 hours. The reaction mixture was allowed to cool to room temperature and was taken up in hexane (20 mL). The liquid was separated from the thick brown oil, which formed upon addition of hexane. The brown oil was further extracted with hexane (2 x 20 mL) and the combined extracts were filtered through a short pad of silica and concentrated under reduced pressure to afford a colourless oil, which appeared to be a 1:1 mixture of starting material and desired silane **219** according to crude ^{1}H NMR. This mixture was treated with dibromodifluoromethane (70.2 mmol, 6.4 mL), ethanolamine (61.1 mmol, 1.10 mL), *tert*-butanol (35.1 mmol, 3.40 mL) and copper (I) chloride (350 μmol, 35 mg) as described above for an additional 40 hours. The reaction mixture was worked up in the same way to leave a pale yellow liquid (8.32 g). Purification by distillation under reduced pressure afforded the desired silane as a colourless liquid (8.77 g, 67 %, 95 % by GC). Bp 112-113 °C/0.1 mmHg; δ_H (300 MHz, $CDCl_3$) 7.56-7.35 (5H, m, -C_6H_5), 3.25 (1H, dd, *J* 9.9, 2.9, H-1), 2.89-2.63 (2H, m, H-2), 0.49 (3H, s, -CH_3), 0.48 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 134.7, 134.5, 130.6, 128.7, 123.0 (dd, $^{1}J_{C\text{-}F}$ 309.8, 308.2), 47.9 (t, $^{2}J_{C\text{-}F}$ 21.9), 31.3 (dd, $^{3}J_{C\text{-}F}$ 2.5, 1.0), -3.6, -5.1; δ_F (282 MHz, $CDCl_3$) -45.5 (t, $^{3}J_{F\text{-}H}$ 13.3). Satisfactory mass spectroscopic data could not be obtained for silane **219**.

Preparation of (3-bromo-3,3-difluoro-propyl)-dimethyl-phenyl-silane 221



Sodium borohydride (32.4 mmol, 1.23 g) was added portionwise to a heated (80 °C) solution of silane **219** (21.6 mmol, 8.06g) in DMSO (50 mL) at a rate such as the temperature of the reaction mixture remained between 80 and 90 °C. After completion of the addition, the mixture was cooled to 0 °C, diluted with hexane (50 mL) and carefully quenched with 12 N HCl until no further gas evolution was observed. The hexane layer was separated and washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (4.02 g). Distillation under reduced pressure afforded the desired silane **221** as a colourless liquid (3.83 g, 61 %). Bp 100-102 °C/0.1 mmHg; δ_H (300 MHz, $CDCl_3$) 7.56-7.40 (5H, m, -C_6H_5), 2.40-2.20 (2H, m, H-2), 1.12-1.06 (2H, m, H-1); 0.36 (6H, s, 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 137.7, 133.9, 129.8, 128.4, 124.9 (dd, $^1J_{C\text{-}F}$ 308.1, 307.7), 40.0 (t, $^2J_{C\text{-}F}$ 22.6), 10.3, -3.0; δ_F (282 MHz, $CDCl_3$) -45.5 (t, $^3J_{F\text{-}H}$ 13.3). Satisfactory mass spectroscopic data could not be obtained for silane **221**.

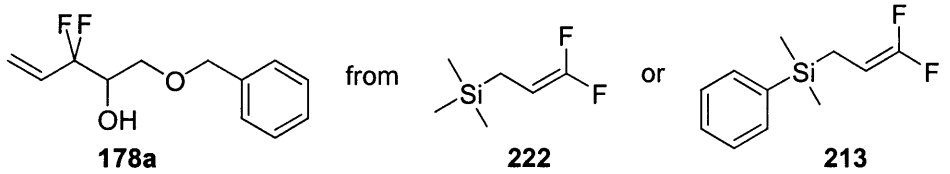
Preparation of (3,3-difluoro-allyl)-dimethyl-phenyl-silane 213



A mixture of silane **221** (10.0 mmol, 2.93 g) and DBU (15.0 mmol, 2.30 mL) was heated under reduced pressure in a Kugelrohr distillation apparatus. The desired allyl silane **213** distilled as a colourless liquid (2.00 g, 94 %). Bp 100 °C/10 mmHg (Lit[85] 120-130 °C/23 mmHg); δ_H (300 MHz, $CDCl_3$) 7.55-7.37 (5H, m, -C_6H_5), 4.11 (1H, dtd,

$^{3}J_{H\text{-}F}$ 25.0, *J* 8.8, $^{3}J_{H\text{-}F}$ 2.6, H-2), 1.31 (2H, ddd, *J* 8.8, $^{4}J_{H\text{-}F}$ 1.8, 1.5, H-1), 0.33 (6H, s , 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 156.3 (t, $^{1}J_{C\text{-}F}$ 284.7), 137.1, 133.9, 129.3, 127.8, 79.5 (t, $^{2}J_{C\text{-}F}$ 18.5), 22.4, -4.3; δ_F (282 MHz, $CDCl_3$) -90.5 (1F, dd, J_{gem} 52.8, $^{3}J_{F\text{-}H}$ 2.5), -93.6 (1F, dd, J_{gem} 52.8, $^{3}J_{F\text{-}H}$ 25.4). Satisfactory mass spectroscopic data could not be obtained for silane **213**. The rest of the spectral data were in agreement with those reported by Hiyama *et al.*.[85]

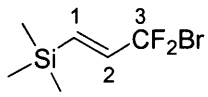
Attempted preparation of 1-benzyloxy-3,3-difluoro-pent-4-en-2-ol 178a from (3,3-difluoro-allyl)-trimethyl-silane 222 or (3,3-difluoro-allyl)-dimethyl-phenyl-silane 213



178a **222** **213**

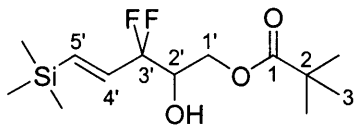
In a typical procedure, tris(diethylamino)sulfonium difluorotrimethylsilicate (0.10 mmol, 36 mg) or tetra-*n*-butylammonium fluoride difluorotriphenyl-stannate (0.10 mmol, 63 mg) was added to a solution of benzyloxyacetaldehyde (1.0 mmol, 0.14 mL) and silane **222** (1.0 mmol, 150 mg) or silane **213** (1.0 mmol, 210 mg) in DMPU (2 mL) or THF (2 mL). The reaction mixture was stirred at room temperature for 18 hours, quenched with HCl (5 mL of a 1N solution) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford pale yellow oils. Crude ^{19}F NMR of the crude reaction mixture did not show any fluorinated products.

Preparation of (*E*)-(3-bromo-3,3-difluoro-propenyl)-trimethyl-silane 230[87]



DBU (185 mmol, 27.7 mL) was added slowly over 15 minutes to a cold (0 °C) solution of silane **218** (124 mmol, 38.3 g) in diethyl ether (250 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 hour after which time a white precipitate had formed. The solid was filtered and washed with diethyl ether (2 x 100 mL). The organic filtrate was washed with water (3 x 200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (26.06 g). Purification by distillation under reduced pressure afforded the desired alkene **230** as a colourless liquid (16.34 g, 58 %). Bp 63-64 °C/50 mmHg (Lit.[87] 42 °C/15 mmHg); ν_{max} (film)/cm^{-1} 2959 m (=C-H); δ_H (250 MHz, $CDCl_3$) 6.25 (1H, dt, J_{trans} 18.7, $^4J_{H\text{-}F}$ 1.6, H-1), 6.04 (1H, dt, J_{trans} 18.7, $^3J_{H\text{-}F}$ 8.4, H-2), 0.00 (9H, s, -Si(CH_3)$_3$); δ_C (63 MHz, $CDCl_3$) 140.7 (t, $^2J_{C\text{-}F}$ 24.7), 137.7 (t, $^3J_{C\text{-}F}$ 4.9), 119.2 (t, $^1J_{C\text{-}F}$ 302.5), 0.0; δ_F (235 MHz, $CDCl_3$) -47.7 (d, $^3J_{F\text{-}H}$ 8.4). Satisfactory mass spectroscopic data could not be obtained for silane **230**. The rest of the spectral data were in agreement with those reported by Purrington *et al.*.[87]

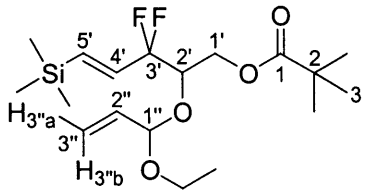
Preparation of (*E*)-2,2-dimethyl-propionic acid 3',3'-difluoro-2'-hydroxy-5'-trimethyl-silanyl-pent-4'-enyl ester 231



A suspension of indium powder (35.0 mmol, 4.02 g), alkene **230** (35.0 mmol, 8.02 g) and aldehyde **203** (35.0 mmol, 5.05 g) in water (100 mL) was stirred vigorously at room temperature for 16 hours. The reaction mixture was quenched with HCl (100

mL of a 1N solution) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil (8.67 g). Purification by column chromatography (15 % diethyl ether in light petroleum ether) afforded the desired difluorinated homoallylic alcohol **231** as a colourless oil (4.79 g, 46 %). R_f (20 % diethyl ether in light petroleum) 0.38; ν_{max} (film)/cm^{-1} 3464 br m (O-H), 2960 m (C-H), 1715 s (C=O), 1481m (C=C); δ_H (250 MHz, $CDCl_3$) 6.33 (1H, d, J_{trans} 19.2, H-5'), 5.98 (1H, dt, J_{trans} 19.2, $^3J_{H\text{-}F}$ 10.8, H-4'), 4.17-3.98 (2H, m, H-1'), 3.93-3.86 (1H, m, H-2'), 3.02 (1H, br s, -O*H*), 1.09 (9H, s, -C(CH_3)$_3$), 0.00 (9H, s, -Si(CH_3)$_3$); δ_C (63 MHz, $CDCl_3$) 180.8, 140.0, 137.1 (t, $^2J_{C\text{-}F}$ 25.7), 120.5 (t, $^1J_{C\text{-}F}$ 244.7), 73.9 (t, $^2J_{C\text{-}F}$ 30.0), 65.3 (t, $^3J_{C\text{-}F}$ 3.6), 40.6, 28.9, 0.00; δ_F (235 MHz, $CDCl_3$) -107.5 (1F, d, J_{gem} 250.8), -111.3 (1F, dt, J_{gem} 250.8, $^3J_{F\text{-}H}$ 10.9); [HRMS (FAB, $[M+H]^+$) Found: 295.15414, calc. for $C_{13}H_{25}O_3F_2Si$: 295.15411; *m/z* (FAB) 295 (50%, $[M+H]^+$), 275 (47).

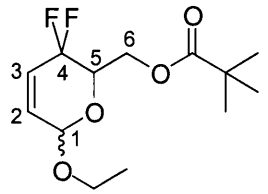
Preparation of 2,2-dimethyl-propionic acid 2'-(1''-ethoxy-allyloxy)-3',3'-difluoro-5'-trimethylsilanyl-pent-4'-enyl ester 233



A solution of alcohol **231** (15.4 mmol, 4.54 g), acrolein diethyl acetal (30 mmol, 4.6 mL) and PPTS (120 μmol, 30 mg) in dry toluene (40 mL) was stirred at 30-40 °C under reduced pressure (P = 60 mmHg) for 4 hours to remove ethanol azeotropically. An additional portion of acrolein diethyl acetal (30 mmol, 4.6 mL) was added and the solution was stirred for an additional 4 hours under the conditions described above.

The reaction mixture was quenched with sodium carbonate (50 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (5.61 g). Purification by column chromatography (5 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired acetal **233** as a pale yellow oil (4.99 g, 86 %). R_f (5 % diethyl ether in light petroleum) 0.32; ν_{max} (film)/cm^{-1} 2975m (C-H), 2902w (=C-H), 1736s (C=O), 1480m (C=C), 1461w (C=C); δ_H (250 MHz $CDCl_3$) **mixture:** 6.37-6.25 (1H, m, H-5'), 6.06-5.87 (1H, m, H-4'), 5.76-5.62 (1H, m, H-2''), 5.33-5.15 (2H, m, H-3''a and H-3''b), 4.99-4.94 (1H, m, H-1''), 4.24-4.15 (1H, m, H-2'), 4.03-3.88 (2H, m, H-1'), 3.64-3.35 (2H, m, -OC$H_2$$CH_3$), 1.09 (3H, s, -$OCH_2CH_3$), 1.08 (9H, s, -C($CH_3$)$_3$), 0.00 (9H, s, -Si($CH_3$)$_3$); δ_C (63 MHz, $CDCl_3$) **mixture:** 179.7, 139.3 (t, $^3J_{C\text{-}F}$ 6.4), 139.1 (t, $^3J_{C\text{-}F}$ 6.4), 137.6, (t, $^2J_{C\text{-}F}$ 25.2), 137.5 (t, $^2J_{C\text{-}F}$ 25.7), 136.6, 120.8 (t, $^1J_{C\text{-}F}$ 245.9), 120.7, 120.5 (t, $^1J_{C\text{-}F}$ 245.4), 120.4, 104.5, 103.9, 76.7 (t, $^2J_{C\text{-}F}$ 26.7), 75.9 (t, $^2J_{C\text{-}F}$ 27.0), 64.6, 63.1, 62.9, 40.5, 28.9, 28.8, 19.9, 0.0; δ_F (235 MHz, $CDCl_3$) **diastereoisomer 1:** -103.0 (1F, dt, J_{gem} 250.8, $^3J_{F\text{-}H}$ 8.6), -108.5 (1F, dt, J_{gem} 250.8, $^3J_{F\text{-}H}$ 9.3), **diastereoisomer 2:** -103.1 (1F, dt, J_{gem} 252.1, $^3J_{F\text{-}H}$ 8.6), -108.8 (1F, dt, J_{gem} 252.1, $^3J_{F\text{-}H}$ 10.0). Further characterisation could not be obtained for acetal **233** because of its instability.

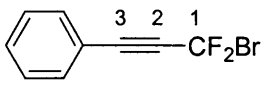
Attempted preparation of ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-pivaloyloxy-DL-*glycero*-hex-2-enopyranoside 207 from 2,2-dimethyl-propionic acid 2'-(1''-ethoxy-allyloxy)-3',3'-difluoro-5'-trimethylsilanyl-pent-4'-enyl ester 233



Method A: a mixture of acetal **233** (5.0 mmol, 1.9 g) and Grubbs' catalyst **92** (250 μmol, 206 mg) in dry degassed DCM (100 mL) was refluxed for 5 days under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to leave a dark brown oil (2.03 g). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired dihydropyrans **207** as a pale yellow oil (195 mg, 14 %).

Method B: a mixture of acetal **233** (5.0 mmol, 1.9 g) and Nolan's catalyst **94** (250 μmol, 213 mg) in dry degassed DCM (100 mL) was refluxed for 5 days under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to leave a dark brown oil (2.01 g). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of the desired dihydropyrans **207** as a pale yellow oil (334 mg, 24 %).

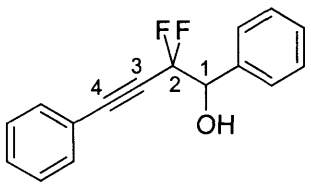
Preparation of 1-bromo-1,1-difluoro-3-phenyl-prop-2-yne 75



n-Buthyllithium (250.0 mmol, 156.5 mL of a 1.6 N solution in hexanes) was added dropwise to a cold (-78 °C) solution of phenylacetylene (250 mmol, 27.5 mL) in THF (500 mL). After completion of the addition a white precipitate formed and the

suspension was stirred at 0 °C for 15 minutes and recooled to -78 °C. A cold (-70 °C) solution of dibromodifluoromethane (275 mmol, 25 mL) in THF (250 mL) was added dropwise through a cold jacketed dropping funnel over 1 hour. After completion of the addition, the brown solution was stirred at -78 °C for 1 hour and at 0 °C for 1 hour. The reaction mixture was quenched with ammonium chloride (500 mL of a saturated aqueous solution). The layers were separated and the aqueous layer further extracted with diethyl ether (3 x 500 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil (52.23 g). Distillation under reduced pressure afforded the desired alkyne **75** as pale yellow oil (47.37 g, 82 %, 96 % by GC). Bp 60 °C/1.5 mmHg (Lit.[91] 50 °C/1.0 mmHg); ν_{max} (film)/cm^{-1} 3060w (Ar-H); 2253s (C≡C) δ_H (300 MHz, $CDCl_3$) 7.57-7.37 (m, -C_6H_5); δ_C (75 MHz, $CDCl_3$) 132.3 (t, $^5J_{C-F}$ 2.3), 130.9, 128.7, 118.8 (t, $^4J_{C-F}$ 2.3), 102.1 (t, $^1J_{C-F}$ 289.4), 90.0 (t, $^3J_{C-F}$ 5.7), 81.0 (t, $^2J_{C-F}$ 38.4); δ_F (282 MHz, $CDCl_3$) -45.4 (s); *m/z* (EI) 232 (27 %, $M^+[^{81}Br]$), 230 (27, $M^+[^{79}Br]$), 213 (17), 211 (18), 151 (80). Spectral data were in agreement with those reported by Wakselman *et al.*.[91]

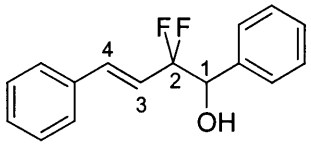
Preparation of 2,2-difluoro-1,4-diphenyl-but-3-yn-1-ol 247[72]



A solution of 1-bromo-1,1-difluoro-3-phenyl-prop-2-yne **75** (10.0 mmol, 2.31 g) in THF (10 mL) was added dropwise over 1.5 hour to a cold (0 °C) suspension of benzaldehyde (10.0 mmol, 1.02 mL), zinc powder (30.0 mmol, 1.96 g), mercury (II) chloride (0.50 mmol, 0.14 g) in THF (30 mL). After completion of the addition, the

mixture was stirred for 5 hours at 0 °C and quenched with HCl (40 mL of a 1N solution). The biphasic mixture was filtered through a short pad of Celite® to remove unreacted zinc powder. The aqueous layer was separated and extracted further with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown thick oil (2.54 g). Purification by column chromatography (20 % diethyl ether in light petroleum) afforded the desired difluorinated homopropargylic alcohol **247** as a pale yellow solid (1.88 g, 73 %). Mp 67-68 °C; R_f (20 % diethyl ether in light petroleum) 0.22; ν_{max} (KBr)/cm^{-1} 3398s br (O-H), 2244s (C≡C); δ_H (300 MHz, $CDCl_3$) 7.58-7.31 (10H, m, 2 x -C_6H_5), 5.05 (1H, t, $^3J_{H\text{-}F}$ 8.9, H-1), 2.77 (1H, br s, -O*H*); δ_C (75 MHz, $CDCl_3$) 135.4 (t, $^4J_{C\text{-}F}$ 1.1), 132.2 (t, $^4J_{C\text{-}F}$ 2.3), 130.1, 129.1, 128.5, 128.2, 127.9, 119.9 (t, $^3J_{C\text{-}F}$ 2.8), 114.3 (t, $^1J_{C\text{-}F}$ 237.9), 89.7 (t, $^3J_{C\text{-}F}$ 6.8), 79.4 (t, $^2J_{C\text{-}F}$ 39.3), 76.6 (dd, $^2J_{C\text{-}F}$ 30.2, 28.5); δ_F (282 MHz, $CDCl_3$) -93.0 (1F, dd, first half of an AB quartet, J_{gem} 273.4, $^3J_{F\text{-}H}$ 8.9), -93.9 (1F, dd, second half of an AB quartet, J_{gem} 273.4, $^3J_{F\text{-}H}$ 8.9); *m/z* (CI) 276 (30 %, $[M+NH_4]^+$), 259 (6, $[M+H]^+$), 239 (100), 219 (36). Spectral data were in agreement with those reported by Kirihara *et al.*.[72]

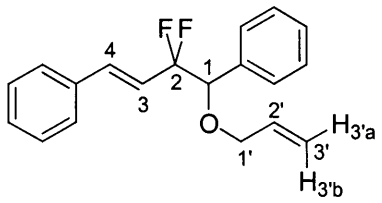
Preparation of (*E*)-2,2-difluoro-1,4-diphenyl-but-3-en-1-ol 248



Red-Al (12.0 mmol, 3.90 mL of a 65 wt. % solution in toluene) was added dropwise to a cold (-20 °C) solution of difluorinated homopropargylic alcohol **247** (6.0 mmol, 1.5 g) in THF (30 mL). After completion of the addition, the mixture was stirred for 3 hours at -20 °C, carefully quenched with HCl (40 mL of a 5N solution) and extracted

with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a thick yellow oil (1.70 g). Purification by column chromatography (30 % diethyl ether in light petroleum) afforded the desired alcohol **248** (1.08, 69 %) as pale yellow solid. R_f (30 % diethyl ether in light petroleum) 0.36; Mp 87-88 °C; ν_{max}(KBr)/cm^{-1} 3419m br (O-H), 3058w (Ar-H), 3033w (=C-H), 1661m (C=C); δ_H (300 MHz, $CDCl_3$) 7.48-7.30 (10H, m, 2 x -C_6H_5), 6.84 (1H, dt, J_{trans} 16.2, $^4J_{H\text{-}F}$ 2.4, H-4), 6.13 (1H, dt, J_{trans} 16.2, $^3J_{H\text{-}F}$ 10.2, H-3), 4.99 (1H, td, $^3J_{H\text{-}F}$ 10.2, J 3.7, H-1), 2.56 (1H, br d, J 3.7, -O*H*); δ_C (75 MHz, $CDCl_3$) 136.3, 135.9 (t, $^3J_{C\text{-}F}$ 9.3), 134.9, 129.2, 128.9, 128.8, 128.4, 127.8 (t, $^4J_{C\text{-}F}$ 1.1), 120.5 (t, $^1J_{C\text{-}F}$ 244.7), 119.8 (t, $^2J_{C\text{-}F}$ 24.9), 76.5 (dd, $^2J_{C\text{-}F}$ 31.3, 29.7), due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (282 MHz, $CDCl_3$) -105.0 (1F, dt, first half of an AB quartet, J_{gem} 244.8, $^3J_{F\text{-}H}$ 10.2), -106.6 (1F, dt, second half of an AB quartet, J_{gem} 244.8, $^3J_{F\text{-}H}$ 10.2); [HRMS (ES, $[M+Na]^+$) Found: 283.0909, calc. for $C_{16}H_{14}OF_2Na$: 293.011]; *m/z* (ES) 283 (100 %, $[M+Na]^+$).

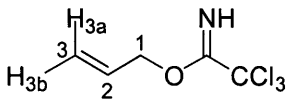
Preparation of (*E*)-1-allyloxy-2,2-difluoro-1,4-phenyl-but-3-enyl 253



Sodium hydroxide (21 mmol, 1.1 mL of a 50 wt. % solution in water), allyl bromide (3.6 mmol, 0.30 mL) and tetra-*n*-butylammonium hydrogensulfate (0.15 mmol, 50 mg) were added to a cold (0 °C) solution of (*E*)-2,2-difluoro-1,4-diphenyl-3-buten-1-ol **248** in DCM (5 mL). The mixture was stirred at 0 °C for 2 hours and at room temperature for 18 hours. The reaction mixture was quenched with ammonium

chloride (10 mL of a saturated aqueous solution). The aqueous layer was separated and extracted further with DCM (3 x 20 mL). The combined organic extracts were washed successively with water (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired allyl ether **253** as a yellow oil, which solidified on standing (0.90 g, 100 %), which was used without further purification. R_f (5 % diethyl ether in light petroleum) 0.48; Mp 43-44 °C; ν_{max}(KBr)/cm^{-1} 3061w (Ar-H), 3028w (=C-H), 2897w (C-H), 1658m (C=C); δ_H (300 MHz, $CDCl_3$) 7.42-7.26 (10H, m, 2 x -C_6H_5), 6.81 (1H, dt, J_{trans} 16.5, $^4J_{H\text{-}F}$ 2.3, H-4), 6.26 (1H, ddd, J_{trans} 16.5, $^3J_{H\text{-}F}$ 12.9, 11.1, H-3), 5.97-5.84 (1H, m, H-2'), 5.31-5.18 (2H, m, H-3'a and H-3'b), 4.66 (1H, t, $^3J_{H\text{-}F}$ 9.6, H-1), 4.12 (1H, dd, J_{gem} 13.1, J 5.0, H-1'a), 3.94 (1H, dd, J_{gem} 13.1, J 6.0, H-1'b); δ_C (75 MHz, $CDCl_3$) 135.2 (t, $^3J_{C\text{-}F}$ 9.0), 135.0, 134.9, 134.0, 128.9, 128.8, 128.7, 128.6, 128.2, 127.2, 120.6 (t, $^2J_{C\text{-}F}$ 24.9), 119.7 (t, $^1J_{C\text{-}F}$ 244.7), 117.7, 82.5 (t, $^2J_{C\text{-}F}$ 30.8), 70.5, due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (282 MHz, $CDCl_3$) -101.4 (1F, ddd, first half of an AB quartet, J_{gem} 246.7, $^3J_{F\text{-}H}$ 9.5, 2.5), -106.3 (1F, dt, second half of an AB quartet, J_{gem} 246.7, $^3J_{F\text{-}H}$ 11.4, 11.4); [HRMS (ES, $[M+Na]^+$) Found: 323.1221, calc. for $C_{19}H_{18}OF_2Na$: 323.1224; *m/z* (ES) 323 (100 %, $[M+Na]^+$).

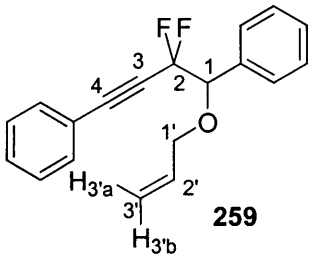
Preparation of allyl trichloroacetimidate 270[97]



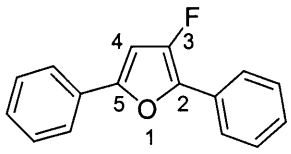
A solution of allyl alcohol (52.5 mmol, 3.60 mL) in dry diethyl ether (10 mL) was added dropwise to a suspension of sodium hydride (5.0 mmol, 0.20 g of a 60 wt. % suspension in mineral oil, from which the oil was removed by washing with dry hexane) in dry diethyl ether (5 mL). The solution was stirred at room temperature for

dropwise. The reaction mixture was allowed to warm to room temperature over 1 hour and concentrated under reduced pressure to afford a yellow oil. Upon addition of hexane (5 mL) and methanol (0.1 mL) and after vigorous shaking, a brown precipitate formed, which was filtered and washed with hexane (3 x 5 mL). The combined filtrate and organic extracts were concentrated under reduced pressure to afford the desired trichloroacetamidate **270** as a pale yellow oil (8.95 g, 88 %), which was used without any further purification. ν_{max} (film)/cm^{-1} 3344m (N-H), 1664s (C=N); δ_H (235 MHz, $CDCl_3$) 8.29 (1H, br s, =N*H*), 6.06-5.91 (1H, m, H-2), 5.40 (1H, ddd, J_{trans} 17.2, ^4J 3.0, J_{gem} 1.5, H-3a), 5.26 (1H, ddd, J_{cis} 10.6, ^4J 2.5, J_{gem} 1.5, H-3b), 4.77 (2H, d, J 5.5, H-1); δ_C (63 MHz, $CDCl_3$) 162.8, 131.8, 118.8, 91.8, 70.0; Spectral data were in agreement with those reported by Bundle *et al.*.[97]

Preparation of 1-allyloxy-2,2-difluoro-1,4-diphenyl-but-3-yne 259 and 3-fluoro-2,5-diphenyl-furan 261



259



261

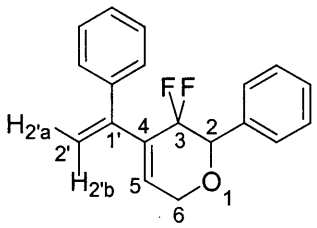
Method A: a 50 wt. % aqueous solution of sodium hydroxide (19 mmol, 1.0 mL) was added to a cold (0 °C) solution of homopropargylic alcohol **247** (0.71 g, 2.8 mmol), allyl bromide (3.3 mmol, 0.29 mL) and tetra-*n*-butylammonium hydrogenphosphate in DCM (5 mL). The mixture was stirred at 0 °C for 30 minutes, then at room temperature for 18 hours, quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with DCM (3 x 15 mL). The combined organic

($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil (0.92 g). Purification by column chromatography (2 % diethyl ether in light petroleum) afforded the desired allylic ether **259** as a pale yellow oil (0.49 g, 59 %) along with fluorofuran **261** as a white solid (0.20 g, 32 %). Data for fluorofuran **261**: R_f (light petroleum) 0.60; Mp 52-53 °C; ν_{max}(KBr)/cm^{-1} 3104w (Ar-H), 1628m (C=C), 1596m (C=C); δ_H (250 MHz, $CDCl_3$) 7.70-7.14 (10H, m, 2 x -C_6H_5), 6.57 (1H, d, $^3J_{H\text{-}F}$ 0.9); δ_C (63 MHz, $CDCl_3$) 151.0 (d, $^1J_{C\text{-}F}$ 253.8), 150.6 (d, $^3J_{C\text{-}F}$ 8.6), 136.4 (d, $^2J_{C\text{-}F}$ 20.3), 130.6 (d, $^4J_{C\text{-}F}$ 2.0), 129.5 (d, $^3J_{C\text{-}F}$ 5.1), 129.2 (d, $^4J_{C\text{-}F}$ 2.0), 128.5, 127.5, 124.1, 124.0, 123.9, 99.7 (d, $^2J_{C\text{-}F}$ 20.3); δ_F (235 MHz, $CDCl_3$) -69.4 (s); [HRMS (FAB, M^+) Found: 238.07931, calc. for $C_{16}H_{11}OF$: 238.07939]; *m/z* (ES) 238 (100 %, M^+).

Method B: a solution of allyl trichloroacetamidate **270** (1.4 mmol, 281 mg) and trifluoromethanesulphonic acid (1 drop) in hexane (4 mL) was added to a solution of alcohol **247** (690 μmol, 179 mg) in DCM (2 mL) and the mixture was stirred for 3 days at room temperature. A white precipitate formed during the reaction and was filtered off. The filtrate was washed successively with sodium hydrogencarbonate (4 mL of a saturated aqueous solution) and water (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow solid (225 mg). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded exclusively the desired allyl ether **259** as a pale yellow oil (273 mg, 81 %). R_f (10 % diethyl ether in light petroleum) 0.23; ν_{max} (film)/cm^{-1} 2980m (=C-H), 2865m (C-H), 2242s (C≡C), 1652w (C=C); δ_H (250 MHz, $CDCl_3$) 7.54-7.28 (10H, m, 2 x -C_6H_5), 6.01-5.85 (1H, m, H-2'), 5.31 (1H, ddd, J_{trans} 17.2, J_{gem} 3.0, ^4J 1.5, H-3'a), 5.22 (1H, ddd, J_{cis} 10.3, J_{gem} 3.0, ^4J 1.3, H-3'b), 4.72 (1H, t, $^3J_{H\text{-}F}$ 8.5, H-1), 4.19 (1H, ddt, J_{gem} 13.1, J 4.7, ^4J 1.5, H-1'a), 4.03 (1H, ddt, J_{gem} 13.1, J 6.1, ^4J 1.3, H-1'b); δ_C (63 MHz,

$CDCl_3$) 134.7, 134.2, 132.5 (t, $^4J_{C\text{-}F}$ 2.3), 130.3, 129.5, 129.1, 128.8, 128.6, 120.6 (t, $^3J_{C\text{-}F}$ 3.1), 118.4, 113.9 (t, $^1J_{C\text{-}F}$ 238.5), 89.2 (t, $^4J_{C\text{-}F}$ 6.2), 82.7 (t, $^2J_{C\text{-}F}$ 29.2), 80.6 (t, $^2J_{C\text{-}F}$ 39.2), 71.3; δ_F (235 MHz, $CDCl_3$) -91.6 (1F, dd, first half of an ABX system, J_{gem} 275.3, $^3J_{F\text{-}H}$ 8.6), -92.6 (1F, dd, second half of an ABX system, J_{gem} 275.3, $^3J_{F\text{-}H}$ 8.6); [HRMS (ES, $[M+Na]^+$) Found: 321.1064, calc. for $C_{19}H_{16}OF_2Na$: 321.1067]; *m/z* (ES) 321 (100 %, $[M+Na]^+$).

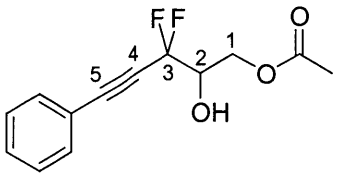
Preparation of 3,3-difluoro-2-phenyl-4-(1'-phenyl-ethenyl)-3,6-dihydro-2*H*-pyran 260



A solution of homopropargyl-allyl ether **259** (0.50 mmol, 150 mg) and Grubbs' catalyst **92** (25 μmol, 21 mg) in dry degassed DCM was refluxed for 18 hours and concentrated under reduced pressure to leave a dark brown oil. Purification by column chromatography (5 % diethyl ether in light petroleum) afforded the desired diene **260** as a pale yellow oil (127 mg, 43 %). R_f (5 % diethyl ether in light petroleum) 0.35; ν_{max} (KBr)/cm^{-1} 3059m (Ar-H), 3033m (Ar-H), 2941w (=C-H), 2829m (C-H), 1600m (C=C); δ_H (250 MHz, $CDCl_3$) 7.45-7.21 (10H, m, 2 x -C_6H_5), 5.99 (1H, dd, *J* 5.3, 2.5, H-5), 5.53 (1H, s, H-2'b), 5.31 (1H, s, H-2'a), 4.67 (1H, dd, $^3J_{H\text{-}F}$ 19.2, 3.1, H-2), 4.43-4.38 (2H, m, H-6); δ_C (63 MHz, $CDCl_3$) 143.0, 141.3, 134.9, 134.6 (t, $^3J_{C\text{-}F}$ 6.6), 134.4 (dd, $^2J_{C\text{-}F}$ 26.7, 9.9), 129.2, 128.9, 128.8, 128.6, 128.5, 128.3, 118.3, 115.2 (dd, $^1J_{C\text{-}F}$ 250.2, 239.6), 79.9 (dd, $^2J_{C\text{-}F}$ 66.7), due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (235 MHz, $CDCl_3$) -103.2

(1F, ddt, J_{gem} 273.7, $^{3}J_{F\text{-}H}$ 18.6, $^{4}J_{F\text{-}H}$ 6.6, $^{5}J_{F\text{-}H}$ 6.6), -110.8 (1F, d, J_{gem} 273.7); [HRMS (ES, $[M+Na]^{+}$) Found: 321.1065, calc. for $C_{19}H_{16}OF_2Na$: 321.1067]; *m/z* (ES) 321 (100 %, $[M+Na]^{+}$).

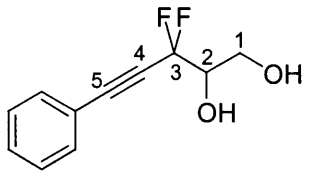
Preparation of acetic acid 3,3-difluoro-2-hydroxy-5-phenyl-pent-4-ynyl ester 284



A solution of 1-bromo-1,1-difluoro-3-phenyl-prop-2-yne **75** (20 mmol, 4.6 g) in THF (20 mL) was added dropwise over 2 hours to a cold (0 °C) suspension of acetoxyacetaldehyde **199** (20.0 mmol, 2.04 g), zinc powder (60.0 mmol, 3.92 g), mercury (II) chloride (1.0 mmol, 0.27 g) in THF (60 mL). After completion of the addition, the mixture was stirred for 5 hours at 0 °C and quenched with HCl (50 mL of 1N solution). The biphasic mixture was filtered through a short pad of Celite® to remove unreacted zinc powder. The aqueous layer was separated and further extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a thick brown oil (5.32 g). Purification by column chromatography (30 % diethyl ether in light petroleum) afforded the desired difluorinated homopropargylic alcohol **284** (2.86 g, 56 %) as a pale yellow oil. R_f (50 % diethyl ether in light petroleum) 0.27; ν_{max} (film)/cm^{-1} 3380s br (O-H), 2875m (C-H), 2240s (C≡C), 1717s (C=O); δ_H (300 MHz, $CDCl_3$) 7.54-7.33 (5H, m, -C_6H_5), 4.45 (1H, dd, J_{gem} 11.9, *J* 3.3, H-1a), 4.37 (1H, dd, J_{gem} 11.9, *J* 7.0, H-1b), 4.27-4.17 (1H, m, H-2), 3.02 (1H, br s, -O*H*), 2.10 (1H, s, -CH_3); δ_C (75 MHz, $CDCl_3$) 171.4, 132.3 (t, $^{4}J_{C\text{-}F}$ 2.3), 130.4, 128.6, 119.6, 113.1 (t, $^{1}J_{C\text{-}F}$ 237.4), 89.5 (t, $^{3}J_{C\text{-}F}$ 6.8), 78.7 (t, $^{2}J_{C\text{-}F}$ 39.0), 72.8 (t, $^{2}J_{C\text{-}F}$ 29.1),

20.7, due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (282 MHz, $CDCl_3$) -93.9 (1F, dd, first half of an AB quartet, J_{gem} 279.8, $^3J_{F\text{-}H}$ 8.9), -94.2 (1F, dd, second half of an AB quartet, J_{gem} 279.8, $^3J_{F\text{-}H}$ 8.9); [HRMS (ES, $[M+Na]^+$) Found: 277.0724, calc. for $C_{11}H_{10}O_2F_2Na$: 277.0732]; *m/z* (ES) 277 (100, $[M+Na]^+$).

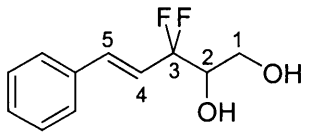
Preparation of 3,3-difluoro-5-phenyl-pent-4-yne-1,2-diol 287



A mixture of sodium iodide (89.0 mmol, 13.3 g), mercury (II) acetate (4.4 mmol, 1.4 g), glycolaldehyde dimer (89.0 mmol, 10.7 g) and zinc powder (89.0 mmol, 5.79 g) was added in one portion to a solution of alkyne **75** (89.0 mmol, 20.5 g) in THF (350 mL). Upon addition, a gentle reflux was observed and the solution was stirred at room temperature for 18 hours. The reaction mixture was quenched with HCl (350 mL of a 2N solution) and extracted with ethyl acetate (3 x 250 mL). The combined organic extracts were washed with sodium sulfite (200 mL of a saturated aqueous solution), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil (18.90 g). Purification by column chromatography (40 % ethyl acetate in light petroleum) afforded the desired diol **287** as a yellow oil, which solidified on standing (12.98 g, 69 %, 100 % by GC). R_f (40 % ethyl acetate in light petroleum) 0.25; Mp 35-36 °C; (Found C, 62.35; H, 4.85; $C_{11}H_{10}F_2O_2$ requires: C, 62.26; H, 4.75 %); ν_{max} (KBr)/cm^{-1} 3370s br (O-H), 2944m (Ar-H), 2241s (C≡C); δ_H (250 MHz, $CDCl_3$) 7.43-7.20 (5H, m, -C_6H_5), 4.08-3.96 (1H, m, H-2), 3.87 (1H, dd, J_{gem} 11.8, *J* 3.3, H-1a), 3.79 (1H, dd, J_{gem} 11.8, *J* 7.6, H-1b), 3.53 (2H, br s, 2 x -O*H*);

δ_C (63 MHz, $CDCl_3$) 132.7, 130.6, 128.9, 120.0 (t, $^4J_{C\text{-}F}$ 2.8), 113.9 (t, $^1J_{C\text{-}F}$ 237.0), 89.6 (t, $^3J_{C\text{-}F}$ 6.9), 79.5 (t, $^2J_{C\text{-}F}$ 38.9), 74.8 (t, $^2J_{C\text{-}F}$ 27.7), 61.9; δ_F (235 MHz, $CDCl_3$) -94.0 (1H, dd, first half of an AB quartet, J_{gem} 279.3, $^3J_{F\text{-}H}$ 8.6), -94.8 (1H, dd, second half of an AB quartet, J_{gem} 279.3, $^3J_{F\text{-}H}$ 9.9); [HRMS (ES, $[M+Na]^+$) Found: 235.0548, calc. for $C_{11}H_{10}O_2F_2Na$: 235.0547]; *m/z* (ES) 235 (100 %, $[M+Na]^+$).

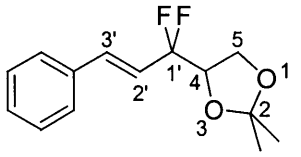
Preparation of (*E*)-3,3-difluoro-5-phenyl-pent-4-ene-1,2-diol 298



Red-Al (102 mmol, 30.6 mL of a 65 wt. % solution in toluene) was added dropwise over one hour to a cold (0 °C) solution of alkyne **287** (51.0 mmol, 10.8 g) in THF (200 mL). After completion of the addition, the reaction mixture was stirred at 0 °C for 3 hours, quenched carefully with HCl (200 mL of a 2N solution) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil (12.12 g). Purification by column chromatography (40 % ethyl acetate in light petroleum) afforded the desired alkene **298** as an orange oil, which solidified on standing (7.90 g, 72 %). R_f (40 % ethyl acetate in light petroleum) 0.23; Mp 42-43 °C; ν_{max}(KBr)/cm^{-1} 3430s br (O-H), 2983w (C-H), 1658m (C=C); δ_H (250 MHz, $CDCl_3$) 7.34-7.20 (5H, m, -C_6H_5), 6.87 (1H, dt, J_{trans} 16.2, $^4J_{H\text{-}F}$ 7.2, H-5), 6.16 (1H, dt, J_{trans} 16.2, $^3J_{H\text{-}F}$ 12.2, H-4), 3.97-3.61 (3H, m, H-1 and H-2), 3.37 (2H, br s, 2 x -O*H*) ; δ_C (63 MHz, $CDCl_3$) 135.8 (t, $^3J_{C\text{-}F}$ 9.4), 135.6, 135.0, 129.2, 127.7, 120.5 (t, $^1J_{C\text{-}F}$ 243.6), 120.4 (t, $^2J_{C\text{-}F}$ 24.4), 74.4 (t, $^2J_{C\text{-}F}$ 29.2), 61.8 (t, $^3J_{C\text{-}F}$ 3.3); δ_F (235 MHz, $CDCl_3$) -105.6 (1F, dt, J_{gem} 251.4, $^3J_{F\text{-}H}$

10.6), -108.6 (1F, dt, J_{gem} 251.4, $^{3}J_{F\text{-}H}$ 11.3); [HRMS (ES, $[M+Na]^{+}$) Found: 237.0700, calc. for $C_{11}H_{12}O_2F_2Na$]; *m/z* (ES) 237 (100 %, $[M+Na]^{+}$).

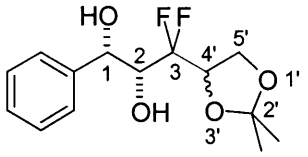
Preparation of (*E*)-4-(1',1'-difluoro-3'-phenyl-allyl)-2,2-dimethyl-[1,3]dioxolane 299



A suspension of diol **298** (5.52 g, 25.7 mmol), *p*-toluenesulphonic acid monohydrate (0.20 g, 1.0 mmol) and anhydrous copper sulfate in acetone (200 mL) was stirred at room temperature for 18 hours. The reaction mixture was quenched with ammonium chloride (100 mL of a saturated aqueous solution) and water (100 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil (6.76 g). Purification by column chromatography (10 % diethyl ether in light petroleum) afforded the desired acetonide **299** as a pale yellow oil (6.21g, 95 %); ν_{max} (film)/cm^{-1} 3061w (=C-H), 3029w (=C-H), 2989m (C-H), 2936m (C-H), 1660m (C=C); δ_H (250 MHz, $CDCl_3$) 7.57-7.42 (5H, m, -C_6H_5), 7.12 (1H, dt, J_{trans} 16.1, $^{4}J_{H\text{-}F}$ 2.6, H-3'), 6.38 (1H, dt, J_{trans} 16.1, $^{3}J_{H\text{-}F}$ 11.9, H-2'), 4.54-4.42 (1H, m, H-4), 4.34-4.19 (2H, m, H-5), 1.58 (3H, s, -CH_3), 1.50 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 136.0 (t, $^{3}J_{C\text{-}F}$ 9.4), 135.2, 129.2, 127.7, 120.3 (t, $^{2}J_{C\text{-}F}$ 24.9), 116.0 (t, $^{1}J_{C\text{-}F}$ 242.6), 111.6, 77.5 (t, $^{2}J_{C\text{-}F}$ 32.7), 65.0 (t, $^{3}J_{C\text{-}F}$ 3.2), 26.4, 25.4, due to overlapping, one of the peaks for the aromatic carbons could not be observed; δ_F (235 MHz, $CDCl_3$) -104.7 (1F, dt, J_{gem} 252.8, $^{3}J_{F\text{-}H}$ 9.3), -109.7 (1F, dt, J_{gem} 252.8, $^{3}J_{F\text{-}H}$ 10.9),

[HRMS (FAB, $[M+H]^+$) Found: 255.11967, calc. for $C_{14}H_{17}O_2F_2$: 255.11966]; *m/z* (FAB) 255 (100%, $[M+H]^+$), 239 (82).

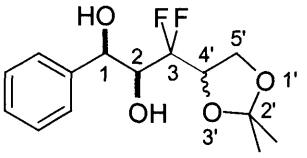
Preparation of 3-(2',2'-dimethyl-[1',3']dioxolan-4'-yl)-3,3-difluoro-1-phenyl-propane-1,2-diol 300a



A mixture of AD mix α (21.0 g), methanesulfonamide (15.0 mmol, 1.43 g) in *tert*-butanol (75 mL) and water (75 mL) was stirred at room temperature until both phases were clear. Alkene **299** (15.0 mmol, 3.81 g) was added in one portion and the mixture was stirred at room temperature for 3 days. The reaction mixture was quenched with sodium sulfite (22.5 g), allowed to warm to room temperature, stirred for 45 minutes and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with potassium hydroxide (50 mL of a 2N aqueous solution) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil (4.36 g). Purification by column chromatography (50 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of desired diol **300a** as a pale yellow oil (3.59 g, 83 %); R_f (50 % diethyl ether in light petroleum) 0.32; ν_{max}(film)/cm^{-1} 3442s br (O-H), 3063w (Ar-H), 3032w (Ar-H), 2990m (C-H), 2938m (C-H), δ_H (250 MHz, $CDCl_3$) **mixture:** 7.41-7.25 (5H, m, -C_6H_5), 5.09-5.06 (1H, m, H-1), 4.64-4.42 (1H, m, H-4'), 4.29-3.91 (3H, m, H-2 and H-5'), 3.23 (2H, br s, 2 x -O*H*), 1.48 (1.5H, s, -CH_3), 1.40 (3H, s, -CH_3), 1.33 (1.5H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) **mixture:** 141.4, 140.9, 128.9, 128.8, 128.4, 128.3, 126.7, 126.5, 121.2 (dd, $^1J_{C\text{-}F}$ 254.1, 249.5), 120.4 (dd, $^1J_{C\text{-}F}$ 254.3, 246.2), 112.0, 111.4, 76.1 (dd, $^2J_{C\text{-}F}$ 30.5,

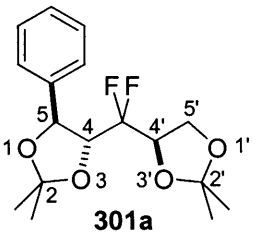
24.9), 73.9 (dd, $^{2}J_{C\text{-}F}$ 26.5, 24.4), 73.7 (dd, $^{2}J_{C\text{-}F}$ 24.2, 21.1), 72.8 (dd, $^{2}J_{C\text{-}F}$ 36.6, 23.9), 70.3 (t, $^{3}J_{C\text{-}F}$ 2.0), 70.1 (dd, $^{3}J_{C\text{-}F}$ 6.6, 2.0), 64.5 (t, $^{3}J_{C\text{-}F}$ 3.8), 64.0 (dd, $^{3}J_{C\text{-}F}$ 4.3, 2.3), 26.2, 26.0, 25.6, 25.4; δ_F (235 MHz, $CDCl_3$) **diastereoisomer 1:** -112.6 (1F, ddd, J_{gem} 268.0, $^{3}J_{F\text{-}H}$ 11.9, 2.7), -125.4 (1F, ddd, J_{gem} 268.0, $^{3}J_{F\text{-}H}$ 21.2, 6.6), **diastereoisomer 2:** -124.7 (1F, ddd, first half of an AB quartet, J_{gem} 258.1, $^{3}J_{F\text{-}H}$ 18.7, 5.3), -125.7 (1F, ddd, second half of an AB quartet, J_{gem} 258.1, $^{3}J_{F\text{-}H}$ 19.9, 5.3); [HRMS (FAB, $[M\text{-}H]^-$) Found: 287.10956, calc. for $C_{14}H_{17}O_4F_2$: 287.10949]; *m/z* (ES).287 (100 %, $[M\text{-}H]^-$).

Preparation of 3-(2',2'-dimethyl-[1',3']dioxolan-4'-yl)-3,3-difluoro-1-phenyl-propane-1,2-diol 300b

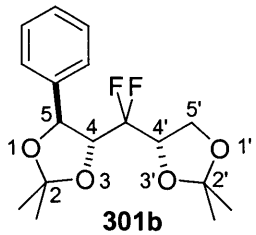


A mixture of AD mix β (21.0 g), methanesulfonamide (15.0 mmol, 1.43 g) in *tert*-butanol (75 mL) and water (75 mL) and alkene **299** (15.0 mmol, 3.81 g) were treated as described for the preparation of diol **300a**. The same work-up as for **300a** afforded a yellow oil (4.62 g). Purification by column chromatography (50 % diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1:1) of desired diol **300b** as a pale yellow oil (3.93 g, 91 %); Spectral data for diols **300b** were identical to those of their enantiomers **300a**.

Preparation of (4*R*,5*S*)-4-[(4'*R*)-2',2'-dimethyl-[1',3']dioxolan-4'-yl-difluoro-methyl]-2,2-dimethyl-5-phenyl-[1,3]dioxolane 301a and (4*R*,5*S*)-4-[(4'*S*)-2',2'-dimethyl-[1',3']dioxolan-4'-yl-difluoro-methyl]-2,2-dimethyl-5-phenyl-[1,3]dioxolane 301b



301a

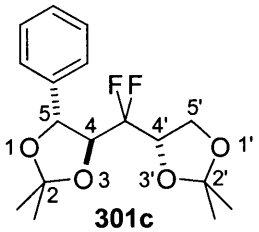


301b

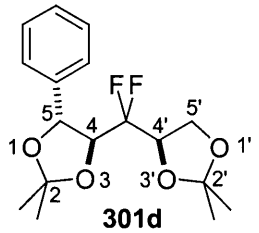
A suspension of diol **300a** (12.5 mmol, 3.59 g), anhydrous copper sulfate (25.0 mmol, 3.98 g) and *p*-toluenesulphonic acid monohydrate (1.20 mmol, 118 mg) in acetone (100 mL) was stirred at room temperature for 18 hours. The reaction mixture was quenched with ammonium chloride (50 mL) and water (50 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude diastereoisomeric mixture (1:1) of *bis*-acetonides as a yellow oil (4.23 g). Purification by column chromatography (10 % diethyl ether in light petroleum) allowed the separation of the diastereoisomers. **Diastereoisomer 1 (301a)** was obtained as a white solid (1.76 g, 43 %, 100 % by GC). R_f (10 % diethyl ether in light petroleum) 0.24; Mp 67-68 °C; (Found C, 62.08; H, 6.84; $C_{17}H_{22}F_2O_4$ requires: C, 62.18; H, 6.75 %); $[\alpha]_D$ (*c* 1.08 in MeOH) 10.9; ν_{max}(film)/cm^{-1} 3066w (Ar-H), 3036w (Ar-H), 2989m (C-H), 2936m (C-H); δ_H (250 MHz, $CDCl_3$) 7.38-7.19 (5H, m, -C_6H_5), 5.27 (1H, d, *J* 7.4, H-5), 4.34-4.29 (1H, m, H-4'), 4.27-4.00 (3H, m H-4 and H-5'), 1.50 (3H, s, -CH_3), 1.43 (3H, s, -CH_3), 1.28 (6H, s, 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 138.8, 128.9, 128.7, 127.2, 119.6 (t, $^1J_{C\text{-}F}$ 250.0), 111.8, 111.4, 80.9 (dd, $^2J_{C\text{-}F}$ 36.1, 22.9), 77.8 (d, $^3J_{C\text{-}F}$ 4.1), 74.5 (dd, $^2J_{C\text{-}F}$ 37.1, 22.9),

64.0 (d, $^{3}J_{C\text{-}F}$ 2.5), 27.8, 26.7, 26.2, 25.5; δ_F (235 MHz, $CDCl_3$) -124.6 (1F, ddd, J_{gem} 257.4, $^{3}J_{F\text{-}H}$ 22.5, 4.0), -126.9 (1F, dd, J_{gem} 257.4, $^{3}J_{F\text{-}H}$ 21.2); Satisfactory mass spectroscopic data could not be obtained for bis-acetonide **301a**. **Diastereoisomer 2** (**301b**) was obtained as a pale yellow oil (1.88 g, 46 %, 100 % by GC). R_f (10 % diethyl ether in light petroleum) 0.21; $[\alpha]_D$ (*c* 0.91 in MeOH) 3.6; ν_{max}(film)/cm^{-1} 3035w (Ar-H), 2989m (C-H), 2936m (C-H); δ_H (235 MHz, $CDCl_3$) 7.47-7.29 (5H, m, -C$_6$*H*$_5$), 5.41 (1H, d, *J* 8.0, H-5), 4.55-4.41 (1H, m, H-4'), 4.24-4.09 (3H, m H-4 and H-5'), 1.59 (3H, s, -C*H*$_3$), 1.56 (3H, s, -C*H*$_3$), 1.47 (3H, s, -C*H*$_3$), 1.36 (3H, s, -C*H*$_3$); δ_C (63 MHz, $CDCl_3$) 138.1, 128.9, 128.8, 127.5, 119.6 (dd, $^{1}J_{C\text{-}F}$ 252.8, 244.1), 111.6, 111.5, 82.2 (dd, $^{2}J_{C\text{-}F}$ 29.8, 27.7), 78.4 (t, $^{3}J_{C\text{-}F}$ 6.1), 74.6 (dd, $^{2}J_{C\text{-}F}$ 31.0, 25.4), 64.6 (t, $^{3}J_{C\text{-}F}$ 4.1), 27.7, 26.7, 26.2, 25.7; δ_F (235 MHz, $CDCl_3$) -113.1 (1F, dt, J_{gem} 268.0, $^{3}J_{F\text{-}H}$ 9.3), -122.4 (1F, dt, J_{gem} 268.0, $^{3}J_{F\text{-}H}$ 11.9); *m/z* (EI) 313 (10 %, $[M\text{-}CH_3]^+$), 256 (12), 255 (55); Satisfactory elemental analysis could not be obtained for *bis*-acetonide **301b**.

Preparation of (4*S*,5*R*)-4-[(4'*S*)-2',2'-dimethyl-[1',3']dioxolan-4'-yl-difluoro-methyl]-2,2-dimethyl-5-phenyl-[1,3]dioxolane 301c and (4*S*,5*R*)-4-[(4'*R*)-2',2'-dimethyl-[1',3']dioxolan-4'-yl-difluoro-methyl]-2,2-dimethyl-5-phenyl-[1,3]dioxolane 301d



301c

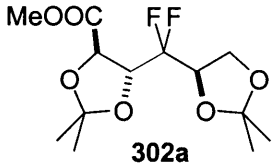


301d

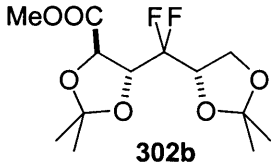
A suspension of diol **300b** (13.6 mmol, 3.93 g), anhydrous copper sulfate (27.3 mmol, 4.36 g) and *p*-toluenesulphonic acid monohydrate (1.40 mmol, 266 mg) in acetone (100 mL) was stirred at room temperature for 18 hours. The reaction mixture

was quenched with ammonium chloride (50 mL) and water (50 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude diastereoisomeric mixture (1:1) of *bis*-acetonides as a yellow oil (4.31 g). Purification by column chromatography (10 % diethyl ether in light petroleum) allowed the separation of the diastereoisomers. **Diastereoisomer 1** (**301c**) was obtained as a white solid (1.84 g, 41 %). Data for *bis*-acetonide **301c** were identical to those of its enantiomer **301a** except for Mp 66-67 °C and $[\alpha]_D$ (*c* 1.11 in MeOH) -11.9. **Diastereoisomer 2** (**301d**) was obtained as a pale yellow oil (2.15 g, 48 %). Data for *bis*-acetonide **301d** were identical to those of its enantiomer **301b** except for $[\alpha]_D$ (*c* 1.01 in MeOH) -4.6.

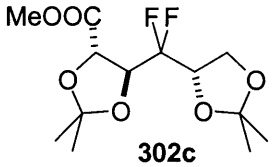
Attempted preparation of methyl 5-[(2,2-dimethyl-1,3-dioxolan-4-yl)-difluoro-methyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylates 302a-d



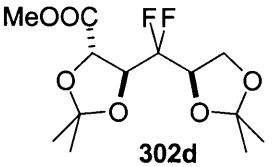
302a



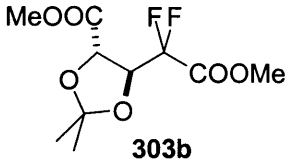
302b



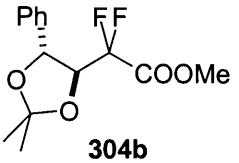
302c



302d



303b

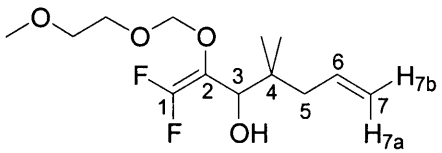


304b

In a typical procedure, a solution of bis-acetonide **301c** (2.0 mmol, 0.66 g) in ethyl acetate (15 mL) was added dropwise to a solution of sodium periodate (40.0 mmol, 8.60 g) and ruthenium (III) chloride monohydrate (0.20 mmol, 45 mg) in acetonitrile (15 mL) and water (30 mL). The reaction mixture was stirred at room temperature for 18 hours during which time a white precipitate formed. The mixture was filtered and the filtrate 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 a brown oil. This crude mixture was taken up in benzene (16 mL) and methanol (4 mL) and trimethylsilyl-diazomethane (3.0 mmol, 1.5 mL of a 2N solution in hexanes) was added dropwise. The reaction mixture was stirred for 15 minutes and the excess diazomethane was quenched with acetic acid (4 mL). Concentration under reduced pressure afforded a brown oil containing the desired ester **302c** along with esters **303b** and **304b** (0.52 g), which were impossible to separate by standard column chromatography. Data for **302c**: δ_F (235 MHz, $CDCl_3$) -115.0 (1F, dt, J_{gem} 267.4, $^3J_{F\text{-}H}$ 8.6), -124.3 (1F, dt, J_{gem} 267.4, $^3J_{F\text{-}H}$ 12.6); *m/z* (EI) 295 (50 %, $[M\text{-}CH_3]^+$), 237 (100); Data for **303b**: δ_F (235 MHz, $CDCl_3$) -113.9 (1F, dt, J_{gem} 265.3, $^3J_{F\text{-}H}$ 3.3), -124.3 (1F, dd, J_{gem} 265.3, $^3J_{F\text{-}H}$ 15.9); *m/z* (EI) 253 (100 %, $[M\text{-}CH_3]^+$); Data for **304b**: δ_F (235 MHz, $CDCl_3$) -126.0 (1F, ddd, J_{gem} 257.4, $^3J_{F\text{-}H}$ 158.6, 2.7), -128.1 (1F, ddd, J_{gem} 257.4, $^3J_{F\text{-}H}$ 21.2, 4.0); *m/z* (EI) 271 (100 %, $[M\text{-}CH_3]^+$).

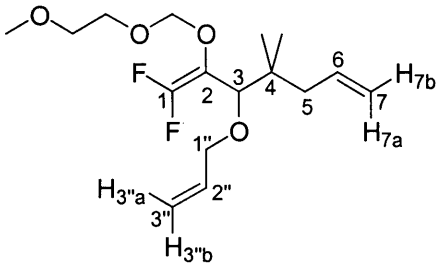
Preparation of 1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-dien-3-ol 336



Acetal **334** (30.0 mmol, 5.65 g) was added dropwise to a cold (-78 °C) solution of LDA (prepared by the slow addition of *n*BuLi (62.9 mmol, 26.0 mL of a 2.42 M solution in hexanes) to a cold (-78 °C) solution of di*iso*propylamine (63.0 mmol, 8.80 mL) in THF (60 mL) under a nitrogen atmosphere). The reaction was stirred at this temperature for 2 hours and 2,2-dimethyl-4-pentenal (36 mmol, 4.9 mL) was added in one portion. The mixture was allowed to warm to -30 °C over 2 hours and quenched

with ammonium chloride (40 mL of a saturated aqueous solution). Water (30 mL) was added and the mixture was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil (7.81 g). Kugelrohr distillation afforded the desired difluoroallylic alcohol **336** (7.56 g, 90 %) as a colourless oil. Bp 100 °C/0.1 mmHg; ν_{max} (film)/cm^{-1} 3401m br (O-H), 2934s (C-H), 2892s (C-H), 1639m (C=C); δ_H (300 MHz, $CDCl_3$) 5.80-5.75 (1H, m, H-6), 5.06-5.02 (2H, m, H-7a and H-7b), 5.02 (1H, d, J_{gem} 6.3, -OC*H*$_a$H$_b$O-), 4.83 (1H, d, J_{gem} 6.3, -OCH$_a$*H*$_b$O-), 3.96-3.89 (2H, m, -OC*H*$_2$CH$_2$OCH$_3$), 3.79-3.72 (1H, m, H-3), 3.57-3.54 (2H, m, -OCH$_2$C*H*$_2$OCH$_3$), 3.38 (3H, s, -OC*H*$_3$), 3.18 (1H, br s, -O*H*), 2.01 (1H, dd, J_{gem} 13.5, *J* 7.7, H-5a), 2.14 (1H, dd, J_{gem} 13.5, *J* 7.7, H-5b), 0.93 (3H, s, -C*H*$_3$), 0.88 (3H, s, -C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 155.0 (dd, $^1J_{C\text{-}F}$ 291.6, 285.4), 135.0, 117.5, 98.5 (dd, $^2J_{C\text{-}F}$ 4.5, 2.8), 72.6 (t, $^3J_{C\text{-}F}$ 2.6), 71.5, 69.0, 59.0, 55.9, 43.5, 39.0 (t, $^4J_{C\text{-}F}$ 2.3), 23.1, 22.9; δ_F (282 MHz, $CDCl_3$) -100.3 (1F, d, *J* 66.1), -108.1 (1F, dd, *J* 66.1, $^4J_{F\text{-}H}$ 4.5); [HRMS (ES, $[M+Na]^+$) Found: 303.1382, calc. for $C_{13}H_{22}O_4F_2Na$: 303.1384]; *m/z* (ES) 303 (100 %, $[M+Na]^+$).

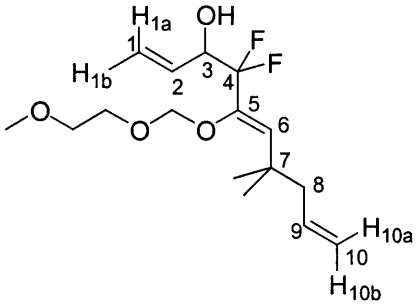
Preparation of 3-allyloxy-1,1-difluoro-2-(2'-methoxy-ethoxymethoxy)-4,4-dimethyl-hepta-1,6-diene 337



A mixture of difluoroallylic alcohol **336** (25.8 mmol, 7.25 g), allyl bromide (31 mmol, 2.7 mL), 50 % aqueous sodium hydroxide (181 mmol, 9.50 mL) and tetra-*n*-butylammonium hydrogensulfate (1.29 mmol, 430 mg) was stirred at 0 °C for 30 min.

The mixture was allowed to warm to room temperature, stirred overnight, quenched with ammonium chloride (30 mL of a saturated aqueous solution), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired ether **337** as a pale yellow oil (7.54 g, 91 %), which was used without any further purification. R_f (10 % diethyl ether in light petroleum) 0.26; ν_{max} (film)/cm^{-1} 2957s (C-H), 2930s (C-H), 1638m (C=C); δ_H (300 MHz, $CDCl_3$) 5.93-5.72 (2H, m, H-6 and H-2''), 5.26 (1H, dq, J_{trans} 17.3, J_{gem} 1.5, ^4J 1.5, H-3''a), 5.15 (1H, dq, J_{cis} 5.1, J_{gem} 1.5, ^4J 1.5, H-3''b), 5.05-4.97 (2H, m, H-7a and H7b), 4.99 (1H, d, J_{gem} 5.9, -OCH_aH_bO-), 4.88 (1H, d, J_{gem} 5.9, -OCH_aH_bO-), 4.13-3.71 (4H, m, -$OCH_2CH_2OCH_3$), 3.62 (1H, dd, $^4J_{H\text{-}F}$ 4.1, 2.2, H-3), 3.57-3.51 (2H, m, H-1''), 3.38 (3H, s, -OCH_3), 2.16 (1H, dd, J_{gem} 13.6, ^3J 7.7, H-5a), 2.04 (1H, dd, J_{gem} 13.6, ^3J 7.7, H-5b), 0.99 (3H, s, -CH_3), 0.91 (3H, s, -CH_3); δ_C (75 MHz, $CDCl_3$) 156.9 (dd, $^1J_{C\text{-}F}$ 293.9, 286.0), 135.0, 134.4, 117.4, 117.0, 112.1 (dd, $^2J_{C\text{-}F}$ 33.9, 10.2), 97.2 (dd, $^3J_{C\text{-}F}$ 4.0, 2.8), 80.1 (t, $^4J_{C\text{-}F}$ 2.8), 71.7, 69.8, 68.3, 59.0, 44.0, 38.5 (t, $^4J_{C\text{-}F}$ 1.7), 23.5, 23.1; δ_F (282 MHz, $CDCl_3$) -97.4 (1F, d, J 61.7), -108.2 (1F, d, J 61.7); [HRMS (ES, $[M+Na]^+$) Found: 343.1698, calc. for $C_{16}H_{26}O_4F_2Na$: 343.1697]; *m/z* (ES) 343 (100 %, $[M+Na]^+$).

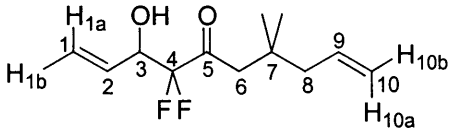
Preparation 4,4-difluoro-5-(2'-methoxy-ethoxymethoxy)-7,7-dimethyl-deca-1,5,9-trien-3-ol 338



A solution of allyl ether **337** (21.3 mmol, 6.83 g) in THF (20 mL) was added dropwise to a cold (-78 °C) solution of LDA (prepared by the slow addition of *n*BuLi (46.9 mmol, 19.4 mL of a 2.42 M solution in hexanes) to a cold (-78 °C) solution of diisopropylamine (43 mmol, 6.0 mL) in THF (40 mL) under a nitrogen atmosphere) After stirring for 2 hours at -78 °C, the solution was warmed slowly to -30 °C and stirred at this temperature for 18 hours. The reaction mixture was quenched with ammonium chloride (40 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 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil. Purification by column chromatography (30 % diethyl ether in light petroleum) afforded the alcohol **338** as a yellow oil (2.71 g, 55 %). R_f (30 % diethyl ether in light petroleum) 0.26; ν_{max} (film)/cm^{-1} 3432m br (O-H), 2959s (C-H), 2929s (C-H), 1668w (C=C), 1639m (C=C); δ_H (300 MHz, $CDCl_3$) 5.95-5.68 (2H, m, H-2 and H-9), 5.46 (1H, d, J_{trans} 17.3, H-1a), 5.40 (1H, s, H-6), 5.33 (1H, d, J_{cis} 10.7 H-1b), 5.04-4.98 (4H, m, H-10a, H-10b, and -O*CH*$_2$O-), 4.58-4.50 (1H, m, H-3), 3.85-3.81 (2H, m, -O*CH*$_2$CH$_2$OCH$_3$), 3.58-3.55 (2H, m, -OCH$_2$*CH*$_2$OCH$_3$), 3.37 (3H, s, -O*CH*$_3$), 2.71 (1H, br s, -O*H*), 2.15 (2H, d, *J* 6.6, H-8), 1.13 (3H, s, -C*H*$_3$), 1.12 (3H, s, -C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 142.3 (t, $^2J_{C-F}$

24.9), 135.2, 132.4 (t, $^{3}J_{C\text{-}F}$ 3.1), 128.4 (t, $^{3}J_{C\text{-}F}$ 5.4), 118.7, 118.4 (t, $^{1}J_{C\text{-}F}$ 250.1), 117.1, 98.2, 72.6 (t, $^{2}J_{C\text{-}F}$ 28.5), 71.4, 68.8, 58.8, 47.4, 35.0, 27.8; δ_F (282 MHz, $CDCl_3$) -109.9 (1F, dd, J_{gem} 251.8, $^{3}J_{F\text{-}H}$ 10.1), -112.0 (1F, dd, J_{gem} 251.8, $^{3}J_{F\text{-}H}$ 12.7); [HRMS (ES, $[M+Na]^+$) Found: 343.1694, calc. for $C_{16}H_{26}O_4F_2Na$: 343.1697]; *m/z* (ES) 365 (16%, $[M+2Na-H]^+$), 343 (100, $[M+Na]^+$).

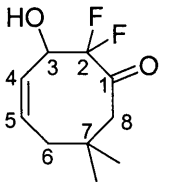
Preparation of 4,4-difluoro-3-hydroxy-7,7-dimethyl-deca-1,9-dien-5-one 339



Thionyl chloride (6.7 mmol, 0.49 mL) was added dropwise to a cold (0 °C) solution of alcohol **338** (6.70 mmol, 2.15 g) in methanol (50 mL). The mixture was allowed to warm to room temperature and stirred for 4 hours. The methanol was removed under reduced pressure. The residue was taken up in water (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil. Purification by column chromatography (10 % diethyl ether in light petroleum) afforded the hydroxyketone **339** as a yellow oil (1.01 g, 65 %). R_f (10 % diethyl ether in light petroleum) 0.23; ν_{max} (film)/cm^{-1} 3453m br (O-H), 2961s (C-H), 1740s (C=O), 1639m (C=C); δ_H (300 MHz, $CDCl_3$) 5.96-5.69 (2H, m, H-2 and H-9), 5.49 (1H, dt, $^{3}J_{trans}$ 17.3, J_{gem} 1.5, ^{4}J 1.5, H-1a), 5.41 (1H, dt, $^{3}J_{cis}$ 10.7, J_{gem} 1.5, ^{4}J 1.5, H-1b), 5.07-4.97 (2H, m, H-10a and H-10b), 4.61-4.50 (1H, m, H-3), 2.59 (2H, s, H-6), 2.49 (1H, d, ^{3}J 5.5, -O*H*), 2.13 (2H, dt, ^{2}J 7.7, ^{4}J 1.1, H-8), 1.02 (6H, s, -CH_3); δ_C (75 MHz, $CDCl_3$) 201.2 (dd, $^{2}J_{C\text{-}F}$ 30.0, 27.1), 134.6, 131.5 (t, $^{3}J_{C\text{-}F}$ 2.8), 120.2, 117.9, 114.5 (dd, $^{1}J_{C\text{-}F}$ 261.7, 257.7), 72.0 (dd, $^{2}J_{C\text{-}F}$ 28.3, 24.9), 47.1, 46.0, 33.5, 26.9; δ_F (282 MHz, $CDCl_3$) -113.8 (1F, dd, J_{gem} 274.7, $^{3}J_{F\text{-}H}$ 7.6), -122.8 (1F, dd, J_{gem} 274.7, $^{3}J_{F\text{-}H}$ 15.2); [HRMS (ES,

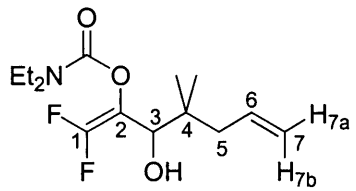
$[M+NH_4]^+$) Found: 250.161786, calc. for $C_{12}H_{22}NO_2F_2$: 250.161864]; *m/z* (ES) 343 (100 %, $[M+Na]^+$); *m/z* (CI) 250 (100 %, $[M+NH_4]^+$), 230 (13), 210 (31), 193 (92).

Preparation of 2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooct-4-enone 348



Titanium (IV) *iso*propoxide (0.60 mmol, 0.18 mL) was added to a solution of diene **339** (2 mmol, 0.46 g) in dry degassed DCM (200 mL). This solution was refluxed for 1 hour and Grubbs' catalyst (0.1 mmol, 41 mg) was added as solution in dry degassed DCM (10 mL) and the reaction mixture was further refluxed for 24 hours. Evaporation under reduced pressure of the solvent followed by column chromatography (30 % diethyl ether in light petroleum) afforded cyclooctenone **348** as a pale yellow oil (0.32 g, 78 %). R_f (30 % diethyl ether in light petroleum) 0.23; ν_{max} (film)/cm^{-1} 3444s (O-H), 3033w (=C-H), 2963m (C-H), 2928m (C-H), 2870m (C-H), 1738s (C=O), 1652w (C=C); δ_H (400 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, -O*H*), 2.50 (1H, dd, J_{gem} 12.0, $^4J_{H-F}$ 2.7, H-8a), 2.35 (1H, d, J_{gem} 12.0, H-8b), 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, $^2J_{C-F}$ 25.7), 131.8, 129.3 (d, $^3J_{C-F}$ 3.3), 117.3 (t, $^1J_{C-F}$ 258.2), 68.1 (t, $^2J_{C-F}$ 23.2), 47.6, 40.2, 37.7, 30.6, 26.9; δ_F (376 MHz, $CDCl_3$, 223 K) **major conformer:** -108.3 (1F, d, J_{gem} 240.4), -136.1 (1F, dd, J_{gem} 240.4, $^3J_{F-H}$ 20.3), **minor conformer:** -115.4 (1F, d, J_{gem} 229.3), -129.1 (1F, dd, J_{gem} 229.3, $^3J_{F-H}$ 26.1); [HRMS (ES, $[M+Na]^+$) Found: 227.0860, calc. for $C_{10}H_{14}O_2F_2Na$: 227.0860]; *m/z* (ES) 227 (100, $[M+Na]^+$).

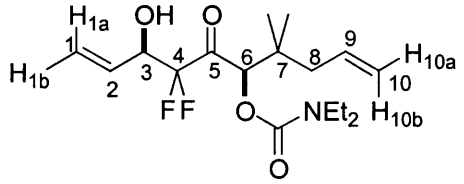
Preparation of 2-(*N,N*-diethylcarbamoyloxy)-1,1-difluoro-4,4-dimethyl-hepta-1,6-dien-3-ol 352[124]

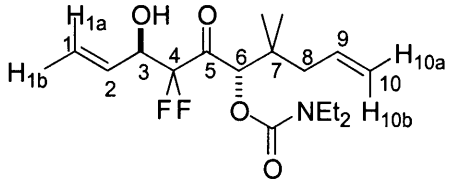


Carbamate **352** was prepared by following a procedure described by Thomas.[124] *n*BuLi (394 mmol, 246.3 mL of a 1.6 N solution in hexanes) was added dropwise to a cold (-70 °C) solution of di*iso*propylamine (394 mmol, 55.2 mL) in dry THF (750 mL). After completion of the addition, the mixture was allowed to warm to -30 °C and recooled to -70 °C. A solution of carbamate **349** (197 mmol, 39.24 g) in THF (250 mL) was added at a rate to maintain the temperature between -70 °C and -60 °C. After completion of the addition the mixture changed from yellow to purple through orange and red. 2,2-Dimethyl-4-pentenal (217 mmol, 29.5 mL) was then added at a rate to maintain the temperature between -70 °C and -60 °C and the mixture was stirred for 1 hour at -70 °C. Boron trifluoride dimethyl etherate (394 mmol, 50.0 mL) was added in one portion and the reaction mixture was allowed to warm to 0 °C over 2 hours and stirred at this temperature for 1 hour. During this time, the solution turned from purple to yellow through green. The reaction mixture was quenched with ammonium chloride (750 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 x 750 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil, which was combined with the crude product from a second batch on the same scale to afford a total of 121.0 g of an orange oil. Purification by (Biotage) column chromatography (15 % diethyl ether in light petroleum) afforded the desired alcohol **352** as a pale yellow oil

(75.74 g, 66 %, 100 % by GC). R_f (15% diethyl ether in light petroleum) 0.24; ν_{max} (film)/cm^{-1} 3448s br (O-H), 3075m (=C-H), 2977s (C-H), 2937s (C-H), 1762s (C=O), 1710s (C=O), 1639m (C=C); δ_H (250 MHz, $CDCl_3$) 5.85-5.68 (1H, m, H-6), 5.01 (1H, s, H-7a), 4.98-4.93 (1H, m, H-7b), 4.08 (1H, dd, $^4J_{H\text{-}F}$, *J* 1.8, H-3), 3.56 (1H, br s, -O*H*), 3.33-3.19 (4H, m, -N(CH_2CH_3)$_2$), 2.12 (1H, dd, J_{gem} 13.5, *J* 7.4, H-5a), 1.94 (1H, dd, J_{gem} 13.5, *J* 7.3, H-5b), 1.15-1.07 (6H, m, -N(CH_2CH_3)$_2$), 0.89 (3H, s, -CH_3), 0.84 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 155.6 (dd, $^1J_{C\text{-}F}$ 292.5, 285.8), 155.4, 135.2, 117.8, 112.2 (dd, $^2J_{C\text{-}F}$ 39.7, 11.7), 72.8, 43.7, 43.1, 42.4, 39.0, 23.2, 22.9, 14.3, 13.4; δ_F (235 MHz, $CDCl_3$) -96.2 (1F, d, J_{gem} 53.1), -105.0 (1F, dd, J_{gem} 53.1, $^4J_{F\text{-}H}$ 4.0); [HRMS (ES, $[M+Na]^+$ Found: 314.1536, calc. for $C_{14}H_{23}NO_3F_2Na$: 314.1544]; *m/z* (ES) 314 (100 %, $[M+Na]^+$). Spectral data were in agreement with those reported by Thomas.[124]

Preparation of 6-(*N,N*-diehtylcarbamoyloxy)-4,4-difluoro-3-hydroxy-7,7-dimethyl-deca-1,9-dien-5-ones *syn*-355 and *anti*-355[124]



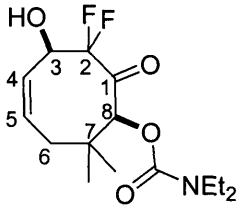


Aldol products *syn*-**355** and *anti*-**355** were prepared by modifying a procedure described by Thomas.[124] *n*BuLi (120 mmol, 75 mL of a 1.6 N solution in hexanes) was added dropwise to a cold (-78 °C) solution of alcohol **352** in THF (1 L). After completion of the addition, the mixture was allowed to warm to -10 °C and acrolein (132 mmol, 8.8 mL) was added dropwise as a solution in THF (100 mL). After completion of the addition the mixture was allowed to warn to 0 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched with ammonium chloride

(1 L of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 x 750 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$) filtered and concentrated under reduced pressure to afford a pale yellow oil, which was combined with the crude product from a second batch on the same scale to afford a total of 100.6 g of a 1:1 diastereoisomeric mixture (1:1) of aldol products *syn*-**355** and *anti*-**355** as a pale yellow oil. Purification by (Biotage) column chromatography (1 to 5% ethyl acetate in light petroleum) allowed he separation of the diastereoisomers. **Diastereoisomer 1** (*syn*-**355**)[120] was obtained as a colourless oil (25.06 g, 33 %, 98 % by GC). R_f (15 % ethyl acetate in light petroleum) 0.23; ν_{max} (film)/cm^{-1} 3407s br (O-H), 3078m (=C-H), 2979s (C-H), 2935s (C-H), 2978s (C-H), 1740s (C=O), 1684s (C=O), 1650m (C=C), 1640m (C=C) ; δ_H (250 MHz, $CDCl_3$) 5.96-5.66 (2H, m, H-2 and H-9), 5.52 (1H, ddd, J_{trans} 17.2, J_{gem} 1.4, ^4J 1.6, H-1a), 5.36 (dt, J_{cis} 10.6, J_{gem} 1.4, ^4J 1.4, H-1b), 5.08-4.94 (4H, m, H-10a, H-10b, H-6 and -O*H*), 4.51 (1H, dd, $^3J_{F-H}$ 22.0, *J* 5.4, H-3), 3.32-3.10 (4H, m, -N(CH_2CH_3)$_2$), 2.18 (1H, dd, J_{gem} 13.5, *J* 7.8, H-8a), 2.03 (1H, dd, J_{gem} 13.5, *J* 6.9, H-8b), 1.16 (3H, t, *J* 7.1, -N(CH_2CH_3)$_2$), 1.06-0.95 (9H, m, -N(CH_2CH_3)$_2$ and 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 201.8 (dd, $^2J_{C-F}$ 36.4, 22.2), 155.6, 133.6, 131.2, 120.3, 119.2, 115.3 (dd, $^1J_{C-F}$ 266.8, 256.6), 80.5, 71.7 (dd, $^2J_{C-F}$ 28.7, 22.6), 44.4, 42.8, 42.2, 38.5, 23.5, 23.4, 14.3, 13.6; δ_F (235 MHz, $CDCl_3$) -106.2 (1F, d, J_{gem} 262.7), -132.4 (1F, dd, J_{gem} 262.7, $^3J_{F-H}$ 22.5); *m/z* (ES) 348 (100 %, $[M+H]^+$). Spectral data were in agreement with those reported by Thomas.[124]. **Diastereoisomer 2** (*anti*-**355**)[120] was obtained as a colourless oil (23.54 g, 31 %, 100 % by GC). R_f (15 % ethyl acetate in light petroleum) 0.17; ν_{max}(film)/cm^{-1} 3397s br (O-H), 3078m (=C-H), 2977s (C-H), 2936m (C-H), 2880m (C-H), 1745s (C=O), 1703s (C=O), 1651m (C=C), 1640m (C=C); δ_H (250 MHz, $CDCl_3$) 5.93-5.66 (2H, m, H-2 and H-9), 5.39 (1H, d,

J_{trans} 17.0, H-1a), 5.26 (1H, dd, J_{cis} 10.6, J_{gem} 1.4, H-1b), 5.08-4.94 (3H, m, H-10a, H-10b and H-6), 4.54-4.37 (2H, m, H-3 and -O*H*), 3.30-3.12 (4H, m, -N(CH_2CH_3)$_2$), 2.16 (1H, dd, J_{gem} 13.6, *J* 7.9, H-8a), 2.03 (1H, dd, J_{gem} 13.6, *J* 7.1, H-8b), 1.14 (3H, t, *J* 7.1, -N(CH_2CH_3)$_2$), 1.05-0.95 (9H, m, -N(CH_2CH_3)$_2$ and 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 199.6 (dd, $^2J_{C\text{-}F}$ 33.6, 23.9), 155.6, 133.7, 132.1 (dd, $^3J_{C\text{-}F}$ 4.6, 1.5), 119.1, 118.8, 116.0 (t, $^1J_{C\text{-}F}$ 260.2), 80.0, 74.1 (t, $^2J_{C\text{-}F}$ 28.0), 44.4, 42.8, 42.3, 38.7, 23.5, 23.3, 14.4, 13.6; δ_F (235 MHz, $CDCl_3$) -113.6 (1F, dd, J_{gem} 261.4, $^3J_{F\text{-}H}$ 11.9), -115.5 (1F, d, J_{gem} 261.4); *m/z* (ES) 348 (100 %, $[M+H]^+$). Spectral data were in agreement with those reported by Thomas.[124]

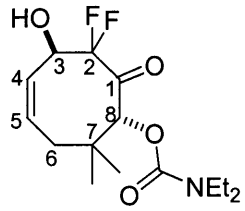
Preparation of *cis*-8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooct-4-en-1-one *cis-356*



Titanium (IV) *iso*propoxide (4.50 mmol, 1.33 mL) was added to a solution of diene *anti*-**355** (15.0 mmol, 5.21 g) in dry, degassed DCM (1.5 L) at room temperature. The reaction mixture was refluxed for 1 hour and Grubbs' catalyst (113 μmol, 309 mg) was added as a solution in DCM (10 mL). After 3 days more Grubbs' catalyst **92** (113 μmol, 309 mg) was added as a solution in DCM (10 mL) and the reaction was refluxed for another 4 days. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford a black solid (5.83 g). The black solid was filtered through a short pad of silica, eluting with 50 % ethyl acetate in light petroleum. Fractions containing the product were concentrated under reduced pressure to afford a green solid (3.80 g), which was recrystallised in diethyl

ether/light petroleum to afford the desired difluorinated cyclooctenone *cis*-**356** as colourless cubes (3.31 g, 69 %). R_f (50 % ethyl acetate in light petroleum) 0.41; Mp 117-118 °C; $\nu_{max}(KBr)_{/cm}^{-1}$ 3362s br (O-H), 2985m (C-H), 2943m (C-H), 1741s (C=O), 1693s (C=O); δ_H (400 MHz, $CDCl_3$, 323 K) 5.82 (1H, dd, *J* 11.0, 11.0, 11.0, H-5), 5.65 (1H, ddd, *J* 11.0, 11.0, 11.0, H-4), 5.09 (1H, s, H-8), 5.05-4.92 (1H, m, H-3), 3.59 (1H, br s, -O*H*), 3.34-3.14 (4H, m, -N(CH_2CH_3)$_2$), 2.32-2.19 (2H, m, H-6), 1.18-1.04 (9H, m, -N(CH_2CH_3)$_2$ and -CH_3), 0.97 (3H, s, -CH_3); δ_C (101 MHz, $CDCl_3$, 323 K) 195.8 (t, $^2J_{C\text{-}F}$ 26.0), 154.6, 132.0, 129.1, 116.5 (t, $^1J_{C\text{-}F}$ 260.2), 78.9, 67.6 (t, $^2J_{C\text{-}F}$ 23.8), 42.2, 41.7, 38.5, 28.4, 20.5, 13.9, 13.3; δ_F (376 MHz, $CDCl_3$, 223 K) **major conformer:** -102.4 (1F, d, J_{gem} 239.5), -133.4 (1F, dd, J_{gem} 239.5, $^3J_{F\text{-}H}$ 21.5), **minor conformer:** -110.8 (1F, d, J_{gem} 250.3), -110.4 (1F, d, J_{gem} 250.3); *m/z* (ES) 320 (46%, $[M+H]^+$). Spectral data were in agreement with those reported by Thomas.[124]

Preparation of *trans*-8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooct-4-en-1-one *trans*-356

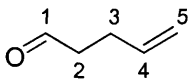


Method A: titanium (IV) *iso*propoxide (4.5 mmol, 1.33 mL), diene *syn*-**355** (15.0 mmol, 5.21 g) and Grubbs' catalyst (2 x 113 μmol, 2 x 309 mg) were treated as described previously for the preparation of *cis*-**356** to afford a crude black solid (6.78 g). The black solid was filtered though a short pad of silica eluting with 50 % ethyl acetate in light petroleum. Fractions containing the product were concentrated under reduced pressure to afford a green solid (4.02 g), which was recrystallised in diethyl ether/light petroleum to afford the desired difluorinated cyclooctenone *trans*-**356** as

colourless cubes (3.70 g, 77 %). **Method B:** titanium (IV) *iso*propoxide (1.5 mL, 0.44 mL) was added to a solution of diene *syn*-**355** (5.0 mmol, 1.74 g) in dry degassed DCM (500 mL) and the reaction mixture was refluxed for 1 hour. Nolan's catalyst (125 μmol, 106 mg) was added as a solution in dry degassed DCM (5 mL), the reaction mixture was refluxed for an additional 18 hours and concentrated under reduced pressure to leave a brown solid (2. 55g) Work up as described for method A afforded the desired cyclooctenone *trans*-**356** as colourless cubes (1.20 g, 75 %). **Method C:** a solution of diene *syn*-**355** (2.5 mmol, 0.87 g) and Nolan's catalyst (63 μmol, 53 mg) in dry degassed DCM (250 mL) was refluxed for 3 days and concentrated under reduced pressure to leave a pale brown solid (0.85 g). Work up as described for method A afforded the desired cyclooctenone *trans*-**356** as colourless cubes (0.65 g, 82 %). R_f (50 % ethyl acetate in light petroleum) 0.50; Mp 118-119 °C; ν_{max}(KBr)/cm^{-1} 3364s br (O-H), 2985m (C-H), 2943m (C-H), 1740s (C=O), 1685s (C=O); δ_H (400 MHz, $CDCl_3$, 243 K) **major conformer:** 5.90-5.84 (1H, m, H-5), 5.67-5.62 (1H, m, H-4), 4.70 (1H, s, H-8), 4.63 (1H, dd, $^3J_{H\text{-}F}$ 24.0, *J* 4.4, H-3), 3.32-3.12 (5H, m, -N(C*H*$_2$CH$_3$)$_3$ and -O*H*), 1.98 (1H, dd, J_{gem} 14.4, *J* 6.4, H-6a), 1.79 (1H, d, J_{gem} 14.4, H-6b), 1.15 (3H, s, -C*H*$_3$), 1.12 (3H, t, *J* 8.0, -N(CH$_2$C*H*$_3$)$_2$), 1.08 (3H, s, -C*H*$_3$), 1.05 (3H, t, *J* 7.0, -N(CH$_2$C*H*$_3$)$_2$), **minor conformer:** 5.85-5.76 (1H, m, H-5), 5.49 (1H, t, *J* 10.0, H-4), 5.28 (1H, t, $^3J_{H\text{-}F}$ 22.0, H-3), 4.96 (1H, s, H-8), 3.41-3.15 (5H, m, -N(C*H*$_2$CH$_3$)$_2$ and -O*H*), 2.60 (1H, dd, J_{gem} 13.6, *J* 9.6, H-6a), 1.84 (1H, t, J_{gem} 13.6, H-6b), 1.22 (3H, t, *J* 7.0, -N(CH$_2$C*H*$_3$)$_2$), 1.10 (3H, t, *J* 8.5, -N(CH$_2$C*H*$_3$)$_2$), 1.07 (3H, s, -C*H*$_3$), 0.99 (3H, s, -C*H*$_3$); δ_C (101 MHz, $CDCl_3$, 243 K) **major conformer:** 198.7 (t, $^2J_{C\text{-}F}$ 25.0), 154.9, 129.6, 127.8, 117.0 (t, $^1J_{C\text{-}F}$ 260.1), 75.3, 68.1 (t, $^2J_{C\text{-}F}$ 22.8), 41.9, 41.5, 38.4, 37.1, 26.5, 22.7, 13.9, 13.4, **minor conformer:** 194.7 (t, $^2J_{C\text{-}F}$ 23.5), 154.1, 132.8, 129.0 (d, $^3J_{C\text{-}F}$ 4.2), 116.4 (dd, $^1J_{C\text{-}F}$

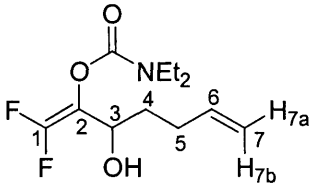
263.8, 256.3), 83.6, 67.1 (t, $^{2}J_{C\text{-}F}$ 21.2), 42.9, 42.1, 41.1, 35.0, 28.9, 22.4, 14.1, 13.0; δ_F (376 MHz, $CDCl_3$, 223 K) **major conformer:** -114.1 (1F, d, J_{gem} 233.5), -126.1 (1F, dd, J_{gem} 235.5, $^{3}J_{F\text{-}H}$ 25.8), **minor conformer:** -104.1 (1F, J_{gem} 248.5), -130.2 (1F, dd, J_{gem} 248.5, $^{3}J_{F\text{-}H}$ 21.8); *m/z* (ES) 320 (38 %, $[M+H]^+$). Spectral data were in agreement with those reported by Thomas.[124]

Preparation of pent-4-enal 358



Allylvinyl ether (530 mmol, 44.6 g) was heated at 150 °C in an Ace tube for 16 hours. The reaction mixture was allowed to cool, then distilled to afford the desired pentenal **358** as a colourless liquid (39.90 g, 90 %, 97 % by GC). Bp 103-105 °C/760 mmHg (Lit.[134] 100 °C/760 mmHg); ν_{max} (film)/cm^{-1} 3080 m (C-H), 2979 m (C-H), 1917 m (C-H), 1825 m (C-H), 2725 m (C-H), 1725 s (C=O); δ_H (250 MHz, $CDCl_3$) 9.99 (1H, t, *J* 1.5, H-1), 6.13-5.97 (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 (63 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.*.[134]

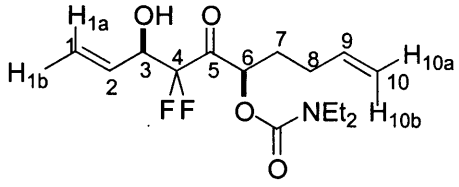
Preparation of 2-(*N,N*-diethylcarbamoyloxy)-1,1-difluoro-hepta-1,6-dien-3-ol 359

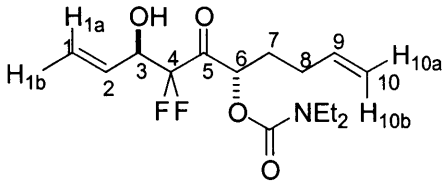


*n*BuLi (400 mmol, 160 mL of a 2.5 N solution in hexanes) was added dropwise to a cold (-70 °C) solution of di*iso*propylamine (400 mmol, 56.1 mL) in dry THF (750 mL). After completion of the addition, the mixture was allowed to warm to -30 °C and

recooled to -70 °C. A solution of carbamate **349** (200 mmol, 39.8 g) in THF (250 mL) was added at a rate to maintain the temperature between -70 °C and -60 °C. After completion of the addition the mixture changed from yellow to purple through orange and red. Pentenal **358** (220 mmol, 18.5 g) was then added at a rate to maintain the temperature between -70 °C and -60 °C and the mixture was stirred for 1 hour at -70 °C. Boron trifluoride dimethyl etherate (400 mmol, 51.0 mL) was added in one portion and the reaction mixture was allowed to warm to 0 °C over 2 hours and stirred at this temperature for 1 hour. During this time, the solution turned from purple to yellow through green. The reaction mixture was quenched with ammonium chloride (500 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 x 500 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil (54.30 g). Purification by column chromatography (20 % diethyl ether in light petroleum) afforded the desired alcohol **359** as a pale yellow oil (41.61 g, 79 %). R_f (20 % ether in light petroleum) 0.22; ν_{max}(film)/cm^{-1} 3448s br (O-H), 3079w (=C-H), 2978s (C-H), 2937s (C-H), 1769 (C=O), 1711s (C=O), 1641m (C=C) ; δ_H (250 MHz, $CDCl_3$); 5.75 (1H, ddt, J_{trans} 17.0, J_{cis} 10.2, J 6.7, H-6), 5.02-4.89 (2H, m, H-7a and H-7b), 4.37-4.31 (1H, m, H-3), 3.65 (1H, br s, -O*H*), 3.28 (4H, q, J 7.1, -N(CH_2CH_3)$_2$), 2.15-1.99 (2H, m, H-5), 1.78-1.49 (2H, m, H-4), 1.15-1.05 (6H, m, -N(CH_2CH_3)$_2$); δ_C (65 MHz, $CDCl_3$) 155.2, 155.0 (dd, $^1J_{C-F}$ 293.2, 285.6), 137.9, 115.5, 113.5 (dd, $^2J_{C-F}$ 42.5, 12.0), 66.6, 43.2, 42.6, 33.1, 29.9, 14.3, 13.5; δ_F (235 MHz, $CDCl_3$) -96.3 (1F, d, J_{gem} 51.8), -106.3 (1F, dd, J_{gem} 51.8, $^4J_{F-H}$ 2.6); [HRMS (FAB, $[M+H]^+$) Found: 264.14117, calc. for $C_{12}H_{20}NO_3F_2$: 264.14113]; *m/z* (FAB) 264 (20 %, $[M+H]^+$), 246 (100).

Preparation of 6-(*N,N*-diethylcarbamoyloxy)4,4-difluoro-3-hydroxy-deca-1,9-dien-5-ones *syn*-360 and *anti*-360

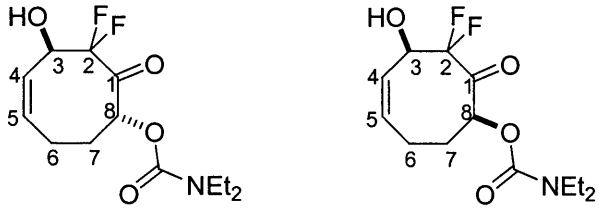




*n*BuLi (100 mmol, 40.0 mL of a 2.5 M solution in hexanes) was added dropwise to a cold (-78 °C) solution of alcohol **359** (100 mmol, 26.3 g) in THF (900 mL). After completion of the addition, the mixture was allowed to warm to -10 °C and acrolein (100 mmol, 7.3 mL) was added dropwise as a solution in THF (100 mL). After completion of the addition the mixture was allowed to warn to 0 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched with ammonium chloride (500 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 x 500 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$) filtered and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography (20 % ethyl acetate in light petroleum) afforded an inseparable diastereoisomeric mixture (1:2) of the desired aldol products *syn*-**360** and *anti*-**360** as a pale yellow oil (18.8 g, 58 %). R_f (20 % ethyl acetate in light petroleum) 0.28; ν_{max}(film)/cm^{-1} 3399s br (O-H), 3078w (=C-H), 2978s (C-H), 2937s (C-H), 2878s (C-H), 1744s (C=O), 1682s (C=O), 1640m (C=C); δ_H(250 MHz, $CDCl_3$) ***syn/anti*-mixture:** 5.98-5.66 (2H, m, H-2 and H-9), 5.56-5.29 (3H, m, H-1a, H-1b and H-10b), 5.04-4.97 (3H, m, H-10a, H-6 and -O*H*), 4.50-4.32 (1H, m, H-3), 3.32-3.15 (4H, m, -N(CH_2CH_3)$_2$), 2.24-1.68 (4H, m, H-7 and H-8), 1.17-1.02 (6H, m, -N(CH_2CH_3)$_2$; δ_C (65 MHz, $CDCl_3$) ***syn/anti*-mixture:** 200.0 (dd, $^2J_{C\text{-}F}$ 34.1, 21.9), 198.2 (dd, $^2J_{C\text{-}F}$ 30.5, 24.9), 155.8, 155.7, 136.8, 136.7, 131.3 (t, $^3J_{C\text{-}F}$ 3.1), 130.6 (d, $^3J_{C\text{-}F}$ 2.5), 120.5, 120.0, 116.9 (dd, $^1J_{C\text{-}F}$ 261.1, 256.6),

116.6, 116.5, 116.4 (dd, $^{1}J_{C\text{-}F}$ 261.4, 259.4), 76.9, 75.9, 73.4 (t, $^{2}J_{C\text{-}F}$ 27.2), 71.8 (dd, $^{2}J_{C\text{-}F}$ 29.0, 23.4), 42.7, 42.2, 29.9, 29.4 (d, $^{4}J_{C\text{-}F}$ 1.5), 29.2 (d, $^{4}J_{C\text{-}F}$ 2.5), 14.2, 14.1, 13.6 ; δ_F (235 MHz, $CDCl_3$) **major diastereoisomer** (*syn*-**360**)[120]: -109.8 (1F, d, J_{gem} 256.7), -133.9 (1F, dd, J_{gem} 256.7, $^{3}J_{F\text{-}H}$ 22.5), **minor diastereoisomer** (*anti*-**360**)[120]: -117.6 (d, $^{3}J_{F\text{-}H}$ 9.3); [HRMS (FAB, $[M+H]^+$) Found: 320.16737, calc. for $C_{15}H_{24}NO_4F_2$: 320.16734; *m/z* (FAB) 320 (100 %, $[M+H]^+$).

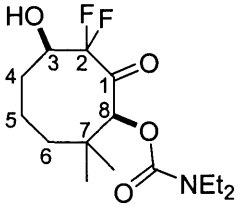
Preparation of 8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-3-hydroxy-cyclooct-4-en-1-ones *trans*-361 and *cis*-361



A solution of diastereoisomeric mixture (2:1) of dienes *syn*-**360** and *anti*-**360** (15.0 mmol, 4.79 g) and titanium (IV) *iso*propoxide (4.50 mmol, 1.16 mL) in DCM (1.5 L) was refluxed for 30 minutes. Nolan's catalyst **94** (150 μmol, 127 mg) was added as a solution in DCM (5 mL) and the reaction mixture was refluxed for 2 days. Another portion of Nolan's catalyst **94** (150 μmol, 127 mg) was added as a solution in DCM (5 mL) and the reaction mixture was stirred for an additional day. The mixture was concentrated under reduced pressure to leave a crude diastereoisomeric mixture (1:2) as a brown oil (4.53 g). Purification by column chromatography (40 % ethyl acetate in light petroleum) allowed the separation of the two diastereoisomers. **Major diastereoisomer** (*trans*-**361**) was obtained as a white solid (1.88 g, 43 %). R_f (40% ethyl acetate in light petroleum) 0.30; Mp 93-94 °C; (Found C, 53.17; H, 7.39; N, 4.79; $C_{13}H_{21}F_2NO_4$ requires: C, 53.23; H, 7.22; N, 4.78 %); ν_{max}(KBr)/cm^{-1} 3393s br

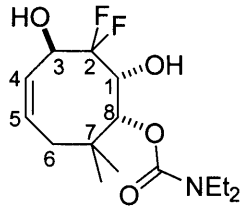
(O-H), 2978m (C-H), 1741s (C=O), 1686s (C=O); δ_H (400 MHz, $CDCl_3$, 323 K) 5.94-5.86 (1H, m, H-4), 5.57-5.52 (1H, m, H-5), 5.41 (1H, dt, *J* 7.0, 3.4, ^4J 3.4, H-8), 5.09-4.98 (1H, m, H-3), 3.38-3.29 (5H, m, -O*H* and -N(CH_2CH_3)$_2$), 2.41-1.99 (4H, env., H-6 and H-7), 1.20-1.12 (6H, m, -N(CH_2CH_3)$_2$); δ_C (63 MHz, $CDCl_3$) 198.5 (t, $^2J_{C\text{-}F}$ 24.6), 154.6, 132.9, 129.5 (d, $^3J_{C\text{-}F}$ 5.1), 117.9 (t, $^1J_{C\text{-}F}$ 260.9), 75.5, 68.4 (t, $^2J_{C\text{-}F}$ 22.1), 42.6, 41.9, 32.4, 22.7, 14.3, 13.6; δ_F (376 MHz, $CDCl_3$, 223 K) **major conformer:** -107.6 (1F, d, J_{gem} 246.1), -131.5 (1F, dd, J_{gem} 246.1, $^3J_{F\text{-}H}$ 21.8), **minor conformer:** -114.8 (1F, d, J_{gem} 231.7), -128.0 (1F, br d, J_{gem} 231.7); [HRMS (FAB, $[M+H]^+$) Found: 292.13608, calc. for $C_{13}H_{20}NO_4F_2$: 292.13604], *m/z* (ES) 292 (100 %, $[M+H]^+$). An analytical sample was recrystallised by vapour diffusion to afford colourless cubes, which were used to obtain an X-ray crystal structure of cyclooctene *trans*-**361**. **Minor diastereoisomer** (*cis*-**361**) was obtained as a pale yellow solid (0.87 g, 20 %). R_f (40 % ethyl acetate in light petroleum) 0.24; Mp 51-52 °C; (Found C, 53.37; H, 7.20; N, 4.65; $C_{13}H_{21}F_2NO_4$ requires: C, 53.23; H, 7.22; N, 4.78 %); ν_{max}(KBr)/cm^{-1} 3393s br (O-H), 2977m (C-H), 1741s (C=O), 1687s (C=O); δ_H (400 MHz, $CDCl_3$, 323 K) 5.93-5.86 (1H, m, H-4), 5.70-5.55 (1H, m, H-5), 5.33-5.30 (1H, m, H-8), 5.07-4.99 (1H, m, H-3), 3.35-3.29 (5H, m, -N(CH_2CH_3)$_2$ and -O*H*), 2.47-1.85 (4H, H-6 and H-7), 1.17-1.13 (6H, m, -N(CH_2CH_3)$_2$); δ_C (63 MHz, $CDCl_3$) 196.0 (dd, $^2J_{C\text{-}F}$ 27.2, 23.9), 153.4, 132.2, 127.1 (d, $^3J_{C\text{-}F}$ 5.6), 115.5 (t, $^1J_{C\text{-}F}$ 260.4), 73.0 (d, $^3J_{C\text{-}F}$ 2.5), 66.1 (dd, $^2J_{C\text{-}F}$ 25.4, 20.9), 41.2, 40.6, 32.3, 22.2, 12.8, 12.3; δ_F (376 MHz, $CDCl_3$, 323 K) **major conformer:** -106.7 (1F, d, J_{gem} 244.7), -131.3 (1F, dd, J_{gem} 244.7, $^3J_{F\text{-}H}$ 18.9), **minor conformer:** -115.1 (1F, d, J_{gem} 263.0), -119.2 (1F, dd, J_{gem} 263.0, $^3J_{F\text{-}H}$ 17.6); [HRMS (FAB, $[M+H]^+$) Found: 292.13606, calc. for $C_{13}H_{20}NO_4F_2$: 292.13604], *m/z* (ES) 292 (100 %, $[M+H]^+$).

Preparation of *cis*-8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-3-hydroxy-7,7-dimethyl-cyclooctan-1-one 362



A suspension of alkene *cis*-**356** (320 mg, 1.0 mmol) and palladium on carbon (106 mg) in ethanol (20 mL) was stirred under an atmosphere of hydrogen for 2 days. The reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (30 % ethyl acetate in light petroleum) to afford the desired cyclooctanone **362** as a white solid (320 mg, 100 %). R_f (40 % ethyl acetate in light petroleum) 0.35; Mp 112-113 °C; (Found C, 56.14; H, 7.69; N, 4.44; $C_{15}H_{25}F_2NO_4$ requires: C, 56.06; H, 7.84; N, 4.36 %); ν_{max}(KBr)/cm^{-1} 3400s br (O-H), 2978m (C-H), 2940m (C-H), 2977m (C-H), 1708s (C=O), 1674s (C=O); δ_H (250 MHz, $CDCl_3$) 5.01 (1H, s, H-8), 4.34-4.21 (1H, m, H-3), 3.25-3.11 (4H, m, -N(C*H*$_2$CH$_3$)$_2$), 1.82-1.13 (12H, env., H-4, H-5, H-6 and -N(CH$_2$C*H*$_3$)$_2$), 1.02 (3H, s, -C*H*$_3$), 0.92 (3H, s, -C*H*$_3$); δ_C (63 MHz, $CDCl_3$) 199.3 (t, $^2J_{C\text{-}F}$ 27.0), 155.3, 115.2 (t, $^1J_{C\text{-}F}$ 255.6), 79.1, 71.6 (t, $^2J_{C\text{-}F}$ 25.9), 42.6, 42.0, 39.8, 39.4, 31.8, 29.6, 20.6, 16.1, 14.4, 13.7; δ_F (376 MHz, $CDCl_3$, 223 K) **major conformer:** -104.7 (1F, d, J_{gem} 263.2), -135.6 (1F, unresolved s), **minor conformer:** -103.9 (1F, d, J_{gem} 266.5), -116.0 (1F, d, J_{gem} 266.5); [HRMS (FAB, $[M+H]^+$) Found: 322.18302, calc. for $C_{15}H_{26}NO_4F_2$: 322.18299]; *m/z* (FAB) 322 (100 %, $[M+H]^+$). An analytical sample was recrystallised by vapour diffusion (ethyl acetate/light petroleum) to afford colourless needles, which were used to obtain an X-ray crystal structure of cyclooctane **362** (**Appendix 2**).

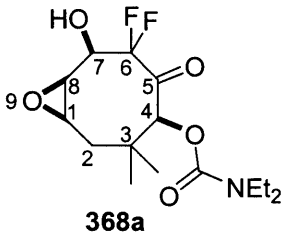
Preparation of 8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-7,7-dimethyl-cyclooct-4-en-1,3-diol 363



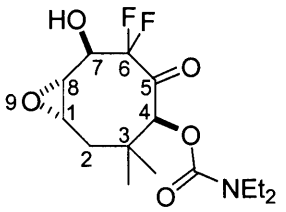
Sodium borohydride (1.8 mmol, 70 mg) was added in 5 portions to a cold (0 °C) solution of ketone *trans*-**356** (1.8 mmol, 0.59 g) in ethanol (10 mL). After completion of the addition, the reaction mixture was allowed to warm to room temperature, stirred for 2 hours at this temperature and poured over a mixture of ice and water (25 mL). HCl (10 mL of a 1N solution) was added cautiously and the mixture was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a white solid (0.51 g). Purification by column chromatography (40 % ethyl acetate in light petroleum) afforded the desired diol **363** as a white solid (0.43 g, 72 %). R_f (40 % ethyl acetate in light petroleum) 0.29; Mp 115-116 °C; (Found C, 56.17; H, 7.71; N, 4.29; $C_{15}H_{25}F_2NO_4$ requires: C, 56.06; H, 7.84; N, 4.36 %); ν_{max}(KBr)/cm^{-1} 3460s br (O-H), 3356s br (O-H), 2977m (=C-H), 2877m (C-H), 1671s (C=O); δ_H (250 MHz, $CDCl_3$) 5.83 (1H, dd, *J* 18.5, *J* 9.0, H-5), 5.53 (1H, t, *J* 9.0, *J* 9.0, H-4), 4.84 (1H, ddd, $^3J_{H\text{-}F}$ 21.3, 8.0, *J* 4.1, H-3), 4.48 (1H, d, *J* 5.7, H-8), 4.18-4.04 (1H, m, H-1), 3.42-3.10 (5H, m, -O*H* and -N(CH_2CH_3)$_2$), 2.45 (1H, dd, J_{gem} 13.8, *J* 8.5, H-6a), 2.17 (1H, br s, -O*H*), 1.77 (1H, dd, J_{gem} 13.8, *J* 8.3, H-6b), 1.18-0.93 (12H, m, -N(CH_2CH_3)$_2$ and 2 x -CH_3); δ_C(63 MHz, $CDCl_3$) 157.4, 131.4, 131.3 (d, $^3J_{C\text{-}F}$ 6.6), 122.8 (dd, $^1J_{C\text{-}F}$ 253.1, 246.9), 87.4 (d, $^3J_{C\text{-}F}$ 9.2), 70.8 (dd, $^2J_{C\text{-}F}$ 23.9, 19.8), 68.4 (dd, $^2J_{C\text{-}F}$ 23.9, 20.9), 42.8, 42.0, 39.8, 34.9, 30.4, 24.3, 14.5, 13.4; δ_F (235 MHz, $CDCl_3$) -118.5 (1F, dddd, J_{gem} 241.5, $^3J_{H\text{-}F}$ 21.2, 10.6, $^4J_{F\text{-}H}$ 6.6), -122.1 (1F, dd, J_{gem} 241.5, $^3J_{F\text{-}H}$ 16.6); [HRMS

(FAB, $[M+H]^+$) Found: 322.18293, calc. for $C_{15}H_{26}NO_4F_2$: 322.18299] ; *m/z* (FAB) 322 (100 %, $[M+H]^+$). An analytical sample was recrystallised by vapour diffusion (ethyl acetate/light petroleum) to afford colourless needles, which were used to obtain an X-ray crystal structure of **363** (**Appendix 2**).

Preparation of 4-(*N,N*-diethylcarbamoyloxy)-6,6-difluoro-7-hydroxy-3,3-dimethyl-9-oxa-bicyclo[6.1.0]non-5-ones 368a and 368b



368a

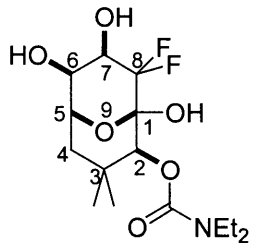


368b

Freshly recrystallised *m*CPBA (0.69 g, 4.0 mmol) was added to solution of cyclooctenone *cis*-**356** (0.64 g, 2.0 mmol) in DCM (10 mL). The mixture was refluxed for 18 hours, filtered and washed successively with sodium sulfite (10 mL of a saturated aqueous solution) and sodium hydrogencarbonate (10 mL of a saturated aqueous solution). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude mixture of diastereoisomers of epoxides **368a** and **368b** as a white solid (0.63 g). Purification by column chromatography (10 % ethyl acetate in light petroleum) allowed the separation of the diastereoisomers. **Diastereoisomer 1** (**368a**) was obtained as a white solid (275 mg, 41 %). R_f (10 % ethyl acetate in light petroleum) 0.30; Mp 146-147 °C; (Found C, 53.87; H, 7.02; N, 4.23; $C_{15}H_{23}F_2NO_5$ requires: C, 53.72; H, 6.91; N, 4.18 %); ν_{max} (KBr)/cm^{-1} 3332s br (O-H), 2981s (C-H), 2934m (C-H), 1746s (C=O), 1694s (C=O); δ_H (250 MHz, $CDCl_3$) 5.30 (1H, d, $^4J_{F\text{-}H}$ 2.1, H-4), 4.90 (1H, ddd, $^3J_{F\text{-}H}$ 11.5, 4.4, *J* 2.1, H-7), 3.57-3.36 (6H, m, H-1, H-8 and -N(CH_2CH_3)$_2$), 2.78 (1H, br s, -O*H*), 2.17 (1H,

dd, J_{gem} 14.5, J 3.3, H-2a), 1.90 (1H, dd, J_{gem} 14.5, J 11.5, H-2b), 1.46 (3H, s, -CH_3), 1.39-1.26 (9H, m, -N(CH_2CH_3)$_2$ and -CH_3); δ_C (63 MHz, $CDCl_3$) 196.0 (dd, $^2J_{C\text{-}F}$ 27.2, 24.7), 155.1, 116.6 (t, $^1J_{C\text{-}F}$ 257.6), 76.7, 68.8 (dd, $^2J_{C\text{-}F}$ 32.8, 27.2), 53.1, 52.9, 42.7, 42.1, 38.1, 37.5, 27.0, 23.9, 14.5, 13.8; δ_F (235 MHz, $CDCl_3$) -108.6 (1F, dd, J_{gem} 266.7, $^3J_{F\text{-}H}$ 11.3), -111.8 (1F, d, J_{gem} 266.7); [HRMS (FAB, $[M+H]^+$) Found: 336.16221, calc. for $C_{15}H_{24}NO_5F_2$: 336.16225]; *m/z* (ES) 336 (100 %, $[M+H]^+$). An analytical sample was recrystallised by vapour diffusion (ethyl acetate/light petroleum) to afford colourless plates, which were used to obtain an X-ray crystal structure of epoxide **368a** (**Appendix 2**). **Diastereoisomer 2** (**368b**) was obtained as a white solid (243 mg, 36 %). 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} (KBr)/cm^{-1} 3328s br (O-H), 2981s (C-H), 2934m (C-H), 1746s (C=O), 1682s (C=O); δ_H (376 MHz, $CDCl_3$, 323 K) 5.04 (1H, d, $^4J_{H\text{-}F}$ 1.8), 4.00 (1H, dt, $^3J_{H\text{-}F}$ 19.2, 7.7, J 7.7), 3.35-3.30 (4H, m, -N(CH_2CH_3)$_2$), 3.12-3.02 (3H, m, H-1, H-8 and -O*H*), 2.22 (1H, dd, J_{gem} 15.0, J 4.2, H-2a), 1.38-1.30 (1H, m, H-2b), 1.26-1.12 (12H, m, -N(CH_2CH_3)$_2$ and 2 x -CH_3); δ_C (63 MHz, $CDCl_3$) 196.5 (t, $^2J_{C\text{-}F}$ 21.9), 154.9, 115.9 (t, $^1J_{C\text{-}F}$ 259.4), 70.0 (dd, $^2J_{C\text{-}F}$ 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, $CDCl_3$) **major conformer:** -106.2 (1F, dd, J_{gem} 247.6, $^3J_{F\text{-}H}$ 5.3), -129.1 (1F, dd, J_{gem} 247.6, $^3J_{F\text{-}H}$ 19.1), **minor conformer:** -108.4 (1F, d, J_{gem} 252.7), -123.1 (1F, dd, J_{gem} 252.7, $^3J_{F\text{-}H}$ 26.4); [HRMS (FAB, $[M+H]^+$) Found: 336.16224, calc. for $C_{15}H_{24}NO_5F_2$: 336.16225]; *m/z* (ES) 336 (100 %, $[M+H]^+$). An analytical sample was recrystallised by vapour diffusion (ethyl acetate/light petroleum) to afford colourless plates, which were used to obtain an X-ray crystal structure of epoxide **368b** (**Appendix 2**).

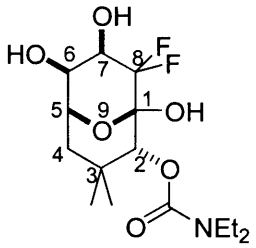
Preparation of 8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-7,7-dimethyl-9-oxa-bicyclo[3.3.1]nona-1,3,4-triol 365a



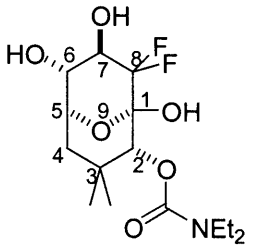
A solution of *N*-methylmorpholine-*N*-oxide (21.7 mmol, 2.54 g) in water (2.5 mL) was added to a cold (0 °C) solution of alkene *cis*-**356** (10.9 mmol, 3.47 g) in acetone (20 mL) and *tert*-butanol (20 mL). The mixture was stirred for 10 minutes and osmium tetraoxide (220 μmol, 2.7 mL of a 2.5 wt. % solution in *tert*-butanol) was added. The reaction mixture was stirred at 0 °C for 24 hours, quenched with sodium sulfite (40.0 mmol, 5.05 g), allowed to warm to room temperature and stirred at this temperature for 30 minutes. The resulting mixture was dissolved with water (20 mL) and extracted with ethyl acetate (5 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow solid (3.75 g). Purification by recrystallisation (ethyl acetate) afforded the desired triol **365a** as colorless needles (3.15 g, 81 %). R_f (80 % ethyl acetate in light petroleum) 0.22; Mp 171-172 °C; (Found C, 50.97; H, 7.19; N, 3.91; $C_{15}H_{25}F_2NO_6$ requires: C, 50.99; H, 7.13; N, 3.96 %); ν_{max} (KBr)/cm^{-1} 3358s br (O-H), 2974m (C-H), 2875m (C-H), 1681s (C=O); δ_H (250 MHz, DMSO-d_6); 6.73 (1H, s, -O*H*), 5.29 (1H, d, *J* 16.5, -O*H*), 4.88 (1H, d, *J* 4.1, -O*H*), 4.86 (1H, s, H-2), 4.44-4.21 (2H, m, H-5 and H-7), 3.73-3.56 (2H, H-6 and -N(CH_aH$_b$CH$_3$)$_2$), 3.42-3.24 (3H, m, -N(CH$_a$$H_bCH_3$)$_2$ and -N(CH_2CH$_3$)$_2$), 2.02 (1H, dd, J_{gem} 14.2, *J* 11.5, H-4a), 1.44 (1H, dd, J_{gem} 14.2, *J* 5.8, H-4b), 1.33 (3H, s, -CH_3), 1.30-1.13 (6H, m, -N(CH$_2$CH_3)$_2$), 0.99 (3H, s, -CH_3); δ_c (65 MHz, DMSO-d_6) 154.6, 118.0 (t, $^1J_{C\text{-}F}$ 256.9), 94.8 (dd, $^2J_{C\text{-}F}$ 25.7, 20.1), 73.8, 72.3 (d, $^3J_{C\text{-}F}$ 6.6), 70.7,

65.0 (t, $^{2}J_{C\text{-}F}$ 18.8), 41.7, 41.0, 35.0, 34.5, 29.2, 22.9, 14.5, 13.8; δ_F (235 MHz, DMSO-d_6) -122.1 (1F, d, J_{gem} 236.2), -129.2 (1F, dd, J_{gem} 236.2, $^{3}J_{F\text{-}H}$ 2.9); [HRMS (FAB, $[M+H]^+$) Found: 354.17238, calc. for $C_{15}H_{26}NO_6F_2$: 354.17283]; *m/z* (ES) 354 (100 %, $[M+H]^+$).

Preparation of 8-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-7,7-dimethyl-9-oxa-bicyclo[3.3.1]nona-1,3,4-triols 365b and 365c



365b

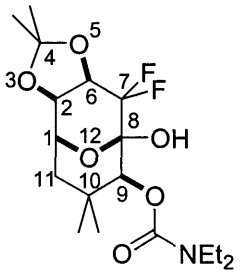


365c

A solution of *N*-methylmorpholine-*N*-oxide (4.0 mmol, 0.47 g) in water (0.5 mL) was added to a cold (0 °C) solution of alkene *trans*-**356** (2.0 mmol, 0.64 g) in acetone (5 mL) and *tert*-butanol (5 mL). The mixture was stirred for 10 minutes and a 2.5 wt. % solution of osmium tertroxide in *tert*-butanol (40 μmol, 0.5 mL) was added. The reaction mixture was stirred at 0 °C for 48 hours, quenched with sodium sulfite (8.0 mmol, 1.01 g), allowed to warm to room temperature and stirred at this temperature for 30 minutes. The resulting mixture was dissolved with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a diastereoisomeric mixture (4.5:1) as a pale yellow oil (872 mg). Purification by column chromatography (70 % ethyl acetate in light petroleum) allowed the separation of the two diastereoisomers. **Major diastereoisomer** (**365c**) was obtained as a white solid (506 mg, 72 %). R_f (80 % ethyl acetate in light petroleum) 0.41; Mp 153-154 °C; (Found C, 51.11; H, 7.12; N, 4.01; $C_{15}H_{25}F_2NO_6$ requires: C, 50.99; H, 7.13; N, 3.96 %); ν_{max}

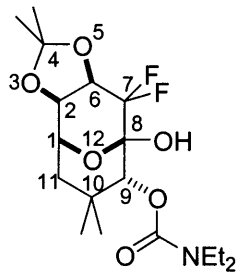
(KBr)/cm^{-1} 3358s br (O-H), 2980m (C-H), 1682s (C=O); δ_H (250 MHz, DMSO-d_6) 6.57 (1H, d, *J* 1.2, -O*H*), 6.40 (1H, d, *J* 5.5, -O*H*), 5.60 (1H, d, $^4J_{F-H}$ 1.4, H-2), 5.19 (1H, d, *J* 3.7, -O*H*), 4.28 (1H, dd, *J* 11.2, 5.5, H-5), 4.12-4.05 (1H, m, H-7), 3.81-3.71 (1H, m, H-6), 3.45-3.30 (4H, m, -N(C*H*$_2$CH$_3$)$_2$), 2.08 (1H, dd, J_{gem} 13.8, *J* 6.1, H-4a), 1.97 (1H, dd, J_{gem} 13.8, *J* 11.4, H-4b), 1.39 (3H, s, -C*H*$_3$), 1.36-1.18 (6H, m, -N(CH$_2$C*H*$_3$)$_2$), 1.02 (3H, s, -C*H*$_3$); δ_C (63 MHz, DMSO-d_6) 154.8, 115.9 (dd, $^1J_{C-F}$ 262.5, 254.3), 93.8 (dd, $^2J_{C-F}$ 28.0, 19.8), 73.6 (t, $^2J_{C-F}$ 19.3), 73.3, 73.1 (d, $^3J_{C-F}$ 2.5), 72.2, 41.5, 41.0, 34.8, 34.3, 29.5, 23.4, 14.5, 13.9; δ_F (235 MHz, DMSO-d_6) -114.8 (1F, dd, J_{gem} 246.8, $^3J_{F-H}$ 11.3), -121.1 (1F, d, J_{gem} 246.8); [HRMS (FAB, [M+H]$^+$) Found: 354.17280, calc. for $C_{15}H_{26}NO_6F_2$: 354.17282; *m/z* (ES) 354 (100 %, [M+H]$^+$). **Minor diastereoisomer** (**365b**) was obtained as a white solid (113 mg, 16 %). R_f (80 % ethyl acetate in light petroleum) 0.22; Mp 160-161 °C; (Found C, 51.00; H, 7.20; N, 4.00; $C_{15}H_{25}F_2NO_6$ requires: C, 50.99; H, 7.13; N, 3.96 %); ν_{max} (KBr)/cm^{-1} 3422s br (O-H), 2980m (C-H), 2874m (C-H), 1694s (C=O); δ_H (250 MHz, DMSO-d_6) 7.03 (1H, s, -O*H*), 5.16 (1H, d, *J* 9.2, -O*H*), 5.02 (1H, s, H-2), 4.94 (1H, d, *J* 4.1, -O*H*), 4.47-4.30 (2H, m, H-5 and H-7), 3.83-3.78 (1H, m, H-6), 3.45-3.07 (4H, m, -N(C*H*$_2$CH$_3$)$_2$), 1.86 (1H, t, J_{gem} 12.7, *J* 12.7, H-4a), 1.41-1.34 (4H, m, H-4b and -C*H*$_3$), 1.32-1.17 (6H, m, -N(CH$_2$C*H*$_3$)$_3$), 0.94 (3H, s, -C*H*$_3$); δ_C (63 MHz, DMSO-d_6) 154.3, 118.4 (dd, $^1J_{C-F}$ 260.5, 253.3), 95.8 (t, $^2J_{C-F}$ 21.4), 79.6, 72.7 (d, $^3J_{C-F}$ 5.1), 71.7, 65.6 (t, $^2J_{C-F}$ 18.3), 41.9, 40.9, 34.5, 30.9, 27.6, 26.5, 14.3, 13.5; δ_F (235 MHz, DMSO-d_6) -119.8 (1F, d, J_{gem} 242.8), -121.3 (1F, dd, J_{gem} 242.8, $^3J_{F-H}$ 23.2); [HRMS (FAB, [M+H]$^+$) Found: 354.17278, calc. for $C_{15}H_{26}NO_6F_2$: 354.17282; *m/z* (ES) 354 (100 %, [M+H]$^+$).

Preparation of 9-(*N,N*-diethylcarbamoyloxy)-7,7-difluoro-4,4,10,10-tetramethyl-3,5,12-trioxa-tricyclo[6.3.1.$0^{2,6}$]dodecan-8-ol 367a



A suspension of diol **365a** (5.0 mmol, 1.8 g), *p*-toluenesulphonic acid monohydrate (250 μmol, 48 mg) and anhydrous copper sulfate (10.0 mmol, 1.60 g) in acetone (50 mL) was stirred at room temperature for 16 hours. The reaction mixture was quenched with ammonium chloride (50 mL of a saturated aqueous solution) and water (50 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with sodium hydrogencarbonate (50 mL of a saturated aqueous solution) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired acetonide **367a** as a white solid (1.96 g, 100 %), which was not purified any further. R_f (30 % diethyl ether in light petroleum) 0.27; Mp 162-163 °C; (Found C, 55.13; H, 7.43; N, 3.49; $C_{18}H_{29}F_2NO_6$ requires: C, 54.95; H, 7.43; N, 3.56 %); ν_{max} (KBr)/cm^{-1} 3512s br (O-H), 2968m (C-H), 1694s (C=O); δ_H (235 MHz; $CDCl_3$) 4.77 (1H, d, $^4J_{H\text{-}F}$ 1.2, H-9), 4.66-4.48 (2H, m, H-1 and H-6), 4.02-3.98 (1H, m, H-2), 3.50 (1H, d, $^4J_{H\text{-}F}$ 1.6, -O*H*), 3.40-3.17 (4H, m, -N(CH_2CH$_3$)$_2$), 2.15 (1H, dd, J_{gem} 14.5, *J* 11.7, H-11a), 1.55-1.48 (4H, m, H-11b and -CH_3), 1.31 (3H, s, -CH_3), 1.22 (3H, s, -CH_3), 1.15-1.02 (6H, m, -N(CH$_2$CH_3)$_2$), 0.89 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 154.6, 115.1 (t, $^1J_{C\text{-}F}$ 256.6), 111.6, 94.1 (dd, $^2J_{C\text{-}F}$ 27.2, 20.6), 79.5 (d, $^3J_{C\text{-}F}$ 7.6), 73.8 (d, $^2J_{C\text{-}F}$ 26.2, 18.6), 73.7, 67.1, 42.7, 41.8, 39.7, 38.4, 29.0, 26.3, 26.2, 22.7, 14.6, 13.7; δ_F (235 MHz, $CDCl_3$) -120.0 (1F, dd, J_{gem} 243.1, $^3J_{F\text{-}H}$ 10.6), -119.4 (1F, dd, J_{gem} 243.1, $^3J_{F\text{-}H}$ 13.9); *m/z* (ES) 394 (100 %, $[M+H]^+$).

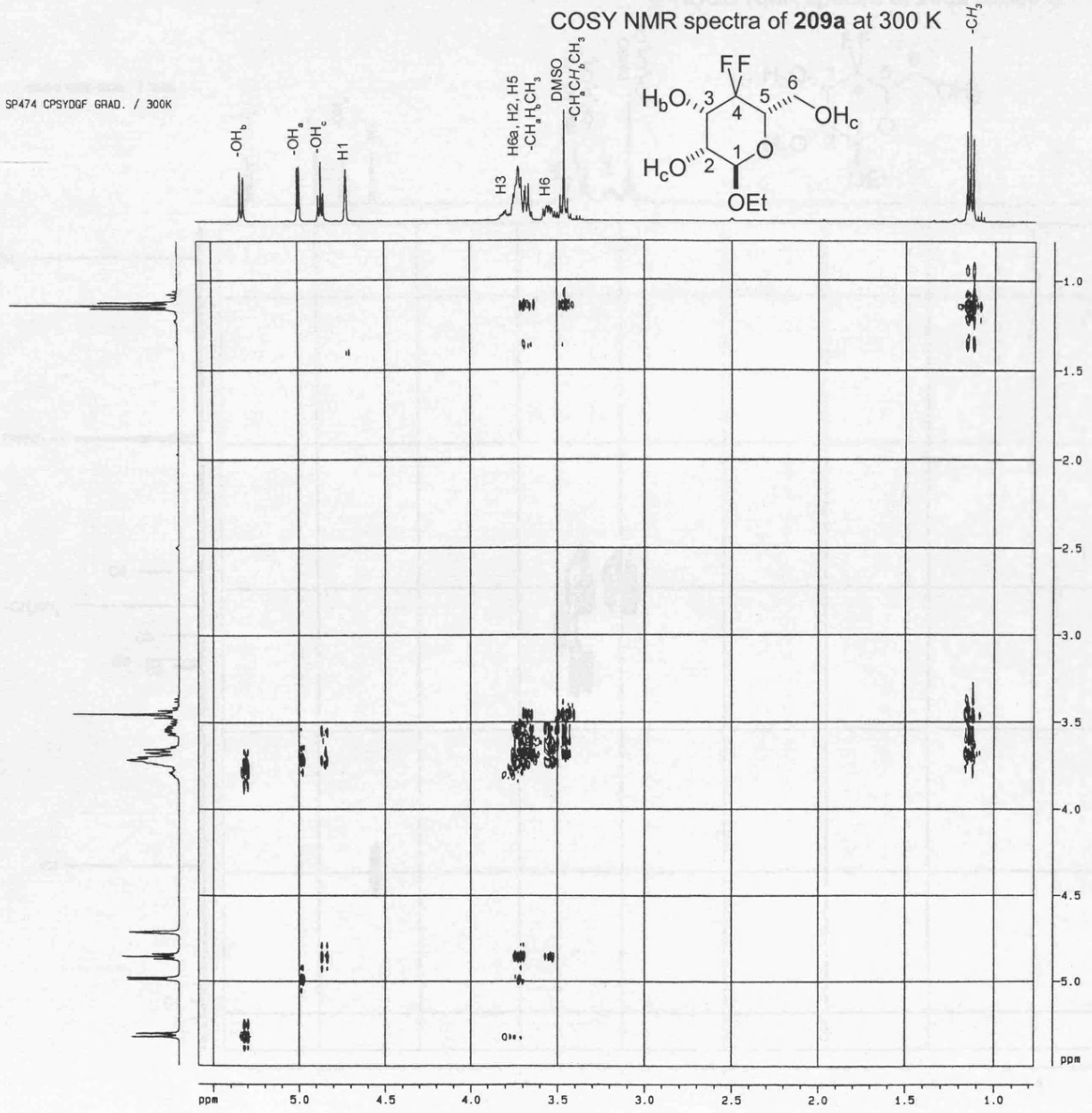
Preparation of 9-(*N,N*-diethylcarbamoyloxy)-7,7-difluoro-4,4,10,10-tetramethyl-3,5,12-trioxa-tricyclo[6.3.1.$0^{2,6}$]dodecan-8-ol 367b



A suspension of diol **365b** (1.0 mmol, 0.35 g), *p*-toluenesulphonic acid monohydrate (50 μmol, 10 mg) and anhydrous copper sulfate (2.0 mmol, 0.32 g) in acetone (50 mL) was stirred at room temperature for 16 hours. The reaction mixture was quenched with ammonium chloride (10 mL a saturated aqueous solution) and water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with sodium hydrogencarbonate (10 mL of a saturated aqueous solution) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired acetonide **367b** as a white solid (0.39 g, 100 %), which was not purified any further. R_f (30 % diethyl ether in light petroleum) 0.29; Mp 159-160 °C; δ_H (250 MHz, $CDCl_3$) 5.06 (1H, s, H-9), 4.65-4.53 (2H, m, H-1 and H-6), 4.08-4.04 (1H, m, H-2), 3.77 (1H, d, $^4J_{H\text{-}F}$ 2.8, -O*H*), 3.37-3.15 (4H, m, -N(CH_2CH_3)$_2$), 1.88 (1H, ddd, J_{gem} 14.0, *J* 11.0, ^4J 1.0, H-11a), 1.52 (3H, s, -CH_3), 1.36-1.19 (7H, m, 2 x -CH_3 and H-11b), 1.15-1.03 (6H, m, -N(CH_2CH_3)$_2$), 0.89 (3H, s, -CH_3); δ_C (63 MHz, $CDCl_3$) 154.9, 115.2 (t, $^1J_{C\text{-}F}$ 256.4), 111.6, 96.1 (t, $^2J_{C\text{-}F}$ 22.6), 79.1 (d, $^3J_{C\text{-}F}$ 4.1), 78.6, 74.2 (t, $^2J_{C\text{-}F}$ 21.4), 68.1, 42.4, 41.0, 39.3, 34.5, 34.3, 28.3, 26.3, 26.1, 14.4, 13.4; δ_F (235 MHz, $CDCl_3$) -116.3 (1F, dd, first half of an ABX system, J_{gem} 248.5, $^3J_{F\text{-}H}$ 12.6), -116.7 (1F, dd, second half of an ABX system, J_{gem} 248.5, $^3J_{F\text{-}H}$ 10.6); [HRMS (FAB, $[M+H]^+$) Found: 394.20398, calc. for: $C_{18}H_{30}NO_6F_2$: 394.20413]; *m/z* (ES) 394 (100 %, $[M+H]^+$).

APPENDICES

COSY NMR spectra of **209a** at 300 K



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CHANNEL f1

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p2	19.20 usec
PL1	0.00 dB
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GRADIENT CHANNEL

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GPNAM2	sine.100
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GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	20.00 %
P16	1000.00 usec

F1 - Acquisition parameters

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TD	256
SFO1	400.1316 MHz
FIDRES	12.520032 Hz
SW	8.010 ppm

F2 - Processing parameters

SI	1024
SF	400.1300030 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	400.1300030 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	22.00 cm
CX1	22.00 cm
F2PLO	5.586 ppm
F2LO	2236.09 Hz
F2PHI	0.770 ppm
F2HI	308.01 Hz
F1PLO	5.495 ppm
F1LO	2198.53 Hz
F1PHI	0.785 ppm
F1HI	314.27 Hz
F2PPMCM	0.21903 ppm/cm
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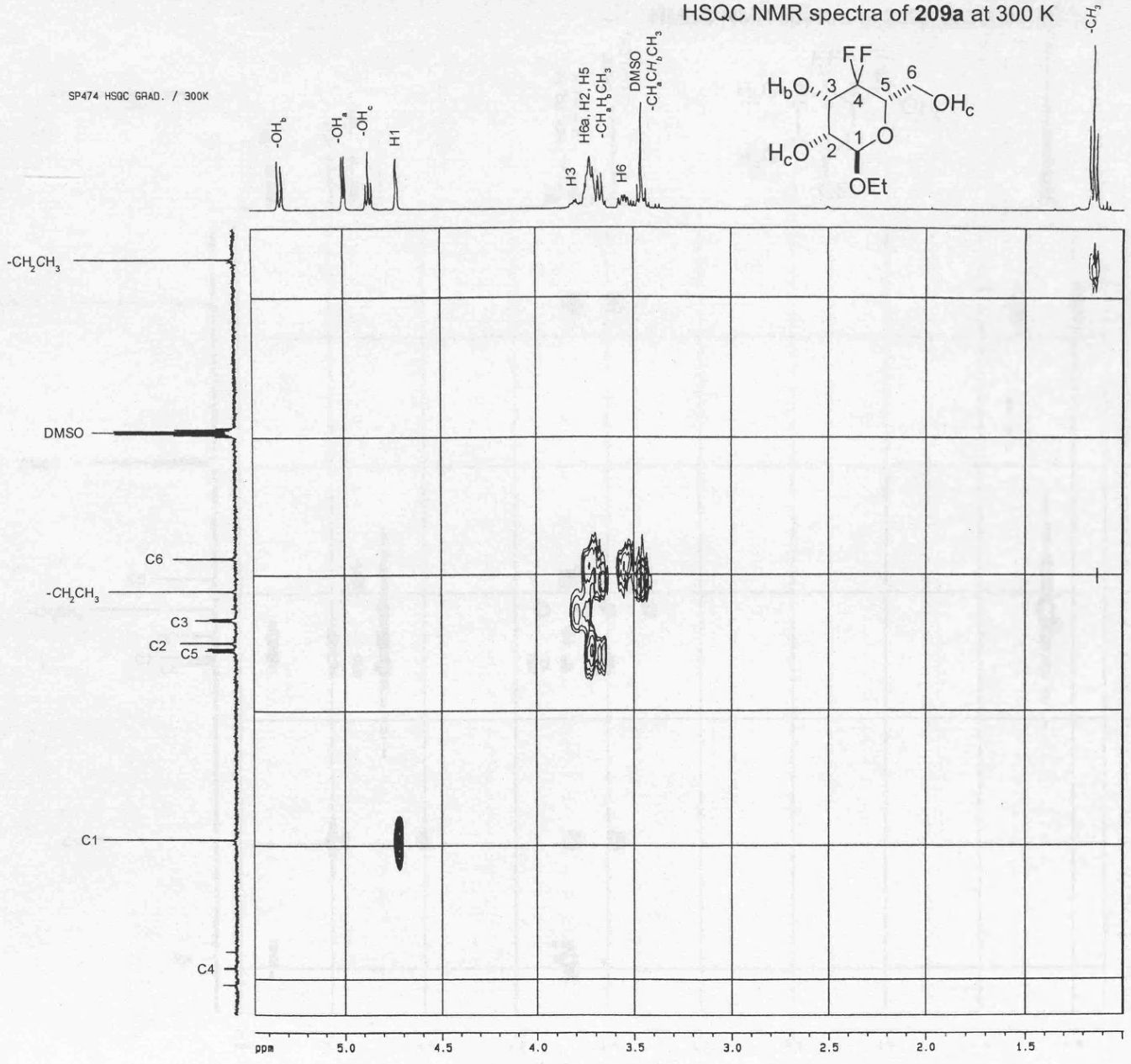
HSQC NMR spectra of **209a** at 300 K



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CHANNEL f2

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GRADIENT CHANNEL

GPNAM1	sine.100
GPNAM2	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	80.00 %
GPZ2	20.10 %
P16	1000.00 usec

F1 - Acquisition parameters

MO0	2
TD	128
SF01	100.6248 MHz
FIDRES	220.692093 Hz
SW	200.732 ppm

F2 - Processing parameters

SI	1024
SF	400.1300013 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

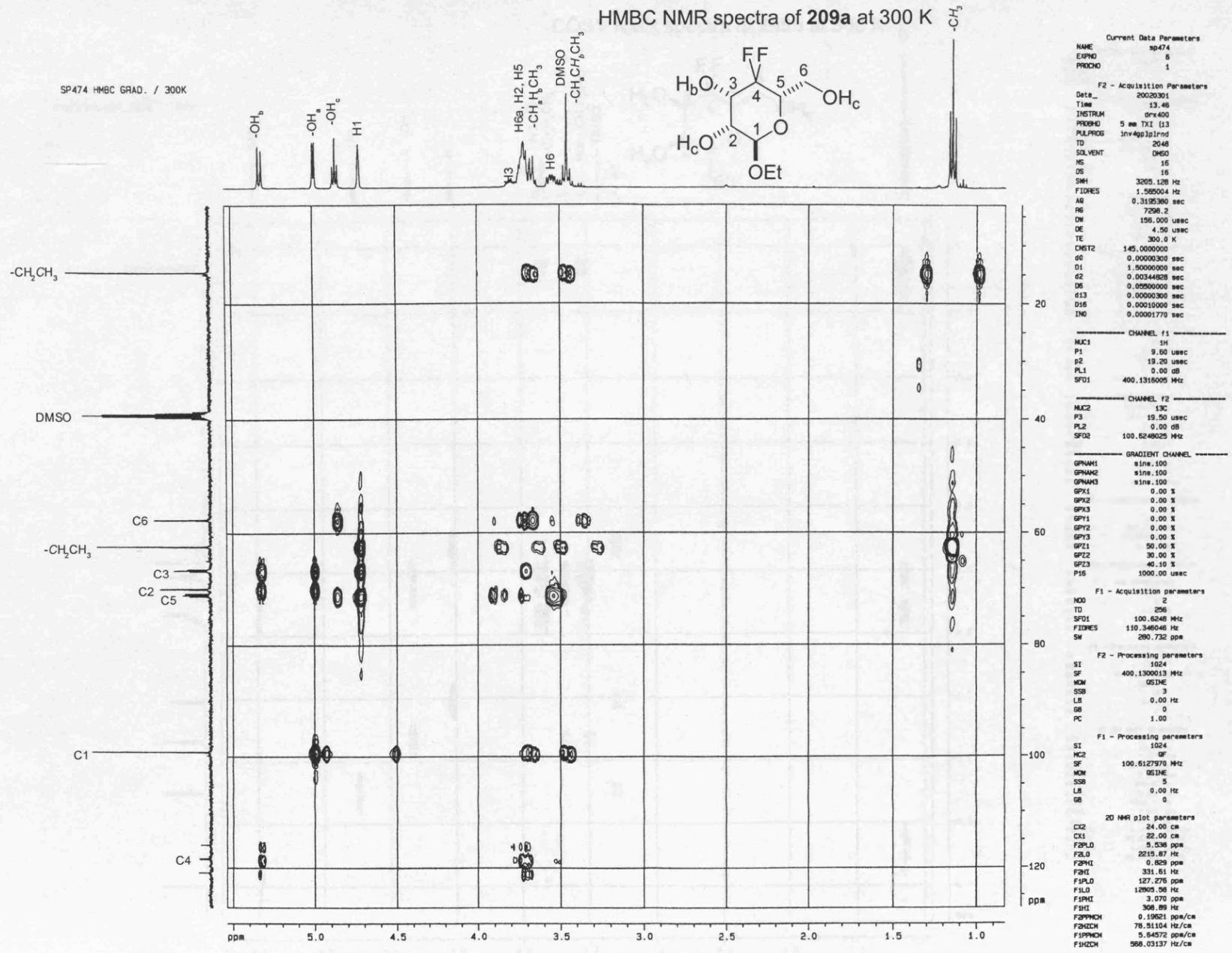
F1 - Processing parameters

SI	1024
MC2	echo-antiecho
SF	100.6127970 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	24.00 cm
CX1	22.00 cm
F2PLO	5.475 ppm
F2LO	2190.83 Hz
F2PHI	0.993 ppm
F2HI	397.34 Hz
F1PLO	125.357 ppm
F1LO	12612.48 Hz
F1PHI	10.196 ppm
F1HI	1026.15 Hz
F2PPMCM	0.18678 ppm/cm
F2HZCM	74.72894 Hz/cm
F1PPMCM	5.23444 ppm/cm
F1HZCM	526.65143 Hz/cm

HMBC NMR spectra of **209a** at 300 K



Current Data Parameters

NAME	sp474
EXPNO	5
PROCNO	1

F2 - Acquisition Parameters

Date_	20020301
Time	13.46
INSTRUM	drx400
PROBHD	5 mm TXI (13
PULPROG	inv4gplpnd
TD	2048
SOLVENT	DMSO
NS	16
DS	16
SWH	3205.128 Hz
FIDRES	1.565004 Hz
AQ	0.3195360 sec
RG	7298.2
DW	156.000 usec
DE	4.50 usec
TE	300.0 K
CNST2	145.0000000
d0	0.00000300 sec
D1	1.50000000 sec
d2	0.00344828 sec
D6	0.05500000 sec
d13	0.00000300 sec
D16	0.00010000 sec
IN0	0.00001770 sec

CHANNEL f1

NUC1	1H
P1	9.60 usec
p2	19.20 usec
PL1	0.00 dB
SFO1	400.1316005 MHz

CHANNEL f2

NUC2	13C
P3	19.50 usec
PL2	0.00 dB
SFO2	100.6248025 MHz

GRADIENT CHANNEL

GPNAM1	sine.100
GPNAM2	sine.100
GPNAM3	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPZ1	50.00 %
GPZ2	30.00 %
GPZ3	40.10 %
P16	1000.00 usec

F1 - Acquisition parameters

NDO	2
TD	256
SFO1	100.6248 MHz
FIDRES	110.346046 Hz
SW	280.732 ppm

F2 - Processing parameters

SI	1024
SF	400.1300013 MHz
WDW	QSINE
SSB	3
LB	0.00 Hz
GB	0
PC	1.00

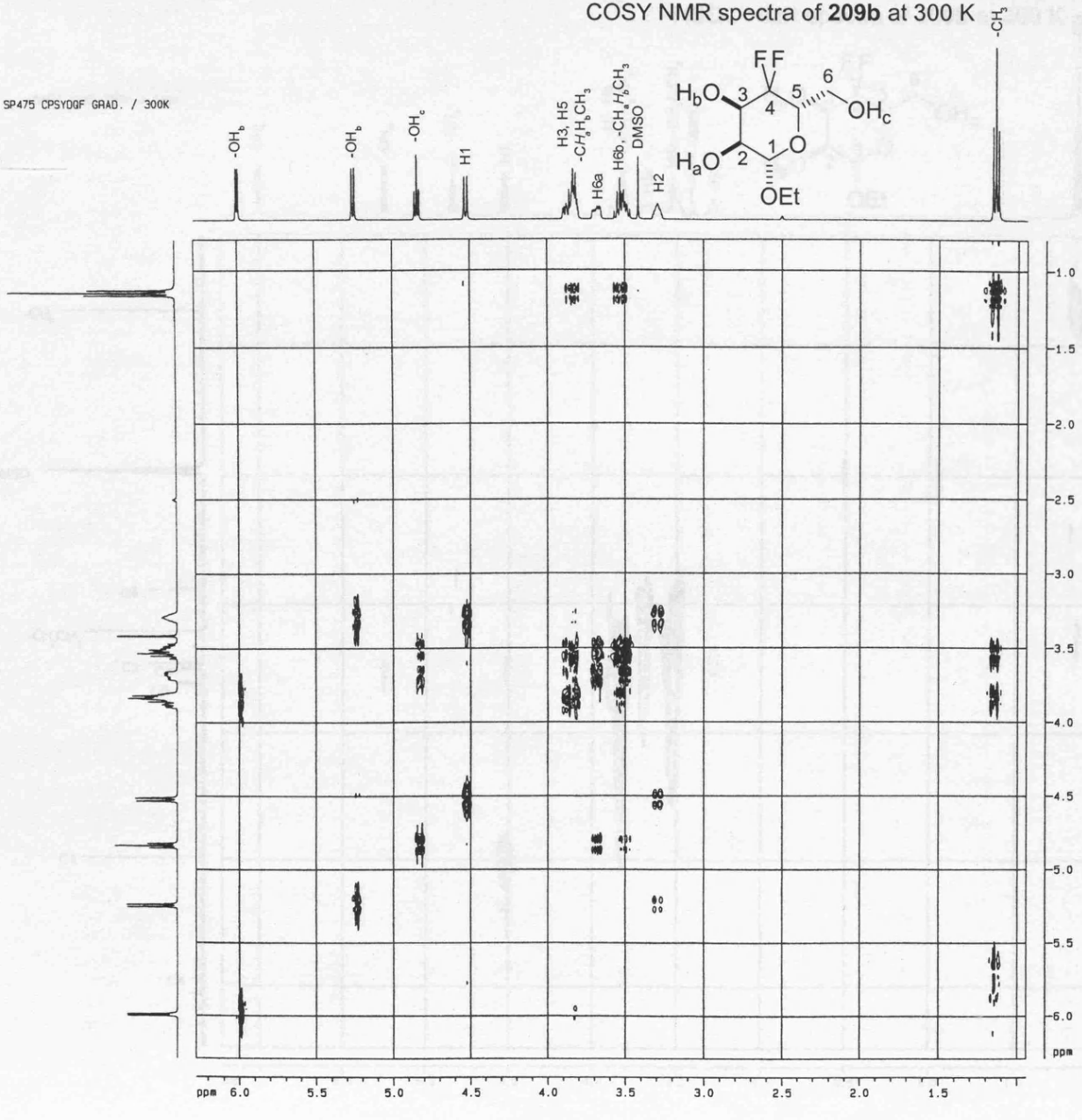
F1 - Processing parameters

SI	1024
MC2	QF
SF	100.6127970 MHz
WDW	QSINE
SSB	5
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	24.00 cm
CX1	22.00 cm
F2PLO	5.536 ppm
F2LO	2215.87 Hz
F2PHI	0.829 ppm
F2HI	331.61 Hz
F1PLO	127.276 ppm
F1LO	12805.56 Hz
F1PHI	3.070 ppm
F1HI	308.89 Hz
F2PPMCM	0.19621 ppm/cm
F2HZCM	78.51104 Hz/cm
F1PPMCM	5.64572 ppm/cm
F1HZCM	568.03137 Hz/cm

COSY NMR spectra of **209b** at 300 K



Current Data Parameters

NAME	sp475
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20020218
Time	10.12
INSTRUM	drx400
PROBHD	5 mm TXI (i3
PULPROG	cosygpqftp
TD	2048
SOLVENT	DMSO
NS	4
DS	16
SWH	3205.128 Hz
FIDRES	1.565004 Hz
AQ	0.3195380 sec
RG	14596.5
DW	156.000 usec
DE	4.50 usec
TE	300.0 K
d0	0.00000300 sec
D1	1.50000000 sec
d13	0.00000300 sec
D16	0.00010000 sec
d20	0.00110300 sec
IN0	0.00015600 sec

CHANNEL f1

NUC1	1H
P1	9.60 usec
p2	19.20 usec
PL1	0.00 dB
SFO1	400.1316005 MHz

GRADIENT CHANNEL

GPNAM1	sine.100
GPNAM2	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPZ1	10.00 %
GPZ2	20.00 %
P16	1000.00 usec

F1 - Acquisition parameters

ND0	2
TD	256
SFO1	400.1316 MHz
FIDRES	12.520032 Hz
SW	8.010 ppm

F2 - Processing parameters

SI	1024
SF	400.1300030 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

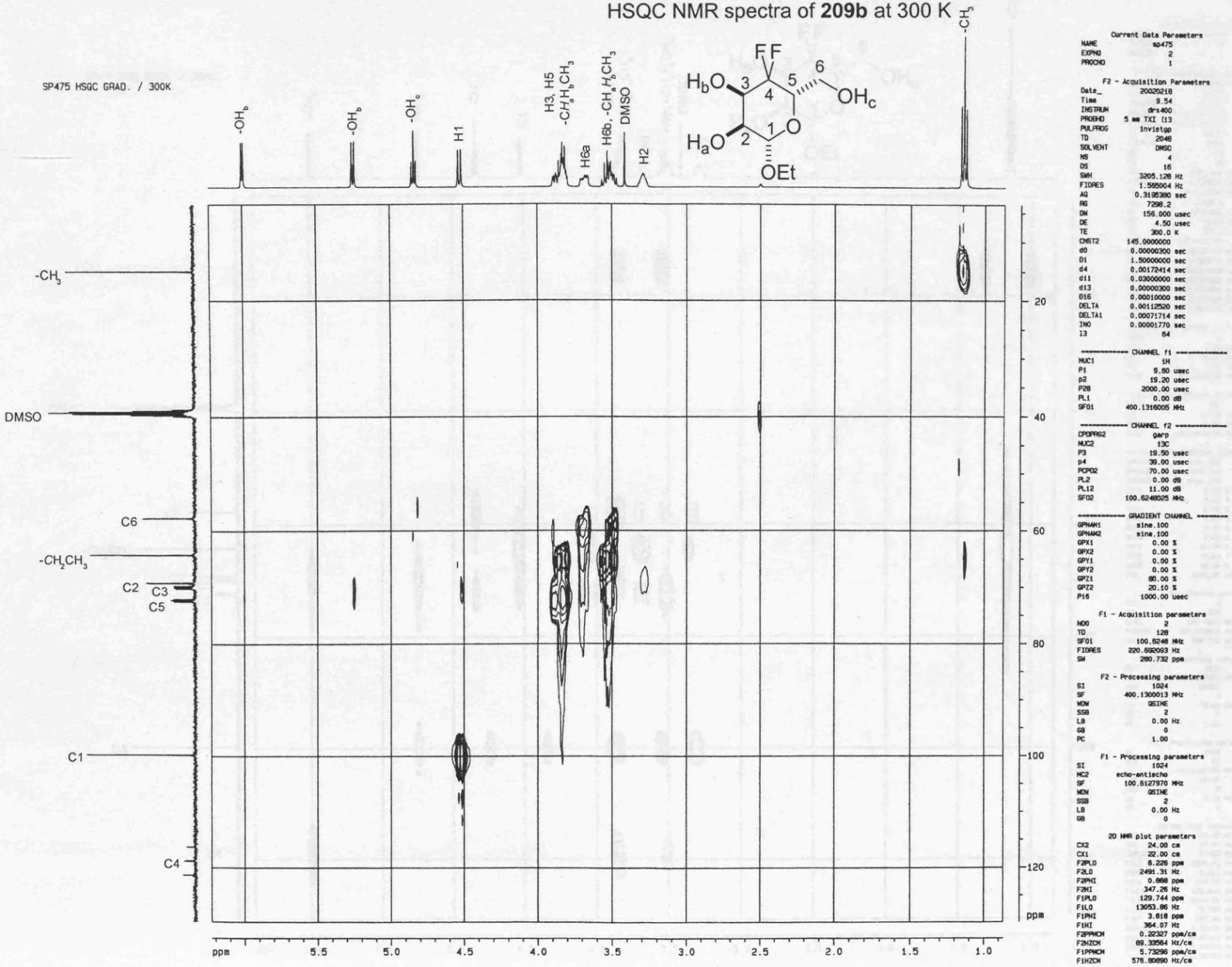
F1 - Processing parameters

SI	1024
MC2	TPPI
SF	400.1300030 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	22.00 cm
CX1	22.00 cm
F2PLO	6.277 ppm
F2LO	2511.53 Hz
F2PHI	0.942 ppm
F2HI	376.87 Hz
F1PLO	6.292 ppm
F1LO	2517.79 Hz
F1PHI	0.801 ppm
F1HI	320.53 Hz
F2PPMCM	0.24250 ppm/cm
F2HZCM	97.03025 Hz/cm
F1PPMCM	0.24961 ppm/cm
F1HZCM	99.87571 Hz/cm

HSQC NMR spectra of **209b** at 300 K




```
Current Data Parameters
NAME                  sp475
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20020218
Time                   9.54
INSTRUM              drx400
PROBHD     5 mm TXI (13
PULPROG          invietgp
TD                     2048
SOLVENT                DMSO
NS                        4
DS                       16
SWH               3205.128 Hz
FIDRES            1.565004 Hz
AQ                0.3195380 sec
RG                   7298.2
DW                 156.000 usec
DE                   4.50 usec
TE                  300.0 K
CNST2             145.0000000
d0                0.00000300 sec
D1                1.50000000 sec
d4                0.00172414 sec
d11               0.03000000 sec
d13               0.00000300 sec
D16               0.00010000 sec
DELTA             0.00112520 sec
DELTA1            0.00071714 sec
IN0               0.00001770 sec
13                        64

========== CHANNEL f1 ==========
NUC1                      1H
P1                      9.80 usec
p2                     19.20 usec
P28                  2000.00 usec
PL1                     0.00 dB
SF01              400.1316005 MHz

========== CHANNEL f2 ==========
CPDPRG2                 garp
NUC2                     13C
P3                     19.50 usec
p4                     39.00 usec
PCPD2                  70.00 usec
PL2                     0.00 dB
PL12                   11.00 dB
SF02              100.6248025 MHz

========== GRADIENT CHANNEL ==========
GPNAM1               sine.100
GPNAM2               sine.100
GPX1                    0.00 %
GPX2                    0.00 %
GPY1                    0.00 %
GPY2                    0.00 %
GPZ1                   80.00 %
GPZ2                   20.10 %
P16                 1000.00 usec

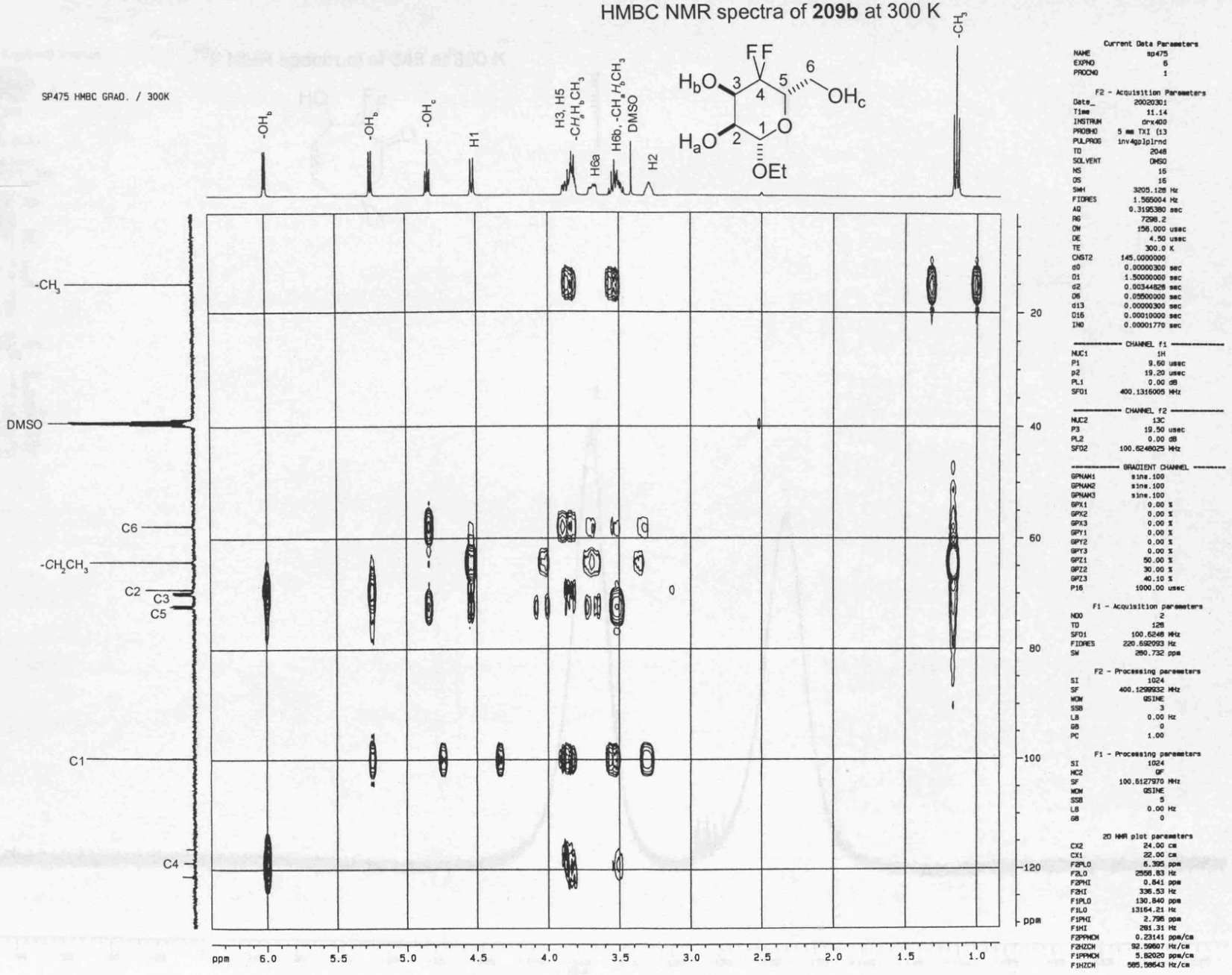
F1 - Acquisition parameters
MDD                       2
TD                      128
SF01              100.6248 MHz
FIDRES            220.692093 Hz
SW                280.732 ppm

F2 - Processing parameters
SI                     1024
SF                400.1300013 MHz
WDW                    QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
PC                     1.00

F1 - Processing parameters
SI                     1024
MC2            echo-antiecho
SF                100.6127970 MHz
WDW                    QSINE
SSB                       2
LB                     0.00 Hz
GB                        0

2D NMR plot parameters
CX2                   24.00 cm
CX1                   22.00 cm
F2PLO                 8.226 ppm
F2LO                2491.31 Hz
F2PHI                 0.868 ppm
F2HI                 347.26 Hz
F1PLO               129.744 ppm
F1LO               13053.86 Hz
F1PHI                 3.618 ppm
F1HI                 364.07 Hz
F2PPMCM           0.22327 ppm/cm
F2HZCM           89.33584 Hz/cm
F1PPMCM           5.73296 ppm/cm
F1HZCM          576.80690 Hz/cm
```

HMBC NMR spectra of **209b** at 300 K



Current Data Parameters

NAME	sp475
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

Date_	20020301
Time	11.14
INSTRUM	drx400
PROBHD	5 mm TXI (i3
PULPROG	inv4gplplrnd
TD	2048
SOLVENT	DMSO
NS	16
DS	16
SWH	3205.128 Hz
FIDRES	1.565084 Hz
AQ	0.3195380 sec
RG	7298.2
DW	156.000 usec
DE	4.50 usec
TE	300.0 K
CNST2	145.0000000
d0	0.00000300 sec
D1	1.50000000 sec
d2	0.00344828 sec
D6	0.05500000 sec
d13	0.00000300 sec
D16	0.00010000 sec
IN0	0.00001770 sec

CHANNEL f1

NUC1	1H
P1	9.60 usec
p2	19.20 usec
PL1	0.00 dB
SFO1	400.1316005 MHz

CHANNEL f2

NUC2	13C
P3	19.50 usec
PL2	0.00 dB
SFO2	100.6248025 MHz

GRADIENT CHANNEL

GPNAM1	sine.100
GPNAM2	sine.100
GPNAM3	sine.100
GPX1	0.00 %
GPX2	0.00 %
GPX3	0.00 %
GPY1	0.00 %
GPY2	0.00 %
GPY3	0.00 %
GPZ1	50.00 %
GPZ2	30.00 %
GPZ3	40.10 %
P16	1000.00 usec

F1 - Acquisition parameters

NDO	2
TD	128
SFO1	100.6248 MHz
FIDRES	220.692093 Hz
SW	280.732 ppm

F2 - Processing parameters

SI	1024
SF	400.1299932 MHz
WDW	QSINE
SSB	3
LB	0.00 Hz
GB	0
PC	1.00

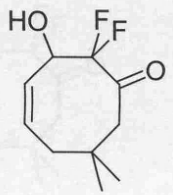
F1 - Processing parameters

SI	1024
MC2	QF
SF	100.6127970 MHz
WDW	QSINE
SSB	5
LB	0.00 Hz
GB	0

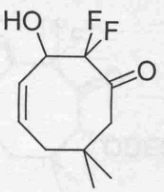
2D NMR plot parameters

CX2	24.00 cm
CX1	22.00 cm
F2PLO	6.395 ppm
F2LO	2558.83 Hz
F2PHI	0.841 ppm
F2HI	336.53 Hz
F1PLO	130.840 ppm
F1LO	13164.21 Hz
F1PHI	2.796 ppm
F1HI	281.31 Hz
F2PPMCM	0.23141 ppm/cm
F2HZCM	92.59607 Hz/cm
F1PPMCM	5.82020 ppm/cm
F1HZCM	585.58643 Hz/cm

^{19}F NMR spectrum of **348** at 300 K



^{19}F NMR spectrum of **348** at 223 K



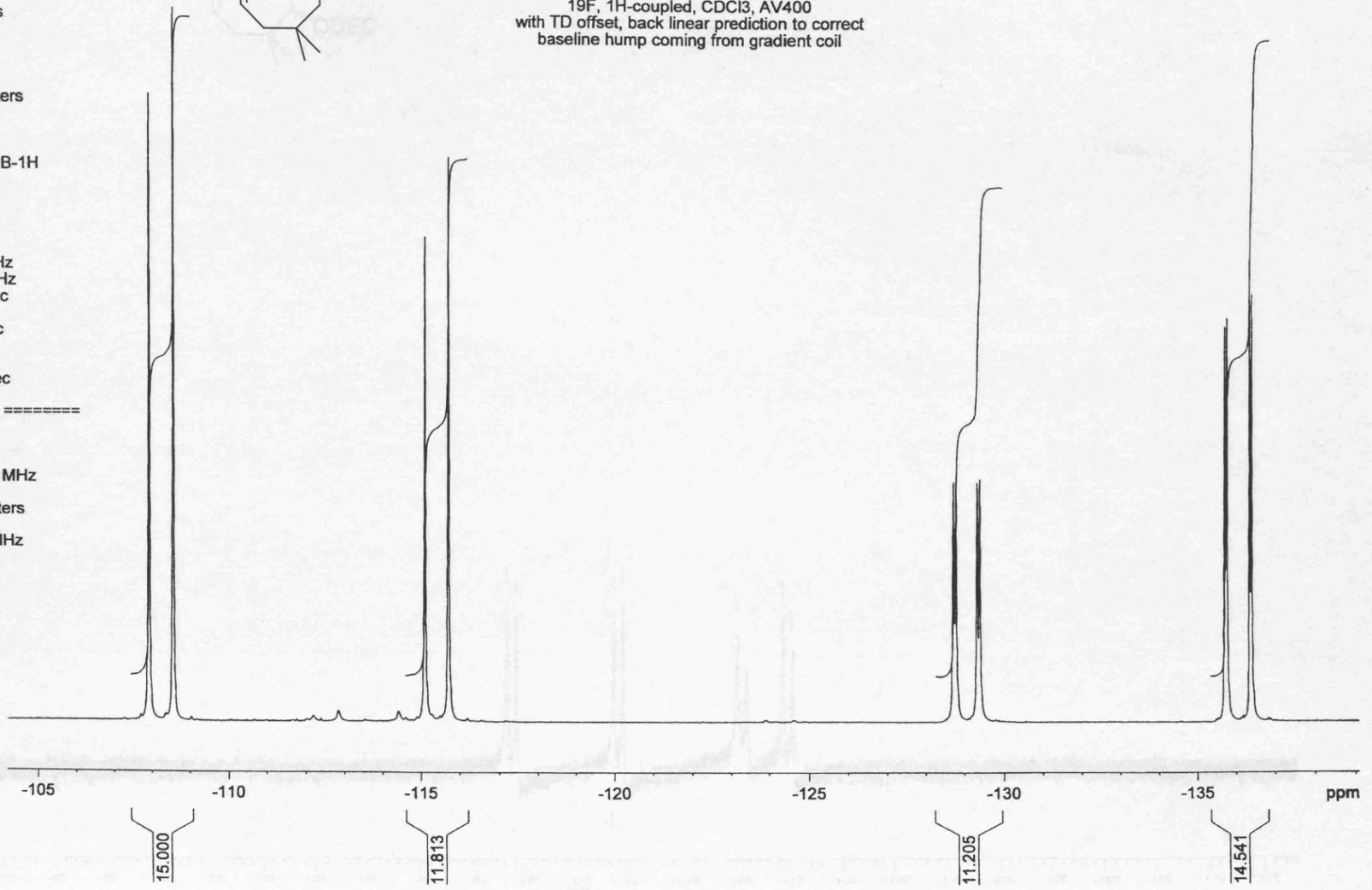
Current Data Parameters
NAME jn20sp1f
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010620
Time 10.22
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgflqn
TD 130982
SOLVENT CDCl3
NS 32
DS 0
SWH 75187.969 Hz
FIDRES 0.574033 Hz
AQ 0.8710803 sec
RG 32
DW 6.650 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

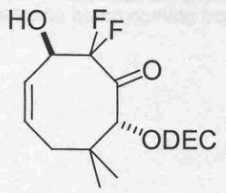
======== CHANNEL f1 ========
NUC1 19F
P1 11.00 usec
PL1 -3.00 dB
SFO1 376.4128980 MHz

F2 - Processing parameters
SI 131072
SF 376.4468510 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.20

Stephane Pintat Sample 1 in CDCl3 at -50C, set temp
19F, 1H-coupled, CDCl3, AV400
with TD offset, back linear prediction to correct
baseline hump coming from gradient coil



^{19}F NMR spectrum of *trans*-**356** at 300 K




```
STP - STEPHANE PINTAT
BRUKER
PPM
JN010S.103
AU PROG:
 X03.AU
DATE 1-6-73

SA.NA B04111
SA.NO JN01  103
SF    282.407
SY 282.0
O1  -4147.000
SI  65536
TD  65536
SW  41666.667
HZ/PT   1.272

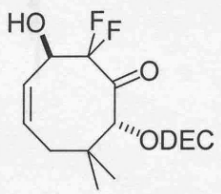
PW      0.0
RD      0.0
AQ      .786
RG     32
NS     32
TE    297

FW  52100
O2   4900.000
DP  63L PO

LB      1.000
GB      0.0
CX     40.00
CY      4.01
F1    -39.997P
F2   -179.996P
HZ/CM 988.420
PPM/CM  3.500
SR  27499.73
```

Stephane Pintat Sample SP360 in CDCl3 at -50C, set temp
19F, 1H-coupled, CDCl3, AV400
with TD offset, back linear prediction to correct
baseline hump coming from gradient coil

^{19}F NMR spectrum of *trans*-**356** at 223 K



Current Data Parameters
NAME ja11sp1f
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20010620
Time 11.00
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgflqn
TD 130982
SOLVENT CDCl3
NS 32
DS 0
SWH 75187.969 Hz
FIDRES 0.574033 Hz
AQ 0.8710803 sec
RG 32
DW 6.650 usec
DE 6.00 usec
TE 223.0 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 19F
P1 11.00 usec
PL1 -3.00 dB
SFO1 376.4128980 MHz

F2 - Processing parameters
SI 131072
SF 376.4468510 MHz
WDW EM
SSB 0
LB 0.50 Hz
GB 0
PC 0.20

STP - STEPHANE PINTAT

BRUKER

PPM

JN010S.147
AU PROG:
XO3.AU
DATE 1-6-73

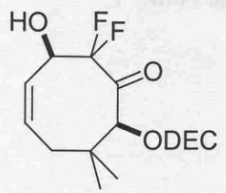
SA.NA B04111
SA.NO JN01 147
SF 282.407
SY 282.0
O1 -4147.000
SI 65536
TD 65536
SW 41666.667
HZ/PT 1.272

PW 0.0
RD 0.0
AQ .786
RG 32
NS 32
TE 297

FW 52100
O2 4900.000
DP 63L PO

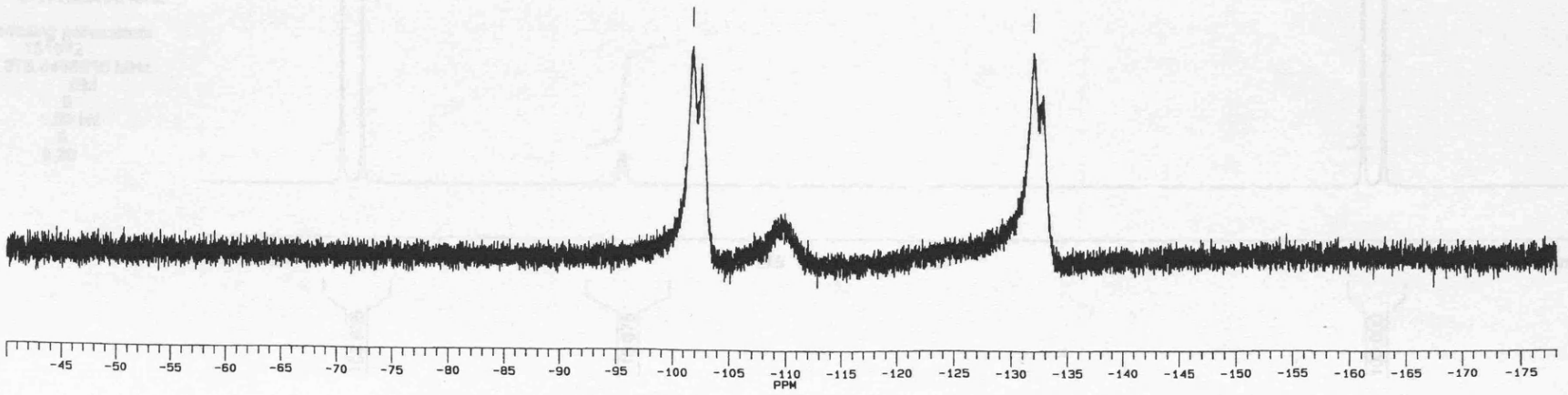
LB 1.000
GB 0.0
CX 40.00
CY 4.47
F1 -39.997P
F2 -179.996P
HZ/CM 988.420
PPM/CM 3.500
SR 27499.73

^{19}F NMR spectrum of *cis*-**356** at 300 K



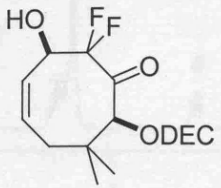
-101.955

-132.005



Stephane Pintat Sample SP361 in CDCl3 at -50C, set temp
19F, 1H-coupled, CDCl3, AV400
with TD offset, back linear prediction to correct
baseline hump coming from gradient coil

^{19}F NMR spectrum of *cis*-**356** at 223 K

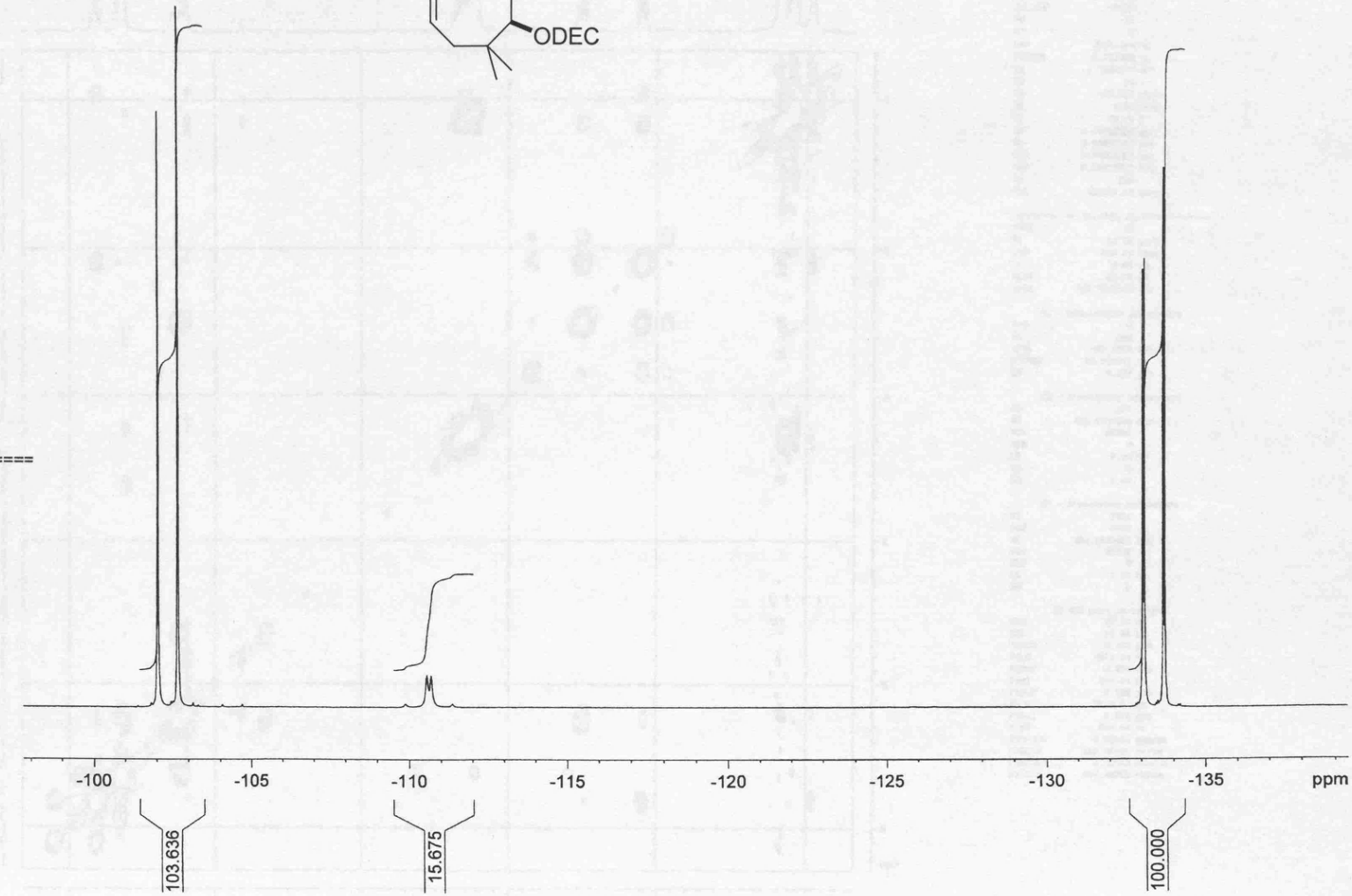


Current Data Parameters
NAME jn20sp3f
EXPNO 2
PROCNO 1

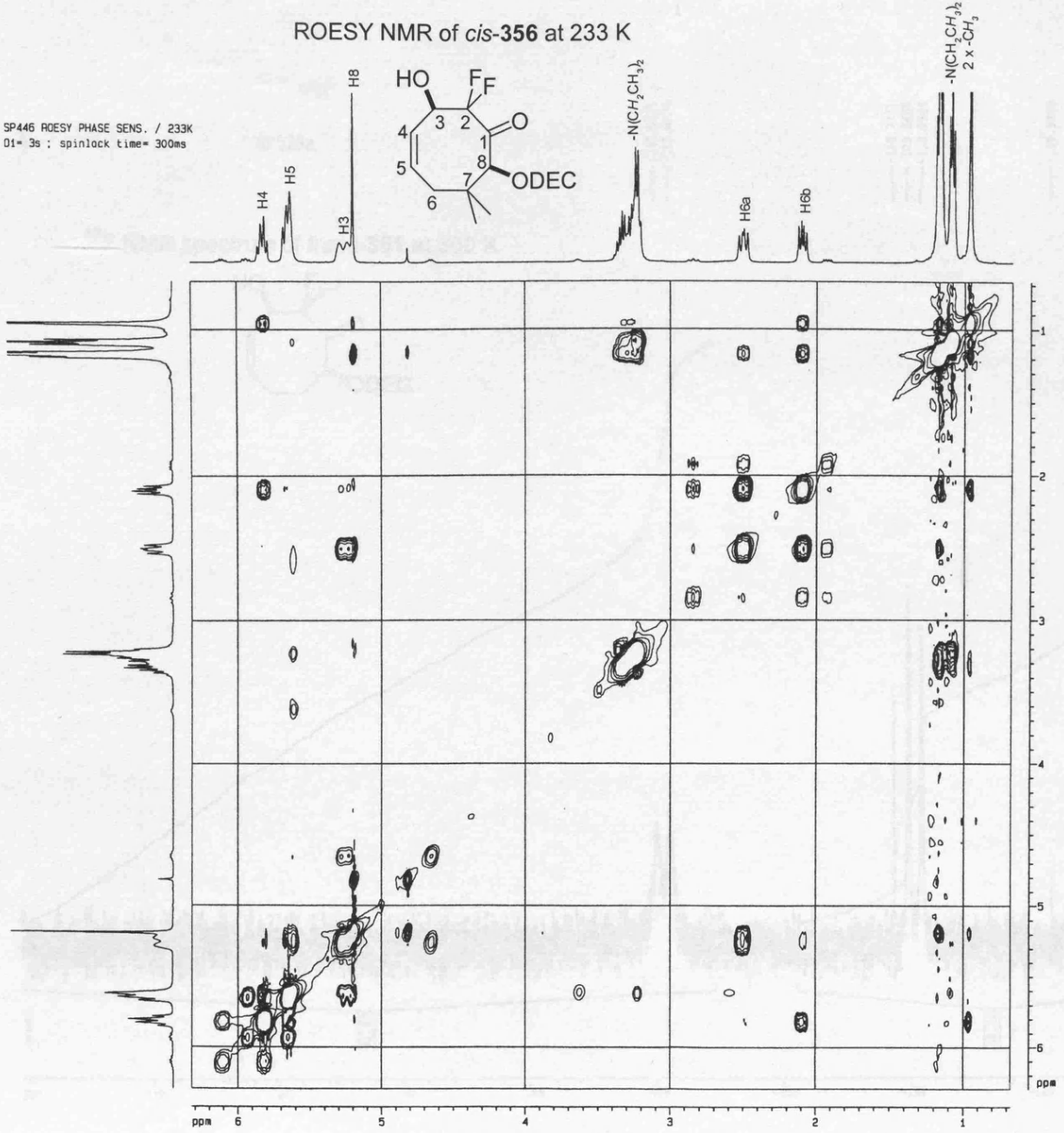
F2 - Acquisition Parameters
Date_ 20010620
Time 11.25
INSTRUM av400
PROBHD 5 mm BBO BB-1H
PULPROG zgflqn
TD 130982
SOLVENT CDCl3
NS 32
DS 0
SWH 75187.969 Hz
FIDRES 0.574033 Hz
AQ 0.8710803 sec
RG 32
DW 6.650 usec
DE 6.00 usec
TE 223.0 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 19F
P1 11.00 usec
PL1 -3.00 dB
SFO1 376.4128980 MHz

F2 - Processing parameters
SI 131072
SF 376.4468510 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.20



ROESY NMR of *cis*-**356** at 233 K



Current Data Parameters

NAME	sp446
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20020501
Time	11.44
INSTRUM	drx400
PROBHD	5 mm GHP 1H
PULPROG	roesytp.2
TD	2048
SOLVENT	CDCl3
NS	16
DS	16
SWH	3591.954 Hz
FIDRES	1.753884 Hz
AQ	0.2851316 sec
RG	50
DW	139.200 usec
DE	4.50 usec
TE	233.0 K
d0	0.00000300 sec
D1	3.00000000 sec
d12	0.00002000 sec
IN0	0.00013920 sec
l4	625
P15	300000.00 usec

---------- CHANNEL f1 ----------

NUC1	1H
P1	13.00 usec
P25	240.00 usec
PL1	0.00 dB
PL11	21.00 dB
SFO1	400.1315509 MHz

F1 - Acquisition parameters

ND0	2
TD	256
SFO1	400.1316 MHz
FIDRES	14.031071 Hz
SW	8.977 ppm

F2 - Processing parameters

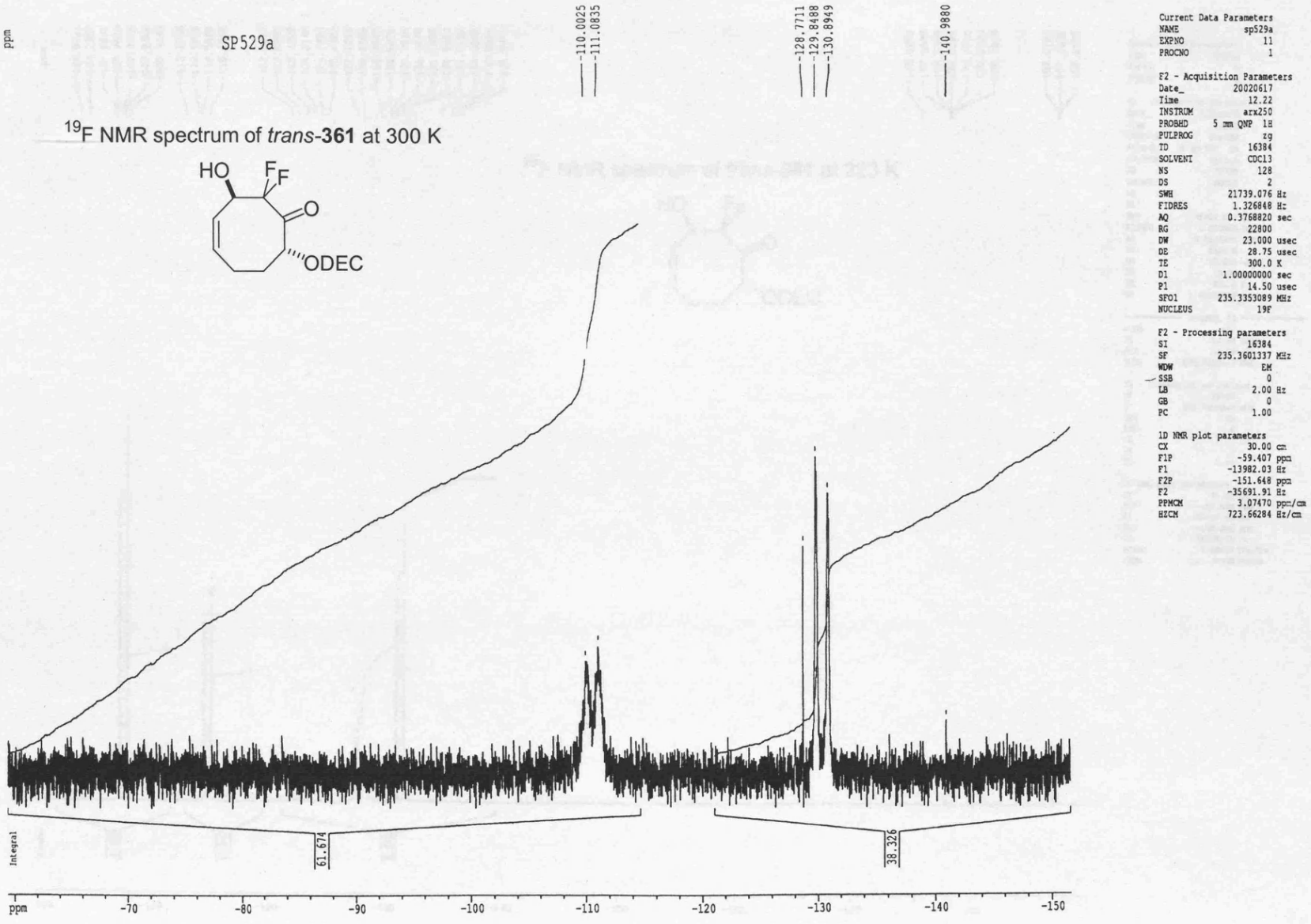
SI	1024
SF	400.1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	400.1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	22.00 cm
CX1	22.00 cm
F2PLO	6.322 ppm
F2LO	2529.54 Hz
F2PHI	0.676 ppm
F2HI	270.54 Hz
F1PLO	6.295 ppm
F1LO	2519.02 Hz
F1PHI	0.676 ppm
F1HI	270.54 Hz
F2PPMCM	0.25662 ppm/cm
F2HZCM	102.68192 Hz/cm
F1PPMCM	0.25543 ppm/cm
F1HZCM	102.20359 Hz/cm

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Current Data Parameters
NAME                  sp529a
EXPNO                     11
PROCNO                     1

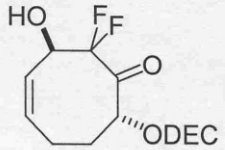
F2 - Acquisition Parameters
Date_              20020617
Time                  12.22
INSTRUM             arx250
PROBHD     5 mm QNP  1H
PULPROG                 zg
TD                     16384
SOLVENT                CDCl3
NS                       128
DS                         2
SWH               21739.076 Hz
FIDRES             1.326848 Hz
AQ                 0.3768820 sec
RG                     22800
DW                    23.000 usec
DE                    28.75 usec
TE                    300.0 K
D1                1.00000000 sec
P1                    14.50 usec
SFO1              235.3353089 MHz
NUCLEUS                 19F

F2 - Processing parameters
SI                     16384
SF                235.3601337 MHz
WDW                       EM
SSB                        0
LB                     2.00 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                    30.00 cm
F1P                  -59.407 ppm
F1                -13982.03 Hz
F2P                 -151.648 ppm
F2                -35691.91 Hz
PPMCM               3.07470 ppm/cm
HZCM              723.66284 Hz/cm
```

SP529A 19F /223K

^{19}F NMR spectrum of *trans*-**361** at 223 K



Current Data Parameters

NAME	sp529a
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

Date_	20020923
Time	14.07
INSTRUM	drx400
PROBHD	5 mm GNP 1H
PULPROG	zgflqn
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	41407.867 Hz
FIDRES	1.263668 Hz
AQ	0.3957236 sec
RG	1625.5
DW	12.075 usec
DE	15.09 usec
TE	223.0 K
D1	1.00000000 sec

CHANNEL f1

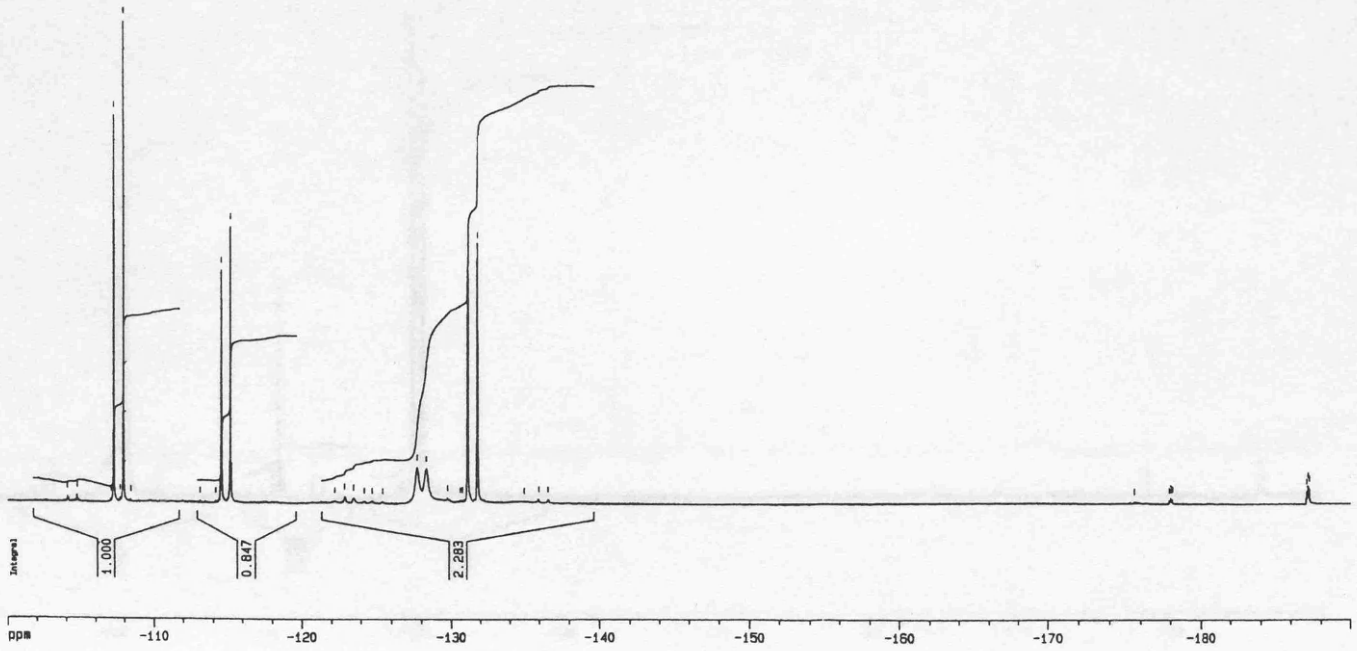
NUC1	19F
P1	14.60 usec
PL1	-3.00 dB
SFO1	376.4439417 MHz

F2 - Processing parameters

SI	32768
SF	376.4985340 MHz
WDW	EM
SSB	0
LB	1.50 Hz
GB	0
PC	2.00

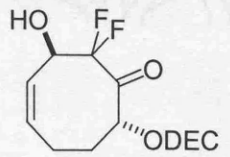
1D NMR plot parameters

CX	30.00 cm
F1P	-100.000 ppm
F1	-37649.86 Hz
F2P	-190.000 ppm
F2	-71534.72 Hz
PPMCM	3.00000 ppm/cm
HZCM	1129.49548 Hz/cm



SP529A 19F /323K

^{19}F NMR spectrum of *trans*-**361** at 323 K



Current Data Parameters
NAME sp529a
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020923
Time 9.37
INSTRUM drx400
PROBHD 5 mm QNP 1H
PULPROG zgflqn
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 41407.867 Hz
FIDRES 1.263668 Hz
AQ 0.3957236 sec
RG 2580.3
DW 12.075 usec
DE 15.09 usec
TE 323.0 K
D1 1.00000000 sec

CHANNEL f1
NUC1 19F
P1 14.60 usec
PL1 -3.00 dB
SFO1 376.4439417 MHz

F2 - Processing parameters
SI 32768
SF 376.4985340 MHz
WDW EM
SSB 0
LB 1.50 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 30.00 cm
F1P -100.000 ppm
F1 -37649.86 Hz
F2P -190.000 ppm
F2 -71534.72 Hz
PPMCM 3.00000 ppm/cm
HZCM 1129.49548 Hz/cm

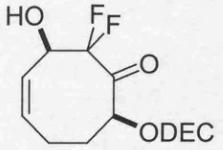
ppm
-64.7359
SP529b
19F NMR spectrum of cis-361 at 300 K
HO
F
F
O
ODEC
-100.4433
-105.5864
-106.6231
-106.7968
-108.4724
-109.5933
-114.0065
-115.1288
-117.9015
-117.9753
-119.0255
-119.0989
-120.2573
-120.3244
-121.3715
-121.4395
-125.8641
-127.1027
-127.1929
-128.1717
-128.7690
-131.7281
-131.8116
-132.7641
-132.8482
Integral
31.964
70.653
-2.617
ppm
-70
-80
-90
-100
-110
-120
-130
-140
Current Data Parameters
NAME sp529b
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20020508
Time 11.34
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 128
DS 2
SWH 21739.076 Hz
FIDRES 1.326848 Hz
AQ 0.3768820 sec
RG 16384
DW 23.000 usec
DE 28.75 usec
TE 300.0 K
D1 1.00000000 sec
P1 14.50 usec
SFO1 235.1353089 MHz
NUCLEUS 19F
F2 - Processing parameters
SI 16384
SF 235.3601337 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 30.00 cm
F1P -60.027 ppm
F1 -14127.98 Hz
F2P -151.270 ppm
F2 -35603.01 Hz
PPMCM 3.04144 ppm/cm
HZCM 9344? Hz/cm

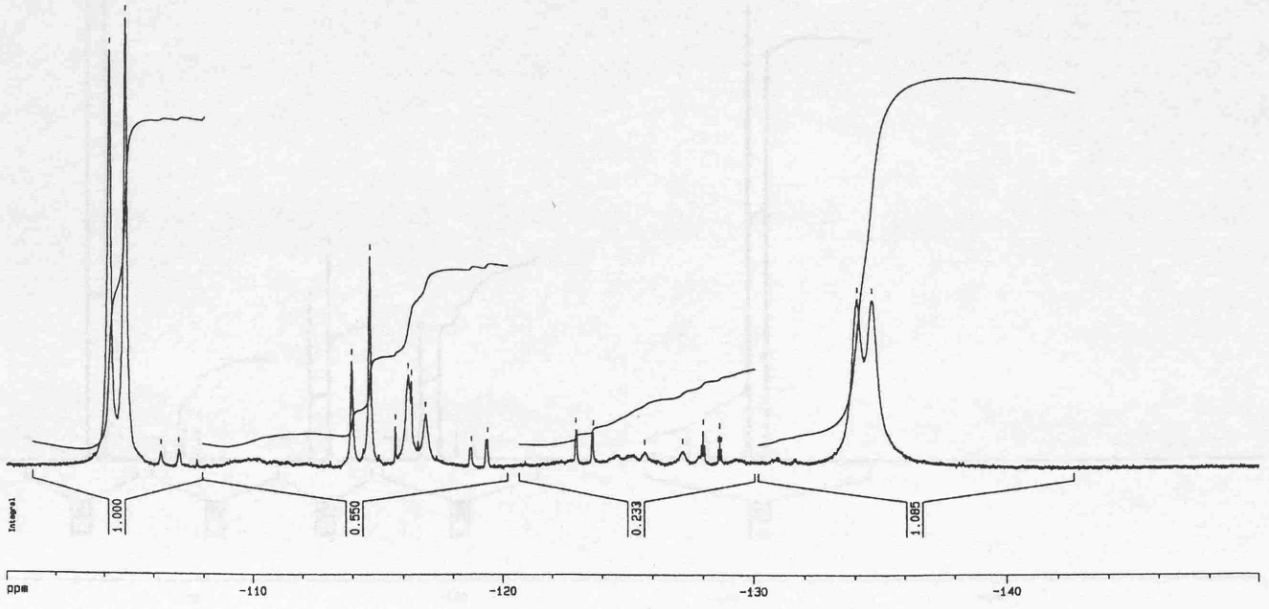
SP529B 19F /223K

ppm

104.2089
104.8508
106.3111
107.0092
113.9744
114.6863
115.7042
116.2259
116.3564
116.9296
118.7457
119.4035
122.9498
123.6367
125.7017
127.2095
128.0097
128.6049
128.6662
128.7284
134.0752
134.6813

^{19}F NMR spectrum of *cis*-**361** at 223 K





Current Data Parameters
NAME sp529b
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020923
Time 14.15
INSTRUM drx400
PROBHD 5 mm QNP 1H
PULPROG zgflqn
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 41407.067 Hz
FIDRES 1.263668 Hz
AQ 0.3957236 sec
RG 1625.5
DW 12.075 usec
DE 15.09 usec
TE 223.0 K
D1 1.00000000 sec

CHANNEL f1
NUC1 19F
P1 14.60 usec
PL1 -3.00 dB
SFO1 376.4439417 MHz

F2 - Processing parameters
SI 32768
SF 376.4985340 MHz
WDW EM
SSB 0
LB 1.50 Hz
GB 0
PC 4.00

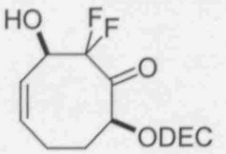
1D NMR plot parameters
CX 30.00 cm
F1P -100.000 ppm
F1 -37649.86 Hz
F2P -150.000 ppm
F2 -56474.78 Hz
PPMCM 1.66667 ppm/cm
HZCM 627.49744 Hz/cm

SP5298 19F /323K

ppm

106.3778
107.0273
109.2488
109.7949
109.9468
110.5015
114.7053
115.4039
115.4854
116.1465
118.8143
118.8610
119.5129
119.5597
120.1240
120.1642
120.8211
120.8616
126.0219
127.4342
127.4927
128.7124
128.7728
129.4320
129.4821
130.9499
131.0002
131.6001
131.6502

^{19}F NMR spectrum of *cis*-**361** at 323 K



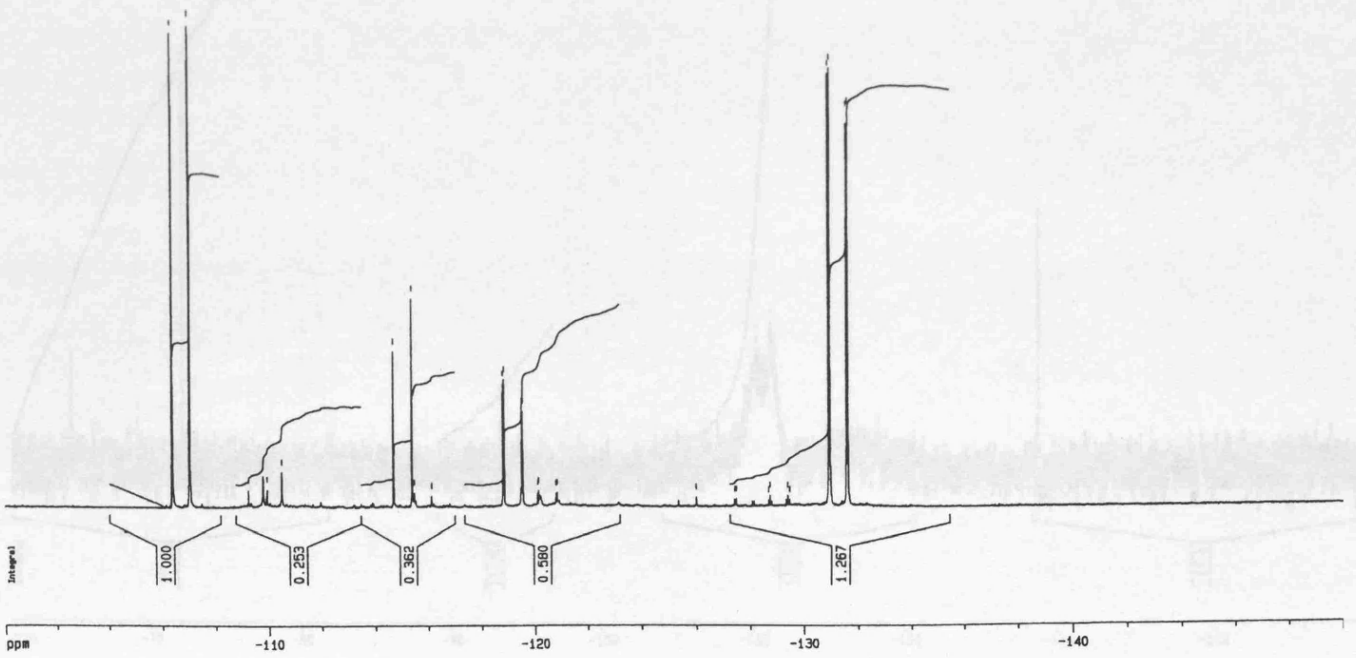
Current Data Parameters
NAME sp5298
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020923
Time 11.46
INSTRUM drx400
PROBHD 5 mm BNP 1H
PULPROG zgflqn
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 41407.967 Hz
FIDRES 1.263668 Hz
AQ 0.3957236 sec
RG 1625.5
DW 12.075 usec
DE 15.09 usec
TE 323.0 K
D1 1.00000000 sec

---------- CHANNEL f1 ----------
NUC1 19F
P1 14.60 usec
PL1 -3.00 dB
SFO1 376.4439417 MHz

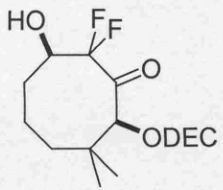
F2 - Processing parameters
SI 32768
SF 376.4985340 MHz
WDW EM
SSB 0
LB 1.50 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 30.00 cm
F1P -100.000 ppm
F1 -37649.86 Hz
F2P -150.000 ppm
F2 -56474.78 Hz
PPMCM 1.66667 ppm/cm
HZCM 627.49744 Hz/cm



SP485

^{19}F NMR spectrum of **362** at 300 K



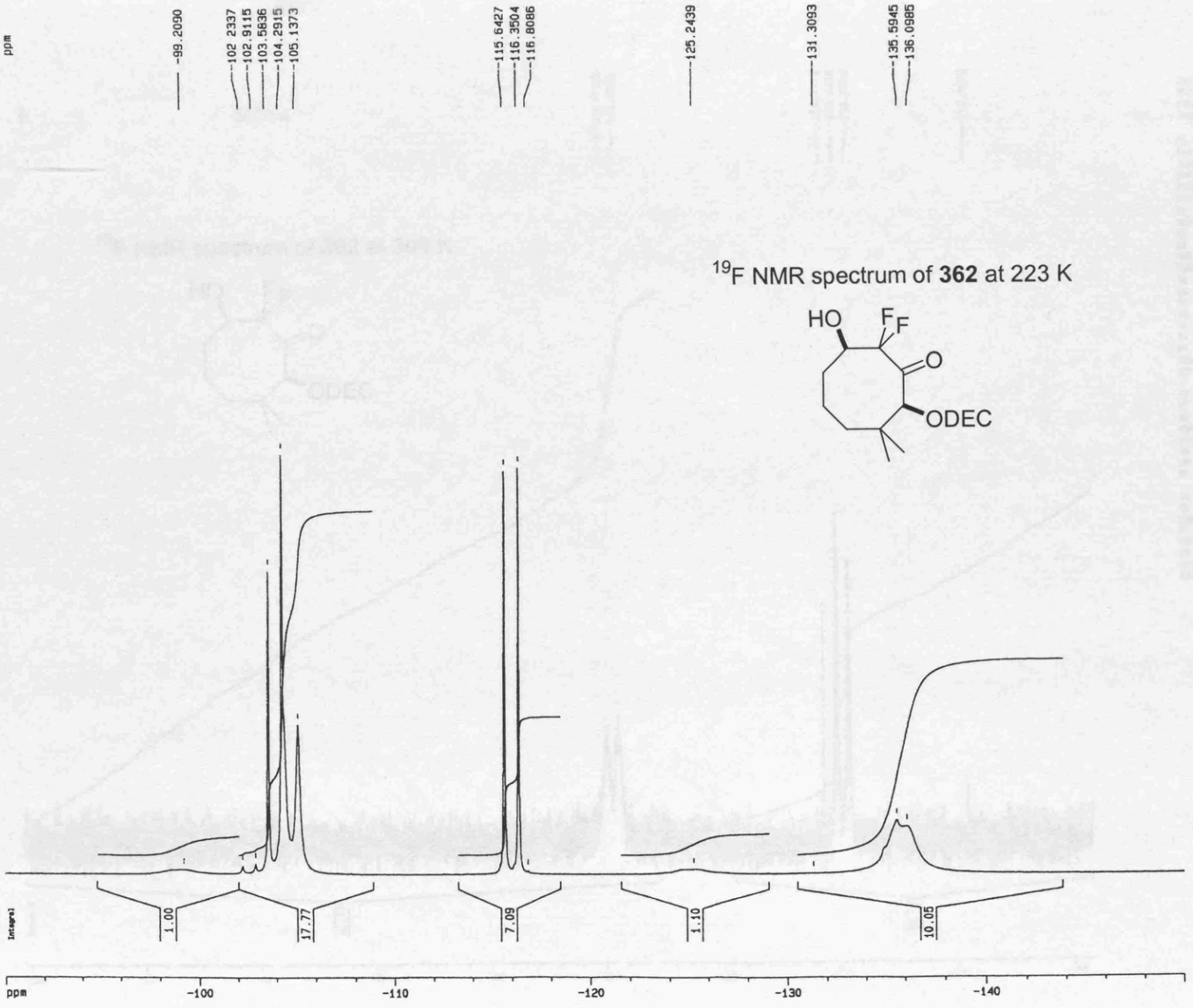

```
Current Data Parameters
NAME                 sp485
EXPNO                   21
PROCNO                   1

F2 - Acquisition Parameters
Date_             20020826
Time                 15.53
INSTRUM              arx250
PROBHD     5 mm QNP  1H
PULPROG                 zg
TD                   16384
SOLVENT              CDCl3
NS                     128
DS                       2
SWH              21739.076 Hz
FIDRES            1.326848 Hz
AQ                0.3768820 sec
RG                   11400
DW                  23.000 usec
DE                  28.75 usec
TE                  300.0 K
D1                1.00000000 sec
P1                  14.50 usec
SFO1             235.3353089 MHz
NUCLEUS                 19F

F2 - Processing parameters
SI                   16384
SF               235.3601337 MHz
WDW                     EM
SSB                      0
LB                    2.00 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   30.00 cm
F1P                -60.754 ppm
F1                -14299.14 Hz
F2P                -150.148 ppm
F2                -35338.97 Hz
PPMCM              2.97981 ppm/cm
HZCM              701.32751 Hz/cm
```

SP485 19F /223K



^{19}F NMR spectrum of **362** at 223 K

Current Data Parameters

NAME	sp485
EXPNO	6
PROCNO	1

F2 - Acquisition Parameters

Date_	20020923
Time	12.58
INSTRUM	drx400
PROBHD	5 mm BNP 1H
PULPROG	zgflqn
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	41407.867 Hz
FIDRES	1.263668 Hz
AQ	0.3957236 sec
RG	256
DW	12.075 usec
DE	15.09 usec
TE	223.0 K
D1	1.00000000 sec

CHANNEL f1

NUC1	19F
P1	14.60 usec
PL1	-3.00 dB
SFO1	376.4495892 MHz

F2 - Processing parameters

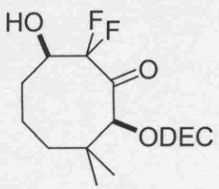
SI	32768
SF	376.4986340 MHz
WDW	EM
SSB	0
LB	1.50 Hz
GB	0
PC	2.00

1D NMR plot parameters

CX	30.00 cm
F1P	-90.000 ppm
F1	-33884.87 Hz
F2P	-150.000 ppm
F2	-56474.78 Hz
PPMCM	2.00000 ppm/cm
HZCM	752.99707 Hz/cm

SP529a

^{19}F NMR spectrum of **362** at 300 K



Current Data Parameters

NAME	sp529a
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

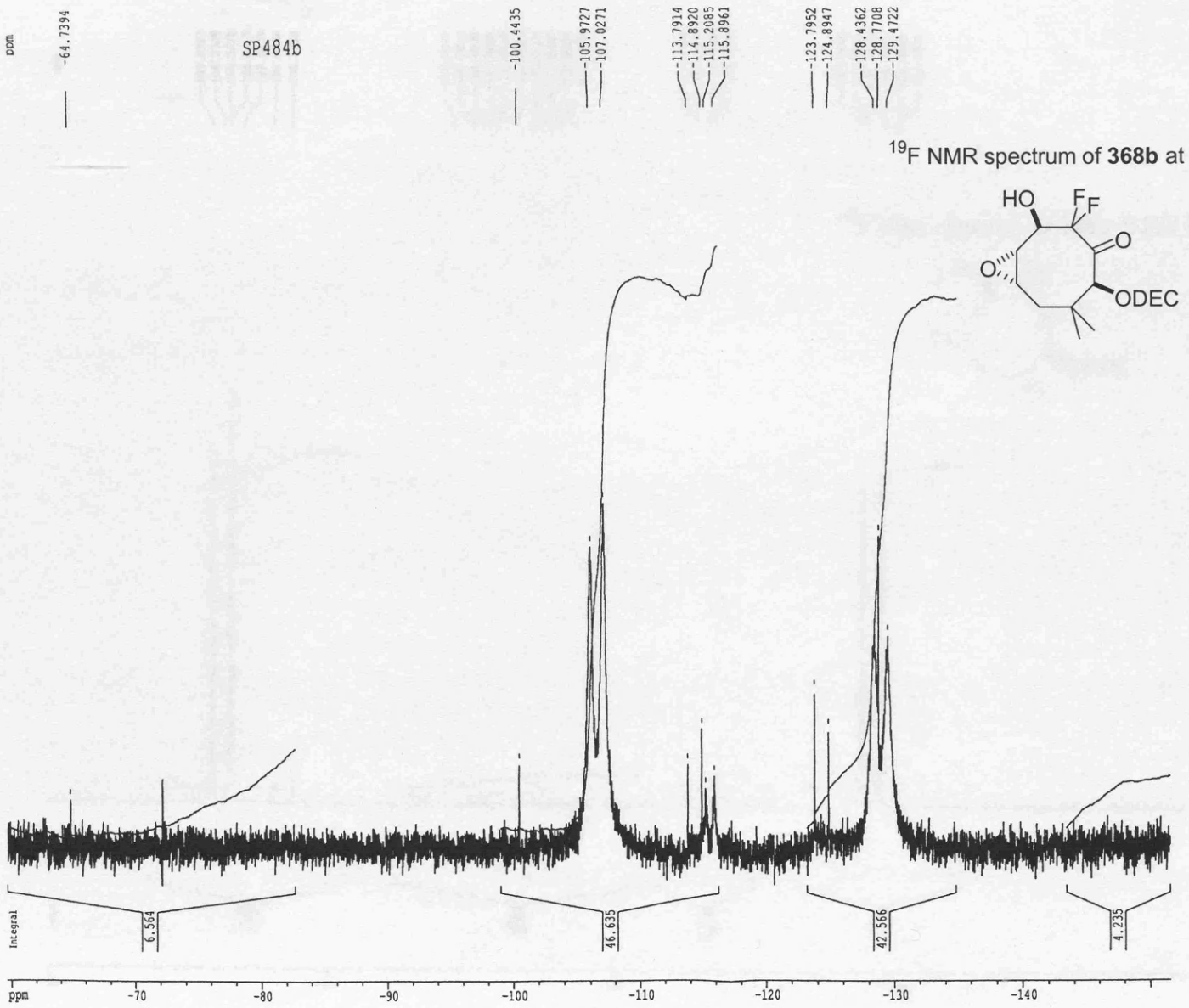
Date_	20020617
Time	12.22
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg
TD	16384
SOLVENT	CDCl3
NS	128
DS	2
SWH	21739.076 Hz
FIDRES	1.326848 Hz
AQ	0.3768820 sec
RG	22800
DW	23.000 usec
DE	28.75 usec
TE	300.0 K
D1	1.00000000 sec
P1	14.50 usec
SFO1	235.3353089 MHz
NUCLEUS	19F

F2 - Processing parameters

SI	16384
SF	235.3601337 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	30.00 cm
F1P	-59.407 ppm
F1	-13982.03 Hz
F2P	-151.648 ppm
F2	-35691.91 Hz
PPMCM	3.07470 ppm/cm
HZCM	723.66284 Hz/cm



^{19}F NMR spectrum of **368b** at 300 K

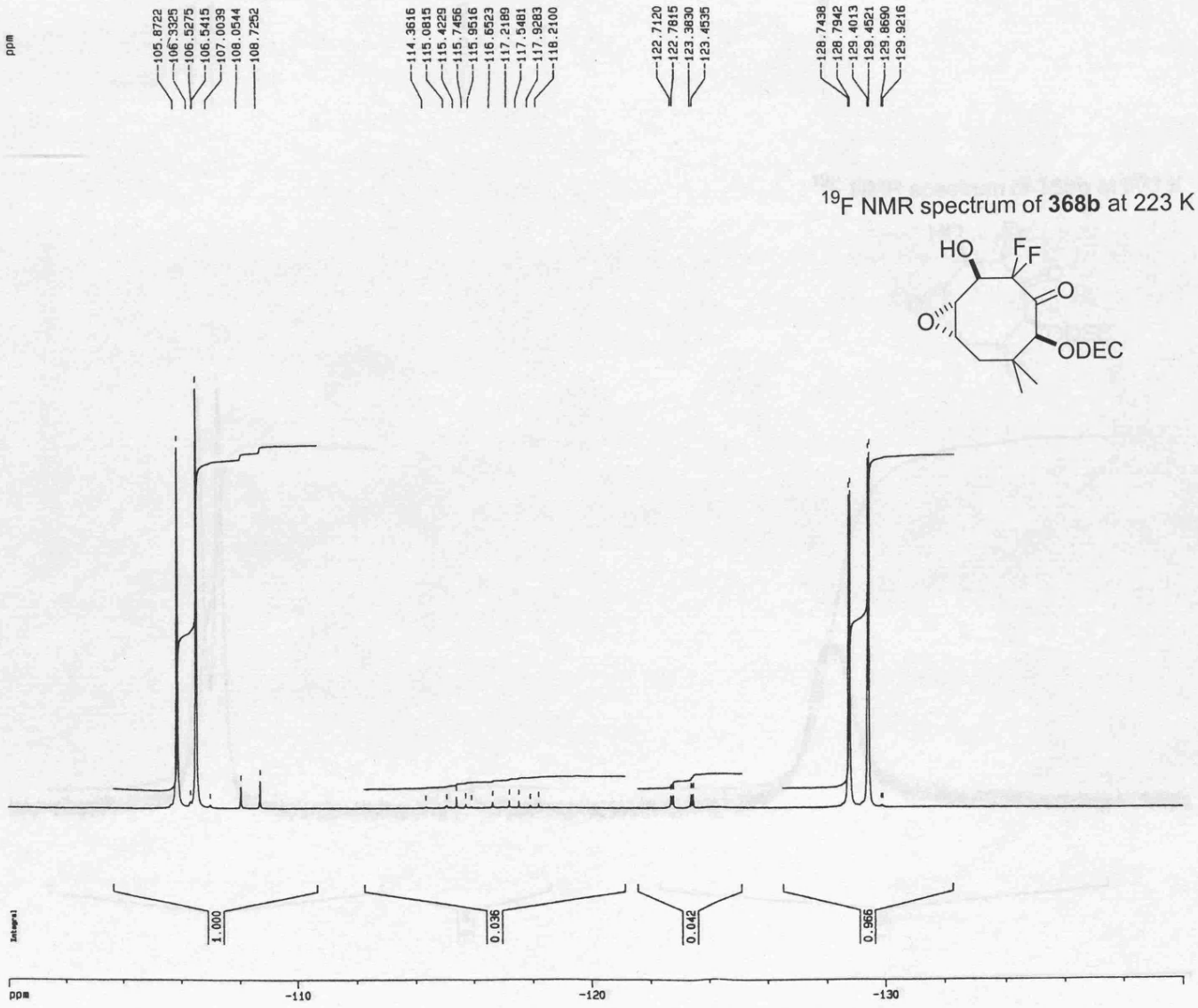
```
Current Data Parameters
NAME                  sp484b
EXPNO                     21
PROCNO                     1

F2 - Acquisition Parameters
Date_              20020208
Time                  20.54
INSTRUM              arx250
PROBHD     5 mm QNP  1H
PULPROG                   zg
TD                     16384
SOLVENT                CDCl3
NS                       128
DS                         2
SWH               21739.076 Hz
FIDRES             1.326848 Hz
AQ                 0.3768820 sec
RG                     16384
DW                    23.000 usec
DE                    28.75 usec
TE                    300.0 K
D1                1.00000000 sec
P1                    14.50 usec
SFO1              235.3353089 MHz
NUCLEUS                 19F

F2 - Processing parameters
SI                     16384
SF                235.3601337 MHz
WDW                       EM
SSB                        0
LB                    2.00 Hz
GB                         0
PC                     1.00

1D NMR plot parameters
CX                    30.00 cm
F1P                  -59.644 ppm
F1                -14037.75 Hz
F2P                 -151.552 ppm
F2                -35669.36 Hz
PPMCM              3.06362 ppm/cm
HZCM              721.05334 Hz/cm
```

SP484B 19F /223K



^{19}F NMR spectrum of **368b** at 223 K

Current Data Parameters
NAME sp484b
EXPNO 6
PROCNO 1

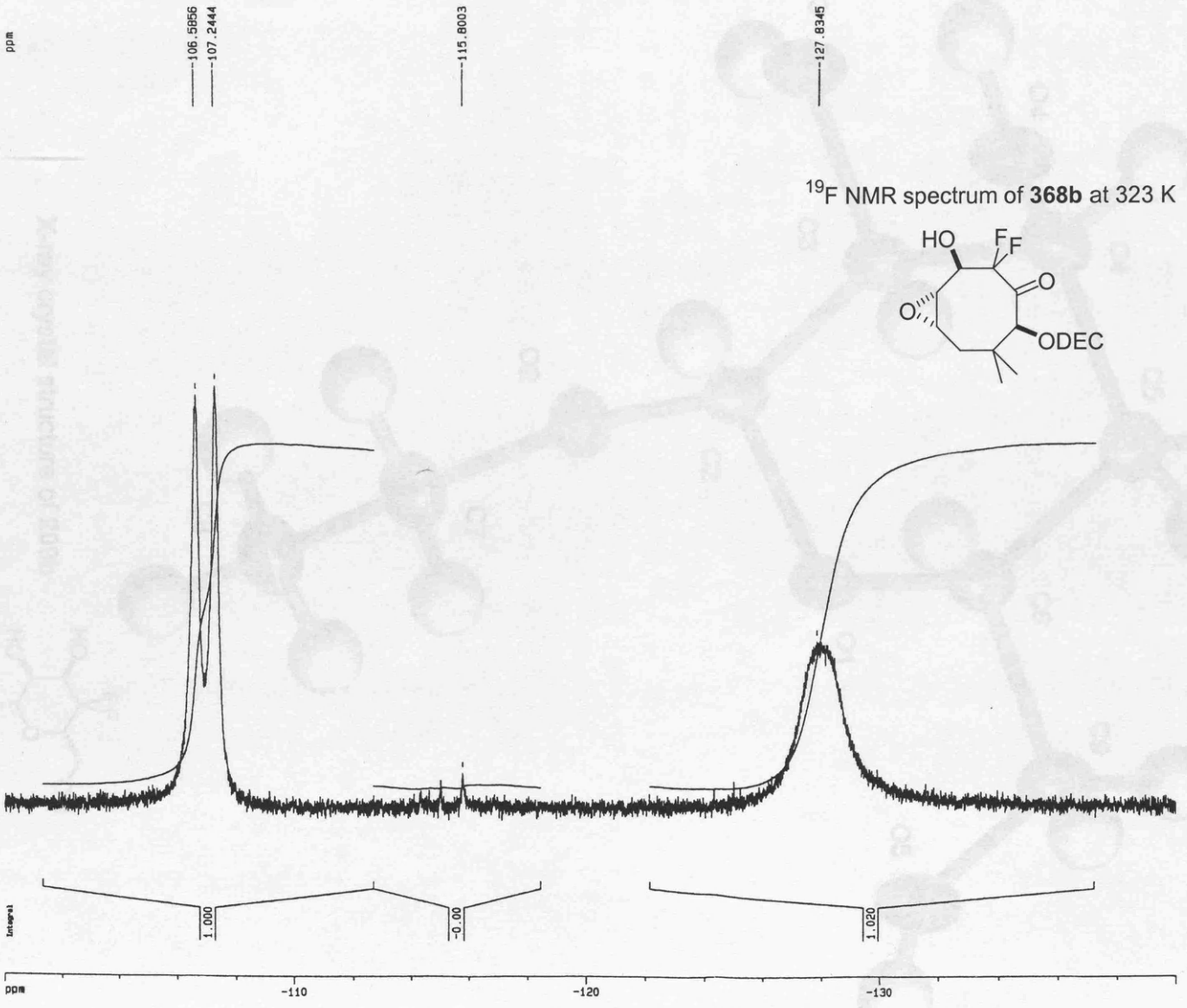
F2 - Acquisition Parameters
Date_ 20020923
Time 14.26
INSTRUM drx400
PROBHD 5 mm QNP 1H
PULPROG zgflqn
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 41407.867 Hz
FIDRES 1.263668 Hz
AQ 0.3957236 sec
RG 1290.2
DW 12.075 usec
DE 15.09 usec
TE 223.0 K
D1 1.00000000 sec

CHANNEL f1
NUC1 19F
P1 14.50 usec
PL1 -3.00 dB
SFO1 376.4495692 MHz

F2 - Processing parameters
SI 32768
SF 376.4985340 MHz
WDW EM
SSB 0
LB 1.50 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 30.00 cm
F1P -100.000 ppm
F1 -37649.86 Hz
F2P -140.000 ppm
F2 -52709.80 Hz
PPMCM 1.33333 ppm/cm
HZCM 501.99796 Hz/cm

SP484B 19F /323K



^{19}F NMR spectrum of **368b** at 323 K


```
Current Data Parameters
NAME                  sp484b
EXPNO                      5
PROCNO                     1

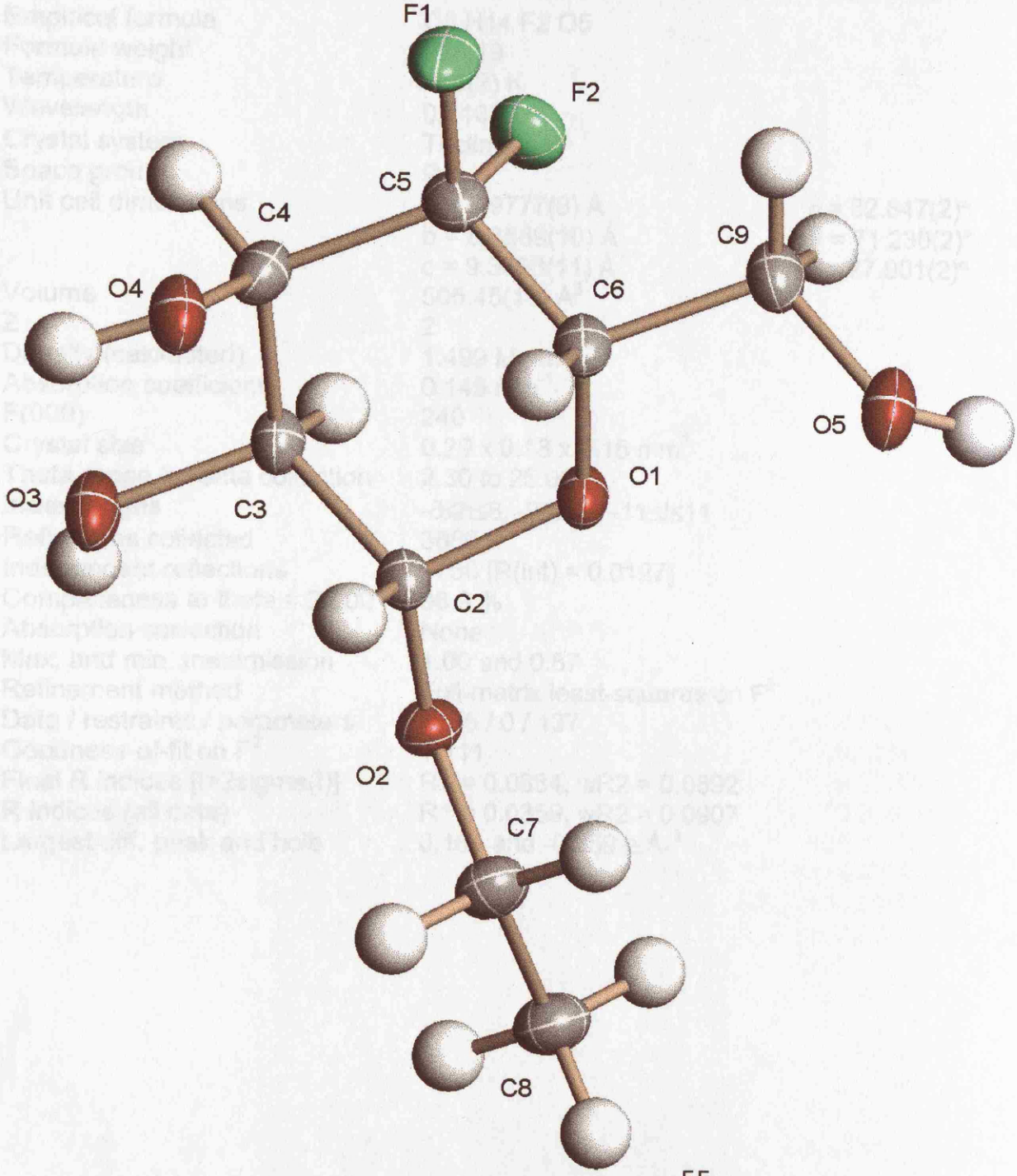
F2 - Acquisition Parameters
Date_              20020923
Time                   9.11
INSTRUM              drx400
PROBHD     5 mm QNP  1H
PULPROG              zgflqn
TD                    32768
SOLVENT               CDCl3
NS                       64
DS                        2
SWH                41407.867 Hz
FIDRES             1.263668 Hz
AQ                 0.3957236 sec
RG                    5792.6
DW                   12.075 usec
DE                   15.09 usec
TE                     323.0 K
D1                1.00000000 sec

========== CHANNEL f1 ==========
NUC1                     19F
P1                     14.60 usec
PL1                    -3.00 dB
SFO1             376.4495892 MHz

F2 - Processing parameters
SI                    32768
SF               376.4985340 MHz
WDW                      EM
SSB                       0
LB                     1.50 Hz
GB                        0
PC                     2.00

1D NMR plot parameters
CX                    30.00 cm
F1P                 -100.000 ppm
F1                -37649.86 Hz
F2P                 -140.000 ppm
F2                -52709.80 Hz
PPMCM                1.33333 ppm/cm
HZCM               501.99796 Hz/cm
```

Appendix 2: X-ray crystal structures



X-ray crystal structure of **209b**

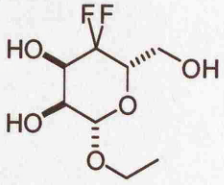


Table 1.Crystal data and structure refinement for **209b**.

Empirical formula	C8 H14 F2 O5	
Formula weight	228.19	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.9777(8) Å	α = 82.847(2)°
	b = 8.3569(10) Å	β = 71.230(2)°
	c = 9.3808(11) Å	γ = 77.901(2)°
Volume	505.45(10) $Å^3$	
Z	2	
Density (calculated)	1.499 Mg/m^3	
Absorption coefficient	0.145 mm^{-1}	
F(000)	240	
Crystal size	0.29 x 0.18 x 0.16 mm^3	
Theta range for data collection	2.30 to 25.00°	
Index ranges	$-8\leq h\leq 8$, $-9\leq k\leq 9$, $-11\leq l\leq 11$	
Reflections collected	3650	
Independent reflections	1756 [R(int) = 0.0127]	
Completeness to theta = 25.00°	98.9 %	
Absorption correction	None	
Max. and min. transmission	1.00 and 0.87	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1756 / 0 / 137	
Goodness-of-fit on F^2	1.111	
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0892	
R indices (all data)	R1 = 0.0359, wR2 = 0.0907	
Largest diff. peak and hole	0.184 and -0.259 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **209b**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
F(1)	8274(1)	4065(1)	-1(1)	34(1)
F(2)	8819(1)	2645(1)	1985(1)	34(1)
O(1)	4577(1)	3473(1)	3592(1)	21(1)
O(2)	2684(1)	1485(1)	4616(1)	22(1)
O(3)	4688(1)	-308(1)	1971(1)	26(1)
O(4)	5384(1)	2410(1)	1(1)	26(1)
O(5)	4736(1)	6845(1)	3653(1)	27(1)
C(2)	3687(2)	2206(2)	3254(1)	20(1)
C(3)	5437(2)	952(2)	2381(1)	21(1)
C(4)	6638(2)	1780(2)	925(1)	23(1)
C(5)	7340(2)	3232(2)	1288(2)	24(1)
C(6)	5600(2)	4399(2)	2292(1)	21(1)
C(7)	656(2)	2372(2)	5315(2)	28(1)
C(8)	-91(2)	1697(2)	6904(2)	31(1)
C(9)	6398(2)	5693(2)	2812(2)	26(1)

Table 3. Bond lengths (Å) and angles (°) for **209b**

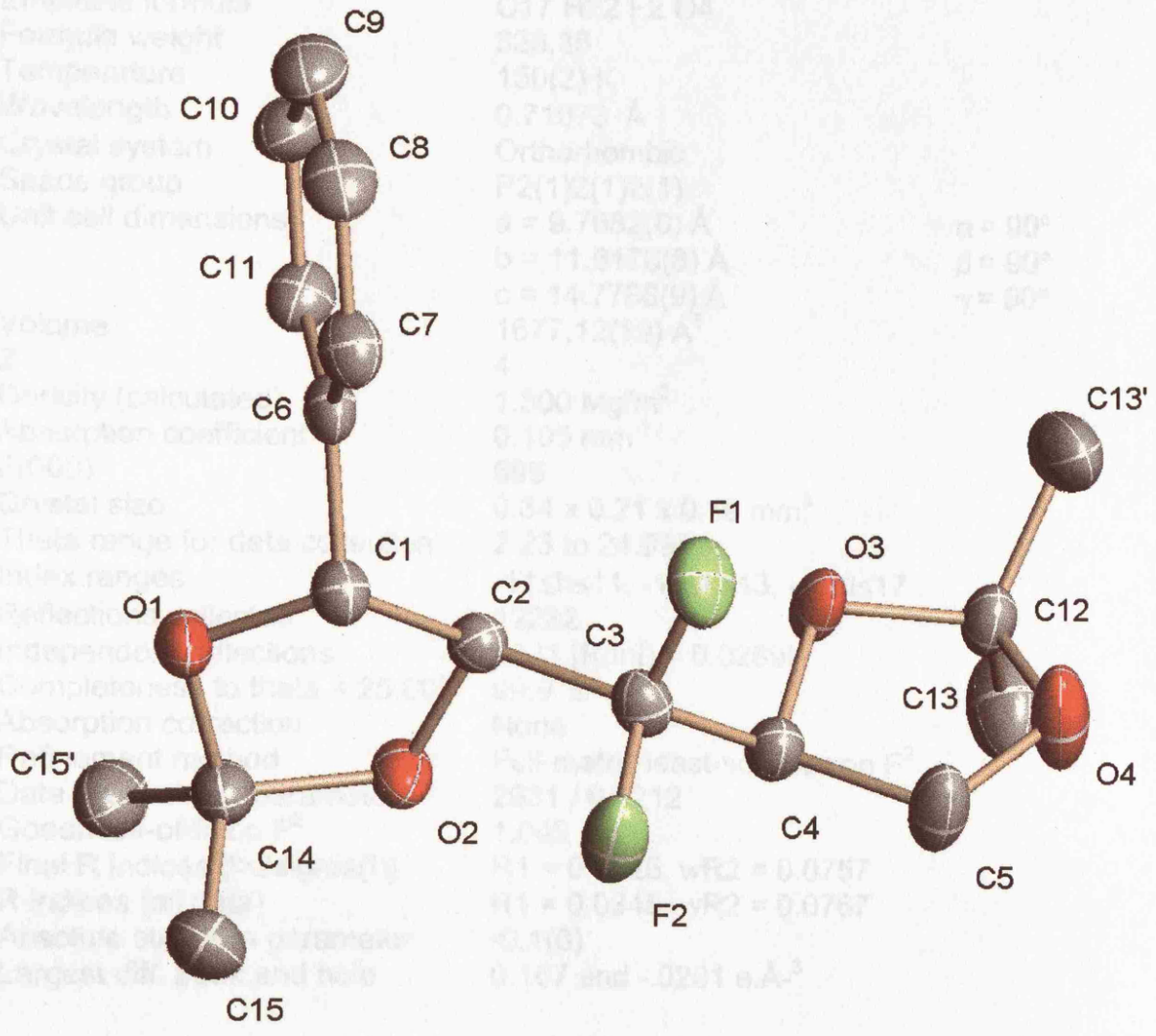
F(1)-C(5)	1.3585(15)	O(3)-C(3)-C(4)	107.05(10)
F(2)-C(5)	1.3695(15)	C(2)-C(3)-C(4)	109.25(10)
O(1)-C(6)	1.4255(14)	O(4)-C(4)-C(5)	106.23(10)
O(1)-C(2)	1.4464(15)	O(4)-C(4)-C(3)	110.99(10)
O(2)-C(2)	1.3767(15)	C(5)-C(4)-C(3)	109.48(10)
O(2)-C(7)	1.4373(15)	F(1)-C(5)-F(2)	105.92(10)
O(3)-C(3)	1.4110(15)	F(1)-C(5)-C(4)	110.39(11)
O(4)-C(4)	1.4059(15)	F(2)-C(5)-C(4)	107.97(10)
O(5)-C(9)	1.4233(16)	F(1)-C(5)-C(6)	109.55(10)
C(2)-C(3)	1.5148(17)	F(2)-C(5)-C(6)	109.68(11)
C(3)-C(4)	1.5227(17)	C(4)-C(5)-C(6)	113.06(11)
C(4)-C(5)	1.5128(19)	O(1)-C(6)-C(9)	108.10(10)
C(5)-C(6)	1.5189(18)	O(1)-C(6)-C(5)	108.20(9)
C(6)-C(9)	1.5092(17)	C(9)-C(6)-C(5)	111.53(11)
C(7)-C(8)	1.4921(19)	O(2)-C(7)-C(8)	108.66(10)
		O(5)-C(9)-C(6)	110.54(10)
C(6)-O(1)-C(2)	113.88(9)		
C(2)-O(2)-C(7)	113.53(9)		
O(2)-C(2)-O(1)	106.73(9)		
O(2)-C(2)-C(3)	109.27(10)		
O(1)-C(2)-C(3)	107.66(10)		
O(3)-C(3)-C(2)	111.14(10)		

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **209b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	41(1)	33(1)	24(1)	-2(1)	3(1)	-19(1)
F(2)	26(1)	36(1)	41(1)	-6(1)	-13(1)	-5(1)
O(1)	29(1)	19(1)	16(1)	-2(1)	-6(1)	-9(1)
O(2)	23(1)	21(1)	20(1)	0(1)	-3(1)	-5(1)
O(3)	43(1)	19(1)	21(1)	-1(1)	-10(1)	-11(1)
O(4)	42(1)	22(1)	19(1)	-1(1)	-12(1)	-1(1)
O(5)	43(1)	21(1)	21(1)	-3(1)	-13(1)	-7(1)
C(2)	25(1)	19(1)	17(1)	-1(1)	-7(1)	-7(1)
C(3)	26(1)	18(1)	20(1)	-3(1)	-8(1)	-5(1)
C(4)	28(1)	21(1)	19(1)	-3(1)	-4(1)	-4(1)
C(5)	26(1)	26(1)	20(1)	1(1)	-5(1)	-9(1)
C(6)	28(1)	19(1)	17(1)	2(1)	-7(1)	-8(1)
C(7)	22(1)	31(1)	27(1)	-4(1)	-5(1)	-1(1)
C(8)	25(1)	36(1)	27(1)	-3(1)	-2(1)	-5(1)
C(9)	34(1)	23(1)	24(1)	-1(1)	-10(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **209b**

	x	y	z	U(eq)
H(3)	4632	-1086	2635	40
H(4)	5025	1634	-280	40
H(5)	4876	6907	4500	41
H(2)	2714	2677	2662	24
H(3A)	6368	473	3003	25
H(4A)	7855	982	371	28
H(6)	4609	4935	1732	25
H(7A)	-288	2255	4756	33
H(7B)	695	3552	5299	33
H(8A)	-153	535	6910	46
H(8B)	-1467	2302	7398	46
H(8C)	855	1811	7448	46
H(9A)	7275	5167	3448	31
H(9B)	7252	6270	1925	31



X-ray crystal structure of **301c**
Hydrogen atoms omitted for clarity

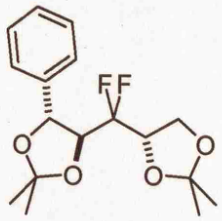


Table 1.Crystal data and structure refinement for **301c**.

Empirical formula	C17 H22 F2 O4	
Formula weight	328.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.7682(6) Å	$\alpha = 90°$
	b = 11.6176(8) Å	$\beta = 90°$
	c = 14.7786(9) Å	$\gamma = 90°$
Volume	1677.12(19) $Å^3$	
Z	4	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	696	
Crystal size	0.34 x 0.21 x 0.19 mm^3	
Theta range for data collection	2.23 to 24.99°	
Index ranges	$-11 \le h \le 11$, $-13 \le k \le 13$, $-17 \le l \le 17$	
Reflections collected	12232	
Independent reflections	2931 [R(int) = 0.0269]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2931 / 0 / 212	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0325, wR2 = 0.0757	
R indices (all data)	R1 = 0.0345, wR2 = 0.0767	
Absolute structure parameter	-0.1(6)	
Largest diff. peak and hole	0.167 and -.0201 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **301c**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
F(1)	2240(1)	4020(1)	1494(1)	40(1)
F(2)	3394(1)	5462(1)	2053(1)	44(1)
O(1)	4229(1)	3328(1)	3953(1)	31(1)
O(2)	5368(1)	3996(1)	2722(1)	32(1)
O(3)	4389(1)	3381(1)	434(1)	34(1)
O(4)	3840(2)	4639(1)	-662(1)	56(1)
C(1)	3201(2)	3456(1)	3265(1)	26(1)
C(2)	4092(2)	3569(1)	2412(1)	24(1)
C(3)	3535(2)	4376(1)	1705(1)	28(1)
C(4)	4376(2)	4471(1)	857(1)	30(1)
C(5)	3803(2)	5275(2)	135(1)	44(1)
C(6)	2270(2)	2433(1)	3282(1)	27(1)
C(7)	872(2)	2565(2)	3387(1)	32(1)
C(8)	25(2)	1613(2)	3408(1)	38(1)
C(9)	560(2)	524(2)	3319(1)	38(1)
C(10)	1957(2)	383(2)	3206(1)	35(1)
C(11)	2800(2)	1328(1)	3187(1)	31(1)
C(12)	4492(2)	3571(1)	-520(1)	32(1)
C(13)	5956(2)	3627(2)	-797(1)	59(1)
C(13')	3690(3)	2659(2)	-997(1)	59(1)
C(14)	5354(2)	4023(2)	3700(1)	32(1)
C(15)	5186(2)	5246(2)	4019(1)	43(1)
C(15')	6647(2)	3457(2)	4036(1)	43(1)

Table 3. Bond lengths (Å) and angles (°) for **301c**

F(1)-C(3)	1.3668(19)
F(2)-C(3)	1.3687(18)
O(1)-C(14)	1.4145(19)
O(1)-C(1)	1.4369(18)
O(2)-C(2)	1.4178(19)
O(2)-C(14)	1.445(2)
O(3)-C(4)	1.4120(19)
O(3)-C(12)	1.4305(19)
O(4)-C(5)	1.390(2)
O(4)-C(12)	1.411(2)
C(1)-C(6)	1.497(2)
C(1)-C(2)	1.537(2)
C(2)-C(3)	1.505(2)
C(3)-C(4)	1.504(2)
C(4)-C(5)	1.524(2)
C(6)-C(7)	1.383(2)
C(6)-C(11)	1.391(2)
C(7)-C(8)	1.382(2)
C(8)-C(9)	1.374(3)
C(9)-C(10)	1.384(2)
C(10)-C(11)	1.373(2)
C(12)-C(13)	1.489(3)
C(12)-C(13')	1.494(3)
C(14)-C(15)	1.506(2)
C(14)-C(15')	1.508(2)

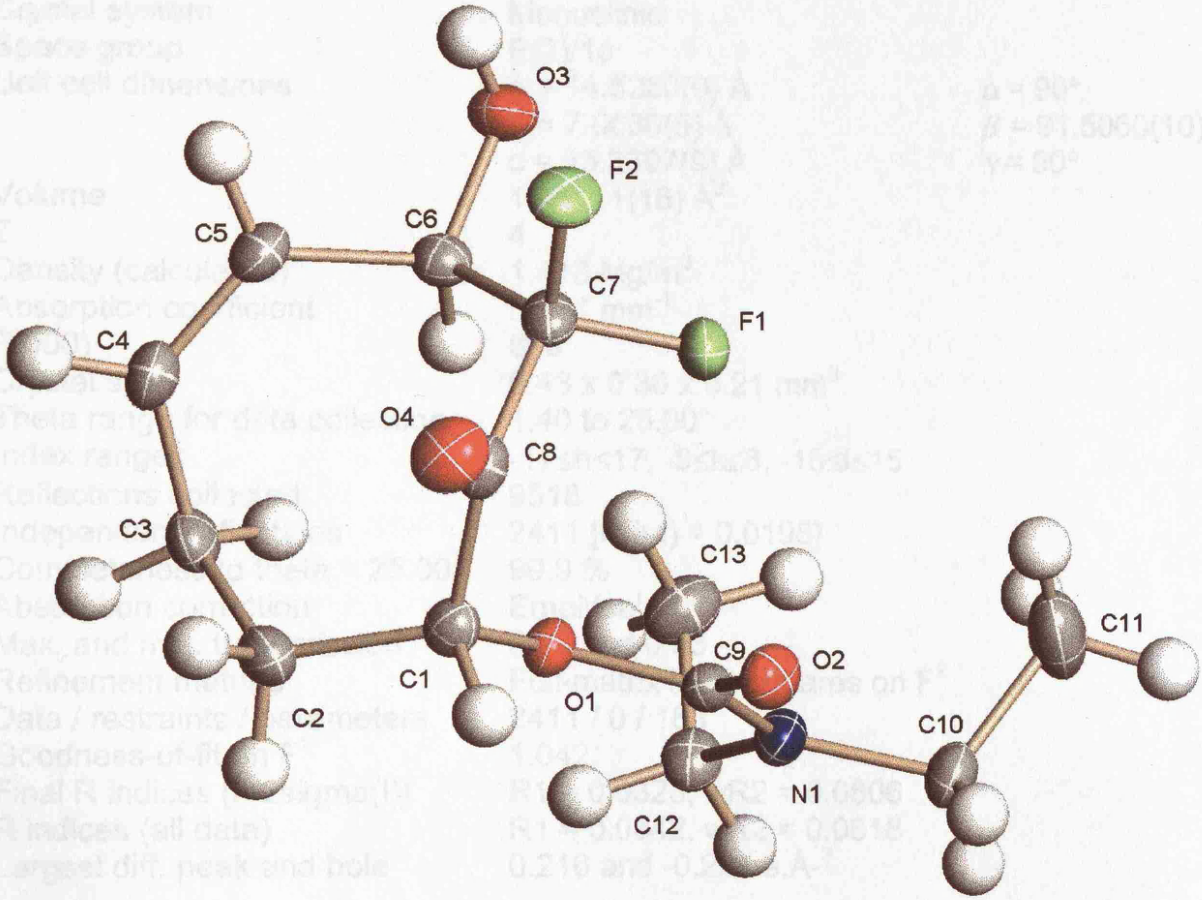
C(14)-O(1)-C(1)	107.25(11)
C(2)-O(2)-C(14)	108.82(12)
C(4)-O(3)-C(12)	107.33(11)
C(5)-O(4)-C(12)	110.64(13)
O(1)-C(1)-C(6)	109.23(12)
O(1)-C(1)-C(2)	101.14(11)
C(6)-C(1)-C(2)	115.18(13)
O(2)-C(2)-C(3)	108.91(12)
O(2)-C(2)-C(1)	105.22(11)
C(3)-C(2)-C(1)	114.62(13)
F(1)-C(3)-F(2)	105.76(12)
F(1)-C(3)-C(4)	109.71(13)
F(2)-C(3)-C(4)	107.52(13)
F(1)-C(3)-C(2)	107.75(13)
F(2)-C(3)-C(2)	110.47(13)
C(4)-C(3)-C(2)	115.24(13)
O(3)-C(4)-C(3)	107.96(13)
O(3)-C(4)-C(5)	104.07(13)
C(3)-C(4)-C(5)	115.34(15)
O(4)-C(5)-C(4)	104.95(14)
C(7)-C(6)-C(11)	118.75(15)
C(7)-C(6)-C(1)	120.88(15)
C(11)-C(6)-C(1)	120.37(14)
C(8)-C(7)-C(6)	120.29(16)
C(9)-C(8)-C(7)	120.49(15)
C(8)-C(9)-C(10)	119.69(17)
C(11)-C(10)-C(9)	119.90(18)
C(10)-C(11)-C(6)	120.88(15)
O(4)-C(12)-O(3)	104.54(12)
O(4)-C(12)-C(13)	110.73(17)
O(3)-C(12)-C(13)	110.20(15)
O(4)-C(12)-C(13')	108.47(16)
O(3)-C(12)-C(13')	108.56(14)
C(13)-C(12)-C(13')	113.90(17)
O(1)-C(14)-O(2)	105.02(13)
O(1)-C(14)-C(15)	111.82(15)
O(2)-C(14)-C(15)	109.54(14)
O(1)-C(14)-C(15')	108.31(13)
O(2)-C(14)-C(15')	108.16(15)
C(15)-C(14)-C(15')	113.58(16)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **301c**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	29(1)	58(1)	34(1)	4(1)	-3(1)	7(1)
F(2)	72(1)	30(1)	28(1)	-2(1)	3(1)	17(1)
O(1)	33(1)	39(1)	21(1)	3(1)	-3(1)	-8(1)
O(2)	29(1)	43(1)	25(1)	4(1)	-1(1)	-8(1)
O(3)	56(1)	26(1)	19(1)	1(1)	6(1)	5(1)
O(4)	100(1)	43(1)	25(1)	-2(1)	-10(1)	27(1)
C(1)	27(1)	31(1)	22(1)	0(1)	0(1)	1(1)
C(2)	26(1)	24(1)	23(1)	-1(1)	2(1)	0(1)
C(3)	33(1)	28(1)	24(1)	-4(1)	-1(1)	5(1)
C(4)	39(1)	26(1)	24(1)	0(1)	1(1)	0(1)
C(5)	74(1)	33(1)	25(1)	1(1)	2(1)	12(1)
C(6)	28(1)	36(1)	17(1)	1(1)	0(1)	0(1)
C(7)	28(1)	43(1)	24(1)	-1(1)	3(1)	4(1)
C(8)	24(1)	55(1)	34(1)	0(1)	3(1)	-1(1)
C(9)	33(1)	44(1)	37(1)	5(1)	2(1)	-9(1)
C(10)	35(1)	33(1)	37(1)	5(1)	1(1)	-4(1)
C(11)	23(1)	37(1)	32(1)	4(1)	2(1)	1(1)
C(12)	44(1)	30(1)	21(1)	3(1)	2(1)	2(1)
C(13)	51(1)	93(2)	33(1)	2(1)	9(1)	4(1)
C(13')	86(2)	58(1)	32(1)	-7(1)	1(1)	-23(1)
C(14)	33(1)	35(1)	26(1)	3(1)	-3(1)	-6(1)
C(15)	50(1)	39(1)	39(1)	-5(1)	-5(1)	-6(1)
C(15')	40(1)	47(1)	43(1)	9(1)	-9(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **301c**

	x	y	z	U(eq)
H(1)	2666	4179	3365	32
H(2)	4229	2790	2138	29
H(4)	5332	4705	1013	35
H(5A)	2853	5504	282	53
H(5B)	4373	5976	81	53
H(7)	492	3314	3446	38
H(8)	-933	1711	3484	45
H(9)	-26	-128	3334	45
H(10)	2331	-368	3142	42
H(11)	3757	1226	3109	37
H(13A)	6015	3811	-1443	89
H(13B)	6394	28822	-683	89
H(13C)	6424	4226	-446	89
H(13D)	2730	2700	-808	88
H(13E)	4063	1900	-843	88
H(13F)	3752	2778	-1652	88
H(15D)	4318	5556	3792	64
H(15E)	5946	5715	3790	64
H(15F)	5185	5264	4682	64
H(15A)	6637	3433	4698	65
H(15B)	7443	3898	3829	65
H(15C)	6701	2671	3797	65



X-ray crystal structure of *trans*-**361**

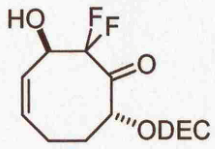


Table 1.Crystal data and structure refinement for *trans*-**361**.

Empirical formula	C13 H19 F2 N O4	
Formula weight	291.29	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P(2)/1c	
Unit cell dimensions	a = 14.5260(9) Å	$\alpha = 90°$
	b = 7.0680(5) Å	$\beta = 91.5060(10)°$
	c = 13.3397(9) Å	$\gamma = 90°$
Volume	1369.11(16) $Å^3$	
Z	4	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	616	
Crystal size	0.43 x 0.36 x 0.21 mm^3	
Theta range for data collection	1.40 to 25.00°	
Index ranges	$-17 \leq h \leq 17$, $-8 \leq k \leq 8$, $-15 \leq l \leq 15$	
Reflections collected	9518	
Independent reflections	2411 [R(int) = 0.0198]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.98 and 0.93	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2411 / 0 / 183	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0806	
R indices (all data)	R1 = 0.0342, wR2 = 0.0818	
Largest diff. peak and hole	0.216 and -0.221 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *trans*-**361**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
F(1)	7943(1)	11910(1)	4285(1)	29(1)
F(2)	7064(1)	13823(1)	3425(1)	33(1)
O(1)	7135(1)	8303(1)	4689(1)	22(1)
O(2)	7310(1)	10151(1)	6062(1)	28(1)
O(3)	8165(1)	11904(1)	2195(1)	30(1)
O(4)	5700(1)	12281(1)	4259(1)	35(1)
N(1)	8266(1)	7655(2)	5798(1)	24(1)
C(1)	6260(1)	9192(2)	4506(1)	23(1)
C(2)	5715(1)	7922(2)	3781(1)	28(1)
C(3)	6137(1)	7591(2)	2757(1)	27(1)
C(4)	6035(1)	9243(2)	2060(1)	27(1)
C(5)	6602(1)	10701(2)	2009(1)	25(1)
C(6)	7447(1)	10941(2)	2666(1)	23(1)
C(7)	7207(1)	11967(2)	3629(1)	24(1)
C(8)	6339(1)	11228(2)	4155(1)	24(1)
C(9)	7565(1)	8801(2)	5569(1)	22(1)
C(10)	8833(1)	8077(2)	6689(1)	31(1)
C(11)	9649(1)	9314(3)	6486(1)	49(1)
C(12)	8468(1)	5969(2)	5204(1)	28(1)
C(13)	9094(1)	6346(2)	4344(1)	37(1)

Table 3. Bond lengths (Å) and angles (°) for *trans*-**361**.

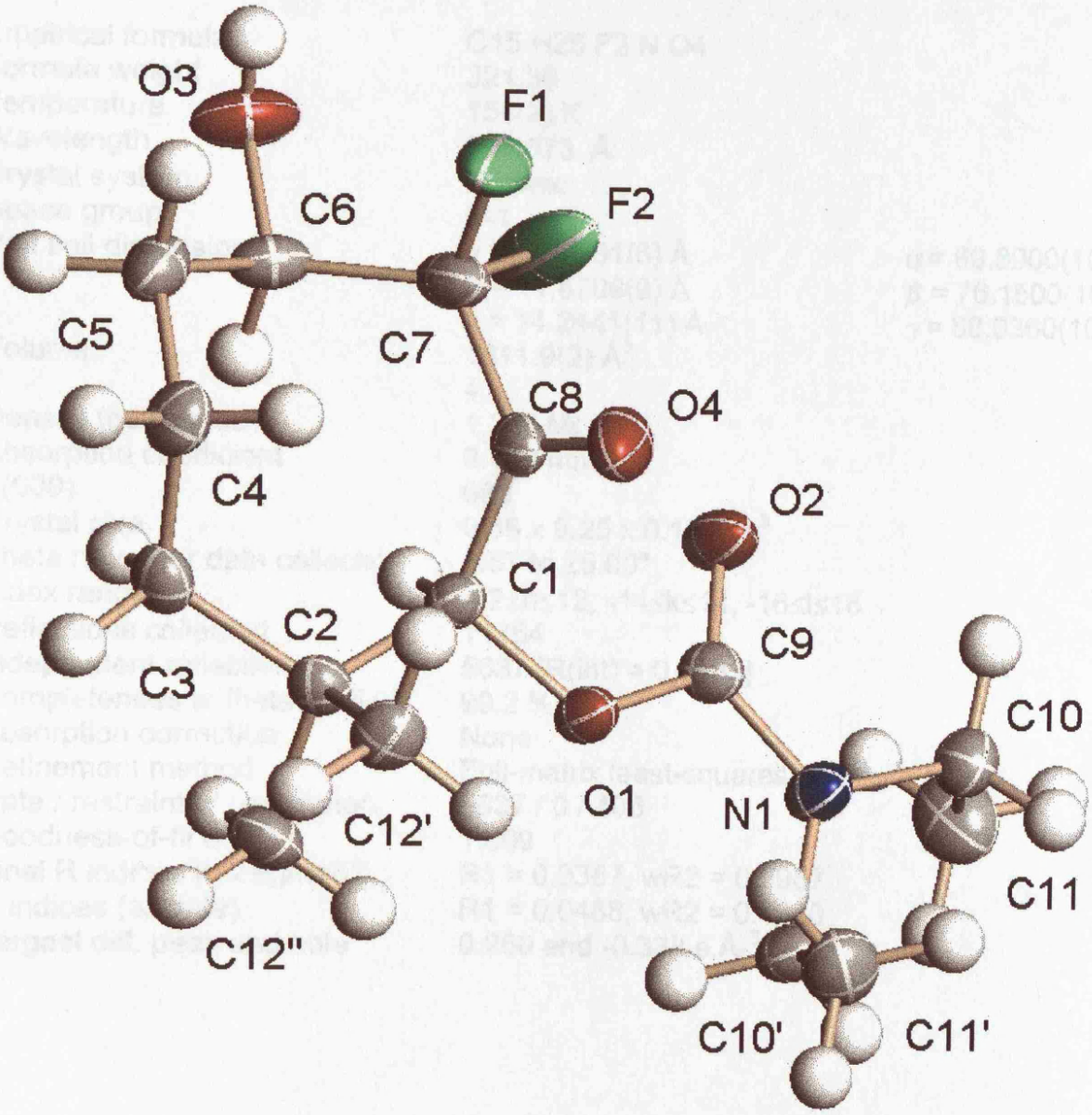
F(1)-C(7)	1.3643(14)	O(2)-C(9)-N(1)	126.39(11)
F(2)-C(7)	1.3546(14)	O(2)-C(9)-O(1)	121.85(11)
O(1)-C(9)	1.3616(14)	N(1)-C(9)-O(1)	111.77(11)
O(1)-C(1)	1.4337(15)	N(1)-C(10)-C(11)	113.75(12)
O(2)-C(9)	1.2209(15)	N(1)-C(12)-C(13)	113.67(11)
O(3)-C(6)	1.4074(15)		
O(4)-C(8)	1.1997(16)		
N(1)-C(9)	1.3311(16)		
N(1)-C(10)	1.4592(16)		
N(1)-C(12)	1.4651(17)		
C(1)-C(8)	1.5189(18)		
C(1)-C(2)	1.5255(18)		
C(2)-C(3)	1.5299(19)		
C(3)-C(4)	1.4979(19)		
C(4)-C(5)	1.3232(19)		
C(5)-C(6)	1.4983(17)		
C(6)-C(7)	1.5240(18)		
C(7)-C(8)	1.5498(18)		
C(10)-C(11)	1.503(2)		
C(12)-C(13)	1.506(2)		
C(9)-O(1)-C(1)	114.70(9)		
C(9)-N(1)-C(10)	118.34(11)		
C(9)-N(1)-C(12)	122.28(11)		
C(10)-N(1)-C(12)	119.37(11)		
O(1)-C(1)-C(8)	113.19(10)		
O(1)-C(1)-C(2)	107.09(10)		
C(8)-C(1)-C(2)	113.84(10)		
C(1)-C(2)-C(3)	116.26(11)		
C(4)-C(3)-C(2)	113.54(11)		
C(5)-C(4)-C(3)	125.97(12)		
C(4)-C(5)-C(6)	124.08(12)		
O(3)-C(6)-C(5)	113.53(10)		
O(3)-C(6)-C(7)	109.58(10)		
C(5)-C(6)-C(7)	110.20(10)		
F(2)-C(7)-F(1)	105.75(10)		
F(2)-C(7)-C(6)	109.15(10)		
F(1)-C(7)-C(6)	109.51(10)		
F(2)-C(7)-C(8)	107.16(10)		
F(1)-C(7)-C(8)	109.48(10)		
C(6)-C(7)-C(8)	115.34(10)		
O(4)-C(8)-C(1)	119.17(12)		
O(4)-C(8)-C(7)	118.94(12)		
C(1)-C(8)-C(7)	121.84(10)		

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for *trans*-**361**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	29(1)	31(1)	27(1)	1(1)	-7(1)	-6(1)
F(2)	46(1)	17(1)	35(1)	1(1)	0(1)	3(1)
O(1)	24(1)	22(1)	20(1)	-2(1)	-3(1)	3(1)
O(2)	34(1)	26(1)	24(1)	-5(1)	0(1)	2(1)
O(3)	28(1)	30(1)	32(1)	6(1)	4(1)	-1(1)
O(4)	32(1)	35(1)	39(1)	0(1)	2(1)	13(1)
N(1)	26(1)	23(1)	22(1)	1(1)	-4(1)	0(1)
C(1)	20(1)	27(1)	23(1)	0(1)	0(1)	1(1)
C(2)	24(1)	29(1)	30(1)	1(1)	-2(1)	-5(1)
C(3)	29(1)	24(1)	28(1)	-4(1)	-5(1)	-5(1)
C(4)	28(1)	31(1)	23(1)	-4(1)	-6(1)	2(1)
C(5)	30(1)	26(1)	20(1)	1(1)	-3(1)	4(1)
C(6)	24(1)	20(1)	26(1)	2(1)	1(1)	1(1)
C(7)	26(1)	18(1)	26(1)	2(1)	-5(1)	1(1)
C(8)	24(1)	27(1)	19(1)	-4(1)	-4(1)	4(1)
C(9)	25(1)	21(1)	18(1)	1(1)	1(1)	-4(1)
C(10)	32(1)	35(1)	24(1)	1(1)	-8(1)	-1(1)
C(11)	38(1)	67(1)	41(1)	-13(1)	-3(1)	-18(1)
C(12)	30(1)	22(1)	30(1)	0(1)	-3(1)	3(1)
C(13)	47(1)	37(1)	28(1)	0(1)	4(1)	8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for *trans*-**361**.

	x	y	z	U(eq)
H(3)	7949	12832	1874	45
H(1)	5929	9203	5154	28
H(2A)	5096	8483	3671	33
H(2B)	5630	6678	4106	33
H(3A)	6800	7303	2856	32
H(3B)	5840	6471	2440	32
H(4)	5514	9243	1613	33
H(5)	6466	11656	1526	30
H(6)	7676	9652	2853	28
H(10A)	9056	6873	6987	37
H(10B)	8446	8710	7189	37
H(11A)	10037	8699	8992	73
H(11B)	10006	9515	7110	73
H(11C)	9434	10536	6222	73
H(12A)	7882	5436	4935	33
H(12B)	8758	5006	5649	33
H(13A)	8827	7343	3917	56
H(13B)	9163	5187	3950	56
H(13C)	9698	6754	4606	56



X-ray crystal structure of **362**

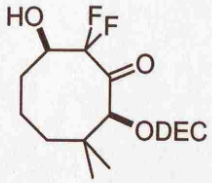


Table 1.Crystal data and structure refinement for **362**.

Empirical formula	C15 H25 F2 N O4	
Formula weight	321.36	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.4701(8) Å	α = 69.8900(10)°
	b = 11.8709(9) Å	β = 76.1500(10)°
	c = 14.2441(11) Å	γ = 88.0360(10)°
Volume	1611.9(2) $Å^3$	
Z	4	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	688	
Crystal size	0.36 x 0.25 x 0.16 mm^3	
Theta range for data collection	1.57 to 25.00°	
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-16 \le l \le 16$	
Reflections collected	11754	
Independent reflections	5637 [R(int) = 0.0183]	
Completeness to theta = 25.00°	99.2 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5637 / 0 / 405	
Goodness-of-fit on F^2	1.009	
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.0987	
R indices (all data)	R1 = 0.0488, wR2 = 0.1030	
Largest diff. peak and hole	0.260 and -0.338 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **362**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-1536(1)	-1131(1)	3162(1)	65(1)
F(2)	258(1)	-1034(1)	3647(1)	85(1)
O(1)	1020(1)	2479(1)	2207(1)	29(1)
O(2)	2204(1)	828(1)	2433(1)	41(1)
O(3)	-1692(1)	-1767(1)	5307(1)	46(1)
O(4)	-482(1)	892(1)	1835(1)	42(1)
N(1)	3109(1)	2658(1)	1314(1)	32(1)
C(1)	-46(1)	1773(1)	3010(1)	26(1)
C(2)	-1132(1)	2666(1)	3139(1)	27(1)
C(3)	-2340(1)	2048(1)	4002(1)	31(1)
C(4)	-3147(1)	1081(1)	3869(1)	34(1)
C(5)	-3065(1)	-179(1)	4613(1)	34(1)
C(6)	-1688(1)	-586(1)	4615(1)	32(1)
C(7)	-886(1)	-495(1)	3553(1)	38(1)
C(8)	-473(1)	762(1)	2708(1)	30(1)
C(9)	2143(1)	1898(1)	2019(1)	31(1)
C(10)	4354(1)	2172(1)	949(1)	36(1)
C(11)	5364(2)	2241(2)	1525(2)	53(1)
C(10')	2986(2)	3956(1)	919(1)	35(1)
C(11')	2360(2)	4363(1)	19(1)	46(1)
C(12')	-1535(1)	3300(1)	2128(1)	35(1)
C(12'')	-556(2)	3612(1)	3456(1)	36(1)

Table 3. Bond lengths (Å) and angles (°) for **362**

F(1)-C(7)	1.3599(17)
F(2)-C(7)	1.3526(18)
O(1)-C(9)	1.3612(17)
O(1)-C(1)	1.4314(15)
O(2)-C(9)	1.2100(16)
O(3)-C(6)	1.4087(16)
O(4)-C(8)	1.2007(17)
N(1)-C(9)	1.3409(18)
N(1)-C(10')	1.4596(18)
N(1)-C(10)	1.4611(18)
C(1)-C(8)	1.520(2)
C(1)-C(2)	1.5498(18)
C(2)-C(12')	1.5299(19)
C(2)-C(3)	1.5323(19)
C(2)-C(12'')	1.534(2)
C(3)-C(4)	1.536(2)
C(4)-C(5)	1.521(2)
C(5)-C(6)	1.505(2)
C(6)-C(7)	1.513(2)
C(7)-C(8)	1.556(2)
C(10)-C(11)	1.505(2)
C(10')-C(11')	1.504(2)

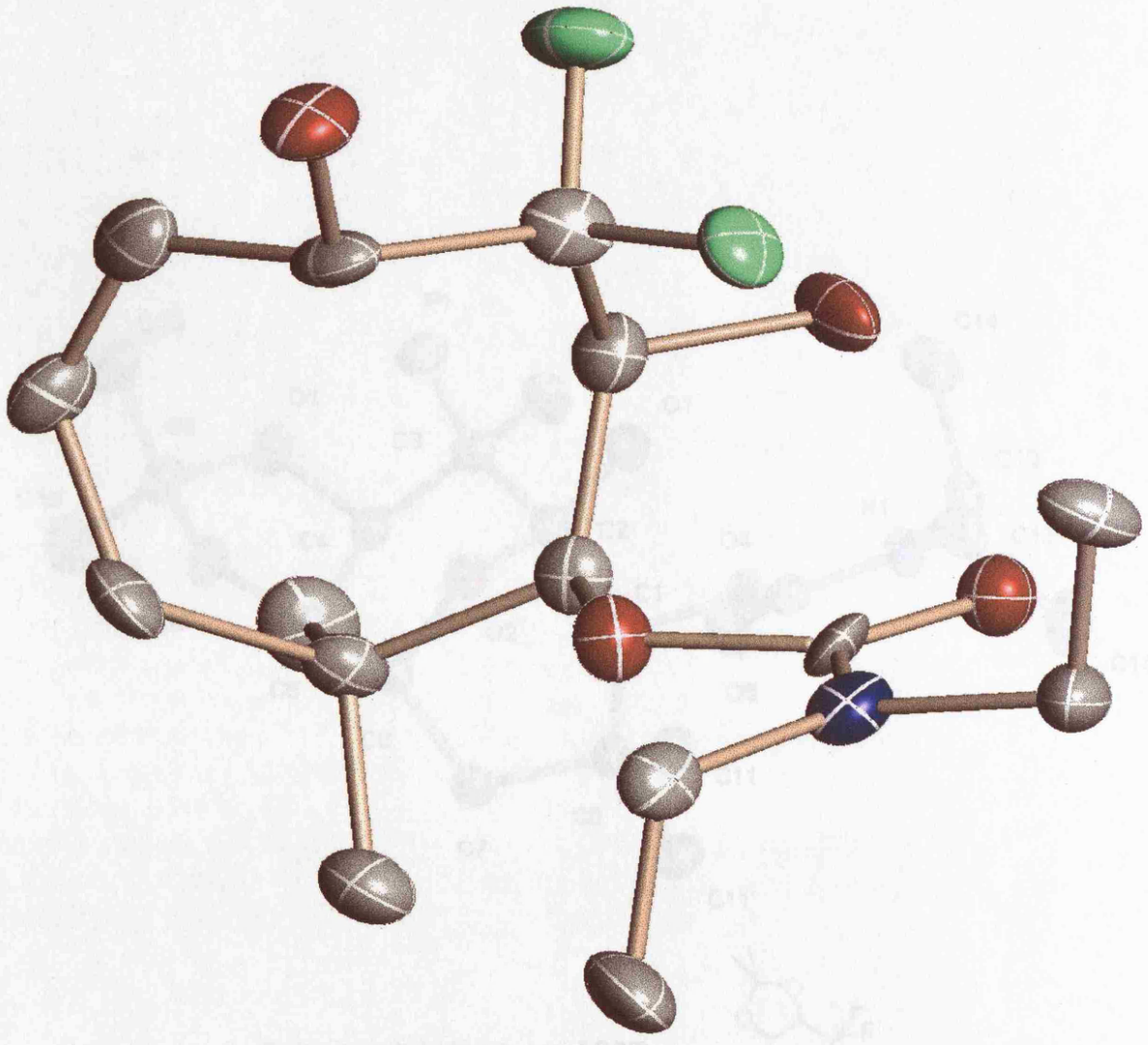
C(9)-O(1)-C(1)	115.80(10)
C(9)-N(1)-C(10')	122.89(12)
C(9)-N(1)-C(10)	118.62(12)
C(10')-N(1)-C(10)	118.46(11)
O(1)-C(1)-C(8)	109.23(11)
O(1)-C(1)-C(2)	105.31(10)
C(8)-C(1)-C(2)	113.72(11)
C(12')-C(2)-C(3)	110.39(11)
C(12')-C(2)-C(12'')	108.69(11)
C(3)-C(2)-C(12'')	107.16(11)
C(12')-C(2)-C(1)	111.37(11)
C(3)-C(2)-C(1)	111.80(11)
C(12'')-C(2)-C(1)	107.24(11)
C(2)-C(3)-C(4)	118.40(12)
C(5)-C(4)-C(3)	113.87(12)
C(6)-C(5)-C(4)	114.83(12)
O(3)-C(6)-C(5)	111.55(12)
O(3)-C(6)-C(7)	109.81(12)
C(5)-C(6)-C(7)	112.60(12)
F(2)-C(7)-F(1)	106.32(13)
F(2)-C(7)-C(6)	108.50(14)
F(1)-C(7)-C(6)	109.04(12)
F(2)-C(7)-C(8)	105.00(11)
F(1)-C(7)-C(8)	107.34(13)
C(6)-C(7)-C(8)	119.83(12)
O(4)-C(8)-C(1)	122.30(13)
O(4)-C(8)-C(7)	118.70(13)
C(1)-C(8)-C(7)	118.99(13)
O(2)-C(9)-N(1)	126.63(13)
O(2)-C(9)-O(1)	122.31(13)
N(1)-C(9)-O(1)	111.03(12)
N(1)-C(10)-C(11)	112.34(13)
N(1)-C(10')-C(11')	113.29(13)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **362**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

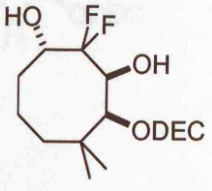
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	85(1)	49(1)	57(1)	-35(1)	20(1)	-34(1)
F(2)	38(1)	31(1)	136(1)	8(1)	14(1)	15(1)
O(1)	23(1)	23(1)	36(1)	-6(1)	-3(1)	2(1)
O(2)	32(1)	25(1)	55(1)	-7(1)	-2(1)	4(1)
O(3)	59(1)	27(1)	51(1)	1(1)	-30(1)	-7(1)
O(4)	44(1)	49(1)	38(1)	-24(1)	-2(1)	-6(1)
N(1)	25(1)	27(1)	38(1)	-6(1)	-4(1)	-1(1)
C(1)	24(1)	23(1)	26(1)	-5(1)	-5(1)	0(1)
C(2)	28(1)	24(1)	28(1)	-8(1)	-8(1)	6(1)
C(3)	30(1)	31(1)	32(1)	-11(1)	-6(1)	11(1)
C(4)	23(1)	40(1)	36(1)	-10(1)	-5(1)	4(1)
C(5)	32(1)	36(1)	29(1)	-10(1)	-3(1)	-5(1)
C(6)	37(1)	23(1)	34(1)	-4(1)	-15(1)	-3(1)
C(7)	29(1)	25(1)	57(1)	-16(1)	-3(1)	1(1)
C(8)	22(1)	31(1)	36(1)	-15(1)	-1(1)	2(1)
C(9)	26(1)	28(1)	38(1)	-12(1)	-7(1)	2(1)
C(10)	29(1)	38(1)	38(1)	-13(1)	-4(1)	0(1)
C(11)	38(1)	61(1)	69(1)	-30(1)	-21(1)	10(1)
C(10')	33(1)	27(1)	41(1)	-6(1)	-5(1)	-4(1)
C(11')	53(1)	39(1)	38(1)	-7(1)	-9(1)	6(1)
C(12')	34(1)	32(1)	35(1)	-5(1)	-11(1)	7(1)
C(12'')	43(1)	26(1)	41(1)	-14(1)	-11(1)	7(1)

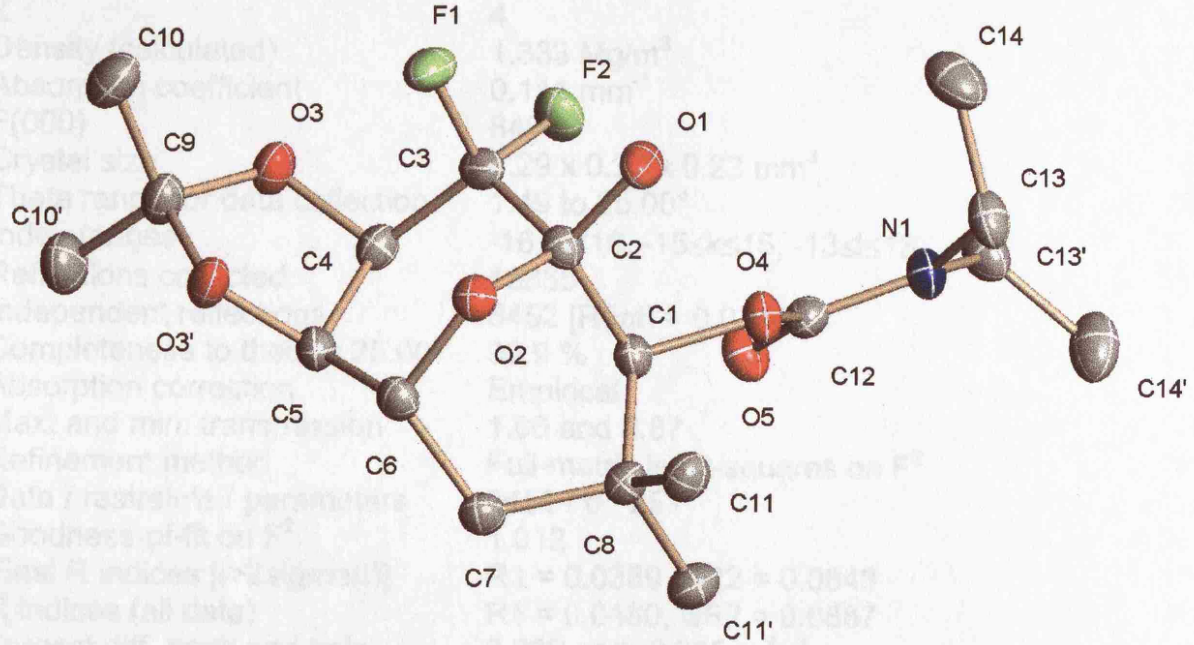
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **362**

	x	y	z	U(eq)
H(3)	-2183	-2221	5189	69
H(1)	251	1426	3664	31
H(3B)	-2942	2680	4106	37
H(3C)	-2041	1677	4644	37
H(4A)	-4081	1292	3966	41
H(4B)	-2832	1084	3155	41
H(5A)	-3517	-214	5318	40
H(5B)	-3549	-751	4438	40
H(6)	-1239	-45	4855	38
H(10C)	4706	2625	206	43
H(10D)	4193	1323	1029	43
H(11G)	5532	3081	1443	79
H(11H)	6184	1917	1248	79
H(11I)	5034	1771	2257	79
H(10A)	3873	4360	706	42
H(10B)	2452	4208	1481	42
H(11A)	2884	4121	-542	68
H(11B)	2321	5240	-219	68
H(11C)	1466	3995	232	68
H(12D)	-1887	2703	1910	52
H(12E)	-764	3738	1597	52
H(12F)	-2212	3866	2232	52
H(12A)	234	4014	2928	54
H(12B)	-323	3220	4116	54
H(12C)	-1211	4206	3527	54



Preliminary X-ray crystal structure of **363**
Hydrogen atoms omitted for clarity





X-ray crystal structure of **367a**
Hydrogen atoms omitted for clarity

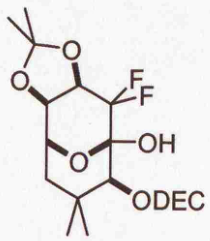


Table 1.Crystal data and structure refinement for **367a**.

Empirical formula	C18 H29 F2 N O6	
Formula weight	393.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.0963(11) Å	$\alpha = 90°$
	b = 12.8611(10) Å	$\beta = 104.3220(1)°$
	c = 11.1642(9) Å	$\gamma = 90°$
Volume	1961.1(3) $Å^3$	
Z	4	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	840	
Crystal size	0.29 x 0.27 x 0.23 mm^3	
Theta range for data collection	1.49 to 25.00°	
Index ranges	$-16 \le h \le 16$, $-15 \le k \le 15$, $-13 \le l \le 13$	
Reflections collected	13865	
Independent reflections	3452 [R(int) = 0.0344]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	1.00 and 0.87	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3452 / 0 / 251	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0843	
R indices (all data)	R1 = 0.0480, wR2 = 0.0887	
Largest diff. peak and hole	0.239 and -0.205 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **367a**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
F(1)	3589(1)	976(1)	1991(1)	32(1)
F(2)	2349(1)	784(1)	401(1)	33(1)
O(1)	2100(1)	2038(1)	2344(1)	27(1)
O(2)	3309(1)	3077(1)	2048(1)	23(1)
O(3)	4421(1)	1092(1)	152(1)	27(1)
O(4)	847(1)	2630(1)	301(1)	24(1)
O(5)	610(1)	2145(1)	-1712(2)	29(1)
O(3')	5113(1)	2529(1)	1207(1)	27(1)
N(1)	-566(1)	1893(1)	-666(1)	24(1)
C(1)	1828(1)	2965(1)	344(1)	21(1)
C(2)	2535(1)	2402(1)	1447(1)	22(1)
C(3)	3041(1)	1490(1)	996(1)	23(1)
C(4)	3660(1)	1816(1)	113(1)	23(1)
C(5)	4194(1)	2854(1)	458(1)	23(1)
C(6)	3734(1)	3623(1)	1188(1)	23(1)
C(7)	2986(1)	4366(1)	386(1)	24(1)
C(8)	1922(1)	4148(1)	440(1)	23(1)
C(9)	5349(1)	1567(1)	724(2)	27(1)
C(10)	5891(1)	913(1)	1785(2)	35(1)
C(11)	1683(1)	4580(1)	1607(1)	28(1)
C(12)	317(1)	2209(1)	-775(1)	22(1)
C(13)	-833(1)	1893(1)	517(1)	30(1)
C(14)	-471(1)	935(2)	1274(2)	43(1)
C(10')	5901(1)	1728(1)	-264(2)	40(1)
C(11')	1229(1)	4649(1)	-679(1)	30(1)
C(13')	-1210(1)	1334(1)	-1689(1)	30(1)
C(14')	-2120(1)	1950(2)	-2290(2)	43(1)

Table 3. Bond lengths (Å) and angles (°) for **367a**

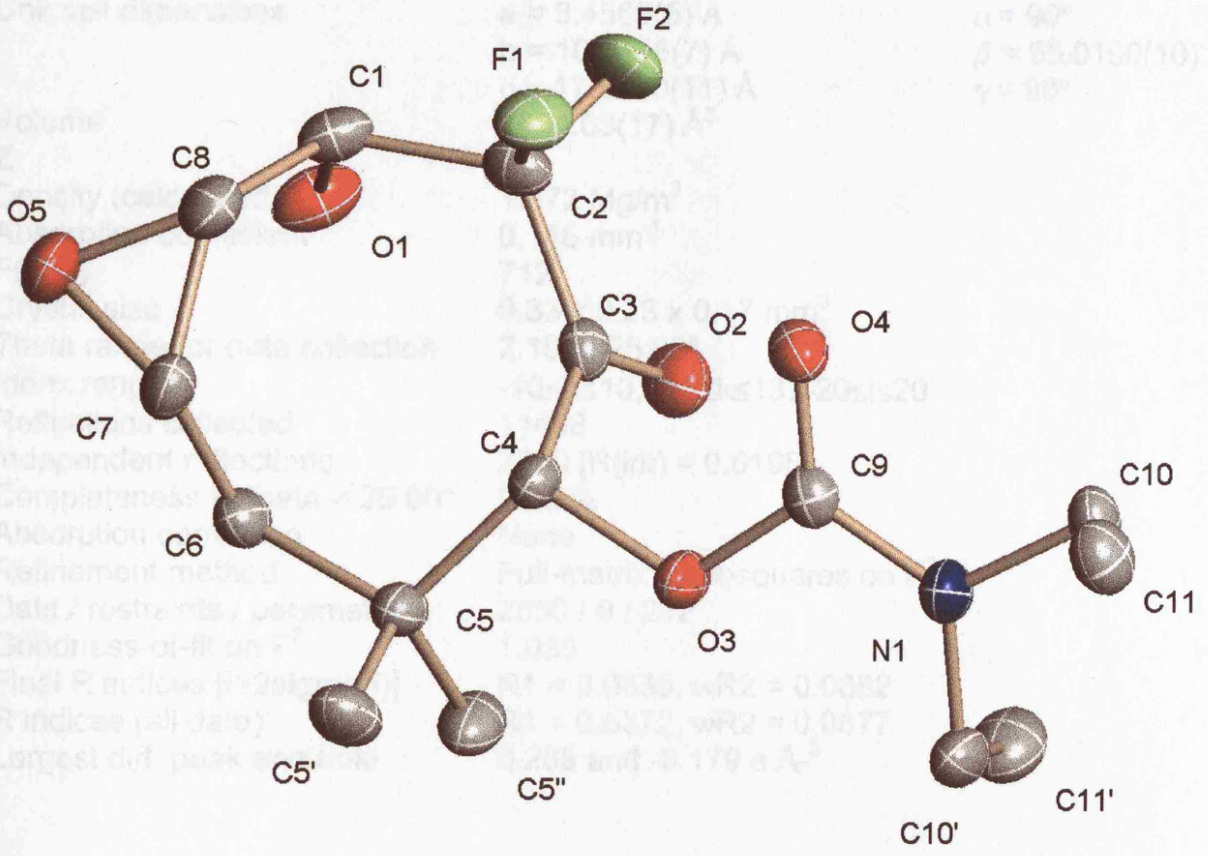
F(1)-C(3)	1.3584(16)	O(2)-C(2)-C(1)	110.76(11)
F(2)-C(3)	1.3772(17)	C(3)-C(2)-C(1)	110.88(12)
O(1)-C(2)	1.3791(17)	F(1)-C(3)-F(2)	105.34(12)
O(2)-C(2)	1.4254(17)	F(1)-C(3)-C(2)	108.85(12)
O(2)-C(6)	1.4350(17)	F(2)-C(3)-C(2)	109.46(12)
O(3)-C(4)	1.4139(17)	F(1)-C(3)-C(4)	111.19(12)
O(3)-C(9)	1.4417(18)	F(2)-C(3)-C(4)	108.67(12)
O(4)-C(12)	1.3601(17)	C(2)-C(3)-C(4)	113.04(12)
O(4)-C(1)	1.4385(18)	O(3)-C(4)-C(3)	110.47(12)
O(5)-C(12)	1.2185(18)	O(3)-C(4)-C(5)	104.09(12)
O(3')-C(5)	1.4200(18)	C(3)-C(4)-C(5)	113.63(12)
O(3')-C(9)	1.4213(18)	O(3')-C(5)-C(6)	108.80(12)
N(1)-C(12)	1.3438(19)	O(3')-C(5)-C(4)	102.20(12)
N(1)-C(13)	1.4593(19)	C(6)-C(5)-C(4)	116.82(12)
N(1)-C(13')	1.4600(19)	O(2)-C(6)-C(5)	110.12(12)
C(1)-C(8)	1.528(2)	O(2)-C(6)-C(7)	110.75(12)
C(1)-C(2)	1.558(2)	C(5)-C(6)-C(7)	114.40(12)
C(2)-C(3)	1.523(2)	C(6)-C(7)-C(8)	113.42(12)
C(3)-C(4)	1.527(2)	C(11')-C(8)-C(1)	109.62(13)
C(4)-C(5)	1.534(2)	C(11')-C(8)-C(11)	108.22(12)
C(5)-C(6)	1.525(2)	C(1)-C(8)-C(11)	112.85(13)
C(6)-C(7)	1.537(2)	C(11')-C(8)-C(7)	108.85(12)
C(7)-C(8)	1.542(2)	C(1)-C(8)-C(7)	104.29(12)
C(8)-C(11')	1.525(2)	C(11)-C(8)-C(7)	112.90(13)
C(8)-C(11)	1.529(2)	O(3')-C(9)-O(3)	105.34(11)
C(9)-C(10)	1.499(2)	O(3')-C(9)-C(10)	108.08(13)
C(9)-C(10')	1.513(2)	O(3)-C(9)-C(10)	109.94(13)
C(13)-C(14)	1.510(2)	O(3')-C(9)-C(10')	111.66(13)
C(13')-C(14')	1.515(2)	O(3)-C(9)-C(10')	107.99(13)
		C(10)-C(9)-C(10')	113.52(14)
C(2)-O(2)-C(6)	112.38(10)	O(5)-C(12)-N(1)	125.13(14)
C(4)-O(3)-C(9)	109.46(11)	O(5)-C(12)-O(4)	123.87(14)
C(12)-O(4)-C(1)	117.48(11)	N(1)-C(12)-O(4)	111.00(13)
C(5)-O(3')-C(9)	107.34(11)	N(1)-C(13)-C(14)	112.30(14)
C(12)-N(1)-C(13)	122.28(13)	N(1)-C(13')-C(14')	112.60(14)
C(12)-N(1)-C(13')	119.25(12)		
C(13)-N(1)-C(13')	117.28(12)		
O(4)-C(1)-C(8)	111.51(12)		
O(4)-C(1)-C(2)	107.96(11)		
C(8)-C(1)-C(2)	112.28(12)		
O(1)-C(2)-0(2)	106.94(11)		
O(1)-C(2)-C(3)	107.93(12)		
O(2)-C(2)-C(3)	104.97(12)		
O(1)-C(2)-C(1)	114.83(12)		

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **367a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	34(1)	30(1)	32(1)	9(1)	10(1)	9(1)
F(2)	30(1)	26(1)	45(1)	-7(1)	10(1)	-8(1)
O(1)	25(1)	34(1)	26(1)	7(1)	12(1)	4(1)
O(2)	22(1)	25(1)	19(1)	-2(1)	3(1)	-1(1)
O(3)	21(1)	25(1)	34(1)	-6(1)	5(1)	4(1)
O(4)	18(1)	32(1)	21(1)	-3(1)	5(1)	-2(1)
O(5)	28(1)	40(1)	22(1)	-4(1)	9(1)	-6(1)
O(3')	19(1)	25(1)	36(1)	-4(1)	3(1)	2(1)
N(1)	19(1)	31(1)	23(1)	-2(1)	5(1)	-3(1)
C(1)	18(1)	24(1)	20(1)	-1(1)	6(1)	-1(1)
C(2)	22(1)	25(1)	19(1)	1(1)	6(1)	-2(1)
C(3)	22(1)	22(1)	23(1)	2(1)	1(1)	-2(1)
C(4)	22(1)	24(1)	23(1)	-2(1)	5(1)	4(1)
C(5)	19(1)	25(1)	26(1)	2(1)	7(1)	0(1)
C(6)	22(1)	22(1)	26(1)	-1(1)	6(1)	-3(1)
C(7)	26(1)	20(1)	27(1)	0(1)	7(1)	0(1)
C(8)	22(1)	22(1)	23(1)	-1(1)	4(1)	2(1)
C(9)	21(1)	26(1)	34(1)	-4(1)	6(1)	2(1)
C(10)	30(1)	32(1)	39(1)	-3(1)	-1(1)	6(1)
C(11)	27(1)	26(1)	30(1)	-3(1)	7(1)	4(1)
C(12)	22(1)	21(1)	21(1)	0(1)	3(1)	2(1)
C(13)	22(1)	43(1)	26(1)	-2(1)	9(1)	-5(1)
C(14)	44(1)	50(1)	32(1)	9(1)	7(1)	-13(1)
C(10')	32(1)	42(1)	50(1)	-2(1)	20(1)	3(1)
C(11')	32(1)	27(1)	30(1)	3(1)	6 (1)	5(1)
C(13')	27(1)	33(1)	28(1)	-1(1)	5(1)	8(1)
C(14')	28(1)	66(1)	32(1)	2(1)	3(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **367a**

	x	y	z	U(eq)
H(1)	1613	2410	2359	41
H(1A)	1994	2740	-438	25
H(4)	3236	1858	-748	28
H(5)	4292	3199	-306	28
H(6)	4277	4061	1684	28
H(7A)	3031	4039	-483	29
H(7B)	3157	5089	661	29
H(10A)	6521	1240	2168	53
H(10B)	6004	220	1483	53
H(10C)	5503	852	5398	53
H(11A)	1709	5341	1594	42
H(11B)	2162	4320	2338	42
H(11C)	1025	4356	1638	42
H(13C)	-1554	1931	364	36
H(13D)	-553	2518	992	36
H(14D)	-762	315	818	64
H(14E)	-660	972	2061	64
H(14F)	244	896	1434	64
H(10D)	5509	2159	-928	59
H(10E)	6027	1052	-600	59
H(10F)	6525	2076	97	59
H(11D)	1365	4375	-1438	45
H(11E)	1325	5404	-646	45
H(11F)	551	4490	-671	45
H(13A)	-1408	668	-1380	36
H(13B)	-845	1173	-2319	36
H(14A)	-2490	2101	-1675	64
H(14B)	-2528	1543	-2966	64
H(14C)	-1930	2603	-2618	64



X-ray crystal structure of **368a**
Hydrogen atoms omitted for clarity

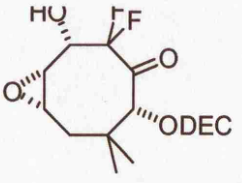


Table 1.Crystal data and structure refinement for **368a**.

Empirical formula	C15 H23 F2 N O5	
Formula weight	335.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.4569(5) Å	α = 90°
	b = 10.9438(7) Å	β = 95.0190(10)°
	c = 17.6150(11) Å	γ = 90°
Volume	1624.03(17) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	712	
Crystal size	0.33 x 0.23 x 0.17 mm^3	
Theta range for data collection	2.19 to 25.00°	
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 13$, $-20 \le l \le 20$	
Reflections collected	11488	
Independent reflections	2850 [R(int) = 0.0198]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2850 / 0 / 212	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0852	
R indices (all data)	R1 = 0.0372, wR2 = 0.0877	
Largest diff. peak and hole	0.265 and -0.179 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **368a**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-1796(1)	-2490(1)	3332(1)	35(1)
O(2)	163(1)	-1667(1)	1912(1)	34(1)
O(3)	1182(1)	726(1)	1929(1)	27(1)
O(4)	-1010(1)	1010(1)	1118(1)	27(1)
O(5)	-2196(1)	-651(1)	4415(1)	38(1)
F(1)	-3202(1)	-107(1)	2102(1)	35(1)
F(2)	-2857(1)	-2011(1)	1801(1)	43(1)
N(1)	1460(1)	1265(1)	727(1)	25(1)
C(1)	-2777(2)	-1507(1)	3097(1)	28(1)
C(2)	-2356(2)	-1133(1)	2312(1)	27(1)
C(3)	-574(2)	-902(1)	2218(1)	23(1)
C(4)	179(2)	306(1)	2494(1)	22(1)
C(5)	1282(2)	213(1)	3243(1)	24(1)
C(6)	427(2)	-436(1)	3863(1)	26(1)
C(7)	-1168(2)	84(1)	3985(1)	28(1)
C(8)	-2663(2)	-412(1)	3631(1)	29(1)
C(9)	438(2)	1006(1)	1237(1)	23(1)
C(10)	838(2)	1600(1)	-49(1)	27(1)
C(11)	675(2)	2963(1)	-154(1)	34(1)
C(5'')	2783(2)	-513(2)	3124(1)	35(1)
C(5')	1731(2)	1519(1)	3495(1)	35(1)
C(10')	3180(2)	1079(1)	877(1)	31(1)
C(11')	3643(2)	-233(2)	755(1)	41(1)

Table 3. Bond lengths (Å) and angles (°) for **368a**

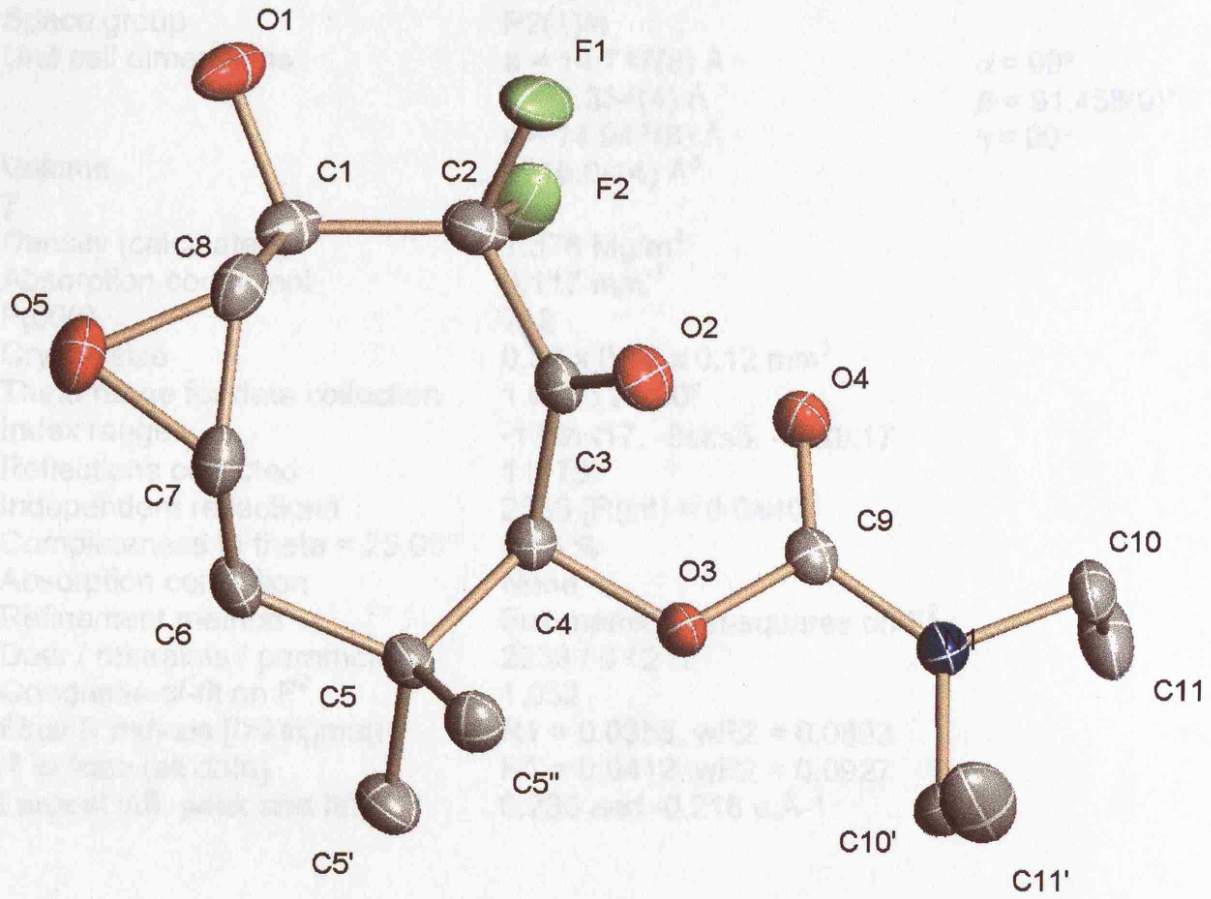
O(1)-C(1)	1.3985(16)
O(2)-C(3)	1.1985(15)
O(3)-C(9)	1.3568(15)
O(3)-C(4)	1.4393(15)
O(4)-C(9)	1.2246(16)
O(5)-C(8)	1.4283(17)
O(5)-C(7)	1.4474(16)
F(1)-C(2)	1.3653(16)
F(2)-C(2)	1.3590(15)
N(1)-C(9)	1.3303(17)
N(1)-C(10)	1.4679(16)
N(1)-C(10')	1.4695(17)
C(1)-C(2)	1.513(2)
C(1)-C(8)	1.5206(19)
C(2)-C(3)	1.5517(18)
C(3)-C(4)	1.5277(18)
C(4)-C(5)	1.5511(17)
C(5)-C(5'')	1.5280(19)
C(5)-C(5')	1.534(2)
C(5)-C(6)	1.5353(17)
C(6)-C(7)	1.4967(19)
C(7)-C(8)	1.4651(19)
C(10)-C(11)	1.508(2)
C(10')-C(11')	1.509(2)
C(9)-O(3)-C(4)	115.99(9)
C(8)-O(5)-C(7)	61.25(9)
C(9)-N(1)-C(10)	118.76(11)
C(9)-N(1)-C(10')	122.70(11)
C(10)-N(1)-C(10')	118.06(10)
O(1)-C(1)-C(2)	107.27(11)
O(1)-C(1)-C(8)	114.79(12)
C(2)-C(1)-C(8)	110.12(11)
F(2)-C(2)-F(1)	106.01(10)
F(2)-C(2)-C(1)	109.23(11)
F(1)-C(2)-C(1)	108.08(10)
F(2)-C(2)-C(3)	107.07(10)
F(1)-C(2)-C(3)	109.12(10)
C(1)-C(2)-C(3)	116.81(11)
O(2)-C(3)-C(4)	121.97(12)
O(2)-C(3)-C(2)	118.80(12)
C(4)-C(3)-C(2)	119.21(10)
O(3)-C(4)-C(3)	108.06(10)
O(3)-C(4)-C(5)	105.18(9)
C(3)-C(4)-C(5)	114.68(10)
C(5'')-C(5)-C(5')	109.69(1)
C(5'')-C(5)-C(6)	107.80(11)
C(5')-C(5)-C(6)	110.19(11)
C(5'')-C(5)-C(4)	111.24(11)
C(5')-C(5)-C(4)	107.50(11)
C(6)-C(5)-C(4)	110.43(10)
C(7)-C(6)-C(5)	114.34(11)
O(5)-C(7)-C(8)	58.73(8)
O(5)-C(7)-C(6)	116.98(12)
C(8)-C(7)-C(6)	123.56(12)
O(5)-C(8)-C(7)	60.02(9)
O(5)-C(8)-C(1)	116.84(11)
C(7)-C(8)-C(1)	124.14(12)
O(4)-C(9)-N(1)	125.65(12)
O(4)-C(9)-O(3)	122.20(11)
N(1)-C(9)-O(3)	112.15(11)
N(1)-C(10)-C(11)	112.44(11)
N(1)-C(10')-C(11')	111.81(12)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **368a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(1)	24(1)	54(1)	9(1)	10(1)	-1(1)
O(2)	34(1)	33(1)	34(1)	-7(1)	6(1)	5(1)
O(3)	23(1)	37(1)	21(1)	7(1)	3(1)	-3(1)
O(4)	25(1)	30(1)	25(1)	-2(1)	1(1)	5(1)
O(5)	35(1)	51(1)	28(1)	2(1)	11(1)	-8(1)
F(1)	23(1)	40(1)	40(1)	9(1)	-1(1)	3(1)
F(2)	40(1)	47(1)	42(1)	-19(1)	1(1)	-16(1)
N(1)	28(1)	28(1)	20(1)	3(1)	4(1)	-1(1)
C(1)	21(1)	26(1)	38(1)	1(1)	5(1)	-3(1)
C(2)	26(1)	25(1)	31(1)	-5(1)	-1(1)	-3(1)
C(3)	26(1)	27(1)	18(1)	1(1)	2(1)	3(1)
C(4)	20(1)	26(1)	20(1)	2(1)	4(1)	-1(1)
C(5)	21(1)	30(1)	21(1)	3(1)	1(1)	-3(1)
C(6)	25(1)	31(1)	20(1)	3(1)	0(1)	-2(1)
C(7)	30(1)	31(1)	23(1)	-1(1)	8(1)	-4(1)
C(8)	25(1)	32(1)	29(1)	1(1)	8(1)	1(1)
C(9)	28(1)	18(1)	22(1)	-1(1)	2(1)	1(1)
C(10)	34(1)	29(1)	19(1)	0(1)	3(1)	-2(1)
C(11)	42(1)	32(1)	27(1)	4(1)	-1(1)	-1(1)
C(5")	23(1)	52(1)	29(1)	8(1)	1(1)	5(1)
C(5')	35(1)	38(1)	31(1)	1(1)	-3(1)	-13(1)
C(10')	26(1)	42(1)	26(1)	5(1)	4(1)	-7(1)
C(11')	31(1)	50(1)	44(1)	5(1)	5(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **368a**

	x	y	z	U(eq)
H(1)	-2322	-3008	3555	53
H(1A)	-3901	-1801	3051	34
H(4)	-673	922	2557	26
H(6A)	296	-1309	3724	31
H(6B)	1106	-394	4349	31
H(7)	-1179	980	4097	33
H(8)	-3537	199	3537	34
H(10C)	-214	1212	-165	33
H(10D)	1558	1278	-415	33
H(11A)	-117	3275	172	50
H(11B)	335	3144	-688	50
H(11C)	1700	3355	-13	50
H(5"A)	3370	-104	2741	52
H(5"B)	2491	-1339	2948	52
H(5"C)	3453	-563	3606	52
H(5'A)	2350	1495	3992	53
H(5'B)	763	1999	3536	53
H(5'C)	2365	1897	3119	53
H(10A)	3514	1318	1409	38
H(10B)	3742	1613	535	38
H(11D)	3156	-756	1122	62
H(11E)	4801	-311	829	62
H(11F)	3273	-483	236	62



X-ray crystal structure of **368b**
Hydrogen atoms omitted for clarity

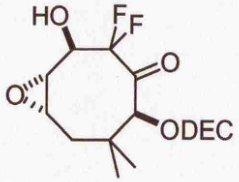


Table 1.Crystal data and structure refinement for **368b**.

Empirical formula	C15 H23 F2 N O5	
Formula weight	335.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 14.747(8) Å	$\alpha = 90°$
	b = 7.334(4) Å	$\beta = 91.458(9)°$
	c = 14.947(8) Å	$\gamma = 90°$
Volume	1616.0(14) $Å^3$	
Z	4	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	712	
Crystal size	0.33 x 0.17 x 0.12 mm^3	
Theta range for data collection	1.92 to 25.00°	
Index ranges	$-17 \leq h \leq 17$, $-8 \leq k \leq 8$, $-17 \leq l \leq 17$	
Reflections collected	11175	
Independent reflections	2833 [R(int) = 0.0440]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2833 / 0 / 212	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0893	
R indices (all data)	R1 = 0.0412, wR2 = 0.0927	
Largest diff. peak and hole	0.230 and -0.218 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **368b**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor.

	x	y	z	U(eq)
O(1)	727(1)	9000(2)	6633(1)	35(1)
O(2)	1204(1)	11330(1)	9421(1)	27(1)
O(3)	2661(1)	9459(1)	10160(1)	23(1)
O(4)	3290(1)	11469(1)	9219(1)	26(1)
O(5)	-269(1)	6525(2)	8020(1)	37(1)
F(1)	2301(1)	10348(1)	7582(1)	45(1)
F(2)	1032(1)	11827(1)	7728(1)	47(1)
N(1)	3655(1)	11473(2)	10718(1)	24(1)
C(1)	948(1)	8643(1)	7537(1)	27(1)
C(2)	1462(1)	10251(2)	7947(1)	28(1)
C(3)	1576(1)	10194(2)	8981(1)	21(1)
C(4)	2153(1)	8680(1)	9417(1)	21(1)
C(5)	1612(1)	7091(2)	9848(1)	22(1)
C(5')	1073(1)	7779(2)	10642(1)	27(1)
C(5'')	2311(1)	5669(2)	10174(1)	30(1)
C(6)	978(1)	6118(2)	9164(1)	26(1)
C(7)	145(1)	7148(1)	8854(1)	28(1)
C(8)	112(1)	8320(2)	8060(1)	28(1)
C(9)	3220(1)	10871(2)	9979(1)	21(1)
C(10)	4316(1)	12959(2)	10653(1)	26(1)
C(11)	5264(1)	12267(2)	10483(1)	37(1)
C(10')	3515(1)	10689(2)	11602(1)	34(1)
C(11')	2727(2)	11597(3)	12061(1)	52(1)

Table 3. Bond lengths (Å) and angles (°) for **368b**

O(1)-C(1)	1.4054(19)
O(2)-C(3)	1.2021(17)
O(3)-C(9)	1.3549(17)
O(3)-C(4)	1.4421(17)
O(4)-C(9)	1.2245(18)
O(5)-C(8)	1.431(2)
O(5)-C(7)	1.4478(19)
F(1)-C(2)	1.3663(18)
F(2)-C(2)	1.3553(18)
N(1)-C(9)	1.3380(19)
N(1)-C(10')	1.461(2)
N(1)-C(10)	1.4667(18)
C(1)-C(8)	1.495(2)
C(1)-C(2)	1.523(2)
C(2)-C(3)	1.551(2)
C(3)-C(4)	1.533(2)
C(4)-C(5)	1.5607(19)
C(5)-C(5')	1.530(2)
C(5)-C(5'')	1.537(2)
C(5)-C(6)	1.543(2)
C(6)-C(7)	1.505(2)
C(7)-C(8)	1.466(2)
C(10)-C(11)	1.515(2)
C(10')-C(11')	1.517(3)
C(9)-O(3)-C(4)	117.14(11)
C(8)-O(5)-C(7)	61.19(9)
C(9)-N(1)-C(10')	122.76(12)
C(9)-N(1)-C(10)	119.72(12)
C(10')-N(1)-C(10)	117.50(12)
O(1)-C(1)-C(8)	111.01(12)
O(1)-C(1)-C(2)	110.09(12)
C(8)-C(1)-C(2)	108.71(12)
F(2)-C(2)-F(1)	106.38(12)
F(2)-C(2)-C(1)	109.71(12)
F(1)-C(2)-C(1)	109.03(12)
F(2)-C(2)-C(3)	107.59(12)
F(1)-C(2)-C(3)	108.89(12)
C(1)-C(2)-C(3)	114.89(12)
O(2)-C(3)-C(4)	121.73(13)
O(2)-C(3)-C(2)	119.12(13)
C(4)-C(3)-C(2)	119.16(12)
O(3)-C(4)-C(3)	108.19(11)
O(3)-C(4)-C(5)	103.82(11)
C(3)-C(4)-C(5)	115.60(11)
C(5')-C(5)-C(5'')	109.60(12)
C(5')-C(5)-C(6)	110.39(12)
C(5'')-C(5)-C(6)	106.63(12)
C(5')-C(5)-C(4)	110.81(12)
C(5'')-C(5)-C(4)	106.97(12)
C(6)-C(5)-C(4)	112.27(12)
C(7)-C(6)-C(5)	116.60(12)
O(5)-C(7)-C(8)	58.85(10)
O(5)-C(7)-C(6)	115.9(12)
C(8)-C(7)-C(6)	123.56(13)
O(5)-C(8)-C(7)	59.96(10)
O(5)-C(8)-C(1)	116.83(12)
C(7)-C(8)-C(1)	120.42(13)
O(4)-C(9)-N(1)	126.74(13)
O(4)-C(9)-O(3)	121.63(12)
N(1)-C(9)-O(3)	111.63(12)
N(1)-C(10)-C(11)	112.34(12)
N(1)-C(10')-C(11')	111.35(14)

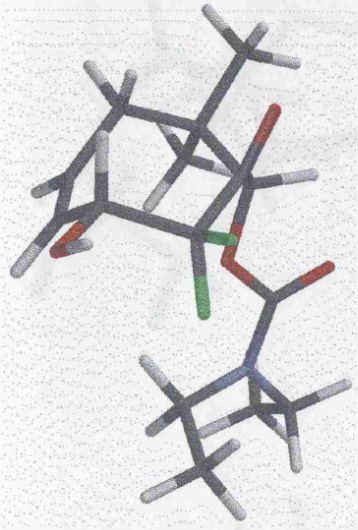
Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **368b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	45(1)	38(1)	21(1)	-4(1)	-4(1)	17(1)
O(2)	25(1)	24(1)	32(1)	-3(1)	2(1)	2(1)
O(3)	22(1)	24(1)	23(1)	1(1)	-3(1)	-6(1)
O(4)	27(1)	28(1)	24(1)	1(1)	1(1)	-6(1)
O(5)	33(1)	39(1)	39(1)	-9(1)	-10(1)	-8(1)
F(1)	40(1)	66(1)	28(1)	2(1)	8(1)	-17(1)
F(2)	75(1)	26(1)	38(1)	5(1)	-17(1)	8(1)
N(1)	22(1)	23(1)	26(1)	1(1)	-4(1)	-3(1)
C(1)	30(1)	28(1)	22(1)	-2(1)	-2(1)	9(1)
C(2)	31(1)	26(1)	28(1)	4(1)	1(1)	3(1)
C(3)	18(1)	21(1)	26(1)	-1(1)	2(1)	-4(1)
C(4)	18(1)	23(1)	22(1)	-2(1)	0(1)	-1(1)
C(5)	21(1)	21(1)	25(1)	1(1)	0(1)	-2(1)
C(5')	25(1)	29(1)	27(1)	0(1)	3(1)	-4(1)
C(5'')	30(1)	24(1)	36(1)	4(1)	-2(1)	1(1)
C(6)	26(1)	21(1)	29(1)	-1(1)	2(1)	-5(1)
C(7)	23(1)	31(1)	30(1)	-8(1)	-1(1)	-5(1)
C(8)	24(1)	31(1)	29(1)	-9(1)	-5(1)	3(1)
C(9)	17(1)	20(1)	26(1)	-1(1)	1(1)	2(1)
C(10)	24(1)	21(1)	33(1)	-3(1)	-4(1)	-3(1)
C(11)	25(1)	28(1)	60(1)	-7(1)	-2(1)	-3(1)
C(10')	43(1)	30(1)	27(1)	5(1)	-12(1)	-8(1)
C(11')	79(1)	47(1)	30(1)	-3(1)	17(1)	-12(1)

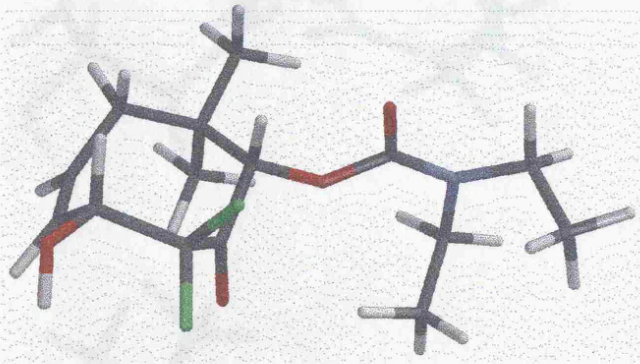
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **368b**

	x	y	z	U(eq)
H(1)	1022	8294	6307	52
H(1A)	1341	7533	7574	32
H(4)	2580	8175	8970	25
H(5'A)	733	6765	10897	40
H(5'B)	649	8731	10438	40
H(5'C)	1491	8281	11098	40
H(5"A)	2748	6245	10590	45
H(5"B)	2631	5179	9660	45
H(5"C)	1999	4676	1047	45
H(6A)	1334	5816	8631	31
H(6B)	781	4952	9431	31
H(7)	-288	7476	9333	34
H(8)	-333	9349	8070	34
H(10A)	4324	13668	11217	32
H(10B)	4124	13787	10161	32
H(11A)	5434	11356	10936	56
H(11B)	5692	13287	10515	56
H(11C)	5278	11710	9887	56
H(10C)	4073	10839	11976	41
H(10D)	3392	9367	11541	41
H(11D)	2846	12907	12120	77
H(11E)	2658	11062	12657	77
H(11F)	2169	11409	11704	77

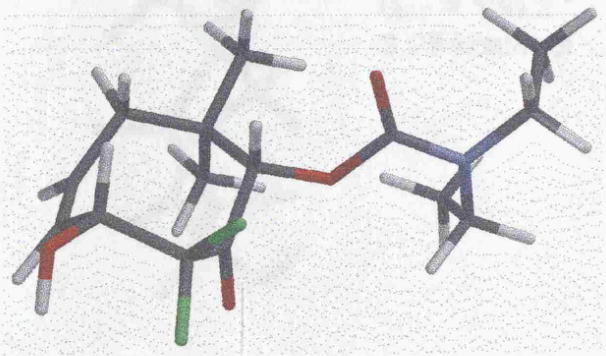
Appendix 3: Conformers of *cis*-356



$\theta_{H\text{-}F}$ = 148.6 °
0.00 kcal/mol

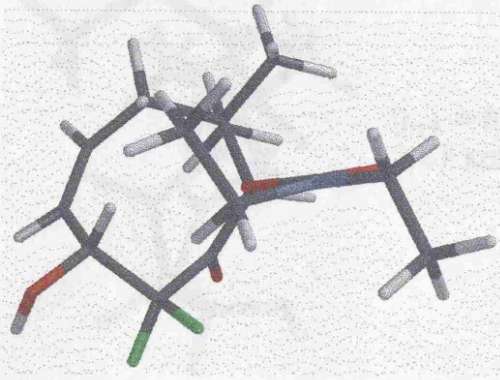


$\theta_{H\text{-}F}$ = 143.5 °
0.11 kcal/mol

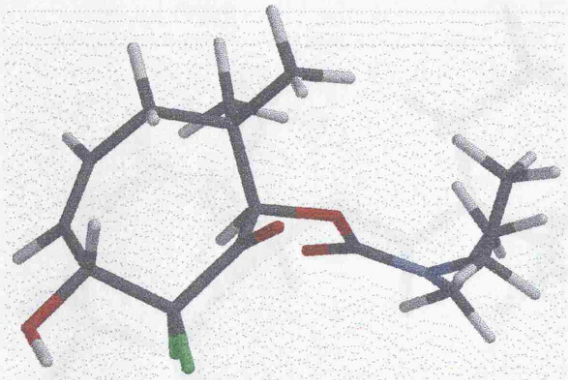


$\theta_{H\text{-}F}$ = 175.3 °
3.26 kcal/mol

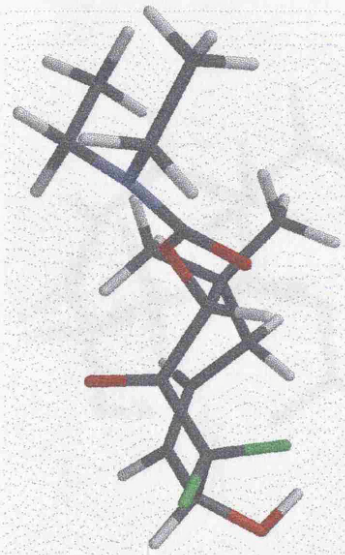
Appendix 3: Conformers for *trans*-356



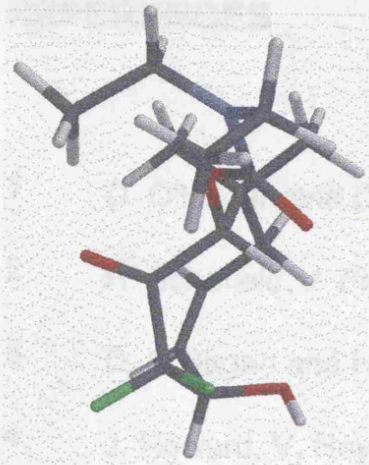
$\theta_{H\text{-}F}$ = 158.0 °
0.00 kcal/mol



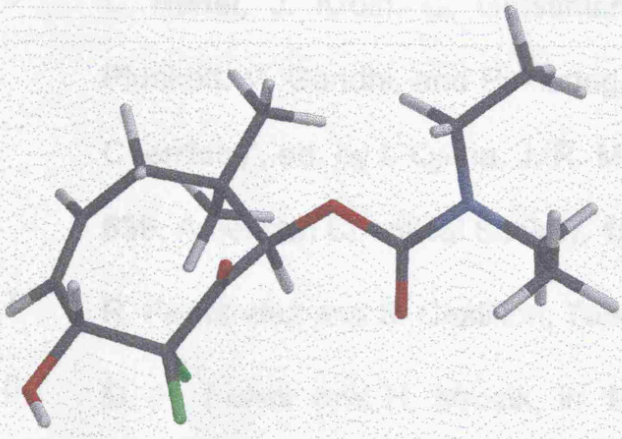
$\theta_{H\text{-}F}$ = 174.0 °
1.23 kcal/mol



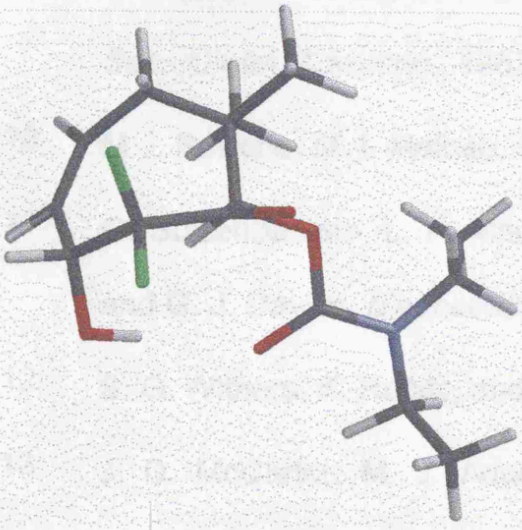
$\theta_{H\text{-}F}$ = 130.2 °
3.25 kcal/mol



$\theta_{H\text{-}F}$ = 82.0 °
3.57 kcal/mol



$\theta_{H\text{-}F}$ = 163.5 °
5.26 kcal/mol



$\theta_{H\text{-}F}$ = 58.9 °
6.04 kcal/mol

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