SOME NEW REACTIONS OF ANOMERIC DIFLUOROMETHYLENE CARBOHYDRATE DERIVATIVES

A thesis submitted by

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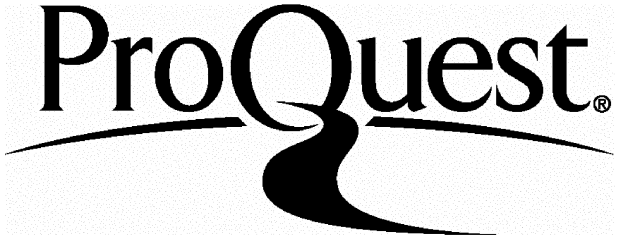

Abstract

This thesis is divided into three chapters. Chapter one presents a review of the preparation of *gem*-difluoromethylene substituted natural product analogues by the fluorinated synthon approach. The reactivity and versatility of various synthons are discussed with particular reference to the disconnection of complex *gem*-difluorinated molecules.

Chapter Two describes some new radical and ionic reactions for the conversion of exocyclic carbohydrate *gem*-difluoroenol ethers into fluorinated natural product analogues. The first section outlines the preparation of carbohydrate *gem*-difluoroenol ethers from the corresponding lactones by a Wittig-type reaction. The following section describes their conversion into difluoroglycophosphonates by reaction with diethyl phosphite or diethyl (phenylselenyl)phosphonate, a new reagent for the efficient generation of phosphonyl radicals under mild conditions. The reaction of *gem*-difluoroenol ethers with nucleophilic radicals is reported as a general route to difluoromethylene bridged disaccharides and glycopeptides. The procedures involve the addition of radicals generated from 6-iodopyranoside or bromo-β-alanine derivatives to these ethers using tin mediated conditions. The preparation of a new and versatile amino acid synthon for radical reactions is also described. The reaction of electrophilic carbon centred radicals with carbohydrate *gem*-difluoroenol ethers has been envisaged, and applied to the preparation of spirofused difluorocarbocycles under atom transfer conditions. In the final section, the conversion of carbohydrate *gem*-difluoroenol ethers into *gem*-difluorocyclitols is explored.

Chapter Three provides a formal description of the experimental results and procedures.

Contents

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Finally, I would like to thank Carole and my parents for their continuous love and support.

To Carole

Sit before facts as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatever abyss nature leads, or you shall learn nothing.

Thomas Huxley

Abbreviations

A	adenine
Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
b.p.	boiling point
Bu	butyl
Bz	benzoyl
C	citosine
Cbz	benzyloxycarbonyl
CI	chemical ionisation
d	doublet
dd	double doublet
ddd	double double doublet
DBU	diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethylsulphoxide
dt	double triplet
ee	enantiomeric excess
EI	electon impact

Et	ethyl
EWG	electron withdrawing group
FAB	fast atom bombardment
gem	geminal
HMPA	hexamethyl phosphoramide
HMPT	hexamethylphosphorus triamide
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
IR	infra red
LDA	lithium diisopropylamine
L.A.	Lewis acid
LUMO	lowest unoccupied molecular orbital
m	multiplet or meta depending on the context
mCPBA	*m*-chloroperbenzoic acid
Me	Methyl
MEM	Methoxyethoxylmethyl
m.p.	melting point
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Pr	propyl
q	quartet
r.t.	room temperature
s	singlet
SET	single electron transfer

SOMO	singly occupied molecular orbital
t	triplet
td	triplet of doublet
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulphate
TBDMS	*t*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluyl
Ts	toluenesulphonate
U	uracyl
Z	benzyloxycarbonyl

Chapter One:

Preparation of *gem*-Difluoromethylene Substituted Compounds:

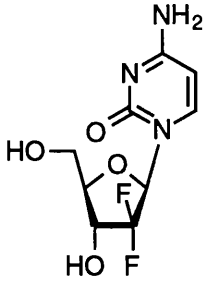
The Fluorinated Synthon Approach

Introduction

Fluorinated molecules have become a popular class of compounds with many applications in polymers, liquid crystals, dyes, plastics, surfactants, coatings, agrochemicals, medicinal chemistry[1,2] and biomedicine.[3] The specific properties of fluorinated molecules originate from the peculiar atomic characteristics of this element. Described by Linus Pauling as a "superhalogen", fluorine is by far the most electronegative element, with an electronegativity of 3.98,[4] compared to 3.44 for oxygen and 3.16 for chlorine. Fluorine, with a van der Waals radius[5] of 1.47 Å, is slightly larger than hydrogen (1.20 Å) and nearly isosteric with oxygen (1.52 Å). It contains three tightly bound non-bonding electrons pairs which can act as hydrogen bond acceptors.[6]

These characteristics endow fluorinated molecules with physical, chemical and biological properties significantly different from their non-fluorinated counterparts. Fluorination modifies lipophilicity, acidity, basicity and hydrogen bond donating and accepting abilities.[7] Polarised CH groups in fluorinated molecules,[8] and in particular the difluoromethyl group,[9] have been shown to act as hydrogen bond donors. Fluorination also leads to considerable modification of the chemical reactivity, because the high electronegativity of fluorine changes the electronic characteristics of the molecule. It has been observed[7] that α-fluorination increases C-O and C=O bond energy and that β-fluorination significantly decreases C-H bond strength. Both α- and β-fluorination decrease the reactivity of saturated systems towards nucleophilic displacement. However, it is the change they induce in biological activity that causes fluorinated compounds to be such in demand.[1] Biological activity depends on diverse properties such as steric hindrance, electronegativity, dipole interaction, lipohilicity, conformation, hydrogen bonding and chemical reactivity, all of which can be significantly modified by fluorination.

Of particular interest are difluoromethylene substituted compounds. Several effects have been associated with the introduction of two geminal fluorine atoms in biologically active compounds. Fluorine is used as a mimic for hydrogen or the hydroxy group in natural product analogues. An example is the cytosine analogue Gemcitabine **1**, which is undergoing clinical development for activity against lung, ovarian, renal, pancreatic and head and neck cancers.[10-12] The difluoromethylene group has also been used as an isoelectronic and isosteric replacement for oxygen in phosphate analogues, Although the analogy between difluoromethylene phosphonates and their parent phosphate has been argued,[13-15] the replacement has provided several natural products analogues with significant biological activity.[16-18]. Examples include the difluorophosphonates **2a** and **2b** which have proved to be good analogues of 1,3-bis(phosphoglyceric) acid as tight binders to yeast phosphoglycerate kinase.[17] Another type of activity is based on the observation that α,α-difluoroketones in aqueous solutions exist predominantly in the hydrated form, making them good candidates for transition state analogues of the sp^3 hydrated carbonyl at the cleavage site of a substrate. Thus, peptide analogues containing the motif **3** have provided potent and selective renin inhibitors.[19] Finally, *gem*-difluoro and monofluoro alkenes have been designed as suicide inhibitors of oxidative enzymes.[20] Oxidation by monoamine oxidase of allylic amine **4** produced a Michael acceptor which can alkylate any nucleophilic residue in the active site.[21] The presence of the fluorine atoms increased the electrophilicity with minimal perturbation of the steric requirement.



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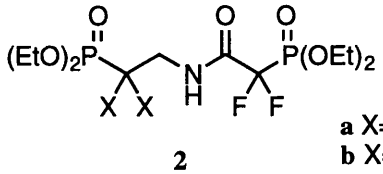
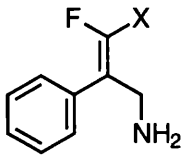


a X=F
b X=H

2

3



X=F,H

4

The preparation of *gem*-difluoromethylene substituted molecules falls broadly into two classes. The first involves direct fluorination, and the second draws from the pool of fluorinated reagents to incorporate an intact CF_2-synthon. A general difficulty associated with the preparation of complex fluorinated molecules is that the change in chemical reactivity brought about by fluorine often leads to unexpected difficulties in reactions commonly used in organic synthesis. For example, reversal of selectivity has been observed in aldol reactions involving Evans's[22] or Oppolzer's[23] chiral auxiliaries in the case of α,α-difluoro carbonyl compounds. Utilisation of a fluorinating agent at a late stage in the synthesis somewhat circumvents that problem and in addition allows the use of a common intermediate for several analogues. However, the forcing conditions associated with most fluorinating agents, especially when *gem*-difluorination is involved, are sometimes incompatible with the sensitivity of an advanced intermediate. The toxicity and the difficulty in handling most fluorinating reagents is another disadvantage. On the other hand, the use of a fluorinated synthon allows the introduction of a difluoromethylene group early in the synthesis using a non-toxic and mild reaction. The difficulties associated with the unpredictable reactivity of fluorinated molecules have been lessened by the development of more elaborate synthons and new reactions to manipulate them.

The preparation of fluorinated molecules and their biological activity has been reviewed several times in the past.[24-32] In particular, the preparation of *gem*-difluoromethylene substituted compounds has been reviewed in 1990.[33] The purpose of this review is to present modern and practical methods for the selective introduction of a *gem*-difluoromethylene group in organic molecules, and will concentrate on

reactions at the fluorinated centre. Although important methods for further elaborating these products have been developed, they will only be mentioned as examples. With a view to the disconnection of *gem*-difluoromethylene substituted molecules, this chapter is organised around the possible reactivities of the CF_2-synthons: nucleophilic, electrophilic and radical synthons will be examined as well as strategies employing difluoroalkenes and difluorocyclopropanes. Along with the reactions to incorporate these synthons, the typical reactivity of the intermediates involved will be discussed.

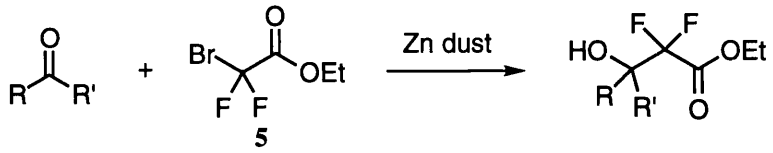
1 Nucleophilic Difluoromethylene Synthons.

Nucleophilic difluoromethylene synthons usually involve CF_2 carbanions, which are particularly reactive as the destabilising electron pair repulsion predominates over the inductive stabilisation.[7] Reactions of difluoroenolates, difluoroallyl anions and difluorophosphonyl anions with electrophiles are the three main classes of methodologies used for the incorporation of nucleophilic CF_2 synthons.

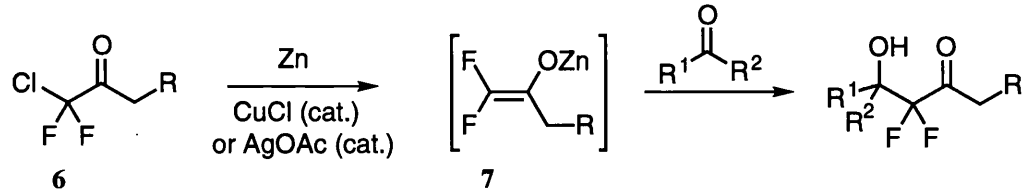
1.1 The Reformatsky and Related Reactions.

The Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the favourite reaction for the introduction of a difluoromethylene unit. One of the reasons is presumably the wide interest in α,α-difluoromethylene ketones as transition state analogues for peptidases.[2] Since several accounts on the Reformatsky reaction of difluoromethylene compounds have been published,[24,33] this section will concentrate on the key developments and the recent progress.

The low stability and reactivity of lithium difluoro enolates[34,35] has made necessary the search for alternative routes to difluoroenolates. In 1984, Fried[36] reported the preparation of 2,2-difluoro-3-hydroxy esters by the Reformatsky reaction of ethyl bromodifluoroacetate **5** with aldehydes and ketones (Scheme 1.1.1). At the same time Ishihara[37] reported the reaction of chlorodifluoromethyl ketones **6** with carbonyl compounds mediated by zinc and a catalytic amount of titanium tetrachloride to prepare 2,2-difluoro-3-hydroxy ketones in moderate yields (Scheme 1.1.2). This procedure was later improved by using copper chloride as a catalyst for the reaction with aldehydes and silver acetate with ketones.[38,39] An intermediate zinc enolate **7** has been observed by ^{19}F NMR.



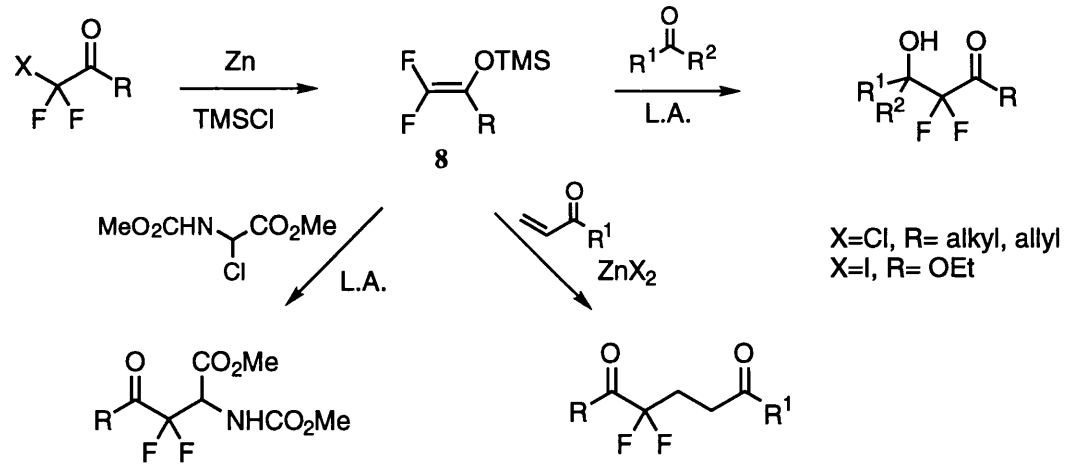
Scheme 1.1.1



Scheme 1.1.2

Several improvements and variations of the reaction conditions have been reported. Reaction in DMF instead of THF or ether allowed, in certain cases, the replacement of bromodifluoroacetates by readily available but less reactive chlorodifluoroacetates.[40] Addition of a catalytic amount of $CeCl_3$[41] or Et_2AlCl with a catalytic amount of AgOAc[42] permitted the use of milder conditions. Ultrasonication[43] allowed the organozinc reagent to be prepared from ethyl bromodifluoroacetate prior to the addition of the aldehyde, which enabled the Reformatsky reaction to be carried out in a two step process as is usually required for aldehydes and ketones bearing a nitro group. An electrochemical nickel catalysed Reformatsky reaction[43] with methyl chlorodifluoroacetate using a sacrificial zinc anode has been described as a low cost, mild and easy to scale up process. A few examples of electroreductive couplings of methyl chlorodifluoroacetate with aldehydes using a lead cathode have also been reported.[44]

The zinc enolates formed under Reformatsky conditions could be trapped as their trimethylsilyl derivative **8** (Scheme 1.1.3). The silyl enolethers generated from halodifluoroketones[45] could be isolated but the ones generated from halodifluoroesters[46] were unstable and usually reacted *in situ*, with the zinc dihalide acting as a Lewis acid. Under these conditions, both types of enolates condensed with aldehydes and ketones and the latter also underwent Michael additions[47] and nucleophilic substitutions[48] as shown by the examples in scheme 1.1.3.



Scheme 1.1.3.

One advantage of using the silyl enolether as an intermediate is an improvement in the stereoselectivity of the reaction. In general,[24] these Reformatsky reactions yield preferentially the *syn-* product with α-alkoxyimines and α-aminoaldehydes and the *anti-* with α-hydroxy aldehydes. The rationale proposed[49] for this difference in selectivity is that in the first two cases there is chelation between oxygen, zinc and nitrogen (Figure 1.1.1, model B) and in the third case the Felkin-Anh model applies (Figure 1.1.1, model A).

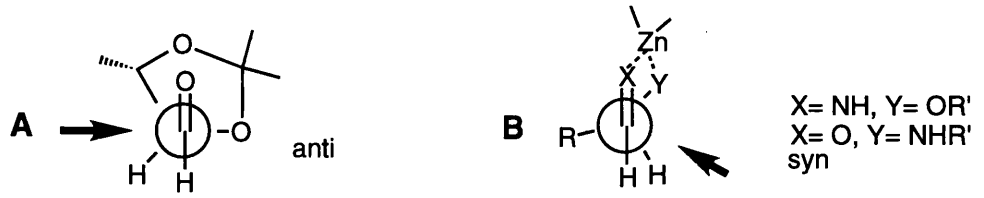
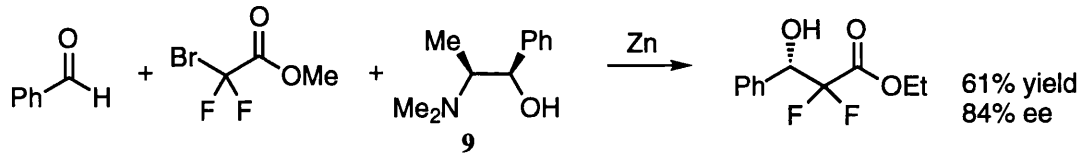


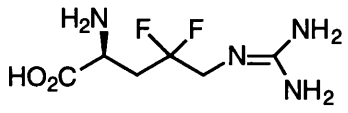
Figure 1.1.1

The first enantioselective Reformatsky reaction of a *gem*-difluoromethyl substituted substrate has recently been reported: in the presence of the chiral β-amino alcohol **9**, benzaldehyde reacted with methyl bromodifluoroacetate in 61% yield and 84% enantiomeric excess (Scheme 1.1.4).[50]



Scheme 1.1.4

The versatility of the Reformatsky reaction is admirably illustrated by the diversity of structural types for which it has been employed. Reformatsky approaches have been used to prepare difluoromethylene analogues of amino acids for incorporation into peptides.[2] Several recent examples include 4,4-difluoro-L-arginine[51] **10** prepared *via* an ultrasound promoted reaction, potent HIV protease inhibitors[52] incorporating fragment **11** and renin inhibitors[53] containing fragment **12**, both prepared *via* standard unactivated reactions . Oxidation of the alcohol formed in the Reformatsky reaction has been found to be problematic using Swern, Collins or PDC procedures.[54] The Dess-Martin periodinane has become the method of choice[55,56], but recently a modified Pfitzner-Moffat reaction has been reported to suppress epimerisation problems encountered with the Dess-Martin reagent in the preparation of renin inhibitors containing fragment **3**.[54] Peptides containing fragment **3** have also been described as human leukocyte elastase inhibitors.[55] The tripeptide analogue **13**, prepared from benzylimine **14** *via* intermediate **15** (Scheme 1.1.5), has been used for mechanistic studies on the biosynthesis of isopenicillin.[57]



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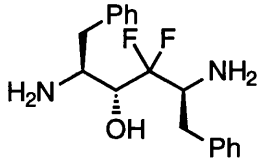

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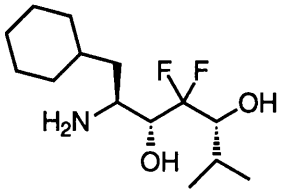

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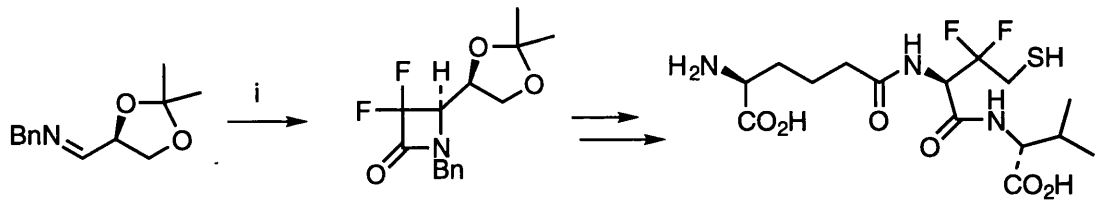
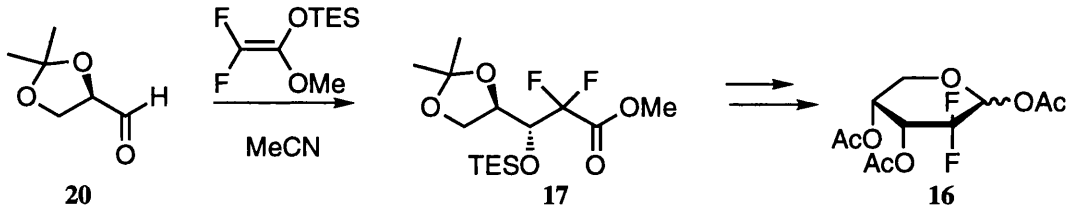


14 15 13

Conditions: i. $BrCF_2COOEt$, Zn.

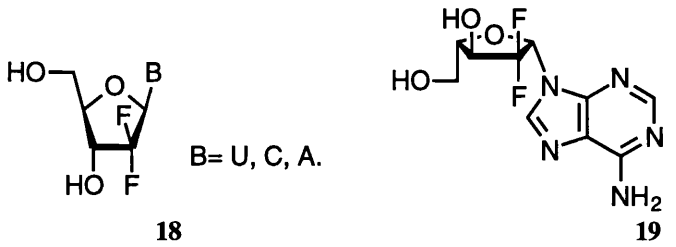
Scheme 1.1.5

Carbohydrate[46,49] and nucleoside analogues have also been prepared using the Reformatsky reaction. An example[46] is the preparation of the ribopyranose analogue **16** by reduction and deprotection **17** obtained from the silylenol ether version of the Reformatsky reaction (Scheme 1.1.6). There is a wide interest in 2',2'-difluorosubstituted nucleoside analogues with the natural D-configuration[11,12] **18** for their activity as antiviral, antimetabolite and antitumour agents.[10,58] Recently, the L-nucleoside analogue[59] **19**, prepared by a classical Reformatsky reaction, has been reported to be a promising anti HIV agent.



20 17 16

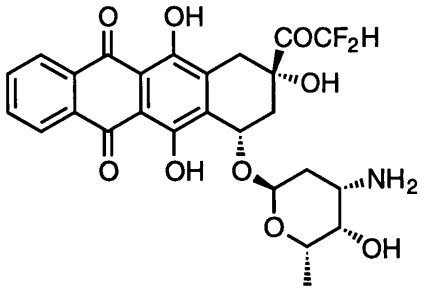
Scheme 1.1.6



18 19

Syntheses using the Reformatsky reaction as a key step were also applied to natural product analogues: 14,14 difluoro-4-demethoxydaunomycin[60,61] **21** was prepared by a classical Reformatsky reaction followed by a decarboxylation. Other

recent examples include (+)-10,10-difluorothromboxane[62] A2 **22**, difluorinated analogues of vitamin D[63]such as **23** and difluoro-N-substituted dibenzoxazepines[64] **24**.



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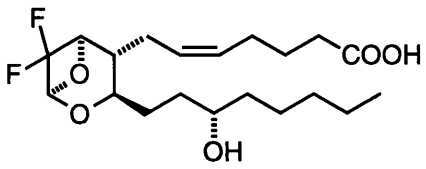

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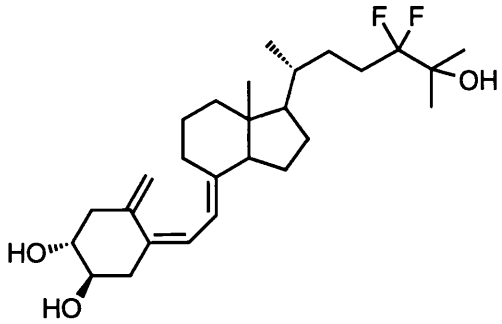

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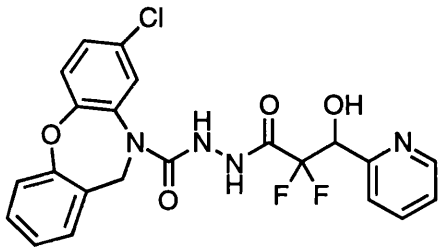
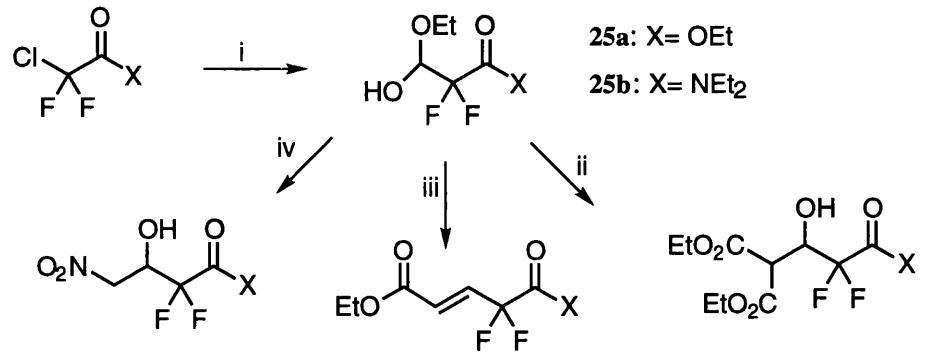


24

Finally, Reformatsky reactions have been used to produce general synthons for further functionalisation. Formylation of the Reformatsky reagent derived from chlorodifluoroacetic acid provided the difluorinated hemiacetals **25a** and **25b,** which were conveniently used as aldehyde equivalents (scheme 1.1.7).[65,66]



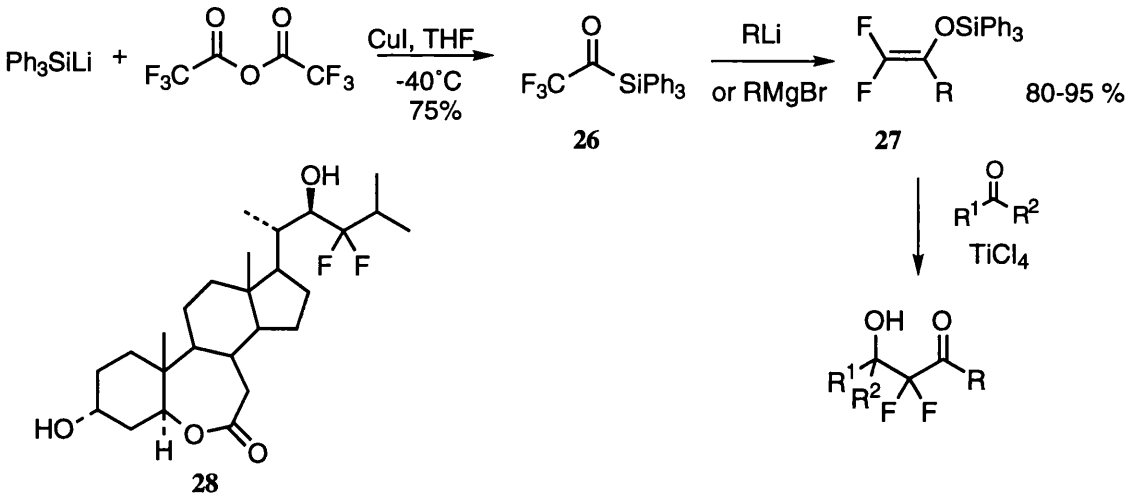
Conditions: i. Zn, DMF, $EtOSO_3Et$; ii. $CH_2(COOEt)_2$, ZnI_2; iii. $(EtO)_2POCH_2CO_2Et$, Et_3N, LiBr; iv. CH_3NO_2, K_2CO_3.

Scheme 1.1.7

A vast number of the examples described above have employed the classical Reformatsky reaction with the conditions initially reported by Fried, and most of the variants and improvements have not yet been been applied to the synthesis of complex fluorinated products. Nevertheless, the Reformatsky reaction is a convenient entry into difluoro aldol products, and the extensive literature attests to the reliability and breadth of application of this route.

1.2 Other Enolates.

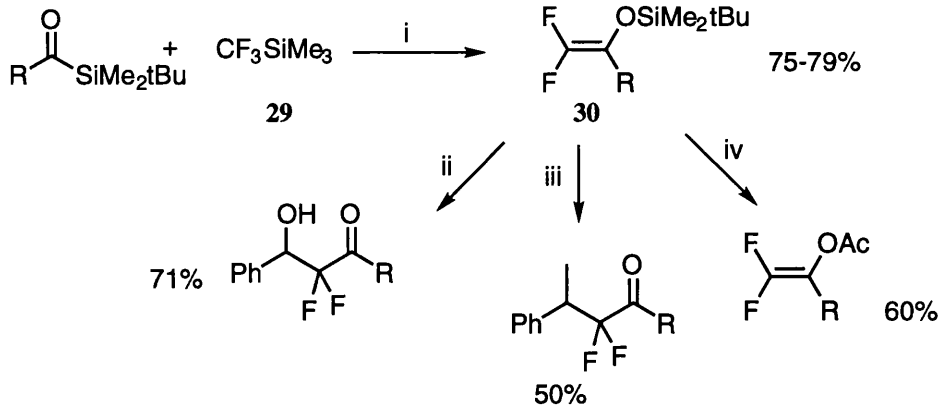
Recently, novel approaches to the formation of difluoroenolates have appeared in the literature. Xu[67,68] has reported the preparation of trifluoroacetyltriphenylsilane **26** and its conversion to triphenylsilylenol ethers **27** upon treatment with Grignards or organolithium reagents (Scheme 1.2.1). The silylenol ethers **27** condensed with aldehydes and ketones with good diastereoselectivity in the presence of a Lewis acid. The difluorinated analogue of a Brassino steroid **28** has been synthesised as an example of the versatility of this approach.



Scheme 1.2.1.

A similar reaction[69] for the preparation of silylenol ethers involved the condensation of trifluoromethyltrimethylsilane **29** (TFMTMS) with acylsilanes

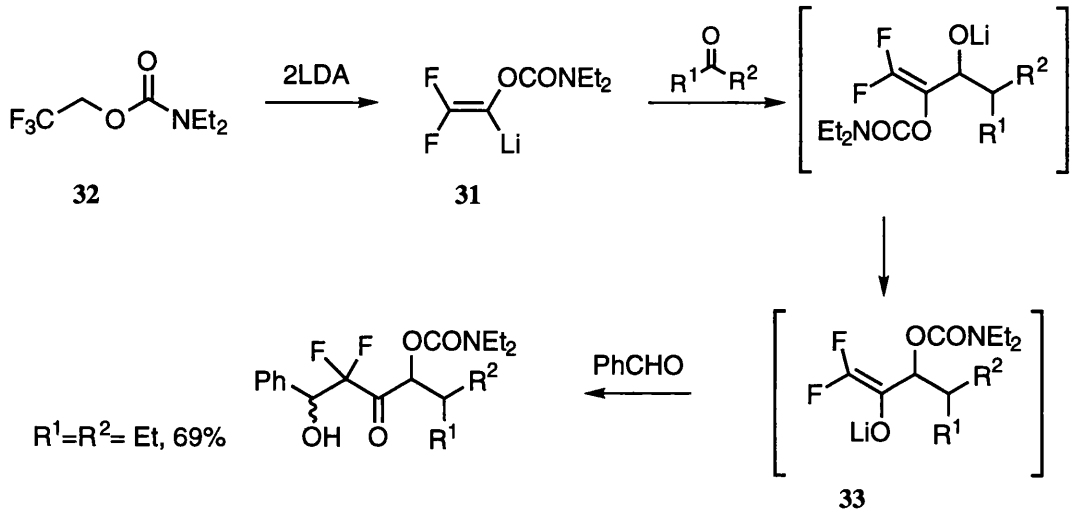
catalysed by fluoride to prepare silylenol ethers **30** which reacted with aldehydes, halides and acid chlorides in a one pot sequence (Scheme 1.2.2).



Conditions: i. $Bu_4N\ Ph_3SnF_2$, THF -78°C to -24°C; ii. PhCHO, $TiCl_4$; iii. $ZnBr_2$, PhCH(Me)Br; iv. $ZnBr_2$, MeCOCl.

Scheme 1.2.2

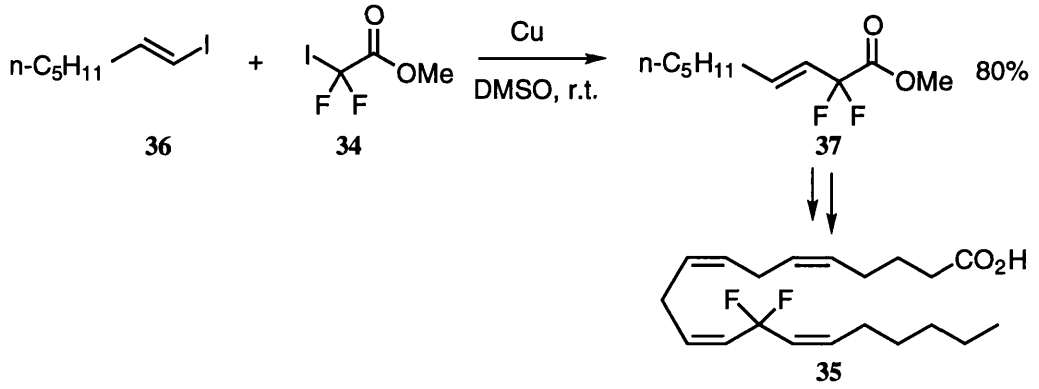
Percy[70] has prepared lithium enolates of difluoroketones from the recently described acyl anion equivalent[71] **31**, readily available from the *N,N*-diethyl carbamate ester of trifluoroethanol **32** (Scheme 1.2.3). Reaction of **31** with an aldehyde or a ketone produced the lithium enolate **33,** which in turn reacted with non-enolisable aldehydes to produce highly functionalised aldol products in one pot and good yields.



32 31 33

Scheme 1.2.3

An approach which does not involve a difluoroenolate but which produces compounds similar to aldol products is the copper mediated coupling of difluoroiodoacetates such as **34** with organic halides (Scheme 1.2.4).[72,73] The reaction has seldom been used in synthesis, and a rare example is the preparation of the difluoroallyl synthon **12** which was subsequently employed in the synthesis of the arachidonic acid analogue **35**.[74]

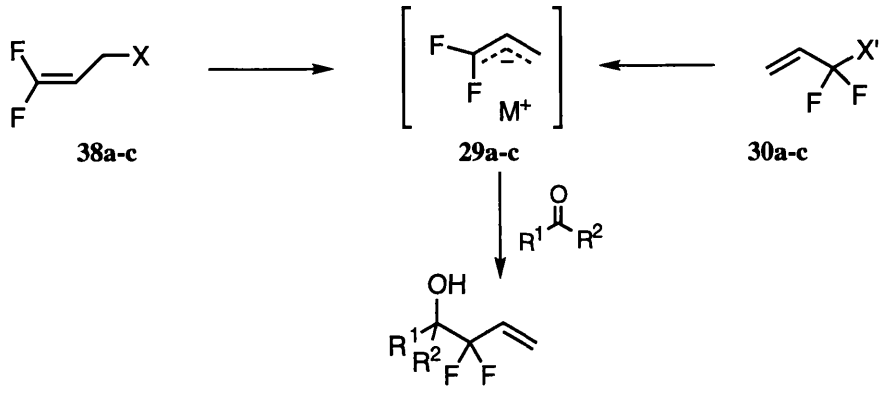


36 **34** **37** **35**

Scheme 1.2.4

1.3 Difluoroallyl Anions.

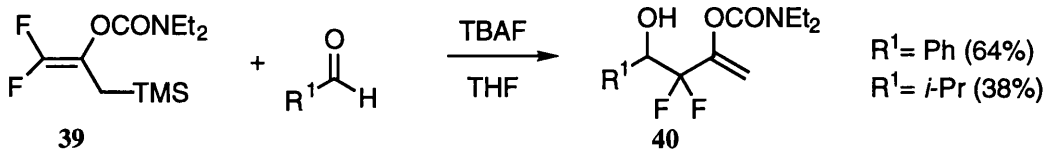
Difluoroallyl anions are emerging as versatile synthons for the synthesis of *gem*-difluorinated molecules, and three different approaches have been described. Difluoroallyl lithium was first reported by Seyferth[75] in 1979, by transmetallation of the *gem*-difluoroallyl stannane **38a** with butyllithium, along with its reaction with several electrophiles. The presence of a "symmetrical" allyl anion intermediate **29a** was suggested by the observation[76,77] that reaction of the anion generated from 3-bromodifluoropropene **30a** by lithium-halogen exchange afforded the same products, consistently corresponding to substitution at the CF_2 terminus (Scheme 1.3.1). Difluoroallyl lithium reacted with aldehydes and ketones in moderate to good yields, but competing *n*-butyllithium addition became a problem with reactive carbonyl groups.



Entry	Substrates	M^+	Conditions
a	X= $SnMe_3$, X'= Br	Li	*n*-BuLi, -95°C
b	X= X'= $SiMe_2Ph$	$(Me_2N)_3S$	$(Me_2N)_3$-Me_2SiF_2 (cat), DMPU, r.t.
c	X= Br, X= I	ZnBr/ ZnI	Zn, THF, 0°C-r.t.

Scheme 1.3.1

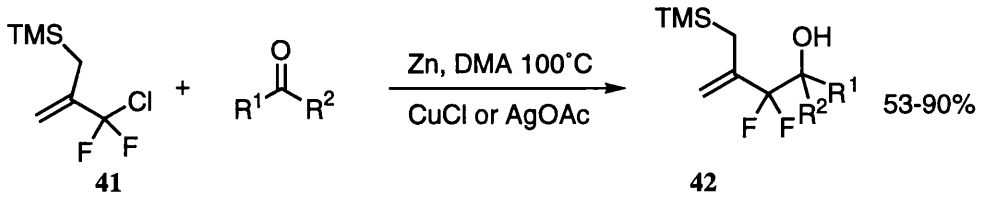
A different approach to a similar reactive intermediate **29b** involved the preparation of the difluoroallyl silane[78-80] **38b** and its addition to carbonyl compounds catalysed by fluoride (scheme 1.3.1). Once again generation of the difluoroallyl anion from both isomers afforded a common free anion intermediate **29b**, which reacted only on the CF_2 terminus. Reactions with aldehydes and ketones proceeded in moderate to good yields and a recent application is the condensation of the difluoro carbamoyloxy allylsilane **39** with aldehydes to the produce functionalised synthons[81] **40** (Scheme 1.3.2).



Scheme 1.3.2

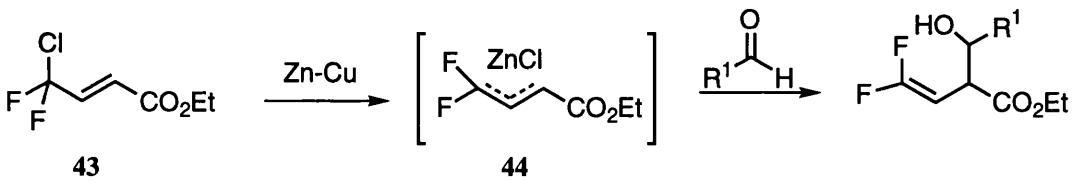
The most practical method described so far for the generation of a difluoroallyl anion was inspired by the Reformatsky reaction and involves the preparation and reaction of a *gem*-difluoroallyl zinc intermediate.[82,83] The reaction of easily available

3-bromodifluoropropene **30c** or 1,1-difluoro-3-iodopropene **38c** with zinc generated a common intermediate **29c**, which condensed with aldehydes and ketones to afford the corresponding homoallylic alcohols in good yields (Scheme 1.3.1). An example of that reaction is the zinc copper chloride or silver acetate promoted coupling of 2-trimethylsilyl-methyl-3-chloro-3,3,-difluoro propene **41** with carbonyl compounds to prepare the synthon **42** for further functionalisation[84] (Scheme 1.3.3).



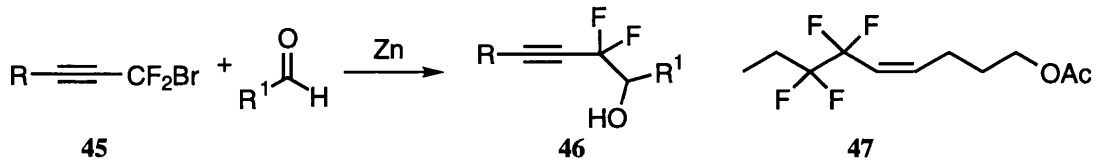
Scheme 1.3.3

The systematic reaction of difluoroallyl anions at the carbon bearing the two fluorines, irrespective of whether the electrophile is hard or soft, is in agreement with an *ab initio* theoretical study[85] of the structure and stability of the 1,1-difluoroallyl anion and its lithiated counterpart. In the free and lithiated anion, the charge distribution is towards the CF_2 terminus, which accounts for the reaction with hard electrophiles, and the largest coefficient of the highest occupied molecular orbital (HOMO) is also on the CF_2 terminus, explaining the outcome of the reaction with soft electrophiles. An opposite reactivity has been observed in the reaction of halodifluoromethylene α,β-unsaturated esters **43** under Reformatsky conditions (Scheme 1.3.4).[86] The zinc chloride allylic anion **44** reacted with aldehydes to afford α-substituted products only, in moderate to good yields.



Scheme 1.3.4

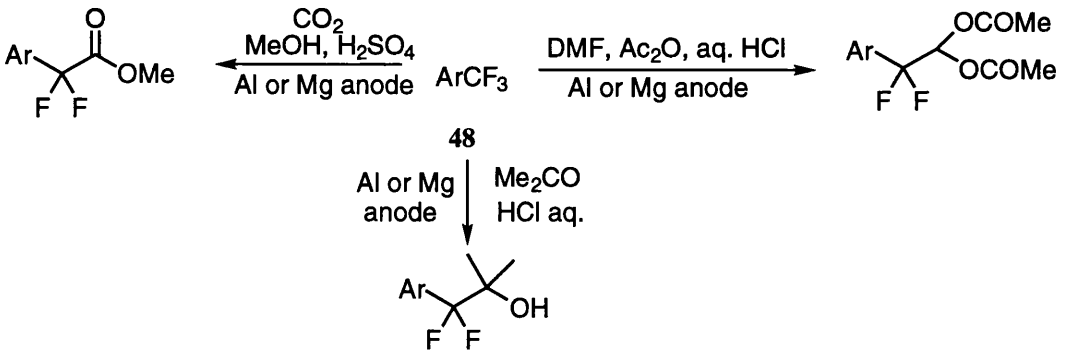
An approach related to the difluoroallyl zinc reaction is the reaction[87] of zinc intermediates, generated from bromodifluoromethyl acetylene derivatives **45**, with carbonyl compounds to prepare difluorinated propargyl alcohols **46**. This reaction was used as a key step to introduce the two allylic fluorines in the synthesis of the fluorinated analogue[88] of (Z)-5-decenyl acetate **47** (Scheme 1.3.5).



45 **46** **47**

Scheme 1.3.5

A close relative of the difluoroallyl anion is the difluorobenzylic anion, an equivalent of which was generated by the electroreduction of trifluoromethylarene **48**. When performed in the presence of electrophiles such as carbon dioxide, acetone or *N*,*N*-dimethylformamide using a sacrificial magnesium or aluminium anode, $ArCF_2$ branched molecules were obtained in good yields (Scheme 1.3.6).[89]



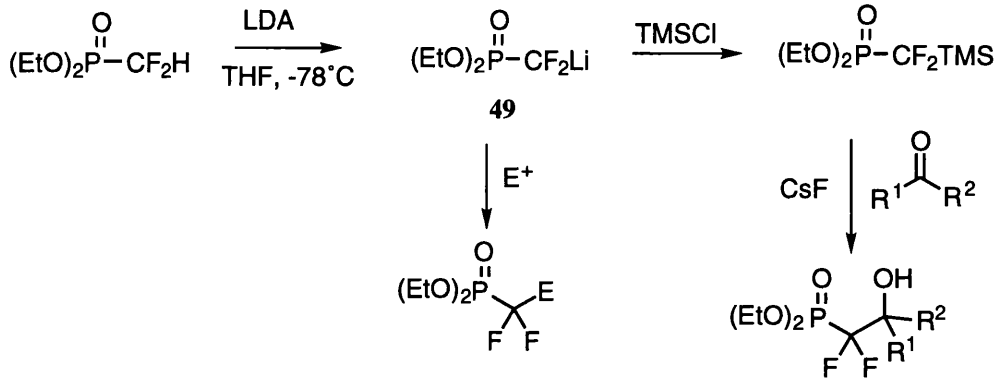
Scheme 1.3.6

1.4 Difluoromethylenephosphonates.

There is a wide interest in difluoromethylenephosphonates as hydrolytically stable analogues of phosphate esters (See introduction). The preparation of these compounds commonly involves the introduction of the difluoromethylene phosphonate

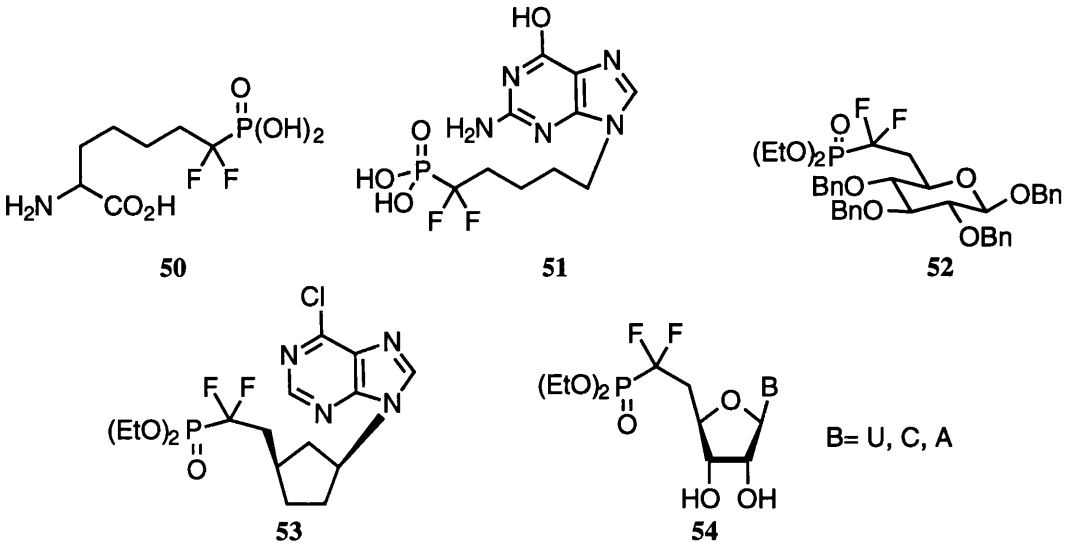
moiety by reaction of lithium difluoromethyl phosphonates or similar cadmium or zinc reagents with electrophiles.[24]

Obayashi and Kondo[90] reported in 1982 the preparation of lithium diethyl difluoromethyl phosphonate **49** by treatment of diethyl difluoromethylphosphonate[91] with LDA at -78°C, and its reaction *in situ* with organic halides and aldehydes (Scheme 1.4.1). For base sensitive electrophiles, **49** can be sylilated with TMSCl and subsequently reacted with aldehydes or ketones using the cesium fluoride protocol.[92]

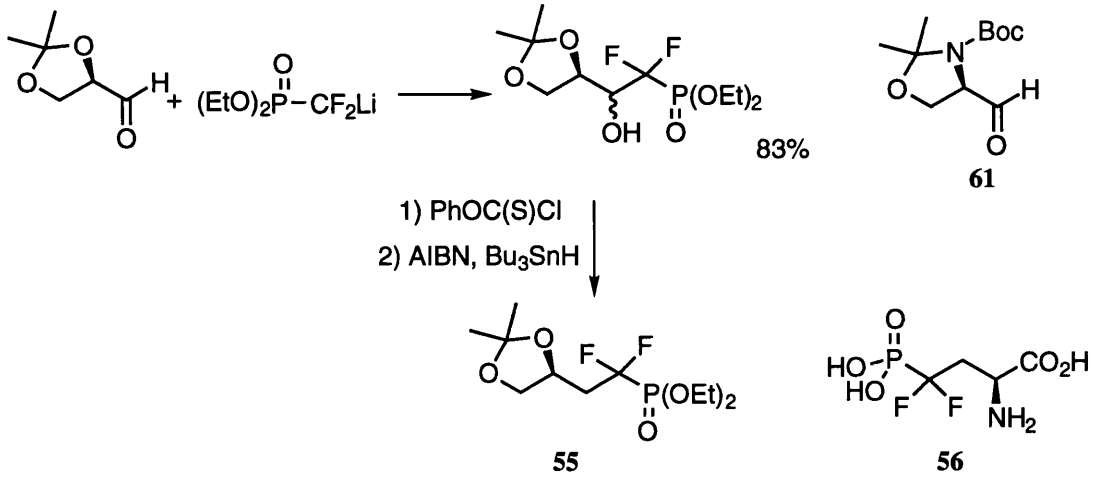


Scheme 1.4.1

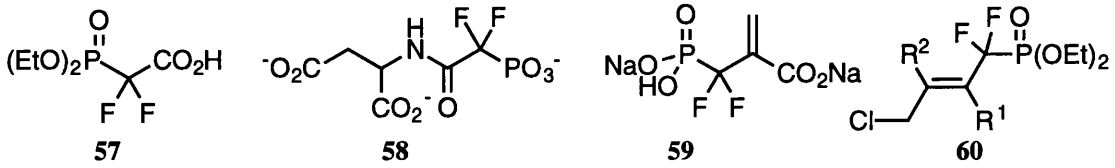
Although nucleophilic substitution of primary bromides and iodides with lithium diethyl difluoromethylphosphonate **49** has been used in the preparation of compounds such as the amino acid analogue **50**[93] and the purine nucleoside phosphorylase inhibitor **51**,[94] it has been reported to be problematic.[95] The displacement of triflates seems to be a reliable alternative and has been used in carbohydrate and nucleoside chemistry: examples include analogues of naturally occurring monosaccharide phosphates such as **52**[95] and nucleosides analogues such as **53**[96] and **54**[97,98].



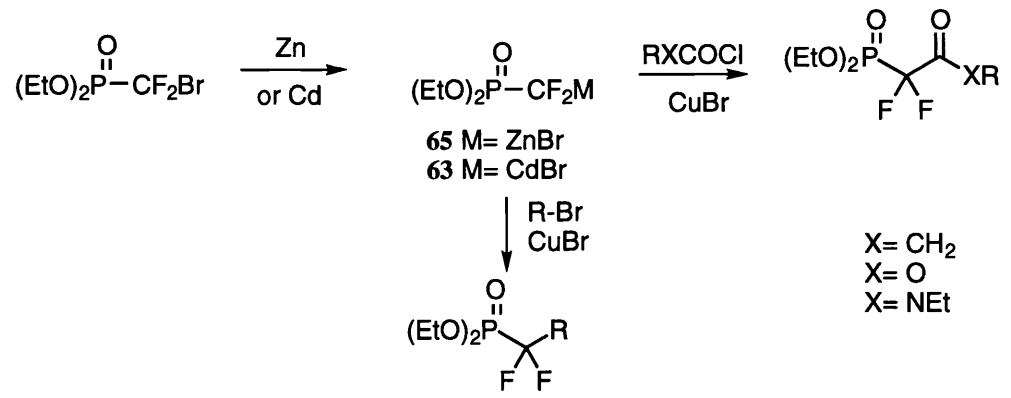
Another alternative for the nucleophilic substitution of primary halides with lithium diethyl difluoromethylphosphonate **49** is the condensation of this reagent with aldehydes combined with a Barton-McCombie deoxygenation[99] (Scheme 1.4.2). This approach has been used for the preparation of enantiopure **55** from glyceraldehyde[15,99] and of the amino acid analogue **56** from Garner's aldehyde (Scheme 1.4.2).[100] In general, lithium diethyl difluoromethylphosphonate **49** reacted in good yields with aldehydes, ketones, ester and phosphinyl chlorides[101]. Blackburn[102] has reported its reaction with carbon dioxide to produce the fluorinated phosphonoacetic acid **57**, which in turn has been used for the synthesis of the aspartame transcarbamoylase (ATC) inhibitor[103] **58**. The reaction of lithium diethyl difluoromethylphosphonate **49** with di-*tert*-butyl oxalate was the first step in the preparation of the phosphoenolpyruvate analogue[104] **59**, and a 1,2 addition of **49** onto α,β-unsaturated aldehydes and ketones followed by conversion of the unstable allylic alcohol to the allylic chloride provided a route to **60**, a versatile intermediate for the preparation of allylic difluorophosphonates.[105] Cerium mediated conjugate addition of **49** to nitroalkenes has also recently been reported.[106]



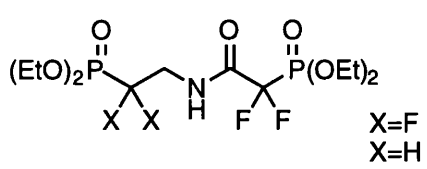
Scheme 1.4.2



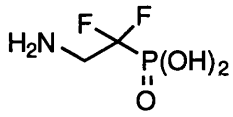
By analogy with the Reformatsky reaction, a convenient zinc reagent[107] prepared from bromodifluoromethyl phosphonate has been reported by Burton[108] in 1982. It condensed with acid chlorides and chloroformates[109,110] and reacted with allylic and primary bromides[111] in presence of a catalytic amount of copper(I) bromide (Scheme 1.4.3). Examples include the preparation of 1,3-bis(phosphoglyceric) acid analogues[17] such as **1** and the preparation of 2-amino-1,1-difluoroethylphosphonic acid[112] **62**. A similar cadmium reagent[113] **63** has been used for reactions with allylic bromides: reaction of **63** with 3-bromopropene and subsequent dihydroxylation afforded the difluoromethylene analogue of glycerol-3-phosphate[16,114] **64**.



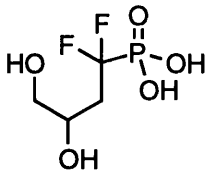
Scheme 1.4.3



1



62



64

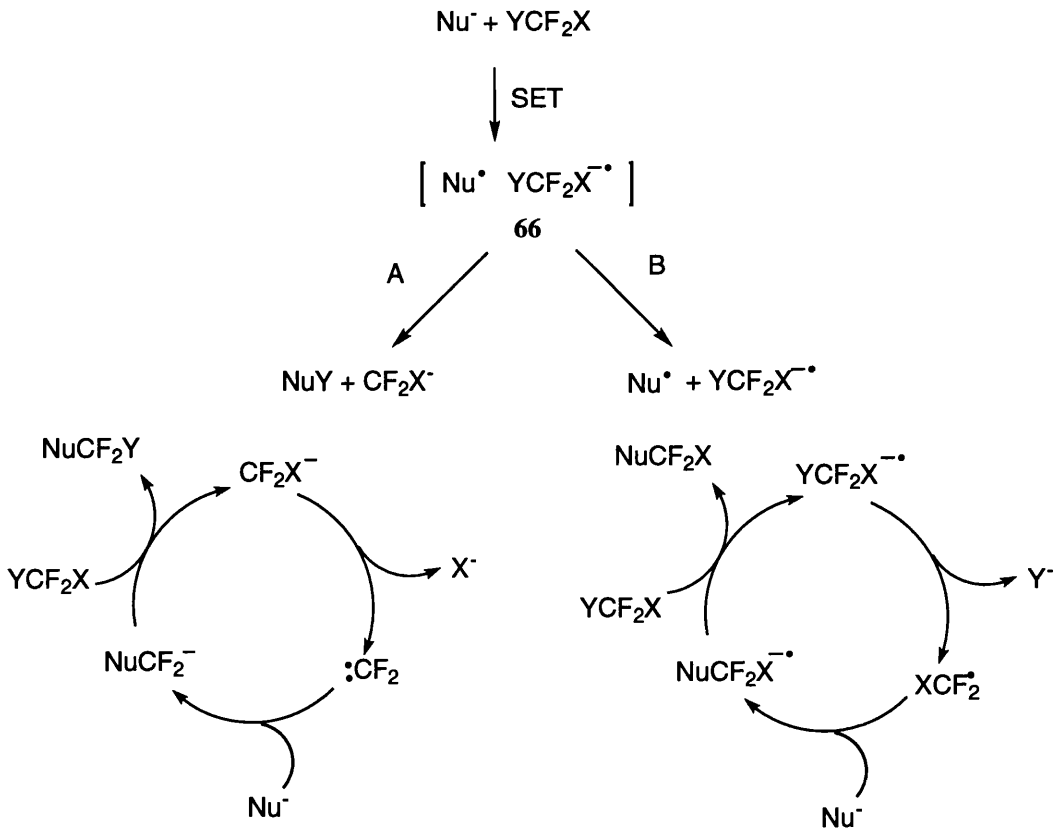
The foregoing methods represent a large proportion of the literature on *gem*-difluorinated synthons and this dominant view of the difluoromethylene unit as a nucleophile should be borne in mind when disconnecting *gem*-difluorinated target molecules. Reformatsky reagents and difluoromethylphosphonate anions are well established techniques, and the manipulation of their reaction products is well documented. Difluoroallylic anions have appeared more recently, but there is no doubt that they will also become popular reagents.

2 Electrophilic Difluoromethylene Synthons.

There are two main types of reactions of difluoromethylene units with nucleophiles: the apparent "nucleophilic substitution" of halodifluoromethanes which usually involves a radical or carbene mechanism and nucleophilic addition to halodifluoroalkenes and Michael acceptors.

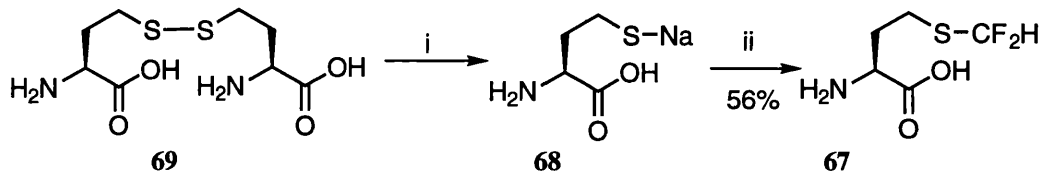
2.1 Reactions of Halodifluoromethane Derivatives.

Halodifluoromethanes react with nucleophiles such as phenoxides, thiophenoxides, carbanions or enamines in an apparent nucleophilic displacement reaction, which involves two possible mechanisms[115] (Scheme 2.1.1). Depending on the nature of the nucleophile and the solvent used, the reaction follows either the carbene path A or the radical path B, with a common radical/radical anion pair intermediate **66** initiated by a single electron transfer. Path B is favoured when the radicals Nu• are stable or the solvent favours dissociation of the radical/radical anion intermediate **66**.



Scheme 2.1.1

Reactions of thiophenoxides[116,117] and phenoxides[117-121] with halodifluoromethanes proceed *via* the carbene mechanism (A) to produce difluoromethylated sulphides or alkoxides. Wakselman[115] has shown that, in the case of thiophenoxides, changing the solvent from benzene to DMF switches the mechanism from the carbene to a concurrence of carbene and radical mechanisms. From a synthetic point of view, these reactions have been used to prepare di- and trifluoromethyl alkoxides and sulphides in moderate to good yields. An example[122] is the preparation of the difluorinated cysteine analogue **67** by reaction of the sodium salt of homocysteine **68** with chlorodifluoromethane (Scheme 2.1.2).

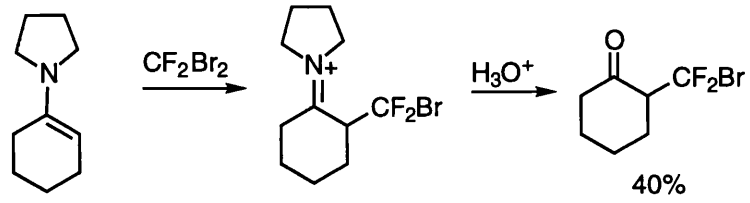


69 **68** **67**

Conditions: i. Na NH_3; ii. CHF_2Cl, KOtBu, MeOH.

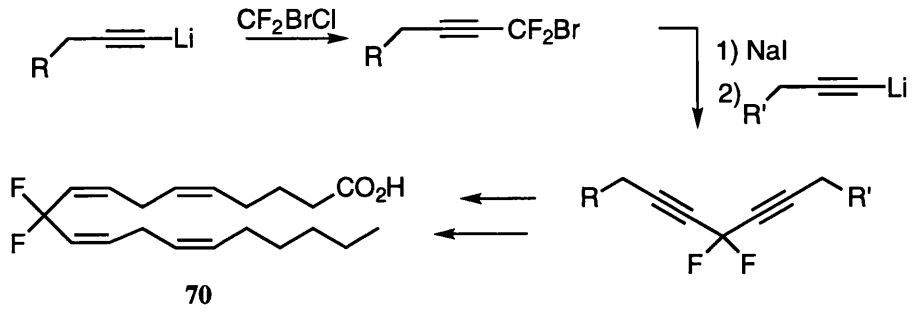
Scheme 2.1.2

Enamine and ynamines condense with dibromodifluoro- and bromochlorodifluoromethane in a radical chain mechanism[123] (Scheme 2.1.3). The reaction proceeds in moderate to good yields but until now has had surprisingly few synthetic applications.

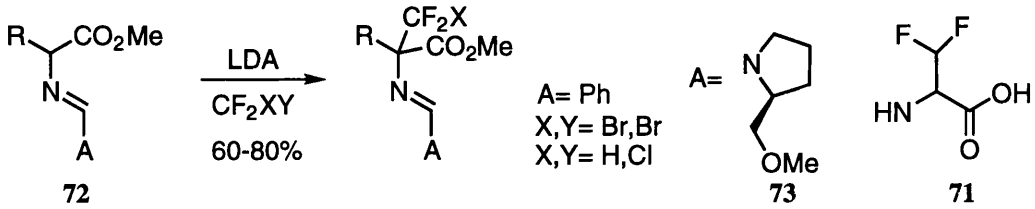


Scheme 2.1.3

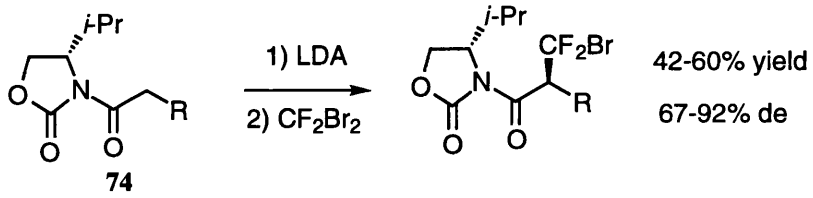
In contrast, the reaction of halodifluoromethanes with carbanions has received much synthetic attention. Acetylenic carbanions and enolates react with halodifluoromethanes *via* the carbene mechanism, in capricious and unpredictable yields ranging from poor to very good, depending on the substrate.[124] Fried[125] has used the reaction of acetylenic carbanions with bromochlorodifluoromethane in a synthesis of the fluorinated analogue of arachidonic acid **70** (Scheme 2.1.4). Amino acid analogues, such as difluoroalanine[126] **71** have been prepared by difluorocarbene insertion into enolates, and a general high yielding method[127,128] involving imines **72** has been developed for their synthesis (Scheme 2.1.5). An asymmetric version[129] involving the chiral auxiliary **73** met with limited success. Recently Kobayashi and Iseki[130] have described the diastereoselective bromodifluoromethylenation of the chiral imide enolate **74**, by insertion of difluorocarbene (Scheme 2.1.6), which occurred with consistent and acceptable yields when the concentration of the enolate was carefully controlled.



Scheme 2.1.4

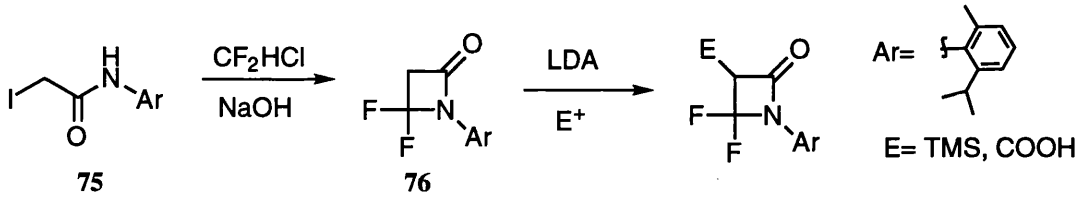


Scheme 2.1.5



Scheme 2.1.6

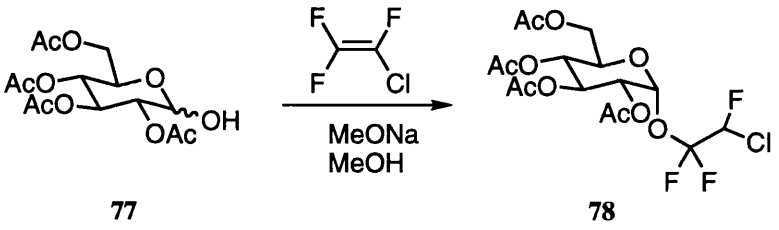
One example[131] of the reaction of an amide ion with chlorodifluoromethane has been reported in the preparation of fluorinated lactams. The amide ion generated from **75** underwent "carbene insertion" followed by nucleophilic displacement of the iodide to produce the fluorinated lactam **76** in low yields (Scheme 2.1.7).



Scheme 2.1.7

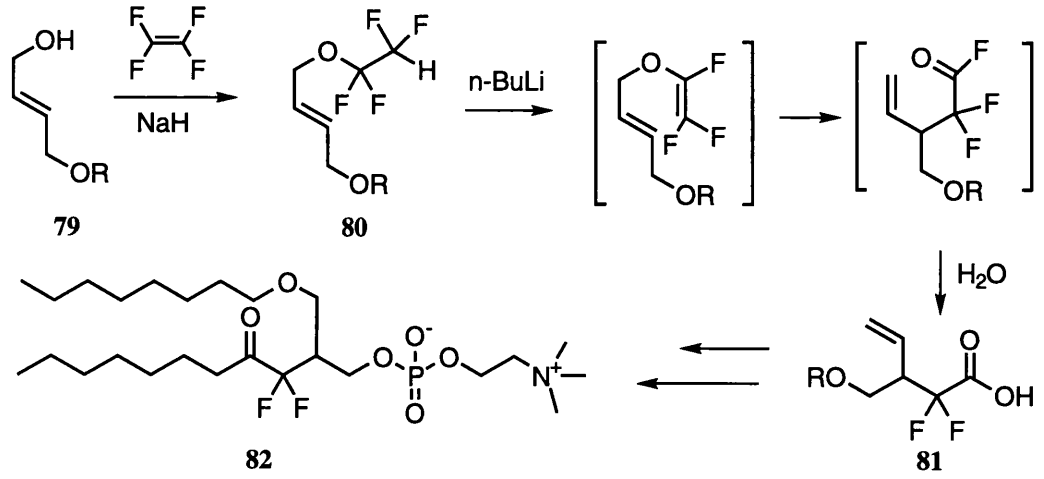
2.2 Nucleophilic Additions to Difluoroalkenes and Miscellaneous Approaches.

Most examples of nucleophilic addition to fluorinated alkenes involve tri- or tetrafluorinated ethylenes and hence the reaction product contains, in addition to the difluoromethylene group, one or two more fluorine atoms.[120,121,132] An interesting example[133] is the reaction of the protected glucopyranose **77** with chlorotrifluoroethylene to produce the glucosidase inhibitor **78** (Scheme 2.2.1). Compounds containing only two fluorine atoms have, nevertheless, been prepared from these higher fluorinated intermediates: when tetrafluoroethylene was reacted with the allylic alcohol **79**, elimination and Claisen rearrangement of the tetrafluorinated intermediate **80** allowed the preparation of the difluoromethylene carboxylic acid **81** as a key intermediate in the synthesis of the cobra venom phospholipase inhibitor[134] **82** (Scheme 2.2.2).



77 **78**

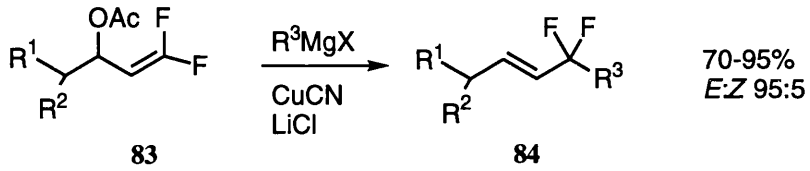
Scheme 2.2.1



79 **80** **82** **81**

Scheme 2.2.2

A nucleophilic addition onto functionalised *gem*-difluoroalkenes has been described as a general and convenient access to molecules bearing a difluoromethylene unit in the allylic position. The nucleophilic addition-elimination sequence of Grignards with *gem*-difluoro-3-oxyacetate **83** afforded fluorinated alkenes **84** in good yields (Scheme 2.2.3),[135,136] and this reaction has been applied to the preparation of the sex pheromone analogue **85**. Reaction with thionyl chloride instead of Grignard reagents afforded the chlorinated synthon[137] **86** which could subsequently be used in radical reactions, or to generate a difluoroallylanion (see section 1.3).

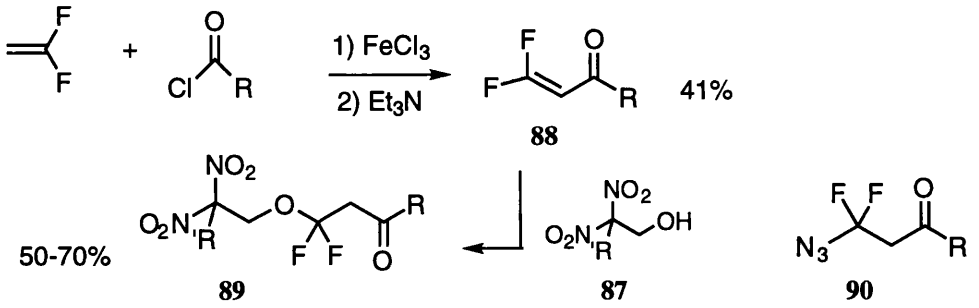


83 **84**

Scheme 2.2.3

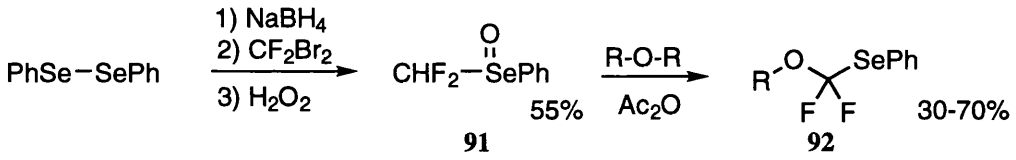
85 **86**

There are few examples of Michael-type additions onto β,β-difluoro α,β-unsaturated carbonyl compounds. The reason is presumably the high reactivity and consequent instability of these compounds,[138] a profitable manifestation of which is their tendency to undergo addition-elimination[139] and thereby act as intermediates in the synthesis of monofluorinated products. Nevertheless, recent methods have been developed for the preparation of β,β-difluoro-α,β-unsaturated carbonyl compounds[140] (see section 5.1) and an interesting example[141] has made the most of their reactivity in the preparation of difluoronitroethers. Geminal β-dinitroalcohols **87**, which do not react with non-fluorinated Michael acceptors, condensed with β,β-difluoro-α,β-unsaturated ketones and esters **88**, prepared by nucleophilic acylation of 1,1-difluoroethylene with subsequent dehydrochlorination (Scheme 2.3.1). Difluoronitro ethers **89** were thus produced in good yields and a similar reaction with sodium azide afforded azido difluoro derivatives **90**.



Scheme 2.3.1

In addition to the methods mentioned thus far, it is worth noting an interesting approach[142,143] to a difluorocation equivalent *via* a Pummerer type reaction of difluoromethyl phenyl selenoxide **91**. This compound was prepared by reaction of diphenyldiselenide and dibromodifluoromethane under reductive conditions followed by oxidation, and it reacted with cyclic or acyclic ethers in presence of acetic anhydride to afford the corresponding difluoromethyl ethers **92**, which in turn could be used in radical reactions (Scheme 2.3.2).



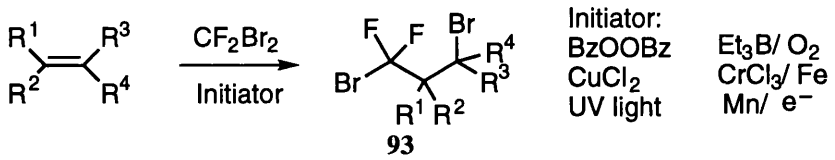
Scheme 2.3.2

3 Difluoromethylene Radicals.

Difluoroalkyl radicals are very promising intermediates for the preparation of complex fluorinated molecules under mild conditions. They are usually more reactive than the corresponding non-fluorinated radicals in carbon-carbon bond forming reactions because of the σ-nature of the radical and the increased strength of the bond formed.[144,145] Difluoromethylene radicals are generally considered as strongly electrophilic,[7] although in some additions to alkenes better results have been obtained with electron deficient rather than electron rich alkenes.[146]

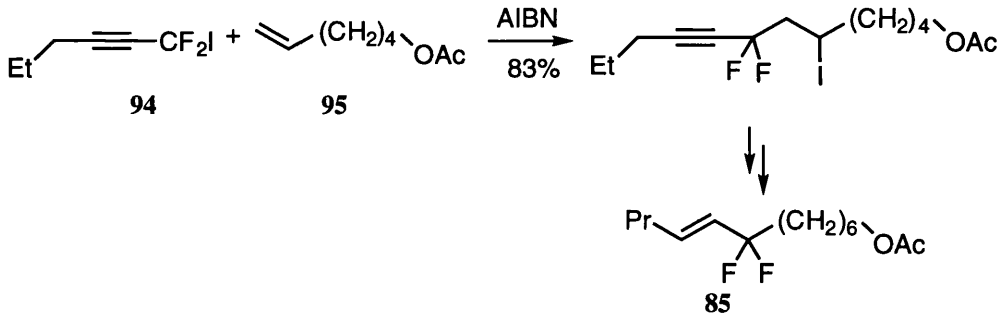
3.1 Addition of Halodifluoroalkyl Radicals onto Alkenes.

The addition of dibromodifluoromethane across alkenes initiated by dibenzoyl peroxide,[147] copper(II) chloride,[148] or UV light[149] in the case of electron rich alkenes, has been known for a long time (Scheme 3.1.1).[148] Recently, new initiators for this reaction have been reported, such as triethylborane/oxygen at room temperature for the addition across alkenes and alkynes,[150] a chomium trichloride/iron bimetal redox system[151] and a manganese mediated electrochemical initiation.[152] Reduction of the 1,3-dibromo-1,1-difluoroalkane **93** with sodium borohydride has been shown in some cases, to remove selectively one bromine atom, leaving the bromodifluoromethyl group intact for further functionalisation.[153] Difluorodiiodomethane[154] has recently been reported as a good source of difluoroiodomethyl radicals, and its reaction with alkenes initiated by dibenzoyl peroxide afforded 1,3-diiodo-1,1-difluoroalkanes in good yields.[155]

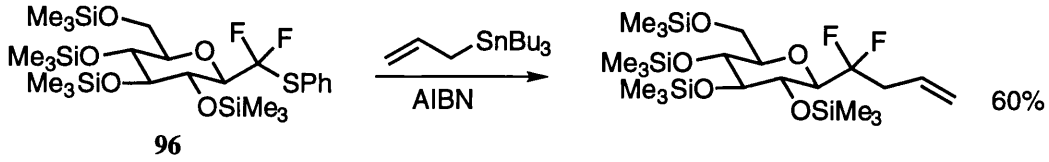


Scheme 3.1.1

The majority of recent synthetic examples of radical reactions of halodifluoroalkanes with alkenes involve intramolcular cylisations, which are described in section 3.3. Fried[156] has reacted the iodide **94** (prepared from the corresponding bromide: see Scheme 2.1.4) with the alkene **95** in the first synthesis of the fluorinated analogue of the oriental fruit moth sex pheromone **85** (Scheme 3.1.2) (for another synthesis of **85** see Scheme 2.2.3). Carbohydrate anomeric *gem*-difluoro radicals have been generated from the corresponding phenylsulfide **96** and reacted with allystannanes, in a general route to CF_2-glycosides (Scheme 3.1.3).[157]

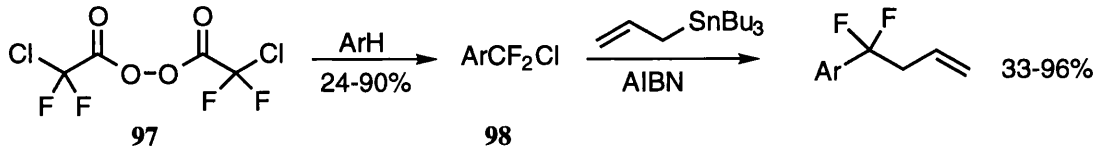


Scheme 3.1.2



Scheme 3.1.3

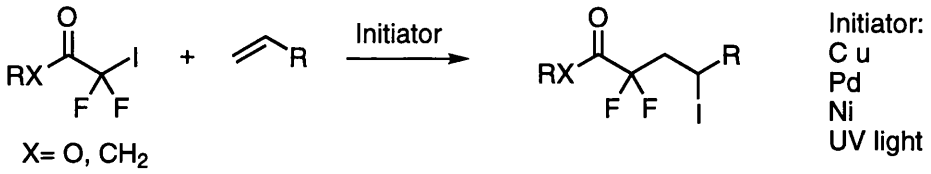
Recently, a novel entry into difluoromethylarene substituted compounds by radical reactions has been reported.[158,159] Reaction of *bis*(chlorodifluoroacetyl) peroxide **97** with aromatic rings afforded chlorodifluoromethylarenes **98** which could subsequently be functionalised by radical reactions with allylstannanes (Scheme 3.1.4).



Scheme 3.1.4

3.2 Difluoroacetyl Radicals.

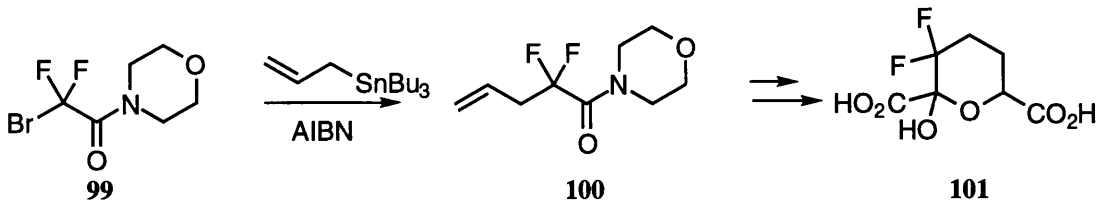
Radical additions of difluoroiodo esters and ketones across alkenes has emerged as a mild and convenient alternative to the Reformatsky reaction for the preparation of α,α-difluorinated esters and ketones (Scheme 3.2.1). Kobayashi[160] and Burton[161] reported, at about the same time, the atom transfer reaction of difluoroiodoacetyl derivatives with electron rich alkenes initiated by a copper catalyst. Later, a one pot atom transfer reaction of difluoroiodoesters and reduction of the resulting iodide was described, using zinc metal and a catalytic amount of nickel chloride.[162,163] Difluoroiodoketones have been shown to react in good yields with electron rich olefins in atom transfer reactions initiated by palladium,[164,165] and UV light initiation allowed the reaction to proceed with electron deficient alkenes.[166] Evidence for the radical nature of these reactions was provided by radical trapping experiments and inhibition by radical scavengers.



Scheme 3.2.1

Other initiators have been used to produce difluoroacetyl radicals, such as electrochemistry[167] or AIBN/organostannane systems.[168] Reaction of the bromoamide **99** with tributylallyltin initiated by AIBN afforded the intermediate **100** in the

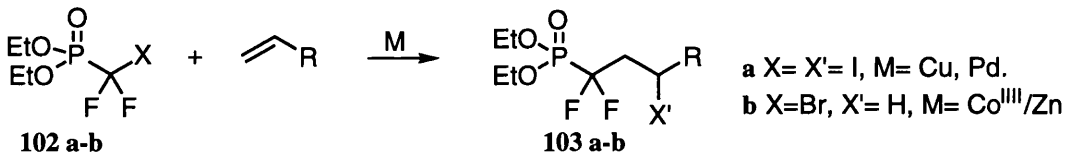
preparation of **101**, an analogue of the hydrated form of tetrahydrodipicolinic acid (Scheme 3.2.2).



99 **100** **101**

Scheme 3.2.2

Radical reactions have also appeared as a mild route to difluorophosphonates. Atom transfer reaction of ethyl iododifluoromethylphosphonate **102a** with alkenes initiated by copper or palladium has been reported.[169,170] The similar reaction of ethyl bromodifluoromethylphosphonate **102b** with electron deficient alkenes in the presence of a bromo(pyridine)cobaloxime(III)/zinc bimetal redox system led to the reduced adduct **103b** (Scheme 3.2.3).[171]



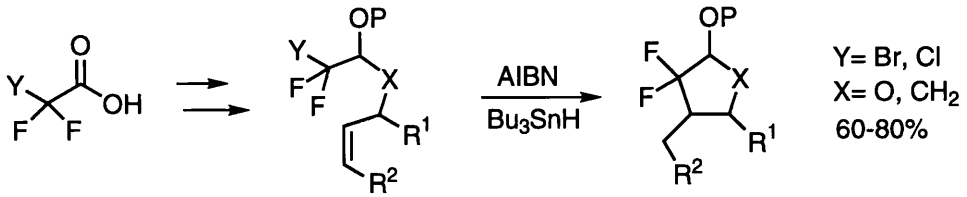
102 a-b **103 a-b**

Scheme 3.2.3

3.3 Intramolecular Cyclisations.

Intramolecular radical cyclisations have been used as a convenient route to difluoromethylene substituted three, five or six membered rings. Radical cyclisations of bromo- or chlorodifluoromethyl esters[172] and ketones,[173] prepared from the corresponding acid **104**, to form five membered rings were first investigated. It was noticed in both cases that the cyclisation under tin mediated conditions would only proceed if the carbonyl compound was reduced to the alcohol and protected.[172,174] Under these conditions, difluorinated cyclopentanes and lactols were prepared in good yields by 5-*exo* radical cyclisation on alkenes and alkynes (Scheme 3.3.1). A

comparative study on 5-*exo* radical cyclisations onto alkenes and alkynes reported that reactions mediated by organosilanes, samarium diiodide and organocobalt complexes proceeded sometimes in higher yields than with organotin hydrides and, in the case of organocobalt complexes, allowed further functionalisation.[146]

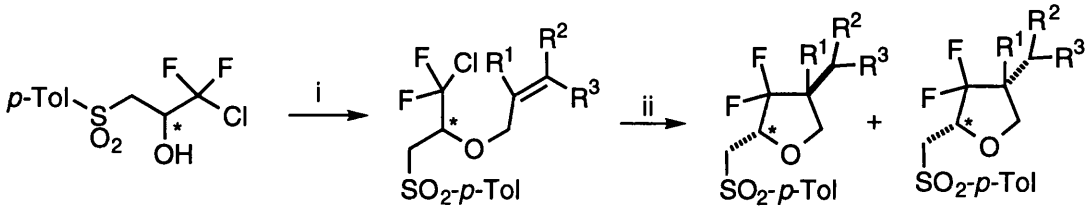


104 **105** **106**

Scheme 3.3.1

Cavicchio and Bravo have investigated an interesting stereocontrolled route to functionalised furans, cyclopentanes and cyclohexanes involving sulfur substituted chiral intermediates. The chiral difluorinated synthons **107a-b**, prepared by microbial reduction of the corresponding ketones, reacted with allylic bromides and the resulting chloroalkenes underwent 5-*exo-trig* cyclisation as a general route to functionalised furans **108** (Scheme 3.3.2).[175,176] A moderate to fair diastereoselection was observed in these reactions, always in favour of the *trans*-isomer. A similar approach has studied the stereochemical outcome of 5-*exo-trig* and 6-*exo-trig* cyclisations of all four diastereomers of **109** and **110**. In the cyclopentane series,[177] a moderate diastereoselectivity was found in favour of the isomer having the methyl and the sulfinyl group in a 1,3-*cis*-relationship (Scheme 3.3.3). A possible explanation was that the molecule in an early transition state **111** adopted preferentially a conformation in which the lager sulfinyl substituent was in a pseudo-equatorial position. Five membered ring intermediates **112** could then be converted into functionalised cyclopentanes such as **113** and **114**. In the cyclohexane series,[178] when the arylsulfinyl and hydroxy substituents had a relative *threo*-configuration, an equimolar mixture of the two diastereomers **115a** and **115b** was produced, whereas when they had an *erythro*-relative arrangement, a single cyclisation product **116** was observed. The rationale proposed to explain this difference of selectivity was that in the first case, both

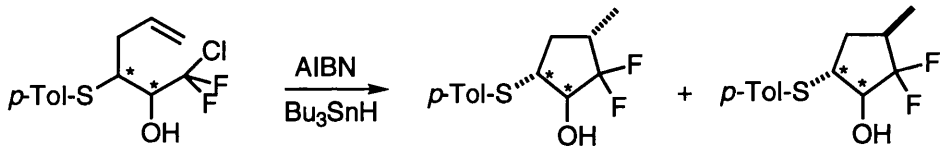
transitions states **117a** and **117b** were similarly populated whereas in the second case a 1,3-diaxial relationship between the alkene and the hydroxy groups in **118a** favoured transition states **118b**.



107a (R), **107b** (S) **108** ***trans*** **108** ***cis***

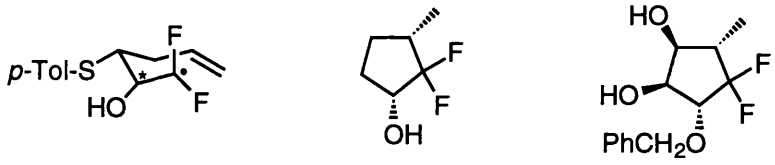
Conditions: i. $BrCH_2\text{-}CR^1{=}CR^2R^3$; ii. AIBN, Bu_3SnH.

Scheme 3.3.2

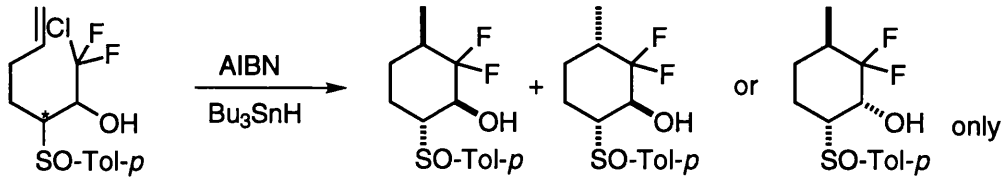


109 **112**

Scheme 3.3.3

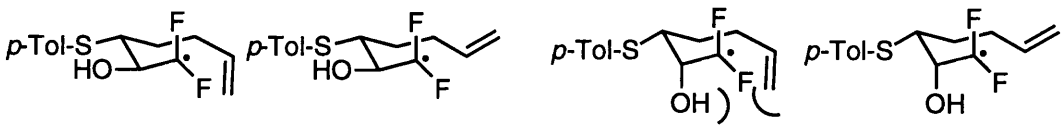


111 **113** **114**



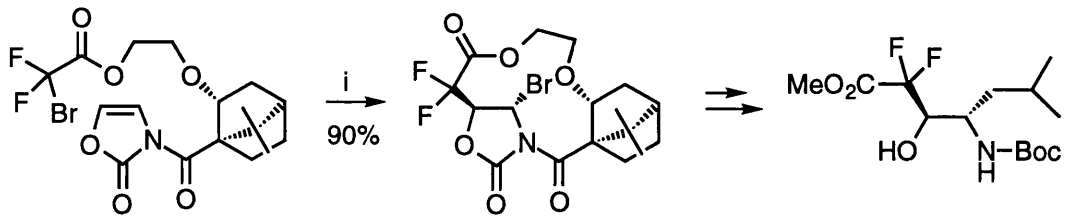
110 **115a** 1:1 **115b** **116**

Scheme 3.3.4



117a **117b** **118a** **118b**

Removable tethers have been used to induce stereoselectivity in intramolecular radical cyclisations. A key step in the preparation of 2,2-difluorostatine **119** was the ruthenium catalysed efficient intramolecular addition of a difluoroacetyl radical onto a 2-oxazolone derivative, permitting introduction of the difluoromethylene group with high diastereoselectivity (Scheme 3.3.5).[179]

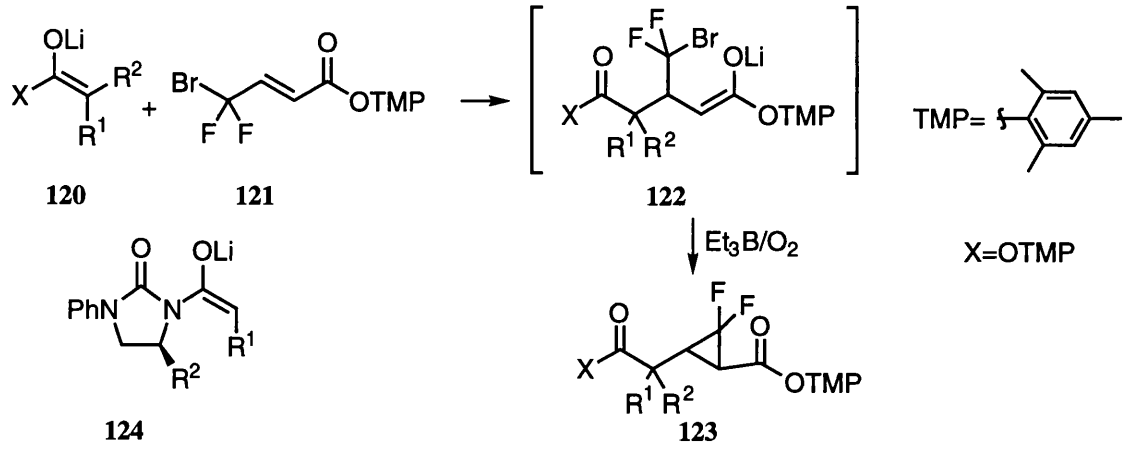


119

Conditions: i. $RuCl_2(PPh_3)_3$, benzene, reflux.

Scheme 3.3.5

Finally, difluorocyclopropanes have been prepared by the cyclisation of a lithium enolate,[180] although the radical nature of this reaction is open to discussion. Michael addition of lithium enolates **120** to the ester **121**, followed by triethylborane-oxygen induced cyclopropanation of intermediates **122** afforded the cyclopropanes **123** in good yields (Scheme 3.3.6). An asymmetric version using the lithium enolate of *N*-acylimidazolidinone **124** has also been reported.[181]



Scheme 3.3.6

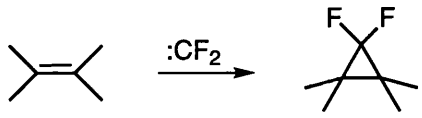
Radical methodologies are being developed as mild alternatives to reactions involving fluorine substituted carbanions. Most of the reactions described in this section are still being investigated but there is little doubt that they hold an increasingly important position on the palette of methodologies for the synthesis of fluorinated compounds.

4 Difluorocarbene and Cyclopropanes.

gem-Difluorocyclopropanes were considered fifteen years ago as versatile intermediates for the preparation of difluoromethylene substituted compounds,[182] but since then have not extensively been used in synthesis. They are almost invariably prepared by the addition of difluorocarbene to double bonds, and are involved in several possible ring opening reactions. *gem*-Difluorocarbene is very electrophilic and exists as a ground state singlet.[183,184] As such, it adds stereospecifically to alkenes and does not insert into C-H bonds in competition with C=C addition.[185,186]

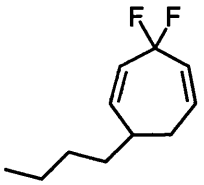
4.1 Generation of Difluorocarbenes.

A variety of methods exists for the generation of difluorocarbene (Scheme 4.1.1). Tin[187] and mercury[188-190] trifluoromethyl complexes are toxic but efficient difluorocarbene sources in the presence of sodium iodide. The mercury complex has been used recently[191] in the preparation of the algal pheromone dictyotene analogue **125** (*vide infra*). Thermolysis of sodium chlorodifluoroacetate[192] has long been the method of choice for the generation of difluorocarbene, but Burton's phosphonium salt/ potassium fluoride system[193] is now being recognised as the most convenient source for synthesis. Recently, a dramatic increase in yield was noticed when a catalytic amount of 18-crown-6 was added to the reaction mixture,[194] and the reagent has been used in the preparation of fluorinated insecticides[195] of type **126** and of *gem*-difluorocyclopropenes[196] **127**. Halofluorosulfonyldifluoroacetic acids have been reported as an easy to handle source of difluorocarbene under mild conditions, [197,198] and were used in a new preparation of iododifluoromethane.[199]

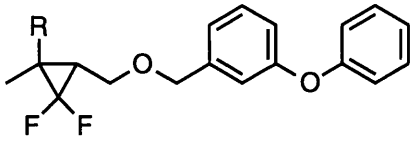


Me_3SnCF_3[187]
$PhHgCF_3$[188-190]
ClF_2CCO_2Na[192]
ClF_2CCO_2Me/ LiCl/ HMPA[200,201]
$[(Me_2N)_3PCF_2Br]^+Br^-$/ KF[193,194]
$[Ph_3PCF_2Br]^+Br^-$/ KF[193,194]
CF_2Br_2/ $TiCl_4$/ $LiAlH_4$[202]
CF_2Br_2/ Zn/ I_2 (cat.)[203]
CF_2Br_2/ $CHBr_3$/ KOH/ TBAHS[204,205]
$FO_2SCF_2CO_2H$/ Nu^-[197]

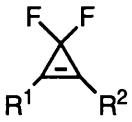
Scheme 4.1.1



125

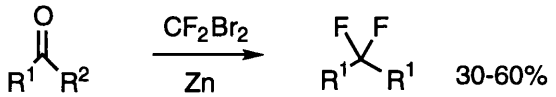


126

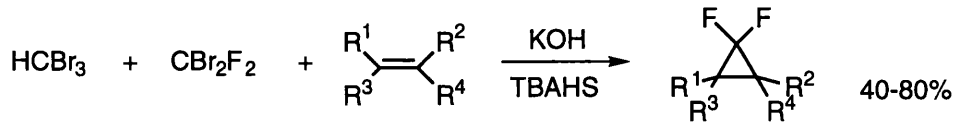


127

New methods for the generation of difluorocarbene have recently been reported: reaction of dibromodifluoromethane with alkenes in presence of titanium tetrachloride and lithium aluminium hydride afforded cyclopropanes in low yields.[202] Dibromodifluoromethane, zinc and a catalytic amount of iodine constitutes a convenient preparation of difluorocarbene, which reacted with alkenes in yields comparable to Burton's phosphonium salt method.[203] Interestingly, carbenes generated from CF_2Br_2/ Zn act as fluorinating agents with aldehydes and ketones to form the corresponding *gem*-difluoro compounds (Scheme 4.1.2).[206] A remarkably economical and simple procedure for the synthesis of *gem*-difluorocyclopropanes, using a phase transfer catalysed system, has been reported:[204,205] stirring a mixture of bromoform, dibromodifluoromethane and nucleophilic alkenes with 60% aqueous potassium hydroxide and tetrabutylammonium hydrogensulphate (TBAHS) afforded the corresponding difluorocyclopropanes in moderate to good yields (Scheme 4.1.3).



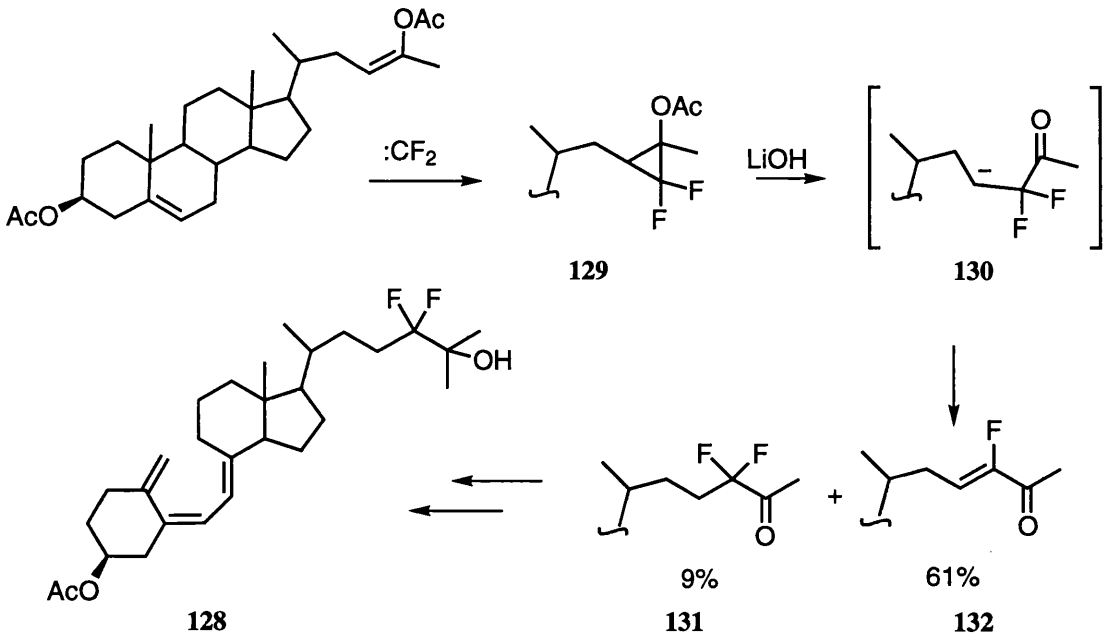
Scheme 4.1.2



Scheme 4.1.3

4.2 Reactions of *gem*-Difluorocyclopropanes.

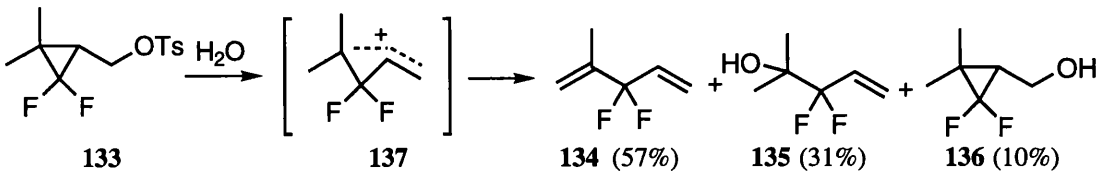
Several ring opening reactions of *gem*-difluorocyclopropanes involving anionic, cationic or radical intermediates are known. A problem generally associated with the anionic ring opening is that the β,β-difluoro anion produced has a tendency to eliminate, leading to monofluoroalkenes.[205] An interesting example of this phenomenon[207] can be found in the synthesis of 24,24-difluoro-25-hydroxy-vitamin-D3 **128** where ring opening of the intermediate **129** *via* the β,β-difluoro anion **130** afforded only 9% of the protonated product **131** and 61% of the elimination product **132** (Scheme 4.2.1).



Scheme 4.2.1

There is one report[208] of a cationic ring opening of a difluorocyclopropane: solvolysis of the tosylate **133** in refluxing aqueous dioxane afforded the homoconjugated diene **134** along with the tertiary alcohol **135** and the primary alcohol

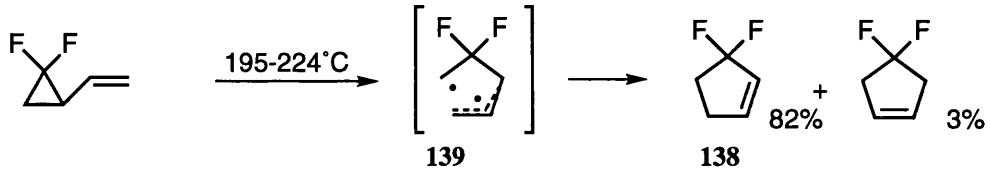
136. A non-classical cation **137** was proposed as a common intermediate for the three products (Scheme 4.2.2).



133 **137** **134** (57%) **135** (31%) **136** (10%)

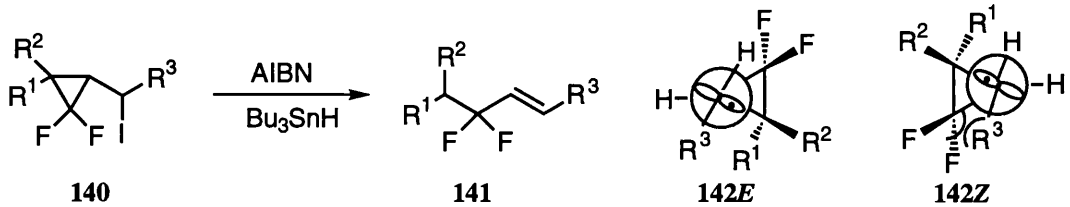
Scheme 4.2.2

In contrast to their non-fluorinated counterparts, homolytic ring opening of monocyclic difluorocyclopropanes are synthetically useful reactions because the bond opposite to the difluoromethylene unit is weaker than the other two, hence good regioselectivity is usually obtained.[209] Thus difluorovinylcyclopropane undergoes a thermally induced ring opening reaction[210] to produce cyclopentene **138** as the major product, presumably *via* a diradical intermediate **139** (Scheme 4.2.3).[211] Radical induced ring opening of difluorocyclopropanes not only occur with good regioselectivity,[212] but also with good stereoselectivity.[213] Reaction of radicals generated from iodides **140** afforded mainly the *E*-alkenes **141** (Scheme 4.2.4). A rationale proposed for this selectivity is that steric repulsion between R^3 and the cyclopropane ring disfavours the transition state **142*Z*** compared to the transition state **142*E***.



139 **138**

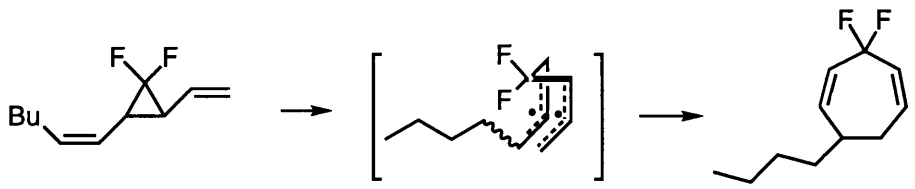
Scheme 4.2.3



140 **141** **142*E*** **142*Z***

Scheme 4.2.4

Sigmatropic rearrangements involving difluorocyclopropanes are also more facile and selective than the ones with non-fluorinated cyclopropanes. A recent example is the preparation of **125**, a fluorinated analogue of marine brown algae pheromone, by a [3,3]-sigmatropic rearrangement of the divinylcyclopropane **143**, which proceeded at room temperature, presumably *via* a diradical intermediate **144** (Scheme 4.2.5).[191]



143 **144** **125**

Scheme 4.2.5

Considering the vast number of methods available to prepare *gem*-difluorocyclopropanes and their facile regio- and stereoselective ring opening under mild conditions, it is very surprising that this approach has not been more frequently employed in the synthesis of difluoromethylene substituted compounds.

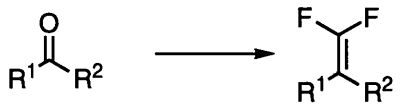
5 Difluoroalkenes.

gem-Difluoroalkenes have become versatile intermediates in the synthesis of fluorinated molecules. Much effort has been put into the search for efficient and general methods for their preparation and a review has been published on the subject.[25] Most of the present work is being carried out towards the development of new reactions to convert *gem*-difluoroalkenes to fluorinated target molecules.

5.1 Preparation of *gem*-Difluoroalkenes.

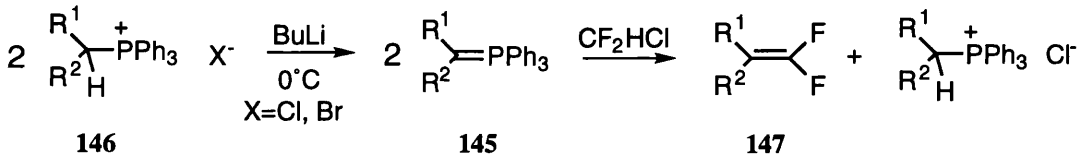
A variety of methods have been reported for the preparation of fluorinated *gem*-difluoroalkenes, based on Wittig, organometallic or elimination approaches. Wittig approaches (Scheme 5.1.1) have been used for the conversion of aldehydes, ketones and even lactones to the corresponding difluoroalkenes. Generation of the ylid is generally made by reaction of a difluorocarbene with a phosphine[214] or reduction of a phosphonium salt by phosphines[215,216] or zinc metal.[217] Triphenylphosphine, dibromodifluoromethane and zinc are the reagents of choice, and *tris*-dimethylaminophosphine has been used for less reactive carbonyl compounds.[217] Replacement of zinc by a second equivalent of phosphine produces an olefinating solution with long lasting reactivity, but in this case the reaction is very sensitive to water.[216-218] Wadsworth-Emmons[219] and Horner[220] approaches, using either commercially available ethyl difluoromethylenephosphonate or diphenyldifluoromethylphosphine oxide, have also been reported. The opposite approach,[221,222] where a non-fluorinated ylid is reacted with a fluorinated synthon has been developed as an economical and easy to scale up process: one equivalent of the ylid **145,** generated from the phosphonium salt **146** at 0°C, deprotonated chlorodifluoromethane to generate a difluorocarbene, which reacted with the second equivalent of the ylid **145** to afford the difluoroalkene **147** in good yield along with one

equivalent of the starting phosphonium salt (scheme 5.1.2). Recent applications of the Wittig methodology include the preparation of carbohydrate exocyclic *gem*-difluoroenolethers **148** from the corresponding lactones (Scheme 5.1.3).[223,224]



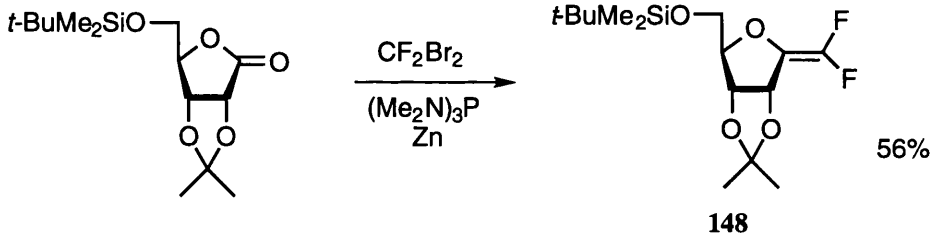
$ClCF_2CO_2Na$/ Ph_3P/ 160°C[214]
CF_2Br_2/ Ph_3P (2eq)[215]
CF_2Br_2/ $(Me_2N)_3P$ (2eq)[216]
CF_2Br_2/ Ph_3P (1eq)/ Zn[217]
CF_2Br_2/ $(Me_2N)_3P$ (1eq)/ Zn[217]
$HCF_2PO(OEt)_2$/ base[219]
HCF_2POPh_2/ base[220]

Scheme 5.1.1



146 **145** **147**

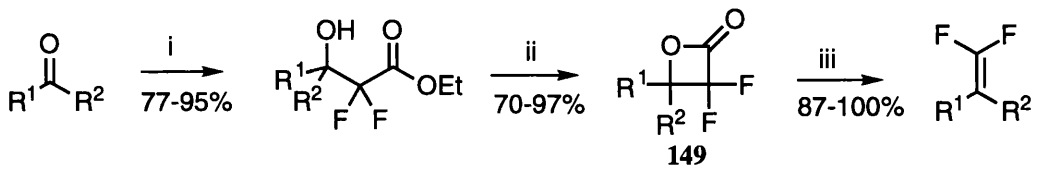
Scheme 5.1.2



148

Scheme 5.1.3

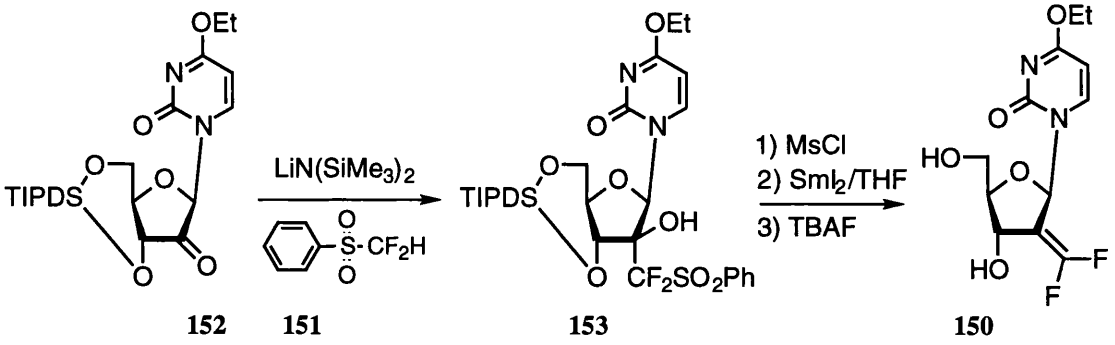
A formal difluoromethylenation of carbonyl substrates *via* α,α-difluoro-β-lactones has been described: the combination of a Reformatsky reaction followed by hydrolysis of the ester and cyclisation afforded β-lactones **149** which underwent thermal decarboxylation to produce the difluoroalkenes in high yields (Scheme 5.1.4).[225]



Conditions: i. BrF_2CCO_2Et, Zn; ii. 1) NaOH; 2) $PhSO_2Cl$, pyridine; iii. 100-150 °C.

Scheme 5.1.4

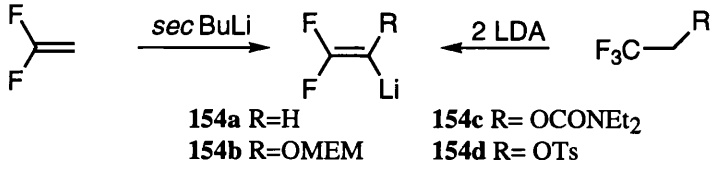
A modified Julia approach to 1,1-difluoroolefins has recently been reported, for the preparation of 2'-deoxy-2'-difluoromethylene cytidine **150**, when reaction with difluoromethyldiphenylphosphine or Wittig olefination with CF_2Br_2/ $(Me_2N)_3P$ had failed (Scheme 5.1.5).[226] Addition of lithium hexamethyldisilazide to a mixture of the sulfone **151** and the ketone **152** afforded the alcohol **153**, which was then converted to the corresponding mesylate. Reductive elimination with samarium diiodide/THF followed by deprotection, produced the citidine analogue **150**, a mechanism based inhibitor of ribonucleoside diphosphate reductase.



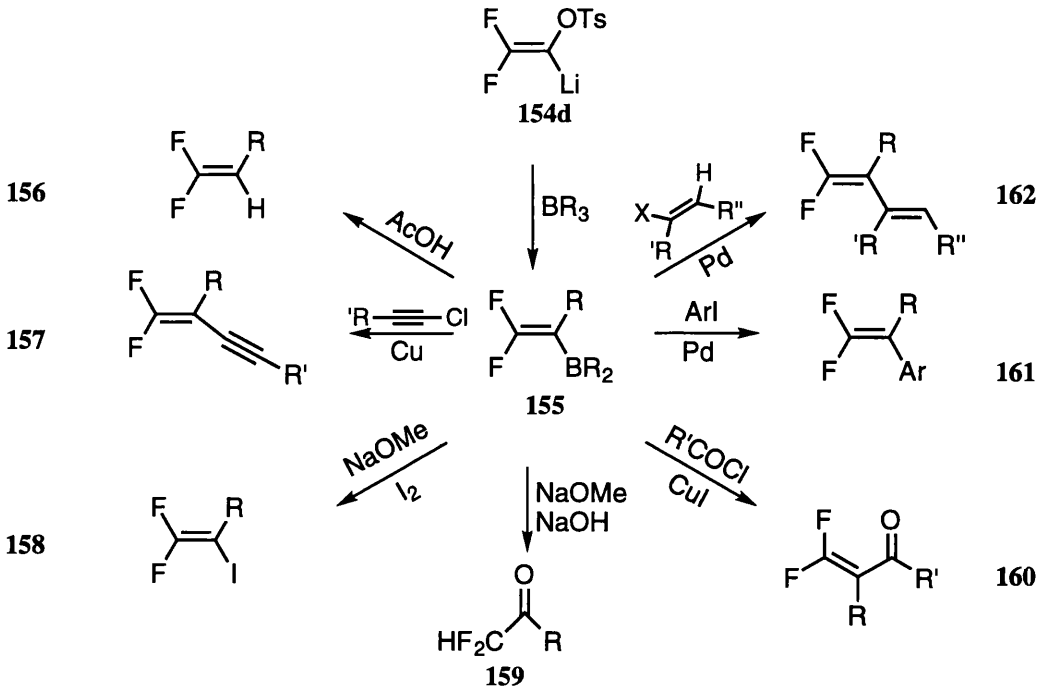
Scheme 5.1.5

Organometallic approaches constitute the second class of reactions used in the preparation of *gem*-difluoroalkenes, and a review has been published on the preparation and reactivity of metal-fluorovinyl reagents.[227] From a synthetic point of view, difluorovinyl lithium reagents have received a lot of attention and have proved to be versatile intermediates (Scheme 5.1.6). Normant[228] reported the first preparation of diflurovinyllithium **154a** (R=H) from difluoroethylene and its reaction with aldehydes and ketones. Percy[229,230] prepared the stabilised difluorovinyl anion **154b**

(R=OMEM) and the acyl anion equivalent **154c** (R= $OCONEt_2$, see section 1.2 for reactions of **154c**) from derivatives of trifluoroethanol, and described their reactions with electrophiles.[70,71] By converting the difluorovinyllithium tosylate **154d** to 2,2-alkenylborane[231] **155**, Ichikawa has developed a synthon for the synthesis of a wide range of difluoroalkenes (Scheme 5.1.7). Thus, protonation with acetic acid afforded monosubstituted difluoroalkenes **156**,[231] copper mediated coupling with acetylenes provided a general route to enynes **157**,[232] reaction with iodine and sodium methoxide furnished the vinyl iodide **158** for coupling reactions,[233] treatment with alkaline base produced difluoromethylketones **159**,[234] coupling with acid chlorides opened a general access to Michael acceptors **160**,[235] and palladium coupling with arenes and alkenes afforded styrenes[236] **161** and dienes[237] **162** (Scheme 5.1.7).

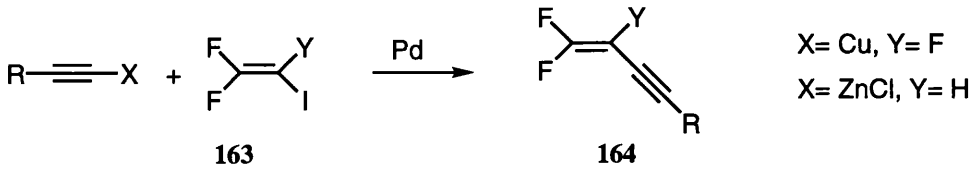


Scheme 5.1.6



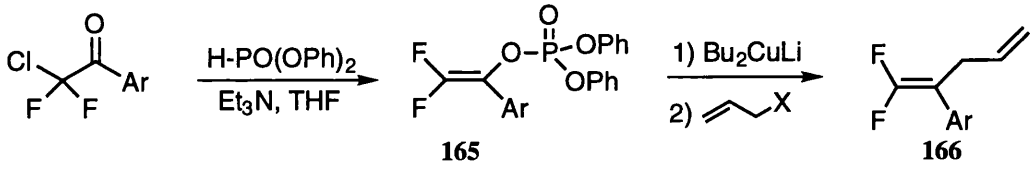
Scheme 5.1.7

Other difluorovinyl organometallic reagents have been reported. Palladium catalysed coupling of difluorovinyliodides **163** with alkenes has been used in the preparation of fluorinated enynes **164** (Scheme 5.1.8).[238,239] Organocuprates, prepared from difluoroenolphosphate **165,** reacted with allylhalides to produce homoconjugated dienes **166** (Scheme 5.1.9).[240] Finally, the reaction of dichlorotrifluoroethane (HCFC-123) with aldehydes and zinc produced allylic alcohol **167**, supposedly *via* the organometallic intermediate **168** (Scheme 5.1.10).[241-243]



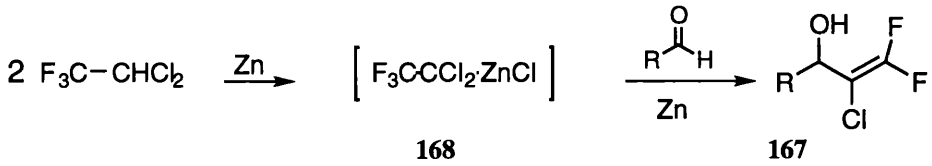
163 **164**

Scheme 5.1.8



165 **166**

Scheme 5.1.9

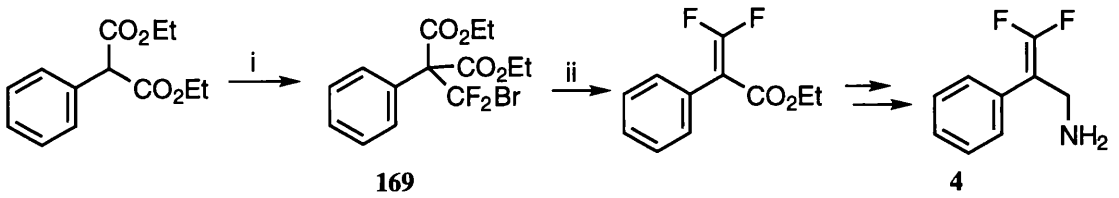


168 **167**

Scheme 5.1.10

A third general approach to the preparation of *gem*-difluoroalkenes is *via* β-elimination or addition-elimination. Reaction of dibromodifluoromethane with enolates (carbene insertion) or alkenes (radical addition), followed by β-elimination or decarboxylative elimination is a convenient access to difluoroalkenes.[138,244] An example is the synthesis of the mononamine oxidase inhibitor **4** by decarboxylative elimination of the bromide **169** (Scheme 5.1.11).[20] Elimination of hydrogen fluoride to form a difluoroalkene from the corresponding trifluoromethyl derivative is another possibility. This is illustrated by the preparation of the substrate **170** by β-elimination

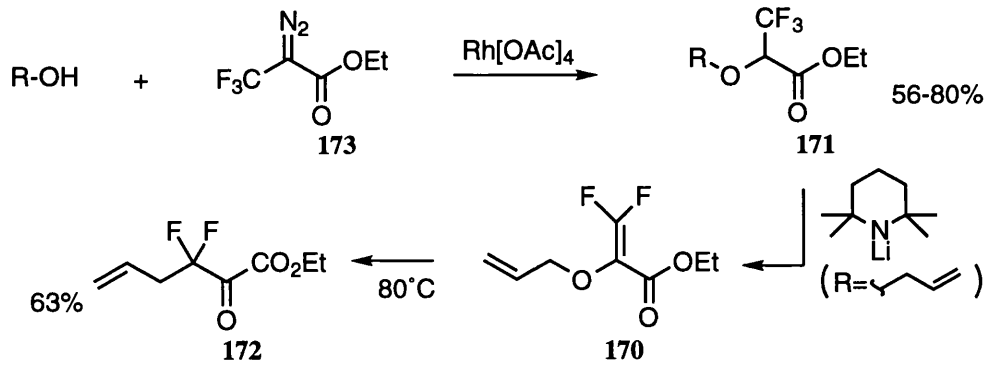
of the trifluoromethyl derivative **171**, which subsequently underwent a Claisen rearrangement (*vide infra*) to produce the β,β-difluoro ketoester **172** (Scheme 5.1.12). It is interesting to note that the trifluoromethyl substituted ether **171** was prepared by a rhodium mediated insertion of the carbene generated from the trifluorodiazo synthon[245] **173** into an allylic alcohol and that the overall sequence constitutes a new entry into difluoromethylene substituted compounds.[246]



169 **4**

Conditions: i. LDA, CF_2Br_2, 83%; ii. CF_3COOH, NaOH, 96%.

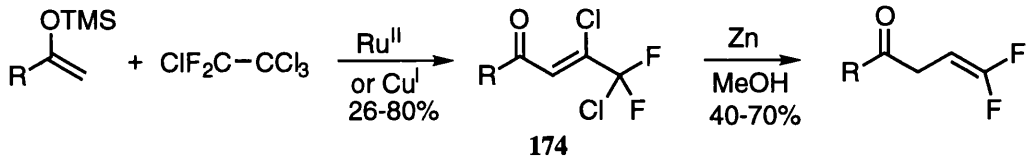
Scheme 5.1.11



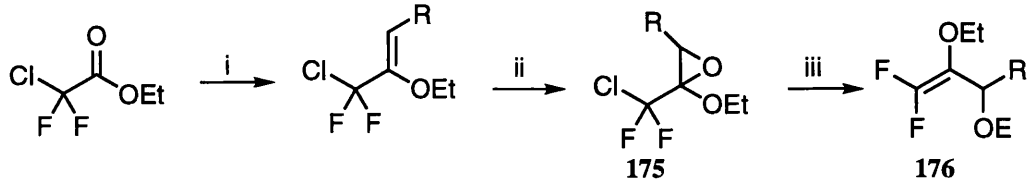
173 **171** **172** **170**

Scheme 5.1.12

Reductive dehalogenations have also been used to prepare *gem*-difluoroalkenes by zinc metal reduction or lithium halogen exchange. A recent example is the reductive hydrodechlorination of the adduct **174,** which was obtained by radical addition of difluorotetrachloroethane to a trimethylsilyl enolether, followed by spontaneous elimination (Scheme 5.1.13).[247] Lithium halogen exchange,[248] followed by ring opening of an epoxide has been reported as part of a general route to *gem*-difluoro-ethoxyallylic alcohols from ethyl chlorodifluoroacetate (Scheme 5.1.14): Wittig olefination of ethyl chlorodifluoroacetate, followed by epoxydation and treatment of the epoxide **175** with *t*-BuLi and an electrophile, produced the *gem*-difluoroenolether **176.**



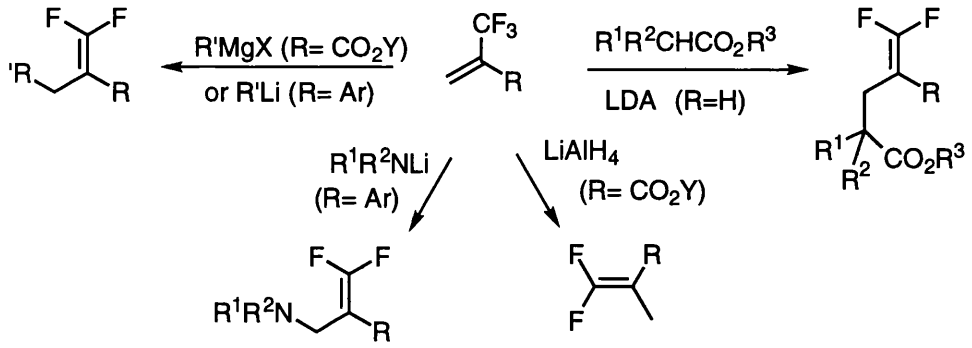
Scheme 5.1.13



Conditions: i. Ph_3P=CHR; ii. *m*-CPBA; iii. *t*-BuLi, E^+ (TMSCl, NH_4Cl).

Scheme 5.1.14.

Finally, nucleophilic addition-elimination with trifluoromethylvinyl compounds has become a general preparation of difluorinated alkenes. Reaction of organolithiums,[249] Grignards,[139,249,250], N-lithiated amines,[251] lithium aluminium hydride[139] or ester enolates[252] with trifluoromethyl substituted olefins afforded the corresponding *gem*-difluoroalkenes (Scheme 5.1.15).



Scheme 5.1.15

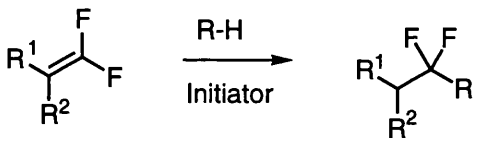
5.2 Reactions of *gem*-Difluoroalkenes.

Several types of reactions involving *gem*-difluoroalkenes have gained synthetic utility and they can be divided in three main categories: radical and nucleophilic

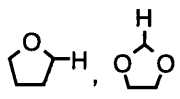
additions, cycloadditions and rearrangements. Nucleophilic additions have already been covered in section 2.2 and 2.3.

The kinetics and orientation of free radical additions onto fluorinated alkenes are governed by a complex combination of steric and polar factors, but in most examples involving substituted 1,1-difluoroalkenes, addition occurred at the CF_2 terminus.[253-257] Computerised coefficients[258] have predicted that *gem*-difluoroalkenes have a slightly lower LUMO and a much lower HOMO than their non-fluorinated counterparts and this dominance of the SOMO-LUMO interaction is consistent with the electrophilic behaviour observed.[254,256]

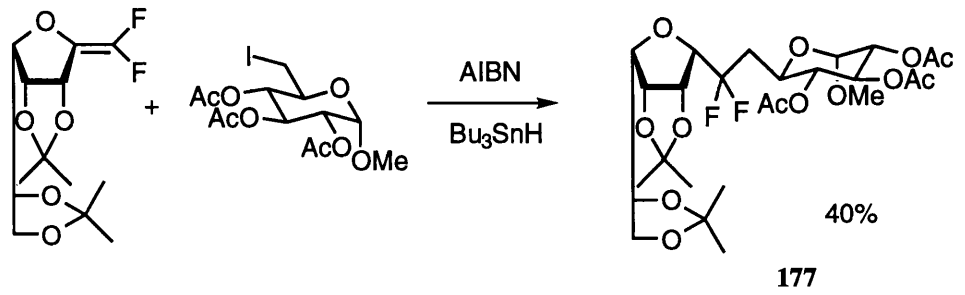
Radical additions onto *gem*-difluoroalkenes have been used for synthetic purposes since 1981, when Suda[259] reported the addition of thiols and aldehydes across CF_2-olefins initiated by dibenzoyl peroxide (Scheme 5.2.1A). Several radical methodologies have since then been reported: addition of tetrahydrofuran, hexanal and benzaldehyde to β,β-difluoroacrylate initiated by benzoyl peroxides or AIBN produced the corresponding β,β-difluoroesters in moderate to good yields (Scheme 5.2.1B).[260] An interesting access to difluoromethylene glycosides, such as CF_2-disaccharide **177,** has been reported *via* radical addition onto carbohydrate exocyclic *gem*-difluoroenolethers under tin-mediated conditions (Scheme 5.2.2).[157,261] A general route to α,α-difluorocarboxylic acids **178** has been described, involving radical addition of Barton esters **179** onto difluorodichloroethylene, followed by hydrolysis with aqueous silver nitrate (Scheme 5.2.3).[262,263]



A: R^1= $C_{10}H_{21}$, Ar
R^2= H
R-H= PhS-H, RS-H, RCOH

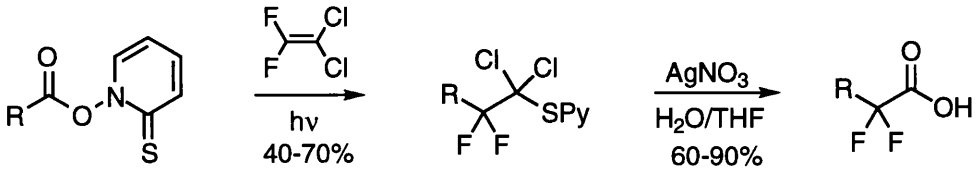
B: R^1= CO_2Et
R^2= Me
R-H= RCOH, 

Scheme 5.2.1



177

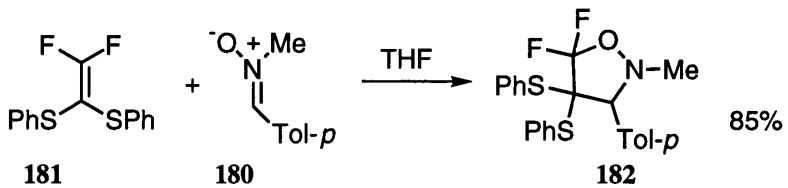
Scheme 5.2.2



179 178

Scheme 5.2.3

Cycloadditions involving difluoroalkenes have been long thought to be limited to [2+2] additions.[186] Fluoroalkenes usually undergo [2+2] reactions much faster than [4+2] reactions[264] and theoretical studies[265] have suggested that this is because fluorine stabilises diradical intermediates. Nevertheless, [3+2] and [4+2] cycloaddition reactions have recently been described using difluorinated alkenes or difluorinated dienes. Purrington[266,267] has reported an example of [3+2] cycloaddition of the nitrone **180** with difluorodiphenylthioethylene **181** as a preparation of the fluorinated isoxazolidine **182** (Scheme 5.2.4).



181 180 182

Scheme 5.2.4

Two examples in which a difluoroalkene underwent a [4+2] cycloaddition with a non-fluorinated diene have been reported. The Michael acceptor **183a** was shown to react with furan to produce the adduct[138] **184a**, and the oxygen substituted

difluoroalkene **183b** with cyclopentadiene to afford **184b**, which was then converted to the functionalised cyclopentane **185** (Scheme 5.2.5).[268]

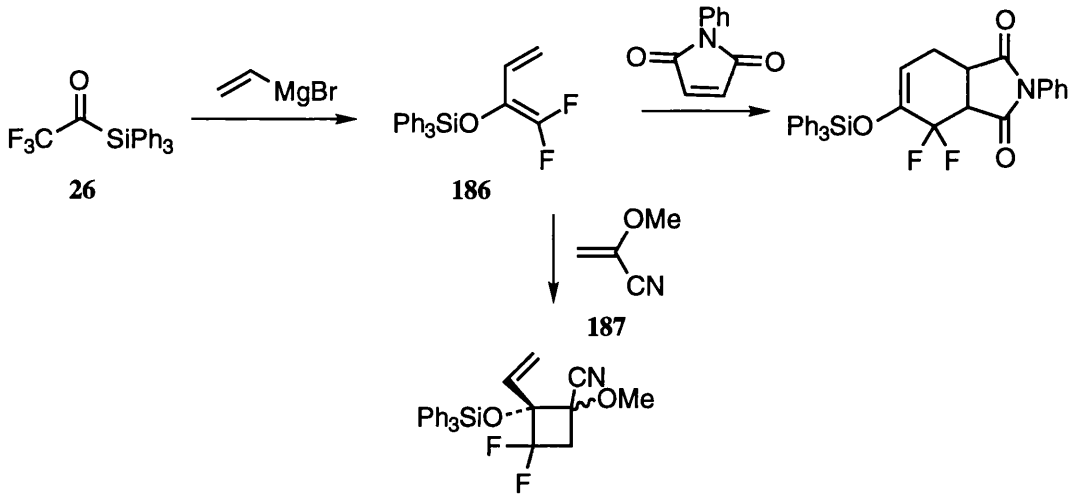
183a R= CO_2Et
183b R= $OCONEt_2$

184a R= CO_2Et, X= O
184b R= $OCONEt_2$, X= CH_2

185

Scheme 5.2.5

Difluorodienes have also been used in Diels-Alder reactions: 1,1-difluoro-2-triphenylsiloxybuta-1,3-diene **186**, prepared by reaction of vinyl magnesium bromide with trifluoroacetyltriphenylsilane **26**, reacted in [4+2] reactions with typical dienophiles such as *N*-phenylmaleimide and in [2+2] reactions with olefins with captodative substitution (e.g. **187**, Scheme 5.2.6).[269] Lewis acid promoted reaction of the similar diene **188** with aldehydes provided an interesting route to difluoropyranosides **189** (Scheme 5.2.7).[270]

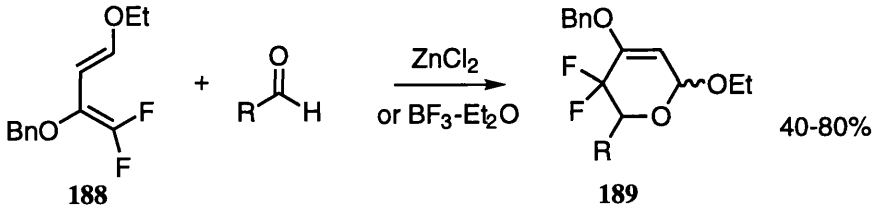


26

186

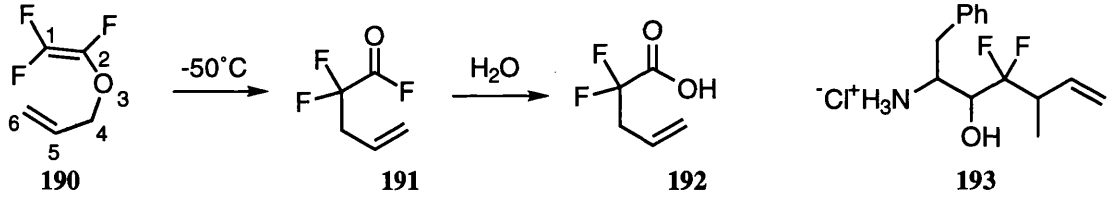
187

Scheme 5.2.6



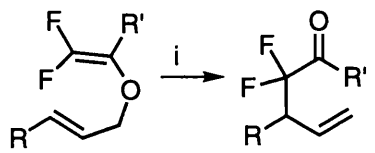
Scheme 5.2.7

[3,3]-Sigmatropic rearrangements have been reviewed recently,[271] and they constitute a third class of reactions of *gem*-difluoroalkenes. The effects of fluorine substitution on the Cope[272] and Claisen rearrangements have been studied. Electron acceptor substituents on the 2,4,5-carbons are known to accelerate the Claisen rearrangement[273,274] and the reaction of the trifluorinated compound **190** proceeded easily at -50°C to produce the acid fluoride **191** which was hydrolysed *in situ* to the acid **192** (Scheme 5.2.8).[275] A preparative flow technique for this reaction has been reported in the large scale preparation[276] of the acid **192** which has been used in the synthesis of the fluorinated intermediate **193** for incorporation into peptides analogues.[277-280] The same reaction has been mentioned in section 2.2 for the preparation of the cobra venom phospholipase inhibitor **82**.



Scheme 5.2.8

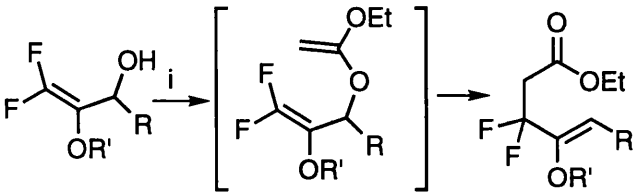
The Claisen rearrangement of functionalised difluoroalkenes as a route to α,α- and β,β-difluoro carbonyl compounds has also been reported. Reaction of dienes **194**, generally prepared by elimination of the corresponding trifluoromethyl substrate (see section 5.1), proceeded smoothly to afford ketones and aldehydes **195** (Scheme 5.2.9).[281] A slightly different approach involved the reaction of difluoroallylic alcohols **196** with triethyl orthoacetate, followed by an orthoacetate Claisen rearrangement to prepare β,β-difluoroesters **197** in good yields (Scheme 5.2.10).[281,282]



194 195

Conditions: i. CCl_4, 80°C.

Scheme 5.2.9

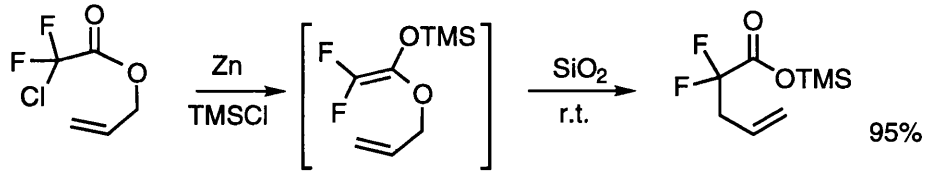


196 197

Conditions: i. $HC(OEt)_3$, $CH_3CH_2CO_2H$, 120°C.

Scheme 5.2.10

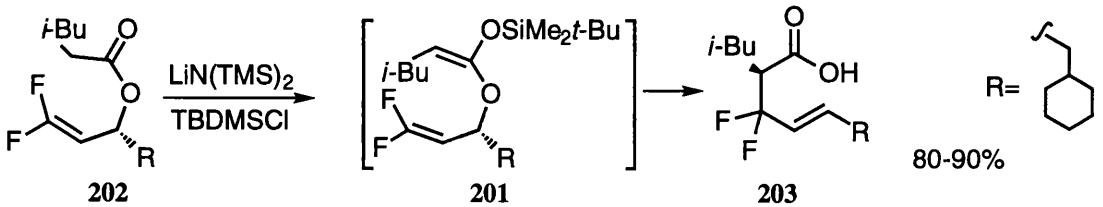
Two approaches utilising the Ireland-Claisen rearrangement with different positions of fluorination have been described: a Reformatsky-Claisen[283] rearrangement of the chlorodifluoroester **198**, through the silylenol ether **199**, has been used to prepare the α,α-difluoroester **200** in high yield (Scheme 5.2.11). The second approach involves the generation of the silylenol ether **201** from the ester **202**, followed by a [3,3]-sigmatropic rearrangement to prepare the β,β-difluoroacid **203** with very good stereoselectivity, and high yield (Scheme 5.2.12). The stereochemical outcome was consistent with formation of the *E*-enolether and cyclisation *via* the expected chair transition state.[284] The β,β-difluoroacid **203** was subsequently converted to the dipeptide analogue **204** .[285]



198 199 200

95%

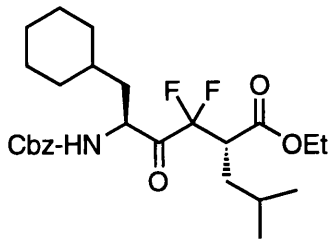
Scheme 5.2.11



202 201 203

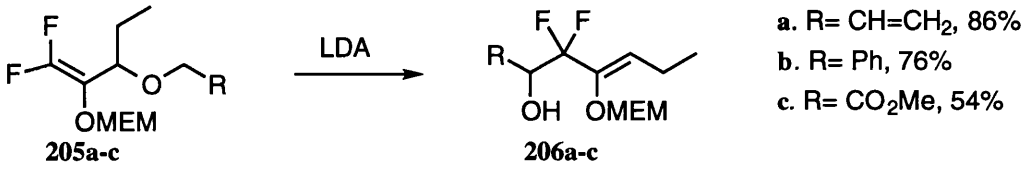
80-90%

Scheme 5.2.12



204

Finally, another type of rearrangement has been recently explored for fluorinated substrates: compounds **205a-c**, upon treatment with LDA, underwent a [2,3]-Wittig rearrangement to afford alcohols **206a-c** in good yields (Scheme 5.2.13).[286]



205a-c **206a-c**

a. R= $CH{=}CH_2$, 86%
b. R= Ph, 76%
c. R= CO_2Me, 54%

Scheme 5.2.13

The wealth of practical methods for their preparation and their versatility for further conversion has made 1,1-difluoroalkenes particularly attractive intermediates in the synthesis of difluoromethylene substituted compounds.

Conclusion

It was more than a hundred years ago that molecular fluorine was isolated by Moissant and since then, a vast amount of work has been done towards the introduction of fluorine into organic molecules. A wide range of sophisticated fluorinating agents have been developed in a constant search for selectivity. In parallel, a new chemistry has emerged for the preparation and manipulation of fluorinated compounds: modification of old methodologies and the invention of new ones are providing an arsenal of reactions for the synthetic organic chemist. All these efforts have been, and no doubt will be, rewarded by the production of increasingly more complex fluorinated molecules with many applications for the chemical and pharmaceutical industries.

gem-Difluoromethylene substituted molecules constitute a particular class of fluorinated compounds and a special chemistry is being been developed for their preparation. While some methodologies have been known for some time, the last fifteen years have witnessed a considerable increase in new approaches for the incorporation of a *gem*-difluoromethylene unit into organic molecules. As the number of methodologies continues to expand and the existing ones are refined by the demands of more complex syntheses, the options are manifold for chemists wishing to incorporate and manipulate the *gem*-difluoromethylene unit.

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Chapter Two:

Results and Discussion

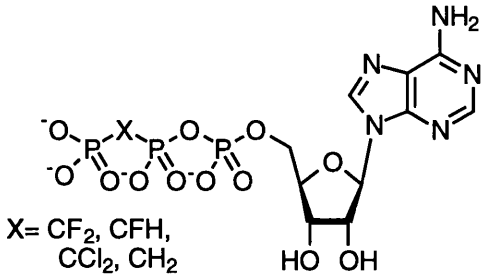
Introduction.

The selective introduction of fluorine into organic molecules has led to compounds with interesting biological properties[1] and many drug candidates have been produced by replacing a hydrogen atom or a hydroxy group by fluorine in natural product analogues.[2,3] Of particular interest is the isoelectronic replacement of an oxygen atom by a *gem*-difluoromethylene unit, because both are tetrahedral and the lone pairs of fluorine may mimic those of the oxygen atom in their ability to form hydrogen bonds (Figure 1.1.1).

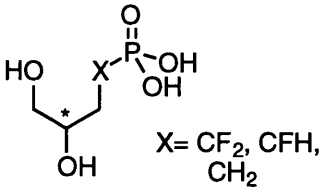
Figure 1.1.1

This analogy has been extensively investigated in the comparison of difluoromethylene phosphonates with their corresponding phosphates. Blackburn showed that, in a series of nucleotide analogues, the difluoromethylene phosphonate **1a** (X= CF_2) had physical properties (Phosphorus NMR, pKa) very close to the parent compound.[4] Subsequently, Chambers described the difluoromethylene analogue of a glycolitic phosphate **2a** (X= CF_2, racemic) as an isoelectronic and isosteric mimic which showed significant activity as an inhibitor of glycerol-3-phosphonate dehydrogenase.[5] A discussion on the relative size and geometry of the CF_2 group and the oxygen atom was provided by a comparison of the crystal structure of 2-amino-1,1-difluoromethylphosphoric acid **3** with one of the parent phosphate.[6] In contrast, an *ab initio* study[7] of fluorinated phosphonates as mimics of phosphate biomolecules has argued that they make poor ground state analogues because the CF_2 unit is larger than the oxygen atom, the P-C bond is longer than the P-O bond and the geometry of the electronic cloud available for hydrogen bonding around the CF_2 group is slightly

different from that encountered around the oxygen atom. An experimental confirmation was provided by a comparative study of CH_2, CHF and CF_2 phosphonate analogues of glycerol-3-phosphate **2** (X= CF_2, CH_2, CFH, single enantiomer (S)) which reported that the CF_2 analogue was the poorest substrate.[8]



1



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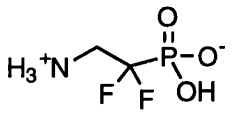
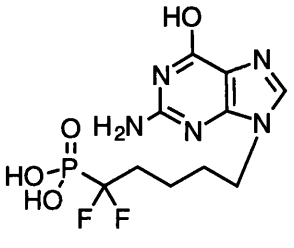


3

Nevertheless, the replacement of a phosphate moiety by a difluoromethylene phosphonate has led to the preparation of several compounds with significant biological activity such as **4**, a potent inhibitor of purine nucleoside phosphorylase,[9] the nucleotide analogue **5** for incorporation into RNA strands[10] or **6**, an analogue of 1,3-bis-phosphoglyceric acid.[11] In practice, the difluoromethylene unit seems to be a good oxygen mimic in terms of physical properties and hydrogen bonding ability. In several instances, it has been shown that the C-H bond in a difluoromethyl group can act as a H-bond donor.[12] On the other hand the CF_2 unit is somewhat larger than the oxygen atom and it is expected that the replacement will prove effective when the steric requirements are not too demanding.



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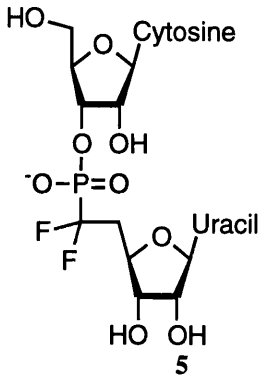

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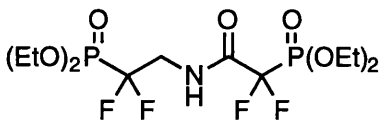
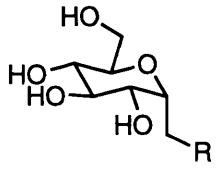
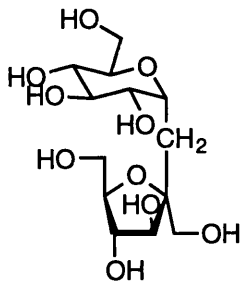


6

To the best of our knowledge, the analogy between the CF_2 unit and the oxygen atom has only been used in phosphate analogues and we decided to investigate this replacement in carbohydrate chemistry. Carbohydrates in which the anomeric oxygen atom has been replaced by a methylene unit (C-glycosides **7**) have become a popular class of compounds. As they are stable to hydrolysis, they act as potent inhibitors of glycosidases,[13] a property which has been associated with antiviral,[14] antitumoural,[15] antihyperglycemic[16] and antiobesity[17] activities, and they are employed for enzymatic and metabolic studies. For example, the sucrose analogue **8** has been used in a study of the relationship between structure and sweetness.[18,19] In addition, C-glycosides serve as a readily accessible source of chiral synthons possessing more carbon functionality than O-glycosides.[20] The methods for their synthesis and their chemistry have been extensively reviewed[21-25] and commonly involve Wittig reactions, nucleophilic displacements, metal couplings and free radical approaches.



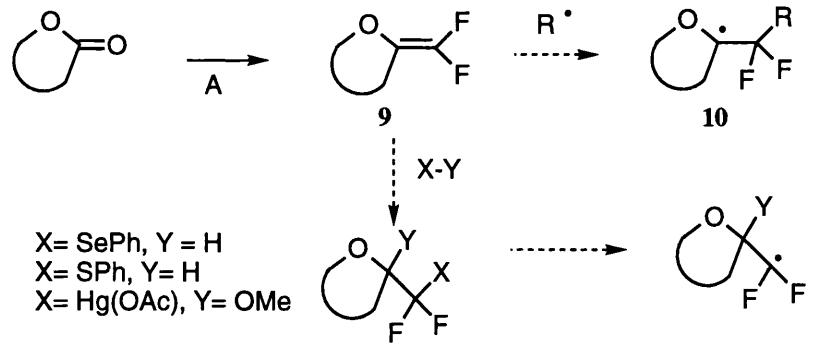
7



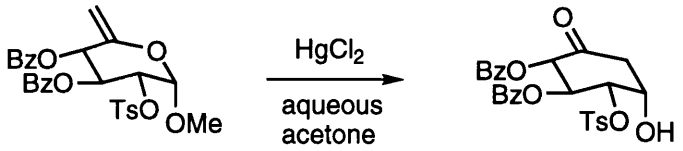
8

The *gem*-difluoromethylene unit being a better mimic for the oxygen atom than the methylene unit, we reasoned that *gem*-difluoromethylene glycosides (CF_2-glycosides) would constitute an interesting new class of bioactive compounds. In addition, we expected such CF_2-glycosides to provide valuable chiral synthons for the synthesis of other fluorinated molecules. We have envisaged a general route for their preparation involving carbohydrate exocyclic *gem*-difluoroenol ethers **9**, whose preparation from the corresponding lactone *via* a Wittig-type reaction has already been studied in our group[26-29] (Scheme 0.1.1, step A). We planned to explore the versatility of these fluorinated synthons in several approaches (Scheme 0.1.1), and radical reactions seemed particularly appropriate as their mild conditions and selectivity are

compatible with a wide range of functionalities. Either addition of a radical to a *gem*-difluoroenol ether, or addition of thiophenol, phenylselenol or mercury acetate across the double bond and reaction of a subsequently generated difluoromethyl radical were envisaged.[30] In addition, a general access to *gem*-difluorinated cyclohexanes and cyclopentanes was considered, employing some rearrangements[31] developed for exomethylene carbohydrates such as the Ferrier[32] rearrangement (Scheme 0.1.2). The work described in this chapter focusses on the addition of radicals to the *gem*-difluoroenol ether unit and an investigation of the Ferrier rearrangement of these substrates is also reported. Different types of radicals were envisaged to access several types of analogues: phosphorus centred radicals for phosphate mimics, and radicals derived from a carbohydrate or an amino acid for disaccharide and glycopeptide analogues.



Scheme 0.1.1



Scheme 0.1.2

Interesting questions arose when we tried to predict the reactivity of the difluoroenol ethers **9** in radical additions. The kinetics and orientation of free radical additions to fluorinated olefins are governed by a combination of polar and steric effects.[33-36] Steric effects have been shown to be the key factors controlling the orientation of the addition, and they are usually quantified[37] by the deformation energy

of the alkene at the atom changing from sp2 to sp3 hybridisation. In practice, intermolecular additions have always been observed at the CF_2 terminus of substituted difluoroolefins. The kinetics of the reaction are mainly influenced by polar effects which are modelled in terms of SOMO-LUMO and SOMO-HOMO interactions in frontier orbital theory.[36,38] Although it is generally accepted that the oxygen substituent will mainly give electrons from its non-bonding pairs to the double bond and will effectively increase the energy of the HOMO and the LUMO,[38] there is an ambiguity about fluorine. Its high electronegativity withdraws electrons in an inductive effect whereas its lone pairs can give electrons by a π-effect. Theoretical calculations[39] have shown that 1,1-difluoroethylene has a HOMO much lower in energy and a LUMO slightly lower in energy than ethylene. This would indicate that the geminal fluorine atoms have mainly an electron withdrawing effect, and is consistent with some AM1 molecular orbital calculations on *gem*-difluoroenol ethers previously performed in our group[26] (Table 0.1). These calculations describe the difluoroenol ethers as having a captodative[40] character, with a HOMO energy comparable to a non-fluorinated nucleophilic enol ether and a LUMO energy in the range of electron deficient alkenes. Thus, a good reactivity both with electrophilic and nucleophilic radicals can be expected from *gem*-difluoroenol ethers in free radical addition reactions.

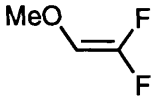
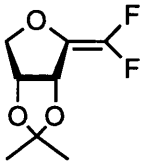
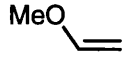
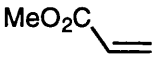
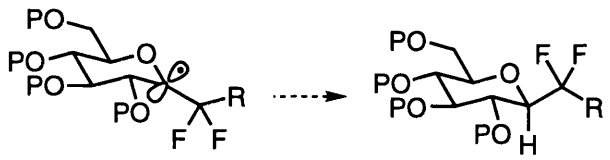
	HOMO Energy (eV)	LUMO Energy (eV)
	-10.8	0.7
	-10.7	0.6
	-10.8	1.9
	-13.0	0.2

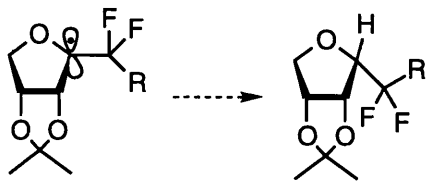
Table 0.1

Most of the reactions which we had planned to use were radical chain reactions where the anomeric radical **10** resulting from the addition would abstract a hydrogen atom, and this second step was expected to have an influence on the overall efficiency of the reaction. The anomeric radical is substituted with an electron donating α-oxygen and three electron withdrawing β-substituents (two fluorine and one oxygen atom): this captodative[40] aspect, coupled with a fairly hindered site should stabilise it and make the hydrogen atom abstraction step relatively slow.

We hoped to benefit from two different effects to direct the hydrogen atom abstraction and hence control the stereochemistry at the anomeric centre. In the pyranoside series, we expected the radical anomeric effect to favour abstraction from the α-face, affording predominantly the β-anomer[41] (Scheme 0.1.3). In the furanoside series we anticipated that the *cis*-fused dioxolane ring, formed by protection of the oxygen atoms at C-2 and C-3 as an isopropylidene acetal, would direct the hydrogen atom abstraction to occur from the least hindered, convex face to produce predominantly the α-anomer[41,42] (Scheme 0.1.4).

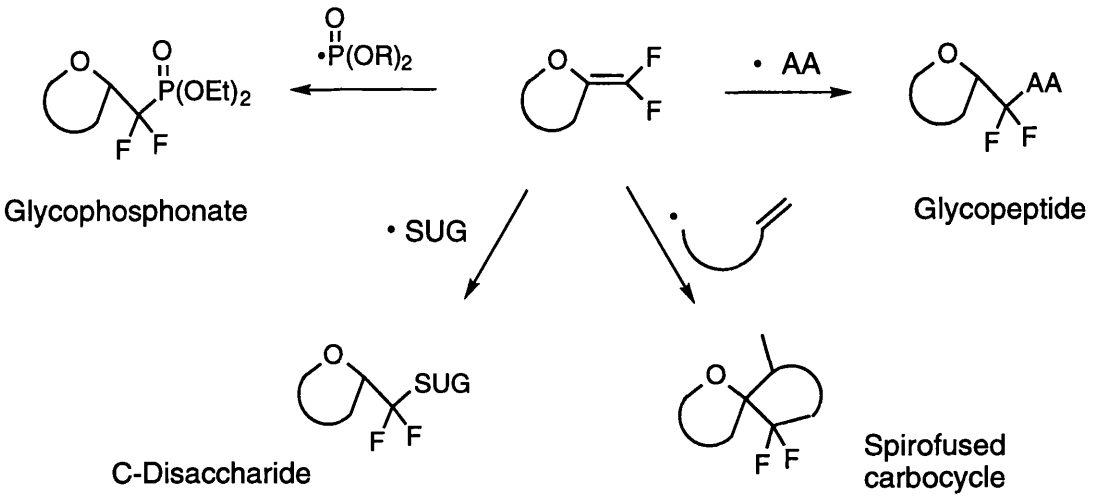


Scheme 0.1.3



Scheme 0.1.4

With these promising considerations in mind, we investigated the addition of phosphorus centred radicals and of radicals generated from sugars or amino acids onto *gem*-difluoroenol ethers as a general route to phosphate, disaccharide and glycopeptide analogues (Scheme 0.1.5). Addition of allylic radicals followed by cyclisation were also studied as a route to spirofused carbocycle analogues.

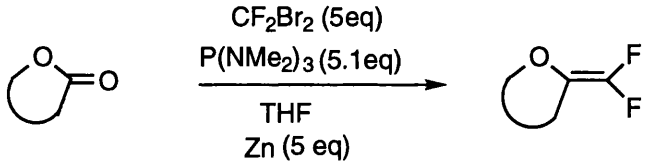

O
P(OEt)2
F F
Glycophosphonate
O
•P(OR)2
O
F
F
• AA
O
AA
F F
Glycopeptide
• SUG
O
SUG
F F
C-Disaccharide
O
F F
Spirofused
carbocycle

Scheme 0.1.5

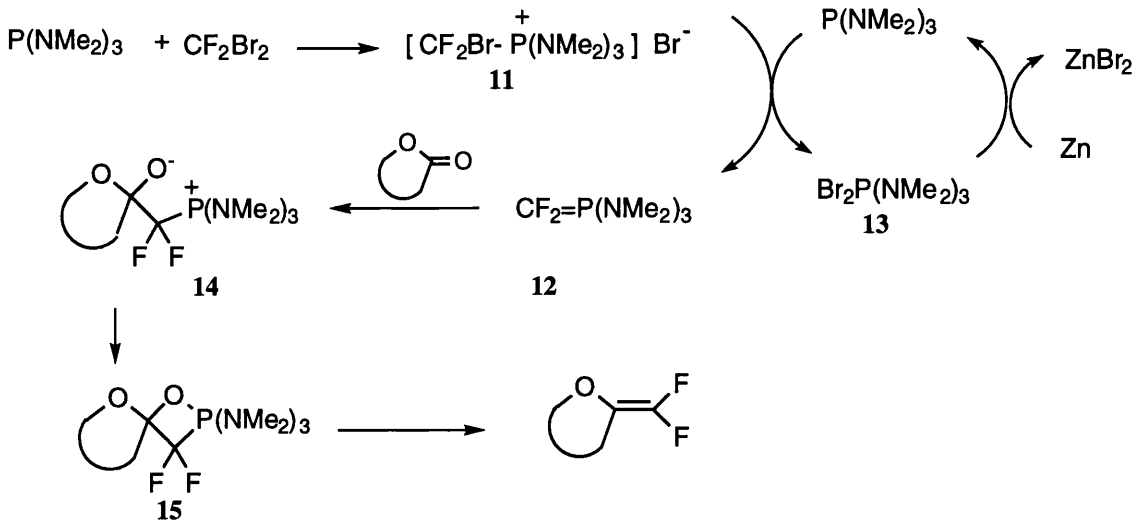
1 Preparation of *gem*-Difluoroenol Ethers.

1.1 The *gem*-Difluoromethylenation of Carbohydrate Lactones.

A general reaction for the preparation of *gem*-difluoroenol ethers from the corresponding lactones has been developed in our group.[26-30] The methodology is based on a Wittig-type reaction initially reported by Burton,[43-45] in which a difluoromethylene ylid[46] is generated from dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc and reacted with a carbonyl compound (Scheme 1.1.1). The proposed mechanism (Scheme 1.1.2) involves the formation of a phosphonium salt **11**, and its reduction by a catalytic amount of *tris*(dimethylamino) phosphine to form the ylid **12** which then reacts with the lactone in a Wittig reaction. The catalytic amount of *tris*(dimethylamino) phosphine is regenerated by reduction of the dibromophosphonium salt **13** by the zinc metal. Evidence for the reduction of the phosphonium salt by the phosphine and not the zinc metal was provided by the observation that addition of a slight excess of phosphine completely suppressed the reproducibility problems that were encountered when a stoichiometric combination of dibromodifluoromethane and *tris*(dimethylamino) phosphine was employed.[28]

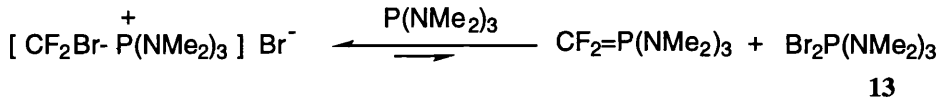


Scheme 1.1.1



Scheme 1.1.2

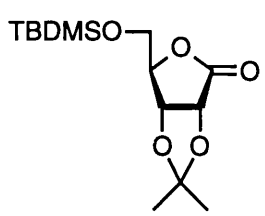
Several variations of the difluoromethylenation reaction have been reported by Burton. Although utilisation of triphenylphosphine instead of *tris*(dimethylamino) phosphine avoids the production of the toxic *tris*(dimethylamino) phosphine oxide,[45] the ylid in this case was not nucleophilic enough to react with lactones.[47] Replacement of zinc by a second equivalent of phosphine produces a long lasting olefinating solution,[44] presumably because the ylid is in equilibrium[48] with the phosphonium salt, with the equilibrium shifted towards the stable phosphonium salt (Scheme 1.1.3). However, it has been observed that in such cases, the reaction is much more sensitive to water.[45] In the reaction with zinc, reduction of the dibromophosphonium salt **13** displaces the equilibrium towards the ylid which then reacts or decomposes.



Scheme 1.1.3

In the present work, several carbohydrate *gem*-difluoroenol ethers have been prepared by this method (Table 1.1.1) some of which (entries **a**,**b**,**e**) have previously been reported in our group,[26,27] and others (entries **c**,**d**,**f**,**g**) which are new compounds. In the furanose series, the starting lactones were protected as isopropylidene acetals

using Kartha's method,[49] and the *t*-butyldimethylsilyl ether and methyl ether derivatives were introduced using standard methods.[50] In the pyranose series, α-D-gluconolactone was conveniently protected as its trimethylsilyl ether or triethylsilyl ether as previously reported,[51] and 2-deoxy-3,4,6-tri-O-benzyl-glucoconolactone **16** was prepared by PCC oxidation of the corresponding glycal **17**.[52] Lactones **18** and **19** were prepared in several steps *via* the ozonolysis of the corresponding exo-methylene derivatives and their synthesis is described in section 4.2.



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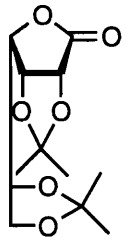

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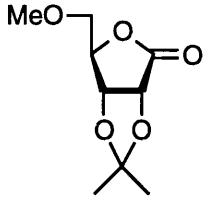

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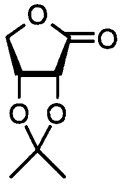

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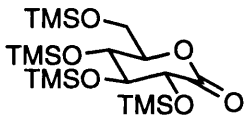

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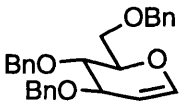

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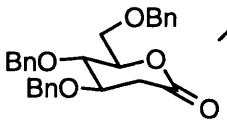

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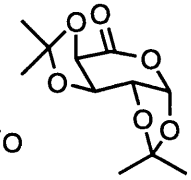

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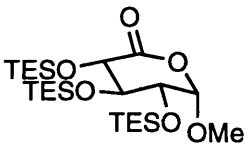
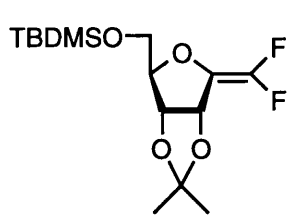


19

Entry	Lactone	Enol Ether	Yield	Method
a	**20**	**25**	45%	A
b	**21**	**26**	64%	A
c	**22**	**27**	31%	A
d	**23**	**28**	51%	A
e	**24**	**29**	30%	B
f	**16**	**30**	12%	A
g	**18**	**31**	22%	B
h	**19**	-	-	A & B
i	**32**	-	-	A

Method A: CF_2Br_2/ $P(NMe_2)_3$/ Zn, THF reflux; Method B: CF_2Br_2/ 2 $(PNMe_2)_3$, THF reflux.

Table 1.1.1



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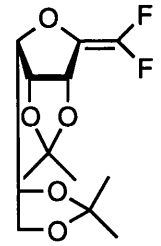

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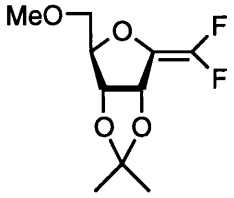

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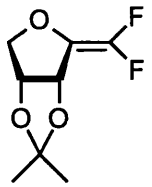

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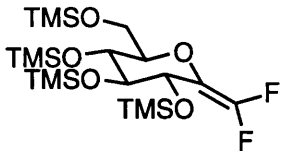

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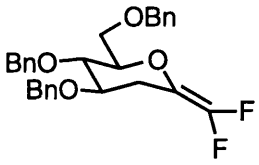

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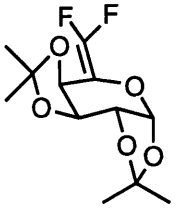

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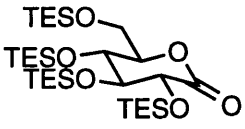


32

These results warrant several remarks. Firstly, in the case of the trimethylsilyl protected gluconolactone **24** (entry **e**), the reaction was found to be very sensitive to the quality of the zinc employed and replacement of the zinc by another equivalent of phosphine provided a more reliable method. The corresponding difluoroenol ether **29** has been shown to adopt preferentially a twisted boat conformation[26] (Figure 1.1.1), presumably because of an A(1,3) allylic strain[53,54] between the fluorine and the substituent at C-2 in the chair conformation. This allylic strain could *a priori* be envisaged in terms of electronic or steric repulsion, but it is interesting to note that increasing the steric bulk of the substituent in the allylic position from a trimethyl silyl ether to a triethylsilyl ether had a dramatic effect on the outcome of the reaction. The TES derivative **32** (entry **i**) proved to be completely unreactive under the dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc conditions and subsequent work in our group[55] has shown that it required several days under the dibromodifluoromethane/ 2 *tris*(dimethylamino) phosphine conditions to obtain a low yield of the difluoroenol ether. Similarly the TES derivative **19** (entry **h**) did not react with dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc and decomposed under prolonged exposure to the dibromodifluoromethane/ 2 *tris*(dimethylamino) phosphine reagent system.

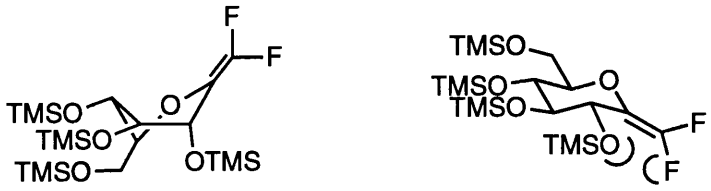
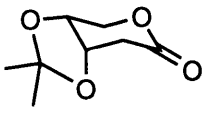


Figure 1.1.1

A second poor substrate which is also worthy of comment is the 2-deoxy-gluconolactone derivative **16** which underwent the difluoromethylenation in poor yields and with little recovery of starting material, irrespective of the conditions which were employed (entry **f**). This was all the more surprising as it was expected that the absence of A(1,3) allylic strain would facilitate the reaction. It is worth noting that another example of an unreactive 2-deoxy pyranose has also been observed in our group.[55] Thus, the lactone **33** did not react under dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc conditions. On the other hand, 2-deoxy five membered ring lactones such as **34** and **35** were converted to the corresponding difluoroenol ethers in yields comparable to their 2-oxosubstituted congeners.[26,55] Two possible reasons for the low reactivity of 2-deoxy pyranoses are that the α-oxygen is increasing the electrophilicity of the carbonyl group or that it is coordinating to the ylid and thereby facilitating and possibly directing the nucleophilic attack on the carbonyl group. α-Oxygen substitution is known to have a dramatic influence on the stereochemical outcome of Wittig reactions,[56] although few examples of improvement in rate or reactivity have been reported.



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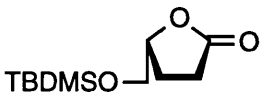

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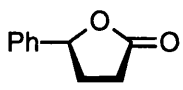
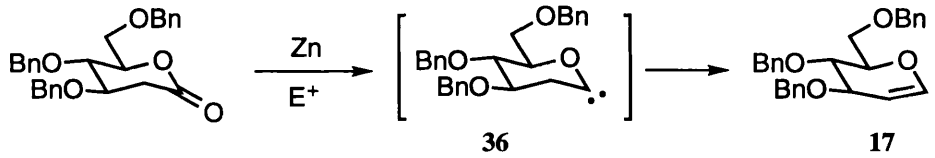


35

Another explanation for the poor result with the 2-deoxy substrate **16** stems from our observation of the formation of the glycal **17** (Scheme 1.1.4) as a by-product from the reaction with dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc in *ca.* the same amount as the difluoroenol ether **30**. A possible mechanism to account for

this involves the intermediacy of a carbene or zinc carbenoid **36**. The generation of zinc carbenoids from carbonyl compounds and bis-silicon electrophiles has been reported through an electron transfer mechanism.[57-61] Therefore it is possible that reaction of the lactone with zinc and an electrophile such as dibromodifluoromethane or a phosphonium salt would generate the carbene (or zinc carbenoid) **36** which could then undergo C-H insertion to form the glycal. Competition between the Wittig reaction and generation of a zinc carbenoid could explain the low yield of difluoroenol ether formed and the poor recovery of starting material in the case where the reagent system dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc was used. However, it cannot be the only explanation as changing the zinc for another equivalent of phosphine (method B) did not improve the yield, although it did suppress the formation of the glycal **17**. The inefficient reactions of the δ-lactones in the 2-deoxy series continues to be a mystery at the present time.



36 **17**

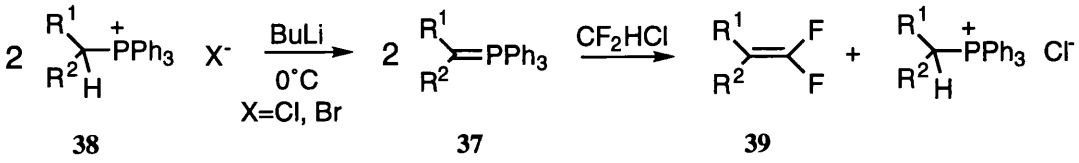
Scheme 1.1.4

1.2 Alternative Approaches.

In light of these limitations and because of the toxicity associated with the production of *tris*(dimethylamino) phosphine oxide, we sought to find alternative methods to prepare carbohydrate *gem*-difluoroenol ethers. Two approaches attracted our attention as convenient, non toxic and practical for large scale synthesis.

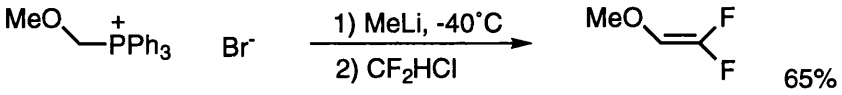
The first method involves the reaction of a difluorocarbene with a non fluorinated ylid, and has been developed by Burton[62,63] for the large scale preparation of difluoroalkenes (Scheme 1.2.1). One equivalent of the ylid **37,** generated from the phosphonium salt **38** at 0°C, deprotonated chlorodifluoromethane to generate a difluorocarbene, which then reacted with the second equivalent of the ylid **37** to afford the difluoroalkene **39** in good yield along with one equivalent of the starting

phosphonium salt. Preparation of difluorinated enolethers such as methyl 1,1-difluorovinyl ether by this method have been described but the unstable ylid had to be generated and reacted at temperatures below -40°C (Scheme 1.2.2).



38 37 39

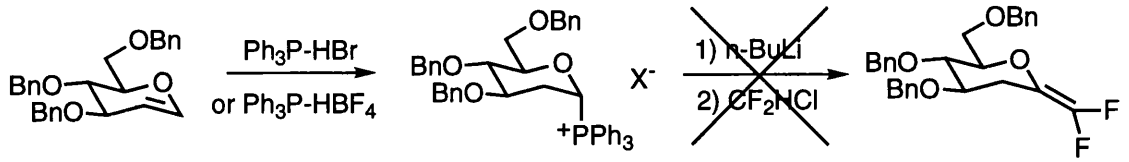
Scheme 1.2.1



Yield based on recovered starting material.

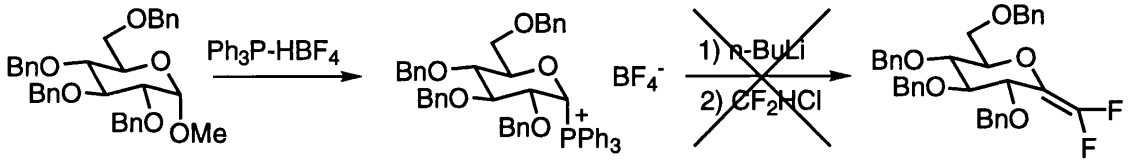
Scheme 1.2.2

The three phosphonium salts **40**, **41** and **42** were chosen as substrates (Scheme 1.2.4 and 1.2.5). The first two were prepared by treating the glycal **17** with triphenylphosphine hydrogen bromide or triphenylphosphine tetrafluoroboric acid complex at room temperature (Scheme 1.2.3),[64] and the third one by reacting the protected methyl glucopyranoside **43** with triphenylphosphine tetrafluoroboric acid complex (Scheme 1.2.4).[65] For the three substrates, the ylid was generated at -78°C with one equivalent of *n*-butyllithium or methyllithium, and after stirring for 30 mn at -78°C, an excess of chlorodifluoromethane was condensed slowly into the reaction mixture which was allowed to warm to room temperature. The characteristic orange colour of the ylid was observed upon addition of *n*-butyllithium, but no fluorinated product was detected on examination of the ^{19}F-NMR spectrum of the crude reaction mixture. Several variants of these conditions were used without success (*e.g.* 2 equivalents of *n*-butyllithium, controlled volume of chlorodifluoromethane condensed), and therefore this approach was abandoned.



17 **40** (X=Br)
41 (X= BF_4)

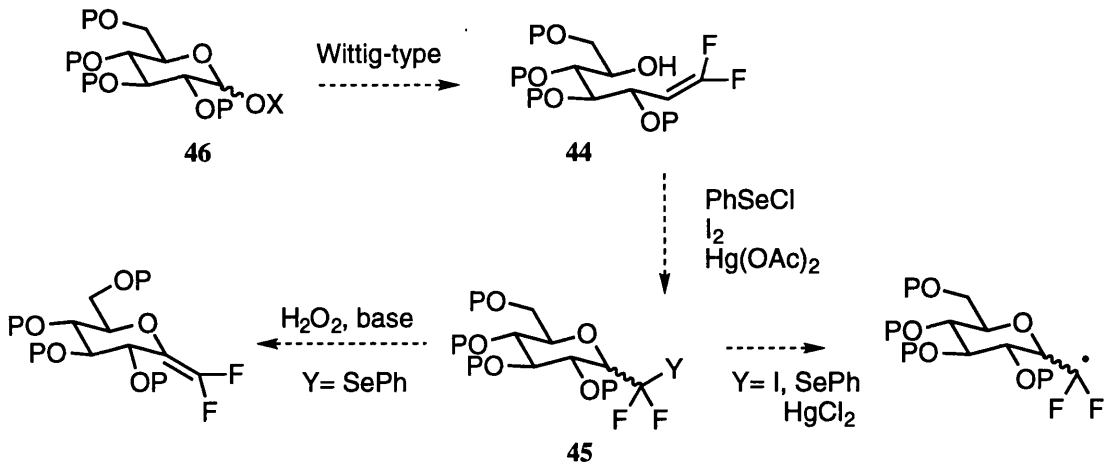
Scheme 1.2.3



43 **42**

Scheme 1.2.4

The second approach which was considered involved a two step preparation of *gem*-difluoromethylene glycosides by a Wittig-type reaction on the lactol followed by a selenium, mercury or iodine promoted cyclisation (Scheme 1.2.5). Lactols, as masked aldehydes, are more reactive than lactones and we planned to use the convenient procedures which have been described for the difluoromethylenation of aldehydes such as the reaction with the ylid generated from dibromodifluoromethane/ triphenyl phosphine/ zinc, or Wadsworth-Emmons or Horner type approaches (See Chapter 1, section 5.1). Several precedents of non fluorinated Wittig and Wittig-Horner[65] reactions on lactols have been reported: when stabilised ylids were used, reaction of lactols (X=H) proceeded in good yields, but with unstabilised ylids, the lactols had to be converted to their lithium salts (X=Li) prior to reaction with the ylid, in order to obtain good results.[66,67] Cyclisation of the intermediates **44** could be effected by several reagents such as phenylselenyl chloride,[68] phenylselenyl phthalimide,[67] iodine[69] or mercury acetate,[66] and the CF_2-glycosides **45** thus produced could subsequently be used as precursors, to generate difluoromethylene radical intermediates for further functionalisation. In the case of the phenylselenyl derivative, a one pot oxidation elimination developed by Barrett[68] would provide a convenient route to *gem*-difluoroenol ethers.



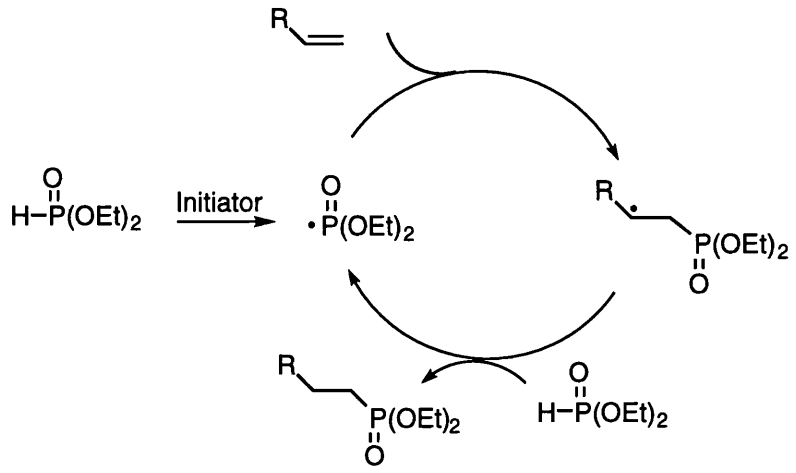
Scheme 1.2.5

Unfortunately, all of our the preliminary attempts to convert the lactol **46** (X=H, Li; P= Bn) to the corresponding difluoroalkene **44** using dibromodifluoromethane/ triphenyl phosphine/ zinc, dibromodifluoromethane/ *tris*(dimethylamino) phosphine/ zinc, conversion to the lithium salt and reaction with dibromodifluoromethane/ 2 *tris*(dimethylamino) phosphine or the lithium salt of diethyl difluoromethylphosphonate were unsuccessful. Nevertheless, different reaction conditions and different substrates would still need to be attempted before ruling this potentially versatile approach as unsuitable for the preparation of CF_2-glycosides.

2 Addition of Phosphorus Centred Radicals.

Difluoromethylene phosphonates constitute a class of compounds which has received a lot of attention as hydrolytically stable isoelectronic mimics of phosphates. Their preparation usually involves the reaction of lithium difluoromethyl phosphonates or similar cadmium or zinc reagents with electrophiles (see Chapter 1, section 1.4). Also two radical approaches involving formation of a carbon-carbon bond *via* difluoromethylenephosphonate radicals have been reported (Chapter 1, section 3.2). We envisaged that a mild and convenient access to carbohydrate anomeric *gem*-difluoromethylene phosphonates could be achieved by formation of the carbon-phosphorus bond *via* the radical addition of a phosphorus centred radical onto a *gem*-difluoroenol ether.

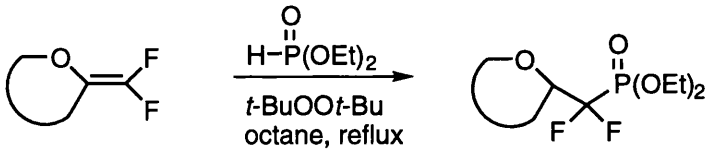
Phosphonyl radicals ($R_2P(O)\cdot$) and their addition to alkenes are well documented.[70,71] They are fairly stable radicals, which undergo facile hydrogen atom abstraction and generally add reversibly to alkenes. From a synthetic point of view, dialkyl phosphites have been reported to add across olefins in moderate yields, in radical chain reactions which usually require high temperature (80°C-170°C) and initiators such as peroxides or AIBN (Scheme 2.0.1). These radical reactions usually require the slow addition of the initiator to ensure the constant generation of a very small concentration of radicals to initiate new chains.



Scheme 2.0.1

2.1 Addition of Diethyl Phosphite.

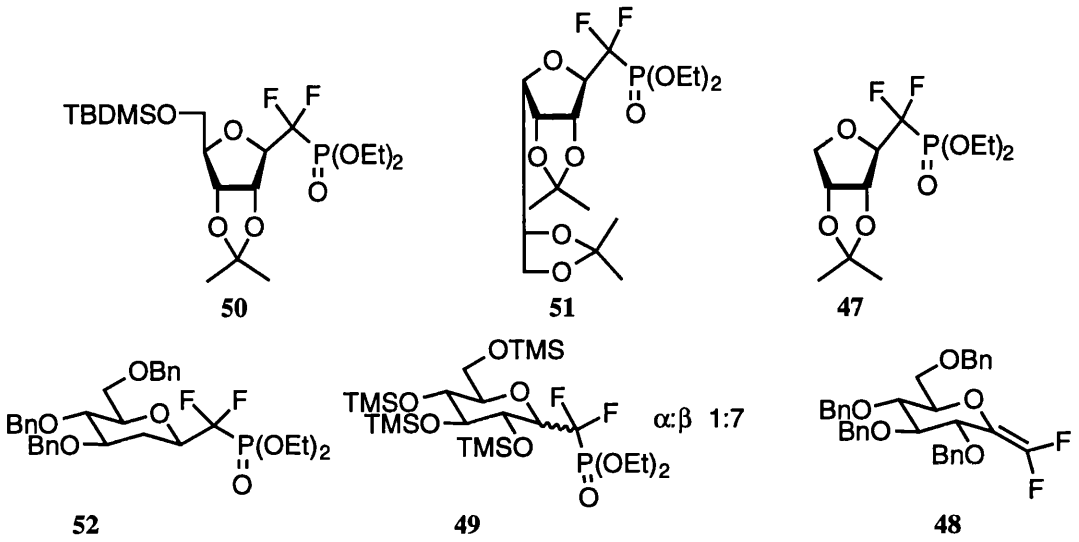
Previous work in our group[28] had examined the addition of diethyl phosphite across carbohydrate *gem*-difluoroenol ethers and found that refluxing octane and slow addition of di-*t*-butyl peroxide as intiator were suitable conditions (Scheme 2.1.1).



Scheme 2.1.1

We have investigated this reaction with various substrates and the results are summarised in table 2.1.1. The low yield observed with the erythrose derivative **47** (entry **c**) is attributed to its volatility: its boiling point of *ca.* 100°C prevented the use of refluxing octane and the reaction was affected both by the use of a lower boiling solvent and the evaporation of the starting material. The reaction conditions seem not to be compatible with benzyl protecting groups, presumably because abstraction of a benzylic hydrogen by the phosphonyl radical competes with its addition. It had been observed[28] that the reaction did not proceed with the benzyl protected glucose derivative **48** and the 2-deoxy glucose derivative **30** (entry **d**) reacted in poor yield. Finally, entry **e** should

be taken with caution as, although the phosphonate **49** has been unambiguously characterised, it was not possible to reproduce its preparation.



Entry	Enol Ether	Phosphonate	Yield	Method
a	**25**	**50**	47%	A
b	**26**	**51**	23%	A
c	**28**	**47**	8%	B
d	**30**	**52**	9%	A
e	**29**	**49**	18%	A

Method A: $HPO(OEt)_2$, refluxing octane, slow addition of *t*-BuOO*t*-Bu (10 hr); Method B: $HPO(OEt)_2$, refluxing dioxane, slow addition of BzOOBz (10 hr).

Table 2.1.1

A surprising feature of this reaction is the stereochemistry observed at the anomeric centre. Whereas in the pyranose series (entries **d** and **e**) the β-anomer was produced predominantly in accord with the radical anomeric effect, the furanose derivatives (entries **a**,**b**,**c**) afforded exclusively the β-anomers, corresponding to the delivery of the hydrogen atom from the most hindered face of the ring. The stereochemistry of the pyranose derivatives was assigned by the coupling constant between the anomeric proton and its vicinal neighbour for **52** ($J_{3ax\text{-}2}$= 12 Hz) and the analogy of chemical shift of the anomeric proton on ^1H NMR with closely related

compounds for **49** (δ= 3.85 for major isomer of **49**, for a comparison of chemical shifts of α- and β- anomers, see compound **53** and **54** in section 3.1). The stereochemistry of the furanose derivatives was determined by the typical coupling constant between the anomeric proton and its vicinal neighbour on the ring for compounds **51** and **47** and by nOe experiments for the ribose derivative **50** (figure 2.1.1). It is interesting to note that while in the ribose derivative **50**, the ring adopts a conformation in which the substituents at C-2 and C-5 are pseudo equatorial to minimise 1,3 diaxial interactions, in the glucose and erythrose derivatives **51** and **47**, the difluoromethylene substituent at C-2 apparently adopts a pseudo axial position.

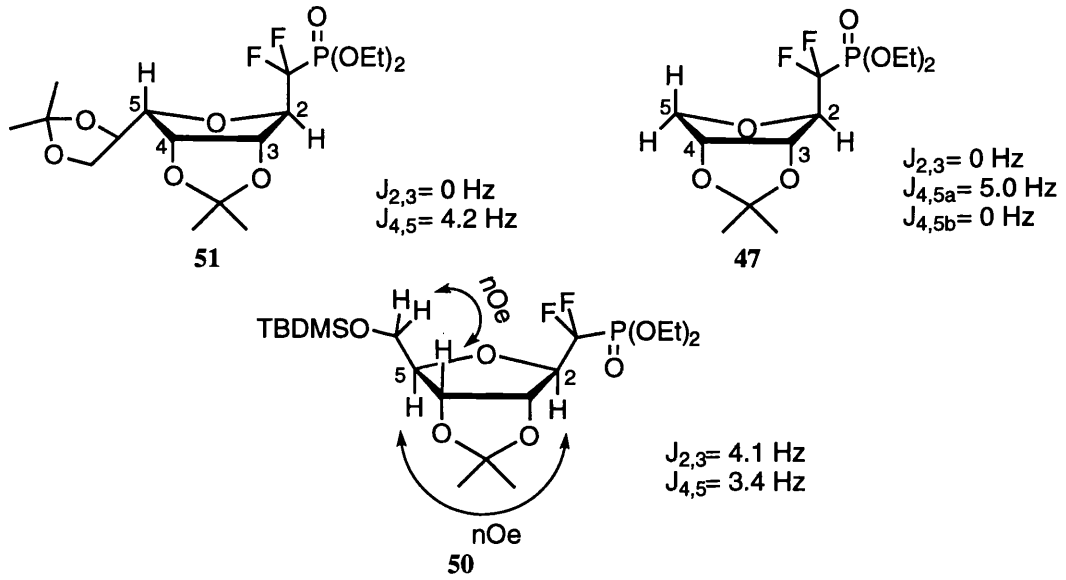
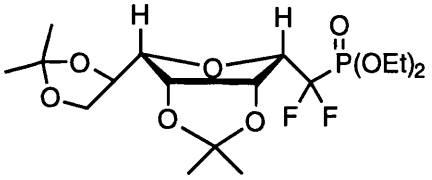


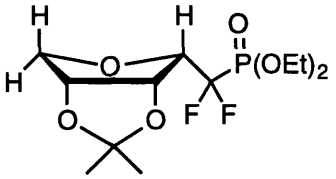
Figure 2.1.1

The stereochemical outcome of these reactions is all the more surprising given that, in the case of compounds **51** and **47**, the product of the reaction is neither the thermodynamic nor the expected kinetic product. Molecular modelling calculations (Alchemy III, Tripos Associates) of the energy of the most stable conformers for both the α– and β– anomers have predicted the α-anomer lower in energy, as would be expected when the substituents at C-2 and C-5 are pseudo equatorial and 1,3 diaxial interactions are minimised[72] (figure 2.1.2). Although these calculations are only to be taken for their qualitative information, they indicate that **55** and **56** are respectively lower in energy than **51** and **47**. Therefore, reversible delivery of the hydrogen atom by

diethyl phosphite leading to a thermodynamic product cannot be given as an explanation for the stereochemical outcome of this reaction. Another surprising point is that this stereoselectivity is characteristic only of the reaction with phosphorus radicals. The addition of carbon centred radicals occurrs with abstraction of the hydrogen atom from the least hindered convex face (*vide infra*).



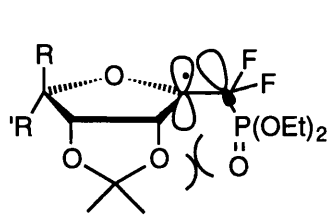
55



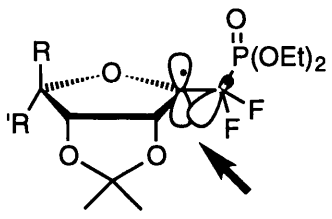
56

Figure 2.1.2

A possible rationale for this selectivity arose from reports that α-phosphorus substituted radicals prefer to adopt a conformation in which the overlap between the radical's π orbital and the $\sigma^*_{C\text{-}P}$ orbital is maximal as observed by ESR spectroscopy.[71] Application of this preference in the furanose series would lead to two possible favoured intermediates **57** and **58**. Steric interaction between the phosphonate moiety and the hindered concave face in **57** would presumably favour the intermediate **58** in which the phosphorus substituent would block the top face and induce hydrogen delivery on the concave bottom face. Although it is difficult to believe that the stabilisation brought by the overlap of the radical's π orbital and the $\sigma^*_{C\text{-}P}$ orbital could stabilise the radical intermediate in one conformation at 130°C, this reversal of kinetic preference due to a favoured conformation in which the phosphorus substituent blocks the less hindered face accounts well for the stereochemistry observed. Additional stabilisation of the radical in the conformation **58** would be required to give more weight to such an explanation.

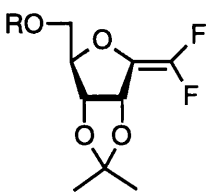


57

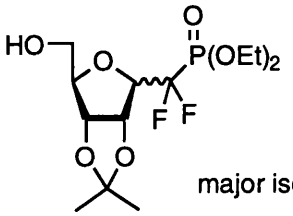


58

From a synthetic point of view, the addition of diethyl phosphite across *gem*-difluoroenol ethers suffered three severe limitations: the high temperature (130°C), the incompatibility with substrates containing benzylic hydrogens and the modest yields. To tackle the difficulty associated with the high temperature, we studied the reaction with various initiators and solvent systems (Table 2.1.2). Benzoyl peroxide/ refluxing dioxane is a frequently employed reagent system with dialkyl phosphites,[70] and triethyl borane/oxygen at room temperature has been employed to initiate reactions mediated by diethyl phosphite.[73] Lowering the reaction temperature to 110°C with dioxane/benzoyl peroxide afforded the addition products in poorer yields (entry **c** and **f**), and at lower temperature no addition occurred. In general these reactions proceeded with a poor mass balance. Surprisingly, the *t*-butyldimethylsilyl protecting group of the ribose derivative **25** was found to be cleaved under mild radical conditions at room temperature or in refluxing dioxane (entries **a**, **c**) and compounds **59** and radical adduct **60** were produced in moderate yields. Blank experiments without initiator (entries **d**,**e**) afforded only the protected starting material, confirming the radical nature of the deprotection. Although several examples of bimolecular homolytic substitution at the silicon atom have been reported, to the best of our knowledge none have involved the cleavage of a silicon-oxygen bond.[74] Further investigation would be required to clarify whether it is the radical generated from the initiator or the phosphorus radical which is involved, and to expand the synthetic scope of this mild deprotection.



59 R= H
25 R= TBDMS



major isomer β

60

Entry	Enol Ether	Conditions	Products (yield)
a	**25**	Et_3B/O_2 (50%), 12h add., hexane, r.t.	**25** (60%) **59** (26%)
b	**25**	Et_3B/O_2 (50%), 5 h add., benzene reflux	**25** only
c	**25**	BzOOBz (50%) 12h add., dioxane reflux	**60** (30%)
d	**25**	No initiator, dioxane reflux , 12h	**25** only
e	**25**	No initiator. Et_3B (50%), hexane, r.t., 12h	**25** only
f	**26**	BzOOBz (50%), 12h add., dioxane, reflux	**51** (16%)
g	**26**	Et_3B/O_2 (50%) 12h add., hexane, r.t.	**26** (11%)

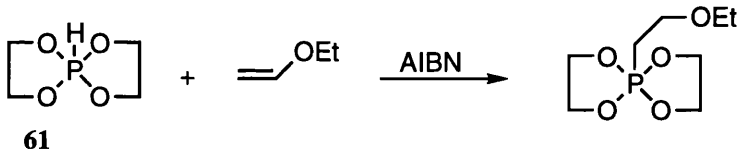
Table 2.1.2

2.2 Spirophosphoranes and Diethyl Phenylselenyl Phosphonate.

In the search for a more efficient reaction to prepare carbohydrate *gem*-difluoromethylene phosphonates, other precursors of phosphorus centred radicals were considered. We reasoned that in the reaction with diethyl phosphite, the slow and inefficient step might be the hydrogen abstraction due to the strength of the phosphorus-hydrogen bond coupled with the captodative stability of the anomeric radical. As a consequence we turned our attention to reagents in which we expected the phosphorus-hydrogen bond to be weaker such as spirophosphoranes, or to systems

which could generate a phosphorus radical without breaking a phosphorus-hydrogen bond.

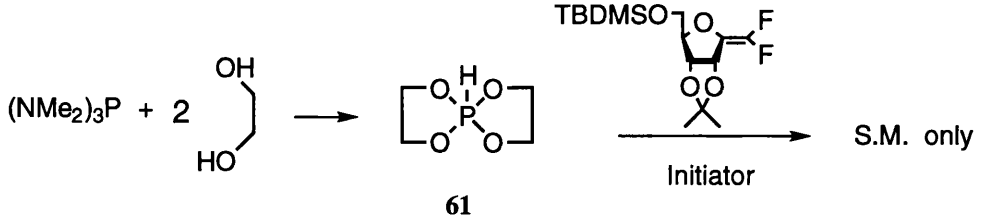
There is a report in the literature[75,76] of the radical addition of the spirophosphorane **61** across an enol ether initiated by AIBN at 85°C which proceeded in 65% yield (Scheme 2.2.1). Although spirophosphoranes have scarcely been used in radical reactions for synthetic purposes, we envisaged that they could provide interesting substrates for the addition of phosphorus radicals on to *gem*-difluoroenol ethers. Phosphoranyl radicals ($R_4P\cdot$) generally show a different reactivity from phosphonyl ($R_2(O)P\cdot$) radicals as they are subject to alpha or beta scission, and are usually unstable.[77] Nevertheless it has been shown that spirophosphoranyl radicals are exceptionally stable towards alpha and beta scission and are hence possible reagents for addition to olefins.[78]



61

Scheme 2.2.1

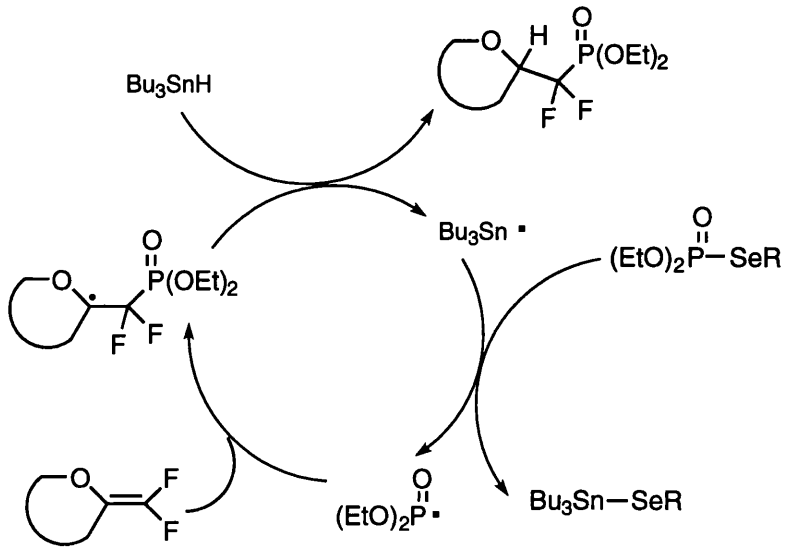
The spirophosphorane **61** was prepared in 80% yield from *tris*-dimethylamino phosphine and ethylene glycol as reported by Burgada,[79] and was reacted with the ribose derivative **25** under a variety of conditions (AIBN/ refluxing benzene, AIBN/refluxing acetonitrile, t-butyl peroxide/refluxing octane). Unfortunately only starting material was recovered in each case, and no addition product was observed (Scheme 2.2.2).



61

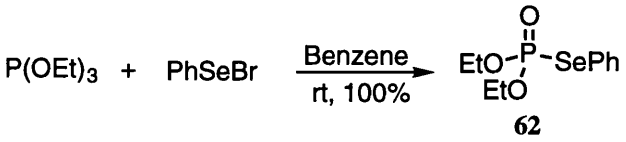
Scheme 2.2.2

An alternative strategy in the search for a more efficient reaction was to replace the phosphorus-hydrogen bond by a phosphorus-selenium bond or a phosphorus-sulphur bond, and to introduce a third component into the reaction such as the good hydrogen atom donor tri-*n*-butyltin hydride (Scheme 2.2.3). Alkyl sulphides undergo bimolecular homolytic substitution reactions (S_H2) with tin radicals, with the formation of a strong tin-sulphur bond as a driving force.[74] We anticipated that a similar substitution reaction could cleave a sulphur-phosphorus bond, or a selenium-phosphorus bond, since the behaviour of selenium and sulphur are similar in S_H2 reactions.[74] We thereby envisaged a three component chain reaction whereby an initiator (AIBN) would generate the tin radical from Bu_3SnH, which could cleave the phosphorus-selenium bond, generating a phosphorus radical that could add to a *gem*-difluoroenol ether. Hydrogen abstraction from tri-*n*-butyltin hydride by the anomeric radical would afford the difluoromethylenephosphonate and generate another tin radical to continue the chain. Such three component reaction are usually subject to a kinetic competition between the addition of the phosphorus radical to the double bond and its ability to abstract a hydrogen atom from Bu_3SnH. Efficiency is usually achieved by a slow addition of the hydrogen atom donor and its concentration in solution is therefore an important parameter.[80]



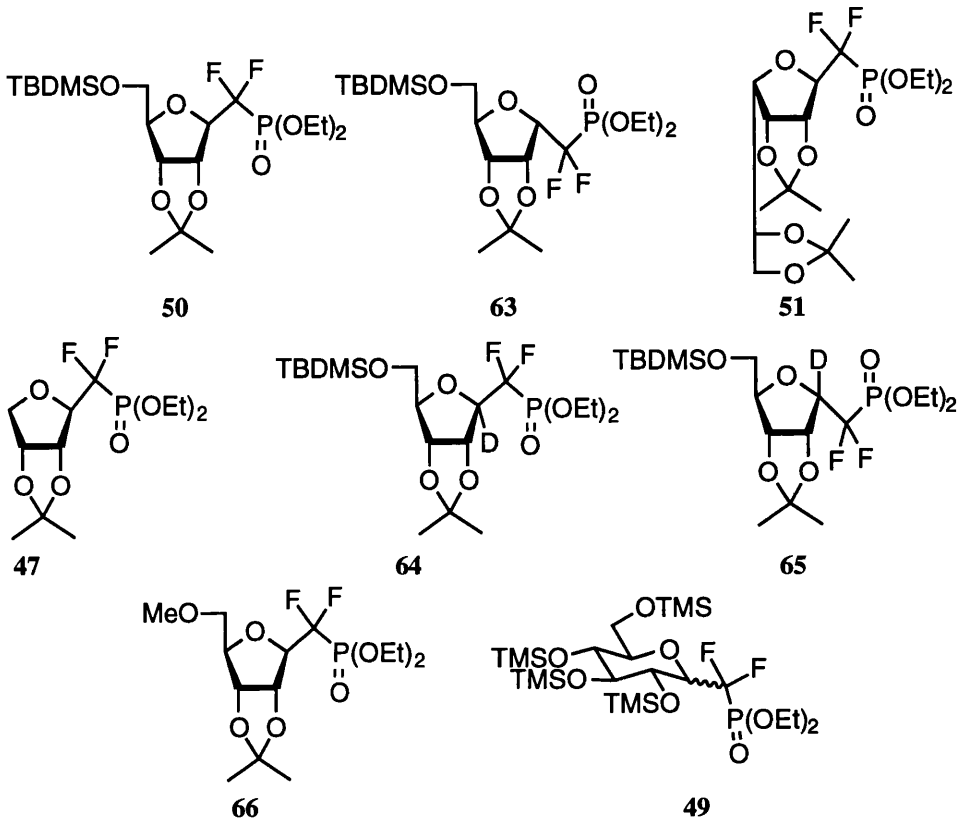
Scheme 2.2.3

The preparation of phenylselenyl phosphonate **62** by an Arbuzov reaction of triethyl phosphite and phenylselenyl bromide has been described[81] (Scheme 2.2.4), but to the best of our knowledge, the reagent has never been used in radical chain reactions. With the reagent in hand, we were pleased to find that it added to difluoroenol ethers under AIBN/ Bu_3SnH mediated conditions in refluxing benzene with higher yields than in the reaction with diethyl phosphite (Scheme 2.2.3, Table 2.2.1). Reaction in refluxing octane with di-*t*-butyl peroxide as initiator afforded improved yields in the case of the ribose derivative **25** (75% *versus* 45% with AIBN/benzene, entry **a**) but did not make any difference for the gulose derivative **26** (entry **b**). The volatile substrate **28** benefited from the milder conditions employed and the yield was considerably improved (entry **c**). The glucose derivative **29** decomposed completely under these conditions, and neither the starting material nor the expected product was found upon chromatographic separation of the crude reaction mixture. Varying the addition time of the solution of AIBN and tri-*n*-butyltin hydride in the case of the gulose derivative **26** showed that the best yields were obtained with addition times between 6 h and 12 h; shorter addition times resulted in the isolation of unreacted starting material whilst longer addition times caused a drop in yield. A blank experiment was conducted by heating the enol ether **26** and the phosphorus reagent **62** in benzene at reflux. The absence of any reaction confirmed that this reagent *per se* does not add across the double bond either in an ionic or non initiated radical chain reaction.



62

Scheme 2.2.4



Entry	Enol Ether	Phosphonate	Yield (ratio)	Previous Yield	Method
a	**25**	**50:63**	75% (6:1)	47% (1:0)	B
b	**26**	**51**	28%	23%	A & B
c	**28**	**47**	35%	8%	A
d	**25**	**64:65**	68% (8:1)	na	C
e	**27**	**66**	24%	na	A
f	**29**	**49**	0%	18%	A

Method A: $PhSePO(OEt)_2$, refluxing benzene, slow addition of AIBN and Bu_3SnH (10 hr); Method B: $PhSePO(OEt)_2$, refluxing octane, slow addition of tBuOOtBu and Bu_3SnH(10 hr); Method C: $PhSePO(OEt)_2$, refluxing octane, slow addition of tBuOOtBu and Bu_3SnD (10 hr).

Table 2.2.1

The stereochemical outcome of the reaction at the anomeric centre was observed to be the same as with diethyl phosphite. Interestingly, a small amount of the α-anomer was observed with the TBDMS protected ribose derivative **25** (entry **a,d**). Although no trace of the α-anomer was observed when the TBDMS group was replaced by a methyl

ether protecting group (entry **e**), the lower yield and small scale of the reaction might have prevented its detection. The surprising aspect of this observation is that, when the top face of the molecule is hindered by a bulky protecting group, some hydrogen delivery occurs from this face, whereas when the compound has a completely unhindered top face (entries **b**, **c**) the only product corresponds to hydrogen atom abstraction from the reagent on the other face (Figure 2.2.1). These observations are consistent with the hypothesis that some interactions are stabilising the anomeric radical in conformations in which there is an optimal overlap of the radical's π orbital and the $\sigma^*_{C\text{-}P}$ orbital (see **57** and **58**, section 2.1). In the case of the TBDMS protected ribose **25**, the bulky protecting group could destabilise intermediate **58** by steric hindrance and therefore allow some of the radicals to exist in the conformation **57**.

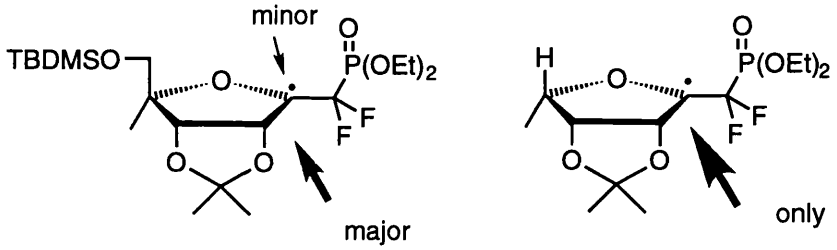


Figure 2.2.1

In order to verify that the hydrogen atom abstracted originated from tributyltin hydride and that the stereochemical outcome of the reaction was not due to a more complex process, tri-*n*-butyltin hydride was replaced by tri-*n*-butyltin deuteride in the reaction with the ribose derivative **25** (entry **d**). The products obtained were deuterated only at the anomeric position and the incorporation of deuterium was respectively 75% and 82% for **64** and **65**, showing that the hydrogen abstraction was occurring mainly from the organostannane.

In summary, a convenient, mild and general route to anomeric *gem*-difluoromethylene phosphonates has been described. Although the reactions involved proceed in modest yields, it should be stressed that they constitute the first route to such compounds. Both methods, the reaction involving diethyl phosphite and the one

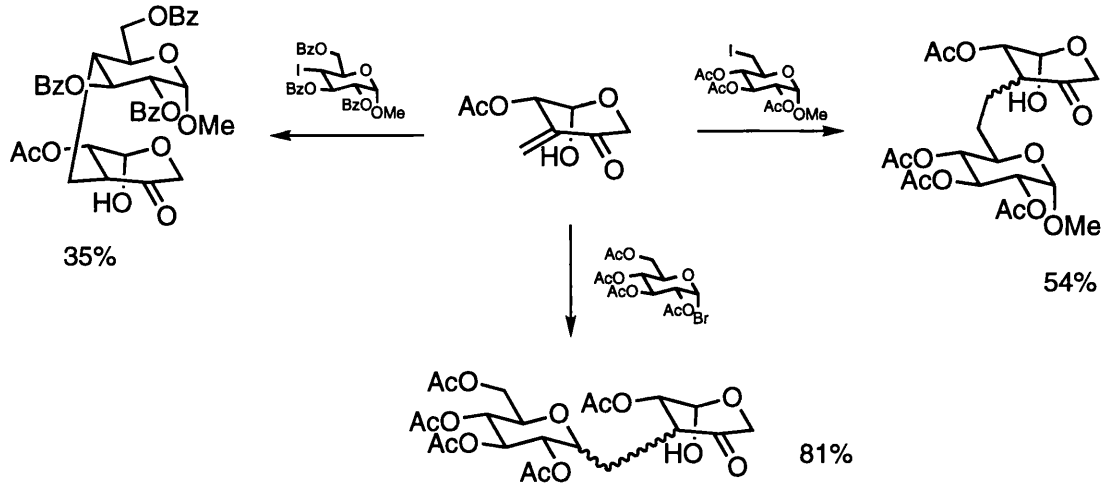
involving the phosphorus reagent **62**, should be useful, the first one being non toxic and convenient for large scale preparation while the second one seems more appropriate for small scale reactions and sensitive substrates. From a theoretical standpoint, the conformational behaviour of carbon centered radicals substituted at the β position by a phosphorus-carbon bond is certainly worthy of further study given the current interest in the development of highly stereoselective radical reactions.

3 Carbon Centred Radicals.

With a view to developing a general methodology for the preparation of CF_2-glycosides from *gem*-difluoroenol ethers, the addition of carbon centred radicals was considered. For intermolecular reactions, the kinetically favoured addition of a nucleophilic radical to an electron deficient alkene is the most common approach, but the addition of such a radical to an electron rich enol ether is seldom attempted. As discussed in the introduction, we anticipated that *gem*-difluoroenol ethers should behave as electron rich alkenes with electrophilic radicals, but we also expected an increased reactivity toward nucleophilic radicals. Therefore, the intermolecular addition of nucleophilic radicals was envisaged as a route to disaccharide and glycopeptide analogues, and the addition of electrophilic radicals was studied as an access to difluorospiroacetal derivatives.

3.1 CF_2-Disaccharides.

Radical reactions have been used as a mild method of providing access to CH_2-glycosides[21] and in particular, workers in this field have devised elegant strategies to prepare methylene linked disaccharides. Giese[82] reported in 1986 the preparation of disaccharide analogues by the addition of radicals generated from carbohydrates onto an exocyclic electron deficient carbohydrate alkene under tin mediated conditions (Scheme 3.1.1). Since then, similar approaches have been described: good stereoselectivity[83] has been observed when the carbohydrate exocyclic alkene **67** was used with pyranosyl radicals and Vogel[84] prepared a variety of methylene bridged disaccharides from the adduct of the "naked sugar" **68** with a glucose derived anomeric radical.

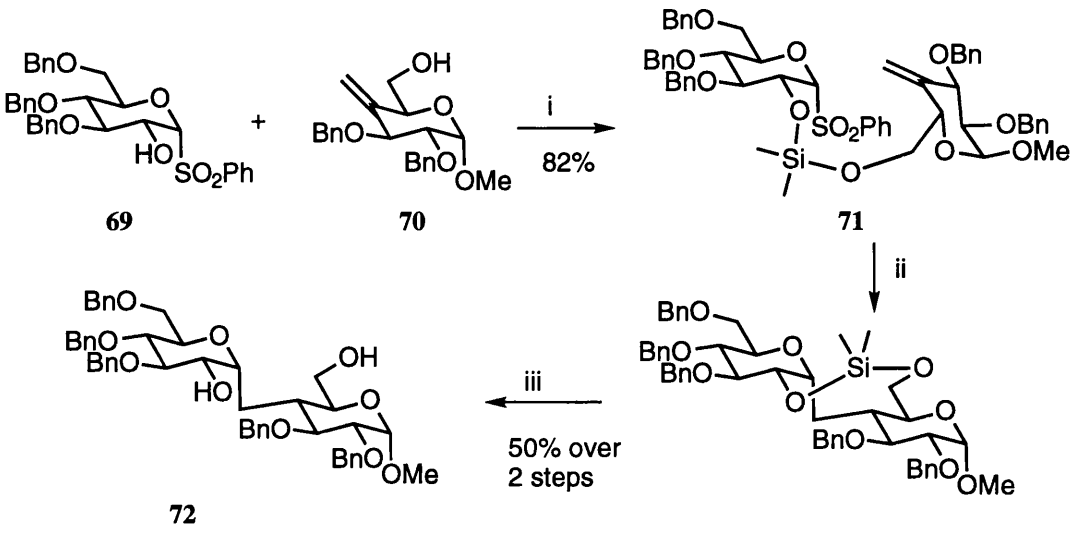


Conditions: AIBN, Bu_3SnH, benzene.

Scheme 3.1.1

67 **68**

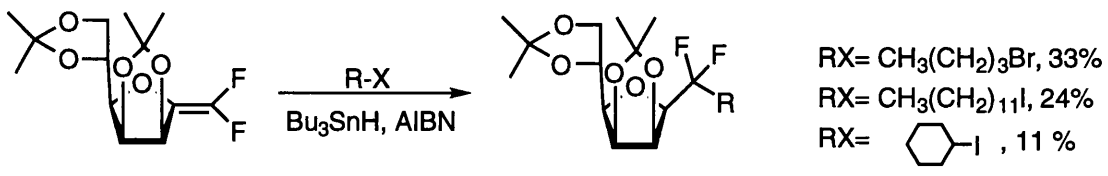
Recently, methods have been developed to couple the two sugars in an intramolecular reaction, usually by using a temporary silaketal tether, and high stereoselectivities have thus been achieved.[85-87] An elegant example from the group of Sinay[88] is the connection of the sulfone **69** to the alkene **70** *via* a silicon tether, followed by a samarium diiodide induced 9-*endo-trig* cyclisation of **71** and removal of the tether to afford the C-disaccharide **72** (Scheme 3.1.2).



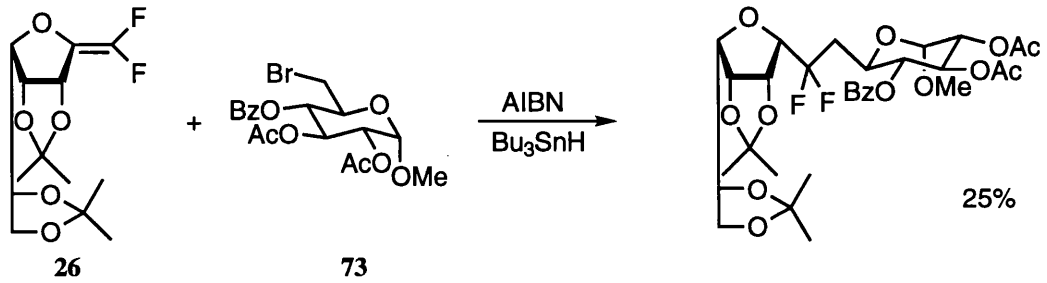
Conditions: i. *n*-BuLi, Me_2SiCl_2, imidazole, THF; ii. SmI_2, HMPA, benzene; iii. HF_{aq}, rt.

Scheme 3.1.2

Precedents have been reported in our group for additions of nucleophilic radicals derived from simple alkyl halides onto carbohydrate *gem*-difluoroenol ethers under tin mediated conditions (Scheme 3.1.3). These three components chain reactions typically required pseudo high dilution conditions with the addition over several hours of tin hydride and AIBN.[80] The preparation of a disaccharide analogue had been described by coupling the carbohydrate *gem*-difluoroenol ether **26** with the 6-bromo-glucose derivative **73** in 25% yield (Scheme 3.1.4). We have investigated the similar formation of CF_2-disaccharides with various substrates and the results are summarised in table 3.1.1. The preparation of the iodides **74** and **75** is outlined in section 4.



Scheme 3.1.3



26 73

Scheme 3.1.4

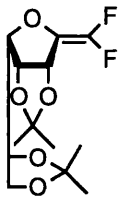
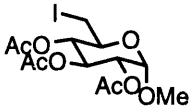
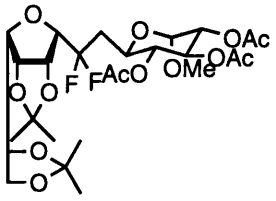
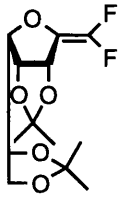
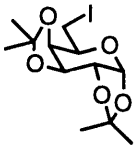
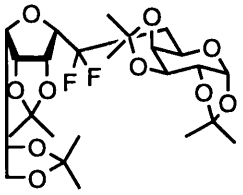
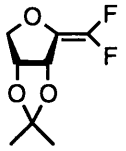
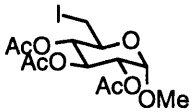
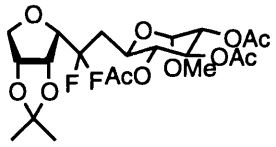
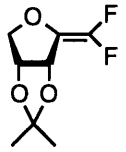
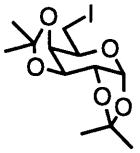
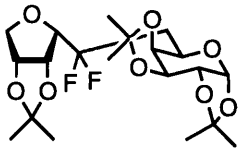
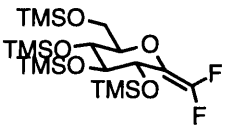
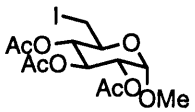
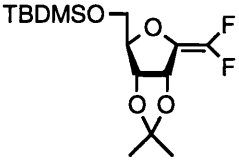
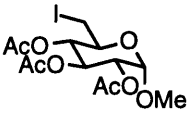
Entry	Difluoroenol ether	Halide	Disaccharide (yield)
a	 **26**	 **75**	 **76** (40%)
b	 **26**	 **74**	 **77** (20%)
c	 **28**	 **75**	 **78** (23%)
d	 **28**	 **74**	 **79** (14%)
e	 **29**	 **75**	-
f	 **25**	 **75**	-

Table 3.1.1

In all of these reactions, the mass balance in fluorinated product was mysteriously low, but usually a large amount of the reduced halide was isolated from the reaction mixture. The coupling of the iodide **75** with **26** (entry **a**) occurred in a much higher yield than in the case the bromide **73** (Scheme 3.1.4), and this is attributed to the smaller steric bulk around the radical when the benzyl protecting group at C-4 is replaced by an acetyl. In the case of **79** (entry **d**), isolation required repeated chromatography and the volatility of the starting enol ether **28** may contribute to the generally reduced efficiency of this and other reactions (entry **c**) in which it had been used. No coupling was observed between **75** and both the ribose and glucose derivatives **25** and **29** (entries **e** and **f**), presumably because the double bond of these substrates was less accessible.

Only one anomer was observed in these couplings, and the α-stereochemistry at the anomeric centre corresponds to the delivery of the hydrogen atom from the least hindered convex face of the molecules. This stereochemistry was assigned by the typical coupling constant between the anomeric proton and its vicinal neighbour on the ring (J= 3.7 Hz for **76** and **77**, J= 3.6 Hz for **78** and J= 4 Hz for **79**).

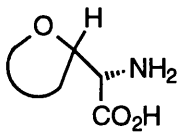
These examples attest for the unusual reactivity of the difluoroenol ether system towards nucleophilic radicals, and in addition provide a route to a wide range of CF_2-disaccharides. The intramolecular coupling of a *gem*-difluoroenol ether with another sugar *via* a temporary tether would be an interesting extension of this work to investigate.

3.2 CF_2-Glycopeptides.

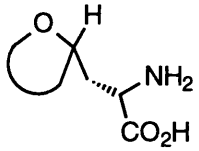
Encouraged by these promising results in the preparation of CF_2-bridged disaccharides we have investigated a similar approach to glycopeptide analogues by addition of a nucleophilic radical to a *gem*-difluoroenol ether. The potential of glycopeptides in medicinal chemistry has attracted much interest recently due to the change in activity, stability and metabolism observed for glycosylated peptide drugs.[89] In addition, glycoproteins constitute an important class of protein present in living

organisms and their carbohydrate moiety is involved in many processes of molecular recognition.[90,91] The amino acid component is usually bound to the sugar portion via an O- or N-glycosidic bond. Different and more stable linkages are of interest for the study of the structure-activity relationship in glycoproteins and for the development of analogues with modified biological activity. Resistance towards enzymatic deglycosylation is particularly attractive in the search for orally available drugs.

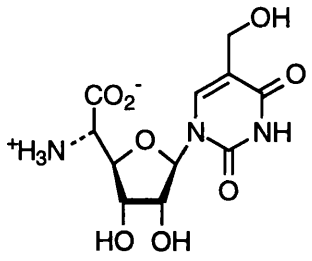
Several methods have been reported for the synthesis of C-glycosyl amino acids of the type **80**, in which the anomeric carbon is directly bound to the α-carbon of the amino acid.[92-99] This structure is found is several natural products such as polyoxins (polyoxin C, **81**). In contrast, only a few methods have been described for the preparation of methylene bridged glycopeptides (CH_2-glycopeptides **82**) which incorporate a further methylene group to mimic the anomeric oxygen atom. They usually involved the functionalisation of a pre-formed C-glycoside,[100,101] and to date only two approaches have envisaged the formation of the "C-anomeric linkage", both in a radical addition. Kessler[102] described the addition of an anomeric radical onto dehydroalanine derivatives in good yields but with poor diastereoselectivity at the α-carbon (Scheme 3.2.1). Beckwith[103] reacted the anomeric radical generated from **83** with the *t*-butyl methyleneoxazolidinone derivative **84** to afford the methylene bridged glycopeptide **85** in high yield with the *t*-butyl group and the radical anomeric effect cooperating to induce a high stereoselectivity both at the α-carbon of the amino acid and the anomeric centre (Scheme 3.2.2). Hydrogenolysis of **85** furnished the amino acid **86**.



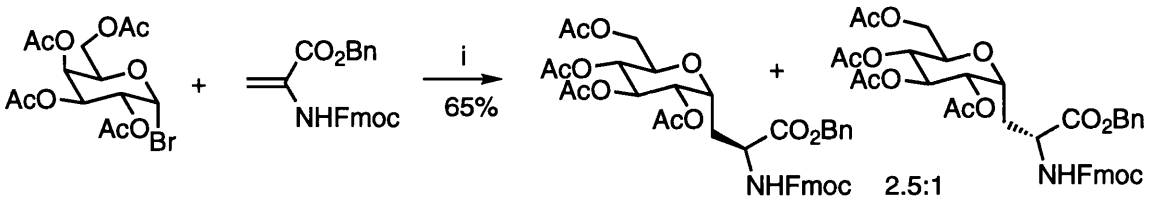
80



82

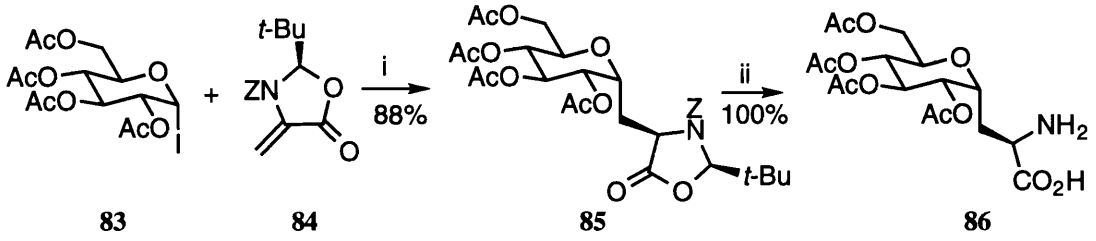


81



Conditions: i. AIBN, Bu_3SnH, benzene.

Scheme 3.2.1

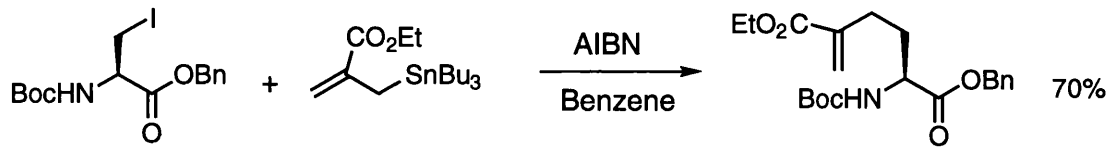


83 **84** **85** **86**

Conditions: i. $NaBH_3CN$, Bu_3SnCl; ii. H_2, Pd/C.

Scheme 3.2.2

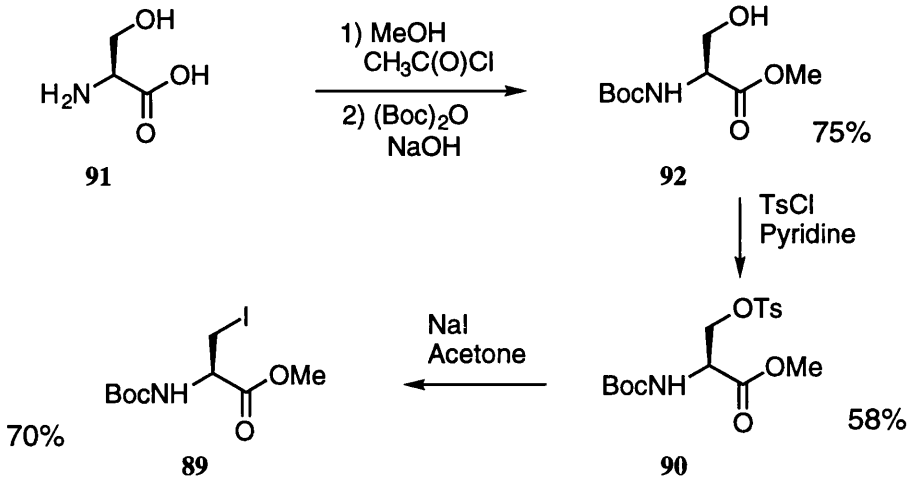
We were interested in the opposite approach, in which a radical is generated from the amino acid and reacted with a *gem*-difluoroenol ether. Reactions involving amino acid derived radicals have been reported in the past. Baldwin[104,105] described the addition of the primary radical from a protected β-iodo alanine derivative **87** to the electron deficient allylstannane **88** in good yield (Scheme 3.2.3). The main advantage of such a strategy was to benefit from the radical anomeric effect and its counterpart in the furanose series to control the sterochemistry at the anomeric centre and from the mild neutral conditions to preserve the stereochemistry at the α-carbon of the amino acid.



87 **88**

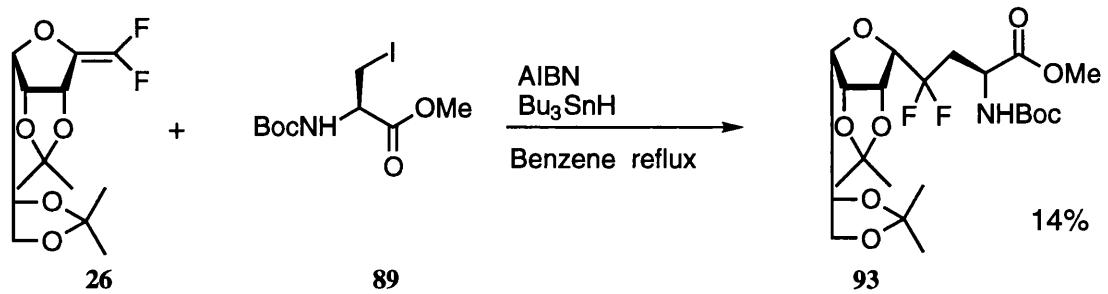
Scheme 3.2.3

We initially planned to use a similar β-iodo alanine derivative, and **89** was therefore prepared in four steps from L-Serine (Scheme 3.2.4). The acid was protected as a methyl ester and the amine as its *t*-butoxycarbonyl derivative, and subsequently the alcohol was converted to a primary iodide *via* the tosyl derivative **90**.[106,107]



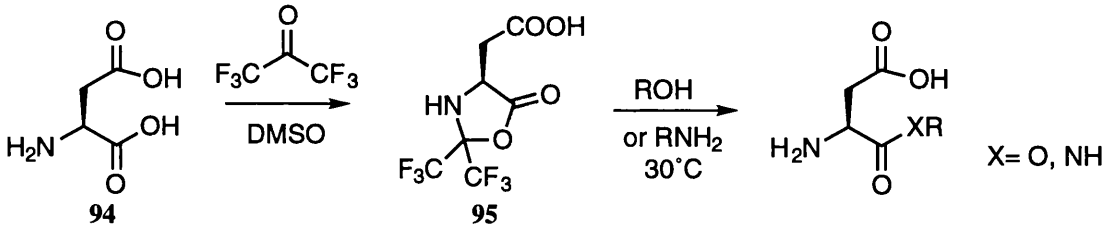
Scheme 3.2.4

Reaction of **89** with the gulose derived difluoroenol ether **26** using slow addition of AIBN and tributyltin hydride in refluxing benzene afforded the glycopeptide analogue **93** in 14% yield (Scheme 3.2.5). As in the case of CF_2-disaccharides, only the anomer corresponding to the delivery of the hydrogen atom from the least hindered face was produced, as was determined by the typical coupling constant between the anomeric proton and its vicinal neighbour on the ring (J= 3.7 Hz). Unfortunately, varying the reaction conditions did not improve the low yield and other substrates such as the ribose derivative **25** failed to react with the amino acid precursor **89**.



Scheme 3.2.5

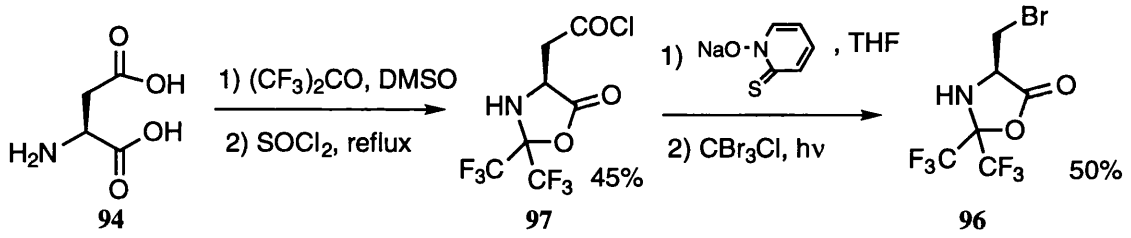
Capitalising on our experience in the disaccharide series, we reasoned that the radical derived from **89** was too sterically congested to add onto the enol ether efficiently, and as a consequence was being competitively reduced by the tin hydride. We anticipated that replacing the bulky *t*-butoxycarbonyl protecting group by a smaller one, or even protecting both the acid and amine functionalities in a five-membered ring would minimise the steric bulk around the radical and allow a more efficient addition to take place. In the event, an elegant method developed by Burger[108] provided us with a practical solution in which both the amine and the acid group of aspartic acid could be protected as a *bis*(trifluoromethyl) oxazolidinone by treatment with gaseous hexafluoroacetone at room temperature (Scheme 3.2.6). This protecting group was shown to be extremely labile in presence of nucleophiles[109] -it was cleaved by treatment with an alcohol or a primary amine at 30°C for a few minutes- but proved to be thermally stable and to suffer minimal deprotection (<10%) upon flash chromatography on silica gel.



Scheme 3.2.6

The conversion of the acid **95** to the acid chloride has been described[109] and we planned to convert the acid chloride to the primary bromide **96** by radical bromination of the corresponding Barton ester (Scheme 3.2.7).[80,110] The protection with hexafluoroacetone is usually carried out by passing a flow of the gas above a suspension of the amino acid in DMSO at room temperature and completion of the reaction is determined by the disappearance of the precipitate and the condensation of hexafluoroacetone from a dry ice condenser. In our hands however, the protection of aspartic acid required the reaction mixture to be maintained at 50°C, because at room temperature the reaction was slow and the refluxing hexafluoroacetone was lowering

the temperature to -26°C. Separation of the acid **95** from DMSO proved troublesome as repeated aqueous extraction resulted in deprotection, but treatment of the crude acid **95** containing *ca.* 15% of DMSO with thionyl chloride, followed by distillation, afforded the pure acid chloride **97** in good yields and multigram quantities. Bromination was effected by treating the acid chloride with the sodium salt of 2-mercaptopyridine-1-oxide in THF at -15°C, followed by irradiation in bromoform. Upon distillation of the crude reaction mixture, we were surprised to repeatedly observe a small amount of the primary chloride (*ca.* 10%) inseparable from the bromide **96**. Fortunately, when the crude reaction mixture was purified by chromatography, only the bromide was isolated.

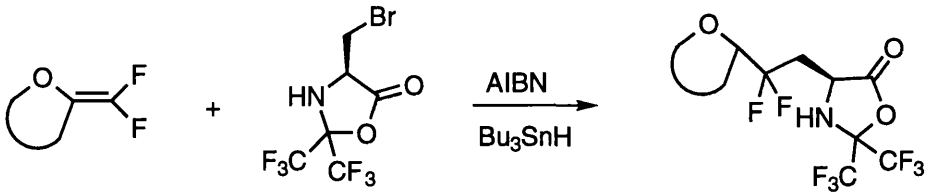


94 **97** **96**

Scheme 3.2.7

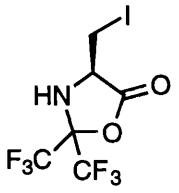
With the primary bromide **96** in hand, we then examined its addition to *gem*-difluoroenol ethers under tin mediated conditions and were pleased to find that the reactions proceeded in acceptable yields with a range of substrates (Table 3.2.1). The glucose derivative **29** (entry **e**) and the *t*-butyl dimethylsilyl protected ribose derivative **25** (entry **c**) did not react, presumably once again because their double bond was less accessible, but replacing the bulky TBDMS protecting group of **25** by a methoxy group led to a dramatic improvement as **27** reacted in 41% yield (entry **d**). The stereoselectivity of the reaction was excellent for the gulose and erythrose derivatives **26** and **28**, and the only isomer detected was the expected α-anomer, corresponding to the abstraction of hydrogen from the less hindered convex face. In the case of the methoxy protected ribose derivative **27** (entry **d**), an equimolar mixture of both anomers was observed, presumably because the methoxy substituent is hindering the top face of the ring, making both faces similarly congested. For all of these compounds, the stereochemistry was assigned by the typical coupling constant between

the anomeric proton and its vicinal neighbour on the ring. The bromide **96** was converted to the iodide **98** by treatment with sodium iodide in acetone, but no improvement was observed when **98** was used in radical reactions. The certainty that no epimerisation had occurred during the preparation and reaction of the amino acid **96** was established by the presence of only one diastereoisomer for **99** and **100**.



Entry	Enol Ether	Amino acid	Yield
a	**26**	**99**	30%
b	**28**	**100**	19%
c	**25**	-	-
d	**27**	**101:102**	41% (1:1)
e	**29**	-	-

Table 3.2.1



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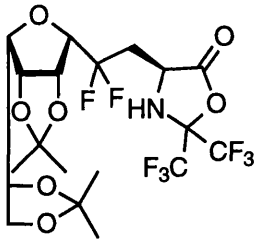
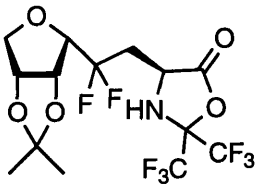
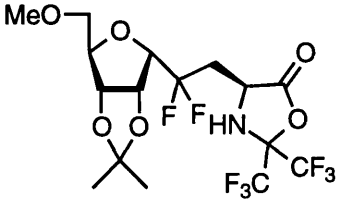


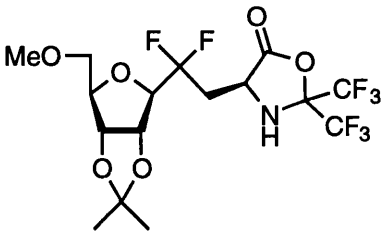
99



100



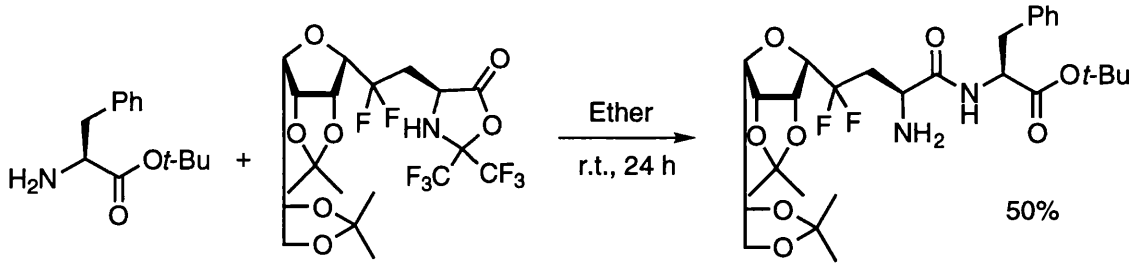
101



102

This general approach, combining the mild conditions of radical reactions with an extremely labile protecting group, revealed its versatility upon incorporation of the

adducts into peptide fragments. Simple treatment of **99** with L-phenylalanine-*t*-butyl ester **103** in ether at room temperature afforded the dipeptide **104**, with concomitant liberation of the free amino terminus for further coupling reactions (Scheme 3.2.8). The yield of this reaction was not optimised but the exceptionally mild conditions for this coupling should be noted.



103 **99** **104**

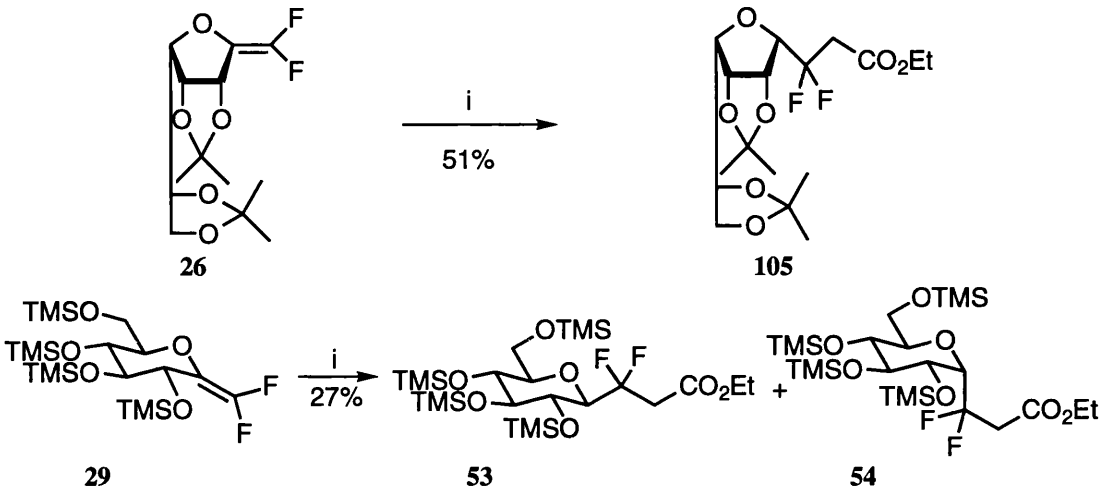
Scheme 3.2.8

The reaction of *gem*-difluoroenol ethers with nucleophilic radicals under tin mediated conditions is therefore a convenient stereocontrolled route to novel glycopeptide analogues. Although the yields for these couplings were moderate, they constitute an unusual combination of an electron rich enol ether with a nucleophilic radical in a three component chain reaction.

3.3 Spirofused CF_2-Carbocycles.

Having demonstrated the synthetic potential of *gem*-difluoroenol ethers as acceptors of nucleophilic radicals, we have investigated their reactions with electrophilic radicals. As outlined in the introduction, we expected that this would constitute a favourable association and we were not contradicted by preliminary results with simple halides (Scheme 3.3.1). The gulose derivative **26** reacted with ethyl bromoacetate under tin hydride mediated conditions to afford the expected β-anomer **105** in 51% yield[26] and the usually unreactive glucose derivative **29** was transformed in 27% yield to a 10:3 mixture of the β- and α- anomers **53** and **54**. The stereochemistry of the major isomer **53** was assigned on the basis of the typical diaxial coupling

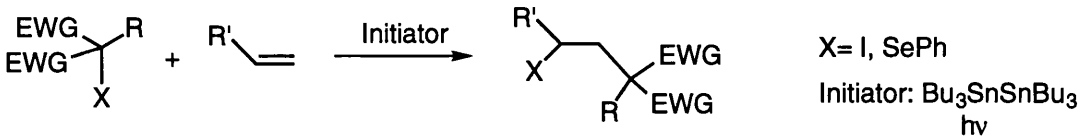
constant (8.4 Hz) between the anomeric proton and its vicinal neighbour and the relative chemical shifts of the anomeric protons (δ= 3.95 ppm for **53** versus δ= 4.54 ppm for **54**). The corresponding coupling constant for **54** was 5.3 Hz. The predominance of **53** could be anticipated from the radical anomeric effect.[41]



Conditions: AIBN, Bu_3SnH, $BrCH_2CO_2Et$, benzene, reflux.

Scheme 3.3.1

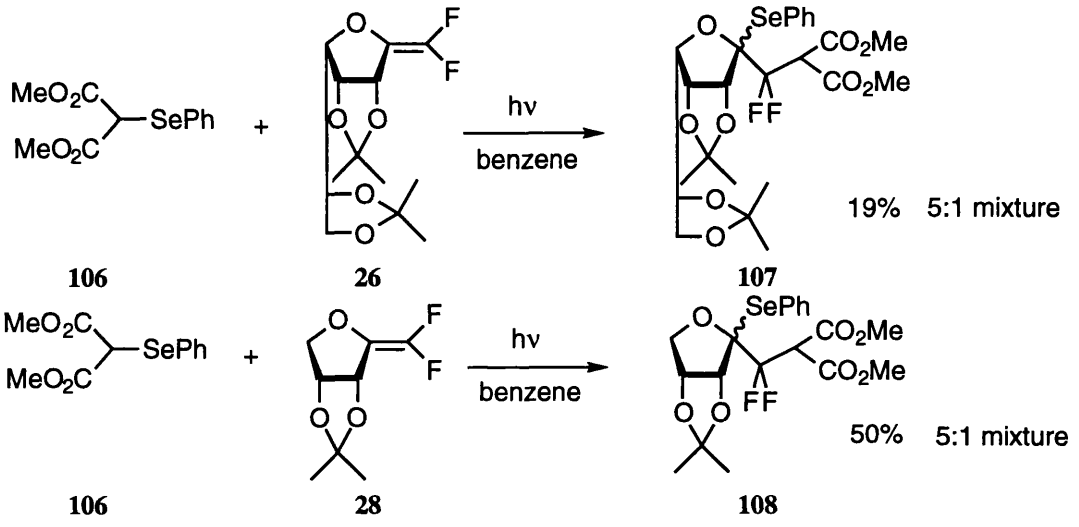
A powerful extension of this approach was found in the addition cyclisation of diethyl allyliodomalonate and the addition of dimethyl phenylselenyl-propanedioate under the atom transfer conditions developed by Curran.[111-116] Atom transfer reactions have the advantage of being efficient two component chain reactions which enable the preservation rather than the reduction of a functional group during reaction (Scheme 3.3.2).



Scheme 3.3.2

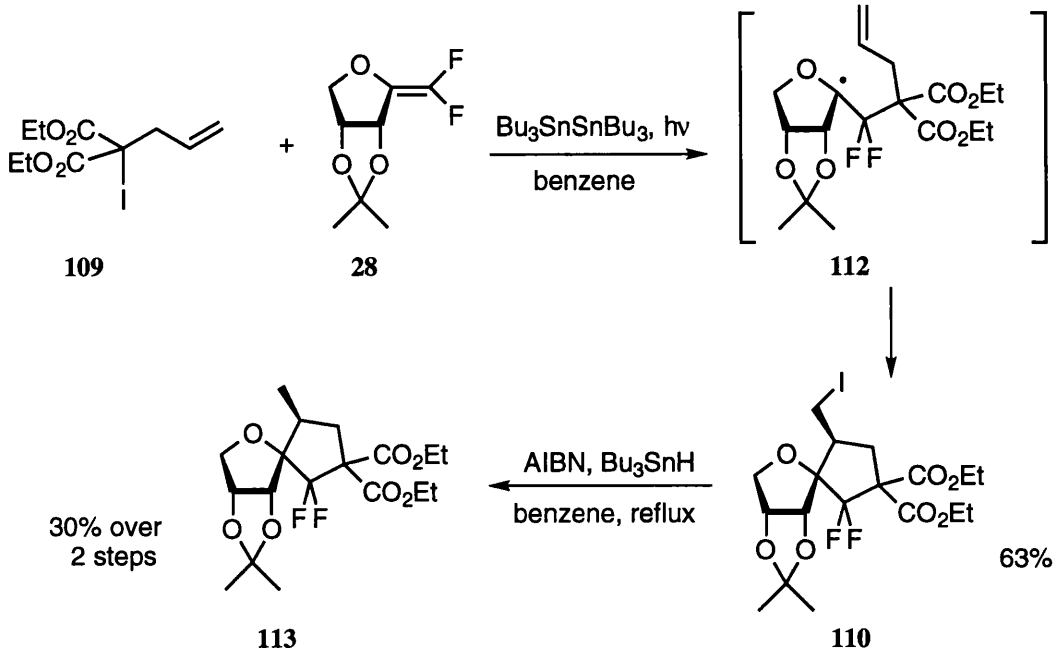
We initially investigated reactions involving transfer of the phenylseleno group[114-116] with the substrate **106** prepared from dimethyl malonate and phenyl selenyl bromide as described by Byers.[115] Upon irradiation, **106** reacted with the

gulose derivative **26** or the erythrose derivative **28** to afford the corresponding adducts **107** and **108** as an inseparable mixture of anomers (Scheme 3.3.3). No reason could be found to explain the difference in yield for the reaction of these two similar substrates Unfortunately, it was not possible to determine which isomer was in excess on the basis of NMR data or nOe experiments.

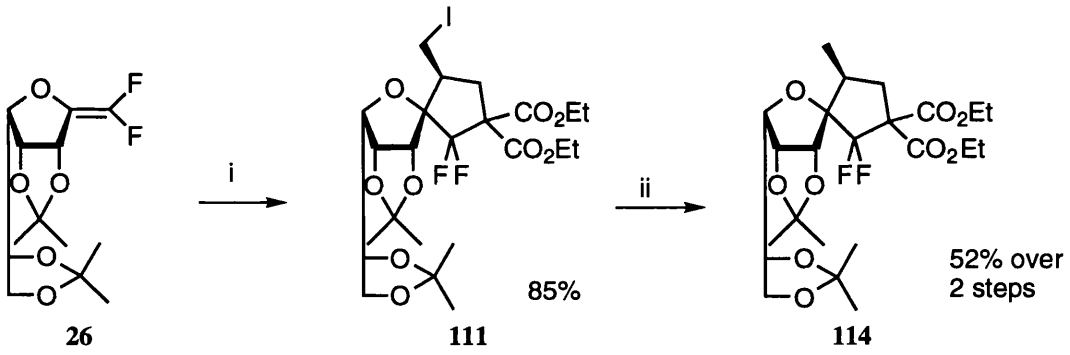


Scheme 3.3.3

We subsequently studied the addition cyclisation of diethyl iodomalonate under iodine atom transfer conditions as a route to difluoro spirofused carbocycles. Diethyl iodomalonate **109** was prepared from allylmalonate and N-iodo-succinimide, and reacted with the difluoroenol ethers **26** and **28** in presence of a catalytic amount of hexabutylditin and light (Scheme 3.3.4 and Scheme 3.3.5). The reaction sequence involved the addition of the electrophilic malonate radical to the difluoroenol ether, followed by 5-*exo* cyclisation of the anomeric radical and iodine atom transfer. That no evidence was found for products arising from quenching of the intermediate anomeric radical can be attributed to the efficiency of the cyclisation.[117] The iodides **110** and **111** could either be isolated in very good yield or subsequently reduced *in situ* with tri-*n*-butyltin hydride and AIBN.



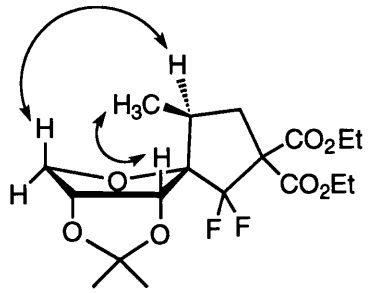
Scheme 3.3.4



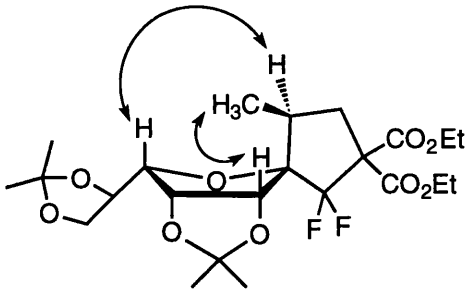
Conditions: i. **109**, $Bu_3SnSnBu_3$, hv, benzene, r.t.; ii. AIBN, Bu_3SnH, benzene, reflux.

Scheme 3.3.5

From examination of the ^1H and ^{13}C spectra of **110, 113, 111** and **114**, only one diastereoisomer was observed, and only on the ^{19}F NMR spectra could the trace of a second inseparable diastereoisomer be detected. Thus these cyclisations proceeded with good stereoselection, both at the anomeric centre and the methyl group. The configurations of the major isomers were determined by nOe experiments on **114** and **113** (Figure 3.3.1). For both compounds, nOe effects were observed between the proton at C-2 on the ring and the methyl group, and between the proton at C-4 facing upward and the proton on the carbon bearing the methyl group. Not enough information could be obtained from the spectra to rigorously identify the minor isomer.



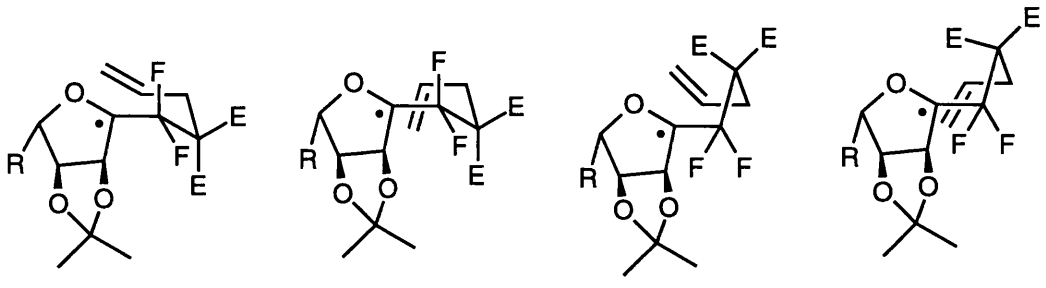
113



114

Figure 3.3.1

The anomeric stereochemistry corresponds, as expected, to a cyclisation which occurs from the least hindered face. The stereochemistry at the methyl group, however, is more difficult to account for, since Beckwith's guidelines[117] for predicting the stereochemical outcome of intramolecular cyclisations cannot be applied. In the four possible chair intermediates **A**, **B**, **C**, **D** (Figure 3.3.2) the substituents on the 2, 3 and 4 positions have no influence on the selection of one intermediate. The only relevant factor seems to be the difference between the two substituents in position 1, *i.e.* whether the double bond will eclipse the C-O bond as in **A** or **C** or the C-C bond as in **B** or **D**. Electronic repulsion between the lone pairs of oxygen and the π-system would disfavour intermediates **A** and **C**. An attractive interaction between the CH group and the π-system, as has been proposed in the radical cyclisation of cis-cyclopentyl,[118] would also favour intermediates **B** and **D**. Although it is difficult to quantify these factors, it appears that the chair transition states **B** and **D** should be favoured and these are the intermediates which lead to the observed products **111** and **110**.



A

B

C

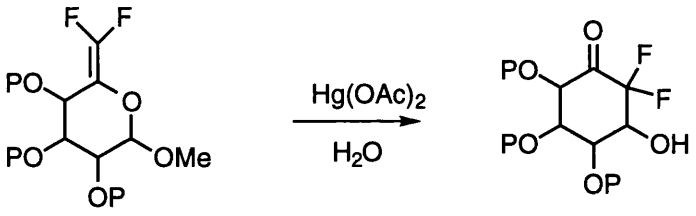
D

Figure 3.3.2

These examples demonstrate that electrophilic radicals are particularly good substrates for reactions with *gem*-difluoroenol ethers. When additions are carried out under atom transfer conditions, these processes are efficient and new difluoro spirofused carbocyles are obtained in high yields.

4 Difluoro Cyclitols.

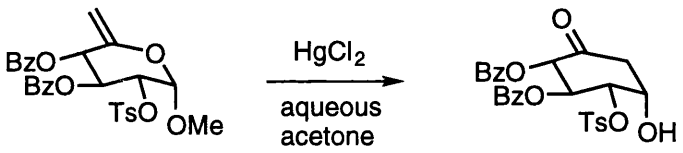
The synthetic potential of *gem*-difluoroenol ethers is not necessarily limited to radical reactions and it was, of course, our intention to investigate other avenues. Amongst these, a general approach to functionalised difluoro cyclopentanes and cyclohexanes from carbohydrates was particularly appealing, as it would provide an entry into carbohydrate analogues in which the ring oxygen atom is replaced by a CF_2 unit. These sugar mimics are expected to be stable to hydrolysis as the assistance of the ring oxygen for the departure of the group at the anomeric position is suppressed, and hence would constitute a new class of glycosidase inhibitors. The synthesis of cyclopentanes and cyclohexanes from non-fluorinated carbohydrates has recently been reviewed,[31] and in particular the Ferrier rearrangement captured our attention as a possible reaction for the conversion of pyranose derived *gem*-difluoroenol ethers to difluorocyclitols (Scheme 4.1.1).



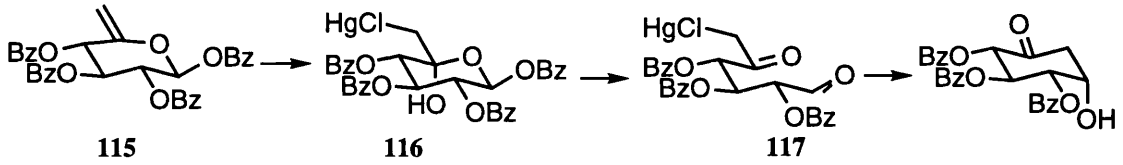
Scheme 4.1.1

Ferrier[32] reported the mercury(II) chloride induced rearrangement of carbohydrate *exo*-methylene derivatives to cyclohexanones in 1979 (Scheme 4.1.2) and since then a variety of examples[31,119-122] and modifications[123-125] of the original reaction conditions have been described. Examples include the use of a catalytic amount of a mercury salt ($Hg(OAc)_2$ or $HgCl_2$) at room temperature[124] and the replacement of mercury salts by palladium acetate.[125] The mechanism proposed by Ferrier[126] (Scheme 4.1.3) involves the oxy-mercuration of the enol ether **115**, followed

by ring opening of the intermediate **116** and intramolecular aldol like attack of the mercury enolate onto the aldehyde in **117**. It has sometimes been necessary to use the more electrophilic[127] mercury(II) trifluoroacetate reagent for the oxy-mercuration step and then to convert the mercury trifluoroacetate enolate to the more nucleophilic[128] mercury chloride enolate for the cyclisation to proceed.[122,126] The stereochemistry at the β-carbon is governed by the conformation ($^4C_1$ or $^1C_4$) of the starting carbohydrate,[123] although the reaction conditions influence the ratio of the two isomers.[122,123]

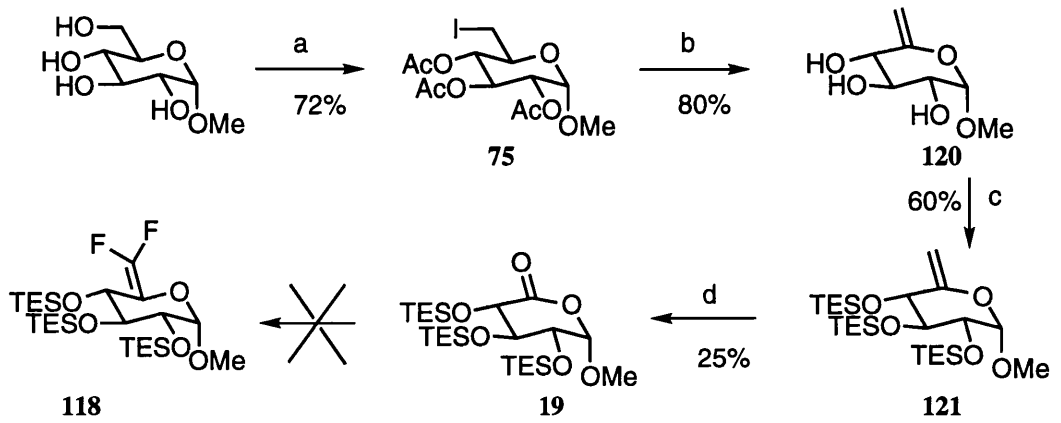


Scheme 4.1.2



Scheme 4.1.3

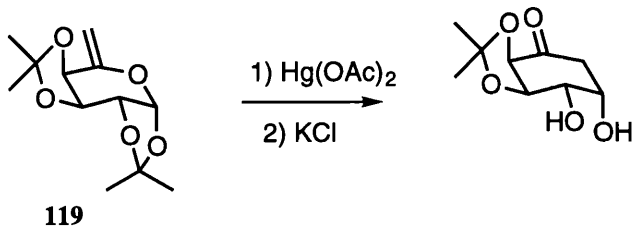
A literature procedure[129] described the preparation of the lactone **19** which we expected to convert to the corresponding *gem*-difluoroenol ether **118**, a possible substrate for the rearrangement and containing the same *exo*-methylene-methyl-glycoside configurational sequence as in Ferrier's original substrate (Scheme 4.1.4). A slight modification of the published synthesis provided **19**: iodination of methyl α-D-glucopyranoside was achieved using Samuelsson's procedure[130] involving triphenylphosphine, imidazole and iodine in toluene instead of carbon tetraiodide and pyridine.[129] Elimination of the acetyl protected iodo-glucose derivative **75** proceeded in good yield with DBU and replacement of the acetyl protecting groups of the enol ether **119** by triethylsilyl ethers followed by ozonolysis (unoptimised yield) afforded **19**. Unfortunately, all attempts to convert lactone **19** to the corresponding *gem*-difluoroenol ether were uniformly unsuccessful (see section 1.1).



Conditions: a) i. Ph_3P, I_2, imidazole, toluene, 70°C; ii. Ac_2O, pyridine, r.t.; b) i. DBU, THF, reflux; ii. NaOMe, MeOH, r.t.; c) Et_3SiCl, Et_3N, NaH, DMAP, DCM, reflux; d) i. O_3, DCM, -78°C; ii. Me_2S.

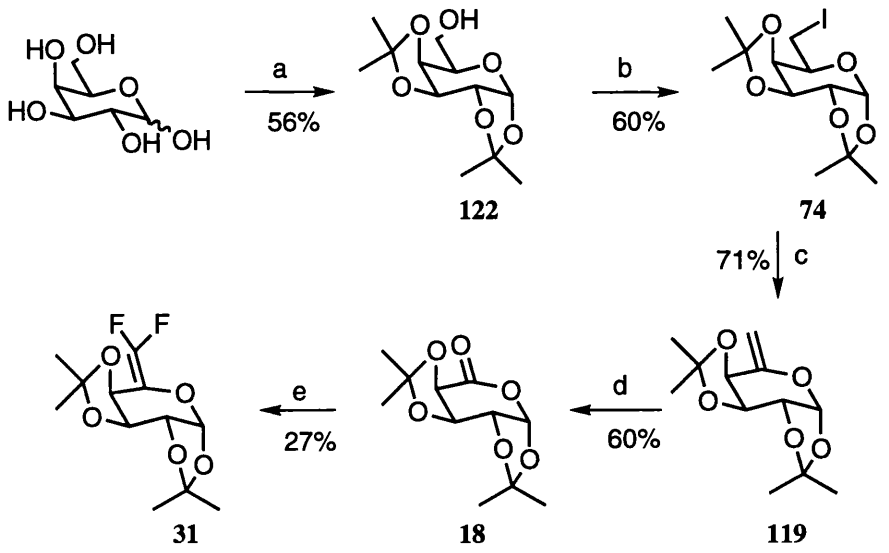
Scheme 4.1.4

The difficulty encountered in the difluoromethylenation of the lactone **19** led us to consider another substrate for the Ferrier rearrangement. Reasoning that a A(1,3) allylic strain was the prime factor responsible for our failure to prepare **118**, we looked for substrates in which the allylic substituent would be axial and small. The isopropylidene protected galactopyranose derivative **18** fulfilled these conditions, and the Ferrier rearrangement of the corresponding exo-methylene derivative **119** had once again been reported, albeit requiring more severe conditions (Scheme 4.1.5).[126,131] The synthesis of the lactone **18** followed the route described for the preparation of the exo-methylene derivative **119** (Scheme 4.1.6).[131,132] D-galactose was protected as its isopropylidene derivative using Kartha's procedure,[49] and then iodinated using Samuelsson's method[133] involving diphenylchlorophosphine, imidazole and iodine. DBU failed to give elimination, and silver fluoride in pyridine[132] afforded the enol-ether **119** in poor yield. Sodium hydride in DMF at 80°C produced **119** in 71% yield, and ozonolysis of the enol-ether provided the lactone **18**. The best conditions for the difluoromethylenation of **18** involved dibromodifluoromethane with two equivalents of *tris*(dimethylamino)phosphine and no zinc, but the yield remained lower than 30% (see Section 1.1).



119

Scheme 4.1.5

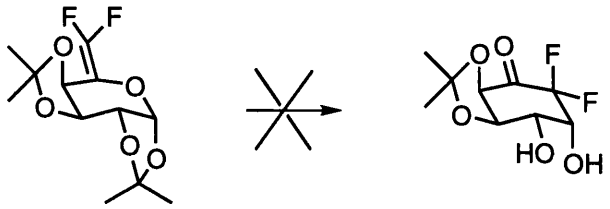


Conditions: a) acetone, I_2, r.t.; b) Ph_2PCl, I_2, imidazole, toluene, r.t.; c) NaH, DMF, 80°C; d) i. O_3, DCM, -78°C; ii. SMe_2; e) CF_2Br_2, $(Me_2N)_3P$, THF, reflux.

Scheme 4.1.6

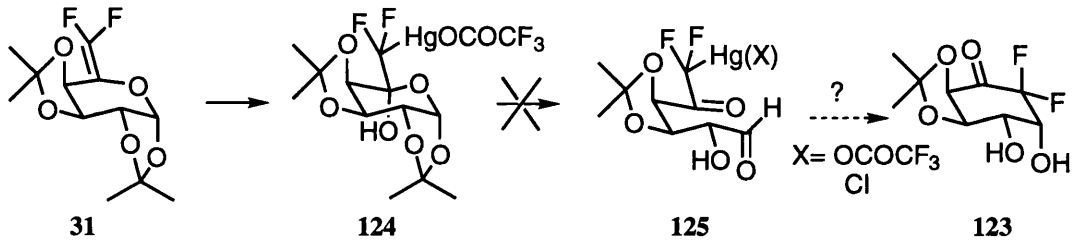
With the substrate **31** in hand, the Ferrier rearrangement protocol to afford the *gem*-difluoro cyclitol **123** was attempted. Unfortunately, irrespective of the conditions employed, none of the cyclohexanone **123** was produced (Scheme 4.1.7). Assuming that the reaction follows the mechanism proposed by Ferrier,[126] several explanations can account for the different reactivities of **119** and its fluorinated counterpart **31**. When **31** was treated with an excess of mercury(II) trifluoroacetate, the enol ether was consumed in a few hours. Precedents in our group have shown that mercury(II) acetate[28] and trifluoroacetate[55] add to *gem*-difluoroenol ethers in good yields under these conditions, and although the organomercurial **124** was not isolated, we believe that it was formed during the course of the reaction (Scheme 4.1.8). The presence of the fluorine substituents is expected to stabilise the acetal **124** and make the opening of the ring more difficult. This increase in activation energy, coupled with the cleavage of

one of the isopropylidene groups, could prevent the ring opening of **124** from taking place. Alternatively, **124** might be converted to the mercury enolate **125** whose behaviour on cyclisation is difficult to predict. Attempts to convert the hypothetical mercury acetate enolate to the more nucleophilic mercury chloride enolate by adding potassium chloride did not change the outcome of the reaction.



31 **123**

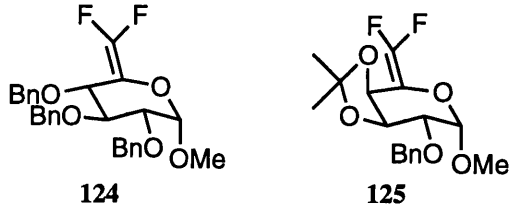
Scheme 4.1.7



31 **124** **125** **123**

Scheme 4.1.8

Although these preliminary experiments failed to afford the expected product, the investigation of the Ferrier rearrangement as a general route to *gem*-difluoro cyclitols should be continued. The disappearance of the starting material and precedents in our group for oxy-mercuration of *gem*-difluoroenol ethers are encouraging observations and the selection of substrates with a good leaving group at the anomeric position would facilitate the ring opening step. Whether substrates such as **124** and **125** could be prepared and would rearrange, are questions which should be addressed before discarding this approach.



124 **125**

Conclusion

In summary, we have established general routes to a range of new *gem*-difluoromethylene substituted analogues of carbohydrates, including CF_2-anomeric phosphonates, CF_2-disaccharides and CF_2-glycopeptides. Capitalising on our ability to form carbohydrate *gem*-difluoroenol ethers from the corresponding lactones, we have developed new radical chain reactions to convert them into highly functionalised molecules in a mild and selective manner. In the course of these investigations, we have demonstrated the unusual versatility of these *gem*-difluoroenol ethers as 'radicophiles', which combine the reactivity of an electron rich enol ether towards electrophilic radicals with a high affinity for nucleophilic radicals.

Nevertheless, we have only explored one avenue in terms of the possible functionalisations of *gem*-difluoroenol ethers. Generation of the difluoromethylene radical, from their reaction product with phenylselenol, thiophenol or mecury(II) acetate, opens a further range of possible new radical reactions. Ionic or radical rearrangements to convert difluoroenol ethers to highly functionalised difluoromethylene substituted cylohexanes and cyclopentanes, also deserve further investigation. In general, much attention still needs to be devoted to the preparation and manipulation of *gem*-difluoroenol ethers and *gem*-difluoromethylene glycosides, as new reactions are required to extend their synthetic utility beyond the field of carbohydrate chemistry and promote them as powerful synthons in the preparation of other *gem*-difluoromethylene substituted natural product analogues.

Chapter Three:

Experimental

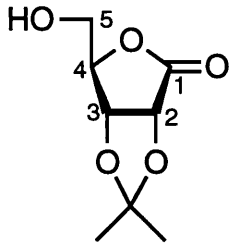
Melting points were determined on a Kofler and a Reichert hot stage and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 983G grating infrared spectrophotometer and a Perkin Elmer 1600 infrared spectrophotometer as thin films or dichloromethane solutions. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 270 MHz and 62.9 MHz respectively on a Bruker WM-250, 400 MHz and 100.6 MHz respectively on a Varian VXR400, at 500 and 125.8 MHz respectively on a Bruker AM 500 instrument. Residual protic solvent was used as the internal standard. ^{19}F-NMR spectra were recorded at 84.3 MHz on a Jeol FX90Q instrument and at 376.3 MHz on a Varian VXR400 instrument, using fluorotrichloromethane as the internal standard. Mass spectra were recorded on a VG 7070B mass spectrometer, a VG 305 mass spectrometer and a VG ZAB SE mass spectrometer. Accurate mass measurements were made on a VG 7070b at Imperial College, by the SERC Mass Spectrometry Service or by The School of Pharmacy Mass Spectrometry Service. Optical rotations were measured on an Optical Activity AA1000 polarimeter. Elemental analysis were performed by the staff of the Imperial College Microanalytical Laboratory and by the staff of University College Microanalytical Laboratory.

Petrol refers to redistilled light petroleum ether (b.p. 40-60°C). Tetrahydrofuran and ether were distilled from sodium-benzophenone ketyl under nitrogen. Benzene and toluene were distilled from sodium under nitrogen. Dichloromethane was distilled from phosphorous pentoxide under nitrogen and acetonitrile was distilled from calcium hydride under nitrogen. Diethyl phosphite was distilled under reduced pressure. Dimethyl formamide was distilled from calcium hydride and stored under nitrogen over 4Å molecular sieves. Pyridine and triethylamine were distilled from potassium hydroxide and stored over potassium hydroxide under nitrogen. Thionyl chloride was distilled from triethyl phosphite. Zinc was activated by acid wash. All other reagent were purified by standard procedures.

Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merk Kieselgel 60 F_{254}) and visualised by ultraviolet light (254 nm), iodine, acidic ammonium molybdate(IV) or potassium permanganate aqueous solutions as appropriate. Preparative column chromatography was performed at low positive pressure on Merck Kiesel 60 (230-400 mesh) and Sorbsil C60 40/60 A. Preparative High Pressure Liquid Chromatography was performed with a Gilson 305 apparatus with a Bischoff RI 8110 detector or a Shimadzu UV-VIS SPD-10A detector, using a Partisil 5 silica gel column. A MB/U Osram 400W Medium Pressure Mercury Arc Lamp was used for photolysis.

All reaction flasks were oven dried and, unless otherwise stated, all reactions were performed under a positive pressure of nitrogen.

Preparation of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone[50] (126).



126

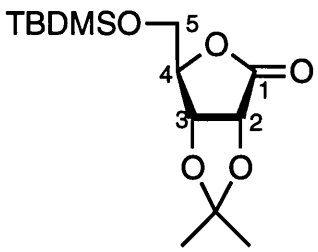
Iodine (1.2 g, 4.73 mmol) was dissolved in acetone (200 ml), 1,4-ribonolactone (**127**) (4.0 g, 27.0 mmol) was added and the mixture was stirred at room temperature. After 0.5 hr the lactone was completely dissolved and TLC showed that the reaction had gone to completion. The solution was stirred with saturated sodium thiosulphate until decolourisation, acetone was evaporated *in vacuo* and the aqueous phase was extracted with chloroform (3x50 ml). The combined organic extracts were washed with water (30 ml), brine, dried over magnesium sulphate and concentrated *in vacuo* to afford 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**126**) (4.49 g, 91%) as white crystals (mp. 138°C, lit.[50] 138-139°C).

^{1}H NMR (270 MHz, $CDCl_3$): 4.82 (1H, d, J= 5.6 Hz, H-2), 4.78 (1H, d, J= 5.6 Hz, H-3), 4.60 (1H, t, J= 1.9 Hz, H-4), 4.00 (1H, ddd, J= 2.4, 5.3, 12.4 Hz, H-5a), 3.76 (1H, ddd, J= 1.7, 5.8, 12.4 Hz, H-5b), 2.78 (1H, t, J= 5.5 Hz, OH), 1.46 (3H, s, Me), 1.37 (3H, s, Me).

IR (DCM): ν_{max}= 3468 (OH), 1775 (C=O), 1379, 1224, 1201, 1156, 856 cm^{-1}.

m/z (EI): 173 $[M\text{-}Me]^+$, 59, 43.

Preparation of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone[134] (20).



20

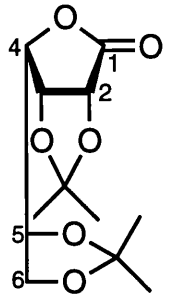
2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**126**) (4.0 g, 22 mmol), imidazole (3.7 g, 55.0 mmol) and *tert*-butyldimethylsilylchloride (3.9 g, 26.0 mmol) were mixed in dimethyl formamide (10 ml). The mixture was stirred at room temperature for 24 hr, and was directly chromatographed (20% ether/petrol) to afford 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**20**) (7.18 g, 90%) as a white solid (mp. 77-79°C, lit.[134] 69-70°C).

^{1}H NMR (270 MHz, $CDCl_3$): 4.71 (2H, m, H-2 H-3), 4.60 (1H, t, J= 1.7 Hz, H-4), 3.88 (1H, dd, J= 2.0, 11.2 Hz, H-5a), 3.79 (1H, dd, J= 1.5, 11.2 Hz, H-5b), 1.47 (3H, s, Me), 1.36 (3H, s, Me), 0.87 (9H, s, *t*-Bu), 0.07 (3H, s, Me-Si), 0.05 (3H, s, Me-Si).

IR (DCM): ν_{max}= 3055, 2989, 2955, 1789 (C=O), 1386, 1378, 1266, 1188, 1120, 1097, 1083, 838, 738 cm^{-1}.

m/z (EI): 288 $[M\text{-}Me]^+$, 217, 129, 117, 88.

Preparation of 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (21).



21

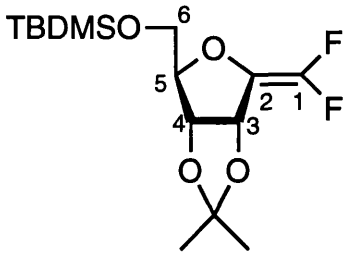
Iodine (3.0 g, 11.8 mmol) was dissolved in acetone (250 ml), D-gulono-1,4-lactone **(128)** (10.0 g, 56.0 mmol) was added and the mixture was stirred at room temperature for 12 hr. Aqueous sodium thiosulphate was added until decolourisation and the acetone was evaporated *in vacuo*. The aqueous phase was extracted with dichloromethane (3x200 ml), and the combined organic phases were washed with brine, dried over magnesium sulphate and concentrated *in vacuo* to afford a white solid. Recrystallisation from ethyl acetate afforded 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone **(21)** (10.3 g, 71%) as white crystals (mp. 152°C, lit.[135] 150-151°C).

^{1}H NMR (270 MHz, $CDCl_3$): 4.84 (1H, d, J= 5.6 Hz, H-2), 4.74 (1H, dd, J= 3.4, 5.6 Hz, H-3), 4.42 (2H, m, H-4 H-5), 4.20 (1H, dd, J= 6.6, 8.8 Hz, H-6a), 3.83 (1H, dd, J= 6.1, 8.8 Hz, H-6b), 1.47 (6H, s, 2 Me), 1.39 (3H, s, Me), 1.37 (3H, s, Me).

IR (DCM): ν_{max}= 2994, 2938, 1789 (C=O), 1380, 1263, 1213, 1075, 980, 738 cm^{-1}.

m/z (EI): 243 $[M\text{-}Me]^+$, 101, 59, 43.

Preparation of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol[26,27] (25).



25

Dibromodifluoromethane (2.7 ml, 29.8 mmol) was added to a solution of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**20**) (2.0 g, 6.6 mmol) in tetrahydrofuran (60 ml) at -20°C using a cooled syringe, followed by hexamethylphosphorus triamide (6.5 ml, 35.7 mmol). A dense white precipitate formed. The mixture was allowed to warm to room temperature and stirred for 20 min. Then zinc (1.9 g, 29.8 mmol) was added along with another portion of hexamethylphosphorus triamide (1.0 ml, 5.5 mmol). The white precipitate turned to a light brown solution which was refluxed for 18 hr. The dark reaction mixture was poured into ether (70 ml) and washed with aqueous copper sulphate until the copper sulphate solution remained blue (5x20 ml), then with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (3% ether/petrol) afforded 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (**25**) (1.0 g, 45%) as a colourless oil.

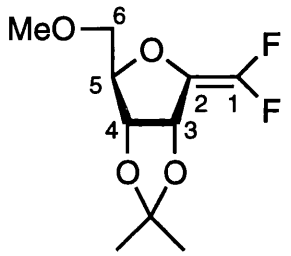
^{1}H NMR (270 MHz, $CDCl_3$): 5.28 (1H, dd, J= 3.2, 6.1 Hz, H-3), 4.79 (1H, dd, J= 1.0, 6.3 Hz, H-4), 4.44 (1H, t, J= 1.2 Hz, H-5), 3.78 (1H, dd, J= 2.7, 11.2 Hz, H-6a), 3.73 (1H, dd, J= 2.9, 11.2 Hz, H-6b), 1.50 (3H, s, Me), 1.38 (3H, s, Me), 0.87 (9H, s, *t*-Bu), 0.04 (3H, s, Me-Si), 0.02 (3H, s, Me-Si).

^{19}F NMR (84 MHz, $CDCl_3$): -105.0 (d, J= 93 Hz), -121.2 (d, J= 93 Hz).

IR (neat): ν_{max}= 2956, 2935, 2860, 1793 (C=C), 1635, 1473, 1464, 1384, 1376, 1343, 1280, 1256, 1215, 1158, 1116, 1086, 1017, 973, 938, 921, 900, 874, 837, 776, 741, 704, 662 cm^{-1}.

m/z (EI): 321 $[M\text{-}Me]^+$, 279 $[M\text{-}C_3H_6]^+$, 221 $[M\text{-TBDMS}]^+$, 165, 97, 42.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-6-*O*-methyl-D-*ribo*-hex-1-enitol (27).



27

Dibromodifluoromethane (0.68 ml, 7.5 mmol) was added to a solution of 2,3-*O*-isopropylidene-5-*O*-methyl-D-ribono-1,4-lactone[50] (**22**) (300 mg, 1.5 mmol) in tetrahydrofuran (30 ml) at -20°C using a cooled syringe, followed by hexamethylphosphorus triamide (1.35 ml, 7.5 mmol). A dense white precipitate formed. The mixture was allowed to warm to room temperature and stirred for 20 min. Then zinc (482 mg, 7.5 mmol) was added along with another portion of hexamethylphosphorus triamide (0.13 ml, 0.72 mmol). The white precipitate turned to a light brown solution which was refluxed for 6 hr. The dark reaction mixture was poured into ether (30 ml) and washed with aqueous copper sulphate until the copper sulphate solution remained blue (4x20 ml), then with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (15% ether/petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-6-*O*-methyl-D-*ribo*-hex-1-enitol (**27**) (112 mg, 31%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 5.29 (1H, dd, J= 3.1, 6.1 Hz, H-3), 4.75 (1H, dt, J= 1.5, 6.0 Hz, H-4), 4.49 (1H, m, H-5), 3.52 (1H, dd, J= 3.6, 10.7 Hz, H-6a), 3.48 (1H, dd, J= 3.7, 10.7 Hz, H-6b), 3.35 (3H, s, OMe), 1.50 (3H, s, Me), 1.38 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 150.0 (dd, J= 271, 286 Hz, C-1), 120.5 (dd, J= 14, 49 Hz, C-2), 113.3 ($\underline{C}Me_2$), 85.9, 81.2, 77.85 (t, J= 4 Hz, C- 3), 72.8, 59.6 (OMe), 26.8 (Me), 25.6 (Me).

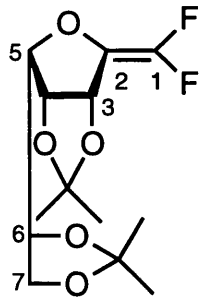
^{19}F NMR (373 MHz, $CDCl_3$),: -104.5 (d, J= 91 Hz), -120.0 (d, J= 91 Hz).

IR (neat): ν_{max}= 2991, 2940, 2895, 1792 (C=C), 1458, 1383, 1275, 1238, 1213, 1157, 1114, 1085, 1041, 1011, 871 cm^{-1}.

m/z (EI): 236 $[M]^+$, 235 $[M-H]^+$, 137, 135, 113, 100, 87, 73, 68, 59, 55.

Accurate Mass (FAB): Observed $[M-H]^+$: 235.0787; $C_{10}H_{13}O_4F_2$ requires: 235.0782.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol[26,27] (26).



26

Dibromodifluoromethane (6.2 ml, 67.5 mmol) was added to a solution of 2,3;4,5-di-*O*-isopropylidene-D-gulono-1,4-lactone **(21)** (3.5 g, 13.5 mmol) in tetrahydrofuran (100 ml) at -20°C using a cooled syringe, followed by hexamethylphosphorus triamide (12.35 ml, 67.5 mmol). A dense white precipitate formed. The mixture was allowed to warm to room temperature and stirred for 20 min. Zinc (4.43 g, 67.5 mmol) was then added along with another portion of hexamethylphosphorus triamide (2.4 ml, 13.5 mmol). The mixture was refluxed for 4 hr. The dark reaction mixture was poured into ether (150 ml) and washed with aqueous copper sulphate until the copper sulphate

solution remained blue (5x50 ml), then with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (40% ether/petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol **(26)** (2.46 g, 64%) as a yellow oil.

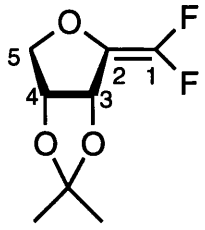
^{1}H NMR (270 MHz, $CDCl_3$): 5.33 (1H, dd, J= 2.9, 6.1 Hz, H-3), 4.70 (1H, m, H-4), 4.40 (1H, dt, J= 6.8, 8.0 Hz, H-6), 4.20 (1H, dd, J= 6.6, 8.5 Hz, H-7a), 3.95 (1H, dd, J= 4.2, 8.0 Hz, H-5), 3.70 (1H, dd, J= 6.6, 8.5 Hz, H-7b), 1.43 (3H, s, Me), 1.45 (3H, s, Me), 1.37 (3H, s, Me), 1.33 (3H, s, Me).

^{19}F NMR (83 MHz, $CDCl_3$): -100.5 (d, J= 83 Hz), -117.5 (d, J= 83 Hz).

IR (neat): ν_{max}= 2989, 2939, 1790 (C=C), 1456, 1374, 1329, 1287, 1214, 1162, 1113, 1071, 973, 929, 894, 850, 735 cm^{-1}.

m/z (EI): 292 $[M]^+$, 277 $[M\text{-}Me]^+$, 219 $[M\text{-}\ CH_3C(O)CH_3]^+$, 177, 159, 149, 133, 131, 117, 102, 101, 86, 85, 83, 73, 72, 43.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (28).



28

Dibromodifluoromethane (4.19 ml, 45.8 mmol) and hexamethylphosphorous triamide (8.34 ml, 45.8 mmol) were added to a solution of (-)2,3-*O*-isopropylidene-D-erythronolactone **23** (1.45 g, 9.2 mmol) in tetrahydrofuran (80 ml) at -20°C. A white precipitate formed and the mixture was allowed to warm to room temperature for 20 min. Zinc (3.0 g, 45.8 mmol) was added along with another portion of hexamethylphosphorous triamide (1.6 ml, 9.2 mmol) and the mixture was refluxed for 4

hr. The dark mixture was poured into ether (300 ml), washed with aqueous copper sulphate until the copper sulphate solution remained blue (4x100 ml), water (100 ml), brine (100 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (15% ether/petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol **(28)** (896 mg, 51%) as a pale yellow oil.

$[\alpha]_D$= -206.04° (c= 2.15, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 5.30 (1H, dd, J= 3.0, 6.2 Hz, H-3), 4.85 (1H, m, H-4), 4.28 (1H, d, J= 10.5 Hz, H-5a), 3.93 (1H, dd, J= 4.2, 10.5 Hz, H-5b), 1.46 (3H, s, Me), 1.35 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 150.2 (dd, J= 273, 288 Hz, C-1), 119.4 (dd, J= 13, 48 Hz, C-2), 113.2 ($\underline{C}Me_2$), 79.0, 77.0, 75.2, 26.4 (Me), 25.2 (Me).

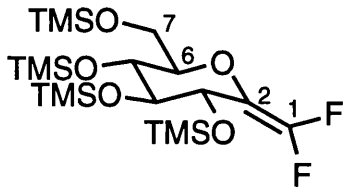
^{19}F NMR (376 MHz, $CDCl_3$): -102.5 (d, J= 85 Hz), -118.0 (d, J= 85 Hz).

IR (neat): ν_{max} = 2992, 2943, 1790 (C=C), 1384, 1275, 1277, 1232, 1211, 1159, 1114, 1061, 1031, 982, 885, 866 cm^{-1}.

m/z (EI): 192 $[M]^+$, 177 $[M\text{-}Me]^+$, 109, 76.

Accurate Mass (EI): Observed $[M]^+$: 192.0591; $C_8H_{10}O_3F_2$ requires : 192.0598.

Preparation of 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol[26,27] (29).



29

2,3,4,6-Tetra-*O*-(trimethylsilyl)-D-glucono-1,5-lactone[51] **(24)** (1.0 g, 2.13 mmol), was dissolved in tetrahydrofuran (25 ml) and cooled to -20°C. Dibromodifluoromethane (0.96 ml, 10.6 mmol) was added using a cooled syringe followed by hexamethylphosphorus triamide (3.86 ml, 21.3 mmol). A dense white

precipitate formed and the mixture was refluxed for 6 hr. The dark brown reaction mixture was poured into ether (100 ml) and washed with aqueous copper sulphate until the copper sulphate solution remained blue (4x50 ml), then with brine. It was dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (3% ether/petrol+1% triethylamine) afforded 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (**29**) (320 mg, 30%) as a colourless oil.

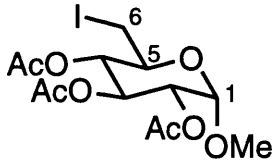
^{1}H NMR (400 MHz, $CDCl_3$): 4.10 (1H, t, J= 3.7 Hz, H-3), 3.83 (1H, m, H-6), 3.80 (1H, dd, J= 2.4, 11.5 Hz, H-7a), 3.71 (1H, dd, J= 4.2, 11.5 Hz, H-7b), 3.61-3.67 (2H, m, H-4 H-5), 0.14 (9H, s, TMS), 0.13 (9H, s, TMS), 0.11 (9H, s, TMS), 0.10 (9H, s, TMS).

^{19}F NMR (376 MHz, $CDCl_3$): -102.8 (d, J= 77 Hz), -117.6 (d, J= 77 Hz).

IR (neat): ν_{max}= 2950, 1753 (C=C), 1256, 1090, 960, 842, 765 cm^{-1}.

m/z (FAB): 500 $[M]^+$, 321 $[M\text{-}OTMSx2\text{-}H]^+$, 217, 191, 165, 147, 73 $[TMS]^+$.

Preparation of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside[130] (75).



75

Methyl-α-D-glucopyranoside (**129**) (5.0 g, 26.6 mmol), triphenylphosphine (10.0 g, 38.1 mmol), imidazole (5.3 g, 77.0 mmol) and iodine (9.2 g, 36.2 mmol) were mixed in toluene (200 ml) and stirred vigorously at 70°C for 3 hr during which the reaction mixture changed from dark yellow to light yellow. The reaction mixture was allowed to cool to room temperature, water (100 ml) was added and the mixture stirred for 15 min. The toluene phase was extracted with water (5x100 ml). The aqueous phase was washed with a small amount of toluene (50 ml) and concentrated *in vacuo*. Pyridine (60 ml, 742 mmol) and acetic anhydride (40 ml, 420 mmol) were added, the mixture

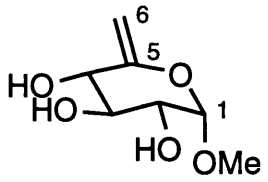
was stirred at room temperature for 6 hr and concentrated *in vacuo*. The residue was taken up in toluene (100 ml), washed with water (3x50 ml), dried over magnesium sulphate and concentrated *in vacuo*. Recrystallisation from ethanol afforded methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**75**) (8.0 g, 70%) as white crystals (mp. 144°C, lit.[130] 148-149°C)

^{1}H NMR (270 MHz, $CDCl_3$): 5.47 (1H, t, J= 9.7 Hz, H-3), 4.95 (1H, d, J= 3.6 Hz, H-1), 4.87 (2H, m, H-4 H-2), 3.80 (1H, td, J= 2.0, 7.8 Hz, H-5), 3.47 (3H, s, OMe), 3.30 (1H, dd, J= 2.5, 11.0 Hz, H-6a), 3.10 (1H, dd, J= 8.1, 10.7 Hz, H-6b), 2.06 (3H, s, OAc), 2.04 (3H, s, OAc), 2.00 (3H, s, OAc).

IR (DCM): ν_{max}= 1737, 1379, 1262, 1253, 1036 cm^{-1}.

m/z (EI): 303 $[M-I]^+$, 243, 157, 141, 43 $[CH_3CO]^+$.

Preparation of methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranoside[129] (120).



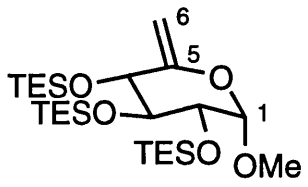
120

To a solution of methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**75**) (1.0 g, 2.3 mmol) in tetrahydrofuran (20 ml) was added diazabicyclo[5.4.0]undec-7-ene (2.1 ml, 14.0 mmol). The mixture was refluxed for 13 hr. Removal of the solvent gave a brown oil which was taken up in methanol (20 ml) and sodium methoxide (1 ml of a 10% solution in methanol) was added. The solution was neutralized with acetic acid and concentrated *in vacuo*. Chromatography (10% ethanol/ 30% DCM/ 60% ether+1% triethylamine) afforded methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranoside (**120**) (350 mg, 85%) as a yellow oil. The product was stored with a few drops of triethylamine at 6°C.

^{1}H NMR (270 MHz, $CDCl_3$): 5.30 (3H, br s, OH), 4.82 (1H, s, H-6a), 4.78 (1H, d, J= 3.2 Hz, H-1), 4.65 (1H, s, H-6b), 4.00 (1H, d, J= 8.2 Hz, H-4), 3.73 (1H, t, J= 9.5 Hz, H-3), 3.65 (1H, dd, J= 3.4, 10.0 Hz, H-2), 3.42 (3H, s, OMe).

IR (neat): ν_{max}= 3380 (OH), 3055, 2933, 1665 (C=C), 1364, 1267, 1190, 1145, 1064, 1027, 737 cm^{-1}.

Preparation of methyl 6-deoxy-2,3,4-tri-*O*-(triethylsilyl)-α-D-*xylo*-hex-5-enopyranoside[129] (121).



121

Methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranoside **(120)** (1.0 g, 5.68 mmol) was dissolved in triethylamine (4.74 ml, 34.1 mmol) and dichloromethane (120 ml). Dimethylaminopyridine (trace) was added along with sodium hydride (681 mg in 60% oil dispersion, 17.4 mmol) and chlorotriethylsilane (4.29 ml, 25.6 mmol). The mixture was refluxed for 18 hr, then triethylamine (1.18 ml, 8.52 mmol) and chlorotriethylsilane (1.48 ml, 8.5 mmol) were added and the mixture was refluxed for an hour. More triethylamine (1.18 ml, 8.5 mmol) and chlorotriethylsilane (1.48 ml, 8.5 mmol) were added, and the mixture was refluxed for 3 hr. On cooling dichloromethane (100 ml) and water (100 ml) were added. The organic phase was separated, washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (2% ether/ petrol) afforded methyl 6-deoxy-2,3,4-tri-*O*-(triethylsilyl)-α-D-*xylo*-hex-5-enopyranoside **(121)** (1.62 g, 60%) as a yellow oil.

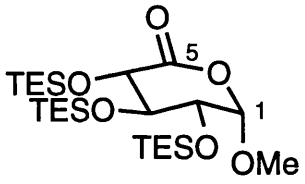
^{1}H NMR (270 MHz, $CDCl_3$): 4.79 (1H, d, J= 1.6 Hz, H-6a), 4.65 (1H, d, J= 3.4 Hz, H-1), 4.63 (1H, d, J= 1.5 Hz, H-6b), 3.81 (1H, d, J= 8.6 Hz, H-4), 3.76 (1H, t, J= 8.5 Hz,

H-3), 3.60 (1H, dd, J= 3.2, 8.3 Hz, H-2), 3.39 (3H, s, OMe), 1.02-0.90 (27H, m, Si-CH_2-C$\underline{H}_3$), 0.73-0.60 (18H, m, Si-C$\underline{H}_2$-CH_3).

IR (neat): ν_{max}= 2958, 1666 (C=C), 1461, 1414, 1378, 1239, 1209, 1164, 1015, 922, 864, 811, 742 cm^{-1}.

m/z (EI): 518 $[M]^+$, 489 $[M-Et]^+$, 458 $[M-OMe-Et]^+$, 358, 343, 301, 188, 159, 131, 115 $[TES]^+$, 103, 87, 75, 59, 47.

Preparation of [methyl 2,3,4-tri-*O*-(triethylsilyl)-α-D-xylopyranoside]-urono-5,1-lactone[129] (19).



19

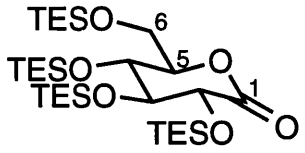
Methyl 6-deoxy-2,3,4-tri-*O*-(triethylsilyl)-α-D-*xylo*-hex-5-enopyranoside **(121)** (1.62 g, 3.31 mmol) was dissolved in dichloromethane (30 ml) and ozone was bubbled through the solution at -78°C for 20 mn. (solution turned blue). After the excess ozone had been removed by bubbling oxygen, dimethylsulphide (0.3 ml, 3.97 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was poured into 10% aqueous sodium bisulphite (30 ml), extracted with dichloromethane (3x20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (5% ether/petrol) afforded [methyl 2,3,4-tri-*O*-(triethylsilyl)-α-D-xylopyranoside]-urono-5,1-lactone **(19)** (530 mg, 25%) as a colourless oil.

^1H NMR (270 MHz, $CDCl_3$): 4.90 (1H, d, J= 3.1 Hz, H-1), 4.00 (2H, m, H-3 H-4), 3.80 (1H, dd, J= 1.7, 7.5 Hz, H-2), 3.39 (3H, s, OMe), 1.05-0.90 (27H, m, Si-CH_2-C$\underline{H}_3$), 0.74-0.60 (18H, m, Si-C$\underline{H}_2$-CH_3).

IR (neat): ν_{max}= 2956, 2878, 1768 (C=O), 1461, 1415, 1124, 1006, 806, 741 cm^{-1}.

m/z (EI): 175 $[M-3xTES]^+$, 144 $[M-3xTES-OMe]^+$, 115 $[TES]^+$, 87.

Preparation of 2,3,4,6-tetra-*O*-(triethylsilyl)-D-glucono-1,5-lactone (32).



32

Chlorotriethylsilane (1.13 ml, 6.72 mmol) was added to a solution of D-glucono-1,5-lactone **(130)** (200 mg, 1.12 mmol) and triethylamine (1.25 ml, 3.36 mmol) in dichloromethane (3 ml). The mixture was refluxed for 19 hr. Water (20 ml) and dichloromethane (20 ml) were added, the organic phase was extracted with dichloromethane (3x10 ml), washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (2% ether/petrol) afforded 2,3,4,6-tetra-*O*-(triethylsilyl)-D-glucono-1,5-lactone **(32)** (539 mg, 75%).

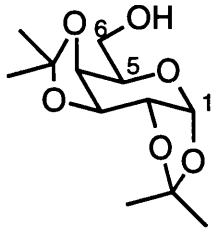
^{1}H NMR (270 MHz, $CDCl_3$): 4.55 (1H, m, H-5), 4.08 (1H, dd, J= 1.2, 4.1 Hz, H-2), 3.95 (1H, dd, J= 1.2, 7.6 Hz, H-4), 3.81 (2H, m, H-6a H-6b), 3.75 (1H, m, H-3), 1.02-0.92 (36H, m, Si-CH_2-C$\underline{H}_3$), 0.70-0.60 (24H, m, Si-C$\underline{H}_2$-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.8 (C-1), 81.4, 77.2, 73.7, 71.1, 61.8, 6.7-6.5 (m, TES), 5.2-4.3 (m, TES).

IR (neat): ν_{max}= 2956, 2912, 2877, 1769 (C=O), 1458, 1415, 1339, 1241, 1007, 963, 882, 743 cm^{-1}.

m/z (EI): 445 $[M\text{-OTES-2xEt}]^+$, 289 $[M\text{-3xTES}]^+$, 259, 217, 145, 87, 59.

Preparation of 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose[49] (122).



122

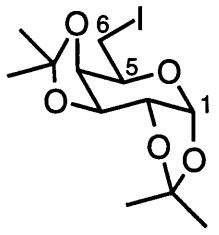
Iodine (3.0 g, 11.8 mmol) was dissolved in acetone (500 ml) and finely powdered D-galactose (**131**) (10.0 g, 55.5 mmol) was added. The mixture was stirred at room temperature for 19 hr, then saturated sodium thiosulphate was added until decolourisation. Acetone was evaporated *in vacuo*, and the residue was extracted with dichloromethane (3x150 ml). The combined organic extracts were washed with water (50 ml), brine, dried over magnesium sulphate, and concentrated *in vacuo* to afford of 1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (**122**) (9.26 g, 64%) as a yellow oil, which was used without further purification.

^{1}H NMR (270 MHz, $CDCl_3$): 5.55 (1H, d, J= 4.9 Hz, H-1), 4.60 (1H, dd, J= 2.4, 7.8 Hz, H-3), 4.32 (1H, dd, J= 2.4, 4.9 Hz, H-2), 4.25 (1H, dd, J= 1.7, 8.0 Hz, H-4), 3.80 (3H, m, H-5 H-6a H-6b), 1.50 (3H, s, Me), 1.43 (3H, s, Me), 1.31 (6H, s, 2 Me).

IR (neat): ν_{max}= 3477 (OH), 2988, 2937, 1383, 1257, 1212, 1167, 1064, 1004, 900 cm^{-1}.

m/z (EI): 245 $[M\text{-}Me]^+$.

Preparation of 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose[133] (74).

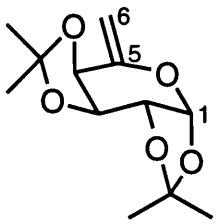


74

1,2;3,4-di-*O*-isopropylidene-D-galactopyranose **(122)** (8.25 g, 31.7 mmol), chlorodiphenylphosphine (7.4 ml, 41.2 mmol), imidazole (4.8 g, 69.7 mmol) and iodine (10.4 g, 41.2 mmol) were mixed in toluene (350 ml) and stirred at room temperature for 2 hr. The reaction mixture was poured into an equal volume of saturated sodium carbonate in a separating funnel. Iodine was then added in portions. When the toluene phase remained iodine coloured, the organic layer was separated, washed with aqueous sodium thiosulphate, water (3x60 ml), dried over magnesium sulphate, and concentrated *in vacuo*. Chromatography (50% ether/petrol) afforded 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose **(74)** (7g, 60%) as white crystals (mp. 54°C, lit.[133] 58°C).

^{1}H NMR (400 MHz, $CDCl_3$): 5.55 (1H, d, J= 4.9 Hz, H-1), 4.63 (1H, dd, J= 2.7, 8.0 Hz, H-3), 4.41 (1H, dd, J= 1.7, 7.8 Hz, H-4), 4.32 (1H, dd, J= 2.4, 5.1 Hz, H-2), 3.95 (1H, td, J= 1.7, 7.1 Hz, H-5), 3.24 (1H, dd, J= 6.9, 9.8 Hz, H-6a), 3.20 (1H, dd, J= 6.9, 9.8 Hz, H-6b), 1.55 (3H, s, Me), 1.45 (3H, s, Me), 1.35 (3H, s, Me), 1.33 (3H, s, Me).
IR (DCM): ν_{max}= 3054, 2988, 1384, 1266, 1214, 1070, 998, 897, 738, 705 cm^{-1}.
m/z (EI): 370 $[M]^+$, 355 $[M\text{-}Me]^+$, 297 $[M\text{-}C_3H_6O_2]^+$, 243 $[M\text{-}I]^+$.

Preparation of 1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-hex-5-enopyranose (119).

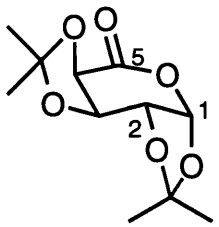


119

To a solution of 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (**74**) (6.8 g, 18.3 mmol) in dimethyl formamide (80 ml) was added sodium hydride (1.08 g, 54.9 mmol). The mixture was stirred at 80°C for 18 hr. Methanol (10 ml) was added, the mixture was poured into aqueous sodium hydrogen carbonate (70 ml) and extracted with ether (3x60 ml). The combined organic extracts were dried over magnesium sulphate, concentrated *in vacuo*. Recrystallisation from methanol afforded 1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-hex-5-enopyranose (**119**) (3.15 g, 71%) as a white solid (mp. 85-86°C, lit.[132] 86°C).

^{1}H NMR (500 MHz, $CDCl_3$,): 5.60 (1H, d, J= 3.7 Hz, H-1), 4.77 (1H, d, J= 0.7 Hz, H-6a), 4.66 (1H, d, J= 0.6 Hz, H-6b), 4.58 (2H, m, H-3 H-4), 4.25 (1H, dt, J= 3.6, 1.0 Hz, H-2), 1.48 (3H, s, Me), 1.46 (3H, s, Me), 1.36 (3H, s, Me), 1.34 (3H, s, Me).
IR (DCM): ν_{max}= 3055, 2988, 1650 (C=C), 1370, 1265, 737 cm^{-1}.
m/z (EI): 227 $[M\text{-}Me]^+$.

Preparation of 1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-urono-5,1-lactone (18).



18

1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-hex-5-enopyranose **(119)** (2.65 g, 10.95 mmol) was dissolved in dichloromethane and ozone was bubbled through the solution at -78°C for 20 mn. Oxygen was bubbled until the solution had lost its blue colour. Dimethyl sulphide (0.884 ml, 12.05 mmol) was added and the mixture was allowed to warm to room temperature, concentrated *in vacuo* and recrystallized from ethanol to afford 1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-urono-5,1-lactone **(18)** (1.56 g, 58%) as white crystals (mp. 98-100°C).

^{1}H NMR (400 MHz, $CDCl_3$): 5.94 (1H, d, J= 2.6 Hz, H-1), 4.69 (1H, dd, J= 2.3, 5.6 Hz, H-3), 4.57 (1H, d, J= 5.8 Hz, H-4), 4.38 (1H, t, J= 2.4 Hz, H-2), 1.49 (3H, s, Me), 1.46 (3H, s, Me), 1.43 (3H, s, Me), 1.40 (3H, s, Me).

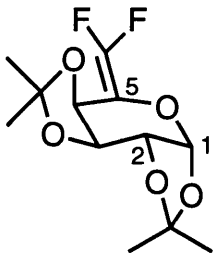
IR (DCM): ν_{max}= 3056, 2993, 1756 (C=O), 1386, 1377, 1266, 1246, 1216, 1169, 1158, 1131, 1111, 1091, 1065, 1052, 1017, 738, 704 cm^{-1}.

m/z (FAB): 245 $[M+H]^+$, 229 $[M-Me]^+$, 187 $[M-Me_2CO]^+$, 149, 143, 129, 113, 85, 73, 59, 43.

Found: C 53.76 H 6.64 %, $C_{11}H_{16}O_6$ requires: C 54.10 H 6.56 %.

Accurate Mass (FAB): Observed: $[M+H]^+$: 245.1021; $C_{11}H_{17}O_6$ requires: 245.1025.

Preparation of 6-deoxy-6,6-difluoro-1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-hex-5-enopyranose (31).



31

Dibromodifluoromethane (1.40 ml, 15.37 mmol) was added to a solution of 1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-urono-5,1-lactone **(18)** (500 mg, 2.05 mmol) in tetrahydrofuran (30 ml) at -20°C using a cooled syringe, followed by hexamethylphosphorus triamide (5.58 ml, 30.74 mmol). A dense white precipitate formed. The mixture was allowed to warm to room temperature and refluxed for 18 hr. The dark brown reaction mixture was poured into ether (60 ml) and washed with aqueous copper sulphate until the copper sulphate solution remained blue (4x30 ml). The organic phase was then washed with brine, dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (25% ether/petrol) afforded 6-deoxy-6,6-difluoro-1,2;3,4-di-*O*-isopropylidene-D-*lyxo*-hex-5-enopyranose **(31)** (121 mg, 21.5 %) as white crystals (mp. 81°C).

^{1}H NMR (400 MHz, $CDCl_3$): 5.60 (1H, dd, J= 2.0, 4.3 Hz, H-1), 4.84 (1H, dt, J= 2.8, 7.5 Hz, H-3), 4.67 (1H, dm, J= 7.6 Hz, H-4), 4.42 (1H, dd, J= 2.7, 4.3 Hz, H-2), 1.49 (3H, s, Me), 1.45 (3H, s, Me), 1.38 (3H, s, Me), 1.34 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 154.2 (dd, J= 283, 293 Hz, C-6), 110.5 ($\underline{C}Me_2$), 110.3 ($\underline{C}Me_2$), 109.2 (m, C-5), 97.5, 71.9, 70.1, 67.3, 26.4 ($C\underline{Me}_2$), 26.2 ($C\underline{Me}_2$), 25.4 ($C\underline{Me}_2$), 24.6 ($C\underline{Me}_2$).

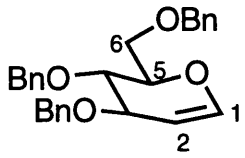
^{19}F NMR (376 MHz, $CDCl_3$): -98.0 (d, J= 60 Hz), -112.0 (d, J= 60 Hz)

IR (DCM): ν_{max}= 3055, 2989, 2938, 1773 (C=C), 1454, 1383, 1292, 1256, 1217, 1162, 1107, 1074, 1030, 1014, 933, 740 cm^{-1}.

m/z (EI): 278 $[M]^+$, 263 $[M\text{-}Me]^+$, 220, 205, 163, 133, 113, 96, 77, 59.

Accurate Mass (EI): Observed $[M]^+$: 278.0966; $C_{12}H_{16}O_5F_2$ requires: 278.0957.

Preparation of tri-*O*-benzyl-D-glucal (17).



17

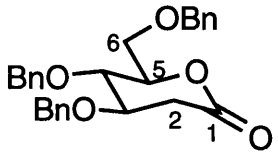
Sodium (84 mg, 3.6 mmol) was dissolved in methanol and tri-*O*-acetyl-D-glucal (**132**) (5.0 g, 18.3 mmol) was added. The mixture was stirred for 2 hr at room temperature, concentrated *in vacuo* and dried under vacuum for 2 hr. The residue was taken up in dry dimethyl sulphoxide (50 ml) and a mixture of dimethyl sulphoxide (10 ml) and oil free sodium hydride (1.8 g, 73.2 mmol) was added dropwise. The mixture was stirred for 1 hr at room temperature, then benzyl chloride (6.76 ml, 58.6 mmol) was added. The mixture was stirred for 2 hr, poured into ice (500 ml) and extracted with ether (3x200 ml). The combined ether extracts were washed with water (50 ml), dried over magnesium sulphate and concentrated *in vacuo*. Recrystalisation from ethanol afforded tri-*O*-benzyl-D-glucal (**17**) (4.8 g, 63%) as white crystals (mp. 56-57°C, lit.[136] 57-57.5°C).

^1H NMR (400 MHz, $CDCl_3$): 7.40-7.20 (15H, m, Ph), 6.43 (1H, d, J= 6.0 Hz, H-1), 4.89 (1H, dd, J= 2.7, 6.1 Hz, H-2), 4.80-4.50 (6H, m, $C\underline{H_2}$-Ph), 4.20 (1H, m, H-3), 4.06 (1H, m, H-4), 3.72-3.90 (3H, m, H-5 H-6a H-6b).

IR (DCM): ν_{max}= 2898, 2861, 1649 (C=C), 1453, 1245, 1140 cm^{-1}.

m/z (FAB): 417 $[M+H]^+$, 369, 309, 307 $[M\text{-}Bn]^+$, 201, 185, 93.

Preparation of 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone[52] (16).



16

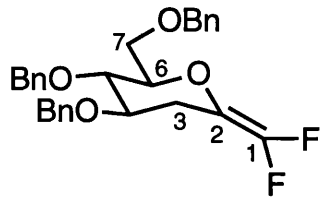
Tri-*O*-benzyl-D-glucal (**17**) (10.0 g, 24.2 mmol) was added to a solution of pyridinium chlorochromate (11.0 g, 48.4 mmol) in 1,2-dichloroethane (500 ml) and stirred at room temperature for 3.5 days. Another portion of pyridinium chlorochromate (5.0 g, 22.1 mmol) was added and the mixture was stirred for 5.5 days at room temperature. The dark reaction mixture was concentrated *in vacuo* and chromatography (30% ethyl acetate/petrol) afforded 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**16**) (6.12 g, 59%) as a white solid (mp. 74-76°C, lit.[52] 82-83°C).

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.20 (15H, m, Ph), 4.68-4.48 (6H, m, C$\underline{H}_2$-Ph), 4.31 (1H, dt, J= 4.1, 7.6 Hz, H-5), 3.95 (1H, q, J= 4.5 Hz, H-3), 3.90 (1H, dd, J= 3.9, 7.4 Hz, H-4), 3.72 (2H, m, H-6a H-6b), 2.82 (1H, dd, J= 4.5, 16.5 Hz, H-2a), 2.78 (1H, dd, J= 4.3, 16.5 Hz, H-2b).

IR (DCM): ν_{max}= 3054, 1758 (C=O), 1265, 1095, 738, 702 cm^{-1}.

m/z (FAB): 433 $[M+H]^+$, 341 $[M-Bn]^+$, 325 $[M-OBn]^+$, 271, 181, 91 $[Bn]^+$.

Preparation of 2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,1-difluoro-D-*arabino*-hept-1-enitol (30).



30

Dibromodifluoromethane (0.264 ml, 2.90 mmol) was added to a solution of 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone **(16)** (250 mg, 0.58 mmol) in tetrahydrofuran (10 ml) at -20°C, followed by hexamethylphosphorus triamide (0.526 ml, 2.90 mmol). A dense white precipitate formed and the mixture was stirred at room temperature for 20 mn. Zinc (194 mg, 2.90 mmol) was added along with another portion of hexamethylphosphorus triamide (0.1 ml, 0.55 mmol). The reaction mixture was refluxed for 14 hr, then concentrated *in vacuo* and the dark black residue was taken up in dichloromethane (50 ml). Aqueous copper sulphate was added, the biphasique mixture was stirred for 10 min and filtered over Celite. The two phases were separated and the organic phase was washed with aqueous copper sulphate (3x20 ml), water (20 ml) and dried over magnesium sulphate. Chromatography (15% ether/petrol) afforded 2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,1-difluoro-D-*arabino*-hept-1-enitol **(30)** (34 mg, 12.5 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (15H, m, Ph), 5.00-4.50 (6H, m, C$\underline{H}_2$-Ph), 3.77-3.71 (3H, m, H-5 H-7a H-7b), 3.65 (1H, ddd, J= 5.3, 8.4, 10.3 Hz, H-6), 3.55 (1H, dt, J= 2.9, 9.0 Hz, H-4), 2.80 (1H, dt, J= 3.4, 13.7 Hz, H-3a), 2.15 (1H, m, H-3b).

^{13}C NMR (100 MHz, $CDCl_3$): 152.8 (dd, J= 277, 287 Hz, C-1), 138.1, 138.0, 137.9 (Ph), 128.4, 128.35, 128.32, 128.2, 128.1, 128.0, 127.93, 127.88, 127.8, 127.7, 127.69, 127.64, 127.58, 127.47, 127.42 (Ph), 112.3 (dd, J= 16, 44 Hz, C-2), 80.7, 78.8, 77.1, 74.9, 73.5, 71.7, 68.4, 27.3 (C-3).

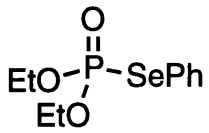
^{19}F NMR (376 MHz, $CDCl_3$): -103.0 (dd, J= 6, 74 Hz), -107.0 (d, J= 74 Hz).

IR (DCM) ν_{max}= 2920, 2870, 1779 (C=C), 1454, 1364, 1248, 1099, 737, 698 cm^{-1}.

m/z (FAB): 465 $[M-H]^+$, 181, 91 $[Bn]^+$.

Accurate Mass (FAB): Observed $[M-H]^+$: 465.1972; $C_{28}H_{27}O_4F_2$ requires: 465.1977.

Preparation of diethyl (phenylselenyl)phosphonate[81] (62).



62

Triethylphosphite (4.27 ml, 25.7 mmol) was dissolved in benzene (75 ml) and phenylselenyl bromide (5 g, 21 mmol) was added slowly at room temperature. The solution turned yellow and TLC showed completion after 5 min. After 3 hr stirring at room temperature, a dilute solution of sodium hydrogen carbonate (200 ml) was added and the aqueous phase was extracted with ether (3x130 ml). The combined organic phases were dried over magnesium sulphate, concentrated *in vacuo* and chromatography (30% petrol/ether) afforded diethyl (phenylselenyl)phosphonate **(62)** as a yellow oil (6.2 g, 100%).

^1H NMR ($CDCl_3$, 400 MHz): 7.60 (2H, d, J= 6.8 Hz, Ph), 7.28 (3H, m, Ph), 4.15 (4H, m, CH_2), 1.20 (6H, t, J= 7.0 Hz, CH_3).

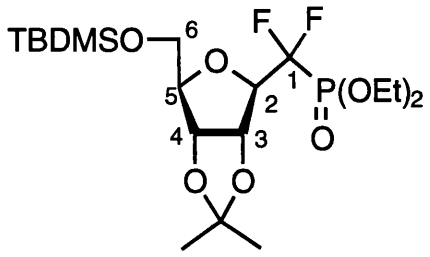
^{13}C NMR ($CDCl_3$, 100 MHz): 135.3 (Ph), 135.2 (Ph), 129.2 (Ph), 128.6 (Ph), 123.0 (Ph), 63.6 (CH_2), 63.6 (CH_2), 15.7 (CH_3), 15.7 (CH_3).

IR (neat): ν_{max}= 2984, 1579, 1477, 1440, 1251, 1013, 973, 740, 690 cm^{-1}.

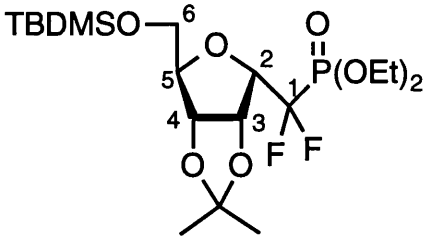
m/z (EI): 294 $[M(^{80}Se)]^+$, 158 $[H^{80}SePh]^+$, 109, 81, 29.

Accurate Mass (CI): Observed $[M(^{80}Se)+NH_4]^+$: 312.0268; $C_{10}H_{19}O_3N^{80}SeP$ requires: 312.0268.

Preparation of diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate (50) and diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate (63).



50



63

Preparation with diethyl phosphite:

A solution of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol **(25)** (200 mg, 0.59 mmol) and diethyl phosphite (0.23 ml, 1.77 mmol) in octane (5 ml) was degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide (55 µl, 0.30 mmol) in degassed octane (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr, concentrated *in vacuo*, and chromatography (52 % ether/petrol) afforded diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate **(50)** (130 mg, 47%) as a yellow oil.

Preparation with diethyl (phenylselenyl)phosphonate:

A solution of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol **(25)** (150 mg, 0.45 mmol) and diethyl (phenylselenyl)phosphonate **(62)** (390 mg, 1.33 mmol) in octane (7 ml) was degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide (41 µl, 0.23 mmol) and tri-n-butyltin hydride (0.480 ml, 1.78 mmol) in degassed octane (4 ml) over 5 hr *via* syringe pump. The black reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (52 % ether/petrol) afforded a 6:1 mixture of diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-

1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate **(50)** and diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate **(63)** (155 mg, 75%). HPLC (25% ethyl acetate/ hexane) allowed the separation of the two isomers, as two yellow oils.

Diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate (50):

^{1}H NMR (400 MHz, $CDCl_3$): 4.92 (1H, dd, J= 4.1, 6.4 Hz, H-3), 4.63 (1H, dd, J= 3.4, 6.4 Hz, H-4), 4.43-4.36 (1H, m, H-2), 4.25 (4H, m, $OC\underline{H}_2CH_3$), 4.17 (1H, q, J= 4.8 Hz, H-5), 3.74 (1H, dd, J= 4.8, 11.0 Hz, H-6a), 3.66 (1H, dd, J= 5.4, 11.0 Hz, H-6b), 1.55 (3H, s, $C\underline{Me}_2$), 1.35 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$), 0.90 (9H, s, *t*-Bu), 0.05 (6H, s, Me-Si).

^{13}C NMR (100 MHz, $CDCl_3$): 117.5 (ddd, J= 209, 261, 269 Hz, C-1), 114.3 ($\underline{C}Me_2$), 86.2, 84.0 (ddd, J= 14, 21, 28 Hz, C-2), 81.6, 79.9, 64.8 (t, J= 7 Hz, $O\underline{C}H_2CH_3$), 63.0, 27.4 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_3$), 25.5 ($C\underline{Me}_2$), 18.1 ($\underline{C}Me_3$), 16.4 ($OCH_2\underline{C}H_3$), 16.3 ($OCH_2\underline{C}H_3$), -5.6 (Me-Si), -5.8 (Me-Si).

^{19}F NMR (376 MHz, $CDCl_3$): -118.5 (ddd, J= 9, 100, 313 Hz), -124.5 (ddd, J= 18, 100, 313 Hz).

IR (neat): ν_{max}= 3056, 2987, 2932, 2859, 1472, 1385, 1266, 1215, 1025, 838, 779, 740, 705 cm^{-1}.

m/z (EI): 459 $[M\text{-}Me]^+$, 417, 267, 73.

Accurate Mass (FAB): Observed $[M+Na]^+$: 497.1916; $C_{19}H_{37}O_7F_2PSiNa$ requires: 497.1912.

Diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate (63):

^{1}H NMR (400 MHz, $CDCl_3$): 4.98 (1H, dd, J= 4.5, 5.9 Hz, H-3), 4.84 (1H, d, J= 6.2 Hz, H-4), 4.60 (1H, m, H-2), 4.25 (5H, m, $OC\underline{H}_2CH_3$, H-5), 3.81 (1H, dd, J= 3.1, 11.0 Hz, H-6a), 3.73 (1H, dd, J= 2.8, 11.0 Hz, H-6b), 1.53 (3H, s, $C\underline{Me}_2$), 1.37 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$), 0.90 (9H, s, *t*-Bu), 0.05 (6H, s, Me-Si).

^{13}C NMR (100 MHz, $CDCl_3$): 117.5 (m, C-1), 113.3 ($\underline{C}Me_2$), 85.0, 82.6, 81.4, 80.0 (m, C-2), 65.2, 64.8 (m, $O\underline{C}H_2CH_3$), 26.0 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_3$), 28.0 ($C\underline{Me}_2$), 18.1 ($\underline{C}Me_3$), 16.4 ($OCH_2\underline{C}H_3$), 16.3 ($OCH_2\underline{C}H_3$), -5.6 (Me-Si), -5.8 (Me-Si).

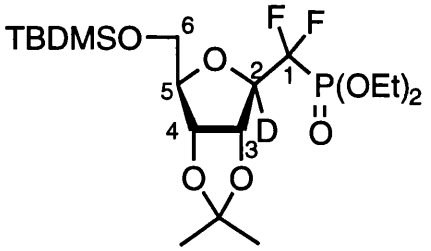
^{19}F NMR (376 MHz, $CDCl_3$): -118.7 (ddd, J= 18, 102, 314 Hz), -121.1 (ddd, J= 8, 101, 314 Hz).

IR (neat): ν_{max}= 3056, 2987, 2932, 2859, 1472, 1385, 1266, 1215, 1025, 838, 779, 740, 705 cm^{-1}.

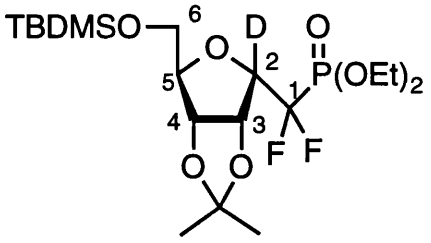
m/z (EI): 459 $[M\text{-}Me]^+$, 417, 267, 73.

Accurate Mass (FAB): Observed $[M+H]^+$: 497.1916; $C_{19}H_{37}O_7F_2PSiNa$ requires: 497.1912.

Preparation of diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-O-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate (64) and diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate (65).



64



65

A solution of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (**25**) (32.5 mg, 0.10 mmol) and diethyl (phenylselenyl)phosphonate (34.0 mg, 0.30 mmol) in octane (3 ml) was degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide (10 µl, 0.05 mmol) and tri-n-butyltin deuteride (0.104 ml, 0.40 mmol) in degassed octane (2.3 ml) over 6 hr *via* syringe pump. The black reaction mixture was refluxed for 2 hr, filtered over celite, concentrated *in vacuo* and chromatography (52 % ether/petrol) afforded diethyl (2,5-anhydro-6-*O*-(*tert*-

butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-L-*galacto*-hexos-1-yl)-phosphonate **(64)** (75% incorporation of deuterium by ^{19}F NMR) (24 mg) as a yellow oil and a 4:3 mixture of diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-L-*galacto*-hexos-1-yl)-phosphonate **(64)** (75% incorporation of deuterium by ^{19}F NMR) and of diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate **(65)** (82% incorporation of deuterium by ^{19}F NMR) (7 mg). Overall yield: 68%, 9:1 mixture of **64**:**65**.

Diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-D-*galacto*-hexos-1-yl)-phosphonate (64):

^1H NMR (400 MHz, $CDCl_3$): 4.95 (1H, d, J= 6.5 Hz, H-3), 4.65 (1H, dd, J= 3.4, 6.5 Hz, H-4), 4.25 (4H, m, $OC\underline{H}_2CH_3$), 4.16 (1H, q, J= 4.8 Hz, H-5), 3.73 (1H, dd, J= 4.8, 11.0 Hz, H-6a), 3.66 (1H, dd, J= 5.4, 11.0 Hz, H-6b), 1.55 (3H, s, $C\underline{Me}_2$), 1.35 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$), 0.89 (9H, s, *t*-Bu), 0.06 (3H, s, Me-Si), 0.05 (3H, s, Me-Si).

^{13}C NMR (100 MHz, $CDCl_3$): 117.5 (ddd, J= 209, 262, 269 Hz, C-1), 114.2 ($\underline{C}Me_2$), 86.1, 83.9 (m, C-2), 81.6, 79.8, 64.7 (t, J= 7 Hz, $O\underline{C}H_2CH_3$), 62.9, 27.4 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_3$), 25.5 ($C\underline{Me}_2$), 18.1 ($\underline{C}Me_3$), 16.4, 16.3 ($OCH_2\underline{C}H_3$), -5.5 (Me-Si).

^{19}F NMR (376 MHz, $CDCl_3$):-119.2 (dd, J= 99, 313 Hz), -124.5 (dd, J= 100, 313 Hz).

IR (neat): ν_{max}= 2986, 2932, 2858, 1473, 1463, 1383, 1274, 1258, 1214, 1159, 1088, 1023, 979, 838, 778 cm^{-1}.

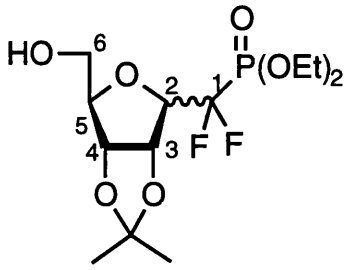
m/z (FAB): 476 $[M+H]^+$, 460 $[M-Me]^+$, 418, 267, 73.

Diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-2-deutero-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate (65):

^1H NMR (400 MHz, $CDCl_3$): 4.99 (1H, d, J= 5.9 Hz, H-3), 4.84 (1H, d, J= 6.2 Hz, H-4), 4.25 (5H, m, $OC\underline{H}_2CH_3$ H-5), 3.81 (1H, dd, J= 3.1, 11.0 Hz, H-6a), 3.73 (1H, dd, J= 2.8, 11.0 Hz, H-6b), 1.53 (3H, s, $C\underline{Me}_2$), 1.37 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$), 0.90 (9H, s, *t*-Bu), 0.05 (6H, s, Me-Si).

^{19}F NMR (376 MHz, $CDCl_3$): -118.7 (dd, J= 102, 314 Hz), -121.1 (dd, J= 101, 314 Hz).

Preparation of diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate and diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate as a mixture (133).



133

A solution of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (**25**) (200 mg, 0.59 mmol) and diethyl phosphite (0.38 ml, 2.95 mmol) in dioxane (4.5 ml) was degassed at reflux under argon for 40 min. To this refluxing solution was added a solution of benzoyl peroxide (72 mg, 0.3 mmol) in degassed dioxane (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (10% methanol/ether) afforded diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate and diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate as a mixture (**133**) (100 mg, 47%).

^1H NMR (400 MHz, $CDCl_3$) (major isomer): 4.94 (1H, dd, J= 4.1, 6.4 Hz, H-3), 4.63 (1H, dd, J= 3.4, 6.4 Hz, H-4), 4.41 (1H, m, H-2), 4.25 (5H, m, $OC\underline{H_2}CH_3$, H-5), 3.84 (1H, br s, OH), 3.74 (1H, m, H-6a), 3.31 (1H, m, H-6b), 1.56 (3H, s, $C\underline{Me_2}$), 1.32 (9H, m, $C\underline{Me_2}$ $OCH_2C\underline{H_3}$).

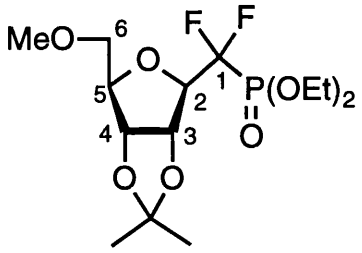
^{19}F NMR (376 MHz, $CDCl_3$): -112.1 (ddd, J= 10, 94, 314 Hz), -121.5 (ddd, J= 17, 105, 314 Hz).

IR (DCM): ν_{max}= 3384 (OH), 2984, 2920, 1376, 1252, 1107, 1021 cm^{-1}.

m/z (EI): 345 [M-Me^+], 295, 272.

The mixture of isomers (100 mg, 0.32 mmol), imidazole (47 mg, 0.70 mmol) and *tert*-butyldimethylsilylchloride (50 mg, 0.33 mmol) were mixed in dimethyl formamide (0.2 ml) and stirred at room temperature for 48 hr. Chromatography (52 % ether/petrol) afforded diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*allo*-hexos-1-yl)-phosphonate **(50)** (10 mg, 8 %) and diethyl (2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*altro*-hexos-1-yl)-phosphonate **(63)** (7.5 mg, 6 %), identical with the compounds previously described.

Preparation of diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-6-*O*-methyl-D-*allo*-hexos-1-yl)-phosphonate (66).



66

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-6-*O*-methyl-D-*ribo*-hex-1-enitol **(27)** (26 mg, 0.11 mmol) and diethyl (phenylselenyl)phosphonate (97 mg, 0.33 mmol) in octane (3 ml) were degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide (10 µl, 0.05 mmol) and tri-n-butyltin hydride (0.118 ml, 0.44 mmol) in degassed octane (2.3 ml) over 9 hr *via* syringe pump. The black reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (70 % ether/petrol) afforded diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-6-*O*-methyl-D-*allo*-hexos-1-yl)-phosphonate **(66)** (10 mg, 24%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 5.01 (1H, dd, J= 2.9, 6.5 Hz, H-3), 4.60 (1H, dd, J= 4.3, 6.6 Hz, H-4), 4.42 (1H, m, H-2), 4.29 (4H, m, $OC\underline{H}_2CH_3$), 4.23 (1H, q, J= 5.0 Hz, H-5), 3.54 (1H, dd, J= 5.8, 10.2 Hz, H-6a), 3.47 (1H, dd, J= 5.8, 10.3 Hz, H-6b), 3.39 (3H, s, OMe), 1.55 (3H, s, $C\underline{Me}_2$), 1.36 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 118.5 (ddd, J= 209, 263, 268 Hz, C-1), 114.7 ($\underline{C}Me_2$), 84.6, 84.1 (ddd, J= 14, 23, 28 Hz, C-2), 82.0, 80.2 (d, J= 4 Hz, C-3), 72.5, 64.8 (d, J= 7 Hz, $O\underline{C}H_2CH_3$), 59.4 (OMe), 27.3 ($C\underline{Me}_2$), 25.4 ($C\underline{Me}_2$), 18.8 (m, $OCH_2\underline{C}H_3$).

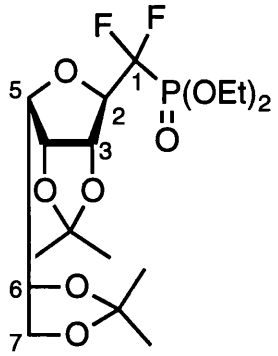
^{19}F NMR (376 MHz, $CDCl_3$): -117.4 (ddd, J= 9, 97, 313 Hz), -123.3 (ddd, J= 16, 99, 313 Hz).

IR (neat): ν_{max}= 2987, 2936, 1454, 1374, 1272, 1214, 1159, 1021, 865 cm^{-1}.

m/z (FAB): 397 $[M+Na]^+$, 375 $[M+H]^+$, 369, 359 $[M-Me]^+$, 239, 65.

Accurate Mass (FAB): Observed $[M+Na]^+$: 397.1200; $C_{14}H_{25}F_2O_7PNa$ requires: 397.1204.

Preparation of diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*glycero*-D-*talo*-heptos-1-yl)-phosphonate (51).



51

Preparation with diethyl phosphite:

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.68 mmol) and diethyl phosphite (0.264 ml, 2.04 mmol) in octane (3 ml) was degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide (63 µl, 0.34 mmol) in

octane (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr, concentrated *in vacuo*, and chromatography (60% ether/petrol) afforded diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*glycero*-D-*talo*-heptos-1-yl)-phosphonate **(51)** (68 mg, 23%) as a colourless oil.

Preparation with diethyl (phenylselenyl)phosphonate:

To a refluxing solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol **(26)** (200 mg, 0.68 mmol) and diethyl-(phenylselenyl)phosphonate (600 mg, 2.04 mmol) in degassed benzene (10 ml) was added a solution of AIBN (56 mg, 0.34 mmol) and tri-n-butyltin hydride (0.552 ml, 2.04 mmol) in degassed benzene (4 ml) over 12 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (60% ether/petrol) afforded diethyl (2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*glycero*-D-*talo*-heptos-1-yl)phosphonate **(51)** (85 mg, 28%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): 5.15 (1H, d, J= 6.0 Hz, H-3), 4.70 (1H, dd, J= 4.2, 6.1 Hz, H-4), 4.50 (1H, ddd, J= 3.0, 9.2, 23.2 Hz, H-2), 4.30 (5H, m, $OC\underline{H}_2CH_3$ H-6), 4.15 (1H, dd, J= 6.7, 8.4 Hz, H-7a), 4.07 (1H, m, H-5), 3.65 (1H, dd, J= 7.1, 8.4 Hz, H-7b), 1.45 (3H, s, $C\underline{Me}_2$), 1.38 (3H, s, $C\underline{Me}_2$), 1.37-1.34 (6H, m, $OCH_2C\underline{H}_3$), 1.33 (3H, s, $C\underline{Me}_2$), 1.28 (3H, s, $C\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 119.0 (ddd, J= 208, 267, 270 Hz, C-1), 113.5 ($\underline{C}Me_2$), 109.7 ($\underline{C}Me_2$), 85.5, 84.1 (ddd, J= 13, 21, 27 Hz, C-2), 81.2, 81.1, 76.1, 66.0, 64.9 (t, J= 6 Hz, $O\underline{C}H_2CH_3$), 26.7 ($C\underline{Me}_2$), 26.2 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 24.8 ($C\underline{Me}_2$), 16.5 ($OCH_2\underline{C}H_3$).

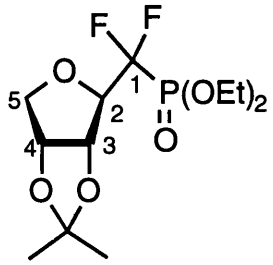
^{19}F NMR (376 MHz, $CDCl_3$): -115.0 (ddd, J= 10, 98, 317 Hz), -122.2 (ddd, J= 24, 98, 317 Hz).

IR (neat): ν_{max}= 2987, 2938, 1445, 1373, 1265, 1212, 1185, 1164, 1068, 1026, 975, 912, 853, 796, 735 cm^{-1}.

m/z (EI): 415 $[M\text{-}Me]^+$, 357, 138, 101.

Accurate Mass (FAB): Observed $[M+Na]^+$: 453.1461; $C_{17}H_{29}F_2O_8PNa$ requires: 453.1466.

Preparation of diethyl (2,5-anyhdro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hexos-1-yl)-phosphonate (47).



47

Preparation with diethyl phosphite:

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-pent-1-enitol (**28**) (200 mg, 0.1 mmol) and diethyl phosphite (0.405 ml, 0.31 mmol) in dioxane (5 ml) was degassed at reflux under nitrogen for 1 hr. To this refluxing solution was added a solution of dried benzoyl peroxide (126 mg, 0.05 mmol) in dioxane (3.5 ml) over 10 hr *via* syringe pump. The mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (20% petrol/ether) afforded diethyl (2,5-anyhdro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hexos-1-yl)-phosphonate (**47**) as a colourless oil (26 mg, 7.5%).

Preparation with diethyl (phenylselenyl)phosphonate

To a refluxing solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-pent-1-enitol (**28**) (100 mg, 0.52 mmol) and diethyl (phenylselenyl)phosphonate (458 mg, 1.56 mmol) in degassed benzene (8 ml) was added a solution of AIBN (43 mg, 0.26 mmol) and tri-n-butyltin hydride (0.56 ml, 2.08 mmol) in degassed benzene (3.5 ml) over 5 hr *via* syringe pump. The black reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (80 %

ether/petrol) afforded diethyl (2,5-anyhdro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hexos-1-yl)-phosphonate (**47**) (61 mg, 35.5 %) as a colourless oil.

$[\alpha]_D$= -32.3° (c= 0.7, DCM)

^{1}H NMR (400 MHz, $CDCl_3$): 5.05 (1H, d, J= 6.1 Hz, H-3), 4.85 (1H, t, J= 5.0 Hz, H-4), 4.40 (1H, dd, J= 8.7, 24.4 Hz, H-2), 4.28 (4H, m, $OC\underline{H}_2CH_3$), 4.08 (1H, m, H-5a), 4.00 (1H, dt, J= 3.9, 10.4 Hz, H-5b), 1.48 (3H, s, $C\underline{Me}_2$), 1.40-1.31 (9H, m, $OCH_2C\underline{H}_3$ $C\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 119.0 (ddd, J= 208, 267, 269 Hz, C-1), 113.1 ($\underline{C}Me_2$), 84.3 (ddd, J= 13, 20, 27 Hz, C-2), 81.1, 80.7, 74.8, 64.8 (m, $O\underline{C}H_2CH_3$), 26.5 ($C\underline{Me}_2$), 24.9 ($C\underline{Me}_2$), 16.43 ($OCH_2\underline{C}H_3$), 16.39 ($OCH_2\underline{C}H_3$).

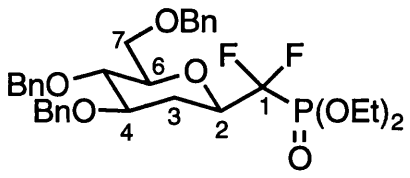
^{19}F NMR (376 MHz, $CDCl_3$): -114.9 (ddd, J= 8, 98, 315 Hz), -121.6 (ddd, J= 24, 100, 315 Hz).

IR (DCM): ν_{max}= 2987, 1735, 1382, 1375, 1266, 1211, 1161, 1109, 1028, 738 cm^{-1}.

m/z (FAB): 331 $[M+H]^+$, 315 $[M-Me]^+$, 273, 217, 43.

Accurate Mass (FAB): Observed $[M+H]^+$: 331.1125; $C_{12}H_{22}F_2O_6P$ requires: 331.1122.

Preparation of diethyl (2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,1-difluoro-D-*glycero*-D-*galacto*-heptos-1-yl)-phosphonate (52).



52

A solution 2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,1-difluoro-D-*arabino*-hept-1-enitol (**30**) (79 mg, 0.17 mmol) and diethyl phosphite (65 µl, 0.51 mmol) in octane (4 ml) was degassed at reflux under nitrogen for 1hr. To this refluxing solution

was added a solution of di-*tert*-butyl peroxide (15 µl, 0.08 mmol) in degassed octane (3 ml) over 10hr *via* syringe pump. TLC showed that the reaction had not gone to completion. Diethyl phosphite (0.1 ml, 0.85 mmol) was added and another solution of di-*tert*-butyl peroxide (15 µl, 0.08 mmol) in degassed octane (3ml) was added over 10 hr *via* syringe pump. The mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (10% petrol/ether) afforded diethyl (2,6-anhydro-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,1-difluoro-D-*glycero*-D-*galacto*-heptos-1-yl)-phosphonate (**52**) (9 mg, 9%) as a colourless oil.

^{1}H NMR (400 MHz, C_6D_6): 7.30-7.00 (15H, m, Ph), 5.00-4.30 (6H, m, OC$\underline{H}_2$Ph), 4.30-4.08 (4H, m, OC$\underline{H}_2$CH$_3$), 3.93 (1H, m, H-2), 3.62 (2H, m, H-7a H-7b), 3.57 (1H, t, J= 9.5 Hz, H-5), 3.39 (2H, m, H-4 H-6), 2.30 (1H, m, H-3eq), 2.07 (1H, q, J= 12.3 Hz, H-3ax), 1.04 (6H, m, OCH$_2$C$\underline{H}_3$).

^{13}C NMR (100 MHz, C_6D_6): 139.0 (dd, J= 24, 35 Hz, C-2), 128.9-127.0 (m, Ph), 80.4, 80.0, 78.1, 75.0, 73.3, 71.0, 69.6, 64.4 (dd, J= 6, 14 Hz, O$\underline{C}$H$_2$CH$_3$), 30.0 (m, C-3), 16.4 (OCH$_2\underline{C}$H$_3$).

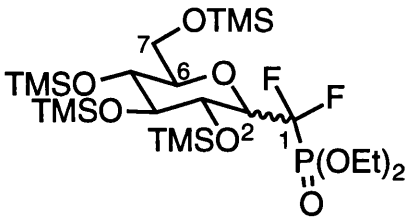
^{19}F NMR (376 MHz, $CDCl_3$): -116.8 (ddd, J= 7, 100, 310 Hz), -124.7 (ddd, J= 16, 99, 310 Hz).

IR (neat): ν_{max}= 2931, 1726, 1454, 1265, 1101, 1027, 910, 734 cm^{-1}.

m/z (FAB): 605 $[M+H]^+$, 299, 181, 91.

Accurate Mass (FAB): Observed $[M+H]^+$ 605.2491; $C_{32}H_{40}F_2O_7P$ requires: 605.2480.

Preparation of diethyl (2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-heptos-1-yl)-phosphonate and diethyl (2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*ido*-heptos-1-yl)-phosphonate as a mixture (49).



49

A solution of 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol **(29)** (200 mg, 0.39 mmol) and diethyl phosphite (0.153 ml, 1.17 mmol) in octane (6 ml) was degassed at reflux under nitrogen for 1hr. To this refluxing solution was added a solution of di-*tert*-butyl peroxide in degassed octane (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr, concentrated *in vacuo* and chromatography (ether) afforded a 7:1 mixture of diethyl (2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-heptos-1-yl)-phosphonate and diethyl (2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*ido*-heptos-1-yl)-phosphonate **(49)** (46.1 mg, 18%) as a yellow oil.

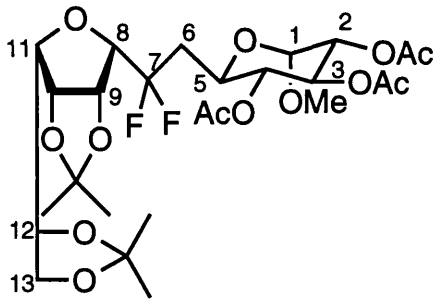
^{1}H NMR (400 MHz, $CDCl_3$) major isomer (β): 4.25 (4H, m, $OC\underline{H}_2CH_3$), 3.85 (1H, dd, J= 5.5, 15.8 Hz, H-2), 3.75 (2H, m, H-7b H-3), 3.54 (1H, dd, J= 8.4, 11.3 Hz, H-7a), 3.49 (1H, t, J= 7.8 Hz, H-4), 3.40 (1H, td, J= 2.8, 8.6 Hz, H-6), 3.27 (1H, t, J= 8.7 Hz, H-5), 1.35 (6H, t, J= 7.3 Hz, $OCH_2C\underline{H}_3$), 0.20-0.07 (36H, m, TMS).

^{19}F NMR (376 MHz, $CDCl_3$): major isomer (β): -112.0 (dd, J= 94, 308 Hz), -127.0 (ddd, J= 24, 115, 308 Hz); minor isomer (α): -111.0 (dd, J= 97, 308 Hz), -126.5 (ddd, J= 22, 113, 308 Hz).

IR (neat) ν_{max}= 3054, 2995, 2966, 1420, 1265, 1104, 1027, 871, 846, 741, 704 cm^{-1}.

m/z (FAB): 639 $[M+H]^+$, 567, 217, 73 $[TMS]^+$.

Preparation of methyl 2,3,4-tri-*O*-acetyl-8,11-anhydro-6,7-dideoxy-7,7-difluoro-9,10-12,13-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-α-D-*gluco*-tridecopyranoside (76).



76

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.68 mmol) and methyl-2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**75**) (880 mg, 2.04 mmol) in benzene (7 ml) was degassed at reflux under nitrogen for 0.5 hr. To the refluxing solution was added a degassed solution of AIBN (56 mg, 0.34 mmol) and tri-n-butyltin hydride (0.663 ml, 2.48 mmol) in benzene (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 3 hr and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel. The organic phase was separated, washed with saturated potassium fluoride (3x20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (25% petrol/ether) afforded methyl 2,3,4-tri-*O*-acetyl-8,11-anhydro-6,7-dideoxy-7,7-difluoro-9,10-12,13-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-α-D-*gluco*-tridecopyranoside (**76**) (162 mg, 40%) as white crystals (mp. 68°C, ether-petrol).

$[\alpha]_D$= +72.7° (c= 0.22, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): 5.46 (1H, dd, J= 9.1, 10.1 Hz, H-3), 4.88 (3H, m, H-1 H-2 H-4), 4.80 (1H, dd, J= 3.7, 6.0 Hz, H-9), 4.65 (1H, dd, J= 3.9, 5.8 Hz, H-10), 4.36

(1H, q, J= 7.5 Hz, H-5), 4.24 (2H, m, H-13a H-12), 3.80 (1H, dt, J= 3.6, 14.6 Hz, H-8), 3.71 (1H, dd, J= 7.7, 8.5 Hz, H-13b), 3.61 (1H, dd, J= 4.0, 7.9 Hz, H-11), 3.42 (3H, s, OMe), 2.55-2.22 (2H, m, H-6) 2.07 (3H, s, OAc), 2.05 (3H, s, OAc), 2.00 (3H, s, OAc), 1.46 (3H, s, Me), 1.45 (3H, s, Me), 1.39 (3H, s, Me), 1.28 (3H, s, Me).

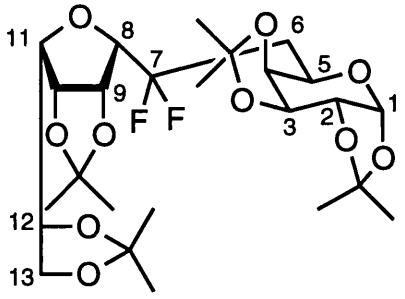
^{19}F NMR (376 MHz, $CDCl_3$): -96.2 (dm, J= 262 Hz), -102.8 (ddd, J= 11, 29, 262 Hz).

IR (DCM): ν_{max}= 2989, 2940, 1750, 1382, 1972, 1266, 1248, 1225, 1163, 1122, 1109, 1047 cm^{-1}.

m/z (FAB): 595 $[M-H]^+$, 581 $[M-Me]^+$, 565 $[M-OMe]^+$, 539 $[M-Me-CMe_2]^+$, 345, 100 , 84, 57, 41.

Accurate Mass (FAB): Observed $[M-Me]^+$: 581.2037; $C_{25}H_{35}O_{13}F_2$ requires: 581.2045.

Preparation of 8,11-anhydro-6,7-dideoxy-7,7-difluoro-1,2;3,4;9,10;12,13-tetra-*O*-isopropylidene-D-*glycero*-L-*galacto*-α-D-*galacto*-tridecopyranose (77).



77

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.68 mmol) and 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**74**) (760 mg, 2.04 mmol) in benzene (7 ml) was degassed at reflux under nitrogen for 0.5 hr. To the refluxing solution was added a degassed solution of AIBN (56 mg, 0.34 mmol) and tri-n-butyltin hydride (0.663 ml, 2.482 mmol) in benzene (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 3 hr and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated

in vacuo. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel. The organic phase was separated, washed with saturated potassium fluoride (3x20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (60% petrol/ethyl acetate) afforded 8,11-anhydro-6,7-dideoxy-7,7-difluoro-1,2;3,4;9,10;12,13-tetra-*O*-isopropylidene-D-*glycero*-L-*galacto*-α-D-*galacto*-tridecopyranose (**77**) (70 mg, 21%) as white crystals (mp. 158 °C, ethanol).

$[\alpha]_D$= -43.8° (c= 0.14, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): 5.46 (1H, d, J= 5.0 Hz, H-1), 4.81 (1H, dd, J= 3.7, 6.1 Hz, H-9), 4.59 (2H, m, H-2 H-10), 4.39 (1H, q, J= 6.0 Hz, H-5), 4.26 (1H, dd, J= 2.5, 5.0 Hz, H-2), 4.18 (1H, dd, J= 6.7, 8.4 Hz, H-13a), 4.10 (2H, m, H-4 H-12), 3.86 (1H, dt, J= 4.2, 15.5 Hz, H-8), 3.68 (1H, t, J= 7.7 Hz, H-13b), 3.60 (1H, dd, J= 3.9, 7.8 Hz, H-11), 2.55-2.22 (2H, m, H-6) , 1.50 (3H, s, Me), 1.43 (3H, s, Me), 1.42 (6H, s, Me), 1.37 (3H, s, Me), 1.31 (3H, s, Me), 1.29 (3H, s, Me), 1.24 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 121.0 (t, J= 241 Hz, C-7), 113.3 ($\underline{C}Me_2$), 109.8 ($\underline{C}Me_2$), 109.2 ($\underline{C}Me_2$), 108.7 ($\underline{C}Me_2$), 96.4 (C-1), 83.6, 82.0 (t, J= 26 Hz, C-8), 80.5, 80.0, 75.4, 73.4, 70.8, 70.1, 65.9, 63.4, 35.3 (t, J= 23 Hz, C-6), 26.6 ($C\underline{Me}_2$), 26.0 ($C\underline{Me}_2$), 25.9 ($C\underline{Me}_2$), 25.5 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 24.9 ($C\underline{Me}_2$), 24.5 ($C\underline{Me}_2$), 24.4 ($C\underline{Me}_2$).

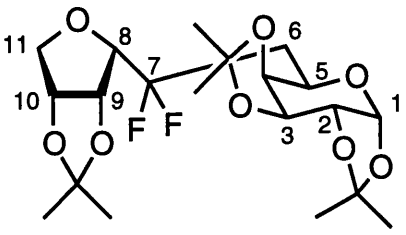
^{19}F NMR (376 MHz, $CDCl_3$): -97.0 (d, J= 258 Hz), -101.5 (dt, J= 18, 258 Hz).

IR (DCM):ν_{max}= 2976, 2934, 2884, 1444, 1382, 1350, 1121, 1075, 739 cm^{-1}.

m/z (FAB): 535 $[M-H]^+$, 521 $[M-Me]^+$, 479, 113, 101, 85, 59, 43.

Found: C 55.91, H 7.14 %; $C_{25}H_{38}O_{10}F_2$ requires C 55.96, H 7.11 %.

Preparation of 8,11-anhydro-6,7-dideoxy-7,7-difluoro-1,2;3,4;9,10-tri-*O*-isopropylidene-D-*arabino*-α-D-*galacto*-undecopyranose (79).



79

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (**28**) (165 mg, 0.85 mmol) and 6-deoxy-6-iodo-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**74**) (950 mg, 2.55 mmol) in benzene (7 ml) was degassed at reflux under nitrogen for 0.5 hr. To the refluxing solution was added a solution of AIBN (70 mg, 0.42 mmol) and tri-n-butyltin hydride (0.663 ml, 3.1 mmol) in degassed benzene (3.5 ml) over 10 hr *via* syringe pump. The reaction mixture was refluxed for 3 hr and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel. The organic phase was separated, washed with saturated potassium fluoride (3x20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (50% petrol/ether) afforded 8,11-anhydro-6,7-dideoxy-7,7-difluoro-1,2;3,4;9,10-tri-*O*-isopropylidene-D-*arabino*-α-D-*galacto*-undecopyranose (**79**) (51 mg, 13%) as white crystals (mp. 93-97 °C, ethanol).

$[\alpha]_D$= -62.8° (c= 0.18, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): 5.46 (1H, d, J= 5.0 Hz, H-1), 4.81 (2H, m, H-9 H-10), 4.58 (1H, dd, J= 2.5, 7.5 Hz, H-3) , 4.26 (1H, dd, J= 2.5, 5.0 Hz, H-2), 4.12 (3H, m, H-4 H-5 H-11a), 3.75 (1H, dt, J= 5.0, 14.8 Hz, H-8), 3.53 (1H, dd, J= 3.9, 10.4 Hz, H-11b), 2.65-2.22 (2H, m, H-6), 1.50 (3H, s, Me), 1.46 (3H, s, Me), 1.42 (3H, s, Me), 1.31 (3H, s, Me), 1.29 (3H, s, Me), 1.28 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 121.5 (dd, J= 241, 247 Hz, C-7), 112.8 ($\underline{C}Me_2$), 109.3 ($\underline{C}Me_2$), 108.8 ($\underline{C}Me_2$), 96.4 (C-1), 82.5 (dd, J= 24, 29 Hz, C-8), 80.6, 79.7, 73.5, 72.7, 70.7, 70.2, 62.8, 35.6 (t, J= 23.2 Hz, C-6), 26.0 ($C\underline{Me_2}$), 25.9 ($C\underline{Me_2}$), 25.7 ($C\underline{Me_2}$), 25.0 ($C\underline{Me_2}$), 24.7 ($C\underline{Me_2}$), 24.5 ($C\underline{Me_2}$).

^{19}F NMR (376 MHz, $CDCl_3$): -98.0 (dq, J= 17, 256 Hz), -101.5 (dtd, J= 6, 21, 256 Hz).

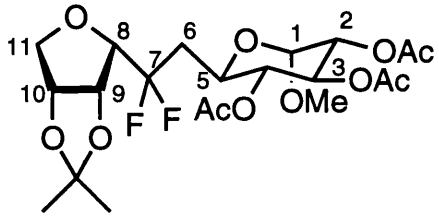
IR (DCM):ν_{max}= 2989, 2938, 1379, 1287, 1212, 1166, 1120, 1100, 1068, 994, 913, 862, 744, 703 cm^{-1}.

m/z (FAB) : 437 $[M+H]^+$, 421 $[M-Me]^+$, 379, 113, 85, 59, 43.

Found: C 54.61, H 6.90 %; $C_{20}H_{30}O_8F_2$: requires C 55.04, H 6.93 %.

Accurate Mass (FAB): Observed $[M+H]^+$: 437.1982; $C_{20}H_{31}O_8F_2$ requires: 437.1987.

Preparation of methyl 8,11-anhydro-2,3,4-tri-*O*-acetyl-6,7-dideoxy-7,7-difluoro-9,10-*O*-isopropylidene-D-*arabino*-α-D-*gluco*-undecopyranoside (78).



78

A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (**28**) (200 mg, 1.04 mmol) and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**75**) (1.34 g, 3.12 mmol) in benzene (10 ml) was degassed at reflux under nitrogen for 0.5 hr. To the refluxing solution was added a solution of AIBN (85 mg, 0.52 mmol) and tri-n-butyltin hydride (1.02 ml, 3.8 mmol) in degassed benzene (4 ml) over 12 hr *via* syringe pump. The reaction mixture was refluxed for 2 hr and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel.

The organic phase was separated, washed with saturated potassium fluoride (3x 20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (30% petrol/ether) afforded methyl 8,11-anhydro-2,3,4-tri-*O*-acetyl-6,7-dideoxy-7,7-difluoro-9,10-*O*-isopropylidene-D-*arabino*-α-D-*gluco*-undecopyranoside (**78**) (119 mg, 23%) as white crystals (mp. 55 °C, ether-petrol).

$[\alpha]_D$= +71.42° (c= 0.7, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): 5.42 (1H, t, J= 10.2 Hz, H-3), 4.89 (1H, d, J= 3.6 Hz, H-1), 4.85-4.70 (4H, m, H-2 H-4 H-9 H-10), 4.22 (1H, t, J= 9.8 Hz, H-5), 4.10 (1H, d, J= 10.7 Hz, H-11a), 3.67 (1H, dt, J= 3.6, 14.6 Hz, H-8), 3.53 (1H, dd, J= 3.6, 10.8 Hz, H-11b), 3.40 (3H, s, OMe), 2.65-2.25 (2H, m, H-6) , 2.04 (3H, s, OAc), 2.00 (3H, s, OAc), 1.97 (3H, s, OAc), 1.45 (3H, s, Me), 1.28 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 170.2 (OAc), 170.0 (OAc), 169.9 (OAc), 121.3 (t, J= 243 Hz, C-7), 113 ($\underline{C}Me_2$), 96.4 (C-1), 82.9 (dd, J= 26, 34 Hz, C-8), 80.4, 79.4, 72.9, 71.8, 70.8, 70.0, 63.5, 55.4 (OMe), 35.3 (t, J= 22 Hz, C-6), 25.6 ($\underline{C}Me_2$), 24.4 ($\underline{C}Me_2$), 20.7 (OAc), 20.6 (OAc).

^{19}F NMR (376 MHz, $CDCl_3$): -96.0 (dm, J= 265 Hz), -103.0 (ddd, J= 12, 28, 265 Hz).

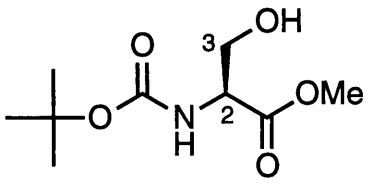
IR (DCM):ν_{max}= 2989, 2941, 2753, 1372, 1266, 1240, 1225, 1165, 1121, 1074, 1047, 993, 738, 704 cm^{-1}.

m/z (FAB) : 495 $[M-H]^+$, 481 $[M-Me]^+$, 465, 303, 245, 137.

Found: C 51.48, H 6.23 %; $C_{21}H_{30}O_{11}F_2$: requires C 50.81, H 6.09 %.

Accurate Mass (FAB): Observed $[M-H]^+$: 495.1685; $C_{21}H_{29}O_{11}F_2$ requires: 495.1678.

Preparation of methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropionate[106,107] (92).



92

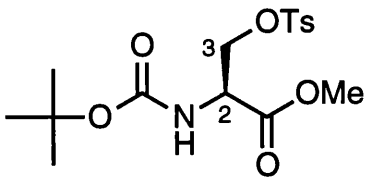
Acetyl chloride (7.0 ml, 96.6 mmol) was added dropwise over 10 min to methanol (40 ml) cooled in ice. The solution was stirred for 5 min, then (L)-serine (**91**) (3.3 g, 32.15 mmol) was added, and the mixture was refluxed for 2 hr. Cooling and removal of the solvent *in vacuo* gave the crude ester hydrochloride, which was suspended in THF (100 ml). Triethylamine (9.64 ml, 69.1 mmol) was added, and the resulting suspension was cooled to 0 °C. Di-*tert*-butyl dicarbonate (7.52 ml, 230 mmol) was added dropwise as a solution in THF (50 ml) over 30 min. The mixture was allowed to warm up to room temperature, stirred for 6 hr and warmed at 50 °C for 2 hr. The solvent was removed *in vacuo* and the residue partitioned between ether (100 ml) and water (100 ml). The aqueous phase was extracted with ether (3x100 ml) and the combined fractions washed with 3% hydrochloric acid (50 ml), 5% sodium hydrogen carbonate (50 ml) and brine. Drying over magnesium sulphate and concentration *in vacuo* gave methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropionate (**92**) (6.0 g, 100%) as a colourless oil.

^{1}H NMR (270 MHz, $CDCl_3$): 5.27 (1H, broad s, NH), 4.35 (1H, broad s, H-2), 3.90 (2H, m, H-3), 3.77 (3H, s, OMe), 2.77 (1H, broad s, OH), 1.23 (9H, s, *t*-Bu).

IR (neat): ν_{max}= 3408 (OH), 2978, 1747 (C=O), 1720 (C=O), 1513, 1368, 1165, 1064, 850, 780 cm^{-1}.

m/z (EI): 189 $[M\text{-}CH_2OH]^+$, 174, 160 $[M\text{-}CO_2Me]^+$, 146 $[M\text{-}t\text{-}BuO]^+$, 86, 57 $[t\text{-}Bu]^+$.

Preparation of methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-*p*-toluenesulphonyl propionate[106,107] (90).



(90)

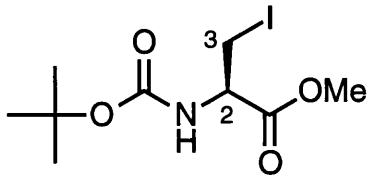
Methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropionate **(92)** (1.0 g, 4.5 mmol) and toluenesulphonyl chloride (921 mg, 4.5 mmol) were cooled to -20 °C, and pyridine (7 ml) was added under a vigorous flow of nitrogen. The mixture was stirred at -10°C for 24 hr. Water (50 ml) was added and the aqueous mixture was extracted with ethyl acetate (3x50 ml). The combined extracts were washed with aqueous copper sulphate until no further colour change occurred, water (50 ml), dried over magnesium sulphate and concentrated *in vacuo* to afford methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-p-toluenesulphonylpropionate **(90)** (1.44 g, 85%) as a white solid which was used without further purification.

^{1}H NMR (270 MHz, $CDCl_3$): 7.75 (2H, d, J= 8.3 Hz, Tol), 7.30 (2H, d, J= 8.5 Hz, Tol), 5.30 (1H, broad d, J= 9.5 Hz, NH), 4.50 (1H, m, H-2), 4.28 (1H, dd, J= 2.9, 10.0 Hz, H-3a), 4.32 (1H, dd, J= 2.9, 10.0 Hz, H-3b), 3.76 (3H, s, OMe), 2.43 (3H, s, Tol), 1.43 (9H, s, *t*-Bu).

IR (DCM): ν_{max}= 3380, 2978, 1753 (C=O), 1712 (C=O), 1598, 1500, 1438, 1366, 1250, 1214, 1178, 1097, 1059, 996, 930, 893, 816, 739, 665 cm^{-1}.

m/z (EI): 314 $[M\text{-}CO_2Me]^+$, 300 $[M\text{-}Ot\text{-}Bu]^+$, 258 $[M\text{-}NBoc]^+$, 214, 155, 57 $[t\text{-}Bu]^+$.

Preparation of methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-iodopropionate[106] (89).



89

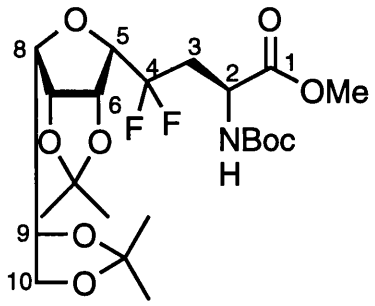
Methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-*p*-toluenesulphonylpropionate **(90)** (5.37 g, 14.3 mmol) was dissolved in acetone (40 ml) and sodium iodide (3.23 g, 21.4 mmol) in acetone (40 ml) was added in the dark. The resulting yellow solution was stirred in the dark, at room temperature for 24 hr, then filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform (60 ml), washed with water (3x30 ml), aqueous sodium thiosulphate (30 ml), dried over magnesium sulphate and concentrated *in vacuo*. The residue was crystallized from petroleum ether to afford methyl-2-S-[(*tert*-butoxycarbonyl)amino]-3-iodopropionate **(89)** (2.7 g, 57%) as white crystals (mp. 46°C, lit.[106] 51°C).

^{1}H NMR (270 MHz, $CDCl_3$): 5.35 (1H, broad s, NH), 4.50 (1H, m, H-2), 3.80 (3H, s, OMe), 3.56 (2H, t, J= 3.2 Hz, H-3), 1.45 (9H, s, *t*-Bu).

IR (DCM): ν_{max}= 3425, 2981, 1749 (C=O), 1718 (C=O), 1500, 1368, 1455, 1439, 1393, 1347, 1298, 1266, 1212, 1164, 1121, 1066, 1003, 738, 704 cm^{-1}.

m/z (EI): 329 $[M]^+$, 270 $[M\text{-}CO_2Me]^+$, 256 $[M\text{-}Ot\text{-}Bu]^+$, 228 $[M\text{-}CO_2t\text{-}Bu]^+$, 57 $[t\text{-}Bu]^+$.

Preparation of methyl 5,8-anhydro-2,3,4-tri-deoxy-2-[(*tert*-butoxycarbonyl)-amino]-4,4-difluoro-6,7;9,10-di-*O*-isopropylidene-D-*gulo*-L-*galacto*-decanonate (93).



(93)

A solution of methyl 2-S-[(*tert*-butoxycarbonyl)amino]-3-iodopropionate **(89)** (676 mg, 2.04 mmol) and 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol **(26)** (200 mg, 0.68 mmol) in benzene (7 ml) was degassed at reflux for 0.5 hr. To this refluxing solution was added a solution of AIBN (50 mg, 0.34 mmol) and tri-n-butyltin hydride (0.672 ml, 2.48 mmol) in benzene (3.5 ml) over 12 hr *via* syringe pump. Carbon tetrachloride (0.5 ml) and iodine (30 mg, 0.12 mmol) were added, the mixture was stirred for 30 min at room temperature, concentrated *in vacuo* and taken up in ethyl acetate (15 ml). A saturated solution of potassium fluoride (50 ml) was added and the two phase mixture was vigorously stirred for 2 hr at room temperature. It was then filtered, separated and the organic phase was washed with saturated potassium fluoride (4x20 ml), aqueous sodium thiosulphate (20 ml), water (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (35% petrol/ether) afforded methyl 5,8-anhydro-2,3,4-tri-deoxy-2-[(*tert*-butoxycarbonyl)-amino]-4,4-difluoro-6,7;9,10-di-*O*-isopropylidene-D-*gulo*-L-*galacto*-decanonate **(93)** (50 mg, 14%) as white crystals (mp. 52-54°C).

^{1}H NMR (400 MHz, $CDCl_3$): 5.19 (1H, d, J= 8.1 Hz, NH), 4.78 (1H, dd, J= 6.0, 3.7 Hz, H-6), 4.62 (1H, dd, J= 5.6, 3.9 Hz, H-7), 4.56 (1H, m, H-2), 4.36 (1H, q, J= 7.2 Hz, H-9), 4.20 (dd, J= 6.7, 8.5 Hz, H-10a), 3.72 (4H, m, OMe H-5), 3.68 (1H, dd, J= 7.3, 8.5 Hz, H-10b), 3.60 (1H, dd, J= 4.2, 8.0 Hz, H-8), 2.82 (1H, m, H-3a), 2.58 (1H, m, H-3b),

1.44 (3H, s, C$\underline{Me}_2$), 1.42 (3H, s, C$\underline{Me}_2$), 1.41 (9H, s, C$\underline{Me}_3$), 1.40 (3H, s, C$\underline{Me}_2$), 1.37 (3H, s, C$\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 172.3 (C-1), 155.2 ($\underline{C}O_2t$-Bu), 122 (t, J= 244 Hz, C-4), 113 ($\underline{C}Me_2$), 110 ($\underline{C}Me_2$), 84.2, 82.3 (dd, J= 29, 36, C-5), 80.35, 79.9, 79.8, 75.4, 66.0, 52.5 (OMe), 48.6 (C-2), 35.4 (t, J= 21 Hz, C-3), 28.3 (C$\underline{Me}_3$), 26.7 (C$\underline{Me}_2$), 25.4 (C$\underline{Me}_2$), 25.3 (C$\underline{Me}_2$), 24.2 (C$\underline{Me}_2$).

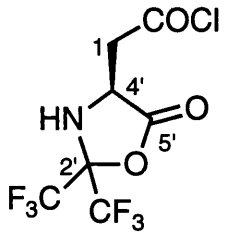
^{19}F NMR (376 MHz, $CDCl_3$): -92.3 (dddd, J= 7, 14, 33, 266 Hz), -105.6 (dd, J= 30, 266 Hz).

IR (DCM): ν_{max}= 3055, 2988, 1750 (C=O), 1717 (C=O), 1266, 738, 704 cm^{-1}.

m/z (EI): 480 $[M\text{-}Me]^+$, 406, 336 $[M\text{-}CO_2t\text{-}Bu]^+$, 230, 101 $[CO_2t\text{-}Bu]^+$, 57$[t\text{-}Bu]^+$.

Accurate Mass (FAB): Observed $[M+H]^+$: 496.2369; $C_{22}H_{36}NO_9F_2$ requires: 496.2358.

Preparation of [4'S] [2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-acetyl chloride [108,109] (97).



(97)

L-Aspartic acid **(94)** (5.0 g, 37.6 mmol) was suspended in dimethyl sulfoxide (15 ml) in a three neck flask equipped with a dry-ice condenser and a gas outlet connected to a water-ice bubbler. A flow of hexafluoroacetone was passed over the suspension. After a short induction period, the flow was set so that all the hexafluoroacetone was absorbed and no condensation was observed. The reaction mixture was stirred at 40°C for 30 min after which it had turned into a clear solution and hexafluoroacetone had started refluxing. The flow of hexafluoroactone was stopped and the mixture was stirred at room temperature for 2.5 hr. The solution was poured into ice-water (60 ml),

extracted with dichloromethane (4x30 ml). The combined organic extracts were washed with ice-water (6x20 ml), dried over magnesium sulphate and concentrated *in vacuo* to afford the crude acid (6.6 g) which was taken up in freshly distilled thionyl chloride (25 ml) and refluxed for 4.5 hr. The reaction mixture was concentrated *in vacuo* and distilled under reduced pressure to afford [4'S] [2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-acetyl chloride **(97)** (5.17 g, 45%) as a yellow oil (bp. 85°C/ 8 mm Hg).

$[\alpha]_D$= -14.5° (c= 1.15, $CHCl_3$, lit.[109] -21°).

^1H NMR (400 MHz, $CDCl_3$): 4.41 (1H, ddd, J= 2.4, 7.0, 9.6 Hz, H-4'), 3.54 (2H, dd, J= 2.5, 18.6 Hz, H-1a, NH), 3.24 (1H, dd, J= 9.8, 18.6 Hz, H-1b).

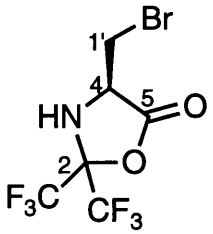
^{13}C NMR (100 MHz, $CDCl_3$): 172.1 (COCl), 168.5 (C-5'), 120.2 (2q, J= 288 Hz, CF_3), 88.4 (m, C-2'), 51.0 (C-4'), 50.0 (C-1).

^{19}F NMR (376 MHz, $CDCl_3$): -80.5 (q, J= 8 Hz), -81.7 (q, J= 8 Hz).

IR (neat): ν_{max}= 3375 (NH), 2933, 1835 (C=O), 1790 (C=O), 1397, 1328, 1243, 1115, 1018, 874, 720 cm^{-1}.

m/z (EI): 263 $[M-HCl]^+$, 235 $[M-HCOCl]^+$, 218, 191, 122, 68, 43.

Preparation of [4R] 2,2-bis-(trifluoromethyl)-4-bromomethyl-1,3-oxazolidin-5-one (96).



(96)

A suspension of the sodium salt of 2-mercaptopyridine-1-oxide (2.5 g, 17.7 mmol) in tetrahydrofuran (20 ml) was added to a solution of [4'S] [2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-acetyl chloride **(97)** (5.0 g, 16.1 mmol) in

THF (100 ml) at -15°C. The mixture was stirred in the dark at -15°C for 1 hr and concentrated *in vacuo*. The residue was dissolved in bromotrichloromethane (100 ml) and irradiated under nitrogen in a water bath for 50 min. The yellow solution was concentrated *in vacuo*, and chromatography (40% dichloromethane/petrol) afforded [4R] 2,2-bis-(trifluoromethyl)-4-bromomethyl-1,3-oxazolidin-5-one **(96)** (2.42 g, 48%) as a yellow oil (bp. 80°C, 8 mm Hg).

$[\alpha]_D$= -10.23° (c= 1.47, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.32 (1H, td, J= 3.4, 6.7 Hz, H-4), 3.72 (1H, dd, J= 3.4, 11.2 Hz, H-1'a), 3.62 (1H dd, J= 6.5, 11.2 Hz, H-1'b), 3.44 (1H, d, J= 7.8 Hz, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 167.8 (C-5), 120.2 (m, CF_3), 56.0 (C-4), 30.5 (C-1').

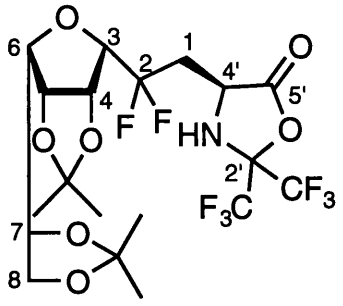
^{19}F NMR (376 MHz, $CDCl_3$): -80.0 (q, J= 8 Hz), -80.7 (q, J= 8 Hz).

IR (neat): ν_{max}= 3373 (NH), 2934, 1830 (C=O), 1420, 1232, 1108, 973, 748, 722 cm^{-1}.

m/z (EI): 317/315 $[M]^+$, 270/268, 248/246 $[M-CF_3]^+$, 222 $[M-CH_2Br]^+$, 220/218 $[M-COCF_3]^+$, 192, 138, 122, 111, 96, 83.

Accurate Mass (FAB): Observed $[M+H]^+$: 314.9336; $C_6H_4NO_2F_6{}^{79}Br$ requires: 314.9330.

Preparation of [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5;7,8-di-*O*-isopropylidene-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*glycero*-L-*galacto*-octose (99).



(99)

To a refluxing solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol **(26)** (100 mg, 0.34 mmol) and [4R] 2,2-bis-(trifluoromethyl)-4-bromomethyl-1,3-oxazolidin-5-one **(96)** (215 mg, 0.68 mmol) in degassed benzene (7 ml) was added a solution of AIBN (24 mg, 0.17 mmol) and tri-n-butyltin hydride (0.184 ml, 0.65 mmol) in degassed benzene (3.5 ml) over 36 hr *via* syringe pump. The mixture was concentrated *in vacuo*, taken up in acetonitrile (20 ml) and washed with petrol (6x10 ml). The acetonitrile phase was concentrated *in vacuo* and chromatography (25%/40% ether/petrol/dichloromethane) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol **(26)** (26.0 mg, 26%) and [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5;7,8-di-*O*-isopropylidene-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*glycero*-L-*galacto*-octose **(99)** (54.3 mg, 30%) as a colourless oil.

$[\alpha]_D$= -5.9° (c= 2.35, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.85 (1H, dd, J= 3.5, 5.9 Hz, H-4), 4.68 (1H, t, J= 4.3 Hz, H-5), 4.40 (1H, q, J= 7.2 Hz, H-7), 4.31 (1H, m, H-4'), 4.22 (1H, dd, J= 6.7, 8.7 Hz, H-8a), 3.91 (1H, dd, J= 3.6, 14.2 Hz, H-3), 3.79 (1H, d, J= 5.9 Hz, NH), 3.74 (1H, dd, J= 6.6, 8.7 Hz, H-8b), 3.64 (1H, dd, J= 4.2, 8.2 Hz, H-6), 2.88 (1H, m, H-1a), 2.66 (1H, m, H-1b), 1.50 (3H, s, Me), 1.46 (3H, s, Me), 1.37 (3H, s, Me), 1.30 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 170.6 (C-5'), 120.2 (m, C-2 CF_3), 113.8 ($\underline{C}Me_2$), 110.2 ($\underline{C}Me_2$), 84.4, 81.0 (dd, J= 30, 38 Hz, C-3), 80.1, 79.9, 74.7, 65.9, 50.0 (m, C-4'), 38.9 (t, J= 23 Hz, C-1), 26.7 (Me), 25.1 (Me), 24.9 (Me), 24.0 (Me).

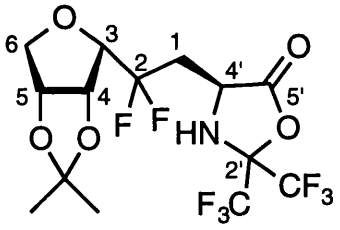
^{19}F NMR (376 MHz, $CDCl_3$): -80.4 (q, J= 8 Hz, CF_3), -81.2 (q, J= 9 Hz, CF_3), -89.3 (dq, J= 21, 271 Hz, F-2a), -102.1 (dt, J= 11, 270 Hz, F-2b).

IR (neat): ν_{max}= 3373 (NH), 2991, 2941, 1833 (C=O), 1384, 1232, 1165, 1125, 1072, 972, 913, 845, 737, 721 cm^{-1}.

m/z (FAB): 528 $[M-H]^+$, 514 $[M-Me]^+$, 472, 314, 101, 59, 43.

Accurate Mass (FAB): Observed $[M+Na]^+$: 552.1240; $C_{19}H_{23}NO_7F_8Na$ requires: 552.1244 .

Preparation of [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*arabino*-hexose (100).



100

To a refluxing solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol **(28)** (70 mg, 0.36 mmol) and [4R] 2,2-bis-(trifluoromethyl)-4-bromomethyl-1,3-oxazolidin-5-one **(96)** (403 mg, 1.27 mmol) in degassed benzene (8 ml) was added a solution of AIBN (35 mg, 0.18 mmol) and tri-n-butyltin hydride (0.343 ml, 1.27 mmol) in degassed benzene (3.5 ml) over 48 hr *via* syringe pump. The mixture was concentrated *in vacuo*, taken up in ethyl acetate (30 ml) and stirred with a saturated solution of potassium fluoride (20 ml) for 2 hr. The mixture was filtered, separated and the organic phase was washed with saturated potassium fluoride (3x20 ml), water (20 ml) dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (10%/40% ether/petrol/dichloromethane)

afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (**28**) (14 mg, 20%) and [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*arabino*-hexose (**100**) (29 mg, 19%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.82 (2H, m, H-4, H-5), 4.32 (1H, dd, J= 4.8, 10.1 Hz, H-4'), 4.15 (1H, dd, J= 1.8, 10.8 Hz, H-6a), 3.75 (1H, dm, J= 15.1 Hz, H-3), 3.61 (1H, dd, J= 3.6, 10.9 Hz, H-6b), 3.52 (1H, d, J= 5.5 Hz, NH), 2.95 (1H, m, H-1a), 2.55 (1H, m, H-1b), 1.51 (3H, s, Me), 1.33 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (C-5'), 120.2 (m, C-2 CF_3), 113.2 ($\underline{C}Me_2$), 82.3 (dd, J= 27, 37 Hz, C-3), 80.2, 79.4, 73.4, 50.0 (m, C-4'), 38.0 (t, J= 22 Hz, C-1), 25.3 (Me), 24.0 (Me).

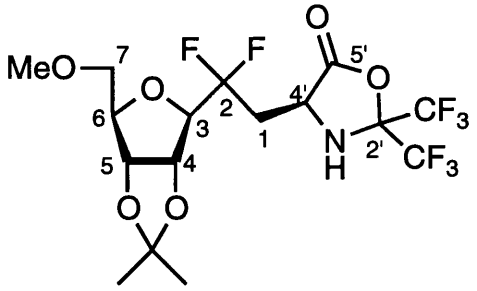
^{19}F NMR (376 MHz, $CDCl_3$): -80.8 (q, J= 8 Hz, CF_3), -81.1 (q, J= 8 Hz, CF_3), -90.5 (dquin, J= 15, 209 Hz, F-2a), -102.1 (ddd, J= 10, 23, 208 Hz, F-2b).

IR (neat): ν_{max}= 3332 (NH), 2942,1832 (C=O), 1378, 1231, 1195, 1121, 970, 720 cm^{-1}.

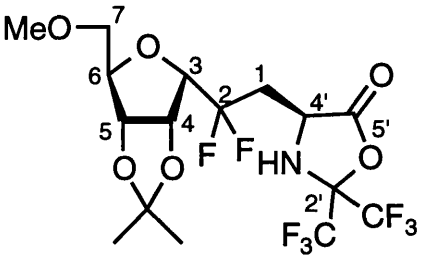
m/z (FAB): 452 $[M+Na]^+$, 430 $[M+H]^+$, 414 $[M-Me]^+$, 113, 58.

Accurate Mass (FAB): Observed $[M+Na]^+$: 452.0731; $C_{14}H_{15}NO_5F_8Na$ requires: 452.0720.

Preparation of [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*allo*-heptose (102) and [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*altro*-heptose (101).



102



101

To a refluxing solution of 2,5-anhydro-6-*O*-methyl-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (**27**) (40 mg, 0.17 mmol) and [4R] 2,2-bis-(trifluoromethyl)-4-bromomethyl-1,3-oxazolidin-5-one (**96**) (187 mg, 0.59 mmol) in degassed benzene (4 ml) was added a solution of AIBN (14 mg, 0.08 mmol) and tri-n-butyltin hydride (0.168 ml, 0.59 mmol) in degassed benzene (2.5 ml) over 16 hr *via* syringe pump. The mixture was concentrated *in vacuo*, taken up in ethyl acetate (8 ml) and stirred with a saturated solution of potassium fluoride (5 ml) for 2 hr. The mixture was filtered, separated, and the organic phase was washed with saturated potassium fluoride (3x20 ml), water (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (25% ether/petrol) afforded in order of elution [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*allo*-heptose (**102**) (15 mg, 19%) as a colourless oil and [4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*altro*-heptose (**101**) (19 mg, 22%) as white crystals (m.p. 78-82°C).

[4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*allo*-heptose (102):

^{1}H NMR (400 MHz, $CDCl_3$): 4.90 (1H, dd, J= 3.1, 6.6 Hz, H-4), 4.52 (1H, dd, J= 4.6, 6.2 Hz, H-5), 4.25 (3H, m, H-3, H-6, H-4'), 3.98 (1H, d, J= 6.0 Hz, NH), 3.50 (1H, dd, J= 4.3, 10.5 Hz, H-7a), 3.46 (1H, dd, J= 7.0, 10.4 Hz, H-7b), 3.37 (3H, s, OMe), 2.70 (1H, m, H-1a), 2.28 (1H, m, H-1b), 1.56 (3H, s, Me), 1.37 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 170.2 (C-5'), 120.2 (m, C-2 CF_3), 114.8 ($\underline{C}Me_2$), 84.9 (dd, J= 25, 31 Hz, C-3), 84.6, 81.3, 80.1 (d, J= 3 Hz, C-4), 72.6, 59.2 (OMe), 50.0 (m, C-4'), 38.0 (t, J= 25 Hz, C-1), 27.3 (Me), 25.3 (Me).

^{19}F NMR (376 MHz, $CDCl_3$): -80.7 (q, J= 8 Hz, CF_3), -81.5 (q, J= 9 Hz, CF_3), -103.4 (dt, J= 13, 261 Hz, F-2a), -113.5 (dq, J= 20, 262 Hz, F-2b).

IR (neat): ν_{max}= 3358 (NH), 2992, 2940, 1834 (C=O), 1376, 1233, 1113, 971, 720 cm^{-1}.

m/z (FAB): 496 $[M+Na]^+$, 474 $[M+H]^+$, 458 $[M-Me]^+$, 125, 113, 99, 91.

Accurate Mass (FAB): Observed $[M+Na]^+$: 496.0981; $C_{16}H_{19}NO_6F_8Na$ requires: 496.0982 .

[4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5-*O*-isopropylidene-7-*O*-methyl-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*altro*-heptose (101):

^{1}H NMR (400 MHz, $CDCl_3$): 4.85 (2H, d, J= 2.8 Hz, H-4, H-5), 4.39 (1H, dm, J= 14.0 Hz, H-3), 4.30 (1H, dd, J= 5.3, 10.0 Hz, H-4'), 4.27 (1H, m, H-6), 3.59 (1H, dd, J= 3.2, 10.0 Hz, H-7a), 3.52 (2H, dd, J= 3.0, 10.0 Hz, H-7b, NH), 3.34 (3H, s, OMe), 2.92 (1H, m, H-1a), 2.52 (1H, m, H-1b), 1.52 (3H, s, Me), 1.34 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 170.5 (C-5'), 120.2 (m, C-2 CF_3), 113.4 ($\underline{C}Me_2$), 83.8, 82.6, 82.5 (dd, J= 30, 35 Hz, C-3), 80.6 (d, J= 8 Hz, C-4), 74.5, 59.5 (OMe), 49.9 (m, C-4'), 37.7 (t, J= 23 Hz, C-1), 25.6 (Me), 24.1 (Me).

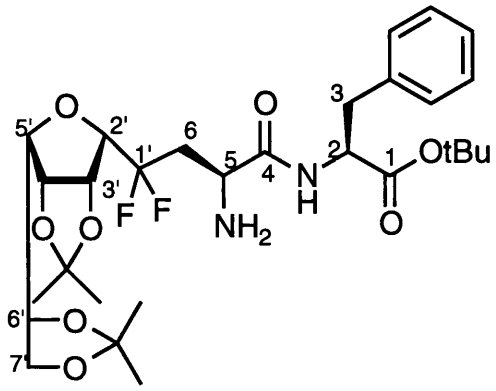
^{19}F NMR (376 MHz, $CDCl_3$): -80.8 (q, J= 8 Hz, CF_3), -81.1 (q, J= 8 Hz, CF_3), -92.3 (dqin, J= 11, 267 Hz, F-2a), -105.0 (ddd, J= 10, 24, 267 Hz, F-2b).

IR (neat): ν_{max}= 3371 (NH), 2991, 2943, 1831 (C=O), 1383, 1233, 1196, 1125, 1093, 971, 720 cm^{-1}.

m/z (FAB): 496 $[M+Na]^+$, 474 $[M+H]^+$, 458 $[M-Me]^+$, 125, 113, 99.

Accurate Mass (FAB): Observed $[M+Na]^+$: 496.0987; $C_{16}H_{19}NO_6F_8Na$ requires: 496.0982 .

Preparation of L-(2,5-dehydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptosyl)-alanyl-L-phenylalanine-*tert*-butylester (104).



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[4'S] 3,6-anhydro-1,2-dideoxy-2,2-difluoro-4,5;7,8-di-*O*-isopropylidene-1-[2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one-4-yl]-D-*glycero*-L-*galacto*-octose **(99)** (39 mg, 0.073 mmol) and L-phenylalanine-*t*-butyl ester **(103)** (21 mg, 0.096 mmol) were stirred in ether for 24h. The mixture was concentrated *in vacuo* and chromatography (5% ethanol/ether) afforded L-(2,5-dehydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptosyl)-alanyl-L-phenylalanine-*tert*-butylester (20 mg, 47%) as a colourless oil.

$[\alpha]_D$= +16.0° (c= 1.3, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (1H, d, J= 8.2 Hz, NH), 7.31-7.16 (5H, m, Ph), 4.80 (1H, dd, J= 3.9, 6.1 Hz, H-3'), 4.72 (1H, q, J= 6.3 Hz, H-2), 4.65 (1H, dd, J= 4.4, 5.8 Hz, H-4'), 4.41 (1H, q, J= 7.2 Hz, H-6'), 4.24 (1H, dd, J= 6.7, 8.5 Hz, H-7'a), 3.78 (2H, m, H-2', H-5), 3.72 (1H, dd, J= 7.3, 8.4 Hz, H-7'b), 3.61 (1H, dd, J= 4.0, 8.0 Hz, H-5'), 3.11 (1H, dd, J= 6.0, 13.7 Hz, H-3a), 3.04 (1H, dd, J= 6.4, 13.7 Hz, H-3b), 2.95 (1H, m,

H-6a), 2.11 (1H, m, H-6b), 1.67 (2H, s, NH_2), 1.47 (3H, s, Me), 1.46 (3H, s, Me), 1.41 (3H, s, Me), 1.40 (9H, s, *t*-Bu), 1.28 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$): 173.4 (C-1), 170.6 (C-4), 136.3 (Ph), 129.5 (Ph), 128.3 (Ph), 126.8 (Ph), 122.5 (t, J= 243 Hz, C-1'), 113.6 ($\underline{C}Me_2$), 110.0 ($\underline{C}Me_2$), 84.2, 82.6 (dd, J= 29, 35 Hz, C-2'), 82.0 ($\underline{C}Me_3$), 80.3, 79.8 (d, J= 7 Hz, C-3'), 75.3, 65.9, 53.2 (C-2), 50.0 (C-5), 38.2 (t, J= 21 Hz, C-6, C-3), 27.9 ($C\underline{Me}_3$), 26.7 ($C\underline{Me}_2$), 25.5 ($C\underline{Me}_2$), 25.4 ($C\underline{Me}_2$), 24.2 ($C\underline{Me}_2$).

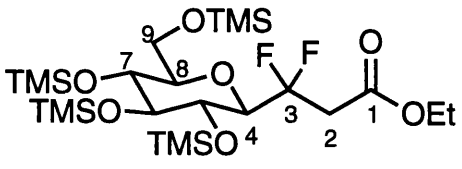
^{19}F NMR (376 MHz, $CDCl_3$): -91.2 (ddd, J= 14, 35, 261 Hz), -106.1 (dd, J= 29, 261 Hz).

IR (neat): ν_{max}= 3342 (NH), 2981, 2936, 1731 (C=O), 1673 (C=O), 1507, 1456, 1370, 1258, 1209, 1155, 1119, 1059, 976, 847, 140, 701 cm^{-1}.

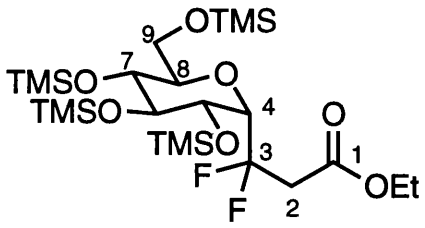
m/z (FAB): 585 $[M+H]^+$, 569 $[M-Me]^+$, 529, 166, 120, 57.

Accurate Mass (FAB): Observed $[M+H]^+$: 585.2998; $C_{29}H_{43}N_2O_8F_2$ requires: 585.2987.

Preparation of ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-nononate (53) and ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*ido*-nononate (54).



53



54

Ethyl bromoacetate (0.132 ml, 1.2 mmol) was added to a solution of 2,6-anhydro-1-deoxy-1,1-difluoro-tetra-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (**29**) (200 mg, 0.4 mmol) in degassed benzene (7 ml) and to this mixture at reflux was added a solution of AIBN (32.5 mg, 0.2 mmol) and tri-n-butyltin hydride (0.390 ml, 1.46 mmol) in

degassed benzene (3.5 ml) over 12 hr *via* syringe pump. The crude mixture was concentrated *in vacuo*, taken up in undistilled ether (25 ml) and diazabicyclo[5.4.0]undec-7-ene (0.3 ml, 2 mmol) was added precipitating a white solid. The mixture was titrated with iodine, filtered through a small silica column eluting with ether and concentrated *in vacuo*. Chromatography (10% ether/petrol) afforded a 10:3 mixture of ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-nononate **(53)** and ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl-D-*glycero*-D-*ido*-nononate) **(54)** (64 mg, 27%) as a colourless oil. HPLC (5% ethyl acetate/hexane) allowed separation of the two isomers.

Ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-nononate (53):

$[\alpha]_D$= +9.9° (c= 0.6, DCM).

^{1}H NMR (400 MHz, toluene-d8): 3.95 (1H, ddd, J= 4.7, 8.4, 21.1 Hz, H-4), 3.86 (1H, m, H-5), 3.83 (2H, q, J= 7.4 Hz, $OC\underline{H}_2CH_3$), 3.61 (2H, m, H-9a H-9b), 3.58 (1H, t, J= 8.6 Hz, H-7), 3.50 (1H, t, J= 8.6 Hz, H-6), 3.14 (2H, m, H-2a H-8), 2.8 (1H, td, J= 8.5, 15.1 Hz, H-2b), 0.87 (3H, t, J= 7.1 Hz, $OCH_2C\underline{H}_3$), 0.25-0.06 (36H, m, TMS).

^{13}C NMR (100 MHz, $CDCl_3$): 167.1 (C-1), 120.6 (t, J= 248 Hz, C-3), 81.5, 79.0, 77.8 (t, J= 25 Hz, C-4), 71.0, 70.9, 62.1, 60.9 ($O\underline{C}H_2CH_3$), 40.1 (t, J= 27 Hz, C-2), 14.2 ($OCH_2\underline{C}H_3$), 1.40 (TMS), 1.10 (TMS), 0.90 (TMS), 0.30 (TMS).

^{19}F NMR (376 MHz, $CDCl_3$): -101.5 (dt, J= 19, 257 Hz), -106.0 (ddt, J= 10, 20, 257 Hz).

Ethyl 4,8-anhydro-2,3-dideoxy-3,3-difluoro-5,6,7,9-tetra-*O*-(trimethylsilyl)-D-*glycero*-D-*ido*-nononate (54):

$[\alpha]_D$= +11.1° (c= 0.2, DCM).

^{1}H NMR (400 MHz, toluene-d8): 4.54 (1H, ddd, J= 5.3, 10.9, 20.2 Hz, H-4), 4.00 (1H, t, J= 6.1 Hz, H-7), 3.92 (1H, dd, J= 5.4, 7.3 Hz, H-5), 3.84 (2H, q, J= 7.2 Hz, $OC\underline{H}_2CH_3$), 3.66 (4H, m, H-6 H-8 H-9a H-9b), 3.15 (1H, m, H-2a), 2.95 (1H, td, J= 11.2, 16.6 Hz, H-2b), 0.90 (3H, t, J= 7.2 Hz, $OCH_2C\underline{H}_3$), 0.34-0.08 (36H, m, TMS).

^{19}F NMR (376 MHz, $CDCl_3$): - 95.4 (ddd, J= 20, 30, 260 Hz), -101.5 (m).

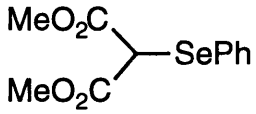
Mixture:

IR (DCM): ν_{max}= 2958, 1745, 1401, 1378, 1264, 1251, 1154, 1106, 1026, 966, 870, 844, 742 cm^{-1}.

m/z (FAB) : 589 $[M+H]^+$, 574 $[M+H-Me]^+$, 498 $[M-OTMS-H]^+$, 483, 463, 409, 393, 373, 353, 319, 305, 299, 275, 249, 217, 191, 147, 129.

Accurate Mass (FAB): Observed $[M+H]^+$: 589.2680; $C_{23}H_{51}O_7F_2Si_4$ requires: 589.2679.

Preparation of dimethyl 2-(phenylselenyl)propanedioate[137] (106).



106

Dimethyl malonate (10.9 g, 82.5 mmol) was added dropwise to a suspension of sodium hydride (2.0 g, 82.5 mmol) in THF (140 ml) at 0°C and the mixture was stirred for 0.5 hr. A solution of phenylselenyl bromide (2.38 g, 10.1 mmol) in THF (10 ml) was added dropwise at -25 °C and the resulting mixture was slowly allowed to warm to room temperature. After stirring overnight, the mixture was poured into ether (300 ml). The organic phase was washed with 2M HCl (70 ml), brine (70 ml), water (3x70 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (15 % ethyl acetate/petrol) afforded a mixture of dimethyl malonate and 2-(phenylselenyl)-propanedioate **(106)**, which was stirred under vacuum at 40°C for 24 hr to afford pure dimethyl 2-(phenylselenyl)propanedioate **(106)** (2.37 g, 82%) as a yellow oil.

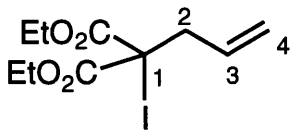
^1H NMR (400 MHz, $CDCl_3$): 7.67 (2H, m, Ph), 7.32 (3H, m, Ph), 4.50 (1H, s), 3.71 (6H, s, OMe)

^{13}C NMR (100 MHz, $CDCl_3$): 167.7 (C=O), 135.7 (Ph), 129.2 (Ph), 129.4 (Ph), 127.4 (Ph), 53.2 (OMe), 45.8.

IR (neat): ν_{max}= 2953, 1734 (C=O), 1578 (Ph), 1437, 1246 cm^{-1}.

m/z (EI): 288 $[M]^+$, 157, 77.

Preparation of diethyl allyliodomalonate[138] (109).



109

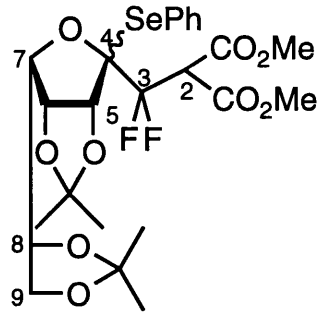
A solution of allylmalonate (2.85 g, 14.2 mmol) in THF (10 ml) was added to a suspension of oil-free sodium hydride (366 mg, 15.3 mmol) in THF (45 ml) and the yellow solution was stirred for 30 min at room temperature. The reaction vessel was covered with foil and a solution of N-iodo-succinimide (3.71 g, 15.7 mmol) in THF (20 ml) was added *via* cannula. A precipitate formed. The mixture was stirred for 2 hr at room temperature, filtered and concentrated *in vacuo*. The orange residue was filtered through a small column of silica, eluting with ether, to afford diethyl allyliodomalonate **(109)** (4.03 g, 87%) as an orange oil.

^1H NMR (400 MHz, $CDCl_3$): 5.71 (1H, m, H-3), 5.15 (2H, m, H-4), 4.20 (4H, q, J= 7.2 Hz, $O\underline{CH_2}CH_3$), 2.94 (2H, d, J= 7.3 Hz, H-2), 1.23 (6H, t, J= 7.2 Hz, $OCH_2\underline{CH_3}$).

IR (neat): ν_{max}= 2982, 1736 (C=O), 1642 (C=C) cm^{-1}.

m/z (EI): 326 $[M]^+$.

Preparation of methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6;8,9-di-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-D-*glycero*-L-*galacto*-nononate and methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6;8,9-di-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-D-*glycero*-L-*talo*-nononate (107).



107

A solution of dimethyl 2-(phenylselenyl)propanedioate (**106**) (590 mg, 2.04 mmol) and 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.68 mmol) in degassed benzene (7 ml) was irradiated for 12 hr. The bright yellow solution was concentrated *in vacuo* and chromatography (40% ether/petrol) afforded an inseparable 5:1 mixture (by ^{19}F NMR) of methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6;8,9-di-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-D-*glycero*-L-*galacto*-nononate and methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6;8,9-di-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-D-*glycero*-L-*talo*-nononate (**107**) (75 mg, 19%) as a yellow oil.

Major isomer:

^1H NMR (400 MHz, $CDCl_3$): 7.48 (2H, d, J= 6.5 Hz, Ph), 7.15 (3H, m, Ph), 4.65 (3H, m, H-2 H-5 H-6), 4.20 (1H, q, J= 8.5 Hz, H-8), 4.02 (1H, dd, J= 6.8, 8.7 Hz, H-9a), 3.98 (1H, dd, J= 4.7, 8.6 Hz, H-7), 3.65 (3H, s, OMe), 3.57 (4H, m, OMe, H-9b), 1.49 (3H, s, $C\underline{Me}_2$), 1.16 (3H, s, $C\underline{Me}_2$), 1.13 (3H, s, $C\underline{Me}_2$), 1.12 (3H, s, $C\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 164 (m, C=O), 138.3 (Ph), 135.3 (Ph), 128.8 (Ph), 128.4 (Ph), 118.0 (dd, J= 246, 261 Hz, C-3), 114.2 ($\underline{C}Me_2$), 109.6 ($\underline{C}Me_2$), 96.5 (m, C-4), 86.5, 85.2, 79.8, 73.9, 66.0, 56.5 (t, J= 23 Hz, C-2), 53.1 (OMe), 53.0 (OMe), 26.6 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 25.0 ($C\underline{Me}_2$), 23.7 ($C\underline{Me}_2$).

^{19}F NMR (376 MHz, $CDCl_3$): -91.0 (dd, J= 28, 273 Hz), -101.0 (d, J= 273 Hz).

Minor isomer:

^{1}H NMR ($CDCl_3$, 400 MHz): 7.70 (1H, d, J= 6.5 Hz, Ph), 7.60 (1H, d, J= 6.5 Hz, Ph), 7.20 (3H, m, Ph), 4.65 (3H, m, H-2, H-5, H-6), 4.20 (1H, m, H-8), 4.00 (2H, m, H-7 H-9a), 3.65 (3H, s, OMe), 3.58 (4H, m, OMe, H-9b), 1.29 (3H, s, $C\underline{Me}_2$), 1.16 (3H, s, $C\underline{Me}_2$), 1.13 (3H, s, $C\underline{Me}_2$), 1.12 (3H, s, $C\underline{Me}_2$).

^{13}C NMR ($CDCl_3$, 100 MHz): 164 (m, C=O), 135.6 (Ph), 129.2 (Ph), 129.1 (Ph), 128.1 (Ph), 113.0 ($\underline{C}Me_2$), 109.0 ($\underline{C}Me_2$), 86.1, 83.9, 79.9, 76.3, 65.7, 53.8 (m, C-2), 52.9 (OMe), 52.8 (OMe), 26.4 ($C\underline{Me}_2$), 25.4 ($C\underline{Me}_2$), 24.8 ($C\underline{Me}_2$), 23.9 ($C\underline{Me}_2$).

^{19}F NMR (376 MHz, $CDCl_3$): -98.4 (d, J= 268 Hz), -110.7 (dd, J= 27, 268 Hz).

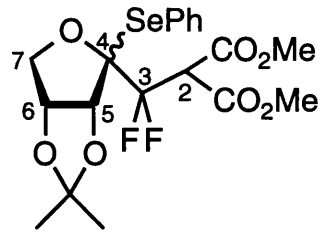
Mixture:

IR (neat): ν_{max}= 2988, 2955, 1744 (C=O), 1437, 1381, 1267, 1211, 1161, 1105, 1067, 1031, 580, 740 cm^{-1}.

m/z (FAB): 423 $[M\text{-}SePh]^+$, 385, 365, 157, 101, 77, 59, 43.

Accurate Mass (FAB): Observed $[M+Na]^+$: 603.0925; $C_{24}H_{30}F_2O_9SeNa$ requires 603.0921.

Preparation of methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-L-*galacto*-heptonate and methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-L-*talo*-heptonate (108).



108

A solution of dimethyl 2-(phenylselenyl)propanedioate (**106**) (896 mg, 3.12 mmol) and 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-

enitol (**28**) (200 mg, 1.04 mmol) in degassed benzene (10 ml) was irradiated for 12 hr. The bright yellow solution was concentrated *in vacuo* and chromatography (45% ether/petrol) afforded an inseparable 7:1 mixture (^{1}H NMR) of methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-L-*galacto*-heptonate and methyl 4,7-anhydro-2,3-dideoxy-3,3-difluoro-5,6-*O*-isopropylidene-2-methoxycarbonyl-4-phenylselenyl-L-*talo*-heptonate (**108**) (247 mg, 50%) as a yellow oil.

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$): 7.63 (2H, d, J= 6.7 Hz, Ph), 7.28 (3H, m, Ph), 4.95 (1H, t, J= 5.4 Hz, H-6), 4.88 (1H, dd, J= 3.3, 23.0 Hz, H-2), 4.77 (1H, d, J= 5.9 Hz, H-5), 4.04 (1H, dd, J= 4.5, 10.4 Hz, H-7a), 3.93 (1H, d, J= 10.4 Hz, H-7b), 3.80 (3H, s, OMe), 3.67 (3H, s, OMe), 1.62 (3H, s, C$\underline{Me}_2$), 1.31 (3H, s, C$\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 164.2 (C=O), 136.2 (Ph), 129.0 (Ph), 128.7 (Ph), 119.0 (dd, J= 246, 261 Hz, C-3), 113.9 ($\underline{C}Me_2$), 98.0 (dd, J= 27, 40 Hz, C-4), 86.3, 80.0, 74.6, 56.3 (t, J= 24 Hz, C-2), 53.1 (OMe), 52.6 (OMe), 25.4 (C$\underline{Me}_2$), 24.0 (C$\underline{Me}_2$).

^{19}F NMR (376 MHz, $CDCl_3$): -92.2 (dd, J= 26, 273 Hz), -100.4 (d, J= 274 Hz).

Minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (2H, d, J= 7.0 Hz, Ph), 7.32 (3H, m, Ph), 5.10 (1H, d, J= 6.5 Hz, H-5), 4.89 (1H, m, H-6), 4.58 (1H, dd, J= 6.7, 21.7 Hz, H-2), 4.10 (1H, m, H-7a), 3.98 (1H, m, H-7b), 3.76 (3H, s, OMe), 3.66 (3H, s, OMe), 1.48 (3H, s, C$\underline{Me}_2$), 1.37 (3H, s, C$\underline{Me}_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 163.8 (C=O), 163.7 (C=O), 137.7 (Ph), 128.9 (Ph), 128.5 (Ph), 126.9 (Ph), 122.0 (dd, J= 230, 258 Hz, C-3), 114.9 ($\underline{C}Me_2$), 83.4, 79.0, 74.4, 54.4 (t, J= 21, C-2), 53.0 (OMe), 52.7 (OMe), 25.5 (C$\underline{Me}_2$), 24.8 (C$\underline{Me}_2$).

^{19}F NMR (376 MHz, $CDCl_3$): -98.4 (d, J= 269 Hz), -100.4 (dd, J= 21, 268 Hz).

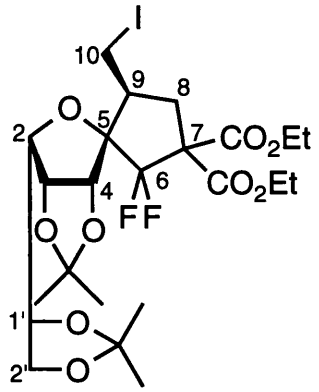
Mixture:

IR (DCM) ν_{max}= 2991, 2954, 1745 (C=O), 1436, 1266, 1210, 1162, 1098, 990, 872, 737, 703 cm^{-1}.

m/z (FAB): 323 $[M\text{-}SePh]^+$, 213, 181, 59, 43.

Accurate Mass (FAB): Observed $[M+Na]^+$ 503.0392; $C_{19}H_{22}F_2O_7SeNa$ requires: 503.0397.

Preparation of [2S(1R)3R4R5S9S] 2-(1,2-isopropylenedioxy-ethyl)-3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-iodomethyl-1-oxaspiro[4,4]nonane (111).



111

To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.684 mmol) and diethyl allyliodomalonate (**109**) (670 mg, 2.0 mmol) in degassed benzene (15 ml) was added hexabutylditin (0.103 ml, 0.2 mmol) and the solution was irradiated for 1.5 hr. TLC showed that the reaction had not gone to completion. Hexabutylditin (0.05 ml, 0.1 mmol) was added and the solution was irradiated for 1.5 hr. The mixture was concentrated *in vacuo* and chromatography (40% ether/petrol) afforded [2S(1R)3R4R5S9S] 2-(1,2-isopropylenedioxy-ethyl)-3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-iodomethyl-1-oxaspiro[4,4]nonane (**111**) (348 mg, 85%) as a light yellow oil.

$[\alpha]_D$= -17.2° (c= 2.5, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.96 (1H, d, J= 6.0 Hz, H-4), 4.72 (1H, dd, J= 4.1, 5.9 Hz, H-3), 4.40-4.10 (6H, m, H-1' H-2'a $OC\underline{H}_2CH_3$), 3.70 (2H, m, H-2 H-2'b), 3.10 (3H, m, H-9, H-10), 2.56 (1H, t, J= 9.1 Hz, H-8a), 1.85 (1H, ddd, J= 3.3, 9.0, 13.5 Hz, H-8b), 1.50 (3H, s, $C\underline{Me}_2$), 1.40 (3H, s, $C\underline{Me}_2$), 1.35-1.20 (12H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 165.3 (C=O), 164.4 (C=O), 123.2 (dd, J= 252, 286 Hz, C-6), 114.0 ($\underline{C}Me_2$), 109.5 ($\underline{C}Me_2$), 89.0 (dd, J= 18, 31 Hz, C-5), 81.6, 81.2, 81.1, 75.2, 66.0, 62.8 ($O\underline{C}H_2CH_3$), 62.3 ($O\underline{C}H_2CH_3$), 61.4 (m, C-7), 45.1, 36.2, 26.8 ($C\underline{Me}_2$), 25.6 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 24.7 ($C\underline{Me}_2$), 14.0 ($OCH_2\underline{C}H_3$), 13.8 ($OCH_2\underline{C}H_3$), 5.9 (C-10).

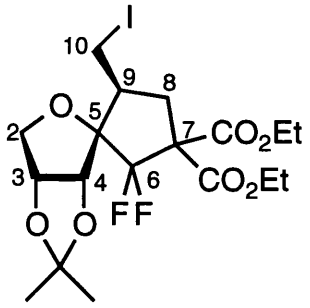
^{19}F NMR (376 MHz, $CDCl_3$): -110.4 (d, J= 252 Hz), -111.6 (d, J= 252 Hz).

IR (neat): ν_{max}= 2984, 1740 (C=O), 1445, 1371, 1240, 1164, 1109, 1045, 912, 852, 733 cm^{-1}.

m/z (FAB): 619 $[M+H]^+$, 603 $[M-Me]^+$, 561 $[M+H-Me_2C(O)]^+$, 101, 43.

Accurate Mass (FAB): Observed $[M+Na]^+$ 641.1031; $C_{23}H_{33}F_2IO_9Na$ requires: 641.1035.

Preparation of [3R4R5S9S] 3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-iodomethyl-1-oxaspiro[4,4]nonane (110).



110

To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (**28**) (200 mg, 1.04 mmol) and diethyl allyliodomalonate (**109**) (1.01g, 3.1 mmol) in degassed benzene (10 ml) was added hexabutylditin (0.158 ml, 0.3 mmol) and the solution was irradiated for 3.5 hr. The mixture was concentrated *in vacuo* and chromatography (40% petrol/ether) afforded [3R4R5S9S] 3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-iodomethyl-1-oxaspiro[4,4]nonane (**110**) (413 mg, 63%) as a white solid (m.p. 129-130 °C, ethanol).

$[\alpha]_D$= -41.2° (c= 1.65, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.85 (2H, m, H-3, H-4), 4.21 (4H, m, $OC\underline{H}_2CH_3$), 4.00 (1H, d, J= 10.9 Hz, H-2a), 3.69 (1H, dd, J= 4.0, 10.9 Hz, H-2b), 3.11 (2H, d, J= 7.8 Hz, H-10), 2.98 (1H, m, H-8a), 2.47 (1H, td, J= 2.5, 8.2 Hz, H-9), 1.90 (1H, ddd, J= 3.4, 8.5, 13.8, H-8b), 1.56 (3H, s, $C\underline{Me}_2$), 1.50 (3H, s, $C\underline{Me}_2$), 1.24-1.22 (6H, m, $OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 165.2 (C=O), 164.2 (C=O), 123.4 (dd, J= 248, 289 Hz, C-6), 113.6 ($\underline{C}Me_2$), 89.0 (m, C-5), 80.8, 80.7, 71.3, 62.5 ($O\underline{C}H_2CH_3$), 62.24 ($O\underline{C}H_2CH_3$), 44.9 ($C\underline{Me}_2$), 36.2 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_2$), 25.0 ($C\underline{Me}_2$), 13.9 ($OCH_2\underline{C}H_3$), 13.8 ($OCH_2\underline{C}H_3$), 5.8 (C-10).

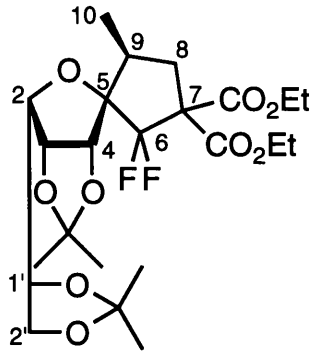
^{19}F NMR (376 MHz, $CDCl_3$): -108.5 (d, J= 255 Hz), -111.9 (d, J= 255 Hz).

IR (neat) ν_{max}= 2984, 1744 (C=O), 1373, 1266, 1235, 1106, 1042, 738, 704 cm^{-1}.

m/z (FAB): 518 $[M]^+$, 502 $[M\text{-}Me\text{-}H]^+$, 414, 391 $[M\text{-}I]^+$, 154, 136, 43, 29.

Observed C 41.61, H 4.91 %; $C_{18}H_{25}F_2IO_7$ requires: C 41.71, H 4.91 %.

Preparation of [2S(1R)3R4R5S9S] 2-(1,2-isopropylenedioxy-ethyl)-3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-methyl-1-oxaspiro[4,4]nonane (114).



114

To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**26**) (200 mg, 0.68 mmol) and diethyl allyliodomalonate (**109**) (670 mg, 2.0 mmol) in degassed benzene (7 ml) was added hexabutylditin (0.103 ml, 0.2 mmol) and the solution was irradiated for 1.5 hr. Tri-n-butyltin hydride (0.667 ml,

2.4 mmol) was added, the mixture was refluxed overnight and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel. The organic phase was separated, washed with saturated potassium fluoride (3x20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (40% ether/petrol) afforded [2S(1R)3R4R5S9S] 2-(1,2-isopropylenedioxy-ethyl)-3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-methyl-1-oxaspiro[4,4]nonane **(114)** (177 mg, 52%) as a colourless oil.

$[\alpha]_D$= -22.2° (c= 0.9, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.88 (1H, d, J= 5.9 Hz, H-4), 4.62 (1H, dd, J= 4.3, 5.9 Hz, H-3), 4.30 (5H, m, H-1' O$\underline{C}H_2CH_3$), 4.16 (1H, dd, J= 6.8, 8.6 Hz, H-2'a), 3.66 (1H, t, J= 8.5 Hz, H-2'b), 3.62 (1H, dd, J= 4.3, 7.6 Hz, H-2), 2.87 (1H, m, H-8a), 2.29 (1H, m, H-9), 1.80 (1H, ddd, J= 3.1, 9.3, 12.9 Hz, H-8b), 1.50 (3H, s, C$\underline{C}H_3$), 1.39 (3H, s, C$\underline{C}H_3$), 1.31-1.28 (12H, m, C$\underline{C}H_3$ OCH$_2$C$\underline{H}_3$), 1.07 (3H, d, J= 7.4 Hz, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 165.8 (C=O), 165.0 (C=O), 123.0 (dd, J= 249, 288 Hz, C-6), 113.6 (C$\underline{C}H_3$), 109.4 (C$\underline{C}H_3$), 89.3 (dd, J= 17, 31 Hz, C-5), 81.4, 80.6, 75.5, 66.1, 63.3 (dd, J= 18, 41 Hz, C-7), 62.7 (O$\underline{C}H_2CH_3$), 62.1 (O$\underline{C}H_2CH_3$), 36.4, 35.7, 26.9 (C$\underline{C}H_3$), 25.8 (C$\underline{C}H_3$), 25.4 (C$\underline{C}H_3$), 24.9 (C$\underline{C}H_3$), 18.8 (C-10), 14.0 (OCH$_2\underline{C}H_3$), 13.8, (OCH$_2\underline{C}H_3$).

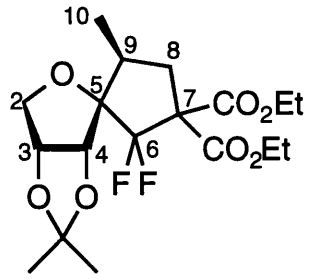
^{19}F NMR (376 MHz, $CDCl_3$): -109.5 (d, J= 252 Hz), -112.3 (d, J= 252 Hz).

IR (DCM): ν_{max}= 2986, 1742 (C=O), 1382, 1372, 1265, 1211, 1109, 1069, 738, 704 cm^{-1}.

m/z (FAB): 493 $[M+H]^+$, 477 $[M-Me]^+$, 435, 137, 101.

Accurate Mass (FAB): Observed $[M+H]^+$: 493.2244; $C_{23}H_{35}O_9F_2$ requires: 493.2249.

Preparation of [3R4R5S9S] 3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-methyl-1-oxaspiro[4,4]nonane (113).



113

To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*erythro*-penta-1-enitol (**28**) (200 mg, 1.04 mmol) and diethyl allyliodomalonate (**109**) (1.01 g, 3.1 mmol) in degassed benzene (10 ml) was added hexabutylditin (0.158 ml, 0.3 mmol) and the solution was irradiated for 1.5 hr. Tri-n-butyltin hydride (1.02 ml, 3.8 mmol) was added, the mixture was refluxed overnight and allowed to cool to room temperature. Iodine (30 mg, 0.12 mmol) and carbon tetrachloride (0.5 ml) were added and the mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate (15 ml), stirred vigorously with a saturated solution of potassium fluoride (20 ml) for 2 hr and filtered into a separating funnel. The organic phase was separated, washed with saturated potassium fluoride (3x20 ml), water (20 ml), brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo*. Chromatography (50% ether/petrol) afforded [3R4R5S9S] 3,4-isopropylenedioxy-6,6-difluoro-7,7-di-ethoxycarbonyl-9-methyl-1-oxaspiro[4,4]nonane (**113**) (122 mg, 30%) as a yellow oil.

$[\alpha]_D$= -34.7° (c= 0.6, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): 4.84 (1H, d, J= 5.9 Hz, H-4), 4.77 (1H, dd, J= 4.4, 5.4 Hz, H-3), 4.23 (4H, m, $OC\underline{H}_2CH_3$), 3.70 (1H, d, J= 10.8 Hz, H-2a), 3.66 (1H, dd, J= 4.1, 10.4 Hz, H-2b), 2.8 (1H, m, H-8a), 2.24 (1H, m, H-9), 1.87 (1H, ddd, J= 3.1, 5.3, 9.2 Hz, H-8b), 1.54 (3H, s, $C\underline{Me}_2$), 1.35 (3H, s, $C\underline{Me}_2$), 1.27 (6H, m, $OCH_2C\underline{H}_3$), 1.08 (3H, d, J= 7.3 Hz, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 165.8 (C=O), 165.3 (C=O), 123.5 (dd, J= 249, 288 Hz, C-6), 113.4 ($\underline{C}Me_2$), 90.2 (dd, J= 17, 31 Hz, C-5), 81.2, 80.4, 71.4, 63.3 (dd, J= 19, 42 Hz, C-7), 62.3 ($O\underline{C}H_2CH_3$), 62.1 ($O\underline{C}H_2CH_3$), 36.2, 35.9, 26.1 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 18.6 (C-10), 14.0 ($OCH_2\underline{C}H_3$), 13.8 ($OCH_2\underline{C}H_3$).

^{19}F NMR (376 MHz, $CDCl_3$): -107.5 (d, J= 255 Hz), -112.5 (d, J= 255 Hz).

IR (DCM): ν_{max} = 2984, 1743 (C=O), 1300, 1267, 1232, 1101, 1069, 737 cm^{-1}.

m/z (FAB): 393 $[M+H]^+$, 377 $[M-Me]^+$, 347, 289, 121, 93, 59, 43, 29.

Accurate Mass (FAB): Observed $[M+Na]^+$: 415.1548; $C_{18}H_{26}O_7F_2Na$ requires: 415.1544.

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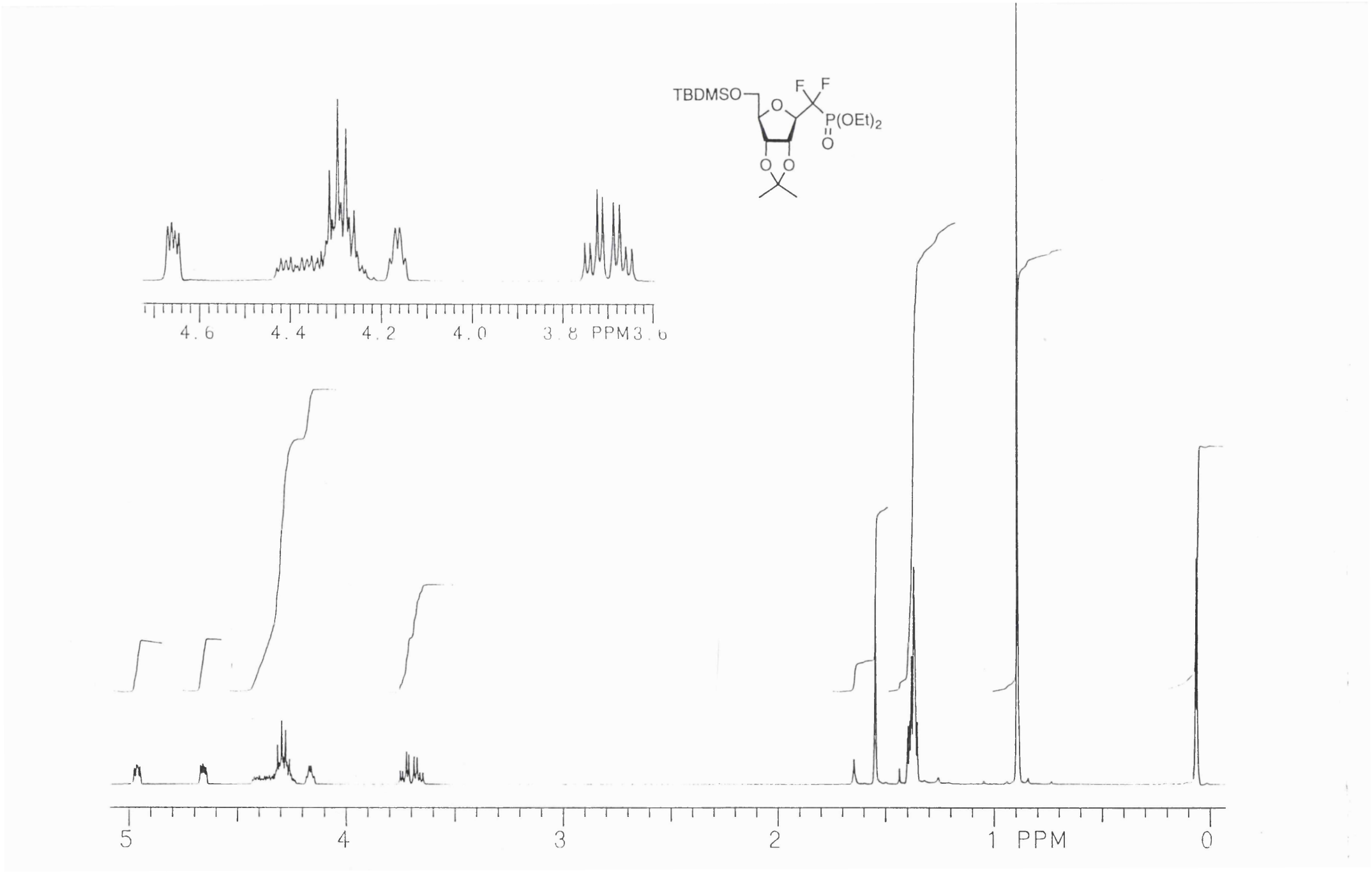
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O
P(OEt)2
O
O
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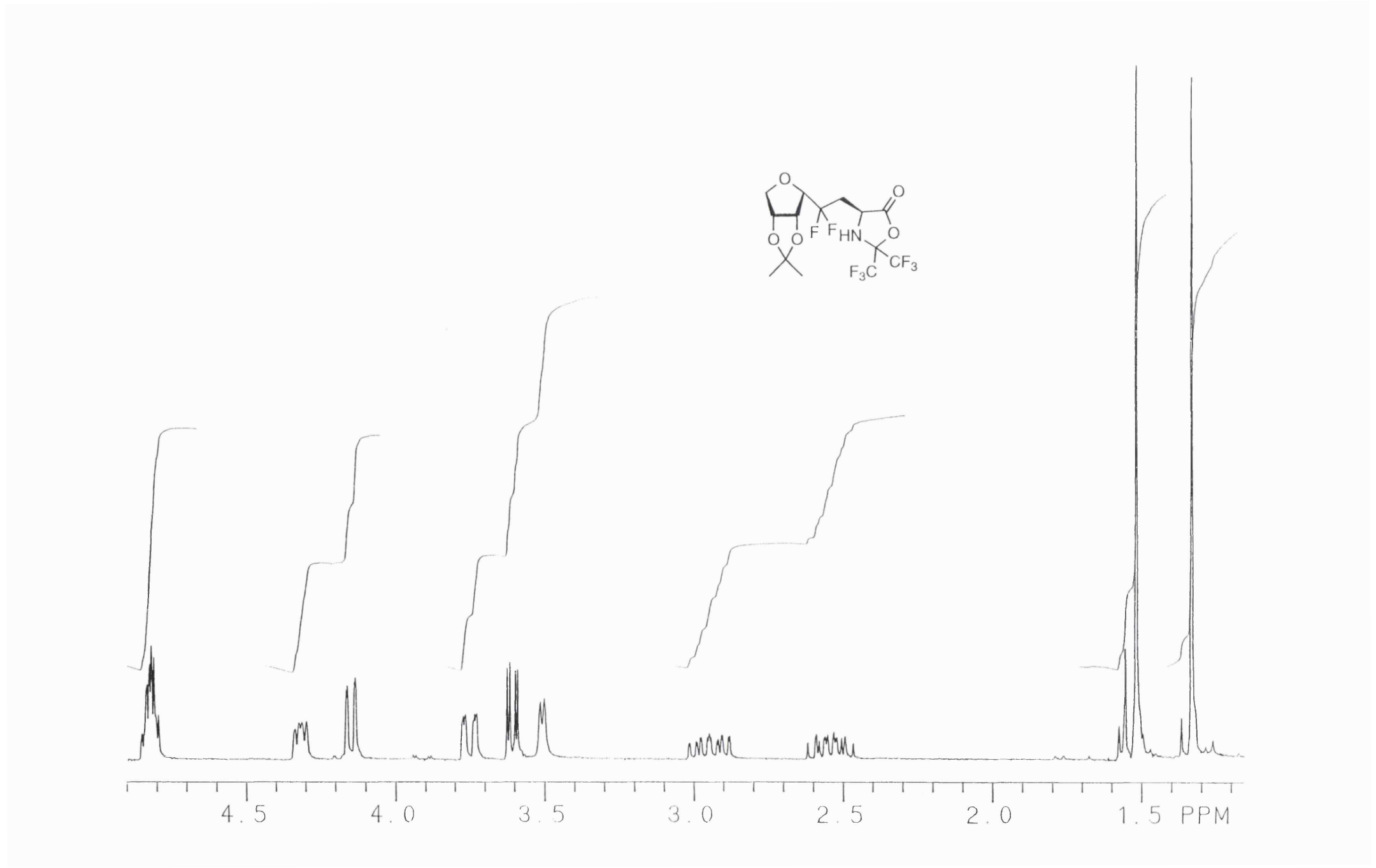
4.4
4.2
4.0
3.8 PPM3.6
5
4
3
2
1 PPM
0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F
HN
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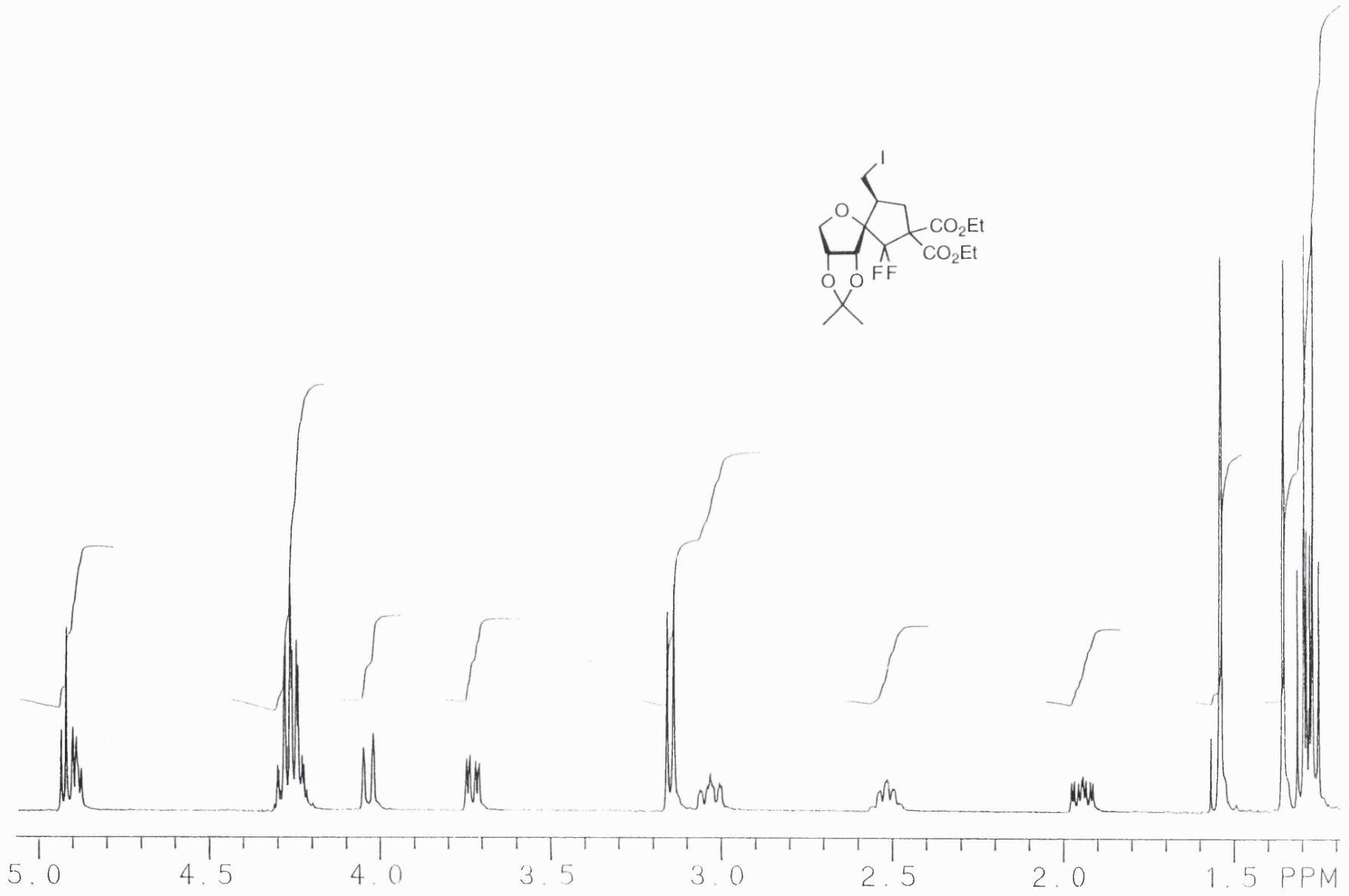
3.5
3.0
2.5
2.0
1.5 PPM


I
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CO2Et
CO2Et
F F
O O
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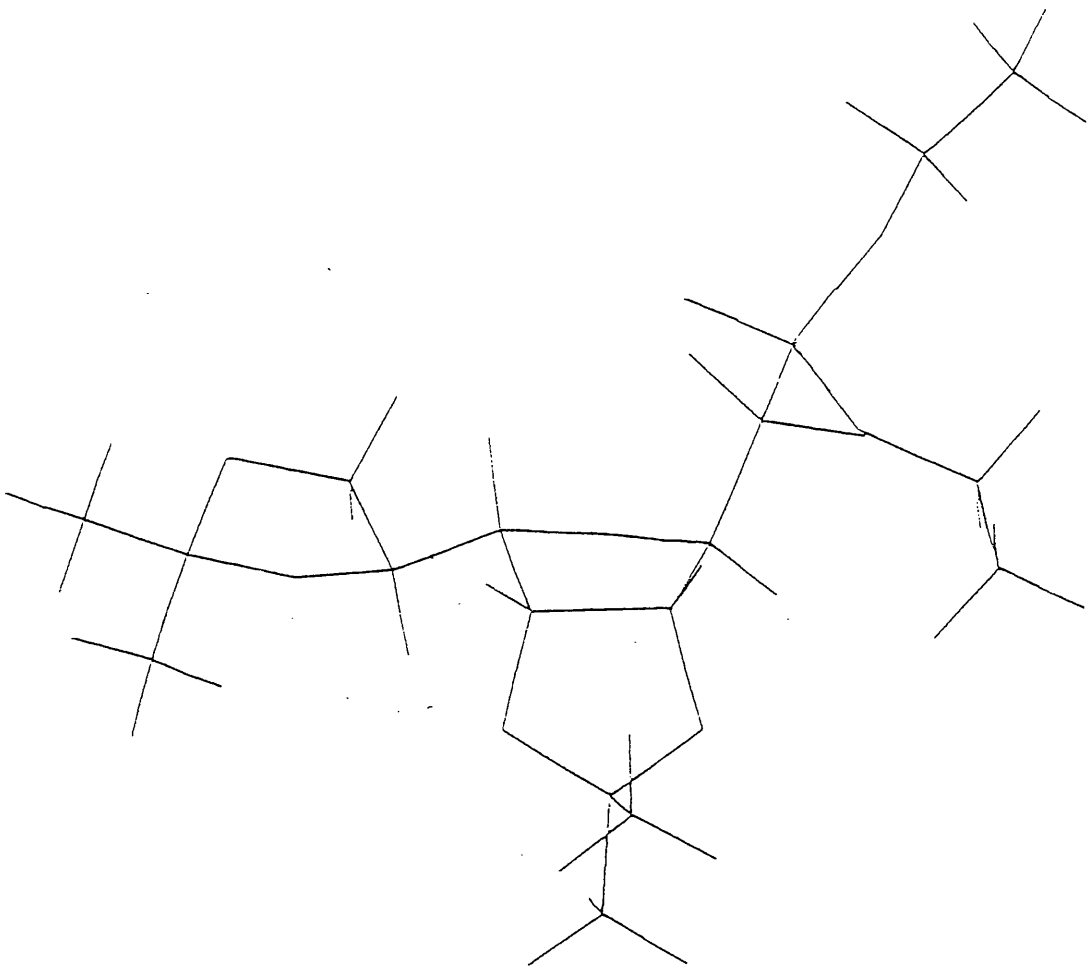
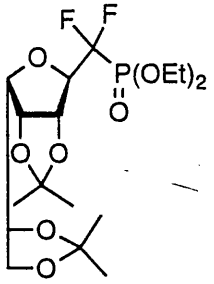
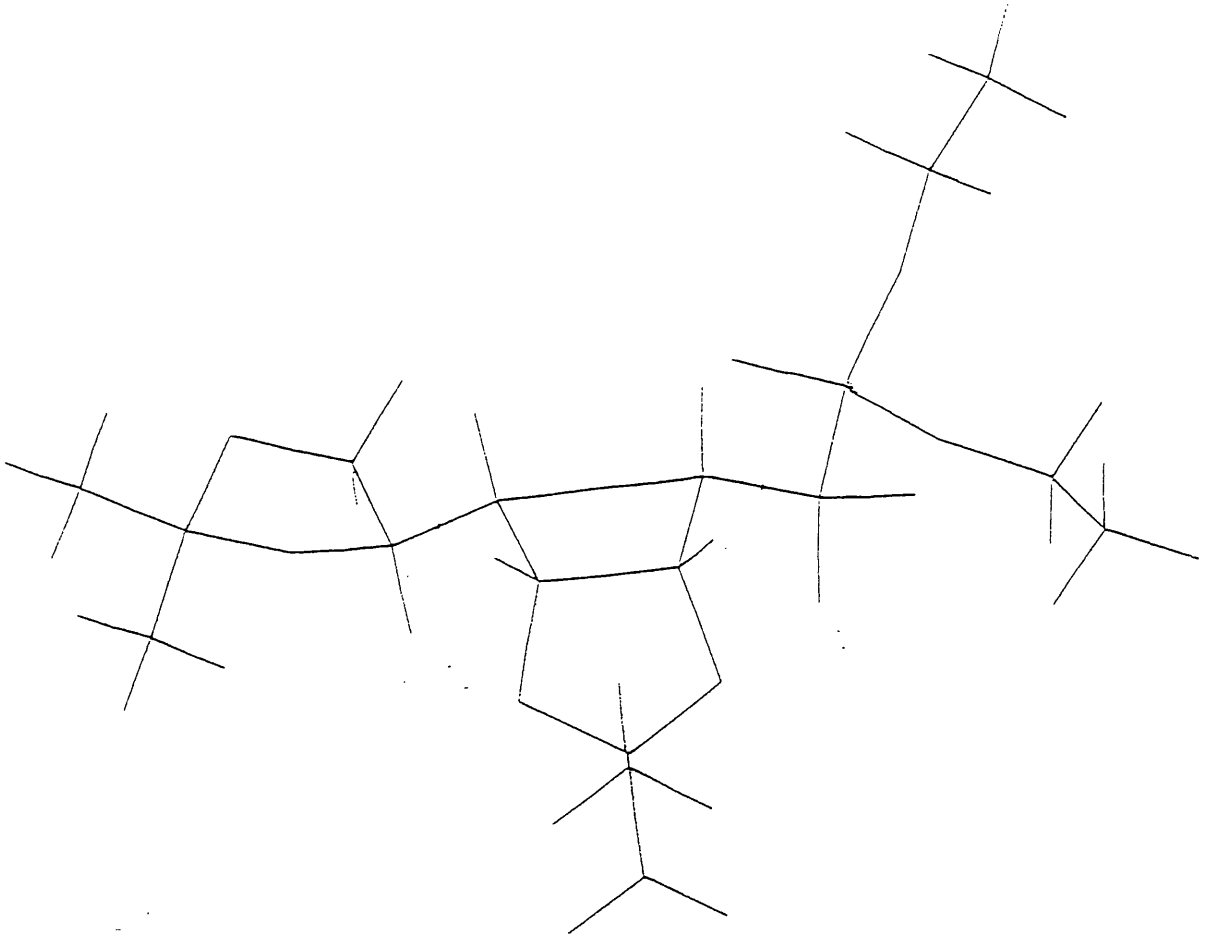
3.5
3.0
2.5
2.0
1.5 PPM

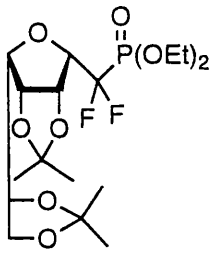




E= 23.82

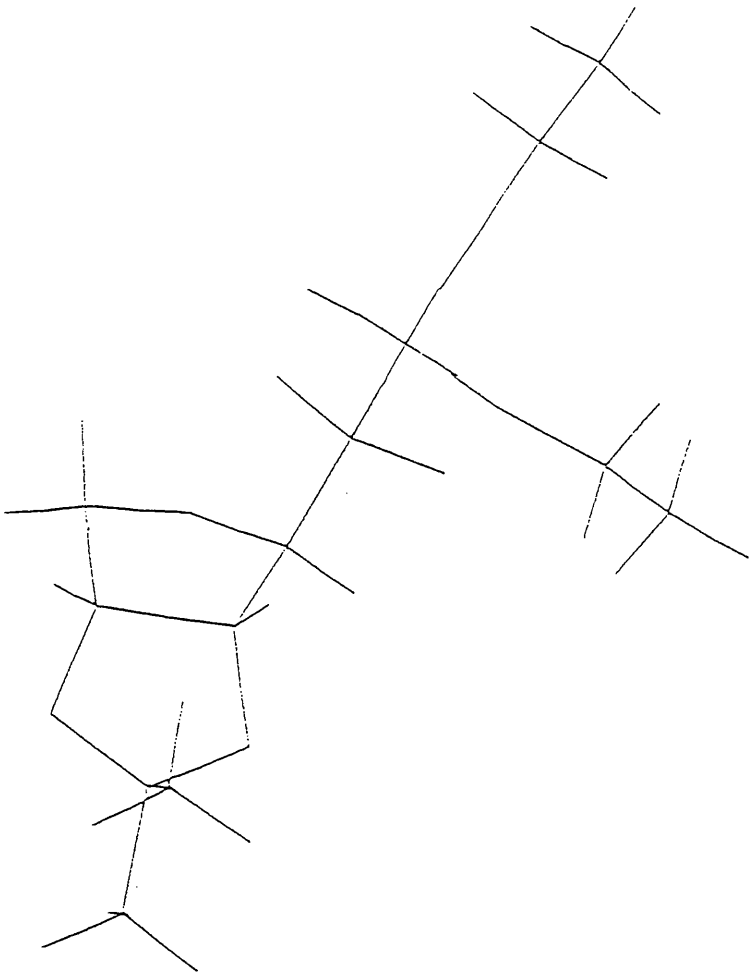
Computer minimised structure of (51).

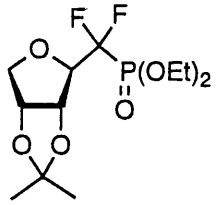




E= 23.19

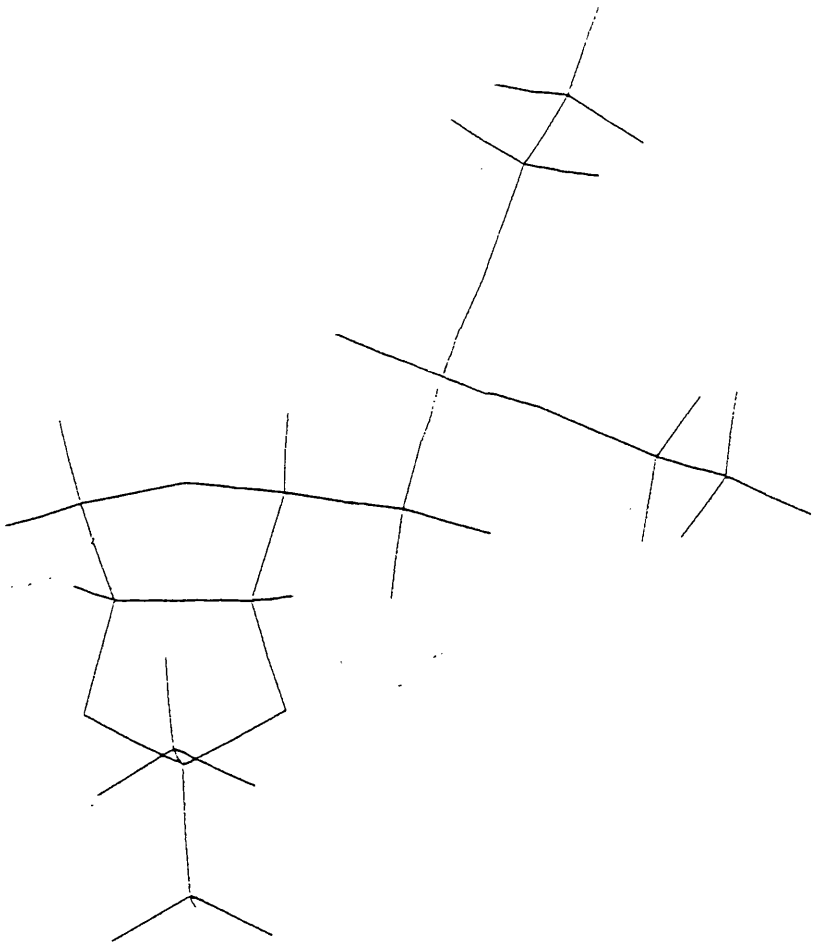
Computer minimised structure of the α-anomer of (51).

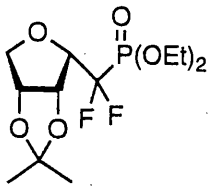




E= 14.91

Computer minimised structure of (47).





E= 14.07

Computer minimised structure of the α-anomer of (47).

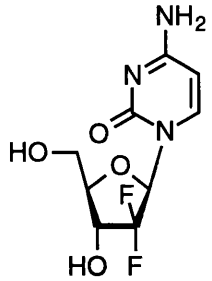
Corrigenda

p.7 line 11: cytosine

p.8 line 10 diisopropylamide

p.11 line 25: lipophilicity

p.13 structure **1:**

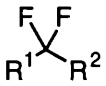


p.24 scheme 1.3.1: $(Me_2N)_3S\text{-}Me_2SiF_2$

p.38 line 11: copper(I) chloride

p.39 scheme 3.1.1: initiator CuCl

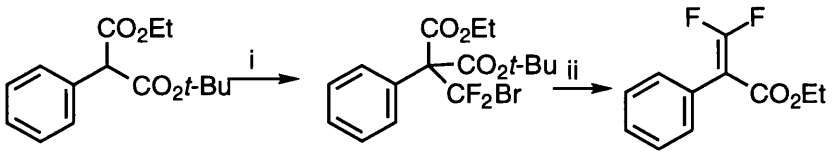
p.47 scheme 4.1.2:



p.54 line 8: ... treatment with alkaline base... should be replaced by:

... oxidation with alkaline hydrogen peroxide...

p.56 scheme 5.1.11:



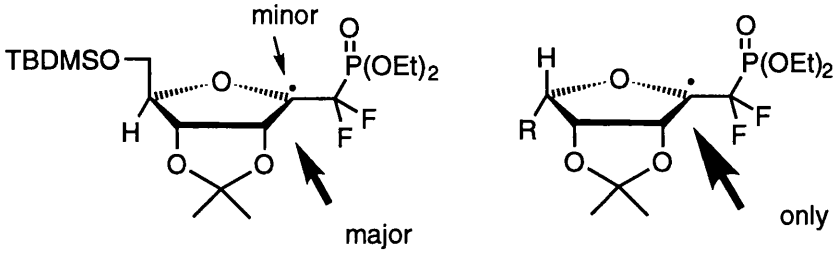
p.65 reference 4: Springer Verlag

p.75 reference 258: Pasto, D.J.

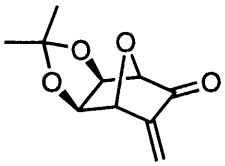
p.84 table 1: $P(NMe_2)_3$

p.98 line 4: occurs; line 6: β-phosphorus

p.105 figure 2.2.1:



p.108 structure **68**:



p.116 line 16: bromoform should be replaced by bromotrichloromethane

p.116 scheme 3.2.7: CBr_3Cl should be replaced by $CBrCl_3$

p.125 line 15 carbon tetraiodide, triphenylphosphine and pyridine