PARTIALLY FLUOROUS MOLECULES AND LIPASE MEDIATED ENANTIOMERIC RESOLUTIONS IN FLUOROUS SOLVENTS

A thesis presented for the degree of Doctor of Philosophy to the University of St. Andrews on the 13th October, 2004

by

Ing. Petr Beier

DECLARATIONS

I, Petr Beier, hereby certify that this thesis, which is approximately 47 000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

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I was admitted as a research student in September 2001 and as a candidate for the degree of Ph.D. in September 2001; the higher study for which this is a record was carried out in the University of St. Andrews between September 2001 and September 2004.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Ph.D. in the University of St. Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Professor David O'Hagan

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ABSTRACT

In **Chapter 1** the chemistry of organo-fluorine compounds, methods for phase separation in organic synthesis and the use of enzymes as catalysts for preparative organic synthesis are introduced.

In **Chapter 2** lipase catalysed kinetic resolutions of racemic carboxylic acids/esters and racemic alcohols with highly fluorinated alcohols and highly fluorinated acyl donors respectively were explored in homogeneous perfluorocarbon-hydrocarbon solvent systems. Liquid/liquid, fluorous/organic extraction or filtration using fluorous silica gel enabled enantiomeric partitioning of the products. In several cases high enantiomeric excesses were achieved.

Chapter 3 describes the preparation of a series of long chain fatty acids with alternating blocks of fluorocarbon and hydrocarbon. This hybrid construction provided three phases (fluorous, hydrocarbon and hydrophilic) on the same molecule. The ability of the monocarboxylic acids to form monolayers on water was explored and in selected cases, X-ray structure analysis of the dicarboxylic acids provided information on the conformation and solid state organisation of these molecules. The hybrid molecules displayed surface behaviour and showed packing distances which are intermediate between hydrocarbon and perfluorocarbon chains.

Chapter 4 details the experimental procedures for the compounds synthesised in this thesis.

ACKNOWLEDGEMENT

I would like to thank and express my appreciation to Prof. David O'Hagan for giving me the opportunity to study the Ph.D. degree in his active group, for introducing me to the modern organo-fluorine chemistry and also for his encouragement and support during the last three years.

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Very special thanks to my wife Dana, who followed me to Scotland, has supported me and cared for me during our stay here. Finally, I would like to thank my parents, family and friends for their support.

ABBREVIATIONS AND SYMBOLS

A	GC-MS signal area
Å	Ångström
Ac	acetyl
$[\alpha]_D$	optical rotation
AIBN	azo-bis-*iso*-butyronitrile
aq.	aqueous
bp	boiling point
br s	broad signal
^{t}Bu	tertiary butyl
c	extent of conversion; concentration
CAL-B	*Candida antarctica-B* lipase
cat.	catalytical
CFCs	chlorofluorocarbons
CI	chemical ionisation
CRL	*Candida rugosa* lipase
D	deuterium
D	bond dissociation energy
d	doublet
δ	chemical shift
δ	Hildebrand solubility parameter
δ^h	non-specific cohesion parameter

DAST	dimethylaminosulfur trifluoride
de	diastereomeric ratio
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DSC	differential scanning calorimetry
E	enantiomeric ratio
ee	enantiomeric excess
EI	electron impact ionisation
ESI	electrospray ionisation
Et	ethyl
$^{z}\Delta E$	group contribution of the molar vaporisation energy
F	weight percentage of fluorine in a molecule
f	fluorophilicity
FC-43	perfluorotributylamine
FC-70	perfluorotripentylamine
FC-71	perfluorotrihexylamine
FC-72	perfluorohexane(s)
FC-77	perfluorooctane(s)
FC-84	perfluoroheptane(s)
FRPSG	fluorous reverse phase silica gel
GC-MS	gas chromatography-mass spectroscopy
h	hour(s)
HPLC	high performance liquid chromatography
IR	infra red spectroscopy
J	coupling constant

k_{rel}	relative rate constant
M	mol per litre (concentration units)
m	multiplet
Me	methyl
min.	minute(s)
mp	melting point
m/z	mass to charge ratio
ν_{max}	wave number corresponding to maximal absorption in infra red spectra
NMR	nuclear magnetic resonance
P	partition coefficient
Pd-C	palladium on activated carbon
PEG	polyethylene glycol
PFD	perfluorodecalin
PFF	perfluorofluorene
PFH	perfluorohexane
PFMC	perfluoro(methylcyclohexane)
PFTMB	perfluoro(tetramethylbutane)
Ph	phenyl
PPL	porcine pancreatic lipase
ppm	parts per million
PSL	*Pseudomonas cepacia* lipase
q	quartet
R	universal gas constant
R^2	*R*-squared value in linear regression

R*	chiral racemic group
R**	enantiomerically enriched group
Ra-Ni	Raney nickel
R_{fn}	perfluoroalkyl group, $CF_3(CF_2)_{n-1}$-
R_f	highly fluorinated residue
r.t.	room temperature
RTN	Research Training Network
r_w	van der Waals radius
s	singlet
sat.	saturated
Selectfluor™	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
s_D	standard deviation
σ_m	substituent constant in *meta* position
σ_p	substituent constant in *para* position
STM	scanning tunnelling microscopy
T	temperature
t	triplet
TBAF	tetrabutyl ammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
TsCl	*p*-toluenesulfonyl chloride
V	molar volume
V_r	van der Waals volume
^zV	group contribution of the molar volume

CONTENTS

1 INTRODUCTION

1.1 Synopsis

This chapter introduces the chemistry of organo-fluorine compounds including a summary of the methods for their preparation and the electronic properties that fluorine impacts into organic molecules. Steric effects as well as other characteristic features of organo-fluorine compounds are briefly mentioned.

Modern methods for efficient phase separation in organic synthesis are discussed. The emphasis is placed on phase separation techniques which make use of highly fluorinated groups: fluorous biphase catalysis and fluorous synthesis.

The last part of this chapter deals with the use of enzymes in organic synthesis. In particular lipases catalysed reactions in organic solvents are discussed.

1.2 General aspects of organo-fluorine chemistry

1.2.1 The element fluorine

Elemental fluorine is a highly corrosive, poisonous, pale yellow-green gas.[1] It is the lightest halogen and it is difficult to isolate from its fluorides. No other element is a sufficiently powerful oxidizing agent, to replace it. Fluorine was first isolated by the French chemist Henri Moissan in 1886 from the electrolysis of a solution of potassium fluoride in anhydrous hydrogen fluoride.[2, 3, 4]

Fluorine is the most reactive of all the elements. It reacts with most of the other elements except oxygen, nitrogen, helium, neon, argon and krypton to form ionic or covalent fluorides. Notably it reacts with the noble gas xenon. Many metals form a protective fluoride coating on contact with fluorine at low concentrations and can be passivated towards further reaction at higher concentrations.[1] The oxidation state of -1 is the only one observed for fluorine compounds and unlike the other halogens, the higher oxidation states are unobtainable.

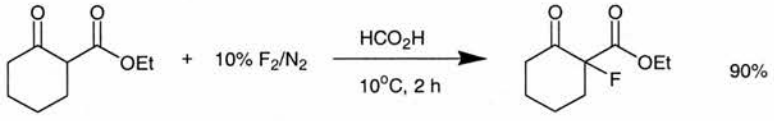
1.2.2 Fluorinated compounds

Fluorine is the 13th most abundant element on Earth and it makes up about 0.0585% of the Earth's crust[5] in the form of inorganic fluorides mainly in the mineral fluorite (fluorospar, CaF_2) but also in cryolite (Na_3AlF_6) and fluoroapatite ($Ca_5(PO_4)_3F$). Treatment of fluorite with sulfuric acid gives hydrogen fluoride (HF) a process first described in 1771 by Scheele.[6] Hydrogen fluoride is employed in the preparation of inorganic and organic fluorine compounds; *e.g.,* sodium aluminium fluoride (Na_3AlF_6), used as an electrolyte in the preparation of aluminium metal[7] and uranium hexafluoride (UF_6), utilized in the fractional diffusion process for

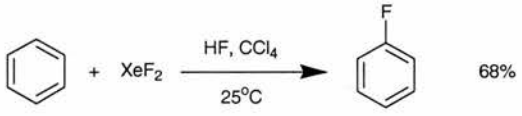
separating ^{235}U from ^{238}U.[8] Aqueous solutions of hydrogen fluoride are used in industry for cleaning metals and for etching glass.

With a few exceptions organic compounds containing fluorine are entirely synthetic and of anthropogenic origin. Important methods for the preparation of organo-fluorine compounds from hydrocarbons or their derivatives include:[9]

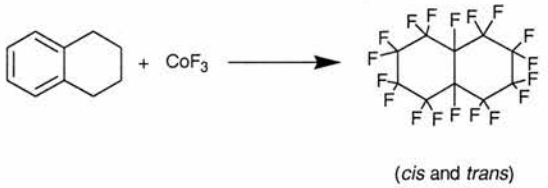
- Fluorination with elemental fluorine by reaction with saturated and unsaturated compounds or halogen derivatives, Scheme 1 .
- Fluorination with fluorides (metal fluorides or non-metallic fluorides) by reaction with hydrocarbons (Scheme 2), unsaturated compounds (Scheme 3), halogen or hydroxyl derivatives (Scheme 4) or carbonyl compounds, Scheme 5.
- Electrolytic fluorination in anhydrous hydrogen fluoride.



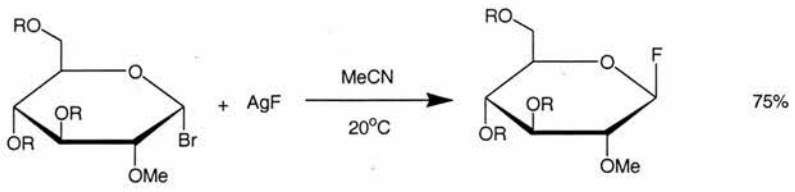
Scheme 1: An example of selective fluorination with elemental fluorine.[10]



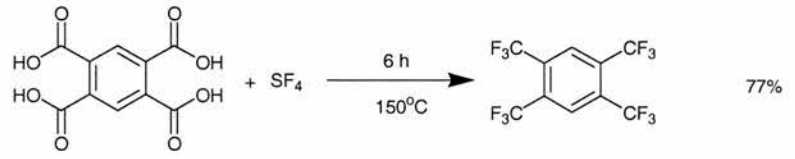
Scheme 2: Monofluorination of benzene with xenon difluoride in the presence of hydrogen fluoride.[11]



Scheme 3: Perfluorination of tetralin (1,2,3,4-tetrahydronaphthalene) using cobalt trifluoride.[12, 13]

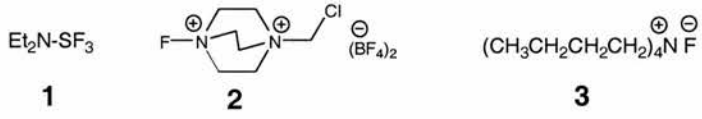


Scheme 4: Reaction of glucosyl bromide with silver fluoride.[14]



Scheme 5: Reaction of an aromatic tetra-acid with sulfur tetrafluoride.[15]

Recently mild, selective and easy to handle fluorinating reagents have been developed, *e.g.*, dimethylaminosulfur trifluoride[16] (DAST) **1**, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[17] (Selectfluor™) **2** and tetrabutyl ammonium fluoride[18] (TBAF) **3**, Figure 1.



1 **2** **3**

Figure 1: Selected fluorinating reagents.

After billions of years of evolution Nature has hardly developed a biochemistry where fluoride is introduced into organic systems. Only about 13 fluorinated natural products are known,[19] compared to over 3000 other halogenated natural products. Some of the fluorinated natural products are shown in Figure 2.[20] This has been attributed mainly to the very low availability of soluble fluoride in surface water. In sea water[5] fluoride concentrations are about 1.3 ppm. Also the low reactivity of solvated fluoride ion in water further mitigates against its involvement in biochemistry. Recently, a fluorinating enzyme of bacterial origin was isolated and characterized.[21, 22] The molecular structure of the enzyme was described and

the mechanism of bio-fluorination, which involves a nucleophilic substitution, was revealed.[23]

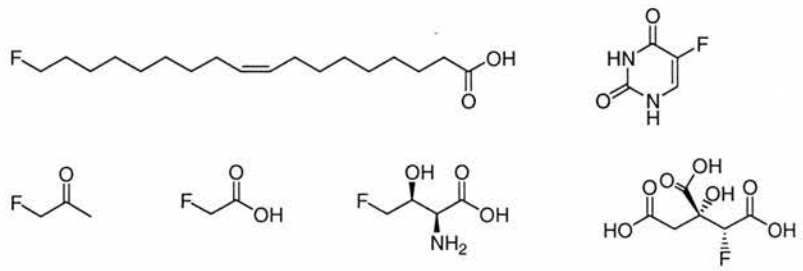


Figure 2: Examples of rare fluorinated metabolites.

In 1930s the first chlorofluorocarbons (CFCs) were prepared.[24] These compounds were used as safe and non-flammable refrigerants and aerosol propellants. Their chemical inertness and high volatility made these materials technologically attractive, however they persist in the atmosphere for many years.[25] At altitudes of 20-40 km these compounds undergo photolytic dissociation to form chlorine radicals, which can catalyse the destruction of ozone and oxygen radicals in the atmosphere. The global use of CFCs caused a rapid depletion of the ozone layer mostly in the Antarctic region.[26] A series of international agreements such as the Montreal Protocol banned the use of such materials. As a consequence, novel more environmentally friendly hydrofluorocarbon alternatives were developed.[27]

1.2.3 The electronic properties of fluorine

Fluorine and its compounds can exhibit extreme properties. As a natural consequence of being the most electronegative element, some fluorine containing compounds have the distinction of being among the most reactive of all compounds, while others are found among the most inert.

When bonded to other atoms, fluorine always polarizes the bond, drawing electrons towards it. The electron-attracting inductive effect is clearly shown by the enhanced acidity of acetic acid and its fluorinated derivatives, Table 1.[28]

Table 1: pK_a values of acetic acid and its fluorinated derivatives in water at 25 °C.[28]

Compound	CH_3COOH	FCH_2COOH	$F_2CHCOOH$	F_3CCOOH
pK_a	4.75	2.66	1.24	0.23

The electron withdrawing ability of the fluorine atom is also evident from a comparison of the substituent constant, σ, based on the method of Hammett.[29] A series of typical σ parameters is given in Table 2.

Table 2: Selected substituent constants, σ, based on the measurement of dissociation constants of substituted benzoic acids.[30]

Substituent	H	F	Cl	Br	I	CF_3
σ_m [a]	0.00[c]	+ 0.34	+ 0.37	+ 0.39	+ 0.35	+ 0.43
σ_p [b]	0.00[c]	+ 0.06	+ 0.23	+ 0.23	+ 0.28	+ 0.54

[a] Substituent constant in *meta* position. [b] Substituent constant in *para* position. [c] The value is zero by definition.

A comparison of the σ_m(F) and σ_p(F) reveals a positive mesomeric effect when fluorine is in the *para* position.

The bonds formed by fluorine are among the strongest covalent bonds known, particularly to carbon and hydrogen, where it forms stronger single bonds than any other element, Table 3. An exception is in F_2 where the F-F bond in fluorine is relatively weak compared to other halogens as fluorines are pulling electron density in opposite directions, Table 4.

Table 3: Bond dissociation energy, *D*, values at 25 °C of some molecules.[31]

D (kJ·mol^{-1})	-H	-F	-Cl	-Br	-I	-OH	-CH_3	-CF_3
-H	436	570	432	366	298	497	439	450
-CH_3	439	472	350	293	239	385	377	423
-CF_3	450	547	362	294	227	-	423	413

Table 4: Bond dissociation energy, *D*, values at 25 °C of some diatomic molecules.[32]

Molecule	H_2	He_2	O_2	N_2	F_2	Cl_2	Br_2	I_2
D (kJ·mol^{-1})	436	3.8	498	945	159	243	193	151

Of all the bonds involving carbon, the C-F bond is the shortest single bond apart from C-H, Table 5.

Table 5: Typical lengths of single covalent bonds.[33]

Single bond	C-H	C-F	C-O	C-C	C-Cl	C-S	C-Br	C-I
Bond length (Å)	1.09	1.39	1.42	1.53	1.79	1.82	1.94	2.13

1.2.4 Steric effect of fluorine

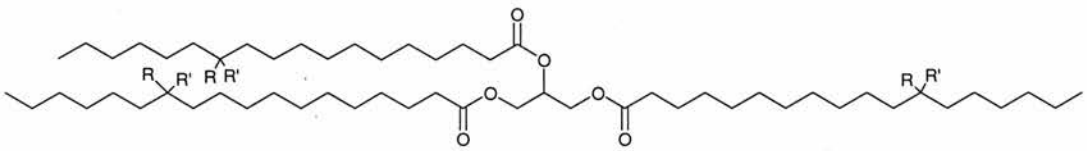
The van der Waals radii, calculated from X-ray diffraction data, serve as a good parameter to judge the size of atoms and groups. It can be seen from Table 6 that the size of a fluorine atom in molecules lies between the size of hydrogen and oxygen. Very often substitution of hydrogen or hydroxyl for fluorine introduces only minor steric perturbations into a molecule.

Table 6: The van der Waals radii, r_w, and contributions to van der Waals volumes, V_r, of selected bound atoms and groups.[34, 35, 36]

Atom / Group	-H	-F	-O-	-Cl	-Br	-I	$-CH_3$	$-CF_3$
r_w (Å)	1.20	1.47	1.52	1.76	1.85	2.01	2.01	2.7
V_r (Å^3)	5.48	9.50	9.13	19.3	23.9	31.8	22.7	35.4

In one study a single fluorine substitution in the hydrocarbon chain of stearic acid had virtually no excess area demand in the molecular ordering of the compound. This was observed by scanning tunnelling microscopy when the fatty acid was adsorbed onto graphite.[37] Enzyme substrate analogues, where one hydrogen is replaced by fluorine usually retain a high affinity for their target protein.[38]

Replacement of a methylene for a difluoromethylene group can be much more dramatic than the single substitution. For example various tristearins containing one or two fluorine substitutions at the C-12 methylene groups of the hydrocarbon chain were synthesised and their melting points, polymorphic phase behaviour and X-ray powder diffraction pattern were compared with unsubstituted tristearin **4**, Figure 3.[39]



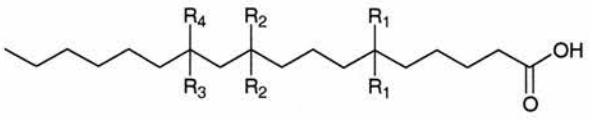
4	R= R'= H	mp 72 °C
5	R= H, R'= F	mp 73 °C
6	R= R'= F	mp 58 °C

Figure 3: Melting point of tristearin **4** and its fluorinated analogues **5** and **6**.

Substitution of one fluorine atom at C-12, **5**, has very little effect on the melting point and other characteristics when compared to **4**, however the introduction of second fluorine, **6**, induces a significant lowering of the melting point and the

polymeric phase behaviour and X-ray powder diffraction pattern become quite different (data not shown).[39]

The stability of Langmuir films of the fluorinated stearic acids was also investigated, Figure 4.[40] 12-Fluorostearic acid, **8**, like stearic acid, **7**, formed a stable monolayer on the surface of an aqueous subphase and the area occupied by each molecule was 21 $Å^2$ and 23 $Å^2$ respectively. However the monolayer for 12,12-difluorostearic acid, **9** was unstable and reorganised rapidly to a bilayer indicating increased disorder, Figure 5.



	R_1	R_2	R_3	R_4
7	H	H	H	H
8	H	H	H	F
9	H	H	F	F
10	H	F	H	H
11	F	H	H	H

Figure 4: Stearic acid and its fluorinated analogues.

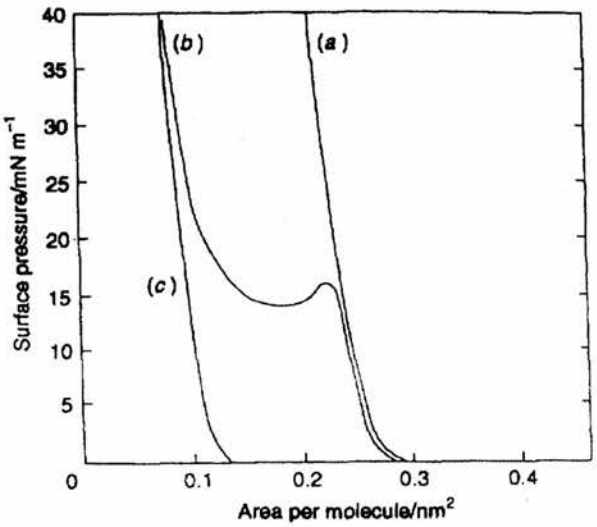


Figure 5: Langmuir isotherms for 12,12-difluorostearic acid **9** showing condensed pressure versus area curves for three successive compressions: (a) first; (b) second and (c) third compression.

Langmuir isotherms for 10,10-difluorostearic acid, **10**, also displayed characteristics initially of a monolayer which collapsed on the second compression and reorganised to a bilayer/multilayer indicated by the plateau in that isotherm, Figure 6. The bilayer remained stable for subsequent compressions. At lower temperatures (15 °C) a transition occurs where successive compressions result in an incremental reduction in the surface area with each compression, until a bilayer is fully established (data not shown).

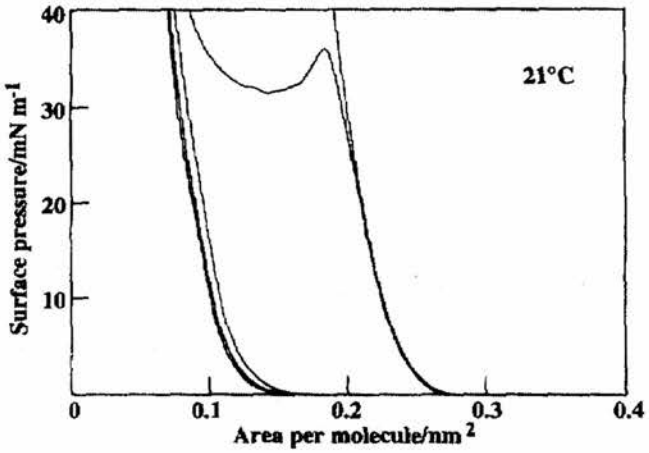


Figure 6: Langmuir isotherms for 10,10-difluorostearic acid **10** showing condensed pressure versus area curves for repeated compressions at 21 °C.

6,6-Difluorostearic acid, **11**, generates the expanded isotherm shown in Figure 7, indicating a conformationally more dynamic monolayer, which again reorganises on subsequent compressions. This behaviour is not observed in singly fluorinated fatty acids.

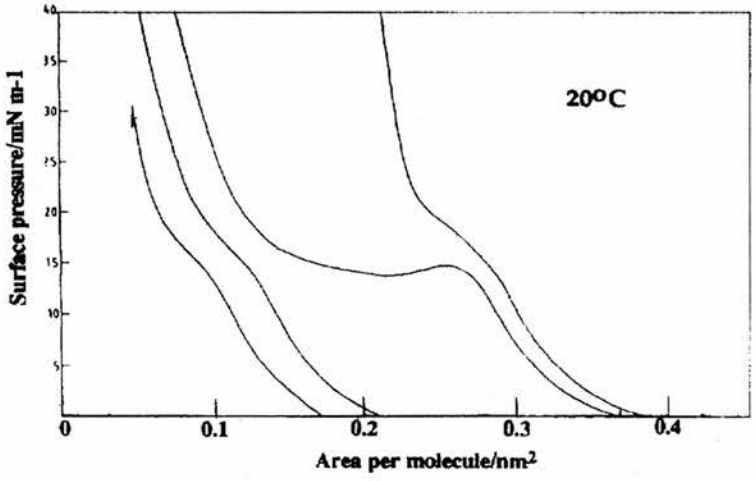
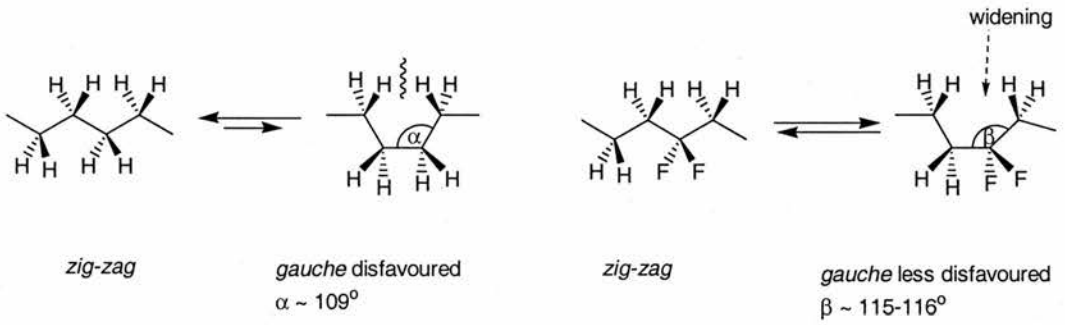


Figure 7: Langmuir isotherms for 6,6-difluorostearic acid **11** showing condensed pressure versus area curves for repeated compressions at 20 °C.

The progressively lower stability of monolayers in the series of acids **9**, **10** and **11** can be explained by a combination of steric effect and conformational differences

between the C-CH_2-C and C-CF_2-C systems. *Ab initio* calculations[41] predict, and X-ray results[42] suggest, that the C-CF_2-C angle in the chain widens to at least 115-116°. In hydrocarbon chains *gauche* conformations are disfavoured due to 1,4-hydrogen interactions, so the preferred conformation is *zig-zag*, Scheme 6. However in a chain containing a CF_2 group the widening of the angle increases the 1,4-hydrogen distance and relaxes those interactions, making the *gauche* conformations lower in energy. Thus these chains display a higher degree of conformational flexibility, which destabilises the integrity of the monolayer in the acids **9**, **10** and **11**.

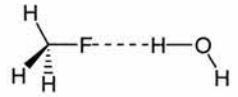


Scheme 6: Schematic representation of 1,4-hydrogen interactions and the preference for *gauche* or *zig-zag* conformations.

Based on a comparison of van der Waals volumes (Table 6) the CF_3 group is at least one and a half times larger than the CH_3 group. Other assessments suggest a steric influence close to that of an isopropyl group.[43, 44] However there are several cases in asymmetric synthesis[45] where the directing influence of the CF_3 group has been assessed relative to other substituents and a close analogy with the phenyl ring or even a *tert*-butyl group has been found. The origin of this large steric effect is not obvious but must be attributed to steric as well as polar and electrostatic influences arising in a given situation.

1.2.5 Fluorine as a hydrogen bonding acceptor

Recent theoretical calculations[46] have measured the strength of an optimum F····H bond to be 10 kJ·mol^{-1} in an adduct between fluoromethane and water **12** as shown in Figure 8.



12

Figure 8: Depiction of an F···H interaction in an adduct of fluoromethane and water **12**.

This 'hydrogen bonding' is considerably weaker then the O····H hydrogen bonds, which are estimated[47] to be ca. 21 kJ·mol^{-1}, so clearly fluorine is a poorer hydrogen bond acceptor than OH group due to its greater electronegativity and consequently the lower polarizability of fluorine over oxygen.[48] Intra- and inter-molecular C-F····H-C interactions have been observed in some other compounds but statistically they are infrequent.[49, 50]

1.2.6 The fluorine *gauche* and *cis* effects

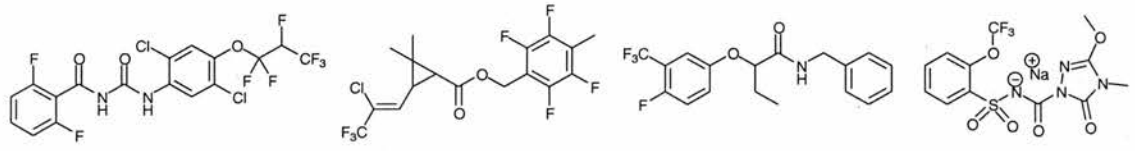
The *gauche* effect recognises that the lowest energy conformation for 1,2-difluoroethane has the fluorine atoms *gauche* rather than *anti* parallel[51, 52, 53] to each other, as illustrated in Scheme 7. The *cis* effect is probably related in origin to the *gauche* effect, and recognises that the *cis* geometric isomer of 1,2-difluoroethene is more stable than the *trans* by about 4-8 kJ·mol^{-1}. Various hypotheses exist to rationalise these observations.[54, 55]

2-4 kJ.mol^{-1} *cis* more stable than *trans* by 4-8 kJ.mol^{-1}

Scheme 7: The *gauche* and *cis* effects favour a *syn* relationship between vicinal fluorine atoms.

1.2.7 Fluorinated biologically active compounds

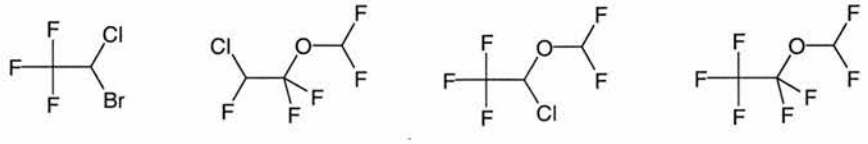
Fluorine atoms and fluorinated groups in bioactive compounds can alter the chemical and physical properties with respect to their non-fluorinated analogues. In agrochemicals (e.g. Figure 9) fluorine substitution has served as a tool to increase lipophilicity or resistance towards metabolic decomposition.



Lufenuron insecticide | *Tefluthrin* insecticide | *Beflubutamid* herbicide | *Flucarbazone sodium* herbicide

Figure 9: Some examples of fluorinated agrochemicals.[56]

Anaesthesia and consequently medical surgery has been revolutionised by organo-fluorine chemistry and anaesthetics of the past such as ether and chloroform, have now been replaced by non-flammable and more easily handled alternatives such as those shown in Figure 10.[57]



Halothane | Enflurane | Isoflurane | Desfluorane

Figure 10: Some examples of fluorinated anaesthetics.[58, 59]

In 1954 Fried and Sabo prepared the fluorinated steroids, which proved to be considerably more biologically active than the parent steroids.[60] Since then many fluorinated drugs have been marketed as antibiotics, antidepressants, anticancer and antiviral agents, some of them emerging as commercial blockbusters, Figure 11.[61]

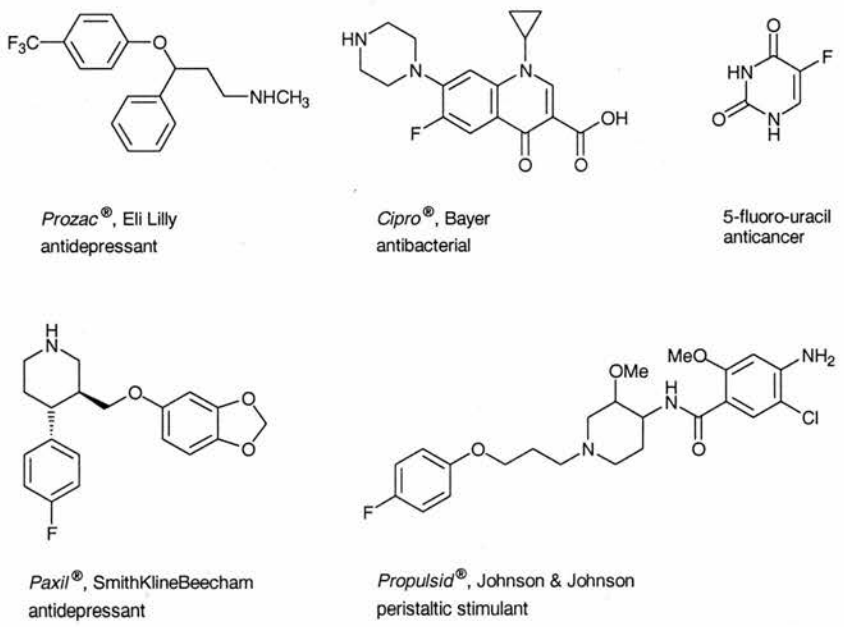


Figure 11: Selected drugs containing fluorine.[62, 63]

1.2.8 Perfluorinated (fluorous) compounds

Perfluorinated systems are compounds containing only carbon and fluorine. This class of compounds was first synthesised over 60 years ago and they have since been utilised in a variety of industrial applications.[57, 64] These compounds are entirely synthetic and they are usually prepared by reaction of hydrocarbons with metal or non-metallic fluorides (e.g. Scheme 3), by halogen exchange or by direct fluorination with elemental fluorine. As mentioned above the C-F bond is very

strong (Table 3 and Table 5) and it becomes shorter and stronger as successive fluorines are added, as illustrated in Table 7.

Table 7: Bond lengths and bond dissociation energy, *D*, of C-F bond for fluorinated derivatives of methane[65, 66]

	CFH_3	CF_2H_2	CF_3H	CF_4
Bond length (Å)	1.39	1.36	1.33	1.32
D ($kJ \cdot mol^{-1}$)	448	459	477	485

As a consequence perfluorinated compounds are much more thermally and chemically stable than hydrocarbons. For example the predicted atmospheric lifetime of perfluoroalkanes is more than 2000 years, however they are not ozone depleting.[67]

Since the molecular weight of a fluorocarbon is considerably higher than the corresponding hydrocarbon we might anticipate boiling points to be increased. It can be seen from Figure 12 that this is so only for perfluorocarbons with carbon number up to three.[68] After that a reverse effect occurs.

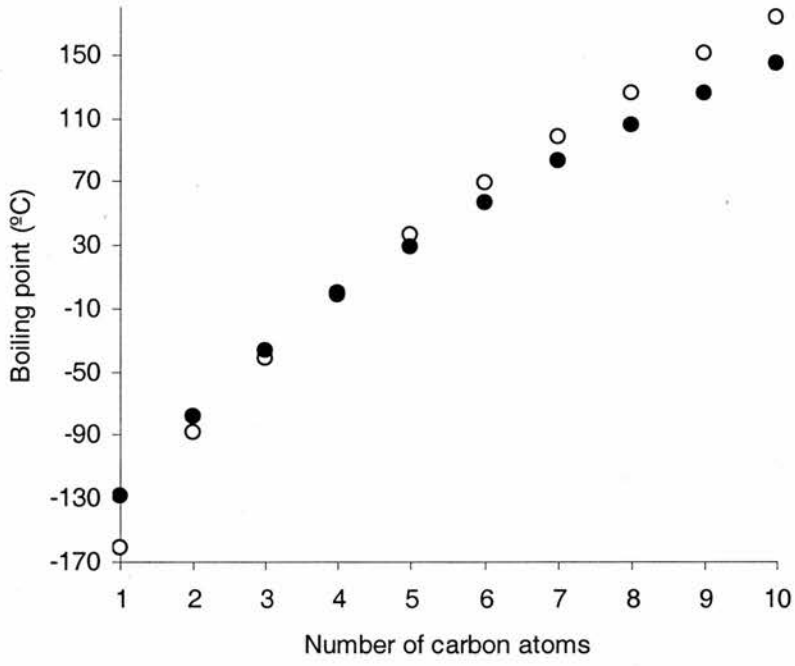


Figure 12: Relation between boiling points and number of carbon atoms of linear hydrocarbons (○) and perfluorocarbons (●).[68]

Among other peculiar properties of perfluorocarbon fluids is their extremely non-polar character (discussed later), low refractive index (polarizability), low surface tension, high compressibility, high density and high vapour pressure.[69] In addition these compounds are non-toxic and non-flammable. Fluorocarbon fluids dissolve large quantities of gases, particularly carbon dioxide and oxygen and have been investigated as temporary intravascular respiratory gas-carriers and tissue oxygenated fluids, so called 'blood substitutes'.[70] Fluorocarbon liquids are immiscible with aqueous-based systems including blood, but they can be injected intravascularly as emulsions stabilised by the addition of fluoro-surfactants. Perfluorocarbon fluids are not metabolised in the body and they are excreted mainly as a vapour through the lungs. One such emulsion, a commercial

perfluorooctyl bromide-based formulation, Oxygent™ is in advanced clinical trials.

Fluoropolymers have found wide spread use in applications ranging from non-stick coatings on cookware (Teflon®), waterproof clothing (Gore-tex®) and as high performance lubricants.

1.3 Fluorous separation technologies

The yield and practicality of every reaction is limited not only by the efficiency of the reaction but also by the ability to separate and recover the product from the reaction mixture. In the laboratory, the synthetic chemist generally spends more time trying to separate and purify products than actually conducting chemical reactions. In the chemical industry separation steps and waste management are one of the most time consuming and expensive operations. Over the last few decades there have been improvements in the purification techniques and the best processes allow products to be isolated by using simple workup techniques such as evaporation, extraction and filtration. There is a tendency to avoid any subsequent chromatographic purification step, especially when working with larger quantities of organic compounds.

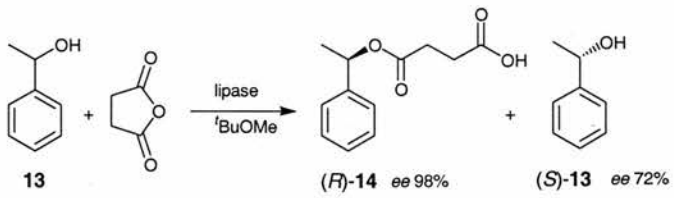
In an ideal purification protocol the product is partitioned into a different phase from everything else that is present in the final reaction mixture. This can be achieved by phase labelling where a substituent is attached to the substrate such that the subsequent product can be extracted more efficiently into a given phase.[71] Ideally, phase labelling should not compromise the reaction, identification and analysis stages of a synthetic step. The most common phase labels are: ionised groups, polymers, dendrimers or highly fluorinated groups.

1.3.1 Ionised groups in phase labelling

1.3.1.1 Acid-base chemistry

Acid-base extractions have long been used for workup and purifications. Protonation or deprotonation changes the properties of the product and transfers

molecules from the organic to the aqueous phase in liquid/liquid extractions. For example both enantiomers of enantiomerically enriched 1-phenylethanol **13** were obtained on a kilogram scale from the racemate by enzymatic acylation with succinic anhydride in organic solvent. Extraction with $NaHCO_3$ separated the acylated product (*R*)-**14** from the unreacted alcohol (*S*)-**13** as illustrated in Scheme 8.[72]



Scheme 8: An example of acid-base, aqueous-organic extraction to separate enantiomers.[72]

1.3.1.2 Ion exchange chromatography

Ion exchange chromatography is a type of solid-phase separation where a mixture containing neutral compounds and an ionisable product is loaded onto an ion exchange column. The ionic compound is fixed to the column by electrostatic interactions. The neutral impurities are eluted immediately with a suitable solvent. Subsequent elution with either acidic or basic solvent then provides a second liquid phase to release the ionic compounds from the column.[73]

1.3.1.3 Ionic liquids

Ionic liquids represent salts with a low melting point (<100 °C). Their vapour pressure is negligible below their decomposition temperatures so ionic liquids used as reaction media are not lost by evaporation. Some ionic liquids show liquid behaviour over a range of several hundred degrees centigrade and thus they can be employed over a wide temperature range. The common classes of ionic liquids are:

alkyl ammonium salts, alkyl phosphonium salts, *N,N'*-dialkyl imidazolium salts and *N*-alkyl pyridinium salts, Figure 13.[74]

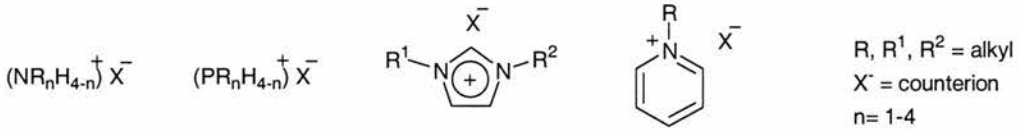
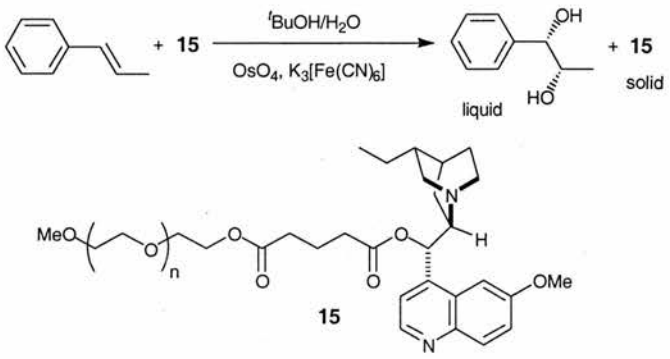


Figure 13: Common classes of ionic liquids.

Ionic liquids with non-coordinating anions represent highly polar organic solvents that dissolve polar transition-metal complexes without affecting their properties. The starting materials are either dissolved in an organic solvent or used as neat liquids. The reactions are carried out with vigorous stirring and/or heating of the biphasic system. Separation of products from the immobilised catalyst is then achieved by liquid/liquid extraction or distillation of the volatile products. Unless the starting materials are at least partially soluble in the ionic liquid then the reactions are usually very slow.[75] None-the-less ionic liquids are attracting a lot of attention at the moment in process technology.

1.3.2 Polymers in phase labelling

Polymer-bound reagents and catalyst are becoming increasingly popular. They allow straightforward purification by filtration. Reagents attached to 'soluble polymers' represent an especially useful class, because they can be made soluble during the reaction stage, but are precipitated at the purification stage by changes in the solvent or the temperature.[76] The most popular and useful reagents to date in this class are bound to polyethylene glycol ethers (PEGs).[77] For example the PEG-conjugated catalyst for asymmetric dihydroxylation **15** is readily separated from the products and recovered for reuse by precipitation, Scheme 9.[78]



Scheme 9: An example of polymer tagged catalyst **15** for asymmetric dihydroxylation.

Solid phase synthesis was the first significant strategic alternative to traditional liquid/liquid extraction in organic synthesis and represents an ideal case of phase planning. It has been used widely in peptide and oligonucleotide synthesis, synthesis of libraries of small compounds and natural products.[79, 80, 81] A small organic molecule is initially attached through a covalent bond to a polymer. This is a phase-labelling event and most applications make use of insoluble polymers. The reaction is then conducted at the solid-liquid interface and an excess of reagents can be used. The purification is very easy; the insoluble polymer with bound product is filtered from the soluble reaction components. The limitations are relatively low loading capacities, a heterogeneous reaction and problems with identification and analysis. However new strategies have emerged to overcome these limitations.

1.3.3 Dendrimers in phase labelling

In dendrimer synthesis[82] the substrate is covalently attached to a dendrimer and after the reaction the dendrimer tagged product is separated from the small molecules by size exclusion chromatography. In size exclusion chromatography a

suitable support is charged with the mixture to be purified and it is then eluted with a solvent. Smaller molecules are retained better by the column, while larger molecules move faster. The purification tends to resemble a filtration rather than a chromatographic separation. Dendrimers are usually soluble in organic solvents so the reaction takes place under homogeneous conditions. Also the loading level of substrates on a dendrimer is generally higher than that of a typical polymer.

1.3.4 Highly fluorinated groups in phase labelling

It has been know for half a century that perfluorocarbons are relatively insoluble in their hydrocarbon analogues and this solubility is temperature dependent.[83] Moreover they are usually insoluble in other polar organic solvent and in water.[84] This is due to their non-polar character and their inability to form hydrogen bonds with protic solvents.[85] Highly fluorinated solvents and compounds that partition into them form a separate phase called the 'fluorous phase', in which organic and inorganic compounds have little or no tendency to dissolve. Three types of liquid/liquid extractions are therefore possible: 'fluorous/organic', 'fluorous/aqueous' and 'fluorous/organic/aqueous'.

1.3.4.1 Perfluorinated solvents as a reaction media

Perfluorocarbons have been used as an inert reaction media for esterification, transesterification and related reactions that give small polar molecules like methanol or water as co-products. These are rapidly expelled in a Dean-Stark trap shifting the equilibrium towards the target compounds.[84] Oxygen saturated perfluorohexane has been found to be an ideal reaction medium for the oxidation of organozinc bromides to hydroperoxides.[86] Fluorous solvents have been used as

phase screens between reagent and reactant phases and they can regulate transport of reagents towards reactants. For example when perfluorohexane is mixed with a heavier reagent like bromine, two phases result with the reagent at the bottom. When an organic solvent containing a substrate is added, the fluorous solvent locates in the middle and acts as a liquid membrane that prevents mixing but permits passive transport of the reagent from the bottom to the top layer. As the reagent is consumed the bottom phase vanishes. Bromination of olefins[87] and other reactions[88] have been examined based on this concept. Alternatively a U-tube can be used to hold a lower fluorous phase separate from an upper reagent and organic phases.[88] The limitation which restricts the wider use of these methods is that only a small number of reagents are able to pass through the fluorous layer. Very recently immobilized baker's yeast reduction of ketones in a fluorous media was described.[89]

However, fluorous solvents can also perform another function apart from being inert reaction media. They can constitute another phase, which is orthogonal to the organic and aqueous phases.

1.3.4.2 Fluorous biphase systems

The term 'fluorous' was introduced as an analogue to 'aqueous' to describe the behaviour of highly fluorinated compounds.[90] As summarised in Table 8 a variety of 'fluorous' solvents are commercially available.[91] They are commonly immiscible with organic solvents, however certain solvent mixtures containing hydrophobic organic solvents and 'fluorous' solvents become miscible at elevated temperatures, Table 9.[91, 92, 93, 94]

Table 8: Representative commercially available 'fluorous' solvents.[91]

Solvent	Common name	Formula	Bp/mp (°C)
perfluoro(methylcylohexane)	PFMC	$CF_3C_6F_{11}$	76.1/-44.7
perfluoro-1,2-dimethylcyclohexane	-	C_8F_{16}	101.5/-56
perfluoro-1,3-dimethylcyclohexane	-	C_8F_{16}	101/-55
perfluoro-1,3,5-trimethylcyclohexane	-	C_8F_{18}	125/-
perfluorohexane(s)[a]	FC-72	C_6F_{14}	57/-87
pefluoroheptane(s)[a]	FC-84	C_7F_{16}	82/-78
perfluorooctane(s)[a]	FC-77	C_8F_{18}	103-105/-
perfluorodecalin[b]	PFD	$C_{10}F_{18}$	142/-10
1-bromoperfluorooctane	-	$C_8F_{17}Br$	142/-
perfluorotributylamine	FC-43	$C_{12}F_{27}N$	178-180/-50
perfluorotripentylamine	FC-70	$C_{15}F_{33}N$	210-220/-25
perfluorotrihexylamine	FC-71	$C_{18}F_{39}N$	250-260/33
perfluoropolyether M~410	Galden HT70	[c]	70/-
perfluoropolyether M~460	Galden HT90	[c]	90/-
perfluoropolyether M~580	Galden HT110	[c]	110/-

[a] Mixture of isomers. [b] Mixture of *cis* and *trans*.

[c] General formula $CF_3[OCF(CF_3)CF_2]_m[OCF_2]_n\text{-}OCF_3$.

Table 9: Fluorous solvent miscibility data.

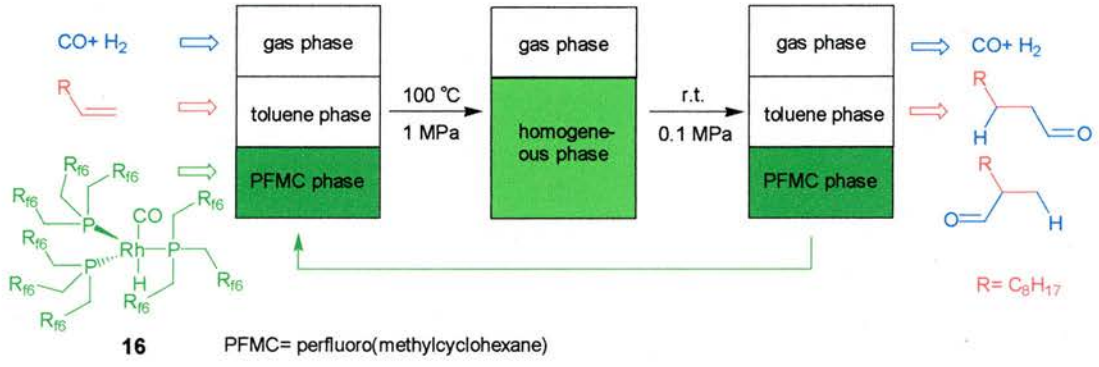
Fluorous solvent	Organic solvent	Volume fraction of organic solvent	Miscibility temperature (°C)
PFH[a]	benzene	0.594	113.5[c]
PFH[a]	chloroform	0.578	78.5[c]
PFH[a]	CCl_4	0.578	58.7[c]
PFH[a]	n-heptane	0.54	50.0[c]
PFH[a]	isooctane[b]	0.55	23.7[c]
PFMC	benzene	0.50	84.9[c]
PFMC	chloroform	0.50	50.1[c]
PFMC	CCl_4	0.50	26.7[c]
PFMC	toluene	0.50	88.6[c]
PFMC	n-hexane	0.50	r.t.[d]
PFMC	n-pentane	0.50	r.t.[d]
PFMC	ether	0.50	r.t[d]
PFD	toluene	0.50	64[d]

[a] *n*-Perfluorohexane. [b] 2,2,4-Trimethylpentane. [c] Consolute temperature. [d] Experimental observation (not a consolute temperature).

1.3.4.3 Perfluoro-tagged catalysts (fluorous biphase catalysis)

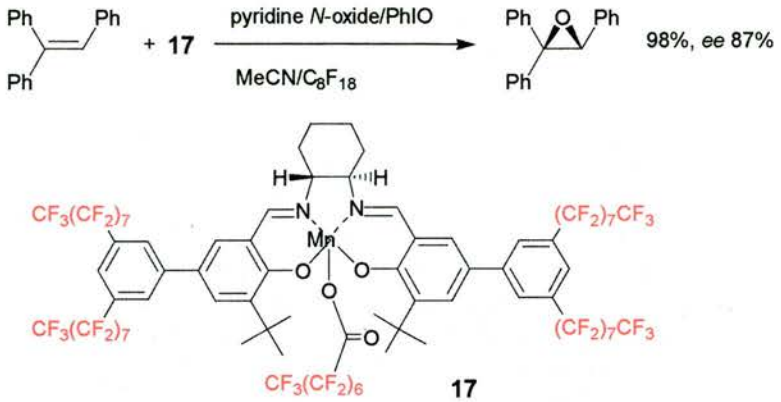
The concept of fluorous biphase catalysis, which represents a new paradigm in separation in homogeneous catalysis, is only a decade or so old. In a 1991 PhD thesis[95] that was not readily available or published in the open literature, M. Vogt presented the first conceptual aspects of fluorous biphase catalysis with an emphasis on oligomerization of alkenes, oxidation of alkenes, hydroformylation of olefins, and telomerization of dienes. It was not until 1994, when Horváth and Rábai published the first archival paper[96] on this simple but elegant concept, that the global chemical community took notice of this novel advance in the more general area of biphasic catalysis. They prepared a catalyst which had high affinity for the fluorous phase and used this catalyst for a hydroformylation reaction. The

catalyst **16** was made fluorous compatible by attaching perfluoroalkyl chains, termed 'fluorous ponytails' onto a phosphine liqand of the ruthenium complex. The reaction was conducted in a biphasic system of toluene and perfluoro(methylcyclohexane) and upon completion the two phases separated. The hydroformylation products were recovered by evaporation of the toluene phase. The fluorous rhodium catalyst **16**, which was soluble only in the fluorous phase, could be recovered and reused in a subsequent reaction, Scheme 10.[96, 97]



Scheme 10: Hydroformylation of 1-decene using fluorous catalyst **16** in the fluorous biphase system.

Since then fluorous biphase catalysis have been successfully demonstrated for hydroformylation,[97] hydrogenation,[98, 99] hydride reduction,[100] hydroboration,[101, 102] alkene oxidation[103, 104] palladium catalysed reactions[105, 106] and other reactions.[107] Numerous oxidation reactions have been carried out under fluorous biphasic conditions because of the high solubility of oxygen in the perfluorinated solvents. For example a perfluoro-tagged chiral (salen)manganese complex **17** has been used for asymmetric epoxidation reactions, Scheme 11.[108, 109, 110]



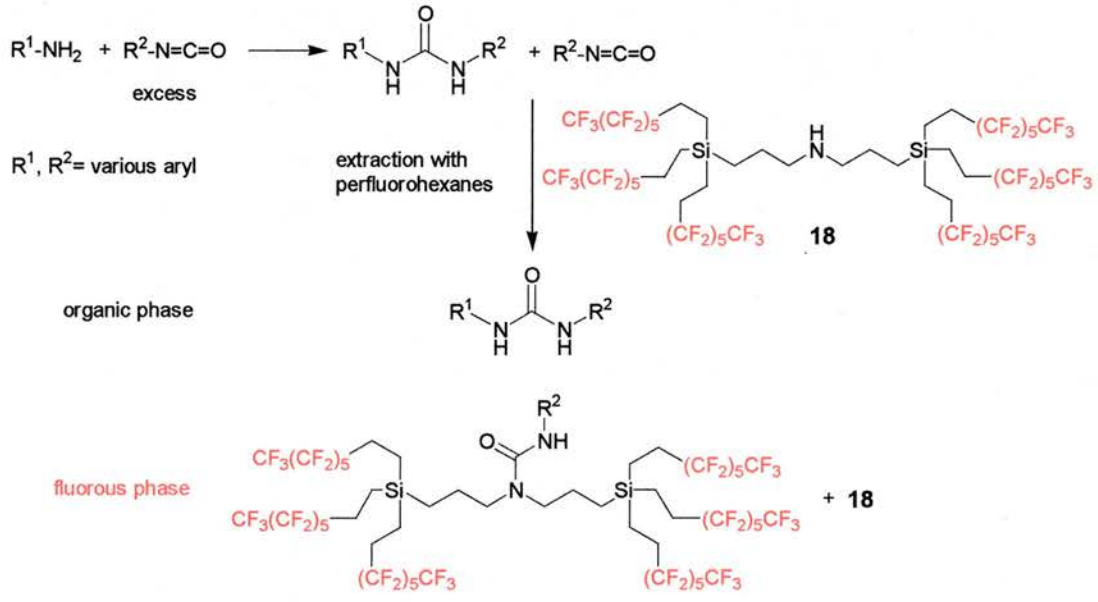
Scheme 11: Assymmetric epoxidation of triphenylethene with PhIO/pyridine N-oxide catalysed by chiral fluorous salen(MnIII) complex **17** under fluorous biphase conditions.

Recently, Gladysz and co-workers employed the fluorous phosphine $P[(CH_2)_2(CF_2)_7CF_3]_3$ as a catalyst for conjugate addition of alcohols to the triple bond of methyl propiolate.[111, 112] During this reaction, the phosphine was dissolved in octane at 80 °C. Subsequently, the catalyst was precipitated at -20 °C and separated by decantation. No fluorous solvent was needed. They have also shown that some other fluorous catalysts developed for various reactions exhibit these 'thermomorphic' properties. They are virtually insoluble in organic solvents at low temperatures but become soluble enough to catalyse reactions at elevated temperatures.[112]

1.3.4.4 Perfluoro-tagged reagents

By analogy to fluorous biphase catalysis where the catalyst is immobilised in the fluorous phase, perfluoro-tagged reagents can be used for easy separation of by-products and excess reagents from the product by extraction into fluorous solvents. This approach is especially attractive in combinatorial syntheses of libraries of compounds or if the reagents or by-products are toxic, expensive or difficult to remove.

For example fluorous trialkyl tin reagents have been used for radical dehalogenations[113] and Stille coupling reactions,[114] perfluorinated ylides were used in Wittig reactions[115] and fluorous amine **18** was used to scavenge excess isocyanate from an automated synthesis of a library of ureas, Scheme 12.[116]



Scheme 12: Application of fluorous amine **18** as an isocyanate scavenger in the synthesis of ureas.

1.3.4.5 Perfluoro-tagged products (fluorous synthesis)

Fluorous phase labelling can be applied not only to catalysts and reagents, but also to substrates. The approach is conceptually similar to the soluble variant of solid-phase synthesis. A substrate is attached to a fluorous label that has sufficient fluorine content to draw the labelled substrate and its subsequent products into the fluorous phase. After the reaction the fluorous product is separated from the non-fluorinated compounds by either fluorous/organic liquid/liquid extraction (Figure 14) or by fluorous solid/liquid extraction (see Section 1.3.4.6).

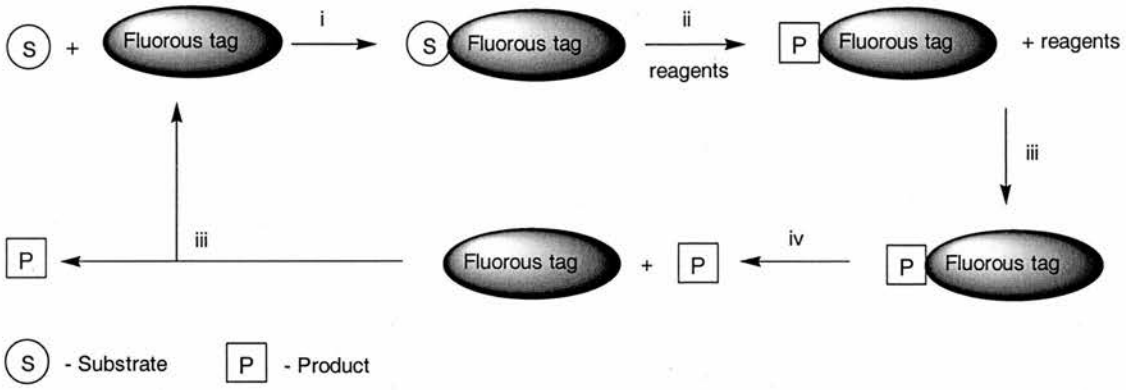
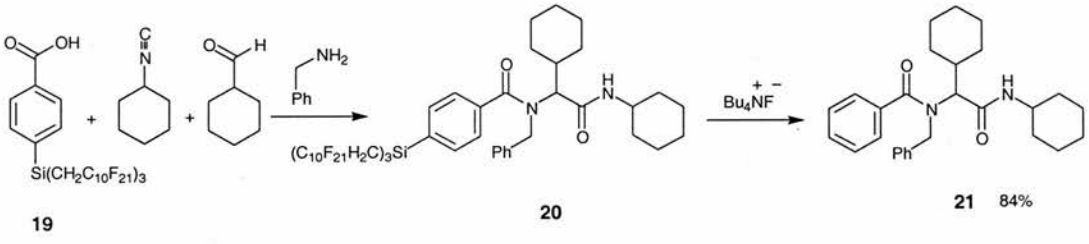


Figure 14: Schematic representation of fluorous phase synthesis. i) attachment of fluorous label onto a substrate; ii) reaction with excess of reagents to form a fluorous-tagged product; iii) liquid/liquid fluorous/organic separation; iv) detachment of the fluorous tags. Note that the fluorous-tagged product can be used in subsequent reaction steps and that step iv can be performed at the end of the synthesis.[117]

While permanent labelling is necessary for catalysts or reagents, only temporary attachment of the fluorous tag to the substrate is required in fluorous synthesis. For example a fluorous acid **19** was subjected to an Ugi multi-component reaction, where a very large excess of the other three components can be used. The desired fluorous product **20** can be separated from the starting reagents and partially reacted compounds by liquid/liquid extraction to give the amide. Finally desilylation provides the Ugi product **21**, Scheme 13.[118]



Scheme 13: Use of a fluorous silyl protecting group in Ugi reaction.[118]

1.3.4.6 Fluorous solid-phase extraction

Fluorous solid-phase extraction is an alternative to liquid/liquid extraction where the crude reaction mixture is loaded onto a column containing fluorous reverse-phase silica gel (FRPSG).[119] Organic compounds cannot interact with the column and are eluted instantly using a polar solvent. On the other hand, weak non-specific interactions that allow one fluorous compound to dissolve in another help to hold the fluorous-tagged compounds on the column. These interactions are disrupted by elution with a less polar solvent.[71] The fluorous reverse-phase silica gel can be prepared by silylation of silica gel with $ClSi(Me)_2CH_2CH_2C_6F_{13}$ or $(EtO)_3SiCH_2CH_2C_8F_{17}$.[120] The fluorous solid-phase extraction is simpler than traditional chromatography and operationally resembles filtration.[121] Solid-phase extraction with FRPSG is now beginning to replace liquid/liquid fluorous extraction procedures mainly because it is successful with fewer fluorine atoms in the fluorous domain of the tagged compound compared to liquid/liquid extractions. In the latter case heavily fluorinated compounds (more than 60% fluorine content by weight) must be used in order to secure favourable partitioning. The technique has been used in reactions with fluorous reagents,[122] scavengers,[123] catalysts,[120] protecting groups[124, 125] and in fluorous synthesis.[126, 127]

So called fluorous mixture synthesis[128] is a technique which allows the preparation of libraries of compounds in a homogeneous solution yet still allows the reliable separation of individual products at the end. A typical fluorous mixture synthesis consists of:

1. Individual tagging of a set of substrates with a corresponding set of homologous fluorous tags with increasing fluorine content.

2. Mixing the tagged substrates together.

3. Multi-step synthesis which can be a combination of one-pot reactions or split-parallel reactions.

4. Separation of the mixture of tagged products by preparative HPLC over a FRPSG column to give separated tagged products.

5. Removal of fluorous tags to release final products.[121, 129]

This principle was demonstrated for the synthesis of a 560-member library of Mapicine analogues[128, 129] and for the synthesis of a stereoisomer library of Murisolin, in order to assign the absolute configuration of the natural product.[130]

1.3.4.7 Fluorophilicity and prediction of partitioning coefficients in fluorous chemistry

The successful application of fluorous biphasic techniques would be substantially aided by the ability to predict *a priori* a given molecule's tendency to dissolve in fluorous media. This is most commonly measured by its partition coefficient, P_i, between fluorous and organic layers (Equation 1) where $c_i(fluorous\ phase)$ and $c_i(organic\ phase)$ are concentrations (in $mol \cdot l^{-1}$ or $g \cdot l^{-1}$) of the solute in the fluorous phase and the organic phase, respectively.

$$P_i = \frac{c_i(fluorous\ phase)}{c_i(organic\ phase)} \qquad \text{Equation 1}$$

The standard system has been proposed,[91, 131] namely the partition of molecules between perfluoro(methylcyclohexane) and toluene at 298 K. The quantity $\ln P_i^o$ is usually referred to as the 'fluorophilicity', f_i^o, Equation 2.

$$f_i^\circ = ln\, P_i^\circ = ln\left[\frac{c_i(CF_3C_6F_{11})}{c_i(CH_3C_6H_5)}\right], \quad T = 298\ K \qquad \text{Equation 2}$$

For the prediction of P for fluorous compounds in fluorous biphasic systems, several qualitative trends have been observed, i.e., longer and branched tails, more

tails or a higher weight percentage of fluorine, all lead to higher partition coefficients. Absence of hydrogen bonding or polar groups, which may interact with the organic phase also increase P.[132]

Several attempts to develop a quantitative relationship between P and various parameters have been made.[131, 132, 133, 134] Kiss *et. al.*[131] suggested an *empirical* relationship containing the Hildebrand solubility parameter of the solute, δ_i, (in $MPa^{½}$) and the molar volumes of the solute, V_i, (in $cm^3 \cdot mol^{-1}$) and the fluorous solvent, V_F, along with two empirical coefficients (A and B), Equation 3.

$$ln\, P_i^{\circ} = \frac{V_i}{V_F}(A + B\delta_i) \qquad \text{Equation 3}$$

The Hildebrand solubility parameter describes the cohesive energy density of the substance and correlates strongly with polarity. It can be calculated from tabulated group contributions of the molar vaporisation energy, ${}^{z}\Delta E$ (in $J \cdot mol^{-1}$) and molar volumes ${}^{z}V$ (in $cm^3 \cdot mol^{-1}$) of individual functional groups within a molecule, Equation 4.[135, 136]

$$\delta_i = \sqrt{\frac{\sum {}^{z}\Delta E}{\sum {}^{z}V}} \qquad \text{Equation 4}$$

Empirical coefficients A and B have been determined by linear regression of the natural logarithm of measured P_i^o of a wide range of partially fluorinated organic compounds (59 compounds). However for a better correlation A and B must be determined for different classes of compounds (i.e. fluorinated alcohols or fluorous tin hydrides), requiring the synthesis of a basis set of molecules for each class of compounds.[131]

Platts have used another *empirical* relation between ln P_i^o and a number of solute descriptors to predict fluorophilicity.[132] A sixth descriptor F, being the weight

percentage of fluorine in a molecule, had to be introduced to obtain good correlations and was found to be the most important descriptor.

Recently a powerful *theoretical* model for the prediction of P_i based on the mobile order and disorder theory has appeared.[134] It requires only the knowledge of the molar volumes (V_i, V_F and V_O), where the subscript i stands for solute, F for fluorous solvent and O for organic solvent, and the modified non-specific cohesion parameters (δ'_i, δ'_F and δ'_O), R is the universal gas constant (in $J \cdot K^{-1} \cdot mol^{-1}$) and T is the working temperature (in K), Equation 5.

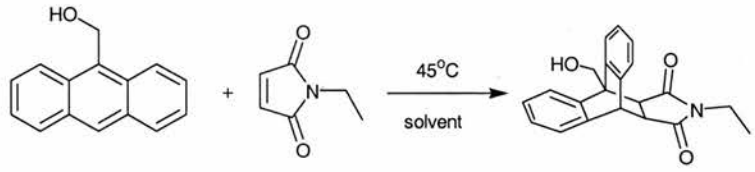
$$\ln P_i = \frac{1}{2}\left[V_i\left(\frac{1}{V_F} - \frac{1}{V_O}\right) + \ln\frac{V_O}{V_F}\right] + \frac{V_i}{RT}\left[\left(\delta'_O - \delta'_i\right)^2 - \left(\delta'_F - \delta'_i\right)^2\right] \qquad \text{Equation 5}$$

The modified non-specific cohesion parameter (δ') used in this expression differs from the Hildebrand solubility parameter (δ), since the former only accounts for the non-specific forces exhibited between similar or different molecules, thus $\delta' \leq \delta$. The functional group contributions to $^z\Delta E'$ and $^zV'$ are also tabulated to determine δ'.[134] Equation 5 has been successfully used to predict P for 88 fluorous and non-fluorous compounds with high accuracy using a standard system of perfluoro(methylcyclohexane) and toluene at 25°C and also for other solvent systems at various temperatures.[134]

1.3.4.8 Hydrophobic and fluorophobic effects

When substances with non-polar regions are dissolved in water, they tend to associate so as to diminish the hydrocarbon-water interfacial area. This 'hydrophobic effect'[137] is a principal contributor to the substrate binding of enzymes and to self-association of amphiphiles in micelles or membranes. It is well established that the rates of certain Diels-Alder reactions in aqueous media

show dramatic accelerations relative to those in organic solvents.[138] Theoretical studies have concluded that the removal of a solvent accessible non-polar surface in the transition state and the enhanced hydrogen bonding of water to the transition state are the main contributors to the rate enhancement.[139] In non-aqueous media, however, solvent effects on Diels-Alder reactions are small. The exceptions are fluorous media in which dramatic rate accelerations have been observed, Scheme 14, Table 10.[140]



Scheme 14: Diels-Alder reaction between 9-hydroxymethylanthracene and (*N*-ethyl)maleimide.

Table 10: Relative rate constants (k_{rel}) for the Diels-Alder reaction between 9-hydroxymethylanthracene and (*N*-ethyl)maleimide at 45°C.

solvent	perfluorohexane[a]	*n*-hexane	acetonitrile	methanol	water
k_{rel}	49.5	7.2	1.0	3.1	206

[a] Perfluorohexane contained 2% (v/v) isooctane for solubilizing starting materials and maintaining stable solutions.

Since fluorous solvents have no hydrogen bond donating capability, the lower rate enhancements compared to water are explained on the basis of solvophobicity alone.[140] Thus reactions with large negative volumes of activation can be expected to be accelerated in fluorous media due to the 'fluorophobic effect'. The fluorophobic effect has also been used in inducing self-assembly of partially fluorinated crown-ethers in fluorous solvents.[141]

1.4 Biocatalysis in organic synthesis

1.4.1 General aspects of biocatalysis

Enzymes are natural catalysts which display remarkable catalytic abilities. They consist of polypeptides constituted from amino acids and operate in cells. In living organisms virtually every chemical reaction is catalysed by an enzyme. The rate enhancements brought about by enzymes are in the range of 5 to 17 orders of magnitude, compared to the corresponding uncatalysed reaction.[142] Enzymes are also very specific, readily discriminating between substrates with quite similar structures. The explanation for these highly selective rate enhancements lies in non-covalent interactions between enzyme and transition state (hydrogen bonds, hydrophobic and ionic interactions) and in chemical reactions which take place between substrate and functional groups on the enzyme. Catalytic functional groups on an enzyme may form a transient covalent bond with a substrate and activate it for further reaction, or some group may be transiently transferred from the substrate to a group on the enzyme. In many cases, these reactions occur only in the enzyme active site. They lower the activation energy by providing an alternative, lower-energy reaction path.

1.4.2 Preparative biotransformations

Man has employed whole cell systems to produce organic compounds since the beginning of history. Probably the oldest known biotransformation is the fermentation of sugar to ethanol by yeast. Modified conditions for this process have allowed the large-scale production of glycerol.[143] Since about 1960, the use of partially purified enzymes as specific catalysts for selected processes has become

hugely significant. Isolated enzymes are typically used for hydrolytic or isomerization reactions. Whole cells are often used for synthetic reactions that require cofactors which are easy to regenerate in metabolically active cells. Both isolated enzymes and whole cells are used in industry today and reaction types span from hydrolysis, condensation, oxidation, reduction, transamination, dehalogenation and many more.[144, 145]

The major synthetic value of enzymes is their selectivity. Enzymes are selective not only in the type of reaction they catalyse, but also in the type of substrate they accept and the position of attack on the substrate. Enzyme catalysed *chemo-, regio-* and *stereoselective* reactions are well documented.[143] There is a number of examples of *enantioselective* enzymatic reactions of one enantiomer of a racemic pair or enantiotopic or diastereotopic group or face attack of a molecule (see Section 1.4.4.1).[143]

The ability of enzymes to catalyse reactions under mild conditions renders them attractive as catalyst in organic synthesis. Enzymes typically function at ambient temperature, atmospheric pressure and neutral pH. In addition the environmental impact of using enzymes is low, particularly when compared to other chemical catalysts, especially those based on transition metals.

1.4.3 Biocatalysis in unnatural media

As long as the use of enzymes is restricted to their natural aqueous reaction media, the scope of bio-conversions, especially for the preparation or production of speciality chemicals and polymers, is limited by a variety of factors. Many such compounds are insoluble in water, and water frequently gives rise to unwanted side reactions and degrades common organic reagents. The thermodynamic equilibria of

many processes are unfavourable in water, and product recovery is sometimes difficult from this medium.[146] Until recently the conventional idea was that enzymes are denaturated in organic solvents.[147] Enzymes generally lose their native structure and thus their catalytic activity in aqueous-organic mixtures. Perversely this is not always the case when an enzyme is suspended in a neat organic solvent containing little or no water.[148] In 1966 Dastol and Price first observed enzymatic activity of crystalline chymotrypsin in anhydrous non-polar organic solvents.[149, 150] More recently it was found that powdered lipase from porcine pancreas catalysed a transesterification between tributyrin (ester of butyric acid and glycerol) and various primary and secondary alcohols in organic media. When the dry lipase is dissolved in phosphate buffer (0.1 M, pH 8.0) at 100 °C it loses its activity almost instantaneously but when placed in the tributyrin-heptanol mixture containing 0.8% and 0.015% of water, its half life at 100 °C is increased to 15 minutes and more than 2 hours respectively.[151] Further experiments examining the role of water in enzymatic reactions in a number of anhydrous polar and non-polar organic solvents concluded that in general enzymes only need a minimum amount of water on the protein surface to retain their catalytically active conformation.[152]

In general, the catalytic activity displayed by enzymes in neat organic solvents is far lower the in water.[153] There are many reasons for this. Proteins are insoluble in almost all organic solvents, so the heterogeneous powder suspensions can exhibit mass-transfer barriers for substrates. The enzyme powders are usually prepared by lyophilisation (freeze-drying) of their aqueous solutions. Very often it is not contact with an organic solvent but the prior dehydratation that causes significant denaturation and results in diminished enzymatic activity in organic solvents. This

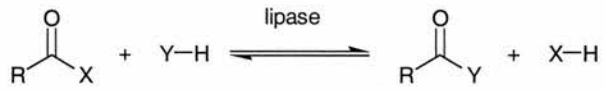
effect can be greatly minimised by dehydrating enzymes in the presence of structure preserving lyoprotectants, such as sugars and poly(ethyleneglycol).[154] The protonation state of the various groups of an enzyme is another important factor for enzyme activity, both in aqueous and organic media. While protonation in water is controlled by adjustment of pH values, this is not the case in organic solvents. A way to control the initial state of enzyme protonation and hence the activity was developed by Zaks and Klibanov,[155] who showed that the enzyme activity in organic solvents was markedly dependent on the pH value of the aqueous solution from which the enzyme was recovered.[156] Alternatively, suitable pairs of crystalline solids (so called solid-state buffers) can be used to control acid-base conditions in low-water organic media.[157] Hydrophobic solvents are usually superior to hydrophilic ones.[158, 159] Thus solvents like heptane, hexane, cyclohexane and toluene are suitable for reactions in which dry enzyme powders are used, while for moderately polar solvents like benzene, chloroform and diethyl ether enzyme immobilisation is recommended for optimal activity. Highly polar solvents like methanol, dioxane, dimethylformamide and dimethyl sulfoxide are not suitable since enzymes are usually deactivated rapidly in these media.

Non-polar organic solvents on the other hand lack the ability to engage in multiple hydrogen bonds with residues on the protein surface. This leads to stronger electrostatic interactions and hence more rigid proteins.

1.4.4 Lipase-mediated reactions

Most of the enzymes used as catalysts for preparative conversions in organic chemistry have been hydrolases and particularly lipases and proteases.[160, 161, 162, 163, 164] Triacylglycerol hydrolases [EC 3.1.1.3], which are termed lipases, have become

one of the most versatile classes of biocatalysts in organic synthesis.[165] This is because lipases can accept a wide range of organic substrates and they work well in organic solvents. Depending on the solvent used, lipases can be applied to hydrolysis reactions or ester synthesis, transesterification and other similar reactions, Scheme 15.



X= OH, OR', SR', OCOR,
Y= OH, OR', SR', NHR'.

Scheme 15: Reactions catalysed by lipases.

Lipases are ubiquitous enzymes and have been found in most organisms. Commercially available lipases are usually prepared by extraction from animal tissue or by cultivation of microorganisms.[165] The activity of many lipases has been found to be low in monomeric substrates but it becomes strongly enhanced once an aggregate (emulsion or micelle) is formed above its saturation limit. This property is quite different from that of the usual esterases acting on water soluble carboxylic ester molecules, and for a long time lipases were considered as a special category of esterases which are highly efficient at hydrolysing molecules aggregated in water.[165]

X-Ray crystallography and kinetic experiments with lipases suggest that this interfacial activation might be due to the presence of an amphiphilic peptidic loop covering the active site of the enzyme in the solution, just like a lid.[166, 167] From the X-ray structure of co-crystals between lipase and substrate analogues, there is strong indirect evidence that, when contact occurs with a lipid/water interface, this lid undergoes a conformational rearrangement which renders the active site

accessible to the substrate as illustrated in Figure 15. However not all lipases having an amphiphilic lid covering the active site show interfacial activation.[168]

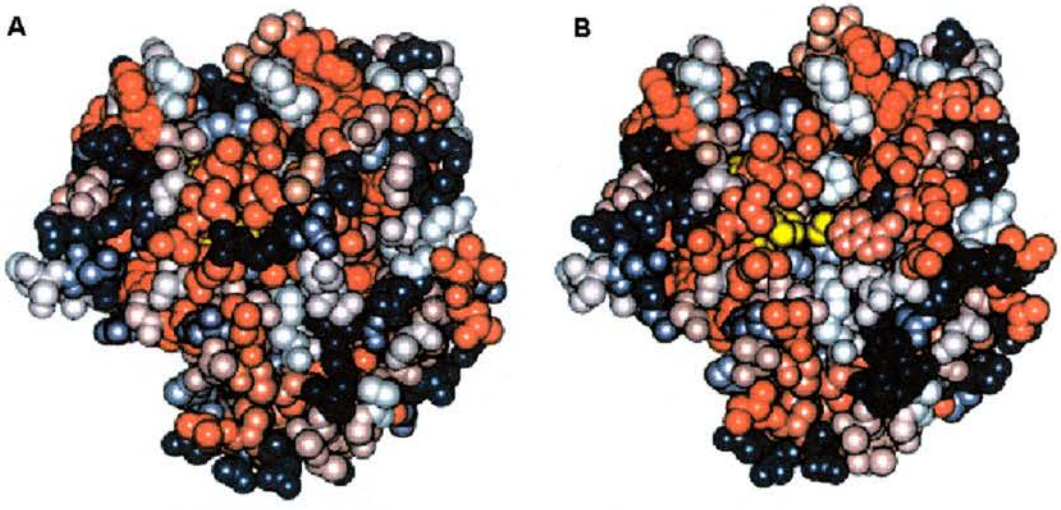


Figure 15: Structure of *Mucor meihei* lipase in space-filling model representation in closed (**A**) and open (**B**) form coloured by decreasing polarity [dark blue (polar) - light blue – white – light red – dark red (non-polar)]. Upon opening the lid, the catalytic triad (yellow) becomes accessible (**B**), and the region binding to the interface becomes significantly less polar.[165, 169]

Lipases catalyse ester hydrolysis by means of a "catalytic triad", composed of a nucleophilic serine residue activated by a hydrogen bond in relay with histidine and aspartate or glutamate.[165] The mechanism of a general lipase catalysed reaction is shown in Figure 16. The activated serine residue attacks the substrate which then becomes covalently bound to the enzyme in an acyl-enzyme complex. The acyl-enzyme complex can then be attacked by an incoming nucleophile to yield the product.[166, 170]

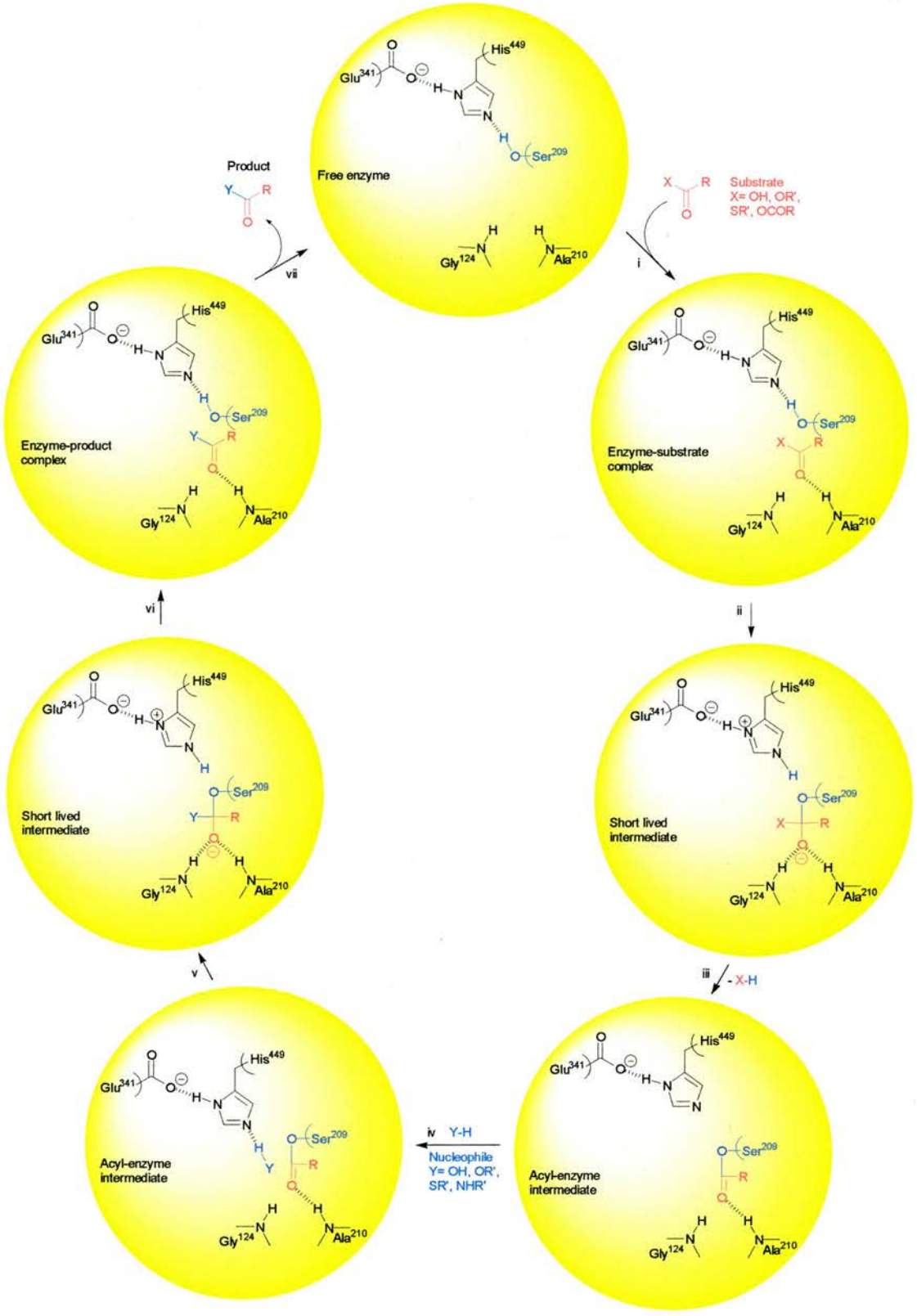


Figure 16: The mechanism of a lipase catalysed reaction.[142] The enzyme active site consists of a "catalytic triad" of serine residue connected with hydrogen bonds with histidine and glutamate or aspartate. The catalytic cycle has seven steps: i) Formation of an enzyme-substrate complex. ii) Acylation of substrate by serine residue to form a short

lived intermediate. The negative charge on the oxygen of the tetrahedral intermediate is stabilised by hydrogen bonding to the amide nitrogens of Gly and Ala residues. iii) Formation of a covalent acyl-enzyme intermediate coupled to cleavage of the ester bond. iv) Activation of a nucleophile in an acyl-enzyme intermediate. v) Deacylation to form a short-lived intermediate. vi) Enzyme-product complex formation. vii) Product formation and free enzyme regeneration. The His and Glu residues provide a general base catalysis of steps ii and v and general acid catalysis of steps iii and vii. The numbering of amino acid residues in this example refers to the lipase from *Candida rugosa*.[171]

1.4.4.1 Lipase catalysed asymmetric transformations in organic solvents

Catalytic asymmetric synthesis is an important and expansive area in organic chemistry. Catalytic enantioselective reactions are usually achieved by either chemocatalysis or biocatalysis. Chemocatalysis is dominated by metal catalysis, however in biocatalysis, lipases prevail.[172] The majority of applications of lipases in catalytic asymmetric synthesis have involved kinetic resolutions of racemates.[160, 161, 162, 163, 164] In an ideal scenario only one enantiomer of the racemic substrate is converted to the product leaving the other enantiomer unchanged. Thus the reaction stops at 50% conversion. However in many cases the difference in reaction rate between the two enantiomers is not large, which causes contamination of the product and unreacted material with the other enantiomer.

The enantioselectivity of a biocatalytic reaction is normally expressed as the E value, a biochemical constant that is for irreversible reactions independent of substrate concentration and the extent of conversion.[158] Enantiomeric excess of the substrate (ee_S) and the product (ee_P), extent of convertion (c) and the E value are linked through Equation 6 and Equation 7.

$$c = \frac{ee_S}{ee_S + ee_P}$$ Equation 6

$$E = \frac{ln[(1-c)(1-ee_S)]}{ln[(1-c)(1+ee_S)]} = \frac{ln[1-c(1+ee_P)]}{ln[1-c(1-ee_P)]}$$ Equation 7

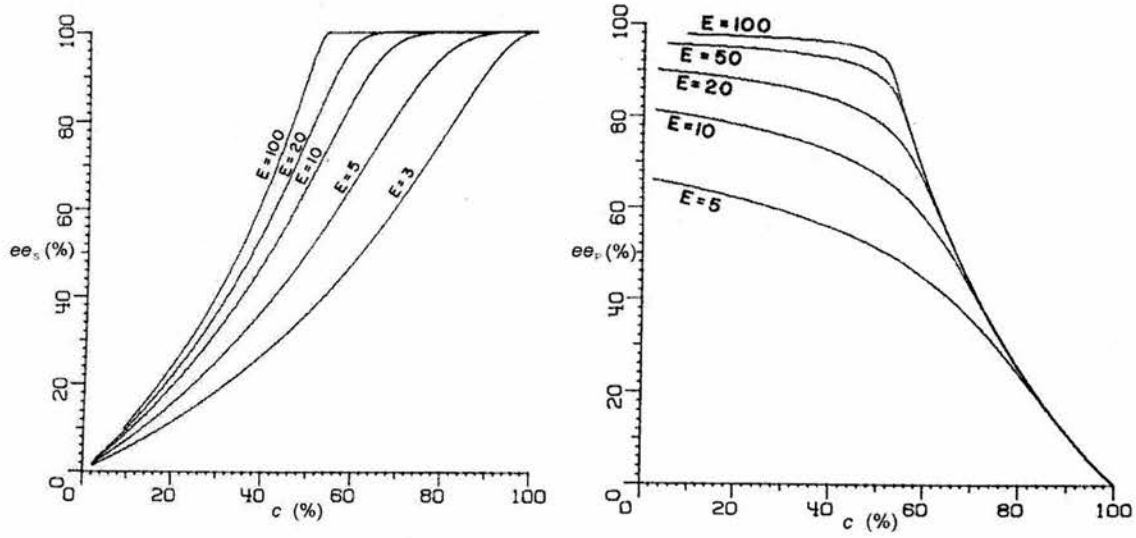
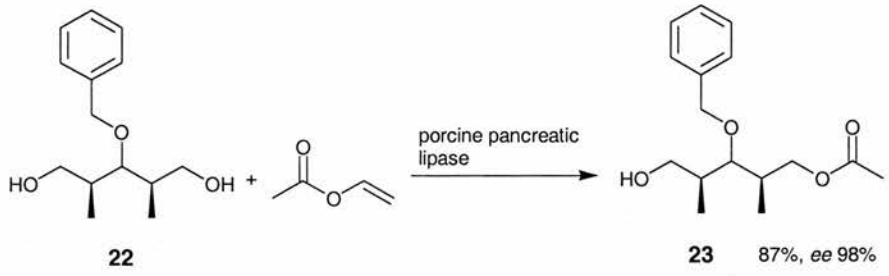


Figure 17: Expression of the enantiomeric excess of product (ee_P) and remaining substrate fractions (ee_S) as a function of the percentage conversion (c) for differend E values of irreversible enzymatic reaction. These curves were generated from Equation 7.[173]

The curves presented in Figure 17 provide a useful overview of the interrelationships between E value, enantiomeric excess and conversion. As the reaction proceeds the substrate, which was initially racemic (ee_S = 0%), is being enriched in slower reacting enantiomer (increase of ee_S) and the enantiomeric excess of product is deteriorating. At 50% conversion the enantiomeric excesses of substrate and product are equal. This graphic representation allows one to predict when to stop the kinetic resolution to maximize chemical and optical yields of the desired reaction constituent after the E value has been determined.

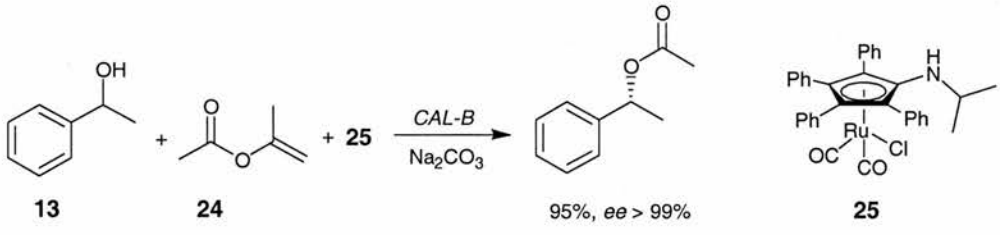
The drawback with kinetic resolutions is that a maximum of 50% of the starting material can be used to give product. One way to circumvent this problem is to employ *meso* or prochiral substrates. For example lipase catalysed acylation of

meso-diol **22** with vinyl acetate gave the optically active alcohol **23** in high yield and *ee*, Scheme 16.[174]



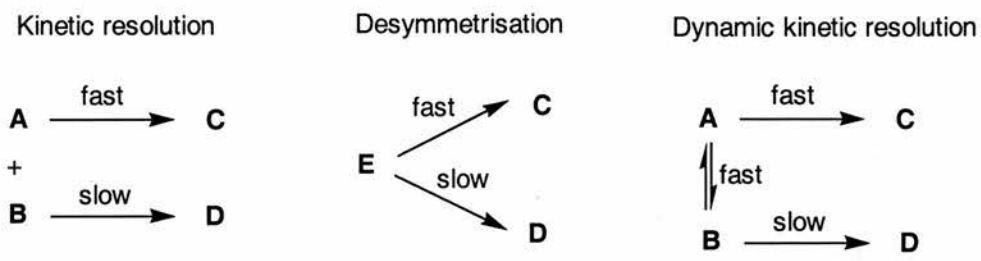
Scheme 16: Lipase catalysed desymmetrisation of *meso*-diol **22**.

Recently, methods to racemize the non-reacting enantiomer in kinetic resolutions have been developed.[172] If racemization is done continuously during the enzymatic resolution, this results in a dynamic kinetic resolution, and in this way all of the racemic starting material can be used for transformation into one enantiomer. As an example, resolution of 1-phenylethanol **13** was achieved by transesterification with isopropenyl acetate **24** catalysed by the lipase from *Candida antarctica* (*CAL-B*). This lead to an efficient dynamic kinetic resolution in the presence of the ruthenium catalyst **25** which can racemise **13** at room temperature, Scheme 17.[175]



Scheme 17: Dynamic kinetic resolution of 1-phenylethanol achieved by a combination of a lipase and a metal catalyst.

The principles of kinetic resolution, desymmetrisation and dynamic kinetic resolution are summarised in Scheme 18.[172, 176]



Scheme 18: Principles of kinetic resolution, desymmetrisation and dynamic kinetic resolution. **A**, **B**- Enatiomers of starting material; **C**, **D**- product enantiomers; **E**- prochiral or meso-starting material.[177]

2 LIPASE REACTIONS AND FLUOROUS SEPARATION

2.1 Synopsis

This Chapter is divided into three parts. In **Part A** lipase mediated esterification and transesterification reactions of non-chiral substrates in fluorous media are explored. The activity of various lipases suspended in hydrocarbon, fluorocarbon or mixed solvent systems is assessed and the thermo stability of lipases in these media is investigated. Furthermore enzymatic reactions with heavily fluorinated reagents or substrates are studied with the aim to prepare novel fluorous esters and to probe fluorous biphase extraction as a method to phase separate products after enzymatic reactions.

The success of this novel approach to lipase mediated reactions for product and/or stereochemical separation relies on an efficient partitioning of the reaction products between the perfluorocarbon and hydrocarbon solvents. In **Part B** the partitioning coefficients of these compounds are measured and structural characteristics which influence the *P* values under different conditions and in different solvent systems are evaluated.

In **Part C** the enantioselective lipase catalysed kinetic resolutions of racemates are described. Enantiomerically enriched alcohols and acids are prepared by fluorous labelling or fluorous delabelling. The products of each enantimeric series are

separated using fluorous biphase methodology (liquid/liquid extraction) or filtration using fluorous silica gel. The efficacy of these processes, the scope of these reactions and their limitations are investigated. The influence of fluorous solvents on the rate and enantioselectivity of the enzymatic reactions are evaluated.

2.2 General

Lipases not only hydrolyse fat in the digestion tract but are surprisingly flexible biocatalysts for the acylation and deacylation of a wide range on unnatural substrates. Lipase catalysed transformations of racemic and prochiral compounds usually proceed with high enantioselectivity, enabling the preparation of enantiomerically pure or enantiomerically enriched building blocks.[165] These enzymatic kinetic resolutions are increasingly conducted in organic solvents because of the better solubility of organic substrates, larger variety of possible reactions and easier isolation of the products compared to the corresponding reactions conducted in aqueous media.[160]

On a preparative scale in the laboratory the separation of each enantiomer of carboxylic esters or an ester from an alcohol is usually carried out by chromatography. This generates a lot of waste, it is very time consuming and it can be considered impractical on a larger scale. Some methods to avoid chromatography have been reported. For example enzymatic acylation of racemic alcohols with succinic anhydride in organic solvents generates ester carboxylic acids which can be removed by acid-base extraction from the unreacted alcohol, Scheme 8.[72] There are also examples of the separation of esters from alcohols by distillation.[178, 179]

We envisioned a new solution to overcome the separation problem. This is based on fluorous biphase extraction. The plan was to perform lipase mediated kinetic resolutions of racemic acids or alcohols in a mixed fluorocarbon/hydrocarbons solvent system. The system would then be heated to the temperature compatible with the lipase and where the two solvents become miscible. After the enzymatic reaction the insoluble enzyme would be easily removed by filtration and the filtrate

would be cooled down to form two phases. Ideally the organic phase would contain only one enantiomer of the product or of the unreacted starting material whereas the fluorous phase would contain only the fluorous tagged enantiomer.

Two general approaches for conducting lipase catalysed reactions in fluorous biphase systems are possible. One is fluorous labelling; the other is fluorous delabelling, as illustrated in Figure 18 and Figure 19 respectively. In fluorous labelling the substrate (acyl donor) is dissolved in a hydrocarbon solvent and the fluorous tagged nucleophile is dissolved in the fluorous solvent. In fluorous delabelling the nucleophile is dissolved in the hydrocarbon solvent and the fluorous tagged substrate is dissolved in the fluorous solvent. On addition of a lipase powder and heating, the two phases become homogeneous while the lipase remains as a suspension during a heterogeneous reaction. Separation of the products is achieved by filtration of the lipase and then cooling which results in the regeneration of the two immiscible liquids. In fluorous labelling the unreacted substrate is recovered from the hydrocarbon phase whereas the fluorous phase contains all of the fluorous tagged products, Figure 18. However in fluorous delabelling the product is recovered from the hydrocarbon phase and the fluorous phase contains unreacted fluorous tagged substrate, Figure 19.

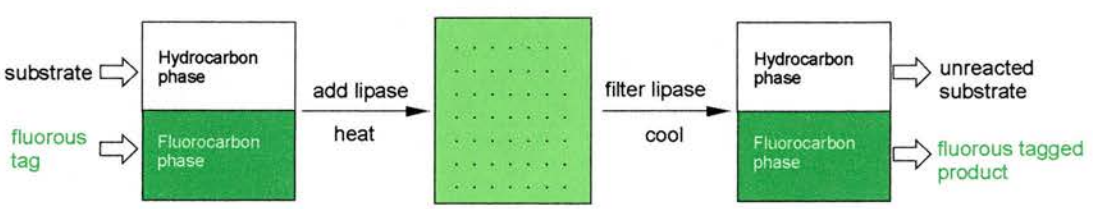


Figure 18: The principle of fluorous labelling in lipase catalysed reactions.

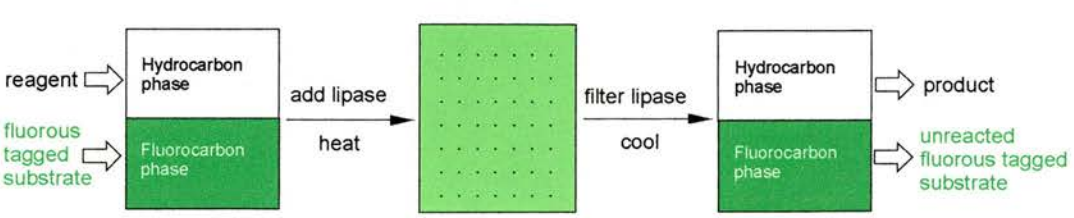
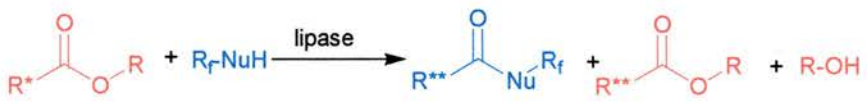


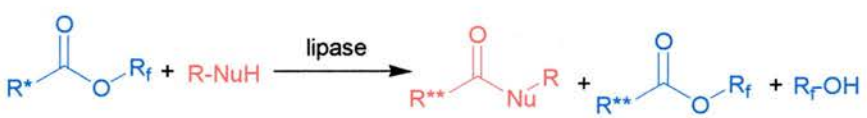
Figure 19: The principle of fluorous delabelling in lipase catalysed reactions.

In principle the methods of fluorous labelling and delabelling could be applied to the resolution of alcohols or carboxylic acid derivatives. Thus there are four strategies of how to approach enzymatic resolutions in the fluorous phase. These are shown in Schemes 19-22.



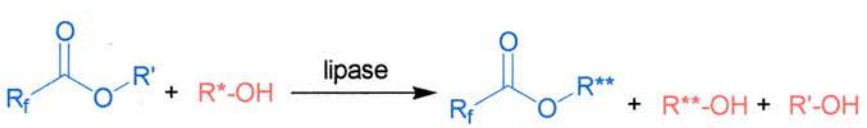
R*= chiral racemic group; R**= enantiomerically enriched group; NuH= OH, NH_2;
R_f= highly fluorinated residue; R= OH, CH_2CCl_3, CH_2CF_3, $CH{=}CH_2$, etc.

Scheme 19: General scheme for the resolution of chiral carboxylic acid derivatives by lipase catalysed fluorous labelling. The structures in blue should be more soluble in the fluorous phase and the structures in red should be more soluble in the organic phase.



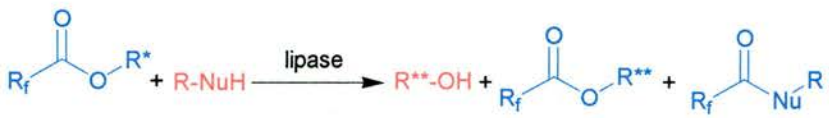
R*= chiral racemic group; R**= enantiomerically enriched group; NuH= OH, NH_2;
R_f= highly fluorinated residue; R= alkyl.

Scheme 20: General scheme for the resolution of chiral carboxylic acid derivatives by lipase catalysed fluorous delabelling.



R*= chiral racemic group; R**= enantiomerically enriched group;
R'= CH_2CF_3, $CH{=}CH_2$; R_f= highly fluorinated residue.

Scheme 21: General scheme for the resolution of chiral alcohols by lipase catalysed fluorous labelling.

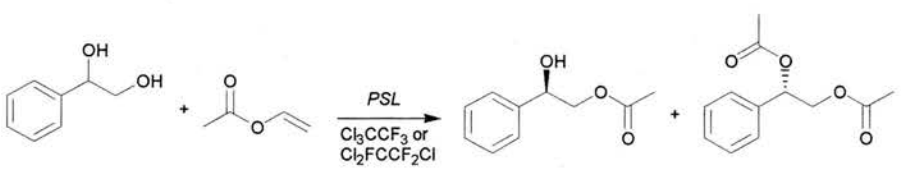


R*= chiral racemic group; R**= enantiomerically enriched group; NuH= OH, NH_2, etc.;
R= alkyl; R_f= highly fluorinated residue.

Scheme 22: General scheme for the resolution of chiral alcohols by lipase catalysed fluorous delabelling.

For the successful application of this methodology it is clearly necessary to establish if perfluorocarbon solvents or the required mixed solvent systems are suitable media for lipase mediated reactions. It is also important to determine if lipases will accept substrates or reagents with a fluorous tag attached. Partitioning of the products between the organic and fluorous phase is another important factor determining the efficiency of the separation.

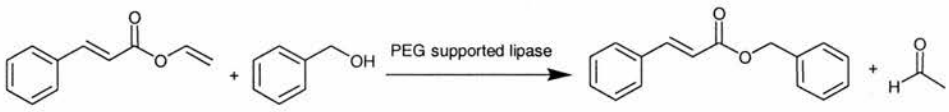
At the beginning of this project there were no reports describing enzymatic reactions in fluorous biphasic systems or fluorous solvents. However there was one report of *PSL* catalysed resolution of phenylethan-1,2-diol by transesterification with vinyl acetate in Freon solvents such as Cl_3CCF_3 and Cl_2FCCF_2Cl, Scheme 23.[180] In particular Cl_2FCCF_2Cl was found to be among the best solvents together with hexane and various organic ethers in terms of reaction rates.



Scheme 23: *PSL* catalysed resolution of phenylethan-1,2-diol in Freon containing solvent.

Perfluocarbons are the most hydrophobic solvents of all[181] and therefore should be ideal media for lipase catalysed reactions. However it is not known how such solvents may influence enzymatic activity and selectivity. Recently Goto[182]

published a study based on our first publication[183] where lipase catalysed transesterification between vinyl cinnamate and benzyl alcohol in a fluorous solvent was investigated, Scheme 24.



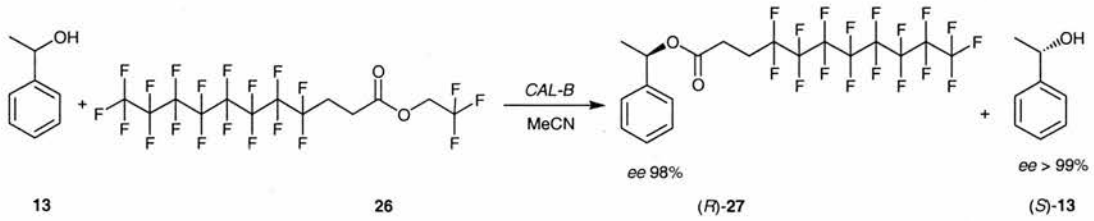
Scheme 24: Transesterification of vinyl cinnamate with benzyl alcohol catalysed by various lipases immobilised by forming poly(ethylene glycol) complexes in fluorous solvent.[182]

They have shown that the transesterification reaction catalysed by lipase *PSL* in a complex with poly(ethylene glycol) in FC-77 proceeded 10-fold faster than in isooctane. It was explained by the localization of substrates around lipase molecules, induced by adsorption of the substrates to the poly(ethylene glycol) layer.

Similarly to the best of our knowledge there was no report on the successful employment of perfluoroalkyl-tagged reagents or substrates for enzymatic reactions. However it has been shown that some substrates containing a pentafluorophenyl group are accepted by lipases.[184, 185] Nevertheless fluorinated aromatics are not fluorophilic.[91]

During the course of our studies on the resolution of carboxylic acid derivatives according to Scheme 19 and Scheme 20 a preliminary report[186] and a full paper[187] were published by Theil reporting lipase catalysed resolution of alcohols by the methods described in Scheme 21 and Scheme 22.[188] They succeeded in the resolution of 1-phenylethanol **13** by enantioselective acylation using four equivalents of fluorous ester **26**. The reaction was catalysed by the lipase from *Candida antarctica-B* (*CAL-B*) in acetonitrile as a solvent, Scheme 25. The

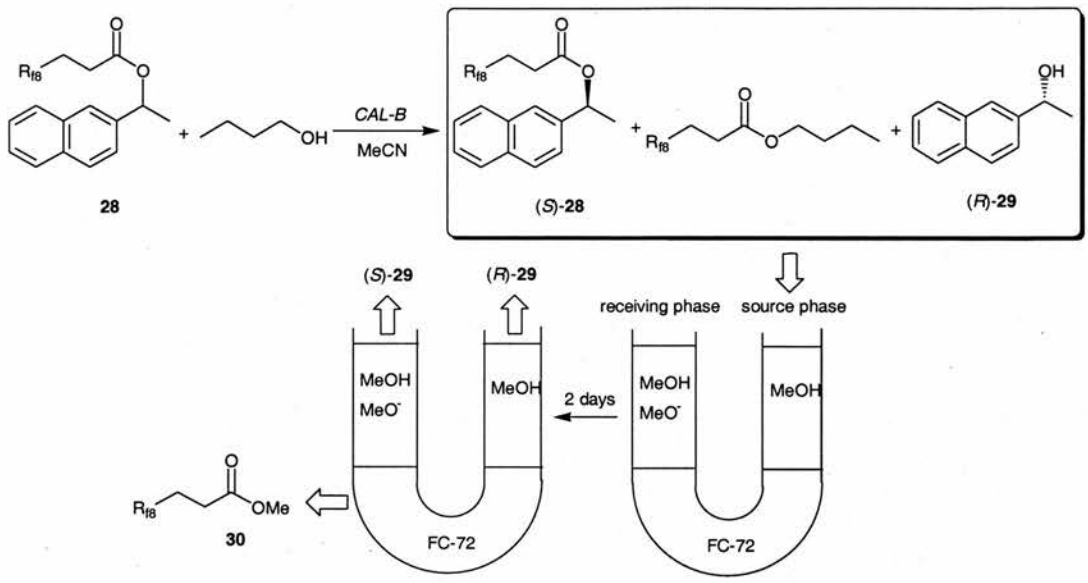
separation of fluorous ester (*R*)-**27** from enantiomerically pure (*S*)-**13** was achieved by partitioning between methanol and the fluorous solvent FC-72.



Scheme 25: Lipase catalysed kinetic resolution of 1-phenylethanol performed in an organic solvent with the product separation by fluorous/organic extraction.[186]

Three other racemic alcohols were resolved using this procedure.[187] Furthermore simultaneous fluorous delabelling and kinetic resolution was achieved by lipase catalysed alcoholysis of highly fluorinated esters of racemic alcohols according to Scheme 22.[188]

Recently coupling of an enzymatic kinetic resolution and a fluorous triphasic reaction was used to resolve 1-(2-naphthyl)ethanol. Deacylation of racemic fluorous ester **28** occurs with high enantioselectivity to provide alcohol (*R*)-**29** and ester (*S*)-**28**. These can be separated by adding the mixture to one side of a U-tube containing methanol. The other side of the U-tube contains MeOH/MeONa, and these two phases are separated by FC-72, which behaves as a liquid membrane allowing only fluorous ester (*S*)-**28** to pass through. After two days the methanol solution contains only (*R*)-**29** and the MeOH/MeONa phase only (*S*)-**29**. The ester **30** could be recovered from the fluorous phase, Scheme 26.[189]

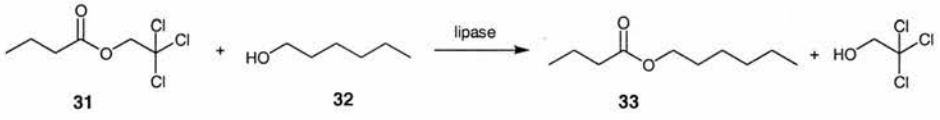


Scheme 26: A combined enzymatic resolution of 1-(2-naphthyl)ethanol and triphasic separation using a U-tube.[189]

2.3 Part A: Lipase catalysed reactions of non-chiral substrates in fluorous biphase systems

2.3.1 Lipase catalysed reaction under fluorous biphase conditions

From the outset of this study it was important to establish if lipases are compatible with a perfluorocarbon/hydrocarbon solvent system. Two commercially available lipases, the *Candida rugosa* (*CRL*) and the porcine pancreatic (*PPL*) lipases, were selected as catalysts for trial transesterification reactions. The reaction between 2,2,2-trichloroethyl butanoate **31** and 1-hexanol **32** in hexane alone or in a mixed solvent system of hexane and FC-72 was followed by GC-MS analyses to determine the degree of conversion to the product hexyl butanoate **33** as illustrated in Scheme 27 and Figure 20 .



Scheme 27: Model lipase catalysed transesterification reaction.

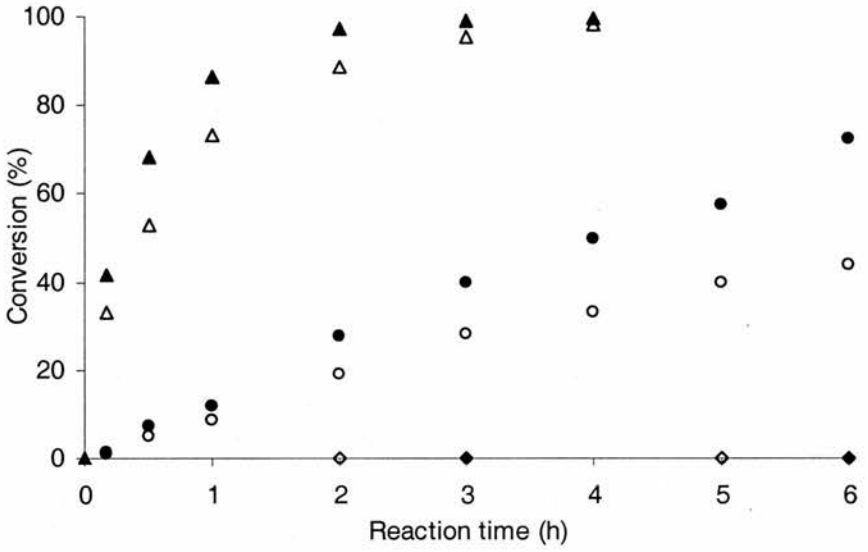


Figure 20: Time versus conversion for the reaction of **31** (1 mmol) with 1-hexanol **32** (2 mmol) at 40 °C, catalysed by *CRL* (100 mg)- (▲,Δ), *PPL* (500 mg)- (●,○) or uncatalysed reaction- (◆,◇). Reactions were conducted in hexane (10 cm^3)- (Δ,○,◇) or mixture of hexane (5 cm^3) and FC-72 (5 cm^3)- (▲,●,◆).

It can be seen from Figure 20 that both lipases catalyse the transesterification reaction between ester **31** and 1-hexanol **32**, however the lipase from *Candida rugosa* (*CRL*) is much more active than that from porcine pancreas (*PPL*). In both cases these reaction progressed with greater efficiency in a mixed solvent system than in hexane alone presumably, due to the increased hydrophobicity of the medium. In the absence of the enzyme there was no reaction observed regardless of the solvent used. It emerged from these trial experiments that the presence of a fluorous solvent can have a positive effect on the rate of the lipase mediated reactions.

2.3.2 Thermo deactivation of lipases

Having demonstrated the beneficial effect of fluorous solvent on a lipase catalysed reaction, the next aim was to investigate the stability of these enzymes in FC-72

and conventional hexane at different temperatures. Preparations of *CRL* and *PPL* powder were suspended in an appropriate solvent and stirred in a closed vessel at a given temperature. After a certain time the enzyme was filtered off and air dried. Enzyme activity was determined as μmols of converted 1-hexanol into hexyl acetate by using 3 equivalents of vinyl acetate per hour with one mg of enzyme powder. The data are presented in Figure 21 and Figure 22.

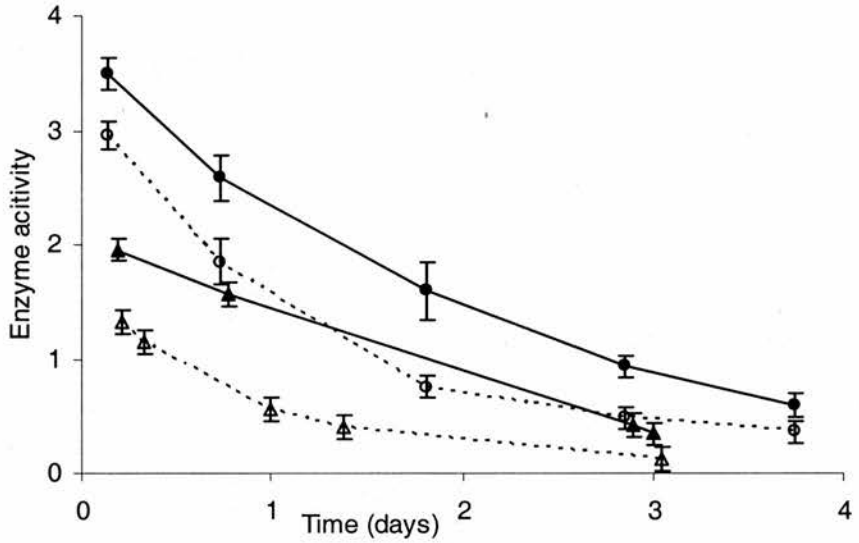


Figure 21: Activity of *CRL* versus time. The lipase was treated in FC-72 at 40 °C (●) or at 50 °C (▲); or in hexane at 40 °C (○) or at 50 °C (Δ).

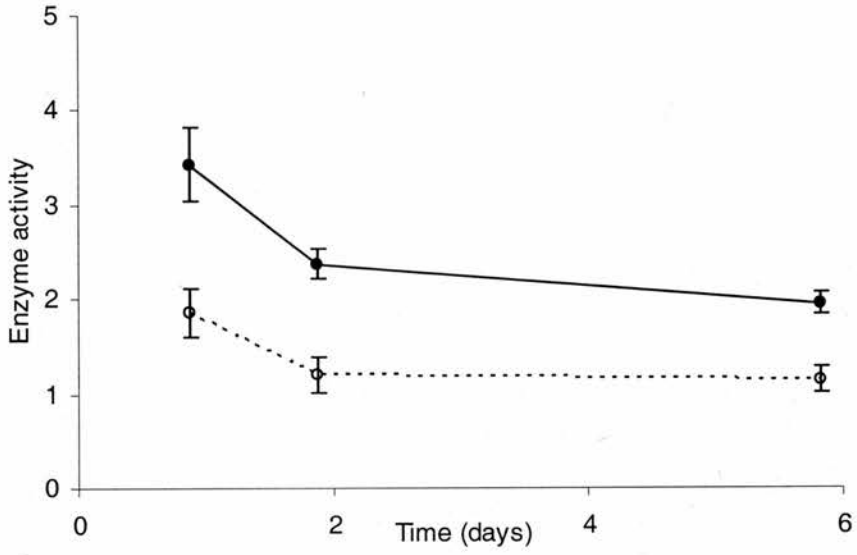
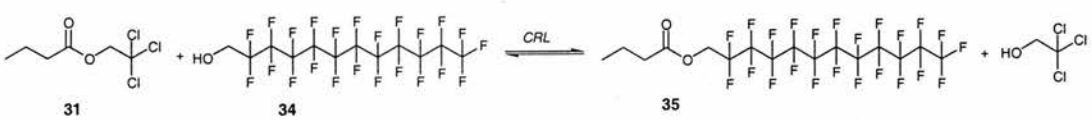


Figure 22: Activity of *PPL* versus time. The lipase was treated at 40 °C in FC-72 (•) or in hexane (○).

It is apparent from Figure 21 and Figure 22 that both lipases are more thermo stable in FC-72 as a medium than in hexane. However the deactivation of *CRL* takes place after a few days regardless of the solvent and the temperature. In contrast *PPL* remains considerably more active in the fluorous solvent even after 6 days.

2.3.3 Lipase catalysed reactions with fluorous tagged reagents

In order to test the ability of the lipases to mediate a reaction between an 'organic' substrate and a 'fluorous tagged' reagent (Figure 18), the transesterification reaction between trichloroethyl butanoate **31** and fluorous alcohol **34** was explored, Scheme 28 and Figure 23.



Scheme 28: Enzyme catalysed transesterification reaction of **31** with fluorous alcohol **34**.

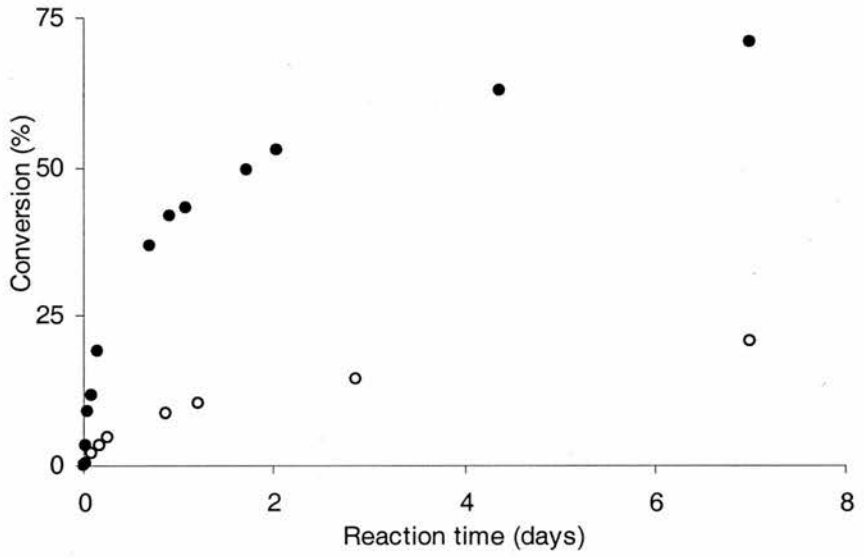


Figure 23: Time versus conversion for the reaction of **31** (0.3 mmol) with **34** (0.3 mmol) at 45 °C, catalysed by *CRL* (200 mg) (•); uncatalysed reaction (○). Reactions were conducted in a mixture of hexane (5 cm^3) and PFD (5 cm^3).

A control reaction without lipase revealed a slow but significant non-enzymatic reaction. The reaction doesn't proceed to completion even after 7 days, suggesting that the process is reversible. This is due to the fact that fluorous alcohol **34** and the generated 2,2,2-trichloroethanol have similar nucleophilicities. However it is clear that **34** can act as a nucleophile in the lipase mediated process to intercept the acylated enzyme intermediate.

Reactions using the more nucleophilic fluorous alcohol **36**, which has two CH_2 spacers between the hydroxyl and perfluoroalkyl group instead of one in **34**, were explored to reduce the reversibility. The same effect could be achieved using vinyl esters as acylating agents, because the liberated vinyl alcohol tautomerises to acetaldehyde, which is not able to act as a nucleophile in the reversible reaction. Anhydrides are also suitable acyl donors releasing a relatively non-nucleophilic acid. Table 11 summarises the transesterification and esterification reactions which

were investigated between esters, acids or anhydrides and the fluorous alcohol nucleophiles.

Table 11: Lipase (*CRL*, 200 mg) catalysed reactions between 'organic' esters, acid or anhydride and fluorous alcohols at 40 °C in a mixed solvent system of hexane (5 cm^3) and FC-72 (5 cm^3).

Acylating agent (2 mmol)	Fluorous Alcohol (1 mmol)	Reaction time (h)	Conversion[a] / Yield[b] (%)	Product ester number
Vinyl acetate	**37**, $R_{f9}CH_2OH$	28	90 / 87	**38**
2,2,2-Trifluoroethyl butanoate	**36**, $R_{f8}(CH_2)_2OH$	23	96 / 83	**39**
Butanoic anhydride	**36**, $R_{f8}(CH_2)_2OH$	9	99.8 / 97	**39**
Pentanoic acid	**36**, $R_{f8}(CH_2)_2OH$	15	95 / 84	**40**

[a] Determined by GC-MS analysis. [b] Isolated yield of the fluorous ester from the combined fluorous phase by filtration of the enzyme, cooling (-10 °C) and washing the hexane phase with FC-72 (5 cm^3).

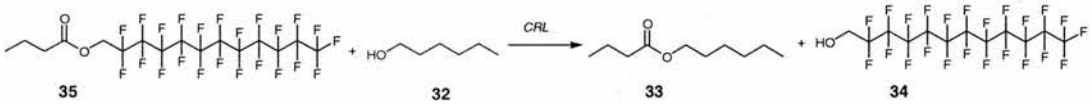
After the reactions the enzyme was filtered off and the two liquid phases were separated after cooling. The hexane phase was washed with FC-72 (5 cm^3) and the fluorous ester products **38-40** were isolated from the combined fluorous phase. These experiments showed that suitable acyl donors react with 'fluorous tagged' alcohol nucleophiles in the lipase mediated reactions. The 'fluorous tagged' products of these reactions could be isolated in high yields from the reaction mixture by fluorous biphase extraction.

2.3.4 Lipase catalysed reactions with fluorous tagged substrates

It was important to test the ability of lipases to mediate a reaction between a 'fluorous tagged' substrate and an 'organic' reagent (Figure 19). Fluorous tagged substrates in this context are esters derived from an 'organic' acid and heavily fluorinated alcohols or an ester of an 'organic' alcohol and a heavily fluorinated acid. Both possibilities were investigated.

2.3.4.1 Lipase catalysed reaction with fluorous tagged substrate derived from a heavily fluorinated alcohol

A transesterification was explored between the fluorous ester **35** and 1-hexanol **32**, as shown in Scheme 29. The data are presented in Figure 24.



Scheme 29: Enzyme catalysed transesterification reaction of ester **35** with 1-hexanol.

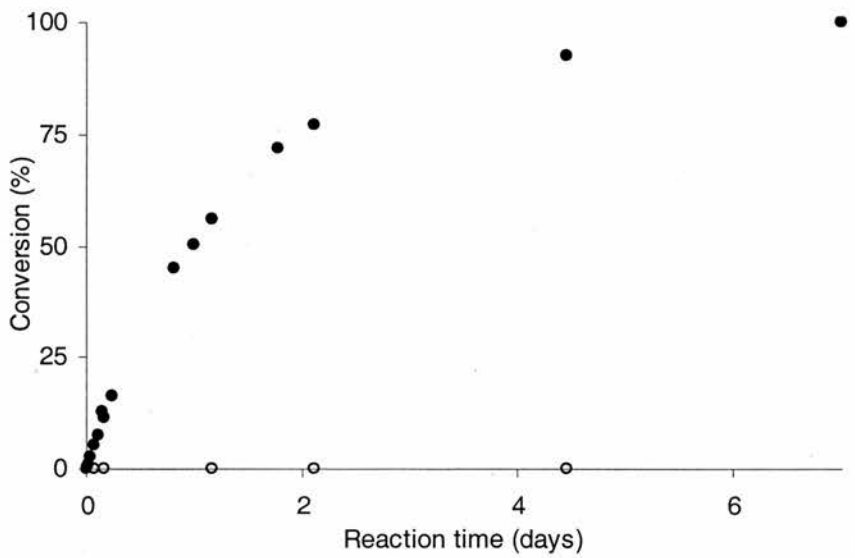
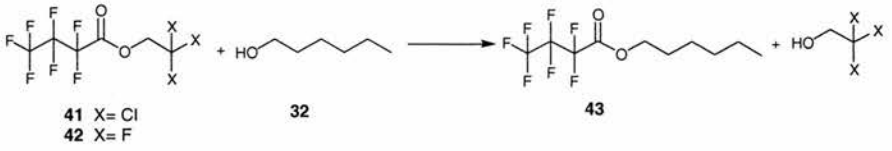


Figure 24: Time versus conversion for the *CRL* (400 mg) catalysed reaction of ester **35** (0.5 mmol) with 1-hexanol (0.5 mmol) at 45 °C (•); uncatalysed reaction (○). Reactions were conducted in a mixture of hexane (10 cm^3) and PFD (10 cm^3).

This reaction proceeded to 100% conversion indicating that the resultant fluorous alcohol **34** is a poor nucleophile relative to 1-hexanol. It can be seen that the starting fluorous ester **35** is accepted as a substrate by the lipase, despite the fact that the molecule in heavily fluorinated. It is important to note that the fluorous tagged ester **35** bears no similarity to the natural substrate- triacylglycerides. After the reaction was completed the enzyme was filtered off and the two phases separated after cooling. The hexane phase was washed with PFD (2×10 cm^3) and ester **33** (98%) was isolated by evaporation, contaminated with less than 0.2% of **34** as judged by GC-MS. The fluorous alcohol **34** was isolated by evaporation of the combined fluorous phase in an excellent yield (98%). Importantly there was no transesterification reaction observed without added enzyme.

2.3.4.2 Lipase catalysed reactions with fluorous tagged substrates derived from a heavily fluorinated acid

The presence of a perfluoroalkyl group on the acid side of the ester opens new possibilities for reactions using both fluorous labelling and delabelling. 2,2,2-Trichloroethyl perfluorobutanoate **41** and 2,2,2-trifluoroethyl perfluorobutanoate **42** were synthesised by a two step procedure starting from perfluorobutanoic acid and thionyl chloride in dimethyl formamide to form volatile perfluorobutanoyl chloride (bp 38-39 °C), which then reacts with the appropriate alcohol in pyridine. The esters **41** and **42** were tested in an enzymatic transesterification with 1-hexanol as shown in Scheme 30 and Figure 25.



Scheme 30: Esterification reaction between esters of perfluorobutanoic acid and 1-hexanol.

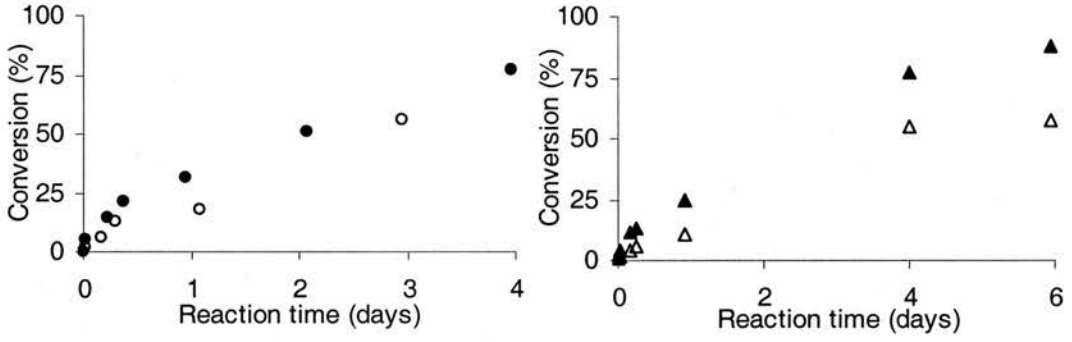


Figure 25: Time versus conversion for the reaction of **41** (0.22 mmol) with 1-hexanol **32** (1.46mmol) at 45 °C, catalysed by *CRL* (200 mg) (•); uncatalysed reaction (○); and for reaction of **42** (0.5 mmol) with 1-hexanol **32** (1.5 mmol) at r.t. catalysed by *CRL* (200 mg) (▲); uncatalysed reaction (Δ); Reactions were conducted in a mixture of hexane (5 cm^3) and FC-72 (5 cm^3).

It emerged from these experiments that the esters **41** and **42** are not suitable substrates as no significant rate enhancement was achieved by addition of the lipase and the observed reaction was not catalysed by the enzyme and therefore non-selective.

2.4 Part B: Partitioning in fluorous biphase systems

Partitioning coefficients of some non-fluorinated compounds, partially fluorinated esters, carbonates and a hydrocarbon were measured in different solvent systems between organic and fluorous solvents. The experimental conditions are given in Table 12. The standard system used for comparison of P^o values involves partitioning of molecules between perfluoro(methylcyclohexane) and toluene at 298 K. This solvent mixture becomes homogeneous at 88.6 °C.[91] However for the purposes of this study it was necessary to evaluate P values in solvent systems which can form homogeneous solutions at temperatures compatible with lipase mediated reactions. Mixtures of FC-72 / hexane and PFD / hexane form homogeneous solution at 25 °C and 40 °C respectively. To ensure complete separation of the organic and fluorous solvent it was necessary to cool down the mixture below room temperature. Some enzymatic reactions were carried out in pure FC-72 and after the removal of the enzyme, methanol was used for extraction. Therefore P values were also evaluated in that solvent system.

Table 12: Measured partitioning coefficients for some acids, alcohols, esters, carbonates and a hydrocarbon. The values are colour coded according to the solvent systems used as follows: PFMC / toluene; FC-72 / hexane; PFD / hexane and FC-72 / methanol.

Entry	Compound number, formula	P; s_D[a]	Partitioning (%) fluorous / organic	Temp.[b] (°C)
1	**26**, $R_{f8}(CH_2)_2CO_2CH_2CF_3$	2.47; 0.10	71 / 29	25
2	**32**, $CH_3(CH_2)_5OH$	< 0.02; -	< 2 / 98	-10
3	**32**	< 0.02; -	< 2 / 98	-10
4	**35**, $CH_3(CH_2)_2CO_2CH_2R_{f11}$	6.26; 0.16	86 / 14	4
5	**36**, $R_{f8}(CH_2)_2OH$	2.54; 0.20	72 / 28	4
6	**36**	0.18; 0.01	15 / 85	4
7	**37**, $R_{f9}CH_2OH$	3.75; 0.26	79 / 21	4
8	**37**	0.24; 0.02	19 / 81	4
9	**38**, $CH_3CO_2CH_2R_{f9}$	5.59; 0.54	85 / 15	25
10	**39**, $CH_3(CH_2)_2CO_2(CH_2)_2R_{f8}$	0.825; 0.04	45 / 55	25
11	**39**	4.85; 0.21	83 / 17	4
12	**40**, $CH_3(CH_2)_3CO_2(CH_2)_2R_{f8}$	0.716; 0.10	42 / 58	25
13	**44**, $CH_3CH_2CH(CH_3)CO_2H$	< 0.001; -	< 0.1 / 99.9	-10
14	**44**	< 0.001; -	< 0.1 / 99.9	-10
15	**44**	< 0.001; -	< 0.1 / 99.9	4
16	**45**, $CH_3(CH_2)_2CH(CH_3)CO_2H$	< 0.001; -	< 0.1 / 99.9	-10
17	**45**	< 0.001; -	< 0.1 / 99.9	-10
18	**45**	< 0.001; -	< 0.1 / 99.9	4
19	**46**, $CH_3(CH_2)_3CH(CH_3)CO_2H$	< 0.001; -	< 0.1 / 99.9	-10
20	**47**, $CH_3CH_2CH(CH_3)CO_2CH_2CF_3$	0.25; 0.01	20 / 80	4
21	**47**	0.36; 0.01	26 / 74	4
22	**47**	0.18; 0.01	15 / 85	4
23	**48**, $CH_3(CH_2)_2CO_2CH_2R_{f9}$	2.25; 0.13	69 / 31	25
24	**48**	21.2; 2.1	95 / 5	4
25	**49**, $CH_3CH_2CH(CH_3)CO_2CH_2R_{f9}$	3.87; 0.16	80 / 20	4
26	**49**	2.23; 0.32	69 / 31	25
27	**50**, $CH_3CH_2CH(CH_3)CO_2(CH_2)_2R_{f8}$	1.23; 0.02	55 / 45	25

[a] Standard deviation of P. [b] Temperature used for separation of organic and fluorous phase.

Table 12: Continued.

Entry	Compound number, formula	P; s_D[a]	Partitioning (%) fluorous / organic	Temp.[b] (°C)
28	**50**, $CH_3CH_2CH(CH_3)CO_2(CH_2)_2R_{f8}$	1.49; 0.03	60 / 40	-10
29	**50**	1.32; 0.03	57 / 43	-10
30	**50**	5.55; 0.06	85 / 15	4
31	**51**, $CH_3(CH_2)_2CH(CH_3)CO_2CH_2R_{f9}$	1.70; 0.09	63 / 37	25
32	**51**	2.32; 0.04	70 / 30	-10
33	**51**	1.79; 0.02	64 / 36	-10
34	**52**, $CH_3(CH_2)_2CH(CH_3)CO_2(CH_2)_2R_{f8}$	0.95; 0.01	49 / 51	25
35	**52**	1.02; 0.01	50 / 50	-10
36	**52**	1.06; 0.02	51 / 49	-10
37	**52**	5.33; 0.15	84 / 16	4
38	**53**, $R_{f8}(CH_2)_2CO_2CH=CH_2$	1.07; 0.07	52 / 48	25
39	**54**, $R_{f9}CH_2OCH_2CO_2CH_2CF_3$	1.81; 0.08	64 / 36	25
40	**55**, $R_{f4}(CH_2)_2OCH_2CO_2CH_2CF_3$	0.216; 0.01	18 / 82	25
41	**56**, $[R_{f9}CH_2O]_2C=O$	97.6; 15	99 / 1	25
42	**57**, $[R_{f8}(CH_2)_2O]_2C=O$	16.3; 0.80	94 / 6	25
43	**57**	70; 4.0	99 / 1	-10
44	**57**	255; 30	> 99 / 1	4
45	**58**, $[R_{f3}CH_2O]_2C=O$	2.13; 0.15	68 / 32	25
46	**59**, $R_{f8}(CH_2)_4R_{f8}$	207; 25	> 99 / 1	25

[a] Standard deviation of P. [b] Temperature used for separation of organic and fluorous phase.

From the data in Table 12 it can be seen that the non-fluorinated compounds partition only into the organic phase (entries 2, 3, 13-19) and in the FC-72 / methanol system the compounds could not be detected in the fluorous phase at all by GC-MS analysis (entries 15 and 18).

At a first approximation it can be concluded from the data that the more fluorine atoms a molecule contains, the better is its partitioning into the fluorous phase (entries 5 and 7, 10 and 12, 10 and 23, 11 and 24, 25 and 28, 26 and 29, 31-36, 39

and 40, 41 and 42). It seems that the structures containing a linear non-fluorinated part of the molecule have lower P values compared to those having more compact branched non-fluorinated moieties (entries 10 and 27, 12 and 27, 12 and 34). As expected compounds containing more polar groups have lower P values (entries 1 and 38, 1 and 39).

Using more polar organic solvents like methanol compared to hexane dramatically increases the P values of fluorophilic molecules (entries 28 and 30, 35 and 37, 43 and 44), while for non-fluorophilic molecules there is a corresponding decrease of the P value when switching from FC-72 / hexane to FC-72 / methanol (entries 20 and 22). Fluorophilic molecules are those with $P^o > 1$.

A special case are the two fluorous alcohols **36** and **37** which behave as highly fluorophilic solutes in the FC-72 / hexane solvent system (entries 5 and 7), but they are significantly non-fluorophilic in FC-72 / methanol (entries 6 and 8). Clearly hydrogen bonding between the solute molecules and methanol is a stronger attractive force than the interaction between the fluorous solvent and the perfluoroalkyl group of the solute molecule. However in hexane there is stronger solvent-solute repulsion than in FC-72.

Interestingly the PFMC / toluene system generally results in the lowest P of all of the solvent systems used ($P^o < P$) for fluorophilic molecules (entries 10 and 11, 23 and 24, 27-30, 31-33, 42-44), however the P^o and P values could not be directly compared.

Modified non-specific cohesion parameters (δ') and molar volumes (V) were calculated using tabulated group contributions.[134, 136] This study was carried out in collaboration with Dr. J. Rábai during a visit to the Eötvös Loránd University, Budapest. It allowed us to calculate partition coefficients $P^o_{pred.}$ using Equation 5

and compare them with P^o values obtained experimentally, Table 13. As can be observed from the comparison between the calculated and experimental partition coefficients reported in Table 13 the P^o values can be predicted with some accuracy. There is a fair correlation between the whole set of predicted and experimental log P^o values as shown in Figure 26.

Table 13: Calculated partition coefficients, experimental partition coefficients, calculated non-specific cohesion parameters and calculated molecular volumes of studied compounds.[a]

Compound number, formula	V ($cm^3 \cdot mol^{-1}$)	δ' ($MPa^{1/2}$)	$P^o_{pred.}$	P^o
26, $R_{f8}(CH_2)_2COOCH_2CF_3$	337.7	12.61	11.9	2.47
38, $CH_3COOCH_2R_{f9}$	307.2	12.44	12.8	5.59
39, $CH_3(CH_2)_2COO(CH_2)_2R_{f8}$	332.4	13.20	3.54	0.825
40, $CH_3(CH_2)_3COO(CH_2)_2R_{f8}$	348.5	13.38	2.62	0.716
48, $CH_3(CH_2)_2COOCH_2R_{f9}$	339.4	12.90	6.76	2.25
50, $CH_3CH_2CH(CH_3)COO(CH_2)_2R_{f8}$	348.8	13.62	1.59	1.23
51, $CH_3(CH_2)_2CH(CH_3)COOCH_2R_{f9}$	371.9	13.49	2.21	1.70
52, $CH_3(CH_2)_2CH(CH_3)COO(CH_2)_2R_{f8}$	364.9	13.77	1.19	0.95
53, $R_{f8}(CH_2)_2COOCH=CH_2$	308.7	13.08	3.96	1.07
54, $R_{f9}CH_2OCH_2COOCH_2CF_3$	364.6	12.84	9.11	1.81
55, $R_{f4}(CH_2)_2OCH_2COOCH_2CF_3$	265.2	13.66	1.25	0.216
56, $[R_{f9}CH_2O]_2C=O$	553.4	12.56	71.1	97.6
57, $[R_{f8}(CH_2)_2O]_2C=O$	519.4	12.95	18.9	16.3
58, $[R_{f3}CH_2O]_2C=O$	256.2	13.67	1.19	2.13
59, $R_{f8}(CH_2)_4R_{f8}$	497.4	11.82	483	207

[a] The values of δ' and V for solvents[134] used in Equation 5 were: $\delta'_{toluene}$= 18.1 $MPa^{1/2}$, $V_{toluene}$= 106.9 $cm^3 \cdot mol^{-1}$, δ'_{PFMC}= 10.66 $MPa^{1/2}$, V_{PFMC}= 196.0 $cm^3 \cdot mol^{-1}$.

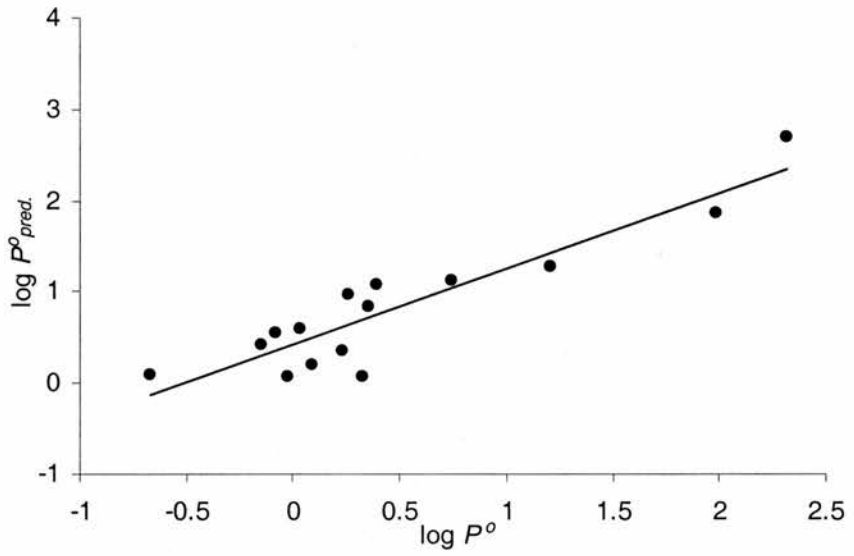


Figure 26: Experimental vs. calculated log P^o of compounds in Table 13. The line represents a linear regression characterized by slope 0.83, intercept 0.42 and R^2= 0.84.

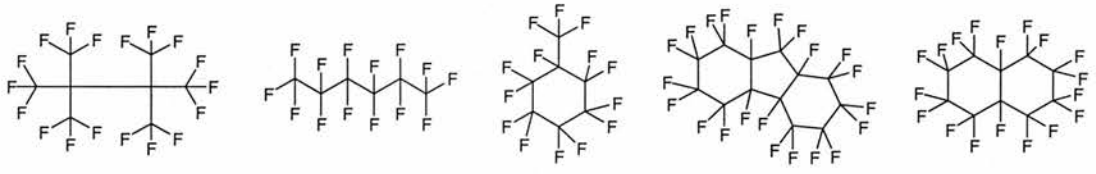
In order to improve the partitioning it would be beneficial to find a way to increase the P value of the fluorinated solutes without compromising the very low P value of the non-fluorinated solutes. One way to achieve this is to increase the fluorophilicity of the solute by using longer perfluoroalkyl chains (so called 'fluorous ponytails'), increase the number of fluorous ponytails or use branched ponytails. This approach has been widely practiced.[91, 131] Alternatively however the organic solvent could be changed to a more polar one (e.g. methanol instead of hexane) as that also improves the partitioning of fluorous molecules into the perfluorinated solvent. The drawback is that these solvent mixtures require much higher temperatures before generating a homogeneous phase. In this regard it was decided to investigate the influence of different perfluorinated solvents on the partition coefficient.

The partition coefficients of two fluorous tagged esters **50** and **52** (Figure 27) were determined in mixtures of toluene and different perfluorinated solvents, Figure 28

and Table 14. These esters were chosen because they have P^o values close to $P^o = 1$, and it was anticipated that the experimental error is less significant around this value.

50 **52**

Figure 27: Solutes used for measurement of the P values between toluene and different fluorous solvents.



PFTMB PFH PFMC PFF PFD

Figure 28: A selection of solvents used with toluene to determine the influence of the fluorous solvent on the partitioning of **50** and **52**.

Table 14: Experimental partition coefficients (P) and standard deviations (s_D) between different fluorous solvents and toluene for esters **50** and **52**.[a]

Solvent system fluorous / organic	P (**50**); s_D	Partitioning (%) fluorous / organic	P (**52**); s_D	Partitioning (%) fluorous / organic
PFTMB / toluene	0.64; 0.05	39 / 61	0.48; 0.06	32 / 68
PFH / toluene	0.98; 0.06	50 / 50	0.68; 0.02	40 / 60
PFMC / toluene	1.23; 0.02	55 / 45	0.95; 0.01	49 / 51
PFF / toluene	1.13; 0.06	53 / 47	0.97; 0.06	49 / 51
PFD / toluene	1.59; 0.05	61 / 39	1.28; 0.07	56 / 44

[a] All partition coefficients were measured at 25 °C except P in PFTMB / toluene which was measured at 40 °C.

From the data in Table 14 it can be seen that both **50** and **52** are either somewhat non-fluorophilic in PFTMB / toluene or PFH / toluene but were 'more fluorophilic' in PFD / toluene.

The highest P values were obtained when solvents containing CF_2 and CF groups (cyclic structures) were used. On the other hand 'superdense' fluorophilic CF_3 groups did not prove to be suitable in designing fluorous solvents, although they are very effective at increasing the fluorophilicity of the solute molecules.

Molar volumes and δ' values for fluorous solvents were taken from literature[136] or they were calculated,[134, 136] which allowed the partition coefficients[190] of **50** and **52** to be predicted in different solvent systems using Equation 5, Figure 29.

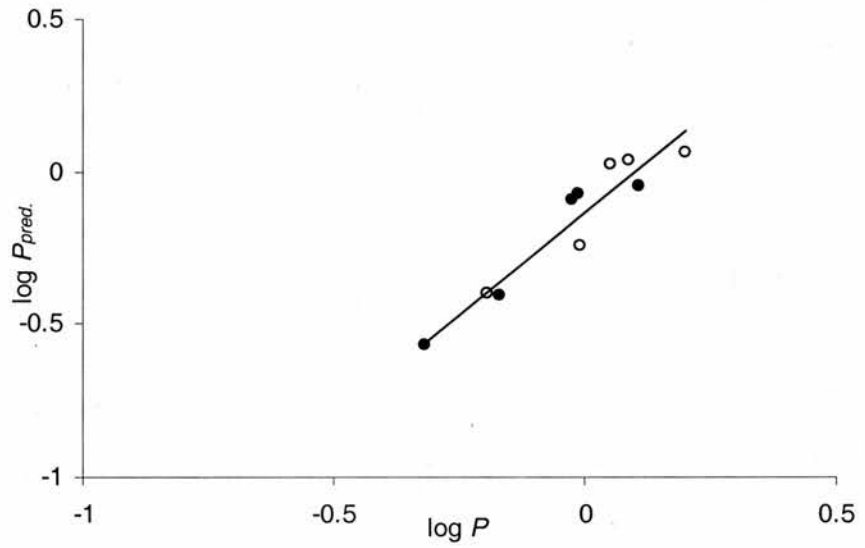


Figure 29: Experimental vs. calculated log P of **50** (○) and **52** (●) using Equation 5. The line represents linear regression of all points characterized by slope 1.33, intercept -0.13 and R^2= 0.90.

The larger the molecular volume of the fluorous solvent the lower P value that is observed. Even though PFF and PFD are structurally similar their P values are different with PFD having a significantly larger value. Changing the fluorous solvent instead of the organic solvent in order to maximize the P value of the fluorous molecules is an advantage for lipase catalysed reactions. The temperature at which the different fluorous solvents form homogeneous solutions with

hydrocarbons is not very different. This contrasts with much more disparate temperatures when modifying the organic solvent.

2.5 Part C: Enantiomeric partitioning using fluorous biphase systems and fluorous filtration after lipase mediated reactions

2.5.1 Resolution of carboxylic acids

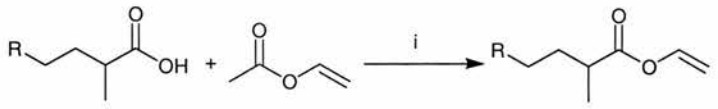
After having demonstrated that lipase catalysed reactions proceed efficiently for non-chiral substrates (Part A), attention was turned to perform the resolution of chiral carboxylic acids and their derivatives according to Scheme 19 and Scheme 20.

In order to investigate the enantiomeric partitioning after a lipase catalysed reaction a suitable racemic carboxylic acid derivative and a suitable fluorous tagged nucleophile had to be identified. The particular lipase used should exhibit high enantioselectivity for the carboxylic acid derivative, which must partition entirely into the organic phase. The fluorous tagged nucleophile must be able to bring sufficient fluorine content to the product to render it fluorophilic enough to be separated by fluorous extraction.

2.5.1.1 Resolution of 2-methylalkanoic acids by fluorous labelling

2-Methylalkanoic acids of high enantiomeric purities are valuable synthetic intermediates in the preparation of biologically active compounds such as pheromones.[191, 192] It was shown that the *Candida rugosa* lipase (*CRL*) catalyses esterification, transesterification or hydrolysis of 2-methylalkanoic acids and their esters with good to high enantioselectivities.[193, 194, 195, 196] Based on the partition coefficients reported in Table 12, 2,2,2-trifluoroethyl esters were ruled out as suitable substrates because they would contaminate the fluorous phase in the

separation step. However vinyl esters **60** and **61** were considered to be good starting substrates for *CRL* catalysed transesterifications because they are not fluorous phase soluble. These esters were prepared by reaction of the corresponding carboxylic acids **44** and **45** with an excess of vinyl acetate, catalysed by mercury(II) acetate, Scheme 31.[197, 198, 199]



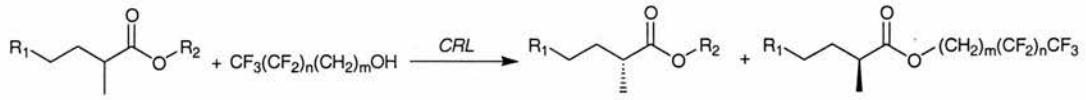
44 R= H
45 R= Me

60 R= H, 25%;
61 R= Me, 69%

Scheme 31: Preparation of vinyl esters **60** and **61**. Reagents and conditions: i) $Hg(OAc)_2$ (1 mol%), H_2SO_4 (cat.), reflux 17 h.

These racemic vinyl esters were then subjected to lipase resolutions. Accordingly they were transesterified with fluorous alcohols **36** and **37** catalysed by the *CRL* lipase, Scheme 32. The reactions were conducted in a (1:1) mixture of hexane and FC-72. The reactions were terminated at about 50% conversion (GC-MS analysis) by filtration of the enzyme. The two phases were then separated by cooling (-10 °C). Because of the non-ideal partitioning of the resulting fluorous tagged esters **49**, **51** and **52** the hexane phase contained both unreacted vinyl esters **60** and **61** as well as fluorous tagged compounds, while the FC-72 phase was free from vinyl esters. Repeated extraction of the hexane phase with fluorous solvent was necessary to minimize the contamination of the hexane phase. The solvent was then removed from the washed hexane phase and the combined fluorous phase. The residual esters were hydrolysed and the enantiomeric excesses of the isolated acids were determined by GC-MS using a chiral column, Table 15 (entries 1-3).

Similarly *CRL* mediated esterification reactions between 2-methylalkanoic acids **44-46** and alcohols **36** and **37** were investigated, Table 15 (entries 4-6).



44 R_1= H; R_2= H
45 R_1= Me; R_2= H
46 R_1= Et; R_2= H
60 R_1= H; R_2= CH=CH_2
61 R_1= Me; R_2= CH=CH_2

36 n= 7; m=2
37 n= 8; m=1

(*S*)-**49** R_1= H; n= 8; m= 1
(*S*)-**50** R_1= H; n= 7; m= 2
(*S*)-**51** R_1= Me; n= 8; m= 1
(*S*)-**52** R_1= Me; n= 7; m= 2
(*S*)-**62** R_1= Et; n= 7; m= 2

Scheme 32: *CRL* catalysed transesterification and esterification reactions.

Table 15: Lipase catalysed kinetic resolutions of carboxylic acids and esters by reaction with fluorous alcohols in a mixed solvent system of hexane and FC-72.[a]

Entry	Ester/acid	Fluorous alcohol	Reaction time (h)	Reaction temperature (°C)	Conversion[b] (%)	*ee*[c] (%)	*ee*[d] (%)	n
1	**60**	**37**	50	30	50	44	40	1
2	**61**	**37**	51	30	51	77	33	2
3	**61**	**36**	44	40	48	72	44	2
4	**44**	**36**	25	40	45	60	45	5
5	**45**	**36**	95	40	53	95	79	5
6	**46**	**36**	149	40	49	95	95	5

[a] Conditions: ester/acid (1 mmol), alcohol (1 mmol), hexane (10 cm^3), FC-72 (10 cm^3) and *CRL* (200 mg) were shaken at 250 rpm. [b] Determined by GC-MS of the reaction mixture. The enzyme was filtered off and the liquid phases were partitioned after cooling. The hexane phase was washed with FC-72 (10 cm^3, n times). The *ee* values were determined by chiral GC-MS of the corresponding acid obtained by hydrolysis of: [c] combined fluorous phase, [d] washed hexane phase.

There was no reaction observed without added enzyme or with porcine pancreatic lipase (*PPL*). The absolute configuration of the enantiomerically enriched carboxylic acids was assigned by comparison with commercially available (*S*)-**44**. For **45** the optical rotation was compared to the reported value. For **46** no direct assignment of absolute configuration was carried out, but it was anticipated that the

elution order of the enantiomers of homologous acids **45** and **46** is the same (see Appendix 1 for conditions). The *CRL* lipase has been previously shown to mediate kinetic resolutions of 2-methylalkanoic acids and reacts faster with the *S* enantiomer.[193, 195] We have confirmed the same stereochemical preference in these studies.

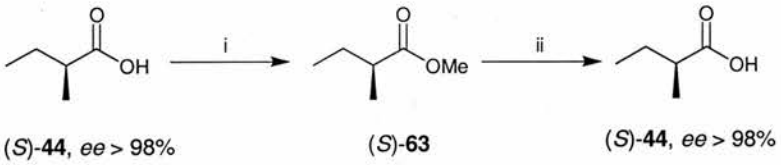
Vinyl esters **60** and **61** are more reactive than the corresponding carboxylic acids **44** and **45**, but the esterification reactions proceeded with a higher enantioselectivity than the transesterification reactions (compare entries 1 and 4, 2 and 5). It was also noted that the reactivity decreases and the enantioselectivity increases with the increasing length of the alkyl chain of the 2-methylalkanoic acid substrates, Table 15 (entries 4-6).

The enantiomeric purity of the carboxylic acids in the hexane phase is compromised to some extent by some solubility of the product esters **49-52** and **62** in hexane. That is the reason why in Table 15 (entries 1-3) the observed *ee* values from the hexane phase are lower than the observed *ee* values from the fluorous phase although the conversion is close to 50%. The problem was overcome by washing the hexane layer with FC-72 for maximum recovery of the fluorous esters and it was found that five washings is enough to reduce the content of the fluorous esters in the hexane phase below 1%, Table 15 (entries 4-6).

The resultant enantiomeric purity of the acids from each phase emerges as a consequence of the inherent stereoselectivity of the enzyme with a particular substrate, the level of conversion and the partitioning of the fluorous esters between the two phases.[183]

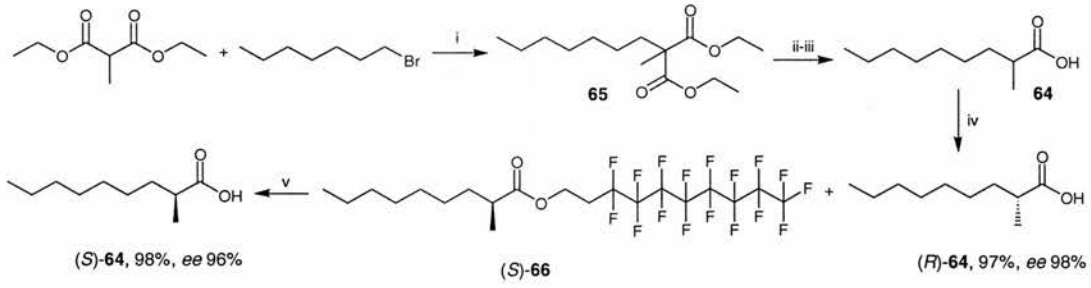
It was important to establish whether any racemisation occurs during the separation process. The most vulnerable step for possible racemisation is the hydrolysis of the

esters **49-52** and **62**. To examine this commercial (*S*)-**44** was reacted with diazomethane to generate methyl (*S*)-2-methylbutanoate, (*S*)-**63** in 90% yield. Alkaline hydrolysis regenerated the acid (*S*)-**44**. Analysis of the enantiomeric purity, as determined by chiral GC-MS, confirmed that there had been no racemisation during alkaline hydrolysis, Scheme 33.



Scheme 33: Investigations into racemisation during ester hydrolysis. Reagents and conditions: i) CH_2N_2, Et_2O, r.t., 90%; ii) LiOH/MeOH, reflux, 3 h, H^+/H_2O, 92%.

2-Methylnonanoic acid **64** was prepared by alkylation of diethyl 2-methylmalonate with 1-bromoheptane in EtONa/EtOH. Hydrolysis and decarboxylation of the resulting diester **65** gave the desired carboxylic acid **64** in 60% overall yield, Scheme 34.[194]



Scheme 34: Synthesis of 2-methylnonanoic acid **64** and lipase catalysed resolution. Reagents and conditions: i) EtONa/EtOH, reflux, 2 h; ii) KOH/EtOH, reflux, 10 h; iii) 190 °C, 2h, 60% overall; iv) **36**, hexane, FC-72, *CRL*, 40 °C, 65 h; v) KOH/EtOH, reflux, 3.5 h.

A preparative *CRL* catalysed esterification of **64** with **36** was conducted in a mixture of hexane and FC-72 as solvents. The reaction was allowed to proceed up to 50% conversion a process which took 65 hours. It was anticipated that multiple

extractions would be needed to separate products **64** and **66**. However this was not the case and the mixture of products was partitioned between MeOH and FC-72 in continuous extractor, Figure 30. After 10 h of continuous extraction (*R*)-**64** (97%, *ee* 98%) was isolated from the methanol phase. Conversely (S)-**64** (98%, *ee* 96%) and **36** (97%) were isolated after hydrolysis from the FC-72 solvent. The continuous extractor uses considerably less solvent and is less labour intensive than multiple fluorous extractions. Thus the preparative process is very practical.

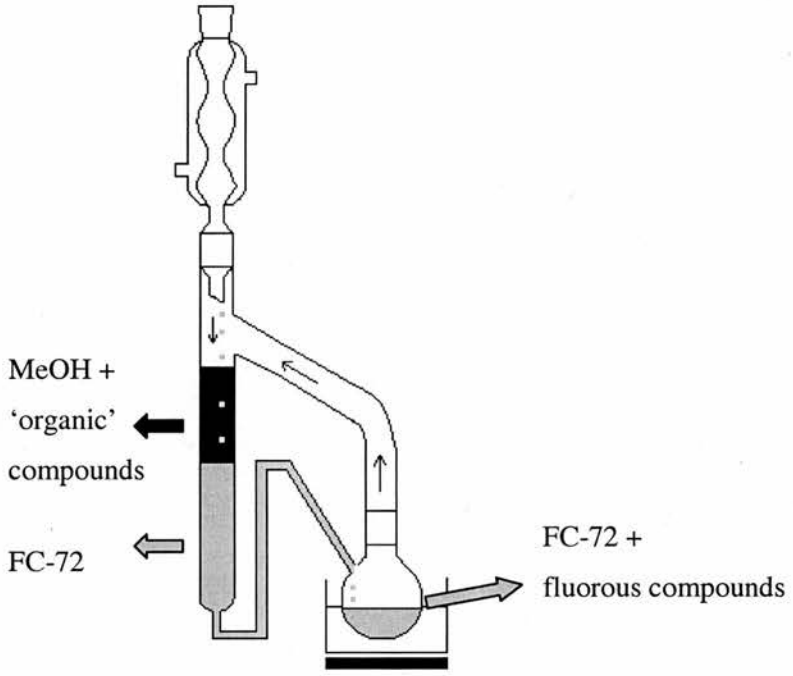


Figure 30: Apparatus for continuous extraction of fluorous tagged compounds from 'organic' ones. The mixture of the fluorous and the 'organic' compounds is dissolved in MeOH and the resulting solution is added in the separator onto the layer of FC-72 solvent. The fluorous compounds partially partition into FC-72, which is continually removed by overflow into the flask. The flask is heated and the FC-72 is distilled off to condense into the separator. After a certain time the top phase in the separator contains only 'organic' compounds in MeOH, and the lower phase contains clean FC-72. The flask contains the fluorous compounds in FC-72.

It is interesting to compare reaction rates and enantioselectivity of our system with that published in the literature.[193] Engel used the *CRL* to catalyse esterification of

acids **44-46** with various alcohols. Long chain alcohols like 1-octanol, 1-decanol and 1-octadecanol were found to give the highest *ee* values. These enzymatic reactions were conducted in heptane and the separation of the products was performed using column chromatography, Table 16.[193]

Table 16: *CRL* catalysed esterification of racemic 2-methylalkanoic acids with alcohols.[a] The data is take from Engel.[193]

Entry	Acid	Alcohol	Reaction time (h)	Conversion (%)	*ee* of ester (%)	*ee* of acid (%)
1	**44**	1-octanol	7	53	43	49
2	**44**	1-octadecanol	3	51	51	52
3	**45**	1-octanol	10	46	93	80
4	**45**	1-octadecanol	12	45	88	72
5	**46**	1-octanol	22	49	80	76
6	**46**	1-decanol	19	48	83	75
7	**46**	1-octadecanol	18	50	84	84

[a] Conditions: acid (0.5 mmol), alcohol (0.5 mmol), heptane (5 cm^3) and *CRL* (500 mg) were shaken at r.t. At 50% conversion the enzyme was filtered off and the products were separated over silica gel.

One noticeable difference between these two studies is the shorter reaction times reported by Engel[193] compared to ours,[183] however in our study five times less catalyst (*CRL*) was used. Additionally the fluorous alcohols **36** and **37** are much less nucleophilic than the non-fluorinated alcohols. We have achieved higher *ee* values especially for carboxylic acids **44** and **46**. Overall it is clear that our approach has resulted in the easier enantiomeric separation.

2.5.1.1.1 Using fluorous reverse phase silica gel for separation of enantiomers

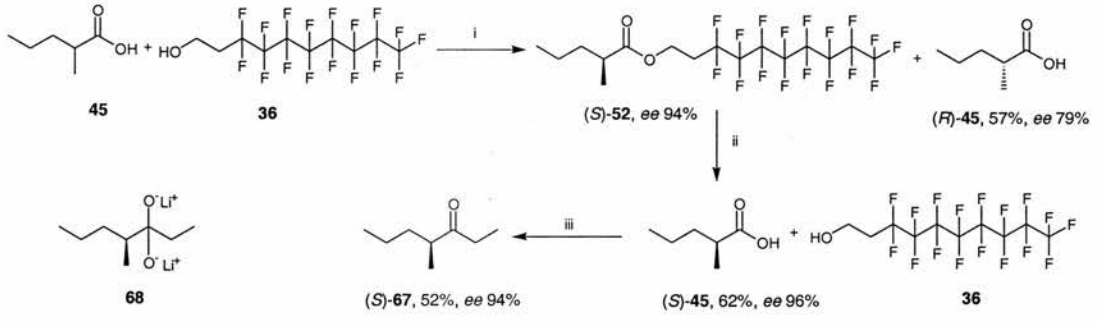
Fluorous reverse phase silica gel (FRPSG) has been introduced in section 1.3.4.6 as an easy and efficient method of separating 'organic' compounds from fluorous ones. Technically the process resembles filtration or columning over an ion exchange resin and is very straightforward. We wanted to probe this technique as an alternative to fluorous liquid/liquid extraction for separation of the fluorous product from the unreacted organic compounds after our lipase reactions. Accordingly a series of experiments was conducted to test the efficacy and limits of separation using fluorous silica.

2-Methylpentanoic acid **45** (1 mmol) and various fluorous alcohols (1 mmol) of the general formula $CF_3(CF_2)_n(CH_2)_2OH$, where n = 7, 5 and 3 were dissolved in hexane (10 cm^3) and FC-72 (10 cm^3) and *CRL* (200 mg) was added. The mixtures were shaken at 30-40 °C and they were periodically analysed by GC-MS to determine the degree of conversion. When the conversion reached 50% (40-50 h) the reactions were stopped by filtration of the enzyme and the solvent was removed under reduced pressure. The residue from each reaction was loaded onto a FRPSG column (0.5 g of the reaction mixture for 5 g of fluorous silica). The first fraction was obtained by elution with 80% aq. MeOH (8 cm^3) and the second fraction was obtained by elution with acetone (15 cm^3). In all cases the first fraction contained unreacted (*R*)-**45** (*ee* 80-89%) and no (*S*) fluorous ester. The second fraction gave fluorous esters which resulted in (*S*)-**45** (*ee* 90-92%) after hydrolysis. However the reaction mixture obtained after the *CRL* catalysed esterification of **45** with $CF_3CF_2(CH_2)_3OH$ could not be separated by fluorous silica gel even when 60% aq. MeOH was used as first elution solvent. This is presumably because of an

insufficient difference in the fluorine content between unreacted **45** and the 'light' fluorous product.

2.5.1.1.2 Preparation of the pheromone of *Atta texana*

With the encouraging results presented in section 2.5.1.1 a preparative scale esterification was conducted. Racemic acid **45** (6 g) was reacted with fluorous alcohol **36** and *CRL* in hexane / FC-72. After reaching a 50% conversion the enzyme was filtered off and the liquid phases were collected, cooled and separated. The hexane phase was washed with FC-72 five times and after removal of solvent (*R*)-**45** (57%, *ee* 79%) was recovered, contaminated with less than 1% of the fluorous ester (*S*)-**52**. The combined fluorous phase contained only alcohol **36** and fluorous ester (*S*)-**52** (*ee* 94%). After solvent removal (about 80% recovery), the residue was suspended in a solution of *CRL* in phosphate buffer (pH 7.0). The suspension was stirred (96 h) and then alcohol **36** (62%) was recovered after extraction into FC-72. Carboxylic acid (*S*)-**45** (62%, *ee* 96%) was isolated from the aqueous solution, Scheme 35. The enzymatic hydrolysis increased the enantiomeric purity of carboxylic acid (*S*)-**45** from 94 to 96% *ee*.



Scheme 35: Synthesis of the pheromone (*S*)-**67** of *Atta texana*. Reagents and conditions: i) **45** (51.6 mmol), **36** (45.8 mmol), hexane (150 cm^3), FC-72 (150 cm^3) and *CRL* (5.00 g), 40 °C, 95 h; ii) *CRL* (2.00 g), phosphate buffer (0.2 M, pH 7.0, 350 cm^3), r.t., 96 h; iii) EtBr, Li, Et_2O, -10 °C then (*S*)-**45**, Et_2O, reflux, 30 min.

To demonstrate the utility of preparing (*S*)-**45**, the principal alarm pheromone (*S*)-**67** of *Atta texana* ants was synthesised, Scheme 35. The target ketone (*S*)-**67** was prepared by reaction of carboxylic acid (*S*)-**45** with ethyl lithium. Ethyl lithium was prepared by reaction of lithium metal with ethyl bromide. Two equivalents of EtLi were used. The first equivalent acts as a base and abstracts a proton from the acid, the second acts as a nucleophile to form the dianion **68**, which gives ketone (*S*)-**67** on addition of water (52% yield). Chiral GC-MS was able to resolve the enantiomers of **67**. The product had an optical purity of 94% *ee*.

There was no racemisation observed during the addition of ethyl lithium, presumably because ethyl lithium doesn't abstract the α-hydrogen from the carboxylate. The acidity of that α-hydrogen is much decreased due to the presence of the nearby carboxylate negative charge. Previous preparation of the pheromone (*S*)-**67** involved a six-step synthesis and a tedious multiple recrystallization of the quinine salt of 2-methyl-4-pentenoic acid. In that case only a few *mg*s was prepared with an overall yield of less than 1%.[200, 201] The fluorous biphase approach led to the preparation of 0.46 g of the target pheromone with an overall yield of 34% starting from racemic carboxylic acid **45**.

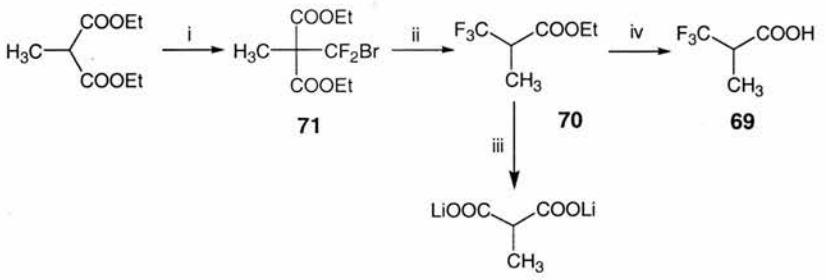
2.5.1.2 Resolution of a trifluoromethyl substrate

Compounds containing the trifluoromethyl group at a stereogenic center are an important class of molecules and there has been a recent emergence of commercial products carrying the CF_3 group at a stereogenic center.[202, 203, 204] In this program of lipase catalysed resolutions we wanted to address the resolution of a suitable carboxylic acid containing the CF_3 α to the carboxylate. In α-trifluoromethylated carbonyl compounds the active hydrogen α to the carbonyl moiety has been the

most significant factor in preventing the creation of chirality by chemical methods.[205] Accordingly biochemical methods have some prospects.

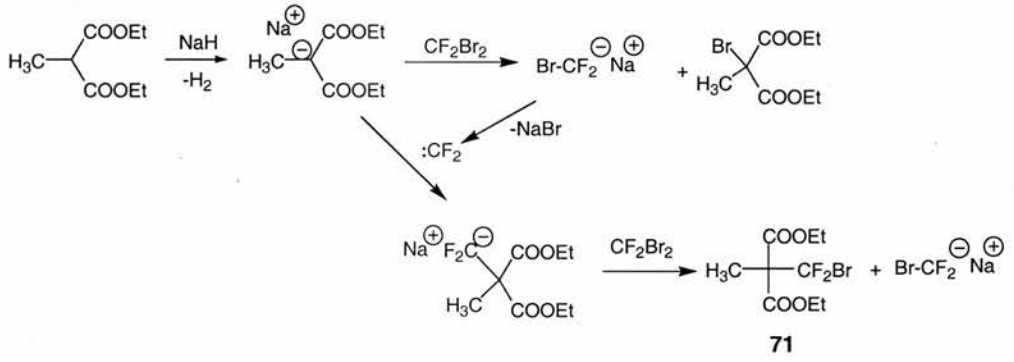
The simplest member of this class of compound amenable to a lipase catalysed reaction is 3,3,3-trifluoro-2-methylpropanoic acid **69**. The only reported preparation of enantio-enriched **69** was achieved by hydrogenation of 2-(trifluoromethyl)acrylic acid with H_2 in the presence of Ru-(*R*)-BINAP catalyst.[206, 207] However the product **69** was not isolated but was directly transformed into (2*S*)-3,3,3-trifluoro-2-methyl-1-propanol (*ee* 80%). Some α-trifluoromethylated carboxylic acids have been obtained in optically active form (unknown absolute stereochemistry) by enzymatic hydrolysis of their esters using the *PSL* in an aqueous medium,[205] yet the resolution of **69** was not described. The resolution of **69** therefore emerged as an attractive target for this new methodology.

Racemic α-(trifluoromethyl)alkanoic acids are relatively uncommon compounds and there are only a few reactions available in the literature to access them.[208, 209, 210, 211, 212] Ethyl 3,3,3-trifluoro-2-methylpropanoate **70** has been prepared in two steps by alkylation of diethyl 2-methylmalonate with dibromo(difluoro)methane to form ester **71**. This ester was then converted to **70** after bromide fluoride exchange accompanied by de-ethoxycarbonylation.[213] Hydrolysis of ester **70** was unsuccessful under alkaline conditions leading to the conversion of the CF_3 group to a carboxylate and the generation of 2-methylmalonate.[211] However under acidic conditions the hydrolysis was successful and gave **69** in 55% yield as illustrated in Scheme 36.



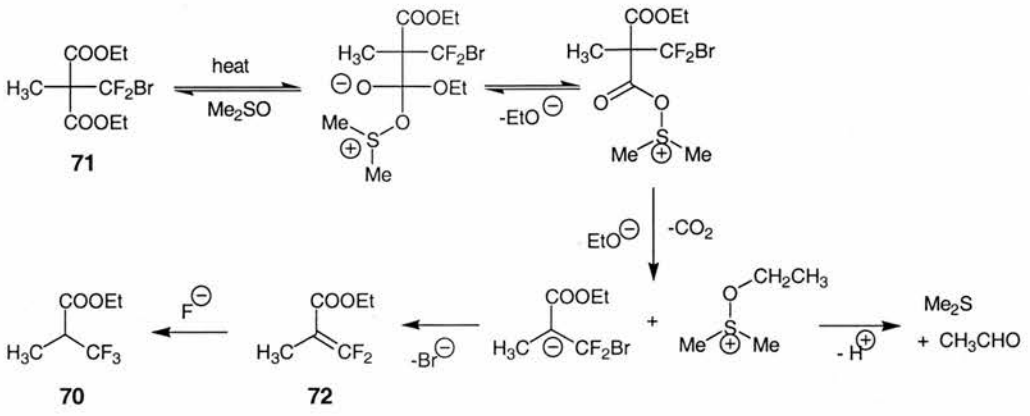
Scheme 36: Preparation of 3,3,3-trifluoro-2-methylpropanoic acid **69**. Reagents and conditions: i) NaH, CF_2Br_2, THF, r.t., 22 h, 48%; ii) KF, DMSO, 150-170 °C, 1.5 h, 91%; iii) LiOH/MeOH, reflux, 2 h; iv) HCl, dioxane, reflux, 15 h, 55%.

The mechanism of the first two reaction steps shown in Scheme 36 is not obvious and deserves some discussion. Although the formation of diester **71** appears to be direct alkylation from CF_2Br_2, the actual pathway consists of an ionic chain mechanism involving difluorocarbene, Scheme 37. The presence of a small amount of the hydrogenated by-product $Me(CF_2H)C(COOEt)_2$ supports this mechanism.[214]



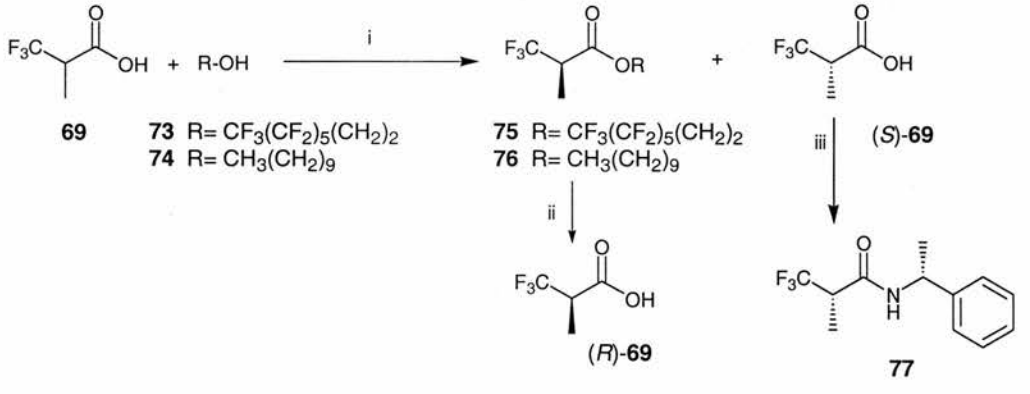
Scheme 37: The mechanism of alkylation of diethyl 2-methylmalonate with CF_2Br_2.

The mechanism for the conversion of the diester **71** to the ester **70** is shown in Scheme 38. It is supported by the isolation of the α,β-unsaturated fluorinated ester **72** in addition to the dimethyl sulfide and acetaldehyde by-products.[213]



Scheme 38: The mechanism of bromide fluoride exchange of **71** and de-ethoxycarbonylation.

Fortunately, GC-MS equipped with the chiral column Supelco β-DEX 120 was able to separate the enantiomers of **69** (see Appendix 1). This allowed the direct determination of the enantiomeric excess during the lipase catalysed esterifications. Two alcohols were selected for the lipase mediated esterifications of **69**. These were fluorinated alcohol **73** and 1-decanol **74**. The *CAL-B* displayed no enantioselectivity for **69** when reacted with alcohol **73**, but the *CRL* gave enantiomerically enriched esters (**75** and **76**) and carboxylic acid **69** on esterification with alcohols **73** or **74**, Scheme 39.



Scheme 39: Lipase (*CRL*) catalysed esterification of **69**. Reagents and conditions: i) *CRL*, hexane, (FC-72), 37 °C; ii) HCl, dioxane, reflux, 15 h, 55%; iii) N-methylmorpholine, $ClCO_2Me$, (1*R*)-1-phenylethylamine, THF, -10 °C, 90%.

The *CRL* catalysed esterification of carboxylic acid **69** with fluorous alcohol **73** was carried out in hexane at 37 °C. After 18 h the enzyme was removed by filtration and the residue after solvent removal was loaded onto FRPSG column. Elution with aq. MeOH gave carboxylic acid **69** (66%, *ee* 90%) and elution with acetone gave fluorous ester **75** and unreacted alcohol **73**. After acidic hydrolysis carboxylic acid **69** (54%, *ee* 68%) was isolated, Scheme 39. At this point the relationship between optical rotation and the absolute configuration of the enantiomerically enriched acids was not known, because these were new compounds.

It was found that the hydrolysis of ester **75** under basic conditions (NaOH or LiOH in methanol) did not give acid **69** but led to decomposition. However refluxing carboxylic acid **69** (*ee* 90%) under acidic conditions (HCl in dioxane for 15 h) did not cause any racemisation.

A *CRL* mediated kinetic resolution of **69** *via* enantioselective esterification with 1-decanol **74** in hexane gave the decyl ester **76**. When this reaction was stopped after 4 h and decyl ester **76** was recovered and then hydrolysed, enantiomerically enriched carboxylic acid **69** was obtained (36%, *ee* 90%). Longer reaction times (20 h) gave the other enantiomer of **69** which was recovered as the unreacted and enantiomerically pure acid (74%, *ee* > 98%), Scheme 39. In this case the separation of decyl ester **76** from carboxylic acid **69** was achieved by acid-base extraction between diethyl ether and aq. $NaHCO_3$.[215] The enantiomers of **69** are related by the interconversion of a CF_3 and a CH_3 group. Interestingly the optical rotation values were found to be close to zero.

To determine the absolute configuration of the recovered **69** (*ee* 98%), amide **77** was prepared[216] by reaction with (1*R*)-1-phenylethylamine, Scheme 39. The

diastereoisomeric ratio for **77** was 98% *de* as determined by ^{19}F NMR and by GC-MS. Column chromatography on silica gel permitted the isolation of the major diastereoisomer (*de* 100%) of **77**. X-Ray diffraction analysis of a single crystal of amide **77** reported the *S* absolute configuration on C(5), and therefore the lipase preference for enantiomer (*R*)-**69** as shown in Figure 31. For the crystallographic details of amide **77** see Appendix 3.

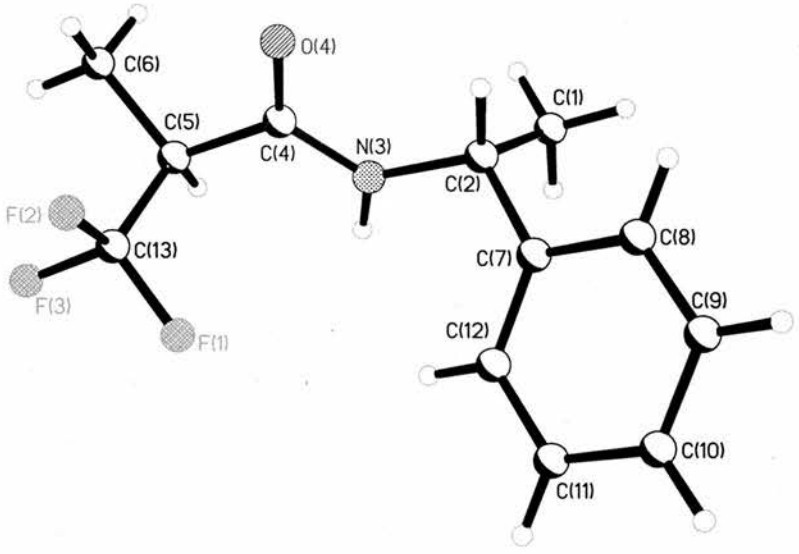
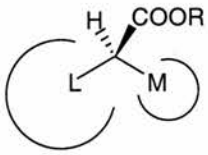


Figure 31: The X-ray derived structure of (2*S*)-3,3,3-trifluoro-2-methyl-*N*-[(1*R*)-1-phenyl]propanamide **77**.

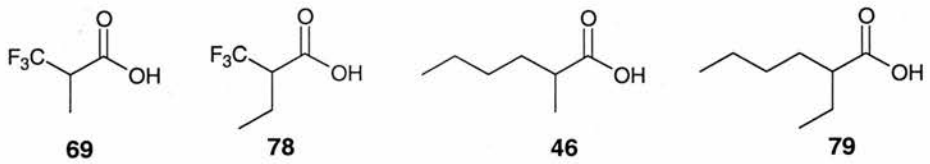
The observed selectivity of the *CRL* for acids **69**, **44-46** and **64** is fully compatible with the predictive rule obtained for *CRL* catalysed hydrolyses of esters derived from chiral acids.[195, 217] The rule predicts that faster reacting enantiomers have a stereochemistry as shown in Figure 32, where (L) is the largest substituent and (M) is the smallest substituent. This configurational preference is persistent through enzymatic hydrolysis, esterification or transesterification reactions with this lipase.



L= CF_3; $(CH_2)_nCH_3$, n= 1, 2, 3, 6
M= CH_3
R= H, $CH=CH_2$

Figure 32: The observed stereochemistry of faster reacting enantiomer with *CRL* where (L) is the largest substituent and (M) is the smallest substituent.

2-(Trifluoromethyl)butanoic acid **78** was synthesised from diethyl 2-ethylmalonate and CF_2Br_2 in a similar manner to **69**. A comparative study was carried out on esterification of **69**, **78**, **46** and 2-ethylhexanoic acid **79** with 1-decanol **74**, Figure 33, Table 17.



69 **78** **46** **79**

Figure 33: Various branched acids used for *CRL* esterification with 1-decanol.

Table 17: Lipase catalysed esterification of acids with 1-decanol.[a]

Entry	Acid	Reaction time (h)	Conversion[b] (%)	*E*[c]
1	**69**	8	48	16[d]
2	**78**	8	1.5	-
3	**78**	95	24	3[e]
4	**46**	8	50	>100[f]
5	**79**	8	0.0	-
6	**79**	95	10	0

[a] Conditions: Acid (0.5 mmol), 1-decanol (1 mmol), hexane (10 cm^3) and *CRL* (200 mg) were shaken at 250 rpm/37 °C. [b] Determined by GC-MS of the reaction mixture. [c] *E* values were determines from *ee* of unreacted acid and *ee* of acid isolated from hydrolysis of the decyl esters using Equations 6 and 7. The configuration of faster reacting enantiomer: [d] *R*, [e] unknown, [f] *S*.

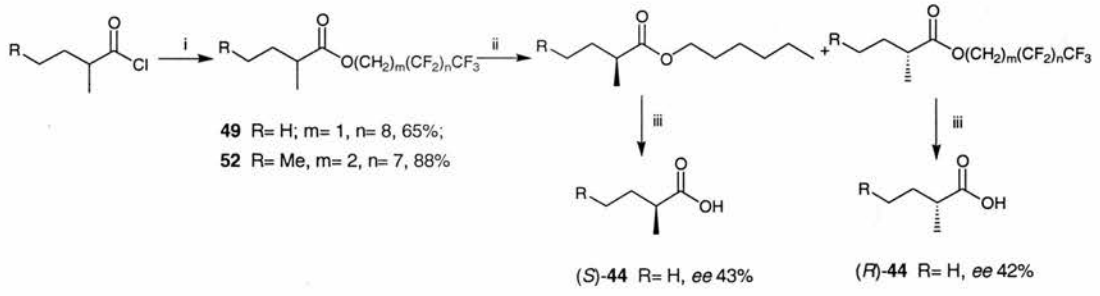
As can be seen from Table 17 (entry 1) carboxylic acid **69** is esterified with 1-decanol in the presence of *CRL*. Within 8 h the conversion is close to 50% under the conditions used. The enantioselectivity of this process is moderate (E = 16) and the configuration of the faster enantiomer follows from Figure 32. However acid **78** is a much less reactive substrate (entry 2) compared with **69** and very long reaction times are needed to achieve a modest degree of conversion (entry 3). The enantioselectivity is also very low and it is not known which enantiomer is preferred by the lipase. 2-Methylhexanoic acid **46** is an excellent substrate for this lipase and the enantiomeric discrimination is very high (E > 100, entry 4). The observed stereochemistry also fits Figure 32. However a minor change in the structure causes big differences in *CRL* catalysed esterification. 2-Ethylhexanoic acid **79** proved to be even less reactive than **78** (compare entry 2 and 5) and the lipase is not able to distinguish between the enantiomers of **79** (entry 6). Based on these results it seems that the ethyl group is too large to represent the smaller substituent (M) in Figure 32, but the CF_3 group in **69** or **78** may fit, explaining the moderate selectivity for the esterification of **69** and the low but existing reactivity of **78**. These conclusions follow if the stereoselectivity is controlled by steric hindrance alone. It would be interesting to determine the absolute configuration of the faster reacting enantiomer of **78** to see whether there is a change in the preference of the lipase.

2.5.1.3 Resolution of carboxylic acids by fluorous delabelling

After having demonstrated the use of highly fluorinated alcohols for the kinetic resolution of racemic 2-methylalkanoic acids with *CRL* our next aim was to investigate the possibility of an enantiomer selective delabelling according to Scheme 20. The starting highly fluorinated esters of 2-methylalkanoic acids should

afford enantiomerically enriched 'organic' esters upon transesterification with an appropriate alcohol. This strategy has been shown to proceed efficiently with non-chiral substrate (see section 2.3.4.1).

The required racemic fluorous tagged esters **49** and **52** were prepared by reaction of appropriate 2-methylalkanoyl chloride with the fluorous alcohols **37** or **36**, Scheme 40. 1-Hexanol **32** (0.6 mmol) and fluorous ester **49** (0.57 mmol) were dissolved in hexane (5 cm^3) and PFD (5 cm^3). Lipase *CRL* (200 mg) was added and the mixture was shaken at 250 rpm/40 °C. After 40 h (53% conversion) the enzyme was filtered off and the liquid phases separated on cooling (4 °C). The hexane phase was washed with PFD (2 × 5 cm^3) and then the solution was hydrolysed in LiOH/MeOH yielding (*S*)-**44** (*ee* 43%). Conversely the combined fluorous phase was hydrolysed under the same conditions giving (*R*)-**44** (*ee* 42%), Scheme 40.



Scheme 40: Preparation of esters **49** and **52** and *CRL* catalysed transesterifications. Reagents and conditions: i) **37** or **36**, 120-150 °C, 24-48 h; ii) 1-hexanol, *CRL*, 40 °C; iii) LiOH/MeOH, reflux, 1 h.

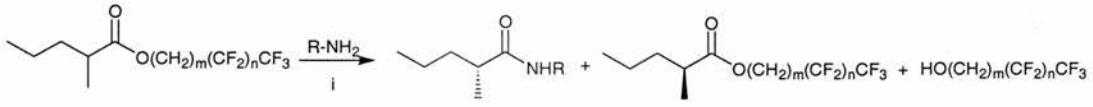
In a control reaction when 1-hexanol (2 mmol) and **52** (1 mmol) were dissolved in hexane (5 cm^3), PFD (5 cm^3) and *CRL* (200 mg) was added there was no hexyl 2-methylpentanoate observed, even after shaking the mixture at 250 rpm/40 °C for 48 h.

The esters of racemic 2-methylalkanoic acids and a fluorous alcohol, with one methylene group between perfluoroalkyl and hydroxyl such as **37**, are suitable

substrates for lipase catalysed fluorous delabelling. The observed *ee* values are similar to those found in the resolution of **44** using fluorous labelling methods. On the other hand the fluorous ester **52** did not react presumably because it is derived from the less nucleophilic alcohol **36** (compared with **37**).

2.5.1.3.1 Resolution of carboxylic acids by lipase catalysed aminolysis

Although lipases are most widely used for enantioselective hydrolysis, esterification and transesterification reactions where the nucleophile is either water or alcohol, there are some reports of using lipases to perform aminolysis and even transamidation reactions.[218, 219, 220] Amines can react non-enzymatically with various activated esters due to the increased nucleophilicity of amines over alcohols.[219] Generally however transamidations are very sluggish even in the presence of enzymes.[219] In this study we decided to investigate aminolysis between the fluorous esters **51** and **52** and benzylamine or cyclohexylamine, Scheme 41.



51 n= 8, m= 1
52 n= 7, m=2

(*R*)-**80** R= CH_2Ph
(*R*)-**81** R= C_6H_{11}

(*S*)-**51** n= 8, m= 1
(*S*)-**52** n= 7, m=2

37 n= 8, m= 1
36 n= 7, m=2

Scheme 41: Lipase catalysed aminolysis of fluorous esters. Reagents and conditions: i) ester (0.5 mmol), amine (1.5 mmol), hexane (10 cm^3) and *CAL-B* (400 mg) were shaken at 250 rpm/40 °C. After the reaction the enzyme was filtered off and the solvent was removed. The residue was partitioned between MeOH/FC-72 (10 cm^3 of each) and the MeOH phase was washed with FC-72 (10 cm^3).

Ester **51** was treated with benzylamine in the presence three lipases, *CAL-B*, *CRL* and *PPL*. Only the *CAL-B* catalysed the reaction to form amide (*R*)-**80** (*ee* 47%) and unreacted fluorous ester (*S*)-**51** (*ee* 45%) after 3.5 h (conversion 49%). After

workup the washed MeOH phase contained all of the amide **80** and ester **51** was present only in FC-72 phase. However the by-product fluorous alcohol **37** was distributed through both phases. Without added enzyme the reaction between **51** and benzylamine proceeded only to 5% conversion after 72 h and thus the background reaction was essentially insignificant.

Ester **51** also reacted with cyclohexylamine in the presence of *CAL-B* to form amide (*R*)-**81** (*ee* 42%) and unreacted fluorous ester (*S*)-**51** (*ee* 42%) after 3.5 h (conversion 50%). Without added enzyme there was no **81** detected after 72 h. Ester **52** reacted with benzylamine in the presence of *CAL-B* to form amide (*R*)-**80** (*ee* 27%) and unreacted fluorous ester (*S*)-**52** (*ee* 13%) after 17 h (conversion 19%).

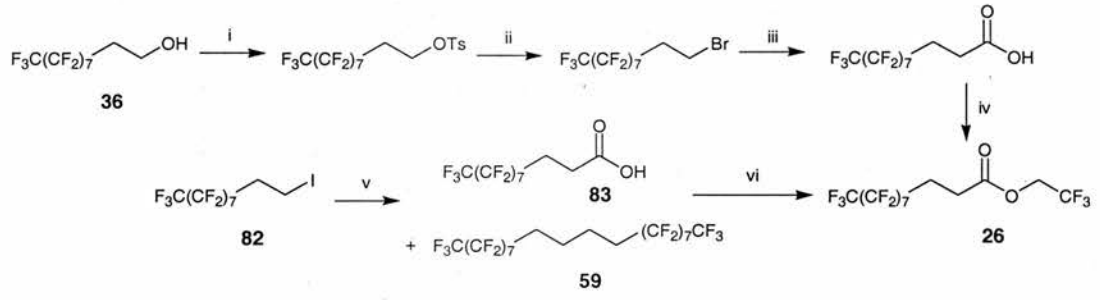
Unlike the transesterifications of esters of 2-methylpentanoic acid, which are catalysed by *CRL* enzyme with good to high enantioselectivity, the studied aminolyses are catalysed only by *CAL-B* and the enantioselectivities are considerably lower. The low enantioselectivities clearly limit the utility of these reactions.

2.5.2 Resolution of alcohols

Kinetic resolutions of primary and secondary alcohols in organic solvents are carried out, in most cases, through lipase catalysed transesterification and esterification reactions.[221] In order to shift the equilibrium inherent in these reactions towards desired products, activated esters such as vinyl acetate are employed as acyl donors.[164, 222, 223] It is possible to perform the resolution of chiral alcohols by both lipase catalysed fluorous labelling and fluorous delabelling strategies according to Scheme 21 and Scheme 22. Indeed the lipase catalysed

resolution of 1-phenylethanol **13** by enantioselective acylation using the highly fluorinated acyl donor **26** was studied, Scheme 25.[186, 187, 188] These enzymatic reactions were carried out in acetonitrile as a solvent followed by extraction into a fluorous solvent as a separate step.

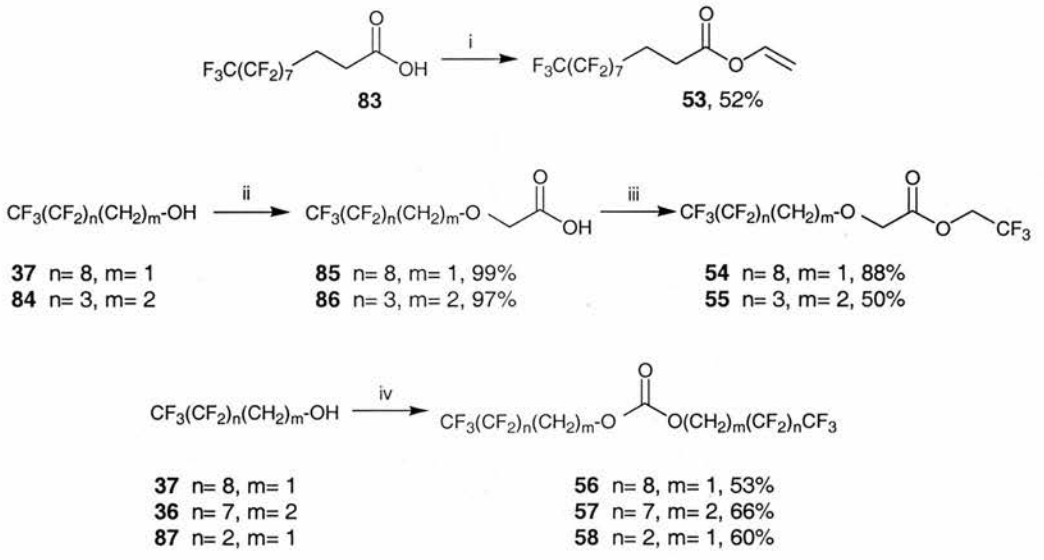
The highly fluorinated acylating agent **26** was prepared in five steps from alcohol **36** in an overall yield of 53%, Scheme 42.[187] Some improvements were made to the preparation of **26** starting from iodide **82**. Alkyl magnesium iodide was generated from **82** followed by the addition of CO_2 to give acid **83** in 89% yield. The side product **59** of this Grignard reaction was formed in about 5% yield. Finally an acid catalysed esterification with trifluoroethanol gave **26** in an overall yield of 59% and in only three steps, Scheme 42.



Scheme 42: Preparation of highly fluorinated acyl donor **26**. Reagents and conditions: i) TsCl, Et_3N, THF, reflux, 10 h, 88%; ii) LiBr, acetone, reflux, 7 h, 93%; iii) Mg, THF, reflux, 6 h, CO_2, 88%; iv) CF_3CH_2OH, H_2SO_4 (cat.), reflux, 6 h, 74%; v) Mg, Et_2O, 30 °C, 3 h, CO_2, **83** 89%, **59** 5%; vi) CF_3CH_2OH, H_2SO_4 (cat.), 75 °C, 10 h, 74%.

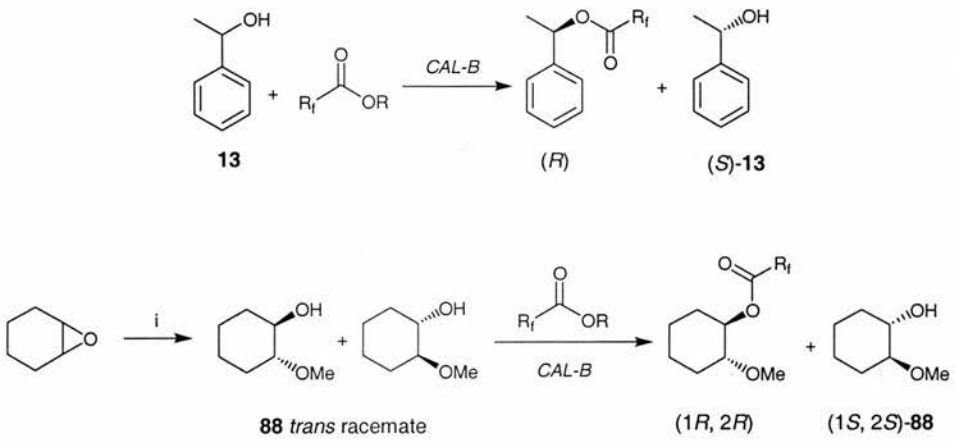
In addition some other highly fluorinated acyl donors were prepared which were used in the enzymatic resolution of chiral alcohols, Scheme 43. The highly fluorinated vinyl ester **53** was efficiently prepared by mercuric catalysed acidolysis of vinyl acetate. 'Heavy' and 'light' fluorous 2,2,2-trifluoroethyl esters **54** and **55** were prepared in two steps from alcohols **37**, **84** and bromoacetic acid to form carboxylic acids **85** and **86** also in good yield.[224] These carboxylic acids were

subjected to acid catalysed esterification. Finally the fluorous carbonates **56-58** were prepared from alcohols **37**, **36** or **87** in one step by reaction with a phosgene solution, Scheme 43. These novel acyl donors were explored in lipase reactions.



Scheme 43: Preparation of highly fluorinated acyl donors for lipase catalysed resolution. Reagents and conditions: i) $CH_3CO_2CH{=}CH_2$, $Hg(OAc)_2$ (cat.), H_2SO_4 (cat.), 65 °C, 20 h; ii) NaH, $BrCH_2CO_2H$, THF, r.t., 24 h; iii) CF_3CH_2OH, H_2SO_4 (cat.), reflux, 22 h; iv) $COCl_2$ (20% solution in toluene), pyridine, toluene, 50 °C, 1 h.

The resolution of racemic 1-phenylethanol **13** and *trans*-2-methoxycyclohexanol **88** was carried out by fluorous labelling using the acyl donors **26**, **53-58** according to Scheme 44. Racemic *trans* 2-methoxycyclohexanol **88** was prepared by iodine catalysed ring opening of cyclohexene oxide with methanol.[225] In this reaction only the *trans* isomer is formed as was confirmed by GC-MS analysis of prepared **88** and commercial 2-methoxycyclohexanol which was a mixture of *cis* and *trans*. Enantiomerically pure **88** is a valuable chiral building block used in the synthesis of potent antibiotics[226] and it has previously been prepared by biochemical methods.[227] The absolute configuration of the enantiomerically enriched alcohols was assigned by a comparison with commercial sample of enantiomerically pure **13** or by comparison of the optical rotation of **88** with the literature value.[228]



Scheme 44: Preparation of racemic *trans* 2-methoxycyclohexanol **88** and lipase catalysed kinetic resolution of chiral alcohols **13** and **88** by fluorous labelling using highly fluorinated acyl donors. R_f = highly fluorinated residue. Reagents and conditions: i) MeOH, I_2 (cat.), r.t., 45 min., 38%.

The results of the lipase catalysed resolutions of alcohols **13** and **88** by fluorous labelling are presented in Table 18. The preparative resolution of **13** using **26**, reported by Theil,[186] by separation between MeOH and FC-72 is listed in entry 1, Table 18. Our resolutions are listed in entries 2-14. Those in entry 9 and 13 were conducted on a preparative scale. The *CAL-B* lipase can catalyse transesterification of 1-phenylethanol **13** in high enantioselectivity. The highly fluorinated acyl donor **54** derived from glycolic acid is much more reactive than the original acyl donor **26** developed by Thiel (compare reaction times of 10 h vs. 30 h, entry 2 and 3). Similar rate accelerations were observed for *CRL* catalysed transesterification of secondary alcohols with trichloroethyl methoxyacetate when compared with trichloroethyl butanoate and thus the presence of the β-oxygen appears to accelerate the reaction rate.[229]

The fluorous tagged product was efficiently separated from unreacted alcohol (*S*)-**13** by filtration using fluorous reverse phase silica gel (FRPSG), but it proved also possible to perform the separation using fluorous extraction (entry 4). Highly

fluorinated vinyl ester **53** emerged as a very reactive acyl donor (entry 5). All highly fluorinated esters **26**, **53** and **54** acylate **13** with high enantioselectivity in the presence of the enzyme. Unfortunately, highly fluorinated carbonates **56** and **57** were not very reactive and only less than 5% and 10% of alcohol **13** respectively was transesterified after 112 h (entry 6 and 7). However when 'light' fluorous carbonate **58** was used as an acylating agent for the resolution of **13** neither fluorous extraction nor filtration using fluorous silica was capable of separating the products (entry 8). When the reaction mixture was loaded onto a FRPSG column the first fraction contained both unreacted **13** and the product- mixed carbonate, and the second fraction gave only the mixed carbonate. In this case presumably the tagged product was not fluorophilic enough to be retained on the fluorous silica.

Table 18: Lipase (*CAL-B*) catalysed kinetic resolutions of alcohols by transesterification with fluorous acyl donors, Scheme 44.[a] Results presented in entry 1 were taken from the literature.[186]

Entry	Alcohol; (mmol)	Acyl donor; (mmol)[b]	*CAL-B* (g)	Reaction time (h); temp. (°C); conversion (%)[c]	Type of separation[d]	*ee*; yield[e] (%)	*ee*; yield[f] (%)
1[186]	**13**; 10.0	**26**; 15.0	2.00	19; 25; 50	MeOH/FC-72	98; 94	99; 96
2	**13**; 0.53	**26**; 0.64	0.100	30; 37; 49	FRPSG	98; -	98; -
3	**13**; 0.53	**54**; 0.64	0.100	10; 37; 49	FRPSG	98; -	97; -
4	**13**; 0.60	**54**; 0.65	0.200	48; 37; 48	MeOH/FC-72	98; -	90; -
5	**13**; 0.46	**53**; 0.46	0.200	6; 40; 50	MeOH/FC-72	97; -	98; -
6	**13**; 1.00	**56**; 1.00	0.200	112; 40; < 5	MeOH/FC-72	98; -	<10; -
7	**13**; 1.00	**57**; 1.00	0.200	112, 40; 10	MeOH/FC-72	98; -	10; -
8	**13**; 1.00	**58**; 1.00	0.200	40; 40; 50	FRPSG	97; -	-; -
9	**88**; 13.1	**26**; 17.4	2.00	65; 30; 45	MeOH/FC-72	99; 70	>80; 98
10	**88**; 0.37	**26**; 0.45	0.050	44; 30; 14	MeOH/FC-72	99; -	14; -
11	**88**; 0.37	**26**; 0.45	0.050	44; 30; 26	MeOH/FC-72	99; -	26; -
12	**88**; 0.52	**53**; 0.49	0.200	5; 40; 50	MeOH/FC-72	99; -	90; -
13	**88**; 1.58	**55**; 3.96	1.00	17; 37; 50	FRPSG	99; 87	>90; 93
14	**88**; 1.28	**58**; 1.32	0.200	70; 30; 50	FRPSG	97; -	-; -

[a] Conditions: Alcohol, acyl donor, solvent (10 cm^3 per 1 mmol of racemic alcohol) and *CAL-B* were shaken at 250 rpm. [b] Reaction solvent used is as follows: MeCN for entry 1 and 10; hexane/FC-72 for entry 2,3,5,6,7,8 and 12; FC-72 for entry 4,9,11 and 14; hexane for entry 13. [c] Determined by GC-MS of the reaction mixture. [d] After the reaction the enzyme was filtered off the solvent was removed and the residue was partitioned between MeOH and FC-72, the MeOH phase was washed with FC-72 five times. Alternatively the reaction mixture (~0.5 g) was loaded onto FRPSG column (5 g) and eluted with 80% aqueous MeOH (8 cm^3) to obtain the non-fluorinated compounds and then with acetone (15 cm^3) to obtain the fluorous compounds. [e] Isolated yield and enantiomeric excess of the alcohol obtained by hydrolysis of combined fluorous phase or fluorous fraction after separation on fluorous silica. [f] Isolated yield and enantiomeric excess of the alcohol obtained from MeOH phase or 'organic' fraction after separation on fluorous silica. Reactions were conducted on an analytical scale when yield values are missing.

T*rans* 2-methoxycyclohexanol **88** was found to be a suitable substrate for the *CAL-B* and the resolution of **88** using **26** was conducted on a preparative scale using FC-72 as a solvent (entry 9). The reaction proceeded to about 45% conversion and then the enzyme was filtered off and methanol was added. The mixture was left to separate and the MeOH phase was washed five times with FC-72. The resultant MeOH phase contained only (1*S*, 2*S*)-**88** (98%, *ee* > 80%). The combined fluorous solvent was evaporated and after hydrolysis (1*R*, 2*R*)-**88** (70%, *ee* 99%) was isolated (entry 9). There was about an 80% recovery of the fluorous solvent and the fluorous tag could be recovered in 90% in the form of the lithium salt of carboxylic acid **83**.

It was interesting to compare the reaction rates of transesterification of **88** with **26** in different solvent systems (entry 10 and 11). The reaction between **88** and **26** proceeds to only 14% in acetonitrile whereas it reached 26% conversion in FC-72 after 44 h. Highly fluorinated vinyl acyl donor **53** gave high *ee* values for resolution of **88** in a relatively short reaction time (entry 12).

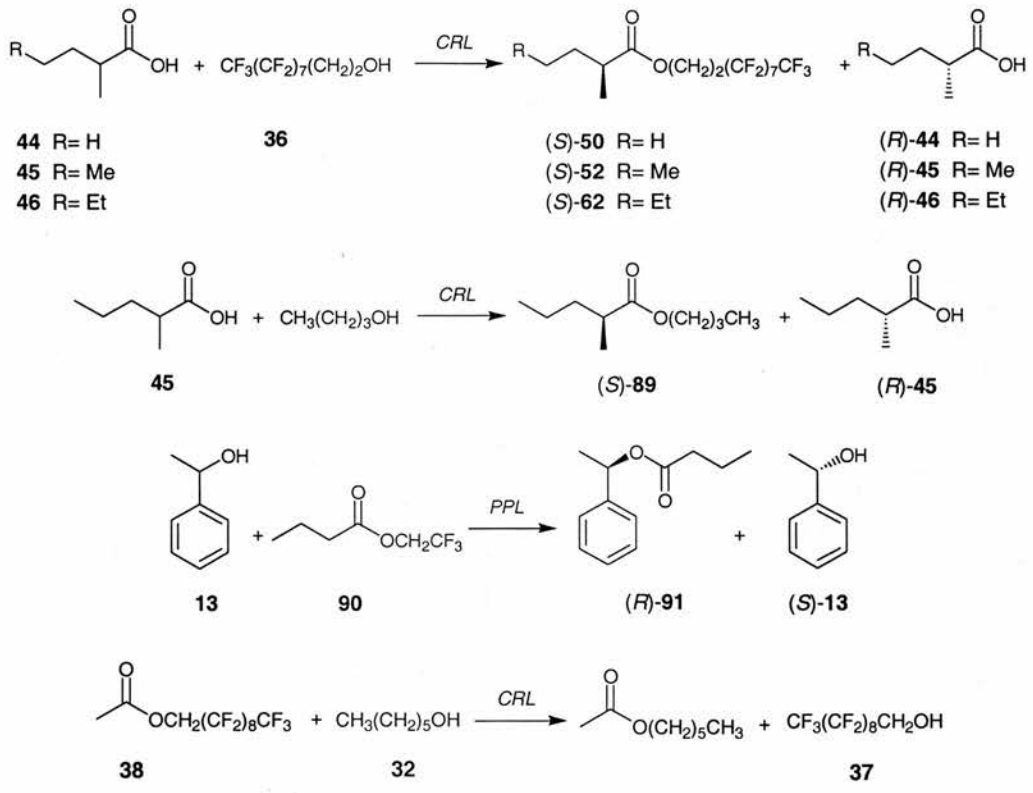
The resolution of alcohol **88** with the 'light' fluorous acyl donor **55** derived from glycolic acid (entry 13) was also carried out on a preparative scale. High enantioselectivities and yields were achieved and it was possible to separate the fluorous labelled product from the unreacted alcohol by filtration using FRPSG. In this case the fluorous biphase extraction was not a practical method because multiple extractions were needed, so fluorous silica gel offered a clear advantage for separating the 'organic' compounds from the 'light' fluorous ones. The fluorous tag was again recovered in 90% in the form of the lithium salt of **86**. Again the 'light' fluorous carbonate **58** was not a suitable acylating agent for the

resolution of **88** (entry 14). Neither fluorous extraction nor filtration using fluorous silica was capable of separation of the products.

2.5.3 The influence of fluorous solvents on the reactivity and enantioselectivity of lipase catalysed reactions

2.5.3.1 Influence on reactivity

Preliminary investigations on the influence of fluorous solvents on the reaction rate and on the thermo-stability of the lipases were presented in sections 2.3.1 and 2.3.2. It was shown that for two lipases (*CRL* and *PPL*) the transesterification between 2,2,2-trichloroethyl butanoate **31** and 1-hexanol **32** is considerably faster in the mixed solvent system of FC-72/hexane (1/1) than in hexane alone, Figure 20. One of the reasons for this rate enhancement has already been identified as the increased thermal stability of lipases in the fluorous solvent, section 2.3.2. In order to have a better understanding of this phenomenon it was decided to study the rates of different lipase catalysed reactions in different solvents. The lipase catalysed reactions listed in Scheme 45 were investigated.



Scheme 45: Lipase catalysed reactions examined to study the influence of the fluorous solvent on reactivity and enantioselectivity.

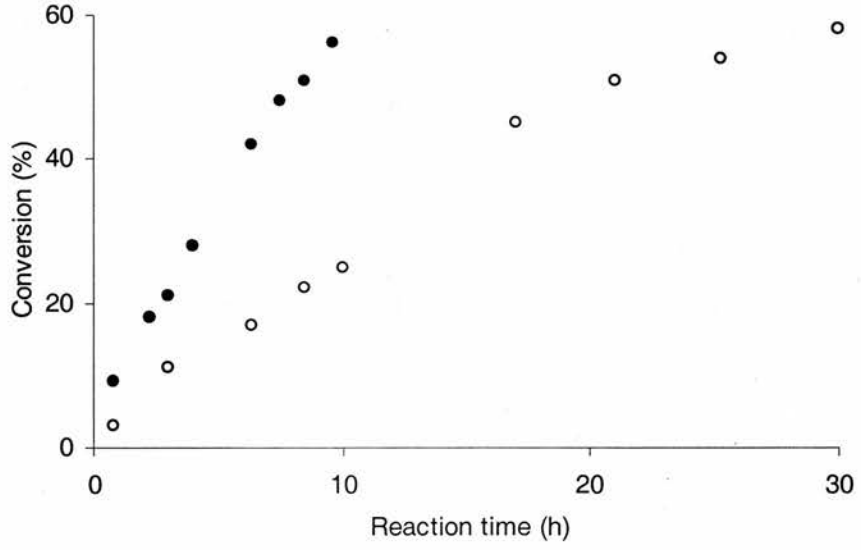


Figure 34: Conversion vs. reaction time for esterification of carboxylic acid **44** (0.65 mmol) with fluorous alcohol **36** (0.60 mmol) catalysed by *CRL* (100 mg) at 40 °C in a mixture of FC-72/hexane (10 cm^3): 19/1 (•); 1/19 (○).

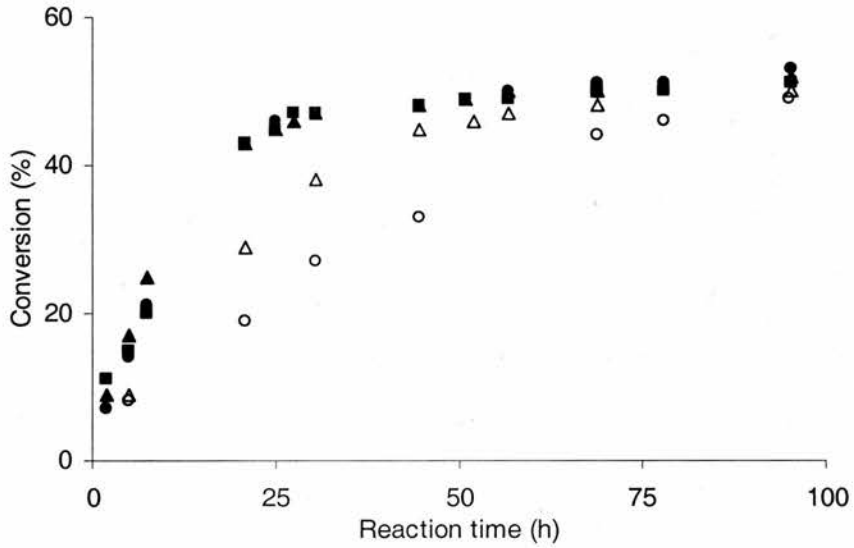


Figure 35: Conversion vs. reaction time for esterification of carboxylic acid **45** (0.65 mmol) with fluorous alcohol **36** (0.60 mmol) catalysed by *CRL* (100 mg) at 40 °C in a solvent (10 cm^3): FC-72/hexane, 19/1 (●); PFD/hexane, 19/1 (▲); PFMC/hexane, 19/1 (■); PFD/cyclohexane, 1/19 (Δ) and FC-72/hexane, 1/19 (○).

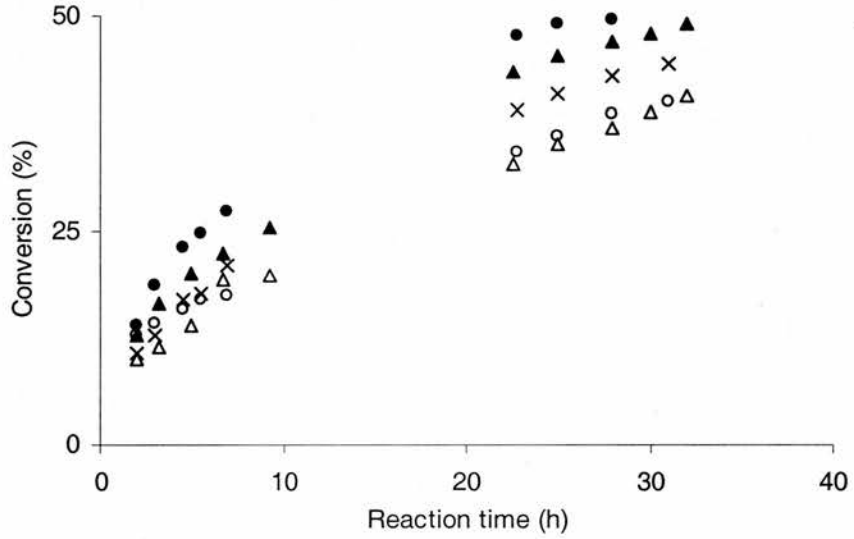


Figure 36: Conversion vs. reaction time for esterification of carboxylic acid **45** (0.50 mmol) with fluorous alcohol **36** (0.50 mmol) catalysed by *CRL* (200 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 49/1 (●); PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×); PFD/hexane, 1/3 (Δ) and hexane (○).

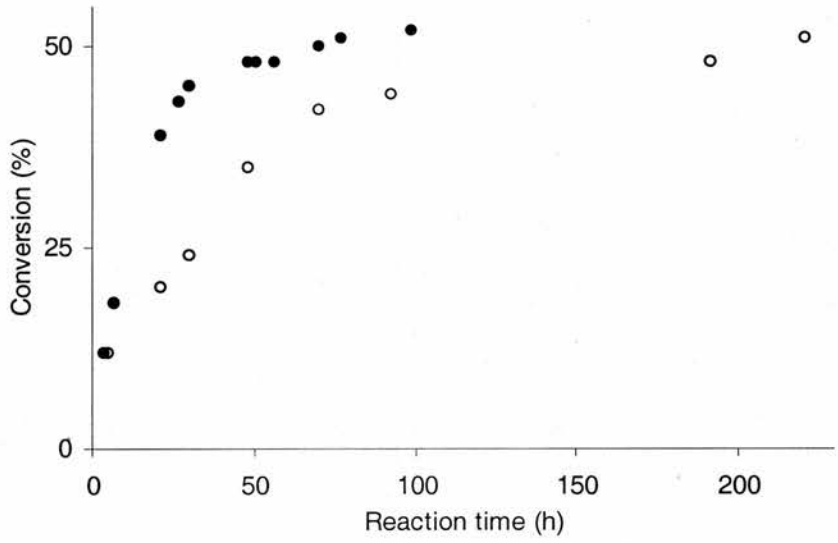


Figure 37: Conversion vs. reaction time for esterification of carboxylic acid **46** (0.65 mmol) with fluorous alcohol **36** (0.60 mmol) catalysed by *CRL* (100 mg) at 40 °C in a mixture of FC-72/hexane (10 cm^3): 19/1 (●); 1/19 (○).

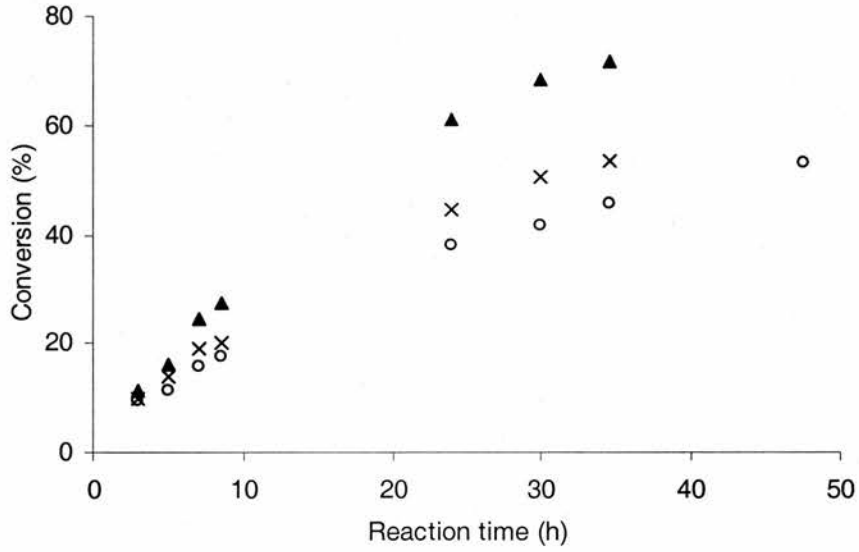


Figure 38: Conversion vs. reaction time for esterification of carboxylic acid **45** (0.50 mmol) with 1-butanol (1.50 mmol) catalysed by *CRL* (200 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×) and hexane (○).

It can be seen from the results in Figures 34-38 that when both the acyl donor and the nucleophile are non-fluorinated or when a non-fluorinated acyl donor is combined with a fluorous nucleophile than the increasing amount of fluorous solvent dramatically increases the rate of the enzymatic reaction. The particular

fluorous solvent has no significant influence and there is a similar rate enhancement observed for FC-72, PFD or PFMC, Figure 35.

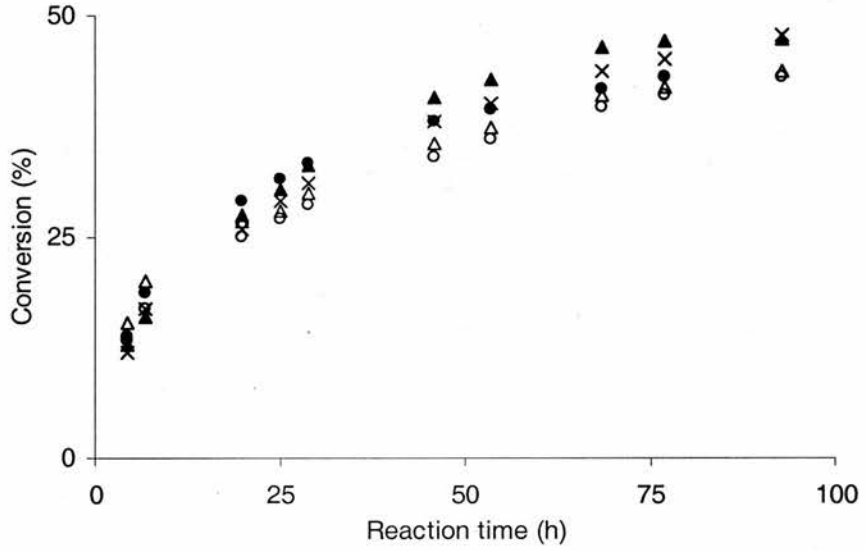


Figure 39: Conversion vs. reaction time for transesterification of 1-phenylethanol **13** (0.50 mmol) with trifluoroethyl butanoate **90** (1.50 mmol) catalysed by *PPL* (500 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 49/1 (•); PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×); PFD/hexane, 1/3 (Δ) and hexane (○).

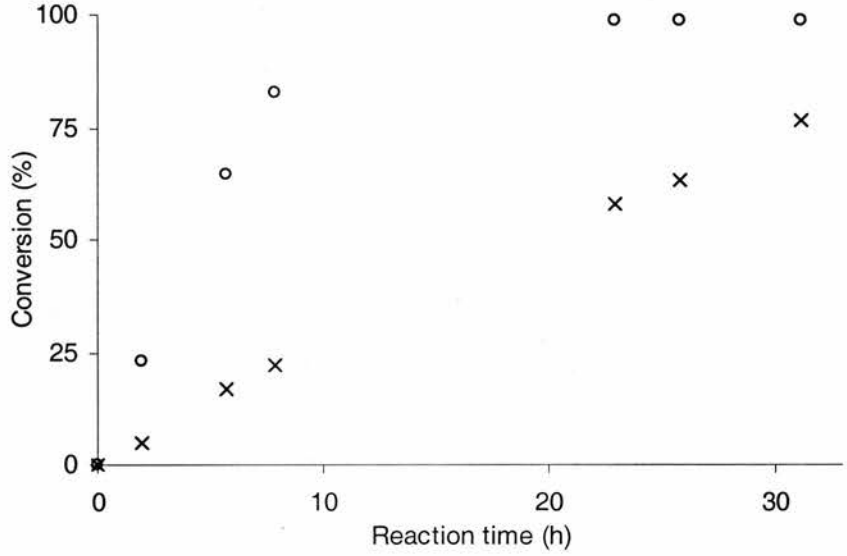


Figure 40: Conversion vs. reaction time for transesterification of fluorous acetate **38** (0.50 mmol) with 1-hexanol **32** (1.00 mmol) catalysed by *CRL* (100 mg) at 40 °C in a solvent (5 cm^3): hexane (○) and FC-72/hexane, 1/1 (×).

However when trifluoroethyl butanoate **90** was used as acyl donor in a transesterification reaction with 1-phenylethanol **13**, increasing the ratio of PFD/hexane did not influence the rate of the reaction at all, Figure 39. More importantly when the perfluorinated acetate ester **38** was transesterified with 1-hexanol **32** a dramatic decrease in the reaction rate was observed in FC72/hexane (1/1) compared to hexane alone, Figure 40.

It seems from this study that there is not any special activation caused by the fluorous solvent except an increase in the fluorophobic effect of the reaction constituents in the fluorous solvent. In reactions with a high proportion of fluorous solvent, polar molecules are not solvated and therefore tend to associate together presumably on the surface of the enzyme. This increases the effective concentration of the substrates around the enzyme. If the acyl donor is not fluorinated the reaction rate is higher in solvent with a higher proportion of perfluoroalkanes. There is evidence from the literature that for most *CRL* catalysed hydrolyses, esterifications and transesterifications, the first step involving the formation of the acyl-enzyme intermediate, is rate limiting.[195] Therefore when fluorous alcohol **36** is used for example the reaction rate is higher in a solvent with a higher proportion of perfluoroalkanes, Figures 34-37.

Conversely, fluorous acyl donors like **38** are solvated well in the fluorous solvent and the reaction rate is then considerably slower in the FC-72/hexane (1/1) mixture relative to hexane, Figure 40. The acyl donor **90** has a CF_3 group but this is not sufficiently fluorophilic so the two influences operate against each other.

2.5.3.2 Influence on enantioselectivity

The influence of fluorous solvent on the enantioselectivity of the lipase catalysed reactions was investigated and the data is presented in Figures 41-43. In this case

chiral GC-MS allowed determination of *ee* values for both the product and the unreacted chiral substrate directly from the reaction mixture. Thus the *ee* values are reported without recourse to any separation.

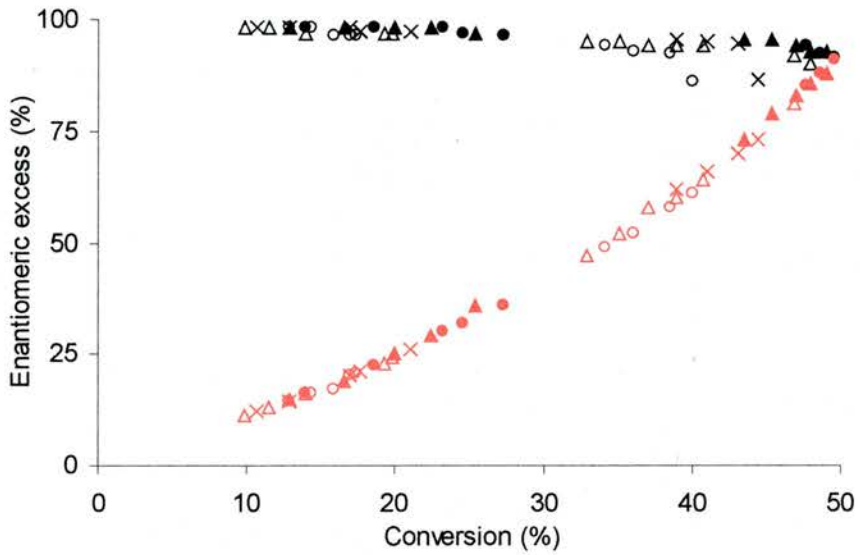


Figure 41: The enantiomeric excess values vs. conversion for esterification of carboxylic acid **45** (0.50 mmol) with fluorous alcohol **36** (0.50 mmol) catalysed by *CRL* (200 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 49/1 (●); PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×); PFD/hexane, 1/3 (Δ) and hexane (○). The *ee* of unreacted carboxylic acid (*R*)-**45** are shown in red and those of fluorous ester (*S*)-**52** in black symbols.

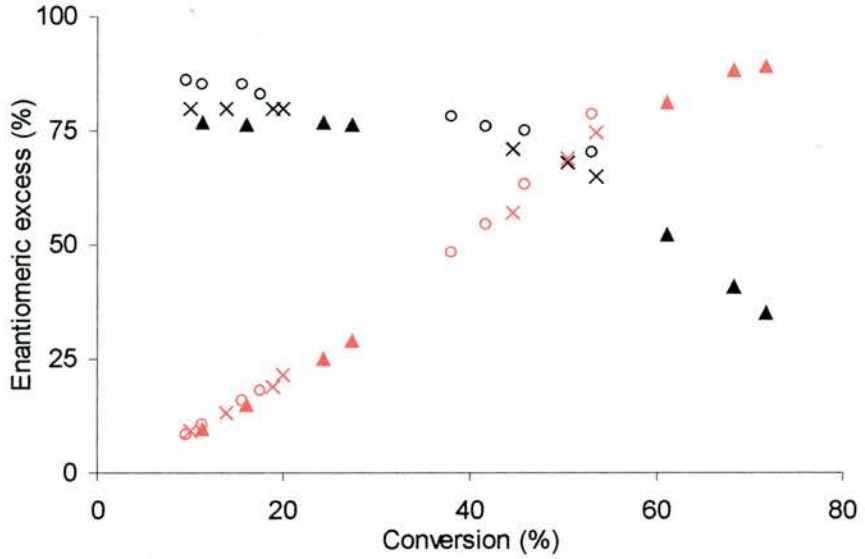


Figure 42: The enantiomeric excess values vs. conversion for esterification of carboxylic acid **45** (0. 50 mmol) with 1-butanol (1.50 mmol) catalysed by *CRL* (200 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×) and hexane (○). The *ee* of unreacted carboxylic acid (*R*)-**45** are shown in red and those of (*S*)-**89** in black symbols.

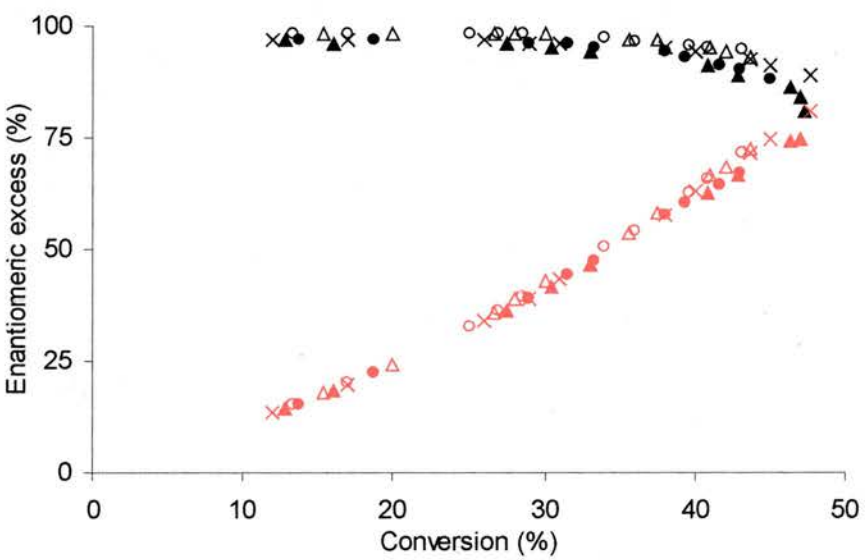


Figure 43: The enantiomeric excess values vs. conversion for transesterification of 1-phenylethanol **13** (0.50 mmol) with trifluoroethyl butanoate **90** (1.50 mmol) catalysed by *PPL* (500 mg) at 40 °C in a solvent (10 cm^3): PFD/hexane, 49/1 (●); PFD/hexane, 3/1 (▲); PFD/hexane, 1/1 (×); PFD/hexane, 1/3 (Δ) and hexane (○). The *ee* of unreacted alcohol (*S*)-**13** are shown in red and those of (*R*)-**91** in black symbols.

From the data shown in Figures 41-43 it is apparent that the fluorous solvent does not have any dramatic effect on the enantioselectivity of these esterification and transesterification reactions. Increasing the PFD/hexane ratio has a small positive effect on enantioselectivity of esterification of carboxylic acid **45** with fluorous alcohol **36**, neutral effect on esterification of the acid **45** with 1-butanol and small negative effect on the transesterification of alcohol **13** with acyl donor **90**. However these effects are too small to be significant.

2.6 Summary and conclusions

Part A Lipase mediated esterification and transesterification reactions have been explored in fluorous solvents. We have demonstrated for the first time that different kinds of lipases operate efficiently not only in hydrophobic organic solvents such as hexane but also in perfluorocarbons. The widespread notion so far was that the best solvents for enzymatic reactions in organic media are hydrocarbons, but it has been shown that lipases are even more active in a mixed system of hydrocarbons and perfluorocarbons as the reaction media. Additionally the stability of *CRL* and *PPL* lipases has been found to be better in a fluorous solvent than in hexane.

Fluorous alcohols can act as nucleophiles in enzymatic reactions so it is possible to prepare various esters derived from them by esterification and transesterification reactions in high yield. The reversibility of some transesterification reactions can be avoided by employing more nucleophilic fluorous alcohols having two CH_2 spacer units insulating the electron withdrawing effect of the perfluoroalkyl group from the hydroxyl functionality or by utilising different acylating agents such as acids, anhydrides or vinyl esters instead of 2,2,2-trichloroethyl esters.

Additionally fluorous-tagged esters for example **35** are suitable substrates for lipase catalysed transesterification reactions with alcohols. On the other hand activated esters of perfluorobutanoic acid, **41** and **42** are not suitable for enzymatic transesterifications. Under the conditions used, **41** and **42** reacted with 1-hexanol non-enzymatically with a similar rate to that with the enzyme.

In enzymatic reactions where one of the starting materials and one of the products formed was fluorous tagged and the other was non-fluorinated, the mixed solvent system served as a medium to separate the product by liquid/liquid,

fluorous/organic extraction. The limiting factor for efficient separation was the difference in partitioning of each product in each phase.

Part B Partition coefficients for 24 compounds were measured in different solvent systems and at various temperatures. For the purpose of this study P values in FC-72 or PFD and hexane were required rather than P^o values. It has been found that the non-fluorinated compounds partition only into the organic phase. For the fluorinated compounds several factors including polarity, the length of the fluorous ponytail, the bulkiness of the non-fluorinated moiety of the solute and the solute-solvent hydrogen bonding all have a significant effect of the partitioning coefficients. There is also a dramatic effect on partitioning when the organic solvent is changed. Partition coefficients of 15 compounds were calculated using de Wolf's method[134] and a fair correlation has been found with experimental values.

The effect of fluorous solvents on partitioning of the esters **50** and **52** was determined experimentally and correlated well with the trends predicted by Equation 5. Perfluorodecalin was shown to be the most effective fluorous solvent for the extraction of fluorophilic solutes.

Part C Lipase catalysed kinetic resolutions of racemic 2-methylalkanoic acids using fluorous labelling (Scheme 19) with highly fluorinated alcohols was successfully achieved. The more reactive vinyl esters **60** and **61** displayed lower enantioselectivities than the corresponding acids **44** and **45** in *CRL* catalysed reactions with fluorous alcohols **36** and **37**. It was found that the reactivity decreases and enantioselectivity increases on increasing the length of the alkyl chain of the 2-methylalkanoic acids. The advantage of using highly fluorinated alcohols as nucleophiles for the lipase catalysed (trans)esterifications is that the

enantiomerically enriched products (fluorous esters) are easily separated from unreacted ester or acid by liquid/liquid, fluorous/organic extraction. No chromatography is required. One of the main limiting factors for efficient separation of the enantiomeric series is inefficient partitioning. The enantiomeric purity of products isolated from the organic phase is compromised to some extent by some solubility of the fluorous ester products. For complete separation either repeated extraction of the organic phase with a fluorous solvent, or use of a continuous fluorous extractor was necessary. By this method high enantiomeric excesses were obtained in the resolution of carboxylic acids **45**, **46** and **64**. These novel conditions for lipase catalysed esterifications interestingly gave the same or better enantioselectivities when compared to literature studies[193] using long chain alcohols. Our fluorous tag approach leads to a much simpler separation of enantiomers compared with chromatography and in some cased higher *ee* values were achieved. Prolonged reaction times were needed when using less nucleophilic fluorous alcohols **36** and **37**.

An attractive alternative to fluorous extraction was fluorous filtration using FRPSG. This was successfully applied to the separation of enantiomers of fluorous ester and the unreacted acid after *CRL* catalysed esterifications (e.g. **45**). It was found that fluorous alcohols $CF_3(CF_2)_n(CH_2)_2OH$, n= 7, 5, 3 bring sufficient fluorine content to separate the fluorous ester from the carboxylic acid **45**, unlike $CF_3CF_2(CH_2)_3OH$. The advantage of such fluorous filtration over extraction is that 'light' fluorous tags of insufficient partitioning for the fluorous phase can be used.

The methodology of enzymatic fluorous labelling was successfully applied to the multigram synthesis of both enantiomers of 2-methylpentanoic acid **45** in high *ee*s and good yields. The resultant (*S*)-**45** was converted into a natural pheromone (*S*)-

67 greatly improving the yield for its preparation and considerably reducing the number of reaction steps as used to prepare the pheromone in the literature.[200, 201]

Racemic 3,3,3-trifluoro-2-methylpropanoic acid **69** was synthesised in three steps and the *CRL* catalysed esterification with fluorous alcohol **73** or decanol **74** with the separation by fluorous filtration or acid-base extraction allowed the preparation of both enantiomers of **69** for the first time. The absolute stereochemistry of these enantiomers, which are related by interconversion of the CF_3 and CH_3 groups, was unambiguously determined by X-ray diffraction of a diastereoisomeric derivative **77**. The stereochemical preference of *CRL* towards **69** was found to follow the pattern for 2-methylalkanoic acids as expected.

A comparative study on esterification of 2-methyl branched acids **69** and **46** and 2-ethyl branched acids **78** and **79** was also carried out. It was found that 2-methyl branched carboxylic acids react much faster and display better enantioselectivity than 2-ethyl branched carboxylic acids.

The resolution of racemic alcohols 1-phenylethanol **13** and *trans* 2-methoxycyclohexanol **88** was investigated using a variety of fluorous acyl donors. The synthesis of acyl donor **26** was improved compared to the literature[187] preparation in terms of yield and the number of reaction steps required. Additionally, routes to new and more reactive 'heavy' and 'light' fluorous acyl donors were developed.

Fluorous extraction or filtration using FRPSG was employed to separate fluorous esters from the corresponding unreacted alcohols after lipase transesterifications. The *ee* values of the resolved alcohols were generally high and in resolutions performed on a preparative scale, high yields could also be achieved.

The influence of the fluorous solvent on the reactivity and the enantioselectivity of various lipase catalysed reactions were investigated. It was found that in those lipase reactions where the acyl donor is not fluorinated the addition of different types of fluorous solvent dramatically increased the reaction rate. However, in the case of transesterifications with fluorinated esters such as the fluorous acetate **38** with hexanol, the effect of the fluorous solvent is negative on the reaction rate. In all cases this behaviour can be explained by the fluorophobic effect. The fluorous solvent had little effect on the enantioselectivity of studied reactions.

In conclusion, the weaknesses as well as the advantages of biocatalysis and fluorous separation apply to the methodology which combines them. There is a limited number of substrates for which lipases, active in organic solvents, display good enantioselectivity. Out of these compounds, only the substrates with are not too voluminous and do not contain many polar functionalities are suitable. Using fluorous biphase extraction as a separation method requires sufficiently long fluorous tags to secure favourable partitioning of the separated species. High molecular weights of those tags mean that a relatively high mass must be used. Filtration using FRPSG seems to eliminate these problems as much shorter fluorous groups are sufficient for the complete separation.

Although the cost of highly fluorinated tags and solvents remains high, the methodology of combination of enzyme catalysis and fluorous separation could be used successfully and scaled up for a high value product. We have demonstrated that efficient recycling protocols are practical and that the fluorous phase separation offers clear advantage to the chromatographic one.

3 SYNTHESIS AND STRUCTURE OF FLUORINATED ACIDS

3.1 Synopsis

This Chapter describes the synthesis of amphiphilic molecules containing a carboxylic acid as a polar group, hydrocarbon chain and a perfluorocarbon segment. The methods of preparation of these partially fluorinated acids are discussed. The physical properties of these amphiphiles are investigated and in some cases the X-ray derived crystal structures have been solved and are discussed. Furthermore, the assembly of some of these molecules at the air water interphase is studied by Langmuir surface pressure / area isotherms.

3.2 General

Highly fluorinated amphiphiles have diverse uses in material science[230] as well as emerging applications in the biomedical field.[231, 232] Many of these applications involve colloidal systems stabilised by monomolecular interfacial films of fluorinated amphiphiles. It is therefore essential to understand and control the structure and properties of these films. A unique characteristic of fluorocarbon chains is their simultaneous hydrophobic and lipophobic nature. This property adds a new dimension to the hydrophobic segregation effect. Structurally, fluorous chains strongly differ from hydrocarbon chains by their bulkiness and helical conformation. The cross sectional area for fluorous chains is ~28 $Å^2$ compared to 18 $Å^2$ for hydrocarbon chains.[233] Also the helical nature of perfluorocarbon chain has been widely discussed.[234, 235] Studies on Teflon predict a helical twist[236, 237] and there is crystallographic support for this[238] including an unpublished structure of perfluorohexane[239] indicating a tendency towards helicity with $C(F_2)$-$C(F_2)$-$C(F_2)$-$C(F_2)$ torsion angles of 13°.[240] Theoretical calculations on perfluorooctadecane also predict a helical conformation (Figure 44), which has been attributed to repulsive 1,3-difluoro interactions.[234]

Figure 44: Space-filling models of perfluorooctadecane (left) showing a helical conformation and of octadecane (right) with the classical planar *zig-zag* conformation of hydrocarbon chains.[234]

One of the few published X-ray crystal structures of a molecule containing a polar head, hydrocarbon and a perfluorocarbon chain is 12,12,13,13,14,14,15,15,16, 16,17,17,17-tridecafluoroheptadecan-1-ol, **92**, Figure 45.[241]

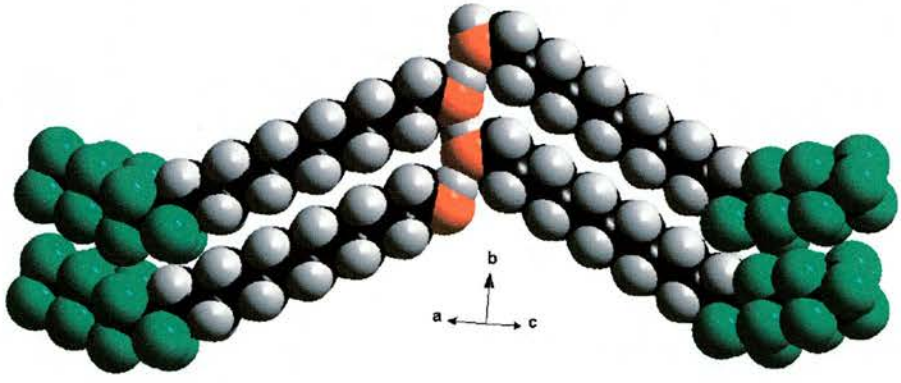


Figure 45: X ray crystal structure of CF_3-$(CF_2)_5$-$(CH_2)_{11}$-OH, **92** taken from the literature.[241] The molecules are shown in a space filling format.

In the structure of **92** the hydrocarbon moieties are linear and the fluorocarbon moieties show a slight helical twist with the $C(F_2)$-$C(F_2)$-$C(F_2)$-$C(F_2)$ torsion angles ranging from 4.5° to 8.3°. There is a bend at the junction of the two segments which allows the short intermolecular C···C distances between successive chains to differ; these distances are about 4 Å between the hydrocarbon chains and about 5 Å between fluorocarbon chains.[240] The hydrocarbon and perfluorocarbon segments of **92** tend to segregate in distinct layers, presumably due to favourable van der Waal's interactions between the hydrocarbon moieties.

This behaviour in the aliphatic series is in sharp contrast to the strong electrostatic interactions observed between arenes and perfluoroarenes.[242] Benzene (mp 5.5 °C, bp 80 °C) and hexafluorobenzene (mp 3.9 °C, bp 80.5 °C) are known to have very similar phase transitions temperatures. In contrast, an equimolar mixture of both

compounds gives a 1:1 crystalline complex which melts at 23.7 °C.[243] In the structure of this adduct[244] the benzene and hexafluorobenzene rings alternate with an inter-layer distance of 3.4 Å as shown in Figure 46.

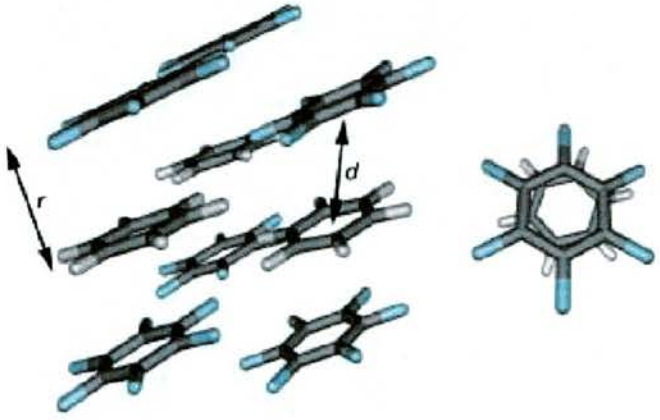


Figure 46: The structure of the $C_6H_6 \cdot C_6F_6$ co-crystal at 30 K.[244] Views along the *b* axis (left) and the *c* axis (right) are shown. r= 3.4 Å; d= 3.7 Å. Fluorine atoms are shown in an aqua colour.[242]

Fatty acids form coherent monolayers on water, as evinced by Langmuir pressure area isotherm analysis.[245] These isotherms have proven to be a sensitive method to explore conformational flexibility of long chain amphiphilic molecules on a water surface and they have provided information on the nature of these monolayers. Typically in a condensed monolayer each fatty acid will occupy an area of 20 $Å^2$. This value is always found to be the same regardless the length of the fatty acid indicating that the hydrocarbon chains are orientated perpendicular to the subphase.[246] It is noteworthy too that perfluoroalkanes, *without a carboxylate head group*, also form monolayers on water although in this case each molecule occupies a much greater area of about 30 $Å^2$.[247] This indicates that hydrocarbons pack more closely than fluorocarbons. Similar behaviour has been observed for some semifluorinated alkanes of the general formula $F(CF_2)_m(CH_2)_nH$.[248, 249]

Furthermore reverse micelles of these diblocks were formed in fluorous solvent.[250] Since these amphiphiles do not contain any polar group typical of a surface active molecule, they have been termed 'primitive surfactants'.[250]

In order to develop further our understanding of the structure and behaviour of perfluorinated compounds, we were led to explore an amphiphilic system that had the three phases, hydrocarbon, fluorocarbon and hydrophilic regions, along the same molecule. Long chain fatty acids emerged as ideal candidates because of their ability to form self assembled monolayers on water.[246] It was also anticipated that such compounds may also be amenable to X-ray crystallography and that differential scanning calorimetry (DSC) may reveal additional details of their polymorphic behaviour.

A number of different arrangements of the perfluoro blocks were envisaged compatible with pragmatic syntheses. The molecules were either monoacids (fatty acids) or diacids. Docosanoic acid **93** (C_{22}) was used as a reference compound for comparison with the fluorinated acids **94** and **95**. Acid **94** is also a C_{22} fatty acid which has a four carbon perfluoro block inserted between C_{11} and C_{15}, and acid **95** is a C_{21} fatty acid where the last 10 carbon atoms are perfluorinated in a fluorous tail as shown in Table 19.

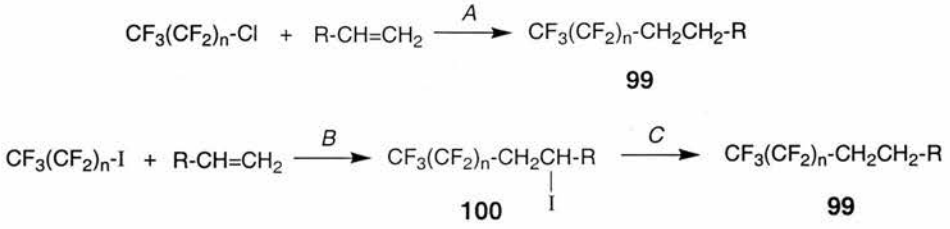
The dicarboxylic acids **96-98** also emerged as synthetic targets. Long chain dicarboxylic acids with a perfluoro unit inserted into the chain have not been previously prepared but it was anticipated that these materials may crystallise by head to head hydrogen bonding. The nature of any fluorocarbon/fluorocarbon and fluorocarbon/hydrocarbon contacts could then be examined in the solid phase. The structures for the mono- and di- carboxylic acids prepared in this study are illustrated schematically in Table 19.

Table 19: Molecular formulae and colour codes for acids and diacids **93-98**. The fluorous units are represented by green blocks, the hydrocarbon chains by black lines and the carboxylate groups by red dots.

Compound number	Code	Formula
93		CH_3-$(CH_2)_{20}$-CO_2H
94		CH_3-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H
95		CF_3-$(CF_2)_9$-$(CH_2)_{10}$-CO_2H
96		HO_2C-$(CH_2)_{10}$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H
97		HO_2C-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H
98		HO_2C-$(CH_2)_{10}$-$(CF_2)_6$-$(CH_2)_{10}$-CO_2H

3.2.1 Synthesis

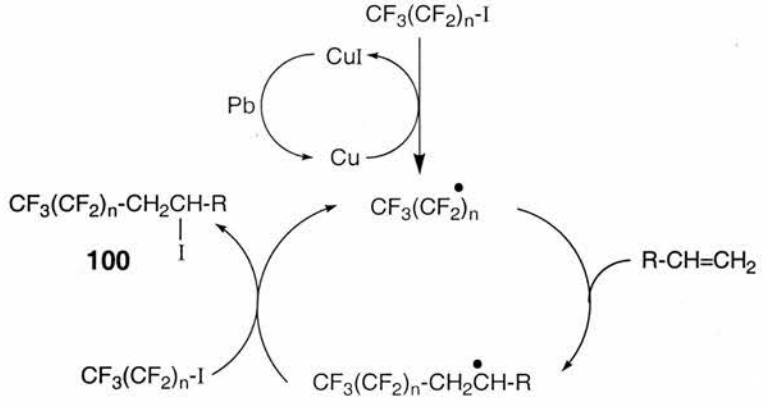
The acid **93** is commercially available but the fluorinated acids **94-98** were prepared by synthesis. The most important method for introducing perfluoroalkyl groups into organic compounds involves the addition of perfluoroalkyl halides to alkenes or alkynes.[251] Such processes are traditionally accomplished with photochemical,[252] thermal,[253] electrolytic[254] and free radical initiations.[255] Various initiators have been used including peroxides, main-group metals, transition metal complexes, oxidants and others.[256, 257, 258, 259, 260] These additions can occur through free-radical, ionic or single-electron transfer mechanisms and the reactivity generally decreases in the following order: R_{fn}-I > R_{fn}-Br > R_{fn}-Cl.[261] In Scheme 46 various initiators are listed for radical addition of perfluoroalkyl chlorides and iodides to alkenes. The initiators *A*, which are able to break C-Cl bonds in perfluoroalkyl chlorides, also catalyse addition of perfluoroalkyl iodides to alkenes. The reactions of perfluoroalkyl chlorides with initiator *A* and alkenes often give the reduced product **99** directly[257, 258] but perfluoroalkyl iodides give iodo adducts **100** which must be deiodinated to give **99**.[262]



A: $Na_2S_2O_4$; $Zn/NiCl_2/PPh_3$ or $(NH_4)_2S_2O_8/HCO_2Na$;
B: $Na_2S_2O_4$; Ra-Ni, $Pd(PPh_3)_4$; $Ce(SO_4)_2$; $(NH_4)_2Ce(NO_3)_6$; $KMnO_4$; AIBN or $Pb/Cu(OAc)_2$;
C: Zn/HCl; Bu_3SnH or H_2/Pd-C;
R= alkyl.

Scheme 46: A general scheme for addition of perfluoroalkyl iodides and chlorides to alkenes.

Taking into account the reaction conditions, the use of different solvents and the methods of separation of the final compounds, we decided to use the redox system of lead powder and copper(II) acetate as the radical initiator. Dehalogenation would then be conducted using hydrogen and palladium on carbon.[263] It is thought that the mechanism involves the conversion of copper metal (Cu°) to Cu(I)I to generate the perfluoroalkyl radical. The radical then adds to the electron-rich double bond of the alkene and subsequent halogen abstraction affords product **100**, Scheme 47.[264]

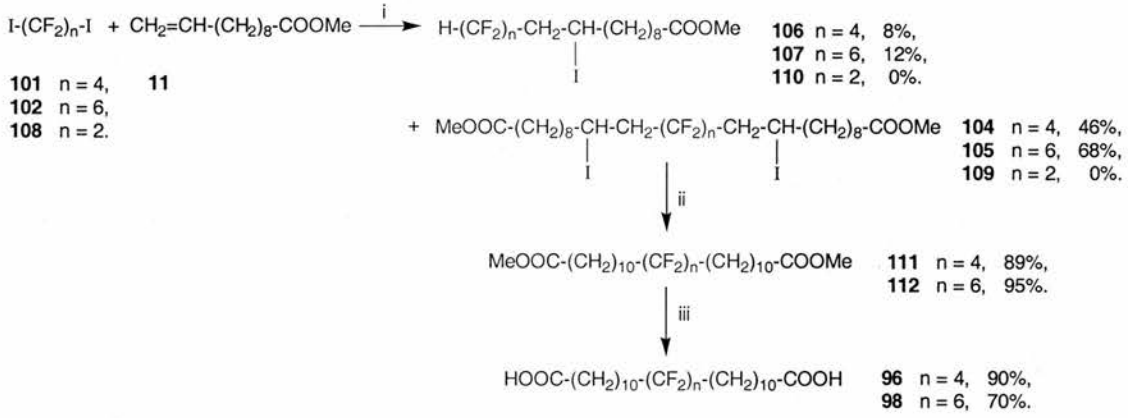


Scheme 47: Mechanism of the Cu-initiated addition of perfluoroalkyl iodides to alkenes.[264]

3.3 Results and discussion

3.3.1 Synthesis of fluorinated acids and diacids

Diacids **96** and **98** (Scheme 48) were prepared by free radical addition of diiodoperfluoroalkanes **101** and **102** to an excess of unsaturated ester **103**, initiated by lead powder and a catalytic amount of copper(II) acetate.[263]



Scheme 48: Synthesis of symmetrical fluorinated diacids **96** and **98**. Reagents and conditions: i) Pb, $Cu(OAc)_2$ (12 mol %), MeOH, r.t., 48 h; ii) H_2, Pd-C, $NaHCO_3$, MeOH, r.t., 24 h; iii) KOH, EtOH, reflux, 17 h.

These reactions were carried out at room temperature in methanol as a solvent and the addition products **104** and **105** were obtained in good yields, Scheme 48. The ^{19}F NMR spectra of these addition products showed that the diastereotopic fluorine atoms (*2* and *3*) have very similar chemical shifts except for the CF_2 groups (*1*) adjacent to the iodo substituent as shown in Figure 47, for a typical example (compound **105**).

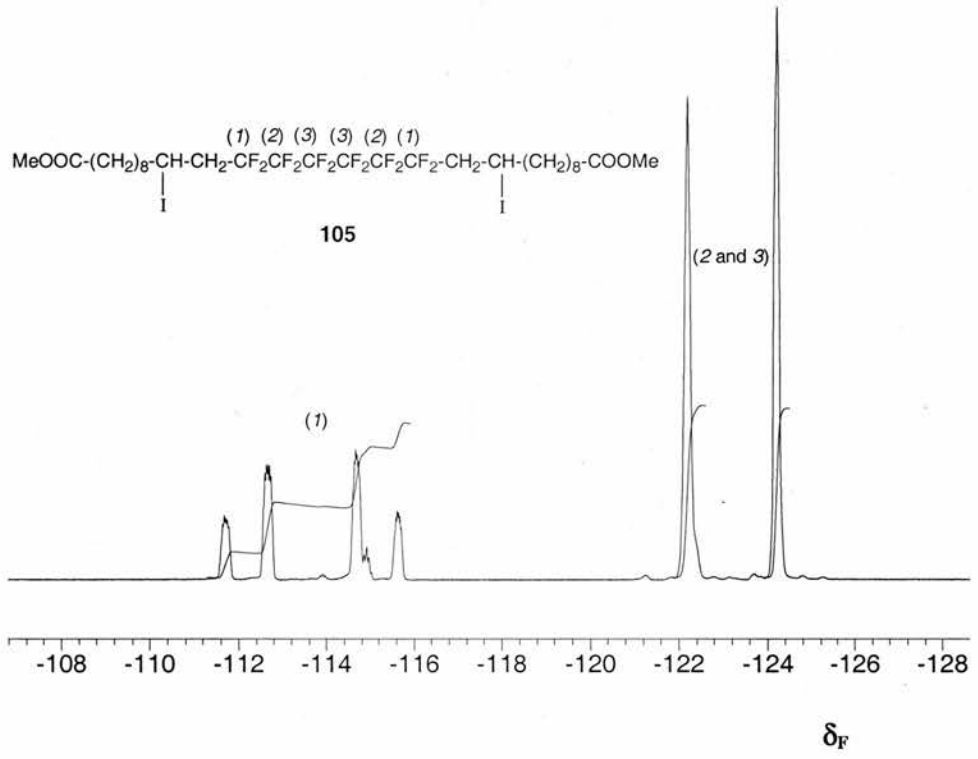
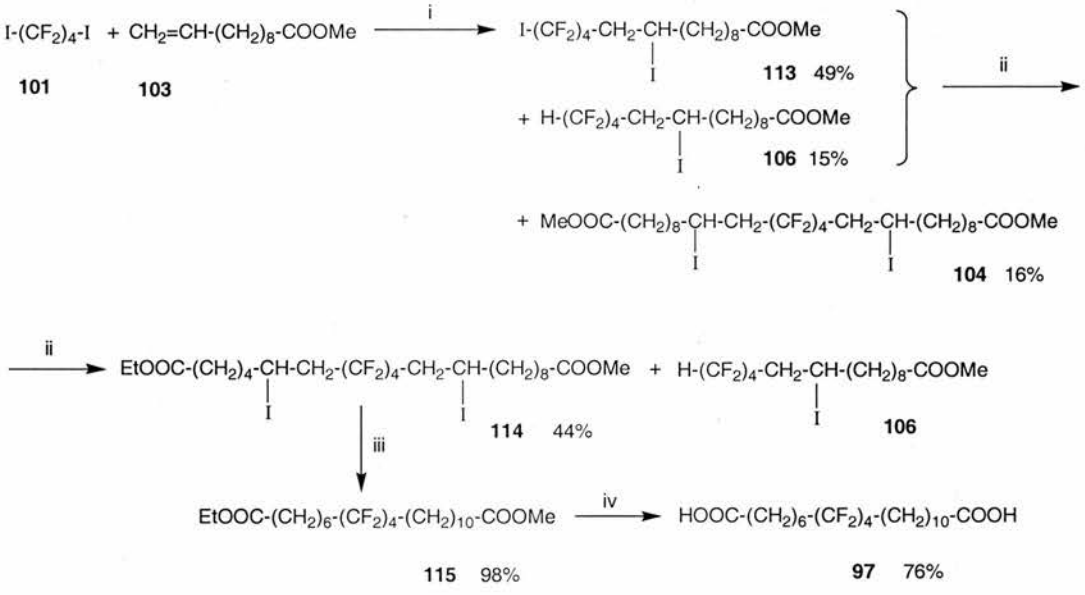


Figure 47: An expansion of the ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) spectrum of the diiodo adduct **105** showing diastereotopic fluorine atoms of which only fluorines (*1*) have noticeably different chemical shift.

Partially reduced mono-adducts **106** and **107** were isolated as by-products, Scheme 48. When the unsaturated ethyl ester [CH_2=$CH(CH_2)_8CO_2Et$] was used instead of the methyl ester **103** up to 10% transesterification was observed. Surprisingly, the analogous radical coupling of **108** with **103** produced neither **109** nor **110**. An evolution of gas from the reaction mixture was observed and after 48 h only unsaturated ester **103** was recovered. This appears to be a special case and possibly the diiodoperfluoroethane **108** is converted to volatile tetrafluoroethylene (CF_2=CF_2), rather than the anticipated products.

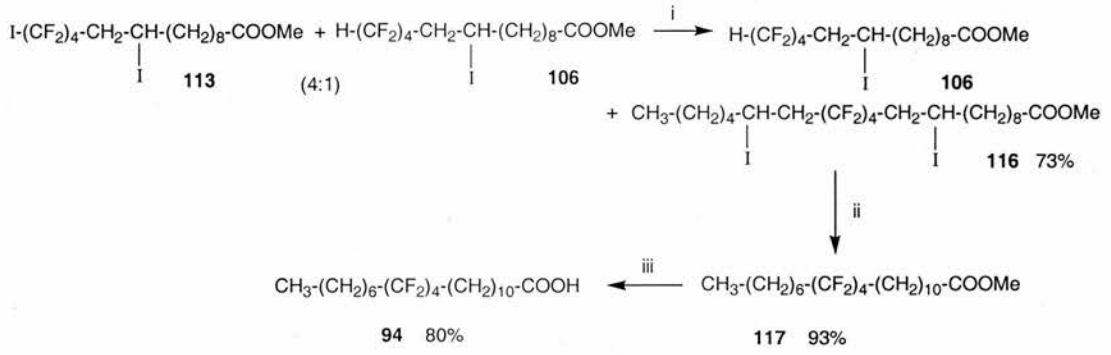
The reductive dehalogenation of the addition products **104** and **105** was carried out with Pd-C and hydrogen under atmospheric pressure to give the fluorinated methyl esters **111** and **112** in high yields. Alkaline hydrolysis then afforded the fluorinated symmetrical diacids **96** and **98** also in good to high yields.

For the synthesis of the unsymmetrical diacid **97**, the diiodo mono-adduct **113** was required as a starting material. Reaction of up to a four molar excess of **101** with the unsaturated ester **103** gave only **104** (50%), **106** (10%) and no **113**. The reaction was conducted using Pb/$Cu(OAc)_2$ (12 mol %) in daylight or in the dark. However using a low catalyst loading afforded the desired diiodo mono-adduct **113** which could be separated from **104** but unfortunately this product remained contaminated with **106**, Scheme 49. Purification of the mixture of **113** and **106** by silica gel chromatography actually lead to a reduction and conversion of **113** to **106**. In order to cut such losses the mixture of **113** and **106** was therefore used to prepare diiodo diester **114** directly. After hydrogenation of **114** and hydrolysis the desired asymmetric diacid **97** could be recovered as illustrated in Scheme 49.



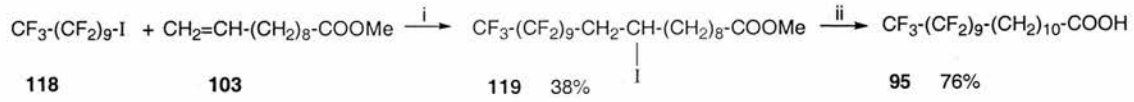
Scheme 49: Synthesis of asymmetrical fluorinated diacid **97**. Reagents and conditions: i) Pb, $Cu(OAc)_2$ (3 mol %), MeOH, dark, r.t., 17 h; ii) Pb, $Cu(OAc)_2$ (12 mol %), CH_2=$CH(CH_2)_4COOEt$, MeOH, r.t., 48 h; iii) H_2, Pd-C, $NaHCO_3$, MeOH, r.t., 24 h; iv) KOH, EtOH, reflux, 17 h.

The fluorinated acid **94** was prepared by free radical addition to diiodo ester **113**. In this case the mixture of **113** with **106** prepared as discussed above was used. In the event an excess of 1-heptene and the mixture in a reaction catalysed by lead powder and copper(II) acetate in methanol, gave the diiodo ester **116** in good yield. Hydrogenation and hydrolysis then gave the desired fluorinated acid **94** as illustrated in Scheme 50.



Scheme 50: Synthesis of fluorinated acid **94**. Reagents and conditions: i) Pb, $Cu(OAc)_2$ (12 mol %), $CH_2=CH(CH_2)_4CH_3$, MeOH, r.t., 24 h; (ii) H_2, Pd-C, $NaHCO_3$, MeOH, r.t., 24 h; (iii) KOH, EtOH, reflux, 17 h.

The reaction of 1-iodoperfluorodecane **118** with **103** using $Pb/Cu(OAc)_2$ as the catalyst in methanol, did not give any coupled product **119**. This may have been due to the low solubility of **118** in methanol. Instead the desired fluorinated acid **95** was prepared in two steps by reaction of **118** and **103** initiated by AIBN under solvent free conditions.[265] This generated adduct **119** which was then subjected to reductive dehalogenation and hydrolysis to give **95**, as illustrated in Scheme 51.



Scheme 51: Preparation of fluorinated acid **95**. Reagents and conditions: i) AIBN (2 mol %), 80 °C, 19 h; ii) H_2, Pd-C, $NaHCO_3$, MeOH/THF, r.t., 18 h; then KOH, EtOH, reflux, 24 h.

3.3.2 Melting points of hybrid fatty acids

The prepared acids (**94-98**) as well as some of their ester (**111, 112, 115, 117** and **119**) precursors are white solids, while other esters are colourless liquids at room temperature. The melting points of these materials were determined accurately using differential scanning calorimetry (DSC) and the data is reported in Table 20.

Table 20: Measured melting points, solvents used for recrystallization and melting points determined by DSC analysis of prepared acids and esters.

Entry	Compound number; formula	m.p. (°C)[a]	m.p. (°C)[b]
1	**94**; CH_3-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-COOH	82-84 [c]	80.1
2	**95**; CF_3-$(CF_2)_9$-$(CH_2)_{10}$-COOH	109-109.5 [c]	111.9
3	**96**; HOOC-$(CH_2)_{10}$-$(CF_2)_4$-$(CH_2)_{10}$-COOH	130-131 [d]	127.0; 131.8
4	**97**; HOOC-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-COOH	117.5-118 [d]	112.0
5	**98**; HOOC-$(CH_2)_{10}$-$(CF_2)_6$-$(CH_2)_{10}$-COOH	134.5-135.5 [d]	135.1
6	**111**; MeOOC-$(CH_2)_{10}$-$(CF_2)_4$-$(CH_2)_{10}$-COOMe	73-74 [c]	-
7	**112**; MeOOC-$(CH_2)_{10}$-$(CF_2)_6$-$(CH_2)_{10}$-COOMe	78-79 [c]	-
8	**115**; EtOOC-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-COOMe	48.5-49 [c]	-
9	**117**; CH_3-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-COOMe	48-49	-
10	**119**; CF_3-$(CF_2)_9$-CH_2-CHI-$(CH_2)_8$-COOMe	56-58 [e]	-

[a] As measured on melting point apparatus; [b] As determined by DSC analysis, for details see Appendix 2. Solvents used for recrystallization: [c] hexane, [d] ethyl acetate, [e] ethanol.

Obviously the esters have lower melting points than the corresponding acids. The difference of the melting points within the acid and ester series is rather small although the difference in molecular weight in some cases is considerable (ΔM_r = 100 g·mol^{-1}), e.g. entry 3 and 5, 6 and 7, Table 20. However the shortening of the hydrocarbon chain has a dramatic effect on lowering the melting point (entry 3 and 4). Differential scanning calorimetry (DSC) analysis of the acid **96** showed two peaks on the graph of heat flow versus temperature with maxima at 127.0 °C and 131.8 °C. On second heating however the second maximum is shifted to 129.5 °C as illustrated in Figure 48. It is difficult to explain this observation especially considering the fact that the analogue dicarboxylic acids **98** and **97** as well as acids **94** and **95** do not show this behaviour (see Appendix 2).

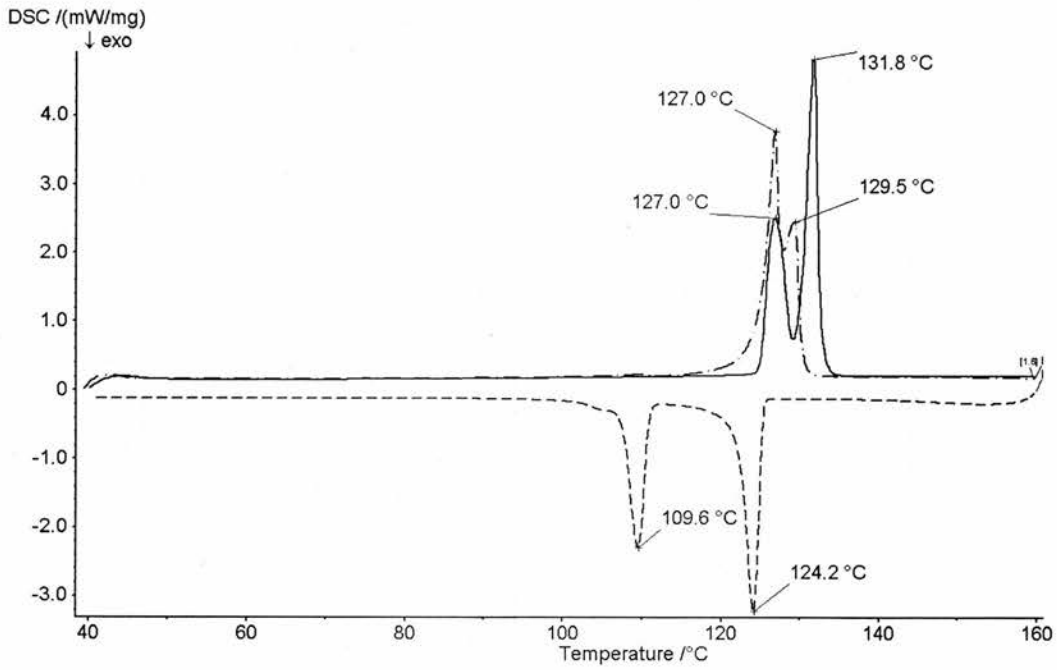


Figure 48: DSC thermogrammes showing heat flow versus temperature curves for dicarboxylic acid **96**. — First heating; ---- cool down; -·-· second heating.

3.3.3 X-Ray structural studies

Suitable crystals of diacids **96** and **98** were subjected to X-ray diffraction analysis and the structures are shown in Figures 49 and 50 (Appendix 3).

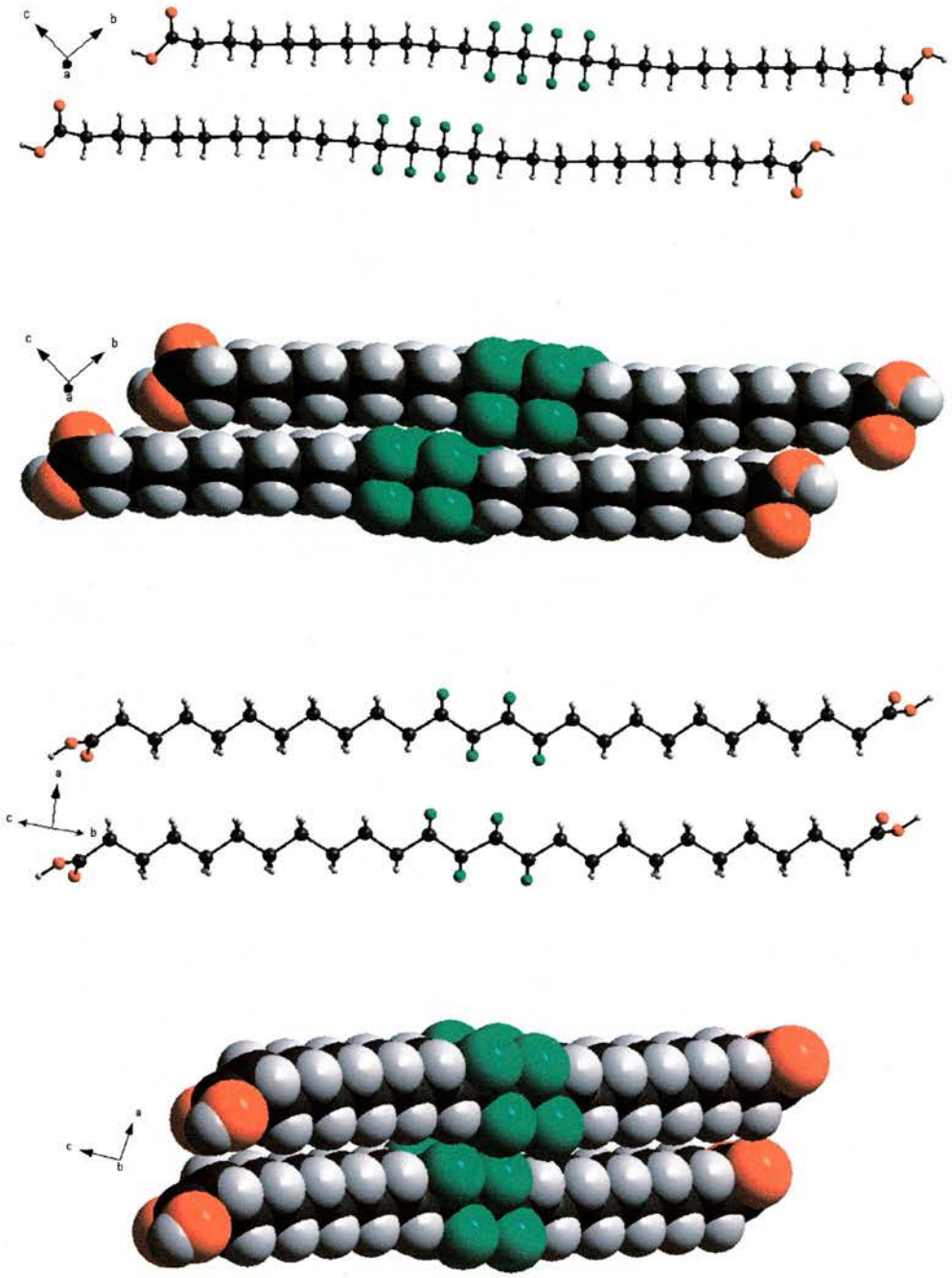


Figure 49: X-Ray derived crystal structure of **96** showing the molecular packing in ball-and-stick and in space-filling formats.

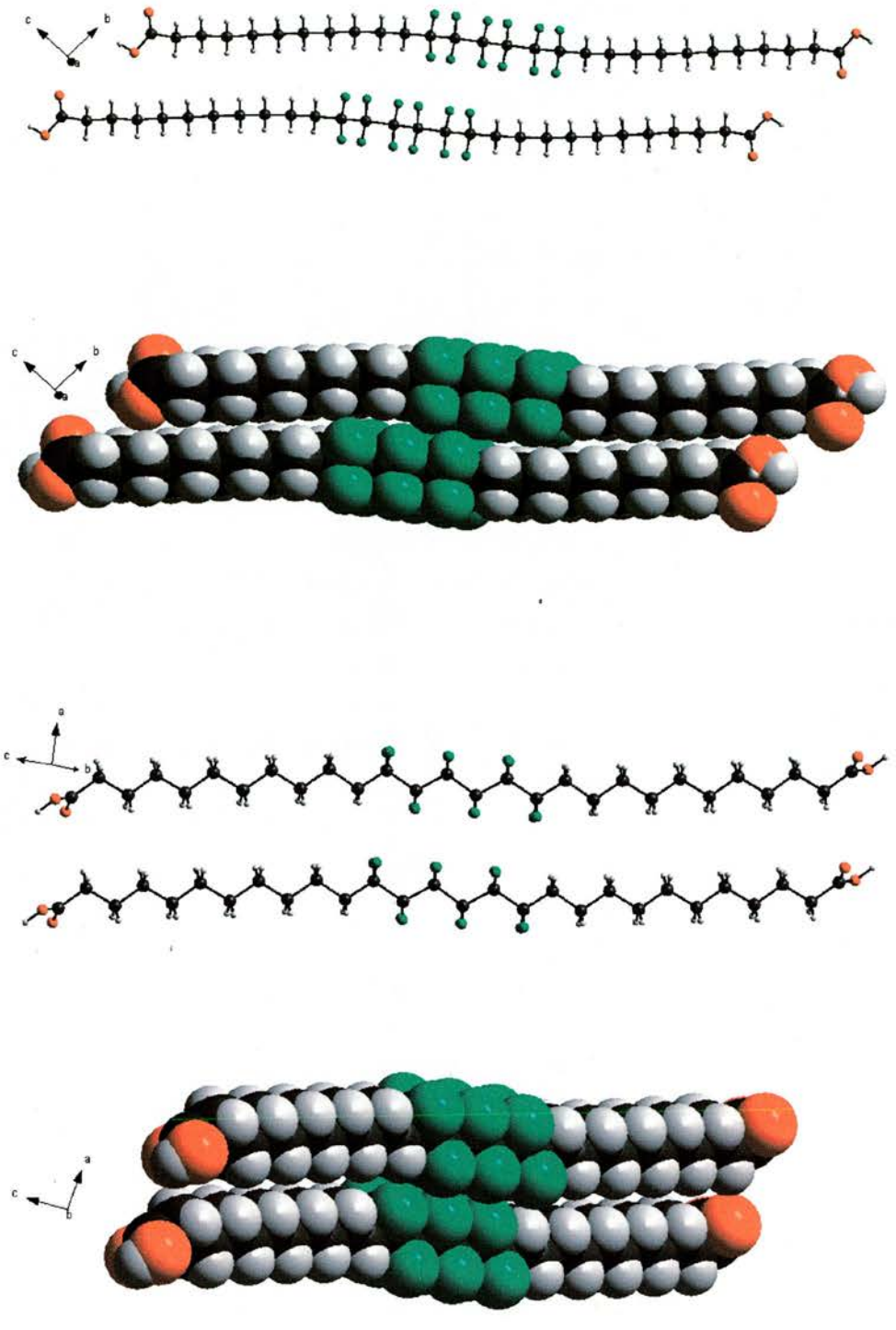


Figure 50: X-Ray derived crystal structure of **98** showing the molecular packing in ball-and-stick and in space-filling formats.

In both cases it is apparent that the hydrocarbon chains connecting the perfluoroalkyl segments bend in opposite directions to generate elongated '*S*' shaped molecules. The angle between the axis of the hydrocarbon chain and the perfluorinated segment is 166° and 164° for **96** and **98** respectively along the *a* axis, Figure 49. The molecules are a little compressed in that direction and the distances between the first and last carbon atoms in the chain are 31.7 Å and 34.3 Å for **96** and **98** respectively.

The C_4 and C_6 perfluoro blocks of **96** and **98** are relatively short however in these structures there is no compelling evidence to suggest that the perfluorocarbons twist along the carbon chain. The measured $C(F_2)$-$C(F_2)$-$C(F_2)$-$C(F_2)$ torsion angles are ~0-2°. The overcrowding of the fluorine atoms in the perfluorocarbon chain is perhaps reduced by a widening of the C-C-C bond angle from 111-113° in the hydrocarbon segments to 115-117° in the perfluorocarbon segments.

In the unit cell the molecules are organized by head to head hydrogen bonding between the carboxylate groups. The packing of these molecules is such that when viewed along the *a* axis the fluorocarbon blocks of adjacent molecules are offset relative to each other by three CF_2 groups, so in **96** there is only one CF_2 overlap (Figure 49) and in **98** there are three CF_2 overlaps, Figure 50. However when viewed along the *b* axis the fluorocarbon blocks are perfectly aligned and overlap fully.

It was of interest to examine the intermolecular packing distances, particularly between the fluorocarbon and hydrocarbon segments. The values of the shortest inter-chain C···C, H···H, F···F and H···F distances are summarized in Table 21.

Table 21: The shortest inter-chain distances in diacids **96** and **98** as determined from X-ray diffraction data.

Atom types	Distance[a] (Å) **96**	Distance[b] (Å) **96**	Distance[a] (Å) **98**	Distance[b] (Å) **98**
$C(H_2)\cdots C(H_2)$	4.2	4.2	4.2	4.2
$C(H_2)\cdots C(F_2)$	4.5	4.2	4.5	4.3
$C(F_2)\cdots C(F_2)$	4.5	4.3	4.7	4.3
H···H	2.8	3.1	2.8	3.1
H···F	2.7	2.8	2.8	2.8
F···F	2.9	2.9	2.9	2.9

[a] Inter-chain distances of the molecules packed along the *a* axis. [b] Inter-chain distances of the molecules packed along the *b* axis.

In structure **96** the hydrocarbon chains are closer than the fluorocarbon chains along the *a* axis. For example the shortest C···C distances of 4.2 Å for the hydrocarbon moiety can be compared with that of 4.5 Å for the fluorocarbon moiety in **96**. There is no obvious difference in packing distances between these moieties along the *b* axis. The F···F distance is shorter than H···H distance for packing along the *b* axis but it's about the same for packing along the *a* axis. For structure **98** a similar conclusion can be drawn. The shortest intermolecular C···C distance is 4.2 Å for the hydrocarbon chains versus 4.7 Å for the fluorocarbon chain along the *a* axis. The shortest intermolecular distances along the *b* axis are much more similar.

It is useful to compare these structures to the fluorinated alcohol **92**. In diacids **96** and **98** there is also a bend at the fluorocarbon hydrocarbon junctions, but in contrast with **92**, there is no marked difference in inter-chain distances between the fluorocarbon and hydrocarbon moieties. The observed C···C distances in diacids **96** and **98** are intermediate to that found between hydrocarbon chains and that found

between perfluorocarbon chains of **92**. The inter-chain $C(H_2)\cdots C(H_2)$ distances in *n*-alkanes such as *n*-hexane is 4.0 Å.[266]

The asymmetric dicarboxylic acid **97** proved much more difficult to crystallise, and although crystals were successfully grown they did not diffract coherently such that a structure could be solved. This difficulty may lie in the asymmetry of this molecule. The two limiting possibilities for packing molecules of **97** can be envisaged as summarised in Figure 51. The short perfluorocarbon segments can either stack above each other or avoid each other.

Figure 51: The two limiting ways for packing of unsymmetrical diacid **97** in the solid state, where ● denotes CO_2H group; —— denotes $-(CH_2)_6-$ chain; ———— denotes $-(CH_2)_{10}-$ chain and ▬ denotes $-(CF_2)_4-$ chain.

Perhaps a more disordered array emerged in the solid state which resulted in incoherent X-ray diffraction.

3.3.4 Langmuir isotherms analyses

The Langmuir pressure / area isotherms of docosanoic acid **93** and the fluorinated acids **94** and **95** were evaluated and are shown in Figure 52. This data was recorded at the University of Durham by Prof. M. Petty and Dr. C. Pearson.

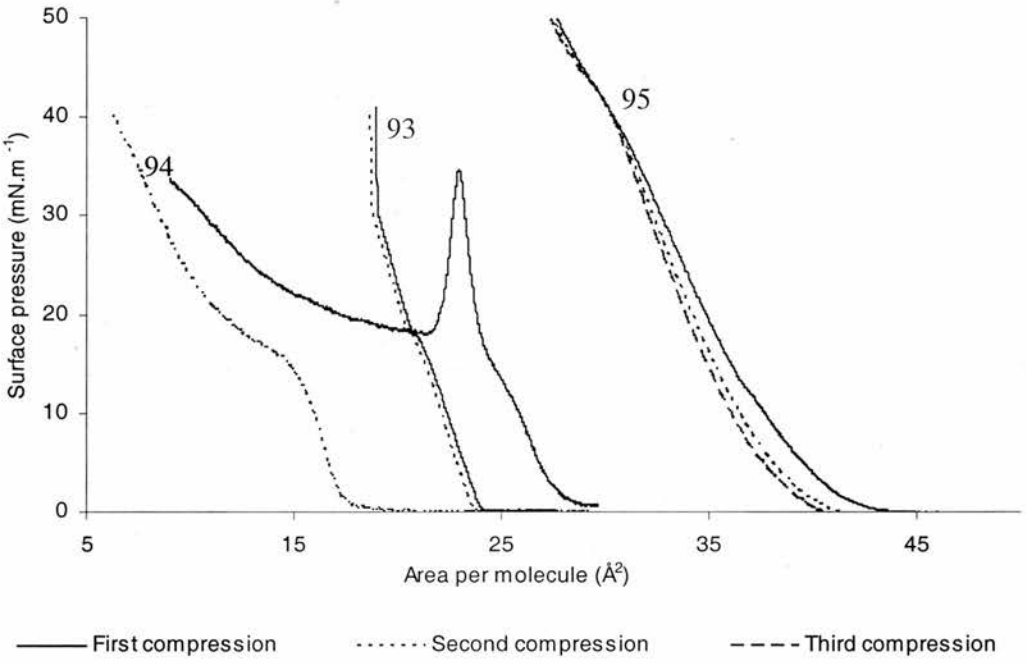


Figure 52: Surface pressure versus area per molecule isotherms for acids: **93** $CH_3(CH_2)_{20}$-COOH; **94** CH_3-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-COOH and **95** CF_3-$(CF_2)_9$-$(CH_2)_{10}$-COOH for repeated compressions at 20 °C.

Docosanoic (C_{22}) acid **93** formed a monolayer with a limiting area per molecule of around 20 Å^2, Figure 52. The monolayer is stable and reversible which is in good agreement with the literature data on Langmuir isotherms of other long chain fatty acids.[245, 246, 267] At compressions above 30 mN·m^{-1} the 2D-solid-like state can be observed in which the absorbed molecules become immobile.[268]

The highly fluorinated C_{21} acid **95** also formed a monolayer, which was stable even after three successive compressions. This resulted in a much more expanded area per molecule, at 37-40 Å^2, Figure 52. There is some literature on surface pressure / area measurement of analogous fluorinated acids and the observed limiting molecular area ranged from 34 Å^2 to 41 Å^2.[267, 269] It has been argued that the increased area per molecule in these cases is due to the presence of the sterically more demanding perfluoroalkyl chains, especially the relatively bulky terminal CF_3

group. Consequently, the adjacent hydrocarbon chains are hindered from forming a coherent close-packed array. Since the intermolecular forces between adjacent perfluoroalkane chains are weaker than those of the hydrocarbon chains, comfortable cohesion of the chains in inhibited.[267] Films of these types of molecules are though to be in liquid to liquid-condensed state, which is manifested by a smaller negative slope of the surface pressure versus area curves relative to fatty acids.

Evaluation of the C_{22} fatty acid **94** revealed a much more complex behaviour on the water subphase. This compound has a C_4 perfluorous segment inserted into the hydrocarbon chain. The first compression generated an unstable monolayer with a limiting area per molecule of about 25 $Å^2$, Figure 52. This value is somewhere between that of **93** and **95**, and it presumably reflects the increased steric influence of the short perfluorinated block. The maximum surface pressure of 34.6 $mN \cdot m^{-1}$ was observed at 23.0 $Å^2$. On further compression there is a collapse of the monolayer and a reorganization toward a bilayer/multilayer characterized by a highly compressible film. After expansion of this film and second compression the bilayer/multilayer is preserved. Unlike acids **93** and **95** which formed stable and reversible monolayers acid **94** showed quite different surface behaviour. Compound **94** is unstable on a water subphase although it contains only a short perfluoroalkyl block and it is dominated by hydrocarbon. There has been some discussion about the destabilising effect of the dipole at the $-CH_2-CF_2-$ linkage on the stability of monolayers of perfluoroalkylalkanoic acids[267] and ω-trifluoromethylalkanoic acids.[270] In the case of acid **94** there are two such dipoles in each molecule and when the adjacent chains are brought close together during film compression the repulsion between the dipoles of the same sign perhaps

facilitates the collapse of the monolayer as illustrated in Figure 53. Alternatively an explanation for low stability of a monolayer of **94** could lie in an increased conformational mobility of the hydrocarbon chains due to a geometric 'kink' in the chain at the fluorocarbon-hydrocarbon discontinuity, e.g. as observed in structure **92**. Such a bend is also evident in the solid state structures of **96** and **98**.

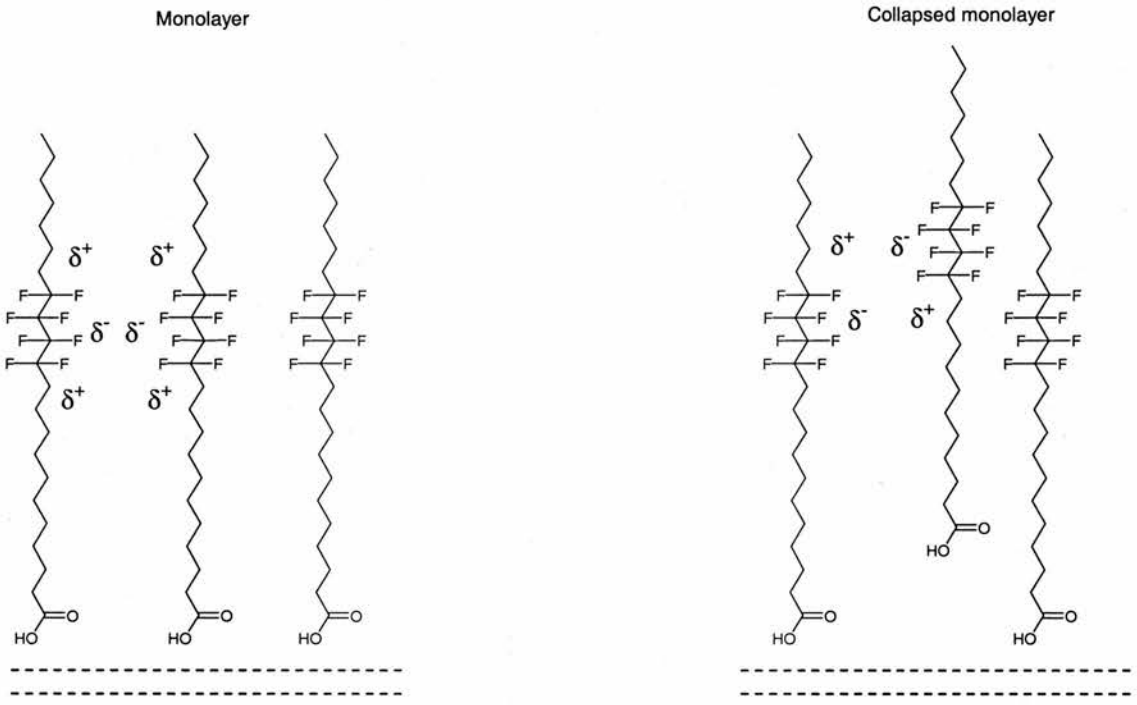


Figure 53: Schematic representation of the collapse of monolayer of **94** at the water subphase (broken lines) assisted by repulsion between the dipoles at the $-CH_2-CF_2-$ linkage.

3.4 Summary and conclusions

The synthesis of novel compounds containing hydrocarbon, perfluorocarbon and hydrophilic moieties along a single carbon chain has been accomplished. These molecules included fluorinated mono- and di- carboxylic fatty acids. The key step in the synthesis involved a radical coupling reaction of perfluoroalkyl iodides with olefins. These reactions were carried out under mild conditions and are excellent synthetic protocols for perfluoroalkylation. X-Ray crystal structure analysis of the symmetrical diacids **96** and **98** revealed an unexpected sigmoidal shape to the molecule although the perfluoroalkyl segments are in a planar *zig-zag* conformation and no helicity was observed. The three dimensional packing of these molecules is such that the fluorocarbon block of adjacent molecules is offset relative to each other by three CF_2 groups along the *a* axis, although when the molecules are viewed along the axis *b* the fluorocarbon blocks fully overlap. The comparison of the shortest inter-chain C···C distances suggests that the bend in the chain accommodates increased distance between perfluorinated segments. The hydrocarbon chains are further apart than usual C···C distance found in *n*-alkanes.

The unsymmetrical diacid **97** was not amenable to X-ray structure analysis. The crystals did not diffract well perhaps indicating disorder in packing. This compound was synthesised with the aim of investigating whether in the solid state the perfluorocarbon segments will segregate to minimise perfluorocarbon-hydrocarbon interactions or rather align in an alternating fashion in order to minimise steric crowding.

Langmuir isotherm analysis of the fatty acid **94** containing a C_4 fluorous block revealed quite different surface behaviour to the analogous docosanoic acid **93** and perfluorofatty acid **95**. Unlike **93** or **95** the presence of a perfluorocarbon segment

within the hydrocarbon chain of **94** had the effect of destabilising the monolayer in such a way that no coherent supraphase structure emerged.

4 EXPERIMENTAL

4.1 General experimental procedures

4.1.1 Reagents and solvents

All commercially available materials were purchased from Sigma-Aldrich, Lancaster, Apollo Scientific, Fluorochem, Acros or Fluka unless otherwise stated and purified according to literature[271] where necessary.

The solvents used in the reactions were dried, distilled and stored under nitrogen prior to use: diethyl ether (sodium, benzophenone), dichloromethane (calcium hydride or calcium sulfate), tetrahydrofuran (THF) (sodium, benzophenone), methanol (calcium sulfate). Dry dimethylformamide (DMF), toluene and dimethyl sulfoxide (DMSO) were purchased from Acros. Petrol refers to the 40-60°C boiling fraction of petroleum ether and ether refers to diethyl ether.

Potassium permanganate stain was prepared by dissolving $KMnO_4$ (3 g), K_2CO_3 (20 g) and NaOH (0.25 g) in water (400 cm^3). Molybdenum stain was prepared by dissolving $(NH_4)_6Mo_7O_{24}.4H_2O$ (100 g) and $Ce(SO_4)_2$ (40 g) in diluted sulfuric acid (5%, 2500 cm^3).

Porcine pancreatic (*PPL*) (Type II.) and *Candida rugosa* (*CRL*) lipases were purchased from the Sigma Chemical Co. and had a specific activity of 187 units/mg protein (lipase powder contains 25% of protein) and 724 units/mg respectively. One unit will hydrolyze 1 μeq. of fatty acid from olive oil in one hour at pH= 7.7 and pH= 7.2 respectively, at 37 °C. Lipase from *Candida antarctica-B*

(Novoenzyme® 435) immobilized on macropourous acrylic resin was purchased from Sigma Chemical Co. All lipases were used "straight from the bottle".

4.1.2 Reaction conditions

Where non-aqueous conditions were required, reaction glassware was oven dried (150 °C) and cooled under a nitrogen atmosphere. Reaction temperatures of -78 °C to -10 °C were obtained using solid carbon dioxide pellets and acetone and temperatures of -10 °C to +4 °C were obtained in a an ice/water/NaCl bath. Reactions requiring reflux or heating were carried out using an oil bath equipped with a contact thermometer.

4.1.3 Chromatography

Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygam Sil G/UV_{254} plates and were visualised by the use of a UV lamp or by the use of potassium permanaganate or molybdenum stains.

Silica gel column chromatography was performed using Silica Gel LC60A (35-70 micron) from Fluorochem. Fractions were collected in test tubes and analysed using TLC as described above.

Gas chromatography-mass spectroscopy (GC-MS) analysis was conducted using an Agilent 5890 plus gas chromatograph equipped with a 5973N mass selective detector and 7683 series injector. Chromatographic separations were performed using an Agilent HP 19091S-433 5% phenyl methyl siloxane (30m x 250 μm with a film thickness of 0.25 μm) column or Supelco β-DEX 120 fused silica (30 m × 250 μm with a film thickness of 0.25 μm) chiral column. The carrier gas was

helium, with a flow rate of 1.1 $cm^3.min^{-1}$. The injection port temperature was 280 °C. For the summary of temperature profiles and conditions used for GC-MS analysis of chiral compounds see Appendix 1.

4.1.4 Melting point analysis

Melting points were determined in Pyrex capillaries using a Gallenkamp variable heater and were uncorrected.

4.1.5 Fourier transform infra red spectra (FT-IR)

FT-IR spectra were recorded in the range 4000-440 cm^{-1} on a Perkin-Elmer system 2000 Fourier transform as a thin layer between NaCl discs or as a KBr pellets.

4.1.6 Elemental analysis

Carbon, hydrogen and nitrogen analyses were obtained using a CE Instrument EA 1110 CHNS analyzer. The analyses were done by Mrs. Sylvia Williamson.

4.1.7 Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded on a Varian Unity Plus 300 (^1H at 299.908 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz) or Bruker Advance 300 (^1H at 300.06 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz). Chemical shifts are reported in parts per million (ppm) and quoted relative to internal standards (Me_4Si and $CFCl_3$) or the residual proton peak of $CDCl_3$, acetone-d_6, C_6D_6 or DMSO-d_6. Signal splitting patterns are described as: s - singlet, d - doublet, t - triplet, q - quartet or m -

multiplet. A broad signal is denoted by br s. Coupling constants (*J*) are given in Hertz (Hz) and represent $^{3}J_{H\text{-}H}$ unless otherwise stated. ^{13}C-NMR spectra were ^{1}H decoupled.

4.1.8 Mass spectrometry

High-resolution mass spectrometry was performed on a VG AUTOSPEC spectrometer operating in EI or CI (CH_4) positive mode or on an LCT mass spectrometer. The LCT comprised of a Waters 2795 HPLC, 4×24/48/96 autosampler and a Micromass LCT mass spectrometer with electrospray ionization (ESI) or APCI ionization operating in both positive and negative modes. LockSpray was used to obtain accurate mass data in ESI mode. These analyses were carried out by Mrs. Caroline Horsburgh and Dr. Robin Antrobus.

Low resolution CI (CH_4) and EI mass spectra were recorded on an Agilent HP GC-MS instrument (see Section 4.1.3) or Micromass LCT mass spectrometer with electrospray ionization.

4.1.9 Differential scanning calorimetry (DSC) analysis

DSC Analyses were performed using a Netzsch DSC 204 instrument in the range of -50 to 160 °C. Nitrogen was used as a protective gas and the heating and cooling were conducted at a rate of 5 $K \cdot min^{-1}$. These analyses were carried out by Mrs. Sylvia Williamson.

4.1.10 Single crystal X-Ray diffraction analysis

X-ray diffraction measurements were made with graphite-monochromated Mo-Kα X-radiation (λ = 0.71073 Å) using a Bruker SMART diffractometer, intensity data were collected using 0.3° or 0.15° width ω steps accumulating area detector frames spanning at least a hemisphere of reciprocal space for all structures (data were integrated using the SAINT program). All data were corrected for Lorentz, polarisation and long-term intensity fluctuations. Absorption effects were corrected on the basis of multiple equivalent reflections or by semi-empirical methods. Structures were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). All calculations were made with SHELXTL (Bruker AXS, Madison 1999). The analyses and calculations were carried out by Dr. Alexandra M. Z. Slawin.

4.1.11 Optical rotation measurement

Optical rotations were measured using Optical Polarimeter Ltd. A-1000. $[\alpha]_D$ values are measured at 589 nm and are given in 10^{-1} deg.cm^2.g^{-1}. Concentration of measured compound (in g per 100 cm^3 of the resulting solution) and the solvent used are given in parentheses.

4.1.12 Surface pressure vs. area measurement

Surface pressure versus area isotherms were measured using a Molecular Photonics LB700 series trough. The subphase was pure water at a temperature of 20 °C and pH of 5.8. For spreading, the materials were dissolved in chloroform to a

concentration of 1.0 $g \cdot l^{-1}$. These analyses were carried out at the University of Durham by Prof. Michael C. Petty and Dr. Christopher Pearson.

4.1.13 Partition coefficients determination

The measured compound was dissolved in either organic or fluorous solvent at a concentration of ~ 4 mM. The solution of the measured compound (4 cm^3) was added to the pure organic or fluorous solvent (4 cm^3) in a screw cap vial (15 cm^3). The mixture was shaken at 300 rpm at 50°C for 2 h and then left to separate/equilibrate at a given temperature for 10-30 h. Two samples from each phase were taken (1.6 cm^3) for GC-MS analysis and each sample was analysed four times to determine average peak areas. The signal of the measured compound was separated from the other signals of higher boiling fluorous solvents. The linearity of area versus concentration, in the range 1-4 mM, was independently verified. The ratio of average peak areas gave the partition coefficient, *P'*. The reported partition coefficient (*P*) was calculated as the average of three independent experiments.

In the cases where perfluoro(2,2,3,3-tetramethylbutane) (mp 40 °C) was the fluorous solvent, the toluene phase was removed from the fluorous one by decanting and diluted with toluene till a the total volume of 12 cm^3. The fluorous phase was dissolved in FC-72 to make a total volume of 12 cm^3. Each solution was analysed on GC-MS as described above.

4.1.14 Thermal deactivation of the lipases

The lipase (1.00 g) was suspended in FC-72 (10 cm^3) or hexane (10 cm^3) and the mixture was stirred in a sealed tube at 250 rpm at a given temperature. Periodically aliquots (~0.5 cm^3 of the suspension) were taken and filtered. The solid on the filter was air dried for 10-15 min. The dried enzyme (10 mg) was added to a solution (1 cm^3) of hexanol (0.14 M) and vinyl acetate (0.414 M) in hexane. The mixture was shaken at 250 rpm/30 °C for 1 hour and then analysed by GC-MS. The enzyme activity was expressed in μmols of converted hexanol into hexyl acetate per hour with one mg of enzyme powder and was reported as an average of three independent measurements.

4.2 Lipase catalysed reactions

4.2.1 General method

The acylating agent and nucleophile were dissolved in a mixture of fluorous and/or organic solvent in a conical flask. The lipase was added and the mixture was shaken on an orbital shaker at 250-300 rpm at a given temperature. Periodically aliquots were taken and analysed by GC-MS to determine the conversion and/or the enantiomeric excess. After a given time the reaction was terminated by the filtration of the enzyme. The enzyme was washed with both organic and fluorous solvents. The filtrate was worked up using Methods A, B or C as described below. The yields in kinetic resolutions are calculated on theoretical recovery of each enantiomer. Thus the maximum yield of each enantiomer is 100%.

4.2.1.1 Method A (separation using fluorous biphase extraction)

The two phases separated on cooling. The organic phase was repeatedly washed with the fluorous solvent. Organic and fluorous products were isolated by solvent removal from the washed organic and combined fluorous phase respectively.

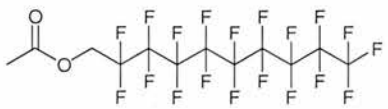
4.2.1.2 Method B (separation using continuous fluorous extraction)

The solvent was removed under reduced pressure. The residue was dissolved in methanol and the resulting solution was added onto the FC-72 layer of the separator. After a certain time of continuous extraction the organic and fluorous compounds were isolated by solvent removal from the MeOH and FC-72 phase respectively.

4.2.1.3 Method C (separation using fluorous reverse phase silica)

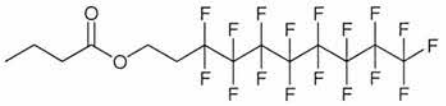
The solvent was removed under reduced pressure. The residue was loaded onto a FRPSG column (Fluorochem, Pittsburgh, USA), loading 0.5 g of the reaction mixture (per 5 g of fluorous silica). The first fraction containing only organic compounds was obtained by elution with 80-85% aq. methanol (8 cm^3). The second fraction containing only fluorous compounds was obtained by elution with acetone (15 cm^3).

4.2.2 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Nonadecafluorodecyl acetate, 38



Alcohol **37** (500.1 mg, 1.00 mmol) was dissolved in hexane (5 cm^3) and FC-72 (5 cm^3). Vinyl acetate (172 mg, 2.00 mmol) and *CRL* (200 mg) were added and the mixture was shaken (300 rpm) at 40 °C for 28 h. The lipase was filtered off and washed with hexane (5 cm^3) and FC-72 (5 cm^3). The liquid phases were separated after cooling (-10 °C) and the hexane phase was washed with FC-72 (5 cm^3). The product was isolated as a colourless liquid after solvent removal of the combined fluorous phase (471 mg, 87%). ***m/z*** (CI+) 543.005152 (M+H. $C_{12}H_6O_2F_{19}$ requires 543.006441); ν_{max} (film)/cm^{-1} 1773 (CO), 1210, 1079; δ_H (300 MHz, $CDCl_3$) 4.58 (2 H, t, $^3J_{H\text{-}F}$ 13.6, OCH_2), 2.16 (3 H, s, CH_3); δ_F (282 MHz, $CDCl_3$) -81.5 (3 F, t, $^3J_{F\text{-}F}$ 10.0, CF_3); -120.0 to -120.3 (2 F, m, CF_2), -122.1 to -122.6 (8 F, m, 4 × CF_2), -123.1 to -123.4 (2 F, m, CF_2), -123.7 to -124.0 (2 F, m, CF_2), -126.6 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 169.3 (s, *C*O), 126-106 (m, C_9F_{19}), 59.5 (t, $^2J_{C\text{-}F}$ 27, OCH_2), 20.0 (s, CH_3); ***m/z*** (EI+) 523 (15%, M-F), 413 (7), 169 (10, R_{f3}), 131 (20), 119 (15, CF_3CF_2), 69 (20, CF_3), 43 (100, CH_3CO).

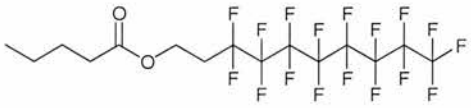
4.2.3 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl butanoate, 39



Preparation (1): The title compound was prepared from alcohol **36** (464 mg, 1.00 mmol), 2,2,2-trifluoroethyl butanoate (340 mg, 2.00 mmol) and the *CRL* lipase (23 h) in a similar manner to the preparation of **38** as described in 4.2.2. The product was recovered as a colourless liquid (443 mg, 83%).

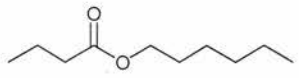
Preparation (2): The title compound was also prepared from alcohol **36** (464 mg, 1.00 mmol), butanoic anhydride (316 mg, 2.00 mmol) and the *CRL* lipase (9 h) in a similar manner to the preparation of **38** as described in 4.2.2. The product was recovered as a colourless liquid (518 mg, 97%). ***m/z*** (CI+) 535.057712 (M+H. $C_{14}H_{12}O_2F_{17}$ requires 535.056585); ν_{max} (film)/cm^{-1} 2974, 1748 (CO), 1169, 704, 657; δ_H (300 MHz, $CDCl_3$) 4.38 (2 H, t, *J* 6.4, OCH_2), 2.47 (2 H, tt, $^3J_{H\text{-}F}$ 18.4, *J* 6.4, CH_2CF_2), 2.31 (2 H, t, *J* 7.4, CH_2CO), 1.66 (2 H, sextet, *J* 7.4, CH_3CH_2), 0.96 (3 H, t, *J* 7.4, CH_3); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 10, CF_3), -114.0 to -114.2 (2 F, m, CF_2), -122.0 to -122.6 (6 F, m, 3 × CF_2), -123.1 to -123.3 (2 F, m, CF_2), -123.9 to -124.2 (2 F, m, CF_2), -126.5 to -126.7 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 173.6 (s, *C*O), 138-90 (m, C_8F_{17}), 56.4 (s, OCH_2), 36.3 (s, CH_2CO), 30.9 (t, $^2J_{C\text{-}F}$ 21.8, CH_2CF_2), 18.6 (s, CH_3CH_2), 13.9 (s, CH_3); *m/z* (CI+) 563 (15%, M+Et), 535 (100, M+1), 515 (10, M-F), 71 (15, C_3H_7CO).

4.2.4 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl pentanoate, 40



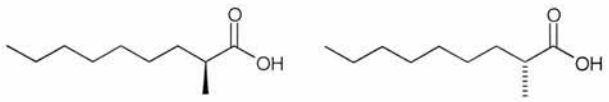
The title compound was prepared from alcohol **36** (464 mg, 1.00 mmol), pentanoic acid (204 mg, 2.00 mmol) and the *CRL* lipase (15 h) in a similar manner to the preparation of **38** as described in 4.2.2. The product was recovered as a colourless liquid (460 mg, 84%). ***m/z*** (CI+) 549.074677 (M+H. $C_{15}H_{14}O_2F_{17}$ requires 549.072235); ν_{max} (film)/cm^{-1} 2967, 1747 (CO), 1208; δ_H (300 MHz, $CDCl_3$) 4.38 (2 H, t, *J* 6.4, OCH_2), 2.47 (2 H, tt, $^3J_{H\text{-}F}$ 18.4, *J* 6.4, CH_2CF_2), 2.33 (2 H, t, *J* 7.4, CH_2CO), 1.62 (2 H, pentet, *J* 7.4, $CH_3CH_2CH_2$), 1.35 (2 H, sextet, *J* 7.4, CH_3CH_2), 0.92 (3 H, t, *J* 7.4, CH_3); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 10, CF_3), -114.0 to -114.3 (2 F, m, CF_2), -122.0 to -122.6 (6 F, m, 3 × CF_2), -123.1 to -123.4 (2 F, m, CF_2), -124.0 to -124.2 (2 F, m, CF_2), -126.5 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 173.4 (s, *C*O), 130-107 (m, C_8F_{17}), 56.1 (s, OCH_2), 33.8 (s, CH_2CO), 30.9 (t, $^2J_{C\text{-}F}$ 21.6, CH_2CF_2), 26.8 (s, $CH_3CH_2CH_2$), 22.2 (s, CH_3CH_2), 13.6 (s, CH_3); ***m/z*** (EI+) 548 (1%, M), 519 (30, M-F), 506 (52), 169 (7, R_{f3}), 131 (10), 119 (10, CF_3CF_2), 85 (100), 69 (20, CF_3), 57 (40), 43 (15).

4.2.5 Hexyl butanoate, 33



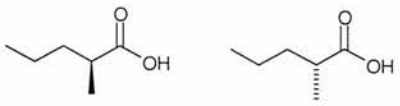
Ester **35** (335 mg, 0.50 mmol) and hexanol (51 mg, 0.50 mmol) were dissolved in hexane (10 cm^3) and PFD (10 cm^3). *CRL* (400 mg) was added and the mixture was shaken (300 rpm) at 45 °C for 165 h. The lipase was filtered off and washed with hexane (5 cm^3) and PFD (5 cm^3). The liquid phases were separated after cooling (-10 °C) and the hexane phase was washed with PFD (2 × 10 cm^3). The product was isolated as a colourless liquid after solvent removal of the washed hexane phase (84 mg, 98%) contaminated with less than 0.2% of the fluorous alcohol **34** as judged by GC-MS. ν_{max} (film)/cm^{-1} 2960, 1739 (CO), 1468, 1433, 1253, 1180, 1079, 996, 734, 678, 508; δ_H (300 MHz, $CDCl_3$) 4.03 (2 H, t, *J* 6.7, OCH_2), 2.44 (2 H, t, *J* 7.4, CH_2CO), 1.68-1.54 (4 H, m, 2 × CH_2), 1.36-1.21 (6 H, m, 3 × CH_2), 0.91 (3 H, t, *J* 7.4, CH_3), 0.86 (3 H, t, *J* 6.8, CH_3); δ_C (75 MHz, $CDCl_3$) 173.7 (s, *C*=O), 64.3 (s, OCH_2), 36.2 (s, CH_2CO), 31.4 (s, CH_2), 28.6 (s, CH_2), 25.5 (s, CH_2), 22.5 (s, CH_2), 18.4 (s, CH_2), 13.9 (s, CH_3), 13.6 (s, CH_3); ***m/z*** (EI+) 171 (1%, M), 89 (80), 84 (40), 71 (100, C_3H_7CO), 56 (60), 43 (100), 41 (40).

4.2.6 Resolution of 2-methylnonanoic acid, 64



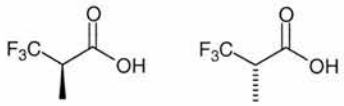
Racemic 2-methylnonanoic acid **64** (189 mg, 1.10 mmol) and fluorous alcohol **36** (1.202 g, 2.59 mmol) were dissolved in hexane (20 cm^3) and FC-72 (10 cm^3). *CRL* (500 mg) was added and the mixture was shaken (300 rpm) at 40 °C for 65 h. The lipase was filtered off and washed with hexane (5 cm^3) and FC-72 (5 cm^3). After solvent removal under reduced pressure the residue was dissolved in MeOH (15 cm^3). The separation was conducted using continuous extraction (Method B, 4.2.1.2) with FC-72 (35 cm^3) to 10 h. (*R*)-2-Methylnonanoic acid (91.7 mg, 97%, *ee* 98%), $[\alpha]_D^{25}$= - 8.4 (c 0.20, Et_2O), was isolated after solvent removal of the MeOH phase. The fluorous phase was concentrated and hydrolysed by refluxing with the solution of KOH (350 mg, 5.93 mmol) in 90% aq. MeOH (10 cm^3) for 3.5 h. Methanol was removed under reduced pressure and water (10 cm^3) was added. Extraction with ether (3 × 15 cm^3) gave the fluorous alcohol **36** (1.166 g, 97%). Acidification with concentrated hydrochloric acid and extraction with ether (3 × 10 cm^3) gave the (*S*)-2-methylnonanoic acid (92.6 mg, 98%, *ee* 96%), $[\alpha]_D^{19}$= + 8.0 (c 0.22, Et_2O), lit.[272] $[\alpha]_D^{25}$= +9.2 (*c* 18, Et_2O) as a colourless liquid. Spectroscopic data were identical to the racemic 2-methylnonanoic acid, 4.3.17.

4.2.7 Resolution of 2-methylpentanoic acid, 45



Racemic 2-methylpentanoic acid **45** (6.00 g, 51.6 mmol) and the fluorous alcohol **36** (23.1 g, 45.8 mmol) were dissolved in hexane (150 cm^3) and FC-72 (150 cm^3). *CRL* (5.00 g) was added and the mixture was shaken (250 rpm) at 40 °C for 95 h. $MgSO_4$ was added, the lipase was filtered off and washed with hexane (15 cm^3) and FC-72 (15 cm^3). The separation was conducted using fluorous biphase extraction (Method A, Section 4.2.1.1). The two phases were separated after cooling (-10 °C) and the hexane phase was washed with FC-72 (5 × 150 cm^3). The solvent was removed from the washed hexane phase yielding (*R*)-2-methylpentanoic acid (1.71 g, 57%, *ee* 79%,), $[\alpha]_D^{19}$= -7.5 (*c* 3.1, Et_2O) as a colourless liquid, contaminated with less than 1% of the fluorous ester **52**. The combined fluorous phase was concentrated and the residue was suspended in a solution of *CRL* (2.00 g) in phosphate buffer (350 ml, 0.2 M, pH 7.0). After 96 h of stirring **36** (13.3 g, 62%) was recovered by extraction into FC-72 (5 × 150 cm^3). Acidification with concentrated hydrochloric acid and extraction into ether gave (*S*)-2-methylpentanoic acid (1.86 g, 62%, *ee* 96%,), $[\alpha]_D^{22}$ = +19.03 (*c* 3.8, Et_2O), lit.[273] $[\alpha]_D$= +19.3 (*c* 3.5, Et_2O) as a colourless liquid. ν_{max} (film)/cm^{-1} 3470, 2962, 1708 (CO), 933, 640, 553; δ_H (300 MHz, $CDCl_3$) 11.7 (1 H, br s, O*H*), 2.47 (1 H, sextet, *J* 6.9, C*H*), 1.74-1.63 (1 H, m, CH^aCH^bCH), 1.48-1.30 (3 H, m, $CH_3CH_2CH^aH^b$), 1.18 (3 H, d, *J* 6.9, CH_3CH), 0.92 (3 H, t, *J* 7.2, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 183.9 (s, *C*O), 39.2 (s, *C*H), 35.6 (CH_2), 20.3 (s, CH_3CH_2), 16.8 (s, CH_3CH), 13.9 (s, CH_3CH_2); ***m/z*** (EI+) 87 (20%, M-Et), 74 (100), 73 (20), 43 (50, C_3H_7), 41 (30), 29 (15, Et).

4.2.8 Resolution (1) of 3,3,3-trifluoro-2-methylpropanoic acid, 69

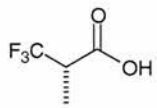


Fluorous alcohol **73** (6.204 g, 17.0 mmol) and racemic 3,3,3-trifluoro-2-methylpropanoic acid **69** (1.208 g, 8.51 mmol) were dissolved in hexane (50 cm^3) and FC-72 (20 cm^3). The lipase from *Candida rugosa* (5.00 g) was added and the mixture was shaken (250 rpm) at 37°C for 18 h. The reaction was terminated by addition of $MgSO_4$ (1 g) and the mixture was filtered. The solid was washed with diethyl ether (15 cm^3) and the solvent was removed under reduced pressure. The separation was conducted using the fluorous reverse phase silica gel filtration (Method C, 4.2.1.3). The residue was split into ~0.5 g portions and each was loaded onto a FRPSG (5 g) column. Elution with aq. methanol (80%, 8 cm^3) gave the first fraction and elution with acetone (15 cm^3) gave the second fraction. The MeOH fractions were combined and the solvent was partially removed under reduced pressure. Water (20 cm^3) was added and the mixture was extracted into ether (3 × 20 cm^3). The organic phase was dried over $MgSO_4$ and after removal of the solvent (2*S*)-3,3,3-trifluoro-2-methylpropanoic acid was isolated as a colourless liquid (400 mg, 66%, *ee* 90%).

The solvent was removed from the combined acetone fractions and the residue was refluxed in a solution of 1,4-dioxane (10 cm^3) and concentrated hydrochloric acid (5 cm^3) for 15 h. The mixture was diluted with water (15 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The combined organic phase was washed with aq. $NaHCO_3$ (0.8 M, 3 × 10 cm^3). Acidification of the aq. phase and extraction with ether gave (2*R*)-3,3,3-trifluoro-2-methylpropanoic acid as a colourless liquid

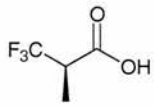
(326 mg, 54%, *ee* 68%). Spectroscopic data for each enantiomer were identical to the racemic 3,3,3-trifluoro-2-methylpropanoic acid, 4.3.21.

4.2.9 Resolution (2), (2*S*)-3,3,3-trifluoro-2-methylpropanoic acid, (*S*)-69



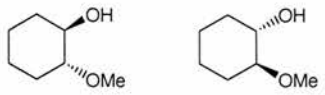
1-Decanol (6.708 g, 42.38 mmol) and 3,3,3-trifluoro-2-methylpropanoic acid (3.009 g, 21.19 mmol) were dissolved in hexane (200 cm^3). The lipase from *Candida rugosa* (7.5 g) was added and the mixture shaken (250 rpm) at 37°C for 20 h. The reaction was terminated by addition of $MgSO_4$ (5 g) and the mixture was filtered. The solid was washed with diethyl ether (3 × 15 cm^3), the solvent was removed under reduced pressure and the residue dissolved in diethyl ether (50 cm^3). The product was isolated by extraction with aq. $NaHCO_3$ (0.8 M, 3 × 40 cm^3), acidification with concentrated hydrochloric acid to pH 0-2 and extraction into diethyl ether (3 × 20 cm^3). Drying and solvent removal gave the product as a colourless liquid (1.111 g, 74%, *ee* > 98%). $[\alpha]_D^{19}$ -0.8 (*c* 1.23, MeOH). Spectroscopic data were identical to racemic 3,3,3-trifluoro-2-methylpropanoic acid, 4.3.21.

4.2.10 Resolution (2), (2*R*)-3,3,3-trifluoro-2-methylpropanoic acid, (*R*)-69



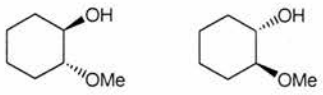
1-Decanol (6.708 g, 42.38 mmol) and 3,3,3-trifluoro-2-methylpropanoic acid (3.009 g, 21.19 mmol) were dissolved in hexane (200 cm^3). The lipase from *Candida rugosa* (7.5 g) was added and the mixture shaken (250 rpm) at 37°C for 4 h. The reaction was terminated by addition of $MgSO_4$ (5 g) and the mixture was filtered. The solid was washed with diethyl ether (3 × 15 cm^3), the solvent was removed under reduced pressure and the residue dissolved in diethyl ether (50 cm^3). The solution was washed with aq. $NaHCO_3$ (0.8 M, 3 × 40 cm^3), solvent was removed from organic phase and the residue hydrolysed (HCl in 1,4-dioxane). Similar workup as for the racemic acid afforded the product as a colourless liquid (541 mg, 36%, *ee* 90%). $[\alpha]_D^{19}$ < +1 (*c* 1.12, MeOH). Spectroscopic data were identical to racemic 3,3,3-trifluoro-2-methylpropanoic acid, 4.3.21.

4.2.11 Resolution (1) of *trans* 2-methoxycylohexanol, 88



Ester **26** (10.00 g, 17.42 mmol) was dissolved FC-72 (65 cm^3), racemic *trans* 2-methoxycylohexanol (1.698 g, 13.06 mmol) and *CAL-B* (2.00 g) were added. The mixture was shaken (250 rpm) at 30 °C for 65 h. The lipase was filtered off and washed with FC-72 (15 cm^3) and then with MeOH (4 × 20 cm^3). The separation was conducted using fluorous biphase extraction (Method A, 4.2.1.1). The two phases were separated after cooling (4 °C) and the MeOH phase was washed with FC-72 (5 × 80 cm^3). Solvent was removed from the washed MeOH phase yielding *trans* (1*S*, 2*S*)-2-methoxycylohexanol (832 mg, 98%, *ee* > 80%), $[\alpha]_D^{21}$= +57 (*c* 3.0, CH_2Cl_2). (lit.[228] $[\alpha]_D^{20}$= +69.5 (*c* 2.0, CH_2Cl_2). The combined fluorous phase was concentrated and the residue was refluxed in a solution of lithium hydroxide monohydrate (1.83 g, 43.6 mmol) in water (2 cm^3) and THF (20 cm^3) for 12 h. Solvent was removed under reduced pressure, cyclohexane (120 cm^3) was added and the mixture was filtered giving lithium salt of **83** as a white solid (7.803 g, 90%). The filtrate was dried over $MgSO_4$ and the solvent was removed under reduced pressure yielding *trans* (1*R*, 2*R*)-2-methoxycylohexanol (594 mg, 70%, *ee* 99%), $[\alpha]_D^{21}$= -68 (*c* 3.2, CH_2Cl_2). Spectroscopic data for both enantiomers were identical to racemic *trans* 2-methoxycylohexanol, 4.3.34.

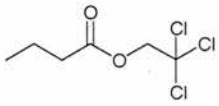
4.2.12 Resolution (2) of *trans* 2-methoxycylohexanol, 88



Racemic *trans* 2-methoxycyclohexanol (205 mg, 1.58 mmol) and ester **55** (1.602 g, 3.96 mmol) were dissolved in hexane (15 cm^3). *CAL-B* (1.00 g) was added and the mixture was shaken (250 rpm) at 37 °C for 17 h. The lipase was filtered off, washed with hexane (5 cm^3) and the solvent was removed under reduced pressure. The separation was conducted using fluorous reverse phase silica gel filtration (Method C, 4.2.1.3). The residue was split into ~0.5 g portions and each was loaded onto a FRPSG (5 g) column. Elution with aq. methanol (80%, 8 cm^3) gave the first fraction and elution with acetone (15 cm^3) gave the second fraction. The MeOH fractions were combined and the solvent was partially removed under reduced pressure. Water (10 cm^3) was added and the mixture was extracted with ether (3 × 10 cm^3). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduce pressure yielding *trans* (1*S*, 2*S*)-2-methoxycylohexanol (95 mg, 93%, *ee* > 90%). The solvent was removed from the combined acetone fractions and the residue was refluxed in a solution of lithium hydroxide monohydrate (885 mg, 21.1 mmol) in methanol (20 cm^3) for 3 h. Solvent was removed under reduced pressure, cyclohexane (20 cm^3) was added and the mixture was filtered giving lithium salt of **86** as a white solid (1.170 g, 90%). The filtrate was dried over $MgSO_4$ and the solvent was removed under reduced pressure yielding *trans* (1*R*, 2*R*)-2-methoxycylohexanol (98 mg, 87%, *ee* 99%). Spectroscopic data for both enantiomers were identical to racemic *trans* 2-methoxycylohexanol, 4.3.34.

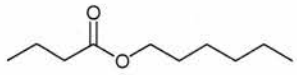
4.3 Synthesis of compounds

4.3.1 Synthesis of 2,2,2-trichloroethyl butanoate, 31



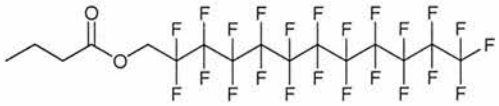
A mixture of butanoic anhydride (32.22 g, 0.21 mol), 2,2,2-trichloroethanol (14.9 g, 0.1 mol) and pyridine (12.66 g, 0.16 mol) was stirred under nitrogen at room temperature for 72 h. The reaction was terminated by addition of hydrochloric acid (1 M, 110 cm^3) and extracted into ether (3 × 100 cm^3). The combined organic phases were washed with aqueous sodium hydrogen carbonate (5%, 2 × 100 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Vacuum distillation gave the product as a colourless liquid (15.8 g, 72%), bp 85-87 °C at 20 mm Hg. (lit.[274] 119.8-120 °C at 48 mm Hg.). ν_{max} (film)/cm^{-1} 2969, 2938, 2879, 1756 (CO), 1460, 1384, 1156, 1029, 929, 809, 785, 721, 570; δ_H (300 MHz, $CDCl_3$) 4.74 (2 H, s, OCH_2), 2.43 (2 H, t, *J* 7.3, CH_2CO), 1.71 (2 H, m, CH_3CH_2), 0.98 (3 H, t, *J* 7.4, CH_3); δ_C (75 MHz, $CDCl_3$) 172.0 (s, *C*O), 95.0 (s, CCl_3), 73.8 (s, OCH_2), 35.9 (s, CH_2CO), 18.1 (s, CH_2), 13.6 (s, CH_3); ***m/z*** (EI+) 218 (1%, M), 192 (30), 190 (30), 183 (20, M-Cl), 133 (7, CH_2CCl_3), 131 (7, CH_2CCl_3), 71 (100, C_3H_7CO), 60 (27), 43 (50), 41 (22), 27 (10).

4.3.2 Synthesis of hexyl butanoate, 33



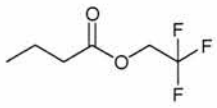
A mixture of butanoic acid (22.11 g, 0.25 mol), 1-hexanol (12.82 g, 0.126 mol) and sulfuric acid (98%, 1.33 cm^3) was heated at 170 °C for 17 h. The upper layer of the product was separated and washed with aqueous potassium carbonate (10%, 4 × 150 cm^3). The combined aqueous layers were extracted with ether (100 cm^3), dried over $MgSO_4$ and concentrated. Distillation gave the product as a colourless liquid (18.8 g, 87%), bp 95-100 °C at 20 mm Hg. (lit.[275] 207.88°C at 760 mm Hg). Spectroscopic data were identical to hexyl butanoate prepared enzymatically 4.2.5.

4.3.3 Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-tricosafluorododecyl butanoate, 35



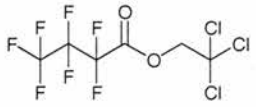
Butanoyl chloride (0.487 g, 4.57 mmol) was added to alcohol **34** (2.00 g, 3.17 mmol) at 120 °C. The reaction mixture was stirred at 150-160 °C for 48 h, then cooled and dissolved in ether (200 cm^3). The ether solution was washed with aqueous potassium carbonate (10%, 3×150 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Vacuum distillation gave the product as a white waxy solid (1.303 g, 61%), bp 78 °C at 0.2 mm Hg, mp 62 °C. ***m/z*** (EI+) 670.0256 (M. $C_{16}H_9O_2F_{23}$ requires 670.0235); ν_{max} (KBr)/cm^{-1} 2975, 1763 (CO), 1350, 1205, 1152, 868, 649, 557; δ_H (300 MHz, $CDCl_3$) 4.59 (2 H, t, $^3J_{H\text{-}F}$ 13.7, OCH_2), 2.40 (2 H, t, *J* 7.4, CH_2CO), 1.69 (2 H, sextet, *J* 7.4, CH_3CH_2), 0.97 (3 H, t, *J* 7.4, CH_3); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 9.3, CF_3); -119.9 to -120.2 (2 F, m, CF_2), -122.0 to -122.5 (12 F, m, $6 \times CF_2$), -123.1 to -123.4 (2 F, m, CF_2), -123.7 to -124.0 (2 F, m, CF_2), -126.5 to -126.7 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 172.0 (s, *C*O), 125-110 (m, $C_{11}F_{23}$), 59.2 (t, $^2J_{C\text{-}F}$ 34.0, O*C*H_2), 35.5 (s, *C*H_2CO), 18.2 (s, *C*H_2), 13.4 (s, *C*H_3); ***m/z*** (EI+) 670 (1%, M), 655 (4, M-Me), 651 (6, M-F), 642 (7, M-C_2H_4), 169 (5), 131 (15, CF_2=C-CF_3), 119 (9, CF_3CF_2), 71 (100, C_3H_7CO), 69 (25, CF_3), 43 (80), 41 (15).

4.3.4 Synthesis of 2,2,2-trifluoroethyl butanoate, 90



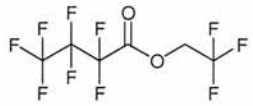
The title compound was prepared from butanoic anhydride (31.64 g, 0.2 mol), 2,2,2-trifluroethanol (10.0 g, 0.1 mol) and pyridine (12.56 g, 0.16 mol) in a similar manner to the preparation of 2,2,2-trichloroethyl butanoate **31** as described in 4.3.1. The product was recovered as a colourless liquid (11.6 g, 68%), bp 113-115 °C (lit.[276] 105-115 °C). ν_{max} (film)/cm^{-1} 2974, 2883, 1765 (CO), 1413, 1283, 1164, 1103, 979, 842, 663, 556; δ_H (300 MHz, $CDCl_3$) 4.45 (2 H, q, $^3J_{H-F}$ 8.7, OCH_2), 2.38 (2 H, t, *J* 7.2, CH_2CO), 1.68 (2 H, m, CH_3CH_2), 0.95 (3 H, t, *J* 7.5, CH_3); δ_F (282 MHz, $CDCl_3$) -74.5 (3 F, t, $^3J_{F-H}$ 8.7, CF_3); δ_C (75 MHz, $CDCl_3$) 172.0 (s, *C*O), 123.0 (q, $^1J_{C-F}$ 277, CF_3), 60.0 (q, $^2J_{C-F}$ 36, OCH_2), 35.4 (s, CH_2CO), 18.2 (s, CH_2), 13.4 (s, CH_3); ***m/z*** (EI+) 170 (1%, M), 155 (20, M-Me), 151 (5, M-F), 142 (90), 83 (40, CH_2CF_3), 71 (70, C_3H_7CO), 69 (10, CF_3), 43 (100), 41 (40), 27 (30).

4.3.5 Synthesis of 2,2,2-trichloroethyl 2,2,3,3,4,4,4-heptafluorobutanoate, 41



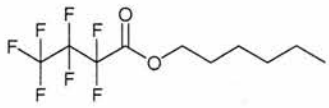
Dimethylformamide (0.76 g, 14.4 mmol) was added dropwise to a stirred solution of perfluorobutanoic acid (11.18 g, 52 mmol) and thionyl chloride (12.43 g, 144 mmol) at 0 °C. Perfluorobutanoyl chloride, (bp 38-39 °C, 11 g, 90%) was distilled out to the ice-cooled receiving flask. Pyridine (1.7 g, 21.5 mmol) was added dropwise to the solution of perflurobutanoyl chloride (4.94 g, 21.2 mmol) and 2,2,2-trichloroethanol (2.9 g, 19.4 mmol) at 0 °C. The reaction mixture was stirred for 4 h at 35 °C and then acidified to pH 3-4 by adding a few drops of concentrated hydrochloric acid. The product was extracted into chloroform (3×80 cm^3), washed with aqueous sodium hydrogen carbonate (10%, 3×80 cm^3), the organic phase was separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual oil was distilled to yield the product as a colourless liquid (1.93 g, 29%), bp 65 °C at 20 mm Hg (lit.[277] 96-100 °C at 80 mm Hg). ν_{max} (film)/cm^{-1} 2970, 1797 (CO), 1678, 1445, 1382, 1356, 1237, 1146, 1099, 995, 922, 802, 730, 573; δ_H (300 MHz, $CDCl_3$) 4.97 (s, OCH_2); δ_F (282 MHz, $CDCl_3$) -81.0 (3 F, t, $^3J_{F\text{-}F}$ 8.8, CF_3); -119.4 to -119.6 (2 F, m, CF_3CF_2), -126.9 (2 F, s, CF_2CO); δ_C (75 MHz, $CDCl_3$) 160.9 (t, $^2J_{C\text{-}F}$ 29, *C*O), 130-100 (m, $CF_3CF_2CF_2$), 99.0 (s, CCl_3), 76.1 (s, OCH_2); ***m/z*** (EI+) 313 (4%, M-Cl), 311 (24, M-Cl), 309 (38, M-Cl), 227 (60, M-CCl_3), 197 (50, $R_{f3}CO$), 169 (100, R_{f3}), 135 (15), 133 (46), 131 (50, CCl_3CH_2), 119 (25, CF_3CF_2), 95 (30), 69 (60, CF_3).

4.3.6 Synthesis of 2,2,2-trifluoroethyl 2,2,3,3,4,4,4-heptafluorobutanoate, 42



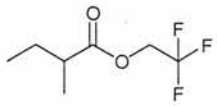
The title compound was prepared from pyridine (1.90 g, 24 mmol), 2,2,2-trifluroethanol (2.58 g, 25.8 mmol) and perflurobutanoyl chloride (6.00 g, 25.8 mmol) in a similar manner as preparation of **41** as described in 4.3.5. The product was recovered as a colourless liquid (3.82 g, 50%), bp 88-90 °C (lit.[278] 92 °C at 737 mm Hg). ν_{max} (film)/cm^{-1} 2990, 1801 (CO), 1453, 1416, 1357, 1187, 1143, 1090, 1018, 981, 874, 810, 758, 743, 723, 653; δ_H (300 MHz, $CDCl_3$) 4.73 (q, $^3J_{H\text{-}F}$ 7.8, OCH_2); δ_F (282 MHz, $CDCl_3$) -74.4 (3 F, t, $^3J_{F\text{-}H}$ 7.7, CF_3CH_2), -81.4 (3 F, t, $^3J_{F\text{-}F}$ 8.3, CF_3); -119.7 to -119.8 (2 F, m, CF_3CF_2), -127.5 (2 F, s, CF_2CO); δ_C (75 MHz, $CDCl_3$) 162.9 (s, *C*O), 122.1 (q, $^1J_{C\text{-}F}$ 277, CH_2CF_3), 124-107 (m, $CF_3CF_2CF_2$), 63.2 (q, $^2J_{C\text{-}F}$ 38.2, CH_2); ***m/z*** (EI+) 277 (1%, M-F), 197 (3, $R_{f3}CO$), 169 (22, R_{f3}), 127 (13), 119 (5, CF_3CF_2), 100 (10, CF_3CH_2OH), 83 (100, CF_3CH_2), 69 (50, CF_3).

4.3.7 Synthesis of hexyl 2,2,3,3,4,4,4-heptafluorobutanoate, 43



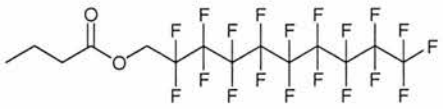
The title compound was prepared from pyridine (2.37 g, 30 mmol), 1-hexanol (3.3 g, 32 mmol) and perflurobutanoyl chloride (6.8 g, 29 mmol) in a similar manner as preparation of **41** as described in 4.3.5. The product was recovered as a colourless liquid (2.5 g, 29%), bp 64 °C at 20 mm Hg. (lit.[279] 169-170 °C). ν_{max} (film)/cm^{-1} 2936, 2865, 1783 (CO), 1470, 1356, 1304, 1217, 1146, 1085, 971, 940, 826, 743, 721, 651, 589, 531; δ_H (300 MHz, $CDCl_3$) 4.37 (2 H, t, *J* 6.7, OCH_2), 1.81-1.69 (2 H, m, CH_2), 1.45-1.26 (6 H, m, 3 × CH_2), 0.89 (3 H, t, *J* 6.9, CH_3); δ_F (282 MHz, $CDCl_3$) -81.4 (3 F, t, $^3J_{F-F}$ 8.3, CF_3); -120.0 to -120.1 (2 F, m, CF_3CF_2), -127.6 (2 F, s, CF_2CO); δ_C (75 MHz, $CDCl_3$) 158.6-158.2 (m, *C*O), 125-100 (m, $CF_3CF_2CF_2$), 69.7 (s, OCH_2), 31.2 (s, CH_2), 28.0 (s, CH_2), 25.1 (s, CH_2), 22.4 (s, CH_2), 13.8 (s, CH_3); ***m/z*** (EI+) 197 (3%, $R_{f3}CO$), 119 (5, CF_3CF_2), 100 (5, CF_3CH_2OH), 84 (15), 69 (80, CF_3), 56 (100), 55 (60).

4.3.8 Synthesis of 2,2,2-trifluoroethyl 2-methylbutanoate, 47



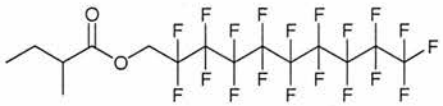
Pyridine (1.26 g, 16 mmol) was added drop-wise to a solution of 2-methylbutanoyl chloride (1.92 g, 16 mmol) and 2,2,2-trifluoroethanol (1.59 g, 16 mmol). The reaction mixture was stirred for 2 h at room temperature and for further 2 h at 80 °C and then acidified to pH 3-4 by adding a few drops of concentrated hydrochloric acid. The product was extracted into chloroform and washed with aqueous sodium hydrogen carbonate (1%). The organic phase was separated, dried over $MgSO_4$ and concentrated. The residual oil was distilled to yield the product as a colourless liquid (1.71 g, 58%), bp 101 °C. ν_{max} (film)/cm^{-1} 2976, 2943, 2884, 1759 (CO), 1464, 1412, 1282, 1172, 1094, 978, 761, 667; δ_H (300 MHz, $CDCl_3$) 4.47 (2 H, dq, $^3J_{H\text{-}F}$ 8.5, $^5J_{H\text{-}H}$ 2.7, OCH_2), 2.55-2.43 (1 H, m, CH), 1.79-1.64 (1 H, m, $CH_3CH^aH^b$), 1.59-1.45 (1 H, m, $CH_3CH^aH^b$), 1.18 (3 H, d, J 6.9, CH_3CH), 0.92 (3 H, t, J 7.4, CH_3); δ_F (282 MHz, $CDCl_3$) -74.4 (3 F, t, $^3J_{F\text{-}H}$ 8.5, CF_3); δ_C (75 MHz, $CDCl_3$) 175.0 (s, CO), 123.1 (q, $^1J_{C\text{-}F}$ 278, CF_3), 60.0 (q, $^2J_{C\text{-}F}$ 37.0, OCH_2), 40.7 (s, CH), 26.6 (s, CH_2), 16.4 (s, CH_3CH), 11.4 (s, CH_3CH_2); ***m/z*** (EI+) 184 (1%, M), 169 (20, M-Me), 165 (10, M-F), 157 (10, M-Et), 156 (100, M-C_2H_4), 85 (30), 83 (30, CF_3CH_2), 69 (20, CF_3), 57 (100), 41 (60), 29 (50).

4.3.9 Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl butanoate, 48



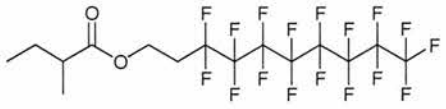
The title compound was prepared from butanoyl chloride (2.052 g, 19.28 mmol) and alcohol **37** (2.510 g, 5.02 mmol) in a similar manner to the preparation of the ester **35** as described in 4.3.3. The product was isolated by the chromatography over silica (petrol:ether; 97:3) as a colourless liquid (2.74 g, 96%). ***m/z*** (CI+) 571.0386 (M+H. $C_{14}H_{10}O_2F_{19}$ requires 571.0377); ν_{max} (film)/cm^{-1} 2975, 2883, 1764 (CO), 1212, 1151, 975, 708, 659, 560; δ_H (300 MHz, $CDCl_3$) 4.59 (2 H, t, $^3J_{H\text{-}F}$ 13.7, OCH_2), 2.40 (2 H, t, *J* 7.4, CH_2CO), 1.69 (2 H, sextet, *J* 7.4, CH_3CH_2), 0.97 (3 H, t, *J* 7.4, CH_3); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 10.2, CF_3); -119.9 to -120.1 (2 F, m, CF_2), -122.2 to -122.6 (8 F, m, 4 × CF_2), -123.1 to -123.3 (2 F, m, CF_2), -123.7 to -123.9 (2 F, m, CF_2), -126.5 to -126.7 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 172.0 (s, *C*O), 125-110 (m, C_9F_{19}), 59.3 (t, $^2J_{C\text{-}F}$ 27.0, O*C*H_2), 35.5 (s, *C*H_2CO), 18.2 (s, *C*H_2), 13.4 (s, *C*H_3); ***m/z*** (CI+) 599 (10%, M+Et), 571 (100, M+H), 551 (15, M-F), 71 (20, C_3H_7CO).

4.3.10 Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl 2-methylbutanoate, 49



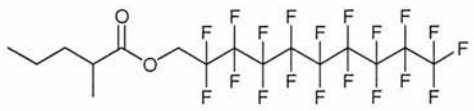
The title compound was prepared from 2-methylbutanoyl chloride (0.52 g, 4.3 mmol) and alcohol **37** (1.954 g, 3.71 mmol) in a similar manner to the preparation of **35** as described in 4.3.3. The product was dissolved in chloroform (100 cm^3) and washed with aqueous solution of potassium carbonate (10%, 3 × 50 cm^3). Distillation gave the product as a colourless liquid (1.40 g, 65%), bp 165 °C at 1.5 mm Hg. ***m/z*** (EI+) 584.0480 (M. $C_{15}H_{11}O_2F_{19}$ requires 584.0456); ν_{max} (film)/cm^{-1} 2977, 2944, 2886, 1760 (CO), 1466, 1337, 1213, 1093, 975, 659, 560, 530; δ_H (300 MHz, $CDCl_3$) 4.58 (2 H, t, $^3J_{H\text{-}F}$ 13.6, OCH_2), 2.53-2.42 (1 H, m, CH), 1.78-1.63 (1 H, m, $CH_3CH^aH^b$), 1.58-1.43 (1 H, m, $CH_3CH^aCH^b$), 1.17 (3 H, d, J 7.0, CH_3CH), 0.90 (3 H, t, J 7.2, CH_3CH_2); δ_F (282 MHz, $CDCl_3$) -81.7 (3 F, m, CF_3); -120.0 to -120.4 (2 F, m, CF_2), -122.3 to -122.9 (8 F, m, 4 × CF_2), -123.3 to -123.7 (2 F, m, CF_2), -123.9 to -124.2 (2 F, m, CF_2), -126.8 to -127.1 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 175.0 (s, CO), 120-103 (m, C_9F_{19}), 59.3 (t, $^2J_{C\text{-}F}$ 27, CH_2CF_2), 40.8 (s, CH), 26.5 (s, CH_3CH_2), 16.2 (s, CH_3CH), 11.2 (s, CH_3CH_2); ***m/z*** (EI+) 584 (2%, M), 569 (14, M-Me), 556 (90, M-C_2H_4), 527 (10), 169 (4, R_{f3}), 131 (14), 119 (10), 85 (40), 69 (27, CF_3), 57 (100).

4.3.11 Synthesis of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl 2-methylbutanoate, 50



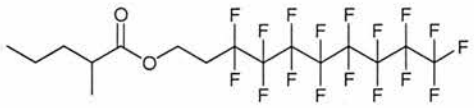
2-Methylbutanoyl chloride (1.60 g, 13.28 mmol) was added to alcohol **36** (5.57 g, 12 mmol). The mixture was heated under nitrogen at 120 °C for 24 h, then cooled and dissolved in chloroform (100 cm^3). The solution of product was washed with aqueous potassium carbonate (10%, 3 × 50 cm^3), the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Distillation gave the product as a colourless liquid (5.93 g, 90%), bp 65 °C at 0.4 mm Hg. ***m/z*** (CI+) 549.074355 (M+H. $C_{15}H_{14}O_2F_{17}$ requires 549.072235); ν_{max} (film)/cm^{-1} 2975, 1743 (CO), 1466, 1246, 704; δ_H (300 MHz, $CDCl_3$) 4.39 (2 H, t, *J* 6.4, OCH_2), 2.55-2.34 (3 H, m, C*H*, CH_2CF_2), 1.76-1.62 (1 H, m, $CH_3CH^aH^b$), 1.55-1.35 (1 H, m, $CH_3CH^aH^b$), 1.15 (3 H, d, *J* 7.2, CH_3CH), 0.91 (3 H, t, *J* 7.4, CH_3CH_2); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F-F}$ 10, CF_3), -114.0 to -114.2 (2 F, m, CF_2), -122.2 to -122.6 (6 F, m, 3 × CF_2), -123.1 to -123.4 (2 F, m, CF_2), -123.9 to -124.1 (2 F, m, CF_2), -126.5 to -126.7 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 176.2 (s, *C*O), 127-105 (m, C_8F_{17}), 56.1 (s, OCH_2), 40.9 (s, *C*H), 30.6 (t, $^2J_{C-F}$ 22, CH_2CF_2), 26.6 (s, CH_3CH_2), 16.3 (s, CH_3CH), 11.4 (s, CH_3CH_2); ***m/z*** (EI+) 548 (3%, M), 533 (12, M-Me), 520 (100, $R_{f8}H$), 491 (3, M-C_4H_9), 131 (9), 119 (7, CF_3CF_2), 85 (50, C_4H_9CO), 57 (70).

4.3.12 Synthesis of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl 2-methylpentanoate, 51



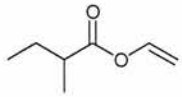
The title compound was prepared from 2-methylpentanoyl chloride (1.956 g, 14.5 mmol) and alcohol **37** (2.436 g, 4.87 mmol) in a similar manner to the preparation of **35** as described in 4.3.3. The product was dissolved in chloroform (100 cm^3) and washed with aqueous solution of potassium carbonate (10%, 3 × 50 cm^3). Purification over silica gel (petrol:ether, 49:1) gave the product as a pale yellow liquid (2.844 g, 97%). ***m/z*** (CI+) 599.071247 (M+H. $C_{16}H_{14}O_2F_{19}$ requires 599.06904); ν_{max} (film)/cm^{-1} 2968, 2881, 1761 (CO), 1460, 1170, 974, 708, 659; δ_H (300 MHz, $CDCl_3$) 4.59 (2 H, t, $^3J_{H\text{-}F}$ 13.8, OCH_2), 2.57 (1 H, sextet, *J* 6.9, C*H*), 1.74-1.62 (1 H, m, CH^aCH^bCH), 1.50-1.26 (3 H, m, $CH_3CH_2CH^aH^b$), 1.19 (3 H, d, *J* 6.9, CH_3CH), 0.91 (3 H, t, *J* 7.4, CH_3CH_2); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 10.2, CF_3); -119.9 to -120.1 (2 F, m, CF_2), -122.1 to -122.6 (8 F, m, 4 × CF_2), -123.1 to -123.4 (2 F, m, CF_2), -123.7 to -123.9 (2 F, m, CF_2), -126.6 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 175.5 (s, *C*O), 130-90 (m, C_9F_{19}), 59.6 (t, $^2J_{C\text{-}F}$ 27, CH_2CF_2), 39.4 (s, *C*H), 35.9 (CH_2), 20.6 (s, CH_3CH_2), 17.1 (s, CH_3CH), 14.1 (s, CH_3CH_2); ***m/z*** (CI+) 627 (10%, M+Et), 599 (100, M+1), 579 (20, M-F), 99 (20).

4.3.13 Synthesis of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl 2-methylpentanoate, 52



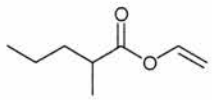
The title compound was prepared from 2-methylpentanoyl chloride (4.25 g, 31.6 mmol) and alcohol **36** (7.335 g, 15.84 mmol) in a similar manner to the preparation of **50** as described in 4.3.11. Distillation gave the product as a colourless liquid (7.80 g, 88%), bp 90-105 °C at 2 mm Hg. ***m/z*** (CI+) 563.089962 (M+H. $C_{16}H_{16}O_2F_{17}$ requires 563.087885); ν_{max} (film)/cm^{-1} 2968, 1743 (CO), 1466, 1167, 704, 657; δ_H (300 MHz, $CDCl_3$) 4.38 (2 H, t, *J* 6.5, OC*H*$_2$), 2.58-4.38 (3 H, m, C*H*, C*H*$_2$CF$_2$), 1.73-1.57 (1 H, m, CH$_3$CH$_2$C*H*^{a}H^b), 1.46-1.28 (3 H, m, CH$_3$C*H*$_2$CH^a*H*^{b}), 1.15 (3 H, d, *J* 7.2, C*H*$_3$CH), 0.90 (3 H, t, *J* 7.2, C*H*$_3$CH$_2$); δ_F (282 MHz, $CDCl_3$) -81.2 (3 F, t, $^3J_{F\text{-}F}$ 10, C*F*$_3$), -114.0 to -114.2 (2 F, m, C*F*$_2$), -122.0 to -122.6 (6 F, m, 3 × C*F*$_2$), -123.1 to -123.4 (2 F, m, C*F*$_2$), -123.9 to -124.2 (2 F, m, C*F*$_2$), -126.5 to -126.7 (2 F, m, C*F*$_2$); δ_C (75 MHz, $CDCl_3$) 176.5 (s, *C*O), 56.1 (s, O*C*H$_2$), 39.2 (s, *C*H), 35.7 (s, *C*H$_2$), 30.6 (t, $^2J_{C\text{-}F}$ 21, *C*H$_2$CF$_2$), 20.3 (s, CH$_3$*C*H$_2$), 16.8 (s, *C*H$_3$CH), 13.9 (s, *C*H$_3$CH$_2$); ***m/z*** (EI+) 562 (1%, M), 547 (2, M-Me), 543 (1, M-F), 534 (13, M-C_2H_4), 520 (100, M-42), 169 (10, R_{f3}), 131 (10), 119 (5), 99 (32), 71 (40), 69 (15, CF_3), 43 (25).

4.3.14 Synthesis of vinyl 2-methylbutanoate, 60



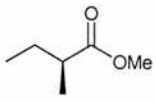
A solution of 2-methylbutanoic acid (5.115 g, 50.15 mmol), vinyl acetate (25.8 g, 300 mmol) and mercury(II) acetate (0.21 g, 0.66 mmol) was stirred under nitrogen at room temperature for 30 min. Sulfuric acid (98%, 0.075 cm^3) was added and the mixture was refluxed for 17 h. After cooling, sodium acetate trihydrate (2 g) was added and excess of vinyl acetate was distilled off. The product was dissolved in ether (300 cm^3), washed with saturated aqueous sodium chloride (3 × 200 cm^3). The organic phase was dried over $MgSO_4$ and solvent was removed under reduced pressure. Distillation gave the product as a colourless liquid (1.60 g, 25%), bp 30 °C at 20 mm Hg. ν_{max} (film)/cm^{-1} 2972, 1754 (CO), 1648, 1464, 1376, 1216, 1148, 1012, 951, 872; δ_H (300 MHz, $CDCl_3$) 7.29 (1 H, dd, *J* 14.0, *J* 6.3, OC*H*), 4.88 (1 H, dd, *J* 14.0, $^2J_{H\text{-}H}$ 1.9, OCHCH_2), 4.56 (1 H, dd, *J* 6.3, $^2J_{H\text{-}H}$ 1.9, OCHCH_2), 2.45 (1 H, sextet, *J* 6.8, C*H*), 1.80-1.66 (1 H, m, $CH_3CH^aH^b$), 1.59-1.45 (1 H, m, $CH_3CH^aH^b$), 1.19 (3 H, d, *J* 6.8, CH_3CH), 0.93 (3 H, t, *J* 7.2, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 173.8 (s, *C*O), 141.3 (s, O*C*H), 97.4 (s, OCH*C*H_2), 40.8 (s, *C*H), 26.5 (s, CH_3CH_2), 16.3 (s, CH_3CH), 11.5 (s, CH_3CH_2); ***m/z*** (EI+) 85 (40%, M-OCH=CH_2), 57 (100), 43 (60), 41 (50), 29 (40).

4.3.15 Synthesis of vinyl 2-methylpentanoate, 61



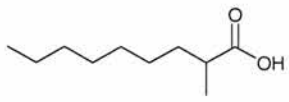
The title compound was prepared from 2-methylpentanoic acid (6.64 g, 57.2 mmol), vinyl acetate (29.42 g, 342 mmol), mercury(II) acetate (0.24 g, 0.75 mmol) and sulfuric acid (98%, 0.075 cm^3) was in a similar manner to the preparation of vinyl 2-methylbutanoate **60** as described in 4.3.14. The product was recovered as a colourless liquid (5.58 g, 69%), bp 45-50 °C at 15-20 mm Hg. (lit.[280] 148.8 °C). ν_{max} (film)/cm^{-1} 2963, 1753 (CO), 1647, 1459, 1376, 1215, 1148, 951, 874; δ_H (300 MHz, $CDCl_3$) 7.28 (1 H, dd, *J* 14.0, *J* 6.3, OC*H*), 4.88 (1 H, dd, *J* 14.0, $^2J_{H\text{-}H}$ 1.5, OCHCH_2), 4.56 (1 H, dd, *J* 6.3, $^2J_{H\text{-}H}$ 1.5, OCHCH_2), 2.52 (1 H, sextet, *J* 6.8, C*H*), 1.75-1.63 (1 H, m, CH^aH^{b}CH), 1.49-1.28 (3 H, m, CH_2CH^aH^bCH), 1.19 (3 H, d, *J* 6.8, CH_3CH), 0.92 (3 H, t, *J* 7.2, CH_3CH$_2$); δ_C (75 MHz, $CDCl_3$) 174.0 (s, *C*O), 141.3 (s, O*C*H), 97.4 (s, OCH*C*H$_2$), 39.0 (s, *C*H), 35.6 (s, *C*H$_2$CH), 20.3 (s, CH$_3$*C*H$_2$), 16.7 (s, *C*H$_3$CH), 13.9 (s, *C*H$_3$CH$_2$); ***m/z*** (EI+) 99 (40%, M-OCH=CH$_2$), 71 (80), 55 (30), 43 (100), 41 (40), 29 (30), 27 (30).

4.3.16 Synthesis of methyl (2*S*)-2-methylpentanoate, (*S*)-63



A solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (430 mg, 2 mmol) in dry ether (20 cm^3) was added drop-wise to a solution of potassium hydroxide (300 mg, 5.36 mmol) in water (5 cm^3) and di(ethylenglycol)ethylether (5 cm^3) at 65-68 °C. Evolved gas was condensed to a solution of (*S*)-2-methylbutanoic acid (85.7 mg, 0.84 mmol, *ee* > 98%) in dry ether (2 cm^3). Excess of diazomethane was evaporated by standing at room temperature for 2 h. Solvent removal gave the product as a colourless liquid (88 mg, 90%). $[\alpha]_D^{24}$= +24.9 (*c* 1.35, ether), lit.[281] $[\alpha]_D$= +15 (*c* 4.0, MeOH); lit.[282] $[\alpha]_D^{19}$= +23.1 (*c* 1.11, $CHCl_3$). ν_{max} (film)/cm^{-1} 2971, 2880, 1739 (CO), 1464, 1436, 1383, 1265, 1198, 1154, 1090, 1016, 984, 870, 797, 755; δ_H (300 MHz, $CDCl_3$) 3.67 (3 H, s, OCH_3), 2.44-2.32 (1 H, m, C*H*), 1.75-1.61 (1 H, m, $CH_3CH^aH^b$), 1.54-1.40 (1 H, m, $CH_3CH^aH^b$), 1.14 (3 H, d, *J* 7.4, CH_3CH), 0.90 (3 H, t, *J* 7.4, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 177.0 (s, *C*O), 51.2 (s, OCH_3), 40.8 (s, *C*H), 26.7 (s, CH_2), 16.5 (s, CH_3CH), 11.4 (s, CH_3CH_2); ***m/z*** (EI+) 116 (2%, M), 101 (20, M-Me), 88 (100), 85 (20, M-OMe), 57 (70, C_4H_9), 41 (30), 29 (15).

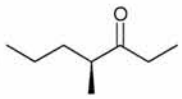
4.3.17 Synthesis of 2-methylnonanoic acid, 64



Sodium (612 mg, 26.6 mmol) was dissolved in ethanol (20 cm^3) and to this solution diethyl malonate (4.90 g, 28.13 mmol) was added drop-wise during 15 min. The solution was refluxed for 10 min. and then 1-bromoheptane (4.50 g, 25.12 mmol) was added during 15 min. followed by reflux of the mixture for 2 h. Concentrated acetic acid (3 drops) was added to neutralize excess of EtONa and the solvent was removed under reduced pressure. Water (30 cm^3) was added and the mixture was extracted into ether (3 × 20 cm^3). The combined organic phases were washed with saturated NaCl solution (15 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual oil was refluxed for 10 h in a solution of potassium hydroxide (5.6 g, 0.1 mol) in ethanol (50 cm^3). Ethanol was removed under reduced pressure, water (50 cm^3) was added and the mixture was washed with ether (2 × 10 cm^3). The aqueous phase was acidified with concentrated hydrochloric acid till pH 0-1 and extracted into ether (4 × 20 cm^3). The combined organic phases were washed with water (10 cm^3), saturated NaCl solution (10 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual oil was heated to 190 °C for 2 h, then dissolved in aq. K_2CO_3 (20%, 80 cm^3) and washed with ether (15 cm^3). The aqueous phase was acidified with concentrated hydrochloric acid to pH 0-1 and extracted into ether (4 × 30 cm^3). The organic phase was washed with saturated NaCl solution (20 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Distillation gave the product as a colourless liquid (2.605 g, 60.3%), bp 125-130 °C at 0.7-1.0 mm Hg (lit.[283] 76-77 °C at 0.5 mm Hg). ν_{max} (film)/cm^{-1} 2929, 2858,

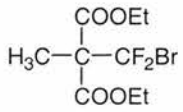
2658, 1707 (CO), 1467, 1417, 1380, 1291, 1233, 1102, 942, 723; δ_H (300 MHz, $CDCl_3$) 11.2 (1 H, br s, O*H*), 2.52 (1 H, sextet, *J* 6.9, C*H*), 1.75-1.63 (1 H, m, C*H*^{a}H^{b}CH), 1.49-1.23 (11 H, m, (C*H*$_2$)$_5$CH^a*H*^{b}CH), 1.18 (3 H, d, *J* 6.9, C*H*$_3$CH), 0.99 (3 H, t, *J* 6.9, C*H*$_3$CH$_2$); δ_C (75 MHz, $CDCl_3$) 183.6 (s, *C*O), 39.4 (s, *C*H), 33.5 (s, *C*H$_2$CH), 31.8 (s, *C*H$_2$), 29.4 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 27.1 (s, *C*H$_2$), 22.6 (s, CH$_3$*C*H$_2$), 16.8 (s, *C*H$_3$CH), 14.1(s, *C*H$_3$CH$_2$). ***m/z*** (EI+) 172 (5%, M), 143 (8, M-Et), 129 (15, M-C_3H_7), 115 (10, M-C_4H_9), 87 (40), 74 ($CH_3CH_2CO_2H$), 55 (20), 41 (30).

4.3.18 Synthesis of (4*S*)-4-methyl-3-heptanone, (*S*)-67



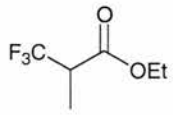
Ethyl bromide (2 drops) was added at to a stirred mixture of cut lithium wire (0.50 g, 72 mmol) in dry ether (20 cm^3). After 5 min. the mixture was cooled to -10 °C and ethyl bromide (3.14 g, 29 mmol) was added drop-wise within 30 min. to maintain -10 °C. After 1 h the mixture was let to warm spontaneously to 0°C and stirred for 2 h. The solution of ethyl lithium in ether (12 cm^3) was added at room temperature to a rapidly stirred solution of (*S*)-2-methylpentanoic acid (802 mg, 6.9 mmol, *ee* 96%) in dry ether (5 cm^3). The mixture was refluxed for 30 min. and then slowly dropped to cold water (50 cm^3) and stirred for 5 min. The product was extracted into ether (3 × 50 cm^3). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (hexane:ethyl acetate; 20:1) afforded the product as a colourless liquid (458 mg, 52%, *ee* 94%). $[\alpha]_D^{24}$= +19.1 (*c* 2.9, hexane), lit.[200] $[\alpha]_D^{27}$= +21.0 (*c* 1.0, hexane). ν_{max} (film)/cm^{-1} 2961, 2934, 2875, 1715 (CO), 1460, 1378, 1105, 1027, 976, 802, 737; δ_H (300 MHz, $CDCl_3$) 2.56-2.48 (1 H, m, C*H*), 2.44 (2 H, dq, *J* 7.3, $^4J_{H\text{-}H}$ 1.4, CH_2CO), 1.67-1.55 (1 H, m, CH^aH^bCH), 1.35-1.20 (3 H, m, $CH_2CH^aH^bCH$), 1.05 (3 H, d, *J* 7.3, CH_3CH), 1.03 (3 H, t, *J* 7.3, CH_3CH_2), 0.90-0.84 (3 H, m, *J* 7.3, CH_3CH_2); δ_C (75 MHz, $CDCl_3$) 215.3 (s, *C*O), 45.9 (s, *C*H), 35.3 (s, CH_2), 34.2 (s, CH_2), 20.5 (s, CH_2), 16.4 (s, CH_3CH), 14.1 (s, CH_3), 7.8 (s, CH_3); ***m/z*** (EI+) 128 (2%, M), 99 (10, M-Et), 86 (50), 71 (70), 57 (100), 43 (70), 41 (20), 29 (30).

4.3.19 Synthesis of diethyl 2-[bromo(difluoro)methyl]-2-methylmalonate, 71



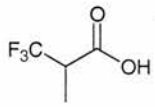
Sodium hydride (60% oil dispersion, 4.09 g, 102 mmol) was placed into a two neck flask and washed free of the oil with hexane. THF (60 cm^3) was added, and then diethyl 2-methylmalonate (16.55 g, 95.0 mmol) was added drop-wise. The addition of the malonate took about 30 min. Heat was generated and hydrogen evolved as the sodium salts of the malonic esters formed. The reaction mixture was stirred for further 30 min. and then cooled to 5 °C. Dibromo(difluoro)methane (bp 24 °C, 21.62 g, 103 mmol) was added. The reaction mixture was stirred for 1 min. and then transferred into a flask and sealed. Within minutes white solid precipitates and the solution becomes yellow. The mixture was stirred at room temperature for 22 h, then the sealed flask was opened and the solvent was removed under reduced pressure. Water was added (150 cm^3), extraction into ether (3 × 30 cm^3), drying over $MgSO_4$ and removal of the solvent gave the crude product. Vacuum distillation at 93-98 °C and 1 mm Hg (lit.[213] 66 °C/0.2 mm Hg) provided pure product as a colourless liquid (13.74 g, 48%). ν_{max} (film)/cm^{-1} 2987, 2943, 2909, 1747 (CO), 1456, 1384, 1368, 1268, 1093, 1018, 958, 885, 642; δ_H (300 MHz, $CDCl_3$) 4.28 (4 H, q, *J* 7.0, 2 × OCH_2), 1.75 (3 H, s, CH_3), 1.30 (6 H, t, *J* 7.0, 2 × OCH_2CH_3); δ_F (282 MHz, $CDCl_3$) -49.7 (s, CF_2Br); δ_C (75 MHz, $CDCl_3$) 165.5 (s, *C*=O), 120.3 (t, $^1J_{C\text{-}F}$ 315, CF_2Br), 62.6 (s, OCH_2), 61.3 (s, $BrCF_2C$), 18.6 (s, CH_3), 13.8 (s, CH_2CH_3); ***m/z*** (ESI+) 327 (100%, M+Na), 325 (100, M+Na), 305 (80, M+H), 303 (80, M+H), 291 (20), 289 (20), 277 (20), 275 (20), 197 (30).

4.3.20 Synthesis of ethyl 3,3,3-trifluoro-2-methylpropanoate, 70



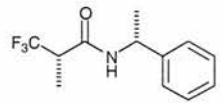
Diethyl 2-[bromo(difluoro)methyl]-2-methylmalonate **71** (13.74 g, 45.4 mmol) was dissolved in dry DMSO (40 cm^3) in a round-bottom flask fitted with a short path distilling unit and thermometer. Anhydrous potassium fluoride (5.27 g, 90.7 mmol) was added and the heterogeneous mixture was stirred at 150-153 °C for 30 min. Then the temperature was maintained at 169-174 °C for 1 h during which gas evolved, distillate was collected and the DMSO solution developed dark colour. The distillate was heated to 70 °C to remove low boiling dimethyl sulfide and acetaldehyde. Distillation of the residue at 110-112 °C (lit.[213] bp 112 °C) afforded the product as a colourless liquid (7.05 g, 91%). ν_{max} (film)/cm^{-1} 2987, 2943, 1745 (CO), 1665, 1465, 1373, 1335, 1279, 1210, 1179, 1124, 1024, 910, 734, 650; δ_H (300 MHz, $CDCl_3$) 4.16 (2 H, q, *J* 7.2, 2 × OCH_2), 3.20-3.05 (1 H, m, C*H*), 1.34 (3 H, d, *J* 7.4, CH_3), 1.23 (3 H, t, *J* 7.2, OCH_2CH_3); δ_F (282 MHz, $CDCl_3$) -70.5 (d, $^3J_{F-H}$ 8.6, CF_3); δ_C (75 MHz, $CDCl_3$) 167.9 (s, *C*=O), 124.9 (q, $^1J_{C-F}$ 279, CF_3), 61.7 (s, OCH_2), 44.5 (q, $^2J_{C-F}$ 29, *C*H), 13.9 (s, CH_2CH_3), 10.9 (q, $^3J_{C-F}$ 2.8, $CHCH_3$); ***m/z*** (EI+) 170 (10%, M), 142 (30, M-C_2H_4), 125 (100, M-OEt), 97 (40, $MeCHCF_3$), 77 (30, CF_2=CMe), 69 (20, CF_3), 29 (25, Et).

4.3.21 Synthesis of 3,3,3-trifluoro-2-methylpropanoic acid, 69



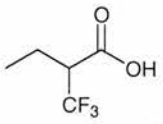
Ethyl 3,3,3-trifluoro-2-methylpropanoate **70** (4.615 g, 27.1 mmol) was dissolved in 1,4-dioxane (40 cm^3) and concentrated hydrochloric acid (36 %, 20 cm^3) was added. The mixture was refluxed for 15 h and then cooled down. Dichloromethane (50 cm^3) was added and the two phases were separated. The aqueous phase was washed with dichloromethane (3 × 15 cm^3) and the combined organic phases were extracted with aq. $NaHCO_3$ (0.8 M, 3 × 60 cm^3). The combined aqueous phases were acidified with concentrated hydrochloric acid till pH ~ 1 and the product was isolated by extraction into dichloromethane (3 × 20 cm^3), drying over $MgSO_4$ and removal of the solvent under reduced pressure. Distillation under reduced pressure (bath temperature 80 °C/ 20 mm Hg) gave the product as a colourless liquid (2.11 g, 55%). ***m/z*** (CI+) 143.0316 (M+H. $C_4H_6O_2F_3$ requires 143.0320); ν_{max} (film)/cm^{-1} 2923, 2853, 2689, 1701 (CO), 1471, 1327, 1083, 1043, 965, 702; δ_H (300 MHz, $CDCl_3$) 9.9 (1 H, br s, O*H*), 3.33-3.18 (1 H, m, C*H*), 1.47 (3 H, d, *J* 7.2, CH_3); δ_F (282 MHz, $CDCl_3$) -70.5 (d, $^3J_{F\text{-}H}$ 6.9, CF_3); δ_C (75 MHz, $CDCl_3$) 173.3 (s, *C*=O), 124.7 (q, $^1J_{C\text{-}F}$ 279, *C*F_3), 44.4 (q, $^2J_{C\text{-}F}$ 29, *C*H), 11.0 (s, *C*H_3); ***m/z*** (EI+) 142 (1%, M), 125 (30, M-OH), 122 (20, M-F), 102 (35), 78 (70), 77 (100, CF_2=CMe), 69 (20, CF_3), 45 (35).

4.3.22 Synthesis of (2*S*)-3,3,3-trifluoro-2-methyl-*N*-[(1*R*)-1-phenylethyl]-propanamide, 77



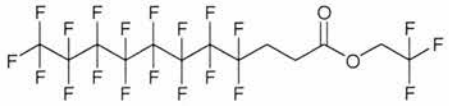
(2*S*)-3,3,3-Trifluoro-2-methylpropanoic acid, (*S*)-**69** (*ee* > 98%, 106 mg, 0.746 mmol) was dissolved in dry THF (12 cm^3) and the resulting solution was cooled to -10 °C under nitrogen. 4-methylmorpholine (81 mg, 0.8 mmol) and methyl chloridocarbonate (75 mg, 0.8 mmol) was added and after 1 min. of stirring (1*R*)-1-phenylethylamine (113 mg, 0.93 mmol) was added. The solution was stirred at -5 to -10 °C for 40 min. and then aqueous solution of citric acid (5%, 150 cm^3) was added. The mixture was extracted into ethyl acetate (3 × 40 cm^3), the organic phase was washed with aqueous solution of sodium hydrogen carbonate (0.8 M, 3 × 20 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue (*de* 98%) was purified over silica gel (petrol:ether; 1:3) to give the major diastereomer as a white solid (*de* 100%, 165 mg, 90%), mp 138.5-139 °C (from hexane). $[\alpha]_D^{25}$ +88.7 (*c* 0.345, $CHCl_3$); ***m/z*** (CI+) 246.1107 (M+H. $C_{12}H_{15}OF_3N$ requires 246.1107); ν_{max} (KBr)/cm^{-1} 3308, 3093, 2987, 2972, 1651 (CO), 1560, 1268, 1239, 1175, 1125, 1006, 754, 701; δ_H (300 MHz, $CDCl_3$) 7.38-7.25 (5 H, m, C_6H_5), 5.9 (1 H, br s, N*H*), 5.19-5.09 (1 H, m, NHC*H*), 3.09-2.93 (1 H, m, CF_3CH), 1.51 (3 H, d, *J* 6.8, NHCHCH_3), 1.39 (3 H, d, *J* 7.2, CHCH_3); δ_F (282 MHz, $CDCl_3$) -69.9 (d, $^3J_{F\text{-}H}$ 8.6, CF_3); δ_C (75 MHz, $CDCl_3$) 165.6 (s, *C*=O), 142.4 (s, C_{Ar}), 128.8 (s, *o*-CH_{Ar}), 127.6 (s, *m*-CH_{Ar}), 126.0 (s, *p*-CH_{Ar}), 125.6 (q, $^1J_{C\text{-}F}$ 280, CF_3), 49.2 (s, NHCH), 46.3 (q, $^2J_{C\text{-}F}$ 28, $CHCF_3$), 21.5 (s, CH_3), 11.0 (s, CH_3); ***m/z*** (EI+) 245 (60%, M), 230 (50, M-Me), 120 (20), 106 (100), 105 (40, PhCHMe), 77 (30, Ph); ***m/z*** (ESI-) 244 (100%, M-H).

4.3.23 Synthesis of 2-(trifluoromethyl)butanoic acid, 78



The title compound was prepared in three steps from sodium hydride (60% oil dispersion, 6.00 g, 156 mmol), diethyl 2-ethylmalonate (26.25 g, 139 mmol) and dibromo(difluoro)methane (31.6 g, 151 mmol) in a similar manner to the preparation of 3,3,3-trifluoro-2-methylpropanoic acid **69** as described in 4.3.21. The product was recovered as a colourless liquid (7.009 g, 32% overall), bp 90-95 °C at 20 mm Hg. ***m/z*** (CI+) 157.0481 (M+H. $C_5H_8O_2F_3$ requires 157.0476); ν_{max} (film)/cm^{-1} 2982, 2684, 1729 (CO), 1466, 1427, 1367, 1259, 1176, 1134, 1037, 923, 861, 786, 658; δ_H (300 MHz, $CDCl_3$) 11.63 (1 H, br s, O*H*), 3.15-3.02 (1 H, m, C*H*), 2.02-1.89 (2 H, m, CH_2), 1.07 (3 H, t, *J* 7.5, CH_3); δ_F (282 MHz, $CDCl_3$) -68.6 (d, $^3J_{F-H}$ 8.0, CF_3); δ_C (75 MHz, $CDCl_3$) 173.6 (s, *C*=O), 124.4 (q, $^1J_{C-F}$ 280, CF_3), 51.7 (q, $^2J_{C-F}$ 27, *C*H), 19.6 (s, CH_2), 11.2 (s, CH_3); ***m/z*** (EI+) 156 (1%, M), 139 (10, M-OH), 128 (100, M-C_2H_4), 108 (60), 91 (50), 77 (50, CF_2=CMe), 69 (20, CF_3), 45 (15).

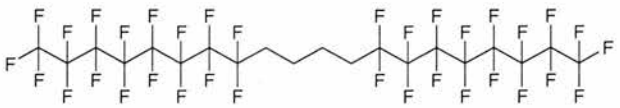
4.3.24 Synthesis of 2,2,2-trifluoroethyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate, 26



In a two neck flask (500 cm^3), equipped with a rubber septum and condenser, magnesium (1.27 g of Mg turnings and 0.1 g of Mg powder, 56.4 mmol) was placed. Ether (30 cm^3) was added and the mixture was warmed to 37 °C. A solution (3 cm^3) of iodo compound **82** (24.72 g, 43.07 mmol) in ether (60 cm^3) was added and the mixture was stirred for 30 min. The rest of the solution was added drop-wise over the period of 1.5 h. The yellow/grey reaction mixture was stirred for further 1.5 h at 28-30 °C before being cooled to ~0 °C. Solid carbon dioxide (5.0 g, 113.6 mmol) was added slowly per portions. The mixture was foaming and pieces of brown solid precipitated. The mixture was stirred for 10 min. and then solution of dilute (25%) sulfuric acid was added until the excess of magnesium starts to dissolve. The aqueous phase was extracted with *tert*-butyl methyl ether (4 × 70 cm^3). The organic phase was dried over $MgSO_4$ and the solvent removed under reduces pressure to give brown solid of crude carboxylic acid **83**. The acid **83** was dissolved in 2,2,2-trifluoroethanol (56.3 g, 563 mmol). Sulfuric acid (98%, 3.7 cm^3) was added and the mixture was refluxed for 11 h. The excess of the 2,2,2-trifluoroethanol was recovered by distillation under reduced pressure and the residue was partitioned between *tert*-butyl methyl ether (60 cm^3) and water (50 cm^3). The aqueous phase was extracted with *tert*-butyl methyl ether (60 cm^3), the combined organic phases were washed with saturated aqueous sodium chloride (30 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica (ether:hexane; 1:9)

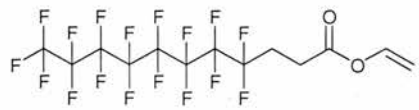
giving side product **59** (white solid) and the desired product **26** as a colourless liquid (12.01 g, 63%). ν_{max} (film)/cm^{-1} 2981, 1768 (CO), 1415, 1207, 1151, 983, 705, 658, 559, 530; δ_H (300 MHz, $CDCl_3$) 4.52 (2 H, q, $^3J_{H\text{-}F}$ 8.3, CH_2CF_3), 2.77 (2 H, t, *J* 7.4, CH_2CO), 2.60-2.43 (2 H, m, CH_2CF_2); δ_F (282 MHz, $CDCl_3$) -74.4 (3 F, t, $^3J_{F\text{-}H}$ 8.3, CF_3), -81.3 (3 F, t, $^3J_{F\text{-}F}$ 9.8, CF_3), -115.2 to -115.4 (2 F, m, CF_2), -122.1 to -122.6 (6 F, m, 3 × CF_2), -123.1 to -123.4 (2 F, m, CF_2) , -123.9 to -124.1 (2 F, m, CF_2), -126.5 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 169.7 (s, *C*=O), 122.8 (q, $^1J_{C\text{-}F}$ 276, CF_3), 128-107 (m, C_8F_{17}), 60.7 (q, $^2J_{C\text{-}F}$ 37, CF_3CH_2), 26.3 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2), 25.0 (t, $^3J_{C\text{-}F}$ 4.4, CH_2CO); ***m/z*** (EI+) 555 (15%, M-F), 475 (100, M-OCH_2CF_3), 205 (40), 127 (50), 83 (100, CF_3CH_2), 69 (50, CF_3).

4.3.25 Synthesis of 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,13,13,14,14,15,15,16,16,17,17,18,18,19,19,20,20,20-tetratriacontafluoro-icosane, 59



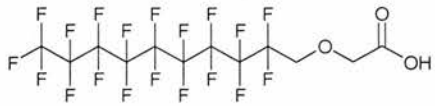
The title compound was isolated as a side product from the reaction described in 4.3.24. White solid (1.94 g, 5%), mp 92-93 °C (from CCl_4). ν_{max} (KBr)/cm^{-1} 2960, 1474, 1374, 1333, 1253, 1223, 1148, 1115, 1063, 1031, 952, 895, 704, 657; δ_H (300 MHz, FC-72; Me_4Si) 2.22-2.02 (4 H, m, CH_2CF_2), 1.81-1.71 (4 H, m, CH_2); δ_F (282 MHz, C_6F_6; C_6D_6) -79.4 (6 F, t, $^3J_{F-F}$ 10.2, 2 × CF_3), -112.6 to -112.9 (4 F, m, 2 × CF_2), -119.2 to -119.6 (12 F, m, 6 × CF_2), -120.2 to -120.4 (4 F, m, 2 × CF_2) , -121.2 to -121.4 (4 F, m, 2 × CF_2), -123.9 to -124.1 (4 F, m, 2 × CF_2); δ_C (75 MHz, C_6F_6; C_6D_6) 125-100 (m, C_8F_{17}), 30.5 (t, $^2J_{C-F}$ 23, CH_2CF_2), 19.7 (s, CH_2); ***m/z*** (EI+) 505 (40%), 485 (35), 441 (30), 395 (30), 377 (100), 197 (20), 169 (20), 131 (20), 91 (30), 69 (25).

4.3.26 Synthesis of vinyl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate, 53



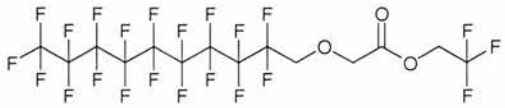
A solution of carboxylic acid **83** (4.314 g, 8.77 mmol), vinyl acetate (18.68 g, 21.7 mmol) and mercury(II) acetate (0.11 g, 0.35 mmol) was stirred under nitrogen at room temperature for 2 h. Sulfuric acid (98%, 40 μl) was added and the mixture was heater at 65 °C for 20 h. After cooling, sodium acetate trihydrate (2 g) was added and the excess of vinyl acetate was distilled off. The residue was dissolved in *tert*-butyl methyl ether (100 cm^3), washed with saturated aqueous sodium chloride (2 × 50 cm^3). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residual liquid was purified over silica gel (ether:hexane; 3:97) to give the product as a pale yellow low-melting solid (2.35 g, 52%), mp 25-28 °C. ***m/z*** (CI+) 519.0258 (M+H. $C_{13}H_8O_2F_{17}$ requires 519.0253); ν_{max} (film)/cm^{-1} 2969, 1762 (CO), 1651, 1338, 1207, 984, 950, 879, 705, 658, 559, 530; δ_H (300 MHz, $CDCl_3$) 7.29 (1 H, dd, *J* 14.1, *J* 6.1, OC*H*), 4.94 (1 H, dd, *J* 14.1, $^2J_{H\text{-}H}$ 1.8, OCHCH_2), 4.64 (1 H, dd, *J* 6.1, $^2J_{H\text{-}H}$ 1.8, OCHCH_2), 2.74 (2 H, t, *J* 7.4, CH_2CO), 2.60-2.42 (2 H, m, C$H_2$$CF_2$); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 9.8, CF_3), -115.1 to -115.4 (2 F, m, CF_2), -122.0 to -122.5 (6 F, m, 3 × CF_2), -123.1 to -123.4 (2 F, m, CF_2), -123.8 to -124.1 (2 F, m, CF_2), -126.5 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 168.3 (s, *C*=O), 140.9 (s, *C*H=CH_2), 125-105 (m, C_8F_{17}), 98.4 (s, CH=*C*H_2), 26.3 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2), 25.2 (t, $^3J_{C\text{-}F}$ 4.4, *C*H_2CO); ***m/z*** (EI+) 475 (100, M-OCHCH_2), 427 (20), 169 (20), 131 (30), 69 (40, CF_3).

4.3.27 Synthesis of [(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl)oxy]acetic acid, 85



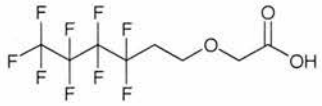
Sodium hydride (60% oil dispersion, 1.65 g, 41 mmol) was transferred to an anhydrous two neck reaction flask under nitrogen and washed free of the oil with hexane. Dry THF (20 cm^3) was added, and then a solution of fluorous alcohol **37** (3.38 g, 6.8 mmol) in dry THF (25 cm^3) was added drop-wise over a 30 min. period. The mixture was stirred for 1 h at room temperature and then a solution of bromoacetic acid (1.85 g, 13.3 mmol) dissolved in dry THF (30 cm^3) was added drop-wise over a period of 1 h. Addition of bromoacetic acid produces a lot of foam. The mixture was stirred for 24 h and then transferred to a 2 litre flask with water (200 cm^3). THF was removed under reduces pressure and the residue was acidified with aqueous HCl (6 M) till pH ~0 and extracted into ethyl acetate (4 × 100 cm^3). The combined organic phases were washed with water (100 cm^3), dried over $MgSO_4$ and evaporated under reduced pressure yielding a white solid of the product (3.77 g, 99%), mp 90-91 °C (from hexane). **Found:** C, 25.5; H, 0.7. $C_{12}H_5F_{19}O_3$ **requires** C, 25.8; H, 0.9%; ν_{max} (KBr)/cm^{-1} 3073, 1732 (CO), 1425, 1255, 1184, 1032, 976, 912, 770, 657, 561; δ_H (300 MHz, acetone-d_6) 4.38-4.27 (4 H, m, CH_2OCH_2), 2.90 (1 H, br s, O*H*); δ_F (282 MHz, acetone-d_6) -82.0 (3 F, t, $^3J_{F\text{-}F}$ 7.7, CF_3), -120.8 to -121.0 (2 F, m, CF_2), -122.4 to -123.0 (8 F, m, 4 × CF_2), -123.4 to -123.7 (2 F, m, CF_2) , -124.0 to -124.3 (2 F, m, CF_2), -126.9 to -127.1 (2 F, m, CF_2); δ_C (75 MHz, acetone-d_6) 171.8 (s, *C*=O), 140-85 (m, C_9F_{19}), 70.0 (s, CH_2CO), 69.1 (t, $^2J_{C\text{-}F}$ 27, CF_2CH_2); ***m/z*** (ESI+) 581 (100%, M+Na); ***m/z*** (ESI-) 557 (100%, M-H).

4.3.28 Synthesis of 2,2,2-trifluoroethyl [(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl)oxy]acetate, 54



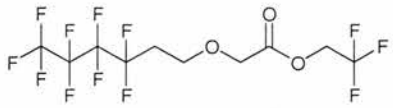
To a solution of carboxylic acid **85** (2.816 g, 5.05 mmol) in 2,2,2-trifluoroethanol (13.0 g, 130 mmol), sulfuric acid (98%, 0.4 cm^3) was added and the mixture was refluxed for 22 h. The excess of the 2,2,2-trifluoroethanol was recovered by distillation under reduced pressure and the residue was partitioned between ether (20 cm^3) and water (20 cm^3). The aqueous phase was extracted with ether (20 cm^3), the combined organic phases were washed with saturated aq. NaCl (10 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on a short silica gel column (ethyl acetate:cyclohexane; 1:7) to remove the traces of sulfuric acid. The product was isolated as a white low-melting solid (2.83 g, 88%), mp 38-39 °C. ***m/z*** (ESI+) 662.9896 (M+Na. $C_{14}H_6O_3F_{22}Na$ requires 662.9863); ν_{max} (KBr)/cm^{-1} 1770 (CO), 1305, 1285, 1207, 1153, 980, 963, 655, 641, 561; δ_H (300 MHz, $CDCl_3$) 4.56 (2 H, q, $^3J_{H\text{-}F}$ 8.2, CH_2CF_3), 4.37 (2 H, s, CH_2CO), 4.13 (2 H, t, $^3J_{H\text{-}F}$ 13.6, CH_2CF_2); δ_F (282 MHz, $CDCl_3$) -74.5 (3 F, t, $^3J_{F\text{-}H}$ 8.2, CF_3), -81.4 (3 F, t, $^3J_{F\text{-}F}$ 9.8, CF_3), -120.4 to -120.6 (2 F, m, CF_2), -122.2 to -122.7 (8 F, m, 4 × CF_2), -123.2 to -123.5 (2 F, m, CF_2) , -123.8 to -124.1 (2 F, m, CF_2), -126.6 to -126.9 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 167.8 (s, *C*=O), 122.6 (q, $^1J_{C\text{-}F}$ 277, CF_3), 125-100 (m, C_9F_{19}), 68.6 (s, CH_2CO), 68.1 (t, $^2J_{C\text{-}F}$ 25, CF_2CH_2), 60.6 (q, $^2J_{C\text{-}F}$ 37, CF_3CH_2); ***m/z*** (EI+) 620 (10%, M-F), 563 (15), 513 (100, M-$CO_2CH_2CF_3$), 251 (20), 142 (30), 113 (50), 69 (20, CF_3).

4.3.29 Synthesis of [(3,3,4,4,5,5,6,6,6-nonafluorohexyl)oxy]acetic acid, 86



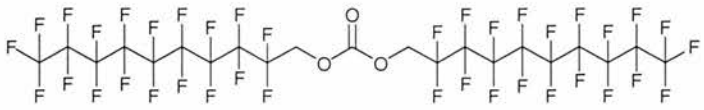
The title compound was prepared from sodium hydride (60% oil dispersion, 4.846 g, 121 mmol), fluorous alcohol **84** (5.331 g, 20.19 mmol) and bromoacetic acid (5.61 g, 40.37 mmol) in a similar manner to the preparation of carboxylic acid **85** as described in 4.3.27. The product was recovered as a yellow liquid (6.305 g, 97%). ***m/z*** (ESI+) 345.0155 (M+Na. $C_8H_7O_3F_9Na$ requires 345.0149); ν_{max} (KBr)/cm^{-1} 3126, 2908, 1735 (CO), 1432, 1356, 1236, 1135, 1018, 880, 718; δ_H (300 MHz, $CDCl_3$) 9.80 (1 H, br s, O*H*), 4.19 (2 H, s, CH_2CO), 3.88 (2 H, t, *J* 6.7, CH_2O), 2.58-2.41 (2 H, m, CF_2CH_2); δ_F (282 MHz, $CDCl_3$) -81.5 (3 F, tt, $^3J_{F\text{-}F}$ 9.7, $^4J_{F\text{-}F}$ 3.2, CF_3), -114.0 to -114.3 (2 F, m, CF_2), -125.0 to -125.2 (2 F, m, CF_2), -126.4 to -126.6 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 175.9 (s, *C*=O), 130-100 (m, C_4F_9), 67.9 (s, CH_2CO), 63.7 (s, CH_2CH_2O), 31.3 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2); ***m/z*** (ESI+) 345 (100%, M+Na); ***m/z*** (ESI-) 321 (100%, M-H), 301 (60), 261 (50).

4.3.30 Synthesis of 2,2,2-trifluoroethyl [(3,3,4,4,5,5,6,6,6-nonafluorohexyl)oxy]acetate, 55



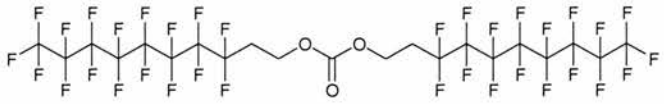
The title compound was prepared in from carboxylic acid **86** (5.286 g, 16.42 mmol), 2,2,2-trifluoroethanol (27.82 g, 278 mmol) and sulfuric acid (98%, 1.3 cm^3) in a similar manner to the preparation of **54** as described in 4.3.28. The product was recovered as a pale yellow liquid (3.304 g, 50%). ***m/z*** (ESI+) 427.0185 (M+Na. $C_{10}H_8O_3F_{12}Na$ requires 427.0180); ν_{max} (film)/cm^{-1} 2979, 2903, 1782 (CO), 1416, 1357, 1286, 1135, 1017, 980, 880, 717; δ_H (300 MHz, $CDCl_3$) 4.55 (2 H, q, $^3J_{H\text{-}F}$ 8.3, CH_2CF_3), 4.24 (2 H, s, CH_2CO), 3.87 (2 H, t, *J* 6.9, CH_2O), 2.58-2.40 (2 H, m, CF_2CH_2); δ_F (282 MHz, $CDCl_3$) -74.6 (3 F, t, $^3J_{F\text{-}H}$ 8.3, CF_3), -81.8 (3 F, tt, $^3J_{F\text{-}F}$ 9.7, $^5J_{F\text{-}F}$ 3.2, CF_3), -114.2 to -114.4 (2 F, m, CF_2), -125.2 to -125.3 (2 F, m, CF_2), -126.6 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 168.5 (s, *C*=O), 122.7 (q, $^1J_{C\text{-}F}$ 277, CF_3), 130-100 (m, C_4F_9), 67.9 (s, CH_2CO), 63.8 (s, CH_2CH_2O), 60.4 (q, $^2J_{C\text{-}F}$ 37, CF_3CH_2), 31.4 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2); ***m/z*** (EI+) 385 (5%, M-F), 277 (100, M-$CO_2CH_2CF_3$), 227 (40), 142 (90), 113 (70), 69 (20, CF_3), 31 (30).

4.3.31 Synthesis of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluorodecyl) carbonate, 56



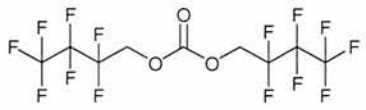
Toluene solution of phosgene (20%, 8.8 cm^3) was added drop-wise into a solution of fluorous alcohol **37** (9.858 g, 19.7 mmol) in dry pyridine (1.56 g, 19.7 mmol) and toluene (20 cm^3). The addition took 30 min. and the temperature of the mixture was between 25-38 °C. The mixture was stirred for further 1 h at 50 °C before being poured into a mixture of ice and water (100 g) and filtered. The filtrate was washed with chloroform (2 × 30 cm^3) and after drying over $MgSO_4$ and evaporation of the solvent the residue was combined with the solid on the filter. Crystallization gave a white solid of the product (5.326 g, 53%), mp 78-79°C (from ethanol). **Found:** C, 24.3; H, -. $C_{21}H_4F_{38}O_3$ **requires** C, 24.6; H, 0.4%; ***m/z*** (APCI+) 1026.9301 (M+H. $C_{21}H_4O_3F_{38}$ requires 1026.9632); ν_{max} (KBr)/cm^{-1} 1773 (CO), 1209, 1149, 990, 662, 559, 529; δ_H (300 MHz, acetone-d_6) 5.09-4.99 (m, CH_2); δ_F (282 MHz, acetone-d_6) -82.1 (6 F, t, $^3J_{F\text{-}F}$ 10.2, 2 × CF_3), -120.7 to -120.8 (4 F, m, 2 × CF_2), -122.6 to -123.1 (16 F, m, 8 × CF_2), -123.6 to -124.0 (4 F, m, 2 × CF_2), -124.2 to -124.4 (4 F, m, 2 × CF_2), -127.1 to -127.3 (4 F, m, 2 × CF_2); δ_C (75 MHz, C_6F_6; C_6D_6) 153.5 (s, *C*=O), 120-105 (m, C_9F_{19}), 63.1 (t, $^2J_{C\text{-}F}$ 27, CH_2). ***m/z*** (EI+) 607 (10%), 513 (20), 483 (10, $R_{f9}CH_2$), 413 (100), 169 (10, R_{f3}), 131 (15, $CF_3C{=}CF_2$), 69 (20, CF_3).

4.3.32 Synthesis of bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl) carbonate, 57



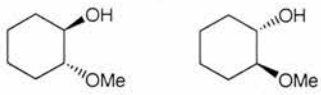
The title compound was prepared from toluene solution of phosgene (20%, 15 cm^3), fluorous alcohol **36** (15.56 g, 33.53 mmol) and pyridine (2.65 g, 33.53 mmol) in dry toluene (10 cm^3) in a similar manner to the preparation of the carbonate **56** as described in 4.3.31. The product was recovered as a white solid (10.5 g, 66%), mp 53-54.5 °C (from MeOH). ***m/z*** (ESI+) 976.9845 (100%, M+Na. $C_{21}H_8O_3F_{34}Na$ requires 976.9845); ν_{max} (KBr)/cm^{-1} 1753 (CO), 1469, 1285, 1203, 1148, 1117, 796, 705, 660; δ_H (300 MHz, $CDCl_3$) 4.48 (4 H, t, *J* 6.6, 2 × OCH_2), 2.62-2.45 (4 H, m, 2 × CH_2CF_2); δ_F (282 MHz, $CDCl_3$) -81.3 (6 F, t, $^3J_{F\text{-}F}$ 10.2, 2 × CF_3), -114.1 to -114.2 (4 F, m, 2 × CF_2), -122.1 to -122.6 (12 F, m, 6 × CF_2), -123.1 to -123.4 (4 F, m, 2 × CF_2) , -123.8 to -124.1 (4 F, m, 2 × CF_2), -126.5 to -126.8 (4 F, m, 2 × CF_2); δ_C (75 MHz, acetone-d_6) 156.1 (s, *C*=O), 125-107 (m, C_8F_{17}), 61.8 (t, $^3J_{C\text{-}F}$ 4.5, CH_2O), 31.9 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2).

4.3.33 Synthesis of bis(2,2,3,3,4,4,4-heptafluorobutyl) carbonate, 58



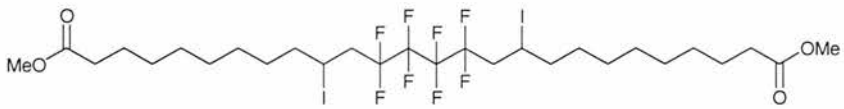
The title compound was prepared from toluene solution of phosgene (20%, 27.5 cm^3), alcohol **87** (12.29 g, 61.45 mmol) and pyridine (4.86 g, 61.45 mmol) in dry toluene (30 cm^3) in a similar manner to the preparation of the carbonate **56** as described in 4.3.31. The product was recovered as a colourless liquid (7.873 g, 60%), bp 73°C at 15-20 mm Hg. ***m/z*** (CI+) 427.0013 (M+H. $C_9H_5O_3F_{14}$ requires 427.0015); ν_{max} (film)/cm^{-1} 2984, 1782 (CO), 1446, 1414, 1350, 1231, 1126, 1023, 960, 912, 742, 627, 534; δ_H (300 MHz, $CDCl_3$) 4.70 (tt, $^3J_{H\text{-}F}$ 13.0, $^5J_{H\text{-}F}$ 1.2, CH_2); δ_F (282 MHz, $CDCl_3$) -81.5 (6 F, t, $^3J_{F\text{-}F}$ 9.5, 2 × CF_3), -121.5 to -121.7 (4 F, m, 2 × CF_2), -128.3 to -128.4 (4 F, m, 2 × CF_2); δ_C (75 MHz, C_6F_6; C_6D_6) 153.2 (s, C=O), 120-109 (m, C_3F_7), 63.3 (t, $^2J_{C\text{-}F}$ 26, CH_2); ***m/z*** (EI+) 407 (5%, M-F), 213 (30), 183 (40, $R_{f3}CH_2$), 119 (20, CF_3CF_2), 113 (100), 69 (40, CF_3).

4.3.34 Synthesis of *trans* 2-methoxycyclohexanol, 88



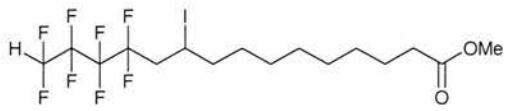
Iodine (1.27 g, 10 mmol) was added into a solution of cyclohexene oxide (7-oxabicyclo[4.1.0]heptane) (10.00 g, 0.1 mol) in methanol (300 cm^3). The mixture was stirred for 45 min. at room temperature and then methanol was removed under reduced pressure. The residue was dissolved in ether (300 cm^3) and washed with 10% aqueous solution of $Na_2S_2O_3$ until disappearance of the iodine colour. The aqueous layer was separated and washed with ether (3 × 30 cm^3). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was distilled at 100-103 °C/ 20 mm Hg to give the product as a colourless liquid (4.95 g, 38%). ν_{max} (film)/cm^{-1} 3442 (OH), 2934, 2825, 1453, 1190, 1102, 997, 913, 847; δ_H (300 MHz, $CDCl_3$) 3.45-3.37 (4 H, m, C*H*OH, OC*H*$_3$), 3.14 (1 H, br s, O*H*), 2.98-2.90 (1 H, m, C*H*OCH_3), 2.15-2.08 (1 H, m, C*H*$_2$), 2.02-1.96 (1 H, m, C*H*$_2$), 1.76-1.67 (2 H, m, C*H*$_2$), 1.36-1.01 (4 H, m, C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 84.8 (s, *C*H), 73.4 (s, *C*H), 56.1 (s, O*C*H_3), 32.0 (s, *C*H_2), 28.2 (s, *C*H_2), 23.9 (s, *C*H_2), 23.8 (s, *C*H_2); ***m/z*** (EI+) 130 (40%, M), 98 (30), 84 (40), 71 (100), 70 (70), 41 (40).

4.3.35 Synthesis of dimethyl 12,12,13,13,14,14,15,15-octafluoro-10,17-diiodohexacosanedioate, 104



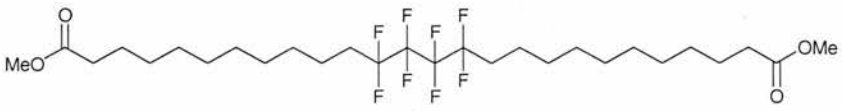
A mixture of lead powder 325 mesh (3.315 g, 16.0 mmol) and copper(II) acetate (363 mg, 2.00 mmol) in dry methanol (65 cm^3) was stirred for 30 min. Then 1,1,2,2,3,3,4,4-octafluoro-1,4-diiodobutane **101** (2.95 g, 6.50 mmol) and methyl 10-undecenoate **103** (3.00 g, 15.1 mmol) were slowly added and the mixture was stirred for 48 h at room temperature. The solvent was subsequently removed under reduced pressure, diethyl ether (40 cm^3) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure and the residual liquid purified over silica gel (ether:petrol; 1:9) to give excess of the olefin **103**, by-product **106** (431 mg, 8%) and the desired product **104** (2.513 g, 46%) as a colourless liquid. ***m/z*** (ESI+) 873.1096 (50%, M+Na. $C_{28}H_{44}O_4F_8NaI_2$ requires 873.1099), 851 (100, M+H), 747 (50), 725 (90); ν_{max} (film)/cm^{-1} 2930, 2856, 1741 (CO), 1436, 1365, 1171, 1121, 864, 725; δ_H (300 MHz, $CDCl_3$) 4.40-4.27 (2 H, m, 2 × C*H*I), 3.67 (6 H, s, 2 × OCH_3), 3.00-2.63 (4 H, m, 2 × CF_2CH_2), 2.31 (4 H, t, *J* 7.5, 2 × CH_2CO), 1.87-1.20 (28 H, m, 14 × CH_2); δ_F (282 MHz, $CDCl_3$) -111.7 to -112.9 (2 F, m, 2 × C$F^aF^bCH_2$), -114.8 to -115.9 (2 F, m, 2 × C$F^aF^bCH_2$), -123.8 to -124.1 (4 F, m, 2 × $CF_2CF_2CH_2$); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 124-97 (m, CF_2), 51.4 (s, OCH_3), 42.0-41.4 (m, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 29.5-28.9 (m, CH_2), 28.4 (s, $CHCH_2CH_2$), 24.9 (s, CH_2CH_2CO), 21.4-21.3 (m, CHI).

4.3.36 Synthesis of methyl 12,12,13,13,14,14,15,15-octafluoro-10-iodopentadecanoate, 106



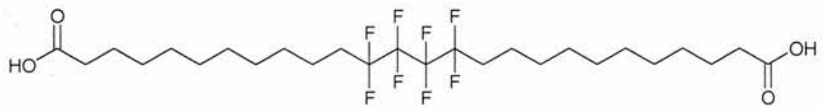
The title compound was isolated as a side product from the reaction described in 4.3.35. Colourless liquid (431 mg, 8%). ***m/z*** (CI+) 527.0686 (M+H. $C_{16}H_{24}O_2F_8I$ requires 527.0693); ν_{max} (film)/cm^{-1} 2932, 2856, 1739 (CO), 1438, 1364, 1170, 1128, 901, 807; δ_H (300 MHz, $CDCl_3$) 6.04 (1 H, tt, $^2J_{H\text{-}F}$ 52.0, $^3J_{H\text{-}F}$ 5.5, HCF_2), 4.4-4.26 (1 H, m, C*H*I), 3.67 (3 H, s, OCH_3), 3.03-2.67 (2 H, m, CF_2CH_2), 2.31 (2 H, t, *J* 7.4, CH_2CO), 1.89-1.26 (14 H, m, 7 × CH_2); δ_F (282 MHz, $CDCl_3$) -111.8 to -112.7 (1 F, m, $CF^aF^bCH_2$), -114.6 to -115.6 (1 F, m, $CF^aF^bCH_2$), -126.0 to -126.2 (2 F, m, $CF_2CF_2CH_2$); -130.1 to -130.3 (2 F, m, HCF_2CF_2), -137.7 (2 F, d, $^2J_{F\text{-}H}$ 52.0, HCF_2); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 124-100 (m, $HCF_2CF_2CF_2CF_2$), 107.6 (tt, $^1J_{C\text{-}F}$ 254, $^2J_{C\text{-}F}$ 31, HCF_2), 51.4 (s, OCH_3), 41.4 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 29.5-29.0 (m, CH_2), 28.4 (s, $CHCH_2CH_2$), 24.9 (s, CH_2CH_2CO), 20.8 (s, CHI); ***m/z*** (EI+) 495 (10%, M-OMe), 399 (100, M-I), 367 (100), 349 (67), 325 (30, M-$H(CF_2)_4$), 283 (80), 97 (17), 69 (30).

4.3.37 Synthesis of dimethyl 12,12,13,13,14,14,15,15-octafluorohexacosanedioate, 111



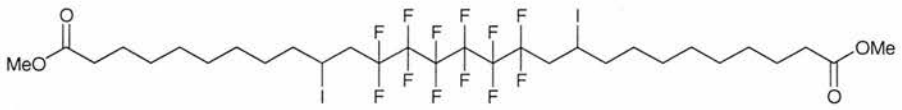
Sodium hydrogen carbonate (0.5 g) and Pd-C (10%, 0.3 g) were added to a solution of diiodo compound **104** (2.00 g, 2.35 mmol) in methanol (100 cm^3). The mixture was stirred under a balloon filled with hydrogen at room temperature for 24 h and then concentrated under reduced pressure. Ether was added (50 cm^3) and the mixture was filtered. The filtrate was washed with water (10 cm^3) and saturated aq. sodium chloride (10 cm^3). The organic phase was dried over $MgSO_4$ and the solvent removed to give a pale yellow solid (1.251 g, 89%), mp 73-74 °C (from hexane). ***m/z*** (ESI+) 621.3176 (M+Na. $C_{28}H_{46}O_4F_8Na$ requires 621.3166); ν_{max} (KBr)/cm^{-1} 2917, 2850, 1736 (CO), 1471, 1438, 1277, 1117, 1031, 885, 824, 705; δ_H (300 MHz, $CDCl_3$) 3.67 (6 H, s, 2 × OCH_3), 2.31 (4 H, t, *J* 7.5, 2 × CH_2CO), 2.12-1.94 (4 H, m, 2 × CF_2CH_2), 1.7-1.53 (8 H, m, 4 × CH_2), 1.40-1.27 (24 H, m, 12 × CH_2); δ_F (282 MHz, $CDCl_3$) -114.9 to -115.0 (4 F, m, 2 × CH_2CF_2), -124.1 to -124.2 (4 F, m, 2 × $CH_2CF_2CF_2$); δ_C (75 MHz, $CDCl_3$) 174.3 (s, *C*=O), 124-97 (m, CF_2), 51.4 (s, OCH_3), 34.1 (s, CH_2CO), 31.0 (t, $^2J_{C\text{-}F}$ 23, CF_2CH_2) 29.3-29.1 (m, CH_2), 24.9 (s, CH_2CH_2CO), 20.1 (s, $CF_2CH_2CH_2$); ***m/z*** (ESI+) 621 (60%, M+Na), 599 (100, M+H).

4.3.38 Synthesis of 12,12,13,13,14,14,15,15-octafluorohexacosanedioic acid, 96



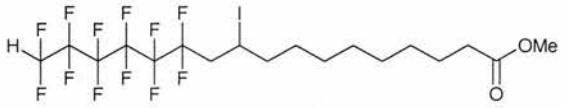
Potassium hydroxide (6.06 g, 108 mmol) was added to a solution of diester **111** (1.17 g, 1.96 mmol) in methanol (50 cm^3). The mixture was refluxed for 17 h, cooled and then water (50 cm^3) was added. After acidification with concentrated hydrochloric acid (till pH 0-2) white solid precipitated. The solid was filtered and the filtrate was heated to 90 °C and extracted with ethyl acetate (20 cm^3). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. Combined solids from filtration and from ethyl acetate extract were re-crystallized twice to give the product as a white solid, (1.00 g, 90%), mp 130.5-131°C (from ethyl acetate). **Found:** C, 54.7; H, 7.9. $C_{26}H_{42}F_8O_4$ **requires** C, 54.7; H, 7.4%; ν_{max} (KBr)/cm^{-1} 2922, 2853, 2662, 1701 (CO), 1471, 1204, 1115, 1010, 958, 823, 702; δ_H (300 MHz, DMSO-d_6) 3.35 (2 H, br s, O*H*), 2.22-2.04 (8 H, m, 2 × CH_2CO, 2 × C$H_2$$CF_2$), 1.58-1.45 (8 H, m, 4 × CH_2), 1.37-1.21 (24 H, m, 12 × CH_2); δ_F (282 MHz, acetone-d_6) -115.3 to -115.6 (4 F, m, 2 × CH_2CF_2), -124.6 to -124.7 (4 F, m, 2 × $CH_2CF_2CF_2$); δ_C (75 MHz, DMSO-d_6) 174.4 (s, *C*=O), 130-100 (m, *C*F_2), 33.7 (s, *C*H_2CO), 30.2-29.5 (m, CF_2CH_2), 28.7 (s, *C*H_2), 28.6 (s, *C*H_2), 28.6 (s, *C*H_2), 28.5 (s, *C*H_2), 28.4 (s, *C*H_2), 28.2 (s, *C*H_2), 24.4 (s, *C*H_2CH_2CO), 19.7 (s, *C*H_2); ***m/z*** (ESI+) 593 (100%, M+Na), 571 (20, M+H).

4.3.39 Synthesis of dimethyl 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-10,19-diiodooctacosanedioate, 105



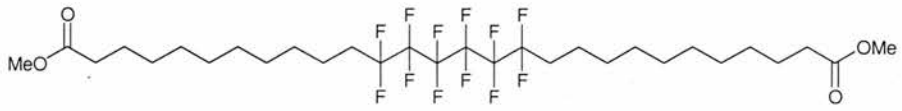
The title compound was prepared from 1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoro-1,6-diiodohexane **102** (2.500 g, 4.51 mmol), methyl 10-undecenoate **103** (2.08 g, 10.5 mmol), lead powder 325 mesh (2.30 g, 11.1 mmol) and copper(II) acetate (252 mg, 1.39 mmol) in a similar manner to the preparation of **104** as described in 4.3.35. The product was recovered as a colourless liquid (2.931 g, 68 %). ***m/z*** (ESI+) 973.1000 (M+Na. $C_{30}H_{44}O_4F_{12}NaI_2$ requires 973.1035); ν_{max} (film)/cm^{-1} 2931, 2857, 1740 (CO), 1436, 1372, 1199, 1141, 723, 694; δ_H (300 MHz, $CDCl_3$) 4.38-4.29 (2 H, m, 2 × C*H*I), 3.67 (6 H, s, 2 × OCH_3), 3.02-2.67 (4 H, m, 2 × CF_2CH_2), 2.31 (4 H, t, *J* 7.5, 2 × CH_2CO), 1.88-1.25 (28 H, m, 14 × CH_2); δ_F (282 MHz, $CDCl_3$) -111.6 to -112.7 (2 F, m, 2 × $CF^aF^bCH_2$), -114.5 to -115.7 (2 F, m, 2 × $CF^aF^bCH_2$), -122.0 to -122.4 (4 F, m, 2 × CF_2), -124.1 to -124.4 (4 F, m, 2 × CF_2); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 124-97 (m, CF_2), 51.4 (s, OCH_3), 41.7 (t, $^2J_{C-F}$ 21, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 29.5 (s, CH_2), 29.1 (s, CH_2), 29.1 (s, CH_2), 29.0 (s, CH_2), 28.4 (s, CH_2), 24.9 (s, CH_2CH_2CO), 21.0 (s, CHI); ***m/z*** (ESI+) 973 (50%, M+Na), 951 (100, M+H), 847 (10), 825 (20).

4.3.40 Synthesis of methyl 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluoro-10-iodoheptadecanoate, 107



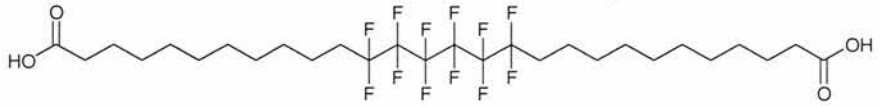
The title compound was isolated as a side product from the reaction described in 4.3.39. Colourless liquid (393 mg, 12 %). ***m/z*** (CI+) 627.0625 (M+H. $C_{18}H_{24}O_2F_{12}I$ requires 627.0629); ν_{max} (film)/cm^{-1} 2932, 2858, 1739 (CO), 1438, 1365, 1200, 1140, 717, 544; δ_H (300 MHz, $CDCl_3$) 6.05 (1 H, tt, $^2J_{H\text{-}F}$ 52.0, $^3J_{H\text{-}F}$ 5.1, HCF_2), 4.38-4.29 (1 H, m, C*H*I), 3.67 (3 H, s, OCH_3), 3.02-2.67 (2 H, m, CF_2CH_2), 2.31 (2 H, t, *J* 7.4, CH_2CO), 1.90-1.22 (14 H, m, 7 × CH_2); δ_F (282 MHz, $CDCl_3$) -111.7 to -112.8 (1 F, m, $CF^aF^bCH_2$), -114.6 to -115.7 (1 F, m, $CF^aF^bCH_2$), -122.2 to -122.5 (2 F, m, CF_2), -124.0 to -124.2 (2 F, m, CF_2), -129.9 to -130.2 (2 F, m, CF_2), -137.6 (2 F, d, $^2J_{F\text{-}H}$ 52.0, HCF_2); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 130-100 (m, CF_2), 107.6 (tt, $^1J_{C\text{-}F}$ 254, $^2J_{C\text{-}F}$ 32, HCF_2), 51.4 (s, OCH_3), 41.7 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 29.5 (s, CH_2), 29.3 (s, CH_2), 29.1 (s, CH_2), 29.0 (s, CH_2), 28.4 (s, CH_2), 24.9 (s, CH_2CH_2CO), 20.8 (s, CHI); ***m/z*** (EI+) 595 (5%, M-OMe), 499 (90, M-I), 467 (80), 449 (70), 383 (100), 369 (40), 97 (30), 69 (50).

4.3.41 Synthesis of dimethyl 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluorooctacosanedioate, 112



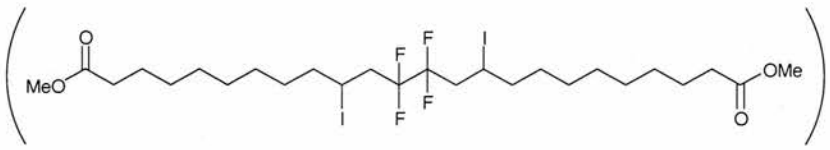
The title compound was prepared from the diiodo ester **105** (2.467 g, 2.60 mmol), sodium hydrogen carbonate (0.5 g) and Pd-C (10%, 0.3 g) in a similar manner to the preparation of **111** as described in 4.3.37. The product was recovered as a white solid (1.721g, 95%), mp 78-79 °C (from hexane). ***m/z*** (ESI+) 721.3123 (M+Na. $C_{30}H_{46}O_4F_{12}Na$ requires 721.3102); ν_{max} (KBr)/cm^{-1} 2916, 2849, 1736 (CO), 1471, 1438, 1211, 1136, 1050, 1010, 885, 723, 690, 646; δ_H (300 MHz, $CDCl_3$) 3.66 (6 H, s, 2 × OC*H*$_3$), 2.30 (4 H, t, *J* 7.5, 2 × C*H*$_2$CO), 2.13-1.95 (4 H, m, 2 × CF_2CH_2), 1.69-1.54 (8 H, m, 4 × C*H*$_2$), 1.40-1.24 (24 H, m, 12 × C*H*$_2$); δ_F (282 MHz, $CDCl_3$) -114.7 to -114.8 (4 F, m, 2 × CH_2CF_2), -122.2 to -122.3 (4 F, m, 2 × C*F*$_2$), -124.1 to -124.2 (4 F, m, 2 × C*F*$_2$); δ_C (75 MHz, $CDCl_3$) 174.3 (s, *C*=O), 130-100 (m, *C*F$_2$), 51.4 (s, O*C*H$_3$), 34.1 (s, *C*H$_2$CO), 31.0 (t, $^2J_{C\text{-}F}$ 23, CF_2CH_2) 29.3-29.1 (m, *C*H$_2$), 24.9 (s, CH_2CH_2CO), 20.1 (s, $CF_2CH_2CH_2$); ***m/z*** (ESI+) 721 (100%, M+Na), 699 (100, M+H).

4.3.42 Synthesis of 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluorooctacosanedioic acid, 98



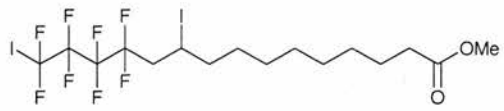
The title compound was prepared from the diester **112** (2.223 g, 3.185 mmol) and potassium hydroxide (7.56 g, 134.7 mmol) in a similar manner to the preparation of **96** as described in 4.3.38. The product was recovered as a white solid (1.494 g, 70%), mp 134.5-135.5 °C (from ethyl acetate). **Found:** C, 50.2; H, 6.3. $C_{28}H_{42}F_{12}O_4$ **requires** C, 50.2; H, 6.3%; ν_{max} (KBr)/cm^{-1} 2926, 2855, 1709 (CO), 1472, 1415, 1216, 1137, 1052, 958, 724, 688, 630; δ_H (300 MHz, DMSO-d_6) 11.9 (2 H, br s, O*H*), 2.27-2.07 (8 H, m, 2 × C*H*$_2$CO, 2 × C*H*$_2$CF$_2$), 1.55-1.41 (8 H, m, 4 × C*H*$_2$), 1.39-1.17 (24 H, m, 12 × C*H*$_2$); δ_F (282 MHz, DMSO-d_6) -113.7 to -114.0 (4 F, m, 2 × CH$_2$C*F*$_2$), -122.1 to -122.4 (4 F, m, 2 × C*F*$_2$), -123.5 to -123.8 (4 F, m, 2 × C*F*$_2$); δ_C (75 MHz, DMSO-d_6) 174.4 (s, *C*=O), 130-100 (m, *C*F$_2$), 33.6 (s, *C*H$_2$CO), 29.7 (t, $^2J_{C\text{-}F}$ 22, CF$_2$*C*H$_2$), 28.7 (s, *C*H$_2$), 28.6 (s, *C*H$_2$), 28.6 (s, *C*H$_2$), 28.5 (s, *C*H$_2$), 28.4 (s, *C*H$_2$), 28.1 (s, *C*H$_2$), 24.4 (s, *C*H$_2$CH$_2$CO), 19.7 (s, *C*H$_2$); ***m/z*** (ESI+) 693 (100%, M+Na), 671 (40, M+H).

4.3.43 Attempted synthesis of dimethyl 12,12,13,13-tetrafluoro-10,15-diiodotetracosanedioate, 109



A mixture of lead powder 325 mesh (7.50 g, 36.2 mmol) and copper(II) acetate (780 mg, 4.33 mmol) in dry methanol (100 cm^3) was stirred under nitrogen for 30 min. Then 1,1,2,2-tetrafluoro-1,2-diiodoethane **108** (5.115 g, 14.46 mmol) and methyl 10-undecenoate **103** (10.43 g, 49.12 mmol) were slowly added. An evolution of gas from the reaction mixture was observed and after 48 h no expected product was detected by GC-MS, TLC or ^{19}F NMR.

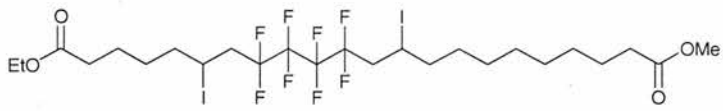
4.3.44 Synthesis of methyl 12,12,13,13,14,14,15,15-octafluoro-10,15-diiodopentadecanoate, 113



A mixture of lead powder 325 mesh (4.255 g, 20.53 mmol) and copper(II) acetate (157 mg, 0.86 mmol) in dry methanol (90 cm^3) was stirred under nitrogen for 30 min. Then 1,1,2,2,3,3,4,4-octafluoro-1,4-diiodobutane **101** (15.00 g, 33.05 mmol) and methyl 10-undecenoate **103** (4.07 g, 20.53 mmol) were slowly added and the mixture was stirred in dark for 17 h at room temperature. The solvent and unreacted **101** were subsequently removed under reduced pressure, the residue was dissolved in diethyl ether (40 cm^3) and the suspension was filtered. The filtrate was concentrated under reduced pressure and the residual pale yellow liquid was purified over silica (ether:petrol; 1:10) to give a by-product **104** (2.703 g, 15.5%) and a mixture of product **113** (49%) and **106** (15%) as a colourless light sensitive liquid (8.15 g) in a ratio of 4:1 (judged by GC-MS and ^{19}F-NMR). Further chromatographic purification decreased the yield of **113** and increases the amount of **106**. ν_{max} (film)/cm^{-1} 2931, 2857, 1740 (CO), 1437, 1365, 1178, 1128, 713, 675; δ_H (300 MHz, $CDCl_3$) 6.03 (1/5 H, tt, $^2J_{H\text{-}F}$ 52.0, $^3J_{H\text{-}F}$ 5.5, HCF_2), 4.4-4.26 (1 H, m, C*H*I), 3.67 (3 H, s, OCH_3), 3.03-2.66 (2 H, m, CF_2CH_2), 2.30 (2 H, t, *J* 7.7, CH_2CO), 1.89-1.22 (14 H, m, 7 × CH_2); δ_F (282 MHz, $CDCl_3$) -59.0 to -59.2 (2 F, m, ICF_2), -111.6 to -115.6 (4 F, m, $CF_2CF_2CF_2CH_2$), -123.0 to -123.2 (2 F, m, $CF_2CF_2CH_2$), -126.0 to -126.1 (2/5 F, m, $CF_2CF_2CH_2$); -130.0 to -130.2 (2/5 F, m, HCF_2CF_2), -137.6 (2/5 F, d, $^2J_{F\text{-}H}$ 52.0, HCF_2); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 130-100 (m, $ICF_2CF_2CF_2CF_2$), 51.4 (s, OCH_3), 41.9-41.4 (m, CF_2CH_2),

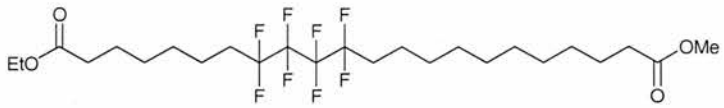
40.3 (s, CH*C*H$_2$CH$_2$), 34.0 (s, *C*H$_2$CO), 29.5-29.0 (m, *C*H$_2$), 28.4 (s, CHCH$_2$*C*H$_2$), 24.9 (s, *C*H$_2$CH$_2$CO); ***m/z*** (EI+) 621 (2%, M-OMe), 525 (50, M-I), 493 (70), 475 (50), 409 (80), 97 (60), 74 (90), 69 (100), 55 (100).

4.3.45 Synthesis of 1-ethyl 22-methyl 8,8,9,9,10,10,11,11-octafluoro-6,13-diiododocosanedioate, 114



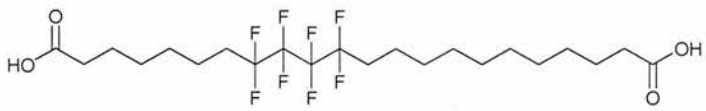
A mixture of lead powder 325 mesh (1.525 g, 7.36 mmol) and copper(II) acetate (160 mg, 0.88 mmol) in dry methanol (30 cm^3) was stirred under nitrogen for 30 min. Then a mixture of **113** and **106** (4:1, 4.80 g of the mixture, 5.89 mmol of **113**) and ethyl 6-heptenoate (1.56 g, 10 mmol) were slowly added and the mixture was stirred for 48 h at room temperature. The solvent was subsequently removed under reduced pressure, diethyl ether (30 cm^3) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure and the residual liquid was purified over silica (ether:petrol; 1:10) to give excess of the olefin, unreacted **106** and the product **114** (2.044 g, 44%) as a colourless liquid. ***m/z*** (ESI+) 831.0652 (M+Na. $C_{25}H_{38}O_4F_8NaI_2$ requires 831.0630); ν_{max} (film)/cm^{-1} 2933, 2858, 1737 (CO), 1436, 1374, 1170, 1119, 913, 864, 734; δ_H (300 MHz, $CDCl_3$) 4.40-4.27 (2 H, m, 2 × C*H*I), 4.13 (2 H, q, *J* 7.2, OCH_2), 3.66 (3 H, s, OCH_3), 3.00-2.63 (4 H, m, 2 × CF_2CH_2), 2.30 (4 H, t, *J* 7.7, 2 × CH_2CO), 1.87-1.28 (20 H, m, 10 × CH_2), 1.26 (3 H, t, *J* 7.2, OCH_2CH_3); δ_F (282 MHz, $CDCl_3$) -111.6 to -115.7 (4 F, m, 2 × CF_2CH_2), -123.8 to -124.0 (4 F, m, 2 × $CF_2CF_2CH_2$); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 173.3 (s, *C*=O), 130-100 (m, CF_2), 60.3 (s, OCH_2), 51.4 (s, OCH_3), 41.8 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 39.9 (s, $CHCH_2CH_2$), 34.1-33.9 (m, CH_2CO), 29.5-28.4 (m, CH_2), 28.4 (s, CH_2), 24.9 (s, CH_2CH_2CO), 23.8 (s, CH_2CH_2CO), 21.6-20.7 (m, CHI), 14.2 (s, CH_2CH_3); ***m/z*** (EI+) 763 (1%, M-OEt), 681 (10, M-I), 649 (20), 603 (100), 475 (80), 207 (100), 128 (90), 55 (100).

4.3.46 Synthesis of 1-ethyl 22-methyl 8,8,9,9,10,10,11,11-octafluorodocosanedioate, 115



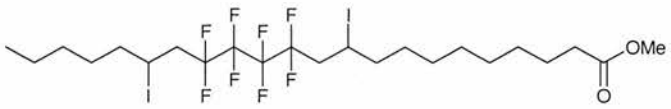
The title compound was prepared from the diiodo compound **114** (1.744 g, 2.16 mmol), sodium hydrogen carbonate (0.53 g) and Pd-C (10%, 0.35 g) in a similar manner to the preparation of **111** as described in 4.3.37. The product was recovered as a white solid (1.176 g, 98%), mp 48.5-49 °C (from hexane). ***m/z*** (ESI+) 579.2696 (60%, M+Na. $C_{25}H_{40}O_4NaF_8$ requires 579.2697), 557 (100, M+H); ν_{max} (KBr)/cm^{-1} 2937, 2854, 1737 (CO), 1474, 1438, 1178, 1117, 1041, 823, 702; δ_H (300 MHz, $CDCl_3$) 4.13 (2 H, q, *J* 7.2, OC*H*$_2$), 3.66 (3 H, s, OC*H*$_3$), 2.34-2.28 (4 H, m, 2 × C*H*$_2$CO), 2.12-1.94 (4 H, m, 2 × CF$_2$C*H*$_2$), 1.69-1.28 (24 H, m, 12 × C*H*$_2$), 1.26 (3 H, t, *J* 7.2, C*H*$_3$); δ_F (282 MHz, $CDCl_3$) -114.8 to -115.1 (4 F, m, 2 × C*F*$_2$CH$_2$), -124.1 to -124.2 (4 F, m, 2 × C*F*$_2$CF$_2$CH$_2$); δ_C (75 MHz, $CDCl_3$) 174.3 (s, *C*=O), 173.7 (s, *C*=O), 130-100 (m, *C*F$_2$), 60.2 (s, OCH$_2$), 51.4 (s, OCH$_3$), 34.2-34.0 (m, *C*H$_2$CO), 31.3-30.5 (m, CF$_2$*C*H$_2$), 29.3-28.7 (m, *C*H$_2$), 24.9 (s, *C*H$_2$CH$_2$CO), 24.7 (s, *C*H$_2$CH$_2$CO), 20.0 (s, CF$_2$CH$_2$*C*H$_2$), 14.2 (s, *C*H$_3$).

4.3.47 Synthesis of 8,8,9,9,10,10,11,11-octafluorodocosanedioic acid, 97



The title compound was prepared from the diester **115** (910 mg, 1.64 mmol) and potassium hydroxide (3.35 g, 59.7 mmol) in a similar manner to the preparation of **96** as described in 4.3.38. The product was recovered as a white solid (635 mg, 76%), mp 117.5-118 °C (from ethyl acetate). **Found:** C, 51.4; H, 7.0. $C_{22}H_{34}F_8O_4$ **requires** C, 51.4; H, 6.7%; ν_{max} (KBr)/cm^{-1} 2923, 2853, 2689, 1701 (CO), 1471, 1327, 1213, 1084, 1043, 965, 823, 702; δ_H (300 MHz, acetone-d_6) 10.4 (2 H, br s, 2 × O*H*), 2.33-2.25 (4 H, m, 2 × CH_2CO), 2.20-2.08 (4 H, m, 2 × CF_2CH_2), 1.66-1.55 (8 H, m, 4 × CH_2), 1.48-1.29 (16 H, m, 8 × CH_2); δ_F (282 MHz, acetone-d_6) -115.2 to -115.6 (4 F, m, 2 × CF_2CH_2), -124.6 to -124.7 (4 F, m, 2 × C$F_2CF_2CH_2$); δ_C (75 MHz, DMSO-d_6) 174.4 (s, *C*=O), 174.3 (s, *C*=O), 124-107 (m, *C*F_2), 33.6 (s, *C*H_2CO), 33.4 (s, *C*H_2CO), 30.3-29.6 (m, CF_2CH_2), 28.7 (s, *C*H_2), 28.7 (s, *C*H_2), 28.6 (s, *C*H_2), 28.5 (s, *C*H_2), 28.4 (s, *C*H_2), 28.2 (s, *C*H_2), 28.0 (s, *C*H_2), 27.9 (s, *C*H_2), 24.4 (s, *C*H_2CH$_2$CO), 24.1 (s, *C*H_2CH$_2$CO), 19.7 (s, *C*H_2), 19.6 (s, *C*H_2); ***m/z*** (ESI+) 537 (100%, M+Na), 515 (70, M+H).

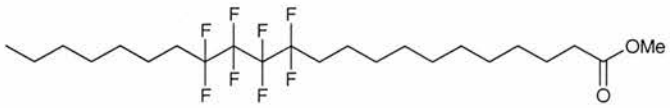
4.3.48 Synthesis of methyl 12,12,13,13,14,14,15,15-octafluoro-10,17-diiododocosanoate, 116



A mixture of lead powder 325 mesh (176 mg, 0.85 mmol) and copper(II) acetate (13 mg, 0.07 mmol) in dry methanol (5 cm^3) was stirred under nitrogen for 30 min. Then a mixture of **113** and **106** (4:1, 551 mg of the mixture, 0.676 mmol of the diiodo compound) and 1-heptene (167 mg, 1.7 mmol) in methanol (5 cm^3) was added and the mixture was stirred for 24 h at room temperature. The solvent was subsequently removed under reduced pressure, diethyl ether (20 cm^3) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure and the residual liquid purified over silica (ether:petrol; 1:5) to give unreacted **106** and the product **116** as a colourless liquid (378 mg, 73%). ***m/z*** (ESI+) 773.0542 (M+Na. $C_{23}H_{36}O_2NaF_8I_2$ requires 773.0575); ν_{max} (KBr)/cm^{-1} 2931, 2857, 1742 (CO), 1461, 1436, 1377, 1169, 1121, 863, 725, 513; δ_H (300 MHz, $CDCl_3$) 4.40-4.27 (2 H, m, 2 × C*H*I), 3.67 (3 H, s, OCH_3), 3.00-2.64 (4 H, m, 2 × CF_2CH_2), 2.31 (2 H, t, *J* 7.5, CH_2CO), 1.88-1.71 (4 H, m, 2 × CHCH_2CH_2), 1.67-1.21 (18 H, m, 9 × CH_2), 0.91 (3 H, t, *J* 7.0, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) -111.7 to -112.9 (2 F, m, 2 × C$F^aF^bCH_2$), -114.8 to -115.9 (2 F, m, 2 × C$F^aF^bCH_2$), -123.9 to -124.2 (4 F, m, 2 × C$F_2CF_2CH_2$); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 125-110 (m, CF_2), 51.4 (s, OCH_3), 41.7 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2), 40.2 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 30.6 (s, CH_2), 29.5 (s, CH_2), 29.2 (s, CH_2), 29.1 (s, CH_2), 29.1 (s, CH_2), 29.0 (s, CH_2), 28.4 (s, CH_2), 24.9 (s, CH_2), 22.6 (s, CH_2CH_3),

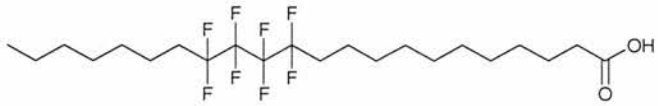
21.4 (s, *C*HI), 13.9 (s, CH_2CH_3); ***m/z*** (EI+) 719 (1%, M-OMe), 623 (60, M-I), 591 (60), 463 (70), 445 (50), 379 (40), 128 (40), 97 (60), 74 (80), 69 (100), 55 (100).

4.3.49 Synthesis of methyl 12,12,13,13,14,14,15,15-octafluorodocosanoate, 117



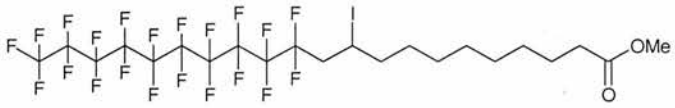
The title compound was prepared from the diiodo ester **116** (320 mg, 0.427 mmol), sodium hydrogen carbonate (81 mg) and Pd-C (10%, 96 mg) in a similar manner to the preparation of **111** as described in 4.3.37. The product was recovered as a white solid (198 mg, 93%), mp 48-49 °C. ***m/z*** (CI+) 499.2828 (M+H. $C_{23}H_{39}O_2F_8$ requires 499.2822); ν_{max} (KBr)/cm^{-1} 2926, 2855, 1737 (CO), 1471, 1438, 1218, 1176, 1114, 1048, 991, 884, 821, 701, 602, 538; δ_H (300 MHz, $CDCl_3$) 3.65 (3 H, s, OC*H*$_3$), 2.29 (2 H, t, *J* 7.4, C*H*$_2$CO), 2.13-1.91 (4 H, m, 2 × CF_2CH_2), 1.67-1.52 (4 H, m, 2 × $CF_2CH_2CH_2$), 1.41-1.17 (22 H, m, 11 × CH_2), 0.87 (3 H, t, *J* 6.9, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) -115.0 to -115.2 (4 F, m, 2 × CF_2CH_2), -124.2 to -124.3 (4 F, m, 2 × $CF_2CF_2CH_2$); δ_C (75 MHz, $CDCl_3$) 174.2 (s, *C*=O), 125-100 (m, CF_2), 51.4 (s, OCH_3), 34.0 (s, CH_2CO), 31.6 (s, $CH_3CH_2CH_2$), 31.0 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2), 29.3-28.9 (m, CH_2), 25.9 (s, CH_2CH_2CO), 22.6 (s, CH_3CH_2), 20.1 (s, $CF_2CH_2CH_2$), 14.0 (s, CH_2CH_3); ***m/z*** (EI+) 498 (10%, M), 467 (7, M-OMe), 455 (15, M-C_3H_7), 143 (20), 87 (80), 74 (100).

4.3.50 Synthesis of 12,12,13,13,14,14,15,15-octafluoro-docosanoic acid, 94



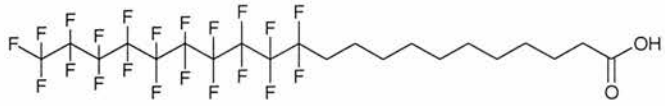
The title compound was prepared from the ester **117** (154 mg, 0.309 mmol) and potassium hydroxide (742 mg, 13.2 mmol) in a similar manner to the preparation of **96** as described in 4.3.38. The product was recovered as a white solid (119 mg, 80%), mp 82-84 °C (from petrol). **Found:** C, 54.7; H, 7.7. $C_{22}H_{36}F_8O_2$ **requires** C, 54.5; H, 7.5%; ν_{max} (KBr)/cm^{-1} 2926, 2855, 1716 (CO), 1473, 1220, 1155, 1115, 1050, 957, 822, 700; δ_H (300 MHz, $CDCl_3$) 7.3 (1 H, br s, O*H*), 2.35 (2 H, t, *J* 7.5, CH_2CO), 2.14-1.92 (4 H, m, 2 × CF_2CH_2), 1.69-1.53 (6 H, m, 3 × CH_2), 1.41-1.21 (20 H, m, 10 × CH_2), 0.93-0.85 (3 H, m, CH_2CH_3); δ_F (282 MHz, $CDCl_3$) -115.0 to -115.2 (4 F, m, 2 × CF_2CH_2), -124.2 to -124.4 (4 F, m, 2 × $CF_2CF_2CH_2$); δ_C (75 MHz, $CDCl_3$) 179.29 (s, *C*=O), 130-100 (m, CF_2), 34.0 (s, CH_2CO), 31.6 (s, $CH_3CH_2CH_2$), 31.4-30.7 (m, CF_2CH_2), 29.3-28.9 (m, CH_2), 24.6 (s, CH_2CH_2CO), 22.6 (s, CH_3CH_2), 20.2 (s, $CF_2CH_2CH_2$), 14.0 (s, CH_2CH_3); ***m/z*** (ESI+) 517 (60%, M+MeOH+H), 507 (100, M+Na) , 485 (70, M+H).

4.3.51 Synthesis of methyl 12,12,13,13,14,14,15,15,16,16,17,17, 18,18,19,19,20,20,21,21,21-henicosafluoro-10-iodohenicosanoate, 119



1-Iodoperfluorodecane **118** (2.500 g, 3.87 mmol), methyl 10-undecenoate **103** (921 mg, 4.64 mmol) and azo-bis-*iso*-butyronitrile (18 mg, 0.109 mmol) were placed into a flask under a nitrogen atmosphere. The mixture was stirred at 80°C for 19 h. Ethanol (30 cm^3) was added; the mixture was cooled to -10°C and filtered. Re-crystallization gave the product as a white solid (975 mg, 38%), mp 56-58°C (from ethanol). ***m/z*** (ESI+) 867.0218 (100%, M+Na. $C_{22}H_{22}O_2F_{21}NaI$ requires 867.0227); ν_{max} (KBr)/cm^{-1} 2931, 2857, 1733 (CO), 1437, 1242, 1205, 1151, 910, 734, 666, 649, 559; δ_H (300 MHz, $CDCl_3$) 4.38-4.29 (1 H, m, C*H*I), 3.67 (3 H, s, OCH_3), 3.04-2.70 (2 H, m, CF_2CH_2), 2.31 (2 H, t, *J* 7.2, CH_2CO), 1.87-1.22 (14 H, m, 7 × CH_2); δ_F (282 MHz, $CDCl_3$) -81.3 (3 F, t, $^3J_{F\text{-}F}$ 10.3, CF_3), -111.5 to -112.6 (1 F, m, $CF^aF^bCH_2$), -114.5 to -115.5 (1 F, m, $CF^aF^bCH_2$), -121.7 to -122.2 (10 F, m, 5 × CF_2), -123.1 to -123.3 (2 F, m, CF_2), -123.8 to -124.1 (2 F, m, CF_2), -124.6 to -126.8 (2 F, m, CF_2); δ_C (75 MHz, $CDCl_3$) 174.3 (s, *C*=O), 125-100 (m, $C_{10}F_{21}$), 51.4 (s, OCH_3), 41.7 (t, $^2J_{C\text{-}F}$ 21, CF_2CH_2), 40.3 (s, $CHCH_2CH_2$), 34.0 (s, CH_2CO), 29.5 (s, CH_2), 29.1 (s, CH_2), 29.1 (s, CH_2), 29.0 (s, CH_2), 28.4 (s, CH_2), 24.9 (s, CH_2CH_2CO), 20.9-20.7 (m, CHI).

4.3.52 Synthesis of 12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19,20,20,21,21,21-henicosafluorohenicosanoic acid, 95



Sodium hydrogen carbonate (0.15 g) and Pd-C (10%, 0.11 g) were added to a solution of **119** (1.118 g, 1.324 mmol) in THF (15 cm^3) and methanol (70 cm^3). The mixture was stirred under a balloon filled with hydrogen at room temperature for 18 h and then concentrated under reduced pressure. Dichloromethane (50 cm^3) was added and the mixture was filtered. The filtrate was washed with water (20 cm^3) and saturated aq. sodium chloride (10 cm^3). The organic phase was dried over $MgSO_4$ and the solvent removed to give a white solid, (846 mg), mp 67°C (from hexane), which was dissolved in methanol (25 cm^3). Potassium hydroxide (2.345 g, 41.8 mmol) was added and the mixture was refluxed for 24 h. Water (25 cm^3) was added and after acidification with concentrated hydrochloric acid (till pH 0-2) white solid precipitated. The solid was filtered, washed with water (2 × 10 cm^3) and dried in vacuum. Re-crystallization gave the product as a white solid (709 mg, 76%), mp 109-109.5°C (from hexane). **Found:** C, 36.0; H, 2.7. $C_{21}H_{21}F_{21}O_2$ **requires** C, 35.8; H, 3.0%; ν_{max} (KBr)/cm^{-1} 2921, 2853, 1707 (CO), 1472, 1437, 1376, 1217, 1152, 1052, 958, 880, 665, 646, 557, 529; δ_H (300 MHz, acetone-d_6) 10.38 (1 H, br s, O*H*), 2.33-2.14 (4 H, m, CH_2CO, CH_2CF_2), 1.67-1.54 (4 H, m, 2 × CH_2), 1.48-1.29 (12 H, m, 6 × CH_2); δ_F (282 MHz, acetone-d_6) -82.1 (3 F, t, $^3J_{F-F}$ 10.2, CF_3), -115.1 to -115.3 (2 F, m, CF_2), -122.6 to -123.0 (10 F, m, 5 × CF_2), -123.6 to -123.8 (2 F, m, CF_2), -124.4 to -124.5 (2 F, m, CF_2), -127.1 to -127.2 (2 F, m, CF_2); δ_C (75 MHz, acetone-d_6) 175.6 (s, *C*=O), 125-100 (m, $C_{10}F_{21}$), 35.3 (s,

CH_2CO), 32.5 (t, $^2J_{C\text{-}F}$ 22, CF_2CH_2), 31.2 (s, CH_2), 31.1 (s, CH_2), 31.1 (s, CH_2), 30.9 (s, CH_2), 30.9 (s, CH_2), 30.7 (s, CH_2), 26.7 (s, CH_2), 22.0-21.9 (m, $CF_2CH_2CH_2$); ***m/z*** (ESI-) 703 (100%, M-H).

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APPENDIXES

A.1 Appendix 1: GC-MS Separation of chiral compounds

See Table A.1 for the summary of the temperature profiles and conditions used for GC-MS analysis of chiral compounds shown in Figure A.1. Enantiomeric excess values (*ee*) were determined from the peak areas of the enantiomers (A_S, A_R) using Equation A.1.

$$ee\,(\%) = \frac{|A_S - A_R|}{A_S + A_R} \cdot 100 \qquad \text{Equation A.1}$$

GC-MS methods used for the separation of enantiomers are listed in Table A.2 together with the retention times for each enantiomer.

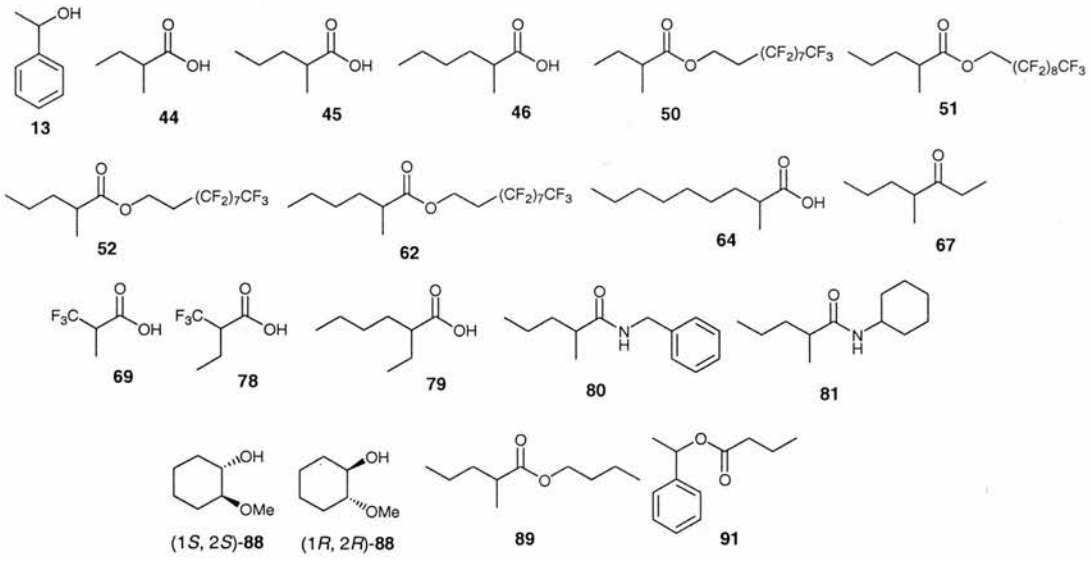

Figure A.1: Chiral compounds chromatographically separated by GC-MS using a chiral column.

Table A.1: Summary of the temperature profiles and conditions used for GC-MS analysis of chiral compounds. Supelco β-DEX 120 fused silica (30 m × 250 μm with a film thickness of 0.25 μm) chiral column was used.

GC-MS Method	Velocity ($cm \cdot s^{-1}$)	Temperature profile	*m/z*
A	38	115 °C, 20 min.; 12 °C·min.$^{-1}$ (115-190 °C); 190 °C, 6 min.	40-800
B	39	110 °C, 13 min.; 25 °C·min.$^{-1}$ (110-170 °C); 170 °C, 3 min.	29-600
C	36	100 °C, 14 min.; 25 °C·min.$^{-1}$ (110-110 °C); 110 °C, 1 min.	10-800
D	39	110 °C, 14 min.; 10 °C·min.$^{-1}$ (110-130 °C); 130 °C, 3 min.	10-800
E	40	150 °C, 20 min.	29-800
F	40	70 °C, 15 min.; 60 °C·min.$^{-1}$ (70-180 °C); 180 °C, 1.2 min.	20-300
G	38	75 °C, 20 min.; 10 °C·min.$^{-1}$ (75-100 °C); 100 °C, 11 min.; 40 °C·min.$^{-1}$ (100-190 °C); 190 °C, 2.5 min.	40-650
H	38	100 °C, 24 min.; 40 °C·min.$^{-1}$ (100-190 °C); 190 °C, 7.5 min.	33-650
J	38	120 °C, 24 min.	33-650
K	39	100 °C, 8 min.; 12 °C·min.$^{-1}$ (100-170 °C); 170 °C, 25 min.	15-800
L	40	83 °C, 41 min.; 20 °C·min.$^{-1}$ (83-220 °C); 220 °C, 23 min.	10-800
M	39	80 °C, 22 min.; 20 °C·min.$^{-1}$ (80-120 °C); 120 °C, 4 min.; 20 °C·min.$^{-1}$ (120-140 °C); 140 °C, 1 min.	10-400

Table A.2: Summary of GC-MS methods used for separation of enantiomers and the retention times for each enantiomer.

Compound	GC-MS method	Retention time (min.)
13	A	15.98 min. (*R*); 16.99 min. (*S*)
44	C	13.08 min. (*S*); 13.72 min. (*R*)
45	B	13.61 min. (*S*); 14.09 min. (*R*)
46	D	17.33 min. (*S*[a]); 17.94 min. (*R*[a])
50	C	14.10 min. (*R*); 14.30 min. (*S*)
51	K	7.28 min. (*R*); 7.52 min. (*S*)
52	B	9.21 min. (*R*); 9.42 min. (*S*)
62	D	12.18 min. (*R*); 12.46 min. (*S*)
64	E	14.34 min. (*S*); 15.17 min. (*R*)
67	F	11.23 min. (*R*); 11.48 min. (*S*)
69	G	29.71 min. (*S*); 30.18 min. (*R*)
78	H	22.18 min. (?); 23.17 min. (?)
79	J	21.89 min. (?); 22.63 min. (?)
80	K	12.27 min. (*S*); 12.48 min. (*R*)
81	K	12.29 min. (*S*); 12.51 min. (*R*)
88	L	37.73 min. (1*S*, 2*S*); 38.73 min. (1*R*, 2*R*)
89	M	21.06 min. (*R*); 21.33 min. (*S*)
91	A	32.43 min. (*S*); 32.67 min. (*R*)

[a] Expected absolute configuration based on the elution order of carboxylic acids **44** and **45**.

A.2 Appendix 2: Differential scanning calorimetry (DSC) analysis

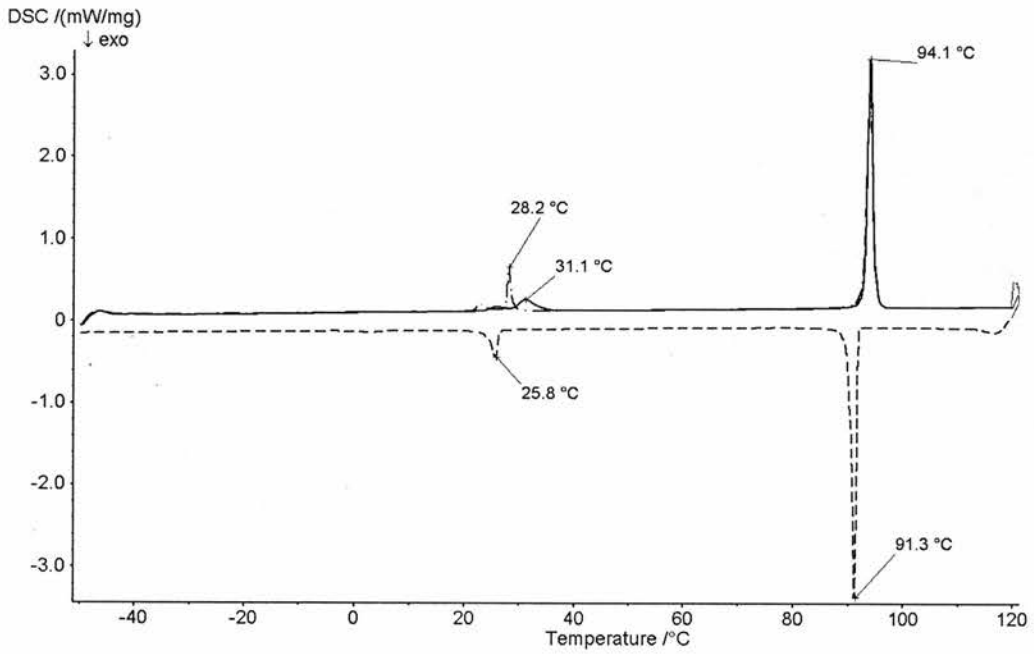

Figure A.7: DSC thermogrammes showing heat flow versus temperature curves for CF_3-$(CF_2)_7$-$(CH_2)_4$-$(CF_2)_7$-CF_3, **59**. — First heating; ---- cool down; -·-· second heating.

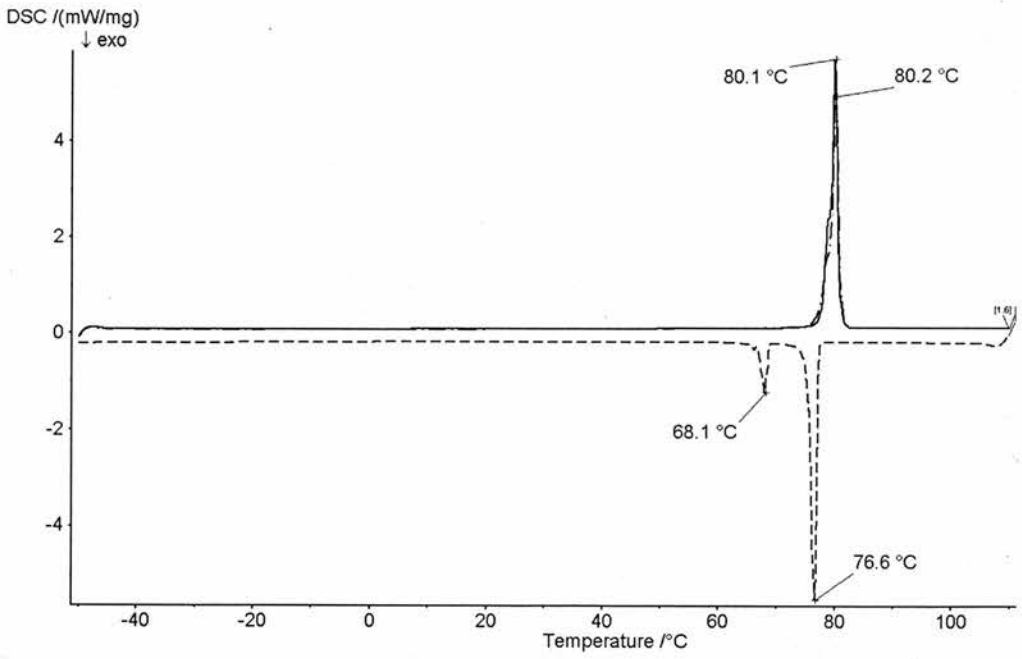

Figure A.5: DSC thermogrammes showing heat flow versus temperature curves for CH_3-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H, **94**. — First heating; ---- cool down; -·-· second heating.

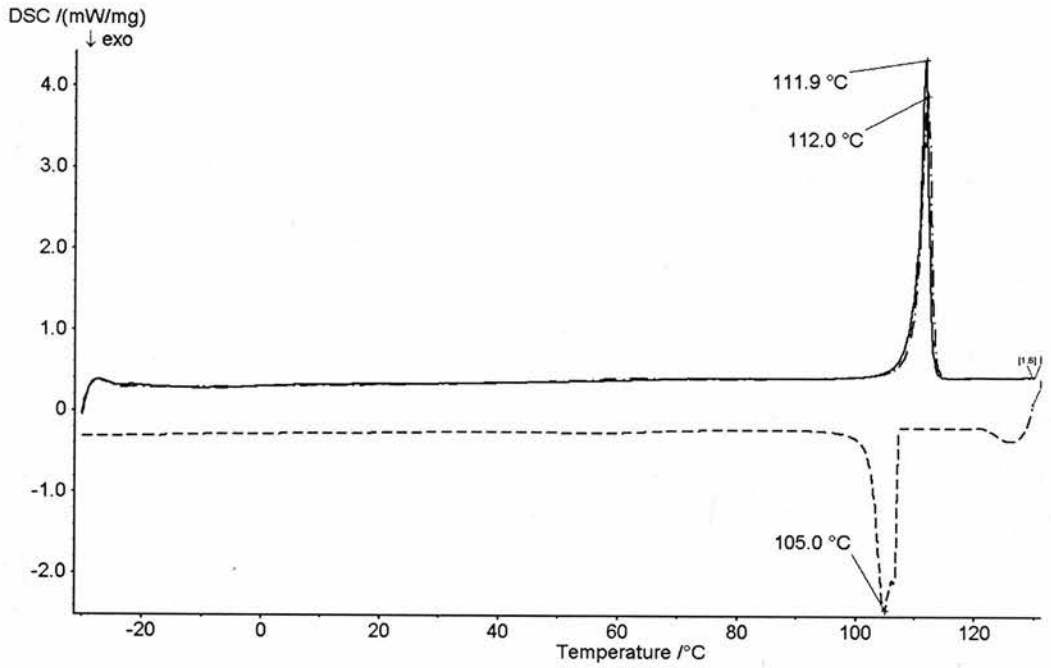

Figure A.6: DSC thermogrammes showing heat flow versus temperature curves for CF_3-$(CF_2)_9$-$(CH_2)_{10}$-CO_2H, **95**. — First heating; ---- cool down; ·-·- second heating.

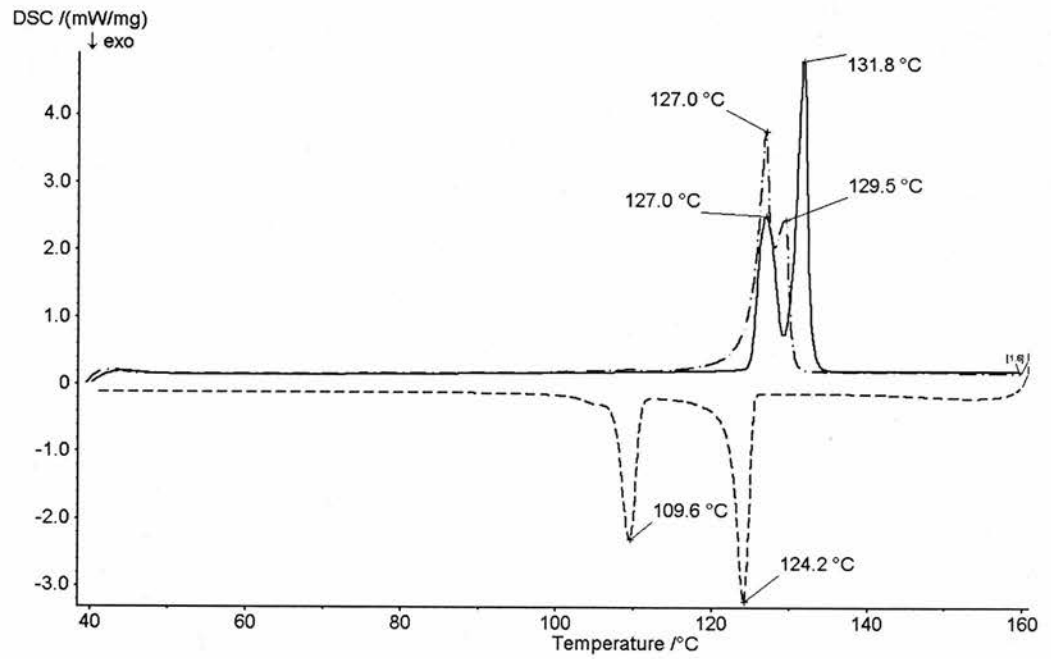

Figure A.2: DSC thermogrammes showing heat flow versus temperature curves for HO_2C-$(CH_2)_{10}$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H, **96**. — First heating; ---- cool down; ·-·- second heating.

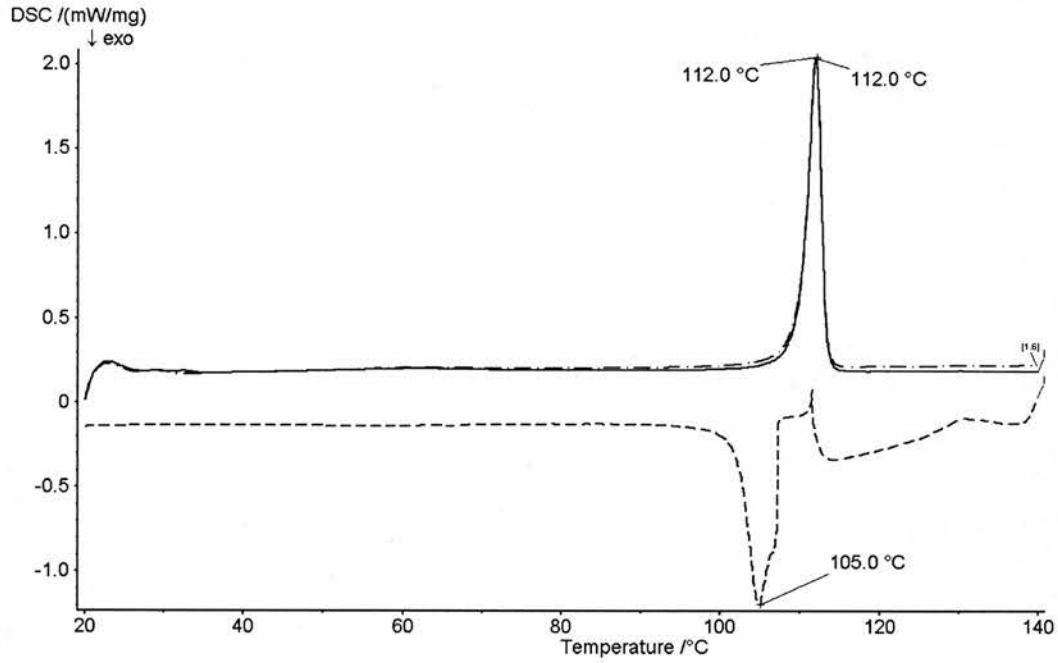

Figure A.4: DSC thermogrammes showing heat flow versus temperature curves for HO_2C-$(CH_2)_6$-$(CF_2)_4$-$(CH_2)_{10}$-CO_2H, **97**. — First heating; ---- cool down; ·-·- second heating.

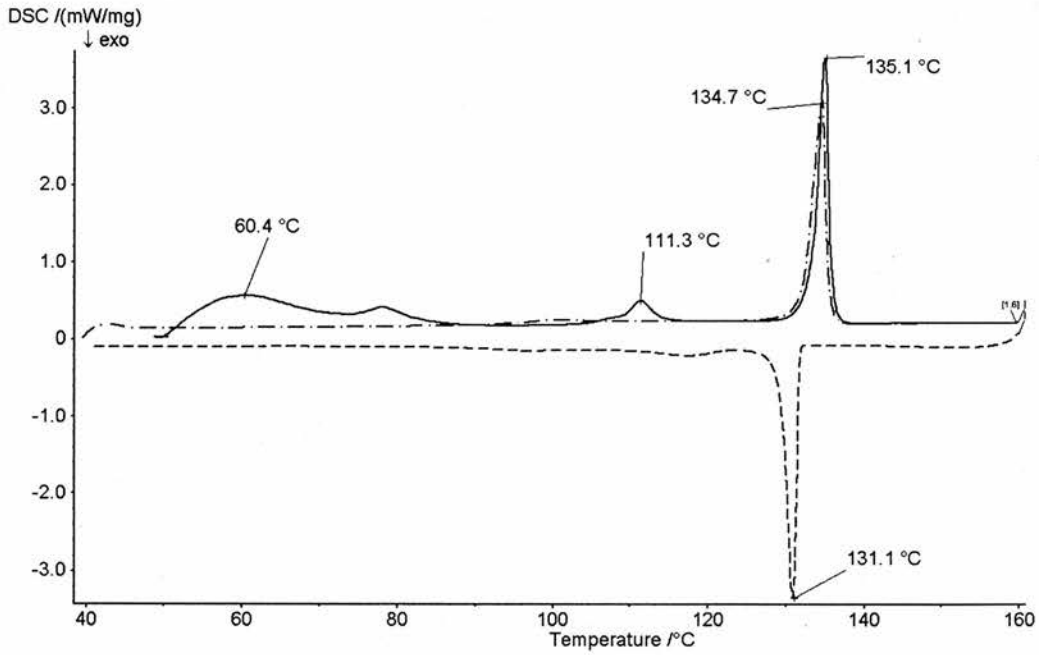

Figure A.3: DSC thermogrammes showing heat flow versus temperature curves for HO_2C-$(CH_2)_{10}$-$(CF_2)_6$-$(CH_2)_{10}$-CO_2H, **98**. — First heating; ---- cool down; ·-·- second heating.

A.3 Appendix 3: X-Ray crystallographic data

A.3.1 X-Ray data for (2*S*)-3,3,3-trifluoro-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamide, 77 (CCDC 23 6631)

All N-H hydrogen atoms were refined isotropically subject to a distance constraint (N-H= 0.98 Å). All remaining hydrogen atoms were assigned riding isotropic displacement parameters and constrained to idealised geometries. Refinements converged to residuals and details of the structure determinations are given in Table A.3.

Table A.3: Crystal data and structure refinement for **77**.

Identification code	**77**	
Empirical formula	$C_{12}H_{14}F_3NO$	
Formula weight	245.24	
Temperature	125(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 4.8905(10) Å	α= 90°.
	b = 9.0509(18) Å	β= 97.356(3)°.
	c = 13.314(3) Å	γ = 90°.
Volume	584.5(2) Å^3	
Z	2	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	256	
Crystal size	.87 x .15 x .01 mm^3	
Theta range for data collection	2.73 to 25.32°.	
Index ranges	-5<=h<=5, -10<=k<=10, -15<=l<=15	
Reflections collected	3619	
Independent reflections	2008 [R(int) = 0.0064]	
Completeness to theta = 25.32°	98.3 %	

Absorption correction	MULTISCAN
Max. and min. transmission	1.00000 and 0.901758
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2008 / 2 / 159
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0728
R indices (all data)	R1 = 0.0279, wR2 = 0.0735
Absolute structure parameter	0.2(5)
Extinction coefficient	0.045(7)
Largest diff. peak and hole	0.137 and -0.147 e.$Å^{-3}$

Table A.4: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **77**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7985(4)	-5244(2)	2542(1)	32(1)
C(2)	6637(3)	-3763(2)	2231(1)	24(1)
N(3)	7685(2)	-2626(1)	2962(1)	23(1)
C(4)	6057(3)	-1821(2)	3479(1)	19(1)
O(4)	3536(2)	-1952(1)	3414(1)	28(1)
C(5)	7579(3)	-675(2)	4203(1)	19(1)
C(6)	6160(3)	-469(2)	5151(1)	27(1)
C(7)	7066(3)	-3383(2)	1151(1)	24(1)
C(8)	5481(4)	-4120(2)	361(1)	38(1)
C(9)	5909(4)	-3895(2)	-635(1)	43(1)
C(10)	7902(4)	-2921(2)	-864(1)	39(1)
C(11)	9461(4)	-2161(2)	-92(1)	40(1)
C(12)	9046(3)	-2389(2)	912(1)	30(1)
C(13)	7748(3)	777(2)	3655(1)	23(1)
F(1)	8993(2)	657(1)	2825(1)	34(1)
F(2)	5263(2)	1379(1)	3371(1)	34(1)
F(3)	9201(2)	1780(1)	4255(1)	36(1)

Table A.5. Bond lengths [Å] and angles [°] for **77**.

C(1)-C(2)	1.528(2)	C(13)-F(2)	1.3416(18)	C(5)-C(6)-H(6C)	109.5
C(1)-H(1A)	0.9800	C(13)-F(3)	1.3496(17)	H(6A)-C(6)-H(6C)	109.5
C(1)-H(1B)	0.9800	C(2)-C(1)-H(1A)	109.5	H(6B)-C(6)-H(6C)	109.5
C(1)-H(1C)	0.9800	C(2)-C(1)-H(1B)	109.5	C(12)-C(7)-C(8)	118.29(15)
C(2)-N(3)	1.4628(18)	H(1A)-C(1)-H(1B)	109.5	C(12)-C(7)-C(2)	123.27(13)
C(2)-C(7)	1.519(2)	C(2)-C(1)-H(1C)	109.5	C(8)-C(7)-C(2)	118.37(14)
C(2)-H(2A)	1.0000	H(1A)-C(1)-H(1C)	109.5	C(9)-C(8)-C(7)	121.01(17)
N(3)-C(4)	1.3337(19)	H(1B)-C(1)-H(1C)	109.5	C(9)-C(8)-H(8A)	119.5
N(3)-H(3N)	0.9797(11)	N(3)-C(2)-C(7)	113.05(12)	C(7)-C(8)-H(8A)	119.5
C(4)-O(4)	1.2302(18)	N(3)-C(2)-C(1)	109.55(12)	C(10)-C(9)-C(8)	120.29(16)
C(4)-C(5)	1.5415(18)	C(7)-C(2)-C(1)	110.36(12)	C(10)-C(9)-H(9A)	119.9
C(5)-C(13)	1.5106(19)	N(3)-C(2)-H(2A)	107.9	C(8)-C(9)-H(9A)	119.9
C(5)-C(6)	1.5277(19)	C(7)-C(2)-H(2A)	107.9	C(9)-C(10)-C(11)	119.51(16)
C(5)-H(5A)	1.0000	C(1)-C(2)-H(2A)	107.9	C(9)-C(10)-H(10A)	120.2
C(6)-H(6A)	0.9800	C(4)-N(3)-C(2)	123.09(12)	C(11)-C(10)-H(10A)	120.2
C(6)-H(6B)	0.9800	C(4)-N(3)-H(3N)	120.2(11)	C(10)-C(11)-C(12)	120.36(17)
C(6)-H(6C)	0.9800	C(2)-N(3)-H(3N)	116.6(11)	C(10)-C(11)-H(11A)	119.8
C(7)-C(12)	1.388(2)	O(4)-C(4)-N(3)	124.76(13)	C(12)-C(11)-H(11A)	119.8
C(7)-C(8)	1.394(2)	O(4)-C(4)-C(5)	120.53(12)	C(7)-C(12)-C(11)	120.52(15)
C(8)-C(9)	1.384(3)	N(3)-C(4)-C(5)	114.71(11)	C(7)-C(12)-H(12A)	119.7
C(8)-H(8A)	0.9500	C(13)-C(5)-C(6)	110.63(11)	C(11)-C(12)-H(12A)	119.7
C(9)-C(10)	1.377(3)	C(13)-C(5)-C(4)	109.58(11)	F(1)-C(13)-F(2)	107.04(12)
C(9)-H(9A)	0.9500	C(6)-C(5)-C(4)	111.40(11)	F(1)-C(13)-F(3)	106.51(12)
C(10)-C(11)	1.382(3)	C(13)-C(5)-H(5A)	108.4	F(2)-C(13)-F(3)	106.43(12)
C(10)-H(10A)	0.9500	C(6)-C(5)-H(5A)	108.4	F(1)-C(13)-C(5)	112.90(12)
C(11)-C(12)	1.393(2)	C(4)-C(5)-H(5A)	108.4	F(2)-C(13)-C(5)	112.70(12)
C(11)-H(11A)	0.9500	C(5)-C(6)-H(6A)	109.5	F(3)-C(13)-C(5)	110.85(11)
C(12)-H(12A)	0.9500	C(5)-C(6)-H(6B)	109.5		
C(13)-F(1)	1.3322(18)	H(6A)-C(6)-H(6B)	109.5		

Table A.6: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **77**. 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}
C(1)	47(1)	24(1)	27(1)	-2(1)	9(1)	-4(1)
C(2)	21(1)	25(1)	28(1)	-7(1)	6(1)	-6(1)
N(3)	17(1)	26(1)	26(1)	-6(1)	5(1)	-4(1)
C(4)	17(1)	18(1)	22(1)	1(1)	2(1)	-2(1)
O(4)	17(1)	31(1)	36(1)	-9(1)	5(1)	-1(1)
C(5)	17(1)	20(1)	21(1)	-1(1)	1(1)	0(1)
C(6)	30(1)	30(1)	22(1)	-3(1)	7(1)	-2(1)
C(7)	23(1)	23(1)	26(1)	-3(1)	2(1)	6(1)
C(8)	41(1)	38(1)	33(1)	-6(1)	-3(1)	-8(1)
C(9)	55(1)	40(1)	30(1)	-7(1)	-7(1)	4(1)
C(10)	49(1)	41(1)	25(1)	2(1)	6(1)	18(1)
C(11)	41(1)	47(1)	33(1)	5(1)	10(1)	1(1)
C(12)	29(1)	34(1)	28(1)	-2(1)	4(1)	-4(1)
C(13)	24(1)	21(1)	25(1)	-1(1)	2(1)	-1(1)
F(1)	42(1)	31(1)	31(1)	4(1)	13(1)	-7(1)
F(2)	35(1)	25(1)	41(1)	5(1)	-1(1)	7(1)
F(3)	45(1)	25(1)	38(1)	-5(1)	-1(1)	-12(1)

Table A.7: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **77**.

	x	y	z	U(eq)
H(1A)	7692	-5475	3240	48
H(1B)	9968	-5187	2498	48
H(1C)	7161	-6021	2088	48
H(2A)	4610	-3863	2255	29
H(3N)	9690(6)	-2510(20)	3087(13)	28(4)
H(5A)	9496	-1039	4415	23
H(6A)	7171	266	5595	41
H(6B)	6136	-1412	5511	41
H(6C)	4265	-128	4956	41
H(8A)	4086	-4786	509	46
H(9A)	4823	-4416	-1163	51
H(10A)	8203	-2772	-1547	46
H(11A)	10822	-1478	-246	48
H(12A)	10126	-1861	1438	36

Table A.8: Torsion angles [°] for **77**.

C(7)-C(2)-N(3)-C(4)	114.12(15)	C(2)-C(7)-C(8)-C(9)	-175.55(16)
C(1)-C(2)-N(3)-C(4)	-122.35(14)	C(7)-C(8)-C(9)-C(10)	-0.7(3)
C(2)-N(3)-C(4)-O(4)	1.1(2)	C(8)-C(9)-C(10)-C(11)	-0.4(3)
C(2)-N(3)-C(4)-C(5)	-179.48(12)	C(9)-C(10)-C(11)-C(12)	0.8(3)
O(4)-C(4)-C(5)-C(13)	-89.75(16)	C(8)-C(7)-C(12)-C(11)	-1.2(2)
N(3)-C(4)-C(5)-C(13)	90.82(14)	C(2)-C(7)-C(12)-C(11)	175.74(16)
O(4)-C(4)-C(5)-C(6)	33.00(18)	C(10)-C(11)-C(12)-C(7)	0.0(3)
N(3)-C(4)-C(5)-C(6)	-146.42(12)	C(6)-C(5)-C(13)-F(1)	179.47(12)
N(3)-C(2)-C(7)-C(12)	22.0(2)	C(4)-C(5)-C(13)-F(1)	-57.32(15)
C(1)-C(2)-C(7)-C(12)	-101.06(17)	C(6)-C(5)-C(13)-F(2)	-59.10(15)
N(3)-C(2)-C(7)-C(8)	-161.08(14)	C(4)-C(5)-C(13)-F(2)	64.11(15)
C(1)-C(2)-C(7)-C(8)	75.84(17)	C(6)-C(5)-C(13)-F(3)	60.06(15)
C(12)-C(7)-C(8)-C(9)	1.5(3)	C(4)-C(5)-C(13)-F(3)	-176.72(11)

Table A.9: Hydrogen bonds for **77** [Å and °].

D-H...Ad(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3N)...O(4)#1	0.9797(11), 1.942(4), 2.9126(16)		170.7(18)

Symmetry transformations used to generate equivalent atoms: #1 x+1,y,z

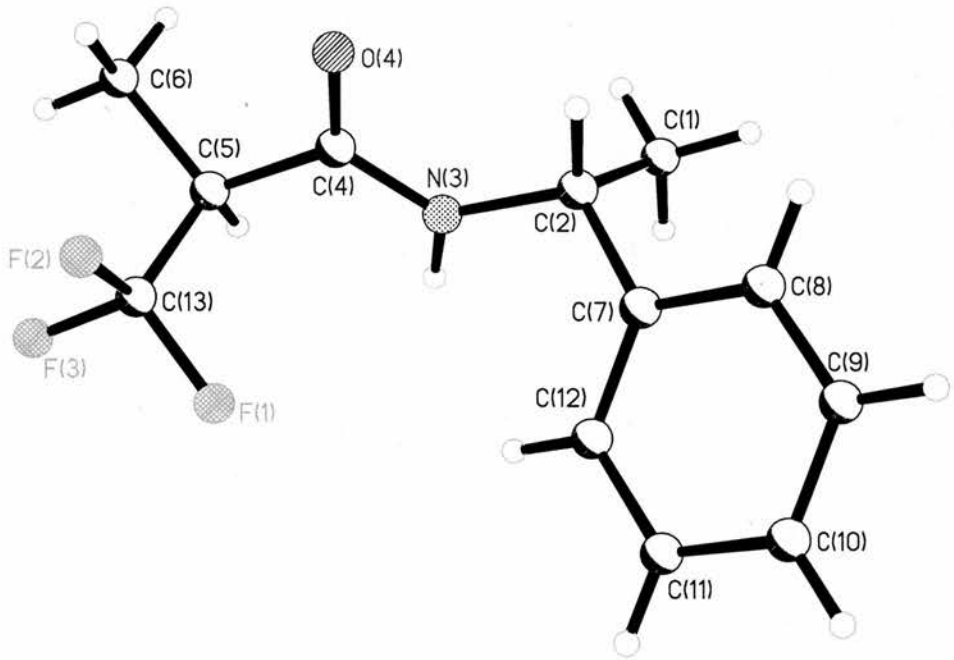

Figure A. 8: X-Ray derived structure of (3*S*)-3,3,3-trifluoro-2-methyl-*N*-[(1*R*)-1-phenyl]propanamide, **77**.

A.3.2 X-Ray data for 12,12,13,13,14,14,15,15-octafluorohexacosanedioic acid, 96

Details of the structure determinations are given in Table A.10.

Table A.10: Crystal data and structure refinement for **96**.

Identification code	**96**	
Empirical formula	$C_{26}H_{42}F_8O_4$	
Formula weight	570.60	
Temperature	125(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 4.9611(15) Å	α= 92.768(5)°.
	b = 6.2541(19) Å	β= 93.277(5)°.
	c = 22.623(7) Å	γ = 100.977(5)°.
Volume	686.7(4) $Å^3$	
Z	1	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.126 mm^{-1}	
F(000)	302	
Crystal size	.15 x .1 x .01 mm^3	
Theta range for data collection	1.81 to 25.38°.	
Index ranges	-5<=h<=5, -7<=k<=6, -26<=l<=27	
Reflections collected	4291	
Independent reflections	2422 [R(int) = 0.0103]	
Completeness to theta = 25.38°	96.1 %	
Absorption correction	MULTISCAN	
Max. and min. transmission	1.00000 and 0.922270	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2422 / 1 / 177	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0393, wR2 = 0.0945	
R indices (all data)	R1 = 0.0544, wR2 = 0.1020	

Extinction coefficient	0.006(3)
Largest diff. peak and hole	0.216 and -0.204 e.Å^{-3}

Table A.11: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **96**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8430(3)	22421(2)	-4907(1)	35(1)
O(2)	7572(3)	25507(2)	-4494(1)	36(1)
C(1)	7109(3)	23414(3)	-4570(1)	25(1)
C(2)	4890(4)	22162(3)	-4233(1)	27(1)
C(3)	6018(3)	20580(3)	-3831(1)	25(1)
C(4)	3764(3)	19123(3)	-3525(1)	26(1)
C(5)	4883(3)	17581(3)	-3117(1)	26(1)
C(6)	2649(3)	15992(3)	-2842(1)	25(1)
C(7)	3779(3)	14459(3)	-2433(1)	25(1)
C(8)	1564(3)	12871(3)	-2151(1)	24(1)
C(9)	2745(3)	11391(3)	-1731(1)	22(1)
C(10)	539(3)	9888(2)	-1423(1)	21(1)
C(11)	1833(3)	8572(2)	-971(1)	20(1)
F(11)	-1943(2)	5608(1)	-1045(1)	25(1)
F(12)	-1969(2)	8225(1)	-373(1)	23(1)
C(12)	-278(3)	7084(2)	-650(1)	18(1)
F(13)	2653(2)	7247(1)	205(1)	21(1)
F(14)	2585(2)	4594(1)	-470(1)	22(1)
C(13)	1006(3)	5774(2)	-183(1)	16(1)

Table A.12: Bond lengths [Å] and angles [°] for **96**.

O(1)-C(1)	1.250(2)	C(12)-C(13)	1.550(2)	C(9)-C(10)-C(11)	111.10(13)
O(2)-C(1)	1.287(2)	F(13)-C(13)	1.3570(16)	C(12)-C(11)-C(10)	112.79(13)
C(1)-C(2)	1.494(2)	F(14)-C(13)	1.3460(17)	F(12)-C(12)-F(11)	106.03(11)
C(2)-C(3)	1.536(2)	C(13)-C(13)#1	1.556(3)	F(12)-C(12)-C(11)	111.12(12)
C(3)-C(4)	1.523(2)	O(1)-C(1)-O(2)	122.84(16)	F(11)-C(12)-C(11)	110.40(12)
C(4)-C(5)	1.523(2)	O(1)-C(1)-C(2)	119.92(14)	F(12)-C(12)-C(13)	108.20(12)
C(5)-C(6)	1.524(2)	O(2)-C(1)-C(2)	117.25(15)	F(11)-C(12)-C(13)	107.44(11)
C(6)-C(7)	1.523(2)	C(1)-C(2)-C(3)	111.26(14)	C(11)-C(12)-C(13)	113.32(12)
C(7)-C(8)	1.525(2)	C(4)-C(3)-C(2)	112.64(13)	F(14)-C(13)-F(13)	108.57(11)
C(8)-C(9)	1.526(2)	C(3)-C(4)-C(5)	112.76(14)	F(14)-C(13)-C(12)	107.24(12)
C(9)-C(10)	1.526(2)	C(4)-C(5)-C(6)	113.64(14)	F(13)-C(13)-C(12)	107.03(11)
C(10)-C(11)	1.531(2)	C(7)-C(6)-C(5)	113.41(14)	F(14)-C(13)-C(13)#1	108.82(14)
C(11)-C(12)	1.506(2)	C(6)-C(7)-C(8)	113.96(14)	F(13)-C(13)-C(13)#1	107.62(14)
F(11)-C(12)	1.3704(16)	C(7)-C(8)-C(9)	113.06(13)	C(12)-C(13)-C(13)#1	117.30(14)
F(12)-C(12)	1.3601(17)	C(10)-C(9)-C(8)	113.13(13)		

Symmetry transformations used to generate equivalent atoms: #1 -x,-y+1,-z

Table A. 13: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **96**. 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)	42(1)	22(1)	44(1)	9(1)	16(1)	4(1)
O(2)	48(1)	19(1)	38(1)	3(1)	14(1)	-5(1)
C(1)	29(1)	19(1)	25(1)	7(1)	-2(1)	1(1)
C(2)	27(1)	21(1)	33(1)	9(1)	5(1)	1(1)
C(3)	28(1)	22(1)	26(1)	8(1)	2(1)	1(1)
C(4)	28(1)	22(1)	28(1)	9(1)	2(1)	1(1)
C(5)	28(1)	20(1)	26(1)	8(1)	2(1)	-1(1)
C(6)	27(1)	22(1)	25(1)	8(1)	2(1)	2(1)
C(7)	27(1)	21(1)	25(1)	8(1)	3(1)	-1(1)
C(8)	25(1)	22(1)	24(1)	8(1)	2(1)	2(1)
C(9)	23(1)	19(1)	23(1)	6(1)	3(1)	2(1)
C(10)	20(1)	21(1)	24(1)	6(1)	0(1)	2(1)
C(11)	18(1)	18(1)	23(1)	6(1)	3(1)	2(1)
F(11)	26(1)	20(1)	24(1)	4(1)	-6(1)	-5(1)
F(12)	22(1)	20(1)	29(1)	8(1)	6(1)	9(1)
C(12)	16(1)	15(1)	21(1)	2(1)	-1(1)	1(1)
F(13)	19(1)	16(1)	24(1)	4(1)	-4(1)	-3(1)
F(14)	21(1)	19(1)	29(1)	7(1)	8(1)	8(1)
C(13)	14(1)	14(1)	21(1)	0(1)	1(1)	1(1)

Table A.14: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **96**.

	x	y	z	U(eq)
H(2O)	8930(40)	26180(40)	-4760(10)	94(9)
H(2A)	3422	21329	-4515	32
H(2B)	4069	23192	-3988	32
H(3A)	7003	19653	-4071	30
H(3B)	7361	21430	-3525	30
H(4A)	2440	18253	-3830	32
H(4B)	2756	20051	-3290	32
H(5A)	6099	18457	-2795	31
H(5B)	6014	16739	-3346	31
H(6A)	1514	16834	-2614	30
H(6B)	1435	15112	-3164	30
H(7A)	5007	15342	-2114	30
H(7B)	4903	13613	-2663	30
H(8A)	365	11956	-2469	28
H(8B)	410	13712	-1928	28
H(9A)	3814	10491	-1959	26
H(9B)	4026	12307	-1427	26
H(10A)	-652	8876	-1723	26
H(10B)	-627	10770	-1219	26
H(11A)	2987	7686	-1178	23
H(11B)	3048	9592	-677	23

Table A.15: Torsion angles [°] for **96**.

O(1)-C(1)-C(2)-C(3)	58.74(19)	C(10)-C(11)-C(12)-F(11)	60.49(16)
O(2)-C(1)-C(2)-C(3)	-121.14(16)	C(10)-C(11)-C(12)-C(13)	-178.94(11)
C(1)-C(2)-C(3)-C(4)	-174.55(13)	F(12)-C(12)-C(13)-F(14)	177.66(10)
C(2)-C(3)-C(4)-C(5)	-178.95(13)	F(11)-C(12)-C(13)-F(14)	63.59(14)
C(3)-C(4)-C(5)-C(6)	-175.69(13)	C(11)-C(12)-C(13)-F(14)	-58.64(15)
C(4)-C(5)-C(6)-C(7)	-179.84(13)	F(12)-C(12)-C(13)-F(13)	-66.00(14)
C(5)-C(6)-C(7)-C(8)	179.52(13)	F(11)-C(12)-C(13)-F(13)	179.93(10)
C(6)-C(7)-C(8)-C(9)	-178.54(12)	C(11)-C(12)-C(13)-F(13)	57.70(16)
C(7)-C(8)-C(9)-C(10)	176.86(12)	F(12)-C(12)-C(13)-C(13)#1	54.96(18)
C(8)-C(9)-C(10)-C(11)	-175.42(12)	F(11)-C(12)-C(13)-C(13)#1	-59.12(19)
C(9)-C(10)-C(11)-C(12)	179.30(12)	C(11)-C(12)-C(13)-C(13)#1	178.65(14)
C(10)-C(11)-C(12)-F(12)	-56.86(16)		

Symmetry transformations used to generate equivalent atoms: #1 -x,-y+1,-z

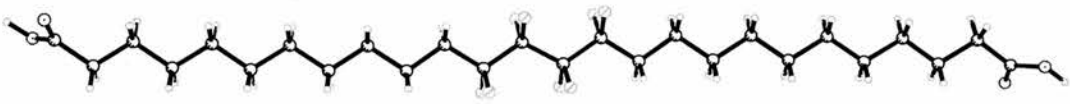

Figure A. 8: X-Ray derived structure of 12,12,13,13,14,14,15,15-octafluorohexacosanedioic acid, **96**.

A.3.3 X-Ray data for 12,12,13,13,14,14,15,15,16,16,7,17-dodecafluorooctacosanedioic acid, 98

Details of the structure determinations are given in Table A.16.

Table A.16: Crystal data and structure refinement for **98**.

Identification code	**98**	
Empirical formula	$C_{28}H_{42}F_{12}O_4$	
Formula weight	670.62	
Temperature	125(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.014(2) Å	α= 96.155(7)°.
	b = 6.202(3) Å	β= 93.431(7)°.
	c = 24.852(11) Å	γ = 100.819(8)°.
Volume	752.1(6) Å^3	
Z	1	
Density (calculated)	1.481 Mg/m^3	
Absorption coefficient	0.146 mm^{-1}	
F(000)	350	
Crystal size	.12 x .1 x .01 mm^3	
Theta range for data collection	1.65 to 25.49°.	
Index ranges	-6<=h<=6, -5<=k<=7,	
	-29<=l<=29	
Reflections collected	4774	
Independent reflections	2663 [R(int) = 0.0302]	
Completeness to theta = 25.49°	95.1 %	
Absorption correction	MULTISCAN	
Max. and min. transmission	1.00000 and 0.690563	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2663 / 1 / 204	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0994, wR2 = 0.2564	
R indices (all data)	R1 = 0.1318, wR2 = 0.2903	

Extinction coefficient	0.008(7)
Largest diff. peak and hole	0.485 and -0.462 e.Å^{-3}

Table A.17: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **98**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	Z	U(eq)
O(1)	13476(8)	12445(6)	5093(2)	43(1)
O(2)	12607(8)	15661(6)	5456(2)	41(1)
C(1)	12144(11)	13542(9)	5390(2)	32(1)
C(2)	9971(10)	12341(8)	5692(2)	31(1)
C(3)	11066(10)	10873(9)	6066(2)	30(1)
C(4)	8853(11)	9459(8)	6338(2)	30(1)
C(5)	9938(10)	8023(8)	6717(2)	28(1)
C(6)	7737(11)	6481(8)	6961(2)	31(1)
C(7)	8858(10)	5036(8)	7345(2)	28(1)
C(8)	6669(10)	3492(8)	7598(2)	27(1)
C(9)	7824(10)	2126(8)	7988(2)	27(1)
C(10)	5658(10)	658(8)	8263(2)	27(1)
C(11)	6951(9)	-552(8)	8678(2)	23(1)
C(12)	4887(9)	-1928(7)	8977(2)	19(1)
F(11)	3240(5)	-714(4)	9218(1)	27(1)
F(12)	3230(6)	-3559(4)	8627(1)	30(1)
C(13)	6218(9)	-3089(7)	9420(2)	20(1)
F(13)	7916(5)	-1490(4)	9751(1)	26(1)
F(14)	7696(5)	-4431(4)	9167(1)	28(1)
C(14)	4270(8)	-4463(7)	9772(2)	16(1)
F(15)	2742(5)	-3160(4)	10020(1)	25(1)
F(16)	2625(5)	-6101(4)	9443(1)	25(1)

Table A.18: Bond lengths [Å] and angles [°] for **98**.

O(1)-C(1)	1.255(6)	C(14)-C(14)#1	1.583(9)	C(9)-C(8)-H(8A)	108.9
O(2)-C(1)	1.282(6)	C(1)-O(2)-H(2O)	101(6)	C(7)-C(8)-H(8A)	108.9
O(2)-H(2O)	0.9800(19)	O(1)-C(1)-O(2)	123.0(5)	C(9)-C(8)-H(8B)	108.9
C(1)-C(2)	1.489(7)	O(1)-C(1)-C(2)	118.9(5)	C(7)-C(8)-H(8B)	108.9
C(2)-C(3)	1.517(7)	O(2)-C(1)-C(2)	118.1(5)	H(8A)-C(8)-H(8B)	107.7
C(2)-H(2A)	0.9900	C(1)-C(2)-C(3)	112.1(4)	C(8)-C(9)-C(10)	113.7(4)
C(2)-H(2B)	0.9900	C(1)-C(2)-H(2A)	109.2	C(8)-C(9)-H(9A)	108.8
C(3)-C(4)	1.519(6)	C(3)-C(2)-H(2A)	109.2	C(10)-C(9)-H(9A)	108.8
C(3)-H(3A)	0.9900	C(1)-C(2)-H(2B)	109.2	C(8)-C(9)-H(9B)	108.8
C(3)-H(3B)	0.9900	C(3)-C(2)-H(2B)	109.2	C(10)-C(9)-H(9B)	108.8
C(4)-C(5)	1.509(7)	H(2A)-C(2)-H(2B)	107.9	H(9A)-C(9)-H(9B)	107.7
C(4)-H(4A)	0.9900	C(2)-C(3)-C(4)	113.3(4)	C(11)-C(10)-C(9)	111.2(4)
C(4)-H(4B)	0.9900	C(2)-C(3)-H(3A)	108.9	C(11)-C(10)-H(10A)	109.4
C(5)-C(6)	1.519(6)	C(4)-C(3)-H(3A)	108.9	C(9)-C(10)-H(10A)	109.4
C(5)-H(5A)	0.9900	C(2)-C(3)-H(3B)	108.9	C(11)-C(10)-H(10B)	109.4
C(5)-H(5B)	0.9900	C(4)-C(3)-H(3B)	108.9	C(9)-C(10)-H(10B)	109.4
C(6)-C(7)	1.530(7)	H(3A)-C(3)-H(3B)	107.7	H(10A)-C(10)-H(10B)	108.0
C(6)-H(6A)	0.9900	C(5)-C(4)-C(3)	113.4(4)	C(12)-C(11)-C(10)	112.8(4)
C(6)-H(6B)	0.9900	C(5)-C(4)-H(4A)	108.9	C(12)-C(11)-H(11A)	109.0
C(7)-C(8)	1.527(6)	C(3)-C(4)-H(4A)	108.9	C(10)-C(11)-H(11A)	109.0
C(7)-H(7A)	0.9900	C(5)-C(4)-H(4B)	108.9	C(12)-C(11)-H(11B)	109.0
C(7)-H(7B)	0.9900	C(3)-C(4)-H(4B)	108.9	C(10)-C(11)-H(11B)	109.0
C(8)-C(9)	1.512(7)	H(4A)-C(4)-H(4B)	107.7	H(11A)-C(11)-H(11B)	107.8
C(8)-H(8A)	0.9900	C(4)-C(5)-C(6)	114.0(4)	F(11)-C(12)-F(12)	106.2(3)
C(8)-H(8B)	0.9900	C(4)-C(5)-H(5A)	108.8	F(11)-C(12)-C(11)	111.5(4)
C(9)-C(10)	1.526(6)	C(6)-C(5)-H(5A)	108.8	F(12)-C(12)-C(11)	110.8(4)
C(9)-H(9A)	0.9900	C(4)-C(5)-H(5B)	108.8	F(11)-C(12)-C(13)	108.2(4)
C(9)-H(9B)	0.9900	C(6)-C(5)-H(5B)	108.7	F(12)-C(12)-C(13)	107.1(3)
C(10)-C(11)	1.521(7)	H(5A)-C(5)-H(5B)	107.6	C(11)-C(12)-C(13)	112.8(4)
C(10)-H(10A)	0.9900	C(5)-C(6)-C(7)	113.6(4)	F(13)-C(13)-F(14)	108.7(4)
C(10)-H(10B)	0.9900	C(5)-C(6)-H(6A)	108.8	F(13)-C(13)-C(14)	108.2(4)
C(11)-C(12)	1.500(6)	C(7)-C(6)-H(6A)	108.8	F(14)-C(13)-C(14)	108.3(4)
C(11)-H(11A)	0.9900	C(5)-C(6)-H(6B)	108.8	F(13)-C(13)-C(12)	106.8(4)
C(11)-H(11B)	0.9900	C(7)-C(6)-H(6B)	108.8	F(14)-C(13)-C(12)	107.5(4)
C(12)-F(11)	1.343(5)	H(6A)-C(6)-H(6B)	107.7	C(14)-C(13)-C(12)	117.0(4)
C(12)-F(12)	1.371(5)	C(8)-C(7)-C(6)	114.2(4)	F(15)-C(14)-F(16)	108.8(3)
C(12)-C(13)	1.561(6)	C(8)-C(7)-H(7A)	108.7	F(15)-C(14)-C(13)	109.1(3)
C(13)-F(13)	1.345(5)	C(6)-C(7)-H(7A)	108.7	F(16)-C(14)-C(13)	108.3(3)
C(13)-F(14)	1.346(5)	C(8)-C(7)-H(7B)	108.7	F(15)-C(14)-C(14)#1	107.5(4)
C(13)-C(14)	1.548(6)	C(6)-C(7)-H(7B)	108.7	F(16)-C(14)-C(14)#1	108.1(4)
C(14)-F(15)	1.342(5)	H(7A)-C(7)-H(7B)	107.6	C(13)-C(14)-C(14)#1	114.9(4)
C(14)-F(16)	1.344(5)	C(9)-C(8)-C(7)	113.3(4)		

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y-1,-z+2

Table A.19: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **98**. 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)	38(2)	29(2)	66(3)	11(2)	24(2)	6(2)
O(2)	43(2)	21(2)	57(3)	4(2)	22(2)	-6(2)
C(1)	27(3)	24(3)	45(3)	8(2)	5(2)	3(2)
C(2)	23(3)	22(3)	51(3)	11(2)	14(2)	4(2)
C(3)	25(3)	23(3)	43(3)	8(2)	8(2)	-1(2)
C(4)	25(3)	24(3)	43(3)	9(2)	12(2)	5(2)
C(5)	23(3)	21(3)	43(3)	11(2)	10(2)	1(2)
C(6)	26(3)	22(3)	42(3)	11(2)	9(2)	-3(2)
C(7)	18(2)	24(3)	43(3)	9(2)	11(2)	4(2)
C(8)	20(2)	23(3)	40(3)	8(2)	10(2)	1(2)
C(9)	21(3)	23(3)	40(3)	12(2)	9(2)	4(2)
C(10)	22(3)	17(2)	42(3)	8(2)	7(2)	1(2)
C(11)	14(2)	18(2)	37(3)	8(2)	11(2)	1(2)
C(12)	11(2)	11(2)	36(3)	3(2)	9(2)	2(2)
F(11)	18(1)	24(2)	47(2)	14(1)	16(1)	13(1)
F(12)	25(2)	20(2)	41(2)	8(1)	1(1)	-7(1)
C(13)	12(2)	15(2)	34(2)	2(2)	10(2)	4(2)
F(13)	14(1)	20(2)	42(2)	7(1)	3(1)	-6(1)
F(14)	18(2)	22(2)	49(2)	10(1)	16(1)	12(1)
C(14)	6(2)	8(2)	34(2)	0(2)	7(2)	1(2)
F(15)	16(1)	21(2)	46(2)	12(1)	16(1)	12(1)
F(16)	15(1)	17(1)	42(2)	7(1)	2(1)	-5(1)

Table A.20: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **98**.

	x	y	z	U(eq)
H(2O)	13960(160)	16000(180)	5190(30)	140(40)
H(2A)	8535	11423	5429	37
H(2B)	9131	13429	5909	37
H(3A)	12372	11814	6350	36
H(3B)	12071	9893	5854	36
H(4A)	7829	10439	6545	36
H(4B)	7564	8502	6054	36
H(5A)	11124	8988	7015	34
H(5B)	11078	7126	6516	34
H(6A)	6553	5512	6663	37
H(6B)	6595	7376	7162	37
H(7A)	9989	4135	7143	33
H(7B)	10058	6009	7641	33
H(8A)	5506	4385	7793	32
H(8B)	5501	2485	7304	32
H(9A)	9067	3133	8271	33
H(9B)	8915	1181	7788	33
H(10A)	4487	1578	8447	32
H(10B)	4492	-435	7985	32
H(11A)	8055	-1519	8490	27
H(11B)	8193	545	8943	27

Table A.21: Torsion angles [°] for **98**.

O(1)-C(1)-C(2)-C(3)	58.2(7)	C(11)-C(12)-C(13)-F(13)	55.7(5)
O(2)-C(1)-C(2)-C(3)	-120.2(5)	F(11)-C(12)-C(13)-F(14)	175.3(3)
C(1)-C(2)-C(3)-C(4)	-174.4(4)	F(12)-C(12)-C(13)-F(14)	61.3(4)
C(2)-C(3)-C(4)-C(5)	-179.1(4)	C(11)-C(12)-C(13)-F(14)	-60.9(5)
C(3)-C(4)-C(5)-C(6)	-175.9(4)	F(11)-C(12)-C(13)-C(14)	53.3(5)
C(4)-C(5)-C(6)-C(7)	-179.9(4)	F(12)-C(12)-C(13)-C(14)	-60.7(5)
C(5)-C(6)-C(7)-C(8)	179.5(4)	C(11)-C(12)-C(13)-C(14)	177.1(4)
C(6)-C(7)-C(8)-C(9)	-178.4(4)	F(13)-C(13)-C(14)-F(15)	63.5(4)
C(7)-C(8)-C(9)-C(10)	177.2(4)	F(14)-C(13)-C(14)-F(15)	-178.8(3)
C(8)-C(9)-C(10)-C(11)	-176.1(4)	C(12)-C(13)-C(14)-F(15)	-57.2(5)
C(9)-C(10)-C(11)-C(12)	177.2(4)	F(13)-C(13)-C(14)-F(16)	-178.2(3)
C(10)-C(11)-C(12)-F(11)	-55.6(5)	F(14)-C(13)-C(14)-F(16)	-60.6(5)
C(10)-C(11)-C(12)-F(12)	62.5(5)	C(12)-C(13)-C(14)-F(16)	61.1(5)
C(10)-C(11)-C(12)-C(13)	-177.5(4)	F(13)-C(13)-C(14)-C(14)#1	-57.3(5)
F(11)-C(12)-C(13)-F(13)	-68.1(4)	F(14)-C(13)-C(14)-C(14)#1	60.4(6)
F(12)-C(12)-C(13)-F(13)	177.8(3)		

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y-1,-z+2

Table A.22: Hydrogen bonds for **98** [Å and °].

D-H...Ad(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2O)...O(1)#2	0.9800(19),	1.70(4), 2.626(5)	157(10)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y-1,-z+2 #2 -x+3,-y+3,-z+1

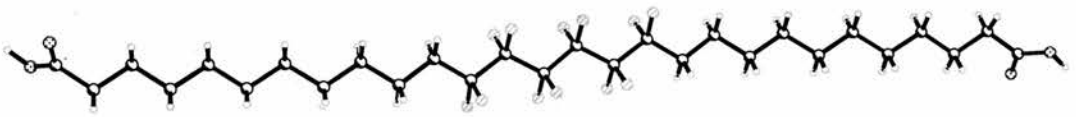

Figure A. 8: X-Ray derived structure of 12,12,13,13,14,14,15,15,16,16,17,17-dodecafluorooctacosanedioic acid, **98**.

A.4 Appendix 4: Additional information

A.4.1 Publications

A.4.1.1 MSc publication

- P. Beier, J. Mindl, V. Štěrba and J. Hanusek, *Org. Biomol. Chem.*, 2004, **2**, 562. *Kinetics and mechanism of base-catalysed degradations of substituted aryl-N-hydroxycarbamates, their N-methyl and N-phenyl analogues.*

A.4.1.2 PhD publications

- P. Beier and D. O'Hagan, *Chem. Commun.,* 2002, 1680. *Enantiomeric partitioning using fluorous biphase methodology for lipase-mediated (trans)esterifications.*
- P. Beier and D. O'Hagan D, *Handbook of Fluorous Chemistry*, ed. by J. A. Gladysz, D. P. Curran and I. T. Horváth, Wiley, Weinheim, 2004, 333 (one chapter).
- P. Beier, M. Z. Slawin and D. O'Hagan, *Tetrahedron: Asymmetry*, 2004, **15**, 2447. *Lipase mediated preparation of the enantiomers of 3,3,3-trifluoro-2-methylpropanoic acid.*
- P. Beier, D. O'Hagan, C. Pearson, M. C. Petty and A. M. Z. Slawin, *J. Fluorine Chem.*, 2004, **125**, (in press). *The structure and properties of hybrid fluorous-hydrocarbon fatty acids.*

A.4.2 Conferences and meetings attended

- TRA (Polymer Materials), COST (Fluorous Medium as a Tool for Environmentally Compatible Oxidation Processes) and RTN (Development of Fluorous Phase Technology for Oxidation Processes) joint meeting, University of Padova, Padova, Italy, 13th-17th February, 2002- **Poster presented.**
- 13th Scottish Graduate Symposium on Novel Organic Chemistry, University of St. Andrews, St. Andrews, 11th April, 2002.
- RSC Fluorine Subject Group Postgraduate Meeting, University of Manchester, Manchester, 4th September, 2002- **Poster presented.**
- The Merck Lectureship Reunion (Celebrating 15 years of the Merck Lectureship and the Chemistry of Ian Fleming, Tony Kirby and Jim Stauton), University of Cambridge, Cambridge, 22th-25th September, 2002.
- RTN (Development of Fluorous Phase Technology for Oxidation Processes) annual meeting, University of St. Andrews, St. Andrews, 17th-20th October, 2002- **Oral presentation.**
- 31st Scottish Regional Perkin Meeting for the Reading of Original Papers, University of Dundee, Dundee, 18th December, 2002.
- 14th Scottish Graduate Symposium on Novel Organic Chemistry, University of Aberdeen, Aberdeen, 9th April, 2003.
- RTN (Development of Fluorous Phase Technology for Oxidation Processes) annual meeting, Budapest, Hungary, 5th-8th June, 2003- **Oral presentation.**
- 3rd RSC Fluorine Subject Group Postgraduate Meeting, University of St. Andrews, St. Andrews, 4th-5th September, 2003- **Poster presented.**
- 32nd Scottish Regional Perkin Meeting for the Reading of Original Papers, University of Edinburgh, Edinburgh, 17th December, 2003.

- SCI Young Chemists' Panel Review Meeting (Organic synthesis: It's not just carbon), University of Strathclyde, Glasgow, 9th January 2004.
- RTN (Development of Fluorous Phase Technology for Oxidation Processes) annual meeting, Milan, Italy, 5th-7th March, 2004- **Oral presentation.**
- 14th European Symposium on Fluorine Chemistry, Adam Mickiewicz University, Poznań, Poland, 11th-16th July, 2004- **Poster presented.**
- 4th RSC Fluorine Subject Group Postgraduate Meeting, University of Durham, Durham, 2nd-3rd September, 2004- **Oral presentation.**