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at the University of Leicester

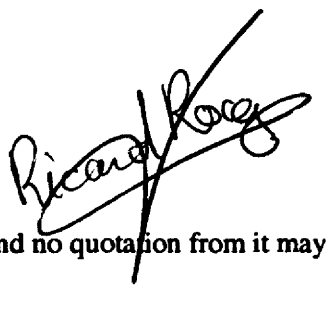
by

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University of Leicester

May 2006



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In Memory

of

My grandmother

Felicidad Ramírez Cerrato

1914-2002

My uncle

Francisco Ramírez Cacenave

1946-2003

My grandfather

Francisco Sánchez Márquez

1917-2004

My aunt

Piedad Ramírez Cerrato

1909-2005

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Finally I want to dedicate this thesis to the people that I care about the most, my parents, Sabina (for her love, patience and bringing me to life) and José María (for showing me the path to science), and my girlfriend/fiancée Austina (for her love and invaluable support). I also would like to dedicate this thesis to "Els Corleone" (Josep, Sergi, Benito, Pepe, Isaac, Campa, Carles, Alexis, Toni, Tomàs and Xavi), for our friendship and especially for the laughs and the good times that we shared studying Chemistry.

Other Work

Some of the results described in this thesis have been presented as Oral Communication at National and International Conferences:

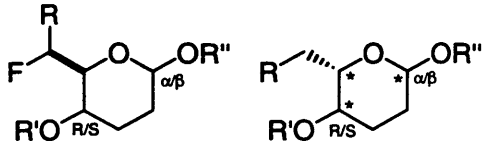
- "22nd International Carbohydrate Symposium", Glasgow (UK) July 2004;
- "4th Annual RSC Fluorine Subject Group Postgraduate Meeting", Durham (UK) September 2004;
- "VII Jornadas de Carbohidratos", Tarragona (Spain) September 2004;
- "16th SCI Fine Chemicals Group Regional Graduate Symposium", York (UK) March 2005
- "5th Annual RSC Fluorine Subject Group Postgraduate Meeting", Oxford (UK) September 2005.

SYNTHESIS OF 6-DEOXY-6-FLUOROSUGARS

Ricard Roig

6-Deoxysugars, especially highly deoxygenated sugars like amicetose and rhodinose, are components of major importance in the biosynthesis of a range of polyketide antibiotics. As there are no examples of fluorosaccharide end-product molecules in nature, 6-deoxy-6-fluorosugars could potentially be used as substrates for the combinatorial biosynthesis of novel structures. Introducing fluorine into pharmaceutical compounds can increase the biological activity and stability to metabolism.

In this thesis, different synthetic routes have been developed for the synthesis of fluoro analogues of 2,3,6-trideoxysugars. A novel route for the racemic synthesis of 6-fluoro and 6,6-difluoro analogues of amicetose and rhodinose has been developed succesfully from commercially available trifluoroethanol. Enantiomerically enriched 6-fluoro analogues have also been synthesized succesfully by a route which includes kinetic resolution using Sharpless Asymmetric Epoxidation as a key step. The determination of enantiomeric excess of different intermediates was performed without derivatisation by a facile NMR method using di*iso*propyl tartrate as chiral solvent; the results were confirmed by standard (HPLC) methods.



R: H, F; R': H, Bn, Bz; R": H, Me.

Amicetose exists as an equilibrium mixture of furanoses and pyranoses, while the furanose form becomes the sole isomer as the number of fluorines at C-6 is increased, due to the strong inductive electron withdrawing effect of fluorine. Protection of the hydroxyl at C-4 before the final ozonolysis is essential to deliver pyranoses exclusively.

Two very efficient new fluorinating methods have been developed, one with *in situ* cis/trans-isomerisation of a double bond with a mixture of TBAI and TBAF at reflux in THF, and another with highly regioselective epoxide ring-opening using a solvent free mixture of KHF_2 and TBAF at 120 °C.

In addition to the synthesis of 6-deoxy-6-fluorosugars, a long lived difluoroenol, formed upon addition of an HCl precursor to an enol acetal starting material with an acid labile protecting group (MEM), was discovered and fully characterised. The rates of formation of the more stable ketonic product and solvent kinetic isotope effect were also measured.

Abbreviations

$(DHQ)_2PHAL$	1,4-Bis(9-O-dihydroquinine)phthalazine
$(DHQD)_2PHAL$	1,4-Bis(9-O-dihydroquinidine)phthalazine
8-DMTC	8-Demethyl-tetracenomycin C
Å	Angstrom(s)
Ac	Acetyl
AD	Asymmetric Dihydroxylation
Bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
bp	Boiling Point
Bu	Butyl
CHN	Elemental Carbon, Hydrogen, Nitrogen analysis
CI	Chemical Ionization
COSY	Correlation Spectroscopy
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
DDQ	2,3-Dichloro-5, 6-dicyano-p-benzoquinone
de	diastereoisomeric excess
DET	Diethyl tartate
DFT	Density Functional Theory
DIBAL-H	Di*iso*butylaluminum hydride
DIPT	Di*iso*propyl tartrate
DMDO	Dimethyldioxirane
DMF	*N,N*-Dimethylformamide
DNA	Deoxyribonucleic acid

DNP	2,4-Dinitrophenyl
EC_{50}	Effective concentration 50%
ee	enantiomeric excess
EI-MS	Electron Ionisation Mass Spectrometry
ElmGT	sugar flexible glycosyl transferase
ES	Electrospray
Et	Ethyl
FAB	Fast Atom Bombardment
GC	Gas Chromatography
GTs	Glycosyl Transferases
HMBC	Heteronuclear Multiple-Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IC_{50}	Inhibitory concentration 50%
IR	Infrared
IVG	In vitro glycorandomization
J	Coupling constant
LDA	Lithium di*iso*propylamide
m/z	mass-to-charge ratio
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MEM	(2-Methoxyethoxy)methyl
MHz	Megahertz
mol	mole(s)
mp	Melting Point

Ms	Mesylate
MS	Mass Spectrometry
mw	molecular weight
NBS	*N*-Bromosuccinimide
NDP	Nucleoside diphosphate
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
NRPSs	Nonribosomal peptide synthases
Nu	Nucleophile
°C	degrees Celsius
PG	Protecting group(s)
Ph	Phenyl
PKSs	Polyketide synthases
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PNBz	*para*-Nitrobenzoyloxy
ppm	part(s) per million
Pr	Propyl
Red-Al®	Bis(2-methoxyethoxy)aluminium hydride
Rf	Retention factor
RNA	Ribonucleic acid
rt	room temperature
SAE	Sharpless Asymmetric Epoxidation
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetra-*n*-butyl ammonium fluoride

TBAI	Tetra-*n*-butylammonium iodide
TBHP	*Tert*-Butyl Hydroperoxide
TDP	Thiamine diphosphate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
Ts	*para*-Toluenesulfonyl

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1 Introduction

1.1 Introduction

The emergence of pathogenic bacteria resistant to many commonly used antibiotics poses a serious threat to human health. This project is based on the synthesis of 6-deoxy-6-fluorosugars, compounds which can potentially be used to enhance the biological activity of novel antibiotics, as will be described in the following sections.

The optimism of pharmaceutical companies in the 1980's lead to a reduction in programmes which sought the development of antibiotics at the expense of those aimed at new drugs for cancer, heart disease, and neurological conditions. This optimism was soon shaken by a series of outbreaks and epidemics of new and re-emerging anti-microbial-resistant infections, and marked a new low point in humans' struggle with infectious diseases.[1]

1.1.1 Bacterial Resistance to antibiotics

As is widely known, after a new antibiotic is introduced, that sooner or later, the targeted organisms will develop resistance to it. It has been demonstrated that bacterial antibiotic resistance arises under the evolutionary pressure for survival, and once it appears in one strain, it can quickly spread to others.[2] This is because the resistance determinants (resistance genes) found in pathogens are predominantly located in plasmids, which are easily transferred from one bacterium to another, as well as between strains.[3]

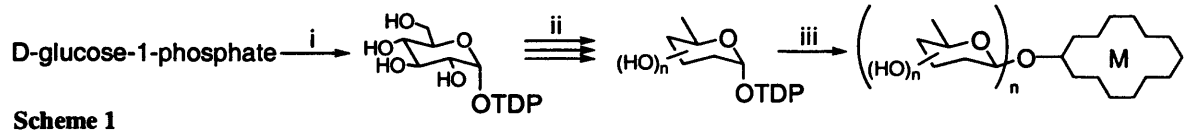
Three major resistance mechanisms have been identified in pathogenic bacteria: (i) drug efflux from the cell, (ii) target modification, and (iii) inactivation of the antibiotic. In

fact, most antibiotic-producing species utilize one or more of these mechanisms to protect themselves from intoxication by their own metabolites. It has been suggested that antibiotic producing species might be the source of at least some of the resistance determinants found in the pathogens with an acquired resistance.[4]

1.1.2 Polyketide Antibiotics

Polyketide antibiotics consist of a cyclic aglycone that nature has decorated with one or more deoxysugar moieties. The aglycone is formed first, followed by the tailored attachment of deoxysugar residues to form a structure that after further post-assembly modifications of both the aglycone core (e.g. hydroxylation) and deoxysugars (e.g. methylation), becomes an active polyketide antibiotic.

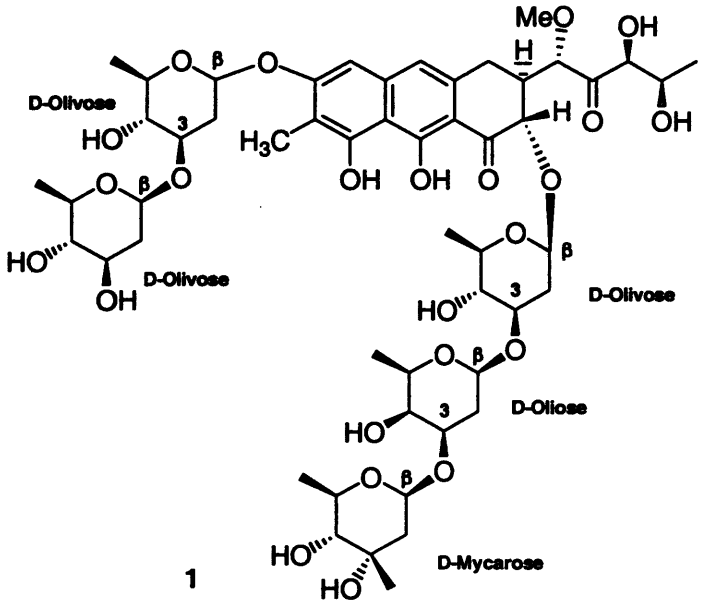
The deoxyhexose moieties of macrolide antibiotics are biosynthesized by dedicated genes, and then used for glycosylation. The general approach to glycosylation of a polyketide with a deoxysugar follows the following path: (i) activation of D-glucose-1-phosphate to TDP- α-D-glucose by thymidylyltransferase; (ii) modification of TDP- α-D-glucose to the desired deoxysugar moiety by a series of enzymes; (iii) coupling of the deoxysugar to the aglycone through a nucleophilic displacement of TDP catalysed by a specific glycosyltransferase (Scheme 1).



Scheme 1
i) Activation; ii) Dehydration and other modifications; iii) Glycosyltransferase.

A wide variety of 6-deoxysugars are found in many secondary metabolites[5,6] like lipopolysaccharides, glycoproteins, glycolipids and particularly structurally complex

antibiotics. In some instances, the sugar moieties serve to solubilize natural products by enabling the hydrophobic aglycone portions to partition into aqueous phases, thereby achieving useful intracellular and extracellular concentration. The highly specialized sugar appendices offer a mix of hydrophobic and hydrophilic surfaces as well as hydrogen-bonding capacity, and most likely enable specific recognition by biological targets.[7]



1

Mithramycin **1**[8] is a structurally complex antitumor antibiotic natural product which contains several 2,6-dideoxycarbohydrate components. It belongs to the aureolic acid group of molecules that consist of a number of structurally related drugs (mithramycin, chromomycin, olivomycin) synthesized by different *Streptomycete* species. These drugs are effective against a variety of experimental and human tumors; **1** has been used clinically for the treatment of cancer, even though the correct chemical structure of the oligosaccharide motifs was only recently determined. The anticancer activity of this compound is due in part to the presence and constitution of the oligosaccharide motifs.

Natural product sugar ligands have been shown to be critical to the ability of these antibiotics to achieve DNA-recognition and inhibition of DNA-processing, RNA-

recognition and inhibition of translation, inhibition of cell wall synthesis and membrane recognition, as well as targeting specific proteins and/or protein complexes.[9] Antibiotic polyketides are thought to block the peptide exit tunnel, preventing the extension of the nascent peptide from the peptidyl transferase center.

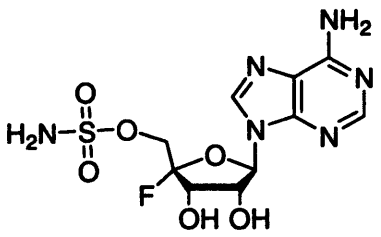
Natural products have traditionally played an important role in the discovery of therapeutic agents for infectious diseases and other illnesses. However, as the ability to find new therapeutic agents with desired properties from natural sources has become increasingly difficult, some scientists have turned towards a technology referred to as combinatorial biosynthesis to produce novel natural products for drug development.[10]

1.1.3 Unnatural Deoxysugars

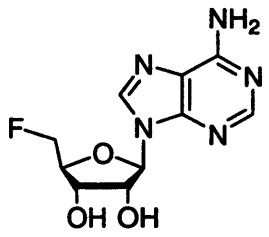
In many cases, these unusual sugars are indispensable for the activity of the parent molecule, and can mediate drug targeting, biological activity and pharmacology, which suggests that modifying the structure and/or composition of the deoxysugar components on secondary metabolites has a high potential for varying and/or enhancing the biological activities of the parent systems and for the generation of novel therapeutics.[9]

Although fluorine is the most abundant halogen in the earth's crust, the incidence of fluorinated natural products is extremely low and only thirteen fluorine-containing secondary metabolites have been identified.[11] Nucleocidin **2** is an antitrypanosomal antibiotic[12] and one of the very few naturally occurring fluorinated compounds;[13] 5'-fluoro-5'-deoxyadenosine **3** is an intermediate involved in the biosynthesis of fluoroacetate and fluorothreonine, from inorganic fluoride by *Streptomyces cattleya*.[14] There are no examples of fluorosaccharide end-product molecules in nature, so novel

architectures will result from the incorporation of fluorosugars within oligosaccharides or complex antibiotics.

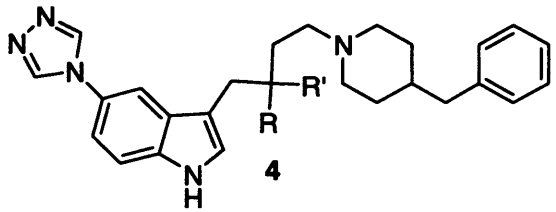


2



3

Introducing fluorine into pharmaceutical compounds can increase biological activity and metabolic stability. Fluorine can reduce the basicity of the adjacent groups in a compound, resulting in better membrane permeation and thus improved bioavailability. Table 1 shows the effect on pK_a and bioavailability by introducing fluorine into a drug.[15]



4

R	R'	pK_a	IC_{50}	EC_{50}	
H	H	9.7	0.3	0.6	very low bioavailability
F	H	8.7	0.9	0.9	medium bioavailability
F	F	6.7	78		low binding affinity

Table 1

In the table below (Table 2), we can observe the different physical properties of O, H or F substituents.

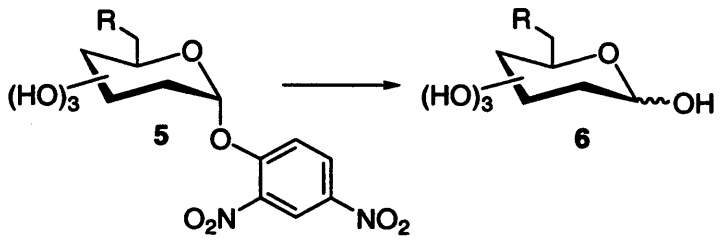
	O	H	F
Bond Length (Å)	1.32-1.76	1.0-1.11	1.26-1.41
Atomic Radius (Å)	0.65	0.79	0.57
Covalent Radius (Å)	0.73	0.32	0.72
Ionic Radius (Å)	1.42	1.10	1.33
Electronegativity(Pauling)	3.44	2.20	3.98
Hydrogen Bond Donor	✓	x	x
Hydrogen Bond Acceptor	✓	x	?

Table 2

Fluorine has a similar ionic radius and bond length (to carbon) to hydrogen, meaning that the inclusion of a C-F bond alters steric size minimally (compared to a C-H bond in

the molecule). However, the fluorine atom is significantly more electronegative than hydrogen, being more like oxygen in this respect (according to the Pauling scale), establishing polar interactions as a weak hydrogen bond acceptor.[16]

Hydrolytic stability is critical for the integrity of polysaccharides and glycosylated antibiotic structures. Studies in this field have been made by Withers and co-workers;[17,18] they compared the spontaneous hydrolysis rates of a range of 2,4-dinitrophenyl glycosides (Table 3).

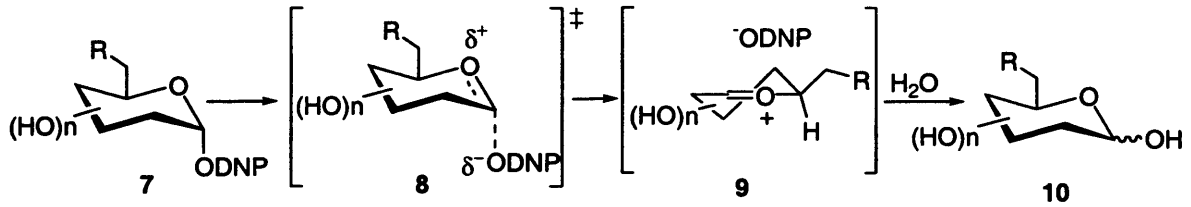


	OH	6-H	6-F	2-F
DNP-glucose	$5.58 \cdot 10^{-6}$ 1.00	$2.60 \cdot 10^{-5}$ 4.66	$1.99 \cdot 10^{-6}$ 0.36	$1.45 \cdot 10^{-7}$ 0.03
DNP-galactose	$2.61 \cdot 10^{-5}$ 1.00	$1.61 \cdot 10^{-4}$ 6.17	$9.40 \cdot 10^{-6}$ 0.36	$1.25 \cdot 10^{-6}$ 0.05

Rate Constant Hydrolysis at 37°C (sec^{-1})
Relative Rate

Table 3. Kinetic Data for the Spontaneous Hydrolysis of the DNP Glycosides.

If we compare the rate constants of hydrolysis at 37 °C we will see that 6-deoxysugars hydrolyse at least four times more rapidly than the parent non-deoxygenated hexoses (Scheme 2).



Scheme 2

Fluorine, due to its high electronegativity, inductively destabilises any oxacarbenium ion in which it is close to the locus of positive charge. That makes 6-deoxy-6-

fluorosugars three times, and 2-deoxy-2-fluorosugars thirty times, more stable towards hydrolysis than normal sugars and, ten and hundred times respectively more stable than any 6-deoxysugars. Even relatively modest stabilising effects like this could extend the lifetimes of therapeutically important species significantly. Because the fluorine atom is replacing a hydrogen atom and not a hydroxyl group at a primary carbon in the 6-deoxy-6-fluorosugars, the recognition of the saccharide may be subverted minimally in complex antibiotic structures.[19,20] The ability to make different 6-deoxy-6-fluorosugars and attach them to different aglycones would afford wholly new and possibly highly selective glycosylated architectures with novel antibiotic and anti-cancer action.

1.1.4 Combinatorial Biosynthesis

This emerging technology is based on the genetic manipulation of the biosynthetic machinery (polyketide synthases (PKSs), glycosyl transferases (GTs) and nonribosomal peptide synthases (NRPSs)) that produces antibiotics in bacteria and other microorganisms, to produce novel natural products for drug development.[10]

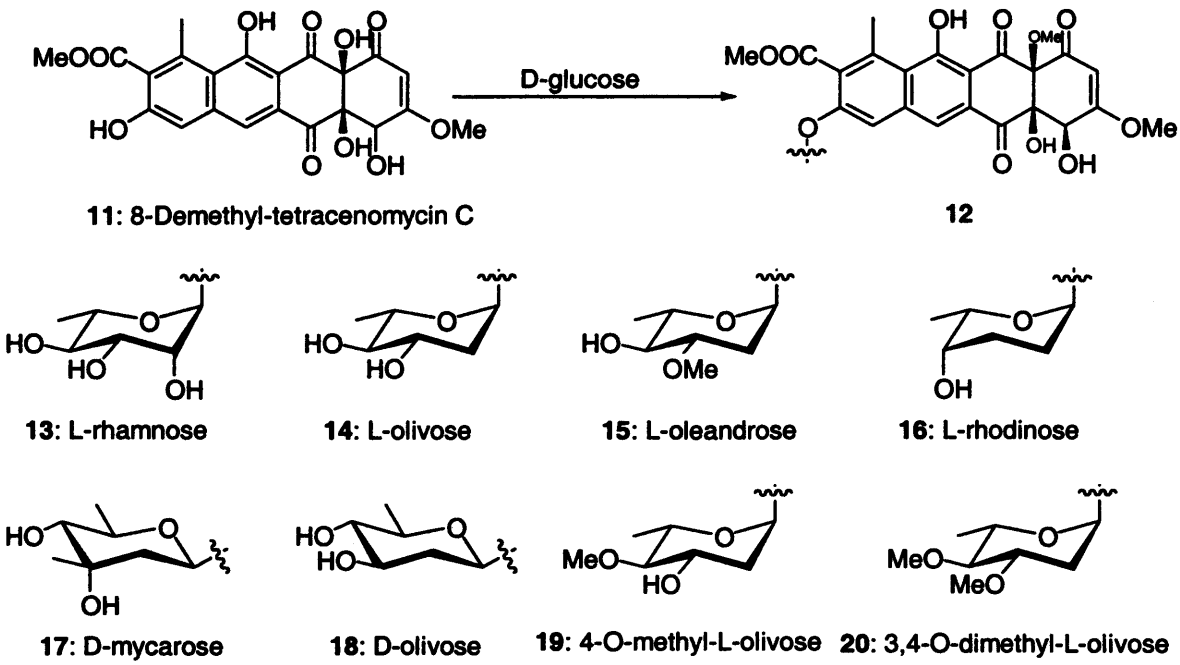
It is clear that altering the composition of sugar appendages in polyketide antibiotics is a promising strategy for creating new products with novel and enhanced biological activities. Effective glycosylation strategies have been pursued by scientists and recently significant progress has been made using genetic and biochemical methods to perform glycosylation *in vivo*. Some glycosyltransferases have been shown to possess relaxed substrate specificity and be able to couple diverse sugar and aglycone structures *in vivo*.[7,21,22] The simplest way to alter the glycosylation pattern of a macrolide is the inactivation of the specific glycosyltransferase gene, thereby preventing the attachment

of the corresponding sugar moiety, and introduction and activation of a flexible glycosyltransferase gene.

Salas and coworkers have employed the 'sugar flexible' glycosyltransferase involved in elloramycin biosynthesis, ElmGT, for the glycosylation of an aromatic aglycone with diverse deoxysugars.[23,24] A plasmid pLN2 containing the genes required for the formation of TDP-L-oleandrose from the oleandomycin pathway was created first. This plasmid was modified further by the gene deletion and replacement to create sets of genes for the biosynthesis of TDP-L- and -D-olivose, TDP-L-rhamnose, and TDP-L-rhodinose.

Derivatives of plasmid pLN2 were then used to complement a *Streptomyces albus* mutant expressing the ElmGT gene. The aglycone was either supplemented by feeding or produced endogenously from the cosmid containing tetracenomycin C biosynthetic genes. The detection of four glycosylated derivatives of tetracenomycin C, confirmed the production of the desired sugar residues and illustrated the versatility of the glycosyltransferase ElmGT.[23]

Rohr and Salas[24-27] were able to produce a range of novel tetracenomycins by transforming cosmid 16F4 from the elloramycin A **12** biosynthetic pathway of *Streptomyces olivaceus*, into mutants of *S. fradiae* and *S. argillaceus*. The transformation encoded a sugar-flexible glycosyltransferase (*Elm*GT), which is capable of transferring a range of different 6-deoxysugars (Scheme 3) to its natural substrate, aglycon 8-demethyl-tetracenomycin C (8-DMTC) **11**.



Scheme 3

However, the yields are generally low, and product isolation from the fermentation broth is tedious. Moreover, such an *in vivo* approach has limited general applicability since the production of antimicrobial agents would cause inhibition of cell growth or cell death. One potential solution to overcome these hurdles is to carry out the glycosylation step *in vitro* using isolated glycosyltransferases. The *in vitro* approach would also be facilitated by using genetically engineered glycosyltransferases with the desired substrate specificity. A marvellous glycosyltransferase for the combinatorial biosynthesis would be one capable of coupling "unnatural" aglycones with "unnatural" carbohydrates.

A chemoenzymatic approach to the production of glycosylated secondary metabolites which carries out the glycosyl transfer step *in vitro* has been developed by Thorson and coworkers.[28] The strategy, termed glycorandomization, takes advantage of the versatility of the chemical synthesis to make diverse sugar structures and the promiscuity of sugar kinases and nucleotidylyltransferases to create activated carbohydrate building blocks.[9] Coupled with a substrate flexible glycosyltransferase,

glycorandomization potentially allows the construction of a large library of glycosylated molecules *in vitro*. Thorson and coworkers have demonstrated the viability of this approach by creating 21 novel monoglycosylated vancomycin analogs using the vancomycin aglycone, a library of sugar-1-phosphates, and GtfE the glycosyltransferase from the vancomycin biosynthetic pathway.[29]

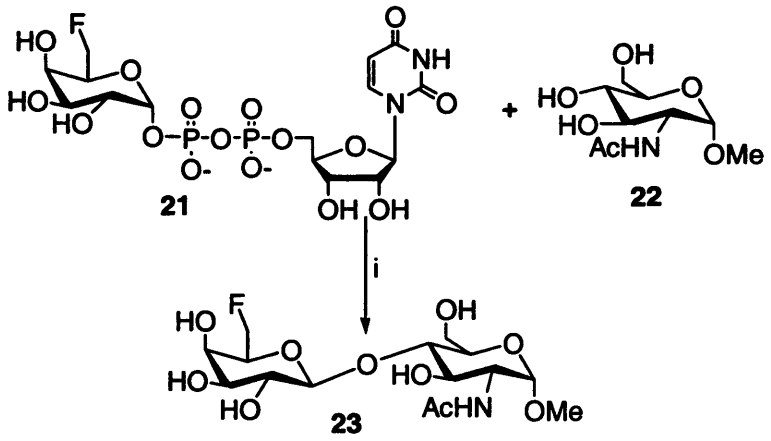
In vitro glycorandomization (IVG) combines the advantages of the limitless flexibility of chemical synthesis, with the inherent or engineered substrate promiscuity of enzymes (sugar kinases and nucleotidyltransferases) to activate and attach (glycosyltransferases) these carbohydrates to various natural product aglycons. Specifically for IVG, natural and "unnatural" sugar precursors are chemically synthesized and attached to various aglycons via a single pot, three enzyme (sugar kinase-nucleotidyltransferase-glycosyltransferase) process. This methodology is advantageous in that it combines the strength and flexibility of chemical synthesis with the ease of regio- and stereo-specific enzymatic coupling of sugars to extremely complex aglycon structures.[9]

If we can synthesize the 6-deoxy-6-fluorosugars, activate them, feed the activated species to microorganisms and thus effect transfer to the aglycone cores of polyketide natural products, a new chemoenzymatic route to novel molecules with antibiotic potential will be established.

1.1.5 Glycosyltransferases

According to literature references, activated 6-deoxy-6-fluorosugars have been successfully transferred into disaccharides using normal galactosyltransferases (GT). Kodama[30] was able to use a galactosyl transferase to add 6-fluoro-6-deoxygalactose to

an antennary oligosaccharide though at a low (0.2 %) relative transfer rate compared to that of the galactosyl moiety (Scheme 4), whereas Schengrund[31] found that a very similar reaction failed (albeit at a much lower loading of enzyme and after a much shorter reaction time) suggesting that fluorination at the 6-position impairs either a key recognition event or the transfer step, or both. Considering that we are substituting a C-OH bond from the native substrate of the galactosyl transferase with a C-F bond, and that the galactosyl transferases recognise the C-OH bond of the native substrate and presumably uses some binding energy from the interaction to drive the catalytic reaction, 6-fluorosugars would be expected to perform considerably less well as substrates as the C-F bond is a weak proton acceptor and has no proton donor capabilities.



Scheme 4
i) ß-(1- 4)-galactosyltransferase, [7 mU], 48 h, 59 %.

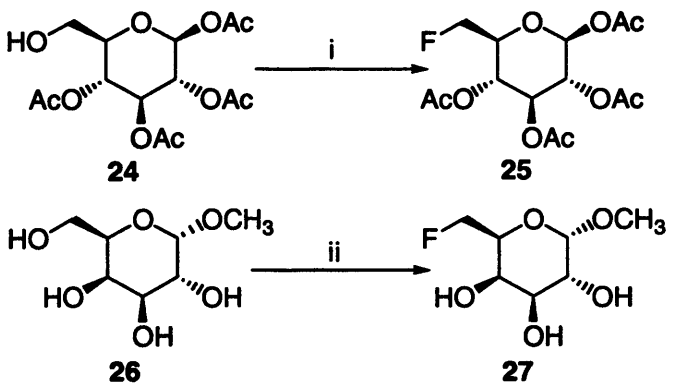
As carbohydrates play an essential role in a vast array of biological processes, it is not surprising that glycosylating enzymes and glycosyltransferases are abundant in all living organisms; selective inhibition of these enzymes has received increasing attention for the promise of new therapeutics, and many studies have been carried out using fluorosugars to investigate the transition-state of reactions catalysed by several glycosyltransferases. Studies by Ley, Wong and co-workers with human fucosyl transferases and 2-deoxy-2-fluoro and 6-deoxy-6-fluoro fucose show that, placing

fluorine at any position results in mechanism-based inhibition. Both types of modified substrate behave as competitive inhibitors, and as they both are equidistant from the ring oxygen, they exert similar electronic effects.[32]

1.2 Synthesis of 6-deoxy-6-fluorosugars

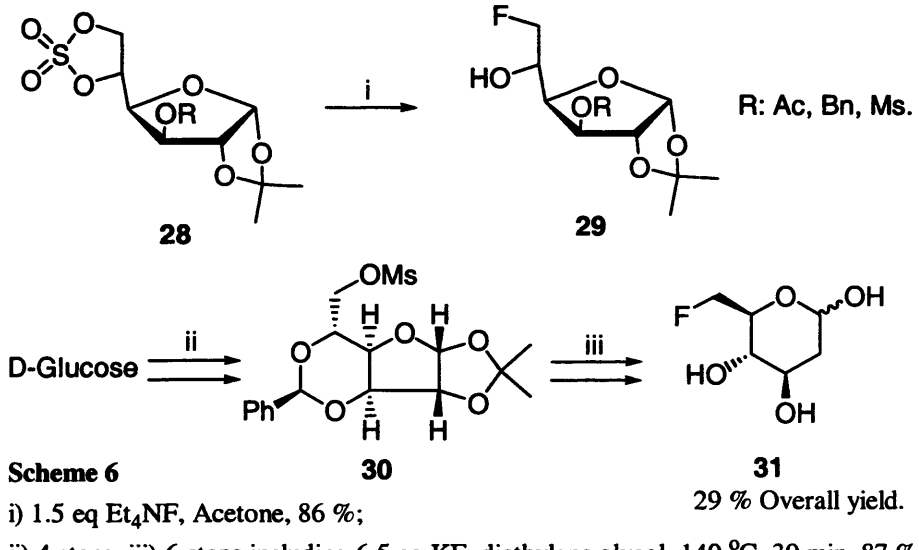
The syntheses of 6-deoxy-6-fluorosugars often involve transformation by replacement of the 6-hydroxyl group on an existing sugar by a fluorinating agent. However, because numerous protection and deprotection steps may be required to set up the desired hydroxyl group for substitution with fluorine, introduction of fluorine into carbohydrate moiety can be difficult,[13] time consuming and inflexible.

According to literature procedures described by Withers *et al.*[18] and Schengrund *et al.*[31] (Scheme 5), 6-deoxy-6-fluorosugars can be obtained using DAST with moderate yield, but protection of all the other hydroxyl groups in the sugars will be required because DAST is not a selective nucleophilic fluorinating reagent. Without the right protection, low yields and mixtures of products will be obtained. In Scheme 5, 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose **24** is deoxofluorinated using two equivalents of DAST in moderate yield (68 %) to obtain 6-fluoro-1,2,3,4-tetra-O-acetyl-β-D-quinovose **25**. However, 6-fluoro-O-methyl-α-D-fucose **27** is obtained in lower yield (25 %) from **26** and as part of a mixture of products when using 6 equivalents of DAST and no protecting groups (apart from the one at the anomeric hydroxyl group).



Scheme 5
i) 2eq DAST, DCM, -20 °C, 68 %; ii) 6eq DAST, DCM, -40 °C, 25 %.

Instead of selective fluorination of carbohydrates using DAST, selective nucleophilic displacement of a good leaving group at C-6 by fluoride ion has been successfully employed for the synthesis of 6-deoxy-6-fluoro-1,2-O-*iso*propylidene-α-D-glucofuranoses[33,34] and for the synthesis of 6-fluoro-D-olivose (Scheme 6).[35]



Scheme 6
i) 1.5 eq Et_4NF, Acetone, 86 %;
ii) 4 steps; iii) 6 steps including 6.5 eq KF, diethylene glycol, 140 °C, 30 min, 87 %.
29 % Overall yield.

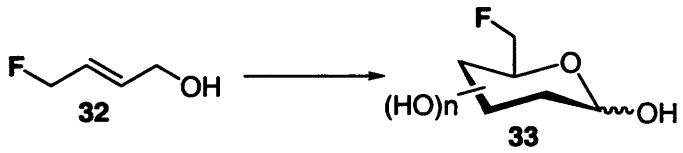
These methods raise some problems, especially where potential precursors are expensive or commercially unavailable (Table 4). They also require extensive protecting group manipulation, which represents a new and a different synthetic challenge for each target.

	£/mol
D-(+)-Glucose	5
L-(-)-Glucose	4574
D-(+)-Galactose	17
D-(+)-Allose	31780
L-(-)-Mannose	7862
D-(+)-Fucose	4669
2-Deoxy-D-glucose	1875
6-Fluoro-6-deoxy-D-galactopyranose	566204
6-Fluoro-6-deoxy-D-glucopyranose	871238

Table 4. Selling prices of different carbohydrates.
Aldrich UK catalogue 2005-2006 and
ABCR Fluorochemicals EU catalogue 2006-2007.

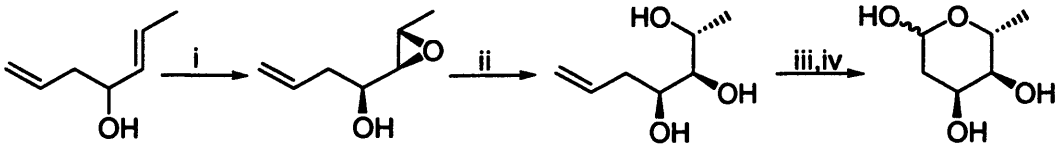
An alternative to the selective fluorination of organic compounds using DAST is the use of modern asymmetric transformations of achiral fluorinated building blocks, a strategy which is becoming more popular for the construction of fluorinated organic molecules. Our proposals for the asymmetric synthesis of 6-deoxy-6-fluorosugars are described in the following section.

1.2.1 Sharpless Asymmetric Epoxidation Route to 6-deoxy-6-fluorohexoses



Scheme 7

Allylic fluoride **32** could be a very useful substrate for deploying Sharpless Asymmetric Epoxidation (SAE) chemistry (Scheme 7). This reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity (>90 % ee),[36] and the strategy has been used for the stereoselective synthesis of hexoses and other carbohydrates[37-39] including D-digitoxose **37** as shown in Scheme 8.[40]

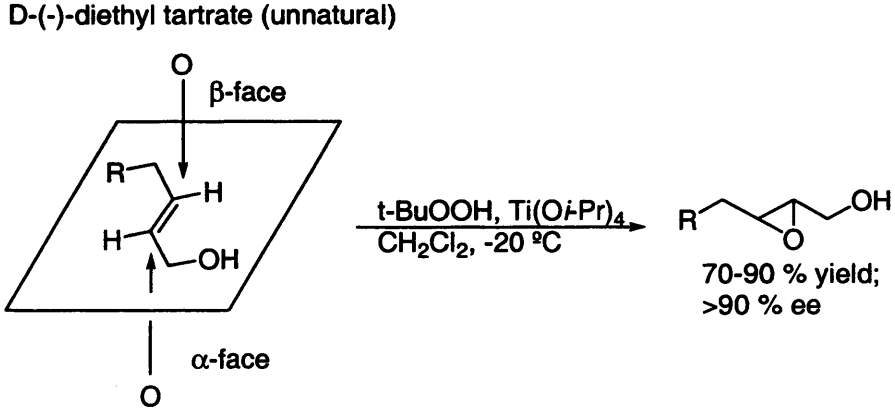


34 **35** **36** **37**

Scheme 8

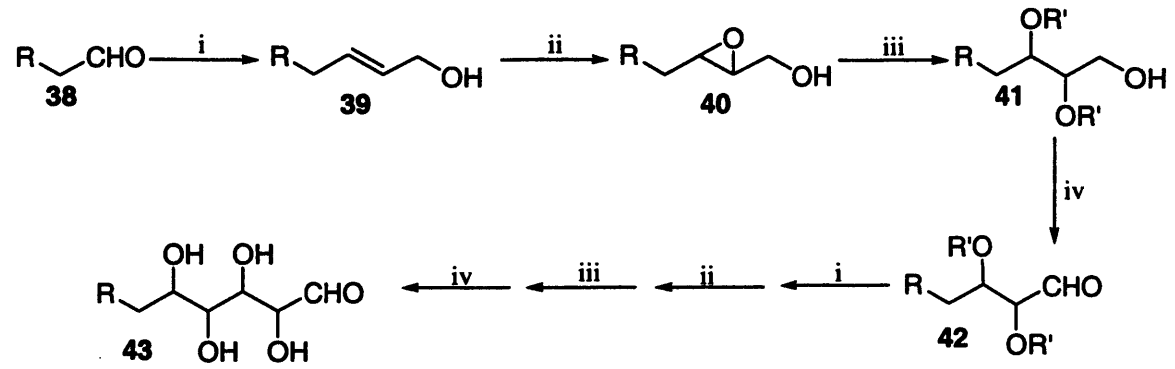
i) $Ti(O^iPr)_4$, TBHP, (+)-DET, CH_2Cl_2, -20 °C; ii) H_2O, Me_2SO; iii) O_3, MeOH, -20 °C; iv) Me_2S.

The stereoselective oxidation is achieved using a titanium (IV) tetra*iso*propoxide as a Lewis acid, *tert*-butyl hydroperoxide, and enantiomerically pure dialkyl tartate. The enantiofacial selectivity of the reaction is predictable;[41] when the D-(-)-tartrate ligand is used in the SAE reaction, the oxygen atom is delivered to the top face (β-face) of the olefin when the allylic alcohol is depicted as in Scheme 9 (i.e. OH group in lower right-hand corner). On the other hand, the L-(+)-tartrate ligand allows the bottom face (α-face) of the olefin to be epoxidized. The SAE reaction exhibits exceptional enantiofacial selectivity (*ca.* 100:1), and provides convenient access to synthetically versatile epoxy alcohols.[42]



Scheme 9

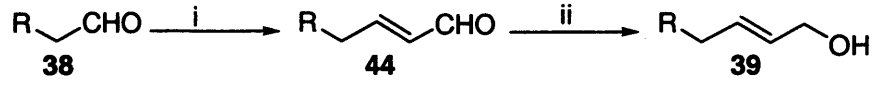
The Masamune-Sharpless hexose synthesis strategy is based on the reiterative application of a two-carbon chain extension cycle. One cycle consists of the following four key transformations (Scheme 10): (a) homologation of an aldehyde to an allylic alcohol; (b) Sharpless asymmetric epoxidation of the allylic alcohol; (c) stereospecific and regioselective opening of the epoxide ring; and (d) oxidation of the primary alcohol to the corresponding aldehyde thereby setting the stage for another cycle.



Scheme 10
i) reductive homologation of an aldehyde to an allylic alcohol;
ii) Sharpless asymmetric epoxidation;
iii) stereospecific and regioselective opening of the oxirane ring;
iv) oxidation of the primary alcohol to the corresponding aldehyde

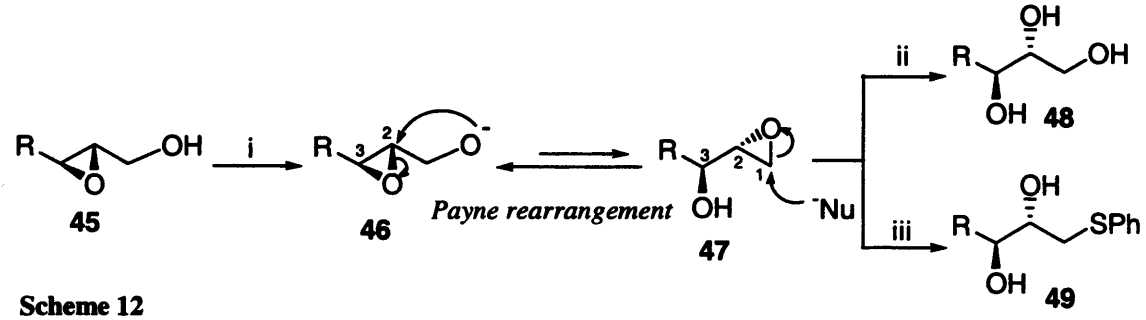
This concise and flexible strategy provides several opportunities for controlling stereochemical relationships. With respect to stage (i) of the cycle, it ought to be possible to define the geometry of the allylic alcohol **39** *via* an *E* or *Z* selective Wittig reaction. In stage (ii), the stereo-directing influence of the appropriate tartrate ligand determines which face of the allylic alcohol is epoxidized. But even if the first two stages proceed with exceptional stereoselectivity, correct relative stereochemical relationships can be secured only in stage (iii) when the intermediate epoxy alcohol **40** can be manipulated in a regio- and stereoselective manner.

The Masamune-Sharpless reiterative two-carbon extension cycle starts with a *E* selective Wittig reaction; treatment with formylmethylenetriphenylphosphorane smoothly achieves the desired two-carbon extension (Scheme 11), furnishing the corresponding *E*-enal **44** (α,β-unsaturated aldehyde) in excellent yields usually with >20:1 stereoselectivity. Sodium borohydride reduction of the aldehyde gives the corresponding *E*-allylic alcohol **39**.



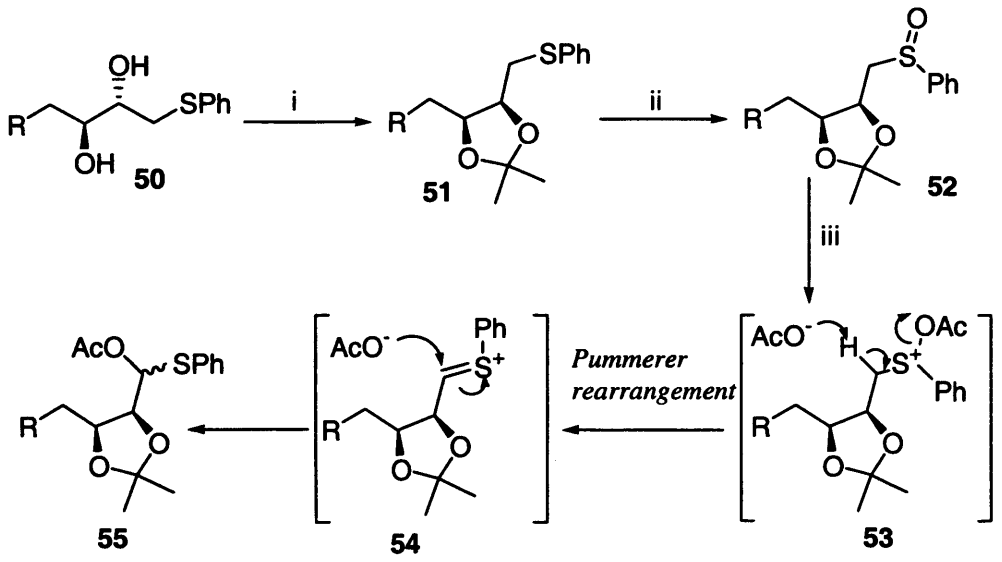
Scheme 11
(i) Ph_3P=CHCHO; (ii) $NaBH_4$.

The next stage involves Sharpless asymmetric epoxidation of the allylic alcohol **39**. The 2,3-epoxy alcohol **46** obtained possesses two electrophilic sites: one at C-2, and another at C-3. But in addition, C-1 of a 2,3-epoxy alcohol also has latent electrophilic reactivity. 2,3-Epoxy alcohols can undergo a reversible, base-induced epoxide migration reaction which is known as the *Payne rearrangement* (Scheme 12).



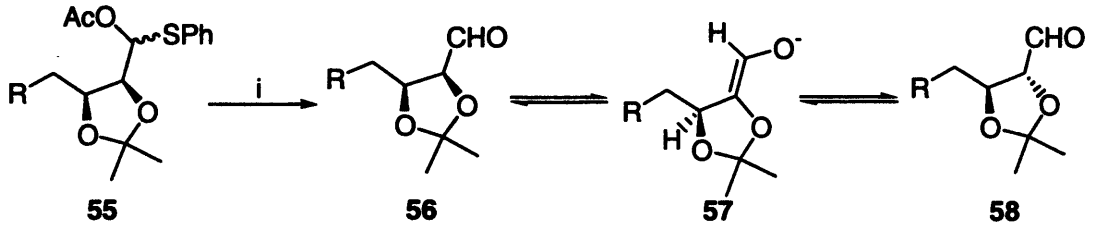
Scheme 12
(i) NaOH; (ii) H_2O / *t*-BuOH; (iii) PhSH, H_2O / *t*-BuOH.

Triol **48** is not suitable for the direct production of polyhydroxylated hexoses because it contains three free hydroxyl groups which would be difficult to manipulate selectively. In the Masamune-Sharpless reiterative cycle, the addition of a suitable nucleophile (thiophenol) to the equilibrating mixture of the epoxy alcohols can result in the regioselective and irreversible interception of the less hindered 1,2-epoxy-3-ol isomer **47** generated in the *Payne rearrangement*, generating the 1-phenylthio-2,3-*erythro*-diol **49** (2,3-*anti*).



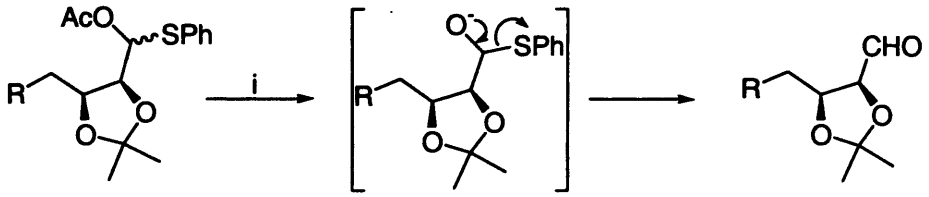
Scheme 13
(i) 2-methoxy-propene; (ii) *m*-CPBA; (iii) Ac_2O, NaOAc.

Release of the aldehyde from the phenylthio hemiacylal (geminal acetoxy sulfide) after the protection of the vicinal hydroxyl groups, will set up another cycle. The oxidation of the sulfide atom to the corresponding sulfoxide with *m*CPBA, followed by *Pummerer rearrangement*, affords geminal acetoxy sulfide **55** (Scheme 13).



Scheme 14
(i) K_2CO_3, MeOH.

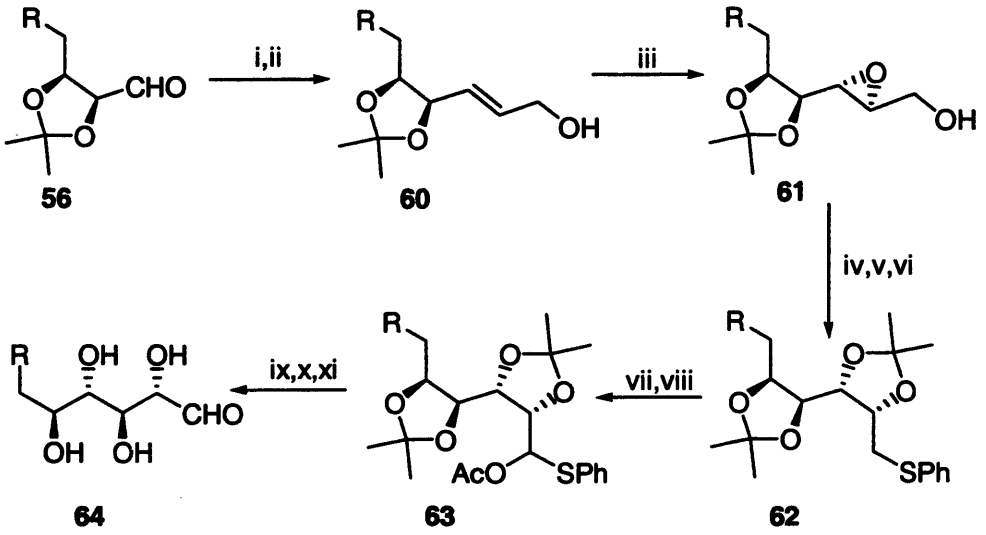
The acetoxythioacetal function in **55** is simply a latent aldehyde, which with basic methanol will release the *erythro* aldehyde **56**, which will give the more stable *threo* (*syn*) diastereoisomer **58** after a base-induced epimerization at C-2 (Scheme 14). The C2-C3 cyclic ketal in addition to its protecting group role, also prevents a destructive β-elimination of the C-3 alkoxy substituent, by maintaining orthogonality between the enolate π system and the C3-O σ bond.



Scheme 15
i) DIBAL-H, -78 °C.

The conversion of the acetoxythioacetal **55** to *erythro* aldehyde **56** can be accomplished with di*iso*butylaluminum hydride (DIBAL-H), a non-basic reagent which promotes reductive cleavage of the C-1 acetoxy group, collapse of the tetrahedral alkoxide intermediate and expulsion of the benzenethiolate anion to afford the desired *erythro* aldehyde **56** without epimerization at C-2 (Scheme 15).

The synthesis of aldehyde intermediates **56** and **58** marked the completion of the first turn of the cycle and set the stage for the second turn where they are pivotal synthetic intermediates from which all eight L-hexose diastereoisomers can be derived.

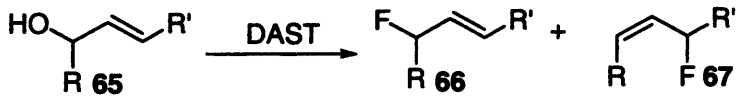


Scheme 16
(i) Ph_3P=CHCHO; (ii) $NaBH_4$; (iii) SAE, (+)-DIPT; (iv) NaOH, PhSH; (v) H_2O / *t*-BuOH; (vi) 2-methoxy-propene; (vii) *m*-CPBA; (viii) Ac_2O, NaOAc; (ix) DIBAL-H, -78 °C; (x) TFA-H_2O; (xi) H_2, Pd-C.

L-allose analogue **64** could be derived from *threo* aldehyde **56** (Scheme 16); treatment of **56** with formylmethylenetriphenylphosphorane smoothly achieves the desired two-carbon extension, furnishing the corresponding *E*-enal; sodium borohydride reduction of the aldehydes give the correponding *E*-allylic alcohol **60** which is epoxidized with (+)-di*iso*propyl tartrate [(+)-DIPT] ligand. Epoxide ring opening and simultaneous protection and oxidation of sulfide **62** will afford an acetoxythioacetal **63**. Final acetoxythioacetal cleavage without epimerization with DIBAL-H and deprotection via cleavage of the *iso*propylidene ketals with aqueous trifluoroacetic acid afforded the desired L-allose analogue **64**.

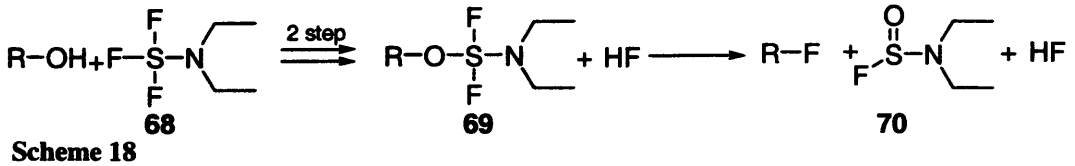
Although fluoroallylic alcohol **32** could be useful for deployment in Sharpless Asymmetric Epoxidation chemistry, it is not a readily available fluorine-containing building block. To explore a Sharpless-based approach, we need a reliable economic and scaleable synthesis of this substrate on the laboratory scale.

Although diethylaminosulfur trifluoride (DAST) is used in a one-step reaction for the introduction of fluorine into organic compounds, **32** cannot be synthesized using this reagent because it will produce a mixture of the desired and rearranged products according to literature precedents described by Smith *et al.*(Scheme 17).[43]



Scheme 17

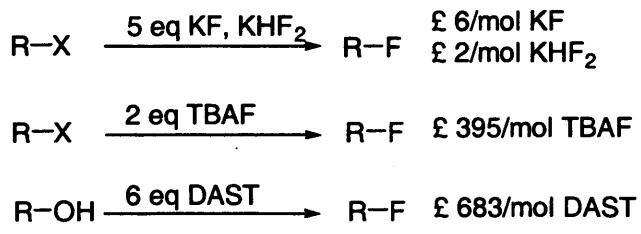
There are other disadvantages related to the direct nucleophilic fluorination with DAST, which are the cost of the reagent, the need to use a large excess of reagent in many cases, and because it decomposes exothermically to generate hydrofluoric acid during the reaction (Scheme 18).



Scheme 18

Alternatively, the synthesis of the fluorine-containing species can also be accomplished by the nucleophilic displacement of halides, sulfonates and tosylates by fluoride ion, which is the most economic method for the introduction of a single fluorine atom into organic compounds.

Scheme 19 compares the costs of using different fluorinating agents. Although the prices per mole of DAST and TBAF are very similar, DAST is even more costly because a large excess is often required.



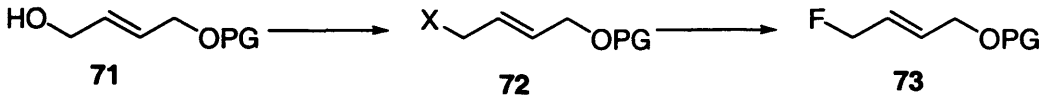
Scheme 19. Comparison of cost of different fluorinating reagents.
Aldrich UK catalogue 2005-2006

Alkali metal fluorides such as potassium fluoride (KF), calcium fluoride (CaF_2) and cesium fluoride (CsF) are the traditional reagents. However, limited solubility in organic solvents and low nucleophilicity mean that vigorous conditions are generally required.[44] Tetrabutylammonium fluoride, has been shown to be effective for the substitution of halides and tosylates with high yields, but its large molecular weight compared to that of KF makes TBAF relatively expensive and creates too much chemical waste.

The synthesis of fluoroallylic alcohol **32** seems challenging; also the size and structure of the molecule, which could easily be metabolized to fluoroacetic acid presents a potentially serious health hazard during manipulation. However, this is true of any terminally-fluorinated molecule with an even number of carbon atoms. Although this strategy presents many difficulties, an alternative to Sharpless Asymmetric Epoxidation is the Asymmetric Dihydroxylation.

1.2.2 Sharpless Asymmetric Dihydroxylation

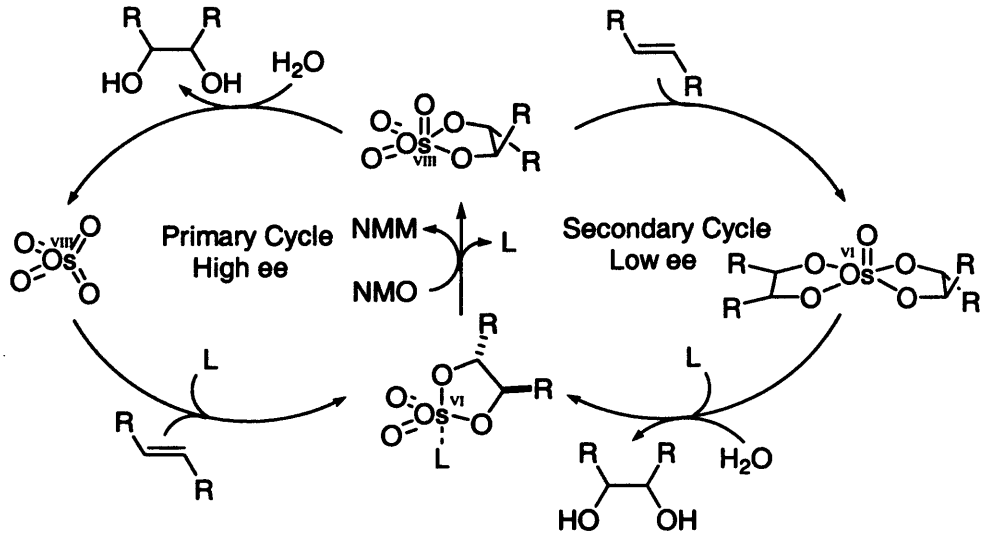
Compounds like allylic fluoride **73** can be synthesized (Scheme 20), but they are not the most appropriate substrates for deployment in Sharpless Asymmetric Epoxidation (SAE) chemistry, because SAE requires the presence of an allylic alcohol for the control of the enantioselectivity during the epoxidation.



71 **72** **73**

Scheme 20

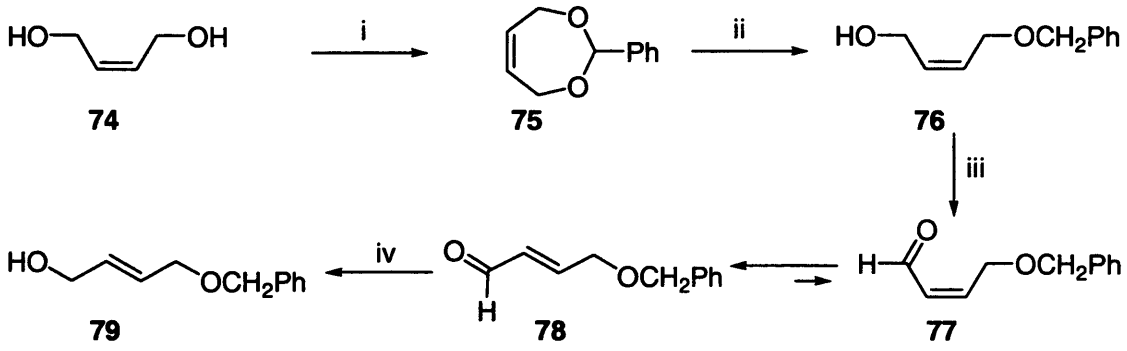
They could however be very useful for enantioselective dihydroxylation by Sharpless Asymmetric Dihydroxylation.[45-47]



Scheme 21

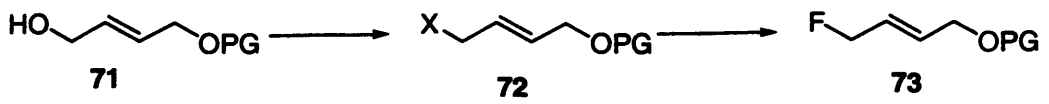
Sharpless Asymmetric Dihydroxylation (S-AD) requires the presence of an *E*-allylic substrate for the control of the enantioselectivity. *Z*-allylic substrates are not viable substrates for Sharpless AD, reacting slowly and often with low stereoselectivity; they can, however, be *cis* dihydroxylated[48] under typical UpJohn conditions, using *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant (Scheme 21).[49]

According to literature procedure of Danishefsky *et al.*,[50] and used by Sharpless *et al.*,[37] the monoprotected *E*-allyl alcohol **79** can be synthesized from commercial *cis*-2-buten-1,4-diol (Scheme 22).



Scheme 22
(i) PhCHO, acid catalyst; (ii) DIBAL-H; (iii) oxidation (see text); (iv) $NaBH_4$.

This allyl alcohol **79** could then be fluorinated by the nucleophilic displacement of a halide, mesylate or tosylate, giving a novel fluorinated building block. However, no details have ever been published for the oxidation of **76** to **77**.

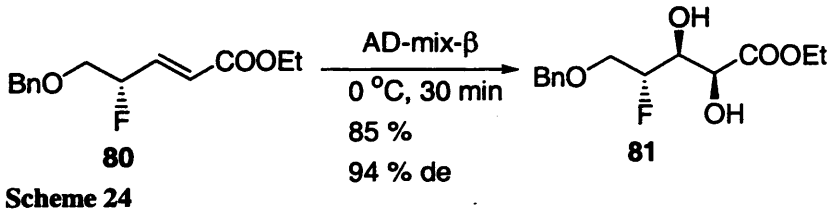


Scheme 23

X: Halide, OMs or OTs
PG: Bn or PMB

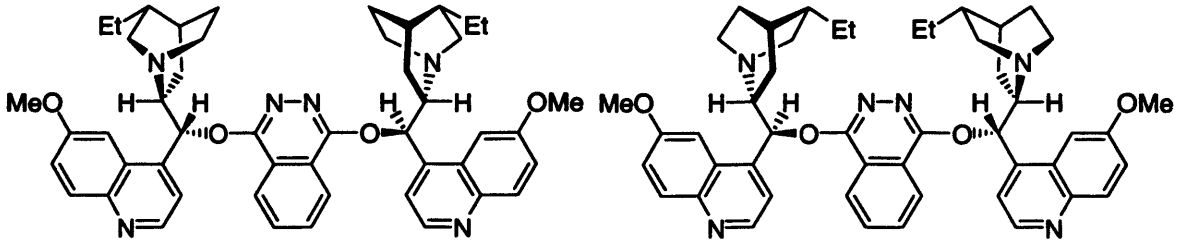
This strategy would allow us to use compound **73** without deprotection, avoiding the disadvantages of the deprotected allyl fluoride **32** (PG = H, Scheme 23), a compound with low molecular weight and presumably, high volatility.

Sharpless AD accomplishes the dihydroxylation of alkenes with excellent stereoselectivity (>90 % ee) depending on the olefin substituents. Even though OsO_4 is an electrophilic reagent, and thus the rate of osmylation of electron-deficient olefins such as α,β-unsaturated carbonyl compounds can be very slow,[51] Davis *et al.*[52] successfully performed the dihydroxylation of allyl fluoride **80**, in short time, good yield and excellent stereoselectivity (Scheme 24).



Scheme 24

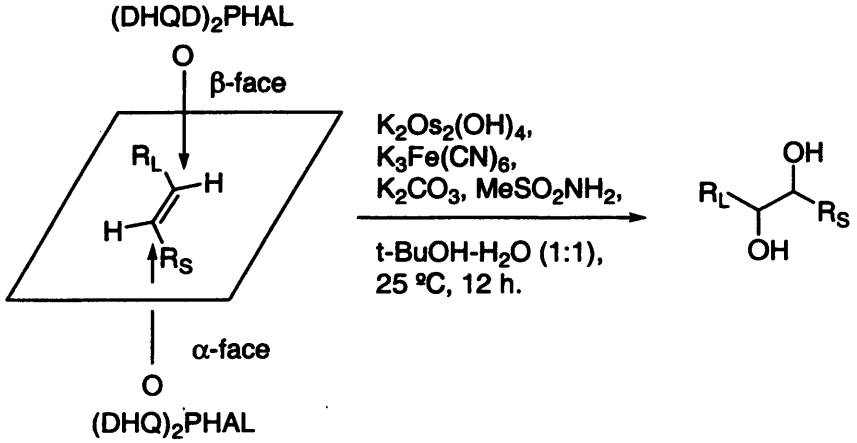
The dihydroxylation is performed using: dipotassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$) (catalytic oxidant, 0.4-0.2 %), with $K_3Fe(CN)_6$ (stoichiometric oxidant), $MeSO_2NH_2$ (base) and enantiomerically pure alkaloid dihydroquinine phthalazine **82** [$(DHQ)_2PHAL$] ligand (2.5:1 ligand/Os), to dihydroxylate the α-bottom face, or dihydroquinidine phthalazine **83** [$(DHQD)_2PHAL$] ligand to dihydroxylate the β-top face, in equal amounts of water and *tert*-butanol. Performing the reaction at low (typically 0 °C) temperature increases stereoselectivity. The combination of ligand, osmium and iron reagents is a commercially available solid mixture known as "AD-mix α" or "AD-mix β" (depending on the ligand).[45]



$(DHQ)_2PHAL$
82

$(DHQD)_2PHAL$
83

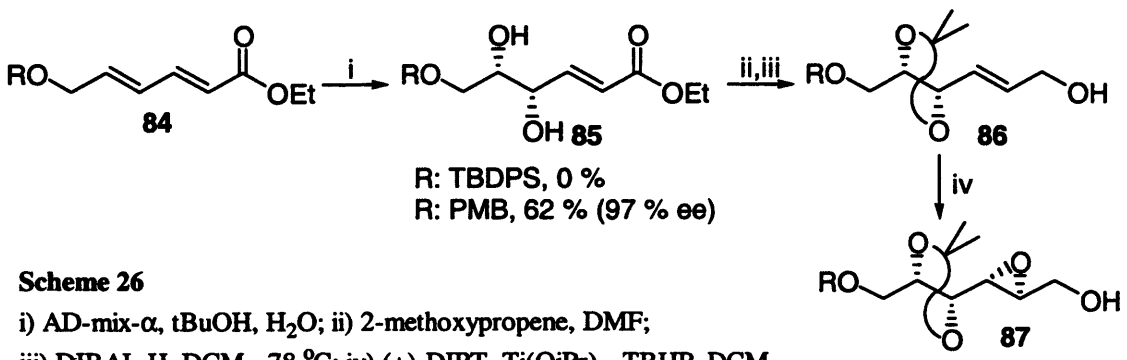
The stereochemistry of the reaction is predictable when the largest substituents of the olefin are located as in Scheme 25. The AD reaction exhibits exceptional enantiofacial selectivity (*ca.* 100:1), and provides convenient access to synthetically versatile diols.[45]



Scheme 25
R_L: Largest Substituent; R_S: Smallest substituent;
The composition containing $(DHQ)_2PHAL$ is termed AD-mix-α
The composition containing $(DHQD)_2PHAL$ is termed AD-mix-β

R_L and R_S are the substituents of the olefin; in our case R_S would be a CH_2F group and R_L the protected hydroxymethyl group.

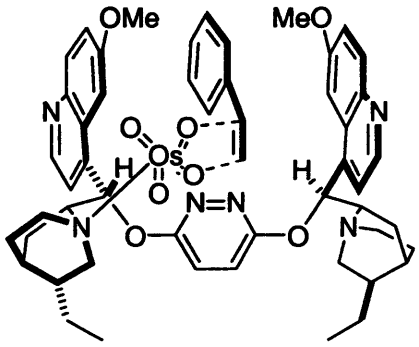
The enantioselectivity obtained in asymmetric dihydroxylation of 6-hydroxyhexa-2,4-dienoic acid derivatives is sensitive to the nature of the hydroxyl protecting group.[53] *p*-Methoxybenzyl protection has been used effectively in Sharpless AD on different substrates giving fast reactions with good yields and excellent stereoselectivity (Scheme 26).[46,47]



Scheme 26

i) AD-mix-α, tBuOH, H_2O; ii) 2-methoxypropene, DMF;
iii) DIBAL-H, DCM, -78 °C; iv) (+)-DIPT, $Ti(OiPr)_4$, TBHP, DCM.

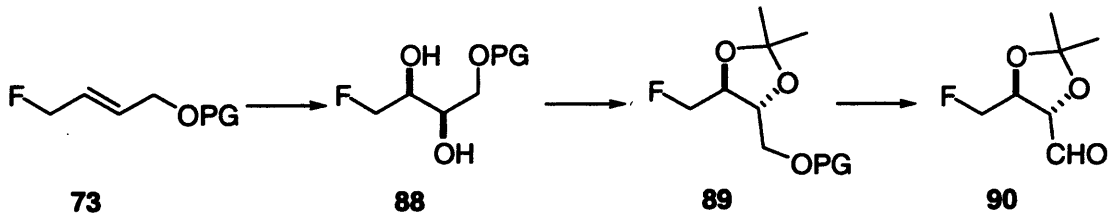
Excellent binding of allyl *p*-methoxybenzoate or *p*-methoxyphenyl ether can be expected because of extensive π-contact of both faces of the allyl and anisoate moieties with the two methoxyquinoline units and edge contact with the pyridazine ring.[54] The proposed transition-state assembly for the face-selective dihydroxylation of styrene is shown in Figure 1, where the mechanistic pathway has a preference for the U-shaped conformation, which has the ability to hold olefinic substrates in a binding pocket composed of the two parallel methoxyquinoline units, OsO_4 and the pyridazine connector.[55]



$(DHQD)_2PYDZ$
Figure 1

The regioselectivity of mono-dihydroxylation of a diene is determined both by electronic and by steric effects. The dihydroxylation occurs in the more electron rich double bond, distant to the electron withdrawing ester group due to the unfavorable interactions with the binding pocket of the AD ligand. The sterically most accessible site is dihydoxylated preferentially.[51]

Once protected-*E*-allylic fluoride **73** is dihydroxylated, protected and oxidized (Scheme 27), it can be taken through the Masamune-Sharpless hexose route or cycle (Scheme 16).

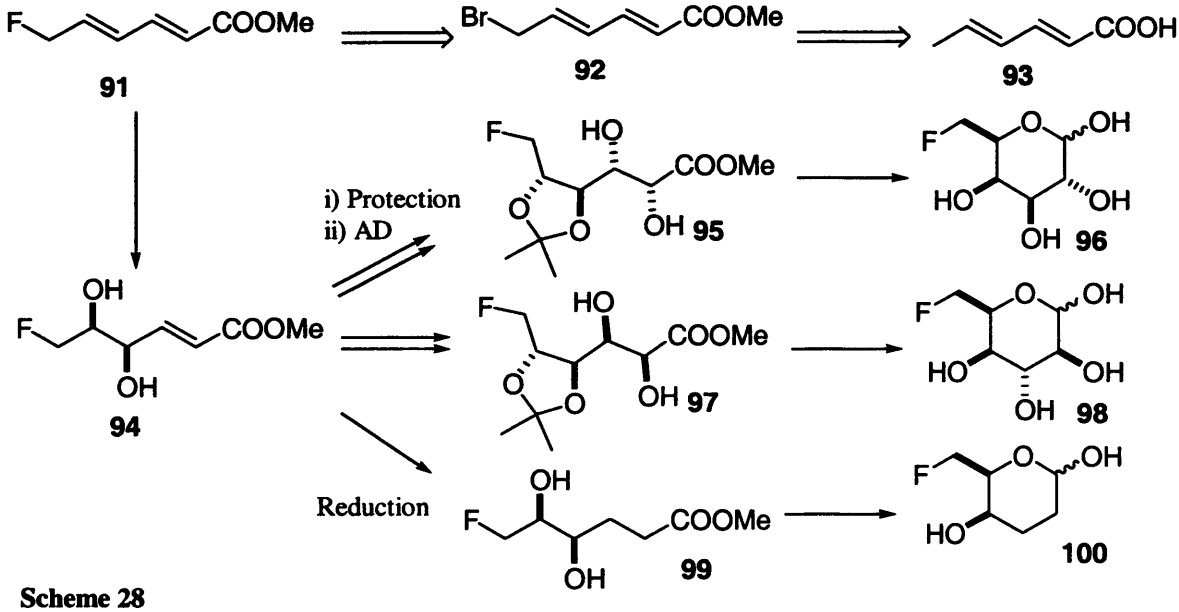


73 **88** **89** **90**

Scheme 27

1.2.3 Route to 6-fluoro-2,3,6-deoxyhexoses and 6-deoxy-6-fluorohexoses

Another strategy for the stereoselective synthesis of 6-deoxy-6-fluorosugars is based upon cheap and commercially available sorbic acid, where the successful preparation of ester **91** sets the stage for a new general fluorine-containing building block approach (Scheme 28).

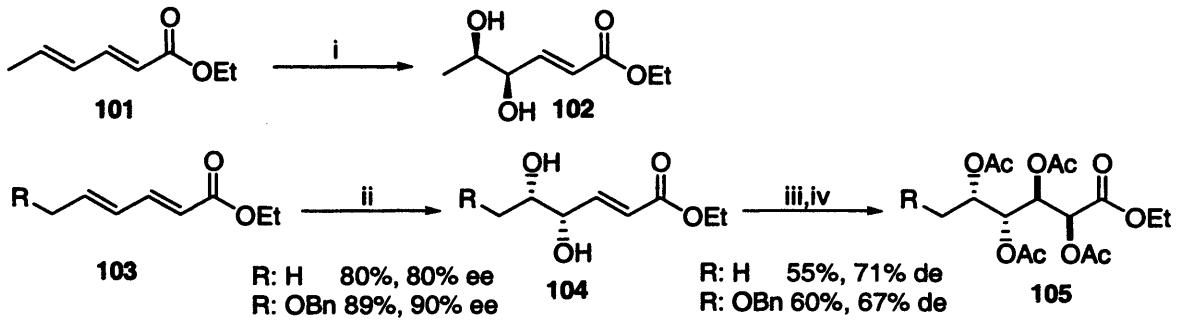


Scheme 28

Although the rate of dihydroxylation of protected diols is lower than the corresponding free diols, they are preferred as tetrols are difficult to purify and also low enantioselectivities are generally obtained in the dihydroxylation of allylic alcohols;[47] reduction of the ester and lactonisation would deliver **96**. For the dihydroxylation of

conjugated dienes, $K_3Fe(CN)_6$ is preferentially used as the stoichiometric oxidant, to avoid the formation of tetrols, in place of NMO, where the trioxo Os(VIII) glycolate has stronger affinity for first formed ene diol.[56]

The 6-deoxy-6-fluorohexoses can be derived initially from the asymmetric dihydroxylation of diene **91**, where ene diol **94** would be the expected product as described for ethyl sorbate[56,57] and other 6-deoxy substituted sorbic esters (Scheme 29).[58,59]

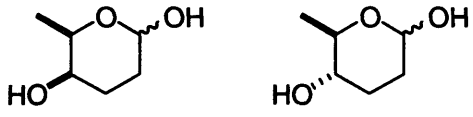


Scheme 29

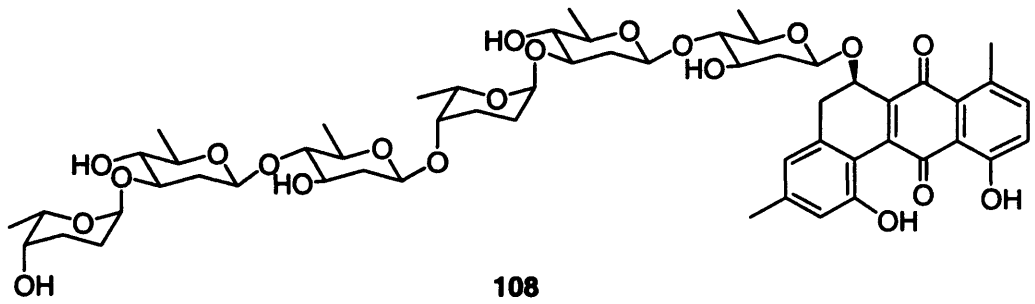
i) AD-mix-β, 78%, 92 % ee; ii) AD-mix-α; iii) OsO_4, NMO, ^tBuOH, Acetone; iv) Ac_2O, Pyridine.

The synthesis of 6-fluoro-2,3,6-trideoxyhexoses **100** could also be achieved from the reduction and lactonisation of **99**, synthesized from the hydrogenation of allylic diol **94**.

1.2.4 Synthesis of 6-deoxy-2,3,6-trideoxysugars

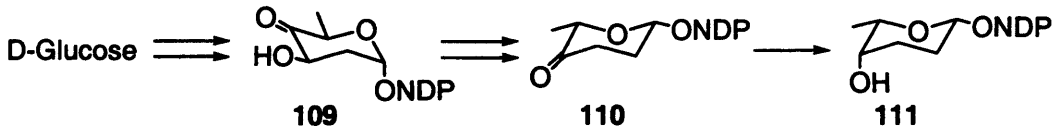


2,3,6-Trideoxyhexoses rhodinose **106** (2,3,6-trideoxy-D-*threo*-hexose) and amicetose **107** (2,3,6-trideoxy-D-*erythro*-hexose) are found as glycosidic components in a wide range of antibiotics including landomycins (Landomycin A in figure **108**)[60], urdamycins[21], kerriamycins A and B (isotetracenone antibiotics),[61] axenomycin[62,63] and amicetin[64,65] in which the sugar is always linked to an aglycone.[66]



108

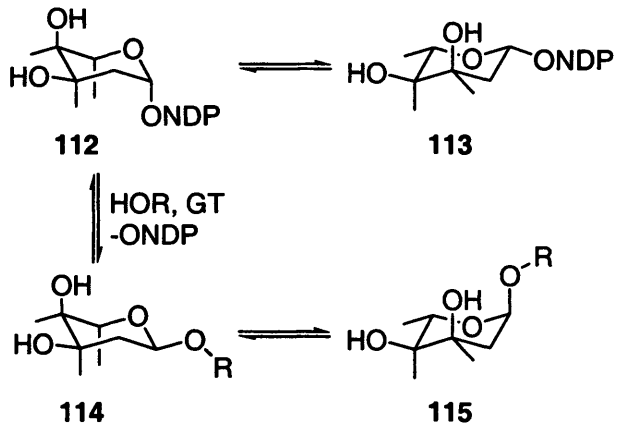
Deoxygenated hexoses are biosynthetically derived from D-glucose, and the biosynthetic pathway for rhodinose has been extensively studied; part of the pathway is shown in Scheme 30.[23,60]



109 110 111

Scheme 30

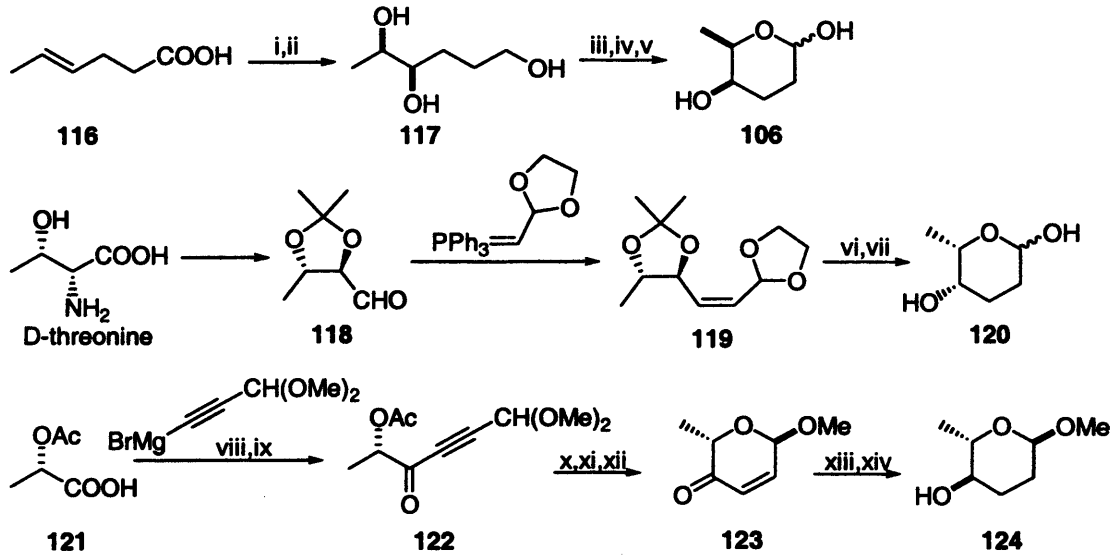
Landomycin A contains olivoses and rhodinoses, all bonded through an α–glucosidic linkage and the substrate is β-*O*-NDP-activated deoxysugar; although this is the expected substrate that delivers the α–glucosidic linkage with inversion of configuration, there is some ambiguity as this substrate lacks anomeric stabilization. From studies of spinosyn biosynthesis, it has been found that the substrate is flipped to its higher-energy (but anomerically stabilized) conformer (Scheme 31)[67] before glycosylation.



112 113 114 115

Scheme 31

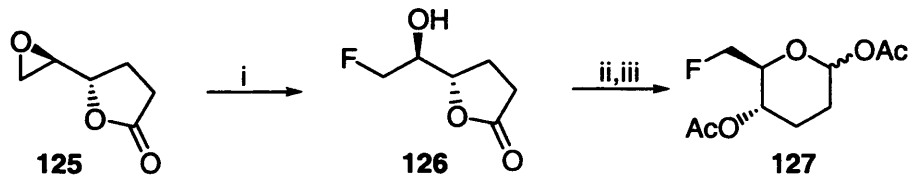
Amicetose **107** and rhodinose **106** have been prepared in their optically active forms by lengthy reaction-sequences starting from abundant natural sugars[68,69] or natural products[66,70-72], or in racemic form by simple routes (Scheme 32).[73,74]



Scheme 32

i) $LiAlH_4$; ii) H_2O_2, HCOOH; iii) Acetone, $CuSO_4$, H_2SO_4; iv) $AgCO_3$, C_6H_6; v) H_2SO_4; vi) Pd/C, H_2; vii) AcOH; viii) $SOCl_2$; ix) CuCl; x)$Pd/BaSO_4$, H_2; xi) NaOH, H_2O, dioxane; xii) CCl_4, H_3PO_4; xiii) Pd/C, H_2; xiv) $LiAlH_4$, Et_2O.

Fluoro analogues of amicetose have been synthesized from 5,6-epoxyhexonolactone **125** as described in scheme 33,[75] but this approach is not convenient for larger scale preparations as synthesis of epoxide **125** already involves 4 steps (22 % yield) from calcium D-gluconate,[76-78] giving 6-fluoroamicetoside **127** in a 5 % overall yield.

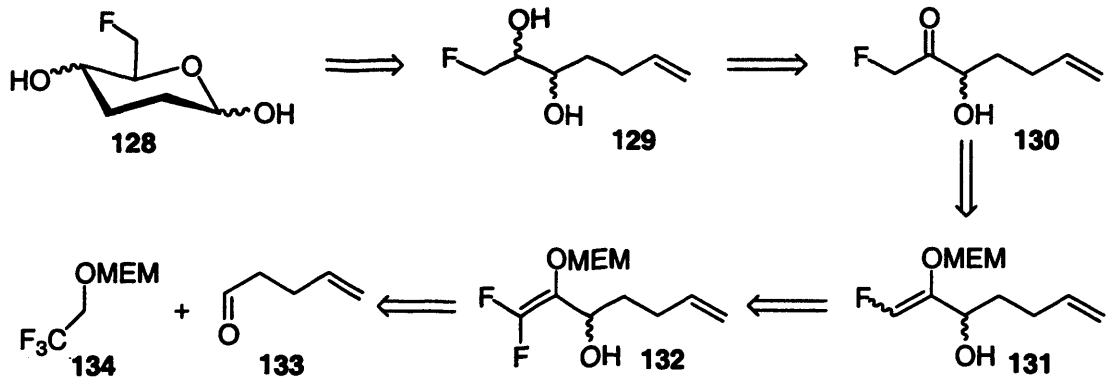


Scheme 33

i) $Et_3N{\cdot}3HF$; ii) disiamylborane; iii) Ac_2O, pyridine.

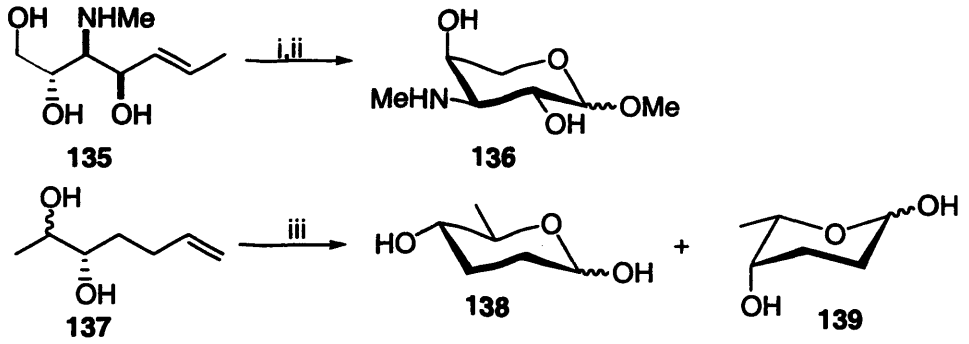
1.2.5 A Rapid Route to racemic 6,6-difluoro- and 6-fluoro-2,3,6-trideoxyhexoses

We were also interested in developing a rapid and potentially flexible route to a range of highly deoxygenated fluoro and difluoro sugar analogues based on known chemistry from trifluoroethanol. A short synthesis of 6-fluoro-2,3,6-trideoxyhexoses, analogues of rhodinose **106** and amicetose **107**, is outlined retrosynthetically below (Scheme 34).



Scheme 34

The most crucial step in the synthesis involves the ozonolysis of the alkenyl group in unprotected diol **129**. However, Weinreb *et al.*[79] described the ozonolysis of highly functionalised and unprotected species **135** on silica gel (*p*-toluensulfonic acid is used to protonate and protect the very easy-to-oxidise amino group) (Scheme 35). The synthesis of a mixture amicetose and rhodinose has also been performed using this procedure.[80] As the aldehyde is formed, it is trapped intramolecularly as an hemiacetal.



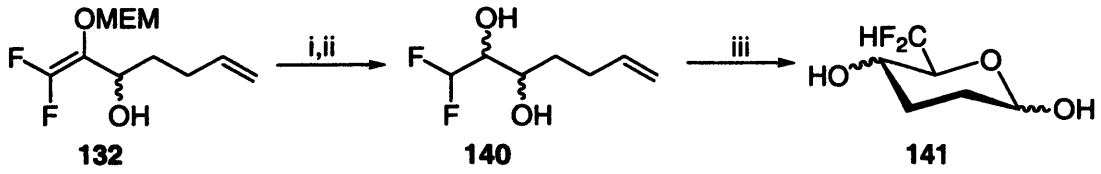
Scheme 35

i) *p*-TsOH, O_3, silica gel, -78 °C; ii) Me_2S, MeOH.

Diol **129** can be obtained from the reduction of ketone **130**. From a stereochemical point of view, compound **129** possesses two contiguous oxygen-bearing stereocenters. Initially non-selective reduction at C-2 of **130** will afford a mixture of *syn*- and *anti*-diol **129**. Further studies may allow stereoselective reduction to be carried out. Compound **130** could be derived from protected allylic alcohol **131**. An important step in the conversion is the cleavage of the (methoxyethoxy)methoxy (MEM) protecting group from the enol function, under mild acid conditions according to literature procedures described by Percy *et al.*.[81] Reductive defluorination of **132** furnishes monofluoroallylic

alcohol **131** and retrosynthetic cleavage of the carbon-carbon bond in **132** provides aldehyde **133** and trifluoroethanol **134** as potential precursors.

The differences between mono- and difluoro species can be compared by synthesizing 6,6-difluoro-2,3,6-trideoxyhexoses **141** from difluoroallylic alcohol **140** (Scheme 36).



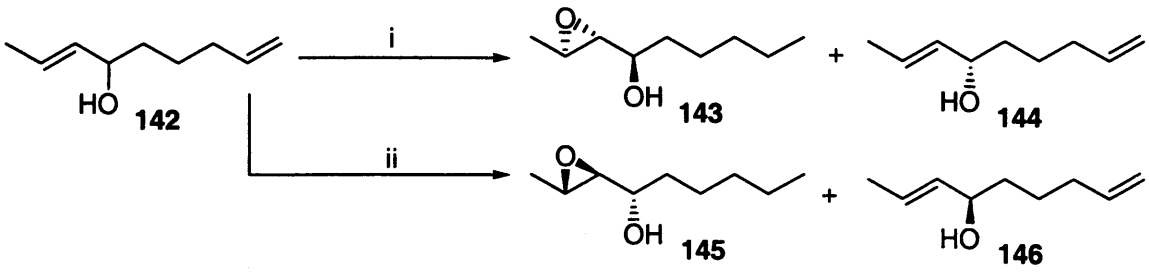
132 **140** **141**

Scheme 36
i) TMSCl / MeOH; (ii) $NaBH_4$; (iii) O_3.

Allylic alcohols related to **132** have been synthesized on a multigramme scale and given the small number of steps involved (5 or 6), this route has great potential for the rapid synthesis of two classes of sugar analogues.

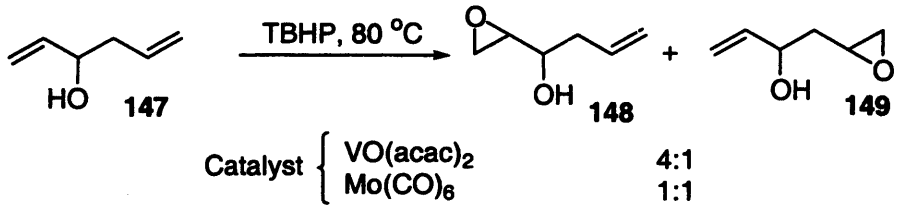
1.2.6 Asymmetric Route using SAE

The key intermediate for the asymmetric synthesis of 6-fluoro-2,3,6-trideoxy-sugars is the enantio-pure form of fluoro diol **129** previously described, which can be synthesized using Sharpless Asymmetric Epoxidation. Similar epoxidations have been described in the literature.[82-84] Kinetic resolution is performed under Sharpless Asymmetric Epoxidation giving one single enantiomer with predictable stereochemistry as described in Scheme 37. In comparison with Sharpless Asymmetric Dihydroxylation, SAE is much more effective at kinetic resolution.[45]



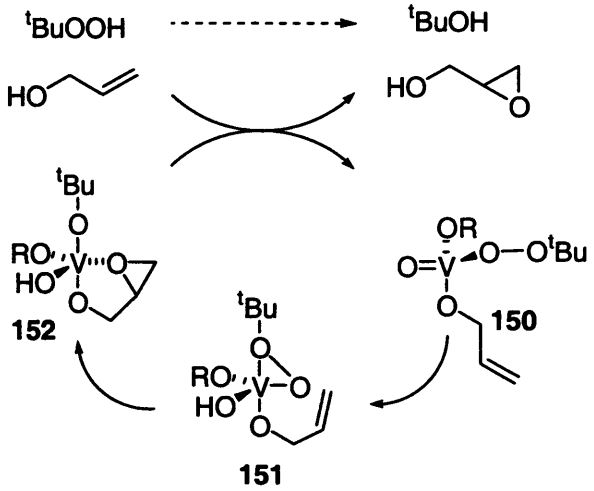
Scheme 37. Sharpless Asymmetric Epoxidation (SAE) and kinetic resolution.
i) $Ti(O^iPr)_4$, D-(-)-DIPT, TBHP, CH_2Cl_2;
ii) $Ti(O^iPr)_4$, L-(+)-DIPT, TBHP, CH_2Cl_2.

Allylic alcohol **142** contains two possible alkene sites for epoxidation, but by using Sharpless Asymmetric Epoxidation, only the allylic group next to the hydroxyl group is oxidized. This regioselective epoxidation can also be performed non-asymmetrically using vanadyl bis(acetonylacetonate), giving racemic and regioisomeric mixtures as described in Scheme 38 for a very similar substrate (the lower homologue).[85,86] The selectivity of these metal-catalyzed epoxidations has been studied showing that selectivity is poor and dependent on the structure of the substrate.[86]



Scheme 38. Directed Metal-Catalyzed Epoxidation.

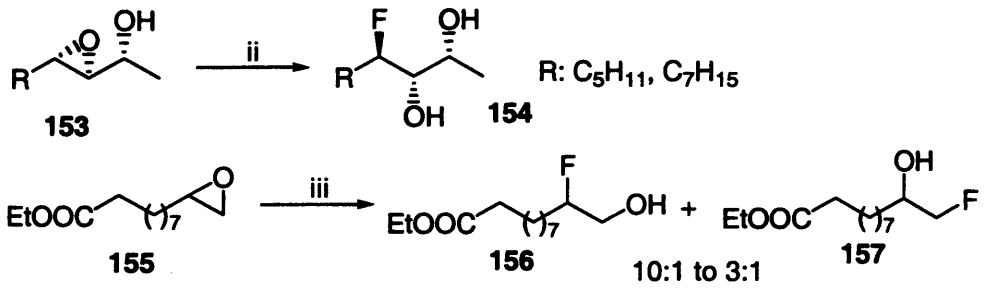
Sharpless has proposed that the vanadium-catalyzed reaction proceeds through the cycle depicted in scheme 39,[86] where the lower valent $VO(acac)_2$ complex is oxidized by TBHP to a catalytically active d^0 vanadate ester ($VO(OR)_3$), which undergoes rapid ligand exchange to provide **150**. Following activation of the alkylperoxide by bidentate coordination (**151**), nucleophilic attack by the alkene in the rate- and stereochemistry-determining step yields the epoxy alcohol complex **152**.



Scheme 39

Fluorination of terminal epoxides presents another synthetic challenge as they contain two possible centers of nucleophilic attack, one primary and the other secondary.

Fluorinations of terminal epoxides have been reported in the literature, with potassium hydrogen difluoride (KHF_2) used as the fluorinating reagent in ethane-1,2-diol[87] or with tetrabutylammonium dihydrogen trifluoride as catalyst in a solid-liquid phase transfer catalysed reaction.[88-91] Amine·HF salts have also been used to open epoxides as shown in Scheme 40, but while they can be completely regioselective with internal epoxides,[92] they may have very poor regioselectivity with terminal epoxides.[65]

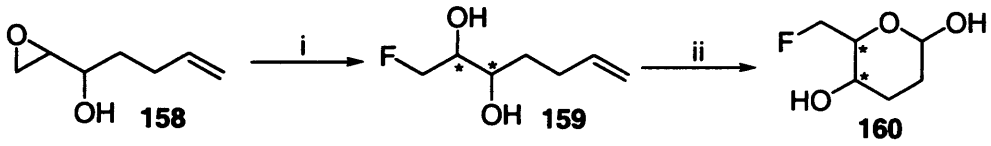


Scheme 40

i) HF·pyridine, CH_2Cl_2, 10 °C, 4h, 62-72 %;

ii) 50-70% HF·pyridine, CH_2Cl_2, 10 °C, 74-83 %.

Successful preparation of fluoro diol **159** sets the stage for an asymmetric synthesis of 6-fluoro-2,3,6-trideoxysugars. Diols **159** could be ozonolysed to afford analogues of amicetose and rhodinose (Scheme **41**).



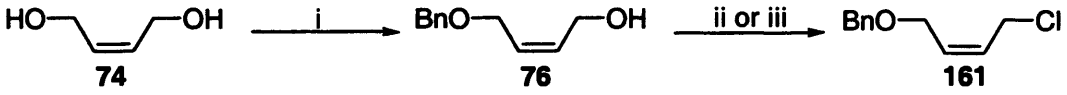
Scheme 41

i) Fluorination; ii) Ozonolysis.

2 Results and Discussion

2.1 Synthesis of allyl fluorides

Before Sharpless asymmetric methodologies can be used, synthetic routes to allyl fluorides must be secured, so our first objective was to explore reactions of allyl halides with different nucleophilic fluoride sources. For this purpose we selected allyl chloride **161** as the first substrate. It was synthesized according to literature procedures from known allyl alcohol **74** (Scheme 42).

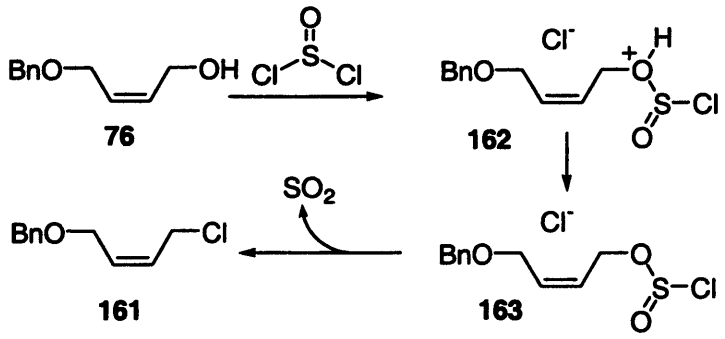


74 **76** **161**

Scheme 42
i) NaH, BnBr, DMF,75 %; ii) MsCl, *s*-collidine, LiCl, DMF, 81 %; or iii) $SOCl_2$, Et_2O, 82 %.

Allyl alcohol **76** was prepared from cheap and commercially available *Z*-1,4-butenediol and benzyl bromide (75 %);[93] allyl chloride **161** was obtained in good yield (81 %), after Kugelrohr distillation, by the treatment of allyl alcohol **76** with freshly distilled mesyl chloride, *s*-collidine and anhydrous lithium chloride.[94] The reaction mechanism of this procedure involves the formation of a reactive sulfonic ester intermediate and ends with the displacement of the mesylate by chloride.

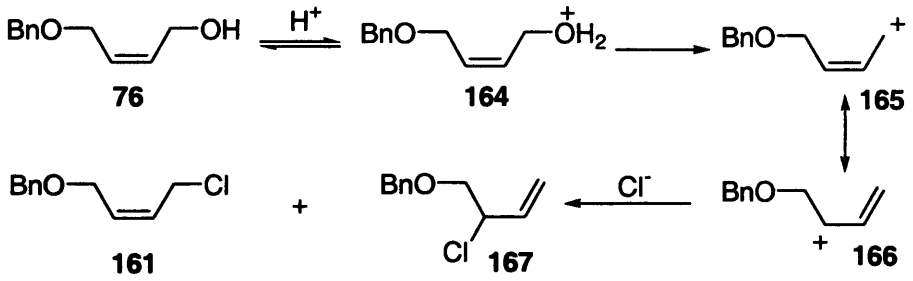
Alternatively, according to another literature procedure on different substrates,[95] allyl chloride **161** was also synthesized more easily and efficiently in good yield by a simple addition of thionyl chloride ($SOCl_2$) to a solution of allyl alcohol **76** in diethyl ether, affording a clear, colourless oil which was purified by Kugelrohr distillation. The allyl chloride was obtained in 82 % yield on a 34 mmole scale in this way.



Scheme 43

The reaction follows an S_N2 mechanism (Scheme 43) that starts with the reaction of thionyl chloride with allyl alcohol **76** to form an allyl chlorosulfite **162**, an unstable and highly electrophilic intermediate. Deprotonation of the intermediate, and thus HCl formation, gives an electrophile powerful enough to react even with weakly nucleophilic Cl^- giving the desired allyl chloride **161** and sulphur dioxide. Loss of the gaseous by product drives the reaction to completion.

In this procedure, it is essential to avoid the presence of water, because thionyl chloride hydrolyses rapidly to SO_2 and HCl. Reaction of allyl alcohol **76** with HCl, instead of thionyl chloride, generates an oxonium ion **164** (Scheme 44), which eliminates water to produce an unsymmetrical allylic cation **165**. Trapping the most stable resultant secondary carbocation with the gegenion of the acid (Cl^-) gives a mixture of allyl chlorides **161** and **167**.



Scheme 44

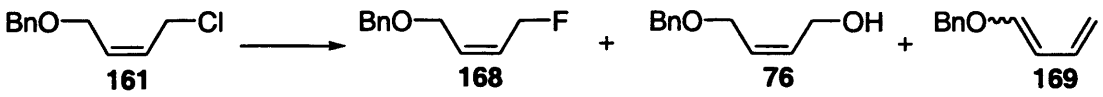
Allyl chloride **161** was used for the study of the nucleophilic displacement of halides with different sources of fluoride under a range of reaction conditions. Our first attempts

to react alkali metal fluorides such as anhydrous potassium fluoride with allyl chloride **161** neat or in solution with different solvents (CH_3CN, THF) at reflux were unsuccessful.

Lipophilic quaternary ammonium fluorides, in particular tetrabutylammonium fluoride (TBAF), find widespread use as organic sources of fluoride anion for nucleophilic fluorination reactions in aprotic solvents.[96] However, the high hygroscopicity of these salts imposes severe limitations upon their use. Tetraalkylammonium fluorides are obtained as stable trihydrate products, whereas attempts at complete dehydration are usually accompanied by extensive decomposition of the quaternary fluoride via a Hofmann-like elimination reaction. Even so, "anhydrous" TBAF can be prepared by heating the commercial TBAF trihydrate at 40 °C under high vacuum for several hours.[97]

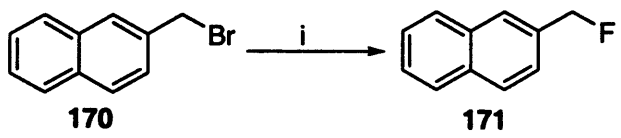
The distribution of the reaction products depends strongly on the TBAF hydration state. It has been reported that "anhydrous" TBAF gives moderate yields of fluorination and elimination products, while pentahydrated TBAF in the absence of solvent gives the best results.[96] TBAF is a powerful nucleophilic fluorinating agent, and increasing the hydration level results in the basicity being much decreased relative to its nucleophilicity.[96]

In our case "anhydrous" TBAF behaved as a poor source of nucleophilic fluoride, generating the expected fluoro derivative **168** in poor yield; elimination and hydrolysis side products identified by GC-MS dominated the reaction mixture (Scheme 45).



Scheme 45

The yields and outcomes of our initial fluorination reactions with TBAF were poor to moderate and difficult to reproduce. Ionic liquids have been regarded as eco-friendly replacements for volatile organic solvents in current chemical processing due to their unique physical and chemical properties. According to a literature reference, a new method of fluorination using KF in $BmimBF_4$ was reproduced successfully (Scheme 46).[44]



170 **171**

Scheme 46
i) KF, [bmim][BF_4], H_2O, acetonitrile, 90 °C, 2 h, 73 % (Lit. yield 93 %).

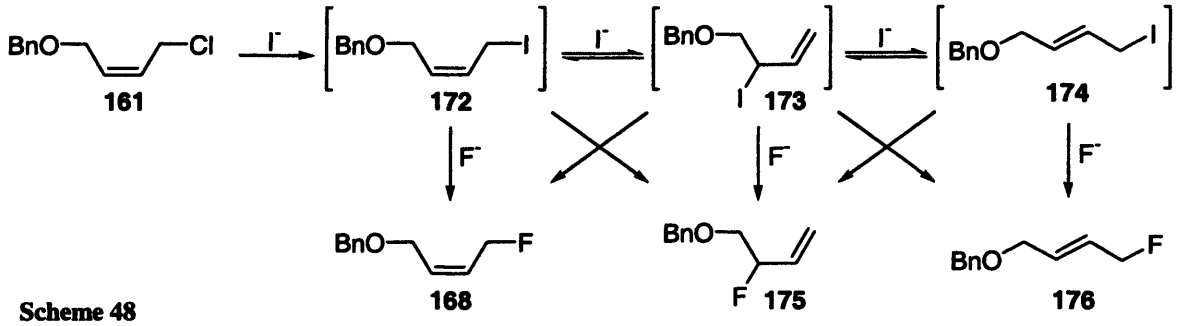
However, using this method with allyl chloride **161** lead to the formation of the fluorinated product in low yield, and in an attempt to improve the reaction, changing the counter ion of $BmimBF_4$ to PF_6, resulted in no reaction. This difference in reactivity between the two ionic liquids tested, is due to different physical properties; $BmimBF_4$ can solvate cations better than $BmimPF_6$ and is therefore a superior solvent for very polar inorganic salts.[98,99]

To improve the global exchange of fluorination, we employed a solid-liquid phase mixture of potassium fluoride and tetrabutylammonium iodide to synthesize catalytic amounts of TBAF *in situ* (Scheme 47).[100,101]

$$Bu_4NX + KF \rightleftharpoons Bu_4NF + KX \xrightarrow{R\text{-}X} R\text{-}F + Bu_4NX$$

Scheme 47

This reaction was followed by GC-MS and we obtained very exciting and unexpected results. We observed that the chromatogram contained another peak, with nearly the same retention time and the exactly the same molecular weight as our *Z*-allyl fluoride product **168**. We propose that during the experiment, there were two consecutive S_N2' halogen displacements to obtain *E*-allyl fluoride **176** (Scheme 48).



Scheme 48

The proposed reaction mechanism for the formation of *Z*-allyl fluoride **168** and *E*-allyl fluoride **176** is shown in Scheme 48. Once the chloride ion is displaced, an equilibrium between iodide species is established, the ratios between species is determined by their relative energy, where the *E* isomer is the most stable and the geminal isomer the least stable (Table 5).[102] The rate of the reaction for the replacement of chloride with I^- is faster than with F^- as the higher nucleophilic strength of I^- allows the quick replacement of a carbon-chloride bond for carbon-iodide bond. In the meantime, although nucleophilicity of F^- is lower, it is also replacing chloride and iodide, forming carbon-fluoride bonds (products **168**, **175** and **176**), which are very strong and much more stable than any others (Table 6),[103] rendering whole sequence irreversible.

	$\Delta_f H°$(KJ/mol)	
1-butene	-20.8	
cis-2-butene	-29.8	
trans -2-butene	-33.3	

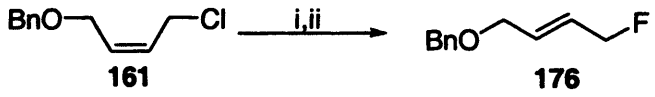
Table 5

Bond Strengh	$D°_{298}$ (KJ/mol)
C-F	552
C-Cl	397
C-Br	280
C-I	209
C-H	338

Table 6

Z-allyl chloride **161** contains two electrophilic sites at C-1 and C-3 (latent). The S_N2' attack of nucleophilic iodide at C-3 of the olefin allows the transposition of the *Z* double bond and the displacement of chloride as a leaving group generating a terminal olefin **173**. The new product **173** possesses two electrophilic sites, one at C-1 and another at C-3; like a conjugate addition, the attack of nucleophilic fluoride at the terminal olefin carbon will allow the transposition of the terminal double bond and the displacement of iodide as a good leaving group, generating the more stable *E*-allyl fluoride **176**.

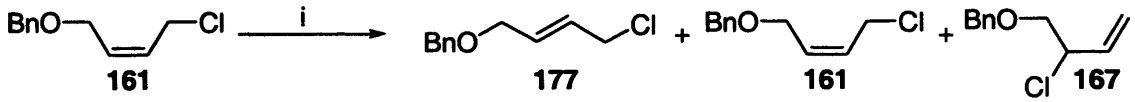
Allowing formation of the iodide to go to completion before the fluorination allowed the successful synthesis of *E*-allyl fluoride **176** as the major product. The addition of TBAI to a solution of allyl chloride **161** in THF at 80 °C, followed after 4 h by the addition of a solution of TBAF in THF to the semi-solid mixture afforded *E*-allyl fluoride **176** albeit in moderate yield (55 %, Scheme 49).



161 **176**

Scheme 49
i) TBAI, THF, reflux 4 h; ii) TBAF, THF, reflux 5 h, 55 %.

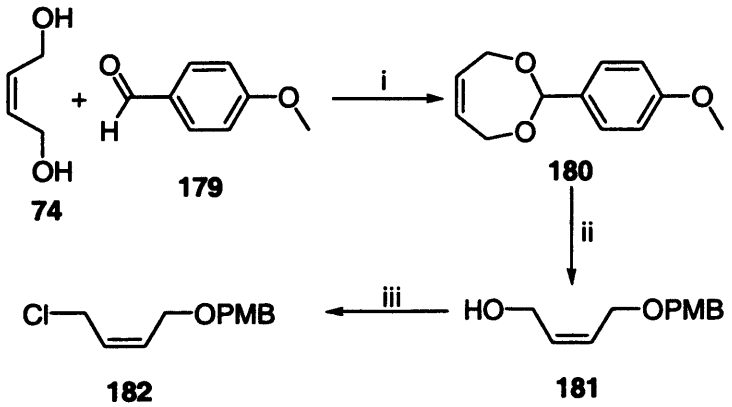
With these results in hand we wished to produce *E*-allyl chloride **177**, a potential important synthetic intermediate, in larger scale. *E*-allyl chloride **177** was successfully synthesized (95 % on a 6 mmol scale, Scheme 50) as a 13:1:4 mixture of allyl chlorides by treating *Z*-allyl chloride **161** with at least 2 equivalents of TBAI in THF at reflux for 12 h. The excess of TBAI is essential to minimize the formation of the terminal-allyl chloride.



161 **177** **161** **167**

Scheme 50
i) TBAI, THF at reflux, 12 h, 95 %. 13:1:4

For the synthesis of the *para*-methoxybenzyl protected allyl fluoride **186**, the substrate required for the deployment of Sharpless Asymmetric Dihydroxylation methodology, cyclic ketal **180** was prepared by the reaction between cheap and commercially-available *cis*-2-butene-1,4-diol **72** and *p*-anisaldehyde **179** in presence of *p*-toluenesulfonic acid (acid catalyst) to generate a cyclic 1,3-dioxepin **180** in good yield (72 %, Scheme 51), according to a literature procedure by Williams *et al.*.[104,105]

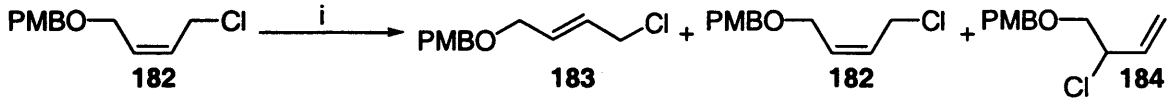


Scheme 51
i) TsOH, Toluene, -H_2O, 72 %; ii) DIBAL-H, 85 %;
iii) $SOCl_2$, pyridine 50 %; or iii) MsCl, *s*-collidine, LiCl, DMF, 96 %.

Acetal **180** was easily cleaved by di*iso*butylaluminum hydride (DIBAL-H) according to the literature procedure of Takano *et al.*,[106] to afford the corresponding mono protected *Z*-allyl alcohol **181** in good yield.

From the procedures previously described for the halogen displacement of allyl alcohols, only the procedure using mesyl chloride and *s*-collidine was effective affording the desired allyl chloride **182** in good yield (96 %). The procedure using thionyl chloride afforded complex crude mixtures of decomposition products due to the low stability of the *para*-methoxybenzyl (PMB) group under acidic conditions. In an attempt to modify the conditions of the procedure using thionyl chloride by adding pyridine to the mixture (Darzen's method to convert HCl by-product in a source of nucleophilic chloride) resulted only in moderate yields (50 %).

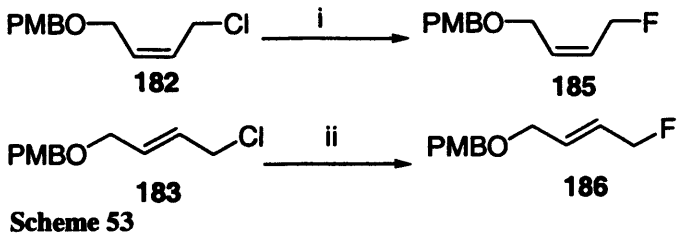
E-Allyl chloride **183** was synthesized successfully using the procedure described previously in excellent yield (96 %), in large scale (up to 26 mmol), as a 14:1:1 mixture of allyl chlorides (Scheme 52).



Scheme 52
i) TBAI, THF at reflux, 24 h, 96 %.

Z-Allyl fluoride **185** was synthesized successfully in moderate yield (65 %, Scheme 53) by reluxing allyl chloride **182** in THF with TBAF for 6 h. Performing the reaction over molecular sieves improved the yield and decreased the reaction time. *E*-Allyl fluoride

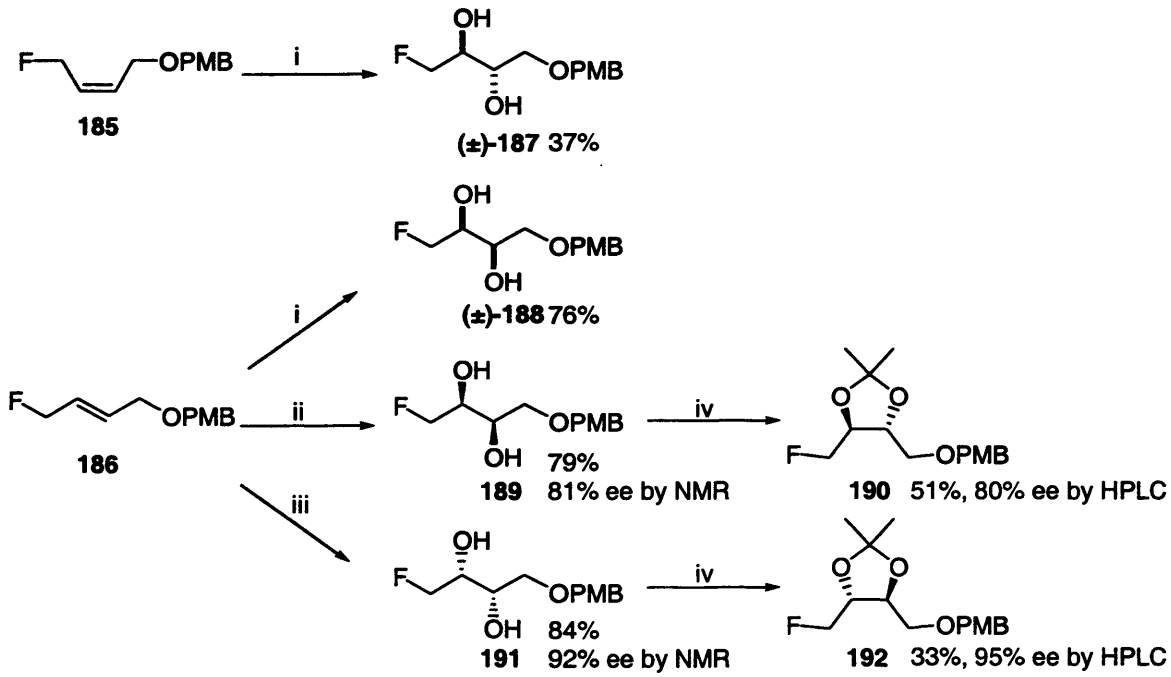
186 was synthesized in good yield (82 %) and in large scale (up to 20 mmol) under these conditions in only 1 h.



Scheme 53
i) TBAF, THF reflux, 6 h, 65 %; ii) TBAF, molecular sieves, THF reflux, 1 h, 82 %.

2.1.1 Dihydroxylation

Allylic fluorides **185** and **186** were dihydroxylated successfully under UpJohn and Sharpless AD[52] conditions giving the expected *anti* and *syn* diols **187** and **188** respectively in good yields as shown in scheme 54.



Scheme 54
i) OsO_4, NMO, ^tBuOH, H_2O, Acetone; ii) AD mix α, $MeSO_2NH_2$, *t*-BuOH, H_2O;
iii) AD mix β, $MeSO_2NH_2$, *t*-BuOH, H_2O; iv) *p*-TsOH, $CuSO_4$, Acetone.

HPLC determination of ee was attempted on the free diols; however, adequate baseline separation could not be achieved, so the diols were converted to the acetonides in low yield (mg scale). HPLC assay was carried out on a range of columns (Chiralpak AD, AS, Chiralcel OD-H and OJ) using non-polar solvents (999:1 hexane ^iPrOH).

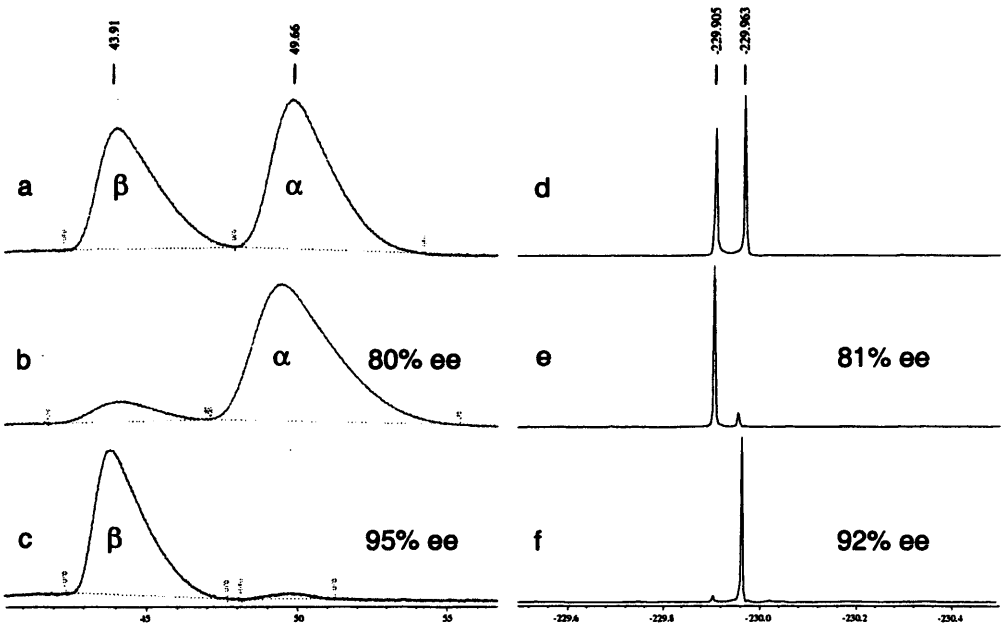
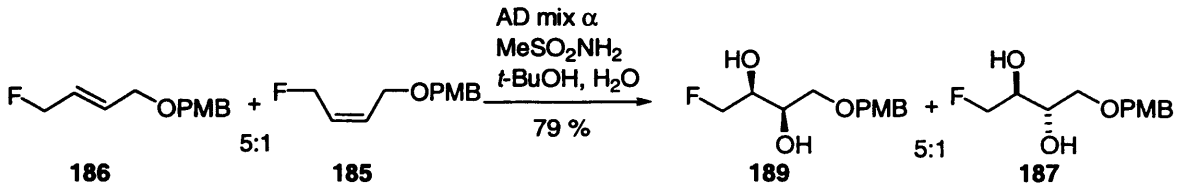


Figure 2. HPLC Chromatograms(Chiralcel OD-H, 999:1 hexane ^{i}PrOH) of acetonides **190** (b), **192** (c) and a mixture of both (a); Partial ^{19}F {H} NMR (300MHz, L-(+)-DIPT/$CDCl_3$, 300K) of diols **189** (e), **191** (f) and a mixture of both (d).

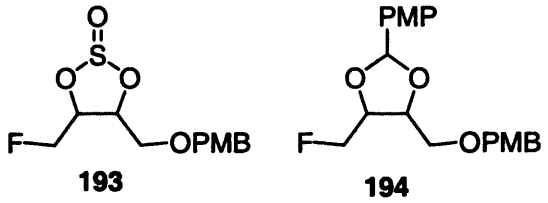
Although the determination of enantiomeric purity is often performed by GC and HPLC (sensitivity an accuracy), derivatization of enantiomers and NMR determination is also widely used.[107] The enantiomeric excesses of the diols were successfully assessed in a more convenient manner as shown in Figure 2 by ^{19}F NMR ($\Delta\delta_F$ = 0.06 ppm between enantiomers) using cheap and enantiomerically enriched di*iso*propyl tartrate in $CDCl_3$. NMR determination of enantiomeric purity with chiral solvating agents has been described in the literature,[108] for example: α-methylbenzylamine was used to observe the racemate of 2,2,2-trifluoro-1-phenyl-ethanol in ^{19}F NMR ($\Delta\delta_F$ = 0.04 ppm),[109] and in another case a chiral liquid crystalline medium was used to resolve a racemic mixtures of fluoroalkanes.[110]



Scheme 55

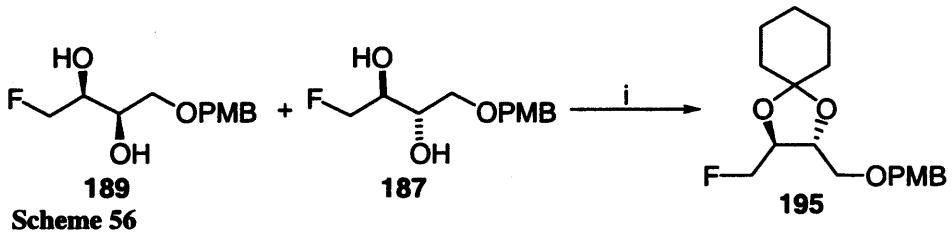
Unfortunately, the *Z*-allyl fluoride impurities also were dihydroxylated under AD conditions decreasing the de of the products (Scheme 55). Though the crude

dihydroxylation products were solid, improvement of the ee by recrystallisation proved impossible.



193 **194**

To improve the synthesis, we attempted to generate a more crystalline acetal. Different possibilities included cyclic sulfinate **193** or a *p*-methoxybenzyl acetal **194**. These would result in the formation of an additional stereogenic center, which would cause further difficulties. Instead we decided to protect the diol as a cyclohexylidene acetal.[111]



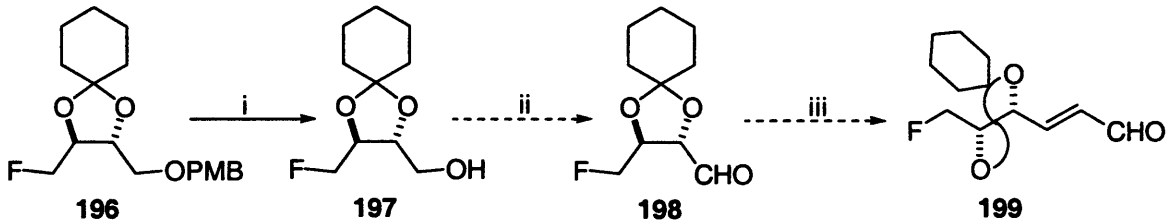
189 **187** **195**

Scheme 56

i) Cyclohexanone, p-TsOH, $CuSO_4$, THF, 38 %.

The reaction was successful (38 % small scale, 90 % large scale, Scheme 56); though the cyclohexylidene didn't crystallize as hoped, the product was easier to separate from the corresponding *cis* cyclohexylidenes by column chromatography.

The synthesis was scaled up to this point with racemic material. The deprotection of PMB was easily performed using DDQ (73 %) and if the alcohol was transformed into aldehyde **198**, an excellent intermediate would be produced towards the synthesis of 6-deoxy-6-fluorosugars.



196 **197** **198** **199**

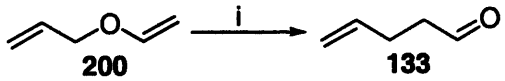
Scheme 57

i) DDQ, DCM, 73 %; ii) PCC; iii) Ph_3P=CHCHO.

This project was not progressed because of developments in other areas.

2.2 Synthesis of 6-fluoro-2,3,6-trideoxyhexoses

2.2.1 Route to 6,6-difluoro-2,3,6-trideoxyhexoses

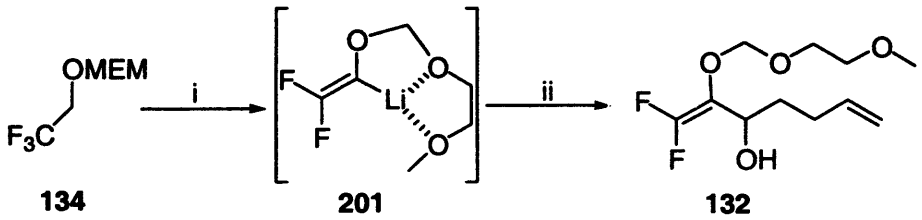


200 **133**

Scheme 58

i) microwave, variable power, maximum 50W, 150 °C, 5h.

Allylvinyl ether **200** was heated under microwave (at 50W) to effect a Claisen-[3,3]-sigmatropic rearrangement to yield γ,δ-unsaturated aldehyde **133** (Scheme 58) in only 5 h. Under non-microwave conditions, the rearrangement requires heating for 16 hours in an Ace tube to reach completion.



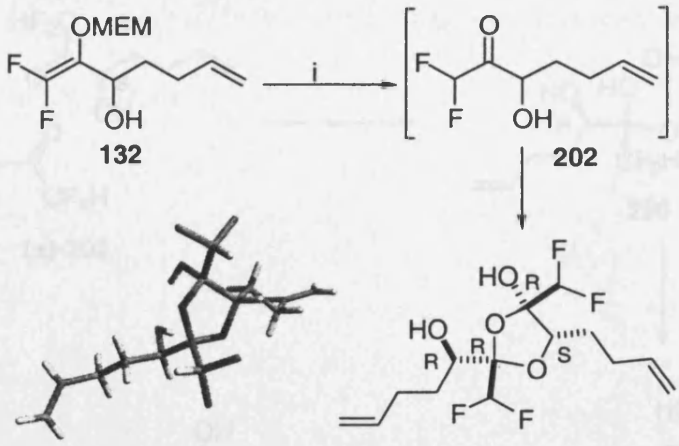
134 **201** **132**

Scheme 59

i) LDA, THF, -78 °C, 2 h; ii) pent-4-enal from -78 °C to -30 °C, 2 h. 78 %

The reaction of the metallated enol acetal **201** of trifluoroethanol,[112] derived from the reaction of MEM ether **134** with lithium di*iso*propylamide (LDA), with aldehyde **133** resulted in the formation of difluoroallylic alcohol **132** in good yield (78 %, Scheme 59) and in large scale (up to 70 mmol). The crude product was extracted and the oil purified by Kugelrohr distillation to afford allylic alcohol **132**; product was shown to be pure by GC. The NMR spectra (^{1}H, ^{13}C and ^{19}F) were assigned fully and they are in agreement with those reported by Broadhurst *et al.*[81] for similar difluoroallylic alcohols.

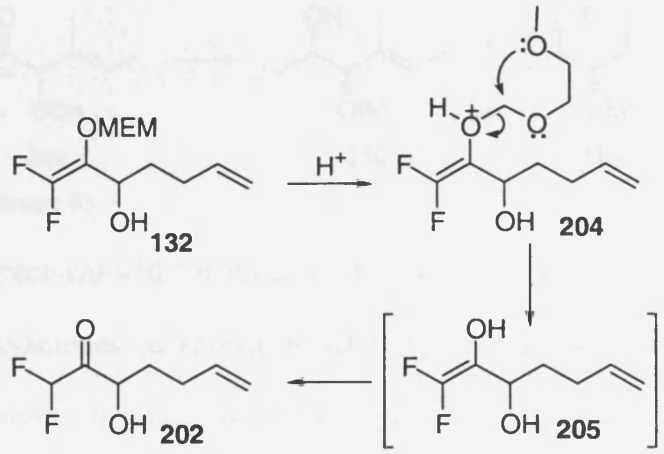
The reaction mechanism involved dehydrofluorination and subsequent metallation to afford **201**; careful temperature control and accurate BuLi titration is essential to prevent excessive elimination of LiF from **201** and decomposition.



Scheme 60
i) TMSCl, MeOH, r.t., 82 %.

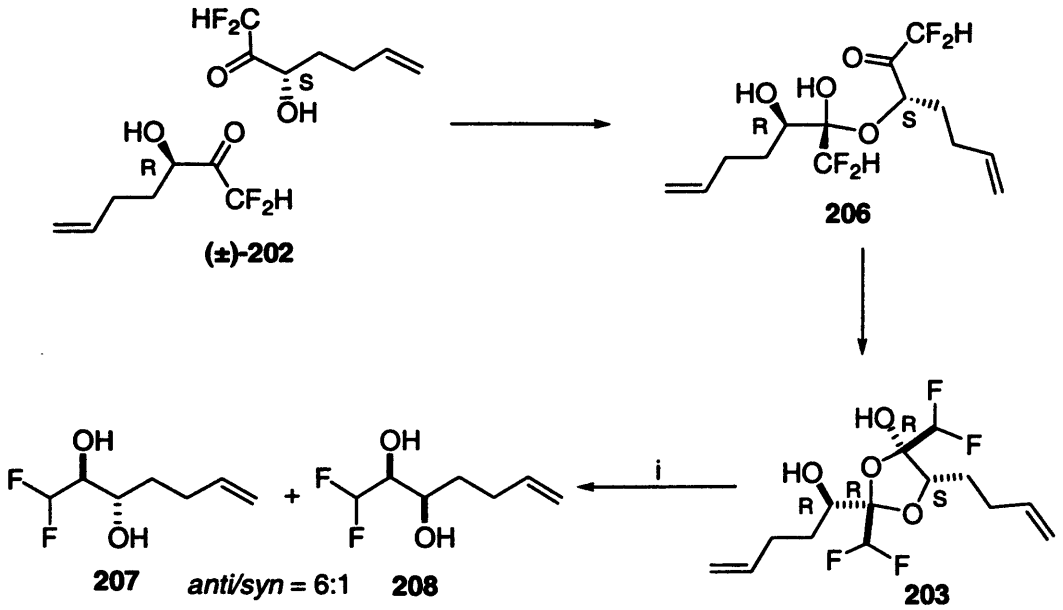
According to literature procedures,[81,113] the cleavage of the MEM-group occurred upon the addition of trimethylchlorosilane to a solution of difluoroallylic alcohol **132** in methanol (Scheme 60); dry HCl is produced under these conditions. Instead of the expected ketone, a crude mixture with a complex NMR spectrum was obtained. Finally a crystalline solid was isolated and identified as a racemic dioxolane dimer **203** by X-ray crystallographic analysis.

The reaction mechanism proposed for the cleavage of the MEM acetal and ketone formation is shown in Scheme 61.



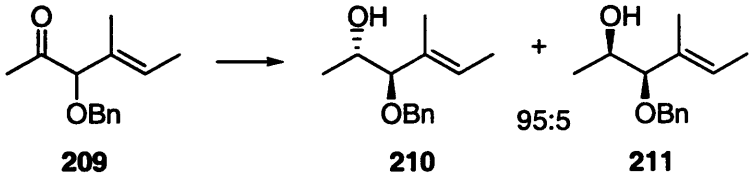
Scheme 61
TMSCl in methanol, r.t., 24 h.

Scheme 62 shows the stereochemistry and the proposed mechanism of formation of the 5-membered dioxolane dimer, which suggest that the formation of a more symmetrical 6-membered ring product is not favoured.



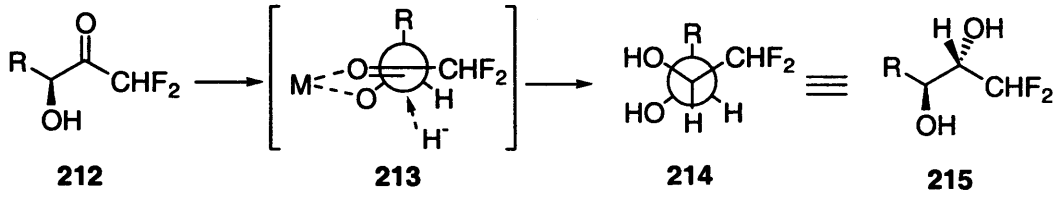
Scheme 62
i) $NaBH_4$, Et_2O, 84 %.

Solid dioxolane **203** was then reduced with a suspension of sodium borohydride, in diethyl ether to give a (6:1) mixture of diastereoisomers in high yield (84 %). To verify the stereochemistry of the major diol, volatile acetonide **216** was synthesized (63 %, Scheme 65), and NOESY proved that the reduction had delivered *anti/erythro* diol **207** (*cis* acetonide) as major isomer. Scheme 63 also shows the same behaviour with a similar substrate.[114]



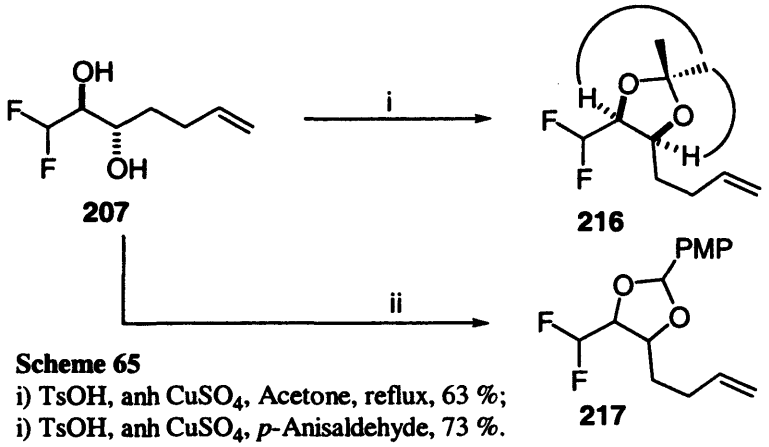
Scheme 63

This result is in agreement with the proposed Felkin-Ahn nucleophilic addition model to chelated α–hydroxyketones, as shown in Scheme 64, although sodium borohydride is not thought to promote chelation control. It appears that some substrates have a strong intrinsic preference for the reduction to the *anti*-product.[115]



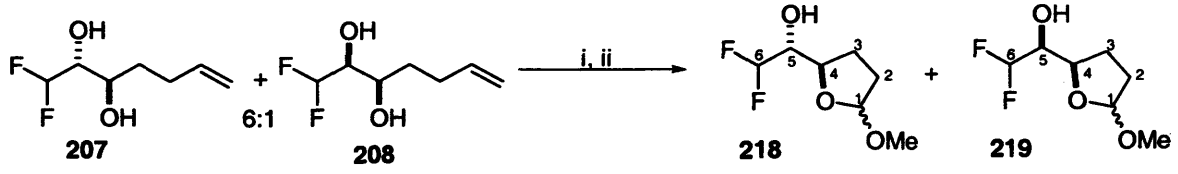
Scheme 64

Acetal **217** was also prepared (73 %) in the hope that a crystalline solid would be obtained; unfortunately, **217** was an oil.



Scheme 65
i) TsOH, anh $CuSO_4$, Acetone, reflux, 63 %;
i) TsOH, anh $CuSO_4$, *p*-Anisaldehyde, 73 %.

Diol **207** was then ozonolysed under different conditions; standard ozonolysis in dichloromethane, or on silica as described by Weinreb *et al.*[79] afforded crude inseparable mixtures of products with very complex NMR and TLC, suggesting the formation of pyranoses and furanoses together with oligomers.



Scheme 66
i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, r.t., 63 %.

Performing the ozonolysis in methanol under mild acidic conditions (by adding a small amount of trimethylchlorosilane) delivered a simpler but inseparable mixture of methyl glycosides (63 %, Scheme 66). Although the NMR spectra are complex, all the anomeric protons are very distinctive (Figure 3), with $^3J_{H\text{-}H}$ between 3.6 and 4.2 Hz (none of them with $^3J_{H\text{-}H}$ corresponding to pyranoses), and HMBC spectra show a clean cross peak between the anomeric proton H-1 and carbon C-4, proving that the products formed are 5-membered ring furanosides, instead of the 6-membered pyranosides as desired.

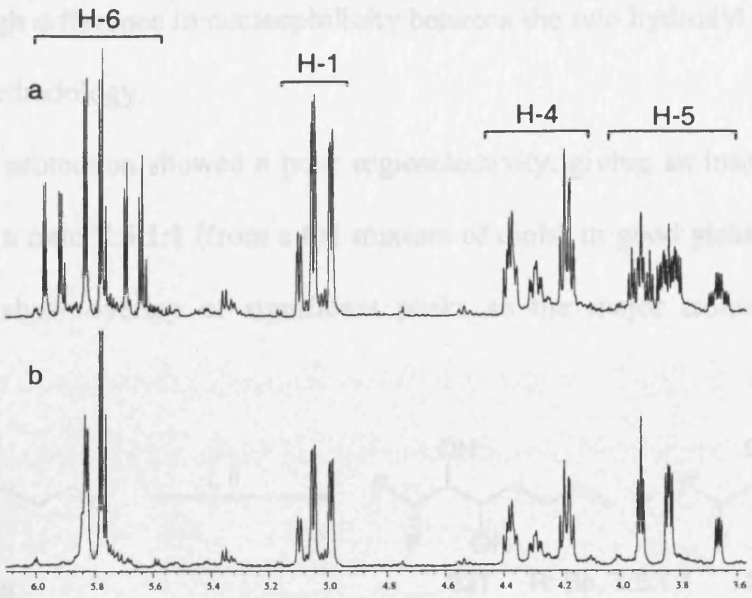
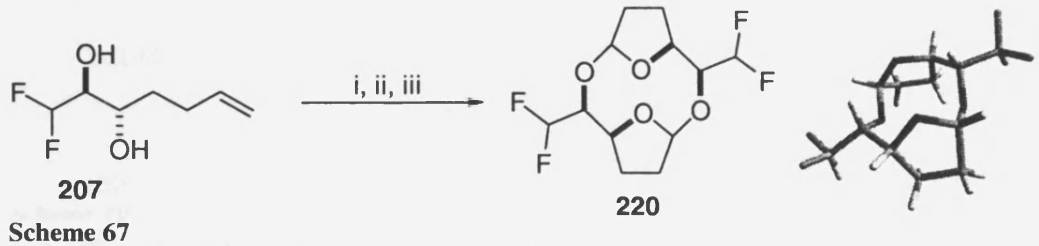


Figure 3. Partial ^{1}H(a) and $^{1}H\{^{19}F\}$(b) NMR (400MHz, $CDCl_3$, 300K) spectra of methyl difluoroamicetoside **218** and **219**.

This result suggests that the formation of furanosides is strongly favoured because of the low nucleophilicity of the hydroxyl group at C-5, due to the electron withdrawing effect of the adjacent β C-F bonds.

During analysis by NMR in $CDCl_3$, the methyl furanosides cleaved very easily giving a racemic dimer (22 %, Scheme 67), which crystallized. The 10-membered ring could be seen clearly and the relative configuration identified by X-ray crystallography analysis, confirming furanoside formation and the *anti*- stereochemistry of the diols. Similar 10-membered heterocycles have been synthesized from carbohydrates in connection with studies on conformational properties of cyclic polyethers.[116]



207 **220**

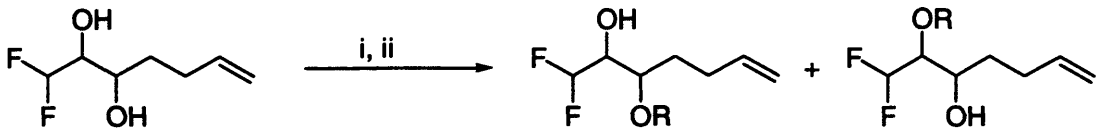
Scheme 67

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, r.t.; iii) $CDCl_3$, 22 %.

The formation of the pyranosides requires the protection of the hydroxyl at C-4; in an attempt to exploit the high stereoselectivity of the dioxolane reduction we attempted to

exploit the high difference in nucleophilicity between the two hydroxyl groups by using stannylene methodology.

Initial benzyl protection showed a poor regioselectivity, giving an inseparable mixture of isomers in a ratio 7:5:1:1 (from a 6:1 mixture of diols) in good yield (75 %, Scheme 68). HMBC show overlap of significant peaks so the major isomer could not be assigned.



207/208

221 R: Bn, 7:5:1:1 **222**
223 R: Bz, 35:6:5:1 **224**

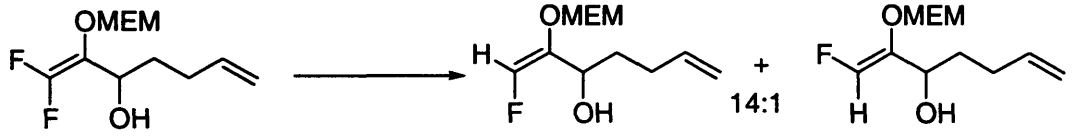
Scheme 68

i) $Bu_2Sn(OMe)_2$; (R=Bn) ii) TBAI, BnBr, 75 %; or (R=Bz) ii) TBAI, BzCl, 95 %.

Benzoylation occurred with better regioselectivity; a 35:6:5:1 ratio of isomers was observed by NMR.

2.2.2 Route to 6-fluoro-2,3,6-trideoxyhexoses

For the synthesis of the monofluorinated analogues, the reaction of difluoroallylic alcohol **132** with *bis*(2-methoxyethoxy)aluminium hydride (Red-Al®) (Scheme 70) resulted in the reductive monodefluorination of the substrate and formation of a *E/Z* (14:1) mixture of inseparable alkene regioisomers **227/228** in excellent yield (97 %). The NMR spectra were in agreement with those reported by Patel *et al.*[120] for similar monofluoro-alkene compounds.



132 **227** **228**

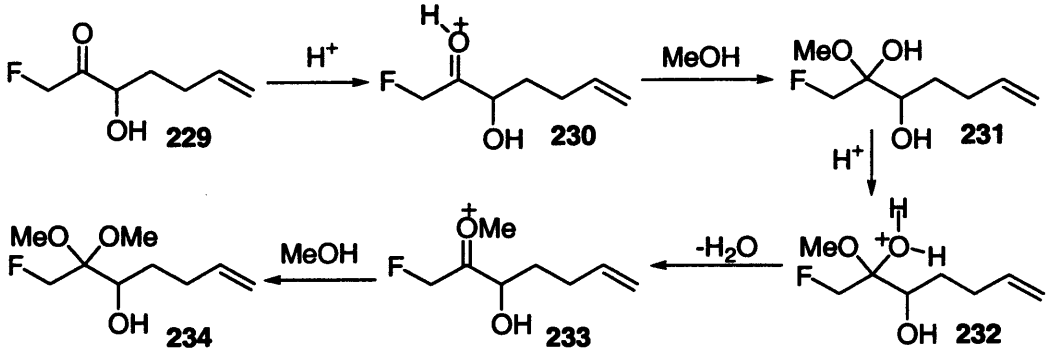
Scheme 70

Red-Al®, hexane, reflux, 3 h. 97 %

As previously described, the cleavage of the MEM-group occurred when adding trimethylchlorosilane to a solution of monofluoroallylic alcohol **227/228** in methanol.

Instead of the expected ketone, or dioxolane dimer, dimethyl acetal **234** was obtained as the only product (51 %).

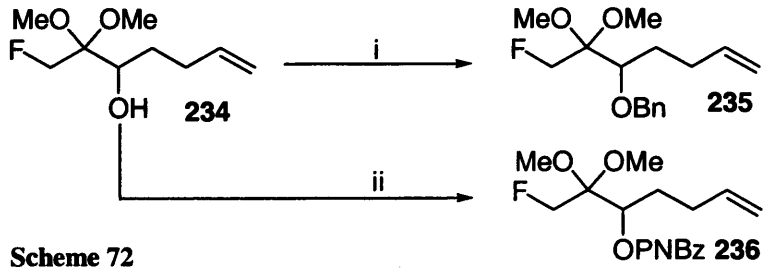
The reaction mechanism proposed for the formation of the dimethyl acetal is shown in scheme 71. In this case the quick conversion of the monofluoro electron deficient ketone into a dimethyl acetal instead of a dioxolane dimer can be explained by the formation of a oxacarbenium ion, intermediate **233** which is highly destabilised for the difluoroanalogues due to the strong electron withdrawing effect of the fluorine atoms.



Scheme 71

Reduction of the dimethyl acetal **234** with sodium borohydride was ineffective. Probably an acidic reducing agent like $NaCNBH_3$ would have been more effective in this case.[104]

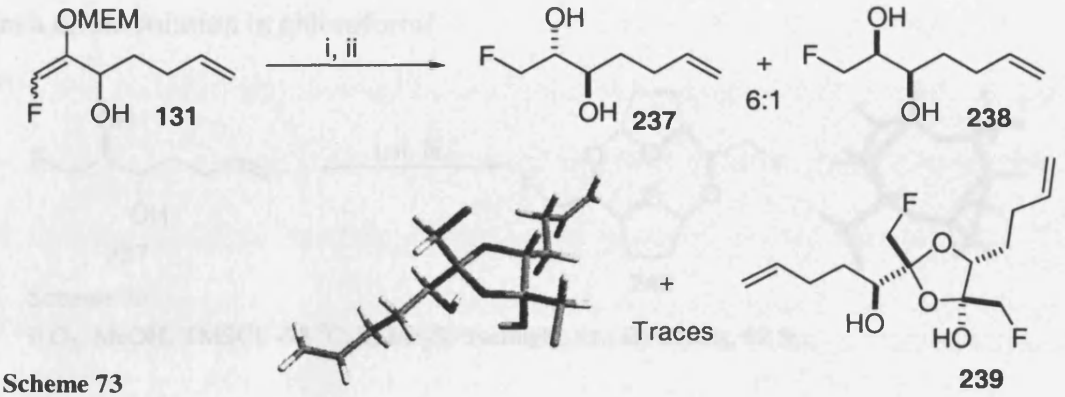
To attempt to obtain a crystalline derivative for X-ray characterization and CHN analysis of dimethyl acetal **234**, we decided to derivatise it to benzyl ether **235** (60 %, Scheme 72) and *p*-nitrobenzoyl ester **236** (66 %), which solidified but did not crystallize well enough for x-ray diffraction analysis.



Scheme 72
i) NaH, BnBr, THF, 60 %; ii) NaH, PNBCl, THF, 66 %.

The MEM ether is cleaved successfully by using concentrated HCl in THF. The intermediate under these conditions is also a dioxolane dimer which crystallized from a

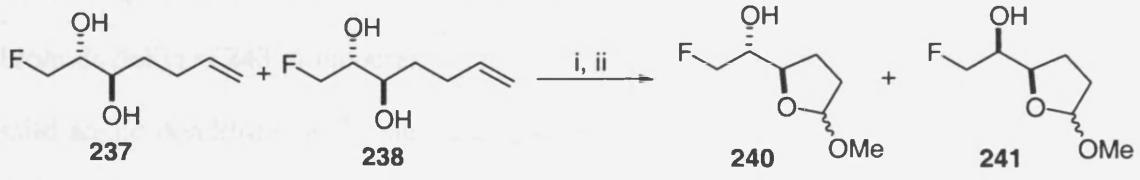
small column fraction. The intermediate then underwent reduction with sodium borohydride in a diethyl ether suspension to give a mixture of *anti* and *syn* diol diastereoisomers in 6:1 ratio in good yield (82 %, Scheme 73) and a small amount of dimer **239**.



Scheme 73
i) HCl, THF; ii) $NaBH_4$, Et_2O, 82 %.

Although at this stage we did not verify whether the major isomer was the *anti* or *syn* diol, we believed that according to the literature and the precedent of the difluorinated analogues it was an *anti* diol. At a latter stage during the asymmetric synthesis of 6-fluoro analogues of amicetose described in section 2.3 (p. 60), we have proved by NMR comparison that the major isomer is the *anti* diol.

Ozonolysis under the same conditions previously detailed in mildly acidic methanol, gave methyl furanosides **240/241** in good yield (81 %, Scheme 74).

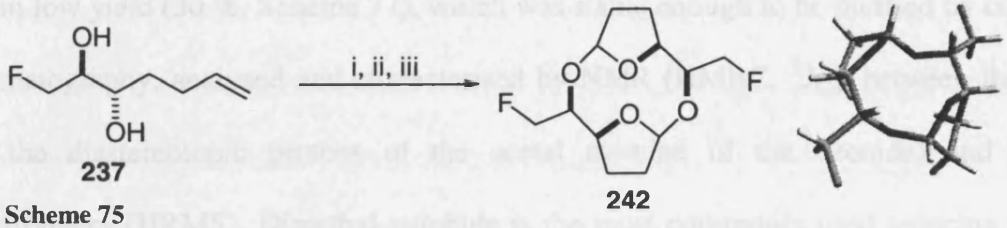


Scheme 74
i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, r.t., 81 %.

The full characterisation of the different anomers and diastereoisomers of the crude mixture was impossible as all of them have very similar retention times and are thus inseparable by column chromatography. For the major products (both anomers of the

major (*anti*) diol diastereoisomer), the full characterisation is detailed in p. 154-156, where they have been synthesized enantiomerically pure by a different route.

Dimer **242** was also obtained (62 %, Scheme 75) in this case, following crystallisation from a dilute solution in chloroform.



237 **242**

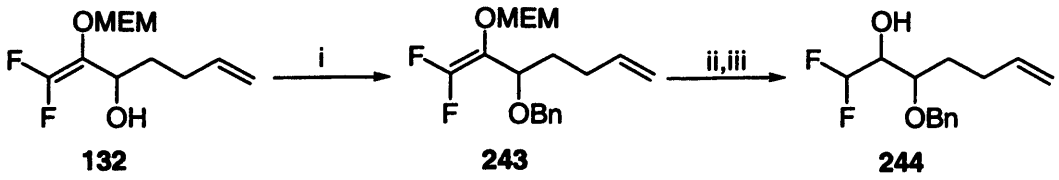
Scheme 75

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, r.t.; iii) $CHCl_3$, 62 %.

2.2.3 Formation of pyranoses requires the protection of the OH at C-4

In both mono and difluoro cases, the furanose ring is favoured due to the electron withdrawing effect of the fluorine atom(s) β to the adjacent C-O bond, so the formation of the pyranosides requires the protection of the hydroxyl at C-4. For this purpose we protected the difluoroallylic alcohol as a benzyl ether, which can be easily removed at the end of the synthesis by palladium-catalyzed hydrogenolysis.

According to literature procedures,[121] the reaction of difluoroallylic alcohol **132** with sodium hydroxide in water with the presence of a phase transfer catalyst and benzyl bromide delivers **243** in moderate yield (69 %, Scheme 76). The product was exposed to mild acidic conditions and reduced as previously described. Racemic difluoro alcohol **244** was obtained in moderate yield (61 %), but the stereoselectivity of the previous reductions was lost (a 1:1 diastereoisomer mixture was obtained).

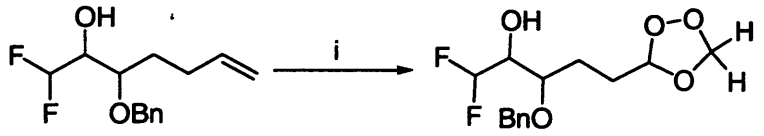


132 **243** **244**

Scheme 76

i) BnBr, NaOH, $TBAHSO_4$, H_2O, 69 %; ii) TMSCl, MeOH; iii) $NaBH_4$, Et_2O, 61 %.

Initial attempts to ozonolyse our susbtrates lead to the unexpected isolation of ozonide **245** in low yield (30 %, Scheme 77), which was stable enough to be purified by column chromatography, analysed and characterised by NMR (HMBC, $^3J_{C\text{-}H}$ between the C-6 and the diastereotopic protons of the acetal methine of the ozonide) and Mass Spectrometry (HRMS). Dimethyl sulphide is the most commonly used reducing agent for ozonides, but its slow reaction (up to 72 h with 10 equivalents depending on the substrate),[122] sometimes lead to incomplete ozonide cleavage. Other reducing agents like triphenylphosphine are faster, but present purification difficulties.

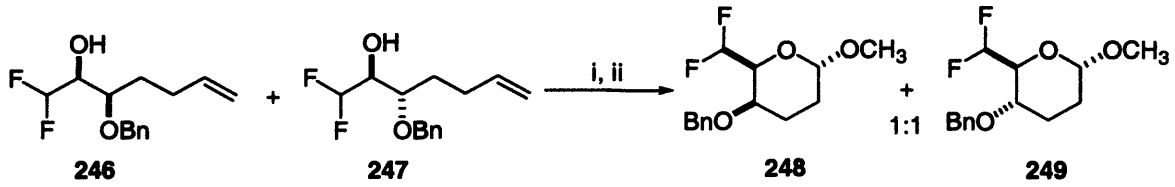


244 **245**

Scheme 77

i) O_3, MeOH, TMSCl, -78 °C 30 %.

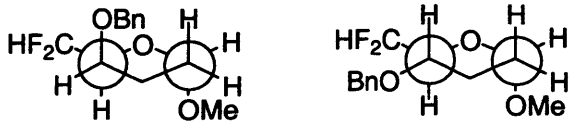
The racemic 1:1 mixture of *syn* and *anti* alcohols **246** and **247** was ozonolysed in acidic methanol and quenched with dimethyl sulfide to give the desired glycosides in excellent yield (81 %) as a mixture of only the two α-anomer diastereoisomers of the difluoro analogues **248** and **249** of rhodinose and amicetose respectively (Scheme **78**). Benzyl ether protective groups are oxidized by ozone at temperatures above –50 °C.[123] Although the ozonolysis was performed at –78 °C, this lead to the formation of small amount of benzoate impurities, which were removed by adding solid sodium hydroxide to the methanolic solution after the treatment with dimethyl sulfide, and subsequent neutralization.



Scheme 78

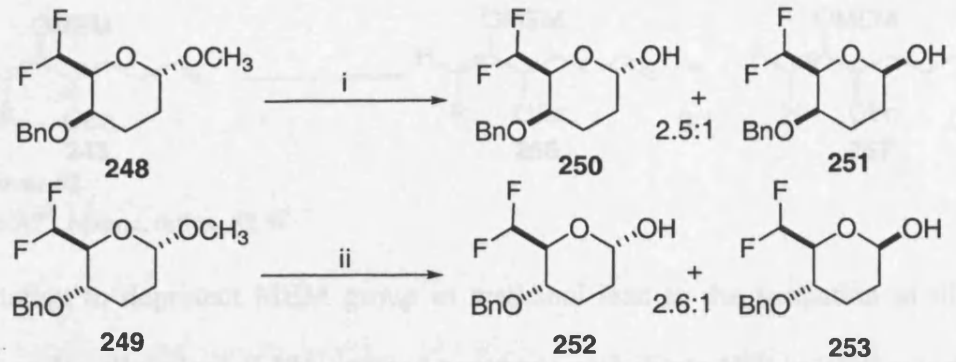
i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, 81 %.

We were able to isolate both stereoisomers by flash column chromatography on silica gel, and determine the structure from the NMR spectra. These preliminary results suggested that both diastereoisomers were present as single α–anomers. This was proved by the magnitude of the coupling constant between anomeric proton 1 and protons 2; these were 3.2 and 3 Hz for **248** and **249** respectively. The size is consistent only with an equatorial anomeric proton in each case. The coupling constant between protons 4 and 5 was determined to distinguish configuration between the analogues of rhodinose and amicetose; these values were $^3J_{H\text{-}H}$ 1.8 Hz (rhodinosyl) and $^3J_{H\text{-}H}$ 9.8 Hz (amicetosyl). NOESY spectra for **248** and **249** contained cross peaks linking axial H-5 with the methoxy protons. This is only possible in the α–anomers (Scheme 79).



Scheme 79

These methyl pyranosides were deprotected and converted into the corresponding hemiacetals separately in good yield (65 and 70 % respectively, Scheme 80), delivering a 2.5:1 mixture of the corresponding α and β anomers in each case. This was performed under dilute acid conditions with microwave heating.



Scheme 80

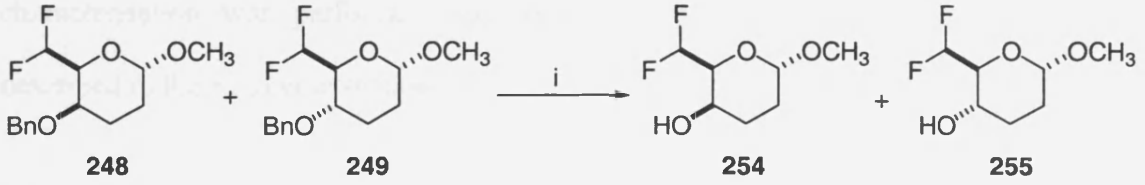
i) HCl, H_2O, THF, Microwave 50W, 2h, 100 °C, 65 %; ii) 70 %.

The amicetose hemiacetal crystallized as very thin needles, but only the α anomer made a good quality crystal for X-ray crystallographic analysis, which was used to verify our assignment of relative configuration (Figure 4).



Figure 4

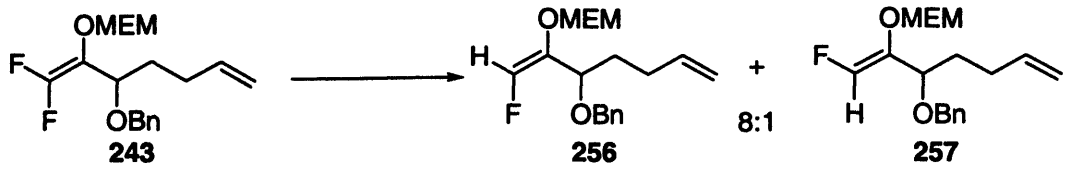
The final deprotection of the benzyl ether was achieved successfully (Scheme 81), under conditions described by Heathcock *et al.*,[124] for palladium catalysed hydrogenolysis. The low yield (50 %) in this reaction is explained due to an insufficient washing of the celite filter bed which left product adsorbed on the filter aid.



Scheme 81

i) 10 % Pd/C, EtOH, H_2, 50 %.

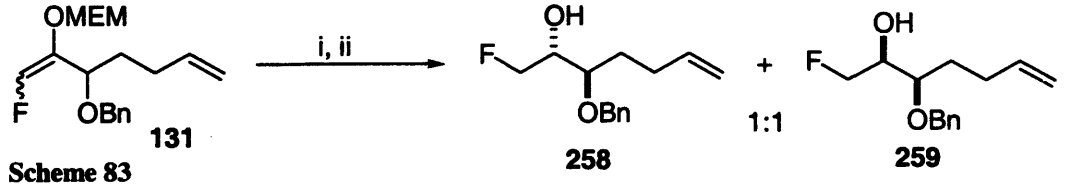
For the synthesis of the monofluorinated analogues, the difluoro benzyl ether was subjected to a reductive elimination of fluorine with Red-Al in pentane at reflux to give a mixture of *E*/*Z* isomers in a 8:1 ratio in excellent yield (82 %, Scheme 82).



Scheme 82

Red-Al®, hexane, reflux, 82 %

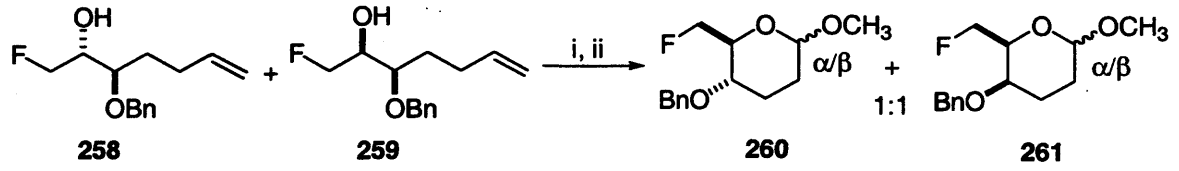
Any attempt to deprotect MEM group in methanol lead to the formation of dimethyl acetals, as for allyl alcohol **131**; instead treatment with dilute HCl in THF successfully cleaved the MEM group. Reduction with sodium borohydride gave a 1:1 mixture of monofluoro *anti* and *syn* alcohols **258/259** in good yield (69 %, Scheme 83).



Scheme 83

i) HCl, THF; ii) $NaBH_4$, Et_2O, 69 %.

Ozonolysis as previously described gave an inseparable mixture of α and β methyl pyranosides of both analogues of amicetose **260** and rhodinose **261** (86 %, Scheme 84).



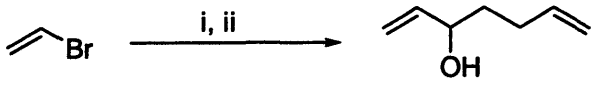
Scheme 84

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, 86 %.

The asymmetric synthesis of 6-deoxy-6-fluoro amicetose and rhodinose with full characterisation was performed successfully using a different approach which is described in the following section.

2.3 Asymmetric Route using SAE

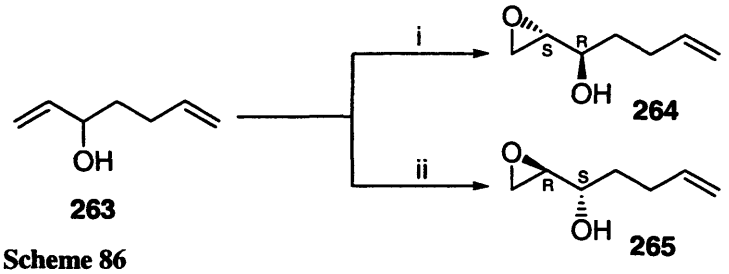
In situ preparation of vinylmagnesium bromide and addition to 1-pentenal gave allylic alcohol **263** in good yield (81 %, Scheme 85) on a 90 mmole scale. The product was relatively volatile and was purified by careful Kugelrohr distillation.



262 **263**

Scheme 85
i) Mg, THF; ii) 4-pentenal, 81 %.

The heptadienol was subjected to standard catalytic Sharpless Asymmetric Epoxidation conditions[84] for kinetic resolution at -30 °C in the freezer for 15 days with 4 Å molecular sieves and $Ti(O^iPr)_4$ to deliver, in good yield (78 and 74 % respectively) (Scheme 86), the desired epoxy alcohols **264** or **265** depending on which tartrate ligand was used (for the catalyst).

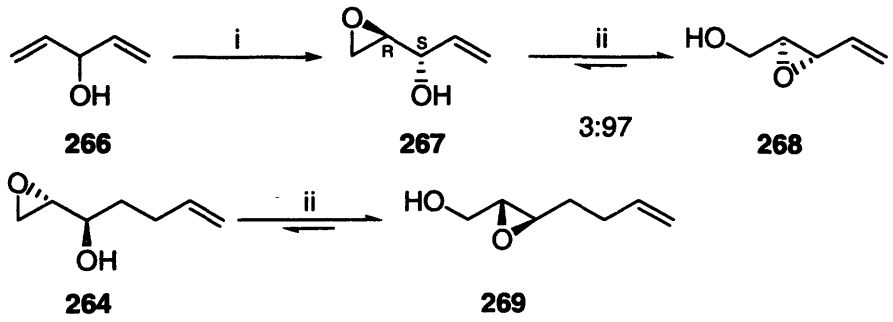


263 **264** **265**

Scheme 86
i) $Ti(O^iPr)_4$, D-(-)-DIPT, TBHP, CH_2Cl_2, 4 Å sieves, 78 %;
ii) $Ti(O^iPr)_4$, L-(+)-DIPT, TBHP, CH_2Cl_2, 4 Å sieves, 74 %.

As described by Sharpless *et al.*,[36] the role of powdered molecular sieves is dramatic, as one equivalent of water with respect to the catalyst is enough to destroy it. For very slow reacting substrates like terminal allyl alcohol **263**, more than 10 days reaction time are required. Stoichiometric amounts of TBHP were used, as it is known that faster reactions are observed with increased amounts of TBHP, but with a slight decrease in stereoselectivity. The ee determination will be described in p. 72.

The standard ferrous sulfate / tartaric acid workup procedure described by Sharpless *et al.*[36] was used; this consists of using a cold (0 °C) solution of ferrous sulfate and tartaric acid in water to remove the unreacted TBHP and $Ti(O^iPr)_4$, extraction with diethyl ether, then treatment of the combined extracts with a cold (0 °C) solution of sodium hydroxide in brine to remove the remaining tartrate ester. Although the procedure described by Sharpless *et al.*[36] suggests stirring with base for 1h, we have observed that treatment for more than 30 min lead to excessive epoxide migration or Payne rearrangement, which in our substrate leads to a more stable internal epoxide (Scheme 87).[125]

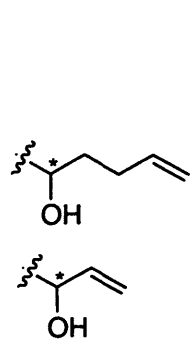


Scheme 87

i) $Ti(O^iPr)_4$, L-(+)-DET, TBHP, CH_2Cl_2, 4 Å sieves;

ii) $NaOH_{aq}$ (0.5 M), rt, 1h, 85 %.

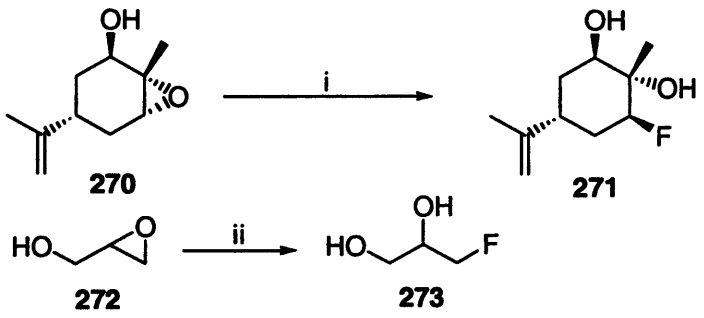
The configuration of the epoxides **264** and **265** was verified by comparison of the optical rotations with literature examples (Table 7).[125] It is interesting to notice that the ring opening affects in such extent the molecule that the sign of the optical rotations are inverted.



		2R	**2S**	**2S**	**2R**	**2R**	**2S**
	3R		-16		+7		
	3S	+27		-6			
	3R		-58				+24
	3S	+53				-26	

Table 7

The next step is critical for the viability of the route. Different fluorinating reagents and procedures were tried. The first one, which is used widely for the fluorination of epoxides (Scheme 88),[126] $Bu_4NH_2F_3$ delivered only starting materials.



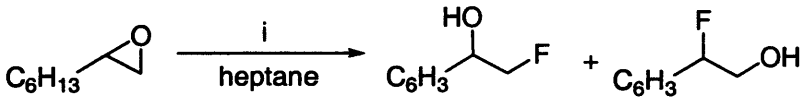
Scheme 88

i) $^{n}Bu_4NH_2F_3$, $C_2H_4Cl_2$, reflux, 80 %; or

i) $^{n}Bu_4NH_2F_3$, 95 °C, 24 h, 99 %;

ii) KHF_2, $Bu_4N^{+}H_2F_{3(cat)}$, 80 °C, 30 h, 47 %.

This reagent is not commercial but can be easily prepared.[127] The reaction using it in catalytic amounts with potassium hydrogen difluoride,[88,89] also delivered starting materials only. Amine·HF salts were not explored for this reaction because of the known regioselectivity problem with terminal epoxides (p. 33).



274 **275** **276**

i	T (°C)	time (h)	Yield (%)	Ratio (275/276)
$^{n}Bu_4NF$	100	18	37	(84:16)
$^{n}Bu_4NF·5H_2O$	100	18	36	(72:28)
$^{n}Bu_4NHF_2$	100	18	78	(90:10)
$^{n}Bu_4NHF_2$	120	4	73	(90:10)

Table 8

TBAF, another very well used fluorinating reagent (which is not very popular for the fluorination of epoxides) (Table 8),[91,128] delivered only small amounts of fluorinated products, with poor regioselectivity. Figure 5 shows the ^{19}F NMR spectrum of a fluorination of epoxide **264** with low regioselectivity (a, 1:1:30) and high regioselectivity (c, 0:1:30), where the signals corresponding to the fluorination at the

secondary carbon appear between δ_F –203 and –205 ppm (b), and the signals corresponding to the fluorination at the primary carbon appear between δ_F –230 and –231 ppm for the *syn* diol, and between δ_F –232 and –235 for the *anti* diol ppm (d).

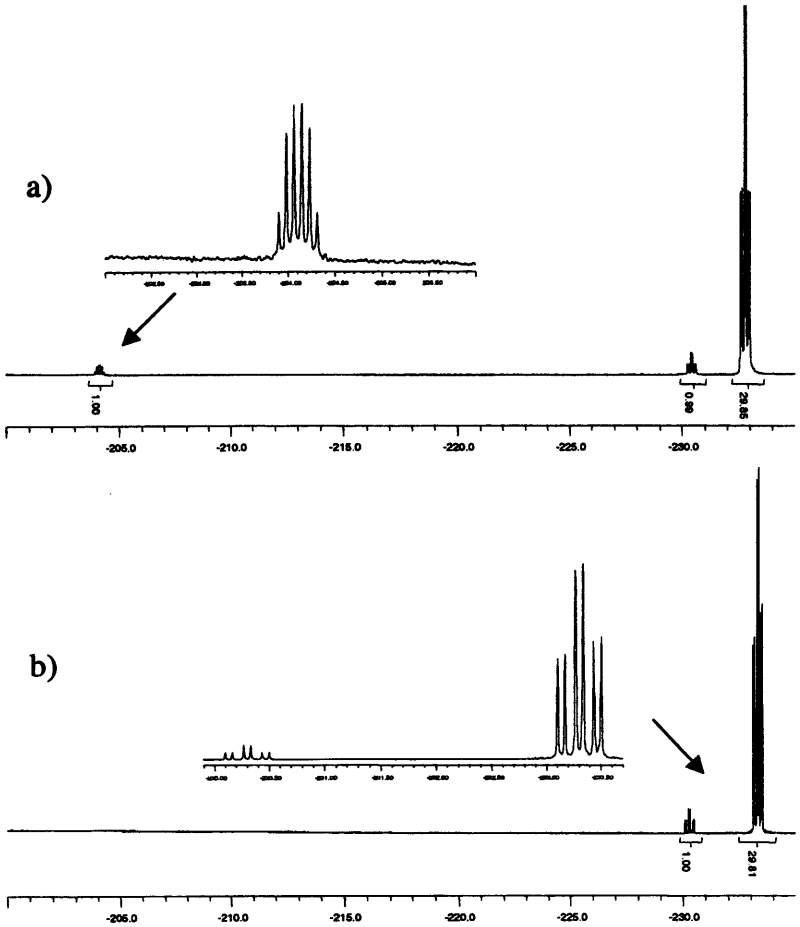
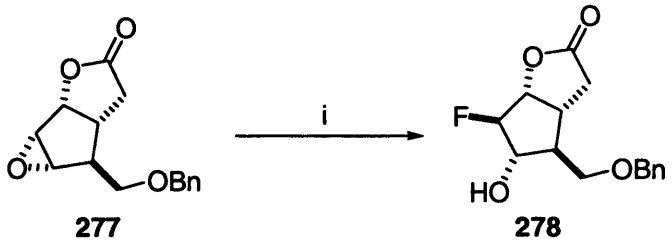


Figure 5. ^{19}F NMR spectra (300MHz, $CDCl_3$, 300K) of products from the reaction of **264** with fluoride sources: a) TBAF; b) KHF_2 + TBAF.

As TBAF is a basic fluorinating agent, modification of the procedure by adding *para*-toluenesulfonic acid was explored,[129,130] but this delivered starting materials only.

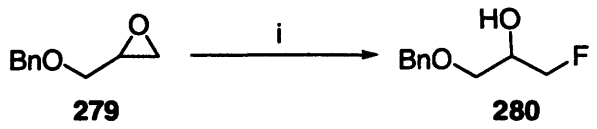


277 **278**

Scheme 89
i) KHF_2, ethylene glycol, 40 %.

Other conditions described in the literature as the only successful ones for the synthesis of a number of fluoro analogues of prostaglandins (Scheme 89),[90] delivered the

fluorinated product with the desired regioselectivity but in low yield. The major product arose from the nucleophilic attack by the solvent, in contrast to the excellent result of 80 %, on very similar substrates, claimed by a different author (Scheme 90).[87]



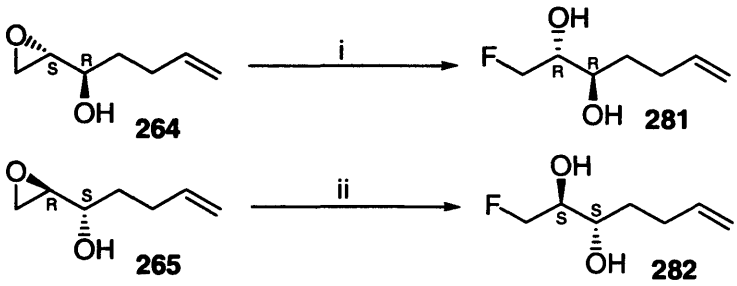
279 **280**

Scheme 90
i) KHF_2, ethylene glycol, 130 °C, 80 %.

After different attempts to modify these conditions using different solvents, the best results were obtained using 1 equivalent of TBAF with 4 equivalents of potassium hydrogen difluoride (Scheme 91). It is notable that the reaction time to reach completion is only 30 minutes and that leaving the reaction for longer time does not lead to product decomposition.

These conditions result in excellent regioselectivity; fluoride attack at the less hindered position of the epoxide is the sole pathway; and any internal epoxide present in the starting material can be recovered without degradation at the end of the reaction.

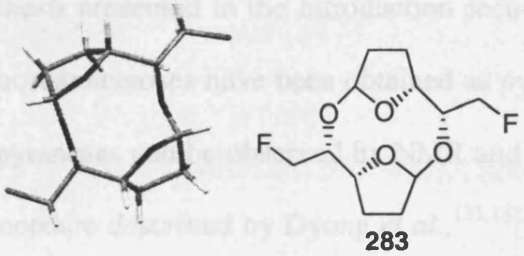
Traces of the undesired secondary fluoride have been found, but they can be considered negligible.



Scheme 91
i) KHF_2, $TBAF{\cdot}3H_2O$, 150 °C, 76 %, 94% ee by NMR; ii) KHF_2, $TBAF{\cdot}3H_2O$, 100 °C, 69 %, 96% ee by NMR.

Diol **281** was ozonolysed and dimer **283** (Figure 6) was also obtained, which crystallized, and the relative configuration was identified by X-ray crystallography analysis, confirming the stereochemistry of epoxidation and ring opening by fluorine. At present the only reliable method available for proof of absolute stereochemistry is a

single-crystal X-ray structure using the enantiomorph polarity estimation method developed by Flack, which relies on the anomalous scattering effect. The reliability of the determination can be measured by the enantiomorph distinguishing power, which is the standard error on the Flack parameter. For a rigorous absolute stereochemistry determination, the Flack parameter should return a value of zero (or below zero) with an error of less than 0.1.

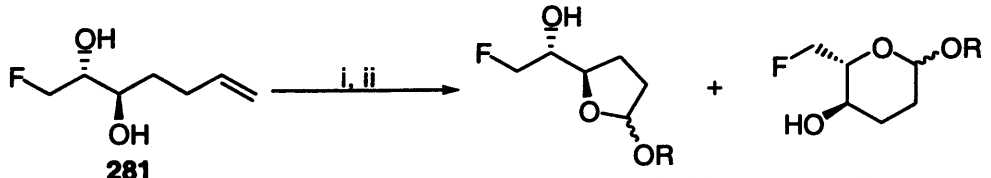


283

Figure 6

In this crystal structure the Flack parameter is -1.1 with an error of 0.7. Although the Flack parameter is good enough, the error is quite big, this is because compounds containing only first row light atoms i.e. C, H, N, O and F have very small anomalous contributions to the scattering factor when using Mo-Ka radiation. The alternative to enhance the enantiomorph distinguishing power is, essentially, to collect data at longer wavelength such as Cu-Ka, which is not currently available at the Department.

Diol **281** was ozonolysed successfully in good yield (72 %) as previously described to give a mixture of methyl furanosides and pyranosides (Scheme 92), in a 3:1 ratio (determined by NMR). And a mixture of furanose and pyranose free hemiacetals were obtained in a ratio 1:2 ratio (determined by NMR) in good yield (91 %).



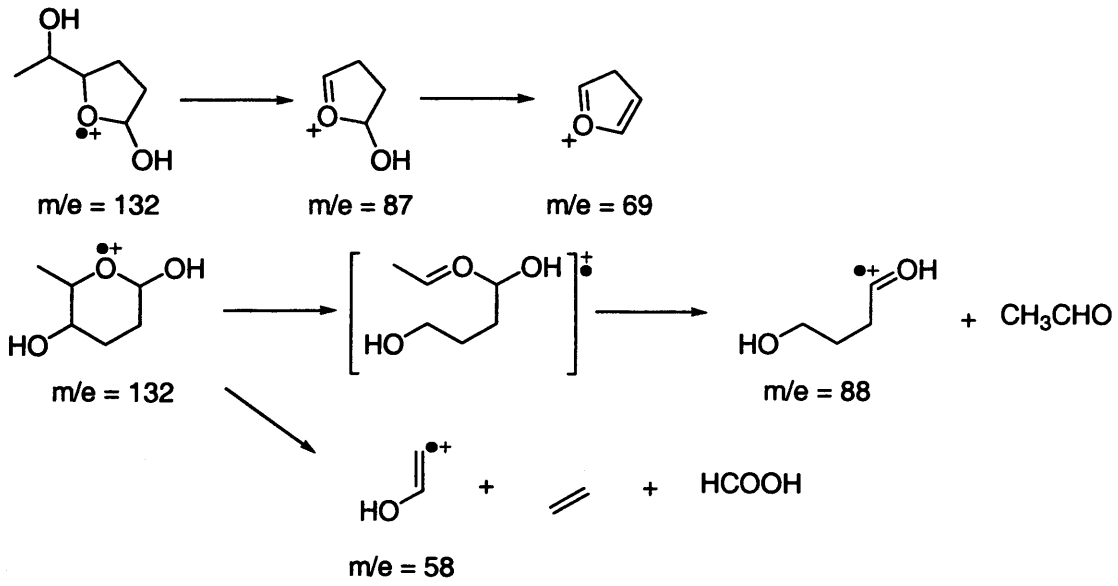
284 R: Me, 3:1 **285**
286 R: H, 1:1.9 **287**

Scheme 92

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, rt, 72 % (R=Me); or
i) O_3, MeOH, -78 °C; ii) Me_2S, overnight, rt, 91 % (R=H).

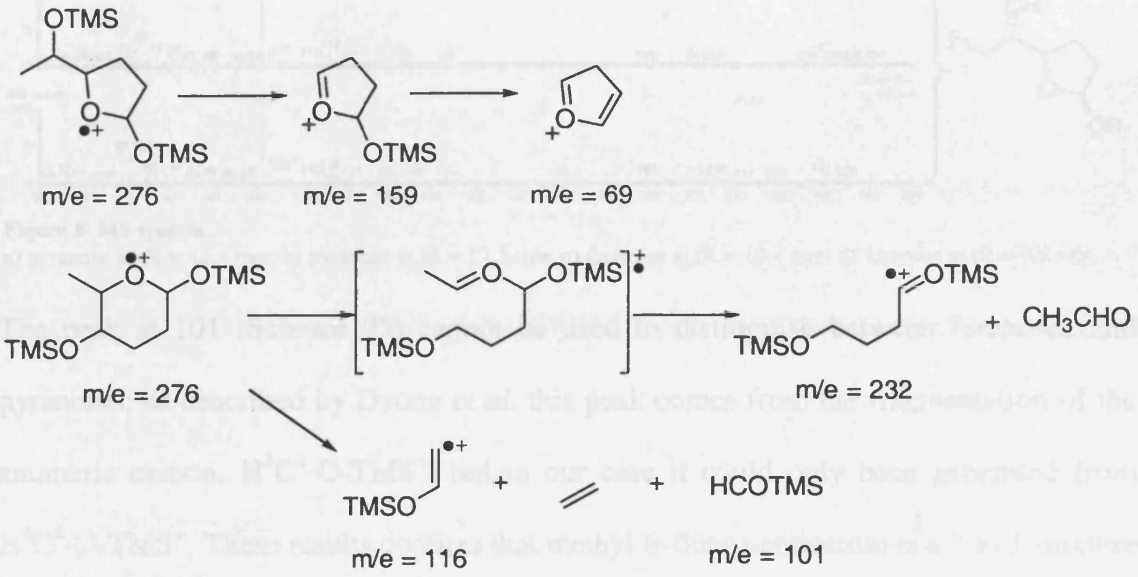
These results, which show clearly that there is equilibration between species, are not in agreement with the synthesis presented in the Introduction section (p. 29-30), where 6-deoxy and 6-deoxy-6-fluoroamicetoses have been obtained as pyranoses only. The ratio between furanoses and pyranoses can be observed by NMR and was confirmed by GC-MS following an old procedure described by Dyong *et al.*,[131,132] to study rhodinose and amicetose.

This GC-MS procedure is very simple; the different components of a mixture separate efficiently in the GC and it is possible to assign which peaks correspond to furanose or pyranose by analysing the fragmentation pattern of the parent ions. Dyong *et al.* determined which are the characteristic fragmentations of furanose and pyranose for amicetose and rhodinose, as shown in scheme 93.[132]



Scheme 93

All these characteristic fragments have very low mass and although it is possible to initially assign the peaks, it can lead to mistakes and uncertainties. Dyong *et al.* used TMS derivatives to increase the weight of all the fragments substantially; the new fragmentation pattern is as shown in scheme 94.



Scheme 94

Dyong *et al.* found that the most stable ions (the intensities in the mass spectra are important) are those corresponding to 159 for furanoses and 116 and 101 for pyranoses. In an attempt to reproduce these experiments, another worker in this laboratory,[133] used amicetose as substrate obtaining results similar to those obtained by Dyong *et al.*. I also performed the experiment, but using 6-fluoro methyl amicetosides instead, obtaining a spectra showing the corresponding peaks of 101 and 69 for furanoses and 174, 116 and 101 for pyranoses (Figures 7 and 8).

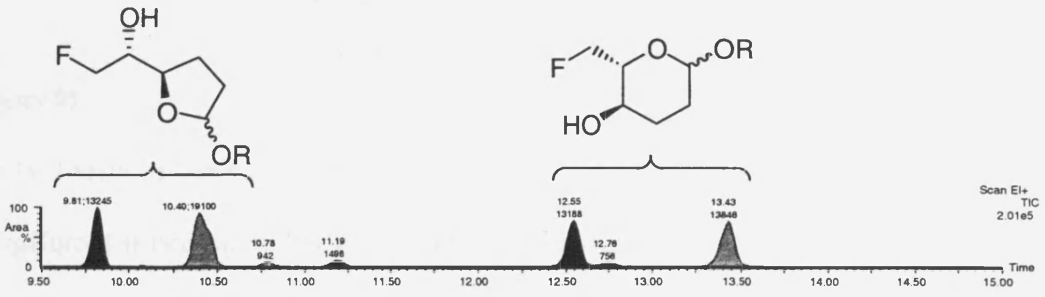


Figure 7. GC chromatogram.
Mixture of furanoses and pyranoses.

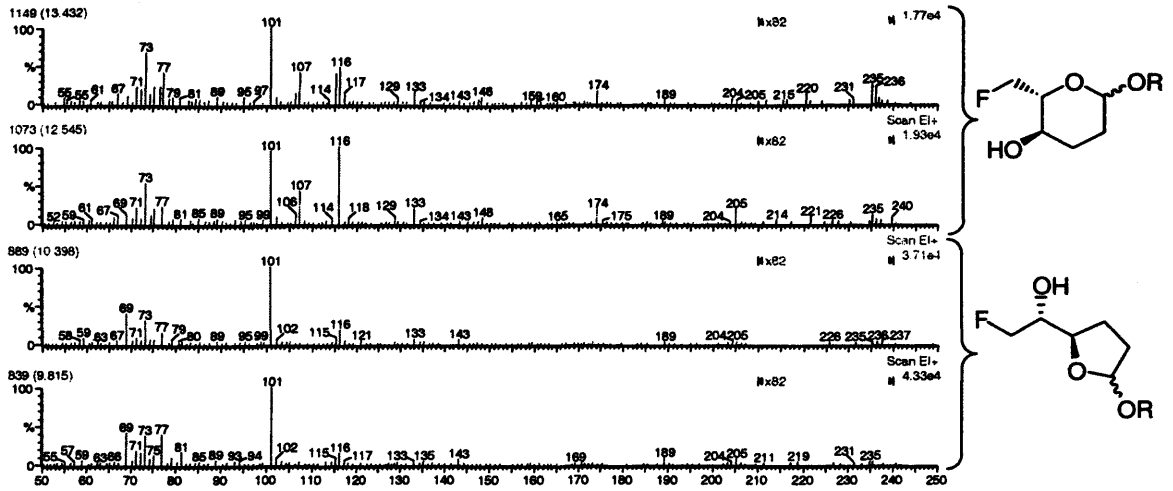
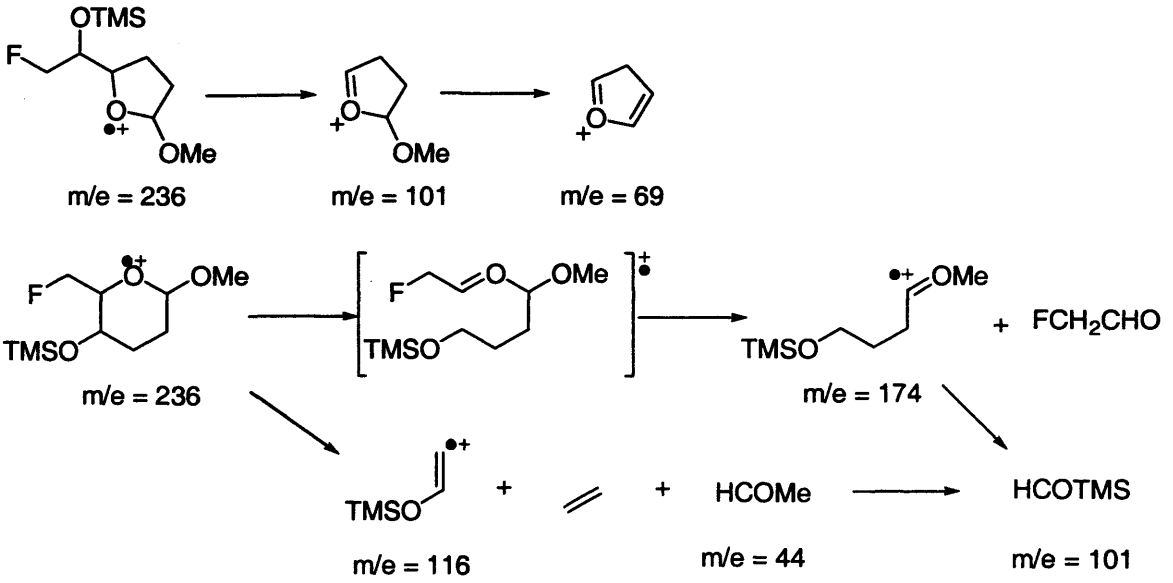


Figure 8. MS spectra.
a) pyranose at tR = 13.4 min; b) pyranose at tR = 12.5 min; c) furanose at tR = 10.4 min; d) furanose at tR = 9.8 min.

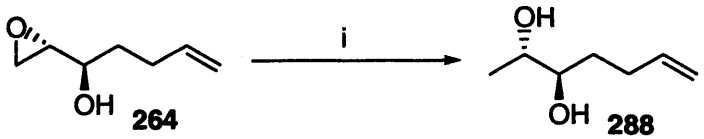
The peak at 101 (Scheme 95) cannot be used to distinguish between furanoses and pyranoses; as described by Dyong *et al.* this peak comes from the fragmentation of the anomeric carbon, H^1C^1-O-TMS$^+$, but in our case it could only been generated from H^4C^4-O-TMS$^+$. These results confirm that methyl 6-fluoro-amicetose is a 3 to 1 mixture of pyranose and furanose isomers.



Scheme 95

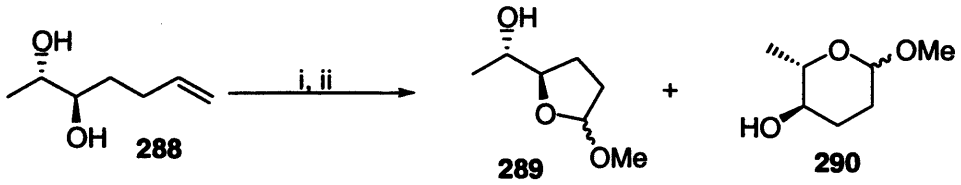
The synthesis of the non-fluoro 6-deoxysugar precursor could be achieved using one of the different procedures that have been described in the literature to open the epoxides with hydride reagents. RedAl,[82] and $LiAlH_4$,[134] have been used but according to a procedure described by Kitching *et al.*,[135] inexpensive and easy to handle sodium

borohydride was used to synthesise diol **264** (Scheme 96) with excellent regioselectivity, as shown for the fluorination. However, **288** was formed only in low yield (57 %) due to the volatility of the product.



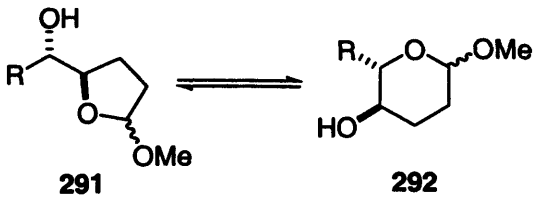
Scheme 96
i) $NaBH_4$, EtOH, reflux, 57 %.

This diol was then ozonolysed as previously described giving the expected methyl glycosides as a 1:1 mixture of furanoses and pyranoses (measured by NMR). The yield was moderate (43 %, Scheme 97) because they were also volatile.



Scheme 97
i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, rt, 43 %.

Table 9 summarises the ratios between furanoses and pyranoses for methyl amicetosides, 6-fluoro and 6,6-difluoro analogues. There appears to be a trend between the position of the furanose/pyranose equilibrium and the anticipated nucleophilicity of the hydroxyl group next to the fluorinated centre. The inductive effect of the fluorine atoms, which makes the simple alcohols more strongly acidic, should lower the nucleophilicity of the C-5 hydroxyl under neutral conditions, by opposing the development of positive charge at oxygen. The level of correlation between these ratios and the pK_a's of ethanol, 2-fluoro ethanol and 2,2-difluoro ethanol[136] is very high, suggesting that there is a clear electron withdrawing inductive effect of the fluorines in the nucleophilicity of the hydroxyl group at C-5, thus favouring the equilibrium towards furanoses.

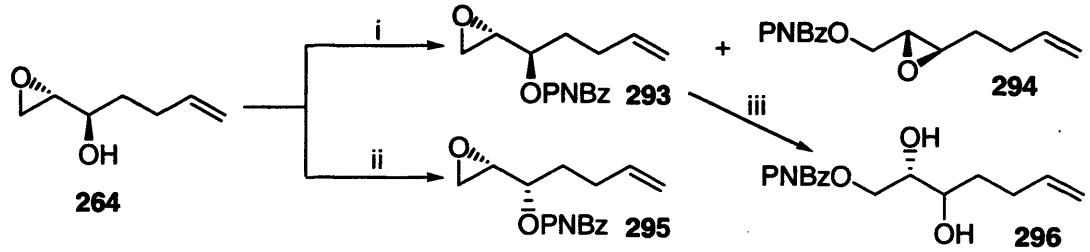


291 292

R	Furanose:Pyranose	pK_a	Model Alcohol
CH_3	1:1	15.83	CH_3CH_2OH
CH_2F	3:1	14.20	CH_2FCH_2OH
CHF_2	1:0	13.11	CHF_2CH_2OH

Table 9

The protection of the hydroxyl group at C-4 is required for the synthesis of pyranoses. At first, protection as a *para*-nitrobenzoyloxy group was attempted; applying Mitsunobu methodology[137] would allow the rhodinose precursor to be synthesized from the same substrate as the amicetose analogues.

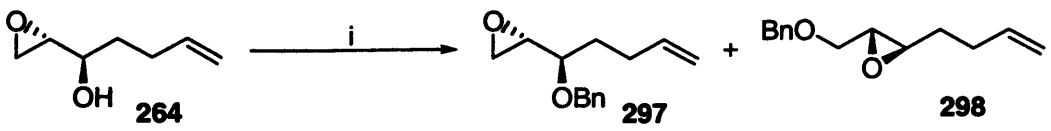


Scheme 98

i) PNBzCl, Et_3N, CH_2Cl_2, 90 %; ii) PNBzOH, DEAD, PPh_3, Toluene, 34 %;
iii) KHF_2, TBAF·$3H_2O$, 120 °C 14 %.

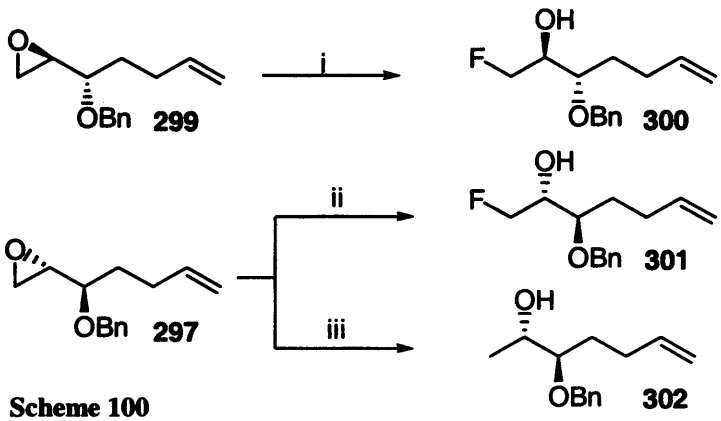
But although the PNB protected epoxy ester was synthesized successfully for both diastereoisomers (90 and 34 % respectively, Scheme 98), they could not be fluorinated as described previously giving traces of fluorinated products and mainly the rearranged by-product **296** (14 %), which was identified by a clear HMBC $^3J_{C\text{-}H}$ cross peak between C=O and H-1.

The protection of the epoxide as a benzyl ether was also successful under trapping conditions (64 %, Scheme 99) in DCM (a solvent chosen by mistake but which worked quite well), giving the desired product and small amounts of the Payne product (11 %), that could be separated by column chromatography.



Scheme 99
i) BnBr, TBAI, CH_2Cl_2, NaH, 64 % and 11 %.

Epoxide ring opening of the benzyl ethers was succesful with fluoride and hydride nucleophiles (63, 68 and 87 % respectively, Scheme 100) and trouble free, in contrast with the PNB protected epoxides. These fluoro alcohols were characterised and the enantiomeric purity was determined by HPLC, and by ^{19}F NMR ($\Delta\delta_F$ = 0.12 ppm between enantiomers) (Figure 9).



Scheme 100
i) KHF_2, TBAF·$3H_2O$, 100 °C, 63 %; ii) KHF_2, TBAF·$3H_2O$, 110 °C, 68 %;
iii) $NaBH_4$, EtOH, reflux, 87 %.

These benzyl ethers together with their non-fluoro analogue, which was synthesized as previously described, become very valuable intermediates for the synthesis of 6-deoxysugars.

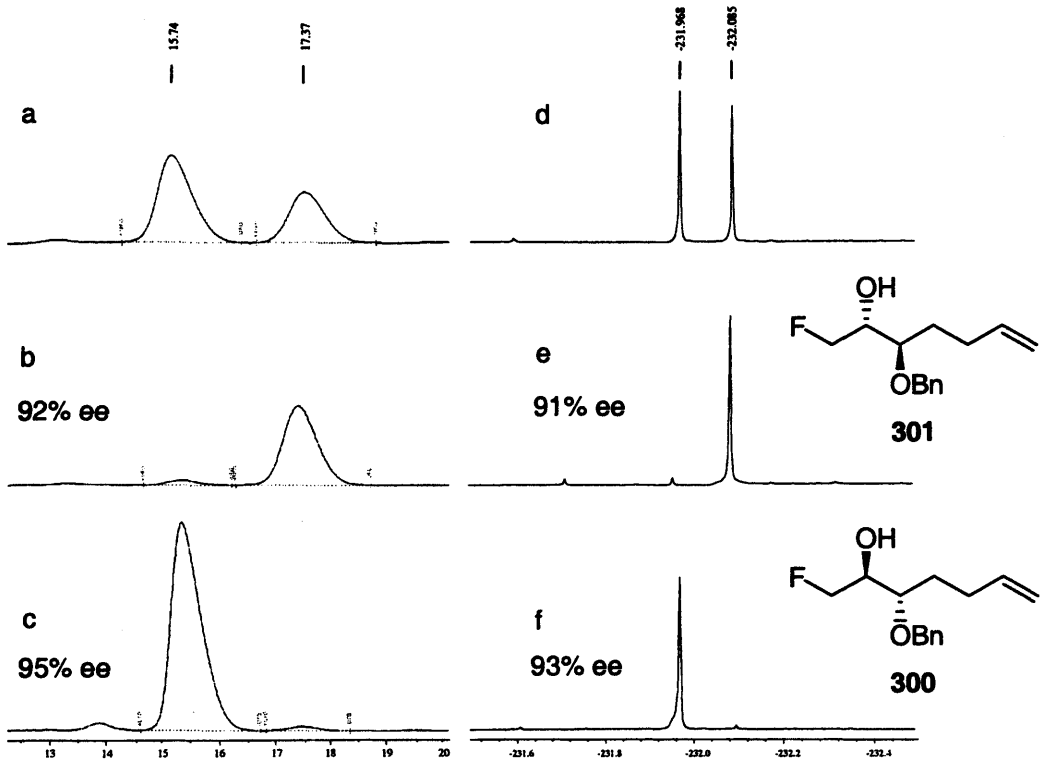
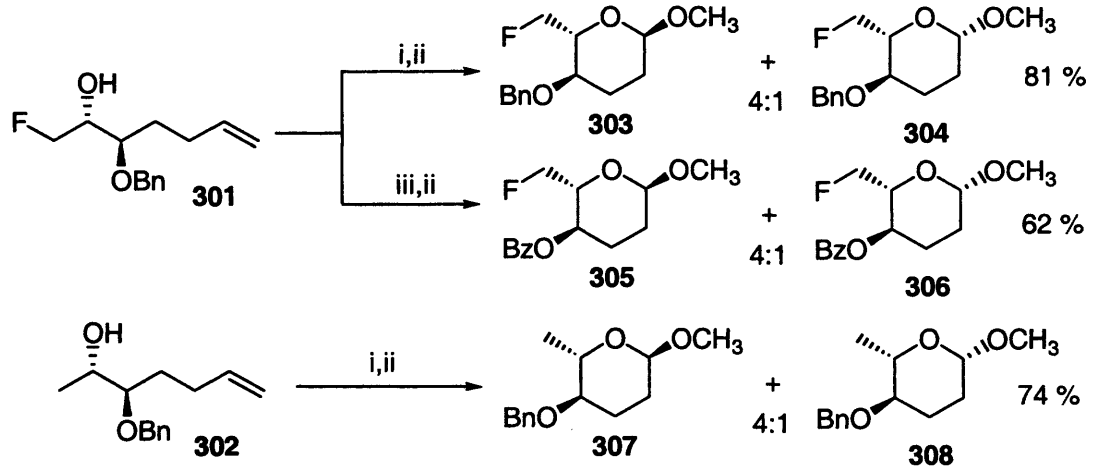


Figure 9. HPLC Chromatograms (Chiralcel OD-H, 999:1 hexane ^{i}PrOH) and ^{19}F {H} NMR (300MHz, L-(+)-DIPT/$CDCl_3$, 300K) spectra of alcohols **301** (b,e), **300** (c,f) and a mixture of both (a,d).

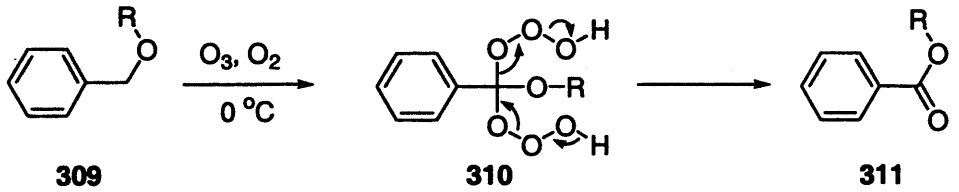
Ozonolysis of fluoro and non-fluoro benzyl ethers **301** and **302** delivered the expected methyl pyranosides in good yield (81 and 74 % respectively, Scheme 101). The $[\alpha]_D$ of methyl 4-*O*-benzyl-2,3,6-trideoxy-α-L-erythro-hexopyranoside **307** ($[\alpha]_D$ -121^{o}) was in agreement with that reported by Haines ($[\alpha]_D$ -175^{o}).[138] The amicetoside was synthesized from deoxygenation of 6-deoxy-L-mannose in this case.



Scheme 101

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, rt; iii) O_3, MeOH, TMSCl, 0 °C, 5 h.

The benzoate esters were also obtained in moderate yield (62 %) after performing a long ozonolysis at 0 °C. As described in p. 56, benzyl ether protective groups are oxidized by ozone at temperatures above –50 °C,[123] and as described in the literature,[139] producing the corresponding benzoates, following the mechanism shown in Scheme 102.

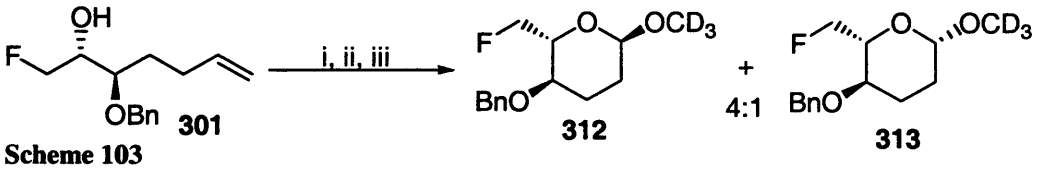


309 **310** **311**

Scheme 102. Mechanism for the oxidative conversion of benzyl ethers into benzoate esters.

All different crude reaction products contained a mixture of 2 anomers, with the α anomer as the major; we were able to purify these by column chromatography giving lightly enantiomerically enriched single anomers, which were characterised fully by NMR. This result suggests that the effect of the different substituents in the ring has no effect on the ratio between α and β anomers, contrary to what happened in the difluoro species where the α anomer was the only one observed.

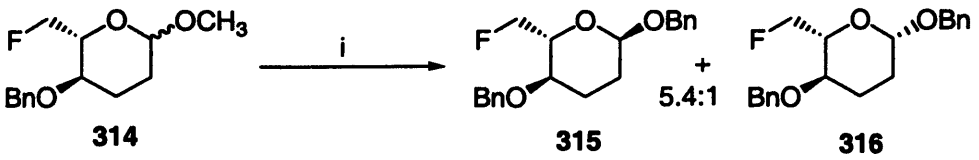
The deuteromethyl amicetosides **312** and **313** were also synthesized in moderate yield (63 %, Scheme 103) by exchanging the methyl with mild acidic deuteromethanol after the ozonolysis was complete. These compounds were synthesized to obtain NMR spectra without the strong signal from the methoxy group, which can overlap with and obscure the signals corresponding to protons 4 and 5.



Scheme 103

i) O_3, MeOH, TMSCl, -78 °C; ii) Me_2S, overnight, rt; iii) CD_3OD, TMSCl, 63 %.

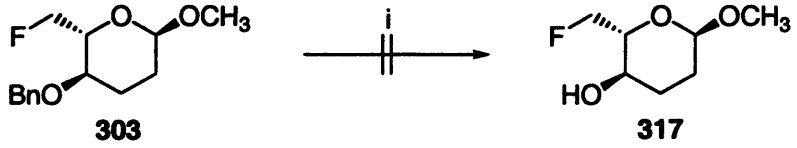
The benzyl amicetosides were also synthesized in the same manner as previously described, this time from the purified methyl pyranosides in excellent yield (99%, Scheme 104).



314 **315** **316**

Scheme 104
i) BnOH, TMSCl, 99 %.

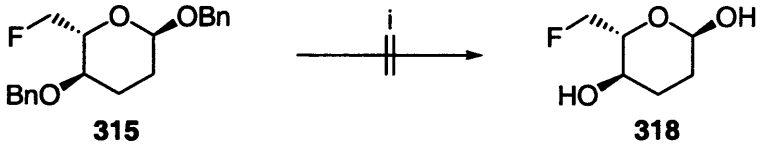
At the final steps of the synthesis, the deprotection of the benzyl ethers to reveal the methyl pyranosides under palladium catalysed debenzylation conditions was successful (96 %, Scheme 105), as previously described in p 58.[124]



303 **317**

Scheme 105
i) 10 % Pd/C, EtOH, H_2, 96 %.

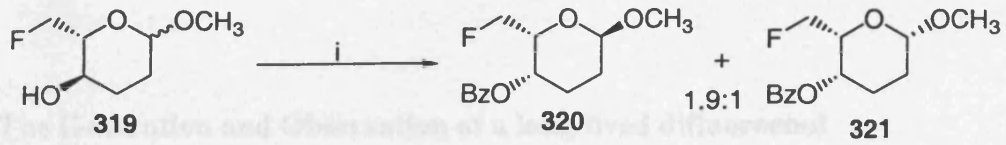
Benzyl amicetosides **315/316** were subjected to debenzylation conditions as well in an attempt to obtain the corresponding free hemiacetals in chloroform (Scheme 106), to avoid the presence of a protic solvent, but instead it led to the formation of a very complex mixture of products observed by NMR and TLC, suggesting the formation of oligosaccharides. Similar results were obtained when performing the ozonolyses in dichloromethane; only one of the different products was isolated and identified as previously described 10-membered ring dimer **283**.



315 **318**

Scheme 106
i) 10 % Pd/C, $CHCl_3$, H_2.

The rhodinose analogue was synthesized successfully from methyl 6-fluoro amicetoside **319** following Mitsunobu conditions using benzoic acid as nucleophile, giving the diastereoisomer of the previously synthesized methyl *O*-benzoyloxyl amicetoside **305/306** in moderate yield (67 %, Scheme 107).



Scheme 107
i) BzOH, DEAD, PPh_3, Toluene, 67 %.

The relative configuration was identified by X-ray crystallographic analysis of methyl 4-*O*-benzyloxy-6-deoxy-6-fluoro-α-L-rhodinopyranoside **320** which crystallized (Figure 10). In this compound the Flack parameter is –0.74, and the error is 1.3, but as previously discussed, proof of absolute stereochemistry of X-ray single-crystal of molecules with no heavy atoms, which have very small contributions to the scattering factor, is only possible by collecting the data at a longer wavelength.

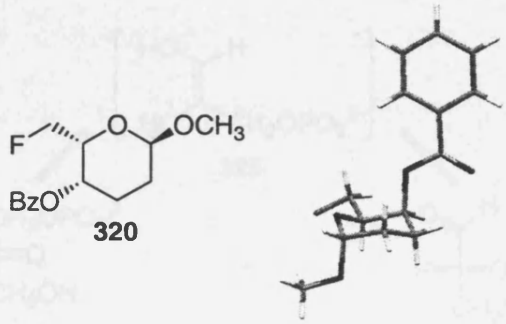
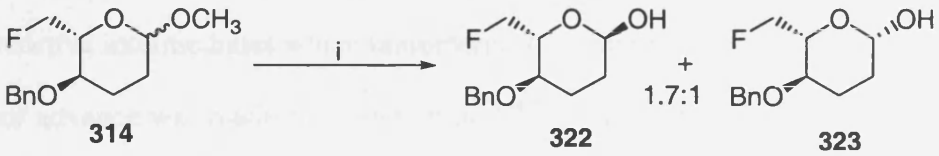


Figure 10

The corresponding hemiacetal of benzyl protected amicetose was also synthesized in good yield (80 %, Scheme 108) with the procedure previously described in p. 57.

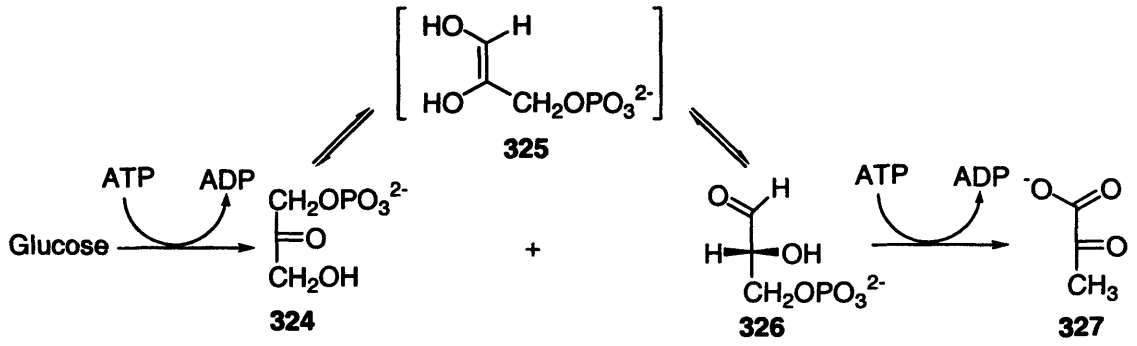


Scheme 108
i) HCl, H_2O, THF, Microwave 50W, 1h, 120 °C, 80 %.

2.4 The Generation and Observation of a long-lived difluoroenol

2.4.1 Introduction

The relationship between enols and their aldehyde and ketone tautomers is one of the most fundamental in organic chemistry and is central to life. A correct understanding of the phenomenon informs many ideas about reactions of profound importance, both *in vivo* and *in vitro*. For example, type of enol intermediate **325** (enediol) plays a key role in glycolysis, a pathway used by all living things for production of energy through the breakdown of glucose (Scheme 109).[140]



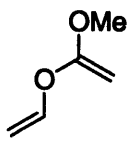
Scheme 109

Through the groundbreaking work of Capon,[141] Kresge,[142] Rappoport[143] and others, we have learned techniques for the generation and direct observation of enols, ynols and other reactive intermediates which tautomerise to carbonyl compounds.

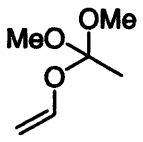
A major advance was made by Capon *et al.*,[144,145] who found that reactive ketene acetal **328** and orthoester **329** hydrolysed sufficiently rapidly for vinyl alcohol **330** to be observed in acetone-water (99:1). Relatively long-lived solutions of **330** (for example $t_{1/2}$ *ca.* 10 minutes, MeCN, 20 °C) could be prepared by manipulating reaction conditions subtly. Kresge developed the laser flash photolysis technique[146,147] to allow the direct study of a wider range of reactive intermediates in water and to reveal structure reactivity relationships. For example, enols **331** and **332** are *ca.* 10^2 times ($t_{1/2}$

ca. 0.5 s) and 4 times ($t_{1/2}$ *ca.* 10 s) more reactive than **330** ($t_{1/2}$ *ca.* 35-45 s between pH 3.5 and 5.0) respectively.

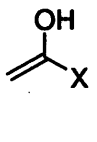
The presence of electron withdrawing substituents can extend the lifetime of enols dramatically. For example, Knunyants and co-workers[148] described how **333** could be stored indefinitely and distilled without significant tautomerisation to the corresponding ketone **336**.



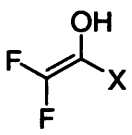
328



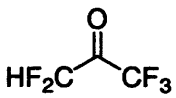
329



330, X = H;
331, X = CH_3;
332, X = CH_2Cl.



333, X = CF_3;
334, X = CO_2Me;
335, X = H

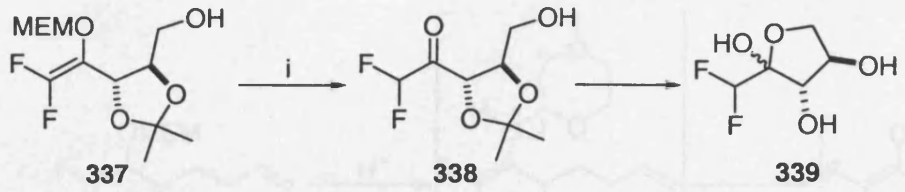


336

More recently, Burger prepared **334**, and noted that it was stable under acid conditions.[149] Both -CO_2Me and –CF_3 groups are powerful electron withdrawing (-*I* in both cases, -*R* in the former only) and their effects can be understood by referring to the accepted ketonisation mechanism in which general acid catalysed protonation at carbon leads to oxacarbenium ion formation, followed by proton loss from oxygen to afford the neutral carbonyl species. Both **333** and **334** contain a –*I* substituent at every available position, so the difficulty of positive charge development is reasonable.

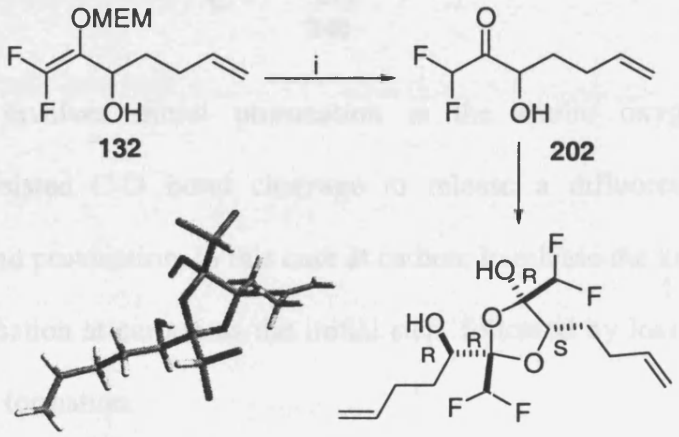
2.4.2 Results and Discussion

As previously described in p. 47, the cleavage of the MEM-group occurred when adding trimethylchlorosilane to a solution of difluoroallylic alcohol **337** in methanol,[81,113,150] delivering ketone **338** which is captured intramolecularly giving a discrete product **339** (Scheme 110).[150] Dry HCl is produced under these conditions.



Scheme 110
i) 1.2 eq TMSCl, MeOH, rt, 88 %

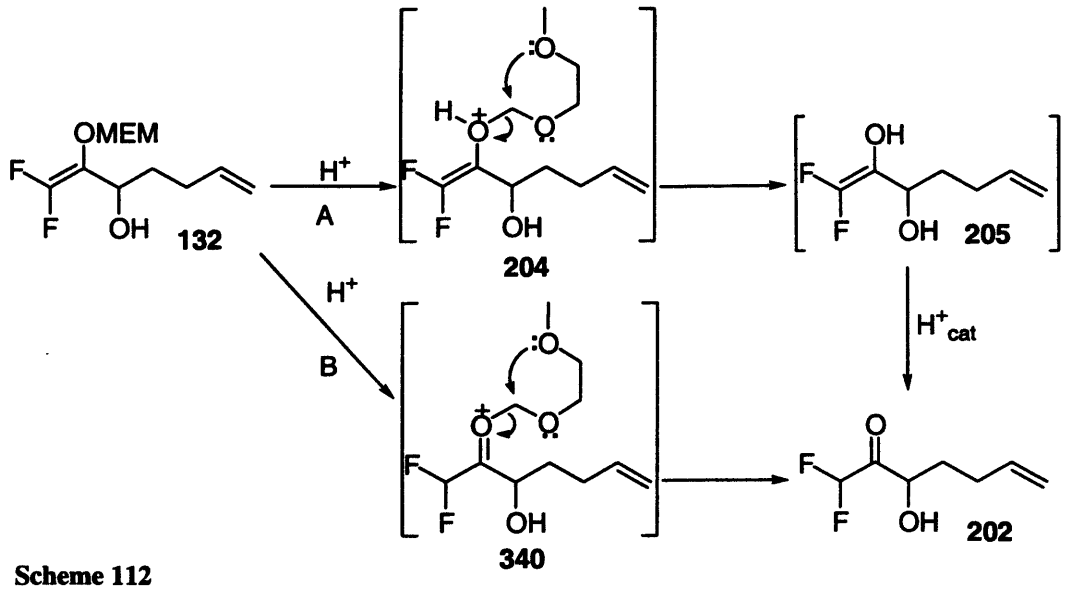
With substrate **132**, a crude mixture with a complex NMR spectrum was obtained, and finally a crystalline solid was isolated and identified by X-ray as racemic dioxolane dimer **203**, instead of the expected ketone.



Scheme 111
i) TMSCl, MeOH, r.t., 82 %.

Formation of dioxolane dimer **203** is explained by the strong electron withdrawing effect of the two fluorine atoms, making the carbonyl group much more electron deficient and reactive. Initially, dioxolane dimer **203** was an undesired product that we wished to avoid; as result of studying its formation, a very long-lived enol intermediate was found and characterised.

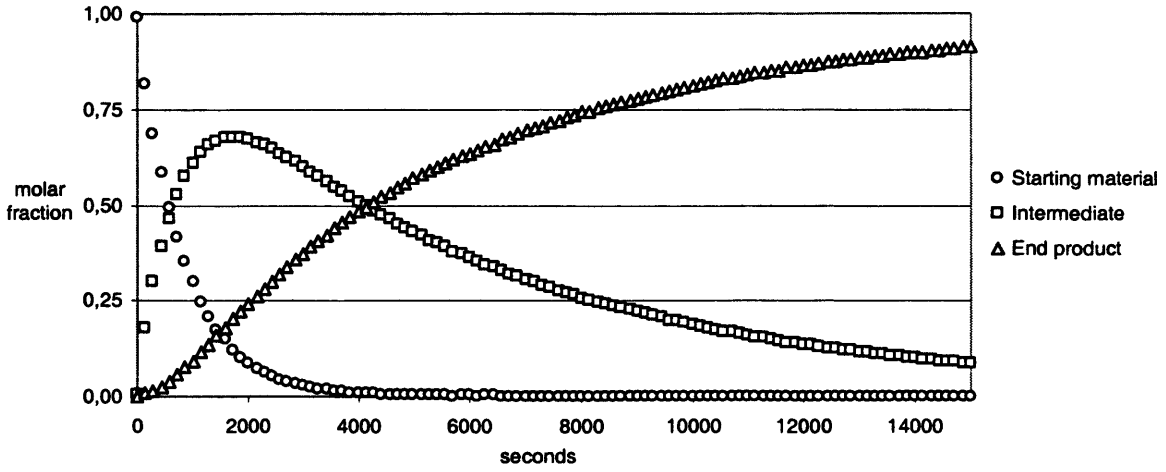
There are two possible mechanisms for the cleavage of the MEM acetal and ketone formation which are shown in Scheme 112.



Scheme 112

Mechanism A, involves initial protonation at the enolic oxygen followed by anchimerically-assisted C-O bond cleavage to release a difluoroenol, which then undergoes a second protonation, in this case at carbon, to release the ketone. Mechanism B involves protonation at carbon as the initial step, followed by loss of the protecting group and ketone formation.

Following the methanolysis by ^{19}F NMR after adding a catalytic amount of TMSCl to a solution of difluoroallylic alcohol **132** in deuteromethanol, revealed complete consumption of the starting material (○), together with the build up of an intermediate □), which decayed to the end product (△) on a longer timescale (Graphic 1).



Graphic 1

This intermediate was identified as another difluoroalkene, with the corresponding signals clearly visible in the ^{19}F and ^{13}C NMR spectra (Figures 11 and 12).

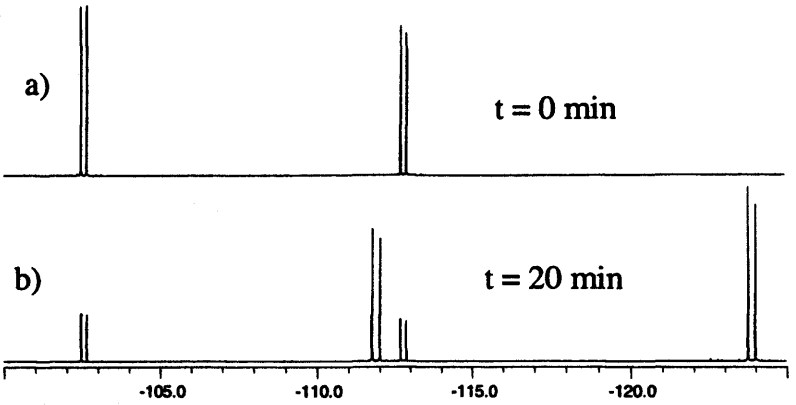


Figure 11. ^{19}F NMR spectra (300MHz, CD_3OD, 300K).
a) difluoroallylic alcohol **132**;
b) difluoroallylic alcohol **132** + intermediate **205**.

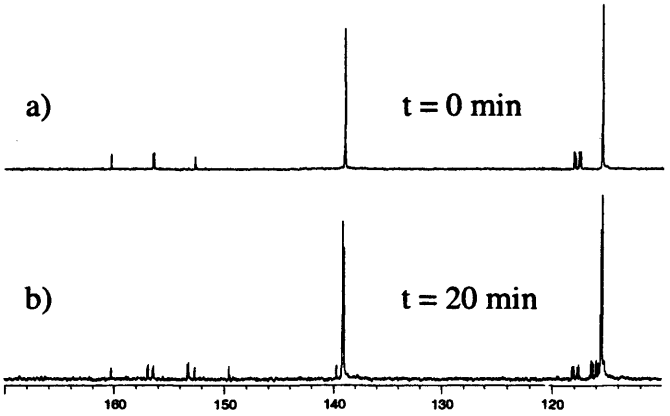
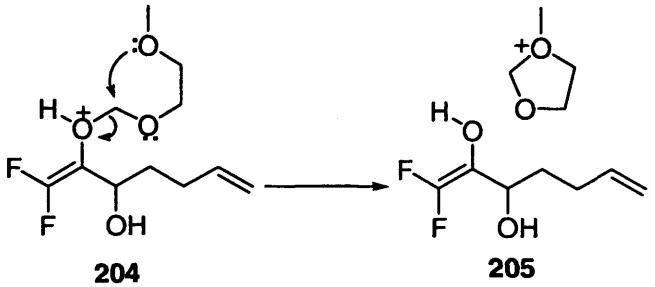


Figure 12. ^{13}C NMR spectra (300MHz, CD_3OD, 300K).
a) difluoroallylic alcohol **132**;
b) difluoroallylic alcohol **132** + intermediate **205**.

These spectra indicate unambiguously that the first-formed intermediate is another difluoroalkene, suggesting that the reaction follows mechanism A previously described (scheme 112). However, it is not possible to distinguish which of the intermediates proposed by the mechanism this one corresponds to. The critical feature distinguishing them, is the connection between the enolic oxygen and the acetal carbon of the leaving group, present in the first and cleaved in the latter (Scheme 113).



204 **205**

Scheme 113

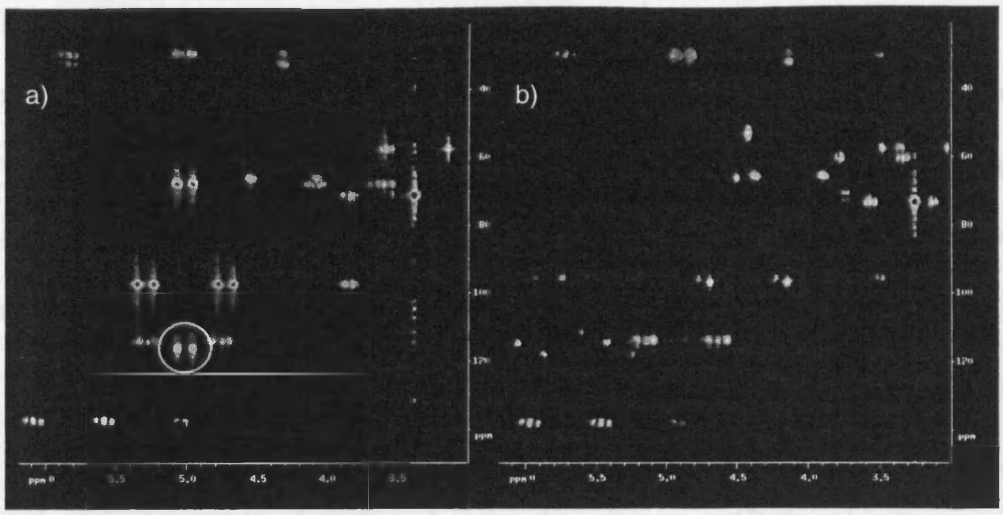


Figure 13. HMBC spectra (300 MHz, CD_3OD, 300K).
a) Allylic alcohol **132**, t = 0 min
b) Enol **205**, t = 100 min

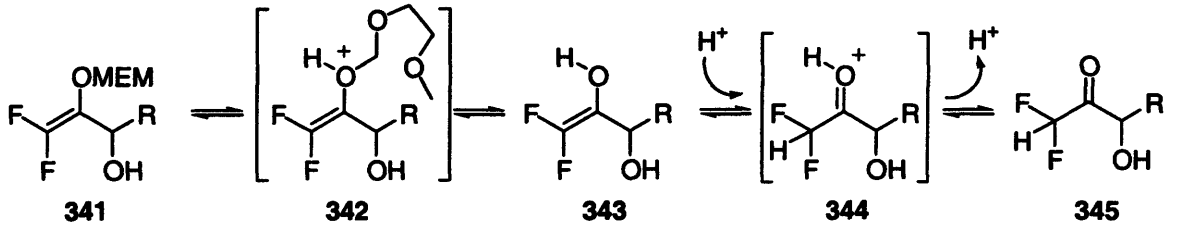
Figure 13 shows the HMBC spectrum of the starting material and the HMBC of the solution where the starting material has been consumed completely 100 minutes after adding TMSCl

The connectivity is verified by looking at the $^3J_{C\text{-}H}$ cross peak between the methylene protons and C-2 of the substrate. These protons are diastereotopic and appear as an AB quartet centred at 5.0 ppm (Figure 13a, white circle). The other signals at 5.0 ppm correspond first to a $^3J_{C\text{-}H}$ of proton 6, another $^3J_{C\text{-}H}$ of the methylene protons, and at both sides around 5.0 ppm also appear the unsuppressed $^1J_{C\text{-}H}$ signals corresponding the methylene and carbon 6.

The signals of the starting material have disappeared, and the ones corresponding to the leaving group have been displaced from 5 to 4.5 ppm due to the ether oxygen being less electron-withdrawing than the enolic oxygen.

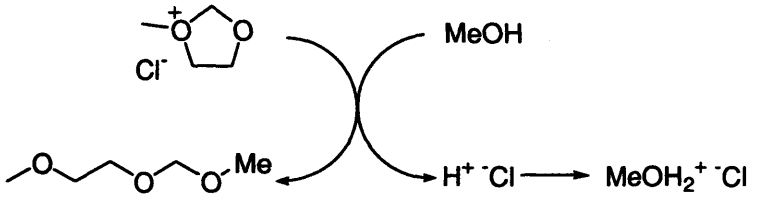
The HMBC in Figure 13b shows that there is no connection between the new C-2 carbon and the acetal methylene, consistent only with cleavage of the key C-O bond and enol formation. Vinyl acetals are known to undergo initial acetal hydrolysis to release the enol, followed by ketonisation.[151]

Looking in more detail at the concentration/time profile, Scheme 114 reveals that the reaction involves two consecutive first order reactions; the first one is the deprotection which occurs when adding trimethylchlorosilane to the solution of the starting material in methanol, which generates HCl *in situ*. This proton is then used to protonate the starting material and remove the acetal protecting group.



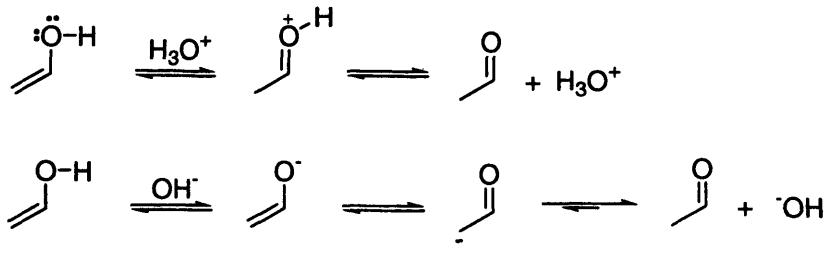
Scheme 114

Although this behaviour would be considered second order because we have two molecules reacting with each other, it is fact *pseudo* first order in acid because the concentration of acid in the solution remains constant. This is due to the regeneration of HCl from the stabilisation of the leaving group with one molecule of solvent (Scheme 115).



Scheme 115

The second step of the reaction is the ketonization or decay of the enol intermediate which is *pseudo* first order as well, because although it is catalysed by acid and the rate is dependent on the concentration of acid, the concentration of acid remains constant. In scheme 116 are shown the mechanisms of catalysed acid/base ketonization.



Scheme 116

The measured half-life of **205** in CD_3OD (0.1 M in DCl, 300 K) is 1.19 x 10^4 s (3.3 hours). The literature value for the half-life of vinyl alcohol in water is between 35 and 45 seconds, while it can reach up to 10 minutes in acetonitrile, studied directly with laser flash photolysis technique developed by Kresge.

The rate of disappearance of **205** was measured (Appendix II) at three different acid concentrations in CD_3OD/DCl and CD_3OH/HCl affording values of $k_D^+ = 4.76 \times 10^{-4}$ M^{-1} s^{-1} and $k_H^+ = 1.92 \times 10^{-3}$ M^{-1} s^{-1}, corresponding to a reactivity difference of 10^6 with acetone enol ($k_H^+ = 4.7 \times 10^3$ M^{-1} s^{-1} at 25 °C in water), and to a solvent kinetic isotope effect of 4.04, which compares well with literature values of 4.61 and 2.98 for vinyl alcohol and ethyl vinyl ether protonation respectively in water.[146,147]

(CD_3OD)	[132]/M	[TMSCl]/M	k_{obs}
1	0.648	0.113	$5.70 \cdot 10^{-5}$
2	0.546	0.333	$1.59 \cdot 10^{-4}$
3	0.576	0.162	$7.28 \cdot 10^{-5}$

(CH_3OH)	[132]/M	[TMSCl]/M	k_{obs}
4	0.531	0.282	$5.32 \cdot 10^{-4}$
5	0.544	0.255	$4.82 \cdot 10^{-4}$
6	0.495	0.328	$6.47 \cdot 10^{-4}$

Table 10

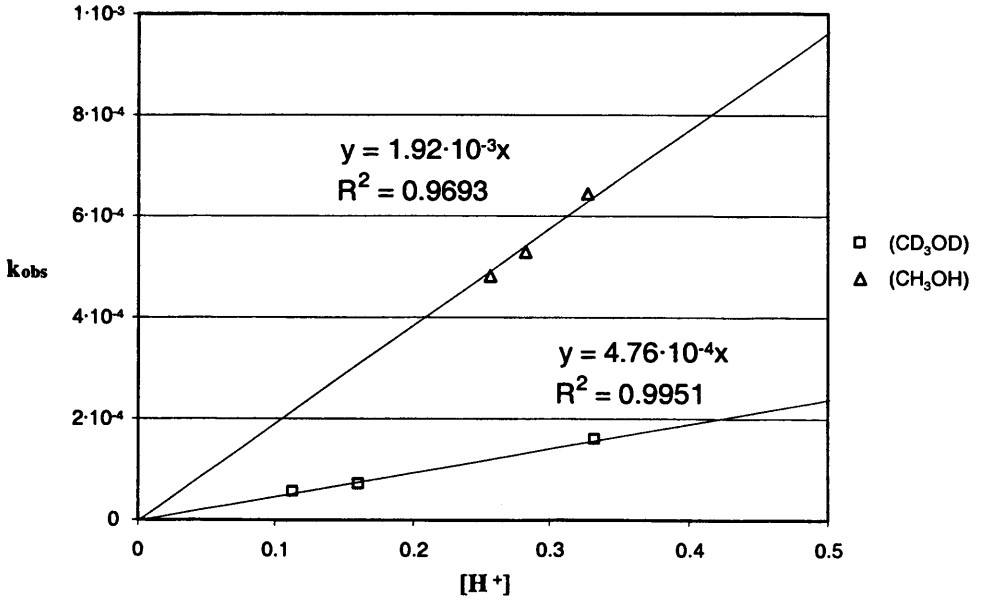


Figure 14

The measured rate data is shown in Table 10 and the graphical treatments follow. Given that the uncatalysed rate for enol consumption is very slow on this timescale (estimated at $< 5 \times 10^{-7}\ s^{-1}$), the regression lines were fitted to the origin (Figure 14).



Scheme 117

Accidental preparation of a sample of **132** containing traces of acid led to an interesting observation (Scheme 117). The MEM acetal was cleaved but the enol was stable for weeks. This corresponds to a half-life of much greater than 2 weeks.

2.4.3 Computational Modelling

In an attempt to understand the difference in the reactivity of vinyl alcohol and the difluoro analogue, Ian H. Hillier and Mark A. Vincent from the University of Manchester, have used density functional theory (DFT) methods to study the structures and energetics of the enol form and the corresponding transition states leading to the keto form.

The model used for the calculations involves methanol molecules, which are involved in the proton transfer from and to solvent, and a single chloride counterion. The number of additional solvent molecules and counterions is somewhat arbitrary, but will probably have little effect on the overall reactivity. The calculations have employed the B3LYP functional together with a large Gaussian basis set (6-311++G**).

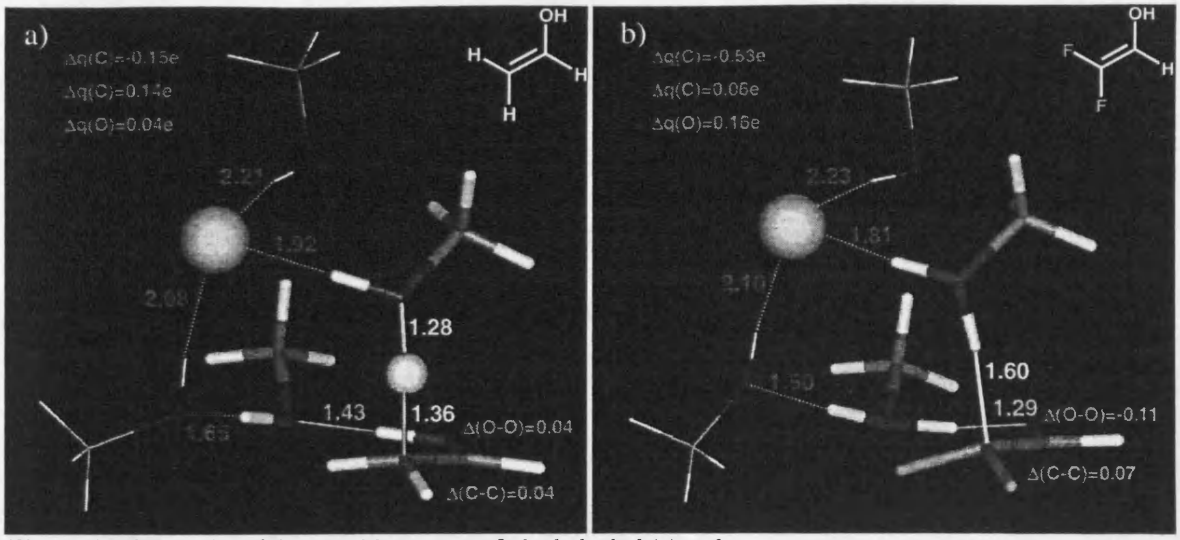
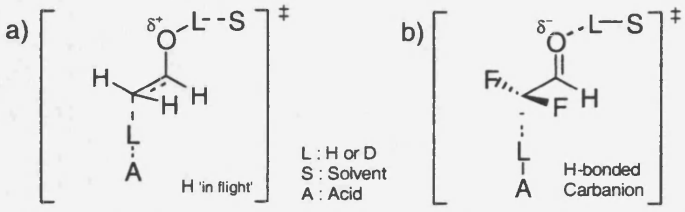


Figure 15. 3D model of the transition states of vinyl alcohol (a) and 2,2-difluoro-vinyl alcohol (b).

The structures of both transition states for the formation of the corresponding aldehyde have been identified and properly characterized; and substantial differences between the two transition states have been found, Figure 15.



Scheme 118. Representation of the transition states of vinyl alcohol (a) and 2,2-difluoro-vinyl alcohol (b).

In the transition state for the tautomerization of vinyl alcohol, the proton is visualised as "in flight" between oxygen and carbon (Scheme 117). In this case the intermediate is developing oxacarbenium ion character while the situation is very different for the difluoro analogue. Although the reaction is performed under acid conditions, the intermediate has lost the enol character and looks like a hydrogen bonded carbanion, where there is considerably less C-H bond formation and considerable increase in the electron density.

These differences result in a larger free energy barrier for the difluoro species to progress through protonation of 71 kJ/mol compared to 20 kJ/mol for vinyl alcohol,

values leading to a relative difference in reactivity between enol **330** and difluoro enol **335** of 6.0 x 10^8 in line with the experimental measurements.

The prediction of a change of mechanism is also interesting and consistent with the electron withdrawing effect exerted by the two fluorine atoms. By refining the proton transfer in this way, positive charge development in the difluoro enol fragment is avoided. The pyramidal nature of the relatively electron-rich CF_2 centre avoids p/π repulsion which is known to destabilise α-fluorinated carbanions. Hine[152,153] showed that isotopic exchange reactions of methyl fluoroacetate and difluoroacetate occurred more slowly than expected due to this phenomenon, whereas the corresponding fluoromethyl and difluoromethyl sulfoxides which exchange *via* sp^3-type carbanions exchange more quickly than the methyl congener.

3 Conclusions

Enantiomerically enriched and racemic 6-fluoro and racemic 6,6-difluoro analogues of Amicetose and Rhodinose have been synthesized succesfully using different and scaleable strategies from commercially available starting materials.

Although the racemic route is rapid, it fails to deliver the sugars in a practical way because of the complexity of the solution equilibria, and our inability to carry out the reduction stereoselectively once the allylic alcohol has been protected. This lead to the development of an asymmetric alternative route, from which 6-fluoro analogues of amicetose have been synthesized using benzyl and benzoyl protecting groups. After easy deprotection and inversion of the configuration, a 6-fluoro analogue of rhodinose has also been synthesized.

The equilibria between furanoses and pyranoses of methyl amicetosides, 6-fluoro and 6,6-difluoro analogues has been studied and compared with the pK_a's of ethanol, 2-fluoroethanol and 2,2-difluoroethanol showing that there is clear electron withdrawing inductive effect of the fluorine atoms on the nucleophilicity of the hydroxyl group at C-5.

New synthetic methods have been discovered, including:

- the *in situ cis/trans*-isomerisation and fluorination of an allylic chloride, with a mixture of TBAI and TBAF, to deliver a potentially versatile intermediate for use in the Masamune-Sharpless total synthesis of hexoses;
- the fluorination of an epoxide with excellent regioselectivity with a mixture of KHF_2 and TBAF;
- the discovery of a facile NMR method for the determination of enantiomeric excess without derivatisation, and confirmed by HPLC.

These routes have also lead to the unusual findings, including the discovery of a long-lived difluoroenol. The increase in energy of the transition state makes difluoroenols very long-lived, a longevity remarkable given the absence of additional electron withdrawing groups. The lifetime of the enol was 3.3 hours.

4 Experimental

4.1 General Procedures

NMR spectra were recorded on a Bruker ARX 250 (^{1}H, 250.13 MHz; ^{13}C, 62.90 MHz; ^{19}F, 235.36 MHz) spectrometer, a Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{19}F, 282.40 MHz, COSY, HMQC, HMBC) spectrometer or a Bruker DRX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz; ^{19}F, 376.45 MHz, COSY, HMQC, HMBC, NOESY) spectrometer using Norell 507-HP NMR tubes. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded using deuterated solvent as the lock and residual solvent as the internal standard. ^{19}F NMR spectra were referenced to CCl_3F as the external standard. They are reported consecutively as chemical shift (δ_H, δ_C, or δ_F), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, td = triplet of doublets, m = multiplet, env. = envelope, app. = apparent and br.s = broad singlet), coupling constant (J / Hz) and assignment. Electron Impact (EI) mass spectra were recorded on Kratos Concept 1H mass spectrometer. Chemical Ionization (CI) mass spectra were recorded on a Kratos Concept 1H mass spectrometer using ammonia as the reagent gas. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H mass spectrometer using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC mass spectrometer. High Resolution Mass Spectrometry (HRMS) was measured on a Kratos Concept 1H mass spectrometer using peak matching to stable reference peaks, depending on the technique used. Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40-63μ) and HPFC Biotage Horizon system with

Biotage silica prepacked Flash+ purification cartridges and Samplet sample-loading cartridges (12+M, 12+S, 25+M, 40+M and 40+S). Column fractions were collected and monitored by Thin Layer Chromatography (TLC) carried out on precoated aluminium backed silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F_{254}, thickness 0.2 mm) or on precoated glass plates supplied by Merck (Silica gel 60 F_{254}). The compounds were visualized using UV light (λ = 254 nm), potassium permanganate, *p*-anisaldehyde, 2,4-dinitrophenylhydrazine or phosphomolybdic acid (PMA) stains. Gas Chromatograms were recorded on a Perkin Elmer Autosystem Gas Chromatograph linked to a Perkin Elmer Turbomass mass spectrometer. The chromatograph was fitted with a PE5 MS (5 % phenyl, 95 % dimethylpolysiloxane phase column (30 m)); experiments were carried out between 45 to 250 °C with a 10 °C min^{-1} ramp. Microwave experiments were carried in a CEM Discover instrument (variable power, max. 300W). Infra-red (IR) spectra were obtained on a Perkin Elmer 1600 series FT-IR spectrometer from solution samples in dry CH_2Cl_2 (DCM) in a NaCl cell, or as neat samples in a Perkin Elmer SpectrumOne FT-IR spectrometer. Enantiomeric excesses (ee) were obtained from Perkin Elmer Series 200 Autosampler HPLC using Diacel Chemical Industries, Ltd. Chiralpak AD, AS, Chiralcel OD-H and OJ columns, diameter 4.6 mm, length 25 cm, flow = 1 ml/min, T = 25 °C. Optical and Specific Rotations were obtained in a Perkin Elmer 341 Polarimeter (λ = 589 nm Na) in a 100 mm Perkin Elmer 6047 cell using HPLC grade chloroform. pH measurements were obtained on a RadioMeter Copenhagen PHM83 AUTOCAL pH Meter. X-Ray reflections were collected on a Bruker SMART APEX 4K CCD diffractometer (R_{int} = 0.0202) using Mo-Kα radiation (λ = 0.71073 Å). Refinement was carried out using SHELXL-97.

Light petroleum refers to the fraction boiling between 40-60 °C. Tetrahydrofuran (THF) was dried by refluxing with benzophenone over sodium wire under an atmosphere of

nitrogen, and was distilled and collected by syringe as required. Dichloromethane, diethyl ether, toluene and acetonitrile were dried by refluxing with calcium hydride, they were then distilled and collected by dry syringe as required, or from Pure-Solv Solvent Purification Systems from Innovative Technology, Inc.. Dry DMF was used supplied by Aldrich. Acetone was used as reagent grade. *n*-Butyllithium was titrated immediately before use according to the method described by Duhamel *et al.*[154] using 4-phenylbenzylidene benzylamine as the indicator. 4 Å Molecular sieves, silica gel, lithium chloride and copper sulfate were dried by heating to 100 °C under reduced pressure (below 50 mmHg) and handled under nitrogen. Tetrabutylammonium fluoride (TBAF) trihydrate was dried by heating to 40 °C under reduced pressure (<0.1 mmHg) with P_2O_5 to obtain *"anhydrous"* TBAF.[97] Ozone was generated by a 500M Fischer Technology ozone generator operating at a power of 0.7 A and using oxygen at a flow rate of 2 l/min. All other chemicals and solvents were used as received without any further purification.

4.1.1 Measurement of reaction rates

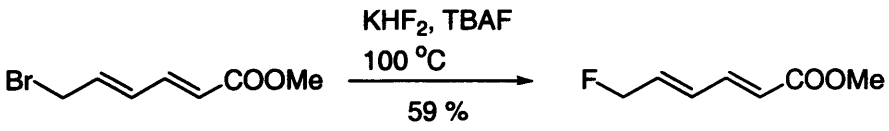
Alcohol **132** was exchanged (OH for OD) by evaporation from CD_3OD several times before use for deuteriation experiments. Reactions were intiated by the addition of TMS-Cl to a CD_3OD or CD_3OH solution of substrate respectively from a Hamilton microsyringe in an NMR tube which was immediately capped, sealed with Parafilm and transferred to the probe of a Bruker DRX 400 spectrometer. (Trifluoromethoxy)benzene was used as an internal standard (δ_F –59.3 ppm). Between 60 and 240 datapoints were recorded for each kinetic run. Each spectrum was automatically phased and integrated. Data were transferred to Excel spreadsheets and normalised against the internal standard. The data fitted well to first order plots ($R^2 = 0.999$ typically).

4.1.2 Measurement of Enantiomeric Excess by Capillary NMR

Substrate (at least 0.01 mmol) was added to a NMR tube and, diluted with a premixed solution (0.35 mL) of di*iso*propyl L-tartrate (5.3 mmol, 1.25 g) in HPLC grade chloroform (13.0 mmol, 1.55 g)). After solution had been achieved, a sealed capillary containing $CDCl_3$ was added and the spectrum was recorded.

4.2 Experimentals

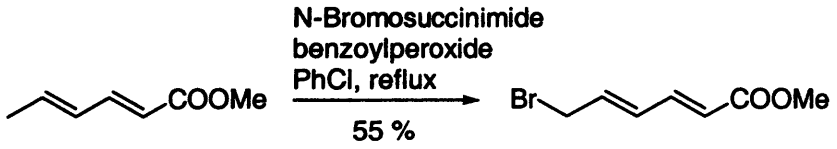
6-Fluoro-hexa-2,4-dienoic acid methyl ester 91



Tetrabutylammonium fluoride trihydrate (12.39 mmol, 3.91 g) and potassium hydrogen difluoride (49.56 mmol, 3.87 g) were heated and stirred in a round-bottomed flask at 100 °C until melting ocourred. Allylic bromide **92** (12.39 mmol, 2.54 g) was then added and the resulting viscous suspension was stirred vigorously for 30 minutes at 100 °C. The reaction mixture was then cooled to room temperature and the mixture was diluted with Et_2O (25 mL) and H_2O (10 mL) to solubilise all the salts. The organic layer was separated and the aqueous layer was neutralized with solid $NaHCO_3$ (2 g) and extracted with Et_2O (3 x 50 mL). The combined organic extracts and original layer were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a brown oil which was purified by column chromatography (gradient 0 to 10 % Et_2O in hexane) to give fluoro ester **91**

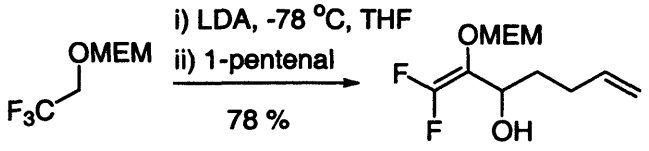
(1.05 g, 59 % yield, 98 % by GC-MS) as a pale yellow solid; mp 27-29 °C; R_f (10 % ethyl acetate in hexane) 0.46; υ_{max} (neat)/cm^{-1} 3003-2837w (C-H), 1661w (C=C), 1612, 1586w, 1511s (C=C), 1463, 1359, 1302 (CH_2), 1245s, 1173, 1109, 1079, 1034s (C-O-C), 988s (C=C-H); δ_H (300 MHz, $CDCl_3$) 7.28 (1H, ddd, *J* 15.5, 10.8, ^4J 1.5, H-3), 6.43 (1H, tdddd, *J* 15.5, 10.8, $^4J_{H\text{-}F}$ 3.2, ^4J 1.7, ^4J 0.6, H-4), 6.18 (1H, tddd, $^3J_{H\text{-}F}$ 20.6, *J* 15.5, 5.3, ^4J 1.5, H-5), 5.94 (1H, ddd, *J* 15.5, ^4J 1.2, 0.6, H-2), 4.97 (2H, ddd, $^2J_{H\text{-}F}$ 46.4, *J* 5.3, ^4J 1.7, H-6), 3.74 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.1 (C-1), 143.0 (C-3), 135.5 (d, $^2J_{C\text{-}F}$ 15.7, C-5), 129.8 (d, $^3J_{C\text{-}F}$ 12.0, C-4), 122.5 (C-2), 82.0 (d, $^1J_{C\text{-}F}$ 165.7, C-6), 51.7 (OCH_3); δ_F (282 MHz, $CDCl_3$) -217.45 (1F, tddd, ^2JF-H 46.4, ^3JF-H 20.6, ^4JF-H 3.2, ^5JF-H 2.1); [HRMS (EI, M^+) Found: 144.05861 Calc. for $C_7H_9FO_2$ 144.05866]; m/z (EI) 144 (28 %, M^+), 113 (53, M-OCH_3), 111 (100, M-OCH_3+2H), 85 (70) The stereochemistry and identity of this product were confirmed by XRD analysis; Crystal data: $C_7H_9O_2F$, crystal size 0.23 x 0.16 x 0.15 mm^3, *M* = 144.14, monoclinic, space group C2/c, unit cell dimensions *a* = 8.4626(16), *b* = 8.02276(16), *c* = 21.142(4) Å, α = 90°, β = 90.378(5)°, γ = 90°, *V* = 1436.2(5) $Å^3$, *Z* = 8, D_{calc} = 1.333 Mg m^{-3}, *F*(000) = 608, μ(Mo-Kα) = 0.113 mm^{-1}, *T* = 150(2) K, 4948 total reflections measured, 1256 independent, (R_{int} = 0.0410) which were used in all calculations. Final *R* indices (for reflections with $I > 2\sigma(I)$) were *R*1 = 0.0455, ω*R*2 = 0.1063; *R* indices (all data) *R*1 = 0.0535, ω*R*2 = 0.1101. The compound appears to be very volatile only at high purity.

6-Bromo-hexa-2,4-dienoic acid methyl ester 92



Methyl sorbate (79.3 mmol, 10.0 g)[155] and *N*-bromosuccinimide (83.4 mmol, 15.0 g) in dry chlorobenzene (60 mL) were slowly heated to 100 °C and benzoyl peroxide (3.6 mmol, 0.88 g) was then added cautiously in portions. After the addition, the reaction mixture was heated under reflux for 2 hours, cooled and the chlorobenzene was removed by evaporation under reduced pressure. The residual paste was triturated with Et_2O (100 mL), filtered and the ethereal solution was washed with 5 % aqueous solution of sodium hydroxide (3 x 50 mL) until the washings were colorless. The organic layer was then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified first by distillation (Kugelrohr, bp 80-90 °C/0.06 mmHg) and then by column chromatography (gradient 0 to 10 % ethyl acetate in hexane) to afford bromo ester **92** as a colourless oil (8.9 g, 55 % yield, 97 % by GC-MS); R_f (20 % ethyl acetate in hexane) 0.54; υ_{max} (neat)/cm^{-1} 3000-2952w (C-H), 1716s (C=O), 1662w, 1645w, 1615w (C=C), 1435m, (CH_2), 1250m, 997m, 977m (C=C-H); δ_H (300 MHz, $CDCl_3$) 7.24 (1H, dd, *J* 15.6 0, 10.8, H-3), 6.37 (1H, qdd, *J* 15.3, 10.8, ^4J 0.9, H-4), 6.22 (1H, tdd, *J* 15.3, 7.5, ^4J 0.6, H-5), 5.92 (1H, d, *J* 15.3, H-2), 4.02 (2H, dd, *J* 7.5, ^4J 0.6, H-6), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 166.9 (C-1), 142.8 (C-3), 136.7 (C-5), 131.8 (C-4), 122.7 (C-2), 51.7 (OCH_3), 31.2 (C-6); [HRMS (EI, M^+) Found: 203.97850 Calc. for $C_7H_9{}^{79}BrO_2$ 203.97850]; m/z (EI) 206 (6 %, MH^+), 204 (6), 175 (10), 173 (10, M-OCH_3), 125 (92, $[M-Br]^+$), 93 (96), 66 (100, $[M-COOCH_3Br]^+$); The data were in agreement with those reported by Durrant *et al.*.[155]

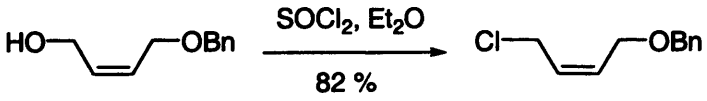
1,1-Difluoro-2-(2-methoxy-ethoxy)methoxy-hepta-1,6-diene- 3-ol 132



n-Butyllithium (75 mmol, 32 mL of 2.40 M solution in hexane) was added dropwise to a cold (-78 °C) solution of di*iso*propylamine (78 mmol, 9.8 mL) in dry THF (36 mL) under nitrogen. The solution was allowed to warm up to –30 °C and then cooled again to -78 °C. 2-(Methoxy-ethoxymethoxy)-1,1,1-trifluoroethane **134** (36 mmol, 6.6 g) was added dropwise over 30 mins to this freshly-made LDA solution. The reaction was stirred at this temperature for 40 mins, then 5-penten-1-al **133** (42 mmol, 3.6 g) was added in one portion. The mixture was allowed to warm to –30 °C over 2 hours, then quenched with NH_4Cl (30 mL of a saturated aqueous solution). Water (30 mL) was added to the mixture which was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Kugelrohr distillation afforded difluoroallylic alcohol **132** (6.9 g, 78 %, 100% by GC-MS) as a clear, colourless oil; bp 80-85 °C / 0.25 mmHg; ν_{max}(neat)/cm^{-1} 3475br (OH), 2934s (CH_2), 1751s, 1641w (C=C), 1453w, 1229s, 1107s, 1018s; R_f (20 % ethyl acetate in hexane) 0.34; δ_H (300 MHz, $CDCl_3$) 5.80 (1H, ddt, *J* 16.9, 10.2, 6.6, H-6), 5.04 (1H, ddd, *J* 16.9, ^2J 3.5, ^4J 1.6, H-7$_a$), 5.01 (1H, d, ^2J 6.6, OC*H*$_a$H$_b$O), 4.98 (1H, ddd, *J* 10.2, ^2J 3.5, ^4J 1.2, H-7$_a$), 4.88 (1H, d, ^2J 6.6, OCH$_a$*H*$_b$O), 4.30-4.22 (1H, m, H-3), 3.96 (1H, ddd, ^2J 10.8, *J* 6.2, 3.7, $OCH_2CH_aH_bO$), 3.77 (1H, ddd, ^2J 10.8, *J* 4.8, 3.1, $OCH_2CH_aH_bO$), 3.60-3.55 (2H, m, OCH_2CH_2O), 3.39 (4H, s, CH_3, OH), 2.15-2.04 (2H, m, H-5), 1.88-1.64 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 154.6 (dd, $^1J_{C\text{-}F}$ 291.6, 285.2, C-1), 137.7 (C-6), 118.2 (dd, $^2J_{C\text{-}F}$ 36.7, 9.9, C-2), 115.1 (C-7), 98.0 (dd, $^4J_{C\text{-}F}$ 4.1, 3.0, OCH_2O), 71.5 (OCH_2CH_2OMe), 68.5 (OCH_2CH_2OMe), 66.5 (dd, $^3J_{C\text{-}F}$ 3.1, 2.0, C-3), 59.0 (OCH_3), 33.1 (C-4), 29.7 (C-5); δ_F (282 MHz, $CDCl_3$) -100.2 (1F, dt, $^2J_{F\text{-}F}$ 64.0, $^4J_{F\text{-}H}$ 1.1), -110.0

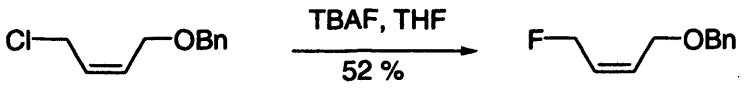
(1F, ddd, $^{2}J_{F\text{-}F}$ 64.0, $^{4}J_{F\text{-}H}$ 3.0, $^{5}J_{F\text{-}H}$ 1.8); [HRMS (EI, M^{+}) Found: 252.11729. Calc. For $C_{11}H_{18}O_4F_2$ 252.11732]; m/z (CI) 270 (52 %, $[M+NH_4]^{+}$), 215 (10), 137 (10), 89 (100, MEM^{+}), 59 (99, $MeOCH_2CH_2^{+}$).

4-Benzyloxy-1-chloro-Z-but-2-ene 161



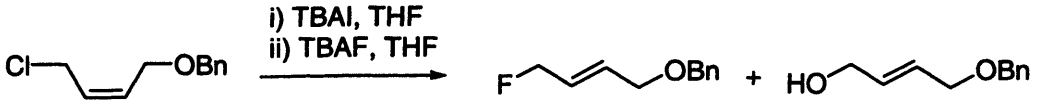
Allyl alcohol **76** (34 mmol, 6.1 g)[93] was added dropwise to a stirred solution of thionyl chloride (51 mmol, 6.1 g) in diethyl ether (850 mL). After stirring for 24 h at room temperature, the solution was diluted with water (300 mL), the phases were separated and the aqueous phase was extracted with diethyl ether (2 x 300 mL). The combined organic extracts and original ether phase were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a clear oil which was purified by Kugelrohr distillation (134-136 °C/0.25 mmHg) to afford allyl chloride **161** (5.6 g, 82 %, 92 % by GC-MS) as a clear, colourless oil; R_f (50 % diethyl ether in light petroleum) 0.28; δ_H (250 MHz, $CDCl_3$) 7.40-7.24 (5H, m, ArH), 5.83-5.77 (2H, m, H-2, H-3), 4.52 (2H, s, OCH_2Ph), 4.13-4.00 (4H, m, H-1, H-4); δ_C (63 MHz, $CDCl_3$) 138.4, 131.2 (C-3), 128.9, 128.8, 128.3, 128.2 (C-2), 72.9 (CH_2Bn), 65.6 (C-4), 39.6 (C-1); *m/z* (EI) 161 (2 %, M^{+}-Cl), 105 (6, $[M-C_7H_7]^{+}$), 91 (100, $C_7H_7^{+}$). The data were in agreement with those reported by Yadav *et al.*[93]

Z-1-fluoro-4-benzyloxy-but-2-ene 168



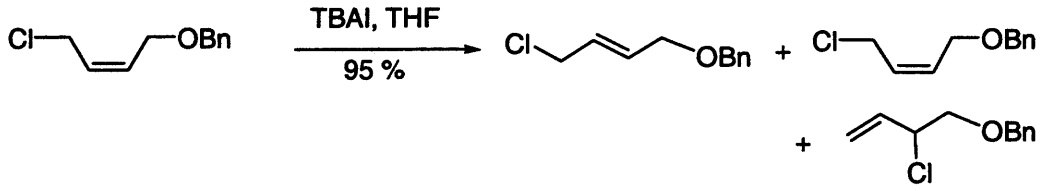
Allyl chloride **161** (1.0 mmol, 197 mg) was added to a stirred solution of commercial tetrabutylammonium fluoride trihydrate (2.1 mmol, 0.67 g) in tetrahydrofuran (5 mL) at reflux. After 6 h, the solution was diluted with water (2 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* to leave a clear oil which was purified by column chromatography (gradient 0 to 20 % ethyl acetate in hexane) to afford allyl fluoride **168** (94 mg, 52 %, 99 % by GC-MS) as a clear, colourless oil; R_f (20 % ethyl acetate in hexane) 0.83; ν_{max}(neat)/cm^{-1} 2858w (CH_3), 1454w, 1073s (C-O), 973s; δ_H (300 MHz, $CDCl_3$) 7.39-7.23 (5H, m, Ph), 5.89-5.73 (2H, m, H-2, H-3), 5.05-4.83 (2H, m, inc. app. d, $^2J_{H\text{-}F} \approx 46.0$, H-1), 4.51 (2H, s, OCH_2Ph), 4.13-4.05 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 137.9, 131.0 (d, $^3J_{C\text{-}F}$ 10.2, C-3), 128.5, 127.9, 127.8, 127.2 (d, $^2J_{C\text{-}F}$ 19.4, C-2), 78.9 (d, $^1J_{F\text{-}C}$ 159.4, C-1), 72.5 (CH_2Ph), 65.7 (d, $^4J_{C\text{-}F}$ 1.4, C-4); δ_F (282 MHz, $CDCl_3$) (–212.7)-(-213.2) (m); $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) –212.98 (s); [HRMS (EI, M^+) Found: 180.09498 Calc. For $C_{11}H_{13}OF$ 180.09504]; *m/z* (EI) 180 (21 %, M^+), 136 (56), 105 (73), 91 (100, $C_7H_7^+$).

***E*-1-fluoro-4-benzyloxy-but-2-ene 176 and *E*-4-benzyloxy-but-2-en-1-ol 79**



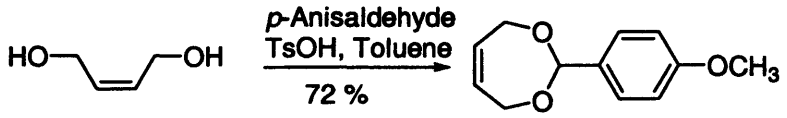
Allyl chloride **161** (2.1 mmol, 0.41 g) was added to a stirred solution of tetrabutylammonium iodide (2.0 mmol, 0.75 g) in dry tetrahydrofuran (5 mL) at reflux. After 4 h, neat commercial tetrabutylammonium fluoride trihydrate (4.3 mmol, 1.38 g) was added. After 5 h, the solution was diluted with water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were concentrated *in vacuo* to leave a clear oil which was purified by column chromatography (gradient 0 to 20 % ethyl acetate in hexane) to afford allyl fluoride **176** (206 mg, 55 %, 99 % by GC-MS) as clear, colourless oil; R_f (20 % ethyl acetate in hexane) 0.83; ν_{max}(neat)/cm^{-1} 2855w (CH_3), 1454w, 1360w, 1103s (C-O), 968s; δ_H (300 MHz, $CDCl_3$) 7.36-7.22 (5H, m, Ph), 5.94-5.86 (2H, m, H-2, H-3), 4.92-4.73 (2H, m, inc. app. d, $^2J_{H\text{-}F} \approx 46.7$, H-1), 4.50 (2H, s, OCH_2Ph), 4.07-4.00 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.1, 131.3 (d, $^3J_{C\text{-}F}$ 11.6, C-3), 128.4, 127.7, 127.7, 126.9 (d, $^2J_{C\text{-}F}$ 17.0, C-2), 82.7 (d, $^1J_{C\text{-}F}$ 163.1, C-1), 72.4, 69.5 (d, $^4J_{C\text{-}F}$ 1.5, C-4); δ_F (282 MHz, $CDCl_3$) –(212.7)-(-213.2) (m); [HRMS (EI, M^+) Found: 180.09500 Calc. For $C_{11}H_{13}OF$ 180.09504]; *m/z* (EI) 180 (1 %, M^+), 136 (3), 105 (10), 91 (100, $C_7H_7^+$); and allyl alcohol **79** (105 mg, 29 %, 99 % by GC-MS) as clear, colourless oil; R_f (20 % ethyl acetate in hexane) 0.22; ν_{max}(neat)/cm^{-1} 3372br (OH), 2856w (CH_3), 1454w, 1361w, 1092s (C-O), 969s; δ_H (300 MHz, $CDCl_3$) 7.36-7.23 (5H, m, Ph), 5.92-5.71 (2H, m, H-2, H-3), 4.50 (2H, s, OCH_2Ph), 4.12-3.98 (4H, m, H-1, H-4); δ_C (75 MHz, $CDCl_3$) 138.2, 132.5 (C=C), 128.4, 127.8, 127.7 (C=C), 127.5, 72.3 (CH_2Ph), 70.2, 62.7; [HRMS (EI, M^+) Found: 178.09937 Calc. For $C_{11}H_{14}O_2$ 178.09938]; *m/z* (EI) 178 (1 %, M^+), 160 (1), 134 (2), 107 (12), 91 (100, $C_7H_7^+$).

4-Benzyloxy-1-chloro-*E*-but-2-ene 177, 4-benzyloxy-1-chloro-*Z*-but-2-ene 161 and 1-benzyloxy-2-chloro-but-3-ene 167



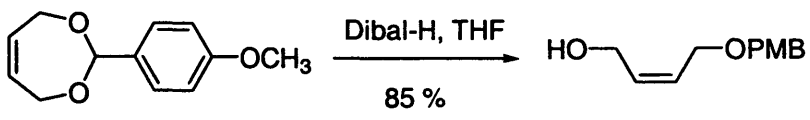
Allyl chloride **161** (6.6 mmol, 1.29 g) was added to a solution of tetrabutylammonium iodide (13.4 mmol, 5.03 g) in dry tetrahydrofuran (15 mL). After 12 h at reflux, the mixture was diluted with diethyl ether (20 mL), filtered and concentrated *in vacuo* to leave a clear oil which was distilled (Kugelrohr 62-65 °C / 0.09 mmHg) to afford allyl chloride **177** (1.23 g, 95 %, 80 % by GC-MS) as the major product in a mixture of inseparable isomers (*E*:*Z*:terminal = 13:1:4) as a clear, colourless oil. A small sample was columned to afford pure **177** (92 % by GC-MS); R_f (20 % ethyl acetate in hexane) 0.83; ν_{max}(solution)/cm^{-1} 2854w (CH_2), 1454w, 1361w, 1111s; δ_H (300 MHz, $CDCl_3$) 7.40-7.24 (5H, m, ArH), 5.95-5.77 (2H, m, H-2, H-3), 4.52 (2H, s, OCH_2Ar), 4.13-3.99 (4H, m, H-1, H-4); δ_C (75 MHz, $CDCl_3$) 138.1, 131.2 (C-3), 128.5, 128.4, 127.8, 127.7 (C-2), 72.9 (CH_2Bn), 65.5 (C-4), 44.4 (C-1); [HRMS (EI, M^+) Found: 196.06539 Calc. For $C_{11}H_{13}OCl$ 196.06549]; *m/z* (EI) 196 (1 %, M^+), 161 (2, $[M-C]^+$), 126 (4), 105 (8, $[M-C_7H_7]^+$), 91 (100, $C_7H_7^+$).

4,7-Dihydro-2-(4-methoxyphenyl)-1,3-dioxepin 180



A mixture of *p*-anisaldehyde (0.195 mmol, 27.1 g), *cis*-2-butene-1,4-diol (0.238 mmol, 21.6 g), and TsOH (0.22 mmol, 42 mg) in toluene (90 mL) was refluxed with azeotropic (Dean-Stark) removal of water. After 24 h the dark brown mixture was cooled to room temperature and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the resulting oil was distilled (Kugelrohr bp 150-155 °C/0.25 mmHg) to afford dioxepin **180** (29.2 g, 72 %, 89 % by GC-MS) as a clear, colourless, viscous oil; R_f (20 % ethyl acetate in hexane) 0.59; ν_{max}(solution)/cm^{-1} 3035w, 2947w (CH_2), 2838w (CH_3), 1612s (C=C), 1513s, 1445w, 1034s; δ_H (250 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.6, ArH), 6.90 (2H, d, *J* 8.6, ArH), 5.83 (1H, s, H-2), 5.76 (2H, t, J=1.8, H-5, H-6), 4.43-4.20 (4H, m, H-4, H-7), 3.81 (3H, s, OCH_3); δ_C (63 MHz, $CDCl_3$) 160.1 (C), 131.6 (C), 130.3 (CH), 128.1 (ArCH), 113.9 (ArCH), 102.4 (CH), 64.8 (CH_2), 55.6 (CH_3); *m/z* (EI) 206 (3 %, M^+), 160 (27), 147 (18), 136 (46, $[M\text{-OPMB}]^+$), 135 (100, $OPMB^+$), 77 (33); the data were in agreement with those reported by Williams *et al.*.[104]

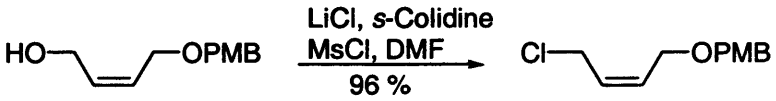
Z-4-(*p*-Methoxybenzyloxy)-but-2-en-1-ol 181



Neat di*iso*butylaluminum hydride (84 mmol, 15 mL) was added dropwise to a stirred solution of dioxepin **180** (48.5 mmol, 10 g) in dry tetrahydrofuran (40 mL) at 0 °C. After stirring overnight at room temperature, the mixture was diluted with methanol (20

mL), followed by NaOH (20 mL of a 10 % aqueous solution) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil which was distilled (Kugelrohr, bp 140-145 °C/0.06 mmHg) to afford alcohol **181** (8.6 g, 85 %, 99 % by GC-MS) as a clear, colourless, viscous oil; R_f (20 % ethyl acetate in hexane) 0.10; ν_{max}(solution)/cm^{-1} 3446br, 2956w (CH_2), 2838w (CH_3), 1612s (C=C), 1514s, 1464w, 1034s; δ_H (300 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.7, ArH), 6.85 (2H, d, *J* 8.7, ArH), 5.86-5.62 (2H, m, H-2, H-3), 4.46 (2H, s, OCH_2Ar), 4.12-4.03 (4H, m, H-1, H-4), 3.80 (3H, s, OCH_3), 2.01 (1H, bs, OH); δ_C (75 MHz, $CDCl_3$) 159.7, 132.7 (C-2), 130.3, 129.9, 128.7 (C-3), 114.2, 72.6 (CH_2Ar), 65.7 (C-4), 59.1 (C-1), 56.7 (OCH_3); *m/z* (EI) 207 (1 %, M^+), 138 (38), 136 (19 %, [M-OPMB] $^+$), 122 (14), 121 (100, PMB^+), 77 (24); The data were in agreement with those reported by Williams *et al.*.[104]

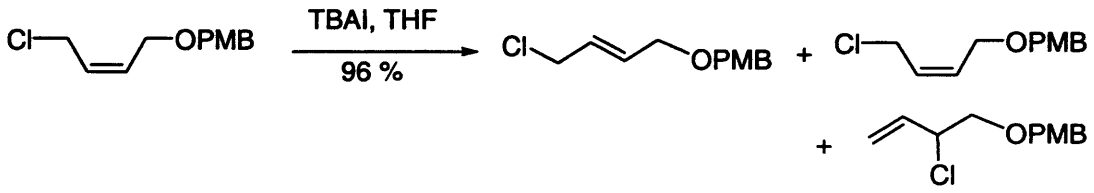
Z-1-Chloro-4-(*p*-methoxybenzyloxy)but-2-ene 182



Methanesulfonyl chloride (63.3 mmol, 7.25 g) was added at 0 °C to a stirred mixture of alcohol **181** (26.5 mmol, 5.51 g), *s*-collidine (25.4 mmol, 3.07 g) and dry lithium chloride (51.9 mmol, 2.20 g) in dry dimethylformamide (25 mL). After stirring for 1.5 h the suspension was quenched with water (30 mL) and the mixture extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), neutralized with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the allyl chloride **182** (5.78 g, 96 %, 99 % by GC-MS) as a clear colorless oil. R_f (20% ethyl acetate in hexane) 0.62; ν_{max}(neat)/cm^{-1} 2935w (CH_2), 2837w (CH_2), 1611w, 1511s, 1245s, 1033s; δ_H (400 MHz, $CDCl_3$) 7.26

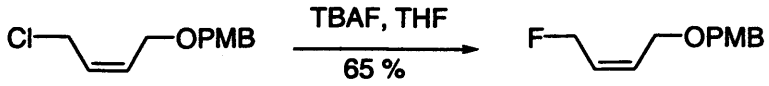
(2H, d, *J* 8.8, ArH), 6.88 (2H, d, *J* 8.8, ArH), 5.82-5.72 (2H, m, H-2, H-3), 4.44 (2H, s, CH_2Ar), 4.14-4.06 (4H, m, H-1, H-4), 3.80 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 130.9 (C-3), 130.3, 129.5, 128.4 (C-2), 114.2, 72.1 (CH_2Ar), 64.8 (C-4), 55.6 (OCH_3), 39.6 (C-1); [HRMS (EI, M^+) Found: 226.07613 Calc. For $C_{12}H_{15}O_2Cl$ 226.07606]; *m/z* (EI) 226 (3%, M^+), 191 (10), 161 (5), 136 (13, $[M\text{-}OPMB]^+$), 121 (100, PMB^+), 109 (9).

_E_-1-Chloro-4-(_p_-methoxybenzyloxy)-but-2-ene 183, _Z_-1-chloro-4-(_p_-methoxybenzyloxy)-but-2-ene 182 and 2-chloro-1-(_p_-methoxybenzyloxy)-but-3-ene 184



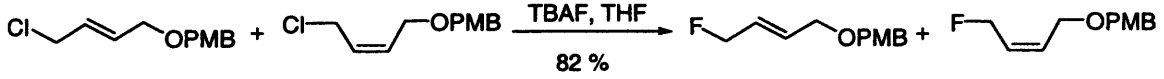
Allyl chloride **182** (26.5 mmol, 6.00 g) was added to a solution of tetrabutylammonium iodide (52.9 mmol, 19.6 g) in dry tetrahydrofuran (70 mL). After 24 h at reflux, the mixture was diluted with diethyl ether (20 mL), filtered and concentrated *in vacuo* to obtain a crude mixture of inseparable allylic chlorides (*E*:*Z*:terminal = 14:1:1) in which *E*-allylic chloride **183** (5.73, 96 %, 83 % by GC-MS) was the major component as a brown and viscous oil; R_f (20% ethyl acetate in hexane) 0.62; ν_{max}(neat)/cm^{-1} 2954w (CH_2), 2837w (CH_2), 1612w (C=C), 1512s, 1245s, 1033s; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.7, ArH), 6.88 (2H, d, *J* 8.7, ArH), 5.91-5.86 (2H, m, H-2, H-3), 4.45 (2H, s, CH_2Ar), 4.08-4.05 (2H, m, H-1), 4.02-4.00 (2H, m, H-4), 3.80 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 131.4 (C-3), 130.1, 129.4, 128.3 (C-2), 113.8, 72.1 (CH_2Ar), 69.2 (C-4), 55.3 (OCH_3), 44.4 (C-1); [HRMS (EI, M^+) Found: 226.07611 Calc. For $C_{12}H_{15}O_2Cl$ 226.07606]; *m/z* (EI) 226 (4 %, M^+), 191 (12), 161 (5), 136 (16, $[M\text{-}OPMB]^+$), 135 (14), 121 (100, PMB^+), 109 (10).

***Z*-1-Fluoro-4-(*p*-methoxybenzyloxy)-but-2-ene 185**



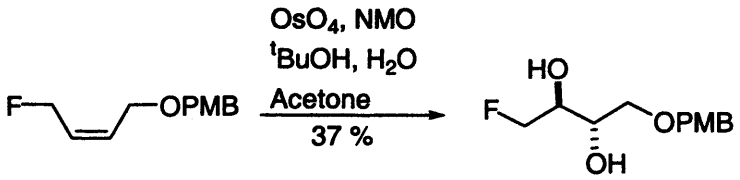
Allyl chloride **182** (0.44 mmol, 100 mg) was added to a stirred solution of commercial tetrabutylammonium fluoride trihydrate (0.92 mmol, 0.30 g) in tetrahydrofuran (3 mL) at reflux. After 6 h, the solution was diluted with water (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were concentrated *in vacuo* to leave a clear oil which was purified by column chromatography (20 % ethyl acetate in hexane) to afford allyl fluoride **185** (60 mg, 65 %, 92 % by GC-MS) as a clear, colourless oil; R_f (20 % ethyl acetate in hexane) 0.61; ν_{max}(neat)/cm^{-1} 2838w (CH_3), 1612s (C=C), 1512s, 1464w, 1245s, 1033s (C-O); δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.8, ArH), 6.88 (2H, d, *J* 8.8, ArH), 5.88-5.73 (2H, m, H-2, H-3), 5.04-4.84 (2H, m, inc. app. d, $^2J_{H\text{-}F} \approx 47.0$, H-1), 4.43 (2H, s, OCH_2Ar), 4.11-4.01 (2H, m, H-4), 3.79 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 131.1 (d, $^3J_{C\text{-}F}$ 10.2, C-3), 130.0, 129.5, 127.1 (d, $^2J_{C\text{-}F}$ 19.4, C-2), 113.9, 78.9 (d, $^1J_{F\text{-}C}$ 159.3, C-1), 72.1 (CH_2Ar), 65.3 (d, $^4J_{C\text{-}F}$ 1.5, C-4), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) (-212.7)-(-213.2) (m); $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) – 212.87 (s); [HRMS (EI, M^+) Found: 210.10564. Calc. For $C_{12}H_{15}O_2F$ 210.10561]; *m/z* (EI) 210 (5 %, M^+), 179 (4), 136 (19, $[M\text{-}OPMB]^+$), 135 (17), 122 (21), 121 (100, PMB^+), 77 (25).

_E_-1-Fluoro-4-(_p_-methoxybenzyloxy)but-2-ene 186 and _Z_-1-Fluoro-4-(_p_-methoxybenzyloxy)-but-2-ene 185



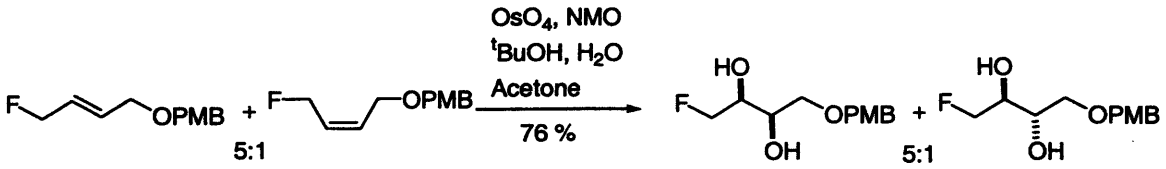
Allyl chloride **183** (20.0 mmol, 4.53 g) was added to a stirred solution of commercial tetrabutylammonium fluoride trihydrate (30.0 mmol, 9.46 g) in dry tetrahydrofuran (45 mL) containing activated molecular sieves (4 Å, 25 g) at reflux and under nitrogen. After 1 h, the solution was diluted with ethyl acetate (100 mL), filtered and concentrated *in vacuo*. The residue was taken up in diethyl ether (100 mL), filtered and concentrated *in vacuo* to leave an oil which was purified by column chromatography (20 % ethyl acetate in hexane) to afford crude mixture of inseparable allylic fluorides in which *E*-allylic fluoride **186** (3.43 g, 82 %, 60% by GC-MS) was the major component as a clear, colourless oil; R_f (20 % ethyl acetate in hexane) 0.60; ν_{max}(neat)/cm^{-1} 2937w (CH_2), 2838w (CH_3), 1612w (C=C), 1512s, 1245s, 1033s (C-O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.8, ArH), 6.85 (2H, d, *J* 8.8, ArH), 5.96-5.84 (2H, m, H-2, H-3), 4.82 (2H, m, inc. app. d, $^2J_{F\text{-}H} \approx 46.8$, H-1), 4.43 (2H, s, OCH_2Ar), 4.04-3.97 (2H, m, H-4), 3.74 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 131.5 (d, $^3J_{C\text{-}F}$ 11.6, C-3), 130.2, 129.4, 126.9 (d, $^2J_{C\text{-}F}$ 16.9, C-2), 113.8, 82.8 (d, $^1J_{F\text{-}C}$ 162.9, C-1), 72.1 (CH_2Ar), 69.3 (d, $^4J_{C\text{-}F}$ 1.5, C-4), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) (–212.7)-(-213.1) (m); $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) –212.85 (s); [HRMS (EI, M^+) Found: 210.10558. Calc. For $C_{12}H_{15}O_2F$ 210.10561]; *m/z* (EI) 210 (8 %, M^+), 179 (6), 136 (30, $[M\text{-}OPMB]^+$), 135 (27), 122 (22), 121 (100, PMB^+), 77 (29).

(2R*, 3S*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 187



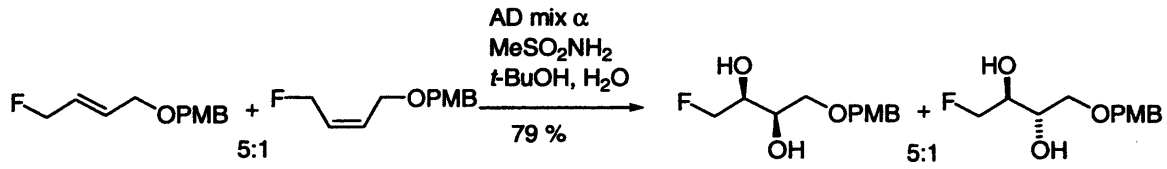
A solution of 4-methylmorpholine *N*-oxide (0.66 mmol, 80 mg) in water (0.1 mL) was added to a stirred cold (0 °C) solution of allylic fluoride **185** (0.33 mmol, 70 mg) in acetone (0.7 mL), and *t*-butanol (0.7 mL) was added in a single portion. After 10 min, osmium tetroxide (70 μL of a 2.5 wt % solution in *t*-butanol). After stirring overnight at 0 °C, the mixture was quenched with solid sodium sulfite (20 mg), followed by solid sodium hydrogen carbonate (20 mg). The mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 15% to 35% ethyl acetate in hexane) to afford diol **187** (30 mg, 37 %, 99 % by GC-MS) as a clear, colourless oil; R_f (35 % ethyl acetate in hexane) 0.17; ν_{max}(neat)/cm^{-1} 3413br (OH), 2911w (CH_2), 1612w, 1513s, 1245s, 1075s (C-O), 1030s (C-O); δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, ^2J 8.7, ArH), 6.88 (2H, d, ^2J 8.7, ArH), 4.67-4.40 (2H, m, H-1), 4.48 (2H, s, CH_2Ar), 3.94-3.55 (4H, m, H-2, H-3, H-4), 3.79 (3H, s, OCH_3), 2.80 (2H, br.s, OH); δ_C (75 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.5 (d, $^1J_{C\text{-}F}$ 167.3, C-1), 73.3 (CH_2Ar), 71.4 (d, $^2J_{C\text{-}F}$ 18.8, C-2), 70.8 (d, $^4J_{C\text{-}F}$ 1.3, C-4), 69.9 (d, $^3J_{C\text{-}F}$ 6.2, C-3), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) –233.8 (td, $^2J_{F\text{-}H}$ 47.6, 20.9); [HRMS (EI, M^+) Found: 244.11105 Calc. For $C_{12}H_{17}O_4F$ 244.11109]; *m/z* (EI) 244 (4 %, M^+), 159 (2), 78 (22), 121 (100, PMB^+).

(2R*, 3R*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 188 and (2R*, 3S*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 187



A solution of 4-methylmorpholine N-oxide (11.67 mmol, 1.37 g) in water (1.8 mL) was added to a stirred cold (0 °C) solution of allylic fluoride **186** (5.84 mmol, 1.23 g) in acetone (12 mL), and *t*-butanol (12 mL). After 10 min, osmium tetroxide (0.12 mmol, 1.2 mL of a 2.5 wt % solution in *t*-butanol) was added in a single portion. After stirring overnight at 0 °C, the mixture was quenched with solid sodium sulfite (20 mg), followed by solid sodium hydrogen carbonate (20 mg). The mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 15% to 35% ethyl acetate in hexane) to afford diol **188** (1.08 g, 76 %, 94 % by GC-MS) as a clear, colourless oil; R_f (35 % ethyl acetate in hexane) 0.17; ν_{max}(neat)/cm^{-1} 3400br (OH), 2911w (CH_2), 1611w, 1513s, 1246s, 1079s (C-O), 1030s (C-O); δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, ^2J 8.8, ArH), 6.88 (2H, d, ^2J 8.8, ArH), 4.46 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 4.9, CH_aH_bF), 4.42 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 5.7, CH_aH_bF), 4.47 (2H, s, CH_2Ar), 3.94-3.74 (2H, m, H-2, H-3), 3.79 (3H, s, OCH_3), 3.62-3.53 (2H, m, H-4), 2.89 (2H, br.s, OH); δ_C (75 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.0 (d, $^1J_{C\text{-}F}$ 168.9, C-1), 73.3 (CH_2Ar), 71.5 (d, $^4J_{C\text{-}F}$ 1.2, C-4), 70.7 (d, $^2J_{C\text{-}F}$ 20.0, C-2), 69.3 (d, $^3J_{C\text{-}F}$ 5.8, C-3), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) –230.4 (td, $^2J_{F\text{-}H}$ 47.2, 16.6); minor *anti* diol **187**: δ_F (282 MHz, $CDCl_3$) –233.8 (td, $^2J_{F\text{-}H}$ 47.5, 20.8); both diastereoisomers: [HRMS (EI, M^+) Found: 244.11114 Calc. For $C_{12}H_{17}O_4F$ 244.11109]; *m/z* (EI) 244 (19 %, M^+), 137 (82), 121 (100, PMB^+).

(+)-(2R, 3R)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 189 and (2R*, 3S*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 187

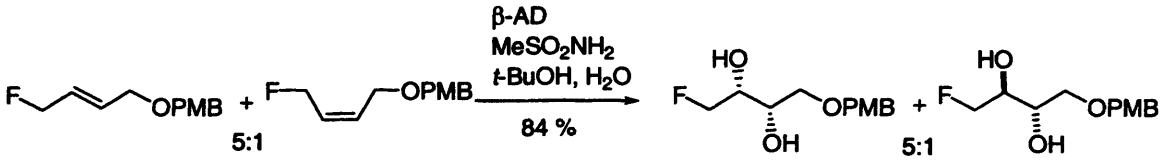


Allylic fluoride **186** (0.50 mmol, 106 mg) was added to a cold (0 °C) solution of commercial AD mix α (0.708 g) in water (2.5 mL) and *t*-butanol (2.5 mL). After 48 h, the mixture was quenched with $Na_2S_2O_5$ (3 mL of a saturated aqueous soln) and extracted with ethyl acetate (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 15% to 35% ethyl acetate in hexane) to afford alcohol **189** (97 mg, 79 %, 99 % by GC-MS, 86 % de, 81 % ee by NMR*) as a clear, colourless oil which solidified as a white solid in the refrigerator; mp 34-36 °C; R_f (35 % ethyl acetate in hexane) 0.17; (Found: C, 58.9; H, 6.9; $C_{12}H_{17}O_4F$ requires: C, 59.0; H, 7.0 %); ν_{max}(neat)/cm^{-1} 3455br (OH), 2928w (CH_2), 2878w, 1610w, 1514s, 1247s, 1088s (C-O), 1028s (C-O); $[\alpha]_D^{20}$ = +5.5° (*c* = 1.04, AcOEt); δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, ^2J 8.8, ArH), 6.88 (2H, d, ^2J 8.8, ArH), 4.46 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 4.9, CH_aH$_b$F), 4.42 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 5.7, CH$_a$H$_b$F), 4.47 (2H, s, CH_2Ar), 3.94-3.74 (2H, m, H-2, H-3), 3.79 (3H, s, OCH_3), 3.62-3.53 (2H, m, H-4), 2.89 (2H, br.s, OH); δ_C (75 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.0 (d, $^1J_{C\text{-}F}$ 168.9, C-1), 73.3 (CH_2Ar), 71.5 (d, $^4J_{C\text{-}F}$ 1.2, C-4), 70.7 (d, $^2J_{C\text{-}F}$ 20.0, C-2), 69.3 (d, $^3J_{C\text{-}F}$ 5.8, C-3), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) –230.4 (td, $^2J_{F\text{-}H}$ 47.2, 16.6); [HRMS (EI, M$^+$) Found: 244.11106 Calc. For $C_{12}H_{17}O_4F$ 244.11109]; *m/z* (EI) 244 (5 %, M$^+$), 137 (25, OPMB$^+$), 121 (100, PMB$^+$), 77 (13). The relatively low de is caused by traces of non-

* The method for the determination of ee by NMR is described on p. 43-44, 92.

enantioenriched diol obtained from the *Z*-fluoride. These compounds are described in p. 43-44.

(-)-(2S, 3S)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 191 and (2R*, 3S*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-diol 187

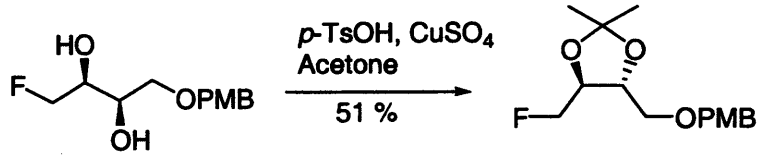


Allylic fluoride **186** (0.50 mmol, 106 mg) was added to a cold (0 °C) solution of commercial AD mix β (0.708 g) in water (2.5 mL) and *t*-butanol (2.5 mL). After 48 h, the mixture was quenched with $Na_2S_2O_5$ (3 mL of a saturated aqueous soln) and extracted with ethyl acetate (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 15% to 35% ethyl acetate in hexane) to afford alcohol **191** (103 mg, 84 %, 99 % by GC-MS, 91 % de, 92 % ee by NMR*) as a clear, colourless oil; R_f (35 % ethyl acetate in hexane) 0.17; ν_{max}(neat)/cm^{-1} 3395br (OH), 2909w (CH_2), 1612w, 1513s, 1245s, 1079s (C-O), 1030s (C-O); $[\alpha]_D^{20}$ = -4.1° (*c* = 0.90, AcOEt); δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, ^2J 8.8, ArH), 6.88 (2H, d, ^2J 8.8, ArH), 4.46 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 4.9, CH_aH_bF), 4.42 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 9.6, J 5.7, CH_aH_bF), 4.47 (2H, s, CH_2Ar), 3.94-3.74 (2H, m, H-2, H-3), 3.79 (3H, s, OCH_3), 3.62-3.53 (2H, m, H-4), 2.89 (2H, br.s, OH); δ_C (75 MHz, $CDCl_3$) 159.5, 129.6, 129.5, 114.0, 84.0 (d, $^1J_{C\text{-}F}$ 168.9, C-1), 73.3 (CH_2Ar), 71.5 (d, $^4J_{C\text{-}F}$ 1.2, C-4), 70.7 (d, $^2J_{C\text{-}F}$ 20.0, C-2), 69.3 (d, $^3J_{C\text{-}F}$ 5.8, C-3), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) –230.4 (td, $^2J_{F\text{-}H}$

* The method for the determination of ee by NMR is described on p. 43-44, 92.

47.2, 16.6); [HRMS (EI, M^+) Found: 244.11108 Calc. For $C_{12}H_{17}O_4F$ 244.11109]; *m/z* (EI) 244 (5 %, M^+), 137 (25, $OPMB^+$), 121 (100, PMB^+), 77 (13). The relatively low de is caused by traces of non-enantioenriched diol obtained from the *Z*-fluoride. These compounds are described in p. 43-44.

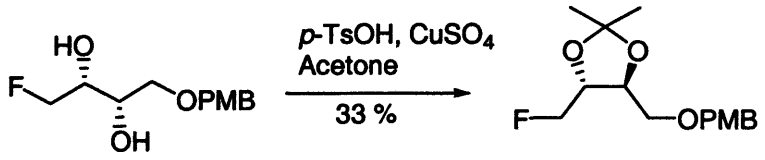
(+)-(2R, 3R)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-acetonide 190



p-Toluenesulfonic acid (0.08 mmol, 15 mg) was added to a stirred mixture of diol **189** (0.19 mmol, 46 mg) and anhydrous copper sulfate (2.4 mmol, 0.377 g) in dry acetone (10 mL). After 5 h, the mixture was filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 5% to 10% ethyl acetate in hexane) to afford acetal **190** (30 mg, 51 %, 99 % by GC-MS, 80 % ee by HPLC) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.60; ν_{max}(neat)/cm^{-1} 2988w (CH_2), 2937w (CH_2), 1612w, 1513s, 1246s, 1086s; $[\alpha]_D^{22}$ = +10.2° (*c* = 0.40, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, ^2J 8.7, ArH), 6.88 (2H, d, ^2J 8.7, ArH), 4.55 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, *J* 2.8, CH_aH_bF), 4.51 (2H, s, CH_2Ar), 4.41 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, *J* 4.5, CH_aH_bF), 4.12-3.98 (2H, m, H-2, H-3), 3.80 (3H, s, OCH_3), 3.64 (1H, dd, ^2J 10.0, *J* 4.9, CH_aH_bOPMB), 3.55 (1H, dd, ^2J 10.0, *J* 5.0, CH_aH_bOPMB), 1.42 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 129.8, 129.3, 113.8, 110.1, 82.6 (d, $^1J_{C\text{-}F}$ 173.0, C-1), 77.8 (d, $^2J_{C\text{-}F}$ 19.5, C-2), 75.3 (d, $^3J_{C\text{-}F}$ 6.7, C-3), 73.3 (CH_2Ph), 70.0 (C-4), 55.3 (OCH_3), 27.0, 26.7; δ_F (282 MHz, $CDCl_3$) –229.1 (td, $^2J_{F\text{-}H}$ 47.3, 20.7); [HRMS (EI, M^+) Found: 284.14234 Calc. For $C_{15}H_{21}O_4F$ 284.14239]; *m/z* (EI) 284 (2 %, M^+),

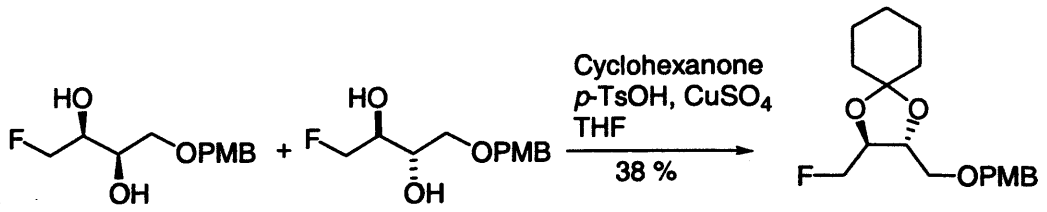
226 (13), 195 (8), 137 (10), 135 (13), 121 (100, PMB^+); HPLC: Chiralcel OD-H. Hexane-^{i}PrOH, 999:1, 1mL/min, 254 nm; t_R (major) = 48.1 min; t_R (minor) = 44.0 min.

(-)-(2S, 3S)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-acetonide 192



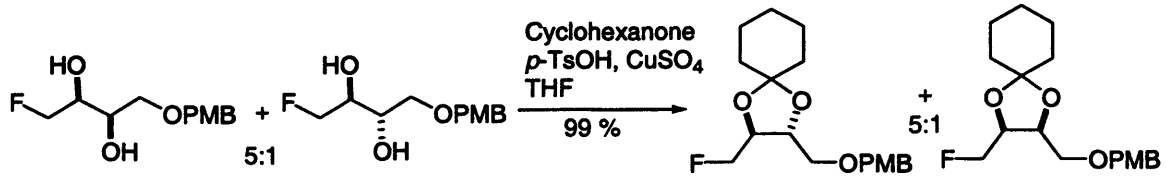
p-Toluenesulfonic acid (0.16 mmol, 30 mg) was added to a stirred mixture of diol **191** (0.13 mmol, 31 mg) and anhydrous copper sulfate (2.2 mmol, 0.342 g) in dry acetone (5 mL). After 5 h, the mixture was filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 5% to 10% ethyl acetate in hexane) to afford acetal **192** (13 mg, 33 %, 99 % by GC-MS, 95 % ee by HPLC) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.60; ν_{max}(neat)/cm^{-1} 2988w (CH_2), 2937w (CH_2), 1610w, 1513s, 1246s, 1086s; $[\alpha]_D^{22}$ = -14.0° (*c* = 0.10, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, ^2J 8.7, ArH), 6.88 (2H, d, ^2J 8.7, ArH), 4.55 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, J 2.8, C*H*$_a$H$_b$F), 4.51 (2H, s, CH_2Ar), 4.41 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, J 4.5, CH$_a$*H*$_b$F), 4.12-3.98 (2H, m, H-2, H-3), 3.80 (3H, s, OCH_3), 3.64 (1H, dd, ^2J 10.0, J 4.9, C*H*$_a$H$_b$OPMB), 3.55 (1H, dd, ^2J 10.0, J 5.0, CH$_a$*H*$_b$OPMB), 1.42 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 129.8, 129.3, 113.8, 110.1, 82.6 (d, $^1J_{C\text{-}F}$ 173.0, C-1), 77.8 (d, $^2J_{C\text{-}F}$ 19.5, C-2), 75.3 (d, $^3J_{C\text{-}F}$ 6.7, C-3), 73.3 (CH_2Ph), 70.0 (C-4), 55.3 (OCH_3), 27.0, 26.7; δ_F (282 MHz, $CDCl_3$) –229.1 (td, $^2J_{F\text{-}H}$ 47.3, 20.7); [HRMS (EI, M^+) Found: 284.14243 Calc. For $C_{15}H_{21}O_4F$ 284.14239]; *m/z* (EI) 284 (2 %, M^+), 226 (13), 195 (8), 137 (10), 135 (13), 121 (100, PMB^+); HPLC: Chiralcel OD-H. Hexane-^{i}PrOH, 999:1, 1mL/min, 254 nm; t_R (major) = 43.3 min; t_R (minor) = 50.6 min.

(+)-(2R, 3R)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-cyclohexylidene acetal 195



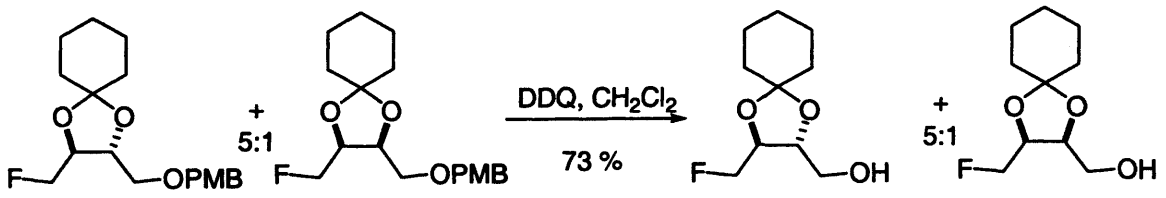
p-Toluenesulfonic acid (0.05 mmol, 10 mg) was added to a stirred mixture of diol **189** (0.62 mmol, 153 mg of a 5:1 mixture of diastereoisomers, 81 % ee, 86 % de) and anhydrous copper sulfate (2.31 mmol, 0.362 g) in cyclohexanone (1.64 mmol, 163 mg). After 5 h at reflux, the mixture was diluted with ethyl acetate (20 mL), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 5% to 10% ethyl acetate in hexane) to afford acetal **195** (77 mg, 38 %, 99 % by GC-MS) as a clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.63; ν_{max}(neat)/cm^{-1} 2935s (CH_2), 2861w (CH_3), 1612w, 1513s, 1246s, 1087s (C-O), 1033s; $[\alpha]_D^{22}$ = +5.0° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.7, ArH), 6.88 (2H, d, *J* 8.7, ArH), 4.56 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, *J* 2.8, C*H*$_a$H$_b$F), 4.51 (2H, s, CH_2Ar), 4.44 (1H, ddd, $^2J_{H\text{-}F}$ 47.3, ^2J 10.1, *J* 4.5, CH$_a$*H*$_b$F), 4.11-3.97 (2H, m, H-2, H-3), 3.80 (3H, s, OCH_3), 3.65 (1H, dd, ^2J 10.2, *J* 4.6, C*H*$_a$H$_b$OPMB), 3.54 (1H, dd, ^2J 10.2, *J* 5.1, CH$_a$*H*$_b$OPMB), 1.67-1.33 (10H, env., C_6H_{10}); δ_C (75 MHz, $CDCl_3$) 159.3, 130.0, 129.3, 113.8, 110.6, 82.8 (d $^1J_{C\text{-}F}$ 173.0, C-1), 77.5 (d $^2J_{C\text{-}F}$ 19.5, C-2), 75.0 (d $^3J_{C\text{-}F}$ 6.7, C-3), 73.3 (CH_2Ph), 70.3 (C-4), 55.3 (OCH_3), 36.6, 36.3, 25.1, 23.9, 23.8; δ_F (282 MHz, $CDCl_3$) –228.9 (tdd, $^2J_{F\text{-}H}$ 47.3, 23.8, 3.0); [HRMS (EI, M$^+$) Found: 324.17374 Calc. For $C_{18}H_{25}O_4F$ 324.17369]; *m/z* (EI) 324 (1 %, M$^+$), 281 (3), 226 (3), 195 (3), 175 (7), 136 (12, OPMB$^+$), 121 (100, PMB$^+$).

(2R*, 3R*)-1-Fluoro-4-(*p*-methoxybenzyloxy)butan-2,3-cyclohexylidene acetal 196



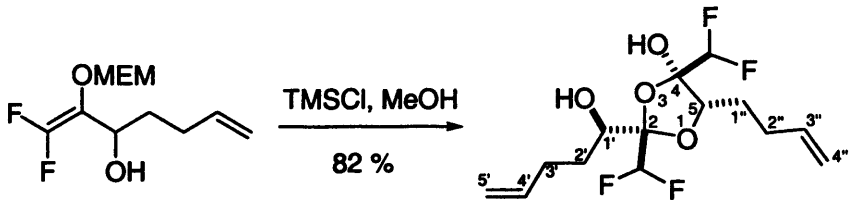
p-Toluenesulfonic acid (0.05 mmol, 10 mg) was added to a stirred mixture of diol **188** (13.57 mmol, 3.32 g) and anhydrous copper sulfate (16.04 mmol, 2.56 g) in cyclohexanone (64.56 mmol, 6 mL). After 5 h at reflux, the mixture was diluted with ethyl acetate (20 mL), filtered and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford acetal **196** (4.39 g, 99 %, 90 % by GC-MS) as a clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.63; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.7, ArH), 6.88 (2H, d, *J* 8.7, ArH), 4.67-4.31 (4H, env., H-1, CH_2Ar), 4.15-3.87 (2H, env., H-2, H-3), 3.80 (3H, s, OCH_3), 3.73-3.51 (2H, env., CH_2OPMB), 1.90-1.23 (10H, env., C_6H_{10}); δ_F (282 MHz, $CDCl_3$) –228.9 (tdd, $^2J_{F-H}$ 47.3, 23.8, 3.0); minor *cis* cyclohexylidene: δ_F (282 MHz, $CDCl_3$) –227.3 (tdd, $^2J_{F-H}$ 47.2, 22.0, 2.3); both diastereoisomers: *m/z* (EI) 324 (1 %, M^+), 281 (3), 226 (3), 195 (3), 175 (7), 136 (12, $OPMB^+$), 121 (100, PMB^+). A full characterisation was obtained for the enantiomerically enriched material.

4-fluorobutan-1-ol 2,3-cyclohexylidene acetal 197



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.83 mmol, 0.19 g) was added in small portions to a cold (0 °C) stirred solution of cyclohexylidene acetal **196** (0.73 mmol, 0.24 g) in CH_2Cl_2 (12 mL) and H_2O (0.6 mL). After stirring at room temperature for 6 h, the mixture was quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark oil which was purified by silica gel column chromatography (gradient 10% to 20% ethyl acetate in hexane) to obtain alcohol **197** (0.11 g, 73 %, 87 % by GC-MS) as a mixture of inseparable diastereoisomers as colourless oil; R_f (35% ethyl acetate in hexane) 0.33; ν_{max}(neat)/cm^{-1} 3427br (OH), 2936s (CH_2), 2863w, 1450w, 1367w, 1165s, 1106s, 1046s; Major: δ_H (300 MHz, $CDCl_3$) 4.67-4.29 (2H, m, H-1), 4.18-3.93 (2H, m, H-2, H-3), 3.91-3.64 (2H, m, H-4), 2.70 (1H, br.s, OH), 1.71-1.32 (10H, env., C_6H_{10}); δ_C (75 MHz, $CDCl_3$) 110.5, 82.4 (d, $^1J_{C\text{-}F}$ 173.0, C-1), 76.8 (d, $^3J_{C\text{-}F}$ 9.8, C-3), 75.5 (d, $^2J_{C\text{-}F}$ 20.3, C-2), 62.0 (C-4), 36.6, 36.2, 25.0, 23.8, 23.7; δ_F (282 MHz, $CDCl_3$) -229.8 (td, $^2J_{F\text{-}H}$ 47.3, 20.1); Minor: δ_H (300 MHz, $CDCl_3$) 4.67-4.29 (2H, m, H-1), 4.18-3.93 (2H, m, H-2, H-3), 3.91-3.64 (2H, m, H-4), 2.70 (1H, br.s, OH), 1.71-1.32 (10H, m, C_6H_{10}); δ_C (75 MHz, $CDCl_3$) 110.7, 81.7 (d, $^1J_{C\text{-}F}$ 169.8, C-1), 76.6 (d, $^3J_{C\text{-}F}$ 3.6, C-3), 74.6 (d, $^2J_{C\text{-}F}$ 21.8, C-2), 64.0 (C-4), 37.3, 35.6, 24.0, 23.9, 23.6; δ_F (282 MHz, $CDCl_3$) –225.9 (td, $^2J_{F\text{-}H}$ 47.1, 16.9); [HRMS (EI, M^+) Found: 204.11621 Calc. For $C_{10}H_{17}O_3F$ 204.11617]; *m/z* (EI) 204 (10 %, M^+), 175 (36), 161 (100, $[M\text{-}C_2H_3O]^+$), 99 (11), 89 (44), 55 (90).

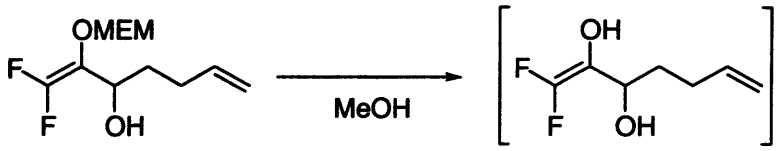
(*1'R, *2R**, *4R**, *5S**)-5-But-3-enyl-2,4-bis-difluoromethyl-2-(1-hydroxy-pent-4-enyl)-[1,3]dioxolan-4-ol 203**



Trimethylchlorosilane (10.2 mmol, 1.30 mL) was added slowly to a solution of difluoroallylic alcohol **132** (10.0 mmol, 2.52 g) in methanol (10 mL). The solution was stirred overnight at room temperature. The solution was concentrated *in vacuo* to leave a clear oil which was purified by column chromatography (gradient 10 to 50 % ethyl acetate in hexane) to afford dioxolane **203** (1.35 g, 82 %) as a clear, colourless oil, which crystallized in the refrigerator as colourless needles; mp 32-34 °C; R_f (20% ethyl acetate in hexane) 0.53; (Found: C, 51.3; H, 6.1; $C_{14}H_{20}O_4F_4$ requires: C, 51.2; H, 6.1 %); ν_{max}(neat)/cm^{-1} 3428br (OH), 2931s (CH_2), 1642s (C=C), 1453w, 1244w, 1073s (C-O); δ_H (300 MHz, $CDCl_3$) 5.82-5.64 (2H, m, H-3'', H-4'), 5.73 (2H, t, $^2J_{F-H}$ 53.7, CHF_2), 5.70 (4H, t, $^2J_{F-H}$ 53.7, CHF_2), 5.07-4.89 (4H, m, H-4'', H-5'), 4.65 (2H, br.s, OH), 4.28-4.10 (1H, m, H-1'), 3.82-3.72 (1H, m, H-5), 2.30-2.00 (4H, m, H-3', H-2''), 1.83-1.50 (4H, m, H-1', H-2''); δ_C (300 MHz, $CDCl_3$) 137.5, 137.1, 115.8, 115.5, 112.8 (t, $^1J_{C-F}$ 251.0), 112.6 (t, $^1J_{C-F}$ 247.9), 107.7 (t, $^2J_{C-F}$ 22.0), 100.2 (t, $^2J_{C-F}$ 25.5), 81.0, 70.0, 29.9, 29.7, 29.4, 28.4; δ_F (300 MHz, $CDCl_3$) -130.4 (1F, dd, $^2J_{F-F}$ 292.3, $^2J_{F-H}$ 54.9), -132.7 (1F, dd, $^2J_{F-F}$ 293.3, $^2J_{F-H}$ 54.4), -133.9 (1F, dd, $^2J_{F-F}$ 292.3, $^2J_{F-H}$ 54.7), -135.5 (1F, dd, $^2J_{F-F}$ 293.3, $^2J_{F-H}$ 54.1); *m/z* (EI) 328 (1 %, M^+), 310 (1, $[M-H_2O]^+$), 300 (2), 243 (18), 224 (43), 147 (43), 84 (100); The relative stereochemistry and identity of this product were confirmed by XRD analysis; Crystal data: $C_{14}H_{20}O_4F_4$, crystal size 0.31 x 0.26 x 0.22 mm^3, M = 164.15, monoclinic, space group P2(1)/n, unit cell dimensions a = 12.8189(9), b = 7.7506(5), c = 15.7635(11) Å, α = 90°, β = 94.2810(10)°, γ = 90°, V = 1561.80(18) Å^3, Z = 4, D_{calc} = 1.396 Mg m^{-3}, F(000) = 688,

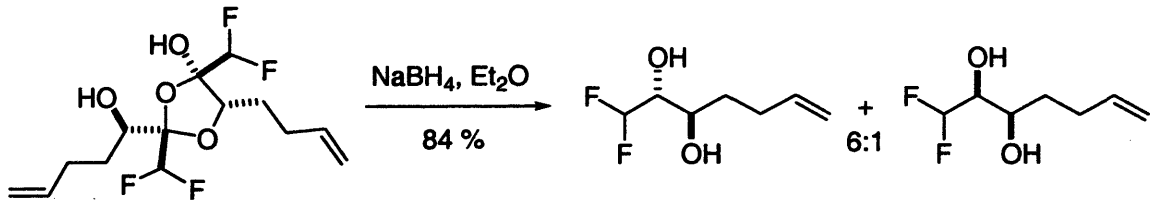
μ(Mo-Kα) = 0.130 mm^{-1}, T = 150(2) K, 10838 total reflections measured, 2748 independent, (R_{int} = 0.0202) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0362, $\omega R2$ = 0.1626; R indices (all data) $R1$ = 0.0387, $\omega R2$ = 0.0954.

1,1-difluoro-hept-1,6-dien-2,3-diol 205



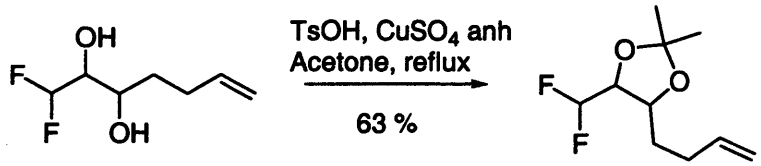
Difluoroallylic alcohol **132** (0.23 mmol, 58 mg) was added to a solution of trifluoromethoxy benzene (0.10 mmol, 11 mg) in d^4-methanol (0.397 g). After 16 days the ^{19}F NMR spectrum show that enol **205** was the only species present. δ_H (300 MHz, CD_3OD) 5.76 (1H, ddt, J 16.9, 10.2, 6.7, H-6), 4.96 (1H, ddt , J 16.9, ^2J 2.1, ^4J 1.6, H-7$_a$), 4.90 (1H, ddt, J 10.2, ^2J 2.1, ^4J 1.3, H-7$_b$), 4.19 (1H, dtd, J 7.3, $^4J_{H\text{-}F}$ 3.7, $^4J_{H\text{-}F}$ 2.1, H-3), 2.06-1.95 (2H, m, H-5), 1.75-1.61 (2H, m, H-4); δ_C (300 MHz, CD_3OD) 153.3 (dd, $^1J_{C\text{-}F}$ 282.2, 273.6, C-1), 139.1 (C-6), 116.1 (dd, $^2J_{C\text{-}F}$ 35.9, 12.5), 115.4 (C-7), 67.3 (dd, $^3J_{C\text{-}F}$ 3.7, 1.8, C-3), 33.6 (t, $^4J_{C\text{-}F}$ 2.1, C-4), 30.9 (C-5); δ_F (300 MHz, CD_3OD) –111.8 (dd, $^2J_{F\text{-}F}$ 93.5, $^4J_{F\text{-}H}$ 2.1), –123.8 (d, $^2J_{F\text{-}F}$ 93.5, $^4J_{F\text{-}H}$ 3.7).

(2*R,3*R**)-1,1-Difluoro-hept-6-en-2,3-diol 207 and (2*S**,3*R**)-1,1-difluoro-hept-6-en-2,3-diol 208**



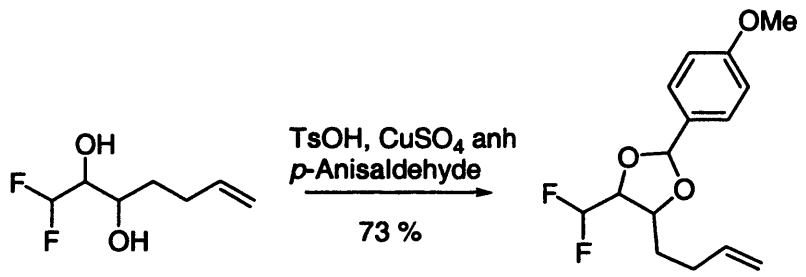
Sodium borohydride (1.2 mmol, 46 mg) was added in portions to a solution of dioxolane **203** (0.58 mmol, 0.19 g) in diethyl ether (10 mL). After stirring overnight at room temperature, the mixture was diluted with water (5 mL), neutralised with concentrated HCl, and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford difluoro diol **207/208** (0.16 g, 84 %, 99% by GC-MS) as a mixture (6:1 by NMR) of inseparable diastereoisomers as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.20; ν_{max}(neat)/cm^{-1} 3366br (OH), 2923w (CH_2), 1642w (C=C), 1417w, 1151s (C-O), 1048s (C-O); Major: δ_H (300 MHz, $CDCl_3$) 5.90 (1H, ddd, $^2J_{H\text{-}F}$ 56.0, 55.0, *J* 4.0, H-1), 5.84 (1H, ddt, *J* 17.1, 10.2, 6.8, H-6), 5.09 (1H, ddd, *J* 17.1, ^2J 3.3, ^4J 1.7, H-7_a), 5.02 (1H, ddd, *J* 10.2, ^2J 3.3, ^4J 1.2, H-7_b), 3.95-3.66 (2H, m, H-2. H-3), 3.04 (1H, br.s, OH), 2.46 (1H, br.s, OH), 2.36-2.06 (2H, m, H-5), 1.79-1.58 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 137.8 (C-6), 137.6, 115.5 (C-7), 115.0 (dd, $^1J_{C\text{-}F}$ 241.9, 242.5, C-1), 77.4 (dd, $^2J_{C\text{-}F}$ 23.3, 20.4, C-2), 70.7 (dd, $^3J_{C\text{-}F}$ 4.4, 3.0, C-3), 31.3 (d, $^4J_{C\text{-}F}$ 2.0, C-4), 29.8; δ_F (282 MHz, $CDCl_3$) –128.3 (1F, ddd, $^2J_{F\text{-}F}$ 292.1, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 7.1 CH*F*$_a$F$_b$), -132.0 (1F, ddd, $^2J_{F\text{-}F}$ 292.1, $^2J_{F\text{-}H}$ 56.2, $^3J_{F\text{-}H}$ 15.2, CHF$_a$*F*$_b$); [HRMS (EI, M^+) Found: 166.08044 Calc. For $C_7H_{12}F_2O_2$ 166.08054]; *m/z* (EI) 148 (2 %, $[M+NH_4]^+$), 130 (4), 111 (5), 97 (19), 85 (30), 67 (100), 57 (42); Minor: δ_F (282 MHz, $CDCl_3$) -129.2 (1F, dddd, $^2J_{F\text{-}F}$ 292.0, $^2J_{F\text{-}H}$ 55.7, $^3J_{F\text{-}H}$ 9.9, $^4J_{F\text{-}H}$ 1.1, CH*F*$_a$F$_b$), -130.4 (1F, ddd, $^2J_{F\text{-}F}$ 292.0, $^2J_{F\text{-}H}$ 56.6, $^3J_{F\text{-}H}$ 10.6, CHF$_a$*F*$_b$).

1,1-difluoro-hept-6-en-2,3-acetonide 216



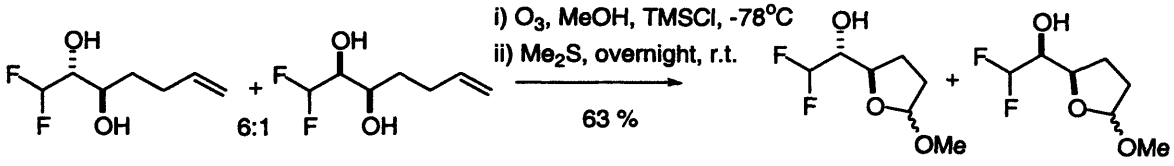
p-Toluenesulfonic acid monohydrate (0.15 mmol, 28 mg) was added to a stirred solution of anhydrous copper sulfate (2.6 mmol, 0.403 g) and diol **207/208** (0.76 mmol, 127 mg) in dry acetone (25 mL). After 5 h at reflux the mixture was cooled, filtered and concentrated *in vacuo* to leave a colourless oil. Kugelrohr distillation afforded acetonide **216** (100 mg, 63 %, 99 % by GC-MS) as a mixture of isomers (8:1 by NMR) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.67; bp 20 °C/0.07 mmHg; ν_{max}(neat)/cm^{-1} 2988w (CH_2), 2939w (CH_2), 1642w (C=C), 1373w, 1220s, 1070s (C-O); Major: δ_H (400 MHz, $CDCl_3$) 5.75 (1H, ddd, *J* 17.1, 10.2, 6.9, H-6), 5.61 (1H, ddd, $^2J_{H\text{-}F}$ 55.7, 54.6, *J* 5.6, H-1), 5.00 (1H, dddd, *J* 17.1, ^2J 1.9, ^4J 1.6, 1.2, H-7_a), 4.94 (1H, ddt, *J* 10.2, ^2J 1.9, ^4J 1.2, H-7_b), 4.18 (1H, dddd, *J* 8.0, 5.8, 6.4, $^3J_{H\text{-}F}$ 2.3, H-3), 4.00 (1H, ddt, $^3J_{H\text{-}F}$ 10.5, 9.0, *J* 5.8, H-2), 2.30-2.17 (1H, m, H-5_a), 2.15-2.03 (1H, m, H-5_b), 1.72-1.62 (1H, m, H-4), 1.41 (CH_3), 1.30 (CH_3); δ_C (75 MHz, $CDCl_3$) 137.3 (C-6), 115.5 (C-7), 113.9 (dd, $^1J_{C\text{-}F}$ 244.7, 242.2, C-1), 110.6, 76.0 (dd, $^2J_{C\text{-}F}$ 28.2, 21.5, C-2), 75.7 (dd, $^3J_{C\text{-}F}$ 4.5, 0.6, C-3), 30.7 (d, $^5J_{C\text{-}F}$ 1.3, C-5), 27.8 (d, $^4J_{C\text{-}F}$ 3.0, C-4), 27.6, 25.3; δ_F (282 MHz, $CDCl_3$) –125.1 (1F, ddd, $^2J_{F\text{-}F}$ 297.2, $^2J_{F\text{-}H}$ 54.6, $^3J_{F\text{-}H}$ 9.0), -127.3 (1F, dddd, $^2J_{F\text{-}F}$ 297.2, $^2J_{F\text{-}H}$ 55.7, $^3J_{F\text{-}H}$ 10.5, $^4J_{F\text{-}H}$ 2.3); Minor: δ_C (75 MHz, $CDCl_3$) 137.5 (C-6), 115.2 (C-7), 114.8 (dd, $^1J_{C\text{-}F}$ 244.0, 243.2, C-1), 110.6, 79.3 (dd, $^2J_{C\text{-}F}$ 27.0, 24.9, C-2), 77.2 (C-3), 32.8, 29.8, 27.3, 26.4; δ_F (282 MHz, $CDCl_3$) –124.0 (1F, ddd, $^2J_{F\text{-}F}$ 296.0, $^2J_{F\text{-}H}$ 55.4, $^3J_{F\text{-}H}$ 9.1), -128.8 (1F, ddd, $^2J_{F\text{-}F}$ 296.0, $^2J_{F\text{-}H}$ 55.5, $^3J_{F\text{-}H}$ 9.9); [HRMS (EI, M^+) Found: 206.11187 Calc. For $C_{10}H_{16}O_2F_2$ 206.11184]; *m/z* (EI) 206 (1 %, M^+), 191 (100, [M-CH_3]$^+$), 164 (11), 151 (16), 131 (25), 111 (66), 91 (29), 85 (26), 67 (25), 59 (40).

1,1-difluoro-hept-6-en-2,3-(*p*-methoxy)benzylidene 217



p-Toluenesulfonic acid monohydrate (0.16 mmol, 30 mg) was added to a stirred solution of anhydrous copper sulfate (3.2 mmol, 0.440 g) and diol **207/208** (1.0 mmol, 165 mg) in *p*-anisaldehyde (3.7 mmol, 0.5 g). After 5h the mixture was filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford dioxolane **217** (207 mg, 73 %, 99 % by GC-MS) as a mixture of diastereoisomers (8:8:1:1 by GCMS) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.53; ν_{max}(neat)/cm^{-1} 2937w (CH_2), 2841w (CH_2), 1642w (C=C), 1615w, 1518w, 1248s, 1082s (C-O); all four components unresolved: δ_H (300 MHz, $CDCl_3$) 7.45-7.33 (2H, m, ArH), 6.94-6.86 (2H, m, ArH), 6.18-5.57 (3H, env., CHF_2, H-6), 5.13-4.99 (2H, m, H-7), 4.40-3.85 (3H, env., H-2, H-3, CH-PMP), 3.81 (3H, s, OCH_3), 2.43-1.54 (4H, env., H-4, H-5); δ_C (75 MHz, $CDCl_3$) 160.8, 137.9, 137.3, 137.2, 137.1, 132.0, 129.4, 128.8, 128.3, 128.1, 127.4, 117.7, 117.2, 115.7, 115.6, 115.5, 115.4, 115.0, 114.5, 114.3, 113.9, 113.9, 113.8, 111.2, 110.7, 104.6, 104.0, 103.6, 103.2, 80.2, 79.9, 79.2, 78.9, 78.6, 78.1, 78.0, 77.5, 77.2, 77.0, 76.6, 76.2, 76.0, 75.8, 75.7, 75.4, 75.4, 55.6, 55.3, 32.7, 32.3, 31.4, 30.8, 30.6, 29.8, 29.7, 29.6, 27.5; $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) –124.7 (1F, d, $^2J_{F\text{-}F}$ 295.2), –125.5 (1F, d, $^2J_{F\text{-}F}$ 296.6), –125.6 (1F, d, $^2J_{F\text{-}F}$ 296.2), –127.0 (1F, d, $^2J_{F\text{-}F}$ 296.6), –128.6 (1F, d, $^2J_{F\text{-}F}$ 291.8), –129.6 (1F, d, $^2J_{F\text{-}F}$ 295.2), –130.4 (1F, d, $^2J_{F\text{-}F}$ 296.2), –132.6 (1F, d, $^2J_{F\text{-}F}$ 291.8); [HRMS (EI, M^+) Found: 284.12245 Calc. For $C_{15}H_{18}O_3F_2$ 2284.12240]; *m/z* (EI) 284 (4 %, M^+), 229 (3), 176 (3), 153 (6), 135 (100, $C_8H_7O_2^+$), 121 (16), 108 (41).

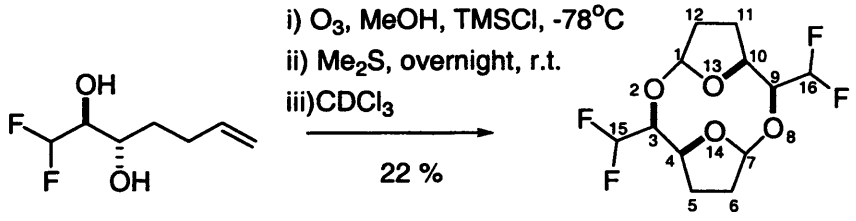
Methyl 6,6-difluoro-amicetofuranoside 218 and methyl 6,6-difluoro-rhodinofuranoside 219



Trimethylchlorosilane (0.08 mmol, 10 μl) was added to a stirred solution of diol **207/208** (0.44 mmol, 73 mg) in methanol (5 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 35% to 50% ethyl acetate in hexane) to afford methyl furanosides **218/219** (50 mg, 63 %, 99 % by GC-MS) as a 2.9:2.5:1 (a:b:c) mixture of inseparable isomers as clear colourless oil; R_f (50 % ethyl acetate in hexane) 0.66; ν_{max}(neat)/cm^{-1} 3409br (OH), 2959w (CH_2), 1444w, 1207w, 1150w, 1031s (C-O); δ_H (400 MHz, $CDCl_3$) 5.83 (1H, td, $^2J_{H\text{-}F}$ 55.1, *J* 3.3, anomer b H-6), 5.78 (1H, td, $^2J_{H\text{-}F}$ 55.2, *J* 3.6, anomer a H-6), 5.77 (1H, td, $^2J_{H\text{-}F}$ 56.0, *J* 4.8, anomer c H-6), 5.10 (1H, dd, *J* 4.2, 1.4, anomer c H-1), 5.05 (1H, dd, *J* 3.6, 1.4, anomer a H-1), 4.99 (1H, dd, *J* 4.2, 0.9, anomer b H-1), 4.38 (1H, td, *J* 7.0, 3.8, anomer b H-4), 4.29 (1H, td, *J* 7.0, 2.8, anomer c H-4), 4.18 (1H, ddd, *J* 13.1, 5.5, 1.8, anomer a H-4), 3.93 (1H, ddt, $^3J_{H\text{-}F}$ 12.7, 11.7, *J* 3.8, anomer b H-5), 3.84 (1H, dddd, $^3J_{H\text{-}F}$ 16.2, 7.7, *J* 5.5, 3.6, anomer a H-5), 3.66 (1H, tdd, $^3J_{H\text{-}F}$ 9.8, *J* 5.4, 2.8, anomer c H-5), 3.48 (1H, s, anomer c OH), 3.38 (3H, s, anomer b OCH_3), 3.34 (3H, s, anomer c OCH_3), 3.33 (3H, s, anomer a OCH_3), 2.96 (1H, s, anomer a OH), 2.88 (1H, s, anomer b OH), 2.19-1.81 (12H, env., H-2, H-3); δ_C (100 MHz, $CDCl_3$) 115.1 (t, $^1J_{C\text{-}F}$ 256.9, anomer c C-6), 115.3 (t, $^1J_{C\text{-}F}$ 242.4, C-6), 115.0 (dd, $^1J_{C\text{-}F}$ 243.2, 241.6, C-6), 105.7 (anomer c C-1), 105.4 (anomer b C-1), 105.2 (anomer a, C-1), 78.8 (t, $^3J_{C\text{-}F}$ 4.0, C-4),

76.1 (t, $^3J_{C\text{-}F}$ 4.1, C-4), 74.8 (t, $^3J_{C\text{-}F}$ 3.8, anomer c C-4), 72.6 (t, $^2J_{C\text{-}F}$ 22.4, C-5), 72.3 (t, $^2J_{C\text{-}F}$ 21.4, anomer c C-5), 72.1 (t, $^2J_{C\text{-}F}$ 22.0, C-5), 32.8 (anomer b OCH_3), 32.1 (anomer c OCH_3), 31.9 (anomer a OCH_3), 32.8 (C-2), 32.1 (anomer c C-2), 31.9 (C-2), 25.5 (anomer c C-3), 24.3 (C-3), 23.0 (C-3); δ_F (282 MHz, $CDCl_3$) –128.60 (1F, d, $^2J_{F\text{-}H}$ 56.0, anomer c), -128.63 (1F, d, $^2J_{F\text{-}H}$ 56.0, anomer c), -129.7 (1F, d, $^2J_{F\text{-}F}$ 290.3, $^2J_{F\text{-}H}$ 55.2, $^3J_{F\text{-}H}$ 7.7, anomer a), -130.0 (1F, d, $^2J_{F\text{-}F}$ 291.3, $^2J_{F\text{-}H}$ 55.1, $^3J_{F\text{-}H}$ 11.7, anomer b), -130.4 (1F, d, $^2J_{F\text{-}F}$ 291.3, $^2J_{F\text{-}H}$ 55.1, $^3J_{F\text{-}H}$ 12.7, anomer b), -133.0 (1F, d, $^2J_{F\text{-}F}$ 290.3, $^2J_{F\text{-}H}$ 55.2, $^3J_{F\text{-}H}$ 16.2, anomer a); [HRMS (EI, $[M\text{-}1]^+$) Found: 181.06765 Calc. For $C_7H_{11}O_3F_2$ 181.06763]; *m/z* (EI) 182 (1 %, M^+), 150 (14, $[M\text{-}CH_4O]^+$), 133 (1), 104 (10), 101 (68, $[M\text{-}C_2H_4OF_2]^+$), 85 (6), 69 (100, $C_4H_5O^+$).

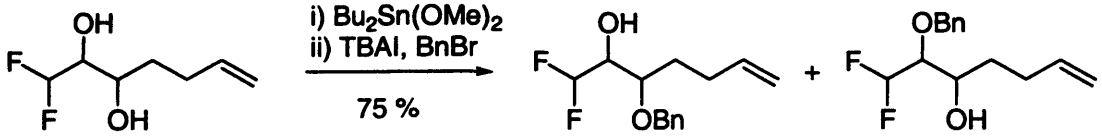
3,9-Bis-difluoromethyl-2,8,13,14-tetraoxa-tricyclo[8.2.1.14,7]tetradecane 220



Trimethylchlorosilane (0.08 mmol, 10 µl) was added to a stirred solution of diol **207/208** (0.30 mmol, 0.05 g) in methanol (5 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was taken up in $CDCl_3$ (0.35 mL). After 1h, the solution was concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford dimer **220** (10

mg, 22 %, 99 % by GC-MS) as clear colourless needles; mp 105-109 °C; R_f (20 % ethyl acetate in hexane) 0.46; (Found: C, 47.9; H, 5.2; $C_{12}H_{16}O_4F_4$ requires: C, 48.0; H, 5.4 %); ν_{max}(neat)/cm^{-1} 2967w (CH_2), 2925w (CH_2), 1317w, 1196w, 1092s (C-O), 1046s (C-O); δ_H (300 MHz, $CDCl_3$) 5.52 (2H, td, $^2J_{H\text{-}F}$ 55.2, J 4.8, H-15, H-16), 5.09 (2H, d, J 4.2, H-1, H-7), 4.26 (2H, t, J 7.9, H-4, H-10), 4.07-3.96 (2H, m, H-3, H-9), 2.34-2.16 (2H, m, H-5$_a$, H-11$_a$), 2.11-1.97 (2H, m, H-6$_a$, H-12$_a$), 1.87-1.66 (4H, m, H-6$_b$, H-12$_b$, H-5$_b$, H-11$_b$); δ_C (75 MHz, $CDCl_3$) 115.1 (t, $^1J_{C\text{-}F}$ 245.3, C-15, C-16), 103.5 (C-1, C-7), 78.0 (t, $^3J_{C\text{-}F}$ 4.0, C-4, C-10), 75.1 (d, $^2J_{C\text{-}F}$ 21.3, C-3, C-9), 33.6 (C-6, C-12), 21.7 (C-5, C-11); δ_F (282 MHz, $CDCl_3$) –126.3 (2F, dd, $^2J_{F\text{-}H}$ 55.2, $^3J_{F\text{-}H}$ 6.6), -126.3 (2F, dd, $^2J_{F\text{-}H}$ 55.2, $^3J_{F\text{-}H}$ 7.4); [HRMS (EI, M$^+$) Found: 300.09841 Calc. For $C_{12}H_{16}O_4F_4$ 300.09847]; *m/z* (EI) 300 (1 %, M$^+$), 239 (11), 219 (16), 192 (28), 176 (56), 150 (29), 138 (32), 133 (33), 104 (18), 99 (16), 85 (55), 69 (100, $C_4H_5O^+$). The relative stereochemistry and identity of this product were confirmed by XRD analysis; Crystal data: $C_{12}H_{16}O_4F_4$, crystal size 0.25 x 0.17 x 0.15 mm^3, M = 300.25, monoclinic, space group C2/c, unit cell dimensions a = 17.5445(16), b = 9.0382(8), c = 8.2241(8) Å, α = 90°, β = 102.802(2)°, γ = 90°, V = 1271.7(2) Å^3, Z = 4, D_{calc} = 1.568 Mg m^{-3}, F(000) = 624, μ(Mo-Kα) = 0.152 mm^{-1}, T = 150(2) K, 4503 total reflections measured, 1126 independent, (R_{int} = 0.0368) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0505, $\omega R2$ = 0.1428; R indices (all data) $R1$ = 0.0536, $\omega R2$ = 0.1454.

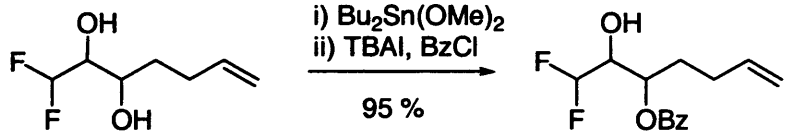
3-benzyloxy-1,1-difluoro-hept-6-en-2-ol 221 and 2-benzyloxy-1,1-difluoro-hept-6-en-3-ol 222



Dibutyltin dimethoxide (1.4 mmol, 0.43 g) was added to a stirred solution of diol **207/208** (1.0 mmol, 169 mg) in dry toluene (40 mL). After 30 min at reflux under a Dean-Stark trap, the solution was concentrated by removing toluene (20 mL), cooled to room temperature, then tetrabutylammonium iodide (1.0 mmol, 0.36 g) and benzyl bromide (1.1 mmol, 0.13 mL) were added. After 3 h at reflux, the mixture was cooled to room temperature and quenched with water (20 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The original organic phase and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 5 % to 20 % ethyl acetate in hexane) to afford alcohol **221/222** (195 mg, 75 %, 95 % by GC-MS) as a mixture of regio- and diastereo- isomers a:b:c:d = 7:5:1.3:1 (by ^{19}F NMR) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.55; ν_{max}(neat)/cm^{-1} 3434br (OH), 2934w (CH_2), 1641w (C=C), 1455w, 1056s (C-O); all four components unresolved: δ_H (300 MHz, $CDCl_3$) 7.40-7.24 (5H, m, Ph), 6.12-5.54 (2H, m, H-1, H-6), 5.09-4.47 (4H, m, H-7, CH_2Ph), 3.92-3.38 (2H, m, H-2, H-3), 2.68-1.24 (5H, m, H-4, H-5, OH); δ_C (75 MHz, $CDCl_3$) 138.1 (C-6), 138.0 (C-6), 137.7 (C-6), 137.3 (C-6), 128.6, 128.6, 128.6, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 115.8 (dd, $^1J_{C\text{-}F}$ 245.5, 243.5, C-1), 115.5 (C-7), 115.4 (C-7), 115.2 (C-7), 115.1 (dd, $^1J_{C\text{-}F}$ 243.4, 240.6, C-1), 80.3 (dd, $^2J_{C\text{-}F}$ 23.0, 19.1, C-2), 77.4 (dd, $^3J_{C\text{-}F}$ 7.5, 4.0 C-3), 74.8 (CH_2Ph), 74.5 (CH_2Ph), 72.5 (CH_2Ph), 72.4 (CH_2Ph), 71.7 (dd, $^2J_{C\text{-}F}$ 23.2, 20.6, C-2), 70.2 (dd, $^3J_{C\text{-}F}$ 5.6, 2.9, C-3), 32.9, 31.3 (d, $^5J_{C\text{-}F}$ 2.5, C-4), 29.8, 29.7, 29.6, 29.4, 29.0 (d, $^5J_{C\text{-}F}$ 1.6, C-4), 28.9; δ_F (282 MHz, $CDCl_3$) –124.3 (app dd, $^2J_{F\text{-}F}$ 294.1, $^2J_{F\text{-}H}$

54.7, CHF_aF$_b$, isomer c), -125.0 (ddd, $^2J_{F\text{-}F}$ 294.2, $^2J_{F\text{-}H}$ 60.8, $^3J_{F\text{-}H}$ 6.2, CHF_aF$_B$, isomer b), -128.6 (ddd, $^2J_{F\text{-}F}$ 294.1, $^2J_{F\text{-}H}$ 57.0, $^3J_{F\text{-}H}$ 11.0, CHF$_a$$F_b$, isomer c), -128.8 (ddd, $^2J_{F\text{-}F}$ 294.2, $^2J_{F\text{-}H}$ 55.7, $^3J_{F\text{-}H}$ 13.9, CHF$_a$$F_b$, isomer b), -128.9 (ddd, $^2J_{F\text{-}F}$ 289.9, $^2J_{F\text{-}H}$ 55.9, $^3J_{F\text{-}H}$ 9.7, CHF_aF$_b$, isomer d), -129.1 (ddd, $^2J_{F\text{-}F}$ 289.9, $^2J_{F\text{-}H}$ 56.4, $^3J_{F\text{-}H}$ 10.6, CHF$_a$$F_b$, isomer d), -129.3 (ddd, $^2J_{F\text{-}F}$ 289.8, $^2J_{F\text{-}H}$ 54.9, $^3J_{F\text{-}H}$ 6.0, CHF_aF$_b$, isomer a), -132.5 (ddd, $^2J_{F\text{-}F}$ 289.8, $^2J_{F\text{-}H}$ 56.2, $^3J_{F\text{-}H}$ 17.0, CHF$_a$$F_b$, isomer a); [HRMS (EI, M$^+$) Found: 256.12744 Calc. For $C_{14}H_{18}O_2F_2$ 256.12749]; *m/z* (EI) 256 (1 %, M$^+$), 235 (1), 189 (2), 175 (50), 108 (43), 91 (100, $C_7H_7^+$).

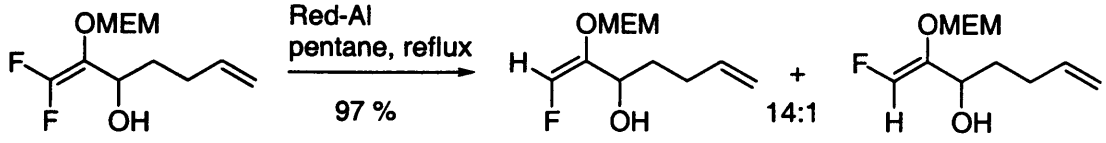
3-benzoyloxy-1,1-difluoro-hept-6-en-2-ol 223 and 2-benzoyloxy-1,1-difluoro-hept-6-en-2-ol 224



Dibutyltin dimethoxide (0.8 mmol, 0.18 g) was added to a stirred solution of diol **207/208** (0.8 mmol, 133 mg) in dry toluene (40 mL). After 30 min at reflux in a Dean-Stark system, the solution was concentrated by removing toluene (20 mL), coooled to room temperature, then tetrabutylammonium iodide (0.8 mmol, 0.30 g) and benzoyl chloride (0.8 mmol, 0.09 mL) were added. After 3 h at reflux, the mixture was cooled to room temperature and quenched with water (20 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The original organic phase and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 5 % to 10 % ethyl acetate in hexane) to afford alcohol **223/224** (206 mg, 95 %, 99 % by GC-MS) as a mixture of regio- and diastereo- isomers

a:b:c:d = 35:6:5:1 (by ^{19}F NMR) a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.46; ν_{max}(neat)/cm^{-1} 3454br (OH), 2979w (CH_2), 1705s (C=O), 1452w, 1268s, 1068s; all four components unresolved: δ_H (300 MHz, $CDCl_3$) 8.13-8.02 (2H, m, Ph), 7.64-7.55 (1H, m, Ph), 7.50-7.42 (2H, m, Ph), 6.34-5.60 (2H, m, H-1, H-6), 5.41-5.23 (1H, m, H-3), 5.11-4.95 (2H, m, H-7), 4.11-3.88 (1H, m, H-2), 2.35-0.89 (5H, m, H-4, H-5, OH); δ_C (75 MHz, $CDCl_3$) 166.4 (C=O), 137.0 (C-6), 133.5, 129.8, 129.4, 128.6, 115.7 (C-7), 114.6 (t, $^1J_{C\text{-}F}$ 243.8, C-1), 73.4 (dd, $^2J_{C\text{-}F}$ 4.2, 2.8, C-3), 72.3 (dd, $^2J_{C\text{-}F}$ 23.7, 21.6, C-2), 29.4 (C-5), 29.3 (d, $^4J_{C\text{-}F}$ 2.0, C-4); δ_F (282 MHz, $CDCl_3$) –127.5 (ddd, $^2J_{F\text{-}F}$ 292.6, $^2J_{F\text{-}H}$ 54.7, $^3J_{F\text{-}H}$ 7.8, CHF_aF_b, isomer a), -128.0 (ddd, $^2J_{F\text{-}F}$ 292.1, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 9.3, CHF_aF_b, isomer b), -128.4 (ddd, $^2J_{F\text{-}F}$ 295.5, $^2J_{F\text{-}H}$ 54.8, $^3J_{F\text{-}H}$ 8.1, $^4J_{F\text{-}H}$ 2.0, CHF_aF_b, isomer d), -128.8 (ddd, $^2J_{F\text{-}F}$ 292.5, $^2J_{F\text{-}H}$ 54.3, $^3J_{F\text{-}H}$ 8.3, CHF_aF_b, isomer c), -129.9 (ddd, $^2J_{F\text{-}F}$ 295.5, $^2J_{F\text{-}H}$ 56.3, $^3J_{F\text{-}H}$ 11.3, CHF_aF_b, isomer d), -130.1 (ddd, $^2J_{F\text{-}F}$ 292.1, $^2J_{F\text{-}H}$ 55.8, $^3J_{F\text{-}H}$ 11.0, CHF_aF_b, isomer b), -130.1 (ddd, $^2J_{F\text{-}F}$ 292.6, $^2J_{F\text{-}H}$ 55.6, $^3J_{F\text{-}H}$ 13.9, CHF_aF_b, isomer a), -130.9 (ddd, $^2J_{F\text{-}F}$ 292.5, $^2J_{F\text{-}H}$ 54.7, $^3J_{F\text{-}H}$ 15.4, CHF_aF_b, isomer c); [HRMS (EI, M^+) Found: 270.10667 Calc. For $C_{14}H_{16}O_3F_2$ 270.10675]; *m/z* (EI) 252 (1 %, $[M\text{-}H_2O]^+$), 189 (1), 148 (5), 122 (10), 105 (100, $C_7H_5O^+$).

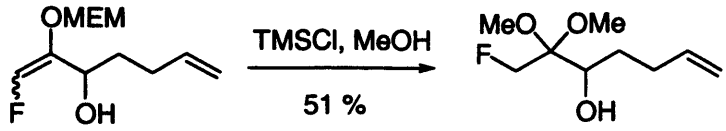
_E_-1-fluoro-2-(2-methoxy-ethoxy)methoxy-hept-1,6-dien-3-ol 227 and _Z_-1-fluoro-2-(2-methoxy-ethoxy)methoxy-hept-1,6-dien-3-ol 228



A solution of difluoroallylic alcohol **132** (5.7 mmol, 1.4 g) and sodium *bis*(2-methoxy-ethoxy)aluminium hydride (22.7 mmol, 6.5 mL of a 3.5 M solution in toluene) in dry hexane (10 mL) was heated to reflux over 3 h. The reaction mixture was cooled and

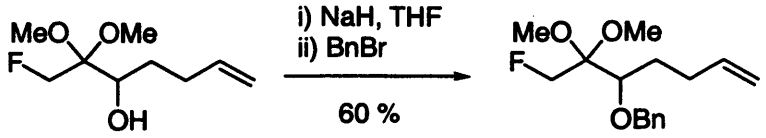
poured carefully into a beaker containing ice (5 g). The resultant white suspension was neutralised (to pH 7) with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which contained a 14:1 (by NMR) mixture of stereoisomers which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford major fluoroallylic alcohol **227/228** (1.3 g, 97 %, 85 % by GC-MS) as a mixture of inseparable isomers as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.23; ν_{max}(neat)/cm^{-1} 3424br (OH), 2930w (CH_2), 1641w (C=C), 1453w, 1112s, 1069s (C-O); Major: δ_H (300 MHz, $CDCl_3$) 6.9 (1H, d, $^2J_{H\text{-}F}$ 80.1, H-1), 5.83 (1H, ddt, *J* 16.8, 10.2, 6.6, H-6), 5.04 (1H, ddd, *J* 16.8, 3.4, 1.8, H-7_a), 5.01-4.95 (1H, m, H-7_b), 4.97 (1H, d, ^2J 6.6, OCH_aH$_b$O), 4.93 (1H, d, ^2J 6.6, OCH$_a$$H_b$O), 4.68-4.55 (1H, m, H-3), 3.78-3.74 (2H, m, OCH_2CH$_2$OMe), 3.58-3.54 (2H, m, CH_2OMe), 3.39 (3H, s, OCH_3), 2.53 (1H, br.s, OH), 2.22-2.02 (2H, m, H-5), 1.86-1.63 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 146.6 (d, $^2J_{C\text{-}F}$ 26.3, C-2), 137.9 (C-6), 137.8 (d, $^1J_{C\text{-}F}$ 240.8, C-1), 115.0 (C-7), 95.5 (OCH_2O), 71.5 (OCH_2CH_2OMe), 67.7 (OCH_2CH$_2$OMe), 65.5 (d, $^3J_{C\text{-}F}$ 2.4, C-3), 59.0 (OCH_3), 33.4 (d, $^4J_{C\text{-}F}$ 2.5, C-4), 29.7 (C-5); δ_F (282 MHz, $CDCl_3$) –171.8 (dd, $^2J_{F\text{-}H}$ 80.1, $^4J_{F\text{-}H}$ 3.6); Only one signal was distinct for the Minor: δ_H (300 MHz, $CDCl_3$) 6.5 (1H, d, $^2J_{H\text{-}F}$ 77.2); δ_F (282 MHz, $CDCl_3$) –156.9 (1F, dd, $^2J_{F\text{-}H}$ 77.2); [HRMS (FAB, MH^+) Found: 235.13454. Calc. For $C_{11}H_{20}O_4F$ 235.13456]; *m/z* (EI) 112 (8), 90 (5), 89 (89 %, MEM^+), 59 (100 %, $C_3H_7O^+$).

2,2-Dimethoxy-1-fluoro-hept-6-en-3-ol 234



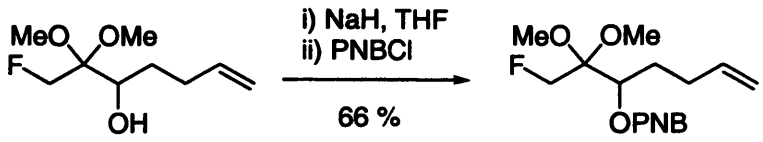
Trimethylchlorosilane (7.5 mmol, 1.0 mL) was added slowly to a cold (0 °C) solution of allyl alcohol **227/228** (5.6 mmol, 1.3 g) in dry methanol (20 mL). The mixture was stirred at 0 °C for 10 minutes then stirred overnight at r.t.. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were concentrated *in vacuo* to leave a yellow oil which was purified by column chromatography (50 % ethyl acetate in hexane) to afford alcohol **234** (0.54 g, 51 %, 84 % by GC-MS) as a clear, colourless oil; ν_{max}(neat)/cm^{-1} 3489br (OH), 2947w (CH_2), 2839w (CH_3), 1641w (C=C), 1462w (CH_3), 1068s (C-O); R_f (20 % ethyl acetate in hexane) 0.30; δ_H (300 MHz, $CDCl_3$) 5.85 (1H, dddd, *J* 17.2, 10.2, 7.1, 6.3, H-6), 5.07 (1H, ddd, *J* 17.2, ^2J 3.6, ^4J 1.6, H-7$_a$), 4.99 (1H, ddd, *J* 10.2, ^2J 3.6, ^4J 1.2, H-7$_b$), 4.48 (1H, dd, $^2J_{H\text{-}F}$ 47.1, ^2J 10.5, C*H*$_a$H$_b$F), 4.41 (1H, ddd, $^2J_{H\text{-}F}$ 47.1, ^2J 10.5, ^4J 0.6, CH$_a$*H*$_b$F), 3.79 (1H, d, *J* 10.8, H-3), 3.33 (6H, s, OCH_3), 2.42-2.29 (1H, m, H-5$_a$), 2.32 (1H, br.s, OH), 2.20-2.07 (1H, m, H-5$_b$), 1.77-1.66 (1H, m, H-4$_a$), 1.63-49 (1H, m, H-4$_b$); δ_C (75 MHz, $CDCl_3$) 138.6 (C-6), 115.4 (C-7), 100.0 (d, $^2J_{C\text{-}F}$ 17.7, C-2), 80.0 (d, $^1J_{C\text{-}F}$ 176.0, C-6), 71.4 (C-3), 49.7 (OCH_3), 49.4 (OCH_3), 31.2 (C-5), 30.1 (d, $^4J_{C\text{-}F}$ 2.8, C-4); δ_F (282 MHz, $CDCl_3$) -232.6 (t, $^2J_{F\text{-}H}$ 47.1); [HRMS (EI, M$^+$) Found: 192.11621. Calc. For $C_9H_{17}O_3F$ 192.11617]; m/z (CI) 210 (10 %, [M+NH_4]$^+$), 178 (33), 161 (15), 146 (54), 129 (42 %, [M-$C_2H_7O_2$]$^+$), 107 (100), 77 (25).

3-Benzyloxy-2,2-dimethoxy-1-fluoro-hept-6-en 235



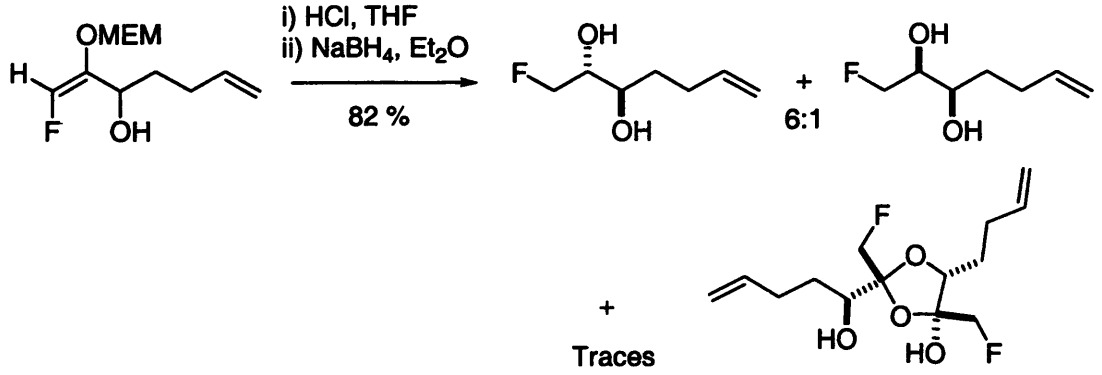
Sodium hydride (0.40 mmol, 16 mg) was washed by stirring with hexane (1 mL) for 30 minutes. Hexane was removed by Pasteur pipette, then dry THF (1 mL) and alcohol **234** (0.21 mmol, 40 mg) were added. After stirring for 2 h, benzyl bromide (0.51 mmol, 0.87 g) was added. After 10 h at room temperature, the mixture was diluted with diethyl ether (3 mL), filtered, concentrated *in vacuo* and purified by column chromatography (20 % ethyl acetate in hexane) to afford benzyl ether **235** (35 mg, 60 %) as a clear, colourless oil; ν_{max}(DCM)/cm^{-1} 2947s (CH_2), 1721w, 1641w (C=C), 1454w (CH_3), 1074s (C-O); R_f (20 % ethyl acetate in hexane) 0.72; δ_H (300 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 5.80 (1H, dddd, *J* 17.3, 10.2, 7.3, 6.0, H-6), 5.04-4.93 (2H, m, H-7), 4.84 (1H, d, ^2J 11.2, C*H*$_a$H$_b$Ph), 4.57 (1H, dd, $^2J_{H\text{-}F}$ 47.2, ^2J 10.4, C*H*$_a$H$_b$F), 4.52 (1H, d, ^2J 11.2, CH$_a$*H*$_b$Ph), 4.48 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 10.4, *J* 0.5, CH$_a$*H*$_b$F), 3.62 (1H, ddd, *J* 9.9, 2.7, 1.5, H-3), 3.35 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 2.36-2.22 (1H, m, H-5$_a$), 2.15-2.01 (1H, m, H-5$_b$), 1.80-1.57 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.9, 138.5 (C-6), 128.3, 127.8, 127.5, 115.0 (C-7), 101.0 (d, $^2J_{C\text{-}F}$ 17.6, C-2), 80.4 (d, $^1J_{F\text{-}C}$ 176.1, C-1), 79.0 (C-3), 74.3 (CH_2Ph), 49.2 (OCH_3), 49.0 (OCH_3), 30.9 (C-5), 30.0 (d, $^4J_{C\text{-}F}$ 2.9, C-4); δ_F (282 MHz, $CDCl_3$) –233.2 (t, $^2J_{F\text{-}H}$ 47.2); *m/z* (EI) 113 (1), 109 (4), 108 (6), 107 (100), 91 (92); CAUTION: there is a 2 fold excess of unreacted pyrophoric NaH collected in the filter. This reaction was performed on a micro scale only and great care should be taken if the procedure is to be repeated on a longer scale.

2,2-Dimethoxy-1-fluoro-3-nitrobenzoyloxy-hept-6-en 236



Sodium hydride (0.45 mmol, 18 mg) was washed with hexane (1 mL). After stirring for 30 minutes, the hexane was removed by Pasteur pipette, then dry tetrahydrofuran (1.0 mL) and alcohol **234** (0.22mmol, 43 mg) were added. After stirring for 2 h, *p*-nitrobenzoyl chloride (0.47 mmol, 90 mg) was added. After 10 h the mixture was diluted with diethyl ether (3 mL), filtered, concentrated *in vacuo* and purified by column chromatography (20 % ethyl acetate in hexane) to afford ester **236** (47 mg, 66 %, 99 % by GC-MS) as a pale yellow solid; mp 51-54 °C; ν_{max}(solution)/cm^{-1} 2976s (CH_2), 1728w (Ar), 1640w (C=C), 1530vs (NO_2), 1343vs (NO_2), 1075s; R_f (20 % ethyl acetate in hexane) 0.75; (Found: C, 56.3; H, 5.7; N, 4.0; $C_{16}H_{20}O_6NF$ requires: C, 56.3; H, 5.9; N, 4.1 %); δ_H (300 MHz, $CDCl_3$) 8.33-8.19 (4H, m, ArH), 5.80 (1H, ddt, *J* 16.8, 10.2, 6.5, H-6), 5.48 (1H, dd, *J* 10.2, 2.8, H-3), 5.07-4.94 (2H, m, H-7), 4.58 (1H, dd, $^2J_{H\text{-}F}$ 47.2, ^2J 10.7, CH_aH$_b$F), 4.50 (1H, ddd, $^2J_{H\text{-}F}$ 47.2, ^2J 10.7, ^4J 0.7, CH$_a$$H_b$F), 3.37 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 2.19-1.83 (4H, m, H-4, H-5); δ_C (75 MHz, $CDCl_3$) 163.9 (CO), 150.7, 137.2 (C-6), 135.5, 130.9, 123.6, 115.6 (C-7), 99.1 (d, $^2J_{C\text{-}F}$ 18.8, C-2), 79.5 (d, $^1J_{F\text{-}C}$ 177.3, C-1), 73.2 (C-3), 49.3 (OCH_3), 49.0 (OCH_3), 30.4 (d, $^5J_{C\text{-}F}$ 1.1, C-5), 28.8 (d, $^4J_{C\text{-}F}$ 3.9, C-5); δ_F (282 MHz, $CDCl_3$) -230.5 (td, $^2J_{F\text{-}H}$ 47.2, ^4J 1.9); [HRMS (EI, M^+) Found: 341.12752. Calc. For $C_{16}H_{20}O_6NF$ 341.12747]; *m/z* (EI) 308 (1 %, [M-CH_3OH_2]$^+$), 255 (1), 150 (18), 120 (3), 108 (4), 107 (100), 104 (9), 76 (6), 73 (10).

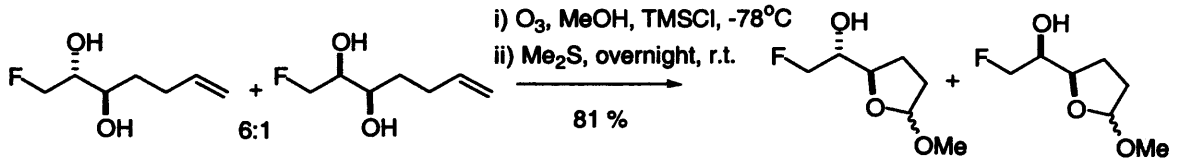
(*2S*,3R)-1-Fluoro-hept-6-en-2,3-diol 237, (*2R*,3R**)-1-fluoro-hept-6-en-2,3-diol 238 and (*1'R*, 2R*, 4R*, 5S**)-5-but-3-enyl-2,4-bis-fluoromethyl-2-(1-hydroxy-pent-4-enyl)-[1,3]dioxolan-4-ol 239**



Hydrochloric acid (0.2 mL) was added to a solution of monofluoroallyl alcohol **227/228** (2.30 mmol, 0.538 g) in THF (10 mL). After stirring overnight (12 h), the mixture was diluted with Et_2O (10 mL), then sodium borohydride (5.54 mmol, 0.214 g) was added in portions. After stirring overnight, the mixture was diluted with water (5 mL), neutralised with concentrated HCl, extracted with AcOEt (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford monofluoro diol **237/238** (0.279 g, 82 %, 99% by GC-MS) as a mixture (6:1 by NMR) of inseparable diastereoisomers as a clear colourless oil; (Found: C, 56.7; H, 9.0; $C_7H_{13}O_2F$ requires: C, 56.7; H, 8.8 %); Major: R_f (50 % ethyl acetate in hexane) 0.57; ν_{max}(neat)/cm^{-1} 3319br (OH), 3224br (OH), 2947w (CH_2), 2909w (CH_2), 1644w (C=C), 1474w, 1106w, 1067s (C-O); δ_H (300 MHz, $CDCl_3$) 5.85 (1H, ddt, *J* 17.1, 10.2, 6.7, H-6), 5.08 (1H, ddd, *J* 17.1, ^2J 3.4, ^4J 1.6, H-7a), 5.01 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.2, H-7_b), 4.61 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.7, *J* 3.3, CH_aH$_b$F), 4.55 (1H, ddd, $^2J_{H\text{-}F}$ 47.7, ^2J 9.7, *J* 6.1, CH$_a$$H_b$F), 3.86-3.72 (2H, m, H-2, H-3), 2.98 (2H, s, OH), 2.37-2.09 (2H, m, H-5), 1.74-1.51 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 136.9 (C-6), 114.3 (C-7), 83.3 (d, $^1J_{C\text{-}F}$ 166.0, C-1), 72.1 (d, $^2J_{C\text{-}F}$ 18.0, C-2), 70.5 (d, $^3J_{C\text{-}F}$ 7.1, C-3), 30.6 (C-4), 29.0 (C-5); δ_F (282 MHz, $CDCl_3$) –233.7 (ddd, $^2J_{F\text{-}H}$

47.7, 47.5, $^3J_{F\text{-}H}$ 20.8, CH_2F); [HRMS (EI, M^+) Found: 148.08995 For $C_7H_{13}FO_2$ 148.08996]; *m/z* (CI) 166 (26 %, $[M+NH_4]^+$), 133 (7), 107 (6), 97 (15), 85 (100), 71 (86), 67 (75), 57 (57), 55 (61); Minor: δ_C (75 MHz, $CDCl_3$) 136.9 (C-6), 114.3 (C-7), 83.7 (d, $^1J_{C\text{-}F}$ 168.5, C-1), 71.7 (d, $^2J_{C\text{-}F}$ 18.7, C-2), 69.3 (d, $^3J_{C\text{-}F}$ 6.4, C-3), 31.5 (C-4), 28.7 (C-5); δ_F (282 MHz, $CDCl_3$) –231.0 (td, $^2J_{F\text{-}H}$ 47.4, $^3J_{F\text{-}H}$ 18.4, CH_2F); and a small fraction (4 mg) containing dioxolane **239** which crystallized as white needles; mp 57-59 °C; [HRMS (+FAB, $[M+1]^+$) Found: 293.15648 For $C_{14}H_{23}F_2O_4$ 293.15644]; (Found: C, 57.6; H, 7.5; $C_{14}H_{22}O_4F_2$ requires: C, 57.5; H, 7.6 %); ; *m/z* (+FAB) 293 (10 %, $[M+1]^+$), 290 (25), 289 (100); The relative stereochemistry and identity of this product were confirmed by XRD analysis; Crystal data: $C_{14}H_{22}O_4F_2$, crystal size 0.26 x 0.20 x 0.14 mm^3, M = 292.32, monoclinic, space group P2(1)/n, unit cell dimensions a = 12.794(3), b = 7.5209(19), c = 15.612(4) Å, α = 90°, β = 95.415(4)°, γ = 90°, V = 1495.5(7) $Å^3$, Z = 4, D_{calc} = 1.298 Mg m^{-3}, $F(000)$ = 624, μ(Mo-Kα) = 0.109 mm^{-1}, T = 150(2) K, 20828 total reflections measured, 2636 independent, (R_{int} = 0.0320) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0363, $\omega R2$ = 0.0859; R indices (all data) $R1$ = 0.0410, $\omega R2$ = 0.0888.

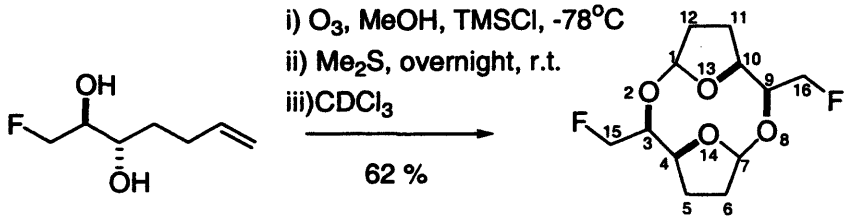
Methyl 6-fluoro-amicetofuranoside 240 and methyl 6-fluoro-rhodinofuranoside 241



Trimethylchlorosilane (0.39 mmol, 50 μl) was added to a stirred solution of diol **237/238** (3.4 mmol, 0.506 g) in methanol (10 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (8.1 mmol, 0.6 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford methyl furanosides **240/241** (455 mg, 50 %, 99 % by GC-MS) as a mixture of inseparable isomers as clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.34; ν_{max}(neat)/cm^{-1} 3397br (OH), 2954w (CH_2), 1460w, 1202w, 1039s (C-O), 978s; δ_H (300 MHz, $CDCl_3$) 5.09 (4H, m, H-1), 4.63-4.30 (8H, m, H-6), 4.26-3.70 (16H, env., H-4, H-5), 3.46 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 2.68-2.29 (4H, br.s, OH), 2.12-1.70 (16H, env., H-2, H-3); δ_C (75 MHz, $CDCl_3$) 105.6 (C-1), 105.5 (C-1), 105.4 (C-1), 105.2 (C-1), 84.5 (d, $^1J_{C\text{-}F}$ 167.8, C-6), 84.3 (d, $^1J_{C\text{-}F}$ 168.6, C-6), 84.4 (d, $^1J_{C\text{-}F}$ 168.4, C-6), 84.5 (d, $^1J_{C\text{-}F}$ 170.5, C-6), 84.2 (d, $^1J_{C\text{-}F}$ 170.7, C-6), 80.3 (d, $^3J_{C\text{-}F}$ 5.8, C-4), 79.7 77.2 (d, $^3J_{C\text{-}F}$ 5.0, C-4), 77.2 (d, $^3J_{C\text{-}F}$ 7.0, C-4), 76.9 77.2 (d, $^3J_{C\text{-}F}$ 6.4, C-4), 72.1 (d, $^2J_{C\text{-}F}$ 19.1, C-5), 72.0 (d, $^2J_{C\text{-}F}$ 19.3, C-5), 71.7 (d, $^2J_{C\text{-}F}$ 18.6, C-5), 71.3 (d, $^2J_{C\text{-}F}$ 20.0, C-5), 55.2 (OCH_3), 55.0 (OCH_3), 54.8 (OCH_3), 54.7 (OCH_3), 32.8, 32.7, 32.2, 31.9, 25.5, 24.5, 24.4, 23.4; δ_F (282 MHz, $CDCl_3$) –229.2 (1F, td, $^2J_{F\text{-}H}$ 47.1, $^3J_{F\text{-}H}$ 13.7), –230.0 (1F, td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 16.8) –233.0 (1F, td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 19.8), –233.2 (1F, td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 20.0); [HRMS (EI, M^+) Found: 164.08484 Calc. For $C_7H_{13}O_3F$ 164.08487]; *m/z* (EI) 164 (1 %,

M^+), 132 (16, $[M-CH_4O]^+$), 115 (4), 101 (76, $[M-C_2H_4OF]^+$), 86 (9), 69 (100, $C_4H_5O^+$); The NMR spectra were too complex to report meaningfully.

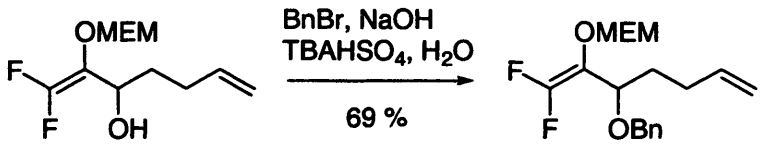
3,9-Bis-fluoromethyl-2,8,13,14-tetraoxa-tricyclo[8.2.1.14,7]tetradecane 242



Trimethylchlorosilane (0.08 mmol, 10 μl) was added to a stirred solution of diol **237/238** (0.42 mmol, 62 mg) in methanol (5 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was taken up in $CHCl_3$ (0.35 mL). After 1h, the solution was concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford dimer **242** (34 mg, 62 %, 99 % by GC-MS) as colourless needles; mp 120-124 °C; R_f (20 % ethyl acetate in hexane) 0.47; (Found: C, 54.6; H, 6.7; $C_{12}H_{18}O_4F_2$ requires: C, 54.5; H, 6.9 %); ν_{max}(neat)/cm^{-1} 2959w (CH_2), 2910w (CH_2), 1455w, 1192s, 1095s, 1069s, 1041s, 985s; δ_H (300 MHz, $CDCl_3$) 5.08 (2H, d, *J* 4.3, H-1, H-7), 4.35-4.02 (8H, m, H-3, H-4, H-9, H-10, H-15, H-16), 2.26-1.46 (8H, env., H-5, H-6, H-11, H-12); δ_C (75 MHz, $CDCl_3$) 103.2 (C-1), 83.4 (d, $^1J_{C\text{-}F}$ 172.1, C-6), 79.3 (d, $^3J_{C\text{-}F}$ 6.4, C-4), 74.7 (d, $^2J_{C\text{-}F}$ 18.0, C-5), 33.6, 21.9; δ_F (282 MHz, $CDCl_3$) –228.7 (ddd, $^2J_{F\text{-}H}$ 47.1, 46.9, $^2J_{F\text{-}H}$ 17.8); [HRMS (EI, M^+) Found: 264.11740 Calc. For $C_{12}H_{18}O_4F_2$ 264.11732]; *m/z* (EI) 264 (1

%, M^+), 221 (17), 201 (31), 174 (16), 158 (35), 132 (29), 115 (22), 111 (10), 94 (16), 83 (30), 69 (100, $C_4H_5O^+$); The stereochemistry and identity of this product were confirmed by XRD analysis; Crystal data: $C_{12}H_{18}O_4F_2$, crystal size 0.12 x 0.10 x 0.09 mm^3, M = 264.26, monoclinic, space group P2(1)/n, unit cell dimensions a = 12.067(3), b = 7.970(2), c = 12.449(3) Å, $\alpha = 90°$, $\beta = 99.192(5)°$, $\gamma = 90°$, V = 1181.9(6) $Å^3$, Z = 4, D_{calc} = 1.485 Mg m^{-3}, $F(000)$ = 560, μ(Mo-Kα) = 0.129 mm^{-1}, T = 150(2) K, 7048 total reflections measured, 1703 independent, (R_{int} = 0.0397) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0301, $\omega R2$ = 0.0712; R indices (all data) $R1$ = 0.0392, $\omega R2$ = 0.0746.

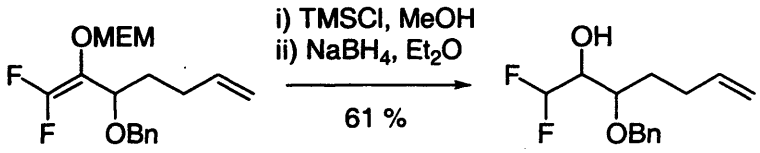
3-Benzyloxy-1,1-difluoro-2-(2-methoxy-ethoxy)methoxy-hept-1,6-diene 243



A mixture of difluoroallylic alcohol **132** (5.0 mmol, 1.26 g), benzyl bromide (7.3 mmol, 0.88 mL), 50 % aqueous sodium hydroxide (37 mmol, 1.49 g), and tetrabutylammonium hydrogen sulfate (0.26 mmol, 90 mg) was stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a clear oil which was purified by Biotage column chromatography (gradient 0 % to 20 % ethyl acetate in hexane) to afford benzyl ether **243** (1.19 g, 69 %, 99 % by GC-MS) as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.59; ν_{max}(neat)/cm^{-1} 2881w (CH_2), 1748s, 1641w (C=C), 1454w, 1228s, 1091s (C-O), 1069s (C-O); δ_H (300 MHz, $CDCl_3$) 7.35-7.24 (5H, m, Ph),

5.76 (1H, ddt, *J* 16.9, 10.2, 6.6, H-6), 5.08 (1H, ^2J 6.1, OC*H*$_a$H$_b$O), 4.96 (1H, ^2J 6.1, OCH$_a$*H*$_b$O), 5.02-4.92 (2H, m, H-7), 4.64 (1H, ^2J 11.7, C*H*$_a$H$_b$Ph), 4.33 (1H, ^2J 11.7, CH$_a$*H*$_b$Ph), 4.06 (1H, dddd, *J* 10.0, $^4J_{H\text{-}F}$ 3.7, *J* 3.1, $^4J_{H\text{-}F}$ 2.1, H-3), 3.90 (1H, ddd, ^2J 10.9, *J* 5.3, 3.7, OCH$_2$C*H*$_a$H$_b$OMe), 3.78 (1H, ddd, ^2J 10.9, *J* 5.3, 3.7, OCH$_2$CH$_a$*H*$_b$OMe), 3.56-3.52 (2H, m, O*CH*$_2$CH$_2$OMe), 3.37 (3H, s, OCH$_3$), 2.19-2.01 (2H, m, H-5), 1.97-1.67 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 156.1 (dd, $^1J_{C\text{-}F}$ 294.2, 284.8, C-1), 137.9, 137.7 (C-6), 128.4, 127.9, 127.7, 115.1 (C-7), 112.4 (dd, $^2J_{C\text{-}F}$ 36.5, 9.9, C-2), 97.1 (OCH$_2$O), 73.9 (t, $^3J_{C\text{-}F}$ 3.2, C-3), 71.6 (OCH$_2$*CH*$_2$OMe), 70.4 (CH$_2$Ph), 68.3 (O*CH*$_2$CH$_2$OMe), 59.0 (OCH$_3$), 31.2 (t, $^4J_{C\text{-}F}$ 2.0, C-4), 29.6 (C-5); δ_F (282 MHz, $CDCl_3$) –97.5 (1F, d, $^2J_{F\text{-}F}$ 63.1, $^4J_{F\text{-}H}$ 2.1), -109.2 (1F, d, $^2J_{F\text{-}F}$ 63.1, $^4J_{F\text{-}H}$ 3.7); *m/z* (EI) 112 (2), 105 (3), 91 (85, $C_7H_7^+$), 59 (100); Satisfactory HRMS (CI, EI, ES) could not be obtained for this compound.

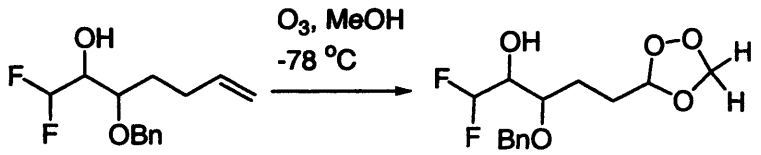
3-Benzyloxy-1,1-difluoro-hept-6-en-2-ol 244



Trimethylchlorosilane (4.73 mmol, 0.6 mL) was added to a solution of difluoroallylic benzyl ether **243** (4.7 mmol, 1.60 g) in MeOH (5 mL). After stirring overnight (12 h), the mixture was concentrated *in vacuo*, diluted with Et_2O (5 mL), then sodium borohydride (9.2 mmol, 0.35 g) was added in portions. After stirring overnight, the mixture was diluted with water (5 mL), neutralised with concentrated HCl, and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to

afford difluoro alcohol **244** (0.732 g, 61 %, 99% by GC-MS) as a mixture (1.2:1 by GC-MS) of inseparable diastereoisomers as a clear colourless oil; R_f (10 % ethyl acetate in hexane) 0.25; ν_{max}(neat)/cm^{-1} 3434br (OH), 2934w (CH_2), 1641w (C=C), 1455w, 1056s (C-O); Major: δ_H (300 MHz, $CDCl_3$) 7.42-7.29 (5H, m, Ph), 5.90-5.77 (1H, m, H-6), 5.76 (1H, ddd, $^2J_{H\text{-}F}$ 56.5, 55.8, *J* 5.2, H-1), 5.11-4.98 (2H, m, H-7), 4.66 (1H, d, ^2J 11.2, C*H*$_a$H$_b$Ph), 4.52 (1H, d, ^2J 11.2, CH$_a$*H*$_b$Ph), 3.74-3.61 (2H, m, H-2, H-3), 2.76 (1H, d, *J* 8.5, OH), 2.33-1.67 (4H, m, H-4, H-5); δ_F (282 MHz, $CDCl_3$) –128.5 (1F, dddd, $^2J_{F\text{-}F}$ 290.0, $^2J_{F\text{-}H}$ 55.8, $^3J_{F\text{-}H}$ 9.4, $^4J_{F\text{-}H}$ 1.5, CH*F*$_a$F$_b$), -129.4 (1F, ddd, $^2J_{F\text{-}F}$ 290.0, $^2J_{F\text{-}H}$ 56.5, $^3J_{F\text{-}H}$ 10.9, CHF$_a$*F*$_b$); Minor: δ_H (300 MHz, $CDCl_3$) 7.42-7.29 (5H, m, Ph), 5.90 (1H, ddd, $^2J_{H\text{-}F}$ 56.2, 55.0, *J* 3.7, H-1), 5.90-5.77 (1H, m, H-6), 5.11-4.98 (2H, m, H-7), 4.61 (1H, d, ^2J 11.3, C*H*$_a$H$_b$Ph), 4.55 (1H, d, ^2J 11.3, CH$_a$*H*$_b$Ph), 3.86 (1H, dddd, $^3J_{H\text{-}F}$ 17.0, 6.2, *J* 6.0, 3.7, H-2), 3.74-3.61 (1H, m, H-3), 2.56 (1H, d, *J* 5.2, OH), 2.33-1.67 (4H, m, H-4, H-5); δ_F (282 MHz, $CDCl_3$) -129.1 (1F, ddd, $^2J_{F\text{-}F}$ 289.8, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 6.2, CH*F*$_a$F$_b$), -132.7 (1F, ddd, $^2J_{F\text{-}F}$ 289.8, $^2J_{F\text{-}H}$ 56.2, $^3J_{F\text{-}H}$ 17.0, CHF$_a$*F*$_b$); both diastereoisomers: δ_C (75 MHz, $CDCl_3$) 138.1 (C-6, diastereoisomer b), 137.7, 137.6 (C-6, diastereoisomer a), 128.6, 128.1, 128.1, 128.0, 127.9, 115.5 (t, $^1J_{C\text{-}F}$ 244.1, C-1, diastereoisomer a), 115.5 (C-7, diastereoisomer a), 115.2 (C-7, diastereoisomer b), 115.1 (dd, $^1J_{C\text{-}F}$ 242.9, 241.1, C-1, diastereoisomer b), 77.4 (dd, $^3J_{C\text{-}F}$ 3.9, 3.6, C-3), 75.7 (dd, $^3J_{C\text{-}F}$ 4.8, 2.7, C-3), 72.5 (CH_2Ph), 72.4 (CH_2Ph), 72.0 (dd, $^2J_{C\text{-}F}$ 24.9, 23.2, C-2, diastereoisomer a), 71.7 (dd, $^2J_{C\text{-}F}$ 23.0, 20.6, C-2, diastereoisomer b), 29.6, 29.4, 29.0, 28.9; [HRMS (EI, M$^+$) Found: 256.12753 Calc. For $C_{14}H_{18}F_2O_2$ 256.12749]; *m/z* (EI) 256 (1 %, M$^+$), 175 (12), 157 (8), 107 (8), 91 (100, $C_7H_7^+$).

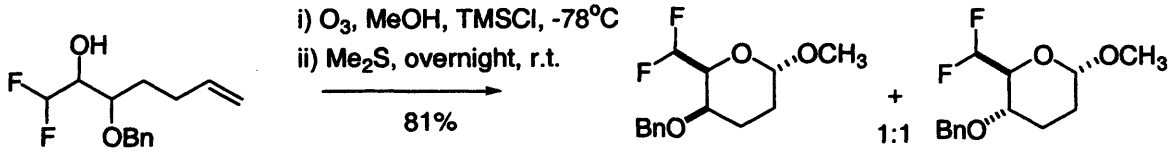
3-Benzyloxy-1,1-difluoro-5-[1,2,4]trioxolan-3-yl-pentan-2-ol 245



Dry Silica gel (1.41 g) was added to a solution of difluoro alcohol **244** (0.60 mmol, 155 mg) in dry dichloromethane (5 mL). The solvent was evaporated in vacuo and the silica gel mixture was dried under vacuum for 1 h at room temperature. The mixture was cooled to –78 °C and a stream of dry O_3 was carefully passed through the silica gel in a U-shaped tube with frit. After 1 hour, the mixture was purged with O_2 and N_2, eluted from the silica with methanol (50 mL), and quenched with dimethyl sulphide (0.5 mL). After concentration, purification by silica gel column chromatography (gradient 0 to 20 % ethyl acetate in hexane afforded ozonide **245** (56 mg, 30 %, 80 % by GC-MS) as a mixture of four racemic diastereoisomers as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.36; δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (10H, m, Ph), 5.90 (1H, ddd, $^2J_{H\text{-}F}$ 56.0, 54.9, *J* 3.4, H-1), 5.76 (1H, ddd, $^2J_{H\text{-}F}$ 56.1, 56.0, *J* 4.9, H-1), 5.20 (1H, s, H-6), 5.19 (1H, s H-6), 5.18 (1H, s, OCH_2O), 5.17 (1H, s, OCH_2O), 5.07 (1H, s, OCH_2O), 5.05 (1H, s, OCH_2O), 4.68-4.42 (4H, m, CH_2Ph), 3.91-3.58 (4H, m, H-2, H-3), 2.55 (1H, br.s, OH), 2.22 (1H, br.s, OH), 1.98-1.55 (8H, m, H-4, H-5); δ_C (100 MHz, $CDCl_3$) 137.4, 137.3, 128.60, 128.59, 128.21, 128.11, 128.08, 127,97, 127,95, 127,80, 115.3 (t, $^1J_{C\text{-}F}$ 244.2, C-1), 114.9 (dd, $^1J_{C\text{-}F}$ 243.7, 240.5, C-1), 103.4, 103.2, 94,14, 94,11, 77.24, 76.96 (t, $^3J_{C\text{-}F}$ 3.8, C-3), 75.4 (t, $^3J_{C\text{-}F}$ 3.4, C-3), 72.7 (CH_2Ph), 72.3 (CH_2Ph), 72.2 (t, $^2J_{C\text{-}F}$ 24.5, C-2), 71.5 (t, $^2J_{C\text{-}F}$ 22.5, C-2), 27.0, 26.3, 24.8, 23.5; δ_F (376 MHz, $CDCl_3$) – 128.86 (1F, dd, $^2J_{F\text{-}F}$ 290.52, $^2J_{F\text{-}H}$ 55.8, $^3J_{F\text{-}H}$ 10.1, CHF_aF_b, isomer a), -128.88 (1F, dd, $^2J_{F\text{-}F}$ 290.50, $^2J_{F\text{-}H}$ 55.6, $^3J_{F\text{-}H}$ 10.8, CHF_aF_b, isomer b), -129.32 (1F, dd, $^2J_{F\text{-}F}$ 290.50, $^2J_{F\text{-}H}$ 56.1, $^3J_{F\text{-}H}$ 17.3, CHF_aF_b, isomer b), -129.35 (1F, dd, $^2J_{F\text{-}F}$ 290.52, $^2J_{F\text{-}H}$ 56.2, $^3J_{F\text{-}H}$ 14.8, CHF_aF_b, isomer a), -129.86 (1F, dd, $^2J_{F\text{-}F}$ 289.46, $^2J_{F\text{-}H}$ 54.9, $^3J_{F\text{-}H}$ 4.8, CHF_aF_b, isomer c), -129.72 (1F, dd, $^2J_{F\text{-}F}$ 289.45, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 5.8, CHF_aF_b, isomer d), -

133.12 (1F, dd, $^2J_{F\text{-}F}$ 289.46, $^2J_{F\text{-}H}$ 56.0, $^3J_{F\text{-}H}$ 17.5, CHF_aF_b, isomer c),-133.27 (1F, dd, $^2J_{F\text{-}F}$ 289.45, $^2J_{F\text{-}H}$ 56.1, $^3J_{F\text{-}H}$ 17.3, CHF_aF_b, isomer d); [HRMS (EI, M^+) Found: 304.11226 Calc. For $C_{14}H_{18}F_2O_5$ 304.11223]; *m/z* (EI) 304 (2 %, M^+), 240 (35), 191 (3), 151 (39), 105 (55), 85 (99), 51 (100).

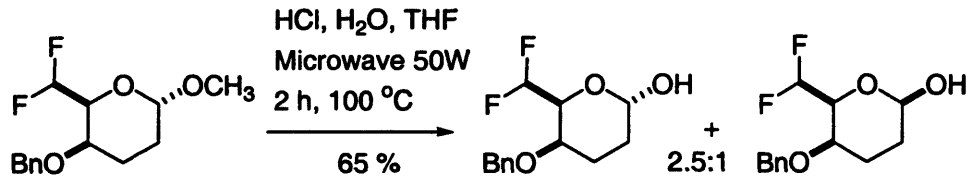
(±)-α-Methyl 5-*O*-benzyl-6,6-difluoro-rhodinoside 248 and (±)-α-methyl 5-*O*-benzyl-6,6-difluoro-amicetoside 249



Trimethylchlorosilane (0.79 mmol, 100 μL) was added to a stirred solution of alcohol **244** (3.99 mmol, 1.02 g) in methanol (50 mL). The solution was cooled to –78 °C and a stream of dry O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (68 mmol, 5.0 mL) was added. The mixture was stirred overnight at room temperature (12 h), then solid NaOH (0.2 g, 5 mmol) was added. After 1 hour the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of diastereoisomers (1:1) which was purified by Biotage column chromatography (gradient 5% to 10% ethyl acetate in hexane) to afford α-methyl rhodinoside **248** (396 mg, 37 %, 99% by GC-MS) and α-methyl amicetoside **249** (352 mg, 32 %, 99 % by GC-MS) as clear colourless oils; Rhodinoside : R_f (20 % ethyl acetate in hexane) 0.59; ν_{max}(neat)/cm^{-1} 2939w (CH_2), 2902w (CH_2), 1454w (CH_3), 1337w, 1219w (C-O-C), 1131s (C-O), 1076s (C-O); δ_H (400 MHz, $CDCl_3$) 7.38-7.27 (5H, m, Ph), 5.93 (1H, ddd, $^2J_{H\text{-}F}$ 58.1, 55.0, *J* 6.8, H-6), 4.80 (1H, d, *J* 3.2, H-1), 4.63

(1H, d, ^2J 11.7, CH_aH$_b$Ph), 4.44 (1H, d, ^2J 11.7, CH$_a$$H_b$Ph), 3.85 (1H, dddd, $^3J_{H\text{-}F}$ 11.4, J 6.8, $^3J_{H\text{-}F}$ 4.1, J 1.8, H-5), 3.71 (1H, br.s, H-4), 3.39 (3H, s, OCH_3), 2.01 (1H, ddt, ^2J 14.0, J 14.0, 4.6, H-2$_a$), 1.98-1.91 (1H, m, H-3$_a$), 1.84 (1H, ddd, ^2J 14.0, J 14.0, 4.2, 2.5, H-3$_b$), 1.60-1.53 (1H, m, H-2$_b$); δ_C (100 MHz, $CDCl_3$) 137.9, 128.4, 127.8, 128.8, 114.9 (dd, $^1J_{C\text{-}F}$ 243.3, 237.9, C-6), 97.9 (C-1), 71.0 (CH_2Ph), 70.2 (dd, $^2J_{C\text{-}F}$ 30.5, 22.9, C-5), 69.8 (dd, $^1J_{C\text{-}F}$ 6.9, 2.0, C-4), 54.8 (OCH_3), 23.7 (C-2), 20.0 (C-3); δ_F (376 MHz, $CDCl_3$) –130.5 (ddd, $^2J_{F\text{-}F}$ 295.4, $^2J_{F\text{-}H}$ 58.1, $^3J_{F\text{-}H}$ 11.4, CHF_aF$_b$), –131.4 (dddd, $^2J_{F\text{-}F}$ 295.4, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 4.1, $^4J_{F\text{-}H}$ 1.8, CHF$_a$$F_b$); [HRMS (EI, M^+) Found: 272.12241 Calc. For $C_{14}H_{18}F_2O_3$ 272.12240]; *m/z* (EI) 272 (1 %, M^+), 240 (4, $[M\text{-}MeOH]^+$), 191 (3), 160 (3), 134 (4), 125 (4), 107 (17), 101 (24), 91 (100, $C_7H_7^+$); Amicetoside : R_f (20 % ethyl acetate in hexane) 0.53; ν_{max}(neat)/cm^{-1} 2939w (CH_2), 1455s (CH_3), 1372w, 1224s (C-O-C), 1127s (C-O), 1050s (C-O); δ_H (400 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 6.06 (1H, dd, $^2J_{H\text{-}F}$ 54.6, 53.8, H-6), 4.76 (1H, d, J 3.0, H-1), 4.64 (1H, d, ^2J 11.5, CH_aH$_b$Ph), 4.46 (1H, d, ^2J 11.5, CH$_a$$H_b$Ph), 3.84 (1H, ddd, $^3J_{H\text{-}F}$ 20.7, J 9.8, $^3J_{H\text{-}F}$ 7.3, H-5), 3.53 (1H, ddd, J 10.1, 9.8, 4.5, H-4), 3.37 (3H, s, OCH_3), 2.10-2.03 (1H, m, H-3$_a$), 1.88-1.64 (3H, m, H-2, H-3$_b$); δ_C (100 MHz, $CDCl_3$) 137.8, 128.5, 127.9, 127.7, 114.0 (dd, $^1J_{C\text{-}F}$ 243.5, 242.5, C-6), 102.1 (C-1), 72.0 (dd, $^3J_{C\text{-}F}$ 6.3, 1.8, C-4), 70.6 (CH_2Ph), 70.0 (t, $^2J_{C\text{-}F}$ 18.9, C-5), 54.7 (OCH_3), 28.3 (C-2), 23.7 (C-3); δ_F (376 MHz, $CDCl_3$) –133.5 (dddd, $^2J_{F\text{-}F}$ 283.2, $^2J_{F\text{-}H}$ 53.8, $^3J_{F\text{-}H}$ 7.3, $^4J_{F\text{-}H}$ 1.7, CHF_aF$_b$), -136.1 (ddd, $^2J_{F\text{-}F}$ 283.2, $^2J_{F\text{-}H}$ 54.6, $^3J_{F\text{-}H}$ 20.7, CHF$_a$$F_b$); [HRMS (EI, M^+) Found: 272.12236 Calc. For $C_{14}H_{18}F_2O_3$ 272.12240]; *m/z* (EI) 272 (1 %, M^+), 240 (4, $[M\text{-}MeOH]^+$), 191 (3), 160 (5), 134 (4), 125 (3), 107 (16), 101 (17), 91 (100, $C_7H_7^+$); and a mixed fraction containing both diastereoisomers (132 mg, 12 %).

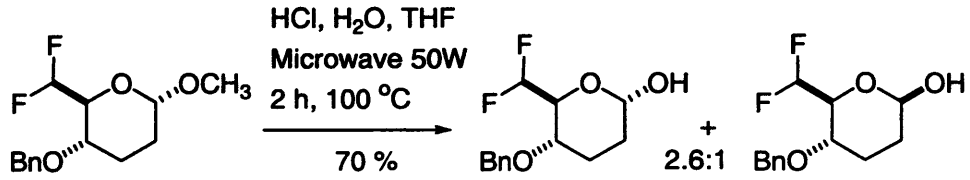
(±)-α-5-*O*-benzyl-6,6-difluoro-rhodinose 250 and (±)-β-5-*O*-benzyl-6,6-difluoro-rhodinose 251



Hydrochloric acid (20 μL) was added to a solution of rhodinoside **248** (0.46 mmol, 126 mg) in THF (4 mL) containing water (250 μL). The solution was stirred and heated (microwave 50W) to 100 °C for 2 h. The tube was cooled, opened and the contents diluted with Et_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford rhodinose **250/251** (78 mg, 65 %, 99% by GC-MS) as a 2.5:1 (by NMR) mixture of inseparable α and β anomers as a clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.51; ν_{max}(neat)/cm^{-1} 3411s (OH), 2954w (CH_2), 2913w (CH_2), 1150s, 1077s, 1046s, 1018s; α-anomer: δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5H, m, Ph), 5.94 (1H, ddd, $^2J_{H\text{-}F}$ 58.2, 54.8, *J* 6.8, H-6), 5.37 (1H, s, H-1), 4.63 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.44 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 4.12 (1H, dddd, $^3J_{H\text{-}F}$ 11.2, *J* 6.4, $^3J_{H\text{-}F}$ 4.2, *J* 1.7, H-5), 3.81-3.09 (2H, m, H-4, OH), 2.22-1.46 (4H, env., H-2, H-3); β-anomer: δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5H, m, Ph), 5.98 (1H, ddd, $^2J_{H\text{-}F}$ 57.5, 55.0, *J* 6.6, H-6), 4.80 (1H, dd, *J* 9.3, 2.4, H-1), 4.61 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.44 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 3.81-3.09 (3H, m, H-4, H-5, OH), 2.22-1.46 (4H, env, H-2, H-3); δ_C both anomers (100 MHz, $CDCl_3$) 137.8, 137.7, 128.4, 127.9, 127.8, 114.9 (dd, $^1J_{C\text{-}F}$ 243.1, 238.2, C-6, α-anomer), 114.2 (dd, $^1J_{C\text{-}F}$ 243.0, 239.1, C-6, β-anomer), 96.3 (C-1, β-anomer), 91.4 (C-1, α-anomer), 77.3 (dd, $^2J_{C\text{-}F}$ 28.8, 24.2, C-5, β-anomer), 71.0 (CH_2Ph, β-anomer), 70.9 (CH_2Ph, α-anomer), 70.2 (dd, $^2J_{C\text{-}F}$ 30.7, 22.6, C-5, α-anomer), 69.7 (dd, $^3J_{C\text{-}F}$ 6.9, 1.9, C-4, α-anomer), 68.8 (dd, $^3J_{C\text{-}F}$ 6.1, 2.5, C-4, β-anomer), 27.0 (C-2, β-anomer), 24.3 (C-3, β-anomer), 23.9 (C-3, α-

anomer), 19.2 (C-2, α-anomer); δ_F (376 MHz, $CDCl_3$) –130.2 (ddd, $^2J_{F\text{-}F}$ 296.3, $^2J_{F\text{-}H}$ 57.5, $^3J_{F\text{-}H}$ 9.8, CHF_aF_b, α-anomer), -130.5 (ddd, $^2J_{F\text{-}F}$ 296.2, $^2J_{F\text{-}H}$ 58.2, $^3J_{F\text{-}H}$ 11.2, CHF_aF_b, β-anomer), -130.8 (dddd, $^2J_{F\text{-}F}$ 296.3, $^2J_{F\text{-}H}$ 55.0, $^3J_{F\text{-}H}$ 4.9, $^4J_{F\text{-}H}$ 1.8, CHF_aF_b, α-anomer), -131.5 (dddd, $^2J_{F\text{-}F}$ 296.2, $^2J_{F\text{-}H}$ 54.8, $^3J_{F\text{-}H}$ 4.2, $^4J_{F\text{-}H}$ 2.0, CHF_aF_b, β-anomer); [HRMS (EI, M^+) Found: 258.10676 Calc. For $C_{13}H_{16}F_2O_3$ 258.10675]; *m/z* (EI) 258 (1 %, M^+), 240 (1), 177 (3), 160 (3), 134 (3), 107 (23), 91 (100, $C_7H_7^+$).

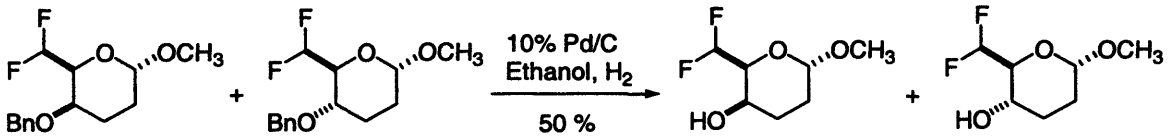
(±)-α-5-*O*-benzyl-6,6-difluoro-amicetose 252 and (±)-β-5-*O*-benzyl-6,6-difluoro-amicetose 253



Hydrochloric acid (20 μL) was added to a solution of amicetoside **249** (0.11 mmol, 30 mg) in THF (4 mL) containing water (250 μL). The solution was stirred and heated (microwave 50W) to 100 °C for 2 h. The tube was cooled, opened and the contents diluted with Et_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford amicetose **252/253** (20 mg, 70 %, 95% by GC-MS) as a 2.6:1 (by NMR) mixture of inseparable α and β anomers as a clear colourless oil, from which one anomer crystallized as white needles; mp 62-65 °C; R_f (35 % ethyl acetate in hexane) 0.57; (Found: C, 60.3; H, 6.3; $C_{13}H_{16}O_3F_2$ requires: C, 60.5; H, 6.2 %); ν_{max}(neat)/cm^{-1} 3410br (OH), 2954w (CH_2), 2873w (CH_2), 1400w, 1353w, 1221w, 1150s (C-O), 1079s (C-O), 1045s (C-O); α-anomer: δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5H, m, Ph), 6.06 (1H, ddd, $^2J_{H\text{-}F}$ 54.5, 54.0, *J* 1.1, H-6), 5.35 (1H, d, *J* 2.8, H-1), 4.66 (1H, d, ^2J 11.4, CH_aH_bPh), 4.48 (1H, d, ^2J 11.4,

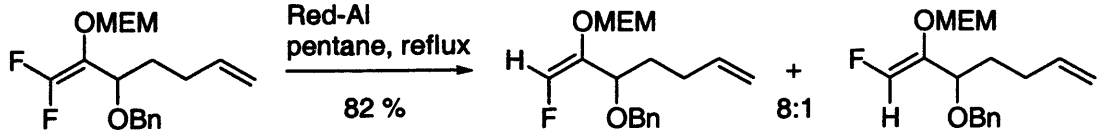
CH_aH_bPh), 4.11 (1H, dddd, $^3J_{F\text{-}H}$ 20.5, 7.4, J 9.9, 1.8, H-5$_a$), 3.75-3.47 (1H, m, H-4), 2.71 (1H, br.s, OH), 2.30-1.44 (4H, m, H-2, H-3); β-anomer: δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5H, m, Ph), 6.04 (1H, ddd, $^1J_{C\text{-}F}$ 54.5, 54.4, J 2.0, H-6), 4.92 (1H, d, J 7.3, H-1), 4.62 (1H, d, ^2J 11.4, CH_aH_bPh), 4.50 (1H, d, ^2J 11.4, CH_aH_bPh), 3.75-3.47 (2H, m, H-4, H-5), 3.08 (1H, br.s, OH), 2.30-1.44 (4H, env, H-2, H-3); δ_C both anomers (100 MHz, $CDCl_3$) 137.8, 137.6, 128.5, 128.5, 128.0, 127.9, 127.8, 127.7, 114.1 (dd, $^1J_{C\text{-}F}$ 243.8, 242.5, C-6 both anomers), 95.8 (C-1, β-anomer), 91.0 (C-1, α-anomer), 72.2 (dd, $^3J_{C\text{-}F}$ 6.1, 1.93, C-4, both anomers), 71.2 (CH_2Ph, β-anomer), 70.7 (CH_2Ph, α-anomer), 70.3 (t, $^1J_{C\text{-}F}$ 18.8, C-5, both anomers), 30.0 (C-2, β-anomer), 28.3 (C-2, α-anomer), 26.1 (C-3, β-anomer), 22.9 (C-3, α-anomer); δ_F (376 MHz, $CDCl_3$) –131.5 (dddd, $^2J_{F\text{-}F}$ 286.3, $^2J_{F\text{-}H}$ 54.5, $^3J_{F\text{-}H}$ 7.7, $^4J_{F\text{-}H}$ 1.5, CHF_aF_b, β-anomer), -133.3 (dddd, $^2J_{F\text{-}F}$ 283.1, $^2J_{F\text{-}H}$ 54.0, $^3J_{F\text{-}H}$ 7.4, $^4J_{F\text{-}H}$ 1.8, CHF_aF_b, α-anomer), -133.7 (ddd, $^2J_{F\text{-}F}$ 286.3, $^2J_{F\text{-}H}$ 54.4, $^3J_{F\text{-}H}$ 17.4, CHF_aF_b, β-anomer), -135.8 (ddd, $^2J_{F\text{-}F}$ 283.1, $^2J_{F\text{-}H}$ 54.5, $^3J_{F\text{-}H}$ 20.5, CHF_aF_b, α-anomer); [HRMS (EI, M^+) Found: 258.10671 Calc. For $C_{13}H_{16}F_2O_3$ 258.10675]; *m/z* (EI) 258 (1 %, M^+), 240 (1), 177 (3), 154 (1), 134 (4), 107 (27), 91 (100, $C_7H_7^+$); The stereochemistry and identity of the crystalline anomer were confirmed by XRD analysis; Crystal data: $C_{13}H_{16}O_3F_2$, crystal size 0.36 x 0.11 x 0.04 mm^3, M = 258.26, monoclinic, space group P2(1)/n, unit cell dimensions a = 20.750(3), b = 4.6956(8), c = 26.025(4) Å, α = 90°, β = 98.453(3)°, γ = 90°, V = 2508.1(7) Å^3, Z = 8, D_{calc} = 1.368 Mg m^{-3}, F(000) = 1088, μ(Mo-Kα) = 0.115 mm^{-1}, T = 150(2) K, 17038 total reflections measured, 4424 independent, (R_{int} = 0.0885) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0471, $\omega R2$ = 0.0880; R indices (all data) $R1$ = 0.0850, $\omega R2$ = 0.0999.

α-Methyl 6,6-difluoro-rhodinoside 254 and α-methyl 6,6-difluoro-amicetoside 255



A flask containing a stirred solution of benzyl rhodinoside **248** and amicetoside **249** (0.38 mmol, 104 mg of a 6.4:1 mixture of diastereoisomers) in ethanol (4 mL) was evacuated and flushed with hydrogen (3 times), then 10 % Palladium on carbon (40 mg) was added. Then the mixture was evacuated and flushed with hydrogen (3 times) again, left under an atmosphere of hydrogen at room temperature and atmospheric pressure for 48 h. The mixture was filtered through Celite; the filter bed was washed with EtOH (3 x 2 mL), and the combined filtrates were concentrated *in vacuo* to afford methyl pyranosides **254/255** (35 mg, 50 %, 99 % by GC-MS) as a mixture of inseparable diastereoisomers (6.4:1 by NMR) as a clear colourless oil; both diastereoisomers: R_f (20 % ethyl acetate in hexane) 0.31; ν_{max}(neat)/cm^{-1} 3366 (OH), 2953 (CH_2), 1460w, 1317w, 1117w, 1050s, 978s; δ_H (300 MHz, $CDCl_3$) 5.86 (ddd, $^2J_{H\text{-}F}$ 56.6, 55.4, J 6.3, H-6), 4.81 (1H, s, H-1), 4.00 (1H, s, H-4), 3.91-3.82 (1H, m, H-5), 3.39 (3H, s, OCH_3), 2.11-1.53 (5H, m, H-2, H-3, OH); δ_C (75 MHz, $CDCl_3$) 114.9 (dd, $^1J_{C\text{-}F}$ 241.7, 240.1, C-6), 98.0 (C-1), 69.9 (dd, $^2J_{C\text{-}F}$ 27.6, 24.6, C-5), 63.1 (dd, $^3J_{C\text{-}F}$ 5.0, 3.6, C-4), 54.9 (OCH_3), 25.0 (C-3), 23.3 (C-2); δ_F (282 MHz, $CDCl_3$) –130.5 (1F, ddd, $^2J_{F\text{-}F}$ 296.6, $^2J_{F\text{-}H}$ 56.6, $^3J_{F\text{-}H}$ 9.9), -131.0 (1F, ddd, $^2J_{F\text{-}F}$ 296.6, $^2J_{F\text{-}H}$ 55.4, $^3J_{F\text{-}H}$ 7.4); amicetoside (minor): δ_F (282 MHz, $CDCl_3$) –130.6 (1F, ddd, $^2J_{F\text{-}F}$ 294.8, $^2J_{F\text{-}H}$ 55.2, $^3J_{F\text{-}H}$ 10.9), -131.7 (1F, dd, $^2J_{F\text{-}F}$ 294.8, $^2J_{F\text{-}H}$ 55.2); both diastereoisomers: [HRMS (EI, M^+) Found: 182.07542 Calc. For $C_7H_{12}O_3F_2$ 182.07545]; *m/z* (EI) 182 (2 %, M^+), 151 (30, $[M\text{-}CH_3O]^+$), 133 (16), 125 (43), 101 (51), 88 (100).

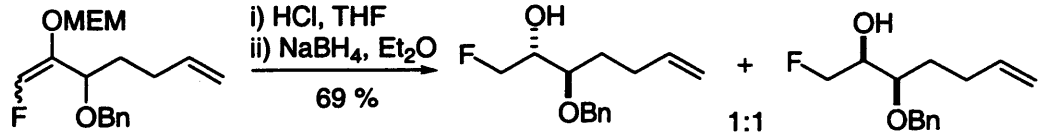
_E_-3-Benzyloxy-1-fluoro-2-(2-methoxy-ethoxy)methoxy-hept-1,6-diene 256 and _Z_-3-benzyloxy-1-fluoro-2-(2-methoxy-ethoxy)methoxy-hept-1,6-diene 257



A solution of difluorobenzyl ether **243** (5.85 mmol, 2.0 g) and sodium *bis*(2-methoxy-ethoxy)aluminium hydride (22.7 mmol, 6.5 mL of a 3.5 M solution in toluene) in dry pentane (20 mL) was heated to reflux over 3 h. The reaction mixture was cooled and poured into a beaker, then ice (5 g) was added carefully. The resultant white suspension was neutralised with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil as a (8:1 by NMR) mixture of isomers which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford major allylic alcohol **256** (1.38 g, 73 %, 99% by GC-MS) and minor allylic alcohol **257** (170 mg, 9 %, 40 % by GC-MS) as clear colourless oils; Major : R_f (35 % ethyl acetate in hexane) 0.78; ν_{max}(neat)/cm^{-1} 2931w (CH_2), 2879 (CH_2), 1641w (C=C), 1454w, 1097s (C-O), 1069s (C-O); δ_H (400 MHz, $CDCl_3$) 7.36-7.24 (5H, m, Ph), 7.10 (1H, d, $^2J_{H\text{-}F}$ 80.8, H-1), 5.79 (1H, ddt, *J* 16.9, 10.2, 6.6, H-6), 4.99 (1H, ddd, *J* 16.9, 3.4, 1.6, H-7_a), 4.97-4.92 (3H, m, OCH_2O, H-7_b), 4.58 (1H, d, ^2J 11.8, C$H_a$$H_b$Ph), 4.41 (1H, td, *J* 7.4, $^4J_{H\text{-}F}$ 3.5, H-3), 4.38 (1H, d, ^2J 11.8, C$H_a$$H_b$Ph), 3.76 (1H, dt, ^2J 11.0, *J* 4.7, OC$H_a$$H_b$$CH_2$OMe), 3.72 (1H, dt, ^2J 11.0, *J* 4.7, OC$H_a$$H_b$$CH_2$OMe), 3.55 (2H, t, *J* 4.7, CH_2OMe), 3.39 (OMe), 2.21-2.01 (2H, m, H-5), 1.95-1.86 (1H, m, H-4_a), 1.71 (1H, ddt, ^2J 13.3, *J* 9.1, 6.5, H-4_b); δ_C (75 MHz, $CDCl_3$) 143.7 (d, $^2J_{C\text{-}F}$ 25.1, C-2), 139.6 (d, $^1J_{C\text{-}F}$ 20.6, C-1), 138.3, 137.9 (C-6), 128.3, 128.0, 127.6, 115.0 (C-7), 94.8 (OCH_2O), 71.8 (d, $^3J_{C\text{-}F}$ 1.3, C-3), 71.5 (OCH_2CH_2OMe), 70.6 (CH_2Ph), 67.5 (OCH_2CH_2OMe), 59.0 (OCH_3), 31.1 (d, $^4J_{C\text{-}F}$ 2.4, C-4), 29.7 (C-5); δ_F (282 MHz, $CDCl_3$) –171.2 (dd, $^2J_{F\text{-}H}$ 80.8, $^4J_{F\text{-}H}$ 3.5); *m/z* (EI) 175 (1), 166 (1), 157 (2),

129 (1), 122 (3), 112 (11), 91 (100, $C_7H_7^+$), 59 (98); Minor : R_f (35 % ethyl acetate in hexane) 0.81; δ_F (282 MHz, $CDCl_3$) −155.8 (1F, d, $^2J_{F\text{-}H}$ 77.5); *m/z* (EI) 175 (1), 166 (1), 157 (2), 129 (1), 122 (3), 112 (11), 91 (100, $C_7H_7^+$), 59 (98); Satisfactory HRMS (CI, EI, ES) could not be obtained for this compound.

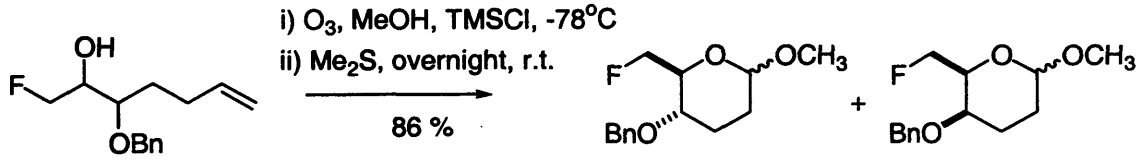
(*2S*,3R)-3-Benzyloxy-1-fluoro-hept-6-en-2-ol 258 and (*2R*,3R**)-3-benzyloxy-1-fluoro-hept-6-en-2-ol 259**



Hydrochloric acid (0.5 mL) was added to a solution of monofluoroallyl ether **131** (3.78 mmol, 1.23 g) in THF (10 mL). After stirring overnight (12 h), the mixture was diluted with Et_2O (10 mL), then sodium borohydride (5.93 mmol, 0.229 g) was added in portions. After stirring overnight, the mixture was diluted with water (5 mL), neutralised with concentrated HCl, extracted with AcOEt (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford monofluoro alcohol **258/259** (0.625 g, 69 %, 99% by GC-MS) as a mixture 1.5:1 (by NMR) of inseparable diastereoisomers as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.46; ν_{max}(neat)/cm^{-1} 3431br (OH), 2921w (CH_2), 1641w (C=C), 1454w, 1073s (C-O); δ_H (300 MHz, $CDCl_3$) 7.41-7.27 (5H, m, Ph), 5.91-5.75 (1H, m, H-6), 5.11-4.94 (2H, m, H-7), 4.83-4.36 (4H, m, H-6, CH_2Ph), 4.02-3.72 (1H, m, H-2), 3.62-3.52 (1H, m, H-3), 2.37-1.62 (5H, m, H-4, H-5, OH); δ_C (75 MHz, $CDCl_3$) 138.2 (C-6, diastereoisomer b), 138.1, 137.9 (C-6, diastereoisomer a), 128.6, 128.5, 128.0, 127.9, 127.9, 115.2 (C-7, diastereoisomer a),

115.1 (C-7, diastereoisomer b), 84.5 (d, $^{1}J_{C\text{-}F}$ 166.8, C-1, diastereoisomer b), 83.9 (d, $^{1}J_{C\text{-}F}$ 170.0, C-1, diastereoisomer a), 78.3 (d, $^{3}J_{C\text{-}F}$ 6.5, C-3, diastereoisomer b), 77.6 (d, $^{3}J_{C\text{-}F}$ 5.3, C-3, diastereoisomer a), 72.7 (CH_2Ph, diastereoisomer a), 72.5 (CH_2Ph, diastereoisomer b), 71.7 (d, $^{2}J_{C\text{-}F}$ 18.8, C-2, diastereoisomer b), 71.2 (d, $^{2}J_{C\text{-}F}$ 19.8, C-2, diastereoisomer a), 29.7, 29.5, 29.4, 29.2; δ_F (282 MHz, $CDCl_3$) –230.0 (td, $^{2}J_{F\text{-}H}$ 47.3, $^{3}J_{F\text{-}H}$ 16.9, CH_2F, diastereoisomer a), -232.9 (td, $^{2}J_{F\text{-}H}$ 47.5, $^{3}J_{F\text{-}H}$ 19.7, CH_2F, diastereoisomer b); [HRMS (EI, M^+) Found: 238.13690 Calc. For $C_{14}H_{19}FO_2$ 238.13691]; *m/z* (EI) 238 (1 %, M^+), 175 (9), 157 (8), 131 (2), 107 (7), 91 (100, $C_7H_7^+$).

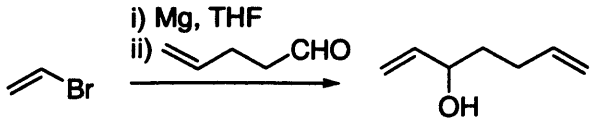
Methyl 5-*O*-benzyl-6-fluoro-amicetoside 260 and methyl 5-*O*-benzyl-6-fluoro-rhodinoside 261



Trimethylchlorosilane (0.16 mmol, 20 μL) was added to a stirred solution of alcohol **258/259** (0.39 mmol, 93 mg) in methanol (5 mL). The solution was cooled to –78 °C and a stream of dry O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then solid NaOH (0.1 g, 2.5 mmol) was added. After 1 hour the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 1% to 2% ethyl acetate in hexane) to afford methyl pyranoside **260/261** (85 mg, 86 %, 99% by GC-MS) as a mixture of inseparable isomers as a clear colourless oil; R_f (20 % ethyl

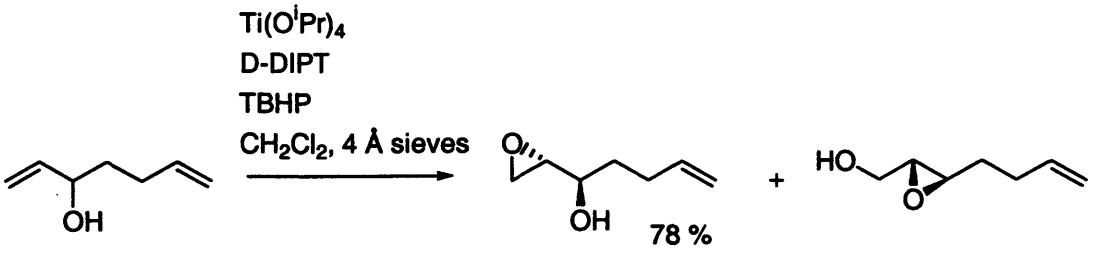
acetate in hexane) 0.68; ν_{max}(neat)/cm^{-1} 2938w (CH_2), 2896w (CH_2), 1454s (CH_3), 1217s (C-O-C), 1128s, 1071s (C-O); for the amicetosides (mixture of anomers): δ_H (300 MHz, $CDCl_3$) 7.36-7.25 (5H, m, Ph), 4.88-4.34 (5H, env., H-1, H-6, CH_2Ph), 4.09-3.99 (1H, m, H-5), 3.83-3.44 (1H, m, H-4), 3.35 (3H, s, OCH_3), 2.22-1.21 (4H, env., H-2, H-3); δ_C (75 MHz, $CDCl_3$) 138.3, 128.4, 127.8, 127.7, 97.6 (C-1), 82.7 (d, $^1J_{C\text{-}F}$ 171.1, C-6), 71.8 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 70.9 (d, $^2J_{C\text{-}F}$ 18.0, C-5), 70.7 (CH_2Ph), 54.5 (OCH_3), 28.8 (C-2), 23.9 (C-3); δ_F (282 MHz, $CDCl_3$) 234.8 (td, $^2J_{F\text{-}H}$ 47.7, $^3J_{F\text{-}H}$ 28.4); [HRMS (EI, M^+) Found: 254.13189 Calc. For $C_{14}H_{19}FO_3$ 254.13182]; *m/z* (EI) 254 (1 %, M^+), 222 (1, $[M\text{-}MeOH]^+$), 191 (3), 147 (1), 107 (17), 101 (14), 91 (100, $C_7H_7^+$); and for the rhodinoside (mixture of anomers): δ_H (300 MHz, $CDCl_3$) 7.36-7.25 (5H, m, Ph), 4.88-4.34 (5H, m, H-1, H-6, CH_2Ph), 4.09-3.99 (1H, m, H-5), 3.83-3.44 (1H, m, H-4), 3.38 (3H, s, OCH_3), 2.22-1.21 (4H, env., H-2, H-3); δ_C (75 MHz, $CDCl_3$) 138.2, 128.4, 127.8, 127.7, 97.9 (C-1), 83.7 (d, $^1J_{C\text{-}F}$ 166.8, C-6), 70.4 (d, $^3J_{C\text{-}F}$ 7.0, C-4), 69.2 (d, $^2J_{C\text{-}F}$ 21.9, C-5), 70.8 (CH_2Ph), 54.7 (OCH_3), 24.1 (C-2), 20.5 (C-3); δ_F (282 MHz, $CDCl_3$) (–230.3)-(-230.7) (m).

Hepta-1,6-dien-3-ol 263



Magnesium turnings (127 mmol, 3.1 g) were washed with HCl (15 mL of a 5 M solution), then water (2 x 10 mL), then acetone (2 x 10 mL), then dried *in vacuo* and allowed to cool under Ar. They were added to an oven-dried 250 mL three-necked round bottomed flask equipped with a magnetic stirrer bead and a dry ice condenser (containing solid CO_2/Acetone at –78 °C) Dry THF (50 mL) was added, then cold (0 °C) vinyl bromide (125 mmol, 9 mL) was added dropwise from a cold (0 °C) syringe under argon. The mixture was warmed gently with a heat-gun to initiate reaction. After the reaction was complete more dry THF (50 mL) was added. 5-Pentenal (90 mmol, 8 g) was added dropwise to the mixture at 0 °C, which was stirred for 30 min then quenched at 0 °C with $NH_4Cl_{(sat)}$, diluted with water (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated carefully *in vacuo* to leave a colourless oil which was distilled (Kugelrohr, bp 20-25 °C/0.2 mmHg) to afford alcohol **263** (8.2 g, 81 %, 95 % by GC-MS) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.76; ν_{max}(neat)/cm^{-1} 3350br (OH), 2934w (CH_2), 1641w (C=C), 1425w, 991s; δ_H (300 MHz, $CDCl_3$) 5.88-5.73 (2H, m, H-1, H-6), 5.19 (1H, ddd, *J* 17.2, ^2J 1.6, ^4J 1.4, H-1_a), 5.07 (1H, ddd, *J* 10.4, ^2J 1.6, ^4J 1.4, H-1_b), 5.01 (1H, ddd, *J* 17.1, ^2J 3.5, ^4J 1.6, H-7_a), 4.94 (1H, ddd, *J* 10.2, ^2J 3.5, ^4J 1.6, H-7_b), 4.08 (1H, ddd, *J* 6.4, 6.3, 1.2, H-3), 2.31 (1H, s, OH), 2.16-2.06 (2H, m, H-5), 1.68-1.50 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 141.0 (C-2), 138.3 (C-6), 114.8, 114.7 (C-1, C-7), 72.5 (C-3), 36.0 (C-4), 29.6 (C-5); [HRMS (EI, M^+) Found: 112.08879 Calc. For $C_7H_{12}O$ 112.08882] *m/z* (EI) 112 (1 %, M^+), 111 (2, $[M-1]^+$), 97 (11), 83 (23), 79 (100, $[M-H_2O-CH_2]^+$), 70 (45), 57 (79). Spectral data were in agreement with those reported by Salomon *et al.*.[156]

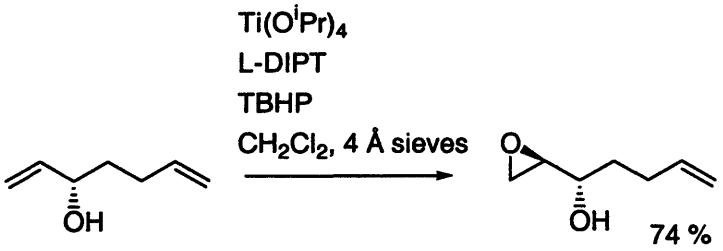
(-)-(2S,3R)-1,2-Epoxyhept-6-en-3-ol 264 and (+)-(2R,3R)-2,3-epoxyhept-6-en-1-ol 269



Powdered 4 Å molecular sieves (6.3 g) in a 250 mL single-necked round bottomed flask equipped with a magnetic stirrer bead, were heated under vacuum (below 50 mmHg) with a Bunsen burner, and cooled to room temperature under argon. Dry CH_2Cl_2 (100 mL) was added *via* cannula and the flask was cooled below –20 °C. Titanium tetra*iso*propoxide (4.79 mmol, 1.50 mL), di*iso*propyl D-tartrate (5.36 mmol, 1.15 mL), allylic alcohol **263** (50 mmol, 5.6 g) and *tert*-butylhydroperoxide (49.5 mmol, 15 mL of a 3.3 M solution in toluene) were added successively. The resulting mixture was stirred below -20 °C for 15 days in the freezer, then the mixture was filtered though filter paper into a cold (0 °C) solution of ferrous sulfate (72 mmol, 20 g) and tartaric acid (40 mmol, 6 g) in water (60 mL). The two-phase mixture was stirred for 15 min then the phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phase and extracts were treated with a cold (0 °C) solution of 30% NaOH (w/v) in saturated brine (10 mL) at 0 °C. The two phase mixture was stirred vigorously for 30 minutes at 0 °C. The two phases were separated and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil, from which the remaining hepta-1,6-dien-3-ol was distilled at reduced pressure (Kugelrohr 10^{-2} mmHg at 25 °C) to afford a mixture of major product epoxy alcohol **264** (2.5 g, 39 %, 78 % kinetic resolution, 80 % by GC-MS) as a colourless oil; R_f (35 % ethyl acetate in hexane) 0.42; ν_{max}(neat)/cm^{-1} 3401 (OH), 2925w (CH_2), 1641s (C=C), 1453w, 1258w, 1018s, 911s; $[\alpha]_D^{19}$ = -16.1° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.84 (1H,

ddd, *J* 17.3, 10.5, 6.7, H-6), 5.06 (1H, ddd, *J* 17.3, ^2J 3.2, ^4J 1.5, H-7_a), 4.99 (1H, ddd, *J* 10.5, ^2J 3.2, ^4J 1.2, H-7_b), 3.88-3.81 (1H, m, H-3), 3.01 (1H, ddd, *J* 4.0, 3.0, 2.8, H-2), 2.81 (1H, dd, ^2J 5.0, *J* 2.8, H-1_a), 2.73 (1H, dd, ^2J 5.0, *J* 4.0, H-1_b), 2.35-2.10 (2H, m, H-5), 1.96 (1H, br.s, OH), 1.78-1.52 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.0 (C-6), 115.1 (C-7), 67.9 (C-3), 54.5 (C-2), 43.5 (C-1), 32.5 (C-4), 29.5 (C-5); [HRMS (EI, M^+) Found: 128.08372 Calc. For $C_7H_{12}O_2$ 128.08373] *m/z* (EI) 128 (1 %, M^+), 108 (18), 97 (18), 95 (19), 79 (96), 67 (100, $[M-H_2O-C_2H_3O]^+$); and (minor Payne product) epoxy alcohol **269** (0.32 g, 5 %, 95 % by GC-MS) as a colourless oil; R_f (35 % ethyl acetate in hexane) 0.27; ν_{max}(neat)/cm^{-1} 3395br (OH), 2927w (CH_2), 1641s (C=C), 1448w, 1084w, 912s; $[\alpha]_D^{23}$ = +30.5° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 17.0, 10.2, 6.7, H-6), 5.06 (1H, ddd, *J* 17.0, ^2J 3.2, ^4J 1.4, H-7_a), 5.00 (1H, ddd, *J* 10.2, ^2J 3.2, ^4J 1.7, H-7_b), 3.89 (1H, ddd, ^2J 12.6, *J* 6.1, 2.6, H-1_a), 3.58 (1H, ddd, ^2J 12.6, *J* 6.7, 4.7, H-1_b), 3.00-2.92 (2H, m, H-2, H-3), 2.74 (1H, dd, *J* 6.7, 6.1, OH), 2.31-2.11 (2H, m, H-5), 1.69 (1H, t, *J* 7.6, H-4_a), 1.69 (1H, t, *J* 7.3, H-4_b); δ_C (75 MHz, $CDCl_3$) 137.4 (C-6), 115.3 (C-7), 61.8 (C-1), 58.8 (C-2), 55.5 (C-3), 30.8 (C-4), 30.0 (C-5); [HRMS (EI, M^+) Found: 128.08372 Calc. For $C_7H_{12}O_2$ 128.08373] *m/z* (EI) 128 (1 %, M^+), 110 (5), 97 (37), 91 (13), 83 (27), 79 (48), 67 (100, $[M-H_2O-C_2H_3O]^+$).

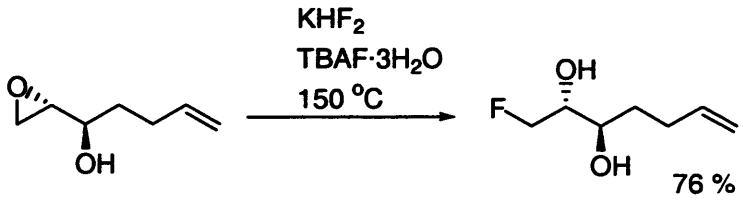
(+)-(2R,3S)-1,2-Epoxyhept-6-en-3-ol 265



Powdered 4 Å molecular sieves (3.2 g) in a 50 mL single-necked round bottomed flask equipped with a magnetic stirrer bead, were heated under vacuum (below 50 mmHg) with a Bunsen burner, and cooled to room temperature under argon. Dry CH_2Cl_2 (25 mL) was added *via* cannula and the flask was cooled below –20 °C. Titanium tetra*iso*propoxide (2.39 mmol, 0.75 mL), di*iso*propyl L-tartrate (2.83 mmol, 0.6 mL), (3R)-hepta-1,6-dien-3-ol **263** (22.3 mmol, 2.5 g) and tert-butylhydroperoxide (22.2 mmol, 6 mL of a 3.7 M solution in toluene) were added successively. The resulting mixture was stirred below -20 °C for 15 days in the freezer, then the mixture was filtered though filter paper into a cold (0 °C) solution of ferrous sulfate (36 mmol, 10 g) and tartaric acid (20 mmol, 3 g) in water (30 mL). The two-phase mixture was stirred for 15 min, then the phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phase and extracts were treated with a cold (0 °C) solution of 30% NaOH (w/v) in saturated brine (10 mL). The two phase mixture was stirred vigorously for 30 minutes at 0 °C. The two phases were separated and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil, from which the remaining hepta-1,6-dien-3-ol was distilled at reduced pressure (10^{-2} mmHg at 25 °C) to afford a mixture of major product epoxy alcohol **265** (2.1 g, 74 %, 99 % by GC-MS) and minor Payne product as a colourless oil; Major: R_f (35 % ethyl acetate in hexane) 0.42; ν_{max}(neat)/cm^{-1} 3418br (OH), 2926w (CH_2), 1641s (C=C), 1259w, 1066w, 911s; $[\alpha]_D^{19}$ = +27.6° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.84 (1H, ddd, *J* 17.3, 10.5, 6.7, H-6), 5.06 (1H, ddd, *J* 17.3, ^2J 3.2, ^4J 1.5, H-7$_a$), 4.99

(1H, ddd, J 10.5, ^2J 3.2, ^4J 1.2, H-7_b), 3.88-3.81 (1H, m, H-3), 3.01 (1H, ddd, J 4.0, 3.0, 2.8, H-2), 2.81 (1H, dd, ^2J 5.0, J 2.8 H-1_a), 2.73 (1H, dd, ^2J 5.0, J 4.0, H-1_b), 2.35-2.10 (2H, m, H-5), 1.96 (1H, br.s, OH), 1.78-1.52 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.0 (C-6), 115.1 (C-7), 67.9 (C-3), 54.5 (C-2), 43.5 (C-1), 32.5 (C-4), 29.5 (C-5); [HRMS (EI, M^+) Found: 128.08375 Calc. For $C_7H_{12}O_2$ 128.08373] *m/z* (EI) 128 (1 %, M^+), 108 (18), 97 (18), 95 (19), 79 (96), 67 (100, $[M-H_2O-C_2H_3O]^+$). The Payne product was not characterised.

(+)-(2S,3R)-1-Fluorohept-6-en-2,3-diol 281

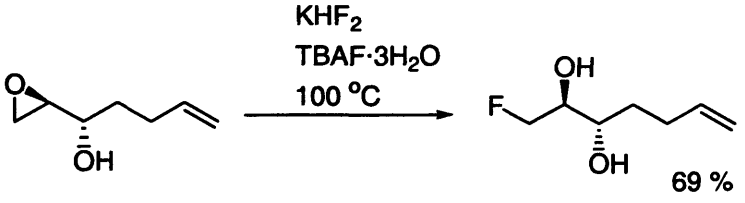


Epoxy alcohol **264** (1.92 mmol, 0.246 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (1.56 mmol, 0.503 g) and potassium hydrogen difluoride (13.6 mmol, 1.063 g) at 150 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (10 mL), then carefully neutralised with $NaHCO_3$ (12.0 mmol, 1.0 g). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined original organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark red oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford diol **281** (216 mg, 76 %, 99 % by GC-MS, 94 % ee and 99 % de by NMR*) as white flakes; mp 63-65 °C; R_f (35 % ethyl acetate in hexane) 0.26; (Found: C, 56.8; H, 8.9; $C_7H_{13}O_2F$ requires: C, 56.7; H, 8.8 %);

* The method for the determination of ee by NMR is described on p. 92.

ν_{max}(neat)/cm^{-1} 3319br (OH), 3221br (OH), 2909w (CH_2), 1644w (C=C), 1474w, 1067s (C-O); $[\alpha]_D^{23}$ = +6.8° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.77 (1H, ddt, *J* 17.1, 10.2, 6.7, H-6), 5.00 (1H, ddd, *J* 17.1, ^2J 3.2, ^4J 1.7, H-7$_a$), 4.94 (1H, ddd, *J* 10.2, ^2J 3.2, ^4J 1.2, H-7$_b$), 4.51 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.7, *J* 3.4, C*H*$_a$H$_b$F), 4.47 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.7, *J* 6.1, CH$_a$*H*$_b$F), 3.79-3.65 (2H, m, H-2, H-3), 2.64 (2H, s, OH), 2.29-2.01 (2H, m, H-5), 1.63-1.43 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 137.9 (C-6), 115.4 (C-7), 84.4 (d, $^1J_{C\text{-}F}$ 165.9, C-1), 73.1 (d, $^2J_{C\text{-}F}$ 18.0, C-2), 71.6 (d, $^3J_{C\text{-}F}$ 7.0, C-3), 31.6 (C-4), 30.0 (C-5); δ_F (282 MHz, $CDCl_3$) –234.1 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 20.5); [HRMS (EI, M$^+$) Found: 148.08994 Calc. For $C_7H_{13}O_2F$ 148.08996]; *m/z* (EI) 148 (1 %, M$^+$), 106 (3), 97 (10), 85 (33, [M-H_2O-H_2O-C_2H_3]$^+$), 79 (28), 67 (100, [M-H_2O-H_2O-C_2H_2F]$^+$).

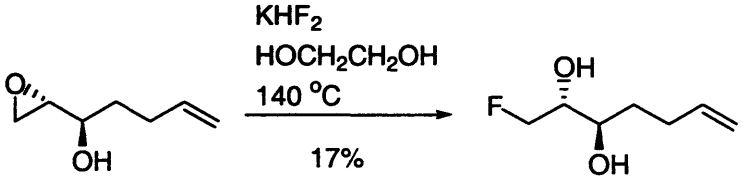
(-)-(2R,3S)-1-Fluorohept-6-en-2,3-diol 282



Epoxy alcohol **265** (3.1 mmol, 0.398 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (3.1 mmol, 1.00 g) and potassium hydrogen difluoride (13.0 mmol, 1.02 g) at 100 °C. After 1 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (10 mL), then carefully neutralised with $NaHCO_3$ (12.0 mmol, 1.00 g). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined original organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark red oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford diol **282** (318 mg, 69 %, 99 % by GC-

MS, 96 % ee and 98 % de by NMR*) as white flakes; mp 64-66 °C; R_f (35 % ethyl acetate in hexane) 0.26; (Found: C, 56.8; H, 8.9;** $C_7H_{13}O_2F$ requires: C, 56.7; H, 8.8 %); ν_{max}(neat)/cm^{-1} 3317br (OH), 3218br (OH), 2909w (CH_2), 1644w (C=C), 1474w, 1067s (C-O); $[\alpha]_D^{23}$ = -6.2° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.77 (1H, ddt, *J* 17.1, 10.2, 6.7, H-6), 5.00 (1H, ddd, *J* 17.1, ^2J 3.2, ^4J 1.7, H-7$_a$), 4.94 (1H, ddd, *J* 10.2, ^2J 3.2, ^4J 1.2, H-7$_b$), 4.51 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.7, *J* 3.4, C*H*$_a$H$_b$F), 4.47 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.7, *J* 6.1, CH$_a$*H*$_b$F), 3.79-3.65 (2H, m, H-2, H-3), 2.64 (2H, s, OH), 2.29-2.01 (2H, m, H-5), 1.63-1.43 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 137.9 (C-6), 115.4 (C-7), 84.4 (d, $^1J_{C\text{-}F}$ 165.9, C-1), 73.1 (d, $^2J_{C\text{-}F}$ 18.0, C-2), 71.6 (d, $^3J_{C\text{-}F}$ 7.0, C-3), 31.6 (C-4), 30.0 (C-5); δ_F (282 MHz, $CDCl_3$) –234.1 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 20.5); [HRMS (EI, M^+) Found: 148.09004 Calc. For $C_7H_{13}O_2F$ 148.08996]; *m/z* (EI) 148 (1 %, M^+), 106 (4), 97 (9), 85 (47, [M-H_2O-H_2O-C_2H_3]$^+$), 79 (16), 67 (100, [M-H_2O-H_2O-C_2H_2F]$^+$).

Attempted preparation of (2S,3R)-1-fluorohept-6-en-2,3-diol 281



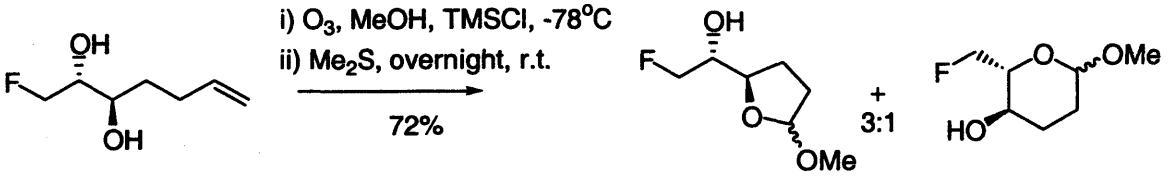
Epoxy alcohol **264** (1.55 mmol, 0.199 g) was added to a stirred mixture of potassium hydrogen difluoride (4.9 mmol, 0.395 g) in ethane-1,2-diol at 140 °C. After 15 min, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (10 mL), then carefully neutralised with $NaHCO_3$ (5.0 mmol, 0.42 g). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined original organic phase and extracts were dried ($MgSO_4$), filtered

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* The method for the determination of ee by NMR is described on p. 92.
** This data results from two independent analyses

and concentrated *in vacuo* to leave an oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford diol **265** (40 mg, 17 %).

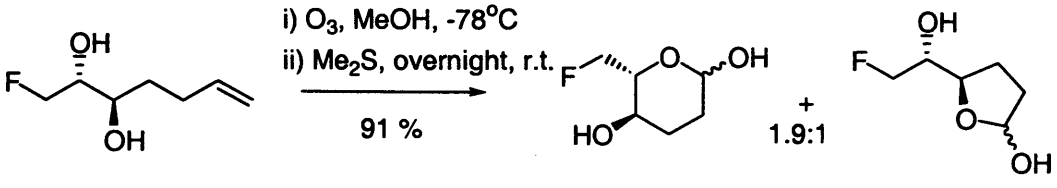
L-Methyl 6-fluoro-amicetofuranoside 284 and L-methyl 6-fluoro-amicetopyranoside 285



Trimethylchlorosilane (0.39 mmol, 50 µl) was added to a stirred solution of diol **281** (1.03 mmol, 0.153 g) in methanol (7 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford methyl furanosides **284** (122 mg, 72 %, 99 % by GC-MS) as a (1:1) mixture of inseparable anomers (retention times at 100 °C isothermal GC-MS: 5.26 and 5.47 min) and *β*-methyl pyranoside **285** (5 mg, 3 %) as clear colourless oils; Major: R_f (35 % ethyl acetate in hexane) 0.34; ν_{max}(neat)/cm^{-1} 3397br (OH), 2954w (CH_2), 1460w, 1202w, 1039s (C-O), 978s; δ_H (300 MHz, $CDCl_3$) 5.00 (1H, dd, *J* 4.4, 1.2, H-1, anomer a), 4.95 (1H, d, *J* 2.6, H-1, anomer b), 4.61-4.30 (4H, m, H-6, both anomers), 4.18 (1H, dt, *J* 7.2, 7.0, H-4, anomer b), 4.04 (1H, dd, *J* 12.9, 5.8, H-4, anomer a), 3.94-3.77 (2H, m, H-5, both anomers), 3.33 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 2.10-1.75 (8H, m, H-2, H-3, both anomers); δ_C (75 MHz, $CDCl_3$) 105.4 (C-1, anomer b), 105.2 (C-1, anomer a),

84.6 (d, $^1J_{C\text{-}F}$ 168.0, C-6), 84.4 (d, $^1J_{C\text{-}F}$ 168.4, C-6), 80.1 (d, $^3J_{C\text{-}F}$ 6.1, C-4, anomer b), 77.2 (d, $^3J_{C\text{-}F}$ 7.0, C-4, anomer a), 72.3 (d, $^2J_{C\text{-}F}$ 19.0, C-5), 71.7 (d, $^2J_{C\text{-}F}$ 18.6, C-5), 54.9 (OCH_3), 54.7 (OCH_3), 32.8, 31.8, 24.5, 23.8; δ_F (282 MHz, $CDCl_3$) –233.0 (1F, td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 19.8), –233.2 (1F, td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 20.0); the α and β anomers cannot be assigned on the basis of this data; [HRMS (EI, M^+) Found: 164.08488 Calc. For $C_7H_{13}O_3F$ 164.08487]; *m/z* (EI) 164 (1 %, M^+), 133 (8, $[M\text{-}CH_4O]^+$), 115 (3), 101 (71, $[M\text{-}C_2H_4OF]^+$), 86 (8), 69 (100, $C_4H_5O^+$); and Minor β-pyranoside: R_f (35 % ethyl acetate in hexane) 0.28; δ_H (400 MHz, $CDCl_3$) 4.59 (1H, dd, $^2J_{H\text{-}F}$ 47.5, *J* 2.1, H-6_a), 4.59 (1H, dd, $^2J_{H\text{-}F}$ 47.5, *J* 1.0, H-6_b), 4.35 (1H, dd, *J* 8.9, 2.1, H-1), 3.74-3.24 (3H, m, H-4, H-5, OH), 3.43 (3H, s, OCH_3), 2.08-2.02 (1H, m, H-3_a), 1.87-1.81 (1H, m, H-2_a), 1.58-1.42 (2H, m, H-2_b, H-3_b); δ_C (100 MHz, $CDCl_3$) 102.6 (C-1), 83.0 (d, $^1J_{C\text{-}F}$ 170.8, C-6), 78.1 (d, $^2J_{C\text{-}F}$ 18.2, C-5), 65.5 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 56.4 (OCH_3), 30.7, 29.9; δ_F (376 MHz, $CDCl_3$) –234.7 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 22.8); *m/z* (EI) 164 (1 %, M^+), 133 (15, $[M\text{-}CH_4O]^+$), 115 (6), 102 (17, $[M\text{-}C_2H_3OF]^+$), 76 (15), 69 (37), 58 (100, $C_3H_6O^+$); and a mixed fraction containing both methyl furanosides and pyranosides (15 mg, 9 %) as a (1:1) mixture of anomers (retention times at 100 °C isothermal GC-MS: 6.96 and 7.56 min). See p.65-68 for the origin of the furanoside:pyranoside ratio.

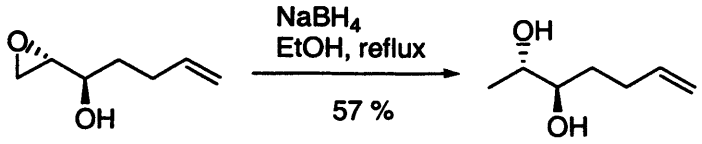
L-6-Fluoro-amicetofuranose 286 and L-6-fluoro-amicetopyranose 287



A stream of O_3 (0.2 L/min) was carefully bubbled through a solution of diol **281** (0.53 mmol, 78 mg) in methanol (6 mL) at –78 °C until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (0.27

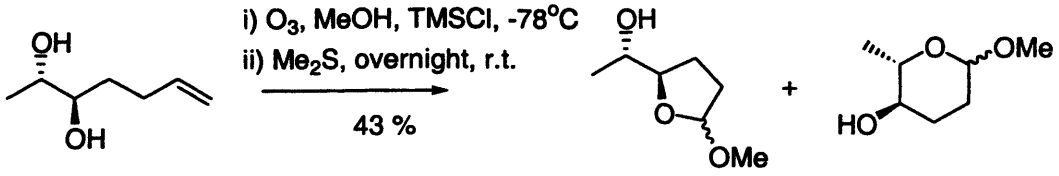
mmol, 0.2 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 40% to 60% ethyl acetate in hexane) to afford amicetosides **286/287** (72 mg, 91 %, 99 % by GC-MS) as a 1.9:1 (by NMR) mixture of inseparable anomers of pyranoses and furanoses as clear colourless oil; R_f (50 % ethyl acetate in hexane) 0.15; ν_{max}(neat)/cm^{-1} 3366br (OH), 2953w (CH_2), 1459w, 1117w 1050s (C-O), 978s (C-O); δ_H (400 MHz, D_2O) 5.49 (1H, dd, *J* 4.5, 2.1, furanose a anomer), 5.44 (1H, d, *J* 4.4, furanose b anomer), 5.23 (1H, d, *J* 2.3, pyranose α anomer), 4.86 (1H, dd, *J* 9.3, 2.0, pyranose β anomer), 4.80-3.30 (16H, env., H-4, H-5, H-6, contained signals for all forms), 2.12-1.11 (16H, env., H-2, H-3, contained signals for all forms); δ_C (100 MHz, D_2O) 98.4 (C-1), 98.1 (C-1), 95.7 (C-1), 90.6 (C-1), 85.0 (d, $^1J_{C\text{-}F}$ 165.1, C-6), 84.7 (d, $^1J_{C\text{-}F}$ 165.4, C-6), 82.8 (d, $^1J_{C\text{-}F}$ 166.5, C-6), 82.7 (d, $^1J_{C\text{-}F}$ 166.8, C-6), 78.7 (d, $^3J_{C\text{-}F}$ 7.5, C-4), 78.2 (d, $^2J_{C\text{-}F}$ 17.1, C-5), 77.5 (d, $^3J_{C\text{-}F}$ 7.5, C-4), 72.8 (d, $^2J_{C\text{-}F}$ 17.6, C-5), 72.1 (d, $^2J_{C\text{-}F}$ 17.0, C-5), 71.2 (d, $^2J_{C\text{-}F}$ 17.8, C-5), 64.2 (d, $^3J_{C\text{-}F}$ 7.1, C-4), 63.9 (d, $^3J_{C\text{-}F}$ 7.2, C-4), 32.9, 32.2, 31.0, 29.7, 28.9, 25.6, 25.5, 24.4; δ_F (376 MHz, D_2O) –232.8 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 23.7, pyranose α anomer), –233.8 (td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 24.6, pyranose β anomer), –234.2 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 26.5, furanose α anomer), –235.3 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 28.9, furanose β anomer); [HRMS (EI, $[M\text{-}H]^+$) Found: 149.06130 Calc. For $C_6H_{10}O_3F$ 149.06140]; *m/z* (EI) 149 (2 %, $[M\text{-}H]^+$), 133 (29), 99 (25), 87 (100).

(+)-(2S,3R)-Hepta-6-en-2,3-diol 288



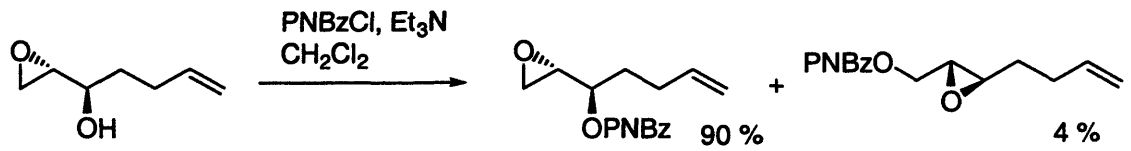
Sodium borohydride (5.1 mmol, 0.2 g) was added to a solution of epoxy alcohol **264** (4.0 mmol, 0.510 g) in ethanol (30 mL). The solution was stirred at reflux for 3 h, then filtered, concentrated *in vacuo*, diluted with Et_2O (30 mL) then water (20 mL), and neutralised with concentrated HCl (0.5 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3x10 mL). The combined original organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford diol **288** (297 mg, 57 %, 99 % by GC-MS) as a colourless oil; R_f (50 % ethyl acetate in hexane) 0.42; ν_{max}(neat)/cm^{-1} 3372br (OH), 2977w (CH_2), 1641w (C=C), 1375w, 1061s (C-O); $[\alpha]_D^{22}$ = +12.8° (*c* = 0.20, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.80 (1H, ddt, *J* 17.0, 10.1, 6.6, H-6), 5.02 (1H, ddd, *J* 17.0, ^2J 3.4, ^4J 1.6, H-7_a), 4.94 (1H, ddt, *J* 10.1, ^3J 3.4, ^4J 1.2, H-7_b), 3.74 (1H, qd, *J* 6.4, 3.1, H-2), 3.58 (1H, ddd, *J* 8.2, 5.2, 3.1, H-3), 3.15 (2H, br.s, OH), 2.30-2.00 (2H, m, H-5), 1.52-1.42 (2H, m, H-4), 1.10 (3H, d, *J* 6.4, H-1); δ_C (75 MHz, $CDCl_3$) 138.3 (C-6), 114.9 (C-7), 74.3 (C-3), 70.4 (C-2), 30.8 (C-4), 30.2 (C-5), 16.6 (C-1); [HRMS (EI, M^+) Found: 130.09943 Calc. For $C_7H_{14}O_2$ 130.09938]; *m/z* (EI) 130 (1 %, M^+), 112 (1, [M-H_2O]$^+$), 85 (63), 67 (100, [M-H_2O-H_2O-C_2H_3]$^+$).

L-Methyl amicetofuranoside 289 and L-methyl amicetopyranoside 290



Trimethylchlorosilane (0.19 mmol, 25 μl) was added to a stirred solution of diol **288** (0.62 mmol, 81 mg) in methanol (4 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (2.7 mmol, 0.2 mL) was added. The mixture was stirred overnight at room temperature (12 h), then concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford methyl furanoside **289** (39 mg, 43 %, 99 % by GC-MS) as a (1:1) mixture of inseparable anomers as clear colourless oil; R_f (50 % ethyl acetate in hexane) 0.40; ν_{max}(neat)/cm^{-1} 3420br (OH), 2904w (CH_2), 1366w, 1204w, 1097s (C-O), 1038 (C-O); δ_H (300 MHz, $CDCl_3$) 4.98 (1H, dd, *J* 4.7, 1.3, H-1, anomer a), 4.90 (1H, dd, *J* 4.3, 1.4, H-1, anomer b), 4.03 (1H, ddd, *J* 7.3, 7.1, 3.0, H-4, anomer b), 3.96-3.86 (3H, m, H-4 anomer a, H-5 both anomers), 3.31 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 2.04-1.69 (6H, m, H-2, H-3, OH, OH, both anomers), 1.07 (3H, d, *J* 6.4, H-6), 1.05 (3H, d, *J* 6.5, H-6); δ_C (75 MHz, $CDCl_3$) 105.4 (C-1, anomer b), 105.3 (C-1, anomer a), 85.2 (C-4, anomer b), 81.6 (C-4, anomer a), 68.1 (C-5), 67.7 (C-5), 55.0 (OCH_3), 54.6 (OCH_3), 32.9 (C-2), 32.3 (C-2), 22.2 (C-3), 21.3 (C-3), 18.1 (C-6, both anomers); [HRMS (EI, M^+) Found: 146.09430 Calc. For $C_7H_{14}O_3$ 146.09429]; *m/z* (EI) 146 (1 %, M^+), 114 (7), 101 (100), 69 (24). We were not able to isolate any pure pyranosides, though they are clearly visible in the ^{1}H NMR. See p.69 for the origin of the furanoside:pyranoside ratio.

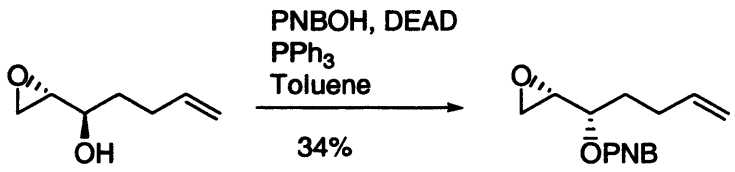
(2S,3R)-3-*p*-Nitrobenzyloxy-1,2-epoxyhept-6-en ester 293 and (2R,3R)-1-*p*-nitrobenzyloxy-2,3-epoxyhept-6-en ester 294



p-Nitrobenzoyl chloride (4.6 mmol, 0.881 g) was added to a stirred solution of epoxy alcohol **264** (3.1 mmol, 0.396 g) in dry CH_2Cl_2 (6 mL) at r.t., then triethylamine (6.2 mmol, 0.860 mL) was added dropwise. After 12 h, the mixture was filtered, the filter bed was washed with Et_2O (3 x 5 mL) and the combined filtrates were concentrated *in vacuo* to leave a yellow liquid which was purified by Biotage column chromatography (gradient 20 % to 30 % ethyl acetate in hexane) to afford ester **293** (771 mg, 90 %, 80 % by GC-MS) as a yellow oil; R_f (20 % ethyl acetate in hexane) 0.46; ν_{max}(neat)/cm^{-1} 2933w (CH_2), 1724s (C=O), 1607w (C=C), 1525s, 1348w, 1265s, 1101s (C-O); δ_H (300 MHz, $CDCl_3$) 8.33-8.18 (4H, m, ArH), 5.84 (1H, ddt, *J* 16.9, 10.2, 6.6, H-6), 5.12-4.98 (3H, m, H-7, H-3), 3.15 (1H, dt, *J* 5.2, 3.2, H-2), 2.83 (2H, d, *J* 3.2, H-1), 2.35-2.14 (2H, m, H-5), 2.06-1.90 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 164.0, 150.7, 137.0 (C-6), 135.4, 130.8, 123.6, 115.7 (C-7), 74.0 (C-3), 52.1 (C-2), 45.5 (C-1), 30.5 (C-4), 29.3 (C-5); [HRMS (EI, M^+) Found: 277.09503 Calc. For $C_{14}H_{15}NO_5$ 277.09502] *m/z* (EI) 277 (1 %, M^+), 222 (12), 167 (2), 150 (100, $C_7H_4NO_3^+$); and Payne product **294** (36 mg, 4 %, 80 % by GC-MS) as a yellow oil; R_f (20 % ethyl acetate in hexane) 0.43; ν_{max}(neat)/cm^{-1} 2927w (CH_2), 1723s (C=O), 1607w (C=C), 1524s, 1347w, 1264s, 1100s (C-O); δ_H (300 MHz, $CDCl_3$) 8.37-8.13 (4H, m, ArH), 5.89-5.71 (1H, m, H-6), 5.31 (1H, dd, *J* 12.3, 5.8, H-3), 5.10-4.96 (2H, m, H-7), 4.08 (1H, ddd, *J* 7.4, 5.8, 3.4, H-2), 3.75 (1H, dd, ^2J 11.4, *J* 3.4, H-1_a), 3.63 (1H, dd, ^2J 11.4, *J* 7.4, H-1_b), 2.31-1.92 (4H, m, H-4, H-5); δ_C (75 MHz, $CDCl_3$) 164.2 (C=O), 150.7, 137.0 (C-6), 135.1, 130.9, 123.7, 115.7 (C-7), 75.5 (C-3), 72.5 (C-2), 46.6 (C-1), 29.5, 29.4; [HRMS (EI, M^+) Found:

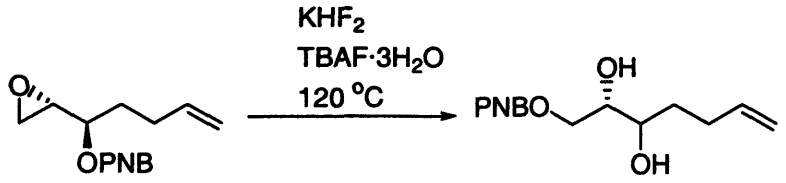
277.09510 Calc. For $C_{14}H_{15}NO_5$ 277.09502] *m/z* (EI) 277 (1 %, M^+), 222 (1), 188 (2), 168 (3), 150 (100, $C_7H_4NO_3^+$), 104 (31).

(2S,3S)-3-*p*-Nitrobenzyloxy-1,2-epoxyhept-6-en ester 295



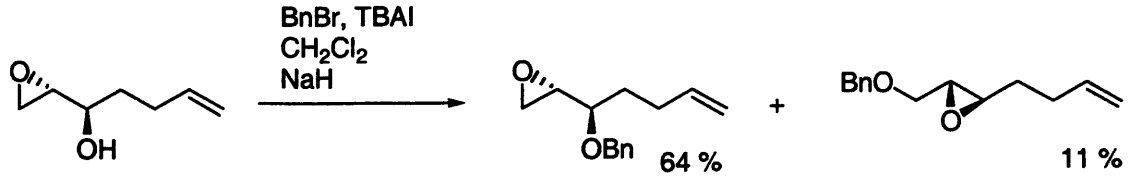
Diethylazodicarboxylate (6.3 mmol, 1 mL) was added to a stirred solution of epoxy alcohol **264** (2.97 mmol, 0.381 g), triphenylphosphine (6.13 mmol, 1.625 g) and *p*-nitrobenzoic acid in dry toluene (25 mL) at room temperature. After 3 h, the mixture was concentrated *in vacuo* to leave a yellow liquid which was purified by Biotage column chromatography (gradient 10 % to 20 % ethyl acetate in hexane) to afford ester **295** (280 mg, 34 %, 85 % by GCMS) as a yellow oil; R_f (20 % ethyl acetate in hexane) 0.46; ν_{max}(neat)/cm^{-1} 2930w (CH_2), 1722s (C=O), 1608w (C=C), 1525s, 1348w, 1268s, 1101s (C-O); δ_H (300 MHz, $CDCl_3$) 8.32-8.21 (4H, m, Ph), 5.84 (1H, ddt, *J* 16.8, 10.3, 6.5, H-6), 5.12-4.98 (3H, m, H-7, H-3), 3.26 (1H, ddd, *J* 6.5, 4.2, 2.6, H-2), 2.91 (1H, dd, ^2J 4.8, *J* 4.2, H-1_a), 2.74 (1H, dd, ^2J 4.8, *J* 2.6, H-1_b), 2.30-2.18 (2H, m, H-5), 2.08-1.87 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 164.0 (C=O), 150.6, 136.9 (C-6), 135.3, 130.8, 123.5, 115.7 (C-7), 75.4 (C-3), 52.1 (C-2), 45.0 (C-1), 30.4 (C-4), 29.3 (C-5); [HRMS (EI, M^+) Found: 277.09506 Calc. For $C_{14}H_{15}NO_5$ 277.09502] *m/z* (EI) 277 (1 %, M^+), 222 (6), 167 (2), 150 (100, $C_7H_4NO_3^+$); and a yellow oil identified as starting material **264**.

(2S)-1-p-Nitrobenzoyloxy-hept-6-en-2,3-diol 296



Epoxy ether **293** (1.08 mmol, 0.300 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (1.17 mmol, 0.376 g) and potassium hydrogen difluoride (3.84 mmol, 0.300 g) at 120 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (10 mL), then carefully neutralised with $NaHCO_3$ (0.3 g). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark red oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford diol **296** (44 mg, 14 %, 99 % by GC-MS) as a colourless oil; R_f (35 % ethyl acetate in hexane) 0.38; ν_{max}(neat)/cm^{-1} 3226br (OH), 2928w (CH_2), 1727s (NO), 1641w (C=C), 1526s, 1345s, 1267s, 1077s; δ_H (300 MHz, $CDCl_3$) 8.31-8.17 (4H, m, ArH), 5.85 (1H, ddt, *J* 17.0, 10.2, 6.7, H-6), 5.08 (1H, ddd, *J* 17.0, ^2J 3.4, ^4J 1.6, H-7$_a$), 5.01 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.2, H-7$_b$), 4.56 (1H, dd, ^2J 11.0, *J* 3.9, C*H*$_a$H$_b$OPNB), 4.51 (2H, dd, ^2J 11.0, *J* 6.4, CH$_a$*H*$_b$OPNB), 3.97 (1H, ddd, *J* 6.4, 4.3, 3.9, H-2), 3.81 (1H, dt, *J* 8.7, 4.3, H-3), 2.85 (2H, br.s, OH), 2.39-2.11 (2H, m, H-5), 1.78-1.58 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 165.2, 150.6, 137.9 (C-6), 135.1, 130.8, 123.6, 115.4 (C-7), 72.8 (C-2), 72.1 (C-3), 66.8 (C-1), 31.5, 30.0; [HRMS (EI, M$^+$) Found: 295.10554 Calc. For $C_{14}H_{17}NO_6$ 295.10559]; *m/z* (EI) 296 (1 %, [M+1]$^+$), 267 (23), 224 (14), 150 (28), 129 (14), 117 (100, $C_7H_7^+$).

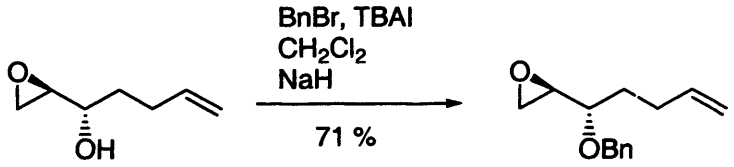
(+)-(2S,3R)-3-Benzyl-1,2-epoxyhept-6-en ether 297 and (-)-(2R,3R)-1-benzyl-2,3-epoxyhept-6-en ether 298



Sodium hydride (1.28 mmol, 51 mg of a 60 % dispersion in mineral oil, from which the oil had been washed with dry hexane), was added in portions to a stirred solution of epoxy alcohol **264** (1.00 mmol, 0.130 g), benzyl bromide (1.07 mmol, 0.130 mL) and tetrabutylammonium iodide (1.00 mmol, 0.379 g) in dichloromethane (2 mL) at room temperature. After 2h, the white suspension was filtered through filter paper, concentrated *in vacuo*, diluted with diethyl ether (10 mL), filtered through cotton wool and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 3 % to 10 % ethyl acetate in hexane) to afford ether **297** (140 mg, 64 %, 99 % by GC-MS) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.80; ν_{max}(neat)/cm^{-1} 2921w (CH_2), 1640s (C=C), 1454s, 1070s (C-O); $[\alpha]_D^{23}$ = +14.5° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.6, H-6), 5.02 (1H, ddd, *J* 17.0, ^2J 3.4, ^4J 1.7, H-7$_a$), 4.96 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.7, H-7$_b$), 4.66 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.49 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 3.28 (1H, dt, *J* 6.7, 5.4, H-3), 2.93 (1H, ddd, *J* 5.4, 3.9, 2.6, H-2), 2.77 (1H, dd, ^2J 5.3, *J* 3.9, H-1$_a$), 2.71 (1H, dd, ^2J 5.3, *J* 2.6, H-1$_b$), 2.36-2.09 (2H, m, H-5), 1.77-1.62 (2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 138.5, 138.2 (C-6), 128.4, 127.8, 127.7, 115.0 (C-7), 77.5 (C-3), 72.4 (CH_2Ph), 53.5 (C-2), 45.7 (C-1), 32.1 (C-5), 29.4 (C-4); [HRMS (EI, M$^+$) Found: 218.13064 Calc. For $C_{14}H_{19}FO_3$ 218.13068] *m/z* (EI) 218 (1 %, M$^+$), 175 (1), 157 (1), 107 (38), 91 (100, $C_7H_7^+$); and Payne product **298** (24 mg, 11 %, 98 % by GC-MS) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.74; ν_{max}(neat)/cm^{-1} 3330br (OH), 2926w (CH_2), 1721w, 1641w, 1452w, 1272s, 1096s (C-O), 1070s; $[\alpha]_D^{22}$ = -7.3°

(c = 0.80, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 5.83 (1H, ddt, J 16.9, 10.2, 6.6, H-6), 5.06 (1H, ddd, J 16.9, ^2J 3.3, ^4J 1.6, H-7_a), 5.00 (1H, ddd, J 10.2, ^2J 3.0, ^4J 1.2, H-7_b), 4.59 (1H, d, ^2J 11.9, CH_aH$_b$Ph), 4.55 (1H, d, ^2J 11.9, CH$_a$$H_b$Ph), 3.71 (1H, dd, ^2J 11.4, J 3.3, H-1_a), 3.47 (1H, dd, ^2J 11.4, J 5.6, H-1_b), 2.96 (1H, ddd, J 5.6, 3.3, 2.3, H-2), 2.85 (1H, ddd, J 5.8, 5.6, 2.3, H-3), 2.31-2.11 (2H, m, H-5), 1.78-1.55 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.0, 137.5 (C-6), 128.4, 127.7, 127.7, 115.3 (C-7), 73.3 (CH_2Ph), 70.4 (C-1), 57.1 (C-2), 55.6 (C-3), 31.0 (C-4), 30.1 (C-5); [HRMS (EI, M^+) Found: 218.13075 Calc. For $C_{14}H_{19}FO_3$ 218.13068] m/z (EI) 218 (1 %, M^+), 201 (1), 175 (15), 107 (47), 91 (100, $C_7H_7^+$); and a mixed fraction containing both isomers (41 mg, 19 %).

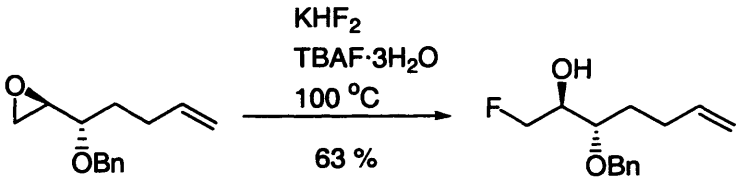
(-)-(2R,3S)-3-Benzyloxy-1,2-epoxyhept-6-ene 299



Sodium hydride (2.45 mmol, 98 mg of a 60 % dispersion in mineral oil), from which the oil had been washed with dry hexane, was added in portions to a stirred solution of epoxy alcohol **265** (2.00 mmol, 0.254 g), benzyl bromide (2.06 mmol, 0.250 mL) and tetrabutylammonium iodide (1.13 mmol, 0.425 g) in dichloromethane (4 mL) at room temperature. After 2h, the white suspension was filtered through filter paper, concentrated *in vacuo*, diluted with diethyl ether (10 mL), filtered through cotton wool and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 3 % to 10 % ethyl acetate in hexane) to afford ether **299** (307 mg, 71 %, 99 % by GC-MS) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.80; ν_{max}(neat)/cm^{-1} 2922w (CH_2), 1641s (C=C), 1454s, 1100s (C-O); $[\alpha]_D^{18}$ =

-18.8° (c = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 5.80 (1H, ddt, J 17.0, 10.2, 6.6, H-6), 5.02 (1H, ddd, J 17.0, ^2J 3.4, ^4J 1.7, H-7_a), 4.96 (1H, ddd, J 10.2, ^2J 3.4, ^4J 1.7, H-7_b), 4.66 (1H, d, ^2J 11.6, CH_aH$_b$Ph), 4.49 (1H, d, ^2J 11.6, CH$_a$$H_b$Ph), 3.28 (1H, dt, J 6.7, 5.4, H-3), 2.93 (1H, ddd, J 5.4, 3.9, 2.6, H-2), 2.77 (1H, dd, ^2J 5.3, J 3.9, H-1_a), 2.71 (1H, dd, ^2J 5.3, J 2.6, H-1_b), 2.36-2.09 (2H, m, H-5), 1.77-1.62 (2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 138.5, 138.2 (C-6), 128.4, 127.8, 127.7, 115.0 (C-7), 77.5 (C-3), 72.4 (CH_2Ph), 53.5 (C-2), 45.7 (C-1), 32.1 (C-5), 29.4 (C-4); [HRMS (EI, M^+) Found: 218.13069 Calc. For $C_{14}H_{19}FO_3$ 218.13068] m/z (EI) 218 (1 %, M^+), 175 (2), 157 (2), 107 (59), 91 (100, $C_7H_7^+$).

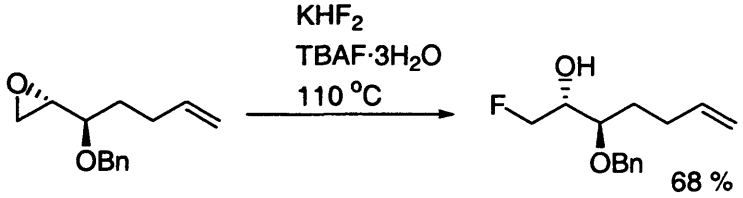
(+)-(2R,3S)-3-benzyloxy-1-fluorohept-6-en-2-ol 300



Epoxy ether **299** (1.17 mmol, 0.256 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (1.23 mmol, 0.399 g) and potassium hydrogen difluoride (5.11 mmol, 0.395 g) at 100 °C. After 1 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (5 mL), then carefully neutralised with solid $NaHCO_3$ (0.4 g). The organic phase is separated and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark red oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford alcohol **300** (175 mg, 63 %, 99 % by GC-MS, 92 % de and

93 % ee by NMR*, 95 % ee by HPLC) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.51; ν_{max}(neat)/cm^{-1} 3446br (OH), 2919w (CH_2), 1641w (C=C), 1454w, 1089s (C-O); $[\alpha]_D^{18}$ = +5.3° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.36-7.23 (5H, m, Ph), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.6, H-6), 5.01 (1H, ddd, *J* 17.0, ^2J 3.4, ^2J 1.6, H-7$_a$), 4.99 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.1, H-7$_b$), 4.54 (2H, s, CH_2Ph), 4.50 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.6, *J* 3.8, C*H*$_a$H$_b$F), 4.49 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.6, *J* 5.6, CH$_a$*H*$_b$F), 3.87 (1H, dtd, $^3J_{H\text{-}F}$ 20.1, *J* 5.6, 3.8, H-2), 3.49 (1H, ddd, *J* 7.3, 5.6, 4.4, H-3), 2.72 (1H, s, OH), 2.29-2.04 (2H, m, H-5), 1.79-1.58 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.4 (C-6), 138.2, 128.5, 128.0, 127.9, 115.1 (C-7), 84.6 (d, $^1J_{C\text{-}F}$ 166.9, C-1), 78.4 (d, $^3J_{C\text{-}F}$ 6.5, C-3), 72.5 (CH_2Ph), 71.7 (d, $^2J_{C\text{-}F}$ 18.7, C-2), 29.5 (C-4), 29.3 (C-5); δ_F (282 MHz, $CDCl_3$) –232.3 (1F, td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 20.1); [HRMS (EI, M^+) Found: 238.13698 Calc. For $C_{14}H_{19}O_2F$ 238.13691]; *m/z* (EI) 254 (1 %, M^+), 200 (1, [M-H_2O-HF]$^+$), 157 (8), 91 (100; $C_7H_7^+$); HPLC: Chiralcel OD-H. Hexane-^{i}PrOH, 99:1, 1mL/min, 254 nm; t_R (major) = 15.5 min; t_R (minor) = 17.5 min.

(-)-(2S,3R)-3-benzyloxy-1-fluorohept-6-en-2-ol 301



Epoxy ether **297** (1.00 mmol, 0.218 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (1.10 mmol, 0.356 g) and potassium hydrogen difluoride (3.88 mmol, 0.302 g) at 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and water (10 mL), then carefully

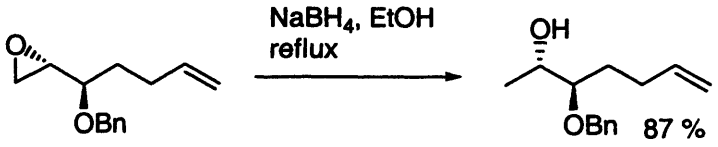
* The method for the determination of ee by NMR is described on p. 72, 92.

neutralised with $NaHCO_3$ (0.25 g). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase and extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a dark red oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford alcohol **301** (162 mg, 68 %, 99 % by GC-MS, 83 % de and 91 % ee by NMR*, 92 % ee by HPLC) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.51; ν_{max}(neat)/cm^{-1} 3424br (OH), 2920w (CH_2), 1641w (C=C), 1455w, 1090s (C-O); $[\alpha]_D^{23}$ = -4.6° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.36-7.23 (5H, m, Ph), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.6, H-6), 5.01 (1H, ddd, *J* 17.0, ^2J 3.4, ^2J 1.6, H-7$_a$), 4.99 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.1, H-7$_b$), 4.54 (2H, s, CH_2Ph), 4.50 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.6, *J* 3.8, C*H*$_a$H$_b$F), 4.49 (1H, ddd, $^2J_{H\text{-}F}$ 47.5, ^2J 9.6, *J* 5.6, CH$_a$*H*$_b$F), 3.87 (1H, dtd, $^3J_{H\text{-}F}$ 20.1, *J* 5.6, 3.8, H-2), 3.49 (1H, ddd, *J* 7.3, 5.6, 4.4, H-3), 2.72 (1H, s, OH), 2.29-2.04 (2H, m, H-5), 1.79-1.58 (2H, m, H-4); δ_C (75 MHz, $CDCl_3$) 138.4 (C-6), 138.2, 128.5, 128.0, 127.9, 115.1 (C-7), 84.6 (d, $^1J_{C\text{-}F}$ 166.9, C-1), 78.4 (d, $^3J_{C\text{-}F}$ 6.5, C-3), 72.5 (CH_2Ph), 71.7 (d, $^2J_{C\text{-}F}$ 18.7, C-2), 29.5 (C-4), 29.3 (C-5); δ_F (282 MHz, $CDCl_3$) –232.3 (1F, td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 20.1); [HRMS (EI, M$^+$) Found: 238.13692 Calc. For $C_{14}H_{19}O_2F$ 238.13691]; *m/z* (EI) 254 (1 %, M$^+$), 200 (1, [M-H_2O-HF]$^+$), 157 (8), 91 (100, $C_7H_7^+$); HPLC: Chiralcel OD-H. Hexane-^{i}PrOH, 99:1, 1mL/min, 254 nm; t_R (major) = 17.5 min; t_R (minor) = 15.9 min.

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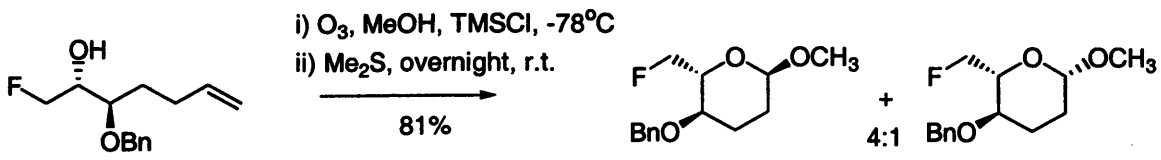
* The method for the determination of ee by NMR is described on p. 72, 92.

(+)-(2S,3R)-3-benzyloxy-hept-6-en-2-ol 302



Sodium borohydride (2.60 mmol, 100 mg) was added to a solution of epoxy ether **297** (1.27 mmol, 0.278 g) in ethanol (3 mL). The mixture was stirred at reflux for 3 h, then cooled to room temperature, diluted with water (5 mL), neutralised with concentrated HCl, and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil which was purified by Biotage column chromatography (gradient 10% to 20% ethyl acetate in hexane) to afford alcohol **302** (244 mg, 87 %, 99 % by GC-MS) as a colourless oil; R_f (20 % ethyl acetate in hexane) 0.44; ν_{max}(neat)/cm^{-1} 3434br (OH), 2934s (CH_2), 1640s (C=C), 1454s (CH_3), 1069s (C-O); $[\alpha]_D^{23}$ = +13.9° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 5.81 (1H, ddt, *J* 17.1, 10.2, 6.8, H-6), 5.01 (1H, ddd, *J* 17.1, ^2J 3.4, ^4J 1.6, H-7_a), 4.96 (1H, ddd, *J* 10.2, ^2J 3.4, ^4J 1.6, H-7_b), 4.60 (1H, d, ^2J 11.5, C$H_a$$H_b$Ph), 4.56 (1H, d, ^2J 11.5, C$H_a$$H_b$Ph), 3.99 (1H, qd, *J* 6.5, 3.3, H-2), 3.36 (1H, ddd, *J* 7.5, 3.9, 3.3, H-3), 2.32-2.02 (3H, m, OH, H-5), 1.78-1.47 (2H, m, H-4), 1.16 (3H, d, *J* 6.5, H-1); δ_C (75 MHz, $CDCl_3$) 138.5 (C-6), 128.5, 127.8, 127.7, 114.9 (C-7), 82.3 (C-3), 72.2 (CH_2Ph), 67.9 (C-2), 29.9 (C-5), 28.2 (C-4), 17.8 (C-1); [HRMS (EI, M^+) Found: 220.14636 Calc. For $C_{14}H_{19}FO_3$ 220.14633]; *m/z* (EI) 220 (1 %, M^+), 175 (5), 157 (3), 107 (2), 91 (100, $C_7H_7^+$).

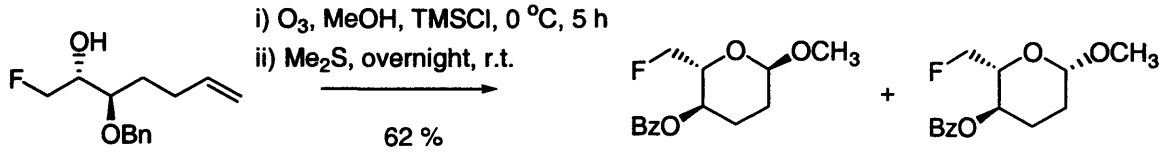
(-)-L-α-Methyl 5-*O*-benzyl-6-fluoro-amicetoside 303 and (-)-L-β-methyl 5-*O*-benzyl-6-fluoro-amicetoside 304



Trimethylchlorosilane (0.39 mmol, 50 μL) was added to a stirred solution of alcohol **301** (0.78 mmol, 0.187 g) in methanol (5 mL). The solution was cooled to –78 °C and a stream of dry O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then solid NaOH (0.2 g, 5 mmol) was added. After 1 hour the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers (α:β = 4:1 by GC-MS) which was purified by Biotage column chromatography (gradient 1% to 2% ethyl acetate in hexane) to afford major α-methyl amicetoside **303** (98 mg, 49 %, 99% by GC-MS) and minor β-methyl amicetoside **304** (35 mg, 18 %, 82 % by GC-MS) as clear colourless oils; Major anomer: R_f (20 % ethyl acetate in hexane) 0.63; ν_{max}(neat)/cm^{-1} 2950w (CH_2), 2897w (CH_2), 1455s (CH_3), 1223s (C-O-C), 1053s (C-O); $[\alpha]_D^{23}$ = -144.0° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.40-7.29 (5H, m, Ph), 4.70 (1H, d, *J* 3.1, H-1), 4.67 (1H, ddd, $^2J_{H\text{-}F}$ 47.7, *J* 10.0, 3.7, C*H*$_a$H$_b$F), 4.63 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.57 (1H, ddd, $^2J_{H\text{-}F}$ 47.7, *J* 10.0, 1.6, CH$_a$*H*$_b$F), 4.48 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 3.75 (1H, dddd, $^3J_{H\text{-}F}$ 28.4, *J* 9.7, 3.7, 1.6, H-5), 3.48 (1H, ddd, *J* 10.1, 9.7, 4.7, H-4), 3.34 (3H, s, OCH_3), 2.13-2.06 (1H, m, H-3$_a$), 1.91-1.68 (3H, m, H-2, H-3$_b$); δ_C (75 MHz, $CDCl_3$) 138.3, 128.4, 127.8, 127.7, 97.6 (C-1), 82.7 (d, $^1J_{C\text{-}F}$ 171.1, C-6), 71.8 (d, $^3J_{C\text{-}F}$ 6.7, C-4), 70.9 (d, $^2J_{C\text{-}F}$ 18.0, C-5), 70.8 (CH_2Ph), 54.5 (OCH_3), 28.8 (C-2), 23.9 (C-3); δ_F (282 MHz, $CDCl_3$) -234.51 (td, $^2J_{F\text{-}H}$ 47.7, $^3J_{F\text{-}H}$ 28.4); [HRMS (EI, M$^+$) Found: 254.13184 Calc. For $C_{14}H_{19}FO_3$

254.13182]; *m/z* (EI) 254 (1 %, M^+), 222 (2, $[M\text{-}MeOH]^+$), 191 (5), 107 (16), 101 (37), 91 (100, $C_7H_7^+$); Minor anomer: R_f (20 % ethyl acetate in hexane) 0.54; ν_{max}(neat)/cm^{-1} 2954w (CH_2), 2869w (CH_2), 1455s (CH_3), 1221s (C-O-C), 1063s (C-O); $[\alpha]_D^{18}$ = -7.4° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.37-7.26 (5H, m, Ph), 4.63 (2H, dd, $^2J_{H\text{-}F}$ 47.6, *J* 3.3, H-6), 4.61 (1H, d, ^2J 11.4, CH_aH_bPh), 4.47 (1H, d, ^2J 11.4, CH_aH_bPh), 4.41 (1H, dd, *J* 8.7, 2.2, H-1), 3.54 (1H, ddt, $^3J_{H\text{-}F}$ 24.7, *J* 9.2, 3.2, H-5), 3.49 (3H, s, OCH_3), 3.48 (1H, ddd, *J* 9.4, 9.2, 4.8, H-4), 2.26 (1H, ddd, *J* 4.6, 3.9, 3.0, H-3_a), 1.91 (1H, ddd, *J* 7.8, 3.0, 2.2, H-2_a), 1.60-1.46 (2H, m, H-2_b, H-3_b); δ_C (75 MHz, $CDCl_3$) 138.0, 128.5, 127.9, 127.8, 102.7 (C-1), 82.6 (d, $^1J_{C\text{-}F}$ 171.8, C-6), 77.3 (d, $^2J_{C\text{-}F}$ 18.0, C-5), 71.8 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 71.3 (CH_2Ph), 56.4 (OCH_3), 29.7 (C-2), 27.1 (C-3); δ_F (282 MHz, $CDCl_3$) -232.72 (td, $^2J_{F\text{-}H}$ 47.6, $^3J_{F\text{-}H}$ 24.7); [HRMS (EI, M^+) Found: 254.13175 Calc. For $C_{14}H_{19}FO_3$ 254.13182]; *m/z* (EI) 254 (1 %, M^+), 222 (1, $[M\text{-}MeOH]^+$), 191 (3), 107 (16), 101 (22), 91 (100, $C_7H_7^+$); and a mixed fraction containing both anomers (28 mg, 14 %).

(-)-L-α-methyl-5-*O*-benzoyl-6-fluoro-amicetoside 305 and (-)-L-β-methyl-5-*O*-benzoyl-6-fluoro-amicetoside 306

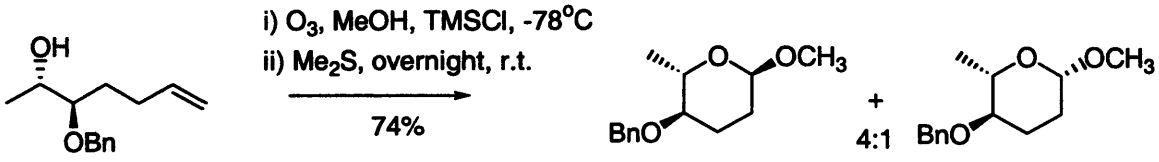


Trimethyl chlorosilane (0.39 mmol, 50 μL) was added to a stirred solution of alcohol **301** (2.15 mmol, 0.513 g) in methanol (10 mL). The solution was cooled to 0 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through it for 5 h. The solution was purged for 5 min with a stream of O_2, then dimethyl sulfide (9.4 mmol, 0.7 mL) was added. The mixture was stirred overnight at room temperature (12 h), the solution was

concentrated *in vacuo* to leave a yellow oil which was purified by Biotage column chromatography (gradient 1% to 2% ethyl acetate in hexane) to afford major α-methyl amicetoside **305** (247 mg, 46 %, 99 % by GC-MS) and minor β-methyl amicetoside **306** (59 mg, 11 %, 94 % by GC-MS) as clear colourless oils; Major anomer: R_f (35 % ethyl acetate in hexane) 0.70; ν_{max}(neat)/cm^{-1} 2954w (CH_2), 1718s (C=O), 1451w (CH_3), 1276s, 1051s (C-O); $[\alpha]_D^{23}$ = -155.5° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02 (2H, dd, *J* 7.5, 1.3, Ph), 7.56 (1H, tt, *J* 7.5, 1.3, Ph), 7.43 (2H, t, *J* 7.5, Ph), 5.03 (1H, ddd, *J* 10.3, 10.2, 5.0, H-4), 4.77 (1H, t, *J* 2.2, H-1), 4.54 (1H, dd, $^2J_{H\text{-}F}$ 47.5, *J* 3.9, C*H*$_a$H$_b$F), 4.54 (1H, d, $^2J_{H\text{-}F}$ 47.5, *J* 2.5, CH$_a$*H*$_b$F), 4.07 (1H, dddd, $^3J_{H\text{-}F}$ 24.6, *J* 10.2, 3.9, 2.5, H-5), 3.41 (3H, s, OCH_3), 2.18-2.12 (1H, m, H-3$_a$), 2.06-1.82 (3H, m, H-2, H-3$_b$); δ_C (75 MHz, $CDCl_3$) 165.3 (C=O), 133.2, 129.9, 129.6, 128.4, 97.5 (C-1), 82.4 (d, $^1J_{C\text{-}F}$ 172.8, C-6), 69.5 (d, $^2J_{C\text{-}F}$ 18.3, C-5), 67.6 (d, $^3J_{C\text{-}F}$ 7.3, C-4), 54.7 (OCH_3), 28.6 (C-3), 24.0 (C-2); δ_F (282 MHz, $CDCl_3$) –232.9 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 24.6); [HRMS (EI, [M-1]$^+$) Found: 267.10323 Calc. For $C_{14}H_{16}O_4F$ 267.10326]; *m/z* (EI) 268 (1 %, M$^+$), 237 (5), 206 (1), 145 (15), 114 (11), 105 (100, $C_7H_5O^+$); Minor anomer: R_f (35 % ethyl acetate in hexane) 0.56; ν_{max}(neat)/cm^{-1} 2959w (CH_2), 1718s (C=O), 1451w (CH_3), 1267s, 1059s (C-O); $[\alpha]_D^{21}$ = -18.0° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.02 (2H, dd, *J* 7.5, 1.3, Ph), 7.58 (1H, tt, *J* 7.5, 1.3, Ph), 7.45 (2H, t, *J* 7.5, Ph), 4.97 (1H, ddd, *J* 9.2, 9.0, 4.9, H-4), 4.58 (1H, d, $^2J_{H\text{-}F}$ 47.5, *J* 3.5, C*H*$_a$H$_b$F), 4.57 (1H, d, $^2J_{H\text{-}F}$ 47.2, *J* 4.7, CH$_a$*H*$_b$F), 4.54 (1H, d, *J* 2.5, H-1), 3.89 (1H, dddd, $^3J_{H\text{-}F}$ 21.0, *J* 9.0, 4.7, 3.5, H-5), 3.52 (3H, s, OCH_3), 2.42-2.32 (1H, m, H-3$_a$), 2.04-1.66 (3H, m, H-2, H-3$_b$); δ_C (75 MHz, $CDCl_3$) 165.5 (C=O), 133.3, 129.8, 129.6, 128.5, 102.3 (C-1), 82.4 (d, $^1J_{C\text{-}F}$ 173.1, C-6), 75.8 (d, $^2J_{C\text{-}F}$ 19.2, C-5), 67.5 (d, $^3J_{C\text{-}F}$ 6.9, C-4), 56.4 (OCH_3), 29.2 (C-2), 26.6 (C-3); δ_F (282 MHz, $CDCl_3$) –230.7 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 21.0); [HRMS (EI, [M-1]$^+$) Found: 267.10320 Calc. For $C_{14}H_{16}O_4F$ 267.10326]; *m/z* (EI) 268 (1 %, M$^+$), 237 (3), 146 (10),

126 (4), 114 (6), 105 (100, $C_7H_5O^+$); and a mixed fraction containing both anomers (30 mg, 6 %).

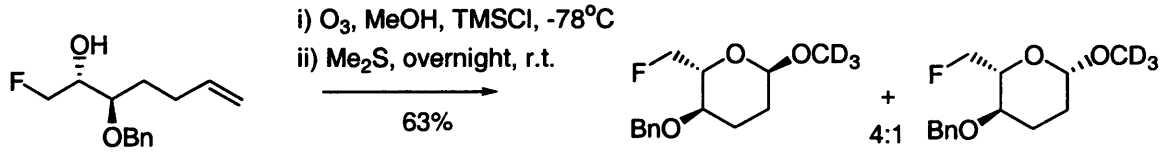
(-)-L-α-Methyl 5-*O*-benzyl-amicetoside 307 and (-)-L-β-methyl 5-*O*-benzyl-amicetoside 308



Trimethylchlorosilane (0.39 mmol, 50 μL) was added to a stirred solution of alcohol **302** (0.71 mmol, 0.157 g) in methanol (6 mL). The solution was cooled to –78 °C and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred overnight at room temperature (12 h), then solid NaOH (0.2 g, 5 mmol) was added. After 1 hour the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers (α:β = 4:1 by GC-MS) which was purified by Biotage column chromatography (gradient 1% to 2% ethyl acetate in hexane) to afford major L-α-methyl amicetoside **307** (73 mg, 43 %, 99% by GC-MS) and minor β-methyl amicetoside **308** (20 mg, 12 %, 95 % by GC-MS) as clear colourless oils; Major anomer: R_f (20 % ethyl acetate in hexane) 0.69; ν_{max}(neat)/cm^{-1} 2932w (CH_2), 2892w (CH_2), 1454w (CH_3), 1211w (C-O-C), 1127s, 1055s (C-O); $[\alpha]_D^{23}$ = -121.2° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.36-7.25 (5H, m, Ph), 4.64 (1H, d, ^2J 11.7, C*H*$_a$H$_b$Ph), 4.61 (1H, d, *J* 2.0, H-1), 4.47 (1H, d, ^2J 11.7, CH$_a$*H*$_b$Ph), 3.72 (1H, dq, *J* 9.2, 6.2, H-5), 3.34 (3H, s, OCH_3), 3.08 (1H, ddd, *J* 10.2, 9.2, 4.4, H-4), 2.02-1.97 (1H, m, H-3$_a$), 1.87-

1.63 (3H, m, H-2, H-3_b), 1.27 (3H, d, *J* 6.2, H-6); δ_C (75 MHz, $CDCl_3$) 138.6, 128.4, 127.7, 127.6, 97.3 (C-1), 78.8 (C-4), 70.6 (CH_2Ph), 67.8 (C-5), 54.3 (OCH_3), 29.3 (C-3), 23.9 (C-2), 18.3 (C-6); [HRMS (EI, M^+) Found: 236.14125 Calc. For $C_{14}H_{20}O_3$ 236.14125]; *m/z* (EI) 236 (1 %, M^+), 204 (1, $[M\text{-}MeOH]^+$), 192 (1), 107 (17), 101 (43), 91 (100, $C_7H_7^+$); Minor anomer: R_f (20 % ethyl acetate in hexane) 0.64; ν_{max}(neat)/cm^{-1} 2932w (CH_2), 2867w (CH_2), 1453w (CH_3), 1390w, 1068s (C-O); $[\alpha]_D^{22}$ = -7.2° (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 4.65 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.50 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 4.39 (1H, dd, *J* 8.9, 2.1, H-1), 3.47 (1H, dq, *J* 9.8, 6.2, H-5), 3.10 (1H, ddd, J 10.0, 9.8, 4.5, H-4), 2.26-2.20 (1H, m, H-3_a), 1.96-1.90 (1H, m, H-2_a), 1.60-1.46 (2H, m, H-2_b, H-3_b), 1.37 (3H, d, *J* 6.2, H-6); δ_C (75 MHz, $CDCl_3$) 138.4, 128.4, 127.7, 127.6, 102.5 (C-1), 78.5 (C-4), 74.6 (C-5), 71.3 (CH_2Ph), 56.2 (OCH_3), 30.3 (C-2), 27.4 (C-3), 18.5 (C-6); [HRMS (EI, M^+) Found: 236.14111 Calc. For $C_{14}H_{20}O_3$ 236.14125]; *m/z* (EI) 236 (1 %, M^+), 134 (1), 107 (7), 101 (35), 91 (100, $C_7H_7^+$); and a mixed fraction containing both anomers (32 mg, 19 %).

L-α-(d_3-Methyl) 5-*O*-benzyl-6-fluoro-amicetoside 312 and L-β-(d_3-methyl) 5-*O*-benzyl-6-fluoro-amicetoside 313

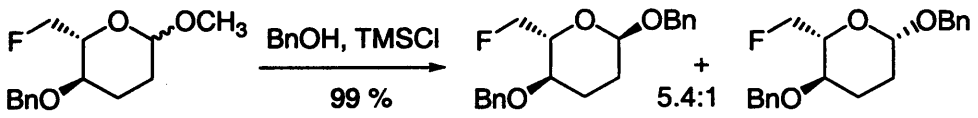


Trimethylchlorosilane (0.39 mmol, 50 μL) was added to a stirred solution of alcohol **301** (2.65 mmol, 0.633 g) in methanol (10 mL). The solution was cooled to –78°C and a stream of dry O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (13.6 mmol, 1.0 mL) was added. The mixture was stirred

overnight at room temperature (12 h), concentrated *in vacuo*, diluted with acidic d_3-methanol (1 ml + 10 μL TMSCl) and stirred for 1 h. Solid NaOH (0.2 g, 5 mmol) was added and after 1 hour the solution was neutralised with concentrated HCl (0.7 mL), concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers which was purified by Biotage column chromatography (gradient 1% to 2% ethyl acetate in hexane) to afford major α-methyl amicetoside **312** (134 mg, 20 %, 99% by GC-MS) and minor β-methyl amicetoside **313** (60 mg, 9 %, 99 % by GC-MS) as clear colourless oils; Major anomer: R_f (20 % ethyl acetate in hexane) 0.63; ν_{max}(neat)/cm^{-1} 2952w (CH_2), 2895w (CH_2), 1456s (CH_3), 1371w, 1224s (C-O-C), 1046s (C-O); $[\alpha]_D^{20}$ = -141.1° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.36-7.22 (5H, m, Ph), 4.68 (1H, d, *J* 3.0, H-1), 4.66 (1H, ddd, $^2J_{H\text{-}F}$ 47.7, ^2J 9.9, *J* 3.8, C*H*$_a$H$_b$F), 4.63 (1H, d, ^2J 11.6, C*H*$_a$H$_b$Ph), 4.56 (1H, ddd, $^2J_{H\text{-}F}$ 47.7, ^2J 9.9, *J* 1.7, CH$_a$*H*$_b$F), 4.46 (1H, d, ^2J 11.6, CH$_a$*H*$_b$Ph), 3.74 (1H, dddd, $^3J_{H\text{-}F}$ 28.3, *J* 9.7, 3.8, 1.7, H-5), 3.47 (1H, ddd, *J* 9.9, 9.7, 4.7, H-4), 2.09-1.99 (1H, m, H-3$_a$), 1.86-1.61 (3H, m, H-2, H-3$_b$); δ_C (75 MHz, $CDCl_3$) 138.3, 128.4, 128.2, 127.7, 97.5 (C-1), 82.7 (d, $^1J_{C\text{-}F}$ 171.2, C-6), 71.9 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 70.9 (d, $^2J_{C\text{-}F}$ 17.6, C-5), 70.8 (CH_2Ph), 28.8 (C-2), 23.9 (C-3); δ_F (282 MHz, $CDCl_3$) -234.40 (td, $^2J_{F\text{-}H}$ 47.7, $^3J_{F\text{-}H}$ 28.3); [HRMS (EI, M$^+$) Found: 257.15072 Calc. For $C_{14}H_{19}D_3O_3F$ 257.15035]; *m/z* (EI) 257 (1 %, M$^+$), 222 (2, [M-CD_3OH]$^+$), 194 (4), 107 (10), 104 (25), 91 (100, $C_7H_7^+$); Minor anomer: R_f (20 % ethyl acetate in hexane) 0.54; ν_{max}(neat)/cm^{-1} 2953w (CH_2), 2865w (CH_2), 1455s (CH_3), 1397w, 1169s (C-O-C), 1074s (C-O); $[\alpha]_D^{20}$ = -3.8° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38-7.24 (5H, m, Ph), 4.63 (2H, dd, $^2J_{H\text{-}F}$ 47.7, *J* 3.2, H-6), 4.62 (1H, d, ^2J 11.5, C*H*$_a$H$_b$Ph), 4.47 (1H, d, ^2J 11.5, CH$_a$*H*$_b$Ph), 4.41 (1H, dd, *J* 8.8, 2.2, H-1), 3.54 (1H, ddt, $^3J_{H\text{-}F}$ 24.8, *J* 9.1, 3.2, H-5), 3.50-3.39 (1H, m, H-4), 2.28-2.20 (1H, m, H-3$_a$), 1.95-1.85 (1H, m, H-2$_a$), 1.67-1.44 (2H, m, H-2$_b$, H-3$_b$); δ_C (75 MHz, $CDCl_3$) 138.0, 128.5, 127.9, 127.8, 102.6 (C-1), 82.6 (d, $^1J_{C\text{-}F}$ 171.8, C-6), 77.3 (d, $^2J_{C\text{-}F}$ 18.1, C-5), 71.8 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 71.3 (CH_2Ph), 29.7 (C-2), 27.1

(C-3); δ_F (282 MHz, $CDCl_3$) -232.72 (td, $^2J_{F-H}$ 47.7, $^3J_{F-H}$ 24.8); [HRMS (EI, M^+) Found: 257.15071 Calc. For $C_{14}H_{19}D_3O_3F$ 257.15035]; *m/z* (EI) 257 (1 %, M^+), 222 (1, $[M-CD_3OH]^+$), 194 (2), 107 (5), 104 (9), 91 (100, $C_7H_7^+$); and a mixed fraction containing both anomers (238 mg, 35 %).

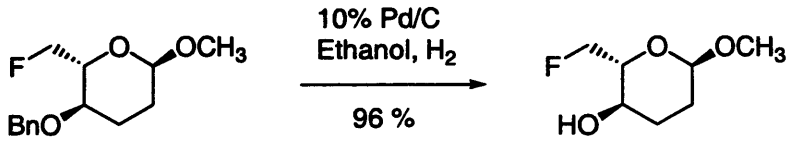
L-α-Benzyl 5-*O*-benzyl-6-fluoro-amicetoside 315 and L-β-benzyl 5-*O*-benzyl-6-fluoro-amicetoside 316



A mixture of trimethylchlorosilane (20 μL) and benzyl alcohol (3.2 mmol, 0.35 g) was added to a flask containing methyl amicetoside **314** (0.44 mmol, 111 mg). The solution was stirred and heated (50 °C) for 3 h, then purified by Biotage column chromatography (gradient 0 % to 10 % ethyl acetate in hexane) to afford benzyl amicetosides **315/316** (144 mg, 99 %, 99% by GC-MS) as a 5.4:1 (by NMR) mixture of anomers as a clear colourless oil; R_f (20 % ethyl acetate in hexane) 0.88; ν_{max}(neat)/cm^{-1} 2951w (CH_2), 1455w, 1126w, 1073s (C-O), 1025s, 972s; α-anomer (Major): δ_H (300 MHz, $CDCl_3$) 7.37-7.15 (10H, m, Ph), 4.90 (1H, d, *J* 3.2, H-1), 4.77-4.41 (6H, m, H-6, CH_2Ph), 3.90-3.65 (1H, m, H-5), 3.63-3.32 (1H, m, H-4), 2.28-1.39 (4H, m, H-2, H-3); δ_C (75 MHz, $CDCl_3$) 138.3, 138.0, 128.54, 128.50, 127.99, 127.93, 127.84, 127.75, 95.9 (C-1), 82.7 (d, $^1J_{C-F}$ 171.3, C-6), 72.1 (d, $^3J_{C-F}$ 6.7, C-4), 71.4 (d, $^2J_{C-F}$ 17.5, C-5), 71.0 (CH_2Ph), 68.9 (CH_2Ph), 29.0 (C-3), 24.0 (C-2); δ_F (282 MHz, $CDCl_3$) –234.4 (td, $^2J_{F-H}$ 47.7, $^3J_{F-H}$ 28.6); β-anomer (Minor): δ_H (300 MHz, $CDCl_3$) 7.37-7.15 (10H, m, Ph), 4.77-4.41 (7H, m, H-1, H-6, CH_2Ph), 3.90-3.65 (1H, m, H-5), 3.63-3.32 (1H, m, H-4), 2.28-1.39 (4H, m, H-2, H-3); δ_C (75 MHz, $CDCl_3$) 138.2, 137.8, 128.6, 128.5, 128.1, 127.9, 127.8, 127.8, 100.5 (C-1), 82.7 (d, $^1J_{C-F}$ 171.3, C-6), 71.8 (d, $^3J_{C-F}$ 6.9, C-4), 77.4 (d, $^2J_{C-F}$ 18.0,

C-5), 71.0 (CH_2Ph), 70.3 (CH_2Ph), 29.9, 27.2; δ_F (282 MHz, $CDCl_3$) –232.2 (td, $^2J_{F\text{-}H}$ 47.6, $^3J_{F\text{-}H}$ 24.2); [HRMS (EI, M^+) Found: 330.16321 Calc. For $C_{20}H_{23}FO_3$ 330.16312]; *m/z* (EI) 330 (1 %, M^+), 223 (2), 177 (2), 133 (3), 116 (4), 107 (15), 91 (100, $C_7H_7^+$).

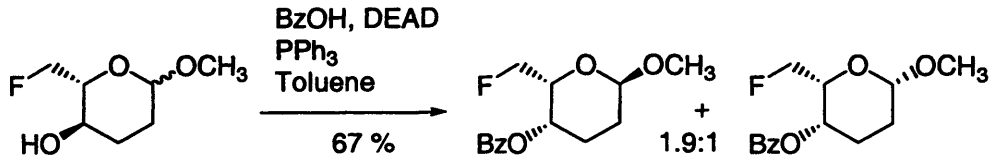
L-α-Methyl 6-fluoro-amicetoside 317



A flask containing a stirred solution of benzyl ether **303** (0.39 mmol, 98 mg) in ethanol (6 mL) was evacuated and flushed with hydrogen (3 times), then 10 % Palladium on carbon (30 mg) was added. The mixture was evacuated and flushed with hydrogen (3 times) again, left under an atmosphere of hydrogen at room temperature and atmospheric pressure for 48 h. The mixture was filtered through Celite; the filter bed was washed with EtOH (3 x 2 mL), and the combined filtrates were concentrated *in vacuo* to leave a dark oil which was purified by Biotage column chromatography (gradient 30% to 50% ethyl acetate in hexane) to afford methyl pyranoside **317** (61 mg, 96 %, 99 % by GC-MS) as a clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.28; ν_{max}(neat)/cm^{-1} 3408br (OH), 2943w (CH_2), 1370w, 1129s (C-O), 1048s (C-O); $[\alpha]_D^{20}$ = -135.6° (*c* = 0.70, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.68 (1H, ddd, $^2J_{H\text{-}F}$ 47.6, ^2J 10.0, *J* 3.6, H-6_a), 4.71 (1H, d, *J* 2.6, H-1), 4.60 (1H, ddd, $^2J_{H\text{-}F}$ 47.6, ^2J 10.0, *J* 1.8, H-6_b), 3.71-3.58 (2H, m, H-4, H-5), 3.47 (3H, s, OCH_3), 2.20 (1H, br.s, OH), 1.93-1.73 (4H, m, H-2, H-3); δ_C (75 MHz, $CDCl_3$) 97.5 (C-1), 82.8 (d, $^1J_{C\text{-}F}$ 170.4, C-6), 72.2 (d, $^2J_{C\text{-}F}$ 17.5, C-5), 65.2 (d, $^3J_{C\text{-}F}$ 7.1, C-4), 54.6 (OCH_3), 29.0 (C-3), 27.4 (C-2); δ_F (282 MHz, $CDCl_3$) –234.7 (td, $^2J_{F\text{-}H}$ 47.6, $^3J_{F\text{-}H}$ 26.8); [HRMS (EI, $[M\text{-}1]^+$) Found: 163.07703 Calc.

For $C_7H_{12}O_3F$ 163.07705]; *m/z* (EI) 164 (1 %, M^+), 133 (15, $[M-CH_4O]^+$), 115 (6), 102 (17, $[M-C_2H_3OF]^+$), 76 (15), 69 (37), 58 (100, $C_3H_6O^+$).

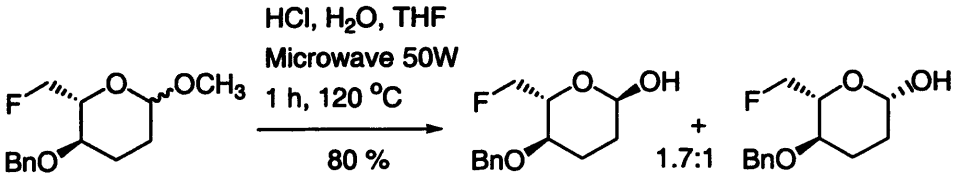
(+)-L-α-Methyl 5-*O*-benzoyl-6-fluoro-rhodinoside 320 and (-)-L-β-methyl 5-*O*-benzoyl-6-fluoro-rhodinoside 321



Diethylazodicarboxylate (4.76 mmol, 0.75 mL) was added to a stirred solution of methyl pyranoside **319** (0.81 mmol, 0.133 g) and triphenylphosphine (4.95 mmol, 1.312 g) in dry toluene (10 mL) at room temperature, then benzoic acid (4.95 mmol, 0.610 g) was added immediately after. After 3 h, the mixture was concentrated *in vacuo* to leave a yellow liquid which was purified by Biotage column chromatography (gradient 10 % to 20 % ethyl acetate in hexane) to afford α-methyl rhodinoside **320** (95 mg, 44 %, 98 % by GC-MS), which crystallized very slowly as white needles, and β-methyl rhodinoside **321** (51 mg, 23 %, 99 % by GC-MS) as clear colourless oils; Major: mp 51-54 °C; R_f (35 % ethyl acetate in hexane) 0.71; ν_{max}(neat)/cm^{-1} 2941w (CH_2), 2900w (CH_2), 1716s (C=O), 1451w, 1268s, 1111s, 1022s (C-O); $[\alpha]_D^{20}$ = +59.6° (*c* = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 8.13-8.06 (2H, m, Ph), 7.63-7.54 (1H, m, Ph), 7.50-7.41 (2H, m, Ph), 5.21 (1H, s, H-4), 4.88 (1H, d, *J* 2.4, H-1), 4.51 (1H, dd, $^2J_{H\text{-}F}$ 46.9, *J* 5.8, H-6_a), 4.49 (1H, dd, $^2J_{H\text{-}F}$ 46.9, *J* 5.8, H-6_b), 4.27 (1H, dtd, $^3J_{H\text{-}F}$ 15.2, *J* 5.8, 1.0, H-5), 3.44 (OCH_3), 2.25-1.74 (3H, m, H-2_a, H-3), 1.70-1.61 (1H, m, H-2_b); δ_C (75 MHz, $CDCl_3$) 165.8 (C=O), 133.6, 130.0, 129.7, 128.5, 97.9 (C-1), 83.0 (d, $^1J_{C\text{-}F}$ 169.7, C-6), 68.1 (d, $^2J_{C\text{-}F}$ 21.6, C-5), 67.1 (d, $^3J_{C\text{-}F}$ 7.2, C-4), 54.9 (OCH_3), 24.3 (C-2), 22.6 (C-3); δ_F (282 MHz, $CDCl_3$) –230.8 (td, $^2J_{F\text{-}H}$ 46.9, $^3J_{F\text{-}H}$ 15.2); [HRMS (EI, M^+) Found: 268.11107 Calc. For

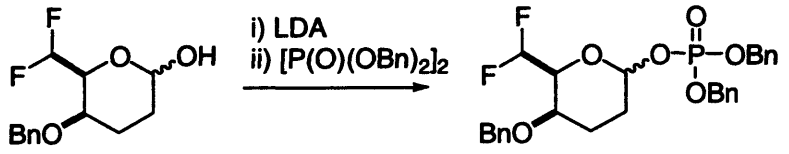
$C_{14}H_{17}FO_4$ 268.11109]; *m/z* (EI) 268 (1 %, M^+), 237 (6), 206 (4), 146 (5), 126 (3), 114 (6), 105 (100, $C_7H_5O^+$); The stereochemistry and identity of the crystalline anomer were confirmed by XRD analysis; Crystal data: $C_{14}H_{17}O_4F$, crystal size 0.13 x 0.10 x 0.08 mm^3, M = 268.28, orthorhombic, space group P2(1)2(1)2, unit cell dimensions a = 13.508(3), b = 7.6277(15), c = 13.127(3) Å, α = 90°, β = 90°, γ = 90°, V = 1352.6(4) $Å^3$, Z = 4, D_{calc} = 1.317 Mg m^{-3}, $F(000)$ = 568, μ(Mo-Kα) = 0.104 mm^{-1}, T = 150(2) K, 1401 total reflections measured, 1401 independent, (R_{int} = 0.0000) which were used in all calculations. Final R indices (for reflections with $I > 2\sigma(I)$) were $R1$ = 0.0512, $\omega R2$ = 0.0701; R indices (all data) $R1$ = 0.0763, $\omega R2$ = 0.0757; Minor: R_f (35 % ethyl acetate in hexane) 0.51; ν_{max}(neat)/cm^{-1} 2961w (CH_2), 2842w (CH_2), 1716s (C=O), 1452w, 1268s, 1110s, 1078s (C-O); $[\alpha]_D^{19}$ = -32.7° (c = 1.00, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 8.13-8.05 (2H, m, Ph), 7.62-7.55 (1H, m, Ph), 7.50-7.41 (2H, m, Ph), 5.19-5.16 (1H, m, H-4), 4.57 (1H, dd, $^2J_{H\text{-}F}$ 46.8, J 6.4, H-6_a), 4.56 (1H, dd, $^2J_{H\text{-}F}$ 46.8, J 5.2, H-6_b), 4.52 (1H, dd, J 8.5, 2.7, H-1), 4.03 (1H, dddd, $^3J_{H\text{-}F}$ 13.2, J 6.3, 5.6, 1.6, H-5), 3.58 (OCH_3), 2.29-215 (1H, m, H-2_a), 1.96-1.71 (3H, env., H-2_b, H-3); δ_C (75 MHz, $CDCl_3$) 165.8 (C=O), 133.3, 130.2, 129.8, 128.5, 103.0 (C-1), 82.2 (d, $^1J_{C\text{-}F}$ 169.7, C-6), 75.2 (d, $^2J_{C\text{-}F}$ 22.3, C-5), 66.0 (d, $^3J_{C\text{-}F}$ 6.4, C-4), 56.5 (OCH_3), 26.8 (C-2), 26.2 (C-3); δ_F (282 MHz, $CDCl_3$) –230.6 (td, $^2J_{F\text{-}H}$ 46.8, $^3J_{F\text{-}H}$ 13.2); [HRMS (EI, M^+) Found: 268.11120 Calc. For $C_{14}H_{17}FO_4$ 268.11109]; *m/z* (EI) 268 (1 %, M^+), 237 (2), 206 (3), 146 (4), 126 (4), 105 (100, $C_7H_5O^+$).

L-α-5-*O*-benzyl-6-fluoro-amicetose 322 and L-β-5-*O*-benzyl-6-fluoro-amicetose 323



Concentrated hydrochloric acid (20 μL) was added to a solution of amicetoside **314** (0.40 mmol, 101 mg) in THF (4 mL) and H_2O (150 mg). The solution was stirred and heated (microwave 50W) at 120 °C for 1 h. The mixture was diluted with Et_2O (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil containing a mixture of anomers which was purified by Biotage column chromatography (gradient 20% to 50% ethyl acetate in hexane) to afford amicetose **322/323** (76 mg, 80 %, 99% by GC-MS) as a (1.7:1 by NMR) mixture of inseparable anomers as a clear colourless oil; R_f (35 % ethyl acetate in hexane) 0.43; ν_{max}(neat)/cm^{-1} 3414br (OH), 2951w (CH_2), 2874w (CH_2), 1455w, 1220w, 1068s (C-O), 978s; α-anomer (Major): δ_H (300 MHz, $CDCl_3$) 7.38-7.25 (5H, m, Ph), 5.29 (1H, d, *J* 3.1, H-1), 4.77-4.44 (4H, m, H-6, CH_2Ph), 4.03 (1H, dddd, $^3J_{H\text{-}F}$ 27.5, *J* 9.6, 3.8, 1.4, H-5), 3.73-3.35 (1H, m, H-4), 2.32-1.42 (5H, m, H-2, H-3, OH); δ_C (75 MHz, $CDCl_3$) 138.2, 128.5, 127.9, 127.7, 91.0 (C-1), 82.9 (d, $^1J_{C\text{-}F}$ 170.9, C-6), 72.1 (d, $^3J_{C\text{-}F}$ 6.9, C-4), 71.0 (d, $^2J_{C\text{-}F}$ 17.4, C-5), 70.8 (CH_2Ph), 28.9 (C-3), 23.1 (C-2); δ_F (282 MHz, $CDCl_3$) –234.5 (td, $^2J_{F\text{-}H}$ 47.7, $^3J_{F\text{-}H}$ 27.6); β-anomer (Minor): δ_H (300 MHz, $CDCl_3$) 4.84 (1H, dd, *J* 8.6, 1.8, H-1), 4.77-4.44 (4H, m, H-6, CH_2Ph), 3.73-3.35 (2H, m, H-4, H-5), 2.32-1.42 (5H, m, H-2, H-3, OH); δ_C (75 MHz, $CDCl_3$) 137.9, 128.5, 127.9, 127.8, 96.1 (C-1), 82.6 (d, $^1J_{C\text{-}F}$ 171.5, C-6), 77.4 (d, $^2J_{C\text{-}F}$ 17.7, C-5), 71.5 (d, $^3J_{C\text{-}F}$ 6.8, C-4), 71.3 (CH_2Ph), 31.3 (C-2), 27.3 (C-3); δ_F (282 MHz, $CDCl_3$) –233.2 (td, $^2J_{F\text{-}H}$ 47.6, $^3J_{F\text{-}H}$ 24.9); [HRMS (EI, M^+) Found: 240.11611 Calc. For $C_{13}H_{17}FO_3$ 240.11617]; *m/z* (EI) 240 (1 %, M^+), 176 (1), 147 (3), 136 (23), 107 (2), 91 (100, $C_7H_7^+$).

Attempted preparation of 5-O-benzyl-6,6-difluoro-rhodinose 1-dibenzylphosphate



A solution of protected rhodinose **250/251** (0.30 mmol, 78 mg) in dry THF (1 mL) was cooled to –78 °C under N_2 and LDA (0.7 mL of a solution prepared with ^{n}BuLi (0.34 mL of 2.35 M solution in hexane) and DIPA (0.10 mL)) was added dropwise. After 30 min a solution of tetrabenzyl pyrophosphate (0.42 mmol, 0.255 g) was added. The reaction was warmed to 0 °C and stirred 3 h. The soution was subsequently diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to obtain a yellow oil identified by NMR as starting material **250/251**.

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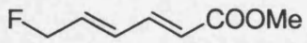
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6 Appendix

6.1 Appendix I, Crystal Structures

6.1.1 6-Fluoro-hexa-2,4-dienoic acid methyl ester 91



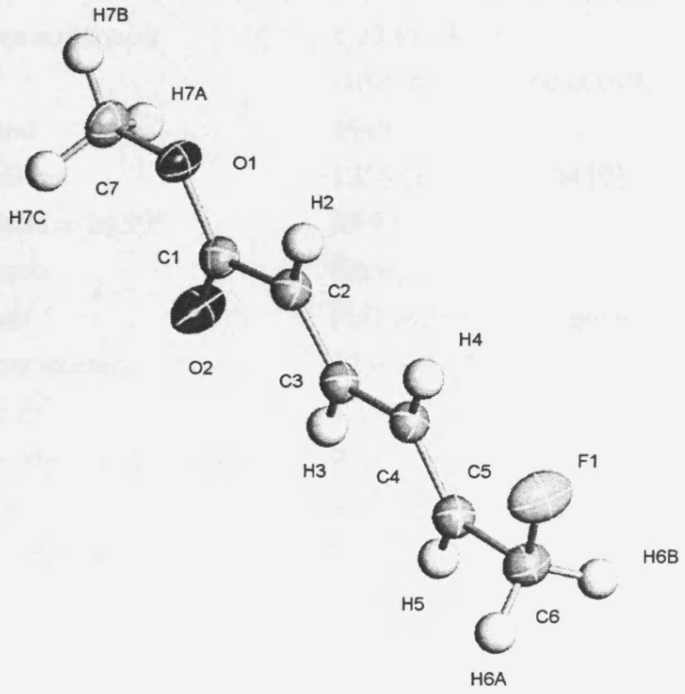


Table 1. Crystal data and structure refinement for 05063.

Identification code	05063	
Empirical formula	C7 H9 F O2	
Formula weight	144.14	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 8.4625(16) Å	α = 90°.
	b = 8.0276(16) Å	β = 90.378(5)°.
	c = 21.142(4) Å	γ = 90°.
Volume	1436.2(5) $Å^3$	
Z	8	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.113 mm^{-1}	
F(000)	608	
Crystal size	0.23 x 0.16 x 0.15 mm^3	
Theta range for data collection	1.93 to 24.99°.	
Index ranges	-10<=h<=10, -9<=k<=9, -25<=l<=24	
Reflections collected	4948	
Independent reflections	1256 [R(int) = 0.0410]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1256 / 0 / 92	
Goodness-of-fit on F^2	1.151	
Final R indices [I>2sigma(I)]	R1 = 0.0455, wR2 = 0.1063	
R indices (all data)	R1 = 0.0535, wR2 = 0.1101	
Largest diff. peak and hole	0.223 and -0.140 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 05063. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	-3650(1)	2355(1)	7003(1)	49(1)
O(1)	4134(1)	1829(2)	5490(1)	32(1)
O(2)	4017(2)	4366(2)	5926(1)	44(1)
C(1)	3408(2)	3036(2)	5814(1)	28(1)
C(2)	1815(2)	2528(2)	6012(1)	28(1)
C(3)	896(2)	3557(2)	6338(1)	28(1)
C(4)	-677(2)	3174(2)	6560(1)	28(1)
C(5)	-1532(2)	4252(2)	6890(1)	30(1)
C(6)	-3140(2)	3960(2)	7141(1)	33(1)
C(7)	5722(2)	2204(2)	5289(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for 05063.

F(1)-C(6)	1.390(2)
O(1)-C(1)	1.338(2)
O(1)-C(7)	1.444(2)
O(2)-C(1)	1.208(2)
C(1)-C(2)	1.472(2)
C(2)-C(3)	1.330(2)
C(2)-H(2)	0.9500
C(3)-C(4)	1.447(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.329(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.483(2)
C(5)-H(5)	0.9500
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800

C(1)-O(1)-C(7)	115.57(14)
O(2)-C(1)-O(1)	122.93(17)
O(2)-C(1)-C(2)	125.40(17)
O(1)-C(1)-C(2)	111.67(15)
C(3)-C(2)-C(1)	121.04(16)
C(3)-C(2)-H(2)	119.5
C(1)-C(2)-H(2)	119.5
C(2)-C(3)-C(4)	125.37(17)
C(2)-C(3)-H(3)	117.3
C(4)-C(3)-H(3)	117.3
C(5)-C(4)-C(3)	122.49(17)
C(5)-C(4)-H(4)	118.8
C(3)-C(4)-H(4)	118.8
C(4)-C(5)-C(6)	126.13(17)
C(4)-C(5)-H(5)	116.9
C(6)-C(5)-H(5)	116.9
F(1)-C(6)-C(5)	110.85(15)
F(1)-C(6)-H(6A)	109.5
C(5)-C(6)-H(6A)	109.5
F(1)-C(6)-H(6B)	109.5
C(5)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	108.1
O(1)-C(7)-H(7A)	109.5
O(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
O(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05063. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

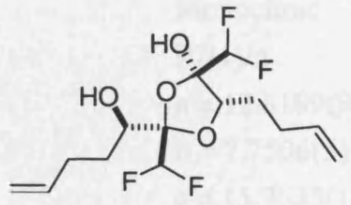
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	43(1)	41(1)	63(1)	-5(1)	20(1)	-14(1)
O(1)	26(1)	30(1)	39(1)	-4(1)	8(1)	-3(1)
O(2)	30(1)	33(1)	68(1)	-13(1)	10(1)	-8(1)
C(1)	26(1)	25(1)	32(1)	1(1)	0(1)	-1(1)
C(2)	26(1)	26(1)	31(1)	0(1)	-1(1)	-3(1)
C(3)	26(1)	27(1)	30(1)	1(1)	-2(1)	-3(1)
C(4)	26(1)	26(1)	31(1)	1(1)	0(1)	-3(1)
C(5)	29(1)	28(1)	33(1)	1(1)	0(1)	-2(1)
C(6)	32(1)	33(1)	35(1)	0(1)	6(1)	-2(1)
C(7)	22(1)	42(1)	42(1)	-1(1)	7(1)	-1(1)

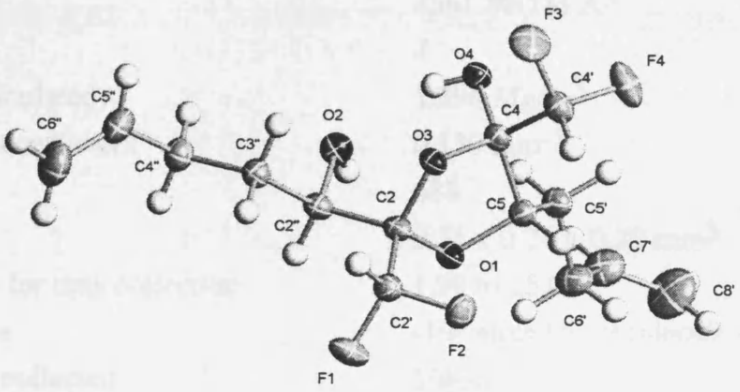
Table 6. Torsion angles [°] for 05063.

C(7)-O(1)-C(1)-O(2)	1.0(3)
C(7)-O(1)-C(1)-C(2)	-178.66(14)
O(2)-C(1)-C(2)-C(3)	0.7(3)
O(1)-C(1)-C(2)-C(3)	-179.70(16)
C(1)-C(2)-C(3)-C(4)	-179.34(16)
C(2)-C(3)-C(4)-C(5)	179.18(17)
C(3)-C(4)-C(5)-C(6)	-179.31(17)
C(4)-C(5)-C(6)-F(1)	1.9(3)

Symmetry transformations used to generate equivalent atoms:

6.1.2 (*1'R, *2R**, *4R**, *5S**)-5-But-3-enyl-2,4-bis-difluoromethyl-2-(1-hydroxy-pent-4-enyl)-[1,3]dioxolan-4-ol 203**





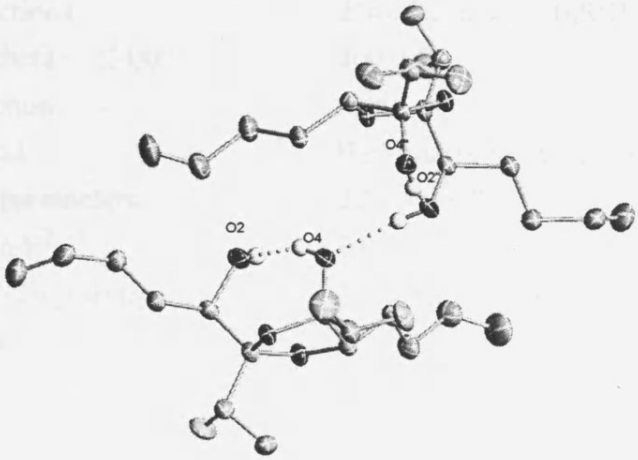


Table 1. Crystal data and structure refinement for 03132.

Identification code	03132	
Empirical formula	C14 H20 F4 O4	
Formula weight	164.15	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.8189(9) Å	α = 90°.
	b = 7.7506(5) Å	β = 94.281(1)°.
	c = 15.7635(11) Å	γ = 90°.
Volume	1561.80(18) $Å^3$	
Z	4	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	0.130 mm^{-1}	
F(000)	688	
Crystal size	0.31 x 0.26 x 0.22 mm^3	
Theta range for data collection	1.98 to 25.00°.	
Index ranges	-15<=h<=15, -9<=k<=9, -18<=l<=18	
Reflections collected	10838	
Independent reflections	2748 [R(int) = 0.0202]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2748 / 0 / 201	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0362, wR2 = 0.0936	
R indices (all data)	R1 = 0.0387, wR2 = 0.0954	
Largest diff. peak and hole	0.240 and -0.237 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 03132. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9460(1)	2588(1)	7928(1)	25(1)
C(2)	9443(1)	3081(2)	8780(1)	22(1)
O(3)	9368(1)	4915(1)	8802(1)	23(1)
C(4)	9109(1)	5519(2)	7965(1)	23(1)
C(5)	9534(1)	4093(2)	7407(1)	24(1)
O(2)	7584(1)	2805(1)	8631(1)	28(1)
O(4)	8041(1)	5826(1)	7828(1)	25(1)
C(2')	10478(1)	2665(2)	9281(1)	26(1)
F(1)	10597(1)	941(1)	9352(1)	39(1)
F(2)	11278(1)	3250(1)	8841(1)	36(1)
C(4')	9675(1)	7224(2)	7904(1)	29(1)
F(3)	9297(1)	8367(1)	8449(1)	47(1)
F(4)	9501(1)	7880(1)	7113(1)	44(1)
C(5')	8924(1)	3794(2)	6561(1)	28(1)
C(6')	9329(1)	2256(2)	6079(1)	37(1)
C(7')	8678(1)	1943(2)	5268(1)	42(1)
C(8')	9012(2)	1907(3)	4518(1)	64(1)
C(2")	8485(1)	2248(2)	9139(1)	23(1)
C(3")	8354(1)	2738(2)	10054(1)	26(1)
C(4")	7423(1)	1847(2)	10411(1)	31(1)
C(5")	7339(1)	2267(2)	11328(1)	36(1)
C(6")	7497(2)	1188(3)	11956(1)	52(1)

Table 3. Bond lengths [Å] and angles [°] for 03132.

O(1)-C(2)	1.3989(15)
O(1)-C(5)	1.4336(16)
C(2)-O(3)	1.4255(16)
C(2)-C(2')	1.5273(18)
C(2)-C(2")	1.5315(19)
O(3)-C(4)	1.4157(15)
C(4)-O(4)	1.3912(16)
C(4)-C(4')	1.514(2)

C(4)-C(5)	1.5366(18)
C(5)-C(5')	1.5132(18)
O(2)-C(2")	1.4230(16)
C(2')-F(1)	1.3491(17)
C(2')-F(2)	1.3579(16)
C(4')-F(4)	1.3489(16)
C(4')-F(3)	1.3491(17)
C(5')-C(6')	1.525(2)
C(6')-C(7')	1.495(2)
C(7')-C(8')	1.287(3)
C(2")-C(3")	1.5120(19)
C(3")-C(4")	1.523(2)
C(4")-C(5")	1.494(2)
C(5")-C(6")	1.300(3)

C(2)-O(1)-C(5)	109.52(10)
O(1)-C(2)-O(3)	107.52(10)
O(1)-C(2)-C(2')	111.28(11)
O(3)-C(2)-C(2')	104.80(10)
O(1)-C(2)-C(2")	108.08(10)
O(3)-C(2)-C(2")	110.77(11)
C(2')-C(2)-C(2")	114.20(11)
C(4)-O(3)-C(2)	108.60(9)
O(4)-C(4)-O(3)	111.12(10)
O(4)-C(4)-C(4')	108.17(11)
O(3)-C(4)-C(4')	105.51(10)
O(4)-C(4)-C(5)	114.91(10)
O(3)-C(4)-C(5)	103.12(10)
C(4')-C(4)-C(5)	113.55(11)
O(1)-C(5)-C(5')	109.19(11)
O(1)-C(5)-C(4)	102.50(10)
C(5')-C(5)-C(4)	115.62(11)
F(1)-C(2')-F(2)	106.80(11)
F(1)-C(2')-C(2)	109.88(11)
F(2)-C(2')-C(2)	109.00(11)
F(4)-C(4')-F(3)	107.35(12)
F(4)-C(4')-C(4)	109.89(11)
F(3)-C(4')-C(4)	109.64(12)
C(5)-C(5')-C(6')	112.66(11)
C(7')-C(6')-C(5')	111.29(13)

C(8')-C(7')-C(6')	125.87(18)
O(2)-C(2")-C(3")	108.49(11)
O(2)-C(2")-C(2)	107.67(10)
C(3")-C(2")-C(2)	113.30(11)
C(2")-C(3")-C(4")	112.64(11)
C(5")-C(4")-C(3")	111.99(12)
C(6")-C(5")-C(4")	125.31(17)

Symmetry transformations used to generate equivalent atoms:

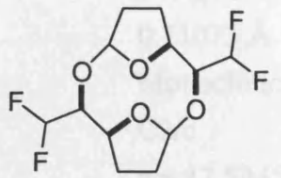
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03132. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

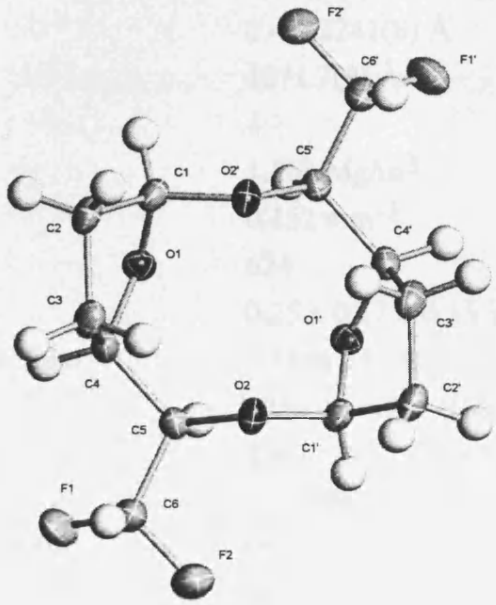
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	35(1)	23(1)	17(1)	-2(1)	0(1)	3(1)
C(2)	29(1)	20(1)	17(1)	-3(1)	-1(1)	3(1)
O(3)	30(1)	20(1)	17(1)	-1(1)	-3(1)	2(1)
C(4)	24(1)	25(1)	18(1)	2(1)	-3(1)	1(1)
C(5)	24(1)	26(1)	20(1)	1(1)	-1(1)	1(1)
O(2)	26(1)	32(1)	23(1)	-3(1)	-6(1)	-2(1)
O(4)	24(1)	26(1)	26(1)	3(1)	-1(1)	2(1)
C(2')	26(1)	27(1)	25(1)	1(1)	1(1)	2(1)
F(1)	39(1)	28(1)	48(1)	5(1)	-7(1)	9(1)
F(2)	25(1)	50(1)	33(1)	5(1)	4(1)	1(1)
C(4')	35(1)	26(1)	24(1)	2(1)	-4(1)	-2(1)
F(3)	62(1)	26(1)	53(1)	-11(1)	6(1)	-5(1)
F(4)	54(1)	41(1)	35(1)	17(1)	-11(1)	-14(1)
C(5')	32(1)	31(1)	19(1)	0(1)	-2(1)	2(1)
C(6')	43(1)	41(1)	25(1)	-7(1)	-2(1)	7(1)
C(7')	46(1)	47(1)	32(1)	-12(1)	-4(1)	0(1)
C(8')	70(1)	93(2)	29(1)	-17(1)	-5(1)	-1(1)
C(2")	26(1)	22(1)	21(1)	-1(1)	-4(1)	1(1)
C(3")	28(1)	27(1)	21(1)	-1(1)	-1(1)	-1(1)
C(4")	30(1)	38(1)	26(1)	-1(1)	2(1)	-3(1)
C(5")	31(1)	48(1)	31(1)	-4(1)	7(1)	-2(1)
C(6")	52(1)	73(1)	31(1)	6(1)	10(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03132.

	x	y	z	U(eq)
H(5)	10284	4329	7314	28
H(2)	7458	2110	8228	41
H(4)	7708	5009	8032	38
H(2')	10504	3212	9857	31
H(4')	10443	7057	8041	35
H(5'1)	8965	4843	6206	33
H(5'2)	8179	3599	6659	33
H(6'1)	10062	2474	5952	44
H(6'2)	9320	1214	6442	44
H(7')	7951	1754	5309	51
H(8'1)9733	2090	4446	77	
H(8'2)	8538	1698	4037	77
H(2")	8545	965	9097	28
H(3"1)	8262	4003	10090	31
H(3"2)	8999	2428	10406	31
H(4"1)	6773	2209	10080	38
H(4"2)	7494	583	10346	38
H(5")	7154	3416	11464	44
H(6"1)	7683	26	11848	62
H(6"2)	7427	1560	12523	62

6.1.3 3,9-Bis-difluoromethyl-2,8,13,14-tetraoxa-tricyclo[8.2.1.14,7]tetradecane 220





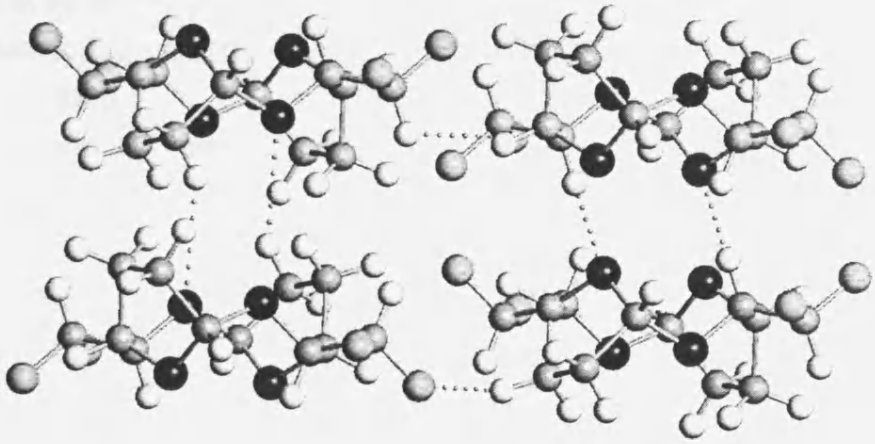


Table 1. Crystal data and structure refinement for 04090.

Identification code	04090	
Empirical formula	C12 H16 F4 O4	
Formula weight	300.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 17.5445(16) Å	α = 90°.
	b = 9.0382(8) Å	β = 102.802(2)°.
	c = 8.2241(8) Å	γ = 90°.
Volume	1271.7(2) $Å^3$	
Z	4	
Density (calculated)	1.568 Mg/m^3	
Absorption coefficient	0.152 mm^{-1}	
F(000)	624	
Crystal size	0.25 x 0.17 x 0.15 mm^3	
Theta range for data collection	2.38 to 24.98°.	
Index ranges	-20<=h<=20, -10<=k<=10, -9<=l<=9	
Reflections collected	4503	
Independent reflections	1126 [R(int) = 0.0368]	
Completeness to theta = 24.98°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1126 / 0 / 91	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1428	
R indices (all data)	R1 = 0.0536, wR2 = 0.1454	
Largest diff. peak and hole	0.936 and -0.295 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04090. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(2)	9508(1)	7798(2)	3922(2)	26(1)
C(5)	8936(1)	6775(2)	3079(3)	25(1)
O(1)	9443(1)	6153(2)	667(2)	24(1)
C(1)	9869(1)	7149(2)	-113(3)	26(1)
C(4)	8817(1)	6931(2)	1190(3)	25(1)
C(2)	9300(1)	8360(3)	-817(3)	29(1)
C(3)	8828(1)	8512(3)	526(3)	30(1)
C(6)	8187(1)	7066(3)	3655(3)	35(1)
F(1)	7636(1)	6064(2)	2955(2)	54(1)
F(2)	8313(1)	6833(2)	5325(2)	51(1)

Table 3. Bond lengths [Å] and angles [°] for 04090.

O(2)-C(1)#1	1.423(3)
O(2)-C(5)	1.426(3)
C(5)-C(6)	1.514(3)
C(5)-C(4)	1.528(3)
O(1)-C(1)	1.411(3)
O(1)-C(4)	1.448(3)
C(1)-O(2)#1	1.423(3)
C(1)-C(2)	1.508(3)
C(4)-C(3)	1.531(3)
C(2)-C(3)	1.527(3)
C(6)-F(1)	1.357(3)
C(6)-F(2)	1.359(3)
C(1)#1-O(2)-C(5)	114.71(16)
O(2)-C(5)-C(6)	107.54(17)
O(2)-C(5)-C(4)	110.88(17)
C(6)-C(5)-C(4)	111.70(18)
C(1)-O(1)-C(4)	109.73(16)

O(1)-C(1)-O(2)#1	110.70(16)
O(1)-C(1)-C(2)	105.43(17)
O(2)#1-C(1)-C(2)	107.89(17)
O(1)-C(4)-C(5)	108.41(16)
O(1)-C(4)-C(3)	106.10(17)
C(5)-C(4)-C(3)	116.09(18)
C(1)-C(2)-C(3)	101.92(17)
C(2)-C(3)-C(4)	103.06(18)
F(1)-C(6)-F(2)	105.5(2)
F(1)-C(6)-C(5)	109.73(19)
F(2)-C(6)-C(5)	109.31(19)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y,-z+1/2

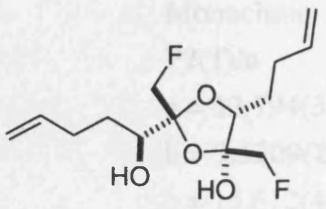
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04090. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

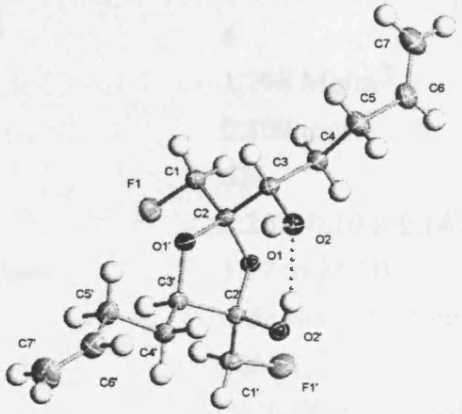
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(2)	25(1)	25(1)	23(1)	-2(1)	-2(1)	3(1)
C(5)	22(1)	28(1)	24(1)	-2(1)	4(1)	1(1)
O(1)	24(1)	24(1)	25(1)	-3(1)	7(1)	0(1)
C(1)	28(1)	30(1)	18(1)	-1(1)	3(1)	-4(1)
C(4)	20(1)	30(1)	24(1)	-4(1)	1(1)	2(1)
C(2)	32(1)	32(1)	20(1)	2(1)	-2(1)	-1(1)
C(3)	31(1)	32(1)	25(1)	0(1)	0(1)	8(1)
C(6)	28(1)	51(2)	27(1)	-2(1)	5(1)	4(1)
F(1)	28(1)	89(1)	46(1)	-15(1)	12(1)	-15(1)
F(2)	41(1)	81(1)	33(1)	-3(1)	13(1)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04090.

H(5)	9117	5746	3407	30
H(1)	10069	6646	-1017	31
H(4)	8309	6459	649	30
H(2B)	8964	8069	-1901	35
H(2A)	9575	9292	-957	35
H(3B)	8292	8869	46	36
H(3A)	9085	9199	1417	36
H(6)	7998	8097	3369	42

6.1.4 (*1'R*, 2R*, 4R*, 5S**)-5-but-3-enyl-2,4-bis-fluoromethyl-2-(1-hydroxy-pent-4-enyl)-[1,3]dioxolan-4-ol 239





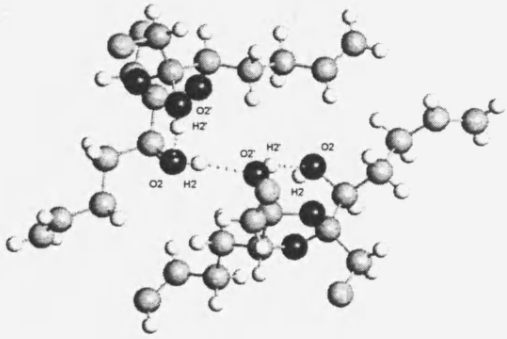


Table 1. Crystal data and structure refinement for 04174.

Identification code	04174	
Empirical formula	C14 H22 F2 O4	
Formula weight	292.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.794(3) Å	α = 90°.
	b = 7.5209(19) Å	β = 95.415(4)°.
	c = 15.612(4) Å	γ = 90°.
Volume	1495.5(7) $Å^3$	
Z	4	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	624	
Crystal size	0.26 x 0.20 x 0.14 mm^3	
Theta range for data collection	1.97 to 25.00°.	
Index ranges	-15<=h<=15, -8<=k<=8, -18<=l<=18	
Reflections collected	20828	
Independent reflections	2636 [R(int) = 0.0320]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.98 and 0.91	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2636 / 0 / 183	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0363, wR2 = 0.0859	
R indices (all data)	R1 = 0.0410, wR2 = 0.0888	
Largest diff. peak and hole	0.254 and -0.191 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04174. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	6280(1)	2038(1)	3839(1)	35(1)
O(1)	4422(1)	81(1)	3790(1)	21(1)
O(2)	2529(1)	2135(1)	3613(1)	26(1)
C(1)	5432(1)	2616(2)	4263(1)	25(1)
C(2)	4422(1)	1982(2)	3771(1)	21(1)
C(3)	3440(1)	2743(2)	4132(1)	22(1)
C(4)	3334(1)	2227(2)	5057(1)	25(1)
C(5)	2411(1)	3160(2)	5418(1)	33(1)
C(6)	2322(1)	2732(2)	6341(1)	33(1)
C(7)	2436(1)	3872(3)	6974(1)	44(1)
F(1')	4449(1)	-3504(1)	3445(1)	40(1)
O(1')	4378(1)	2491(1)	2896(1)	23(1)
O(2')	3065(1)	-911(1)	2825(1)	24(1)
C(1')	4716(1)	-2288(2)	2833(1)	28(1)
C(2')	4150(1)	-562(2)	2947(1)	22(1)
C(3')	4516(1)	945(2)	2381(1)	22(1)
C(4')	3913(1)	1184(2)	1507(1)	25(1)
C(5')	4284(1)	2794(2)	1026(1)	31(1)
C(6')	3698(1)	3003(2)	157(1)	35(1)
C(7')	4118(2)	3059(3)	-569(1)	51(1)

Table 3. Bond lengths [Å] and angles [°] for 04174.

F(1)-C(1)	1.3927(16)
O(1)-C(2')	1.4146(16)
O(1)-C(2)	1.4298(16)
O(2)-C(3)	1.4300(16)
C(1)-C(2)	1.5174(19)
C(2)-O(1')	1.4140(16)
C(2)-C(3)	1.5346(19)
C(3)-C(4)	1.5149(19)
C(4)-C(5)	1.526(2)
C(5)-C(6)	1.492(2)

C(6)-C(7)	1.306(2)
F(1')-C(1')	1.3885(17)
O(1')-C(3')	1.4346(16)
O(2')-C(2')	1.4079(16)
C(1')-C(2')	1.505(2)
C(2')-C(3')	1.5364(19)
C(3')-C(4')	1.5135(19)
C(4')-C(5')	1.524(2)
C(5')-C(6')	1.494(2)
C(6')-C(7')	1.301(2)

C(2')-O(1)-C(2)	108.83(10)
F(1)-C(1)-C(2)	109.01(11)
O(1')-C(2)-O(1)	106.91(10)
O(1')-C(2)-C(1)	110.98(11)
O(1)-C(2)-C(1)	107.73(11)
O(1')-C(2)-C(3)	107.12(10)
O(1)-C(2)-C(3)	111.37(11)
C(1)-C(2)-C(3)	112.60(11)
O(2)-C(3)-C(4)	108.43(11)
O(2)-C(3)-C(2)	108.92(11)
C(4)-C(3)-C(2)	113.89(11)
C(3)-C(4)-C(5)	112.11(11)
C(6)-C(5)-C(4)	112.94(12)
C(7)-C(6)-C(5)	125.17(16)
C(2)-O(1')-C(3')	109.02(10)
F(1')-C(1')-C(2')	109.55(11)
O(2')-C(2')-O(1)	110.01(10)
O(2')-C(2')-C(1')	107.62(11)
O(1)-C(2')-C(1')	109.01(11)
O(2')-C(2')-C(3')	114.19(11)
O(1)-C(2')-C(3')	102.78(10)
C(1')-C(2')-C(3')	113.09(11)
O(1')-C(3')-C(4')	109.26(11)
O(1')-C(3')-C(2')	102.44(10)
C(4')-C(3')-C(2')	116.67(11)
C(3')-C(4')-C(5')	112.50(12)
C(6')-C(5')-C(4')	112.24(13)
C(7')-C(6')-C(5')	125.61(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04174. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	23(1)	49(1)	34(1)	-4(1)	4(1)	-3(1)
O(1)	26(1)	19(1)	18(1)	0(1)	-2(1)	-1(1)
O(2)	23(1)	30(1)	23(1)	3(1)	-4(1)	2(1)
C(1)	25(1)	26(1)	24(1)	-2(1)	2(1)	-2(1)
C(2)	25(1)	18(1)	19(1)	2(1)	-1(1)	-1(1)
C(3)	24(1)	20(1)	21(1)	0(1)	-2(1)	0(1)
C(4)	25(1)	28(1)	21(1)	2(1)	-1(1)	3(1)
C(5)	31(1)	43(1)	26(1)	3(1)	4(1)	8(1)
C(6)	27(1)	43(1)	29(1)	4(1)	4(1)	2(1)
C(7)	42(1)	59(1)	32(1)	-2(1)	8(1)	6(1)
F(1')	53(1)	23(1)	45(1)	7(1)	4(1)	2(1)
O(1')	31(1)	20(1)	18(1)	1(1)	1(1)	-2(1)
O(2')	22(1)	25(1)	26(1)	-3(1)	0(1)	-3(1)
C(1')	33(1)	25(1)	25(1)	0(1)	1(1)	2(1)
C(2')	21(1)	24(1)	19(1)	-2(1)	-2(1)	-2(1)
C(3')	22(1)	23(1)	22(1)	-1(1)	0(1)	-1(1)
C(4')	29(1)	27(1)	20(1)	0(1)	0(1)	-2(1)
C(5')	34(1)	34(1)	25(1)	5(1)	-1(1)	-5(1)
C(6')	37(1)	35(1)	31(1)	9(1)	-5(1)	0(1)
C(7')	61(1)	62(1)	29(1)	12(1)	-4(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04174.

	x	y	z	U(eq)
H(2)	2419	2792	3179	38
H(1A)	5434	3930	4299	30
H(1B)	5487	2132	4856	30
H(3)	3467	4070	4095	26
H(4A)	3990	2538	5414	30
H(4B)	3236	925	5092	30
H(5A)	2493	4461	5356	40
H(5B)	1753	2807	5075	40
H(6)	2170	1535	6480	39
H(7A)	2588	5081	6862	53
H(7B)	2366	3492	7546	53
H(2')	2736	-85	3042	37
H(1'1)	4521	-2764	2249	33
H(1'2)	5484	-2083	2898	33
H(3')	5279	788	2308	27
H(4'1)	3157	1322	1581	30
H(4'2)	3995	102	1158	30
H(5'1)	4189	3879	1369	37
H(5'2)	5042	2667	960	37
H(6')	2956	3105	134	42
H(7'1)	4858	2963	-576	61
H(7'2)	3685	3196	-1094	61

6.1.5 3,9-Bis-fluoromethyl-2,8,13,14-tetraoxa-tricyclo[8.2.1.14,7]tetradecane 242

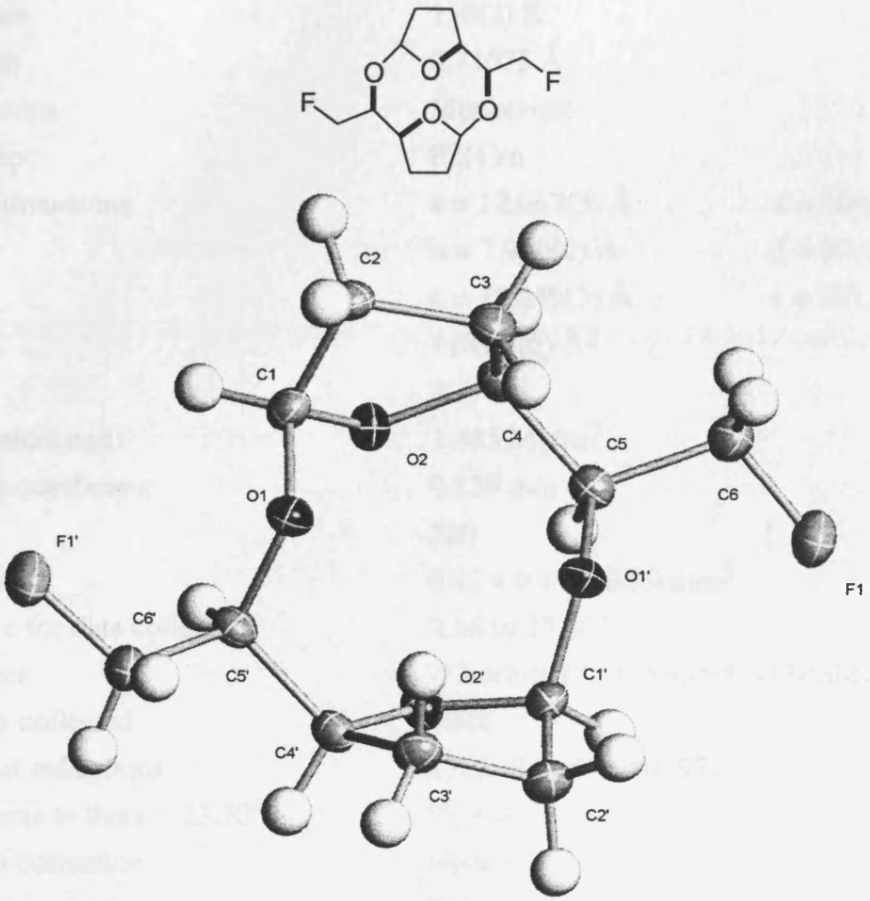


Table 1. Crystal data and structure refinement for 04097.

Identification code	04097	
Empirical formula	C12 H18 F2 O4	
Formula weight	264.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.067(3) Å	α = 90°.
	b = 7.970(2) Å	β = 99.192(5)°.
	c = 12.449(3) Å	γ = 90°.
Volume	1181.9(6) $Å^3$	
Z	4	
Density (calculated)	1.485 Mg/m^3	
Absorption coefficient	0.129 mm^{-1}	
F(000)	560	
Crystal size	0.12 x 0.10 x 0.09 mm^3	
Theta range for data collection	2.18 to 23.30°.	
Index ranges	-13<=h<=13, -8<=k<=8, -13<=l<=13	
Reflections collected	7048	
Independent reflections	1703 [R(int) = 0.0397]	
Completeness to theta = 23.30°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1703 / 0 / 163	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0301, wR2 = 0.0712	
R indices (all data)	R1 = 0.0392, wR2 = 0.0746	
Largest diff. peak and hole	0.152 and -0.138 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04097. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	416(1)	244(1)	-2964(1)	39(1)
O(1)	3366(1)	-753(1)	1222(1)	22(1)
O(2)	3802(1)	-905(1)	-541(1)	23(1)
C(1)	3966(1)	-1631(2)	505(1)	23(1)
C(2)	3481(1)	-3370(2)	346(1)	27(1)
C(3)	2466(1)	-3081(2)	-530(1)	26(1)
C(4)	2866(1)	-1694(2)	-1220(1)	22(1)
C(5)	2002(1)	-377(2)	-1641(1)	22(1)
C(6)	1137(1)	-1060(2)	-2544(1)	29(1)
F(1')	5041(1)	85(1)	2994(1)	36(1)
O(1')	1434(1)	210(1)	-798(1)	23(1)
O(2')	2664(1)	2358(1)	-97(1)	24(1)
C(1')	1556(1)	1937(2)	-549(1)	24(1)
C(2')	859(1)	2311(2)	321(1)	29(1)
C(3')	1648(1)	1752(2)	1341(1)	26(1)
C(4')	2809(1)	2180(2)	1076(1)	23(1)
C(5')	3732(1)	927(2)	1463(1)	22(1)
C(6')	4090(1)	1075(2)	2674(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for 04097.

F(1)-C(6)	1.4014(18)
O(1)-C(1)	1.4203(19)
O(1)-C(5')	1.4268(18)
O(2)-C(1)	1.4097(18)
O(2)-C(4)	1.4423(18)
C(1)-C(2)	1.506(2)
C(2)-C(3)	1.522(2)
C(3)-C(4)	1.525(2)
C(4)-C(5)	1.513(2)
C(5)-O(1')	1.4225(19)
C(5)-C(6)	1.509(2)

F(1')-C(6')	1.3976(18)
O(1')-C(1')	1.4131(19)
O(2')-C(1')	1.4055(19)
O(2')-C(4')	1.4498(18)
C(1')-C(2')	1.503(2)
C(2')-C(3')	1.527(2)
C(3')-C(4')	1.528(2)
C(4')-C(5')	1.516(2)
C(5')-C(6')	1.505(2)

C(1)-O(1)-C(5')	115.01(12)
C(1)-O(2)-C(4)	110.12(12)
O(2)-C(1)-O(1)	111.57(13)
O(2)-C(1)-C(2)	105.18(13)
O(1)-C(1)-C(2)	108.01(13)
C(1)-C(2)-C(3)	101.94(13)
C(2)-C(3)-C(4)	102.80(13)
O(2)-C(4)-C(5)	109.41(12)
O(2)-C(4)-C(3)	105.97(12)
C(5)-C(4)-C(3)	115.80(14)
O(1')-C(5)-C(6)	108.09(13)
O(1')-C(5)-C(4)	111.05(13)
C(6)-C(5)-C(4)	111.42(13)
F(1)-C(6)-C(5)	108.99(13)
C(1')-O(1')-C(5)	115.89(12)
C(1')-O(2')-C(4')	109.52(12)
O(2')-C(1')-O(1')	112.31(13)
O(2')-C(1')-C(2')	105.67(13)
O(1')-C(1')-C(2')	107.47(13)
C(1')-C(2')-C(3')	101.24(13)
C(2')-C(3')-C(4')	103.10(13)
O(2')-C(4')-C(5')	110.42(12)
O(2')-C(4')-C(3')	105.79(13)
C(5')-C(4')-C(3')	115.88(13)
O(1)-C(5')-C(6')	108.31(13)
O(1)-C(5')-C(4')	111.39(13)
C(6')-C(5')-C(4')	110.22(13)
F(1')-C(6')-C(5')	109.44(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04097. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	36(1)	40(1)	36(1)	1(1)	-9(1)	5(1)
O(1)	26(1)	20(1)	22(1)	-1(1)	5(1)	-2(1)
O(2)	21(1)	28(1)	20(1)	2(1)	2(1)	-1(1)
C(1)	23(1)	25(1)	21(1)	2(1)	2(1)	5(1)
C(2)	32(1)	20(1)	27(1)	1(1)	4(1)	4(1)
C(3)	29(1)	20(1)	30(1)	-2(1)	3(1)	-3(1)
C(4)	23(1)	24(1)	19(1)	-6(1)	1(1)	-1(1)
C(5)	25(1)	23(1)	19(1)	0(1)	5(1)	-2(1)
C(6)	30(1)	28(1)	26(1)	0(1)	1(1)	4(1)
F(1')	34(1)	35(1)	35(1)	3(1)	-8(1)	2(1)
O(1')	24(1)	21(1)	23(1)	-3(1)	6(1)	-1(1)
O(2')	27(1)	24(1)	21(1)	3(1)	2(1)	-4(1)
C(1')	25(1)	20(1)	25(1)	1(1)	-1(1)	4(1)
C(2')	28(1)	28(1)	31(1)	-4(1)	5(1)	5(1)
C(3')	30(1)	27(1)	24(1)	-2(1)	8(1)	4(1)
C(4')	29(1)	21(1)	18(1)	-1(1)	2(1)	-2(1)
C(5')	25(1)	19(1)	22(1)	-1(1)	5(1)	-5(1)
C(6')	27(1)	26(1)	28(1)	-1(1)	-3(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04097.

	x	y	z	U(eq)
H(1)	4784	-1681	811	28
H(2A)	3256	-3805	1024	32
H(2B)	4020	-4159	96	32
H(3A)	1806	-2715	-208	32
H(3B)	2269	-4110	-965	32
H(4)	3144	-2222	-1855	27
H(5)	2393	591	-1929	27
H(6A)	1512	-1535	-3127	34
H(6B)	701	-1964	-2260	34
H(1')	1298	2629	-1212	29
H(2'1)	153	1655	214	35
H(2'2)	680	3521	347	35
H(3'1)	1576	534	1469	32
H(3'2)	1496	2374	1991	32
H(4')	3039	3294	1409	28
H(5')	4391	1168	1092	26
H(6'1)	4262	2261	2871	33
H(6'2)	3474	701	3055	33

6.1.6 (±)-α-5-*O*-benzyl-6,6-difluoro-amicetose 252

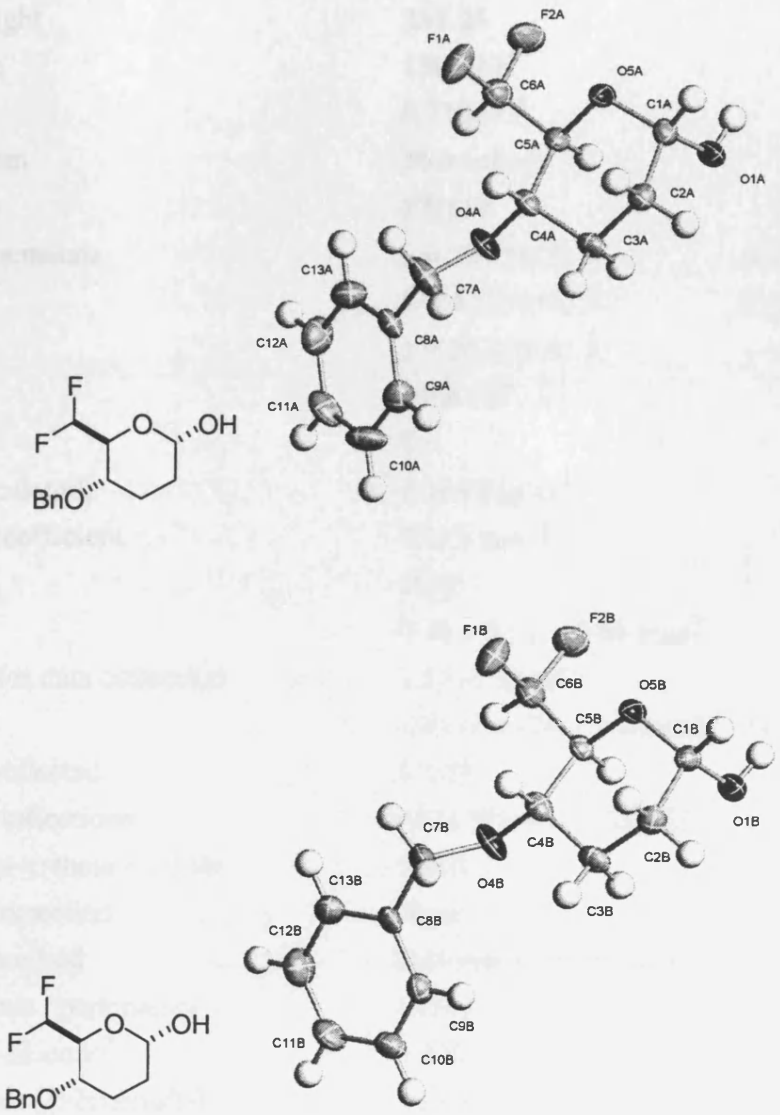


Table 1. Crystal data and structure refinement for 04190.

Identification code	04190	
Empirical formula	C13 H16 F2 O3	
Formula weight	258.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 20.750(3) Å	α = 90°.
	b = 4.6956(8) Å	β = 98.453(3)°.
	c = 26.025(4) Å	γ = 90°.
Volume	2508.1(7) $Å^3$	
Z	8	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	1088	
Crystal size	0.36 x 0.11 x 0.04 mm^3	
Theta range for data collection	1.17 to 24.99°.	
Index ranges	-24<=h<=24, -5<=k<=5, -30<=l<=30	
Reflections collected	17038	
Independent reflections	4424 [R(int) = 0.0885]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4424 / 0 / 327	
Goodness-of-fit on F^2	0.936	
Final R indices [I>2sigma(I)]	R1 = 0.0471, wR2 = 0.0880	
R indices (all data)	R1 = 0.0850, wR2 = 0.0999	
Largest diff. peak and hole	0.193 and -0.172 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 04190. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1A)	-10(1)	7473(3)	3254(1)	32(1)
O(4A)	2128(1)	6297(3)	3784(1)	33(1)
O(5A)	667(1)	4199(3)	2920(1)	28(1)
F(1A)	1825(1)	2412(3)	2640(1)	55(1)
F(2A)	1431(1)	6193(3)	2225(1)	51(1)
C(1A)	171(1)	4630(4)	3247(1)	28(1)
C(2A)	416(1)	3690(4)	3799(1)	29(1)
C(3A)	1060(1)	5137(4)	4004(1)	29(1)
C(4A)	1548(1)	4683(4)	3636(1)	28(1)
C(5A)	1259(1)	5705(4)	3095(1)	26(1)
C(6A)	1710(1)	5240(5)	2701(1)	36(1)
C(7A)	2631(1)	4718(5)	4089(1)	49(1)
C(8A)	3190(1)	6693(4)	4256(1)	29(1)
C(9A)	3300(1)	7753(5)	4755(1)	40(1)
C(10A)	3809(1)	9601(5)	4903(1)	49(1)
C(11A)	4212(1)	10419(5)	4555(1)	48(1)
C(12A)	4102(1)	9349(5)	4059(1)	49(1)
C(13A)	3599(1)	7508(5)	3916(1)	42(1)
O(1B)	10050(1)	2739(3)	1938(1)	32(1)
O(4B)	7912(1)	1492(3)	1428(1)	38(1)
O(5B)	9395(1)	-651(3)	2267(1)	27(1)
F(1B)	8254(1)	-2557(3)	2558(1)	49(1)
F(2B)	8648(1)	1199(3)	2986(1)	45(1)
C(1B)	9879(1)	-128(4)	1934(1)	28(1)
C(2B)	9624(1)	-983(4)	1379(1)	31(1)
C(3B)	8970(1)	419(5)	1191(1)	33(1)
C(4B)	8494(1)	-124(4)	1568(1)	29(1)
C(5B)	8797(1)	837(4)	2108(1)	25(1)
C(6B)	8361(1)	293(5)	2508(1)	34(1)
C(7B)	7386(1)	-139(5)	1163(1)	41(1)
C(8B)	6912(1)	1798(4)	846(1)	28(1)
C(9B)	7084(1)	3182(5)	418(1)	33(1)
C(10B)	6651(1)	4940(5)	118(1)	37(1)
C(11B)	6033(1)	5316(5)	241(1)	41(1)

C(12B)	5856(1)	3953(5)	666(1)	45(1)
C(13B)	6294(1)	2209(5)	970(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for 04190.

O(1A)-C(1A)	1.388(2)
O(4A)-C(7A)	1.422(2)
O(4A)-C(4A)	1.427(2)
O(5A)-C(5A)	1.433(2)
O(5A)-C(1A)	1.442(2)
F(1A)-C(6A)	1.363(2)
F(2A)-C(6A)	1.364(2)
C(1A)-C(2A)	1.519(3)
C(2A)-C(3A)	1.523(3)
C(3A)-C(4A)	1.509(3)
C(4A)-C(5A)	1.525(3)
C(5A)-C(6A)	1.500(3)
C(7A)-C(8A)	1.500(3)
C(8A)-C(13A)	1.369(3)
C(8A)-C(9A)	1.377(3)
C(9A)-C(10A)	1.377(3)
C(10A)-C(11A)	1.374(3)
C(11A)-C(12A)	1.373(3)
C(12A)-C(13A)	1.363(3)
O(1B)-C(1B)	1.391(2)
O(4B)-C(7B)	1.426(2)
O(4B)-C(4B)	1.428(2)
O(5B)-C(5B)	1.431(2)
O(5B)-C(1B)	1.442(2)
F(1B)-C(6B)	1.366(2)
F(2B)-C(6B)	1.365(2)
C(1B)-C(2B)	1.516(3)
C(2B)-C(3B)	1.523(3)
C(3B)-C(4B)	1.513(3)
C(4B)-C(5B)	1.522(3)
C(5B)-C(6B)	1.499(3)
C(7B)-C(8B)	1.495(3)
C(8B)-C(13B)	1.382(3)

C(8B)-C(9B)	1.382(3)
C(9B)-C(10B)	1.376(3)
C(10B)-C(11B)	1.378(3)
C(11B)-C(12B)	1.373(3)
C(12B)-C(13B)	1.383(3)

C(7A)-O(4A)-C(4A)	113.18(16)
C(5A)-O(5A)-C(1A)	113.40(15)
O(1A)-C(1A)-O(5A)	111.16(16)
O(1A)-C(1A)-C(2A)	108.65(17)
O(5A)-C(1A)-C(2A)	110.41(16)
C(1A)-C(2A)-C(3A)	110.87(17)
C(4A)-C(3A)-C(2A)	110.54(17)
O(4A)-C(4A)-C(3A)	111.91(17)
O(4A)-C(4A)-C(5A)	106.45(16)
C(3A)-C(4A)-C(5A)	109.43(17)
O(5A)-C(5A)-C(6A)	107.67(17)
O(5A)-C(5A)-C(4A)	109.88(16)
C(6A)-C(5A)-C(4A)	112.61(18)
F(1A)-C(6A)-F(2A)	105.76(18)
F(1A)-C(6A)-C(5A)	111.05(18)
F(2A)-C(6A)-C(5A)	110.37(18)
O(4A)-C(7A)-C(8A)	108.21(18)
C(13A)-C(8A)-C(9A)	118.4(2)
C(13A)-C(8A)-C(7A)	120.8(2)
C(9A)-C(8A)-C(7A)	120.8(2)
C(8A)-C(9A)-C(10A)	120.4(2)
C(11A)-C(10A)-C(9A)	120.4(2)
C(12A)-C(11A)-C(10A)	119.0(2)
C(13A)-C(12A)-C(11A)	120.2(2)
C(12A)-C(13A)-C(8A)	121.5(2)
C(7B)-O(4B)-C(4B)	113.39(16)
C(5B)-O(5B)-C(1B)	113.18(15)
O(1B)-C(1B)-O(5B)	111.00(16)
O(1B)-C(1B)-C(2B)	108.49(17)
O(5B)-C(1B)-C(2B)	110.52(17)
C(1B)-C(2B)-C(3B)	111.24(17)
C(4B)-C(3B)-C(2B)	110.72(17)
O(4B)-C(4B)-C(3B)	110.70(17)
O(4B)-C(4B)-C(5B)	107.29(16)

C(3B)-C(4B)-C(5B)	109.20(17)
O(5B)-C(5B)-C(6B)	107.62(16)
O(5B)-C(5B)-C(4B)	110.21(16)
C(6B)-C(5B)-C(4B)	112.37(17)
F(2B)-C(6B)-F(1B)	105.91(17)
F(2B)-C(6B)-C(5B)	110.61(18)
F(1B)-C(6B)-C(5B)	110.88(18)
O(4B)-C(7B)-C(8B)	109.55(17)
C(13B)-C(8B)-C(9B)	118.7(2)
C(13B)-C(8B)-C(7B)	120.9(2)
C(9B)-C(8B)-C(7B)	120.3(2)
C(10B)-C(9B)-C(8B)	121.1(2)
C(9B)-C(10B)-C(11B)	119.8(2)
C(12B)-C(11B)-C(10B)	119.8(2)
C(11B)-C(12B)-C(13B)	120.4(2)
C(8B)-C(13B)-C(12B)	120.3(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04190. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	32(1)	35(1)	26(1)	1(1)	-3(1)	6(1)
O(4A)	23(1)	31(1)	40(1)	5(1)	-11(1)	-5(1)
O(5A)	22(1)	36(1)	27(1)	-9(1)	3(1)	-5(1)
F(1A)	54(1)	52(1)	66(1)	-11(1)	29(1)	8(1)
F(2A)	47(1)	77(1)	29(1)	0(1)	9(1)	-3(1)
C(1A)	22(1)	29(1)	32(1)	-3(1)	3(1)	-2(1)
C(2A)	30(1)	28(1)	29(1)	1(1)	6(1)	0(1)
C(3A)	31(1)	30(1)	24(1)	3(1)	-4(1)	2(1)
C(4A)	22(1)	27(1)	31(1)	0(1)	-4(1)	-2(1)
C(5A)	21(1)	29(1)	28(1)	-5(1)	1(1)	-5(1)
C(6A)	32(1)	41(2)	34(2)	-2(1)	4(1)	-4(1)
C(7A)	31(1)	45(2)	63(2)	15(1)	-15(1)	-4(1)
C(8A)	22(1)	31(1)	32(2)	7(1)	-4(1)	1(1)
C(9A)	42(2)	46(2)	33(2)	9(1)	11(1)	3(1)
C(10A)	66(2)	51(2)	25(2)	-4(1)	-8(1)	2(2)

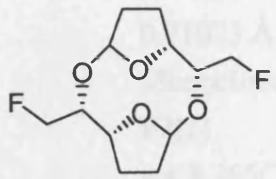
C(11A)	30(2)	48(2)	60(2)	-1(1)	-10(1)	-11(1)
C(12A)	34(2)	56(2)	60(2)	-3(1)	19(1)	-8(1)
C(13A)	49(2)	46(2)	31(2)	-3(1)	4(1)	-3(1)
O(1B)	34(1)	34(1)	26(1)	0(1)	-2(1)	-6(1)
O(4B)	29(1)	34(1)	45(1)	-9(1)	-15(1)	8(1)
O(5B)	22(1)	32(1)	25(1)	5(1)	2(1)	5(1)
F(1B)	47(1)	44(1)	61(1)	4(1)	22(1)	-9(1)
F(2B)	43(1)	63(1)	29(1)	-3(1)	7(1)	1(1)
C(1B)	25(1)	31(1)	28(1)	3(1)	5(1)	2(1)
C(2B)	32(1)	32(1)	28(1)	-5(1)	7(1)	-2(1)
C(3B)	39(1)	31(1)	25(1)	-4(1)	-5(1)	-1(1)
C(4B)	27(1)	24(1)	33(1)	-2(1)	-4(1)	5(1)
C(5B)	19(1)	27(1)	29(1)	2(1)	-1(1)	3(1)
C(6B)	29(1)	37(2)	35(2)	0(1)	1(1)	3(1)
C(7B)	32(1)	38(2)	46(2)	10(1)	-10(1)	-8(1)
C(8B)	25(1)	31(1)	26(1)	-3(1)	-5(1)	-3(1)
C(9B)	25(1)	39(2)	34(2)	-2(1)	3(1)	0(1)
C(10B)	39(2)	40(2)	29(1)	3(1)	-3(1)	0(1)
C(11B)	34(2)	43(2)	43(2)	5(1)	-7(1)	11(1)
C(12B)	31(2)	48(2)	55(2)	-3(1)	9(1)	9(1)
C(13B)	35(2)	44(2)	30(1)	0(1)	4(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04190.

	x	y	z	U(eq)
H(1A)	-235	7899	2969	48
H(1A1)	-220	3468	3108	33
H(2A1)	476	1598	3808	35
H(2A2)	88	4174	4026	35
H(3A1)	986	7203	4045	34
H(3A2)	1233	4347	4350	34
H(4A)	1659	2614	3623	33
H(5A)	1160	7785	3111	32
H(6A)	2131	6260	2812	43
H(7A1)	2773	3129	3882	58
H(7A2)	2468	3911	4397	58

H(9A)	3024	7207	4998	48
H(10A)	3883	10314	5248	59
H(11A)	4561	11705	4656	57
H(12A)	4377	9895	3814	58
H(13A)	3532	6773	3572	50
H(1B)	10276	3140	2224	48
H(1B1)	10276	-1280	2060	33
H(2B1)	9574	-3079	1360	37
H(2B2)	9942	-417	1150	37
H(3B1)	9032	2496	1155	39
H(3B2)	8790	-350	845	39
H(4B)	8387	-2200	1573	35
H(5B)	8891	2925	2099	30
H(6B)	7936	1300	2408	41
H(7B1)	7164	-1180	1418	49
H(7B2)	7554	-1553	934	49
H(9B)	7508	2915	329	39
H(10B)	6777	5892	-174	44
H(11B)	5731	6515	34	50
H(12B)	5430	4209	751	53
H(13B)	6169	1289	1265	43

6.1.7 3,9-Bis-fluoromethyl-2,8,13,14-tetraoxa-tricyclo[8.2.1.14,7]tetradecane 283



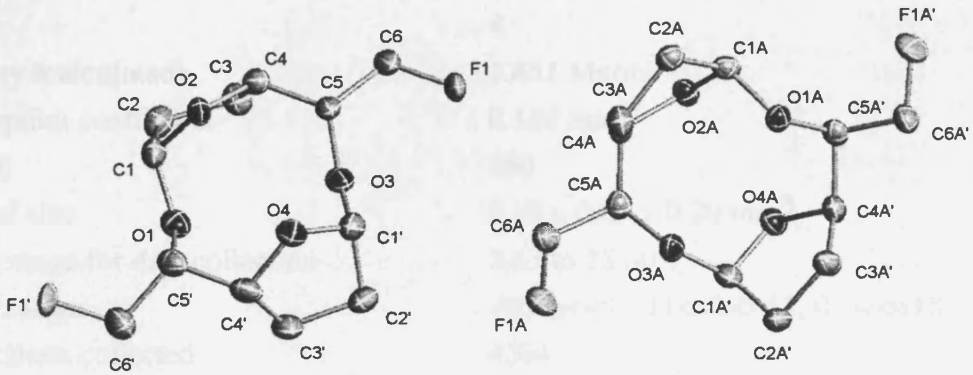


Table 1. Crystal data and structure refinement for 05119a.

Identification code	05119a	
Empirical formula	C12 H18 F2 O4	
Formula weight	264.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.365(2) Å	α = 90°.
	b = 9.350(2) Å	β = 90.002(4)°.
	c = 15.462(4) Å	γ = 90°.
Volume	1209.3(5) $Å^3$	
Z	4	
Density (calculated)	1.451 Mg/m^3	
Absorption coefficient	0.126 mm^{-1}	
F(000)	560	
Crystal size	0.30 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.43 to 25.00°.	
Index ranges	-9<=h<=9, -11<=k<=11, 0<=l<=18	
Reflections collected	4204	
Independent reflections	4204 [R(int) = 0.0000]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4204 / 1 / 325	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1078	
R indices (all data)	R1 = 0.0464, wR2 = 0.1100	
Absolute Flack structure parameter	-1.1(7)	
Largest diff. peak and hole	0.377 and -0.157 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 05119a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7006(2)	8132(2)	9575(1)	33(1)
O(2)	8839(2)	7198(2)	8586(1)	27(1)
O(3)	5969(2)	8314(2)	7606(1)	29(1)
O(4)	5329(2)	6201(2)	8336(1)	33(1)
F(1)	6436(2)	8204(2)	5839(1)	54(1)
C(1)	8619(3)	7976(3)	9351(2)	31(1)
C(2)	9281(3)	9445(3)	9177(2)	36(1)
C(3)	8833(3)	9664(3)	8229(2)	36(1)
C(4)	8832(3)	8151(3)	7852(2)	29(1)
C(5)	7455(3)	7826(3)	7250(2)	26(1)
C(6)	7736(3)	8540(3)	6396(2)	36(1)
F(1')	6901(2)	6869(2)	11315(1)	47(1)
C(1')	4834(3)	7212(3)	7715(2)	32(1)
C(2')	3339(3)	7874(4)	8091(2)	39(1)
C(3')	3692(3)	7901(4)	9046(2)	41(1)
C(4')	4772(3)	6609(3)	9187(2)	35(1)
C(5')	6180(3)	6855(3)	9790(2)	33(1)
C(6')	5623(4)	6987(4)	10718(2)	45(1)
O(1A)	2107(2)	7960(2)	2704(1)	27(1)
O(2A)	3760(2)	9415(2)	3549(1)	27(1)
O(3A)	858(2)	8808(2)	4633(1)	31(1)
O(4A)	352(2)	10430(2)	3516(1)	30(1)
F(1A)	1394(2)	9799(2)	6351(1)	45(1)
C(1A)	3705(3)	8307(3)	2929(2)	26(1)
C(2A)	4424(3)	7028(3)	3376(2)	29(1)
C(3A)	3762(3)	7193(3)	4287(2)	33(1)
C(4A)	3741(3)	8808(3)	4407(2)	27(1)
C(5A)	2334(3)	9393(3)	4921(2)	28(1)
C(6A)	2522(3)	9030(3)	5867(2)	35(1)
F(1A')	1959(2)	8118(2)	887(1)	47(1)
C(1A')	-238(3)	9810(3)	4284(2)	31(1)
C(2A')	-1718(3)	8998(4)	4017(2)	38(1)
C(3A')	-1229(3)	8410(3)	3136(2)	36(1)
C(4A')	-151(3)	9594(3)	2780(2)	30(1)

C(5A')	1279(3)	9062(3)	2264(2)	27(1)
C(6A')	676(3)	8493(3)	1412(2)	31(1)

Table 3. Bond lengths [Å] and angles [°] for 05119a.

O(1)-C(1)	1.401(3)
O(1)-C(5')	1.419(3)
O(2)-C(1)	1.400(3)
O(2)-C(4)	1.443(3)
O(3)-C(1')	1.412(3)
O(3)-C(5)	1.434(3)
O(4)-C(1')	1.409(3)
O(4)-C(4')	1.447(3)
F(1)-C(6)	1.423(3)
C(1)-C(2)	1.505(4)
C(1)-H(1)	1.0000
C(2)-C(3)	1.526(4)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.530(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.512(3)
C(4)-H(4)	1.0000
C(5)-C(6)	1.497(3)
C(5)-H(5)	1.0000
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
F(1')-C(6')	1.417(3)
C(1')-C(2')	1.512(4)
C(1')-H(1')	1.0000
C(2')-C(3')	1.506(4)
C(2')-H(2'1)	0.9900
C(2')-H(2'2)	0.9900
C(3')-C(4')	1.523(4)
C(3')-H(3'1)	0.9900
C(3')-H(3'2)	0.9900
C(4')-C(5')	1.521(4)

C(4')-H(4')	1.0000
C(5')-C(6')	1.513(4)
C(5')-H(5')	1.0000
C(6')-H(6'1)	0.9900
C(6')-H(6'2)	0.9900
O(1A)-C(5A')	1.416(3)
O(1A)-C(1A)	1.419(3)
O(2A)-C(1A)	1.412(3)
O(2A)-C(4A)	1.444(3)
O(3A)-C(1A')	1.418(3)
O(3A)-C(5A)	1.423(3)
O(4A)-C(1A')	1.411(3)
O(4A)-C(4A')	1.443(3)
F(1A)-C(6A)	1.402(3)
C(1A)-C(2A)	1.506(4)
C(1A)-H(1A)	1.0000
C(2A)-C(3A)	1.520(4)
C(2A)-H(2A1)	0.9900
C(2A)-H(2A2)	0.9900
C(3A)-C(4A)	1.521(4)
C(3A)-H(3A1)	0.9900
C(3A)-H(3A2)	0.9900
C(4A)-C(5A)	1.522(4)
C(4A)-H(4A)	1.0000
C(5A)-C(6A)	1.510(4)
C(5A)-H(5A)	1.0000
C(6A)-H(6A1)	0.9900
C(6A)-H(6A2)	0.9900
F(1A')-C(6A')	1.390(3)
C(1A')-C(2A')	1.510(4)
C(1A')-H(1A')	1.0000
C(2A')-C(3A')	1.524(4)
C(2A')-H(2A3)	0.9900
C(2A')-H(2A4)	0.9900
C(3A')-C(4A')	1.531(4)
C(3A')-H(3A3)	0.9900
C(3A')-H(3A4)	0.9900
C(4A')-C(5A')	1.521(3)
C(4A')-H(4A')	1.0000
C(5A')-C(6A')	1.508(3)

C(5A')-H(5A')	1.0000
C(6A')-H(6A3)	0.9900
C(6A')-H(6A4)	0.9900

C(1)-O(1)-C(5')	116.1(2)
C(1)-O(2)-C(4)	110.08(19)
C(1')-O(3)-C(5)	113.41(19)
C(1')-O(4)-C(4')	110.35(19)
O(2)-C(1)-O(1)	112.9(2)
O(2)-C(1)-C(2)	105.9(2)
O(1)-C(1)-C(2)	107.7(2)
O(2)-C(1)-H(1)	110.1
O(1)-C(1)-H(1)	110.1
C(2)-C(1)-H(1)	110.1
C(1)-C(2)-C(3)	101.8(2)
C(1)-C(2)-H(2A)	111.4
C(3)-C(2)-H(2A)	111.4
C(1)-C(2)-H(2B)	111.4
C(3)-C(2)-H(2B)	111.4
H(2A)-C(2)-H(2B)	109.3
C(2)-C(3)-C(4)	104.0(2)
C(2)-C(3)-H(3A)	111.0
C(4)-C(3)-H(3A)	111.0
C(2)-C(3)-H(3B)	111.0
C(4)-C(3)-H(3B)	111.0
H(3A)-C(3)-H(3B)	109.0
O(2)-C(4)-C(5)	111.3(2)
O(2)-C(4)-C(3)	105.7(2)
C(5)-C(4)-C(3)	114.9(2)
O(2)-C(4)-H(4)	108.2
C(5)-C(4)-H(4)	108.2
C(3)-C(4)-H(4)	108.2
O(3)-C(5)-C(6)	109.5(2)
O(3)-C(5)-C(4)	111.10(19)
C(6)-C(5)-C(4)	109.5(2)
O(3)-C(5)-H(5)	108.9
C(6)-C(5)-H(5)	108.9
C(4)-C(5)-H(5)	108.9
F(1)-C(6)-C(5)	108.4(2)
F(1)-C(6)-H(6A)	110.0

C(5)-C(6)-H(6A)	110.0
F(1)-C(6)-H(6B)	110.0
C(5)-C(6)-H(6B)	110.0
H(6A)-C(6)-H(6B)	108.4
O(4)-C(1')-O(3)	111.9(2)
O(4)-C(1')-C(2')	104.8(2)
O(3)-C(1')-C(2')	107.7(2)
O(4)-C(1')-H(1')	110.8
O(3)-C(1')-H(1')	110.8
C(2')-C(1')-H(1')	110.8
C(3')-C(2')-C(1')	102.8(2)
C(3')-C(2')-H(2'1)	111.2
C(1')-C(2')-H(2'1)	111.2
C(3')-C(2')-H(2'2)	111.2
C(1')-C(2')-H(2'2)	111.2
H(2'1)-C(2')-H(2'2)	109.1
C(2')-C(3')-C(4')	104.0(2)
C(2')-C(3')-H(3'1)	110.9
C(4')-C(3')-H(3'1)	110.9
C(2')-C(3')-H(3'2)	110.9
C(4')-C(3')-H(3'2)	110.9
H(3'1)-C(3')-H(3'2)	109.0
O(4)-C(4')-C(5')	110.4(2)
O(4)-C(4')-C(3')	105.7(2)
C(5')-C(4')-C(3')	115.3(2)
O(4)-C(4')-H(4')	108.4
C(5')-C(4')-H(4')	108.4
C(3')-C(4')-H(4')	108.4
O(1)-C(5')-C(6')	107.7(2)
O(1)-C(5')-C(4')	111.1(2)
C(6')-C(5')-C(4')	110.8(2)
O(1)-C(5')-H(5')	109.1
C(6')-C(5')-H(5')	109.1
C(4')-C(5')-H(5')	109.1
F(1')-C(6')-C(5')	112.2(2)
F(1')-C(6')-H(6'1)	109.2
C(5')-C(6')-H(6'1)	109.2
F(1')-C(6')-H(6'2)	109.2
C(5')-C(6')-H(6'2)	109.2
H(6'1)-C(6')-H(6'2)	107.9

C(5A')-O(1A)-C(1A)	114.39(18)
C(1A)-O(2A)-C(4A)	109.57(18)
C(1A')-O(3A)-C(5A)	115.2(2)
C(1A')-O(4A)-C(4A')	109.84(19)
O(2A)-C(1A)-O(1A)	111.39(19)
O(2A)-C(1A)-C(2A)	104.95(19)
O(1A)-C(1A)-C(2A)	107.90(19)
O(2A)-C(1A)-H(1A)	110.8
O(1A)-C(1A)-H(1A)	110.8
C(2A)-C(1A)-H(1A)	110.8
C(1A)-C(2A)-C(3A)	101.5(2)
C(1A)-C(2A)-H(2A1)	111.5
C(3A)-C(2A)-H(2A1)	111.5
C(1A)-C(2A)-H(2A2)	111.5
C(3A)-C(2A)-H(2A2)	111.5
H(2A1)-C(2A)-H(2A2)	109.3
C(2A)-C(3A)-C(4A)	102.6(2)
C(2A)-C(3A)-H(3A1)	111.2
C(4A)-C(3A)-H(3A1)	111.2
C(2A)-C(3A)-H(3A2)	111.2
C(4A)-C(3A)-H(3A2)	111.2
H(3A1)-C(3A)-H(3A2)	109.2
O(2A)-C(4A)-C(3A)	106.1(2)
O(2A)-C(4A)-C(5A)	110.3(2)
C(3A)-C(4A)-C(5A)	115.5(2)
O(2A)-C(4A)-H(4A)	108.3
C(3A)-C(4A)-H(4A)	108.3
C(5A)-C(4A)-H(4A)	108.3
O(3A)-C(5A)-C(6A)	107.89(19)
O(3A)-C(5A)-C(4A)	111.7(2)
C(6A)-C(5A)-C(4A)	110.2(2)
O(3A)-C(5A)-H(5A)	109.0
C(6A)-C(5A)-H(5A)	109.0
C(4A)-C(5A)-H(5A)	109.0
F(1A)-C(6A)-C(5A)	109.4(2)
F(1A)-C(6A)-H(6A1)	109.8
C(5A)-C(6A)-H(6A1)	109.8
F(1A)-C(6A)-H(6A2)	109.8
C(5A)-C(6A)-H(6A2)	109.8
H(6A1)-C(6A)-H(6A2)	108.2

O(4A)-C(1A')-O(3A)	111.47(19)
O(4A)-C(1A')-C(2A')	105.3(2)
O(3A)-C(1A')-C(2A')	107.5(2)
O(4A)-C(1A')-H(1A')	110.8
O(3A)-C(1A')-H(1A')	110.8
C(2A')-C(1A')-H(1A')	110.8
C(1A')-C(2A')-C(3A')	101.9(2)
C(1A')-C(2A')-H(2A3)	111.4
C(3A')-C(2A')-H(2A3)	111.4
C(1A')-C(2A')-H(2A4)	111.4
C(3A')-C(2A')-H(2A4)	111.4
H(2A3)-C(2A')-H(2A4)	109.3
C(2A')-C(3A')-C(4A')	102.7(2)
C(2A')-C(3A')-H(3A3)	111.2
C(4A')-C(3A')-H(3A3)	111.2
C(2A')-C(3A')-H(3A4)	111.2
C(4A')-C(3A')-H(3A4)	111.2
H(3A3)-C(3A')-H(3A4)	109.1
O(4A)-C(4A')-C(5A')	111.20(19)
O(4A)-C(4A')-C(3A')	106.25(19)
C(5A')-C(4A')-C(3A')	114.6(2)
O(4A)-C(4A')-H(4A')	108.2
C(5A')-C(4A')-H(4A')	108.2
C(3A')-C(4A')-H(4A')	108.2
O(1A)-C(5A')-C(6A')	109.1(2)
O(1A)-C(5A')-C(4A')	111.77(19)
C(6A')-C(5A')-C(4A')	108.1(2)
O(1A)-C(5A')-H(5A')	109.3
C(6A')-C(5A')-H(5A')	109.3
C(4A')-C(5A')-H(5A')	109.3
F(1A')-C(6A')-C(5A')	109.9(2)
F(1A')-C(6A')-H(6A3)	109.7
C(5A')-C(6A')-H(6A3)	109.7
F(1A')-C(6A')-H(6A4)	109.7
C(5A')-C(6A')-H(6A4)	109.7
H(6A3)-C(6A')-H(6A4)	108.2

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05119a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	37(1)	31(1)	30(1)	-1(1)	4(1)	4(1)
O(2)	30(1)	28(1)	23(1)	0(1)	-3(1)	4(1)
O(3)	28(1)	31(1)	29(1)	1(1)	3(1)	7(1)
O(4)	34(1)	32(1)	32(1)	-3(1)	5(1)	0(1)
F(1)	34(1)	105(2)	23(1)	14(1)	-4(1)	10(1)
C(1)	33(1)	33(1)	27(1)	0(1)	-6(1)	3(1)
C(2)	35(1)	34(2)	38(2)	-7(1)	-7(1)	-2(1)
C(3)	44(2)	30(1)	34(1)	2(1)	-2(1)	-3(1)
C(4)	28(1)	29(1)	29(1)	2(1)	0(1)	1(1)
C(5)	22(1)	31(1)	25(1)	1(1)	1(1)	5(1)
C(6)	28(1)	51(2)	28(1)	7(1)	1(1)	10(1)
F(1')	33(1)	83(1)	24(1)	-11(1)	-16(1)	4(1)
C(1')	28(1)	40(2)	28(1)	-1(1)	-3(1)	-1(1)
C(2')	24(1)	54(2)	37(2)	-3(1)	-1(1)	3(1)
C(3')	32(1)	56(2)	36(2)	2(1)	8(1)	11(1)
C(4')	33(1)	39(2)	33(1)	4(1)	9(1)	-1(1)
C(5')	36(1)	32(2)	32(1)	6(1)	5(1)	5(1)
C(6')	48(2)	55(2)	34(2)	7(1)	3(1)	3(2)
O(1A)	26(1)	28(1)	27(1)	2(1)	-3(1)	-5(1)
O(2A)	31(1)	27(1)	24(1)	1(1)	0(1)	-5(1)
O(3A)	28(1)	37(1)	26(1)	2(1)	-3(1)	-6(1)
O(4A)	32(1)	32(1)	24(1)	-3(1)	1(1)	-1(1)
F(1A)	44(1)	65(1)	28(1)	-6(1)	7(1)	1(1)
C(1A)	25(1)	27(1)	26(1)	-1(1)	3(1)	-5(1)
C(2A)	25(1)	29(1)	33(1)	1(1)	0(1)	-3(1)
C(3A)	38(1)	33(1)	28(1)	1(1)	-4(1)	1(1)
C(4A)	28(1)	30(1)	24(1)	2(1)	-5(1)	-4(1)
C(5A)	30(1)	29(1)	27(1)	0(1)	-4(1)	-5(1)
C(6A)	36(2)	41(2)	28(1)	-4(1)	-2(1)	-2(1)
F(1A')	46(1)	69(1)	26(1)	-12(1)	7(1)	2(1)
C(1A')	30(1)	39(2)	24(1)	-1(1)	5(1)	3(1)
C(2A')	24(1)	60(2)	29(1)	1(1)	3(1)	-3(1)
C(3A')	28(1)	52(2)	28(1)	-1(1)	1(1)	-10(1)
C(4A')	30(1)	37(1)	22(1)	2(1)	-3(1)	-1(1)

C(5A')	29(1)	27(1)	24(1)	6(1)	1(1)	-6(1)
C(6A')	35(1)	35(2)	23(1)	-1(1)	-2(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 05119a.

	x	y	z	U(eq)
H(1)	9219	7514	9836	37
H(2A)	10454	9472	9260	43
H(2B)	8775	10173	9552	43
H(3A)	9628	10276	7932	43
H(3B)	7764	10110	8176	43
H(4)	9852	8011	7525	34
H(5)	7394	6769	7158	31
H(6A)	7811	9588	6476	43
H(6B)	8751	8197	6141	43
H(1')	4596	6735	7150	39
H(2'1)	3166	8851	7864	46
H(2'2)	2385	7282	7965	46
H(3'1)	2697	7814	9388	49
H(3'2)	4245	8797	9211	49
H(4')	4110	5810	9424	42
H(5')	6934	6028	9743	40
H(6'1)	5090	7923	10797	54
H(6'2)	4827	6229	10839	54
H(1A)	4338	8567	2404	31
H(2A1)	5606	7068	3372	35
H(2A2)	4067	6122	3107	35
H(3A1)	4464	6726	4718	39
H(3A2)	2673	6786	4332	39
H(4A)	4750	9094	4708	33
H(5A)	2301	10457	4855	34
H(6A1)	2361	7991	5955	42
H(6A2)	3615	9278	6063	42
H(1A')	-505	10564	4719	37
H(2A3)	-2655	9640	3970	45
H(2A4)	-1964	8218	4429	45

H(3A3)	-2172	8258	2761	43
H(3A4)	-639	7498	3195	43
H(4A')	-809	10220	2395	36
H(5A')	2025	9877	2155	32
H(6A3)	-8	7646	1513	37
H(6A4)	23	9233	1120	37

Table 6. Torsion angles [°] for 05119a.

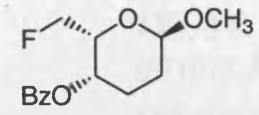
C(4)-O(2)-C(1)-O(1)	89.5(2)
C(4)-O(2)-C(1)-C(2)	-28.1(2)
C(5')-O(1)-C(1)-O(2)	65.3(3)
C(5')-O(1)-C(1)-C(2)	-178.1(2)
O(2)-C(1)-C(2)-C(3)	35.7(3)
O(1)-C(1)-C(2)-C(3)	-85.4(2)
C(1)-C(2)-C(3)-C(4)	-29.8(3)
C(1)-O(2)-C(4)-C(5)	-117.2(2)
C(1)-O(2)-C(4)-C(3)	8.2(3)
C(2)-C(3)-C(4)-O(2)	14.4(3)
C(2)-C(3)-C(4)-C(5)	137.6(2)
C(1')-O(3)-C(5)-C(6)	117.8(2)
C(1')-O(3)-C(5)-C(4)	-121.1(2)
O(2)-C(4)-C(5)-O(3)	74.4(3)
C(3)-C(4)-C(5)-O(3)	-45.7(3)
O(2)-C(4)-C(5)-C(6)	-164.6(2)
C(3)-C(4)-C(5)-C(6)	75.3(3)
O(3)-C(5)-C(6)-F(1)	-58.7(3)
C(4)-C(5)-C(6)-F(1)	179.3(2)
C(4')-O(4)-C(1')-O(3)	90.3(2)
C(4')-O(4)-C(1')-C(2')	-26.2(3)
C(5)-O(3)-C(1')-O(4)	65.4(3)
C(5)-O(3)-C(1')-C(2')	-179.94(19)
O(4)-C(1')-C(2')-C(3')	35.1(3)
O(3)-C(1')-C(2')-C(3')	-84.2(3)
C(1')-C(2')-C(3')-C(4')	-30.6(3)
C(1')-O(4)-C(4')-C(5')	-118.8(2)
C(1')-O(4)-C(4')-C(3')	6.4(3)
C(2')-C(3')-C(4')-O(4)	15.9(3)

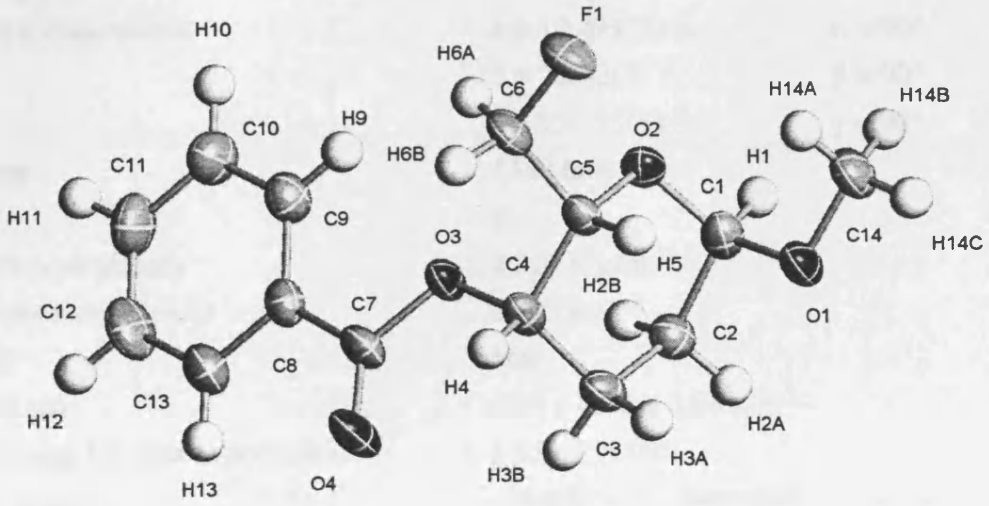
C(2')-C(3')-C(4')-C(5')	138.1(2)
C(1)-O(1)-C(5')-C(6')	118.3(2)
C(1)-O(1)-C(5')-C(4')	-120.1(2)
O(4)-C(4')-C(5')-O(1)	71.7(3)
C(3')-C(4')-C(5')-O(1)	-47.9(3)
O(4)-C(4')-C(5')-C(6')	-168.6(2)
C(3')-C(4')-C(5')-C(6')	71.8(3)
O(1)-C(5')-C(6')-F(1')	-72.6(3)
C(4')-C(5')-C(6')-F(1')	165.7(2)
C(4A)-O(2A)-C(1A)-O(1A)	90.2(2)
C(4A)-O(2A)-C(1A)-C(2A)	-26.3(2)
C(5A')-O(1A)-C(1A)-O(2A)	66.2(2)
C(5A')-O(1A)-C(1A)-C(2A)	-179.13(19)
O(2A)-C(1A)-C(2A)-C(3A)	38.4(2)
O(1A)-C(1A)-C(2A)-C(3A)	-80.5(2)
C(1A)-C(2A)-C(3A)-C(4A)	-35.4(2)
C(1A)-O(2A)-C(4A)-C(3A)	3.1(3)
C(1A)-O(2A)-C(4A)-C(5A)	-122.7(2)
C(2A)-C(3A)-C(4A)-O(2A)	20.9(3)
C(2A)-C(3A)-C(4A)-C(5A)	143.4(2)
C(1A')-O(3A)-C(5A)-C(6A)	121.8(2)
C(1A')-O(3A)-C(5A)-C(4A)	-117.0(2)
O(2A)-C(4A)-C(5A)-O(3A)	72.9(3)
C(3A)-C(4A)-C(5A)-O(3A)	-47.3(3)
O(2A)-C(4A)-C(5A)-C(6A)	-167.2(2)
C(3A)-C(4A)-C(5A)-C(6A)	72.6(3)
O(3A)-C(5A)-C(6A)-F(1A)	-69.0(3)
C(4A)-C(5A)-C(6A)-F(1A)	168.9(2)
C(4A')-O(4A)-C(1A')-O(3A)	90.4(2)
C(4A')-O(4A)-C(1A')-C(2A')	-25.9(3)
C(5A)-O(3A)-C(1A')-O(4A)	65.2(3)
C(5A)-O(3A)-C(1A')-C(2A')	-179.95(19)
O(4A)-C(1A')-C(2A')-C(3A')	37.2(3)
O(3A)-C(1A')-C(2A')-C(3A')	-81.8(2)
C(1A')-C(2A')-C(3A')-C(4A')	-33.8(3)
C(1A')-O(4A)-C(4A')-C(5A')	-121.6(2)
C(1A')-O(4A)-C(4A')-C(3A')	3.7(3)
C(2A')-C(3A')-C(4A')-O(4A)	19.5(3)
C(2A')-C(3A')-C(4A')-C(5A')	142.7(2)
C(1A)-O(1A)-C(5A')-C(6A')	123.5(2)

C(1A)-O(1A)-C(5A')-C(4A')	-117.0(2)
O(4A)-C(4A')-C(5A')-O(1A)	72.4(3)
C(3A')-C(4A')-C(5A')-O(1A)	-48.1(3)
O(4A)-C(4A')-C(5A')-C(6A')	-167.5(2)
C(3A')-C(4A')-C(5A')-C(6A')	72.1(3)
O(1A)-C(5A')-C(6A')-F(1A')	-63.7(2)
C(4A')-C(5A')-C(6A')-F(1A')	174.5(2)

Symmetry transformations used to generate equivalent atoms:

6.1.8 (+)-L-α-Methyl 5-*O*-benzyl-6-fluoro-rhodinoside 320





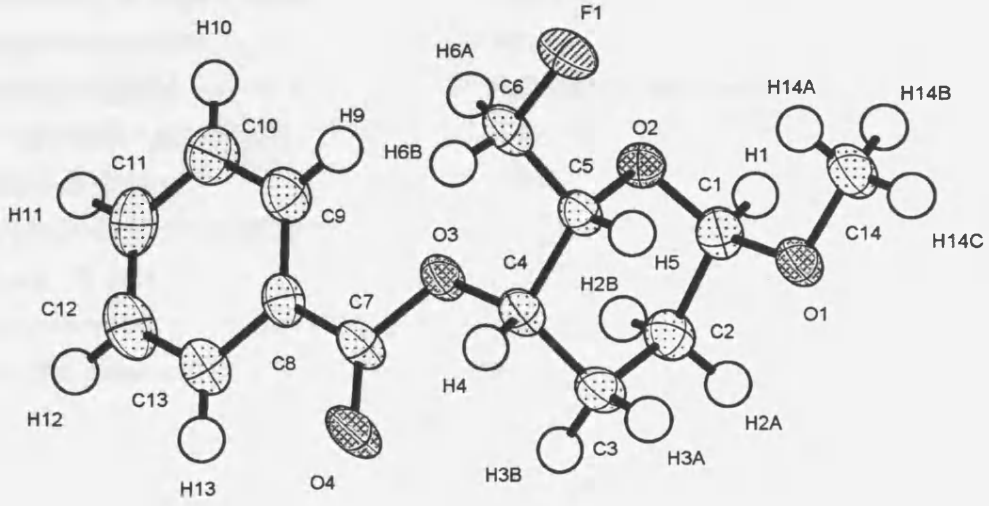


Table 1. Crystal data and structure refinement for 05130a.

Identification code	05130a	
Empirical formula	C14 H17 F O4	
Formula weight	268.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 13.491(5) Å	α = 90°.
	b = 7.632(3) Å	β = 90°.
	c = 13.118(5) Å	γ = 90°.
Volume	1350.6(9) $Å^3$	
Z	4	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	568	
Crystal size	0.15 x 0.12 x 0.08 mm^3	
Theta range for data collection	1.55 to 25.00°.	
Index ranges	-16<=h<=15, -9<=k<=9, -15<=l<=15	
Reflections collected	9737	
Independent reflections	2388 [R(int) = 0.0926]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2388 / 0 / 173	
Goodness-of-fit on F^2	0.994	
Final R indices [I>2sigma(I)]	R1 = 0.0552, wR2 = 0.0754	
R indices (all data)	R1 = 0.0852, wR2 = 0.0825	
Absolute structure parameter	-0.7(13)	
Largest diff. peak and hole	0.163 and -0.189 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 05130a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	6535(1)	11490(2)	1786(1)	48(1)
O(1)	6484(1)	6335(3)	388(1)	38(1)
O(2)	6735(1)	7763(3)	1936(1)	31(1)
O(3)	8690(1)	7942(3)	2764(1)	32(1)
O(4)	10324(1)	7685(3)	2468(1)	48(1)
C(1)	6710(2)	6139(4)	1433(2)	35(1)
C(2)	7686(2)	5185(4)	1507(2)	36(1)
C(3)	8537(2)	6342(4)	1158(2)	36(1)
C(4)	8510(2)	8120(4)	1677(2)	32(1)
C(5)	7491(2)	8926(4)	1568(2)	29(1)
C(6)	7386(2)	10601(4)	2132(2)	39(1)
C(7)	9638(2)	7755(4)	3061(2)	35(1)
C(8)	9739(2)	7636(4)	4182(2)	32(1)
C(9)	8959(2)	8003(4)	4825(2)	40(1)
C(10)	9080(2)	7907(5)	5870(2)	48(1)
C(11)	9988(3)	7441(5)	6267(2)	51(1)
C(12)	10760(2)	7075(5)	5632(3)	51(1)
C(13)	10650(2)	7172(4)	4584(2)	41(1)
C(14)	5566(2)	7238(4)	218(2)	44(1)

Table 3. Bond lengths [Å] and angles [°] for 05130a.

F(1)-C(6)	1.408(3)
O(1)-C(1)	1.412(3)
O(1)-C(14)	1.435(3)
O(2)-C(1)	1.404(3)
O(2)-C(5)	1.436(3)
O(3)-C(7)	1.344(3)
O(3)-C(4)	1.453(3)
O(4)-C(7)	1.210(3)
C(1)-C(2)	1.509(4)
C(1)-H(1)	1.0000

C(2)-C(3)	1.519(4)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.519(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.512(4)
C(4)-H(4)	1.0000
C(5)-C(6)	1.484(4)
C(5)-H(5)	1.0000
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.480(4)
C(8)-C(9)	1.378(4)
C(8)-C(13)	1.384(4)
C(9)-C(10)	1.381(4)
C(9)-H(9)	0.9500
C(10)-C(11)	1.378(4)
C(10)-H(10)	0.9500
C(11)-C(12)	1.362(4)
C(11)-H(11)	0.9500
C(12)-C(13)	1.385(4)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800

C(1)-O(1)-C(14)	112.8(2)
C(1)-O(2)-C(5)	113.9(2)
C(7)-O(3)-C(4)	116.9(2)
O(2)-C(1)-O(1)	111.6(2)
O(2)-C(1)-C(2)	112.0(2)
O(1)-C(1)-C(2)	107.5(2)
O(2)-C(1)-H(1)	108.6
O(1)-C(1)-H(1)	108.6
C(2)-C(1)-H(1)	108.6
C(1)-C(2)-C(3)	111.1(2)
C(1)-C(2)-H(2A)	109.4
C(3)-C(2)-H(2A)	109.4

C(1)-C(2)-H(2B)	109.4
C(3)-C(2)-H(2B)	109.4
H(2A)-C(2)-H(2B)	108.0
C(2)-C(3)-C(4)	111.5(2)
C(2)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3B)	109.3
C(4)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
O(3)-C(4)-C(5)	106.4(2)
O(3)-C(4)-C(3)	110.7(2)
C(5)-C(4)-C(3)	110.1(2)
O(3)-C(4)-H(4)	109.9
C(5)-C(4)-H(4)	109.9
C(3)-C(4)-H(4)	109.9
O(2)-C(5)-C(6)	107.3(2)
O(2)-C(5)-C(4)	111.2(2)
C(6)-C(5)-C(4)	113.0(2)
O(2)-C(5)-H(5)	108.4
C(6)-C(5)-H(5)	108.4
C(4)-C(5)-H(5)	108.4
F(1)-C(6)-C(5)	109.4(2)
F(1)-C(6)-H(6A)	109.8
C(5)-C(6)-H(6A)	109.8
F(1)-C(6)-H(6B)	109.8
C(5)-C(6)-H(6B)	109.8
H(6A)-C(6)-H(6B)	108.2
O(4)-C(7)-O(3)	123.2(3)
O(4)-C(7)-C(8)	124.4(3)
O(3)-C(7)-C(8)	112.4(2)
C(9)-C(8)-C(13)	119.8(3)
C(9)-C(8)-C(7)	121.7(3)
C(13)-C(8)-C(7)	118.4(3)
C(8)-C(9)-C(10)	120.4(3)
C(8)-C(9)-H(9)	119.8
C(10)-C(9)-H(9)	119.8
C(11)-C(10)-C(9)	119.6(3)
C(11)-C(10)-H(10)	120.2
C(9)-C(10)-H(10)	120.2
C(12)-C(11)-C(10)	120.0(3)

C(12)-C(11)-H(11)	120.0
C(10)-C(11)-H(11)	120.0
C(11)-C(12)-C(13)	121.0(3)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(8)-C(13)-C(12)	119.1(3)
C(8)-C(13)-H(13)	120.4
C(12)-C(13)-H(13)	120.4
O(1)-C(14)-H(14A)	109.5
O(1)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(1)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05130a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	31(1)	51(1)	62(1)	4(1)	-1(1)	9(1)
O(1)	26(1)	55(1)	32(1)	1(1)	-3(1)	1(1)
O(2)	28(1)	38(1)	28(1)	0(1)	5(1)	-3(1)
O(3)	23(1)	48(1)	26(1)	3(1)	-2(1)	0(1)
O(4)	23(1)	77(2)	43(1)	7(1)	-1(1)	3(1)
C(1)	33(2)	45(2)	27(2)	4(2)	1(2)	-7(2)
C(2)	33(2)	42(2)	32(2)	4(2)	-3(2)	3(2)
C(3)	27(2)	53(2)	28(2)	3(2)	0(2)	5(2)
C(4)	25(2)	51(2)	22(2)	7(2)	2(1)	-2(2)
C(5)	22(2)	39(2)	27(2)	3(2)	1(2)	-3(2)
C(6)	25(2)	48(2)	42(2)	7(2)	-6(2)	5(2)
C(7)	22(2)	44(2)	40(2)	4(2)	0(2)	-3(2)
C(8)	32(2)	29(2)	34(2)	5(2)	-7(1)	-2(2)
C(9)	37(2)	46(2)	36(2)	5(2)	-5(2)	0(2)
C(10)	51(2)	63(3)	30(2)	3(2)	-4(2)	3(2)
C(11)	60(2)	60(3)	34(2)	1(2)	-17(2)	-7(2)

C(12)	45(2)	56(3)	52(2)	14(2)	-22(2)	4(2)
C(13)	33(2)	46(2)	44(2)	5(2)	-4(2)	-3(2)
C(14)	30(2)	59(2)	44(2)	1(2)	-8(2)	3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 05130a.

	x	y	z	U(eq)
H(1)	6185	5397	1756	42
H(2A)	7662	4117	1078	43
H(2B)	7800	4818	2221	43
H(3A)	8498	6504	410	43
H(3B)	9174	5756	1314	43
H(4)	9019	8910	1368	39
H(5)	7367	9156	828	35
H(6A)	7327	10364	2871	46
H(6B)	7980	11339	2020	46
H(9)	8334	8324	4549	48
H(10)	8541	8160	6311	58
H(11)	10076	7375	6985	61
H(12)	11382	6748	5912	61
H(13)	11194	6924	4146	49
H(14A)	5617	8437	480	66
H(14B)	5030	6623	573	66
H(14C)	5424	7271	-514	66

Table 6. Torsion angles [°] for 05130a.

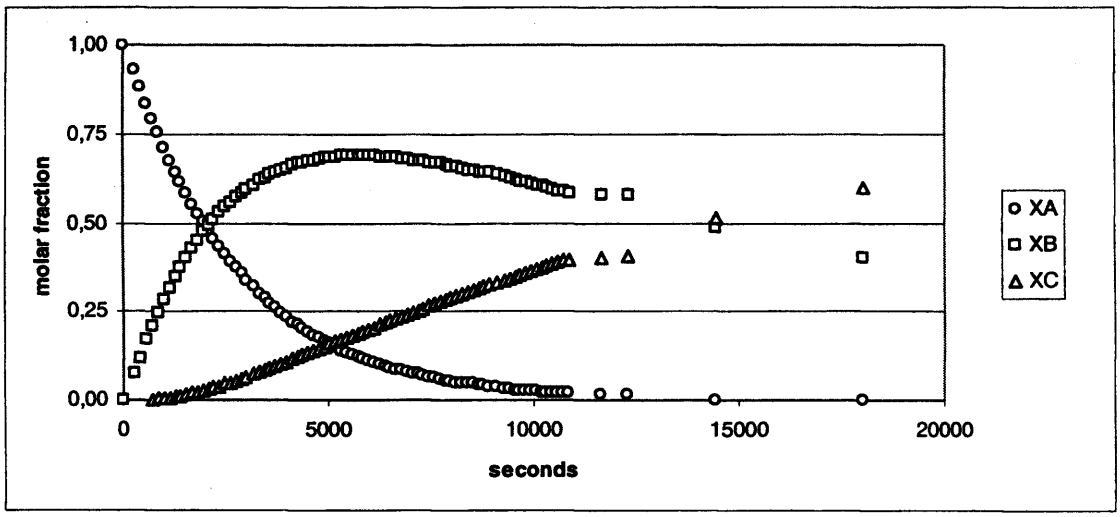
C(5)-O(2)-C(1)-O(1)	-62.8(3)
C(5)-O(2)-C(1)-C(2)	57.8(3)
C(14)-O(1)-C(1)-O(2)	-56.6(3)
C(14)-O(1)-C(1)-C(2)	-179.8(2)
O(2)-C(1)-C(2)-C(3)	-52.6(3)
O(1)-C(1)-C(2)-C(3)	70.3(3)
C(1)-C(2)-C(3)-C(4)	50.2(3)
C(7)-O(3)-C(4)-C(5)	-160.7(3)
C(7)-O(3)-C(4)-C(3)	79.8(3)
C(2)-C(3)-C(4)-O(3)	66.1(3)
C(2)-C(3)-C(4)-C(5)	-51.3(3)
C(1)-O(2)-C(5)-C(6)	177.0(2)
C(1)-O(2)-C(5)-C(4)	-59.1(3)
O(3)-C(4)-C(5)-O(2)	-65.4(3)
C(3)-C(4)-C(5)-O(2)	54.5(3)
O(3)-C(4)-C(5)-C(6)	55.3(3)
C(3)-C(4)-C(5)-C(6)	175.2(2)
O(2)-C(5)-C(6)-F(1)	-72.5(3)
C(4)-C(5)-C(6)-F(1)	164.6(2)
C(4)-O(3)-C(7)-O(4)	-2.0(5)
C(4)-O(3)-C(7)-C(8)	178.4(3)
O(4)-C(7)-C(8)-C(9)	169.4(3)
O(3)-C(7)-C(8)-C(9)	-11.0(5)
O(4)-C(7)-C(8)-C(13)	-9.4(5)
O(3)-C(7)-C(8)-C(13)	170.2(3)
C(13)-C(8)-C(9)-C(10)	-0.1(5)
C(7)-C(8)-C(9)-C(10)	-179.0(3)
C(8)-C(9)-C(10)-C(11)	0.0(5)
C(9)-C(10)-C(11)-C(12)	-0.1(5)
C(10)-C(11)-C(12)-C(13)	0.4(6)
C(9)-C(8)-C(13)-C(12)	0.4(5)
C(7)-C(8)-C(13)-C(12)	179.3(3)
C(11)-C(12)-C(13)-C(8)	-0.5(6)

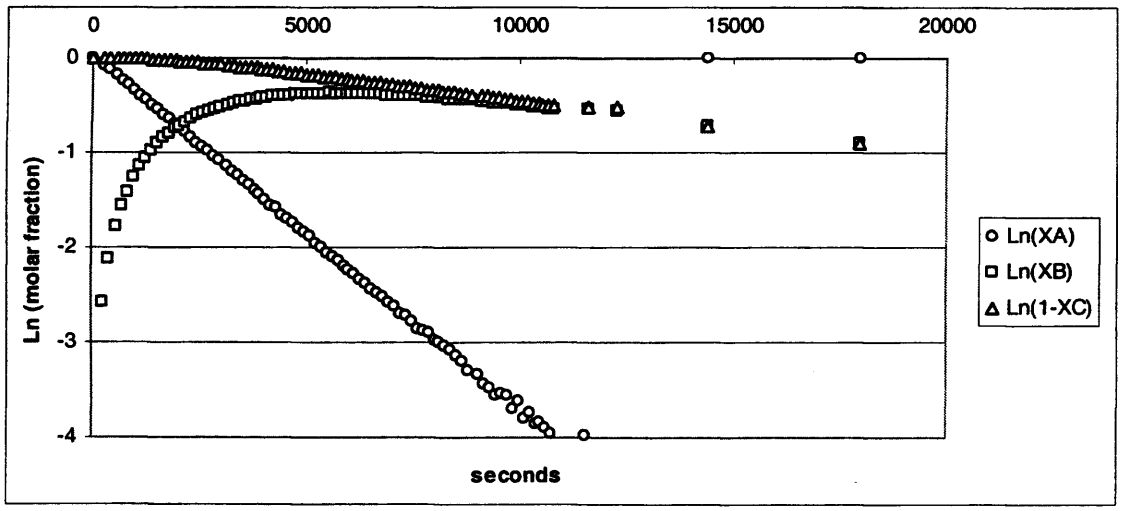
Symmetry transformations used to generate equivalent atoms:

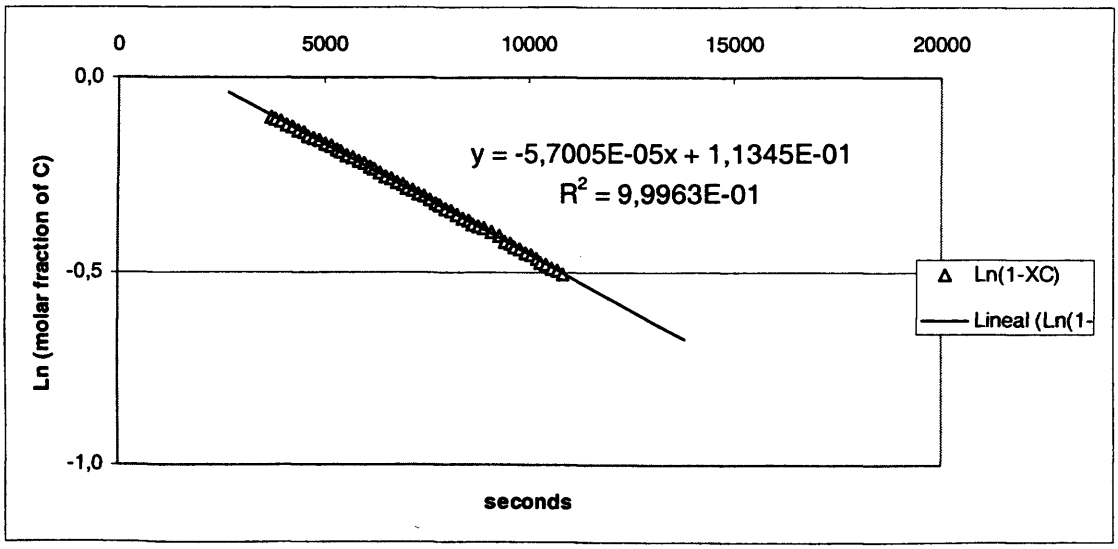
6.2 Appendix II, Methanolysis

6.2.1 Experiment in CD_3OD Entry 1

[132] = 0.648 mol/l
[TMSCl] = 0.113 mol/l
$k_{obs}= 5.70 \cdot 10^{-5}\ s^{-1}$





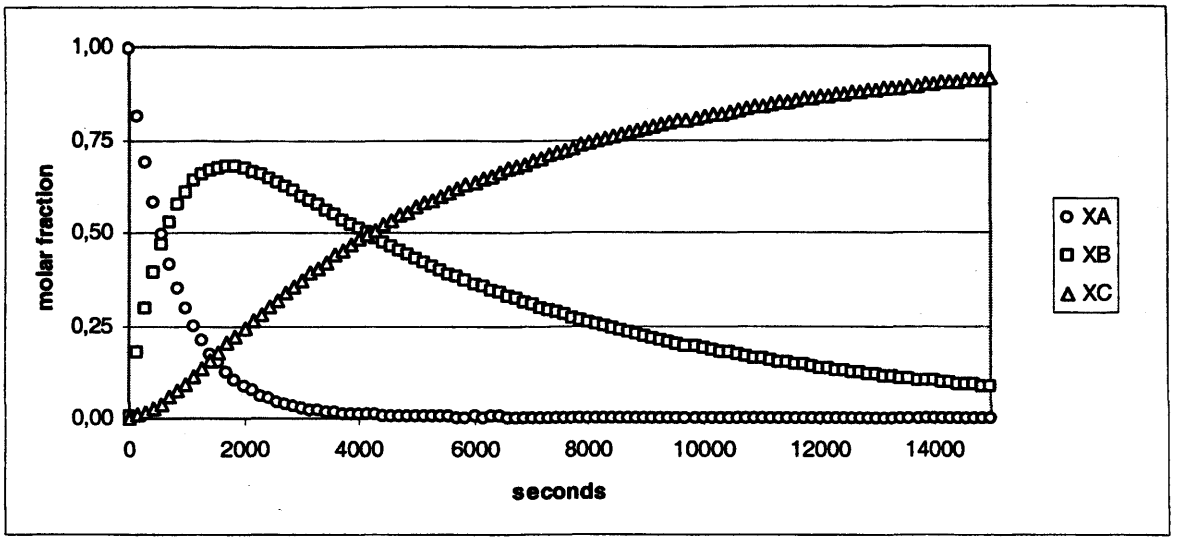


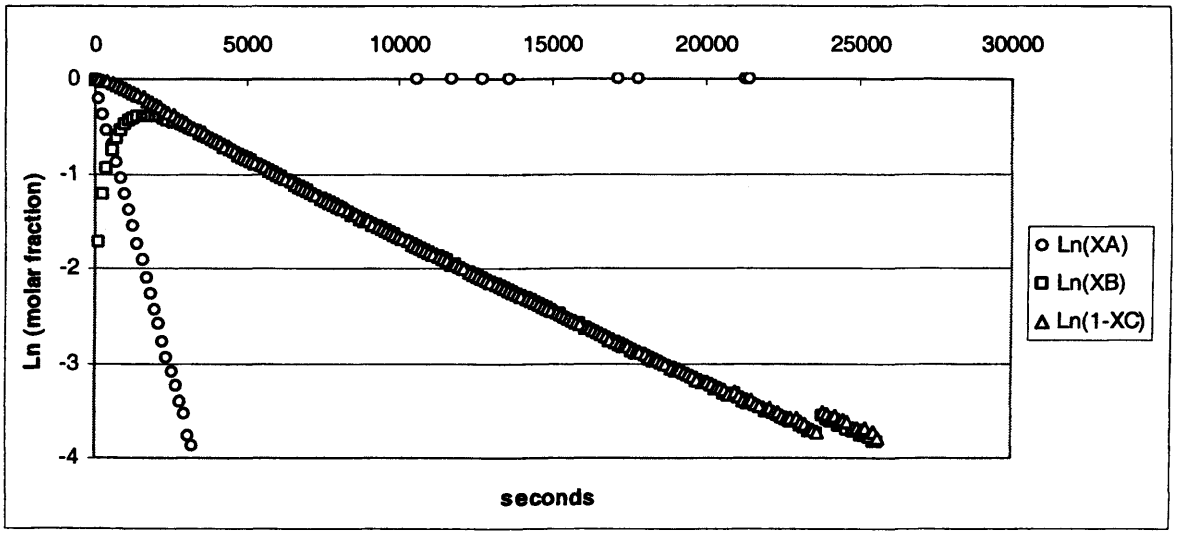
Time (s)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.6 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	$Ln(X_A)$	$Ln(X_B)$	$Ln(1-X_C)$
0	1000.00	0.37	1140.25	1.64	-7.43	2134.8	1.003	0.001	-0.003	0.003	-6.969	0.003
277	838.21	60.20	930.94	82.70	-12.23	1899.8	0.931	0.075	-0.006	-0.071	-2.587	0.006
415	780.83	89.39	877.37	135.27	-7.68	1875.2	0.884	0.120	-0.004	-0.123	-2.122	0.004
567	730.10	136.41	816.64	178.29	-7.45	1854.0	0.834	0.170	-0.004	-0.181	-1.773	0.004
709	685.23	167.28	771.46	220.21	-1.72	1842.5	0.791	0.210	-0.001	-0.235	-1.559	0.001
844	637.74	183.00	730.88	258.96	5.09	1815.7	0.754	0.243	0.003	-0.283	-1.413	-0.003
979	600.32	220.69	681.85	288.55	7.40	1798.8	0.713	0.283	0.004	-0.339	-1.262	-0.004
1119	561.82	247.37	639.40	317.01	11.69	1777.3	0.676	0.318	0.007	-0.392	-1.147	-0.007
1255	526.85	264.56	603.48	345.07	15.67	1755.6	0.644	0.347	0.009	-0.440	-1.058	-0.009
1390	493.90	281.97	567.74	368.38	21.36	1733.4	0.612	0.375	0.012	-0.490	-0.980	-0.012
1526	461.88	300.41	531.67	389.83	26.08	1709.9	0.581	0.404	0.015	-0.543	-0.907	-0.015
1659	432.78	313.43	499.57	409.52	32.14	1687.4	0.553	0.428	0.019	-0.593	-0.848	-0.019
1792	405.66	323.95	470.33	426.55	37.31	1663.8	0.526	0.451	0.022	-0.642	-0.796	-0.023
1925	381.01	337.40	441.06	441.62	42.80	1643.9	0.500	0.474	0.026	-0.693	-0.747	-0.026
2058	359.48	343.24	419.79	457.13	50.40	1630.0	0.478	0.491	0.031	-0.738	-0.711	-0.031
2191	336.07	350.41	393.27	469.16	56.49	1605.4	0.454	0.511	0.035	-0.789	-0.672	-0.036
2324	315.96	357.34	372.29	480.69	63.23	1589.5	0.433	0.527	0.040	-0.837	-0.640	-0.041
2456	295.41	362.49	348.46	492.02	72.46	1570.8	0.410	0.544	0.046	-0.892	-0.609	-0.047
2589	279.55	368.17	328.02	500.89	78.86	1555.5	0.391	0.559	0.051	-0.940	-0.582	-0.052
2722	262.42	372.44	309.37	508.30	83.98	1536.5	0.372	0.573	0.055	-0.988	-0.557	-0.056
2855	245.95	370.36	295.96	515.47	91.62	1519.4	0.357	0.583	0.060	-1.031	-0.540	-0.062
2988	231.07	374.85	278.22	522.38	100.45	1507.0	0.338	0.595	0.067	-1.085	-0.519	-0.069
3167	217.95	377.04	263.73	528.74	108.37	1495.8	0.322	0.606	0.072	-1.133	-0.502	-0.075
3296	203.51	382.56	246.87	539.13	118.99	1491.1	0.302	0.618	0.080	-1.197	-0.481	-0.083
3427	192.44	383.88	235.32	549.06	128.88	1489.6	0.287	0.626	0.087	-1.248	-0.468	-0.090
3559	182.60	389.89	222.44	551.24	136.45	1482.6	0.273	0.635	0.092	-1.298	-0.454	-0.097
3692	172.41	390.74	212.39	560.26	146.64	1482.4	0.260	0.642	0.099	-1.349	-0.444	-0.104
3825	164.78	396.55	201.12	562.69	153.25	1478.4	0.247	0.649	0.104	-1.396	-0.433	-0.109
3957	156.42	401.51	192.80	568.32	161.64	1480.7	0.236	0.655	0.109	-1.445	-0.423	-0.116
4090	148.52	405.69	178.48	575.43	171.59	1479.7	0.221	0.663	0.116	-1.510	-0.411	-0.123
4223	141.51	410.16	171.97	577.28	179.75	1480.7	0.212	0.667	0.121	-1.553	-0.405	-0.129
4356	133.79	407.56	169.31	580.29	187.79	1478.7	0.205	0.668	0.127	-1.585	-0.403	-0.136
4489	126.06	409.72	156.76	586.34	199.11	1478.0	0.191	0.674	0.135	-1.654	-0.395	-0.145
4622	120.80	410.63	150.60	588.40	207.46	1477.9	0.184	0.676	0.140	-1.695	-0.392	-0.151
4755	114.15	413.24	142.80	590.64	217.20	1478.0	0.174	0.679	0.147	-1.750	-0.387	-0.159
4888	109.07	417.56	136.97	589.45	223.45	1476.5	0.167	0.682	0.151	-1.792	-0.383	-0.164
5021	103.61	417.38	130.87	592.20	234.00	1478.1	0.159	0.683	0.158	-1.841	-0.381	-0.172
5154	98.09	417.46	125.79	592.67	243.06	1477.1	0.152	0.684	0.165	-1.887	-0.380	-0.180
5287	93.02	420.41	114.65	594.73	250.23	1473.0	0.141	0.689	0.170	-1.959	-0.372	-0.186
5419	88.96	418.31	110.69	597.60	259.99	1475.6	0.135	0.688	0.176	-2.000	-0.373	-0.194
5552	84.09	421.49	102.38	597.30	268.79	1474.0	0.127	0.691	0.182	-2.068	-0.369	-0.201
5685	80.18	420.41	100.52	597.88	277.65	1476.6	0.122	0.690	0.188	-2.101	-0.372	-0.208
5818	76.18	421.75	96.87	595.63	286.37	1476.8	0.117	0.689	0.194	-2.144	-0.373	-0.216
5951	72.74	421.59	89.53	598.60	296.11	1478.6	0.110	0.690	0.200	-2.210	-0.371	-0.223
6083	68.97	422.40	88.05	594.95	304.01	1478.4	0.106	0.688	0.206	-2.242	-0.374	-0.230
6217	65.92	420.93	84.78	594.86	314.19	1480.7	0.102	0.686	0.212	-2.285	-0.377	-0.239
6349	61.77	419.45	81.15	592.30	321.84	1476.5	0.097	0.685	0.218	-2.335	-0.378	-0.246
6483	58.86	417.53	77.50	592.79	331.89	1478.6	0.092	0.683	0.224	-2.384	-0.381	-0.254
6616	56.11	417.69	73.34	592.32	340.61	1480.1	0.087	0.682	0.230	-2.437	-0.382	-0.262
6749	53.13	417.52	71.74	591.83	351.35	1485.6	0.084	0.679	0.237	-2.476	-0.386	-0.270
6882	50.63	417.15	69.11	591.69	361.56	1490.1	0.080	0.677	0.243	-2.521	-0.390	-0.278
7014	48.49	416.94	65.46	590.96	369.38	1491.2	0.076	0.676	0.248	-2.572	-0.392	-0.285
7147	46.54	416.50	61.20	588.35	377.63	1490.2	0.072	0.674	0.253	-2.627	-0.394	-0.292

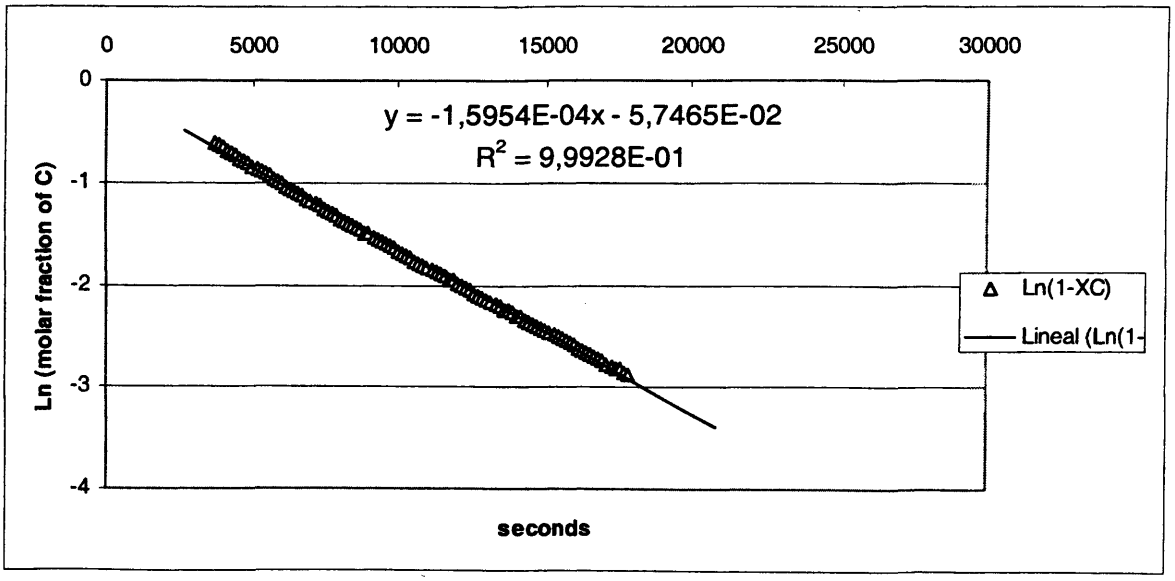
7280	44.35	417.05	56.41	585.81	385.74	1489.4	0.068	0.673	0.259	-2.693	-0.395	-0.300
7413	41.81	412.64	56.53	584.61	394.97	1499.5	0.066	0.669	0.265	-2.719	-0.402	-0.308
7546	40.09	413.20	51.92	581.80	402.64	1489.7	0.062	0.668	0.270	-2.784	-0.404	-0.315
7679	37.46	412.83	48.40	579.65	411.38	1489.7	0.058	0.666	0.276	-2.854	-0.406	-0.323
7812	36.05	410.21	47.49	579.80	421.34	1494.9	0.056	0.662	0.282	-2.884	-0.412	-0.331
7945	34.53	408.84	47.68	577.81	429.92	1498.8	0.055	0.658	0.287	-2.903	-0.418	-0.338
8077	32.10	409.79	43.48	574.75	439.82	1499.9	0.050	0.656	0.293	-2.988	-0.421	-0.347
8211	31.57	405.88	43.22	572.98	447.02	1500.7	0.050	0.652	0.298	-2.999	-0.427	-0.354
8344	29.75	402.48	41.32	570.22	455.71	1499.5	0.047	0.649	0.304	-3.049	-0.433	-0.362
8477	28.55	400.66	40.18	568.42	463.34	1501.1	0.046	0.646	0.309	-3.084	-0.438	-0.369
8609	27.22	399.53	38.14	565.46	473.38	1503.7	0.043	0.642	0.315	-3.136	-0.444	-0.378
8742	25.57	399.76	35.38	562.53	482.26	1505.5	0.040	0.639	0.320	-3.207	-0.448	-0.386
8875	24.90	400.44	30.49	559.36	485.95	1501.1	0.037	0.639	0.324	-3.300	-0.447	-0.391
9077	23.65	399.55	29.70	557.05	496.56	1506.5	0.035	0.635	0.330	-3.341	-0.454	-0.400
9253	22.10	397.21	26.28	552.58	504.94	1503.1	0.032	0.632	0.336	-3.436	-0.459	-0.409
9369	21.15	393.26	25.45	549.95	520.05	1509.9	0.031	0.625	0.344	-3.478	-0.470	-0.422
9507	20.11	392.12	23.04	546.66	526.30	1508.2	0.029	0.622	0.349	-3.554	-0.474	-0.429
9637	18.77	389.30	25.20	544.88	537.99	1516.1	0.029	0.616	0.355	-3.540	-0.484	-0.438
9770	18.28	387.06	25.01	543.06	543.82	1517.2	0.029	0.613	0.358	-3.557	-0.489	-0.444
9902	17.49	389.33	20.05	539.25	551.97	1518.1	0.025	0.612	0.364	-3.700	-0.492	-0.452
10035	15.43	382.41	24.95	538.26	561.27	1522.3	0.027	0.605	0.369	-3.630	-0.503	-0.460
10167	15.60	384.27	18.62	532.90	568.13	1519.5	0.023	0.604	0.374	-3.793	-0.505	-0.468
10300	14.63	377.89	21.30	531.18	576.17	1521.2	0.024	0.598	0.379	-3.746	-0.515	-0.476
10433	14.22	377.55	17.88	527.14	582.46	1519.2	0.021	0.595	0.383	-3.857	-0.518	-0.484
10565	12.90	373.09	20.06	525.00	592.17	1523.2	0.022	0.590	0.389	-3.833	-0.528	-0.492
10699	12.76	371.74	17.84	521.92	598.57	1522.8	0.020	0.587	0.393	-3.907	-0.533	-0.499
10831	12.45	372.36	16.69	520.54	608.55	1530.6	0.019	0.583	0.398	-3.961	-0.539	-0.507
11628	11.37	370.50	17.18	518.77	617.11	1534.9	0.019	0.579	0.402	-3.985	-0.546	-0.514
12293	9.32	368.21	17.56	516.08	624.42	1535.6	0.018	0.576	0.407	-4.045	-0.552	-0.522
14419	0.00	1.00	0.00	1.38	2.50	4.9	0.000	0.487	0.513	#¡NUM!	-0.719	-0.719
17976	0.00	1.00	0.00	1.36	3.49	5.9	0.000	0.403	0.597	#¡NUM!	-0.909	-0.909
25371	0.00	1.00	0.00	1.34	5.36	7.7	0.000	0.304	0.696	#¡NUM!	-1.191	-1.191
37734	0.00	1.00	0.00	1.33	11.98	14.3	0.000	0.163	0.837	#¡NUM!	-1.814	-1.814
43925	0.00	1.00	0.00	1.28	16.34	18.6	0.000	0.122	0.878	#¡NUM!	-2.100	-2.100
86280	0.00	1.00	0.00	1.21	39.97	42.2	0.000	0.052	0.948	#¡NUM!	-2.947	-2.947
105941	0.00	1.00	0.00	1.12	69.78	71.9	0.000	0.030	0.970	#¡NUM!	-3.522	-3.522
174228	0.00	1.00	0.00	0.81	227.83	229.6	0.000	0.008	0.992	#¡NUM!	-4.845	-4.845

6.2.2 Experiment in CD_3OD Entry 2

[**132**] = 0.546 mol/l
[TMSCl] = 0.333 mol/l
k_{obs}= $15.95 \cdot 10^{-5}$ s^{-1}







Time (s)	Int S δ_F (-59.3 Hz)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.8 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	$Ln(X_A)$	$Ln(X_B)$	$Ln(1-X_C)$
0	1000.00	1672.93	17.07	1844.90	1.93	7.35	4544.2	0.993	0.005	0.002	-0.007	-5.229	-0.002
143	1013.57	1336.63	279.44	1515.30	340.40	29.80	4515.1	0.814	0.177	0.009	-0.205	-1.732	-0.009
286	976.67	1054.00	425.55	1216.47	557.26	50.75	4280.7	0.687	0.297	0.015	-0.375	-1.212	-0.015
428	938.15	824.53	500.28	979.00	713.19	80.46	4035.6	0.582	0.392	0.026	-0.541	-0.937	-0.026
571	907.16	651.58	535.01	794.65	825.57	115.79	3829.8	0.495	0.466	0.040	-0.704	-0.765	-0.040
714	889.89	527.45	580.74	648.90	912.58	164.87	3724.4	0.415	0.527	0.058	-0.879	-0.641	-0.060
857	889.09	440.59	623.54	545.45	992.16	212.92	3703.7	0.350	0.574	0.076	-1.049	-0.555	-0.079
1000	895.04	370.09	656.77	465.56	1058.62	260.69	3706.8	0.297	0.610	0.093	-1.213	-0.494	-0.097
1142	894.39	307.65	684.49	382.90	1093.89	320.77	3684.1	0.248	0.637	0.115	-1.396	-0.450	-0.122
1285	897.45	258.35	704.70	326.26	1130.04	379.93	3696.7	0.209	0.655	0.136	-1.566	-0.422	-0.146
1428	897.96	216.75	718.28	269.47	1146.09	440.82	3689.4	0.174	0.668	0.158	-1.748	-0.404	-0.172
1571	904.83	183.27	723.91	234.00	1167.52	497.67	3711.2	0.149	0.674	0.177	-1.906	-0.395	-0.195
1714	894.36	150.96	728.07	187.95	1159.73	564.29	3685.4	0.121	0.676	0.202	-2.108	-0.391	-0.226
1856	900.06	128.68	726.25	159.79	1159.40	620.41	3694.6	0.103	0.675	0.222	-2.271	-0.393	-0.251
1999	900.96	107.94	723.44	135.91	1159.09	677.01	3704.4	0.087	0.672	0.241	-2.442	-0.398	-0.276
2142	906.47	91.07	716.83	120.23	1156.69	737.93	3729.2	0.075	0.664	0.261	-2.592	-0.410	-0.303
2285	899.05	76.73	710.18	96.96	1134.94	793.65	3711.5	0.062	0.656	0.282	-2.785	-0.422	-0.332
2428	897.28	65.13	700.38	81.77	1119.19	849.52	3713.3	0.052	0.646	0.302	-2.953	-0.437	-0.359
2570	904.86	56.30	691.54	72.20	1107.97	904.69	3737.6	0.045	0.635	0.319	-3.093	-0.454	-0.385
2713	901.41	47.18	681.15	63.00	1093.57	960.14	3746.5	0.039	0.624	0.337	-3.251	-0.472	-0.412
2856	904.48	40.11	670.40	54.48	1077.78	1015.38	3762.6	0.033	0.612	0.355	-3.408	-0.492	-0.439
2999	910.95	34.86	659.72	48.24	1064.15	1070.39	3788.3	0.029	0.599	0.372	-3.545	-0.512	-0.465
3142	903.96	27.49	649.02	38.69	1041.53	1125.54	3786.2	0.023	0.587	0.391	-3.774	-0.534	-0.495
3284	911.03	24.88	638.46	35.91	1027.37	1179.67	3817.3	0.021	0.573	0.406	-3.867	-0.557	-0.521
3427	912.06	20.58	623.62	30.87	1002.85	1224.12	3814.1	0.018	0.560	0.422	-4.033	-0.579	-0.548
3570	905.71	18.11	611.88	23.38	979.78	1276.70	3815.6	0.014	0.547	0.439	-4.250	-0.603	-0.578
3713	905.52	14.68	599.50	22.13	962.37	1323.60	3827.8	0.013	0.534	0.453	-4.374	-0.626	-0.603
3856	906.52	13.83	587.72	17.93	941.84	1369.86	3837.7	0.011	0.522	0.467	-4.525	-0.650	-0.630
3998	907.27	11.08	574.41	15.47	919.69	1413.41	3841.3	0.009	0.509	0.482	-4.705	-0.675	-0.657
4141	909.08	10.48	563.53	16.21	906.47	1457.65	3863.4	0.009	0.498	0.493	-4.706	-0.698	-0.680
4284	911.86	8.86	552.66	16.04	891.87	1508.76	3890.0	0.008	0.485	0.507	-4.784	-0.724	-0.706
4427	913.68	7.41	541.74	9.47	865.76	1554.41	3892.5	0.006	0.473	0.522	-5.173	-0.750	-0.738
4570	912.96	6.97	530.55	9.72	849.60	1593.80	3903.6	0.006	0.461	0.533	-5.188	-0.773	-0.761
4712	903.92	4.72	518.85	5.79	828.66	1640.54	3902.5	0.004	0.449	0.547	-5.653	-0.800	-0.792
4855	914.22	5.74	507.79	10.73	817.65	1676.34	3932.5	0.005	0.439	0.555	-5.211	-0.823	-0.811
4998	912.52	3.98	496.72	6.59	795.32	1711.37	3926.5	0.004	0.429	0.568	-5.653	-0.847	-0.839
5141	914.08	4.40	485.89	7.39	779.16	1748.97	3939.9	0.004	0.418	0.578	-5.548	-0.872	-0.863
5284	916.00	3.87	475.00	9.09	766.48	1787.01	3957.5	0.004	0.408	0.588	-5.458	-0.896	-0.886
5426	909.66	2.90	464.68	7.39	747.79	1818.04	3950.5	0.003	0.399	0.598	-5.688	-0.919	-0.911
5569	920.42	2.64	455.70	9.98	737.98	1859.76	3986.5	0.004	0.389	0.607	-5.493	-0.943	-0.933
5712	912.41	2.43	444.74	4.19	712.95	1889.84	3966.6	0.002	0.379	0.619	-6.134	-0.970	-0.964
5855	917.80	1.98	435.99	6.27	701.42	1921.16	3984.6	0.003	0.371	0.626	-5.919	-0.992	-0.985
5998	916.81	2.44	426.87	8.26	688.34	1954.58	3997.3	0.003	0.362	0.635	-5.663	-1.016	-1.006
6140	909.77	1.89	416.61	4.05	669.14	1981.73	3983.2	0.002	0.353	0.645	-6.249	-1.041	-1.035
6283	913.04	2.54	407.98	6.72	657.73	2013.49	4001.5	0.003	0.345	0.652	-5.810	-1.064	-1.055
6426	925.69	2.60	400.22	8.63	646.41	2046.02	4029.6	0.004	0.337	0.659	-5.622	-1.087	-1.076
6569	915.08	2.49	389.69	4.05	625.13	2068.92	4005.3	0.002	0.328	0.669	-6.159	-1.114	-1.107
6712	916.13	1.35	382.82	4.79	614.11	2105.71	4024.9	0.002	0.321	0.677	-6.228	-1.137	-1.131
6854	914.63	1.67	375.27	5.04	603.51	2141.85	4042.0	0.002	0.313	0.685	-6.145	-1.162	-1.155
6997	913.76	0.85	366.98	3.59	590.29	2173.63	4049.1	0.001	0.305	0.693	-6.559	-1.186	-1.182
7140	917.76	1.65	358.80	4.57	578.59	2203.27	4064.7	0.002	0.298	0.700	-6.226	-1.211	-1.204
7283	924.15	2.35	352.44	3.63	565.63	2232.05	4080.3	0.002	0.291	0.707	-6.268	-1.235	-1.228
7426	921.19	1.71	344.02	1.69	550.86	2255.05	4074.5	0.001	0.284	0.715	-6.835	-1.260	-1.256

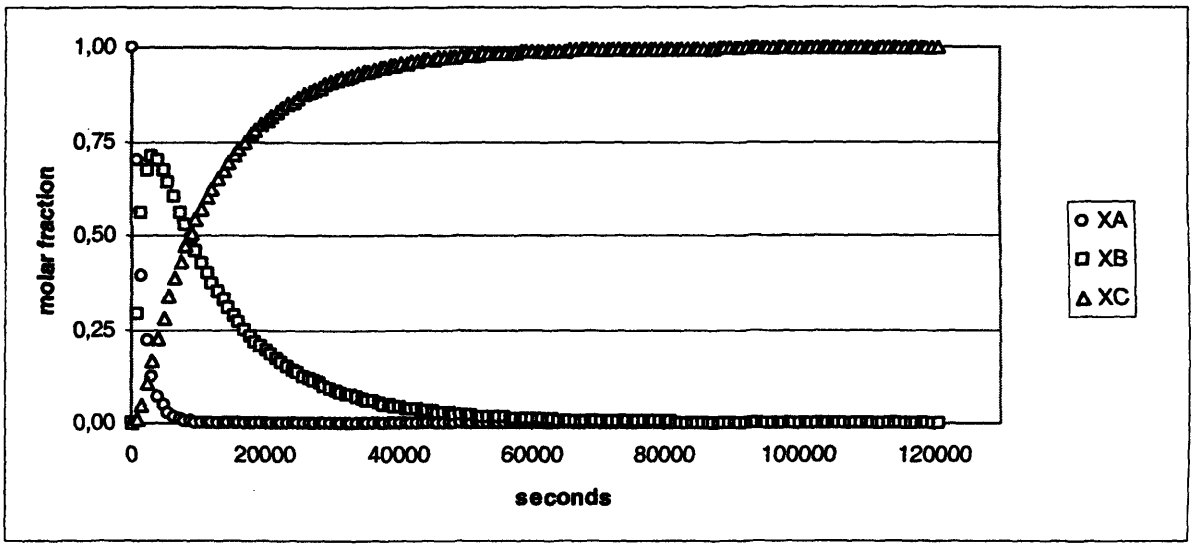
7568	923.98	1.10	337.45	4.79	542.42	2284.18	4093.9	0.002	0.278	0.721	-6.288	-1.282	-1.275
7711	917.76	2.53	329.17	3.62	528.77	2301.78	4083.6	0.002	0.271	0.727	-6.244	-1.306	-1.299
7854	914.57	-0.11	322.44	1.54	515.98	2329.24	4083.7	0.000	0.265	0.735	-7.700	-1.330	-1.328
7997	913.91	-0.75	314.87	0.81	506.48	2366.60	4101.9	0.000	0.258	0.742	#####	-1.356	-1.356
8140	924.06	1.19	309.78	3.41	499.46	2391.15	4129.0	0.001	0.252	0.746	-6.546	-1.376	-1.371
8282	919.28	0.92	303.27	0.13	484.63	2406.38	4114.6	0.000	0.247	0.753	-8.018	-1.400	-1.399
8425	922.54	1.15	296.41	0.98	475.03	2431.71	4127.8	0.001	0.241	0.759	-7.313	-1.424	-1.422
8568	925.08	1.13	290.76	2.25	467.52	2458.66	4145.4	0.001	0.235	0.763	-6.857	-1.446	-1.442
8711	921.95	0.86	283.79	1.96	455.36	2473.68	4137.6	0.001	0.230	0.769	-7.039	-1.470	-1.466
8854	920.45	0.75	278.18	1.38	445.71	2494.28	4140.8	0.001	0.225	0.775	-7.318	-1.493	-1.490
8996	921.46	2.23	273.22	4.19	439.11	2518.44	4158.7	0.002	0.220	0.778	-6.222	-1.514	-1.505
9139	917.26	1.54	266.55	2.76	428.87	2534.58	4151.6	0.001	0.215	0.784	-6.622	-1.537	-1.531
9282	921.99	1.18	261.21	4.65	420.36	2555.00	4164.4	0.002	0.210	0.788	-6.321	-1.560	-1.551
9425	918.55	0.17	255.36	2.41	408.96	2562.00	4147.5	0.001	0.206	0.793	-7.129	-1.581	-1.577
9568	922.73	1.03	249.46	2.82	400.99	2591.62	4168.6	0.001	0.200	0.798	-6.738	-1.607	-1.602
9710	924.90	2.48	244.39	2.85	391.90	2602.53	4169.1	0.002	0.196	0.802	-6.411	-1.629	-1.621
9853	926.56	1.19	238.93	3.12	383.66	2621.62	4175.1	0.001	0.192	0.807	-6.625	-1.652	-1.645
9996	920.26	2.75	233.09	1.89	373.76	2630.81	4162.6	0.001	0.187	0.811	-6.551	-1.676	-1.668
10139	925.08	1.21	229.81	2.63	368.43	2661.31	4188.5	0.001	0.183	0.816	-6.746	-1.697	-1.690
10282	923.05	1.44	225.02	1.69	361.19	2682.28	4194.7	0.001	0.179	0.820	-6.950	-1.719	-1.714
10424	921.44	1.06	220.45	1.93	353.23	2704.32	4202.4	0.001	0.175	0.824	-7.001	-1.744	-1.739
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10710	919.18	-0.07	210.18	1.57	338.66	2736.42	4205.9	0.000	0.167	0.833	-7.691	-1.790	-1.787
10853	920.28	0.71	205.71	1.66	330.64	2751.89	4210.9	0.001	0.163	0.836	-7.236	-1.814	-1.810
10996	923.10	0.87	202.07	2.89	323.87	2763.38	4216.2	0.001	0.160	0.839	-6.775	-1.834	-1.827
11138	920.22	0.24	197.47	0.62	316.03	2770.24	4204.8	0.000	0.156	0.843	-8.251	-1.856	-1.854
11281	921.04	1.14	192.56	0.72	309.24	2785.61	4210.3	0.001	0.153	0.847	-7.478	-1.880	-1.877
11424	922.71	0.91	188.59	1.27	302.37	2797.95	4213.8	0.001	0.149	0.850	-7.317	-1.903	-1.898
11567	930.40	2.66	185.58	2.47	298.10	2824.42	4243.6	0.002	0.146	0.852	-6.470	-1.924	-1.914
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11995	922.41	0.30	173.37	2.13	278.21	2863.68	4240.1	0.001	0.136	0.863	-7.218	-1.994	-1.989
12138	922.52	1.64	170.87	1.91	273.16	2882.51	4252.6	0.001	0.133	0.866	-6.842	-2.015	-2.007
12281	919.15	0.80	167.37	-0.33	266.34	2887.21	4240.5	0.000	0.131	0.869	-8.858	-2.036	-2.035
12424	920.02	0.59	163.29	0.45	261.14	2901.16	4246.7	0.000	0.128	0.872	-8.065	-2.059	-2.057
12566	920.05	-0.05	160.06	0.82	255.75	2914.63	4251.3	0.000	0.125	0.875	-8.364	-2.081	-2.079
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12995	917.11	0.37	150.22	1.94	239.55	2941.85	4251.0	0.001	0.117	0.882	-7.276	-2.146	-2.140
13138	913.34	0.08	146.82	0.92	233.80	2940.83	4235.8	0.000	0.115	0.885	-8.114	-2.167	-2.164
13280	916.80	0.38	143.58	1.53	229.37	2956.90	4248.6	0.001	0.112	0.887	-7.464	-2.190	-2.185
13423	916.72	1.28	140.97	1.12	224.93	2971.12	4256.1	0.001	0.110	0.890	-7.238	-2.211	-2.205
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13852	917.72	2.41	131.92	1.22	210.86	2990.95	4255.1	0.001	0.103	0.896	-6.825	-2.276	-2.265
13994	916.51	0.35	129.34	0.12	204.58	2994.28	4245.2	0.000	0.100	0.900	-8.857	-2.299	-2.298
14137	923.11	2.16	126.33	1.79	202.09	3015.80	4271.3	0.001	0.098	0.901	-6.742	-2.322	-2.310
14280	918.33	1.21	123.76	1.46	196.82	3021.87	4263.5	0.001	0.096	0.903	-7.131	-2.345	-2.337
14423	915.04	0.96	120.77	0.72	192.24	3019.29	4249.0	0.001	0.094	0.906	-7.591	-2.366	-2.360
14566	915.94	0.95	118.55	0.84	188.63	3032.31	4257.2	0.001	0.092	0.908	-7.529	-2.387	-2.381
14708	919.08	1.51	115.74	1.30	185.60	3047.86	4271.1	0.001	0.090	0.909	-7.085	-2.409	-2.400
14851	917.03	1.93	112.97	1.04	181.46	3051.28	4265.7	0.001	0.088	0.911	-7.025	-2.431	-2.421
14994	919.88	2.06	111.43	2.17	178.57	3069.25	4283.4	0.001	0.086	0.913	-6.677	-2.451	-2.436
15137	918.22	1.48	109.12	1.67	175.03	3086.32	4291.8	0.001	0.084	0.915	-6.979	-2.474	-2.463
15280	918.98	0.77	107.96	0.63	171.24	3095.65	4295.2	0.000	0.083	0.917	-7.784	-2.493	-2.488
15422	915.87	1.31	104.46	1.37	166.58	3098.71	4288.3	0.001	0.080	0.919	-7.136	-2.521	-2.511
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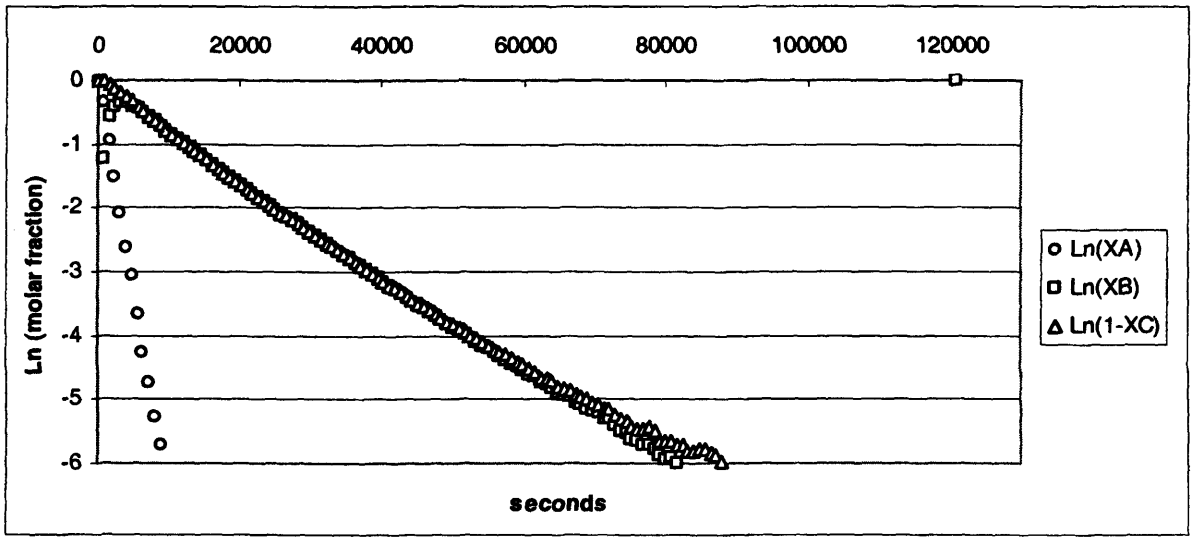
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15994	912.87	1.65	97.47	0.74	153.51	3122.63	4288.9	0.001	0.074	0.925	-7.253	-2.599	-2.590
16136	913.80	1.25	92.86	0.50	150.64	3140.96	4300.0	0.001	0.072	0.928	-7.569	-2.632	-2.625
16279	909.54	1.29	91.86	1.04	146.29	3125.25	4275.3	0.001	0.071	0.929	-7.275	-2.649	-2.639
16422	915.80	0.37	90.64	2.07	144.40	3152.09	4305.4	0.001	0.069	0.930	-7.239	-2.669	-2.658
16565	913.46	0.54	88.19	2.27	141.04	3159.30	4304.8	0.001	0.068	0.932	-7.097	-2.694	-2.682
16708	914.35	0.62	87.56	0.96	136.95	3154.62	4295.1	0.000	0.066	0.933	-7.669	-2.712	-2.705
16850	909.49	1.19	84.20	1.42	134.62	3152.98	4283.9	0.001	0.065	0.934	-7.164	-2.736	-2.724
16993	911.67	0.28	82.69	1.77	132.04	3167.08	4295.5	0.001	0.063	0.936	-7.408	-2.757	-2.748
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17279	916.57	0.48	79.50	1.60	127.31	3195.64	4321.1	0.001	0.061	0.939	-7.403	-2.801	-2.791
17422	913.85	-0.39	77.88	1.25	124.93	3197.85	4315.4	0.000	0.060	0.940	-8.282	-2.820	-2.815
17564	921.13	2.95	76.98	1.65	122.11	3228.37	4353.2	0.001	0.058	0.941	-6.615	-2.847	-2.824
17707	913.72	0.56	74.82	0.80	119.37	3203.08	4312.3	0.000	0.057	0.942	-7.822	-2.862	-2.855
17850	904.47	-0.64	72.62	0.46	116.49	3198.92	4292.3	0.000	0.056	0.944	#¡NUM!	-2.886	-2.887
17993	907.55	0.90	71.85	0.60	114.67	3194.83	4290.4	0.000	0.055	0.944	-7.720	-2.898	-2.890
18136	914.24	1.13	70.42	1.03	112.33	3227.34	4326.5	0.001	0.054	0.946	-7.364	-2.927	-2.915
18278	912.27	-1.42	68.63	1.84	110.08	3227.78	4319.2	0.000	0.052	0.947	-9.008	-2.948	-2.945
18421	913.56	1.40	67.57	0.46	107.52	3231.65	4322.2	0.001	0.051	0.948	-7.511	-2.969	-2.958
18564	910.05	0.16	65.83	1.25	105.58	3223.15	4306.0	0.000	0.050	0.949	-7.781	-2.986	-2.978
18707	910.98	0.98	65.09	0.76	102.43	3217.82	4298.1	0.001	0.049	0.950	-7.575	-3.007	-2.996
18850	912.68	2.07	63.66	0.91	99.97	3242.48	4321.8	0.001	0.048	0.951	-7.043	-3.037	-3.019
18992	911.66	0.81	61.69	-0.01	99.02	3251.87	4325.0	0.000	0.047	0.953	-8.357	-3.056	-3.051
19135	910.04	0.86	60.46	1.14	97.42	3262.32	4332.2	0.001	0.046	0.953	-7.447	-3.076	-3.064
19278	910.59	1.57	59.79	1.56	94.01	3254.44	4322.0	0.001	0.045	0.954	-6.994	-3.099	-3.079
19421	910.71	1.44	57.92	1.82	92.69	3253.41	4318.0	0.001	0.044	0.955	-6.953	-3.119	-3.098
19564	910.27	1.65	56.81	1.53	90.19	3252.17	4312.6	0.001	0.043	0.956	-6.975	-3.142	-3.120
19706	908.28	1.41	55.33	1.40	88.57	3254.57	4309.6	0.001	0.042	0.957	-7.099	-3.163	-3.143
19849	910.18	1.02	54.56	0.67	86.63	3259.90	4312.9	0.000	0.041	0.958	-7.611	-3.182	-3.170
19992	908.10	0.68	53.59	0.71	84.79	3258.74	4306.6	0.000	0.041	0.959	-7.796	-3.201	-3.191
20135	906.39	1.03	53.03	1.24	83.52	3259.32	4304.5	0.001	0.040	0.959	-7.313	-3.214	-3.198
20278	905.72	1.89	51.83	0.87	82.03	3266.03	4308.4	0.001	0.039	0.960	-7.118	-3.236	-3.215
20420	904.25	-0.27	49.24	0.47	80.71	3270.49	4304.9	0.000	0.038	0.962	-9.772	-3.265	-3.263
20563	903.61	0.71	49.57	1.37	78.30	3263.54	4297.1	0.001	0.038	0.962	-7.397	-3.279	-3.262
20706	908.92	2.62	48.35	0.93	75.52	3291.37	4327.7	0.001	0.036	0.963	-6.870	-3.318	-3.290
20849	910.59	0.93	47.03	0.90	74.86	3300.53	4334.8	0.001	0.036	0.964	-7.535	-3.336	-3.321
20992	908.96	2.87	47.69	1.45	71.72	3222.51	4255.2	0.001	0.036	0.963	-6.651	-3.333	-3.298
21134	911.51	0.84	46.05	0.78	71.74	3306.80	4337.7	0.000	0.034	0.965	-7.654	-3.370	-3.357
21277	907.30	-0.80	44.68	-0.88	71.07	3303.73	4325.1	0.000	0.034	0.967	#¡NUM!	-3.385	-3.400
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21563	910.75	2.25	43.20	0.79	68.47	3317.92	4343.4	0.001	0.033	0.967	-7.027	-3.425	-3.399
21706	912.32	1.77	42.02	0.51	67.44	3320.40	4344.5	0.001	0.032	0.967	-7.316	-3.445	-3.425
21848	912.15	0.79	41.78	1.73	65.24	3329.78	4351.5	0.001	0.031	0.968	-7.215	-3.470	-3.447
21991	907.37	0.27	39.63	0.37	63.71	3327.43	4338.8	0.000	0.030	0.970	-8.575	-3.503	-3.496
22134	910.49	2.45	39.64	1.38	63.08	3324.73	4341.8	0.001	0.030	0.969	-6.798	-3.509	-3.472
22277	911.44	0.58	39.20	2.07	60.87	3336.61	4350.8	0.001	0.029	0.970	-7.167	-3.537	-3.511
22420	906.57	2.59	37.61	0.55	60.44	3320.65	4328.4	0.001	0.029	0.970	-6.991	-3.552	-3.521
22562	908.54	0.88	36.76	0.99	58.52	3323.83	4329.5	0.001	0.028	0.972	-7.514	-3.581	-3.561
22705	906.04	2.05	36.63	0.44	57.05	3320.19	4322.4	0.001	0.027	0.972	-7.227	-3.596	-3.570
22848	909.34	1.70	36.39	1.30	56.40	3339.67	4344.8	0.001	0.027	0.972	-7.045	-3.612	-3.580
22991	901.24	2.28	36.07	1.48	52.74	3202.22	4196.0	0.001	0.027	0.972	-6.776	-3.614	-3.572
23134	905.99	1.69	34.55	0.86	54.01	3325.89	4323.0	0.001	0.026	0.973	-7.200	-3.653	-3.624
23276	912.77	3.14	33.76	1.75	52.68	3360.82	4364.9	0.001	0.025	0.974	-6.560	-3.687	-3.632
23419	908.19	-0.44	32.57	0.51	52.52	3354.88	4348.2	0.000	0.025	0.975	#####	-3.700	-3.699
23562	911.96	-0.33	31.95	1.26	51.74	3367.91	4364.5	0.000	0.024	0.975	-8.212	-3.720	-3.709
23705	905.08	1.38	31.79	0.47	49.07	3335.28	4323.1	0.001	0.024	0.976	-7.522	-3.744	-3.721

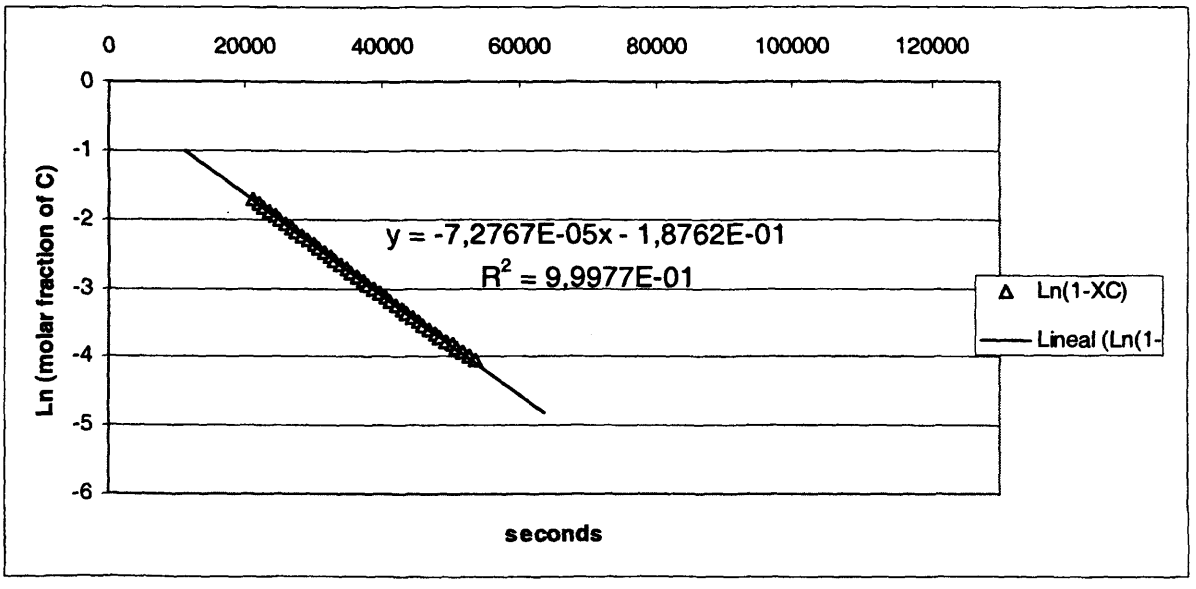
23848	597.46	1.32	23.55	1.56	32.75	1931.07	2587.7	0.001	0.028	0.970	-6.540	-3.565	-3.516
23990	597.19	2.02	22.74	0.98	31.77	1927.74	2582.4	0.002	0.027	0.971	-6.497	-3.595	-3.542
24133	591.93	1.76	22.58	0.53	30.64	1913.44	2560.9	0.001	0.027	0.972	-6.756	-3.611	-3.569
24276	585.71	0.65	22.40	1.41	30.65	1897.90	2538.7	0.001	0.027	0.972	-6.856	-3.606	-3.568
24419	591.44	2.11	21.16	1.09	28.91	1918.13	2562.8	0.002	0.025	0.973	-6.423	-3.673	-3.611
24562	588.91	1.56	21.67	0.66	29.63	1916.66	2559.1	0.001	0.026	0.973	-6.787	-3.648	-3.606
24704	591.90	2.17	20.51	1.50	28.55	1925.95	2570.6	0.002	0.025	0.973	-6.291	-3.697	-3.625
24847	590.81	1.29	20.52	1.07	27.12	1921.08	2561.9	0.001	0.024	0.975	-6.728	-3.723	-3.674
24990	588.44	1.44	19.92	0.78	26.93	1906.45	2544.0	0.001	0.024	0.975	-6.782	-3.731	-3.685
25133	592.95	1.98	18.88	1.33	26.69	1923.15	2565.0	0.002	0.023	0.975	-6.390	-3.768	-3.697
25276	589.70	1.83	19.12	1.79	26.29	1912.09	2550.8	0.002	0.023	0.975	-6.297	-3.765	-3.689
25418	588.63	0.04	18.52	1.00	25.70	1928.54	2562.4	0.001	0.022	0.977	-7.547	-3.798	-3.775
25561	595.24	2.28	18.53	2.14	24.35	1929.54	2572.1	0.002	0.022	0.976	-6.103	-3.831	-3.733
25704	581.60	0.75	17.43	1.06	24.84	1903.82	2529.5	0.001	0.022	0.977	-6.981	-3.830	-3.788

6.2.3 Experiment in CD_3OD Entry 3

[132] = 0.576 mol/l
[TMSCl] = 0.162 mol/l
$k_{obs}= 7.28 \cdot 10^{-5}\ s^{-1}$







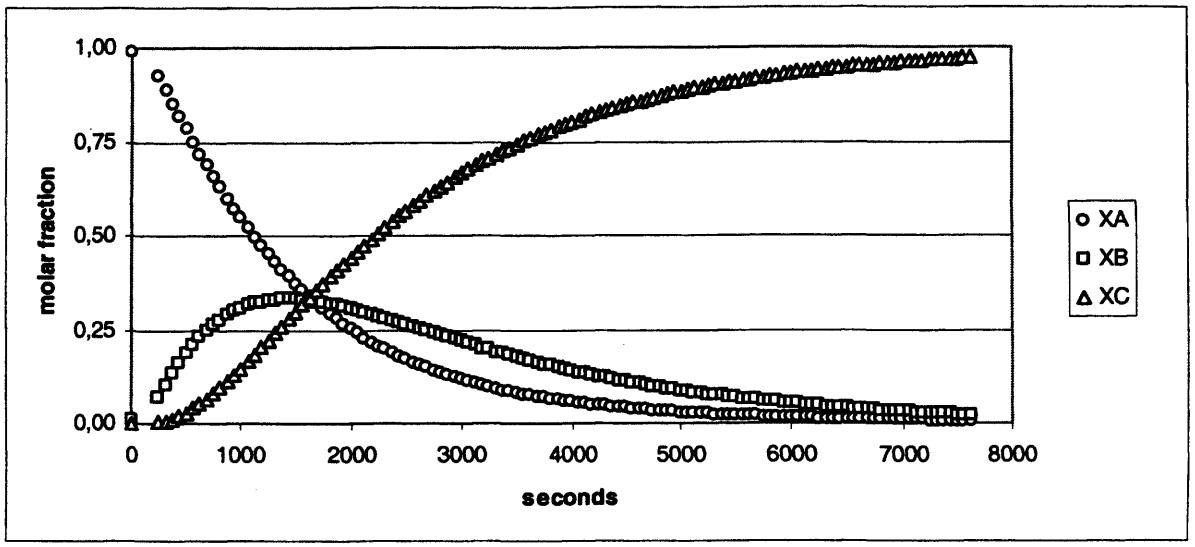
Time (s)	Int S δ_F (-59.3 Hz)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.6 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	Ln(X_A)	Ln(X_B)	Ln(1-X
0	1000.00	1498.08	6.43	1622.79	-0.32	-0.22	4126.8	0.998	0.002	0.000	-0.002	-6.238	0.000
810	959.99	972.24	381.81	1073.26	460.42	29.40	3877.1	0.701	0.289	0.010	-0.355	-1.242	-0.010
1619	922.76	494.25	660.90	558.94	839.94	134.18	3611.0	0.392	0.558	0.050	-0.937	-0.583	-0.051
2429	905.83	261.38	756.05	304.21	984.60	277.71	3489.8	0.219	0.674	0.107	-1.519	-0.395	-0.114
3238	894.86	141.93	772.91	172.42	1018.31	427.87	3428.3	0.124	0.707	0.169	-2.087	-0.347	-0.185
4048	889.77	78.71	756.67	103.17	1001.58	572.55	3402.4	0.072	0.700	0.228	-2.626	-0.357	-0.259
4857	888.61	44.88	725.39	71.35	965.33	708.72	3404.3	0.046	0.672	0.282	-3.075	-0.397	-0.331
5667	919.84	26.49	719.22	41.42	944.11	876.38	3527.5	0.026	0.638	0.336	-3.648	-0.450	-0.410
6477	939.40	15.26	698.16	22.79	906.93	1029.24	3611.8	0.014	0.601	0.385	-4.252	-0.510	-0.486
7286	942.92	8.85	659.26	14.89	853.92	1158.13	3638.0	0.009	0.561	0.430	-4.732	-0.577	-0.562
8096	951.42	4.92	625.13	8.99	807.11	1284.99	3682.6	0.005	0.524	0.470	-5.280	-0.645	-0.636
8905	954.59	3.04	587.68	5.94	756.75	1391.06	3699.1	0.003	0.490	0.507	-5.723	-0.714	-0.707
9715	954.52	1.46	550.09	4.01	707.92	1488.06	3706.1	0.002	0.457	0.541	-6.221	-0.783	-0.778
10525	955.99	0.66	515.40	3.44	663.07	1580.37	3718.9	0.001	0.427	0.572	-6.514	-0.852	-0.849
11334	959.30	0.46	486.06	3.17	623.62	1670.60	3743.2	0.001	0.399	0.600	-6.643	-0.920	-0.917
12144	960.18	-0.38	456.54	3.24	584.51	1745.79	3749.9	0.001	0.373	0.626	-6.883	-0.986	-0.983
12953	962.14	-0.55	429.35	2.96	549.48	1827.43	3770.8	0.001	0.349	0.651	-7.058	-1.054	-1.052
13763	962.82	-1.01	403.43	3.17	515.78	1895.24	3779.4	0.001	0.326	0.673	-7.171	-1.120	-1.117
14572	966.89	-0.33	380.76	2.43	483.47	1953.95	3787.2	0.001	0.306	0.693	-7.202	-1.183	-1.180
15382	968.01	-0.84	357.68	2.10	454.55	2017.73	3799.2	0.000	0.287	0.713	-7.713	-1.249	-1.247
16192	967.67	-0.71	335.58	2.22	426.24	2074.38	3805.4	0.001	0.268	0.731	-7.541	-1.315	-1.313
17001	961.27	-0.45	310.31	1.98	396.77	2120.83	3790.7	0.001	0.250	0.750	-7.520	-1.387	-1.385
17811	954.34	-0.91	287.22	2.80	370.52	2165.90	3779.9	0.001	0.233	0.767	-7.311	-1.458	-1.455
18620	952.16	-0.76	267.69	2.19	346.30	2209.49	3777.1	0.001	0.217	0.782	-7.592	-1.526	-1.524
19430	953.58	-1.19	251.76	2.09	325.99	2256.50	3788.7	0.000	0.204	0.796	-8.053	-1.591	-1.589
20240	958.56	-1.00	239.64	2.19	307.20	2295.30	3801.9	0.000	0.192	0.807	-7.785	-1.649	-1.646
21049	962.26	-0.66	227.68	1.99	289.52	2333.64	3814.4	0.000	0.181	0.818	-7.671	-1.707	-1.705
21859	965.80	-0.85	215.82	1.97	272.52	2368.21	3823.5	0.000	0.171	0.829	-7.843	-1.767	-1.764
22668	968.79	-0.71	204.22	1.90	256.67	2401.53	3832.4	0.000	0.161	0.839	-7.785	-1.827	-1.824
23478	968.84	-0.79	192.73	1.97	242.57	2437.94	3843.3	0.000	0.151	0.848	-7.796	-1.888	-1.885
24287	965.57	-0.81	180.15	2.18	227.38	2456.39	3830.9	0.000	0.142	0.857	-7.648	-1.950	-1.947
25097	963.16	-0.85	169.02	2.68	213.45	2482.35	3829.8	0.001	0.133	0.866	-7.359	-2.014	-2.009
25907	964.02	-1.22	159.24	2.35	200.87	2510.53	3835.8	0.000	0.125	0.874	-7.845	-2.076	-2.073
26716	965.58	-1.07	150.84	2.20	189.68	2535.33	3842.6	0.000	0.118	0.881	-7.844	-2.134	-2.131
27526	967.34	-0.81	143.05	2.57	178.33	2555.75	3846.2	0.001	0.112	0.888	-7.403	-2.193	-2.187
28335	969.18	-0.89	135.01	2.16	168.40	2583.45	3857.3	0.000	0.105	0.895	-7.736	-2.253	-2.249
29145	968.90	-1.12	127.56	2.19	158.67	2602.28	3858.5	0.000	0.099	0.901	-7.893	-2.312	-2.308
29954	968.28	-1.13	120.31	2.47	149.03	2620.94	3859.9	0.000	0.093	0.906	-7.675	-2.374	-2.369
30764	967.18	-1.05	113.28	2.80	140.63	2638.31	3861.1	0.001	0.088	0.912	-7.410	-2.433	-2.427
31574	966.31	-1.03	106.57	2.69	132.67	2656.99	3864.2	0.001	0.083	0.917	-7.465	-2.494	-2.487
32383	964.75	-1.18	100.35	2.32	124.67	2667.39	3858.3	0.000	0.078	0.922	-7.842	-2.554	-2.549
33193	963.77	-0.71	94.70	2.86	117.01	2680.52	3858.2	0.001	0.073	0.926	-7.205	-2.615	-2.605
34002	963.09	-0.79	89.44	2.75	109.95	2694.63	3859.1	0.001	0.069	0.930	-7.297	-2.676	-2.666
34812	963.50	-1.07	84.49	2.71	103.51	2708.90	3862.0	0.001	0.065	0.935	-7.481	-2.736	-2.727
35622	962.58	-0.83	79.53	2.64	98.87	2724.76	3867.5	0.001	0.061	0.938	-7.385	-2.790	-2.780
36431	966.17	-0.43	75.50	2.43	90.54	2737.79	3872.0	0.001	0.057	0.942	-7.281	-2.862	-2.850
37241	963.95	-1.18	71.03	2.47	86.18	2752.18	3874.6	0.000	0.054	0.946	-7.721	-2.919	-2.910
38050	961.14	-1.16	66.79	2.34	81.24	2759.98	3870.3	0.000	0.051	0.949	-7.814	-2.978	-2.970
38860	960.01	-0.30	63.09	2.80	74.93	2757.98	3858.5	0.001	0.048	0.952	-7.057	-3.045	-3.027
39669	959.19	-0.34	59.45	2.70	70.70	2766.87	3858.6	0.001	0.045	0.954	-7.115	-3.104	-3.086
40479	957.92	-0.76	56.37	2.62	67.03	2782.82	3866.0	0.001	0.042	0.957	-7.353	-3.160	-3.145
41289	957.26	-0.83	52.72	2.59	63.54	2795.22	3870.5	0.001	0.040	0.959	-7.414	-3.221	-3.206
42098	955.39	-0.97	49.77	2.77	59.67	2799.86	3866.5	0.001	0.038	0.962	-7.388	-3.281	-3.265

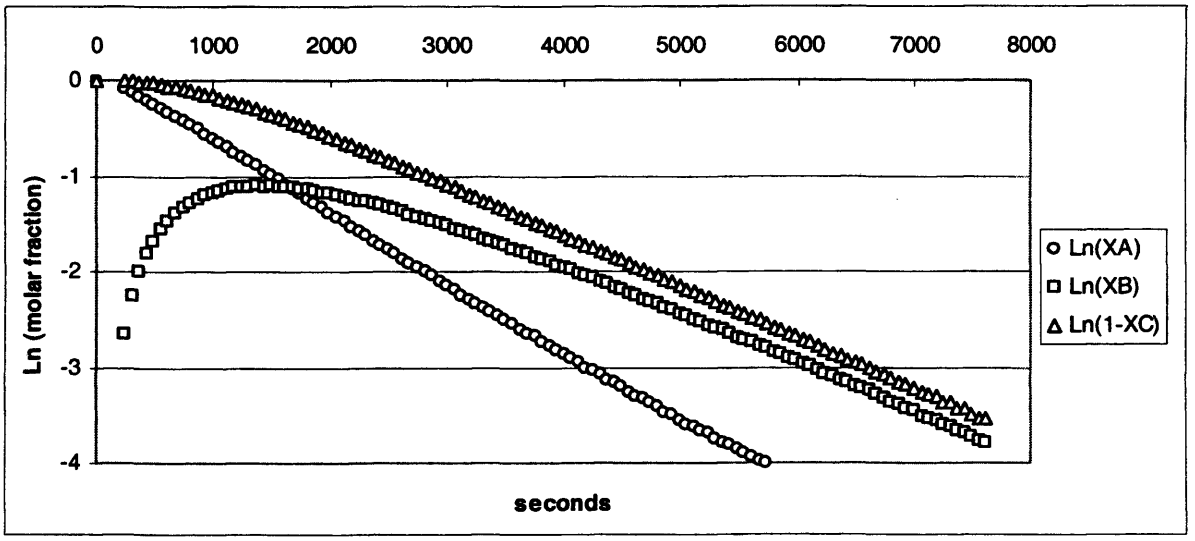
42908	954.55	-0.49	47.21	2.65	55.05	2796.95	3855.9	0.001	0.035	0.964	-7.205	-3.345	-3.32E
43717	953.65	-0.32	44.78	3.03	51.93	2805.18	3858.3	0.001	0.033	0.966	-6.978	-3.402	-3.37E
44527	952.61	-0.46	41.83	2.78	49.65	2819.07	3865.5	0.001	0.031	0.968	-7.137	-3.461	-3.43E
45336	951.83	-0.73	39.71	2.72	46.84	2824.96	3865.3	0.001	0.030	0.970	-7.290	-3.516	-3.494
46146	951.06	-0.82	37.36	2.53	44.53	2831.58	3866.3	0.001	0.028	0.971	-7.441	-3.572	-3.552
46956	952.72	-0.84	35.72	2.86	41.63	2839.89	3872.0	0.001	0.026	0.973	-7.277	-3.631	-3.60E
47765	952.75	-1.03	33.60	2.67	39.14	2846.02	3873.2	0.001	0.025	0.975	-7.485	-3.692	-3.67C
48575	953.67	-0.79	31.83	2.96	36.96	2852.89	3877.5	0.001	0.024	0.976	-7.204	-3.749	-3.71E
49384	953.45	-0.95	30.06	2.88	34.83	2862.69	3883.0	0.001	0.022	0.977	-7.325	-3.810	-3.781
50194	953.81	0.10	29.07	3.28	31.94	2859.24	3877.4	0.001	0.021	0.978	-6.763	-3.870	-3.81E
51004	953.33	-0.96	27.47	2.83	30.83	2871.12	3884.6	0.001	0.020	0.979	-7.359	-3.918	-3.88E
51813	952.98	-0.53	25.74	2.78	28.64	2869.82	3879.4	0.001	0.019	0.981	-7.172	-3.985	-3.94E
52623	952.66	-0.83	24.36	2.97	27.42	2877.30	3883.9	0.001	0.018	0.982	-7.219	-4.036	-3.99E
53432	954.02	-0.92	23.11	3.01	25.92	2882.63	3887.8	0.001	0.017	0.983	-7.247	-4.092	-4.05C
54242	953.96	-1.15	22.07	3.16	24.07	2887.67	3889.8	0.001	0.016	0.984	-7.289	-4.153	-4.111
55051	953.75	-0.95	21.01	3.08	23.00	2893.86	3893.8	0.001	0.015	0.984	-7.229	-4.202	-4.154
55861	953.23	-1.05	19.73	2.83	21.62	2896.40	3892.7	0.001	0.014	0.985	-7.412	-4.264	-4.222
56671	952.29	-0.83	18.94	3.08	20.44	2902.03	3895.9	0.001	0.013	0.986	-7.178	-4.314	-4.25E
57480	952.13	-0.48	17.92	3.21	19.16	2904.87	3896.8	0.001	0.013	0.986	-6.981	-4.375	-4.303
58290	952.51	-0.48	16.93	3.46	17.48	2904.40	3894.3	0.001	0.012	0.987	-6.895	-4.449	-4.36E
59099	951.92	-0.77	16.27	2.78	16.75	2911.72	3898.7	0.001	0.011	0.988	-7.286	-4.492	-4.432
59909	953.42	-0.51	15.57	3.47	15.45	2910.27	3897.7	0.001	0.011	0.988	-6.902	-4.553	-4.462
60719	953.42	-0.36	14.77	3.47	14.18	2915.61	3901.1	0.001	0.010	0.989	-6.854	-4.623	-4.521
61528	951.86	-0.74	14.09	2.95	13.96	2923.38	3905.5	0.001	0.009	0.990	-7.197	-4.657	-4.581
62338	951.85	-1.11	13.29	2.82	12.98	2924.89	3904.7	0.001	0.009	0.991	-7.455	-4.722	-4.65E
63147	951.99	-0.73	13.10	3.37	11.74	2923.90	3903.4	0.001	0.008	0.991	-7.021	-4.777	-4.677
63957	952.09	-0.55	12.40	3.60	10.95	2926.18	3904.7	0.001	0.008	0.991	-6.875	-4.840	-4.717
64766	950.83	-1.30	11.30	3.10	10.94	2933.08	3908.0	0.001	0.008	0.992	-7.404	-4.890	-4.812
65576	950.99	-0.73	11.16	3.22	10.19	2937.06	3911.9	0.001	0.007	0.992	-7.083	-4.932	-4.822
66386	950.08	-0.58	10.76	3.09	9.84	2937.15	3910.4	0.001	0.007	0.992	-7.071	-4.968	-4.852
67195	949.37	-0.75	10.21	3.30	8.78	2936.89	3907.8	0.001	0.006	0.993	-7.058	-5.049	-4.923
68005	948.43	-0.65	9.50	3.40	8.71	2941.39	3910.8	0.001	0.006	0.993	-6.982	-5.092	-4.951
68814	946.96	-0.46	9.35	3.25	8.11	2942.17	3909.4	0.001	0.006	0.993	-6.965	-5.134	-4.98E
69624	945.06	-0.84	8.57	3.14	8.06	2946.17	3910.2	0.001	0.006	0.994	-7.158	-5.184	-5.054
70433	944.09	-0.95	8.79	3.52	7.25	2941.82	3904.5	0.001	0.005	0.994	-7.048	-5.218	-5.06E
71243	944.56	-0.68	8.05	3.50	6.56	2944.52	3906.5	0.001	0.005	0.994	-6.958	-5.312	-5.13E
72053	943.33	-1.09	7.97	3.46	6.81	2949.00	3909.5	0.001	0.005	0.994	-7.130	-5.302	-5.153
72862	943.87	-0.92	7.47	3.24	5.99	2950.32	3910.0	0.001	0.005	0.995	-7.150	-5.395	-5.23E
73672	945.14	-0.84	6.97	3.33	5.23	2948.73	3908.6	0.001	0.004	0.995	-7.082	-5.492	-5.307
74481	942.82	-0.90	6.83	3.56	4.86	2946.15	3903.3	0.001	0.004	0.995	-7.015	-5.534	-5.329
75291	945.57	-0.95	6.24	3.21	4.46	2952.79	3911.3	0.001	0.004	0.996	-7.182	-5.624	-5.433
76101	944.54	-1.12	6.24	3.36	3.98	2947.03	3904.0	0.001	0.003	0.996	-7.186	-5.668	-5.47C
76910	943.36	-0.63	6.01	3.29	3.72	2947.38	3903.1	0.001	0.003	0.996	-7.014	-5.717	-5.47E
77720	942.37	-0.35	6.25	3.49	3.62	2946.26	3901.6	0.001	0.003	0.996	-6.851	-5.703	-5.42E
78529	943.02	-0.88	5.93	3.59	3.38	2954.58	3909.6	0.001	0.003	0.996	-6.998	-5.764	-5.50E
79339	944.70	-1.01	5.48	3.12	2.79	2955.50	3910.6	0.001	0.003	0.997	-7.251	-5.882	-5.65E
80148	944.24	-0.62	5.17	3.11	2.76	2955.32	3910.0	0.001	0.003	0.996	-7.081	-5.924	-5.651
80958	944.05	-0.83	5.14	3.19	2.87	2956.88	3911.3	0.001	0.003	0.997	-7.136	-5.915	-5.65E
81768	943.75	-0.74	5.21	3.18	2.18	2959.45	3913.0	0.001	0.002	0.997	-7.101	-5.996	-5.71C
82577	942.94	-0.76	4.94	3.38	2.19	2960.49	3913.2	0.001	0.002	0.997	-7.035	-6.031	-5.71E
83387	942.46	-0.83	4.41	3.32	2.08	2966.38	3917.8	0.001	0.002	0.997	-7.084	-6.127	-5.802
84196	941.33	-1.14	4.60	3.14	2.36	2969.87	3920.2	0.001	0.002	0.997	-7.306	-6.059	-5.80E
85006	941.92	-0.55	4.50	3.67	1.68	2966.87	3918.1	0.001	0.002	0.997	-6.862	-6.177	-5.76E
85815	941.47	-0.98	4.45	3.70	2.09	2971.61	3922.3	0.001	0.002	0.997	-6.998	-6.123	-5.77E
86625	942.36	-0.65	4.12	3.32	1.89	2973.07	3924.1	0.001	0.002	0.997	-7.018	-6.207	-5.84C
87435	945.19	-0.32	4.28	3.76	0.54	2969.83	3923.3	0.001	0.002	0.997	-6.764	-6.424	-5.887
88244	943.83	-0.41	4.07	3.49	0.56	2968.34	3919.9	0.001	0.002	0.997	-6.874	-6.466	-5.95E

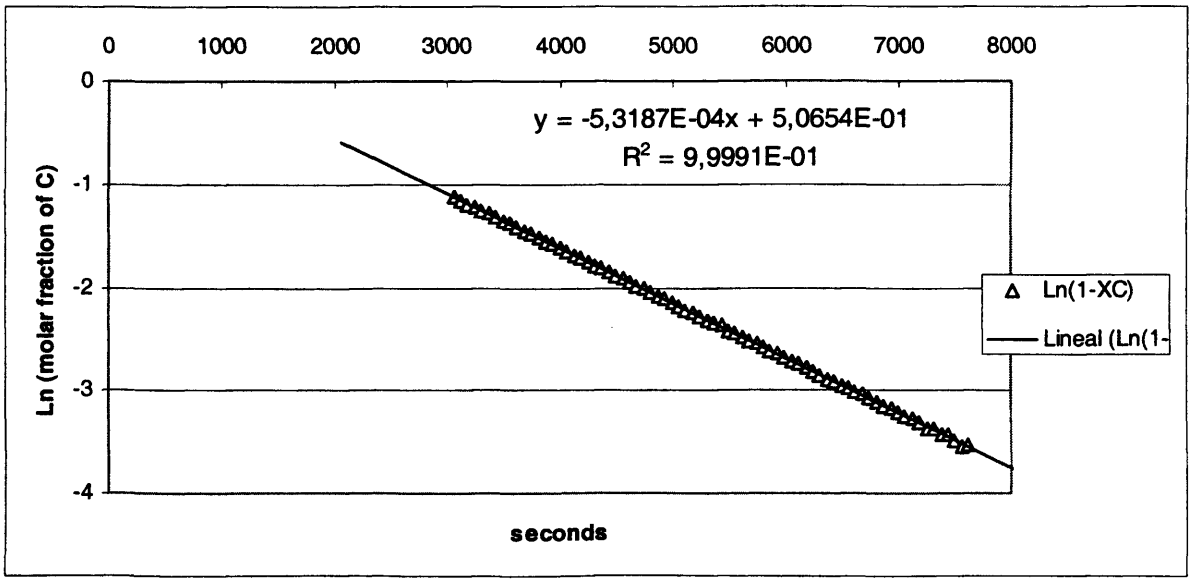
89054	942.94	-1.05	3.93	3.37	0.88	2971.11	3921.2	0.001	0.002	0.998	-7.158	-6.428	-6.034
89863	943.43	-0.95	3.75	3.27	0.45	2973.68	3923.6	0.001	0.001	0.998	-7.157	-6.564	-6.124
90673	942.60	-0.52	3.82	3.08	0.43	2974.96	3924.4	0.001	0.001	0.998	-7.061	-6.552	-6.081
91483	943.87	-0.65	3.56	3.29	-0.22	2973.74	3923.6	0.001	0.001	0.998	-7.029	-6.792	-6.210
92292	943.36	-0.85	3.71	3.18	0.54	2976.21	3926.1	0.001	0.001	0.998	-7.157	-6.555	-6.118
93102	942.79	-0.73	3.52	3.46	-0.09	2973.92	3922.9	0.001	0.001	0.998	-6.999	-6.765	-6.182
93911	942.52	-0.72	3.12	3.63	-0.26	2972.51	3920.8	0.001	0.001	0.998	-6.930	-6.948	-6.246
94721	941.75	-0.83	3.33	3.34	0.41	2977.79	3925.8	0.001	0.001	0.998	-7.081	-6.683	-6.169
95530	942.23	-1.04	3.20	3.39	0.26	2980.35	3928.4	0.001	0.001	0.998	-7.149	-6.760	-6.243
96340	941.59	-0.66	2.97	3.32	-0.24	2981.33	3928.3	0.001	0.001	0.998	-7.025	-6.999	-6.319
97150	941.81	-0.74	2.91	3.41	-0.55	2979.10	3925.9	0.001	0.001	0.998	-7.019	-7.143	-6.386
97959	942.70	-0.95	3.03	3.18	-0.41	2978.48	3926.0	0.001	0.001	0.998	-7.200	-7.038	-6.422
98769	943.05	-1.05	3.11	3.36	-0.71	2978.24	3926.0	0.001	0.001	0.998	-7.163	-7.124	-6.450
99578	941.97	-0.65	3.24	3.50	-1.23	2972.69	3919.5	0.001	0.001	0.998	-6.950	-7.296	-6.415
100388	939.46	-0.67	3.13	3.19	-0.35	2973.47	3918.2	0.001	0.001	0.998	-7.075	-6.975	-6.331
101198	935.46	-1.11	2.99	3.47	-0.42	2969.71	3910.1	0.001	0.001	0.998	-7.140	-7.054	-6.403
102007	924.82	-0.37	2.94	3.52	-0.07	2938.95	3869.8	0.001	0.001	0.998	-6.842	-6.931	-6.192
102817	924.34	-0.79	2.82	3.73	-0.35	2934.25	3864.0	0.001	0.001	0.998	-6.906	-7.082	-6.297
103626	925.57	-0.86	2.79	3.43	0.50	2946.18	3877.6	0.001	0.001	0.998	-7.046	-6.799	-6.222
104436	929.03	-0.63	2.84	3.73	-0.39	2953.32	3887.9	0.001	0.001	0.998	-6.858	-7.098	-6.278
105245	925.05	-1.13	2.89	3.34	0.06	2949.47	3879.7	0.001	0.001	0.998	-7.195	-6.910	-6.349
106055	928.44	-0.72	2.61	3.43	-0.63	2952.44	3885.6	0.001	0.001	0.998	-6.993	-7.311	-6.446
106865	937.91	-0.69	2.63	3.36	-0.92	2969.38	3911.7	0.001	0.001	0.999	-7.016	-7.459	-6.520
107674	937.08	-0.95	2.58	3.23	-0.87	2969.47	3910.5	0.001	0.001	0.999	-7.172	-7.461	-6.613
108484	929.33	-0.91	2.64	3.21	-0.91	2954.39	3887.7	0.001	0.001	0.999	-7.161	-7.446	-6.600
109293	928.44	-0.89	2.49	3.18	-0.57	2951.56	3884.2	0.001	0.001	0.999	-7.161	-7.341	-6.554
110103	938.10	-0.38	2.60	3.21	-1.52	2967.07	3909.1	0.001	0.000	0.999	-6.957	-7.911	-6.631
110912	935.88	-0.60	2.37	3.54	-1.17	2964.42	3904.4	0.001	0.000	0.999	-6.919	-7.811	-6.576
111722	937.31	-0.94	2.38	3.59	-1.40	2969.09	3910.0	0.001	0.000	0.999	-7.022	-8.013	-6.707
112532	938.60	-0.54	2.38	3.26	-1.80	2970.23	3912.1	0.001	0.000	0.999	-6.997	-8.542	-6.804
113341	938.43	-0.59	2.76	3.43	-1.45	2972.26	3914.8	0.001	0.000	0.999	-6.954	-7.729	-6.575
114151	939.05	-0.27	2.64	3.43	-1.96	2972.81	3915.7	0.001	0.000	0.999	-6.847	-8.387	-6.653
114960	939.36	-0.39	2.45	3.50	-2.17	2972.51	3915.3	0.001	0.000	0.999	-6.861	-9.261	-6.774
115770	937.14	-0.67	2.47	3.08	-1.85	2968.30	3908.5	0.001	0.000	0.999	-7.115	-8.475	-6.887
116580	930.26	-0.89	2.26	3.26	-1.21	2958.34	3892.0	0.001	0.000	0.999	-7.130	-7.948	-6.764
117389	931.41	-0.76	2.35	3.38	-1.09	2959.75	3895.0	0.001	0.000	0.999	-7.033	-7.763	-6.640
118199	927.40	-0.69	2.50	3.45	-1.31	2951.03	3882.4	0.001	0.000	0.999	-6.976	-7.817	-6.618
119008	927.47	-0.54	2.29	3.42	-1.77	2951.75	3882.6	0.001	0.000	0.999	-6.933	-8.660	-6.770
119818	926.48	-0.38	2.13	3.16	-1.26	2948.55	3878.7	0.001	0.000	0.999	-6.968	-8.129	-6.695
120627	933.14	-0.85	2.36	3.34	-2.52	2957.64	3893.1	0.001	0.000	0.999	-7.083	#¡NUM!	-7.151

6.2.4 Experiment in CD_3OH Entry 4

[**132**] = 0.531 mol/l
[TMSCl] = 0.282 mol/l
$k_{obs}= 5.32 \cdot 10^{-4}\ s^{-1}$







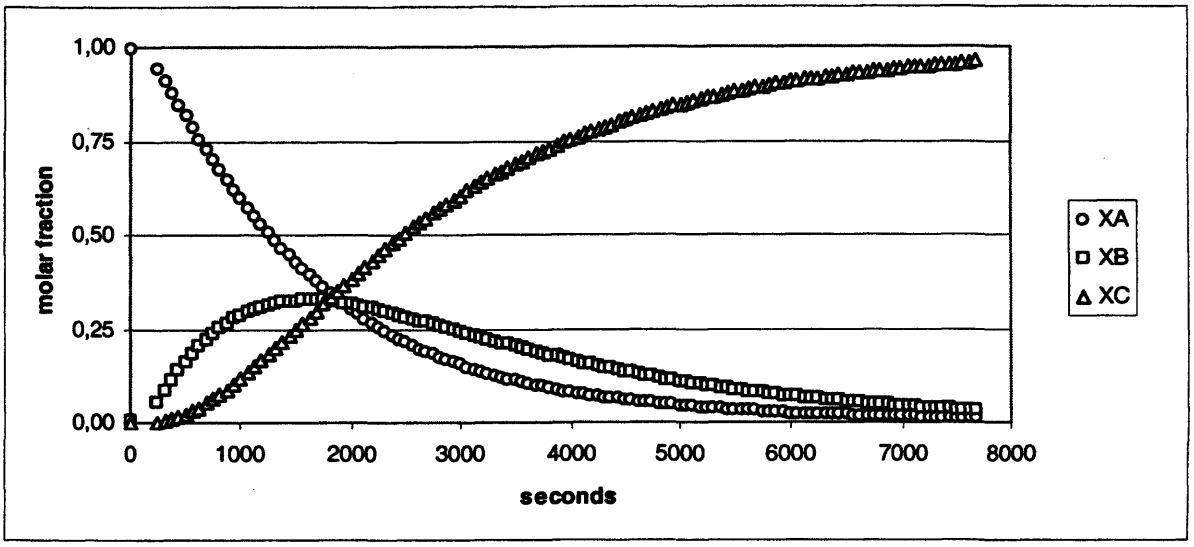
Time (s)	Int S δ_F (-59.3 Hz)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.6 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	Ln(X_A)	Ln(X_B)	Ln(1-X_C)
0	1000.00	1977.30	36.96	2177.16	-0.97	3.58	5194.0	0.991	0.009	0.001	-0.009	-4.758	-0.001
250	1006.21	1843.13	155.43	2068.87	144.59	14.32	5232.6	0.926	0.071	0.003	-0.077	-2.645	-0.003
312	1005.37	1759.35	217.92	1972.98	220.14	30.85	5206.6	0.888	0.104	0.007	-0.118	-2.261	-0.007
375	1006.18	1677.94	273.43	1887.31	289.88	55.97	5190.7	0.852	0.135	0.013	-0.160	-2.005	-0.013
437	1003.62	1605.70	322.99	1804.72	352.92	87.09	5177.0	0.817	0.162	0.021	-0.202	-1.820	-0.021
500	999.38	1530.44	367.07	1727.55	408.38	122.77	5155.6	0.784	0.187	0.030	-0.243	-1.679	-0.030
562	995.68	1455.49	407.08	1649.62	460.47	171.22	5139.6	0.749	0.209	0.041	-0.289	-1.564	-0.042
625	990.45	1387.90	443.41	1573.55	507.39	217.18	5119.9	0.717	0.230	0.053	-0.332	-1.469	-0.054
687	988.51	1326.52	474.10	1505.91	546.43	270.83	5112.3	0.687	0.247	0.066	-0.376	-1.396	-0.068
750	984.96	1265.13	503.35	1440.03	581.07	328.91	5103.4	0.657	0.263	0.080	-0.420	-1.334	-0.083
812	983.98	1207.27	522.91	1376.92	615.90	392.97	5100.0	0.628	0.277	0.095	-0.465	-1.285	-0.100
874	982.54	1152.84	543.59	1315.99	642.57	465.50	5103.0	0.599	0.288	0.113	-0.512	-1.245	-0.120
937	975.32	1099.16	562.92	1254.99	667.07	530.44	5089.9	0.572	0.299	0.129	-0.558	-1.208	-0.138
999	974.54	1049.16	578.47	1199.97	686.28	597.97	5086.4	0.547	0.308	0.145	-0.603	-1.179	-0.157
1062	970.77	1003.23	591.55	1149.06	707.56	678.88	5101.0	0.521	0.315	0.164	-0.652	-1.157	-0.180
1124	972.10	955.77	603.12	1096.27	723.99	755.28	5106.5	0.496	0.321	0.183	-0.701	-1.136	-0.202
1187	969.36	912.88	611.55	1045.25	733.69	838.38	5111.1	0.473	0.325	0.202	-0.749	-1.125	-0.226
1249	969.06	869.73	618.46	1000.03	743.83	919.70	5120.8	0.450	0.328	0.222	-0.798	-1.114	-0.250
1312	962.23	831.54	623.69	957.46	753.98	1004.41	5133.3	0.429	0.330	0.241	-0.847	-1.108	-0.275
1374	962.09	795.48	626.11	913.95	759.44	1083.02	5140.1	0.409	0.332	0.259	-0.894	-1.104	-0.300
1437	961.43	761.09	628.67	878.06	762.15	1171.30	5162.7	0.390	0.331	0.279	-0.941	-1.105	-0.327
1499	957.57	727.47	630.30	838.95	766.82	1251.46	5172.6	0.372	0.331	0.297	-0.990	-1.104	-0.352
1562	958.26	695.48	627.10	804.11	767.19	1330.15	5182.3	0.355	0.330	0.315	-1.036	-1.108	-0.378
1624	955.20	667.28	626.63	769.31	766.54	1424.66	5209.6	0.338	0.327	0.335	-1.086	-1.116	-0.408
1686	956.80	639.33	627.13	735.69	767.58	1518.63	5245.2	0.321	0.325	0.354	-1.137	-1.123	-0.437
1749	955.31	614.58	623.68	702.97	763.84	1602.10	5262.5	0.306	0.322	0.372	-1.185	-1.133	-0.465
1811	956.16	587.64	620.92	675.01	760.88	1690.71	5291.3	0.291	0.319	0.390	-1.234	-1.143	-0.494
1874	953.71	558.91	614.15	645.75	756.00	1771.55	5300.1	0.277	0.315	0.408	-1.283	-1.154	-0.524
1936	953.40	537.95	608.61	620.27	749.62	1856.69	5326.5	0.265	0.311	0.425	-1.329	-1.169	-0.553
1999	952.85	514.51	602.46	594.64	744.95	1950.20	5359.6	0.252	0.306	0.443	-1.380	-1.185	-0.584
2061	953.91	493.13	596.19	570.67	736.56	2034.30	5384.8	0.240	0.301	0.459	-1.427	-1.201	-0.615
2124	949.93	470.35	591.11	546.68	728.88	2114.14	5401.1	0.228	0.297	0.475	-1.476	-1.216	-0.644
2186	952.05	450.42	583.79	522.40	719.55	2200.36	5428.6	0.217	0.291	0.492	-1.526	-1.234	-0.676
2249	951.26	434.80	577.16	500.93	714.60	2295.92	5474.7	0.207	0.286	0.508	-1.576	-1.253	-0.708
2311	953.02	414.20	569.18	479.58	703.01	2380.53	5499.5	0.197	0.280	0.524	-1.627	-1.274	-0.741
2373	952.22	396.82	561.54	458.64	695.11	2458.72	5523.0	0.187	0.275	0.538	-1.676	-1.291	-0.772
2436	950.01	383.51	552.53	439.19	682.89	2534.12	5542.2	0.179	0.269	0.552	-1.720	-1.313	-0.803
2498	952.58	367.13	543.70	422.31	675.41	2616.51	5577.6	0.171	0.264	0.566	-1.768	-1.333	-0.834
2561	951.45	349.78	536.49	403.94	662.03	2692.46	5596.1	0.162	0.258	0.580	-1.818	-1.355	-0.867
2623	948.75	336.01	526.18	388.80	652.84	2772.20	5624.8	0.155	0.252	0.593	-1.864	-1.378	-0.899
2686	951.97	321.70	515.90	372.07	639.79	2840.85	5642.3	0.148	0.246	0.606	-1.911	-1.401	-0.931
2748	948.17	309.99	505.87	355.77	628.58	2917.51	5665.9	0.141	0.240	0.618	-1.958	-1.425	-0.963
2811	952.92	296.35	499.50	339.89	618.37	2990.32	5697.4	0.134	0.236	0.630	-2.009	-1.446	-0.995
2873	951.58	286.43	487.69	328.32	606.02	3056.28	5716.3	0.129	0.230	0.641	-2.048	-1.472	-1.026
2936	948.30	273.20	476.90	313.76	594.95	3131.98	5739.1	0.123	0.224	0.654	-2.099	-1.497	-1.061
2998	950.84	260.47	467.73	302.09	583.94	3203.52	5768.6	0.117	0.218	0.665	-2.148	-1.522	-1.093
3061	949.29	252.65	457.72	291.71	570.94	3270.00	5792.3	0.112	0.212	0.675	-2.186	-1.549	-1.125
3123	950.51	239.63	449.75	277.05	558.57	3338.92	5814.4	0.106	0.207	0.686	-2.242	-1.574	-1.160
3185	952.70	228.07	438.81	267.87	548.21	3413.59	5849.2	0.101	0.202	0.697	-2.290	-1.602	-1.194
3248	951.41	221.48	429.54	255.34	535.37	3471.25	5864.4	0.097	0.196	0.707	-2.332	-1.628	-1.226
3310	949.20	210.90	419.76	245.34	524.28	3547.64	5897.1	0.092	0.191	0.717	-2.384	-1.657	-1.262
3373	951.69	203.54	412.11	236.21	512.87	3593.95	5910.4	0.089	0.187	0.725	-2.423	-1.679	-1.290
3435	951.28	197.51	403.24	227.31	501.28	3654.13	5934.7	0.085	0.182	0.733	-2.462	-1.706	-1.321

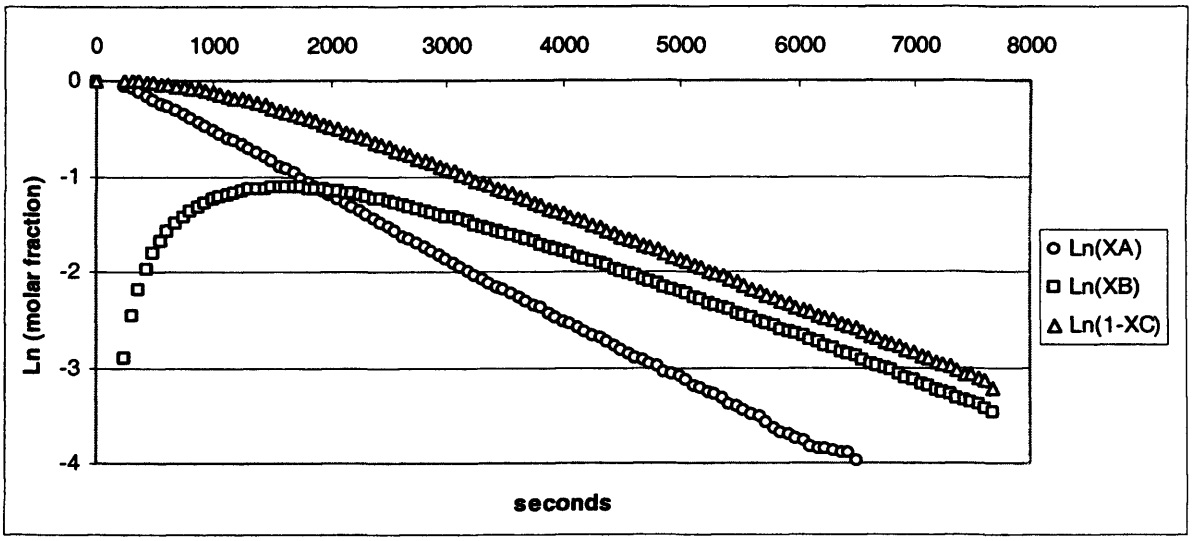
3498	952.07	189.72	393.10	218.62	490.09	3711.60	5955.2	0.082	0.177	0.742	-2.506	-1.734	-1.354
3560	951.83	180.64	385.04	210.12	477.36	3770.93	5975.9	0.078	0.172	0.751	-2.554	-1.762	-1.389
3623	952.38	173.49	376.27	200.21	464.11	3824.14	5990.6	0.074	0.167	0.759	-2.601	-1.791	-1.423
3685	952.03	167.90	365.02	191.60	453.90	3873.62	6004.1	0.071	0.162	0.767	-2.643	-1.820	-1.456
3748	952.04	160.53	357.97	185.76	443.99	3922.69	6023.0	0.068	0.158	0.774	-2.684	-1.844	-1.485
3810	955.00	153.51	349.42	178.92	432.93	3976.46	6046.2	0.065	0.154	0.781	-2.729	-1.873	-1.519
3873	954.00	147.28	339.45	170.36	423.85	4039.60	6074.5	0.062	0.149	0.789	-2.780	-1.903	-1.555
3935	957.10	143.51	333.91	165.25	411.86	4081.71	6093.3	0.060	0.145	0.795	-2.811	-1.930	-1.583
3997	954.64	137.22	323.63	157.62	402.34	4132.96	6108.4	0.057	0.141	0.802	-2.861	-1.960	-1.619
4060	954.67	128.97	316.07	153.02	392.00	4180.97	6125.7	0.055	0.137	0.809	-2.909	-1.988	-1.653
4122	956.02	125.16	309.16	144.96	379.38	4233.77	6148.5	0.052	0.133	0.815	-2.956	-2.020	-1.689
4185	954.84	120.53	301.24	138.11	372.68	4265.39	6152.8	0.050	0.130	0.821	-3.001	-2.043	-1.718
4247	960.02	117.36	294.83	133.82	363.72	4317.97	6187.7	0.048	0.126	0.826	-3.036	-2.072	-1.749
4310	956.51	114.16	285.21	128.07	352.02	4354.75	6190.7	0.046	0.122	0.832	-3.073	-2.106	-1.784
4372	956.64	106.42	279.59	123.13	343.71	4400.43	6209.9	0.044	0.119	0.838	-3.130	-2.132	-1.818
4435	958.05	102.68	271.48	119.89	335.31	4443.53	6230.9	0.042	0.115	0.843	-3.165	-2.162	-1.850
4497	958.30	100.04	265.40	114.60	325.41	4488.12	6251.9	0.041	0.112	0.848	-3.205	-2.193	-1.883
4560	960.10	93.81	258.47	110.59	313.75	4520.05	6256.8	0.039	0.108	0.853	-3.255	-2.225	-1.920
4622	959.24	91.51	251.88	105.31	308.52	4551.58	6268.0	0.037	0.106	0.857	-3.295	-2.248	-1.947
4685	958.00	87.59	245.13	101.80	297.10	4592.96	6282.6	0.036	0.102	0.863	-3.336	-2.284	-1.985
4747	959.77	85.53	238.63	98.26	291.73	4628.41	6302.3	0.034	0.099	0.866	-3.370	-2.310	-2.012
4809	958.11	82.44	231.43	93.88	283.61	4667.18	6316.7	0.033	0.096	0.871	-3.414	-2.342	-2.048
4872	958.26	77.65	226.93	89.65	274.26	4696.11	6322.9	0.031	0.093	0.875	-3.468	-2.371	-2.083
4934	962.03	76.44	218.20	87.14	267.40	4726.00	6337.2	0.030	0.090	0.879	-3.492	-2.404	-2.114
4997	962.49	69.74	211.68	84.67	258.81	4766.31	6353.7	0.029	0.087	0.884	-3.553	-2.439	-2.155
5059	961.01	68.45	206.08	80.04	252.33	4797.48	6365.4	0.027	0.085	0.888	-3.594	-2.467	-2.187
5122	962.65	67.47	201.03	77.33	245.79	4838.31	6392.6	0.027	0.082	0.891	-3.624	-2.498	-2.217
5184	963.74	64.86	196.65	75.65	238.13	4857.71	6396.7	0.026	0.080	0.894	-3.655	-2.525	-2.245
5247	963.97	62.09	191.33	73.10	228.90	4879.25	6398.6	0.025	0.077	0.898	-3.694	-2.560	-2.281
5309	966.40	58.90	186.27	69.29	221.62	4894.96	6397.4	0.024	0.075	0.901	-3.746	-2.589	-2.316
5372	967.10	56.35	180.87	66.94	216.74	4943.75	6431.7	0.023	0.073	0.905	-3.792	-2.621	-2.350
5434	962.76	55.74	177.54	66.17	210.70	4955.92	6428.8	0.022	0.071	0.907	-3.803	-2.645	-2.372
5496	965.76	52.94	169.05	62.25	204.59	4989.48	6444.1	0.021	0.068	0.911	-3.862	-2.685	-2.417
5559	964.47	52.03	165.82	59.88	199.31	5002.61	6444.1	0.020	0.067	0.913	-3.891	-2.709	-2.441
5621	967.44	47.68	160.88	59.03	192.29	5045.08	6472.4	0.019	0.064	0.916	-3.943	-2.746	-2.482
5684	967.05	48.79	157.83	55.29	184.39	5063.22	6476.6	0.019	0.062	0.919	-3.969	-2.779	-2.513
5746	967.42	45.60	152.13	55.51	181.37	5095.69	6497.7	0.018	0.060	0.921	-4.002	-2.808	-2.544
5809	968.62	42.91	148.40	52.20	175.75	5122.90	6510.8	0.017	0.058	0.924	-4.065	-2.839	-2.582
5871	968.63	42.82	143.69	49.01	170.78	5142.64	6517.6	0.017	0.057	0.927	-4.101	-2.870	-2.614
5934	969.39	40.39	141.18	49.14	163.48	5156.25	6519.8	0.016	0.055	0.929	-4.127	-2.902	-2.645
5996	971.01	37.99	137.50	45.21	159.44	5180.81	6532.0	0.015	0.053	0.932	-4.202	-2.930	-2.683
6059	971.23	38.57	131.37	45.11	154.19	5194.25	6534.7	0.015	0.051	0.934	-4.197	-2.970	-2.713
6121	973.50	38.28	128.39	43.34	149.94	5223.93	6557.4	0.015	0.050	0.936	-4.226	-2.999	-2.742
6184	974.55	35.08	123.82	43.04	145.46	5240.04	6562.0	0.014	0.048	0.938	-4.270	-3.033	-2.778
6246	973.69	32.25	120.97	39.25	140.13	5263.22	6569.5	0.013	0.047	0.941	-4.360	-3.065	-2.823
6308	973.08	31.96	116.83	37.45	135.45	5293.59	6588.4	0.012	0.045	0.943	-4.393	-3.103	-2.860
6371	972.89	30.78	112.96	35.74	132.72	5303.39	6588.5	0.012	0.044	0.944	-4.436	-3.129	-2.890
6433	973.79	28.99	110.27	35.26	128.52	5310.55	6587.4	0.011	0.043	0.946	-4.470	-3.157	-2.919
6496	974.59	28.24	107.02	34.89	124.49	5326.76	6596.0	0.011	0.041	0.948	-4.489	-3.190	-2.949
6558	974.30	27.25	106.07	34.27	119.93	5342.91	6604.7	0.011	0.040	0.949	-4.517	-3.215	-2.975
6621	974.53	24.73	101.95	34.10	116.56	5355.42	6607.3	0.010	0.039	0.951	-4.562	-3.250	-3.011
6683	977.64	26.62	96.92	32.84	112.99	5377.59	6624.6	0.011	0.037	0.952	-4.553	-3.292	-3.043
6746	978.14	26.12	96.05	30.47	108.04	5386.22	6625.0	0.010	0.036	0.954	-4.603	-3.320	-3.076
6808	980.27	24.09	93.17	29.04	102.75	5408.55	6637.9	0.009	0.035	0.956	-4.668	-3.363	-3.123
6871	979.13	23.87	89.38	28.95	100.40	5415.81	6637.5	0.009	0.034	0.957	-4.674	-3.395	-3.150
6933	978.36	23.60	87.24	28.16	96.31	5426.54	6640.2	0.009	0.032	0.958	-4.695	-3.429	-3.181
6996	978.96	21.28	84.96	27.08	93.69	5441.29	6647.3	0.009	0.032	0.960	-4.764	-3.457	-3.218

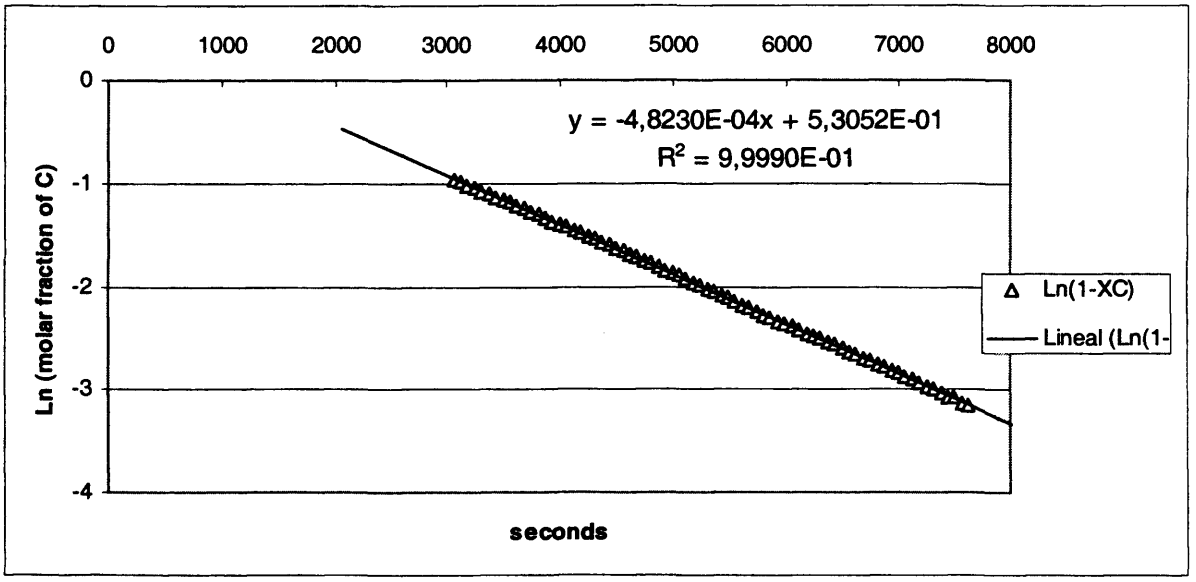
7058	979.69	23.44	81.45	25.04	88.68	5453.47	6651.8	0.009	0.030	0.961	-4.762	-3.507	-3.256
7120	978.78	21.71	79.26	24.77	87.46	5456.33	6648.3	0.008	0.029	0.962	-4.804	-3.527	-3.281
7183	978.44	20.91	75.29	25.44	85.12	5473.98	6659.2	0.008	0.028	0.964	-4.809	-3.567	-3.313
7245	981.62	18.03	74.68	23.04	80.87	5487.88	6666.1	0.007	0.027	0.965	-4.930	-3.599	-3.364
7308	979.28	19.98	73.84	23.04	79.63	5501.44	6677.2	0.008	0.027	0.966	-4.886	-3.614	-3.367
7370	980.13	18.02	71.55	21.49	74.90	5509.13	6675.2	0.007	0.026	0.967	-4.971	-3.661	-3.422
7433	981.21	19.66	68.33	23.10	73.88	5520.61	6686.8	0.007	0.025	0.968	-4.894	-3.692	-3.429
7495	981.17	15.70	67.02	20.72	70.80	5535.48	6690.9	0.006	0.024	0.969	-5.055	-3.724	-3.489
7558	982.84	14.97	64.25	19.26	66.88	5547.50	6695.7	0.006	0.023	0.971	-5.117	-3.774	-3.542
7620	984.63	15.86	62.67	21.46	67.37	5566.55	6718.5	0.007	0.023	0.971	-5.035	-3.786	-3.534

6.2.5 Experiment in CD_3OH Entry 5

[132] = 0.544 mol/l
[TMSCl] = 0.255 mol/l
k_{obs}= $4.82 \cdot 10^{-4}$ s^{-1}







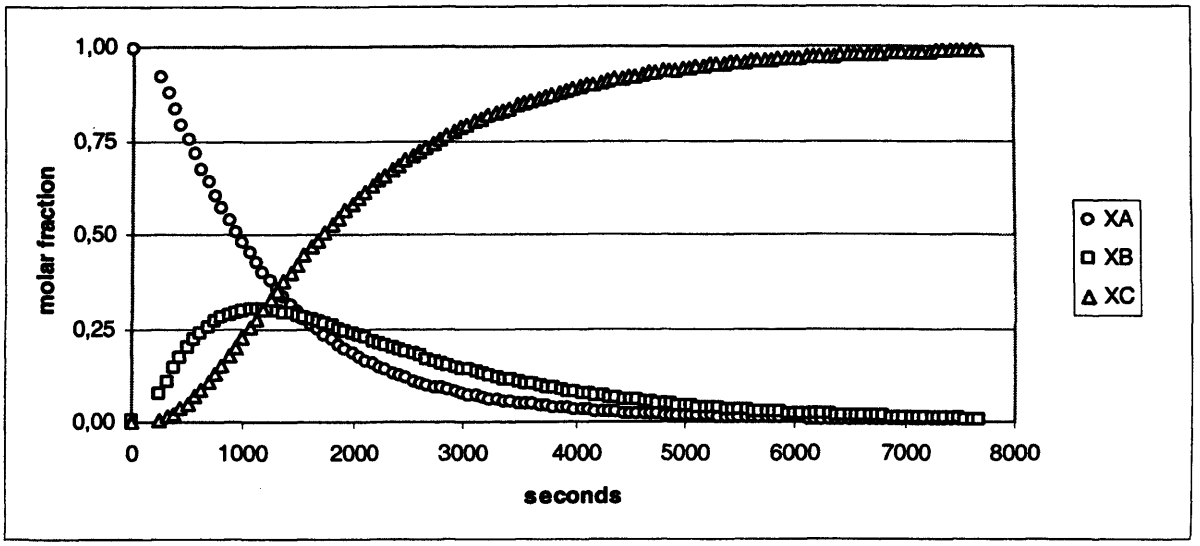
Time (s)	Int S δ_F (-59.3 Hz)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.6 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	$Ln(X_A)$	$Ln(X_B)$	$Ln(1-X_C)$
0	1000.00	2577.89	18.95	2832.92	-0.65	2.41	6431.5	0.996	0.003	0.000	-0.004	-5.693	0.000
250	1003.38	2427.11	145.50	2718.68	151.57	12.22	6458.5	0.943	0.054	0.002	-0.058	-2.910	-0.002
312	997.29	2321.36	216.08	2605.74	244.29	27.66	6412.4	0.910	0.085	0.005	-0.094	-2.465	-0.005
375	999.25	2226.84	281.94	2506.16	325.95	45.89	6386.0	0.879	0.113	0.009	-0.129	-2.182	-0.009
437	994.25	2136.08	343.31	2408.02	403.70	87.08	6372.4	0.845	0.139	0.016	-0.169	-1.974	-0.016
500	991.64	2051.49	401.72	2318.80	474.49	118.67	6356.8	0.815	0.163	0.022	-0.205	-1.812	-0.022
562	987.24	1966.07	452.18	2220.98	534.42	166.91	6327.8	0.784	0.185	0.031	-0.243	-1.689	-0.032
625	981.48	1883.96	497.39	2136.06	593.02	211.67	6303.6	0.755	0.205	0.040	-0.281	-1.585	-0.041
687	984.50	1808.77	538.91	2053.51	644.49	274.79	6305.0	0.726	0.222	0.052	-0.320	-1.503	-0.053
750	980.62	1733.08	572.19	1972.57	692.59	333.57	6284.6	0.699	0.238	0.063	-0.359	-1.434	-0.065
812	979.48	1668.70	612.08	1895.79	735.41	406.73	6298.2	0.670	0.253	0.076	-0.400	-1.373	-0.080
874	977.62	1598.83	635.30	1820.82	774.58	468.58	6275.7	0.645	0.266	0.088	-0.438	-1.324	-0.093
937	969.66	1528.24	658.86	1750.98	806.83	539.95	6254.5	0.620	0.277	0.102	-0.477	-1.283	-0.108
999	968.61	1470.37	679.93	1685.02	832.33	622.71	6259.0	0.596	0.286	0.118	-0.517	-1.252	-0.125
1062	968.46	1409.67	703.11	1621.40	860.37	702.43	6265.4	0.572	0.295	0.133	-0.558	-1.220	-0.142
1124	967.21	1352.09	722.27	1558.31	888.75	793.54	6282.2	0.548	0.303	0.149	-0.602	-1.194	-0.162
1187	964.50	1298.82	738.62	1502.86	905.59	876.70	6287.1	0.526	0.309	0.165	-0.642	-1.175	-0.180
1249	964.98	1252.54	751.87	1446.80	925.44	965.76	6307.4	0.505	0.314	0.181	-0.683	-1.158	-0.199
1312	961.72	1199.63	758.18	1389.43	938.70	1051.51	6299.2	0.485	0.318	0.197	-0.723	-1.146	-0.219
1374	961.19	1156.55	770.81	1340.84	955.93	1148.74	6334.1	0.465	0.321	0.214	-0.766	-1.135	-0.241
1437	959.93	1113.08	779.83	1290.50	967.30	1248.39	6359.0	0.445	0.324	0.231	-0.809	-1.128	-0.263
1499	962.89	1070.43	787.47	1240.91	972.06	1342.46	6376.2	0.427	0.325	0.248	-0.851	-1.124	-0.285
1562	960.60	1026.07	791.20	1192.96	980.09	1440.86	6391.8	0.409	0.326	0.265	-0.895	-1.120	-0.308
1624	960.63	987.64	793.45	1147.05	983.91	1534.02	6406.7	0.392	0.326	0.282	-0.937	-1.120	-0.331
1686	959.50	949.84	793.49	1106.00	984.97	1630.64	6424.4	0.376	0.325	0.298	-0.978	-1.123	-0.354
1749	967.63	916.97	804.49	1055.25	993.06	1745.77	6483.2	0.358	0.326	0.317	-1.028	-1.121	-0.381
1811	961.91	877.61	799.67	1016.99	985.54	1835.71	6477.4	0.344	0.324	0.333	-1.069	-1.128	-0.405
1874	963.95	846.06	801.15	976.88	989.67	1949.74	6527.4	0.328	0.322	0.350	-1.116	-1.134	-0.431
1936	960.06	815.06	797.96	942.51	984.23	2042.91	6542.7	0.315	0.319	0.366	-1.156	-1.142	-0.456
1999	963.72	783.74	795.24	902.17	980.60	2154.61	6580.1	0.300	0.316	0.384	-1.203	-1.151	-0.484
2061	959.87	752.50	784.74	869.52	970.09	2237.56	6574.3	0.289	0.313	0.399	-1.242	-1.163	-0.508
2124	960.20	724.50	779.19	837.63	967.25	2353.02	6621.8	0.276	0.308	0.416	-1.288	-1.176	-0.537
2186	959.15	697.45	770.71	805.12	958.49	2439.65	6630.6	0.265	0.305	0.430	-1.328	-1.188	-0.562
2249	958.55	669.25	761.88	774.14	946.93	2532.81	6643.6	0.254	0.301	0.446	-1.371	-1.202	-0.590
2311	952.18	640.20	750.98	742.11	934.85	2622.41	6642.7	0.243	0.296	0.461	-1.415	-1.217	-0.618
2373	948.93	614.43	737.26	715.53	923.80	2717.22	6657.2	0.233	0.291	0.476	-1.457	-1.234	-0.646
2436	945.52	587.83	726.21	685.97	910.90	2810.42	6666.9	0.223	0.286	0.491	-1.502	-1.251	-0.676
2498	946.96	565.30	716.44	662.09	899.85	2899.94	6690.6	0.214	0.281	0.505	-1.543	-1.268	-0.703
2561	944.31	541.97	702.57	634.66	884.79	2991.19	6699.5	0.204	0.276	0.520	-1.587	-1.288	-0.733
2623	940.76	518.28	691.36	610.80	873.27	3083.05	6717.5	0.195	0.271	0.534	-1.632	-1.306	-0.763
2686	940.24	504.45	681.39	593.01	862.54	3159.82	6741.5	0.189	0.266	0.545	-1.665	-1.324	-0.787
2748	944.61	482.65	672.53	570.77	848.85	3259.24	6778.6	0.181	0.261	0.559	-1.712	-1.344	-0.818
2811	942.99	470.88	665.24	546.71	838.11	3345.32	6809.2	0.173	0.256	0.570	-1.752	-1.362	-0.845
2873	944.12	453.35	655.34	529.06	824.01	3429.94	6835.8	0.167	0.251	0.582	-1.791	-1.382	-0.873
2936	947.79	434.48	644.95	513.02	811.54	3514.17	6865.9	0.160	0.246	0.594	-1.832	-1.402	-0.901
2998	947.41	422.80	637.53	495.68	801.52	3605.34	6910.3	0.154	0.241	0.605	-1.871	-1.422	-0.928
3061	946.37	407.19	629.16	477.48	789.23	3690.76	6940.2	0.148	0.237	0.616	-1.913	-1.441	-0.956
3123	949.82	387.99	618.50	461.15	775.75	3769.94	6963.2	0.141	0.232	0.627	-1.958	-1.462	-0.986
3185	951.99	375.27	605.48	443.26	762.44	3847.89	6986.3	0.136	0.227	0.638	-1.998	-1.484	-1.015
3248	947.69	364.14	594.01	426.23	746.70	3945.26	7024.0	0.130	0.221	0.649	-2.040	-1.511	-1.048
3310	951.91	348.87	586.43	407.90	736.06	4017.22	7048.4	0.124	0.217	0.659	-2.086	-1.528	-1.076
3373	952.50	337.14	572.90	395.25	720.88	4084.28	7063.0	0.120	0.212	0.668	-2.121	-1.552	-1.104
3435	948.34	323.81	562.46	381.65	710.75	4172.20	7099.2	0.115	0.207	0.678	-2.166	-1.575	-1.134

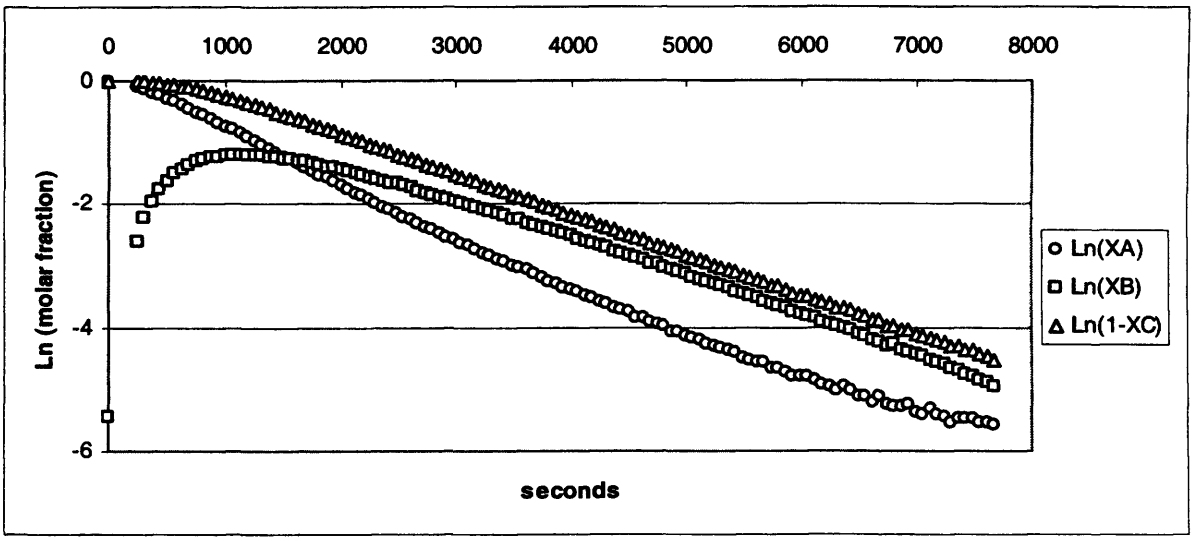
3498	946.29	312.14	550.64	368.77	694.69	4213.51	7086.0	0.111	0.203	0.686	-2.199	-1.595	-1.159
3560	943.57	302.50	538.43	357.77	674.92	4264.15	7081.3	0.108	0.198	0.695	-2.230	-1.621	-1.187
3623	949.57	288.87	529.33	342.76	665.11	4357.64	7133.3	0.102	0.193	0.705	-2.281	-1.644	-1.220
3685	947.26	282.58	516.17	330.01	648.79	4411.57	7136.4	0.099	0.188	0.713	-2.313	-1.670	-1.248
3748	945.77	268.14	507.61	319.81	633.17	4475.91	7150.4	0.095	0.184	0.721	-2.356	-1.694	-1.278
3810	946.64	264.09	496.23	311.08	622.70	4541.24	7182.0	0.092	0.179	0.728	-2.383	-1.718	-1.303
3873	951.91	250.10	488.72	294.91	614.19	4632.00	7231.8	0.087	0.176	0.738	-2.444	-1.739	-1.338
3935	948.05	238.13	476.10	286.21	599.25	4693.00	7240.7	0.083	0.171	0.746	-2.485	-1.767	-1.370
3997	950.97	231.76	467.58	276.20	586.85	4748.99	7262.3	0.080	0.167	0.752	-2.520	-1.789	-1.396
4060	948.32	225.98	458.46	265.34	573.69	4804.14	7275.9	0.078	0.163	0.759	-2.556	-1.813	-1.424
4122	949.32	217.94	444.98	259.16	559.87	4866.19	7297.5	0.075	0.158	0.767	-2.588	-1.843	-1.455
4185	948.60	207.42	435.47	249.04	546.81	4907.90	7295.2	0.072	0.155	0.773	-2.632	-1.866	-1.484
4247	948.73	202.01	423.74	239.29	530.98	4964.29	7309.0	0.069	0.150	0.781	-2.668	-1.896	-1.516
4310	950.83	195.34	415.05	232.22	518.99	5031.81	7344.3	0.067	0.146	0.787	-2.705	-1.923	-1.547
4372	955.14	189.52	408.11	223.57	509.93	5088.66	7374.9	0.064	0.143	0.793	-2.743	-1.945	-1.573
4435	952.85	182.69	398.34	217.56	497.67	5149.52	7398.6	0.062	0.139	0.799	-2.779	-1.973	-1.604
4497	954.86	173.88	388.43	210.88	485.31	5193.00	7406.4	0.060	0.135	0.805	-2.819	-1.999	-1.634
4560	952.91	169.55	379.41	203.01	475.46	5244.95	7425.3	0.058	0.132	0.810	-2.855	-2.024	-1.663
4622	953.85	160.86	370.69	196.03	464.42	5296.15	7442.0	0.055	0.129	0.816	-2.900	-2.050	-1.694
4685	951.20	157.60	362.44	190.51	449.34	5340.83	7451.9	0.054	0.125	0.822	-2.927	-2.080	-1.724
4747	955.81	152.24	351.99	182.63	437.76	5379.08	7459.5	0.051	0.121	0.827	-2.966	-2.108	-1.755
4809	953.02	150.74	343.58	176.12	430.26	5418.92	7472.6	0.050	0.119	0.831	-2.993	-2.131	-1.779
4872	954.06	141.67	337.76	170.48	416.34	5474.61	7494.9	0.048	0.115	0.837	-3.042	-2.160	-1.814
4934	953.12	137.77	328.22	164.04	407.27	5513.43	7503.8	0.046	0.112	0.842	-3.078	-2.187	-1.843
4997	957.68	134.48	321.73	160.55	395.68	5547.70	7517.8	0.045	0.109	0.846	-3.102	-2.213	-1.869
5059	959.58	126.39	312.08	159.01	388.38	5599.42	7544.9	0.043	0.106	0.850	-3.139	-2.241	-1.899
5122	958.78	123.95	305.32	147.53	377.53	5644.61	7557.7	0.041	0.103	0.855	-3.191	-2.268	-1.934
5184	957.48	121.04	298.34	142.57	368.75	5690.43	7578.6	0.040	0.101	0.859	-3.224	-2.295	-1.962
5247	957.71	116.52	290.43	138.73	357.40	5734.44	7595.2	0.038	0.098	0.864	-3.258	-2.327	-1.995
5309	960.97	114.14	283.80	135.13	349.95	5785.02	7629.0	0.037	0.095	0.868	-3.287	-2.353	-2.022
5372	962.30	109.01	277.08	131.31	342.27	5828.31	7650.3	0.036	0.093	0.871	-3.326	-2.379	-2.052
5434	961.47	103.17	270.94	124.72	333.57	5860.73	7654.6	0.034	0.090	0.876	-3.380	-2.404	-2.085
5496	961.32	99.90	263.83	119.88	325.47	5897.37	7667.8	0.033	0.088	0.879	-3.418	-2.432	-2.115
5559	961.06	95.66	257.44	115.50	313.89	5918.82	7662.4	0.032	0.085	0.883	-3.457	-2.462	-2.148
5621	960.07	92.12	249.24	112.33	306.09	5955.49	7675.3	0.030	0.083	0.887	-3.492	-2.493	-2.179
5684	961.86	91.58	242.17	109.21	299.11	5994.39	7698.3	0.030	0.080	0.890	-3.513	-2.521	-2.206
5746	963.89	84.75	235.93	105.08	292.18	6043.88	7725.7	0.028	0.078	0.894	-3.573	-2.550	-2.243
5809	973.87	82.23	234.21	98.92	293.35	6209.48	7892.1	0.026	0.076	0.898	-3.643	-2.574	-2.278
5871	973.96	78.72	228.63	94.26	284.88	6238.76	7899.2	0.025	0.074	0.901	-3.690	-2.602	-2.311
5934	972.65	79.51	222.07	89.51	279.14	6266.03	7908.9	0.024	0.072	0.903	-3.714	-2.627	-2.337
5996	972.52	77.01	212.87	88.42	271.48	6294.90	7917.2	0.024	0.070	0.906	-3.737	-2.663	-2.369
6059	972.35	73.46	210.04	86.32	264.51	6308.99	7915.7	0.023	0.068	0.909	-3.772	-2.683	-2.393
6121	973.62	67.53	203.57	84.43	256.51	6333.82	7919.5	0.022	0.066	0.912	-3.822	-2.715	-2.429
6184	969.36	65.27	199.66	80.12	245.96	6324.47	7884.8	0.021	0.064	0.915	-3.862	-2.742	-2.460
6246	966.36	64.21	192.34	81.02	236.92	6293.16	7834.0	0.021	0.063	0.916	-3.856	-2.773	-2.481
6308	967.58	65.07	186.06	77.87	231.78	6319.44	7847.8	0.021	0.061	0.918	-3.874	-2.801	-2.507
6371	964.50	62.31	179.92	76.28	218.92	6302.51	7804.4	0.020	0.058	0.921	-3.899	-2.842	-2.544
6433	966.18	60.74	174.93	77.46	215.57	6320.53	7815.4	0.020	0.057	0.923	-3.903	-2.864	-2.561
6496	963.63	58.31	174.39	70.70	205.97	6329.73	7802.7	0.019	0.056	0.926	-3.970	-2.889	-2.597
6558	966.69	54.75	166.43	67.91	200.80	6357.11	7813.7	0.018	0.054	0.928	-4.022	-2.926	-2.637
6621	961.72	53.55	161.30	68.06	194.55	6386.12	7825.3	0.018	0.052	0.930	-4.033	-2.959	-2.665
6683	963.73	53.11	156.93	67.61	187.74	6392.76	7821.9	0.018	0.050	0.932	-4.040	-2.991	-2.690
6746	964.74	52.22	153.77	61.52	182.32	6428.74	7843.3	0.017	0.049	0.935	-4.102	-3.019	-2.727
6808	965.28	49.50	149.71	61.66	179.02	6444.17	7849.3	0.016	0.048	0.936	-4.126	-3.042	-2.750
6871	968.91	49.49	144.40	61.33	174.22	6458.00	7856.4	0.016	0.046	0.938	-4.129	-3.073	-2.775
6933	964.66	48.00	140.93	57.81	165.43	6475.04	7851.9	0.015	0.044	0.940	-4.176	-3.113	-2.816
6996	966.33	47.39	137.67	55.95	162.89	6497.68	7867.9	0.015	0.044	0.941	-4.201	-3.134	-2.838

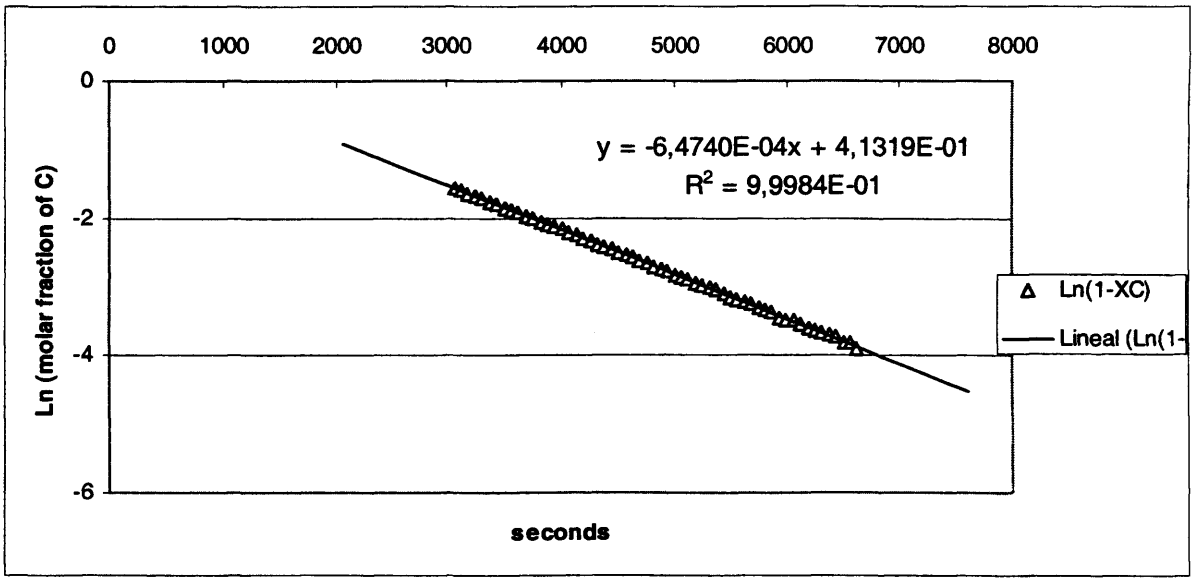
7058	967.22	44.12	132.64	53.64	157.49	6537.95	7893.1	0.014	0.042	0.944	-4.261	-3.173	-2.882
7120	968.01	43.53	131.16	53.02	154.25	6561.00	7911.0	0.014	0.041	0.945	-4.275	-3.192	-2.900
7183	967.24	41.42	125.66	50.02	147.41	6551.55	7883.3	0.013	0.039	0.947	-4.326	-3.232	-2.943
7245	971.74	38.30	122.61	50.61	144.16	6583.63	7911.0	0.013	0.038	0.949	-4.357	-3.259	-2.971
7308	968.93	41.95	119.51	48.31	139.97	6604.33	7923.0	0.013	0.037	0.950	-4.344	-3.288	-2.990
7370	971.98	35.50	115.66	48.63	136.58	6628.46	7936.8	0.012	0.036	0.952	-4.416	-3.318	-3.030
7433	967.97	34.29	112.08	43.41	134.16	6681.83	7973.7	0.011	0.035	0.954	-4.502	-3.348	-3.074
7495	970.98	36.03	111.33	46.38	129.06	6688.19	7982.0	0.012	0.034	0.954	-4.443	-3.373	-3.078
7558	971.61	31.63	107.61	40.95	128.89	6715.67	7996.4	0.010	0.034	0.956	-4.573	-3.391	-3.124
7620	975.04	34.02	105.24	40.99	122.43	6726.51	8004.2	0.011	0.032	0.957	-4.540	-3.430	-3.145
7683	973.96	28.70	99.20	35.61	118.27	6770.82	8026.6	0.009	0.031	0.960	-4.698	-3.479	-3.220

6.2.6 Experiment in CD_3OH Entry 6

[132] = 0.495 mol/l
[TMSCl] = 0.0.328 mol/l
$k_{obs}= 6.47 \cdot 10^{-4}\ s^{-1}$







Time (s)	Int S δ_F (-59.3 Hz)	Int A δ_F (-102.4 Hz)	Int B δ_F (-111.7 Hz)	Int A δ_F (-102.6 Hz)	Int B δ_F (-123.7 Hz)	Int C δ_F (-135.1 Hz)	Σ(Int)	X_A	X_B	X_C	$Ln(X_A)$	$Ln(X_B)$	$Ln(1-X_C)$
0	1000.00	856.05	8.91	987.69	-1.02	1.15	2852.8	0.995	0.004	0.001	-0.005	-5.459	-0.001
250	875.04	705.61	58.57	823.21	64.48	12.20	2539.1	0.919	0.074	0.007	-0.085	-2.604	-0.007
312	869.82	666.81	83.64	780.24	97.85	22.53	2520.9	0.876	0.110	0.014	-0.132	-2.208	-0.014
375	871.13	633.46	107.68	742.46	129.30	38.56	2522.6	0.833	0.143	0.023	-0.183	-1.941	-0.024
437	866.19	601.25	127.43	705.16	156.31	59.06	2515.4	0.792	0.172	0.036	-0.233	-1.760	-0.036
500	863.79	568.61	144.37	668.79	180.41	83.10	2509.1	0.752	0.197	0.051	-0.285	-1.623	-0.052
562	860.64	538.59	160.24	634.89	201.26	110.88	2506.5	0.713	0.220	0.067	-0.338	-1.516	-0.070
625	856.68	509.77	174.32	601.08	219.87	144.53	2506.2	0.673	0.239	0.088	-0.395	-1.431	-0.092
687	852.38	482.37	184.70	569.97	234.42	177.68	2501.5	0.638	0.254	0.108	-0.449	-1.370	-0.114
750	848.22	454.53	194.20	540.33	247.35	215.11	2499.7	0.602	0.267	0.130	-0.507	-1.319	-0.140
812	844.53	431.65	202.31	511.76	258.95	253.92	2503.1	0.569	0.278	0.153	-0.564	-1.280	-0.166
874	839.32	405.48	208.25	483.78	267.66	294.12	2498.6	0.536	0.287	0.177	-0.624	-1.249	-0.195
937	838.20	385.92	213.96	460.57	275.94	336.03	2510.6	0.506	0.293	0.201	-0.681	-1.228	-0.224
999	836.32	365.90	217.17	437.33	282.02	382.29	2521.0	0.477	0.296	0.227	-0.741	-1.216	-0.257
1062	831.69	346.18	219.29	415.02	286.38	424.29	2522.9	0.450	0.299	0.251	-0.798	-1.207	-0.289
1124	831.21	328.57	222.12	393.78	290.26	472.52	2538.5	0.423	0.300	0.277	-0.860	-1.204	-0.324
1187	828.12	311.55	222.39	374.12	292.84	521.85	2550.9	0.398	0.299	0.303	-0.921	-1.207	-0.361
1249	824.50	295.64	223.88	355.70	294.06	565.71	2559.5	0.375	0.299	0.326	-0.980	-1.209	-0.395
1312	822.72	279.89	222.74	337.91	294.81	614.13	2572.2	0.353	0.296	0.351	-1.041	-1.218	-0.432
1374	820.47	265.00	221.82	320.71	294.18	661.50	2583.7	0.332	0.293	0.375	-1.102	-1.229	-0.470
1437	819.51	251.34	220.48	305.54	292.50	709.04	2598.4	0.313	0.288	0.399	-1.161	-1.244	-0.508
1499	816.57	238.90	219.45	289.50	291.16	756.48	2612.1	0.294	0.284	0.421	-1.223	-1.257	-0.547
1562	815.45	225.87	217.64	275.51	288.61	803.32	2626.4	0.277	0.280	0.444	-1.284	-1.275	-0.586
1624	813.78	214.85	214.82	261.73	286.13	856.33	2647.6	0.260	0.273	0.467	-1.348	-1.298	-0.629
1686	813.34	205.14	212.18	249.64	283.62	900.45	2664.4	0.246	0.268	0.486	-1.404	-1.317	-0.666
1749	811.84	194.43	209.68	237.07	279.74	945.53	2678.3	0.231	0.262	0.507	-1.465	-1.339	-0.706
1811	811.98	185.80	205.94	226.02	276.01	989.81	2695.6	0.219	0.256	0.525	-1.520	-1.363	-0.745
1874	810.69	176.59	203.08	215.28	271.04	1034.90	2711.6	0.206	0.249	0.544	-1.579	-1.389	-0.786
1936	811.63	168.44	198.92	204.91	267.16	1080.81	2731.9	0.194	0.243	0.563	-1.638	-1.416	-0.827
1999	810.62	160.29	196.39	195.61	263.63	1124.25	2750.8	0.183	0.237	0.579	-1.696	-1.439	-0.866
2061	810.81	152.97	192.80	186.78	257.97	1168.80	2770.1	0.173	0.230	0.597	-1.752	-1.469	-0.908
2124	810.57	145.34	189.47	177.61	253.23	1213.29	2789.5	0.163	0.224	0.613	-1.813	-1.497	-0.950
2186	811.04	138.75	185.34	169.28	248.77	1256.74	2809.9	0.154	0.217	0.629	-1.870	-1.527	-0.991
2249	810.12	131.54	182.43	161.39	244.30	1295.29	2825.1	0.145	0.212	0.643	-1.928	-1.552	-1.030
2311	812.23	125.25	178.17	153.94	238.17	1337.45	2845.2	0.137	0.205	0.658	-1.985	-1.586	-1.073
2373	811.45	119.19	173.88	146.66	232.57	1377.85	2861.6	0.130	0.198	0.672	-2.043	-1.618	-1.115
2436	811.84	114.43	170.32	140.45	227.33	1414.80	2879.2	0.123	0.192	0.684	-2.093	-1.648	-1.153
2498	812.69	108.78	166.00	133.74	222.38	1448.79	2892.4	0.117	0.187	0.697	-2.149	-1.678	-1.193
2561	811.72	103.37	162.30	127.20	216.97	1485.94	2907.5	0.110	0.181	0.709	-2.207	-1.709	-1.234
2623	811.57	99.14	157.49	121.30	212.05	1521.30	2922.9	0.104	0.175	0.721	-2.259	-1.743	-1.275
2686	810.80	95.09	153.23	115.79	206.04	1560.11	2941.1	0.099	0.169	0.732	-2.313	-1.780	-1.318
2748	812.53	90.05	149.95	110.82	200.67	1595.49	2959.5	0.094	0.163	0.743	-2.369	-1.812	-1.359
2811	812.17	85.40	146.03	106.36	195.06	1624.99	2970.0	0.089	0.158	0.753	-2.421	-1.845	-1.399
2873	811.40	80.95	142.35	100.45	189.90	1659.65	2984.7	0.083	0.153	0.764	-2.483	-1.878	-1.442
2936	813.94	78.79	138.14	96.16	184.70	1694.12	3005.8	0.080	0.147	0.773	-2.528	-1.915	-1.482
2998	815.80	74.35	134.52	91.86	179.50	1731.19	3027.2	0.075	0.142	0.783	-2.588	-1.952	-1.527
3061	817.41	71.97	131.07	87.82	174.46	1758.32	3041.1	0.072	0.137	0.791	-2.633	-1.985	-1.564
3123	816.56	67.68	126.58	84.52	170.08	1785.99	3051.4	0.068	0.133	0.799	-2.687	-2.019	-1.605
3185	816.62	64.62	124.24	80.19	164.57	1814.63	3064.9	0.064	0.128	0.807	-2.742	-2.052	-1.646
3248	817.25	62.12	119.63	76.84	159.46	1841.05	3076.3	0.062	0.124	0.815	-2.789	-2.091	-1.687
3310	816.02	59.16	116.14	72.96	154.58	1862.53	3081.4	0.058	0.120	0.822	-2.842	-2.124	-1.727
3373	816.67	56.73	112.74	69.35	150.31	1887.43	3093.2	0.055	0.116	0.829	-2.894	-2.158	-1.767
3435	817.13	54.32	109.65	67.04	145.61	1913.37	3107.1	0.053	0.111	0.836	-2.938	-2.194	-1.805

3498	818.21	51.72	105.77	64.00	140.32	1937.76	3117.8	0.050	0.107	0.843	-2.989	-2.235	-1.849
3560	818.61	49.54	102.85	61.54	137.49	1958.85	3128.9	0.048	0.104	0.848	-3.035	-2.263	-1.883
3623	819.54	47.53	99.90	59.17	132.24	1982.73	3141.1	0.046	0.100	0.854	-3.080	-2.303	-1.924
3685	821.12	45.74	96.70	55.99	129.14	2013.00	3161.7	0.043	0.096	0.860	-3.136	-2.338	-1.966
3748	822.69	43.93	92.90	53.34	123.81	2032.26	3168.9	0.041	0.092	0.866	-3.183	-2.382	-2.011
3810	823.89	40.93	90.99	50.62	119.67	2056.59	3182.7	0.039	0.089	0.872	-3.249	-2.416	-2.055
3873	823.01	39.35	86.96	49.88	115.91	2078.84	3194.0	0.038	0.086	0.877	-3.280	-2.458	-2.094
3935	823.93	36.94	85.27	46.69	111.99	2102.15	3207.0	0.035	0.083	0.882	-3.350	-2.492	-2.138
3997	824.96	35.50	82.66	44.80	109.75	2118.61	3216.3	0.034	0.080	0.886	-3.394	-2.520	-2.171
4060	826.31	34.28	79.24	43.04	104.67	2135.49	3223.0	0.032	0.077	0.891	-3.434	-2.567	-2.216
4122	826.46	32.80	77.30	40.56	100.88	2157.71	3235.7	0.030	0.074	0.896	-3.492	-2.604	-2.259
4185	828.04	31.77	74.69	38.94	98.18	2176.10	3247.7	0.029	0.071	0.899	-3.533	-2.639	-2.296
4247	828.50	29.76	72.02	37.69	94.50	2192.08	3254.5	0.028	0.069	0.904	-3.583	-2.679	-2.339
4310	830.15	28.27	69.62	36.05	90.88	2208.30	3263.3	0.026	0.066	0.908	-3.633	-2.719	-2.382
4372	831.06	27.15	67.07	34.39	87.91	2224.39	3272.0	0.025	0.063	0.911	-3.680	-2.757	-2.422
4435	830.51	26.35	64.61	32.63	84.78	2239.03	3277.9	0.024	0.061	0.915	-3.726	-2.796	-2.463
4497	831.58	25.29	63.18	32.10	81.51	2257.24	3290.9	0.023	0.059	0.918	-3.758	-2.833	-2.499
4560	831.71	23.13	60.75	30.18	79.18	2270.80	3295.7	0.022	0.057	0.922	-3.833	-2.868	-2.546
4622	833.74	23.44	59.30	28.72	76.07	2286.92	3308.2	0.021	0.055	0.924	-3.859	-2.906	-2.580
4685	834.44	21.05	56.23	28.16	73.00	2299.15	3312.0	0.020	0.052	0.928	-3.919	-2.953	-2.631
4747	835.33	21.45	54.61	26.55	71.34	2313.44	3322.7	0.019	0.051	0.930	-3.948	-2.983	-2.660
4809	835.04	20.63	52.43	25.67	67.92	2327.55	3329.2	0.019	0.048	0.933	-3.987	-3.031	-2.706
4872	835.93	19.10	51.53	23.84	65.23	2338.27	3333.9	0.017	0.047	0.936	-4.063	-3.063	-2.750
4934	836.60	19.45	49.18	23.05	63.81	2350.54	3342.6	0.017	0.045	0.938	-4.077	-3.099	-2.780
4997	836.52	18.28	47.36	22.15	60.65	2361.97	3346.9	0.016	0.043	0.941	-4.129	-3.146	-2.828
5059	836.50	16.92	45.94	21.32	58.54	2371.27	3350.5	0.015	0.042	0.943	-4.186	-3.181	-2.869
5122	837.16	17.29	43.80	20.74	56.28	2383.14	3358.4	0.015	0.040	0.945	-4.194	-3.227	-2.904
5184	837.81	14.82	42.75	20.25	54.51	2393.95	3364.1	0.014	0.038	0.948	-4.277	-3.257	-2.949
5247	837.90	15.02	40.81	19.20	52.61	2405.46	3371.0	0.014	0.037	0.950	-4.304	-3.300	-2.988
5309	839.15	14.88	39.81	18.16	50.30	2410.34	3372.6	0.013	0.036	0.951	-4.340	-3.336	-3.024
5372	838.97	14.38	38.90	17.63	48.27	2419.72	3377.9	0.013	0.034	0.953	-4.373	-3.372	-3.059
5434	839.32	13.65	37.17	17.09	45.65	2428.75	3381.6	0.012	0.033	0.955	-4.415	-3.424	-3.109
5496	840.59	12.41	36.01	16.11	43.73	2439.21	3388.1	0.011	0.031	0.957	-4.492	-3.464	-3.158
5559	840.89	12.15	34.40	15.63	42.58	2447.94	3393.6	0.011	0.030	0.959	-4.520	-3.501	-3.193
5621	840.87	12.03	34.03	14.86	40.41	2455.61	3397.8	0.011	0.029	0.960	-4.555	-3.537	-3.228
5684	840.35	11.80	31.94	15.12	39.14	2462.22	3400.6	0.011	0.028	0.962	-4.555	-3.584	-3.263
5746	841.44	9.83	30.87	14.39	38.41	2469.97	3404.9	0.009	0.027	0.964	-4.662	-3.611	-3.311
5809	840.82	10.08	29.76	14.31	36.94	2480.84	3412.8	0.009	0.026	0.965	-4.658	-3.652	-3.341
5871	841.86	9.60	29.19	13.53	35.43	2487.54	3417.1	0.009	0.025	0.966	-4.713	-3.685	-3.379
5934	843.22	8.56	28.08	12.74	32.76	2492.41	3417.8	0.008	0.024	0.968	-4.795	-3.745	-3.445
5996	843.09	8.28	26.17	12.95	31.88	2498.27	3420.6	0.008	0.023	0.969	-4.799	-3.793	-3.482
6059	843.48	9.16	26.12	12.19	30.63	2505.51	3427.1	0.008	0.022	0.970	-4.796	-3.818	-3.499
6121	842.72	8.47	24.59	11.77	30.36	2511.10	3429.0	0.008	0.021	0.971	-4.851	-3.852	-3.538
6184	843.80	7.97	24.11	10.80	28.39	2517.44	3432.5	0.007	0.020	0.972	-4.927	-3.898	-3.593
6246	843.57	7.76	23.67	10.56	26.96	2526.30	3438.8	0.007	0.020	0.973	-4.954	-3.937	-3.628
6308	843.96	7.96	22.65	9.05	26.36	2531.57	3441.5	0.007	0.019	0.975	-5.029	-3.970	-3.672
6371	844.75	7.78	21.80	10.63	25.19	2534.37	3444.5	0.007	0.018	0.975	-4.950	-4.013	-3.683
6433	845.44	7.11	21.13	10.01	24.55	2543.23	3451.5	0.007	0.018	0.976	-5.025	-4.044	-3.725
6496	844.81	6.37	20.21	9.14	22.56	2542.52	3445.6	0.006	0.016	0.978	-5.122	-4.108	-3.798
6558	844.77	6.23	19.74	9.37	22.07	2547.87	3450.0	0.006	0.016	0.978	-5.118	-4.132	-3.815
6621	846.29	6.01	18.76	8.18	20.12	2551.24	3450.6	0.005	0.015	0.980	-5.212	-4.205	-3.893
6683	846.46	6.24	18.39	9.32	19.94	2565.63	3466.0	0.006	0.015	0.979	-5.126	-4.225	-3.884
6746	846.81	5.69	17.32	8.00	18.14	2563.35	3459.3	0.005	0.014	0.981	-5.251	-4.299	-3.973
6808	846.40	5.33	17.39	7.80	19.01	2567.52	3463.4	0.005	0.014	0.981	-5.295	-4.275	-3.967
6871	846.19	5.53	16.36	7.56	16.92	2573.30	3465.9	0.005	0.013	0.982	-5.299	-4.366	-4.034
6933	847.70	5.91	16.21	7.64	15.98	2575.66	3469.1	0.005	0.012	0.983	-5.265	-4.400	-4.049
6996	847.44	4.89	15.70	7.19	15.75	2582.94	3473.9	0.005	0.012	0.983	-5.381	-4.425	-4.100

7058	846.62	4.88	14.68	6.78	15.21	2594.21	3482.4	0.004	0.011	0.984	-5.421	-4.479	-4.150
7120	847.83	5.81	14.11	7.28	13.89	2591.52	3480.4	0.005	0.011	0.984	-5.304	-4.544	-4.160
7183	847.01	5.17	13.62	6.57	14.24	2597.40	3484.0	0.004	0.011	0.985	-5.415	-4.550	-4.199
7245	849.03	4.73	13.26	6.55	13.05	2599.78	3486.4	0.004	0.010	0.986	-5.455	-4.608	-4.251
7308	848.14	4.30	12.54	6.18	12.29	2606.52	3490.0	0.004	0.009	0.987	-5.530	-4.667	-4.315
7370	849.67	4.46	12.52	6.40	11.77	2607.59	3492.4	0.004	0.009	0.987	-5.494	-4.690	-4.320
7433	849.65	4.54	12.15	6.41	10.71	2606.95	3490.4	0.004	0.009	0.987	-5.486	-4.750	-4.358
7495	848.86	4.24	11.40	6.66	10.79	2610.13	3492.1	0.004	0.008	0.987	-5.491	-4.781	-4.381
7558	850.01	4.12	10.89	6.32	9.65	2615.80	3496.8	0.004	0.008	0.988	-5.535	-4.859	-4.448
7620	849.92	4.15	10.72	6.29	9.12	2621.77	3502.0	0.004	0.007	0.989	-5.537	-4.895	-4.473
7683	851.14	4.36	10.37	5.82	8.29	2623.08	3503.1	0.004	0.007	0.989	-5.562	-4.957	-4.521