FLUORINATION STUDIES USING DIFLUOROIODOTOLUENE

A Thesis Presented by

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ABSTRACT

This thesis is divided into three parts.

The first part is an introduction to the fluorination chemistry of difluoroiodotoluene and consists of two reviews. The first review concerns the use of iodine (III) difluorides in the formation of carbon-fluorine bonds. The second deals with the Fluoro-Pummerer reaction, introduction of fluorine into the α-position of sulfoxides or sulfides *via* sulfonium ion intermediates.

The second part is a discussion of the results obtained with difluoroiodotoluene in the fluorination of sulfur-containing compounds. Early results indicated that the reagent could perform Fluoro-Pummerer chemistry, and this transformation forms the basis of much of the work. A range of α-fluoro sulfides could be formed cleanly and in good yield by treatment of β-oxo sulfides with one equivalent of difluoroiodotoluene in dichloromethane solution. Difluorination of substrates was also feasible, and treatment with excess reagent was found to produce α-fluoro sulfoxides. The reaction was established as being promoted by electron-withdrawing groups in the α-position, accordingly simple dialkyl sulfides were found not to undergo the Fluoro-Pummerer reaction with difluoroiodotoluene. In cases were substrates had β-hydrogens an elimination reaction was found to operate, producing vinyl sulfides. These vinyl sulfides could then add two equivalents of fluoride *via* an additive-Pummerer reaction to produce α, β-difluorosulfides. In this manner a range of novel 3,4-difluoro pyrrolidinones and piperidinones were synthesised. Certain α-phenylsulfanyl acetamides were found to be resistant to fluorination, undergoing preferential oxidation to the sulfoxides. Arguments based on a coordination of the β-carbonyl oxygen to the iodine centre of the putative iodosulfonium salt, forming a stabilised chelate complex are advanced to explain this behaviour.

The chemistry of hypervalent tellurium difluorides in carbon-fluorine bond formation is discussed. The synthesis of α, α-difluoroethers from fluorodesulfurisation of thione esters and dithioorthoester derivatives using difluoroiodotoluene was attempted. Such fluorination reactions were successful but the hydrolytic instability of the products renders purification and analysis difficult.

Part three is an account of the experimental results and procedures employed throughout this work.

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Finally, I would like to acknowledge the love and support given to me by my parents, sisters and brother throughout my long education. This thesis is dedicated to them.

ABBREVIATIONS

^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{19}F NMR	Fluorine Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{125}Te NMR	Tellurium Nuclear Magnetic Resonance
AcOH	Acetic acid
AIBN	Azodiisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
br	Broad
Bn	Benzyl
b.p.	Boiling point
Bu^t	*tert*-Butyl
cat.	Catalytic amount
d	Doublet
Δ	Heating
DAST	Diethylamino sulfur trifluoride
DBH	Dibromohydantoin
DCM	Dichloromethane
dcmp	Decomposes
DEPT	Distortionless Enhancement by Polarisation Transfer
DFIT	Difluoroiodotoluene
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electron Impact
equiv.	Molar Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol

EWG	Electron-withdrawing Group
FAB	Fast Atom Bombardment
GC	Gas Chromatography
hr	Hour
HPLC	High Pressure Liquid Chromatography
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m	Multiplet
m	Meta
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minute
m.p.	Melting Point
MTA	Methyl thioadenosine
NGP	Neighbouring Group Participation
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl Pyrrolidinone
NOE	Nuclear Overhauser Effect
p	Para
PE	Petroleum ether
Ph	Phenyl
ppm	Parts per million
Pr^i	Isopropyl
q	Quartet
r	Reference substituent
s	Singlet
sat.	Saturated
SET	Single Electron Transfer
SM	Starting material
SCE	Standard Calomel Electrode

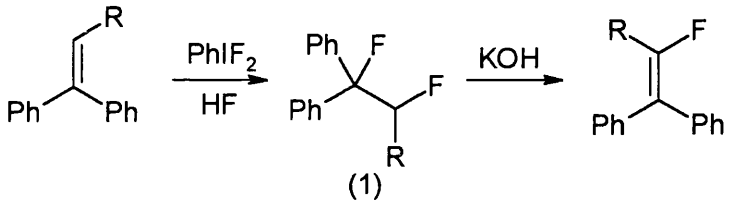
t	Triplet
TAG	Tetraacetyl glucose
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
TsOH	*p*-Toluenesulfonic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
tol	Tolyl
UV	Ultra Violet

Part 1. Introduction

Chapter 1. Difluoroiodine (III) Reagents in Fluorination

1.1 Fluorination of Olefins

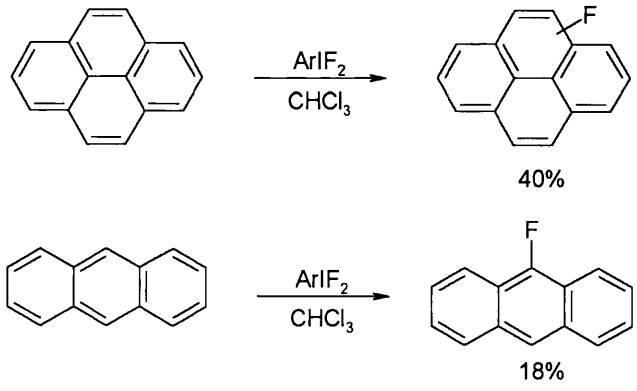
Aryl difluoroiodine (III) reagents were first introduced by Bockemuller over sixty years ago.[1] He reported the transformation of 1,1-diphenyl ethylenes to 1,2-difluoro-1,1-diphenylethanes (1) upon treatment with difluoroiodobenzene and hydrogen fluoride in chloroform. Dehydrofluorination of the ethane derivative produced 2-fluoro-1,1-diphenylethenes (scheme 1).



Scheme 1

The same transformation could be achieved with lead tetrafluoride in the presence of hydrogen fluoride, although the difluoroiodoarene was observed to be far superior.

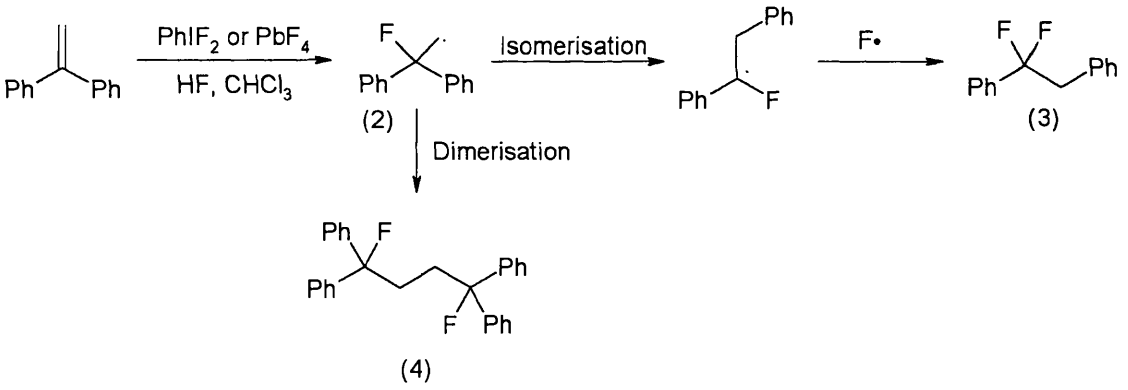
Garvey investigated the fluorination of aromatic polynuclear hydrocarbons with difluoroiodotoluene (DFIT) in 1937.[2] The fluorinating agent was prepared by fluorination of *p*-iodosotoluene with aq. hydrofluoric acid in glacial acetic acid. Monofluorides were obtained from pyrene, anthracene and benzanthrone with unspecified coupling products reported for acenaphthene, fluoranthene and anthrone (scheme 2).



Scheme 2

The authors stated that the reaction was not general, many aromatic substrates either failing to react or producing intractable tars. Subsequent work by Badger found this chemistry to be irreproducible and DFIT was declared to be unsatisfactory for the preparation of fluorine-substituted polycyclic compounds in reasonable quantity.[3]

The work of Bockemuller on the fluorination of diphenylethylene with difluoroiodobenzene was reexamined by Bornstein in 1963.[4] He had prepared 1,2-difluoro-1,1-diphenylethane unambiguously and noted significant differences with the compound described by Bockemüller. Through synthesis and degradation studies he formulated the actual structure as 1,1-difluoro-1,2-diphenylethane (3). A study of the mechanism of the fluorination using lead tetrafluoride was then conducted. The isolation of previously unidentified dimeric material (4) led the author to propose a radical mechanism shown in scheme 3. No satisfactory explanation for the formation of radical (2) could be made, although any involvement of fluorine radicals in a hydrogen abstraction process was rejected.



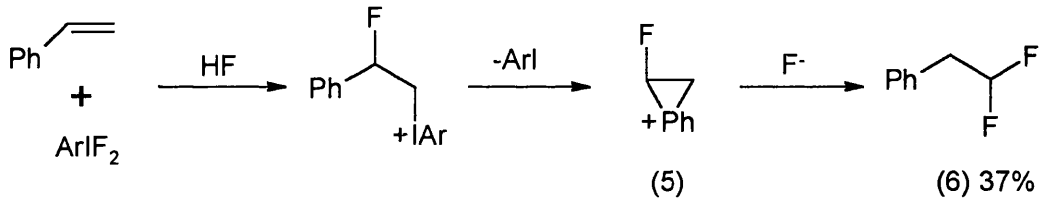
Scheme 3

In 1966 Carpenter introduced a simple and rapid preparation of difluoroiodoarenes involving treatment of the appropriate dichloroiodoarene with yellow mercuric oxide and aqueous hydrofluoric acid in DCM.[5] The DCM solution is then used directly for fluorination, with the concentration being determined by iodometric analysis. This procedure avoids the use of iodosobenzene which is slightly unstable, disproportionating to iodobenzene and iodoxybenzene on standing.

Carpenter studied the fluorination of styrene and found difluoroiodo(*p*-chlorobenzene) to be the most convenient fluorinating agent. It is easily prepared in high yield and keeps well in the refrigerator. The phenyl and tolyl derivatives were also successful although there was a tendancy for partial chlorination of the aromatic ring during

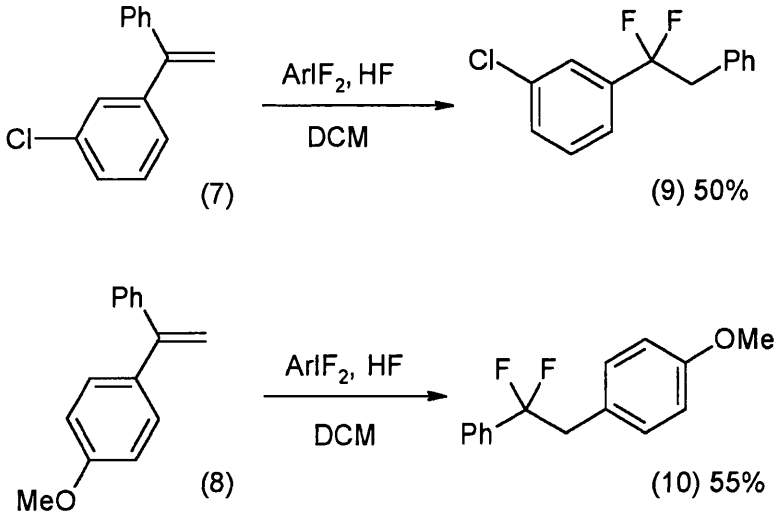
preparation of the dichloride. Dichloroiodo(*p*-nitrobenzene) was not sufficiently soluble in DCM to permit preparation of the difluoride. Chloroform and benzene were reported to be good solvents whilst saturated hydrocarbons were poor; THF and acetonitrile allegedly reacted with the reagents. Polyethylene vessels were used whenever possible to avoid the decomposition of the reagent on glass surfaces.

The fluorination of styrene produced 1,1-difluoro-2-phenylethane (6) in 37% yield, the availability of ^{19}F nmr spectroscopy at this time greatly facilitating characterisation. Carpenter favoured a polar mechanism for this transformation, postulating a rearrangement *via* phenonium ion (5) catalysed by residual hydrofluoric acid in the fluorinating solution. If the acid is removed through magnesium oxide treatment then no reaction can occur (scheme 4).



Scheme 4

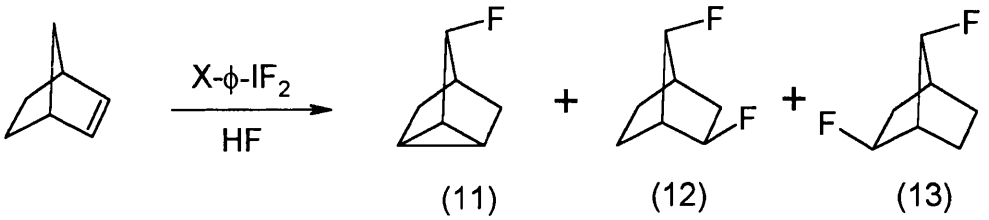
Zupan presented an alternative synthesis of difluoroiodoarenes using xenon difluoride as the fluorinating agent in DCM in the presence of anhydrous HF.[6] He provided further support for the phenonium ion intermediate in the fluorination of phenyl-substituted olefins by fluorinating 1-phenyl-1-(*m*-chlorophenyl)ethylene (7) and 1-phenyl-1-(*p*-methoxyphenyl)ethylene (8). The reactions resulted in 1,1-difluoro-1-(*m*-chlorophenyl)-2-phenylethane (9) and 1,1-difluoro-1-phenyl-2-(*p*-methoxyphenyl)ethane (10) respectively (scheme 5).



Scheme 5

The fluorination of phenyl-substituted cycloolefins with difluoroiodoarenes to give *gem*-difluoro compounds was also reported.

The bicyclic olefin norbonene has been used for elucidating the stereochemistry and mechanism of various reactions.[6a] Analysis of product distribution can lead to insights into radical, cationic or concerted addition pathways. Zupan found that the fluorination of norbornene with difluoroiodoarenes produced three products, with 2-*exo*-7-*syn*-difluoronorbornane (12) being the major one (scheme 6).[6b]



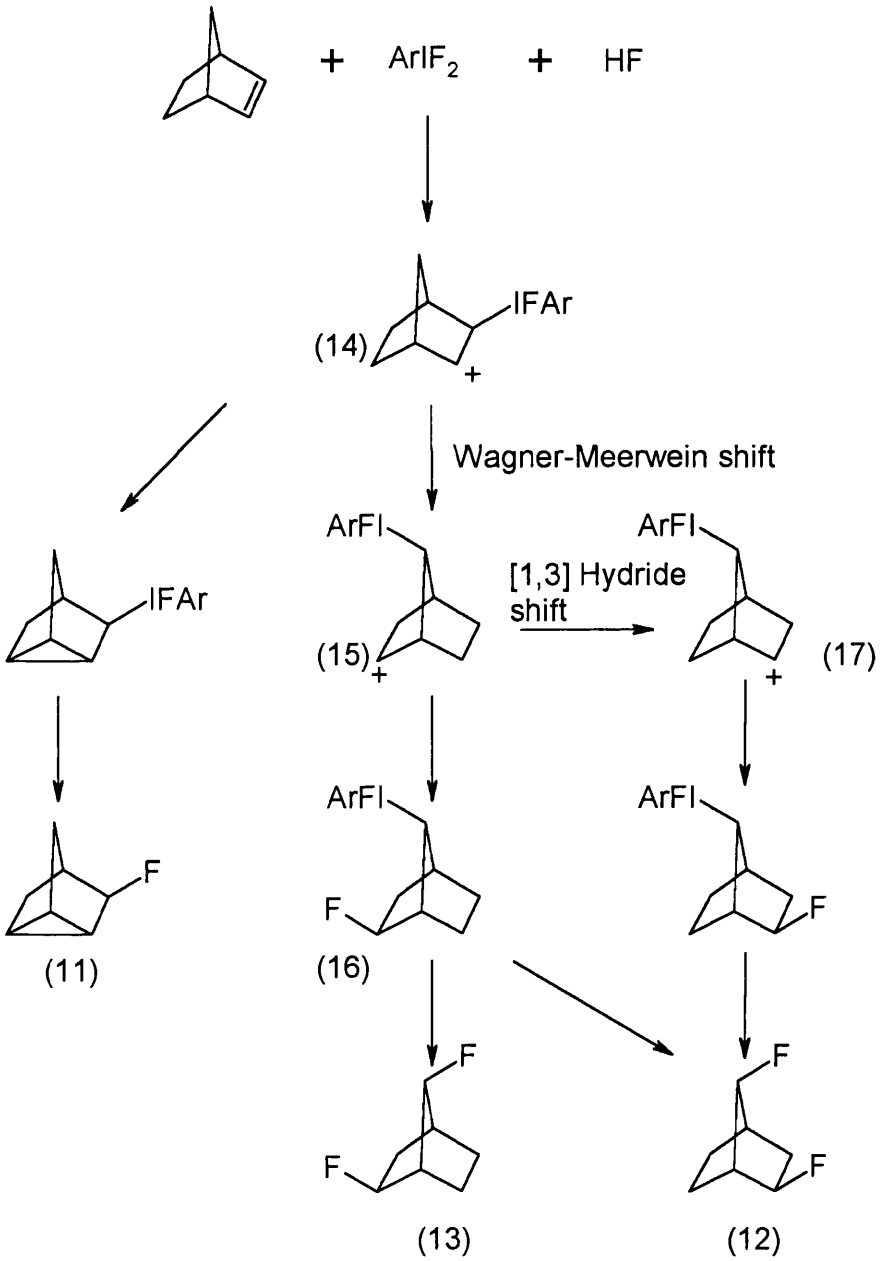
Relative yields (GC)

X	(11)	(12)	(13)
p-OCH_3	12	75	13
m-OCH_3	18	74	8
H	9	84	7
m-Cl	6	88	6
m-NO_2	9	86	5

Scheme 6

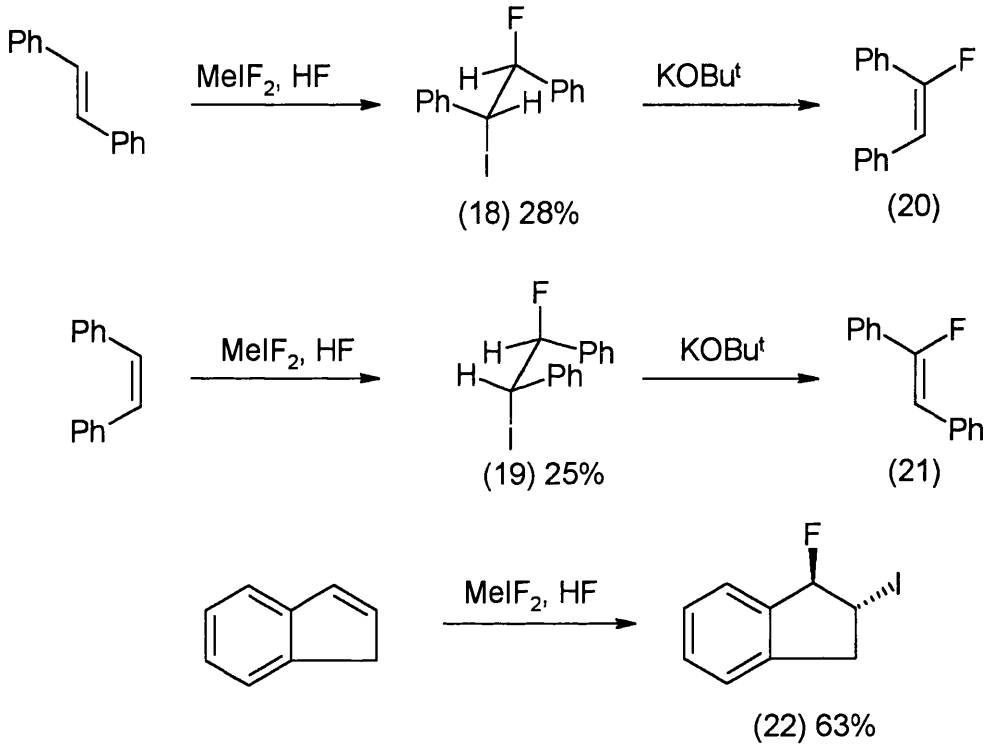
The reaction of norbornene with the polarised difluoroiodoarene molecule would be expected to form carbonium ion (14). Wagner-Meerwein rearrangement to (15)

followed by fluoride addition leads to the fluoroiodonorbornane (16). S_N2 substitution of the aryliodo functionality by fluoride then produces the minor product (13). The major product 2-*exo*-7-*anti*-difloronorbornane (12) could be formed from a 6-1 hydride shift from (15) to (17) and subsequent fluoride additions (scheme 7). The formation of (12) in high yield was attributed to the operation of an additional reaction pathway involving 1,3 fluorine transfer from iodine to carbon in (16) to give (12). In contrast the reaction of dichloroiodobenzene with norbornene is believed to follow radical pathways.[7]



Scheme 7

In sharp contrast to the reactions of difluoroiodoarenes with olefins, difluoroiodomethane acts as an iodofluorination reagent.[8] *E*- and *Z*-stilbene react with the reagent and HF to give *erythro*- and *threo*-1-fluoro-2-iodo-1,2-diphenylethane respectively (18) and (19). The reaction was reported to be clean although isolated yields were quite low owing to the instability of the products. A catalytic amount of tributylamine prevented decomposition, resulting in a good yield of *E*-1-fluoro-2-iodoindane (22) from the iodofluorination of indene (scheme 8).

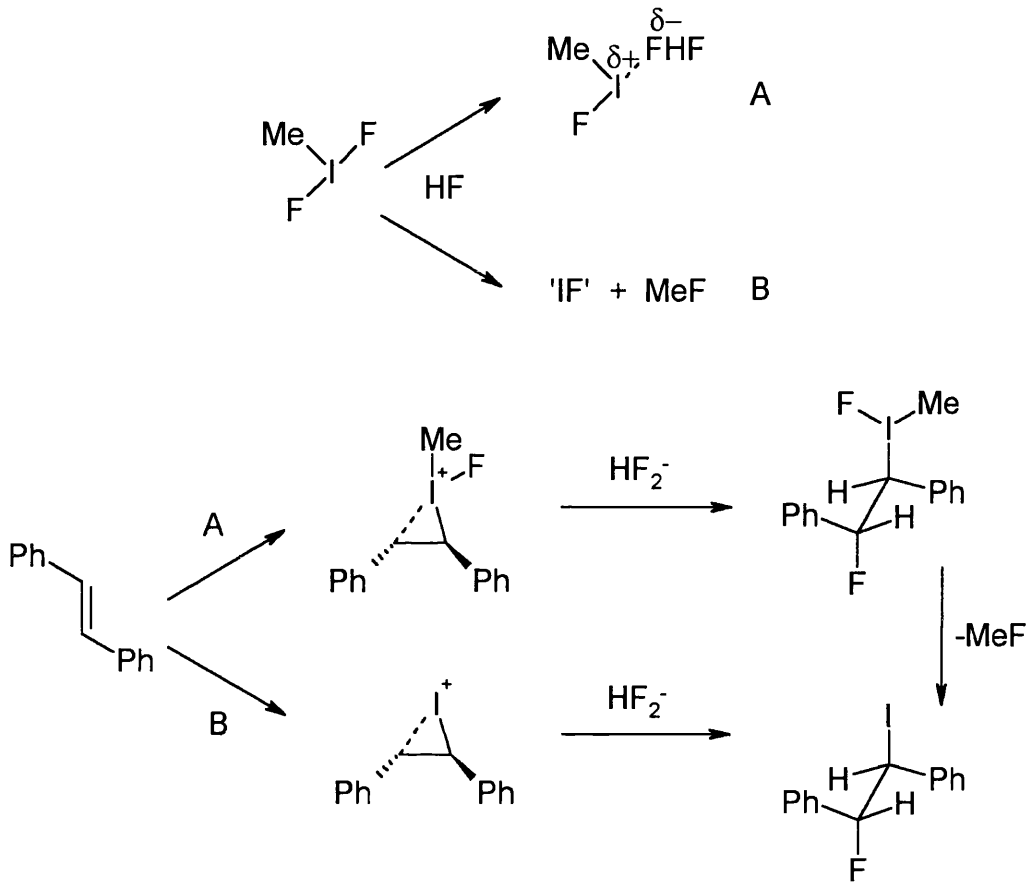


Scheme 8

As in the difluoroiodoarene case the reactions were extremely slow in the absence of HF. Elimination of HI under basic conditions provided the *E*- and *Z*-fluoroolefins (20) and (21).

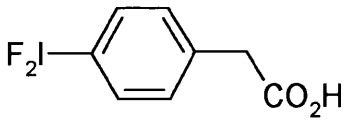
Zupan offered two possible explanations for the unusual behaviour of difluoroiodomethane. The reagent could decompose in the presence of HF to give methyl fluoride and a reactive iodine fluoride species (B). Addition of IF across the double bond could take place *via* a bridged iodonium species to give the *anti* iodofluorides. Alternatively the HF could polarise the I-F bond of the difluoroiodomethane (A) and the electrophilic iodine could add to the olefin as in

Carpenter's fluorination of styrene (*vide supra)*. Methyl fluoride was then postulated to be lost at a later stage (scheme 9).



Scheme 9

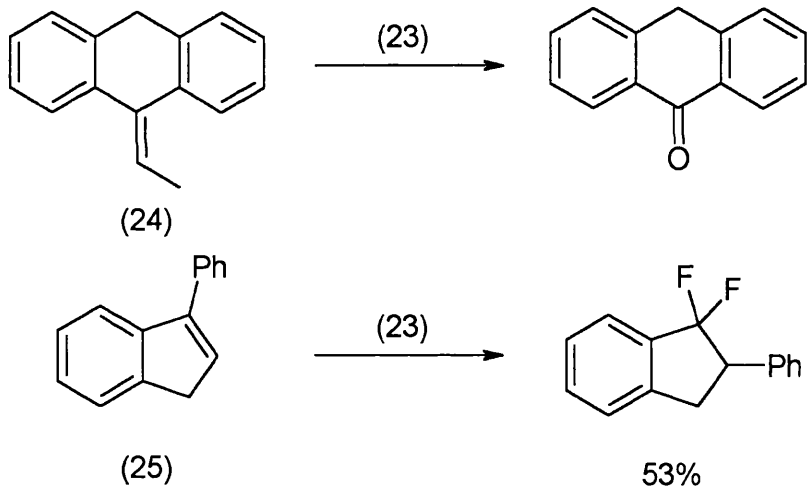
A major problem in the fluorination of non-polar olefins such as styrene with difluoroiodoarenes is the removal of the iodoarene from the products. Zupan circumvented this problem through immobilising the iodoarene on a solid support and producing polymer-bound $ArIF_2$ through fluorination with xenon difluoride (*vide infra*).[9,10] Patrick sought an alternative synthesis of polymer-bound difluoroiodoarenes as xenon difluoride is extremely expensive. Unfortunately, the application of Carpenter's simple mercuric oxide mediated fluorination of iodoarene dichlorides failed for the polymer-bound case. Instead, Patrick prepared (*p*-iodophenyl)acetic acid difluoride (23).[11] The (*p*-iodophenyl)acetic acid by-product could then be easily extracted in work-up. The acid function was not placed directly on the aromatic ring because electron-withdrawing substituents are known to decrease the yield of fluorinated products from difluoroiodoarenes.



(23)

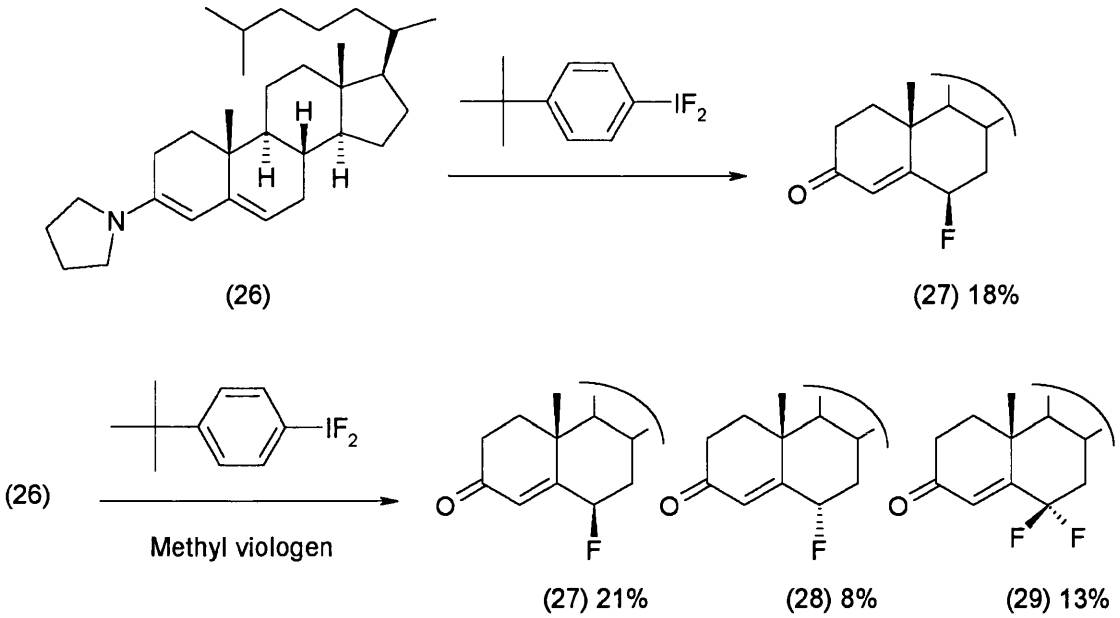
A range of *para*-substituted 1,1-diphenylethenes reacted with (23) in DCM to give the expected geminal difluorides with phenyl migration. From measurements of relative rates of fluorination and migratory aptitudes of the various substituted phenyl groups Patrick concluded that an electrophilic addition of the difluoroiodoarene followed by a rearrangement step involving a phenonium ion was the likely mechanism; in agreement with Carpenter and Zupan.

When 9-ethylidenefluorene (24) and 1-phenylindene (25) were used as substrates no ring contraction products were observed (scheme 10).



Scheme 10

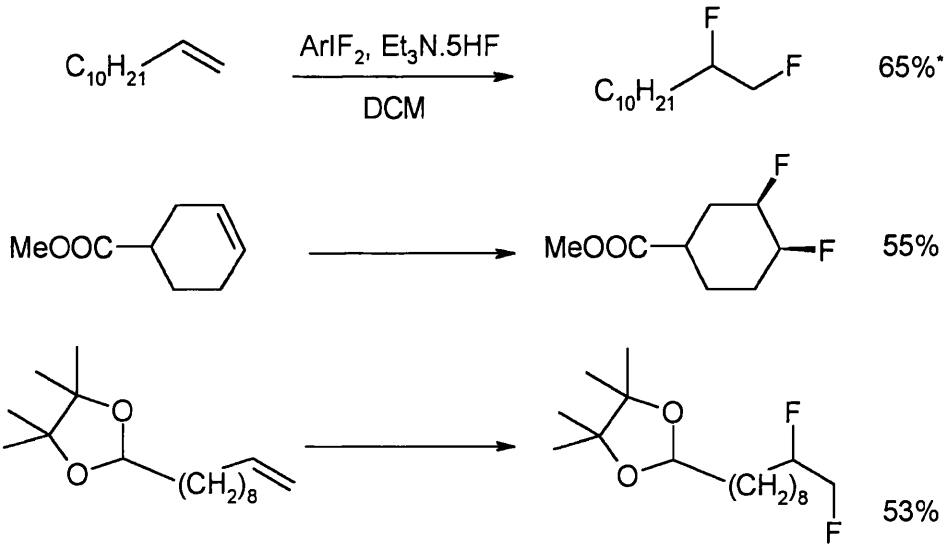
Difluoroiodo(*p*-t-butyl)benzene has been used in the "pretence" electrophilic fluorination of dienamines.[12] Motherwell found that treatment of the steroidal dienamine (26) with the difluoroiodoarene gave the thermodynamically less stable 6β-fluoride (27) in low yield. Considering the potential of (26) to act as a one electron donor, a variety of electron transfer catalysts were screened to improve the procedure. Addition of two equivalents of methyl viologen was indeed found to be beneficial, with fluorides (27) (21%), (28) (8%) and (29) (13%) being formed indicating 55% of the difluoroiodoarene had been involved in fluorination (scheme 11).



Scheme 11

An electron transfer chain pathway was advocated to account for the results, with methyl viologen acting as a mediator.

More recently Hara and co-workers have studied the fluorination of alkenes using DFIT.[13] They reported that terminal olefins could be vicinally fluorinated with DFIT in the presence of $Et_3N.5HF$. The reaction was quite general tolerating the ester, chloro and hydroxyl functionalities, and in one instance a cyclohexene derivative was successfully fluorinated (scheme 12).



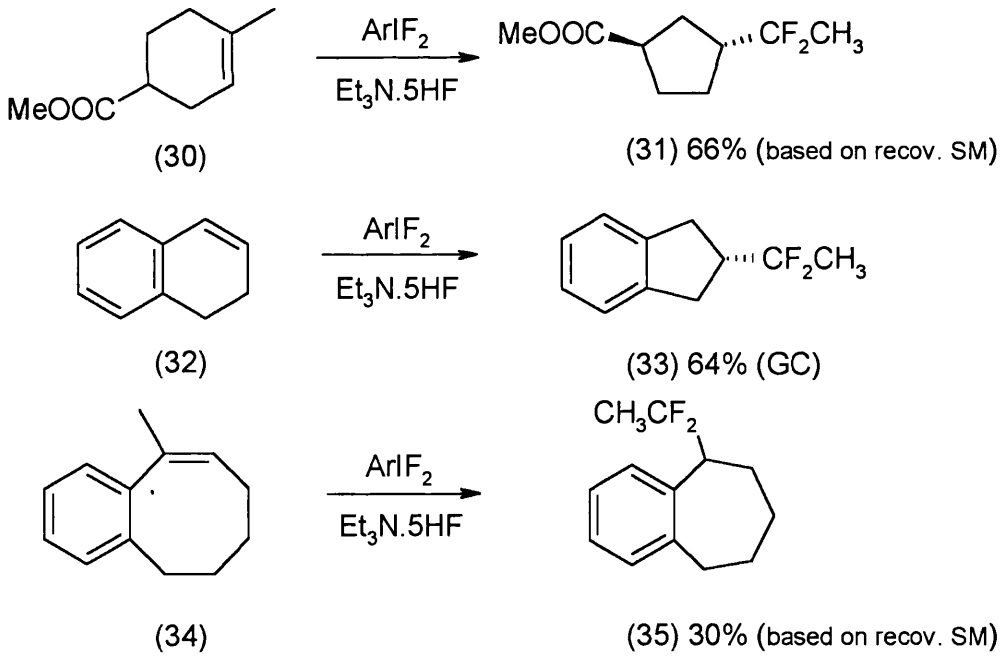
*All yields based on recovered SM

Scheme 12

The reaction was entirely ineffective in the absence of $Et_3N.5HF$ or in the presence of alternative triethylamine-HF mixtures such as the popular $Et_3N.3HF$. Reactions were conducted in teflon vessels.

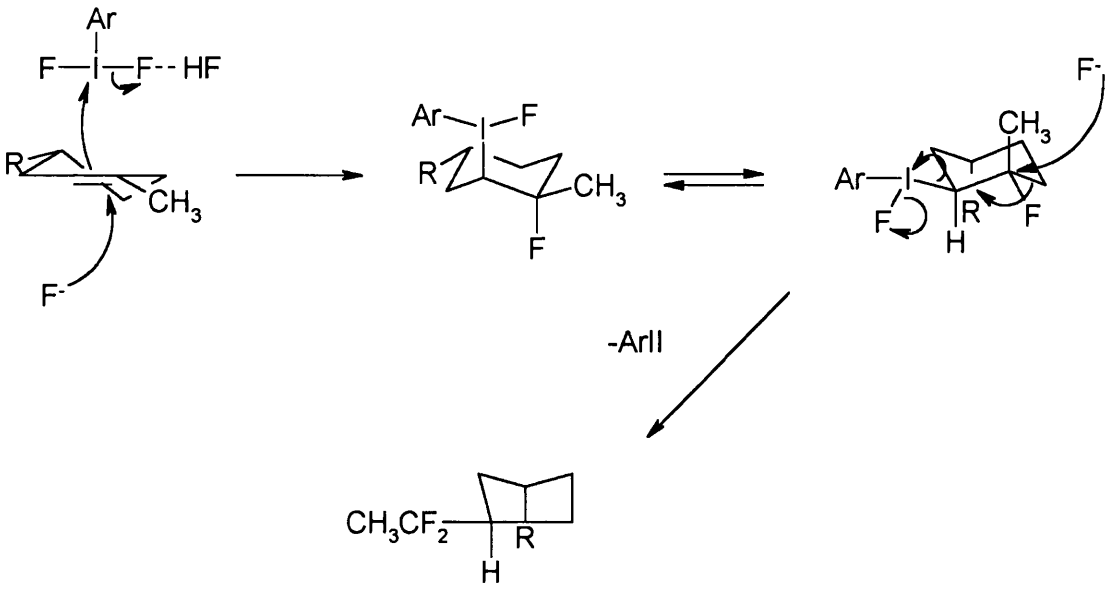
Hara proposed the familiar electrophilic addition mechanism to rationalise the reaction followed by a fluoride displacement of the iodo moiety to introduce the second fluorine atom. The $Et_3N.5HF$ was considered to be a simple source of HF to activate DFIT.

When methyl-substituted cyclic olefins were treated with DFIT and $Et_3N.5HF$ exclusive fluorinative ring-contraction was observed.[14] Methyl-4-methyl-3-cyclohexene-1-carboxylate (30) gave methyl 3-(1,1-difluoroethyl)cyclopentane-1-carboxylate (31) selectively with no trace of the *gem*-difluorocyclohexane resulting from methyl migration. The ester group in the 4-position and the difluoroethyl group were exclusively *trans* (scheme 13). The reaction was applicable to certain unsubstituted cycloalkenes when a benzene ring was fused (32). Cyclobutane derivatives could not be obtained from 1-methylcyclopentane or indene derivatives



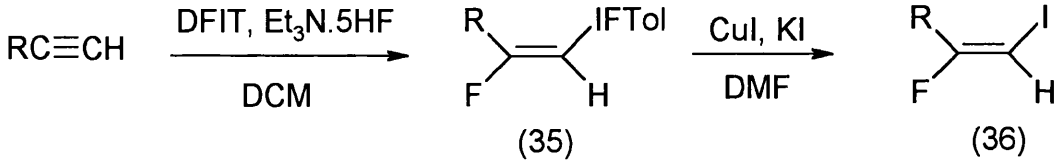
Scheme 13

Trans-diaxial addition of activated DFIT and fluoride across the olefin followed by the *trans*-coplanar migration shown leads to ring contraction and accounts for the observed product stereochemistry (scheme 14).



Scheme 14

Alkynes were also found to be suitable substrates for the DFIT and $Et_3N.5HF$ system.[15] The fluorinating agent was prepared *via* anodic oxidation of iodotoluene in $Et_3N.5HF$ using a divided teflon cell. The resulting $Et_3N.5HF$ solution of DFIT was used directly, alk-1-ynes were stereoselectively converted to *E*-(2-fluoroalk-1-enyl)(4-methyl-phenyl)iodonium fluorides (35), which could be isolated and characterised. Iodination of (36) then provided the *E*-2-fluoro-1-iodoalk-1-enes, a novel approach to the pharmacologically important vinyl fluoride moiety (scheme 15).



Scheme 15

1.2 Polymer-Supported Difluoroiodoarenes

The chief advantage of a polymer-supported difluoroiodoarene is the simplicity of work-up and purification. The iodoarene produced from solution fluorinations can be difficult to remove from non-polar products by chromatography. With the polymer-supported version the separation procedure is reduced to filtration of the polymeric iodobenzene from the reaction products. To this end Zupan iodinated 'pop-corn' polystyrene with iodine and iodine (V) acid for 160hr at 110°C.[9,10] Elemental analysis

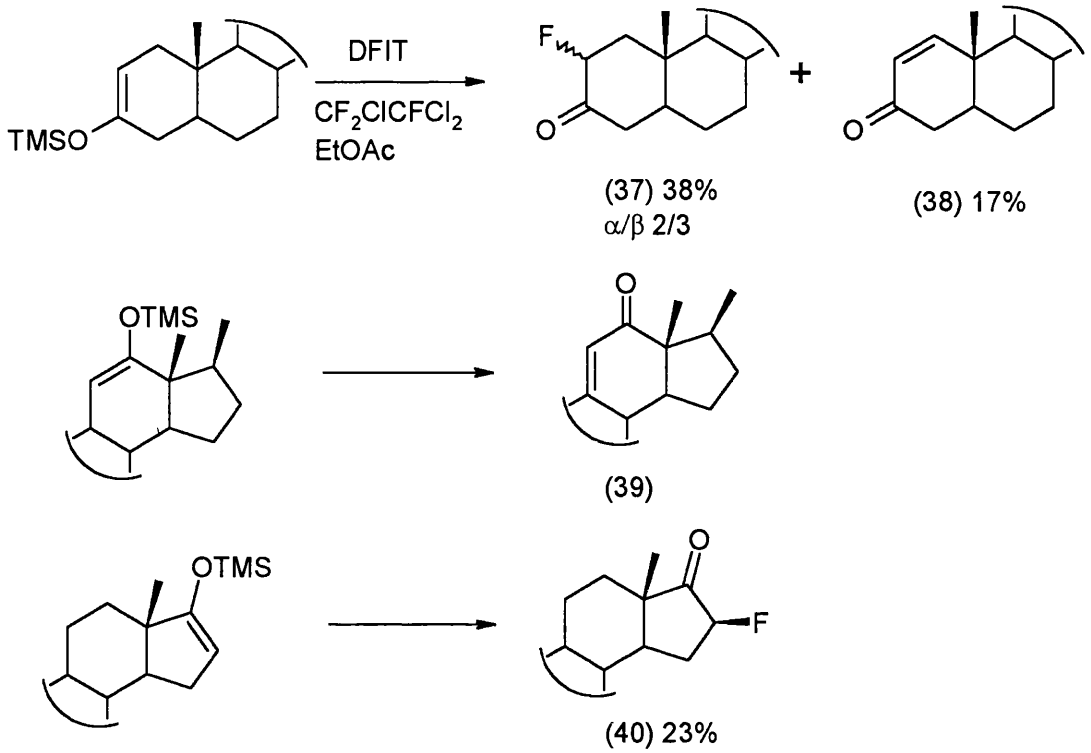
suggested that approximately one-third of the phenyl rings were iodinated. Reaction with xenon difluoride in the presence of HF in DCM gave the polymeric difluoride. He assessed the quantity of active fluorine through iodometry, estimating that 75-90% of iodobenzene had been converted into the difluoride. Adding considerable excess of xenon difluoride was found to be detrimental due to aryl ring fluorination, optimum conditions were established as 2.4mmol XeF_2 per gram of the polymer support. Cross-linked polystyrene containing 2% divinylbenzene was not as good a support. Xenon difluoride treatment of the appropriate iodide resulted in polyaryliododifluoride containing only one-half of the amount of active fluorine relative to the 'pop-corn' polystyrene case.

When applied to the geminal difluorination of phenyl-substituted olefins yields were uniformly excellent, 1,1-diphenylethene being fluorinated in 96% yield. Following purification the polymeric iodobenzene could be re-used several times.

Aside from one other application to the norbornene case (*vide supra*) there have been no other reports of fluorinations using this promising reagent. The high cost of xenon difluoride that appears to be essential[11] for the polymer preparation could be the principal sticking point.

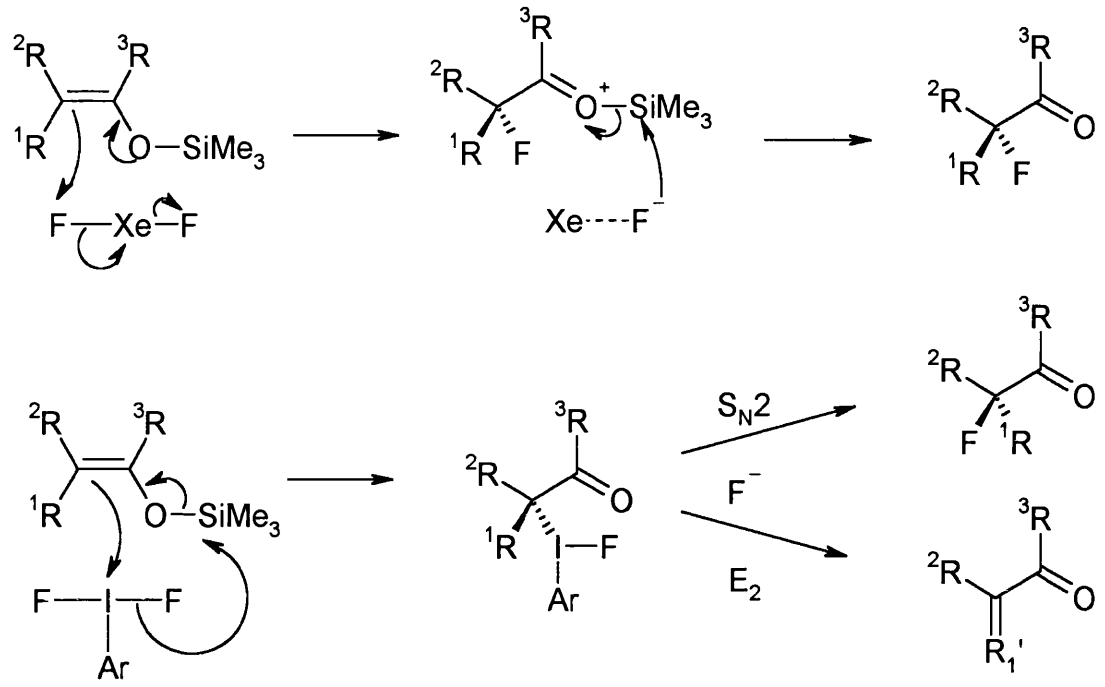
1.3 α-Fluorination of Carbonyl Compounds

Tsushima studied the α-fluorination of silyl enol ethers using xenon difluoride and DFIT.[16] Treating various steroidal silyl enol ethers with DFIT in the absence of any catalyst gave α-fluoro products in low yield (scheme 16 (part structures)).



Scheme 16

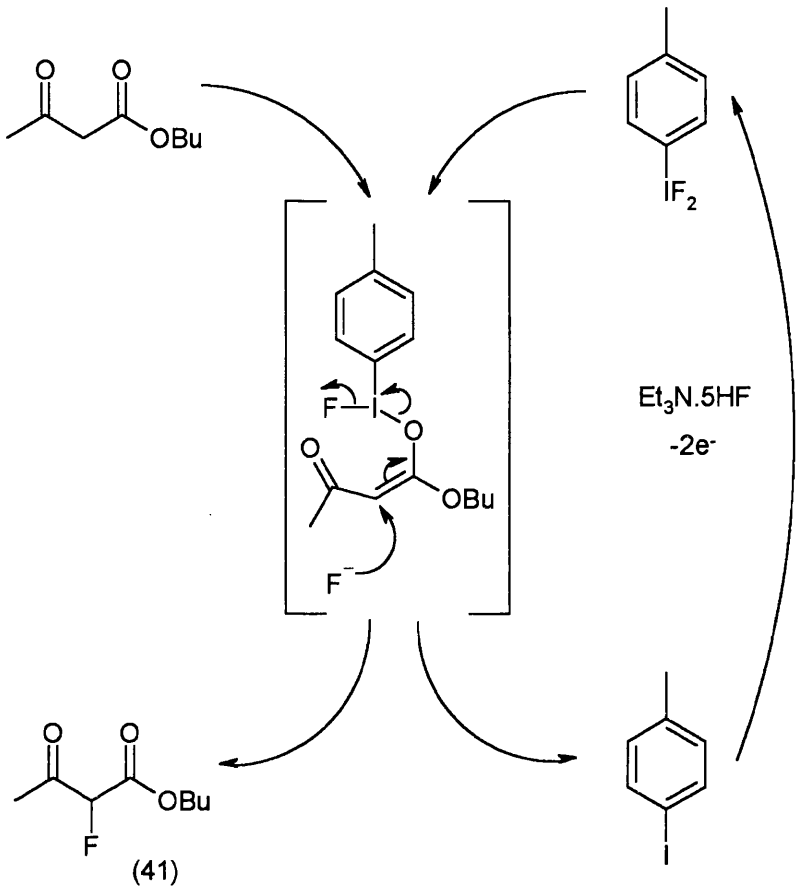
There was a marked preference for the β-orientated fluorides either through kinetically-controlled addition or subsequent enolisation and protonation from the less hindered face. The reaction was observed to be very sluggish at sterically hindered centres and elimination products such as (39) displaced fluorination. In contrast the reactions using xenon difluoride produced the sterically less hindered α-orientated fluorides cleanly and in good yields. The divergence in product stereochemistry clearly points to two separate fluorination mechanisms. Tsushima proposed an electrophilic fluorination mechanism for xenon difluoride, although current opinion favours a SET pathway;[80] and a mechanism involving an iodonium ion intermediate and subsequent S_N2 displacement with fluoride or β-proton loss for the reaction with DFIT (scheme 17)



Scheme 17

Hence xenon difluoride is a source of electrophilic fluorine and DFIT a nucleophilic source. The authors noted that molecular oxygen had no effect on either reaction, ruling out any radical pathways.

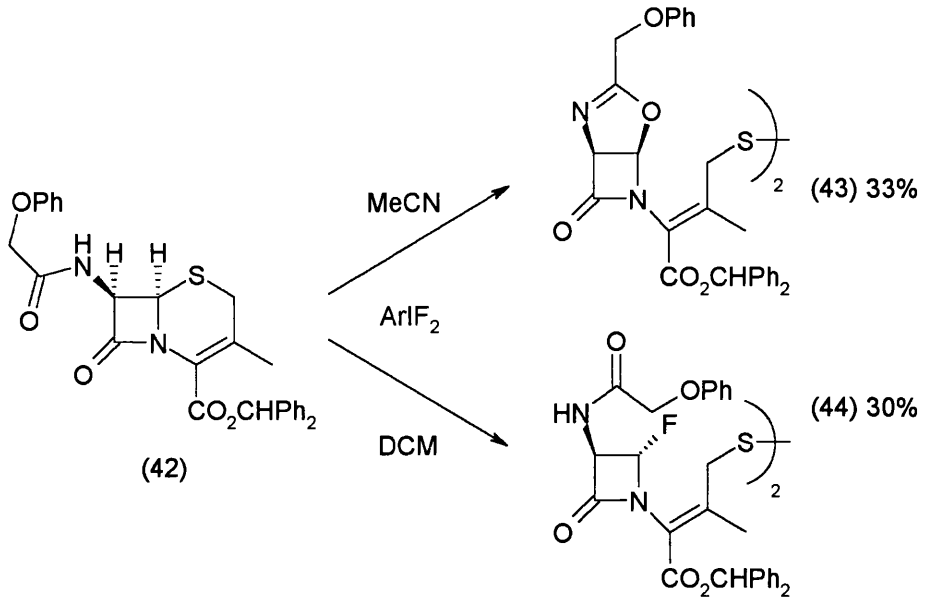
The selective fluorination of β-ketoesters using DFIT under HF catalysis has been reported.[17] Yields of α-fluoroketoesters were good for simple cases, substitution at the α-position giving poorer results. Many amine-HF complexes gave effective results but py-9HF (Olah's reagent) was found to be the best, whilst the uncatalysed reaction was completely ineffective. The reaction could be performed electrochemically with DFIT acting as an 'in-cell mediator'. Accordingly electrolysis of a 1:1 mixture of iodotoluene and butyl-3-oxobutanoate in $Et_3N.5HF$ in an undivided cell under constant potential gave 2-fluoro-3-oxobutanoate (41) in 79% yield based on recovered SM. The reaction took place at relatively low oxidation potential and iodotoluene is indispensable for the fluorination (scheme 18).



Scheme 18

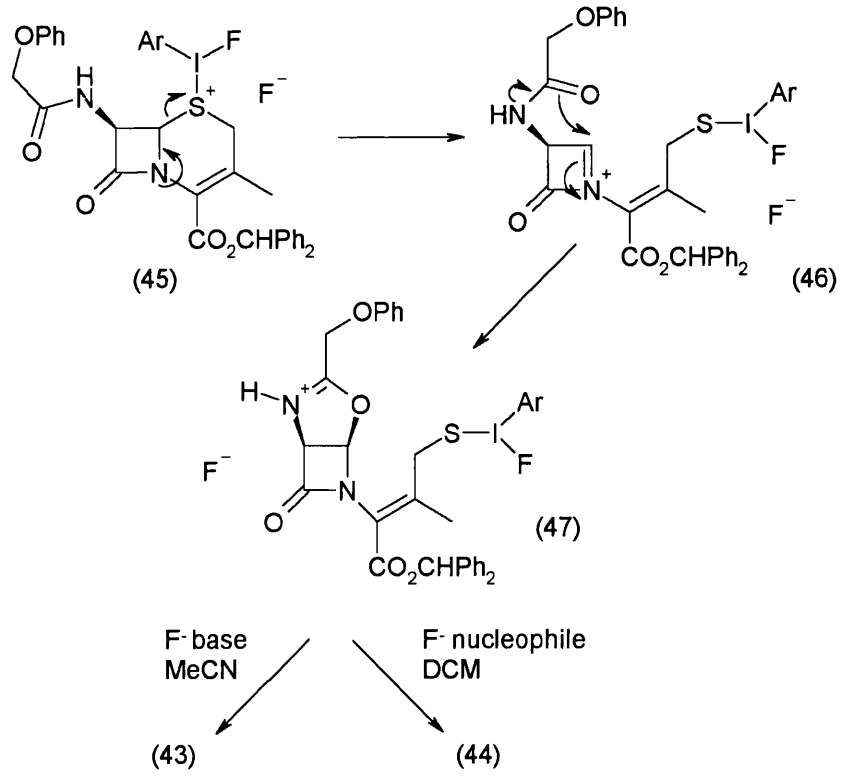
1.4 Fluorination of Sulfur-Containing Functional Groups

Motherwell has investigated the fluorination of cephalosporin V esters with difluoroiodo(4-*t*-butylbenzene).[18] Given the affinity for sulfur exhibited by dichloroiodobenzene in the oxidation of penicillin derivatives, an analogous thiophilic interaction may be expected for the difluoroiodoarene case.[100] In the event, treatment of the cephalosporin (42) with one equivalent of difluoroiodo(4-*t*-butylbenzene) in acetonitrile gave oxazoline (43) as the only product. Switching to DCM however produced the fluoro-azetidinone disulfide (44) (scheme 19).



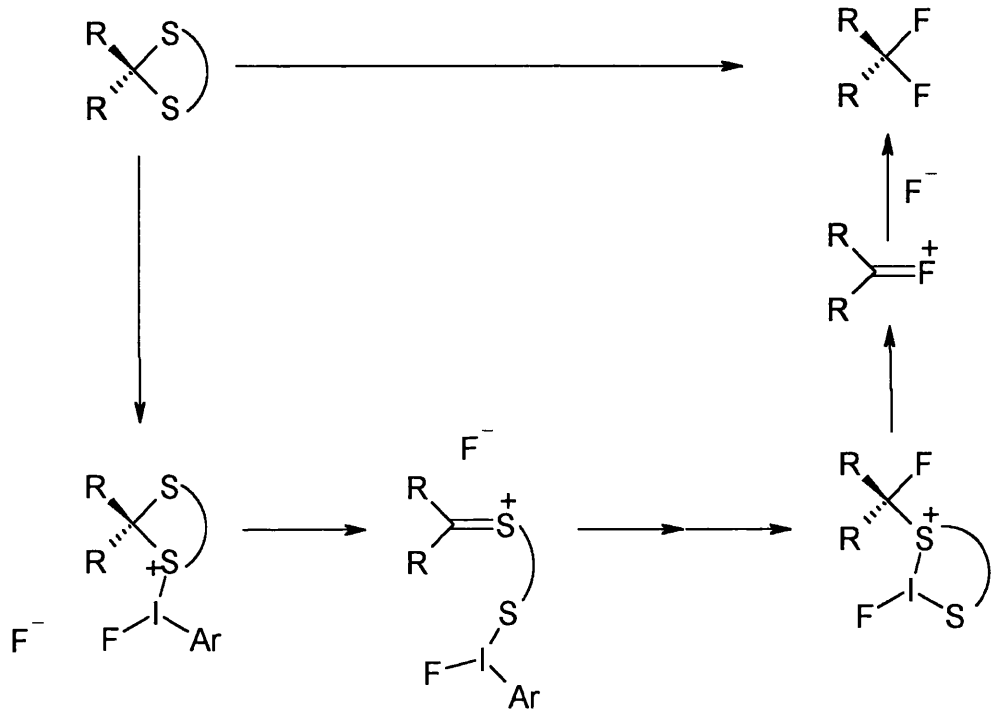
Scheme 19

Mechanistically, an initial coordination to sulfur through nucleophilic attack on electrophilic iodine gives (45). Ring opening *via* the acyl iminium species (46) leads to intermediate (47). The increased basicity of fluoride in acetonitrile allows deprotonation of (47) producing the oxazoline (43). Nucleophilic fluoride in DCM forms the fluoroazetidinone (44) (scheme 20).



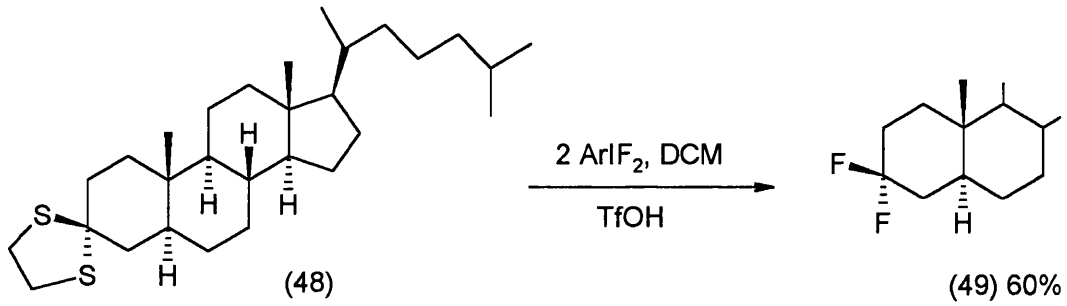
Scheme 20

Having established the thiophilic character of the difluoroiodoarenes Motherwell then examined the fluorination of dithioketals with difluoroiodotoluene.[19] Such a procedure represents a novel indirect synthesis of the *gem*-difluoro group from carbonyl compounds, a transformation most often achieved using DAST. The transformation involves sequential formation of two carbocations, stabilised first by sulfur and then by fluorine, each in turn being quenched with fluoride. Katzenellenbogen's fluorodesulfurisation of thioketals with py.9HF / DBH[20] and Stork's conversion of dithioketals to ketones using iodobenzene diacetate in aqueous methanol[21] both operate by similar mechanisms (scheme 21).



Scheme 21

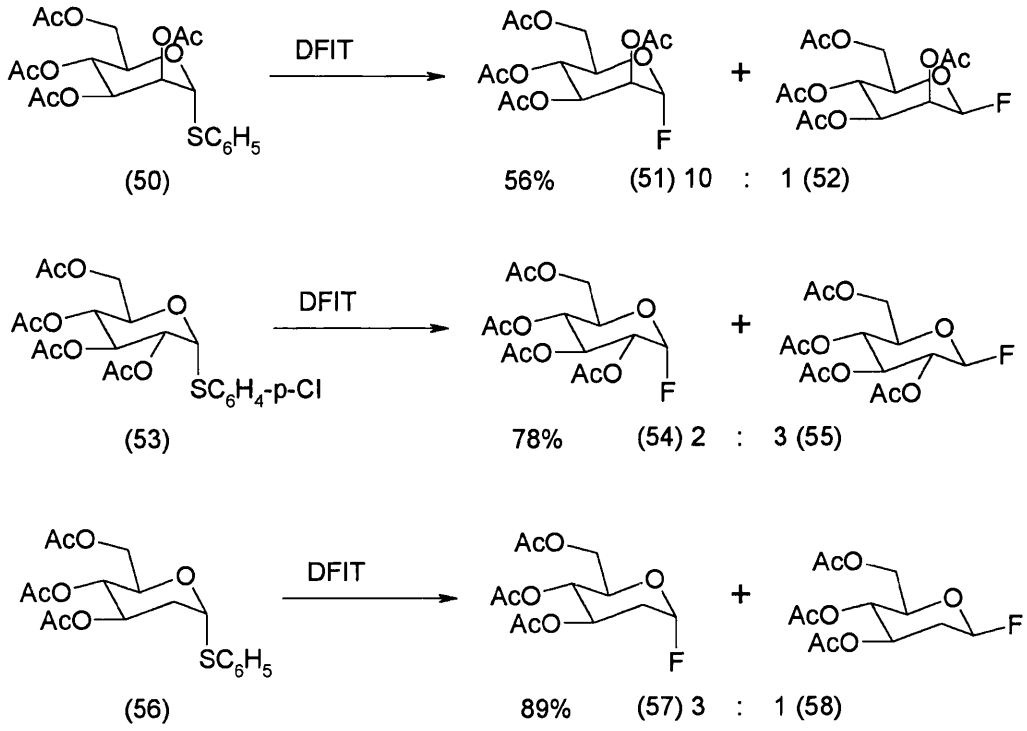
Dithioketals derived from diaryl ketones gave the *gem*-difluorocompounds in good to excellent yields with the dithiolane derivatives giving higher yields than the dithianes. At least two molar equivalents of DFIT were required for efficient conversion although in theory both fluorine atoms in the product could be derived from a single molecule of reagent. Applications to aliphatic and alicyclic thioketals were generally not successful, reflecting the requirement for carbocation stabilisation in the reaction. The cholestane derivative (48) was difluorinated successfully, although the addition of triflic acid was essential to prevent the formation of elimination products (scheme 22).



Scheme 22

Fuchigami has also reported the fluorination of dithioketals derived from benzophenones.[22] He synthesised *p*-nitro and *p*-methoxybenzene iododifluorides *via* an electrochemical method and found them to be effective *gem*-difluorination reagents. Performing the entire fluorination electrochemically in $Et_3N.3HF$ with catalytic iodotoluene mediating the reaction (*vide supra*) gave difluorinated products in excellent yield.

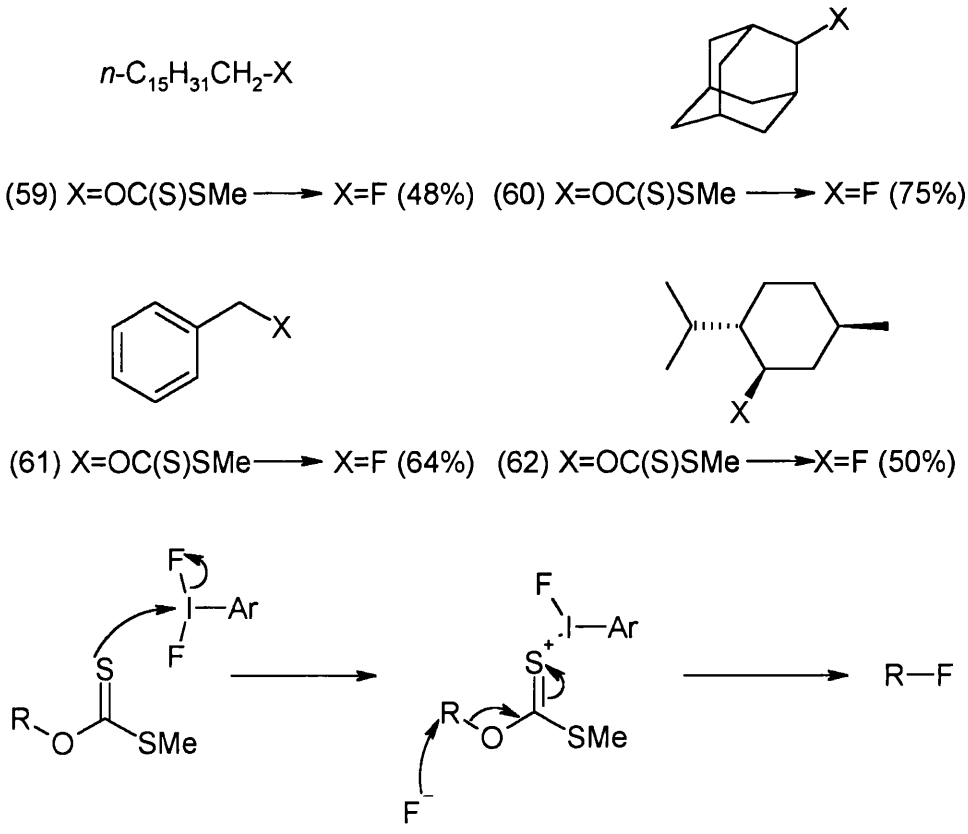
Synthesis of fluorogylcosides from thioglycosides can be achieved using DFIT.[23] Fluoroglycosides are important for stereoselective glycosylations as well as being useful probes for biological mechanisms of action in their own right.[176] Fluorination of arylthioglycosides with one equivalent of DFIT afforded a range of fluoroglycosides in good yield (scheme 23)



Scheme 23

Reactions generally proceeded with neighbouring-group participation to give mixtures of the axial and equatorial fluorides. In cases where NGP would be negligible such as the 2-deoxy-glucopyranose (56), fluorination with inversion *via* an S_N2-like mechanism was observed. Modification of the aromatic portion of the thioglycoside improved the process, fluoroglycosides were formed in significantly higher yields from the *p*-chloro-phenylthioglycosides (53). The reaction was extended to phenylselenoglycosides, with fluoroglycosides being formed in moderate yields. In contrast to the thioglycoside series there was a tendancy for S_Ni-like retention in the absence of neighbouring-group effects. The alcohol to fluoride transformation is a useful approach to organofluorides and is frequently accomplished using DAST. Motherwell has published an alternative procedure using xanthate esters, which are easily made from alcohols.[24] Fluorination using thiophilic DFIT then furnishes the required alcohol. The disadvantage of the extra step is counterbalanced by the mild, non-toxic character of the fluorination.

Xanthates derived from simple primary, secondary and benzylic substrates are fluorinated in moderate-to-good yield using ordinary laboratory glassware (scheme 24)



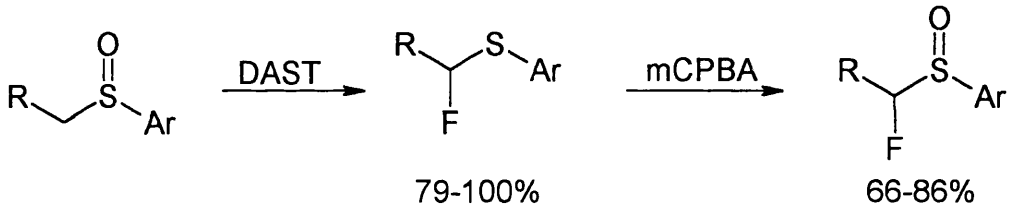
Scheme 24

Activation of the thiocarbonyl moiety by DFIT forms a leaving group capable of displacement by the concomitantly liberated fluoride.

Chapter 2. The Fluoro-Pummerer Reaction

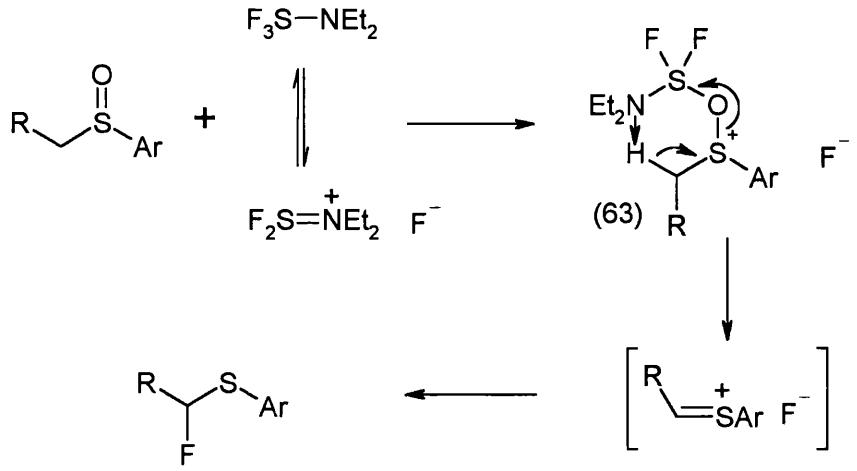
2.1 DAST

In 1985 McCarthey introduced the Fluoro-Pummerer reaction,[25] reasoning that DAST should react with sulfoxides as does acetic anhydride in the Pummerer rearrangement[26]. He found that treating methyl phenyl sulfoxide with DAST in chloroform at room temperature for 24hr and then at 50°C for several hours gave an 85% yield of fluoromethyl phenyl sulfide. As α-fluoro sulfides are at the carbonyl oxidation level, they are analogous to thioacetals and are sensitive to acidic conditions. Similarly they are relatively stable to basic conditions. Hence the fluorinated products were isolated only after conversion to the corresponding stable sulfoxide or sulfone derivative (scheme 25).



Scheme 25

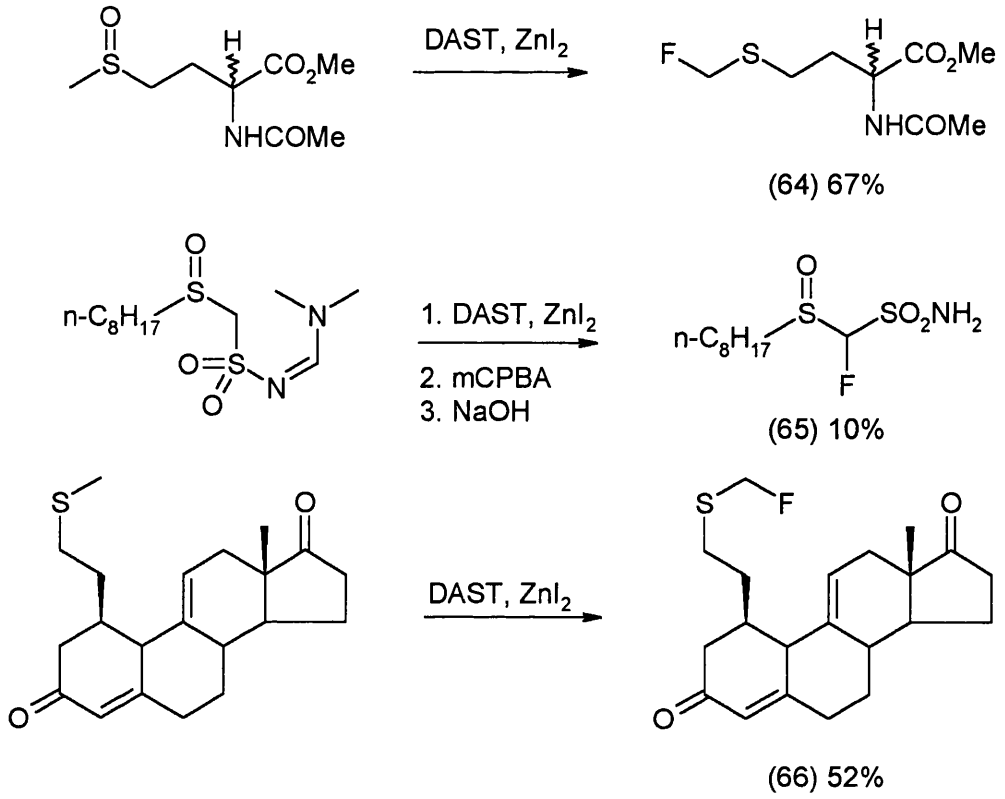
The transformation was compatible with a number of functional groups including nitriles, esters, amides and ethers. Two important observations were made concerning the rate of reaction. Firstly, the introduction of a *p*-methoxy group on the aryl ring resulted in a dramatic rate increase. Secondly it was found that a Lewis acid, notably ZnI_2, catalysed the reaction. Given that the thermal instability of DAST precludes strong heating[27], catalysis is essential for sluggish reactions. McCarthey proposed a mechanism similar to that of the Pummerer rearrangement to account for these facts (scheme 26).



Scheme 26

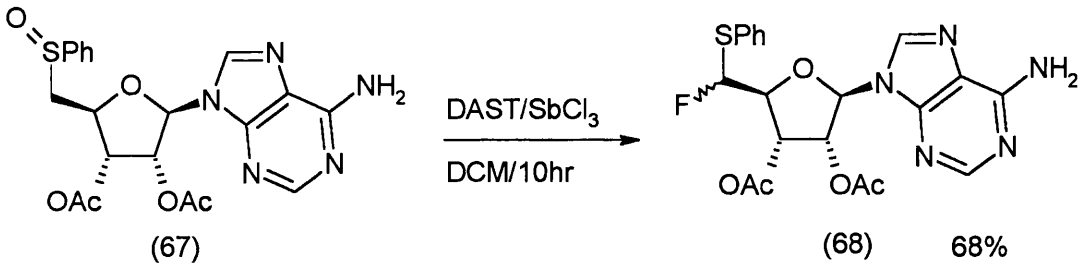
Initial rate determining addition of DAST to the sulfoxide is consistent with the observed increase in rate for the *p*-methoxyphenyl alkyl sulfoxides over the phenyl analogues. The six-membered transition state (63) in which nitrogen acts as a base explains the regioselective formation of fluoromethyl ethyl sulfide from methyl ethyl sulfoxide as a result of steric considerations. The catalytic effect of ZnI_2 can be understood by the formation of a reactive sulfiminium cation from DAST. Alternative approaches to fluoromethyl phenyl sulfoxide involved treating chloromethyl phenyl sulfoxide with rigorously dried potassium fluoride and 18-crown-6 in acetonitrile at reflux for several days.[28] The Fluoro-Pummerer reaction thus offers a considerably more convenient and shorter route to this useful reagent.

The DAST-mediated Fluoro-Pummerer reaction has since been employed in the syntheses of fluorinated methionines (64),[29] inhibitors of carbonic anhydrase (65)[30] and steroidal aromatase inhibitors (66)[31] (scheme 27).



Scheme 27

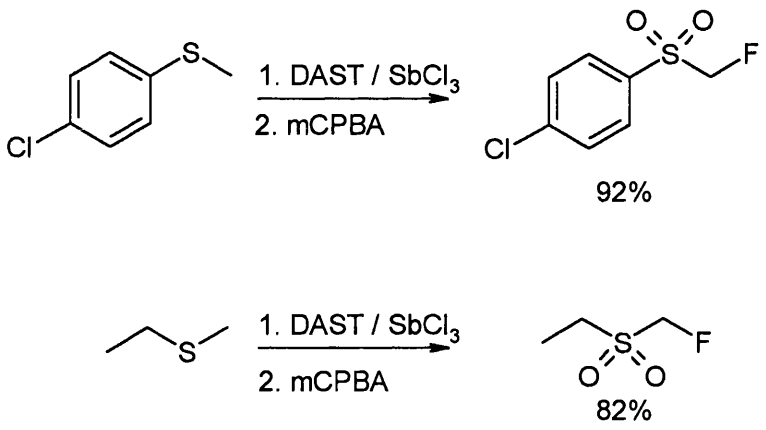
In the course of a synthesis of fluorinated arylthioadenosine analogues designed to inhibit the *S*-adenosylmethionine cycle, Robbins experienced difficulties in applying the McCarthey Fluoro-Pummerer protocol.[32] Addition of DAST / ZnI_2 resulted in highly predominant deoxygenation at sulfur, without any fluorination. Similar problems were reported in the attempted Fluoro-Pummerer reaction of protected methylthioadenosine sulfoxides. Finch and co-workers experienced difficulties with the reproducibility of fluorination yields using DAST / ZnI_2 in the fluorination of methyl phenyl sulfoxide, deoxygenation again being the main problem.[33] Noting that a similar reduction of sulfoxides using sodium iodide and boron trifluoride had been reported,[34] Robbins found that results could be significantly improved through the replacement of ZnI_2 with the alternative Lewis acid $SbCl_3$. Attempted fluorination of thioadenosine (67) with DAST / ZnI_2 in DCM gave the required fluorinated products in low yield plus deoxygenated material. DAST / $SbCl_3$ provided rapid reaction with minimal side-product formation (scheme 28).



Scheme 28

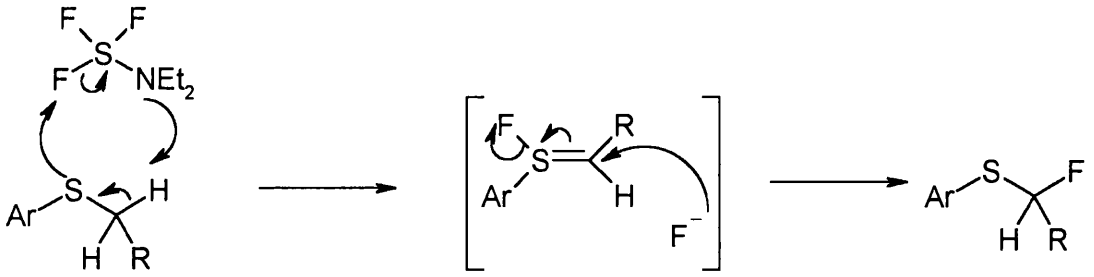
When applied to the fluorination of methyl phenyl sulfoxide the antimony(III) halide catalysis proved superior in all respects to the ZnI_2 / DAST system: cleaner, more reproducible and faster reactions.

The scope of the reaction was extended further when Robbins reported the efficient conversion of thioethers to α-fluoro thioethers with the DAST / $SbCl_3$ system, rendering the oxidation of thioethers to sulfoxides unnecessary.[35] Thioanisole was quantitatively converted to fluoromethylthiobenzene in 4hr at ambient temperatures. The antimony Lewis acid exerted less dramatic catalysis of the thioether process relative to its acceleration of the Fluoro-Pummerer reaction. The transformation works well even with deactivating groups such as *p*-chlorophenyl present, avoiding the use of expensive *p*-methoxyphenyl substrates as activators (scheme 29).



Scheme 29

Treatment of α-fluoro thioethers with DAST / $SbCl_3$ did not produce the expected α, α-difluoro thioethers, in contrast to XeF_2[36] or electrochemical[37] methods. A six-membered transition state (69) was postulated to account for the fluorination (scheme 30). Intramolecular 3-centred fluorine rearrangement or conjugate nucleophilic attack by external fluoride ion on (70) would produce the fluorides.



(69) (70) (71)

Scheme 30

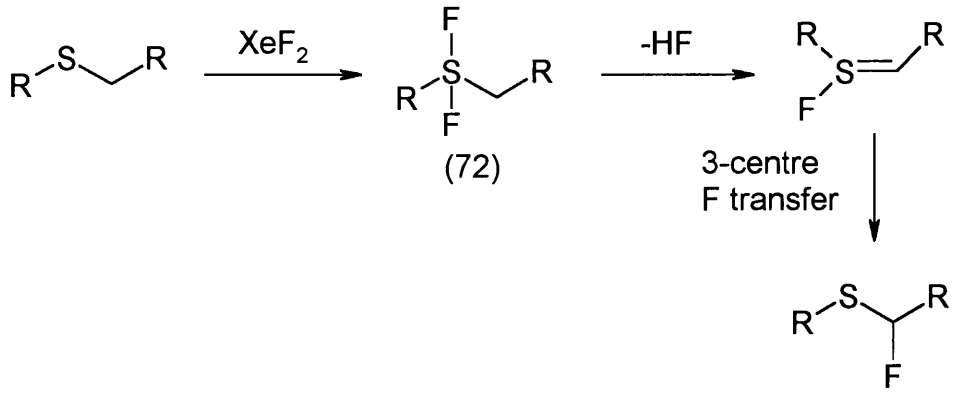
The formal nucleophilic addition to electrophilic fluorine is very unusual, as DAST is generally a source of nucleophilic fluoride.

2.2 Xenon difluoride

Xenon difluoride is a popular fluorinating agent of organic compounds.[38] It is a stable solid that is relatively easily manipulated, having the great attraction of affording in elemental xenon a highly volatile, inert co-product. The overriding disadvantage remains the high cost of purchasing the reagent from chemical suppliers.

The reaction of xenon difluoride with sulfides was first studied by Zupan, who treated methyl phenyl sulfide with a single equivalent each of xenon difluoride and hydrogen fluoride.[36] Fluoromethyl phenyl sulfide was produced in 67% yield. A further fluorination was also possible, accessing difluoromethyl phenyl sulfide. Janzen reported similar results with simple sulfides, in the absence of any HF catalysis.[39] Phenyl isopropyl sulfide, for example, was monofluorinated in >90% yield with xenon difluoride at -10°C. Thiophene and thiols were not good substrates for the reagent. Hexamethyldisilazane was found to be a useful addition to the reaction, removing the liberated HF which could decompose the acid labile α-fluoro sulfides.

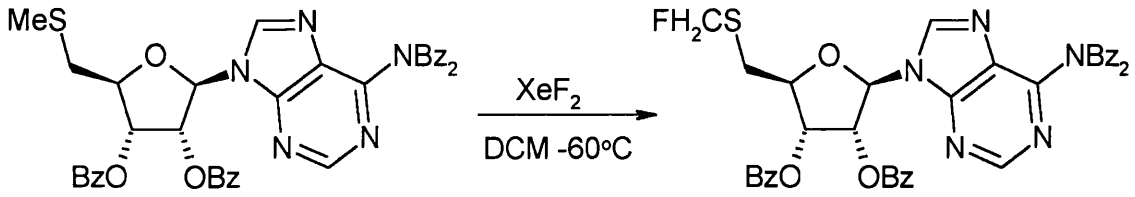
Given that diaryl sulfides undergo oxidative-fluorination to sulfur (IV) difluorides very efficiently with xenon difluoride, Janzen favoured a similar reaction as the first step in the aryl alkyl sulfide fluorination (scheme 31).



Scheme 31

Loss of HF from (72) followed by fluorine transfer *via* a 3-centre step gives the observed α-fluoro sulfide. It should be noted that Zupan failed to find any evidence of intermediate S-F compounds by ^{19}F nmr in this reaction.[36]

Following these two early reports the scope of the reaction has increased somewhat, with fluorinated biotin,[40] methionine[41] and cysteine[42] derivatives being prepared using this methodology. The reagent has proved particularly successful in the fluorination of methylthioadenosine nucleosides (*vide supra*). MTA (73) was regioselectively fluorinated in the methylthio position in good yield on treatment with xenon difluoride in DCM (scheme 32).[43] DAST-mediated Fluoro-Pummerer reaction of the sulfoxide derivative of (73) was reported to be highly variable, with time, temperature and DAST stoichiometry being critical factors.[32,44] The regioisomeric 5'-fluoro compound and reduced, unfluorinated sulfide (73) were extremely difficult to separate from the desired product (74).

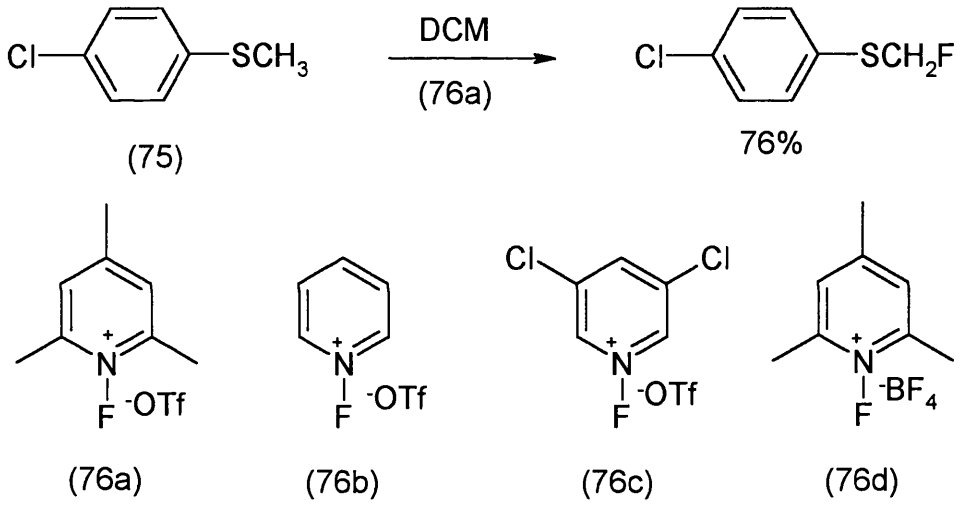


(73) (74) 70%

Scheme 32

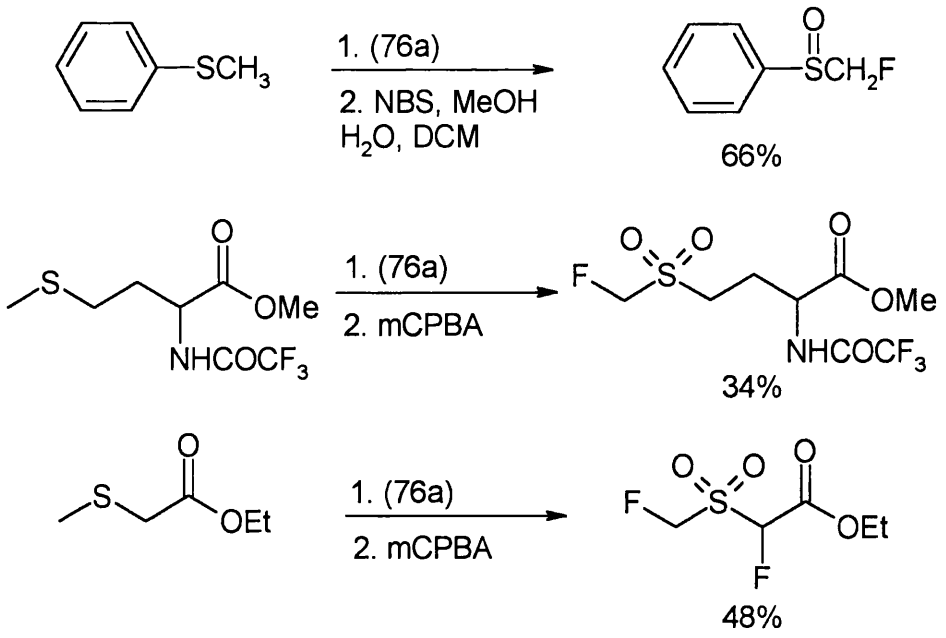
2.3 N-F Reagents

N-Fluoro-pyridinium salts are easily handled electrophilic fluorinating agents which have been shown to α-fluorinate sulfides.[45] A study of the fluorination of *p*-chlorophenyl methyl sulfide (75) with fluoropyridiniums (76a)-(76d) found (76a) to be by far the most effective, despite being the least reactive reagent (scheme 33). The triflic acid formed upon reaction is immediately trapped by the collidine which is simultaneously liberated. The relative failure of reagents (76b) and (76c) was proposed to be due to the relative acidic reaction conditions because of the lower basicities of pyridine and 3,5-dichloropyridine respectively.



Scheme 33

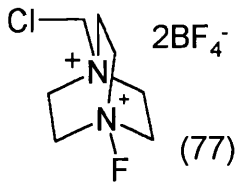
The reagent was effective in the fluorination of a range of alkyl and phenyl sulfides, giving moderate to good yields of the α-fluoro compounds (scheme 34). The *N*-fluoro salt (76a) was notable in successfully fluorinating dialkyl sulfides, methyl dodecyl sulfide, for example, was fluorinated in 44% yield.



Scheme 34

The authors postulated an initial oxidative-fluorination of the sulfur atom, in common with the mechanism proposed by Janzen for the reaction with xenon difluoride (*vide supra*). Monitoring the reactions by NMR however, again failed to provide any evidence in support of this proposal.

The *N*-fluoro derivatives of 1,4-diazabicyclo[2.2.2]octane known as Selectfluor reagents (77) are more recent homologations of the *N*-fluoro pyridinium reagents. Despite being generally more effective and easy to use than salts such as (76) they are not as good for Fluoro-Pummerer chemistry. Over a very similar set of substrates (77) produced the α-fluoro sulfides in consistently lower yields.[46]

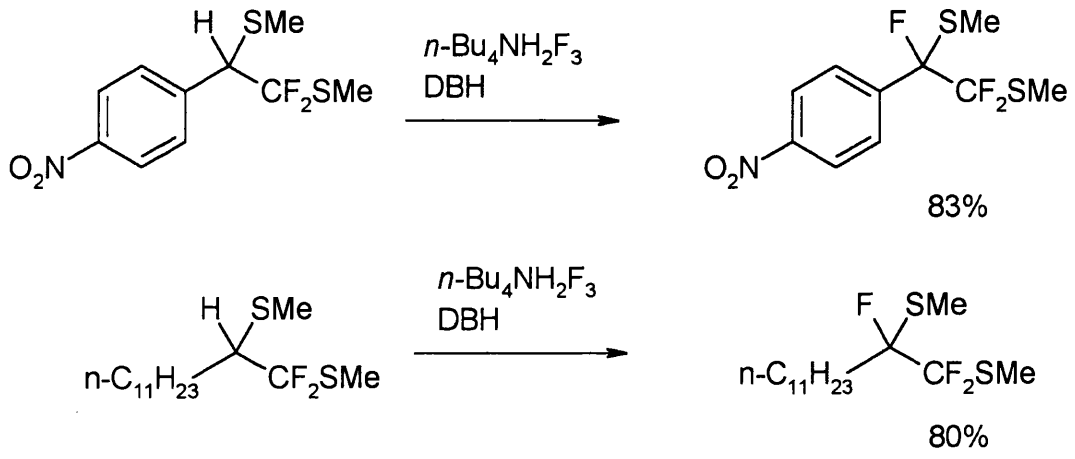


(77)

Selectfluor has found application in the α-fluorination of thioaryl-substituted nucleosides.[47]

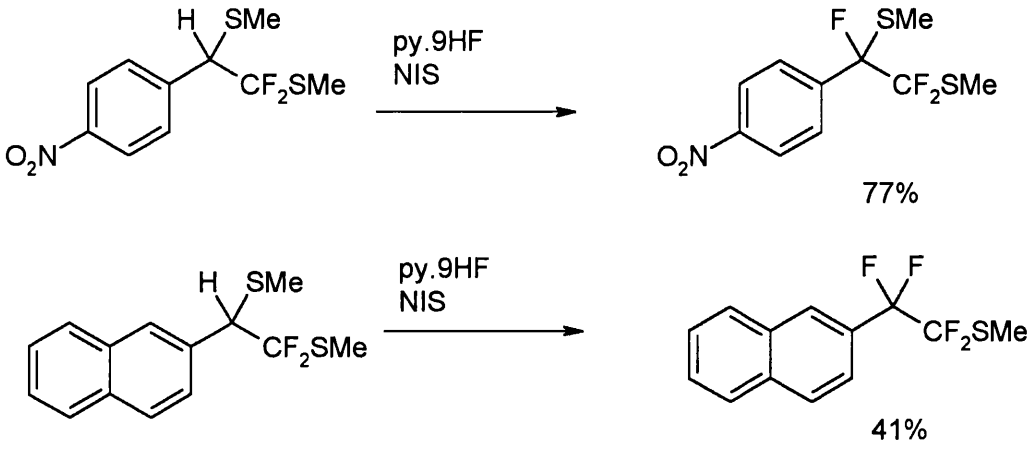
2.4 Tetrabutylammonium Dihydrogentrifluoride

Tetrabutylammonium dihydrogentrifluoride, n-$Bu_4NH_2F_3$ is a safe, stable and easy to handle solid that can be used in conventional glassware without any special precaution. In combination with an oxidant such as dibromohydantoin it was found to be an effective reagent for the α-fluorination of sulfides.[48,49] The reaction was optimised on the familiar range of thioanisole derivatives; p-cyanophenyl methyl sulfide reacted with 1.4eq of n-$Bu_4NH_2F_3$ and 1.4eq of DBH in DCM at room temperature for 20min affording fluoromethyl 4-cyanophenyl sulfide in 75% yield. Hiyama applied the reaction to a range of difluorosulfides and synthesised a range of trifluorosulfides (scheme 35)



Scheme 35

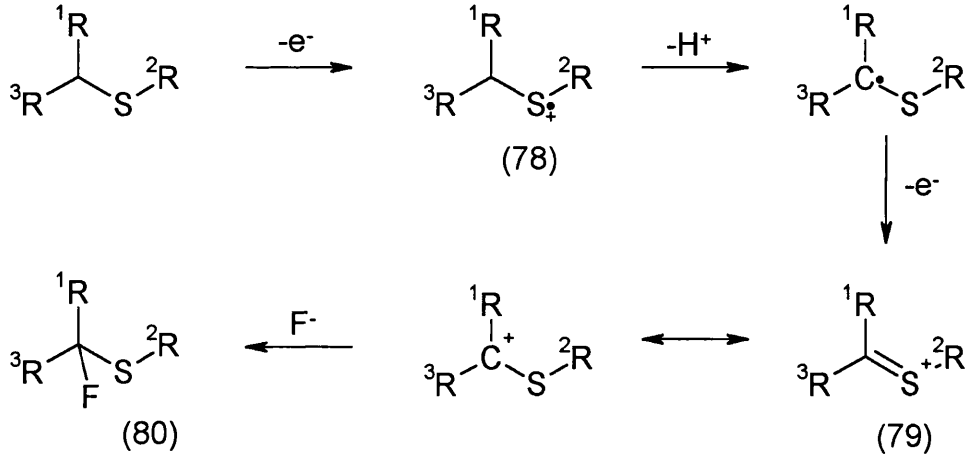
When py.9HF was employed for the fluorination in place of n-$Bu_4NH_2F_3$ Fluoro-Pummerer products were observed in some cases but desulfurisation-fluorination pathways were also found to operate (scheme 36). The py.9HF / DBH or NIS reagent combination is a well precedented technique for the desulfurisation-fluorination of thioketals in the synthesis of geminal difluorides.[20]



Scheme 36

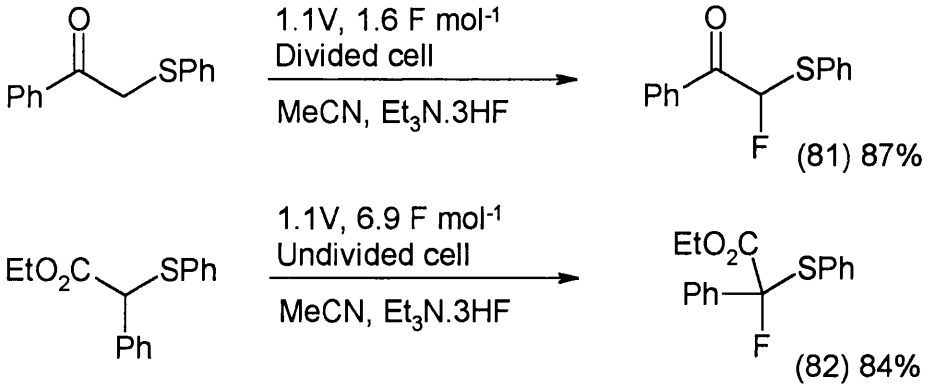
2.5 Electrochemical Generation of α-Fluoro Sulfides

The sulfonium ions generated in the Pummerer rearrangement can also be obtained through electrochemical oxidation.[50] If this reaction is carried out in the presence of fluoride ions then the formation of α-fluoro sulfides can be expected through the ECEC mechanism[51] shown in scheme 37.



Scheme 37

Laurent reported that the constant potential electrolysis of certain sulfides carried out on a platinum electrode in acetonitrile containing $Et_3N.3HF$ produced α-fluoro sulfides (80) in excellent yield (scheme 38).[52] Aliphatic substrates gave products resulting from predominant sulfide oxidation. The $H_2F_3^-$ anion is not basic enough to deprotonate the radical cation (78) leading to sulfonium ion formation unless electron-withdrawing groups are present to increase the α-proton acidity.

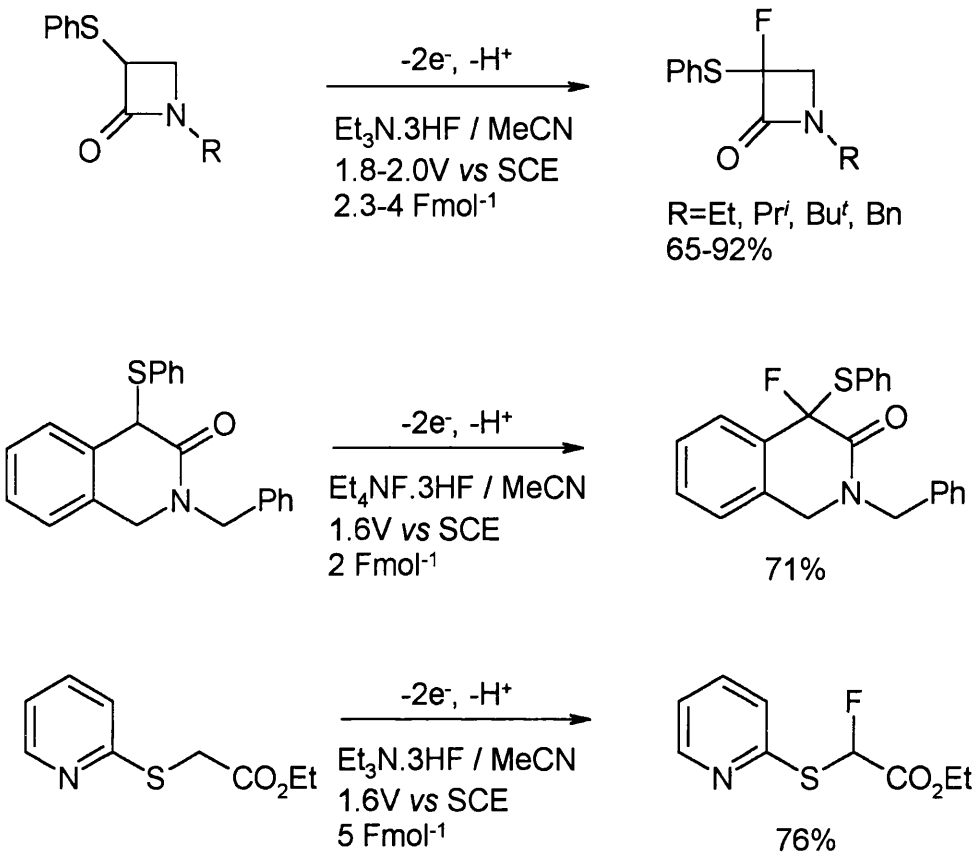


Scheme 38

A second fluorine atom could be introduced into (81) by increasing the potential during the electrolysis. Comparison against chemical oxidation using DBH and $Et_3N.3HF$ showed the electrochemical route to be more general and higher yielding.

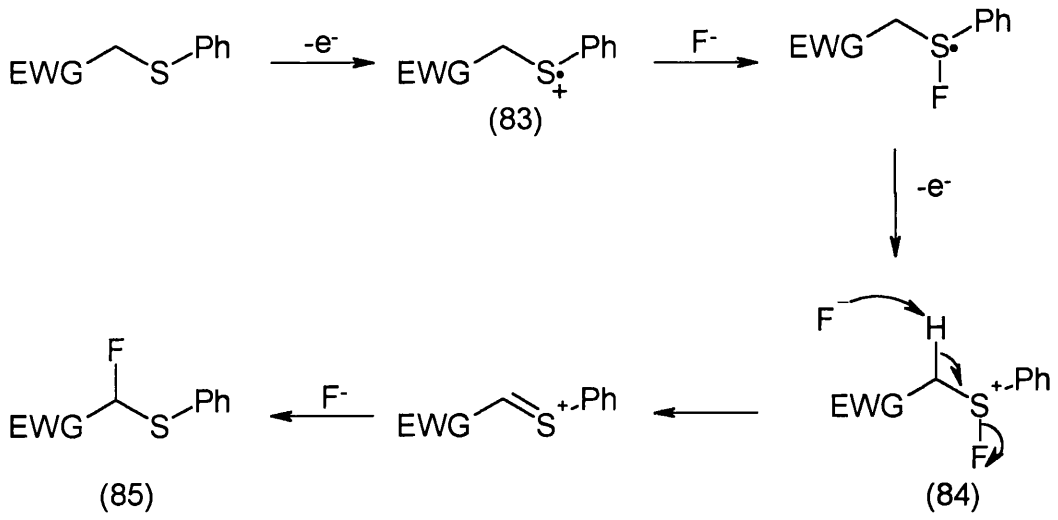
Almost simultaneously Fuchigami's group reported their results on the anodic monofluorination of sulfides.[53] In accordance with Laurent they found electron-withdrawing substituents in the α-position were essential for the success of the reaction and exemplified this in a wide range of fluoro-sulfide syntheses using $Et_3N.3HF$ in an undivided cell. Comparison with chemical methods, in this case with the effective Fluoro-Pummerer reagent *N*-fluoropyridinium triflate, again showed the electrochemical oxidation-fluorination procedure to be distinctly superior.

Following on from their initial report the Fuchigami group have rigorously exploited their electrochemical approach to the α-fluorination of sulfides[54-66], with many applications to pharmacologically important heterocycles (scheme 39).



Scheme 39

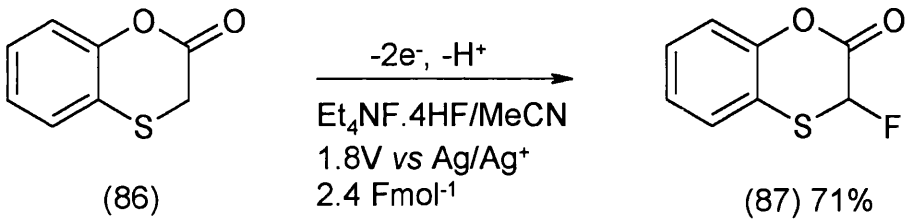
In certain cases the α-fluorination was observed to occur in the absence of any electron-withdrawing substituent. Thioanisole, for example, was monofluorinated in 50% yield in THF.[54] This contrasts with the failure of anodic methoxylation on similar unactivated substrates. As methoxylation is well established to proceed *via* ECEC pathways the mechanism of anodic fluorination may be different.[51] On this basis the authors proposed a Pummerer-type mechanism for anodic fluorination, in contrast to the conventional ECEC manifold initially suggested by Laurent (scheme 40).



Scheme 40

The trapping of the radical cation (83) with fluoride is postulated to suppress side reactions such as dimerisation, even when deprotonation is slow. Similar intermediates featuring the sulfur-fluorine bond have been postulated as intermediates in many Fluoro-Pummerer transformations.[35,39,45]

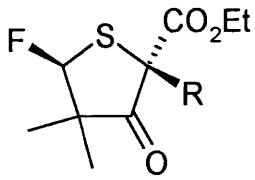
Optimisation studies have centred on the choice of supporting electrolyte that provides the fluoride anion source, with $Et_3N.3HF$ and $Et_4NF.3HF$ found to be generally effective. $Et_3N.2HF$ and py.9HF were much less efficient despite being more nucleophilic sources of fluoride. In some cases strong passivation of the anode was seen to occur. This problem can be partially alleviated through pulse electrolysis techniques, although more recent reports show that using $Et_4NF.4HF$ in place of $Et_3N.3HF$ entirely circumvents the problem. Attempted anodic monofluorination of the 3*H*-1,4-benzoxathian-2-one (86) in $Et_3N.3HF$ / MeCN gave a 5% yield of the expected fluoro derivative (87) owing to severe anode passivation.[67] Use of $Et_4NF.4HF$ produced (87) in good yield with no passivation and at a high current density (scheme 41). Anode passivation is believed to be a consequence of the free Et_3N present at equilibrium in the $Et_3N.3HF$ electrolyte.



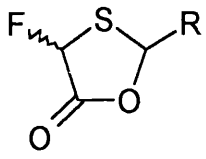
(86) (87) 71%

Scheme 41

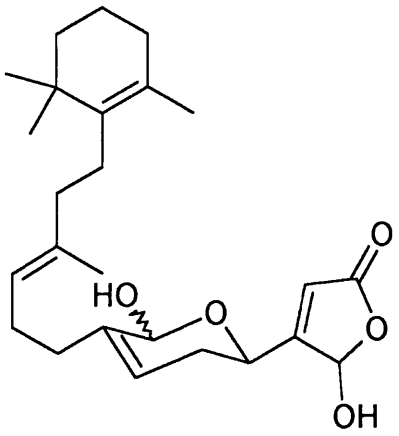
Fuchigami has synthesised a range of fluorinated 3-thiolanones (88) and 1,3-oxathiolanones (89) through the electrochemical Fluoro-Pummerer methodology and assayed their *in vitro* human type II phospholipase A_2 (PLA_2) inhibitory activity.[61,65]



(88)



(89)



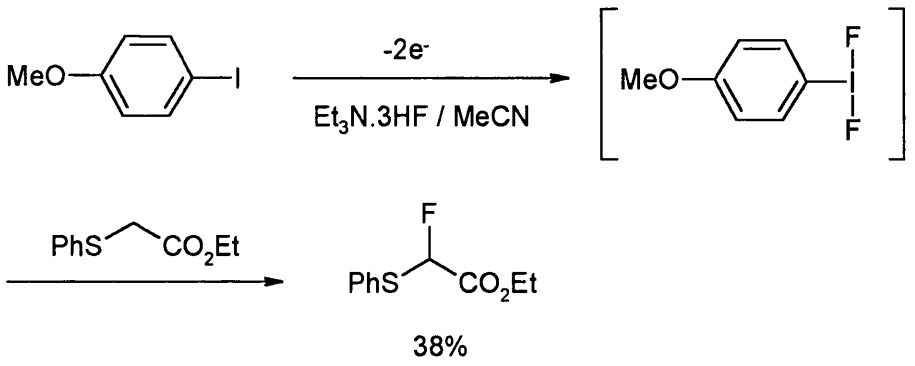
(90)

The PLA_2 isozyme family plays crucial roles in regulating diverse cellular responses, especially inflammation. The 3-thiolanone derivative (88) with R=Bn had an IC_{50} of 0.21μg/mL, an encouraging lead relative to the well known PLA_2 inhibitor manoalide (90) (IC_{50}=0.14-0.34μg/mL).

2.6 Difluoroiodoarenes

There is a single report concerning difluoroiodoarenes in the Fluoro-Pummerer reaction.[68] Fuchigami examined the reaction of anodically generated difluoroiodoarenes with ethyl 2-phenylsulfanyl acetate, a substrate that undergoes the electrochemical Fluoro-Pummerer reaction in high yield. *p*-Chloro and *p*-nitro substituted reagents were wholly ineffectual whereas difluoroiodo(*p*-methoxybenzene) gave the Fluoro-Pummerer product in moderate yield. The reaction involved electrolysis of a solution of *p*-methoxyiodobenzene in $Et_3N.3HF$ in a divided cell. The electrolytic solution was then added to the appropriate sulfide and stirred overnight. The reaction was slow, requiring two equivalents of fluorinating agent for reaction with substantial quantities of starting material being recovered. Benzylsulfanyl and alkylsulfanyl derivatives were studied, with the latter failing to undergo any fluorination. A mechanism was proposed involving nucleophilic attack of sulfur on iodine followed by deprotonation with

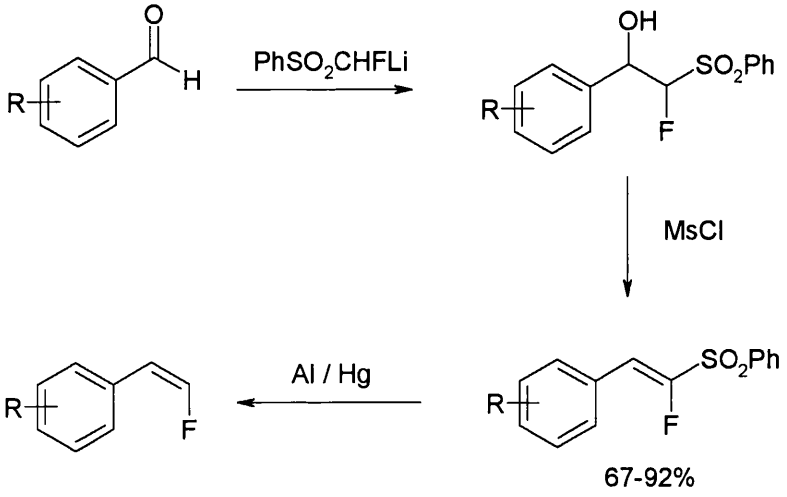
fluoride, in accordance with the generally accepted Fluoro-Pummerer scheme (*vide supra*). The supporting electrolyte, $Et_3N.3HF$ could also provide the basic fluoride source (scheme 42).



Scheme 42

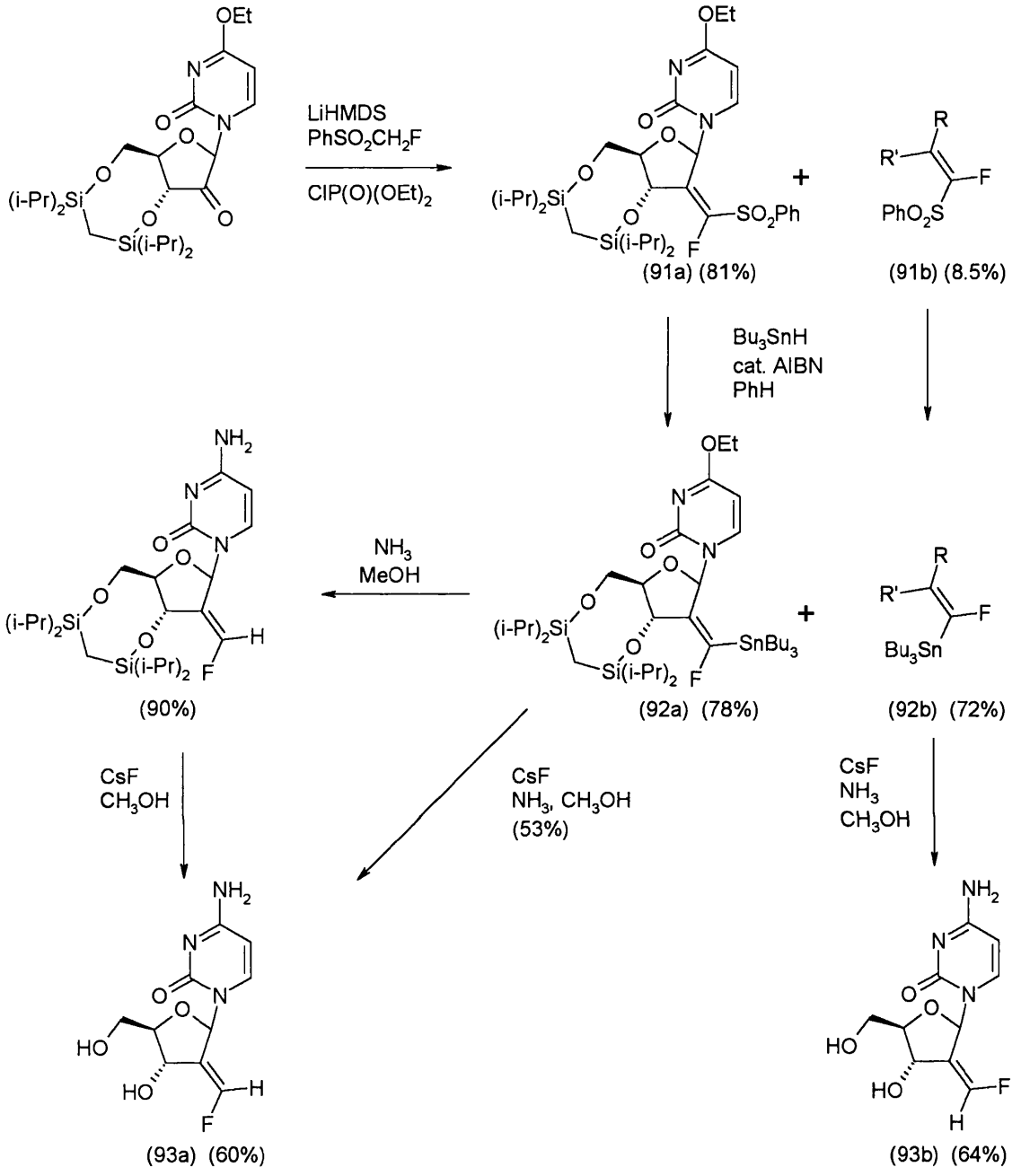
2.7 α-Fluoro Sulfides in the Synthesis of Vinyl Fluorides

The vinyl fluoride functionality is of particular importance in medicinal chemistry due to the prevalence of this group in a number of enzyme inhibitors.[69] Reutrakul first reported the alkylation of fluoromethyl phenyl sulfoxide and subsequent pyrolysis as a route to terminal vinyl fluorides.[70] McCarthey has synthesised fluoromethyl phenyl sulphone on a 30g scale through the fluoro-Pummerer reaction of phenyl methyl sulfoxide followed by oxidation with m-CPBA.[71] The reagent was demonstrated to be useful for the conversion of aromatic aldehydes to *Z*-vinyl fluorides as shown in scheme 43.[72]



Scheme 43

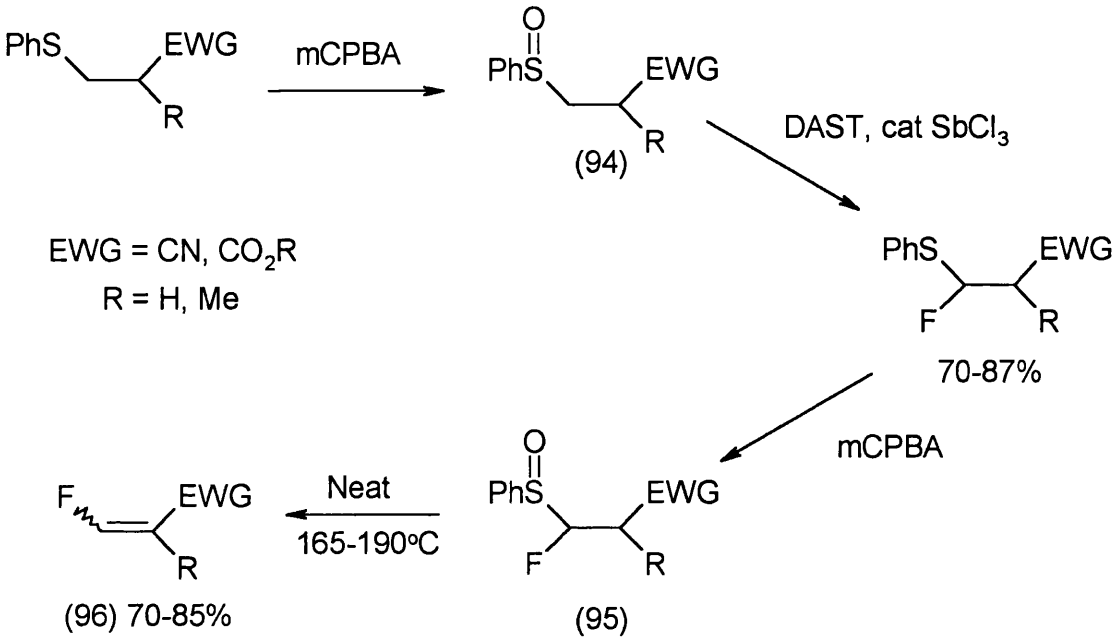
The generality of this method was improved through the application of the Horner Wittig reaction. The carbanion of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate can be generated *in situ* from fluoromethyl phenyl sulfone, diethyl chlorophosphate and two equivalents of LDA.[71] Addition of carbonyl compounds produces the α-fluoro-α,β-unsaturated sulfones (91) in good to excellent yields. Scheme 44 shows this approach to vinyl fluorides in the synthesis of a bioprecursor of a ribonucleoside diphosphate reductase inhibitor (93).[73] Aluminium amalgam reduction of the sulfonyl group was not successful, leading to the discovery that tributyltin hydride could effect a stereospecific transformation to the stannanes (92). Destannylation in methanolic ammonia followed by deprotection affords the required fluoro olefins with stereodefined double bond geometry.



Scheme 44

Sampson used the Fluoro-Pummerer reaction to prepare β-fluoro-α,β-unsaturated esters and nitriles with a view to examining their reactivity as Michael acceptors.[74] DAST-mediated Fluoro-Pummerer rearrangement of β-carboalkoxy sulfoxides (94) proceeded cleanly and efficiently. By way of contrast, the formation of significant amounts (13-36%) of non-fluorinated, deoxygenated material was observed with the corresponding β-cyano sulfoxides, even with rigorously purified DAST. As ZnI_2 was not employed in these reactions the iodide-based deoxygenation mechanism alluded to by Robbins cannot apply. It appears that DAST itself can operate as a deoxygenating agent with

certain substrates. The fluoro-olefins (96) were accessed through reoxidation to the sulfoxides (95) and subsequent pyrolytic elimination (scheme 45).



Scheme 45

Chapter 3. Conclusions and Future Outlook

Hypervalent iodine reagents have received scant attention in fluorination chemistry, in contrast to their high profile in more mainstream areas of organic synthesis. The foregoing review aims to be comprehensive and includes just twenty-four references over a sixty-nine year period. The lack of a definitive synthesis of difluoroiodoarenes in the literature combined with a general perception of reagent instability has no doubt curtailed potential applications. In recent years the situation has changed somewhat, the modern emphasis on mild, non-toxic fluorinating agents stimulating a reexamination of these compounds. Work from this group has established the thiophilic nature of difluoroiodotoluene and exploited this in the fluorination of various sulfur-containing functionalities, preferring the use of the pure hypervalent iodine reagent in the absence of any external fluoride sources. Japanese fluorination chemists, led by the Hara and Fuchigami groups have advocated an electrochemical approach to the synthesis of the reagent and invariably used it in combination with an amine-HF complex. The majority of their applications centre on the fluorination of alkenes, a functional group transformation of great importance. Catalytic uses of iodoarenes in electrochemical fluorination *via* the putative hypervalent difluorides are among the most impressive applications yet reported for this class of compounds.

The utility of hypervalent iodine difluorides such as DFIT in fluorination has therefore been established. Reactions proceed under extremely mild conditions and no special precautions need be taken to rigorously exclude air and moisture. The reagent is non-toxic and the chief by-product, iodotoluene, is safe and may even be reused. However, the scope of the reagent must be substantially expanded if it is to be used routinely in organic synthesis.

The Fluoro-Pummerer reaction is now a well-established synthetic transformation that appears in standard undergraduate text-books.[75] Of the many reagents that may be used to effect the fluorination DAST is undoubtedly the most versatile, giving the highest yields on the greatest range of substrates. The utility of the reaction has been improved considerably through the work of Robbins, firstly *via* the replacement of the unreliable zinc iodide catalyst with the superior antimony trichloride and secondly by establishing simple sulfides as substrates rather than sulfoxides, a substantial labour-saving implementation. There is still considerable room for improvement however, as the thermal and hydrolytic instability of DAST has been much remarked upon,[27] making it

incompatible with large-scale pharmaceutical applications (although a new DAST analogue with significantly improved thermal stability has recently been reported).[76] Robbins noted the reaction of sulfides with DAST to be vigorously exothermic when carried out on a large scale, for example.

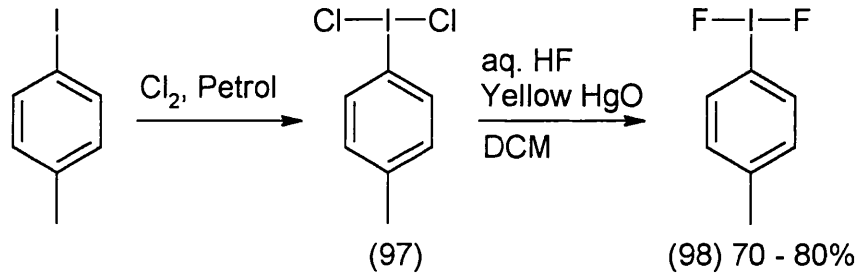
This project aims to explore and develop the scope of the hypervalent iodine reagent difluoroiodotoluene in fluorination. Emphasis will be placed upon the discovery of new carbon-fluorine bond forming reactions that can work over a range of substrates and that may be easily and routinely performed in the context of organic synthesis. Results will show that difluoroiodotoluene may be applied to the Fluoro-Pummerer transformation, and the effectiveness of the reagent in comparison to those discussed in the preceding review will be studied.

Part 2. Results and Discussion

Chapter 1. Difluoroiodotoluene

1.1 Preparation of the Reagent

We chose to prepare the fluorinating agent by mercuric oxide-assisted fluorination of dichloroiodotoluene using aqueous hydrofluoric acid,[5] in keeping with previous work in the group.[77,78] This approach is particularly suited to the research laboratory, being simple to carry out and amenable to multi-gram synthesis. The reagents, although highly toxic, are easily handled and represent a much safer alternative to the anhydrous hydrogen fluoride used in other preparations[6] (scheme 46).



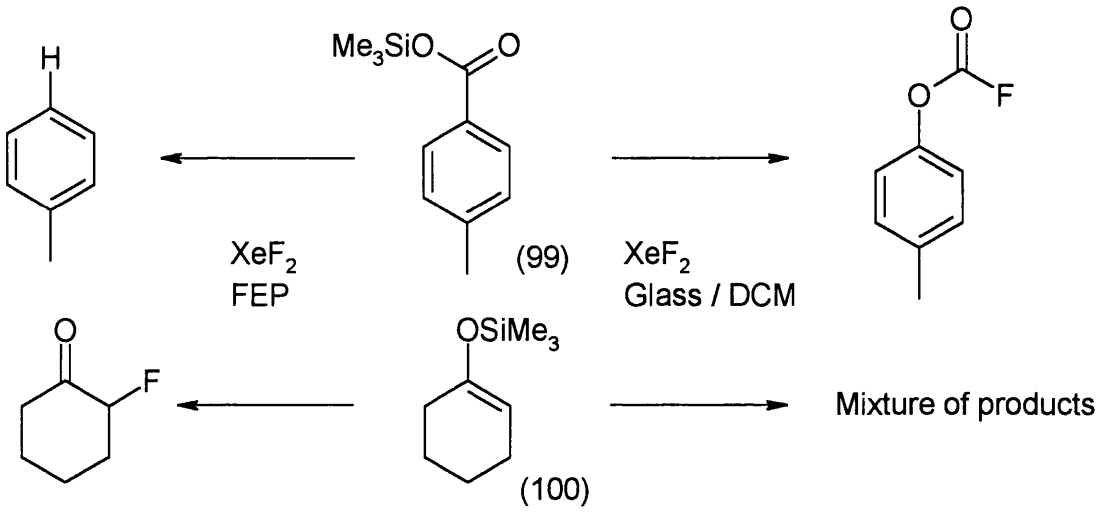
Scheme 46

The chlorination generally works very well, with the bright yellow dichloride (97) precipitating out of solution in nearly quantitative yield, typically after 2-3hrs. Yields are higher if the petrol and chlorine are both dry. The transhalogenation reaction must be carried out in PTFE equipment due to the corrosive nature of hydrofluoric acid, this also applies to the work-up. Excellent yields may be obtained if certain procedures regarding the agitation of the reaction are followed. Previous workers have noted that continuous stirring of the reaction is to be avoided and that periodic shaking, by contrast, gives reliably good results. Why the method of agitation should be crucial is not clear, however it is imperative that the solid mercuric oxide be effectively disturbed so that the reaction goes to completion. The formation of a flocculent white precipitate of mercuric chloride and the discharging of the yellow colour of the organic phase are reliable indicators in this regard. Premature work up of the reaction can lead to a drastic colour change upon removal of the solvent, the clear DCM solution suddenly becoming red. In this event no identifiable products can be isolated and the reaction is a failure.
Reaction was complete in approximately 1hr, although the reaction mixture could be left to stand overnight without problems. The DCM solution of difluoroiodotoluene

(DFIT) (98) obtained after work-up was treated briefly with magnesium oxide before concentration to remove any traces of HF. Concentration *in vacuo* on a standard rotary evaporator, despite the plastic vessel, is the quickest and best way to isolate the compound. The alternative technique of blowing the solvent off with a stream of argon,[77,78] although advocated by previous workers, is awkward and time consuming.
DFIT was isolated as a flaky, white to off-white solid depending on the batch. There were often small amounts of iodotoluene present as a contaminant. This was easily assessed by ^{1}H nmr and accounted for in the stoichiometry of the fluorination reactions.

1.2 The Stability of the Reagent

The reagent is not stable enough to be left on the open bench, but it can be stored for several months in the refrigerator without significant loss of activity (*vide infra*), and in the present work it was kept in plastic vials, under nitrogen at -30°C. Early workers in the field, concerned with possible degradation, prepared the reagent as a DCM solution and used it immediately.[1-8] Work from our group established that such a cautious approach was unnecessary, and that it was far more convenient to manipulate the reagent as a solid. Despite these reports, the preparation of DFIT is still cited as being awkward, and the reagent described as being too unstable to be stored.[22,68] The difficulties or otherwise of reagent preparation are clearly a matter of opinion, but it is misleading to make such statements concerning the stability of DFIT.
Recent studies on the chemistry of the hypervalent fluorinating agent xenon difluoride have established that the nature of the reaction vessel can be crucial to the chemistry. Ramsden has studied the fluorodesilylation of trimethylsilylbenzoates (99) with xenon difluoride and found that fluorination only occurs in glass vessels.[79] It appears that the acidic glass surface can generate the electrophile FXe^+ which is crucial to the success of the reaction. In fluorinated ethylene propylene (FEP) containers, alkali-washed glass or MeCN solution the XeF_2 remains unionised and does not react as an electrophile (scheme 47).



Scheme 47

In non-ionising vessels xenon difluoride reacts *via* SET mechanisms. The reaction of silyl enol ethers (100) with XeF_2 is believed to occur *via* a SET mechanism,[80] and conducting the reaction in a FEP vessel gives a clean and quantitative transformation to the fluoride. Glass vessels lead to a complex mixture of products.

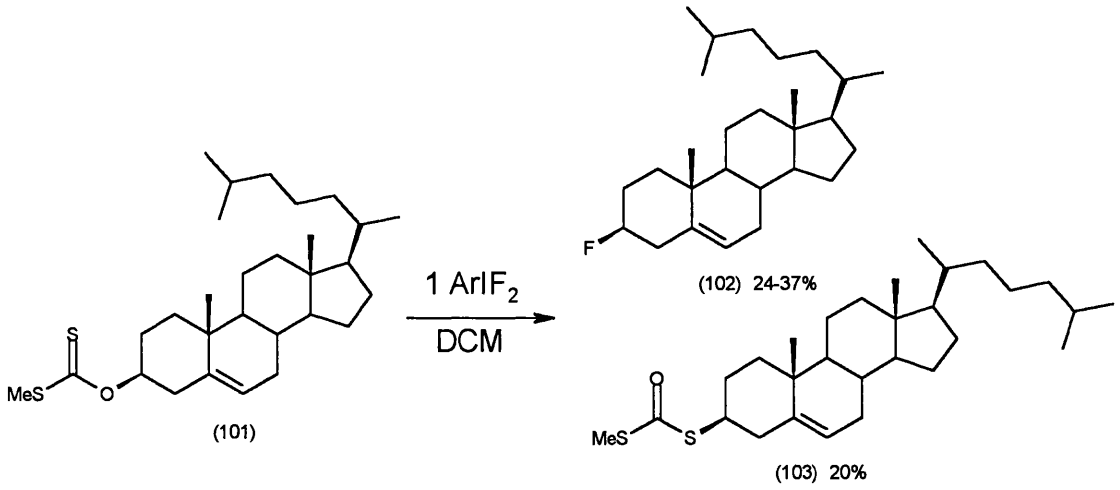
We have never observed any divergence of mechanism when using glass or plastic vessels in the chemistry of DFIT. The reagent does appear to react with glass to a degree, yellowing visibly on contact. NMR analysis of the reagent, for example, generally benefited from an FEP nmr tube liner. However this has had minimal impact on the chemistry, with identical reaction products being isolated from reactions in glass or polypropylene containers. Yields were slightly higher in many cases using polypropylene, so this was adopted as the standard reaction protocol.

Chapter 2 Fluorination of Allylic Xanthates and Sulfides

2.1 Fluorination of Xanthates

It had been shown previously that simple xanthates were good substrates for fluorination (*see introduction, 1.4*).[24] We decided to extend this chemistry by examining the behaviour of allylic xanthates with DFIT. Initially we looked at the behaviour of the homoallylic substrate cholesteryl xanthate (101), as it had previously been fluorinated in excellent yield and would be an appropriate benchmark to test the efficacy of early batches of DFIT.

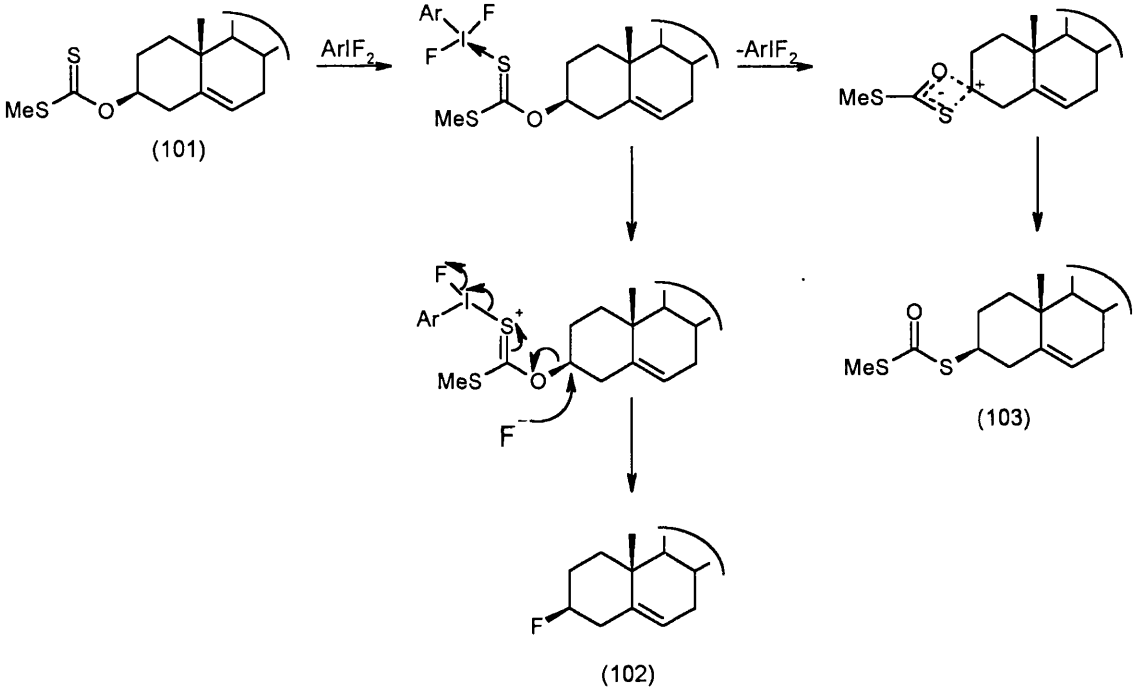
The xanthate was synthesised by treatment of cholesterol with sodium hydride, carbon disulfide and methyl iodide in 55% yield.[160] Treatment with one equivalent of DFIT in DCM produced the expected fluoride (102) in low yields (24-37%), along with the unexpected dithiocarbonate rearrangement product (103) (scheme 48).



Scheme 48

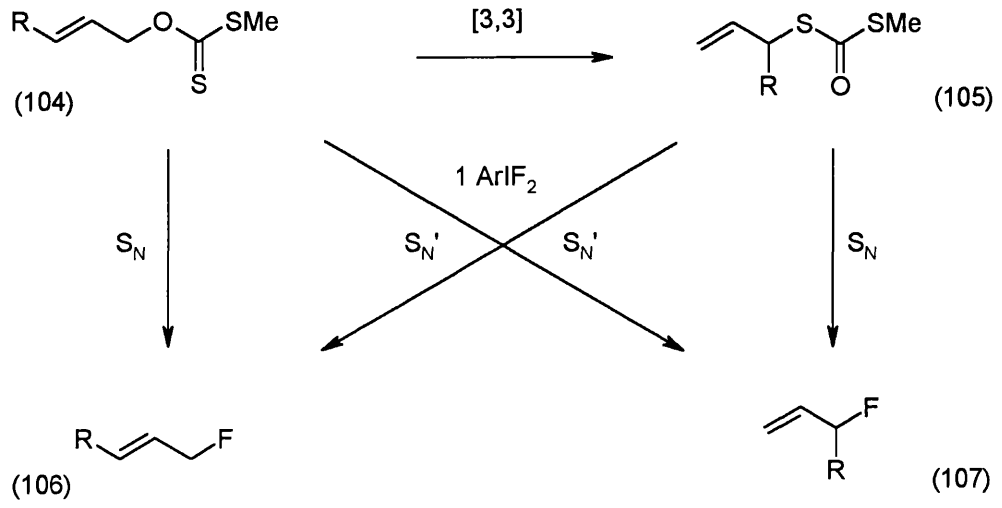
The dithiocarbonate (103) has previously been synthesised from cholesteryl *S*-methyl xanthate by pyrolysis in the presence of hydroquinone,[81] or by heating in the presence of Lewis acids such as boron trifluoride diethyl ethereate and stannic chloride.[82] Crossover experiments have pointed to an ion-pair mechanism, with the retention of configuration being ascribed to classical homoallylic participation. The precise role of the Lewis acid was not clarified in the above examples, in this case DFIT must coordinate to sulfur and initiate the rearrangement, loss of fluoride from the complex

produces a nucleophile which can then compete to capture the intermediate carbocation (scheme 49).



Scheme 49

Fluorination of allylic xanthates (104) with DFIT can potentially occur through an S_N2 or S_N2' mechanism. An additional complication is that allylic xanthates undergo facile, irreversible [3,3]-sigmatropic rearrangement (scheme 50).[83] The dithiocarbonate rearrangement product (105) so formed is also a potential substrate for DFIT.



Scheme 50

The two isomeric fluorides (106) and (107) can therefore be formed by four different pathways. We chose to investigate this system using geranyl xanthate (108) as our allylic substrate. Preparation of pure material was reported to be difficult due to the facility of the aforementioned sigmatropic shift, occurring at room temperature and being catalysed by traces of acid.[84] The compound could therefore not be purified rigorously and had to be stored in the refrigerator once made. Treatment of geranyl xanthate with DFIT failed to effect any fluorination. In keeping with the cholesteryl case we isolated the rearranged dithiocarbonate (109) as the only product from a complex reaction mixture in low yield (scheme 51).

(108) (109) 20%

Scheme 51

A pure sample of the 6-dithiocarbonate was an even worse substrate for fluorination, yielding no identifiable products on treatment with DFIT.

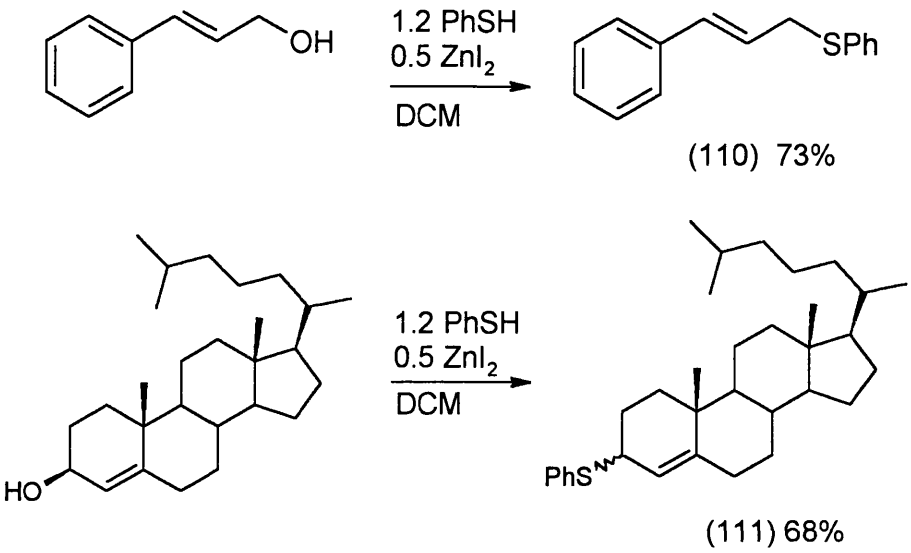
Given the disappointing results of the xanthate system we elected to study the fluorination of an alternative sulfur-based functionality. Allylic sulfides were well described in the literature and represented a simpler system that could still be studied in terms of S_N / S_N' behaviour.

2.2 Synthesis of Allylic Sulfides

Synthesis of the allylic sulfides was not completely straightforward. Application of a modified Mitsunobu protocol[85] to geraniol using thiophenol as the nucleophile gave low yields (*ca.* 10%) of the required sulfide, with substantial amounts of diphenyl disulfide being isolated as the major product. Attempts to preactivate the alcohol with diisopropyl azodicarboxylate / triphenyl phosphine followed by addition of thiophenol failed to alleviate this problem.

Treatment of geraniol with thiophenol and boron trifluoride-diethyl ethereate has been reported to give the sulfide in excellent yield.[86] However, in our hands the success of this procedure could not be reproduced, with complex mixtures resulting. Cinnamyl alcohol proved to be a better substrate, phenyl (*E*-3-phenyl-prop-2-enyl) sulfide (110)

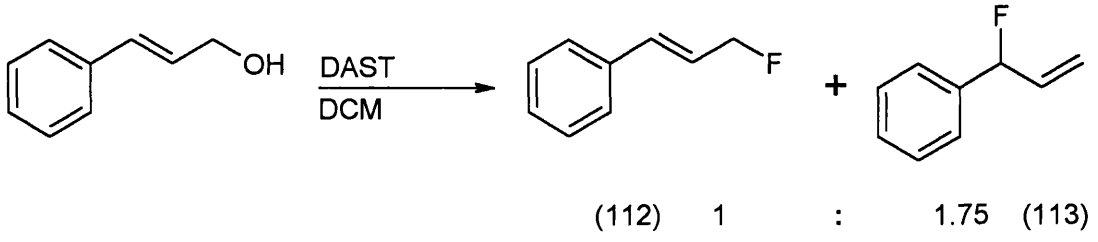
being produced in *ca.* 40% yield. Changing the Lewis acid to the milder zinc iodide, as advocated by Guindon, gave much better results.[87] A range of allylic sulfides were synthesised cleanly and in good yield by this method, although the sulfanylation of geraniol remained an outstanding problem (scheme 52).



Scheme 52

2.3 Fluorination of Phenyl (*E*-3-Phenyl-Prop-2-enyl) Sulfide (110)

The cinnamyl derivative (110) was a convenient substrate to investigate, being an easily-prepared crystalline solid. In addition, a study on the fluorination of cinnamyl alcohol with DAST had been published.[88] At 0°C DAST reacts with *E*-cinnamyl alcohol in DCM to give 3-fluoro-3-phenyl-propene (112) and 3-fluoro-1-phenyl-propene (113) in a 1: 1.75 ratio (scheme 53).



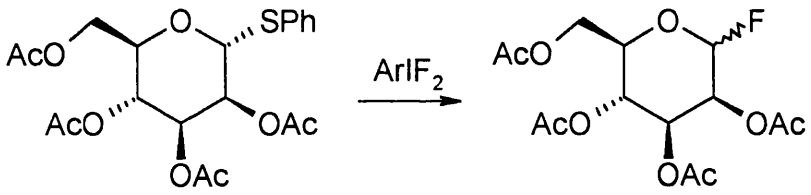
Scheme 53

The authors proposed that the experiment would be eminently suitable for an undergraduate laboratory preparation, emphasising the ease with which the product spread may be identified by ^{19}F nmr. ^{1}H nmr analysis is more difficult due to the

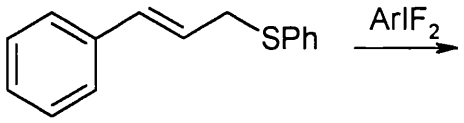
extended multinuclear couplings that exist between protons and fluorine in the allylic system. Yields typically greater than 90% are claimed, despite the publication of a product ^{1}H nmr spectrum which contains many impurities.

A similar preference for S_N2' chemistry with DAST and allylic alcohols was noted by Middleton in his pioneering work on this reagent, fluorination of crotyl alcohol giving a 72: 28 ratio of 3-fluoro-1-butene: 1-fluoro-2-butene.[89]

The reaction of DFIT with arylthioglycosides (50) (*vide supra*) to form glycosyl fluorides (51/52) demonstrated that the activated phenylsulfanyl group was a good nucleofuge, given the anchimeric assistance provided by oxygen.[23] In the allyl system, with a double bond as the neighbouring group, we anticipated similarly clean fluorination. Unfortunately treatment of cinnamyl derivative (110) with the fluorinating agent DFIT produced a complex mixture of products (scheme 54).



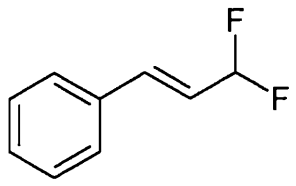
(50) (51/52) 56%



(110) Complex mixture

Scheme 54

The ^{19}F nmr spectrum of the crude mixture invariably showed several signals, including the expected allyl fluorides. The major product in most runs was the unexpected difluoride (114), which was generally isolated in 10-30% yield.



(114)

Purification of (114) by column chromatography was hampered by the co-elution of iodotoluene and poor visualisation characteristics of the compounds on the tlc plate. The compound was isolated as an unstable oil that degraded rapidly on storage. The deshielding effect of the *gem*-difluoro group shifts the 1-H signal 2.5ppm downfield in the ^{1}H NMR spectrum, ^{13}C NMR analysis showed the characteristic J_{CF} triplet splitting pattern of the 1-, 2- and 3-carbon signals. The hydrolysis product of (114), cinnamaldehyde, was occasionally isolated in place of the fluoride in comparable yield, often when acetonitrile was used as solvent. No other pure compounds could be isolated by chromatography.

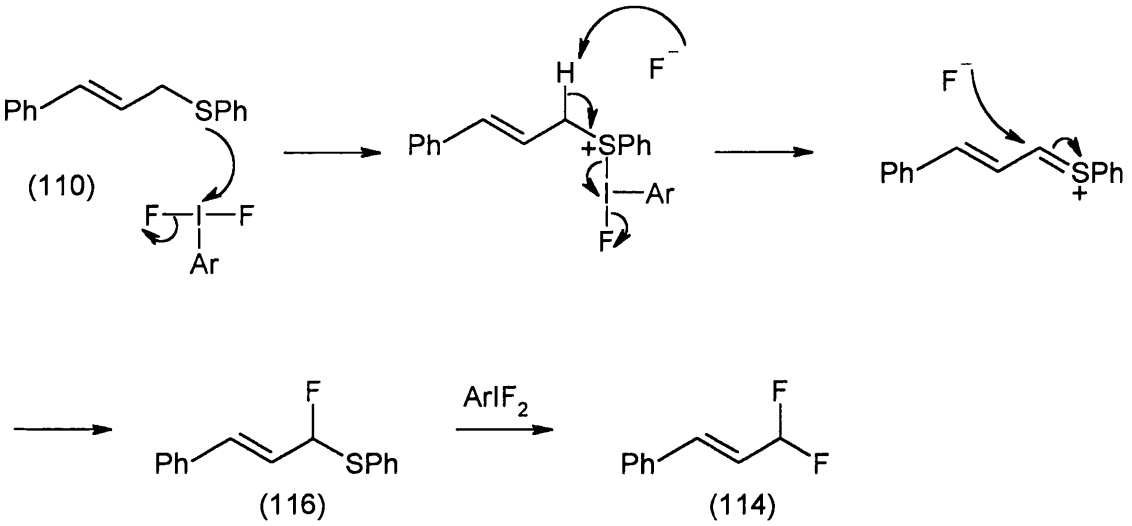
Considerable efforts were made to optimise reaction conditions and stoichiometry to obtain a clean reaction. Using half or one equivalent of DFIT gave mixtures containing no fluorinated material, 1.5 or three equivalents produced similar complex fluorinated mixtures. Conducting the reaction at -78°C or at 40°C in refluxing DCM failed to ameliorate matters. Adding Lewis acids such as the thiophilic mercuric oxide or zinc iodide to coordinate to the sulfur atom were unsuccessful, as was the addition of Hunig's base to scavenge any free HF in the reaction. External nucleophilic fluoride sources such as TBAF also failed to promote the fluorination.

Incorporation of the *p*-methoxy group has been reported to significantly enhance the Fluoro-Pummerer reaction of aryl sulfides with DAST.[25] No such improvement was registered with the DFIT fluorination of the *p*-methoxy substituted analogue (115), similar yields of the difluoride (114) being isolated from a complex mixture.

The difficulties in introducing fluorine into this system were further emphasised when alternative fluorinating agents were examined. py.9HF in combination with oxidants such as DBH or NIS has been shown to be an excellent reagent for fluoro-desulfurisation of certain substrates.[20] Here they were as impotent as DFIT, failing to give clean fluorination, and no major products could be isolated.

The formation of (114) is noteworthy however, as it indicates that DFIT can react in a Fluoro-Pummerer mode. We postulate an initial Fluoro-Pummerer reaction* as the first step, forming the α-fluoro sulfide (116). A second equivalent of DFIT then activates the sulfur to displacement by liberated fluoride (scheme 55).

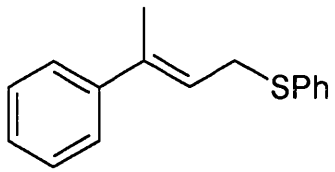
* Such reactions which involve sulfide sulfur rather than sulfoxide sulfur are still labelled as Fluoro-Pummerer transformations in the literature and will be referred to likewise in this work.



Scheme 55

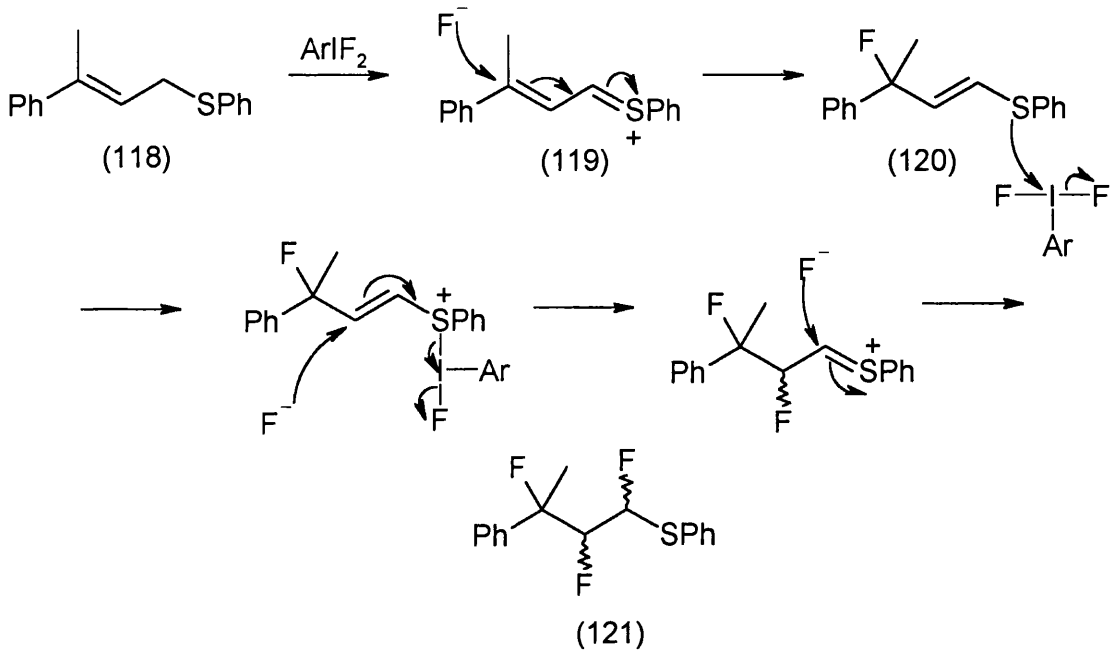
2.4 Fluorination of Phenyl (*E*-3-Methyl-3-Phenyl-Prop-2-enyl) Sulfide (118)

The trisubstituted derivative (118) was initially synthesised with the aim of biasing the expected S_N2' / S_N2 product spread by slightly encumbering the 1-position. In the event reaction with DFIT was slightly cleaner than in the previous case, although several fluorinated compounds were formed they appeared to be diastereoisomeric with one another.



(118)

The ^1H nmr spectrum was surprisingly simple; up to four methyl signals all split into doublets, two other protons giving a complex multiplet between 4-4.6ppm and ten aromatic protons. The ^{19}F nmr by contrast was complicated, showing more than ten signals, all having substantial secondary structure. We proposed an empirical formula of $C_{16}H_{15}F_3S$, (FW=296), based on the ^1H nmr integration and this was confirmed by mass spectrometry. The FAB mass spectrum was quite clean, showing an MH^+ peak at 297 (12%) and an M^+ peak at 296 (26%). The apparent absence of any vinyl protons and the incorporation of three fluorine atoms pointed to the unusual trifluoride (119) as the reaction product (scheme 56)



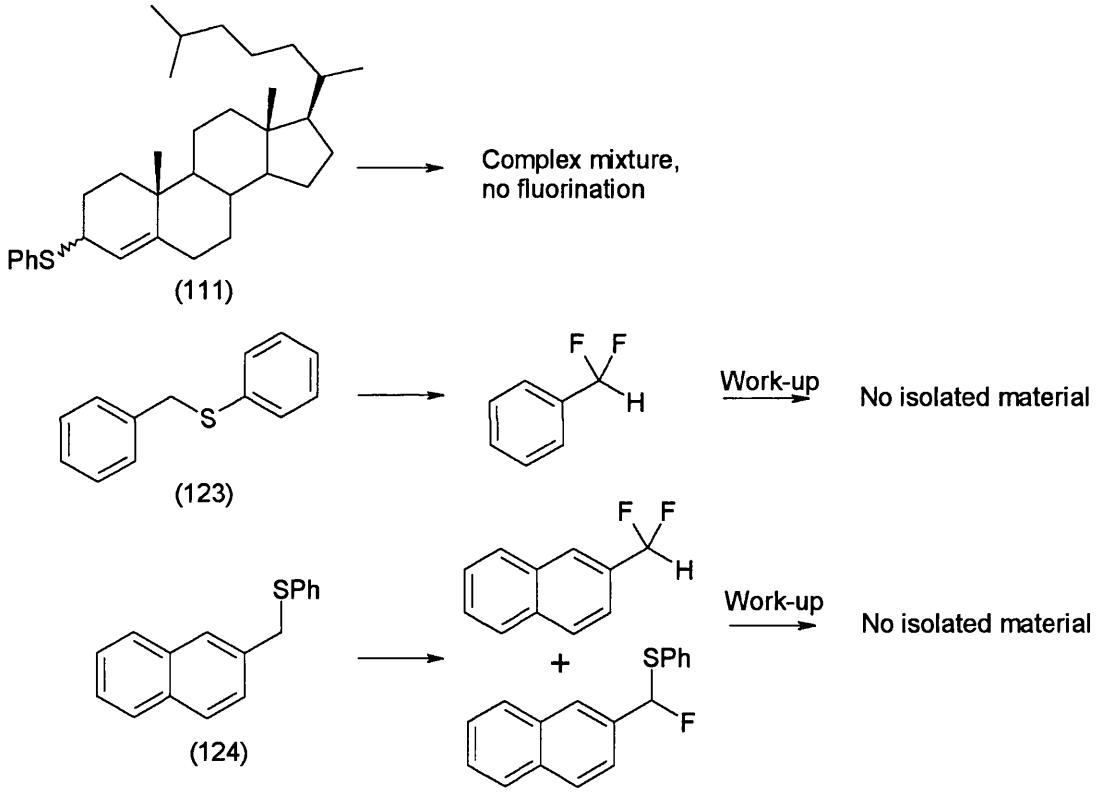
Scheme 56

Formation of trifluoride (121) is consistent with DFIT reacting once again in a Fluoro-Pummerer mode, with the first equivalent of fluorinating agent generating the sulfonium ion intermediate (119), as in scheme 56. Nucleophilic addition of fluoride then occurs at 1-C, rather than at 3-C as in the cinnamyl derivative (110). This is referred to as a vinylogous Pummerer reaction.[90] The methyl group provides extra-stabilisation for the incipient benzylic carbocation at 1-C, increasing its contribution to the resonance canonical of (119). The vinyl sulfide (120) may now undergo a so-called additive Pummerer reaction,[90-93] where two molecules of the fluoride nucleophile are effectively added across the double bond. Both additions may be *syn* or *anti* to the 3-fluoro substituent, producing four diastereoisomeric trifluorides.

The FAB mass spectrum showed fragment peaks at 277, $[M\text{-}F]^+$, 257, $[M\text{-}HF_2]^+$, 173, $[M\text{-}PhCFMe]^+$ and a base peak at 123 $[PhCFMe]^+$. Separation of the diastereoisomers by column chromatography could not be achieved, and this, coupled with the instability of the material precluded further characterisation.

2.5 Fluorination of Benzylic Sulfides

Other activated sulfide systems were examined, without success. Complicated mixtures were invariably obtained, the product fluorides being too unstable to be isolated. The allylic steroidal sulfide (111) failed to incorporate any fluorine when treated with DFIT. Benzyl phenyl sulfide (123) proved a good substrate, with ^{19}F nmr of the crude material showing the expected difluoride. The material proved too unstable or volatile to isolate after work-up. The heavier naphthyl sulfide (124) was less reactive and the product fluorides similarly unstable (scheme 57).



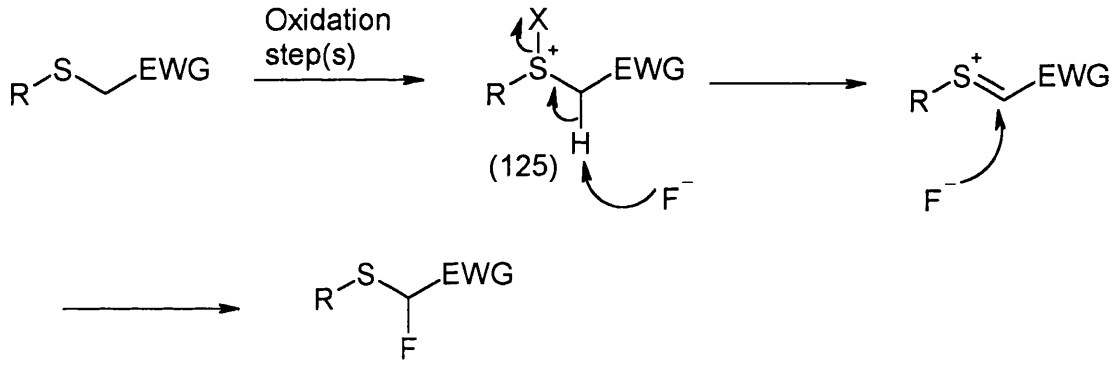
Scheme 57

DFIT has proved to be a good reagent for the fluoro-desulfurisation of certain xanthates and sulfides, forming the simple fluorides cleanly and in good to excellent yield. However, from the foregoing examples it is clear that when these functionalities are in an allylic environment the reactions are messy and the fluorides that are formed are generally unstable, difficult to purify and isolated in low yield. Nevertheless, this chemistry has provided our first indication that DFIT can introduce fluorine adjacent to sulfur, the Fluoro-Pummerer reaction, and it was therefore of interest to investigate the scope of this reaction.

Chapter 3. Fluorination of β-Oxo-Sulfides

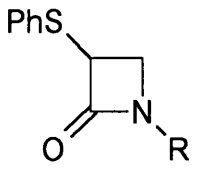
3.1 Fluorination of α-Sulfanyl Lactams

The Fluoro-Pummerer reaction is established in the literature as being promoted by electron-withdrawing groups on the α-carbon. Anodic fluorination of sulfides for example, is generally ineffective with simple dialkyl sulfides.[54] As discussed in the introduction, most authors favour a conventional Pummerer mechanism involving deprotonation of (125) by fluoride, shown in the generalised mechanism in scheme 58. As fluoride anion is a relatively weak base, factors which enhance the acidity of the α-protons can be crucial to reaction *via* this pathway.



Scheme 58

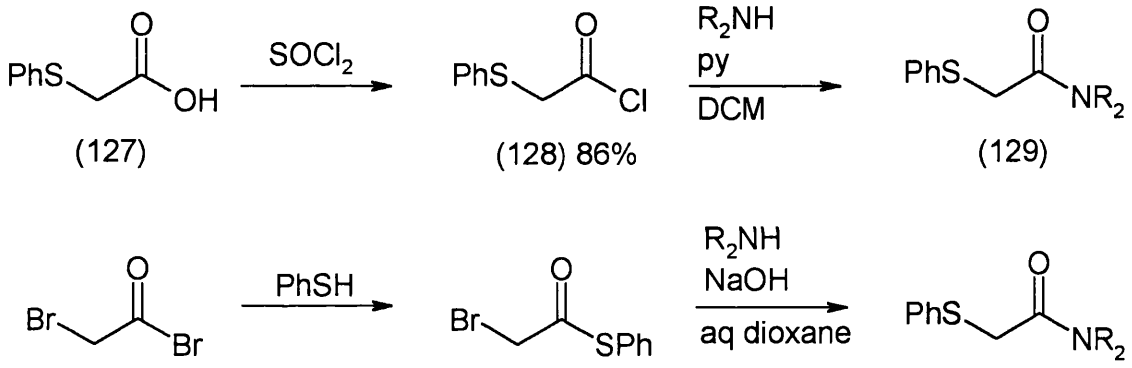
We chose to study the fluorination of sulfur-containing azetidinones (126) with DFIT. Reports by Fuchigami had established these and other lactams to be good substrates for anodic monofluorination.[56] Such partially fluorinated heterocycles are the focus of much biological interest, but the synthesis of these compounds remains problematic.[94]



(126)

3.1.1 Fluorination of Azetidinones

Many syntheses of 4-sulfur-substituted azetidinones have been published in the field of β-lactam research. The analogous 3-substituted compounds are comparatively rare. As the parent heterocycle and simple derivatives are expensive to buy we opted to synthesise the desired compound according to Hirai; treatment of an α-phenylsulfanyl acetamide derivative (129) with an excess of strong base and cyclisation of the resultant 1,3-dianion with methylene iodide.[95] The phenylsulfanyl acetamides can be readily made through acylation of the appropriate amines with (phenylsulfanyl)acetyl chloride (128). We preferred to make made our own batches of the acyl chloride from the cheap and readily available thiophenoxyacetic acid (127) (scheme 59).



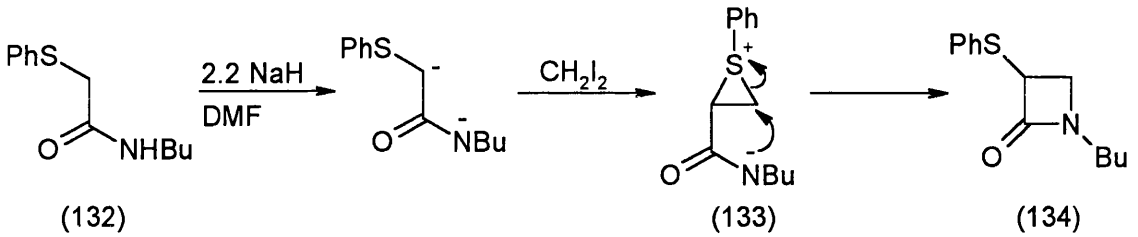
(127) (128) 86% (129)

(130) (131) 85% (129)

Scheme 59

An alternative synthesis starts from bromoacetyl bromide (130).[96] Treatment with neat thiophenol forms the bromoacetyl thiol ester (131) in excellent yield. This is a highly crystalline, low-melting point solid that keeps well in the refrigerator and can be made on a multi-gram scale. The thiol ester undergoes rapid nucleophilic addition of amines with liberation of thiophenol, which then displaces bromide from the intermediate bromoacetamide. The ease with which the amine nucleophile attacks the thiol ester is contingent upon the α-bromine substituent. Acetyl thiophenol was observed to undergo very little reaction with aniline, for example. Both procedures are simple and high yielding, the bromoacetyl thiol ester route is slightly disadvantaged by the need to remove the high-boiling dioxane solvent.

Reported yields for the azetidinone ring forming reaction ranged from poor to moderate, with the best example, 54%, being for cyclohexyl (phenylsulfanyl)acetamide. We considered this substrate to have rather poor nmr characteristics and chose to work on the butylamine derived material instead. *n*-Butyl (phenylsulfanyl)acetamide (132) was treated with 2.2eq of sodium hydride in DMF, followed by 3-5eq of methylene iodide at room temperature. The required azetidinone (134) was isolated in low yields, typically 25-30% with up to 30% recovered starting material, Hirai reported a 38% yield (scheme 60).

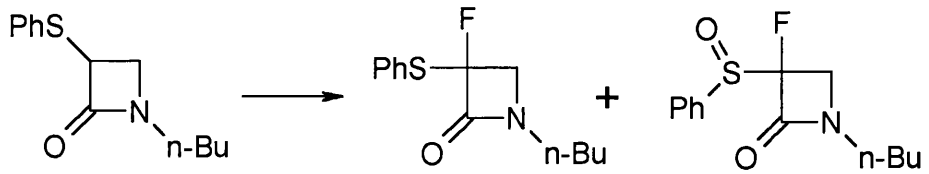


(132) (133) (134)

Scheme 60

Sequential carbon-carbon bond formation was considered to occur first, with the episulfonium species (133) postulated as an intermediate. 4-*exo-trig* Ring closure then produces the azetidinone. Since there are many side products of the reaction, with dimeric material being a major contaminant, the authors thus advocated carrying out the reaction at relatively high dilution, <3% w/v.

Fluorination of azetidinone (134) with two equivalents of DFIT formed the unexpected α-fluoro-sulfoxide (136) as the major product, in 46% yield. The expected α-fluoro-sulfide (135) was isolated as a side product in 9% yield (scheme 61).



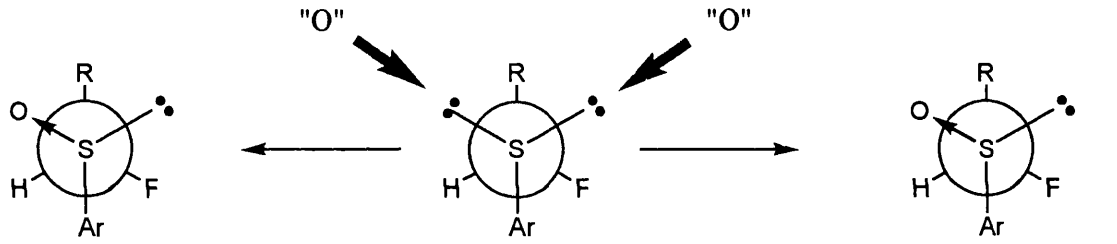
(134) (135) 9% (136) 46%

Scheme 61

The presence of two signals in the ^{19}F nmr spectrum was baffling at first. We considered monofluorination at 4-C giving rise to *cis* and *trans* diastereoisomers, but this was rejected on mechanistic grounds. Mass spectrometry pointed to the sulfoxide,

and this was confirmed unequivocally by treating the material with an excess of mCPBA for several hours. The resulting sulfone (254) showed a single ^{19}F nmr signal and was further characterised by a high-resolution mass measurement.

The diastereoisomers of (136) are formed in a 3: 1 ratio, but it was not possible to assign stereochemistry from the nmr data. The H-F coupling constants were of similar magnitude for the two diastereoisomers, both compounds showing pseudo-triplet signals in the ^{19}F nmr with coupling constants of 8 and 9Hz. The mixture resolved well on GC and moderately well on HPLC, but it was not possible to obtain a preparative separation using flash chromatography. Electrophilic attack of oxidants onto sulfur in simple open chain α-fluorosulfides is known to take place anti to the C-F bond.[97] The strained azetidinone ring and the possibility of chelation effects make such an analysis more difficult in this case (scheme 62).



Major Product

Minor Product

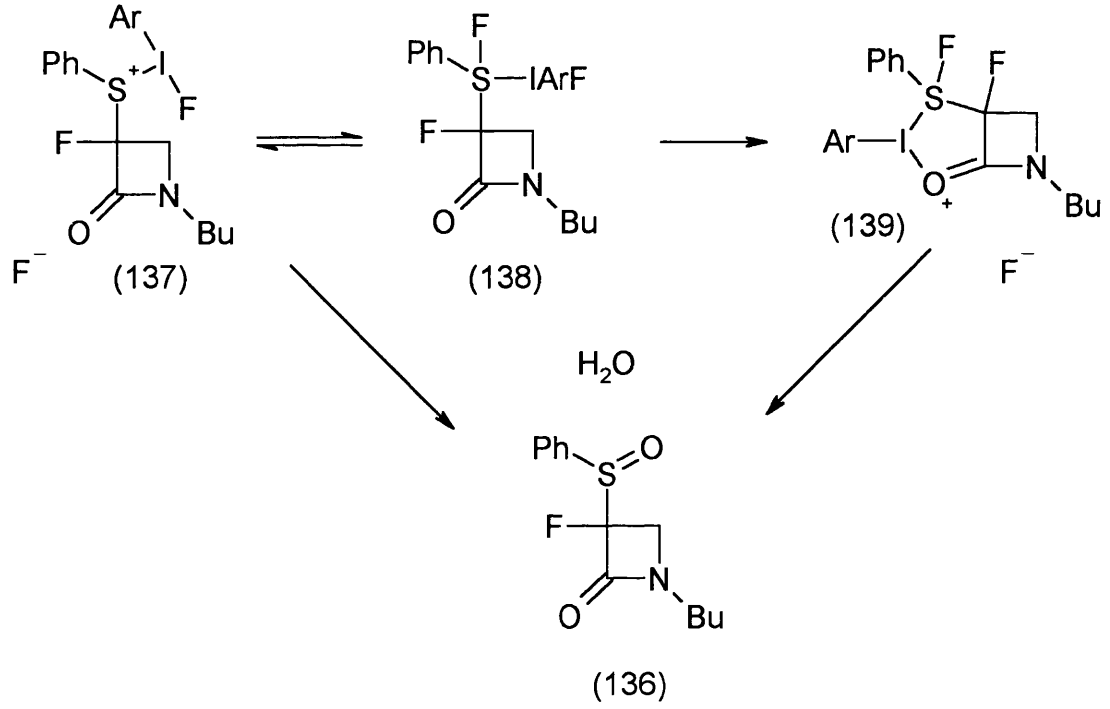
Scheme 62

We failed to obtain single crystals of the product sulfoxide for X-ray analysis, consequently a rigorous characterisation could not be made. Treating the azetidinone with one equivalent of DFIT failed to produce the simple monofluorides, and no products could be isolated from a complex mixture.

There are no reports in the literature of DFIT acting as an oxidising agent with sulfides, although hypervalent iodine reagents such as iodosobenzene[98] and dichloroiodobenzene[99,100] are routinely used for this transformation. Oxidation with dichloroiodobenzene is performed in the presence of aq. pyridine, anhydrous conditions lead to α-chlorosulfides.

The mechanism of sulfide oxidation in this case must involve initial oxidation of the primary fluoro-Pummerer product with DFIT and subsequent nucleophilic displacement with water (scheme 63); the exact details being open to debate. Residual water in the reaction must be considered as it is not possible to conduct reactions under strictly

anhydrous conditions using polypropylene vessels, although the plastic flasks were stored in a vacuum dessicator before use. However, if this were the case some unfluorinated sulfoxide would be formed, and such a compound was never isolated. A more likely explanation is that the sulfonium species (137) may be stabilised by a coordination from the carbonyl oxygen, forming a five-membered chelate (139). The complex may have sufficient stability to persist until the reaction is quenched with water. The iodosulfonium salt postulated for this and other reactions must be considered to exist in equilibrium with the corresponding sulfurane (138).[101]

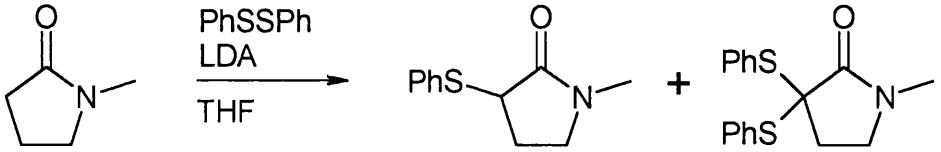


Scheme 63

Electrochemical anodic monofluorination of (134) is reported to proceed in 92% yield to give monofluorinated azetidinone (135) using $Et_3N.3HF$ as the supporting electrolyte.[56] The authors stated that alternative Fluoro-Pummerer reagents such as *N*-fluoro-2,4,6-trimethylpyridinium triflate were entirely unsuccessful with this system. Attempted fluorination of the sulfoxide derived from (134) with DAST also failed. The success of DFIT is therefore significant, and the concomitant oxidation a potentially useful feature (*vide infra*).

3.1.2 Fluorination of Pyrrolidinones

We chose to examine the pyrrolidinone system by synthesising the *N*-methyl pyrrolidinone derivative (140), as the starting lactam is cheap and readily available. Sulfanylation of lactams with LDA and diphenyl disulfide is complicated by the need to control mono *vs* bis sulfenylation (scheme 64).[102,103]

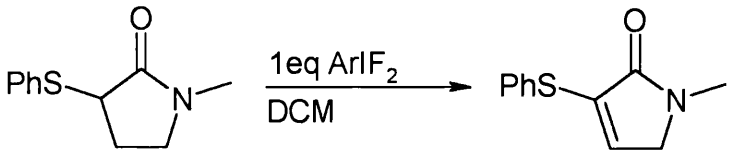


(140) (141)

Scheme 64

Treatment of *N*-methyl-pyrrolidinone with two equivalents of LDA and one equivalent of diphenyl disulfide in THF affords the mono-phenylsulfanylated material (140) in 43% yield, with a small amount of the bis-sulfanylated material (141) as a side product. The product α-proton is more acidic than that of the starting material, and proton transfer to the α-lithiated unsubstituted lactam is assumed to be faster than sulfanylation. The α-lithiated unsubstituted lactam is the better nucleophile, and the role of the excess base is postulated to be to protect the monophenylsulfanylated lactam as the anion, thus allowing the α-lithiated unsubstituted lactam to preferentially react with the electrophile. Using two equivalents of base and two equivalents of electrophile gave good yields of the pure bis-sulfanylated material (141).

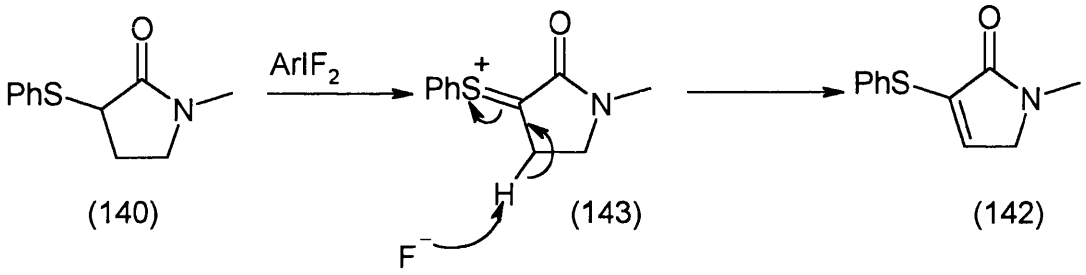
Fluorination with DFIT produced some unexpected results. Our first experiments involved treating the pyrrolidinone derivative with one equivalent of fluorinating agent. In this instance we isolated the enone (142) as the major product in 56% yield, along with small amounts of fluorinated material (scheme 65).



(140) (142) 56%

Scheme 65

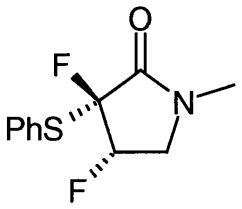
The vinylic proton is prominent in the nmr spectrum, at δ=6.20ppm and was an immediate indicator of structure. The absence of any simple monofluoride is again surprising, but the formation of (142) may be rationalised by the Fluoro-Pummerer mechanism. Vinyl sulfides frequently occur as side products in conventional Pummerer reactions, arising from β-elimination of the nucleophile from the product or by loss of a proton from the sulfonium intermediate (143). Vinyl sulfides are often the sole products of Pummerer reactions of α-keto sulfoxides, this being one of the best methods for synthesising the useful α-keto sulfide functionality.[104] The mechanism for DFIT-mediated vinyl sulfide synthesis is shown in scheme (66)



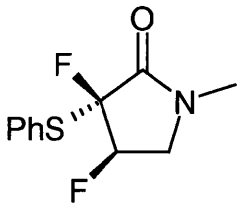
Scheme 66

We have considered the possibility that the Fluoro-Pummerer monofluoride is formed initially and HF is subsequently eliminated. β-Elimination of fluoride is unlikely as fluoride is well known to be a poor leaving group, and the carbon fluorine bond strength is substantial. Fuchigami has reported that the anodic fluorination of lactam (140) yields the monofluoride in 85% yield. No mention is made of any elimination products being formed.[55]

Treatment of the substrate with two equivalents of DFIT produces fluorinated material. A mixture of two diastereoisomeric difluorides in the ratio 1.75: 1 was isolated from the reaction. Careful chromatography achieved some separation, the faster-eluting material being the major product, and the structures were provisionally assigned as the *anti* and *syn* 3,4-difluorides (144) and (145) shown overleaf.



anti (144)



syn (145)

It was not possible to assign stereochemistry from nmr coupling patterns, although the faster-eluting major isomer had significantly simpler spectra. A ^{19}F nOe experiment conducted on the mixture was helpful in this regard. Irradiation of each of the two 3-fluorine signals in turn showed significant enhancement of only one of the two 4-F signals, the other being entirely unaffected. This positive result strongly suggested that the *syn*-stereochemistry be assigned to the compound showing the nOe effect. We were eventually able to grow single crystals of this compound which proved suitable for X-ray diffraction. This unambiguously characterised the major diastereoisomer to have the *syn* geometry, in agreement with the nOe work (figure 1).

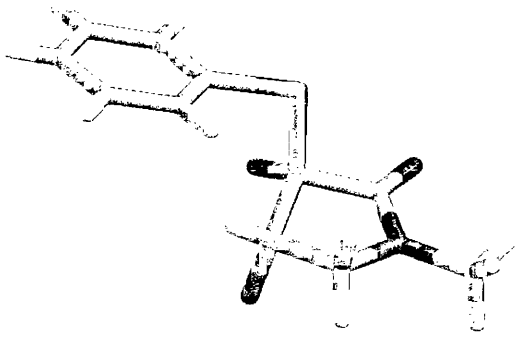
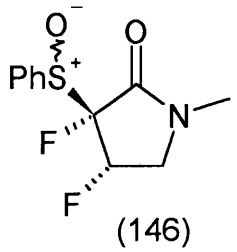


Figure 1

Yields were in the range 32-43% with the *syn*-compound always being the major diastereoisomer, although the selectivity never exceeded 2: 1. The order of GC retention was opposite to that observed on the tlc plate. In some runs a third difluoride was

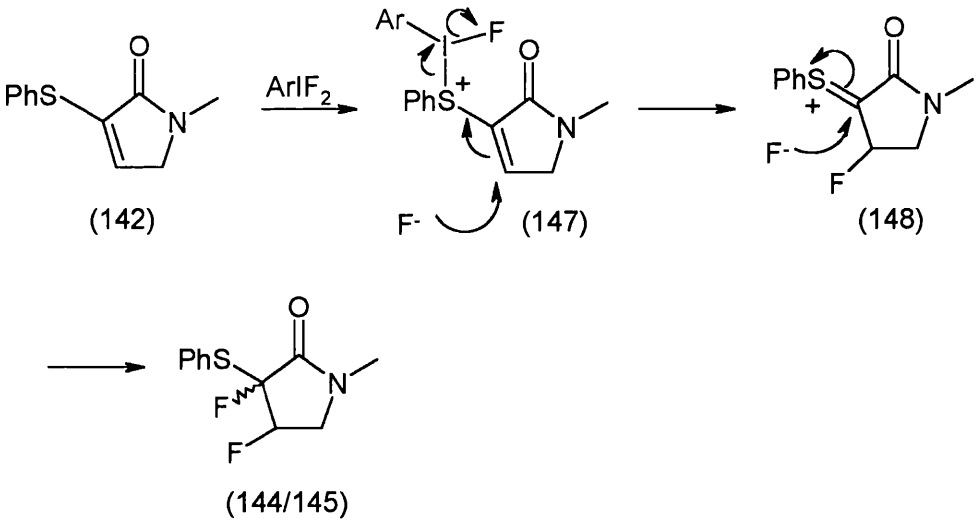
isolated in low yield and characterised as a mixture of two diastereoisomeric sulfoxides (146).



(146)

When four equivalents of DFIT were used sulfoxide (146) was formed in 16% yield as the major product, the two diastereoisomers being in a 1: 1 ratio. The ^{1}H nmr showed similar splitting patterns to the *syn* sulfide (145), with the 4-H signals appearing as simple doublet of doublets. The ^{19}F nmr was also simple, with the 3-F signals of both diastereoisomers being singlets. This leads us to suggest that the molecular geometry of the pyrrolidinone ring is very similar for both isomers, the diastereoisomerism arising from the sulfoxide configuration. Based on the similarities in H-H and H-F coupling patterns between sulfide and sulfoxide we tentatively assign a *syn* relationship to the two fluorine atoms and a 1: 1 *syn / anti* configuration to the sulfoxide, as shown above. The alternative 3, *anti*-4 difluoro sulfoxide was never isolated.

The fluorination mechanism must be considered within the same framework as the mechanism for formation of the enone (142). We postulate that the second equivalent of DFIT must take part in an additive Pummerer reaction. Nucleophilic attack of fluoride at the β-carbon of the activated sulfide (147) leading to the β-fluoro sulfonium ion (148). Trapping with a second fluoride affords the difluoride (144/145) (scheme 67).

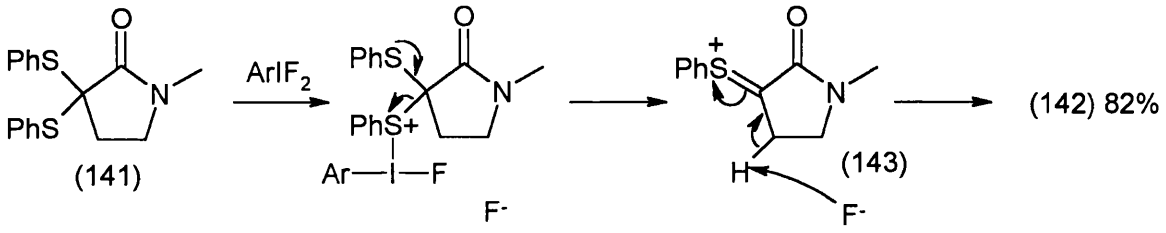


Scheme 67

The low diastereoselectivity illustrates the relatively small influence of the small fluorine atom in the 4-position on the steric approach control of the second fluoride nucleophile.

We briefly examined the seleno-analogue of (140) as a possible substrate for DFIT, previous work having established arylselenoglycosides to be effective in the synthesis of glycosyl fluorides. The Seleno-Pummerer reaction is well established but limited in application due to the facile elimination of RSeOH if β-hydrogens are present.[90] In the event treatment of the appropriate selenoether (149) with two equivalents of DFIT was unsuccessful, with no fluorination taking place.

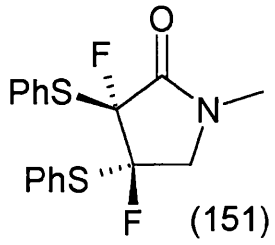
As the bisphenylsulfanylated lactams were also readily prepared from the *N*-methylated pyrrolidinone and piperidinone compounds we chose to examine them as suitable substrates for DFIT. Aryl thioketals had been shown to be excellent precursors to geminal difluorides (*see introduction, 1.5*) with this reagent.[19] The pyrrolidinone derivative (141) was transformed into the familiar enone (142) in excellent yield upon treatment with a single equivalent of DFIT. A plausible mechanism is shown below in scheme 68.



Scheme 68

The generation of the α-acyl sulfonium ion (143) through thioketal cleavage provides a pathway which is substantially lower in energy than the Pummerer-type process expostulated for the mono-phenylsulfanylated compound (scheme 65), thus accounting for the higher yield. Fluorination with 2.2 equivalents of DFIT led to two diastereoisomeric difluorinated products, different to the previously synthesised fluorides (144) and (145). The ^{1}H nmr spectrum indicated ten aromatic protons and only two protons present on the pyrrolidinone skeleton. Clearly the displaced thiophenoxide has reintroduced itself into the molecule, an unsurprising result on reflection, given its excellent nucleophilicity.

The DCM / PE 30-40 solvent system proved to be excellent for growing single crystals of these fluorinated lactams, with this substrate being no different. X-ray diffraction on a single crystal grown of the major diastereoisomer characterised the structure as 3, *anti*-4-difluoro-1-methyl-3,4-diphenylsulfanyl-2-pyrrolidinone (151), shown below (figure 2).



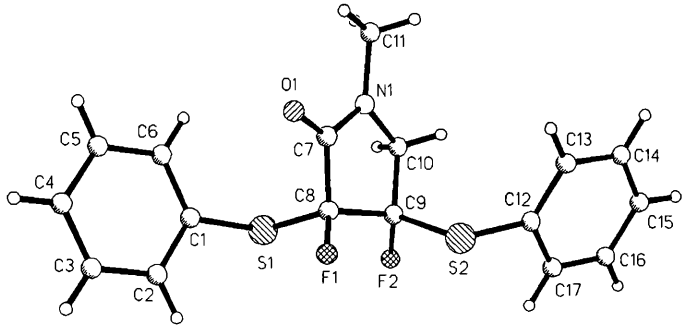
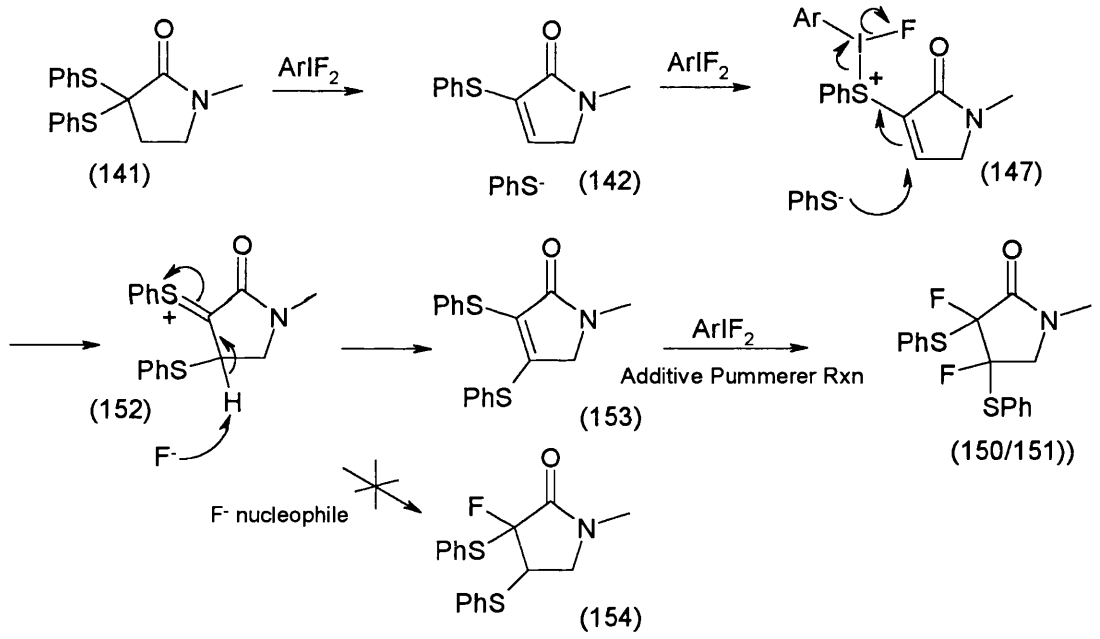


Figure 2

A yield of 38% was recorded using 2.2eq of DFIT, with the *anti*: *syn* ratio being 2: 1. The mechanism of the transformation is intriguing. Nucleophilic addition of thiophenoxide to the 4-position of activated enone (147) would be expected to take place rapidly, as it is a far superior nucleophile to fluoride. A trapping of the sulfonium ion with fluoride, in keeping with the additive Pummerer chemistry established could then occur. This appears quite feasible, but the 3-fluoro-3,4-diphenylsulfanyl derivative (154) so formed was never isolated from the reaction. A final Fluoro-Pummerer reaction could be invoked to introduce the second fluorine to the 4-position. However, this requires a third equivalent of reagent that is not present and DFIT is not generally effective on unactivated sulfides (scheme 69).



Scheme 69

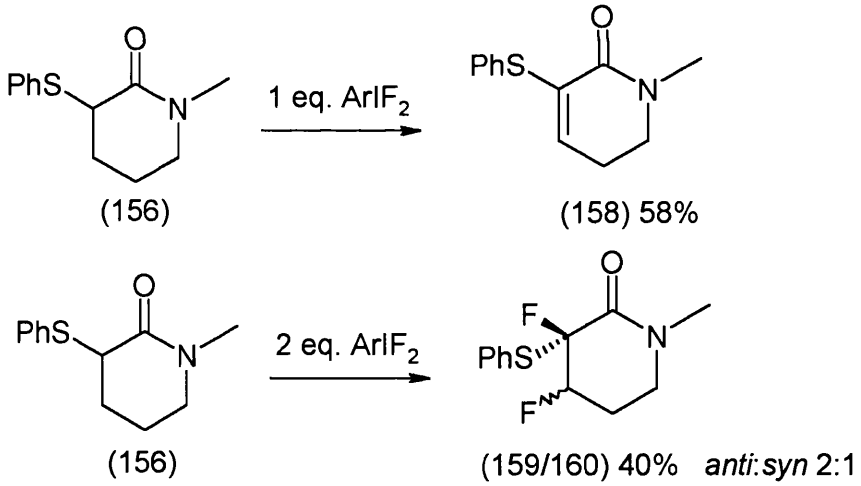
An alternative pathway would involve a second vinyl sulfide forming reaction. The vastly increased acidity of the 4-proton adjacent to sulfur could promote such a step. A final additive Pummerer reaction on the reactive β-phenylsulfanyl vinyl sulfide (153) furnishes the observed product. The additional β-phenylsulfanyl substituent would be expected to dramatically increase the rate of the additive reaction. Three equivalents of DFIT, as dictated by mechanism, led to a slightly improved yield of 46%, with the same stereoselectivity of *anti*: *syn* 2: 1.

There are relatively few reports concerning fluorination with hypervalent iodoarene difluorides which do not involve the use of an acid catalyst, amine.HF complexes being

particularly popular. We have not generally investigated this aspect of the chemistry of DFIT, wary of the lengthy optimisation necessary to secure an effective catalyst. However, it was found that addition of 25mol% of $Et_3N.3HF$ to the reaction of pyrrolidinone (140) with two equivalents of DFIT was beneficial, giving the highest yield of difluorides (144) and (145), 59%.

3.1.3 Fluorination of Higher Order Lactams

The piperidinone analogues were synthesised as above. We observed very similar results to the five-membered lactam series upon fluorination. Treatment with one equivalent of DFIT produces the 5,6-dihydro-2(1*H*)-pyridone derivative (158), whilst a second equivalent forms the fluorinated diastereoisomers (159) and (160) (scheme 70). Yields were in the same range as those for the pyrrolidinone case, *ca.* 40% although the diastereoselectivity was reversed, 2: 1 in favour of the *anti*-isomer.



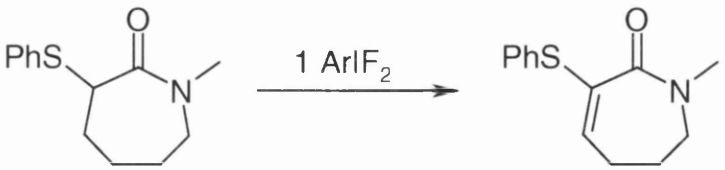
Scheme 70

The 3-F nmr signal of the major isomer appeared as a doublet with a large $^3J_{FF}$ value of 31Hz, suggesting a *trans*-diaxial arrangement of the two fluorine atoms. Single crystals could be grown from an ethyl acetate / DCM mixed solvent system that were suitable for X-ray analysis, and the major product was confirmed as the *anti* isomer (159) (figure 3).

Figure 3

The six-membered ring can be seen to adopt a flattened chair conformation, the C(2), N(1), C(1) and C(5) (X-ray structure numbering) atoms all nearly occupying the same plane around the amide bond. The dihedral angle between the two fluorines is 174°, consistent with the large *J* value observed in the nmr spectra.

The *N*-methyl caprolactam derivative (161) was transformed into the vinylic sulfide (162) on treatment with one equivalent of DFIT. Larger amounts of reagent produced a complex mixture of fluorinated products, and no characterisation was made (scheme 71).

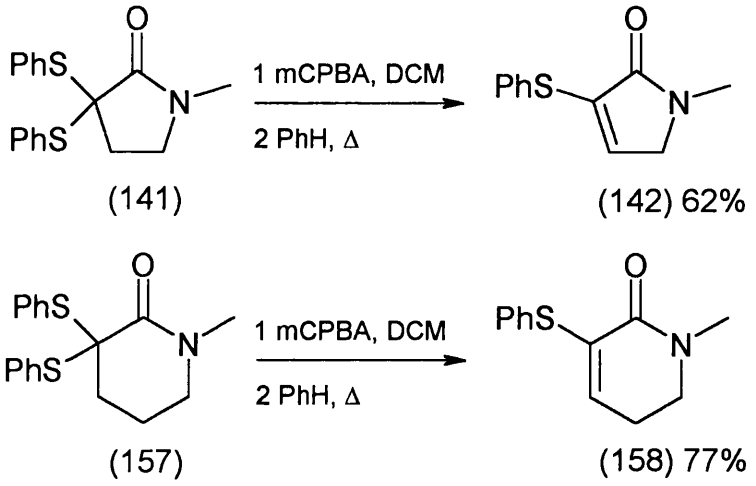


(161) (162) 44%

Scheme 71

3.2 Direct Fluorination of Vinyl Sulfides

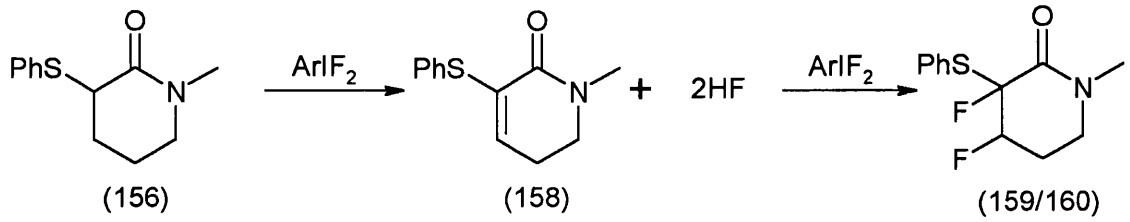
As vinyl sulfides (142) and (158) seem to be the actual fluorination substrates for DFIT, we would expect to be able to fluorinate these compounds directly. The compounds could be synthesised on a larger scale by a literature procedure shown in scheme 72.[105]



Scheme 72

The dihydropyridone (158) was, as expected, an appropriate substrate for fluorination with DFIT. Over two runs the *anti* and *syn* difluorides were isolated in 32 and 36% yield, in a 1: 1 ratio on both occasions. The slightly lower yield is puzzling, particularly as the reactions were observed to be cleaner than those of the corresponding saturated compound. Taken with the complete absence of any stereoselectivity, measured by GC and nmr, we surmise that certain components of the reaction present in the fluorination of the parent heterocycle may be absent in this case. This was emphasised when we examined the fluorination of the pyrroline derivative (142). Reaction was slow, with significant amounts of starting material still present after 24hr. The difluorinated products were formed in low yield, <20%, with many impurities present.

The crucial difference between fluorinating piperidinone (156) with two equivalents of DFIT and fluorinating dihydropyridone (158) with one equivalent is the HF generated in the first reaction (scheme 73).



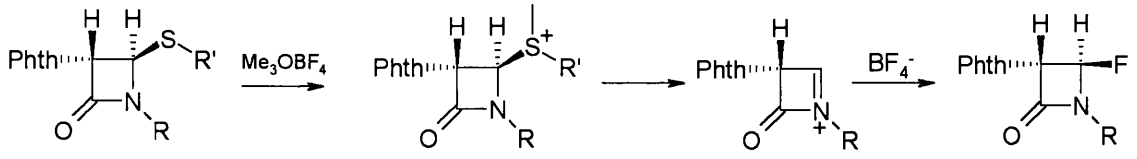
(156) (158) (159/160)

Scheme 73

Vinyl sulfide formation involves two deprotonations with basic fluoride, generating two equivalents of HF; the second fluorination step then requires two separate nucleophilic additions of fluoride nucleophile. When the two steps are performed in the one-pot by using two equivalents of DFIT there are effectively three equivalents of fluoride present for the first nucleophilic addition. The β-carbon of the DFIT-activated vinyl sulfide is not as electrophilic as the α-acyl sulfonium ion trapped by the second fluoride, and efficient nucleophilic addition of the relatively weak fluoride nucleophile will benefit froma higher concentration of fluoride in the reaction. The single equivalent of fluoride liberated upon direct DFIT activation of the vinyl sulfide may thus account for the unexpectedly poor yields observed.

3.3 Fluorination of 5-Sulfanylated Pyrrolidinones

We were aware of Brennan's report concerning the fluorination of 4-sulfur substituted β-lactams (163) with trimethyloxonium tetrafluoroborate.[106] The sulfonium salt generated decomposes to an azetidinium species (164) that is quenched *via* fluoride ion transfer from tetrafluoroborate (scheme 74).

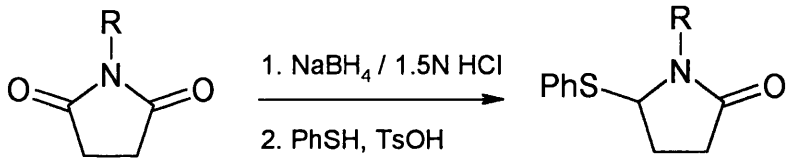


(163) (164) (165) 40%

Scheme 74

Fuchigami had studied similar compounds, finding that anodic oxidation in $Et_3N.3HF$ / MeCN gave efficient fluorodesulfurisation.[67] We were interested to see if DFIT could fluorodesulfurise such compounds, having already generated an azetidinium species in the DFIT-mediated fluorination of cephalosporin derivatives (*see introduction, 1.5*). We

chose to examine the analogous pyrrolidinones initially, synthesising structures (166) and (167) according to a sequence developed by Hart (scheme 75).[107] The appreciable water solubility of the intermediate carbinollactam in the synthesis of (166) accounts for the extremely poor yield.



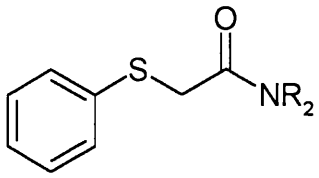
(166) R=Me 6%
(167) R=Bn 80%

Scheme 75

Our attempts at fluorinating the pyrrolidinones proved fruitless. No fluorination was detected by ^{19}F nmr on treatment of either compound with two equivalents of DFIT in DCM. Attempts at purifying the complex reaction mixtures were unsuccessful, and no products could be characterised. The initial generation of the acyl iminium species could be the problem, involving the formation of a weak sulfur-iodine bond and the cleavage of the much stronger carbon-sulfur bond. By contrast, Brennan's use of trimethyloxonium tetrafluoroborate to form the acyl iminium species in the azetidinone case involves the sulfonium intermediate decomposing to a stable sulfide.

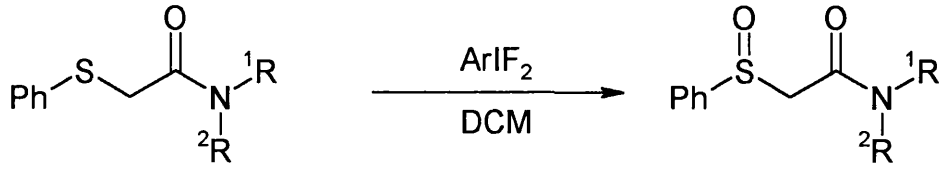
3.4 Fluorination of Acyclic Amides

α-Phenylsulfanyl amides (29) were examined with the aim of cleanly forming monofluorides. The absence of any β-hydrogens was expected to simplify matters, with the α-fluorosulfide being the only feasible product from a Fluoro-Pummerer transformation. The synthesis of such compounds has already been described (*vide supra*).



(29)

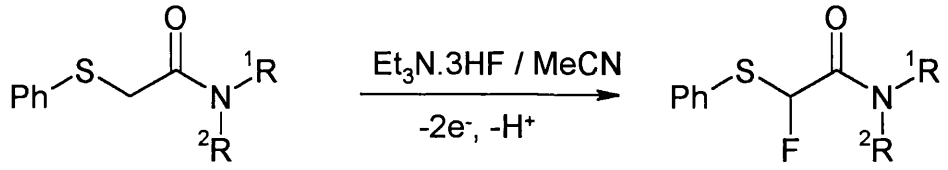
Initial experiments were performed on the *N*-alkyl and *N*-phenyl compounds shown below in scheme 76. We were surprised to find that sulfoxides (170)-(172) were the major products in each case, being formed in excellent yield. Characterisation was straightforward, the starting material SCH_2 nmr singlet being transformed to an AB quartet in the product due to the oxidation rendering the two α-protons diastereotopic.



No	^{1}R	^{2}R	eq. of $ArIF_2$	Sulfoxide yield No (%)
(132)	*n*-Bu	H	2	(170) 86
(168)	Ph	H	1	(171) 78
(169)	Ph	Me	1	(172) 86

Scheme 76

The possibility that the amide group is not sufficiently electron-withdrawing to support the Fluoro-Pummerer reaction is unlikely as Fuchigami has reported the anodic fluorination of similar substrates (173) and (174) to be straightforward (scheme 77).[58]



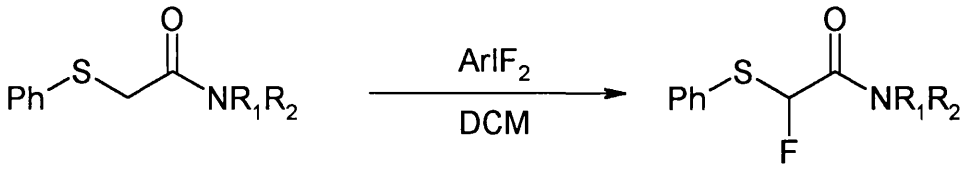
No	^{1}R	^{2}R	Fluoride yield (%)
(173)	*n*-Pr	H	88
(174)	Et	Et	80

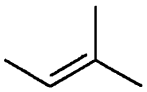
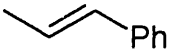
Scheme 77

The mechanism of anodic monofluorination is postulated (*see introduction, 1.2*) to involve the generation of a fluorosulfonium species $[PhS(F)CH_2R]^+$ (90) through SET, the next step being deprotonation with fluoride to form the crucial sulfonium ion $[PhS{=}CHR]^+$. An electron transfer mechanism may be invoked for DFIT mediated fluorination, and indeed has been for the fluorination of steroidal dienes performed by previous workers in the group.[12] When dealing with sulfur functionality however, we have preferred a polar mechanism involving nucleophilic attack at iodine, as this is the dominant mode in hypervalent iodine chemistry. The iodosulfonium intermediate is well established in the oxidation of simple sulfides such as methionine to the cyclic sulfilimine dehydromethionine using iodine, for example.[108,109] Why the sulfonium species $[PhS(IArF)CH_2R]^+$ that we believe to be generated through this mechanism should be less acidic than (90) is not clear. Indeed substrates with markedly less acidic α-protons such as thioanisole (*vide infra*) are good substrates for the Fluoro-Pummerer reaction with DFIT.

Addition of an external base to promote the Fluoro-Pummerer reaction was unsuccessful, treating the *N*-methyl-*N*-phenyl derivative with DFIT and caesium fluoride in acetonitrile providing the sulfoxide in 53% yield.

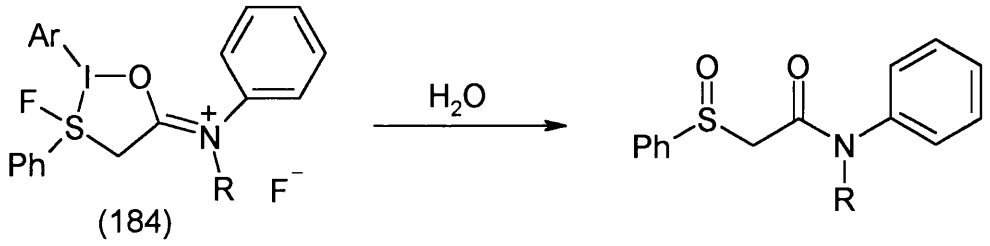
The issue is further complicated by the finding that certain phenylsulfanylacetamides are perfectly good substrates for the DFIT Fluoro-Pummerer reaction. Compounds (175)-(178) were synthesised with the aim of investigating possible olefin cyclisations initiated by the Fluoro-Pummerer reaction (*vide infra*). On treatment with one equivalent of DFIT in DCM at 0°C or at reflux they were cleanly transformed into the corresponding fluorides (scheme 78).



No	R_1	R_2	Temp. (°C)	Fluoride yield No (%)
(175)		H	40	(179) 71
(176)		H	40	(180) 25
(177)		H	40	(181) 55
(178)	CH_2Ph	Me	0	(182) 68

Scheme 78

The resistance of amide substrates (132), (168) and (169) to fluorination leads us to suggest that DFIT may be forming a chelate complex (184) with these compounds similar to that alluded to in the oxidation of azetidinone sulfides (*vide supra*). Disruption of the chelate through deprotonation at the α-carbon may then be energetically unfavourable and the Fluoro-Pummerer transformation cannot take place. Quenching the reaction with an excess of water hydrolyses the complex and produces the sulfoxides (scheme 79).

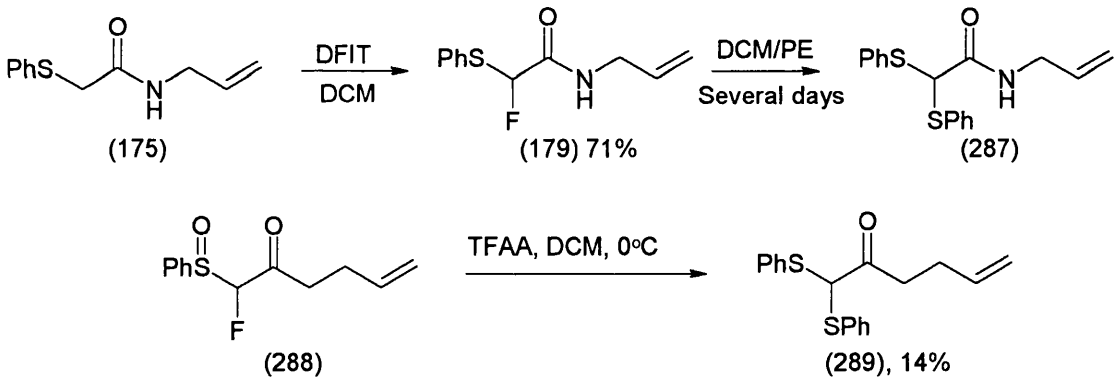


Scheme 79

The phenyl substituent would be expected to offer good stabilisation to the charged nitrogen in (184) in the case of the two aniline derivatives. Those amides which undergo fluorination lack the substituents to support such a feature. The resistance of the *n*-butyl derivative to fluorination is exceptional in this regard.

A second fluoro-Pummerer reaction following the first fluorination is quite feasible, treatment of the allyl derivative (175) with two equivalents of DFIT in DCM at 0°C produced the difluoride in 61% yield. We also chose the amide (175) to demonstrate the robustness of DFIT under storage. A batch of the reagent that had been in the refrigerator for six months was used to fluorinate (175), giving a 66% yield of the monofluoride (179) after 1hr of reflux. The minimal drop in yield demonstrates the ease with which the reagent may be stored for lengthy periods of time and adds to the weight of evidence in favour of the preparation and use of the compound as a solid.

Analysis of (179) produced some interesting results. ^{1}H, ^{13}C and ^{19}F nmr spectra were entirely in accord with the monofluoride structure, but the mass spectrum was consistently at odds with this assignment, indicating a heavier compound (MH^{+} = 316). When the material was recrystallised from DCM / PE 30-40 over several days the pure crystals isolated were characterised by microanalysis and nmr to be the thioacetal (287), in accord with the earlier mass spectrometry results (scheme 80).

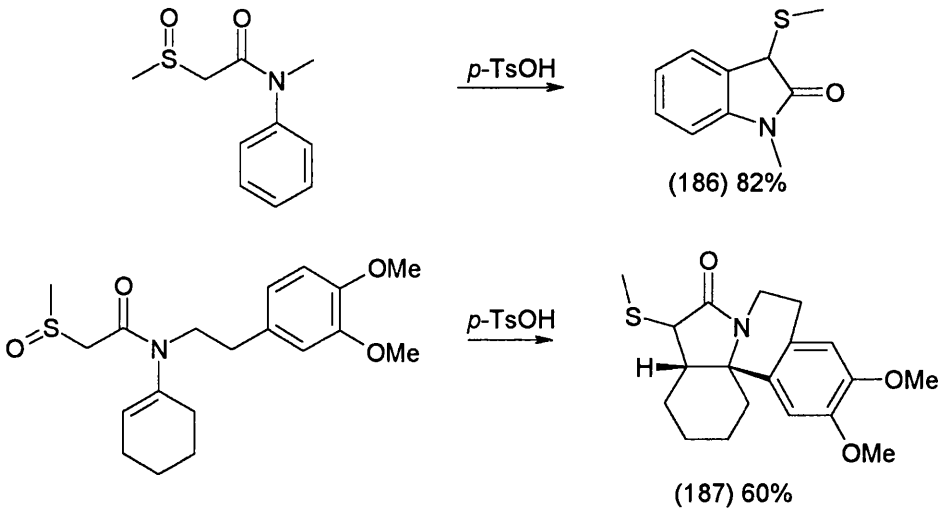


Scheme 80

We can offer no explanation for the exceptional behaviour of the *N*-allyl derivative, but note that Ishibashi reported a related transformation of the sulfoxide (288) with TFAA in an attempted Pummerer-cyclisation.[113]

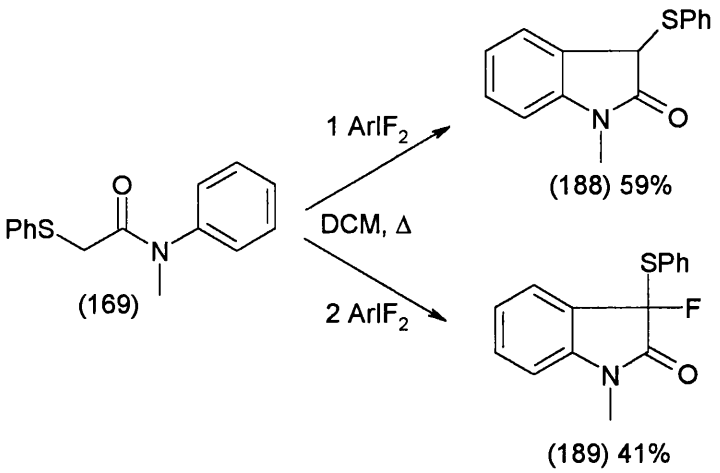
The α-acyl sulfonium ions generated from α-acyl sulfoxides are particularly powerful electrophiles and there are many reports detailing their efficient reaction with nucleophilic carbon species such as alkenes, aromatics and enol ethers; the subject being recently reviewed.[110] The Ishibashi group has published extensively on the intramolecular Friedel-Crafts cyclisation of Pummerer sulfonium ion intermediates to form heterocycles.[110-115] Scheme 81 shows two examples of this chemistry; the

synthesis of an oxindole (186)[114] and the erythrinane skeleton (187)[115] from α-sulfinylacetamides.



Scheme 81

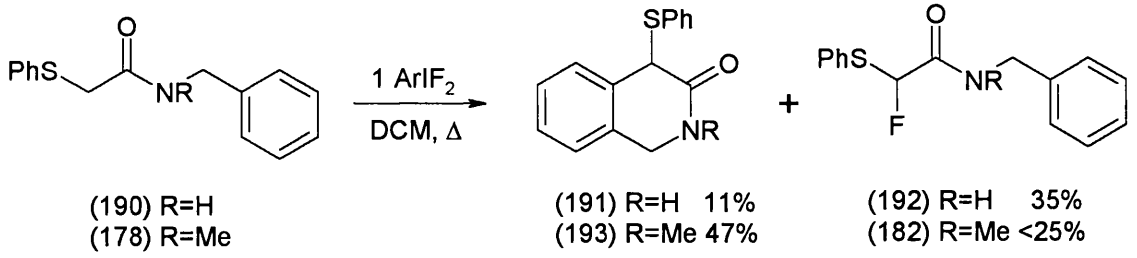
There have been a small number of reports concerning the Pummerer-type reaction using hypervalent iodine reagents.[116,117] Tamura found that *N*-phenyl α-sulfanylacetamides could be cyclised to oxindoles on treatment with phenyl iodosyl bis(trifluoroacetate).[116] Yields were good, although lower than those achieved for the Pummerer reaction of the sulfoxide with *p*-toluenesulfonic acid. The procedure was thought to be more practical as it was not necessary to oxidise the starting material to the sulfoxide. An iodosulfonium salt was postuated as the precursor to the familiar α-acyl sulfonium intermediate. We were accordingly interested to see if the α-acyl sulfonium ions generated in the Fluoro-Pummerer reaction of α-sulfanylacetamides with DFIT could be trapped by intramolecular carbon nucleophiles in a similar fashion. Initial experiments conducted on the *N*-methyl derivative (169) demonstrated the principle to be sound, with the oxindole (188) being produced in 59% yield on treatment with one equivalent of DFIT in refluxing DCM (scheme 82).



Scheme 82

The elevated temperature enables deprotonation of the postulated chelate complex (184) and generation of the required α-acyl sulfonium ion. The stability of DFIT to heating had not previously been demonstrated, and may have significance to future applications. The reaction had to be conducted in a glass vessel as polypropylene would melt at the temperature of refluxing DCM. Two equivalents of reagent produced the expected 3-fluoro-3-phenylsulfanyl-indol-2-one derivative (189) in 41% yield.

The benzylamine derivatives (190) and (178) did not cyclise as effectively as the aniline derivative (169), mixtures of monofluoride and tetrahydroisoquinolines resulting (scheme 83).



(190) R=H
(178) R=Me

(191) R=H 11%
(193) R=Me 47%

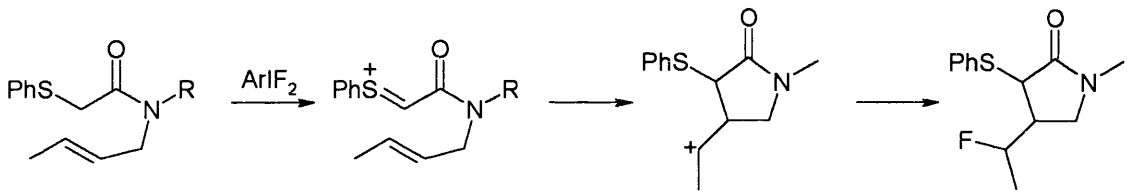
(192) R=H 35%
(182) R=Me <25%

Scheme 83

Conventional Pummerer conditions often lead to the trapping of the α-acyl sulfonium ion with acetate present in the reaction and this can then in turn be displaced by an intramolecular nucleophile, since it is also a good leaving group. Fluoride anion by contrast is a poor leaving group and once the intermediate sulfonium ion is trapped with fluoride in the Fluoro-Pummerer reaction the strength of the carbon-fluorine bond so formed precludes further reaction. In the above example the rate of fluoride addition to

the intermediate sulfonium ion is competitive with the rate of cyclisation and a mixture of products results. The faster rate of 5-*exo-trig* relative to 6-*exo-trig* cyclisation explains the clean transformation of the aniline derivative (169) into cyclised product. The poorer yields for the secondary amide relative to the tertiary amide are in keeping with literature precedent, secondary amides are extremely poor substrates for similar *p*-toluenesulfonic acid-mediated processes.[114]

The success of the Friedel-Crafts alkylation of α-acyl sulfonium ions generated by DFIT, albeit in lower yields than the conventional Pummerer reactions suggested that we could also incorporate a carbon-fluorine bond-forming step into the reaction. Thus we envisaged that trapping of the intermediate with an alkene would generate an alkyl carbocation which can in turn be trapped with fluoride (scheme 84).

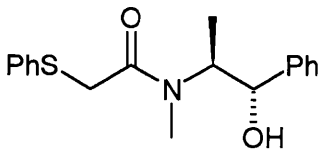


Scheme 84

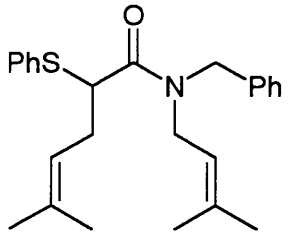
We prepared the *N*-allyl, *N*-prenyl and *N*-cinnamyl phenylsulfanylacetamides (175), (176) and (177) described earlier (scheme 78). The allyl derivative is the least likely of the three substrates to cyclise as 5-*exo*-trig cyclisation forms an unstabilised primary carbocation. The other two substrates are well set up for cyclisation however, the intermediate carbocations being more stable. In the event, as we have seen (scheme 78), treating each of the compounds with one equivalent of DFIT in refluxing DCM gave the monofluoride as the only product.

We ascribe the course of the reaction to the diminished nucleophilicity of the double bond. Whereas an aromatic ring can successfully compete with fluoride to trap the sulfonium cation, the double bond in these two substrates cannot. Displacement of fluoride is not feasible, as mentioned above.

Alternative strategies pursued included the preparation of the ephedrine derivative (194), where oxygen could act as the intramolecular nucleophile, and the prenylated material (195) that has the possibility of a cyclisation cascade. Both substrates however produced complex mixtures on treatment with DFIT.



(194)

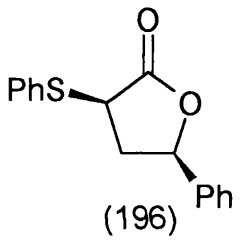


(195)

Chapter 4. Fluorination of Esters

4.1 Fluorination of Lactones

As a comparative study, we examined the fluorination of lactones by first preparing the highly crystalline substrate (196) through bromination of the parent lactone and subsequent displacement of the *anti*-bromide so formed with thiophenoxide anion. The displacement proceeded with clean inversion, forming the *syn* diastereoisomer only. An ^{1}H nmr analysis of the *syn* diastereoisomer (196) has been reported with the aim of elucidating the conformations adopted by such lactones.[118] The heterocycle was found to exist predominately in one conformation with both substituents occupying pseudoequatorial positions.



(196)

Fluorination with one equivalent of DFIT produced the monofluoride (200) as a single diastereoisomer in 62% yield. There was no evidence of any vinyl sulfide arising from β-elimination, in marked contrast to the lactam system. The fluoride was highly crystalline and single crystals could be grown with relative facility from a DCM / PE 30-40 mixed solvent system. The X-ray analysis established a *syn* relationship between the fluorine atom and the 5-phenyl substituent. The phenylsulfanyl group is pseudoaxial and the phenyl group pseudoequatorial, the longer C-S bond length relative to the C-C bond renders the sulfur more stable in the axial position than the phenyl group (figure 4 overleaf).

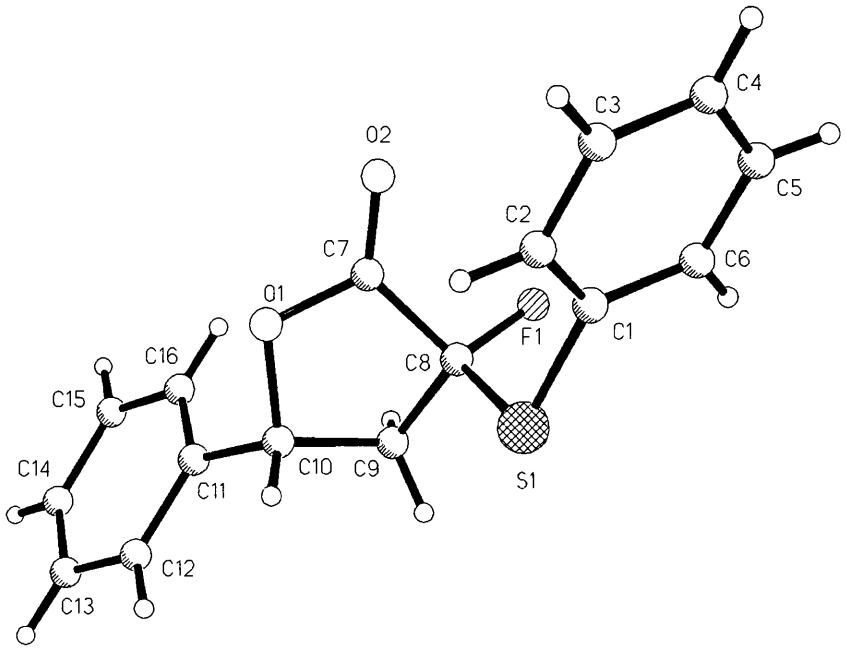
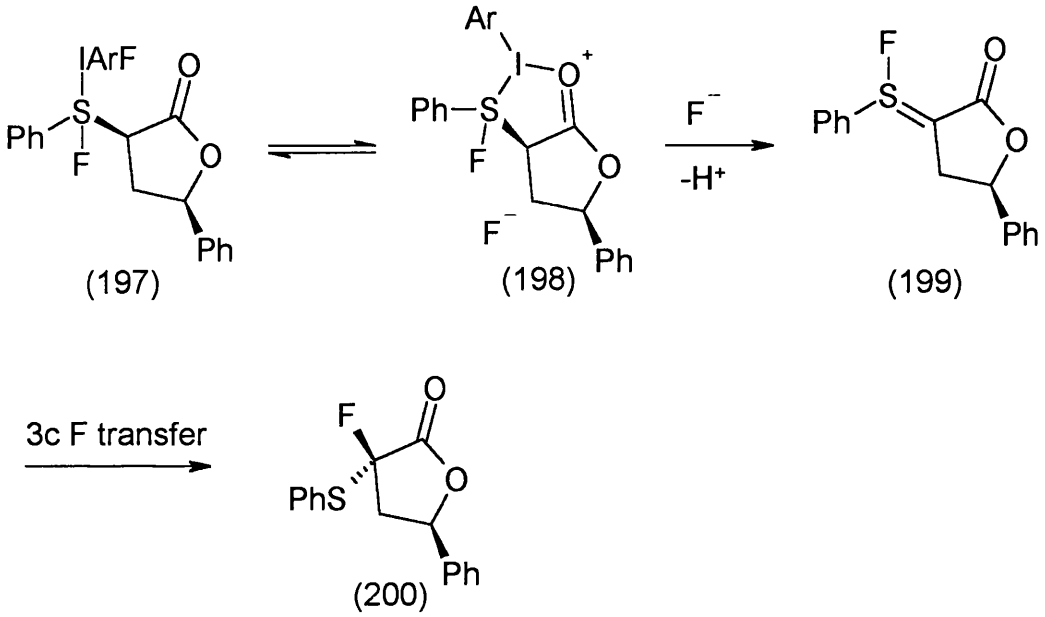


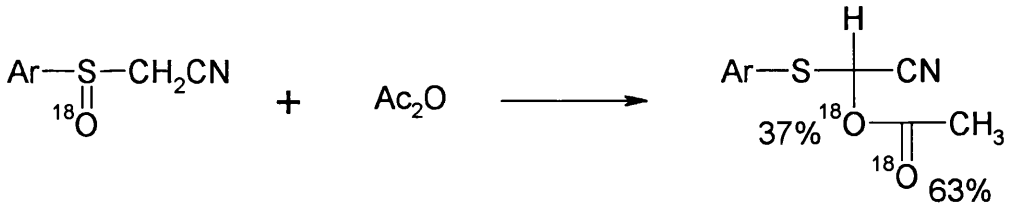
Figure 4

Whilst electrophilic addition to the lithium enolate of (196) was reported to take place *anti* to the phenyl group in the case of methylation and sulfanylation reactions,[118] the nucleophilic addition of fluoride to the planar sulfonium ion in the present case is occurring *syn* to the large phenyl group. This result appears to be at odds with the mechanistic scheme we have been using to rationalise the Fluoro-Pummerer chemistry of DFIT, in which the nucleophilic attack of fluoride would surely take place from the opposite face to the large phenyl substituent. This leads us to consider a possible intramolecular transfer of fluorine from sulfur to carbon, similar to that proposed by Janzen for the α-fluorination of sulfides with xenon difluoride (*see section 1.2.2*).[39] The intermediate sulfurane (197), in equilibrium with the corresponding sulfonium salt, liberates fluoride through oxygen coordination. Deprotonation with basic fluoride generates the sulfonium ylide (199), and a three centre fluorine transfer then forms the observed α-fluoro sulfide. The remote 5-phenyl substituent would have minimal influence on the stereoselectivity of this transfer (scheme 85).



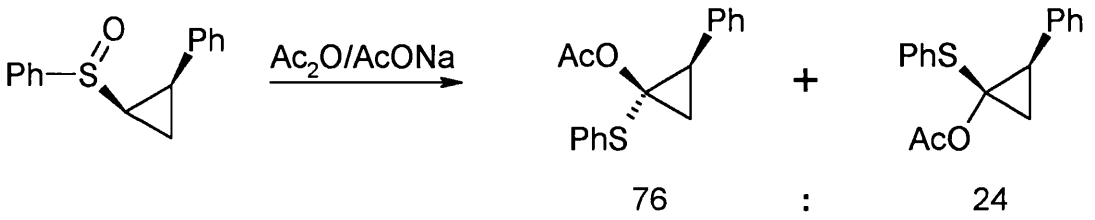
Scheme 85

Intramolecular migration of the nucleophile from sulfur to carbon in the Pummerer reaction has been shown to occur with certain substrates through labelling experiments.[119] The reaction of acetic anhydride with ^{18}O labelled cyanomethyl *p*-tolyl sulfoxide was shown to proceed *via* intramolecular acetoxy migration at least to the extent of 90%. Some of the ^{18}O was found in the ethereal oxygen, suggesting a three-membered sliding mode similar to that proposed above was operating in part (scheme 86).



Scheme 86

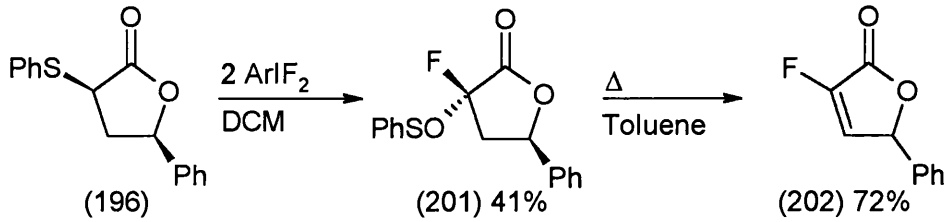
Nucleophilic addition of acetate in the Pummerer reaction to the more hindered face of a substrate was reported for the cyclopropyl compounds shown below in scheme 87.[120] The acetate nucleophile attacks the α-carbon from the back side of the proton removed, leading the authors to propose a highly concerted transition state involving simultaneous deprotonation and nucleophilic attack.



Scheme 87

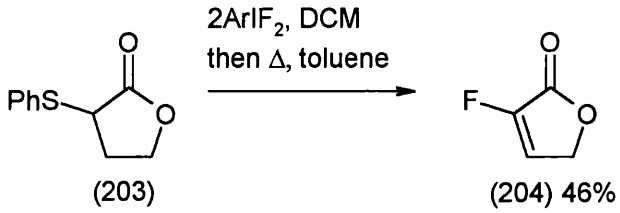
Removal of the α-proton from the lactone in this work must necessarily occur *anti* to the 5-phenyl group. A rapid fluorine transfer from sulfur to carbon from the back-side of the departing proton would then produce the observed fluoride (200), with fluorine *syn* to the phenyl group.

A second equivalent of reagent produced the fluoro-sulfoxide (201) as a 5: 2 mixture of sulfoxide diastereoisomers in 41% yield. We recognised this result to have a significant bearing on our interest in the synthesis of vinyl fluorides as α-fluoro sulfoxides may be converted to these compounds through pyrolytic elimination of sulfenic acid.[121] The clean transformation of (196) to the α-fluoro sulfoxide represents the first clear opportunity we have had to investigate possible vinyl fluoride syntheses through the primary agency of DFIT. In the event heating the material in toluene for 20min provided the expected 3-fluoro-2(5*H*)-furanone derivative (202) in 72% yield (scheme 88). The ubiquity of the furanone ring system in biologically active compounds[122] makes such fluorinated synthons potentially important templates for the synthesis of a variety of fluorinated materials.[123, 124]



Scheme 88

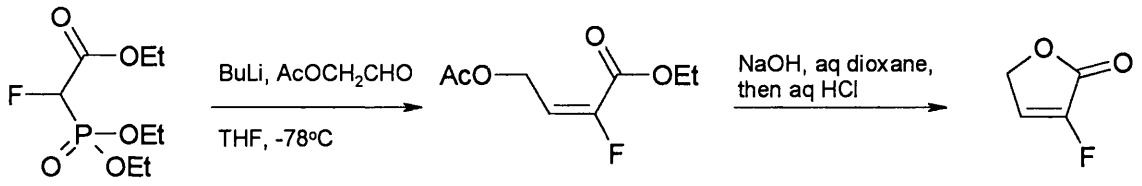
Yields of vinyl fluoride may be improved if the process could be telescoped into a one-pot procedure. With this in mind we took the simple 4,5-dihydro-3-phenylsulfanyl-2(3*H*)-furanone (203) and treated it with two equivalents of DFIT. On completion the reaction was subjected to aqueous work-up, concentrated and taken into toluene. Pyrolytic elimination provided 3-fluoro-2(5*H*)-furanone (204) in 46% yield.



(203) (204) 46%

Scheme 89

Approaches to compounds such as (204) in the literature[124] are based on the Wittig-Horner reaction of fluorophosphonates (205) with an appropriate aldehyde (scheme 90).



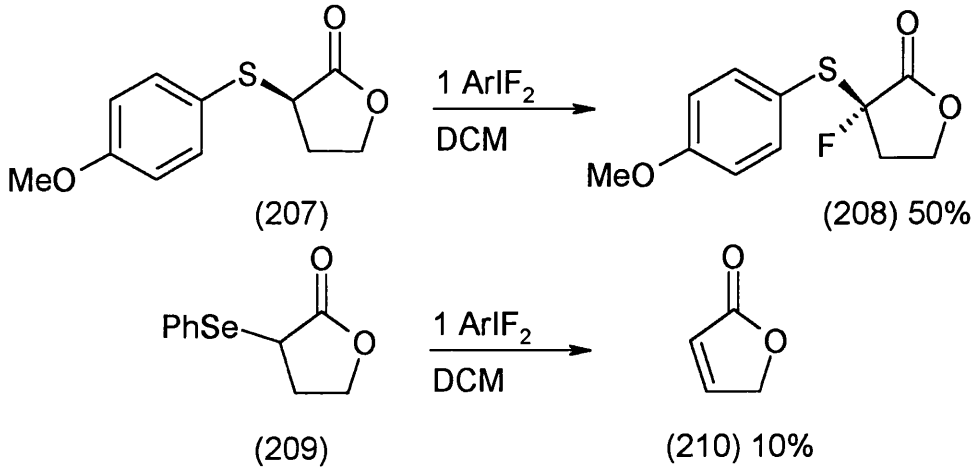
(205) (206) 95% (204) 56%

Scheme 90

The drawbacks of such an approach stem from the inflexibility inherent in any non carbon-fluorine bond forming strategy. The cyclisation is dependant on the 2-fluoro-2-butenoate being formed with the *E*-geometry, an important stereochemical issue that may preclude the use of certain ketones in the preparation of functionalised 3-fluoro-2(5*H*)-furanones by this route. The fluorophosphonate reagent (205) is also relatively expensive. Fluorination of the parent lactone with DFIT represents a more flexible approach. The sulfanylation reaction, although not optimised in this work has been reported to proceed in 91% yield using lithium thiophenoxide.[125] The fluorination-pyrolytic elimination step also works well and would undoubtedly benefit from optimisation studies, making this a potentially versatile approach to these compounds starting from cheap and readily available lactones.

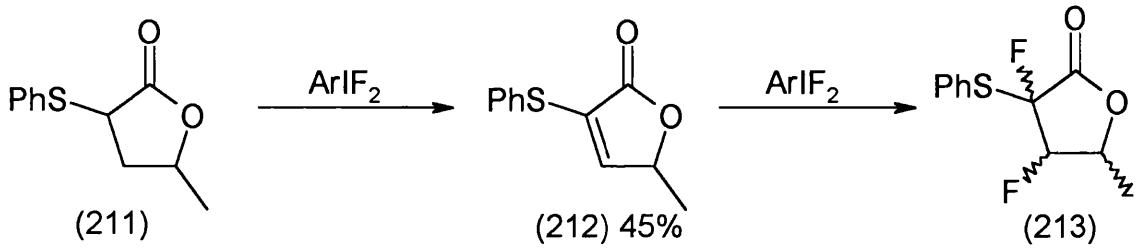
The *p*-methoxyphenyl derivative (207) was examined as a possible substrate as the methoxy substituent in the 4-position of the aryl ring was reported to rapidly accelerate the Fluoro-Pummerer reaction of DAST with certain aryl sulfoxides, as discussed previously. However, no such amelioration was recorded using DFIT, with the fluorosulfide (208) being formed in a slightly lower yield than that observed for the parent sulfide. The selenium analogue (209) proved to be unsuitable for fluorination,

treatment with two equivalents of DFIT giving a low yield of crotonolactone (210) (scheme 91).



Scheme 91

To our surprise the 5-methyl substituted lactone (211) gave different results to previous substrates, with the vinyl sulfide (212) being the primary product of the Fluoro-Pummerer reaction. By analogy with our study of lactam derivatives, a second equivalent of DFIT gave the expected *vic*-difluorides (213), separation of which proved impossible by column chromatography. The additional stereocentre present in this substrate generates a complex mixture of diastereoisomeric difluorides that could not be fully characterised (scheme 92).

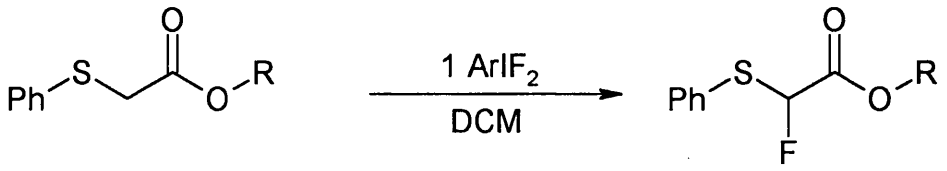


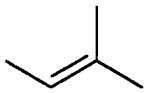
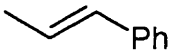
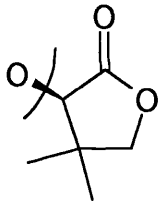
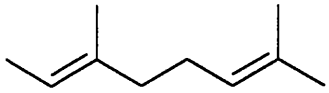
Scheme 92

Vinyl sulfide (212) was reported to be formed as the exclusive product from the Pummerer reaction of the corresponding phenylsulfinyl-lactone with acetic anhydride.[126]

4.2 Fluorination of Acyclic Esters

Simple α-phenylsulfanyl esters proved to be excellent substrates for the Fluoro-Pummerer reaction of DFIT, producing the monofluorides cleanly and in good yield (scheme 93).



No.	R	Yield of fluoride (x) (%)
(214)		(219) 64
(215)		(220) 67
(216)		(221) 53
(217)	Ph	(222) 72
(218)		0

Scheme 93

The (*R*)-pantolactone derivative (216) produced the two diastereoisomeric fluorides in a 1: 1 ratio. The geranyl substrate (218) was surprisingly poor, although fluorination appeared to proceed cleanly from the evidence of the tlc plate. Upon work-up of the reaction mixture the crude DCM solution darkened on standing and no products could be isolated after further purification steps.

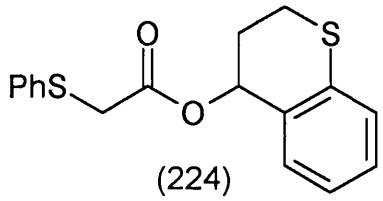
The Fuchigami group has reported the fluorination of such α-phenylsulfanyl esters with *p*-methoxyiodobenzene difluoride (223), this being the only published account of the

Fluoro-Pummerer reaction using hypervalent iodine reagents (*see section 1.2.7*).[68] In contrast to the usually superb yields recorded by this group for the electrochemical Fluoro-Pummerer reaction, the results for the fluorination of ethyl (arylsulfanyl)acetates with electrochemically generated (223) in the presence of a substantial excess of $Et_3N.3HF$ were poor. The clear superiority of pure DFIT in the absence of any amine.HF catalysts for this transformation is noteworthy, although Fuchigami did not investigate the effectiveness of DFIT under his conditions.

There have been far fewer reports concerning the intramolecular alkylation of α-sulfinylesters under the Pummerer reaction conditions to form lactones relative to the corresponding transformation of α-sulfinylamides.[110] Accordingly all of the esters shown above failed to form any lactone derivative after DFIT treatment in refluxing DCM. The phenolic derivative (217) was an exception, with a low yield of the 2-coumaranone derivative identified from the ^1H nmr. Elevated temperatures proved unsuitable for the ester substrates in general as no monofluorides could be isolated after reaction under these conditions.

The increased basicity of fluoride in acetonitrile[127] relative to DCM has been utilised in the group previously to suppress nucleophilic addition of fluoride.[18] We employed acetonitrile as solvent in this instance to increase the chance of carbon-carbon bond formation, however the approach was unsuccessful with the monofluoride being isolated in 60% yield.

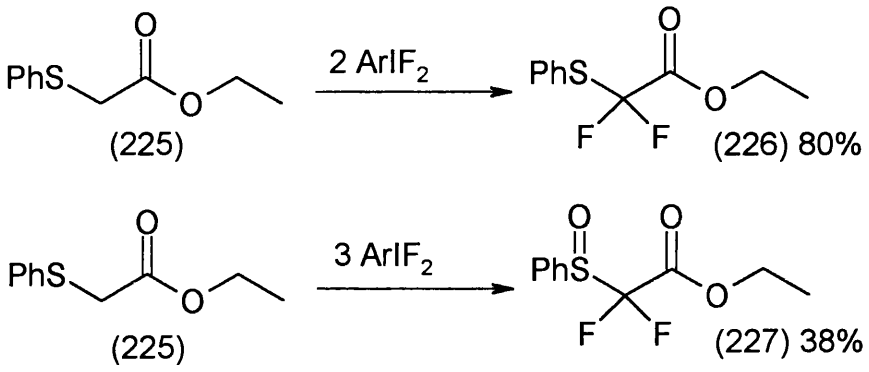
The thiochromanyl derivative (224) was synthesised as a prospective substrate for intramolecular Friedel-Crafts alkylation. However, in spite of containing two sulfur atoms it proved surprisingly unreceptive to DFIT treatment and no products could be characterised from the reaction.



(224)

The difluorination observed with α-phenylsulfanylacetamides could be applied equally well to the ester series. The ethyl ester (225) gave an excellent yield of the difluoride when treated with two equivalents of DFIT. A further oxidation step could be

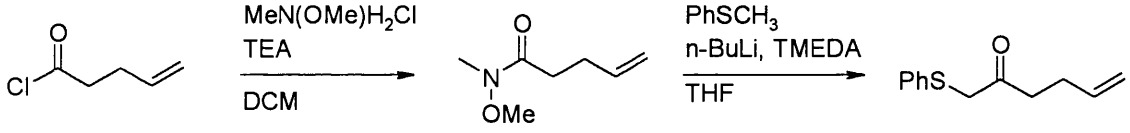
accomplished through treating the material with 3eq, although the yield was lowered substantially (scheme 94).



Scheme 94

Chapter 5. Fluorination of Other β-EWG Sulfides

The chemistry was briefly extended to ketones, with one acyclic and one cyclic substrate being synthesised. We investigated the sulfanylation of 4-methyl-pent-3-enyl methyl ketone with a variety of reagents and found it to be more challenging than expected. Treatment with diphenyl disulfide and LDA was unsuccessful regardless of the stoichiometry, with low yields of the bissulfanylated material being the only product isolated.[128] Formation of the enol borinate and reaction with phenylsulfanyl chloride according to Paterson was similarly unrewarding.[129] We eventually synthesised the Weinreb amide (228) derived from 4-pentenoic acid and treated it with lithiated thioanisole, cleanly forming the required β-oxo sulfide (229) (scheme 95).[130]

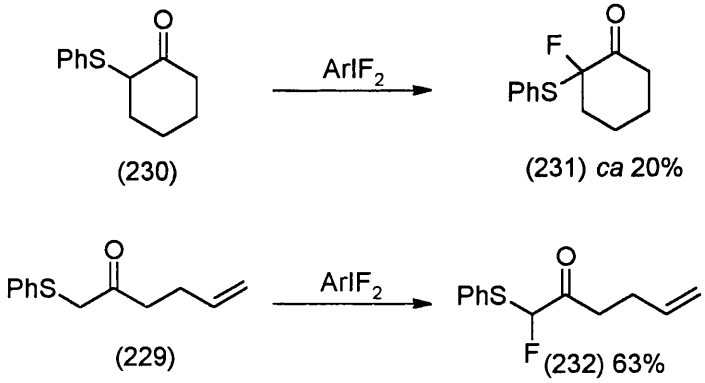


(228) 26% (229) 45%

Scheme 95

Sulfanylation of cyclohexanone was similarly problematic, reaction of the lithium enolate with diphenyl disulfide again failing to give a clean transformation. Treating the trimethylsilyl enol ether with phenylsulfanyl chloride worked well however, with 2-phenylsulfanyl-cyclohexanone (230) being formed in 50% yield.

Fluorination of the acyclic substrate was uneventful, with the monofluoride (232) synthesised in 63% yield. The cyclohexanone proved to be a poorer substrate, with low yields of the simple monofluoride (231) being isolated (scheme 96).



(230) (231) *ca* 20%

(229) (232) 63%

Scheme 96

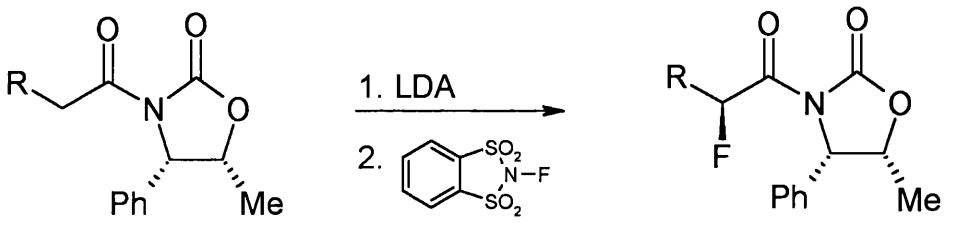
Unlike the majority of α-acyl fluorosulfides that we have prepared, fluoride (231) was markedly unstable, degrading overnight on the bench. Fuchigami has reported the anodic fluorination of substrate (230), finding that the product was difficult to characterise due to the ease with which it eliminated HF.[58] This would seem to be the problem here, the mass spectrum of the fluoride sample showing a 100% [M-HF] peak. However the degradation was certainly not clean and the product vinyl sulfide could not be characterised. The simple Fluoro-Pummerer mode was dominant, regardless of the reaction stoichiometry.

Cyano sulfoxides have been used for the formation of reactive sulfonium ions.[131] The α- and β-cyano phenylsulfides (233) and (234) were therefore prepared to investigate their suitablity for Fluoro-Pummerer chemistry with DFIT.

(233) (234)

α-Fluoro sulfides were formed in 34 and 61% yield respectively. The low yield from fluorination of (233) is rather disappointing as it is potentially a versatile fluorinated-synthon; it can be easily alkylated at the α-position and transformed to the appropriate carbonyl derivative.

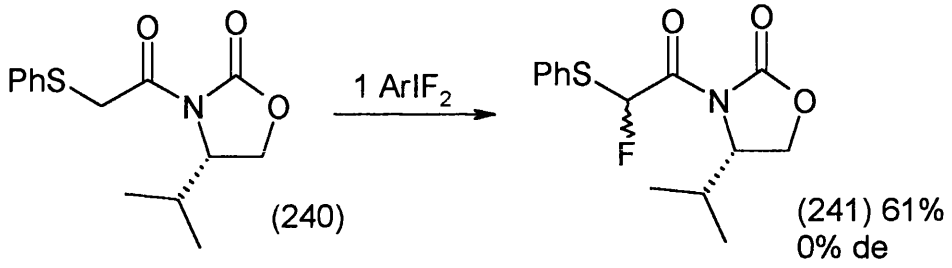
The diastereoselective fluorination of chiral enolates with electrophilic fluorinating agents has recently been reported.[132,133] Fluorination of the imide (237) for example with *N*-fluoro-*o*-benzenedisulfonamide (238) gives α-fluoro carboxamides (239) in 86-95% de (scheme 97). Removal of the chiral auxillary was reported to be problematic due to racemisation as a consequence of the increased acidity of the α-proton.[132]



(237) (238) (239) 61%
86-95% de

Scheme 97

We were interested to see if DFIT would fluorinate a similar imide in a diastereoselective fashion since the product fluorides would be useful synthons and the degree of diastereoselectivity could offer some insights into the mechanism of the DFIT Fluoro-Pummerer reaction. The chiral imide (240) was prepared in standard fashion through acylation of the Evans chiral auxillary derived from L-valinol.[134] Fluorination with one equivalent of DFIT however gave the diastereoisomeric fluorides (241) in a 1: 1 ratio in good yield (scheme 98).



Scheme 98

The success of such systems in enolate chemistry is often ascribed to a rigid conformation enforced by chelation of both carbonyl groups with a metal cation.[134] In this case the iodine centre would be expected to chelate the sulfur and the β-oxygen, allowing significant conformational flexibility of the isopropyl blocking group on the oxazolidinone. This could explain the lack of any selectivity, although we would expect the diastereoselective addition of such a small nucleophile as free fluoride anion to be inherently difficult. The mechanism of fluorination of anions with *N*-fluoro reagents is believed by certain authors to be S_N2 in nature,[135,136] an addition of the chiral enolate onto a large fluorinating agent would be expected to show far better diastereoselectivity.

Chapter 6. Fluorination of Unactivated Sulfides

The Fluoro-Pummerer reaction of simple dialkyl sulfides is not generally effective for reasons set out in the introduction, although potent reagents such as DAST are reported to be successful regardless of the sulfur substituents.[25,32,46] We decided to investigate the fluorination of such substrates with DFIT in any case by synthesising methyl octyl sulfide (242), a compound that will react with certain *N*-fluoro reagents to give the fluoromethyl derivative.[46] Unsurprisingly, it proved to be a poor substrate for DFIT, with complex mixtures resulting under various conditions. The popular technique of oxidising the crude products to the more stable fluoro-sulfoxide or fluoro-sulfone failed to simplify matters.

In contrast to dialkyl sulfides, aryl alkyl sulfides have proven to be excellent substrates for the Fluoro-Pummerer reaction with a variety of reagents, thioanisole derivatives in particular being extensively investigated. The fluoromethyl aryl sulfides formed are typically unstable to work-up techniques and are oxidised *in situ* to the appropriate sulfoxide or sulfone. DAST in particular is very effective for the fluorination of thioanisole under antimony trichloride catalysis, fluoromethyl phenyl sulfone being synthesised in 94% yield after an mCPBA oxidation step.[71] This compound in particular exemplifies the utility of the Fluoro-Pummerer reaction, being an important synthon for vinyl fluoride synthesis.[70-73]

We were surprised to find that treatment of thioanisole with two or more equivalents of DFIT produced difluoromethyl phenyl sulfoxide (243) in good yield. Two Fluoro-Pummerer reactions and an oxidation would dictate the use of three equivalents of reagent, and this was found to give the best yield, 67% (scheme 99).

(243) 67%

Scheme 99

The potential of this transformation is significant. Firstly, the efficiency of the two sequential Fluoro-Pummerer reactions in one pot is unusual. Robbins reported the

attempted difluorination of thioanisole derivatives with 3eq of DAST under antimony trichloride catalysis gave dark mixtures of mainly unreacted starting material.[35] A second fluorination of fluoromethyl phenyl sulfoxide with DAST was also problematic, with a 23% yield of the unstable difluoromethyl phenyl sulfide being recorded.[25] Fluorination of thioanisole with xenon difluoride / anhydrous HF mixtures has been used successfully, but such an approach is both hazardous and expensive.[36,39] Secondly, out of all of the Fluoro-Pummerer reagents DFIT is unique in having the ability to oxidise sulfur to the sulfoxide following fluorination. The mCPBA oxidation step is therefore unneccessary, and the process is simpler and easier to purify. The reaction conditions are far milder than those involving DAST, several hours at 0°C in the absence of any catalyst.

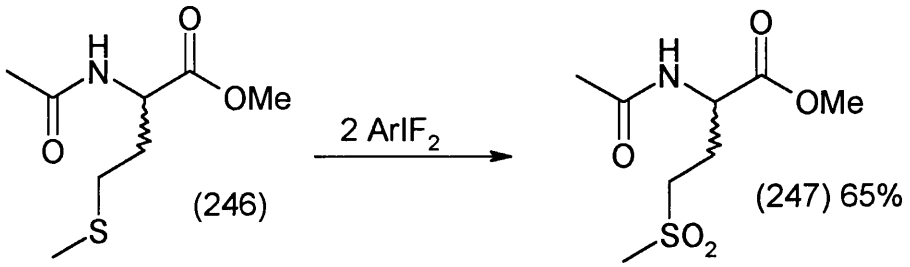
Applications for difluoromethyl phenyl sulfoxide would centre on syntheses of terminal α,α-difluoro olefins. Alkylation followed by pyrolytic elimination of benzenesulfenic acid would be a novel approach to this functionality.

We varied the reaction stoichiometry to try and secure either the difluoromethyl sulfone or monofluoromethyl derivatives. Treatment of thioanisole with a single equivalent of DFIT gave a clean transformation to a volatile compound having slightly lower R_f, however this material could not be characterised as it was unstable to column chromatography. Addition of four equivalents of DFIT to thioanisole and stirring overnight failed to produce any difluoromethyl phenyl sulfone; the sulfoxide was the only product, clearly identifiable from the ^{19}F nmr signal of the two diastereotopic fluorines. However, it was found that between one and two equivalents of DFIT could transform thioanisole to fluoromethyl phenyl sulfoxide (244) in variable yield. The best yields of 55-60% were recorded when a single equivalent of *N*-methyl pyrrolidinone was present in the reaction (the amide was added to test a mechanistic hypothesis that later proved to be wholly false). If the reproducibility of this reaction could be improved we would have a neat approach to this fluorinated synthon that compliments the synthesis of difluoromethyl phenyl sulfoxide.

The success of fluorinating thioanisole could not be extended to the fluorination of other aryl alkyl sulfides. Dodecyl phenyl sulfide (245) gave mixtures of fluorinated material, ^{19}F nmr and mass spectrometry suggested that the difluoride formed from the additive Fluoro-Pummerer reaction on an intermediate vinyl sulfide was the major component.

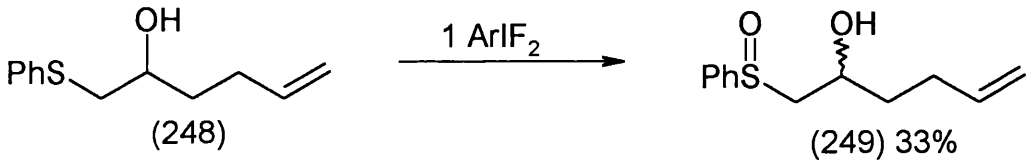
However the instability of the material and the low overall yield precluded further characterisation.

We were surprised to find that the methionine derivative (246) made a good substrate for DFIT, being cleanly oxidised to the sulfone (247) upon treatment with 2eq of DFIT (scheme 100).



Scheme 100

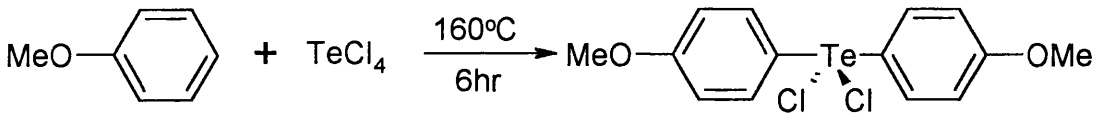
The transformation of a dialkyl sulfide (246) to a single product with DFIT was unexpected, given that methyl octyl sulfide gave a complex mixture that could not be purified. The presence of polar functionality in (246) which can coordinate to the initial iodosulfonium salt and stabilise it may be significant. It appears that the oxidation of sulfides under the Fluoro-Pummerer conditions is contingent on this stabilisation from neighbouring groups. With this idea in mind we synthesised the β-hydroxy sulfide (248) and subjected it to fluorination with 1 eq of DFIT. A 33% yield of the sulfoxide (249) was recorded (scheme 101). Given that no sulfoxide was ever isolated from the reaction of dodecyl phenyl sulfide with DFIT this finding supports our contention that the presence of donor groups in the β-position can coordinate to the iodosulfonium salt, forming a chelate complex that persists until the aqueous quench of the reaction.



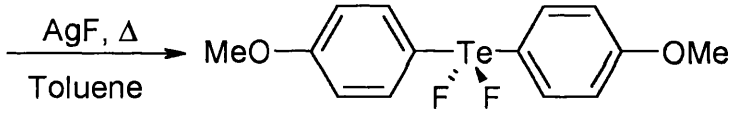
Scheme 101

Chapter 7. Aryl Tellurium Fluorides as Fluorinating Agents

Organotellurium fluorides have received little attention in the literature with respect to their potential as fluorinating agents.[137] We sought to prepare a diaryl tellurium (IV) difluoride and examine it in this context. Tellurium tetrachloride is a commercially available, very hygroscopic solid that reacts with activated aromatic compounds to give bis(aryl)tellurium dichlorides.[138] The *p*-methoxy derivative (250) was prepared by refluxing anisole and the tetrachloride at 160°C for several hours. The fluoride (251) was then accessed according to Smith through transhalogenation with silver fluoride in refluxing toluene (scheme 102).[139]



(250) 61%



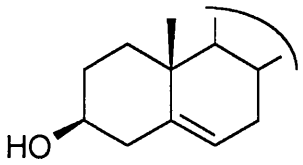
(251) 66%

Scheme 102

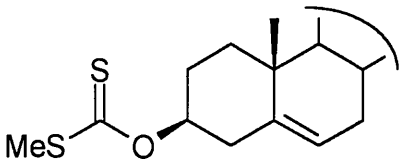
Crystallisation of the crude reaction product from acetonitrile was reported to give pure material, we found this to be a difficult process and crystals of good analytical character could not be grown. The transhalogenation worked equally well if we applied Carpenter's conditions of mercuric oxide and aq. hydrofluoric acid in DCM.[5] The ^{19}F nmr spectrum showed a singlet with a small satellite doublet due to coupling between ^{125}Te and ^{19}F nuclei. The ^{125}Te nmr spectrum of both halides was measured for the sake of completeness, the difluoride showing the expected triplet with a coupling constant of *ca.* 650Hz.

We were unsure whether the tellurium centre would react as an electrophile with nucleophilic substrates in a manner akin to DFIT. To investigate this we reacted one eq of (251) with a range of compounds that had already proven to be good substrates for the iodine reagent, and two that were not (252) and (253). The reactions were stirred overnight at room temperature in DCM or acetonitrile, subjected to aqueous work-up

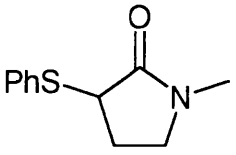
and the crude ^{1}H nmr and ^{19}F nmr spectra measured. In each case there was no discernible reaction whatsoever.



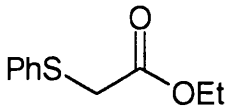
(252)



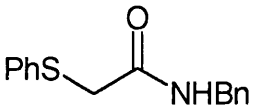
(101)



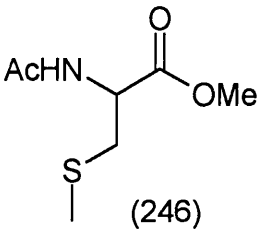
(140)



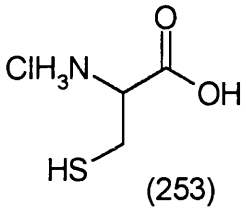
(225)



(190)



(246)



(253)

We were aware that double bonds will react with aryltellurium trichloride in refluxing chloroform to provide chlorotelluration products.[140] Thus (251) was refluxed with an excess of cyclohexene for 1hr to see whether the difluoride might react with an olefin in similar fashion. Unfortunately, despite some reaction indicated by tlc the crude ^{19}F nmr showed the only fluorinated material present to be that of (251). We were not optimistic for the future potential of (251) as a fluorinating agent, given these results. A better compound may well be the aryltellurium trifluoride. However, we failed to prepare the required trichloride for transhalogenation. Refluxing an equimolar amount of tellurium tetrahloride and anisole in carbon tetrachloride for 2hr according to Reichel produced the dichloride in good yield.[141]

Chapter 8. Synthesis of α, α-Difluoroethers

The difluoromethylene unit is often considered to be an isoelectronic replacement for an ether oxygen atom. Accordingly there has been much activity concerning the preparation of difluoromethylenephosphonate analogues of pyro- and –tri phosphates where the bridging oxygen atoms are replaced by a CF_2 group.[142] Work on ATP[143] and geranyl pyrophosphate[144] for example indicate a closely analogous steric and electronic profile of the fluoro-analogue to that of the parent fuctionality.

We were interested in extending this homology to the α, α-difluoroether functionality (255), with the ultimate aim of examining isosteric and isoelectronic relationships to the peroxide group (256).

(255) (256)

Our primary aim was to develop a workable synthesis of such compounds. This is a challenging task, particularly if we aim to utilise DFIT as our reagent of choice. Examination of the literature revealed only three reports concerning their synthesis, two of which employ the harsh reagents chlorine monofluoride or bromine trifluoride.[145,146] The fluorination of thione esters with DAST reported by Bunnelle is the most attractive method, being relatively mild, efficient and convenient.[147] However the approach was not generally applicable, failing to fluorinate thiolactones.

Of particular concern is the hydrolytic stability of the difluoro compounds. Bunnelle states that they are reasonably stable and can be kept for months at 0°C in the absence of moisture. Rozen by contrast maintains that the ethers are not very stable and are unable to be purified by chromatography, eliminating HF with relative ease.[146]

As we considered that a fluoro-desulfurisation approach using DFIT might be promising, the sulfur-based functionalities shown overleaf in figure 5 were prepared as substrates for this transformation.

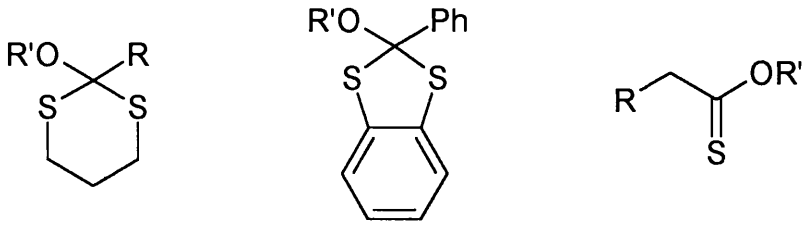
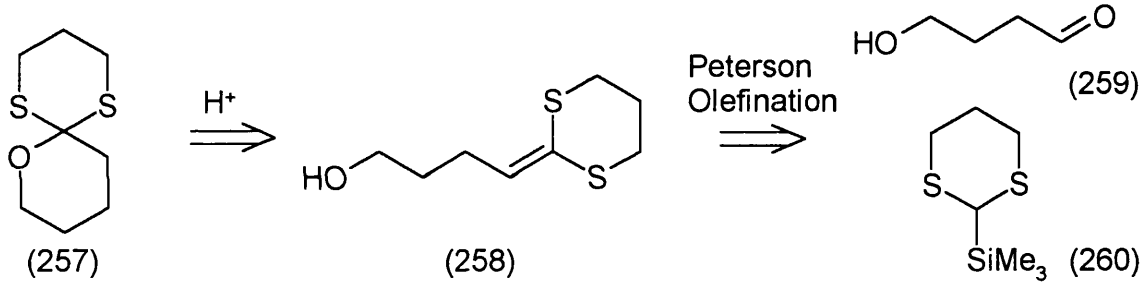


Figure 5

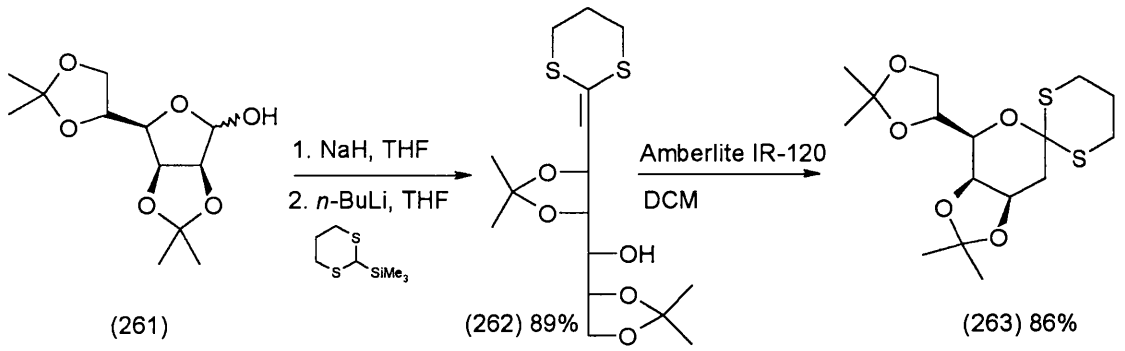
8.1 Synthesis and Fluorination of Dithioorthoesters

The cyclisation of ketene dithioacetals (258) under acidic conditions *via* a sulfur-stabilised cation is a reliable route to dithioorthoesters (257) (scheme 103).[149-151] The required ketene dithioacetals (258) are easily synthesised through a Peterson olefination of an aldehyde (259) with 2-trimethylsilyl-1-3-dithiane (260).[151]



Scheme 103

Portella had recently published a synthesis of a ketene dithioacetal derived from diacetone D-mannose (261), reporting that the cyclisation into the 2-deoxy-heptose derivative (263) was extremely facile, occurring spontaneously on standing.[152] Accordingly we synthesised the ketene dithioacetal (262) and found this to be the case, although the ring closure could be accelerated by stirring with an acidic resin (scheme 104).

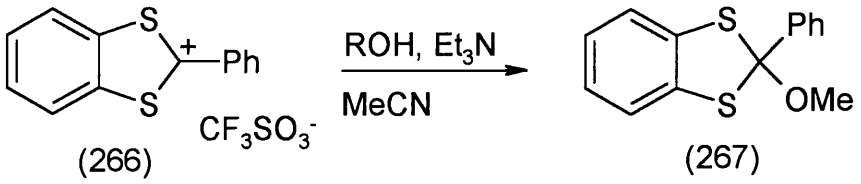


Scheme 104

Our first fluorination experiments involved treating orthoester (263) with two eq of DFIT. Results were poor, with very low yields of the expected fluoro-sugar (264) along with other unidentified fluorinated material. We turned to the reagent combination of py.9HF / DBH which is known to be effective for the geminal fluorination of dithioketals.[20] Treating (263) with a large excess of py.9HF in the presence of DBH at low temperature gave low yields (10-15%) of the difluoride after column chromatography on silica gel. The material was analytically pure, having the elegant nmr spectra characteristic of many carbohydrates. The 1-carbon resonance was significantly deshielded, δ =123ppm, and showing the expected double doublet splitting. One of the fluorine atoms gave a simple doublet signal in the ^{19}F nmr, showing no coupling to the *vic*-hydrogens, whereas the other one appeared as a doublet of doublets of doublets.

The low yield reflects the instability of the product, rather than inefficient transformation. The compound was isolated as a pungent-smelling colourless oil after chromatography, containing significant amounts of an intractable white solid. Upon storage the product degraded further to this solid material. Clearly, the lability of the difluoroether group is problematic. However we did take encouragement from our ability to isolate analytically pure material after column chromatography that was stable enough to be fully characterised.

Stick has reported the synthesis of dithioorthoesters (267) from the benzodithiolyium salt (266) in the context of a benzylation protocol for carbohydrate hydroxy groups (scheme 105).[153] We chose to investigate the fluorination of these compounds as their synthesis appeared to be more convenient than the ketene dithioacetal derived orthoesters.

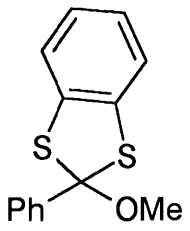


(266) (267)

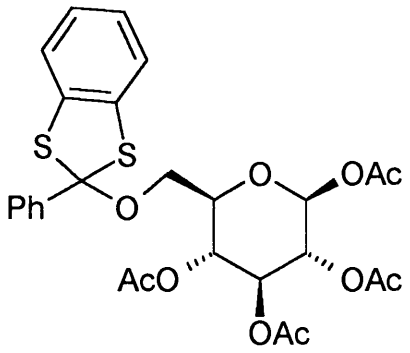
Scheme 105

The salt (266) is made in nearly quantitative yield from the condensation of 1,2-benzenedithiol with phenyl benzoate in the presence of trifluoromethanesulfonic acid at elevated temperature. As 1,2-benzenedithiol is expensive we elected to synthesise it on a large scale through the addition of solid sulfur to ortho-lithiated thiophenol.[154] A reductive work-up yields the required dithiol in moderate yield as a low-melting point solid. Synthesis of the salt was straightforward, although care had to be taken to maintain anhydrous conditions on work-up as the salt is hydrolytically unstable.

Reaction of a simple alcohol such as methanol with salt (266) worked extremely well, producing essentially pure material (268) after aqueous work-up. More functionalised alcohols were less successful, the glucose derivative forming the required orthoester (269) in very low yield and chrysanthemyl alcohol failing to give any product at all.



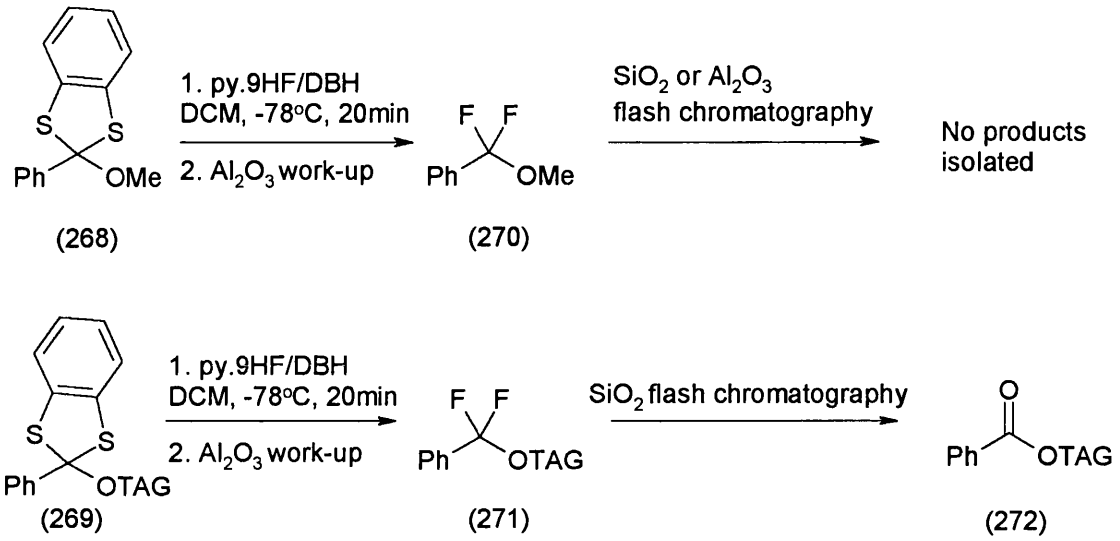
(268) 96%



(269) 9%

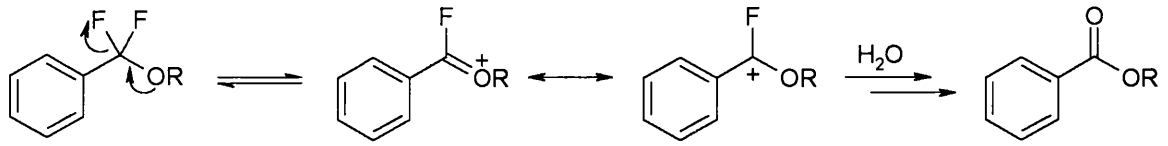
The py.9HF / DBH system proved effective in the fluoro-desulfurisation of the dithioesters, unfortunately the difluoroethers were too unstable to withstand work-up. The reaction with the methyl ester was worked-up by filtering through a short pad of alumina, the crude nmr showing nearly complete transformation to the expected difluoride (270). Further purification by column chromatography over alumina destroyed the product. The glucose derivative displayed similar behaviour, with the

crude ^{19}F nmr spectrum showing a distinctive CF_2 AB quartet at relatively low field, δ=-72ppm. Upon work-up over silica gel however, the ester hydrolysis product (272) was the only material isolated (scheme 106).



Scheme 106

It appears that the phenyl substituent renders the difluoroethers extremely labile to hydrolysis. The extra stability of the benzylic cation (273) must significantly lower the energy for this process (scheme 107). Unless the phenyl group was substituted with electron withdrawing groups to render this decomposition pathway unfavourable there does not appear to be much scope for the synthesis of difluoroethers from this system.



Scheme 107

8.2 Synthesis and Fluorination of Thione Esters

Thione esters are readily synthesised from the parent compounds through treatment with Lawesson's reagent (287) at high temperatures.[155,156] We prepared four thione esters, three lactones, one open chain ester, in this manner and the results are shown in table 1.

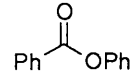
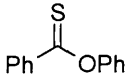
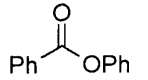
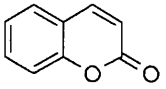
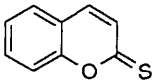
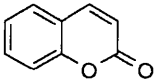
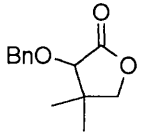
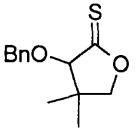
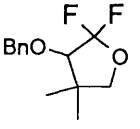
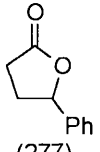
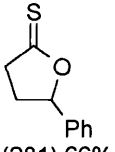
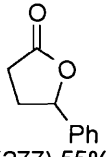
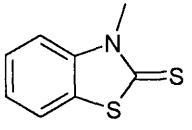
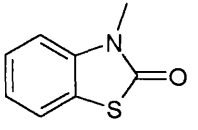
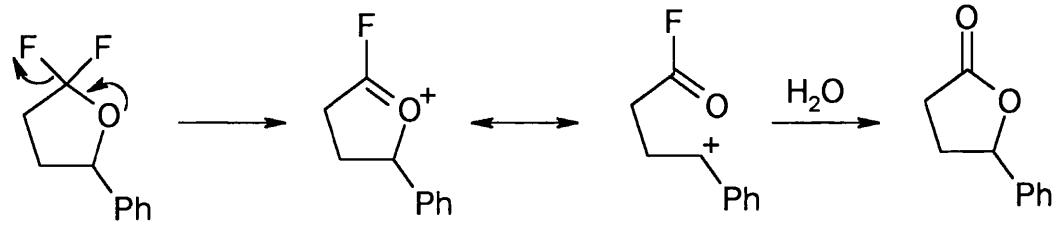
Ester	Thionation Conditions	Thione ester	Fluorination Conditions	Product
 (274)	>2.5 (287), xylene, Δ 3days	 (278) 31%	py.9HF/DBH, DCM, -78°C, 2hr	 (274) 70%
 (275)	1.1 (287), toluene, Δ 2hr	 (279) 87%	py.9HF/DBH, DCM, -78°C, 2hr *or* 2eq.DFIT, DCM, 0°C 40min	 (275) 84% *or* 82%
 (276)	>2 (287), toluene, Δ 2days	 (280) 74%	py.9HF/DBH, DCM, -78°C, 25min *or* 2eq.DFIT, DCM, 0°C 30min	 (284) 30% *or* 20%
 (277)	1.5 (287), toluene, Δ 5hr	 (281) 66%	py.9HF/DBH, DCM, -78°C, 20min *or* 2eq.DFIT, DCM, 0°C 30min	 (277) 55% *or* 34%
	also	 (283)	2eq.DFIT, DCM, 0°C 16hr	 (285) 81%

Table 1

The reactions were simple to carry out and worked well, although substantially better results were obtained using freshly purchased Lawesson's reagent. The reaction stoichiometry refers to the number of equivalents of thiaphosphetane group to ester, i.e one molar eq. of Lawesson's reagent = 2 eq. of reactive thiaphosphetanes.

The py.9HF / DBH system and DFIT each gave similar results for the fluorination of the thiono lactones. The phenyl benzoate derivative (278) falls into the same category as the phenyl-substituted dithioorthoesters (268) and (269) that were examined earlier. After treatment with py.9HF and DBH the crude ^{19}F nmr spectrum showed a singlet at δ = -66ppm corresponding to the difluoroether. Column chromatography isolated the parent ester as the only product. Chromene-2-thione (279) and the dihydrofuran-2-thione (281) were also resistant to fluorination, producing the parent esters with both fluorinating systems. The pantolactone derivative (280) on the other hand proved to be a good substrate for fluorination. DFIT transformed the thiocarbonyl group to the geminal difluoride in 20% yield. The py.9HF / DBH system was superior, producing the difluoroether in 30% yield, with the reaction being noticeably cleaner. The product difluoroether was stable to column chromatography and could be well characterised by nmr. However mass spectrometry using both electron impact and fast-atom bombardment techniques could not provide any meaningful analysis.

It is difficult to see why the dihydrofuran-2-thione (281) should give hydrolysis products whereas the pantolactone derived thione (280) incorporates fluorine. One possible reason could be the 5-phenyl group offering a potential degradation pathway to the difluoroether *via* a stabilised benzyl cation (286) (scheme 108).



(286)

Scheme 108

In conclusion, the α, α-difluoroether functionality is clearly not particularly stable, making routine synthesis very difficult. The instability of the group suggests that any applications to isosteric replacement of peroxides would be difficult to implement and

could only apply to a limited range of substrates. However, the successful fluorination of the thiopantolactone derivative represents the first preparation of such lactone-derived difluoroethers and widens the scope of DFIT somewhat. The dithioorthoesters were actually good substrates for the fluorodesulfurisation reaction, but the products were too unstable to manipulate. Further work is merited if efforts could be made to incorporate features such as electron withdrawing groups that might stabilise the product difluoroethers.

Chapter 9. Conclusions

We have developed the fluorination chemistry of difluoroiodotoluene within the established context of the reagent's demonstrated affinity for sulfur. The most productive area of study has undoubtedly being the Fluoro-Pummerer reaction of DFIT, covered in chapters 3-7. α-Fluoro sulfides are formed cleanly and in good yield from a range of simple substrates, the reactions are easy to perform and take place under mild conditions. When we examine the different types of sulfides successfully fluorinated by DFIT the necessary criterion for reaction is clearly the acidity of the sulfur α-protons. We observe that thioanisole is acidic enough to undergo a smooth Fluoro-Pummerer reaction whereas methyl octyl sulfide is entirely resistant to fluorination, the more acidic α-acyl sulfides generally being excellent substrates. Comparison with existing methods for Fluoro-Pummerer chemistry shows DFIT to have a similar range to electrochemical α-fluorination although yields are slightly lower. It is generally inferior to DAST, although possible advantages may accrue from the excellent safety profile and ease of handling of DFIT relative to this reagent.

DFIT has distinct advantages over alternative fluorinating agents in being able to perform two Fluoro-Pummerer reactions sequentially, forming α, α-difluorosulfides from the starting unfluorinated material. The yields of difluorinated amides and esters synthesised in this manner are comparable to those observed in monofluorination. A third equivalent of DFIT then accesses α, α-difluorosulfoxides, utilised to good effect in the synthesis of the fluorinated synthon difluoromethyl phenyl sulfoxide discussed in chapter 6. No other fluorinating agent in the literature combines this fluorinating / oxidising character, and we have exploited it in our short syntheses of fluoro-butenolides, as described in chapter 4.

The possible coordination of the β-oxo substituent in the α-acyl sulfide substrates to hypervalent iodine has been invoked with reference to the mechanism of sulfur oxidation by DFIT. The formation of sulfoxides under anhydrous conditions does appear to be contingent on a stabilised sulfonium species being formed during reaction that can persist until hydrolytic work-up. Oxidation was observed to take place after fluorination if excess DFIT was present, there being no evidence that sulfoxides are appropriate substrates for this reagent. The oxidation of certain acyclic amides in preference to any Fluoro-Pummerer transformation is exceptional, and supports the

participation of oxygen in the formation of a stabilised chelate, although more work is needed to clarify the role of the nitrogen substituents in these reactions. The presumed coordination of oxygen to iodine is certainly not a necessary criterion for sulfur activation in the Fluoro-Pummerer reaction however, as the successful fluorination of thioanisole and a β-cyano sulfide illustrate.

From a mechanistic perspective the most interesting transformations have involved the Fluoro-Pummerer reaction of substrates with β-hydrogens, with a number of novel additive-Pummerer transformations being discovered leading to new vicinally substituted difluorides. A fine balance exists between the liberated fluoride acting as a base and as a nucleophile. For the lactams presented in chapter 3 the initially generated sulfonium ion is never directly trapped with fluoride nucleophile, but rather undergoes β-deprotonation with basic fluoride to form the vinyl sulfide. The azetidinone substrate is exceptional in this regard as the hypothetical elimination would form an extremely strained double bond in a four-membered ring. The opposite is true for the lactones discussed in chapter 4, where the sulfonium ion is trapped immediately with fluoride. The slightly more electron-withdrawing ester grouping is making this intermediate more electrophilic than in the lactam case, increasing the chances of nucleophilic addition. The balance is a delicate one however, with the 5-methyl substituted lactone being a substrate for basic fluoride and preferring to form the vinyl sulfide. The fluoride base / nucleophile dichotomy is again apparent in the attempted cyclisation of acyclic phenylsulfanyl acetamides with DFIT, fluoride being a strong enough nucleophile to trap the β-acyl sulfonium ion in preference to intramolecular olefinic nucleophiles.

The results presented in chapters 2 and 8 concerning allylic fluorination and α, α-difluoroether synthesis respectively are less satisfactory. In both cases the instability of the fluorinated products made it difficult to properly investigate the questions we had posed concerning the behaviour of DFIT in these systems. The rather cursory examination of hypervalent tellurium in fluorination discussed in chapter 7 was similarly unrewarding, but we feel this to be a consequence of the research being curtailed by time constraints rather than any inherent limitations to the chemistry.

Chapter 10. Perspectives for Future Research

This mechanistic rational of nucleophilic addition of sulfur to electrophilic iodine followed by deprotonation with fluoride to generate a Pummerer-type sulfonium intermediate has served us well in understanding the Fluoro-Pummerer chemistry of DFIT. However, this is unlikely to be the whole story and a more precise structure of the intermediates involved in the reaction is desirable. The unexpected *trans* stereoselective fluorination of phenyl-substituted lactones forced us to consider possible intermediates containing a sulfur-fluorine bond, for example. Studies to elucidate the mechanistic spectrum of the Fluoro-Pummerer reaction using DFIT would therefore significantly enhance future developments of the reagent. ^{19}F nmr is well suited to this task, monitoring a fluorination reaction may potentially show the interchange of iodine-fluorine, sulfur-fluorine and carbon-fluorine bonds, plus the liberation of fluoride.

The reactions reported would all undoubtedly benefit from optimisation studies. In nearly all cases the scale of the reaction was approximately one mmol, and larger scale experiments would expand the scope of the reagent and aid in improving yields.

From a broader perspective the field of fluorination chemistry is changing. The N-F reagents have been steadily improved in recent years, and with several now being commercially available they have become the reagents of choice for electrophilic fluorination.[157] The recent introduction of bis(2-methoxyethyl)aminosulfur trifluoride as a thermally stable DAST analogue may now allow the use of such reagents in nucleophilic fluorinations under forcing conditions or on a large scale.[76] The selective introduction of fluorine into organic molecules, long regarded as a problematic functional group transformation may soon become routine. For hypervalent iodine difluorides such as DFIT to be considered in the same context as such fluorinating agents then future research needs to be focused on refining the reagent structure. DFIT has been an excellent tool for research purposes, establishing a body of novel fluorination chemistry but it possibly lacks fluorinating power. Effective reagents such as selectfluor are the result of years of systematic improvement, and future efforts should be directed in this manner towards the synthesis of better hypervalent iodoarene fluorides that may then be applied to the established transformations.

Part 3. Experimental

Chapter 1. General Experimental Procedures

Melting points were determined using a Reichert hot stage and are uncorrected. Boiling points for Kugelröhr distillations refer to uncorrected air temperatures. Pressure was measured using a standard Gallenkamp manometer.

Optical Rotations were determined using a 'POLAAR 2000' instrument from Optical Activity Ltd.

Infrared spectra were recorded as thin films or nujol mulls on KBr plates, as KBr discs, or as CCl_4 solutions on a Perkin-Elmer FT-IR 1605 instrument. Major features of each spectrum are reported. The abbreviations used to denote peak intensity are w, weak; m, medium; s, strong; br, broad.

^1H NMR Spectra were recorded at 500MHz on a Bruker Avance 500, at 400MHz on a Varian VXR-400 or a Bruker AMX-400 and at 300MHz on a Bruker AMX-300 spectrometer. ^{13}C NMR Spectra were recorded at 125MHz, 100MHz or 75MHz on the instruments above. ^{13}C nmr spectra assignments are supported by DEPT editing. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. (2C) Indicates that the quoted chemical shift refers to two signals separated by less than 0.05ppm. ^{19}F nmr Spectra were recorded at 471MHz, 376MHz or 282MHz on the instruments above. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to $CFCl_3$. ^{125}Te nmr Spectra were recorded at 158MHz on a Bruker Avance 500 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to $PhTe_2Ph$. Coupling constants are measured in Hertz and quoted to the nearest Hertz for all spectra. The abbreviations used to indicate multiplicity are s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; m, multiplet; br, broad.

^{19}F NOE Spectroscopy was performed by Dr H. Toms at QMW.

Low resolution mass spectra were recorded under either electron impact, atmospheric pressure chemical ionisation, or fast atom bombardment conditions on a VG 305 or a VG ZAB SE mass spectrometer at the School of Pharmacy, University of London. Only molecular ions, fragments from molecular ions and other major peaks are reported.

High resolution mass spectra were recorded using a VG 7070b mass spectrometer by the School of Pharmacy Mass Spectrometry Service.

Microanalyses were performed by Mr. Alan Stone and Mrs Jill Maxwell, Christopher Ingold Building, University College London.

X-ray crystallography was performed by Dr D. A. Tocher at UCL and Dr J. Steed at KCL.

Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Keisekgel F_{254}). Components were visualised with ultraviolet light (254nm), and by staining with iodine, basic potassium permanganate, acidic ammonium molybdate (IV), acidic anisaldehyde or acidic palladium chloride solution; all followed by heat.

Flash chromatography was carried out using BDH silica 40-63μm. Gas Chromatography was performed on a Hewlett-Packard 5890A machine (flame ionisation detector) with a 25m x 0.50mm BPX5 column using hydrogen as the carrier gas.

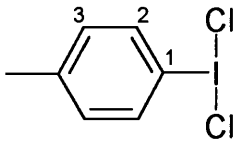
PE refers to petroleum ether. Dimethyl formamide was dried with $MgSO_4$(s) and distilled over Linde type 4A molecular sieves under reduced pressure. Ether refers to diethyl ether and was distilled from sodium-benzophenone ketyl, as was tetrahydrofuran. DCM and chloroform were distilled from either phosphorus pentoxide or calcium hydride. Toluene and benzene were distilled over sodium. Methanol was distilled from magnesium turnings. Triethylamine, pyridine, isopropylamine and acetonitrile were distilled over calcium hydride. All other reagents and solvents were purified as necessary following the usual procedures.*

All reactions were performed using oven-dried glassware under a positive pressure of nitrogen unless otherwise stated.

* Perrin, D. D.; Armerago, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, Second Edition, Pergamon Press, Oxford, 1980.

Chapter 2. Synthesis of Fluorinating Agents

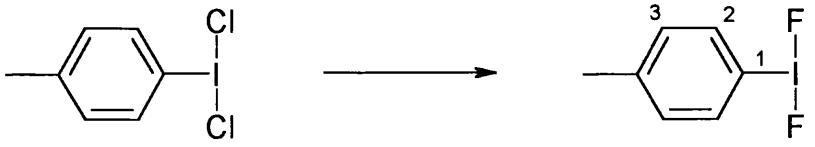
Synthesis of dichloroiodotoluene (97)[158]



(97)

Dry chlorine gas was blown over the surface of a stirred solution of iodotoluene (7.50g, 35mmol) in dry PE 40-60 (65mL) at 0°C in the dark for 1.5hr. After flushing with nitrogen for 1hr the mixture was filtered to give dichloroiodotoluene (97) (9.64g, 95%) as a yellow solid; **m.p.** 62-65°C (dcmp) (lit.[158] 88-90°C dcmp.); **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.48 (3H, s, CH_3), 7.28 (2H, AA'BB' d *J* 9Hz, 3-H, 5-H), 8.05 (2H, AA'BB' d *J* 9Hz, 2-H, 6-H); **MS** (APCI): *m/z* 255 ($[M-^{35}Cl]^+$, 30%), 253 ($[M-^{37}Cl]^+$, 100), 218 ($[C_7H_7I]^+$, 65).

Synthesis of difluoroiodotoluene (98)[5]

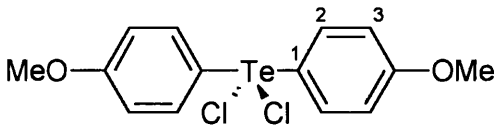


(97) (98)

Dichloroiodotoluene (97) (9.64g) was suspended in DCM (60mL) and yellow mercuric oxide (9.50g, 44mmol) and 48% aq. hydrofluoric acid (13mL, 410mmol) added. The slurry was vigorously shaken periodically over 2hr, then filtered and the organic layer separated. After swirling with MgO the solution was decanted and concentrated *in vacuo* to yield difluoroiodotoluene (98) (5.87g, 66%) as a white solid; **m.p.** 110°C (dcmp.) (DCM) (lit.[159] 111°C dcmp.); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 1636m, 1395w, 1278w, 1116w, 800s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.48 (3H, s, CH_3), 7.40 (2H, AA'BB d *J* 8Hz, 3-H, 5-H), 7.84 (2H, AA'BB' d *J* 8Hz, 2-H, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$):

δ21.2 (CH_3), 130.3, 132.2, 137.3, 142.4; **^{19}F NMR** (376MHz, $CDCl_3$): δ-177.1; **MS** (EI): *m/z* 256 ($M^{\bullet+}$, 15%), 218 ($[C_7H_7I]^+$, 80), 127 (I^+, 7), 91 ($[C_7H_7]^+$, 100); **HRMS** (EI) calcd. for $C_7H_7F_2I$: 255.9561. Found: 255.9570.

Synthesis of bis(p-methoxyphenyl)tellurium dichloride (250)[138]



(250)

Tellurium tetrachloride (3.00g, 11mmol) and anisole (7.3mL, 67mmol) were heated to 160°C for 6hr. After cooling to room temperature the anisole was removed *in vacuo* to give the crude dichloride. Recrystallisation from acetonitrile afforded bis(p-methoxyphenyl)tellurium dichloride (250) (2.79g, 61%) as yellow crystals; **m.p** 180°C (AcOH) (lit.[138] 181-182°C); **^{1}H NMR** (500MHz, DMSO): δ 3.81 (6H, s, OCH_3), 7.10 (4H, AA'BB' d *J* 9Hz, 2-H, 6-H), 7.88 (4H, AA'BB' d *J* 9Hz, 3-H, 5-H); **^{13}C NMR** (126MHz, DMSO): δ54.3 (OCH_3), 114.0, 128.3, 134.9, 159.9 (4-C); **^{125}Te NMR** (158MHz, DMSO): δ587.6; **MS** (FAB): *m/z* 377 ($[M\text{-}Cl]^+$, 100%), 342 ($[M\text{-}2Cl]^+$, 45), 237 (30), 214 (75), 199 (35).

Synthesis of bis(p-methoxyphenyl)tellurium difluoride (251)[139]

(250) (251)

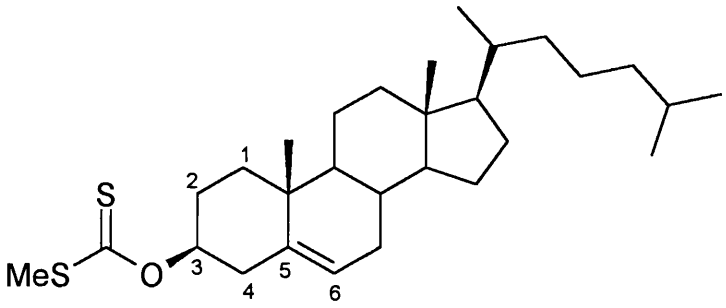
A solution of bis(p-methoxyphenyl)tellurium dichloride (250) (500mg, 1.2mmol) in toluene (20mL) was heated to reflux and silver fluoride (307mg, 2.4mmol) added in portions. After 1hr the mixture was cooled and poured into hexane. Bis(p-

methoxyphenyl)tellurium difluoride (251) (298mg, 66%) slowly crystallised; **m.p.** 129-130°C (hexane) (lit.[139] 120-121°C); **^{1}H NMR** (500MHz, DMSO): δ3.78 (6H, s, OCH_3), 7.12 (4H, AA'BB' d *J* 9Hz, 2-H, 6-H), 7.77 (4H, AA'BB' d *J* 9Hz, 3-H, 5-H); **^{13}C NMR** (126MHz, DMSO): δ63.5 (OCH_3), 123.1, 138.6 (t $^{2}J_{CF}$ 6Hz, 1-C), 141.0, 169.4 (4-C); **^{19}F NMR** (471MHz, DMSO): δ−122.7; **^{128}Te NMR** (158MHz, DMSO): 745.1 (t $^{1}J_{TeF}$ 657Hz); **MS** (EI): *m/z* 379 ($M^{\bullet+}$, 25%), 344 ($[M-2F]^+$, 90), 272 (50), 237 (35), 214 (100), 199 (100), 171 (40); **Anal.** Calcd. for $C_{14}H_{14}F_2O_2Te$: C, 44.27; H, 3.71%. Found: C, 43.93; H, 3.58%.

Chapter 3. Synthesis of Substrates

3.1 Synthesis of Allylic Substrates

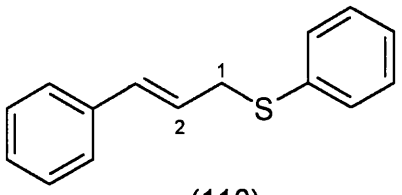
Synthesis of 3β–*O*–cholesteryl-*S*-methyl dithiocarbonate (101)[160]



(101)

To a stirred solution of 3β–cholesterol (3.86g, 10mmol) and imidazole (0.15g, 2.2mmol) in THF (100mL) was added sodium hydride (60% dispersion on mineral oil; 0.7g, 18mmol). The mixture was heated at reflux for 1hr, cooled to room temperature and carbon disulphide (3.8g, 50mmol) added. After heating at reflux for 1hr iodomethane (11.35g, 80mmol) was added, the reaction refluxed for 30min and quenched with sat. aq. NH_4Cl solution (40mL). The resulting mixture was extracted with DCM (2x40mL) and the combined organic extracts washed with sat. aq. $NaHCO_3$ solution (50mL) and brine (50mL). Drying ($MgSO_4$) and concentration *in vacuo* gave a yellow solid (6.23g). Flash chromatography (SiO_2, PE 40-60: ethyl acetate 90: 10) afforded an off-white solid which was recrystallised from ethanol: ether 1: 1 to give 3β–*O*–cholesteryl-*S*-methyl dithiocarbonate (101) (2.51g, 53%) as white needles; **m.p.** 131°C (ethanol / ether) (lit.[161] 126-128°C (ethanol / ether)); $\mathbf{R_f}$ 0.56 (SiO_2, PE 40-60: ethyl acetate 95: 5); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1247w, 1220s (C=S), 1057m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.68-2.04 (43H, m), 2.55 (3H, s, SCH_3), 5.41 (2H, m, 3-H, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 11.9, 18.8, 18.9, 19.4, 21.1, 22.6, 22.9, 23.9, 24.3, 27.2, 28.1, 28.3, 31.9, 32.0, 35.8, 36.2, 36.7, 36.9, 37.5, 39.6, 39.7, 42.3, 50.0, 56.1, 56.7, 83.4, 123.3, 139.2, 215.1; **MS** (FAB): *m/z* 369 (100%).

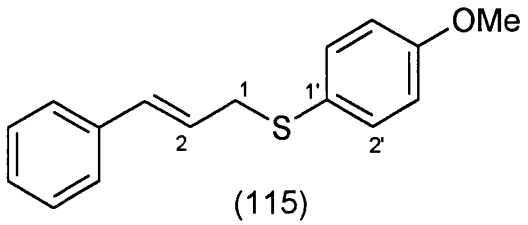
Synthesis of phenyl (*E*-3-phenyl-prop-2-enyl) sulfide (110)[87]



(110)

To a stirred solution of *E*-cinnamyl alcohol (1.50g, 11mmol) and ZnI_2 (1.78g, 5mmol) in DCM (25mL) was added thiophenol (1.45g, 13mmol). After 1hr the reaction was quenched with water (20mL) and the resulting mixture extracted with DCM (3x30mL). The combined organic extracts were washed with 1N NaOH (30mL), brine (40mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (3.14g). Recrystallisation from hexane (15mL) gave phenyl (*E*-3-phenyl-prop-2-enyl) sulfide (110) (1.81g, 73%) as white platelets; **m.p.** 80°C (hexane) (lit.[162] 77.5-78.5°C); $\mathbf{R_f}$ 0.61 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (CCl_4/cm^{-1}): $\tilde{\nu}_{max}$ 3029m (CH), 1580w, 1481s, 1438m, 962s 691s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.73 (2H, d *J* 7Hz, 1-H), 6.25-6.46 (2H, m, 2-H, 3-H), 7.19-7.41 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 37.1 (1-C), 125.1, 126.3, 126.4, 126.9, 128.4, 128.5, 128.9 132.8, 135.8 (C_{ipso}), 136.7 (C_{ipso}); **MS** (FAB): *m/z* 227 ($[MH]^+$, 35%), 226 (M^+, 100); **Anal.** Calcd. for $C_{15}H_{14}S$: C, 79.60; H, 6.23%. Found: C, 79.61; H, 6.16%.

Synthesis of *p*-methoxyphenyl (*E*-3-phenyl-prop-2-enyl) sulfide (115)

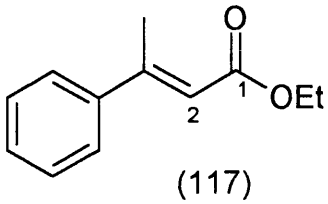


(115)

To a stirred solution of *E*-cinnamyl alcohol (1.50g, 11mmol) and ZnI_2 (1.78g, 5mmol) in DCM (25mL) was added *p*-methoxythiophenol (1.85g, 13mmol). After 2.5hr the reaction was quenched with water (20mL) and the resulting mixture extracted with DCM (3x30mL). The combined organic extracts were washed with 1N NaOH (30mL), brine (40mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an off-white solid

(2.7g). Flash chromatography (SiO_2, PE 40-60: ethyl acetate 90: 10) gave *p*-methoxyphenyl (*E*-3-phenyl prop-2-enyl) sulfide (115) (1.45g, 51%) as white platelets; **m.p.** 110°C (hexane / ethyl acetate); $\mathbf{R_f}$ 0.53 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1594w, 1030m, 968m, 819m, 759m, 689m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.59 (2H, d *J* 6Hz, 1-H), 3.79 (3H, s, OCH_3), 6.24-6.26 (2H, m, 2-H, 3-H), 6.83 (2H, AA'BB' d *J* 9Hz, 3'-H, 5'-H), 7.27-7.30 (5H, m, Ar-H), 7.38 (2H, AA'BB' d *J* 9Hz, 2'-H, 6'-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 39.2 (1-C), 55.3 (OCH_3), 114.4 (2-C), 125.5, 125.6, 126.2, 127.4, 128.4, 132.4, 134.4, 136.8, 159.2; **MS** (FAB): *m/z* 256 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{16}H_{16}OS$: 256.0922. Found: 256.0910.

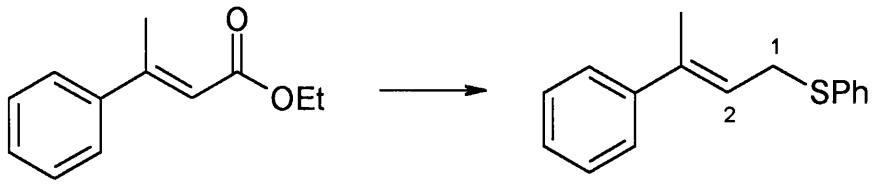
Synthesis of ethyl *E*-3-phenyl-but-2-enoate (117)[163]



(117)

To a stirred solution of acetophenone (24.00g, 0.2mol) and granulated zinc (19.60g, 0.3mol) in refluxing benzene (100mL) was added ethyl bromoacetate (23.4g, 0.14mol) over a period of 10hr. After a further 6hr under reflux the reaction was cooled and filtered through Celite with copious washing with DCM (100mL). The resulting solution was washed with 6N HCl (50 mL), water (40mL) and the excess DCM removed *in vacuo*. The aqueous phase was removed *via* reflux of the resulting azeotrope under Dean-Stark conditions for 1.5hr. After cooling, phosphorus oxychloride (0.82g, 5mmol) was added and azeotropic water removal continued for 0.5hr. Concentration *in vacuo* afforded a brown oil. Flash chromatography (SiO_2, PE 40-60: ethyl acetate 90: 10) gave ethyl *E*-3-phenyl but-2-enoate (117) (3.15g, 11%) as a yellow oil; $\mathbf{R_f}$ 0.58 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2980s (CH), 1711s (C=O), 1629s, 1445s, 1273s, 1165s, 874, 767, 695; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.34 (3H, t *J* 7Hz, $CH_2\underline{C}H_3$), 2.60 (3H, s, 4-H), 4.24 (2H, q *J* 7Hz, $C\underline{H}_2CH_3$), 6.17 (1H, s, 2-H), 7.36-7.51 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 14.4 ($CH_2\underline{C}H_3$), 18.0 (4-C), 59.9 ($\underline{C}H_2CH_3$), 117.2 (2-C), 126.3, 128.5, 129.0, 142.3 (C_{ipso}), 155.6 (3-C), 166.9 (C=O); **MS** (FAB): *m/z* 191 (MH^+, 70%), 145 ($[M-OC_2H_5]^+$, 100).

Synthesis of phenyl (*E*-3-phenyl-but-2-enyl) sulfide (118)

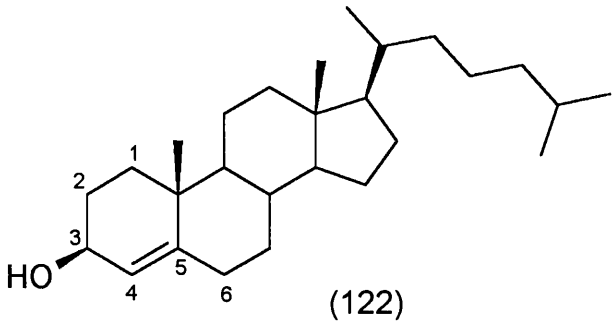


(117) (118)

To a stirred solution of ethyl 3-phenyl-but-2-enoate (117) (2.80g, 15mmol) in toluene (50mL) at -78°C was added DIBAL-H (1.5M in toluene, 28mL, 42mmol) over a period of 40min. After stirring for 70min the reaction was warmed to room temperature and water (6mL) added. The mixture was diluted with ethyl acetate (50mL), dried ($MgSO_4$) and filtered. Concentration *in vacuo* yielded a yellow oil which was subjected to flash chromatography (SiO_2, PE 30-40: ether 50: 50) affording 3-phenyl-but-2-en-1-ol (1.72g, 80%) as a colourless oil; $\mathbf{R_f}$ 0.50 (SiO_2, PE 30-40: ether 60: 40); **MS** (FAB): *m/z* 147 ($[M-H]^+$, 23%), 131 ($[M-OH]^+$, 100).

To a stirred solution of 3-phenyl but-2-en-1-ol (1.5g, 10mmol) and ZnI_2 (1.78g, 5mmol) in DCM (25mL) was added thiophenol (1.32g, 12mmol). After 1hr the reaction was quenched with water (20mL) and the resulting mixture extracted with DCM (3x30mL). The combined organic extracts were washed with 1N NaOH (30mL), brine (40mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Flash chromatography (SiO_2, PE 30-40: ether 90: 10) gave phenyl (*E*-3-phenyl-but-2-enyl) sulfide (118) (1.96g, 80%) as a yellow oil; $\mathbf{R_f}$ 0.64 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1584w, 1218w, 1087w, 759s, 735s 693s; ^{1}**H NMR** (400MHz, $CDCl_3$): δ 1.97 (3H, s, 4-H), 3.75 (2H, d *J* 8Hz, 1-H), 5.90 (1H, t *J* 8Hz, 2-H), 7.23-7.44 (10H, m, Ar-H); ^{13}**C NMR** (100MHz, $CDCl_3$): δ 15.7 (4-C), 33.0 (1-C), 122.7 (2-C), 125.7, 126.4, 127.1, 128.2, 128.8, 130.6, 136.0 (C_{ipso}), 138.5 (C_{ipso}), 143.0 (3-C); **MS** (FAB): *m/z* 240 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{16}H_{16}S$: 240.0973. Found: 240.0960.

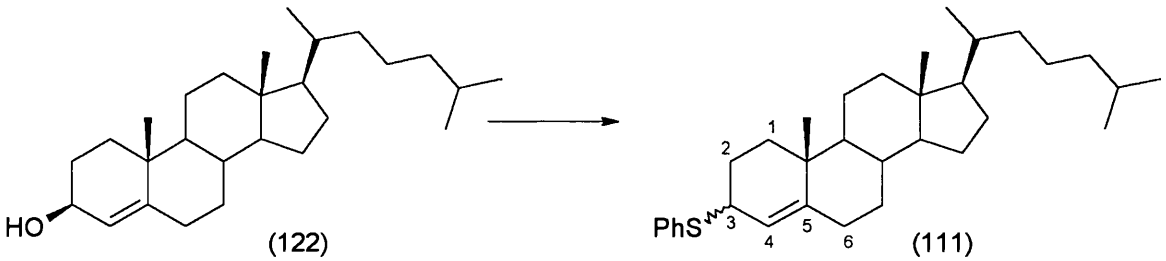
Synthesis of 4-cholesten-3β-ol (122)



(122)

To a stirred solution of 4-cholesten-3-one (2.00g, 5.2mmol) and cerium trichloride heptahydrate (1.94g, 5.2mmol) in methanol (100mL) was added sodium borohydride (0.20g, 5.3mmol) in portions. After 10min the reaction was quenched with water (75mL) and the resulting mixture extracted with DCM (3x100mL). Drying ($MgSO_4$) and concentration *in vacuo* gave 4-cholesten-3β-ol *(122)* (2.07g, quantitative) as a white solid; **m.p.** 132°C (DCM) (lit.[164] 131-132°C); $\mathbf{R_f}$ 0.22 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (nujol mull): $\tilde{\nu}_{max}$ 3346m (OH), 1657w (C=C), 1111w, 1032m, 726m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.65-2.19 (43H, m), 4.14 (1H, m, 3-H), 5.28 (1H, t *J* 2Hz, 4-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 12.0, 18.6, 18.9, 21.0, 22.5, 22.8, 23.8, 24.2, 28.0, 28.2, 29.5, 32.2, 33.1, 35.4, 35.8, 36.0, 36.1, 37.3, 39.5, 39.9, 42.5, 54.5, 56.1, 56.2, 68.0, 123.2 (4-C), 147.7 (5-C); **MS** (FAB): *m/z* 385 ($[M-H]^+$, 43%), 369 ($[M-OH]^+$, 30); **HRMS** (FAB) calcd. for $C_{27}H_{45}O$ (MH^+): 385.3470. Found: 385.3450.

Synthesis of 4-cholesten-3-yl phenyl sulfide (111)

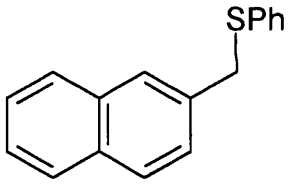


(122) (111)

To a stirred solution of 4-cholesten-3β-ol (122) (1.00g, 2.6mmol) and ZnI_2 (0.41g, 1.3mmol) in DCM (20mL) was added thiophenol (0.34g, 5.2mmol). After 3hr the

reaction was quenched with water (15mL) and the resulting mixture extracted with DCM (3x20mL). The combined organic extracts were washed with 1N NaOH (30mL), brine (30mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an off-white solid (1.38g). Flash chromatography (SiO_2, PE 40-60: ether 90: 10) gave a white solid (1.21g) which was recrystallised from ethanol to yield a mixture of 4-cholesten-3β-yl phenyl sulfide and 4-cholesten-3α-yl phenyl sulfide (111) in the ratio 4.9: 1 as white crystals (0.88g, 68%); $\mathbf{R_f}$ 0.74 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1585w, 1086w, 1025w, 957w, 734m, 689m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.52-2.25 (2x43H, m), 3.75-3.79 (1H, m, 3-H[*3α-PhS*]), 3.83-3.85 (1H, m, 3-H[*3β-PhS*]), 5.34-5.36 (1H, m, 4-H[*3α-PhS*]), 5.43 (1H, d *J* 5Hz, 4-H[*3β-PhS*]), 7.18-7.45 (2x5H, m, Ar-H); **MS** (FAB): *m/z* 477 (MH^+, 43%), 369 ($[M\text{-}PhS]^+$, 100); **Anal.** Calcd. for $C_{33}H_{50}S$: C, 82.78; H, 10.53%. Found: C, 82.50; H, 10.75%.

Synthesis of 2-(methyl phenylsulfide) naphthalene (124)

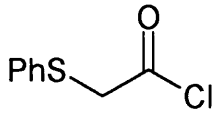


(124)

To a stirred solution of sodium hydride (60% dispersion on mineral oil; 200mg, 5mmol) in THF (10mL) at 0°C was added thiophenol (548mg, 5mmol). After hydrogen evolution had ceased, 2-bromo naphthalene (1g, 4.5mmol) in THF (10mL) was added and the reaction stirred for 15min. Water was added (20mL) and the aqueous phase extracted with ether (3x20mL). Drying ($MgSO_4$) and concentration yielded an off-white solid which was recrystallised from ethanol to give 2-(methyl phenylsulfide) naphthalene (124) as colourless rhombohedra (491mg, 42%); **m.p.** 113-114°C (ethanol) (lit.[165] 99.5-100.5°C (hexane)); $\mathbf{R_f}$ 0.43 (SiO_2, PE 40-60: ethyl acetate 90: 10); **^{1}H NMR** (400MHz, CDCl3): δ 4.28 (2H, s, CH_2), 7.18-7.82 (12H, m, Ar-H); **MS** (FAB): *m/z* 250 (M^+, 17%), 141 ($[M\text{-}PhS]^+$, 100); **Anal.** Calcd. for $C_{17}H_{14}S$: C, 81.56; H, 5.64%. Found: C, 81.40; H, 5.35%.

3.2 Synthesis of Amides

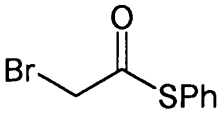
Synthesis of (phenylsulfanyl)acetyl chloride (128)



(128)

(Phenylsulfanyl)acetic acid (4.18g, 25mmol) and thionyl chloride (5.44mL, 75mmol) were stirred at room temperature for 24hr. Excess thionyl chloride was then removed under reduced pressure. The residual oil was distilled at reduced pressure to afford (phenylsulfanyl)acetyl chloride (128) (4.00g, 86%) as a yellow liquid; **b.p.** 101°C / 10mBar (lit.[166] 80°C / 0.3mmHg); **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.85 (2H, s, SCH_2), 7.06-7.26 (5H, m, Ar-H).

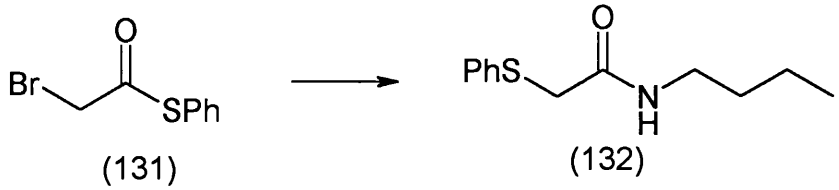
Synthesis of bromoacetyl thiophenol (131)[96]



(131)

Thiophenol (6.0mL, 58mmol) was added dropwise to bromoacetyl bromide (7.2mL, 83mmol) and the mixture stirred under reduced pressure for 1hr. Sat. aq. $NaHCO_3$ solution was then added and the mixture extracted with ether. The extracts were washed twice more with sat. aq. $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Crystallisation from benzene / hexane at -15°C afforded bromoacetyl thiophenol (131) (11.41g, 85%) as colourless crystals; **^{1}H NMR** (300MHz, $CDCl_3$): δ 4.15 (2H, s, CH_2), 7.47 (5H, br s, Ar-H); **^{13}C NMR** (75MHz, CDCl3): δ 133.2 (CH_2), 126.8 (C_{ipso}), 129.4, 129.9, 134.5, 191.0 (C=O); **MS** (FAB): *m/z* 233 ($[MH]^+$ (^{81}Br), 100%), 231 ($[MH]^+$ (^{79}Br), 100); **HRMS** (FAB) calcd. for C_8H_7BrOS: 230.9479. Found: 230. 9460.

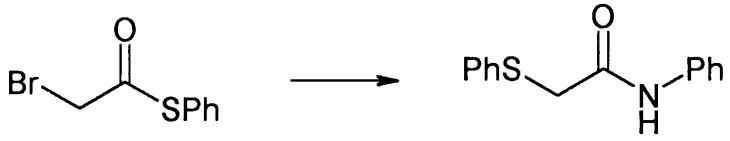
Synthesis of *N*-butyl-(phenylsulfanyl)acetamide (132)[96]



(131) (132)

To *n*-butylamine (0.6mL, 6mmol) was added with stirring 4N NaOH (1.1mL, 4.4mmol), dioxane (15mL) and bromoacetyl thiophenol (131) (693mg, 3mmol). After 10min the mixture was concentrated *in vacuo* and the resultant oil taken into chloroform and filtered. Concentration *in vacuo* gave an off-white semi-solid which was chromatographed (SiO_2, PE 40-60: ether 70: 30) to yield *N*-butyl-(phenylsulfanyl)acetamide (132) (560mg, 84%) as a colourless oil; $\mathbf{R_f}$ 0.46 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3290s (NH) 2931m, 2869s (CH), 1653s (C=O), 1558s, 1442m, 1308m, 1152w, 1038s, 918w; ^{1}**H NMR** (400MHz, $CDCl_3$): δ 0.85 (3H, t *J* 7Hz, CH_3), 1.16-1.26 (2H, m, $C\underline{H}_2CH_3$), 1.36-1.42 (2H, m, $NCH_2C\underline{H}_2$), 3.24 (2H, m, NCH_2), 3.64 (2H, s, SCH_2), 6.81 (1H, br NH), 7.19-7.32 (5H, m, Ar-H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 13.5 (CH_3), 19.8 ($\underline{C}H_2CH_3$), 31.2 ($NCH_2\underline{C}H_2$), 37.1 (SCH_2), 39.4 (NCH_2), 126.4, 127.8, 129.2, 134.6 (C_{ipso}), 167.4 (C=O); **MS** (FAB): *m/z* 224 (M^+, 100%), 123 (57); **HRMS** (FAB) calcd. for $C_{12}H_{17}NOS$: 224.1109. Found: 224.1120.

Synthesis of *N*-phenyl-(phenylsulfanyl)acetamide (168)[96]

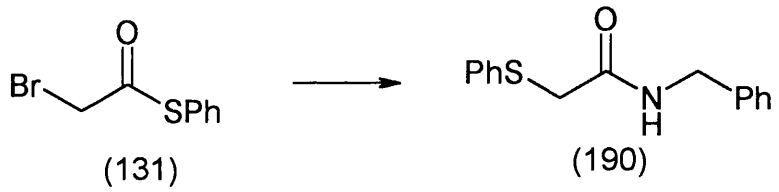


(131) (168)

To aniline (6.5mL, 71mmol) was added with stirring 1N NaOH (19.5mL, 19.5mmol), dioxane (60mL) and bromoacetyl thiophenol (131) (3g, 13mmol). After 10min the mixture was concentrated *in vacuo* and the resultant oil taken into chloroform and filtered. Concentration *in vacuo* followed by flash chromatography (SiO_2, PE 30-40: ether 70: 30) gave a yellow solid. Recrystallisation from DCM / hexane afforded *N*-

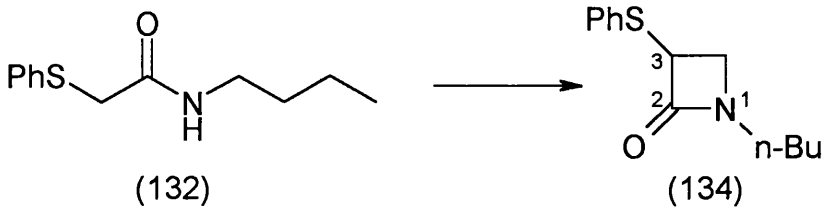
phenyl-(phenylsulfanyl)acetamide (168) (1.10g, 35%) as pink needles; **m.p.** 80-81°C (DCM / hexane) (lit.[96] 75-76°C); $\mathbf{R_f}$ 0.68 (SiO_2, PE 30-40: ethyl acetate 40: 60); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3311s (NH), 3055w, 2924w, 1665s (C=O), 1599m, 1524s, 1439m, 1386m, 1317w, 1237m, 1152w, 1078w, 1025w, 888w, 749s, 688s, 485m; ^{1}**H NMR** (400MHz, $CDCl_3$): δ 3.78 (2H, s, SCH_2), 7.11-7.50 (10H, m, Ar-H), 8.59 (1H, br, NH); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 38.8 (SCH_2), 120.3, 125.2, 127.5, 128.8, 129.5, 129.9, 134.5 (C_{ipso}), 137.6 (C_{ipso}), 166.4 (C=O); **MS** (EI): *m/z* 244 ($M^{\bullet+}$, 90%); **Anal.** Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76; S, 13.18%. Found: C, 68.90; H, 5.33; N, 5.67; S, 12.85%.

Synthesis of *N*-benzyl-(phenylsulfanyl)acetamide (190)



To benzylamine (8.5mL, 78mmol) was added with stirring 4N NaOH (10mL, 40mmol), dioxane (100mL) and bromoacetyl thiophenol (131) (9g, 39mmol). After 20min the mixture was concentrated *in vacuo* and the resultant oil taken into DCM and filtered. Concentration *in vacuo* gave an orange oil which was absorbed onto SiO_2. Washing with PE 30-40: ether 95: 5 and concentration gave *N*-benzyl-(phenylsulfanyl)acetamide (190) (6.75g, 67%) as a white solid; **m.p.** 52-54°C (PE 30-40 / ether); $\mathbf{R_f}$ 0.49 (SiO_2, PE 30-40: ethyl acetate 40: 60); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3287m (NH), 3063w, 2923w, 1651s (C=O), 1532m, 1476w, 1434w, 1315w, 1224w, 1155w, 1085w, 1022w, 742s, 686s; ^{1}**H NMR** (300MHz, $CDCl_3$): δ 3.84 (2H, s, SCH_2), 4.58 (2H, d *J* 6Hz, NCH_2), 7.20-7.46 (10H, m, Ar-H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 37.7 (SCH_2), 44.1 (NCH_2), 127.1, 127.9 (2C), 128.5, 129.7, 129.8, 134.9, 138.1, 168.1 (C=O); **MS** (FAB): *m/z* 280 (MNa^+, 15%), 258 (MH^+, 100); **HRMS** (FAB) calcd. for $C_{15}H_{16}NOS$ (MH^+): 258.0953. Found: 258.0958.

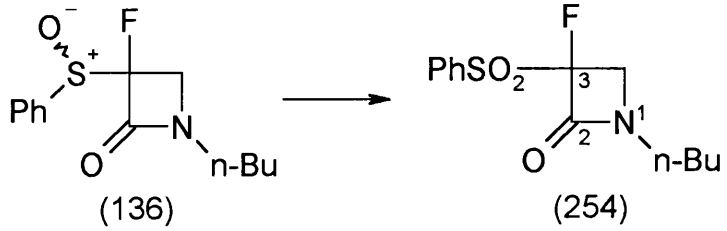
Synthesis of 1-*n*-butyl-3-phenylsulfanyl-2-azetidinone (134)[95]



(132) (134)

To a stirred solution of *N*-butyl-2-phenylsulfanylacetamide (132) (338mg, 1.46mmol) in DMF (13mL) was added sodium hydride (60% dispersion on mineral oil, 140mg, 3.50mmol) and the system purged with nitrogen. After 30min methylene iodide (0.41mL, 5.12mmol) was added and the mixture stirred overnight. Ethyl acetate was added and the reaction mixture was washed with water (x3), brine and dried ($MgSO_4$). Concentration *in vacuo* gave a brown oil which was chromatographed (SiO_2, PE 40-60: ether 50: 50) to yield unreacted starting material (120mg, 36% recovery), plus 1-*n*-butyl-3-phenylsulfanyl-2-azetidinone (133) (107mg, 30%) as a brown oil; $\mathbf{R_f}$ 0.15 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2958s, 2870m (CH), 1752 (C=O), 1475m, 1045m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.84 (3H, t *J* 7Hz, CH_3), 1.10-1.35 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.01-3.22 (2H, m, $NC\underline{H}_2CH_2$), 3.11 (1H, dd *J* 6, 2Hz), 3.59 (1H, t *J* 6Hz, 4-H), 4.34 (1H, dd *J* 5, 2Hz), 7.30-7.55 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 13.6 (CH_3), 19.9 ($\underline{C}H_2CH_3$), 29.4 ($NCH_2\underline{C}H_2$), 41.6, 46.8, 128.1, 129.1, 133.0, 131.7 (C_{ipso}), 165.9 (C=O); **MS** (EI): *m/z* 136 ([M-CH_2CHSPh]$^{\bullet+}$, 100%), 109 ([SPh]$^+$, 100).

Synthesis of 1-*n*-butyl-3-fluoro-3-phenylsulfonyl-2-azetidinone (254)

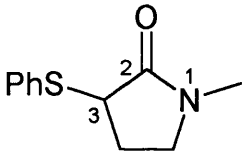


(136) (254)

To a stirred solution of *syn / anti* 1-*n*-butyl-3-fluoro-3-phenylsulfinyl-2-azetidinone (136) (*ca.* 20mg, 0.07mmol) in DCM (1mL) at 0°C was added mCPBA (68%, 50mg,

0.2mmol). After 1hr sat. aq. $NaHSO_3$ solution (1mL) was added and the mixture stirred for a further 3hr. The organic phase was separated and washed with sat. aq. $NaHCO_3$ solution and brine then dried over $MgSO_4$. Concentration *in vacuo* gave 1-*n*-butyl-3-fluoro-3-phenylsulfonyl-2-azetidinone (254) (contaminated with some *m*-chlorobenzoic acid) as a white solid; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.98 (3H, t *J* 7Hz, CH_3), 1.34-1.68 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.29-3.46 (2H, m, $NC\underline{H}_2CH_2$), 3.66 (1H, dd *J* 10, *J* 7Hz, 4-H), 4.18 (1H, t *J* 7Hz, 4-H), 7.28-8.12 (5H, m, Ar-H); **^{19}F NMR** (471MHz, $CDCl_3$): δ –165.8 (t J_{FH} 8Hz); **MS** (FAB): *m/z* 286 (MH^+, 70%); **HRMS** (FAB) calcd. for $C_{13}H_{17}FNO_3S$ (MH^+): 286.0913. Found: 286.0923.

Synthesis of 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (140)[102,103]

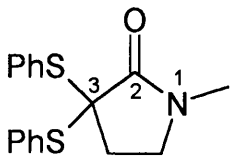


(140)

To a stirred solution of diisopropylamine (15mL, 0.1mol) in THF (40mL) at 0°C was added a solution of *n*-butyllithium (2.54M in hexane, 39.4mL, 0.1mol). After 10min the mixture was cooled to -78°C and *N*-methylpyrrolidinone (5g, 0.05mol) in THF (20mL) was added *via* syringe pump over 15min. After 35min stirring at this temperature a solution of diphenyl disulfide (11g, 0.05mol) in THF (20mL) was added *via* cannula and the reaction left to warm to room temperature overnight. The reaction mixture was poured into water (200mL) and extracted with ether (3x200mL). The combined extracts were washed with 10% aq. NaOH solution (100mL), water (100mL), 10% aq. HCl solution (100mL), water (100mL) and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was purified by Kugelröhr distillation to yield 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (140) (4.48g, 43%) as a viscous oil; **b.p.** 230°C / 1mBar (lit.[102] 130-133°C / 0.05mmHg); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2939m, 2879m (CH), 1695s (C=O), 1581m, 1498m, 1476s, 1435s, 1402m, 1300s, 1274s, 1106m, 745s, 696s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.05-2.12 (1H, m, 4-H), 2.47-2.55 (1H, m, 4-H), 2.82 (3H, s, CH_3), 3.03-3.26 (2H, m, 5-H), 3.81 (1H, dd $J_{3,4}$ 9, 6Hz, 3-H), 7.28-7.33 (3H, m, Ar-H), 7.53-7.57 (2H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 26.5 (4-C), 30.2 (CH_3), 47.3

(5-C), 47.7 (3-C), 127.9, 128.9, 133.1, 133.0 (C_{ipso}), 172.1 (C=O); **MS** (FAB): *m/z* 230 (MNa^+ 5%), 208 (MH^+, 100); **HRMS** (FAB) calcd. for $C_{11}H_{14}NOS$: 208.0796 (MH^+). Found: 208.0811; and 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141) (601mg, 4%) as a viscous oil.

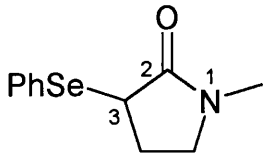
Synthesis of 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141)[102,103]



(141)

To a stirred solution of diisopropylamine (11.2mL, 80mmol) in THF (30mL) at 0°C was added a solution of *n*-butyllithium (2.9M in hexane, 28mL, 80mmol). After 10min the mixture was cooled to -78°C and *N*-methylpyrrolidinone (3.97g, 40mmol) in THF (5mL) was added *via* syringe pump over 15min. After 35min stirring at this temperature a solution of diphenyl disulfide (17.6g, 80mmol) in THF (35mL) was added *via* syringe pump over 15min and the reaction left to warm to room temperature overnight. The reaction mixture was poured into water (200mL) and extracted with ether (3x200mL). The combined extracts were washed with 10% aq. NaOH solution (100mL), water (100mL), 10% aq. HCl solution (100mL), water (100mL) and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, ether) to yield 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141) (6.57g, 52%) as colourless crystals; **m.p.** 84-86°C (ether / methanol) (lit.[102] 87-88.5°C); $\mathbf{R_f}$ 0.53 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3056w, 2880w, 1695s (C=O), 1473w, 1438w, 1401w, 1299w, 1267w, 1103w, 1066w, 1024w, 749m, 693m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.31 (2H, t *J* 6Hz, 4-H), 2.77 (3H, s, CH_3), 2.86 (2H, t *J* 6Hz, 5-H), 7.33-7.68 (10H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 30.6 (CH_3), 33.3 (4-C), 46.1 (5-C), 65.3 (3-C), 128.8, 129.5, 136.3, 131.1 (C_{ipso}), 170.6 (C=O); **MS** (FAB): *m/z* 316 (MNa^+ 10%), 206 ($[M\text{-}PhS]^+$, 100); **Anal.** Calcd. for $C_{17}H_{17}NOS_2$: C, 64.73; H, 5.43; N, 4.44; S, 20.33%. Found: C, 64.77; H, 5.24; N, 4.45; S, 20.37%.

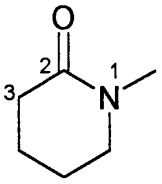
Synthesis of 1-methyl-3-phenylselenyl-2-pyrrolidinone (149)[103]



(149)

To a stirred solution of diisopropylamine (1.41mL, 10mmol) in THF (10mL) at 0°C was added a solution of *n*-butyllithium (2.0M in hexane, 5mL, 10mmol). After 15min the mixture was cooled to -78°C and *N*-methylpyrrolidinone (0.48mL, 5mmol) in THF (5mL) was added *via* cannula over 15min. After 35min stirring at this temperature a solution of phenylselenyl chloride (966mg, 5mmol) in THF (5mL) was added *via* cannula and the reaction left to warm to room temperature over 1hr. After a further 1hr stirring the reaction mixture was poured into water (50mL) and extracted with ether (3x50mL). The combined extracts were washed with 10% aq. NaOH solution (30mL), water (30mL), 10% aq. HCl solution (30mL), water (30mL) and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, ether) to afford 1-methyl-3-phenylselenyl-2-pyrrolidinone (149) (656mg, 51%) as a colourless oil; $\mathbf{R_f}$ 0.03 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2931w, 2876w (CH), 1683 (C=O), 1577w, 1435m, 1401m, 1269m, 1106w, 1022w, 742m, 692m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.09-2.15 (1H, m, 4-H), 2.49-2.55 (1H, m, 4-H), 2.72 (3H, s, CH_3), 2.89 (1H, q *J* 8Hz, 5-H), 3.12 (1H, td *J* 9, 3Hz, 5-H), 3.84 (1H, dd *J* 9, 4Hz, 3-H), 7.23-7.31 (3H, m, Ar-H), 7.62-7.64 (2H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 27.1 (4-C), 30.0 (CH_3), 40.9 (5-C), 47.8 (3-C), 127.2 (C_{ipso}), 128.5, 128.9, 135.8, 172.5 (C=O); **MS** (FAB): *m/z* 256 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{11}H_{14}NOSe$ (MH^+): 256.0241. Found: 256.0245.

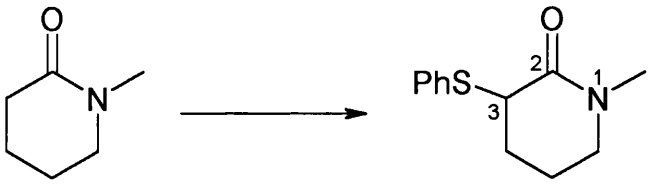
Synthesis of 1-methyl piperidin-2-one (155)[167]



(155)

To a stirred solution of valerolactam (1.98g, 20mmol) in THF (50mL) at -30°C was added a solution of *n*-butyllithium (2.71M in hexane, 8.1mL, 22mmol). After 30min the mixture was cooled to -78°C and iodomethane (1.25mL, 20mmol) was added. After 15min the reaction was warmed to room temperature and concentrated *in vacuo* to give a yellow oil which was partitioned between water and DCM. Extraction with DCM, drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil which was purified by Kugelröhr distillation to give 1-methyl piperidin-2-one (155) (1.62g, 72%) as a clear liquid; **b.p.** 150°C / 19mmHg (lit.[167] 88°C / 7.5mmHg); **IR** (thin film/cm^{-1}) $\tilde{\nu}_{max}$ 2946s, 2872s (CH), 1620s (C=O); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.75-1.78 (4H, m, 4-H, 5-H), 2.34-2.35 (2H, m, 3-H), 2.91 (3H, s, CH_3), 3.23-3.26 (2H, m, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.5, 23.2, 32.3, 34.7 (CH_3), 50.0 (6-C), 170.0 (C=O); **MS** (EI): *m/z* 115 ($M^{+\bullet}$, 100%); **HRMS** (EI) calcd. for $C_6H_{11}NO$: 113.1984. Found: 113.1988.

Synthesis of 1-methyl-3-phenylsulfanyl-2-piperidinone (156)[102,103]

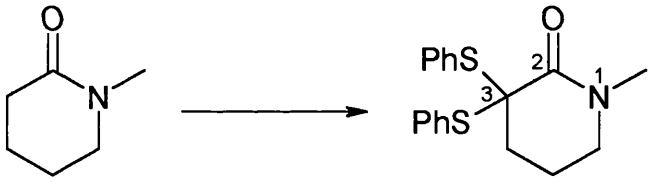


(155) (156)

To a stirred solution of diisopropylamine (3.72mL, 26.6mmol) in THF (10mL) at 0°C was added a solution of *n*-butyllithium (2.54M in hexane, 10.5mL, 26.6mmol). After 10min the mixture was cooled to -78°C and a solution of 1-methylpiperidinone (155) (1.50g, 13.3mmol) in THF (10mL) was added *via* cannula. After 35min stirring at this temperature diphenyl disulfide (2.91g, 13.3mmol) in THF (10mL) was added *via*

syringe pump over 15min and the reaction left to warm to room temperature overnight. The reaction mixture was poured into water (80mL) and extracted with ether (3x100mL). The combined extracts were washed with 10% aq. NaOH solution (50mL), water (50mL), 10% aq. HCl solution (50mL), water (50mL) and dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, ether) to yield 1-methyl-3-phenylsulfanyl-2-piperidinone (156) (2.25g, 81%) as a viscous oil; $\mathbf{R_f}$ 0.18 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2937m (CH), 1637s (C=O), 1497m, 1440m, 1401m, 1350m, 1326w, 1242w, 1212w, 1175w, 1071w, 1026w, 969w, 903w, 744m, 694m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.76-2.12 (4H, m, 4-H, 5-H), 2.97 (3H, s, CH_3), 3.26-3.31 (2H, m, 6-H), 3.88 (1H, t $J_{3,4}$ 5Hz, 3-H), 7.25-7.32 (3H, m, Ar-H), 7.53-7.56 (2H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.2 (4-C), 28.5 (5-C), 35.3 (CH_3), 48.8 (3-C), 49.9 (6-C), 127.4, 129.0, 132.5, 134.7 (C_{ipso}), 168.3 (C=O); **MS** (FAB): *m/z* 222 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{12}H_{16}NOS$ (MH^+): 222.0953; found: 222.0971

Synthesis of 1-methyl-3,3-diphenylsulfanyl-2-piperidinone (157)[103]

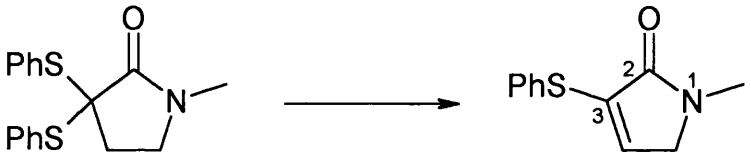


(155) (157)

To a stirred solution of diisopropylamine (3.72mL, 27mmol) in THF (16mL) at 0°C was added a solution of *n*-butyllithium (2.54M in hexane, 11mL, 27mmol). After 10min the mixture was cooled to -78°C and 1-methylpiperidinone (155) (1.5g, 13.3mmol) in THF (5mL) was added *via* cannula. After 35min stirring at this temperature a solution of diphenyl disulfide (5.8g, 27mmol) in THF (5mL) was added *via* cannula and the reaction maintained at -78°C for 35min. The mixture was warmed to -20°C and stirred for a further 20min after which time it was poured into water (100mL) and extracted with ether (3x100mL). The combined extracts were washed with 10% aq. NaOH solution (50mL), water (50mL), 10% aq. HCl solution (50mL), water (50mL) and dried ($MgSO_4$). Concentration *in vacuo* led to the precipitation of 1-methyl-3,3-diphenylsulfanyl-2-piperidinone (157) (1.21g) as a crystalline solid which was isolated

by filtration. The filtrate was concentrated *in vacuo* and chromatographed (SiO_2, ether) to yield a further 1.08g of product (50% overall); **m.p.** 138°C (ether / PE 30-40) (lit.[103] 139°C) $\mathbf{R_f}$ 0.50 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2936w (CH), 1645s (C=O), 1473m, 1439m, 1343m, 1252w, 1198m, 1067w, 748m, 691m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.89-1.99 (4H, m, 4-H, 5-H), 2.92 (3H, s, CH_3), 3.16 (2H, t *J* 6Hz, 6-H), 7.26-7.39 (6H, m, Ar-H), 7.63-7.65 (4H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.6 (4-C), 34.0, 35.8, 50.1 (6-C), 66.1 (3-C), 128.7, 129.4, 136.6, 131.6 (C_{ipso}), 167.3 (C=O); **MS** (FAB): *m/z* 220 ([M-PhS]$^+$ 35%); (EI): 329 ($M^{\bullet+}$, 20%), 220 ([M-PhS]$^+$, 30); **Anal.** Calcd. for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25; S, 19.46%. Found: C, 65.65; H, 5.78; N, 4.26; S, 19.72%.

Synthesis of *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142)[105]

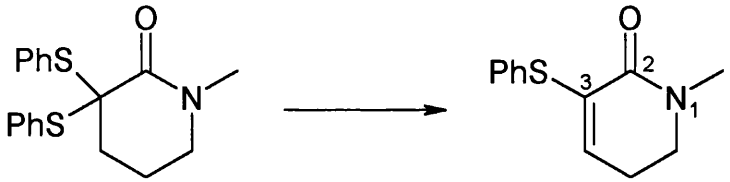


(141) (142)

To a stirred solution of 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141) (1g, 3.2mmol) in DCM (50mL) at 0°C was added a cooled solution (0°C) of mCPBA (66%, 913mg, 3.5mmol) in DCM (10mL) followed by sat. aq. $NaHCO_3$ solution (0.4mL). After 30min the reaction was quenched with sat. aq. $NaHCO_3$ solution and the organic phase washed with brine. Drying (Na_2SO_4) and concentration *in vacuo* gave a residue which was taken into benzene (10mL). The solution was then heated under reflux for 30min, allowed to cool and concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30-40: ether 50: 50) yielded *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142) (405mg, 62%) as a red solid; **m.p.** 75-76°C (hexane / ethyl acetate); $\mathbf{R_f}$ 0.18 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2920w, 1683s (C=O), 1597w, 1475m, 1443m, 1401m, 1291w, 1231w, 1036m, 933m, 801m, 761m, 690m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.02 (3H, s, CH_3), 3.84 (2H, d $J_{5,4}$ 2Hz, 5-H), 6.20 (1H, t $J_{4,5}$ 2Hz, 4-H), 7.31-7.50 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 29.7 (CH_3), 53.6 (5-C), 128.8, 129.5, 130.7, 131.5, 133.7, 137.6, 168.2 (C=O); **MS** (FAB): *m/z* 206 (MH^+, 100%); **Anal.** Calcd. for

$C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.66%. Found: C, 64.47; H, 5.32; N, 6.88; S, 15.78%.

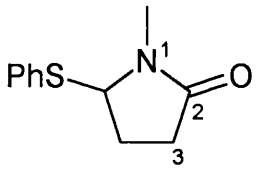
Synthesis of *5,6-dihydro-1-methyl-3-phenylsulfanyl-2(1H)-pyridone* (157)[105]



(157) (158)

To a stirred solution of 1-methyl-3,3-diphenylsulfanyl-2-piperidinone (157) (750mg, 2.3mmol) in DCM (50mL) at 0°C was added a cooled solution (0°C) of mCPBA (65%, 666mg, 3.9mmol) in DCM (10mL) followed by sat. aq. $NaHCO_3$ solution (0.25mL). After 15min the reaction was quenched with sat. aq. $NaHCO_3$ solution and the organic phase washed with brine. Drying (Na_2SO_4) and concentration *in vacuo* gave a residue which was taken into benzene (10mL). The solution was then heated under reflux for 1hr, allowed to cool and concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30-40: ether 50: 50) yielded yielded *5,6-dihydro-1-methyl-3-phenylsulfanyl-2(1H)-pyridone* (158) (387mg, 77%) as a white solid; **m.p.** 95-96°C (DCM / PE 30-40); $\mathbf{R_f}$ 0.32 (SiO_2, ethyl acetate); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3053w, 2932m, 2851m, 1635s (C=O), 1602s, 1480s, 1434s, 1400s, 1347s, 1306m, 1266m, 1212s, 1078s, 1024s, 930w, 856m, 823m, 755m, 695s, **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.27-2.33 (2H, m, 5-H), 3.00 (3H, s, NCH_3), 3.36 (2H, t *J* 7Hz, 6-H), 5.76 (1H, t *J* 5Hz, 4-H), 7.30-7.46 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.6 (5-C), 34.9 (CH_3), 47.6 (6-C), 128.5, 129.4, 130.8 (4-C), 132.0, 134.5, 136.8, 162.8 (C=O); **MS** (FAB): *m/z* 220 (MH^+, 100%); **Anal.** Calcd. for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62%. Found: C, 65.69; H, 5.99; N, 6.35; S, 14.93%.

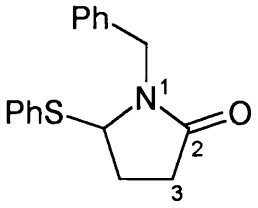
Synthesis of 1-methyl-5-phenylsulfanyl-2-pyrrolidinone (166)[107]



(166)

To a stirred solution of *N*-methyl succinimide (3.46g, 31mmol) in ethanol (120mL) at 0°C was added sodium borohydride (3.41g, 90mmol) in one portion. 1.49N aq. HCl was added at a rate of 3 drops every 5min for 4hr. The resulting mixture was partitioned between water (50mL), brine (50mL) and DCM (150mL) and extracted with DCM (4x100mL). Drying ($MgSO_4$) and concentration *in vacuo* yielded the crude carbinollactam (957mg, 27%) as a colourless oil. The oil was stirred with *p*-toluenesulfonic acid monohydrate (30mg, 0.16mmol) and thiophenol (0.85mL, 8.3mmol) for 3hr. Flash chromatography (SiO_2, ether) yielded 1-methyl-5-phenylsulfanyl-2-pyrrolidinone (166) (373mg, 22%) as a clear oil; $\mathbf{R_f}$ 0.06 (SiO_2, PE 30-40: ether 50: 50); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2918m (CH), 1684s (C=O), 1427m, 1388m, 1256s, 1092m, 974m, 928m, 858m, 749s, 686w, 662s, 600m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.62-1.73 (1H, m), 2.02-2.20 (2H, m), 2.40-2.49 (1H, m), 2.95 (3H, s, CH_3) 4.78 (1H, dd *J* 8, 2Hz, 5-H), 7.28-7.41 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 26.4 (4-C), 28.0 (CH_3), 29.0 (3-C), 69.5 (5-C), 129.0, 129.3, 135.2, 130.1 (C_{ipso}), 174.2 (C=O); **MS** (FAB): *m/z* 208 (MH^+ 100%); **HRMS** (FAB) calcd. for $C_{11}H_{14}NOS$ (MH^+): 208.0796. Found: 208.0782.

Synthesis of 1-benzyl-5-phenylsulfanyl-2-pyrrolidinone (167)[107]

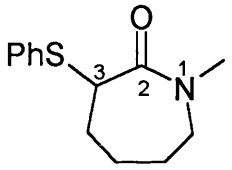


(167)

To a stirred solution of *N*-benzyl succinimide (2.0g, 10.5mmol) in ethanol (60mL) at 0°C was added sodium borohydride (1.18g, 31.2mmol) in one portion. 1.49N aq. HCl

solution was added at a rate of 3 drops every 5min for 2.75hr. The resulting mixture was partitioned between water (50mL), brine (50mL) and DCM (100mL) and extracted with DCM (4x60mL). Drying ($MgSO_4$) and concentration *in vacuo* yielded the crude carbinollactam (2.12g, quant.) as a white solid. The solid was stirred with *p*-toluenesulfonic acid monohydrate (42mg, 0.56mmol) and thiophenol (1.14mL, 11.1mmol) in DCM (6mL) for 5hr. Flash chromatography (SiO_2; PE 30-40: ether 80: 20) yielded 1-benzyl-5-phenylsulfanyl-2-pyrrolidinone (167) (2.38g, 80%) as a clear oil; $\mathbf{R_f}$ 0.32 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058w, 2933w (CH), 1784w, 1695s (C=O), 1409s, 1268s, 1026w, 927w, 746s, 700s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.55-2.12 (4H, m, 3-C, 4-C), 4.08 (1H, d *J* 15Hz, NCH_2), 4.50 (1H, dd *J* 8, 2Hz, 5-H), 5.03 (1H, d *J* 15Hz, NCH_2), 7.05-7.26 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 26.5 (4-C), 29.3 (3-C), 43.7 (NCH_2), 66.4 (5-C), 127.7, 128.5, 128.8, 129.1, 129.3, 135.4, 130.5, (C_{ipso}), 136.1 (C_{ipso}) 174.3 (C=O); **MS** (FAB): *m/z* 284 (MH^+ 50%), 174 ($[M\text{-}PhS]^+$, 100); **HRMS** (FAB) calcd. for $C_{17}H_{18}NOS$ (MH^+): 284.1109. Found: 284.1119.

Synthesis of 1-methyl-3-phenylsulfanyl-caprolactam (161)

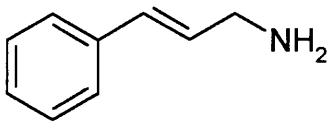


(161)

To a stirred solution of diisopropylamine (4.4mL, 32mmol) in THF (10mL) at -78°C was added a solution of *n*-butyllithium (2.47M in hexane, 12.7mL, 32mmol). After 2hr *N*-methylcaprolactam (2g, 16mmol) in THF (10mL) was added *via* cannula. After 55min stirring at this temperature a solution of diphenyl disulfide (2.91g, 13.3mmol) in THF (10mL) was added and the mixture stirred at -78°C for 30min, then at 0°C for 1hr. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with ether (x3). The combined extracts were washed with 2N aq. NaOH solution, brine then dried ($MgSO_4$). Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 30-40: ether 25: 75) to yield 1-methyl-3-phenylsulfanyl-caprolactam (161) (3.09g, 82%) as an off-white solid; **m.p.** 104°C (PE 30-40 / ether); $\mathbf{R_f}$ 0.33 (SiO_2, ether); **IR** (thin

film/cm^{-1}): $\tilde{\nu}_{max}$ 2933w (CH), 1636s (C=O), 1394s, 745s, 692s, 595m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.52-1.54 (3H, m), 1.74-1.91 (3H, m), 2.89 (3H, s, CH_3), 3.25-3.30 (1H, m, 7-H), 3.53-3.57 (1H, m, 7-H), 4.12 (1H, dd *J* 9, 3Hz, 3-H), 7.06-7.33 (5H, m, Ar-H); **^{13}C NMR** (126MHz, $CDCl_3$): δ 27.7, 27.8, 30.8, 37.2 (NCH_3), 50.8 (7-C), 54.2 (3-C), 127.2, 129.4, 131.5, 135.1 (C_{ipso}), 172.4 (C=O); **MS** (FAB): *m/z* 236 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{13}H_{18}NOS$ (MH^+): 236.1109. Found: 236.1112.

Synthesis of cinnamylamine (183)[168]

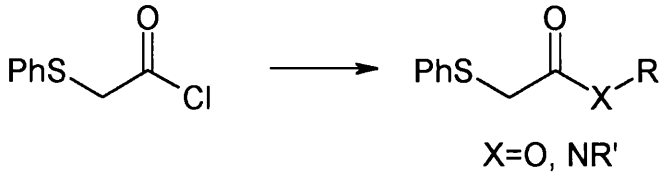


(183)

To a stirred solution of *E*-cinnamyl alcohol (4.0g, 42mmol), triphenylphosphine (12.2g, 46mmol) and phthalimide (7.5g, 50mmol) in THF (150mL) at 0°C was added diisopropylamine dicarboxylate (9.1g, 45mmol) dropwise. The mixture was stirred for 22hr, then concentrated *in vacuo* to afford a white solid. Hexane was added and the insoluble material removed by filtration. Concentration *in vacuo* gave a solid which was chromatographed (SiO_2, PE 30-40: ether 80: 20) to afford *N*-phthaloyl cinnamylamine (1.2g, 10%) as a white solid; $\mathbf{R_f}$ 0.63 (PE 30-40: ether 80: 20).

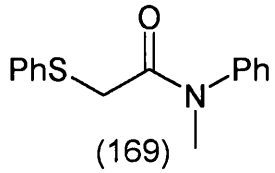
This product was taken into methanol (15mL) and hydrazine hydrate (0.24mL, 7.7mmol) added. The solution was refluxed for 20hr, cooled to room temperature and conc. HCl (3mL) added, then refluxed for a further 30min. The mixture was then cooled to 0°C, filtered and concentrated *in vacuo*. The residue was taken into ethanol, refiltered and concentrated *in vacuo* to afford cinnamylamine (183) (424mg, 72% from *N*-phthaloyl compound) as a yellow oil; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.52 (2H. dd *J* 6, 1Hz, 1-H), 6.36 (1H, dt *J* 16, 6Hz, 2-H), 6.55 (1H, d *J* 16Hz, 3-H), 7.26-7.44 (5H, m, Ar-H).

General procedure for the synthesis of (phenylsulfanyl)acetates / acetamides



Triethylamine or pyridine (1eq) was added to a stirred solution of alcohol or amine (1eq) in DCM (*ca.* 3.3mL $mmol^{-1}$). The mixture was cooled in an ice-salt bath (<0°C) and (phenylsufanyl)acetyl chloride (128) was added dropwise. Consumption of starting alcohol / amine was monitored by tlc and the reaction was quenched with water upon completion. The aqueous phase was extracted with DCM (x2), the combined extracts dried ($MgSO_4$) and concentrated *in vacuo.* Flash chromatography followed by Kugelröhr distillation or recrystallisation afforded pure products.

Synthesis of *N*-phenyl-*N*-methyl-(phenylsulfanyl)acetamide (169)

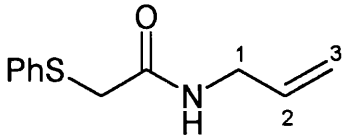


(169)

A solution of *N*-methyl aniline (0.95mL, 8.8mmol), triethylamine (1.23mL, 8.8mmol) and (phenylsulfanyl)acetyl chloride (128) (1.65g, 8.8mmol) in DCM (50mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) gave an oil which was crystallised from DCM / PE 30-40 to afford *N*-phenyl-*N*-methyl-(phenylsulfanyl)acetamide (169) (864mg, 38%) as yellow crystals; **m.p.** 70°C (DCM / PE 30-40) (lit.[175] 70-71°C (hexane)); $\mathbf{R_f}$ 0.53 (SiO_2, PE 30-40: ether 60: 40); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2923w, 1651s (C=O), 1588s, 1383s, 1297s, 1233s, 1118m, 895w, 743s, 697s, 556s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.29 (3H, s, CH_3), 3.52 (2H, s, SCH_2) 7.14-7.40 (10H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 37.2 (SCH_2), 37.9 (NCH_3), 126.7, 127.4, 128.2, 128.9, 129.9, 130.2, 135.6 (SC_{ipso}), 143.4 (NC_{ipso}) 168.7 (C=O); **MS** (EI): *m/z* 257 ($M^{\bullet+}$, 50%);

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87; N, 5.44%. Found: C, 69.91; H, 5.91; N, 5.34%.

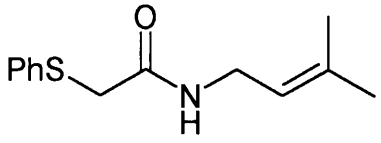
Synthesis of *N*-allyl-(phenylsulfanyl)acetamide (175)



(175)

A solution of allylamine (0.44mL, 5.4mmol), pyridine (0.48mL, 5.9mmol) and (phenylsulfanyl)acetyl chloride (128) (1.00g, 5.4mmol) in DCM (7mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 60: 40) afforded *N*-allyl-(phenylsulfanyl) acetamide (175) (983mg, 88%) as a colourless oil; $\mathbf{R_f}$ 0.22 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3289s (NH), 3075s, 2919s (CH), 1650 (amide I), 1537s (amide II), 1439s, 1311s, 1218s, 1154s, 1098m, 989m, 921m, 739s, 690s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.61 (2H, s, SCH_2), 3.80-3.84 (2H, m, 1-H), 4.94-5.02 (2H, m, 3-H), 5.65-5.73 (1H, 2-H), 6.81 (1H, br, NH), 7.15-7.26 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 37.7 (SCH_2), 42.4 (1-C), 116.7 (3-C), 127.1, 128.4, 129.7, 134.0, 135.0 (C_{ipso}), 168.0 (C=O); **MS** (FAB): *m/z* 208 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{11}H_{14}NOS$ (MH^+): 208.0796. Found: 208.0793.

Synthesis of *N*-(phenylsulfanyl)acetyl-3-methyl-but-2-enyl amine (176)



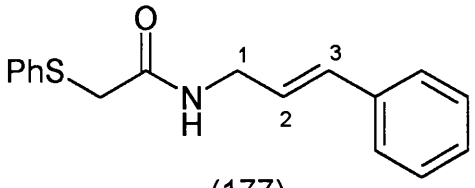
(176)

To a stirred solution of prenol (1.63mL, 16mmol), triphenylphosphine (4.56g, 17mmol) and phthalimide (2.87g, 19mmol) in THF (60mL) at 0°C was added diethylamine dicarboxylate (2.7mL, 17mmol) dropwise. The mixture was stirred for 16hr, then concentrated *in vacuo* to afford a white solid. PE 30-40: ether 50: 50 was added and the

insoluble material removed by filtration. Concentration *in vacuo* gave a solid which was chromatographed (SiO_2, PE 30-40: ether 80: 20) to afford *N*-phthaloyl-3-methyl-but-2-enyl amine (2.47g, 72%) as a white solid; $\mathbf{R_f}$ 0.38 (PE 30-40: ether 80: 20).

This product was taken into methanol (35mL) and hydrazine hydrate (0.60mL, 19mmol) added. The solution was refluxed for 20hr, cooled to room temperature and conc. HCl (7.5mL) added, then refluxed for a further 30min. The mixture was then cooled to 0°C, filtered and concentrated *in vacuo*. The residue was taken into ethanol, refiltered and concentrated *in vacuo*. The crude mixture (1.3g) was then acylated according to the general experimental procedure; phenylsulfanylacetyl chloride (128) (2.85g, 15mmol), pyridine (1.23mL, 25mmol) in DCM (20mL) was stirred for 48hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *N*-(phenylsulfanyl)acetyl-3-methyl-but-2-enyl amine (176) (331mg, 12% from *N*-phthaloyl compound); **m.p.** 72-73°C (ether); $\mathbf{R_f}$ 0.43 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3286s (NH), 2967w (CH), 1649s (C=O), 1544w, 1480w, 735m, 693m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.75 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.78 (2H, s, SCH_2), 3.97 (2H, t *J* 6Hz, 1-H), 5.23 (1H, t *J* 7Hz, 2-H), 6.84 (1H, br, NH), 7.34-7.48 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 18.3, 26.0, 37.7, 38.3, 119.8, 127.0, 128.6, 129.7, 135.0, 137.5, 168.3; **MS** (FAB): *m/z* 258 (MNa^+, 20%), 236 (MH^+, 100); **HRMS** calcd. for $C_{13}H_{18}NOS$ (MH^+): 236.1109. Found: 236.1093.

Synthesis of *N*-cinnamyl-(phenylsulfanyl)acetamide (177)

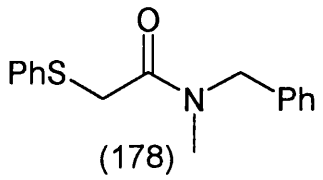


(177)

A solution of cinnamylamine (183) (425mg, 3.2mmol), pyridine (0.28mL, 3.2mmol) and (phenylsulfanyl)acetyl chloride (128) (596mg, 3.2mmol) in DCM (11mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *N*-cinnamyl-(phenylsulfanyl)acetamide (177) (500mg, 55%) as a white solid; **m.p.** 101-102°C (PE 30-40 / ether); $\mathbf{R_f}$ 0.21 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3295m (NH), 3057w, 2915m, 1646s (C=O), 1578m, 1524m, 1483m, 1436m, 1320m, 1246w,

1022w, 968w, 737s, 689s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.62 (2H, s, SCH_2), 3.97 (2H, td *J* 6, 1Hz, 1-H), 5.99 (1H, dt $^{trans}J_{AB}$ 16Hz, $^3J_{2,1}$ 6Hz, 2-H), 6.30 (1H, d $^{trans}J_{AB}$ 16Hz, 3-H), 7.12-7.27 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 37.7, 42.0, 125.3, 126.7, 127.1, 128.1, 128.4, 128.9, 129.8, 132.4, 135.0 (C_{ipso}), 136.8 (C_{ipso}), 168.0 (C=O); **MS** (FAB): *m/z* 306 (MNa^+, 25%), 284 (MH^+, 100); **Anal.** calcd. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.96%. Found: C, 71.73; H, 5.89; N, 4.87%.

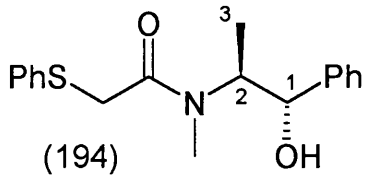
Synthesis of *N*-benzyl-*N*-methyl-(phenylsulfanyl)acetamide (178)



(178)

A solution of *N*-methyl benzylamine (0.38mL, 3mmol), pyridine (0.24mL, 3mmol) and (phenylsulfanyl)acetyl chloride (128) (500mg, 2.7mmol) in DCM (10mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 60: 40) afforded *N*-benzyl-*N*-methyl-(phenylsulfanyl)acetamide (178) (582mg, 79%) as a colourless oil; **R_f** 0.51 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058w, 3028w, 2924w, 1649s (C=O), 1582w, 1480, 1446m, 1400m, 1267w, 1092m, 738m, 696m; **^{1}H NMR** (300MHz, $CDCl_3$): (*E/Z*) δ 2.82 and 2.83 (2x3H, 2xs, NCH_3), 3.66 and 3.69 (2x2H, 2xs, SCH_2), 4.45 (2x2H, s, NCH_2), 7.04-7.43 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): (*E/Z*) δ 34.7 and 35.8 (NCH_3), 37.3 and 37.5 (2-C), 51.6 and 54.3 (NCH_2), 126.4, 126.9 (2C), 127.4, 127.7, 128.0, 128.6, 128.9, 129.0, 130.2, 130.3, 135.4 (C_{ipso}), 135.5 (C_{ipso}), 136.5 (C_{ipso}), 137.3 (C_{ipso}), 169.0 and 169.3 (C=O); **MS** (FAB): *m/z* 272 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{16}H_{17}NOS$ (MH^+): 272.1109. Found: 272.1106.

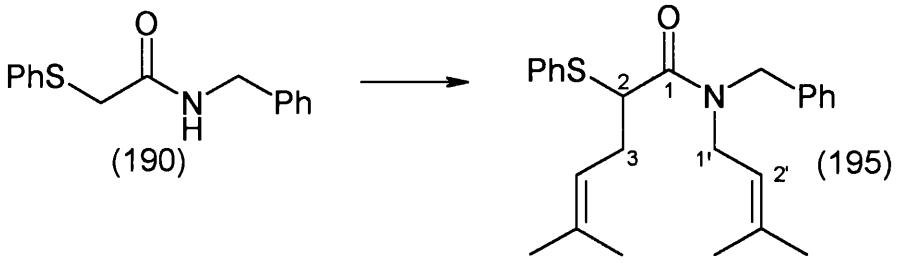
Synthesis of *(1R, 2S)-N*-methyl-*N*-(phenylsulfanyl)acetyl-2-amino-1-phenyl-propan-1-ol (194)



(194)

A solution of (-)-ephedrine (974mg, 5.9mmol), triethylamine (0.82mL, 5.9mmol) and (phenylsulfanyl)acetyl chloride (128) (1g, 5.4mmol) in DCM (15mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *(1R, 2S)-N*-methyl-*N*-(phenylsulfanyl)acetyl-2-amino-1-phenyl-propan-1-ol (194) (1.09g, 64%) as a colourless, viscous oil; $\mathbf{R_f}$ 0.24 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3406s (OH), 3058m, 2984m, 2937m, 1621s (C=O), 1478s, 1447s, 1403m, 1336m, 1250m, 1085m, 1026m, 741m, 697m; **^{1}H NMR** (300MHz, $CDCl_3$): *(E/Z)* δ 1.34 (major) and 1.53 (minor) (2x3H, 2xd *J* 7Hz and *J* 8Hz, 3—H), 2.62 (minor) and 3.83 (major) (2x1H, 2xd *J* 3Hz, OH), 2.98 (major and minor coincident) (2x3H, s, NCH_3), 3.44 (minor) (1H, d J_{AB} 14Hz, SCH_2), 3.62 (minor) (1H, d J_{AB} 14Hz, SCH_2), 3.87 (major) (2H, s, SCH_2), 4.10-4.21 (minor) and 4.56-4.64 (major) (2x1H, m, 2-H), 4.85 (minor) and 5.01 (major) (2x1H, 2xdd *J* 7, 3Hz, 1-H), 7.15-7.87 (2x10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): *(E/Z)* δ 12.1 and 15.2 (3-C), 29.2 and 34.1 (NCH_3) 37.0 and 38.3 (SCH_2), 58.8 and 59.5 (2-C), 76.3 and 77.4 (1-C), 126.4, 126.7, 127.0, 127.5, 128.0, 128.7, 128.8, 129.1, 129.4, 129.5, 130.1, 130.9, 135.3 (C_{ipso}), 135.8 (C_{ipso}), 142.0 (C_{ipso}), 142.2 (C_{ipso}), 168.9 and 170.3 (C=O); **MS** (FAB): *m/z* 316 (MH^+, 15), 298 ($[M-OH]^+$, 20), 148 (100); **HRMS** (FAB) calcd. for $C_{18}H_{22}NO_2S$ (MH^+): 316.1371. Found: 316.1368.

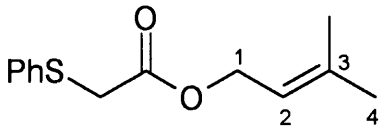
Synthesis of *N-benzyl-N-(3-methyl-but-2-enyl)-5-methyl-2-phenylsulfanyl-hex-4-enoylamide* (195)



To a stirred solution of N-benzyl-(phenylsulfanyl)acetamide (190) (1g, 3.89mmol) in THF(10mL) at 0°C was added sodium hydride (60% disp. on mineral oil, 103mg, 4.30mmol) and the mixture stirred for 2hr. A solution of prenyl bromide (0.5mL, 4.27mmol) in THF (5mL) was added and the mixture stirred overnight. The reaction was quenched with sat. aq NH_4Cl solution and extracted with ether (x2). Drying ($MgSO_4$) followed by concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 30-40: ether 90: 10) to afford *N-benzyl-N-(3-methyl-but-2-enyl)-5-methyl-2-phenylsulfanyl-hex-4-enoylamide* (195) (798mg, 95%) as a colourless oil; $\mathbf{R_f}$ 0.76 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3060m, 3028m, 2970s, 2917s (CH), 1650s (C=O), 1582w, 1442s, 1379m, 1231m, 1027m, 742s, 697m; **^{1}H NMR** (300MHz, $CDCl_3$): δ (*E/Z*) 1.70, 1.74, 1.76, 1.82, 1.86, 1.93, 1.95, 1.99 (2x12H, 8xs, 4xCH_3), 2.72-2.78 and 2.95-3.04 (2x2H, m, 3-H), 3.89-4.18 (2x3H, m, 1'-H, 2-H), 4.46 and 4.68 (2x1H, 2xd J_{AB} 17 and 15Hz, NCH_2Ph), 4.82 and 4.98 (2x1H, 2xd J_{AB} 17 and 15Hz, NCH_2Ph), 5.19-5.41 (2x2H, m, 4-H, 2'-H), 7.35-7.53 (2x10H, m, Ar-H); **MS** (FAB): *m/z* 394 (MH^+, 100%), 284 (95); **HRMS** (FAB) calcd. for $C_{25}H_{32}NOS$ (MH^+): 394.2205. Found: 394.2194.

3.3 Synthesis of Esters

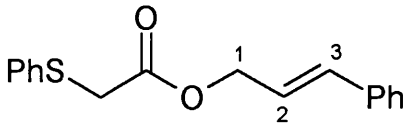
Synthesis of prenyl (phenylsulfanyl)acetate (214)



(214)

A solution of prenol (0.54mmol, 5.4mmol), pyridine (0.48mL, 5.9mmol) and (phenylsulfanyl)acetyl chloride (128) (1g, 5.4mmol) in DCM (18mL) was stirred for 15min. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE: ether 20: 80) yielded a yellow oil which was Kugelröhr distilled to afford prenyl (phenylsulfanyl)acetate (214) (1.05g, 82%) as a colourless oil; **b.p.** 175°C / 0.5mBar; $\mathbf{R_f}$ 0.43 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2924m (CH), 1734s (C=O), 1440w, 1276m, 1130m, 959w, 740m, 688m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.69 (3H, s, CH_3), 1.76 (3H, s, CH_3), 3.66 (2H, s, SCH_2), 4.62 (2H, d *J* 8Hz, 1-H), 5.30 (1H, m, 2-H), 7.23-7.43 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 18.1 (CH_3), 25.8 (CH_3), 36.8 (SCH_2), 62.4 (1-C), 118.1 (2-C), 126.9, 129.0, 130.0, 135.0, 139.9, 169.7 (C=O); **MS** (FAB): *m/z* 236 (M^+, 35%), 123 ($[M\text{-}PhSCH_2]^+$, 100); **Anal.** Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%. Found: C, 65.80; H, 6.58%.

Synthesis of cinnamyl (phenylsulfanyl)acetate (215)

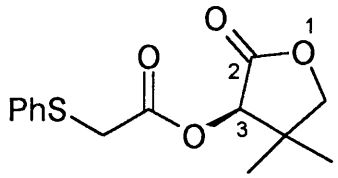


(215)

A solution of *E*-cinnamyl alcohol (717mg, 5.3mmol), triethylamine (0.74mL, 5.3mmol) and (phenylsulfanyl)acetyl chloride (128) (1g, 5.3mmol) in DCM (18mL) was stirred for 3hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE: ether 95: 5) gave *E*-cinnamyl (phenylsulfanyl)acetate (215) (1.26g, 83%) as a green oil; $\mathbf{R_f}$ 0.58 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058m,

2945m (CH), 1732 (C=O), 1583m, 1440s, 1265s, 1141s, 965s, 742s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.71 (2H, s, SCH_2), 4.79 (2H, d *J* 7Hz, 1-H), 6.23 (1H, dt $^{trans}J_{AB}$ 16Hz, $^3J_{2,1}$ 7Hz 2-H), 6.65 (1H, d $^{trans}J_{AB}$ 16Hz, 3-H), 7.19-7.47 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 36.7 (SCH_2), 66.0 (1-C), 122.5 (2-C), 126.6 (2C), 127.1, 128.1, 128.6, 129.0, 130.1, 134.6, 136.0, 169.5 (C=O); **MS** (FAB): *m/z* 417 (MCs^+, 30%), 284 (M^+, 100); **HRMS** (FAB) calcd. for $C_{17}H_{16}O_2S$: 284.0871. Found: 284.0866.

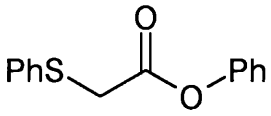
Synthesis of *(3R)-4,5-dihydro-4,4-dimethyl-3-(phenylsulfanyl)acetoxy-2(3H)-furanone* (216)



(216)

A solution of *(R)*-pantolactone (703mg, 5.4mmol), pyridine (0.48mL, 5.9mmol) and (phenylsulfanyl)acetyl chloride (128) (1g, 5.4mmol) in DCM (18mL) was stirred for 30min. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 55: 45) gave *(3R)-4,5-dihydro-4,4-dimethyl-3-(phenylsulfanyl)acetoxy-2(3H)-furanone* (216) (1.04g, 69%) as a viscous yellow oil; **R_f** 0.32 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2967m (CH), 1790s (C=O lactone), 1747s (C=O ester), 1584m, 1470m, 1378m, 1263s, 1128s, 1079s, 1013m, 743s, 690s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.01 (3H, s, CH_3), 1.18 (3H, s, CH_3), 3.60-3.77 (2H, m, 5-H), 4.02 (2H, s, SCH_2), 5.36 (1H, s, 3-H), 7.26-7.48 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 19.6 (CH_3), 22.7 (CH_3), 36.2, 40.2, 75.7, 76.1, 127.2, 129.1, 130.1, 134.3, 168.8, 171.9; **MS** (FAB): *m/z* 413 (MCs^+, 100%), 303 (MNa^+, 25), 281 (MH^+, 75); **HRMS** (FAB) calcd. for $C_{14}H_{16}O_4S$ (MH^+): 281.0848. Found: 281.0830.

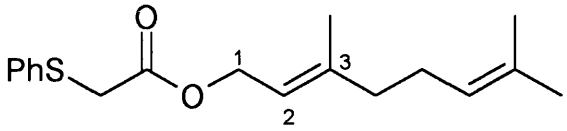
Synthesis of phenyl (phenylsulfanyl)acetate (217)



(217)

A solution of phenol (252mg, 2.7mmol), pyridine (0.24mL, 2.8mmol) and (phenylsulfanyl)acetyl chloride (128) (500mg, 2.7mmol) in DCM (10mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) gave phenyl (phenylsulfanyl)acetate (217) (500mg, 76%) as a colourless oil; $\mathbf{R_f}$ 0.65 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3062m (CH), 1763s (C=O), 1590m, 1488s, 1440w, 1405w, 1252s, 1193s, 1116s, 1024w, 934m, 894m, 742s, 689s; ^{1}**H NMR** (500MHz, $CDCl_3$): δ 3.88 (2H, s, SCH_2), 7.02 (2H, dd *J* 7, 1Hz), 7.25-7.54 (6H, m), 7.55 (2H, dd *J* 7, 1Hz); ^{13}**C NMR** (125MHz, $CDCl_3$): δ 37.4 (SCH_2), 121.7, 126.5, 127.8, 129.6, 129.8, 131.1, 134.8 (SC_{ipso}), 151.0 (OC_{ipso}), 168.7 (C=O); **MS** (FAB): *m/z* 244 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{14}H_{12}O_2S$: 244.0558. Found 244.0567.

Synthesis of geranyl (phenylsulfanyl)acetate (218)

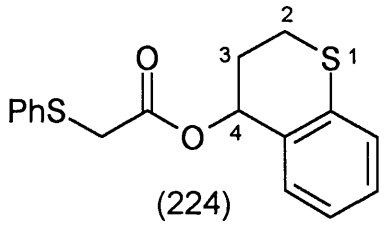


(218)

A solution of geraniol (1g, 6.5mmol), pyridine (0.52mL, 6.5mmol) and (phenylsulfanyl)acetyl chloride (128) (1.21g, 6.5mmol) in DCM (15mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 97: 03) gave geranyl (phenylsulfanyl)acetate (218) (1.75g, 89%) as a colourless oil; $\mathbf{R_f}$ 0.83 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058w, 2967m, 2922s, 2856m, (CH), 1736s (C=O), 1670w, 1582m, 1442s, 1276s, 1136s, 962s, 741s, 691m; ^{1}**H NMR** (500MHz, $CDCl_3$): δ 1.63 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.71 (3H, s, CH_3), 2.05-2.12 (4H, m, 4-H, 5-H), 3.67 (2H, s, SCH_2), 4.65 (2H, d *J* 7Hz, 1-H), 5.10-5.11 (1H, m, 6-H), 5.32 (1H, t *J* 2Hz, 2-H), 7.25-

7.44 (5H, m, Ar-H); **^{13}C NMR** (125MHz, $CDCl_3$): δ 17.4, 18.6, 26.6, 27.2, 37.6, 40.4, 63.3 (1-H), 118.6, 124.6, 127.8, 129.9, 130.9, 132.8, 135.9, 143.9, 170.6; **MS** (FAB): *m/z* 327 (MNa^+, 10%), 304 (M^+, 32); **HRMS** (FAB) calcd. for $C_{18}H_{24}O_2S$: 304.1497. Found: 304.1488.

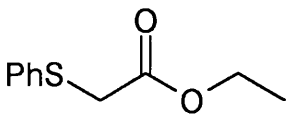
Synthesis of *4-thiochromanyl (phenylsulfanyl)acetate* (224)



(224)

A solution of thiochromanol (500mg, 3mmol), pyridine (0.27mL, 3mmol) and (phenylsulfanyl)acetyl chloride (128) (561mg, 3mmol) in DCM (10mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 05) gave *4-thiochromanyl (phenylsulfanyl)acetate* (224) (903mg, 95%) as a yellow oil; **R_f** 0.55 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058w, 2925w (CH), 1725s (C=O), 1586m, 1477m, 1438m, 1264s, 1126s, 1002m, 962m, 746s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.03-2.13 (1H, m, 3-H), 2.29-2.35 (1H, m, 3-H), 2.75-2.82 (1H, m, 2-H), 3.09-3.19 (1H, m, 2-H), 3.67 (2H, s, SCH_2), 6.05 (1H, t *J* 3Hz, 4-H), 7.01-7.54 (9H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 22.4, 28.7, 37.8, 70.1 (4-C), 125.1, 127.6, 128.0, 130.0, 130.8, 131.1, 132.7, 135.0, 135.5, 169.9 (C=O); **MS** (FAB): *m/z* 316 (M^+, 75%), 219 (35); **HRMS** (FAB) calcd. for $C_{17}H_{16}O_2S_2$ (MH^+): 316.0598. Found: 316.0592.

Synthesis of ethyl (phenylsulfanyl)acetate (225)

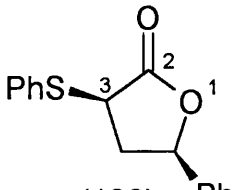


(225)

A solution of ethanol (0.35mL, 5.9mmol), pyridine (0.48mL, 5.9mmol) and (phenylsulfanyl)acetyl chloride (128) (1.00g, 5.4mmol) in DCM (10mL) was stirred for 4hr. Work-up according to the general procedure followed by flash chromatography

(SiO_2, PE: ether 95: 5) gave ethyl (phenylsulfanyl)acetate (225) (1.00g, 95%) as a colourless oil; $\mathbf{R_f}$ 0.65 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2982s (CH), 1736s (C=O), 1582m, 1273s, 1135s, 1028s, 743s, 691s; **^{1}H NMR** (500MHz, $CDCl_3$): δ 1.20 (3H, t J 9Hz, CH_3), 3.61 (2H, s, SCH_2) 4.14 (2H, q J 9Hz, OCH_2), 7.20-7.40 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 14.0 (CH_3), 36.8 (SCH_2), 61.5 (OCH_2), 126.9, 129.0, 129.9, 135.0 (C_{ipso}), 169.8 (C=O); **MS** (FAB): *m/z* 196 (M^+, 65%), 123 (M^+, 100); **HRMS** (FAB) calcd. for $C_{10}H_{12}O_2S$: 196.0558. Found: 196.0550.

Synthesis of *syn*-4,5-dihydro-5-phenyl-3-phenylsulfanyl-2(3*H*)-furanone (196)



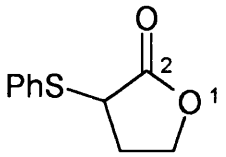
(196)

To a stirred solution of diisopropylamine (1.9mL, 13.6mmol) in THF (10mL) at -78°C was added a solution of *n*-butyllithium (2.47M, 5.5mL, 13.6mmol) and the mixture stirred for 2hr. A solution of γ-phenyl-γ-butyrolactone (1.8mL, 12mmol) in THF (5mL) was added and the mixture stirred for 40min at 40°C, followed by the addition of chlorotrimethylsilane (1.6mL, 12mmol) and a further 50min stirring at -78°C. A solution of bromine (0.64mL, 12mmol) in pentane (10mL) was added and stirring continued for 10min. The reaction was quenched with 2N HCl and the aqueous phase extracted with ethyl acetate (x3). The combined organic extracts were washed with brine and dried (Na_2SO_4). Concentration *in vacuo* gave a brown oil which was chromatographed (SiO_2, PE 30-40: ether 60: 40) to afford *anti*-3-bromo-4,5-dihydro-5-phenyl-2(3*H*)-furanone (2.60g, 90%) as a pale red oil; $\mathbf{R_f}$ 0.56 (SiO_2, PE 30-40: ether 60: 40); **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.66-2.90 (2H, m, 4-H), 4.58 (1H, dd J 6, 2Hz, 3-H), 5.77 (1H, dd J 9, 5Hz, 5-H), 7.35-7.48 (5H, m, Ar-H).

The bromide was taken into DCM (35mL) and sodium thiophenoxide (1.65g, 12.5mmol) added. The mixture was stirred overnight, then quenched with water. Extraction with DCM (x2), drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 30-40: ether 80: 20) to afford *syn*-4,5-dihydro-5-phenyl-3-phenylsulfanyl-2(3*H*)-furanone (196) (1.45g, 47%) as colourless crystals;

m.p. 93-94°C (PE 30-40/ ether) (lit.[118] 90-93°C); $\mathbf{R_f}$ 0.18 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3052w, 2912w, 1763s (C=O), 1575w, 1441m, 1333m, 1219w, 1179m, 1011s, 944s, 735s, 695s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.16-2.27 (1H, m, 4-H), 2.95-3.05 (1H, m, 4-H), 4.09-4.16 (1H, m, 3-H), 5.34-5.39 (1H, m, 5-H), 7.15-7.61 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 38.3 (4-C), 46.7 (3-C), 79.0 (5-C), 125.6, 128.6, 129.2, 131.6 (C_{ipso}), 133.8, 138.2 (C_{ipso}), 174.3 (C=O); **MS** (FAB): *m/z* 270 (M^+, 100%), 253 (35), 225 (50); **Anal** Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86%. Found: C, 71.11; H, 5.11; S, 11.71%.

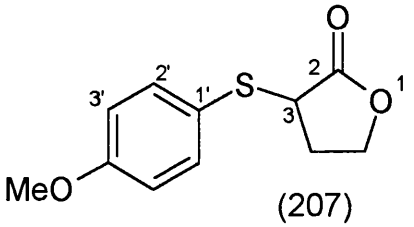
Synthesis of 4,5-dihydro-3-phenylsulfanyl-2(3*H*)-furanone (203)



(203)

To a stirred solution of α-bromo-γ-butyrolactone (9.00g, 54.5mmol) and potassium hydroxide (3.06g, 54.5mmol) in methanol (60mL) was added thiophenol (5.6mL, 54.4mmol). The mixture was stirred overnight, filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, DCM) yielded 4,5-dihydro-3-phenylsulfanyl-2(3*H*)-furanone (203) (4.64g, 44%) as a yellow oil; $\mathbf{R_f}$ 0.13 (SiO_2, PE 30-40: ether 70: 30); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3057m, 2991m, 2913m (CH), 1770s (C=O), 1478m, 1374m, 1157s, 1025m, 746m, 691m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.27-2.35 (1H, m, 4-H), 2.65-2.70 (1H, m, 4-H), 3.88 (1H, dd *J* 9, 6Hz, 3-H), 4.21-4.29 (2H, m, 5-H), 7.35-7.59 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 29.8 (4-C), 44.3 (3-C), 66.4 (5-C), 128.9, 129.1, 131.6, 133.4, 175.0 (C=O); **MS** (FAB): *m/z* 195 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{10}H_{10}O_2S$ (MH^+): 195.0480. Found: 195.0471.

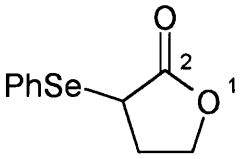
Synthesis of 4,5-dihydro-3-(*p*-methoxyphenyl)sulfanyl-2(3*H*)-furanone (207)



(207)

To a stirred solution of α-bromo-γ-butyrolactone (1.62mL, 19.5mmol) and potassium hydroxide (1.10g, 19.5mmol) in methanol (25mL) was added *p*-methoxybenzenethiol (2.42mL, 19.5mmol). The mixture was stirred overnight, filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30-40: ether 80: 20) yielded 4,5-dihydro-3-(*p*-methoxyphenyl)sulfanyl-2(3*H*)-furanone (207) (3.00g, 74%) as a yellow oil; $\mathbf{R_f}$ 0.08 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2913m, 2839 (CH), 1769s (C=O), 1591m, 1492m, 1373m, 1287m, 1157m, 1026m, 831m, 685m, 640m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.18-2.26 (1H, m, 4-H), 2.57-2.62 (1H, m, 4-H), 3.69 (1H, dd *J* 9, 6Hz, 3-H), 3.78 (3H, s, OCH_3), 4.08-4.40 (2H, m, 5-H), 6.85 (2H, AA'BB' d *J* 10Hz, 3-H', 5'-H), 4.81 (2H, AA'BB' d *J* 10Hz, 2'-H, 6'-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 30.0 (4-C), 45.5 (3-C), 55.7 (OCH_3), 66.9 (5-C), 115.2 (3'-C), 121.8 (1'-C), 137.4 (2'-C), 161.1 (4'-C), 175.6 (C=O); **MS** (FAB): *m/z* 224 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{11}H_{12}O_3S$: 224.0507. Found: 224.0499.

Synthesis of 4,5-dihydro-3-phenylselenyl-2(3*H*)-furanone (209)

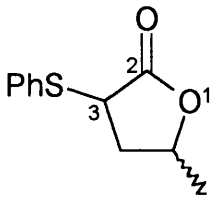


(209)

To a stirred solution of potassium hexamethyldisilazide (4.63g, 23.2mmol) in THF (30mL) at -78°C was added γ-butyrolactone (0.9mL, 11.6mmol) and the mixture stirred for 2.5hr. A solution of phenylselenyl chloride (2.22g, 11.6mmol) in THF (20mL) was added *via* cannula and the reaction allowed to warm to room temperature overnight. The mixture was poured into sat. aq. NH_4Cl solution and extracted with ether (x3). The

combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded 4,5-dihydro-3-phenylsulfanyl-2(3*H*)-furanone (209) (1.57g, 56%) as a colourless oil; $\mathbf{R_f}$ 0.10 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3055m, 2989m, 2912m (CH), 1770s (C=O), 1576m, 1477m, 1441m, 1372m, 1168s, 1024m, 997s, 887s, 742s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.24-2.30 (1H, m, 4-H), 2.64-2.73 (1H, m, 4-H), 3.90 (1H, dd *J* 9, 4Hz, 3-H), 4.07-4.27 (2H, m, 5-H), 7.29-7.38 (3H, m, Ar-H), 7.64-7.67 (2H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 30.5 (4-C), 35.9 (3-C), 66.9 (5-C), 126.5 (C_{ipso}), 129.1, 129.4, 135.9, 176.1 (C=O); **MS** (FAB): *m/z* 243 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{10}H_{10}O_2Se$ (MH^+): 242.9924. Found: 242.9933.

Synthesis of *syn / anti*-4,5-dihydro-5-methyl-3-phenylsulfanyl-2(3*H*)-furanone (211)



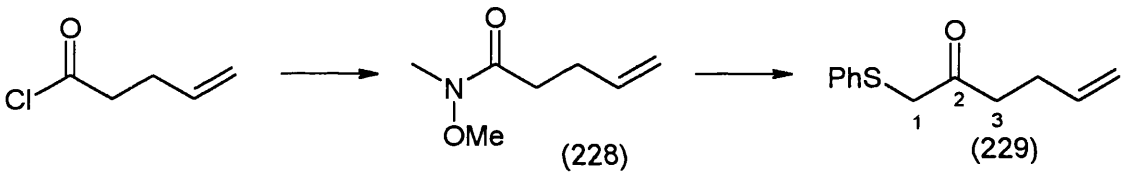
(211)

To a stirred solution of diisopropylamine (8.4mL, 60mmol) and HMPA (7.4mL, 66mmol) in THF (50mL) at 0°C was added a solution of *n*-butyllithium (2.14M in hexane, 28mL, 60mmol). After 10min the mixture was cooled to -78°C and γ-methyl-γ-butyrolactone (3.00g, 30mol) in THF (215mL) was added. After 35min stirring at this temperature a solution of diphenyl disulfide (6.54g, 30mol) in THF (50mL) was added *via* cannula and the reaction left to warm to room temperature for 3hr. The reaction mixture was poured into water (200mL) and extracted with ether (3x200mL). The combined extracts were washed with 10% aq. NaOH solution (100mL), water (100mL), 10% aq. HCl solution (100mL), water (100mL) and dried ($MgSO_4$). All aqueous washings were carefully disposed of into an HMPA waste bottle. Concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 30-40: ether 80: 20) to yield *syn / anti* 4,5-dihydro-5-methyl-3-phenylsulfanyl-2(3*H*)-furanone (211) (3.62g, 58%) as a colourless oil; $\mathbf{R_f}$ 0.72 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3057w, 2979m, 2932m (CH), 1767s (C=O), 1579w, 1478m, 1442m, 1385m, 1342m,

1296m, 1185s, 1086m, 945m, 745s, 693m; **^{1}H NMR** (300MHz, $CDCl_3$): (major diastereoisomer signals marked ′)δ 1.35 (3H, d J 6Hz, CH_3), 1.39 (3H, d, J 6Hz, CH_3′), 1.81-1.92 (1H, m, 4-H), 2.23-2.44 (2H, m, 4′-H), 2.71-2.80 (1H, m, 4-H), 3.92 (1H, dd J 8, 4Hz, 3′-H), 3.99 (1H, dd J 11, 9Hz, 3-H), 4.51-4.58 (1H, m, 5-H), 4.54-4.61 (1H, m, 5′-H), 7.28-7.59 (10H, m, Ar-H), **^{13}C NMR** (126MHz, $CDCl_3$): (major diastereoisomer only) δ 21.2 (CH_3), 38.0 (4-C), 45.8 (3-C), 75.6 (5-C), 129.1, 129.7, 132.4 (C_{ipso}), 133.9, 174.9 (C=O); **MS** (FAB): *m/z* 209 (MH^+ 100%); **HRMS** (FAB) calcd. for $C_{11}H_{13}O_2S$ (MH^+): 209.0636. Found: 209.0640.

3.4 Synthesis of Other β-EWG Sulfides

Synthesis of 1-phenylsulfanyl-hex-5-en-2-one (229)[130]

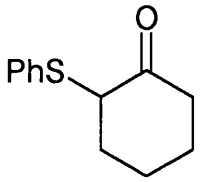


To a stirred solution of 4-pentenoyl chloride (2.4g, 20mmol), and triethylamine (4.2mL, 30mmol) in DCM (30mL) at 0°C was added *N,O*-dimethylhydroxylamine hydrochloride (2.17g, 22mmol). The mixture was stirred for 3hr, then quenched with 2N HCl solution. The organic phase was separated, washed with sat. aq $NaHCO_3$ solution and dried ($MgSO_4$). Concentration *in vacuo* afforded N-methyl-N-methoxy-4-pentenamide (228) (750mg, 26%) as a colourless oil; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.33-2.59 (4H, m, 1-H, 2-H), 3.19 (3H, s, NCH_3), 3.69 (3H, s, OCH_3), 4.98-5.11 (2H, m, 4-H), 5.81-5.94 (1H, m, 3-H).

To a stirred solution of thioanisole (0.6mL, 5mmol) and TMEDA (0.8mL, 5mmol) in THF (4mL) at -20°C was added a solution of *n*-butyllithium (2.54M in hexanes, 2.1mL, 5mmol). After 1hr at this temperature the solution was cannulated into a solution of *N*-methyl-*N*-methoxy-4-pentenamide (750mg, 5mmol) in THF (3mL) at -20°C and the mixture stirred for 3hr. The reaction was quenched with 2N HCl solution and extracted into DCM. The combined extracts were washed with water (x3), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2, PE 30-40: ether 98: 2) yielded 1-

phenylsulfanyl-hex-5-en-2-one (229) (486mg, 45%) as a colourless oil; $\mathbf{R_f}$ 0.64 (SiO_2, PE 30-40: ether 95: 5); **IR** (thin film): $\tilde{\nu}_{max}$ 3076m, 2919s (CH), 1713s (C=O), 1642m, 1583m, 1440m, 1403m, 1087m, 915m, 741s, 690s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.33-2.37 (2H, m, 4-H), 2.72 (2H, t *J* 7Hz, 3-H), 3.69 (2H, s, 1-H), 4.96-5.07 (2H, m, 6-H), 5.75-5.83 (1H, m, 5-H), 7.21-7.38 (5H, m, Ar-H); **MS** (FAB): *m/z* 223 (50%), 206 (M^+, 35), 123 (100); **HRMS** (FAB) calcd. for $C_{12}H_{14}OS$: 206.0765. Found: 206.0774.

Synthesis of 2-phenylsulfanyl-cyclohexanone (230)

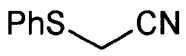


(230)

To a stirred solution of 1-trimethylsilyloxycyclohexene* (1g, 5.8mmol) in DCM (5mL) at -78°C was added a solution of phenylsulfanyl chloride* (845mg, 5.8mmol) in DCM (5mL). The mixture was allowed to warm to room temperature then quenched with sat. aq. $NaHCO_3$ solution. Extraction with DCM (x2), drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil. Flash chromatography (SiO_2, PE 30-40) yielded a yellow oil which was Kugelröhr distilled to afford 3-phenylsulfanyl-cyclohexanone (230) (573mg, 50%) as a pale yellow oil; **b.p.** 200°C / 1mBar; $\mathbf{R_f}$ 0.32 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2936s (CH), 1708s (C=O), 1438s, 744s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.67-2.35 (7H, m), 2.89-2.99 (1H, m), 3.85 (1H, dd *J* 7, 7Hz, 2-H), 7.23-7.53 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 22.7, 27.41, 34.0, 39.1, 56.5 (2-C), 127.5, 129.1, 131.9, 133.8 (C_{ipso}), 207.7 (C=O); **MS** (FAB): *m/z* 207 (MH^+, 100%).

* Prepared according to Varghese, V.; Saha, M.; Nicholas, K. M. *Org. Synth.* **1989**, *67*, 141.
* Prepared according to Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Org. Synth. Coll. Vol. VIII*, **1993**, 550.

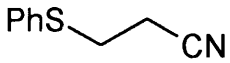
Synthesis of phenylsulfanylacetonitrile (233)[174]



(233)

Thiophenol (5mL, 49mmol), chloroacetonitrile (2.8mL, 44mL) and sodium methoxide (2.63g, 49mmol) were refluxed in methanol (40mL) for 24hr. The reaction was quenched with sat. aq. NH_4Cl solution and the resultant mixture extracted with ethyl acetate (x4). The combined extracts were washed with 2N NaOH, brine and dried ($MgSO_4$). Concentration *in vacuo* gave a colourless oil which was Kugelröhr distilled to yield phenylsulfanylacetonitrile (233) (4.07g, 56%) as a colourless liquid; **b.p.** 110°C / 1mBar (lit.[178] 154-157°C / 2.4KPa); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3060m, 2971m, 2931m (CH), 2246m (C≡N), 1578m, 1479s, 1440s, 1400m, 1025m, 742s, 692s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.59 (2H, s, CH_2), 7.39-7.60 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 21.2 (CH_2), 116.4 (C≡N), 128.8, 129.5, 132.3, 132.0 (C_{ipso}); **MS** (EI): *m/z* 149 ($M^{\bullet+}$, 100%), 109 (PhS^+, 100); **HRMS** (FAB): calcd. for C_8H_7NS: 149.0299. Found: 149.0295.

Synthesis of 3-phenylsulfanylpropionitrile (234)

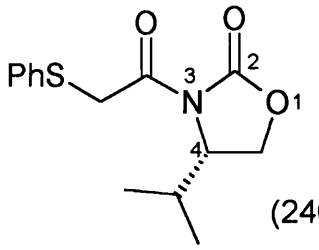


(234)

Thiophenol (10mL, 97mmol) and acrylonitrile (10mL, 152mL) were stirred in water (100mL) containing 10mL of a pH 6 phosphate buffer (made from 0.1M KH_2PO_4, 50mL; 0.1M NaOH, 5.6mL) for 24hr. The solution was extracted with DCM (x4) and the combined extracts washed with phosphate buffer solution (pH 7.2) (x3). Drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil which was distilled to yield 3-phenylsulfanylpropionitrile (234) (12.81g, 81%) as a colourless liquid; **b.p.** 128°C / 1mBar; **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3059m, 2932m (CH), 2251m (C≡N), 1583m, 1482s, 1439s, 1284m, 1232w, 1090m, 1070m, 1025m, 959w, 904w, 742s, 692s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.60 (2H, t *J* 7Hz), 3.13 (2H, t *J* 7Hz), 7.30-7.45 (5H, m, Ar-H);

^{13}C NMR (75MHz, $CDCl_3$): δ 18.5, 30.2, 117.9 (C≡N), 127.6, 129.3, 131.3, 133.1 (C_{ipso}); **MS** (EI): *m/z* 163 ($M^{\bullet+}$, 80%), 123 ($PhSCH_2^+$, 100); **HRMS** (FAB): calcd. for C_9H_9NS: 163.0456. Found: 163.0457.

Synthesis of *(4S)-4-isopropyl-3-(phenylsulfanyl)acetyl-1,3-oxazolidin-2-one* (240)

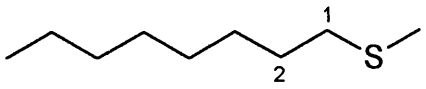


(240)

To a stirred suspension of sodium hydride (60% dispersion on mineral oil, 354mg, 8.9mmol), pre-washed with pentane, in THF (10mL) was added *S*-4-isopropyl-1,3-oxazolidin-2-one (1.04g, 8.05mmol) in THF (5mL) *via* cannula. After stirring for 20hr the mixture was cooled to 0°C and (phenylsulfanyl)acetyl chloride (128) (1.5g, 8.05mmol) was added dropwise. The mixture was left to warm to room temperature overnight and then quenched with sat. aq. $NaHCO_3$ solution. Extraction into DCM followed by drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil which was chromatographed (SiO_2, DCM) to afford *(4S)-4-isopropyl-3-(phenylsulfanyl)acetyl-1,3-oxazolidin-2-one* (240) (1.36g, 61%) as a yellow oil; $[\alpha]_D^{25}$ = +89.0 (DCM, *c*=1); **R_f** 0.63 (SiO_2, PE 30-40: ethyl acetate 40: 60); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2964s, 2876m (CH), 1770s, 1694 (C=O), 1392s, 1316s, 1208s, 1100s, 1025s, 742s, 691s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.89 (3H, d *J* 6Hz, CH_3), 0.92 (3H, d *J* 6Hz, CH_3), 2.30-2.41 (1H, m, C<u>H</u>$(CH_3)_2$), 4.19 (1H, d J_{AB} 15Hz, SCH_2) 4.23-4.47 (3H, m, 4-H, 5-H), 4.38 (1H, d J_{AB} 15Hz, SCH_2), 7.22-7.48 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 14.5 (CH_3), 17.7 (CH_3), 28.1 (<u>C</u>H$(CH_3)_2$), 37.8 (SCH_2), 58.4, 63.5, 127.0, 128.9, 130.3, 134.6 (C_{ipso}), 153.7 (2-C), 168.6 (C=O); **MS** (FAB): *m/z* 280 (MH^+, 35); **HRMS** (FAB) calcd. for $C_{14}H_{17}NO_3S$: 280.1007. Found: 280.0990.

3.5 Synthesis of Unactivated Sulfides

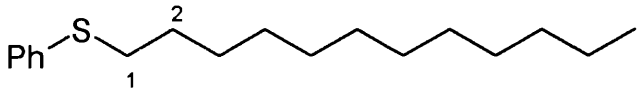
Synthesis of methyl octyl sulfide (242)



(242)

To a suspension of sodium hydride (60% dispersion on mineral oil, 2.20g, 55mmol) in THF (70mL) at 0°C was added octyl mercaptan (8.7mL, 50mmol) and the mixture stirred for 10min. Iodomethane (6.2mL, 100mmol) was added and the mixture stirred for a further 20min, then quenched with sat. aq. NH_4Cl solution The resulting mixture was extracted with ether (2x50mL), dried ($MgSO_4$) and concentrated to give a colourless liquid. Distillation afforded methyl octyl sulfide (242) (5.82g, 73%) as a colourless liquid; **b.p.** 108°C / 19mBar; **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2925s, 2855s (CH), 1462m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.68-0.91 (3H, m), 1.28-2.07 (12H, m), 2.10 (3H, s, SCH_3), 2.49 (2H, t *J* 7Hz, 1-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 14.1 and 15.5 (2xCH_3), 22.6, 28.8, 29.2 (3C), 31.8, 34.3; **MS** (FAB): *m/z* 290 ([2(M-CH_3)]$^+$, 100%); **HRMS** (FAB) calcd. for $C_{16}H_{34}S_2$ (2(M-CH_3)): 290.2102. Found: 290.2907.

Synthesis of dodecyl phenyl sulfide (245)

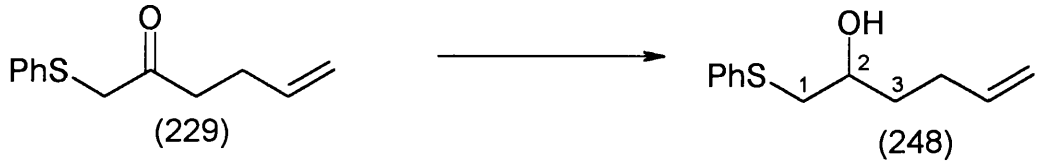


(245)

To a stirred solution of dodecyl iodide (5mL, 23mmol) in DCM (20mL) was added sodium thiophenoxide (3.10g, 23mmol). After 48hr the reaction was quenched with water and the resulting mixture extracted with DCM (x3). The combined organic extracts were washed with brine and dried ($MgSO_4$). Concentration *in vacuo* gave an oil, which was chromatographed (SiO_2, PE 30-40) to yield dodecyl phenyl sulfide (245) (1.41g, 22%) as a yellow oil which crystallised in the refrigerator; $\mathbf{R_f}$ 0.34 (SiO_2, PE 30-

40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3056w, 2924s, 2853s (CH), 1581w, 1474m, 1438m, 1025w, 738s, 689s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.91 (3H, t *J* 6Hz, 12-H), 1.28-1.69 (20H, m), 2.94 (2H, t *J* 7Hz, 1-H), 7.18-7.54 (5H, m, Ar-H); **MS** (FAB): *m/z* 278 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{18}H_{30}S$: 278.2068. Found: 278.2083.

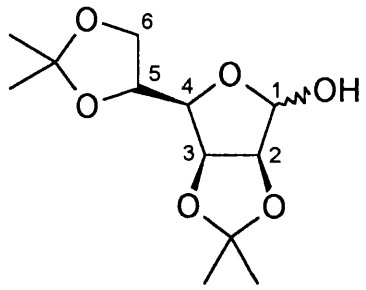
Synthesis of 2-hydroxy-1-phenylsulfanyl-hex-5-ene (248)



To a stirred solution of 1-phenylsulfanyl-hex-5-en-2-one (229) (235mg, 1.1mmol) in methanol (5mL) was added sodium borohydride (43mg, 1.1mmol) in portions. After 1hr the reaction was quenched with water and the resulting mixture extracted with DCM (x4). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (SiO_2, DCM) to afford 2-hydroxy-1-phenylsulfanyl-hex-5-ene (248) (129mg, 57%) as a colourless oil; **R_f** 0.33 (SiO_2, DCM); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3406s (OH), 2921s (CH), 1640m, 1584m, 1480s, 1439s, 1070s, 1025s, 913s, 739s, 690s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.62-1.69 (2H, m, 4-C), 2.14-2.27 (2H, m, 3-C), 2.47 (1H, d *J* 3Hz, OH), 2.84-3.21 (2H, m, 1-H), 3.70-3.73 (1H, m, 2-H), 4.96-5.08 (2H, m, 6-H), 5.78-5.87 (1H, 5-H), 7.21-7.43 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 29.9, 35.0, 42.0, 68.7 (2-C), 114.9 (6-C), 126.5, 129.0, 129.9, 135.1 (C_{ipso}), 137.9.

3.6 Synthesis of Dithioorthoesters and Thione Esters

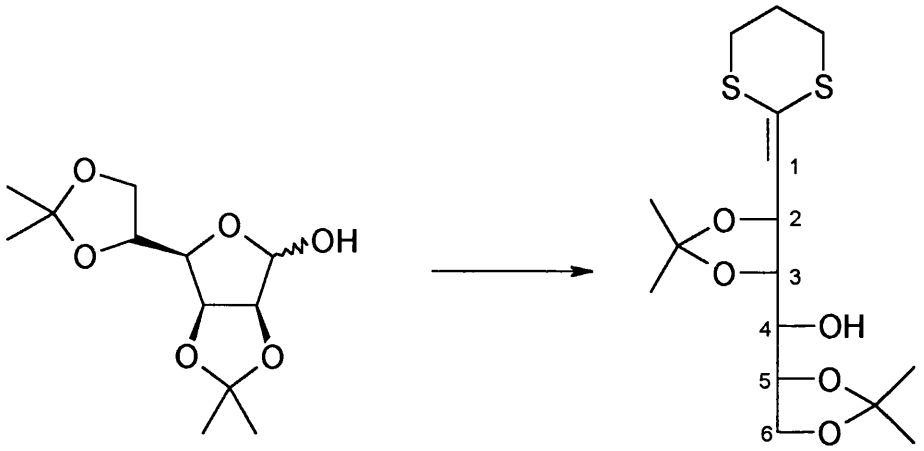
Synthesis of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (261)[169]



(261)

p-Toluenesulfonic acid monohydrate (0.08g, 0.42mmol) was added in one portion to a suspension of D-mannose (4.00g, 22mmol) in dry acetone (130mL). The suspension was refluxed overnight, cooled to room temperature and then stirred with potassium carbonate. Filtration through celite and concentration *in vacuo* yielded an off-white solid that was taken into DCM and filtered through a short silica column topped with celite. Concentration *in vacuo* gave an off-white solid that was recrystallised from ether-hexane to give 2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranose (261) (4.13g, 72%) as colourless crystals; **m.p.** 123°C (ether / hexane) (lit.[169] 120°C (ether / hexane)); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.32 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.455 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.80 (1H, d *J* 2Hz, OH), 4.03-4.10 (2H, m, 6-H), 4.18 (1H, dd *J* 7, 4Hz, 4-H), 4.38-4.41 (1H, m, 5-H), 4.62 (1H, d *J* 6Hz, 2-H), 4.81 (1H, dd *J* 6, 4Hz, 3-H), 5.38 (1H, d *J* 2Hz, 1-H); **MS** (FAB): *m/z* 261 ($[MH]^+$, 10%), 245 ($[M\text{-}CH_3]^+$, 100); **HRMS** (FAB) calcd. for $C_{13}H_{20}O_6$ (MH^+): 261.1338. Found: 261.1330.

Synthesis of 2-(1-deoxy-2,3 :5,6-di-*O*-isopropylidene-D-mannitol-1-ylidene)-1,3-dithiane (262)[152]

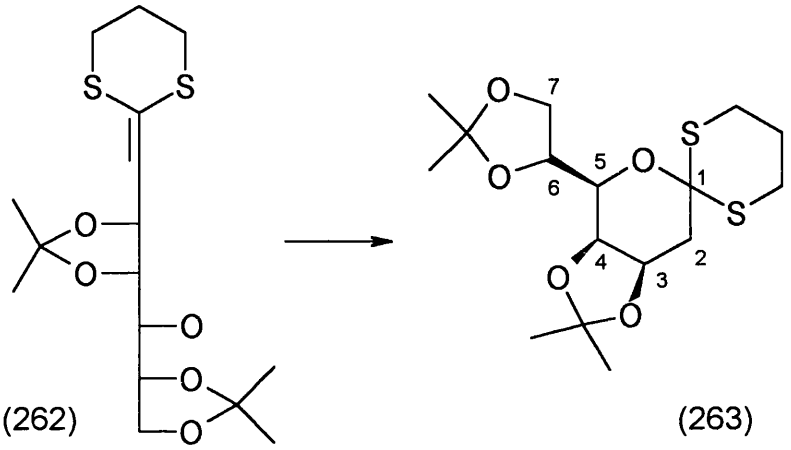


(261) (262)

Sodium hydride (60% dispersion on mineral oil, 129mg, 3.3mmol) was washed with hexane under nitrogen and the resultant solid suspended in THF (20mL) at 0°C. A solution of 2,3:5,6-di-*O*-isopropylidene-*α*-*D*-mannofuranose (261) (700mg, 2.7mmol) in THF (3.3mL) containing a catalytic amount of imidazole was then added *via* cannula and the mixture stirred for 2hr. Concurrently the 2-lithio-2-trimethylsilyl-1,3-dithiane solution was prepared *via* dropwise addition of a solution of *n*-butyllithium (2M in hexane, 1.5mL, 3mmol) to a solution of 2-trimethylsilyl-1,3-dithiane (0.56mL, 3mmol) in THF (6mL) at -40°C and stirring for 2hr. After cooling to -78°C, the two solutions were combined *via* cannula and the mixture stirred overnight. It was then poured into sat. aq. NH_4Cl solution and extracted with DCM. Drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 40-60: ether 80: 20) to yield 2-(1-deoxy-2,3 :5,6-di-*O*-isopropylidene-D-mannitol-1-ylidene)-1,3-dithiane (262) (869mg, 89%) as a viscous oil; $\mathbf{R_f}$ 0.26 (SiO_2, PE 40-60: ethyl acetate 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3414s (OH), 2926s (CH), 1765s, 1696s, 1377s, 1213s, 1069s, 852m; ^{1}**H NMR** (400MHz, $CDCl_3$): δ 1.32 (3H, s, CH_3), 1.39 (6H, s, $C(CH_3)_2$), 1.49 (3H, s, CH_3), 2.08 (1H, d *J* 8Hz, OH), 2.18 (2H, m, $SCH_2C\underline{H}_2$), 2.77-3.00 (4H, m, $2xSCH_2$), 3.36 (1H, m, 4-H), 3.95-4.07 (3H, m, 5-H, 6-H), 4.36 (1H, dd $J_{3,2}$ 8Hz, $J_{3,4}$ 1Hz, 3-H), 5.26 (1H, dd $J_{2,1}$ 8Hz, $J_{2,3}$ 8Hz, 2-H), 6.10 (1H, d $J_{1,2}$ 8Hz, 1-H); ^{13}**C NMR** (100MHz, $CDCl_3$): δ 24.45, 24.49, 25.4, 26.7, 26.9, 29.1, 29.5, 66.8, 70.4, 74.4, 76.2, 76.7, 108.5

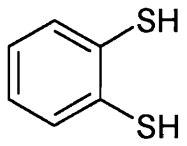
and 109.3 (2x<u>C</u>$(CH_3)_2$), 126.5 (1-C), 134.3 ($C(SR)_2$); **MS** (FAB): *m/z* 363 (MH^+, 55%), 215 (100); **HRMS** (FAB) calcd. for $C_{16}H_{27}O_5S_2$ (MH^+): 363.1300. Found: 363.1302.

Synthesis of 1,2-dideoxy-3,4:6,7-di-*O*-isopropylidene-1,1-[propan-1,3-bis(sulfanediyl)]-D-glycero-D-galacto-heptopyranose (263)[152]



2-(1-Deoxy-2,3 :5,6-di-*O*-isopropylidene-D-mannitol-1-ylidene)-1,3-dithiane (262) (475mg, 1.31mmol) in DCM (10mL) was stirred with amberlite® IR-120 (plus) ion-exchange resin overnight. The resin was removed by filtration and the solution concentrated in vacuo. Flash chromatography (SiO_2, PE 40-60: ether 70: 30) afforded 1,2-dideoxy-3,4:6,7-di-*O*-isopropylidene-1,1-[propan-1,3-bis(sulfanediyl)]-D-glycero-D-galacto-heptopyranose (263) (407mg, 86%) as a white solid plus some unreacted starting material (22mg, 5% recovery); **m.p.** 108°C (PE 40-60 / ether); $\mathbf{R_f}$ 0.33 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2927m (CH), 1375m, 1217s, 1063s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.33 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.93-2.16 (4H, m, 2-H, $SCH_2C\underline{H}_2$), 2.56-2.65 (2H, m, SCH_2), 2.92-3.02 (1H, m, SCH_2), 3.32-3.42 (1H, m, SCH_2), 3.94 (1H, dd $J_{4,3}$ 7Hz, $J_{4,5}$ 2Hz, 4-H), 4.02-4.16 (2H, m, 7-H), 4.16 (1H, dd $J_{5,6}$ 6Hz, $J_{5,4}$ 2Hz, 5-H), 4.39-4.48 (2H, m, 3-H, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ24.6, 25.5 (CH_3), 26.1 (CH_3), 26.2, 26.96 (CH_3), 27.0, 27.7 (CH_3), 39.5 (2-C), 66.9 (7-C), 69.9, 71.0, 72.1, 74.3, 85.6 (1-C), 109.1, 109.3 (2x<u>C</u>$(CH_3)_2$); **MS** (FAB): *m/z* 363 (M^+, 75%), 289 (45), 273 (100); **HRMS** (FAB) calcd. for $C_{16}H_{26}O_5S_2$: 363.1300. Found: 363.1320.

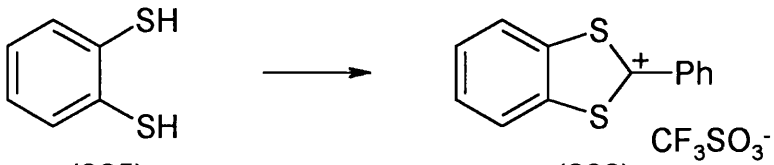
Synthesis of 1,2-benzenedithiol (265)[154]



(265)

To a stirred solution of TMEDA (19g, 0.16mol) and *n*-butyllithium (2.37M in hexanes, 67.5mL, 0.16mol) in cyclohexane (200mL) at 0°C was added a solution of thiophenol (8g, 0.07mol) in cyclohexane (20mL) and the mixture stirred for 24hr at room temperature. During this time a cream-coloured solid formed. Sulfur (sublimed, 5g, 0.16mol) was added and the suspension stirred for an additional 12hr. The cyclohexane was removed *in vacuo* and THF (200mL) added. Lithium aluminium hydride (3g, 0.08mol) was added portionwise and the mixture heated to reflux for 8hr. After cooling to room temperature the solution was carefully poured into 2N HCl (400mL) at 0°C and then extracted into ether (2x500mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was distilled to afford 1,2-benzenedithiol (265) (5.70g, 55%) as a colourless oil which solidified on cooling; **b.p.** 80°C / 1mBar (lit.[154] 75°C / 1mmHg); **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.71 (2H, s, SH), 7.03-7.09 (2H, m), 7.32-7.37 (2H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ 131.1 (2C), 126.7.

Synthesis of 2-phenyl-1,3-benzodithiolyium trifluoromethanesulfonate (266)[153]

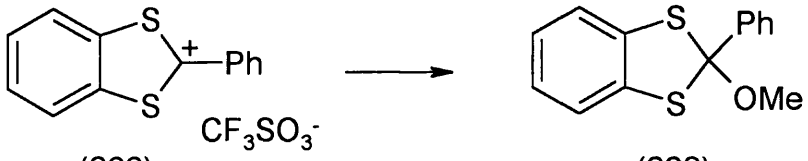


(265) (266)

A mixture of 1,2-benzenedithiol (2.00g, 14.1mmol) and phenyl benzoate (2.75g, 13.8mmol) in trifluoromethanesulfonic acid (1.87mL, 18.7mmol) was heated to 110°C for 10min. After cooling to room temperature the mixture was diluted with acetonitrile (6mL) and the resulting solution added to dry ether (100mL) *via* syringe. The

precipitate was removed by filtration, washed with dry ether (2x25mL) under nitrogen and dried to afford 2-phenyl-1,3-benzodithiolyium trifluoromethanesulfonate (266) (4.45g, 91%) as yellow crystals; **m.p.** 145°C (MeCN / Et_2O) (lit.[153] 149-151°C (MeCN / Et_2O)); **MS** (FAB): *m/z* 229 ([M-CF_3SO_3]$^+$, 100%); **HRMS** (FAB) calcd. for $C_{13}H_9S_2$ (M-CF_3SO_3): 229.0146. Found: 229.0162.

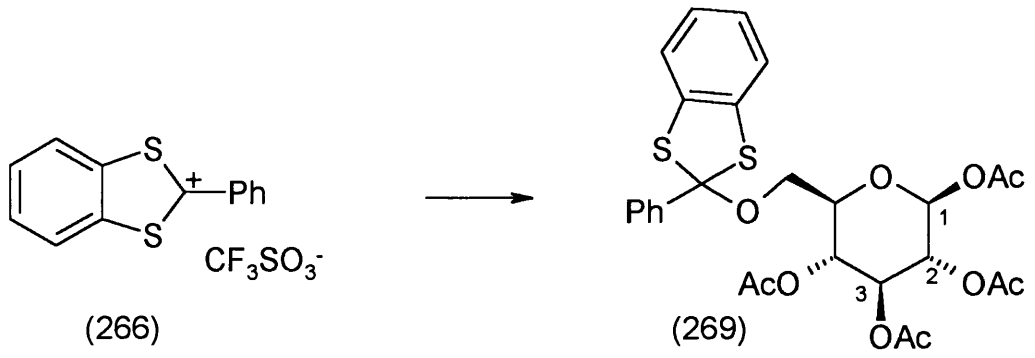
Synthesis of 2-methoxy-2-phenyl-1,3-benzodithiole (268)[153]



(266) (268)

To a stirred solution of 2-phenyl-1,3-benzodithiolyium trifluoromethanesulfonate (266) (760mg, 2mmol) in acetonitrile (2mL) was added a solution of methanol (1M in acetonitrile, 2mL, 2mmol) and triethylamine (1M in acetonitrile, 2mL, 2mmol). After 15min the solution was concentrated *in vacuo* and the residue partitioned between Et_2O and water. Extraction into Et_2O (x2) followed by washing of the combined extracts with sat. aq. $NaHCO_3$ solution, drying ($MgSO_4$) and concentration *in vacuo* gave 2-methoxy-2-phenyl-1,3-benzodithiole (268) (497mg, 96%) as a viscous red oil; **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058m, 2930m (CH), 1445s, 1214m, 1177m, 1120m, 1084s, 943s, 896m, 742s, 718m, 695m, 651w; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.49 (3H, s, OCH_3), 7.06-7.42 (7H, m, Ar-H), 7.97-8.00 (2H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 52.5 (OCH_3), 109.4 ($OCSR_2$), 121.4, 125.9, 128.0, 128.4, 129.1, 137.4 (C_{ipso}), 140.6 (C_{ipso}).

Synthesis of *1,2,3,4-tetra-O-acetyl-6-O-(2-phenyl-1,3-benzodithiol-2-yl)-β-D-glucose* (266)



(266) (269)

To a stirred solution of 2-phenyl-1,3-benzodithiolyium trifluoromethanesulfonate (266) (760mg, 2mmol) in acetonitrile (2mL) was added a solution of 1,2,3,4-tetra-*O*-acetyl-*β*-D-glucopyranose (1M in acetonitrile, 2mL, 2mmol) and triethylamine (1M in acetonitrile, 2mL, 2mmol). After 1hr the solution was concentrated *in vacuo* and the residue partitioned between DCM and water. Extraction into DCM (x2) followed by washing of the combined extracts with sat. aq. $NaHCO_3$ solution, drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was chromatographed (SiO_2, PE 30-40: ether 60: 40) to yield *1,2,3,4-tetra-O-acetyl-6-O-(2-phenyl-1,3-benzodithiol-2-yl)-β-D-glucose* (269) (101mg, 9%) as colourless crystals; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.04, 2.09, 2.10, 2.16 (12H, 4xs, 4x$COCH_3$), 3.76-3.92 (3H, m), 5.19-5.35 (3H, m), 5.76 (1H, d *J* 8Hz, 1-H), 7.17-7.46 (7H, m, Ar-H), 7.98-8.02 (2H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 21.0, 21.06, 21.09, 21.3 (4x$CO\underline{C}H_3$), 62.7 (6-C), 68.6, 70.7, 73.5, 73.6, 92.3 (1-C), 108.4 ($OCSR_2$), 121.1, 121.5, 126.1, 128.1, 128.4, 129.2, 137.0, 140.0, 169.45, 169.48, 169.7, 170.1; **Anal.** Calcd. for $C_{27}H_{28}O_{10}S_2$: C, 56.24; H, 4.89%. Found: C, 56.17; H, 4.75%.

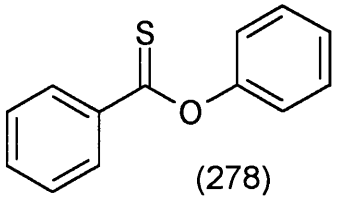
General thionation procedure[155#]

2,4-Bis-(*p*-methoxyphenyl)-1,2,3,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) was added to a solution of lactone / ester in toluene / xylene. The mixture was stirred at reflux, then cooled to room temperature and diluted with a mixture of PE /

[#] Experiments marked # were performed by Ms E. M. M. de la Nava under the direct supervision of the author.

benzene 60: 40 (*ca.* 10mL mol^{-1} of lactone/ester). The precipitated solid was removed by filtration and the filtrate was concentrated *in vacuo*. The reaction products were purified by flash chromatography.

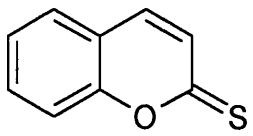
Synthesis of thiobenzoic acid *O*-phenyl ester (278)[#]



(278)

Phenyl benzoate (274) (1.00g, 5.04mmol) and Lawesson's reagent (2.72mg, 6.70mmol) stirred 20hr in xylene (7mL) at reflux. Fresh Lawesson's reagent was then added and refluxing continued for 48hr. Flash chromatography (SiO_2, DCM: PE 30-40 95: 5) afforded thiobenzoic acid *O*-phenyl ester (278) (330mg, 31%) as an orange solid; **m.p.** 35-36°C (ethanol) (lit.[170] 35.5-37.5°C); $\mathbf{R_f}$ 0.88 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 1591s, 1488s, 1450s, 1272s, 1186s, 1071s, 1012s, 770s, 685s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 7.15-7.80 (8H, m, Ar-H), 8.42-8.50 (2H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 122.1, 126.4, 128.3, 129.3, 129.6, 133.3, 137.9 (C_{ipso}), 154.8 (OC_{ipso}), 211.0 (C=S); **MS** (FAB): *m/z* 215 (MH^+, 40%), 121 (100); **Anal.** calcd. for $C_{13}H_{11}OS$: C, 72.87; H, 4.60; S, 14.94%. Found: C, 72.79; H, 4.60; S, 15.10%; and starting material (520mg, 52% recovery).

Synthesis of chromene-2-thione (279)[#]

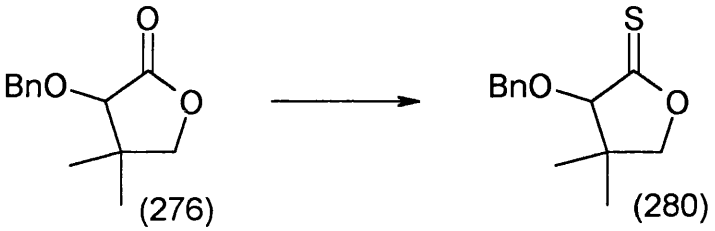


(279)

Coumarin (275) (500mg, 3.42mmol) and Lawesson's reagent (712mg, 1.88mmol) in toluene (3.5mL) at reflux for 2hr. Flash chromatography (SiO_2, PE 30-40: ether 85: 15) afforded chromene-2-thione (279) (480mg, 87%) as an orange solid; **m.p.** 89-91°C (ethanol) (lit.[171] 98-99°C (aq. ethanol)); $\mathbf{R_f}$ 0.33 (SiO_2, PE 30-40: ether 90: 10); **IR** (KBr

disc/cm^{-1}): $\tilde{\nu}_{max}$ 1603m, 1547m, 1247m, 1199s, 1087s, 814s, 748s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 7.22 (1H, d *J* 9Hz), 7.46 (1H, d *J* 9 Hz), 7.28-7.62 (4H, m); **^{13}C NMR** (75MHz, $CDCl_3$): δ 116.8, 120.3, 125.4, 127.7, 129.5, 132.1, 134.4, 156.5, 197.9 (C=S); **MS** (FAB): *m/z* 163 (MH^+, 100%), 154 (40), 136 (42), 107 (30); **Anal.** calcd. for C_9H_6OS: C, 66.67; H, 3.70%. Found: C, 66.43, H, 3.63%; and starting material (50mg, 10% recovery).

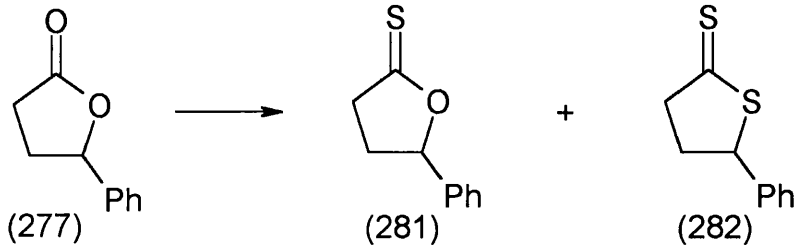
Synthesis of *3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3H)-furanthione* (280)[#]



3-Benzyloxy-4,5-dihydro-4,4-dimethyl-2(*3H*)-furanone[*] (276) (440mg, 2.0mmol) and Lawesson's reagent (809mg, 2.0mmol) in toluene (5mL) at reflux for 5hr. Fresh Lawesson's reagent was then added and stirring at reflux continued for 50hr. Flash chromatography (PE 30-40: ether 90: 10) afforded *3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3H)-furanthione* (280) (346mg, 74%) as a yellow oil; **R_f** 0.45 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2963s (CH), 1454s, 1363s, 1277s, 1126s (C=S), 993m, 741m, 699s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.09 (3H, s, CH_3), 1.13 (3H, s, CH_3), 3.82 (1H, s, 3-H), 4.22 (1H, d J_{AB} 9Hz), 4.37 (1H, d J_{AB} 9Hz), 4.84 (1H, d J_{AB} 12Hz), 5.16 (1H, d J_{AB} 12Hz), 7.30-7.50 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$) 18.5, 22.8, 41.9, 72.5, 84.1, 90.4, 127.9, 128.2, 128.3, 137.3 (C_{ipso}), 221.3 (C=S); **MS** (FAB): *m/z* 237 (MH^+,100), 154 (45), 136 (42), 115 (47), 107 (30); **HRMS** (FAB) calcd. for $C_{13}H_{17}O_2S$ (MH^+): 237.0949. Found: 237.0941; and starting material (60mg, 14% recovery).

- We thank Dr I. Bausanne for the preparation of this compound.

Synthesis of *4,5-dihydro-5-phenyl-2(3H)-furanthione (282)* and *4,5-dihydro-5-phenyl-2(3H)-thiophenethione* (283)[#]



γ-Phenyl-γ-butyrolactone (277) (500mg, 3.08mmol) and Lawesson's reagent (935mg, 2.30mmol) stirring 4.5hr in toluene (7mL) at reflux. Flash chromatography (SiO_2, PE 30-40: ether 90: 10) afforded *4,5-dihydro-5-phenyl-2(3H)-thiophenethione* (282) (31mg, 5%) as an orange solid; **m.p.** 48-50°C; $\mathbf{R_f}$ 0.64 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2900m (CH), 1702w, 1490m, 1449m, 1284w, 1143m, 1038s, 698s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.50-2.70 (1H, m), 2.75-2.90 (1H, m), 3.00-3.20 (1H, m), 3.30-3.50 (1H, m), 5.32 (1H, dd, *J* 10, 6Hz, 5-H), 7.20-7.60 (5H, m, Ar-H); **MS** (FAB): *m/z* 195 (MH^+, 70%), 161 (40), 128 (100), 117 (65), 105 (35); **HRMS** (FAB) calcd. for $C_{10}H_{11}S_2$ (MH^+): 195.0302. Found: 195.0307; and *4,5-dihydro-5-phenyl-2(3H)-furanthione* (281) (360mg, 66%) as a white solid; **m.p.** 40-42°C; $\mathbf{R_f}$ 0.25 (SiO_2, PE 30-40: ether 90: 10); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2900w, 1450s, 1364s, 1275s, 997m, 914m, 750s, 700s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.23-2.38 (1H, m), 2.66-2.78 (1H, m), 3.10-3.40 (2H, m), 5.88 (1H, dd, *J* 8, 7Hz, 5-H), 7.25-7.50 (5H, m, Ar-H) **^{13}C NMR** (75MHz, $CDCl_3$): δ 32.3, 44.9, 90.7, 125.7, 128.7, 128.8, 137.9, 221.9 (C=S); **Anal.** calcd. for $C_{10}H_{10}OS$: C, 67.38; H; 5.54%. Found: C, 67.31; H, 5.54%; and starting material (100mg, 20% recovery).

Chapter 4. Fluorination Reactions

General procedure for the fluorination of substrates using Difluoroiodotoluene (98)

1. Reactions conducted at 0°C

A solution of difluoroiodotoluene (98) in DCM was prepared in a 25mL polypropylene flask protected from light by aluminium foil. The solution was cooled to 0°C in an ice-salt bath and a solution of the substrate in DCM was then added *via* cannula. The mixture was left to stir at this temperature. Upon completion (tlc) the reaction was quenched with water and extracted with DCM. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography yielded pure materials.

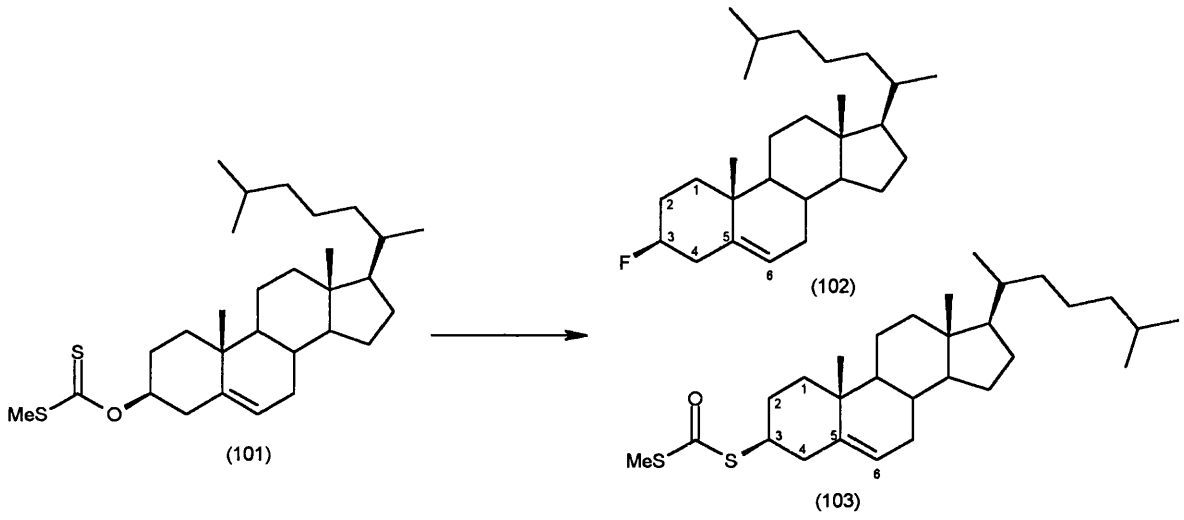
2. Reactions conducted at reflux

A solution of difluoroiodotoluene (98) in DCM was prepared in a 25mL glass round-bottomed flask equipped with a water-cooled reflux condenser. A solution of the substrate in DCM was added *via* cannula and the mixture stirred at reflux. Upon completion (tlc) the reaction was cooled to room temperature and worked up as above.

Any variations to the above protocol will be explicitly stated.

4.1 Fluorination of Allylic Substrates

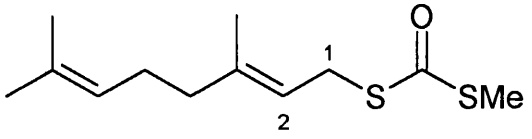
Synthesis of 3β–*S*–cholesteryl-*S*-methyl dithiocarbonate (103) and 3β-fluorocholesterol (102)



A solution of difluoroiodotoluene (98) (150mg, 0.59mmol) and 3β–*O*–cholesteryl-*S*-methyl dithiocarbonate (101) (255mg, 0.53mmol) in benzene (5mL) was stirred for 3hr. The reaction was quenched with sat. aq $NaHCO_3$ solution and worked-up as usual. Flash chromatography (SiO_2, PE 40-60: ethyl acetate 99: 1) yielded 3β-fluorocholestane (102) (81mg, 37%) as a white solid; **m.p.** 96°C (lit[172] 96°C); $\mathbf{R_f}$ 0.54 (SiO_2, PE 40-60: ethyl acetate 92: 8); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1218m, 1057m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.64-2.01 (41H, m), 2.41 (2H, t *J* 7Hz), 4.35 (1H, m, 3-H), 5.37 (1H, d *J* 5Hz, 6-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 11.9, 18.7, 19.3, 21.1, 22.6, 22.8, 23.8, 24.3, 28.0, 28.2, 28.7, 28.9, 31.9, 31.95, 35.8, 36.2, 36.3, 36.4, 36.5, 39.3, 39.50, 39.52, 39.7, 42.3, 50.0, 56.5 (d $^2J_{CF}$ 57Hz, 4-C), 92.9 (d $^1J_{CF}$ 174Hz, 3-C), 123.0 (6-C), 139.3 (d $^3J_{CF}$ 13Hz, 5-C); **^{19}F NMR** (376MHz, $CDCl_3$): δ -168.3 (d $^2J_{FH}$ 45Hz); **MS** (FAB): *m/z* 387 (100%), 369 (41); and 3β–*S*–cholesteryl-*S*-methyl dithiocarbonate (103) (51mg, 20%) as a white solid; **m.p.** 158°C (ethanol) (lit.[81] 158°C (ethyl acetate)); $\mathbf{R_f}$ 0.61 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (nujol mull/cm^{-1}): $\tilde{\nu}_{max}$ 1644s (C=O), 850s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.63-2.09 (41H, m), 2.36 (2H, d *J* 8Hz), 2.43 (3H, s, SCH_3), 3.50 (1H, m, 3-H), 5.39 (1H, d *J* 5Hz, 6-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 11.7, 12.8, 18.6, 19.1, 20.8, 22.4, 22.7, 23.7, 24.1, 27.9, 28.1, 29.1, 31.66, 31.73, 35.7, 36.1, 36.5, 39.1,

39.4, 39.6, 42.2, 45.3, 50.0, 56.0, 56.6, 121.8 (6-C), 140.8 (5-C), 189.0 (C=O); **MS** (FAB): *m/z* 369 (100%); **Anal.** Calcd. for $C_{29}H_{48}S_2O$: C, 73.05; H, 10.15; S, 13.45; Found: C, 72.77; H, 10.25; S, 13.41.

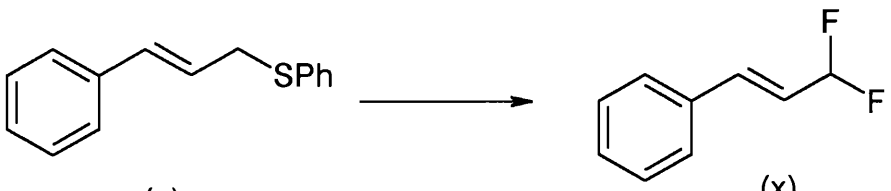
Synthesis of dithiocarbonic acid *S*-(3,7-dimethyl-octa-2,6-dienyl) *S*-methyl ester (109)



(109)

A solution of difluoroiodotoluene (98) (180mg, 0.7mmol) and dithiocarbonic acid *S*-(3,7-dimethyl-octa-2,6-dienyl) *S*-methyl ester (108)* (140mg, 0.5mmol) in benzene (10mL) was stirred for 2hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ethyl acetate 99: 1) yielded dithiocarbonic acid *S*-(3,7-dimethyl-octa-2,6-dienyl) *S*-methyl ester (109) (21mg, 14%) as a colourless oil; $\mathbf{R_f}$ 0.53 (SiO_2, PE 40-60: ethyl acetate 90: 10); **IR** (CCl_4/cm^{-1}): $\tilde{\nu}_{max}$ 2930s (C-H), 1647s (C=O), 1261m, 1097m, 1015m, 871s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.54, 1.58 and 1.66 (9H, s, 3xCH_3), 1.99-2.07 (4H, m, 4-H, 5-H), 2.40 (3H, s, SCH_3), 3.66 (2H, d *J* 8Hz, 1-H), 5.03-5.23 (2H, m, 2-H and 6-H); **MS** (EI): *m/z* 244 (M^+, 5%), 197 ([M-SMe]$^+$, 25), 169 ([M-COSMe]$^+$, 62), 137 ([M-SCOSMe]$^+$, 50).

Synthesis of *E*-(1,1-difluoro-3-phenyl-prop-2-ene) (114)



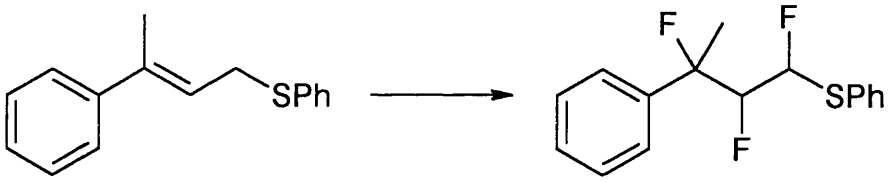
(x) (x)

A solution of difluoroiodotoluene (98) (457mg, 1.8mmol) and phenyl (*E*-3-phenyl-2-propenyl) sulfide (110) (200mg, 0.88mmol) in DCM (5mL) was stirred for 2.5hr. Work-

* We thank Dr M. Cavero-Tomas for the preparation of this material

up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 99: 1) afforded *E*-(1,1-difluoro-3-phenyl prop-2-ene) (114) (29mg, 21%) as a colourless oil; $\mathbf{R_f}$ 0.50 (SiO_2, PE 40-60: ethyl acetate 90 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 1658m, 1495m, 1452m, 1138s, 1016s, 967s, 751s, 691s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 6.26 (1H, td $^2J_{FH}$ 56Hz, $^3J_{HH}$ 6Hz, 1-H), 6.22-6.32 (1H, m, 2-H), 6.87-6.93 (1H, m, 3-H), 7.27-7.47 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 115.4 (t $^1J_{CF}$ 232Hz, 1-C), 121.0 (t $^2J_{CF}$ 24Hz, 2-C), 127.3, 128.8, 129.4, 134.4 (C_{ipso}), 137.1 (t $^3J_{CF}$ 12Hz, 3-C); **^{19}F NMR** (376MHz, $CDCl_3$): δ -109.9 (dd $^2J_{FH}$ 55Hz, 12Hz); **MS** (EI): *m/z* 109 (80%).

Synthesis of *(+/-)-(1-R, 2-R, 3-R / 1-R, 2-S, 3-R / 1-S, 2-S, 3-R / 1-S, 2-R, 3-R)-1,2,3-trifluoro-3-phenyl-1-phenylsulfanyl-butane* (121)

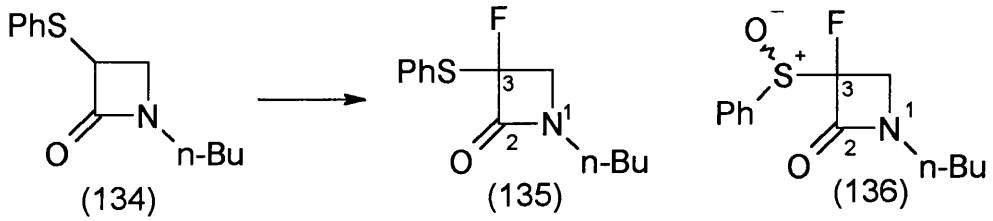


(118) (121)

A solution of difluoroiodotoluene (98) (959mg, 3.6mmol) and phenyl (*E*-3-methyl-3-phenyl-2-propenyl) sulfide (118) (300mg, 1.2mmol) in DCM (8mL) was stirred for 2.5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ether 99: 1) afforded *(+/-)-(1-R, 2-R, 3-R / 1-R, 2-S, 3-R / 1-S, 2-S, 3-R / 1-S, 2-R, 3-R)-1,2,3-trifluoro-3-phenyl-1-phenylsulfanyl-butane* (121) (150mg, 42%) as a colourless oil; $\mathbf{R_f}$ 0.43 (SiO_2, PE 40-60: ethyl acetate 99: 1); **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.86, 1.89, 2.01, 2.03 (4x3H, 2xdd ^3J 23Hz, ^4J 1Hz, 2xd ^3J 24Hz, 4-H), 4.12-4.59 (4x2H, m, 3-H, 2-H), 7.27-7.57 (4x10H, m, Ar-H); **MS** (FAB): *m/z* 297 (MH^+, 12%), 296 (M^+, 26), 277 ($[M-F]^+$, 15), 257 ($[M-HF_2]^+$, 6), 199 (15), 173 ([M-PhCFMe]$^+$, 16), 123 ([PhCFMe]$^+$, 100).

4.2 Fluorination of Amides

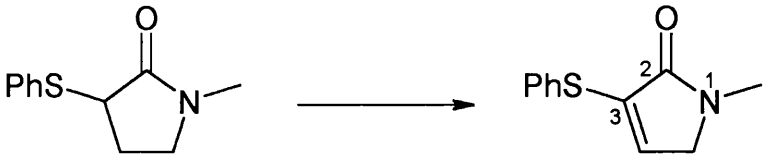
Synthesis of *syn / anti 1-n-butyl-3-fluoro-3-phenylsulfinyl-2-azetidinone* (136) and 1-*n*-butyl-3-fluoro-3-phenylsulfanyl-2-azetidinone (135)[56]



A solution of difluoroiodotoluene (98) (304mg, 1.2mmol) and 1-n-butyl-3-phenylsulfanyl-2-azetidinone (134) (127mg, 0.54mmol) in DCM (4mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, hexane: ether 50: 50) yielded 1-*n*-butyl-3-fluoro-3-phenylsulfanyl-2-azetidinone (135) (12mg, 9%) as a clear oil; **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.94 (3H, t *J* 7Hz, CH_3), 1.31-1.57 (4H, m, $C\underline{H_2}C\underline{H_2}$), 3.22-3.32 (2H, m, $NC\underline{H_2}CH_2$), 3.49 (1H, t, $^2J_{HH}$ 6Hz, $^3J_{HF}$ 6Hz, 4-H), 3.63 (1H, t $^2J_{HH}$ 6Hz, $^3J_{HF}$ 6Hz, 4-H), 7.26-7.67 (5H, m, Ar-H); **^{19}F NMR** (376MHz, $CDCl_3$): δ –137.9 (t, *J* 6Hz); and *syn / anti 1-n-butyl-3-fluoro-3-phenylsulfinyl-2-azetidinone* (136) (66mg, 45%) as a colourless oil; [*ca.* 3: 1 ratio of diastereoisomers (unassigned)]; **R_f** 0.28 (SiO_2, PE 40-60: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2928s and 2874s (CH), 1770 (C=O), 1445m, 1404m, 1280m, 1182m, 1087s, 1055s, 876w, 750s, 689s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.80 (3H, t *J* 7Hz, CH_3 minor diastereoisomer), 0.90 (3H, t *J* 7Hz, CH_3 major), 1.06-1.60 (8H, m, 2x$C\underline{H_2}C\underline{H_2}$), 2.99-3.35 (5H, m, 2x$NCH_2$, 4-H major), 3.52 (1H, dd $^3J_{HF}$ 10Hz, $^3J_{HH}$ 7Hz, 4-H minor), 3.81 (1H, dd, $^2J_{HH}$ 7Hz, $^3J_{HF}$ 7Hz 4-H minor), 3.85 (1H, dd $^2J_{HH}$ 7Hz, $^3J_{HF}$ 7Hz, 4-H major), 7.26-7.75 (10H, m, Ar-H); **^{13}C NMR** (151MHz, $CDCl_3$): δ (major diastereoisomer only) 13.5 (CH_3), 19.9 ($\underline{C}H_2CH_3$), 29.1 ($NCH_2\underline{C}H_2$), 42.1 ($N\underline{C}H_2CH_2$), 46.3 (d $^2J_{CF}$ 22Hz, 4-C), 108.8 (d $^1J_{CF}$ 277Hz, 3-C), 125.4, 129.1, 132.3, 137.6 (C_{ipso}), 159.7 (d $^2J_{CF}$ 22Hz, 2-C); **^{19}F NMR** (470MHz, $CDCl_3$): δ -168.9 (t, J_{FH} 8Hz, major), –165.6 (t J_{FH} 9Hz, minor); **MS** (FAB): *m/z* 292 (MNa^+, 25%), 270 (MH^+, 100), 171 (95).

Synthesis of *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142)

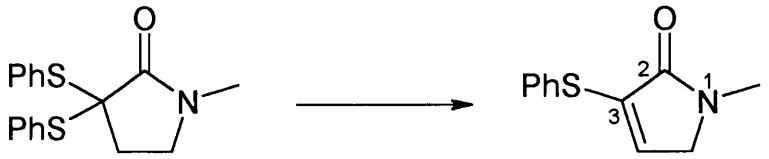
1) From 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (141)



(140) (142)

A solution of difluoroiodotoluene (98) (54%, 494mg, 1.0mmol) and 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (140) (200mg, 0.96mmol) in DCM (6mL) was stirred for 18hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 20: 80) afforded *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142) (110mg, 56%) as a red solid, identical to material previously prepared; plus *3, syn / anti-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (144/145) (29mg, 12%) as a side product.

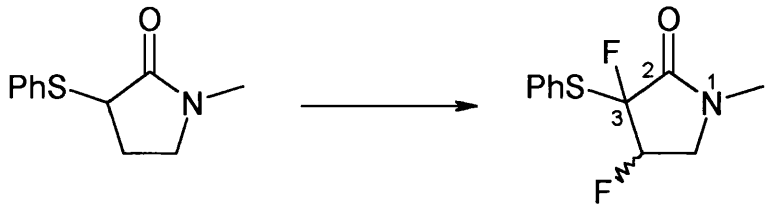
2) From 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141)



(141) (142)

A solution of difluoroiodotoluene (98) (325mg, 1.27mmol) and 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141) (380mg, 1.21mmol) in DCM (5mL) was stirred for 18hr. The crude mixture was diluted with DCM and absorbed onto SiO_2. Flash chromatography (SiO_2, PE 30-40: ether 20: 80) afforded *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142) (202mg, 82%) as a red solid, identical to material previously prepared.

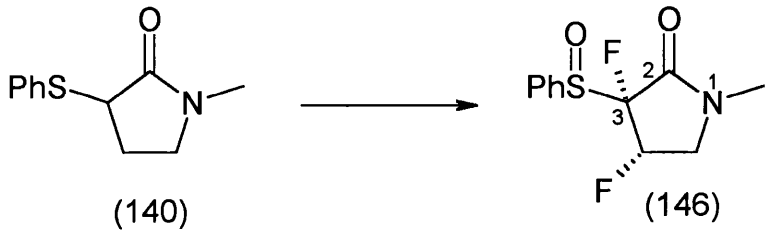
Synthesis of *3, (anti / syn)-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (144/145)



(140) (144/145)

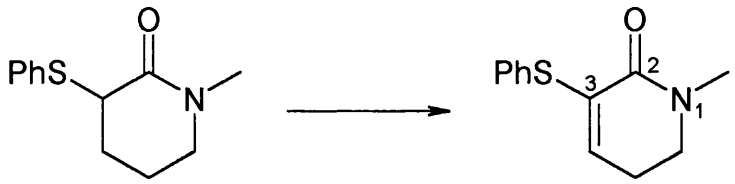
A solution of difluoroiodotoluene (98) (82%, 640mg, 2.1mmol), $Et_3N.3HF$ (0.03mL, 0.19mmol) and 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (140) (200mg, 0.97mmol) in DCM (6mL) was stirred for 16hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 20: 80) afforded *3, (anti / syn)-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (144/145) (139mg, 59%) as a colourless oil; *syn*: *anti* 1.75: 1, from which pure *3, syn-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (145) could be crystallised: **m.p.** 91.5-93°C (DCM / PE); $\mathbf{R_f}$ 0.30 (SiO_2, ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2927w (CH), 1717s (C=O), 1436m, 1307m, 1149m, 1053s, 756m, 694s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.96 (3H, s, CH_3), 3.49 (1H, ddd $^3J_{HF}$ 22Hz, $^2J_{HH}$ 12Hz, $^3J_{HH}$ 1Hz, 5-H), 3.80 (1H, ddd $^3J_{HF}$ 32Hz, $^2J_{HH}$ 12Hz, $^3J_{HH}$ 3Hz, 5-H), 4.85 (1H, dd $^2J_{HF}$ 53Hz, $^3J_{HH}$ 3Hz, 4-H), 7.28-7.62 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 30.2 (CH_3), 51.9 (d $^2J_{CF}$ 24Hz, 5-C), 87.3 (dd $^1J_{CF}$ 199Hz, $^2J_{CF}$ 19Hz, 4-C), 99.6 (dd $^1J_{CF}$ 238Hz, $^2J_{CF}$ 17Hz, 3-C), 127,2 (C_{ipso}), 129.5, 130.2, 135.3, 164.6 (d $^2J_{CF}$ 27Hz, C=O); **^{19}F NMR** (564MHz, $CDCl_3$): δ -190.6--190.8 (m, 4-F), –155.9 (d J_{FF} 17Hz, 3-F); **MS** (FAB): *m/z* 244 (MH^+, 100%); **Anal.** Calcd. for $C_{11}H_{11}F_2NOS$: C, 54.31; H, 4.56; N, 5.76; S, 13.18%. Found: C, 54.17; H, 4.30; N, 5.70; S, 13.37%; *3, anti-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (144): $\mathbf{R_f}$ 0.35 (SiO_2, ether); **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.87 (3H, s, CH_3), 3.43-3.52 (1H, m, 5-H), 3.63-3.70 (1H, m, 5-H), 4.98-5.17 (1H, m, 4-H), 7.29-7.61 (5H, m, Ar-H); **^{19}F NMR** (564MHz, $CDCl_3$): δ –191.64--191.46 (m, 4-F), -136.79 (dd *J* 17, 12Hz, 3-F); plus *1-methyl-2-oxo-3-phenylsulfanyl-3-pyrroline* (142) (20mg, 8%) as a side product.

Synthesis of *3, syn-4-difluoro-1-methyl-3-phenylsulfinyl-2-pyrrolidinone* (146)



A solution of difluoroiodotoluene (98) (54%, 1.70mg, 3.9mmol) and 1-methyl-3-phenylsulfanyl-2-pyrrolidinone (140) (200mg, 0.97mmol) in DCM (15mL) was stirred for 20hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 20: 80) afforded *3, syn-4-difluoro-1-methyl-3-phenylsulfinyl-2-pyrrolidinone* (146) (41mg, 16%) as a colourless oil (sulfoxide diastereoisomers 1: 1, unassigned); $\mathbf{R_f}$ 0.16 (SiO_2, ether); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2928w (CH), 1720s (C=O), 1441m, 1304m, 1174m, 1056s, 744m, 500m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.57 (1H, ddd *J* 30, 12, 5Hz), 2.60 (3H, s), 3.02 (3H, s), 3.29 (1H, ddd *J* 27, 12, 1Hz), 3.53 (1H, ddt *J* 24, 12, 1Hz), 3.80 (1H, ddd *J* 26, 12, 5Hz), 5.18 (1H, ddt *J* 52, 5, 2Hz), 5.39 (1H, dd *J* 52, 5Hz), 7.54-7.73 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 29.8, 30.4, 53.2 (d $^2J_{CF}$ 12Hz), 53.4 (d $^2J_{CF}$ 11Hz), 82.04 (dd $^1J_{CF}$ 198Hz, $^2J_{CF}$ 14Hz), 82.18 (dd $^1J_{CF}$ 198Hz, $^2J_{CF}$ 14Hz), 100.2 (dd $^1J_{CF}$ 252Hz, $^2J_{CF}$ 12Hz), 105.6 (dd $^1J_{CF}$ 241Hz, $^2J_{CF}$ 12Hz), 125.0, 125.7, 129.2, 129.5, 132.9, 133.0, 135.9, 136.8, 161.9 (d $^2J_{CF}$ 25Hz), 163.2 (d $^2J_{CF}$ 23Hz); **^{19}F NMR** (376MHz, $CDCl_3$): δ -147.9 (dt, *J* 52, 25Hz), –144.5—144.1 (m), -122.2, -121.1; **MS** (FAB): *m/z* 392 (MCs^+, 10%), 298 (MK^+, 25), 282 (MNa^+, 45), 260 (MH^+, 75); **Anal.** Calcd. for $C_{11}H_{11}F_2NO_2S$: C, 50.96; H, 4.28; N, 5.40; S, 12.37%. Found: C, 51.06; H, 4.15; N, 5.38; S, 13.52; plus *3, (anti / syn)-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (144/145) (36mg, 15%) as a side product.

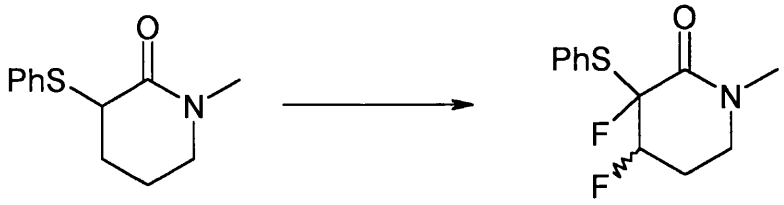
Synthesis of *1-methyl-3-phenylsulfanyl-5,6-dihydro-2(1H)-pyridone* (158)



(156) (158)

A solution of difluoroiodotoluene (98) (54%, 463mg, 0.98mmol) and 1-methyl-3-phenylsulfanyl-2-piperidinone (156) (200mg, 0.90mmol) in DCM (6mL) was stirred for 24hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 20: 80) yielded *1-methyl-3-phenylsulfanyl-5,6-dihydro-2(1H)-pyridone* (158) (114mg, 58%) as a white solid with identical spectroscopic data to material prepared earlier; plus *3, syn / anti-4-difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone* (159/160) (8mg, 3%) as a side product.

Synthesis of *3, (anti / syn)-4-difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone* (159/160)

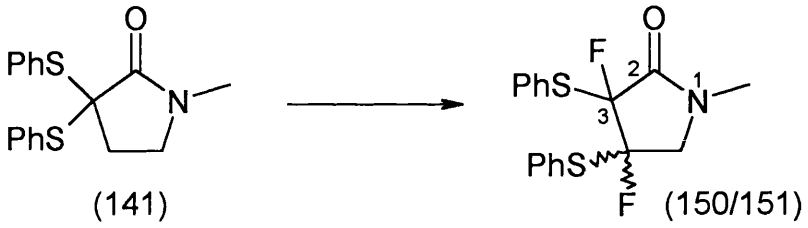


(156) (159/160)

A solution of difluoroiodotoluene (98) (510mg, 1.8mmol) and 1-methyl-3-phenylsulfanyl-2-piperidinone (156) (200mg, 0.9mmol) in DCM (6mL) was stirred for 4hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE: ether 20: 80) yielded *3, (anti / syn)-4-difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone* (159/160) (88mg, 39%) as a clear oil; *anti*: *syn* 2: 1; **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2946m (CH), 1666s (C=O), 1501m, 1441m, 1405m, 1349m, 1212m, 1051m, 1024m, 970m, 842m, 753m. Pure *3, anti-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone* (159) could be crystallised from the mixture: **m.p.** 83-84°C (PE 30-40 / ethyl acetate); $\mathbf{R_f}$ 0.29 (SiO_2, ether); **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.20-2.32 (2H, m,

5-H), 2.97 (3H, s, CH_3), 3.24-3.35 (1H, m, 6-H), 3.52-3.63 (1H, m, 6-H), 4.50 (1H, dm $^2J_{HF}$ 47Hz, 4-H), 7.26-7.63 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.3 (d $^2J_{CF}$ 21Hz, 5-C), 35.2 (CH_3), 44.6 (d $^3J_{CF}$ 7Hz, 6-C), 86.6 (dd $^1J_{CF}$ 183Hz, $^2J_{CF}$ 36Hz, 4-C), 102.0 (dd $^1J_{CF}$ 224Hz, $^2J_{CF}$ 25Hz, 3-C), 127.8 (C_{ipso}), 129.0, 129.9, 136.9, 162.3 (d $^2J_{CF}$ 23Hz, C=O); **^{19}F NMR** (376MHz, $CDCl_3$): δ –136.3--136.0 (m, 4-F), -72.0 (d, J 31Hz, 3-F); **MS** (FAB): *m/z* 258 (MH^+, 100%), 210 (50); **Anal.** Calcd. for $C_{12}H_{13}F_2NOS$: C, 56.02; H, 5.09; N, 5.44; S, 12.46%. Found: C, 56.03; H, 4.93; N, 5.42; S, 12.27%; *3, syn-4-difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone (160)*: **R_f** 0.33 (SiO_2, ether); **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.15-2.24 (1H, m, 5-H), 2.63-2.83 (1H, m, 5-H), 2.98 (3H, s, CH_3), 3.34 (1H, dd J 12, 7Hz, 6-H), 3.59 (1H, td J 12, 5Hz, 6-H), 4.76 (1H, dm $^2J_{HF}$ 51Hz, 4-H), 7.26-7.63 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.8 (d $^2J_{CF}$ 23Hz, 5-C), 35.0 (CH_3), 44.6 (6-C), 88.7 (dd $^1J_{CF}$ 185Hz, $^2J_{CF}$ 22Hz, 4-C), 97.6 (dd $^1J_{CF}$ 238Hz, $^2J_{CF}$ 20Hz, 3-C), 127.1 (C_{ipso}), 129.5, 130.3, 136.0, 163.3 (d $^2J_{CF}$ 25Hz, C=O); **^{19}F NMR** (376MHz, $CDCl_3$): δ –145.3—145.0 (m, 4-F), -93.4 (d, J 18Hz, 3-F).

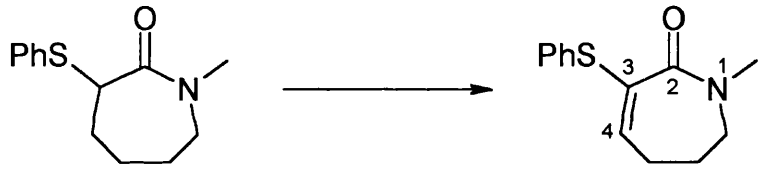
Synthesis of *3, (syn / anti)-4-difluoro-1-methyl-3, syn / anti-4-diphenylsulfanyl-2-pyrrolidinone* (150/151)



A solution of difluoroiodotoluene (98) (402mg, 1.57mmol) and 1-methyl-3,3-diphenylsulfanyl-2-pyrrolidinone (141) (150mg, 0.47mmol) in DCM (6mL) was stirred for 1hr. The reaction was quenched with sat. aq $NaHCO_3$ solution and worked up as normal. Flash chromatography (SiO_2, PE 30-40: ether 75: 25) yielded *3, (syn / anti)-4-difluoro-1-methyl-3, syn / anti-4-diphenylsulfanyl-2-pyrrolidinone* (150/151) (75mg, 45%) as a clear oil; *anti*: *syn* 2: 1. Pure *3, anti-4-difluoro-1-methyl-3, anti-4-diphenylsulfanyl-2-pyrrolidinone* (151) could be crystallised from the mixture: **m.p.** 126-128°C (DCM / PE 30-40); **R_f** 0.33 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 1734s (C=O), 1475w, 1439w, 1404w, 1283w, 1209w, 1045m, 995w, 929w, 893w, 728m, 690m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.81 (3H, s, CH_3), 3.27 (1H, dd

$^{2}J_{HH}$ 11Hz, $^{3}J_{HF}$ 2Hz, 5-H), 3.57 (1H, t *J* 11Hz, 5-H), 7.33-7.74 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 30.4 (NCH_3), 54.5 (d $^{2}J_{CF}$ 34Hz, 5-C), 103.7 (dd $^{1}J_{CF}$ 242Hz, $^{2}J_{CF}$ 19Hz, 4-C) 106.8 (dd $^{1}J_{CF}$ 242Hz, $^{2}J_{CF}$ 19Hz, 3-C), 126.7 (C_{ipso}), 128.4 (C_{ipso}), 129.4, 129.9, 130.5, 130.6, 136.4, 136.9, 163.6 (dd $^{2}J_{CF}$ 30Hz, $^{3}J_{CF}$ 4Hz, 2-C); **^{19}F NMR** (376MHz, $CDCl_3$): δ –144.2 (d $^{3}J_{FF}$ 9Hz 3-F), -132.9 (t, *J* 10Hz, 4-F); **MS** (FAB): *m/z* 484 (MCs^+, 100%), 393 (33), 352 (MH^+, 35%); **Anal.** Calcd. for $C_{17}H_{15}F_2NOS_2$: C, 58.10; H, 4.30; N, 3.98; S, 18.25%. Found: C, 58.11; H, 4.11; N, 4.05; S, 18.40%; *3, syn-4-difluoro-1-methyl-3, syn-4-diphenylsulfanyl-2-pyrrolidinone* (150): **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.81 (3H, s, CH_3), 3.34 (1H, dd $^{3}J_{HF}$ 14Hz, $^{2}J_{HH}$ 11Hz, 5-H), 3.75 (1H, dd $^{2}J_{HF}$ 25Hz, $^{3}J_{HH}$ 11Hz, 5-H), 7.33-7.74 (10H, m, Ar-H); **^{19}F NMR** (376MHz, $CDCl_3$): δ –154.0 (d $^{3}J_{FF}$ 17Hz 3-F), -134.2 (m, 4-F).

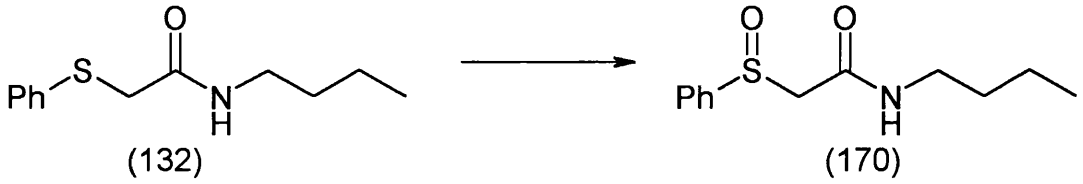
Synthesis of *1-methyl-3-phenylsulfanyl-1,5,6,7-tetrahydroazepin-2-one* (162)



(161) (162)

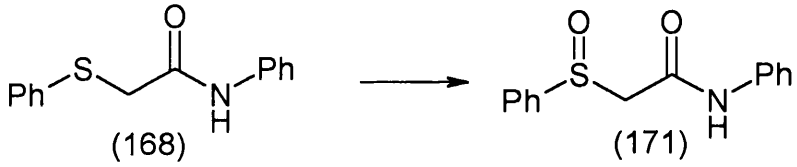
A solution of difluoroiodotoluene (98) (240mg, 0.94mmol) and 1-methyl-3-phenylsulfanyl-caprolactam (161) (200mg, 0.85mmol) in DCM (6mL) was stirred 48hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *1-methyl-3-phenylsulfanyl-1,5,6,7-tetrahydroazepin-2-one* (162) (87mg, 44%) as a yellow oil; $\mathbf{R_f}$ 0.24 (SiO_2, PE 30-40: ethyl acetate 40: 60); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3059m, 2950w, 2892m (CH), 1640s (C=O), 1476m, 1439m, 1396m, 1090m, 918w, 841w, 762m, 691m; **^{1}H NMR** (500MHz, $CDCl_3$): δ 1.94-2.00 (2H, m), 2.20-2.28 (2H, m), 3.06 (3H, s, CH_3), 3.38 (2H, t *J* 6Hz, 7-H), 6.21 (1H, t *J* 7Hz, 4-H), 7.26-7.50 (5H, m, Ar-H); **^{13}C NMR** (126MHz, $CDCl_3$): δ 24.8, 28.8, 35.2, 48.6, 128.1, 129.6, 132.9, 133.9, 134.1, 135.5, 168.2 (C=O); **MS** (FAB): *m/z* 234 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{13}H_{16}NOS$ (MH^+): 234.0953. Found: 234.0936.

Synthesis of *N*-butyl-(phenylsulfinyl)acetamide (170)



A solution of difluoroiodotoluene (98) (468mg, 1.8mmol) and *N*-butyl-(phenylsulfanyl)acetamide (132) (186mg, 0.83mmol) and in DCM (4mL) was stirred for 1.5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ether 50: 50 grading to 10% MeOH) yielded *N*-butyl-(phenylsulfinyl)acetamide (170) (170mg, 86%) as a yellow oil, solidifying in the cold; **R_f** 0.08 (SiO_2, ether); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3300s (NH) 3074m, 2957m, (CH), 1650s (C=O), 1544s, 1479m, 1222m, 1026w; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.91 (3H, t *J* 7Hz, CH_3), 1.30-1.46 (4H, m, CH_2CH_2), 3.19-3.23 (2H, m, NCH_2), 3.50 (1H, AB d J_{AB} 14Hz, SCH_2), 3.71 (1H, AB d J_{AB} 14Hz, SCH_2), 6.86 (1H, br NH), 7.53-7.62 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 13.6 (CH_3), 19.9 ($\underline{C}H_2CH_3$), 31.3 ($NCH_2\underline{C}H_2$), 39.4 (NCH_2), 58.6 (SCH_2), 123.8, 129.3 131.5, 141.4 (C_{ipso}), 163.4 (C=O); **MS** (FAB): *m/z* 262 (MNa^+ 80%), 240 (MH^+, 100); **HRMS** (FAB) calcd. for $C_{12}H_{17}NO_2S$: 239.0980; Found: 239.0971.

Synthesis of *N*-phenyl-(phenylsulfinyl)acetamide (171)



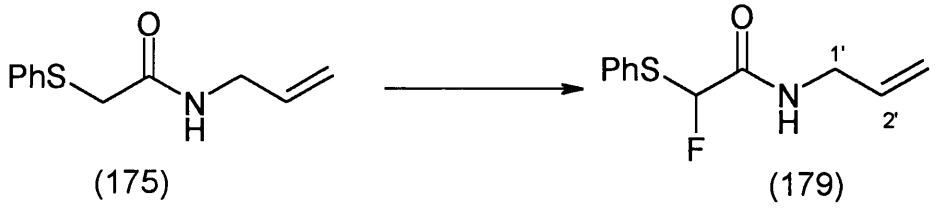
A solution of difluoroiodotoluene (98) (231mg, 0.9mmol) and *N*-phenyl-(phenylsulfanyl)acetamide (168) (200mg, 0.82mmol) in DCM (5mL) was stirred for 5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40 grading to ether) yielded *N*-phenyl-(phenylsulfinyl)acetamide (171) (165mg, 78%) as a white solid; **m.p.** 165-166°C (DCM / PE 30-40); **R_f** 0.19 (SiO_2, ether); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 3454s (NH) 1679s (C=O), 1599m, 1539s, 1443m,

1326m, 1016s (S=O), 745s, 689s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.61 (1H, AB d J_{AB} 14Hz, SCH_2), 3.94 (1H, AB d J_{AB} 14Hz, SCH_2), 7.08-7.65 (10H, m, Ar-H), 9.07 (1H, br NH); **^{13}C NMR** (75MHz, $CDCl_3$): δ 58.9 (SCH_2), 120.3, 124.0, 124.7, 129.0, 129.6, 131.8, 137.4 (C_{ipso}), 140.9 (C_{ipso}), 161.7 (C=O); **MS** (EI): *m/z* 259 ($M^{\bullet+}$, 50%), 211 (20), 106 (100); **Anal.** Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36%. Found: C, 64.79; H, 5.03; N, 5.38; S, 12.08%; plus 41mg (21% recovery) of starting material.

Synthesis of *N*-methyl-*N*-phenyl-(phenylsulfinyl)acetamide (172)

A solution of difluoroiodotoluene (98) (219mg, 0.85mmol) and *N*-methyl-*N*-phenyl-(phenylsulfanyl)acetamide (169) (200mg, 0.78mmol) in DCM (5mL) was stirred for 5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ether 50: 50 grading to 10% MeOH) yielded *N*-methyl-*N*-phenyl-(phenylsulfinyl)acetamide *(172)* (176mg, 86%) as a white solid; **m.p.** 100-101.5°C (DCM / PE 30-40); **R_f** 0.15 (SiO_2; ether); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058w, 2923w, 1650s (C=O), 1593m, 1496m, 1383m, 1297w, 1116m, 1085m, 1047s, 749m, 698s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.14, (3H, s, CH_3), 3.42 (1H, AB d J_{AB} 14Hz, SCH_2), 3.76 (1H, AB d J_{AB} 14Hz, SCH_2), 6.84 (2H, d J 8Hz, Ar-H), 7.24-7.54 (8H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 37.3 (CH_3), 62.1 (SCH_2), 124.3, 127.2, 128.4, 129.1, 129.9, 131.4, 142.5, (C_{ipso}), 143.6 (C_{ipso}), 163.9 (C=O); **MS** (EI): *m/z* 273 ($M^{\bullet+}$, 80%), 225 (40), 148 (100); **Anal.** Calcd. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73%. Found: C, 65.94; H, 5.50; N, 5.12; S, 11.67%; plus 17mg (9% recovery) of starting material.

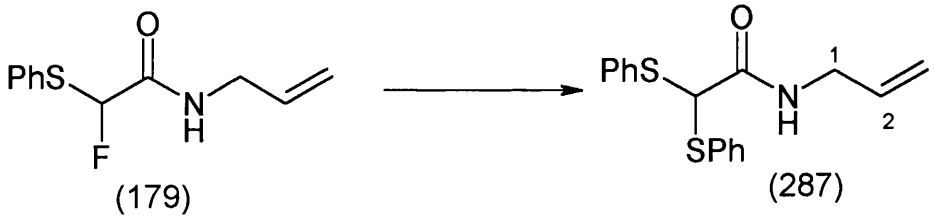
Synthesis of *N-allyl-(2-fluoro-2-phenylsulfanyl)acetamide* (179) and *N*-allyl-(2,2-diphenylsulfanyl)acetamide (287)



(175) (179)

A solution of difluoroiodotoluene (98) (91%, 294mg, 1.1mmol) and N-allyl-(phenylsulfanyl)acetamide (175) (200mg, 0.97mmol) in DCM (7mL) refluxing for 2hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 70: 30) afforded *N-allyl (2-fluoro-2-phenylsulfanyl)acetamide* (179) (168mg, 71%) as a colourless oil; $\mathbf{R_f}$ 0.22 (SiO_2, PE 30-40: ether 40: 60); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3296m (NH), 3077m, 2924w (CH), 1669s (C=O), 1534s (amide II), 1478m, 1437m, 1272m, 1202w, 1070w, 992m, 923m, 825w, 746s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.71 (2H, t *J* 6Hz, 1'-H), 4.92-5.02 (2H, m, 3'-H), 5.46-5.59 (1H, m, 2'-H), 6.07 (1H, d $^2J_{HF}$ 53Hz, 2-H), 6.22 (1H, br, NH), 7.27-7.55 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 41.6 (1'-C), 97.5 (d $^1J_{CF}$ 234Hz, 2-C), 116.9 (3'-C), 129.1, 129.3, 132.8, 132.9 (C_{ipso}), 134.5, 164.7 (d $^2J_{CF}$ 24Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –156.5 (d $^2J_{FH}$ 53Hz).

Recrystallisation from DCM / PE 30-40 or **MS** analysis gave *N*-allyl-(2,2-diphenylsulfanyl)acetamide (287)

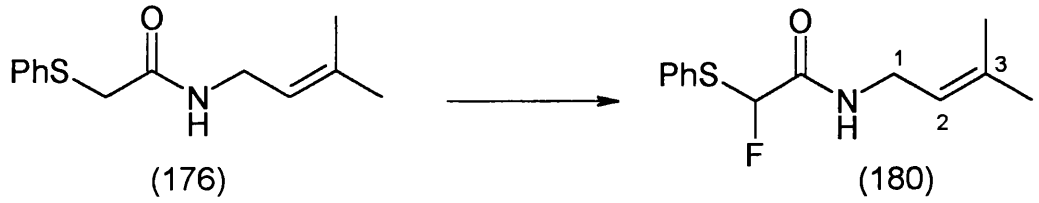


(179) (287)

^{1}H NMR (500MHz, $CDCl_3$): δ 3.77-3.80 (2H, m, 1-H), 4.89 (1H, s, PhS_2CH), 4.98-5.05 (2H, m, 3-H), 5.60-5.65 (1H, m, 2-H), 6.35 (1H, br, NH), 7.26-7.46 (10H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 42.6 (1–C), 58.3 (PhS_2C), 117.2 (2–C), 128.9, 129.6, 132.6, 133.2, 133.6 (C_{ipso}), 167.4 (C=O); **MS** (FAB): *m/z* 316 (MH^+, 60%), 231

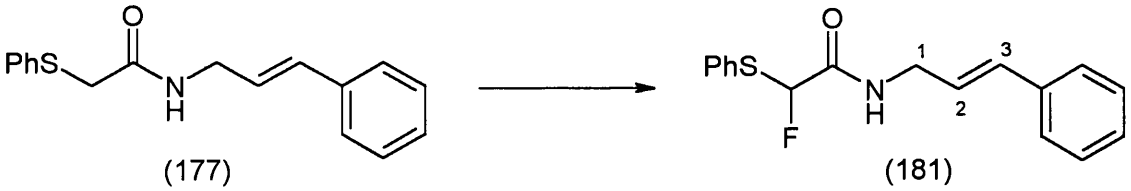
([(PhS)$_2$CH]$^+$, 55), 206 ([M-PhS]$^+$, 90), 178 (90), 153 (45), 123 (100); **Anal.** Calcd. for $C_{17}H_{17}NOS_2$: C, 64.73; H, 5.43; N, 4.44%. Found: C, 64.44; H, 5.37; N, 4.46%.

Synthesis of *N-(2-fluoro-2-phenylsulfanyl)acetyl-3-methyl-but-2-enyl amine* (180)



A solution of difluoroiodotoluene (98) (90mg, 0.35mmol) and *N*-(phenylsulfanyl)acetyl-3-methyl-but-2-enyl amine (176) (75mg, 0.32mmol) in DCM (4mL) refluxing overnight. The reaction mixture was diluted with DCM and bound to SiO_2. Flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *N-(2-fluoro-2-phenylsulfanyl)acetyl-3-methyl-but-2-enyl amine* (180) (20mg, 25%) as a colourless oil; $\mathbf{R_f}$ 0.33 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3299m (NH), 2923w, 1667s (C=O), 1531m, 1442w, 1274w, 978m, 746m, 691m; **^{1}H NMR** (500MHz, $CDCl_3$): δ 1.56 (CH_3), 1.65 (CH_3), 3.62-3.69 (2H, m, 1-H), 4.83-4.86 (1H, m, 2-H), 5.89 (1H, br, NH), 6.06 (1H, d $^2J_{HF}$ 53Hz, SCHF), 7.31-7.56 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 18.2, 26.0, 37.7, 98.0 (d $^1J_{CF}$ 235Hz), 119.3, 129.5, 129.8, 135.1 (2C), 137.6, 165.0 (d $^2J_{CF}$ 24Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –156.2 (d $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 254 (MH$^+$, 100%), 234 ([M-F]$^+$, 30); **HRMS** (FAB) calcd. for $C_{13}H_{17}FNOS$ (MH$^+$): 254.1015. Found: 254.1030.

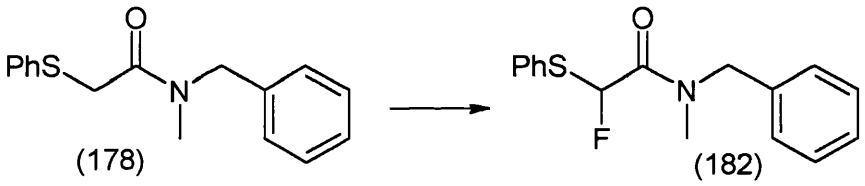
Synthesis of *N-(2-fluoro-2-phenylsulfanyl)acetyl-cinnamylamine* (181)



A solution of difluoroiodotoluene (98) (270mg, 0.97mmol) and *N*-(phenylsulfanyl)acetyl-cinnamylamine (177) (250mg, 0.88mmol) in DCM (5mL) refluxing overnight. Work-up according to the general procedure followed by flash

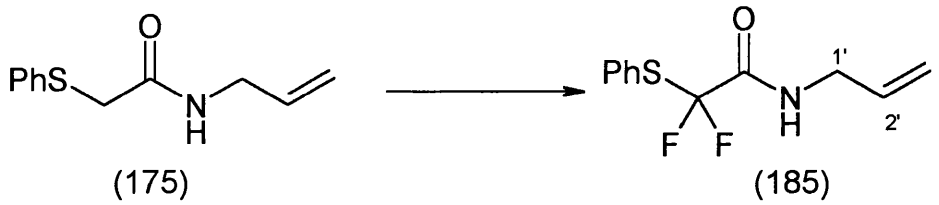
chromatography (SiO_2, PE 30-40: ether 50: 50) afforded *N-(2-fluoro-2-phenylsulfanyl)acetyl-cinnamylamine* (181) (146mg, 55%) as a white solid; **m.p.** 74-78°C (DCM / PE 30-40); $\mathbf{R_f}$ 0.52 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3391m (NH), 3025w, 2925w, 1666s (C=O), 1519s, 1441w, 1362w, 1303w, 1261w, 1011m, 980m, 800w, 746s, 689s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.74-3.92 (2H, m, 1-H), 5.77 (1H, dt $^{trans}J_{AB}$ 16Hz, $^3J_{2,1}$ 6Hz, 2-H), 6.05 (1H, d $^2J_{HF}$ 53Hz, SCHF), 6.09 (1H, br, NH), 6.30 (1H, d $^{trans}J_{AB}$ 16Hz, 3-H), 7.15-7.79 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 41.8 (1-C), 97.9 (d $^1J_{CF}$ 235Hz, SCHF), 124.6, 126.8, 128.3, 129.0, 129.6, 130.0, 133.3, 135.26, 135.28, 136.6, 165.2 (d $^2J_{CF}$ 24Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –156.5 (d $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 302 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{17}H_{17}FNOS$ (MH^+): 302.1015. Found: 302.1017.

Synthesis of *N-benzyl-N-methyl-(2-fluoro-2-phenylsulfanyl)acetamide* (182)



A solution of difluoroiodotoluene (98) (91%, 233mg, 0.83mmol) and *N*-benzyl-*N*-methyl-(phenylsulfanyl)acetamide (178) (207mg, 0.76mmol) in DCM (6mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 70: 30) gave *N-benzyl-N-methyl-(2-fluoro-2-phenylsulfanyl)acetamide (182)* (150mg, 68%) as a colourless oil; $\mathbf{R_f}$ 0.49 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3061m, 2930m, 1666s (C=O), 1449s, 1265m, 1182m, 1115m, 1025s, 913m, 742s, 696s; **^{1}H NMR** (300MHz, $CDCl_3$): δ (*E/Z*) 2.85 and 2.96 (2x3H, s, CH_3), 4.27-4.74 (2x2H, m, NCH_2), 6.24 and 6.25 (2x1H, d $^2J_{HF}$ 55Hz, 2-H), 7.12-7.51 (2x10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ (*E/Z*) 34.0 and 34.5 (CH_3), 51.5 and 53.1 (NCH_2), 96.8 and 97.8 (d $^2J_{CF}$ 232Hz, 2-C) 127.4, 128.1, 128.4, 128.6, 129.2, 129.4, 129.5 (2C), 129.8, 131.8 (2xC_{ipso}), 132.0, 133.4 (2C), 136.0 (C_{ipso}), 136.5 (C_{ipso}), 164.5 and 164.8 (d $^2J_{CF}$ 24Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –153.8 and 151.8 (d $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 290 (MH^+, 20%), 270 ($[M-F]^+$, 30); **HRMS** (FAB) calcd. for $C_{16}H_{17}FNOS$ (MH^+): 290.1015. Found: 290.1007.

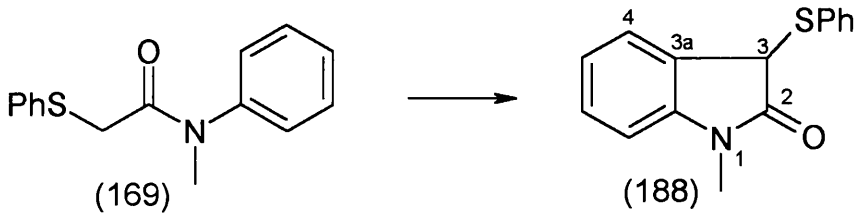
Synthesis of *N-allyl-(2,2-difluoro-2-phenylsulfanyl)acetamide* (185)



(175) (185)

A solution of difluoroiodotoluene (98) (494mg, 1.9mmol) and *N*-allyl-(phenylsulfanyl)acetamide (175) (200mg, 0.97mmol) in DCM (7mL) refluxing for 16hr. The mixture was diluted with DCM and bound to SiO_2. Flash chromatography (SiO_2, PE 30-40: ether 70: 30) afforded *N-allyl-(2,2-difluoro-2-phenylsulfanyl)acetamide* (185) (129mg, 61%) as a colourless oil; $\mathbf{R_f}$ 0.13 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3312s (NH), 3090w (CH), 1678s (C=O), 1538s (amide II), 1436w, 1343w, 1265w, 1129w, 1084m, 1031w, 928m, 805w, 746m, 689m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.85 (2H, t *J* 6Hz, 1'-H), 5.09-5.15 (2H, m, 3'-H), 5.63-5.76 (1H, m, 2'-H), 6.27 (1H, br, NH), 7.32-7.65 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 42.5 (1'-C), 118.1 (3'-C), 122.8 (t $^1J_{CF}$ 289Hz, 2-C), 125.3 (C_{ipso}), 129.7, 131.0, 132.7, 137.2, 161.9 (t $^2J_{CF}$ 28Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –82.8, **MS** (FAB): *m/z* 244 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{11}H_{12}F_2NOS$ (MH^+): 244.0608. Found: 244.0613; plus *N-allyl (2-fluoro-2-phenylsulfanyl)acetamide* (179) (22mg, 10%).

Synthesis of 2,3-dihydro-1-methyl-3-phenylsulfanyl-indol-2-one (188)

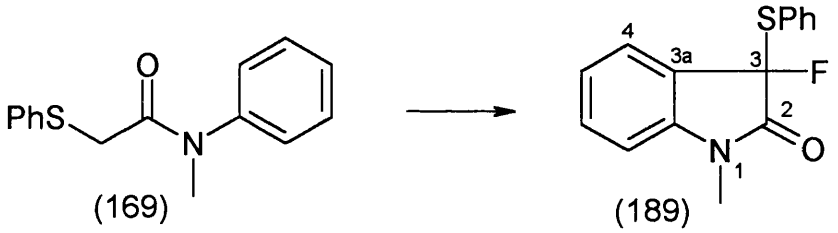


(169) (188)

A solution of difluoroiodotoluene (98) (91%, 237mg, 0.86mmol) and *N*-phenyl-*N*-methyl-phenylsulfanylacetamide (169) (200mg, 0.78mmol) in DCM (7mL) at reflux for 4hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 70: 30) afforded 2,3-dihydro-1-methyl-3-phenylsulfanyl-indol-2-

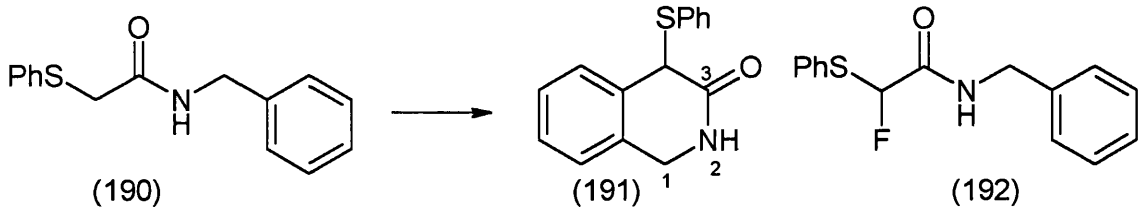
one (188) (117mg, 59%) as a red solid; **R_f** 0.53 (SiO_2, PE 30-40: ether 80: 30); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3056m, 2932m (CH), 1715s (C=O), 1611s, 1470s, 1345s, 1308m, 1258m, 1162m, 1087s, 1021s, 922m, 865w, 746s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.95 (3H, s, CH_3), 4.49 (1H, s 3-H), 6.56 (1H, d *J* 8Hz, 7-H), 6.90-7.31 (8H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 26.7 (CH_3), 49.6 (3-C), 108.5 (7-C), 123.2, 125.6, 126.6, 129.0, 129.4, 131.3, 134.6, 144.3 (7a-C), 174.7 (C=O); **MS** (FAB): *m/z* 256 (MH^+, 40%), 159 (146, 100); **HRMS** (FAB) calcd. for $C_{15}H_{14}NOS$ (MH^+): 256.0796. Found: 256.0801.

Synthesis of 3-fluoro-2,3-dihydro-1-methyl-3-phenylsulfanyl-indol-2-one (189)



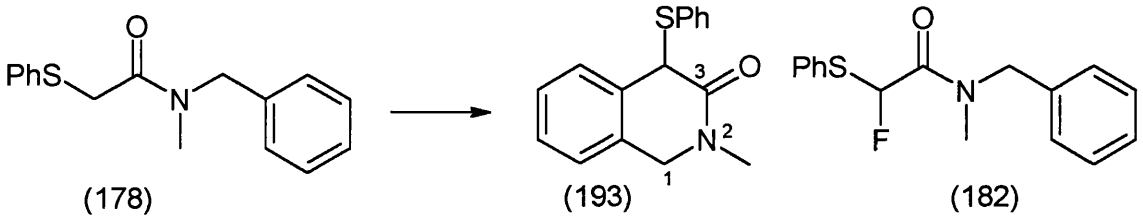
A solution of difluoroiodotoluene (98) (91%, 474mg, 1.68mmol) and *N*-phenyl-*N*-methyl-phenylsulfanylacetamide (169) (200mg, 0.78mmol) in DCM (10mL) at reflux for 16hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) 3-fluoro-2,3-dihydro-1-methyl-3-phenylsulfanyl-indol-2-one (189) (87mg, 41%) as a yellow oil; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.26 (3H, s, CH_3), 7.13-7.70 (9H, m, Ar-H); **^{19}F NMR** (282MHz, $CDCl_3$): δ –70.7.

Synthesis of 3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (191) and *N-benzyl-(2-fluoro-2-phenylsulfanyl)acetamide* (192)



A solution of difluoroiodotoluene (98) (91%, 474mg, 1.76mmol) and *N*-benzyl-(phenylsulfanyl)acetamide (190) (400mg, 1.55mmol) in DCM (10mL) at reflux for 1hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) isolated 3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (191) (45mg, 11%) as a colourless oil; $\mathbf{R_f}$ 0.21 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3248m (NH), 3082w (CH), 1644s (C=O), 1468w, 1420w, 1024w, 730m, 693m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 4.33 (2H, d *J* 6Hz, 1-H), 4.94 (1H, s, 4-H), 6.72 (1H, br, NH), 6.83-7.61 (9H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 43.9 (1-C), 57.7 (4-C), 127.5, 127.7, 128.4, 128.6, 129.2, 129.7, 132.3, 132.7, 137.3, 167.1 (C=O); **MS** (FAB): *m/z* 256 (MH^+, 60%), 231 (55), 199 (40), 146 (100); **HRMS** (FAB) calcd. for $C_{15}H_{13}NOS$ (MH^+): 256.0800. Found: 256.0796; and *N-benzyl-(2-fluoro-2-phenylsulfanyl)acetamide* (192) (152mg, 35%) as colourless crystals; **m.p.** 65°C (DCM / PE 30-40); $\mathbf{R_f}$ 0.22 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3391s (NH), 1669s (C=O), 1516m (amide II), 1420w, 1300w, 1268w, 1065w, 1022w, 983m, 742m, 692m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 4.18-4.32 (2H, m, NCH_2), 6.02 (1H, d $^2J_{HF}$ 52Hz, 2-H), 6.35 (1H, br, NH), 6.90-7.55 (10H, m, Ar-H); **^{19}F NMR** (282MHz, $CDCl_3$): δ −156.8 (dd *J* 53, 3Hz); **MS** (FAB): *m/z* 298 (MNa^+, 20%), 276 (MH^+, 90); **Anal** calcd. for $C_{15}H_{14}FNOS$: C, 65.43; H, 5.12; N, 5.09; S, 11.65%. Found: C, 65.35; H, 5.00; N, 4.98; S, 11.89%.

Synthesis of 2-methyl-3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (193) and *N-benzyl-N-methyl-(2-fluoro-2-phenylsulfanyl)acetamide* (182)

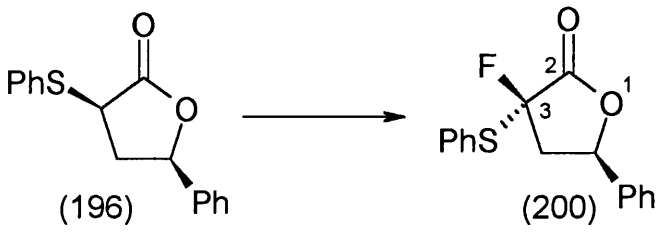


(178) (193) (182)

A solution of difluoroiodotoluene (98) (91%, 337mg, 1.2mmol) and *N*-benzyl-*N*-methyl-(phenylsulfanyl)acetamide (178) (300mg, 1.1mmol) in DCM (6mL) at reflux for 3hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 70: 30) gave 2-methyl-3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (193) (140mg, 47%) as a yellow oil; $\mathbf{R_f}$ 0.32 (SiO_2, PE 30-40: ethyl acetate 40: 60); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$; 3058m, 2926m, 1651s, 1439m, 1402m, 1139m, 1261m, 1087m, 747s, 695s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.90 (3H, s, CH_3), 3.71 (1H, d J_{AB} 13Hz, 1-H), 3.87 (1H, d J_{AB} 16Hz, 1-H), 4.63 (1H, s 3-H), 6.87-7.24 (9H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 35.1 (CH_3), 51.6 (4-C), 52.4 (1-C), 124.6, 127.3, 127.6, 128.3, 128.5, 129.0, 130.9, 132.0, 133.0, 135.6, 167.2 (C=O); **MS** (FAB): *m/z* 292 (MNa^+, 15%), 270 (MH^+, 100); **HRMS** (FAB) calcd. for $C_{16}H_{15}NOS$ (MH^+): 270.0952. Found: 270.0958; and *N-benzyl-N-methyl-(2-phenylsulfanyl-2-fluoro)acetamide* (182) (94mg) as a colourless oil contaminated with an unidentified acetamide derivative.

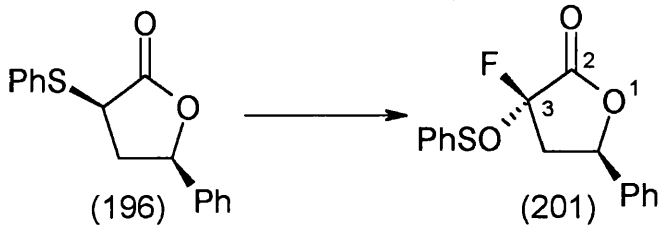
4.3 Fluorination of Esters

Synthesis of *3-fluoro-4,5-dihydro-r-3-phenylsulfanyl-anti-5-phenyl-2(3H)-furanone* (200)



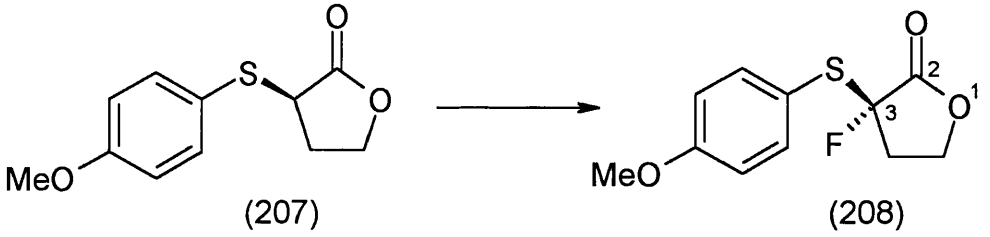
A solution of difluoroiodotoluene (98) (75%, 365mg, 1.1mmol) and *syn*-4,5-dihydro-3-phenylsulfanyl-5-phenyl-2(3*H*)-furanone (196) (300mg, 1.1mmol) in DCM (5mL) was stirred for 7hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 90: 10) afforded *3-fluoro-4,5-dihydro-r-3-phenylsulfanyl-anti-5-phenyl-2(3H)-furanone* (200) (197mg, 62%) as colourless crystals; **m.p.** 98-100°C (PE 30-40 / ether); $\mathbf{R_f}$ 0.29 (SiO_2, PE 30-40: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3062w, 1789s (C=O), 1598w, 1474w, 1442w, 1328w, 1279w, 1203m, 1180m, 1041m, 1014m, 938w, 847w, 749m, 697s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.66-2.74 (1H, m, 4-H), 2.89 (1H, dd *J* 11, 4Hz, 4-H), 5.51 (1H, dd *J* 8, 4Hz, 5-H), 7.33-7.65 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 43.7 (d $^2J_{CF}$ 21Hz, 4-C), 77.1 (d $^3J_{CF}$ 4Hz, 5-C), 99.8 (d $^1J_{CF}$ 246Hz, 3-C), 125.8, 127.3, 128.9, 129.1, 129.3, 130.4, 135.7, 136.6, 167.3 (d $^2J_{CF}$ 31Hz, C=O); **^{19}F NMR** (471MHz, $CDCl_3$): δ −132.4 (d $^3J_{FH}$ 16Hz); **MS** (FAB): *m/z* 288 (M^+, 23%), 269 ($[M-F]^+$, 100), 223 (100); **Anal** calcd. for $C_{16}H_{13}FO_2S$: C, 66.65; H, 4.54; S, 11.12%. Found: C, 66.63; H, 4.45; S, 10.96%.

Synthesis of *3-fluoro-4,5-dihydro-r-3-phenylsulfinyl-anti-5-phenyl-2(3H)-furanone* (201)



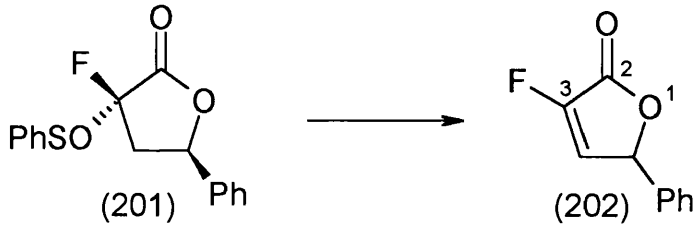
A solution of difluoroiodotoluene (98) (75%, 731mg, 2.2mmol) and *syn*-4,5-dihydro-3-phenylsulfanyl-5-phenyl-2(3*H*)-furanone (196) (300mg, 1.1mmol) in DCM (8mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 90: 10) afforded *3-fluoro-4,5-dihydro-r-3-phenylsulfinyl-anti-5-phenyl-2(3H)-furanone* (201) (136mg, 41%) (sulfoxide diastereomeric ratio 5: 2 , unassigned) as colourless crystals; $\mathbf{R_f}$ 0.27 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3061w, 1785s (C=O), 1444w, 1332w, 1201m, 1086m, 1056m, 940w, 750m, 697m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.23-2.40 (1H, m, 4-H major), 2.65-2.73 (1H, m, 4-H minor), 3.24-3.29 (1H, m, 4-H major), 3.63-3.68 (1H, m, 4-H minor), 4.76-4.79 (1H, m, 5-H minor), 5.60-5.66 (1H, m, 5-H major), 7.24-7.86 (10H, m, Ar-H); **^{19}F NMR** (471MHz, $CDCl_3$): δ −152.7 (dd $^3J_{FH}$ 24, 5Hz, major), -151.1 (d $^3J_{FH}$ 24Hz, minor); **MS** (FAB): *m/z* 327 (MNa^+, 30%), 305 (MH^+, 85), 179 ($[M\text{-}PhSO]^+$, 100); **Anal** calcd. for $C_{16}H_{13}FO_3S$: C, 63.14; H, 4.31; S, 10.54%. Found: C, 63.09; H, 4.19; S, 10.26%.

Synthesis of *3-fluoro-4,5-dihydro-3-(p-methoxyphenyl)sulfanyl-5-phenyl-2(3H)-furanone* (208)



A solution of difluoroiodotoluene (98) (264mg, 1.03mmol) and 4,5-dihydro-3-(*p*-methoxyphenyl)phenylsulfanyl-2(3*H*)-furanone (207) (200mg, 0.94mmol) in DCM (5mL) was stirred for 18hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 85: 15) afforded *3-fluoro-4,5-dihydro-3-(p-methoxyphenyl)sulfanyl-2(3H)-furanone* (208) (109mg, 50%) as a yellow oil; **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.48-2.77 (2H, m, 4-H), 3.78 (3H, s, OCH_3), 4.28-4.39 (2H, m, 5-H), 6.87 (2H, AA'BB' d *J* 10Hz, Ar-H), 7.46 (2H, AA'BB' d *J* 10Hz, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 35.9 (d $^2J_{CF}$ 21Hz, 4-C), 55.8 (OCH_3), 64.5 (d $^3J_{CF}$ 4Hz, 5-C), 99.3 (d $^1J_{CF}$ 245Hz, 3-C), 115.3, 115.9 (C_{ipso}), 138.0, 161.9, 168.7, (d $^2J_{CF}$ 32Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ −135.9 (d $^3J_{FH}$ 14Hz).

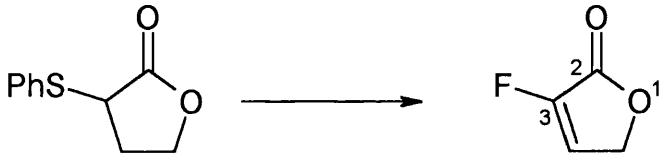
Synthesis of 3-fluoro-5-phenyl-2(5*H*)-furanone (202)



A solution of 3-fluoro-4,5-dihydro-*r*-3-phenylsulfinyl-*trans*-5-phenyl-2(3*H*)-furanone (201) (94mg, 0.31mmol) in toluene (5mL) was refluxed for 20min. Concentration *in vacuo* followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) afforded 3-fluoro-5-phenyl-2(5*H*)-furanone (202) (43mg, 72%) as a colourless oil; **R_f** 0.16 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3108w (CH), 1783s (C=O), 1678m, 1288w, 1108m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 5.88 (1H, dd $^3J_{HF}$ 6Hz, $^3J_{HH}$ 2Hz, 4-H),

6.76 (1H, t $^{3}J_{HH}$ 2Hz, $^{4}J_{HF}$ 2Hz, 5-H), 7.18-7.38 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 79.0 (d $^{3}J_{CF}$ 8Hz, 5-C), 126.1 (d $^{2}J_{CF}$ 6Hz, 4-C), 127.2, 129.6, 130.3, 134.0 (d $^{4}J_{CF}$ 2Hz, C_{ipso}), 148.6 (d $^{1}J_{CF}$ 281Hz, 3-C), 165.0 (d $^{2}J_{CF}$ 32Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –142.1 (d $^{3}J_{FH}$ 6Hz); **MS** (FAB): *m/z* 179 (MH^+, 65%), 159 ([M-F]$^+$, 100); **HRMS** (FAB) calcd. for $C_{10}H_8FO_2$ (MH^+): 179.0508. Found: 179.0502.

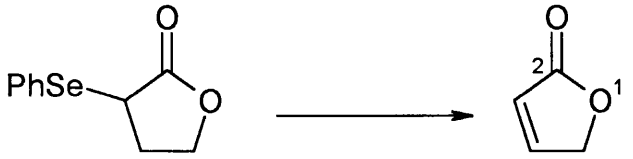
Synthesis of 3-fluoro-2(5*H*)-furanone (204)[124]



(203) (204)

A solution of difluoroiodotoluene (98) (91%, 1.25g, 4.2mmol) and 4,5-dihydro-3-phenylsulfanyl-2(3*H*)-furanone (203) (400mg, 2.1mmol) in DCM (15mL) was stirred overnight. The reaction was worked-up as usual and the crude product taken into toluene (10mL) and stirred at reflux for 30min. After cooling to room temperature the solution was concentrated *in vacuo* then chromatographed (SiO_2, PE 30-40: ether 70: 30) to afford 3-fluoro-2(5*H*)-furanone (204) (92mg, 43%) as a yellow oil; **R_f** 0.27 (SiO_2, DCM); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2929m (CH), 1777s (C=O), 1680s, 1450s, 1332m, 1107s, 1040s, 824m, 760s; **^{1}H NMR** (300MHz, $CDCl_3$): δ4.81 (2H, dd $^{2}J_{HH}$ 6Hz, $^{3}J_{HH}$ 2Hz, 5-H), 6.79 (1H, dd $^{3}J_{HF}$ 4Hz, $^{3}J_{HH}$ 2Hz, 4-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 66.6 (d $^{3}J_{CF}$ 8Hz, 5-C), 123.3 (d $^{2}J_{CF}$ 8Hz, 4-C), 148.5 (d $^{1}J_{CF}$ 275Hz, 3-C), 165.5 (d $^{2}J_{CF}$ 32Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –146.8 (t *J* 6Hz).

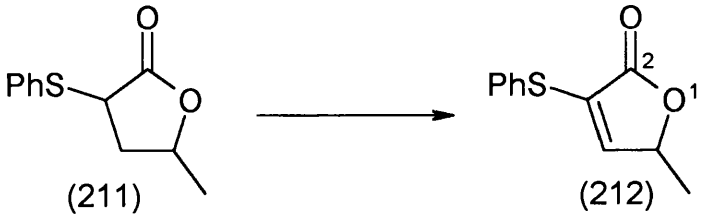
Synthesis of 2(5*H*)-furanone (210)



(209) (210)

A solution of difluoroiodotoluene (98) (689mg, 2.7mmol) and 4,5-dihydro-3-phenylselenyl-2(3*H*)-furanone (209) (300mg, 1.2mmol) in DCM (8mL) was stirred for 18hr. The reaction mixture was diluted with DCM and absorbed onto SiO_2. Flash chromatography (SiO_2, PE 30-40: ether 80: 20) yielded 2(5*H*)-furanone (210) (10mg, 10%) as a colourless oil; **^{1}H NMR** (300MHz, $CDCl_3$): δ 4.85 (2H, t *J* 2Hz, 5-H), 6.10-6.13 (1H, m, 4-H), 7.50-7.53 (1H, m, 3-H).

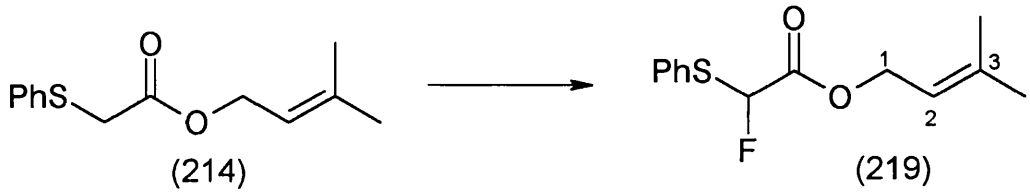
Synthesis of *5-methyl-3-phenylsulfanyl-2(5H)-furanone* (212)



(211) (212)

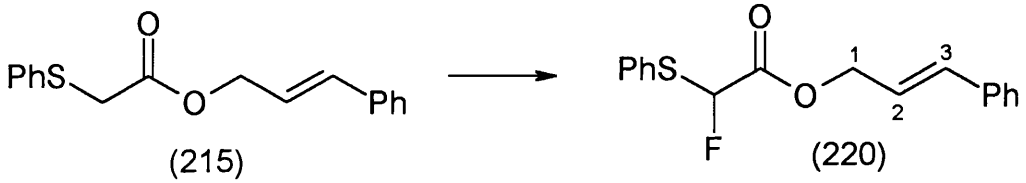
A solution of difluoroiodotoluene (98) (80%, 328mg, 1.0mmol) and 4,5-dihydro-5-methyl-3-phenylsulfanyl-2(3*H*)-furanone (211) (200mg, 0.96mmol) in DCM (10mL) was stirred for 7hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) yielded *5-methyl-3-phenylsulfanyl-2(5H)-furanone* (212) (88mg, 45%) as a white solid; **m.p.** 74-75°C (EtOAc / PE 30-40); **R_f** 0.53 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3061w, 2983w, 2932w, 1755s (C=O), 1596w, 1475w, 1442w, 1316m, 1164m, 1048m, 1001s, 872w, 748m, 692w; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.39 (3H, d *J* 7Hz, CH_3), 5.05 (1H, qd *J* 7, 2Hz, 5-H), 6.55 (1H, d *J* 2Hz, 4-H), 7.40-7.45 (3H, m, Ar-H), 7.53-7.58 (2H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 19.7 (CH_3), 79.4 (5-C), 129.9, 130.2, 130.3, 133.3, 134.5, 145.4, 170.3 (C=O); **MS** (FAB): *m/z* 207 (MH^+, 100%); **Anal.** Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.55%. Found: C, 63.66; H, 4.67; S, 15.43%.

Synthesis of *prenyl (2-fluoro-2-phenylsulfanyl)acetate* (219)



A solution of difluoroiodotoluene (98) (87%, 350mg, 1.2mmol) and prenyl (phenylsufanyl)acetate (214) (257mg, 1.10mmol) in DCM (6mL) was stirred for 2hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 90: 10) yielded *prenyl (2-fluoro-2-phenylsulfanyl)acetate* (219) (178mg, 64%) as a colourless oil; $\mathbf{R_f}$ 0.40 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2975m, 2936m (CH), 1752s (C=O), 1275s, 1177s, 1034s, 957s, 748s, 693s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.68 (3H, s, CH_3), 1.75 (3H, s, CH_3) 4.58 (2H, d *J* 8Hz, 1-H), 5.21-5.25 (1H, m, 2-H), 6.07 (1H, d $^2J_{HF}$ 52Hz, SCHF), 7.33-7.57 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 17.9 (CH_3), 25.7 (CH_3), 63.0 (1-C), 94.2 (d $^1J_{CF}$ 234Hz, SCHF), 117.3 (2-C), 128.9, 129.0, 129.3, 134.0, 140.4, 165.3 (d $^2J_{CF}$ 29Hz, C=O); **^{19}F NMR** (470MHz, $CDCl_3$): δ −158.6 (d, $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 387 (MCs^+, 100%), 293 (MK^+, 60), 277 (MNa^+, 80), 255 (MH^+, 85); **HRMS** (FAB) calcd. for $C_{13}H_{15}FO_2S$: 255.0855. Found: 255.0861.

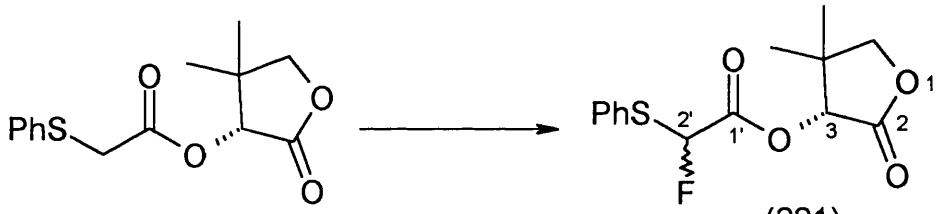
Synthesis of *cinnamyl (2-fluoro-2-phenylsulfanyl)acetate* (220)



A solution of difluoroiodotoluene (98) (80%, 328mg, 1.1mmol) and cinnamyl (phenylsulfanyl)acetate (215) (300mg, 1.1mmol) in DCM (6mL) was stirred for 2.5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) yielded *cinnamyl (2-fluoro-2-phenylsulfanyl)acetate* (220) (221mg, 67%) as a colourless oil; $\mathbf{R_f}$ 0.18 (SiO_2; PE 30-40: ether 90: 10); **IR** (thin

film/cm^{-1}): $\tilde{\nu}_{max}$ 3028s, 2953s (CH), 1756s (C=O), 1441s, 1322s, 1297s, 1175s, 1037s, 967s, 747s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 4.72-4.76 (2H, m, 1-H), 6.12 (1H, d $^2J_{HF}$ 52Hz, SCHF), 6.13 (1H, *dt* $^{trans}J_{2,3}$ 16Hz, $^3J_{2,1}$ 7Hz, 2-H), 6.63 (1H, d $^{trans}J_{3,2}$ 16Hz, 3-H), 7.27-7.57 (10H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 66.7 (1-C), 94.11 (d $^1J_{CF}$ 232Hz, SCHF), 121.6 (2-C), 126.7, 128.3, 128.6, 129.2, 129.5, 134.3 (2C), 135.6, 135.8, 165.1 (d $^2J_{CF}$ 29Hz, C=O); **^{19}F NMR** (376MHz, $CDCl_3$): δ −158.7 (d $^1J_{HF}$ 52Hz); **MS** (FAB): *m/z* 302 (M^+, 100%); **HRMS** (FAB) calcd. for $C_{17}H_{15}FO_2S$: 302.0777. Found: 302.0762.

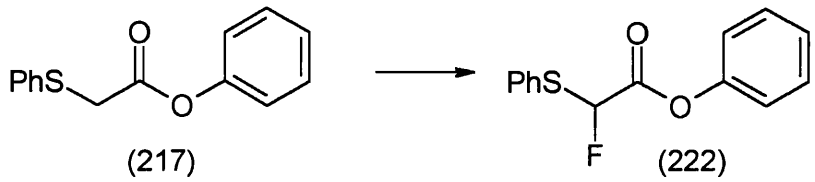
Synthesis of *(3R, 2'R/2'S)-4,5-dihydro-3-(2'-fluoro-2'-phenylsulfanyl)acetoxy-4,4-dimethyl-2(3H)-furanone* (221)



A solution of difluoroiodotoluene (98) (83%, 219mg, 0.71mmol) and (*R*)-4,5-dihydro-4,4-dimethyl-3-(phenylsulfanyl)acetoxy-2(3*H*)-furanone (216) (186mg, 0.62mmol) in DCM (5mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 60: 40) afforded *(3R, 2'S/2'R)-4,5-dihydro-3-(2'-fluoro-2'-phenylsulfanyl)acetoxy-4,4-dimethyl-2(3H)-furanone* (221) (103mg, 53%) as a colourless oil (*3R, 2'R*: *3R, 2'S* 1: 1); **R_f** 0.37 (SiO_2, PE 30-40: ether 60: 40); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2969s (CH), 1770s (C=O), 1476m, 1378m, 1260s, 1157s, 1077s, 1013s, 754s, 692s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.02, 1.06, 1.07, 1.10 (12H, 4xs, 4x CH_3), 3.97-4.04 (4H, m, 5-H), 5.25 (1H, s, 3-H), 5.32 (1H, s, 3-H), 6.18 (1H, d $^2J_{HF}$ 51Hz, 2'-H), 6.23 (1H, d $^2J_{HF}$ 51Hz, 2'-H), 7.49-7.67 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.7 (CH_3), 19.8 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 40.3 (4-C), 40.4 (4-C), 76.1 (3-H), 76.1 (3-H), 76.4 (4-H), 76.5 (4-H), 93.4 (d $^1J_{CF}$ 230Hz, 2'-H), 94.1 (d $^1J_{CF}$ 233Hz, 2'-H), 129.4, 129.4, 129.9, 130.2, 133.2, 133.2, 135.0, 135.0, 164.4 (d $^2J_{CF}$ 13Hz, 1'-C), 164.7 (d $^2J_{CF}$ 13Hz, 1'-C); **^{19}F NMR** (376MHz,

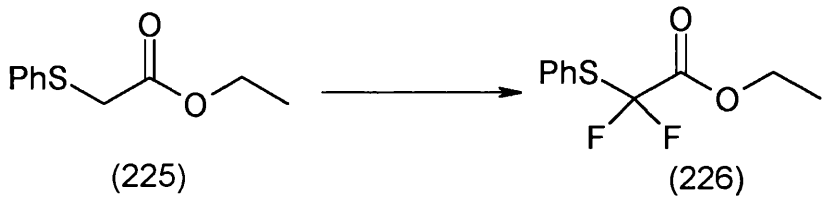
$CDCl_3$): δ −160.2 (d $^2J_{FH}$ 51Hz), -156.3 (d $^2J_{FH}$ 51Hz); **MS** (FAB): *m/z* 298 (M^+ 55%), 279 ($[M-F]^+$, 100); **HRMS** (FAB) calcd. for $C_{14}H_{15}O_4FS$: 298.0675. Found 298.0670.

Synthesis of *phenyl-(2-fluoro-2-phenylsulfanyl)acetate* (217)



A solution of difluoroiodotoluene (98) (185mg, 0.73mmol) and *phenyl (phenylsulfanyl)acetate* (217) (163mg, 0.67mmol) in DCM (5mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) gave *phenyl-(2-fluoro-2-phenylsulfanyl)acetate* (222) (126mg, 72%) as a white solid; $\mathbf{R_f}$ 0.52 (SiO_2, PE 30-40: ether 85: 15); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3049w, 2951w, 1742s (C=O), 1588m, 1483m, 1434m, 1309w, 1246s, 1190s, 1015s, 931m, 840w, 742w, 686m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 6.28 (1H, d $^2J_{HF}$ 51Hz, 2-H), 6.84-7.64 (10H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 93.8 (d $^2J_{CF}$ 234Hz, 2-C) 120.9, 126.4, 129.0 (SC_{ipso}), 129.3, 129.5, 129.7, 134.5, 149.8 (OC_{ipso}), 163.8 (d $^2J_{CF}$ 31Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ −158.5 (d $^2J_{FH}$ 51Hz); **MS** (FAB): *m/z* 285 (MNa^+, 35%), 262 (M^+, 100); **HRMS** (FAB) calcd. for $C_{14}H_{11}FO_2S$: 262.0464. Found: 262.0459; plus unreacted starting material (12%).

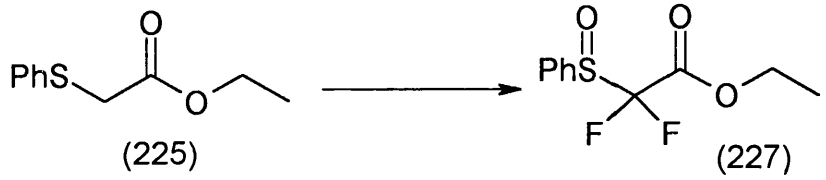
Synthesis of ethyl (2,2-difluoro-2-phenylsulfanyl)acetate (226)



A solution of difluoroiodotoluene (98) (75%, 671mg, 2mmol) and ethyl (phenylsulfanyl)acetate (225) (200mg, 1.00mmol) in DCM (7mL) was stirred overnight.

The crude material was absorbed onto silica gel and washed with PE 30-40. A second wash with PE 30-40: ether 80: 20 afforded ethyl (2,2-difluoro-2-phenylsulfanyl)acetate (226) (188mg, 80%) as a colourless oil; $\mathbf{R_f}$ 0.48 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3063m, 2986s, 2940m (CH), 1767 (C=O), 1476s, 1442s, 1371s, 1234s, 1106s, 1017s, 978s, 753s, 691s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.24 (3H, t *J* 4Hz, CH_3), 4.23 (2H, q *J* 4Hz, CH_2), 7.36-7.61 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 13.76 (CH_3), 63.5 (CH_2), 120.0 (t $^1J_{CF}$ 287Hz), 124.9 (C_{ipso}), 129.3, 130.6, 136.7, 161.6 (t $^2J_{CF}$ 32Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ –82.7; **MS** (FAB): *m/z* 232 (M^+ 100%), 213 ($[M-F]^+$, 20), 159 (90); **HRMS** (FAB) calcd. for $C_{10}H_{10}F_2O_2S$: 232.0370; found: 232.0362.

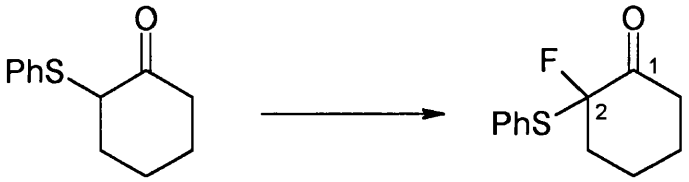
Synthesis of *ethyl (2,2-difluoro-2-phenylsulfinyl)acetate* (227)



A solution of difluoroiodotoluene (98) (75%, 754mg, 2.28mmol) and ethyl (phenylsulfanyl)acetate (225) (150mg, 0.76mmol) in DCM (10mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) afforded *ethyl (2,2-difluoro-phenylsulfinyl)acetate* (227) (71mg, 38%) as a colourless oil; $\mathbf{R_f}$ 0.11 (PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3064m, 2988s, 2942m (CH), 1760s (C=O), 1475s, 1447s, 1373s, 1306s, 1132s, 1062s, 1031s, 964s, 854m, 833m, 752m, 689s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.18 (3H, t *J* 7Hz, CH_3), 4.19 (2H, q *J* 7Hz, CH_2), 7.49-7.67 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 14.2 (CH_3), 64.6 (CH_2), 118.4 (t $^1J_{CF}$ 302Hz, 2-C), 126.4, 129.8, 133.6, 136.44 (C_{ipso}), 159.7 (t $^2J_{CF}$ 28Hz, C=O); **^{19}F NMR** (282MHz, $CDCl_3$): δ -110.3 (ABq $^2J_{FH}$ 578, 228Hz); **MS** (FAB): *m/z* 271 (MNa^+ 10%), 249 (MH^+, 100); **HRMS** (FAB) calcd. for $C_{10}H_{11}F_2O_3S$ (MH^+): 249.0397; found: 249.0388; plus ethyl (2,2-difluoro-2-phenylsulfanyl)acetate (226) (34mg, 19%).

4.4 Fluorination of β-EWG Sulfides

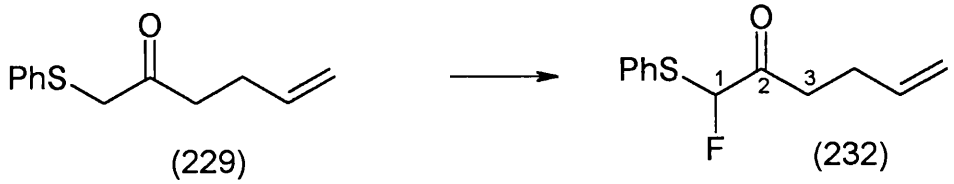
Synthesis of 2-fluoro-2-phenylsulfanyl-cyclohexanone (231)[58]



(230) (231)

A solution of difluoroiodotoluene (98) (80%, 630mg, 2mmol) and 2-phenylsulfanylcyclohexanone (230) (200mg, 1mmol) in DCM (6mL) was stirred for 5hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) afforded 2-phenylsulfanyl-2-fluoro-cyclohexanone (231) (50mg, 22%) as a yellow oil; **R_f** 0.23 (SiO_2, PE 30-40: ether 90: 10); **^{13}C NMR** (75MHz, $CDCl_3$): δ 23.1, 26.7, 38.6, 38.9, 105.4 (d $^1J_{CF}$ 237Hz, 2-C), 127.9 (C_{ipso}), 129.4, 129.6, 134.9, 200.6 (d $^2J_{CF}$ 28Hz, 1-C); **^{19}F NMR** (376MHz, $CDCl_3$): δ –127.4--127.2 (m); **MS** (FAB): *m/z* 204 ([M-HF]$^+$, 100%).

Synthesis of *1-fluoro-1-phenylsulfanyl-hex-5-en-2-one* (232)

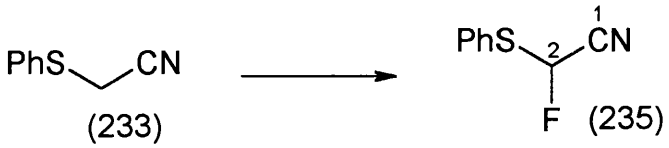


(229) (232)

A solution of difluoroiodotoluene (98) (80%, 331mg, 1.0mmol) and 1-phenylsulfanyl-hex-5-en-2-one (229) (200mg, 0.97mmol in DCM (5mL) was stirred for 3hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 95: 5) yielded *1-fluoro-1-phenylsulfanyl-hex-5-en-2-one* (232) (136mg, 63%) as a yellow oil; **R_f** 0.42 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3077m, 2978m (CH), 1734s (C=O), 1641m, 1474m, 1440s, 1070m, 997m, 916m, 749m, 691m; **^1H NMR** (300MHz, $CDCl_3$): δ 2.17-2.77 (4H, m, 3-H, 4-H), 4.9-5.03 (2H, m, 6-H), 5.64-5.69 (1H, m, 5-H), 6.03 (1H, d $^2J_{HF}$ 53Hz, 2-H), 7.30-7.57 (5H, m, Ar-H); **^{13}C**

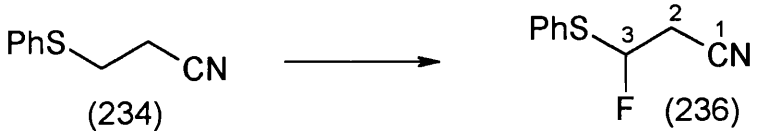
NMR (75MHz, $CDCl_3$): δ 26.8 (4-C), 37.7 (d $^3J_{CF}$ 2Hz, 3-C), 99.6 (d $^1J_{CF}$ 234Hz, 2-C), 115.6 (6-C), 128.6, 129.3, 129.4, 133.8, 136.2, 200.9 (d $^2J_{CF}$ 26Hz, C=O); **MS** (FAB): *m/z* 224 (M^+, 40%), 205 ($[M-F]^+$, 40); **HRMS** (FAB) calcd. for $C_{12}H_{13}FOS$: 224.0671. Found: 224.0665.

Synthesis of 2-fluoro-2-phenylsulfanyl-acetonitrile (235)



A solution of difluoroiodotoluene (98) (378mg, 1.47mmol) and phenylsulfanyl-acetonitrile (233) (200mg, 1.34mmol), in DCM (5mL) was stirred for 7hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40) afforded 2-fluoro-2-phenylsulfanyl-acetonitrile (235) (77mg, 34%) as a colourless oil; $\mathbf{R_f}$ 0.47 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3063m, 2955m (CH), 2252w (C≡N), 1478s, 1442s, 1239m, 998s, 943s, 778s, 734s, 691s; ^{1}**H NMR** (300MHz, $CDCl_3$): δ 6.23 (1H, d $^2J_{HF}$ 49Hz, 2-H), 7.45-7.67 (5H, m, Ar-H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 83.8 (d $^1J_{CF}$ 225Hz, 2-C), 112.4 (d $^2J_{CF}$ 39Hz, 1-C), 127.5 (C_{ipso}), 129.6, 130.7, 136.1; ^{19}**F NMR** (376MHz, $CDCl_3$): δ –118.1 (d, $^2J_{FH}$ 50Hz); **MS** (EI): *m/z* 167 ($M^{\bullet+}$, 80%), 109 (PhS^+, 100); **HRMS** (EI) calcd. for C_8H_6FNS: 167.0205. Found: 167.0200.

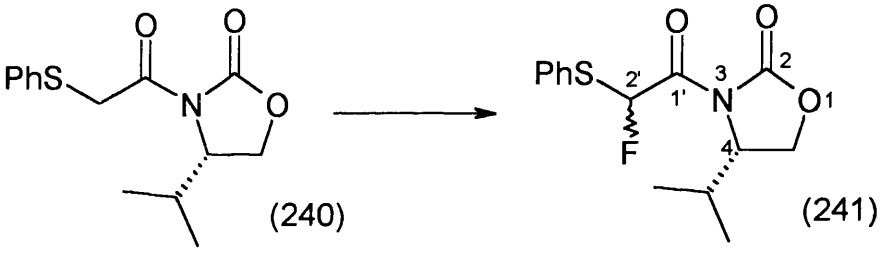
Synthesis of 3-fluoro-3-phenylsulfanyl-propionitrile (234)



A solution of difluoroiodotoluene (98) (346mg, 1.3mmol) and 3-phenylsulfanyl-propionitrile (234) (200mg, 1.2mmol in DCM (6mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40) gave 3-fluoro-3-phenylsulfanyl-propionitrile (236) (133mg, 61%) as a colourless oil; $\mathbf{R_f}$ 0.18 (SiO_2, PE 30-40: ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3061m, 2973m (CH),

2258m (C≡N), 2213w, 1482s, 1441s, 1412m, 1025s, 995s, 842s, 747s, 692s; **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.91-3.00 (2H, m, 2-H), 5.96 (1H, dt $^2J_{HF}$ 51Hz, $^3J_{HH}$ 6Hz, 3-H) 7.39-7.60 (5H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.8 (d $^2J_{CF}$ 31Hz, 2-C), 95.1 (d $^1J_{CF}$ 225Hz, 2-C), 114.7 (d $^3J_{CF}$ 7Hz, 1-C), 129.5, 129.6, 134.1, 131.5 (C_{ipso}); **^{19}F NMR** (376MHz, $CDCl_3$): δ –145.5 (dt $^2J_{FH}$ 51Hz, $^3J_{FH}$ 12Hz); **MS** (EI): *m/z* 181 ($M^{\bullet+}$, 90%), 141 ([M-CH_2CN]$^+$, 100); **HRMS** (EI) calcd. for C_9H_8FNS: 181.0361. Found: 181.0362.

Synthesis of *(4S, 2'R/2'S)-3-(2'-fluoro-2'-phenylsulfanyl)acetyl-4-isopropyl-1,3-oxazolidin-2-one* (241)

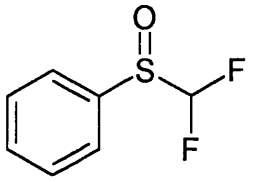


A solution of difluoroiodotoluene (98) (83%, 337mg, 1.1mmol) and (4*S*)-4-isopropyl-3-(phenylsulfanyl)acetyl-1,3-oxazolidin-2-one (240) (275mg, 1mmol) in DCM (8mL) was stirred for 3hr. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 60: 40) afforded both diastereoisomers of *(4S, 2'S / 2'R)-3-(2'-fluoro-2'-phenylsulfanyl)acetyl-4-isopropyl-1,3-oxazolidin-2-one* (241) (192mg, 65%), (*4S, 2'S*: *4S, 2'R* 1: 1); one as a yellow oil; **R_f** 0.38 (SiO_2; DCM); **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.90 (3H, d *J* 7Hz, CH_3), 0.93 (3H, d *J* 7Hz, CH_3), 2.37-2.47 (1H, m, C<u>H</u>$(CH_3)_2$), 4.23-4.47 (3H, m, 4-H, 5-H), 7.18 (1H, d *J* 53Hz, 2'-H), 7.34-7.63 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 14.5 (CH_3), 17.8 (CH_3), 28.2, 58.9, 64.2, 93.9 (d $^1J_{CF}$ 228Hz, 2'-C), 129.1, 129.5, 129.5, 153.0 (2-C), 164.3 (d $^2J_{CF}$ 28Hz 1'-C); **^{19}F NMR** (471MHz, $CDCl_3$): δ –163.5 (d $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 297 (M^+, 65%), 278 ([M-F]$^+$, 100); **HRMS** (FAB) calcd. for $C_{14}H_{16}FNO_3S$: 297.0835. Found: 297.0809; one as colourless crystals; **m.p.** 146-147°C (ethyl acetate / PE 30-40); $[\alpha]_D^{23}$ +42° (*c*=1, DCM); **R_f** 0.53 (SiO_2, DCM); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2967m, 1796s (2-C=O), 1715s (1'-C=O), 1485m, 1399s, 1374s, 1349m, 1263m, 1225m, 1111m, 1057m, 986s, 743m, 718m, 692m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 0.92 (3H, d *J* 7Hz, CH_3), 0.95

(3H, d *J* 7Hz, CH_3), 2.19-2.25 (1H, m, $C\underline{H}(CH_3)_2$), 4.27-4.52 (3H, m, 4-H, 5-H), 7.25 (1H, d *J* 53Hz, 2′-H), 7.35-7.65 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 14.7 (CH_3), 17.7 (CH_3), 27.0 ($\underline{C}H(CH_3)_2$), 58.1, 64.0, 93.4 (d $^1J_{CF}$ 228Hz, 2′-C), 129.2, 129.3, 129.6 (C_{ipso}), 133.8, 152.9 (2-C), 164.3 (d $^2J_{CF}$ 29Hz 1′-C); **^{19}F NMR** (471MHz, $CDCl_3$): δ −164.3 (d $^2J_{FH}$ 53Hz); **MS** (FAB): *m/z* 297 (M^+, 20%), 278 ($[M\text{-}F]^+$, 100); **Anal** calcd. for $C_{14}H_{16}FNO_3S$: C, 56.55; H, 5.42; N, 4.71%. Found: C, 56.58; H, 5.31; N, 4.68%.

4.5 Fluorination of Unactivated Sulfides

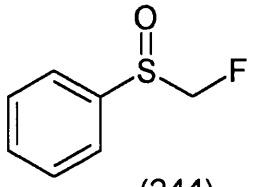
Synthesis of difluoromethyl phenyl sulfoxide (243)



(243)

A solution of difluoroiodotoluene (98) (75%, 1.75g, 7mmol) and thioanisole (0.19mL, 1.6mmol) in DCM (20mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 85: 15) afforded difluoromethyl phenyl sulfoxide (243) (188mg, 67%) as a yellow oil; $\mathbf{R_f}$ 0.55 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3062m, 2974w (CH), 1478m, 1446s, 1281s, 1107s (S=O), 1051s, 998m, 788m, 747s, 688s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 6.07 (1H, t *J* 55Hz), 7.55-7.72 (5H, m, Ar-H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 120.7 (t $^1J_{CF}$ 288Hz), 125.4, 129.5, 132.7, 136.4 (t $^3J_{CF}$ 3Hz); **^{19}F NMR** (470MHz, $CDCl_3$): δ −119.3 (dd *J* 55, 17Hz); **MS** (FAB): *m/z* 177 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_7H_7F_2OS$ (MH^+): 177.0816. Found: 177.0810.

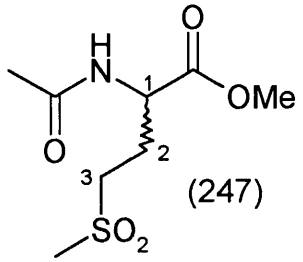
Synthesis of fluoromethyl phenyl sulfoxide (244)



(244)

A solution of difluoroiodotoluene (98) (517mg, 2mmol), thioanisole (0.12mL, 1.0mmol), and *N*-methylpyrrolidinone (0.1mL, 1mmol) in DCM (4mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 50: 50) afforded fluoromethyl phenyl sulfoxide (244) (85mg, 54%) as a yellow oil; $\mathbf{R_f}$ 0.18 (SiO_2, PE 30-40: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3058m, 2930w (CH), 1478m, 1443s, 1307ws, 1093s, 1055s, 919m, 753s, 695s; ^{1}**H NMR** (400MHz, $CDCl_3$): δ 5.04 (2H, dd J 48, 2Hz, 7.49-7.65 (5H, m, Ar-H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 98.1 (d $^1J_{CF}$ 221Hz), 124.5, 129.4, 132.0, 138.3 (d $^3J_{CF}$ 6Hz); ^{19}**F NMR** (282MHz, $CDCl_3$): δ –212.4 (t $^2J_{FH}$ 48Hz); **MS** (FAB): *m/z* 159 (MH^+, 100%); **HRMS** (FAB) calcd. for C_7H_8FOS (MH^+): 159.0280. Found: 159.0286.

Synthesis of *N*-acetyl-DL-methionine sulphone methyl ester (247)

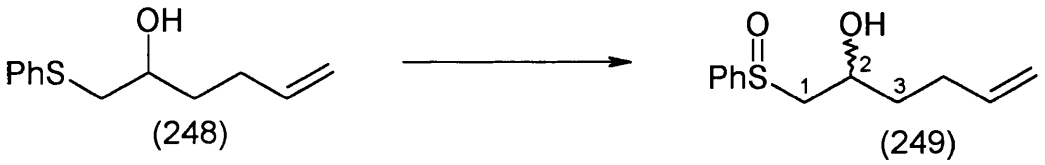


(247)

A solution of difluoroiodotoluene (98) (75%, 641mg, 2mmol) and *N*-acetyl-DL-methionine methyl ester (246) (200mg, 0.97mmol) in DCM (8mL) was stirred overnight. The crude product was heated to 65°C under high vacuum (0.5mBar) to remove iodotoluene, affording *N*-acetyl-DL-methionine sulphone methyl ester (247) (150mg, 65%) as a white solid; **m.p.**113-114°C (DCM); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3311m (NH), 2931w (CH), 1737s (C=O ester), 1656s (amide 1), 1546s (amide 2) 1442m, 1376m, 1293s (SO_2), 1242m, 1128s, 971w, 772w; ^{1}**H NMR** (300MHz, $CDCl_3$):

δ 2.00 (3H, s, $COCH_3$), 2.11-2.42 (2H, 2-H), 2.88 (SO_2CH_3), 3.02-3.16 (2H, m, 3-H), 3.72 (3H, s, $OC\underline{H}_3$), 4.61-4.68 (1H, m, 1-H), 6.86 (1H, d *J* 8Hz, NH); **^{13}C NMR** (75MHz, $CDCl_3$): δ 22.9 ($COCH_3$), 25.3 (2-C), 40.8 (SO_2CH_3), 50.8, 51.1 (3-C), 52.9, 170.8 171.4; **MS** (FAB): *m/z* 260 (MNa^+ 50%), 238 (MH^+, 100); **HRMS** (FAB) calcd. for $C_8H_{16}NO_5S$ (MH^+): 238.0749. Found: 238.0751.

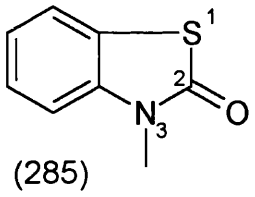
Synthesis of *syn / anti* 2-hydroxy-1-phenylsulfinyl-hex-5-ene (249)



A solution of difluoroiodotoluene (98) (80%, 202mg, 0.65mmol) and 2-hydroxy-1-phenylsulfanyl-hex-5-en-2-one (248) (123mg, 0.59mmol) in DCM (5mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 60: 40) afforded *syn / anti* 2-hydroxy-1-phenylsulfinyl-hex-5-ene (249) (44mg, 33%) as a colourless oil; $\mathbf{R_f}$ 0.33 (SiO_2; DCM); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3364s (OH), 2924s (CH), 1640m, 1444m, 1086s, 1033s (S=O), 977s, 912s, 733s, 690s, 646m; **MS** (FAB): *m/z* 357 (MCs^+, 12%), 247 (MNa^+, 15), 225 (MH^+, 100%); **HRMS** (FAB) calcd. for $C_{12}H_{17}O_2S$ (MH^+): 225.0949. Found: 225.0940.

4.6 Fluorination of Dithioorthoesters and Thione Ester Derivatives

Synthesis of 3-methyl-2(3 *H*)-benzothiazolone (285)



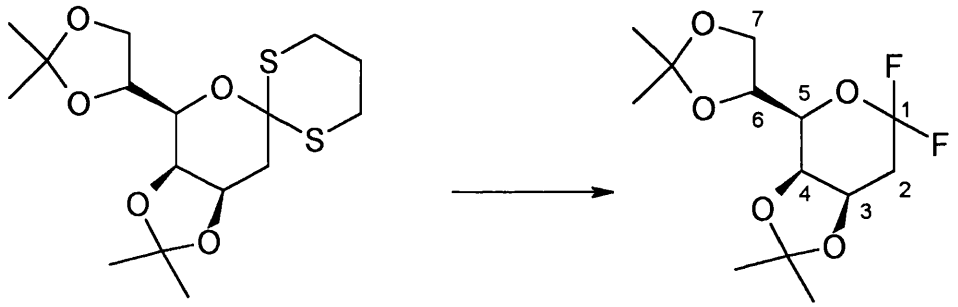
A solution of difluoroiodotoluene (98) (91%, 611mg, 2.2mmol) and 3-methylbenzothiazole-2-thione (283) (200mg, 1.1mmol) in DCM (10mL) was stirred overnight. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) afforded 3-methyl-2(3*H*)-benzothiazolone (285) (147mg, 81%) as colourless crystals; **m.p.** 73-75°C (PE 30-40 / DCM) (lit.[173] 66-72°C); $\mathbf{R_f}$ 0.69 (SiO_2, PE 30-40: ether 60: 40); **IR** (KBr disc/cm^{-1}): $\tilde{\nu}_{max}$ 2938w, 1681s (C=O), 1472s, 1325s, 1243s, 1122s, 867m, 753s, 526s, 422m; **^{1}H NMR** (300MHz, $CDCl_3$): δ 3.58 (3H, s CH_3), 7.03-7.56 (4H, m, Ar-H); **^{13}C NMR**

(75MHz, $CDCl_3$): δ 29.4 (CH_3), 110.8 (4-C), 122.9, 123.0, 123.6, 126.8, 138.2 (3a-C), 170.5 (2-C); **MS** (FAB): *m/z* 166 (MH^+, 100%); **Anal** calcd. for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48; S, 19.41%. Found: C, 57.86; H, 4.04; N, 8.49; S, 19.53%.

General procedure for fluorination using pyridinium poly(hydrogen fluoride) / dibromohydantoin[20]

1,3-Dibromo-5,5-dimethylhydantoin (DBH) (286mg, 1.0mmol), was suspended in 2 mL of DCM and the mixture cooled to -78°C. Pyridinium poly(hydrogen fluoride) (py.9HF, Olah's reagent) was added (0.5 mL, 2.2 mmol, i.e. 20.3 equiv of F^-) *via* polypropylene syringe, followed by dropwise addition of substrate (1mmol) in DCM (1mL) *via* cannula. The reaction was stirred until no more starting material could be detected by TLC. The mixture was diluted with PE or DCM (15 mL) and filtered through a short column of basic alumina in a polypropylene syringe. The reaction products were purified by flash chromatography.

Synthesis of *1,2-dideoxy-3,4:6,7-di-O-isopropylidene-1,1-[propylenebis(sulfanediyl)] - 2,2-difluoro-D-glycero-D-galacto-heptopyranose* (264)

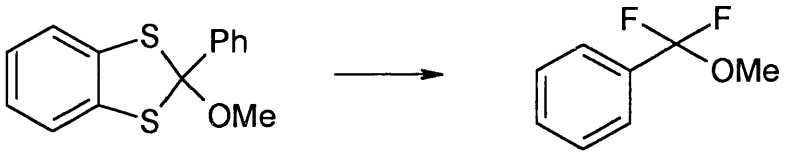


(263) (264)

DBH (155mg, 0.54mmol), py.9HF (0.27mL, 40eq.) and 1,2-dideoxy-3,4:6,7-di-*O*-isopropylidene-1,1-[propylenebis(sulfanediyl)]-D-glycero-D-galacto-heptopyranose (263) in DCM (2mL) at -50°C was stirred for 20min. Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ether 70: 30) afforded *1,2-dideoxy-3,4:6,7-di-O-isopropylidene-1,1-[propylenebis(sulfanediyl)]-2,2-difluoro-D-glycero-D-galacto-heptopyranose* (264) (21mg, 13%) as a colourless oil; $\mathbf{R_f}$ 0.57 (SiO_2 PE 40-60: ether 50: 50); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2989m, 2936m (CH), 1377s,

1256s, 1217s, 1173m, 1128s, 1080s, 849m; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.34, 1.35, 1.41, 1.46 (12H, 4xs, CH_3), 2.06-2.12 (1H, m, 2-H), 2.55-2.62 (1H, m, 2-H), 3.59 (1H, dd $J_{5,4}$ 8Hz, $J_{5,6}$ 1Hz, 5-H), 4.03-4.13 (2H, m, 7-H), 4.39 (1H, d $J_{6,5}$ 8Hz, 6-H), 4.58-4.61 (1H, m, 3-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 24.7, 25.1, 26.0, 27.0 (4xCH_3), 32.3 (dd $^2J_{CF}$ 33Hz, $^2J_{CF}$ 27Hz, 2-C), 66.7 (7-C), 69.6 (d $^3J_{CF}$ 8Hz), 70.9 (4-C), 72.9 (6-C) 75.1, 109.8, 109.9 (2x$\underline{C}(CH_3)_2$), 123.4 (dd $^1J_{CF}$ 257Hz, 249, 1-C); **^{19}F NMR** (376MHz, $CDCl_3$): δ -60.0 (ddd $^2J_{FF}$ 152Hz, $^3J_{FH}$ 20Hz, $^3J_{FH}$ 10Hz), –54.1 (d $^2J_{FF}$ 152Hz); **MS** (FAB): *m/z* 295 (MH^+, 48%), 279 ($[M\text{-}CH_3]^+$ 100); **HRMS** (FAB) calcd. for $C_{13}H_{21}F_2O_5$: 295.1357. Found: 295.1370.

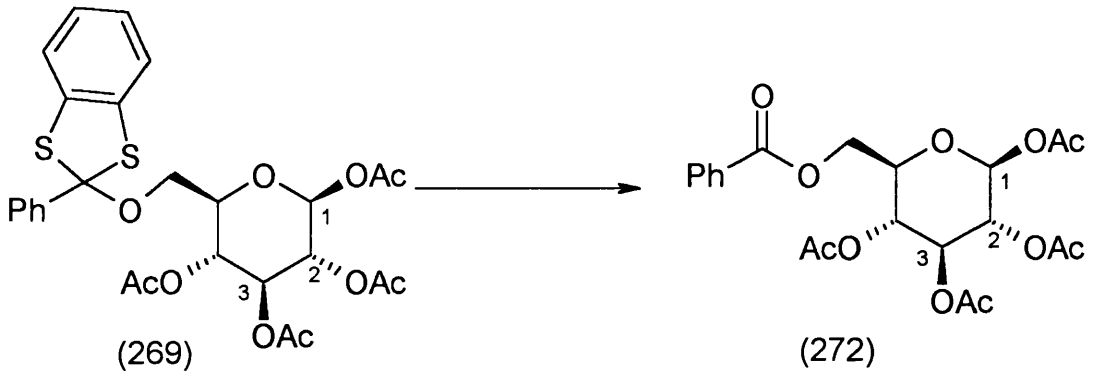
Synthesis of α, α-difluorobenzyl methyl ether (270)



(268) (270)

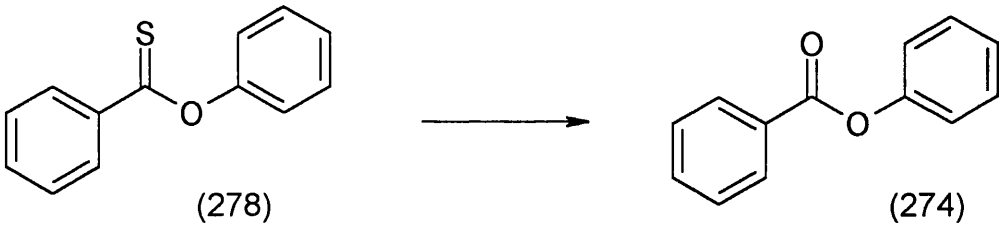
DBH (332mg, 1.15mmol), py.9HF (0.88mL, *ca.* 40eq.) and 2-methoxy-2-phenyl-1,3-benzodithiol (268) (300mg, 1.15mmol) in DCM (14mL) at -78°C was stirred 20min. The crude material was nearly pure α, α-difluorobenzyl methyl ether (270) contaminated with a small amount of starting material; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.89 (3H, s, OCH_3), 7.39-8.03 (5H, m, Ar-H); **^{19}F NMR** (376MHz, $CDCl_3$): δ –72.7. Flash chromatography (Al_2O_3, PE 30-40: ether 50: 50) gave no isolable products.

Synthesis of 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoyl-*β*-D-glucose (272)



DBH (49mg, 0.17mmol), py.9HF (0.13mL, *ca.* 40eq.) and 1,2,3,4-tetra-*O*-acetyl-6-*O*-(2-phenyl-1,3-benzodithiol-2-yl)-*β*-D-glucose (271) (98mg, 0.17mmol) in DCM (2mL) at -78°C was stirred 20min. ^{19}F nmr of the crude product identified the expected difluoroether (271); **^{19}F NMR** (282MHz, $CDCl_3$): δ –72.4 (d, $^2J_{FF}$ 149Hz), -69.3 (d $^2J_{FF}$ 149Hz); Work-up according to the general procedure followed by flash chromatography (SiO_2, PE 40-60: ether 50: 50) afforded 1,2,3,4-tetra-*O*-acetyl-6-*O*-benzoyl-*β*-D-glucose (272) (17mg, 21%) as the sole product as a colourless oil; **R_f** 0.16 (SiO_2 PE 40-60: ether 80: 20); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2962w, (CH), 1759s (C=O), 1725 (C=O), 1450m, 1370s, 1216s, 1075s, 1040s, 914m, 850w, 716s; **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.95, 1.96, 1.98, 2.04, (12H, 4xs, 4xCH_3), 3.89-3.94 (1H, m, 6-H), 4.28-4.45 (2H, m), 5.06-5.51 (3H, m), 5.69 (1H, d *J* 8Hz, 1-H), 7.36-7.54 (3H, m, Ar-H), 7.97-8.00 (2H, m, Ar-H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.0, 21.2, 62.6, 68.5, 70.7, 73.1, 73.3, 92.1, 128.9, 129.9, 130.2, 133.7, 166.5, 169.4, 169.7, 170.5; **MS** (FAB): *m/z* 475 (MNa^+, 15%), 393 ($[M\text{-}OAc]^+$ 90), 363 (20), 307 (50), 289 (40), 251 (100); **HRMS** (FAB) calcd. for $C_{21}H_{24}O_{11}Na$ (MNa^+): 475.1216. Found: 475.1227.

Attempted fluorination of thiobenzoic acid *O*-phenyl ester (278)[#]



(278) (274)

DBH (133mg, 0.47mmol), py.9HF (0.23mL, 0.97mmol) and thiobenzoic acid *O*-phenyl ester (278) (100mg, 0.47mmol) were stirred 2hr at -78°C in DCM (2mL). The crude material contained the expected difluoro ether; **^{19}F NMR** (376MHz, $CDCl_3$): δ –65.9; Flash chromatography (PE 30-40: ether 80: 20) afforded phenyl benzoate (274) (65mg, 70%) as the only product

Attempted fluorination of chromene-2-thione (279)[#]

(279) (275)

1. Using py.9HF / DBH

DBH (352mg, 1.23mmol), py.9HF (0.6mL, 2.7mmol) and chromene-2-thione (279) (200mg, 1.23mmol), were stirred 20 min at -78°C in DCM (4mL). Work-up as usual followed by flash chromatography (PE 30-40: ether 80: 20) afforded coumarin (275) (150mg, 84%).

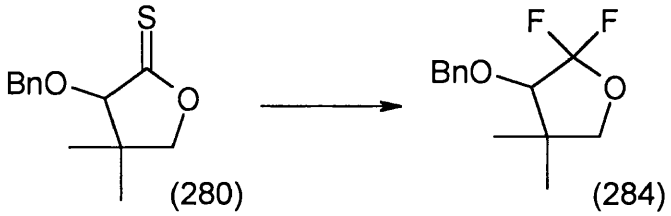
2. Using DFIT

A solution of difluoroiodotoluene (98) (282mg, 1.1mmol) and chromene-2-thione (279) (81mg, 0.50mmol) in DCM (9mL) was stirred 40min. Work-up according to the general

[#] Experiments marked # were performed by Ms. E. M. M. de la Nava under the direct supervision of the author.

procedure followed by flash chromatography (SiO_2, PE 30-40: ether 80: 20) afforded coumarin (275) (60 mg, 82%).

Synthesis of *3-benzyloxy-2,2-difluoro-tetrahydro-4,4-dimethyl-furan* (284)[#]



(280) (284)

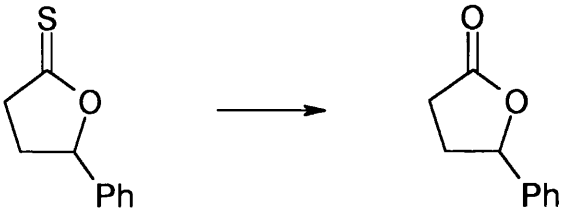
1. Using py.9HF/DBH

DBH (146mg, 0.51mmol), py.9HF (0.25mL, 1.1mmol) and 3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3*H*)-furanthione (280) (112mg, 0.51mmol) were stirred 25min at -78°C in DCM (1.5mL). Work-up according to the general procedure followed by flash chromatography (PE 30-40: ether 95: 5) afforded *3-benzyloxy-2,2-difluoro-tetrahydro-4,4-dimethyl-furan* (284) (35mg, 30%) as a colourless oil; $\mathbf{R_f}$ 0.63 (SiO_2, PE 30-40; ether 90: 10); **IR** (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2968, 1796, 1243, 1132, 1069, 829, 737, 698; ^{1}**H NMR** (300MHz, $CDCl_3$): δ 1.11 (3H, s, CH_3), 1.27 (3H, s, CH_3), 3.70-3.90 (3H, m, 5-H, 3-H), 4.58 (1H, d J_{AB} 12Hz, OCH_2), 4.91 (1H, d J_{AB} 12Hz, OCH_2), 7.30-7.50 (5H, m, Ar-H); ^{13}**C NMR** (75MHz, $CDCl_3$): δ 19.6 (CH_3), 23.7 (CH_3), 40.8, 72.6, 77.8, 84.6 (dd $^2J_{CF}$ 30, 22Hz, 3-C), 127.9, 128.0, 128.5, 129.7 (dd $^1J_{CF}$ 264, 257Hz, 2-C), 137.3 (C_{ipso}); ^{19}**F NMR** (376MHz, $CDCl_3$): δ –74.9 (dt J 143, 7Hz), -66.8 (dt J 143, 5Hz); and 3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3*H*)-furan-2-one (276) (35mg, 30%).

2. Using DFIT

A solution of difluoroiodotoluene (98) (339mg, 1.32mmol) and 3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3*H*)-furanthione (280) (142mg, 0.60mmol) in DCM (11mL) was stirred for 30min. Work-up according to the general procedure followed by flash chromatography (PE 30-40: ether 95: 5) afforded *3-benzyloxy-2,2-difluoro-tetrahydro-4,4-dimethyl-furan* (284) (30mg, 20%) as a colourless oil plus 3-benzyloxy-4,5-dihydro-4,4-dimethyl-2(3*H*)-furanone (276) (76mg, 57%).

Attempted fluorination of 5-phenyl-dihydro-2(3*H*)-furanthione (281)[#]



(281) (277)

1. Using py.9HF / DBH

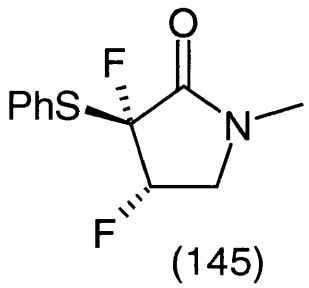
DBH (193mg, 0.67mmol), py.9HF (0.33mL, 1.4mmol) and 4,5-dihydro-5-phenyl-2(3*H*)-furanthione (281) (120mg, 0.67mmol) were stirred 20min at -78°C in DCM (2mL). Work-up according to the general procedure folloed by flash chromatography (PE 30-40: ether 95: 5) afforded γ-phenyl-γ-butyrolactone (277) (60mg, 55%).

3. Using DFIT

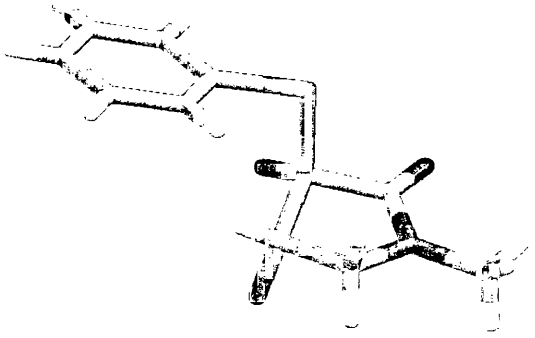
A solution of difluoroiodotoluene (98) (298mg, 1.16mmol) and 4,5- dihydro-2(3*H*)-furanthione (281) (95mg, 0.53mmol) in DCM (10mL) was stirred 30min. Work-up according to the general procedure followed by flash chromatography (PE 30-40: ether 90: 10) afforded γ-phenyl-γ-butyrolactone (277) (30 mg, 34%).

Appendix 1. X-Ray Crystallographic Data

1. 3, *syn*-4-Difluoro-1-methyl-3-phenylsulfanyl-2-pyrrolidinone (145)



(145)



Structure of (145)

Frame time: 15 s, ϕ increment: 3°, DX: 25 mm, temperature -173°C

From systematically absent data and subsequent refinement the space group was found to be $P2_1/n$. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated in idealised positions, assigned an isotropic displacement parameter 1.2 times the atom to which they were attached and a riding model adopted.

Table 1. Crystal data and structure refinement for mfg219. (145)

Identification code	mfg219 (145)
Empirical formula	C11 H11 F2 N O S
Formula weight	243.27
Temperature	100(2) K
Wavelength	0.71070 A
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 7.5687(4) A alpha = 90 deg. b = 13.7172(7) A beta = 90.4250(10) deg. c = 10.6303(5) A gamma = 90 deg.
Volume	1103.62(10) A^3

Z, Calculated density	4, 1.464 Mg/m^3
Absorption coefficient	0.297 mm^-1
F(000)	504
Crystal size	0.50 x 0.50 x 0.40 mm
Theta range for data collection	3.54 to 25.99 deg.
Index ranges	-9<=h<=9, -16<=k<=15, -13<=l<=13
Reflections collected / unique	9585 / 2163 [R(int) = 0.0259]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2163 / 0 / 146
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0830
R indices (all data)	R1 = 0.0413, wR2 = 0.0866
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.339 and -0.274 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for mfg219.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	1950(1)	5650(1)	3128(1)	18(1)
F(1)	1213(2)	8520(1)	3124(1)	29(1)
F(2)	845(1)	7048(1)	4637(1)	26(1)
O(1)	4555(2)	6855(1)	5109(1)	29(1)
N(1)	4726(2)	7564(1)	3144(2)	23(1)
C(1)	3927(2)	7098(1)	4098(2)	19(1)
C(2)	3554(3)	7746(1)	2055(2)	25(1)
C(3)	1713(2)	7629(1)	2595(2)	20(1)
C(4)	2013(2)	6906(1)	3662(2)	18(1)
C(5)	6600(2)	7799(2)	3133(2)	32(1)
C(6)	-265(2)	5560(1)	2561(2)	17(1)
C(7)	-642(2)	5719(1)	1291(2)	21(1)
C(8)	-2365(2)	5618(1)	852(2)	24(1)
C(9)	-3701(2)	5348(1)	1667(2)	22(1)
C(10)	-3326(2)	5173(1)	2928(2)	22(1)
C(11)	-1605(2)	5282(1)	3379(2)	20(1)

Table 3. Bond lengths [A] and angles [deg] for mfg219.

S(1)-C(6)	1.7822(17)
S(1)-C(4)	1.8140(18)
F(1)-C(3)	1.3985(19)
F(2)-C(4)	1.3820(19)
O(1)-C(1)	1.218(2)
N(1)-C(1)	1.346(2)
N(1)-C(5)	1.455(2)
N(1)-C(2)	1.474(2)
C(1)-C(4)	1.540(2)
C(2)-C(3)	1.519(3)
C(3)-C(4)	1.522(2)
C(6)-C(11)	1.394(2)
C(6)-C(7)	1.394(2)
C(7)-C(8)	1.388(2)
C(8)-C(9)	1.387(3)
C(9)-C(10)	1.389(3)
C(10)-C(11)	1.393(2)
C(6)-S(1)-C(4)	101.22(8)
C(1)-N(1)-C(5)	123.72(16)
C(1)-N(1)-C(2)	113.61(15)
C(5)-N(1)-C(2)	122.49(16)
O(1)-C(1)-N(1)	128.30(17)
O(1)-C(1)-C(4)	125.36(16)
N(1)-C(1)-C(4)	106.33(14)
N(1)-C(2)-C(3)	103.54(14)
F(1)-C(3)-C(2)	108.13(14)
F(1)-C(3)-C(4)	107.99(14)
C(2)-C(3)-C(4)	102.56(14)
F(2)-C(4)-C(3)	111.98(13)
F(2)-C(4)-C(1)	110.84(13)
C(3)-C(4)-C(1)	104.36(14)
F(2)-C(4)-S(1)	110.69(11)
C(3)-C(4)-S(1)	112.46(11)
C(1)-C(4)-S(1)	106.19(11)
C(11)-C(6)-C(7)	120.15(16)
C(11)-C(6)-S(1)	119.66(13)
C(7)-C(6)-S(1)	120.12(13)
C(8)-C(7)-C(6)	119.63(16)
C(9)-C(8)-C(7)	120.27(17)
C(8)-C(9)-C(10)	120.29(16)
C(9)-C(10)-C(11)	119.83(16)
C(10)-C(11)-C(6)	119.82(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for mfg219.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	14(1)	17(1)	23(1)	1(1)	-1(1)	0(1)
F(1)	37(1)	20(1)	31(1)	-7(1)	-7(1)	11(1)
F(2)	23(1)	35(1)	21(1)	-5(1)	7(1)	2(1)
O(1)	32(1)	30(1)	24(1)	0(1)	-12(1)	0(1)
N(1)	21(1)	21(1)	27(1)	-1(1)	2(1)	-4(1)
C(1)	20(1)	17(1)	21(1)	-3(1)	-2(1)	1(1)
C(2)	33(1)	19(1)	23(1)	5(1)	4(1)	-1(1)
C(3)	25(1)	16(1)	20(1)	-5(1)	-4(1)	4(1)
C(4)	17(1)	21(1)	15(1)	-2(1)	2(1)	2(1)
C(5)	22(1)	26(1)	48(1)	-1(1)	4(1)	-7(1)
C(6)	15(1)	16(1)	21(1)	-1(1)	0(1)	0(1)
C(7)	22(1)	21(1)	19(1)	0(1)	2(1)	-4(1)
C(8)	27(1)	23(1)	21(1)	2(1)	-5(1)	-3(1)
C(9)	17(1)	19(1)	31(1)	-2(1)	-5(1)	0(1)
C(10)	17(1)	21(1)	28(1)	1(1)	3(1)	-1(1)
C(11)	20(1)	21(1)	19(1)	2(1)	0(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for mfg219.

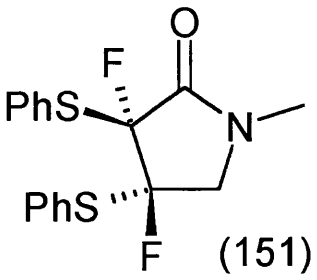
	x	y	z	U(eq)
H(2A)	3766	7266	1377	30
H(2B)	3728	8411	1718	30
H(3)	839	7387	1957	24
H(5A)	7183	7497	3861	38
H(5B)	6751	8508	3173	38
H(5C)	7127	7551	2357	38
H(7)	275	5894	729	25
H(8)	-2630	5735	-10	29
H(9)	-4877	5282	1361	27
H(10)	-4241	4979	3481	27
H(11)	-1345	5168	4242	24

Table 6. Torsion angles [deg] for mfg219.

C(5)-N(1)-C(1)-O(1)	5.1(3)
C(2)-N(1)-C(1)-O(1)	-179.77(18)
C(5)-N(1)-C(1)-C(4)	-174.18(16)
C(2)-N(1)-C(1)-C(4)	1.00(19)
C(1)-N(1)-C(2)-C(3)	18.12(19)
C(5)-N(1)-C(2)-C(3)	-166.63(16)
N(1)-C(2)-C(3)-F(1)	85.15(16)
N(1)-C(2)-C(3)-C(4)	-28.79(16)
F(1)-C(3)-C(4)-F(2)	35.59(18)
C(2)-C(3)-C(4)-F(2)	149.64(14)
F(1)-C(3)-C(4)-C(1)	-84.37(16)
C(2)-C(3)-C(4)-C(1)	29.68(16)
F(1)-C(3)-C(4)-S(1)	160.97(11)
C(2)-C(3)-C(4)-S(1)	-84.98(14)
O(1)-C(1)-C(4)-F(2)	40.3(2)
N(1)-C(1)-C(4)-F(2)	-140.47(14)
O(1)-C(1)-C(4)-C(3)	160.99(17)
N(1)-C(1)-C(4)-C(3)	-19.76(17)
O(1)-C(1)-C(4)-S(1)	-80.00(19)
N(1)-C(1)-C(4)-S(1)	99.26(13)
C(6)-S(1)-C(4)-F(2)	63.40(12)
C(6)-S(1)-C(4)-C(3)	-62.68(13)
C(6)-S(1)-C(4)-C(1)	-176.23(11)
C(4)-S(1)-C(6)-C(11)	-89.01(15)
C(4)-S(1)-C(6)-C(7)	94.16(15)
C(11)-C(6)-C(7)-C(8)	1.3(3)
S(1)-C(6)-C(7)-C(8)	178.13(14)
C(6)-C(7)-C(8)-C(9)	-0.9(3)
C(7)-C(8)-C(9)-C(10)	-0.1(3)
C(8)-C(9)-C(10)-C(11)	0.9(3)
C(9)-C(10)-C(11)-C(6)	-0.5(3)
C(7)-C(6)-C(11)-C(10)	-0.6(3)
S(1)-C(6)-C(11)-C(10)	-177.43(14)

Symmetry transformations used to generate equivalent atoms:

2. 3, *anti*-4-Difluoro-1-methyl-3, *anti*-4-diphenylsulfanyl-2-pyrrolidinone (151)



(151)

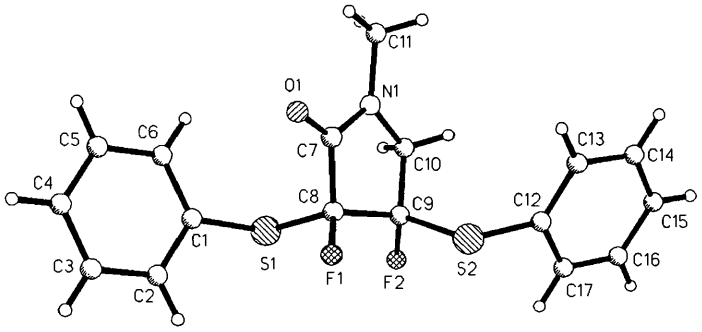


Table 1. Crystal data and structure refinement for 151.

Identification code	str636 (151)
Empirical formula	C17 H15 F2 N O S2
Formula weight	351.42
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 12.474(2) A alpha = 90 deg. b = 7.500(2) A beta = 106.36(3) deg. c = 19.156(4) A gamma = 90 deg.
Volume	1719.6(6) A^3
Z	4
Density (calculated)	1.357 Mg/m^3
Absorption coefficient	0.331 mm^-1
F(000)	728
Crystal size	0.78 x 0.76 x 0.62 mm
Theta range for data collection	2.93 to 25.06 deg.
Index ranges	0<=h<=14, 0<=k<=8, -22<=l<=21
Reflections collected	3158
Independent reflections	3016 [R(int) = 0.0271]

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3004 / 0 / 209
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0399, wR2 = 0.1026
R indices (all data)	R1 = 0.0601, wR2 = 0.1285
Extinction coefficient	0.012(2)
Largest diff. peak and hole	0.204 and -0.187 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	8069(1)	2612(1)	9145(1)	68(1)
S(2)	6266(1)	7583(1)	8866(1)	63(1)
F(1)	7888(1)	5619(2)	9848(1)	67(1)
F(2)	7028(1)	5213(2)	8092(1)	74(1)
N(1)	5380(2)	3404(3)	9148(1)	58(1)
O(1)	6455(2)	3349(3)	10352(1)	69(1)
C(1)	8732(2)	1720(3)	10031(1)	53(1)
C(2)	9828(2)	2235(4)	10377(2)	65(1)
C(3)	10396(3)	1461(5)	11039(2)	80(1)
C(4)	9884(3)	201(5)	11354(2)	84(1)
C(5)	8795(3)	-316(5)	11013(2)	85(1)
C(6)	8216(2)	421(4)	10344(2)	66(1)
C(7)	6319(2)	3663(3)	9703(1)	54(1)
C(8)	7216(2)	4391(3)	9367(1)	53(1)
C(9)	6502(2)	5265(4)	8653(1)	55(1)
C(10)	5457(2)	4060(4)	8441(1)	60(1)
C(11)	4372(2)	2547(4)	9233(2)	75(1)
C(12)	5176(2)	8307(3)	8086(1)	55(1)
C(13)	4075(2)	8353(4)	8123(2)	66(1)
C(14)	3245(3)	9101(5)	7546(2)	88(1)
C(15)	3512(4)	9780(5)	6947(2)	97(1)
C(16)	4598(4)	9706(5)	6910(2)	95(1)
C(17)	5438(3)	8992(4)	7480(2)	75(1)

Table 3. Bond lengths [A] and angles [deg] for 1.

S(1)-C(1)	1.794(3)
S(1)-C(8)	1.830(3)
S(2)-C(12)	1.798(3)
S(2)-C(9)	1.828(3)
F(1)-C(8)	1.402(3)
F(2)-C(9)	1.409(3)
N(1)-C(7)	1.356(3)
N(1)-C(11)	1.462(4)
N(1)-C(10)	1.469(3)
O(1)-C(7)	1.230(3)
C(1)-C(6)	1.394(4)
C(1)-C(2)	1.396(4)
C(2)-C(3)	1.393(4)
C(3)-C(4)	1.372(5)
C(4)-C(5)	1.386(5)
C(5)-C(6)	1.395(4)
C(7)-C(8)	1.538(3)
C(8)-C(9)	1.552(3)
C(9)-C(10)	1.543(4)
C(12)-C(17)	1.391(4)
C(12)-C(13)	1.394(4)
C(13)-C(14)	1.400(4)
C(14)-C(15)	1.379(5)
C(15)-C(16)	1.377(5)
C(16)-C(17)	1.390(5)
C(1)-S(1)-C(8)	101.31(11)
C(12)-S(2)-C(9)	103.48(11)
C(7)-N(1)-C(11)	123.7(2)
C(7)-N(1)-C(10)	114.1(2)
C(11)-N(1)-C(10)	122.1(2)
C(6)-C(1)-C(2)	119.9(2)
C(6)-C(1)-S(1)	121.5(2)
C(2)-C(1)-S(1)	118.4(2)
C(3)-C(2)-C(1)	119.7(3)
C(4)-C(3)-C(2)	120.5(3)
C(3)-C(4)-C(5)	120.1(3)
C(4)-C(5)-C(6)	120.4(3)
C(1)-C(6)-C(5)	119.4(3)
O(1)-C(7)-N(1)	127.4(2)
O(1)-C(7)-C(8)	125.6(2)
N(1)-C(7)-C(8)	107.0(2)
F(1)-C(8)-C(7)	109.2(2)
F(1)-C(8)-C(9)	113.0(2)
C(7)-C(8)-C(9)	102.4(2)
F(1)-C(8)-S(1)	110.7(2)
C(7)-C(8)-S(1)	112.1(2)
C(9)-C(8)-S(1)	109.3(2)
F(2)-C(9)-C(10)	108.8(2)
F(2)-C(9)-C(8)	112.7(2)
C(10)-C(9)-C(8)	102.5(2)
F(2)-C(9)-S(2)	109.6(2)
C(10)-C(9)-S(2)	116.0(2)
C(8)-C(9)-S(2)	107.1(2)
N(1)-C(10)-C(9)	102.9(2)
C(17)-C(12)-C(13)	119.9(3)
C(17)-C(12)-S(2)	120.3(2)

C(13)-C(12)-S(2)	119.4(2)
C(12)-C(13)-C(14)	119.4(3)
C(15)-C(14)-C(13)	120.4(3)
C(14)-C(15)-C(16)	120.0(3)
C(15)-C(16)-C(17)	120.6(3)
C(12)-C(17)-C(16)	119.7(3)

Symmetry transformations used to generate equivalent atoms:

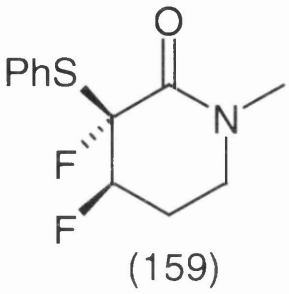
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	74(1)	85(1)	49(1)	9(1)	22(1)	28(1)
S(2)	68(1)	55(1)	57(1)	-3(1)	1(1)	0(1)
F(1)	59(1)	73(1)	60(1)	-3(1)	0(1)	-4(1)
F(2)	83(1)	90(1)	52(1)	13(1)	26(1)	15(1)
N(1)	56(1)	63(1)	53(1)	-2(1)	13(1)	-3(1)
O(1)	76(1)	88(1)	46(1)	2(1)	22(1)	7(1)
C(1)	53(1)	54(1)	50(1)	-1(1)	14(1)	10(1)
C(2)	55(2)	59(2)	81(2)	-2(1)	19(1)	8(1)
C(3)	64(2)	80(2)	81(2)	-16(2)	-4(2)	16(2)
C(4)	104(3)	87(2)	52(2)	2(2)	7(2)	37(2)
C(5)	105(3)	78(2)	77(2)	22(2)	35(2)	16(2)
C(6)	66(2)	62(2)	68(2)	3(1)	14(1)	-1(1)
C(7)	60(1)	55(1)	47(1)	-4(1)	16(1)	7(1)
C(8)	51(1)	61(2)	45(1)	-4(1)	9(1)	1(1)
C(9)	58(1)	64(2)	44(1)	2(1)	14(1)	6(1)
C(10)	67(2)	59(2)	46(1)	-5(1)	4(1)	0(1)
C(11)	68(2)	76(2)	83(2)	-11(2)	22(2)	-10(2)
C(12)	71(2)	42(1)	48(1)	1(1)	11(1)	0(1)
C(13)	72(2)	69(2)	56(2)	0(1)	16(1)	5(2)
C(14)	76(2)	90(2)	84(2)	-6(2)	-2(2)	19(2)
C(15)	131(3)	66(2)	66(2)	5(2)	-18(2)	15(2)
C(16)	147(4)	73(2)	59(2)	20(2)	18(2)	-8(2)
C(17)	94(2)	67(2)	67(2)	8(2)	28(2)	-9(2)

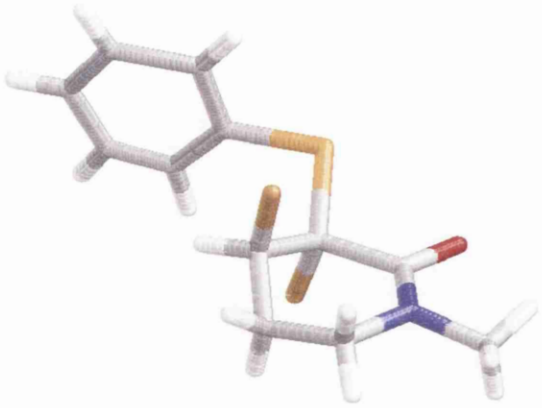
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(2A)	10186(2)	3120(4)	10157(2)	80
H(3A)	11149(3)	1817(5)	11278(2)	80
H(4A)	10285(3)	-331(5)	11808(2)	80
H(5A)	8432(3)	-1178(5)	11239(2)	80
H(6A)	7470(2)	44(4)	10098(2)	80
H(10A)	4804(2)	4725(4)	8192(1)	80
H(10B)	5556(2)	3090(4)	8138(1)	80
H(11A)	4488(2)	2227(4)	9734(2)	80
H(11B)	3752(2)	3355(4)	9086(2)	80
H(11C)	4216(2)	1494(4)	8937(2)	80
H(13A)	3895(2)	7889(4)	8543(2)	80
H(14A)	2485(3)	9134(5)	7567(2)	80
H(15A)	2942(4)	10313(5)	6558(2)	80
H(16A)	4776(4)	10144(5)	6485(2)	80
H(17A)	6198(3)	8967(4)	7460(2)	80

3. 3, *anti*-4-Difluoro-1-methyl-3-phenylsulfanyl-2-piperidinone (159)



(159)



Structure of (159)

Frame time: 30 s, ϕ increment: 3°, DX: 25 mm, temperature -173°C

From systematically absent data and subsequent refinement the space group was found to be Pcmn. The structure exhibited a fascinating disorder in which the whole molecule adopts two orientations either side of the crystallographic mirror plane. This results in all atoms off the mirror plane exhibiting 0.5 occupancy. The phenyl ring is also orientationally disordered over two positions involving C(9) and C(9a), representing an approximately 20° rotation from one ring to another. This disorder was modelled very staisfactorily to give an overall high degree of precision with final wR_2 = 0.1124, corresponding to an R_1 for data with I > 2σ(I) of 0.0507. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated in idealised positions for all appropriate atoms, assigned an isotropic displacement parameter 1.2 times the atom to which they were attached and a riding model adopted. Hydrogen atom occupancies were fixed at those of the atom to which they were attached.

Table 1. Crystal data and structure refinement for mfg221.

Identification code	mfg221 (159)
Empirical formula	C12 H13 F2 N O S
Formula weight	257.29

Wavelength	0.71070 A
Crystal system, space group	Orthorhombic, Pcmn
Unit cell dimensions	a = 9.0729(4) A alpha = 90 deg. b = 9.2890(9) A beta = 90 deg. c = 14.3816(12) A gamma = 90 deg.
Volume	1212.05(16) A^3
Z, Calculated density	4, 1.410 Mg/m^3
Absorption coefficient	0.275 mm^-1
F(000)	536
Crystal size	0.8 x 0.2 x 0.2 mm
Theta range for data collection	3.58 to 25.99 deg.
Index ranges	-11<=h<=11, -11<=k<=11, -17<=l<=17
Reflections collected / unique	10563 / 1255 [R(int) = 0.0464]
Absorption correction	Scalepack
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1255 / 1 / 131
Goodness-of-fit on F^2	1.126
Final R indices [I>2sigma(I)]	R1 = 0.0507, wR2 = 0.1075
R indices (all data)	R1 = 0.0651, wR2 = 0.1124
Extinction coefficient	0.030(5)
Largest diff. peak and hole	0.232 and -0.196 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for mfg221.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	4595(1)	2874(1)	2691(1)	38(1)
F(1)	6169(3)	565(3)	2304(2)	40(1)
F(2)	6948(3)	4037(3)	1412(2)	49(1)
O(1)	6897(3)	2283(18)	3985(2)	37(3)
N(1)	8830(2)	2500	2979(2)	29(1)
C(1)	7392(4)	2279(12)	3188(2)	25(2)
C(2)	9459(3)	2500	2045(2)	33(1)
C(3)	8447(4)	1958(5)	1306(2)	36(1)
C(4)	6911(3)	2500	1430(2)	33(1)
C(5)	6319(4)	2084(4)	2373(3)	27(1)
C(6)	9896(3)	2500	3747(2)	39(1)
C(7)	3565(3)	2500	1652(2)	34(1)
C(8)	3135(2)	1228(3)	1268(2)	58(1)
C(9)	2226(11)	1499(10)	344(6)	46(3)
C(10)	1816(6)	2123(7)	96(4)	39(3)
C(9A)	2272(12)	973(12)	627(6)	44(2)

Table 3. Bond lengths [A] and angles [deg] for mfg221.

S(1)-C(5)	1.788(4)
S(1)-C(7)	1.797(3)
F(1)-C(5)	1.421(4)
F(2)-C(4)	1.429(3)
O(1)-C(1)	1.232(4)
N(1)-C(1)	1.354(4)
N(1)-C(2)	1.460(3)
N(1)-C(6)	1.467(3)
C(1)-C(5)	1.535(5)
C(2)-C(3)	1.492(4)
C(3)-C(4)	1.492(4)
C(4)-C(5)	1.508(4)
C(7)-C(8)	1.361(3)
C(7)-C(8)#1	1.361(3)
C(7)-S(1)#1	1.797(3)
C(8)-C(9A)	1.232(11)
C(8)-C(9)	1.584(9)
C(9)-C(10)#1	1.380(12)
C(10)-C(9A)	1.377(9)
C(10)-C(9)#1	1.380(12)
C(5)-S(1)-C(7)	99.38(14)
C(2)-N(1)-C(6)	115.8(2)
O(1)-C(1)-N(1)	123.8(4)
O(1)-C(1)-C(5)	118.7(3)
N(1)-C(1)-C(5)	117.4(3)
N(1)-C(2)-C(3)	114.5(2)
C(4)-C(3)-C(2)	112.1(3)
F(2)-C(4)-C(3)	108.2(2)
F(2)-C(4)-C(5)	106.3(2)
C(3)-C(4)-C(5)	110.7(3)
F(1)-C(5)-C(4)	103.1(2)
F(1)-C(5)-C(1)	103.4(5)
C(4)-C(5)-C(1)	115.5(3)
F(1)-C(5)-S(1)	110.0(2)
C(4)-C(5)-S(1)	115.9(2)
C(1)-C(5)-S(1)	108.1(3)
C(8)-C(7)-S(1)	130.82(18)
C(9A)-C(8)-C(7)	130.6(6)
C(7)-C(8)-C(9)	110.5(4)
C(10)#1-C(9)-C(8)	120.4(7)
C(9A)-C(10)-C(9A)#1	114.7(11)
C(8)-C(9A)-C(10)	117.2(11)
C(8)-C(9A)-C(10)#1	104.6(8)

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

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for mfg221. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	25(1)	56(1)	32(1)	-13(1)	2(1)	0(1)
F(1)	38(1)	35(1)	48(1)	0(1)	-12(1)	-5(1)
F(2)	37(1)	50(2)	61(2)	20(1)	6(1)	3(1)
O(1)	36(1)	53(9)	22(1)	1(2)	4(1)	2(2)
N(1)	24(1)	41(2)	22(1)	0	-2(1)	0
C(1)	31(2)	16(7)	26(2)	1(2)	0(1)	-2(2)
C(2)	22(1)	49(2)	29(1)	0	1(1)	0
C(3)	27(2)	58(3)	24(2)	-5(2)	2(2)	1(2)
C(4)	26(1)	47(2)	25(1)	0	0(1)	0
C(5)	24(2)	28(3)	30(2)	-3(1)	0(1)	-4(1)
C(6)	32(2)	55(2)	30(2)	0	-8(1)	0
C(7)	18(1)	53(2)	30(2)	0	4(1)	0
C(8)	29(1)	47(2)	97(2)	-16(2)	-4(1)	5(1)
C(9)	33(4)	68(10)	36(7)	-21(5)	-2(4)	0(5)
C(10)	25(2)	68(10)	24(2)	5(3)	0(2)	4(2)
C(9A)	36(3)	58(6)	37(5)	-4(3)	-5(3)	18(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for mfg221.

	x	y	z	U(eq)
H(2A)	10359	1897	2047	40
H(2B)	9759	3495	1886	40
H(3A)	8820	2267	690	43
H(3B)	8439	893	1318	43
H(4)	6256	2124	926	40
H(6A)	10134	3495	3917	47
H(6B)	10796	2001	3552	47
H(6C)	9469	2004	4285	47
H(8)	3356	308	1522	69
H(9)	1962	710	-41	55
H(10)	1320	2007	-481	47
H(9A)	1935	24	505	52

Table 6. Torsion angles [deg] for mfg221.

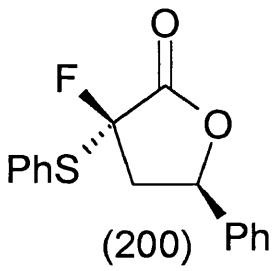
O(1)#1-O(1)-C(1)-C(1)#1	0.000(8)
C(1)#1-O(1)-C(1)-O(1)#1	0.000(9)
O(1)#1-O(1)-C(1)-N(1)	79.4(11)
C(1)#1-O(1)-C(1)-N(1)	79.4(11)
O(1)#1-O(1)-C(1)-C(5)	-97.7(9)
C(1)#1-O(1)-C(1)-C(5)	-97.7(9)
O(1)#1-O(1)-C(1)-C(5)#1	-66.0(8)
C(1)#1-O(1)-C(1)-C(5)#1	-66.0(8)
C(2)-N(1)-C(1)-C(1)#1	-96.3(3)
C(2)#1-N(1)-C(1)-C(1)#1	-96.3(3)
C(6)-N(1)-C(1)-C(1)#1	94.7(3)
C(6)#1-N(1)-C(1)-C(1)#1	94.7(3)
C(1)#1-N(1)-C(1)-O(1)	-83.9(14)
C(2)-N(1)-C(1)-O(1)	179.8(11)
C(2)#1-N(1)-C(1)-O(1)	179.8(11)
C(6)-N(1)-C(1)-O(1)	10.8(16)
C(6)#1-N(1)-C(1)-O(1)	10.8(16)
C(1)#1-N(1)-C(1)-O(1)#1	-63.5(10)
C(2)-N(1)-C(1)-O(1)#1	-159.8(8)
C(2)#1-N(1)-C(1)-O(1)#1	-159.8(8)
C(6)-N(1)-C(1)-O(1)#1	31.2(12)
C(6)#1-N(1)-C(1)-O(1)#1	31.2(12)
C(1)#1-N(1)-C(1)-C(5)	93.2(7)
C(2)-N(1)-C(1)-C(5)	-3.1(11)
C(2)#1-N(1)-C(1)-C(5)	-3.1(11)
C(6)-N(1)-C(1)-C(5)	-172.2(5)
C(6)#1-N(1)-C(1)-C(5)	-172.2(5)
C(1)#1-N(1)-C(1)-C(5)#1	63.1(6)
C(2)-N(1)-C(1)-C(5)#1	-33.1(9)
C(2)#1-N(1)-C(1)-C(5)#1	-33.1(9)
C(6)-N(1)-C(1)-C(5)#1	157.8(3)
C(6)#1-N(1)-C(1)-C(5)#1	157.8(3)
C(1)-N(1)-C(2)-C(3)	-11.0(6)
C(1)#1-N(1)-C(2)-C(3)	-32.5(6)
C(2)#1-N(1)-C(2)-C(3)	0(100)
C(6)-N(1)-C(2)-C(3)	158.25(19)
C(6)#1-N(1)-C(2)-C(3)	158.25(19)
N(1)-C(2)-C(3)-C(4)	41.5(3)
C(4)#1-F(2)-C(4)-C(3)	0(100)
F(1)#1-F(2)-C(4)-C(3)	-126.6(2)
C(3)#1-F(2)-C(4)-C(3)	-0.62(11)
C(5)#1-F(2)-C(4)-C(3)	-119.4(3)
C(4)#1-F(2)-C(4)-C(5)	0(100)
F(1)#1-F(2)-C(4)-C(5)	-7.7(3)
C(3)#1-F(2)-C(4)-C(5)	118.3(3)
C(5)#1-F(2)-C(4)-C(5)	-0.46(8)
C(2)-C(3)-C(4)-F(2)	58.8(4)
C(2)-C(3)-C(4)-C(5)	-57.4(3)
F(2)#1-F(1)-C(5)-C(5)#1	81.3(14)
S(1)#1-F(1)-C(5)-C(5)#1	-52.3(14)
F(2)#1-F(1)-C(5)-C(4)#1	7.3(2)
S(1)#1-F(1)-C(5)-C(4)#1	-126.3(3)
F(2)#1-F(1)-C(5)-C(4)	7.3(2)
S(1)#1-F(1)-C(5)-C(4)	-126.3(3)
F(2)#1-F(1)-C(5)-C(1)	-113.4(3)
S(1)#1-F(1)-C(5)-C(1)	113.0(3)
F(2)#1-F(1)-C(5)-S(1)#1	133.59(19)

F(2)#1-F(1)-C(5)-C(1)#1	-113.9(3)
S(1)#1-F(1)-C(5)-C(1)#1	112.5(3)
F(2)#1-F(1)-C(5)-S(1)	131.4(2)
S(1)#1-F(1)-C(5)-S(1)	-2.23(7)
S(1)#1-F(1)-C(5)-F(2)#1	-133.59(19)
F(2)-C(4)-C(5)-C(5)#1	0.90(16)
C(3)-C(4)-C(5)-C(5)#1	118.2(2)
F(2)-C(4)-C(5)-F(1)	174.1(2)
C(3)-C(4)-C(5)-F(1)	-68.6(3)
F(2)-C(4)-C(5)-C(4)#1	0(100)
C(3)-C(4)-C(5)-C(4)#1	0(100)
F(2)-C(4)-C(5)-C(1)	-73.9(5)
C(3)-C(4)-C(5)-C(1)	43.4(5)
F(2)-C(4)-C(5)-S(1)#1	78.0(3)
C(3)-C(4)-C(5)-S(1)#1	-164.7(3)
F(2)-C(4)-C(5)-C(1)#1	-59.5(5)
C(3)-C(4)-C(5)-C(1)#1	57.9(5)
F(2)-C(4)-C(5)-S(1)	54.0(3)
C(3)-C(4)-C(5)-S(1)	171.3(2)
F(2)-C(4)-C(5)-F(2)#1	-178.2(3)
C(3)-C(4)-C(5)-F(2)#1	-60.9(2)
C(1)#1-C(1)-C(5)-C(5)#1	0.000(4)
O(1)-C(1)-C(5)-C(5)#1	93.6(13)
O(1)#1-C(1)-C(5)-C(5)#1	72.8(11)
N(1)-C(1)-C(5)-C(5)#1	-83.7(8)
C(1)#1-C(1)-C(5)-F(1)	-178.3(2)
O(1)-C(1)-C(5)-F(1)	-84.7(13)
O(1)#1-C(1)-C(5)-F(1)	-105.5(11)
N(1)-C(1)-C(5)-F(1)	98.1(8)
C(5)#1-C(1)-C(5)-F(1)	-178.3(2)
C(1)#1-C(1)-C(5)-C(4)#1	69.9(3)
O(1)-C(1)-C(5)-C(4)#1	163.5(11)
O(1)#1-C(1)-C(5)-C(4)#1	142.7(10)
N(1)-C(1)-C(5)-C(4)#1	-13.7(10)
C(5)#1-C(1)-C(5)-C(4)#1	69.9(3)
C(1)#1-C(1)-C(5)-C(4)	69.9(3)
O(1)-C(1)-C(5)-C(4)	163.5(11)
O(1)#1-C(1)-C(5)-C(4)	142.7(10)
N(1)-C(1)-C(5)-C(4)	-13.7(10)
C(5)#1-C(1)-C(5)-C(4)	69.9(3)
C(1)#1-C(1)-C(5)-S(1)#1	-85.6(3)
O(1)-C(1)-C(5)-S(1)#1	8.0(14)
O(1)#1-C(1)-C(5)-S(1)#1	-12.8(12)
N(1)-C(1)-C(5)-S(1)#1	-169.2(6)
C(5)#1-C(1)-C(5)-S(1)#1	-85.6(3)
O(1)-C(1)-C(5)-C(1)#1	93.6(13)
O(1)#1-C(1)-C(5)-C(1)#1	72.8(11)
N(1)-C(1)-C(5)-C(1)#1	-83.7(8)
C(5)#1-C(1)-C(5)-C(1)#1	0.000(4)
C(1)#1-C(1)-C(5)-S(1)	-61.7(2)
O(1)-C(1)-C(5)-S(1)	31.9(14)
O(1)#1-C(1)-C(5)-S(1)	11.1(12)
N(1)-C(1)-C(5)-S(1)	-145.4(6)
C(5)#1-C(1)-C(5)-S(1)	-61.7(2)
C(1)#1-C(1)-C(5)-F(2)#1	125.7(3)
O(1)-C(1)-C(5)-F(2)#1	-140.7(12)
O(1)#1-C(1)-C(5)-F(2)#1	-161.5(10)
N(1)-C(1)-C(5)-F(2)#1	42.1(10)
C(5)#1-C(1)-C(5)-F(2)#1	125.7(3)
S(1)#1-S(1)-C(5)-C(5)#1	180.0
C(7)-S(1)-C(5)-C(5)#1	106.81(9)

F(1)#1-S(1)-C(5)-C(5)#1	3.92(13)
S(1)#1-S(1)-C(5)-F(1)	5.74(19)
C(5)#1-S(1)-C(5)-F(1)	-174.26(19)
C(7)-S(1)-C(5)-F(1)	-67.4(2)
F(1)#1-S(1)-C(5)-F(1)	-170.3(3)
S(1)#1-S(1)-C(5)-C(4)#1	122.1(2)
C(5)#1-S(1)-C(5)-C(4)#1	-57.9(2)
C(7)-S(1)-C(5)-C(4)#1	48.9(2)
F(1)#1-S(1)-C(5)-C(4)#1	-54.0(2)
S(1)#1-S(1)-C(5)-C(4)	122.1(2)
C(5)#1-S(1)-C(5)-C(4)	-57.9(2)
C(7)-S(1)-C(5)-C(4)	48.9(2)
F(1)#1-S(1)-C(5)-C(4)	-54.0(2)
S(1)#1-S(1)-C(5)-C(1)	-106.5(4)
C(5)#1-S(1)-C(5)-C(1)	73.5(4)
C(7)-S(1)-C(5)-C(1)	-179.7(4)
F(1)#1-S(1)-C(5)-C(1)	77.4(4)
C(5)#1-S(1)-C(5)-S(1)#1	180.0
C(7)-S(1)-C(5)-S(1)#1	-73.19(9)
F(1)#1-S(1)-C(5)-S(1)#1	-176.08(13)
S(1)#1-S(1)-C(5)-C(1)#1	-119.4(4)
C(5)#1-S(1)-C(5)-C(1)#1	60.6(4)
C(7)-S(1)-C(5)-C(1)#1	167.4(4)
F(1)#1-S(1)-C(5)-C(1)#1	64.5(4)
S(1)#1-S(1)-C(5)-F(2)#1	64.1(3)
C(5)#1-S(1)-C(5)-F(2)#1	-115.9(3)
C(7)-S(1)-C(5)-F(2)#1	-9.1(3)
F(1)#1-S(1)-C(5)-F(2)#1	-111.9(3)
S(1)#1-S(1)-C(7)-C(8)	2.1(2)
C(5)#1-S(1)-C(7)-C(8)	90.4(3)
C(5)-S(1)-C(7)-C(8)	64.9(3)
F(1)#1-S(1)-C(7)-C(8)	134.4(3)
S(1)#1-S(1)-C(7)-C(8)#1	178.3(2)
C(5)#1-S(1)-C(7)-C(8)#1	-93.4(2)
C(5)-S(1)-C(7)-C(8)#1	-118.9(2)
F(1)#1-S(1)-C(7)-C(8)#1	-49.4(2)
C(5)#1-S(1)-C(7)-S(1)#1	88.30(14)
C(5)-S(1)-C(7)-S(1)#1	62.82(12)
F(1)#1-S(1)-C(7)-S(1)#1	132.25(8)
C(8)#1-C(7)-C(8)-C(9A)	-6.6(8)
S(1)#1-C(7)-C(8)-C(9A)	170.0(7)
S(1)-C(7)-C(8)-C(9A)	169.2(7)
C(8)#1-C(7)-C(8)-C(9)	3.6(5)
S(1)#1-C(7)-C(8)-C(9)	-179.7(4)
S(1)-C(7)-C(8)-C(9)	179.4(4)
C(9A)-C(8)-C(9)-C(10)#1	151(3)
C(7)-C(8)-C(9)-C(10)#1	-8.0(9)
C(7)-C(8)-C(9A)-C(10)	11.8(13)
C(9)-C(8)-C(9A)-C(10)	-14.7(14)
C(7)-C(8)-C(9A)-C(10)#1	8.7(10)
C(9)-C(8)-C(9A)-C(10)#1	-17.7(16)
C(9)#1-C(10)-C(9A)-C(8)	-5.6(11)
C(9A)#1-C(10)-C(9A)-C(8)	-13.2(15)
C(9)#1-C(10)-C(9A)-C(10)#1	7.5(7)
C(9A)#1-C(10)-C(9A)-C(10)#1	0.000(7)

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

4. 3-Fluoro-4,5-dihydro-*r*-3-phenylsulfanyl-*anti*-5-phenyl-2(3*H*)-furanone (200)



(200)

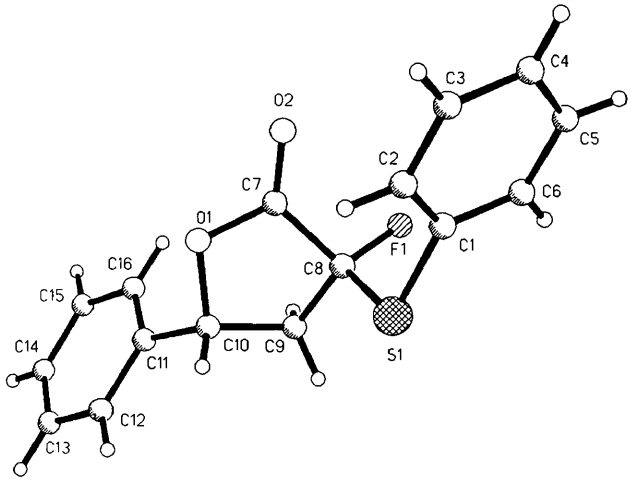


Table 1. Crystal data and structure refinement for 1.

Identification code	str653
Empirical formula	C16 H13 F O2 S
Formula weight	288.32
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	Pc
Unit cell dimensions	a = 6.2010(10) A alpha = 90 deg. b = 7.933(2) A beta = 92.11(3) deg. c = 14.948(3) A gamma = 90 deg.
Volume	734.8(3) A^3
Z	2
Density (calculated)	1.303 Mg/m^3
Absorption coefficient	0.229 mm^-1
F(000)	300
Crystal size	0.70 x 0.15 x 0.12 mm
Theta range for data collection	2.57 to 25.06 deg.
Index ranges	0<=h<=7, 0<=k<=9, -17<=l<=17

Reflections collected	1367
Independent reflections	1367 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1356 / 2 / 181
Goodness-of-fit on F^2	1.107
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1313
R indices (all data)	R1 = 0.0931, wR2 = 0.1842
Largest diff. peak and hole	0.331 and -0.298 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	6983(3)	488(3)	8854(2)	65(1)
F(1)	4617(12)	798(7)	7343(3)	89(2)
O(1)	5041(11)	-3350(8)	8042(4)	71(2)
O(2)	2223(12)	-1641(11)	8317(6)	102(3)
C(1)	4743(15)	1364(9)	9398(5)	55(2)
C(2)	3809(17)	537(11)	10119(5)	63(2)
C(3)	2046(18)	1267(13)	10545(7)	75(3)
C(4)	1180(18)	2813(14)	10259(7)	75(3)
C(5)	2169(20)	3656(13)	9544(6)	79(3)
C(6)	3909(19)	2934(12)	9121(6)	73(3)
C(7)	4076(16)	-1803(13)	8111(6)	65(2)
C(8)	5715(14)	-433(10)	7855(5)	53(2)
C(9)	7377(16)	-1407(10)	7324(6)	60(2)
C(10)	7331(15)	-3185(10)	7725(6)	54(2)
C(11)	7748(14)	-4594(10)	7073(5)	52(2)
C(12)	9680(17)	-5509(12)	7181(6)	67(2)
C(13)	10169(21)	-6787(13)	6535(7)	83(3)
C(14)	8770(19)	-7082(12)	5822(8)	78(3)
C(15)	6852(20)	-6195(13)	5712(7)	81(3)
C(16)	6346(16)	-4932(12)	6339(7)	70(3)

Table 3. Bond lengths [A] and angles [deg] for 1.

S(1)-C(1)	1.777(9)
S(1)-C(8)	1.816(8)
F(1)-C(8)	1.401(9)
O(1)-C(7)	1.371(11)
O(1)-C(10)	1.519(11)
O(2)-C(7)	1.208(11)
C(1)-C(6)	1.404(12)
C(1)-C(2)	1.405(11)
C(2)-C(3)	1.409(13)
C(3)-C(4)	1.399(14)
C(4)-C(5)	1.42(2)
C(5)-C(6)	1.39(2)
C(7)-C(8)	1.546(13)
C(8)-C(9)	1.533(11)
C(9)-C(10)	1.534(11)
C(10)-C(11)	1.512(12)
C(11)-C(16)	1.400(12)
C(11)-C(12)	1.405(12)
C(12)-C(13)	1.441(14)
C(13)-C(14)	1.369(14)
C(14)-C(15)	1.39(2)
C(15)-C(16)	1.415(14)
C(1)-S(1)-C(8)	102.2(4)
C(7)-O(1)-C(10)	111.2(7)
C(6)-C(1)-C(2)	118.8(9)
C(6)-C(1)-S(1)	119.8(7)
C(2)-C(1)-S(1)	121.3(7)
C(1)-C(2)-C(3)	120.2(9)
C(4)-C(3)-C(2)	121.2(10)
C(3)-C(4)-C(5)	118.1(10)
C(6)-C(5)-C(4)	120.7(9)
C(5)-C(6)-C(1)	120.9(9)
O(2)-C(7)-O(1)	122.4(10)
O(2)-C(7)-C(8)	129.0(10)
O(1)-C(7)-C(8)	108.6(7)
F(1)-C(8)-C(9)	113.1(6)
F(1)-C(8)-C(7)	108.3(7)
C(9)-C(8)-C(7)	103.6(7)
F(1)-C(8)-S(1)	110.8(5)
C(9)-C(8)-S(1)	110.5(6)
C(7)-C(8)-S(1)	110.4(5)
C(10)-C(9)-C(8)	103.8(7)
C(11)-C(10)-O(1)	108.8(7)
C(11)-C(10)-C(9)	114.9(7)
O(1)-C(10)-C(9)	103.4(7)
C(16)-C(11)-C(12)	119.6(8)
C(16)-C(11)-C(10)	122.1(8)
C(12)-C(11)-C(10)	118.2(8)
C(11)-C(12)-C(13)	119.1(9)
C(14)-C(13)-C(12)	120.0(10)
C(13)-C(14)-C(15)	121.5(10)
C(14)-C(15)-C(16)	119.4(10)
C(11)-C(16)-C(15)	120.5(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	70(1)	68(1)	55(1)	-9(1)	-1(1)	-5(1)
F(1)	138(6)	72(3)	55(3)	-1(3)	-13(3)	36(4)
O(1)	82(5)	57(4)	75(4)	-3(3)	28(4)	-9(3)
O(2)	57(4)	121(7)	129(7)	-55(5)	23(4)	-15(4)
C(1)	78(6)	47(4)	39(4)	-3(3)	7(4)	-8(4)
C(2)	87(7)	56(5)	48(4)	5(4)	8(4)	-2(5)
C(3)	95(8)	66(6)	65(6)	0(5)	19(5)	-6(6)
C(4)	78(7)	83(7)	64(6)	-17(5)	2(5)	13(6)
C(5)	110(9)	62(6)	65(6)	-8(5)	-5(6)	30(6)
C(6)	116(9)	52(5)	52(5)	7(4)	5(6)	5(6)
C(7)	58(5)	76(6)	61(5)	-17(5)	-2(4)	-3(5)
C(8)	62(5)	51(4)	45(4)	2(3)	-2(4)	13(4)
C(9)	74(6)	47(4)	58(5)	-4(4)	14(5)	4(4)
C(10)	58(5)	49(4)	54(5)	1(4)	5(4)	4(4)
C(11)	58(5)	51(4)	49(4)	7(3)	5(4)	0(4)
C(12)	76(7)	61(5)	65(5)	-2(4)	-10(5)	18(5)
C(13)	101(9)	59(6)	89(7)	-5(5)	-7(7)	21(6)
C(14)	97(8)	53(5)	84(7)	-12(5)	-3(6)	10(6)
C(15)	106(9)	68(6)	68(6)	-6(5)	-5(6)	-13(6)
C(16)	77(7)	57(5)	77(6)	-2(4)	-6(6)	1(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

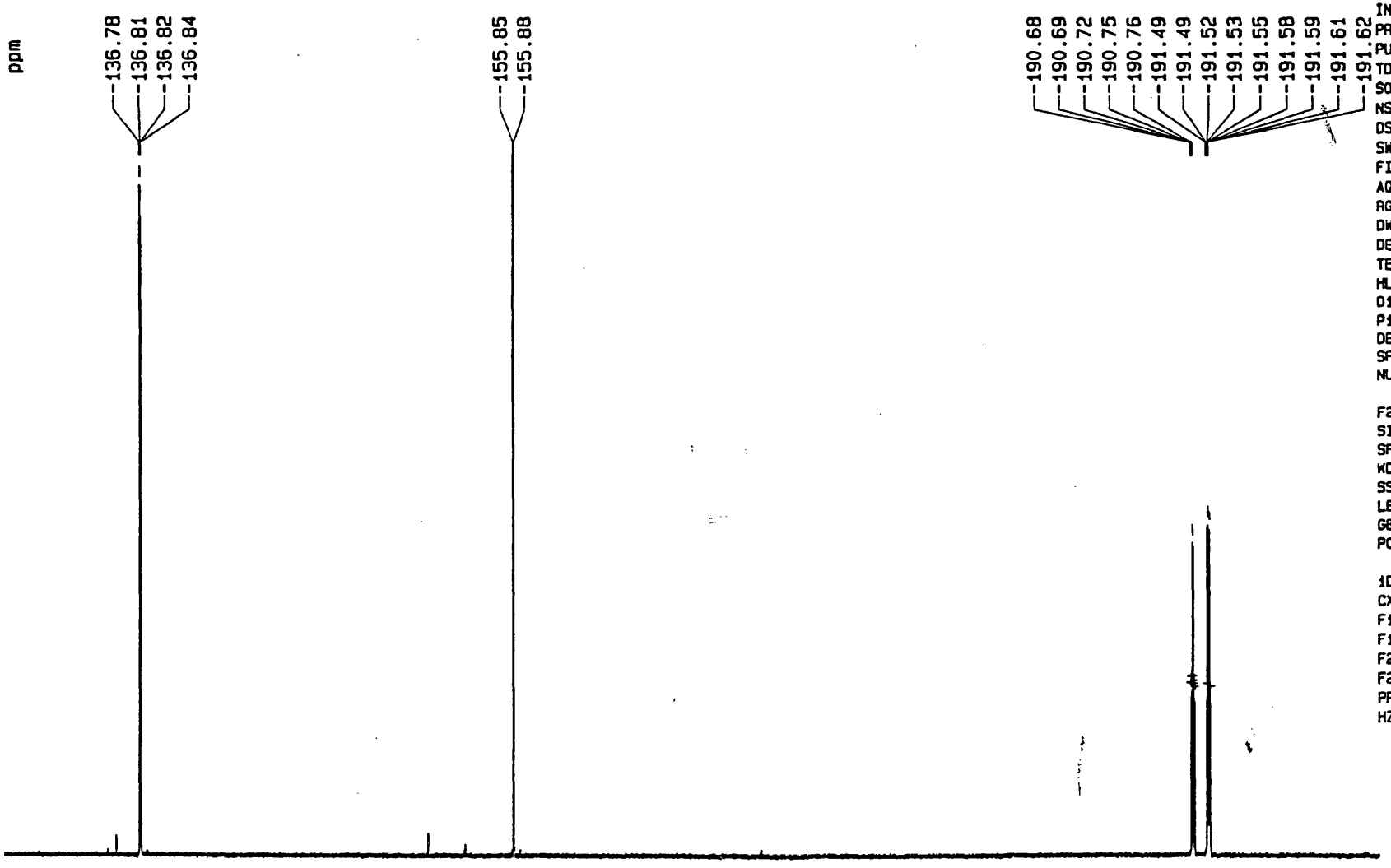
	x	y	z	U(eq)
H(2A)	4378(17)	-528(11)	10322(5)	80
H(3A)	1405(18)	683(13)	11030(7)	80
H(4A)	-41(18)	3296(14)	10541(7)	80
H(5A)	1647(20)	4741(13)	9351(6)	80
H(6A)	4550(19)	3506(12)	8631(6)	80
H(9A)	8786(16)	-914(10)	7399(6)	80
H(9B)	6972(16)	-1430(10)	6698(6)	80
H(10A)	8337(15)	-3257(10)	8227(6)	80
H(12A)	10656(17)	-5290(12)	7681(6)	80
H(13A)	11479(21)	-7426(13)	6601(7)	80
H(14A)	9132(19)	-7928(12)	5394(8)	80
H(15A)	5875(20)	-6436(13)	5215(7)	80
H(16A)	5037(16)	-4292(12)	6264(7)	80

Appendix 2. ^{19}F NOE Data

$J^{HF} = 23 Hz$

$J^{H-} = 17 Hz$

219 Z/E in CDCl3 ; 19F spectrum



Current Data Parameters

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PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zg
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SOLVENT	CDCl3
NS	8
DS	4
SWH	90907.445 Hz
FIDRES	0.693569 Hz
AQ	0.7209070 sec
RG	2048
DW	5.500 usec
DE	7.86 usec
TE	300.0 K
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O1	12.00000000 sec
P1	3.00 usec
DE	7.86 usec
SFO1	564.5973738 MHz
NUCLEUS	19F

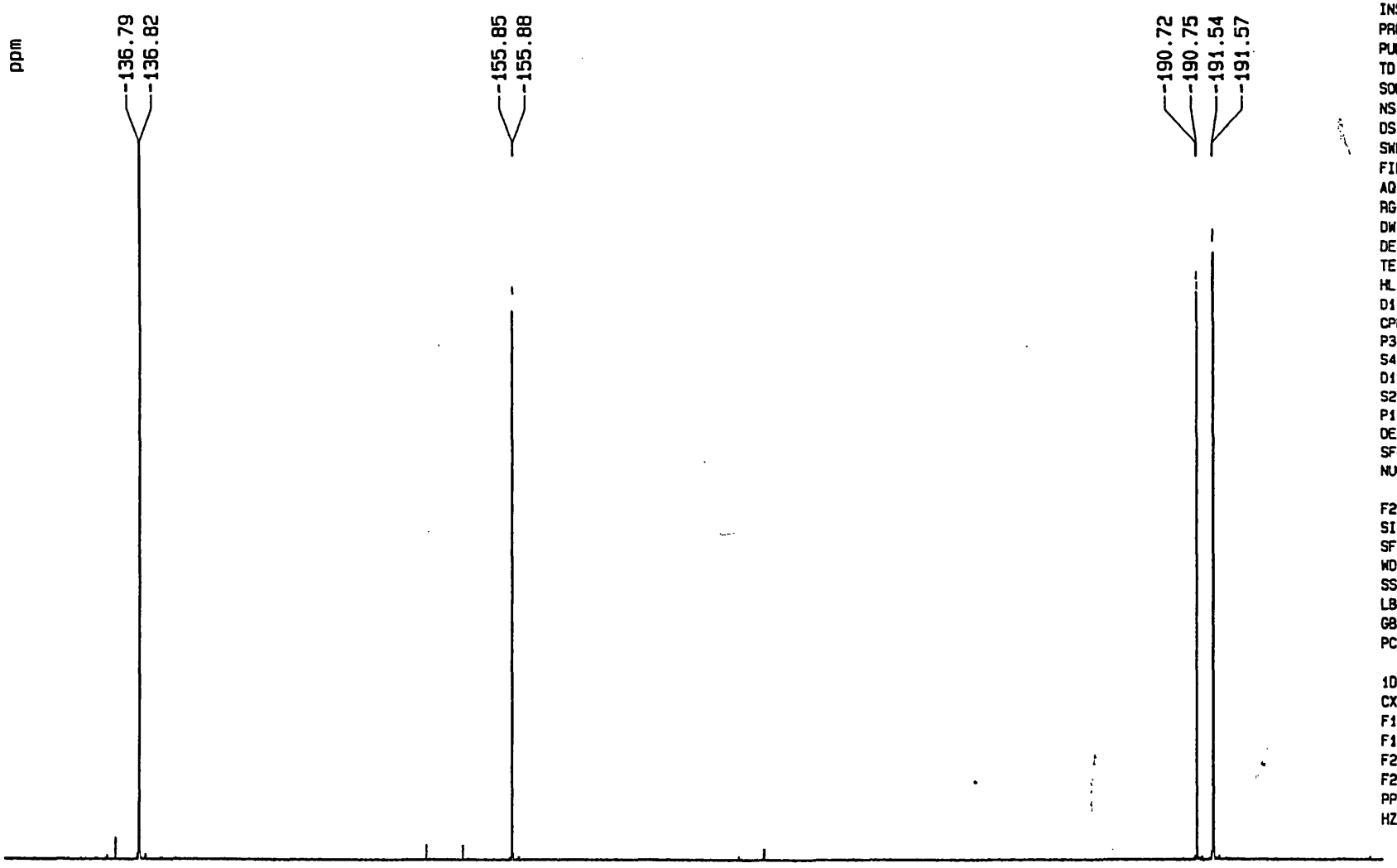
F2 - Processing parameters

SI	131072
SF	564.6867300 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	0.80

1D NMR plot parameters

CX	22.00 cm
F1P	-130.000 ppm
F1	-73409.27 Hz
F2P	-200.000 ppm
F2	-112937.34 Hz
PPMCM	3.18182 ppm/cm
HZCM	1796.73047 Hz/cm

219 Z/E in CDCl3 ; 19F spectrum with 1H decoupling



Current Data Parameters

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PROCNO	1

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TD	131072
SOLVENT	CDCl3
NS	8
DS	4
SWH	90907.445 Hz
FIDRES	0.693569 Hz
AQ	0.7209070 sec
RG	2048
DW	5.500 usec
DE	7.86 usec
TE	300.0 K
HL1	19 dB
D1	12.00000000 sec
CPDPRG	waltz16
P31	112.50 usec
S4	25 dB
D11	0.03000000 sec
S2	19 dB
P1	3.00 usec
DE	7.86 usec
SFO1	564.5973738 MHz
NUCLEUS	19F

F2 - Processing parameters

SI	131072
SF	564.6867300 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	0.80

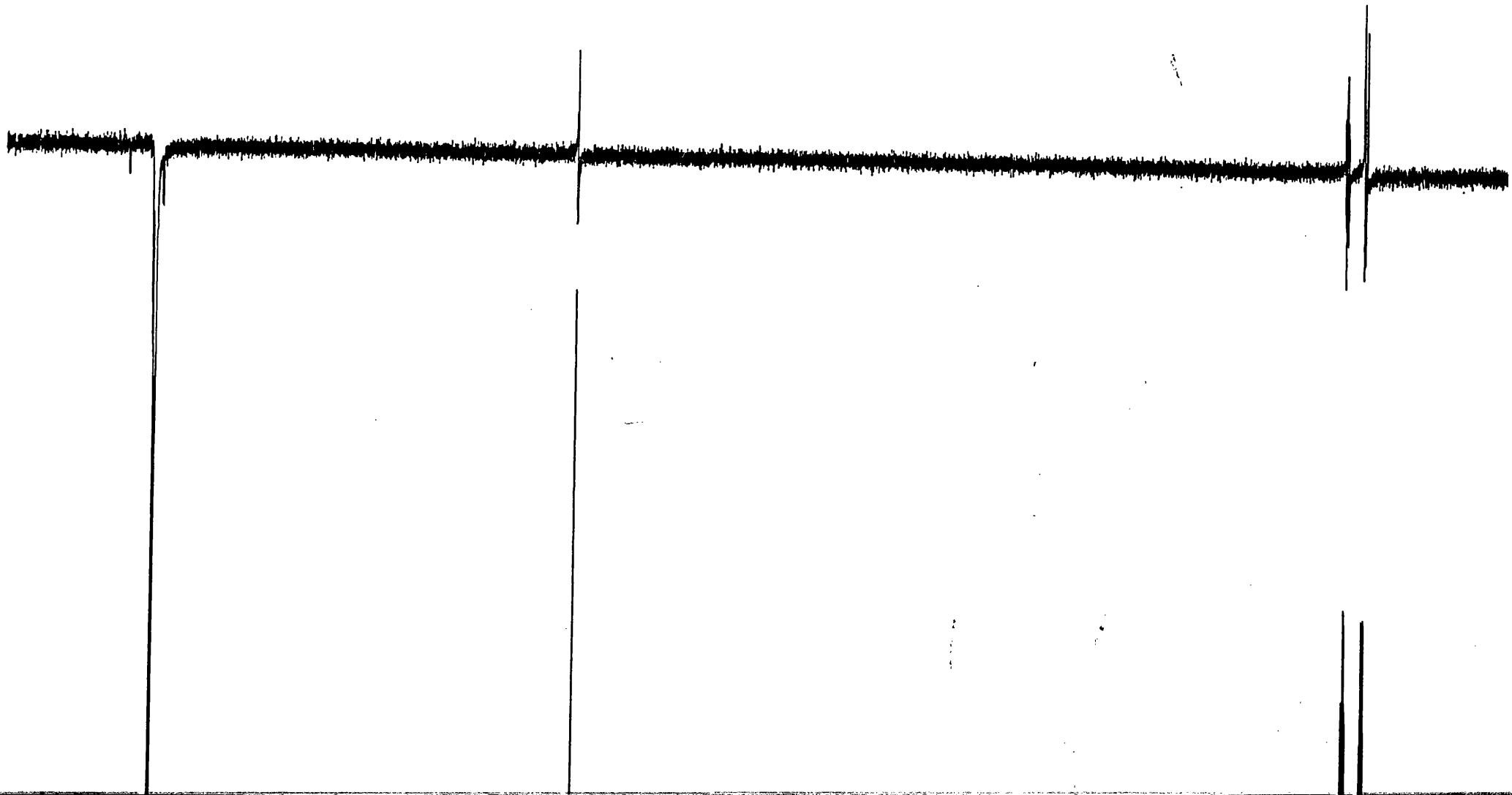
1D NMR plot parameters

CX	22.00 cm
F1P	-130.000 ppm
F1	-73409.27 Hz
F2P	-200.000 ppm
F2	-112937.34 Hz
PPMCM	3.18182 ppm/cm
HZCM	1796.73047 Hz/cm

219 Z/E in $CDCl_3$

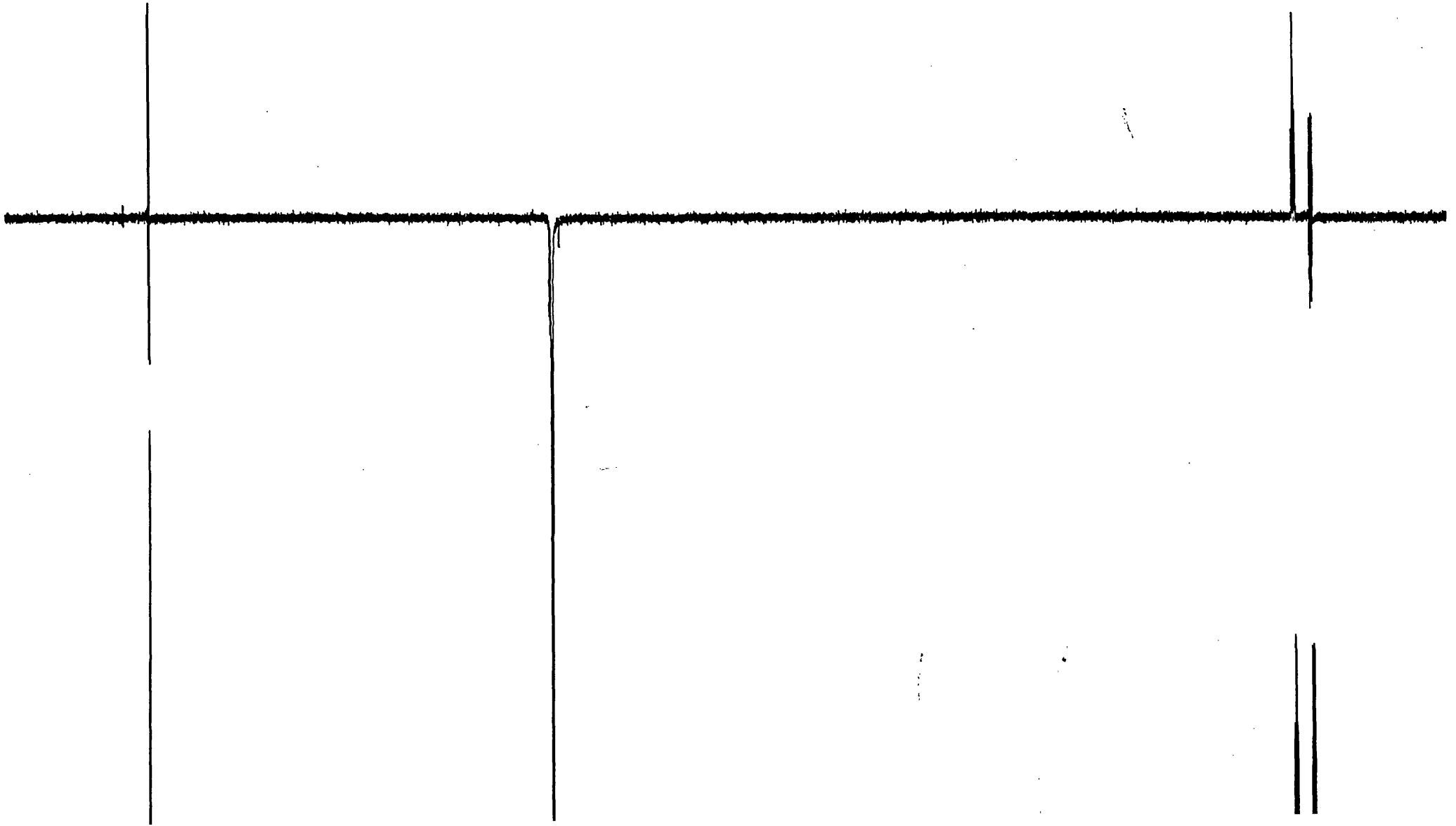
19F nOe difference spectrum : irradiated at -136.8ppm

245



219 Z/E in $CDCl_3$

19F nOe difference spectrum ; irradiated at -155.87ppm



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Corrigenda