BINDING SERVICES
Tel +44 (0)29 2087 4949
Fax +44 (0)29 20371921
e-mail bindery@cardiff.ac.uk

NOVEL ORGANOFLUORINE CHEMISTRY: NUCLEOPHILIC FLUORINATING AGENTS AND POTENTIAL ANTICANCER COMPOUNDS

PhD Thesis

By

Richard Patterson

Cardiff University, School
of Chemistry

2001-2005

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Contents

Acknowledgements

I would like to thank the following for their help and support in the production of this thesis:

Dr. Nick Lawrence for all his help, advice and ideas during both the writing and practical work.

Dr. Mike Coogan for helping in Nick's absence.

Dr. Sylvie Ducki and Darren Cook (Salford University) for carrying out the biological testing on the chalcone molecules.

Rob Jenkins for help and instruction in the use of the various analytical tools which were needed.

Dr. Li-ling Ooi (X-ray crystallographer Laboratory, School of Chemistry, Cardiff University), for providing the crystal structures referred to in the thesis.

Prof. Ken Harris for his part in examining the dimerisation process described in chapter four.

Ben, Chris, Simon, Danny and the others in the lab for day-to-day help and advice. Also to Ben and Danny in particular for proof reading the thesis.

Gary and the other technicians in the stores of the Cardiff University School of Chemistry, for providing all the chemicals and equipment.

And my parents for providing somewhere to live and a computer whilst writing.

Abstract

This thesis covers work investigating the effects of fluorine incorporation on the structure, biological activity, and NMR properties of anticancer chalcones as well as novel methods for the inclusion of fluorinated moieties into organic compounds.

The first chapter looks at the use of silanes as carriers of small fluorinated nucleophiles which can be activated by fluoride anion catalysis to deliver such nucleophiles to organic electrophiles such as aldehydes. The synthesis of a group of such silanes and an assessment of their reactivity towards aromatic aldehydes is described.

The second and third chapters describe the synthesis and compare the structures and biological activities of four series of chalcones; chapter two looks at chalcones which have non fluorinated groups (a nitrile group and an ethyl ester group) on the α position and chapter three looks at chalcones which have F and CF_3 groups on that position. A comparison of the effects of substitution, at both the α position and on the B ring, on structure and cytotoxicity of these compounds is given. Several of the fluorinated chalcones were found to be highly cytotoxic and further assessment of their tubulin-binding properties was carried out.

Chapter four looks at some unusual, long range fluorine-hydrogen coupling interactions which have been observed in the NMR spectra of certain types of chalcones. The effects of various substitutions and structural changes on these coupling patterns are examined.
In addition a brief study into the dimerisation of chalcones is described.

The final chapter looks at the use of FAR type reagents to generate asymmetric fluorinated amides using secondary chiral amines. Synthesis of a number of chiral amines from proline and their addition, with limited success, to trifluorovinyl styrenes is discussed.

Abbreviations

Ac	Acetyl
Ar	Aryl
BBN	9-Borabicyclo[3.3.1]nonane
Bu	Butyl
^{i}Bu	*iso*-Butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-Butyl
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
Bz	Benzoyl
Cy	Cyclohexyl
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
GTP	Guanosine triphosphate
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenzotriazole
LDA	Lithium diiospropylamide
LiHMDS	Lithium hexamethyldisilazane
Me	Methyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
Pr	Propyl
^{i}Pr	*iso*-Propyl
R	Any alkyl or aryl group
SAR	Structure Activity Relationship
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

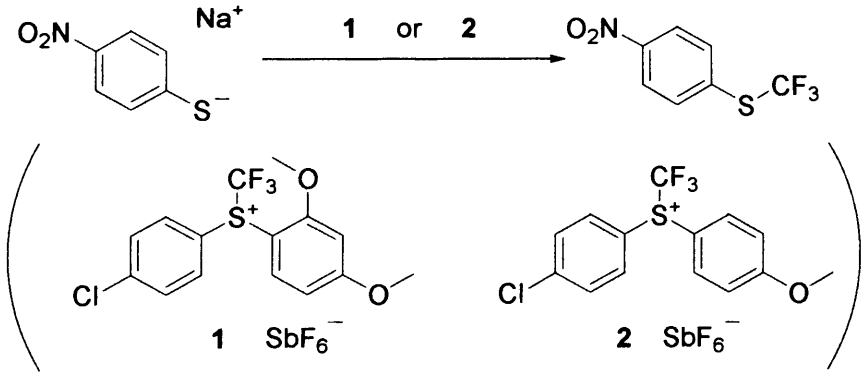
Chapter One

1.1 Introduction

Despite the highly beneficial effects that fluorine is being found to have on biologically active compounds,[1] there are relatively few reagents currently available that can selectively deliver fluorinated groups to organic compounds.

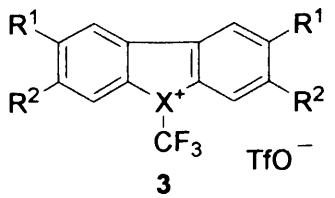
The trifluoromethyl group in particular is a very useful target for many potential drug candidates, although the existing methods of delivering this group are exceedingly limited. In theory the CF_3 group could come in the form of one of three synthons – [CF_3^-] [CF_3^+], or the [$CF_3^{\cdot}$] radical.

Sources of [CF_3^+] include compounds like trifluoromethyl-*p*-chlorophenyl(2,4-dimethyl) phenylsulfonium hexafluoroantimonate (**1**) and trifluoromethyl-*p*-chlorophenyl-*p*-anisylsulfonium hexafluoroantimonate (**2**), which have been shown by Yagupol'skii to deliver the [CF_3^+] synthon to sodium *p*-nitrothiophenolate (*Scheme 1.1*), generating *p*-nitrophenyl trifluoromethyl sulphide.[2] However, both reagents **1** and **2** are hygroscopic and difficult to synthesise.



Scheme 1.1 – Electrophilic trifluoromethylation.

Umemoto *et al.* developed a series of reagents of the type **3**, which trifluoromethylate a range of organic nucleophiles.[3] The reactivity of these compounds can be tuned by varying X (which can be S, Se or Te) and the electronic properties of the aryl substituents R^1 and R^2.



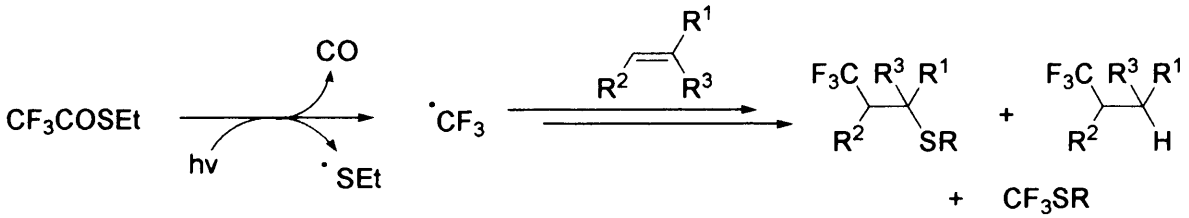
3

Figure 1.1 – Umemoto reagents.

In 1998 Shreeve[4] expanded on this and published work on a very similar group of electrophilic trifluoromethylating agents of the type $Ar_2S^+CF_3$ (TfO^-) which were used to deliver the trifluoromethyl group to aromatic rings, again these could be tuned by altering the nature of the aryl groups. In particular, it was found that having electron withdrawing groups such as NO_2 and F on the rings increased the reactivity, whilst electron donating groups reduced it.

All of these reagents, however, are expensive and difficult to prepare, requiring several steps to synthesise and are all hygroscopic and therefore difficult to store for long periods.

The [CF_3·] radical can be generated photochemically by irradiation of such molecules as CF_3COSR and CF_3SO_2SR, and then used to trifluoromethylate disulfides and alkenes (*Scheme 1.2*).[5]

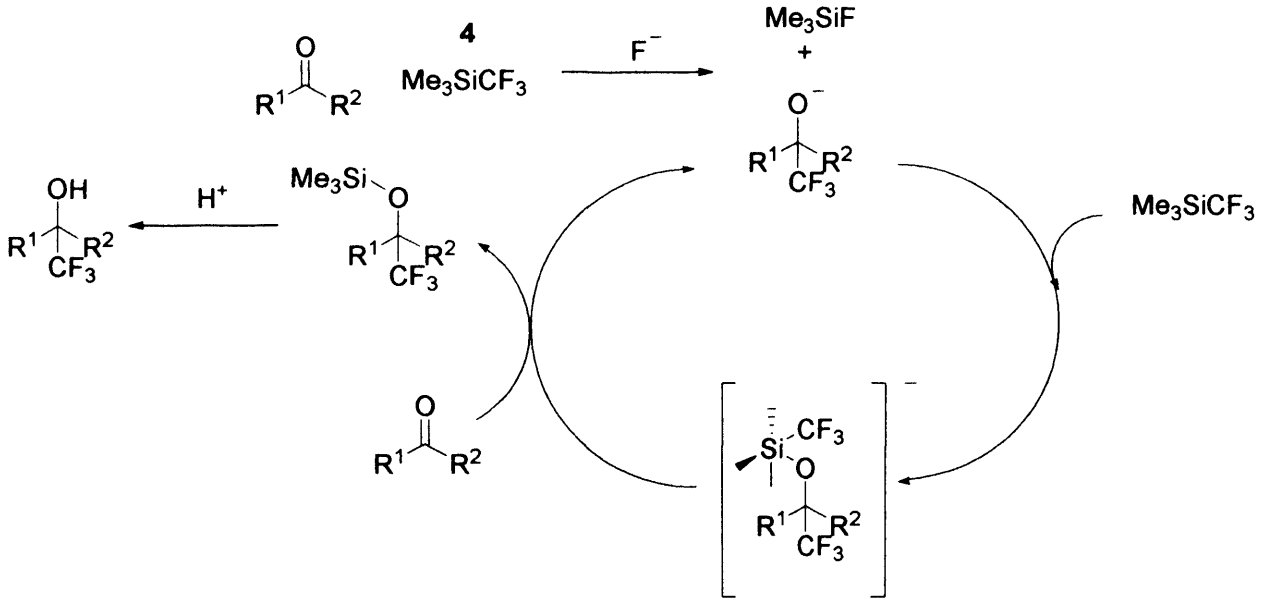


Scheme 1.2 – Free radical trifluoromethylation.

While this reaction does show some regioselectivity, in that the radical prefers to add to the less hindered end of the C=C double bond, it is low yielding, unpredictable and therefore not very suitable for use in the synthesis of large, complicated drug candidates.

This leaves [CF_3^-] as the most convenient synthon,[6] although the trifluoromethyl anion itself is unstable; it rapidly decomposes into fluoride and difluorocarbene[7] and must therefore be stabilised by conversion into a more convenient form.

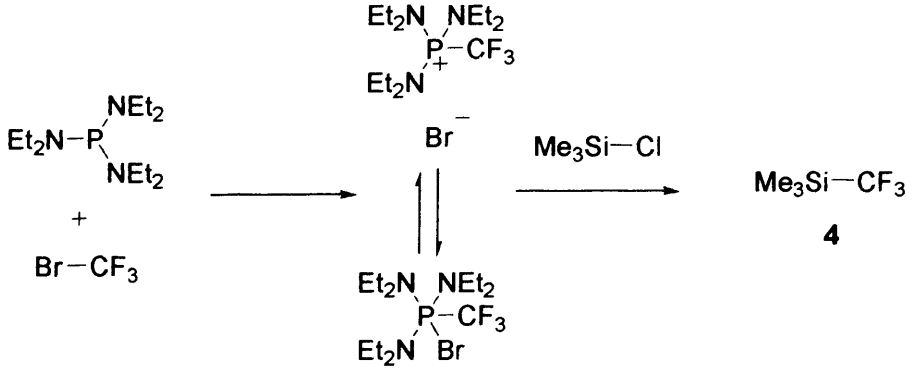
The reagent currently used for this purpose is trifluoromethyltrimethylsilane (Ruppert's reagent,[8] **4**), which is used as a [CF_3^-] synthetic equivalent and when activated by fluoride, can deliver the trifluoromethyl nucleophile to a range of organic electrophiles. The most well documented use of trifluoromethyltrimethylsilane is in the addition of CF_3 to aldehydes and ketones to generate secondary and tertiary trifluoromethyl alcohols (*Scheme 1.3*).



Scheme 1.3 – Nucleophilic trifluoromethylation using Ruppert's reagent.

The chemistry of Ruppert's reagent has been extensively reviewed.[9,10] It has been used to deliver [CF_3^-] to a range of other carbonyl compounds (including enones,[11] porphyrins,[12] esters,[13] aminoesters,[14] amides,[15] imines,[16] thiocyanates and selenocyanates[17]), as well as aromatic rings (via *ipso* attack[18] and F^- substitution[19]) and has even been shown to be able to introduce fluorocarbon ligands into metal complexes.[20]

Ruppert's reagent was first made in 1984 by condensation of CF_3Br and Me_3SiCl with $(Et_2N)_3P$ (*Scheme 1.4*).[21] However, use of CF_3Br is now restricted due to its long survival in the atmosphere. Although a number of alternative methods of making the reagent have been developed, including the replacement of CF_3Br with CF_3I[22] and use of aluminium based reductants,[23] none of these are as effective and there is now call for the development of more reagents that can act as a source of [CF_3^-].

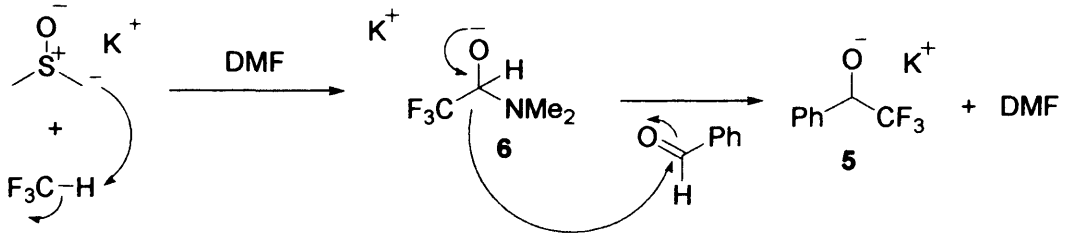


Scheme 1.4 – Synthesis of trifluoromethyltrimethylsilane.

As a result, a number of recent publications have sought to provide more useful, cheaper and greener alternatives to trifluoromethyltrimethylsilane.

Shono *et al.* have found that fluoroform can be deprotonated by a range of bases in the presence of DMF and used to add the trifluoromethyl nucleophile to benzaldehyde to create the alcohol **5**.[24] Normant and co-workers expanded on this and showed that the trifluoromethyl anion was in fact captured by the DMF, since the same reaction failed when THF was used.[25]

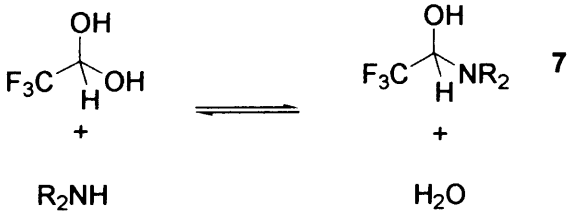
They suggested that in place of the trifluoromethyl anion, the intermediate **6** was formed. It is this species that then delivers the trifluoromethyl group when the aldehyde is added (*Scheme 1.5*).



*Scheme 1.5 – Nucleophilic trifluoromethylation using **6**.*

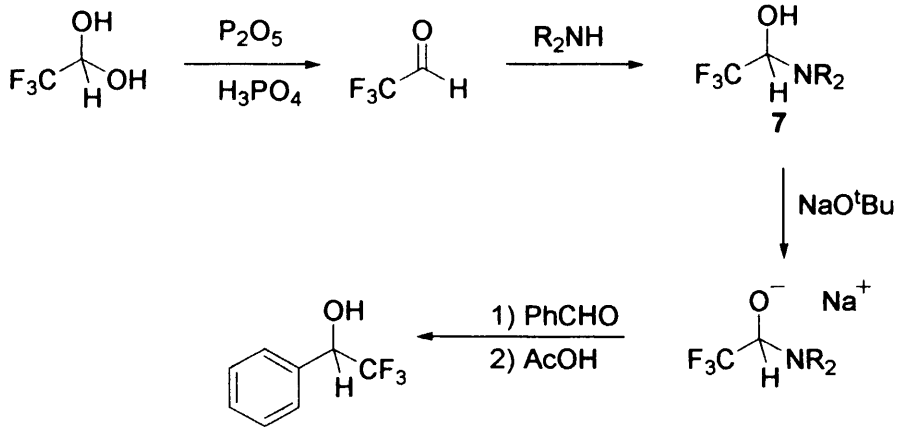
This hypothesis was backed up when they hydrolysed the reaction mixture before addition of any electrophiles and ^{19}F NMR revealed the presence of CF_3CHO.

Roques[26] sought to synthesise similar reagents such as **7** from fluoral hydrate without the presence of metal counterions (*Scheme 1.6*).



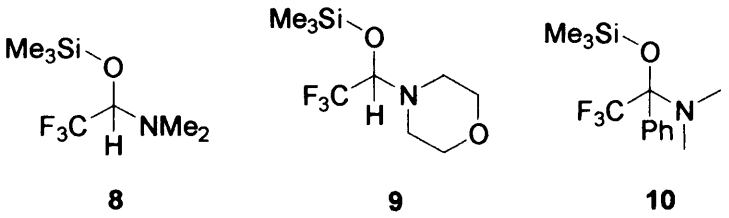
Scheme 1.6 – Amination of fluoral hydrate.

Although this was shown to be successful by ^{19}F NMR, isolation of the hemiaminal **7** from the equilibrium proved difficult when the hydrate was used because of the presence of water. So they generated the aldehyde itself by dehydration of the hydrate (P_2O_5 /H_3PO_4) and reacted this with the amines (*Scheme 1.7*). This enabled the products to be isolated in THF solution, which were then shown to react as expected with benzaldehyde in the presence of base, although the yields were lower than had been achieved previously.



Scheme 1.7 – Nucleophilic trifluoromethylation using 7.

Use of $N(TMS)_3$ / F^- as base in this reaction resulted in formation of the silylether **8** (*Figure 1.2*) rather than the above intermediate **7**.[27]

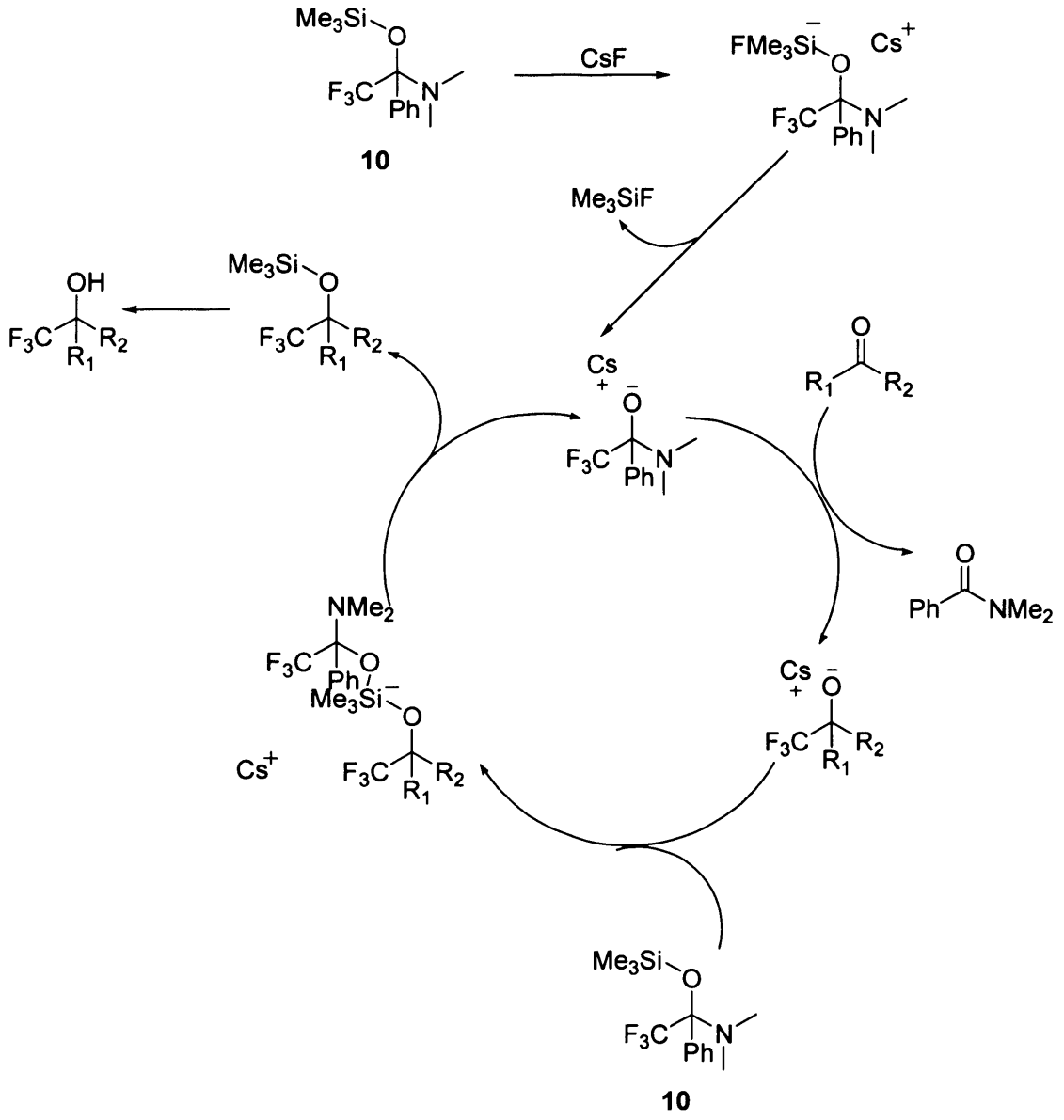


8 **9** **10**

Figure 1.2 – Reagents for nucleophilic trifluoromethylation.

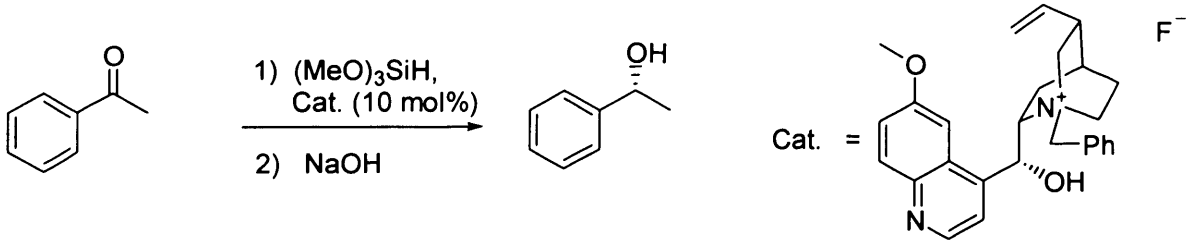
Although **8** could not be isolated, replacement of the DMF with *N*-formylmorpholine resulted in a relatively stable reagent **9**. Interestingly, of a range of *N*-formylamines used, *N*-formylmorpholine was the only one that gave satisfactory results. Reagent **9** was shown to behave in much the same way as Ruppert's reagent, although two equivalents of the reagent and higher temperatures were required to give good yields.[28]

A similar piece of work by Motherwell *et al.* looked at the reaction of trifluoromethylacetophenone with *N,N*-dimethyltrimethylsilylamine, which resulted in formation of the reasonably stable reagent **10**. This, too, was shown to react well with a range of aromatic aldehydes and ketones in the presence of catalytic CsF, delivering the trifluoromethyl nucleophile.[29] They proposed a catalytic reaction mechanism (*Scheme 1.8*), similar to that of Ruppert's reagent.



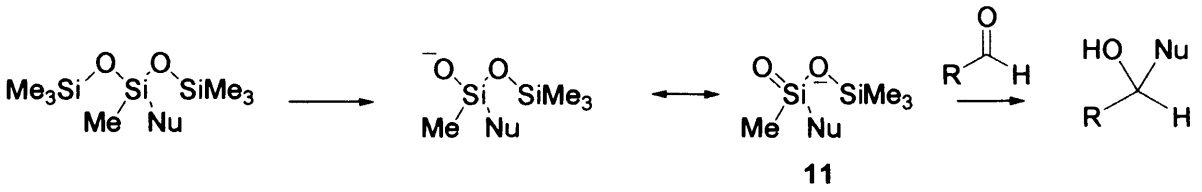
*Scheme 1.8 – Nucleophilic trifluoromethylation using **10**.*

Work within our own group has found that siloxanes can be very useful in the delivery of hydride nucleophiles. PMHS (polymethylhydrosiloxane) and 1,1,3,3-tetramethyldisiloxane in the presence of fluoride catalyst such as TBAF can reduce aldehydes and ketones[30] to their corresponding alcohols, and if quinidine chiral ammonium fluorides are used, the reaction becomes asymmetric[31] with e.e.'s of up to 71% (*Scheme 1.9*).



Scheme 1.9 – Asymmetric reduction of acetophenone using siloxane.

The above reduction using siloxanes is also much faster than reduction using equivalent silanes – PMHS reduces acetophenone in high yields in under a minute whereas it takes hours for the same reaction to occur using an equivalent silane. It is believed that this is due to the formation of a silonate intermediate (**11**) which would be extremely reactive.



11

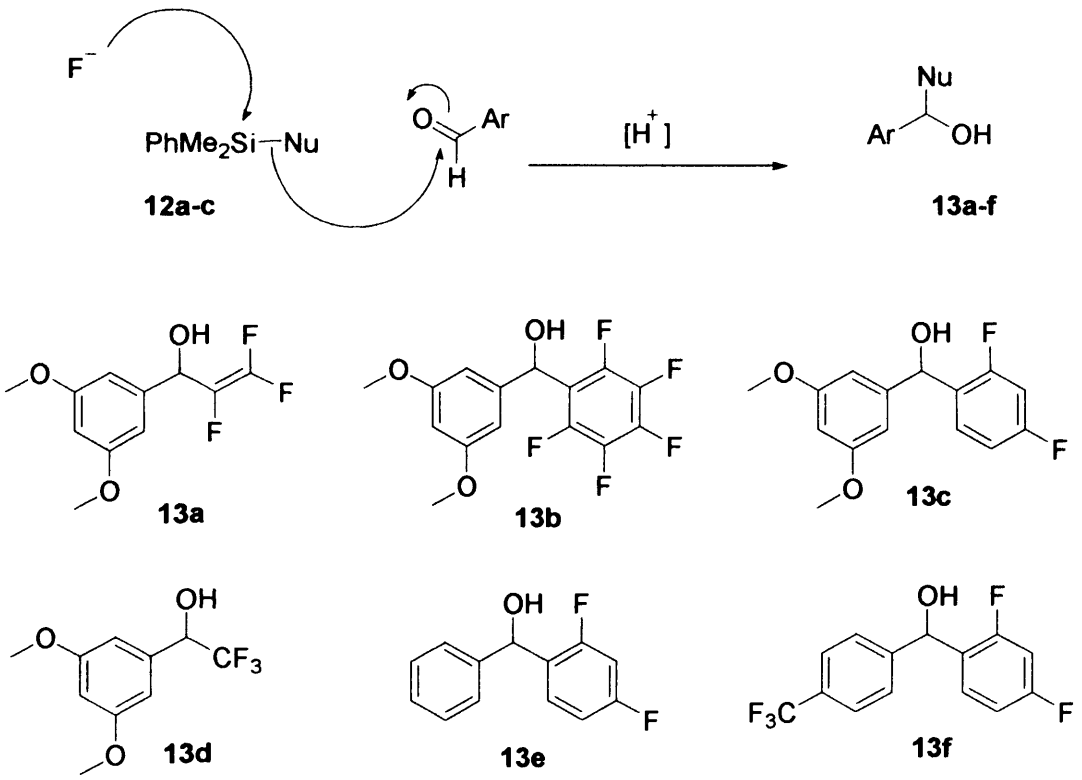
Scheme 1.10 – Formation of silonate intermediate.

If this is the case then siloxanes should also be useful reagents in the delivery of other nucleophiles. This has already been seen with allyl groups[32] and it is expected to work with fluorinated groups too.

1.2.1 Trifluorovinyl Nucleophile

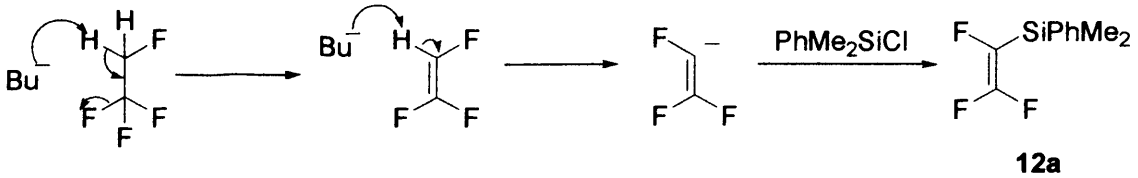
A range of silanes of the type Nu-$SiMe_2Ph$ (**12**) were made where 'Nu' represents a fluorinated nucleophile. In some cases (those of the nucleophiles C_2F_3 and C_6F_5) similar silanes have been used previously to deliver the same fluorinated nucleophiles to organic electrophiles, with varying degrees of success.[33] Although the use of more reactive silanes with the difluorophenyl group, $C_6H_3F_2$, as described here, is novel. These were made in order to assess their reactivity towards organic electrophiles with the intention of then forming the basis for a comparison with the equivalent siloxane reagents.

The alcohols **13a** to **13f** were made by reaction of silanes with various aldehydes (*Scheme 1.11*) and, with the exceptions of **13e** and **13f**,[34] are all novel and full characterisation data is given in chapter 6; all were shown to contain the correct fluorinated group by ^1H and ^{19}F NMR and high resolution mass spec confirmed they had the correct molecular ion.



Scheme 1.11 – Addition of fluorinated nucleophiles to aryl aldehydes using silanes.

Firstly dimethyl(trifluorovinyl)phenylsilane (**12a**) was made in high yield (81%) by double deprotonation of 1,1,1,2-tetrafluoroethane, using two equivalents of BuLi in THF, according to a method developed by Burdon *et al.*[35] This generated the trifluorovinyl anion which was then substituted for the chlorine in chlorodimethylphenylsilane (*Scheme 1.12*). The structure of **12a** was confirmed by ^{1}H and ^{19}F NMR and mass spectrometry, as shown in chapter 6; the three double doublet peaks at –85.7 (J_{FF} = 23.5, 47 Hz), -114.2 (J_{FF} = 47, 160 Hz) and –197.0 (J_{FF} = 23.5, 160 Hz) in the ^{19}F NMR corresponded to the three fluorine atoms, each one coupled to each of the others. Likewise the ^{1}H NMR showed the phenyl protons as a pair of complex multiplets at around 7.3 and 7.5 ppm, and the methyl protons as one singlet at 0.41 ppm.



*Scheme 1.12 – Synthesis of **12a**.*

The vinylsilane **12a** was then used to add the trifluorovinyl nucleophile to 3,5-dimethoxybenxaldehyde to generate **13a** in the same way as Ruppert's reagent.

The ^{1}H NMR spectrum of **13a** showed a singlet at 3.73 ppm corresponding to the two equivalent methoxy groups, a doublet at 6.20 ppm with a J_{HF} value of 36 Hz, corresponding to the α proton coupled to the fluorine atom at the β position, and two doublets at 6.41 (*para*) and 6.63 (*ortho*) with J_{HH} values of 2.4 Hz for the aromatic protons. The ^{19}F NMR had the same pattern as was seen in **12a** - i.e. three double doublets at –66.5, -72.0 and –131.1 with J_{FF} values of 23.5, 52 and 155 Hz (the β fluorine was also coupled to the α proton) - but shifted up field as a result of the electron withdrawing properties of the aryl group.

A range of tests were carried out, looking at different catalysts and reaction conditions for this reaction. While the trifluorovinyl nucleophile was found to react under certain conditions, the yields were disappointing. Results are summarised in *Table 1.1* (where the yield is shown as 0% the aldehyde was recovered unreacted with the exception of the 4-nitro-benzaldehyde in which case the reaction turned deep indigo and no product or starting material could be isolated).

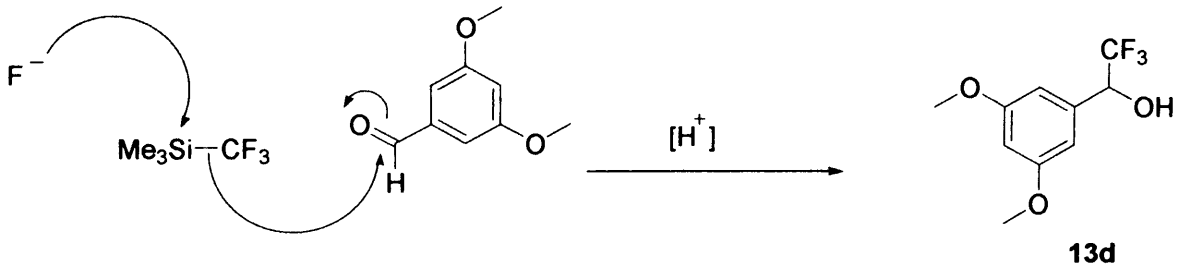
Aldehyde	**Catalyst (mol%)**	**Time, Temperature**	**Yield and Product**
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C no solvent	9%, **13a**
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	0%
3,5-dimethoxy-benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	3 days, 80 °C in THF	0%
3,5-dimethoxy-benzaldehyde	CsF, 100 mol%	3 days, 80 °C	0%
3,5-dimethoxy-benzaldehyde	CuF_2/dppb, 10 mol%	24 hrs, room temp. (under air) in THF	0%
4-nitro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
4-chloro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%

Table 1.1 – Reaction conditions and yields for reactions of ***12a*** *with aryl aldehydes.*

Initially 3,5-dimethoxybenzaldehyde was used as the electrophile and TBAF as fluoride source, since TBAF is the catalyst of choice for reactions with Ruppert's reagent. The reaction conditions were varied from stirring at room temperature with 10 mol% of catalyst to heating at 80 °C with no solvent and stoichiometric quantities of catalyst. This was done to see how harsh the reaction conditions needed to be in order for reaction to take place. In the case of the

trifluorovinyl nucleophile the reaction only worked under the most extreme conditions, and even then the yields were very low. Since most of the aldehyde in this case was recovered unreacted, it would suggest that the trifluorovinyl nucleophile was reacting in some other way in the reaction mixture faster than it was reacting with the aldehyde. The most obvious explanation for this was that water had contaminated the hygroscopic TBAF. In order to test this tetrabutylammonium difluorophenylsilicate was used as a non-hygroscopic fluoride source.[36] This, however, was found to work no better than TBAF.

Ruppert's reagent was then used on the same aldehyde under reflux at 80 °C with one equivalent of TBAF in THF as catalyst, as a test of the TBAF. After only 24 hrs the reaction had gone to completion and the product **13d** was extracted in quantitative yield without the need for column purification. This would suggest that water was not responsible for the disappointing yields in this reaction.



Scheme 1.13 – Test reaction using Ruppert's reagent.

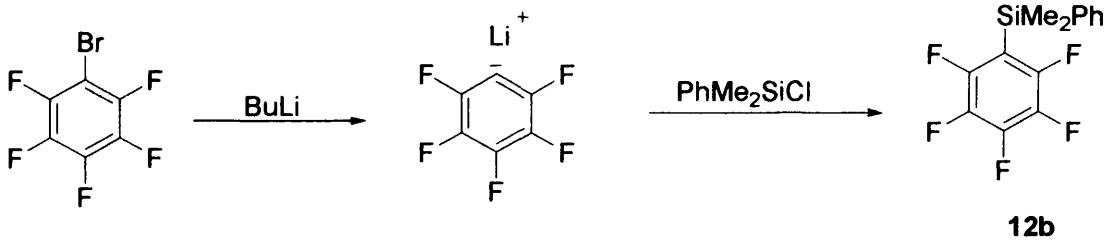
As mentioned previously, Hiyama *et al.* have used $Et_3SiCF{=}CF_2$ to deliver the trifluorovinyl nucleophile to alkyl and aryl aldehydes under catalysis by tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF).[37] They also reported low yields, despite using the silane in excess. The only explanation given in their publication was the α or β–elimination of a fluoride anion from the vinyl nucleophile (which they believed to be present as a naked anion rather than a pentavalent silicon species) forming the fluoride salt of TAS^+ and an alkyne species.

Two more catalysts were then tried. Cesium fluoride was flame-dried under vacuum to ensure it was anhydrous. This did not lead to any improvement. Copper(II) fluoride/dppb (dppb = PPh_2-$(CH_2)_4$-PPh_2) has recently been found to catalyse hydrosilylation of ketones, under an atmosphere of air.[38] Use of this catalyst again did not work on our system.

Two other, more electrophilic aldehydes (4-chlorobenzaldehyde and 4-nitrobenzaldehyde) were also used but again no improvement was seen.

1.2.2 Pentafluorophenyl Nucleophile

After limited success with the trifluorovinyl nucleophile, dimethyl(pentafluorophenyl)phenylsilane (**12b**) was synthesised and used in a similar range of tests to see if the pentafluorophenyl nucleophile could be delivered with any improvement in yield. Again the synthesis of this reagent was straightforward. Pentafluorophenyl lithium was made by addition of BuLi to bromopentafluorobenzene in THF (according to the method developed by Frohn[39] and co-workers) and then added to chlorodimethylphenylsilane to generate silane **12b** in 83% yield (*Scheme 1.14*). ^{19}F NMR analysis showed three multiplet peaks corresponding to the *ortho* (-128 ppm), *meta* (-164 ppm) and *para* (-154 ppm) fluorine atoms and the ^{1}H NMR showed the phenyl protons as two complex multiplets at around 7.3 and 7.4 ppm, and the methyl protons as a singlet at 0.6 ppm. Mass spec data showed the $[M+H]^+$ molecular ion at 303.0623.



Scheme 1.14 – Synthesis of ***12b.***

A similar range of tests was carried out to determine how well this acted as a source of pentafluorophenyl nucleophile. (Once again, where the yield is shown as 0% the aldehyde was recovered unreacted, except for 4-nitro-benzaldehyde).

Aldehyde	Catalyst (mol%)	Time, Temperature	Yield and Product
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C no solvent	20%, **13b**
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	11%, **13b**
3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	0%
3,5-dimethoxy-benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	48 hrs, 80 °C in THF	0%
3,5-dimethoxy-benzaldehyde	CsF, 100 mol%	5 days, 80 °C in THF	0%
3,5-dimethoxy-benzaldehyde	CuF_2/dppb, 10 mol%	24 hrs, room temp. (under air) in THF	0%

4-nitro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
4-chloro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%

Table 1.2 – Reaction conditions and yields for reactions of ***12b*** *with aryl aldehydes.*

Again the reaction was carried out initially on 3,5-dimethoxybenzaldehyde using TBAF as catalyst and varying the extremity of conditions.

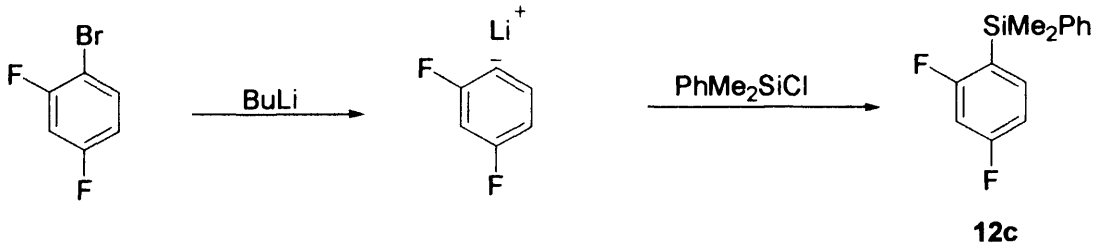
The structure of **13b** was confirmed by proton NMR – singlet at 3.72 ppm corresponding to the 6 methoxy protons, singlet at 6.06 ppm corresponding to the α proton and doublets at 6.33 and 6.47 (J_{HH} = 2.1 Hz) corresponding to the *para* and *ortho* protons respectively. The mass spec. also showed a large peak at 315.0641, corresponding to $(M\text{-}F)^+$.

This time a significant improvement, a two-fold increase, was seen in the yields of **13b** over **13a** for reaction under the same conditions. The silane **12b** was also found to react when TBAF was used in catalytic amounts, unlike **12a**. Clearly the pentafluorophenylsilane is better able to deliver its nucleophile to the aldehyde than the trifluorovinyl analogue, but still the reaction did not go to completion.

Again this silane was then used with the same alternative fluoride sources and aldehydes that had been used with the previous reagent, and no improvement was seen. Since the use of non-hygroscopic fluoride sources, as well as comparisons with Ruppert's reagent, have eliminated the possibility of damp or contaminated TBAF being responsible for the low yields, it is likely that the fluoride nucleophiles are decomposing in some way before reaction with the aldehyde can take place, presumably by elimination of a fluoride anion which in this case would result in a benzyne species.

Hiyama *et al.* also looked at the use of aromatic nucleophiles such as C_6F_5, C_6Cl_5 and 3,5-Cl_2-C_6F_3 in their paper and also saw improved yields, concluding that the fluoride elimination and subsequent decomposition is much less favourable in the case of aromatic nucleophiles than in vinyl nucleophiles.

1.2.3 2,4-Difluorophenyl Nucleophile



12c

Scheme 1.15 – Synthesis of ***12c****.*

The silane **12c** was made in the same way as the pentafluoro-analogue and reacted with 3,5-dimethoxybenzaldehyde to generate **13c**. Structure of **12c** was, again confirmed by ^{19}F and ^{1}H NMR analysis – ^{19}F NMR showing two multiplets and ^{1}H NMR showing the same singlet methyl and multiplet phenyl peaks as were seen in **12a** and **12b** but also three separate multiplets for the three aromatic protons on the 2,4-difluorophenyl ring. Since **12c** was novel, ^{13}C NMR, IR and mass spec data were also recorded. This time not only was there a significant improvement in the yields of **13c** but also the conditions needed for the reaction to occur were shown to be much less harsh. ^{1}H NMR of **13c** contained a singlet at 3.70 ppm corresponding to the 6 methoxy protons, a singlet at 5.96 ppm corresponding to the α proton, two doublets at 6.30 and 6.47 (J_{HH} = 2.1 Hz) corresponding to the *para* and *ortho* protons respectively and three multiplets corresponding to the 3', 5' and 6' protons on the 2,4-difluorophenyl group. The two reagents **12a** and **12b** had only been able to react when TBAF was used as fluoride source, and the reaction was heated under reflux. The 2,4-difluorophenyl nucleophile, however, was found to add to the aldehyde when TBAF was used in catalytic quantities at room temperature. The reaction was also seen to work with $NBu_4SiPh_3F_2$ as fluoride source and with benzaldehyde and 4-trifluoromethylbenzaldehyde, though once again no reaction took place with 4-chlorobenzaldehyde and reaction with 4-nitro-benzaldehyde resulted in an inseparable mixture:

Aldehyde	**Catalyst (mol%)**	**Time, Temperature**	**Yield and Product**
3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C no solvent	39%, **13c**
3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	31%, **13c**
3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	19%, **13c**

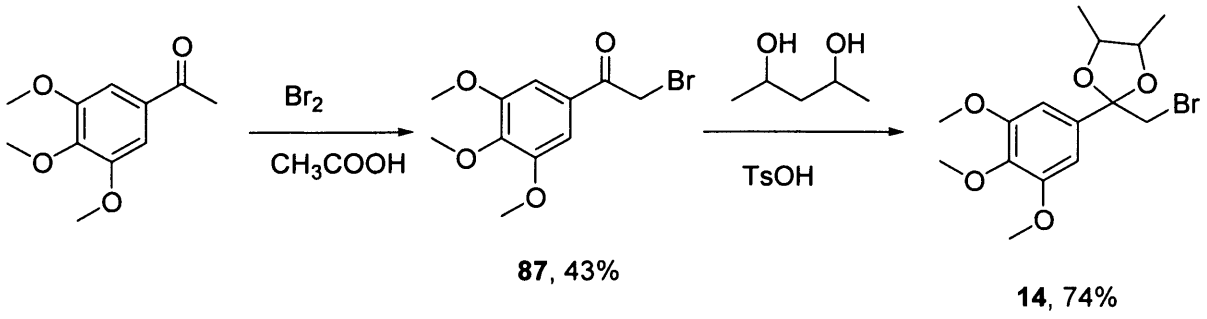
3,5 dimethoxy benzaldehyde	CuF_2/dppb, 10 mol%	48 hrs, room temp. (under air) in THF	0%
3,5 dimethoxy benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	48 hrs, 80 °C in THF	23%, **13c**
benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	17%, **13e**
4-trifluoromethyl-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	29%, **13f**
4-nitro-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%
4-chloro-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%

*Table 1.3 – Reaction conditions and yields for reactions of **12c** with aryl aldehydes.*

Clearly the aromatic nucleophiles are much more stable to fluoride elimination than the trifluorovinyl nucleophile and thus able to react with the electrophiles in much better yields. In the case of the difluorophenyl group this is much more the case than with a pentafluorophenyl species. This is consistent with the electronic properties of the benzyne species which would form from fluoride elimination of these nucleophiles. Tetrafluorobenzyne would be more stable than a monofluoro equivalent because the four electron-withdrawing fluorine atoms would be better able to stabilise the electron rich benzyne ring, thus fluoride elimination from a pentafluorophenyl nucleophile would be more favourable than from a difluorophenyl nucleophile.

1.3 Application to Potential Anticancer Agents

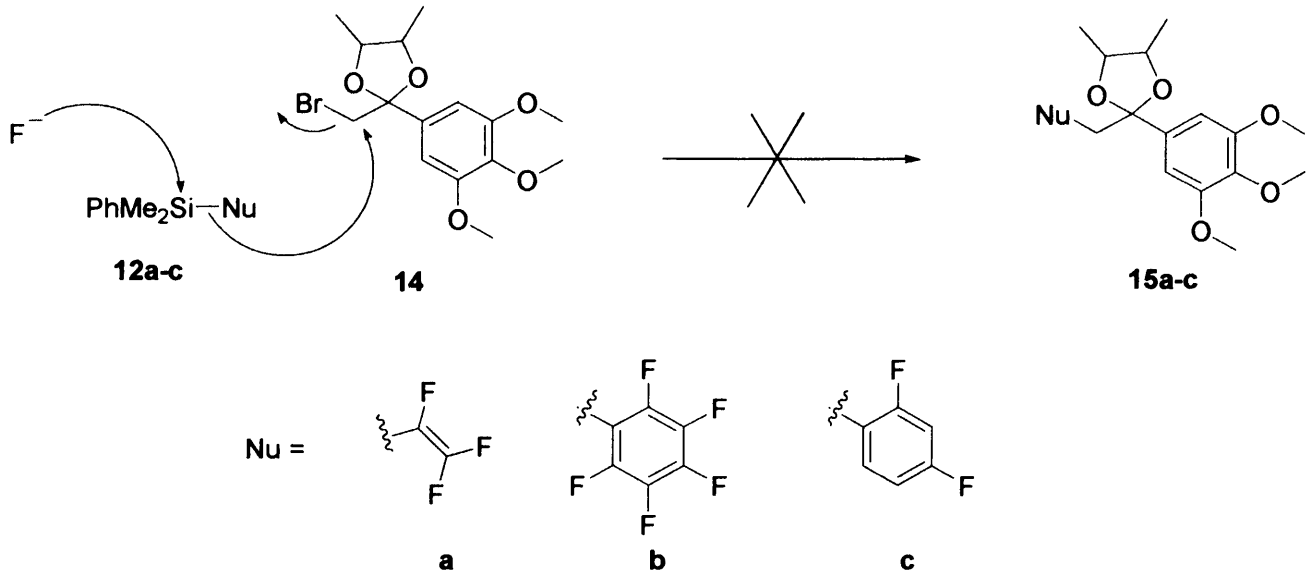
These silane reagents were also used in an attempt to deliver fluorinated nucleophiles to the alkyl bromine electrophile (**14**).



*Scheme 1.16 – Synthesis and protection of **87**.*

This was made by addition of Br_2 to 3,4,5-trimethoxyacetophenone, followed by protection of the carbonyl group with 2,3-butandiol.

It was then reacted with each of the silanes under those conditions which gave the best yields with the aldehydes (*Scheme 1.17*). The expected products **15a-c** could then have been deprotected and used in the chalcone synthesis discussed in later chapters.



*Scheme 1.17 – Reaction of **14** with silanes **12a-c**.*

No reaction took place, however, with any of the three silanes. This could be because this particular alkyl bromide is too sterically hindered. However, it is more likely that the silanes cannot be used as a source of CF_3^- for subsequent S_N2 reactions because this would require CF_3^- to be present as the naked anion. Examples of S_N2 reactions using Ruppert's reagent as a source of CF_3^- are absent from the literature.

1.4 Summary and Conclusions

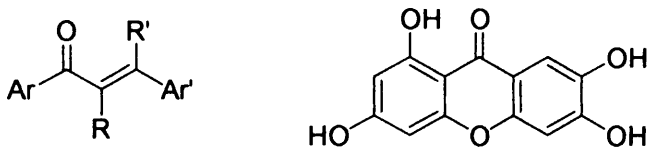
In summary it has been shown that silanes of the type $Me_2PhSiNu$, where Nu represents a small fluorinated nucleophile, can be used to deliver such nucleophiles to electrophilic carbonyl compounds. This reaction seems to give the highest yields when the nucleophile used is aromatic, in particular the nucleophile $[C_6H_3F_2^-]$ works well.

This area of research, despite some interesting results, could not be continued due to lack of industrial support.

Chapter Two

2.1 Introduction

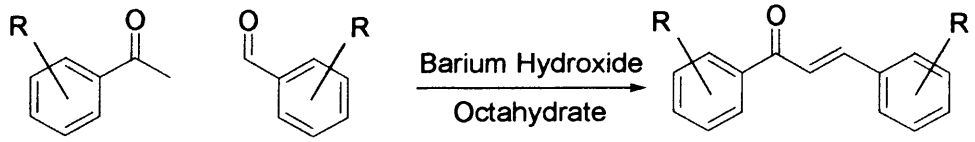
Chalcones, 1,3-diarylprop-1-enones, are a class of organic compounds consisting of two aryl rings linked by an α,β–unsaturated ketone moiety (*Figure 2.1*). Some chalcones are natural products found in various plant species around the world and in the last decade or so they have been shown to display a wide range of medicinal properties. This, combined with the ease with which chalcones can be synthesised in large numbers, makes them a very useful target for pharmaceutical study.



Chalcone **Norathyriol**

Figure 2.1 – Norathyriol and chalcone structures.

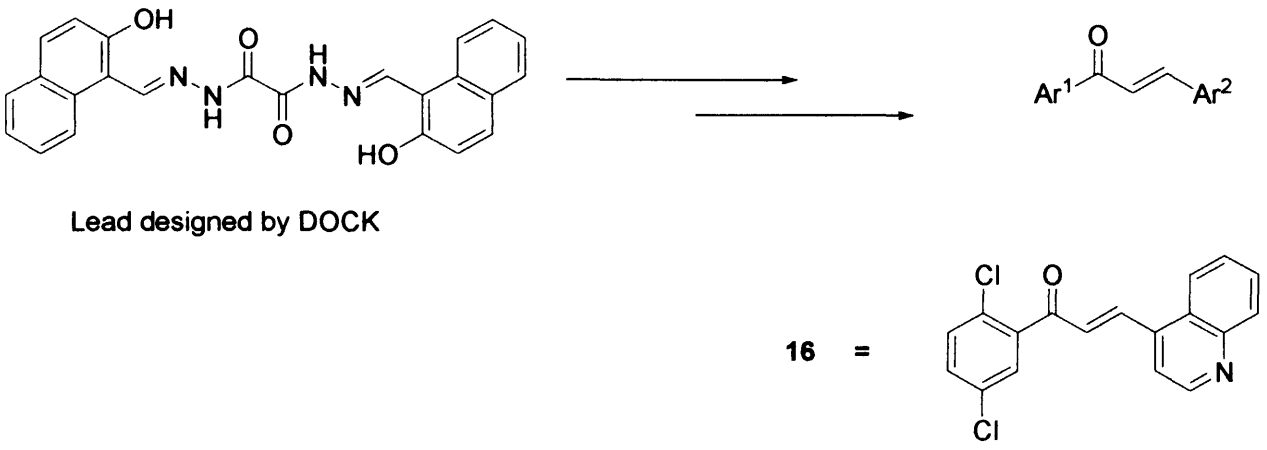
Drugs such as norathyriol (*Figure 2.1*) which can block the release of hormones from mast cells are effective against various inflammatory diseases including asthma, rhinoconjunctivitis and urticaria.[40] Hsieh *et al.* published work on the anti inflammatory effects of chalcones in 1998.[41] A series of chalcones were synthesised by Claisen-Schmidt condensation of appropriate acetophenones with aryl aldehydes (*Scheme 2.1*) and their anti inflammatory activity was tested *in vitro* and *in vivo*. Many were found to be active and evidence was given suggesting that the activity of these chalcones, like that of norathyriol, was due to suppression of the release of chemical mediators from mast cells.



Scheme 2.1 – Chalcone synthesis.

The use of chalcones as anti-malarials to target malarial cysteine protease was investigated by Li and co-workers in 1995.[42] The enzyme is believed to be crucial in the degradation of haemoglobin[43] and compounds which block it have proven effective against Chloroquine-resistant strains of malaria.[44] Modifications to a lead, which was designed computationally to block malarial cysteine protease and not mammalian cysteine protease, led the authors to investigate the use of chalcones for this purpose. SAR studies on a series of chalcones led to a few active compounds, the most potent of which was **16** (*Scheme 2.2*). In this report there was

strong evidence that they were effective against Chloroquine-resistant strains, suggesting that they act through malarial cysteine protease inhibition.



Scheme 2.2 – Anti-malarial chalcones.

Kromann and co-workers recently published a study on the synthesis of a series of anti-bacterial chalcones and compared their activity with that of **17**, which was derived from the known anti-bacterial chalcone Licochalcone A (*Figure 2.2*).[45]

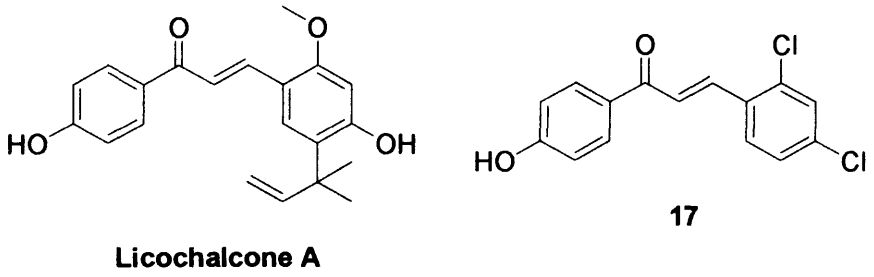


Figure 2.2 – Anti-bacterial chalcones.

They synthesised the chalcones in the usual manner – condensation of the appropriate aryl aldehyde and acetophenone in the presence of NaOH in ethanol.

The aim of the study was to increase the acidity of the hydroxyl group on the A ring, making the molecule more hydrophilic and improving bioavailability. Their first approach was to substitute electron-withdrawing fluorine groups on the A ring to make the phenol more acidic. In compounds **18** and **19** this was done (*Figure 2.3*) and, while it was found that it did increase acidity, at the same time it was also found to reduce biological activity.

Their second approach, which was much more successful, was to replace the hydroxyl group with a carboxylic acid. This resulted in compounds such as **20** and **21** which were almost as potent as Licochalcone A and **17**, and at the same time had much improved hydrophilicity.

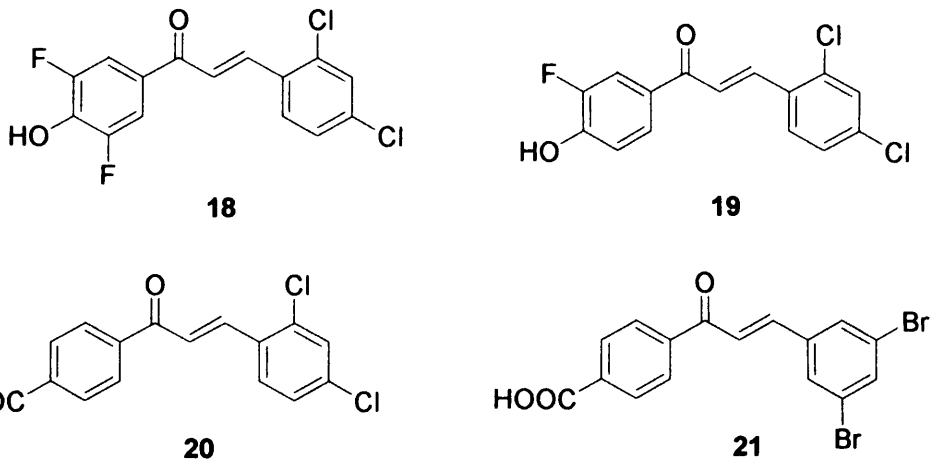


Figure 2.3 – Anti-bacterial chalcones.

Investigation into the substitutions on the B ring led to the most active compound **21.**

This was then tested further to assess the kinetics of bacterial killing. Surprisingly, it was found to have a different mode of action to Licochalcone A; this compound was bacteriostatic and while it inhibited bacterial growth, it did not actually kill the bacteria in the same way that Licochalcone A and **17** did. This can be an advantage in anti-bacterial drugs, as bacteriostatic compounds are usually less toxic to humans than bactereocidal drugs.

The use of chalcones as anticancer agents is another relatively new field, in the late 1980's and early 1990's a number of publications brought to light the antimitotic properties of chalcones and similar compounds. Sukumaran *et al.* isolated dihydrochalcone in 1991 from a fern called *Pityrogramma calomelanos* and found that it showed some cytotoxicity.[46]

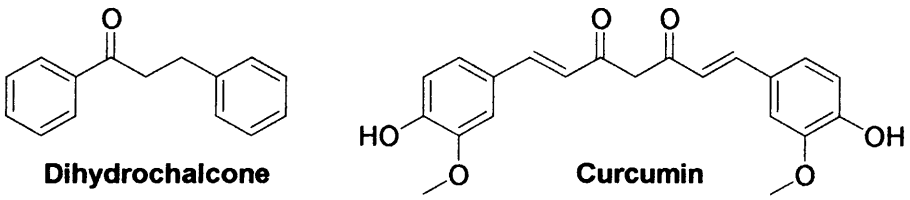


Figure 2.4 – Dihydrochalcone and related structure curcumin.

This was expanded upon in 1995 when they made a range of synthetic chalcones and structurally related compounds[47] and carried out a simple SAR study on the effects of having Cl, OMe, NO_2, OH and CH_3 substituents in different positions on the rings. A comparison of the cytotoxicities of around 34 compounds led to the general conclusion that the addition of Cl, OMe and NO_2 to the aryl rings reduced activity, whereas the presence of OH and CH_3 improved *in vitro* activity. However in the case of the methyl substituted chalcones, activity *in vivo* was reduced. The only explanation given in the paper for the actual mechanism of the chalcones' cytotoxicity was an observation that they are structurally similar to curcumin,[48] a

known antioxidant and chemopreventative compound found in tumeric which acts by scavenging superoxide radicals.

Other papers at around the same time, however, described studies of synthetic chalcones which resemble such known tubulin inhibitors as combretastatin A-4, colchicine and podophyllotoxin, with the intention of designing molecules specifically to block the colchicine-binding site of tubulin.

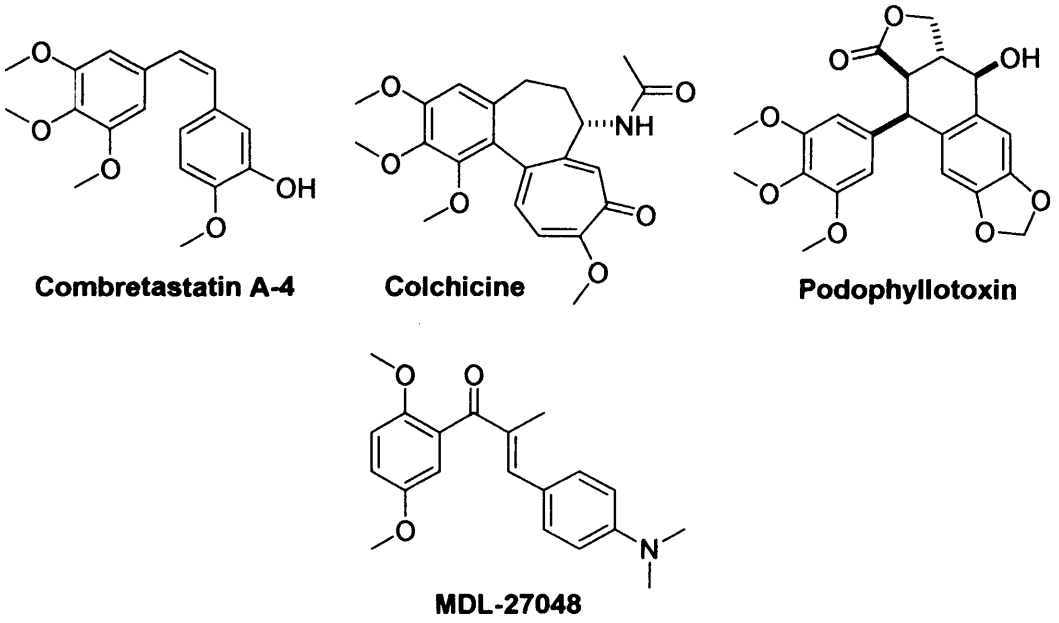


Figure 2.5 -- Known tubulin inhibitors.

In 1987 Edwards *et al.* made the first mention of this.[49] After looking at the cytotoxicities of a number of α-methyl and α-hydrogen chalcones, they discovered the drug MDL 27048. This was shown in a number of follow-up publications to bind to tubulin, with strong evidence that the methoxy-substituted A ring fits into the colchicine-binding site,[50,51] it was also speculated that the B ring amine group interacted with a sulfhydryl residue.[52] No explanation was given in any of these papers, however, for the fact that both the cytotoxicities and tubulin bindings were much greater with a methyl group in place of a proton on the α-carbon.

The discovery was made within our own group that the α,β–unsaturated ketone (*E*)-1-(4'-hydroxyphenyl)but-1-en-3-one (**22**), which was isolated from the plant *Scutellaria barbata*, had some antimitotic activity against human leukaemia cells. The IC_{50} value, which gives the concentration of a compound needed to reduce cell growth by 50% in a certain cell line (in this case human leukaemia cell K562), was 60 μM[53] and this led to an investigation into chalcones.

Of numerous simple chalcones screened, the most active was found to be **23** (*Figure 2.6*). It was also found that the activity of pure (*E*)-isomer was a great deal higher than a mixture of (*E*)- and (*Z*)-isomers.[54]

Further investigation into these chalcones revealed that activity was much improved by inclusion of a methyl group at the α-position, which is consistent with the potency of MDL 27048 above, this discovery lead to the synthesis of **24** with an IC_{50} of 0.21 nM.

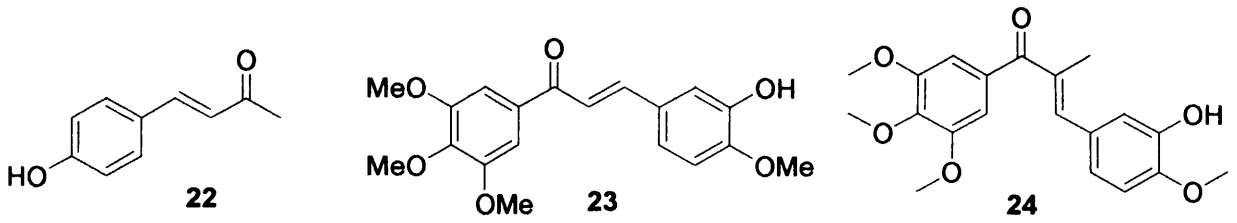


Figure 2.6 – Chalcones designed to bind to tubulin.

X-ray crystallography studies of chalcones with the C-2 methyl group showed that they adopt an s-*trans* conformation, i.e. the C=C and C=O double bonds are arranged *trans* across the C-C single bond, which due to the conjugated nature of the chalcone molecule has some double bond character (*Figure 2.7*), whereas less active derivatives with only a proton at that position are shown to be in an s-*cis* form. This can be explained by steric factors; chalcones are usually more stable in the s-*cis* form but in the case of alpha methyl chalcones such as **24** are forced into the s-*trans* conformation by the relatively bulky methyl group. It would appear that the antimitotic properties of these compounds are improved by this structural change and would be reasonable to conclude that s-*trans* chalcones are better able to fit into the colchicine binding site of tubulin.

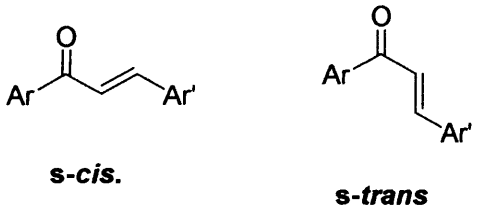


Figure 2.7 – s-cis/s-trans isomerism.

While there is a great deal of evidence for some chalcones binding to tubulin and inhibiting its polymerisation, not all anticancer chalcones share this mode of action. There are many papers which describe cytotoxic chalcones that show no evidence of tubulin binding.

Chalcones such as **25** and **26** have been found to have IC_{50} values in the sub micromolar range (*Figure 2.8*).[55] In the case of **25**, tests into the source of this cytotoxicity revealed that it blocks cells in the G_2/M phase of mitosis,[55] consistent with the molecule binding to tubulin, blocking its polymerisation and preventing the formation of microtubules, which play a vital role in the formation of the mitotic spindle. At the same time, however, other chalcones with very similar structures such as **26**, which is similarly cytotoxic, do not show the same evidence of tubulin binding. Their activity was accredited to the alkylation of the compounds via a biological Michael addition, which has already been seen to infer anticancer properties on (*E*)-1-arylbut-1-en-3-ones of the type **27**.[56]

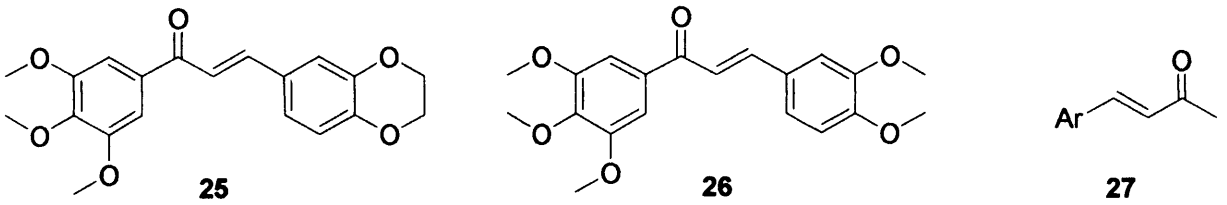


Figure 2.8 – Anticancer chalcones.

Aryl quinolones, of the type **28** and **29** (*Figure 2.9*), which share many structural features with chalcones, show some cytotoxicity.[57] Lee *et al.* have also made a series of 2'-aminochalcones and analysed their anticancer properties,[58] since the 2'-aminochalcones are similar to aryl quinolones but with the B ring uncyclised.

It was found that they, too, showed some activity, the most potent of them being **30**.

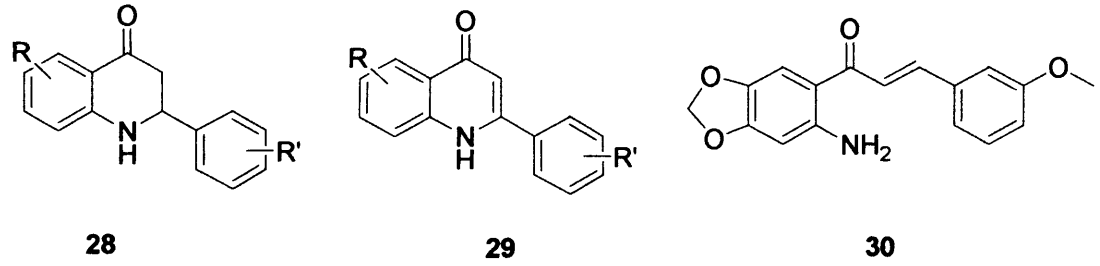
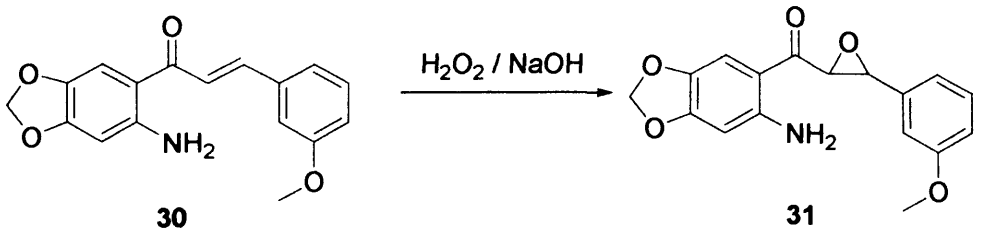


Figure 2.9 – Anticancer quinolones and chalcones.

Comparisons with the other members of the same series led the authors to conclude that the presence of both the methylenedioxy group at the 4', 5' position and the methoxy at the 3-position were needed for high cytotoxicity.

In an effort to understand the mode of action of these chalcones they converted **30** into the corresponding epoxide **31**, destroying the double bond character of the α,β unsaturated ketone moiety (*Scheme 2.3*). They also did this with some of the other 2'-amino chalcones and in all

cases found that doing so rendered the compounds inactive (cytotoxicities in most cases were roughly 10 fold less for the chalcones than epoxides). They concluded from this that the double bond is an essential feature responsible for anticancer activity in chalcones and as a result postulated that their mode of action was an alkylation process involving cellular thiols such as glutathione.



Scheme 2.3 – Chalcone epoxidation.

This is not conclusive, however, as the epoxides would also be electrophilic and may also be able to undergo the same alkylation process. None of these chalcones were tested for tubulin binding and therefore tubulin inhibition cannot be ruled out as a mode of action, it may be that conversion to epoxides reduces activity by altering the structure of the chalcones and hindering tubulin binding.

Another biological target for some chalcones is the enzyme 5-lipoxygenase (5-LO), which mediates the biosynthesis of leukotrienes. Inhibitors of 5-LO have antiinflammatory properties and have been shown to have potential as treatments for asthma, psoriasis, and dermatitis[59] as well as being able to kill human prostate cancer cells.[60] Chalcones have previously exhibited 5-LO inhibition[61] and a more recent publication by Miyataka and co-workers looked at the biological effects of a series of fluorinated chalcones.[62] They found that almost all of the chalcones they made had potent 5-LO inhibitory properties, although the inclusion of fluorine in the compounds was not seen to have any great effect on their biological activity when compared to the non fluorinated compounds. The same chalcones were then tested for cytotoxicity against a range of cells and some were found to be active.

In particular compound **32**, the most active, was screened against a HCC panel of 39 cell lines. The results showed that **32** had a similar overall effect on the cells to the vinca alkaloid vincristine, a known chemotherapy drug whose mode of action is tubulin inhibition (although the vinca alkaloids are active at a different tubulin binding site to that of colchicine and the chalcones described previously). Chalcone **32**, however, was not shown to exhibit any tubulin-binding effects when tested.

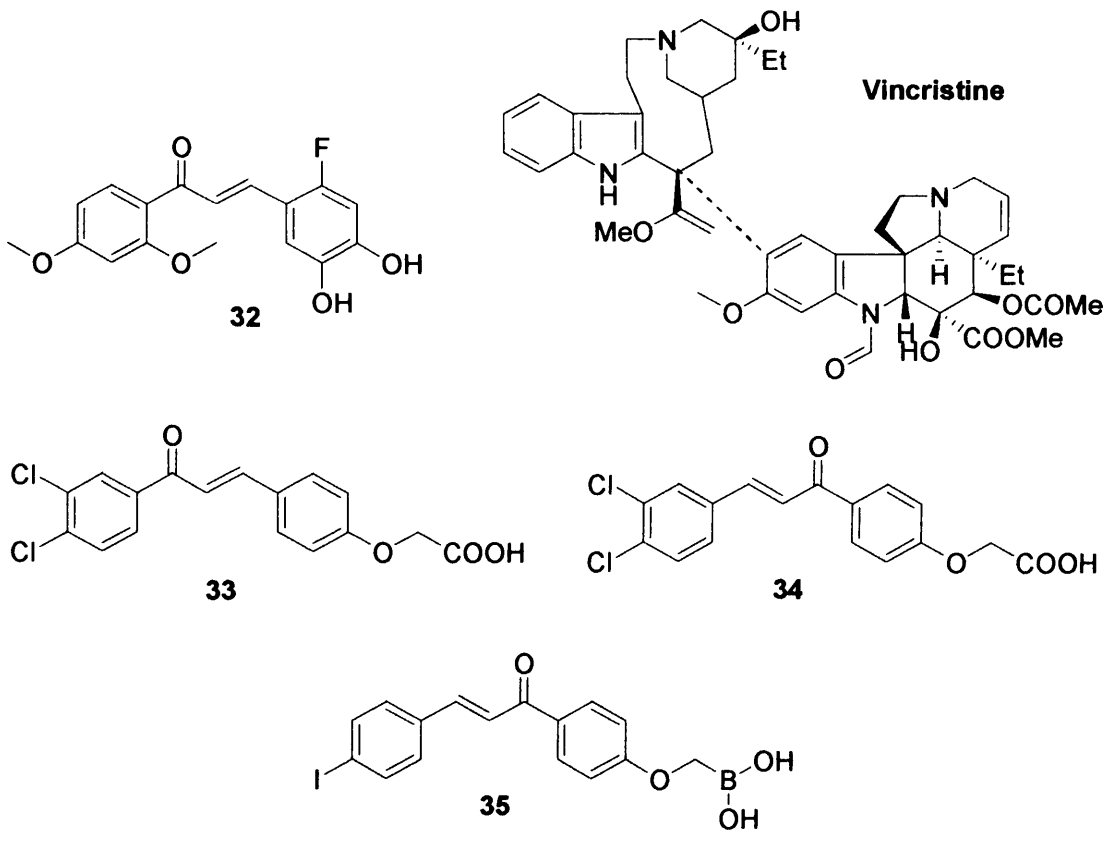


Figure 2.10 – Anticancer chalcones.

Yet another reported target for anticancer chalcones is the p53 gene. This is inactivated by binding to the MDM2 protein, which is over expressed in cancer cells, preventing apoptosis and allowing cells to divide uncontrollably.[63] Some chalcones, such as **33** and **34**, have been shown to bind to the MDM2/p53 complex,[64] releasing p53 and allowing the cell to continue its normal cycle.

The chalcones **33** and **34** are not very selective, however, and kill both cancerous and normal cells. Kahn *et al.* have synthesised and tested a range of chalcones in which the carboxylic acid of the above chalcones was replaced by a boronic acid in the hope that they would prove more selective.[65] They found that many of these, **35** in particular, were up to ten times more toxic towards malignant cells than healthy cells.

Despite the above anomalies, it does appear from the literature that most cytotoxic chalcones act through tubulin binding. Tubulin itself is a heterodimer, consisting of two subunits called α-, and β- tubulin which link together to form the heterodimer. This dimer can couple together

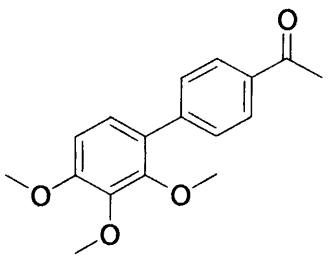
to make profilaments consisting of alternating α and β units, 12 or more profilaments can then further link together to make pipe-like structures called microtubules.

These structures have a + and a – end, with tubulin dimers constantly adding to the + end and being removed from the – end. Microtubules play an important role in a number of biochemical processes vital to cell life, one of these is the formation of the mitotic spindle, without which mitosis would not be able to take place.[66]

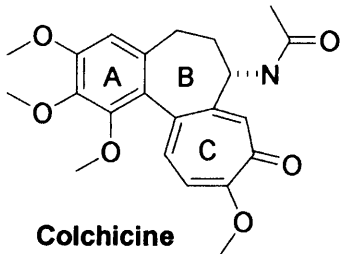
The tubulin molecule has three known binding sites, which are identified by the natural products which are known to bind to them: Taxol® and its derivatives bind to one site and prevent the depolymerisation of microtubules,[67] vinca alkaloids such as vincristine bind to another site, and colchicine binds to the third.[68]

Colchicine is an alkaloid extracted from the seeds of *Colchicum autumnale*, the autumn crocus or meadow saffron. It is known to bind very strongly to the tubulin dimer, resulting in distortion of the secondary structure and inhibiting microtubule formation. Colchicine has been used as a treatment for gout for centuries, *Colchicum autumnale* is described in the *De Materia Medica*, a pharmacopoeia used by the Romans it the first century AD.[69] It is believed that inhibition of microtubule formation prevents a cellular process called amoeboid motility and this in turn prevents leukocyte migration, which is a response to crystallisation of excess uric acid in the blood, believed to be the cause of gout.[70] It has also been considered as a chemotherapy drug but has proved too toxic for clinical use. SAR studies on the molecule in the hope that will lead to the design of less toxic tubulin inhibitors have been abundant.[71]

Andreu and co-workers carried out two detailed studies on the binding of colchicine to tubulin.[72,73] In the first they found that the B ring is not necessary for inhibition of tubulin polymerisation and synthesised a range of biphenyls in an effort to understand the role of the A and C rings. They found that those best able to bind to tubulin were compounds with a –COMe group in the 4' position of the C ring,[72] such as **36**.



36



Colchicine

*Figure 2.11 – Colchicine and related biphenyl **36**.*

They expanded on this two years later with a similar study on the role of the A ring.[73] From this study they concluded that, while the presence of the three methoxy groups of the A ring improves the strength of the drug-tubulin binding, this was not in fact because they bind to tubulin. They concluded instead that the role of these methoxy groups must be in maintaining the correct configuration of the biaryl system by preventing movement of the molecule within the binding site.

Other natural products which bind to the colchicine site of tubulin include Podophyllotoxin, Steganacin and Combretastatin.

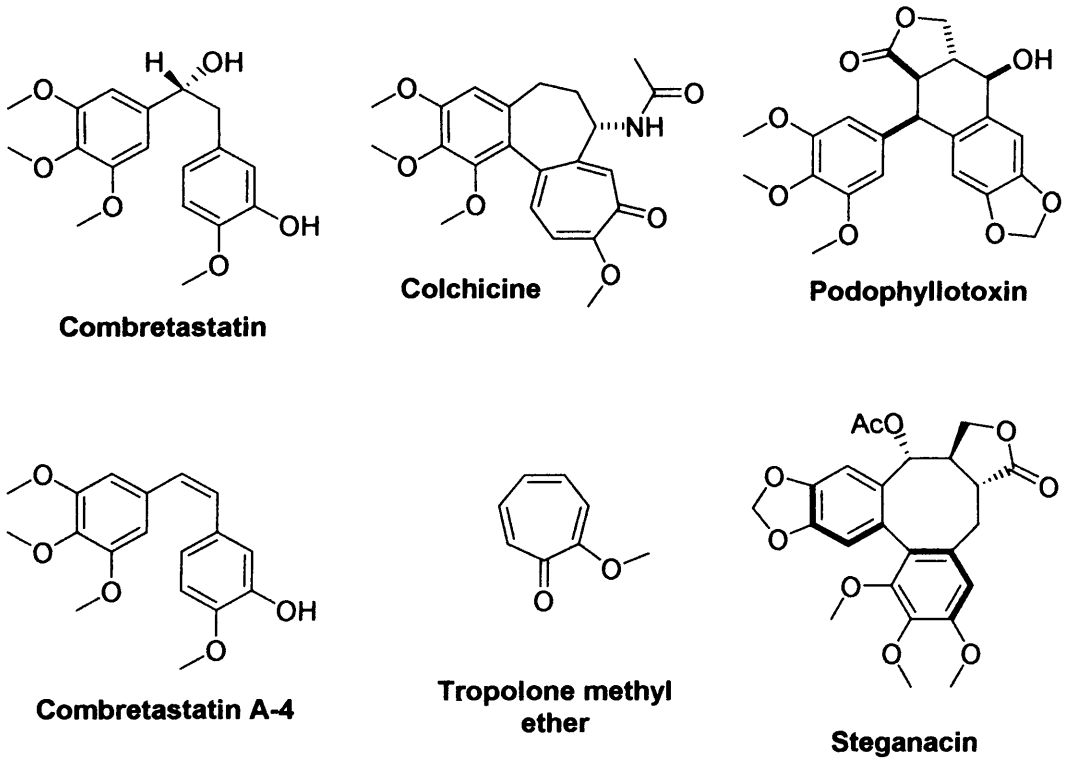


Figure 2.12 – Naturally occurring tubulin inhibitors.

Podophyllotoxin has been known as a pure compound for around 120 years, although it has been used in an impure form for much longer (the first recorded mention of it is in an English book called *Leech Book of Bald* dating from 900-950 AD in which roots of wild chervil and juniper needles, both of which contain podophyllotoxin derivatives, are used in salves for cancer[74]).

Podophyllotoxin is found in a number of plant species but it is most commonly extracted from a resin called podophyllin which comes from the roots of American mandrake (*Podophyllum peltatum*).[75] The pure compound was first isolated in 1880[76] and has since been the subject of numerous studies into microtubule inhibition. It has been found to have similar tubulin inhibitory properties to colchicine[77] and studies with radiolabeled colchicine showed that

colchicine and podophyllotoxin compete for tubulin binding, which would suggest that they share the same binding site.[78] However, it has also been shown that other molecules, such as tropolone methyl ether, compete with colchicine for tubilin binding but not podophyllotoxin.[79] It is believed, therefore, that the binding sites of podophyllotoxin and colchicine in fact overlap and that this area of overlap is on the β part on the tubulin heterodimer (the colchicine binding site is known to be close to the α tubulin-β tubulin link[80]).[81]

Steganacin and Combretastatin are much more recent discoveries. Steganacin and its derivatives are extracted from the east African tree *Stegantaenia araliacea* and, as with podophyllotoxin, it has been used in an impure form in the native medicines of the area for a long time[82] but was isolated as a pure compound in 1973[83] and was shown to display some antimitotic activity.

Structurally Steganacin is similar to Podophyllotoxin as well as colchicine with a three ring system containing one trimethoxybenzene ring and another with similar oxygenated substituents. It also has four chiral centres, as does podophyllotoxin.

Steganacin has been shown to be a competitive inhibitor of colchicine binding to tubulin, which suggests that like podophyllotoxin it shares the same binding site (or at least overlaps it), and is a slightly more potent inhibitor of microtubule formation than colchicine.[84] As well as inhibiting polymerisation, it also induces slow depolymerisation when added to microtubules that have formed.[85]

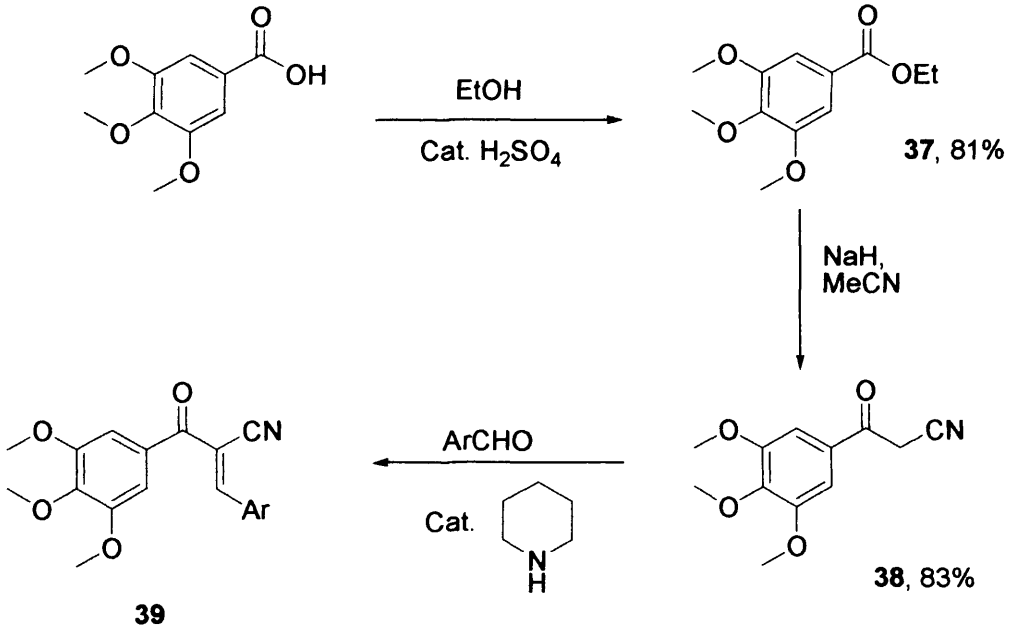
Combretastatin and its derivatives are found primarily in the bark of *Combretum caffrum*, a tree from south Africa and like podophyllotoxin, steganacin and colchicine have been used in traditional medicines before they were isolated as pure compounds.[86]

Again combretastatin shares structural features with colchicine (*Figure 2.12*) – the trimethoxybenzene ring is present in both and the B ring of combretastatin resembles the C ring of colchicine – but overall it is a much simpler compound.

Combretastatin itself is an effective inhibitor of tubulin, again binding to the colchicine binding site[87] but some of its derivatives, in particular combretastatin A4, are even more potent; combretastatin A4 is one of the most powerful tubulin inhibitors known.[88]

2.2.1 α-Nitrile Chalcones

Initially a series of chalcones of the type **39** with a nitrile group at the α position were synthesised and their cytotoxicities examined, these were made to probe the effects of *s-cis/s-trans* isomerism on cytotoxicity. They were made by Knoevenagel addition of a range of benzaldehydes to the keto nitrile **38**. This nitrile **38** was made by addition of the $^{-}CH_2CN$ nucleophile to ester **37**, which was made by standard esterification of 3,4,5-trimethoxybenzoic acid.



Scheme 2.4 – Synthesis of α-nitrile chalcones.

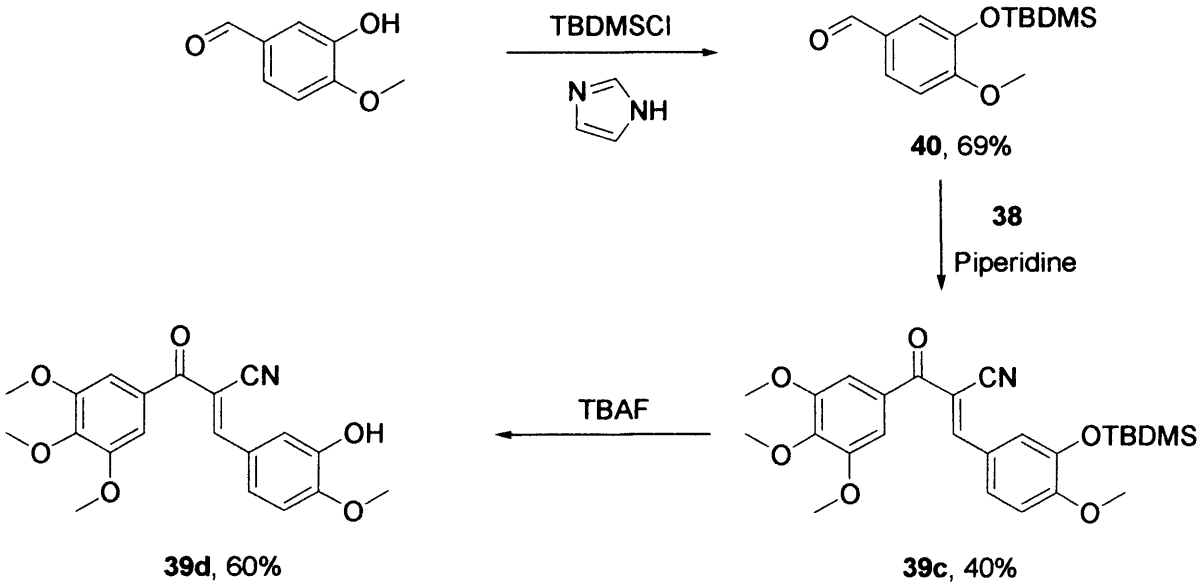
Their cytotoxicities are listed in *Table 2.1.* (Cytotoxicities are expressed as IC_{50} values, this gives the concentration of the compound needed to reduce cell growth by 50% in a particular cell culture. In the case of all cytotoxicities measured in this project, the cell line used was K562, human chronic myelogenous leukemia cell line.[89])

Ar group substitution	Compound number	%Yield	IC_{50} value (compound with IC_{50} greater than 10 μM are considered inactive)
3,4-Methylenedioxy	**39a**	35	>10 μM
4-Methoxy	**39b**	76	>10 μM
3-OTBDMS-4-methoxy	**39c**	40	>10 μM
3-Hydroxy-4-methoxy	**39d**	60	4.2 μM

3,4-Dimethoxy	**39e**	79	>10 μM
2,3,4-Trimethoxy	**39f**	76	>10 μM
4-Trifluoromethyl	**39g**	51	>10 μM
2-Fluoro-4-methoxy	**39h**	41	>10 μM
3-Fluoro-4-methoxy	**39i**	25	>10 μM
3-Bromo-4-methoxy	**39j**	52	>10 μM

Table 2.1 – Yields and cytotoxicities of α-nitrile chalcones.

In the case of **39d** the acidic hydroxy group was protected by conversion to the TBDMS ether prior to the Knoevenagel condensation (*Scheme 2.5*). This was done to prevent direct reaction between the phenol and the basic piperidine catalyst in the Knoevenagel reaction. The protecting group was removed afterwards using TBAF.



Scheme 2.5 – Phenol protection and deprotection.

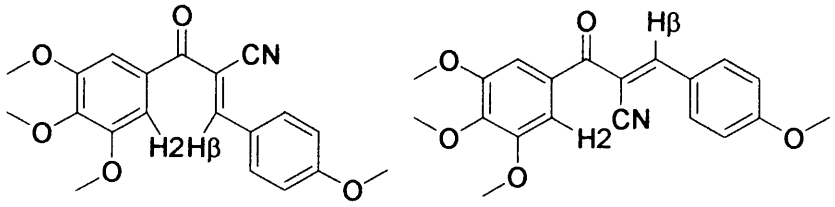
Structures of all these chalcones were confirmed by ^{1}H and ^{13}C NMR and, since they are all novel, full characterisation is given in chapter 7. For example the ^{1}H NMR of **39a** showed 2 singlet methoxy peaks at 3.74 and 3.76 ppm, a singlet at 5.93 ppm corresponding to the two methylenedioxy protons, the protons on the B ring appeared as two doublets at 6.74 ppm (J_{HH} = 8.1 Hz) and 7.61 ppm (J_{HH} = 1.5 Hz) corresponding to protons 5'' and 2'' respectively, each of which is coupled to proton 6'' (a double doublet at 7.27 ppm), the 2' and 6' A ring protons were a singlet at 6.99 ppm and the β proton was a singlet at 7.84.

Most of the chalcones were inactive, although the 3-hydroxy-4-methoxy analogue **39d** was significantly more cytotoxic than the others. This is consistent with previous findings within

the group but **39d** is still roughly 10^4 times less active than α-methyl **24** above (IC_{50} = 0.21 nM)[90] which is surprising given the similarities in the structures.

Although unfortunately none of the nitrile chalcones formed suitable crystals for their structure to be resolved, nOe experiments on chalcone **39b** revealed a 29% enhancement at proton Hβ when irradiated at proton H2/H6 (*Figure 2.13*). This suggests that, like chalcone **24** this compound adopts the s-*trans* conformation. Alpha nitrile chalcones are well known in the literature and most are assumed to adopt this structure, although, with the exception of some work by Currie *et al* on the UV/Vis spectra of α-nitrile chalcones[91] and similar compounds,[92] there is little evidence to support this.

It seems most likely, then, that the nitrile chalcones adopt the structure shown, although it remains unclear why they are so much less active than their methyl analogues.



s-*trans* 39b **s-*cis* 39b**

Figure 2.13 – s-cis/s-trans structures.

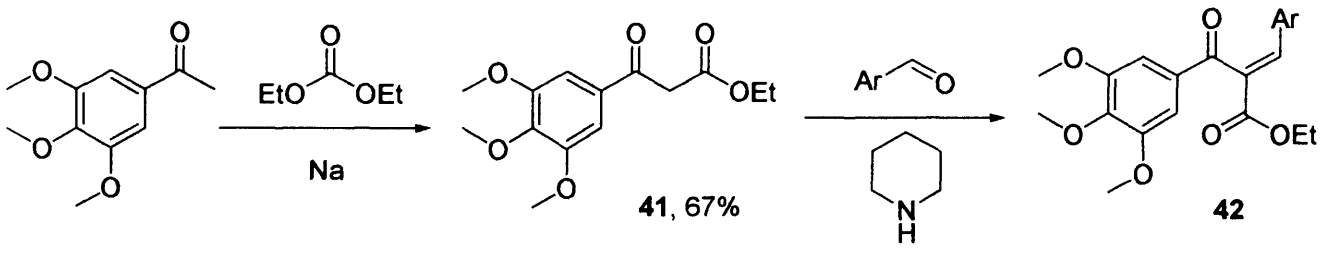
The nitrile group, while similar in size to the methyl group, does have very different electronic properties. The methyl group is weakly electron donating, whereas the nitrile is electron withdrawing. This may be the reason for the inactivity of the α-nitrile chalcones.

The CN group is also more polar, less hydrophobic than a methyl group and capable of acting as an H-bonding acceptor. It is possible, since a number of studies have shown that the 3-hydroxy-4-methoxy substitution pattern on the B ring seems to provide the maximum cytotoxicity and it is believed that this is a result of hydrogen bonding action of the phenolic OH group, that the nitrogen atom of the nitrile group, in this case, interferes with that process - either by binding intramolecularly to the OH group or intermolecularly to the biological target.

2.2.2 α-Ester Chalcones

The second series of chalcones synthesised were α-ethyl esters of the type **42**. Again these chalcones were made by Knoevenagel condensation of aryl aldehydes with the β-keto ester **41**,

which itself was made by addition of sodium 3,4,5-trimethoxyacetophenone enolate to diethyl carbonate (*Scheme 2.6*).



Scheme 2.6 – Synthesis of α-ester chalcones.

Once again these compounds were all novel and full characterisation is given in the experimental section. The ^{1}H NMR of **42a** showed the ethyl group as a triplet (1.24 ppm) and quartet (4.27 ppm) with a coupling constant of 7.1 Hz, three methoxy peaks as singlets at 3.80, 3.86 and 3.96 ppm, the B ring protons were two doublets (J_{HH} = 8.9 Hz) at 6.80 (*meta* positions) and 7.34 ppm (*ortho* positions), the *ortho* protons on A ring were a singlet at 7.25 ppm and the β proton a singlet at 7.94 ppm.

In this case, however, of the 10 aldehydes used, only 5 resulted in a chalcone product. The chalcones which were formed were tested for biological activity, the results shown in *Table 2.2*.

Ar group substitution	Compound number	%Yield	IC_{50} value (compound with IC_{50} greater than 10 μM are considered inactive)
4-Methoxy	**42a**	11	>10 μM
3-OTBDMS-4-methoxy	**42b**	57	4.29 μM
3-Hydroxy-4-methoxy	**42c**[a]	70	0.87 μM
3,4-Dimethoxy	**42d**	35	>10 μM
2,3,4-Trimethoxy	**42e**	48	>10 μM

a) As for the nitrile chalcones **42c** was made by deprotection of **42b**.

Table 2.2 – Yields and cytotoxicities of α-ester chalcones.

The most active is, again, the 3-hydroxy-4-methoxy compound, **42c**, as one would expect. What is unusual this time is that the second most active chalcone is **42b**, the protected version

of **42c**. The unexpectedly high activity of this may be due to loss of the protecting group from the sample before or during the bioassay so that in fact the activity seen is that of **42c**.

42c is 10 fold more active than its nitrile analogue, **39d**, but still much less active that the α-methyl chalcone **24**. In the case of **42c**, crystals were grown of suitable quality for X-ray analysis and showed that, while the molecule does adopt the s-*trans* conformation, it has an *E* configured double bond. This is surprising given that the steric strain involved in this structure means that the molecule is twisted out of the flat geometry which normally makes chalcones so stable and allows them to resonate. However it is not unknown for α-ester chalcones to adopt this sterically hindered conformation[91] and it does explain the biological inactivity which is observed.

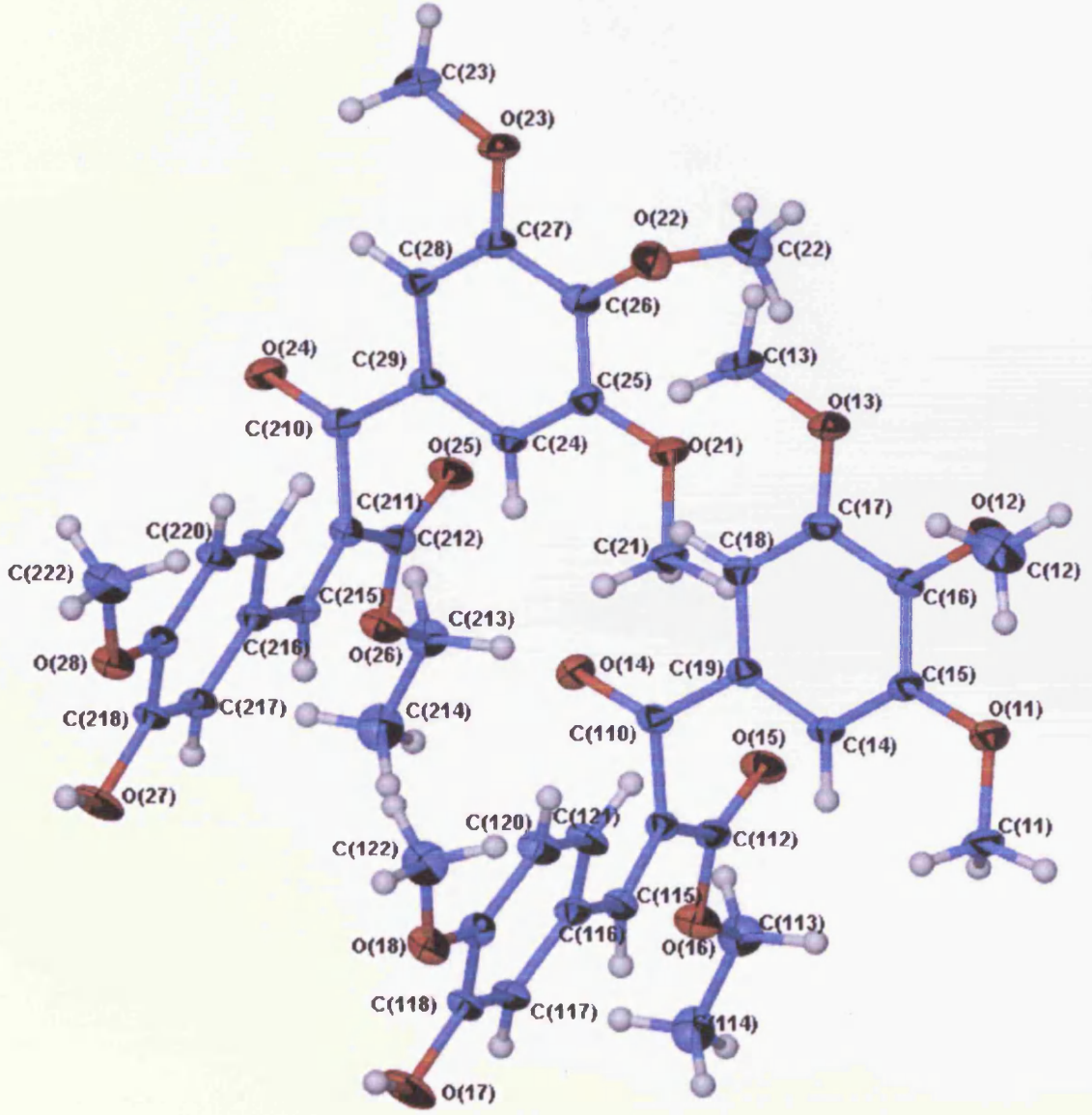


Figure 2.14 – X-ray crystal structure of ***42c.***

2.3 Summary and Conclusions

The synthesis of two series of chalcones and assessment of their biological properties has been described. Neither α-nitrile nor α-ethyl ester chalcones have shown very promising anticancer activity, even when substituted with the 3-hydroxy-4-methoxy B-ring, which usually renders chalcones most cytotoxic.

In the case of α-ethyl ester chalcones this inactivity is easily explained as a result of their unusual structure. In the case of α-nitrile chalcones, it is believed to be a result of the electronic properties of the nitrile group, although in the absence of X-ray data, structural effects cannot be ruled out.

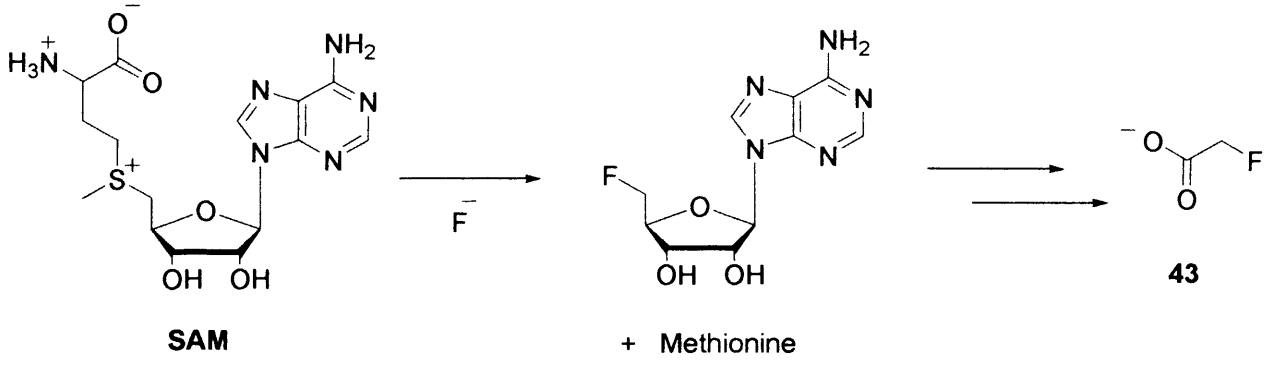
Chapter Three

3.1 Introduction

Despite being the most abundant halogen in the earth's crust, fluorine is exceedingly rare in the field of biochemistry, only 6 unique categories of fluorinated natural products have ever been isolated and almost nothing is known about the biochemistry of fluorination.

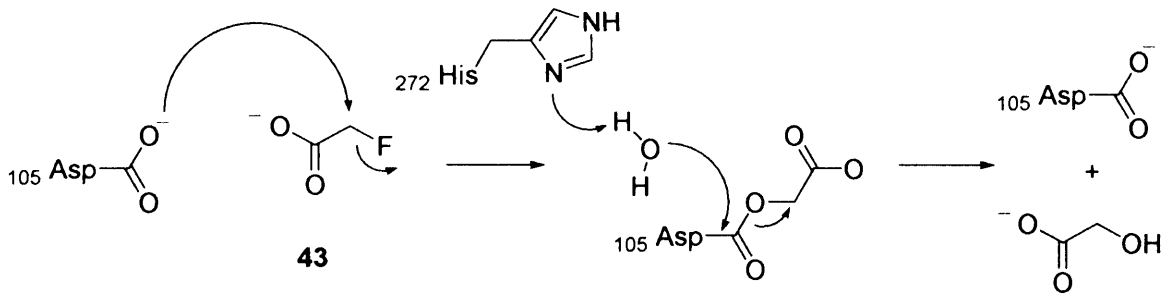
The most common naturally occurring fluorinated compound is fluoroacetate (**43**). This is found in a number of plant species in small concentrations, although some have been found to accumulate it in sufficient quantities to make them toxic. For example, the highest known concentration of fluoroacetate in a plant is in *Dichapetalum braunii* - a shrub found in Tanzania whose seeds contain up to 8000 ppm fluoroacetate[93] and many other toxic fluoroacetate accumulators have been found in Australia.[94]

O'Hagan *et al.* have recently isolated an enzyme from *Streptomyces cattleya* called 5'-fluoro-5'-deoxyadenosine synthase which was shown by crystallographic analysis to synthesise fluoroacetate. The reaction seems to involve attack by a fluoride anion at the 5' position of S-adenosyl-L-methionine (SAM), releasing L-methionine and forming 5'-fluoro-5'-deoxyfluoroadenosine, which is then converted to fluoroacetate by an as yet unknown mechanism (*Scheme 3.1*).[95]



Scheme 3.1 – Biosynthesis of fluoroacetate.

Animal species in areas where such plants are common tend to show unusually high tolerance for fluoroacetate, particularly herbivores; in fact the caterpillar *Sindrus albimaculatus*, which feeds on a fluoroacetate-containing plant called *Dichapetalum cymosum*, stores up the fluoroacetate and uses it as a defence mechanism.[96] Enzymes involved in the metabolism of fluoroacetate have been isolated from bacteria such as *Moraxella sp*[97] and are believed to act as shown in *Scheme 3.2*.



Scheme 3.2 Metabolism of fluoroacetate.

Aspartate-105 acts as nucleophile, displacing fluoride in a S_N2 process to leave an ester, then histidine-272 deprotonates a water molecule and the resulting hydroxide anion hydrolyses the ester releasing glycolate.

The reason fluoroacetate is normally toxic is that it is converted *in vivo* to (2*R*,3*R*)-fluorocitrate (**44**) by substituting for acetate in the Krebs cycle. Unfortunately, of the four isomers of fluorocitrate, the only one produced in this process is (2*R*,3*R*)-fluorocitrate which is also the only one which is toxic (*Figure 3.1*).[98] Its toxicity is believed to be due to its inhibition of aconitase and other enzymes involved in the transport and metabolism of citrate.[99]

In fluoroacetate-accumulating plants, however, fluoroacetate is metabolised differently, it is either anabolised into long chain ω–fluoro fatty acids[100] such as ω-fluorooleic acid, **45** or catabolised into volatile organics. Although little is known about the latter process, fluoroacetate in this case is believed to leave the plant as either fluoroacetone or fluoroacetaldehyde.[101]

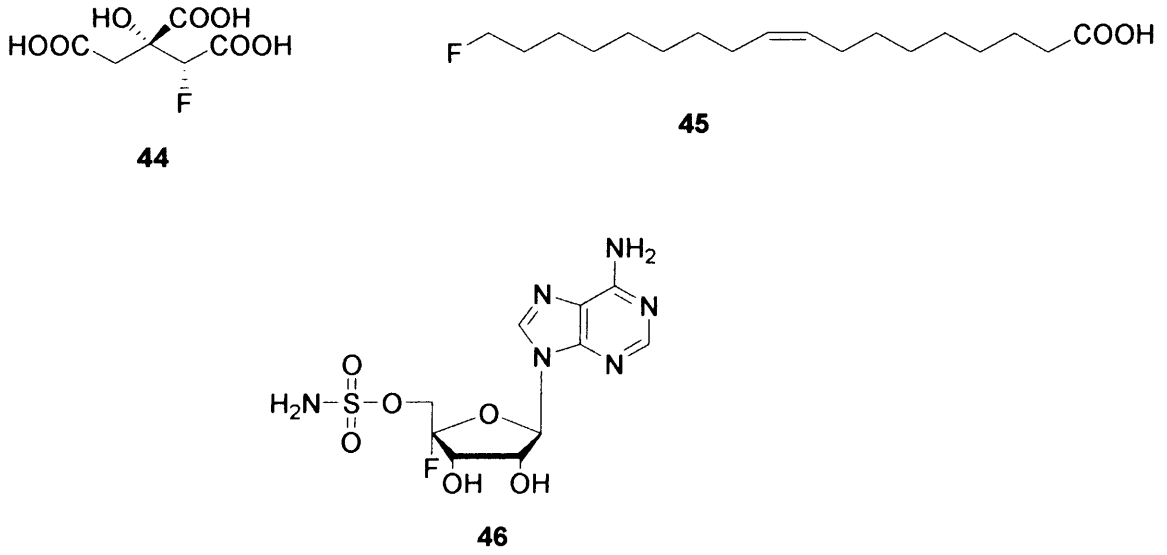


Figure 3.1 Fluorinated natural products.

Possibly the most interesting biological organofluorine compound is nucleocidin **46**, a natural product isolated from *Streptomyces calvus*, which was found in an Indian soil sample. This has some antibiotic activity but has proven too toxic for clinical use.[102] Surprisingly, it contains a fluorine atom on the ribose ring in a position which suggests that it did not come from fluoroacetate. Unfortunately, however, recent attempts to isolate more of the compound from freeze-dried samples of the bacteria have failed and so further investigation into the biosynthesis of this compound has been delayed until more of the bacteria can be collected.[103]

Despite being so rare in nature, fluorinated molecules often have very useful biological properties and have recently received a great deal of attention as drug candidates. The fluorine atom has a Van der Waals radius of 1.47 Å, which is in between that of hydrogen (1.20 Å) and oxygen (1.52 Å).[104] This, along with it's high eletronegativity (4.0) makes fluorine a useful mimic for a number of organic functional groups such as =O, -H and –OH.

Element (X)	Van der Waals radius (Å)	CH_2-X Bond length (Å)	CH_2-X Bond energy (kcal/mol)	Electro-negativity
H	1.20	1.09	99	2.1
O	1.52	1.43	85	3.5
F	1.47	1.39	116	4.0

Table 3.1 Relative properties of fluorine, hydrogen and oxygen.

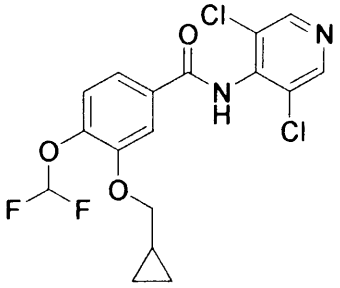
Replacement of hydrogen with fluorine results in only minor steric changes[105] but does have a significant effect on the electronic properties of the molecule, changing pK_a, dipole moments and stability of neighbouring groups. Since the C-F bond is so much stronger that the C-H bond, it is much more resistant to attack by cytochrome P450 and hence this substitution is often used to improve the biological half-life of drug candidates.[106]

Fluorine is also often used to replace the hydroxyl group, as it is believed to be able to act as a hydrogen bond acceptor. Although this has been disputed;[107] the F...H bond is significantly weaker than the O...H (2.38 kcal/mol and 5 kcal/mol respectively).

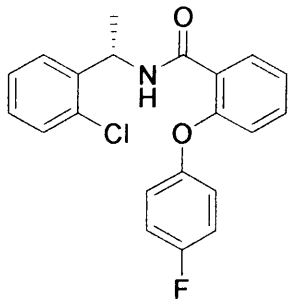
In addition to a single fluorine atom being used in drug candidates, small fluorinated groups can also act as isosteres for existing groups; 2,6-difluorophenol group has been used to replace carboxylic acid groups,[108] CF_2 has been used to replace CH_2[105] as well as O in phosphate esters[109] and the CF_2H group has replaced OH as a H-bond donor.[110] The highly lipophilic CF_3 group is also frequently used in drug candidates as a mimic for isopropyl groups,[111] as well as ^{t}butyl and phenyl groups.[112]

When fluorine is introduced into drug candidates it alters the steric, electronic and lipophilic properties of the molecule and in many cases has been shown to improve biological activity as well as metabolic properties.[113] There are numerous fluorinated drugs currently on the market or in development for treatment of a wide range of conditions. [114]

Roflumilast (**47**) is a fluorinated derivative of Piclamilast which inhibits phosphodiesterase enzyme 4 (PDE4) and is currently in clinical trials as a treatment for asthma (*Figure 3.2*).[115] The related amide **48** has similar anti-inflammatory properties and in particular shows selectivity towards certain subtypes of PDE4.



47

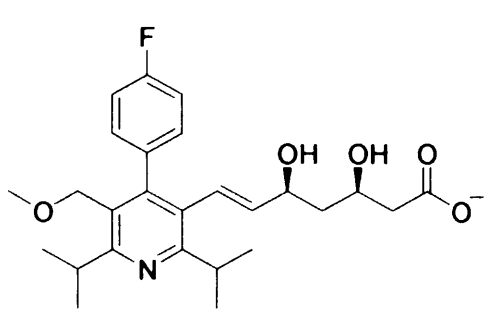


48

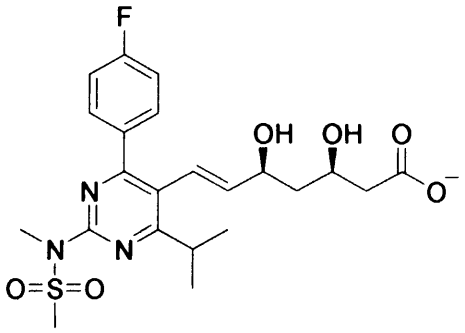
Figure 3.2 Fluorinated anti-inflammatory drugs.

Fluorinated drugs have found use in treatment of heart disease, with Cerivastatin (**49**) and Rosuvastatin (**50**) being found to reduce low-density lipoprotein cholesterol (LDL-C) levels in hypercholesterolaemic patients' blood (*Figure 3.3*). Although **49** has been withdrawn as a drug due to adverse side effects on muscle.[116]

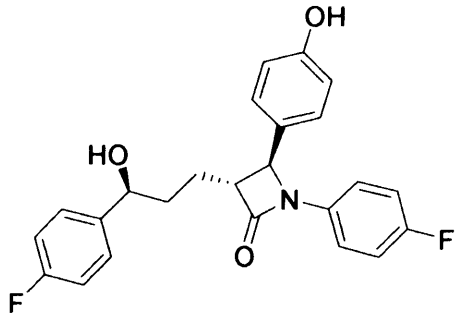
Ezetimibe (**51**) works by inhibiting cholesterol excretion from the gall bladder[117] and BMS 201038 (**52**) inhibits Microsomal triglyceride transfer protein (MTP), which is used in the transport of cholesterol.[118]



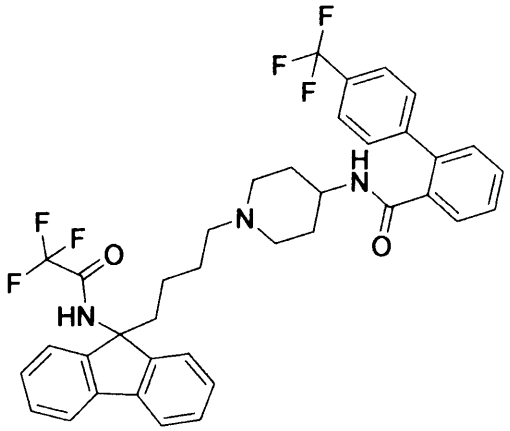
49



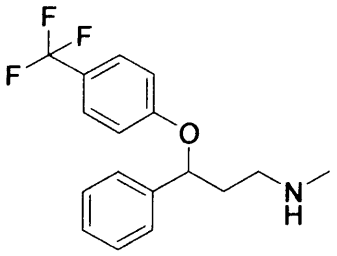
50



51



52



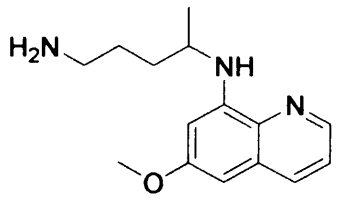
53

Figure 3.3 – Fluorinated drugs.

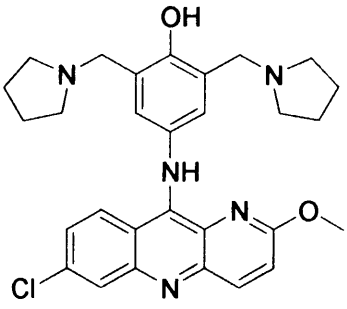
Prozac (Fluoxetine, **53**) is a selective serotonin reuptake inhibitor which lowers the level of the neurotransmitter serotonin in the brain, improving mood and is a popular treatment for depression, obsessive-compulsive disorder and severe shyness.[119]

A few efforts have been made to design fluorinated anti-malarials to replace drugs such as Primaquine (**54**) and Pyronaridine (**55**) which are encountering increasing resistance. Compound **56** is a fluorinated derivative of Primaquine, in which a fluorine atom was incorporated in an attempt to hinder *in vivo* conversion into more toxic metabolites.[120] Pyronaridine analogues **57** and **58** have both shown promising antimalarial activity, in fact **57** is more active than **55** but also more toxic, whereas **58** has more tolerable toxicity but reduced activity (*Figure 3.4*).[121]

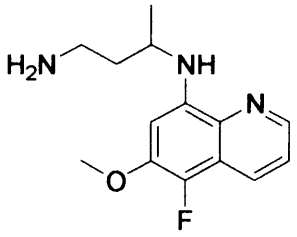
Other examples of fluorinated anti malarials include **59** which is novel and unrelated to any existing drugs and should prove very useful in combating drug-resistant malaria strains.[122]



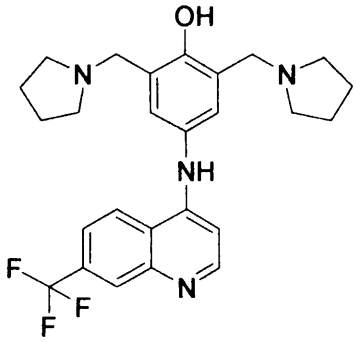
54



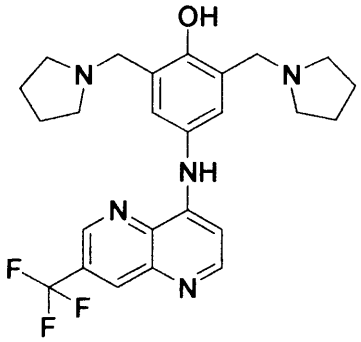
55



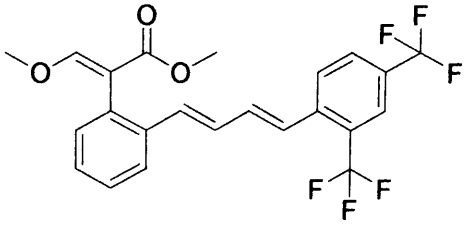
56



57



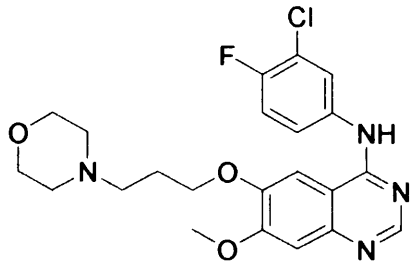
58



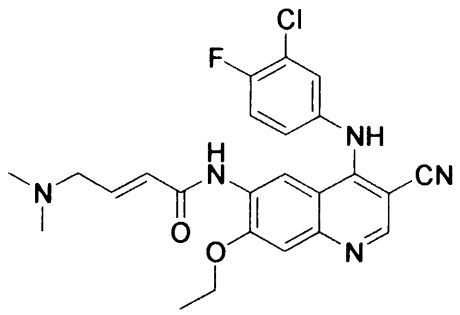
59

Figure 3.4 – Fluorinated drugs.

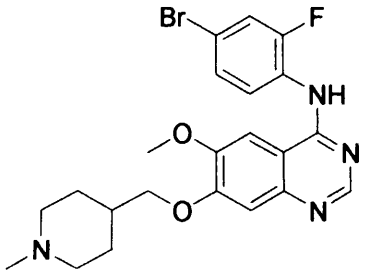
Fluorine has also found much use in anticancer drugs. Iressa (**60**) is a tyrosine kinase inhibitor which blocks signal pathways key to the mitosis of cancer cells.[123] Derivatives of this such as **61** and, in particular **62**, have been rationally designed to improve physical properties.[124] In all these cases the biological half-life of the drug is improved by the presence of the fluorine hindering metabolism.[125]



60



61

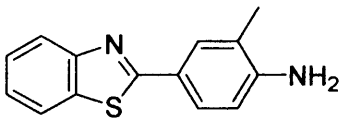


62

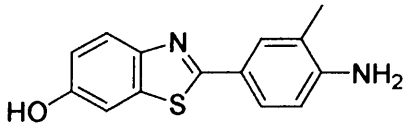
Figure 3.5 – Fluorinated anticancer drugs.

Benzothiazoles such as **63** (*Figure 3.6*) are another class of anticancer agents designed to inhibit tyrosine kinases. These display an unusual dose-response relationship in certain cell lines; at low (nanomolar) concentrations they are cytotoxic but at micromolar concentrations they cause what is called a second growth phase (SGP).[126] This has been attributed to the metabolism of the drugs by sensitive cells resulting in a 6-hydroxylated metabolite **64** which encourages cell growth.

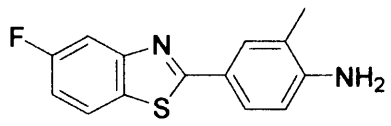
In an attempt to block this metabolism, Hutchinson *et al.* synthesised a series of fluorinated analogues and their activities and metabolic profiles were analysed. They found that compounds with a fluorine at the 5 position and a halogen or methyl group at the 3' position were the most cytotoxic of the fluorinated benzothiazoles and also that the presence of a 5-fluoro group blocked the oxidative metabolism at the 6 position,[127] this enabled them to confirm earlier suspicions that this metabolism was responsible for the deactivation of the non-fluorinated compounds. The most active and metabolically stable candidate was found to be **65**.



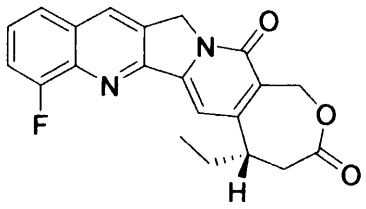
63



64, 6-hydroxy metabolite of **63**.



65



66

Figure 3.6 – Anticancer benzothiazoles.

Another target for anticancer study is the enzyme Topoisomerase I, against which fluorinated Camptothesin analogue **66** has been shown to display high activity. [128]

A less conventional treatment of cancer, called photodynamic therapy (PDT), involves the use of a mixture of porphyrins known as hematoporphyrin derivatives (HpD). This mixture, consisting of protoporphyrin (**67**), Hematoporphyrin (**68**) and 3-vinyl-8-(1-hydroxyethyl)-deuteroporphyrin (**69**) as well as a number of other minor components (*Figure 3.7*), can bind *in vivo* to tumour cells and, when irradiated, fluoresces red enabling detection of cancer at an early stage.[129] HpD also contains some porphyrins which generate active oxygen species such as peroxide, superoxide and hydroxyl radical when photosensitised.[130] These highly reactive species can oxidise and kill cancerous cells and thus be used in treatment as well as detection of cancer.[131]

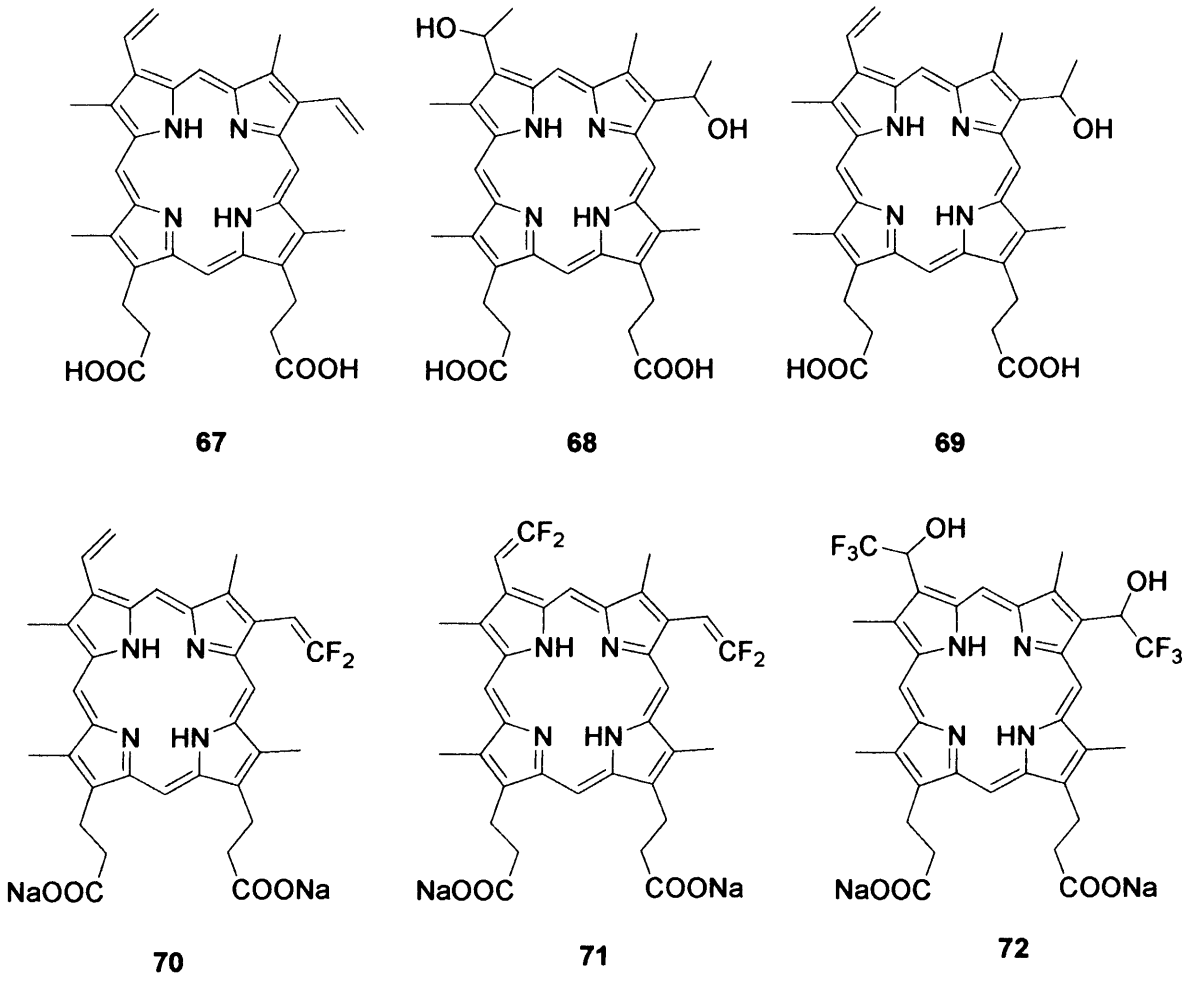


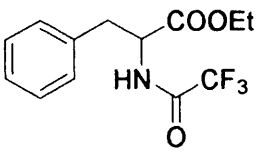
Figure 3.7 – HpD and fluorinated porphyrins.

The problem with HpD itself is that it is a mixture and is light-sensitive. The search for alternative PDT drugs has led to the investigation of fluorinated porphyrins.

Replacement of the vinyl groups of **67** with difluorovinyl groups led to synthesis of **70** and **71** which were shown to selectively bind to specific types of cancer cells – **70** was localised to gastric cancer cells, whereas **71** to rat ascite hepatoma cells. Derivatives of **68** such as **72** were found to be taken up effectively by human liver cancer cells.[132]

The discovery was made by Yamazaki and co-workers that the asymmetric hydrolysis of certain esters by cancer cells resulted in a slightly different enantiomeric ratio in the products compared to the same esters hydrolysed by normal cells.[133] This was attributed to different combinations of esterases in cancer/normal cells, some of which are selective towards *S* enantiomers and others towards *R* enantiomers so that a racemic mixture of a chiral ester may be hydrolysed to give a different enantiomeric excess by one cell compared to another. In theory there could even be a reversal of chirality between cancer cells and healthy cells. They

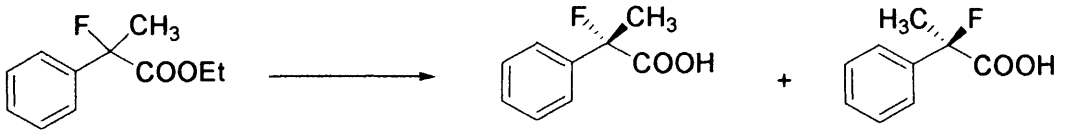
found that with the fluorinated ester **73** there was a particularly large change in e.e. of acid product (% e.e. differing by 6.8) in different types of healthy brain/brain tumor cells.[134]



73

Figure 3.8 – Fluorinated ester.

This led them to further investigate the effect with the intention of designing a fluorinated ester prodrug which would be hydrolysed in cancer cells to give the active enantiomer of a chemotherapy drug but at the same time hydrolysed in normal cells to give an inactive enantiomer. They found that in the case of **74** not only did the e.e. vary depending on the particular cell used to hydrolyse the ester, but in some cases it was reversed (*Scheme 3.3*).[135]



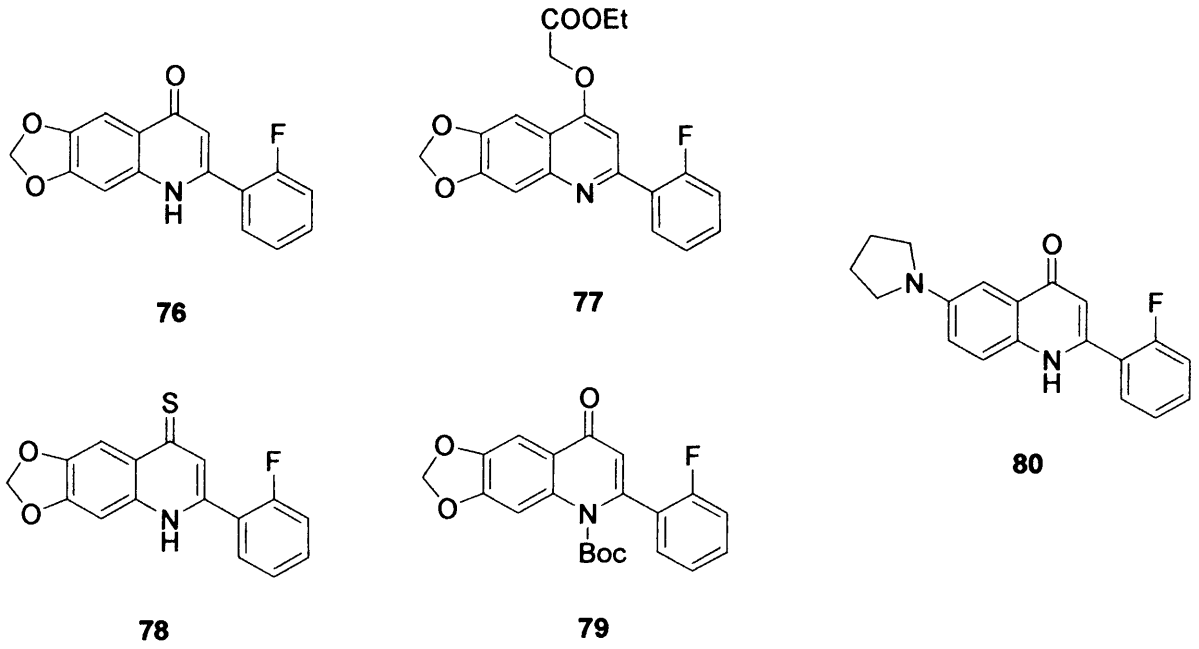
74 *S*-**75** *R*-**75**

Cell type	Configuration of **75**, (% yield)	Enantiomeric excess (%)
Anr4 (cancer)	*S*, (18)	69.3
Anr13-1 (cancer)	*S*, (9)	64.8
H4-II-E (cancer)	*S*, (9)	33.1
McA-RH7777 (cancer)	*R*, (40)	54.8
Liver (healthy)	*R*, (26)	34.3

Scheme 3.3 – Stereospecific enzymatic hydrolysis of esters in different cells.

As mentioned in chapter two , 2-phenyl-4-quinolones show reasonable cytotoxicity and tubulin inhibition. SAR studies by Lee and co workers led to the discovery of the fluorinated compound **76**, which demonstrated good *in vivo* as well as *in vitro* activity.[136] Further studies into the effects of the ketone and amine groups in the molecule on its activity showed that

conversion of the ketone into an enol ether (as in **77**) destroyed the cytotoxicity of the molecule as well as its ability to inhibit tubulin, as did replacement of the ketone with a thioketone (as in **78**).[137] Replacement of the amino hydrogen with a BOC group (**79**) overall reduced the tubulin inhibition, although **79** was more potent than **76** against some sensitive cancer cells, possibly due to conversion into a more cytotoxic metabolite. They found the most potent of the 2-phenyl-4-quinolones to be fluorinated **80**.

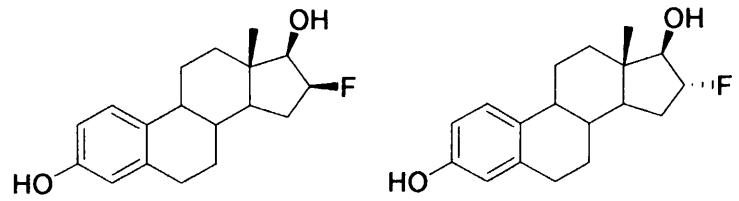


76 **77** **80**

78 **79**

Figure 3.9 – Fluorinated anticancer quinolones.

In addition to the beneficial medicinal properties incorporation of ^{19}F can impart, the isotope ^{18}F can be used in positron emission tomography (PET). This enables the drug to be followed through absorption, metabolism and excretion within the body and can offer a wealth of real time data on the *in vivo* life of the drug.[138] Although this tool is limited by the short half-life ($t_{1/2}$ = 109.6 mins) of ^{18}F which makes synthesis of drugs containing ^{18}F very difficult,[139] nevertheless there are some reagents available that can deliver both nucleophilic ^{18}F synthons (such as $Bu_4N^{18}F$, $K^{18}F$, $Cs^{18}F$, $Br^{18}F$ and $I^{18}F$) and electrophilic synthons (such as $^{18}F_2$ and $CH_3COO^{18}F$).[140] These enable ^{18}F to be incorporated into some drug molecules, in particular ^{18}F substitution in steroids such as estradiol leads to **81** (*Figure 3.10*), which is a very useful tool in imaging of breast cancers.[141]



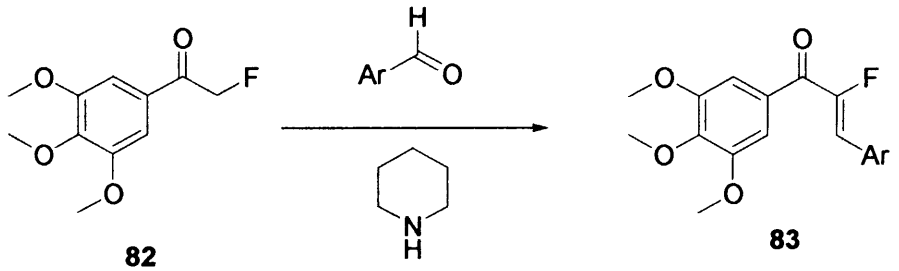
81a **81b**

Figure 3.10 – Fluorinated estradiol.

3.2.1 α-Fluoro Chalcones

Following the investigation into α-nitrile and α-ester chalcones, including some with 2-fluoro-4-methoxy, 3-fluoro-4-methoxy and 4-trifluoromethyl B rings, a series of chalcones with a fluorine atom in the alpha position were made with the intention of investigating the effects of this substitution on both the biological activity and the structure of the chalcones. In particular the effect of the alpha fluorine atom on the s-*cis* / s-*trans* conformation was of interest.

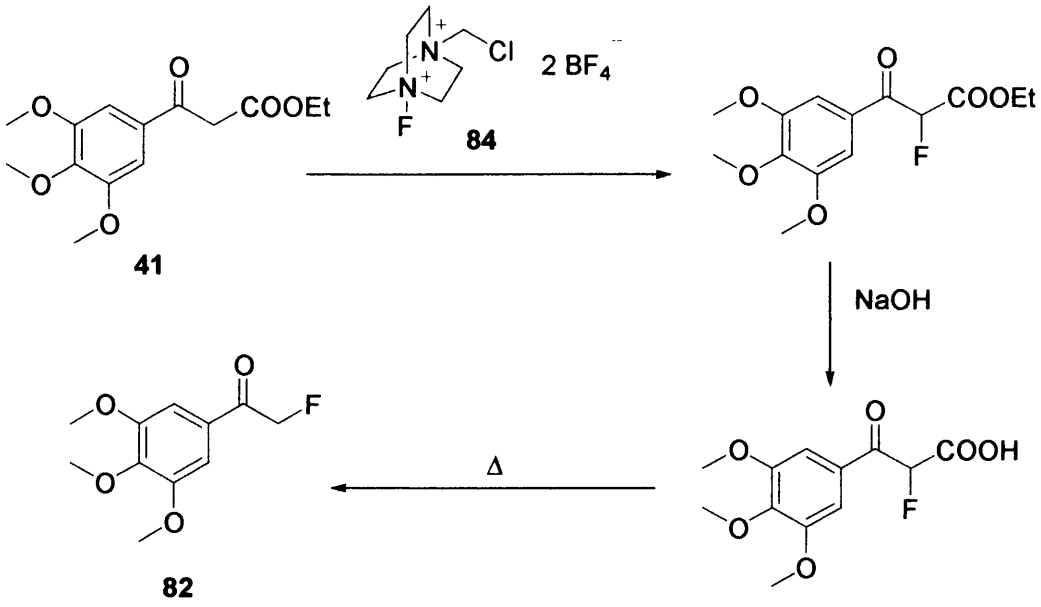
Synthesis of these chalcones (**83**) proved to be more problematic than was first expected. The intention was, again, to synthesise the ketone (**82**) and add the aryl aldehydes via the same Knoevenagel reaction as had been used in chapter two (*Scheme 3.4*).



82 **83**

Scheme 3.4 – Knoevenagel synthesis of α-fluoro chalcones.

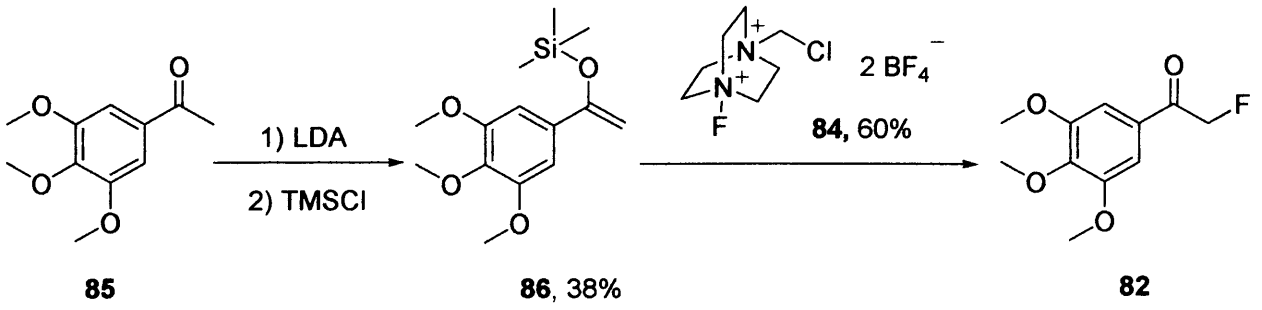
Initially the synthesis of **82** from β-ketoester **41** (which was used in chapter 2.2.2 to make the ester chalcones) was attempted using the Selectfluor™ reagent **84**[142], as shown in *Scheme 3.5*.



*Scheme 3.5 – Synthesis of **82** via electrophilic fluorination of **41**.*

In this attempt, however, the fluorination step proved inefficient and resulted in a mixture of mono and di-fluorinated products as well as unreacted starting material. This has been seen before when fluorinating this type of compound using Selectfluor™.[143]

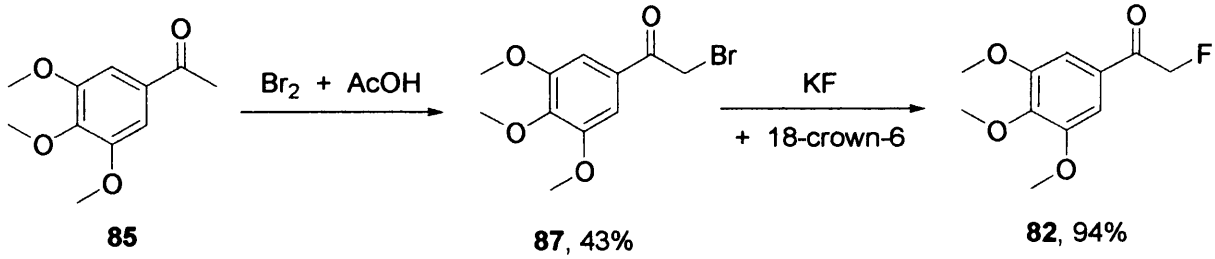
So the silyl enol ether **86** was made by generation of the enolate of ketone **85** and protection with TMS chloride (38%), this is a much more nucleophilic species than the ester **41** and, under mild conditions, is only able to react with one equivalent of F^+. Reaction with Selectfluor™ was carried out according to *Scheme 3.6*.



Scheme 3.6 – *Synthesis of **82** via electrophilic fluorination of silyl enol ether **86**.*

This time the fluorination step was successful, although the yield of **82** was moderate (60%). However, the product had a very similar retention time on a column to the ketone **85**, which was formed in the work up by hydrolysis of **86** so that less than 10% yield of the product overall was isolated as pure material.

So a third method was employed involving the oxidative bromination of ketone **85** using bromine in acetic acid, followed by fluorination of the resulting bromoketone **87** with potassium fluoride in the presence of 18-crown-6 catalyst (*Scheme 3.7*):



85 **87**, 43% **82**, 94%

*Scheme 3.7 – Synthesis of **82** via bromination of **85**.*

This time the fluoroketone **82** was made in good yield (41% overall). Analysis of the ^{1}H NMR spectrum showed that the molecule contained two methoxy peaks at 3.84 and 3.85 ppm, the two α protons were a doublet (J_{HF} = 47 Hz) at 5.49 ppm and the aryl protons, a singlet at 7.07 ppm. High resolution mass spectrometry showed a $[M+H]^+$ molecular ion at 229.0874, within acceptable limits of the structure shown.

The α–fluorochalcones **83** were then made via Knoevenagel condensation with the benzaldehydes (*Scheme 3.4*). The yields, cytotoxicities and, for the most cytotoxic chalcones, tubulin inhibition assays are shown in *Table 3.2*. Cytotoxicities are expressed as IC_{50} values, as described in chapter two, as are tubulin inhibition values.

The tubulin inhibition assay is the easiest way to see the effects of a compound on the polymerisation of tubulin *in vitro*. Tubulin, if it is over a critical concentration and the temperature is >30 °C, polymerises in the presence of GTP and Mg^{2+}. The tubulin assay used here involves warming a mixture of tubulin, GTP and the test compound from 0 °C to 37 °C. Formation of the microtubules, which result from tubulin polymerisation, causes the solution to become turbid and increases the optical density, which is proportional to the concentration of microtubules present in the solution and can be measured. By plotting the concentration of the test compound against the degree of inhibition of tubulin assembly, therefore, a value for the concentration needed to inhibit polymerisation by 50% (i.e. a value of IC_{50}) can be calculated.[144]

Where IC_{50} > 10 μM, the compound is considered inactive.

Ar group substitution	Compound number	Yield (%)	Cytotoxicity IC_{50}	Tubulin inhibition IC_{50}
3,4-Methylenedioxy	**83a**	84	0.8 μM	N/A
4-Methoxy	**83b**	68	0.39 μM	4.6 μM
3-Hydroxy-4-methoxy	**83c**	75	13.7 nM	0.6 μM
3,4-Dimethoxy	**83d**	23	1.21 μM	N/A
2,3,4-Trimethoxy	**83e**	86	>10 μM	N/A
2-Fluoro-4-methoxy	**83f**	74	1.19 μM	N/A
3-Fluoro-4-methoxy	**83g**	28	0.77 μM	N/A
3-Bromo-4-methoxy	**83h**	18	6.0 μM	N/A

Table 3.2 – Yields, cytotoxicities and tubulin inhibition assays for α-fluoro chalcones.

Proton NMR analysis of all these chalcones showed a coupling constant $J_{H\text{-}F}$ of between 36 and 43 Hz for the vinyl proton Hβ, corresponding to the *trans* configuration shown (*cis* F-H coupling constants are <20 Hz).[145] Full structural confirmation is given in the case of the α-fluorochalcone **83c**, for which X-ray crystal analysis showed the molecule adopting the s-*trans* conformation (*Figure 3.11*). This is surprising because the s-*trans* conformation in a chalcone is believed to be a result of steric strain between the alpha group and the A ring and therefore indicative of a bulky alpha group. It would seem that much less steric strain is needed for the molecule to adopt the s-*trans* conformation than one might expect.

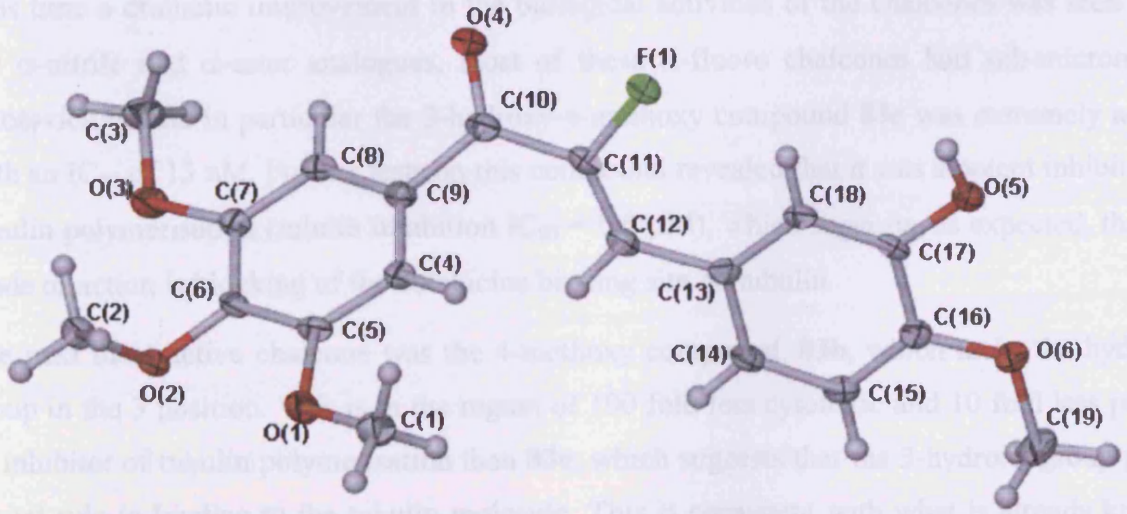
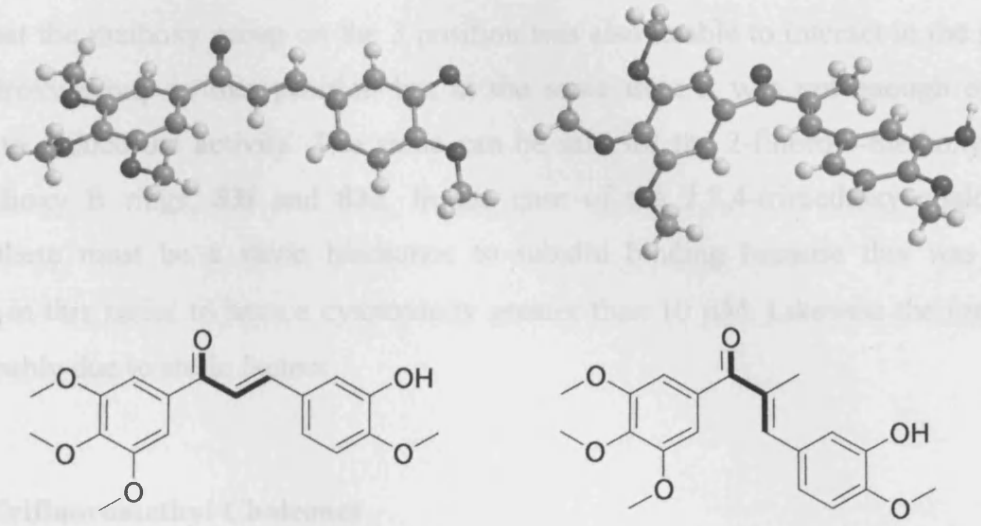


Figure 3.11 – X-ray crystal structure of ***83c***

It has been shown previously within our own group that the potency of chalcones is improved when they are forced to adopt the s-*trans* conformation, as this structure more closely resembles that of combretastatin A4 and is better able to fit the colchicine-binding site of the tubulin dimer. [54] This can be seen in the crystal structures shown in *Figure 3.12*, in which the steric bulk of the α-methyl group forces the molecule into the s-*trans* conformation whereas with only a proton in that position the molecule is more stable in the much less active s-*cis* conformation.



s-*cis*, IC_{50} = 4.3 nM s-*trans*, IC_{50} = 0.21 nM

Figure 3.12 – s-cis/s-trans isomerism.

This time a dramatic improvement in the biological activities of the chalcones was seen over the α-nitrile and α-ester analogues, most of these α-fluoro chalcones had sub-micromolar cytotoxicities and in particular the 3-hydroxy-4-methoxy compound **83c** was extremely active with an IC_{50} of 13 nM. Further tests on this compound revealed that it was a potent inhibitor of tubulin polymerisation (tululin inhibition IC_{50} = 0.6 μM), which suggests, as expected, that its mode of action is blocking of the colchicine binding site on tubulin.

The next most active chalcone was the 4-methoxy compound, **83b**, which lacks the hydroxy group in the 3 position. This is in the region of 100 fold less cytotoxic and 10 fold less potent an inhibitor of tubulin polymerisation than **83c**, which suggests that the 3-hydroxy group plays a vital role in binding to the tubulin molecule. This is consistent with what is already known about chalcones. [54]

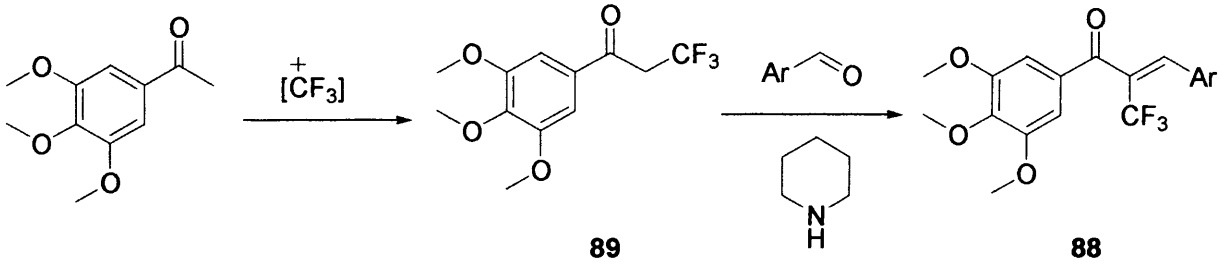
The 3-fluoro-4-methoxy derivative, **83g**, had roughly the same cytotoxicity as **83b**, despite the presence of the fluorine in the same position as the hydroxy group of **83c**. Clearly the fluorine in this case does not substitute for the OH group and if indeed the unusually high activity of **83c** is due to hydrogen bonding interactions within the colchicine binding site of tubulin, then the fluorine atom of **83g** is unable to undergo the same interactions.

In the same way the 3-bromo-4-methoxy chalcone, **83h**, was much less cytotoxic - 10 times less active than **83g** - as would be expected.

The 3,4-dimethoxy compound **83d** had around the same cytotoxicity as **83b** and **83g** which suggests that the methoxy group on the 3 position was also unable to interact in the same way as the hydroxy group in that position but at the same time it was not enough of a steric hindrance to reduce the activity. The same can be said for the 2-fluoro-4-methoxy and 3,4-methylenedioxy B rings, **83f** and **83a**. In the case of the 2,3,4-trimethoxy chalcone **83e**, however, there must be a steric hindrance to tubulin binding because this was the only compound in this series to have a cytotoxicity greater than 10 μM. Likewise the inactivity of **83h** is probably due to steric factors.

3.2.2 α-Trifluoromethyl Chalcones

The next series of chalcones to be examined were those with a CF_3 group in the alpha position **88**. Synthesis of this series proved less straightforward than that of previous chalcones. In order to make them by the Knoevenagel reaction that had been used before, the following ketone **89** would have to be made (*Scheme 3.8*).

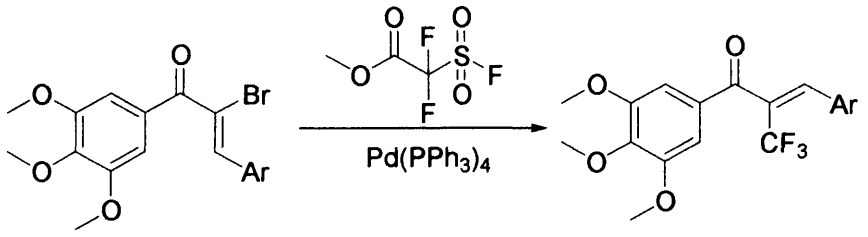


Scheme 3.8 – Knoevenagel synthesis of α-trifluoromethyl chalcones.

This would require a CF_3^+ synthon, all sources of which are unstable and expensive (as discussed in chapter one).

Another option was to add the trifluoromethyl group to the α-bromochalcones **90** via a Pd catalysed coupling reaction (*Scheme 3.9*). There is some precedent in the literature for this[146]

but the reagent used (methyl difluorofluorosulfonylacetate acid) is very expensive and has to be used in excess.

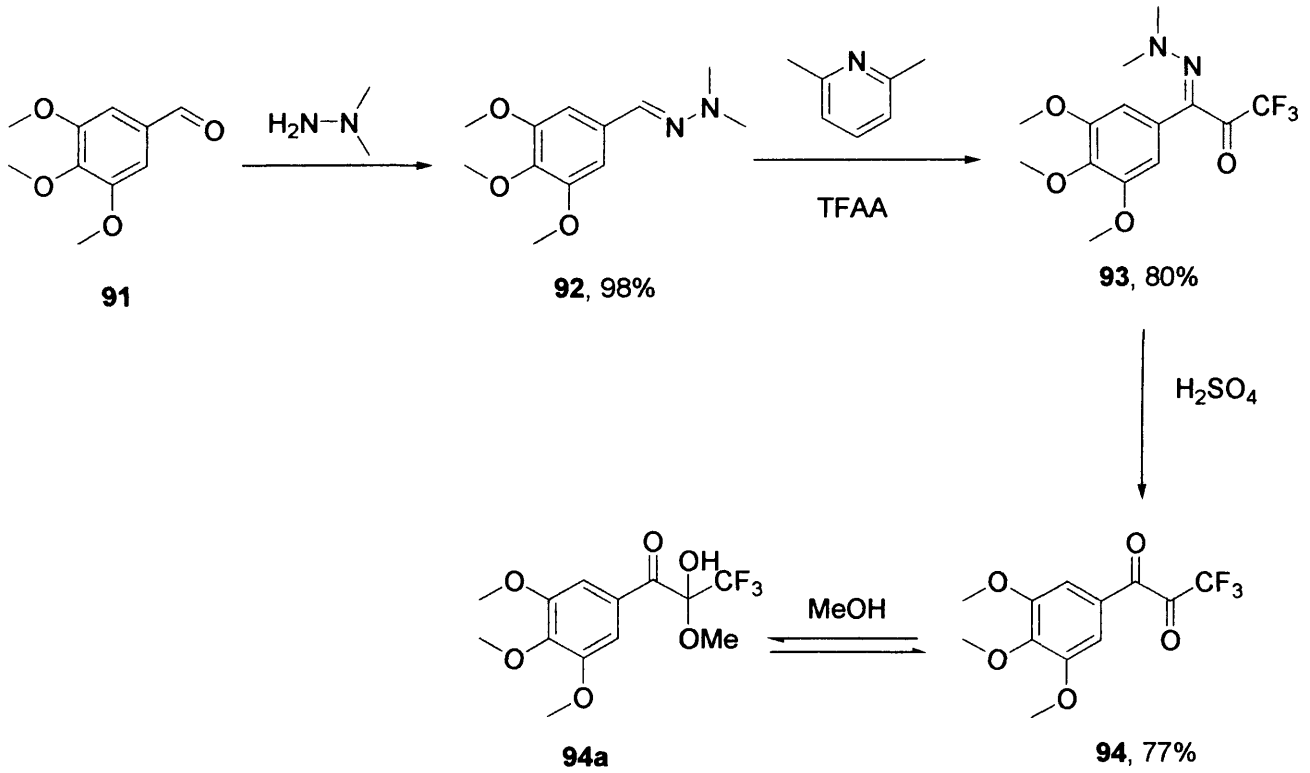


90 **88**

Scheme 3.9 – Synthesis of α-trifluoromethyl chalcones via Pd cross-coupling.

This highlights the problems associated with incorporation of a trifluoromethyl group into an organic molecule, as seen in chapter one.

The method eventually employed in the synthesis of **88** was via the diketone **94**. This was made from the dimethylhydrazone **92** of 3,4,5-trimethoxybenzaldehyde, by reaction with trifluoroacetic anhydride followed by hydrolysis, according to the method developed by Kamitori *et al.* (*Scheme 3.10*).[147]



91 **92**, 98% **93**, 80%

94a **94**, 77%

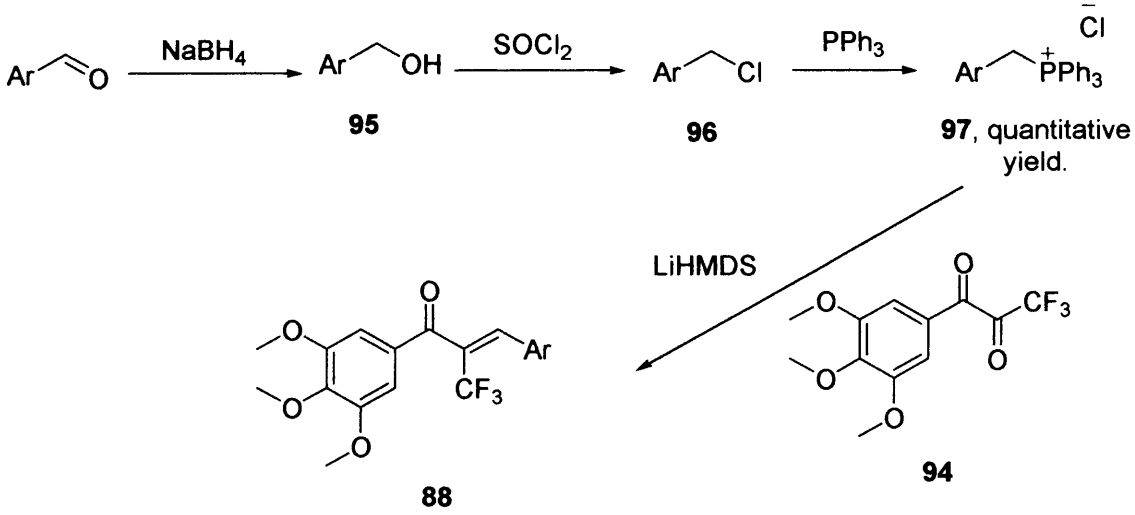
*Scheme 3.10 - Synthesis of diketone **94**.*

Recrystalisation of **94** from MeOH resulted in the hemiacetal **94a**. However when left in an open container for 2-3 days at room temperature the compound turned back into pure keto-

form of **94**. The ^{1}H NMR spectrum of **94** showed two methoxy peaks at 3.84 and 3.92 ppm and the 2 and 6 aromatic protons as a singlet at 7.57 ppm. The ^{19}F NMR spectrum showed the CF_3 group as a singlet at -81.0 ppm.

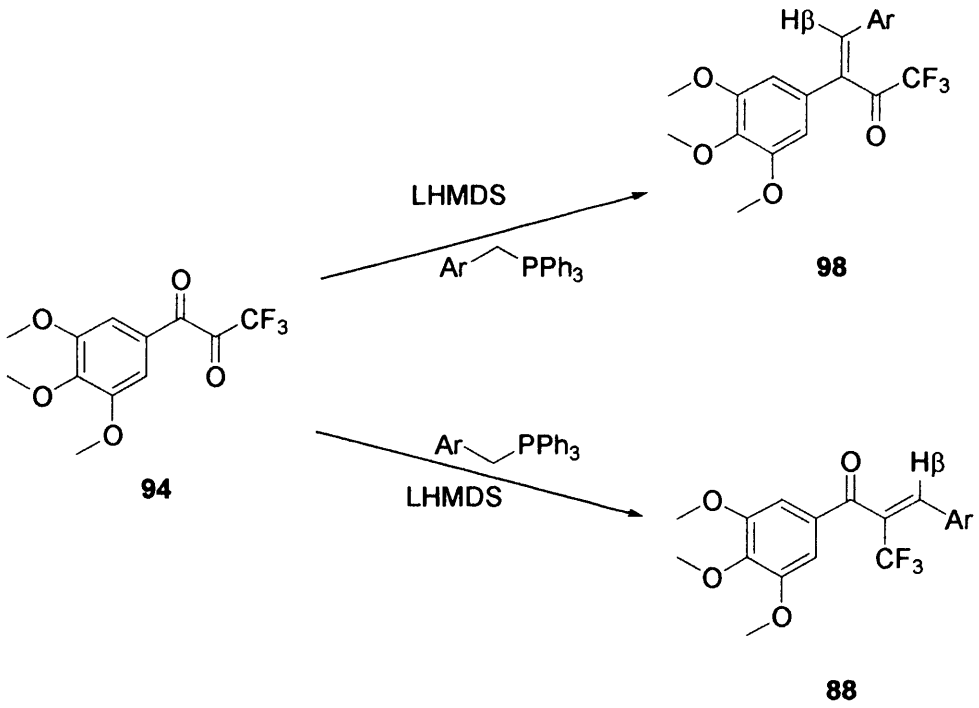
Aldehydes were converted to phosphonium salts **97a-h** via alcohols **95a-h** and chlorides **96a-h** (with the exceptions of the 4-methoxy and 4-trifluoromethyl compounds where the chlorides were purchased directly) according to *Scheme 3.11*. All these reactions gave quantitative yields and the known alcohols and chlorides were identified by ^{1}H NMR spectroscopy and used in subsequent reactions without further purification.

Ketone **94** was used in Wittig reactions with the appropriate phosphonium salt **97** to make the chalcones **88**. It was found that the conventional Wittig reaction using NaOMe as base in MeOH gave very low yields (5%-10 %) in this case so the reaction was carried out in THF using lithium hexamethyldisilazane base according to the method developed by Katzenellenbogen *et al*,[148] this resulted in much more satisfactory yields (*Table 3.3*).



*Scheme 3.11 – Wittig reaction between **94** and phosphonium salts **97**.*

Because there were two carbonyl groups in the diketone **94** it was possible that the Wittig reaction had taken place on the other carbonyl group to that which was intended and formed compound **98** (*Scheme 3.12*), although this was thought to be unlikely because of the activating, electron-withdrawing effects that the trifluoromethyl group would have on the alpha carbonyl.



Scheme 3.12 Alternative Wittig products.

The Wittig reactions all resulted in pure compounds, as seen in the ^{1}H and ^{13}C NMR spectra so there is no doubt that only one of these isomers was made in the reactions. The proton NMR data of the chalcones **88** were compared with that of known compound **99**.[149]

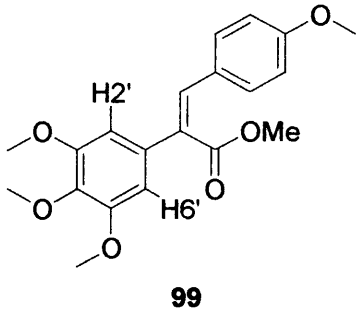


Figure 3.13 – Known unsaturated ester.

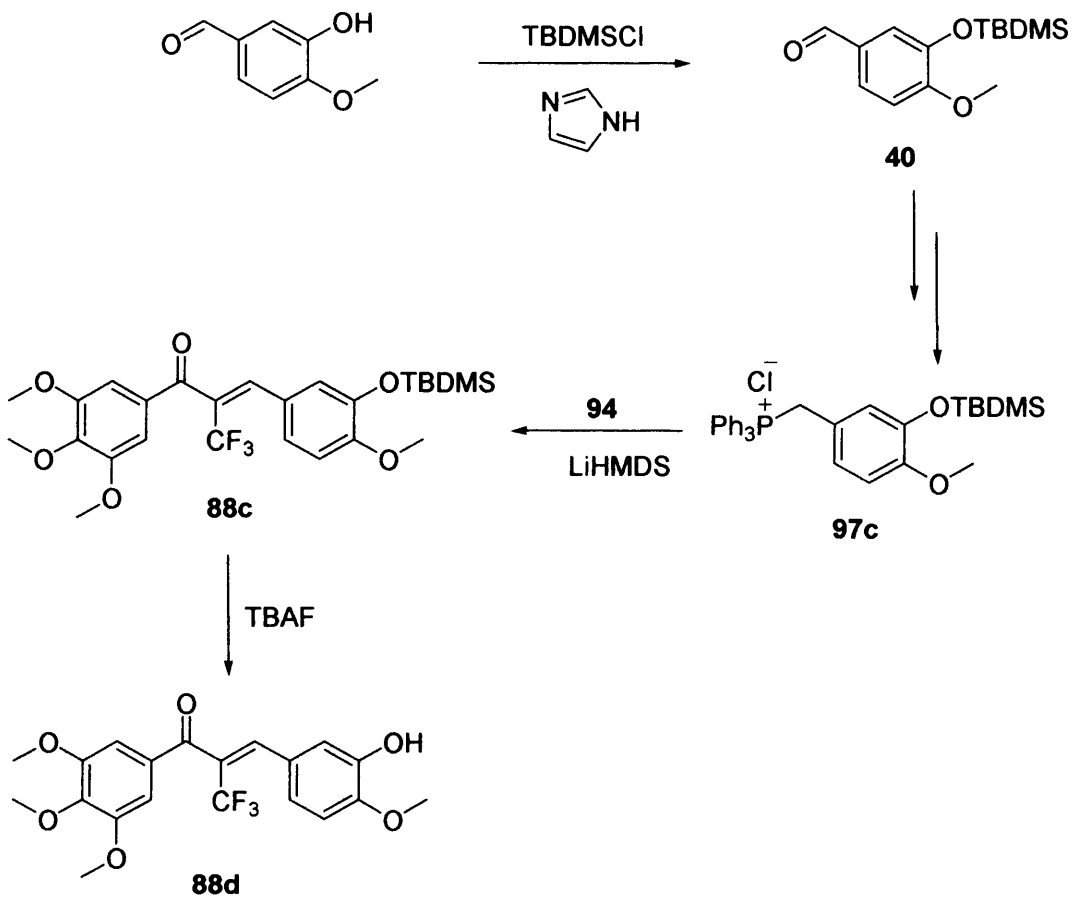
In the ^{1}H NMR spectrum of **99** protons H2' and H6' are reported to form a singlet peak at 6.44 ppm, whereas in the chalcones described here the *ortho* proton peak comes at roughly 7.0-7.2 ppm (see chapter 8). This is consistent with these protons being in conjugation with the electron withdrawing carbonyl group in the chalcones **88** and hence shifted downfield. In addition, the nOe data discussed below revealed no enhancement at Hβ when irradiated at H2'/H6', suggesting that these protons were not spatially close as they would be in *Z*-**98**. Since if **98** were formed it is unlikely, from both a steric and electronic point of view, that it would form *E* isomer, this is further evidence that the structure **88** is correct.

The Wittig reaction was successful with all the aryl groups with the exception of the 3-fluoro-4-methoxy and 3-bromo-4-methoxy ylids. Those chalcones which were isolated were tested for cytotoxicity and tubulin binding and the results summerised in *Table 3.3*, once again cytotoxicity and tubulin inhibition are expressed as IC_{50} values.

Ar group substitution	Compound number	Yield (%)	Cytotoxicity IC_{50}	Tubulin inhibition IC_{50}
3,4-Methylenedioxy	**88a**	58	0.44 μM	3.2 μM
4-Methoxy	**88b**	64	84.6 nM	3.7 μM
3-OTBDMS-4-methoxy	**88c**	49	>10 μM	N/A
3-Hydroxy-4-methoxy	**88d**	86	79.4 nM	3.9 μM
3,4-Dimethoxy	**88e**	71	0.61 μM	>10 μM
2,3,4-Trimethoxy	**88f**	36	1.99 μM	N/A
4-Trifluoromethyl	**88g**	83	0.21 μM	N/A
2-Fluoro-4-methoxy	**88h**	22	0.18 μM	0.7 μM

Table 3.3 – Yields, cytotoxicities and tubulin inhibition assays for α-trifluoromethyl chalcones.

As before, in the case of **88d** the chalcone was initially made with a TBDMS protecting group on the hydroxy substituent which was later removed with TBAF (*Scheme 3.13*).



Scheme 3.13 – Phenol protection and deprotection.

Unfortunately none of these chalcones gave suitable crystals for X-ray analysis and so we are not absolutely certain that the structural assignment is correct. In order to understand whether the molecules adopted the s-*cis* or s-*trans* conformation, however, ^{1}H nOe experiments were carried out with **88d** and **88g**. Protons 2' and 6' were irriadiated with the intention of seeing what enhancement that had on proton β, and surprisingly no effect was seen at all, which means that these chalcones may well be adopting the s-*cis* conformation. One might expect, given the fact that alpha methyl chalcones are known the be s-*trans* and given the similar size of methyl and trifluoromethyl groups, that steric factors would force these molecules into the s-*trans* conformation. It could be, however, that the electrostatic repulsion between the carbonyl oxygen and the fluorine atoms of the trifluoromethyl group overrides this steric effect so that the molecules are in fact s-*cis*.

This, along with the results discussed in section 3.2, reveals a very interesting reversal between the effects of fluorine and hydrogen on s-*trans* / s-*cis* isomerism of chalcones as illustrated in *Figure 3.14*.

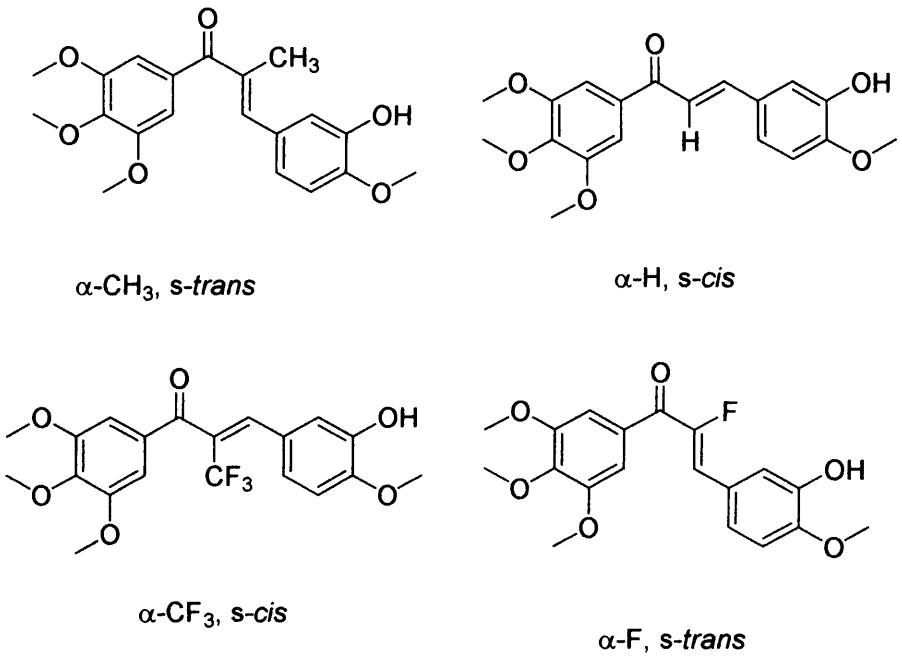


Figure 3.14 – Effects of fluorine on s-cis/s-trans isomerism.

Again, as with all previous chalcones the most cytotoxic of this series was **88d** with the 3-hydroxy-4-methoxy B ring, but in the case of these s-*cis* compounds there were also some significant differences.

Firstly the IC_{50} values of these compounds range from 80 nM to 2 μM - a much smaller range than with the alpha fluoro chalcones (13 nM to 10 μM). The 4-methoxy chalcone **88b** is once again the second most cytotoxic, this time having more or less the same activity as **88d**. It would seem therefore that the hydroxy group in these chalcones is less crucial to the cytotoxicity than in previous cases. It could be that one of the fluorine atoms in the trifluoromethyl group forms a H bond with the hydroxy group and this prevents it from hydrogen bonding within the binding site of the enzyme thus the activity is basically the same as **88b** which has no hydroxy group. Or it could be that because these chalcones are s-*cis* the structural change is such that they fit into the tubulin-binding site in a way that does not allow the OH group to undergo the same hydrogen bonding that is seen in s-*trans* chalcones.

In addition when these two chalcones were tested for tubulin polymerisation inhibition, it was found that while they had similar values, they were not the most potent.

Most of the other chalcones in this set fall within roughly the same range; **88a**, **88e**, **88g** and **88h** all have cytotoxicities in the 0.1 μM range and so are around ten fold less cytotoxic than **88b** and **88d**. When **88a**, **88e**, and **88h** were tested for tubulin inhibition, however, they were found to differ significantly. **88a** showed roughly the same tubulin inhibition as **88b** and **88d**,

despite being less cytotoxic, **88e** was effectively inactive with regard to tubulin inhibition and **88h** was the most potent tubulin inhibitor of the set. While it is clear that these chalcones are both very cytotoxic and, in most cases, potent inhibitors of tubulin polymerisation, it would seem that these two properties do not display a simple linear relationship. It may be that in addition to tubulin binding, these molecules have a second mode of action which contributes to their cytotoxicity.

The least active compound is **88f** with a 2,3,4-trimethoxy B ring with an IC_{50} of 2 μM – 100 fold less active than **88b** and **88d**. It would seem that the loss of activity in this case is due again to steric bulk, i.e. the bulkier the B ring, the more hindrance there is to binding in the active site of tubulin and hence the less cytotoxic the chalcone.

3.3 Summary and Conclusions

Chalcones with α-fluoro and α-trifluoromethyl substitutions, especially **83c** and **88d**, have shown very high cytotoxicity against the human chronic myelogenous leukemia cell, K562. Further investigation into the biological properties of these fluorinated chalcones revealed potent tubulin polymerisation inhibition, which accounts, at least in part, for their powerful cytotoxicities.

Chalcones which have fluoro and trifluoromethyl groups in the α-position also display some unusual structural features, especially in relation to their s-*cis* / s-*trans* conformations. Normally chalcones will adopt the s-*cis* conformation unless forced into the s-*trans* conformation by steric repulsion between a relatively bulky α-group, such as a methyl group, and the A-ring. Both α-fluoro and α-trifluoromethyl chalcones, however, seem to be exceptions to this rule; α-fluoro chalcones, which one would expect to be s-*cis* due to the small size of the fluorine atom, are in fact s-*trans* and α-trifluoromethyl chalcones, which one would expect to be s-*trans*, are s-*cis* (although in the latter case the structural assignment is based only on NMR data since no crystals suitable for X-ray analysis could be grown). The conformation of the α-trifluoromethyl chalcones, at least, can be explained in terms of the electrostatic repulsion which would exist between the carbonyl oxygen and the fluorine atoms in the s-*trans* conformation.

Chapter Four

4.1.1 Introduction (Long Range Fluorine Couplings)

It is well known that fluorine is able to cause unusual, long-range, NMR coupling patterns with other atoms, there are numerous examples in the literature and a few of these are described below.

Charushin and co-workers[150] have observed what is commonly known as 'through-space' coupling effects in fused fluoroquinolones of the type **100** and **101** (*Figure 4.1*):

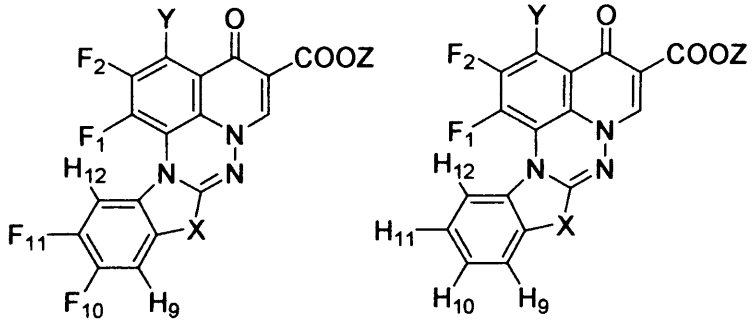
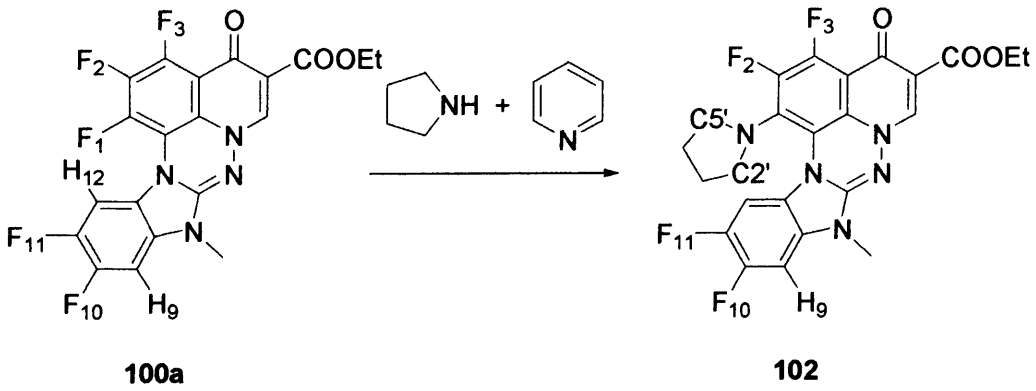


Figure 4.1 – Through-space NMR coupling in fluoroquinolones.

Several examples of these compounds were made as antibacterial targets and the ^{19}F spectra of all of them showed that F1 was coupled not only to F2 and F3 or H3 (where Y=F or H) but also to H12 (J_{FH} = 2.0-3.8 Hz). In the case of **100**, coupling is also seen between F1 and F11 (J_{FF} = 3.5-4.0 Hz). In the ^{1}H spectra H9 is coupled to F10 (J_{HF} = 10.3-10.5 Hz) and F11 (J_{HF} = 7.3-7.5 Hz) but H12 is coupled to F10 (J_{HF} = 7.1-7.5 Hz), F11 (J_{HF} = 10.5-11.6 Hz) and F1 (J_{HF} = 2.0-3.8 Hz). It is believed that these unusual interactions between F1, H12 and F11 are a result of through space effects.

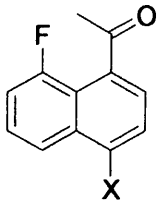
In the same publication the authors converted **100a** into **102** by refluxing with pyridine and pyrrolidine (*Scheme 4.1*).



Scheme 4.1 – Pyrrolidine substitution.

The NMR data of **102** showed more interesting couplings; F2 is seen as a double triplet due to coupling with both F3 (J_{FF} = 19.6 Hz) and H5' (J_{FH} = 3.4 Hz) and F11 demonstrates coupling to F10 (J_{FF} = 21.5 Hz), H12 (J_{FH} = 11.1 Hz) and H2' (J_{FH} = 3.5 Hz).

It is believed that the magnitude of these through space coupling effects is related to the spatial separation between the two atoms involved. This was demonstrated in a paper by Jaime-Figueroa *et al.*[151] They looked at 4-substituted-1-acetyl-8-fluoronaphthalenes **103**.



103

Figure 4.2 – 4-substituted-1-acetyl-8-fluoronaphthalene.

In these compounds there is coupling between the fluorine atom at the 8 position and both the carbon and protons of the acetyl methyl group which is believed to be due to through-space interactions.

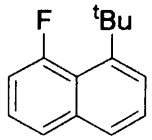
It was found that by altering the nature of the X group on the 4 position, the value of the F-H coupling constant, J_{FH}, could be changed; when X is electron-donating the coupling constant increases (X = OMe, J_{FH} = 4.15 Hz) and when X is electron-withdrawing the coupling constant is reduced (X = SOMe, J_{FH} = 3.15 Hz). In addition it was shown that the nature of the NMR solvent similarly altered the value of coupling constant. When the NMR spectrum of **103a** (X = F) was run in polar solvents such as DMSO-d_6 the J_{FH} coupling constant was significantly lower (2.51 Hz) than when it was run in non-polar solvents such as $CDCl_3$ (3.64 Hz).

Exactly the same effects were seen on the J_{FC} coupling constant between F8 and the methyl carbon.

These observations were explained as a result of the dihedral angle between the plane of the acetyl group and the naphthyl ring system. In the case of **103a** (X = F) X-ray crystal analysis showed this angle to be 65° with the oxygen of the acetyl group and the F4 fluorine in an anti orientation due to electrostatic repulsion. When X is more electron-donating (**103b**, X = OMe), the potential charge of the acetyl oxygen would be increased, the repulsion would increase and the methyl group would be pushed closer to the fluorine, increasing the coupling constant.

Similarly when polar solvents are used, the partial negative charge of the oxygen would be better stablised, the electrostatic repulsion would be reduced and steric factors would pull the fluorine and the methyl group apart, reducing the coupling constant.

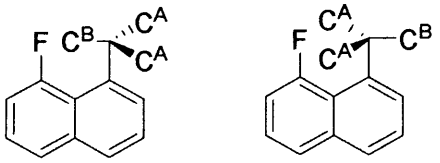
1-*tert*-butyl-8-fluoronaphthalene (**104**) also shows some unusual NMR properties and further demonstrates the dependence on distance of the through-space coupling effect.



104

*Figure 4.3 – 1-*tert*- butyl-8-fluoronaphthalene.*

In 1993, Gribble and co-workers examined the carbon and proton NMR of **104** at different temperatures.[152] They found that at 230K the ^{13}C NMR showed the methyl carbons of the *t*-butyl group as a doublet at δ 32.9 ppm (J_{CF} = 12 Hz) but as the temperature was lowered, this decoalesced and at 110K formed two distinct peaks; a broad singlet at δ_B 35.9 and a doublet at δ_A 30.8 (J_{CF} = 19 Hz). This is consistent with a slowing down of rotation about the C-C bond between the ring and the t-butyl group. At 230K rotation is too fast to be seen on the NMR timescale and all three methyl groups are seen as equivalent but at 110K the NMR detects two different types of methyl group. The doublet is due to two methyl groups lying on either side of the ring and the singlet represents a unique carbon atom lying parallel to the plane of the ring. This means that at 110K the molecule exists as one of the two conformations (*Figure 4.4*).



104a **104b**

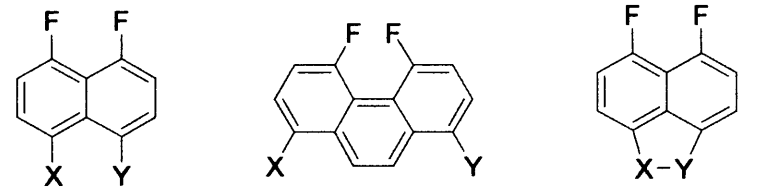
*Figure 4.4 – Alternative comformations of **104**.*

As one would expect, molecular modelling calculations imply a strong repulsive force between the methyl group B and the fluorine atom in **104a** and so it is believed that the most stable conformation of BFN is **104b**. The fact that through-space coupling is observed between fluorine and the A carbons but not the B carbon demonstrates the distance dependence of this effect.

There have been a number of studies into the mechanism of through-space coupling effects of fluorine and it is generally believed that the effect is caused by overlap between lone pair orbitals in the two crowded atoms.[153] In particular, the case of fluorine-fluorine through-space coupling has been studied in detail and it is thought that interaction between the two 2p lone-pair orbitals on the fluorine atoms enables the transmission of nuclear spin information.[154]

Mallory *et al.* in particular have published a number of studies in this area, many of which relate to 1,8-difluoronaphthalenes. They theorised that since the F-F spatial separation, d_{FF}, in 1,8-difluoronaphthalene was around 2.58Å there should be a small degree of σ overlap between the lone pair orbitals on the fluorine atoms. This would result in a weakly bonding and a weakly antibonding orbital and, while no net chemical bonding would result from this, it should explain the so called through-space NMR coupling seen in the NMR data.

If this is the case, then the magnitude of the coupling constant, J_{FF}, should show an exponential dependence on d_{FF}, such that J_{FF} should approach 0 as d_{FF} approaches infinity. Some distance dependence of the F-F coupling effect can easily be seen in the case of 1,8-difluoronaphthalenes **105** compared to 4,5-difluorophenanthrenes **106** and bridged 1,8-difluoronaphthalenes **107** (*Figure 4.5*), the J_{FF} values of **105** range from around 60-85 Hz, the J_{FF} values of **106** are in the range of 165-175 Hz and those of **107** are between 30-35 Hz.



105 J_{FF} = 60-85 Hz

106 J_{FF} = 165-175 Hz

107 J_{FF} = 30-35 Hz

Figure 4.5 – Through-space coupling in fluorinated polyaromatics.

In the case of **106**, however, there may be some contribution to the difference in J_{FF} from the angle of the overlapping lone pairs as well as the F-F separation. So these compounds were not included in the following investigation.

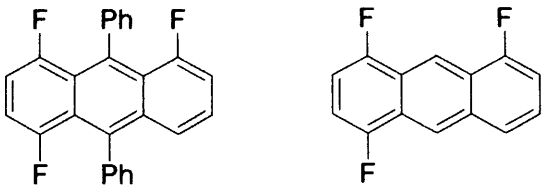
A range of compounds of the type **105** and **107** were made in which subtle variations in X and Y were used to change the F-F separation. In the case of **105** increasing the steric bulk of X and Y distorted the molecule and pushed the fluorine atoms closer together. In the case of **107** variation in the X-Y bond length imposed angular strain on the system and pulled the fluorine atoms apart. In all these cases the J_{FF} values of the molecules were measured and values of d_{FF} were calculated computationally. The value of J_{FF} was then plotted against d_{FF} and they were

found to display an exponential relationship. This would suggest, assuming the through bond F-F coupling in these molecules is negligible, that the through-space coupling is, as expected, a result of lone pair overlap.

This effect has not only been observed directly, as in the cases described above where two fluorine atoms are spatially close together, bizarrely it can also take place when the fluorine atoms are separated by another group, as long as the group contains a lone pair and is positioned so that that orbital can interact with each of the fluorine atoms.

One example of this is when two fluorine atoms are separated by a phenyl ring, such as in the case of 1,5,8-trifluoro-9,10-diphenyl-anthracene (**108**).[155] F1 in this molecule is reported to couple to F8 with a coupling constant of 6.4 Hz, a significantly stronger coupling than is seen in compound **109** ($J_{F1,F8}$ = 1.1 Hz) which lacks the intervening phenyl group (*Figure 4.6*).

The crystal structure of **108** shows the C9 phenyl group to be perpendicular to the plane of the anthracene ring system and the F1 and F8 atoms are each 2.6 Å from the C1' atom of the phenyl ring, so it is believed that the increased F-F coupling in this case is caused by transmission of nuclear spin information from fluorine atom to fluorine atom via the π orbitals of the phenyl ring.



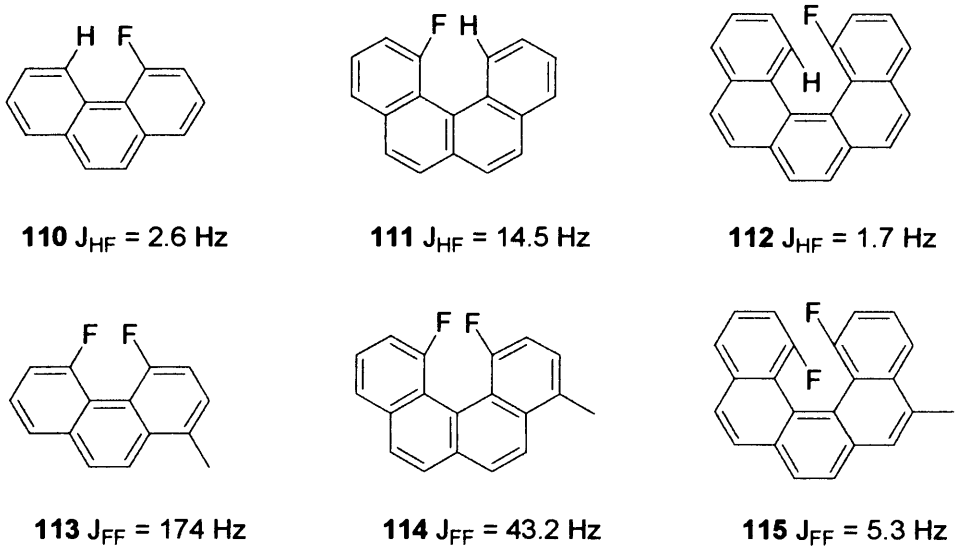
108 **109**

Figure 4.6 – Through-space coupling via an intervening group.

Fluorine-nitrogen[156] and fluorine-carbon[157] through-space coupling patterns have also been studied in some detail and the same correlation between coupling constant and spatial separation as has been described for fluorine-fluorine couplings appears to relate to these cases as well. It is believed that similar lone pair overlap interactions are responsible for the observed effects.

The case of through-space coupling between fluorine and hydrogen, however, is much less well understood, despite numerous publications in which the effect has been reported. It is known that, like F-F couplings, they are independent of the chemical shifts of the atoms involved.[158] But apart from this there are few papers which look in detail at the actual mechanism of through space F-H coupling.

Mallory and co-workers looked at this effect in 1975 by comparing the coupling constants between two fluorine atoms with those between fluorine and hydrogen atoms in a series of polyaromatics. They found that while the F-F couplings seemed to depend on F-F distance, this was not seen in the F-H couplings.[159] This is illustrated by the fact that the values of J_{FH} in **110**, **111** and **112** were not parallel to the values of J_{FF} in **113**, **114** and **115** (*Figure 4.7*). Since fluorine and hydrogen are similar in atomic radii, one would expect that the spatial distances between F and H in **110**, **111** and **112** to be representative of those between F and F in **113**, **114**, and **115**. The coupling constants, however, do not follow this pattern.



110 J_{HF} = 2.6 Hz **111** J_{HF} = 14.5 Hz **112** J_{HF} = 1.7 Hz

113 J_{FF} = 174 Hz **114** J_{FF} = 43.2 Hz **115** J_{FF} = 5.3 Hz

Figure 4.7 – Through-space coupling between two fluorine atoms or a fluorine atom and a hydrogen atom.

Mallory hypothesised, therefore, that in the case of through-space F-H coupling it is the distance between the fluorine atom and the carbon to which the proton is attached, rather than the proton itself, which determines the value of the coupling constant.

A computational study by Wasylishen *et al.* at around the same time looked at the effect of orientation as well as proximity of the H and F nuclei on the coupling effects but was unable to reach any significant conclusions.[160] They followed up more recently with a paper which concluded that fluorine-proton coupling showed the same dependence on $d_{F\text{-}C}$ that F-F coupling shows on $d_{F\text{-}F}$. They also showed that angular effects play a significant role such that the F-H coupling was much greater when the atoms are aligned (i.e. coupling between F and H1 was greater than between F and H2/H3/H4 in *Figure 4.8*) This was attributed to interactions between molecular orbitals on fluorine and carbon, although no explanation seems to be given for why the fluorine cannot interact directly with the proton.

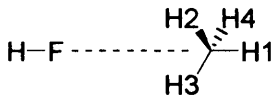
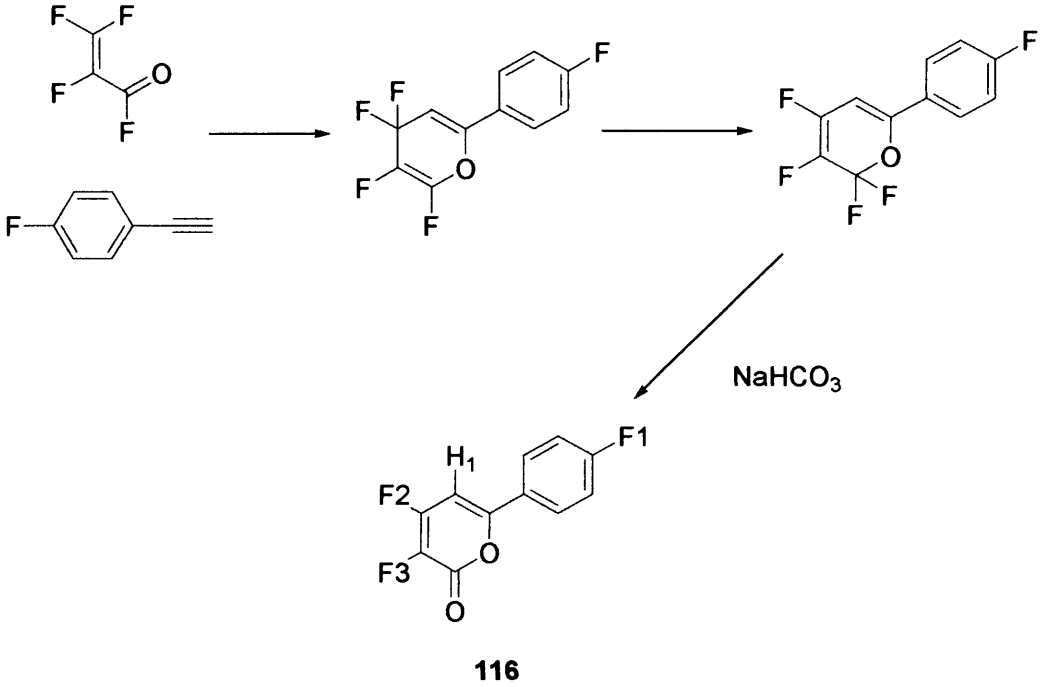


Figure 4.8 – Spatial orientation needed for ^{19}F-^{1}H through-space coupling.

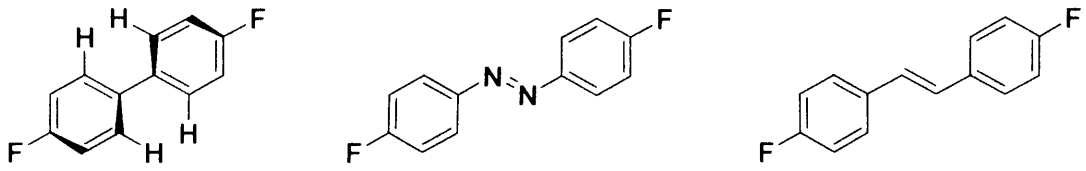
Not all long range coupling effects of fluorine can be explained by these 'through-space' orbital overlaps, however. In 1981 England *et al.* studied the synthesis of the following bicyclic compounds via a Diels Alder reaction between an aryl alkyne and perfluoroacryloyl fluoride (*Scheme 4.2*).



116

*Scheme 4.2 – Synthesis of **116** via Diels Alder coupling.*

They observed some unusual coupling in the proton and fluorine NMR spectra of the product **116**. The proton NMR showed that the vinyl proton H1 was coupled to all three fluorine atoms and the proton decoupled ^{19}F NMR showed that each fluorine atom is coupled to each of the others. Coupling between fluorines F1 and F3 cannot be a 'through-space' interaction because of the distance and the number of bonds separating them, it is thought to be a special type of through-bond coupling due to the planar property of the molecule and the resulting conjugation. Similar coupling patterns are not seen in 4,4'-difluorobiphenyl **117** because the two rings are forced into perpendicular planes by steric hindrances.[161] But in similar compounds which contain two *para*-fluorobenzene rings linked by groups such as -N=N- and -CH=CH- (**118** and **119**) which allow them to adopt a planar conformation, coupling is seen between the two fluorine atoms.[162]



117 118 119

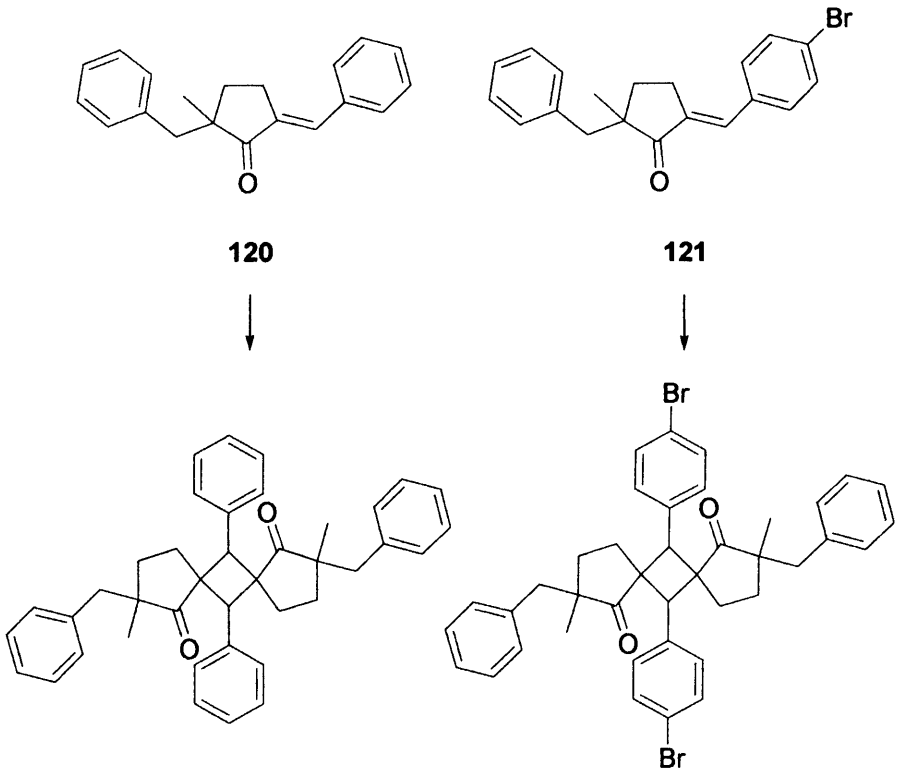
Figure 4.9 – Planar and non-planar biphenyls.

In the case of **116** the oxygen in the *ortho* position of the A-ring reduces the steric interaction enough to enable the molecule to resonate and adopt the planar conformation.[163]

4.1.2 Introduction (Single-Crystal to Single-Crystal Reactions)

There have been a few observed cases of organic crystals growing in such a way that, upon irradiation, they are able to undergo dimerisations and polymerisations within the crystal phase. These 'single-crystal to single-crystal' transformations are of great interest in fields such as polymer science because the stereochemistry of the products is determined by the nature of the monomer lattice. This derives from the topochemical postulate which states that 'reactions in the solid state proceed with minimal atomic and molecular movement'[164] and implies that a conformationally sensitive reaction will only take place if the orientation of monomers within the lattice allows it. It should be possible, therefore, to design crystals which, upon irradiation, react to give polymeric products with specific symmetries.[165] There is some debate, however, as to whether such reactions are truly homogeneous[166] or whether they take place at crystal defects.[167]

There are several known types of single-crystal to single-crystal transformation; polymerisation of diacetylenes,[168] [4+4] dimerisation of anthracenes[169] and [2+2] cyclodimerisations of cinnamic acids and their derivatives. The latter have been of particular interest in studying the single-crystal to single-crystal effect. Jones *et al.* published a few studies on the photodimerisation of **120** and **121**.



Scheme 4.3 – Solid state dimerisations.

They found that the dimerisation reactions of these molecules were indeed single-crystal to single-crystal transformations,[170] although in the case of **121** the monomer crystal must be irradiated slowly to prevent cracking due to the larger changes in crystal parameters between monomer and dimer.

Then, in a later study, they looked at X-ray data on some intermediate, partially reacted crystals consisting of both monomer and dimer in an attempt to understand the mechanism in more detail. In particular they wanted to know whether the reaction took place at defects within the crystal or whether it genuinely took place within the lattice. Their conclusion was that, at least in these two cases, while the dimerisation is homogeneous and does occur within the lattice, it nevertheless takes place at different rates in different parts of the crystal depending on the amount of radiation received.[171]

In order to be able to predict whether or not a given monomer crystal would be able to undergo [2+2] cyclodimerisations, a few attempts have been made to define necessary parameters which would allow reaction to take place.[172]

Turowska-Tyrk and co-workers used the following set of parameters to predict whether or not a [2+2] cyclodimerisation reaction could take place in a series of chalcones. (Single-crystal to single-crystal dimerisations had already been observed in crystals of chalcones.[173])

- Distance between C=C double bonds, d, should be < 4.2 Å.
- Angle between the line of one carbon double bond and a carbon atom of the neighbouring molecule C=C...C, α, should be as close to 90° as possible.
- Angle formed between the two C=C double bonds of adjacent molecules,τ, should be as close to 0° as possible.
- Angle between the two planes formed by the two >C=C< units, ϕ, should be as close to 0° as possible.
- Angle between the plane of one >C=C< unit and the plane of the two C=C bonds from that and an adjacent molecule, κ, should be as close to 90° as possible.

The ideal system is described in *Figure 4.10.*

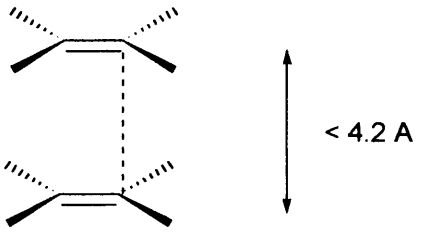


Figure 4.10 – Parameters necessary for single-crystal to single-crystal dimerisations.

They were then able to successfully predict which of the following five chalcones (*Figure 4.11*) would undergo [2+2] cyclodimerisation in the crystal phase based on the above parameters.[174]

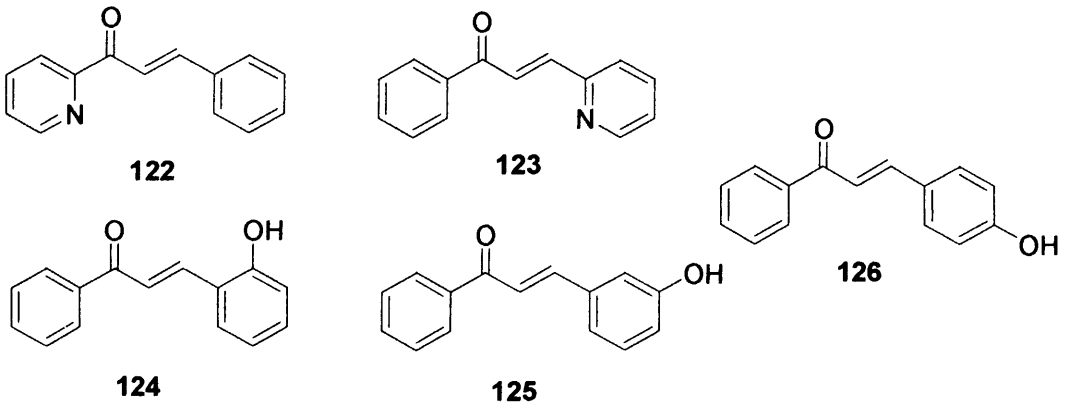


Figure 4.11 – Chalcones which may undergo single-crystal to single-crystal dimerisations.

Chalcone	d (Å)	α (deg)	τ (deg)	ϕ (deg)	κ (deg)	Able to react in crystal form (Y/N)
122	3.890	94.86	0	0	67.67	Y
123	4.197	104.90	180	0	64.30	N
124	3.895	99.94	0	0	58.77	N
125	>4.5					N
126	>4.4					N

Table 4.1 – Key parameters for single-crystal to single-crystal dimerisations of chalcones.

Chalcones **123**, **125** and **126** did not react because of unacceptable values of τ, d and d respectively and **122** did under go a single-crystal to single-crystal dimerisation, as the dimensions would suggest. The only anomaly was **124** in which the values in the table would suggest that it should be able to react when in fact it did not. This has been attributed to hydrogen bonding within the crystal structure, which restricts the movement of monomer molecules to such an extent that they are unable to get close enough to react.

4.2.1 Long range ^{19}F-^{1}H NMR Coupling in Chalcones

It has been observed within our group that certain fluorinated chalcones display unusual, long range, fluorine-proton coupling in the proton NMRs. In particular, in chalcones which have a fluorine atom in the *ortho* position on the A ring and a hydrogen on the alpha position (*Figure 4.12*), there seems to be a coupling interaction between the fluorine atom and the protons in the alpha and beta positions, which both appear as double doublets in the proton NMR. (It is worth noting that where similar chalcones are reported in the literature the alpha and beta protons are usually recorded as simple doublets with no J_{HF} contribution).[175]

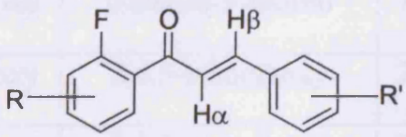
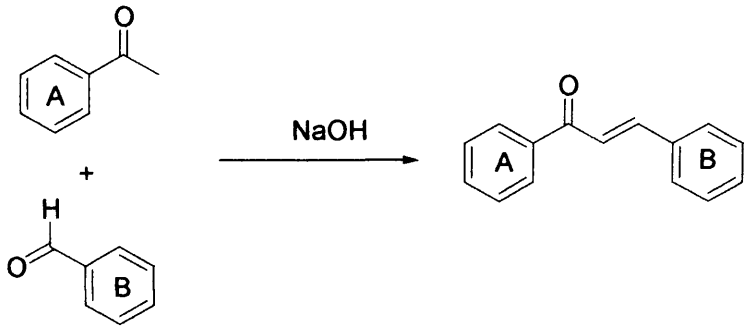


Figure 4.12 – 2-Fluoro-α-hydrogen chalcones.

This was investigated in further detail by synthesising more chalcones of this type and studying the NMR and X-ray data. This would enable us to see what effects the fluorine atom has on

conformation and whether this coupling effect can be used as a tool to probe conformational effects.

Synthesis of alpha hydrogen chalcones is very straightforward and the following were made by Claisen-Schmidt condensation of the appropriate acetophenone and benzaldehyde with methanolic sodium hydroxide (*Scheme 4.4*). All are novel with the exceptions of **129**,[176] **131**,[177] **135** + **142**[178] and **138** + **141**[179] although where these are reported in the literature the J_{HF} coupling is ignored. The proton NMR data is summarised in *Table 4.2*.



Scheme 4.4 - Claisen-Schmidt synthesis of chalcones.

	Yield (%)	A-Ring	B-Ring	α-H			β-H	
				δ	J_{HF}	J_{HH}	δ	J_{HF}
127	57	3,4,5-trimethoxy	2-fluoro-4-methoxy	7.51	0	15.9	7.79	0
128	73	2-fluoro	4-methyl	7.37	2.7	15.7	7.75	1.4
129	71	2-fluoro	3,5-dimethoxy	7.36	2.7	15.7	7.67	1.7
130	62	3-fluoro-4-methoxy	4-methyl	7.48	0	15.6	7.82	0
131	56	2,4-dimethoxy	3,4-difluoro	7.47	0	15.7	7.59	0
132	34	2-fluoro-4-methoxy	2-fluoro-5-bromo	7.45	2.9	15.8	7.73	1.9
133	52	2-fluoro-4-methoxy	2,4,5-trimethoxy	7.40	2.9	15.7	8.09	2.1
134	80	2-fluoro-4-methoxy	3,4,5-trimethoxy	7.36	2.9	15.6	7.71	2.0
135	44	2-fluoro-4-methoxy	4-methyl	7.44	2.9	15.6	7.79	2.0
136	79	2-fluoro-4-methoxy	2-fluoro-4-bromo	7.56	2.8	15.7	7.83	1.2
137	77	2-fluoro-4-methoxy	3,5-dimethoxy	7.43	2.8	15.6	7.71	2.0

138	57	2-fluoro-4-methoxy	4-methoxy	7.37	3.0	15.5	7.78	2.0
139	87	2-fluoro-4-methoxy	2,4-dimethoxy	7.39	3.0	15.7	7.97	2.2
140	34	2-fluoro-4-methoxy	2,3,4-trimethoxy	7.49	3.0	15.8	7.98	2.2
141	49	2-fluoro-4-methoxy	2-fluoro-4-methoxy	7.46	2.9	16.0	7.88	2.0
142	26	2-fluoro-4-methoxy	3-fluoro-4-methoxy	7.32	2.7	15.5	7.69	0
143	30	2-fluoro-4-methoxy	3-hydroxy-4-methoxy	7.35	2.8	15.5	7.73	2.1
144	64	2-fluoro-4-methoxy	3,4-methylenedioxy	7.31	2.9	15.5	7.72	2.1
145	70	2-fluoro-4-methoxy	3-bromo-4-methoxy	7.34	2.7	15.6	7.68	2.0
146	12	2-fluoro-4-methoxy	4-trifluoromethyl	7.46	3.0	15.6	7.71	2.0

Table 4.2 – Yeilds and NMR properties of α-hydrogen chalcones.

It is clear from this data that coupling occurs between the fluorine atom on the 2' position of the A-ring and both the α and β protons of the double bond (the exception to this is in the case of **142** where, for some reason, coupling is only seen to the α proton). No coupling occurs when the fluorine atom is on the 3' position on the A-ring, as can be seen in example **130** and no effect is seen when a fluorine atom is on the B-ring regardless of it's position, as shown by chalcones **127**, **131**, **132**, **136**, **141** and **142**. In the cases of **132**, **136**, **141** and **142** there is a fluorine atom on both rings but the coupling effect is the same as when there is only the fluorine on the 2' position of the A-ring.

The coupling constants to the alpha proton range from 2.7 to 3.0 Hz and for the beta proton, 1.2 to 2.2 Hz. In the case of the alpha proton, this is a small variation is probably not the result of any difference in the electronic properties of the two rings; this is illustrated by chalcones **138** and **146** both of which have a coupling constant of 3.0 Hz between the fluorine and the alpha proton despite the fact that **138** has an electron donating *para*-methoxy group on the B-ring and **146** has an electron-withdrawing trifluoromethyl group in the same position. In the case of the beta proton there is a much more significant variation although again there is no obvious correlation between the value of the coupling constant and the electronic nature of the substituents on the rings.

Since the fluorine atom in these compounds is separated from the alpha and beta protons by four and five carbon atoms respectively it is unlikely that this is a normal through-bond

coupling interaction, this is supported by the fact that no other positions on either the A or B ring seem to facilitate this interaction when substituted with fluorine.

It was possible to grow suitable crystals of three of these chalcones for X-ray analysis and their structures, along with some data derived from them, are shown below.

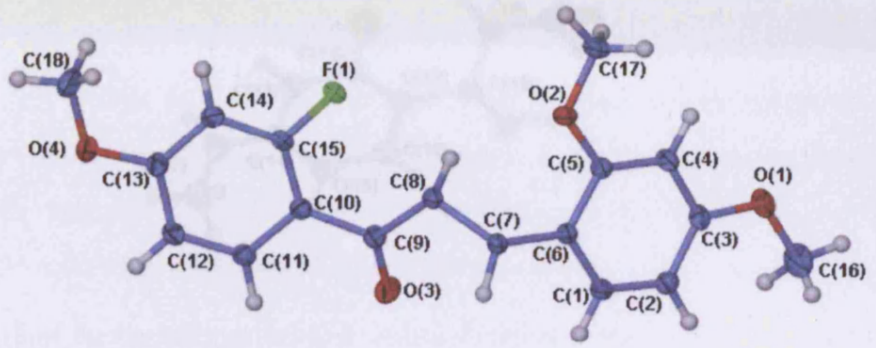


Figure 4.13 – X-ray crystal structure of ***139****.*

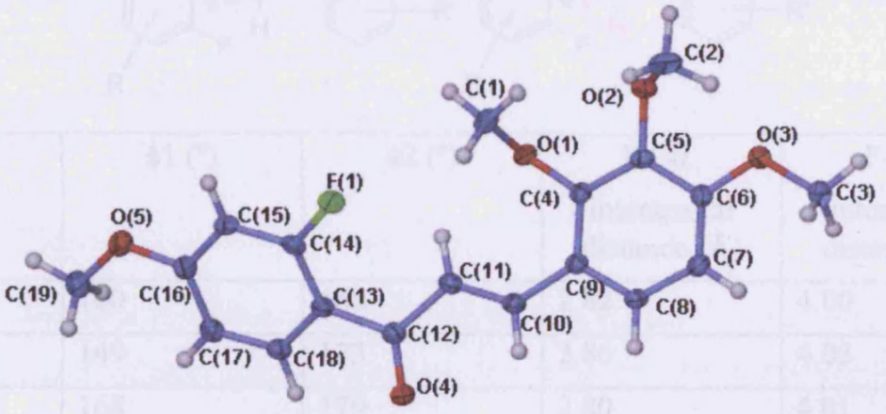


Figure 4.14 – X-ray crystal structure of ***140****.*

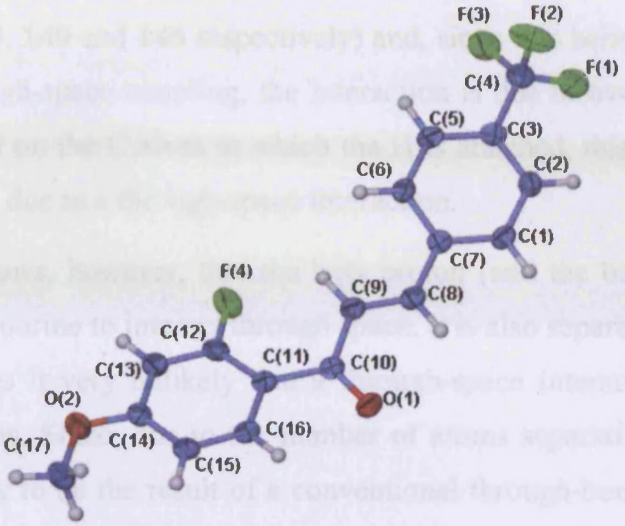
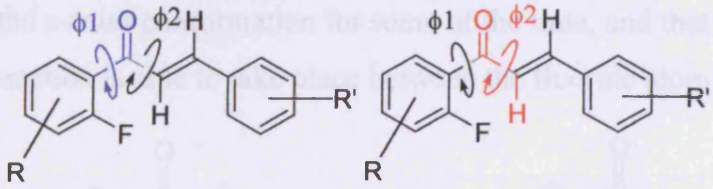


Figure 4.15 – X-ray crystal structure of ***146****.*



	ϕ1 (°)	ϕ2 (°)	F-Cα interspatial distance (Å)	F-Cβ interspatial distance (Å)
139	160	168	2.82	4.00
140	149	173	2.86	4.03
146	168	170	2.80	4.01

Table 4.3 – Structural data for crystaline 2-fluoro-α-hydrogen chalcones.

As would be expected for alpha hydrogen chalcones, the X-ray data shows the molecules to be orientated in the s-*cis* conformation. And in all three cases the fluorine atom is shown to be positioned *anti* to the carbonyl oxygen due, presumably, to electrostatic repulsions between these two highly electronegative atoms. Dihedral angles ϕ1 and ϕ2 all approach 180°, showing the molecules to be relatively flat, which indicates good π-overlap. (The X-ray data shows the configuration only in the crystalline state, of course, and it is likely that in solution there is some rotation about the single bonds, although it is reasonable to assume that the molecule would spend most of the time in the orientation shown.)

This means that the fluorine atom is positioned relatively close to the α carbon in space (2.82, 2.86 and 2.80 Å for **139**, **140** and **146** respectively) and, since it is believed that in the case of fluorine-hydrogen through-space coupling, the interaction is due to overlap between the lone pairs on the F atom and on the C atom to which the H is attached, this supports the idea that this coupling, at least, is due to a through-space interaction.

The X-ray data also shows, however, that the beta proton (and the beta carbon) is not only much too far from the fluorine to interact through space, it is also separated from it by the C=C double bond, this makes it very unlikely that a through-space interaction would take place between these two atoms. Since, due to the number of atoms separating them, this coupling effect is equally unlikely to be the result of a conventional through-bond interaction, it would seem that this is a very unusual type of coupling interaction.

There are limited explanations for this unusual effect. One is that in solution, unlike the crystalline state, the molecule has sufficient rotational freedom about the CO-C=C single bond to allow it to adopt the s-*trans* conformation for some of the time, and that in this conformation a through-space interaction is able to take place between the fluorine atom and Cβ.

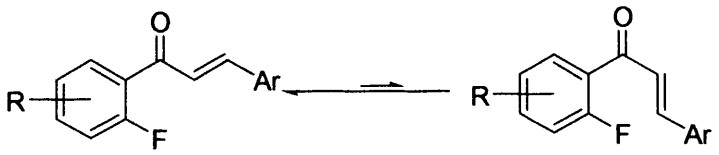


Figure 4.16 – Interconversion of s-cis and s-trans isomers in solution.

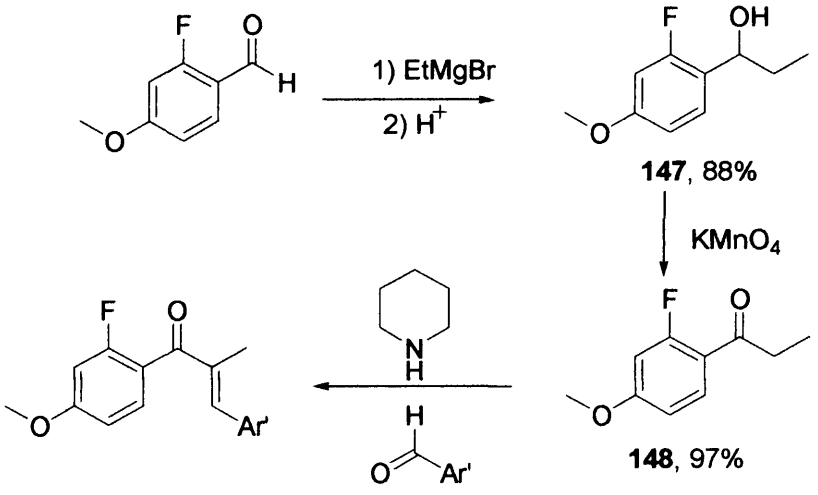
Another explanation is that some sort of through-bond coupling is responsible; it could be that since the crystal structures seem to show the C-F bond roughly perpendicular to the C=C double bond, the through-space interaction between F and Cα is transmitted *through the vinyl bond* to Hβ. (Something similar to this is discussed above, in which a fluorine-fluorine through-space coupling is transmitted through a phenyl group.[155])

Or the coupling could simply be a very long range through-bond effect, resulting from the high degree of resonance within the chalcone molecule. Again an example of this is discussed in the introduction although the effect is not very well understood[163] and it offers no explanation for the fact that this coupling is only possible when the fluorine is in the 2' position.

In order to test the first of these hypotheses a range of alpha methyl chalcones were made. It is well known that alpha methyl chalcones are predominantly s-*trans* so if the F-Hβ coupling constant in the alpha methyl compounds is the same as has been observed in alpha hydrogen

chalcones, that would suggest that the latter is a result of the molecule adopting the s-*trans* conformation in solution.

Initially ketone **148** was made by ethyl Grignard addition to 2-fluoro-4-methoxybenzaldehyde followed by oxidation with $KMnO_4$ (*Scheme 4.5*). Condensation of chalcones from **148** was more difficult than in the case of the alpha hydrogen chalcones and reaction was carried out by refluxing the ketone and aldehyde mixture with piperidine and acetic acid in ethanol.



Scheme 4.5 – Synthesis of α-methyl chalcones.

	Yield (%)	A-Ring	B-Ring	β-H	
				δ	J_{HF}
149	23	2-fluoro-4-methoxy	2,4-dimethoxy	7.16	0
150	20	2-fluoro-4-methoxy	2,3,4-trimethoxy	7.30	0
151	53	2-fluoro-4-methoxy	3-fluoro-4-methoxy	7.00	0
152	18	2-fluoro-4-methoxy	3,4-methylenedioxy	7.03	0
153	61	2-fluoro-4-methoxy	3-bromo-4-methoxy	7.09	0
154	40	2-fluoro-4-methoxy	4-trifluoromethyl	7.09	0

Table 4.4 – Yeilds and NMR properties of α-methyl chalcones.

None of these chalcones display any coupling interaction between the fluorine atom and the beta hydrogen and in all cases Hβ appears as a singlet in the proton NMR. This is surprising since there is a through-space interaction between F2' and Hα in the alpha hydrogen chalcones and one would expect F2' and Cβ to be significantly closer in this case.

Unfortunately no X ray data could be obtained for any of these compounds, although the results of nOe experiments on **151** and **153** show a 1.96 and 1.92% enhancement at H6' respectively when irradiated at Hβ. That there is such an nOe effect is consistent with the compounds adopting the s-*trans* conformation rather than s-*cis*, and the fact that the enhancement in both cases is so small is probably due to restricted rotation about the Ar-CO bond with the F and O positioned anti most of the time.

It may be that in this conformation the F2' and Cβ atoms are so close together that steric hindrance between them forces the molecule to twist in such a way that the atoms are out of plane and therefore cannot undergo through-space coupling. This effect is seen in compound **112** above, although in that example the through-space coupling is not eliminated, merely reduced.

It is clear, though, from these results that the coupling observed in the alpha hydrogen chalcones between the fluorine atom on the 2' position and the proton on the β position is not due to any direct through-space coupling. This must mean that through-bond interactions play at least some role in the observed NMR coupling. If the coupling is transmitted entirely through bonds and is a result of the highly conjugated nature of the chalcone molecule, similar to the effect described by England *et al.*,[163] then it remains to be seen why a similar effect is not observed between alpha and beta protons and fluorine atoms in different positions within the molecule, and also why no such coupling occurs in the equally conjugated alpha methyl chalcones. It seems more likely, at this point, that the observed effects are a combination of through-space and through-bond interactions and the F2' atom is coupled through space to the C=C double bond and that this effect is then transferred through bonds to the alpha and beta protons.

4.2.2 Cytotoxicities

The cytotoxicities of these compounds were also tested and are shown below in *Table 4.5*.

	A Ring	B ring	α Position	Cytotoxicity (μM)
127	3,4,5-trimethoxy	2-fluoro-4-methoxy	H	1.8
128	2-fluoro	4-methyl	H	9.5
129	2-fluoro	3,5-dimethoxy	H	3.6
130	3-fluoro-4-methoxy	4-methyl	H	>10

131	2,4-dimethoxy	3,4-difluoro	H	>10
132	2-fluoro-4-methoxy	2-fluoro-5-bromo	H	8.5
133	2-fluoro-4-methoxy	2,4,5-trimethoxy	H	>10
134	2-fluoro-4-methoxy	3,4,5-trimethoxy	H	6.0
135	2-fluoro-4-methoxy	4-methyl	H	>10
136	2-fluoro-4-methoxy	2-fluoro-4-bromo	H	>10
137	2-fluoro-4-methoxy	3,5-dimethoxy	H	>10
138	2-fluoro-4-methoxy	4-methoxy	H	>10
139	2-fluoro-4-methoxy	2,4-dimethoxy	H	>10
140	2-fluoro-4-methoxy	2,3,4-trimethoxy	H	9.8
141	2-fluoro-4-methoxy	2-fluoro-4-methoxy	H	>10
142	2-fluoro-4-methoxy	3-fluoro-4-methoxy	H	>10
143	2-fluoro-4-methoxy	3-hydroxy-4-methoxy	H	4.5
144	2-fluoro-4-methoxy	3,4-methylenedioxy	H	>10
145	2-fluoro-4-methoxy	3-bromo-4-methoxy	H	>10
146	2-fluoro-4-methoxy	4-trifluoromethyl	H	>10
149	2-fluoro-4-methoxy	2,4-dimethoxy	Me	9.7
150	2-fluoro-4-methoxy	2,3,4-trimethoxy	Me	1.9
151	2-fluoro-4-methoxy	3-fluoro-4-methoxy	Me	2.1
152	2-fluoro-4-methoxy	3,4-methylenedioxy	Me	>10
153	2-fluoro-4-methoxy	3-bromo-4-methoxy	Me	1.9
154	2-fluoro-4-methoxy	4-trifluoromethyl	Me	>10

Table 4.5 – Cytotoxicities of α-hydrogen and α-methyl chalcones.

Of those chalcones with a 2-fluoro-4-methoxy A-ring, most are inactive (cytotoxicity >10 μM) when there is only a proton in the alpha position. As expected, the most active is **143** with a 3-hydroxy-4-methoxy B-ring, but **134** with a 3,4,5-trimethoxy B-ring is almost as active, which suggests that the 3-hydroxy group on the B-ring is much less important in this case than it has been in previous chalcones. This could be because they are s-*cis*.

The α-methyl compounds are s-*trans* and therefore generally more active, **151** is particularly active, as one would expect since the 3-fluoro-4-methoxy B-ring most closely resembles the 3-hydroxy-4-methoxy ring. More surprising is the activity of **150** and **153**, both of which are much more active than one would expect given the bulky nature of the 2,3,4-trimethoxy and 3-bromo-4-methoxy B-rings. In previous chalcone series these B-rings have been shown to reduce activity. It could be that since the A-ring in these particular chalcones is smaller than

usual, the compound is able to fit into the tubulin binding site the opposite way round. Bulky B-rings also seem to increase the activity in the α-hydrogen chalcones, as seen in **134** and **140**. The most active of all these chalcones is **127** with the 3,4,5-trimethoxy A-ring.

4.3 Dimerisation of Chalcones

During the course of the X-ray analysis of compound **139**,[180] it was found that in addition to the yellow crystals of the chalcone monomer described above, there was also a very small percentage of another white crystal present. This was found to be the head-tail cyclobutyl dimer, **155**, as shown below. The mechanism by which this had formed was of interest, in particular whether it was the result of a single-crystal to single-crystal transformation of the monomer crystal or whether it had formed from solution as a separate polymorph (either of dimer or of a monomer which had dimerised upon exposure to light).

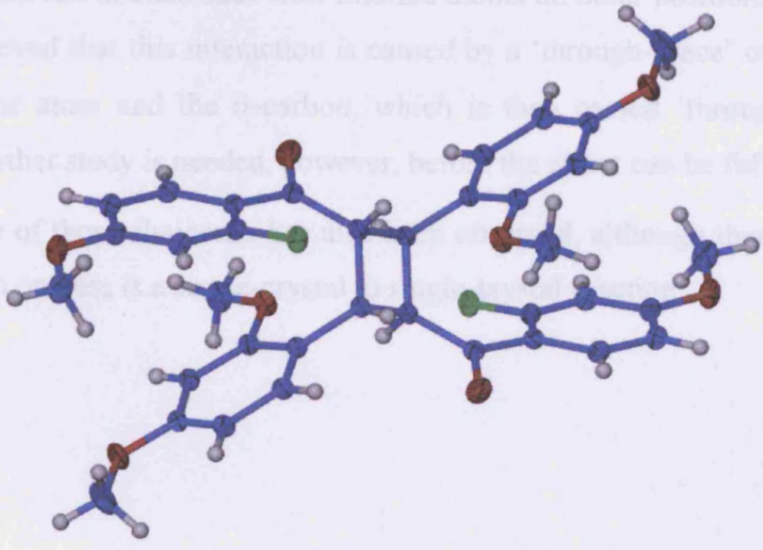


Figure 4.17 – X-ray crystal structure of ***155****.*

Studies of the initial sample suggested that the monomer crystal which made up the bulk of the sample had not formed the dimer; the distance between the C=C double bonds was > 5 Å (for single-crystal to single-crystal dimerisations this needs to be <4.2 Å.[174]), there was no intermediate crystal present i.e. the sample only contained purely monomer and purely dimer crystals, and further irradiation of the sample by high energy UV failed to induce any more dimerisation.

This means that either the dimer formed from solution and crystallised out as a separate compound or that a different polymorph of the monomer was formed which was able to undergo single-crystal to single-crystal dimerisation and did so before the X ray analysis took place.

In order to distinguish between these two possibilities, a new batch of compound **139** was synthesised, this time in darkness, to be analysed by X-ray powder diffraction and solid state NMR.[181]

4.4 Summary and Conclusions

Certain chalcones have been shown to display some unusual, long range NMR coupling interactions. In particular α-hydrogen chalcones with a fluorine atom on the *ortho* position of the A-ring show coupling between this fluorine atom and the α- and β-hydrogen atoms. Since this effect is not observed in chalcones with fluorine atoms on other positions, or in α-methyl chalcones, it is believed that this interaction is caused by a 'through-space' orbital interaction between the fluorine atom and the α-carbon, which is then passed 'through-bonds' to the hydrogen atoms. Further study is needed, however, before the effect can be fully understood.

Dimerisation of one of these chalcones has also been observed, although there is no evidence that the dimerisation process is a single-crystal to single-crystal reaction.

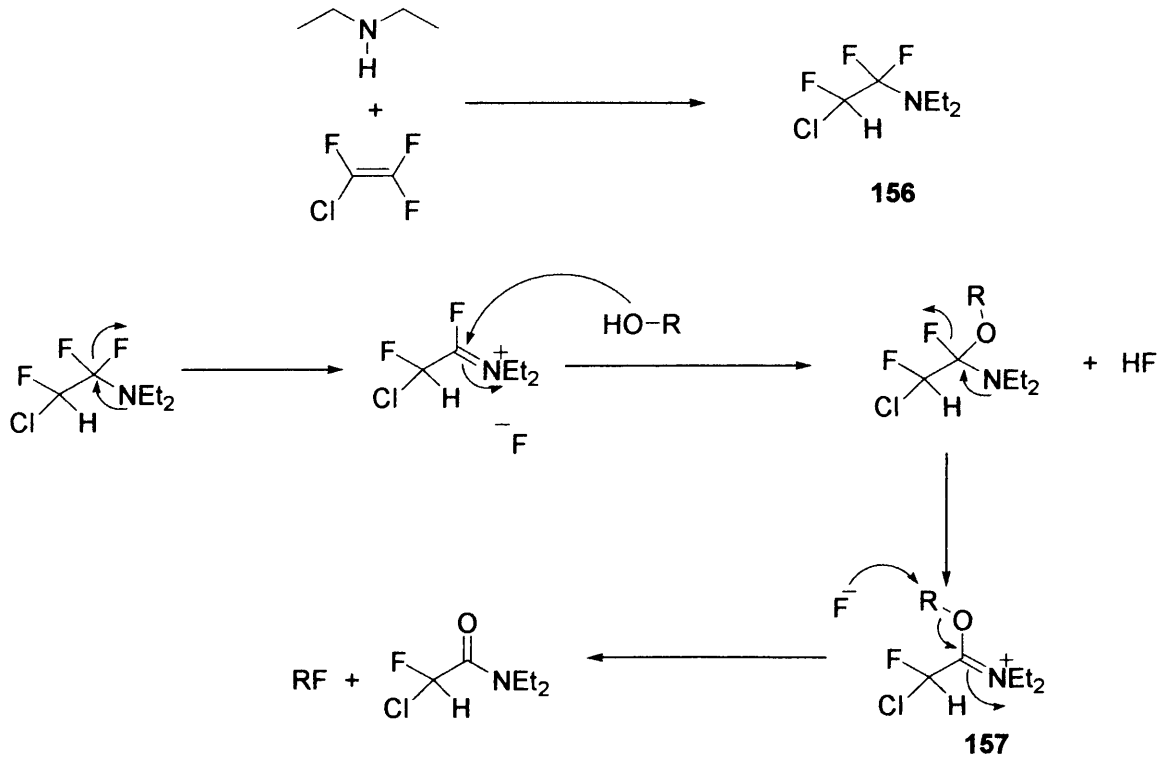
Chapter Five

5.1 Introduction

It has already been shown that incorporation of certain fluorinated synthons into organic molecules is often problematic. Inclusion of fluorine atoms themselves is less so; [F^+] is available in the form of electrophilic N-F based reagents such as Selectfluor™ [182] and [F^-] is available simply as salts such as KF, CsF and tetrabutylammonium fluoride (TBAF), which is particularly useful for its solubility in organic solvents.

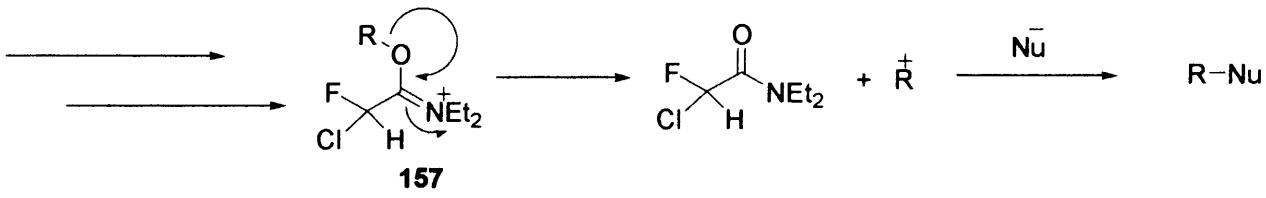
Another convenient source of [F^-] are the fluoroalkylamine reagents (FARs) such as the Yarovenko reagent, 2-chloro-1,1,2-trifluorotriethylamine (**156**). These are able to react specifically with alcohols, substituting fluorine for OH^-. A few such compounds have been studied but compound **156** has been found to be the most effective and convenient one-step method of converting OH to F.[183]

The addition of diethylamine to chlorotrifluoroethylene to generate 2-chloro-1,1,2-trifluorotriethylamine was first carried out by Pruett *et al.* [184] but its utility as a fluorination agent was first realised by Yarovenko.[185] The only real disadvantage of this reagent is that it is unstable and so cannot be stored for more than a few days. It has to be made freshly by addition of diethylamine to chlorotrifluoroethene and used almost immediately. The reaction with alcohols is believed to proceed as shown in *Scheme 5.1*.[186]



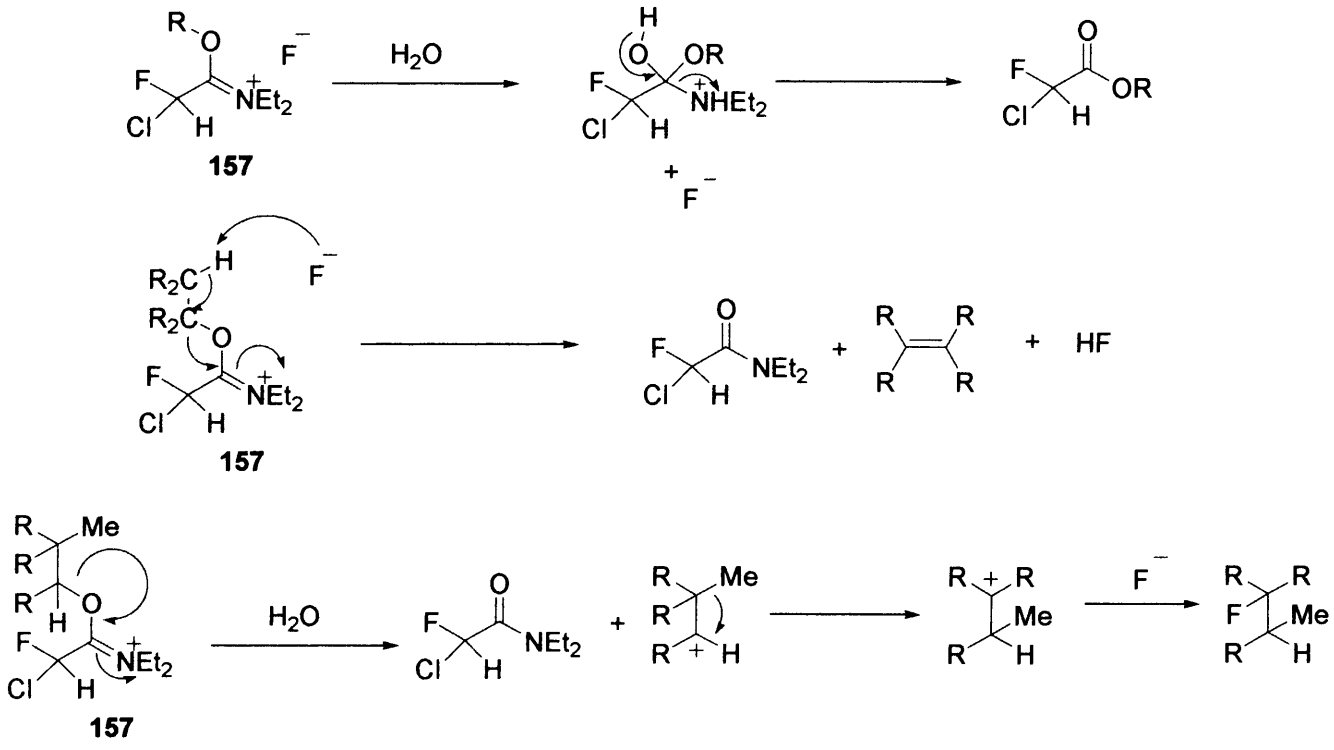
Scheme 5.1 – Fluorination of alcohols using the Yarovenko reagent (S_N2 mechanism).

This S_N2 mechanism accounts for most of the examples in the literature but not all; there are some cases where the stereochemistry of the products indicates that an S_N1 reaction involving a carbonium ion intermediate must be taking place (*Scheme 5.2*).[187]



Scheme 5.2 – Alternative S_N1 mechanism.

Primary alcohols nearly always react cleanly with **156** to give high yields of fluorides, secondary alcohols usually react as well, although yields are reduced because of side reactions which can also take place. Tertiary alcohols (with the exception of bicyclooctanols[188]) do not usually react at all with **156** and when they do it is usually the products of side reactions which are recovered. Common side reactions which can take place include esterification, elimination of water or, in cases where a carbonium ion is formed, rearrangement. These are believed to stem from the intermediate **157**.



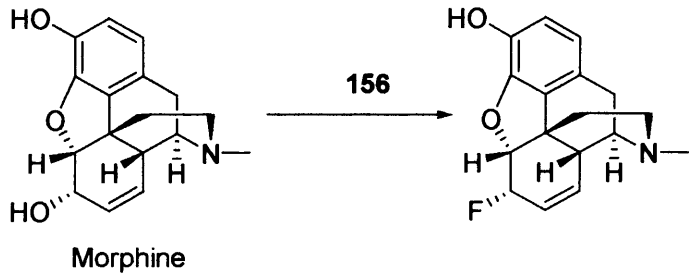
Scheme 5.3 – Side reactions possible during fluorination of alcohols.

Other side reactions can sometimes occur involving the attack of **157** by alternative nucleophiles in place of F^-, usually from the solvent.

As mentioned previously, a major advantage of this type of reagent is that they are selective to alcohols and are usually inert to other functional groups. An exception to this rule is in the case of amines; there have been some attempts to selectively fluorinate alcohols in the presence of primary and secondary amines but all have failed, unless the amine is protected.[189]

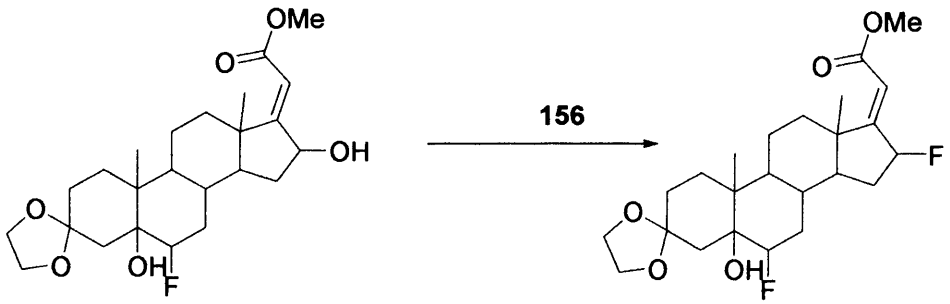
As a result of this selectivity the Yarovenko reagent is able to convert hydroxy groups into fluorides in many large, complicated drug molecules and analysis of these has lead to a great deal of understanding of the biological properties of fluorine.

Alkaloids such Morphine, Codeine and other related structures have been successfully fluorinated using the Yarovenko reagent (*Scheme 5.4*).[190] Efforts have also been made to fluorinate carbohydrates using **156**, although with much less success.[191]



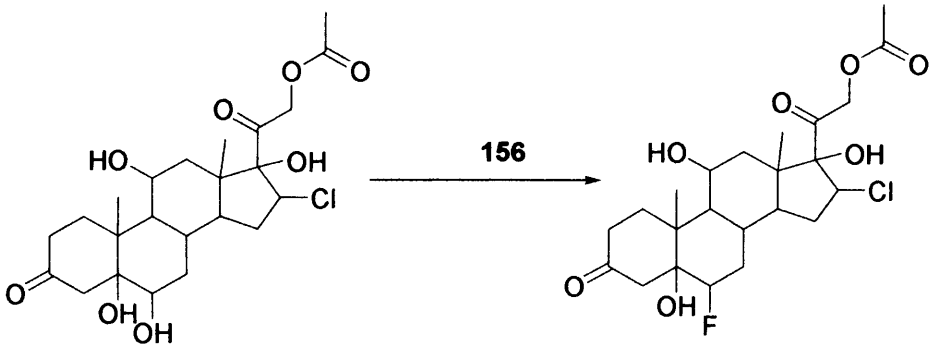
Scheme 5.4 – Fluorination of morphine.

The reagent has been used most extensively, however, in the fluorination of hydroxysteroids and it is this area which makes up most of the existing literature regarding the Yarovenko reagent. Reaction of hydroxysteroids with **156** depends on numerous factors. Generally when the hydroxy group is a primary alcohol situated on a side chain of the steroid skeleton fluorination works very well with minimal side reactions.[192] When the hydroxy group is a secondary or tertiary alcohol attached directly to the ring system, however, the results are much more variable. In some cases the reaction can proceed cleanly to give high yields of the fluorinated product; 16-hydroxysteroids in particular usually react very well.[193]



Scheme 5.5 – Fluorination of 16-hydroxysteroids.

In other cases the reaction predominantly gives by-products and sometimes reaction does not occur at all. An interesting example of this is in the case of the tetrahydroxy steroid **158** (*Scheme 5.6*) which selectively undergoes fluorination by **156** at the 6-position without affecting any of the other three hydroxy groups.[193]



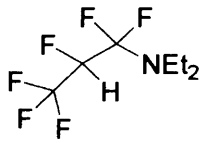
158

*Scheme 5.6 – Selective fluorination of tetrahydroxy steroid **158**.*

Few publications on the Yarovenko reagent have been released in recent years, most of the work on fluorination of steroids and other biological compounds was carried out in the 60s and early 70s. The few papers to be published since then deal mainly with the problem of the Yarovenko reagent's short shelf-life.

As mentioned above, synthesis of the Yarovenko reagent involves addition of diethylamine to the highly volatile chlorotrifluoroethylene, this can be achieved via a few different procedures but all of these involve high pressure and require rigorously anhydrous conditions.[194] Thus a similar reagent with comparable fluorinating power but which could be stored for longer periods would be extremely useful.

Ishikawa and co-workers developed a shelf-stable reagent **159**, very similar to **156** which demonstrated similar reactivity towards alcohols (*Figure 5.1*).[195] Although this can be stored for much longer periods than **156**, it is still not sufficiently stable to be available commercially.

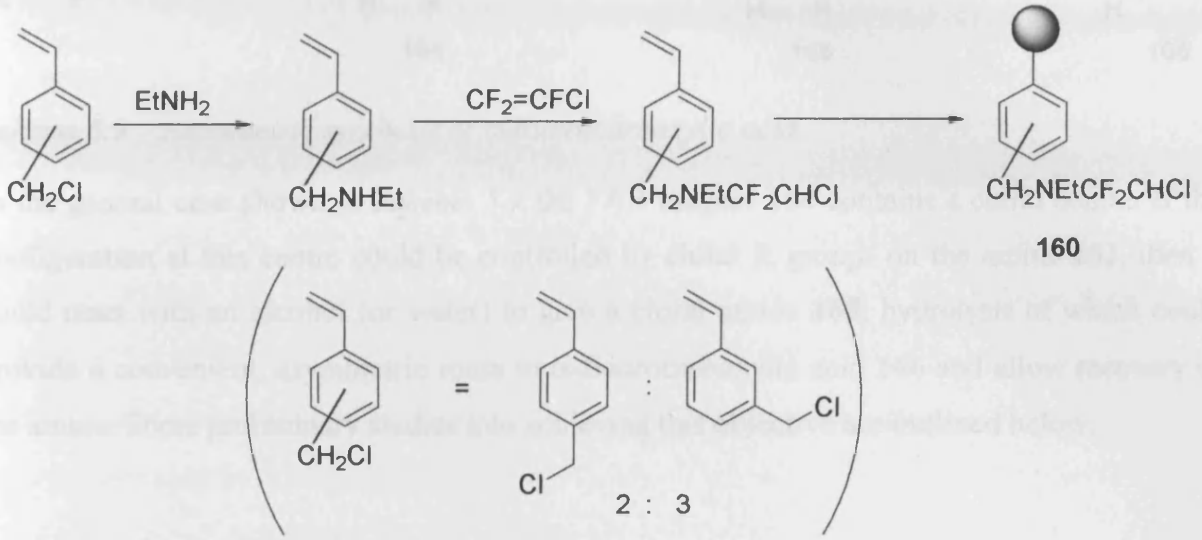


159

Figure 5.1 – More stable alternative to Yarovenko reagent.

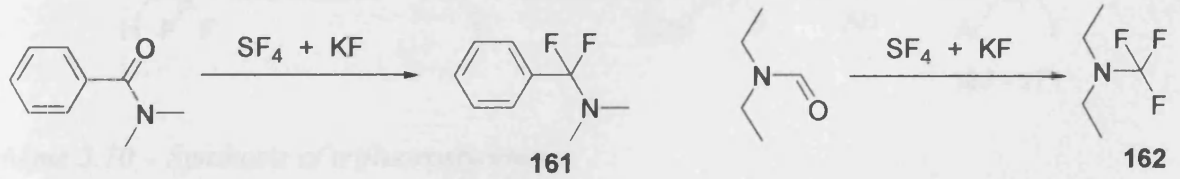
Banks *et al.* focussed their attention on development of a polymer-bound version of the Yarovenko reagent and were able to synthesise polymer **160**.[196] This was not only an effective

fluorinating agent, it was stable enough to be stored for several months under N_2 without loss of reactivity and had the advantages associated with polymer bound reagents in terms of product isolation.



Scheme 5.7 – Polymer bound fluorinating agent.

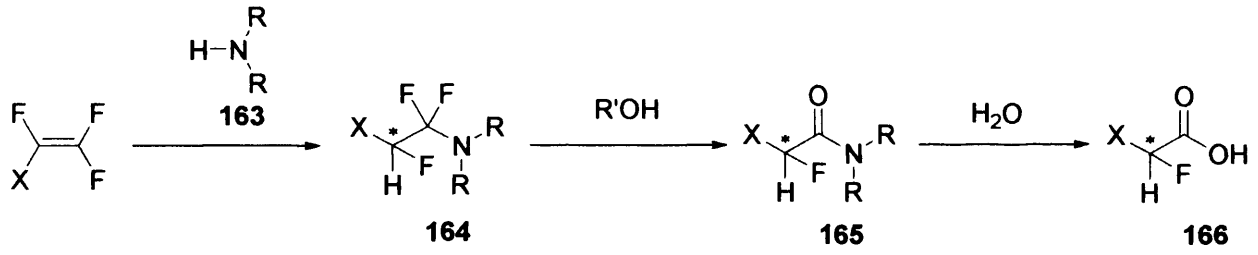
Another paper by Dmowski and co-workers looked at α,α-difluorobenzyldimethylamine (**161**) and diethyltrifluoromethylamine (**162**) as alternatives to the Yarovenko reagent (*Scheme 5.8*). These were synthesised by reaction of the amides with SF_4 and KF.[197]



Scheme 5.8 – More stable alternatives to Yarovenko reagent.

Both of these were found to react with alcohols in a similar way to the Yarovenko reagent and to display the same inertness towards other functional groups. What was of particular interest, however, was that reagent **162** in contrast to the Yarovenko reagent was found to be more reactive towards secondary and tertiary alcohols than it was towards primary alcohols, this makes it a useful alternative.

All of the research on fluoroalkylamine reagents carried out to date concentrates on the fluorination of alcohols but there is also some potentially interesting chemistry regarding the reagent itself.

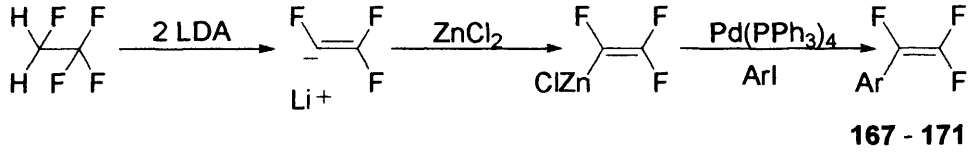


Scheme 5.9 – Asymmetric synthesis of α-fluorocarboxylic acid.

In the general case shown in *Scheme 5.9* the FAR reagent **164** contains a chiral centre. If the configuration at this centre could be controlled by chiral R groups on the amine **163**, then it could react with an alcohol (or water) to give a chiral amide **165**, hydrolysis of which could provide a convenient, asymmetric route to α-fluorocarboxylic acid **166** and allow recovery of the amine. Some preliminary studies into achieving this objective are outlined below.

5.2.1 Synthesis of Trifluorostyrenes

Synthesis of a number of trifluorostyrenes was carried out according to the method developed by Burton *et al.*[198] involving palladium-catalysed cross-coupling of a trifluorovinylzinc chloride with the appropriate aryl iodide.



Scheme 5.10 – Synthesis of trifluorostyrenes.

A number of trifluorostyrenes were made by this method as outlined in Table 5.1.

Compound Number	Ar group	Yield[a]
167	Phenyl	0%
168	4-Methoxyphenyl	82%
169	3-Methylphenyl	58%
170	3,4-Dimethoxyphenyl	63%
171	4-Nitrophenyl	0%

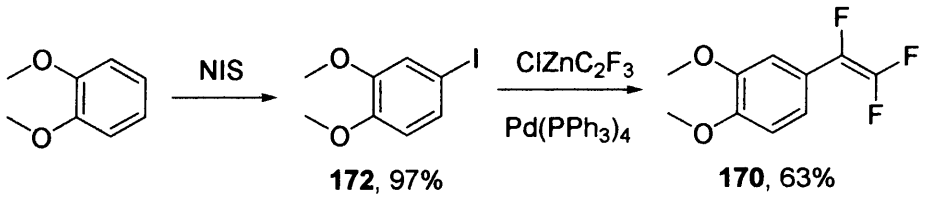
a) Yields calculated from ^{1}H NMR data

Table 5.1 – Yeilds of trifluorostyrenes.

In the case of **170**, the 3,4-dimethoxyphenyliodide (**172**) was made first by NIS iodination of 3,4-dimethoxybenzene[199] as shown in *Scheme 5.11*.

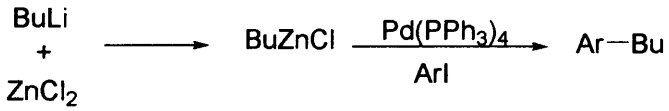
^{1}H NMR data from **170** showed two methoxy peaks at 3.79 and 3.80 ppm, one doublet (J_{HH} = 8.5 Hz) at 6.79 ppm corresponding to H6, and another at 6.84 (J_{HH} = 1.9 Hz) corresponding to H3, both of which were coupled to a double doublet, H5, at 6.92 ppm. Both the methoxy peaks and the aromatic peaks showed a significant shift from the starting material **172**, which had a similar pattern of peaks at 3.88 and 3.89 ppm (methoxy protons), and 6.65, 7.14 and 7.25 ppm (aromatic protons). In addition the ^{19}F NMR of **170** showed 3 double doublet peaks at 101.5 (J_{FF} = 25, 44 Hz), 117.0 (J_{FF} = 44, 170 Hz) and 175.0 (J_{FF} = 25, 170 Hz). Mass spectrometry also showed a molecular ion at m/e = 219.0630, corresponding to $[M+H]^+$.

Although this compound is novel, full characterisation could not be obtained due to the impure nature of the sample.



*Scheme 5.11 – Synthesis of **170**.*

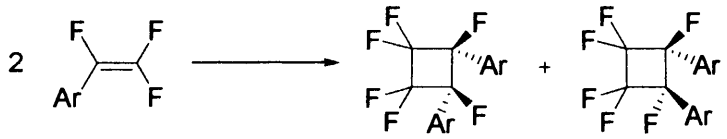
Unfortunately of those trifluorostyrenes which were isolated, all were impure and contained unreacted starting material and, in some cases, *n*-butyl aromatics formed from excess BuLi in the LDA.



Scheme 5.12 – Side reaction in synthesis of trifluorostyrenes.

Neither of these impurities could be removed from the desired product by chromatography and attempts to purify the styrenes by distillation resulted only in quantitative dimerisation of the styrene (*Scheme 5.13*).[200] In the case of **185**, the dimer of **168**, the NMR data showed a roughly 1:1 mixture of the *trans* and *cis* isomers; the ^{1}H NMR had methoxy peaks at 3.71 and 3.78 ppm (*cis* and *trans* respectively) and two pairs of doublets (J_{HH} = 8.8 Hz) at 6.74, 6.91 (for the 3' and 5' protons) and 7.09 and 7.93 ppm (for the 2' and 6' protons), with the *cis* isomer appearing upfield of the *trans*. Similarly the ^{19}F NMR shows the *trans* isomer appears as two singlets at -124.6 and -156.7 ppm, and the *cis* isomer is a pair of doublets (J_{FF} = 255 Hz) at -

121.5 and -128.4 and a singlet at -162.8 ppm. This distinctive ^{19}F NMR pattern is characteristic of dimers of this type, and is clearly seen in the paper by Sauvêtre *et al.*[200]

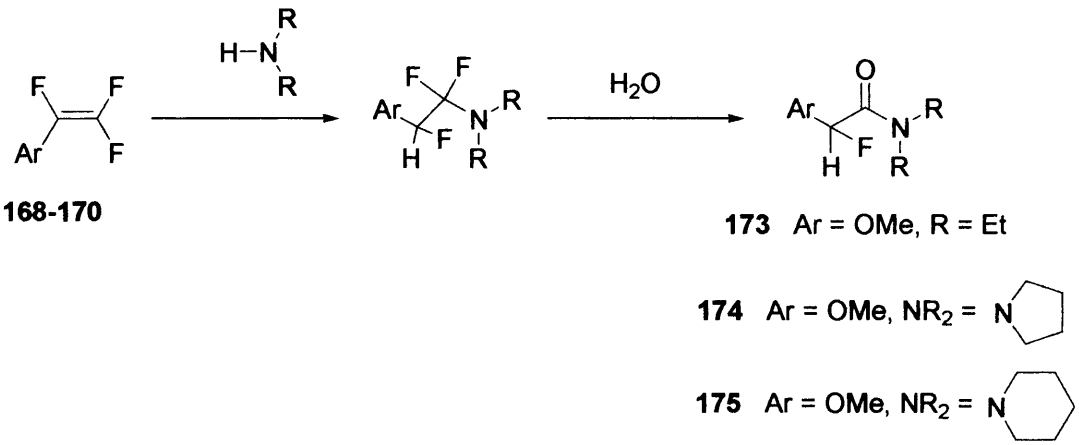


Scheme 5.13 – Dimerisation of trifluorostyrenes.

So the following reactions had to be carried out using impure styrene.

5.2.2 Addition of Non Chiral Amines to Trifluorostyrenes.

Reaction of styrenes **168 – 170** with three commercially available amines (diethylamine, piperidine and pyrrolidine) was attempted in order to generate FAR-type compounds, which would hydrolyse on aqueous work up to give amides (*Scheme 5.14*). The results are summarised in *Table 5.2*. Initially these reactions were carried out at room temperature and under basic conditions.



Scheme 5.14 – Addition of non-chiral amines to trifluorostyrenes.

	Diethylamine	Pyrrolidine	Piperidine
168	**173**, 11%	**174**, 19%	**175**, 13%
169	0%	0%	0%
170	0%	0%	0%

Table 5.2 – Yields of α-fluoro amides.

^{19}F NMR analysis of crude reaction mixtures in all cases showed, by loss of the three distinctive double doublets, that the styrene had reacted. However, presumably because of the

impure nature of the starting material, aqueous work up and extraction yielded a mixture of products which proved very difficult to separate. Although in the case of **168** the amides were isolated, yields were low and isolation was problematic.

Structures of **173**, **174** and **175** were confirmed by ^{1}H and ^{19}F NMR. For example in the case of **174** the proton NMR showed one large multiplet between 1.69 and 1.82 ppm corresponding to protons 3' and 4' on the pyrrolidine ring and a group of multiplets between 3.09 and 3.53 ppm caused by the four magnetically inequivalent 2' and 5' protons; the methoxy group appeared as a singlet at 3.75 ppm and the α proton as a doublet at 5.78 ppm (J_{HF} = 49.2 Hz), the aryl protons were a doublet (J_{HH} = 8.5 Hz) at 6.85 ppm and a double doublet (J_{HH} = 8.5, J_{HF} = 1.7 Hz) at 7.35 ppm.

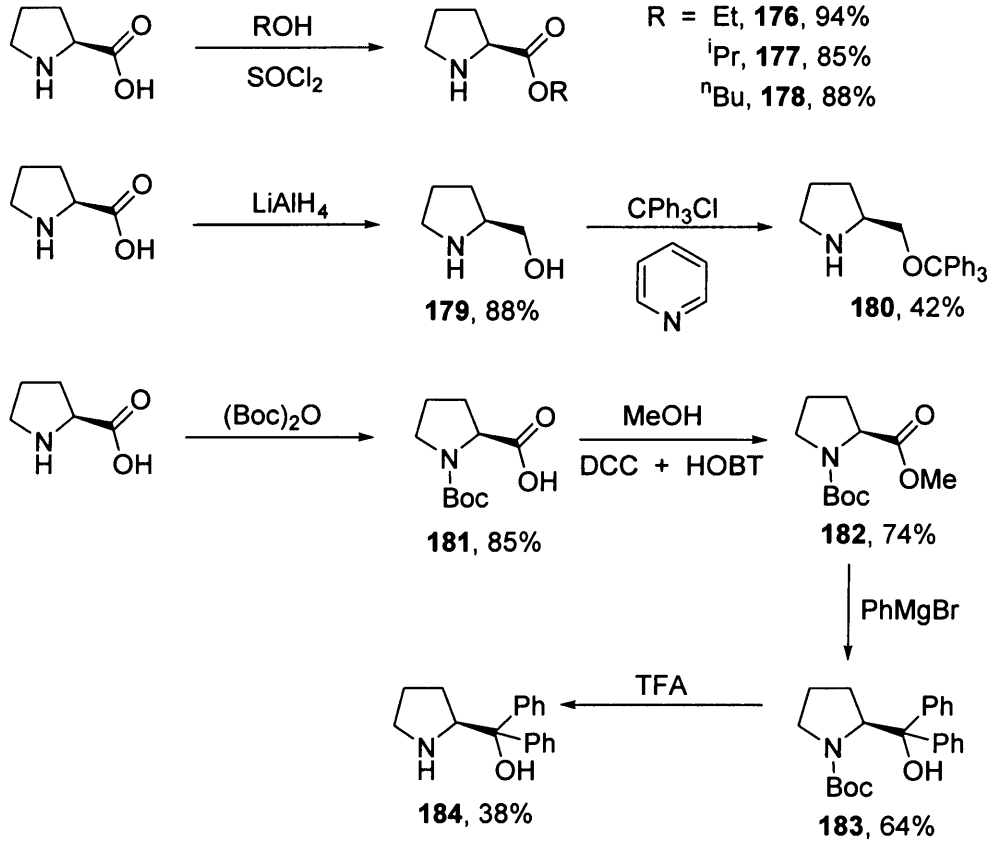
In an attempt to get the addition to work with **169** and **170**, the reaction was repeated at higher temperatures (80-90 °C). This resulted in an equally inseparable mixture, analysis of which by ^{19}F NMR and mass spectrometry showed that most of the styrene had dimerised.

5.2.3 Addition of Chiral Amines to Trifluorostyrenes.

The following chiral amines were synthesised from L-proline as shown in *Scheme 5.15*.

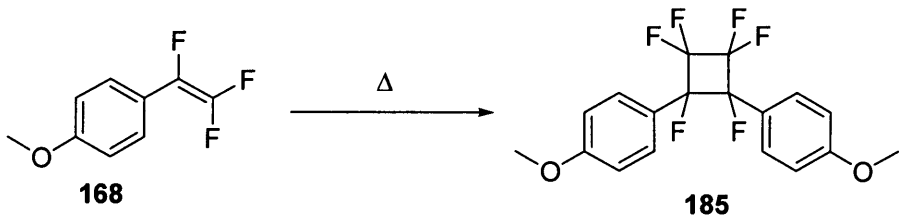
The esters were made by reaction with the appropriate alcohols in the presence of thionyl chloride.[201] L-prolinol was made by reduction of the amino acid with $LiAlH_4$,[202] and the alcohol was then protected with trityl chloride. And **184** was made by BOC protection of L-proline, followed by esterification, Grignard addition and deprotection with TFA.[203]

All these chiral amines are known compounds with the exception of trityl protected (*S*)-prolinol, **180**. ^{1}H NMR of **180** showed multiplet peaks at 1.68 – 1.73, 1.80 – 1.84, 2.84 – 2.94, and 3.30 – 3.33 ppm corresponding to the protons on the pyrrolidine ring at positions 3, 4, 5 and 2 respectively. The coupling between these magnetically inequivalent protons could not be fully analysed. The two protons on the side chain and the aromatic protons also appeared as multiplets at 3.05 – 3.11 and 7.21 – 7.45 ppm. More clear is the ^{13}C NMR which shows the C2, C3, C4 and C5 carbons at 58.4, 28.1, 25.1 and 46.3 ppm respectively and the side chain carbon at 66.5 ppm. The trityl group appears as a tertiary carbon at 86.3 and the aromatic carbons at 126.9, 127.8, 127.9 (para, ortho and meta positions) and 144.2 (C1' position). High resolution mass spectrometry showed the molecular ion ($[M+H]^+$) at 344.2017.



Scheme 5.15 – Synthesis of proline based chiral amines.

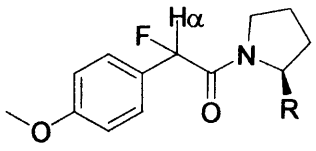
Initially esters **176**, **177** and **178** were made and reaction of these with styrene **168** was carried out under neutral conditions, no reaction occurred and only unreacted starting materials were recovered. The reaction was then repeated at 80 °C but, again heating only resulted in dimerisation of the styrene.



*Scheme 5.16 – Dimerisation of **168**.*

Compounds **180** and **184** were then made (*Scheme 5.15*) and addition of these to **168** was carried out under basic conditions at room temperature. Again, in both cases, this resulted in crude mixtures of products and, although ^{19}F NMR showed, as before, that no styrene remained in either reaction, the amide products could not be isolated as pure compounds, despite repeated chromatography columns. Careful analysis of the crude ^{1}H NMR did show, in both cases, that the alpha proton was present as a pair of doublets (J_{HF} ~ 50 Hz) at around 6 ppm, this would correspond to a pair of diastereoisomers and enabled the ratio of the

diastereoisomers in the amide products to be determined, although at this stage the configuration of the newly created chiral centre of the major diastereoisomer could not be determined.



Amine	R	Ratio of α protons	Diastereoisomeric excess
180	CH_2OCPh_3	2:5	43%
184	$C(Ph_2)OH$	2:3	20%

*Figure 5.2 – Diastereoisomeric excess in addition of chiral amines to trifluorine **168**.*

5.3 Summary and Conclusions

While it has been shown that addition of amines to trifluorostyrenes is successful and, in the case of chiral amines, does result in asymmetry at the α position, the impure nature of the styrenes used has meant that yields are low and isolation of the products is very difficult. Unfortunately this has meant that the amide diastereoisomers cannot yet be separated and their absolute configurations cannot yet be assigned. Nevertheless this provides at least proof-of-principle that the reaction can be used to provide stereochemically enriched α-fluoroamides. Further study of this process is clearly required.

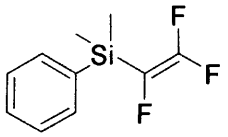
Chapter Six

6.1 Silane Synthesis

General Considerations: All reagents were purchased from commercial suppliers except those described below and used without further purification.

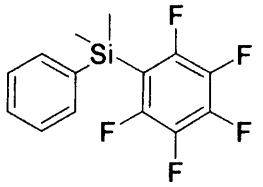
Thin layer chromatography was performed using Merck silica gel 60 F_{254} plates. Column chromatography was performed using silica gel 60 (220-440 mesh). Melting points were obtained using an uncalibrated Electrothermal digital melting point apparatus model 9100. IR spectra was obtained for all previously unreported compounds using a Perkin Elmer 1600 series FTIR instrument. Elemental analyses were performed by Warwick Analytical Services Ltd. ^{1}H NMR and ^{13}C NMR were carried out on a Bruker 400 MHz spectrometer and ^{19}F NMR on a Bruker 300 MHz spectrometer; chemical shifts for ^{1}H NMR are referenced to tetramethylsilane (TMS) as an internal standard, chemical shifts for ^{19}F to $CFCl_3$ and chemical shifts for ^{13}C NMR are referenced to the solvent used. Low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument. High resolution mass spectroscopy was carried out by the EPSRC national mass spectrometry service centre at Swansea University.

Dimethyl(trifluorovinyl)phenylsilane (12a)[204]



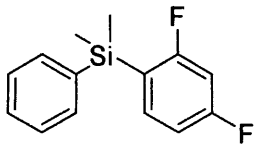
1,1,1,2-Tetrafluoroethane (3.5 g, 34.3 mmol) was condensed into a round-bottomed flask at -78 °C, dry ether (20 ml) was added and the mixture was stirred for 30 mins. *n*-Butyllithium (15 ml of a 1.6 M solution in hexanes) was added drop-wise with stirring and the solution was kept at –78 °C for a further 2.5 hrs. Chlorodimethylphenylsilane (2 g, 12.0 mmol) was then added and the mixture was allowed to warm up to room temperature and was stirred overnight. Aqueous work up followed by extraction into ether, drying over $MgSO_4$ and evaporation yielded **12a** (2.05 g, 81%) as a pale yellow oil, after purification by column chromatography (9:1 hexane:ethyl acetate, v/v). ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.41 (6H, s, $SiMe_2$), 7.24-7.33 (3H, m, H3, H4 and H5), 7.45-7.52 (2H, m, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -85.7 (1F, dd, *J* 23.5, 47 Hz), -114.2 (1F, dd, *J* 47, 160 Hz), -197.0 (1F, dd, *J* 23.5, 160 Hz). (Found $[M+H]^+$, 217.0659, $C_{10}H_{12}SiF_3$ requires $[M+H]^+$, 217.0660).

Dimethyl(pentafluorophenyl)phenylsilane (12b)[205]



Bromopentafluorobenzene (2.8 g, 11.3 mmol) was dissolved in dry ether (20 ml) at –78 °C. *n*-Butyllithium (4.5 ml of a 2.5 M solution in hexanes) was added drop-wise with stirring and the solution was kept at –78 °C for a further 2.5 hrs. Chlorodimethylphenylsilane (1.9 g, 11.1 mmol) was then added and the mixture was allowed to warm up to room temperature and stirred overnight. Aqueous work up followed by extraction into ether, drying over $MgSO_4$ and evaporation yielded **12b** (2.99 g, 83%) as a pale yellow oil, after purification by column chromatography (9:1 hexane ethyl acetate, v/v). ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.61 (6H, s, $SiMe_2$), 7.26-7.34 (3H, m, H3, H4 and H5), 7.43-7.46 (2H, m, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -128.4 (2F, m), -153.7 (1F, m), -163.6 (2F, m). (Found $[M+H]^+$, 303.0623, $C_{14}H_{12}SiF_5$ requires $[M+H]^+$, 303.0628).

Dimethyl(2,4-difluorophenyl)phenylsilane (12c)



2,4-Difluorobromobenzene (3 g, 15.5 mmol) was dissolved in dry ether (20 ml) at –78 °C. *n*-Butyllithium (7 ml of a 2.5 M solution in hexanes) was added drop-wise with stirring and the solution was kept at –78 °C for a further 3 hrs. Chlorodimethylphenylsilane (2.6 g, 15.2 mmol) was then added and the mixture was allowed to warm up to room temperature and stirred overnight. Aqueous work up followed by extraction into ether, drying over $MgSO_4$ and evaporation yielded **12c** (2.21 g, 67%) as a pale yellow oil, after purification by column chromatography (9:1 hexane ethyl acetate, v/v). ν_{max} ($CHCl_3$) 3070 w, 2959w, 1599s, 1487m, 1400s, 1252m, 1133m, 1071m, 966m, 837s cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.50 (6H, s, $SiMe_2$), 6.52-6.65 (1H, m, H3'), 6.70 – 6.79 (1H, m, H5'), 7.15 (1H, q, *J* 8.8 Hz H6'), 7.26 – 7.30 (3H, m, H3, H4 and H5), 7.44 – 7.64 (2H, m, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -98.0 (1F, m), -110.6 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 2.3 (s, $SiMe_2$), 103.5 (dd, *J* 38, 47 Hz, C3'), 111.3 (dd, *J* 6, 32 Hz, C5'), 120.1 (dd, *J* 7.5, 45 Hz, C1'), 128.0 (s, C3 and C5), 129.5 (s, C4), 133.1 (s, C1), 133.8 (s, C2 and C6), 137.1 (dd, *J* 15, 22 Hz, C6'), 164.2 (dd, *J*

18, 249 Hz, C4'), 168.0 (dd, *J* 17, 251 Hz, C2'); (Found $[M-F]^+$, 229.0845, $C_{14}H_{14}FSi$ requires $[M-F]^+$, 354). (229.0849)

6.2 Reaction with Aldehydes

General procedure for the addition of nucleophiles to aldehydes—Aldehyde (0.15 mmol) and silane (0.15 mmol) were added to a round-bottomed flask and dissolved in dry THF (15 ml). Fluoride catalyst was then added and the mixture was stirred at the listed temperature. After a given time, the reaction mixture was quenched with 1M HCl (10 ml), extracted into ethyl acetate, dried and evaporated. Where necessary, products were purified by chromatography (hexane:ethyl acetate 3:7 v/v).

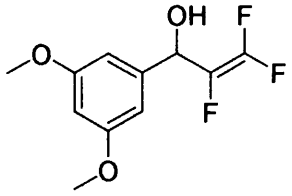
Reaction conditions as detailed in *Table 6.1*:

Silane	Aldehyde	Catalyst (mol%)	Time, Temperature	Yield of **13**
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C no solvent	9%
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	0%
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	3 days, 80 °C in THF	0%
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	CsF, 100 mol%	3 days, 80 °C	0%
Dimethyl(trifluorovinyl) phenylsilane	3,5-dimethoxy-benzaldehyde	CuF_2/dppb, 10 mol%	24 hrs, room temp. (under air) in THF	0%
Dimethyl(trifluorovinyl) phenylsilane	*p*-nitro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(trifluorovinyl) phenylsilane	*p*-chloro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(pentafluoroph enyl)phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C no solvent	20%
Dimethyl(pentafluoroph enyl)phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	11%

Dimethyl(pentafluorophenyl)phenylsilane	3,5-dimethoxy-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	0%
Dimethyl(pentafluorophenyl)phenylsilane	3,5-dimethoxy-benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(pentafluorophenyl)phenylsilane	3,5-dimethoxy-benzaldehyde	CsF, 100 mol%	5 days, 80 °C in THF	0%
Dimethyl(pentafluorophenyl)phenylsilane	3,5-dimethoxy-benzaldehyde	CuF_2/dppb, 10 mol%	24 hrs, room temp. (under air) in THF	0%
Dimethyl(pentafluorophenyl)phenylsilane	*p*-nitro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(pentafluorophenyl)phenylsilane	*p*-chloro-benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(2,4-difluorophenyl)phenylsilane	3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 100 mol%	48 hrs, 80 °C on solvent	39%
Dimethyl(2,4-difluorophenyl)phenylsilane	3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	31%
Dimethyl(2,4-difluorophenyl)phenylsilane	3,5 dimethoxy benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, room temp in THF	19%
Dimethyl(2,4-difluorophenyl)phenylsilane	3,5 dimethoxy benzaldehyde	CuF_2/dppb, 10 mol%	48 hrs, room temp. (under air) in THF	0%
Dimethyl(2,4-difluorophenyl)phenylsilane	3,5 dimethoxy benzaldehyde	$NBu_4SiPh_3F_2$, 100 mol%	48 hrs, 80 °C in THF	23%
Dimethyl(2,4-difluorophenyl)phenylsilane	benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	17%
Dimethyl(2,4-difluorophenyl)phenylsilane	*p*-trifluoromethyl-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	29%
Dimethyl(2,4-difluorophenyl)phenylsilane	*p*-nitro-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%
Dimethyl(2,4-difluorophenyl)phenylsilane	*p*-chloro-benzaldehyde	TBAF (1M in THF), 10 mol%	48 hrs, 80 °C in THF	0%

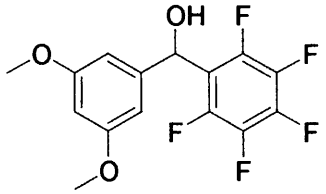
Table 6.1

1-(3,5-Dimethoxy-phenyl)-2,3,3-trifluoro-prop-2-en-1-ol (13a)



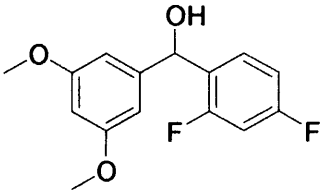
Yellow oil. ν_{max} ($CHCl_3$) 3247w,br, 1607m, 1520w, 1486s, 1286w, 1132m, 936w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.73 (6H, s, OMe), 6.20 (1H, d, *J* 36 Hz, Ar_2CHOH), 6.41 (1H, d, *J* 2.4 Hz, H4), 6.63 (2H, d, *J* 2.4 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -66.5 (1F, ddd, *J* 23.5, 36, 52 Hz) -72.0 (1F, dd, *J* 52, 155 Hz), -131.1 (1F, dd, *J* 23.5, 155 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 249.0730, $C_{11}H_{12}O_3F_3$ requires $[M+H]^+$, 249.0739).

Pentafluorophenyl 3,5-dimethoxybenzylalcohol (13b)



Cubic, colourless crystals, m.p. 132-133 °C; (Found: C, 54.33; H, 3.32. $C_{15}H_{11}O_3F_5$ requires C, 53.90; H, 3.32%); ν_{max} ($CHCl_3$) 3376m,br, 1599s, 1500s, 1298w, 1205m, 1156s, 1060m, 987m, 908m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.72 (6H, s, OMe), 6.06 (1H, s, Ar_2CHOH), 6.33 (1H, d, *J* 2.1 Hz, H4), 6.47 (2H, d, *J* 2.1 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -144.8 (3F, m), -162.8 (2F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M-F]^+$, 315.0641, $C_{15}H_{11}O_3F_4$ requires $[M-F]^+$, 315.0644).

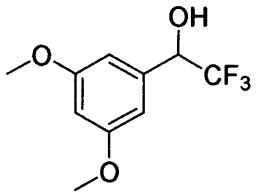
2',4'-difluorophenyl 3,5-dimethoxybenzylalcohol (13c)



Colourless oil. ν_{max} ($CHCl_3$) 3422s,br, 2940m, 1598s, 1460m, 1289m, 1205s, 1157s, 1061m, 966m, 850 cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.70 (6H, s, OMe), 5.96 (1H, s, Ar_2CHOH), 6.30 (1H, d, *J* 2.1 Hz, H4), 6.47 (2H, d, *J* 2.1 Hz, H2 and H6), 6.61-6.73 (1H, m, H3'), 6.78-

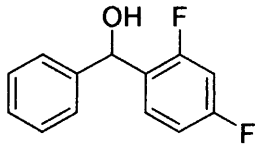
6.89 (1H, m, H5'), 7.30 (1H, q, *J* 7.9 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -111.0 (1F, m), -114.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.4 (s, OMe), 69.4 (s, CHOH), 99.5 (s, C4), 103.8 (dd, *J* 25, 51 Hz, C3'), 104.2 (s, C2 and C6), 111.4 (dd, *J* 4, 21 Hz, C5'), 126.8 (dd, *J* 4, 14 Hz, C1'), 128.7 (dd, *J* 6, 10 Hz, C6'), 145.1 (s, C1), 159.7 (dd, *J* 12, 247 Hz, C4'), 160.9 (s, C3 and C5), 162.3 (dd, *J* 12, 247 Hz, C2'); (Found $[M+H]^+$, 281.0985, $C_{15}H_{15}O_3F_2$ requires $[M+H]^+$, 281.0989).

Trifluoromethyl 3,5-dimethoxybenzylalcohol (13d)



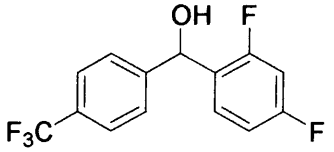
Colourless oil. ν_{max} ($CHCl_3$) 3453s,br, 2943m, 1601s, 1464s, 1265s, 1157s, 1065s, 836m cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.81 (6H, s, OCH_3), 4.93 (1H, q, *J* 6.7 Hz, ArCHOH), 6.50 (1H, d, *J* 2.2 Hz, H4), 6.64 (2H, d, *J* 2.2 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -77.9 (3F, d, *J* 6.7 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.4 (s, OMe), 72.6 (q, *J* 51 Hz, CHOH), 101.3 (s, C4), 105.6 (s, C2 and C6), 124.1 (q, *J* 252 Hz, CF_3), 136.4 (s, C1), 160.8 (s, C3 and C5); (Found $[M+H]^+$, 237.0738, $C_{10}H_{12}O_3F_3$ requires $[M+H]^+$, 237.0739).

(2,4-Difluoro-phenyl)-phenyl-methanol (13e)[206]



Colourless oil; ^{1}H NMR δ (400 MHz; $CDCl_3$), 5.98 (1H, s, CHOH), 6.51-6.64 (1H, m, H3'), 6.75-6.86 (1H, m, H5'), 7.23-7.34 (5H, m, H2, H3, H4, H5 and H6), 7.41 (1H, q, *J* 8.0 Hz, H6').

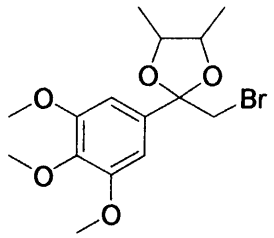
(2,4-Difluoro-phenyl)-(4-trifluoromethyl-phenyl)-methanol (13f)[206]



Colourless oil; ^{1}H NMR δ (400 MHz; $CDCl_3$), 6.11 (1H, s, CHOH), 6.74-6.96 (2H, m, H3' and H5'), 7.39 (1H, q, *J* 7.9 Hz, H6'), 7.50 (2H, d, *J* 8.3 Hz, H2 and H6), 7.60 (2H, d, *J* 8.3 Hz, H3 and H5).

6.3 Anti-cancer Chemistry

2-Ethyl-4,5-dimethyl-2-(3,4,5-trimethoxy-phenyl)-[1,3]dioxolane (14)

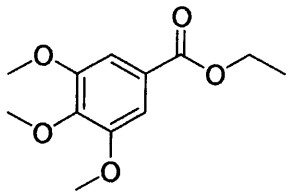


2-Bromo-1-(3',4',5'-trimethoxy-phenyl)-ethanone (1 g, 3.6 mmol), 2,3-butanediol (0.35 g, 3.9 mmol) and *p*-toluene-sulfonic acid (0.1 g, 0.5 mmol) were dissolved in toluene (50 ml) and refluxed at 110 °C overnight. The mixture was diluted with ether (100 ml), washed with water, dried over $MgSO_4$ and evaporated under vacuum to give **14** as a colourless oil (1.14 g, 88%); ν_{max} ($CHCl_3$) 2936m, 1683w, 1591s, 1503s, 1456s, 1413s, 1331s, 1232m, 1127s, 1006m, 926w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.19 (6H, d, *J* 5.5 Hz, Me), 3.54 (2H, s, CH_2Br), 3.80 (6H, s, OMe), 3.83 (3H, s, OMe), 4.10-4.14 (2H, m, OCHMe), 6.68 (2H, s, ArH); ^{13}C NMR δ (100 MHz; $CDCl_3$), 14.2 (s, Me), 36.8 (s, CH_2Br), 55.1 (s, OMe), 55.4 (s, OMe), 73.5 (s, OCHMe), 101.9 (s, C2 and C6), 104.5 (s, CAr), 135.2 (s, C1), 136.8 (s, C4), 152.0 (s, C3 and C5); (Found $[M+H]^+$, 361.0652, $C_{15}H_{21}O_5{}^{79}Br$ requires $[M+H]^+$, 361.0651).

Chapter Seven

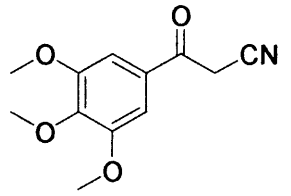
7.1 CN Chalcones

Ethyl 3,4,5-trimethoxybenzoate (37)[207]



3,4,5-Trimethoxybenzoic acid (9 g, 42 mmol) was dissolved in ethanol (50 ml). Conc. sulfuric acid (2 ml) was added and the solution was refluxed at 85 °C with stirring. After 3 hours the reaction mixture was cooled to room temperature, the solvent evaporated under vacuum and the residue taken up in ether (20 ml). This was washed with water and sat. $NaHCO_3$, dried over $MgSO_4$ and evaporated to yield white crystals (8.3 g, 81%). m.p. 53-55 °C (lit.m.p.[207] 60 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.41 (3H, t, J 7.0 Hz, $CH_2C\underline{H}_3$), 3.91 (3H, s, OMe), 3.92 (6H, s, OMe), 4.39 (2H, q, J 7.0 Hz, $C\underline{H}_2CH_3$), 7.32 (2H, s, H2 and H6).

3-Oxo-3-(3',4',5'-trimethoxyphenyl)propionitrile (38)[208]

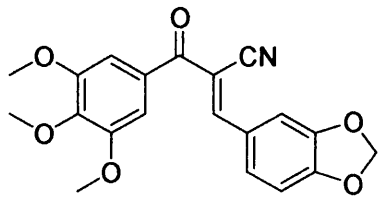


Ethyl 3,4,5-trimethoxybenzoate (**37**, 3.45 g, 14.4 mmol) and 60% dispersion sodium hydride in mineral oil (1.25 g, 31 mmol) were added to dry toluene (50 ml) under nitrogen and the suspension heated to 90 °C. Acetonitrile (1.5 ml, 29.3 mmol) was added drop wise with stirring and the mixture was stirred at 90 °C for a further 24 hrs. It was then cooled to room temperature and filtered. The filtrate was dissolved in water and the pH adjusted to 4 with 1M HCl. This was then extracted with DCM, dried over $MgSO_4$ and evaporated under vacuum to leave a crude solid, recrystallisation from 50/50 EtOH/water yielded yellow crystals (2.8 g, 83%). m.p. 138-140 °C (lit. m.p.[209] 139-140 °C); (Found: C, 60.82; H, 5.60; N, 5.88. $C_{12}H_{13}O_4N$ requires C, 61.27; H, 5.53; N, 5.96%); ν_{max} ($CHCl_3$) 2941s, 2267m, 1679s, 1582s, 1502s, 1459s, 1338m, 1117m, 989m, 757s cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.87 (6H, s, OMe), 3.88 (3H, s, OMe), 4.00 (2H, s, CH_2CN), 7.08 (2H, s, H2' and H6'); ^{13}C NMR δ (100 MHz; $CDCl_3$), 29.3 (s, C2), 56.4 (s, OMe), 61.1 (s, OMe), 106.0 (s, C2' and C6'), 114.0 (s,

C3), 129.3 (s, C1'), 143.9 (s, C4'), 153.3 (s, C3' and C5'), 186.0 (s, C1); (Found $[M+H]^+$, 236, $C_{12}H_{14}O_4N$ requires $[M+H]^+$, 236).

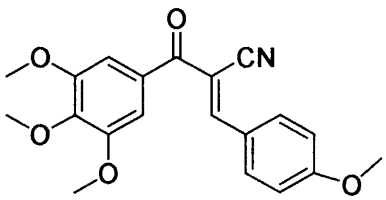
General procedure for the synthesis of chalcones—3-Oxo-3-(3,4,5-trimethoxyphenyl)propionitrile (**38**, 0.1 g, 0.43 mmol) and the appropriate aryl aldehyde (0.45 mmol) were warmed in ethanol (50 ml) until they dissolved. The solution was then cooled to room temperature and piperidine (3-5 drops) was added. If after 48 hours the chalcone product had not precipitated out, the ethanol was removed under vacuum and the residue partitioned between DCM and water. The DCM fraction was evaporated and the chalcone isolated by column chromatography (7:3 hexane:ethyl acetate, v/v).

3-Benzo[1,3]dioxol-5-yl-2-(3',4',5'-trimethoxybenzoyl)acrylonitrile (39a)



Yellow crystals (35%); m.p. 180-182 °C; (Found: C, 65.83; H, 4.85; N, 3.95. $C_{20}H_{17}NO_6$ requires C, 65.40; H, 4.63; N 3.81%); ν_{max} ($CHCl_3$) 2940w, 2248w, 1660m, 1609w, 1581m, 1504m, 1454m, 1416m, 1332s, 1276m, 1216m, 1129s, 1034w, 999w, 924w, 854w, 754m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.74 (6H, s, OMe), 3.76 (3H, s, OMe), 5.93 (2H, s, OCH_2O), 6.74 (1H, d, *J* 8.1 Hz, H5''), 6.99 (2H, s, H2' and H6'), 7.27 (1H, dd, *J* 1.5, 8.1 Hz, H6''), 7.61 (1H, d, *J* 1.5 Hz, H2''), 7.84 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.4 (s, OMe), 61.4 (s, OMe), 102.8 (s, OCH_2O), 107.0 (s, C2), 107.3 (s, C2' and C6'), 109.4 (s, C2'') overlapping 109.4 (s, C6''), 118.3 (s, CN), 126.8 (s, C5''), 130.5 (s, C1''), 131.3 (s, C1'), 143.0 (s, C4'), 149.1 (s, C4''), 152.9 (s, C3''), 153.4 (s, C3' and C5'), 155.7 (s, C3), 188.0 (s, C1); (Found $[M+H]^+$, 368.1134, $C_{20}H_{18}NO_6$ requires $[M+H]^+$, 368.1134).

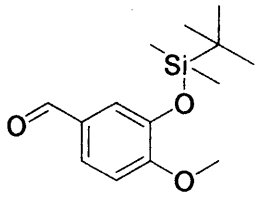
3-(4''-Methoxyphenyl)-2-(3',4',5'-trimethoxybenzoyl)acrylonitrile (39b)



Yellow powder (76%); m.p. 132-133 °C; (Found: C, 67.77; H, 5.55; N, 3.88. $C_{20}H_{19}O_5N$ requires C, 67.99; H, 5.38; N, 3.97%); ν_{max} ($CHCl_3$) 2940w, 2250m, 1660m, 1583s, 1510s, 1455m, 1414m, 1333s, 1268s, 1172s, 1127s, 1027m, 999m, 829m, 754s cm^{-1}; ^1H NMR δ (400

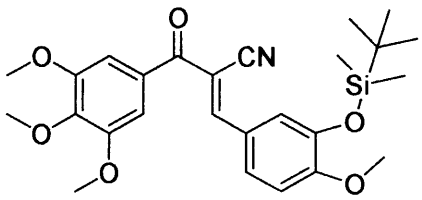
MHz; $CDCl_3$), 3.74 (3H, s, OMe), 3.76 (6H, s, OMe), 3.78 (3H, s, OMe), 6.85 (2H, d, *J* 8.9 Hz, H3'' and H5''), 7.01 (2H, s, H2' and H6'), 7.91 (2H, d, *J* 8.9 Hz, H2'' and H6'') overlapping, 7.94 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.7 (s, OMe), 56.4 (s, OMe), 61.1 (s, OMe), 106.2 (s, C2), 106.9 (2C, s, C2'' and C6''), 114.9 (s, C3' and C5'), 118.1 (s, CN), 124.8 (s, C1'), 131.1 (s, C1''), 133.9 (s, C2' and C6'), 142.5 (s, C4''), 153.0 (s, C3'' and C5''), 155.4 (s, C3), 164.0 (s, C4'), 187.8 (s, C1); (Found $[M+H]^+$, 354.1343, $C_{20}H_{20}O_5N$ requires $[M+H]^+$, 354.1341).

(O)-TBDMS-isovanilin (40)[210]



Isovanillin (1.56 g, 10.3 mmol) was dissolved in DMF (15 ml). TBDMS-Cl (1.76 g, 11.7 mmol) and imidazole (0.82 g) were added and the mixture was stirred overnight at room temperature. Water (100 ml) was then added and the product was extracted into chloroform, dried over $MgSO_4$ and evaporated under vacuum. Column chromatography (8:2 hexane:ethyl acetate, v/v) yielded a brown oil (1.875 g, 69%). ^1H NMR δ (400 MHz; $CDCl_3$), 0.01 (6H, s, $SiMe_2$), 0.83 (9H, s, ^tBu), 3.72 (3H, s, OMe), 6.78 (1H, d, *J* 8.3 Hz, H5), 7.20 (1H, d, *J* 1.9 Hz, H2), 7.31 (1H, dd, *J* 1.9, 8.3 Hz, H6), 9.64 (1H, s, CHO).

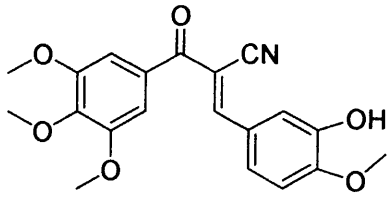
3-[3''-(*tert*-Butyldimethylsilyloxy)-4''-methoxyphenyl]-2-(3',4',5'-trimethoxybenzoyl)-acrylonitrile (39c)



A brown viscous oil (40%); $\nu_{max}(CHCl_3)$ 3015m, 2937m, 2859m, 2210w, 1659m, 1584s, 1504s, 1464s, 1442s, 1415s, 1333s, 1276s, 1242s, 1169s, 1129s, 789w, 753m, 730m, 665m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 0.01 (6H, s, $SiMe_2$), 0.80 (9H, s, ^tBu), 3.70 (3H, s, OMe), 3.71 (6H, s, OMe), 3.72 (3H, s, OMe), 6.74 (1H, d, *J* 8.5 Hz, H5''), 6.97 (2H, s, H2' and H6'), 7.46 (1H, dd, *J* 2.0, 8.5 Hz, H6''), 7.49 (1H, d, *J* 2.0 Hz, H2''), 7.81 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), -4.2 (s, $SiC(CH_3)_3$), -3.2 (s, $SiMe_2$), 26.0 (s, $C(CH_3)_3$), 53.9 (s, OMe), 56.1 (s, OMe), 61.4 (s, OMe), 102.3 (s, C2), 107.2 (s, C2' and C6'), 112.9 (s, C2''),

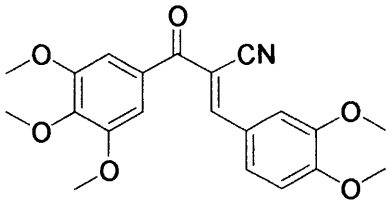
117.0 (s, CN), 117.4 (s, C5''), 126.7 (s, C6''), 126.1 (C1''), 131.4 (s, C1'), 142.2 (s, C3''), 146.6 (s, C4'), 151.9 (s, C4''), 153.4 (s, C3' and C5'), 155.5 (s, C3), 188.5 (s, C1); (Found M^+, 483.2079, $C_{26}H_{33}NO_6Si$ requires M^+, 483.2072).

3-(3''-Hydroxy-4''-methoxyphenyl)-2-(3',4',5'-trimethoxybenzoyl)acrylonitrile (39d)



3-[3''-(*tert*-Butyldimethylsilyloxy)-4''-methoxyphenyl]-2-(3',4',5'-trimethoxybenzoyl)-acrylonitrile (**39c**, 0.254 g, 0.5 mmol) was dissolved in dry THF (20 ml) and TBAF (1 ml of a 1 M solution in THF) was added. This was stirred for 30 mins after which time water (50 ml) was added. The mixture was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography (7:3 hexane:ethyl acetate, v/v) to give yellow crystals (0.117 g, 60%); m.p. 145-147 °C; (Found: C, 65.36; H, 5.57; N, 3.59. $C_{20}H_{19}NO_6$ requires C, 65.04; H, 5.15; N 3.79%); ν_{max} ($CHCl_3$) 2938s, 2255m, 1583m, 1506m, 1415m, 1331m, 1282m, 1127s, 754w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 3.94 (3H, s, OMe), 5.65 (1H, s, ArOH), 6.91 (1H, d, *J* 8.5 Hz, H5''), 7.12 (2H, s, H2' and H6'), 7.58 (1H, dd, *J* 2.2, 8.5 Hz, H6''), 7.65 (1H, d, *J* 2.2 Hz, H2''), 7.96 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.6 (s, OMe), 56.7 (s, OMe), 61.4 (s, OMe), 106.7 (s, C2), 107.3 (s, C2' and C6'), 111.2 (s, C2''), 116.8 (s, CN), 118.2 (s, C5''), 125.8 (s, C6''), 126.6 (C1''), 131.4 (s, C1'), 142.9 (s, C3''), 146.4 (s, C4'), 151.7 (s, C4''), 153.4 (s, C3' and C5'), 155.9 (s, C3), 188.3 (s, C1); (Found $[M+H]^+$, 370.1281, $C_{20}H_{20}NO_6$ requires $[M+H]^+$, 370.1285).

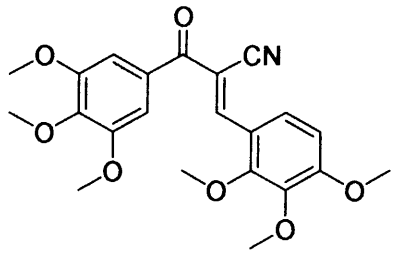
3-(3'',4''-Dimethoxyphenyl)-2-(3',4',5'-trimethoxybenzoyl)-acrylonitrile (39e)



Yellow powder (79%); m.p. 172-173 °C; (Found: C, 66.13; H, 5.66; N, 3.67. $C_{21}H_{21}NO_6$ requires C, 65.80; H, 5.48; N 3.66%); ν_{max} ($CHCl_3$) 2942w, 2205w, 1657m, 1583m, 1505s, 1466m, 1415m, 1333s, 1280s, 1216m, 1165m, 1127s, 1018m, 850w, 756m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.87 (6H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93

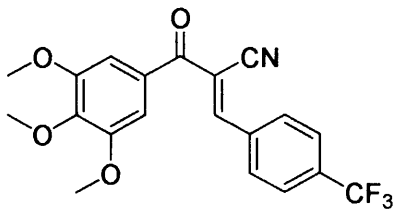
(3H, s, OMe), 6.89 (1H, d, *J* 8.5 Hz, H5''), 7.08 (2H, s, H2' and H6'), 7.46 (1H, dd, *J* 2.1, 8.5 Hz, H6''), 7.84 (1H, d, *J* 2.1 Hz, H2''), 8.02 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.5 (s, OMe), 56.6 (s, OMe), 56.8 (s, OMe), 61.4 (s, OMe), 106.5 (s, C2), 107.3 (s, C2' and C6'), 111.4 (s, C2''), 112.0 (s, C5''), 118.7 (s, CN), 125.4 (s, C6''), 128.8 (s, C1''), 131.5 (s, C1'), 142.9 (s, C4'), 149.7 (s, C4''), 153.4 (s, C3' and C5'), 154.3 (s, C3''), 156.1 (C3), 188.1 (s, C1); (Found $[M+H]^+$, 384.1441, $C_{21}H_{22}NO_6$ requires $[M+H]^+$, 384.1447).

2-(3',4',5'-Trimethoxybenzoyl)-3-(2'',3'',4''-trimethoxyphenyl)-acrylonitrile (39f)



Yellow powder (76%); m.p. 144-145 °C; (Found: C, 63.82; H, 5.68; N, 3.32. $C_{22}H_{23}NO_7$ requires C, 63.92; H, 5.57; N 3.39%); ν_{max} ($CHCl_3$) 2943w, 2237w, 1656m, 1581s, 1497s, 1462m, 1414s, 1330m, 1292s, 1214m, 1171w, 1127s, 1097s, 1004m, 754w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 6.75 (1H, d, *J* 9.0 Hz, H3''), 7.10 (2H, s, H2' and H6'), 8.22 (1H, d, *J* 9.0 Hz, H2''), 8.40 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.3 (s, OMe), 56.4 (s, OMe), 61.0 (s, OMe), 61.1 (s, OMe), 62.1 (s, OMe), 107.0 (s, C2), 107.4 (s, C5''), 107.6 (s, C2' and C6'), 118.0 (s, CN), 119.0 (s, C1''), 125.0 (s, C6''), 131.1 (s, C1'), 141.8 (s, C3''), 142.5 (s, C4'), 149.9 (s, C2''), 153.0 (s, C4''), 155.0 (s, C3' and C5'), 158.6 (s, C3), 188.2 (s, C1); (Found $[M+H]^+$, 414.1554, $C_{22}H_{24}NO_7$ requires $[M+H]^+$, 414.1553).

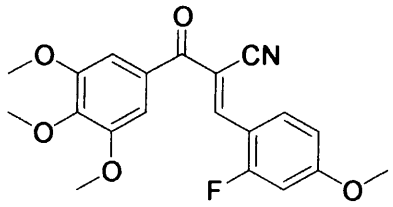
3-(4''-Trifluoromethylphenyl)-2-(3',4',5'-trimethoxybenzoyl)-acrylonitrile (39g)



White powder (51%); m.p. >230 °C; (Found: C, 61.78; H, 4.14; N, 3.21. $C_{20}H_{16}NO_4F_3$ requires C, 61.38; H, 4.09; N 3.58%); ν_{max}($CHCl_3$) 2950w, 2362w, 1716w, 1512w, 1463s, 1377s, 1331m, 1168w, 1129m, 1069w, 721m cm^{-1}; ^{1}H NMR δ (400 MHz; d6-DMSO), 3.67 (3H, s, OMe), 3.75 (6H, s, OMe), 6.55 (1H, s, H3), 6.97 (2H, s, H2' and H6'), 7.78 (2H, d, *J* 8.8 Hz, H3'' and H5''), 7.80 (2H, d, *J* 8.8 Hz, H2'' and H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -60.7

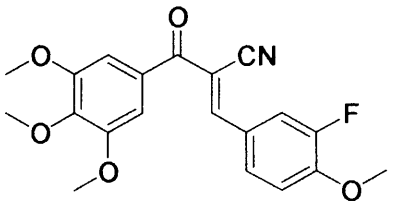
(1F, s); ^{13}C NMR δ (100 MHz; d6-DMSO), 56.3 (s, OMe), 60.3 (s, OMe), 103.0 (s, C2), 107.6 (s, C2' and C6'), 117.4 (s, CN), 123.3 (q, *J* 249 Hz, CF_3), 124.1 (s, C3'' and C5''), 126.9 (s, C2'' and C6''), 131.0 (q, *J* 50 Hz, C4'') 131.1 (s, C1'), 136.6 (s, C3), 139.0 (s, C1''), 142.5 (s, C4'), 155.0 (s, C3' and C5'), 188.3 (s, C1); (Found $[M+H]^+$, 392.1107, $C_{20}H_{17}NO_4F_3$ requires $[M+H]^+$, 392.1109).

3-(2''-Fluoro-4''-methoxyphenyl)-2-(3',4',5'-trimethoxybenzoyl)acrylonitrile (39h)



Yellow needles (41%); m.p. 168-170 °C; (Found: C, 64.58; H, 5.02; N, 3.83. $C_{20}H_{18}NO_5F$ requires C, 64.69; H, 4.85; N 3.77%); ν_{max} ($CHCl_3$) 3452s,br, 2208w, 1660m, 1617m, 1581m, 1503w, 1336w, 1300w, 1282w, 1219m, 1130m, 1097w, 1024w, 853w, 756w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.86 (3H, s, OMe), 3.89 (6H, s, OMe), 3.91 (3H, s, OMe), 6.65 (1H, dd, *J* 2.5, 12.2 Hz, H3''), 6.79 (1H, dd, *J* 2.5, 9.0 Hz, H5''), 7.10 (2H, s, H2' and H6'), 8.28 (1H, s, H3), 8.46 (1H, dd, *J* 8.8, 8.8 Hz, H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -108.6 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 58.9 (s, OMe), 59.2 (s, OMe), 63.9 (s, OMe), 104.6 (d, *J* 25 Hz, C3''), 109.8 (s, C2' and C6'), 110.7 (s, C2), 114.3 (d, *J* 17 Hz, C1''), 115.9 (d, *J* 11 Hz, C5''), 120.4 (s, CN), 133.3 (d, *J* 56 Hz, C6''), 145.5 (s, C1'), 149.1 (d, *J* 8 Hz, C4''), 155.9 (s, C3' and C5'), 166.5 (d, *J* 256 Hz, C2''), 168.3 (s, C4'), 168.4 (s, C3), 190.4 (s, C1); (Found $[M+H]^+$, 372.1241, $C_{20}H_{19}NO_5F$ requires $[M+H]^+$, 372.1247).

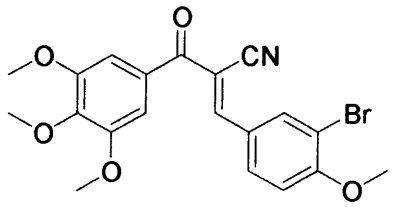
3-(3''-Fluoro-4''-methoxy-phenyl)-2-(3',4',5'-trimethoxy-benzoyl)-acrylonitrile (39i)



Yellow crystals (25%); m.p. 163-164 °C; (Found: C, 64.41; H, 4.83; N, 3.74. $C_{20}H_{18}O_5NF$ requires C, 64.70; H, 4.85; N, 3.77%); ν_{max} ($CHCl_3$) 3438s,br, 2280w, 1655m, 1582m, 1506s, 1415m, 1332s, 1287s, 1210m, 1127s, 1019w, 754m cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.87 (6H, s, OMe), 3.89 (3H, s, OMe), 3.93 (3H, s, OMe), 7.01 (1H, dd, *J* 8.5, 8.5 Hz, H5''), 7.13 (2H, s, H2' and H6'), 7.75 (1H, d, *J* 8.5 Hz, H6''), 7.88 (1H, dd, *J* 2.2, 12.0 Hz, H2''), 7.97 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -132.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$),

56.4 (s, OMe), 56.5 (s, OMe), 61.1 (s, OMe), 107.0 (s, C2' and C6'), 108.7 (s, C2), 109.8 (d, *J* 256 Hz, C3''), 114.3 (d, *J* 7 Hz, C1''), 114.7 (d, *J* 8 Hz, C5''), 117.4 (s, CN), 128.3 (d, *J* 17 Hz, C6''), 130.7 (s, C1'), 142.8 (d, *J* 51 Hz, C4''), 153.0 (s, C3' and C5'), 160.1 (d, *J* 25 Hz, C2''), 161.0 (s, C4'), 163.0 (s, C3), 187.2 (s, C1); (Found $[M+H]^+$, 372.1244, $C_{20}H_{19}NO_5F$ requires $[M+H]^+$, 372.1247).

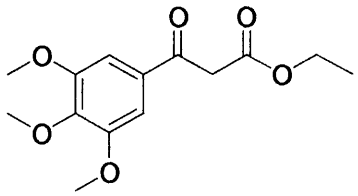
3-(3''-Bromo-4''-methoxyphenyl)-2-(3',4',5'-trimethoxybenzoyl)acrylonitrile (39j)



Yellow crystals (52%); m.p. 168-169 °C; (Found: C, 55.41; H, 4.21; N, 3.10. $C_{20}H_{18}NO_5Br$ requires C, 55.56; H, 4.17; N 3.24%); ν_{max} ($CHCl_3$) 3428s,br, 2242w, 1658m, 1583s, 1497s, 1414m, 1332m, 1275m, 1127s, 1012w, 754m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.87 (6H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 6.96 (1H, d, *J* 8.8 Hz, H5''), 7.12 (2H, s, H2' and H6'), 7.94 (1H, s, H3) 8.07 (1H, dd, *J* 2.3, 8.8 Hz, H6''), 8.16 (1H, d, *J* 2.3 Hz, H2''); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.8 (s, OMe), 57.1 (s, OMe), 61.5 (s, OMe), 107.3 (s, C2' and C6'), 108.1 (s, C2), 112.4 (s, C3''), 113.0 (s, C5''), 118.0 (s, CN), 126.3 (s, C6''), 131.1 (s, C1''), 132.7 (s, C1'), 137.2 (s, C2''), 143.1 (s, C4'), 153.4 (s, C3), 154.0 (s, C3' and C5'), 160.2 (s, C4''), 187.6 (s, C1); (Found $[M+H]^+$, 432.0442, $C_{20}H_{19}NO_5{}^{79}Br$ requires $[M+H]^+$, 432.0441).

7.2 Ester Chalcones

Ethyl 3-oxo-3-(3',4',5'-trimethoxyphenyl)propionate (41)[211]

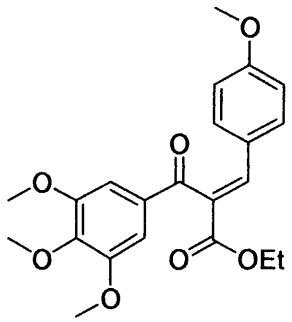


Diethyl carbonate (50 ml) and dibutyl ether (50 ml) were heated to reflux and sodium (2 g, 87 mmol) was added cautiously with stirring over 30 mins. The resulting purple solution was stirred for 30 mins and then 3,4,5-trimethoxyacetophenone (4 g, 19 mmol) was added over 30 mins more. The reaction mixture was refluxed for a further 4 hours, cooled to room temperature and poured over crushed ice and acetic acid (200 ml). This was extracted into ether, evaporated and recrystallisation from methanol yielded **41** as white needles (3.5 g, 67%).

m.p. 90-91 °C (lit. m.p.[212] 93-94 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.28 (3H, t, *J* 7.1 Hz, CH_3), 3.93 (6H, s, OMe), 3.94 (3H, s, OMe), 3.98 (2H, s, $COCH_2CO$) 4.23 (2H, q, *J* 7.1 Hz, CH_2), 7.27 (2H, s, H2' and H6').

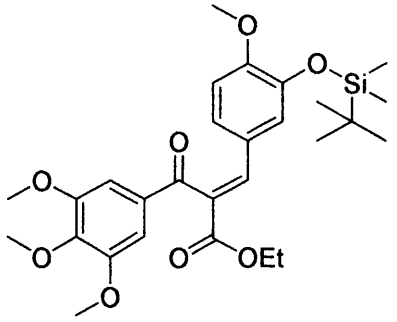
(The following chalcones were prepared by reaction of **41** with aldehydes according to the procedure described above)

(*Z*)-2-Ethoxycarbonyl-3-(4''-Methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)propen-1-one (42a)



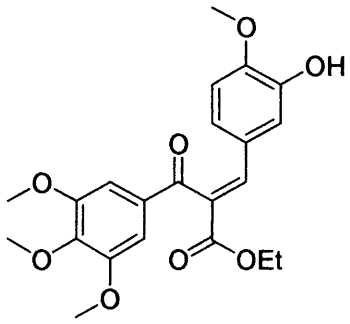
Pale oil (11%); ν_{max} ($CHCl_3$) 2937w, 1714s, 1602s, 1513m, 1414m, 1328s, 1254s, 1175s, 1126s, 1024w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.24 (3H, t, *J* 7.1 Hz, CH_3), 3.80 (3H, s, OMe), 3.86 (6H, s, OMe), 3.96 (3H, s, OMe), 4.27 (2H, q, *J* 7.1 Hz, CH_2), 6.80 (2H, d, *J* 8.9 Hz, H3'' and H5''), 7.25 (2H, s, H2' and H6'), 7.34 (2H, d, *J* 8.9 Hz, H2'' and H6''), 7.94 (1H, s, H3). ^{13}C NMR δ (100 MHz; $CDCl_3$), 14.2 (s, CH_3), 55.3 (s, OMe), 56.2 (s, OMe), 61.0 (s, OMe), 61.4 (s, CH_2), 106.4 (s, C2' and C6'), 114.3 (s, C3'' and C5''), 125.4 (s, C2), 128.3 (s, C1''), 131.3 (s, C1'), 132.3 (s, C2'' and C6''), 142.4 (s, C3), 143.2 (s, C4'), 153.2 (s, C3' and C5'), 161.4 (s, C4''), 165.4 (s, COOEt), 195.0 (s, C1); (Found $[M+H]^+$, 401.1602, $C_{22}H_{25}O_7$ requires $[M+H]^+$, 401.1600).

(*Z*)-2-Ethoxycarbonyl-3-[3''-(*tert*-Butyl-dimethyl-silanyloxy)-4''-methoxy-phenyl]-1-(3',4',5'-trimethoxyphenyl)propen-1-one(42b)



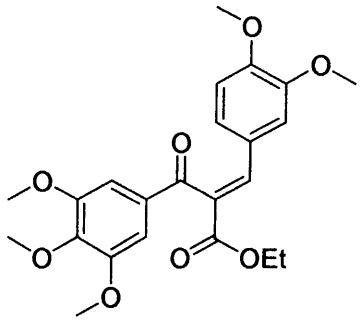
Dark brown oil (57%); ν_{max} ($CHCl_3$) 2937s, 2857m, 1733s, 1713s, 1665s, 1616m, 1510s, 1443s, 1373s, 1267s, 1247s, 1188s, 1162s, 1130s, 1094m, 1000s, 910m, 844s, 810m, 785m, 738s, 704s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 0.00 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $C(CH_3)_3$), 1.28 (3H, t, *J* 7.0 Hz, $OCH_2C\underline{H}_3$), 3.80 (3H, s, OMe), 3.85 (6H, s, OMe), 3.92 (3H, s, OMe), 4.25 (2H, q, *J* 7.0 Hz, $OC\underline{H}_2CH_3$), 6.76 (1H, d, *J* 8.5 Hz, H5''), 6.83 (1H, d, *J* 2.2 Hz, H2''), 7.02 (1H, dd, *J* 2.2, 8.5 Hz, H6''), 7.26 (2H, s, H2' and H6'), 7.86 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), -4.9 (s, $SiMe_2$), 14.2 (s, $CH_2\underline{C}H_3$), 18.3 (s, $\underline{C}Me_3$), 25.6 (s, $C(\underline{C}H_3)_3$), 55.4 (s, OMe), 56.2 (s, OMe), 60.9 (s, OMe), 61.4 (s, $\underline{C}H_2CH_3$), 106.4 (s, C2' and C6'), 111.6 (s, C5''), 121.9 (s, C2''), 125.6 (s, C2), 126.1 (s, C6''), 128.1 (s, C1''), 131.3 (s, C1'), 142.4 (s, C3), 143.2 (s, C3''), 144.9 (s, C4'), 153.3 (s, C3' and C5'), 153.3 (s, C4''), 165.4 (s, COOEt), 194.7 (s, C1); (Found $[M+H]^+$, 531.2410, $C_{28}H_{39}O_8Si$ requires $[M+H]^+$, 531.2414).

(*Z*)-2-Ethoxycarbonyl-3-(3''-Hydroxy-4''-methoxy-phenyl)-1-(3',4',5'-trimethoxyphenyl)propen-1-one (42c)



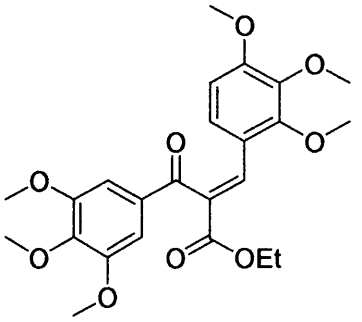
Pale yellow, cubic crystals (70%); m.p. 123-125 °C; (Found: C, 63.46; H, 5.84. $C_{22}H_{24}O_8$ requires C, 63.46; H, 5.77%); ν_{max} ($CHCl_3$) 3412s,br, 2938s, 1664s, 1581s, 1510s, 1459m, 1324m, 1251s, 1128s, 754s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.14 (3H, t, *J* 7.1 Hz, CH_3), 3.76 (6H, s, OMe), 3.77 (3H, s, OMe), 3.84 (3H, s, OMe), 4.16 (2H, q, *J* 7.1 Hz, CH_2), 5.67 (1H, s, OH), 6.65 (1H, d, *J* 8.1 Hz, H5''), 6.84 (1H, dd, *J* 2.2, 8.1 Hz, H6''), overlapping 6.85 (1H, d, *J* 2.2 Hz, H2''), 7.14 (2H, s, H2' and H6'), 7.78 (1H, s, H3). ^{13}C NMR δ (100 MHz; $CDCl_3$), 14.2 (s, CH_3), 55.9 (s, OMe), 56.2 (s, OMe), 60.9 (s, OMe), 61.5 (s, CH_2), 106.4 (s, C2' and C6'), 110.5 (s, C2''), 116.0 (s, C5''), 123.7 (s, C6''), 126.3 (s, C2), 128.9 (s, C1''), 131.4 (s, C1'), 142.5 (s, C3), 143.1 (s, C3''), 145.5 (s, C4'), 148.5 (s, C4''), 153.2 (s, C3' and C5'), 165.3 (s, COOEt), 194.7 (s, C1); (Found $[M+H]^+$, 417.1547, $C_{22}H_{25}O_8$ requires $[M+H]^+$, 417.1544).

(*Z*)-2-Ethoxycarbonyl-3-(3'',4''-dimethoxy-phenyl)-1-(3',4',5'-trimethoxyphenyl)propen-1-one (42d)



Colourless oil (35%); ν_{max} ($CHCl_3$) 2938s, 1713s, 1582s, 1414m, 1325m, 1228s, 1127s, 1023m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.16 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH_3}$), 3.57 (3H, s, OMe), 3.76 (6H, s, OMe), 3.78 (3H, s, OMe), 3.84 (3H, s, OMe) 4.18 (2H, q, *J* 7.1 Hz, $\underline{CH_2}CH_3$), 6.69 (1H, d, *J* 8.4 Hz, H5''), 6.77 (1H, d, *J* 1.8 Hz, H2''), 6.94 (1H, dd, *J* 1.8, 8.4 Hz H6''), 7.17 (2H, s, H2' and H6') 7.82 (1H, s, H3). ^{13}C NMR δ (100 MHz; $CDCl_3$), 14.2 (s, CH_3), 55.6 (s, OMe), 55.9 (s, OMe), 56.3 (s, OMe), 61.0 (s, OMe), 61.5 (s, CH_2), 106.3 (s, C2' and C6'), 110.9 (s, C2''), 112.3 (s, C5''), 125.0 (s, C6''), 125.6 (s, C2), 128.5 (s, C1''), 131.4 (s, C1'), 142.5 (s, C3), 143.3 (s, C4'), 148.7 (s, C4''), 151.0 (s, C3''), 153.3 (s, C3' and C5'), 165.3 (s, COOEt), 194.9 (s, C1); (Found $[M+H]^+$, 431.1701, $C_{23}H_{27}O_8$ requires $[M+H]^+$, 431.1706).

(*Z*)-2-Ethoxycarbonyl-3-(2'',3'',4''-trimethoxy-phenyl)-1-(3',4',5'-trimethoxyphenyl)propen-1-one (42e)



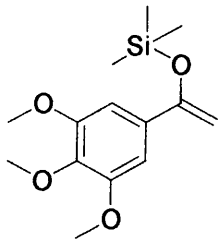
Yellow oil (48%); ν_{max} ($CHCl_3$) 2940s, 2363w, 1714s, 1585s, 1462s, 1326s, 1229s, 1100s, 1006s, 704m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.13 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH_3}$), 3.73 (6H, s, OMe), 3.77 (6H, s, OMe), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 4.18 (2H, q, *J* 7.1 Hz, $\underline{CH_2}CH_3$), 6.39 (1H, d, *J* 8.8 Hz, H5''), 6.87 (1H, d, *J* 8.8 Hz, H6''), 7.12 (2H, s, H2' and H6'), 8.14 (1H, s, H3); ^{13}C NMR δ (100 MHz; $CDCl_3$), 14.2 (s, CH_3), 55.9 (s, OMe), 56.2 (s, OMe), 60.8 (s, OMe), 60.9 (s, OMe), 61.3 (s, OMe), 61.5 (s, CH_2), 106.3 (s, C2' and C6'), 107.3 (s, C5''), 120.0 (s, C1''), 125.1 (s, C6''), 129.3 (s, C2), 131.4 (s, C1'), 137.7 (s, C3), 141.8 (s,

C4'), 142.9 (s, C3''), 153.1 (s, C3' and C5'), 155.8 (s, C2''), 156.0 (s, C4''), 165.3 (s, COOEt), 194.6 (s, C1); (Found $[M+H]^+$, 461.1806, $C_{24}H_{29}O_9$ requires $[M+H]^+$, 461.1812).

Chapter Eight

8.1 α-Fluorochalcones

3,4,5-Trimethoxyacetophenone trimethylsilyl enol ether (86)[213]

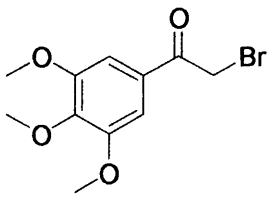


Diisopropylamine (5.5 g, 54.5 mmol) was dissolved in dry THF (100 ml) at 0 °C and BuLi (20 ml of a 2.5 M solution in hexanes) was added drop-wise with stirring. This was then cooled to -78 °C and 3,4,5-trimethoxyacetophenone (10 g, 47.6 mmol) was added, followed by HMPA (8.5 ml). After a further 10 mins, trimethylsilylchloride (6.0 g, 55.0 mmol) in THF (20 ml) was added and the mixture was left to warm slowly to room temperature. It was then diluted with hexane (100 ml), washed with water and sat. NaCl solution, dried over $MgSO_4$ and evaporated under vacuum to leave a colourless oil (5.1 g, 38%). ^1H NMR δ (400 MHz; $CDCl_3$) 0.05 (9H, s, $Si(CH_3)_3$), 3.64 (6H, s, OMe), 3.67 (3H, s, OMe), 4.21 (1H, s, (*Z*)=CH), 4.63 (1H, s, (*E*)=CH), 6.66 (2H, s, ArH).

Fluorination of 3,4,5-trimethoxyacetophenone ^{t}butyldimethylsilyl enol ether

3,4,5-Trimethoxyacetophenone ^{t}butyldimethylsilyl enol ether (0.1 g, 0.31 mmol) and Selectfluor™ (0.11 g, 0.31 mmol) were dissolved in acetonitrile (10 ml) and stirred at room temperature for 2 hrs. The acetonitrile was then evaporated and the residue was partitioned between water and dichloromethane. Evaporation of the DCM yielded 0.083 g of oil, ^1H NMR analysis of which showed it to be a 3:2 mixture of 3,4,5-trimethoxyacetophenone : 2'-fluoro-3,4,5-trimethoxyacetophenone.

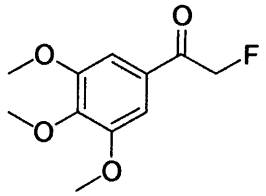
2'-Bromo-3,4,5-trimethoxyacetophenone (87)[214]



3,4,5-Trimethoxyacetophenone (10 g, 47.6 mmol) was dissolved in acetic acid (50 ml) and stirred at room temperature. Bromine (2.5 ml, 48.8 mmol) was added drop-wise with stirring

and the mixture was then left for a further 2 hrs. Water (200 ml) was added and the product was extracted into DCM, washed with sat. NaCl, dried over $MgSO_4$ and evaporated to leave a black oil. Purification by silica chromatography using a 3:7 mixture of EtOAc : hexane (Rf=0.23) yielded **87** as white crystals (5.71 g, 43%). m.p. 67–68 °C (lit.[215] m.p. 68-70 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.87 (3H, s, OMe), 4.35 (2H, s, H2'), 7.19 (2H, s, H2 and H6); (Found $[M+H]^+$, 289, $C_{11}H_{13}O_4{}^{79}Br$ requires $[M+H]^+$, 289).

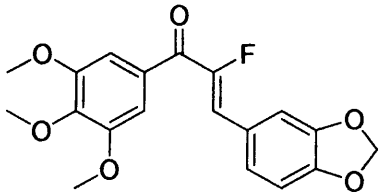
2'-Fluoro-3,4,5-trimethoxyacetophenone (82)



Potassium fluoride (4.0 g, 71 mmol) was dried by heating in a 2 neck, round bottomed flask with a Bunsen flame under high vacuum and then cooled to room temperature under N_2. 2'-Bromo-3,4,5-trimethoxyacetophenone (1.1 g, 4.0 mmol) and 18-crown-6 (0.2 g, 0.76 mmol) in dry MeCN (20 ml) were then added and the mixture was refluxed for 24 hrs. The solvent was then removed under vacuum and the residue partitioned between DCM and water. The DCM fraction was dried and evaporated to leave a brown oil, purification by silica chromatography using a 4:6 mixture of EtOAc : hexane (R_f=0.22) yielded **82** as yellow crystals (0.75 g, 94%). m.p. 120-122 °C; (Found: C, 58.46; H, 5.83. $C_{11}H_{13}O_4F$ requires C, 57.89; H, 5.74%); ν_{max} ($CHCl_3$) 2944m, 2359m, 1702s, 1587s, 1463s, 1416s, 1326m, 1128s, 990 m, 820w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.84 (6H, s, OMe), 3.85 (3H, s, OMe), 5.49 (2H, d, *J* 47.0 Hz, H2'), 7.07 (2H, s, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -173.4 (1F, t, *J* 47 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.4 (s, OMe), 61.0 (s, OMe), 83.6 (d, *J* 226 Hz, C2'), 105.3 (s, C2 and C3), 128.8 (s, C1), 143.4 (s, C4), 153.3 (s, C3 and C5), 192.3 (d, *J* 15 Hz, C1'); (Found $[M+H]^+$, 229.0874, $C_{11}H_{14}O_4F$ requires $[M+H]^+$, 229.0876).

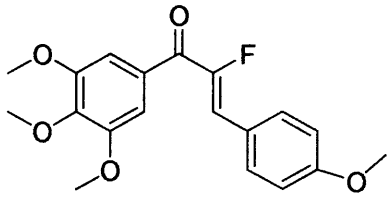
General procedure for the synthesis of α-fluorochalcones—2'-Fluoro-3,4,5-trimethoxyacetophenone (**82**, 0.1 g, 0.44 mmol) and the appropriate aryl aldehyde (0.45 mmol) were warmed in ethanol (50 ml) until they dissolved. The solution was then cooled to room temperature and piperidine (3-5 drops) was added. If after 48 hours the chalcone product had not precipitated out, the ethanol was removed under vacuum and the residue partitioned between DCM and water. The DCM fraction was evaporated and the chalcone isolated by column chromatography (7:3 hexane:ethyl acetate, v/v).

(*Z*)-3-Benzo[1,3]dioxol-5-yl-2-fluoro-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83a)



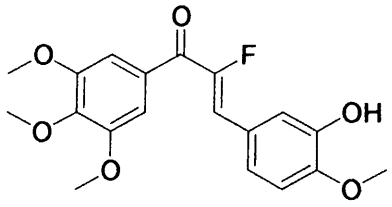
Yellow crystals (84%); m.p. 127-129 °C; (Found: C, 62.71; H, 4.76. $C_{19}H_{17}O_6F$ requires C, 63.33; H, 4.72%); ν_{max} ($CHCl_3$) 3009m, 1667w, 1581s, 1502m, 1450s, 1416m, 1337s, 1228w, 1135s, 1037w, 1000w, 930w, 888w, 799w, 751s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 5.96 (2H, s, OCH_2O), 6.78 (1H, d, *J* 36 Hz, H3), 6.80 (1H, d, *J* 8.1 Hz, H5'') 7.08 (1H, d, *J* 8.1 Hz, H6''), 7.10 (2H, s, H2' and H6'), 7.28 (1H, s, H2''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -122.0 (1F, d, *J* 36 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.3 (s, OMe), 61.0 (s, OMe), 101.7 (s, OCH_2O), 106.9 (d, *J* 5 Hz, C3), 108.7 (s, C2' and C6'), 109.9 (d, *J* 11 Hz, C2''), 120.1 (d, *J* 6 Hz, C5''), 125.5 (d, *J* 4 Hz, C6''), 126.4 (d, *J* 7 Hz, C1''), 131.3 (s, C1'), 142.4 (s, C4'), 148.2 (s, C4''), 149.3 (s, C3''), 152.9 (s, C3' and C5'), 153.7 (d, *J* 269 Hz, C2), 186.4 (d, *J* 28 Hz, C1); (Found $[M+H]^+$, 361.1081, $C_{19}H_{18}O_6F$ requires $[M+H]^+$, 361.1082).

(*Z*)-2-Fluoro-3-(4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83b)



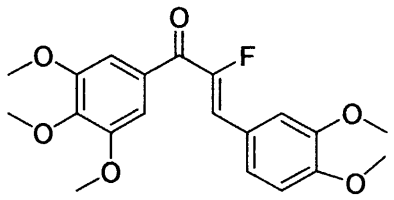
Yellow crystals (68%); m.p. 75-76 °C; (Found: C, 65.21; H, 5.46. $C_{19}H_{19}O_5F$ requires C, 65.90; H, 5.49%); ν_{max} ($CHCl_3$) 3430s, 2938m, 1658m, 1602s, 1512s, 1462m, 1332s, 1257s, 1173s, 1127s, 1029m, 756m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 6.81 (1H, d, *J* 37 Hz, H3), 6.89 (2H, d, *J* 8.8 Hz, H3'' and H5''), 7.10 (2H, s, H2' and H6'), 7.62 (2H, d, *J* 8.8 Hz, H2'' and H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -121.8 (1F, d, *J* 37 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.4 (s, OMe), 56.3 (s, OMe), 61.0 (s, OMe), 106.9 (d, *J* 5 Hz, C2' and C6'), 114.4 (s, C3'' and C5''), 120.2 (d, *J* 6 Hz, C3), 124.1 (d, *J* 4 Hz, C1''), 131.4 (s, C1'), 132.5 (d, *J* 8 Hz, C2'' and C6''), 142.3 (s, C4'), 152.9 (s, C3' and C5'), 153.6 (d, *J* 268 Hz, C2), 161.0 (d, *J* 3 Hz, C4''), 186.6 (d, *J* 27 Hz, C1); (Found $[M+H]^+$, 347.1285, $C_{19}H_{20}O_5F$ requires $[M+H]^+$, 347.1289).

(*Z*)-2-Fluoro-3-(3''-hydroxy-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83c)



Yellow crystals (75%); m.p. 132-135 °C; (Found: C, 62.39; H, 5.16. $C_{19}H_{19}O_6F$ requires C, 62.98; H, 5.25%); ν_{max} ($CHCl_3$) 3423w,br, 2940 M, 1579s, 1506s, 1415m, 1334m, 1253m, 1127s, 1001w, 755w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 5.60 (1H, s, ArOH), 6.77 (1H, d, *J* 37 Hz, H3), 6.83 (1H, d, *J* 8.4 Hz, H5''), 7.11 (2H, s, H2' and H6'), 7.15 (1H, dd, *J* 2.0, 8.4 Hz, H6''), 7.33 (1H, d, *J* 2.0 Hz, H2''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -121.6 (1F, d, *J* 37 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.0 (s, OMe), 56.3 (s, OMe), 61.0 (s, OMe), 106.9 (d, *J* 5 Hz, C3), 110.6 (s, C2' and C6'), 116.3 (d, *J* 10 Hz, C2''), 120.1 (d, *J* 5 Hz, C5''), 124.1 (d, *J* 8 Hz, C6''), 124.9 (d, *J* 4 Hz, C1''), 131.3 (s, C1'), 142.3 (s, C4'), 145.7 (s, C3''), 148.2 (d, *J* 3 Hz, C4''), 152.9 (s, C3' and C5'), 153.8 (d, *J* 269 Hz, C2), 186.5 (d, *J* 28 Hz, C1); (Found $[M+H]^+$, 363.1243, $C_{19}H_{20}O_6F$ requires $[M+H]^+$, 363.1244).

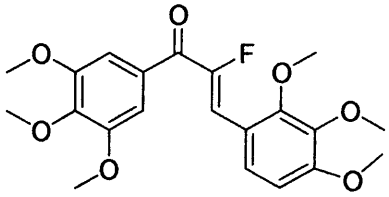
(*Z*)-3-(3'',4''-Dimethoxyphenyl)-2-fluoro-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83d)



Yellow crystals (23%); m.p. 98-100 °C; (Found: C, 63.42; H, 5.55. $C_{20}H_{21}O_6F$ requires C, 63.83; H, 5.59%); ν_{max} ($CHCl_3$) 2939s, 1658m, 1580s, 1514s, 1463s, 1416s, 1334s, 1222s, 1126s, 1024m, 855w, 807w, 755s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 3.88 (3H, s, OMe), 6.80 (1H, d, *J* 36 Hz, H3), overlapping 6.85 (1H, d, *J* 8.2 Hz, H5''), 7.10 (2H, s, H2' and H6'), 7.21 (1H, dd, *J* 1.8, 8.2 Hz, H6''), 7.26 (1H, d, *J* 1.8 Hz, H2''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -121.8 (1F, d, *J* 36 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.2 (s, OMe), 56.3 (s, OMe), 56.7 (s, OMe), 61.4 (s, OMe), 107.3 (d, *J* 5 Hz, C3), 111.4 (s, C2' and C6'), 113.1 (d, *J* 10 Hz, C2''), 120.8 (d, *J* 6 Hz, C5''), 124.6 (d, *J* 4 Hz, C6''), 125.3 (d, *J* 8 Hz, C1''), 131.8 (s, C1'), 142.6 (s, C4'), 149.3 (s,

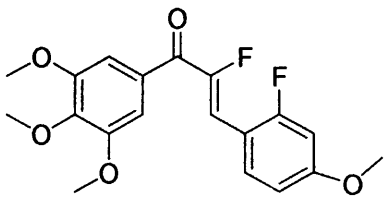
C4''), 151.1 (d, *J* 3 Hz, C3''), 153.3 (s, C3' and C5'), 154.0 (d, *J* 268 Hz, C2), 186.8 (d, *J* 27 Hz, C1); (Found $[M+H]^+$, 377.1399, $C_{20}H_{22}O_6F$ requires $[M+H]^+$, 377.1395).

(*Z*)-2-Fluoro-3-(2'',3'',4''-trimethoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)-prop-2-en-1-one (83e)



Yellow crystals (86%); m.p. 127-129 °C; (Found: C, 61.88; H, 5.64. $C_{21}H_{23}O_7F$ requires C, 62.07; H, 5.67%); ν_{max} ($CHCl_3$) 2942m, 1650w, 1583s, 1496s, 1462s, 1415s, 1327m, 1302s, 1221m, 1128s, 1097s, 1006m, 800w, 757w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, Me), 3.93 (3H, s, OMe), 3.95 (6H, s, OMe), overlapping 3.95 (3H, s, OMe), 3.97 (3H, s, OMe), 6.79 (1H, d, *J* 9.0 Hz, H5''), 7.19 (2H, s, H2' and H6'), 7.30 (1H, d, *J* 38 Hz, H3), 7.80 (1H, d, *J* 9.0 Hz, H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -121.5 (1F, d, *J* 38 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.1 (s, OMe), 56.3 (s, OMe), 60.9 (s, OMe), 61.0 (s, OMe), 61.7 (s, OMe), 106.9 (d, *J* 4 Hz, C3), 107.7 (s, C2' and C6'), 114.5 (d, *J* 4 Hz, C5''), 118.3 (d, *J* 5 Hz, C1''), 126.2 (d, *J* 15 Hz, C6''), 131.6 (s, C1'), 142.1 (d, *J* 17 Hz, C3''), 146.9 (s, C2''), 152.6 (s, C4'), 152.9 (s, C3' and C5'), 154.2 (d, *J* 245 Hz, C2), 155.3 (s, C4''), 186.7 (d, *J* 27 Hz, C1); (Found $[M+H]^+$, 407.1504, $C_{21}H_{24}O_7F$ requires $[M+H]^+$, 407.1501).

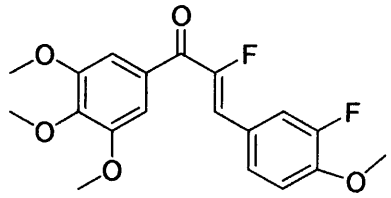
(*Z*)-2-Fluoro-3-(2''-fluoro-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83f)



Yellow crystals (74%); m.p. 143-144 °C; (Found: C, 62.64; H, 4.94. $C_{19}H_{18}O_5F_2$ requires C, 62.64; H, 4.95%); ν_{max} ($CHCl_3$) 2957m, 1620s, 1583m, 1504m, 1455m, 1414m, 1332s, 1294s, 1237s, 1131s, 1106m, 1000m, 876m, 844w, 805w, 759m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.79 (3H, s, OCH_3), 3.86 (6H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.61 (1H, dd, *J* 2.4, 12.2 Hz, H3''), 6.73 (1H, dd, *J* 2.4, 8.9 Hz, H5''), 7.08 (1H, d, *J* 37 Hz, H3), 7.10 (2H, s, H2' and H6'), 7.92 (1H, dd, *J* 8.9, 8.9 Hz, H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -111.6 (1F, m), -120.4 (1F, d, *J* 37 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.8 (s, OMe), 56.3 (s, OMe), 61.0 (s, OMe),

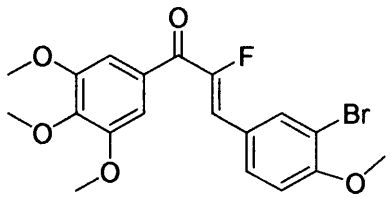
101.5 (d, *J* 25 Hz, C3''), 107.0 (d, *J* 4 Hz, C3), 111.0 (d, *J* 3 Hz, C2' and C6'), 111.9 (m, C5'' and C1''), 131.2 (s, C1'), 131.8 (dd, *J* 3, 15 Hz, C6''), 142.4 (s, C4'), 153.0 (s, C3' and C5'), 154.1 (d, *J* 270 Hz, C2), 161.8 (d, *J* 252 Hz, C2''), 162.4 (d, *J* 9 Hz, C4''),186.4 (d, *J* 27 Hz, C1); (Found $[M+H]^+$, 365.1200, $C_{19}H_{19}O_5F_2$ requires $[M+H]^+$, 365.1195).

(*Z*)-2-Fluoro-3-(3''-fluoro-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83g)



Yellow crystals (28%); m.p. 123-126 °C; (Found: C, 62.49; H, 4.95. $C_{19}H_{18}O_5F_2$ requires C, 62.64; H, 4.95%); ν_{max} ($CHCl_3$) 2940 M, 1660w, 1581s, 1517s, 1463m, 1416m, 1330s, 1278m, 1235w, 1128s, 1002w, 761w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), overlapping 3.88 (3H, s, OMe), 6.77 (1H, d, *J* 36 Hz, H3), 6.93 (1H, dd, *J* 8.5, 8.5 Hz, H5''), 7.12 (2H, s, H2' and H6'), 7.33 (1H, dd, *J* 1.6, 8.5 Hz, H6''), 7.50 (1H, dd, *J* 1.6, 12.5 Hz, H2''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -117.9 (1F, d, *J* 36 Hz), -134.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.5 (s, OMe), 56.7 (s, OMe), 61.4 (s, OMe), 107.2 (d, *J* 5 Hz, C3), 107.9 (d, *J* 8 Hz C2''), 110.8 (s, C2' and C6'), 114.4 (d, *J* 4 Hz, C5''), 122.1 (s, C6''), 127.9 (d *J* 5 Hz, C1''), 131.3 (s, C1'), 142.4 (s, C4'), 150.9 (d, *J* 263 Hz, C3''), 153.2 (s, C3' and C5'), 154.2 (d, *J* 268 Hz, C2), 154.4 (d, *J* 9 Hz, C4''), 186.5 (d, *J* 28 Hz, C1); (Found $[M+H]^+$, 365.1190, $C_{19}H_{19}O_5F_2$ requires $[M+H]^+$, 365.1195).

(*Z*)-3-(3''-Bromo-4''-methoxyphenyl)-2-fluoro-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (83h)

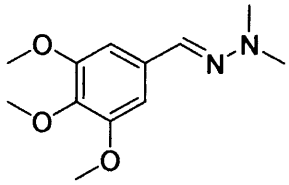


Yellow crystals (18%); m.p. 132-134 °C; (Found: C, 53.75; H, 4.28. $C_{19}H_{18}O_5FBr$ requires C, 53.65; H, 4.24%); ν_{max} ($CHCl_3$) 2941w, 1655w, 1581s, 1498s, 1461w, 1415m, 1329m, 1173m, 1127s, 1054m, 1002m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 6.75 (1H, d, *J* 36.3 Hz, H3), 6.88 (1H, d, *J* 8.6 Hz, H5''), 7.12 (2H, s, H2' and H6'), 7.58 (1H, d, *J* 1.9, 8.6 Hz, H6''), 7.89 (1H, d, *J* 1.9 Hz, H2'');

^{19}F NMR δ (283 MHz; $CDCl_3$), -119.9 (1F, d, *J* 36 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.3 (s, OMe), 56.4 (s, OMe), 61.1 (s, OMe), 107.0 (d, *J* 6 Hz, C3), 111.8 (s, C2' and C6'), 112.2 (s, C3''), 118.2 (d, *J* 6 Hz, C5''), 125.4 (d, *J* 4 Hz, C6''), 131.0 (s, C1'), 131.4 (d, *J* 8 Hz, C2''), 135.3 (s, C1''), 135.4 (s, C4'), 142.5 (s, C4''), 153.0 (s, C3' and C5'), 154.1 (d, *J* 273 Hz, C2), 186.1 (d, *J* 28 Hz, C1); (Found $[M^+]$, 424.0305, $C_{19}H_{19}O_5F^{79}Br$ requires $[M^+]$, 424.0316).

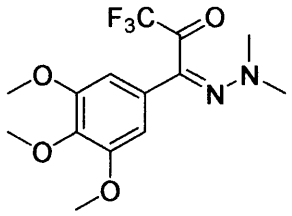
8.2 α-Trifluoromethyl chalcones

N,N-Dimethyl-N'-(3,4,5-trimethoxybenzylidene)hydrazine (92)[216]



3,4,5-Trimethoxybenzaldehyde (3.7 g, 18.9 mmol) was stirred in benzene (10 ml) at room temperature, *N,N*-dimethylhydrazine (1.5 ml, 20 mmol) was added drop-wise and stirred for 4 hours. After this time the mixture was dried over $MgSO_4$ and the solvent removed under vacuum. Recrystallisation from MeOH yielded **92** (4.47 g, 99%). m. p. 74-75 °C; ^1H NMR δ (400 MHz; $CDCl_3$), 2.89 (6H, s, NMe_2), 3.78 (3H, s, OMe), 3.82 (6H, s, OMe), 6.75 (2H, s, ArH).

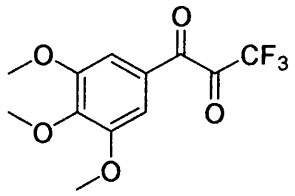
3-(Dimethylhydrazono)-1,1,1-trifluoro-3-(3',4',5'-trimethoxyphenyl)propan-2-one (93)



N,N-Dimethyl-*N'*-(3,4,5-trimethoxybenzylidene)hydrazine (**92**, 4 g, 16.8 mmol) and 2,6-lutidine (4.9 ml, 42 mmol) were dissolved in dry chloroform (40 ml) and cooled in crushed ice. Trifluoroacetic anhydride (24 ml, 171 mmol) was dissolved in dry chloroform (80 ml) and added drop-wise through a pressure equalised dropping funnel. The mixture was then stirred at room temperature for 48 hours, washed with 1M HCl (30 ml), water (30 ml) and sat. Na_2CO_3 (30 ml), the solvent removed under vacuum and the residue purified by silica column chromatography (1:1 ethyl acetate:hexane) to yield **93** (4.45 g, 80%) as a brown oil. ν_{max} ($CHCl_3$) 3436s,br, 2938w, 1685s, 1582m, 1507m, 1127s, 1002w, 849w cm^{-1};

^{1}H NMR δ (400 MHz; $CDCl_3$), 3.04 (6H, s, NMe_2), 3.77 (3H, s, OMe), 3.79 (6H, s, OMe), 6.35 (2H, s, H2' and H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -68.8 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 47.3 (m, NMe_2), 56.6 (s, OMe), 61.3 (s, OMe), 108.2 (s, C2' and C6'), 118.8 (q, *J* 290 Hz, C1), 128.6 (s, C1'), 131.7 (s, C3) 138.5 (s, C4'), 153.1 (s, C3' and C5'), 178.3 (d, *J* 28 Hz, C2); (Found $[M+H]^+$, 335.1216, $C_{14}H_{18}O_4N_2F_3$ requires $[M+H]^+$, 335.1219).

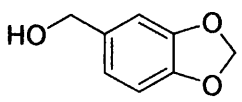
3,3,3-Trifluoro-1-(3',4',5'-trimethoxyphenyl)propane-1,2-dione (94)



3-(Dimethylhydrazono)-1,1,1-trifluoro-3-(3,4,5-trimethoxyphenyl)propan-2-one (**93**, 4.4 g, 13.2 mmol) was dissolved in 5 M H_2SO_4 (50 ml), heated to 60 °C and stirred at this temperature for 48 hrs. The mixture was then extracted into ether, dried over $MgSO_4$ and evaporated under vacuum. Recrystallisation from methanol yielded **94a** which on standing gave **94** as a pale yellow powder (2.96 g, 77%). m. p. 89-91 °C; ν_{max} ($CHCl_3$) 3406s, 2944m, 1678s, 1582s, 1504s, 1332s, 1128s, br, 998m cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.84 (6H, s, OMe), 3.92 (3H, s, OMe), 7.57 (2H, s, H2' and H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -81.0 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.3 (s, OMe), 61.1 (s, OMe), 108.9 (s, C2' and C6'), 121.3 (q, *J* 285 Hz, C3), 126.3 (s, C1'), 144.9 (s, C4'), 152.8 (s, C3' and C5'), 191.6 (s, C1), 196.1 (q, *J* 33 Hz, C2); (Found $[M+NH_4]^+$, 310.0901, $C_{12}H_{15}O_5NF_3$ requires $[M+NH_4]^+$, 310.0897).

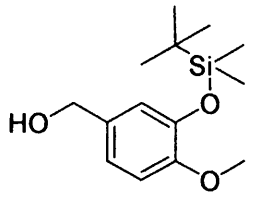
General procedure for the synthesis of alcohols 95—The appropriate aldehyde (1.5 mmol) was dissolved in ethanol (10 ml) and cooled in ice. $NaBH_4$ (2 mmol) was added and the reaction stirred at room temperature overnight. The solvent was then removed under vacuum and the residue partitioned between DCM and water, the DCM fraction was dried over $MgSO_4$ and evaporated under vacuum to give **95** in quantitative yield.

Benzo[1,3]dioxol-5-ylmethanol (95a)[217]



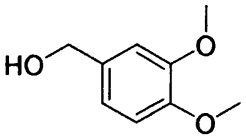
^{1}H NMR δ (400 MHz; $CDCl_3$), 4.46 (2H, s, CH_2OH), 5.85 (2H, s, OCH_2O), 6.67-6.71 (2H, m, H5 and H6), 6.76 (1H, s, H2).

[3-(*tert*-Butyldimethylsilanyloxy)-4-methoxyphenyl]-methanol (95c)[218]



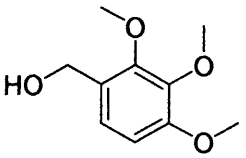
^{1}H NMR δ (400 MHz; $CDCl_3$), (0.00 (6H, s, $SiMe_2$), 0.84 (9H, s, CMe_3), 3.65 (3H, s, OMe), 4.41 (2H, s, CH_2OH), 6.69 (1H, d, *J* 7.6 Hz, H5), 6.73 (1H, dd, *J* 1.9, 7.6 Hz, H6), 6.76 (1H, d, *J* 1.9 Hz, H2).

(3,4-Dimethoxyphenyl)methanol (95e)[217]



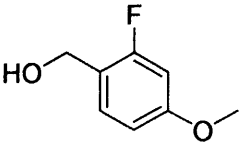
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.72 (3H, s, OMe), 3.73 (3H, s, OMe), 4.45 (2H, s, CH_2OH), 6.68 (1H, d, *J* 8.1 Hz, H5), 6.73 (1H, d, *J* 8.1 Hz, H6), 6.77 (1H, s, H2).

(2,3,4-Trimethoxyphenyl)methanol (95f)[219]



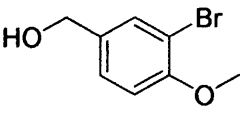
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 3.97 (3H, s, OMe), 4.63 (2H, s, CH_2OH), 6.66 (1H, d, *J* 8.4 Hz, H5), 6.99 (1H, d, *J* 8.4 Hz, H6).

(2-Fluoro-4-methoxyphenyl)methanol (95h)[220]



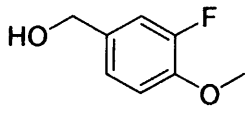
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.82 (3H, s, OMe), 4.50 (2H, s, CH_2OH), 6.64 (1H, dd, *J* 2.5, 11.9 Hz, H3), 6.71 (1H, dd, *J* 2.5, 8.5 Hz, H5), 7.31 (1H, dd, *J* 8.5, 8.5 Hz, H6).

(3-Bromo-4-methoxyphenyl)methanol (95i)[221]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.83 (3H, s, OMe), 4.53 (2H, s, CH_2OH), 6.81 (1H, d, *J* 8.2 Hz, H5), 7.20 (1H, d, *J* 8.2 Hz, H6), 7.49 (1H, s, H2).

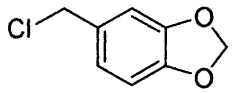
(3-Fluoro-4-methoxyphenyl)methanol (95j)[222]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.79 (3H, s, OMe), 4.34 (2H, s, CH_2OH), 6.83 (1H, dd, *J* 8.2, 8.2 Hz, H5), 6.96 (1H, d, *J* 8.6 Hz, H6), 7.01 (1H, d, *J* 13.7 Hz, H2).

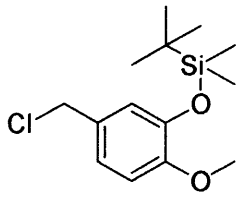
General procedure for the synthesis of chlorides 96—The alcohol **95** (1.5 mmol) was dissolved in DCM and stirred at room temperature. $SOCl_2$ (2 mmol) was added and the reaction mixture was refluxed at 60 °C overnight. The solvent was then removed under vacuum to give **96** in quantitative yield.

5-Chloromethylbenzo[1,3]dioxole (96a)[217]



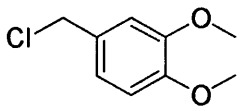
^{1}H NMR δ (400 MHz; $CDCl_3$), 4.55 (2H, s, CH_2Cl), 6.00 (2H, s, OCH_2O), 6.80 (1H, d, *J* 7.9 Hz, H5), 6.87 (1H, dd, *J* 1.7, 7.9 Hz, H6), 6.91 (1H, d, *J* 1.7 Hz, H2).

***tert*-Butyl-(5-chloromethyl-2-methoxyphenoxy)dimethylsilane (96c)**[223]



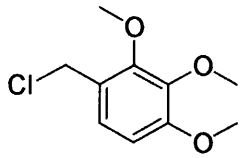
^{1}H NMR δ (400 MHz; $CDCl_3$), (0.00 (6H, s, $SiMe_2$), 0.84 (9H, s, CMe_3), 3.65 (3H, s, OMe), 4.36 (2H, s, CH_2Cl), 6.65 (1H, d, *J* 8.2 Hz, H5), 6.73 (1H, d, *J* 2.2 Hz, H2), 6.78 (1H, dd, *J* 2.2, 8.2 Hz, H6).

4-Chloromethyl-1,2-dimethoxybenzene (96e)[217]



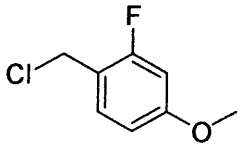
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, OMe), 3.92 (3H, s, OMe), 4.59 (2H, s, CH_2Cl), 6.84 (1H, d, *J* 8.0 Hz, H5), 6.93-6.96 (2H, m, H2 and H6).

1-Chloromethyl-2,3,4-trimethoxybenzene (96f)[224]



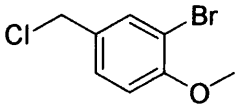
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.92 (3H, s, OMe), 4.54 (2H, s, CH_2Cl), 6.59 (1H, d, *J* 8.5 Hz, H5), 6.98 (1H, d, *J* 8.5 Hz, H6).

1-Chloromethyl-2-fluoro-4-methoxybenzene (96h)[220]



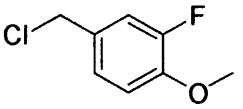
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.83 (3H, s, OMe), 4.63 (2H, s, CH_2Cl), 6.66 (1H, dd, *J* 2.5, 11.7 Hz, H3), 6.76 (1H, dd, *J* 2.5, 8.6 Hz, H5), 7.32 (1H, dd, *J* 8.6, 8.6 Hz, H6).

2-Bromo-4-chloromethyl-1-methoxybenzene (96i)[225]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.84 (3H, s, OMe), 4.46 (2H, s, CH_2Cl), 6.80 (1H, d, *J* 8.4 Hz, H5), 7.23 (1H, dd, *J* 2.2, 8.4 Hz, H6), 7.52 (1H, d, *J* 2.2 Hz, H2).

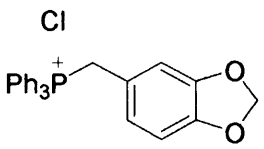
4-Chloromethyl-2-fluoro-1-methoxybenzene (96j)[226]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 4.44 (2H, s, CH_2Cl), 6.83 (1H, dd, *J* 8.4, 8.4 Hz, H5), 7.00 (1H, dd, *J* 2.0, 8.4 Hz, H6), 7.05 (1H, dd, *J* 2.0, 11.7 Hz, H2).

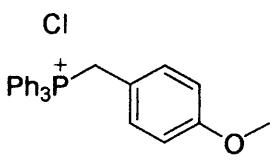
General procedure for the synthesis of phosphonium salts 97—The chloride **96** (1.5 mmol) and triphenylphosphine (1.5 mmol) were refluxed in dry toluene for 4 hours. The reaction mixture was cooled to 0 °C and the phosphonium salt **97** filtered off in quantitative yield.

Benzo[1,3]dioxol-5-ylmethyltriphenylphosphonium chloride (97a)[227]



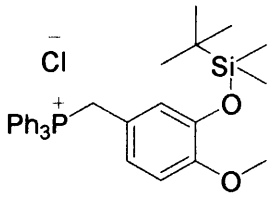
^{1}H NMR δ (400 MHz; $CDCl_3$), 5.66 (2H, d, *J* 14.0 Hz, CH_2P), 6.07 (2H, s, OCH_2O), 6.72-6.81 (3H, m, H2, H5 and H6), 7.82-7.96 (15H, m, PPh_3)

(4-Methoxybenzyl)triphenylphosphonium chloride (97b)[228]



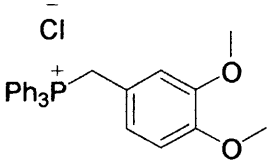
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 5.69 (2H, d, *J* 13.8 Hz, CH_2P), 6.48 (1H, d, *J* 8.7 Hz, H3 and H5), 7.05 (1H, dd, *J* 1.9, 8.7 Hz, H2 and H6), 7.82-7.96 (15H, m, PPh_3)

[3-(*tert*-Butyldimethylsilanyloxy)-4-methoxybenzyl]triphenylphosphonium chloride (97c)[229]



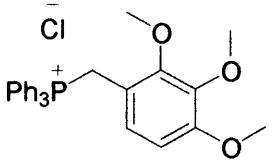
^{1}H NMR δ (400 MHz; $CDCl_3$), 0.03 (6H, s, $SiMe_2$), 0.87 (9H, s, CMe_3), 3.78 (3H, s, OMe), 5.33 (2H, d, *J* 13.7 Hz, CH_2P), 6.30 (1H, t, *J* 2.0 Hz, H2), 6.66 (1H, d, *J* 8.3 Hz, H5), 6.91-6.94 (1H, m, H6), 7.63-7.78 (15H, m, PPh_3).

(3,4-Dimethoxybenzyl)triphenylphosphonium chloride (97e)[230]



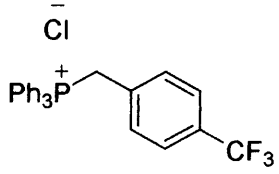
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.56 (3H, s, OMe), 3.75 (3H, s, OMe), 5.61 (2H, d, *J* 13.8 Hz, CH_2P), 6.63 (1H, d, *J* 8.4 Hz, H5), 6.70 (1H, t, *J* 2.2 Hz, H2), 7.44 (1H, dt, *J* 2.2, 8.4 Hz, H6), 5.55-7.73 (15H, m, PPh_3).

Triphenyl(2,3,4-trimethoxybenzyl)phosphonium chloride (97f)[231]



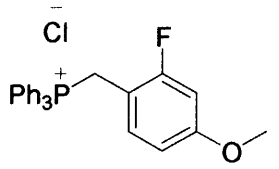
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.52 (3H, s, OMe), 3.60 (3H, s, OMe), 3.80 (3H, s, OMe), 5.33 (2H, d, *J* 13.4 Hz, CH_2P), 6.50 (1H, d, *J* 8.6 Hz, H5), 7.07 (1H, dd, *J* 1.9, 8.6 Hz, H6).

Triphenyl(4-trifluoromethylbenzyl)phosphonium chloride (97g)[232]



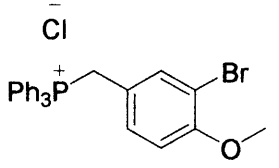
^{1}H NMR δ (400 MHz; $CDCl_3$), 5.95 (2H, d, *J* 15.5 Hz, CH_2P), 7.32-7.37 (4H, m, H2, H3, H5 and H6), 7.61-7.86 (15H, m, PPh_3)

(2-Fluoro-4-methoxybenzyl)triphenylphosphonium chloride (97h)[233]



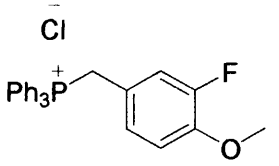
^{1}H NMR δ (400 MHz; $CDCl_3$), 3.74 (3H, s, OMe), 5.53 (2H, d, *J* 13.7 Hz, CH_2P), 6.38 (1H, dd, *J* 2.4, 11.7 Hz, H3), 6.57 (1H, dd, *J* 2.4, 8.7 Hz, H5), 7.52 (1H, ddd, *J* 2.4, 8.7, 8.7 Hz, H6), 7.63-7.84 (15H, m, PPh_3).

(3-Bromo-4-methoxybenzyl)triphenylphosphonium chloride (97i)[234]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.75 (3H, s, OMe), 5.51 (2H, d, *J* 14.0 Hz, CH_2P), 6.63 (1H, d, *J* 8.5 Hz, H5), 6.73 (1H, t, *J* 2.3 Hz, H2), 7.43 (1H, dt, *J* 2.3, 8.5 Hz, H6), 5.57-7.76 (15H, m, PPh_3).

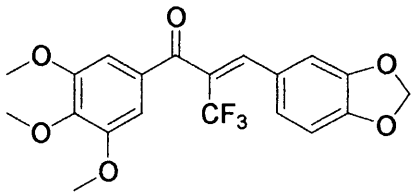
(3-Fluoro-4-methoxybenzyl)triphenylphosphonium chloride (97j)[235]



^{1}H NMR δ (400 MHz; $CDCl_3$), 3.83 (3H, s, OMe), 5.60 (2H, d, *J* 14.1 Hz, CH_2P), 6.66 (1H, d, *J* 11.8 Hz, H2), 6.76 (1H, dd, 8.6, 8.6 Hz, H5), 7.14 (1H, d, *J* 8.6 Hz, H6), 7.65-7.82 (15H, m, PPh_3).

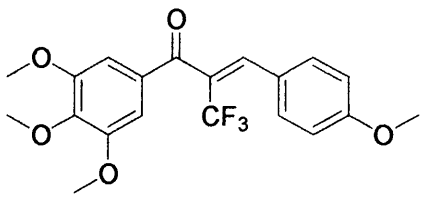
General procedure for the synthesis of chalcones 88—Phosphonium chloride **97** (1 mmol) was dissolved in dry THF (5 ml) and cooled in ice. LiHMDS (1 ml of a 1 M solution in THF) was added drop-wise and stirred for 10 mins. Diketone **94** (1.1 mmol) in THF (5 ml) was then added to resulting the red solution and the reaction mixture was warmed to room temperature and refluxed at 80 °C overnight. The mixture was then quenched with 1 M HCl (10 ml) and extracted with ether, dried over $MgSO_4$ and evaporated under vacuum.)

(*Z*)-3-Benzo[1,3]dioxol-5-yl-2-(Trifluoromethyl) -1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88a)



Pale yellow oil (58%); ν_{max} ($CHCl_3$) 2941m, 1661m, 1582m, 1504s, 1415m, 1327m, 1250s, 1127s, 841m cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.61 (6H, s, OMe), 3.70 (3H, s, OMe), 5.73 (2H, s, CH_2), 6.47 (1H, d, *J* 8.0 Hz, H5''), overlapping 6.48 (1H, d, *J* 1.3 Hz, H2''), 6.61 (1H, dd, *J* 1.3, 8.0 Hz, H6''), 6.97 (2H, s, H2' and H6'), 7.15 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.0 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.2 (s, OMe), 61.0 (s, OMe), 101.7 (s, CH_2), 105.1 (q, *J* 273 Hz, CF_3), 107.0 (s, C2' and C6'), 108.7 (d, *J* 24 Hz, C2''), 121.1 (s, C6''), 125.5 (s, C5''), 126.1 (s, C1''), 126.7 (q, *J* 29 Hz, C2), 130.4 (s, C1'), 136.4 (q, *J* 6 Hz, C3), 143.7 (s, C4'), 148.1 (s, C4''), 149.4 (s, C3''), 153.2 (s, C3' and C5'), 191.5 (s, C1); (Found $[M+H]^+$, 411.1049, $C_{20}H_{18}O_6F_3$ requires $[M+H]^+$, 411.1050).

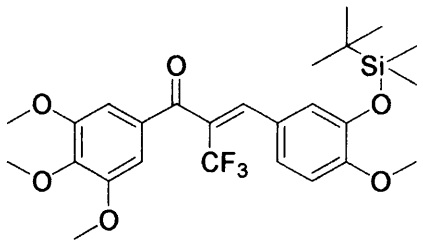
***(Z)*-2-(Trifluoromethyl)-3-(4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88b)**



Pale yellow oil (64%); ν_{max} ($CHCl_3$) 2939w, 1661m, 1604m, 1512m, 1330 M, 1126s, 1030w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.69 (3H, s, OMe), 3.74 (6H, s, OMe), 3.83 (3H, s,

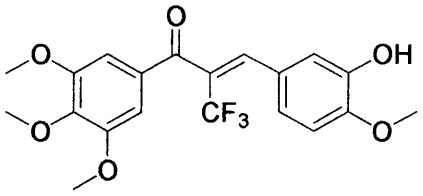
OMe), 6.67 (1H, d, *J* 8.8 Hz, H3'' and H5''), 7.12 (2H, s, H2' and H6'), overlapping 7.13 (2H, d, *J* 8.8 Hz, H2'' and H6''), 7.34 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.0 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.3 (s, OMe), 56.2 (s, OMe), 61.0 (s, OMe), 107.0 (s, C2' and C6'), 114.3 (C3'' and C5''), 124.6 (s, C1'), 130.4 (s, C1''), 131.5 (s, C2'' and C6''), 136.7 (s, C3), 143.6 (s, C4'), 153.1 (s, C3' and C5'), 161.1 (s, C4''), 191.8 (s, C1), (C2 and CF_3 signals were too weak to detect with any certainty); (Found $[M+H]^+$, 397.1261, $C_{20}H_{20}O_5F_3$ requires $[M+H]^+$, 397.1257).

(*Z*)-2-(Trifluoromethyl)-3-[3''-(*tert*-Butyldimethylsilanyloxy)-4''-methoxyphenyl]-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88c)



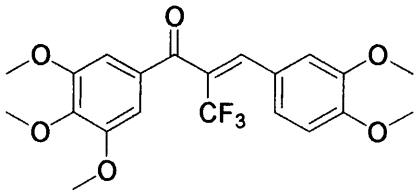
Pale yellow oil (49%); ν_{max} ($CHCl_3$) 2934m, 1662m, 1581m, 1513s, 1415m, 1328m, 1256s, 1128s, 840 M cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.00 (6H, s, $SiMe_2$), 0.92 (9H, s, $C(CH_3)_3$), 3.79 (3H, s, OMe), 3.85 (6H, s, OMe), 3.92 (3H, s, OMe), 6.74 (1H, d, *J* 8.4 Hz, H5''), overlapping 6.75 (1H, d, *J* 2.1 Hz, H2''), 6.91 (1H, dd, *J* 2.1, 8.4 Hz, H6''), 7.24 (2H, s, H2' and H6'), 7.36 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -61.9 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), -4.9 (s, $SiMe_2$), 18.3 (s, $\underline{C}Me_3$), 25.6 (s, $C(\underline{C}H_3)_3$), 55.3 (s, OMe), 56.2 (s, OMe), 61.0 (s, OMe), 104.5 (q, *J* 276 Hz, CF_3), 107.6 (s, C2' and C6'), 111.5 (s, C5''), 121.5 (s, C2''), 124.8 (d, *J* 14 Hz, C6''), 125.8 (q, *J* 30 Hz, C2), 128.5 (d, *J* 12 Hz, C1''), 130.4 (s, C1'), 132.3 (q, *J* 11 Hz, C3), 143.6 (s, C4'), 145.0 (s, C3''), 153.0 (s, C4''), 153.2 (s, C3' and C5'), 191.5 (s, C1); (Found $[M+H]^+$, 527.2068, $C_{26}H_{34}O_6F_3Si$ requires $[M+H]^+$, 527.2071).

(*Z*)-2-(Trifluoromethyl)-3-(3''-hydroxy-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88d)



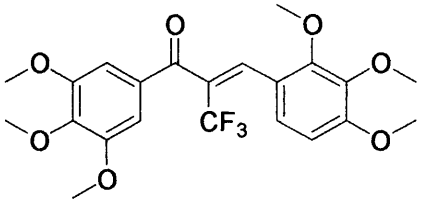
Pale yellow oil (86%); ν_{max} ($CHCl_3$) 3430s,br, 2941m, 1660m, 1583s, 1513m, 1415m, 1327s, 1262s, 1127s, 913w, 732m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.72 (6H, s, OMe), 3.74 (3H, s, OMe), 3.80 (3H, s, OMe), 5.74 (1H, s, OH), 6.57 (1H, d, *J* 8.4 Hz, H5''), 6.68 (1H, dd, *J* 2.1, 8.4 Hz, H6''), 6.76 (1H, d, *J* 2.1 Hz, H2''), 7.08 (2H, s, H2' and H6'), 7.27 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.1 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 56.2 (s, OMe), 61.0 (s, OMe), 65.9 (s, OMe), 108.8 (q, *J* 296 Hz, CF_3), 107.0 (s, C2' and C6'), 110.5 (s, C2''), 115.5 (s, C5''), 122.7 (s, C6''), 125.4 (s, C1''), 126.5 (q, *J* 30 Hz, C2), 130.5 (s, C1'), 136.7 (d, *J* 6 Hz, C3), 143.5 (s, C4'), 145.6 (s, C3''), 148.2 (s, C4''), 153.1 (s, C3' and C5'), 191.6 (s, C1); (Found $[M+H]^+$, 413.1207, $C_{20}H_{20}O_6F_3$ requires $[M+H]^+$, 413.1206).

(*Z*)-2-(Trifluoromethyl)-3-(3'',4''-dimethoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88e)



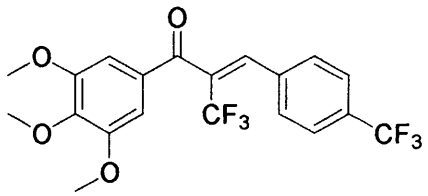
Pale yellow oil (71%); ν_{max} ($CHCl_3$) 2940 M, 1661m, 1583m, 1517m, 1464m, 1415w, 1331m, 1263s, 1127s, 1024m, 732m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.56 (3H, s, OMe), 3.73 (6H, s, OMe), 3.77 (3H, s, OMe), 3.82 (3H, s, OMe), 6.65-6.68 (2H, m, H2'' and H5''), 6.82 (1H, dd, *J* 2.0, 8.4 Hz, H6''), 7.14 (2H, s, H2' and H6'), 7.34 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.0 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 56.2 (s, OMe), 61.0 (s, OMe), 65.9 (s, OMe), 106.9 (s, C2' and C6'), 110.9 (s, C2''), 111.9 (s, C5''), 123.9 (s, C1''), 124.7 (s, C6''), 126.1 (q, *J* 30 Hz, C2), 130.5 (s, C1'), 136.6 (q, *J* 6 Hz, C3), 143.8 (s, C4''), 148.7 (s, C3''), 150.8 (s, C4'), 153.2 (s, C3' and C5'), 191.8 (s, C1), (CF_3 signal was too weak to detect with any certainty); (Found $[M+H]^+$, 427.1365, $C_{21}H_{22}O_6F_3$ requires $[M+H]^+$, 427.1363).

(*Z*)-2-(Trifluoromethyl)-3-(2'',3'',4''-trimethoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88f)



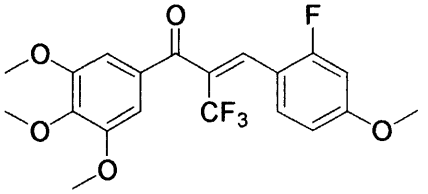
Pale yellow oil (36%); ν_{max} ($CHCl_3$) 2942w, 1662m, 1584m, 1415m, 1126s, 759w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.65 (3H, s, OMe), 3.68 (3H, s, OMe), 3.72 (6H, s, OMe), 3.77 (3H, s, OMe), 3.84 (3H, s, OMe), 6.31 (1H, d, *J* 8.7 Hz, H5''), 6.71 (1H, d, *J* 8.7 Hz, H6''), 7.03 (2H, s, H2' and H6'), 7.59 (1H, d, *J* 1.3 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.0 (3F, s); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 457.1470, $C_{22}H_{24}O_7F_3$ requires $[M+H]^+$, 457.1469).

(*Z*)-2-(Trifluoromethyl)-3-(4''-trifluoromethylphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88g)



White powder (83%); m.p. 73-76 °C; (Found: C, 55.37; H, 3.70. $C_{20}H_{16}O_4F_6$ requires C, 55.30; H, 3.69%); ν_{max} ($CHCl_3$) 2944w, 1661s, 1582s, 1415s, 1323s, 1125s, 1067m, 849m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.65 (6H, s, OMe), 3.75 (3H, s, OMe), 6.99 (2H, s, H2' and H6'), 7.23 (2H, d, *J* 8.3 Hz, H3'' and H5''), 7.32 (1H, s, H3), overlapping 7.35 (2H, d, *J* 8.3 Hz, H2'' and H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.6 (3F, s), -62.9 (3F, s); ^{13}C NMR δ (100 MHz; CDCl3), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 435.1022, $C_{20}H_{17}O_4F_6$ requires $[M+H]^+$, 435.1026).

***(Z)*-2-(Trifluoromethyl)-3-(2''-fluoro-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)prop-2-en-1-one (88h)**



Pale yellow oil (22%); ν_{max} ($CHCl_3$) 2942w, 1665m, 1504m, 1464s, 1329s, 1128s, 1002m, 836m, 758s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.60 (3H, s, OMe), 3.68 (6H, s, OMe), 3.75 (3H, s, OMe), 6.31 (1H, dd, *J* 2.4, 8.7 Hz, H5''), 6.42 (1H, dd, *J* 2.4, 12.3 Hz, H3''), 6.92 (1H, dd, *J* 8.7, 8.7 Hz, H6''), 7.01 (2H, s, H2' and H6'), 7.37 (1H, s, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.0 (3F, s), -81.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.7 (s, OMe), 56.1 (s, OMe), 61.0 (s, OMe), 101.6 (d, *J* 25 Hz, C3''), 106.8 (s, C2' and C6'), 110.5 (s, C5''), 113.0 (d, *J* 20 Hz, C1''), 126.1 (q, *J* 30 Hz, C2), 129.6 (s, C6''), 130.3 (s, C1'), 130.9 (s, C3), 143.6

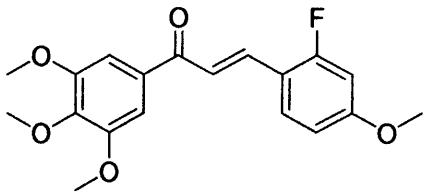
(s, C4'), 153.1 (s, C3' and C5'), 160.8 (d, *J* 251 Hz, C2''), 162.7 (s, C4''), 191.2 (s, C1), (CF_3 signal was too weak to detect with any certainty); (Found $[M+H]^+$, 415.1162, $C_{20}H_{19}O_5F_4$ requires $[M+H]^+$, 415.1163).

Chapter Nine

9.1 α-H ^{19}F Chalcones

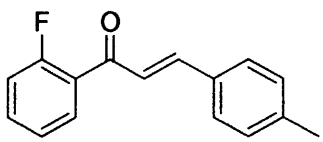
General procedure for the synthesis of α-hydrogen chalcones—2-Fluoro-4-methoxyacetophenone (0.17 g, 1.0 mmol) and aldehyde (1.1 mmol) were dissolved in 1M NaOH in methanol (5 ml, 5 mmol) and left standing until the chalcone precipitated out.

(*E*)-3-(2''-Fluoro-4''-methoxyphenyl)-1-(3',4',5'-trimethoxyphenyl)propen-1-one (127)



Yellow crystals (57%); m.p. 136-138 °C; (Found: C, 65.60; H, 5.50. $C_{19}H_{19}O_5F$ requires C, 65.90; H, 5.49%); ν_{max} ($CHCl_3$) 2940w, 1660m, 1569s, 1505s, 1414w, 1328m, 1272m, 1158s, 1128s, 1089w, 1003w, 854w cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.88 (3H, s, OMe), 3.96 (3H, s, OMe), 3.97 (6H, s, OMe), 6.69 (1H, dd, *J* 2.4, 12.6 Hz, H3''), 6.78 (1H, dd, *J* 2.4, 8.7 Hz, H5''), 7.29 (2H, s, H2' and H6'), 7.51 (1H, d, *J* 15.9 Hz, H2), 7.59 (1H, dd, *J* 8.7, 8.7 Hz, H6''), 7.79 (1H, d, *J* 15.9 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -110.3 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.8 (s, OMe), 56.4 (s, OMe), 61.0 (s, OMe), 102.1 (d, *J* 25 Hz, C3''), 106.0 (s, C2' and C6'), 110.9 (s, C2), 115.7 (d, *J* 12 Hz, C1''), 121.8 (d, *J*, 7 Hz, C5''), 130.9 (d, *J* 5 Hz, C6''), 133.6 (s, C1'), 137.7 (s, C3), 142.3 (s, C4'), 153.1 (s, C3' and C5'), 162.7 (d, *J* 12 Hz, C4''), 162.8 (d, *J* 253 Hz, C2''), 189.4 (s, C1); (Found $[M+H]^+$, 347.1289, $C_{19}H_{20}O_5F$ requires $[M+H]^+$, 347.1289).

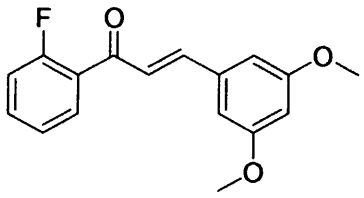
(*E*)-1-(2'-Fluorophenyl)-3-*p*-tolylpropen-1-one (128)



Yellow crystals (73%); m.p. 69-70 °C; (Found: C, 79.87; H, 5.42. $C_{16}H_{13}OF$ requires C, 80.00; H, 5.42%); ν_{max} ($CHCl_3$) 2365w, 1661s, 1592s, 1480m, 1453m, 1330w, 1154w, 987m, 814s cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 2.41 (3H, s, CH_3), 7.16-7.22 (1H, m, H3') overlapping 7.24 (2H, d, *J* 8.0 Hz, H2'' and H6'') overlapping 7.26-7.31 (1H, m, H5'), 7.37 (1H, dd, *J* 2.7, 15.7 Hz, H2), 7.51-7.57 (1H, m, H4') overlapping 7.55 (2H, d, *J* 8.0 Hz, H3'' and H5''), 7.75 (1H, dd, *J* 1.4, 15.7 Hz, H3), 7.83 (1H, ddd, *J* 1.9, 7.6, 7.6 Hz, H6'); ^{19}F NMR δ (283 MHz;

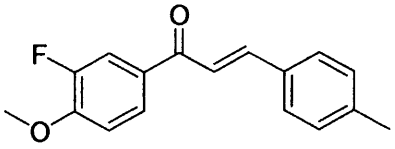
$CDCl_3$), -110.8 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 21.6 (s, Me), 116.5 (d, *J* 23 Hz, C3'), 124.5 (d, *J* 4 Hz, C2), 124.7 (d, *J* 6 Hz, C5'), 127.2 (s, C1'), 128.7 (s, C2'' and C6''), 129.7 (s, C3'' and C5''), 131.0 (d, *J* 3 Hz, C6'), 132.0 (s, C1''), 133.8 (d, *J* 9 Hz, C4'), 141.3 (s, C3), 145.1 (s, C4''), 161.2 (d, *J* 251 Hz, C2'), 189.3 (s, C1); (Found $[M+H]^+$, 241.1025, $C_{16}H_{14}OF$ requires $[M+H]^+$, 241.1023).

(*E*)-3-(3'',5''-Dimethoxyphenyl)-1-(2'-fluorophenyl)propen-1-one (129)[236]



Yellow needles (71%); m.p. 70-71 °C; (Found: C, 71.32; H, 5.27. $C_{17}H_{15}O_3F$ requires C, 71.33; H, 5.24%); ν_{max} ($CHCl_3$) 2940w, 1665m, 1609s, 1452m, 1288s, 1205s, 1155s, 1060m, 767 cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.85 (6H, s, OMe), 6.54 (1H, t, *J* 2.2 Hz, H4''), 6.78 (2H, d, *J* 2.2 Hz, H2'' and H6''), 7.16 - 7.22 (1H, m, H3'), 7.28 (1H, dt, *J* 0.9, 7.5 Hz, H5'), 7.36 (1H, dd, *J* 2.7, 15.7 Hz, H2), 7.52-7.58 (1H, m, H4'), 7.67 (1H, dd, *J* 1.7, 15.7 Hz, H3), 7.83 (1H, ddd, *J* 1.9, 7.5, 7.5 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -110.8 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.5 (s, OMe), 103.0 (s, C4''), 106.4 (s, C2'' and C6''), 116.6 (d, *J* 23 Hz, C3'), 124.5 (d, *J* 3 Hz, C2), 126.1 (d, *J* 6 Hz, C5'), 127.0 (d, *J* 13 Hz, C1'), 131.0 (d, *J* 3 Hz, C6'), 134.0 (d, *J* 9 Hz, C4'), 136.6 (s, C1''), 144.9 (s, C3), 161.0 (s, C3'' and C5''), 161.2 (d, *J* 252 Hz, C2'), 189.1 (d, *J* 2 Hz, C1)); (Found $[M+H]^+$, 287.1080, $C_{17}H_{16}O_3F$ requires $[M+H]^+$, 287.1078).

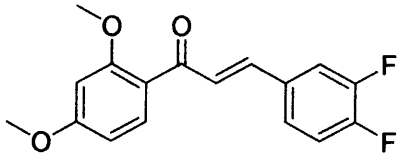
(*E*)-1-(3'-Fluoro-4'-methoxyphenyl)-3-*p*-tolylpropen-1-one (130)



Yellow crystals (62%); m.p. 141-143 °C; (Found: C, 75.12; H, 5.48. $C_{17}H_{15}O_2F$ requires C, 75.56; H, 5.56%); ν_{max} ($CHCl_3$) 1661m, 1594s, 1510w, 1435w, 1139s, 983w, 807s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.46 (3H, s, CH_3), 4.00 (3H, s, OMe), 7.06 (1H, dd, *J* 8.4, 8.4 Hz, H5'), 7.25 (2H, d, *J* 8.0 Hz, H3'' and H5''), 7.48 (1H, d, *J* 15.6 Hz, H2), 7.57 (2H, d, J 8.0 Hz, H2''and H6''), 7.82 (1H, d, J 15.6, H3), 7.83 – 7.89 (2H, m, H2' and H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -134.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 21.6 (s, Me), 56.3 (s, OMe), 112.3 (d, *J* 2 Hz, C5'), 116.2 (d, *J* 19 Hz, C2'), 120.1 (s, C2), 125.7 (d, *J* 3 Hz, C6'),

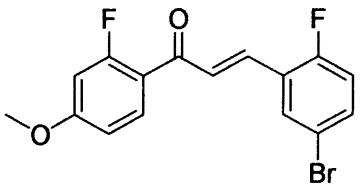
128.5 (s, C2'' and C6''), 129.7 (s, C3'' and C5''), 131.5 (d, *J* 5 Hz, C1'), 132.1 (s, C1''), 141.2 (s, C4''), 144.8 (s, C3), 151.7 (d, *J* 11 Hz, C4'), 152.0 (d, *J* 246 Hz, C3'), 187.9 (s, C1); (Found $[M+H]^+$, 271.1130, $C_{17}H_{16}O_2F$ requires $[M+H]^+$, 271.1129).

(*E*)-3-(3'',4''-Difluorophenyl)-1-(2',4'-dimethoxyphenyl)propen-1-one (131)[237]



Pale yellow crystals (56%); m.p. 130-131 °C; (Found: C, 65.13; H, 4.44. $C_{17}H_{14}O_3F_2$ requires C, 67.11; H, 4.61%); ν_{max} ($CHCl_3$) 1663w, 1601s, 1514m, 1469w, 1271s, 1131m, 970m, 808m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 6.51 (1H, d, *J* 2.1, Hz, H3'), 6.59 (1H, dd, *J* 2.1, 8.7 Hz, H5'), 7.19 (1H, dd, *J* 8.4, 18.2 Hz, H5''), 7.30-7.34 (1H, m, H2''), 7.39-7.44 (1H, m, H6''), 7.47 (1H, d, J 15.7 Hz, H2), 7.59 (1H, d, *J* 15.7 Hz, H3), 7.80 (1H, d, *J* 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -134.8 (1F, m), 136.9 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.6 (s, OMe), 55.8 (s, OMe), 98.6 (s, C3'), 105.3 (s, C5'), 116.2 (d, *J* 17 Hz, C2''), 117.7 (d, *J* 18 Hz, C5''), 121.8 (s, C1'), 125.1 (q, *J* 3 Hz, C2), 128.0 (d, *J* 2 Hz, C6''), 132.8 (m, C1''), 133.1 (s, C6'), 139.3 (s, C3), 150.6 (dd, *J* 13, 237 Hz, C3''), 151.2 (dd, *J* 13, 237 Hz, C4''), 160.6 (s, C2'), 164.5 (s, C4'), 189.7 (s, C1); (Found $[M+H]^+$, 305.0991, $C_{17}H_{15}O_3F_2$ requires $[M+H]^+$, 305.0989).

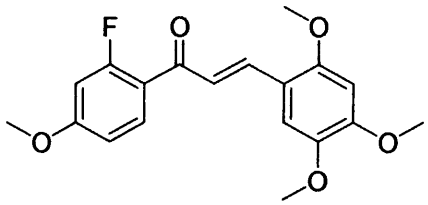
(*E*)-3-(5''-Bromo-2''-fluorophenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (132)



Yellow crystals (34%); m.p. 127-130 °C; (Found: C, 54.45; H, 3.00. $C_{16}H_{11}O_2F_2Br$ requires C, 54.39; H, 3.12%); ν_{max} ($CHCl_3$) 2462w, 1614s, 1487m, 1316w, 1230m, 1099, 990m, 830m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.81 (3H, s, OMe), 6.59 (1H, dd, *J* 2.4, 13.1 Hz, H3'), 6.73 (1H, dd, *J* 2.4, 8.8 Hz, H5'), 6.94 (1H, dd, *J* 8.8, 9.8 Hz, H3''), 7.36-7.41 (1H, m, H4''), 7.45 (1H, dd, *J* 2.9, 15.8 Hz, H2), 7.68 (1H, dd, *J* 2.4, 6.5 Hz, H6''), 7.73 (1H, dd, *J* 1.9, 15.8 Hz, H3), 7.82 (1H, dd, *J* 8.8, 8.8 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.2 (1F, m), -116.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 111.0 (d, *J* 2 Hz, C5'), 117.3 (d, *J* 3 Hz, C1'), 118.0 (d, *J* 24 Hz, C3''), 119.2 (d, *J* 12 Hz, C5''), 125.1 (d, *J* 13 Hz, C2), 128.8 (d, *J* 13 Hz, C1''), 131.6 (d, *J* 3 Hz, C6''), 132.8 (d, *J* 4 Hz, C6'), 134.3 (d, *J*

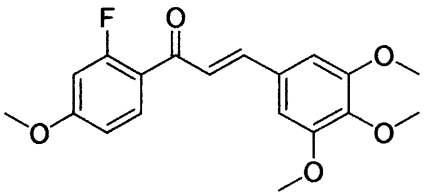
9 Hz, C4''), 134.5 (s, C3), 160.6 (d, *J* 253 Hz, C2''), 163.3 (d, *J* 252 Hz, C2'), 164.9 (d, *J* 12 Hz, C4'), 186.5 (s, C1); (Found $[M+H]^+$, 352.9983, $C_{16}H_{12}O_2F_2{}^{79}Br$ requires $[M+H]^+$, 352.9983).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(2'',4'',5''-trimethoxyphenyl)propen-1-one (133)



Yellow crystals (52%); m.p. 108-110 °C; (Found: C, 65.18; H, 5.06. $C_{19}H_{19}O_5F$ requires C, 65.90; H, 5.49%); ν_{max} ($CHCl_3$) 2937m, 2360m, 1652m, 1613s, 1509m, 1290s, 1020m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.89 (3H, s, OMe), 3.91 (6H, s, OMe), 3.96 (3H, s, OMe), 6.52 (1H, s, H3''), 6.66 (1H, dd, *J* 2.3, 12.8 Hz, H3'), 6.80 (1H, dd, *J* 2.3, 8.7 Hz, H5'), 7.13 (1H, s, H6'') 7.40 (1H, dd, *J* 2.9, 15.7 Hz, H2), 7.88 (1H, dd, *J* 8.7, 8.7 Hz, H6'), 8.09 (1H, dd, *J* 2.1, 15.7 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -107.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.8 (s, OMe), 56.1 (s, OMe), 56.4 (s, OMe), 56.5 (s, OMe), 96.8 (s, C3''), 101.8 (d, *J* 27 Hz, C3'), 110.6 (d, *J* 3 Hz, C5'), 111.1 (s, C6''), 115.5 (s, C1''), 120.3 (d, *J* 13 Hz, C1'), 123.6 (d, *J* 8 Hz, C2), 132.6 (d, *J* 5 Hz, C6'), 139.3 (s, C3), 143.2 (s, C5''), 152.4 (s, C4''), 154.7 (s, C2''), 162.7 (d, *J* 249 Hz, C2'), 164.1 (d, *J* 9 Hz, C4'), 187.7 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 347.1289, $C_{19}H_{20}O_5F$ requires $[M+H]^+$, 347.1289).

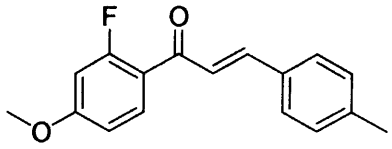
(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(3'',4'',5''-trimethoxyphenyl)propen-1-one (134)



Yellow powder (80%); m.p. 101-102 °C; (Found: C, 65.05; H, 5.05. $C_{19}H_{19}O_5F$ requires C, 65.90; H, 5.49%); ν_{max} ($CHCl_3$) 2256w, 1591s, 1418m, 1323w, 1256m, 1125s, 999m, 819m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, OMe), 3.92 (3H, s, OMe), 3.94 (6H, s, OMe), 6.68 (1H, dd, *J* 2.4, 13 Hz, H3'), 6.82 (1H, dd, *J* 2.4, 8.7 Hz, H5'), 6.87 (2H, s, H2'' and H6''), 7.36 (1H, dd, *J* 2.9, 15.6 Hz, H2), 7.71 (1H, dd, *J* 2.0, 15.6 Hz, H3), 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.7 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 56.2 (s, OMe), 61.0 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 105.6 (s, C2'' and C6''), 110.8 (d, *J* 8 Hz, C5'), 119.6 (d, *J* 13 Hz, C1'), 124.9 (d, *J* 8 Hz, C2), 130.4 (s,

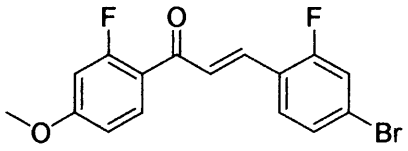
C1''), 132.7 (d, *J* 5 Hz, C6'), 140.2 (s, C4''), 144.1 (s, C3), 153.4 (s, C3'' and C5''), 163.1 (d, *J* 272 Hz, C2'), 164.5 (d, *J* 10 Hz, C4'), 187.1 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 347.1288, $C_{19}H_{20}O_5F$ requires $[M+H]^+$, 347.1289).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-*p*-tolylpropen-1-one (135)[238]



Yellow powder (44%); m.p. 125-128 °C; (Found: C, 74.97; H, 5.59. $C_{17}H_{15}O_2F$ requires C, 75.56; H, 5.56%); ν_{max} ($CHCl_3$) 2266w, 1655m, 1588s, 1443w, 1334m, 1241m, 1104w, 988m, 813m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.41 (3H, s, CH_3), 3.89 (3H, s, OMe), 6.67 (1H, dd, *J* 2.4, 13 Hz, H3'), 6.81 (1H, dd, *J* 2.4, 8.7 Hz, H5'), 7.23 (2H, d, *J* 8.0 Hz, H3'' and H5''), 7.44 (1H, dd, *J* 2.9, 15.6 Hz, H2), 7.55 (2H, d, *J* 8.0 Hz, H2'' and H6''), 7.79 (1H, dd, *J* 2.0, 15.6 Hz, H3), 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.7 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 21.6 (s, Me), 55.9 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 110.8 (d, *J* 2 Hz, C5'), 119.8 (d, *J* 13 Hz, C1'), 124.6 (d, *J* 9 Hz, C2), 128.6 (s, C2'' and C6''), 129.7 (s, C3'' and C5''), 132.2 (s, C1''), 132.7 (d, *J* 5 Hz, C6'), 141.0 (s, C4''), 144.1 (s, C3), 163.0 (d, *J* 252 Hz, C2'), 164.5 (d, *J* 12 Hz, C4'), 187.3 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 288.1395, $C_{17}H_{16}O_2F$ requires $[M+H]^+$, 288.1394).

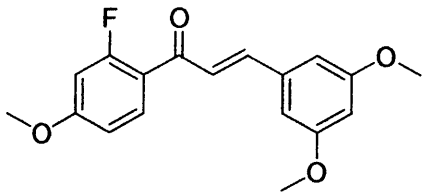
(*E*)-3-(4''-Bromo-2''-fluorophenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (136)



Yellow crystals (79%); m.p. 98–102 °C; (Found: C, 54.15; H, 2.98. $C_{16}H_{11}O_2F_2Br$ requires C, 54.39; H, 3.12%); ν_{max} ($CHCl_3$) 1660w, 1615s, 1494m, 1332m, 1240m, 1100w, 805w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, OMe), 6.67 (1H, dd, *J* 2.2, 13.1 Hz, H3'), 6.81 (1H, dd, *J* 2.2, 8.8 Hz, H5'), 7.31 – 7.37 (2H, m, H3'' and H5''), 7.53 (1H, dd, *J* 7.9, 7.9 Hz, H6'') overlapping 7.56 (1H, dd, *J* 2.8, 15.7 Hz, H2), 7.83 (1H, dd, *J* 1.2, 15.7 Hz, H3) 7.91 (1H, dd, *J* 8.8, 8.8 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.4 (1F, m), -111.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 111.0 (d, *J* 8 Hz, C5'), 119.3 (d, *J* 12 Hz, C1'), 119.9 (d, *J* 25 Hz, C3''), 122.3 (d, *J* 11 Hz, C1''), 124.5 (d, *J* 10 Hz, C4''), 127.9 (d, *J* 3 Hz, C5''), 128.2 (d, *J* 9 Hz, C2), 130.2 (d, *J* 12 Hz, C6''), 132.8 (d, *J* 4 Hz,

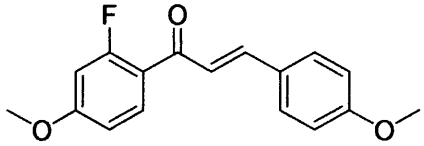
C6'), 135.1 (s, C3), 161.2 (d, *J* 257 Hz, C2''), 162.3 (d, *J* 253 Hz, C2'), 164.8 (d, *J* 12 Hz, C4'), 186.7 (s, C1); (Found $[M+H]^+$, 352.9985, $C_{16}H_{12}O_2F_2{}^{79}Br$ requires $[M+H]^+$, 352.9983).

(*E*)-3-(3'',5''-Dimethoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (137)



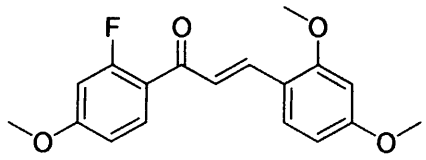
Yellow crystals (77%); m.p. 88-89 °C; (Found: C, 68.26; H, 5.31. $C_{18}H_{17}O_4F$ requires C, 68.35; H, 5.38%); ν_{max} ($CHCl_3$) 2943w, 1614s, 1457, 1284m, 1245m, 1205m, 1156s, 1116w, 836w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (6H, s, OMe), 3.90 (3H, s, OMe), 6.54 (1H, t, *J* 2.2 Hz, H4''), 6.68 (1H, dd, *J* 2.4, 13 Hz, H3'), 6.79 (2H, d, *J* 2.2 Hz, H2'' and H6''), 6.81 (1H, dd, *J* 2.4, 8.9 Hz, H5'), 7.43 (1H, dd, *J* 2.8, 15.6 Hz, H2), 7.71 (1H, dd, *J* 2.0, 15.6 Hz, H3); 7.90 (1H, dd, *J* 8.6, 8.6 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.5 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.5 (s, OMe), 55.9 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 102.7 (s, C4''), 106.3 (s, C2'' and C6''), 110.8 (s, C5'), 119.7 (d, *J* 16 Hz, C1'), 126.1 (d, *J* 8 Hz, C2), 132.7 (d, *J* 4 Hz, C6'), 136.9 (s, C1''), 143.9 (s, C3), 161.0 (s, C3'' and C5''), 162.1 (d, *J* 252 Hz, C2'), 164.6 (d, *J* 12 Hz, C4'), 187.2 (s, C1); (Found $[M+H]^+$, 317.1184, $C_{18}H_{18}O_4F$ requires $[M+H]^+$, 317.1184).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(4''-methoxyphenyl)propen-1-one (138)[239]



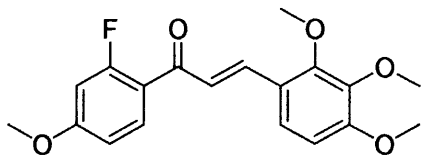
Yellow needles (57%); m.p. >250 °C; (Found: C, 70.36; H, 5.27. $C_{17}H_{15}O_3F$ requires C, 71.33; H, 5.24); ν_{max} ($CHCl_3$) 3407s, 2273w, 1420m, 1282w, 846m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 6.68 (1H, dd, *J* 2.4, 13 Hz H3'), 6.81 (1H, dd, *J* 2.4, 8.8 Hz, H5'), 6.95 (2H, d, *J* 8.6 Hz, H3'' and H5''), 7.37 (1H, dd, *J* 3.0, 15.5 Hz, H2), 7.61 (2H, d, *J* 8.6 Hz, H2'' and H6''), 7.78 (1H, dd, *J* 2, 15.5 Hz H3), 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -107.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.4 (s, OMe), 55.9 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 110.7 (s, C5'), 114.4 (s, C3'' and C5''), 116.7 (d, *J* 14 Hz, C1'), 123.3 (d, *J* 8 Hz, C2), 127.7 (s, C1''), 130.3 (s, C2'' and C6''), 132.6 (d, *J* 5 Hz, C6'), 143.9 (s, C3), 161.6 (s, C4''), 164.5 (d, *J* 262 Hz, C2'), 164.9 (d, *J* 11 Hz, C4'), 188.1 (s, C1); (Found $[M+H]^+$, 287.1080, $C_{17}H_{16}O_3F$ requires $[M+H]^+$, 287.1079).

(*E*)-3-(2'',4''-Dimethoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (139)



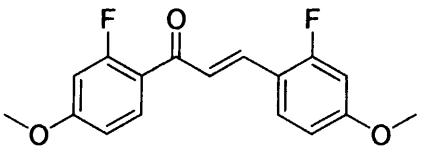
Yellow cubes (87%); m.p. 100-102 °C; (Found: C, 68.36; H, 5.37. $C_{18}H_{17}O_4F$ requires C, 68.35; H, 5.38%); ν_{max} ($CHCl_3$) 2973w, 1650w, 1613s, 1501m, 1456m, 1235s, 1114s, 1017m, 837w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 3.82 (3H, s, OMe), 6.39 (1H, d, *J* 2.4 Hz, H3''), 6.46 (1H, dd, *J* 2.4, 8.6 Hz, H5''), 6.58 (1H, dd, *J* 2.4, 13.0 Hz, H3'), 6.71 (1H, dd, *J* 2.4, 8.7 Hz, H5'), 7.39 (1H, dd, *J* 3.0, 15.7 Hz, H2), 7.50 (1H, d, *J* 8.6 Hz, H6''), 7.79 (1H, dd, *J* 8.6, 8.6 Hz, H6'), 7.97 (1H, dd, *J* 2.2, 15.7 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.9 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 50.2 (s, OMe), 55.5 (s, OMe), 55.8 (s, OMe), 98.3 (s, C3''), 101.8 (d, *J* 27 Hz, C3'), 105.5 (s, C5''), 110.5 (d, *J* 2 Hz, C5'), 117.0 (s, C1''), 120.0 (d, *J* 13 Hz, C1'), 123.6 (d, *J* 8 Hz, C2), 130.8 (s, C6''), 132.5 (d, *J* 5 Hz, C6'), 139.9 (s, C3), 161.6 (s, C2''), 161.8 (d, *J* 268 Hz, C2'), 164.1 (s, C4''), 164.2 (d, *J* 12 Hz, C4'), 188.2 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 317.1181, $C_{18}H_{18}O_4F$ requires $[M+H]^+$, 317.1184).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(2'',3'',4''-trimethoxyphenyl)propen-1-one (140)



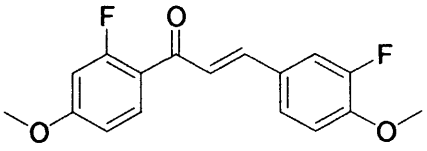
Yellow cubses (34%); m.p. 81-84 °C; (Found: C, 65.65; H, 5.53. $C_{19}H_{19}O_5F$ requires C, 65.90; H, 5.49%); ν_{max} ($CHCl_3$) 2941w, 1614s, 1495s, 1464s, 1258s, 1097s, 1016m, 799w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.89 (3H, s, OMe), 3.91 (3H, s, OMe), 3.93 (3H, s, OMe), 3.96 (3H, s, OMe), 6.68 (1H, dd, *J* 2.4, 13.0 Hz, H3'), 6.74 (1H, d, *J* 8.8 Hz, H5''), 6.81 (1H, dd, *J* 2.4, 8.8 Hz, H5'), 7.40 (1H, d, *J* 8.8 Hz, H6''), 7.49 (1H, dd, *J* 3.0, 15.8 Hz, H2), 7.90 (1H, dd, *J* 8.6, 8.6 Hz, H6'), 7.98 (1H, dd, *J* 2.2, 15.8 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.8 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 50.3 (s, OMe), 55.9 (s, OMe), 60.9 (s, OMe), 61.4 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 107.6 (s, C5''), 110.7 (d, *J* 2 Hz, C5'), 119.8 (d, *J* 13 Hz, C1'), 121.9 (s, C1''), 124.0 (s, C6''), 124.7 (d, *J* 8 Hz, C2), 132.6 (d, *J* 4 Hz, C6'), 139.4 (s, C3), 142.3 (s, C3''), 153.8 (s, C2''), 155.7 (s, C4''), 163.1 (d, *J* 252 Hz, C2'), 164.2 (d, *J* 12 Hz, C4'), 187.9 (s, C1); (Found $[M+H]^+$, 347.1288, $C_{19}H_{20}O_5F$ requires $[M+H]^+$, 347.1289).

(*E*)-1,3-Bis-(*o*-fluoro-*p*-methoxyphenyl)propen-1-one (141)[239]



Yellow powder (49%); m.p. 85-87 °C; CHN analysis failed – sample did not combust completely; ν_{max} ($CHCl_3$) 3448m, 1612s, 1442m, 1238m, 1116m, 753s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 6.67 (1H, dd, *J* 12.8, 2.4 Hz, H3'' or H3'), 6.68 (1H, dd, *J* 12.8, 2.4 Hz, H3'' or H3') 6.76 (1H, dd, *J* 2.4, 8.7 Hz, H5'' or H5'), 6.81 (1H, dd, *J* 2.4, 8.7 Hz, H5'' or H5'), 7.46 (1H, dd, *J* 2.9, 16.0 Hz, H2), 7.58 (1H, dd, *J* 8.7, 8.7 Hz, H6''), 7.88 (1H, dd, *J* 2.0, 16.0 Hz, H3), overlapping 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.6 (1F, m), -110.8 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.8 (s, OMe), 55.9 (s, OMe), 101.7 (d, *J* 25 Hz, C3' or C3''), 102.0 (d, *J* 26 Hz, C3' or C3''), 110.8 (d, *J* 2 Hz, C5' or C5''), 110.9 (d, *J* 3 Hz, C5' or C5''), 115.7 (d, *J* 12 Hz, C1''), 119.8 (d, *J* 13 Hz, C1'), 125.4 (d, *J* 6 Hz, C2), 130.4 (d, *J* 5 Hz, C6''), 132.7 (d, *J* 4 Hz, C6'), 136.6 (s, C3), 162.7 (d, *J* 12 Hz, C4''), 162.8 (d, *J* 253 Hz, C2' or C2''), 163.0 (d, *J* 252 Hz, C2' or C2''), 164.4 (d, *J* 12 Hz, C4'), 187.2 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 305.0983, $C_{17}H_{15}O_3F_2$ requires $[M+H]^+$, 305.0984).

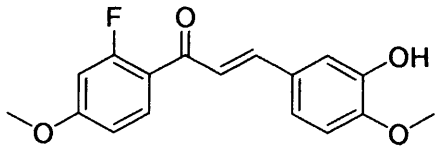
(*E*)-3-(3''-Fluoro-4''-methoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (142)[240]



Yellow crystals (26%); m.p. 105-107 °C; (Found: C, 67.08; H, 4.32. $C_{17}H_{14}O_3F_2$ requires C, 67.11; H, 4.61%); ν_{max} ($CHCl_3$) 3440m, 1614s, 1515m, 1441w, 1279m, 1117m, 758s cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.89 (3H, s, OMe), 3.91 (3H, s, OMe), 6.66 (1H, dd, *J* 2.4, 13.0 Hz, H3'), 6.69 (1H, dd, *J* 2.4, 8.8 Hz, H5'), 6.98 (1H, dd, *J* 8.5, 8.5 Hz, H5''), 7.32 (1H, dd, *J* 2.7, 15.5 Hz, H2), overlapping 7.34 (1H, dd, *J* 2.0, 8.5 Hz, H6''), 7.40 (1H, dd, *J* 2.0, 12 Hz, H2''), 7.69 (1H, d, *J* 15.5 Hz, H3), 7.89 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -107.0 (1F, m), -134.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 56.2 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 110.4 (d, *J* 3 Hz, C5'), 113.1 (d, *J* 2 Hz, C5''), 114.8 (d, *J* 18 Hz, C2''), 119.6 (d, *J* 13 Hz, C1'), 124.4 (d, *J* 9 Hz, C2), 126.1 (d, *J* 3 Hz, C6''), 128.2 (d, *J* 7 Hz, C1''), 132.6 (d, *J* 5 Hz, C6'), 142.6 (s, C3), 149.6 (d, *J* 11 Hz, C4''), 152.4 (d, *J* 245 Hz,

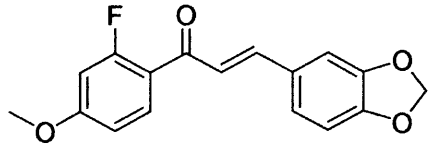
C3''), 163.1 (d, *J* 252 Hz, C2'), 164.5 (d, *J* 11 Hz, C4'), 186.8 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 305.0984, $C_{17}H_{15}O_3F_2$ requires $[M+H]^+$, 305.0984).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(3''-hydroxy-4''-methoxyphenyl)propen-1-one (143)



Yellow crystals (30%); m.p. 116-118 °C; (Found: C, 67.28; H, 4.96. $C_{17}H_{15}O_4F$ requires C, 67.55; H, 4.96%); ν_{max} ($CHCl_3$) 3358m, 1648s, 1613s, 1504s, 1266s, 1096m, 1018m, 797m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, OMe), 3.96 (3H, s, OMe), 5.69 (1H, s, OH) 6.67 (1H, dd, *J* 2.4, 13.0 Hz, H3'), 6.81 (1H, dd, *J* 2.4, 8.7 Hz, H5'), 6.88 (1H, d, *J* 8.3 Hz, H5''), 7.15 (1H, dd, *J* 2.0, 8.4 Hz, H6''), 7.29 (1H, d, *J* 2.0 Hz, H2''), 7.35 (1H, dd, *J* 2.8, 15.5 Hz, H2), 7.73 (1H, dd, *J* 2.1, 15.5 Hz, H3), 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.5 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 56.0 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 110.6 (s, C2'') 110.8 (d, *J* 3 Hz, C5'), 113.2 (s, C5''), 119.8 (d, *J* 13 Hz, C1'), 122.9 (s, C6''), 123.7 (d, *J* 9 Hz, C2), 128.6 (s, C1''), 132.6 (d, *J* 5 Hz, C6'), 144.0 (s, C3), 145.9 (s, C3''), 148.8 (s, C4''), 163.0 (d, *J* 252 Hz, C2'), 164.4 (d, *J* 12 Hz, C4'), 187.2 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 303.1030, $C_{17}H_{16}O_4F$ requires $[M+H]^+$, 303.1027).

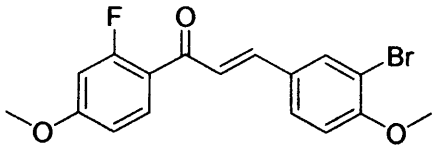
(*E*)-3-Benzo[1,3]dioxol-5-yl-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (144)



Yellow crystals (64%); m.p. 133-135 °C; (Found: C, 66.78; H, 4.30. $C_{17}H_{13}O_4F$ requires C, 68.00; H, 4.33%); ν_{max} ($CHCl_3$) 1654w, 1589s, 1495w, 1237s, 834m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.90 (3H, s, OMe), 6.05 (2H, s, CH_2), 6.66 (1H, dd, *J* 2.4, 13.0 Hz, H3'), 6.81 (1H, dd, *J* 2.4, 8.7 Hz, H5'), 6.86 (1H, d, *J* 8.0 Hz, H5''), 7.13 (1H, dd, *J* 1.6, 8.0 Hz, H6''), 7.17 (1H, d, *J* 1.6 Hz, H2''), 7.31 (1H, dd, *J* 2.9, 15.5 Hz, H2), 7.72 (1H, dd, *J* 2.1, 15.5 Hz, H3), 7.90 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.9 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 101.6 (s, OCH_2O), 101.9 (d, *J* 23 Hz, C3'), 106.7 (s, C2''), 108.6 (s, C5''), 110.8 (d, *J* 3 Hz, C6'), 119.8 (d, *J* 13 Hz, C1'), 123.6 (d, *J* 9 Hz, C2), 125.3 (s, C6''), 129.4 (s, C1''), 132.6 (d, *J* 5 Hz, C6'), 143.8 (s, C3), 148.3 (s, C4''), 149.8 (s,

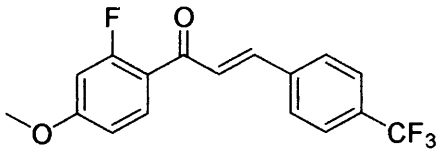
C3''), 163.0 (d, *J* 252 Hz, C2'), 164.4 (d, *J* 12 Hz, C4'), 187.0 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 301.0872, $C_{17}H_{14}O_4F$ requires $[M+H]^+$, 301.0871).

(*E*)-3-(3''-Bromo-4''-methoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)propen-1-one (145)



Pale yellow powder (70%); m.p. 117-120 °C; CHN analysis failed – sample did not combust completely; ν_{max} ($CHCl_3$) 3452w, 1656w, 1614s, 1495m, 1235m, 753m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.86 (3H, s, OMe), 3.91 (3H, s, OMe), 6.67 (1H, dd, *J* 2.3, 13.1 Hz, H3'), 6.80 (1H, dd, *J* 2.4, 8.8 Hz, H5'), 6.93 (1H, d, *J* 8.6 Hz, H5''), 7.34 (1H, dd, *J* 2.7, 15.6 Hz, H2), 7.54 (1H, dd, *J* 2.1, 8.6 Hz, H6''), 7.68 (1H, dd, *J* 2.0, 15.4 Hz, H3), 7.86 (1H, d, *J* 2.1 Hz, H2''), overlapping 7.88 (1H, dd, *J* 8.7, 8.7 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -106.5 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 55.9 (s, OMe), 56.4 (s, OMe), 101.8 (d, *J* 27 Hz, C3'), 110.8 (d, *J* 3 Hz, C5'), 111.8 (s, C5''), 112.3 (s, C3''), 119.6 (d, *J* 13 Hz, C1'), 124.4 (d, *J* 8 Hz, C2), 129.0 (s, C1''), 129.7 (s, C6''), 132.6 (d, *J* 5 Hz, C6'), 132.8 (s, C2''), 142.2 (s, C3), 157.5 (s, C4''), 163.1 (d, *J* 252 Hz, C2'), 164.6 (d, *J* 12 Hz, C4'), 186.9 (d, *J* 4 Hz, C1); (Found $[M+H]^+$, 365.0185, $C_{17}H_{15}O_3F^{79}Br$ requires $[M+H]^+$, 365.0183).

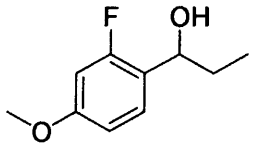
(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-3-(4''-trifluoromethylphenyl)propen-1-one (146)



Yellow powder (12%); m.p. 82-84 °C; CHN analysis failed – sample did not combust completely; ν_{max} ($CHCl_3$) 3367m, 1660m, 1617s, 1324s, 1283w, 1118s, 847w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.75 (3H, s, OMe), 6.60 (1H, dd, *J* 2.3, 13.2 Hz H3'), 6.74 (1H, dd, *J* 2.3, 8.9 Hz, H5'), 7.46 (1H, dd, *J* 3.0, 15.6 Hz, H2), 7.59 (2H, d, *J* 8.3 Hz, H3'' and H5''), 7.65 (2H, d, *J* 8.3 Hz, H2'' and H6''), 7.71 (1H, dd, *J* 2, 15.6 Hz H3), 7.84 (1H, dd, *J* 8.8, 8.8 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.8 (3F, s), -106.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 325.0849, $C_{17}H_{13}O_2F_4$ requires $[M+H]^+$, 325.0846).

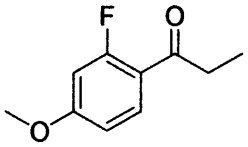
9.2 α-Me ^{19}F Chalcones

1-(2'-Fluoro-4'-methoxyphenyl)propan-1-ol (147)[241]



2-Fluoro-4-methoxybenxaldehyde (2 g, 13 mmol) was dissolved in dry THF (20 ml) and slowly added via cannula to EtMgBr (15 ml of a 1M solution in THF) in ice. The mixture was then stirred at room temperature overnight, cooled in ice again and quenched with sat. NH_4Cl (10 ml). It was extracted with ether, dried over $MgSO_4$ and evaporated under vacuum. Purification by silica column chromatography (3:7 EtOAc:hexane) gave a yellow oil (2.1 g, 88%) ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.84 (3H, t, *J* 7.5 Hz, H3), 1.64-1.81 (2H, m, H2), 3.72 (3H, s, OMe), 4.76-4.80 (1H, m, H1), 6.51 (1H, dd, *J* 2.5, 12.8 Hz, H3'), 6.62 (1H, dd, *J* 2.5, 8.8 Hz, H5'), 7.26 (1H, dd, *J* 8.6, 8.6 Hz, H6').

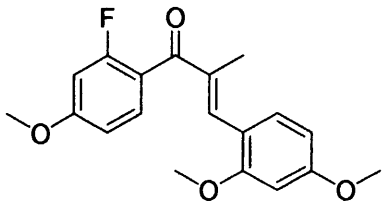
1-(2'-Fluoro-4'-methoxyphenyl)propan-1-one (148)[241]



1-(2-Fluoro-4-methoxyphenyl)propan-1-ol (**147**, 2 g, 11 mmol) and $KMnO_4$ (3.5 g, 22 mmol) were dissolved in DCM and refluxed at 50 °C for 4 hours. The resulting mixture was filtered and the solvent removed under vacuum. Recrystallisation from MeOH yielded **148** as white crystals (1.95 g, 97%). m.p. 30-35 °C; ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.11 (3H, t, *J* 7.5 Hz, H3), 2.86 (2H, dq, *J* 3.3, 7.5 Hz, H2), 3.78 (3H, s, OMe), 6.53 (1H, dd, *J* 2.3, 13.2 Hz, H3'), 6.67 (1H, dd, *J* 2.3, 8.9 Hz, H5'), 7.82 (1H, dd, 8.9, 8.9 Hz, H6').

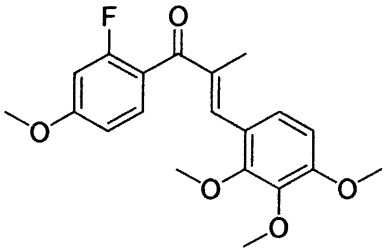
General procedure for the synthesis of α-methyl chalcones—1-(2-Fluoro-4-methoxy-phenyl)-propan-1-one (**148**, 0.18 g, 1.0 mmol) and aldehyde (1.0 mmol) were dissolved in ethanol (5 ml) at room temperature and piperidine (1 ml, 10 mmol) and glacial acetic acid (0.5 ml) were added. The mixture was refluxed for 48 hours, cooled to room temperature, the solvent removed under vacuum and the residue partitioned between DCM and water. The DCM fraction was dried over $MgSO_4$, evaporated under vacuum and purified by silica column chromatography (4:6 EtOAc:hexane).)

(*E*)-3-(2'',4''-Dimethoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)-2-methylpropen-1-one (149)



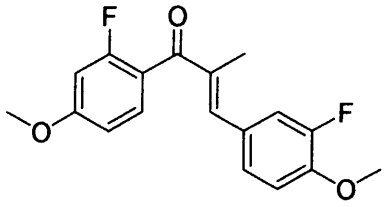
Yellow oil (23%); ν_{max} ($CHCl_3$) 3471m, 2966w, 1617s, 1443m, 1270s, 1116m, 1031m, 950w, 836m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.11 (3H, s, Me), 3.73 (3H, s, OMe), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 6.54-6.59 (2H, m, H3'' and H5''), 6.66-6.70 (2H, m, H3' and H5'), 7.16 (1H, s, H3), 7.33-7.42 (2H, m, H6' and H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -109.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 12.9 (s, Me), 55.4 (s, OMe), 55.6 (s, OMe), 56.3 (s, OMe), 100.0 (s, C3''), 101.4 (d, *J* 26 Hz, C3'), 105.9 (s, C5''), 109.5 (d, *J* 2 Hz, C5'), 113.4 (s, C1''), 116.2 (d, *J* 12 Hz, C1'), 128.9 (s, C6''), 132.0 (s, C2), 132.4 (d, *J* 16 Hz, C6'), 139.4 (s, C3), 155.5 (s, C2''), 159.3 (s, C4''), 164.2 (d, *J* 253 Hz, C2'), 168.3 (d, *J* 12 Hz, C4'), 191.1 (s, C1); (Found $[M+H]^+$, 331.1342, $C_{19}H_{20}O_4F$ requires $[M+H]^+$, 331.1340).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-2-methyl-3-(2'',3'',4''-trimethoxyphenyl)propen-1-one (150)



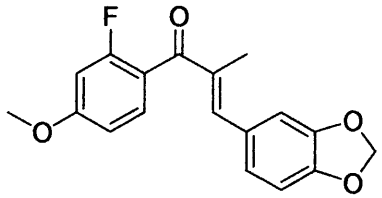
Yellow oil (20%); ν_{max} ($CHCl_3$) 2941w, 1681w, 1590s, 1495m, 1464m, 1290s, 1095s, 1009w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.12 (3H, s, Me), 3.68 (3H, s, OMe), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.97 (3H, s, OMe), 6.58 (1H, dd, *J* 2.3, 11.8 Hz, H3'), 6.66 (1H, d, *J* 8.8 Hz, H5''), 6.69 (1H, dd, *J* 2.3, 8.6 Hz, H5'), 7.13 (1H, d, *J* 8.8 Hz, H6''), 7.30 (1H, s, H3), 7.39 (1H, dd, *J* 8.6, 8.6 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -109.3 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 361.1449, $C_{20}H_{22}O_5F$ requires $[M+H]^+$, 361.1446).

(*E*)-3-(3''-Fluoro-4''-methoxy-phenyl)-1-(2'-fluoro-4'-methoxyphenyl)-2-methyl-propen-1-one (151)



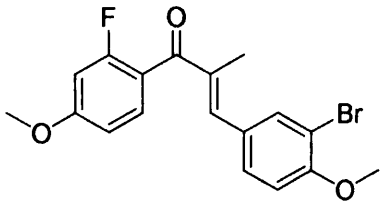
White powder (53%); m.p. 105-107 °C; (Found: C, 67.41; H, 5.00. $C_{18}H_{16}O_3F_2$ requires C, 67.92; H, 5.03%); ν_{max} ($CHCl_3$) 2937w, 1614s, 1515m, 1442w, 1281s, 1126m, 1013m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.16 (3H, s, CH_3), 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 6.57 (1H, dd, *J* 2.4, 11.8 Hz, H3'), 6.69 (1H, dd, *J* 2.4, 8.6 Hz, H5'), 6.90 (1H, dd, *J* 8.6, 8.6 Hz, H5''), 7.00 (1H, s, H3), 7.08 (1H, d, *J* 8.7 Hz, H6''), 7.14 (1H, dd, *J* 2.0, 12.4 Hz, H2''), 7.38 (1H, dd, *J* 8.4, 8.4 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -109.0 (1F, m), -135.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 13.6 (s, Me), 55.8 (s, OMe), 56.3 (s, OMe), 101.8 (d, *J* 26 Hz, C3'), 110.2 (d, *J* 3 Hz, C5'), 113.0 (d, *J* 2 Hz, C5''), 117.3 (d, *J* 19 Hz, C2''), 119.9 (d, *J* 15 Hz, C1'), 126.7 (d, *J* 3 Hz, C6''), 128.9 (d, *J* 7 Hz, C1''), 131.8 (d, *J* 5 Hz, C6'), 137.1 (s, C2), 140.9 (s, C3), 148.0 (d, *J* 11 Hz, C4''), 152.0 (d, *J* 245 Hz, C3''), 161.1 (d, *J* 250 Hz, C2'), 163.1 (d, *J* 11 Hz, C4'), 195.3 (s, C1); (Found $[M+H]^+$, 319.1140, $C_{18}H_{17}O_3F_2$ requires $[M+H]^+$, 319.1139).

(*E*)-3-Benzo[1,3]dioxol-5-yl-1-(2-fluoro-4-methoxyphenyl)-2-methylpropen-1-one (152)



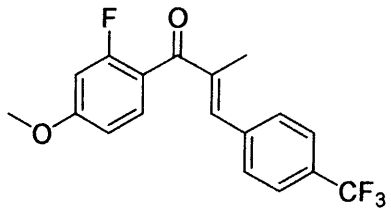
Yellow oil (18%); ν_{max} ($CHCl_3$) 1654w, 1589s, 1495w, 1237s, 834m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.16 (3H, s, CH_3), 3.79 (3H, s, OMe), 5.94 (2H, s, CH_2), 6.57 (1H, dd, *J* 2.4, 11.7 Hz, H3'), 6.69 (1H, dd, *J* 2.4, 8.6 Hz, H5'), 6.77 (1H, d, *J* 8.1 Hz, H5''), 6.84 (1H, dd, *J* 1.4, 8.1 Hz, H6''), 6.90 (1H, d, *J* 1.4 Hz, H2''), 7.03 (1H, s, H3), 7.37 (1H, dd, *J* 8.4, 8.4 Hz, H6'); ^{19}F NMR δ (283 MHz; $CDCl_3$), -109.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), (Insufficient sample for clear ^{13}C NMR); (Found $[M+H]^+$, 315.1030, $C_{18}H_{16}O_4F$ requires $[M+H]^+$, 315.1027).

(*E*)-3-(3''-Bromo-4''-methoxyphenyl)-1-(2'-fluoro-4'-methoxyphenyl)-2-methylpropen-1-one (153)



Yellow needles (61%); m.p. 88-90 °C; (Found: C, 56.20; H, 5.38. $C_{18}H_{16}O_3FBr$ requires C, 56.99; H, 4.22%); ν_{max} ($CHCl_3$) 2942w, 1614s, 1496s, 1440w, 1256s, 1156m, 1012m, 812w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.25 (3H, s, CH_3), 3.88 (3H, s, OMe), 3.95 (3H, s, OMe), 6.66 (1H, dd, *J* 2.3, 11.8 Hz, H3'), 6.78 (1H, dd, *J* 2.3, 8.4 Hz, H5'), 6.94 (1H, d, *J* 8.6 Hz, H5''), 7.09 (1H, d, *J* 2.1 Hz, H2''), 7.39 (1H, dd, *J* 2.1, 8.6 Hz, H6''), 7.47 (1H, dd, *J* 8.4, 8.4 Hz, H6'), 7.64 (1H, d, *J* 2.1 Hz, H3); ^{19}F NMR δ (283 MHz; $CDCl_3$), -109.0 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 13.6 (s, Me), 55.8 (s, OMe), 56.3 (s, OMe), 101.8 (d, *J* 26 Hz, C3'), 110.2 (d, *J* 3 Hz, C5'), 111.6 (s, C3''), 111.7 (s, C5''), 119.8 (d, *J* 15 Hz, C1'), 129.8 (s, C2), 130.4 (s, C2''), 131.8 (d, *J* 5 Hz, C6'), 134.8 (s, C3), 137.2 (s, C1''), 140.7 (d, *J* 2 Hz, C6''), 156.1 (s, C4''), 161.1 (d, *J* 250 Hz, C2'), 163.2 (d, *J* 11 Hz, C4'), 195.3 (s, C1); (Found $[M+H]^+$, 379.0339, $C_{18}H_{17}O_3F^{79}Br$ requires $[M+H]^+$, 379.0340).

(*E*)-1-(2'-Fluoro-4'-methoxyphenyl)-2-methyl-3-(4''-trifluoromethylphenyl)propen-1-one (154)



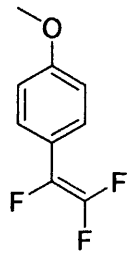
Yellow needles (40%); m.p. 64-66 °C; (Found: C, 62.80; H, 4.07. $C_{18}H_{14}O_2F_4$ requires C, 63.91; H, 4.17%); ν_{max} ($CHCl_3$) 2940w, 1615s, 1444w, 1325s, 1260m, 1162m, 1118s, 1068m, 1011w, 838w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 2.13 (1H, s, CH_3), 3.79 (3H, s, OMe), 6.59 (1H, dd, *J* 2.3, 9.4 Hz H3'), 6.72 (1H, dd, *J* 2.3, 8.6 Hz, H5'), 7.09 (1H, s, H3), 7.42 (2H, d, *J* 7.6 Hz, H3'' and H5''), overlapping 7.46 (1H, dd, *J* 8.3, 8.3 Hz, H6'), 7.58 (2H, d, *J* 7.6 Hz, H2'' and H6''); ^{19}F NMR δ (283 MHz; $CDCl_3$), -62.8 (3F, s), -108.2 (1F, m); ^{13}C NMR δ (100 MHz; $CDCl_3$), 13.8 (s, Me), 55.8 (s, OMe), 101.8 (d, *J* 26 Hz, C3'), 110.4 (d, *J* 3 Hz, C5'), 119.3 (d, *J* 15 Hz, C1'), 123.8 (q, *J* 240 Hz, CF_3), 125.3 (d, *J* 4 Hz, C3'' and C5''), 128.0 (s, C2), 129.7 (s, C2'' and C6''), 130.2 (q, *J* 32 Hz, C4''), 132.1 (d, *J* 4 Hz, C6'), 139.4 (s, C3), 140.0 (s, C1''), 161.4 (d, *J* 250 Hz, C2'), 163.6 (d, *J* 11 Hz, C4'), 195.2 (s, C1); (Found $[M+H]^+$, 339.1005, $C_{18}H_{15}O_2F_4$ requires $[M+H]^+$, 339.1003).

Chapter Ten

10.1 Trifluorostyrenes

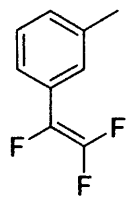
General procedure for the synthesis of trifluorostyrenes[242]—Zinc chloride (4.0 g, 29 mmol) was added to a two-necked round bottomed flask, this was then attached to a high vacuum and heated with a Bunsen burner to remove all traces of water. The flask was then filled with nitrogen and allowed to cool to room temperature. Dry THF (30 ml) was added and the suspension was cooled to –78 °C in dry ice/acetone. 1,1,1,2–tetrafluoroethane (3.5 ml, 40 mmol) was condensed into the flask and stirred at –78 °C. Dry diisopropyl amine (10 ml, 71 mmol) was added to another round bottomed flask, followed by dry THF (30 ml), this was cooled in ice and BuLi (28 ml of a 2.5 M solution in hexanes) was added with stirring. This LDA solution was then added drop-wise via cannula to the zinc chloride and 1,1,1,2–tetrafluoroethane, and the resulting mixture was stirred for 1 hour at –78 °C, before being allowed to warm to room temperature. Aryl iodide (20 mmol) and $Pd(PPh_3)_4$ (0.5 g, 0.4 mmol) were then added and the mixture was refluxed at 80 °C overnight, filtered, extracted with ethyl acetate, dried over $MgSO_4$ and evaporated under vacuum. Purification by silica chromatography using a 1:9 mixture of EtOAc : hexane yielded the following trifluorostyrenes.

1-Methoxy-4-trifluorovinylbenzene (168)[243]



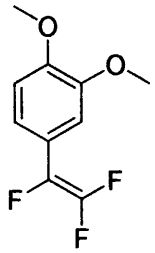
Colourless oil (82%); ^1H NMR δ (400 MHz; $CDCl_3$), 3.80 (3H, s, OMe), 6.92 (2H, d, *J* 8.8 Hz, H2 and H6), 7.36 (2H, d, *J* 8.8 Hz, H3 and H5); ^{19}F NMR δ (283 MHz; $CDCl_3$), -102.1 (1F, dd, *J* 25, 44 Hz), -117.2 (1F, dd, *J* 44, 170 Hz), -175.4 (1F, dd, *J* 25, 170 Hz).

1-Methyl-3-trifluorovinylbenzene (169)[244]



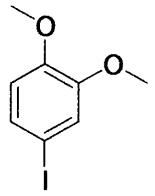
Colourless oil (58%); ^{1}H NMR δ (400 MHz; $CDCl_3$), 2.36 (3H, s, Me), 7.14 (1H, d, *J* 7.1 Hz, H6), 7.26-7.33 (2H, m, H4 and H5), 7.53 (1H, s, H2); ^{19}F NMR δ (283 MHz; $CDCl_3$), -99.8 (1F, dd, *J* 26, 44 Hz), -114.6 (1F, dd, *J* 44, 170 Hz), -176.5 (1F, dd, *J* 26, 170 Hz).

1,2-Dimethoxy-4-trifluorovinylbenzene (170)



Colourless oil (63%); ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 6.79 (1H, d, *J* 8.5 Hz, H6), 6.84 (1H, d, *J* 1.9 Hz, H3), 6.92 (1H, dd, *J* 1.9, 8.5 Hz H5); ^{19}F NMR δ (283 MHz; $CDCl_3$), -101.5 (1F, dd, *J* 25, 44 Hz), -117.0 (1F, dd, *J* 44, 170 Hz), -175.0 (1F, dd, *J* 25, 170 Hz). (Found $[M+H]^+$, 219.0630, $C_{10}H_{10}O_2F_3$ requires $[M+H]^+$, 219.0627

4-Iodo-1,2-dimethoxybenzene (172)[245]

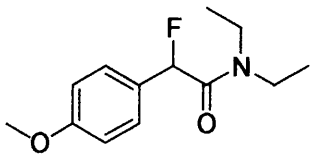


N-iodosuccinamide (1.8 g, 8.0 mmol) was dissolved in acetonitrile (20 ml) and stirred at room temperature under nitrogen. Veratrol (0.9 ml, 7.2 mmol) was added, followed by trifluoroacetic acid (0.15 ml, 2.2 mmol) and the resulting mixture was stirred overnight. The solvent was then removed under vacuum and the residue partitioned between DCM and water. The DCM fraction was dried over $MgSO_4$ and evaporated under vacuum. Recrystallisation from ethanol yielded white crystals (1.84 g, 97%); m.p. 33-35 °C (lit.[246] m.p. 34-35 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 6.65 (1H, d, *J* 8.5 Hz, H6), 7.14 (1H, d, *J* 1.9 Hz, H3), 7.25 (1H, dd, *J* 1.9, 8.5 Hz, H5).

General procedure for the addition of amines to trifluorostyrenes—Amine (1.4 mmol) was dissolved in dry THF (10 ml) and cooled in ice. BuLi (0.6 ml of a 2.5 M solution in hexanes) was added and the mixture was warmed slowly to room temperature, with stirring. The appropriate trifluorostyrene (1.4 mmol) in THF (5 ml) was then added and the mixture was stirred overnight. The solvent was then removed under vacuum and the residue partitioned

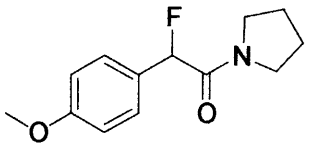
between ether and water. The ether fraction was dried over $MgSO_4$ and evaporated under vacuum. Purification by silica chromatography using a 1:1 mixture of EtOAc : hexane yielded the following amides.

N,N-Diethyl-2-fluoro-2-(4-methoxyphenyl)acetamide (173)



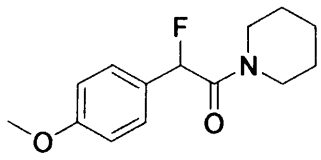
Pale yellow oil (11%); ν_{max} ($CHCl_3$) 2932s, 1702m, 1654s, 1512m, 1459w, 1249m, 1177w, 1032m, 824w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 0.93 (3H, t, *J* 7.1 Hz, CH_3), 1.07 (3H, t, J 7.1 Hz, CH_3), 3.06-3.13 (2H, m, CH_2), 3.31-3.37 (2H, m, CH_2), 3.75 (3H, s, OMe), 5.88 (1H, d, *J* 49.8 Hz, CHF), 6.85 (2H, d, *J* 8.6 Hz, H3 and H5), 7.32 (2H, dd, *J* 1.8, 8.6 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -166.4 (1F, dd, *J* 1.8, 49.8 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 12.7 (s, CH_3), 13.8 (s, CH_3), 40.4 (s, CH_2), 41.2 (s, CH_2), 55.3 (s, OMe), 89.7 (d, *J* 180 Hz, CF), 114.3 (s, C3 and C5), 126.8 (d, *J* 20 Hz, C1), 129.0 (d, *J* 4 Hz, C2 and C6), 160.5 (s, C4), 167.1 (d, *J* 23 Hz, CO); (Found $[M+H]^+$, 240.1392, $C_{13}H_{19}NO_2F$ requires $[M+H]^+$, 240.1394).

2-Fluoro-2-(4-methoxyphenyl)-1-pyrrolidin-1-yl-ethanone (174)



Yellow crystals (19%); m.p. 86-89 °C; (Found: C, 65.57; H, 6.86; N, 5.95. $C_{13}H_{16}NO_2F$ requires C, 65.82; H, 6.75; N 5.91%); ν_{max} ($CHCl_3$) 3468s, br, 2971m, 1651s, 1513m, 1451s, 1248s, 1177m, 1029m, 824w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.69-1.82 (4H, m, H3' and H4'), 3.09-3.53 (4H, m, H2' and H5'), 3.75 (3H, s, OMe), 5.78 (1H, d, *J* 49.2 Hz, CHF), 6.85 (2H, d, *J* 8.5 Hz, H3 and H5), 7.35 (2H, dd, *J* 1.7, 8.5 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -167.8 (1F, dd, *J* 1.7, 49.2 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 23.6 (s, C3'), 26.2 (s, C4'), 45.8 (s, C2'), 46.5 (s, C5'), 55.3 (s, OMe), 89.9 (d, *J* 180 Hz, CF), 114.7 (s, C3 and C5), 126.3 (d, *J* 21 Hz, C1), 129.2 (d, *J* 5 Hz, C2 and C6), 160.6 (s, C4), 166.7 (d, *J* 25 Hz, CO); (Found $[M+H]^+$, 238.1236, $C_{13}H_{17}NO_2F$ requires $[M+H]^+$, 238.1238).

2-Fluoro-2-(4-methoxyphenyl)-1-piperidin-1-yl-ethanone (175)

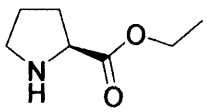


Yellow oil (13%); ν_{max} ($CHCl_3$) 2358m, 1644s, 1512w, 1444w, 1245m, 998w, 842w cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 1.42-1.56 (6H, m, H3', H4' and H5'), 3.14-3.71 (4H, m, H2' and H6'), 3.76 (3H, s, OMe), 5.94 (1H, d, *J* 49.8 Hz, CHF), 6.86 (2H, d, *J* 8.8 Hz, H3 and H5), 7.32 (2H, dd, *J* 1.7, 8.8 Hz, H2 and H6); ^{19}F NMR δ (283 MHz; $CDCl_3$), -167.2 (1F, dd, *J* 1.7, 49.8 Hz); ^{13}C NMR δ (100 MHz; $CDCl_3$), 24.3 (s, C3'), 25.5 (s, C5'), 25.8 (s, C4'), 43.4 (s, C2'), 46.1 (s, C6'), 55.3 (s, OMe), 90.4 (d, *J* 180 Hz, CF), 114.3 (s, C3 and C5), 126.7 (d, *J* 20 Hz, C1), 128.9 (d, *J* 5 Hz, C2 and C6), 160.5 (s, C4), 166.1 (d, *J* 23 Hz, CO); (Found $[M+H]^+$, 252.1396, $C_{14}H_{19}NO_2F$ requires $[M+H]^+$, 252.1394).

10.2 Chiral Amines

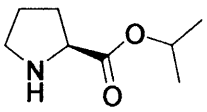
General procedure for the synthesis of proline esters[247]—Proline (0.5 g, 4.3 mmol) was dissolved in the appropriate alcohol (10 ml) and warmed to 60 °C. SO_2Cl (0.42 ml, 5.7 mmol) was added drop-wise and the mixture was stirred overnight. The solvent was then removed under vacuum to yield the following products.

(*S*)-Pyrrolidine-2-carboxylic acid ethyl ester (176)[247]



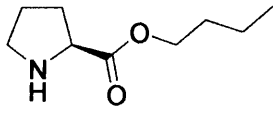
White crystals (94%); m.p. 54-56 °C; ^1H NMR δ (400 MHz; $CDCl_3$), 1.29 (3H, t, *J* 7.2 Hz, CH_3), 1.72-2.19 (4H, m, H3 and H4), 2.94-3.15 (2H, m, H5) overlapping 3.18 (1H, s, NH), 3.78-3.82 (1H, m, H2), 4.20 (2H, q, *J* 7.2 Hz, CH_2).

(*S*)-Pyrrolidine-2-carboxylic acid isopropyl ester (177)[247]



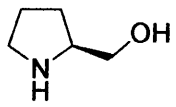
White crystals (85%); m.p. >200 °C; ^1H NMR δ (400 MHz; $CDCl_3$), 1.14-1.19 (6H, m, CH_3), 1.64-2.08 (4H, m, H3 and H4), 2.14 (1H, s, NH), 2.81-3.03 (2H, m, H5), 3.62-3.65 (1H, m, H2), 4.97 (1H, h, *J* 6.2 Hz, CH).

(*S*)-Pyrrolidine-2-carboxylic acid butyl ester (178)[248]



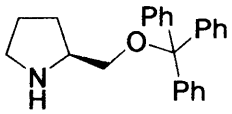
Pale oil (88%); ^{1}H NMR δ (400 MHz; $CDCl_3$), 0.82 (3H, dt, *J* 1.7, 7.4 Hz, H4'), 1.25-1.31 (4H, m, H3' and H4), 1.49-1.56 (4H, m, H2' and H3), 2.74-2.80 (1H, m, H5), 2.93-2.99 (1H, m, H5), 3.63 (1H, dd, *J* 5.5, 8.5 Hz, H2), 4.01 (2H, t, *J* 6.7 Hz, H1').

(*S*)-Pyrrolidin-2-yl-methanol (179)[249]



$LiAlH_4$ (1.3 g, 34.2 mmol) was stirred in dry ether (50 ml) at –10 °C, proline (2 g, 17.4 mmol) was suspended in dry ether (30 ml) and added in small portions. The resulting mixture was warmed to room temperature and stirred overnight. It was then cooled to –10 °C again and water (2 ml) followed by 1M NaOH (5 ml) were added very slowly, it was then filtered and the solvent removed under vacuum. The resulting residue was partitioned between DCM and water and the DCM fraction was dried over $MgSO_4$ and evaporated under vacuum to yield a brown oil (1.5 g, 88%); ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.22-1.30 (1H, m, H3 and H4), 1.53-1.69 (3H, m, H3 and H4), 2.70-2.79 (3H, m, H2 and H5), 2.90 (1H, s, NH), 3.13-3.20 (2H, m, CH_2OH); ^{13}C NMR δ (100 MHz; $CDCl_3$), 25.8 (s, C4), 27.7 (s, C3), 46.5 (s, C5), 60.3 (s, C2), 64.6 (s, CH_2).

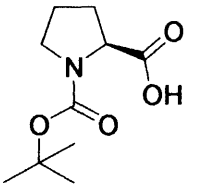
(*S*)-2-Trityloxymethyl-pyrrolidine (180)



Pyrrolidin-2-yl-methanol (**179**, 0.5 g, 5 mmol) was dissolved in dry pyridine (20 ml), trityl chloride (1.5 g, 5.4 mmol) was added and the mixture was refluxed at 120 °C overnight. The pyridine was then evaporated under vacuum and the resulting oil washed with hexane and filtered. The solid residue was partitioned between DCM and 1 M NaOH and the DCM fraction dried over $MgSO_4$ and evaporated under vacuum to give a yellow oil (0.72 g, 42%); ν_{max} ($CHCl_3$) 3057w, 2961m, 1596w, 1490m, 1448s, 1219w, 1069s, 908m, 706s cm^{-1}; ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.68-1.73 (2H, m, H3), 1.80-1.84 (2H, m, H4), 2.84-2.94 (2H, m, H5), 3.05-3.11 (2H, m, CH_2), 3.30-3.33 (1H, m, H2), 7.21-7.45 (15H, m, ArH);

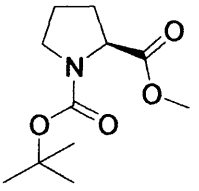
^{13}C NMR δ (100 MHz; $CDCl_3$), 25.1 (s, C4), 28.1 (s, C3), 46.3 (s, C5), 58.4 (s, C2), 66.5 (s, CH_2), 86.3 (s, CPh_3), 126.9 (s, C4'), 127.8 (s, C2' and C6'), 127.9 (s, C3' and C5'), 144.2 (s, C1'); (Found $[M+H]^+$, 344.2017, $C_{24}H_{25}NO$ requires $[M+H]^+$, 344.2014).

(*S*)-*N*-BOC-Proline (181)[250]



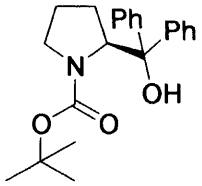
Proline (5 g, 43.5 mmol) and NaOH (1.8 g, 45 mmol) were stirred together in dry THF (50 ml) and cooled to 0 °C. BOC anhydride (10 g, 46 mmol) was added slowly and the mixture was warmed to 60 °C and stirred overnight. The mixture was then quenched with 2M HCl (50 ml) and extracted into ethyl acetate, dried over $MgSO_4$ and evaporated under vacuum to give **181** as white crystals (7.9 g, 85%); m.p. 135-138 °C; (lit.[251] m.p. 138-140 °C); ^1H NMR δ (400 MHz; $CDCl_3$), 1.48 and 1.53 (9H, s, $C(CH_3)_3$), 1.95-2.36 (4H, m, H3 and H4), 3.42-3.57 (2H, m, H5), 4.36 (1H, s, H2).

(*S*)-*N*-BOC-Proline methyl ester (182)[252]



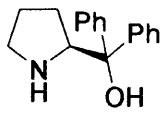
1-Hydroxybenzotriazole (1.9 g, 14 mmol) and (S)-*N*-Boc-proline (**181**, 3.0 g, 14 mmol) were dissolved in DCM (40 ml) at room temperature, methanol (10 ml) was added and the solution was cooled to 0 °C. DCC (2.9 g, 14 mmol) in DCM (10 ml) was added via cannula and the mixture was stirred at room temperature overnight. The mixture was then diluted with DCM (30 ml), washed three times with sat. Na_2CO_3 solution, dried over $MgSO_4$ and evaporated under vacuum. Purification by flash chromatography using a 1:1 mixture of EtOAc : hexane yielded a brown oil (2.4 g, 74%). ^1H NMR δ (400 MHz; $CDCl_3$), 1.40 and 1.44 (9H, s, $C(CH_3)_3$), 1.71-2.20 (4H, m, H3 and H4), 3.48-3.59 (2H, m, H5), 3.95 (3H, s, OMe), 4.19-4.25 (1H, m, H2).

(*S*)-*N*-BOC-2-(Diphenylhydroxymethyl)-pyrrolidine (183)[252]



The BOC ester **182** (1.0 g, 4.4 mmol) was dissolved in dry THF (20 ml) and added drop-wise via a pressure equalised dropping funnel to PhMgBr (10.0 ml of a 1 M solution in THF) in an ice bath. The mixture was warmed to room temperature and stirred for four hours, then cooled to −10 °C. Water (10 ml) was added slowly and the mixture warmed to room temperature again, it was then filtered and the filtrate washed with water and sat. NaCl solution, dried over $MgSO_4$ and evaporated under vacuum. Purification by flash chromatography using a 1:3 mixture of EtOAc : hexane yielded white crystals (1.0 g, 64%) m.p. 103-105 °C; (lit.[252] m.p. 101-103 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.44 (9H, s, $C(CH_3)_3$), 1.50-2.09 (4H, m, H3 and H4), 2.86-3.43 (2H, m, H5), 4.87-4.90 (1H, m, H2), 7.24-7.41 (10H, m, ArH).

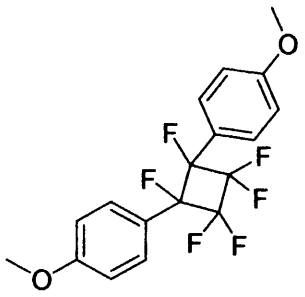
(*S*)-Diphenyl-pyrrolidin-2-yl-methanol (184)[252]



The tertiary alcohol **183** (0.5 g, 1.4 mmol) and KOH (0.75 g, 13.4 mmol) were dissolved in a mixture of DMSO (20 ml) and MeOH (3 ml), heated to 65 °C and stirred overnight. Water (20 ml) was added and the mixture was extracted into hexane, dried over $MgSO_4$ and the solvent removed under vacuum to yield a white solid (0.13 g, 38%) m.p 79-80 °C; (lit.[253] m.p. 79-79.5 °C); ^{1}H NMR δ (400 MHz; $CDCl_3$), 1.02-1.96 (4H, m, H3 and H4), 3.16-3.70 (2H, m, H5), 4.46-4.50 (1H, m, H2), 7.27-7.47 (10H, m, ArH).

General procedure for the addition of chiral amines to 1-methoxy-4-trifluorovinylbenzene under neutral conditions—Amine (1.4 mmol) was dissolved in dry THF (10 ml) and cooled in ice. 1-Methoxy-4-trifluorovinylbenzene (0.26 g, 1.4 mmol) in THF (5 ml) was then added and the mixture was refluxed at 85 °C and stirred overnight. The solvent was then removed under vacuum and the residue partitioned between ether and water. The ether fraction was dried over $MgSO_4$ and evaporated under vacuum. Purification by silica chromatography using a 1:1 mixture of EtOAc : hexane yielded the following dimer.

1,2-(4'-methoxyphenyl)-hexafluorocyclobutane (185)[254]



ν_{max} ($CHCl_3$) 2962w, 1612m, 1518s, 1463w, 1372w, 1261s, 1182s, 1118w, 1020m, 832m cm^{-1}; ^1H NMR δ (400 MHz; $CDCl_3$), 3.71 (3H, s, OMe, *cis*-stereoisomer), 3.78 (3H, s, OMe, *trans*-stereoisomer), 6.74 (2H, d, *J* 8.8 Hz, H3' and H5', *cis*-stereoisomer), 6.91 (2H, d, *J* 8.8 Hz, H3' and H5', *trans*-stereoisomer), 7.09 (2H, d, *J* 8.8 Hz, H2' and H6', *cis*-stereoisomer), 7.93 (2H, d, *J* 8.8 Hz, H2' and H6', *trans*-stereoisomer); ^{19}F NMR δ (283 MHz; $CDCl_3$), 121.5 (2F, d, *J* 255 Hz, *cis*-stereoisomer), 124.6 (4F, s, *trans*-stereoisomer), 128.4 (2F, d, *J* 255 Hz, *cis*-stereoisomer), 156.7 (2F, s, *trans*-stereoisomer), 162.8 (2F, s, *cis*-stereoisomer). (Found $[M-F]^+$, 357, $C_{18}H_{14}F_5O_2$ requires $[M-F]^+$, 357).

General procedure for the addition of chiral amines to 1-methoxy-4-trifluorovinylbenzene under basic conditions—Amine (1.4 mmol) was dissolved in dry THF (10 ml) and cooled in ice. BuLi (0.6 ml of a 2.5 M solution in hexanes) was added and the mixture was warmed slowly to room temperature, with stirring. The appropriate trifluorostyrene (0.26 g, 1.4 mmol) in THF (5 ml) was then added and the mixture was stirred overnight. The solvent was then removed under vacuum and the residue partitioned between ether and water. The ether fraction was dried over $MgSO_4$ and evaporated under vacuum. Repeated chromatography failed to isolate pure amide product.

References

1 R. Filler, Y. Kobayashi, Y.L. Yagulpolskii, *Organofluorine Compounds in Medicinal Chemistry Biomedical Applications*, Elsevier, Amsterdam, **1993**.
2 L. M. Yagupol'skii, N. Y. Kondratenko, *Zh. Org. Khim.*, **1984**, *20*, 115.
3 T. Umemoto, Y. Kuriu, H. Shuyama, O. Miyano, *J. Fluorine Chem.*, **1982**, *20*, 695.
4 J. J. Yang, R. L. Kirchmeier, J. M. Shreeve, *J. Org. Chem.*, **1998**, *63*, 2656.
5 B. R. Langlois, T. Billard, N. Roques, *Tetrahedron Lett.*, **2000**, *41*, 3069-3072.
6 B. R. Langlois, T. Billard, *Synthesis*, **2003**, 185-194.
7 (a) H. J. Emeleus, R. N. Haszeldine, *J.Chem. Soc.*, **1949**, 2948-2952. (b) O. R. Pierce, E. T. McBee, G. F. Judd, *J. Am. Chem. Soc.* **1954**, 76, 474-478.
8 I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.*, **1984**, *25*, 2195.
9 R. P. Singh, J. M. Shreeve, *Tetrahedron*, **2000**, *56*, 7613-7632.
10 C. Lamberth, *J. Prakt Chem.*, **1996**, *338*, 586-587
11 R. P. Singh, R. L. Kirchmeier, J. M. Shreeve, *Org. Lett.* **1999**, *1*, 1047-1049.
12 G. Li, Y. Chen, J. R. Missert, A. Rungta, T. J. Dougherty, Z. D. Grossman, R. K. Pandey, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1785-1787.
13 J. Wiedemann, T. Heiner, G. Mloston, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.*, **1998**, *37*, 820-821.
14 R. P. Singh, J. M. Shreeve, *J. Org. Chem.*, **2000**, *65*, 3241-3243.
15 G. K. S. Prakash, A. K. Yudin, *Chem. Rev.*, **1997**, *97*, 757-786.
16 J. C. Blazejewski, E. Anslem, M. P. Wilmshurst, *Tetrahedron Lett.*, **1999**, *40*, 5475-5479.
17 T. Billard, B. R. Langlois, *Tetrahedron Lett.*, **1996**, *37*, 6865-6868.
18 A. A. Kolomeitsev, V. N. Movchun, Y. L. Yagupol'skii, J. Porwisiak, W. Dmowski, *Tetrahedron Lett.*, **1992**, *33*, 6191.
19 V. V. Bardin, A. A. Kolomeitsev, G. G. Furin, Y. L. Yagupol'skii, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1990**, 1693; *Chem. Abstr.* **1991**, *115*, 279503c.
20 D. Huang, K. G. Caulton, *J. Am. Chem. Soc.*, **1997**, *119*, 3185-3186.
21 I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.*, **1984**, *25*, 2195.
22 G. J. Pawelke, *J. Fluorine Chem.*, **1989**, *42*, 429.
23 J. Grobe, J. Hegge, *Synlett*, **1995**, 641-642.
24 T. Shono, M. Ishifune, T. Okada, S.Kashimura, *J. Org. Chem.*, **1991**, *56*, 2-4.
25 B. Folléas, I. Marek, J. Normant, L. St.Jalmes, *Tetrahedron Lett.*, **1998**, 2973-2976.
26 C. Mispelaere, N. Roques, *Tet. Lett.* **1999**, 6411-6414.
27 S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.*, **2000**, *66*, 4826-4830.
28 T. Billard, S. Bruns, B. R. Langlois, *Org. Lett.*, **2000**, 2101-2103.
29 W. B. Motherwell, L. J. Story, *Synlett*, **2002**, 646-648.
30 M. D. Drew, N. J. Lawrence, D. Fontaine, L. Sehkri, W. Watson, S. A. Bowles, *Synlett*, **1997**, 989.
31 M. D. Drew, N. J. Lawrence, W. Watson, S. A. Bowles, *Tetrahedron Lett.*, **1997**, *38*, 5857.
32 S. M. Bushell, PhD thesis, UMIST, Manchester, UK, November, **2000**.
33 M. Fujita, M. Obayashi, T. Hiyama, *Tetrahedron*, **1988**, *44*, 4135.
34 T. D. Yarwood, A. J. Waring, P. L. Coe, *J. Fluorine Chem.*, **1996**, *78*, 113-119.
35 J. Burdon, P. L. Coe, I. B. Haslock, R. L. Powell, *J. Fluorine Chem.*. **1999**, *99*, 127-131.
36 A. S. Pilcher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.*, **1995**, *117*, 5166.
37 M. Fujita, M. Obayashi, T. Hiyama, *Tetrahedron*, **1988**, *44*, 4135.
38 S. Sirol, J. Courmarcel, N. Mostefai, O. Riant, *Org. Lett.*, **2001**, *3*, 4111-4113.
39 H. J. Frohn, A. Lewin, V. V. Bardin, *J. Organometallic Chem.*, **1998**, *570*, 255-263.
40 J. E. Middleton, C. Kandaswami, *Biochem. Pharmacol.*, **1992**, *43*, 1167-1179.

[41] H. K. Hsieh, T. H. Lee, J. P. Wang, J. J. Wang, C. N. Lin, *Pharm. Research*, **1998**, *15*, 39-46.

[42] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. Rosenthal, J. H. McKerrow, *J. Med. Chem.*, **1995**, *38*, 5031.

[43] J. H. McKerrow, E. Sun, P. J. Rosenthal, J. Bouvier, *Ann. Rev. Microbiol.*, **1993**, *47*, 821-853.

[44] a) E. Bailly, R. Jambou, J. Savel, G. Jaureguiberry, *J. Protozool.*, **1992**, *39*, 593-599. b) P. J. Rosenthal, G. K. Lee, R. E. Smith, *J. Clin. Invest.*, **1993**, *91*, 1052-1056.

[45] S. F. Nielsen, T. Boesen, M. Larsen, K. Schonning, H. Kromann, *Bioorg. Med. Chem.*, **2004**, *12*, 3047-3054.

[46] K. Sukumaran, R. Kuttan, *J. Ethnopharmacol.*, **1991**, *36*, 93-96.

[47] R. J. Anto, K. Sukumaran, G. Kuttan, M. N. A. Rao, V. Subbaraju, R. Kuttan, *Cancer Letters*, **1995**, *97*, 33-37.

[48] K. Elizabeth, M. N. A. Rao, *Int. J. Pharmacol.*, **1990**, *58*, 237-240.

[49] M. L. Edwards, P. J. Lachmann, D. M. Stemerick, P. S. Sunkara, *J. Cell Biol.*, **1987**, *105*, 202a.

[50] V. Peyrot, D. Leynadier, M. Sarrazin, C. Briand, J. M. Andreu, A. Rodriguez, J. M. Nieto, *J. Biol. Chem.*, **1989**, *264*, 21296-21301.

[51] V. Peyrot, D. Leynadier, M. Sarrazin, C. Briand, M. Menendez, J. Laynez, J. M. Andreu, *Biochemistry*, **1992**, *31*, 11125-11132.

[52] M. L. Edwards, D. M. Stemerick, P. S. Sunkara, *J. Med. Chem.*, **1990**, *33*, 1948-1954.

[53] S, Ducki, J. A. Hadfield, N. J. Lawrence, C. Y. Liu, A. T. McGown, X. G. Zhang, *Planta Medica*, **1996**, *62*, 185.

[54] S. Ducki, R. Forrest, J. A. Hadfield, A. Kendall, N. J. Lawrence, A. T. McGown, D. Rennison. *Biorg. Med. Chem. Lett.* **1998**, *8*, 1051.

[55] N. J. Lawrence, A. T. McGown, S. Ducki, J. A. Hadfield, *Anticancer Drug Design*, **2000**, *15*, 135-141.

[56] S. Ducki, J. A. Hadfield, L. A. Hepworth, N. J. Lawrence. C. Y. Liu, A. T. McGown, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 3091-3094.

[57] L. Li, H. K. Wang, S. C. Kuo, T. S. Wu, D. Lednicer, C. Lin, E. Hamel, K. H. Lee, *J. Med. Chem.*, **1994**, *37*, 3400.

[58] Y. Xia, Z. Yang, P. Xia, K. F. Bastow, Y. Nakanishi, K. H. Lee, *Bioorg. Med. Chem. Letters*, **2000**, *10*, 699-701.

[59] S. T. Holgate, P. Bradding, A. P. Sampson, *J. Allergy. Clin. Immunol.*, **1996**, *98*, 1.

[60] J. Ghosh, C. E. Myers, *Proc. Natl. Acad. Sci. U.S.A.*, **1998**, *95*, 13182.

[61] S. Sogawa, Y. Nihro, H. Ueda, A. Izumi, T. Miki, H. Matsumoto, T. Satoh, *J. Med. Chem.*, **1993**, *36*, 3904.

[62] C. Nakamura, N. Kawaski, H. Miyataka, E. Jayachandran, I. H. Kim, K. L. Kirk, T. Taguchi, Y. Takeuchi, H. Hori, T. Satoh, *Bioorg. Med. Chem.*, **2002**, *10*, 699-706.

[63] M. T. Boyde, N. Vlatkovics, D. S. A. Haines, *J. Biol. Chem.*, **2000**, *275*, 31883-31890.

[64] R. Stroll, C. Renner, S. Hensen, S. Palme, C. Klein, A. Belling, W. Zeslawski, M. Kaminonka, T. Rehm, P. Muhlhahn, R. Schumacher, F. Hesse, B. Kaluze, W. Voelter, R. A. Engh, T. A. Holakm, *Biochemistry*, **2001**, *40*, 336-344.

[65] S. K. Kumar, E. Hager, C. Pettit, H. Gurulingappa, N. E. Davidson, S. R. Kahn, *J. Med. Chem.*, **2003**, *46*, 2813-2815.

[66] A. Jordan, J. A. Hadfield, N. J. Lawrence, A. T. McGown, *Med. Res. Rev.*, **1998**, *18*, 259-296.

[67] D. L. Sackett, *Pharmacology and Therapeutics*, **1993**, *59 (2)*, 163-228.

[68] E. Nogales, S. G. Wolf, K. H. Downing, *Nature*, **1998**, *391*, 199-203.

[69] C. Singer, *A History of Scientific Ideas*, Barnes and Nobles, **1996**.
[70] D. Voet, J. G. Voet, *Biochemistry*, **1990**, 758-762.
[71] O. Boye, A. Brossi, *The Alkaloids*, **1992**, *41*, 125-178.
[72] B. Perez-Ramirez, J. M. Andreu, M. J. Gorbunoff, S. N. Timasheff, *Biochemistry*, **1996**, *35*, 3277-3285.
[73] J. M. Andreu, B. Perez-Ramirez, M. J. Gorbunoff, D. Ayala, S. N. Timasheff, *Biochemistry*, **1998**, *37*, 8356-8368.
[74] J. L. Hartwell, A. W. Schrecker, *Fortschr. Chem. Org. Natn.*, **1958**, *15*, 83-166.
[75] D. D. Soejarto, R. B. Faden, N. R. Farnsworth, *Taxon*, **1979**, *28*, 549-551.
[76] V. Podwyssotzki, *Arch. Exp. Path. Pharmak.*, **1880**, *13*, 29-52.
[77] V. Seidlova-Masinova, J. Malinsky, F. Santavy, *J. Natn. Cancer Inst.*, **1957**, *18*, 359-369.
[78] L. Wilson, *Biochemistry*, **1970**, *9*, 4999-5007.
[79] J. M. Andreu, S. N. Timasheff, *Biochemistry*, **1982**, *21*, 6465-6476.
[80] R. B. G. Ravelli, B. Gigant, P. A. Curmi, I. Jourdair, S. Lachkar, A. Sobel, M. Knossow, *Nature*, **2004**, *428*, 198-202.
[81] R. F. Luduena, M. C. Roach, *Pharma. Ther.*, **1991**, *49*, 133-152.
[82] J. O. Kokwaro, *Medicinal Plants of East Africa*, **1976**, East Africa Literature Bureau, Nairobi.
[83] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Bryan, *J. Am. Chem. Soc.*, **1973**, *95*, 1335-1336.
[84] F. Zavala, D. Guenard, J. P. Robin, E. Brown, *J. Med. Chem.*, **1980**, *23*, 546-549.
[85] R. W. Wang, L. I. Rebhun, S. M. Kupchan, *Cancer Res.*, **1977**, *37*, 3071-3079.
[86] G. R. Pettit, G. M. Cragg, S. B. Singh, *J. Nat. Prod.*, **1987**, *50*, 386-391.
[87] R. H. Himes, *Pharmac. Ther.*, **1991**, *51*, 257-268.
[88] G. R. Pettit, S. B. Singh, E. Hamel, C. M. Lin, D. S. Alberts, D. Garcia-Kendall, *Experientia*, **1989**, *45*, 209-211.
[89] All biological testing described in this thesis was carried out by Dr. Sylvie Ducki and Darren Cook at the Centre for Molecular Drug Design at Salford University.
[90] S. Ducki, R. Forrest, J. A. Hadfield, A. Kendall, N. J. Lawrence, A. T. McGown, D. Rennison. *Biorg. Med. Chem. Lett.* **1998**, *8*, 1051.
[91] D. J. Holmes, H. J. Holmes, *Can. J. Chem.*, **1969**, *47*, 863.
[92] D. J. Currie, C. E. Lough, R. F. Silver, H. J. Holmes, *Can. J. Chem.*, **1967**, *45*, 1567-1580.
[93] D. O'Hagan, R. Perry, J. M. Lock, J. J. M. Meyer, L. Dasaradhi, J. T. G. Hamilton, D. B. Harper, *Phytochemistry*, **1993**, *33*, 1043.
[94] L. E. Twigg, D. R. King, *OIKOS*, **1991**, *61*, 412.
[95] C. Dong, F. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan, J. H. Naismith, *Nature*, **2004**, *427*, 561.
[96] J. J. M. Meyer, D. O'Hagan, *Chem. Br.*, **1992**, *28*, 785.
[97] J. Q. Liu, J. T. Kurihara, S. Ichiyama, M. Mayagi, S. Tsunasawa, H. Kawasaki, K. Soda, N. Esaki, *J. Biol. Chem.*, **1998**, *273*, 30897.
[98] E. Kun, R. J. Dummel, *Methods Enzymol.*, **1969**, *13*, 632.
[99] E. Kun, E. Kirsten, M. L. Sharma, *Proc. Nat. Acad. Sci.*, **1977**, *74*, 4942.
[100] P. F. V. Ward, R. J. Hall, R. J. Peters, Nature, 1964, 201, 611
[101] D. O'Hagan, D. B. Harper, *J. Fluorine Chem.*, **1999**, *100*, 127-133.
[102] S. O. Thomas, V. L. Singleton, J. A. Lowery, R. W. Sharpe, L. M. Preuss, J. N. Porter, J. H. Mowat, N. Bohonos, *Antibiotics Ann.*, **1956**, 716.
[103] A. R. Maguire, W. Meng, S. M. Roberts, A. J. Willetts, *J. Chem. Soc., Perkin Trans.*, **1993**, 1795.
[104] F. M. D. Ismail, *J. Fluorine Chem.*, **2002**, *118*, 27-33.
[105] D. O'Hagan, H. S. Rzepa, *Chem. Commun.*, **1997**, *7*, 645-652.

[106] P. Morgan, J. L. Maggs, P. C. B. Page, B. K. Park, *Biochem. Pharmacol.*, **1992**, *44*, 1717-1724.

[107] a) D. A. Dixon, B. E. Smart, *J. Phys. Chem.*, **1991**, *95*, 1609-1612. b) J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron*, **1996**, *52*, 12613-12622.

[108] J. Qiu, S. H. Stevenson, M. J. O'Beirne, R. B. Silverman, *J. Med. Chem.*, **1999**, *42*, 329-332.

[109] M. J. Chen, S. D. Taylor, *Tetrahedron Lett.*, **1999**, *40*, 4149-4152.

[110] D. D. Nelson, G. T. Fraser, W. Klemperer, *Science*, **1987**, *238*, 1670-1674.

[111] G. Bott, L. Field, *J. Am. Chem. Soc.*, **1980**, *102*, 5618-5626.

[112] P. V. Ramachandran, A. V. Teodorovic, H. C. Brown, *Tetrahedron*, **1993**, *49*, 1725-1738.

[113] A. J. Elliott, M. Hudlicky, A. E. Pavlath, Chemistry of organic compounds. II. ACS Monograph 187, American Chemical Society, Washington, DC, 1995, pp. 1119-1125.

[114] F. M. D. Ismail, *J. Fluorine Chem.*, **2002**, *118*, 27-33.

[115] D. S. Bundschuh, M. Eltze, J. Barsig, L. Wollin, A. Hatzelmann, R. Beume, *J. Pharmacol. Exp. Ther.*, **2001**, *297*, 280-290.

[116] J. A. Farmer, *Lancet*, **2001**, *358 (9291)*, 1383-1385

[117] T. Kosoglou, M. Seiberling, P. Statkevich, L. Reyderman, L. Anderson, S. Sun, S. E. Maxwell, M. B. Affrime, E. P. Veltri, *Eur. Heart J.*, **2001**, *22*, 252.

[118] J. R. Wetterau, R. E. Gregg, T. W. Harrity, C. Arbeeny, M. Cap, F. Connoly, C. H. Chu, R. J. George, D. A. Gordon, H. Jamil, K. G. Jolibois, L. K. Kunselman, S. J. Lan, T. J. Maccagan, B. Ricci, M. Yan, D. Young, Y. Chen, O. M. Fryszman, J. V. Logan, C. L. Musial, M. A. Poss, J. A. Robl, L. M. Simpkins, S. A. Biller, *Science*, **1998**, *282* (5389), 751-754.

[119] D. R. Holland (Eli Lilly, USA), *U. S. Patent Application* (**1982**) CODEN: USXXAM US 4329356 A 19820511.

[120] D. G. Heppne, V. R. Ballou, *Curr. Opin. Infect. Dis.*, **1998**, *11*, 519-530.

[121] B. M. Kotecka, G. B. Barlin, M. D. Edstein, K. H. Rieckmann, *Antimicrob. Agents Chemother.*, **1997**, *41*, 1369-1374.

[122] J. Alzeer, J. Chollet, I. Heinze-Krauss, C. Hubschwerlen, H. Matile, R. G. Ridley, *J. Med. Chem.*, **2000**, *43*, 560-568.

[123] J. Baselga, S. D. Averbuch, *Drugs*, **2000**, *60*, 33-40.

[124] S. R. Wedge, D. J. Ogilvie M. Dukes, J. Kendrew, J. O. Curwen, L. F. Hennequin, A. P. Thomas, E. S. E. Stokes, B. Curry, G. H. P. Richmond, P. F. Wadsworth, *Cancer Res.*, **2000**, *60*, 970-975.

[125] J. Torrance, P. E. Jackson, E. Montgomery, K. W. Kinzler, B. Vogelstein, A. Wissner, M. Nunes, P. Frost, C. M. Discafani, *Nat. Med.*, **2000**, *6*, 1024-1028.

[126] T. D. Bradshaw, D. Shi, R. J. Schultz, K. D. Paull, L. Kelland, A. Wilson, H. H. Fiebig, S. Wrigley, M. F. G. Stevens, *Br. J. Cancer*, **1998**, *78*, 421-429.

[127] I. Hutchinson, M. Chua, H. L. Browne, V. Trapani, T. D. Bradshaw, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.*, **2001**, *44*, 1446-1455.

[128] O. Lavergne, D. Demarquay, C. Bailly, C. Lanco, A. Rolland, M. Huchet, H. Coulamb, N. Muller, N. Baroggi, J. Camara, C. L. Breton, E. Manginot, J. B. Cazaux, D. C. H. Bigg, *J. Med. Chem.*, **2000**, *43*, 2285-2289.

[129] W. Hausmann, *Biochem. Z.*, **1911**, *30*, 276.

[130] N. Miyoshi, H. Hisazumi, M. Fukuda, *Photomed. Photobiol.*, **1988**, *10*, 69.

[131] D. Kessel, *Biochem.Pharmacol.*, **1984**, *33*, 1389.

[132] I. Kumadaki, A. Ando, M. Omote, *J. Fluorine Chem.*, **2001**, *109*, 67-81.

[133] Y. Yamazaki, Y. Ogawa, H. Okuno, *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 757.

[134] Y. Yamazaki, Y. Ogawa, A. S. Afify, Y. Kageyama, T. Okada, H. Okuno, Y. Yoshii, T. Nose, *Biochim. Biophys. Acta.*, **1995**, *1243*, 300.

[135] Y. Yamazaki, S. Yusa, Y. Kageyama, H. Tsue, K. Hirao, H. Okuno, *J. Fluorine Chem.*, **1996**, *79*, 167-171.

[136] L. Li, H. K. Wang, S. C. Kuo, T. S. Wu, D. Lednicer, C. M. Lin, E. Hamel, K. H. Lee, *J. Med. Chem.*, **1994**, *37*, 1126-1135.

[137] Y. Xia, Z. Yang, P. Xia, T. Hackl, E. Hamel, A. Mauger, J. Wu, K. Lee, *J. Med. Chem.*, **2001**, *44*, 3932-3936.

[138] J. A. Katzenellenbogen, *J. Fluorine Chem.*, **2001**, *109*, 3-11.

[139] A. O. Koren, A. G. Horti, A. G. Mukhin, D. Grundisch, R. F. Dannals, E. D. London, *J. Label. Comp. Radiopharm.*, **2000**, *43*, 413-423.

[140] J. A. Katzenellenbogen, *J. Fluorine Chem.*, **2001**, *109*, 49-54.

[141] J. A. Katzenellenbogen, C. J. Mathias, H. F. VanBrocklin, J. W. Brodack, M. J. Welch, *Nucl. Med. Biol.*, **1993**, *20*, 735-745.

[142] R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif, R. G. Syvret, *J. Chem. Soc., Chem. Commun.*, **1992**, 595.

[143] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc., Chem. Commun.*, **1994**, 343.

[144] All biological testing described in this thesis was carried out by Dr. Sylvie Ducki and Darren Cook at the Centre for Molecular Drug Design at Salford University.

[145] F. A. Bovey, *Nuclear Magnetic Resonance Spectroscopy*, **1969**, Academic Press New York + London.

[146] Q. Chen, S. Wu, *J. Chem. Soc. Chem. Commun.*, **1989**, *11*, 705-706.

[147] Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, T. Yokoyama, *J. Org. Chem.*, **1988**, *53*, 129-135

[148] M. J. Meyers, J. Sun, K. E. Carlson, G. A. Marriner, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *J. Med. Chem.*, **2001**, *44*, 4230.

[149] M. Cushman, D. Nagarathnam, D. Gopal, H. M. He, C. M. Lin, E. Hamel, *J. Med. Chem.*, **1992**, *35*, 2293-2306.

[150] V. N. Charushin, E. V. Nosova, G. N. Lipunova, M. I. Kodess, *J. Fluorine Chem.*, **2001**, *110*, 25-30.

[151] S. Jaime-Figueroa, L. J. Kurz, Y. Liu, R. Cruz, *Spectrochimica Acta Part A*, **2000**, *56*, 1167-1178.

[152] G. W. Gribble, E. R. Olson, *J. Org. Chem.*, **1993**, *58*, 1631-1634.

[153] F. B. Mallory, *J. Am. Chem. Soc.*, **1973**, *95*, 7747-7752.

[154] F. B. Mallory, C. W. Mallory, K. E. Butler, M. B. Lewis, A. Q. Xia, E. D. Luzik, L. E. Fredenburgh, M. M. Ramanjulu, Q. N. Van, M. M. Francl, D. A. Freed, C. C. Wray, C. Hann, M. Nerz-Stormes, P. J. Carroll, L. E. Chirlian, *J. Am. Chem. Soc.*, **2000**, *122*, 4108-4116.

[155] F. B. Mallory, C. W. Mallory, M. B. Baker, *J. Am. Chem. Soc.*, **1990**, *112*, 2577-2581.

[156] F. B. Mallory, C. W. Mallory, E. D. Luzik, P. J. Carrol, *J. Org. Chem.*, **1992**, *57*, 366-370.

[157] S. Jaime-Figueroa, L. J. Kurz, Y. Liu, R. Cruz, *Spectrochimica Acta Part A*, **2000**, *56*, 1167-1178.

[158] F. B. Mallory, C. W. Mallory, W. M. Ricker, *J. Org. Chem.*, **1985**, *50*, 457-461.

[159] F. B. Mallory, C. W. Mallory, W. M. Ricker, *J. Am. Chem. Soc.*, **1975**, *97*, 4770-4771.

[160] R. E. Wasylishen, M. Barfield, *J. Am. Chem. Soc.*, **1975**, *97*, 4545-4552.

[161] M. A. Cooper, H. E. Weber, S. L. Manatt, *J. Am. Chem. Soc.*, **1971**, *93*, 2369.

[162] P. J. Mitchel, L. Phillips, S. J. Roberts, V. Wray, *Org. Magn, Reson.*, **1974**, *6*, 126.

[163] D. C. England, E. A. Donald, F. J. Weigert, *J. Org. Chem.*, **1981**, *46*, 144-147.

[164] M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.*, **1964**, 1996.

[165] A. I. Kitaigorodskii, *Molecular Crystals and Molecules*, Academic Press, London, **1973**.

[166] H. Nakanishi, W. Jones, J. M. Thomas, M. B. Hursthouse, M. Motevalli, *J. C. S. Chem. Comm.*, **1980**, 611-612.

[167] W. Meyer, G. Lieser, G. Wegner, *J. Polym. Sci. Polym. Phys. Ed.*, **1978**, *16*, 1365.
[168] H. Eichele, M. Schwoerer, R. Huber, D. Bloor, *Chem. Phys. Lett.*, **1976**, *42*, 342.
[169] J. M. Thomas, Phil. Trans. Roy. Soc. London, **1974**, 277, 31.
[170] W. Jones, H. Nakanishi, J. M. Thomas, *Chem. Phys. Lett.*, **1980**, *71*, 44.
[171] W. Jones, H. Nakanishi, J. M. Thomas, M. B. Hursthouse, M. Motevalli, *J. Phys. Chem.*, **1981**, *85*, 3636-3642.
[172] K. Gnanaguru, N. Ramasubbu, K. Venkatesan, V. Ramamurthy, *J. Org. Chem.*, **1985**, *50*, 2337.
[173] a)D. Cesarin-Sobrinho, J. C. Netto-Ferreira, *Quim. Nova*, **2002**, *25*, 62. b)K. Tanaka, F. Toda, *J. Chem. Soc. Chem. Comm.*, **1983**, 593.
[174] I. Turowska-Tyrk, K. Grzesniak, E. Trzop, T. Zych, *J. Sol. State. Chem.*, **2003**, *174*, 459-465.
[175] a) S. F. Nielson, , S. B. Christensen, G. Cruciani, A. Kharazmi, T. Liljefors, *J. Med. Chem.*, **1998**, *41*, 4819-4832. b) R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. Rosenthal, J. H. McKerrow, *J. Med. Chem.*, **1995**, *38*, 5031.
[176] S. F. Nielsen, S. B. Christensen, G. Cruciani, A. Kharazmi, T. Liljefors, *J. Med. Chem.*, **1998**, *41*, 4819-4832.
[177] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. J. Rosenthal, J. H. McKerrow, *J. Med. Chem.*, **1995**, *38*, 5031-5037.
[178] D. Fokas, W. J. Ryan, D. S. Casebier, D. L. Coffen, *Tetrahedron Lett.*, **1998**, *39*, 2235-2238.
[179] T. Kammermeier, W. Wiegrebe, *Arch. Pharm.*, **1994**, *9*, 547-562.
[180] X-ray analysis throughout the project was carried out by Dr. Li-ling Ooi at Cardiff University Chemistry Department.
[181] Solid state NMR and X-ray powder diffraction studies are being carried out by Prof. Ken Harris at Cardiff University Chemistry Department.
[182] R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharif, R. G. Syvret, *J. Chem. Soc., Chem. Commun.*, **1992**, 595.
[183] C. M. Sharts, W. A. Sheppard, *Organic Reactions*, **1974**, *21*, 158-173.
[184] R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson, R. H. Lafferty, *J. Am. Chem. Soc.*, **1950**, *72*, 3646.
[185] N. N. Yarovenko, M. A. Raksha, *J. Gen. Chem. (USSR)*, **1959**, *29*, 2125.
[186] D. E. Ayer, *Tet. Lett.*, **1962**, 1065.
[187] M. Mousseron-Canet, J. L. Borgna, *Bull. Soc. Chim. Fr.*, **1969**, 613.
[188] J. Kopecky, J. Smejkal, M. Hudlicky, *Chem. Ind. (London)*, **1969**, 271.
[189] a) M. Hudlicky, B. Kakac, *Collect. Czech. Chem. Commun.*, **1966**, *31*, 1101. b) E. D. Bergmann, A. M. Cohen, *Isr. J. Chem.*, **1970**, *8*, 925.
[190] D. E. Ayer, U.S. Patent 3,137,701, **1964**.
[191] P. W. Kent, *Chem. Ind. (London)*, **1969**, 1128.
[192] D. E. Ayer, *Tet. Lett.*, **1962**, 1065.
[193] G. B. Spero, J. E. Pike, F. H. Lincoln, J. L. Thompson, *Steroids*, **1968**, *11*, 769.
[194] a) D. E. Ayer, *U.S. Patent 3,153,644*, **1964**. b) E. D. Bergmann, A. M. Cohen, *Isr. J. Chem.*, **1970**, *8*, 925. c) N. N. Yarovenko, M. A. Raksha, *J. Gen. Chem. (USSR)*, **1959**, *29*, 2125.
[195] N. Ishikawa, A. Takaoka, H. Iwakiri, *Bull. Chem. Soc. Japan*, **1979**, *52*, 3377.
[196] R. E. Banks, A. Barrage, E. Khoshdel, *J. Fluorine Chem.*, **1981**, *17*, 93-98.
[197] W. Dmowski, M. Kaminski, *J. Fluorine Chem.*, **1983**, *23*, 219-228.
[198] D. J. Burton, R. Anilkumar, *Tet. Lett.*, **2002**, *43*, 2731-2733.

[199] A. S. Castanet, F. Colobert, P. E. Broutin, *Tet. Lett.*, **2002**, *43*, 5047-5048.
[200] F. Tellier, R. Sauvêtre, J. F. Normant Y. Dromzee, Y. Jeannin, *J. Organomet. Chem.*, **1987**, **331**, 281-298.
[201] L. Ruest, H. Ménard, V. Moreau, F. Laplante, *Can. J. Chem.*, **2002**, *80*, 1662-1667.
[202] F. D. Mills, J. E. Hodge, *Carbohydrate Research*, **1976**, *51*, 10-21.
[203] M. D. Price, M. J. Kurth, N. E. Schore, *J. Org. Chem.*, **2002**, *67*, 7769-7774.
[204] M. Fujita, M. Obayashi, T. Hiyama, *Tetrahedron*, **1988**, *44*, 4135-4146.
[205] H. Frohn, A. Lewin, V. V. Bardin, J. Organomet. Chem., 1998, 570, 255-264.
[206] T. D. Yarwood, A. J. Waring, P. L. Coe, *J. Fluorine Chem.*, **1996**, *78*, 113-120.
[207] R. K. Jaiswal, S. S. Parmar, S. P. Singh, J. P. Barthwal , *J. Heterocyclic Chem.*, **1979**, *16*, 561-564.
[208] P. Seneci, M. Nicola, M. Inglesi, E. Vanotti, G. Resnati, *Synth. Commun.*, **1999**, *29*, 311-342.
[209] R. S. Long, *J. Am. Chem. Soc.*, **1947**, *69*, 990-995.
[210] F. Orsini, F. Pelizzoni, B. Bellini, G. Miglierini, *Carbohydrate Res.*, **1997**, *301*, 95-110.
[211] B. S. Balaji, B. M. Chanda, *Tetrahedron*, **1998**, *54*, 13237-13252.
[212] D. J. Goldsmith, *J. Org. Chem.*, **1961**, *26*, 2078.
[213] T. Itoh, K. Nagata, M. Yokoya, M. Miyazaki, K. Kameoka, S. Nakamura, A. Ohsawa, *Chem. Pharm. Bull.*, **2003**, *51*, 951-955.
[214] N. Nam, Y. Kim, Y. You, D. Hong, H. Kim, B. Ahn, *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 3073-3076.
[215] T. Fujii, S. Yoshifuji, K. Yamada, *Tetrahedron Letters*, **1975**, *16*, 1527-1530.
[216] S. B. Said, J. Skarzewski, J. Mlochowski, *Synthesis*, **1989**, *3*, 223-224.
[217] V. Lisowski, C. Enguehard, J. Lancelot, D. Caignard, S. Lambel, S. Loence, A. Pierre, G. Atassi, P. Renard, S. Rault, *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2205-2208.
[218] S. B. Singh, G. R. Pettit, *J. Org. Chem.*, **1989**, *54*, 4105-4114.
[219] F. R. Hewgill, R. Slamet, J. M. Stewart, *J. Chem. Soc. Perkin Trans. 1*, **1991**, *12*, 3033-3042.
[220] R. Gust, T. Burgemeister, A. Mannschreck, H. Schoenenberger, *J. Med. Chem.*, **1990**, *33*, 2535-2544.
[221] W. Naik, *J. Chem. Soc.*, **1938**, 1780-1782.
[222] I. Cervena, J. Holubek, E. Svatek, M. Valchar, M. Protiva, *Collect. Czech. Chem. Commun.*, **1987**, *52*, 2564-2571.
[223] S. B. Singh, G. R. Pettit, *J. Org. Chem.*, **1989**, *54*, 4105-4114.
[224] F. R. Hewgill, R. Slamet, J. M. Stewart, *J. Chem. Soc. Perkin Trans. 1*, **1991**, *12*, 3033-3042.
[225] W. Naik, *J. Chem. Soc.*, **1938**, 1780-1782.
[226] I. Cervena, J. Holubek, E. Svatek, M. Valchar, M. Protiva, *Collect. Czech. Chem. Commun.*, **1987**, *52*, 2564-2571.
[227] (Bromide salt) R. A. Aitken, G. L. Thom, *Synthesis*, **1989**, *12*, 958-959.
[228] J. Begue, D. Bonnet-Delpon, D. Mesureur, G. Nee, S. Wu, *J. Org. Chem.*, **1992**, *57*, 3807-3814.
[229] S. B. Singh, G. R. Pettit, *J. Org. Chem.*, **1989**, *54*, 4105-4114.
[230] Y. Ukaji, M. Ima, T. Yamada, K. Inomata, *Heterocycles*, **2000**, *52*, 563-566.
[231] G. Mervic, *J. Am. Chem. Soc.*, **1977**, *99*, 7673-7677.
[232] R. Luckenbach, *Phosphorus Relat. Group V Elem.*, **1972**, *1*, 293-296.
[233] S. Schertl, R. W. Hartmann, C. Batzl-Hartmann, R. Schlemmer, T. Spruss, G. Bernhardt, R. Gust, H. Schoenenberger, *Arch. Pharm. (Weinheim Ger.)*, **2001**, *334*, 125-137.
[234] C. S. John, B. B. Lim, S. Iyer, B. C. Geyer, M. E. Smulson, *J. Labelled Compd. Radiopharm.*, **1999**, *42*, 707-709.

[235] H. Shiohara, T. Nakamura, N. Kikuchi, T. Ozawa, M. Kitazawa, *PCT Int. Appl.* (**2003**), 197 pp. CODEN: PIXXD2 WO 2003064369 A1 20030807 CAN 139:164630 AN 2003:610403 CAPLUS
[236] S. F. Nielsen, S. B. Christensen, G. Cruciani, A. Kharazmi, T. Liljefors, *J. Med. Chem.*, **1998**, *41*, 4819-4832.
[237] R. Li, G. L. Kenyon, F. E. Cohen, X. Chen, B. Gong, J. N. Dominguez, E. Davidson, G. Kurzban, R. E. Miller, E. O. Nuzum, P. J. Rosenthal, J. H. McKerrow, *J. Med. Chem.*, **1995**, *38*, 5031-5037.
[238] D. Fokas, W. J. Ryan, D. S. Casebier, D. L. Coffen, *Tetrahedron Lett.*, **1998**, *39*, 2235-2238.
[239] T. Kammermeier, W. Wiegrebe, *Arch. Pharm.*, **1994**, *9*, 547-562.
[240] D. Fokas, W. J. Ryan, D. S. Casebier, D. L. Coffen, *Tetrahedron Lett.*, **1998**, *39*, 2235-2238.
[241] R. W. Hartmann, W. Schwarz, H. Schoenenberger, *J. Med. Chem.*, **1983**, *26*, 1137-1144.
[242] R. Anilkumar, D. J. Burton, *Tetrahedron Letters*, **2002**, *43*, 2731-2733.
[243] F. Tellier, R. Sauvetre, J. F. Normant, Y. Dromzee, Y. Jeannin, *J. Organomet. Chem.*, **1987**, *3*, 281-298.
[244] N. M. Sergeev, O. P. Petrii, N. N. Shapet'ko, *J. Struct. Chem. (Engl. Transl.)*, **1970**, *11*, 828-834.
[245] A. S. Castnet, F. Colobert, P. E. Broutin, *Tetrahedron Letters*, **2002**, *43*, 5047-5048.
[246] D. E. Janssen, C. V. Wilkson, *Org. Synth. Coll.*, **1963**, *4*, 547.
[247] L. Ruest, H. Ménard, V. Moreau, F. Laplante, *Can. J. Chem.*, **2002**, *80*, 1662-1667.
[248] H. Zimmer, A. Amer, F. M. Baumann, M. Haecker, C. G. M. Hess, D. Ho, H. J. Huber, K. Koch, K. Mahnke, C. Schumacher, R. C. Wingfield, *Eur. J. Org. Chem.*, **1999**, *9*, 2419-2428.
[249] F. D. Mills, J. E. Hodge, *Carbohydrate Research*, **1976**, *51*, 10-21.
[250] R. L. E. Furlán, E. G. Mata, O. A. Mascaretti, *Tetrahedron*, **1998**, *54*, 13023-13034.
[251] G. R. Pettit, S. B. Singh, D. L. Herald, P. Lloyd-Williams, D. Kantoci, *J. Org. Chem.*, **1994**, *21*, 6287-6295.
[252] M. D. Price, M. J. Kurth, N. E. Schore, *J. Org. Chem.*, **2002**, *67*, 7769-7774.
[253] D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, *J. Org. Chem.*, **1991**, *18*, 751-762.
[254] P. L. Heinze, D. J. Burton, *J. Org. Chem.*, **1988**, *53*, 2714-2720.

Appendix I, Crystal data for 42c

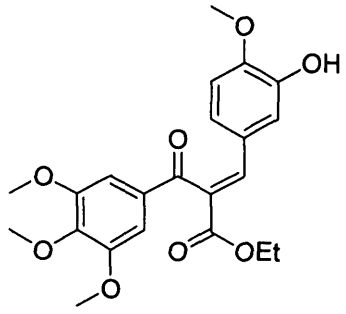


Table 1. Crystal data and structure refinement for **42c**.

Identification code	njl0410	
Empirical formula	C22 H24 O8	
Formula weight	416.41	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.0780(2) Å	α= 86.948(2)°.
	b = 13.5738(3) Å	β= 70.898(2)°.
	c = 15.1885(4) Å	γ = 74.8980(10)°.
Volume	2082.33(8) Å^3	
Z	4	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	880	
Crystal size	0.30 x 0.28 x 0.15 mm^3	
Theta range for data collection	2.93 to 27.49°.	
Index ranges	-14<=h<=14, -17<=k<=17, -19<=l<=19	
Reflections collected	37438	
Independent reflections	9416 [R(int) = 0.1679]	
Completeness to theta = 27.49°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9849 and 0.9702	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9416 / 0 / 553	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0655, wR2 = 0.1557	
R indices (all data)	R1 = 0.1372, wR2 = 0.1889	
Largest diff. peak and hole	0.281 and -0.363 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **42c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(11)	914(3)	2146(2)	2118(2)	35(1)
C(12)	490(3)	5367(2)	1903(2)	48(1)
C(13)	2513(3)	5798(2)	-1359(2)	60(1)
C(14)	1912(2)	2517(2)	213(2)	24(1)
C(15)	1706(2)	3231(2)	904(2)	24(1)
C(16)	1864(2)	4208(2)	662(2)	26(1)

C(17)	2174(2)	4476(2)	-276(2)	28(1)
C(18)	2343(2)	3774(2)	-957(2)	26(1)
C(19)	2232(2)	2793(2)	-714(2)	24(1)
C(110)	2416(2)	2047(2)	-1467(2)	23(1)
C(111)	2488(2)	936(2)	-1250(1)	22(1)
C(112)	3828(2)	324(2)	-1280(2)	26(1)
C(113)	5291(2)	-1342(2)	-1394(2)	34(1)
C(114)	5280(3)	-2396(2)	-1638(2)	40(1)
C(115)	1491(2)	499(2)	-1112(1)	24(1)
C(116)	97(2)	989(2)	-997(1)	23(1)
C(117)	-702(2)	386(2)	-1090(2)	25(1)
C(118)	-2023(2)	807(2)	-990(2)	25(1)
C(119)	-2582(2)	1857(2)	-804(2)	24(1)
C(120)	-1817(2)	2466(2)	-692(2)	29(1)
C(121)	-498(2)	2033(2)	-781(2)	29(1)
C(122)	-4431(3)	3294(2)	-697(2)	39(1)
O(11)	1351(2)	3056(1)	1835(1)	34(1)
O(12)	1798(2)	4893(1)	1324(1)	34(1)
O(13)	2303(2)	5447(1)	-428(1)	43(1)
O(14)	2545(2)	2310(1)	-2261(1)	33(1)
O(15)	4688(2)	719(1)	-1272(1)	35(1)
O(16)	3986(2)	-681(1)	-1320(1)	32(1)
O(17)	-2759(2)	177(1)	-1071(1)	43(1)
O(18)	-3892(2)	2210(1)	-726(1)	30(1)
C(21)	5847(3)	2136(2)	-2870(2)	33(1)
C(22)	6854(3)	5032(2)	-3045(2)	50(1)
C(23)	6963(3)	5986(2)	-6234(2)	34(1)
C(24)	6776(2)	2592(2)	-4753(2)	22(1)
C(25)	6426(2)	3317(2)	-4043(2)	26(1)
C(26)	6398(2)	4341(2)	-4251(2)	27(1)
C(27)	6696(2)	4627(2)	-5181(2)	26(1)
C(28)	7021(2)	3909(2)	-5892(2)	23(1)
C(29)	7062(2)	2893(2)	-5673(2)	21(1)
C(210)	7367(2)	2141(2)	-6449(2)	23(1)
C(211)	7427(2)	1026(2)	-6246(1)	22(1)
C(212)	8765(2)	418(2)	-6269(1)	23(1)
C(213)	10257(2)	-1226(2)	-6393(2)	30(1)
C(214)	10324(3)	-2278(2)	-6682(2)	43(1)
C(215)	6431(2)	591(2)	-6122(1)	22(1)
C(216)	5036(2)	1069(2)	-6019(1)	22(1)
C(217)	4247(2)	436(2)	-6066(2)	26(1)
C(218)	2919(2)	828(2)	-5960(2)	24(1)
C(219)	2337(2)	1879(2)	-5790(2)	23(1)
C(220)	3092(2)	2519(2)	-5731(2)	26(1)
C(221)	4427(2)	2115(2)	-5841(2)	27(1)
C(222)	400(2)	3272(2)	-5638(2)	36(1)
O(21)	6058(2)	3124(1)	-3115(1)	33(1)
O(22)	5977(2)	5087(1)	-3559(1)	39(1)
O(23)	6639(2)	5641(1)	-5306(1)	33(1)
O(24)	7600(2)	2394(1)	-7257(1)	33(1)
O(25)	9609(2)	817(1)	-6233(1)	33(1)
O(26)	8948(2)	-588(1)	-6335(1)	29(1)
O(27)	2184(2)	177(1)	-6004(1)	37(1)
O(28)	1003(2)	2193(1)	-5673(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for **42c**.

C(11)-O(11)	1.437(3)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-O(12)	1.423(3)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-O(13)	1.432(3)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.388(3)
C(14)-C(19)	1.391(3)
C(14)-H(14)	0.9500
C(15)-O(11)	1.364(2)
C(15)-C(16)	1.397(3)
C(16)-O(12)	1.378(3)
C(16)-C(17)	1.403(3)
C(17)-O(13)	1.362(3)
C(17)-C(18)	1.378(3)
C(18)-C(19)	1.388(3)
C(18)-H(18)	0.9500
C(19)-C(110)	1.497(3)
C(110)-O(14)	1.214(2)
C(110)-C(111)	1.513(3)
C(111)-C(115)	1.339(3)
C(111)-C(112)	1.487(3)
C(112)-O(15)	1.213(3)
C(112)-O(16)	1.332(3)
C(113)-O(16)	1.461(3)
C(113)-C(114)	1.501(3)
C(113)-H(11D)	0.9900
C(113)-H(11E)	0.9900
C(114)-H(11F)	0.9800
C(114)-H(11G)	0.9800
C(114)-H(11H)	0.9800
C(115)-C(116)	1.469(3)
C(115)-H(115)	0.9500
C(116)-C(117)	1.394(3)
C(116)-C(121)	1.405(3)
C(117)-C(118)	1.386(3)
C(117)-H(117)	0.9500
C(118)-O(17)	1.361(3)
C(118)-C(119)	1.401(3)
C(119)-O(18)	1.372(3)
C(119)-C(120)	1.380(3)
C(120)-C(121)	1.389(3)
C(120)-H(120)	0.9500
C(121)-H(121)	0.9500
C(122)-O(18)	1.434(3)
C(122)-H(12D)	0.9800
C(122)-H(12E)	0.9800
C(122)-H(12F)	0.9800
O(17)-H(17)	0.8400
C(21)-O(21)	1.430(3)
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-O(22)	1.420(3)
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-O(23)	1.421(2)
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-C(25)	1.386(3)
C(24)-C(29)	1.391(3)
C(24)-H(24)	0.9500
C(25)-O(21)	1.364(2)
C(25)-C(26)	1.403(3)
C(26)-O(22)	1.375(3)
C(26)-C(27)	1.401(3)
C(27)-O(23)	1.367(2)
C(27)-C(28)	1.385(3)
C(28)-C(29)	1.395(3)
C(28)-H(28)	0.9500
C(29)-C(210)	1.494(3)
C(210)-O(24)	1.217(2)
C(210)-C(211)	1.518(3)
C(211)-C(215)	1.339(3)
C(211)-C(212)	1.487(3)
C(212)-O(25)	1.213(3)
C(212)-O(26)	1.332(3)
C(213)-O(26)	1.460(3)
C(213)-C(214)	1.492(3)
C(213)-H(21D)	0.9900
C(213)-H(21E)	0.9900
C(214)-H(21F)	0.9800
C(214)-H(21G)	0.9800
C(214)-H(21H)	0.9800
C(215)-C(216)	1.470(3)
C(215)-H(215)	0.9500
C(216)-C(217)	1.395(3)
C(216)-C(221)	1.402(3)
C(217)-C(218)	1.385(3)
C(217)-H(217)	0.9500
C(218)-O(27)	1.366(3)
C(218)-C(219)	1.404(3)
C(219)-C(220)	1.378(3)
C(219)-O(28)	1.380(3)
C(220)-C(221)	1.393(3)
C(220)-H(220)	0.9500
C(221)-H(221)	0.9500
C(222)-O(28)	1.439(3)
C(222)-H(22D)	0.9800
C(222)-H(22E)	0.9800
C(222)-H(22F)	0.9800

O(27)-H(27)	0.8400
O(11)-C(11)-H(11A)	109.5
O(11)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
O(11)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(12)-C(12)-H(12A)	109.5
O(12)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(12)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(13)-C(13)-H(13A)	109.5
O(13)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(13)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(19)	119.5(2)
C(15)-C(14)-H(14)	120.2
C(19)-C(14)-H(14)	120.2
O(11)-C(15)-C(14)	124.7(2)
O(11)-C(15)-C(16)	115.4(2)
C(14)-C(15)-C(16)	119.9(2)
O(12)-C(16)-C(15)	120.88(19)
O(12)-C(16)-C(17)	119.3(2)
C(15)-C(16)-C(17)	119.7(2)
O(13)-C(17)-C(18)	125.3(2)
O(13)-C(17)-C(16)	114.5(2)
C(18)-C(17)-C(16)	120.2(2)
C(17)-C(18)-C(19)	119.7(2)
C(17)-C(18)-H(18)	120.1
C(19)-C(18)-H(18)	120.1
C(18)-C(19)-C(14)	120.9(2)
C(18)-C(19)-C(110)	118.64(19)
C(14)-C(19)-C(110)	120.5(2)
O(14)-C(110)-C(19)	121.1(2)
O(14)-C(110)-C(111)	118.9(2)
C(19)-C(110)-C(111)	120.01(19)
C(115)-C(111)-C(112)	121.3(2)
C(115)-C(111)-C(110)	124.8(2)
C(112)-C(111)-C(110)	113.70(19)
O(15)-C(112)-O(16)	123.8(2)
O(15)-C(112)-C(111)	122.1(2)
O(16)-C(112)-C(111)	114.0(2)
O(16)-C(113)-C(114)	106.5(2)
O(16)-C(113)-H(11D)	110.4
C(114)-C(113)-H(11D)	110.4
O(16)-C(113)-H(11E)	110.4
C(114)-C(113)-H(11E)	110.4
H(11D)-C(113)-H(11E)	108.6
C(113)-C(114)-H(11F)	109.5
C(113)-C(114)-H(11G)	109.5
H(11F)-C(114)-H(11G)	109.5
C(113)-C(114)-H(11H)	109.5
H(11F)-C(114)-H(11H)	109.5
H(11G)-C(114)-H(11H)	109.5
C(111)-C(115)-C(116)	128.6(2)
C(111)-C(115)-H(115)	115.7
C(116)-C(115)-H(115)	115.7
C(117)-C(116)-C(121)	117.3(2)
C(117)-C(116)-C(115)	118.6(2)
C(121)-C(116)-C(115)	124.0(2)
C(118)-C(117)-C(116)	121.1(2)
C(118)-C(117)-H(117)	119.4
C(116)-C(117)-H(117)	119.4
O(17)-C(118)-C(117)	118.4(2)
O(17)-C(118)-C(119)	121.2(2)
C(117)-C(118)-C(119)	120.4(2)
O(18)-C(119)-C(120)	124.1(2)
O(18)-C(119)-C(118)	116.4(2)
C(120)-C(119)-C(118)	119.5(2)
C(119)-C(120)-C(121)	119.6(2)
C(119)-C(120)-H(120)	120.2
C(121)-C(120)-H(120)	120.2
C(120)-C(121)-C(116)	122.0(2)
C(120)-C(121)-H(121)	119.0
C(116)-C(121)-H(121)	119.0
O(18)-C(122)-H(12D)	109.5
O(18)-C(122)-H(12E)	109.5
H(12D)-C(122)-H(12E)	109.5
O(18)-C(122)-H(12F)	109.5
H(12D)-C(122)-H(12F)	109.5
H(12E)-C(122)-H(12F)	109.5
C(15)-O(11)-C(11)	116.29(18)
C(16)-O(12)-C(12)	114.25(19)
C(17)-O(13)-C(13)	117.43(19)
C(112)-O(16)-C(113)	117.73(18)
C(118)-O(17)-H(17)	109.5
C(119)-O(18)-C(122)	117.57(18)
O(21)-C(21)-H(21A)	109.5
O(21)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(21)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
O(22)-C(22)-H(22A)	109.5
O(22)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
O(22)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
O(23)-C(23)-H(23A)	109.5
O(23)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
O(23)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(25)-C(24)-C(29)	119.5(2)
C(25)-C(24)-H(24)	120.3

C(29)-C(24)-H(24)	120.3
O(21)-C(25)-C(24)	124.8(2)
O(21)-C(25)-C(26)	114.8(2)
C(24)-C(25)-C(26)	120.4(2)
O(22)-C(26)-C(27)	118.9(2)
O(22)-C(26)-C(25)	121.6(2)
C(27)-C(26)-C(25)	119.3(2)
O(23)-C(27)-C(28)	124.89(19)
O(23)-C(27)-C(26)	114.5(2)
C(28)-C(27)-C(26)	120.6(2)
C(27)-C(28)-C(29)	119.3(2)
C(27)-C(28)-H(28)	120.3
C(29)-C(28)-H(28)	120.3
C(24)-C(29)-C(28)	121.0(2)
C(24)-C(29)-C(210)	120.80(19)
C(28)-C(29)-C(210)	118.18(19)
O(24)-C(210)-C(29)	121.7(2)
O(24)-C(210)-C(211)	118.2(2)
C(29)-C(210)-C(211)	120.11(18)
C(215)-C(211)-C(212)	121.8(2)
C(215)-C(211)-C(210)	125.2(2)
C(212)-C(211)-C(210)	112.83(18)
O(25)-C(212)-O(26)	123.6(2)
O(25)-C(212)-C(211)	122.1(2)
O(26)-C(212)-C(211)	114.32(19)
O(26)-C(213)-C(214)	107.2(2)
O(26)-C(213)-H(21D)	110.3
C(214)-C(213)-H(21D)	110.3
O(26)-C(213)-H(21E)	110.3
C(214)-C(213)-H(21E)	110.3
H(21D)-C(213)-H(21E)	108.5
C(213)-C(214)-H(21F)	109.5
C(213)-C(214)-H(21G)	109.5
H(21F)-C(214)-H(21G)	109.5
C(213)-C(214)-H(21H)	109.5
H(21F)-C(214)-H(21H)	109.5
H(21G)-C(214)-H(21H)	109.5
C(211)-C(215)-C(216)	129.5(2)
C(211)-C(215)-H(215)	115.2
C(216)-C(215)-H(215)	115.2
C(217)-C(216)-C(221)	117.4(2)
C(217)-C(216)-C(215)	118.0(2)
C(221)-C(216)-C(215)	124.6(2)
C(218)-C(217)-C(216)	121.4(2)
C(218)-C(217)-H(217)	119.3
C(216)-C(217)-H(217)	119.3
O(27)-C(218)-C(217)	119.2(2)
O(27)-C(218)-C(219)	120.7(2)
C(217)-C(218)-C(219)	120.1(2)
C(220)-C(219)-O(28)	124.5(2)
C(220)-C(219)-C(218)	119.7(2)
O(28)-C(219)-C(218)	115.8(2)
C(219)-C(220)-C(221)	119.6(2)
C(219)-C(220)-H(220)	120.2
C(221)-C(220)-H(220)	120.2
C(220)-C(221)-C(216)	121.9(2)
C(220)-C(221)-H(221)	119.1
C(216)-C(221)-H(221)	119.1
O(28)-C(222)-H(22D)	109.5
O(28)-C(222)-H(22E)	109.5
H(22D)-C(222)-H(22E)	109.5
O(28)-C(222)-H(22F)	109.5
H(22D)-C(222)-H(22F)	109.5
H(22E)-C(222)-H(22F)	109.5
C(25)-O(21)-C(21)	116.33(18)
C(26)-O(22)-C(22)	114.5(2)
C(27)-O(23)-C(23)	117.88(17)
C(212)-O(26)-C(213)	116.99(17)
C(218)-O(27)-H(27)	109.5
C(219)-O(28)-C(222)	117.99(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **42c**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(11)	47(2)	34(2)	27(1)	8(1)	-5(1)	-23(1)
C(12)	40(2)	34(2)	63(2)	-13(1)	-11(2)	-2(1)
C(13)	112(3)	40(2)	49(2)	24(2)	-38(2)	-45(2)
C(14)	24(1)	20(1)	31(1)	6(1)	-9(1)	-10(1)
C(15)	22(1)	25(1)	26(1)	5(1)	-6(1)	-8(1)
C(16)	26(1)	21(1)	34(1)	0(1)	-12(1)	-9(1)
C(17)	28(2)	23(1)	38(1)	8(1)	-14(1)	-12(1)
C(18)	28(1)	26(1)	29(1)	6(1)	-12(1)	-11(1)
C(19)	18(1)	25(1)	31(1)	4(1)	-9(1)	-8(1)
C(110)	17(1)	26(1)	29(1)	4(1)	-7(1)	-9(1)
C(111)	20(1)	23(1)	24(1)	2(1)	-7(1)	-7(1)
C(112)	23(1)	26(1)	29(1)	4(1)	-7(1)	-10(1)
C(113)	21(1)	32(2)	44(2)	2(1)	-9(1)	0(1)
C(114)	41(2)	31(2)	42(2)	-6(1)	-16(1)	4(1)
C(115)	22(1)	22(1)	28(1)	0(1)	-8(1)	-6(1)
C(116)	21(1)	22(1)	27(1)	4(1)	-7(1)	-9(1)
C(117)	22(1)	20(1)	36(1)	1(1)	-10(1)	-7(1)
C(118)	22(1)	23(1)	33(1)	-1(1)	-10(1)	-9(1)
C(119)	17(1)	25(1)	26(1)	0(1)	-5(1)	-4(1)
C(120)	24(1)	22(1)	38(1)	-4(1)	-6(1)	-3(1)
C(121)	23(1)	25(1)	43(1)	-3(1)	-11(1)	-10(1)
C(122)	32(2)	31(2)	52(2)	-3(1)	-18(1)	4(1)
O(11)	46(1)	32(1)	25(1)	4(1)	-7(1)	-20(1)
O(12)	34(1)	28(1)	39(1)	-6(1)	-10(1)	-11(1)
O(13)	76(2)	25(1)	39(1)	9(1)	-24(1)	-27(1)
O(14)	42(1)	33(1)	27(1)	6(1)	-11(1)	-15(1)
O(15)	23(1)	33(1)	53(1)	9(1)	-15(1)	-14(1)
O(16)	20(1)	24(1)	49(1)	1(1)	-11(1)	-4(1)
O(17)	25(1)	26(1)	84(1)	-6(1)	-25(1)	-8(1)
O(18)	19(1)	28(1)	43(1)	-3(1)	-10(1)	-3(1)
C(21)	39(2)	29(1)	29(1)	7(1)	-8(1)	-14(1)
C(22)	75(2)	33(2)	55(2)	3(1)	-31(2)	-22(2)
C(23)	37(2)	23(1)	39(1)	9(1)	-7(1)	-12(1)
C(24)	21(1)	19(1)	30(1)	4(1)	-9(1)	-9(1)
C(25)	25(1)	27(1)	27(1)	6(1)	-9(1)	-9(1)
C(26)	28(1)	19(1)	32(1)	-1(1)	-9(1)	-5(1)
C(27)	23(1)	20(1)	36(1)	5(1)	-10(1)	-6(1)
C(28)	20(1)	25(1)	27(1)	5(1)	-7(1)	-9(1)
C(29)	15(1)	20(1)	29(1)	3(1)	-6(1)	-6(1)
C(210)	13(1)	23(1)	29(1)	3(1)	-4(1)	-5(1)
C(211)	21(1)	21(1)	24(1)	0(1)	-6(1)	-6(1)
C(212)	20(1)	24(1)	24(1)	2(1)	-3(1)	-9(1)
C(213)	21(1)	25(1)	38(1)	0(1)	-8(1)	2(1)
C(214)	41(2)	31(2)	48(2)	-5(1)	-14(1)	6(1)
C(215)	23(1)	19(1)	25(1)	2(1)	-6(1)	-7(1)
C(216)	23(1)	21(1)	25(1)	3(1)	-7(1)	-8(1)
C(217)	24(1)	20(1)	33(1)	2(1)	-10(1)	-6(1)
C(218)	24(1)	23(1)	31(1)	2(1)	-9(1)	-13(1)
C(219)	19(1)	25(1)	27(1)	3(1)	-8(1)	-6(1)
C(220)	26(1)	16(1)	37(1)	-1(1)	-11(1)	-5(1)
C(221)	24(1)	21(1)	40(1)	1(1)	-11(1)	-10(1)
C(222)	23(1)	27(1)	54(2)	-3(1)	-14(1)	1(1)
O(21)	48(1)	26(1)	27(1)	6(1)	-9(1)	-18(1)
O(22)	52(1)	26(1)	40(1)	-4(1)	-19(1)	-7(1)
O(23)	50(1)	19(1)	33(1)	6(1)	-12(1)	-15(1)

O(24)	42(1)	29(1)	28(1)	6(1)	-8(1)	-14(1)
O(25)	22(1)	29(1)	50(1)	6(1)	-13(1)	-11(1)
O(26)	21(1)	19(1)	46(1)	-2(1)	-11(1)	-2(1)
O(27)	22(1)	23(1)	71(1)	-4(1)	-19(1)	-8(1)
O(28)	19(1)	23(1)	42(1)	0(1)	-11(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **42c**.

	x	y	z	U(eq)
H(11A)	181	2147	1891	53
H(11B)	615	2126	2800	53
H(11C)	1646	1545	1855	53
H(12A)	-22	5742	1517	72
H(12B)	524	5841	2354	72
H(12C)	68	4843	2237	72
H(13A)	3349	5379	-1775	89
H(13B)	2551	6512	-1371	89
H(13C)	1784	5744	-1568	89
H(14)	1834	1845	373	29
H(18)	2534	3961	-1590	31
H(11D)	5463	-1336	-794	41
H(11E)	5987	-1107	-1885	41
H(11F)	4521	-2586	-1186	60
H(11G)	6099	-2883	-1622	60
H(11H)	5212	-2408	-2264	60
H(115)	1715	-224	-1085	29
H(117)	-334	-326	-1225	31
H(120)	-2189	3177	-556	35
H(121)	17	2456	-692	35
H(12D)	-4395	3595	-136	59
H(12E)	-5351	3444	-683	59
H(12F)	-3913	3585	-1252	59
H(17)	-3496	528	-1091	64
H(21A)	5191	2019	-3128	49
H(21B)	5524	2099	-2190	49
H(21C)	6681	1614	-3124	49
H(22A)	6914	4400	-2700	75
H(22B)	6523	5619	-2605	75
H(22C)	7733	5039	-3474	75
H(23A)	7870	5621	-6590	51
H(23B)	6892	6720	-6224	51
H(23C)	6352	5853	-6528	51
H(24)	6821	1896	-4613	27
H(28)	7213	4108	-6522	28
H(21D)	10393	-1232	-5780	36
H(21E)	10950	-960	-6856	36
H(21F)	9585	-2509	-6248	64
H(21G)	11161	-2742	-6674	64
H(21H)	10269	-2273	-7313	64
H(215)	6659	-132	-6098	27
H(217)	4627	-278	-6172	31
H(220)	2705	3231	-5616	31
H(221)	4939	2560	-5794	33
H(22D)	496	3596	-5112	54
H(22E)	-541	3386	-5559	54
H(22F)	834	3569	-6220	54
H(27)	1437	515	-6014	55

Appendix II, Crystal data for 83c

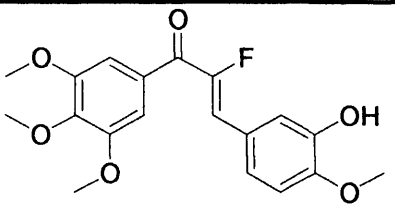


Table 1. Crystal data and structure refinement for **83c**.

Identification code	njl0401	
Empirical formula	C19 H19 F1 O6	
Formula weight	362.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.5705(3) Å	α= 73.516(2)°.
	b = 10.3189(4) Å	β= 74.625(2)°.
	c = 10.5707(5) Å	γ = 81.812(4)°.
Volume	862.06(6) $Å^3$	
Z	2	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	380	
Crystal size	0.33 x 0.20 x 0.08 mm^3	
Theta range for data collection	3.58 to 27.42°.	
Index ranges	-10<=h<=10, -13<=k<=13, -13<=l<=13	
Reflections collected	10700	
Independent reflections	3814 [R(int) = 0.0832]	
Completeness to theta = 27.42°	97.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9912 and 0.9644	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3814 / 0 / 241	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0599, wR2 = 0.1343	
R indices (all data)	R1 = 0.1140, wR2 = 0.1581	
Extinction coefficient	0.045(6)	
Largest diff. peak and hole	0.273 and -0.249 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **83c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6752(3)	445(3)	5730(3)	36(1)
C(2)	2840(3)	3542(3)	7365(2)	32(1)
C(3)	1486(3)	6308(3)	3783(3)	38(1)
C(4)	5852(3)	2487(2)	3549(2)	25(1)
C(5)	4911(3)	2258(2)	4880(2)	25(1)
C(6)	3544(3)	3100(2)	5208(2)	22(1)
C(7)	3139(3)	4246(2)	4236(2)	24(1)
C(8)	4068(3)	4497(2)	2914(2)	25(1)
C(9)	5399(3)	3609(2)	2575(2)	24(1)
C(10)	6430(3)	4022(2)	1164(2)	26(1)
C(11)	7352(3)	2998(3)	459(2)	27(1)
C(12)	6991(3)	1753(2)	590(2)	25(1)
C(13)	7764(3)	795(2)	-219(2)	23(1)
C(14)	7082(3)	-428(2)	34(2)	26(1)
C(15)	7769(3)	-1372(2)	-710(2)	27(1)
C(16)	9188(3)	-1112(2)	-1719(2)	24(1)
C(17)	9905(3)	108(2)	-1978(2)	23(1)
C(18)	9205(3)	1034(2)	-1244(2)	24(1)
C(19)	9346(3)	-3239(3)	-2233(3)	47(1)
O(1)	5236(2)	1236(2)	5948(2)	33(1)
O(2)	2541(2)	2798(2)	6501(2)	25(1)
O(3)	1831(2)	5049(2)	4704(2)	32(1)
O(4)	6534(2)	5226(2)	567(2)	35(1)
O(5)	11317(2)	293(2)	-2952(2)	32(1)
O(6)	9980(2)	-1956(2)	-2511(2)	32(1)
F(1)	8624(2)	3556(1)	-546(2)	40(1)

Table 3. Bond lengths [Å] and angles [°] for **83c**.

C(1)-O(1)	1.434(3)
C(2)-O(2)	1.439(3)
C(3)-O(3)	1.432(3)
C(4)-C(5)	1.396(3)
C(4)-C(9)	1.400(3)
C(5)-O(1)	1.368(3)
C(5)-C(6)	1.383(3)
C(6)-O(2)	1.384(3)
C(6)-C(7)	1.399(3)
C(7)-O(3)	1.364(3)
C(7)-C(8)	1.384(3)
C(8)-C(9)	1.393(3)
C(9)-C(10)	1.495(3)
C(10)-O(4)	1.227(3)
C(10)-C(11)	1.481(3)
C(11)-C(12)	1.324(3)
C(11)-F(1)	1.366(3)
C(12)-C(13)	1.463(3)
C(13)-C(14)	1.394(3)
C(13)-C(18)	1.409(3)
C(14)-C(15)	1.393(3)
C(15)-C(16)	1.390(3)
C(16)-O(6)	1.365(3)
C(16)-C(17)	1.405(3)
C(17)-O(5)	1.362(3)
C(17)-C(18)	1.373(3)
C(19)-O(6)	1.427(3)

C(5)-C(4)-C(9)	118.1(2)
O(1)-C(5)-C(6)	114.7(2)
O(1)-C(5)-C(4)	124.8(2)
C(6)-C(5)-C(4)	120.5(2)
C(5)-C(6)-O(2)	120.0(2)
C(5)-C(6)-C(7)	120.7(2)
O(2)-C(6)-C(7)	119.2(2)
O(3)-C(7)-C(8)	125.2(2)
O(3)-C(7)-C(6)	115.3(2)
C(8)-C(7)-C(6)	119.5(2)
C(7)-C(8)-C(9)	119.5(2)
C(8)-C(9)-C(4)	121.6(2)
C(8)-C(9)-C(10)	116.1(2)
C(4)-C(9)-C(10)	121.9(2)
O(4)-C(10)-C(11)	118.6(2)
O(4)-C(10)-C(9)	120.3(2)
C(11)-C(10)-C(9)	121.1(2)
C(12)-C(11)-F(1)	120.3(2)
C(12)-C(11)-C(10)	128.9(2)
F(1)-C(11)-C(10)	110.3(2)
C(11)-C(12)-C(13)	129.6(2)
C(14)-C(13)-C(18)	117.4(2)
C(14)-C(13)-C(12)	119.6(2)
C(18)-C(13)-C(12)	123.1(2)
C(15)-C(14)-C(13)	121.8(2)
C(16)-C(15)-C(14)	119.8(2)
O(6)-C(16)-C(15)	125.4(2)
O(6)-C(16)-C(17)	115.4(2)
C(15)-C(16)-C(17)	119.3(2)
O(5)-C(17)-C(18)	123.0(2)
O(5)-C(17)-C(16)	116.8(2)
C(18)-C(17)-C(16)	120.2(2)
C(17)-C(18)-C(13)	121.5(2)
C(5)-O(1)-C(1)	117.76(18)
C(6)-O(2)-C(2)	113.22(17)
C(7)-O(3)-C(3)	117.04(18)
C(16)-O(6)-C(19)	117.33(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **83c**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	41(2)	30(2)	31(2)	-1(1)	-9(1)	5(1)
C(2)	39(2)	31(2)	25(1)	-8(1)	-2(1)	-10(1)
C(3)	37(2)	27(2)	38(2)	3(1)	-5(1)	5(1)
C(4)	25(1)	22(1)	26(1)	-5(1)	-1(1)	-3(1)
C(5)	31(1)	21(1)	22(1)	1(1)	-7(1)	-6(1)
C(6)	24(1)	23(1)	19(1)	-2(1)	-1(1)	-9(1)
C(7)	22(1)	22(1)	25(1)	-5(1)	-2(1)	-5(1)
C(8)	28(1)	21(1)	27(1)	-2(1)	-8(1)	-7(1)
C(9)	27(1)	22(1)	22(1)	-4(1)	-4(1)	-8(1)
C(10)	31(1)	24(1)	22(1)	-2(1)	-7(1)	-6(1)
C(11)	29(1)	27(1)	19(1)	-1(1)	1(1)	-7(1)
C(12)	25(1)	26(1)	20(1)	-1(1)	-2(1)	-4(1)
C(13)	23(1)	20(1)	24(1)	-1(1)	-6(1)	-1(1)
C(14)	22(1)	26(1)	26(1)	0(1)	-2(1)	-7(1)
C(15)	28(1)	21(1)	29(1)	-3(1)	-6(1)	-6(1)
C(16)	28(1)	22(1)	22(1)	-4(1)	-7(1)	-1(1)
C(17)	23(1)	24(1)	17(1)	2(1)	-2(1)	-6(1)
C(18)	30(1)	18(1)	21(1)	1(1)	-7(1)	-5(1)
C(19)	53(2)	32(2)	58(2)	-24(2)	5(1)	-17(1)
O(1)	37(1)	29(1)	24(1)	0(1)	-4(1)	6(1)
O(2)	28(1)	22(1)	21(1)	-4(1)	1(1)	-9(1)
O(3)	26(1)	26(1)	33(1)	0(1)	-2(1)	4(1)
O(4)	46(1)	24(1)	26(1)	-1(1)	1(1)	-7(1)
O(5)	35(1)	25(1)	31(1)	-9(1)	7(1)	-11(1)
O(6)	36(1)	24(1)	35(1)	-11(1)	0(1)	-9(1)
F(1)	48(1)	29(1)	34(1)	-7(1)	14(1)	-14(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **83c**.

	x	y	z	U(eq)
H(1A)	6760	-85	5091	54
H(1B)	6892	-170	6595	54
H(1C)	7642	1048	5354	54
H(2A)	3910	3241	7557	48
H(2B)	2005	3381	8219	48
H(2C)	2809	4512	6909	48
H(3A)	2442	6838	3460	57
H(3B)	570	6817	4250	57
H(3C)	1210	6131	3008	57
H(4)	6774	1897	3311	30
H(8)	3799	5268	2244	30
H(12)	6097	1435	1318	30
H(14)	6123	-624	733	31
H(15)	7269	-2191	-528	32
H(18)	9704	1855	-1432	29
H(19A)	9370	-3755	-1304	70
H(19B)	10008	-3742	-2874	70
H(19C)	8225	-3103	-2332	70
H(5)	11717	990	-2951	48

Appendix III, Crystal data for 139

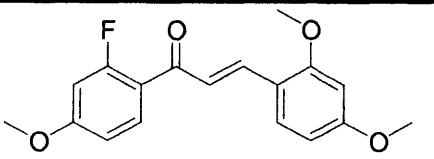


Table 1. Crystal data and structure refinement for **139**.

Identification code	njl0409	
Empirical formula	C18 H17 F O4	
Formula weight	316.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.3101(2) Å	α= 109.4530(10)°.
	b = 9.9407(2) Å	β= 97.2540(10)°.
	c = 11.3162(3) Å	γ = 113.2160(10)°.
Volume	773.47(3) $Å^3$	
Z	2	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	332	
Crystal size	0.50 x 0.30 x 0.25 mm^3	
Theta range for data collection	3.26 to 30.06°.	
Index ranges	-11<=h<=11, -14<=k<=13, -15<=l<=15	
Reflections collected	12456	
Independent reflections	4449 [R(int) = 0.0564]	
Completeness to theta = 30.06°	98.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9747 and 0.9502	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4449 / 0 / 211	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1277	
R indices (all data)	R1 = 0.0580, wR2 = 0.1342	
Largest diff. peak and hole	0.349 and -0.215 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **139**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7965(2)	14117(1)	657(1)	23(1)
C(2)	9084(2)	15709(1)	1580(1)	25(1)
C(3)	9263(2)	16050(1)	2895(1)	25(1)
C(4)	8355(2)	14836(1)	3289(1)	24(1)
C(5)	7233(2)	13278(1)	2347(1)	22(1)
C(6)	7026(2)	12876(1)	1000(1)	21(1)
C(7)	5874(2)	11174(1)	-28(1)	21(1)
C(8)	3839(2)	10266(1)	-81(1)	21(1)
C(9)	2450(2)	10028(1)	-1232(1)	24(1)
C(10)	533(2)	8690(1)	-1689(1)	22(1)
C(11)	-515(2)	8078(1)	-2998(1)	24(1)
C(12)	-2247(2)	6772(1)	-3513(1)	26(1)
C(13)	-2990(2)	6019(1)	-2725(1)	25(1)
C(14)	-2033(2)	6635(1)	-1407(1)	24(1)
C(15)	-304(2)	7950(1)	-938(1)	22(1)
C(16)	11224(3)	18842(2)	3547(2)	52(1)
C(17)	6418(2)	12316(2)	3974(1)	35(1)
C(18)	-5320(2)	3730(2)	-2621(2)	39(1)
F(1)	586(1)	8530(1)	357(1)	27(1)
O(1)	10273(1)	17567(1)	3902(1)	35(1)
O(2)	6271(1)	12012(1)	2632(1)	27(1)
O(3)	2866(1)	10922(1)	-1791(1)	34(1)
O(4)	-4649(1)	4680(1)	-3331(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for **139**.

C(1)-C(6)	1.3851(15)
C(1)-C(2)	1.3976(15)
C(1)-H(1)	0.9500
C(2)-C(3)	1.3861(16)
C(2)-H(2)	0.9500
C(3)-O(1)	1.3757(14)
C(3)-C(4)	1.3964(16)
C(4)-C(5)	1.3838(15)
C(4)-H(4)	0.9500
C(5)-O(2)	1.3675(13)
C(5)-C(6)	1.4092(15)
C(6)-C(7)	1.5045(15)
C(7)-C(8)	1.5532(15)
C(7)-C(8)#1	1.5808(15)
C(7)-H(7)	1.0000
C(8)-C(9)	1.5125(15)
C(8)-C(7)#1	1.5808(15)
C(8)-H(8)	1.0000
C(9)-O(3)	1.2229(14)
C(9)-C(10)	1.4957(15)
C(10)-C(15)	1.3826(15)
C(10)-C(11)	1.4068(15)
C(11)-C(12)	1.3816(16)
C(11)-H(11)	0.9500
C(12)-C(13)	1.3984(16)
C(12)-H(12)	0.9500
C(13)-O(4)	1.3603(14)
C(13)-C(14)	1.3930(16)
C(14)-C(15)	1.3852(16)
C(14)-H(14)	0.9500
C(15)-F(1)	1.3610(12)
C(16)-O(1)	1.4216(18)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-O(2)	1.4243(14)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-O(4)	1.4317(16)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(6)-C(1)-C(2)	122.91(10)
C(6)-C(1)-H(1)	118.5
C(2)-C(1)-H(1)	118.5
C(3)-C(2)-C(1)	118.21(10)
C(3)-C(2)-H(2)	120.9
C(1)-C(2)-H(2)	120.9
O(1)-C(3)-C(2)	124.38(11)
O(1)-C(3)-C(4)	114.68(10)
C(2)-C(3)-C(4)	120.92(10)
C(5)-C(4)-C(3)	119.31(10)
C(5)-C(4)-H(4)	120.3
C(3)-C(4)-H(4)	120.3
O(2)-C(5)-C(4)	123.71(10)
O(2)-C(5)-C(6)	114.70(9)
C(4)-C(5)-C(6)	121.58(10)
C(1)-C(6)-C(5)	117.05(10)
C(1)-C(6)-C(7)	120.90(9)
C(5)-C(6)-C(7)	122.04(10)
C(6)-C(7)-C(8)	118.28(9)
C(6)-C(7)-C(8)#1	121.31(9)
C(8)-C(7)-C(8)#1	88.88(8)
C(6)-C(7)-H(7)	108.9
C(8)-C(7)-H(7)	108.9
C(8)#1-C(7)-H(7)	108.9
C(9)-C(8)-C(7)	115.00(9)
C(9)-C(8)-C(7)#1	122.36(9)
C(7)-C(8)-C(7)#1	91.11(8)

C(9)-C(8)-H(8)	109.0
C(7)-C(8)-H(8)	109.0
C(7)#1-C(8)-H(8)	109.0
O(3)-C(9)-C(10)	119.42(10)
O(3)-C(9)-C(8)	120.96(10)
C(10)-C(9)-C(8)	119.62(9)
C(15)-C(10)-C(11)	116.03(10)
C(15)-C(10)-C(9)	125.35(10)
C(11)-C(10)-C(9)	118.60(10)
C(12)-C(11)-C(10)	121.77(10)
C(12)-C(11)-H(11)	119.1
C(10)-C(11)-H(11)	119.1
C(11)-C(12)-C(13)	119.70(10)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
O(4)-C(13)-C(14)	123.81(11)
O(4)-C(13)-C(12)	115.92(10)
C(14)-C(13)-C(12)	120.26(10)
C(15)-C(14)-C(13)	117.68(10)
C(15)-C(14)-H(14)	121.2
C(13)-C(14)-H(14)	121.2
F(1)-C(15)-C(10)	119.41(10)
F(1)-C(15)-C(14)	116.17(10)
C(10)-C(15)-C(14)	124.41(10)
O(1)-C(16)-H(16A)	109.5
O(1)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(1)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
O(2)-C(17)-H(17A)	109.5
O(2)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(2)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(4)-C(18)-H(18A)	109.5
O(4)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(4)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(3)-O(1)-C(16)	116.64(10)
C(5)-O(2)-C(17)	118.18(9)
C(13)-O(4)-C(18)	117.57(10)

Symmetry transformations used to generate equivalent atoms:

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

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **139**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	23(1)	21(1)	10(1)	7(1)	10(1)
C(2)	25(1)	21(1)	27(1)	11(1)	6(1)	8(1)
C(3)	26(1)	20(1)	24(1)	6(1)	1(1)	8(1)
C(4)	27(1)	23(1)	19(1)	7(1)	5(1)	11(1)
C(5)	23(1)	21(1)	21(1)	9(1)	6(1)	9(1)
C(6)	22(1)	20(1)	20(1)	8(1)	5(1)	8(1)
C(7)	22(1)	19(1)	19(1)	7(1)	5(1)	7(1)
C(8)	22(1)	18(1)	19(1)	7(1)	5(1)	7(1)
C(9)	24(1)	22(1)	24(1)	10(1)	6(1)	10(1)
C(10)	23(1)	21(1)	21(1)	9(1)	6(1)	10(1)
C(11)	26(1)	28(1)	23(1)	13(1)	7(1)	13(1)
C(12)	25(1)	29(1)	21(1)	10(1)	5(1)	12(1)
C(13)	19(1)	27(1)	26(1)	10(1)	5(1)	10(1)
C(14)	23(1)	28(1)	24(1)	12(1)	8(1)	12(1)
C(15)	24(1)	25(1)	18(1)	8(1)	5(1)	13(1)
C(16)	65(1)	20(1)	41(1)	9(1)	1(1)	1(1)
C(17)	41(1)	36(1)	23(1)	16(1)	10(1)	9(1)
C(18)	24(1)	41(1)	45(1)	24(1)	5(1)	5(1)
F(1)	29(1)	30(1)	17(1)	9(1)	5(1)	10(1)
O(1)	43(1)	19(1)	26(1)	5(1)	-1(1)	5(1)
O(2)	33(1)	24(1)	20(1)	11(1)	8(1)	7(1)
O(3)	30(1)	33(1)	40(1)	24(1)	5(1)	8(1)
O(4)	21(1)	35(1)	30(1)	14(1)	2(1)	5(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **139**.

	x	y	z	U(eq)
H(1)	7843	13875	-246	28
H(2)	9706	16535	1312	30
H(4)	8507	15077	4194	29
H(7)	5922	11158	-910	25
H(8)	3654	10863	752	25
H(11)	-17	8577	-3543	29
H(12)	-2930	6386	-4399	31
H(14)	-2549	6170	-849	29
H(16A)	12125	18638	3137	78
H(16B)	11857	19864	4334	78
H(16C)	10348	18901	2926	78
H(17A)	7706	12775	4466	53
H(17B)	5696	11303	4036	53
H(17C)	5953	13080	4341	53
H(18A)	-4423	3393	-2362	58
H(18B)	-6485	2774	-3181	58
H(18C)	-5510	4373	-1836	58

Appendix IV, Crystal data for 155

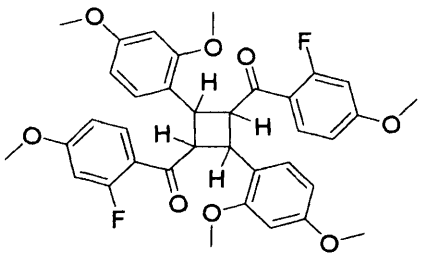


Table 1. Crystal data and structure refinement for **155**.

Identification code	njl0408	
Empirical formula	C36 H34 F2 O8	
Formula weight	632.63	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.3449(2) Å	α= 80.2740(10)°.
	b = 11.9613(3) Å	β= 87.6480(10)°.
	c = 18.3516(5) Å	γ = 73.0120(10)°.
Volume	1519.70(7) $Å^3$	
Z	2	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	664	
Crystal size	0.38 x 0.38 x 0.20 mm^3	
Theta range for data collection	2.94 to 27.48°.	
Index ranges	-9<=h<=9, -15<=k<=15, -23<=l<=23	
Reflections collected	26702	
Independent reflections	6946 [R(int) = 0.1027]	
Completeness to theta = 27.48°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9793 and 0.9612	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6946 / 0 / 421	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0554, wR2 = 0.1234	
R indices (all data)	R1 = 0.0943, wR2 = 0.1421	
Largest diff. peak and hole	0.442 and -0.266 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **155**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(11)	2751(3)	10059(2)	1418(1)	29(1)
C(12)	1699(3)	11193(2)	1481(1)	30(1)
C(13)	1506(3)	11557(2)	2167(1)	28(1)
C(14)	2395(3)	10789(2)	2789(1)	29(1)
C(15)	3459(3)	9638(2)	2719(1)	26(1)
C(16)	3641(3)	9240(2)	2034(1)	27(1)
C(17)	4695(3)	8013(2)	1994(1)	28(1)
C(18)	5044(3)	7475(2)	1400(1)	30(1)
C(19)	6094(3)	6206(2)	1475(1)	30(1)
C(110)	6767(3)	5653(2)	807(1)	26(1)
C(111)	7145(3)	4418(2)	869(1)	30(1)
C(112)	7706(3)	3840(2)	278(1)	31(1)
C(113)	7937(3)	4473(2)	-411(1)	28(1)
C(114)	7650(3)	5686(2)	-495(1)	28(1)
C(115)	7064(3)	6230(2)	112(1)	26(1)
C(116)	177(3)	13130(2)	2861(1)	37(1)
C(117)	4144(3)	9137(2)	4023(1)	39(1)
C(118)	8663(3)	4438(2)	-1691(1)	40(1)
F(11)	6798(2)	7425(1)	2(1)	38(1)
O(11)	426(2)	12699(1)	2174(1)	35(1)
O(12)	4398(2)	8837(1)	3296(1)	32(1)
O(13)	6392(2)	5575(1)	2088(1)	42(1)
O(14)	8463(2)	3823(1)	-967(1)	36(1)
C(21)	3219(3)	5622(2)	3591(1)	27(1)
C(22)	2142(3)	6745(2)	3663(1)	29(1)
C(23)	1300(3)	6964(2)	4337(1)	27(1)
C(24)	1574(3)	6062(1)	4946(1)	26(1)
C(25)	2672(3)	4920(2)	4864(1)	24(1)
C(26)	3508(2)	4668(2)	4185(1)	24(1)
C(27)	4609(3)	3467(2)	4115(1)	25(1)
C(28)	5396(3)	3067(2)	3503(1)	27(1)
C(29)	6375(3)	1796(2)	3520(1)	28(1)
C(210)	6798(3)	1298(2)	2821(1)	25(1)
C(211)	8043(3)	159(2)	2838(1)	29(1)
C(212)	8491(3)	-368(2)	2213(1)	32(1)
C(213)	7692(3)	254(2)	1535(1)	32(1)
C(214)	6415(3)	1366(2)	1499(1)	30(1)
C(215)	5993(3)	1850(2)	2130(1)	26(1)
C(216)	-715(3)	8389(2)	5022(1)	39(1)
C(217)	2241(3)	4186(2)	6139(1)	31(1)
C(218)	9271(3)	-1313(2)	880(1)	46(1)
F(21)	4653(2)	2926(1)	2057(1)	35(1)
O(21)	195(2)	8096(1)	4347(1)	35(1)
O(22)	2983(2)	3980(1)	5427(1)	30(1)
O(23)	6860(2)	1132(1)	4116(1)	41(1)
O(24)	8061(2)	-139(1)	871(1)	44(1)

Table 3. Bond lengths [Å] and angles [°] for **155**.

C(11)-C(12)	1.371(2)
C(11)-C(16)	1.407(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.390(3)
C(12)-H(12)	0.9500
C(13)-O(11)	1.366(2)
C(13)-C(14)	1.390(2)
C(14)-C(15)	1.395(2)
C(14)-H(14)	0.9500
C(15)-O(12)	1.358(2)
C(15)-C(16)	1.405(3)
C(16)-C(17)	1.457(2)
C(17)-C(18)	1.338(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.474(2)
C(18)-H(18)	0.9500
C(19)-O(13)	1.233(2)
C(19)-C(110)	1.489(3)
C(110)-C(115)	1.385(3)
C(110)-C(111)	1.406(2)
C(111)-C(112)	1.370(3)
C(111)-H(111)	0.9500
C(112)-C(113)	1.390(3)
C(112)-H(112)	0.9500
C(113)-O(14)	1.363(2)
C(113)-C(114)	1.386(2)
C(114)-C(115)	1.376(2)
C(114)-H(114)	0.9500
C(115)-F(11)	1.3651(19)
C(116)-O(11)	1.425(2)
C(116)-H(11A)	0.9800
C(116)-H(11B)	0.9800
C(116)-H(11C)	0.9800
C(117)-O(12)	1.430(2)
C(117)-H(11D)	0.9800
C(117)-H(11E)	0.9800
C(117)-H(11F)	0.9800
C(118)-O(14)	1.430(2)
C(118)-H(11G)	0.9800
C(118)-H(11H)	0.9800
C(118)-H(11I)	0.9800
C(21)-C(22)	1.370(2)
C(21)-C(26)	1.412(2)
C(21)-H(21)	0.9500
C(22)-C(23)	1.391(3)
C(22)-H(22)	0.9500
C(23)-O(21)	1.363(2)
C(23)-C(24)	1.392(2)
C(24)-C(25)	1.398(2)
C(24)-H(24)	0.9500
C(25)-O(22)	1.363(2)
C(25)-C(26)	1.406(3)
C(26)-C(27)	1.452(2)
C(27)-C(28)	1.338(2)
C(27)-H(27)	0.9500
C(28)-C(29)	1.475(2)
C(28)-H(28)	0.9500
C(29)-O(23)	1.235(2)
C(29)-C(210)	1.489(3)
C(210)-C(215)	1.393(2)
C(210)-C(211)	1.398(2)
C(211)-C(212)	1.383(3)
C(211)-H(211)	0.9500
C(212)-C(213)	1.392(3)
C(212)-H(212)	0.9500
C(213)-O(24)	1.369(2)
C(213)-C(214)	1.379(3)
C(214)-C(215)	1.366(2)
C(214)-H(214)	0.9500
C(215)-F(21)	1.3619(19)
C(216)-O(21)	1.431(2)
C(216)-H(21A)	0.9800
C(216)-H(21B)	0.9800
C(216)-H(21C)	0.9800
C(217)-O(22)	1.428(2)
C(217)-H(21D)	0.9800
C(217)-H(21E)	0.9800
C(217)-H(21F)	0.9800
C(218)-O(24)	1.424(2)
C(218)-H(21G)	0.9800
C(218)-H(21H)	0.9800
C(218)-H(21I)	0.9800
C(12)-C(11)-C(16)	121.80(17)
C(12)-C(11)-H(11)	119.1
C(16)-C(11)-H(11)	119.1
C(11)-C(12)-C(13)	119.78(16)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
O(11)-C(13)-C(12)	115.52(15)
O(11)-C(13)-C(14)	123.90(17)
C(12)-C(13)-C(14)	120.58(16)
C(13)-C(14)-C(15)	119.11(17)
C(13)-C(14)-H(14)	120.4
C(15)-C(14)-H(14)	120.4
O(12)-C(15)-C(14)	122.97(16)
O(12)-C(15)-C(16)	115.61(15)
C(14)-C(15)-C(16)	121.41(15)
C(15)-C(16)-C(11)	117.28(16)
C(15)-C(16)-C(17)	119.45(15)
C(11)-C(16)-C(17)	123.26(17)
C(18)-C(17)-C(16)	128.38(16)
C(18)-C(17)-H(17)	115.8
C(16)-C(17)-H(17)	115.8
C(17)-C(18)-C(19)	120.37(16)
C(17)-C(18)-H(18)	119.8
C(19)-C(18)-H(18)	119.8
O(13)-C(19)-C(18)	120.94(17)
O(13)-C(19)-C(110)	118.63(16)

C(18)-C(19)-C(110)	120.40(16)
C(115)-C(110)-C(111)	115.07(17)
C(115)-C(110)-C(19)	126.74(16)
C(111)-C(110)-C(19)	118.19(16)
C(112)-C(111)-C(110)	122.15(17)
C(112)-C(111)-H(111)	118.9
C(110)-C(111)-H(111)	118.9
C(111)-C(112)-C(113)	120.08(17)
C(111)-C(112)-H(112)	120.0
C(113)-C(112)-H(112)	120.0
O(14)-C(113)-C(114)	124.28(17)
O(14)-C(113)-C(112)	115.69(16)
C(114)-C(113)-C(112)	120.03(17)
C(115)-C(114)-C(113)	117.77(17)
C(115)-C(114)-H(114)	121.1
C(113)-C(114)-H(114)	121.1
F(11)-C(115)-C(114)	115.64(15)
F(11)-C(115)-C(110)	119.52(16)
C(114)-C(115)-C(110)	124.84(16)
O(11)-C(116)-H(11A)	109.5
O(11)-C(116)-H(11B)	109.5
H(11A)-C(116)-H(11B)	109.5
O(11)-C(116)-H(11C)	109.5
H(11A)-C(116)-H(11C)	109.5
H(11B)-C(116)-H(11C)	109.5
O(12)-C(117)-H(11D)	109.5
O(12)-C(117)-H(11E)	109.5
H(11D)-C(117)-H(11E)	109.5
O(12)-C(117)-H(11F)	109.5
H(11D)-C(117)-H(11F)	109.5
H(11E)-C(117)-H(11F)	109.5
O(14)-C(118)-H(11G)	109.5
O(14)-C(118)-H(11H)	109.5
H(11G)-C(118)-H(11H)	109.5
O(14)-C(118)-H(11I)	109.5
H(11G)-C(118)-H(11I)	109.5
H(11H)-C(118)-H(11I)	109.5
C(13)-O(11)-C(116)	118.34(14)
C(15)-O(12)-C(117)	118.99(14)
C(113)-O(14)-C(118)	117.88(14)
C(22)-C(21)-C(26)	121.87(18)
C(22)-C(21)-H(21)	119.1
C(26)-C(21)-H(21)	119.1
C(21)-C(22)-C(23)	119.72(17)
C(21)-C(22)-H(22)	120.1
C(23)-C(22)-H(22)	120.1
O(21)-C(23)-C(22)	115.47(16)
O(21)-C(23)-C(24)	123.70(17)
C(22)-C(23)-C(24)	120.81(16)
C(23)-C(24)-C(25)	118.85(17)
C(23)-C(24)-H(24)	120.6
C(25)-C(24)-H(24)	120.6
O(22)-C(25)-C(24)	122.76(17)
O(22)-C(25)-C(26)	115.69(15)
C(24)-C(25)-C(26)	121.54(16)
C(25)-C(26)-C(21)	117.18(15)
C(25)-C(26)-C(27)	120.13(15)
C(21)-C(26)-C(27)	122.69(17)
C(28)-C(27)-C(26)	127.62(16)
C(28)-C(27)-H(27)	116.2
C(26)-C(27)-H(27)	116.2
C(27)-C(28)-C(29)	120.61(16)
C(27)-C(28)-H(28)	119.7
C(29)-C(28)-H(28)	119.7
O(23)-C(29)-C(28)	120.33(17)
O(23)-C(29)-C(210)	119.13(15)
C(28)-C(29)-C(210)	120.54(15)
C(215)-C(210)-C(211)	114.97(16)
C(215)-C(210)-C(29)	125.73(15)
C(211)-C(210)-C(29)	119.25(16)
C(212)-C(211)-C(210)	122.62(17)
C(212)-C(211)-H(211)	118.7
C(210)-C(211)-H(211)	118.7
C(211)-C(212)-C(213)	119.33(16)
C(211)-C(212)-H(212)	120.3
C(213)-C(212)-H(212)	120.3
O(24)-C(213)-C(214)	114.60(17)
O(24)-C(213)-C(212)	125.60(17)
C(214)-C(213)-C(212)	119.80(18)
C(215)-C(214)-C(213)	119.01(17)
C(215)-C(214)-H(214)	120.5
C(213)-C(214)-H(214)	120.5
F(21)-C(215)-C(214)	115.60(15)
F(21)-C(215)-C(210)	120.18(15)
C(214)-C(215)-C(210)	124.19(16)
O(21)-C(216)-H(21A)	109.5
O(21)-C(216)-H(21B)	109.5
H(21A)-C(216)-H(21B)	109.5
O(21)-C(216)-H(21C)	109.5
H(21A)-C(216)-H(21C)	109.5
H(21B)-C(216)-H(21C)	109.5
O(22)-C(217)-H(21D)	109.5
O(22)-C(217)-H(21E)	109.5
H(21D)-C(217)-H(21E)	109.5
O(22)-C(217)-H(21F)	109.5
H(21D)-C(217)-H(21F)	109.5
H(21E)-C(217)-H(21F)	109.5
O(24)-C(218)-H(21G)	109.5
O(24)-C(218)-H(21H)	109.5
H(21G)-C(218)-H(21H)	109.5
O(24)-C(218)-H(21I)	109.5
H(21G)-C(218)-H(21I)	109.5
H(21H)-C(218)-H(21I)	109.5
C(23)-O(21)-C(216)	118.65(14)
C(25)-O(22)-C(217)	118.48(13)
C(213)-O(24)-C(218)	117.21(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **155**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(11)	29(1)	35(1)	26(1)	-5(1)	2(1)	-13(1)
C(12)	30(1)	31(1)	27(1)	1(1)	-4(1)	-9(1)
C(13)	25(1)	26(1)	33(1)	-2(1)	1(1)	-9(1)
C(14)	32(1)	30(1)	28(1)	-5(1)	0(1)	-14(1)
C(15)	27(1)	26(1)	27(1)	1(1)	-3(1)	-11(1)
C(16)	24(1)	31(1)	27(1)	-3(1)	1(1)	-11(1)
C(17)	28(1)	30(1)	24(1)	0(1)	-1(1)	-9(1)
C(18)	30(1)	30(1)	25(1)	-1(1)	-1(1)	-6(1)
C(19)	27(1)	34(1)	27(1)	-4(1)	2(1)	-8(1)
C(110)	23(1)	26(1)	27(1)	-3(1)	-2(1)	-6(1)
C(111)	30(1)	30(1)	29(1)	0(1)	2(1)	-7(1)
C(112)	33(1)	24(1)	36(1)	-4(1)	0(1)	-7(1)
C(113)	24(1)	33(1)	27(1)	-7(1)	-2(1)	-7(1)
C(114)	31(1)	30(1)	23(1)	-2(1)	-3(1)	-9(1)
C(115)	29(1)	23(1)	27(1)	-2(1)	-4(1)	-8(1)
C(116)	39(1)	33(1)	35(1)	-6(1)	5(1)	-7(1)
C(117)	58(1)	34(1)	24(1)	-2(1)	-5(1)	-13(1)
C(118)	51(1)	40(1)	25(1)	-10(1)	-2(1)	-3(1)
F(11)	62(1)	26(1)	28(1)	-4(1)	4(1)	-15(1)
O(11)	38(1)	26(1)	34(1)	-2(1)	-2(1)	-3(1)
O(12)	43(1)	28(1)	23(1)	0(1)	-4(1)	-7(1)
O(13)	57(1)	35(1)	25(1)	0(1)	4(1)	-2(1)
O(14)	48(1)	32(1)	29(1)	-10(1)	1(1)	-7(1)
C(21)	27(1)	32(1)	24(1)	-6(1)	1(1)	-12(1)
C(22)	31(1)	29(1)	26(1)	0(1)	-1(1)	-10(1)
C(23)	27(1)	24(1)	31(1)	-6(1)	-2(1)	-7(1)
C(24)	26(1)	28(1)	24(1)	-7(1)	0(1)	-8(1)
C(25)	25(1)	27(1)	22(1)	-2(1)	-4(1)	-10(1)
C(26)	22(1)	28(1)	22(1)	-4(1)	-2(1)	-9(1)
C(27)	27(1)	28(1)	23(1)	-1(1)	-3(1)	-11(1)
C(28)	30(1)	26(1)	25(1)	-2(1)	-1(1)	-8(1)
C(29)	26(1)	27(1)	29(1)	-4(1)	-2(1)	-8(1)
C(210)	24(1)	25(1)	28(1)	-5(1)	1(1)	-10(1)
C(211)	27(1)	26(1)	34(1)	-3(1)	-3(1)	-7(1)
C(212)	28(1)	26(1)	44(1)	-11(1)	1(1)	-6(1)
C(213)	31(1)	37(1)	34(1)	-14(1)	3(1)	-13(1)
C(214)	31(1)	31(1)	28(1)	-5(1)	-1(1)	-9(1)
C(215)	24(1)	23(1)	32(1)	-6(1)	2(1)	-7(1)
C(216)	45(1)	31(1)	33(1)	-9(1)	2(1)	1(1)
C(217)	33(1)	35(1)	23(1)	-1(1)	-1(1)	-9(1)
C(218)	44(1)	41(1)	54(2)	-23(1)	0(1)	-6(1)
F(21)	41(1)	26(1)	32(1)	-4(1)	-5(1)	0(1)
O(21)	42(1)	24(1)	34(1)	-5(1)	0(1)	-2(1)
O(22)	36(1)	28(1)	21(1)	-1(1)	1(1)	-6(1)
O(23)	55(1)	32(1)	30(1)	-2(1)	-7(1)	-2(1)
O(24)	47(1)	42(1)	42(1)	-19(1)	2(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **155**.

	x	y	z	U(eq)
H(11)	2882	9821	946	35
H(12)	1105	11727	1056	36
H(14)	2279	11044	3256	35
H(17)	5198	7534	2449	33
H(18)	4613	7914	926	36
H(111)	7006	3970	1337	36
H(112)	7938	3005	338	37
H(114)	7852	6127	-957	33
H(11A)	-334	12604	3226	55
H(11B)	-713	13930	2793	55
H(11C)	1407	13151	3036	55
H(11D)	4638	9809	4043	58
H(11E)	4835	8454	4381	58
H(11F)	2786	9352	4142	58
H(11G)	7441	5012	-1856	61
H(11H)	9059	3868	-2034	61
H(11I)	9626	4855	-1679	61
H(21)	3787	5481	3127	32
H(22)	1971	7371	3254	34
H(24)	1024	6220	5409	31
H(27)	4791	2899	4555	31
H(28)	5325	3606	3054	33
H(211)	8603	-271	3297	35
H(212)	9336	-1147	2246	39
H(214)	5837	1790	1041	36
H(21A)	-1512	7868	5191	58
H(21B)	-1509	9215	4939	58
H(21C)	255	8284	5399	58
H(21D)	2799	4742	6317	46
H(21E)	2562	3435	6485	46
H(21F)	855	4522	6104	46
H(21G)	10500	-1393	1104	69
H(21H)	9467	-1478	372	69
H(21I)	8677	-1878	1169	69

Appendix V, Crystal data for 140

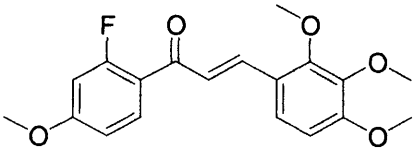


Table 1. Crystal data and structure refinement for **140**.

Identification code	njl0406	
Empirical formula	C19 H19 F O5	
Formula weight	346.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.1463(2) Å	α= 83.9070(10)°.
	b = 9.6851(3) Å	β= 78.4650(10)°.
	c = 11.4708(4) Å	γ = 68.632(2)°.
Volume	825.24(4) $Å^3$	
Z	2	
Density (calculated)	1.394 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	364	
Crystal size	0.23 x 0.15 x 0.10 mm^3	
Theta range for data collection	3.63 to 27.41°.	
Index ranges	-10<=h<=10, -12<=k<=12, -14<=l<=14	
Reflections collected	12386	
Independent reflections	3718 [R(int) = 0.1465]	
Completeness to theta = 27.41°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9893 and 0.9757	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3718 / 0 / 230	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0632, wR2 = 0.1569	
R indices (all data)	R1 = 0.0765, wR2 = 0.1673	
Largest diff. peak and hole	0.408 and -0.321 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **140**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7807(3)	10395(2)	-340(2)	32(1)
C(2)	10492(3)	13053(2)	-1676(2)	43(1)
C(3)	7517(3)	15300(2)	-4802(2)	34(1)
C(4)	6575(2)	12897(2)	-980(1)	23(1)
C(5)	7702(2)	13141(2)	-1999(2)	24(1)
C(6)	6995(2)	14162(2)	-2893(1)	25(1)
C(7)	5166(2)	14924(2)	-2758(2)	26(1)
C(8)	4051(2)	14663(2)	-1734(2)	25(1)
C(9)	4709(2)	13654(2)	-831(1)	24(1)
C(10)	3419(2)	13430(2)	186(2)	25(1)
C(11)	3677(2)	12543(2)	1160(2)	27(1)
C(12)	2142(2)	12457(2)	2062(2)	27(1)
C(13)	2502(2)	11358(2)	3087(2)	25(1)
C(14)	3868(2)	9984(2)	3067(1)	26(1)
C(15)	4100(2)	9000(2)	4018(2)	29(1)
C(16)	2939(2)	9405(2)	5101(2)	27(1)
C(17)	1556(2)	10780(2)	5183(2)	30(1)
C(18)	1341(2)	11707(2)	4183(2)	29(1)
C(19)	2164(3)	8789(2)	7154(2)	34(1)
F(1)	5043(1)	9535(1)	2030(1)	35(1)
O(1)	7344(2)	11931(1)	-104(1)	25(1)
O(2)	9514(2)	12341(1)	-2144(1)	28(1)
O(3)	8220(2)	14333(1)	-3852(1)	31(1)
O(4)	597(2)	13269(2)	2017(1)	37(1)
O(5)	3270(2)	8384(1)	6012(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for **140**.

C(1)-O(1)	1.436(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-O(2)	1.431(2)
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800
C(3)-O(3)	1.426(2)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-O(1)	1.379(2)
C(4)-C(5)	1.392(2)
C(4)-C(9)	1.410(2)
C(5)-O(2)	1.379(2)
C(5)-C(6)	1.402(2)
C(6)-O(3)	1.3701(19)
C(6)-C(7)	1.385(2)
C(7)-C(8)	1.395(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.394(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.460(2)
C(10)-C(11)	1.338(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.477(2)
C(11)-H(11)	0.9500
C(12)-O(4)	1.225(2)
C(12)-C(13)	1.499(2)
C(13)-C(14)	1.388(2)
C(13)-C(18)	1.404(2)
C(14)-C(15)	1.366(3)
C(14)-F(1)	1.3678(17)
C(15)-C(16)	1.398(2)
C(15)-H(15)	0.9500
C(16)-O(5)	1.357(2)
C(16)-C(17)	1.394(3)
C(17)-C(18)	1.378(3)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-O(5)	1.437(2)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
O(1)-C(1)-H(1A)	109.5
O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-C(2)-H(2A)	109.5
O(2)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
O(2)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
O(3)-C(3)-H(3A)	109.5
O(3)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
O(3)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(1)-C(4)-C(5)	117.96(15)
O(1)-C(4)-C(9)	121.08(14)
C(5)-C(4)-C(9)	120.93(15)
O(2)-C(5)-C(4)	119.68(15)
O(2)-C(5)-C(6)	120.05(14)
C(4)-C(5)-C(6)	120.25(15)
O(3)-C(6)-C(7)	124.73(15)
O(3)-C(6)-C(5)	115.64(15)
C(7)-C(6)-C(5)	119.63(15)
C(6)-C(7)-C(8)	119.52(16)
C(6)-C(7)-H(7)	120.2
C(8)-C(7)-H(7)	120.2
C(9)-C(8)-C(7)	122.31(16)
C(9)-C(8)-H(8)	118.8
C(7)-C(8)-H(8)	118.8
C(8)-C(9)-C(4)	117.37(15)
C(8)-C(9)-C(10)	117.83(15)
C(4)-C(9)-C(10)	124.78(16)
C(11)-C(10)-C(9)	130.24(17)
C(11)-C(10)-H(10)	114.9
C(9)-C(10)-H(10)	114.9
C(10)-C(11)-C(12)	120.74(16)
C(10)-C(11)-H(11)	119.6
C(12)-C(11)-H(11)	119.6
O(4)-C(12)-C(11)	122.56(16)
O(4)-C(12)-C(13)	118.99(15)
C(11)-C(12)-C(13)	118.43(15)
C(14)-C(13)-C(18)	115.21(16)
C(14)-C(13)-C(12)	126.53(15)
C(18)-C(13)-C(12)	118.25(15)
C(15)-C(14)-F(1)	116.41(15)
C(15)-C(14)-C(13)	124.19(15)
F(1)-C(14)-C(13)	119.36(15)
C(14)-C(15)-C(16)	118.75(17)
C(14)-C(15)-H(15)	120.6
C(16)-C(15)-H(15)	120.6
O(5)-C(16)-C(17)	124.75(15)
O(5)-C(16)-C(15)	115.50(16)
C(17)-C(16)-C(15)	119.75(16)
C(18)-C(17)-C(16)	119.06(16)
C(18)-C(17)-H(17)	120.5
C(16)-C(17)-H(17)	120.5
C(17)-C(18)-C(13)	122.97(17)

C(17)-C(18)-H(18)	118.5
C(13)-C(18)-H(18)	118.5
O(5)-C(19)-H(19A)	109.5
O(5)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(5)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(4)-O(1)-C(1)	113.77(12)
C(5)-O(2)-C(2)	113.11(13)
C(6)-O(3)-C(3)	116.41(14)
C(16)-O(5)-C(19)	117.17(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **140**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	35(1)	23(1)	32(1)	1(1)	-4(1)	-4(1)
C(2)	25(1)	31(1)	72(2)	-2(1)	-13(1)	-6(1)
C(3)	32(1)	38(1)	29(1)	8(1)	-3(1)	-10(1)
C(4)	24(1)	19(1)	23(1)	-2(1)	-4(1)	-4(1)
C(5)	20(1)	20(1)	28(1)	-5(1)	-2(1)	-2(1)
C(6)	25(1)	22(1)	25(1)	-2(1)	-1(1)	-7(1)
C(7)	26(1)	24(1)	26(1)	1(1)	-6(1)	-6(1)
C(8)	21(1)	22(1)	30(1)	-1(1)	-4(1)	-4(1)
C(9)	22(1)	20(1)	26(1)	-3(1)	-3(1)	-5(1)
C(10)	21(1)	21(1)	31(1)	-4(1)	-2(1)	-5(1)
C(11)	23(1)	25(1)	30(1)	-3(1)	0(1)	-7(1)
C(12)	24(1)	21(1)	32(1)	-2(1)	-1(1)	-6(1)
C(13)	21(1)	23(1)	28(1)	-3(1)	0(1)	-6(1)
C(14)	20(1)	26(1)	25(1)	-7(1)	5(1)	-4(1)
C(15)	24(1)	25(1)	30(1)	-2(1)	0(1)	-1(1)
C(16)	28(1)	26(1)	26(1)	-1(1)	-3(1)	-9(1)
C(17)	28(1)	29(1)	27(1)	-4(1)	2(1)	-8(1)
C(18)	24(1)	22(1)	32(1)	-4(1)	3(1)	-3(1)
C(19)	38(1)	37(1)	23(1)	-1(1)	1(1)	-10(1)
F(1)	31(1)	31(1)	26(1)	-4(1)	7(1)	2(1)
O(1)	24(1)	22(1)	25(1)	0(1)	-5(1)	-2(1)
O(2)	20(1)	25(1)	31(1)	-4(1)	0(1)	-1(1)
O(3)	25(1)	34(1)	27(1)	5(1)	1(1)	-6(1)
O(4)	24(1)	30(1)	45(1)	8(1)	1(1)	-2(1)
O(5)	37(1)	30(1)	27(1)	2(1)	1(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **140**.

	x	y	z	U(eq)
H(1A)	6715	10190	-339	48
H(1B)	8439	9773	279	48
H(1C)	8584	10176	-1119	48
H(2A)	10251	14058	-2032	65
H(2B)	11776	12482	-1865	65
H(2C)	10119	13108	-810	65
H(3A)	6776	14903	-5142	52
H(3B)	8506	15377	-5420	52
H(3C)	6787	16286	-4498	52
H(7)	4675	15619	-3358	31
H(8)	2799	15191	-1650	31
H(10)	2203	14006	149	30
H(11)	4861	11962	1273	32
H(15)	5033	8057	3945	35
H(17)	773	11074	5918	35
H(18)	364	12624	4238	34
H(19A)	2243	9702	7394	51
H(19B)	2575	7989	7744	51
H(19C)	919	8953	7105	51

Appendix VI, Crystal data for 146

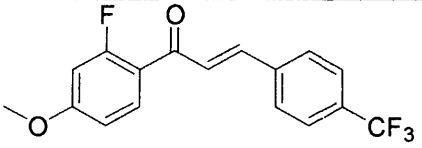


Table 1. Crystal data and structure refinement for **146**.

Identification code	njl0405	
Empirical formula	C17 H12 F4 O2	
Formula weight	324.27	
Temperature	150(2) K	
Wavelength	0.71069 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.910(5) Å	α= 107.392(5)°.
	b = 9.329(5) Å	β= 94.719(5)°.
	c = 13.920(5) Å	γ = 99.669(5)°.
Volume	714.8(8) Å^3	
Z	2	
Density (calculated)	1.507 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	
F(000)	332	
Crystal size	0.30 x 0.23 x 0.07 mm^3	
Theta range for data collection	3.19 to 27.55°.	
Index ranges	-7<=h<=7, -12<=k<=12, -18<=l<=18	
Reflections collected	11479	
Independent reflections	3204 [R(int) = 0.0997]	
Completeness to theta = 27.55°	96.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9908 and 0.9613	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3204 / 0 / 209	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0617, wR2 = 0.1572	
R indices (all data)	R1 = 0.0792, wR2 = 0.1698	
Largest diff. peak and hole	0.671 and -0.297 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **146**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-1446(3)	1169(2)	2738(2)	36(1)
C(2)	-2351(3)	1305(2)	1823(2)	36(1)
C(3)	-934(3)	2060(2)	1310(1)	35(1)
C(4)	-1857(4)	2188(2)	311(2)	41(1)
C(5)	1388(4)	2672(2)	1704(2)	39(1)
C(6)	2271(3)	2541(2)	2616(2)	38(1)
C(7)	871(3)	1789(2)	3153(1)	33(1)
C(8)	1742(3)	1608(2)	4121(2)	35(1)
C(9)	3905(3)	2117(2)	4600(1)	35(1)
C(10)	4606(3)	1815(2)	5555(1)	33(1)
C(11)	6951(3)	2561(2)	6150(1)	31(1)
C(12)	8471(4)	3793(2)	6037(1)	36(1)
C(13)	10626(4)	4405(2)	6601(2)	39(1)
C(14)	11346(3)	3787(2)	7337(1)	33(1)
C(15)	9887(3)	2573(2)	7497(1)	36(1)
C(16)	7746(3)	1989(2)	6906(1)	34(1)
C(17)	14335(4)	3786(3)	8594(2)	46(1)
O(1)	3307(2)	922(2)	5848(1)	42(1)
O(2)	13514(3)	4441(2)	7856(1)	43(1)
F(1)	-4153(2)	2110(2)	199(1)	67(1)
F(2)	-1467(3)	1093(2)	-482(1)	74(1)
F(3)	-934(3)	3520(2)	186(1)	61(1)
F(4)	7823(3)	4501(2)	5368(1)	60(1)

Table 3. Bond lengths [Å] and angles [°] for **146**.

C(1)-C(2)	1.389(3)
C(1)-C(7)	1.396(3)
C(1)-H(1)	0.9500
C(2)-C(3)	1.381(3)
C(2)-H(2)	0.9500
C(3)-C(5)	1.391(3)
C(3)-C(4)	1.497(3)
C(4)-F(2)	1.327(3)
C(4)-F(3)	1.338(2)
C(4)-F(1)	1.340(3)
C(5)-C(6)	1.379(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.399(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.469(3)
C(8)-C(9)	1.331(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.480(3)
C(9)-H(9)	0.9500
C(10)-O(1)	1.220(2)
C(10)-C(11)	1.494(3)
C(11)-C(12)	1.391(3)
C(11)-C(16)	1.397(2)
C(12)-F(4)	1.359(2)
C(12)-C(13)	1.374(3)
C(13)-C(14)	1.389(3)
C(13)-H(13)	0.9500
C(14)-O(2)	1.363(2)
C(14)-C(15)	1.389(3)
C(15)-C(16)	1.380(3)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(17)-O(2)	1.434(2)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(2)-C(1)-C(7)	121.22(17)
C(2)-C(1)-H(1)	119.4
C(7)-C(1)-H(1)	119.4
C(3)-C(2)-C(1)	119.61(18)
C(3)-C(2)-H(2)	120.2
C(1)-C(2)-H(2)	120.2
C(2)-C(3)-C(5)	120.15(18)
C(2)-C(3)-C(4)	120.54(18)
C(5)-C(3)-C(4)	119.28(17)
F(2)-C(4)-F(3)	106.22(18)
F(2)-C(4)-F(1)	105.89(19)
F(3)-C(4)-F(1)	105.29(17)
F(2)-C(4)-C(3)	113.12(17)
F(3)-C(4)-C(3)	112.73(17)
F(1)-C(4)-C(3)	112.95(17)
C(6)-C(5)-C(3)	119.95(17)
C(6)-C(5)-H(5)	120.0
C(3)-C(5)-H(5)	120.0
C(5)-C(6)-C(7)	121.01(18)
C(5)-C(6)-H(6)	119.5
C(7)-C(6)-H(6)	119.5
C(1)-C(7)-C(6)	118.05(17)
C(1)-C(7)-C(8)	119.02(16)
C(6)-C(7)-C(8)	122.92(18)
C(9)-C(8)-C(7)	125.81(17)
C(9)-C(8)-H(8)	117.1
C(7)-C(8)-H(8)	117.1
C(8)-C(9)-C(10)	121.03(17)
C(8)-C(9)-H(9)	119.5
C(10)-C(9)-H(9)	119.5
O(1)-C(10)-C(9)	120.42(18)
O(1)-C(10)-C(11)	119.44(16)
C(9)-C(10)-C(11)	120.10(16)
C(12)-C(11)-C(16)	115.12(17)
C(12)-C(11)-C(10)	126.86(16)
C(16)-C(11)-C(10)	118.02(16)
F(4)-C(12)-C(13)	116.04(17)
F(4)-C(12)-C(11)	120.17(17)
C(13)-C(12)-C(11)	123.74(17)
C(12)-C(13)-C(14)	118.98(18)
C(12)-C(13)-H(13)	120.5
C(14)-C(13)-H(13)	120.5
O(2)-C(14)-C(13)	115.64(17)
O(2)-C(14)-C(15)	124.46(17)
C(13)-C(14)-C(15)	119.91(18)
C(16)-C(15)-C(14)	118.98(17)
C(16)-C(15)-H(15)	120.5
C(14)-C(15)-H(15)	120.5
C(15)-C(16)-C(11)	123.27(17)
C(15)-C(16)-H(16)	118.4
C(11)-C(16)-H(16)	118.4
O(2)-C(17)-H(17A)	109.5
O(2)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(2)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(14)-O(2)-C(17)	116.77(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **146**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	34(1)	35(1)	42(1)	18(1)	8(1)	5(1)
C(2)	33(1)	35(1)	40(1)	13(1)	2(1)	5(1)
C(3)	42(1)	31(1)	33(1)	11(1)	6(1)	11(1)
C(4)	49(1)	38(1)	38(1)	14(1)	5(1)	10(1)
C(5)	41(1)	41(1)	40(1)	20(1)	12(1)	7(1)
C(6)	32(1)	44(1)	41(1)	18(1)	4(1)	5(1)
C(7)	34(1)	32(1)	36(1)	13(1)	6(1)	10(1)
C(8)	36(1)	35(1)	39(1)	17(1)	9(1)	9(1)
C(9)	39(1)	34(1)	34(1)	13(1)	7(1)	5(1)
C(10)	36(1)	31(1)	34(1)	11(1)	9(1)	10(1)
C(11)	37(1)	29(1)	30(1)	9(1)	8(1)	10(1)
C(12)	47(1)	31(1)	31(1)	14(1)	1(1)	7(1)
C(13)	47(1)	33(1)	37(1)	15(1)	2(1)	0(1)
C(14)	38(1)	29(1)	31(1)	7(1)	3(1)	8(1)
C(15)	44(1)	35(1)	33(1)	15(1)	7(1)	13(1)
C(16)	40(1)	31(1)	37(1)	16(1)	10(1)	8(1)
C(17)	47(1)	47(1)	45(1)	18(1)	-4(1)	12(1)
O(1)	38(1)	48(1)	48(1)	27(1)	8(1)	4(1)
O(2)	44(1)	41(1)	41(1)	16(1)	-4(1)	4(1)
F(1)	49(1)	104(1)	59(1)	45(1)	-3(1)	13(1)
F(2)	124(2)	67(1)	36(1)	12(1)	9(1)	45(1)
F(3)	75(1)	54(1)	58(1)	36(1)	-5(1)	2(1)
F(4)	72(1)	50(1)	57(1)	35(1)	-19(1)	-11(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **146**.

	x	y	z	U(eq)
H(1)	-2423	644	3087	43
H(2)	-3934	881	1553	43
H(5)	2364	3179	1346	46
H(6)	3855	2969	2883	46
H(8)	665	1081	4432	42
H(9)	5016	2682	4325	42
H(13)	11609	5239	6489	47
H(15)	10356	2152	8005	43
H(16)	6762	1156	7019	41
H(17A)	13393	3953	9150	69
H(17B)	15958	4274	8865	69
H(17C)	14216	2682	8271	69