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**The Synthesis of Novel Fluorine-  
Containing Natural and Unnatural  
Compounds**

**Submitted by**

**Levan Pivnevi**

**to The Open University as a thesis for the degree of  
Doctor of Philosophy in Chemistry.**

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## Abstract

The project was divided into three parts:

### 1. Synthesis of perfluoro (highly fluorinated chain) compounds

The aim was to prepare modified phosphorous and nitrogen containing organic molecules by attaching to them highly fluorinated tags. A review of the current literature in the area is given. The fluorous compounds at room temperature are typically immiscible with organic solvents and water. The method gives an advantage of simple liquid-liquid separation and in some cases an opportunity to recover partially the starting materials.

### 2. Synthesis of fluorine containing heterocyclic compounds

The incorporation of fluorine in heterocyclic compounds may have only a small effect on their conformation, but may have a large electronic effect. This may give rise to novel biological activity. A review of the current literature in the area is given. Using simple aldehydes as starting materials, in the presence of Lewis acids, a straightforward procedure has been developed to prepare fluorinated heterocycles.

### 3. Synthesis of heterocyclic natural products

Using a related method to the one previously developed in part 2, the same Lewis acid promoted reaction has been applied to the total synthesis of two physiologically active natural products.

Finally, the experimental details for each of the above three sections will be given.

The work described in this thesis is the author's own work, accept where appropriate reference is made. Work previously published by a colleague (*Tetrahedron Lett.*, **2002**, *43*, 2807-2810<sup>66a</sup>) has been repeated herein and the results optimised.

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**Abbreviations**

Ac	Acetyl
acac	acetylacetone
Ar	Aryl
ATPH	Aluminium <i>tris</i> (2,6-diphenylphenoxide)
Bn	Benzyl
Bu	Butyl
BTF	Benzotrifluoride, C <sub>6</sub> H <sub>5</sub> CF <sub>3</sub>
Bz	Benzoyl
C	Concentration
CI	Chemical ionisation
Cp	Cyclopentadienyl
DAST	Diethylaminosulfurtrifluoride
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL-H	<i>Diisobutyl</i> aluminium hydride
DMSO	Dimethyl sulfoxide
EI	Electron impact
eq.	Equivalent
FBC	Fluorous Biphasic Catalysis
FBS	Fluorous Biphasic System
FC-72	Perfluorohexane
<sup>F</sup> DEAD	Fluorous Diethyldiazocarboxilate
fod	<i>tris</i> -(6,6,7,7,8,8,8)Heptafluoro-2,2-dimethyl-3,5-octanedionate
FRPS	Fluorous Reverse Phase Silica
GC	Gas chromatography
h	Hours
Hal	Halogen
HLE	Horse liver esterase
Hz	Hertz
IR	Infra red



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ISMS	Intramolecular silyl modified Sakurai
kJ	Kilojoule
LDA	Lithium diisopropylamide
M	Molarity
MABR	methylaluminium bis(4-bromo-2,6-di- <i>tert</i> -butylphenoxide)
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
MAD	methylaluminium bis(2,6-di- <i>tert</i> -butyl-4-methylphenoxide)
MAPH	methylaluminium bis(2,6-diphenylphenoxide)
Ms	Mesyl (methanesulfonyl)
MHz	megahertz
MOM	Methoxymethyl
Mp	Melting point
MS	Mass spectrometry
<i>m/z</i>	mass to charge ratio
NBS	N-Bromosuccinimide
nm	Nanometer
NMO	4-Methylmorpholine <i>N</i> -oxide
NOE	Nuclear Overhauser enhancement
NMR	Nuclear magnetic resonance
Nu	Nucleophile
P	Protecting group
Ph	Phenyl
Petrol	Petroleum ether (40-60 °C)
Piv	Pivaloyl
PFMC	Perfluoromethylcyclohexane
PMHS	Polymethylhydrosiloxane
PPL	Porcine pancreatic lipase
ppm	parts per million
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Pr	Propyl
Py	Pyridine
RCM	Ring closing metathesis

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rt	room temperature
TBC	Twist-boat-chair
TDP	4,4'-Thiodiphenol
TEMPO	Tetramethylpiperidine-1-oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
tol	Toluene
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBDPS	<i>tert</i> -Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	<i>p</i> -Toluenesulfonyl
WSPA	World Society for the Protection of Animals

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**Chapter 1**  
**INTRODUCTION**

## 1.1 Introduction to Organofluorine Chemistry

Fluorine is the ninth element in the Periodic Table with an exact atomic mass of 18.998. It is a member of group VII, the halogens. Fluorine constitutes 0.078% of the earth's crust and on limited occasions free fluorine has been encountered in minerals. The most important fluorine-containing mineral is fluorospar – calcium difluoride  $\text{CaF}_2$ . Fluoride ion is found in natural water as well as seawater (0.3 mg per litre).

Fluorine is a pale yellow colour halogen gas, reacting easily at room temperature with all metals. The metals, which do not burn, obtain a protective covering of the corresponding metal fluoride. Nickel and some middle weight metal alloys are used to handle fluorine on a large scale.<sup>1</sup>

Emeleus defined three main factors to explain why the chemistry of fluorine is different from the other halogens:

### 1. *The low bond dissociation energy of the fluorine molecule*

**Table 1:** The bond dissociation energies of the halogen-halogen bond:<sup>1</sup>

$$D(\text{F}_2) = 158 \text{ kJ/mol}$$

$$D(\text{Cl}_2) = 242 \text{ kJ/mol}$$

$$D(\text{Br}_2) = 193 \text{ kJ/mol}$$

$$D(\text{I}_2) = 151 \text{ kJ/mol}$$

It is interesting to note that although iodine has nearly the same bond dissociation value as fluorine, it creates much weaker bonds. Thus, the formation of fluorides releases more energy.

### 2. *The relatively high strength of bonds formed between fluorine and non-metallic elements*

**Table 2:** Assorted bond strengths<sup>1</sup>

$$\text{H-F (HF)} = 565 \text{ kJ/mol}$$

$$\text{H-Cl (HCl)} = 431 \text{ kJ/mol}$$

$$\text{H-Br (HBr)} = 364 \text{ kJ/mol}$$

$$\text{H-I (HI)} = 297 \text{ kJ/mol}$$

$$\text{C-F (CF}_4\text{)} = 485 \text{ kJ/mol}$$

$$\text{C-Cl (CCl}_4\text{)} = 326 \text{ kJ/mol}$$

$$\text{C-Br (CBr}_4\text{)} = 242 \text{ kJ/mol}$$

$$\text{C-I (CI}_4\text{)} = 238 \text{ kJ/mol}$$

---

### 3. The relatively small size of the fluorine atom and the fluoride ion<sup>2</sup>

**Table 3:** Comparative radii of various elements

	Covalent radius, nm:	Ionic radius, nm:
F	0.064	0.136
Cl	0.099	0.181
Br	0.114	0.195
I	0.133	0.216
O	0.066	0.140

As shown in Table 3, the radii of  $F^-$  and  $O^{2-}$  are nearly the same. This factor leads to a close similarity in the structures of many ionic fluorides and oxides of the same type.<sup>2</sup>

For many years, the fluorine containing mineral fluorospar has been used as a metallurgical flux. The first studies were done by Marggraf in 1768 by distillation of fluorospar with sulfuric acid.<sup>1</sup> However, elemental fluorine was first isolated in 1886 by Moissan<sup>3</sup>, and a decade later the Belgian chemist Swarts described the synthesis of methyl fluoroacetate by heating methyl iodoacetate with silver fluoride.<sup>4</sup> This synthesis heralded the beginnings of modern fluoro-organic chemistry and later, in 1922, Swarts prepared trifluoroacetic acid<sup>5</sup> and by doing so, laid the foundations for all subsequent organofluorine chemistry. Numerous fluorocarbons were prepared in the years following, for example fluorocarbon polymers (thermally and chemically stable refrigerants and lubricants) and, more recently, aerosol propellants, fire extinguishing agents, anesthetics and blood substitutes.

The biological effects of introducing fluorine into organic molecules were first studied during World War II by both British and German scientists, but it was the demonstration by Marais, in 1943,<sup>5</sup> that the toxicity of the South African plant *Dichapetalum cymosum* was due to monofluoroacetate that provided the impetus for studies on the toxicology and pharmacology of organofluorine compounds. Later studies<sup>6,7</sup> revealed that monofluoroacetate is incorporated into the citric acid cycle, and the enzyme aconitase becomes completely and irreversibly inhibited. This had significant implications for the rational design of enzyme inhibitors, which can be used to great effect in the pharmaceutical industry.

Research in the early 1950s led to the discovery that certain fluorosteroids can actually surpass naturally occurring hormones in their biological activity.<sup>8</sup> The discovery boosted enormously the research in dealing with the introduction of fluorine at specific sites in biologically active molecules. Nowadays such fluorinated analogues are highly desirable targets and research into new synthetic routes to organofluorine compounds continues.

## 1.2 The Effects of Introducing Fluorine Into Organic Molecules

There are three main explanations as to why the introduction of fluorine can lead to desirable changes in the properties and biological activity of organic compounds:<sup>9</sup>

### (i) *Steric Effects*

Fluorine has a van der Waals radius of 0.155 nm making it the smallest substituent after hydrogen (van der Waals radius 0.12nm). Also, the average C-F bond length (0.138 nm) is only marginally greater than the average C-H bond length (0.108 nm).

The size of fluorine is also comparable to that of the hydroxyl group, with the van der Waal radius of oxygen being 0.150 nm. The average C-O bond length is 0.143 nm which, again, is very similar to the average C-F bond length.<sup>10</sup>

### (ii) *Electronic Effects*

Fluorine has an electronegativity value of 4.0 on the Pauling electronegativity index and is the most electronegative of all the elements. This is very much greater than hydrogen, which has a value of just 2.1. Oxygen however, with a value of 3.5, is also highly electronegative and thus fluorine may be able to mimic oxygen and function as a hydrogen bond acceptor.

The high electronegativity of fluorine creates a large  $\delta^+$  on adjacent carbon centres and since fluoride is a relatively good leaving group, nucleophilic attack may occur on the adjacent carbon, displacing the fluoride and leaving the possibility of the remaining organic moiety covalently bonded to another organic compound, for example an enzyme. Having said this, the C-F bond is strong,  $485 \text{ kJmol}^{-1}$ , thus protecting it from unwanted metabolic transformations.<sup>10</sup> Substitution of a hydrogen atom or hydroxyl group by fluorine in

enzyme substrate analogues is widely used in various fields of bioorganic and medicinal chemistry.<sup>11</sup>

The presence of fluorine has a marked effect on the  $pK_a$  value of the most acidic hydrogen/hydrogens in a molecule. For example the  $pK_a$  of acetic acid,  $CH_3COOH$  is 4.76, and the substitution of a single hydrogen on the methyl group for a single fluorine to give fluoroacetic acid,  $CH_2FCOOH$ , increases the acidity to give a  $pK_a$  value of 2.66.<sup>10</sup>

### *(iii) Lipophilicity*

Any C-F bonds in a molecule will substantially increase its lipophilicity. This is of considerable importance in drug design since crossing the phospholipid bilayer of cell membranes is essential if the drug is designed to act within the cell.

## **1.3 Specific Replacements**

The prospects discussed in section 1.2, either individually or in combination, may lead to specific effects when certain atoms or functional groups are replaced by the corresponding number of fluorine atoms.

### *(i) Replacement for Hydrogen*

Replacement of a single hydrogen atom with fluorine introduces only a small steric and geometric perturbation relative to the hydrocarbon counterpart,<sup>12</sup> and if the replacement is within an analogue of an enzyme substrate, the affinity for the target enzyme is usually high.<sup>11</sup> The close isosteric relationship between fluorine and hydrogen, due to the van der Waals radii and bond lengths mentioned in 1.2, makes the introduction of a single fluorine into a biologically active molecule a very useful step since the compound can benefit enormously from the increased lipophilicity and the other unique properties fluorine creates without compromising compatibility for the target.

### *(ii) Replacement for the Hydroxyl Group*

The capacity for organofluorine compounds to act as a hydroxyl mimic has been widely discussed,<sup>13,14</sup> but recent theoretical and crystallographic evidence force the conclusion that fluorine is a poor hydrogen bond acceptor with only a moderate capacity to replace oxygen, or indeed nitrogen, in this role.<sup>11</sup> Although there are examples in the literature which



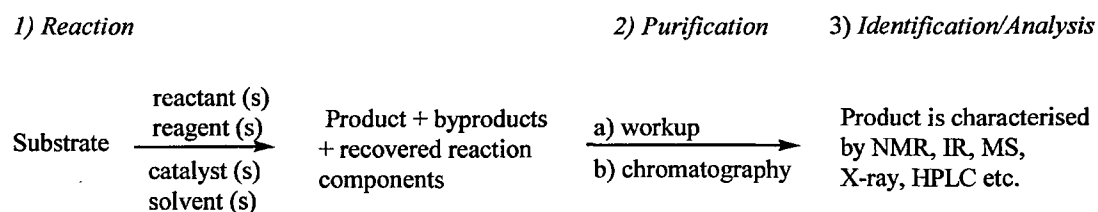
clearly suggest that fluorine can replace OH as a hydrogen bond acceptor, more often than not the substitution proves detrimental<sup>15</sup> since hydrogen bonding is probably the most significant interaction when considering enzyme substrate binding.

### (iii) Replacement for the Ethylene Group

The most significant effect of introducing the CF<sub>2</sub> group into an organic molecule is the difference in bond angle between C-CH<sub>2</sub>-C and C-CF<sub>2</sub>-C. The C-CH<sub>2</sub>-C bond angle is typically 109° whereas the C-CF<sub>2</sub>-C angle ranges from 111° to 119.9°. The introduction of the difluoromethyl group can, therefore, lead to conformational changes in the rest of the molecule, which can alter the physical properties in relation to its hydrocarbon counterpart. In this respect CF<sub>2</sub> is a less than ideal CH<sub>2</sub> mimic for biochemical applications.<sup>16</sup>

## 1.4 Introduction to Fluorous Chemistry

The yield of all chemical reactions are limited both by the efficiency of the reaction and also by the ability to obtain pure product. The transformation of a starting material into a new, desired product is a process that can be divided into three stages: (Scheme 1)



**Scheme 1:** Stages in organic synthesis.<sup>17</sup>

In the first phase, substrate(s), reagent(s) and solvent(s) are mixed; then in the second phase the product is separated from all impurities and finally in the third phase it is characterised.

The primary purification of an organic mixture by “workup” has changed little over the last few decades. Further, the methods of crystallisation, distillation, chromatography are basically similar to those 20 years ago. The development of combinatorial chemistry and automated parallel synthesis has begun a revolution in the way synthesis is carried out, since these methods require simple purification techniques.

In recent years, several new techniques have developed for the purification of reactions and one of them is fluororous phase chemistry. The initial works were published in the early 1990's, with the most influential by Horváth and Rábai in 1994.<sup>18</sup> Horváth<sup>19</sup> and others<sup>19-24</sup> have since developed, in more in detail, the concept of fluororous chemistry.

The term '*fluororous*' is spreading widely across the chemical community. It is well known as a similar name to '*aqueous*' for water-based systems. Thus, it means highly fluorinated. The term perfluorinated is also widely used and is almost synonymous.

### 1.5 Fluororous Molecules

Fluororous molecules are designed to react and behave as organic analogues in terms of their reactivity, but also be easily separable from other organic molecules by value of their high fluorine content. A typical fluororous molecule includes two domains, a highly fluorinated group, which controls the fluororous solubility of the molecule and an organic domain, which directs the reactivity of the compound and resembles a standard organic molecule. Molecules **2**, **4** are two simple examples of fluororous molecules to illustrate this concept. Their design is based on the parent organic molecules **1** and **3**.

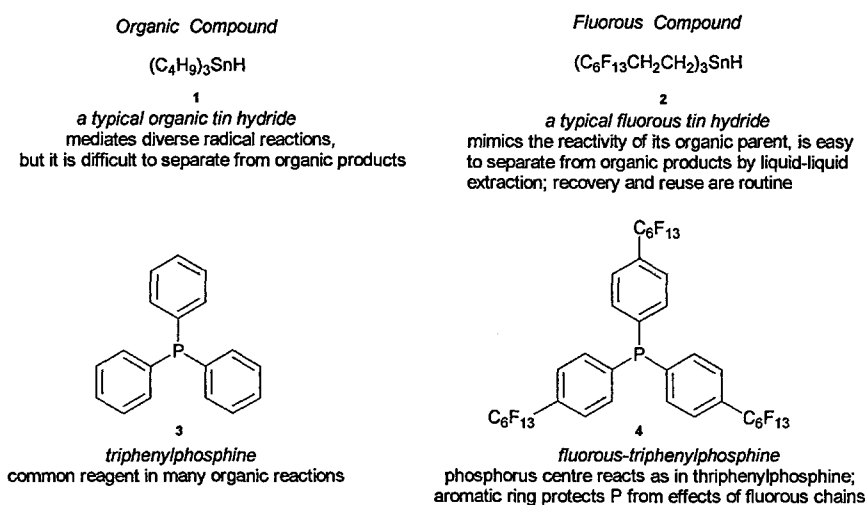


Fig. 1

Phosphine oxides **5** and phosphorus-metal complexes normally are difficult to remove from a reaction mixture, but in the case of having fluororous tags **6** the phosphine oxides can be removed easily by simple liquid-liquid extraction by using a solution of organic and perfluoro solvents to leave the mixture without any phosphine residue.<sup>24</sup>

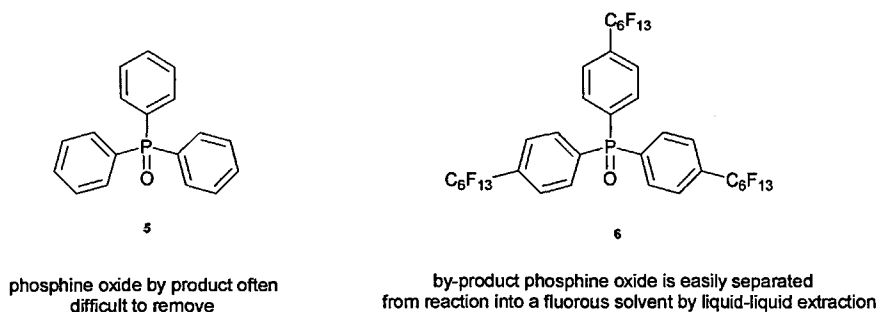


Fig. 2

Fluorous tin compounds are also readily separable from organic compounds using simple fluorous liquid-liquid or solid-liquid extractions. The fluorous tag is always attached to the tin atom, incorporating a short spacer group between the tin and fluorous chain. Tin compounds are recovered at the end of the process and recycled.

### 1.6 Fluorous Solvents

“Fluorous solvent” is a term similar to “fluorous molecule” and means a highly fluorinated solvent. Many are now commercially available from different suppliers (3M, Fluorochem, Lancaster, Aldrich, Oxychem, PCR and Oakwood Products),<sup>24</sup> sold in 80-90% purity. Currently a wide range of fluorous ethers and amines are available and a few of the most commonly used solvents are shown.

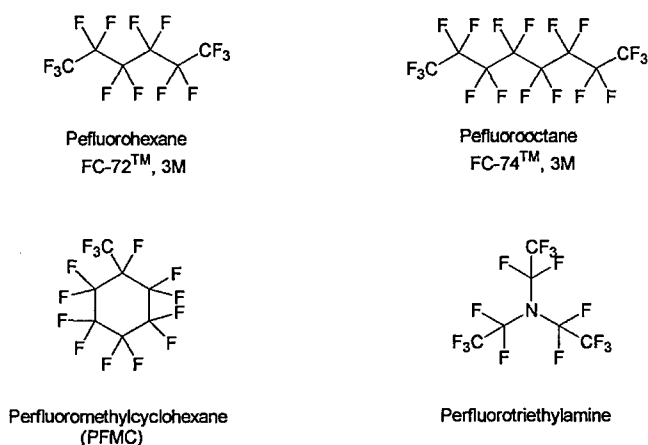


Fig. 3: Example of fluorous solvents

The frequently used solvent perfluorohexane, FC-72 is an analogue of the organic solvent hexane. Fluorous solvents are immiscible with organic or water phases, but this is temperature dependant. At room temperature FC-72 (20 °C) does not mix with most organic solvents and forms a bilayer system. Even a slight rise in temperature can resolve this status quo, the two layers can become miscible at 24 °C depending on the organic solvent. Immiscibility was the paramount factor in early success of fluorous chemistry. Many fluorous chemists still rely on the liquid-liquid extraction technique as the primary technique for the separation.

Chemists are familiar with standard, four phase simple workup-level purification methods: the gas phase, the organic liquid phase, the aqueous liquid phase and the solid phase. Since fluorous chemistry has been adopted by the organic community<sup>18</sup>, it has sometimes been defined as the fifth phase.<sup>21</sup>



Picture is taken from [www.fluorous.com](http://www.fluorous.com)

**Fig. 4**

Liquid-liquid extractions work better when fluorous domains are relatively large. For some cases only a single separation is needed. This method is used when the desired product is organic and other reaction component is fluorous.<sup>25</sup>

However, the costs of perfluoro solvents forced chemists to find alternative solvents for fluorous chemistry. Benzotrifluoride (BTF,  $C_6H_5CF_3$ ) was introduced as a ‘light fluorous’ solvent for use as a reaction medium in place of the traditional organic/fluorous biphase. This solvent gives an advantage of dissolving both organic and fluorous molecules. Also, its price is reasonably low compared to perfluoro solvents.<sup>24</sup> After completing the reaction, BTF can be removed by evaporation and the remaining crude mass extracted by liquid-liquid extraction with organic and fluorous solvents; the desired compound(s) can be

obtained by evaporation from the opposite phase. Thus, no perfluoro solvent is needed during the actual reaction. Fluorous solvents can be stored and re-used many times.

Fluorous molecules, like the solvents, are also expensive compared to their organic analogues. Decreasing the number of fluorine atoms in the molecule lowers the price, but raises the organic solubility of the compound and decreases the fluorous solubility. This effect creates a problem when using liquid-liquid extractions, so 'light fluorous' synthesis uses solid-liquid extractions where possible.

Fluorocarbon-bonded phase silica gel (technically called fluorous reverse-phase silica, FRPS)<sup>26</sup> may be used to adsorb fluorous molecules and separate them from non-adsorbed organic ones. The first case of a silica gel with a fluorocarbon phase was reported in 1978,<sup>27</sup> the silica being silylated with (heptadecafluorodecyl)dimethylsilyl chloride,  $\text{ClSi}(\text{Me})_2\text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$ . Currently, fluorous silica with fluorocarbon phases has been developed and widely used by Fluorous Technologies Inc. including: -  $\text{Si}(\text{Me})_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$  and -  $\text{Si}(\text{Me})_2(\text{CH}_2)_3\text{C}(\text{CF}_3)_2\text{C}_3\text{F}_7$ .<sup>25</sup> Research has shown advantages of fluorous silica over ordinary reverse phase silica gel for analytical and HPLC applications. Fluorous silica also gives an opportunity to separate fluorinated and organic molecules from each other. Organic molecules pass easily through these fluorinated columns while fluorous ones are retained to a high degree. In the separation process, a crude mixture is mixed with appropriate amount of silica gel and the silica is eluted first with a 'fluorophobic' solvent to remove the organic compound while leaving the fluorous compound adsorbed. In situations where the fluorous molecule is desired, a second elution with a 'fluorophilic' solvent gives this material.

In addition, fluorous silica can be used to separate perfluoro compounds on the basis of fluorine content. Curran has employed this technique of fluorous chromatography to separate a number of fluorous compounds based on their fluorine content, from  $\text{C}_3\text{F}_7$  to  $\text{C}_{10}\text{F}_{21}$ .<sup>17,26</sup>

The solid-liquid separations are operationally filtrations and they are easy to manage in parallel settings, either manually or by using various automated techniques. There is no necessity for using fluorous solvents when eluting these fluorous gels. Different organic solvents are normally used, thus reducing operational costs significantly. Solid-liquid extraction can be operated in cases where molecules have fewer fluorines in the fluorous

tag. This method is currently the most common and easily applied fluororous-organic phase separation technique.

### 1.7 Fluororous Biphasic Catalysis

The development of environmentally friendly technologies is one of the most demanding targets of modern chemistry and chemical engineering.<sup>28</sup> Environmentally friendly chemical processes should:

- use environmentally safe compounds and solvents;
- have high product yield
- use efficient reagent or catalyst recycling systems<sup>19</sup>

Acceptance of biphasic liquid-liquid processes, in which a reagent or a catalyst resides in one of the liquid phases and the product moves to the other liquid phase, leads to the commercial applications of many selective reactions. Formation of a liquid-liquid system depends on significantly different intermolecular forces between two liquids.<sup>29</sup> The selection of a catalyst or a reagent mostly depends on the solvent character. The discovery that the miscibility of perfluorocompounds is low with common organic solvents,<sup>30</sup> then lead to the concept of Fluororous Biphasic reactions.<sup>18</sup>

Fluororous Biphasic Catalysis (FBC) was first introduced in 1991, but remained unknown until 1994 when Horváth and Rabái published their work in *Science*.<sup>18</sup> Their seminal paper introduced the idea and terms of FBC, concepts that are now well known by chemists. Since then, the concept of FBC has been at the centre of fluororous chemistry. Large amounts of fluororous catalysts and ligands have been synthesized. The defined feature of FBC is the use of two liquid phases: one fluororous, the other organic.

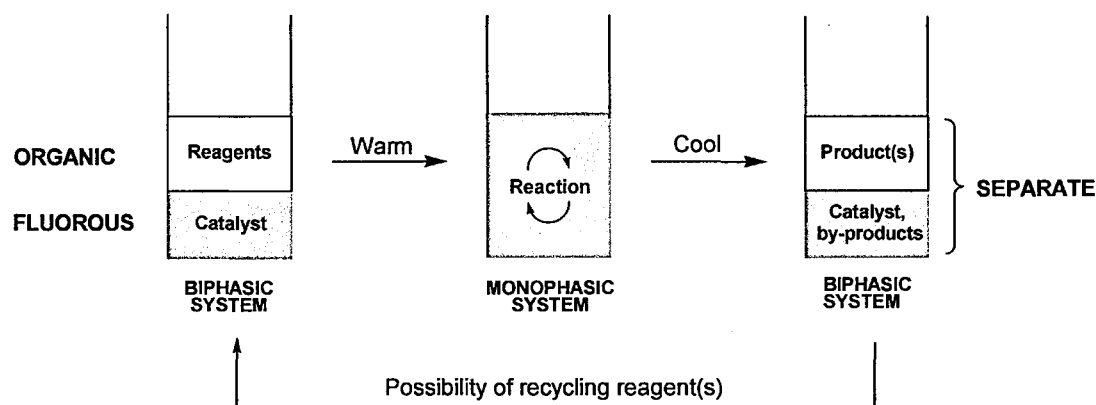


Fig. 5: Fluorous Biphasic Concept

By warming the reaction mixture, the temperature-dependant immiscibility border disappears and the system becomes monophasic, allowing catalysis and thus reaction to happen. By cooling the mixture down, the system returns to two phases and by a simple separation the fluoruous catalyst/ligands are separated from organic products. The advantage of this method is the ability of the biphasic system to become monophasic upon heating.

This approach has widely been used in a variety of catalytic reactions as:

- oxidation<sup>31-35</sup>
- carbon-carbon bond formation<sup>36,37</sup>
- polymerisation<sup>38</sup>
- hydrogenation<sup>39,40</sup>
- hydroboration<sup>41</sup>
- hydroformylation<sup>18, 42, 43</sup>

Studies have focused on fluoruous phosphine ligands as the most widely used class of ligands.<sup>43</sup> A number of methods has been applied to synthesise fluoroalkyl and fluoroaryl phosphines<sup>44-46</sup> employing a variety of spacer groups<sup>47</sup> and their operation has been reviewed.<sup>43</sup> A number of perfluorophosphines are now commercially available from Fluorous Technologies Inc.<sup>25</sup> Numerous fluoruous analogues of metal complexes have been prepared and used, including Vaska's complex analogues:

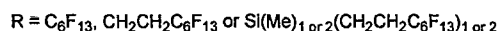
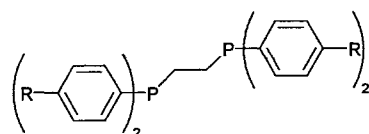


and Wilkinson's catalyst analogues:



The fluoros-Wilkinson's catalyst has been used for hydroboration reactions of alkenes, initially employing a THF/ $\text{CF}_3\text{C}_6\text{F}_{11}$  biphase. Better yields were obtained using the organic solvent.<sup>41, 48</sup> However, a study using a large number of fluoros analogues found that minimal reduction in rate occurred when moving to a  $\text{C}_6\text{H}_4\text{OCH}_2$ -spacer group, thus showing the key importance of the spacer group.<sup>24</sup> In 1994, Horváth illustrated the hydroformylation of 1-octene in 85% yield by using  $[\text{Rh}(\text{CO})_2(\text{acac})]$  with  $\text{P}(\text{C}_2\text{H}_4\text{C}_6\text{F}_{13})_3$  in toluene/perfluoromethylcyclohexane<sup>18</sup>. The experiment also showed the advantage of increased stability of the fluoros catalyst over the organic one in the long-term.

The field has not concentrated solely on phosphines. There exists the possibility to create fluoros analogues of almost any ligands, e.g. the synthesis of a range of *bis*-phosphines, the fluoros analogues of 1,2-*bis*-diphenylphosphinoethane **7**, has been reported.<sup>49</sup>

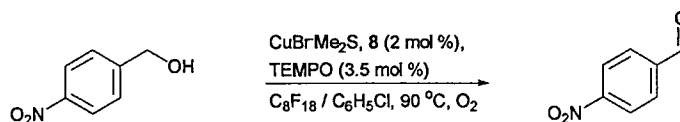


**7**

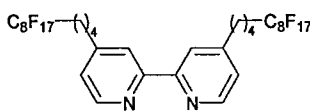
The electron density on phosphorus was unaffected by the fluoros tags when a new silicon spacer group was employed.<sup>24,49</sup>

Alongside fluoros ligands, a variety of reactions using fluoros compounds and solvents has been developed, including alcohol oxidations and epoxidations. An additional character of fluorocarbon solvents is that they dissolve large amounts of molecular oxygen. Betzemein and Knoche<sup>36</sup> have shown that the catalyst generated *in situ* from the perfluoroalkyl bipyridine **8** (2 mol%), with  $\text{CuBrMe}_2\text{S}$  (2 mol%) and TEMPO (3.5 mol%) in the chlorobenzene/perfluorooctane biphasic system is an outstanding system for the aerobic oxidation of alcohols to aldehydes or ketones.



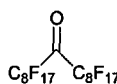


Scheme 2

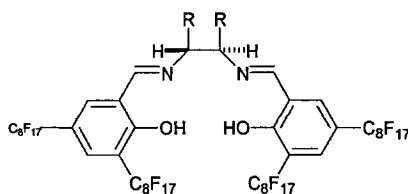
**8**

The catalyst could be recycled using fluoruous solvent and used again for the next eight cycles without losing any activity.

Sheldon<sup>50</sup> has discovered that perfluoroheptadecan-9-one, **9**, (5 mol%) is a mild and selective fluoruous-soluble catalyst. It can be used to epoxidise alkenes by hydrogen peroxide. After the process the fluoruous solvent with the catalyst can be recovered and re-used without decomposition or loss of activity.

**9**

There have been number of studies on fluoruous-based reduction and hydrogenation methods as well. Millard has used the fluoruous ligand<sup>51</sup> **10** with related analogues in the iridium catalysed asymmetric reduction of ketones, using an isopropanol/perfluorooctane biphasic system.

**10**

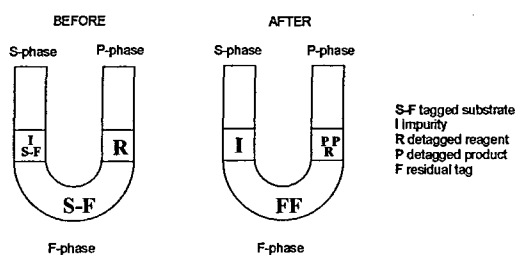
The same catalyst was used by Pozzi<sup>35</sup> as a fluoruous asymmetric epoxidation catalyst. It is fluoruous soluble, and when combined with manganese acetate/*meta*-chloroperbenzoic acid/*N*-methylmorpholine-*N*-oxide it catalyses epoxidation reactions in good yields.

Unfortunately, no catalyst recovery method is without its disadvantages. Results, such as those previously described, demonstrated the excellence of the separation method; no catalyst/ligand was detected across the biphase. Chemists, however, claim the high costs of the fluoruous solvents and their environmental persistence as the main weakness of the FBC method. In 2001 Gladysz and co workers<sup>52</sup> reported FBC without the necessity of fluoruous solvents. Instead they engineered the melting temperature of the fluoruous catalyst to give liquid-liquid separation using an organic solvent. Further steps in this field will be of great benefit for industrial applications of FBC.

### 1.8 Fluoruous Triphasic Reactions

Fluoruous triphasic reactions can be explained by two different senses. Pozzi has used a fluoruous triphasic system for oxidation reactions by using a triphasic dichloromethane/water/ $C_8F_{18}$  reaction medium together with fluoruous bipyridine ligands.<sup>53</sup>

The more accepted triphasic concept has been introduced by Curran. Recently he has completed an innovative experiment using fluoruous triphasic system,<sup>54</sup> but using only fluoruous and organic solvents. The three phases included two organic phases divided by a fluoruous phase; a U-shaped tube is used to separate a bottom fluoruous phase from the upper organic ones.



**Fig. 6:** Fluoruous Triphasic Concept

The fluoruous phase creates a barrier between two organic phases. Consequently, exchange between the two organic phases can happen only *via* the fluoruous phase. Reactants are loaded in to one organic phase (S) and products are collected from the other organic phase (P). The triphasic system is used here to discharge a fluoruous tag from a precursor and at the same time separating detached product from other products or impurities. Organic reactants and fluoruous-tagged compounds are loaded to the phase S and the detached

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reagent R into the phase P. The fluorine-tagged product moves from the S phase into the F phase to interface with the P phase and detagging takes place. The product then moves into the P phase, since it is no longer soluble in the F phase. As the impurities are not attached to fluorine tags, they always remain in the S phase. The removed tag, because of its high fluorine content, migrates back into the F phase. Many examples of this type of triphasic system have been reported by Curran and his group<sup>54</sup>. The major advantage of this system over the biphasic one is the lower fluorine content that is required since the molecules only pass through the fluorine phase. Studies of this method are continuing.

### 1.9 The Need for Fluorine Chemistry

In general, pharmaceutical chemistry can be divided into:

- medicinal chemistry, which includes the discovery of novel lead compounds, their testing and evaluation, and
- process chemistry, which is the development of a synthesis and process for the large-scale synthesis of successful lead compounds.

Using Curran's words<sup>21</sup>, chemists from both divisions are now 'expected to synthesise everything and quickly'. The most required molecules are small ones, under 600 molecular weight. During the last decade, with the advent of parallel synthesis and combinatorial chemistry, medicinal chemists have improved both the number of molecules they can make and also the speed of the processes. But higher numbers of compounds synthesised in shorter times, need faster methods of purification. Also, process chemists require safe techniques that are cheap and environmentally friendly. The best syntheses are those where products are isolated using simple techniques, like extraction or filtration.

Thus interest in FBC has increased and the advantage of the fluorine process has arisen. It was unavoidable that chemists would soon adopt fluorine techniques in organic synthesis. Since the first example of a fluorine tin hydride being synthesised and used in radical reactions,<sup>55</sup> many other fluorine reagents have been developed to aid purification and separation.

Our attempted contribution in this field will now be discussed.

## **Chapter 2**

# **RESULTS & DISCUSSION I: FLUOROUS CHEMISTRY**

## 2.1 Aims

In recent years there has been an explosion of catalytic, environmentally friendly and generally 'green' chemistry. One of the paramount results of this has been the appearance of novel reagents and solvents for use in organic chemistry.<sup>24</sup>

The group V elements nitrogen and phosphorus are used extensively in synthetic chemistry. Phosphines and organophosphorus reagents are amongst the oldest reagents used by chemists. There are often problems with regard to the toxicity of these reagents and their reaction by-products and also with the difficulty associated with their removal.

Nitrogen containing compounds such as amines and amides are amongst the most utilized reagents in modern chemistry.

Medicinal and process chemists are looking to develop techniques for the rapid synthesis of organo-amines and phosphines and also for their prompt separation and purification.<sup>17,24</sup>

The present work aims to combine known chemistry with the advantages of fluororous chemistry to provide a new clean technology for the use, handling and purification of organo phosphorus and amine reactions. During the first stage the project focused on aromatic phosphines and later on aliphatic ones; later work switched to organonitrogen compounds and the preparation of an analogue of DEAD. These reagents would be designed to be preferentially soluble in fluororous solvents rather than in organic ones. By using new fluororous techniques, the fluoro-phosphorus and amino compounds synthesised would be used for an investigation of numerous reactions, including the Wittig and Mitsunobu reactions.

Thus our objectives were:

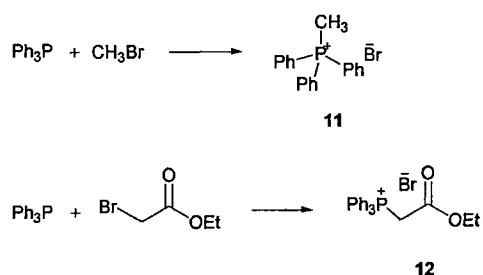
- to develop a new and flexible method for the synthesis of fluororous-containing phosphines, phosphorus-based compounds and fluororous-tagged amines.
- to investigate the potential applications of these fluorinated phosphines and amines in a variety of reactions.
- to investigate the 'cleanness' of these reactions in terms of easy separation and removal of by-products and also for the possibilities of recycling, both of the reagents and solvents.

## 2.2 The Wittig Reaction

The Wittig reaction was discovered in 1949 and named after its discoverer, Georg Wittig.<sup>56</sup> It is a reaction between a carbonyl compound (aldehydes or ketones) and a phosphonium ylid. It is possible to divide this process into two parts: first the preparation of a phosphonium salt, then the formation of a phosphorus ylid and its reaction with a carbonyl compound.

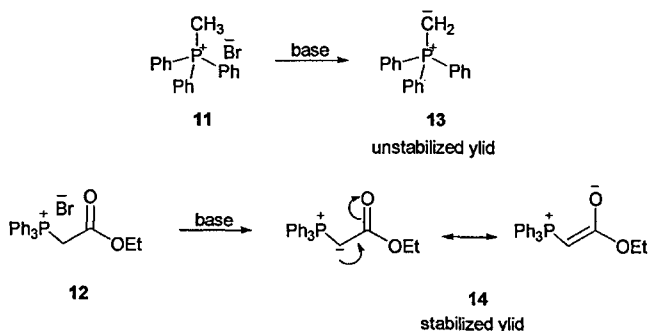
### 2.2.1 Ylids

Ylids are species with positive and negative charges on the adjacent atoms. In phosphonium ylids, the positively charged atom is phosphorus. They can be made from phosphonium salts, which themselves are prepared by the reaction of triphenylphosphine with an alkyl bromide:



**Scheme 3:** Examples and synthesis of phosphonium salts

These are then deprotonated with a strong base such as butyllithium, potassium *tert*-butoxide or sodium hydroxide to yield the desired ylids.



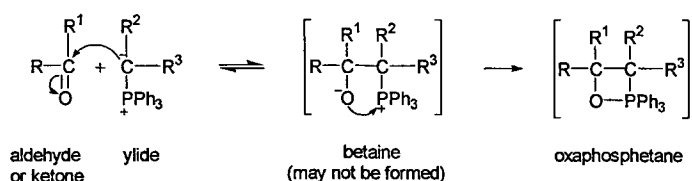
**Scheme 4:** Examples of ylids

There are two kinds of ylids: stabilised and unstabilised ones. In stabilised ylids the negative charge is delocalised by the adjacent functional group, normally by resonance.<sup>57</sup> There is no such effect in the unstabilised ylids. In Figure 9, 14 is a stabilised ylid and 13 an unstabilised one. In general, stabilised ylids give *E*-alkenes in the Wittig reaction and unstabilised ylids *Z*-alkenes.<sup>57</sup>

### 2.2.2 Mechanism of the Wittig Reaction

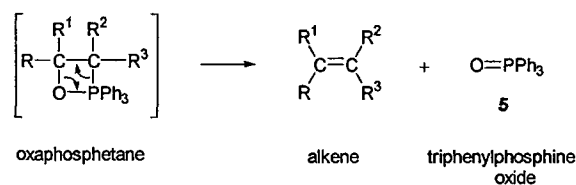
One of the main advantages of the Wittig reaction over most other alkene syntheses is that the double bond is created regioselectively, replacing the carbon-oxygen bond of the carbonyl group.<sup>56</sup>

During the first stage, an aldehyde or ketone reacts with the ylid:



**Scheme 5**

The ylid, acting as a carbanion, attacks the carbonyl carbon of the aldehyde or ketone. By doing so, it forms an unstable intermediate called a betaine *via* intramolecular nucleophilic attack, which cyclises to form an unstable four-membered cyclic system called an oxaphosphetane. The driving force of the Wittig reaction is the creation of a strong phosphorus-oxygen bond in a molecule of triphenylphosphine oxide **5**; the oxaphosphetane loses this part of the system and simultaneously forms an alkene.



**Scheme 6**

Recent studies suggest that the oxaphosphetane may be formed directly without the intermediate betaine.<sup>56</sup>

## 2.3 Model Wittig Reactions

Before applying any fluorous chemistry to the Wittig reaction, model experiments were carried out on simple substrates.

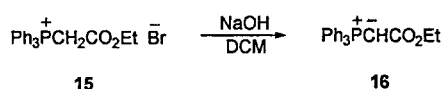
### 2.3.1 Stabilised Ylids

One of the starting materials, carboethoxymethyltriphenylphosphorane was prepared<sup>58</sup> in two steps. First triphenylphosphine **3** and ethyl bromoacetate were reacted in toluene, to give the target phosphonium salt **15** in 87% yield:



**Scheme 7**

This was deprotonated by adding slowly a solution of 0.1 M sodium hydroxide. After crystallisation, the target ylid **16** was isolated in 58% yield:



**Scheme 8**

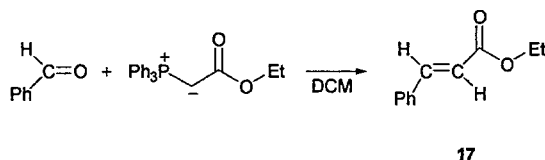
This is termed a stabilised ylid since the negative charge in the phosphorus ylid is stabilised by a resonance effect:



**Scheme 9**



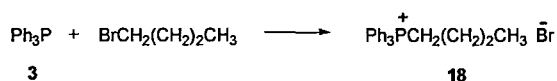
Reaction with phenylacetaldehyde gave the *trans* (*E*) isomer of the alkene, proved by NMR spectroscopy, from the observed olefinic coupling constant of 15.9 Hz. The final alkene **17** was isolated in 60% yield, with no trace by NMR of the *Z*-isomer.



Scheme 10

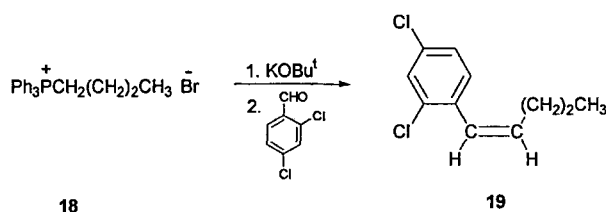
### 2.3.2 Unstabilized Ylids

A similar reaction sequence was performed using an unstabilised ylid<sup>58</sup>. Starting from triphenylphosphine **3** and 1-bromobutane, butyltriphenylphosphonium bromide **18** was first obtained in 26% yield:



Scheme 11

This was then reacted with potassium *tert*-butoxide in dry tetrahydrofuran, followed by 2,4-dichlorobenzaldehyde. Finally, the required product **19** was isolated in 52% yield.

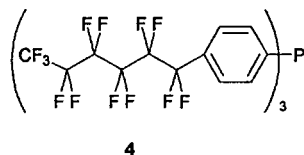


Scheme 12

Knowing that these model systems were successful and reproducible, the next stage was the synthesis of fluororous analogues of triphenylphosphine and then to repeat the Wittig chemistry using this fluorinated triphenylphosphine.

## 2.4 Fluorous phosphines for the Wittig Reaction

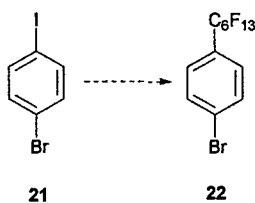
As mentioned above, the first target was a preparation of fluorinated phosphines. After some literature observations<sup>44</sup> was selected the analogue of triphenylphosphine, *tris*(4-tridecafluorohexylphenyl) phosphine **4**, a suitable compound for future studies:



To obtain this compound, several routes were explored. The first can be divided into two parts<sup>44</sup>:

1. preparation of 4-(tridecafluorohexyl)bromobenzene **22**
2. preparation of *tris*(4-tridecafluorohexylphenyl) phosphine **4**.

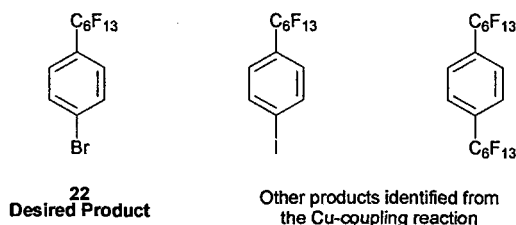
The literature method of Hope *et al.*<sup>44</sup> was attempted for the preparation of 4-(tridecafluorohexyl)bromobenzene **22**. A solution of iodoperfluorohexane (1 eq) in hexafluorobenzene was added dropwise over 3 h to a stirred mixture of 4-bromoiodobenzene **21** (1 eq), copper powder (2.2 eq), 2,2'-bipyridine (0.07 eq), DMSO and hexafluorobenzene at 70°C.<sup>44</sup>



**Scheme 13**

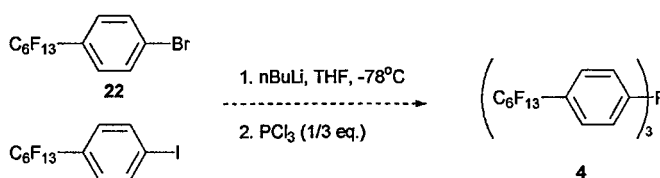
This reaction was repeated several times on different scales, following exactly the procedure described in the literature. Unfortunately, none of the desired compound **22** was obtained. A slight modification of the procedure suggested by Professor Hope was also attempted, but with little success. In place of the desired product, an inseparable mixture of products was obtained. Based on GC-MS analysis of this mixture, it is believed that the

three principle products formed in the reactions are the desired product **22**, along with the iodo-form of this compound (from exchange of the bromine rather than the iodine) and the *bis*-coupled product.



The procedure was repeated using both an excess of copper powder and also activating the copper powder prior to reaction. The powder was activated by washing rapidly with a weak solution of hydrochloric acid (1 M), washed with large quantities of distilled water to remove all traces of the acid, then washed with acetone to remove water and finally washed with diethyl ether. It was dried under vacuum then stored under nitrogen. After this, the experiment was repeated five times using the freshly activated copper powder in varying levels of excess (2.5 eq, 2.8 eq, 3 eq, 4 eq and 5 eq). In all cases no pure sample was isolated. Neither  $^{19}\text{F}$  or  $^{13}\text{C}$  NMR proved helpful in assessing the purity of the mixture. Unfortunately, no pure sample of **22** could ever be obtained, irrespective of the method of purification attempted (distillation or chromatography).

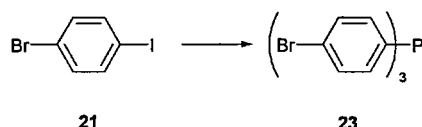
In an attempt to obtain a sample of the fluorous-phosphine analogue to test the Wittig reactions, it was decided to take the mixture of compounds on to the second step in the synthesis, in the hope that both the bromo- and iodo-compounds would react with  $\text{PCl}_3$  to give the desired product and that it would be possible at this stage to separate the desired product from the *bis*-fluorous coupled compound. Consequently, the pale yellow solution from the first stage was reacted with *n*-butyllithium (1 eq.) in THF at  $-78^\circ\text{C}$ , followed by freshly distilled phosphorus trichloride (1/3 eq.) at  $-78^\circ\text{C}$ .<sup>44</sup>



## Scheme 14

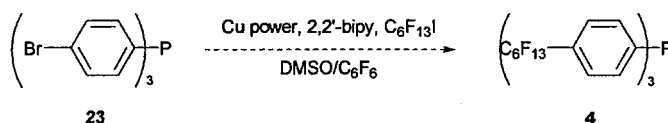
This reaction was largely unsuccessful, possibly due to the mixture of starting materials employed and not knowing the exact molar equivalences to employ. After each successive attempt, however, small quantities (10-15% yield) of the desired product, **4**, were obtained, suggesting that if a better method for the preparation of **22** could be found then this second step may well be useful. The amount of time and effort required to obtain **4**, though, made this route not practical at this stage.

Therefore it was decided to investigate alternative routes to **4**. One proposed method was to look at the direct introduction of the fluorous chain into *tris*(4-bromophenyl)phosphine **23**. This was prepared using the same method as described above for the coupling of aromatic halides with  $\text{PCl}_3$ .<sup>44</sup> Reaction of **21** with *n*-butyllithium followed by  $\text{PCl}_3$  consistently gave high yields (>70%) of the desired *tris*(4-bromophenyl)phosphine **23**, irrespective of the reaction scale and the procedure could be repeated on scales up to 20 g.



## Scheme 15

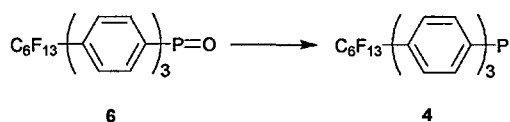
The same method was then applied to couple the fluorous chain to **23**, using activated copper powder and the same molar quantities as in the original publication.<sup>44</sup>



## Scheme 16

Again, the experiment was performed several times on different scales and using both activated and non-activated copper powder, but no **4** was obtained; on some occasions starting materials were recovered and on others no identifiable material was obtained at all.

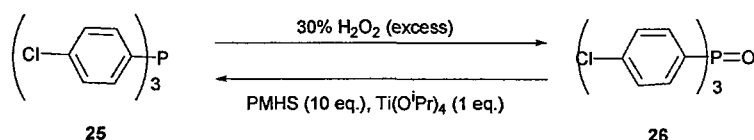
Therefore, a third method was envisaged, which would involve formation of the phosphine oxide **6**, which would then be reduced to **4**.<sup>59</sup>



Scheme 17

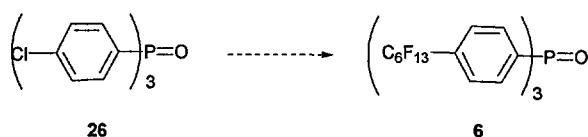
The idea behind this route was that the lone pair of electrons on phosphorus may be interfering with the copper-coupling process. Therefore, if these electrons could be ‘locked up’, or protected, the coupling may proceed in better yields and the phosphorus could be deprotected at a later stage (although unfortunately, this would add an extra couple of steps to the synthesis of **4**).

First, a test reaction was performed using commercially available *tris*(4-chlorophenyl) phosphine **25**. Oxidation was achieved using 30% hydrogen peroxide solution (in excess) to give **26** in near-quantitative yield.<sup>59</sup> This was then reacted with trichlorosilane (5 eq) and triethylamine (7.5 eq) at reflux<sup>45</sup> to give the reduced phosphine **25**, albeit in only low yield (20%). A second method, using polymethylhydrosiloxane and titanium (IV) isopropoxide<sup>60</sup> was attempted; This consistently gave much better yields than the first method for the reduction. Therefore this became the method of choice for the reduction of phosphine oxides.



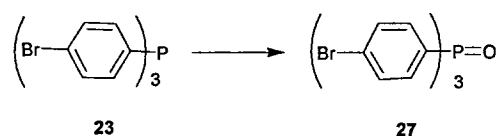
Scheme 18

As it was readily available from commercial material, it was decided to react **26** with  $\text{C}_6\text{F}_{13}\text{I}$  under the copper-promoted conditions. Only starting material was recovered.<sup>45</sup>



## Scheme 19

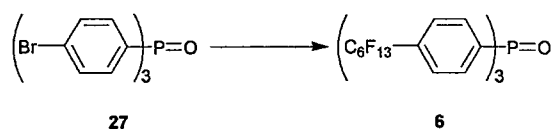
Therefore attention returned to the *tris*(4-bromotriphenyl)phosphine, **23**. This was readily oxidised<sup>59</sup> to the phosphine oxide **27** in excellent yield.



## Scheme 20

With **27** isolated, it was again tested under both sets of conditions for reduction to obtain a phosphine. Again, the first using trichlorosilane (5 eq) and triethylamine (7.5 eq) at reflux temperature<sup>45</sup> was poor, while the second using titanium (IV) catalysis<sup>60</sup> involving (polymethylhydrosiloxane (PMHS) (10 eq) and titanium (IV) isopropoxide (1 eq) was much more successful and gave the desired product (73%).

The newly obtained *tris*(4-bromophenyl) phosphine oxide **27** was reacted with iodoperfluorohexane with activated copper several times.

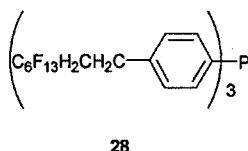


## Scheme 21

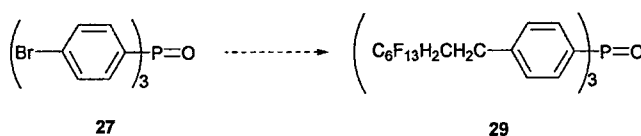
Only once was the product **6** isolated, as a mixture of compounds in very small quantities. It was subsequently reduced with both the titanium and the trichlorosilane/triethylamine methods as before. None of the targeted *tris*(4-tridecafluorohexyl)phosphine **4** was identified.

After observations at a Conference (R.S.C. Annual Congress, Birmingham 2001) and discussions (Professor Dennis Curran, University of Pittsburgh), it was suggested to use fluorous compounds with an organic spacer group between the aromatic ring and the fluorous chain, as this may be easier to prepare. Thus *tris*(4-1H,1H,2H,2H-tridecafluorooctyl)phosphine **28** was targeted. It was suggested that this should be obtained

using *tris*(4-bromophenyl)phosphine **23** and 1H,1H,2H,2H-tridecafluorooctyl iodide, using conditions adopted from above using copper.<sup>44</sup>



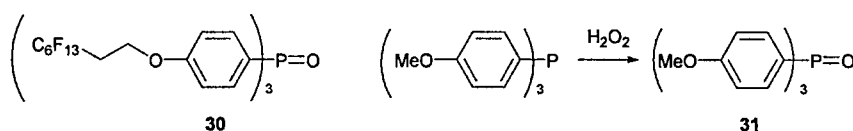
Unfortunately none of the specified compound was isolated, so an identical reaction was carried out with the previously prepared bromosubstituted phosphine oxide **27**



**Scheme 22**

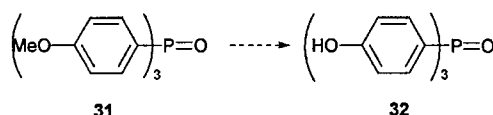
Again, these experiments were carried out several times, using different scales and conditions, but with no product being obtained. An interesting observation, however, which had been noticed before but only in passing, was the homo-coupling of starting materials. During all these experiments there was a potential problem of binding two different molecules by substituting existing halogens. In this latest experiment in particular, dimerisation of the 1H,1H,2H,2H-tridecafluorooctyl iodide was observed as the major reaction product. Re-examination of previous reaction mixtures, which had not necessarily been separated, also showed the presence of dimerisation products, particularly from the fluorous halide, but also with the suggestion of biphenyls as well.

Therefore as an alternative, it was decided to look at a non-halogen-based starting material. It was proposed to make an ether-linked fluorous phosphine, **30**. *Tris*(4-methoxyphenyl)phosphine **31** is commercially available and is readily oxidised with hydrogen peroxide, as before, to the phosphine oxide in quantitative yield.<sup>59</sup>



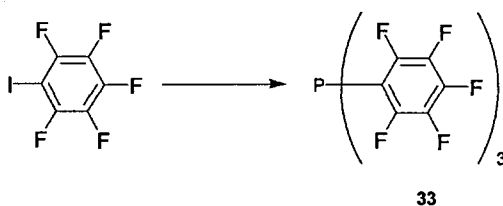
## Scheme 23

The demethylation reaction<sup>61</sup>, to obtain *tris*(hydroxyphenyl)phosphine oxide **32**, is a known literature procedure using boron tribromide. However, none of the desired compound was obtained and no identifiable material could be recovered.



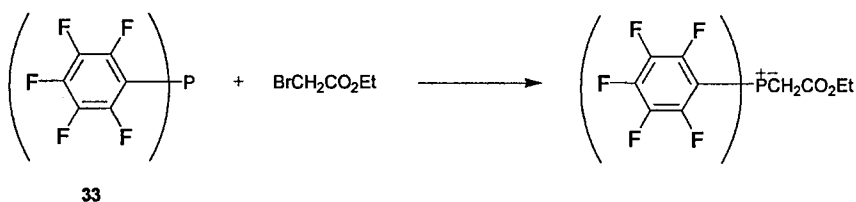
## Scheme 24

In a final attempt to obtain a fluorous-soluble triphenylphosphine analogue, a completely new approach was taken, and instead of trying to add a fluorous chain to an aromatic compound, the fluorines were to be placed directly on the aromatic ring. Commercially available iodopentafluorobenzene was readily transformed into *tris*(pentafluorophenyl)phosphine **33** using standard lithium-halogen exchange with *n*-butyllithium.<sup>44</sup>



## Scheme 25

This was then reacted with bromoethylacetate (1 eq) to form the precursor for a stabilised ylid.

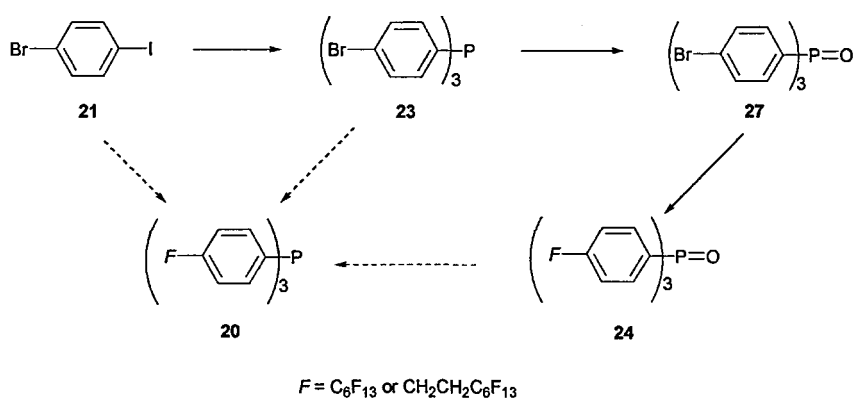


## Scheme 26



Although this reaction gave the mixture of fluorine contained substances (67%), unfortunately the *tris*pentafluorophenylphosphine showed no selective solubility for the fluorous phase over an organic solvent, distributing itself almost equally in test separations. In hindsight, this is hardly surprising since the compound does not possess the pre-requisite minimum 60% fluorine, which is normally suggested as minimum fluorine content required to impart selective fluorous solubility.

**Scheme 27** summarises all the routes attempted to prepare fluorous phosphines.

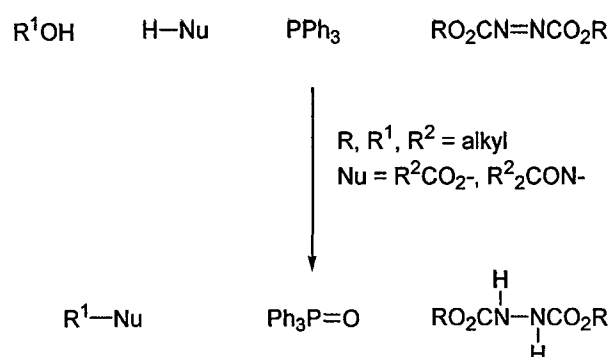


**Scheme 27**

It was at this point that a publication from Sinou<sup>62</sup> reported the first examples of a fluorous-based Wittig reaction. Thus, given the problems encountered preparing the fluorous phosphines and also the appearance in the literature of a related study, it was decided to abandon this line of research and to look at an alternative fluorous-based reagent.

## 2.5 The Mitsunobu Reaction

The condensation reaction of an alcohol with an acidic Nu-H containing nucleophile, using the redox couple of a trialkyl or triaryl phosphine and a dialkyl azodicarboxylate, is known as the Mitsunobu reaction. It is a second reaction that often has associated purification problems, but one that has become very popular in recent years and gives excellent yields of reaction products, although the two by-products in the reaction can often be problematic to remove. The reaction has been extensively reviewed and may be summarized:



**Scheme 28**

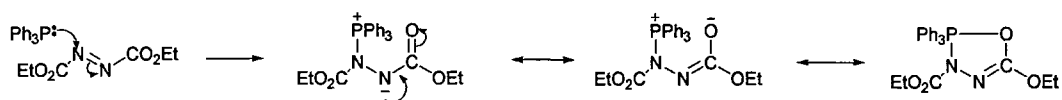
An alcohol ( $R^1OH$ ) and an acidic component ( $H-Nu$ ) are condensed to form the product ( $R^1-Nu$ ), while triphenylphosphine is oxidised to triphenylphosphine oxide and the dialkyl azodicarboxylate is reduced to the hydrazine. Diethyl azodicarboxylate (DEAD) is the usual carboxylate of choice, along with triphenylphosphine, although other combinations are known.<sup>18,19</sup>

As in case of the Wittig reaction, the driving force of the Mitsunobu reaction is the formation of a strong phosphorus-oxygen bond. The reaction is most commonly employed for the direct replacement of a hydroxyl group by a nucleophile.

The reaction is a redox couple, the phosphine bonds with the oxygen of an alcohol, while the azodicarboxylate accepts hydrogen to end with the corresponding hydrazine derivative. The reaction gives good yields (60-90%) and proceeds well with primary and secondary alcohols.<sup>63</sup>

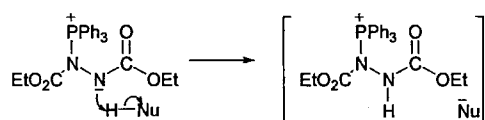
2.5.1 Mechanism <sup>63a</sup>

In the first step, the lone pair of electrons of phosphorus from triphenylphosphine attack one of the nitrogen atoms of DEAD:



Scheme 29

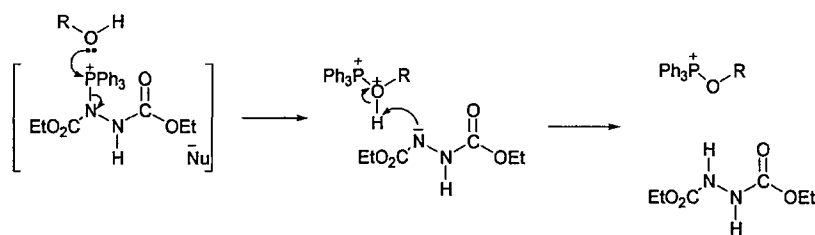
Stabilisation of the nitrogen anion happens by delocalisation onto the adjacent oxygen atom of the carbonyl group. The nucleophile must possess an acidic H atom. The  $pK_a$  should generally be less than 13. Next, the nucleophilic agent reacts.



Scheme 30

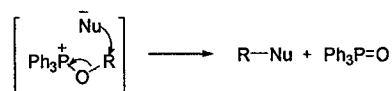
Examples of nucleophilic reagents which can be used are carboxylic acids, thioacids, phenols, thiols, imides, sulfonamides, heterocyclic compounds, hydrogen halides, phosphine diesters, phosphonic acids and certain active methylene compounds.<sup>64</sup>

The lone pair of electrons of the oxygen of the hydroxyl group then attack the positively charged phosphorus atom:



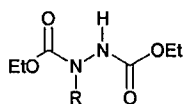
Scheme 31

In the final stage, the negatively charged nucleophile formed in Scheme 30 now attacks the R group from the phosphonium salt in an  $S_N2$  manner and the phosphorous-oxygen double bond forms by finally breaking the O-R bond.



Scheme 32

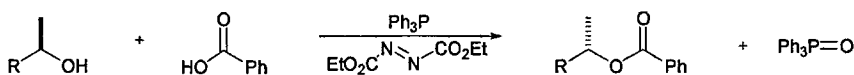
Studies<sup>65</sup> have shown that without acidic components, *N*-alkylhydrazinedicarboxylates can be formed, Scheme 33:



Scheme 33

### 2.5.2 Stereochemistry

The Mitsunobu reaction is a highly stereospecific reaction; one of its major uses is that with optically active substrates, it proceeds with complete inversion of configuration. Since the final step of the mechanism involves an  $S_N2$  reaction, then the overall outcome of the reaction must be that it proceeds with inversion of configuration. For example, in an esterification reaction involving a chiral alcohol, the ester is formed with inversion of configuration.<sup>64</sup>



Scheme 34

### 2.5.3 Order of Addition

Of paramount importance in the Mitsunobu reaction is the order of addition of the various components. Normally non-polar solvents are used as they increase significantly the speed of the reaction. Generally, in the first step, the alcohol, acid and

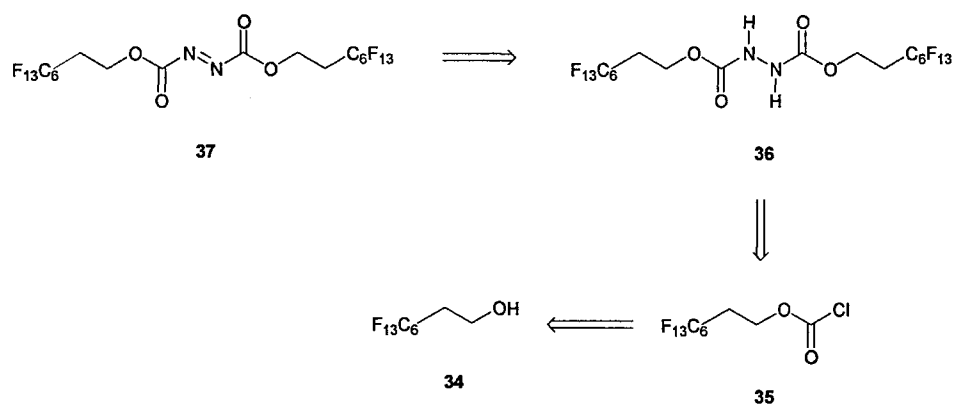
triphenylphosphine are dissolved in the solvent, usually THF, and cooled to 0 °C. Then the DEAD is added slowly and the reaction left stirring at room temperature for several hours.<sup>64</sup>

## 2.6 Fluorous Mitsunobu Reaction

A common problem of the Mitsunobu reaction is the separation of the product from triphenylphosphine oxide and the hydrazine. In conjunction with the preparation of fluorosphosphines for use in the Wittig reaction, it was envisaged that the same phosphines could be utilised in a fluoros version of the Mitsunobu reaction.<sup>66</sup> However, for a fully-fluorous version of the reaction, it would also be necessary to prepare a fluoros version of DEAD, abbreviated <sup>F</sup>DEAD. Although, as previously reported, an effort to prepare fluorosphosphines was unsuccessful, attempts at <sup>F</sup>DEAD were more successful and promised to provide a partially-fluorous Mitsunobu reaction.

### 2.6.1 Retrosynthesis of <sup>F</sup>DEAD

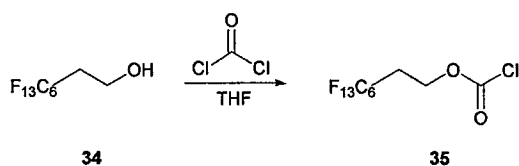
Just as other fluoros reagents have been designed, an alternative to DEAD must be a possible solution to the problem of purifying the Mitsunobu reaction.<sup>66</sup> The aim of this work is to prepare a fluoros analogue of an azodicarboxylate which will react in the Mitsunobu reaction in the same manner as the traditional counterpart, but that can be removed from a reaction mixture using fluoros separation techniques. The proposed version contains large fluorocarbon chains to ensure selective fluoros solubility and also a -CH<sub>2</sub>CH<sub>2</sub>- spacer group to shield the reaction centre from the fluoros chains. The proposed compound also contains greater than the 60% threshold for selective fluoros solubility. The retrosynthetic approach to <sup>F</sup>DEAD is presented in Scheme 35.



Scheme 35

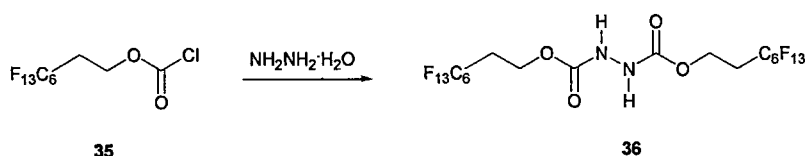
### 2.6.2 Synthesis of <sup>F</sup>DEAD<sup>66</sup>

Commercially available 1*H*,1*H*,2*H*,2*H*-perfluoro-1-octanol **34** was employed as a readily available starting material. This was easily transformed to the corresponding fluorous chloroformate **35** by slow addition to a 20% solution of phosgene in toluene at 0 °C. The reaction was initially performed using 1 equivalent of phosgene, but some starting material always remained. The use of 1.5 equivalents, however, forced the reaction to completion and remaining traces of phosgene could be removed by rotary evaporation. (Safety precautions were taken throughout when handling phosgene). The fluorous chloroformate **35** was isolated as a pale oil which could be used immediately without further purification.



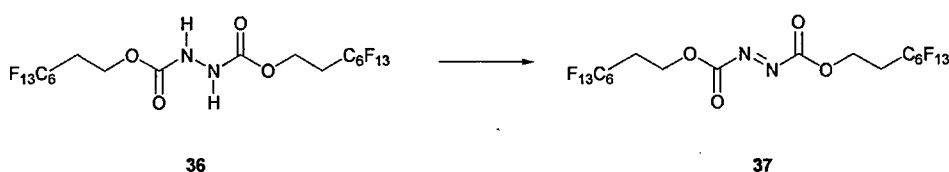
Scheme 36

The fluorous hydrazine **36** was easily formed by reaction of the fluorous chloroformate **35** with hydrazine hydrate in the presence of sodium carbonate in ethanol. Maintaining a constant temperature of 0 °C was important to achieve a high yield. After the addition the mixture was stirred at room temperature for 2 h and after filtration and re-crystallisation from ethanol, the product was obtained as white crystals in 81% yield over the 2 steps. The fluorous hydrazine **36** could be stored easily and without decomposition.



Scheme 37

The final stage involved oxidation of the hydrazine **36** to form the N=N function of the target molecule. Initially, lead tetraacetate was attempted, with little success. Two different oxidants, *N*-bromosuccinimide<sup>66</sup> and molecular bromine were utilised for this transformation. Of these, freshly recrystallised NBS was generally the more successful oxidant, with the product **37** being obtained in 92% yield.



Scheme 38

## 2.7 Partition Coefficients

To determine which solvent combinations were best for liquid-liquid fluoruous extractions (of the fluoruous hydrazine by product from organic solvents), it was decided to determine the partition coefficients of both the fluoruous hydrazine and <sup>F</sup>DEAD for a range of solvent combinations.

Partition coefficients were determined using two different methods.<sup>67</sup> The hydrazine or <sup>F</sup>DEAD was stirred in different combinations of fluoruous and organic solvents for 22 h at 22 °C and then allowed to stand for one hour. The two layers were then separated and each layer analysed against a reference of dodecane in hexane using gas chromatography. Seven injections were made of each sample and an average of the integrations taken. These were then used to calculate the ratio of hydrazine or <sup>F</sup>DEAD in each layer. While reliable for the fluoruous hydrazine, <sup>F</sup>DEAD was not entirely stable to gas chromatography and inconsistent results were obtained. Therefore an alternative accurate weighing method was employed.

The remainder of the two layers were then separately evaporated and the mass of hydrazine or <sup>F</sup>DEAD found in each layer recorded and used to calculate the ratio in each layer. The ratios obtained by this method were identical to the ones obtained *via* the GC method. The results are presented in Table 4.

**Table 4:** Partition coefficients for fluorous hydrazine and <sup>F</sup>DEAD

	Fluorous hydrazine		Fluorous DEAD	
	FC-72	Perfluoromethyl- cyclohexane	FC-72	Perfluoromethyl- cyclohexane
THF	99.3:0.7	98.1:1.9	99.2:0.8	99.6:0.4
Toluene	64.1:35.9	84.8:15.1	69.1:30.9	80.0:20.0
DCM	81.0:19.0	51.0:49.0	71.6:28.3	62.0:38.9
Methanol	95.4:4.5	99.6:0.5	95.5:5.4	96.4:4.3.6
Aq. Methanol (80%)	70.7:29.3	100.0:0.0	91.0:9.0	99.9:0.1

The values obtained for the fluorous hydrazine would be most important, since it would be this compound, as one of the main Mitsunobu reaction by-products, that would need to be separated by fluorous liquid-liquid extraction. The values obtained would suggest that THF and methanol would be the most suitable solvents to employ, since very high levels of selectivity were observed for the fluorous hydrazine in the fluorous solvent, rather than partitioning between the two phases.

## 2.8 Mitsunobu Reactions

After successfully synthesising <sup>F</sup>DEAD, reactions had to be performed to test that it did indeed work as well as traditional DEAD in the Mitsunobu reaction.



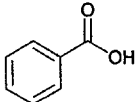
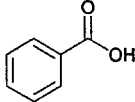

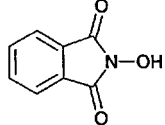
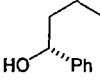
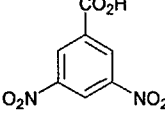

## 2.8.1 Model Mitsunobu Reactions Employing DEAD

A set of Mitsunobu reactions were run using traditional reagents and reaction conditions, as illustrated in Table 5.

Table 5: Test Mitsunobu Reactions

$$\text{RCOOH} + \text{R}^1\text{OH} \xrightarrow[\text{EtO}_2\text{CN=NCO}_2\text{Et}]{\text{PPh}_3} \text{RCOOR}^1$$

ACID                      ALCOHOL

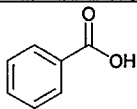
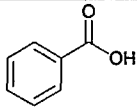

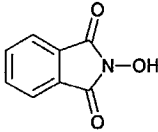
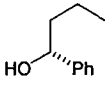
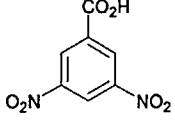

Entry	ACID	ALCOHOL	DEAD+PPh <sub>3</sub> % YIELD	DEAD+S-S- PPh <sub>3</sub> % YIELD
1		Et-OH	85	52
2			78	43
3			81	50
4			92	Not performed

All the Mitsunobu reactions proceeded in high yield, to give the desired products that were easily purified by chromatography. The Mitsunobu reactions were also run with solid-supported (S-S) triphenylphosphine. It was hoped that this would be a useful alternative for triphenylphosphine, giving cleaner separation, but also that it could later be coupled with <sup>F</sup>DEAD to give a Mitsunobu reaction that could be easily purified by filtration and extraction. Unfortunately, the yields for the reactions with solid-supported triphenylphosphine were much lower than expected. It is thought that this is primarily due to the quality of the phosphine; this was found to contain approximately 30% triphenylphosphine oxide upon purchase.

2.8.2 Mitsunobu Reactions Employing <sup>F</sup>DEAD

The identical Mitsunobu reactions from Table 5 were performed, but this time using freshly prepared <sup>F</sup>DEAD. As table 6 shows, comparable yields were obtained. All the reactions proceeded in the same manner as the traditional Mitsunobu reactions, but instead of the need for column chromatography, the reactions were purified using liquid-liquid fluorous extraction. The best combinations were found to be THF and FC-72 or perfluoromethylcyclohexane, although other solvent systems were tested. It was found that 2 or 3 extractions were required to remove all traces of the fluorous hydrazine. This combination is hardly surprising, given the favourable partition coefficients previously described.

Table 6: Mitsunobu Reactions Employing <sup>F</sup>DEAD

$\text{RCOOH} + \text{R}^1\text{OH} \xrightarrow[\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{CO}_2\text{NCO}_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}]{\text{PPh}_3} \text{RCOOR}^1$		
ACID	ALCOHOL	<sup>F</sup> DEAD+PPh <sub>3</sub> % YIELD
	Et-OH	84
		73
		78
		91

Thus it has been shown that <sup>F</sup>DEAD is a viable alternative to DEAD in the Mitsunobu reaction and gives good reaction conversions and easy product separations. Unfortunately, as we could not prepare the fluorous phosphines, it was impossible to prepare a fully

fluorous version of the Mitsunobu reaction, although this has since been reported by Curran.<sup>17,21</sup>

## 2.9 Alternative Uses of DEAD

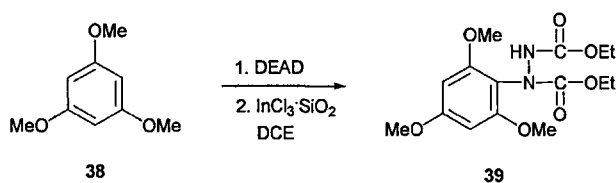
### 2.9.1 Amination Reactions

A second reaction in which DEAD has been widely employed is the amination of aromatic compounds: coupling of an aromatic compound with DEAD in the presence of a catalyst gives an aromatic hydrazine, which may then be reduced to the aniline.<sup>68,69</sup> Potentially, the use of <sup>F</sup>DEAD in these reactions would lead to a much simpler method for the purification of the aromatic hydrazine intermediate prior to the reduction step. Therefore it was decided to use our <sup>F</sup>DEAD in this context, but first, again, it was necessary to perform some model reactions.

### 2.9.2 Conventional Method<sup>68</sup>

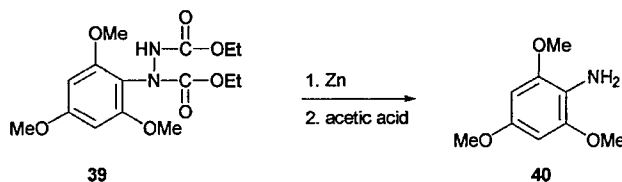
Traditionally, amination reactions of aromatics using DEAD require long reaction times and high temperatures. As well as attempting this method, a second method using microwave irradiation was also tested. Both methods used a mixed indium trichloride and silicon dioxide catalyst.

A mixture of 1,3,5-trimethoxybenzene **38** (1 eq), DEAD (1 eq) and freshly prepared catalyst<sup>68</sup> (0.1 eq) in dichloroethane was stirred at reflux temperature for 10 h. After the work up the crude product **39** was found in high yield (>90%) and almost clean by NMR spectroscopy. Since this was only a test reaction, this compound was not fully purified.



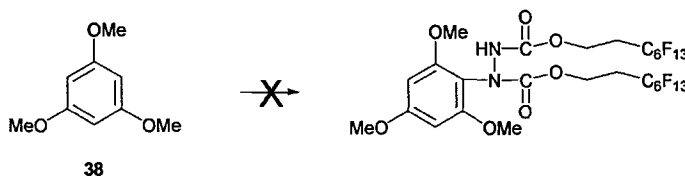
Scheme 39

Freshly obtained 1,3,5-trimethoxy-2-diethylaminodicarboxylate **39** was reacted in crude form with freshly activated zinc in glacial acetic acid to obtain the amino product **40**.<sup>69</sup> The experiment was run several times with only modest yields of product (35-48%) being obtained.



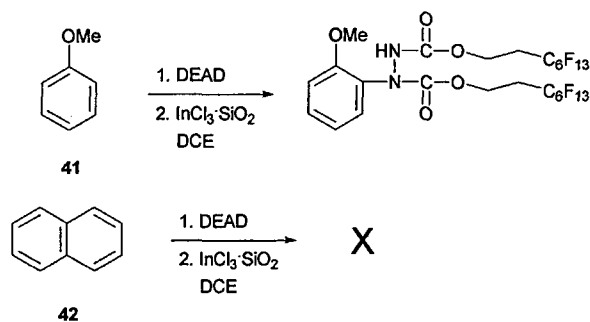
Scheme 40

The identical reactions were then repeated using <sup>F</sup>DEAD instead of normal DEAD, but the reaction failed, with only 1,3,5-trimethoxybenzene being recovered.



Scheme 41

The same reactions were repeated using 1-methoxybenzene **41** and naphthalene **42**. The first reaction with **41** gave a product in a good yield (71 %), whereas after the reaction with naphthalene the starting material being recovered.

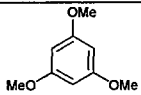
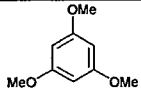
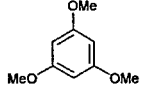
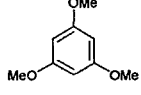
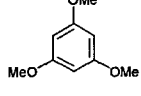
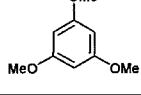
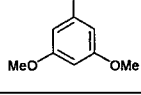
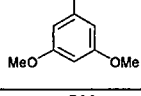

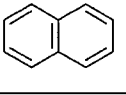
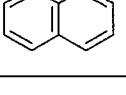


Scheme 42

2.9.3 Microwave Irradiation<sup>68</sup>

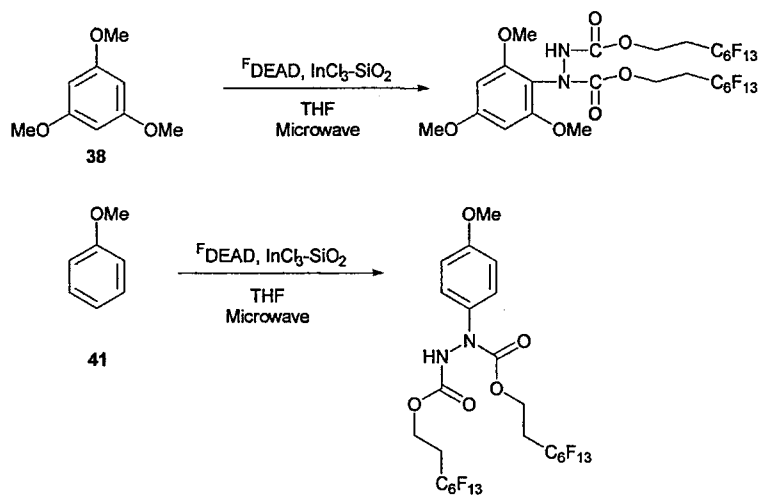
An alternative method of heating that was employed was that of microwave irradiation; this has considerable attraction and advantages over conventional heating methods, particularly with respect to greatly reduced reaction times. The experiments were carried out in few minutes compared to conventional overnight reactions. Various conditions were tested for each experiment and the results summarised in Table 7.

Table 7: Amination Reactions performed in the microwave.

	Compound	Solvent	Power /Watts	Pressure in psi	Temperature	Time /mins	Yield
1		-	300	7	100	3	-
2		-	300	7	200	3	-
3		-	300	7	150	5	69
4		1,2-dichloroethane	300	7	150	5	-
5		THF	300	7	150	7	61
6		THF	300	7	180	7	68
7		THF	300	7	160	8	-
8		1,2-dichloroethane	300	7	165	10	-
9		THF	300	7	160	8	71 (para)
10		THF	300	7	130	6	-
11		THF	300	7	160	8	-

The results show the critical nature of the reaction conditions employed, although it is interesting to note that naphthalene (entries 10 and 11) failed to give any products under both conventional and microwave heating, despite literature reports to the contrary. From entries 5, 6 and 9, it would appear that THF is the solvent of choice for these microwave reactions. Anisole also worked well under microwave irradiation conditions, giving 71% of the para-substituted product, with just a trace (<3%) of the other possible isomers.

Therefore the favoured conditions of entries 3, 6 and 9 were attempted using  $^F$ DEAD. The solvent-free reaction rapidly darkened and no products could be isolated or identified. In THF as solvent, however, under the conditions of entry 6, both anisole and 1,3,5-trimethoxybenzene gave reasonable yields of the fluoros-hydrazine (65 and 58% respectively). Water was added to the THF and the solution extracted with FC-72 and perfluoromethylcyclohexane and evaporated to give these yields. No other purification was performed. Although partition coefficients were not recorded, both compounds had high levels of fluoros solubility and no residual fluorine-containing compounds were found (by  $^{19}\text{F}$  NMR) in the aqueous layer (when extracted with ethyl acetate and evaporated).

**Scheme 43**

Unfortunately, the cleavage of the hydrazine with  $\text{Zn}/\text{AcOH}$  was unsuccessful and time prevented a full investigation of reaction conditions and alternatives to achieve this transformation.

## **2.10 Conclusions**

The original plan had been to prepare fluorous analogues of various phosphines and also DEAD. While the work on the fluorous phosphines was unsuccessful, the studies to prepare a fluorous version of DEAD were successful and this reagent has been successfully applied to the Mitsunobu reaction and, to a lesser extent, to some microwave-based amination reactions.

Attention will now turn to a different area of fluorine chemistry.

## **Chapter 3**

# **INTRODUCTION TO HETEROCYCLES**



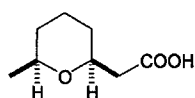
### 3. Oxygen heterocycle-containing natural products

Tetrahydropyrans and dihydropyrans are important units in many natural products and synthetic molecules.

#### 3.1. Tetrahydropyrans

Tetrahydropyrans are the backbones of most carbohydrates and their polymers. These materials are the most abundant biological molecules on earth and play several crucial roles in living organisms. They are found in the cell walls and protective coatings of many organisms and also fuel various metabolic processes.

*Cis*-(6-methyltetrahydropyran-2-yl)acetic acid **43** possesses a *cis*-2,6-disubstituted tetrahydropyran core. It is one of the most important components isolated from *Viverra civetta* and it has long been used as a fixative in the perfume industry.



*cis*-6-(Methyltetrahydropyran-2-yl)acetic acid

43

Various polyethers have been previously isolated from marine sources and their most notable features are the cyclic ethers rings of various sizes.<sup>67</sup> Some of these polycyclic compounds which show diverse biological activities, include ciguatoxins, brevetoxins (neurotoxics), gambierol (used for stomach and lung disease testing), and yessotoxin (controls body weight).<sup>70</sup>

#### 3.2. Dihydropyrans

Penitrem D (**44**, Fig. 7) belongs to an important family of environmental toxins, produced by ergot fungi that grow on a variety of grasses endemic to South Africa, New Zealand and the United States.<sup>71</sup> It is a polycyclic molecule that includes a 2,3,5,6-

tetrasubstituted dihydropyran skeleton and a substituted eight-membered oxygen containing system.

Penostatin D **45** is a tricyclic biactive secondary metabolite produced by *Penicillium* sp. and exhibits significant cytotoxic activity in the P388 lymphocytic leukemia test systems in cell cultures.<sup>72</sup> A long unsaturated alkyl chain is incorporated in the C-2 position of the dihydropyran unit.

Laulimalide **46** is a potent microtubule-stabilising anticancer agent isolated from the Pacific sponges *Hyatella* sp. and *Spongia mycofijiensis* and the Okinawan sponge *Fasciospongia rimosa*.<sup>73</sup> It is a macrolactone containing 2,6- and 4,6-disubstituted dihydropyran units. Nodulisporic acid A (NAA) **47** is a polycyclic molecule featuring a 2,4,5,6-tetrasubstituted dihydropyran ring system. It is an indole-diterpene metabolite produced by *Nodulisporium* sp., an endophytic fungus isolated from a woody plant and it exhibits potent insecticidal activities.<sup>74</sup>

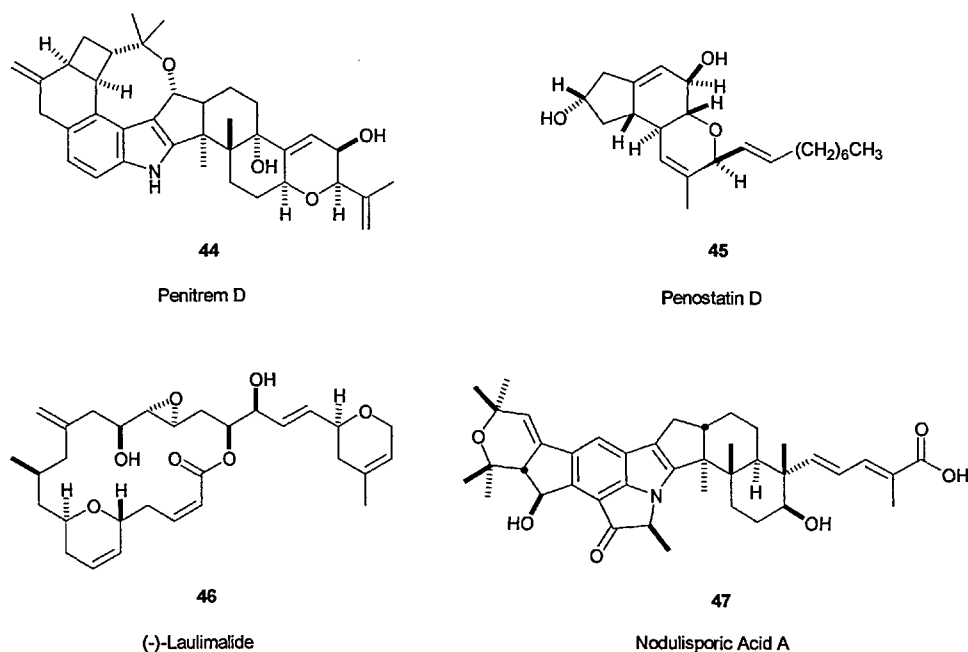


Fig. 7

### 3.3. The combination of tetrahydropyrans and dihydropyrans

The combination of tetrahydropyrans and dihydropyrans is also a common structural feature of many natural products.

Okadaic acid (**48**, Fig. 8) is the causative agent of diarrhetic shellfish poisoning. It was initially isolated from two marine sponges *Halichondria okadaei* and *H. melanodocia* but later found to come from certain varieties of marine plankton and to accumulate in sponges.<sup>75</sup> It contains a 2,4,6-trisubstituted dihydropyran ring system and two spiroketal units, as well as a fused six-membered oxygenated ring system.

Ambruticin **49** was isolated from fermentation extracts of the Mycobacteria species *Polyangium cellulorum* var. *fulvum* and is an orally active antifungal agent showing *in vitro* and *in vivo* activity against a variety of pathogenic fungi.<sup>76-78</sup> This molecule incorporates a 2,3,6-substituted dihydropyran system and a substituted tetrahydropyran ring system which are connected *via* a long unsaturated alkyl chain.

Martiriol **50** is a new cytotoxic compound featuring fused six-membered oxygenated rings, a 2,6-disubstituted dihydropyran ring containing a long alkyl chain in the C-2 position and a substituted tetrahydropyran ring. It was isolated as a secondary metabolite of red algae of the genus *Laurencia*.<sup>79</sup>

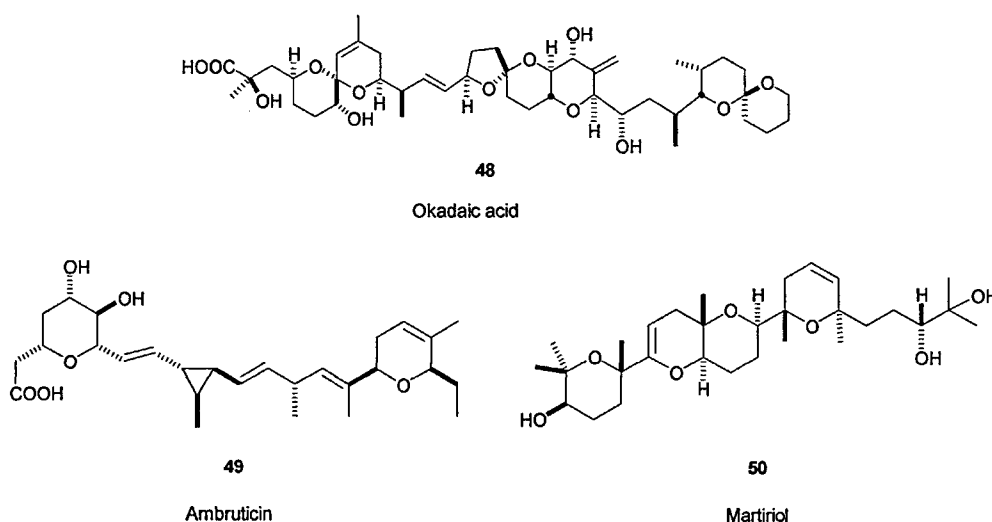
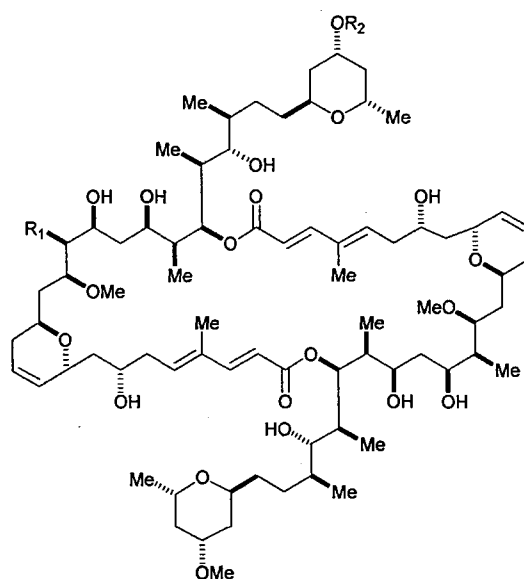


Fig. 8

The natural marine products Swinholides **51**, **52** and **53** (Fig. 9), isolated from the Okinawan marine sponge *Theonella swinhoei*, exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as a broad spectrum of antifungal activity.<sup>80-84</sup> Swinholides are macrolactones containing 2,6-disubstituted and 2,4,6-trisubstituted dihydropyran type structures interconnected by long polysubstituted alkyl chains.



Swinholide **51**:  $R_1 = R_2 = \text{Me}$   
 Swinholide **52**:  $R_1 = \text{H}$ ,  $R_2 = \text{Me}$   
 Swinholide **53**:  $R_1 = \text{Me}$ ,  $R_2 = \text{H}$

Fig. 9

### 3.4 Methods for the Preparation of 5,6-dihydro-2H-pyrans

Having discussed the common dihydropyran skeleton of many natural products a short summary of the main methods for their preparation will be outlined.

#### 3.4.1 Introduction

The oxa-analogues of cyclohexene related to 2H-pyran **54** include 5,6-dihydro-2H-pyran **55** (Fig. 10).<sup>85</sup>

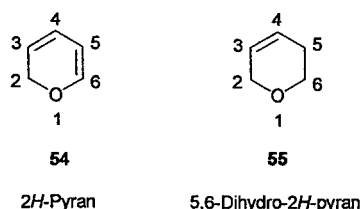


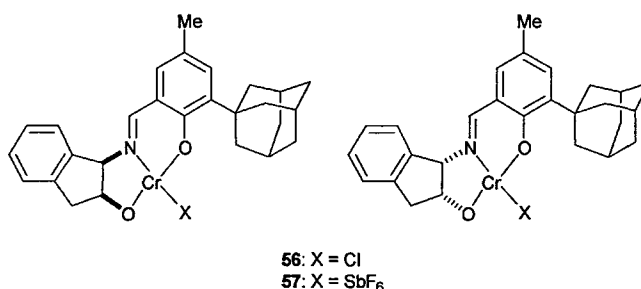
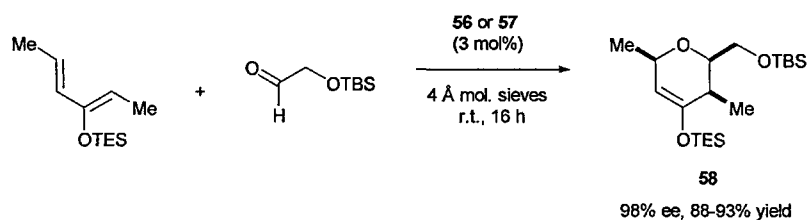
Fig. 10

There are many different routes known in the chemical literature for the preparation of 5,6-dihydro-*2H*-pyran structures. In this short summary only the main methods and some interesting examples for the preparation of 5,6-dihydro-*2H*-pyran structures will be outlined.

### 3.4.2. [4+2] Cycloaddition reactions

[4+2] Cycloaddition reactions, especially the Diels-Alder and hetero-Diels-Alder reactions, are the concerted reactions of  $4\pi$  and  $2\pi$  components to give a cyclohexene ring. Cycloaddition reactions are widely used synthetic methodologies for the regio- and stereoselective construction of 5,6-dihydro-*2H*-pyrans.<sup>86-90</sup> The selectivities of the hetero-Diels-Alder reactions are not always high and considerable attention has been paid to developing new catalysts for improving the reaction.

Recently, the hetero-Diels-Alder approach has been used in the total synthesis of various natural products.<sup>91,92</sup> Jacobsen's group has developed chiral chromium based catalysts **56** and **57** for hetero-Diels-Alder reactions and utilised them during the key step in the total synthesis of FR901464, **58**, the most potent member of a new series of bacterially produced antitumour antibiotics (Scheme 44).<sup>93,94</sup>

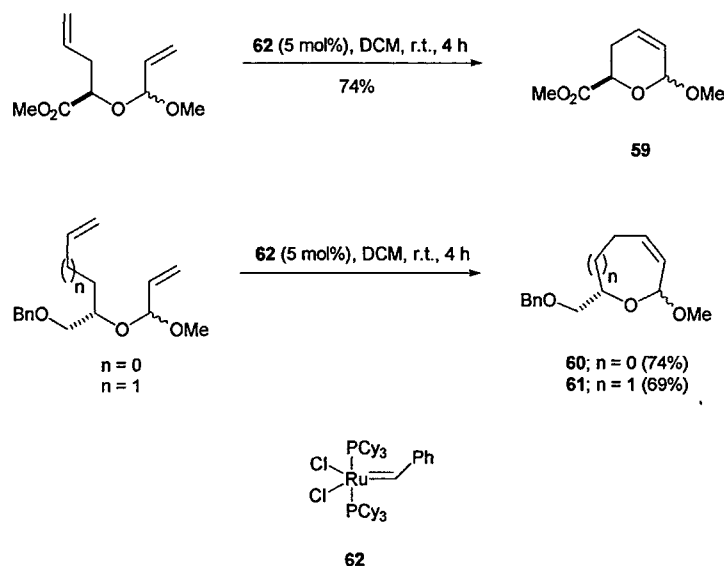


Scheme 44

### 3.4.3. Ring Closing Metathesis

Ring closing metathesis is the transition metal catalysed cyclisation reaction in which two remote alkene parts of a molecule are brought together to form the ring system. Since the development of new ruthenium-based catalysts by Grubbs<sup>95-97</sup> and molybdenum-based catalysts by Schrock,<sup>98,99</sup> ring closing metathesis has become an important and widely used synthetic tool for the construction of many heterocycles, including 5,6-dihydro-2*H*-pyrans. Numerous examples of synthetic routes towards dihydropyrans based on ring closing metathesis are given in the literature.<sup>100-105</sup>

Rutjes and co-workers have developed a method based on ring closing metathesis for the synthesis of functionalised dihydropyrans **59** and tetrahydrooxepines **60** and **61** (Scheme 45).<sup>106</sup>

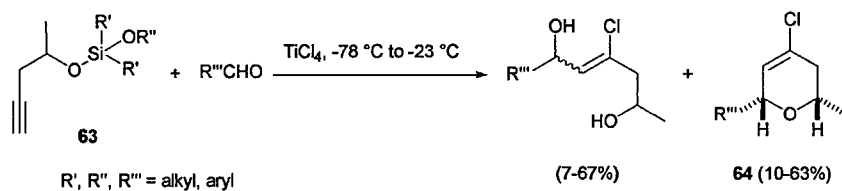


Scheme 45

Ring closing metathesis has been used in the synthesis of a variety of the natural products.<sup>107-111</sup>

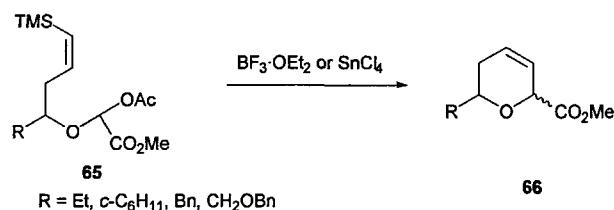
### 3.4.4. Condensation reactions

Condensations reactions are those in which two molecules combine with loss of a small molecule, often water. Condensation reactions of silyl acetals **63** and various aldehydes in the presence of Lewis acids were found to give good yields of chlorinated dihydropyrans **64** (Scheme 46).<sup>112</sup>



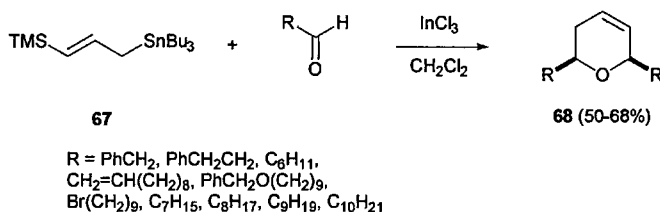
Scheme 46

It has also been reported that in the presence of Lewis acids, acyclic diesters terminated by a vinylsilane moiety **65** lead to dihydropyran building blocks **66** (Scheme 47).<sup>113</sup>



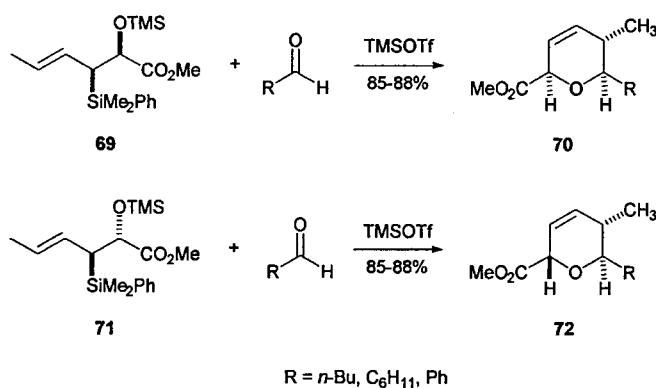
Scheme 47

An indium trichloride-mediated cross-cyclisation reaction of 3-trimethylsilylallyltributylstannane **67** with 2 equivalents of an aldehyde led to the formation of 2,6-dialkyl-3,4-dihydropyrans **68** with *cis* diastereoselectivity (Scheme 48).<sup>114</sup> With this methodology it is only possible to introduce the same substituents in the positions 2 and 6 of the dihydropyran core.



Scheme 48

Optically active dihydropyrans **70** and **72** have been formed by a direct coupling-cyclization of the chiral silanes **69** and **71** with a wide range of aldehydes in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (Scheme 49).<sup>115</sup>



Scheme 49



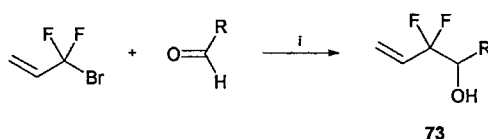
Despite these ring forming reactions, novel methods are still required for the preparation of natural products and the synthesis of their analogues.

### 3.5 Fluorinated heterocycles

In recent years the introduction of the difluoro-fragment into organic compounds has become an attractive sphere of research. Such molecules can inhibit one or more enzymes or can be partially metabolised into more bioactive substances.<sup>116, 117</sup> Halodifluoroacetates, chlorodifluoromethyl ketones and bromodifluoromethyl acetylene<sup>118</sup> have been used widely as reagents to introduce a CF<sub>2</sub> moiety into molecules.

As fluorine chemistry became more popular, it was inevitable that chemists would turn their attention to the preparation of fluorinated carbohydrates. Such targets attracted scientists by their important role in enzyme-carbohydrate interactions and also by their potential biological activity.<sup>119</sup> Fluorinated carbohydrates maintain much of the reactivity of the natural saccharides, but at the same time prevent hydrogen bonding interactions with nucleic acids or proteins.<sup>120</sup>

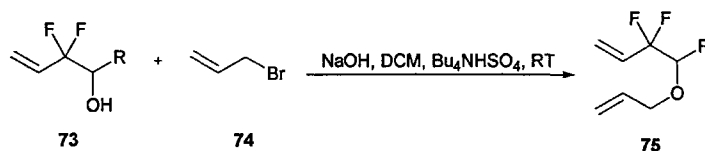
Analogues of difluorinated carbohydrates are usually prepared by DAST difluorination of molecules with ketonic carbonyl groups.<sup>121</sup> Percy's approach was based on metallated difluoroenol derivatives by using a ring closing metathesis (RCM) method.<sup>121-123</sup> He employed allylindium chemistry and at the first stage was synthesised homoallyl alcohol **73** in good yields.<sup>121</sup>



i = In (325-zinc mesh can be used as well) DMF, sonication

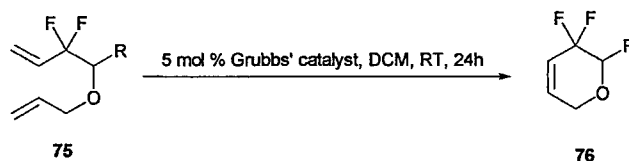
**Scheme 50**

This is followed by *O*-allylation employing allyl bromide **74** and sodium hydroxide in the presence of Bu<sub>4</sub>NHSO<sub>4</sub>:



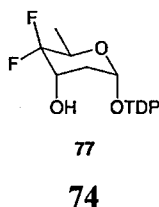
Scheme 51

The final stage used RCM to furnish the difluorinated heterocycle **76** (Scheme 52).<sup>121,122</sup>



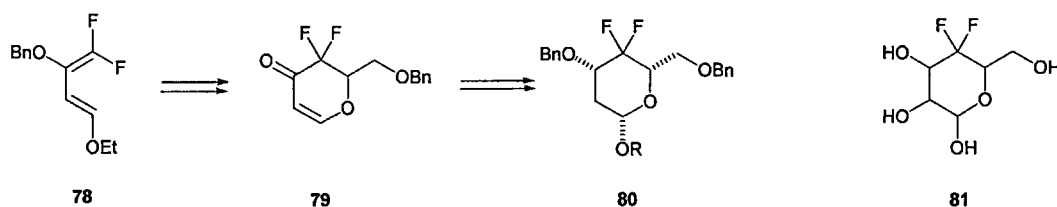
Scheme 52

Several other groups have used DAST to introduce fluorine in sugars, including Liu, who has reported 10 step route to TDP 4,4-difluoro-2,4,6-trideoxy-sugar, **77**.<sup>124</sup>



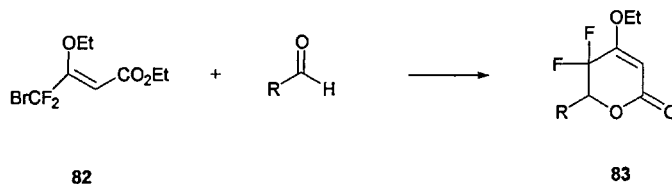
The two fluorine atoms stabilise the bond to the TDP leaving group. Such compounds have the potential to probe the binding sites of glycosyltransferase enzymes.<sup>125</sup>

Taguchi's group<sup>126</sup> prepared dihydropyrone **79** using a hetero Diels-Alder reaction employing 1,1-difluoro-2,4-dialkoxy-1,3-butadiene **78**. The product **79** was developed to a 2,4-dideoxy-4,4-difluorosugar **80**, but the final stage, obtaining 4-deoxy-4,4-difluorosugar **81** was not reported (Scheme 53)



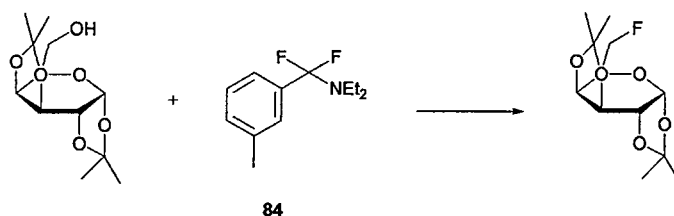
Scheme 53

There have been some other attempts to synthesise difluoroheterocycles. Hu<sup>127</sup> utilized a Reformatsky reaction to obtain 4,4-difluoro-3-ethoxy-2-lactanone **83** using ethyl 4,4-difluoro-ethoxy-4-halocrotonate **82**, an aldehyde and Zn powder (Scheme 54):



Scheme 54

Recently an attractive method to obtain monofluorinated carbohydrates has been introduced. *N,N*-Diethyl- $\alpha,\alpha$ -difluoro-(*m*-methylbenzyl)amine **84** has been found to be a selective reagent for synthesising fluorinated carbohydrates. Hara has employed this reagent for deoxyfluorination of primary hydroxyl groups and anomeric hydroxyl groups in sugars as well.<sup>128</sup>



Scheme 55

At the early stages conventional conditions were exploited, but later the yield was significantly increased by microwave irradiation.

### 3.6 Aims

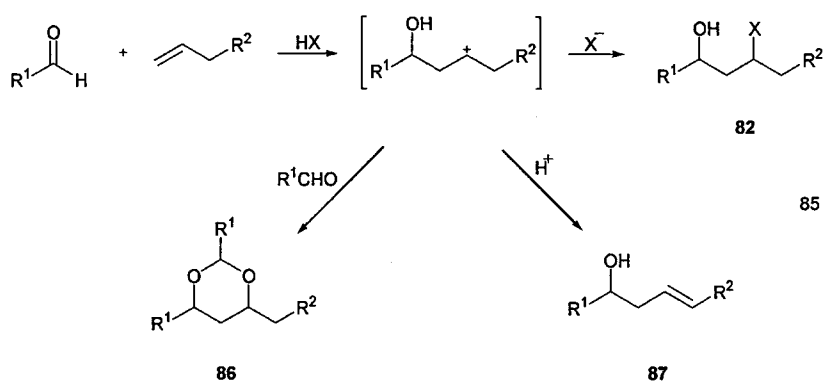
Fluorosugars show great potential for the creation of probes and inhibitors of sugar processing enzymes. This is a new direction of research and there are no reports available about them.

Given the demand for these compounds, it was planned to continue interests in fluorine-containing compounds by devising a novel method for the synthesis of fluorine containing heterocycles. Current expertise in the research group on the Prins reaction would form the

basis for this work, with the fluorine to be incorporated into one of the reactants and also *via* a Lewis acid mediated cyclisation.

### 3.7. The Prins Reaction

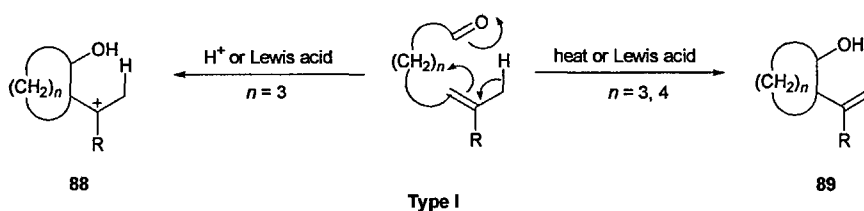
The Prins reaction is generally considered as the addition of aldehydes and ketones to alkenes in the presence of Brønsted acids.<sup>129-131</sup> Under Lewis acid conditions a range of carbonyl compounds react with alkenes to offer homoallylic alcohol ene adducts, but in some cases  $\gamma$ -chloro alcohols are also formed as by products.<sup>132,133</sup> During the first stage, a carbonyl compound and alkene react to generate a  $\beta$ -hydroxy carbocation which then reacts either with a nucleophile (chloride, water) to give **85** or a second molecule of aldehyde to give **86**. When losing a proton it transforms into a homoallylic alcohol **87**.<sup>134</sup>



**Scheme 56**

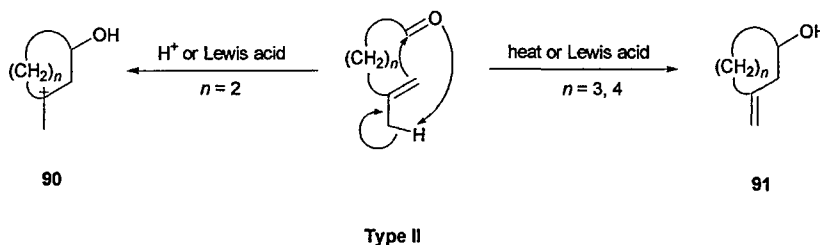
Intramolecular Prins and ene reactions are divided into three types, depending on the connectivity pattern of the carbonyl group and alkene.<sup>135</sup>

Type I ene reactions are restricted to the formation of five and six membered rings. The carbonyl group creates a bond to the internal carbon of the double bond. In the Prins reaction, the reaction ends with products derived from **88**, but with the ene reaction **89** is obtained (Scheme 57).<sup>134</sup>



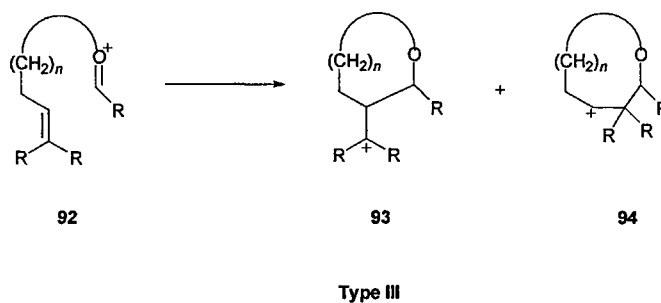
Scheme 57

Although Type II can form five-membered rings, in practice it is restricted to the formation of six- and seven-membered rings. Here, the carbonyl group creates a bond to the terminal carbon of the double bond. The Prins adducts come out from the products derived from **90**, and the ene reaction gives **91**, (Scheme 58)



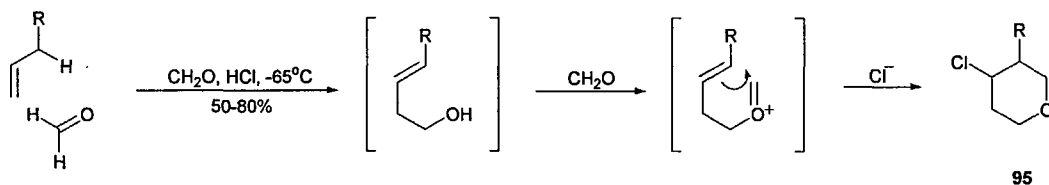
Scheme 58

Type III reactions use an acetal, hemiacetal or enol ethers, which is converted to a cation **92**. This cyclises to **93** or **94** depending on the substitution pattern of the double bond (Scheme 59)



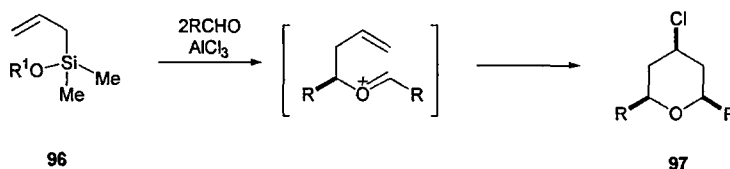
Scheme 59

If the internal end of the double bond is highly substituted, cyclisation proceeds in an endocyclic mode to give **94**. This reaction has been widely reported for the formation of 4-chlorotetrahydropyrans **95**. (Scheme 60)<sup>129-131,136-140</sup>



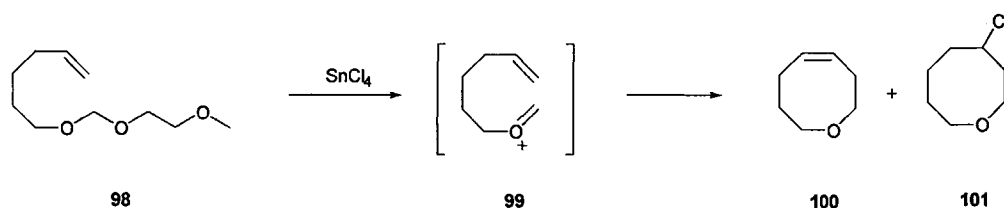
Scheme 60

Interaction of alkoxy-silanes **96** with aldehydes and  $\text{AlCl}_3$ ,  $\text{SnCl}_4$  or  $\text{TiCl}_4$  gives *cis*-2,6-dialkyl-4-chlorotetrahydropyrans **97**<sup>134,140</sup> (Scheme 61)



Scheme 61

The same, type III cyclisations have been used by Overman<sup>141,142</sup> to obtain eight and nine-membered cyclic ethers. He treated **98** with 2 equiv. of  $\text{SnCl}_4$  for 13h at  $-20^\circ\text{C}$  and obtained **96** that cyclises to give a 2:1 mixture of **100** and **101**<sup>143</sup> (Scheme 62).<sup>134</sup>



Scheme 62

The pyran skeleton forms the basis of many natural products and a large number of methodologies have been published for the synthesis of these oxygen-containing heterocycles.<sup>114,144-148</sup>

## **Chapter 4**

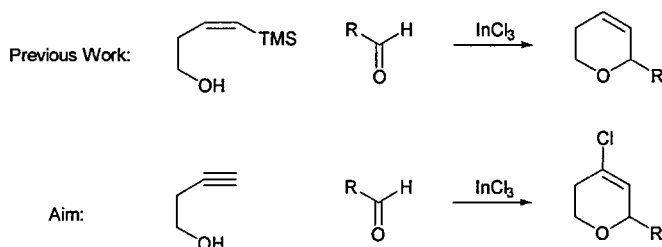
# **RESULTS & DISCUSSION II: NOVEL METHODS TO PREPARE FLUORINATED HETEROCYCLES**

## 4.1 Introduction

Based on previous results within our group of studies on the Prins and silyl-Prins reactions,<sup>149,150</sup> indium trichloride was known to be a mild Lewis acid that is: easy to handle, a solid, non-toxic, and not very hygroscopic. Most importantly of all, it gave good reaction yields. This project aimed to use Prins-type cyclisation reactions employing indium-based Lewis acids to obtain a range of oxygen containing heterocycles, including fluorinated derivatives.

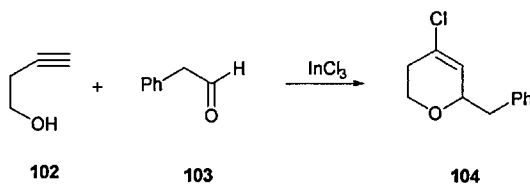
## 4.2 Synthesis of Dihydropyrans from Acetylenes

We have previously reported the synthesis of dihydropyrans from silylated homoallylic alcohols. In place of this starting material, which takes two steps to prepare, attention focussed on using alkynes as suitable precursors to dihydropyrans.



Scheme 63

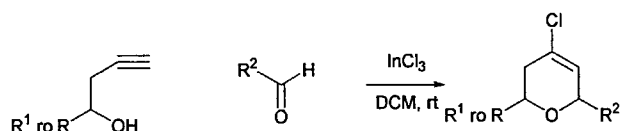
In a preliminary test reaction, phenylacetaldehyde **103** (1 eq) was added to a solution of 3-butyn-1-ol **102** (1 eq) in dichloromethane at room temperature followed by indium chloride (1 eq). These were the identical conditions developed for the silyl-Prins reactions. Pleasingly, the cyclised 4-chlorodihydropyran derivative **104** was obtained in 40% yield. (Scheme 64)



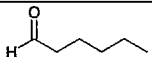
Scheme 64

A wide range of aldehydes and alkynes were then employed in this reaction; the results are summarised in Table 8.

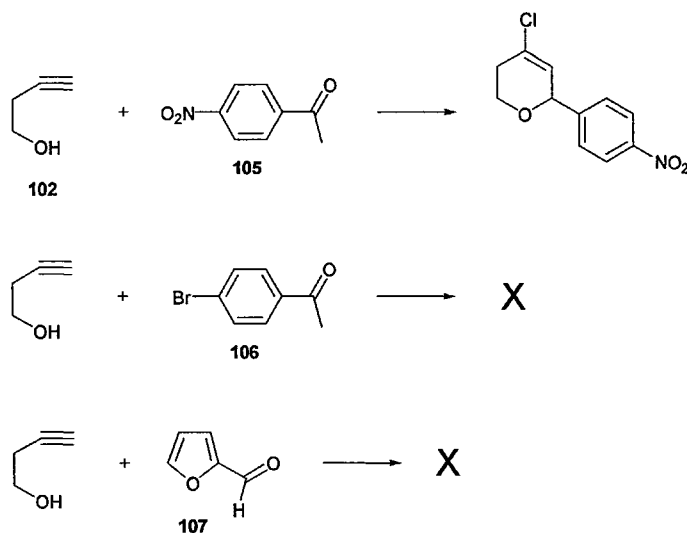


**Table 8:** Cyclisation of homoacetylenic alcohols with aldehydes and indium trichloride.

Entry	Alkyne	Aldehyde	Lewis Acid	Solvent	% Yield
1	R = H		InCl <sub>3</sub>	DCM	40
2	R = H		InCl <sub>3</sub>	DCM	80
3	R = H		InCl <sub>3</sub>	DCM	63
4	R = H		InCl <sub>3</sub>	DCM	48
5	R = H		InCl <sub>3</sub>	DCM	56
6	R = H		InCl <sub>3</sub>	DCM	48
7	R = H		InCl <sub>3</sub>	DCM	41
8	R = H		InCl <sub>3</sub>	DCM	41
9	R = H		InBr <sub>3</sub>	DCM	76(mixture)
10	R = H		InBr <sub>3</sub>	DCM	53(mixture)
11	R = H		InBr <sub>3</sub>	DCM	51 (mixture)
12	R = H		InCl <sub>3</sub>	DCM	-
13	R = H		InCl <sub>3</sub>	DCM	-
14	R = H		InCl <sub>3</sub>	DCM	-
15	R <sup>1</sup> = Me		InCl <sub>3</sub>	DCM	-
16	R <sup>1</sup> = Me		InCl <sub>3</sub>	DCM	-
17	R <sup>1</sup> = Me		InCl <sub>3</sub>	DCM	-
18	R = H		BF <sub>3</sub> O(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	DCM	22
19	R = H		TMSOSO <sub>2</sub> CF <sub>3</sub>	DCM	52

20	R = H		InBr <sub>3</sub>	DBM	71
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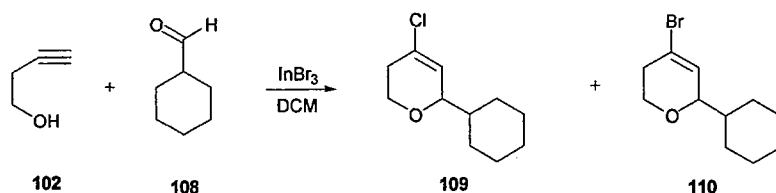
Simple aldehydes were found to react well with 3-butyn-1-ol at room temperature in short reaction times (5 min) in good to excellent yields and as a single diastereomer (Table 8, entries 1-8). As with related cyclisations using indium trichloride,<sup>149</sup> aromatic aldehydes were found to be much less reactive compared to aliphatic ones (entries 7,12 & 14); only 4-nitrobenzaldehyde gave a product, and this reaction required longer reaction times and heating to reflux for two h.  $\alpha,\beta$ -Unsaturated compounds also failed to give any product either at ambient temperature or reflux (entry 13).



Scheme 65

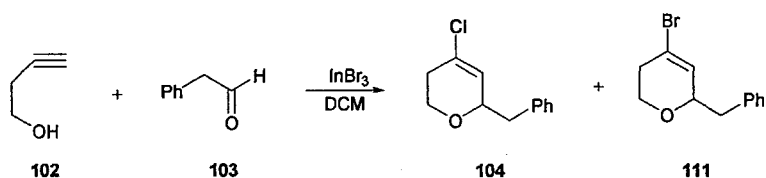
Of more interest was the observation that pent-4-yn-2-ol gave no equivalent product with any aldehyde, only starting material being recovered (entries 15-17). There is no obvious explanation for this observation, but it is in keeping with those reported by Martin<sup>151</sup> in a related study using aluminium-based Lewis acids.

Using other Lewis acids gave interesting results. Replacing indium trichloride with indium tribromide gave the vinyl bromide as the major product (entries 9 & 10), although a second, inseparable product was identified from these reactions as the chlorinated product. Although inseparable by chromatography, by GCMS, the ratio of the two products bromide **110**:chloride **109** was 2.5:1 (Scheme 66).



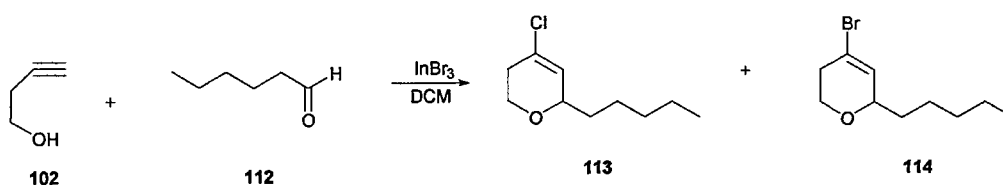
Scheme 66

The use of indium tribromide was also investigated using phenylacetaldehyde. As in the previous example, the experiment afforded an inseparable mixture of bromo 111 and chloro 104 substituted molecules in the ratio (according to GCMS) 2.5:1 (Scheme 67).



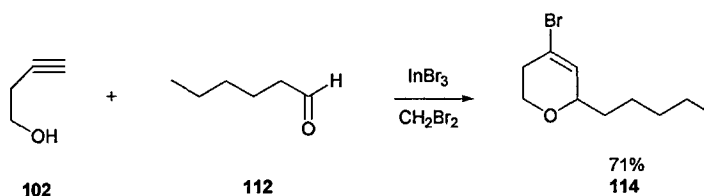
Scheme 67

Indium tribromide was employed in the reaction with hexanal 112 (entry 11). As in the previous examples with  $\text{InBr}_3$  the reaction completed with inseparable mixture of chloro 113 and bromo 114 compounds in the ration (according to GCMS) 3:1 (Scheme 68)



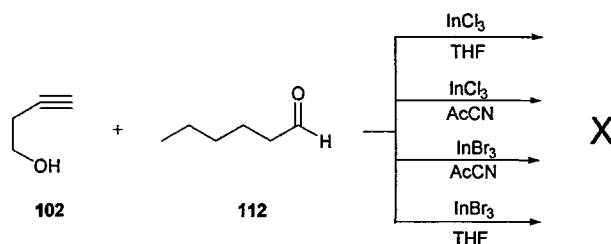
Scheme 68

The indium tribromide was pure by mass spectrometry and microanalysis, and thus not the source of chlorine. Therefore the only explanation is that the chlorine must come *via* the solvent, dichloromethane. Therefore, using this method to prepare heterocyclic vinylbromides would appear to be inefficient. Obviously, to overcome this we must remove the possibility of halogen exchange, and this can be done through the use of dibromomethane (entry 20). In this way, the brominated product comparable to those from the  $\text{InCl}_3/\text{DCM}$  combination were obtained (Scheme 69).



Scheme 69

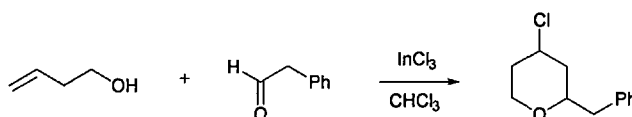
In addition, other solvents were tested: tetrahydrofuran and acetonitrile. Two identical experiments were set in parallel to each other with reactants that were known to react well together: 3-butyn-1-ol **102**, hexanal **112**, and indium trichloride as the Lewis acid. A second set of reactions was performed using indium tribromide in place of indium trichloride. None of the reactions in these solvents gave any product, or indeed any identifiable material (Scheme 70).



Scheme 70

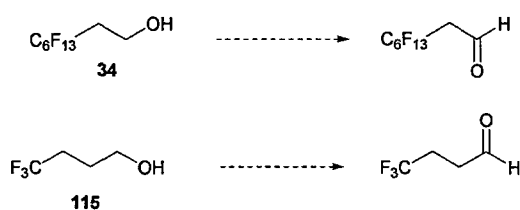
Employing boron trifluoride (entry 18) failed to give any product, either at room temperature or  $-78\text{ }^\circ\text{C}$ . Using TMSOTf, however, was a useful alternative to indium trichloride, generating a vinyl triflate in the product. The reaction, however, required much lower temperatures,  $-78\text{ }^\circ\text{C}$ , to proceed (the reaction mixture decomposed if the reaction was performed at room temperature).

Single experiment has been performed using 3-buten-1-ol **113** and phenylacetaldehyde **103** in chloroform. Overnight reaction gave the product in a good yield (Scheme 71)



Scheme 71

As an intellectual curiosity, and linking back to chapters 1 and 2, it was decided to see if dihydropyrans bearing a fluorinated chain could be prepared *i.e.* to introduce a fluorinated chain *via* a fluorinated aldehyde. The targeted fluorine-containing aldehydes were identified as being potentially available from commercial alcohols under Swern oxidation conditions. 1H,1H,2H,2H-Tridecafluoro octanol **34** and 4,4,4-trifluorobutanol **115** were selected (Scheme 72).



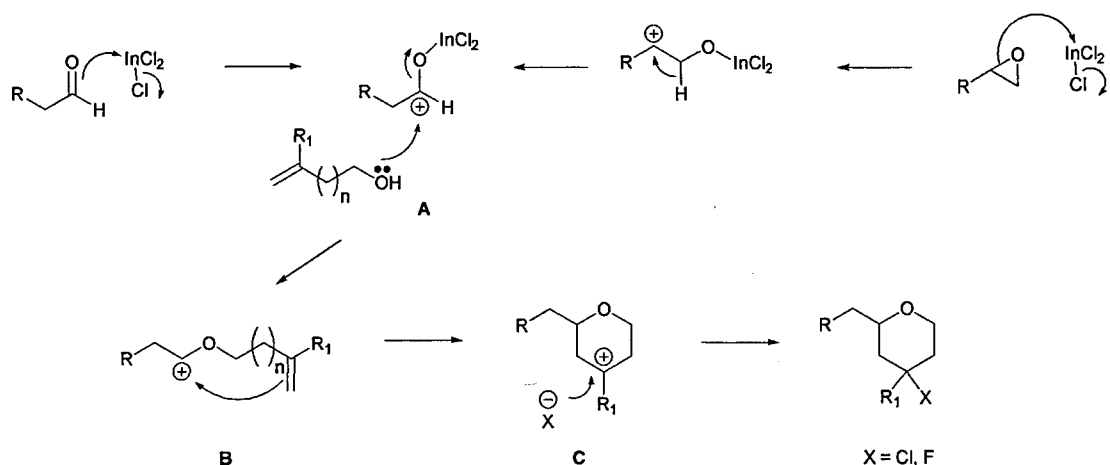
Scheme 72

Unfortunately, both reactions failed and these aldehydes could not be tested.

The results have shown that, beside a few negative examples, indium chloride is a reliable Lewis acid except for a few Prins-cyclisation reactions of acetylenes.

#### 4.3 Application of Prins-type reactions to the synthesis of fluorinated dihydropyrans

The Prins cyclisation is also known as an efficient method for the preparation of tetrahydropyrans.<sup>149</sup> Previous work in our group and also by Li<sup>152</sup> has shown that 4-halotetrahydropyrans are available by the reaction of homoallylic alcohols with aldehydes and a Lewis acid (Scheme 73).

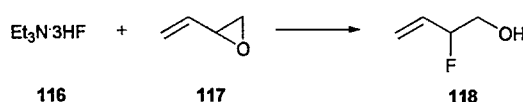


Scheme 73

It was proposed that it may be possible to prepare fluorinated tetrahydropyrans, as precursors to fluorinated heterocycles and sugars, by incorporating fluorine into the homoallylic alcohol starting material.

There are number of examples of opening epoxide rings by fluoride to obtain fluorine containing products.<sup>152-160</sup> The Baklouti group also demonstrated<sup>161</sup> the possibility of epoxide ring opening at room temperature by using hydrogen fluoride and pyridine. Another work of Baklouti's group, in which triethylamine trihydrofluoride **116** as a nucleophile for epoxide opening to obtain mono-fluorinated alcohols as the final product<sup>162</sup> was of particular interest to us in our desire to prepare fluorine-containing cyclisation precursors.

Under a nitrogen atmosphere butadiene monoxide **117** (1 eq) was treated with triethylamine trihydrofluoride **116** (2 eq) for 24 h at room temperature. After work-up, a crude mixture containing the product, 2-fluorobut-3-en-1-ol **118** was obtained (Scheme 74).<sup>162</sup>

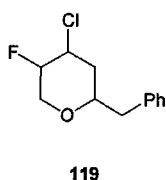


Scheme 74

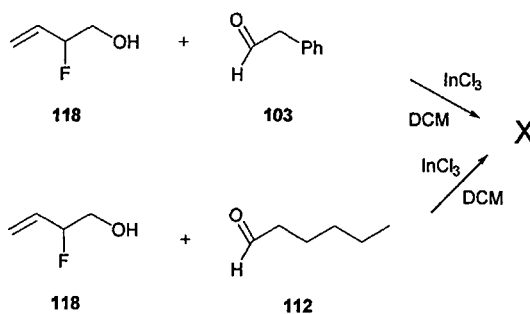
Initial attempts at performing cyclisation reactions using this compound did not furnish the desired product. This is believed to be due to incomplete formation of **118**. Thus the conditions for epoxide opening reaction were changed and instead of stirring for 24h at

room temperature, the mixture was heated at reflux for 70°C for 8h. The title compound **118** was purified by distillation as a colourless oil in good yield (62%).

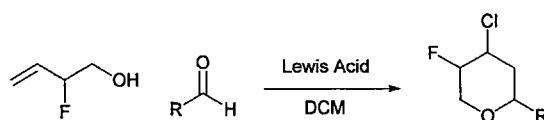
The purified product was then used in a Prins cyclisation reaction.<sup>162</sup> It was reacted with phenylacetaldehyde **103** and indium chloride with a ratio of 1:1:1 to obtain a di-halogenated tetrahydropyran, with chlorine at the 4-position and fluorine at the 5-position (**119**) but initially only in trace amounts.



Two further reactions employing **118** with either hexanal or phenylacetaldehyde with indium chloride in 1:1:1 molar ratio at room temperature, even at prolonged reaction times, failed to produce significant yields of product.



It was decided to vary the ratio between reactants and also instead of stirring at room temperature to heat the reaction mixture to reflux. These variations worked very well, with the best yields of product being obtained with a ratio of alcohol:aldehyde:indium trichloride 1:1.5:2 and heating to reflux for as long as TLC indicated that there was still starting material present. This became the general method for the preparation of fluorinated tetrahydropyrans. The results for various aldehydes are presented in Table 9.

**Table 9:** Reaction of various aldehydes with 2-fluorobut-3-en-1-ol **118**.

Entry	Aldehyde	Lewis Acid	Solvent	% Yield
1		InCl <sub>3</sub>	DCM	70
2		InCl <sub>3</sub>	DCM	65
3		InCl <sub>3</sub>	DCM	Trace amounts
4		InCl <sub>3</sub>	DCM	61
5		InCl <sub>3</sub>	DCM	-
6		TMSOSO <sub>2</sub> CF <sub>3</sub>	DCM	56*
7		BF <sub>3</sub> OEt <sub>2</sub>	DCM	-
8		BF <sub>3</sub> OEt <sub>2</sub>	DCM	-
9		AlCl <sub>3</sub>	DCM	-

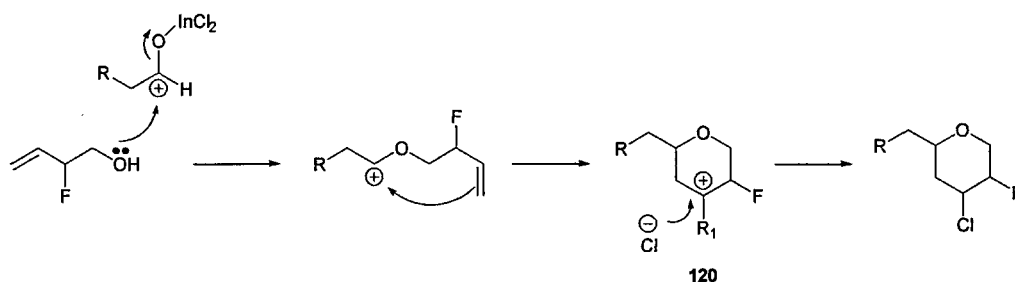
\* not of the tetrahydropyran but rather the fluorinated dihydropyran.

As with previous Prins cyclisations, good yields were obtained under the optimised reaction conditions and molar ratios for a range of aliphatic aldehyde (entries 1-4). The products were always obtained as single diastereomers. Once again, aromatic compounds are much less successful in these reactions and even 4-nitrobenzaldehyde, previously the most reactive of the benzaldehydes, failed to give any identifiable product.

Most pleasing was the fact that the presence of the highly electronegative fluorine atom appeared to have very little effect on the Prins cyclisation, and in particular on the stability of the cation **120**. The stability of this cation was considered as crucial to the cyclisation, but pleasingly the electron withdrawing effect of the fluorine atom does not appear to have

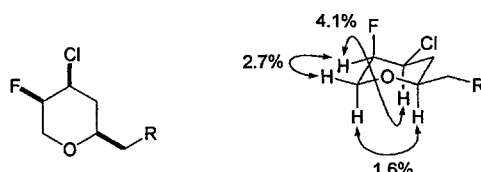


affected this process, with yields for this cyclisation only being slightly lower than those obtained in non-fluorine containing Prins cyclisations.

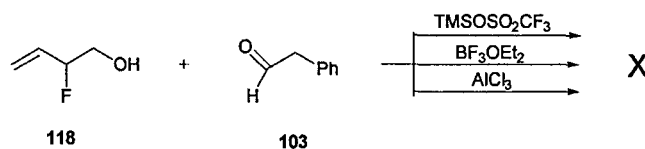


Scheme 76

Finally, it was necessary to examine the stereochemistry of the newly formed heterocycles. nOe NMR experiments were performed on all the fluorinated heterocycles prepared (entries 1-5) and all were found to have the same stereochemistry: the substituents were orientated in an all-*cis* conformation. At present, there is no other data (crystallography) to support the nOe assignments, although the results of the nOe experiments were almost identical for each of the fluorinated compounds prepared.

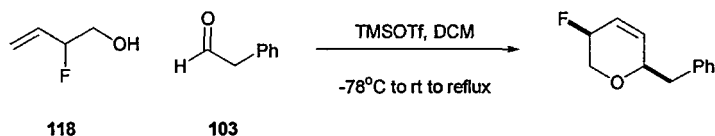


The final part of this section of the project involved looking at other Lewis acids, in order to introduce different substituents at the 4-position, in place of chlorine. Reactions were set-up using 2-fluorobut-3-en-1-ol **118** and phenylacetaldehyde **103** and either trimethylsilyl triflate, boron trifluoride etherate or aluminium chloride (Scheme 77). All three failed to give the desired tetrahydropyrans.



Scheme 77

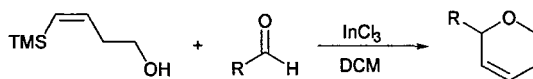
However, a dihydropyran product was obtained from the reaction with TMSOTf (Table 9 entry 7). Rather than the 4-OTf substituted product, the dihydropyran was isolated in 56% yield. It is believed that the tetrahydropyran was probably first formed, but then elimination of the triflate group gave the obtained product. The substituents at the 2- and 5-positions maintained a *cis*-relationship, as judged by nOe studies.



Scheme 78

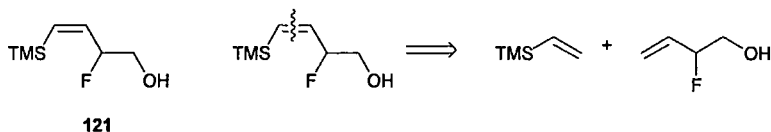
#### 4.4 The silyl-Prins Reaction and fluorinated heterocycles

Our research group has also developed a method for the preparation of dihydropyrans known as the silyl-Prins reaction.<sup>149</sup> This reaction involves the reaction of a vinylsilane-containing homoallylic alcohol with an aldehyde and Lewis acid, to give excellent yields of dihydropyrans.



Scheme 79

We set out to produce fluorinated dihydropyrans *via* this methodology, using fluorinated vinylsilane precursors. This method has the additional advantage that the carbocation intermediate **120** has additional stabilisation *via* the  $\beta$ -effect from the neighbouring silicon atom, prior to being eliminated to form the endocyclic double bond. First, it was necessary to prepare the fluorine containing vinylsilane **121**, and it was proposed to do this *via* a metathesis reaction.

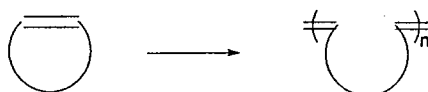


### 4.5 Methathesis

The process, where unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes is called olefin metathesis.<sup>163-165</sup> In the early stages of development, olefin metathesis was carried out using ill-defined multicomponent catalyst systems.<sup>166-168</sup> Only in the past few years have well-defined single component metal carbene complexes been prepared and used in olefin methathesis.<sup>169</sup> Both functional groups in the substrate and solvents (including oxygen and water ) can interfere with the methathesis catalysts. After a broad range of research, Grubbs has found that ruthenium reacts preferentially with carbon-carbon double bonds, making ruthenium-containing catalysts very stable to alcohols, amides, aldehydes and carboxylic acids.<sup>169</sup>

The reactions can be grouped into the three types of methathesis:<sup>122</sup>

#### 1. Ring-Opening Metathesis Polymerisation (ROMP)



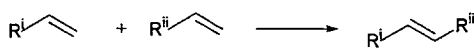
Scheme 80

#### 2. Ring-Closing Methathesis (RCM)



Scheme 81

#### 3. Acyclic Cross Metathesis (ADMET)

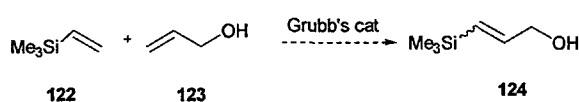


Scheme 82

The first two types (Scheme 80 and 81) are widely used. Much less effort has been concentrated on acyclic cross-methathesis (Scheme 82).<sup>170,171</sup> Until recently, selective cross-metathesis was used for styrenes, acrylonitrile and allylsilanes<sup>172</sup>. The  $\beta$ -effect of silicon means allyltrimethylsilane is a useful reagent for cross-metathesis<sup>170</sup> and vinylsilanes have also been employed. In this article the authors demonstrated the success

of cross-metathesis reactions using epoxyalkenes. Based on this approach, this project aimed to utilise the cross-metathesis method using vinyltrimethylsilane and 2-fluorobut-3-en-1-ol **118** to prepare **121** and then to use this in silyl-Prins cyclisation reactions.

First, the cross-metathesis reaction was tested on non-fluorinated compounds. Vinyltrimethylsilane **122** and 2-propen-1-ol **123** in dry dichloromethane was mixed and a solution of Grubb's catalyst (type I) in dry dichloromethane was added.<sup>170</sup> After 16 h of stirring at room temperature the desired 3-trimethylsilylprop-2-en-1-ol **124** was not obtained (Scheme 83) only starting material being recovered.



Scheme 83

This experiment was repeated several times, but with unsuccessful results. Changing to Grubb's type II catalyst also failed to give any of the desired product. Time prevented any alternative methods for the preparation of **121** being attempted.

#### 4.6 Conclusions

It has been shown that both acetylenes and fluorinated homoallylic alcohols may be used in the Prins cyclisation reaction, to give single diastereomeric products in good yields. This is the first time that fluorinated compounds have been employed in this reaction and the first time that fluorinated tetrahydropyrans have been prepared in this manner. This reaction, in particular, warrants further investigation, for example using additional substituents in the starting material as well as further elaboration of the tetrahydropyran products. Obviously, these compounds will also be of potential interest to biologists.

## **Chapter 5**

### **RESULTS & DISCUSSION III: NATURAL PRODUCT SYNTHESES USING THE PRINS CYCLISATION**

A perfume is a fragrant product that results from the artful blending of certain odoriferous substances in appropriate proportions. Raw materials used in perfumery include natural products of plant or animal origin and synthetic materials. Certain animal secretions contain odoriferous substances that increase the lasting qualities of perfumes. Such substances and some of their constituents act as fixatives, preventing more volatile perfume ingredients from evaporating too rapidly. Examples of animal product fixatives and fragrances include ambergris from the sperm whale, castor from beaver, civet from the civet cat and musk from the musk deer.

As the final part of the project, the Prins cyclisation methodology developed both in this project and within our research group will be applied to the synthesis of two natural, fragrant compounds.

### 5.1. Synthesis of (+)-(*S,S*)-(cis-6-methyltetrahydropyran-2-yl)acetic acid and its previous syntheses

The African civet cat (*Viverra civetta*, Fig. 11) belongs to a large group of mostly nocturnal mammals of the Old World family *Viverridae* (civet family). Civets are not true cats, but the civet family is related to the cat family (*Felidae*) and most civets have catlike bodies, long tails, and weasel-like faces.



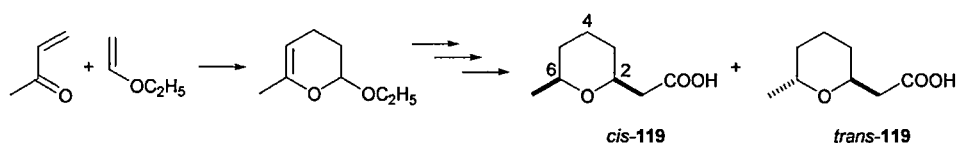
Fig. 11

This group has, for a long time, been employed in the perfume trade, because of their scent-producing glands, located in a double pouch near the genitals. The fatty yellow secretion of this gland has a distinctive musky odour used for territorial marking. Commercially, this substance is known as civet and is used as a perfume fixative. The World Society for the Protection of Animals has reported how African civets have been taken from the wild and made to spend their lives kept individually in primitive and small wooden cages. Typically, the civet is pinned down and its rear end pulled out so that the perineal gland at the base of its tail is exposed. The gland is then opened up, squeezed and the resulting musk scraped out. This can take several minutes and involves injuries to the civet. Today, the African civets are classified as an endangered species.

One of the most important components isolated from civet is (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, **125**, the structure of which was identified and confirmed for the first time by Maurer and co-workers in 1979.<sup>173,174</sup> In the past twenty years a number of different approaches to (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid in its racemic form have been published. In this short overview methods used for the preparation of civet using ring formation as the key synthetic step, will be presented.

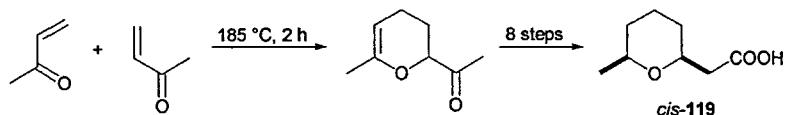
### 5.1.1. Ring formation *via* cycloaddition reactions

One of the first methods used to confirm the structure and to assign the relative configuration of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**119**) was based on Diels-Alder chemistry (Scheme 84).<sup>173</sup>



Scheme 84

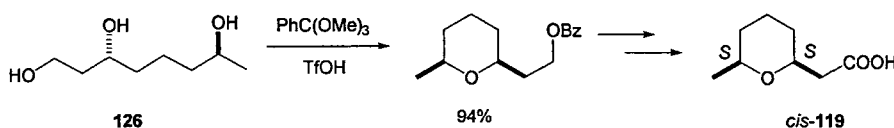
Mundy and Kim<sup>175</sup> have reported a simple stereospecific synthesis of racemic (*cis*-6-methyltetrahydropyran-2-yl)acetic acid based on dimerization of methyl vinyl ketone (Scheme 85).



Scheme 85

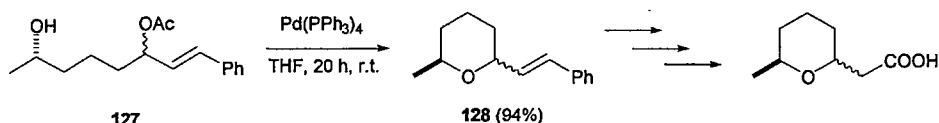
### 5.1.2. Ring formation via 6-*exo*-cyclisation reactions

(+)-(*S,S*)-(Cis-6-methyltetrahydropyran-2-yl)acetic acid was synthesised using, as the key step, a 6-*exo* cyclisation reaction of the triol **126** in the presence of trimethyl *ortho*-benzoate and trifluoromethansulfonic acid as the key step (Scheme 86).<sup>176</sup>



Scheme 86

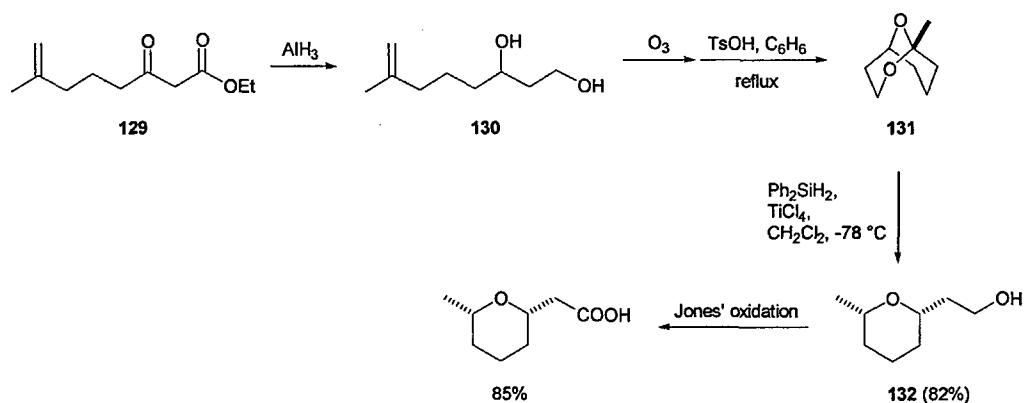
The palladium catalysed cyclisation of the chiral alcohol **127** at room temperature gave **128** in a 94% yield, without need to further activate the nucleophilic hydroxyl group (Scheme 87).<sup>177</sup>



Scheme 87

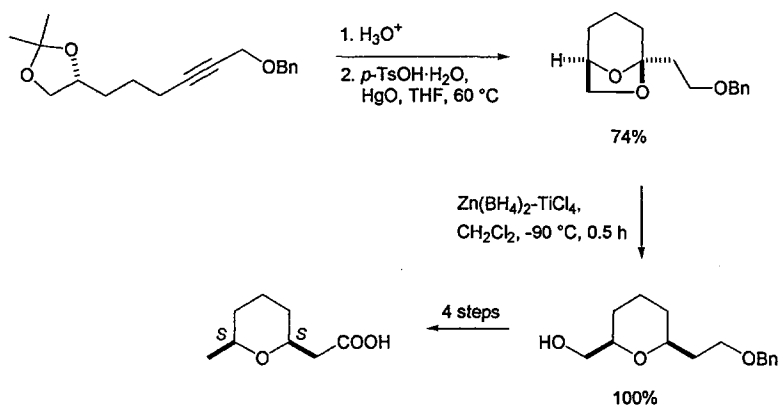
Yamamoto has published the synthesis of the civet cat constituent by the reductive cleavage of bicyclic acetals (Scheme 86).<sup>178</sup> Slow addition of titanium tetrachloride into a solution of bicyclic acetal **131** and diphenylsilane at  $-78\text{ }^\circ\text{C}$  for 4 hours afforded the *cis* isomer **132** as major product (82% yield). The stereochemistry of **132** was determined by oxidation ( $\text{CrO}_3$ ) to the known carboxylic acid.





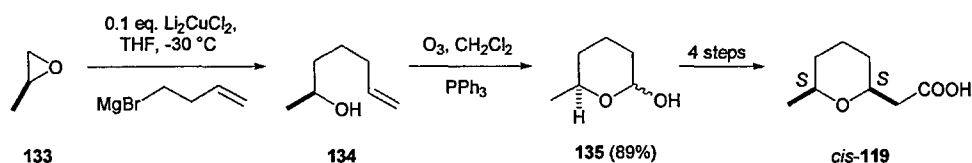
Scheme 88

A similar route, using reductive cleavage of bicyclic ketals, was used by Kotsuki<sup>179</sup> (Scheme 89). The combination of zinc borohydride and titanium tetrachloride acts as a mild reducing agent for the reductive cleavage of bicyclic ketals.



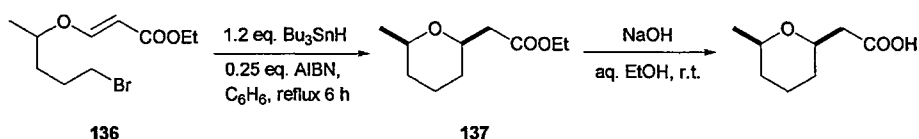
Scheme 89

Ley synthesised (+)-(*S,S*)-(cis-6-methyltetrahydropyran-2-yl)acetic acid from commercially available (-)-(*S*)-propylene oxide (Scheme 90).<sup>180</sup> Ring-opening of (-)-(*S*)-propylene oxide (133) with butenyl Grignard gave alkenol 134 in 95% yield. Conversion of 134 to the lactol 135 (89% yield) *via* open-chain aldehyde was performed by ozonolysis at  $-78^\circ\text{C}$ .



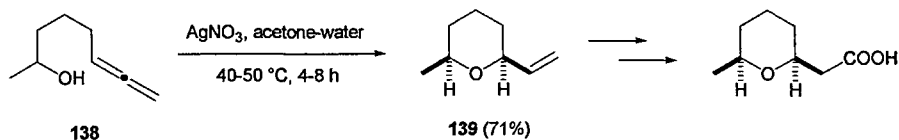
Scheme 90

One of the most direct and specific approaches to the racemic form of the Civet constituent uses a radical cyclisation reaction and is depicted in Scheme 91.<sup>181</sup> Under high dilution radical cyclisation conditions using tributylstannane, six-membered cyclic ether **137** formation was achieved in high yields and diastereoselectivity.



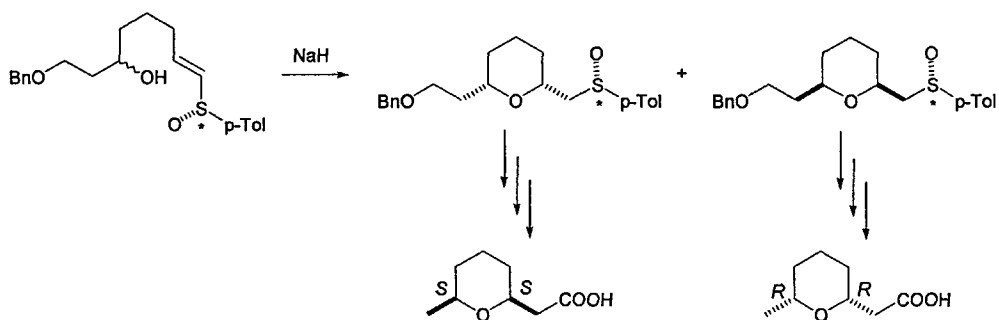
Scheme 91

Gallagher<sup>182</sup> has published a stereoselective route to *cis*-2,6-disubstituted tetrahydropyrans using silver-mediated cyclisation of secondary allenic alcohols **139** (Scheme 92).



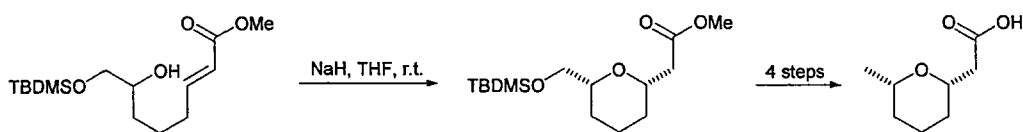
Scheme 92

Mandai has developed a new synthetic method for the preparation of *cis*-2,6-disubstituted tetrahydropyrans by an intramolecular 1,4-addition of  $\alpha,\beta$ -unsaturated sulfoxides and has applied it to the enantioselective synthesis of (+)- and (-)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acids (Scheme 93).<sup>183</sup>



Scheme 93

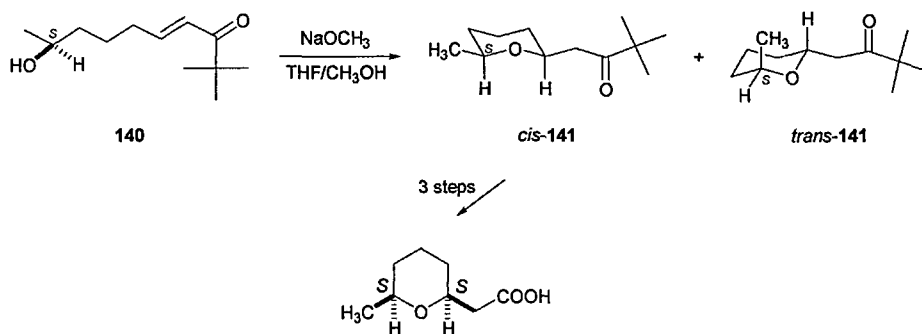
An intramolecular Michael addition of the type shown in Scheme 94 has also been used as a key cyclisation step to prepare (+)-(*S,S*)-(cis-6-methyltetrahydropyran-2-yl)acetic acid.<sup>184</sup>



Scheme 94

### 5.1.3. Ring formation via 6-*exo*-cyclisation reactions

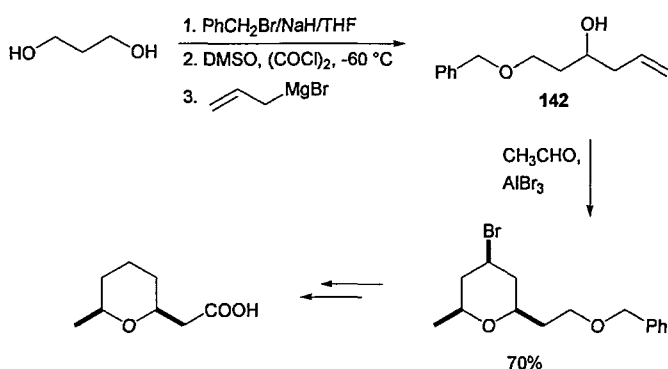
Seebach and Pohmakotr<sup>185</sup> observed that the treatment of *E*-hydroxyketone **140** with sodium methoxide causes the cyclisation to a (3:2)-mixture of *cis*- and *trans*-products **141**. The formation of *trans*-**141** as a kinetic product was observed after 1-2 hours at room temperature, while the thermodynamic *cis*-**141** product was quantitatively isolated after 3-4 days (Scheme 95).<sup>185</sup>



Scheme 95

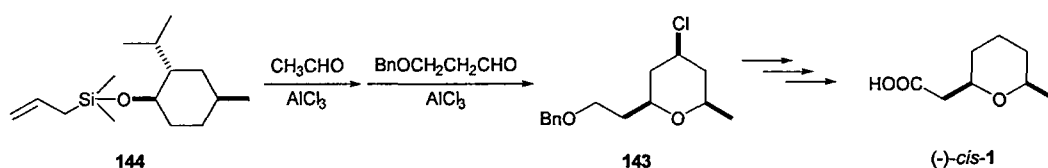
5.1.4. Ring formation *via* condensation reactions

(±)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic acid was synthesised by the condensation reaction of acetaldehyde and the unsaturated alcohol **142** in the presence of aluminium tribromide (Scheme 96).<sup>186</sup>



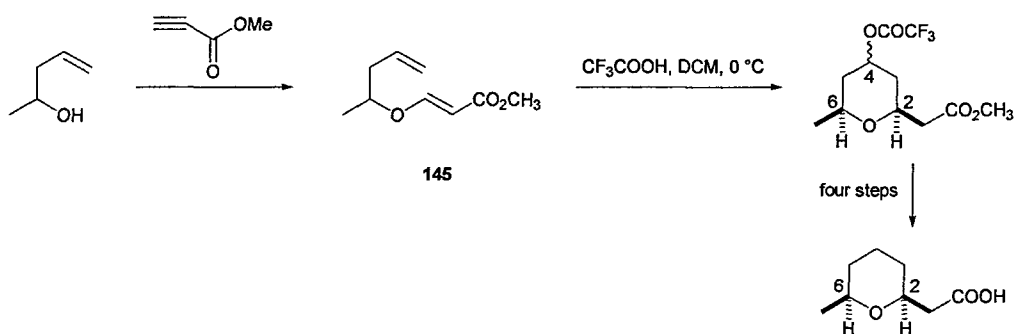
Scheme 96

The tetrahydropyran **143** was prepared in a one-pot synthesis from the optically active alkoxyallylsilane **144**, using acetaldehyde and 3-(benzyloxy)propanal as the aldehyde components and aluminium trichloride as the Lewis acid (Scheme 97).<sup>187</sup>



Scheme 97

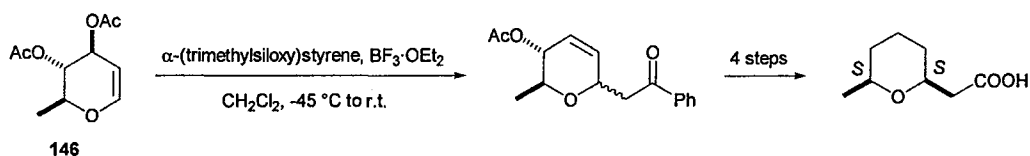
Nussbaumer and Fráter have published the synthesis of (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid from (±)-4-penten-2-ol (Scheme 98).<sup>188</sup> Addition of (±)-4-penten-2-ol to methyl propiolate in the presence of *N*-methylmorpholine afforded the β-alkenyloxyacrylate **145**, which upon exposure to trifluoroacetic acid in DCM at 0 °C cyclized to a mixture of labile trifluoroacetates.



Scheme 98

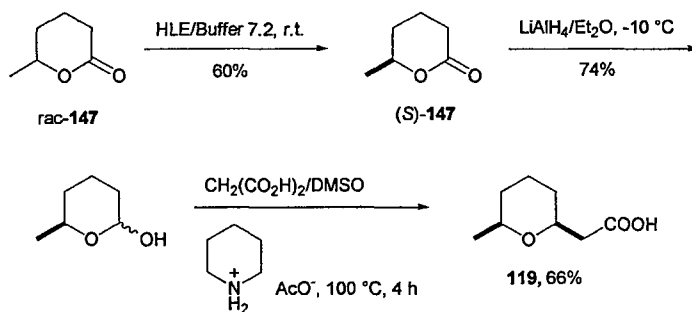
### 5.1.5. Non-cyclisation based methods for the preparation of the Civet cat component

Scheme 99 outlines the employment of a deoxygenated sugar molecule **146** as a chiral building block in the total synthesis of (+)-(*S,S*)-(cis-6-methyltetrahydropyran-2-yl)acetic acid.<sup>189</sup>



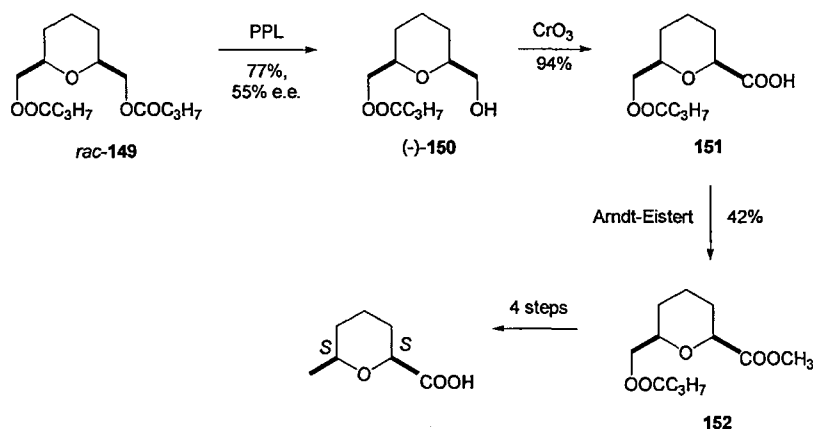
Scheme 99

Several methods for the synthesis of the optically pure form of the Civet cat constituent are based on the chiral catalytic properties of enzymes. (-)-(*S*)-5-Hexanolide **147** is readily available as a colourless oil in an excellent enantiomeric excess by an enzymatic resolution of its racemate (Scheme 100),<sup>190</sup> by horse liver esterase (HLE). (-)-(*S*)-5-Hexanolide was reduced by lithium aluminium hydride in diethyl ether to the corresponding lactol, which was then converted to the natural product **119** in an excellent chemical yield (66%).<sup>190</sup>



Scheme 100

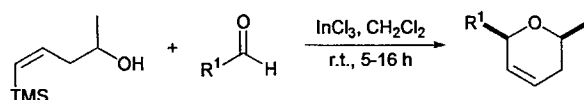
Another enzymatically based approach to the optically active Civet component is outlined in Scheme 101.<sup>191</sup> Commercially available porcine pancreatic lipase (PPL) is one of the most widely applied enzymes in stereospecific transformations on symmetrical substrates. The key stereochemistry of the starting chiron for the synthesis was set by stereoselective PPL-catalysed hydrolysis of **149** to give the alcohol-ester **150** in 55% e.e. and 77% isolated yield. Oxidation of **150** to **151** proceeded smoothly in a 94% yield. Homologation of **151** was effected in a 42% yield by the Arndt-Eistert procedure, a reaction that is known to proceed with retention of configuration at the  $\alpha$ -position of the carboxyl function. The overall yield of the Civet cat constituent was 18%, with the target product having the same e.e. (55%) as the starting chiron.



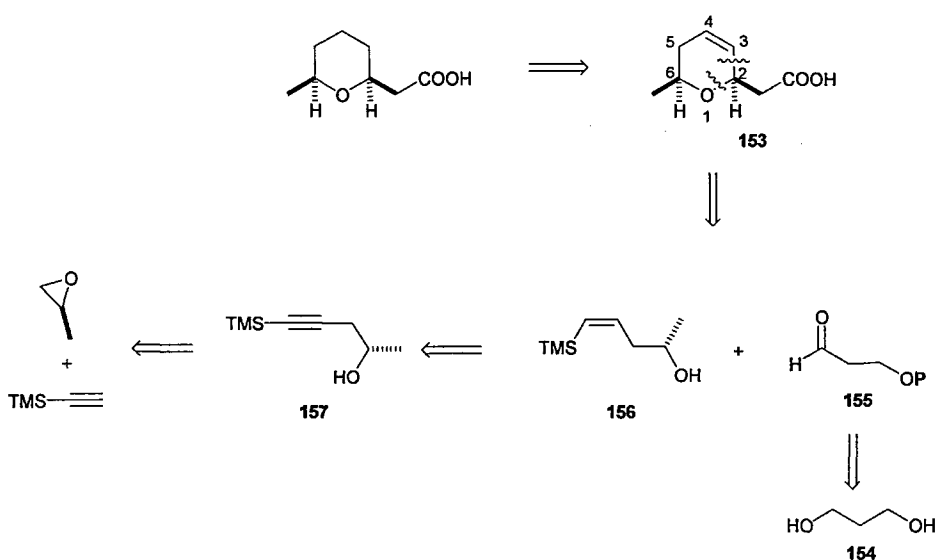
Scheme 101

## 5.2. Synthesis of ( $\pm$ )-(cis-6-methyltetrahydropyran-2-yl)acetic acid using the silyl-Prins cyclisation reaction

The retrosynthetic approach to the Civet cat constituent, ( $\pm$ )-(cis-6-methyltetrahydropyran-2-yl)acetic acid utilising our silyl-Prins methodology is presented in Scheme 100. This methodology has been previously described in chapter 4 and involves the reaction of an silylated homoallylic alcohol with an aldehyde in the presence of a Lewis acid, such as indium trichloride to give a dihydropyran in good yield and excellent diastereoselectivity, producing a single diastereomer with a *cis*-geometry across the oxygen atom of the ring.



### The silyl-Prins Reaction



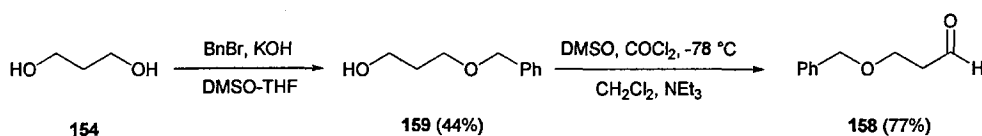
Scheme 102

It was envisaged that the tetrahydropyran core of the natural product could be obtained by reduction of the appropriate *cis*-disubstituted dihydropyran derivative **153**. The stereochemistry for the final product would be set up during a cyclisation process, such as the silyl-Prins reaction. Two disconnections, between C(2)-C(3) and C(2)-O, to identify

optically pure (*R*)-(-)-*Z*-5-trimethylsilylpent-4-en-2-ol (**156**) as a precursor. In turn **156** could be easily obtained in a two step process from (*S*)-(-)-propylene-oxide. The aldehyde component **155** containing a protected alcohol function could be easily prepared in two steps from commercially available propane-1,3-diol (**154**).

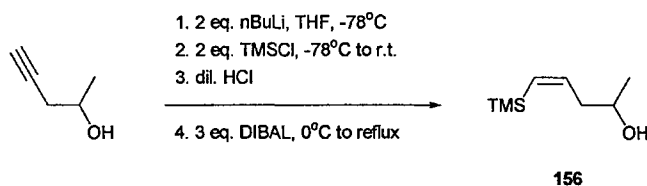
The aim of this investigation was to develop a synthetic route towards optically active (*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid using the silyl-Prins reaction.

The synthesis of racemic ( $\pm$ )-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid was first carried out. Monoprotection of propane-1,3-diol (**154**) afforded 3-benzyloxy-1-propanol (**159**) in a 44% yield that was further oxidised under Swern conditions to give 3-benzyloxypropionaldehyde (**158**) in 77% yield (Scheme 103).



Scheme 103

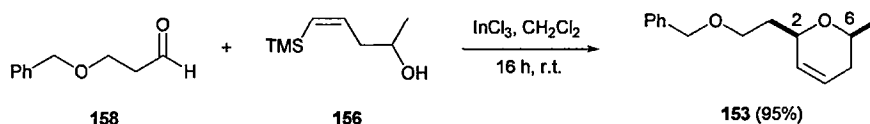
Racemic ( $\pm$ )-*Z*-5-trimethylsilylpent-4-en-2-ol (**156**) was prepared in a two step process: first the trimethylsilyl protection of the acetylene of pent-4-yn-2-ol followed by DiBAL reduction, to give the product in 89 % overall yield.



Scheme 104

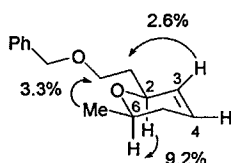
The silyl-Prins reaction using **158** with ( $\pm$ )-*Z*-5-trimethylsilylpent-4-en-2-ol (**156**) under standard conditions afforded ( $\pm$ )-*cis*-2-(2-benzyloxyethyl)-6-methyl-5,6-dihydro-2*H*-pyran (**153**) in a 95% yield (Scheme 103).





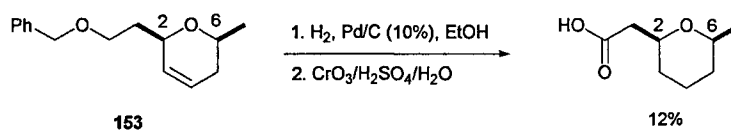
Scheme 105

The relative stereochemistry of the cyclisation product **153** was determined by nOe studies.



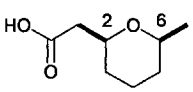
 <b>153</b>	Irradiated	Enhanced
		C(3)H
	C(4)H	C(3)H, +4.1% C(5)H, +6.2%
	C(6)CH <sub>3</sub>	[C(6)H+PhCH <sub>2</sub> OCH <sub>2</sub> ], +3.3% C(5)H <sub>2</sub> , +1.9%
	C(2)H	[C(6)H+PhCH <sub>2</sub> OCH <sub>2</sub> ], +9.2% OCH <sub>2</sub> CH <sub>2</sub> , +3.8% C(3)H, +3.1%

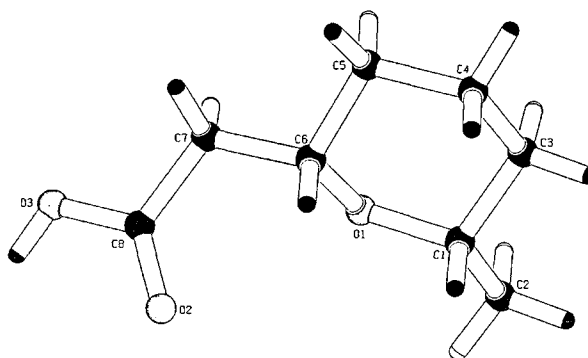
Simultaneous removal of the benzyl protection and the reduction of the endocyclic double bond was achieved by hydrogenation on palladium in dry ethanol over 19 hours (Scheme 105).



Scheme 106

Subsequent Jones' oxidation yielded ( $\pm$ )-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid in 25% yield over the two steps (Scheme 105). The yield was low due to problematic separation of the final product from chromium residues. The final product was fully characterised and the relative stereochemistry established by nOe and further confirmed by X-ray crystallography (Fig. 12 and Appendix 1).

 <i>Cis-1</i>	Irradiated	Enhanced
	C(6)H	C(2)H, +6.5%
	C(2)H	C(6)H, + 6.5%



**Fig. 12:** X-ray crystal structure and nOe data of ( $\pm$ )-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid

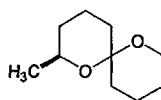
Although the overall yield in the last two steps was low, the amount of the natural product prepared was sufficient to characterise it fully and confirm its structure.

The idea was to repeat this synthetic procedure using enantiomerically pure (*R*)-(-)-*Z*-5-trimethylsilylpent-4-en-2-ol (**156**) in the key cyclisation step which should afford (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2yl)acetic acid, a component of civet. Due to the lack of time this synthesis was not repeated as attention focussed on an alternative natural product.

With the synthetic methodology established, we proceeded to investigate the total synthesis of a second, more complex natural product, but one that would involve utilising similar methodology.

### 5.3 Synthesis of (2*S*, 6*R*)-2-Methyl-1,7-dioxaspiro [5.5]undecane

The second target compound, (2*S*, 6*R*) 2-Methyl-1,7-dioxaspiro [5.5]undecane, is a naturally occurring pheromone component of the fruit fly genus *Dacus ciliatus*.



160

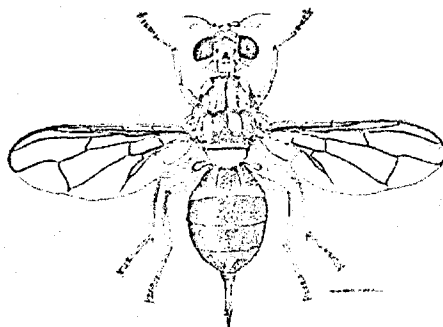


Fig. 12 *Dacus ciliatus*

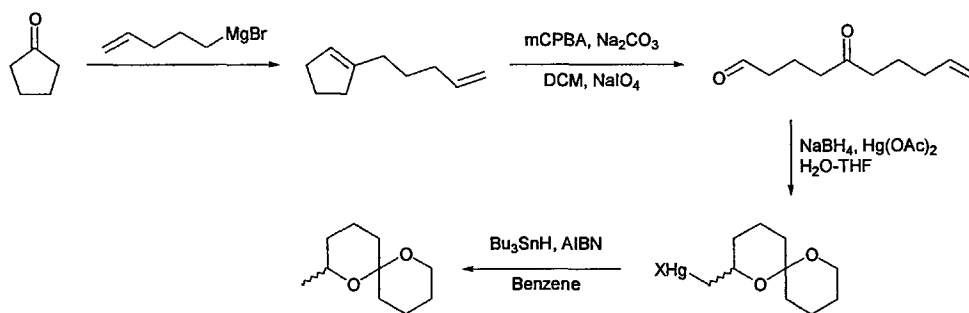
#### 5.3.1 Previous syntheses of (2*S*, 6*R*)-2-Methyl-1,7-dioxaspiro [5.5]undecane

Much less is known about 160 and less synthetic effort has been placed on completing its total synthesis. However, methods for the synthesis of spiroketals are abundant.

The most common method for the synthesis of 152 and its analogues involves the alkylation of the anion of 2-benzenesulfonyltetrahydropyran with a range of different alkylating agents.<sup>192</sup>

Lui has reported the one-pot conversion of 5-phenylthio-2-butanol into the title compound and related compounds in moderate yields.<sup>193</sup>

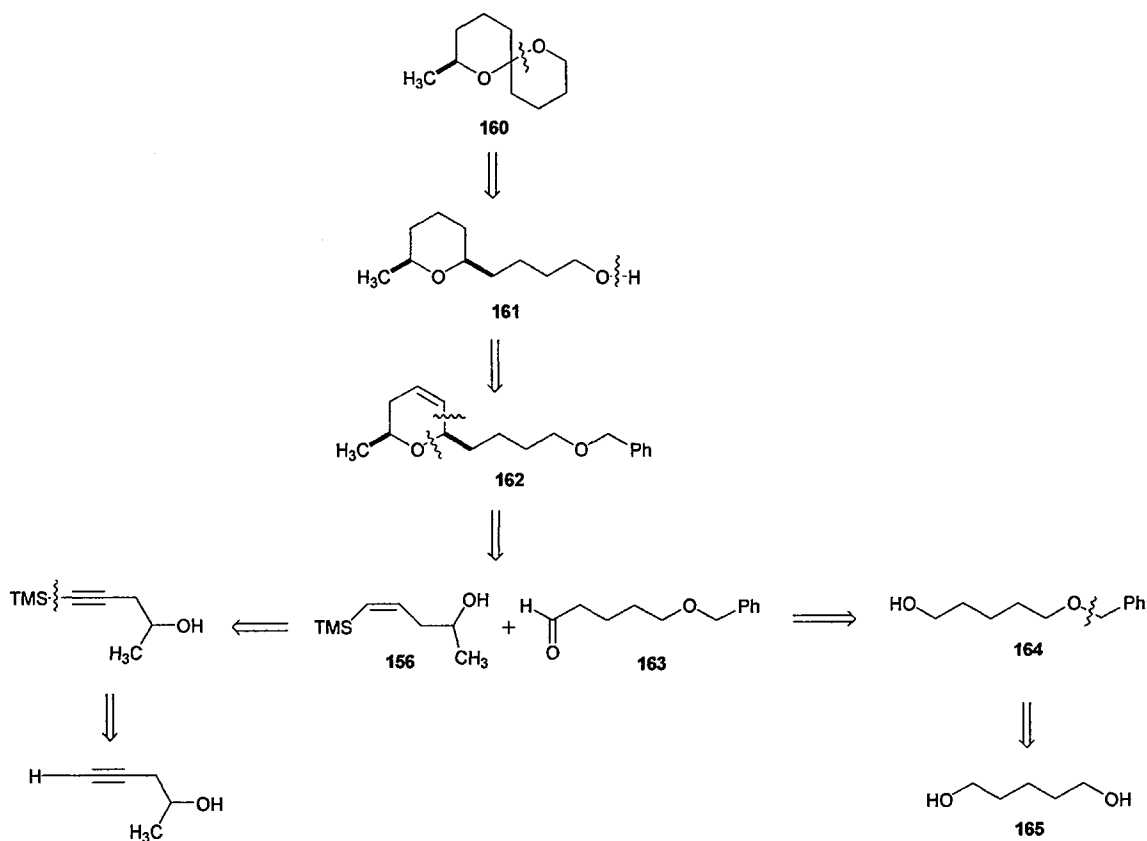
However, the mercury (II) cyclisation of a dienone was found to be the most productive of all methods, giving the title compounds in 56% overall yield (Scheme 107).<sup>194</sup>



**Scheme 107**

## 5.3.2 Retrosynthesis

The retrosynthetic approach to **160** utilising the silyl-Prins methodology is presented in Scheme 107.



Scheme 108

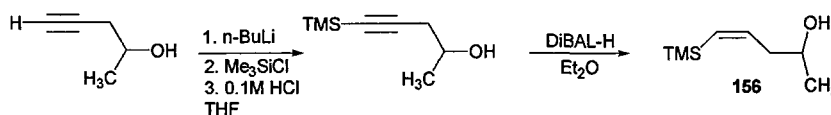
Again, the key intermediate in the synthesis was to be a dihydropyran, **162**, formed from a silyl-Prins cyclisation reaction. As in the Civet synthesis, this dihydropyran would be hydrogenated to **161** and then cyclised to the natural product. The dihydropyran would be formed from the aldehyde **163**. This could be imagined being formed by an analogous route from a 1,5-diol starting material. Mono-protection and Swern oxidation would give the desired aldehyde. The pre-requisite vinylsilane **156** has already been prepared by

reduction reaction of 5-trimethylsilylpent-4-yn-2-ol, itself prepared commercially available 4-pentyn-2-ol *via* deprotonation and silylation.

#### 5.4 Synthesis of (2*S*, 6*R*)-2-Methyl-1,7-dioxaspiro [5.5]undecane

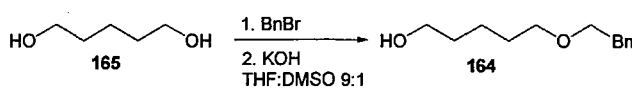
The aim of this investigation was to develop a synthetic route towards **160** using the silyl-Prins reaction.

The first stage, as before, was the preparation of 5-trimethylsilylpent-4-yn-2-ol **156**, starting from 4-pentyn-2-ol and employing *n*-butyllithium and TMS-chloride, followed by reduction of the triple bond using DIBAL.



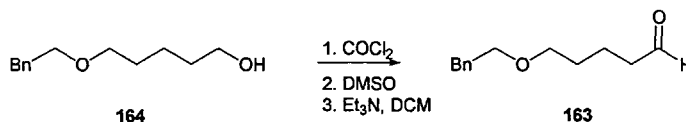
Scheme 109

The aldehyde component **163** for the silyl-Prins reaction was prepared from 1,5-pentadiol. This was first mono-protected with the benzyl group. This was slightly trickier than for propen-1,3-diol and the reaction was carried out several times before optimal conditions for mono-protection were found. This involved using a mixed solvent of THF:DMSO (9:1) and freshly powdered potassium hydroxide. Later investigations also demonstrated the advantage of using benzyl bromide over benzyl chloride. Under these conditions the targeted mono-protected 5-benzyloxy-pentane-1-ol **161** was obtained as a colourless oil 28%. (Scheme 110)



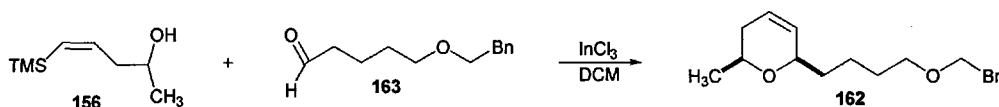
Scheme 110

The next step involved oxidation of the free hydroxyl group in the newly obtained 5-benzyloxypentan-1-ol **164** using a Swern oxidation reaction. The experiment went smoothly and the target 5-benzyloxypentan-1-al **163** was isolated 68%. (Scheme 111)



Scheme 111

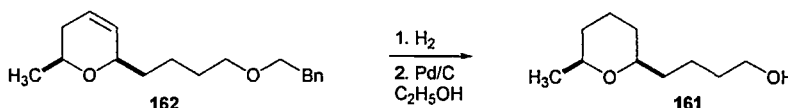
The silyl-Prins cyclisation step was carried out under conditions described previously, using indium trichloride as the Lewis acid. Thus 5-trimethylpent-4-yn-ol **156** and **163** were reacted in 1:1.5 ratio in the presence of InCl<sub>3</sub> (2 eq.) in dichloromethane at room temperature for 8 h to give the cyclised product **162** in 77% yield after purification. (Scheme 112)



Scheme 112

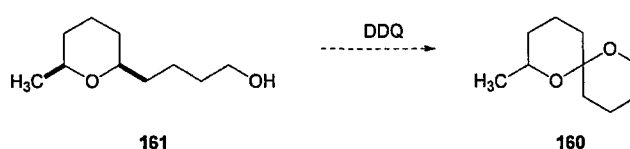
The *cis*-diastereoselectivity across the oxygen atom was again confirmed by nOe, with a 7.1% enhancement observed between H(2) and H(6), similar to the enhancement observed in the previous synthesis of the civet constituent.

The synthesis was designed so that the hydroxyl protecting group could be removed at the same time as reduction of the double bond. Hydrogenation of **162** on a pre-activated Pd/C catalyst gave concomitant olefin reduction and benzyl deprotection to give the hydroxyl-tetrahydropyran **161** in 71% yield.



Scheme 113

The final step was the cyclisation reaction. According to literature, 2,3-dichloro-5,6-dicyanobenzoquinone is an effective reagent for initiating this presumably radical cyclisation.<sup>195</sup> (6-methyltetrahydropyran-2-yl) butanol **161** was treated with freshly recrystallized 2,3-dichloro-5,6-dicyano-benzoquinone. Unfortunately, this reaction did not give the desired natural product and no starting material was recovered. Had there been further time and more material, alternative cyclisation conditions, for example HgO/I<sub>2</sub> would have been attempted.



Scheme 114

## 5.5 Conclusions and Future Work

The synthesis of two natural products have been attempted using cyclisation methods developed in the research group at the Open University and University of Exeter and during this thesis. The first synthesis, of (±)-(cis-6-methyltetrahydropyran-2-yl)acetic acid was successful and the natural product was obtained in good overall yield. Future work would involve repeating the reactions sequence described to perform the enantiospecific total synthesis of both the natural and unnatural forms of the product, starting from the corresponding chiral epoxide. The synthesis of the second product, (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.5]undecane, reached an advanced stage, with a precursor to the final product being obtained. Future work would involve investigation and optimisation of the final radical cyclisation step. Although we could not achieve the cyclisation, the product obtained is a known precursor to the natural product and so this may be considered a formal synthesis of the target.

Thus we have demonstrated the efficiency and usefulness of the silyl-Prins reaction in natural product total synthesis.



## **Chapter 6**

### **EXPERIMENTAL DETAILS**

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**General**

Petrol refers to the fraction boiling between 40°C and 60°C. Dichloromethane and 1,2-dichloroethane were distilled over calcium hydride. Diethyl ether, THF and toluene were distilled over sodium and benzophenone, which was used as an indicator. All other solvents were obtained anhydrous from Aldrich and used directly into the reaction vessel. All reactions were carried out under an atmosphere of nitrogen unless otherwise stated using vacuum/nitrogen manifold. All glassware, syringes and needles were pre-dried in an oven (120-140 °C) and cooled in a nitrogen atmosphere prior to use. Stirring was by internal magnetic follower. All chemicals were purified by distillation or recrystallisation where appropriate. Commercially available compounds were generally used without further purification.

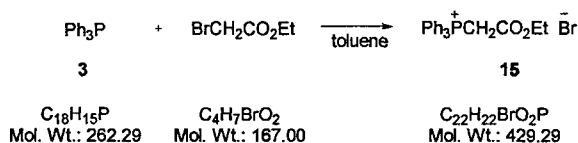
All reactions were followed by TLC. Analytical thin layer chromatography was carried out using aluminum backed plates coated with Merck Kieselgel 60 GF254. Plates were visualized under UV light (at 254 nm) or by staining with acidic ceric ammonium molybdate or acidic potassium permanganate followed by heating. Flash chromatography was carried out using Matrix silica 60, 230-400 mesh; samples were applied as a saturated solution in an appropriate solvent.

Infrared (IR) spectra were recorded in the range 4000-600  $\text{cm}^{-1}$  using a Nicolet Magna IR 550 (Exeter) and Nicolet 205 (OU) spectrometers with internal calibration. Spectra were recorded as potassium bromide discs or as thin films between NaCl plates.

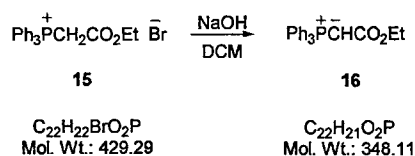
Proton ( $^1\text{H}$ ) NMR spectra at 300 MHz and carbon ( $^{13}\text{C}$ ) NMR spectra at 75 MHz were recorded on a Bruker AV 300 (Exeter) and JEOL LAMBDA300 (OU) instruments in deuterated solvents and at 400 MHz using an Avance DEX 400 (Exeter) or JEOL EX400 (OU) instrument in deuterated solvents. NMR chemical shifts ( $\delta$ ) are quoted in ppm relative to an internal standard ( $\text{CDCl}_3$ ). Spectroscopic data is annotated with the following abbreviations: br – broad, s - singlet, d - doublet, t - triplet, and m – multiplet. Coupling

constants,  $J$ , are expressed in Hz.  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments were made using COSY ( $^1\text{H}$ - $^1\text{H}$  correlation) and HMQC ( $^1\text{H}$ - $^{13}\text{C}$  correlation) NMR techniques.

High and low resolution mass spectra were recorded on a Kratos Profile instrument or Micromass Quattro II instrument (EPSRC Mass Spectrometry Service, Swansea) or a ThermoQuest Trace GC 2000 series or an Agilent 6890 Series GC System, Micromass GCT. Compounds characterised by high-resolution mass spectrometry were chromatographically homogenous.

**Carboethoxymethyl triphenylphosphonium bromide 15**<sup>58</sup>

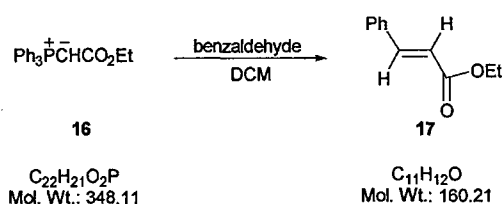
Ethyl bromoacetate (8.35 g, 50 mmol) was added dropwise to triphenylphosphine **3** (13.10 g, 50 mmol) in dry toluene (50 ml). The mixture was stirred for 30 min at room temperature and then heated for another 30 min on a water bath. After cooling, it was filtered, washed with toluene (2 × 20 ml), hexane (2 × 25 ml), the solvents removed *in vacuo* and the solid precipitate dried in an oven overnight. The target compound, carboethoxymethyltriphenylphosphonium bromide **15** was isolated as white solid mass. (18.61 g, 87%).  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.93-7.60 (15H, m, 3Ar), 5.58 (2H, d,  $J_{\text{PH}}$  13.7, CH<sub>2</sub>CO<sub>2</sub>Et), 4.01 (2H, q,  $J$  7.1, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.04 (3H, t,  $J$  7.1). All other data were in agreement with previously reported values.<sup>58</sup>

**Carboethoxymethylenetriphenylphosphorane 16**<sup>58</sup>

Carboethoxymethyltriphenylphosphonium bromide **15** (18.61 g, 43 mmol) was dissolved in a biphasic solution of cold water (150 ml) and dichloromethane (120 ml). The mixture was stirred vigorously and sodium hydroxide (50 ml, 0.1 M solution) added over a period of 5 min. After stirring for a further 10 min, was checked for alkalinity by pH paper. The layers were then separated and the aqueous layer washed with dichloromethane (3 × 40 ml), the organic layers combined, dried over magnesium sulfate and excess solvent removed *in vacuo*. To the resulting syrup was added warm petroleum (~55 ml) and dichloromethane (10 ml) and stirred for 15 min. On cooling to 0 °C, white crystals formed which were

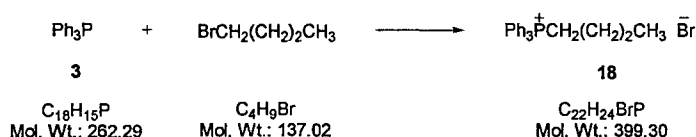
filtered and dried to give carboethoxymethylenetriphenylphosphorane **16** (8.84 g, 58%). This was used immediately in the Wittig reaction without further purification or analysis.

### 3-Phenyl-acrylic acid ethyl ester **17**<sup>58</sup>



Carboethoxymethylenetriphenylphosphorane **16** (8.84 g, 25 mmol) was slowly dissolved in dichloromethane (70 ml). After 20 min a solution of phenylacetaldehyde (2.65 g, 25 mmol) in dichloromethane (25 ml) was added, stirred for 30 min and then the solvent was removed on *vacuo*. The residue was dissolved in warm petrol and refluxed for 20 min on a water bath. After cooling to room temperature the mixture was filtered and the solvent removed *in vacuo*. To the obtained thick liquid was added light petroleum (25 ml) and a pinch of silica gel, the contents stirred for further 10 min, then filtered, and the solvent removed to give pure **17** (2.34 g, 60%).  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.03 (1H, d,  $J$  15.9,  $\text{PhCH}=\text{CH}$ ), 7.40 (5H, m, Ar), 6.33 (1H, d,  $J$  15.9,  $\text{PhCH}=\text{CH}$ ), 4.15 (2H, q,  $J$  7.2,  $\text{OCH}_2\text{CH}_3$ ), 1.24 (3H, t,  $J$  7.1,  $\text{OCH}_2\text{CH}_3$ ). All other data were in agreement with previously reported values.<sup>58</sup>

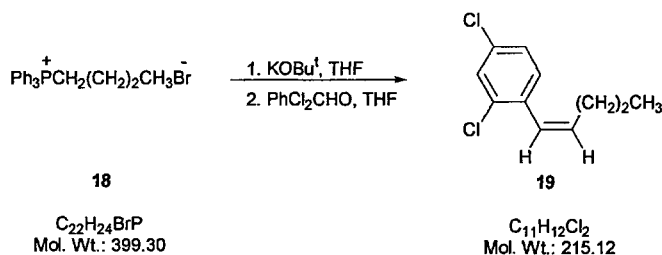
### Butyltriphenylphosphonium bromide **18**<sup>58</sup>



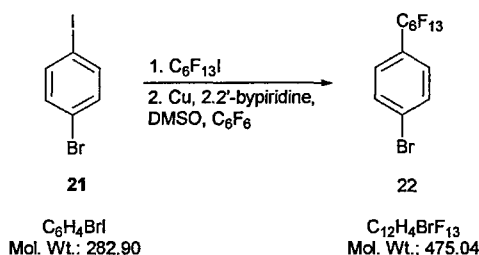
Triphenylphosphine **3** (26.20 g, 0.1 mol) and 1-brombutane (27.00 g, 0.2 mol) were stirred together for 2 h at 100-110 °C. The flask was then cooled to room temperature and transferred to an ice/water bath. After crystallisation was completed, the solution was then filtered, the solid rinsed with portions of petrol and the solvent removed *in vacuo*. Butyltriphenylphosphonium bromide **18** was obtained (10.70 g, 26 %).  $\delta_{\text{H}}$  (300 MHz;

CDCl<sub>3</sub>) 7.83-7.60 (15H, m, 3 Ar), 3.79 (2H, m, Ph<sub>3</sub>PCH<sub>2</sub>), 1.58 (4H, m, overlapping CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.84 (3H, t, *J* 6.9, CH<sub>3</sub>). All other data were in agreement with previously reported values.<sup>58</sup>

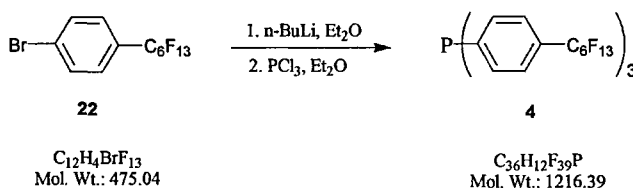
### 2,4-Dichloro-1-(pent-1-enyl)benzene **19**<sup>168</sup>



Under a nitrogen atmosphere, to butyltriphenylphosphonium bromide **18** (8.20 g, 20 mmol) was added the solution of potassium *t*-butoxide (2.50 g, 22 mmol) in dry tetrahydrofuran (50 ml) and the mixture was stirred for 40 min. Over this time the light yellow colour turned to bright red. Then a solution of 2,4-dichlorobenzaldehyde (3.50 g, 20 mmol) in dry tetrahydrofuran (15 ml) was added over 5 min, the reaction flask being cooled in an ice/water bath. The solution changed of the colour to grey. The mixture was filtered and the precipitate was washed with warm petrol (3 × 20 ml). The layers were combined, ~20 ml hexane was added together with a pinch of silica gel. This mixture was stirred for 5 min, filtered and the solvent removed *in vacuo*. A thick syrup of inseparable *E* and *Z* isomers of **19** was obtained (2.24 g, 52%). δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 7.33-6.98 (6H, m, overlapping Ar), 6.55 (1H, d, *J* 14.2, Cl<sub>2</sub>PhCH<sub>E</sub>=CH), 6.30 (1H, d, *J* 8.0, Cl<sub>2</sub>PhCH<sub>Z</sub>=CH), 6.04 (1H, br m, Cl<sub>2</sub>PhCH=CH<sub>E</sub>), 6.67 (1H, m, Cl<sub>2</sub>PhCH=CH<sub>Z</sub>), 2.12-1.97 (4H, m, overlapping 2 × CH=CHCH<sub>2</sub>CH<sub>2</sub>), 1.41-1.24 (4H, m, overlapping 2 × CH=CHCH<sub>2</sub>CH<sub>2</sub>), 0.86-0.74 (6H, m, overlapping 2 × CH<sub>3</sub>). All other data were in agreement with previously reported values.<sup>58</sup>

4-(Tridecafluorohexyl)bromobenzene **22**<sup>44</sup>

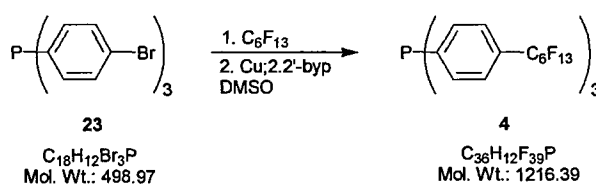
A solution of copper powder (2.94 g, 0.046 mol), 2,2'-bipyridine (0.23 g,  $1.47 \times 10^{-3}$  mol), 4-bromoiodobenzene **21** (5.96 g, 0.021 mol), DMSO (20 ml) and hexafluorobenzene (30 ml) was added dropwise over 3 h to a solution of iodoperfluorohexane (9.39g, 0.021 mol) in hexafluorobenzene (15 ml) at 70 °C. The mixture was subsequently stirred at 70 °C for 72 h before it was poured into a beaker containing dichloromethane and water (50-50 ml). After filtering, the organic layer was separated, washed with water ( $3 \times 25$  ml) and dried over  $CaCl_2$ . After concentration to ~15-20 ml, the crude product was extracted into perfluoro-1,3-dimethylcyclohexane ( $3 \times 10$  ml) and the solvent removed *in vacuo*. Distillation under reduced pressure (bp 75-78 °C/0.1mmHg) gave the product as a colourless liquid **22**, but never completely free from contaminants. (4.59g, 46%).  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.64 (2H, d,  $J$  8.2, 3,5-ArH), 7.44 (2H, d,  $J$  8.5, 2,6-ArH);  $m/z$  CI 476 [(M)<sup>+</sup>,  $C_{12}H_4^{81}BrF_{13}$ , 98%], 474 [(M)<sup>+</sup>,  $C_{12}H_4^{79}BrF_{13}$ , 100%]; All other data were in agreement with previously reported values.<sup>44</sup>

Tris(4-tridecafluorohexylphenyl)phosphine **4**: Method 1<sup>44</sup>

*n*-Butyllithium (3.50 ml, 2.5 M solution in hexane) in diethyl ether (15 ml) was added dropwise over 1 h to impure 4-(tridecafluorohexyl)bromobenzene **22** (4.00 g, 8.4 mmol) in diethyl ether (40 ml) at -78 °C and then stirred at this temperature for a further 1 h. The

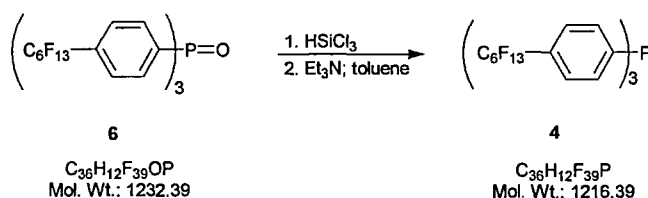
temperature was raised to room temperature and the reaction stirred for 1 h, after which it was cooled back to  $-78\text{ }^{\circ}\text{C}$  and phosphorus trichloride (0.24 ml, 2.6 mmol) in diethyl ether (15 ml) added dropwise over 1 h. The reaction mixture was allowed to warm slowly to room temperature with continuous stirring over a 12 h period. The mixture was hydrolysed with 10 % aqueous  $\text{NH}_4\text{Cl}$  (50 ml), the organic layer separated, washed with water ( $2 \times 15$  ml) and dried over  $\text{MgSO}_4$ . The organic phase was concentrated *in vacuo* to 10 ml and passed quickly through an alumina column, using petrol as eluent. After the solvent was removed the crude product was subject to flash chromatography (hexane : ethyl acetate 1:4), but gave no identifiable material.

### Tris(4-tridecafluorohexylphenyl)phosphine 4: Method 2



A mixture of *tris*(4-bromophenyl)phosphine **23** (2.00 g; 4 mmol), copper powder (1.68 g, 26 mmol) and 2,2'-bipyridine (0.13 g, 0.84 mmol) in hexafluorobenzene (10 ml) was added dropwise over 2 h to a solution of iodoperfluorohexane (5.35 g, 12 mmol) in hexafluorobenzene (15 ml) at  $75\text{ }^{\circ}\text{C}$ . The mixture was stirred at this temperature for 72 h. After cooling to room temperature, it was hydrolysed with 10% aqueous  $\text{NH}_4\text{Cl}$  (30 ml), the organic layer collected, washed with water ( $2 \times 10$  ml) and dried over  $\text{MgSO}_4$ . The organic phase was concentrated *in vacuo* to  $\sim 8\text{-}10$  ml and passed quickly through an alumina pad, using petrol as eluent. After the solvent was removed the crude product was chromatographed on a silica gel column (ethyl acetate: hexane 1:4) to give unidentifiable material.

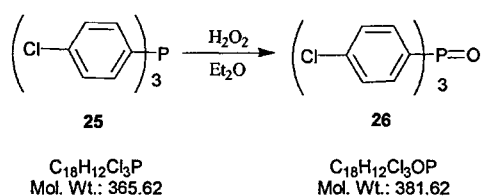
### Tris(4-tridecafluorohexylphenyl)phosphine 4: Method 3<sup>45</sup>



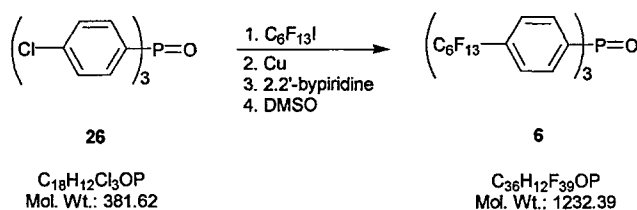


A mixture of *tris*(4-tridecafluorohexylphenyl)phosphine oxide **6** (0.50 g, 0.4 mmol), trichlorosilane (0.2 ml, 2 mmol), triethylamine (0.42 ml, 3 mmol) and toluene (12 ml) was stirred at reflux for 6 h under nitrogen. After cooling to room temperature, a saturated aqueous solution of potassium hydrogencarbonate (1 ml) was added and the mixture stirred for 5 min at room temperature. The solution was filtered through a pad of alumina and washed with toluene (3 × 30 ml) and evaporated under reduced pressure to give the crude product as a white solid. The desired product was subject to column chromatography on silica (ethyl acetate:hexane 1:4) but gave unidentifiable material.

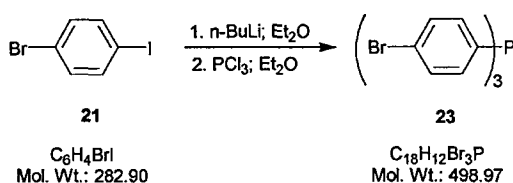
***Tris*(4-chlorophenyl)phosphine oxide **26****<sup>59</sup>



To a solution of *tris*(4-chlorophenyl)phosphine **25** (3.00 g, 8.2 mmol) in diethyl ether (80 ml) was added dropwise a solution of 35% solution of hydrogen peroxide (0.28 g, 8.2 mmol) in diethyl ether (20 ml). The solution was heated to reflux for 3 h. After cooling, the solution was filtered and dissolved into minimum amount of toluene and 0.3 M solution sodium hydroxide (10 ml) added. The layers were separated and the organic layer dried (MgSO<sub>4</sub>), filtered and evaporated *in vacuo* to give the product **26** as white crystals (3.12 g, 99%)  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 1590, 1480, 1195 (P=O), 1020, 995, 760 (C-Cl); all other data in agreement with literature values.<sup>59</sup>

**Tris(4-tridecafluorophenyl)phosphine oxide 6**<sup>45</sup>

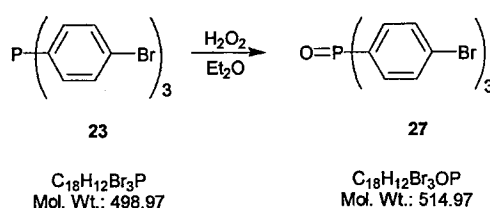
A mixture of *tris*(4-chlorophenyl)phosphine oxide **26** (1.00 g, 2.62 mmol), perfluorohexyl iodide (3.75 g, 8.4 mmol), copper powder (1.20 g, 18.6 mmol), 2,2'-bipyridine (0.82g, 0.53 mmol) and DMSO (40 ml) was stirred at 120 °C for 36 h. After cooling to room temperature, the reaction mixture was diluted with chloroform and water (90 : 90 ml), filtered through a pad of celite and washed with chloroform (2 × 40 ml). The organic layer was separated, washed with 1M hydrochloric acid (2 × 100 ml), water (2 × 100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated under reduced pressure to give the crude product, which could not be identified.

**Tris(4-bromophenyl)phosphine 23**<sup>44</sup>

A solution of n-butyllithium (2.82 ml of 2.5 M in hexane) in diethyl ether (20 ml) at -78 °C was added from a dropping funnel to a solution of 4-bromoiodobenzene **21** (2.00 g, 7 mmol) in dry diethyl ether (30 ml) at -78 °C and stirred for 1 h. The temperature was raised to ambient temperature for 1 h and then cooled again to -78 °C and phosphorus trichloride (0.2 ml, 2.3 mmol) in diethyl ether (10 ml) added dropwise over 1 h. The reaction mixture was allowed to warm slowly to room temperature with continuous stirring over a 12 h period. The mixture was hydrolysed with 10 % aqueous  $\text{NH}_4\text{Cl}$  (2 × 25 ml), the organic layer separated, washed with water (3 × 15 ml) and dried over  $\text{MgSO}_4$ . The organic phase was concentrated *in vacuo* to 10 ml and passed quickly through an alumina

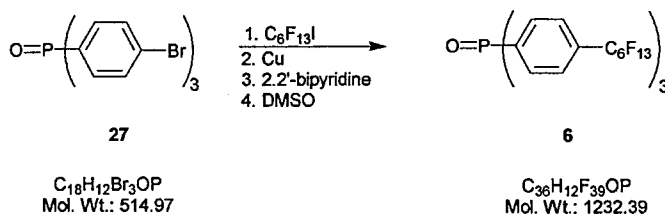
column, using petrol as eluent. After the solvent was removed the product **23** formed as white crystals with yield of 87%. (1.01 g, 2.0 mmol). This reaction was performed on various scales, using 6, 10 and 20 g of 4-bromoiodobenzene; yields of 86%, 84% and 79%, respectively, were obtained.  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.41 (6H, d,  $J$  7.9,  $3 \times 3,5\text{-ArH}$ ), 7.05 (6H, d,  $J$  7.9,  $3 \times 2,6\text{-ArH}$ );  $m/z$  CI 499 [(M)<sup>+</sup>,  $\text{C}_{18}\text{H}_{12}^{81}\text{Br}_3\text{P}$ , 98%], 497 [(M)<sup>+</sup>,  $\text{C}_{18}\text{H}_{12}^{79}\text{Br}_3\text{P}$ , 100%]. All other data were in agreement with previously reported values.

### Tris(4-bromophenyl)phosphine oxide **27**<sup>59</sup>



Hydrogen peroxide (2.74 ml 35% solution) was added dropwise to *tris*(4-bromophenyl)phosphine **23** (5 g, 0.1 mol) in diethyl ether (90 ml) and the solution heated to reflux for 2 h. After cooling, the solution was filtered and the solid dissolved into a minimum amount of toluene to which 0.3 M sodium hydroxide (~10 ml) was added. The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and evaporated *in vacuo* to give the product **27** as white crystals. (3.39 g, 65%).  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 1590, 1480, 1200 (P=O), 1010, 740 (C-Br);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.57 (6H, d,  $J$  8.04,  $3 \times 2,6\text{-ArH}$ ), 7.41 (6H, d,  $J$  8.04,  $3 \times 2,6\text{-ArH}$ ). All other data were in agreement with previously reported values.<sup>46</sup>

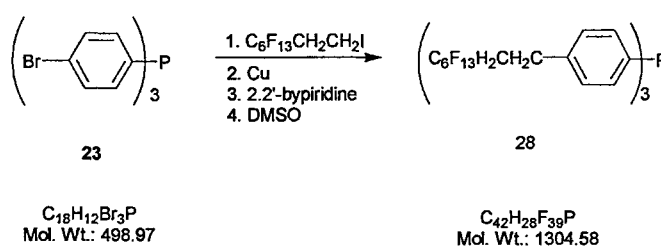
### Tris(4-tridecafluorohexylphenyl)phosphine oxide **6**<sup>45</sup>



A mixture of *tris*(4-bromophenyl)phosphine oxide **27** (1.00 g, 1.94 mmol), perfluorohexyl iodide (2.77 g, 6.2 mmol), copper powder (0.88 g, 13.7 mmol), 2,2'-bipyridine (60 mg,

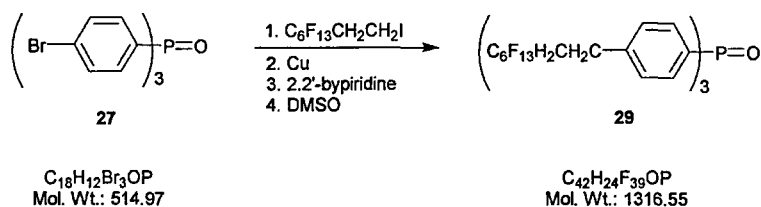
0.38 mmol) and DMSO (40 ml) was stirred at 120 °C for 36 h. After cooling to room temperature the reaction mixture was diluted with chloroform and water (90:90 ml), filtered through a pad of celite and washed with chloroform (2 × 40 ml). The organic layer was separated, washed with 1M hydrochloric acid (2 × 100 ml), water (2 × 100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated under reduced pressure to give the crude product, which upon recrystallisation from ethanol yielded the compound as colourless needles **24** (1.09 g, 46%).  $\delta_F$  (400 MHz; CDCl<sub>3</sub>) -81.0 (CF<sub>3</sub>), -111.5 (CF<sub>2</sub>), -121.6 (CF<sub>2</sub>), -121.8 (CF<sub>2</sub>), -123.0 (CF<sub>2</sub>), -126.4 (CF<sub>2</sub>); *m/z* CI 1232 [(M)<sup>+</sup>, C<sub>36</sub>H<sub>12</sub>F<sub>39</sub>PO, 100%]; No other data was detected. This experiment was repeated several times, but without success.

### **Tris[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine **28****<sup>45</sup>



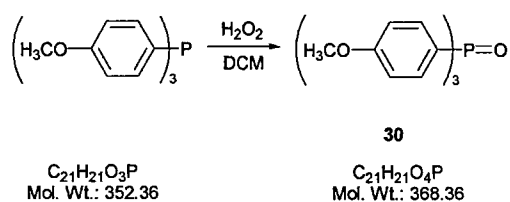
A mixture of *tris*(4-bromophenyl)phosphine **23** (1.00g, 1.94 mmol), 1,1,2,2-tetrahydroperfluorooctyl iodide (2.90 g, 6 mmol), copper powder (0.88 g, 13.7 mmol), 2,2'-bipyridine (0.06 g, 0.38 mmol) and DMSO (30 ml) was stirred at 120 °C for 96 h. After cooling to room temperature the reaction mixture contained only starting materials.

### **Tris[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine oxide **29****<sup>45</sup>

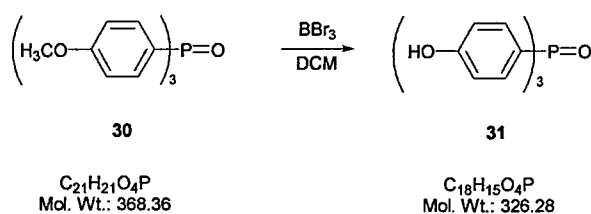


A mixture of *tris*(4-bromophenyl)phosphine oxide **27** (0.50 g, 1 mmol), 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl iodide (1.50 g, 3 mmol), copper powder (0.15g, 2.19 mmol), 2,2'-bipyridine (0.11g, 0.07 mmol) and DMSO (40 ml) was stirred at 120 °C for 36 h. After cooling to room temperature, the reaction mixture was diluted with chloroform and water (90:90 ml), filtered through a pad of celite and the pad washed with chloroform (2 × 40 ml). The organic layer was separated, washed with 1 M hydrochloric acid (2 × 100 ml), water (2 × 100 ml) and brine (100 ml), dried over magnesium sulfate and evaporated under reduced pressure to give no identifiable material.

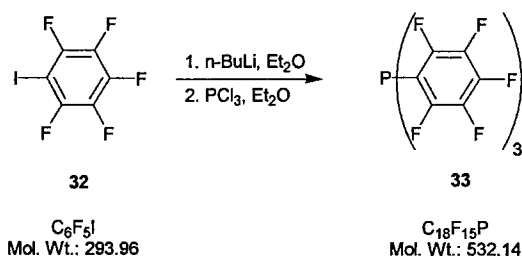
### *Tris*(4-methoxyphenyl)phosphine oxide **30**<sup>59</sup>



To a solution of *tris*(4-methoxyphenyl)phosphine (1.00 g, 2.8 mmol) in dichloromethane (30 ml) was added dropwise a solution of 35% solution of hydrogen peroxide (0.48 g, 14.2 mmol) in dichloromethane (20 ml) and the mixture heated to reflux for 5 h. After cooling, the solution was filtered and dissolved into minimum amount of toluene and 0.3 M solution of sodium hydroxide (10 ml) was added. The layers were separated and the organic layer dried over MgSO<sub>4</sub>, filtered and evaporated *in vacuo* to give the product **30** as white crystals (0.76 g, 66%);  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3100, 1550, 1440, 1120 (P=O), 1005, 820;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.52 (6H, m, 3 × 2,6 ArH), 6.90 (6H, d, *J* 9.4, 3 × 3,5 ArH), 3.72 (9H, s, 3 × CH<sub>3</sub>);  $\delta_{\text{C}}$  (300 MHz; CDCl<sub>3</sub>) 126.2 (3 × C-P), 133.7 (3 × 2,6-ArC), 124.0 (3 × C-O), 113.8 (3 × 3,5-ArC), 55.2 (3 × CH<sub>3</sub>).

**Tris(4-hydroxyphenyl)phosphine oxide 31**<sup>61</sup>

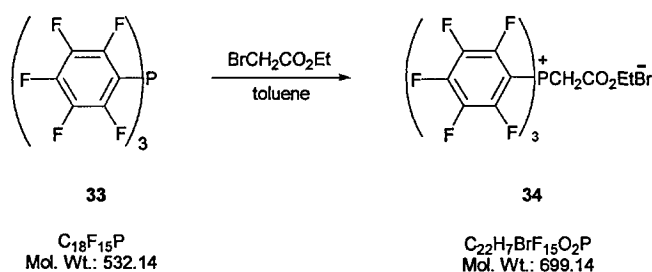
A solution of *tris*(4-hydroxyphenyl)phosphine oxide **30** (0.05 g, 1.37 mmol) in dichloromethane (15 ml) was cooled to  $-78^\circ\text{C}$  and a 1M solution of boron tribromide in dichloromethane (7.8 ml, 7.8 mmol) added dropwise over a 10 min period. The solution was stirred for a further 24 h at room temperature and then poured into a mixture of ice/water (150 ml), stirred for 15 min and mixture then heated to  $55\text{--}60^\circ\text{C}$ . The mixture was extracted with ethyl acetate ( $5 \times 100$  ml), the organic layers collected, washed with water ( $3 \times 40$  ml), dried over  $\text{MgSO}_4$ , then filtered and evaporated. The crude oil was dissolved in a minimum amount of ethyl acetate, warmed and filtered into a round-bottomed flask that was placed in an ice/water bath. No crystals were obtained. The solvent was evaporated and the brown oil checked by NMR. No identifiable signals were seen.

**Tris(pentafluorophenyl)phosphine 33**<sup>44</sup>

A solution of *n*-butyllithium (2.8 ml of 2.5 M in hexane) in diethyl ether (20 ml) at  $-78^\circ\text{C}$  was added from a dropping funnel to a solution of iodopentafluorobenzene **32** (2.00 g, 6.8 mmol) in dry diethyl ether (10 ml) at  $-78^\circ\text{C}$ . The mixture was stirred for 1 h, the temperature raised to ambient for 1 h and then cooled again to  $-78^\circ\text{C}$ . Phosphorus

trichloride (0.20 ml, 2.3 mmol) was added dropwise in diethyl ether (10 ml) over 1 h. The reaction mixture was allowed to warm slowly to room temperature with continuous stirring over 12 h. The mixture was hydrolysed with 10 % aqueous  $\text{NH}_4\text{Cl}$  ( $2 \times 25$  ml), the organic layer separated, washed with water ( $3 \times 25$  ml) and dried over  $\text{MgSO}_4$ . The organic phase was concentrated *in vacuo* to 10 ml and passed quickly through an alumina column, using 40-60 °C light petroleum as eluent. After the solvent was removed the product **33** formed as white crystals with yield of 59%, 0.71g.  $m/z$  (CI) 532 [(M)<sup>+</sup>,  $\text{C}_{18}\text{F}_{15}\text{P}$ , 71%], 365 [(M)<sup>+</sup>,  $\text{C}_6\text{F}_5$ , 55%], 198 [(M)<sup>+</sup>,  $-(\text{C}_6\text{F}_5)_2$ , 20%], 129 [(M)<sup>+</sup>, 100%]; All other data were in agreement with previously reported values.<sup>44</sup>

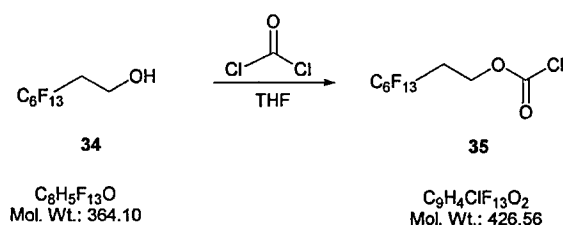
### Carboethoxymethyl *tris*(pentafluorophenyl)phosponium bromide **34**



To *tris*(pentafluorophenyl)phosphine **33** (2.00 g, 3.76 mmol) in dry toluene (40 ml) was added dropwise ethyl bromoacetate (0.63 g, 3.76 mmol). The mixture was stirred for 72 h, but within this period the reaction was not complete, so was decided to stop it.

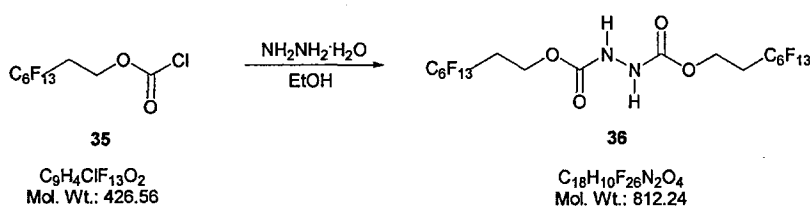
### 1H,1H,2H,2H-Perfluorooctyl chloroformate **35**<sup>66</sup>

NOTE TO FUTURE READERS: SPECIAL PRECAUTIONS SHOULD BE OBSERVED WHEN HANDLING PHOSGENE; REFER TO MSDS AND PERFORM FULL RISK & COSHH ASSESSMENT.



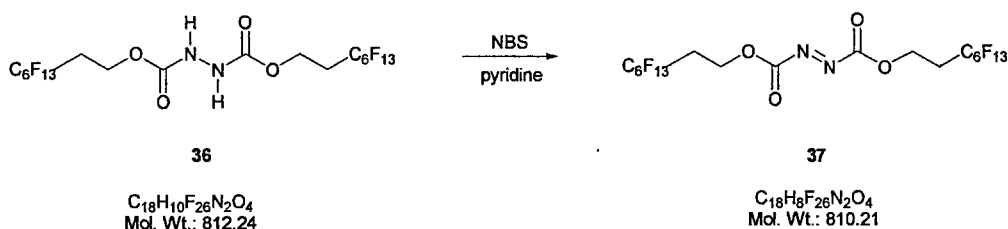
Perfluorooctanol **34** (5 g, 13.74 mmol) in dry THF (40 ml) was added to a solution of phosgene in toluene 20% (11.3 ml, 22.72 mmol) in dry THF (50 ml) at 0 °C under nitrogen. The solution was stirred for 2 h and then the ice bath removed. The solution was stirred at room temperature for 8 h and then heated at reflux temperature for 48 h. The solvent was then removed *in vacuo* giving the fluororous chloroformate as a pale yellow oil, which was used in the next step without further purification.

### 1H,1H,2H,2H-Perfluorooctyl hydrazine-1,2-dicarboxylate **36**<sup>66</sup>



The fluororous chloroformate **35** (3.49 g, 8.2 mmol) in ethanol (15 ml) was cooled to 0 °C and two solutions of hydrazine hydrate (0.41 g, 8.2 mmol) in ethanol (5 ml) and sodium carbonate (0.87 g, 8.2 mmol) in water (20 ml) added simultaneously and dropwise. The ice bath was then removed and the solution stirred at room temperature for 2 h. The hydrazine was formed as a white precipitate, which was removed by filtration. The white solid was re-crystallised in ethanol to give the hydrazine **36** as white crystals (2.68 g, 81% over the 2 steps). Mp 104 °C; R<sub>f</sub> 0.42 (hexane:EtOAc 1:1). Found [M+H]<sup>+</sup> 813.0304; C<sub>18</sub>H<sub>10</sub>F<sub>26</sub>N<sub>2</sub>O<sub>4</sub>+H requires 813.0347.  $\nu_{\max}/\text{cm}^{-1}$  (KBr) 3293 (NH), 3053 (CH), 2351, 1731 (C=O), 1201 (CF);  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 6.35 (2H, s, NH), 4.41 (4H, t, *J* 7, CO<sub>2</sub>CH<sub>2</sub>), 2.40 (2H tt, *J* 6, 12, CH<sub>2</sub>CF<sub>2</sub>);  $\delta_{\text{C}}$  NMR (acetone-*d*<sup>6</sup>) 156.2, 121.4–108.3 (m), 57.2, 30.2 (t, *J*=21.2 Hz);  $\delta_{\text{F}}$  NMR -80.6 (6F), -112.9 (4F), -121.4 (4F), -122.4 (4F), -123.0 (4F), -126.3 (4F).

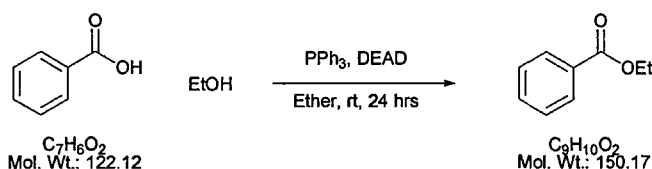


Fluorous DEAD **37**<sup>66</sup>

The fluorous hydrazine **36** (2.00 g, 2.46 mmol) and pyridine (0.4 ml, 4.92 mmol) were dissolved in dichloromethane (25 ml) and the mixture cooled to 0 °C. N-Bromosuccinimide (0.86 g, 4.8 mmol) was added slowly. The ice bath was removed after addition and the reaction stirred vigorously at room temperature for 2 h. The reaction mixture was then diluted with dichloromethane (150 ml) and washed thoroughly with aqueous sodium sulfite solution (3 × 20 ml), sodium hydrogenbicarbonate (3 × 20 ml), brine (3 × 20 ml) and water (3 × 20 ml). The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo* to give fluorous DEAD **37** as a yellow solid (0.35g, 92%). mp 61 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3052 (CH), 1771 (C=O), 1211 (CF);  $\delta_{\text{H}}$  (acetone-*d*<sup>6</sup>) 4.87 (t, *J* 5.9 Hz, 4H), 2.91 (tt, *J* 5.9, 19, 4H);  $\delta_{\text{C}}$  (acetone-*d*<sup>6</sup>) 161.2, 125–104 (m), 62.7, 31.3 (t, *J* 21.1);  $\delta_{\text{F}}$  (acetone *d*<sup>6</sup>)  $\delta$ –80.6 (6F), –112.9 (4F), –121.3 (4F), –122.3 (4F), –123 (4F), –123.6 (4F), –125.7 (4F); *m/z* 812 (*M*<sup>+</sup>+2, 55%), 449 (91%), 327 (85%), 131 (100%).

## Method for Determining of Partition Coefficients

Fluorous hydrazine **36** (~ 20 mg) was dissolved in a mixture of organic solvent (2 ml) and fluorous solvent (2 ml). The mixture was stirred for 22 h at room temperature and then allowed to stand for 1 h. Upon settling a 0.4 ml aliquot was taken from each layer and added to dodecane in hexane (2 ml, 0.0001 M). Each fraction was then analysed by GC (7 injections) and partition coefficients calculated for each pair of solvents tested.

**Ethyl Benzoate<sup>66</sup>****Method 1: Employing DEAD**

Triphenylphosphine (2.62 g, 10 mmol) and ethanol (0.69 g, 11 mmol) in diethyl ether (10 ml) were added dropwise to a stirred solution of DEAD (1.74 g, 11.1 mmol) and benzoic acid (1.22 g, 10 mmol) in diethyl ether under nitrogen. The solution was stirred at room temperature overnight. The white precipitate formed was removed by filtration and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane:EtOAc 1:1) to give the title compound (1.30 g, 85%);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.03 (2H, d,  $J = 7$ ,  $\text{CH}_A$ ), 7.64 (2H, t,  $J = 6.0$ ,  $\text{CH}_B$ ), 7.40 (1H, t,  $J = 7$ ,  $\text{CH}_C$ ), 4.15 (3H, t,  $J = 8.9$ ,  $\text{CH}_3$ ), 1.27 (2H, q,  $J = 8.9$ ,  $\text{CH}_2$ ); all other data in agreement with literature values.<sup>66</sup>

**Method 2: Employing Solid-Supported Triphenylphosphine**

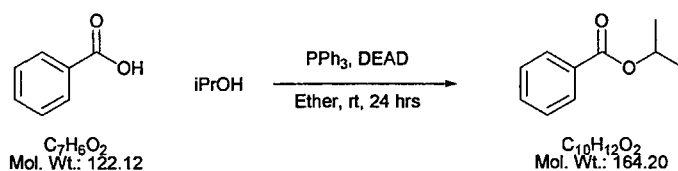
As per method 1, except on 1/10<sup>th</sup> scale and with the following modifications: the solid supported triphenylphosphine (0.50 g, 1.5 mmol) was swelled in dichloromethane (2 ml) for 5 h before adding ethanol (0.069 g, 1.1 mmol). A solution of DEAD (0.261 g, 1.5 mmol) and benzoic acid (0.18 g, 1.5 mmol) in DCM was then added and the solution shaken for 72 h. The solid supported reagent was removed by filtration, the solvent removed *in vacuo* and the product purified by chromatography as before (0.77 g, 52%). All data as reported previously.

**Method 3: Employing <sup>F</sup>DEAD**

As per method 1, except on 1/10<sup>th</sup> scale and using <sup>F</sup>DEAD (0.89 g, 1.1 mmol) in place of DEAD and using THF as the reaction solvent. After 24 h, the reaction mixture was

extracted with FC-72 (3 x 20 ml) to remove the fluoros-hydrazine. The THF layer was evaporated and the residue analysed by  $^1\text{H}$  and  $^{19}\text{F}$  nmr, which showed no fluorine-containing compound(s). The product was then purified by flash chromatography (0.125 g, 84 %) to give the *title compound*; data as reported previously.

### i-Propyl Benzoate<sup>66</sup>



#### Method 1: Employing DEAD

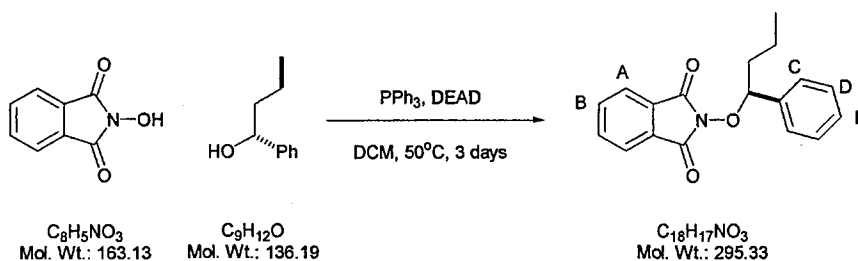
Triphenylphosphine (2.62 g, 10 mmol) and isopropanol (0.66 g, 11 mmol) in diethyl ether (10 ml) were added dropwise to a stirred solution of DEAD (1.74 g, 11.1 mmol) and benzoic acid (1.22 g, 10 mmol) in diethyl ether under nitrogen. The solution was stirred at room temperature overnight. The white precipitate formed was removed by filtration and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane:EtOAc 1:1) to give the *title compound* (1.40 g, 78%);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.31 (2H, d,  $J = 7$ ,  $\text{CH}_A$ ), 7.98 (2H, t,  $J = 6.0$ ,  $\text{CH}_B$ ), 7.65 (1H, t,  $J = 7$ ,  $\text{CH}_C$ ), 5.21 (1H, m, OCHCH<sub>3</sub>), 1.22 (6H, d,  $J = 8.6$ , 2 x CH<sub>3</sub>); all other data in agreement with literature values.

#### Method 2: Employing Solid-Supported Triphenylphosphine

As per method 1, except on 1/10<sup>th</sup> scale and with the following modifications: the solid supported triphenylphosphine (0.50 g, 1.5 mmol) was swelled in dichloromethane (2 ml) for 5 h before adding isopropanol (0.066 g, 1.1 mmol). A solution of DEAD (0.17 g, 1.1 mmol) and benzoic acid (0.18 g, 1.5 mmol) in DCM was then added and the solution shaken for 72 h. The solid supported reagent was removed by filtration, the solvent removed *in vacuo* and the product purified by chromatography as before. All data as reported previously.

**Method 3: Employing <sup>F</sup>DEAD**

As per method 1, except on 1/10<sup>th</sup> scale and using <sup>F</sup>DEAD (0.89 g, 1.1 mmol) in place of DEAD and using THF as the reaction solvent. After 24 h, the reaction mixture was extracted with FC-72 (3 x 20 ml) to remove the fluoros-hydrazine. The THF layer was evaporated and the residue analysed by <sup>1</sup>H and <sup>19</sup>F nmr, which showed no fluorine-containing compound(s). The product was then purified by flash chromatography (1.19 g, 73 %) to give the *title compound*; data as reported previously.

**(S)-(-)-N-1-Phenylbutoxyphthalimide<sup>66, 196</sup>****Method 1: Employing DEAD**

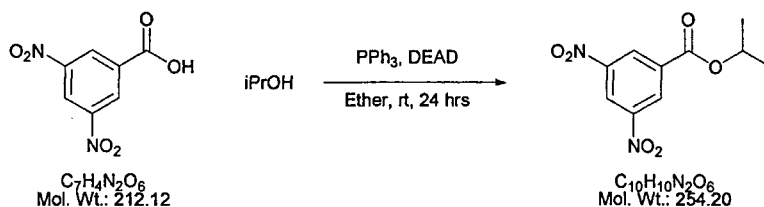
*N*-Hydroxyphthalimide (0.34 g, 2.24 mmol) was added to a solution of triphenylphosphine (0.58 g, 2.22 mmol) and (*R*)-1-phenylbutanol (0.15 g, 1 mmol) in THF (20 ml) under nitrogen. DEAD (0.35 ml, 2.24 mmol) in THF (10 ml) was added slowly with stirring. The resulting mixture was heated at 50 °C for 72 h. After cooling, the solvent was removed *in vacuo* and the residue purified by chromatography (hexane:EtOAc 2:1) to give the title compound as a white solid (0.53 g, 81%).  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.70 (4H, m, Ar), 7.45 (2H, m, Ar), 7.29 (3H, m, Ar), 5.34 (1H, t,  $J = 7.0$ , OCH), 2.16 (1H, m, CHCH<sub>2</sub>), 1.91, (1H, m, CHCH<sub>2</sub>), 1.47 (2H, m, CH<sub>2</sub>Me), 0.97 (3H, t,  $J = 7.4$ , Me);  $[\alpha]_{\text{D}}^{22} = -187.2$  ( $c$  2,  $\text{CH}_2\text{Cl}_2$ ); >95%*ee* by NMR (Eu(hfc)<sub>3</sub> doping); all other data in agreement with literature values. (I would like to thank and acknowledge Professor Chris Moody, University of Exeter, for supplying experimental details and copies of spectra for comparison).<sup>196</sup>

**Method 2: Employing Solid-Supported Triphenylphosphine**

As per method 1, with the following modifications: the solid supported triphenylphosphine (1.0 g, 3 mmol) was swelled in dichloromethane (2 ml) for 5 h before adding (*R*)-1-phenylbutanol (0.15 g, 1 mmol). A solution of DEAD (0.35 ml, 2.24 mmol) and *N*-hydroxyphthalimide (0.34 g, 2.24 mmol) in DCM was then added and the solution shaken for 72 h. The solid supported reagent was removed by filtration, the solvent removed *in vacuo* and the product purified by chromatography as before (0.14 g, 50%). All data as reported previously.

**Method 3: Employing <sup>F</sup>DEAD**

As per method 1, except using <sup>F</sup>DEAD (1.81 g, 2.24 mmol) in place of DEAD and using THF as the reaction solvent. After 72 hours, the reaction mixture was extracted with FC-72 (3 x 20 ml) to remove the fluoros-hydrazine. The THF layer was evaporated and the residue analysed by <sup>1</sup>H and <sup>19</sup>F nmr, which showed no fluorine-containing compound(s). The product was then purified by flash chromatography (1.27 g, 78 %) to give the *title compound*; data as reported previously.

**i-Propyl 3,5-dinitrobenzoate<sup>66</sup>****Method 1: Employing DEAD<sup>66</sup>**

Triphenylphosphine (2.62 g, 10 mmol) and isopropanol (0.6 g, 10 mmol) in THF (2 ml) were added dropwise to a stirred solution of DEAD (1.91 g, 11 mmol) and 3,5-dinitrobenzoic acid (2.48 g, 11 mmol) in THF under nitrogen. The solution was stirred at room temperature overnight. The white precipitate formed was removed by filtration and

the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane:EtOAc 1:1) to give the *title compound* (2.33 g, 92%);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 9.15 (1H, brtr, Ar), 9.08 (2H, m, Ar), 5.30 (1H, m, OCH), 1.37 (6H, d,  $J = 6.1$ , 2 x  $\text{CH}_3$ ); all other data in agreement with literature values.

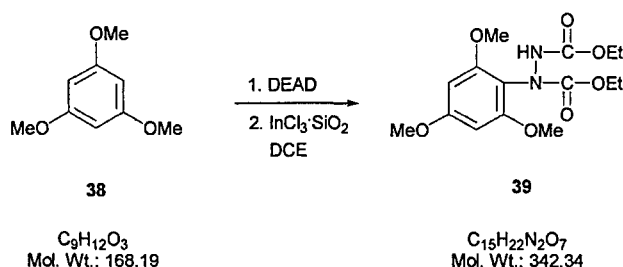
### Method 3: Employing $^{\text{F}}$ DEAD

As per method 1, except on 1/10<sup>th</sup> scale and using  $^{\text{F}}$ DEAD (0.89 g, 1.1 mmol) in place of DEAD. After 24 hours, the reaction mixture was extracted with FC-72 (3 x 20 ml) to remove the fluorous-hydrazine. The THF layer was evaporated and the residue analysed by  $^1\text{H}$  and  $^{19}\text{F}$  nmr, which showed no fluorine-containing compound(s). The product was then purified by flash chromatography (0.24 g, 91%) to give the *title compound*; data as reported previously.

### The Preparation of $\text{InCl}_3 \cdot \text{SiO}_2$ catalyst<sup>68</sup>

Silica gel (6.00 g, 100 mmol, Aldrich, 230-400 mesh) was added to a stirred solution of indium trichloride (0.19 g, 0.9 mmol) in acetonitrile (8 ml), and left overnight after which time the solvent was evaporated *in vacuo*. The catalyst was stored under nitrogen and could be kept indefinitely.

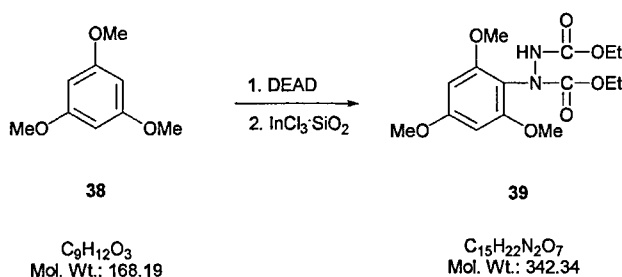
### *N*-(2,4,6-Trimethoxyphenyl)hydrazinecarboxylic acid ethyl ester 39.<sup>69</sup> (Conventional method)



A mixture of 1,3,5-trimethoxybenzene **38** (0.84 g, 5 mmol), DEAD (0.87 g, 5 mmol) and freshly prepared  $\text{InCl}_3 \cdot \text{SiO}_2$  (0.14 g, 0.5 mmol) in 1,2-dichloroethane (10 ml) was stirred at

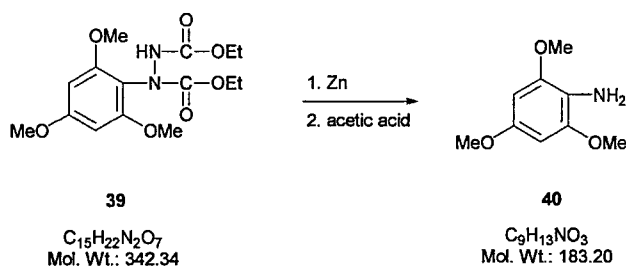
reflux for 10 h. The reaction mixture was diluted with water (20 ml) and extracted with chloroform (3 × 15 ml). The organic layers were combined and dried over magnesium sulfate and the solvent removed *in vacuo* to give the crude product, which was examined by  $^1\text{H}$  NMR.  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.09 (1H, br s, N-H), 6.20 (2H, 2 s overlapping, ArH), 4.28 (4H, m, 2 ×  $\text{CH}_2$ ), 3.92 (9H, m, 3 × Ar $\text{CH}_3$ ), 1.36 (6H, m, 2 ×  $\text{CH}_3$ ).

***N*-(2,4,6-Trimethoxyphenyl)hydrazinecarboxylic acid ethyl ester 39.**<sup>68,69</sup> (Microwave Irradiation)

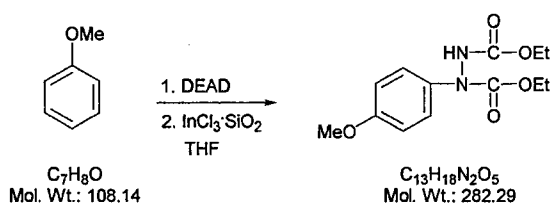


A mixture of 1,3,5-trimethoxy benzene **38** (16.80 mg, 0.1 mmol), DEAD (17.40 mg, 0.1 mmol) and freshly prepared  $\text{InCl}_3 \cdot \text{SiO}_2$  (50.40 mg) was transferred into a microwave tube and exposed to irradiation at 300 watts, 7 psi for 3 min at 100 °C. Since only reactants were present, the temperature was raised to 200 °C and the reaction re-run under the same conditions. The mixture turned black and  $^1\text{H}$  NMR showed no obvious products. Therefore, the reaction was re-commenced with fresh materials, using the following conditions: power: 300 watts; pressure: 7 psi; time: 5 min; temperature: 150 °C.

Two reactions were run using these conditions, one in THF and the other in 1,2-dichloroethane. The reaction proceeded well in THF but failed in 1,2-dichloroethane.  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.40 (1H, br s, N-H), 6.01 (2H, s, 2 × ArH), 4.13 (4H, m, 2 ×  $\text{CH}_2$ ), 3.70 (9H, m, 3 × Ar $\text{CH}_3$ ), 1.20 (6H, m, 2 ×  $\text{CH}_3$ ); Values slightly offset compared to previous data. All other data in agreement with literature values.<sup>68,69</sup>

**2,4,6-Trimethoxyphenylamine 40**<sup>68,69</sup>

To a solution of the newly obtained crude hydrazide **39** (0.50 g, 1.46 mmol) in glacial acetic acid (7.5 ml) under a nitrogen atmosphere, was added newly activated zinc dust (0.8g, 12.33 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by adding water and sodium hydroxide (10 M) to pH 10 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. The product was purified by Kugelrohr distillation, b.p. 113-116 °C /0.5 mmHg. All other data in agreement with literature values.<sup>69</sup>

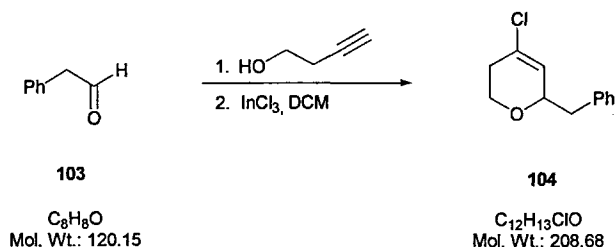
***N*-(2-Methoxyphenyl)-hydrazinecarboxylic acid ethyl ester.**<sup>68,69</sup>

A mixture of methoxybenzene **41** (10.80 mg, 0.1 mmol), DEAD (17.40 mg, 0.1 mmol), the catalyst (50.4 mg) and THF (1 ml) was irradiated in a microwave over at 300 watts, pressure 7 psi for 8 min at 160 °C. The reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (3 × 15 ml). The organic layers were combined and dried over magnesium sulfate and the solvent removed *in vacuo* to give the product as a white solid, 20.04 mg, 71%; mp 57-59 °C; all other data in agreement with literature values.<sup>68</sup>



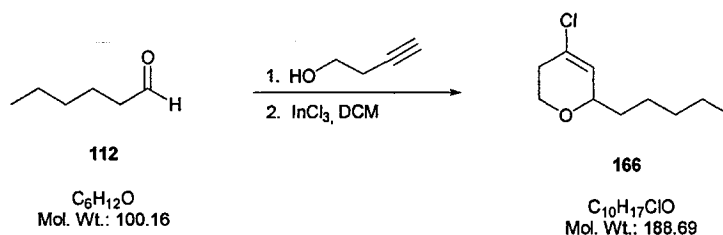


## 4-Chloro-2-benzyl-5,6-dihydro-2H-pyran 104



Prepared according to the general procedure using phenylacetaldehyde **103** (3.42 g, 28.5 mmol), 3-butyn-1-ol (2.00g, 28.5 mmol) and indium chloride (6.38 g, 28.5 mmol). 4-Chloro-6-phenyl-3,6-dihydro-2H-pyran **104** was isolated as a pale yellow oil (2.38 g, 40%).  $R_f$  0.56 (hexane:ethyl acetate 5:1); Found  $[\text{M}+\text{H}]^+$  209.0737;  $\text{C}_{12}\text{H}_{13}\text{OCl}$  requires 209.0733;  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 2915, 2810, 1626 (C=C), 1598, 1314, 1020, 824, 684 (C-Cl);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.31-7.19 (5H, m, Ar), 5.75 (1H, d,  $J$  0.81, ClC=CH), 4.29 (1H, m, OCHCH<sub>2</sub>Ph), 4.00 (1H, m, CH<sub>2</sub>CHHO), 3.65 (1H, ddd,  $J$  14.3, 10.4, 4.0, CH<sub>2</sub>CHHO), 2.92 (1H, dd  $J$  13.6, 7.2, CHHPh), 2.71 (1H, dd,  $J$  13.6, 6.8, CHHPh), 2.40 (2H, m, CH<sub>2</sub>CCl),  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 137.9 (CCl), 130.6 (C<sub>quart</sub> in Ar), 129.8, 128.8, 128.4 (5 × C(Ar)), 126.5 (CCl=CH), 76.2 (OCHCH<sub>2</sub>), 66.3 (CH<sub>2</sub>CH<sub>2</sub>O), 41.5 (CH<sub>2</sub>CH<sub>2</sub>O), 33.2 (CH<sub>2</sub>Ar);  $m/z$  (CI) 209  $[(\text{M}+\text{H})^+]$ , 8%, 173  $[(\text{M}-\text{Cl})^+]$ , 43%, 155 [100%], 143 [81%], 132  $[(\text{M}-\text{Ph})^+]$ , 8%, 117  $[(\text{M}-\text{CH}_2\text{Ph})^+]$ , 57%].

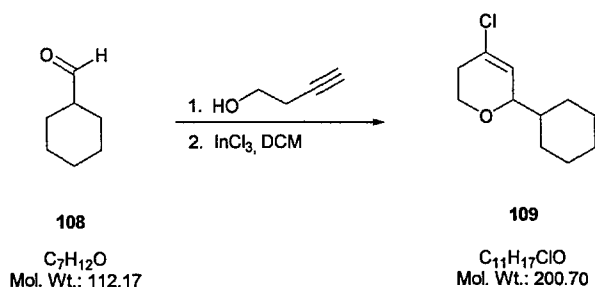
## 4-Chloro-2-pentyl-5,6-dihydro-2H-pyran 166



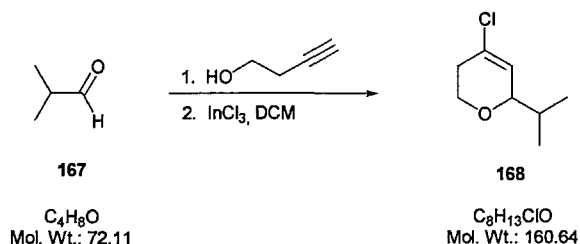
Prepared according to the general procedure using hexanal **112** (0.50 g, 5 mmol), 3-butyn-1-ol (0.35g, 5 mmol) and indium trichloride (1.10 g, 5 mmol). 4-Chloro-6-pentyl-3,6-dihydro-2H-pyran **166** was isolated as a pale yellow oil (0.76 g, 80%).  $R_f$  0.51

(hexane:ethyl acetate 6:1); Found  $[M+H]^+$  189.1027;  $C_{10}H_{17}OCl$  requires 189.1046;  $\nu_{\max}/\text{cm}^{-1}$  (nujol) 2960, 2852, 1654 (C=C), 1598, 1454, 1250, 1101, 978, 702 (C-Cl);  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.69 (1H, d,  $J$  2.8,  $ClC=CH$ ), 3.97 (1H, m,  $OCHCH_2$ ), 3.94 (1H, m,  $CH_2CHHO$ ), 3.60 (1H, ddd,  $J$  15.3, 11.8, 5.9,  $CH_2CHHO$ ), 2.46 (2H, m,  $CH_2CH_2O$ ), 1.43 (2H, m,  $OCHCH_2CH_2$ ), 1.26-1.20 (6H, m,  $3 \times CH_2$ ), 0.81 (3H, t,  $J$  6.5);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 130.8 ( $CCl$ ), 127.0 ( $ClC=CH$ ), 74.5 ( $OCHCH_2$ ), 63.7 ( $CH_2CH_2O$ ), 34.9 ( $OCHCH_2CH_2$ ), 31.7 ( $CH_2CH_2O$ ), 32.8, 24.7, 22.5 ( $3 \times CH_2$ ), 13.8 ( $CH_3$ ).  $m/z$  CI 191  $[(M+H)^+]$ ,  $C_{10}H_{17}^{37}ClO$ , 6%), 189  $[(M+H)^+]$ ,  $C_{10}H_{17}^{35}ClO$ , 19%), 169 [100%], 153  $[(M-Cl)^+]$ , 92%), 123 [68%], 117  $[(M-CH_2CH_2CH_2CH_2CH_3)^+]$ , 93%]

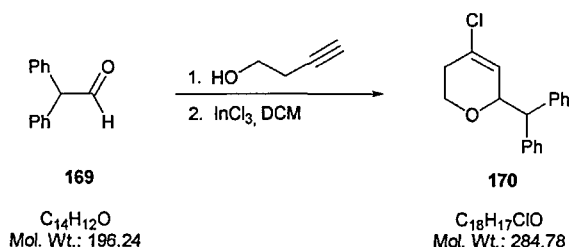
#### 4-Chloro-2-cyclohexyl-5,6-dihydro-2H-pyran 109



Prepared according to the general procedure using cyclohexanecarboxaldehyde **108** (0.37 g, 3 mmol), 3-butyn-1-ol (0.21 g, 3 mmol) and indium trichloride (0.66g, 3 mmol). 4-Chloro-6-cyclohexyl-3,6-dihydro-2H-pyran **109** was isolated as a pale yellow oil (0.38 g, 63%).  $R_f$  0.5 (hexane:ethyl acetate 7:1); Found  $[M+H]^+$  201.1034;  $C_{11}H_{17}OCl$  requires 201.1046;  $\nu_{\max}/\text{cm}^{-1}$  (nujol) 2931, 2854, 1596 (C=C), 1450, 1344, 1079, 732 (C-Cl);  $\delta_H$  (300 MHz;  $CDCl_3$ ) 5.80 (1H, d,  $J$  1.9,  $ClC=CH$ ), 4.00 (1H, m,  $CH_2CHHO$ ), 3.89 (1H, br s,  $OCHCH=CCl$ ), 3.66 (1H, ddd,  $J$  15.0, 11.2, 3.9,  $CH_2CHHO$ ), 2.1 (1H, m,  $CHHCH_2O$ ), 2.13 (1H, d,  $J$  16.8,  $CHHCH_2O$ ), 1.28-1.15 (11H in cyclohexyl);  $\delta_C$  (75 MHz,  $CDCl_3$ ) 130.0 ( $CCl$ ), 126.1 ( $ClC=CH$ ), 79.1 ( $OCH$ ), 64.4 ( $CH_2CH_2O$ ), 42.8 ( $CH$  (cyclohexyl)), 35.0 ( $CH_2CH_2O$ ), 29.1, 28.3, 26.8, 26.3 25.9 ( $5 \times CH_2$  (cyclohexyl));  $m/z$  (CI) 201  $[(M+H)^+]$ , 6 %], 181 [100%], 180 [18%], 165  $[(M)^+]$ , -Cl, 10%), 117  $[(M-C_6H_{11})^+]$ , .8 %].

4-Chloro-2-isopropyl-5,6-dihydro-2H-pyran **168**

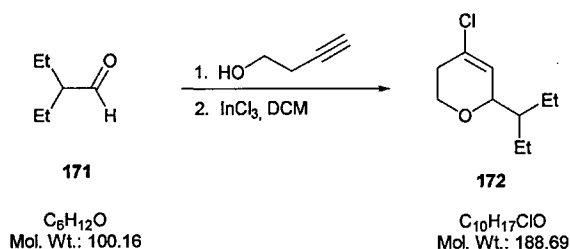
Prepared according to the general procedure using dimethylacetaldehyde **167** (0.29 g, 4 mmol), 3-butyn-1-ol (0.28g, 4 mmol) and indium trichloride (0.88 g, 4 mmol). The desired compound **168** was obtained as a pale yellow oil (0.23g, 26%).  $R_f$  0.31 (hexane : ethyl acetate 10:1); Found  $[M+H]^+$  161.0723;  $C_8H_{13}OCl$  requires 161.0733;  $\nu_{max}/cm^{-1}$  (nujol) 2969, 2867, 1684, 1650 (C=C), 1089, 982, 661 (C-Cl);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 5.78 (1H, d,  $J$  2.3, CCl=CH), 4.03 (1H, m, CH<sub>2</sub>CHHO), 3.65 (1H, ddd, 11.4, 7.5, 4.2, CH<sub>2</sub>CHHO), 2.11 (1H, d, 18.4 CHHCH<sub>2</sub>O), 1.78 (2H, m, CH<sub>3</sub>CHCH<sub>3</sub> overlapping CHHCH<sub>2</sub>O), 0.88 (6H, m, 2 × CH<sub>3</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 130.0 (ClC=CH), 125.4 (ClC=CH), 79.6 (OCH), 64.0 (CH<sub>2</sub>CH<sub>2</sub>O), 33.0 (CH<sub>3</sub>CHCH<sub>3</sub>), 32.4 (CH<sub>2</sub>CH<sub>2</sub>O), 17.9 (CH<sub>3</sub>CHCH<sub>3</sub>), 17.5 (CH<sub>3</sub>CHCH<sub>3</sub>);  $m/z$  (CI) 163  $[(M+H-C_8H_{13}O^{37}Cl)^+]$ , 31%, 161  $[(M+H-C_8H_{13}O^{35}Cl)^+]$ , 100%, 143 [73%], 117  $[(M-C_3H_7)^+]$ , 14 %, 125 [40%].

2-Diphenylmethyl-4-chloro-5,6-dihydro-2H-pyran **170**

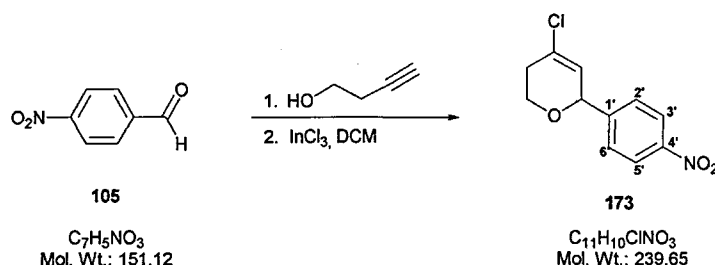
Prepared according to the general procedure using diphenylacetaldehyde **169** (0.59 g, 3 mmol), 3-butyn-1-ol (0.21 g, 3 mmol) and indium trichloride (0.66 g, 3 mmol). The desired compound **170** was obtained as a pale yellow oil (0.39 g, 46%).  $R_f$  0.32 (hexane:ethyl acetate 10:1); Found  $[M+H]^+$  285.1054;  $C_{18}H_{17}OCl$  requires 285.1046;  $\nu_{max}/cm^{-1}$  (nujol) 3060, 3027, 1653 (C=C), 1495, 700 (C-Cl);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 7.32-

7.30 (10H, m, 2 × Ph), 5.72 (1H, d, 2.8, ClC=CH), 4.88 (1H, m, OCH), 4.06 (2H, m, overlapping OCHCH and CH<sub>2</sub>CHHO), 3.72 (1H, ddd, 11.5, 7.5, 5.8, CH<sub>2</sub>CHHO), 2.5 (1H, m, CHHCH<sub>2</sub>O), 2.19 (1H, d, *J* 16.1 CHHCH<sub>2</sub>O); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 141.4, 141.2 (2 × C<sub>quart</sub> (Ar)), 129.7 (CCl), 128.5, 128.3, 126.8 (10 × C (Ar), 125.4 (CCl=CH), 76.8 (OCH), 64.1 (CH<sub>2</sub>CH<sub>2</sub>O), 56.2 (OCHCH), 32.8 (CH<sub>2</sub>CH<sub>2</sub>O); *m/z* (CI) 287 [(M+H-C<sub>18</sub>H<sub>17</sub>O<sup>37</sup>Cl)<sup>+</sup>, 18%], 285 [(M+H-C<sub>18</sub>H<sub>17</sub>O<sup>35</sup>Cl)<sup>+</sup>, 50%], 249 [(M-Cl)<sup>+</sup>, 50%], 231 [100%], 167 [96%], 117 [(M-C<sub>13</sub>H<sub>11</sub>)<sup>+</sup>, 24%]

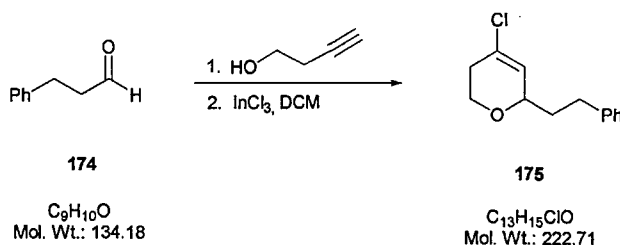
#### 4-Chloro-2-(1-ethylpropyl)-5,6-dihydro-2H-pyran 172



Prepared according to the general procedure using diethylacetaldehyde **171** (0.30 g, 3 mmol), 3-butyn-1-ol (0.21g, 3 mmol) and indium trichloride (0.66 g, 3 mmol). The desired compound **172** was obtained as a pale yellow oil (0.27g, 48%). *R<sub>f</sub>* 0.27 (hexane : ethyl acetate 10:1). Found [M+H]<sup>+</sup> 189.1046; C<sub>11</sub>H<sub>10</sub>ClNO<sub>3</sub> requires 188.0968; ν<sub>max</sub>/cm<sup>-1</sup> (nujol) 2975, 2868, 1682 (C=C), 1572, 1465, 1251, 889, 771 (C-Cl); δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 5.71 (1H, d, *J* 4.0, ClC=CH), 4.09 (1H, br s, OCH), 3.98 (1H, m, CH<sub>2</sub>CHHO), 3.61 (1H, ddd, *J* 14.4, 10.7, 3.6, CH<sub>2</sub>CHHO), 2.51 (1H, m, CHHCH<sub>2</sub>O), 2.05 (1H, d, *J* 18.2, CHHCH<sub>2</sub>O), 1.45-1.27 (5H, m, OCHCH<sub>2</sub>Et overlapping 2 × CH<sub>2</sub> in 2Et), 0.84 (6H, m, 2 × CH<sub>3</sub>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 129.5 (CCl), 126.0 (ClC=CH), 76.5 (OCH), 64.2 (CH<sub>2</sub>CH<sub>2</sub>O), 46.1 (OCHCH<sub>2</sub>Et), 33.0 (CH<sub>2</sub>CH<sub>2</sub>O), 21.8, 21.4 (2 × CH<sub>2</sub>(Et)), 12.0, 11.9 (2 × CH<sub>3</sub>(Et)); *m/z* (CI) 191 [(M+H)<sup>+</sup>, C<sub>10</sub>H<sub>17</sub>O<sup>37</sup>Cl, 28%], 189 [(M+H)<sup>+</sup>, C<sub>10</sub>H<sub>17</sub>O<sup>35</sup>Cl, 91%], 171 [43%], 153 [(M-Cl)<sup>+</sup>, 100%], 117 [(M-CH<sub>2</sub>Et)<sub>2</sub>, 71%].

**4-Chloro-2-(4-nitrophenyl)-5,6-dihydro-2H-pyran 173**

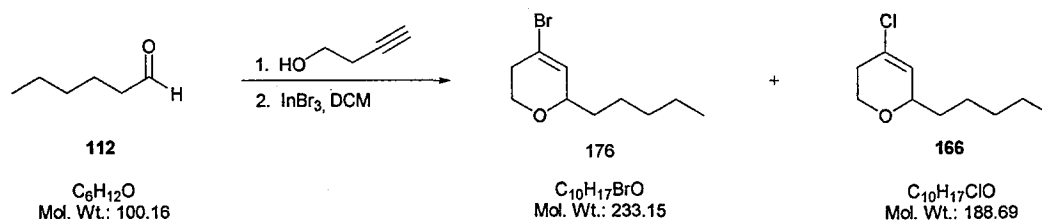
Prepared according to the general procedure using 4-nitrobenzaldehyde **105** (0.60g, 4 mmol), 3-butyn-1-ol (0.28 g, 4 mmol) and indium trichloride (0.88g, 4 mmol). No reaction was observed at room temperature, so it was left refluxing over a weekend. After purification, a pale yellow oil of **173** was obtained (0.40 g, 41%).  $R_f$  0.31 (hexane:ethyl acetate 8:1); Found  $[M+H]^+$  240.0427;  $C_{11}H_{10}ClNO_3$  requires 240.0423;  $\nu_{max}/cm^{-1}$  (nujol) 3077, 2859, 1708, 1652 (C=C), 1525, 1344 (C-NO<sub>2</sub>), 1255, 889, 754 (C-Cl);  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.13 (2H, d,  $J$  8.8, C(3')H, C(5)H), 7.45 (2H, d,  $J$  8.5, C(2')H, C(6)H), 5.83 (1H, d,  $J$  2.1, ClC=CH), 5.18 (1H, br s, OCH), 4.02 (1H, m, CH<sub>2</sub>CHHO), 3.80 (1H, ddd,  $J$  13.2, 9.1, 4.1, CH<sub>2</sub>CHHO), 2.92 (1H, m, CHHCH<sub>2</sub>O), 2.0 (1H, d, 16.9, CHHCH<sub>2</sub>O);  $\delta_C$  (75 MHz; CDCl<sub>3</sub>), 141.6 (CCl), 131.6 (C(1')), 128.2 (C(3')H & C(5')H), 125.2 (ClC=CH), 124.2 (C(2')H & C(6')H), 123.8 (C(4')), 76.1 (OCH), 64.2 (CH<sub>2</sub>CH<sub>2</sub>O), 33.0 (CH<sub>2</sub>CH<sub>2</sub>O);  $\nu_{max}/cm^{-1}$  (nujol) 3446, 2859, 1652, 1525, 1344, 1124, 754, 701;  $m/z$  (CI) 242  $[(M+H)^+ C_{11}H_{10}^{37}ClNO_3, 34\%]$ , 240  $[(M+H)^+ C_{11}H_{10}^{35}ClNO_3, 100\%]$ , 204  $[(M-Cl)^+ 12\%]$ .

**4-Chloro-2-(2-phenethyl)-5,6-dihydro-2H-pyran 175**

Prepared according to the general procedure using 3-phenyl-propionaldehyde **174** (0.40 g, 3 mmol), 3-butyn-1-ol (0.21 g, 3 mmol) and indium trichloride (0.66g, 3 mmol). The desired

compound **175** was obtained as a pale yellow oil (0.27 g, 41%).  $R_f$  0.38 (hexane:ethyl acetate 10:1); Found  $[M+H]^+$  223.0889;  $C_{13}H_{15}OCl$  requires 222.0811;  $\nu_{max}/cm^{-1}$  (nujol) 3027, 2929, 1735, 1656 (C=C), 1344, 1116, 741 (C-Cl), 698;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.31-7.19 (5H, m, Ar), 5.79 (1H, d,  $J$  1.9, ClC=CH), 4.13 (1H, m, OCH), 4.07 (1H, m, CH<sub>2</sub>CHHO), 3.71 (1H, ddd,  $J$  15.3, 11.3, 4.0, CH<sub>2</sub>CHHO), 2.75 (2H, m, CH<sub>2</sub>CH<sub>2</sub>O), 2.40 (1H, m, OCHCHHCH<sub>2</sub>Ph), 2.1 (1H, m, OCHCHHCH<sub>2</sub>Ph), 1.86 (2H, m, CH<sub>2</sub>CH<sub>2</sub>Ph);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 141.7 (CCl), 129.8 (C<sub>quart</sub> in Ar), 128.3, 128.2, 126.8, (5 × C(Ar)), 125.8 (ClC=CH), 73.9 (OCH), 63.7 (CH<sub>2</sub>CH<sub>2</sub>O), 36.6 (OCHCH<sub>2</sub>CH<sub>2</sub>Ph), 33.0 (OCHCH<sub>2</sub>CH<sub>2</sub>Ph), 31.2 (CH<sub>2</sub>CH<sub>2</sub>O);  $m/z$  (CI) 187 [(M-Cl)<sup>+</sup>, 28%], 169 [6%], 159 [21%], 117 [(M-CH<sub>2</sub>CH<sub>2</sub>Ph)<sup>+</sup>, 100%].

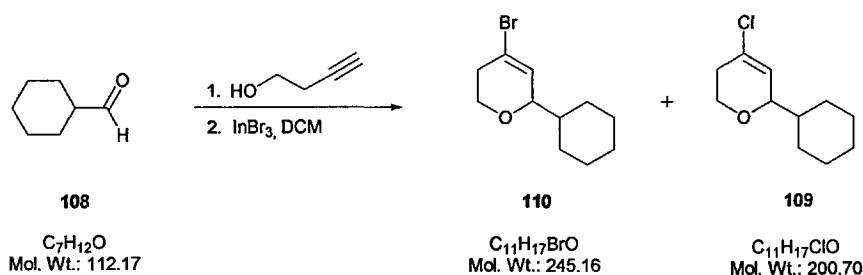
#### 4-Bromo-2-pentyl-5,6-dihydro-2H-pyran **176**



Prepared according to the general method for cyclisation reactions of aldehydes with 3-butyn-1-ol (0.35g, 5 mmol), hexanal **112** (0.50g, 5 mmol), but using indium tribromide (1.77 g, 5 mmol). The product was obtained as a pale yellow oil containing an inseparable mixture of 4-bromo-2-pentyl-5,6-dihydro-2H-pyran **176** and 4-chloro-2-pentyl-5,6-dihydro-2H-pyran **166** (0.59g, 51%) with the ratio of 3:1.  $R_f$  0.54 (hexane:ethyl acetate 6:1); Found  $[M+H]^+$  233.0541;  $C_{10}H_{17}O^{79}Br+H$  requires 232.0463;  $\nu_{max}/cm^{-1}$  (nujol) 2931, 2859, 1733, 1647 (C=C), 1459, 1249, 1103, 1037, 879 (C-Br and C-Cl);  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.94 (1H, d,  $J$  5.1, BrC=CH), 5.71 (1H, d,  $J$  3.8, ClC=CH), 4.00 superimposed (2H, m, 2 × OCHCH<sub>2</sub>), 3.93 superimposed (2H, m, 2 × CH<sub>2</sub>CHHO), 3.63 superimposed (2H, m, 2 × CH<sub>2</sub>CHHO), 2.70 superimposed (2H, m, 2 × CHHCH<sub>2</sub>O), 2.23 (1H, d,  $J$  21.8, (Br)CHHCH<sub>2</sub>O), 2.12 (1H, d,  $J$  11.4, (Cl)CHHCH<sub>2</sub>O), 1.28 super-imposed (4H, m, 2 × OCHCH<sub>2</sub>), 1.27 super-imposed (12H, m, 6 × CH<sub>2</sub>), 0.84 super-imposed (6H, m, 2 × CH<sub>3</sub>);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 131.3 (BrC=CH), 127.0 (ClC=CH), 118.6 (CBr), 104.3 (CCl), 75.8

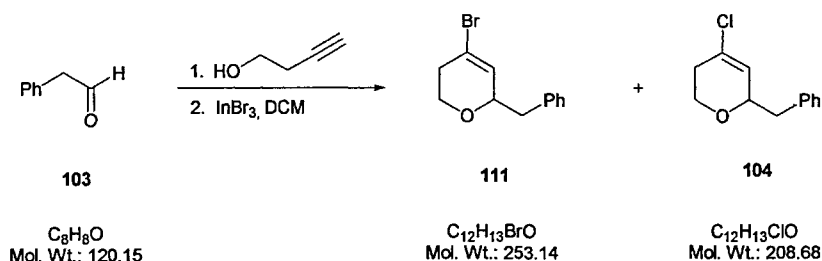
((Br)OCH), 74.7 ((Cl)OCH), 64.2 ((Br)CH<sub>2</sub>CH<sub>2</sub>O), 63.7 ((Cl)CH<sub>2</sub>CH<sub>2</sub>O), 35.1, 34.9, 34.9, 34.8 superimposed (4C, 2 × CH<sub>2</sub>CH<sub>2</sub>O and 2 × CH<sub>2</sub>), 31.7, 31.1, 25.9, 25.7, 22.7, 22.5 (6 × CH<sub>2</sub>), 14.0 ((Br)CH<sub>3</sub>), 13.9 ((Cl)CH<sub>3</sub>); *m/z* (EI) 234 [(M)<sup>+</sup> C<sub>10</sub>H<sub>17</sub><sup>81</sup>BrO, 97%], 232 [(M)<sup>+</sup>, 12%], 231 [100%], 153 [(M-Br)<sup>+</sup>, 86%]

#### 4-Bromo-2-cyclohexyl-5,6-dihydro-2H-pyran 110

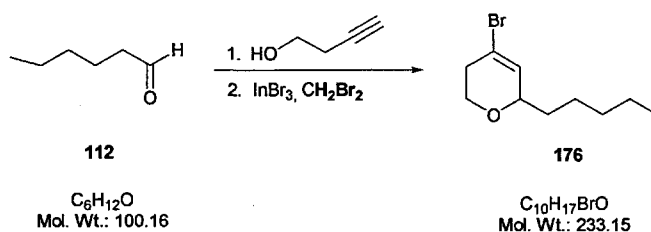


Prepared according the general procedure using 3-butyn-1-ol (0.21 g, 3 mmol), cyclohexyl carboxylaldehyde **108** (0.34g, 3 mmol) and indium tribromide (1.06g, 3 mmol) to give an inseparable mixture of 4-Bromo-6-cyclohexyl-3,6-dihydro-2H-pyran **110** and 4-Chloro-6-cyclohexyl-3,6-dihydro-2H-pyran **109** (0.56 g of mixture, in the ratio of 2.5:1). *R<sub>f</sub>* 0.50 (hexane:ethyl acetate 6:1); Found [M+H]<sup>+</sup> 245.0463; C<sub>11</sub>H<sub>17</sub><sup>79</sup>BrO +H requires 244.0463;  $\nu_{\max}/\text{cm}^{-1}$  (nujol) 2927, 2852, 1650 (C=C), 1450, 1340, 1253, 1081, 860, 759 and 734 (C-Br and C-Cl);  $\delta$ H (300 MHz; CDCl<sub>3</sub>) 6.3 (1H, br s, BrC=CH), 5.80 (1H, br s, ClC=CH), 3.98 super-imposed (2H, m, 2 × CH<sub>2</sub>CHHO), 3.87 super-imposed (2H, m, 2 × OCH), 3.66 super-imposed (2H, m, 2 × CH<sub>2</sub>CHHO), 2.70 (1H, m, (Br)CHHCH<sub>2</sub>O), 2.55 (1H, m, (Cl)CHHCH<sub>2</sub>O), 2.26 (1H, d, *J* 16.1, (Br)CHHCH<sub>2</sub>O), 2.18 (1H, d, *J* 14.1, (Cl)CHHCH<sub>2</sub>O), 1.76-1.67, 1.23-1.07 super-imposed (22H, m, 2 × cyclohexyl);  $\delta$ C (75 MHz; CDCl<sub>3</sub>) 130.4 (BrC=CH), 130.0 (ClC=CH), 119.3, 119.3 super-imposed (BrC), (ClC), 80.4 ((Br)OCH), 79.4 ((Cl)OCH), 64.9 ((Br)CH<sub>2</sub>CH<sub>2</sub>O), 64.4 ((Cl)CH<sub>2</sub>CH<sub>2</sub>O), 42.9, 42.8 super-imposed (2 × OCHCHCH<sub>2</sub>CH<sub>2</sub>), 35.7 ((Br)CH<sub>2</sub>CH<sub>2</sub>O), 33.5 ((Cl)CH<sub>2</sub>CH<sub>2</sub>O), 28.9, 28.8, 28.5, 28.3, 28.3, 26.8, 26.7, 26.5, 26.4, 26.0 (10C, 2 × cyclohexyl); *m/z* (CI) 247 [(M+H)<sup>+</sup>, C<sub>11</sub>H<sub>18</sub><sup>81</sup>BrO, 62%], 245 [(M+H)<sup>+</sup>, C<sub>11</sub>H<sub>18</sub><sup>79</sup>BrO, 73%], 203 [(M+H)<sup>+</sup>, C<sub>11</sub>H<sub>17</sub><sup>37</sup>ClO, 20%], 201 [(M+H)<sup>+</sup>, C<sub>11</sub>H<sub>17</sub><sup>35</sup>ClO, 65%], 165 [100%]

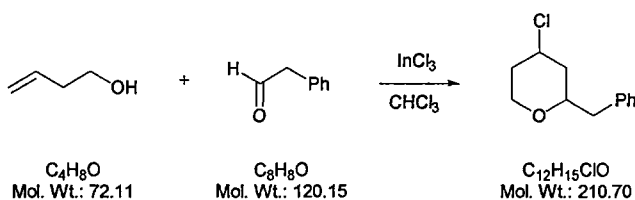


4-Bromo-2-benzyl-5,6-dihydro-2H-pyran **111**

Prepared according to the general procedure 3-butyn-1-ol (0.21 g, 3 mmol), phenylacetaldehyde **103** (0.36 g, 3 mmol) and indium tribromide (1.06g, 3 mmol) gave an inseparable mixture of 4-Bromo-6-phenyl-3,6-dihydro-2H-pyran **111** and 4-Chloro-6-phenyl-3,6-dihydro-2H-pyran **104** (0.4g, of mixture, in the ratio of 2.5:1).  $R_f$  0.46 (hexane:ethyl acetate 8:1); Found  $[\text{M}+\text{H}]^+$  253.0228;  $\text{C}_{12}\text{H}_{14}^{79}\text{BrO}$  requires 252.0150;  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 2922, 2853, 1643 (C=C), 1495, 1455, 1340, 1112, 1051, 906, 841 and 740 (C-Br and C-Cl);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.31-7.20 super-imposed (10H, m, Ar), 6.00 (1H, d,  $J$  5.04, BrC=CH), 5.77 (1H, d,  $J$  1.05, ClC=CH), 4.30 super-imposed (2H, m,  $2 \times \text{OCHCH}_2\text{Ph}$ ), 4.02 super-imposed (2H, m,  $2 \times \text{CH}_2\text{CHHO}$ ), 3.69 (2H, m,  $2 \times \text{CH}_2\text{CHHO}$ ), 2.93 super-imposed (2H, m,  $2 \times \text{CHHPH}$ ), 2.72 super-imposed (2H, m,  $2 \times \text{CHHPH}$ ), 2.66 (1H, m, (Br)CHHCH $_2$ O), 2.58 (1H, m, (Cl)CHHCH $_2$ O), 2.30 (1H, d,  $J$  16.0, (Br)CHHCH $_2$ O), 2.17 (1H, d  $J$  11.2, (Cl)CHHCH $_2$ O);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 137.8, 137.7 super-imposed (BrC), (ClC), 130.7, 130.5, 129.7, 129.3, 128.8, 128.7 super-imposed ( $10 \times \text{C}(\text{Ar})$ ), 126.9 (BrC=CH), 126.4 (ClC=CH), 119.8, 119.7 super-imposed ( $2 \times \text{C}_{\text{quart}}$  in Ar), 77.1 ((Br)OCH), 76.1 ((Cl)OCH), 64.7 ((Br)CH $_2$ CH $_2$ O), 64.2 ((Cl)CH $_2$ CH $_2$ O), 41.8, 41.7 superimposed ( $2 \times \text{CH}_2\text{CH}_2\text{O}$ ), 35.4 ((Br)CH $_2$ Ph), 33.3 ((Cl)CH $_2$ Ph);  $m/z$  (CI) 255  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{13}^{81}\text{BrO}$ , 30%], 253  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{13}^{79}\text{BrO}$ , 32%], 211  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{13}^{37}\text{ClO}$ , 12%], 209  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{13}^{35}\text{ClO}$ , 34%], 173 [61%], 155 [100%]

4-Bromo-2-pentyl-5,6-dihydro-2H-pyran **176**

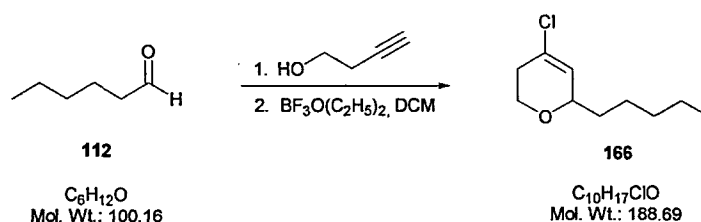
Prepared according to the general procedure and identical to the previous experiment, using 3-butyn-1-ol (0.21 g, 3 mmol), hexanal **112** (0.3 g, 3 mmol) and indium tribromide (1.06g, 3 mmol) but employing  $\text{CH}_2\text{Br}_2$  as the reaction solvent, to give a pure sample of 4-bromo-2-pentyl-5,6-dihydro-2H-pyran **176** (0.49 g, 71%) as a pale yellow oil.  $R_f$  0.46 (hexane:ethyl acetate 7:1); Found  $[\text{M}+\text{H}]^+$  253.0531;  $\text{C}_{10}\text{H}_{17}^{79}\text{BrO}+\text{H}$  requires 232.0463;  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 2910, 2849, 1654 (C=C), 1460, 1312, 1100, 906, 840 (C-Br);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.93 (1H, d,  $J$  5.0, BrC=CH), 3.90 (2H, m, overlapping OCHCH<sub>2</sub> and CH<sub>2</sub>CHHO), 3.63 (1H, ddd,  $J$  12.9, 9.8, 4.9, CH<sub>2</sub>CHHO), 2.40 (2H, m, CH<sub>2</sub>CH<sub>2</sub>O), 1.31-1.18 (8H, m, 4 × CH<sub>2</sub>), 0.82 (3H, t,  $J$  5.1, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 131.7 (BrC=CH), 119.1 (CBr), 76.2 (OCHCH<sub>2</sub>), 64.7 (CH<sub>2</sub>CH<sub>2</sub>O), 33.5 (CH<sub>2</sub>CH<sub>2</sub>O), 32.2, 31.6, 25.2, 22.9 (4 × CH<sub>2</sub>), 14.4 (CH<sub>3</sub>);  $m/z$  (CI) 235  $[(\text{M})^+, \text{C}_{10}\text{H}_{17}^{81}\text{BrO}, 19\%]$ , 233  $[(\text{M})^+, \text{C}_{10}\text{H}_{17}^{79}\text{BrO}, 21\%]$ , 183  $[(\text{M})^+, 16\%]$ , 171  $[(\text{M})^+, 66\%]$ , 153  $[(\text{M})^+, -\text{Br}, 100\%]$ .

4-Chloro-2-benzyltetrahydropyran **114**

Prepared according to the general procedure using 4-phenylacetaldehyde **103** (0.36 g, 3 mmol), 3-buten-1-ol (0.15 g, 2 mmol) and indium trichloride (0.88g, 4 mmol) in chloroform (20 ml). After was left stirring overnight and after purification a pale yellow oil

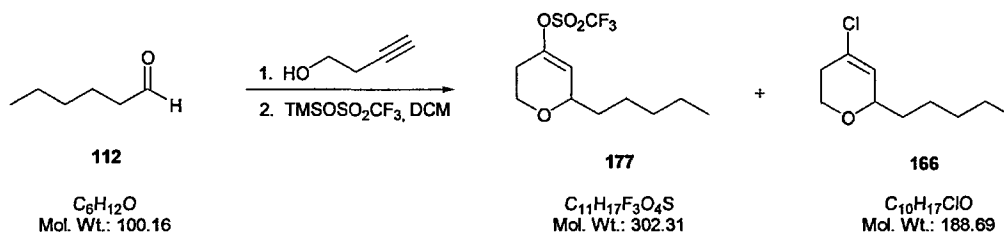
of **114** was obtained (0.36 g, 86%).  $R_f$  0.52 (hexane:ethyl acetate 6:1); Found  $[M+H]^+$  211.0879;  $C_{12}H_{15}ClO$  requires 211.0889;  $m/z$  (CI) 213  $[(M)^+, C_{12}H_{15}^{37}ClO, 31\%]$ , 211  $[(M)^+, C_{12}H_{15}^{35}ClO, 100\%]$ , 175  $[(MH)^+, -Cl, 76\%]$ , 157  $[(M)^+, 80\%]$ , 133  $[(MH)^+, -Ph, 7\%]$ , 131  $[(M)^+, 50\%]$ , 121  $[(MH)^+, -CH_2Ph, 28\%]$ ; All other data were in agreement with previously reported values<sup>152</sup>

#### 4-Chloro-2-pentyl-5,6-dihydro-2H-pyran **166**

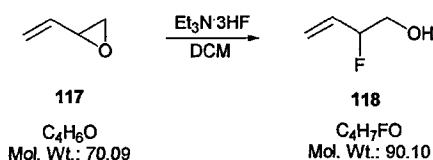


Prepared according to the general procedure, but using boron trifluoride diethyl etherate as the Lewis acid. The title compound was prepared using 3-butyn-1-ol (0.21 g, 3 mmol), hexanal **112** (0.30 g, 3 mmol) and boron trifluoride diethyl etherate (0.43 g, 3 mmol) and was obtained as a pale yellow oil of **166** (0.37 g, 22%) Found  $[M+H]^+$  189.1046;  $C_{10}H_{17}^{35}ClO$  requires 189.1035;  $\nu_{\max}/\text{cm}^{-1}$  (nujol) 2960, 2852, 1727 (C=C), 1461, 1272, 1122, 1072, 742 (C-Cl);  $\delta_H$  (400 MHz;  $\text{CDCl}_3$ ) 5.73 (1H, d,  $J$  4.8,  $\text{ClC}=\text{CH}$ ), 4.11 (1H, br s, OCH), 4.01 (1H, m,  $\text{CH}_2\text{CHHO}$ ), 3.62 (1H, ddd,  $J$  14.4, 10.7, 3.7,  $\text{CH}_2\text{CHHO}$ ), 2.58 (1H, m,  $\text{CHHCH}_2\text{O}$ ), 2.10 (1H, d,  $J$  16.4), 1.34-1.28 (8H, m,  $4 \times \text{CH}_2$ ), 0.88 (3H, m,  $\text{CH}_3$ );  $\delta_C$  (100 MHz;  $\text{CDCl}_3$ ) 132.4 (CCl), 130.8 ( $\text{ClC}=\text{CH}$ ), 76.5 ( $\text{OCHCH}_2$ ), 68.0 ( $\text{CH}_2\text{CH}_2\text{O}$ ), 33.0 ( $\text{CH}_2\text{CH}_2\text{O}$ ), 30.3, 28.9, 23.7, 22.9 ( $4 \times \text{CH}_2$ ), 10.9 ( $\text{CH}_3$ );  $m/z$  CI 191  $[(M+H)^+, C_{10}H_{17}^{37}ClO, 32\%]$ , 189  $[(M+H)^+, C_{10}H_{17}^{35}ClO, 100\%]$ , 153  $[(M-Cl)^+, 88\%]$ , 119 [18%], 117  $[(M-C_5H_{11})^+, 60\%]$ .

## 2-Pentyl-4-trifluoromethanesulfonyloxy-5,6-dihydro-2H-pyran 177



The title compound was prepared using 3-butyn-1-ol (0.21 g, 3 mmol), hexanal **112** (0.30 g, 3 mmol) and trimethylsilyl trifluoromethanesulfonate (0.80 g, 3 mmol) and was obtained as a pale yellow oil (0.47 g, 52%) with the ratio of **177** and **166** in a ratio of 2.1:1.  $R_f$  0.26 (petroleum ether:ethyl acetate 16:1); Found  $[M+H]^+$  303.0869;  $C_{11}H_{17}F_3O_4S + H$  requires 303.0878;  $\nu_{max}/cm^{-1}$  (nujol) 2963, 2858, 1690 (C=C), 1416, 1349, 1206, 1143, 887, 761 (C-Cl)  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.75 (1H, d,  $J$  5.0, ClC=CH), 5.71 (1H, d,  $J$  4.4,  $CF_3SO_2OC=CH$ ), 4.18 superimposed (2H, m,  $2 \times OCH$ ), 4.10-4.05 superimposed (2H, m,  $2 \times CH_2CHHO$ ), 3.71-3.65 (2H, m,  $2 \times CH_2CHHO$ ), 2.62 (1H, m,  $(CF_3SO_2OCCHHCH_2O)$ ), 2.54 (1H, m,  $ClCCHHCH_2O$ ), 2.23 (1H, d,  $J$  12.2,  $CF_3SO_2OCCHHCH_2O$ ), 2.12 (1H, d  $J$  14.0,  $ClCCHHCH_2O$ ), 1.55-1.27 superimposed (16H, m,  $2 \times OCHCH_2CH_2CH_2CH_2CH_3$ ), 0.87 superimposed (6H, m,  $2 \times CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 127.1 (ClC=CH), 120.6 ( $CF_3SO_2OC=CH$ ), 74.8 ((Cl)OCH), 73.3 (( $CF_3SO_2O$ )OCH), 63.8 (ClCCH $_2$ CH $_2$ O), 63.2 ( $CF_3SO_2OCCH_2CH_2O$ ), 35.0, 34.7, 31.6, 31.5 superimposed ( $4 \times CH_2$ ), 28.8 (ClCCH $_2$ CH $_2$ O), 28.3 ( $CF_3SO_2OCCH_2CH_2O$ ), 24.7, 24.5, 22.5, 22.4 superimposed ( $4 \times CH_2$ ), 13.99, 13.94 superimposed ( $2 \times CH_3$ );  $\delta_F$  (376 MHz;  $CDCl_3$ ) 90.0 (3F, s,  $CF_3$ );  $m/z$  (Cl) 303 [15%], 231 [37%], 191  $[(M+H)^+ C_{10}H_{17}^{37}ClO, 22\%]$ , 189  $[(M+H)^+ C_{10}H_{17}^{35}ClO, 69\%]$ , 169 [28%], 153  $[(M-SO_3CF_3, H)^+, 100\%]$ , 123 [42%].

**2-Fluorobut-3-en-1-ol 118**

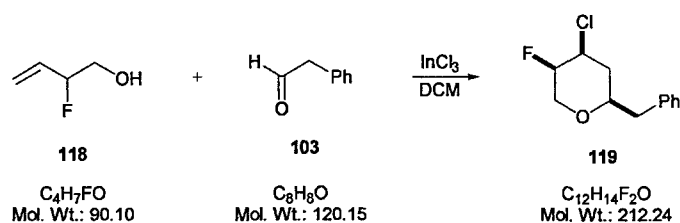
Butadiene monoepoxide **117** (1.40 g, 20 mmol) was cooled to 0°C and triethylamine trihydrofluoride (6.44 g, 40 mmol) added under a nitrogen atmosphere. Stirring was continued for a further 20 min at this temperature and then at 70 °C for 8 h. The mixture was diluted with water (20 ml) and extracted with diethyl ether (3 × 20 ml), the organic layers combined, washed with sodium hydrogencarbonate until the solution became basic, the layers then separated and the organic layer dried over magnesium sulfate. The excess of solvent was removed *in vacuo* and the *title compound* purified by distillation (60-62 °C at atmosphere pressure). The reaction was carried out several times, the best yield being (1.12g, 62%);  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 3386 (-OH), 2924, 1644, 1424, 1050 (C-F), 850;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.87 (1H, m, CH<sub>2</sub>CH), 5.46 (1H, dd, *J* 16.9, 3.0, CH<sub>2</sub>CH<sub>trans</sub>), 5.34 (1H, d, *J* 10.7, CH<sub>2</sub>CH<sub>cis</sub>), 5.06 (1H, m, *J*<sub>HF</sub> 49.2, CHF), 3.74 (2H, m, CHFCH<sub>2</sub>), 2.04 (1H, s, OH);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 132.3 (CH<sub>2</sub>CH), 119.1 (CH<sub>2</sub>CH), 93.7 (d, *J* 167.8, CHF), 64.9 (CHFCH<sub>2</sub>);  $\delta_{\text{F}}$  (376 MHz, CDCl<sub>3</sub>) -24.5 (1F, m, CHF). The sample is too volatile to obtain mass spectrum.

### General method for cyclisation reactions of aldehydes with fluorinated homoallylic alcohols

In a 50 ml round bottom flask containing the fluorinated homoallylic alcohol **118** (1 eq) dissolved in dry dichloromethane (10 ml) at room temperature was added an aldehyde (1.5 eq) and after five min, indium trichloride (2 eq). The mixture was left stirring for a further 20 min at room temperature and then heated to reflux for various lengths of time, as indicated by consumption of starting material *title*. After cooling to room temperature, water (20 ml) was added and the mixture extracted with diethyl ether (3 × 20 ml), the organic layers collected, dried over magnesium sulfate and the solvent removed *in vacuo*.

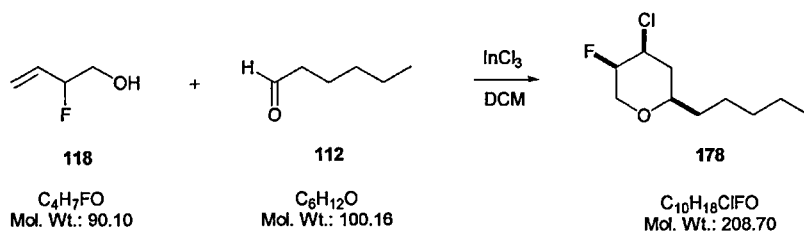
The reaction mixture was then purified by flash column chromatography to afford the corresponding cyclisation product.

#### 4-Chloro-5-fluoro-2-benzyltetrahydropyran **119**



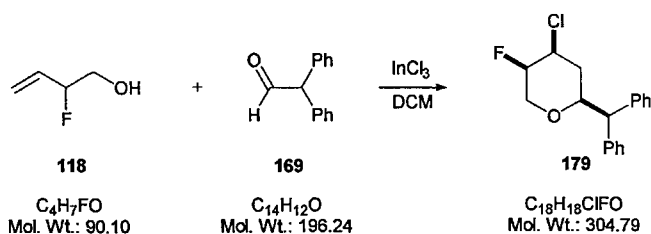
Prepared according to the general procedure using 2-fluorobut-3-en-1-ol **118** (0.20 g, 2.2 mmol), phenylacetaldehyde **103** (0.39 g, 3.3 mmol) and indium trichloride (0.98 g, 4.4 mmol) and heating for 2 h. 4-Chloro-5-fluoro-2-benzyltetrahydropyran **119** was isolated (0.35 g, 70%) as a colourless oil.  $R_f$  0.29 (petroleum ether:ethyl acetate 25:1); Found  $[\text{M}+\text{H}]^+$  229.0790;  $\text{C}_{12}\text{H}_{14}\text{ClFO}$  requires 229.0795;  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 2933, 2850, 1652, 1448, 1118 (C-F), 910, 732, 701 (C-Cl);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.34-7.18 (5H, m, Ar), 4.58 (1H, dm,  $J$  48.1, CHF), 4.24 (1H, m,  $\text{CH}_{\text{eq}}\text{H-O}$ ), 4.02 (1H, m, CHCl), 3.50 (2H, m, overlapping  $\text{CH}_{\text{ax}}\text{H-O}$  and OCH), 3.01 (1H, dd,  $J$  13.7, 6.7,  $\text{CHHAr}$ ), 2.74 (1H, dd,  $J$  13.7, 6.4,  $\text{CHHAr}$ ), 2.01 (2H, m,  $\text{C}(\text{Cl})\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 137.4 (C in benzene ring), 129.4, 128.49, 126.6 (5C, Ar), 87.1 (d,  $J$  182.9, CHF), 78.1 (OCH), 69.0 ( $\text{CH}_2\text{O}$ ), 56.1 (CHCl), 42.0 ( $\text{CH}_2\text{Ar}$ ), 36.2 ( $\text{ClCH}_2$ );  $\delta_{\text{F}}$  (376 MHz;  $\text{CDCl}_3$ ) -35.3 (1F, m, CHF).  $m/z$  (CI) 231  $[(\text{MH})^+, \text{C}_{12}\text{H}_{14}^{37}\text{ClFO}, 33\%]$ , 229  $[(\text{MH})^+, \text{C}_{12}\text{H}_{14}^{35}\text{ClFO}, 100\%]$ , 193  $[(\text{M-Cl})^+, 10\%]$ , 163 [12%] 137  $[(\text{M-CH}_2\text{Ph})^+, 26\%]$ .

#### 4-Chloro-5-fluoro-2-pentyl-tetrahydropyran **178**

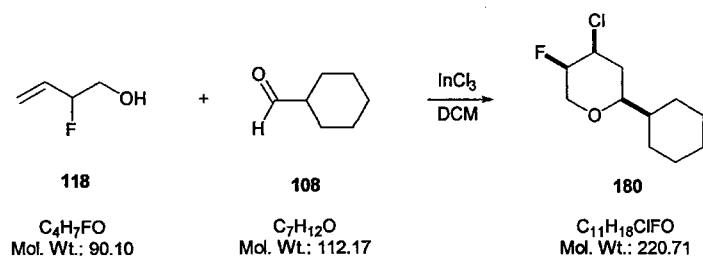


Prepared according to the general procedure using 2-fluorobut-3-en-1-ol **118** (0.20 g, 2.2 mmol), hexanal **112** (0.33 g, 3.3 mmol) and indium trichloride (0.97 g, 4.4 mmol) in DCM (15 ml). The reaction was heated at reflux for 3.5 h and the target compound **178** was isolated as colourless oil. (0.07 g, 65%).  $R_f$  0.18 (petroleum ether:ethyl acetate 22:1); Found  $[M+H]^+$  209.1065;  $C_{10}H_{18}ClFO$  requires 209.1108;  $\nu_{max}/cm^{-1}$  (nujol) 2929, 2852, 1726, 1457, 1114 (C-F), 688 (C-Cl);  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.61 (1H, d,  $J$  56.1, CHF), 4.23 (1H, m,  $CH_{eq}H-O$ ), 4.08 (1H, m,  $CHCl$ ), 3.53 (2H, dd,  $J$  37.1,  $J$  36.9,  $CH_{ax}H-O$ ), 3.33 (1H, m,  $O-CH_{ax}$ ), 2.02-1.97 (2H, m,  $CHClCH_2$ ), 1.58-1.20 (8H, m,  $4 \times CH_2$ ), 0.87 (3H, t,  $J$  6.7,  $CH_3$ );  $^1H$  NMR assignments were made by  $^1H-^1H$ ,  $^1H-^{13}C$  and nOe experiments.  $\delta_C$  (100 MHz;  $CDCl_3$ ) 87.2 (d,  $J$  182.6, CHF), 77.1 (OCH), 68.9 ( $CH_2O$ ), 56.3 (CHCl), 36.7 ( $ClCH_2$ ), 35.5 ( $CH_2$ ), 31.7 ( $CH_2$ ), 24.9 ( $CH_2$ ), 22.5 ( $CH_2$ ), 14.0 ( $CH_3$ );  $\delta_F$  (376 MHz;  $CDCl_3$ ) -38.3 (1F, m, CHF);  $m/z$  (CI) 211  $[(MH)^+$ ,  $C_{10}H_{18}^{37}ClFO$ , 29%], 209  $[(MH)^+$ ,  $C_{10}H_{18}^{35}ClFO$ , 100%], 189  $[(M-F)^+$ , 58%], 173  $[(M-Cl)^+$ , 85%], 153 [25%], 135  $[(M-C_5H_{11})^+$ , 56%].

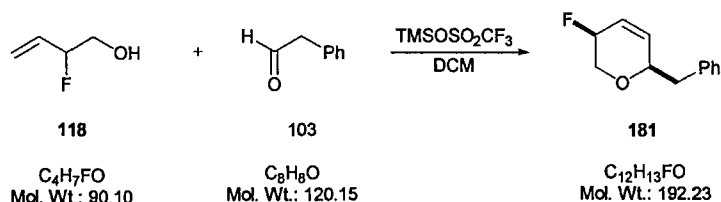
### 2-Diphenylmethyl-4-chloro-5-fluoro-tetrahydropyran **179**



Prepared according to the general procedure using 2-fluorobut-3-en-1-ol **118** (0.15 g, 1.66 mmol), diphenylacetaldehyde **169** (0.49 g, 2.5 mmol) and indium trichloride (0.74 g, 3.32 mmol) in DCM (15 ml). After heating at reflux for 10 hrs the product **179** was observed in trace amounts by GCMS. Found  $[M+H]^+$  305.1111;  $C_{18}H_{18}ClFO$  requires 304.11108.  $m/z$  CI 269  $[(M-Cl)^+$ , 22%], 251 [100%].

4-Chloro-2-cyclohexyl-5-fluoro-tetrahydropyran **180**

Prepared according to the general procedure using 2-fluorobut-3-en-1-ol **118** (0.15 g, 1.66 mmol), cyclohexylcarboxylaldehyde **108** (0.28 g, 2.5 mmol) and indium trichloride (0.74 g, 3.32 mmol) in DCM (15 ml). After heating at reflux for 4 h, 4-chloro-2-cyclohexyl-5-fluorotetrahydropyran **180** was isolated as a colourless oil (0.21 g, 61%).  $R_f$  0.20 (petroleum ether:ethyl acetate 13:1); Found  $[M+H]^+$  221.1186;  $C_{11}H_{18}ClFO$  requires 221.1108;  $\nu_{max}/cm^{-1}$  (nujol), 2927, 2852, 1652, 1558, 1120 (C-F), 690 (C-Cl), 647;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.58 (1H, d,  $J$  46.1, CHF), 4.23 (1H, m,  $CH_{eq}H-O$ ), 4.02 (1H, m, CHCl), 2.48 (3H, m, overlapping  $CH_{ax}H-O$  and  $CHClCH_2$ ), 3.08 (1H, m, OCH), 2.01-1.44 (11H, m, cyclohexyl);  $\delta_C$  (400 MHz;  $CDCl_3$ ) 87.3 (d,  $J$  182.5, CHF), 81.6 (OCH), 69.0 ( $CH_2O$ ), 65.8 ( $CHClCH_2$ ), 56.9 (CHCl), 42.4 (CH in cyclohexyl), 28.4 ( $2 \times CH_2$  in cyclohexyl), 26.2 ( $2 \times CH_2$  in cyclohexyl), 25.9 ( $CH_2$  in cyclohexyl);  $\delta_F$  (376 MHz;  $CDCl_3$ ) -38.3 (1H, m, CHF);  $m/z$  (CI) 223  $[(MH)^+$ ,  $C_{11}H_{18}^{37}ClFO$ , 31%], 221  $[(MH)^+$ ,  $C_{11}H_{18}^{35}ClFO$ , 100%], 201  $[(M-F)^+$ , 52%], 185  $[(M-Cl)^+$ , 69%], 137  $[(M-C_6H_{11})^+$ , 18%].

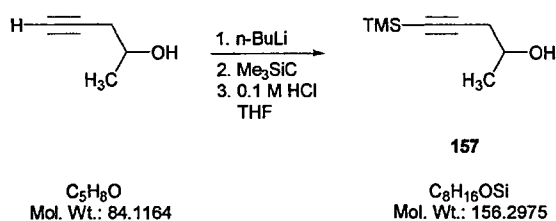
2-Benzyl-5-fluoro-5,6-dihydro-2H-pyran **181**

Prepared according to the general procedure using 2-fluorobut-3-en-1-ol **118** (0.15 g, 1.66 mmol), phenylacetaldehyde (0.30 g, 2.5 mmol) and trimethylsilyl trifluoromethanesulfonate

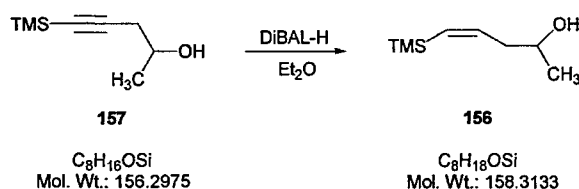


(0.63 g, 3.32 mmol) in place of indium trichloride as Lewis acid. A colourless oil of **181** was isolated. (0.05 g, 56%).  $R_f$  0.21 (petroleum ether:ethyl acetate 10:1). Found  $[M+H]^+$  193.1030;  $C_{12}H_{13}FO+H$  requires 192.0950;  $\nu_{max}/cm^{-1}$  (nujol), 3023, 2927, 1673 (C=C), 1496, 1375, 1097 (C-F), 955, 744;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.16 (5H, m, Ar), 6.57 (1H, dd,  $J$  85.4, CHF), 4.88 (4H, overlapping  $CHFHC=CH$ ,  $CHFHC=CH$  and  $CH_2Ph$ ), 3.73 (1H, m, OCH), 2.76 (1H, m,  $CHFCHHO$ ), 2.49 (1H, m,  $CHFCHHO$ ); [Here the shifts get a bit different from previous phenyl residue].  $\delta_C$  (100 MHz;  $CDCl_3$ ) 148.9 (d,  $J$  206.2, CHF), 133.1 ( $C_{quart}$  in Ar), 126.4, 125.9, 124.2 ( $5 \times C$  Ar), 106.6, 106.5 ( $2 \times C$  (HC=CH)), 74.0 (OCH), 68.2 ( $CH_2Ph$ ), 33.4 ( $CH_2O$ );  $\delta_F$  (376 MHz;  $CDCl_3$ ) -35.2 (1F, m, CHF);  $m/z$  (CI) 193  $[(MH)^+]$ ,  $C_{12}H_{13}FO$ , 75%, 175 [100%], 173 [68%], 145 [63%], 133 [98%], 105 [36%]

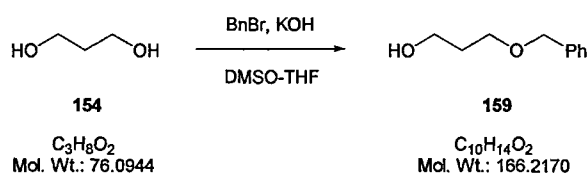
### 5-Trimethylsilylprop-1-yn-2-ol **157**<sup>149,150</sup>



A solution of *n*-butyllithium (2.5 M, 9.6 ml, 24 mmol) was added to a solution of 4-pentyn-2-ol (1.00 g, 12 mmol) in THF (30 ml) at  $-78^\circ\text{C}$  and the mixture stirred at this temperature for 2h. Then trimethylsilyl chloride (3.06 ml, 24 mmol) was added and the solution was allowed to warm to room temperature. During this time the colourless solution became cloudy white. At room temperature, dilute hydrochloric acid (20 ml) was added, the solution stirred for further 30 minutes and then extracted with diethyl ether (3 x 20 ml). The organic layer was washed with water, dried ( $MgSO_4$ ) and concentrated. The desired compound **157** was obtained after distillation ( $70^\circ\text{C}$ , 0.5 mmHg) as a colourless oil. The reaction was repeated several times with the best yield (1.67 g, 89%).  $\delta_H$  (300 MHz;  $CDCl_3$ ) 3.78 (1H, m,  $CH_3CHCH_2$ ), 2.23 (2H, m,  $CH_3CHCH_2$ ), 2.03 (1H, br s,  $CHOH$ ), 1.09 (3H, d,  $J$  6.1,  $CH_3$ ), 0.01 (9H, s,  $3 \times CH_3$ ); All other data were in agreement with previously reported values.<sup>149,150</sup>

**5-Trimethylsilylprop-1-en-2-ol **156****<sup>149,150</sup>

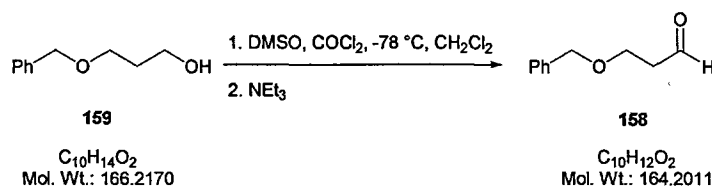
A solution of 5-trimethylsilylprop-1-en-2-yn-2-ol **157** (1.56 g, 10 mmol) in diethyl ether (100 ml) was cooled down to 0 °C and DIBAL (40 ml, 1 M solution in hexane, 40 mmol) was added slowly. After slowly warming to room temperature, the reaction was heated under reflux for 24 hours. After cooling to room temperature and then to 0 °C, diluted sulfuric acid (2 M, 50 ml) was added dropwise to the reaction mixture, which was stirred for a further 45 minutes whilst being allowed to warm to room temperature. The mixture was then filtered through celite, diluted with additional diethyl ether (200 ml) and water (100 ml) and the organic layer separated. The aqueous layer was extracted with diethyl ether (100 ml) and the organic layers combined, washed with cold water, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Distillation gave a pale yellow oil of **156** (0.76 g, 49%; bp 121 °C/2mmHg).  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 6.18 (1H, dt, *J* 7.47, 14.1, CH<sub>2</sub>=CH), 5.55 (2H, d, *J* 13.9, CH<sub>2</sub>=CH), 3.73 (1H, m, CH<sub>3</sub>CH(OH)), 2.16 (2H, m, CH<sub>2</sub>=CHCH<sub>2</sub>), 1.43 (1H, br s, OH), 1.08 (3H, d, *J* 6.2, CH<sub>3</sub>), 0.01 (9H, s, 3 × CH<sub>3</sub>). All other data were in agreement with previously reported values.<sup>149,150</sup>

**3-Benzyloxypropan-1-ol **159****

Finely powdered potassium hydroxide (1.84 g, 33 mmol) was added to a solution of propane-1,3-diol **154** (4.8 ml, 66 mmol) in THF:DMSO (9:1, 120 ml) and after 5 minutes benzyl bromide (3.9 ml, 33 mmol) was added while the reaction mixture was kept at 0 °C

(ice-bath). The mixture was stirred at room temperature for 24 hours. After this time water:diethyl ether (1:1, 250 ml) was added to the reaction mixture and the layers separated. The water layer was extracted with diethyl ether (2×200 ml) and ethyl acetate (2×200 ml), the organic layers were combined, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column chromatography (petrol:diethyl ether = 1:1) to afford the *title compound 159* as a colourless oil (5.72 g, 44%); R<sub>f</sub> 0.18 (petrol:diethyl ether 1:1);  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3385 (OH), 2939 [Ar(C-H)], 1659 (C=C), 1485, 1460, 1367, 1198, 1081, 917, 748, 702;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.13-7.25 (5H, m, Ar-H), 4.39 (2H, s, PhCH<sub>2</sub>O), 3.62 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH), 3.52 (2H, t, *J* 5.9, CH<sub>2</sub>OCH<sub>2</sub>Ph), 2.67 (1H, br s, OH), 1.73 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH);  $\delta_{\text{C}}$  (75 MHz; CDCl<sub>3</sub>) 137.8 (C<sub>ipso</sub>), 128.0 [2×C(Ar)], 127.5 [2×C(Ar)], 127.4 (C(Ar)), 72.9, 68.8, 61.1 and 32.1 (4×CH<sub>2</sub>); *m/z* (CI) 167 [(MH)<sup>+</sup>, 95%], 107 [(MH)<sup>+</sup>-C<sub>3</sub>H<sub>8</sub>O, 100%].

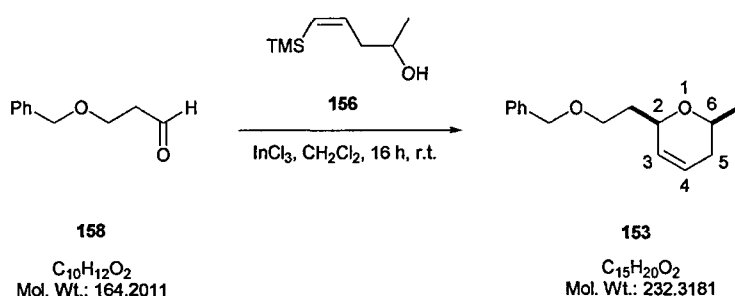
### 3-Benzyloxypropionaldehyde 158



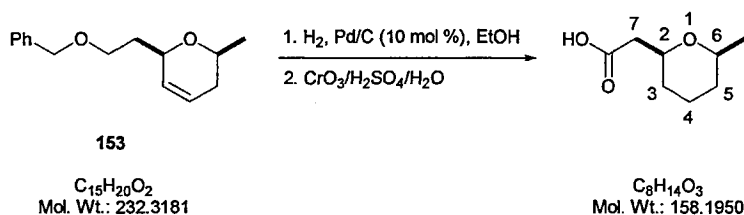
Dimethyl sulfoxide (1.1 ml, 16 mmol) was added to a solution of oxalyl chloride (0.7 ml, 8 mmol) in DCM (100 ml) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 10 minutes after which time 3-benzyloxypropan-1-ol **159** (1.20 g, 1 eq.) in DCM (5 ml) was added dropwise. After 15 minutes, triethylamine (5.1 ml, 36 mmol) was added, the solution stirred for 5 minutes, and then the reaction mixture warmed to room temperature. After stirring for 30 minutes the reaction was quenched with saturated ammonium chloride solution (15 ml), and the aqueous phase was washed with DCM (2×40 ml). The combined organic phase was washed with saturated NaHCO<sub>3</sub> (2×20 ml), brine (20 ml), dried (MgSO<sub>4</sub>) and concentrated. Purification by flash chromatography (petrol:diethyl ether = 2:1) gave the *title compound 158* as a clear oil (0.91 g, 77%); R<sub>f</sub> 0.35 (petrol:diethyl ether 2:1);  $\nu_{\max}/\text{cm}^{-1}$  (neat) 3032 [Ar(C-H)], 1726 (C=O), 1495, 1444, 1362, 1209, 1101, 906,

737, 691;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 9.82 (1H, s, CHO), 7.28-7.41 (5H, m, Ar-H), 4.55 (2H, s,  $\text{PhCH}_2\text{O}$ ), 3.84 (2H, t,  $J$  6.1,  $\text{CH}_2\text{OCH}_2\text{Ph}$ ), 2.72 (2H, t,  $J$  6.1,  $\text{OCH}_2\text{CH}_2\text{CHO}$ );  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 200.9 (CHO), 137.6 ( $\text{C}_{\text{ipso}}$ ), 128.2 [ $2\times\text{C}(\text{Ar})$ ], 127.5 [ $2\times\text{C}(\text{Ar})$ ], 127.4 ( $\text{C}(\text{Ar})$ ), 72.9, 63.5 and 43.6 ( $3\times\text{CH}_2$ );  $m/z$  (CI) 165 [ $(\text{MH})^+$ , 100%], 147 [ $(\text{MH}^+-\text{H}_2\text{O})$ , 40%], 107 [ $(\text{MH})^+-\text{C}_3\text{H}_8\text{O}$ , 95%].

**(±)-Cis-2-(2-Benzyloxyethyl)-6-methyl-5,6-dihydro-2H-pyran 153**



The *title compound* was prepared according to the general procedure for the cyclisation, using 3-benzyloxy-1-propanal **158** (0.40 g, 2.4 mmol), indium trichloride (0.54 g, 2.4 mmol) and (±)-Z-5-trimethylsilylpent-4-en-2-ol **156** (0.39 g, 2.4 mmol), and isolated by flash chromatography (petrol:diethyl ether 5:1) as a colourless oil of **153** (0.54 g, 95%);  $R_{\text{f}}$  0.25 (petrol:diethyl ether 5:1); Found  $[\text{M}+\text{H}]^+$  233.1536;  $\text{C}_{15}\text{H}_{21}\text{O}_2+\text{H}$  requires 233.1541;  $\nu_{\text{max}}/\text{cm}^{-1}$  (neat) 2852 (OCH), 1700 (C=C), 1449, 1357, 1209, 1178, 1157, 1086 (C-O), 896, 732, 691;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.26-7.55 (5H, m, C(Ar)-H), 5.79 (1H, m, C(4)H), 5.64 (1H, dt,  $J$  10.2, 1.9, C(3)H), 4.53 (2H, s,  $\text{PhCH}_2\text{OCH}_2$ ), 4.31 (1H, m, C(2)H), 3.66 (3H, m, C(6)H,  $\text{PhCH}_2\text{OCH}_2$ ), 1.95 (2H, m, C(5) $\text{H}_2$ ), 1.85 (2H, m,  $\text{PhCH}_2\text{OCH}_2\text{CH}_2$ ), 1.22 (3H, d,  $J$  6.2, C(6) $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 138.7 ( $\text{C}_{\text{ipso}}$ ), 130.2 (C(3)H), 128.3 [ $2\times\text{C}(\text{Ar})$ ], 127.6 [ $2\times\text{C}(\text{Ar})$ ], 127.4 (C(Ar)), 124.8 (C(4)H), 72.9 ( $\text{PhCH}_2\text{O}$ ), 72.1 (C(2)H), 69.9 (C(6)H), 66.8 ( $\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$ ), 35.7 ( $\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$ ), 32.9 (C(5) $\text{H}_2$ ), 21.7 (C(6) $\text{CH}_3$ );  $m/z$  (CI) 233 [ $(\text{MH})^+$ , 100%], 189 [ $(\text{MH})^+-\text{C}_2\text{H}_4\text{O}$ , 40%], 171 [ $(\text{MH})^+-\text{C}_2\text{H}_6\text{O}_2$ , 55%], 141 [ $(\text{MH})^+-\text{C}_7\text{H}_8$ , 60%].

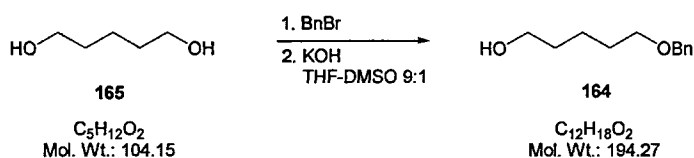
**(±)-Cis-6-(Methyltetrahydropyran-2-yl)acetic acid**

2-(2-Benzyloxyethyl)-6-methyl-5,6-dihydro-2H-pyran (0.40 g, 1.7 mmol) was dissolved in dry EtOH (4 ml) and Pd/C (0.04 g, 10 mol %) was added under a nitrogen atmosphere. The solution was then subjected to a hydrogen atmosphere by first flushing with hydrogen and then slowly bubbling hydrogen under the surface while the solution was vigorously stirred at room temperature. After being stirred under a hydrogen atmosphere overnight (19 h), the reaction mixture was filtered over celite and the solvent was removed *in vacuo* to afford 6-(methyltetrahydropyran-2-yl)ethanol (0.24 g, 99%) which was used in the next step without further purification.  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.81 (2H, m,  $\text{CH}_2\text{OH}$ ), 3.57 (1H, m, C(2 or 6)H), 3.46 (1H, m, C(2 or 6)H), 3.10 (1H, br s, OH), 1.25-2.02 (8H, m, C(3,4,5 and 7)H<sub>2</sub>), 1.14 (3H, d,  $J$  6.2, C(6)CH<sub>3</sub>).

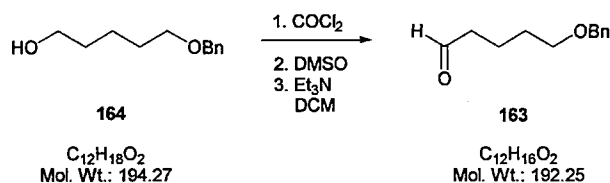
6-(methyltetrahydropyran-2-yl)ethanol (0.24 g, 1.7 mmol) was dissolved in acetone (20 ml) at 0 °C and Jones reagent (12 ml) was added dropwise while the reaction mixture was vigorously stirred. [Preparation of the Jones reagent: concentrated sulfuric acid (1.5 ml, 27 mmol) was added dropwise with swirling to a solution of chromium trioxide (1.69 g, 17 mmol) in distilled water (24 ml) at 0 °C]. The reaction was warmed to room temperature and stirred for 3 h and followed by TLC. The mixture was poured into saturated brine (20 ml) and extracted with chloroform (5×20 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and the solvent was removed *in vacuo* to give the crude oil that was purified by flash chromatography (DCM:diethyl ether = 3:1) to give the *title compound* in the form of colourless crystals (0.07 g, 25%). All data are in the agreement with previously published literature values. Mp 62-64 °C (from DCM/diethyl ether);  $R_f$  0.33 (DCM:diethyl ether 3:1); Found  $[\text{M}+\text{H}]^+$  159.1021;  $\text{C}_8\text{H}_{14}\text{O}_3+\text{H}$  requires 159.1021;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3411 (COOH), 3098, 2934, 2868 (OCH), 1716 (C=O), 1434, 1367, 1301, 1203, 1060, 1029;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 10.29 (1H, br s, COOH), 3.76 (1H, m, C(2)H), 3.50 (1H, m, C(6)H),

2.56 (1H, dd,  $J$  15.6, 7.6, C(7)H<sub>2</sub>), 2.46 (1H, dd,  $J$  15.6, 5.2, C(7)H<sub>2</sub>), 1.18-1.84 (6H, m, C(3, 4 and 5)H<sub>2</sub>), 1.16 (3H, t,  $J$  6.2, C(6)CH<sub>3</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 175.8 [C<sub>quat</sub>(COOH)], 74.4 (C(6)H), 73.9 (C(2)H), 41.3 (C(7)H<sub>2</sub>), 32.8, 30.8 and 23.2 (C(3-5)H<sub>2</sub>), 21.9 (C(6)CH<sub>3</sub>);  $m/z$  (CI) 159 [(MH)<sup>+</sup>, 100%], 141 [(MH)<sup>+</sup>-H<sub>2</sub>O, 60%], 100 [(MH)<sup>+</sup>-C<sub>3</sub>H<sub>7</sub>O, 5%].

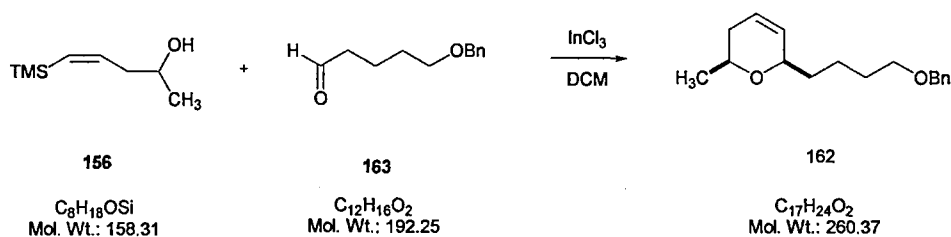
### 5-Benzyloxypentan-1-ol **164**



Finely powdered potassium hydroxide (1.84 g, 33 mmol) was added to a solution of dried pentane-1,5-diol **165** (6.86 ml, 66 mmol) in THF:DMSO (9:1, 120 ml) at 0 °C and after 5 min benzyl bromide (5.64g, 33 ml) was added, being careful to keep the temperature at 0 °C (ice-bath). The mixture was allowed to warm to room temperature and stirred for 24 h. After this time, water-diethyl ether (1:1, 250 ml) was added to the reaction mixture and the layers separated. The water layer was extracted with diethyl ether (2 x 200 ml) and ethyl acetate (2 x 200 ml), the organic layers combined, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column chromatography  $R_f$  0.2 (petrol:diethyl ether = 1:1) to afford the title compound **164** as a colourless oil (3.60 g, 28%); Found [M+H]<sup>+</sup> 195.1384; C<sub>12</sub>H<sub>18</sub>O<sub>2</sub>+H requires 195.1385;  $\nu_{max}/cm^{-1}$  (nujol) 3386 (Bn), 2937, 2861, 1454, 1363, 1099, 736, 698;  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 7.28-7.20 (5H, m, Ar), 4.43 (2H, s, OCH<sub>2</sub>Ph), 3.56 (2H, t,  $J$  6.3, CH<sub>2</sub>CH<sub>2</sub>O), 3.41 (2H, t,  $J$  6.4, HOCH<sub>2</sub>), 1.47 (6H, m, 3 x CH<sub>2</sub>);  $\delta_C$  (75 MHz; CDCl<sub>3</sub>) 138.9 (C<sub>quat</sub> in Ar), 128.7, 128.0, 127.9 (5C in Ar), 73 (OCH<sub>2</sub>Ph), 70 (CH<sub>2</sub>CH<sub>2</sub>O), 63 (HOCH<sub>2</sub>), 32 (CH<sub>2</sub>), 29 (CH<sub>2</sub>), 22 (CH<sub>2</sub>).

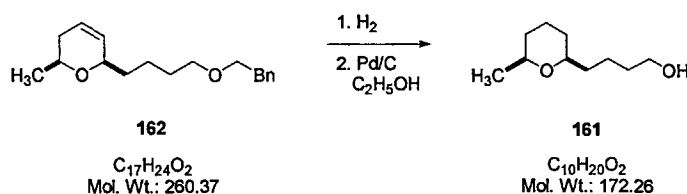
5-Benzyloxypentan-1-al **163**

Dry dimethylsulfoxide (1.1 ml, 16 ml) was added to a solution of oxalyl chloride (1.02 g, 8 mmol) in dry DCM (100 ml) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred for 10 min after which time 5-benzyloxypentan-1-ol **164** (1.55 g, 8 mmol) in DCM (5 ml) was added dropwise. After 20 min, triethylamine (5.1 ml, 36 mmol) was added, the solution was stirred for 5 minutes and then allowed to warm to room temperature. After stirring for 30 min, the reaction was quenched with saturated ammonium chloride solution (15 ml) and the aqueous phase was washed with DCM ( $3 \times 30$  ml). The combined organic phase was washed with saturated  $\text{NaHCO}_3$  ( $3 \times 20$  ml), brine (20 ml), dried ( $\text{MgSO}_4$ ) and concentrated. Purification by flash chromatography (petrol:diethyl ether 2:1) gave the title compound **163** as a clear oil (1.04 g, 68%);  $R_f$  0.36 (petrol:diethyl ether 2:1). Found  $[\text{M}+\text{H}]^+$  193.1223;  $\text{C}_{12}\text{H}_{16}\text{O}_2+\text{H}$  requires 193.1228.  $\nu_{\text{max}}/\text{cm}^{-1}$  (nujol) 2936, 2849, 1718 (CHO), 1457, 1361, 1100;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 9.68 (1H, s, CHO), 7.30-7.22 (5H, m, Ar), 4.42 (2H, s,  $\text{OCH}_2\text{Ar}$ ), 3.41 (2H, t,  $J$  6.1, 5.9,  $\text{OCH}_2\text{CH}_2$ ), 2.39 (2H, m,  $\text{CH}_2\text{CHO}$ ), 1.62 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ );  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 202.9 (CHO), 138.8 ( $\text{C}_{\text{quart}}$  in Ar), 128.8, 128.0, 127.9, (5C in Ar), 73.3 ( $\text{ArCH}_2\text{O}$ ), 70.1 ( $\text{BnOCH}_2$ ), 43.9 ( $\text{CH}_2\text{CHO}$ ), 29.5 ( $\text{CH}_2$ ), 19.3 ( $\text{CH}_2$ );  $m/z$  (CI) 193  $[(\text{M})^+]$ , 34%, 133  $[(\text{M})^+]$ , 107  $[(\text{M})^+-\text{PhCH}_2\text{O}]$ , 100%

 $(\pm)$ -Cis-2-(4-Benzyloxybutyl)-6-methyl-5,6-dihydro-2H-pyran **162**

The aldehyde **163** (0.57 g, 3 mmol) in DCM (20 ml) was added to a solution of the alcohol **156** (0.32 g, 2 mmol) in 20 ml of DCM under atmosphere of nitrogen, stirred for 5 min and then indium chloride (0.88 g, 4 mmol) added. The resulting solution was left stirring overnight and then quenched with distilled water (20 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 ml), the organic layers collected, washed with water (3 × 20 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* and the reaction mixture purified by flash column chromatography, giving the desired compound **162** as pale yellow oil (1.00 g, 27%).  $R_f$  0.28 (hexane: diethyl ether 18:1); Found  $[M+H]^+$  261.1859;  $C_{17}H_{24}O_2$  requires 261.1854;  $\nu_{max}/cm^{-1}$  (nujol) 3029, 2933, 1463, 1363, 1099, 842;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.34 (5H, m, Ar), 5.77 (1H, m,  $CH_2CH=CH$ ), 5.61 (1H, m,  $CH_2CH=CHCH$ ), 4.50 (2H, s,  $OCH_2Ph$ ), 4.12 (1H, br s,  $OCH$ ), 3.67 (1H, m,  $CH_3CHO$ ), 3.48 (2H, m,  $CH_2OCH_2$ ), 1.94 (2H, m,  $CH_2CH=CH$ ), 1.66 (2H, m,  $CH_2CH_2O$ ) 1.53 (4H, m, overlapping  $CHCH_2CH_2CH_2CH_2O$ ), 1.21 (3H, d,  $J$  6.24,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 138.6 ( $C_{quart}$  in Ar), 130.1 ( $CH_2CH=CH$ ), 128.5, 128.4, 127.6 (5C in Ar), 124.7 ( $CH_2CH=CH$ ), 74.7 (OCH), 72.8 ( $OCH_2Ph$ ), 70.3 ( $CH_2OCH_2$ ), 69.9 ( $CH_3CHO$ ), 35.4 ( $CH=CH-CHCH_2$ ), 32.9 ( $CH_2CH=CH$ ), 29.8 ( $CH_2CH_2O$ ), 21.7 (overlapping  $CHCH_2CH_2CH_2CH_2O$  and  $CH_3$ );  $m/z$  (CI) 261  $[(MH)^+$ ,  $C_{17}H_{24}O_2$ , 100%], 225  $[(MH)^+$ , 29%], 217 [49%], 169  $[(M-CH_2Ph)^+$ , 100%], 153  $[(MH-PhCH_2OH)^+$ , 73%], 135, 63%], 107  $[(PhCH_2O)^+$ , 60%].

**(±)-cis-(6-Methyltetrahydropyran-2-yl)butanol 161**

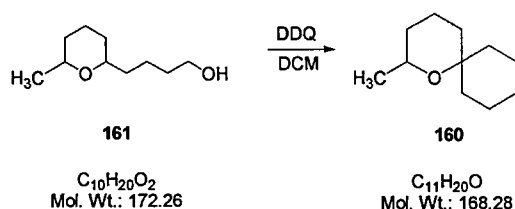


(±)-cis-2-(4-Benzyloxybutyl)-6-methyl-5,6-dihydro-2H-pyran **162** (0.30 g, 1.15 mmol) was dissolved in dry ethanol (4 ml) and Pd/C (0.03g, 10 mol%) was added under a nitrogen atmosphere. The solution was then subjected to a hydrogen atmosphere by first flushing with hydrogen and then slowly bubbling hydrogen under the surface while the solution was vigorously stirred at room temperature. After being stirred under the atmosphere of



hydrogen overnight, the reaction mixture was filtered through celite and the solvent was removed *in vacuo*. The material was further purified by flash chromatography (ethyl acetate:petroleum ether 1:15) to afford **161** (0.14g, 71%).  $R_f$  0.32 (ethyl acetate:petroleum ether 1:15); Found  $[M+H]^+$  173.1533;  $C_{10}H_{20}O_2$  requires 173.1541;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 3.64 (2H, t,  $J$  6.3,  $CH_2OH$ ), 3.40 (1H, m,  $CH_3CHO$ ), 3.27 (1H, m,  $OCHCH_2$ ), 1.80 (1H, br s, OH), 1.54 (12H, m,  $6 \times CH_2$ ), 1.15 (3H, d,  $J$  6.24,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 77.8 ( $OCHCH_2$ ), 73.8 ( $CH_3CHO$ ), 62.7 ( $CH_2OH$ ), 36.0, 33.3, 32.6, 31.2, 23.7, 21.8 ( $6 \times CH_2$ ), 22 ( $CH_3$ );  $m/z$  (CI) 173  $[(MH)^+]$ ,  $C_{10}H_{20}O_2$ , 45%, 155  $[(MH-H_2O)^+]$ , 100%, 137 [52%], 111 [80%].

### Attempted Cyclisation 160



To a solution of freshly crystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.28g, 0.57 mmol) in anhydrous dichloromethane (5 ml) at  $-78$  °C was added ( $\pm$ )-*cis*-(6-methyltetrahydropyran-2-yl)butanol **161** (0.10 g, 0.58 mmol). The mixture was allowed to reach room temperature over a period of 12h. It was filtered through a small amount of silica gel, which was subsequently washed with dichloromethane (200 ml). The combined filtrates were concentrated *in vacuo* and the residue was subject to flash chromatography (ethyl acetate:petrol 1.33:1) to give only unidentified material.

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## **Appendix 1**

X-Ray data and  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for ( $\pm$ )-*cis*-6-(methylterahydropyran-2yl)acetic acid

Table 1. Crystal data and structure refinement.

Identification code	03src0173	
Empirical formula	$\text{C}_8\text{H}_{14}\text{O}_3$	
Formula weight	158.19	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	$a = 6.8220(2)$ Å	$\alpha = 64.2870(10)^\circ$
	$b = 8.2332(2)$ Å	$\beta = 75.3220(10)^\circ$
	$c = 8.7991(3)$ Å	$\gamma = 77.259(2)^\circ$
Volume	$427.27(2)$ Å <sup>3</sup>	
Z	2	
Density (calculated)	1.230 Mg / m <sup>3</sup>	
Absorption coefficient	0.093 mm <sup>-1</sup>	
$F(000)$	172	
Crystal	Plate; colourless	
Crystal size	$0.14 \times 0.08 \times 0.02$ mm <sup>3</sup>	
$\theta$ range for data collection	2.95 – 27.49°	
Index ranges	$-8 \leq h \leq 8, -10 \leq k \leq 10, -11 \leq l \leq 11$	
Reflections collected	9009	
Independent reflections	1944 [ $R_{int} = 0.0423$ ]	
Completeness to $\theta = 27.49^\circ$	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9981 and 0.9871	
Refinement method	Full-matrix least-squares on $F^2$	
Data / restraints / parameters	1944 / 0 / 103	
Goodness-of-fit on $F^2$	0.979	
Final $R$ indices [ $F^2 > 2\sigma(F^2)$ ]	$R1 = 0.0376, wR2 = 0.1047$	
$R$ indices (all data)	$R1 = 0.0452, wR2 = 0.1115$	
Extinction coefficient	0.16(4)	
Largest diff. peak and hole	0.282 and $-0.209$ e Å <sup>-3</sup>	

**Diffraction:** Nonius KappaCCD area detector ( $\phi$  scans and  $\omega$  scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). *J. Appl. Cryst.* **25**, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** Denzo (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307-326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** SORTAV (R. H. Blessing, *Acta Cryst.* **A51** (1995) 33-37; R. H. Blessing, *J. Appl. Cryst.* **30** (1997) 421-426). **Structure solution:** SHELXS97 (G. M. Sheldrick, *Acta Cryst.* (1990) **A46** 467-473). **Structure refinement:** SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

## Special details:

**Table 2.** Atomic coordinates [ $\times 10^4$ ], equivalent isotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] and site occupancy factors.  $U_{eq}$  is defined as one third of the trace of the orthogonalized  $U^{ij}$  tensor.

Atom	$x$	$y$	$z$	$U_{eq}$	$S.o.f.$
C1	3082(2)	2373(2)	9039(1)	22(1)	1
C2	3952(2)	3188(2)	9935(2)	31(1)	1
C3	855(2)	3130(2)	8884(2)	26(1)	1
C4	102(2)	2470(2)	7783(2)	27(1)	1
C5	1571(2)	2859(2)	6074(1)	23(1)	1
C6	3743(2)	2049(1)	6379(1)	18(1)	1
C7	5264(2)	2490(1)	4709(1)	19(1)	1
C8	7334(2)	1394(1)	4876(1)	18(1)	1
O1	4351(1)	2790(1)	7365(1)	19(1)	1
O2	7737(1)	118(1)	6190(1)	24(1)	1
O3	8674(1)	1920(1)	3432(1)	25(1)	1

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

C1–O1	1.4432(12)
C1–C2	1.5149(15)
C1–C3	1.5259(15)
C1–H1	1.0000
C2–H2A	0.9800
C2–H2B	0.9800
C2–H2C	0.9800
C3–C4	1.5273(16)
C3–H3A	0.9900
C3–H3B	0.9900
C4–C5	1.5256(15)
C4–H4A	0.9900
C4–H4B	0.9900
C5–C6	1.5243(14)
C5–H5A	0.9900
C5–H5B	0.9900
C6–O1	1.4315(12)
C6–C7	1.5159(14)
C6–H6	1.0000
C7–C8	1.5029(14)
C7–H7A	0.9900
C7–H7B	0.9900
C8–O2	1.2230(13)
C8–O3	1.3213(12)
O3–H3	0.8400
O1–C1–C2	106.06(9)
O1–C1–C3	110.66(8)
C2–C1–C3	112.49(10)
O1–C1–H1	109.2
C2–C1–H1	109.2
C3–C1–H1	109.2
C1–C2–H2A	109.5
C1–C2–H2B	109.5
H2A–C2–H2B	109.5
C1–C2–H2C	109.5
H2A–C2–H2C	109.5
H2B–C2–H2C	109.5
C1–C3–C4	111.30(9)
C1–C3–H3A	109.4
C4–C3–H3A	109.4
C1–C3–H3B	109.4
C4–C3–H3B	109.4
H3A–C3–H3B	108.0
C5–C4–C3	109.59(9)
C5–C4–H4A	109.8
C3–C4–H4A	109.8
C5–C4–H4B	109.8
C3–C4–H4B	109.8
H4A–C4–H4B	108.2
C6–C5–C4	110.15(9)
C6–C5–H5A	109.6
C4–C5–H5A	109.6
C6–C5–H5B	109.6
C4–C5–H5B	109.6
H5A–C5–H5B	108.1
O1–C6–C7	106.89(8)

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O1-C6-C5	110.18(8)
C7-C6-C5	111.68(8)
O1-C6-H6	109.3
C7-C6-H6	109.3
C5-C6-H6	109.3
C8-C7-C6	114.34(8)
C8-C7-H7A	108.7
C6-C7-H7A	108.7
C8-C7-H7B	108.7
C6-C7-H7B	108.7
H7A-C7-H7B	107.6
O2-C8-O3	123.09(9)
O2-C8-C7	124.05(9)
O3-C8-C7	112.83(9)
C6-O1-C1	112.44(7)
C8-O3-H3	109.5

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Symmetry transformations used to generate equivalent atoms:

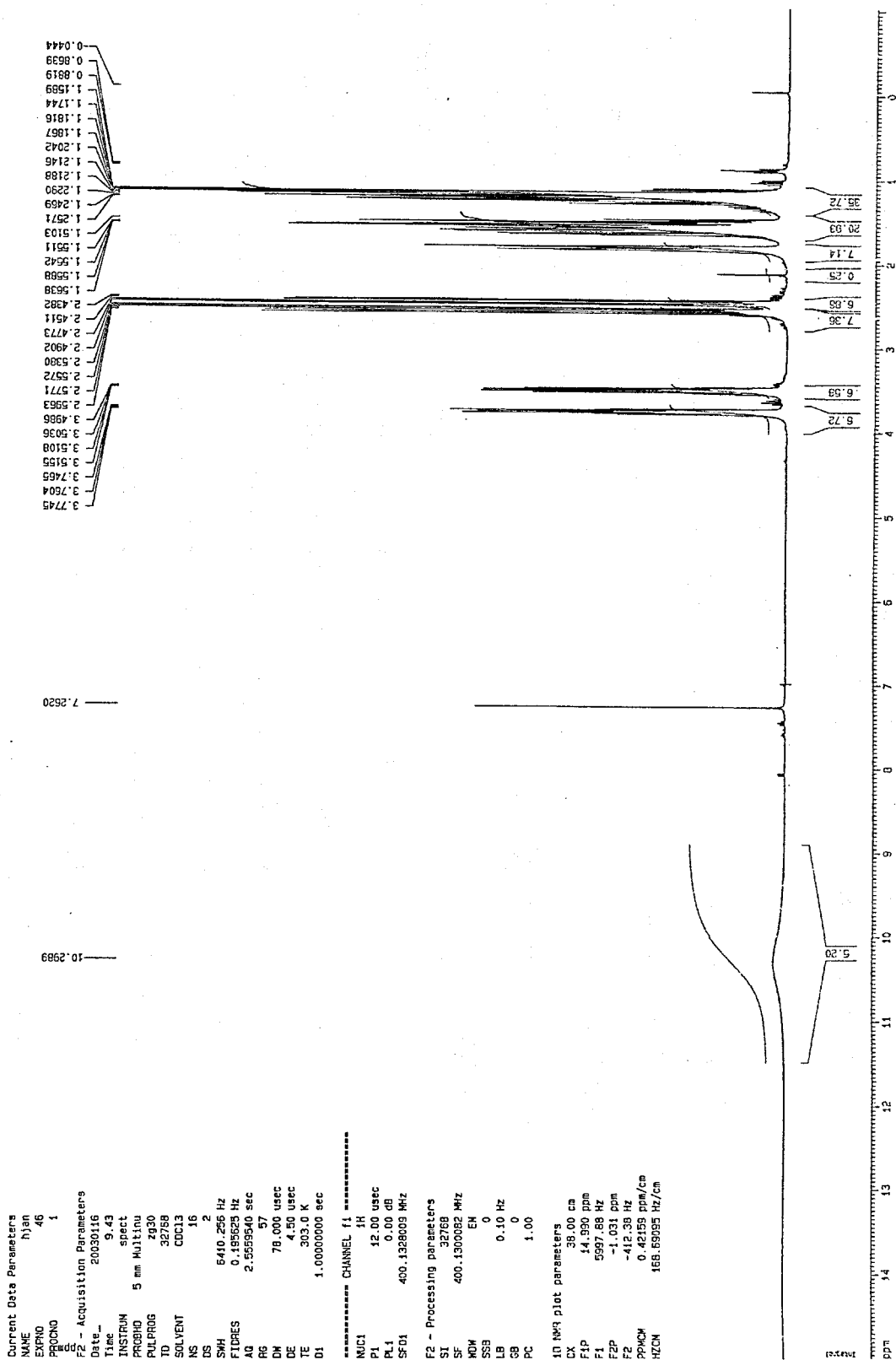
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**Table 4.** Anisotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ]. The anisotropic displacement factor exponent takes the form:  $-2\pi^2[h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$ .

Atom	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
C1	26(1)	21(1)	16(1)	-7(1)	-1(1)	-6(1)
C2	41(1)	35(1)	21(1)	-13(1)	-2(1)	-13(1)
C3	25(1)	26(1)	22(1)	-10(1)	3(1)	-2(1)
C4	17(1)	33(1)	26(1)	-11(1)	-1(1)	-1(1)
C5	17(1)	28(1)	24(1)	-12(1)	-5(1)	0(1)
C6	17(1)	18(1)	19(1)	-9(1)	-4(1)	-1(1)
C7	19(1)	20(1)	19(1)	-9(1)	-3(1)	0(1)
C8	18(1)	19(1)	19(1)	-9(1)	-1(1)	-3(1)
O1	20(1)	22(1)	18(1)	-10(1)	-1(1)	-5(1)
O2	20(1)	25(1)	20(1)	-5(1)	0(1)	2(1)
O3	19(1)	28(1)	20(1)	-6(1)	0(1)	2(1)



<sup>1</sup>H NMR



<sup>13</sup>C NMR

