New Methods for Nucleophilic Fluorination

A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2008 until October 2011, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

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Abstract

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This thesis is concerned with the development of new methods for nucleophilic fluorination using boron fluorides and tetrafluoroborates as sources of nucleophilic fluorine.

Chapter 1 discusses the history and importance of the field of organofluorine chemistry and outlines some of the principle motivations for the site-selective fluorination of organic molecules. Some of the most commonly used methods of nucleophilic fluorination are briefly surveyed, with an emphasis on the formation of fluorinated stereogenic centres. Literature precedent for the use of tetrafluoroborates and boron trifluoride as nucleophilic fluorinating agents is also presented.

Chapter 2 describes the development of a highly regio- and stereoselective S_Ni-type ring-opening fluorination of *trans*-β-substituted aryl epoxides using BF_3•OEt_2 as a nucleophilic fluorinating agent. This robust and scalable protocol grants efficient access to a variety of functionalised benzylic fluoride building blocks, and provides a solution to the problem of stereocontrol in the synthesis of this class of compounds. To highlight the utility of the resultant *syn*-fluorohydrins in the synthesis of stereodefined β-fluoro β-aryl amines, their elaboration to a range of aryl-substituted β-fluoroamphetamines is demonstrated.

Chapter 3 introduces the concept of tuning the reactivity of BF_3 by replacing one or two of the fluoro ligands on boron for electron-donating alkoxy group(s). On this basis, pinacolatoboron fluoride (pinBF) [which may be prepared *in situ* by pre-mixing BF_3•OEt_2 and bis(*O*-trimethylsilyl)pinacol] is identified as a superior reagent to BF_3•OEt_2 for the ring-opening fluorination of *trans*-β-substituted aryl epoxides bearing electron-rich aryl groups.

Chapter 4 details a highly regioselective and stereospecific S_N2-type ring-opening fluorination of 2,3- and 3,4-epoxy amines using HBF_4•OEt_2 as a nucleophilic fluorine source. The reactions are both operationally simple to perform and readily scalable, and proceed to completion within 5 min at ambient temperature, providing a highly practical and economical route to stereodefined amino fluorohydrins. To highlight the synthetic utility of this reaction in the preparation of pharmaceutically-important β-fluoro amines, a concise *de novo* asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol is performed.

Chapter 5 chronicles the successful development of a protocol for the direct hydroxyfluorination of allylic amines to the corresponding amino fluorohydrins, using *m*-CPBA as the oxidant and HBF_4•OEt_2 in a dual role as both the Brønsted acid *N*-protecting agent and nucleophilic fluorine source. With chiral allylic amines which are conformationally biased or constrained, the diastereofacial selectivity of the reaction can be controlled by altering the concentration of HBF_4•OEt_2 employed in the reaction, allowing for a diastereodivergent hydroxyfluorination process. The synthetic utility of this methodology is demonstrated *via* its application to the diastereodivergent synthesis of 4-deoxy-4-fluoro-L-*xylo*-phytosphingosine and 4-deoxy-4-fluoro-L-*lyxo*-phytosphingosine, each in 5 steps from Garner's aldehyde.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in chapters 2, 3, 4 and 5.

First and foremost I would like to express my gratitude to Prof Steve Davies for granting me the privilege of working in his laboratories for the last four years, for his valuable supervision and for his generous funding throughout.

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Contents

Abbreviations

The following abbreviations are used throughout this thesis:

Å	Angstroms
Ac	Acetyl
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
$[\alpha]_D$	Specific rotation
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	*n*-Butyl
^{t}Bu	*t*-Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
Cbz	Carboxylbenzyl
CETP	Cholesteryl ester transfer protein
CI	Chemical ionisation
cm^{-1}	Wavenumber
CNS	Central nervous system
conc	Concentrated
conv	Conversion
COSY	Correlation spectroscopy
Cy	Cyclohexyl
d	Doublet
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DIBAL-H	Di(*iso*-butyl)aluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
δ_F	Fluorine (^{19}F) NMR chemical shift
δ_B	Boron (^{11}B) NMR chemical shift
E2	Elimination, bimolecular
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
emim	1-Ethyl-3-methylimidazolium
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation

g	Grams
GC	Gas chromatography
GCT	Gas chromatograph/time-of-flight
gem	Geminal
h	Hours
Hal	Halogen
HFIP	1,1,1,3,3,3-Hexafluoropropan-2-ol
HMBC	Heteronuclear multiple-bond correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple-quantum correlation
HOESY	Heteronuclear Overhauser effect spectroscopy
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
Hz	Hertz
i	Ipso
i	Iso
IBX	2-Iodoxybenzoic acid
J	Joules
J	Coupling constant
k	Rate constant
K_a	Acid dissociation constant
KHMDS	Potassium hexamethyldisilazide
lit.	Literature
L	Litres
LDA	Lithium di(*iso*-propyl)amide
LUMO	Lowest occupied molecular orbital
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
Mes	Mesityl
mmHg	Millimetres of mercury
m-CBA	*m*-Chlorobenzoic acid
m-CPBA	*m*-Chloroperoxybenzoic acid
MDMA	3,4-Methylenedioxymethamphetamine
Me	Methyl
min	Minutes
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MW	Microwave
m/z	Mass to charge ratio
μ	Micro
n	Normal
NaHMDS	Sodium hexamethyldisilazide
NMDA	*N*-Methyl-D-aspartate
NMP	*N*-Methylpyrrolidine
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	Ortho
p	Para
PET	Positron emission topography
Ph	Phenyl

pin	Pinacolato
PKC	Protein kinase C
PNS	Peripheral nervous system
PPHF	Polypyridinium hydrogen fluoride (Olah's reagent)
ppm	Parts per million
Pr	Propyl
^{i}Pr	*i*-Propyl
Py	Pyridine
q	Quartet
quant	Quantitative
quin	Quintet
R	Unspecified organic group
ref.	Reference
R_f	Retention factor
rt	Room temperature
s	Singlet
SAR	Structure-activity relationship
satd	Saturated
SK	Sphingosine kinase
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
S_Ni	Substitution, nucleophilic, internal
spt	Septet
sxt	Sextet
t	Tertiary
t	Triplet
T	Temperature
$t_{½}$	Half life
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBME	*tert*-Butylmethyl ether
tert	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
ToF	Time-of-flight
Tol	Tolyl
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl
UV	Ultraviolet
V	Volume
vic	Vicinal
v/v	Volume to volume ratio
ν_{max}	Infra red absorption
wrt	With respect to
w/v	Weight to volume ratio (g per 100 mL)
w/w	Mass to mass ratio
X	Unspecified substitutent

Chapter 1: Introduction

This chapter gives a brief overview of organofluorine chemistry and surveys some existing methods for nucleophilic fluorination. Literature precedent for the use of tetrafluoroborates and boron trifluoride as nucleophilic fluorinating agents is also examined.

1.1. The History and Importance of Organofluorine Chemistry

Fluorine is the 13th most abundant element in the Earth's crust and yet, despite its relatively high profusion, organofluorine compounds are scarce in nature, with only 21 fluorinated secondary metabolites identified to date, 8 of which are ω-fluorinated fatty acids isolated from the plant *Dichapetalum toxicarium* (Figure 1).[1] The situation should be contrasted with over 4000 known naturally-occurring organohalogens containing chlorine, bromine and iodine.[2] This discrepancy may be due to a variety of factors, such as the extremely low water solubility of CaF_2 (the most abundant form of natural fluorine), the very low nucleophilicity of the hydrated fluoride ion, and the extremely high reduction potential of fluorine (E^0 = +3.06 V and +2.87 V in acidic and basic aqueous media respectively[3]). In a landmark breakthrough in the field of natural organofluorine compounds, O'Hagan and co-workers reported in 2002 the discovery of the first fluorinating enzyme, isolated from *Streptomyces cattleya*, which can catalyse the formation of 5′-fluoro-5′-deoxyadenosine from *S*-adenosyl-L-methionine and fluoride ion.[4]

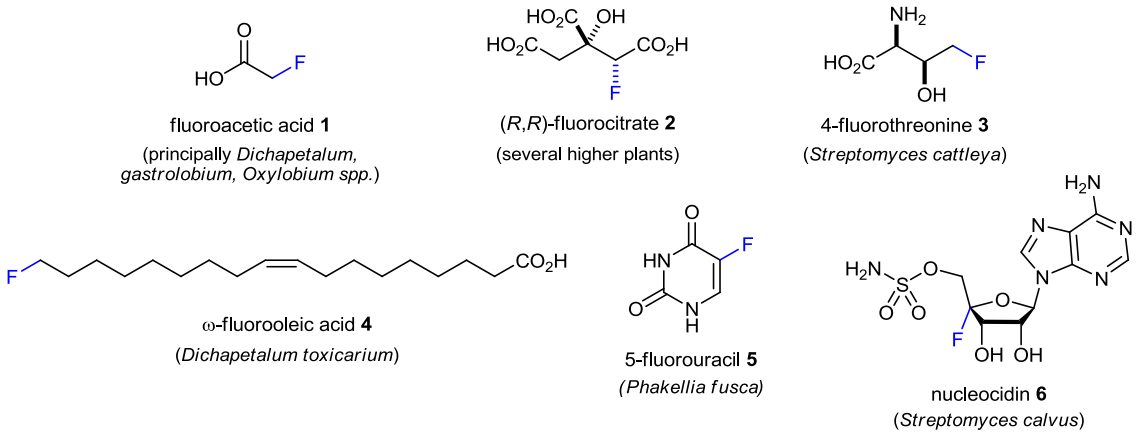


Figure 1. Some fluorinated secondary metabolites and their respective natural sources.

Although elemental fluorine was first isolated in 1886 by Nobel prize-winning French chemist Henri Moissan,[5] it was not until the 1930s that fluorine compounds first began to find commercial applications, with the introduction of the chlorofluorocarbon refrigerant Freon® 12 (CF_2Cl_2) **7** in 1930, followed by the discovery of the "non-stick" fluoropolymer Teflon® (polytetrafluoroethylene) **8** in 1938.[6] The infamous Manhattan Project, initiated in 1941, triggered a tremendous surge in the study of fluorinated materials, with elemental fluorine being produced on a large scale for use in ^{235}U enrichment facilities. In the 1950s and 60s, more civilian applications of fluorinated compounds came to the fore, with the pioneering development in

1954 by Fried and Sabo of the first fluorinated pharmaceutical, fludrocortisone **9**, a treatment for adrenal insufficiency (Figure 2).[7]

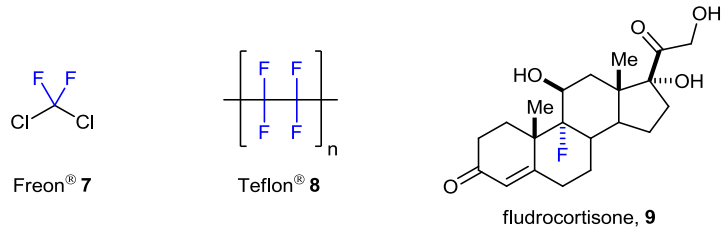


Figure 2. Early examples of organofluorine compounds with commercial applications.

The field of organofluorine chemistry[8,9] has since undergone explosive growth and, on account of the dramatic changes that fluorination can confer on physical, chemical or biological properties,[10] fluorine substitution is becoming increasingly popular in drugs,[11] agrochemicals[12] and organic materials.[8c,13] As testiment to the frequent benefits of fluorination on biologically-active compounds,[14] around 30-40% of agrochemicals and 20% of pharmaceuticals on the market in 2006 contained at least one fluorine atom,[15] as did 10 of the leading 30 blockbuster drugs by sale in the USA in 2008.[11j] For example, drug candidates bearing fluorine at a stereogenic centre include vitamin D_3 analogue Ro 26-9228 **10** for the treatment of benign prostate growth and the prevention of kidney transplant rejection,[16] PSI-6130 **11** for the treatment of hepatitis C,[17] and antibiotic DQ-113 **12** for the treatment of Gram-positive bacterial infections[18] (Figure 3).

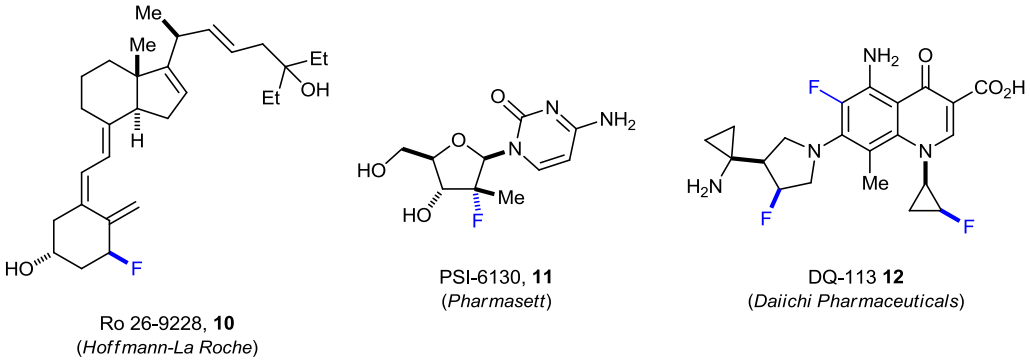


Figure 3. Drugs in development which contain fluorine at a stereogenic centre.

As fluorine is the most electronegative of all the elements (χ = 3.98 on the updated Pauling scale[19]), the powerful negative inductive (−*I*) effect of fluorine can have a dramatic impact on the acidity or basicity of neighbouring functional groups,[8,10,20] a fact routinely exploited to enhance the bioavailability[21] or target binding affinity of drugs.[11] Bioactive amines (pK_{aH} ~10), for example, are usually >99% protonated at physiological pH (7.4), and this can result in poor membrane permeation and low bioavailability. However, β-fluorination can reduce the pK_{aH} of the amino group by ~1.7 units for each additional fluorine atom, such that 2,2,2-trifluoroethylamine is only 2.0% protonated at physiological pH (7.4) (Figure 4).

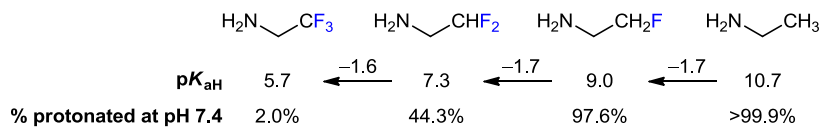


Figure 4. Effect of β-fluorination on amine basicity.

The stability of drugs towards chemical degradation *in vivo*, primarily due to rapid oxidative metabolism by cytochrome P450 enzymes, is another of the key contributing factors affecting bioavailability. In this respect, the C−F bond, which is the strongest known single bond to carbon (441 kJ mol^{-1}), has been used to suppress undesired metabolic pathways, either by direct substitution at the reactive site (a "blocking effect") or by electronic pertubation of neighbouring functionality: for instance the decreasing of amine basicity or the siphoning off of electron-density from oxidisable π-systems. For example, a fluorinated analogue **13** of the antineoplastic agent docetaxel has been shown to be markedly more resilient to oxidative metabolism *in vitro*, due to blocking of the metabolically-labile *para* position of the C(3′)-phenyl ring (Figure 5).[22]

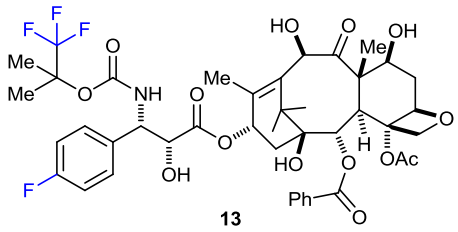


Figure 5. Fluorinated analogue of the antineoplastic agent docetaxel with improved metabolic stability.

As the van der Waals radius of fluorine (1.47 Å) is the next smallest after hydrogen (1.2 Å), fluorine can often successfully "mimic" hydrogen in bioactive molecules. Despite the steric resemblance, however, the high electronegativity of fluorine (3.98) relative to hydrogen (2.20) renders both the polarity and reactivity of the C−F bond orthogonal to that of the C−H bond – a fact which has been exploited in the design of enzyme inhibitors such as 5-fluorouracil **5**, an antineoplastic agent and one of the earliest fluorinated drugs.[23] This mimic effect has also been used in the design of (*S*)-fluorothalidomide **14** as a non-racemisable analogue of thalidomide (Figure 6).[24] (*S*)-**14** was found to be more active than both the (*R*)-isomer and racemic thalidomide in lipopolysaccharide-induced tumour necrosis factor-α production enhancement produced from human peripheral blood lymphocytes cultivated *in vitro*.

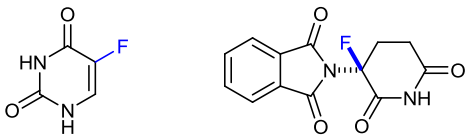


Figure 6. Fluorine as a mimic of hydrogen in bioactive compounds.

The isosteric replacement of hydroxyl groups with fluorine atoms is also a valuable tool for probing the relative importance of hydrogen bonding *versus* bond polarity in biological systems. For example, using

fluorine substitution, the role of the 4-hydroxyl function within hydroxyproline residues (highlighted in **orange**) in stabilising the triple helix structure of collagen has been shown to be due to conformational biasing (mediated by the C−O bond polarity) and *not* due to the formation of additional hydrogen bonds. Specifically, replacement of 4-hydroxyproline residues with 4-fluoroproline residues (and thus removal of any hydrogen bonding capacity) led to an *increase* in triple helix stability, which was attributed to an increased preference for the *trans* amide bond (a dipole effect) and the C(γ)-*exo* pyrrolidine ring pucker (the *gauche* stereoelectronic effect) (Figure 7).[25]

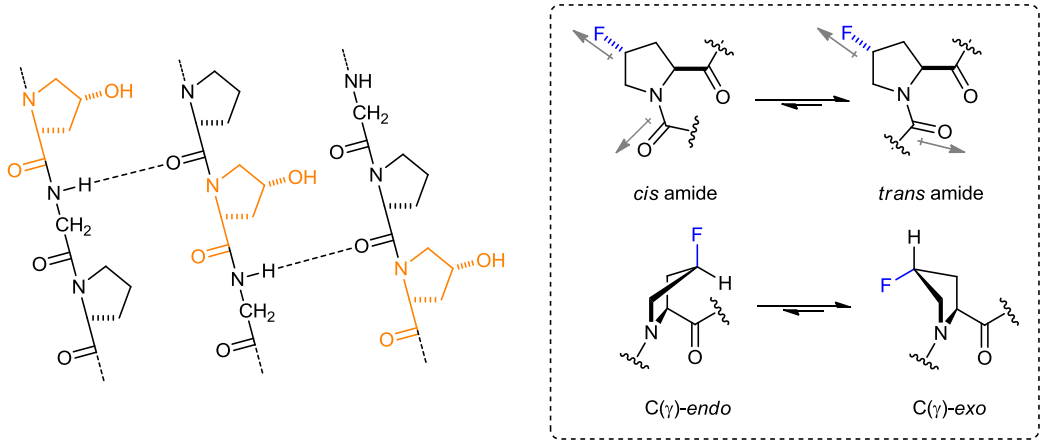
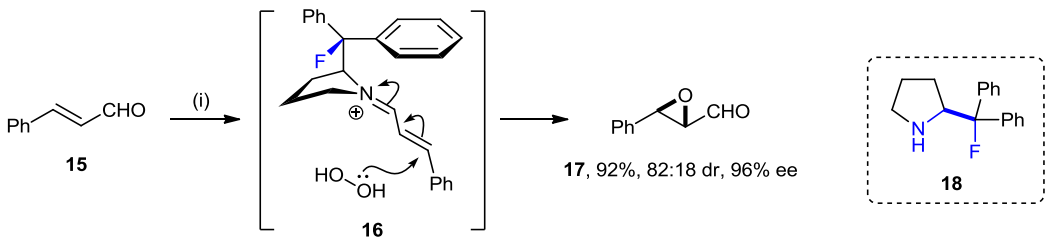


Figure 7. Structure of an arbitrary portion of the collagen triple helix structure (4-hydroxyproline residues highlighted in **orange**) (left) and the conformational preferences of the 4-fluoroproline residue (right).

The placement of fluorine at stereogenic centres is becoming a popular tool for biasing the conformation of organic compounds,[26] typically *via* the fluorine *gauche* effect.[27] For example, Gilmour *et al.* have recently exploited this effect in asymmetric organocatalysis, employing chiral non-racemic β-fluoro amine catalyst **18** in the epoxidation of enals such as **15** (Scheme 1).[28] The authors reasoned that a β-fluoro ammonium interaction[29] would cause the iminium ion intermediate to adopt a *gauche* conformation **16**, enhancing torsional rigidity and assisting asymmetric induction, as well as lowering the LUMO of the iminium ion by inductive withdrawal. Fluorine substitution in other organocatalyst frameworks has also been reported to lead to improved selectivities,[30] although the origin of the enhancement is not always well understood.



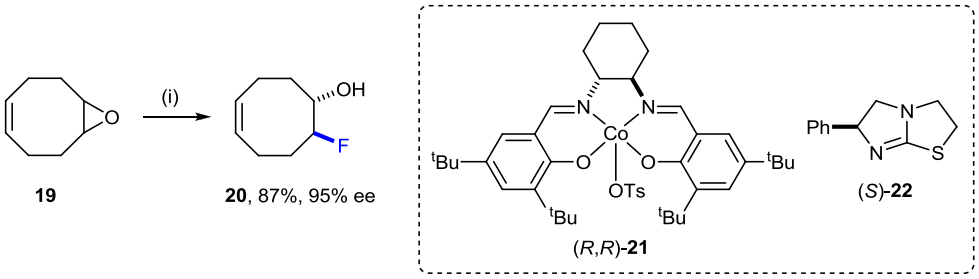
Scheme 1. *Reagents and conditions:* (i) **18** (10 mol%), H_2O_2 (1.3 equiv), $CHCl_3$, rt, 3 h.

Beyond the role of fluorine as a modifier of molecular properties, the excellent NMR profile of the ^{19}F nucleus has made it a popular choice with chemical biologists for the interrogation of macromolecular architectures or binding interactions, as well as the study of metabolic processes.[31] Another area of

organofluorine chemistry of growing importance is the use of the short-lived ($t_{½}$ = 109.7 min) isotope ^{18}F in positron emission topography (PET), an imaging technique used in clinical diagnosis.[32]

1.2. Existing Methods for Fluorination

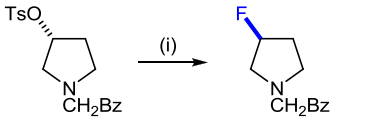
The utility of nucleophilic and electrophilic fluorine sources in the formation of C−F bonds has previously been reviewed,[33] as have methods for the asymmetric synthesis of fluorinated stereogenic centres.[34] Thus, the following discussion will be limited to selected nucleophilic fluorinating agents, including: (a) alkali metal fluorides; (b) tetra-*n*-butylammonium fluoride; (c) amine-HF reagents; (d) fluorosulfuranes and fluorosulfinium salts; (e) tetrafluoroborates and boron trifluoride. Emphasis will be placed on stereoselective transformations, such as the ring-opening fluorination of epoxides to furnish vicinal fluorohydrins.[35] With regard the latter method, it is pertinent to note the recent contribution from Doyle and co-workers of the first catalytic, enantioselective ring-opening fluorination of epoxides – a landmark achievement which also stands as the first example of a catalytic, enantioselective nucleophilic fluorination.[36] With the ingenious use of a PhCOF/HFIP reagent combination as a latent HF source, the highly enantioselective desymmetrisation of epoxides (e.g. **19**) to fluorohydrins (e.g. **20**) could be accomplished *via* a cooperative dual catalysis[37] strategy using a chiral Co(III)-salen catalyst (*R*,*R*)-**21** in conjuction with a chiral isothiourea co-catalyst (*S*)-**22** (Scheme 2). Kinetic resolution of terminal epoxides with selectivity factors >300 also proved possible using this technology. Detailed mechanistic studies revealed that two molecules of the Co(III)-salen catalyst (*R*,*R*)-**21** are likely involved in the turnover-limiting step, and this has spurred the development of a second generation, dimeric Co(III)-salen catalyst which is both more active and more enantioselective.[38]



Scheme 2. *Reagents and conditions:* (i) (*R*,*R*)-**21** (10 mol%), **22** (8 mol%), PhCOF (2 equiv), HFIP (4 equiv), TBME, rt, 72 h.

1.2.1. Alkali Metal Fluorides

Alkali metal fluorides, particularly KF, have classically been used for the nucleophilic displacement of secondary halides and sulfonates, and are especially attractive from a cost and handling perspective. For example, enantiopure (*S*)-3-fluoropyrroline **24** has been obtained from (*R*)-3-(tosyloxy)pyrrolidine **23** in 73% yield by displacement with KF (Scheme 3).[39] However, a major drawback is the frequent requirement for high reaction temperatures (often >100 °C) in high-boiling, polar organic solvents (e.g. DMF, DMSO, sulfolane, NMP, ethylene glycol) to overcome the limited solubility and low reactivity of these fluoride salts.



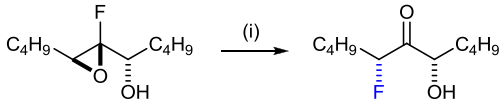
23, >99% ee **24**, 73%, >99% ee

Scheme 3. *Reagents and conditions:* (i) KF, ethylene glycol, 85 °C, 18 h.

In contrast to aqueous solutions, where fluoride ions are heavily solvated and chemically inert, the fluoride ion is largely unsolvated, or "naked", in aprotic solvents and is both a powerful nucleophile and a strong base. Unfortunately, the high basicity of "naked" fluoride tends to lead to the formation of olefinic by-products *via* E2 elimination. One of the major advances in this area has been the use of crown ether derivatives[40] or phase-transfer catalysts with large, lipophilic cations[41] which permit the use of apolar organic solvents as reaction media. Recent investigations have also indicated that ionic liquids[42] or *tert*-alcohols[43] (or combinations thereof)[44] may be superior solvent systems for nucleophilic fluorination with alkali metal fluorides.

1.2.2. Tetra-*n*-butylammonium Fluoride

As an organic-soluble source of nucleophilic fluoride, tetra-*n*-butylammonium fluoride (Bu_4NF) has proven efficacious for the nucleophilic displacement of secondary triflates[33e] and the ring-opening of epoxides,[45] without the requirement for highly elevated temperatures. For example, during studies on the Sharpless asymmetric epoxidation of fluorinated allylic alcohols, Sauvêtre *et al.* demonstrated the ring-opening fluorination of α-fluoro epoxide **25** with Bu_4NF to give α-fluoro ketone **26** in 60% yield (Scheme 4).[46]



25 **26**, 60%

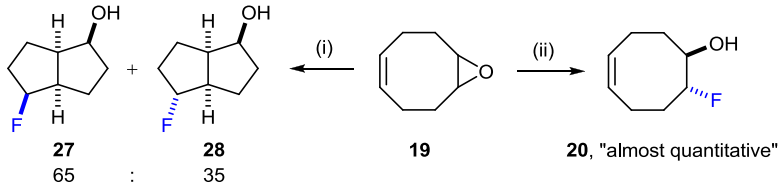
Scheme 4. *Reagents and conditions:* (i) Bu_4NF, THF, rt, 2 h.

To maximise the reactivity of the F^- anion and mitigate competitive hydroxylation pathways, protocols have been developed for obtaining "nearly anhydrous"[47] and "truly anhydrous"[48] Bu_4NF, a nontrivial feat due to decomposition of Bu_4NF *via* Hofmann elimination on heating.[49,50] Unfortunately, decreasing the hydration state of Bu_4NF results in an increased propensity for elimination *versus* substitution in apolar solvents,[51] although the use of less basic $Bu_4NF•(^tBuOH)_4$[52] and Bu_4NHF_2[53] has sought to remedy this problem.

1.2.3. Amine-HF Reagents

To circumvent the hazards associated with the handling of anhydrous HF,[54] Olah has introduced polypyridinium hydrogen fluoride (PPHF, Olah's reagent), a liquid of composition pyridine•9HF (70% HF in pyridine) that is stable up to 55 °C.[55] Amongst other reactions, PPHF has found application in the hydrofluorination of alkenes and alkynes, the dehydroxyfluorination of alcohols and the deaminative fluorination of α-amino acids.[56] $Et_3N•3HF$, an almost pH-neutral amine-HF complex, has also proven

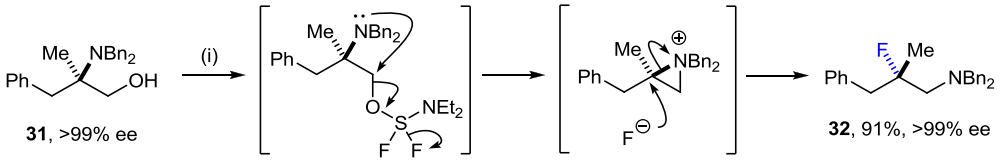
popular on account of the fact it has no HF vapor pressure and does not etch laboratory glassware.[57] Although PPHF and Et_3N•3HF have both been widely used for the ring-opening fluorination of epoxides, the two reagents possess distinct reactivity profiles, with PPHF being significantly more acidic and more reactive than Et_3N•3HF.[35] For instance, Haufe and co-workers reported that the reaction of (*Z*)-9-oxabicyclo[6.1.0]non-4-ene **19** with PPHF occurred at rt to give a 65:35 mixture of 4-fluorooctahydropentalen-1-ol rearrangement products **27** and **28**, respectively, whereas Et_3N•3HF required a reaction temperature of 60 °C and led to fluorohydrin **20** in "almost quantitative" yield (Scheme 5).[58]



Scheme 5. *Reagents and conditions:* (i) PPHF, rt, 90 min; (ii) Et_3N•3HF, 60 °C, 24 h.

1.2.4. Fluorosulfuranes and Fluorosulfinium Salts

Diethylaminosulfur trifluoride (DAST) **29** (Figure 8) was originally developed by Middleton as a more easily handled and chemoselective alternative to SF_4, a powerful fluorinating agent but also a highly toxic, corrosive gas.[59] Along with the safer and more thermally-stable fluorosulfurane Deoxo-Fluor® **30**[60] (Figure 8), these reagents have proven highly popular in effecting a variety of deoxofluorination reactions, such as the direct conversion of alcohols to alkyl fluorides, carboxylic acids to acyl fluorides and carbonyl compounds to *gem*-difluorides.[61] An interesting application of DAST was recently disclosed by Cossy and co-workers in the stereospecific conversion of β-hydroxy amines to rearranged β-fluoro amines *via* aziridinium intermediates.[62] For example, the treatment of enantiopure β-hydroxy amine **31** with 1.5 equiv of DAST in THF gave β-fluoro amine **32** in 91% yield with complete enantiospecificity (Scheme 6).



Scheme 6. *Reagents and conditions:* (i) DAST (1.5 equiv), THF, 0 °C, 1 h then 0 °C to rt, 1 h.

However, the recently developed Xtalfluor® reagents **33** and **34** (which require DBU or Et_3N•3HF as promoters) seem set to supersede DAST **29** and Deoxo-Fluor® **30** as the deoxofluorinating reagents of choice due to their greatly improved safety profile, lower cost and ease of handling as crystalline solids.[63] Another new deoxofluorinating agent with great promise is FLUOLEAD™ **35**, a conveniently handled solid that is surprisingly resistant to hydrolysis (Figure 8).[64]

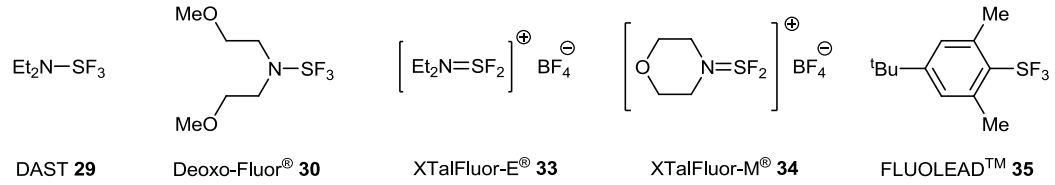


Figure 8. Fluorosulfuranes and fluorosulfinium salts used as deoxofluorinating agents.

1.2.5. Tetrafluoroborates and Boron Trifluoride

In spite of the extremely low nucleophilicity of the tetrafluoroborate ion, BF_4^-, this species has been observed to undergo fluoride transfer to a variety of cationic electrophiles (e.g. alkyl cations,[65] vinyl cations,[66] aryl cations,[67] oxocarbenium ions,[68] halocarbenium ions,[69] acylium ions,[70] alkoxytriphenylphosphonium ions,[71] haliranium ions,[72] halirenium ions,[73] thiiranium ions,[74] thiirenium ions,[75] 2*H*-oxirenium ions[76] and 1,3-dioxolan-2-ylium ions[77]) (Figure 9).

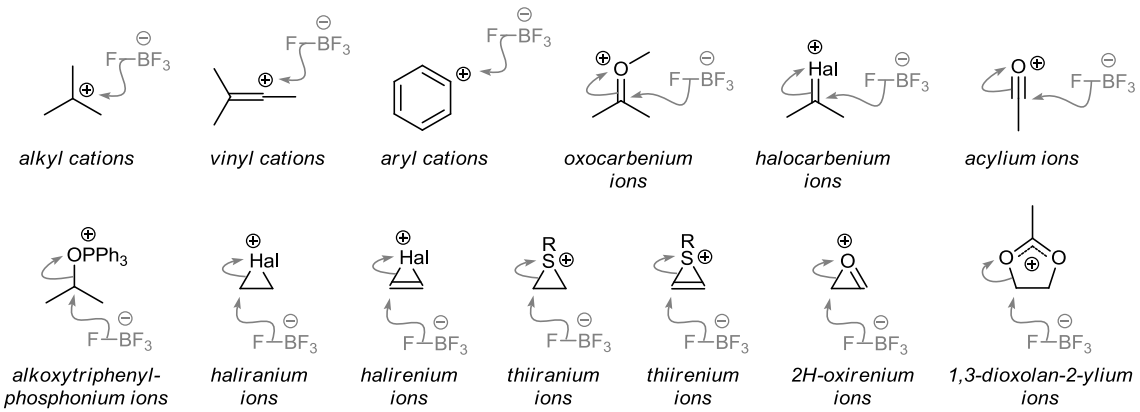
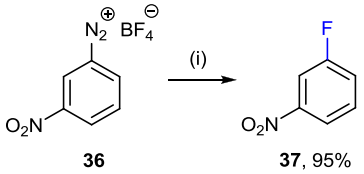


Figure 9. Cationic electrophiles which can undergo nucleophilic trapping by fluoride transfer from the BF_4^- ion.

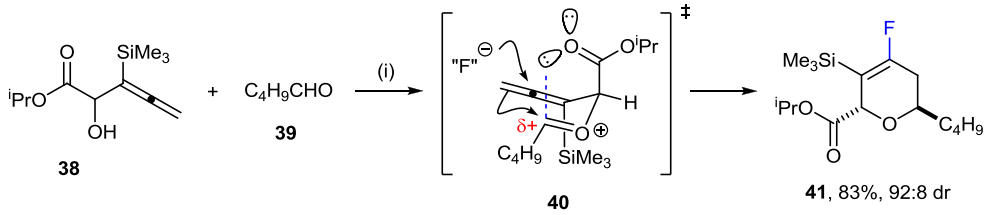
The earliest and perhaps most familiar example of the BF_4^- ion as a nucleophilic fluorine source is the venerable Balz-Schiemann synthesis of aryl fluorides *via* the thermal decomposition of arene diazonium tetrafluoroborate salts, first reported in 1927.[67] Laali and Gettwert have recently reported a modification of this reaction employing ionic liquids as reaction media; for example, *m*-nitrophenyl diazonium salt **36** was thermolysed in 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim][BF_4], at 50 °C to give aryl fluoride **37** in 95% yield (Scheme 7).[78]



Scheme 7. *Reagents and conditions:* (i) [emim][BF_4], 50 °C.

Similarly, BF_3•OEt_2 (which is ubiquitous as a Lewis acid in synthetic chemistry[79]) has also served as an effective source of nucleophilic fluorine in a variety of Lewis acid-mediated reactions, possibly *via* fluoride transfer from *in situ* generated fluoroborates of the form BF_3X^-.[80] Examples include the synthesis of aryl fluorides from aryllead(IV) triacetates,[81] the synthesis of fluorinated carbocycles[82] and heterocycles[83,84,85] *via*

cation-π cyclisation-fluorinations, the synthesis of β-fluoro halides *via* the halofluorination of alkenes,[86] and the synthesis of β-fluoro alcohols and amines *via* the ring-opening fluorination of epoxides and aziridines, respectively (*vide infra*). A recent example of the use of BF_3•OEt_2 as a fluorinating agent was reported by Loh and co-workers in their development of a Prins cyclisation-fluorination reaction for the synthesis of 2,6-*trans*-substituted 4-fluoro-3,4-dihydropyrans, using allenic alcohols as the nucleophilic partner in the presence of BF_3•OEt_2.[85] Thus, treatment of allenic alcohol **38** with *n*-pentanal **39** and 3 equiv of BF_3•OEt_2 in CH_2Cl_2 at 0 °C gave **41** in 83% yield and 92:8 dr. To account for the *trans*-diastereoselectivity of the reaction, the authors proposed a chair-like transition state **40** where the oxocarbenium ion is stabilised by interaction with one of the carbonyl lone pairs of the psuedoaxial ester moiety (Scheme 8).[87]



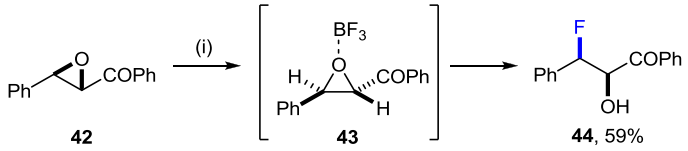
Scheme 8. *Reagents and conditions:* (i) BF_3•OEt_2 (3 equiv), CH_2Cl_2, 0 °C, 3 h.

1.2.5.1. Ring-Opening Fluorination of Epoxides with BF_3•OEt_2

BF_3•OEt_2 has found widespread application as a Lewis acid catalyst for a host of archetypal reactions of epoxides, including polymerisation,[88] addition of nucleophiles[89] and rearrangements to carbonyl compounds[90] or allylic alcohols.[91] In a number of cases, however, the formation of vicinal fluorohydrins arising from ring-opening by fluoride (derived from BF_3•OEt_2) has been reported for a variety of epoxide substrates,[92,93] including aryl epoxides,[94] α-halo epoxides and steroid epoxides, as well as other epoxide[95] and aziridine[96] substrates.

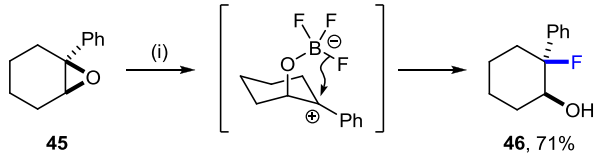
1.2.5.1.1. Aryl Epoxides

The earliest example of unexpected fluorohydrin formation upon treatment of aryl epoxides with BF_3•OEt_2 was described in 1956 by House during his seminal studies into the mechanism of the acid-catalysed rearrangement of α,β-epoxy ketones.[94a,c] Upon treatment of chalcone oxide **42** with 0.5 equiv of BF_3•OEt_2 in Et_2O at reflux for 30 min, *syn*-fluorohydrin **44** was obtained in 59% yield. Although tentatively assigned by the original author, the *syn*-configuration within **44** was later confirmed by other investigators by single crystal X-ray diffraction analysis of a derivative.[97] To rationalise the retention of configuration, House proposed a mechanism involving intramolecular fluoride transfer from boron to the benzylic carbon within epoxide-BF_3 complex **43** (Scheme 9).



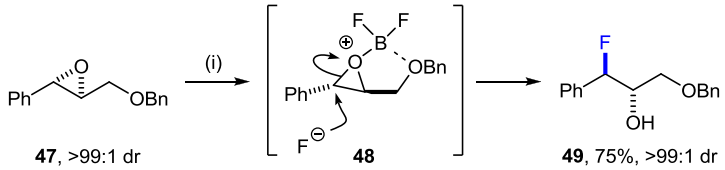
Scheme 9. *Reagents and conditions:* (i) BF_3•OEt_2 (0.5 equiv), Et_2O, reflux, 30 min.

Similarly, Berti *et al.* have reported fluorohydrin formation during investigations into the rearrangement of 1-phenylcyclohexene oxide **45** with BF_3•OEt_2.[94e] Under the agency of 1.4 equiv of BF_3•OEt_2 in Et_2O at rt for 5 min, epoxide **45** gave *syn*-fluorohydrin **46** in 71% yield. The relative configuration within **46** was assigned on the basis of a ^{1}H-^{19}F ^3J NMR coupling constant of 25.5 Hz, indicative of an antiperiplanar arrangement. To account for the retention of configuration, the authors conceived a mechanism involving epoxide cleavage by BF_3, followed by intramolecular fluoride transfer from the *O*-tethered alkoxytrifluoroborate moiety to the benzylic carbocation centre (Scheme 10).



Scheme 10. *Reagents and conditions:* (i) BF_3•OEt_2 (1.4 equiv), Et_2O, rt, 5 min.

More recently, Pericàs and co-workers have described the ring-opening fluorination of a range of enantiopure *trans*-3-arylglycidyl ethers using BF_3•OEt_2 as a nucleophilic fluorine source.[94k] For example, upon treatment of **47** with 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 at −35 °C for 1 h, fluorohydrin **49** was obtained as a single diastereoisomer (>99:1 dr) in 75% yield, demonstrating that all 3 fluorine atoms within BF_3•OEt_2 are transferable in this process. By analogy to the Ti(IV)-mediated ring-opening of epoxy alcohols,[98] the authors posited a mechanism involving formation of a 5-membered ring chelate **48**, followed by S_N2-type attack of the liberated fluoride ion at the benzylic carbon of the activated oxirane.[99] Based purely on this mechanistic hypothesis, an *anti*-configuration was assigned to fluorohydrin **49** and related examples (Scheme 11). However, a failure to provide any evidence for an inversion of configuration, coupled with the aftermentioned observations of House[94a] and Berti[94e] of stereoretentive ring-opening in closely related systems, calls into question the validity of this stereochemical assignment.[100]

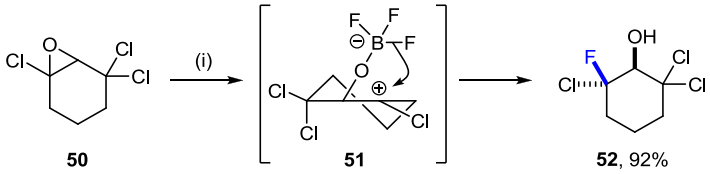


Scheme 11. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –35 °C, 1 h.

1.2.5.1.2. α-Halo Epoxides

The efficient regio- and stereoselective ring-opening fluorination of a number of α-chloro and α-fluoro epoxycyclohexanes with BF_3•OEt_2 has been accomplished by Duhamel and co-workers.[101] For example, on

treatment with 0.53 equiv[102] of BF_3•OEt_2 in DCE for 3.5 h at reflux, α-chloro epoxide **50** was transformed into fluorohydrin **52** in 92% yield. A *syn* relationship between the fluorine and the hydroxy group within **52** was assigned on the basis of ^{1}H-^{19}F ^3J NMR coupling constant analysis and the synthesis of an authentic sample of the diastereoisomeric fluorohydrin. To account for the formation of **52**, the authors proposed an S_N1-type mechanism involving epoxide cleavage to give a stabilised chlorocarbenium ion **51**, followed by an intramolecular delivery of fluoride from the alkoxytrifluoroborate moiety (Scheme 12).

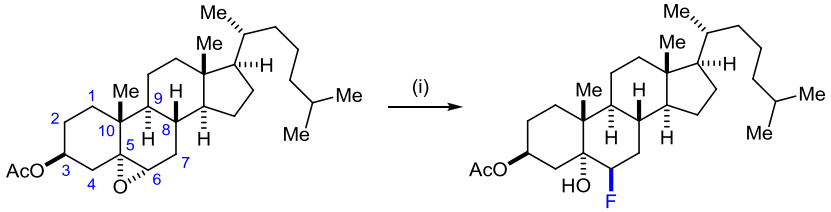


50 **51** **52**, 92%

Scheme 12. *Reagents and conditions:* (i) BF_3•OEt_2 (0.53 equiv), DCE, reflux, 3.5 h.

1.2.5.1.3. Steroid Epoxides

The ring-opening fluorination of 5,6-epoxysteroids using BF_3•OEt_2 as a fluorinating agent was first reported in 1957 by Henbest and Wrigley,[103] and was further developed by Bowers and Ringold in 1958.[104] Most of the ensuing methodological and mechanistic contributions[105] in this area were reviewed in 1974.[106] In many of the studies on the ring-opening fluorination of 5,6-epoxysteroids with BF_3•OEt_2, the requirement for an electron-withdrawing substituent at the C(3)-position has been emphasised, in order to disfavour carbocation formation at C(5) and suppress competing rearrangement pathways to ketonic products.[105b,i,k,m] For example, the treatment of 3β-acetoxy-5α,6α-epoxycholestane **53** with BF_3•OEt_2 in benzene at rt for 5 min gave fluorohydrin **54** in 62% yield.[103] The relative configuration within fluorohydrin **54** was assigned as *anti* on the basis that base-induced ring-closure led to recovery of the starting epoxide (Scheme 13).

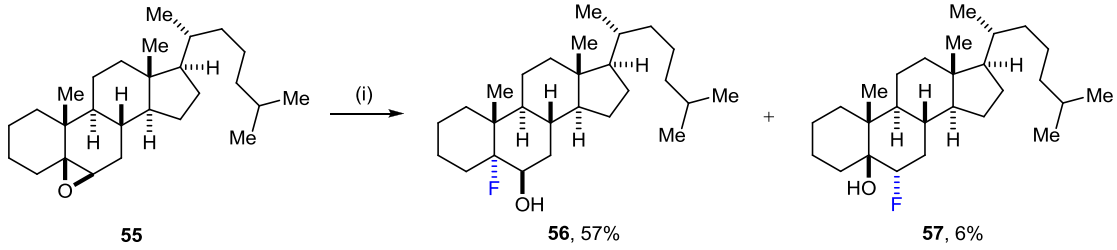


53 **54**, 62%

Scheme 13. *Reagents and conditions:* (i) BF_3•OEt_2 (2.9 equiv), benzene, rt, 5 min.

Further investigations have shown that the scope of these reactions may be greatly improved by the inclusion of Et_2O as an additive/co-solvent with benzene (or simply by performing the reaction in Et_2O alone) and that substrates lacking strongly electron-withdrawing-C(3) substituents can undergo efficient ring-opening fluorination with BF_3•OEt_2 under these conditions.[105f,i-k] Additionally, the rate of reaction decreases significantly as the concentration of Et_2O is increased.[105f,j] Thus, treatment of 5β,6β-epoxycholestane **55** with 3.2 equiv of BF_3•OEt_2 in benzene at rt gave rapid conversion (2 min) to a mixture of non-fluorinated rearrangement products, whereas reaction with 8.1 equiv of BF_3•OEt_2 in Et_2O at rt was much slower (2.5 h)

and gave, in addition to rearrangement products, fluorohydrin **56** in 57% yield and a fluorinated compound tentatively assigned as regioisomeric fluorohydrin **57** in 6% yield (Scheme 14).[105j]



Scheme 14. *Reagents and conditions:* (i) BF_3•OEt_2 (8.1 equiv), Et_2O, rt, 2.5 h.

Although the relative configurations assigned to the fluorohydrin products of these reactions (in all reported cases) are consistent with an S_N2-type epoxide ring-opening process, the identity of the reactive fluorinating species is unclear. However, in the case of 3β-acetoxy-5α,6α-epoxycholestane **53**, experiments have shown that traces of HBF_4 present in unpurified BF_3•OEt_2 appear to be crucial in promoting ring-opening fluorination over Lewis acid catalysed rearrangements.[105g,107]

1.3. Project Aims

Building on existing literature precedent for fluoride transfer from BF_3 and the BF_4^- ion, this thesis seeks to further explore the potential of boron fluorides and tetrafluoroborates as inexpensive and easily handled sources of nucleophilic fluorine. Initial investigations will focus on the ring-opening fluorination of aryl epoxides with BF_3•OEt_2, specifically with regard to the scope and limitations, stereochemical course and probable mechanism of this transformation. A more detailed understanding of the mechanics of this process may then enable the development of other fluorination reactions using BF_3•OEt_2 as a nucleophilic fluorine source.

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[87] Although apparently not considered by the authors, an alternative explanation may be that the ester group prefers a psuedoaxial orientation in order to prevent a destabilising $A^{1,2}$ strain interaction with the bulky trimethylsilyl group. This rationale would also account for the fact that the *trans*-diastereoselectivity of the reaction was diminished with less bulky ester groups – a fact which is not readily explainable using the author's transition state model.

[88] For a representative example see: Nowak, A.; Bolte, O.; Schaumann, E. *Tetrahedron Lett.* **1998**, *39*, 529.

[89] For a representative example which employs BF_3•OEt_2 as a catalyst for the ring-opening fluorination of epoxides with Et_3N•3HF see: Goj, O.; Haufe, G. *Liebigs Ann. Chem.* **1996**, 1289.

[90] For a representative example see: Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem.* **1997**, *62*, 4991.

[91] For a representative example see: Vankar, Y. D.; Chaudhuri, N. C.; Vankar, P. S. *J. Chem. Res.* **1989**, 178.

[92] Whilst the ring-opening fluorination of oxetanes with BF_3•OEt_2 as the nucleophilic fluorine source is unknown as a synthetic method, fluorohydrin by-products have been observed during the cyclic oligomerisation of oxetanes with BF_3•OEt_2; see: Dale, J.; Fredriksen, S. B. *Pure Appl. Chem* **1989,** *61*, 1587.

[93] Notably, the Lewis acid silicon tetrafluoride, SiF_4, has also been described as a reagent for the ring-opening fluorination of epoxides; see: Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1988**, *29*, 4101; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967. For the ring-opening fluorination of oxetanes with SiF_4 see: Shimizu, M.; Kanemoto, S.; Nakahara, Y. *Heterocycles* **2000,** *52*, 117.

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Chapter 2: Ring-Opening Fluorination of Aryl Epoxides with BF_3•OEt_2

This chapter describes investigations into the ring-opening fluorination of aryl epoxides using BF_3•OEt_2 as a nucleophilic fluorinating agent, and the development of this reaction as a general synthetic method to access functionalised benzylic fluoride building blocks (Figure 10).

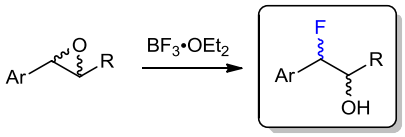


Figure 10. Ring-opening fluorination of aryl epoxides with BF_3•OEt_2.

2.1. Introduction

2.1.1. The Importance of Benzylic Fluorides

The benzylic fluoride motif is finding increasing application in pharmaceutical and agrochemical candidate compounds as an isosteric replacement for benzylic methine or hydroxyl groups. It may serve to increase metabolic stability by blocking benzylic oxidation pathways mediated by cytochrome P450 enzymes,[1] as well as modulating drug-like properties such as lipophilicity, which is known to increase upon fluorination adjacent to π-systems.[2] For example, in the search for NMDA (*N*-methyl-D-aspartate) receptor antagonists for the treatment of neurological disorders, chemists at Merck synthesised[3] a library of benzylic fluorine-containing compounds and identified **58** as a promising candidate.[4] Further examples of biologically-active benzylic fluorides include LY503430 **59** as a potential treatment for Parkinson's disease,[5] CETP (cholesteryl ester transfer protein) inhibitor **60** as a potential treatment for atherosclerosis,[6] and organophosphorus nerve gas immunisation agent **61**[7] (Figure 11).

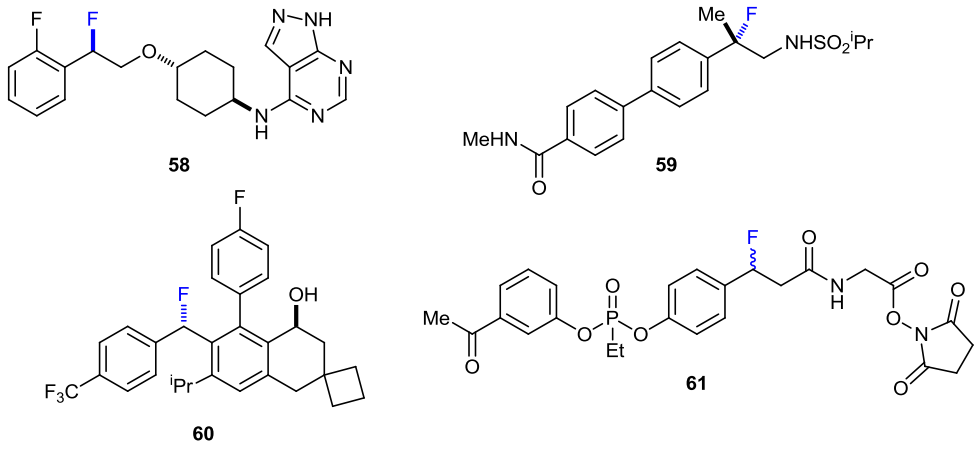


Figure 11. Examples of chiral benzylic fluorides as bioactive compounds.

Enantiopure benzylic fluorides also hold promise as chiral dopants for ferroelectric liquid crystals, as fluorinated stereogenic centres in close proximity to aromatic backbones are known to correlate with high values of spontaneous polarisation.[8] For example, enantiopure benzylic fluoride **62** induced a large negative ferroelectric polarisation when mixed with host ferroelectric liquid crystal **63** (Figure 12).[9]

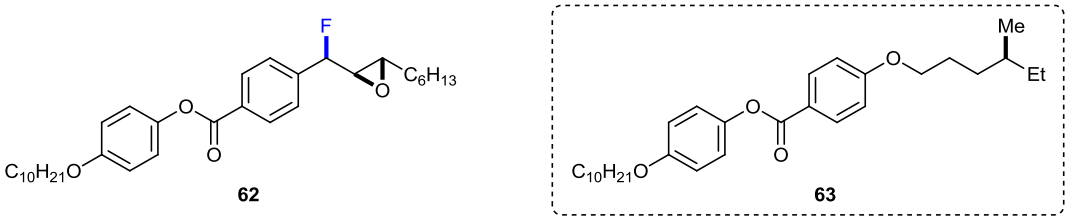
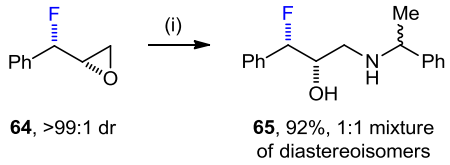


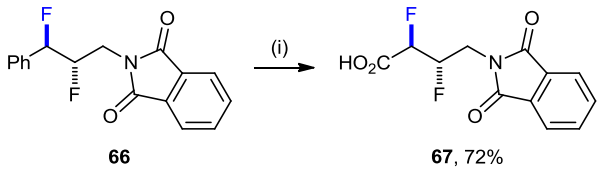
Figure 12. Benzylic fluorides as chiral dopants for ferroelectric liquid crystals.

Chiral benzylic fluorides have also found use as chiral derivatising agents for ee determination.[10] For instance, Pericàs and co-workers have developed enantiopure fluoro epoxide **64** as a chiral derivatising agent for ascertaining the ee of chiral amines such as α-methylbenzylamine (Scheme 15).[10h]



Scheme 15. *Reagents and conditions:* (i) (*RS*)-(α-methylbenzyl)benzylamine, $LiClO_4$, THF, MW, 75 °C.

Stereodefined benzylic fluorides can also serve as valuable precursors to stereodefined α-fluoro carboxylic acids[11] by oxidative degradation of the phenyl ring.[12,13] For example, during a study on the synthesis and conformational analysis of α,β-difluoro-γ-amino acids, Hunter *et al.* performed a RuO_4-catalysed oxidative degradation of benzylic fluoride **66** to give α,β-difluoro acid **67** in 72% yield (Scheme 16).[11c]



Scheme 16. *Reagents and conditions:* (i) $NaIO_4$, $RuCl_3$, H_2O, CH_2Cl_2, MeCN, rt.

However, despite this array of potential applications, this motif remains highly underutilised due to a shortage of reliable, generally applicable methods for its stereoselective synthesis.

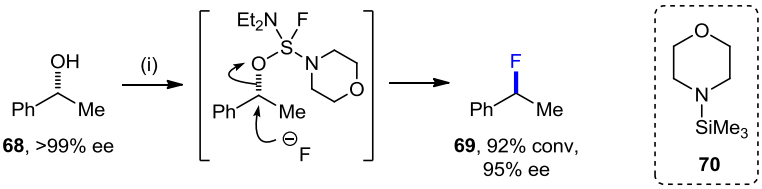
2.1.2. Stereoselective Synthesis of Benzylic Fluorides *via* Nucleophilic Fluorination

As the synthesis of benzylic fluorides has been reviewed,[14] the following discussion will cover nucleophilic fluorination protocols which allow for efficient stereocontrol upon formation of the fluorinated centre.[15]

2.1.2.1. Dehydroxyfluorination of Benzylic Alcohols

A major issue with the dehydroxyfluorination of benzylic alcohols, as with any nucleophilic substitution of benzylic leaving groups with fluoride sources,[8] is that they are often subject to partial or total stereorandomisation due to the intermediacy of benzylic carbocations.[16] One solution to this problem is to use substrates with electron-poor aryl groups, in which an S_N2 reaction (with inversion of configuration) is favoured over an S_N1 pathway,[16] or substrates in which neighbouring group participation can occur (with net retention of configuration).[17] Another approach, pioneered by Bio *et al.*[4] and further developed by O'Hagan and Bresciani,[16] has involved the use of pre-formed, amido-substituted fluorosulfuranes as electronically-

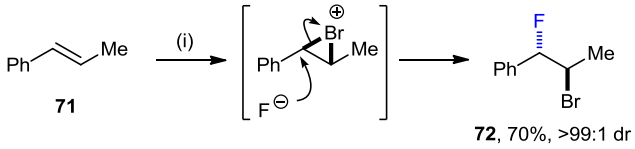
tuned dehydroxyfluorinating agents, a modification which suppresses competing S_N1 processes and facilitates the highly stereospecific dehydroxyfluorination of benzylic alcohols. Thus, on treatment of **68** (>99% ee) with 3 equiv of the fluorinating agent derived from a 1:1 mixture of *N*-(trimethylsilyl)morpholine **70** and DAST, 92% conversion to fluoride **69** with 95% ee was observed (Scheme 17).



Scheme 17. *Reagents and conditions:* (i) **70**:DAST (1:1, 3 equiv), CH_2Cl_2, rt, 15 h.

2.1.2.2. Halofluorination of Aryl Alkenes

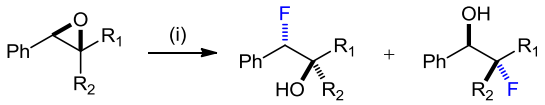
The halofluorination of aryl alkenes with electrophilic halogen reagents in combination with fluoride sources, which proceeds *via* the intermediacy of haliranium ions, is another useful method for the stereocontrolled synthesis of benzylic fluorides.[18] For example, treatment of (*E*)-β-methylstyrene **71** with *N*-bromosuccinimide and 70% aq HF gave β-fluoro bromide **72** in 70% yield as a single diastereoisomer (>99:1 dr) (Scheme 18).[18a] These β-fluoro bromide products are valuable precursors to β-fluoro azides,[19] which can be readily elaborated to β-fluoro amines *via* Staudinger reduction.[20] The principle drawback of the halofluorination approach is the current lack of an enantioselective variant, as the asymmetric halofunctionalisation of olefins is still in its infancy.[21]



Scheme 18. *Reagents and conditions:* (i) *N*-bromosuccinimide (1.4 equiv), 70% aq HF, Et_2O, 0 °C to 15 °C, 1 h.

2.1.2.3. Ring-Opening Fluorination of Aryl Epoxides

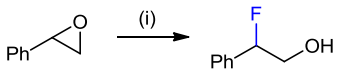
The ring-opening fluorination of epoxides[22] as an approach to the synthesis of enantioenriched benzylic fluorides[23] is especially attractive due to the wealth of asymmetric methods available for the preparation of aryl epoxides[24] (e.g. those protocols developed by Sharpless,[25] Jacobsen,[26,27] Shi,[28] Jørgensen,[29] Yamamoto[30] and Aggarwal[31]). An important consideration, however, is the regioselectivity of epoxide ring-opening, which can exhibit a marked dependence on both the reaction conditions and the oxirane substituents.[22b] For example, the reaction of styrene oxide **73** with $^{i}Pr_2NH$•3HF at 105 °C gave a 75:25 mixture of benzylic to homobenzylic fluorides **76**:**79** in 70% combined yield, with (*E*)-β-methylstyrene oxide **74** giving a 90:10 mixture of benzylic to homobenzylic fluorides **77**:**80** in 83% combined yield under the same conditions. However, β,β-dimethylstyrene oxide **75** gave a 5:95 mixture of benzylic to homobenzylic fluorides **78**:**81** in 88% combined yield under identical conditions (Scheme 19).[32]



Epoxide	Benzylic:Homobenzylic Fluoride Ratio	Combined Yield
73, R_1 = H, R_2 = H	**76**:**79**, 75:25	70%
74, R_1 = Me, R_2 = H	**77**:**80**, 90:10	83%
75, R_1 = Me, R_2 = Me	**78**:**81**, 5:95	88%

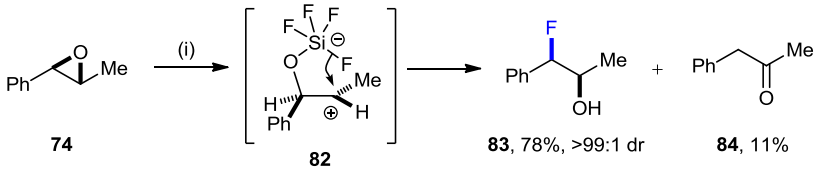
Scheme 19. *Reagents and conditions:* (i) $^{i}Pr_2NH$•3HF, 105 °C.

In an effort to lower the high reaction temperatures characteristically required with amine trihydrofluoride reagents, Haufe and Goj have shown that the addition of BF_3•OEt_2 as a Lewis acid catalyst allows the ring-opening fluorination of aryl epoxides with Et_3N•3HF to proceed at rt.[33] For instance, treatment of styrene oxide **73** with 3 equiv of Et_3N•3HF and 20 mol% of BF_3•OEt_2 in CH_2Cl_2 gave fluorohydrin **76** in 70% yield (Scheme 20).[34]



Scheme 20. *Reagents and conditions:* (i) Et_3N•3HF (3 equiv), BF_3•OEt_2 (20 mol%), CH_2Cl_2, rt, 12 h.

Shimizu and co-workers have demonstrated the utility of SiF_4 as a reagent for the ring-opening fluorination of a range of aliphatic and aryl epoxides to the corresponding fluorohydrins.[35] For example, treatment of (*E*)-β-methylstyrene oxide **74** in CH_2Cl_2 with excess SiF_4 gas, in the presence of $^{i}Pr_2NEt$ as a buffer, gave fluorohydrin **83** in 78% yield as a single diastereoisomer (Scheme 21).[35a] The authors proposed an S_Ni mechanism[36] involving intramolecular delivery of fluoride to the benzylic carbocation **82**.



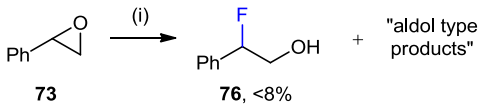
Scheme 21. *Reagents and conditions:* (i) SiF_4 (excess), $^{i}Pr_2NEt$ (0.5 equiv), CH_2Cl_2, 0 °C-rt for 1-5 h.

Although, there have been several reported cases of unexpected fluorohydrin formation upon treatment of aryl epoxides with BF_3•OEt_2,[37] there remains some ambiguity as to the stereochemical course and substrate scope of this process (see chapter 1). Considering the significant practical and economic benefits of using BF_3•OEt_2 as a nucleophilic fluorinating agent (i.e. low cost, high active fluorine content and ease of handling in standard glassware), it was proposed that further investigation into the ring-opening fluorination of aryl epoxides with BF_3•OEt_2 was warranted in order to unambiguously confirm the stereochemical course of the reaction and assess its full potential in the synthesis of stereodefined benzylic fluorides.

2.2. Results and Discussion

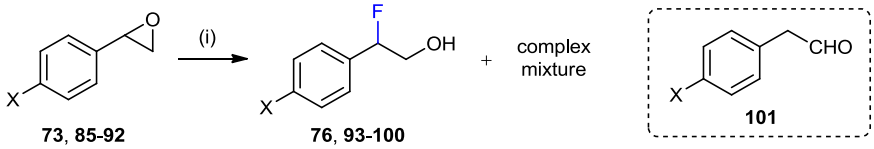
2.2.1. Ring-Opening Fluorination of *p*-Substituted Styrene Oxides with BF_3•OEt_2

During studies into the ring-opening fluorination of 3-phenylglycidol derivatives with BF_3•OEt_2, Pericàs and co-workers reported that subjection of styrene oxide **73** to BF_3•OEt_2 under their standard reaction conditions gave fluorohydrin **76** in <8% isolated yield, with the bulk of the mass comprising a mixture of "aldol type products arising from initial epoxide rearrangement" (Scheme 22).[23]



Scheme 22. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –35 °C, 1 h.

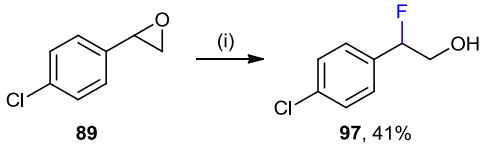
To investigate whether or not changing the nature of the aryl group would lead to an enhancement in fluorohydrin yield, a variety of styrene oxides **85-92** bearing a range of electronically-diverse *p*-substituents were selected. The Brown-Okamoto substituent constant, σ^+, was used to quantify the electronic effect of each *p*-substituent, and define a relative ordering of **73** and **85-92** in terms of the expected stability of a benzylic carbocation intermediate.[38] Using conditions based on those employed by Pericàs *et al.*,[23] styrene oxides **73** and **85-92** were each treated with 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 (0.25 M wrt epoxide) at −40 °C for 1 h, followed by addition of satd aq $NaHCO_3$ (this work up was used for all other fluorinations performed in this chapter). In all cases the reactions proceeded to completion to give complex mixtures of products comprised mainly of unidentified, non-fluorinated compounds, probably arising from acid-catalysed epoxide oligomerisation[39] as well as oligomerisation/aldolisation of the corresponding arylacetaldehydes **101**[40] (which were also present as components of the mixtures). The yield of any fluorinated compound in each case was calculated by integration of the CH*F* resonance in the ^{19}F NMR spectrum of the crude product mixture against a fluorobenzene standard; these values will hereafter be referred to as "NMR yields" to distinguish them from isolated yields (Scheme 23). Styrene oxide **73** gave 8% NMR yield of known fluorohydrin **76**,[41] in conformity with the <8% isolated yield reported by Pericàs *et al.* using similar reaction conditions.[23] Epoxides **85-88** bearing *p*-substituents which would stabilise a benzylic carbocation intermediate (i.e. OMe, Me, Ph and F) gave no detectable fluorinated products. Similarly, epoxides **91** and **92** bearing *p*-substituents which would strongly destabilise a benzylic carbocation intermediate (i.e. CN and NO_2) gave virtually no fluorinated products (<1%).[42] However, substrates **89** and **90** bearing *p*-Cl and *p*-Br substituents, which only moderately destabilise a benzylic carbocation (relative to H), gave rise to products assigned as fluorohydrins **97** and **98** (*vide infra*) in NMR yields of 10 and 11%, respectively.



Epoxide	X	σ^+	Fluorohydrin NMR Yield
85	OMe	−0.78	**93**, 0%
86	Me	−0.31	**94**, 0%
87	Ph	−0.18	**95**, 0%
88	F	−0.07	**96**, 0%
73	H	0.00	**76**, 8%
89	Cl	+0.11	**97**, 10%
90	Br	+0.15	**98**, 11%
91	CN	+0.66	**99**, <1%
92	NO_2	+0.79	**100**, <1%

Scheme 23. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –40 °C, 1 h.

To verify that the fluorinated compound observed on reaction of **89** with BF_3•OEt_2 was indeed fluorohydrin **97**, an authentic sample of **97** was prepared using a literature protocol for the ring-opening fluorination of styrene oxide **73** (*vide supra*).[34] Thus, treatment of *p*-chlorostyrene oxide **89** with 3 equiv of Et_3N•3HF and 20 mol% of BF_3•OEt_2 in CH_2Cl_2 gave fluorohydrin **97** in 41% isolated yield, with all characterisation data in full accord with the proposed structure (Scheme 24). The ^1H and ^{19}F NMR resonances for **97** prepared by this method matched precisely those observed in the spectra of the crude product mixture from the reaction of **89** with BF_3•OEt_2. On this basis, the fluorinated compounds **98**-**100** were also assigned as fluorohydrins.

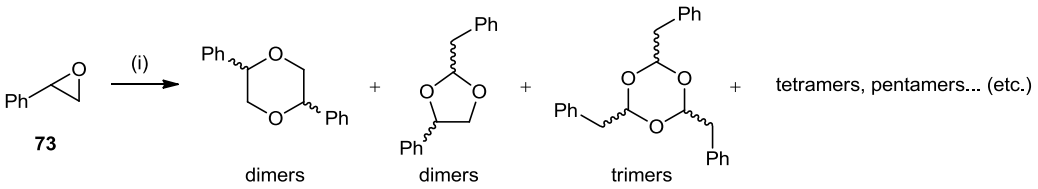


Scheme 24. *Reagents and conditions:* (i) Et_3N•3HF (3 equiv), BF_3•OEt_2 (20 mol%), CH_2Cl_2, rt, 24 h.

2.2.1.1. Mechanistic Considerations

The complex mixtures of products produced (alongside the desired fluorohydrins) in the reactions of styrene oxide derivatives **73** and **85**-**92** with BF_3•OEt_2 suggests that more than one reaction pathway is in operation. For instance, the oligomerisation of styrene oxide **73** with BF_3•OEt_2 has previously been reported by Yamashita, Iwao and Ito, who showed that the dropwise addition of styrene oxide **73** to 4 mol% of BF_3•OEt_2 in dioxane at 20 °C gave a 17:23:49:11 mixture of dimer:trimer:tetramer:pentamer oligoethers, with the product distribution proving relatively insensitive to the nature of the solvent (Scheme 25).[39] It has previously been shown that the cationic polymerisation of (*R*,*R*)-*trans*-2,3-epoxybutane proceeds with inversion of configuration at the oxirane carbons to generate an optically-inactive polyether, implying S_N2 attack of epoxide monomers onto oxiranium ion intermediates.[43] Moreover, recent studies have indicated that

the $TiCl_4$-promoted formation of oligoethers from α-methylstyrene oxide proceeds *via* S_N2 attack of an epoxide monomer onto the epoxide-$TiCl_4$ complex.[44] As BF_3 is less Lewis acidic than $TiCl_4$,[45] and styrene oxide is less prone to S_N1-type reactivity than α-methylstyrene oxide, an S_N2 ring-opening pathway for the BF_3•OEt_2-promoted oligomerisation of styrene oxide **73** seems most probable.



Scheme 25. *Reagents and conditions:* (i) BF_3•OEt_2 (4 mol%), dioxane, 20 °C.

The acid-catalysed isomerisation of styrene oxide **73** to phenylacetaldehyde (an example of the Meinwald rearrangement[46]) is similarly well established,[47] accounting for the formation of arylacetaldehydes **101**. The generally accepted mechanism of this isomerisation process involves heterolytic cleavage of the epoxide-BF_3 complex **103** to generate a benzylic carbocation intermediate **104A**; subsequent C−C bond rotation[48] to bring a C−H σ bond coplanar with the carbocation *p* orbital (e.g. as in conformer **104B**) allows a [1,2]-H shift to occur, giving the arylacetaldehyde **101**. The formation of fluorohydrins **105** may occur from the initially-formed carbocation conformer **104A** *via* an S_Ni-type[36] intramolecular fluoride transfer from the *O*-tethered alkoxytrifluoroborate moiety to the benzylic carbocation (*vide infra*) (Figure 13).

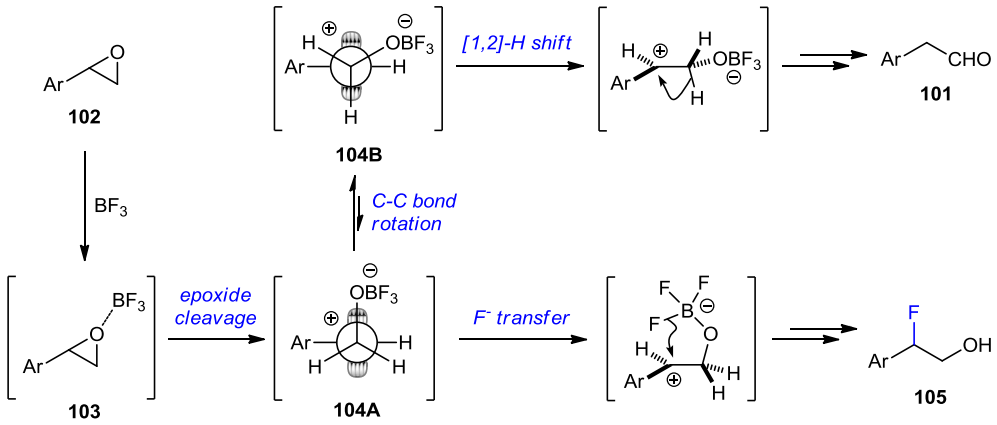


Figure 13. Mechanistic rationale for the formation of arylacetaldehydes **101** and fluorohydrins **105**.

Based on this mechanistic hypothesis, the observed dependence of the fluorohydrin yield on the nature of the aryl *p*-substituent implies that a compromise in carbocation stability *versus* reactivity may be necessary for efficient incorporation of fluorine (Scheme 23). For electron-releasing *p*-substituents, the rate of intramolecular fluoride transfer should be retarded relative to the rate of C−C bond rotation and concomitant [1,2]-H migration, accounting for the absence of fluorinated products from epoxides **85**-**88** bearing *p*-substituents which stabilise a benzylic carbocation intermediate (i.e. OMe, Me, Ph and F). For strongly electron-withdrawing *p*-substituents, ionisation of the epoxide-BF_3 complex **103** may be disfavoured relative to epoxide oligomerisation *via* an S_N2 pathway,[44] accounting for the <1% NMR yields of fluorohydrins from

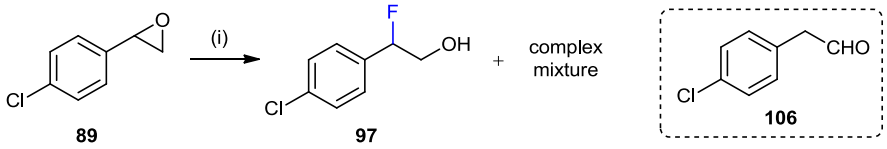
epoxides **91** and **92** bearing *p*-substituents which strongly destabilise a benzylic carbocation intermediate (i.e. CN and NO_2).[49] It seems that only epoxides **73** (X = H), **89** (X = Cl) and **90** (X = Br) strike the necessary balance between the rate of ionisation *versus* oligomerisation and the rate of fluoride transfer *versus* C−C bond rotation for fluorination to become at all competitive with oligomerisation or isomerisation pathways. However, even in these cases the degree of fluorine incorporation is still very low (8-11%).

2.2.1.2. Optimisation Studies with *p*-Chlorostyrene Oxide

For all further studies involving reaction optimisation, *p*-chlorostyrene oxide **89** was selected as a representative substrate.

2.2.1.2.1. Effect of the Reaction Solvent

To determine the effect of solvent variation on the ring-opening fluorination of **89** with BF_3•OEt_2, a range of common aprotic solvents were selected: CH_2Cl_2, $CHCl_3$, DCE, CCl_4, Et_2O, *n*-hexane and PhMe (all dried over 4 Å molecular sieves prior to use). Under reaction conditions analogous to those employed with CH_2Cl_2 (i.e. 0.33 equiv of BF_3•OEt_2, −40 °C, 1 h, 0.25 M), the reactions proceeded to completion in all cases to give a complex mixture of products, including fluorohydrin **97** and aldehyde **106** as components (Scheme 26). Of the solvents tested, CH_2Cl_2, $CHCl_3$ and DCE gave the highest NMR yields (10%) of fluorohydrin **97**, with CCl_4 giving only 2% of **97**. CCl_4 is renowned for its ability to destabilise ionic intermediates; indeed, the formation of benzylic carbocations from aryl epoxides is known to be suppressed in this extremely non-polar solvent, relative to CH_2Cl_2 or $CHCl_3$.[50] The remaining solvents − Et_2O, *n*-hexane and PhMe – all proved inferior to CH_2Cl_2, $CHCl_3$ and DCE under these reaction conditions.[51] CH_2Cl_2 was thus maintained as the solvent of choice for further optimisation studies.

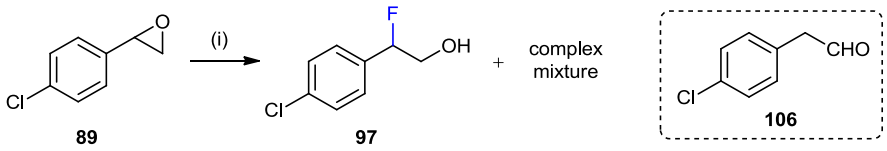


Solvent	Fluorohydrin 97 NMR Yield
CH_2Cl_2	10%
$CHCl_3$	10%
DCE	10%
CCl_4	2%
Et_2O	4%
n-hexane	4%
PhMe	1%

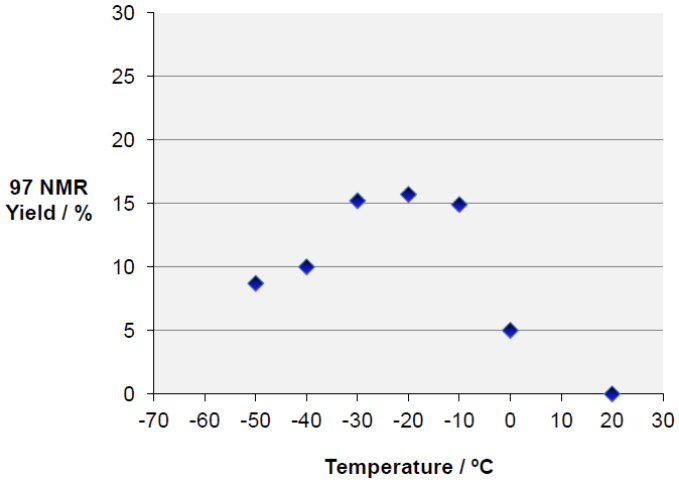
Scheme 26. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), stated solvent, –40 °C, 1 h.

2.2.1.2.2. Effect of the Reaction Temperature

The influence of the reaction temperature was next assessed, ranging from −78 °C to rt (20 °C). A fortuitous observation at this stage was that all reactions of **89** with BF_3•OEt_2 at any temperature were complete after only 5 min, obviating the need to run the reactions for 1 h.[52] On treatment of **89** with 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 (0.25 M wrt **89**) at the stated temperature for 5 min, the reactions all proceeded to completion to give a complex mixture of products, including fluorohydrin **97** and aldehyde **106** as components. A graphical representation of these results shows that the fluorohydrin **97** yield follows a non-linear temperature dependence, and is maximised at –20 °C (Scheme 27).



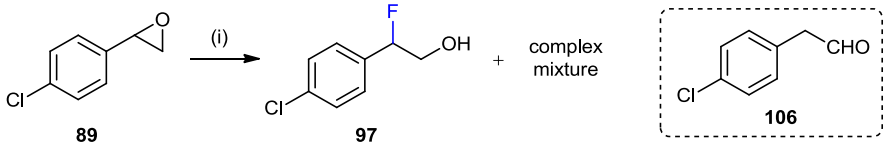
T °C	Fluorohydrin 97 NMR Yield
20 °C	0%
0 °C	5%
−10 °C	15%
−20 °C	16%
−30 °C	15%
−40 °C	10%
−50 °C	9%
−78 °C	8%



Scheme 27. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, T °C, 5 min.

2.2.1.2.3. Effect of the Amount of BF_3•OEt_2

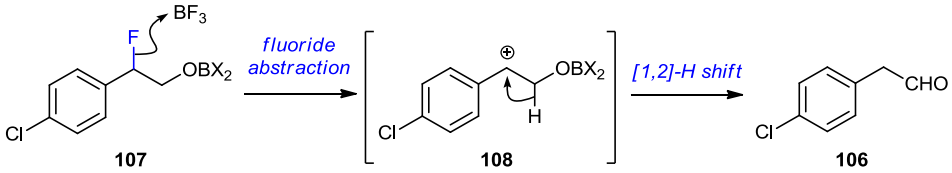
Previous observations in the literature have suggested that in non-Lewis basic solvents, such as CH_2Cl_2, fluorohydrins [or the (*O*-boryl)fluorohydrins *in-situ*] arising from the reaction of aryl epoxides with BF_3•OEt_2 are converted rapidly into carbonyl compounds in the presence of excess BF_3•OEt_2.[37e] To explore this possibility in the present case, **89** was subjected to varying amounts of BF_3•OEt_2 (0.33 to 10 equiv) at –20 °C in CH_2Cl_2 (0.25 M wrt **89**) for 5 min (Scheme 28).



BF_3•OEt_2 Equiv	Fluorohydrin 97 NMR Yield
0.33	16%
0.67	15%
1	13%
5	7%
10	5%

Scheme 28. *Reagents and conditions:* (i) BF_3•OEt_2, CH_2Cl_2, −20 °C, 5 min.

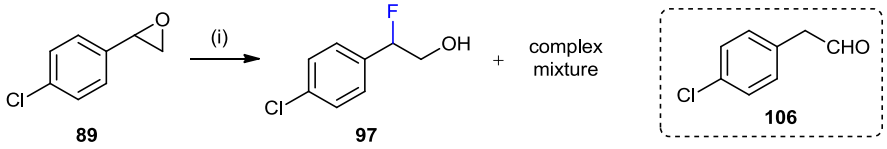
In accord with literature precedent, increasing the quantity of BF_3•OEt_2 led to a decrease in the yield of fluorohydrin **97**, presumably due to abstraction of fluoride from the initially formed (*O*-boryl)fluorohydrin species **107** by excess BF_3 to regenerate the benzylic carbocation intermediate **108**, giving significant amounts of aldehyde **106** after C−C bond rotation and a [1,2]-H shift (Scheme 29).[53]



Scheme 29. Mechanistic rationale for the decrease in fluorohydrin **97** yield in the presence of excess BF_3•OEt_2.

2.2.1.2.4. Effect of the Reaction Dilution

In an effort to promote ring-opening fluorination at the expense of epoxide oligomerisation, the effect of increasing the reaction dilution was next investigated (Scheme 30). Over the range of dilutions tested, the reactions all proceeded to completion within 5 min. Although the reaction was slow to respond to increasing dilution, the NMR yield of fluorohydrin **97** rose from 16 to 23% on a 10-fold increase in solvent volume, and to 28% after a 100-fold increase. At 100-fold dilution (0.0025 M), a 39:61 ratio of fluorohydrin **97** to aldehyde **106** was evident, with only ~30% of oligomeric products – a significant reduction compared to reactions performed at 0.25 M (~60% oligomeric products). This observation vindicates the earlier proposal that other products besides fluorohydrins and arylacetaldehydes arise from oligomerisation pathways.

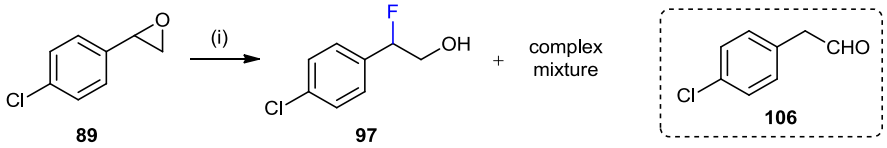


[89]	Dilution Factor	Fluorohydrin 97 NMR Yield
0.25 M	1	16%
0.125 M	2	16%
0.05 M	5	19%
0.025 M	10	23%
0.0025 M	100	28%

Scheme 30. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, −20 °C, 5 min.

2.2.1.2.5. Effect of the Rate of Addition of *p*-Chlorostyrene Oxide

In an effort to simulate the effect of high dilution without using impractically large volumes of solvent, the slow addition of **89** to a solution of BF_3•OEt_2 was next attempted. Thus, a solution of **89** in (minimal) CH_2Cl_2 was added dropwise *via* syringe pump at various different rates to a stirred solution of 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 at −20 °C, such that the final concentration of **89** in the medium would be 0.05 M[54] (Scheme 31). However, slow addition of **89** to the reaction actually decreased the yield of fluorohydrin **97**, consistent with earlier observations that a large excess of BF_3•OEt_2 is detrimental to the reaction.



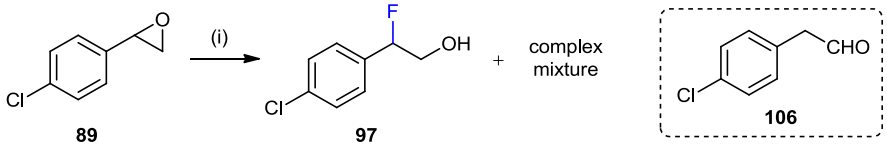
Time Period of Addition of 89	Fluorohydrin 97 NMR Yield
"instant"	19%
10 min	19%
20 min	14%
30 min	11%
40 min	9%

Scheme 31. *Reagents and conditions:* (i) **89** in CH_2Cl_2 added slowly to BF_3•OEt_2 (0.33 equiv) in CH_2Cl_2 at −20 °C then additional stirring at −20 °C for 5 min.

2.2.1.2.6. Effect of the Rate of Addition of BF_3•OEt_2

As the final reaction variable to examine, the rate of addition of BF_3•OEt_2 to the reaction was next studied. Thus, a solution of 0.33 equiv of BF_3•OEt_2 in (minimal) CH_2Cl_2 was added dropwise *via* syringe pump at various different rates to a stirred solution of epoxide **89** in CH_2Cl_2 at −20 °C, such that the final concentration of **89** in the medium would be 0.05 M[55] (Scheme 32). Unfortunately, no significant

improvement was achieved by slow addition of BF_3•OEt_2, although the yield of fluorohydrin **97** did appear to respond to this variable, albeit in a non-linear fashion.



Time Period of Addition of BF_3•OEt_2	Fluorohydrin 97 NMR Yield
"instant"	19%
10 min	25%
20 min	25%
40 min	22%
12.5 h[a]	14%

[a]Final concentration of 0.025 M wrt **89**.

Scheme 32. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv) in CH_2Cl_2 added slowly to **89** (1 equiv) in CH_2Cl_2 at −20 °C then additional stirring at −20 °C for 5 min.

2.2.2. Effect of Oxirane Substituents on Ring-Opening Fluorination of Aryl Epoxides with BF_3•OEt_2

Based on the initial screening of *p*-substituted styrene oxides **73** and **85-92** with BF_3•OEt_2 and the optimisation studies conducted with *p*-chlorostyrene oxide **89**, it transpires that styrene oxides are not viable substrates for a synthetically useful ring-opening fluorination with BF_3•OEt_2. Thus, the effect of introducing substitution onto the oxirane ring was next investigated, and a series of mono-, di- and trimethyl-substituted aryl epoxides **74**, **75** and **109-113** were prepared from the corresponding alkenes *via* bromohydroxylation-cyclisation or epoxidation, or from the corresponding α-bromo ketones *via* reduction-cyclisation (Figure 14).

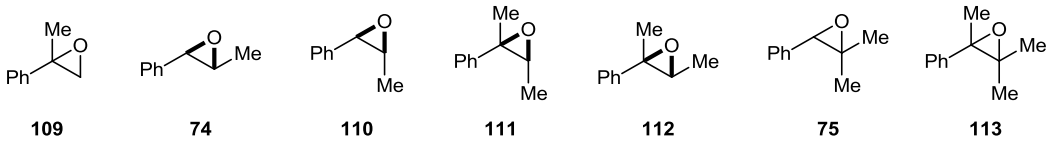
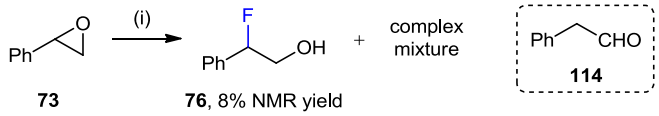


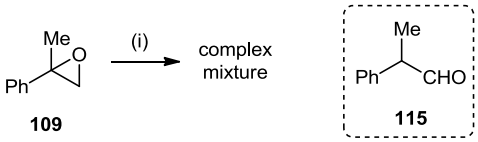
Figure 14. Aryl epoxides **74**, **75** and **109-113** with various oxirane substitution patterns.

To examine the effect of oxirane substitution on the ring-opening fluorination of aryl epoxides with BF_3•OEt_2, the methyl-substituted oxiranes **74**, **75** and **109-113**, in addition to styrene oxide **73** as a reference substrate, were each subjected to 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 (0.25 M wrt epoxide) at –20 °C for 5 min. Under these conditions, styrene oxide **73** produced a complex mixture of products containing fluorohydrin **76** (8% NMR yield) and aldehyde **114** as components (Scheme 33).



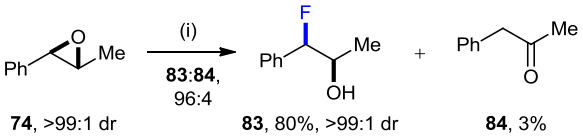
Scheme 33. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Similarly, α-methylstyrene oxide **109** gave a complex mixture of products containing aldehyde **115** as a component, with no fluorohydrin detectable *via* ^{19}F NMR spectroscopic analysis (Scheme 34).



Scheme 34. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Remarkably, (*E*)-β-methylstyrene oxide **74** gave comparatively clean conversion to a 96:4 mixture of fluorohydrin **83** and ketone **84**, with **83** isolated in 80% yield as a single diastereoisomer, in addition to **84** in 3% yield (Scheme 35).[56] Compared to styrene oxide **73**, the significantly lower proportion of oligomeric products (~10%) in the reaction of **74** with BF_3•OEt_2 is consistent with the fact that the cationic polymerisation of epoxides is known to be retarded by additional oxirane substituents due to steric hindrance.[57]



Scheme 35. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

The *syn*-configuration within fluorohydrin **83** was established unambiguously *via* single crystal X-ray diffraction analysis of its *p*-nitrobenzoate derivative **116** (Figure 15).[58] The tendency of aryl epoxides to undergo nucleophilic ring-opening with retention of configuration has previously been documented,[59,60] and it is noteworthy that the ring-opening fluorination of (*E*)-β-methylstyrene oxide **74** with retention of configuration has also been observed with SiF_4,[35a] KH_2F_3[61] and HF (in the presence of various additives)[62] as fluorinating agents.

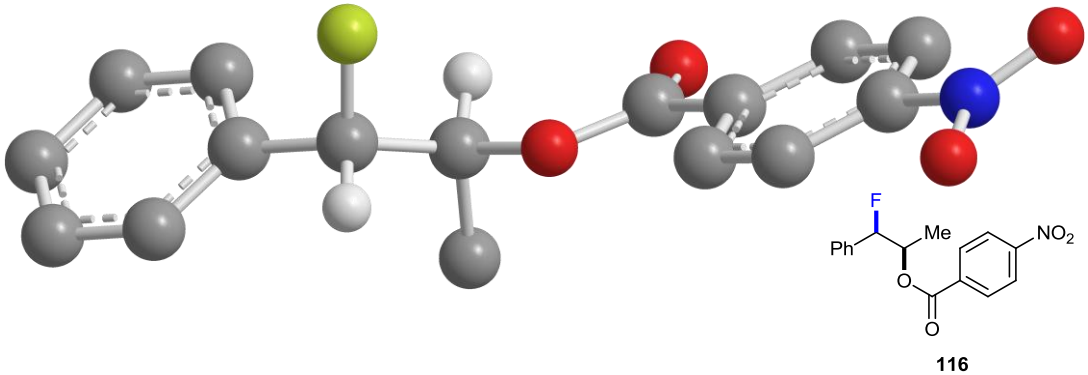
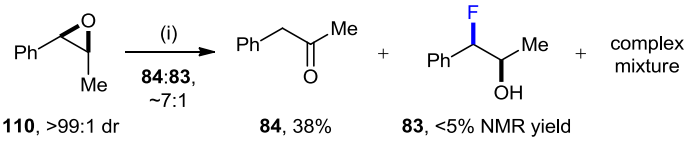


Figure 15. Chem3D representation of the single crystal X-ray diffraction structure of **116** (selected H atoms omitted for clarity).

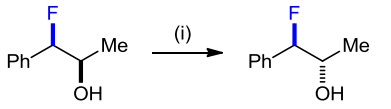
In constrast to the reaction with *trans*-epoxide **74**, the corresponding *cis*-epoxide **110** gave a complex mixture of products containing a ~7:1 ratio of phenylpropan-2-one **84** to *syn*-fluorohydrin **83** (<5% NMR yield), with **84** isolated in 38% yield and **83** isolated as an impure sample (Scheme 36).



110, >99:1 dr **84**, 38% **83**, <5% NMR yield

Scheme 36. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

The synthesis of an authentic sample of the diastereoisomeric *anti*-fluorohydrin **77** *via* a Mitsunobu inversion procedure on **83** confirmed that none of this compound was formed from either *trans*-epoxide **74** or *cis*-epoxide **110** (Scheme 37).



83, >99:1 dr **77**, 57%, >99:1 dr

Scheme 37. *Reagents and conditions:* (i) PPh_3 (2 equiv), *p*-nitrobenzoic acid (1.5 equiv), DEAD (1.7 equiv), THF, 0 °C to rt, 6.5 h then K_2CO_3 (4 equiv), MeOH, rt, 15 h.

The formation of *syn*-fluorohydrin **83** from *trans*-epoxide **74** can be rationalised on the basis of an S_Ni mechanism[36] involving ionisation of the epoxide-BF_3 complex **117** to give a benzylic carbocation in initial conformation **119A**, followed by intramolecular fluoride transfer from the *O*-tethered alkoxytrifluoroborate moiety. The effect of the *trans*-β-methyl substituent may be to sterically bias the carbocation intermediate in its initially formed conformation **119A**, increasing the activation barrier to C–C bond rotation and decreasing the rate of this process (which leads to ketone **84**) relative to fluoride transfer. The fact that all 3 fluorine atoms within BF_3•OEt_2 are transferred in this reaction[23,63] implies that the initially formed (*O*-difluoroboryl)fluorohydrin species **120** is a competent fluorinating agent in its own right, and may react further with any available epoxide **74** (by analogy to BF_3) to generate dialkoxyborane **121** and, ultimately, trialkoxyborane species **122**.[64] The observation that ketone **84** is the major product from the reaction of *cis*-**110** with BF_3•OEt_2 is consistent with ionisation of the epoxide-BF_3 complex **118** to give a benzylic carbocation in initial conformation **119C**, followed by rapid C–C bond rotation to conformer **119B** to alleviate the steric interaction between the Ph and Me substituents. A rapid [1,2]-H shift may then ensue to give ketone **84**. The formation of <5% of *syn*-fluorohydrin **83** from *cis*-**110** implies that some interconversion of conformer **119B** to conformer **119A** occurs in competition with the [1,2]-H shift (Figure 16).[65]

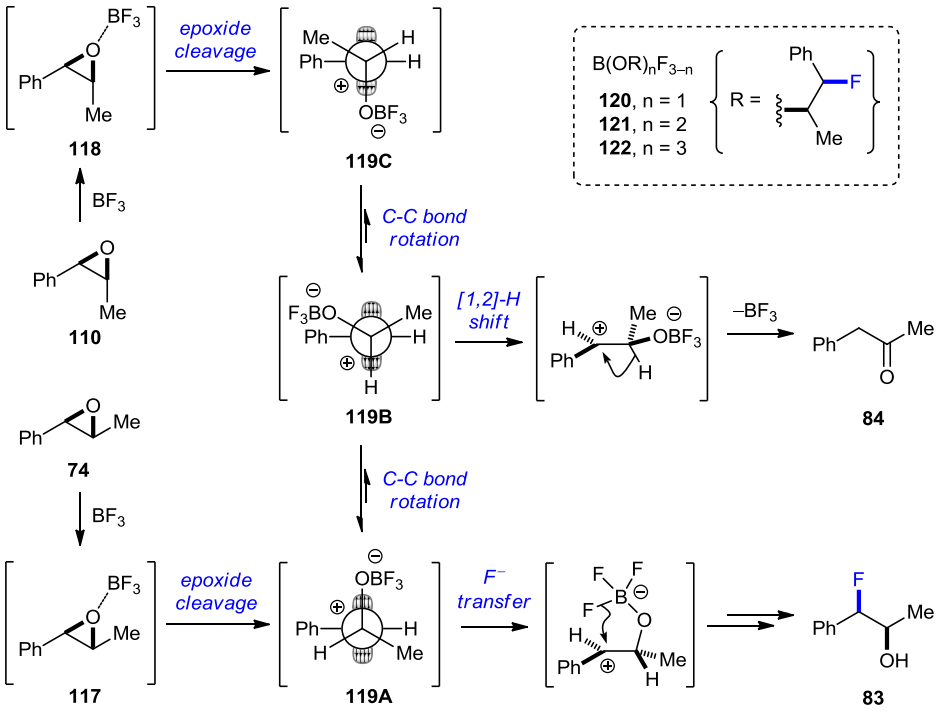


Figure 16. Mechanistic rationale for the formation of fluorohydrin **83** and ketone **84**.

The formation of a complex mixture of non-fluorinated products from *cis*-**110** suggests that epoxide oligomerisation is still operative to a large extent in this case.[66] Notably, the rate of ionisation of *cis*-configured aryl epoxides[67] and aziridines[68] under acidic conditions has previously been observed to be slower than for their *trans*-counterparts due to a steric inhibition of resonance effect,[50a] and this may partly account for the higher proportion of epoxide oligomerisation with *cis*-**110**, as compared to *trans*-**74**. Also, the rate of $HClO_4$-initiated cationic polymerisation of *cis*-2,3-epoxybutane has been reported to be twice as fast as that for *trans*-2,3-epoxybutane,[69] possibly on account of the greater steric accessibility of the oxirane lone pair in the former case, and this may also be true for *trans*-**74** and *cis*-**110** (Figure 17).

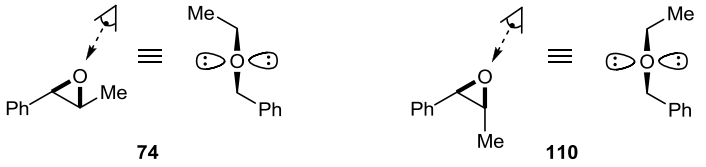
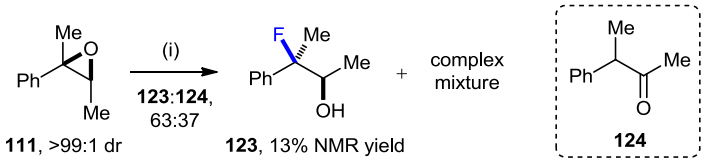


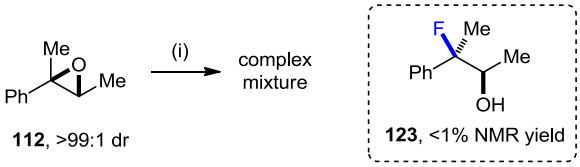
Figure 17. Differential steric accessibility of oxirane lone pairs for *trans*-**74** and *cis*-**110**.

The effect of trisubstitution on the oxirane ring was next investigated. Thus, treatment of (*Z*)-α,β-dimethylstyrene oxide **111** with 0.33 equiv of BF_3•OEt_2 gave a complex mixture of products containing a 63:37 ratio of fluorohydrin **123** (13% NMR yield) to ketone **124** (Scheme 38). Although chromatographic purification provided an impure sample of fluorohydrin **123** as a single diastereoisomer, formation of a *p*-nitrobenzoate derivative for X-ray diffraction analysis proved unsuccessful, simply returning unreacted **123**. The relative configuration within **123** was therefore tentatively assigned on the assumption that ring-opening fluorination had occurred with retention of configuration, by analogy to the ring-opening fluorination of (*E*)-β-methylstyrene oxide **74** (*vide supra*).



Scheme 38. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Contrastingly, the reaction of (*E*)-α,β-dimethylstyrene oxide **112** under the same conditions delivered a complex mixture of products containing <1% NMR yield of a fluorinated compound (Scheme 39). On the basis that the ^{19}F NMR resonance for this compound was identical to that of fluorohydrin **123**, this product was tentatively assigned as **123**.[70] This apparent stereoconvergency, including the fact that one epoxide diastereoisomer (in this case **111**) gives a much higher yield of fluorohydrin than the other, parallels the results obtained with disubstituted epoxides **74** and **110** (*vide supra*).



Scheme 39. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

The relative efficiencies of fluorination of diastereoisomeric epoxides **111** and **112** can be explained using a similar mechanistic rationale as that employed for **74** and **110**, assuming that the Me↔Me steric interaction is more destabilising than the Me↔Ph interaction (i.e. that carbocation conformer **125A** is lower in energy than **125B**) (Figure 18). That the absolute efficiency of fluorination of **111** is so low compared to **74** is consistent with a weaker steric bias to maintain the carbocation in its initially formed conformation, as well as a slower rate of fluoride transfer (relative to C−C bond rotation) due to a diminished reactivity of the benzylic carbocation (i.e. 3° for **111** *versus* 2° for **74**).

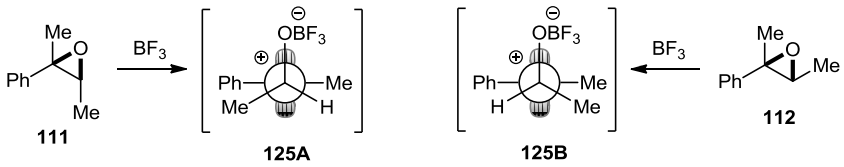
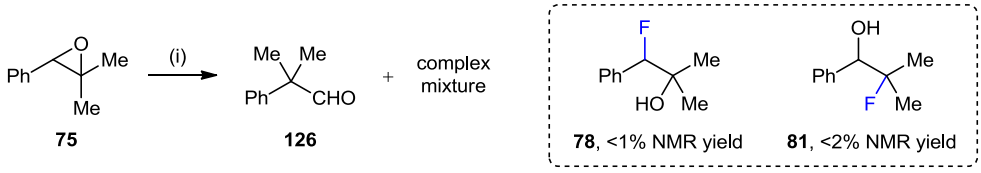


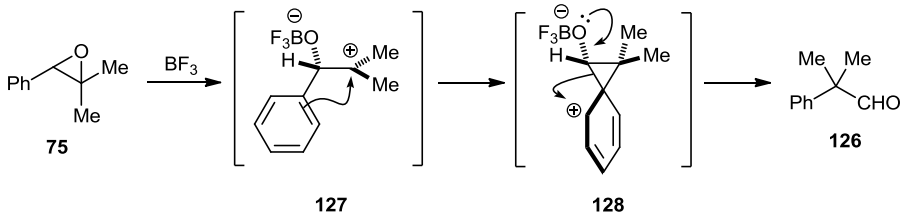
Figure 18. Initially formed conformations of carbocation **125** from diastereoisomeric epoxides **111** and **112**.

β,β-Dimethylstyrene oxide **75** gave a complex mixture of products containing aldehyde **126** as the major component, in addition to known benzylic and homobenzylic fluorides **78** and **81**[71] in <1 and <2% NMR yield respectively (Scheme 40).



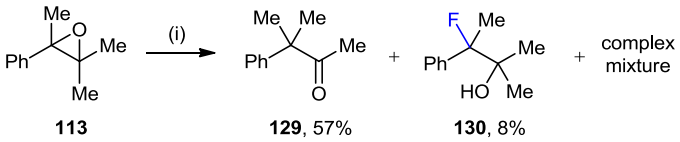
Scheme 40. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

The observation that aldehyde **126** is the major product from the reaction of **75** with BF_3•OEt_2 suggests that ionisation must occur predominantly at the homobenzylic carbon to give 3° carbocation **127**,[72,73] followed by a [1,2]-Ph shift *via* a phenonium intermediate **128** (Scheme 41).



Scheme 41. Mechanistic rationale for the formation of aldehyde **126**.

Lastly, α,β,β-trimethylstyrene oxide **113** gave ketone **129** as the major product in 57% isolated yield, in addition to fluorohydrin **130** in 8% isolated yield (Scheme 42). The balance of the mass comprised a mixture of non-fluorinated products.



Scheme 42. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

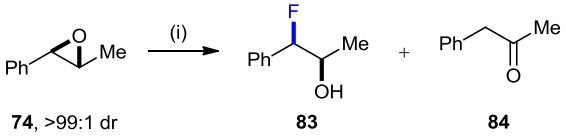
2.2.3. Ring-Opening Fluorination of *trans*-β-Substituted Aryl Epoxides with BF_3•OEt_2: Further Investigation

Having established that *trans*-β-substituted aryl epoxides are a privileged substrate class for ring-opening fluorination with BF_3•OEt_2 in CH_2Cl_2, the effects of temperature variation, functional groups on the oxirane moiety, and the electronics of the aryl ring were next assessed.

2.2.3.1. Effect of the Reaction Temperature

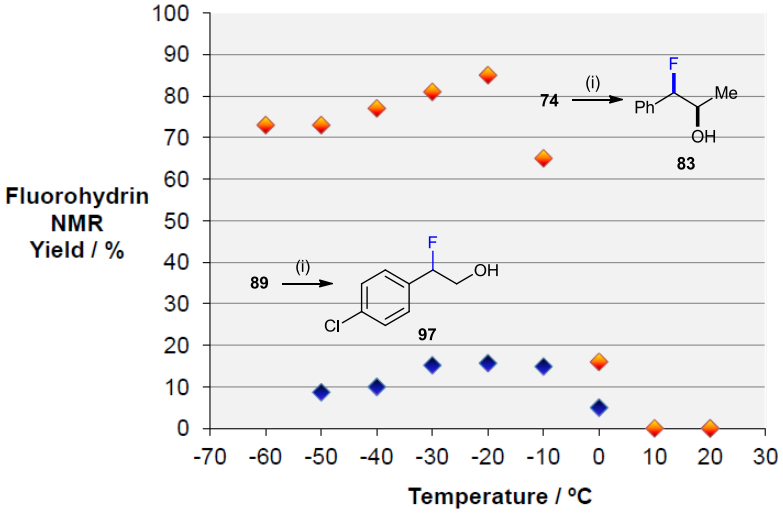
To determine the optimum temperature for the ring-opening fluorination of (*E*)-β-methylstyrene oxide **74** with BF_3•OEt_2 in CH_2Cl_2, a range of experiments were performed at temperatures varying from rt (20 °C) to −60 °C. A graphical representation of these results shows that the fluorohydrin yield follows a non-linear temperature dependence very similar to that observed for *p*-chlorostyrene oxide **89** (**blue line**) (*vide supra*), with the yield of **83** (**orange line**) maximised at –20 °C (Scheme 43). The inverse relationship between the fluorohydrin **83** to ketone **84** ratio and the temperature indicates that C–C bond rotation occurs more rapidly than fluoride transfer at higher temperatures. Below −20 °C, the **83**:**84** ratio is constant, implying that it is no longer a competition between C–C bond rotation and fluoride transfer which is determining the fluorohydrin **83** yield. At temperatures lower than −20 °C, it may be that the rate of ionisation of epoxide-BF_3 complex **117** becomes increasingly slowed (Figure 16), whereas epoxide oligomerisation (which can proceed *via* an S_N2-type pathway[44]) may be less affected. Some support for this assertion can be found in studies relating to the acid-catalysed acetalisation of (*E*)-stilbene oxide in acetone, where the ratio of S_N1 to S_N2 derived

products has been shown to decrease significantly as the temperature is lowered (60:40 S_N1:S_N2 at 25 °C to 20:80 S_N1:S_N2 at −78 °C).[74]



74, >99:1 dr **83** **84**

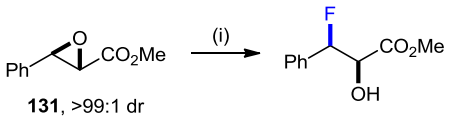
T °C	Fluorohydrin 83 NMR Yield	83:84 Ratio
20 °C	0%	0:100
10 °C	0%	0:100
0 °C	16%	32:68
−10 °C	65%	85:15
−20 °C	85%	96:4
−30 °C	81%	96:4
−40 °C	77%	97:3
−50 °C	73%	97:3
−60 °C	73%	97:3



Scheme 43. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, T °C, 5 min.

2.2.3.2. Tolerance of Functional Groups on the Oxirane Ring

To assess the functional group tolerance of the ring-opening fluorination reaction with BF_3•OEt_2, a range of functionalised epoxides (prepared as single diastereoisomers *via* standard synthetic methods) were next subjected to 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 (0.25 M wrt epoxide) at –20 °C for 5 min (unless otherwise stated). Under these conditions, the reaction of methyl *trans*-3-phenylglycidate **131** proceeded to only 78% conversion, although extension of the reaction time to 30 min allowed for complete conversion,[75] giving fluorohydrin **132** in 65% yield and >99:1 dr (Scheme 44). The *syn*-configuration within **132** was proven unambiguously *via* single crystal X-ray diffraction analysis of its *p*-nitrobenzoate derivative **133** (Figure 19).[58]



131, >99:1 dr **132**, 65%, >99:1 dr

Scheme 44. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 30 min.

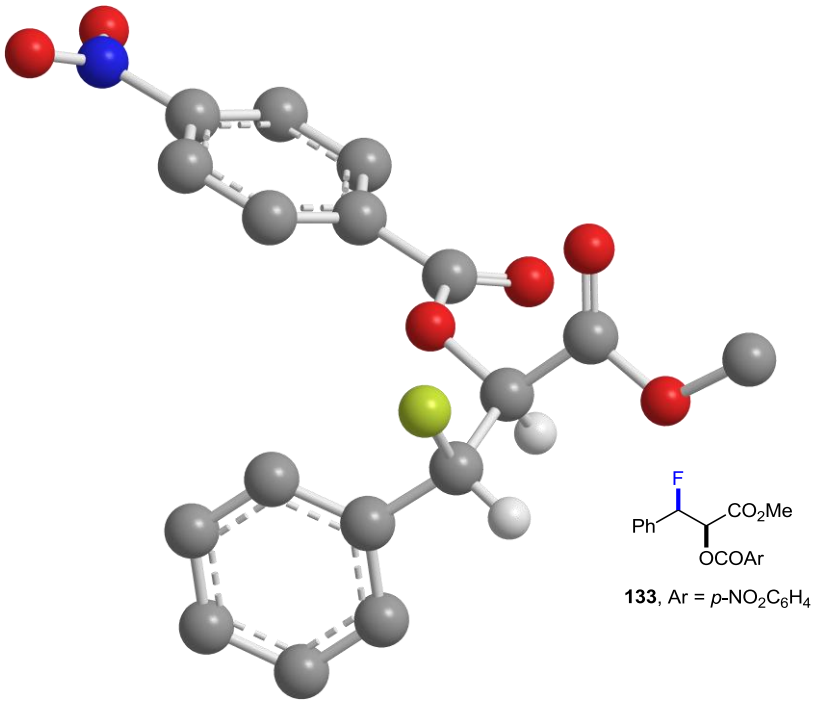
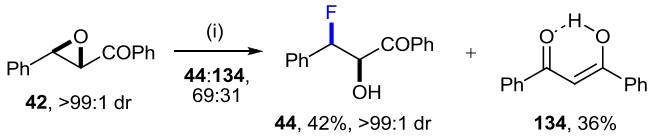


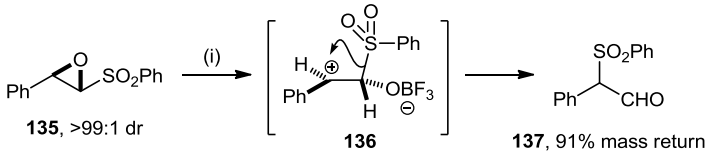
Figure 19. Chem3D representation of the single crystal X-ray diffraction structure of **133** (selected H atoms omitted for clarity).

Similarly, the reaction of (*E*)-chalcone oxide **42** with BF_3•OEt_2 gave a 69:31 ratio of fluorohydrin **44** to keto-enol **134**, with **44** isolated in 42% yield and >99:1 dr and **134** isolated in 36% yield (Scheme 45).



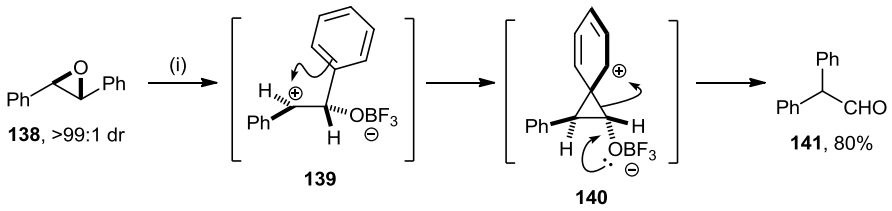
Scheme 45. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Surprisingly, the reaction of phenylsulfonyl-substituted epoxide **135** with BF_3•OEt_2 gave a compound tentatively assigned by ^{1}H NMR spectroscopy as aldehyde **137** as the sole product (91% mass return), which unfortunately decomposed upon attempted purification *via* flash column chromatography. Although **136** may have arisen *via* a [1,2]-phenylsulfonyl shift within carbocation intermediate **136**, the migration of sulfonyl groups to carbocations is unprecedented in the literature (Scheme 46).



Scheme 46. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

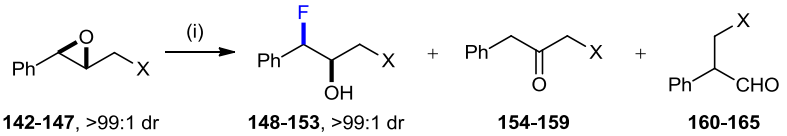
Aldehyde formation was similarly observed on reaction of (*E*)-stilbene oxide **138** with BF_3•OEt_2, giving aldehyde **141** in 80% yield, presumably *via* the intermediacy of phenonium ion **140** (Scheme 47).



138, >99:1 dr **139** **140** **141**, 80%

Scheme 47. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Under the standard conditions, the reaction of *trans*-3-phenylglycidol **142** with BF_3•OEt_2 led to the formation of a complex mixture of non-fluorinated products, presumably as the result of a polymerisation process. However, the analogous reaction of epoxides **143**-**146** bearing chloro, bromo, azido and tosyloxy groups proceeded to give fluorohydrins **149**-**152** in good yield and as single diastereoisomers. In constrast, the reaction of *tert*-butyldimethylsilyloxy substituted epoxide **147** with BF_3•OEt_2 led to a 55:35:10 mixture of aldehyde **165**, fluorohydrin **153** and ketone **159**, with **165** isolated in 41% yield and **153** isolated in 31% yield and >99:1 dr (Scheme 48). The formation of **165** as the major product is consistent with a high propensity for the CH_2OTBDMS group to undergo a [1,2]-shift to the benzylic carbocationic centre, on account of the migrating carbon being both α to oxygen and β to silicon.

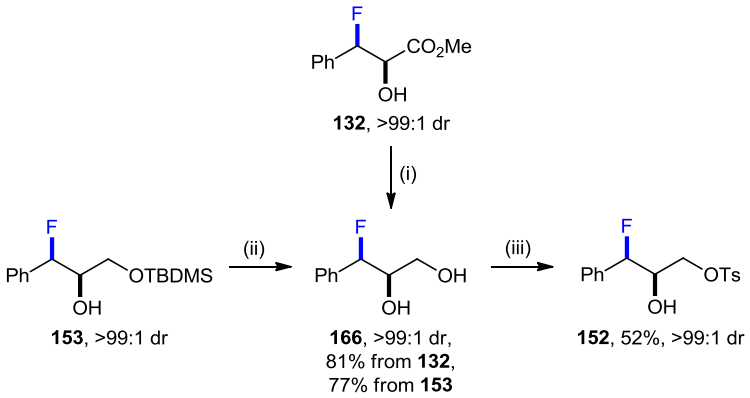


142-**147**, >99:1 dr **148**-**153**, >99:1 dr **154**-**159** **160**-**165**

Epoxide	X	Product Ratio	Fluorohydrin Isolated Yield	Ketone Isolated Yield	Aldehyde Isolated Yield
142	OH	**148**:**154**:**160**, 0:0:0	**148**, 0%	**154**, 0%	**160**, 0%
143	Cl	**149**:**155**:**161**, 78:22:0	**149**, 70%	**155**, not isolated	**161**, 0%
144	Br	**150**:**156**:**162**, 78:22:0	**150**, 72%	**156**, 21%	**162**, 0%
145	N_3	**151**:**157**:**163**, 92:8:0	**151**, 65%	**157**, not isolated	**163**, 0%
146	OTs	**152**:**158**:**164**, 84:16:0	**152**, 84%	**158**, 16%	**164**, 0%
147	OTBDMS	**153**:**159**:**165**, 35:10:55	**153**, 31%	**159**, not isolated	**165**, 41%

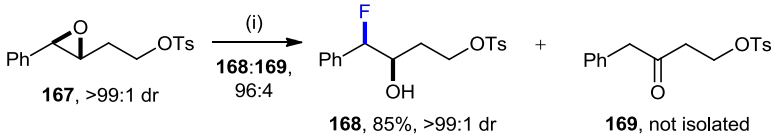
Scheme 48. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, −20 °C, 5 min.

The relative configurations within fluorohydrins **152** and **153** were proven unambiguously as *syn* by chemical correlation to **132** (Scheme 49). On this basis, the relative configurations within fluorohydrins **149**-**151** were also assigned as *syn* by analogy. It should be noted that Pericàs *et al.* have previously assigned the relative configuration within **152** as *anti*,[23] although they have since reassigned **152** as *syn*[76] after re-evaluating their analysis on the basis of the results of this chapter.[77]



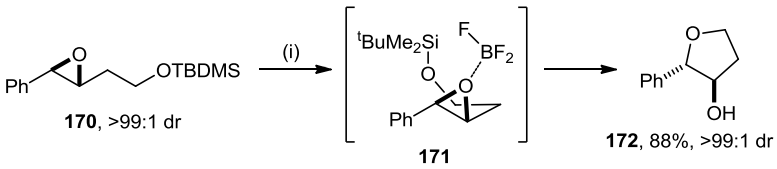
Scheme 49. *Reagents and conditions:* (i) $NaBH_4$ (2 equiv), MeOH, 0 °C to rt, 46 h; (ii) TBAF (1.5 equiv), THF, rt, 12 h; (iii) TsCl (1 equiv), Et_3N (3 equiv), DMAP (2 mol%), CH_2Cl_2, 0 °C to rt, 17 h.

The effect of introducing an additional methylene spacer group was also briefly examined. Thus, the reaction of *p*-toluenesulfonyloxy substituted epoxide **167** with BF_3•OEt_2 gave fluorohydrin **168** in 85% yield and >99:1 dr, with a *syn*-configuration being assigned to **168** (by analogy to **152**) (Scheme 50).



Scheme 50. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

Unexpectedly, the reaction of *tert*-butyldimethylsilyloxy substituted epoxide **170** with BF_3•OEt_2 gave the known tetrahydrofuran **172**[78] as the sole product in 88% yield, possibly arising *via* an intramolecular transfer of fluoride from B to Si accompanied by intramolecular S_N2-type attack of the silyloxy oxygen atom onto the activated epoxide within intermediate **171** (Scheme 51).[79,80] Whether this process is stepwise or concerted remains unclear.[81]

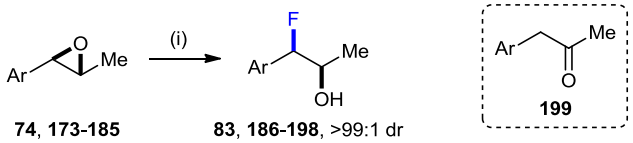


Scheme 51. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, –20 °C, 5 min.

2.2.3.3. Effect of the Electronics of the Aryl Ring

In order to examine the effect of the electronics of the aryl ring on the ring-opening fluorination with BF_3•OEt_2, a variety of *trans*-β-methyl aryl epoxides **173-185** were prepared *via* bromohydroxylation-cyclisation or epoxidation of the corresponding alkenes. The Brown-Okamoto substituent constant, σ^+, was used to quantify the electronic effect of each aryl group, and define a relative ordering of **74** and **173-185** in terms of the anticipated stability of a benzylic carbocation intermediate.[38] Epoxides **173-185** were then each subjected to 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 (0.25 M wrt epoxide) at –20 °C for the stated time (Scheme 52). In similarity to the results obtained for styrene oxides **73** and **85-92** (*vide supra*), epoxides **173-176** bearing electron-rich aryl groups gave only mixtures of non-fluorinated compounds, including the

corresponding arylpropan-2-ones **199** as major components. However, epoxide **177** incorporating a 2-naphthyl moiety did produce a small amount of fluorohydrin **190**, isolated in 21% yield as a single diastereoisomer. Epoxides **178**-**181** bearing electron-neutral through to moderately electron-poor aryl groups gave the highest yields of fluorohydrins (76-83%), whereas substrates **182**-**184** with more strongly electron-poor aryl groups returned slightly lower fluorohydrin yields (64-67%). With epoxide **185** bearing an extremely electron-poor *p*-(trifluoromethyl)phenyl group, the reaction proceeded to only partial conversion to give a complex mixture of products containing a 74:26 ratio of starting material **185** and fluorohydrin **198**. These results lend further credence to a mechanism proceeding *via* the intermediacy of benzylic carbocation intermediates, in which the successful incorporation of fluorine hinges on a compromise between carbocation stability *versus* reactivity (*vide supra*). The relative configurations within fluorohydrins **190**-**198** were assigned as *syn* by analogy to that unambiguously proven for **83** (*vide supra*). In all cases, the ^{1}H-^{1}H ^{3}J NMR coupling constant between the C(1)*H* and C(2)*H* protons was within the range 6.8-7.1 Hz, in close agreement with the value of 7.1 Hz observed for **83** (a value of 4.8 Hz was observed for the diastereoisomeric *anti*-fluorohydrin **77**).



74, **173**-**185** **83**, **186**-**198**, >99:1 dr

Epoxide	Ar	σ^+	Time	Fluorohydrin Isolated Yield
173, 96:4 dr	4-$MeOC_6H_4$	−0.78	5 min	**186**, 0%
174, 96:4 dr	4-$PhOC_6H_4$	−0.50	5 min	**187**, 0%
175, 90:10 dr	4-MeC_6H_4	−0.31	5 min	**188**, 0%
176, 98:2 dr	4-PhC_6H_4	−0.18	5 min	**189**, 0%
177, 96:4 dr	2-naphthyl	−0.13	5 min	**190**, 21%
178, 94:6 dr	4-FC_6H_4	−0.07	5 min	**191**, 76%
74, >99:1 dr	Ph	0.00	5 min	**83**, 80%
179, 93:7 dr	3-$MeOC_6H_4$	+0.05	5 min	**192**, 81%
180, 94:6 dr	4-ClC_6H_4	+0.11	10 min	**193**, 76%
181, 94:6 dr	4-BrC_6H_4	+0.15	10 min	**194**, 78%
182, 95:5 dr	3-FC_6H_4	+0.35	10 min	**195**, 67%
183, 92:8 dr	3-ClC_6H_4	+0.40	10 min	**196**, 64%
184, 91:9 dr	3-BrC_6H_4	+0.41	10 min	**197**, 67%
185, 94:6 dr	4-$CF_3C_6H_4$	+0.61	10 min	**198**, <20%

Scheme 52. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, −20 °C.

2.2.4. Application of Methodology to the Synthesis of β-Fluoroamphetamines

To illustrate the potential of the above fluorination methodology in the synthesis of pharmaceutically-interesting benzylic fluorides, it was envisaged that the fluorohydrins **201** obtained *via* ring-opening fluorination of aryl epoxides **200** with BF_3•OEt_2 could be elaborated to β-fluoroamphetamines **202** (Figure 20).[82]

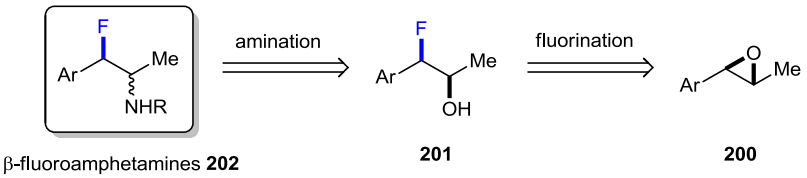


Figure 20. Proposed elaboration of *syn*-fluorohydrins **201** to β-fluoroamphetamines **202**.

2.2.4.1. Previous Interest in Fluorinated Amphetamines

Amphetamines comprise a family of 1-phenylpropan-2-amine derivatives which have a diverse range of effects upon the central nervous system (CNS), including psychoanaleptic, hallucinogenic and empathogenic activity. Synthetic examples include the parent compound amphetamine **203**, methamphetamine **204** and MDMA **205**.[83] Naturally-occurring amphetamine relatives include the *ephedra* alkaloids L-(–)-ephedrine **206** and D-(+)-pseudoephedrine **207** (Figure 21). The synthetic antipodes D-(+)-**206** and L-(–)-**207** are also readily available as products of commerce.

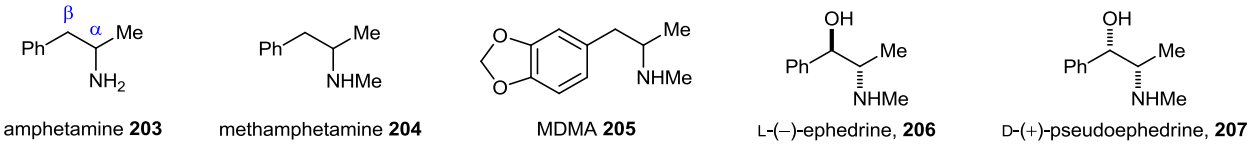
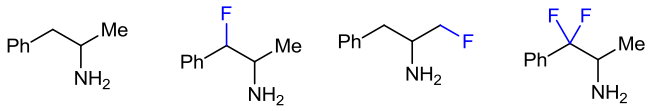


Figure 21. Examples of amphetamines and their close relatives, the *ephedra* alkaloids.

Fluorination β- to amino groups is a common strategy in medicinal chemistry for increasing oral bioavailability by reducing the proportion of protonated amine at physiological pH (7.4) (see chapter 1). This reduction in percentage protonation is of particular relevance to CNS active compounds, such as amphetamines, which must permeate the blood brain barrier, and studies on the biological activity of β-fluoroamphetamines[84] (e.g. **208**), β,β-difluoroamphetamines[84,85] (e.g. **210**) and amphetamines bearing a fluoro substituent on the methyl group[86] (e.g. **209**) have been conducted (Figure 22).[87] For example, Fuller and co-workers reported that β-fluoroamphetamine **208** (racemic with undefined relative configuration), displays similar sympathomimetic[88] activity to amphetamine **203**, but with relatively less undesired CNS excitation.[84]



	203	**208**	**209**	**210**
pK_{aH}	9.5	8.4	7.9	7.0
% protonated at pH 7.4	>99%	90%	76%	27%

Figure 22. Fluorinated amphetamines and their attendent pK_{aH} values (ref. 86b).

Van Dort *et al.* have also synthesised enantiopure ^{18}F-labelled *N*-methyl-β-fluoroamphetamines **211** and **212** as radiotracers for the *in vivo* diagnostic imaging of CNS diseases and tumours (Figure 23).[89] The higher percentage of the free base forms of **211** and **212** in blood meant that they could traverse the blood-brain barrier more readily than their non-fluorinated or β-hydroxy counterparts.

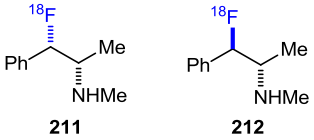
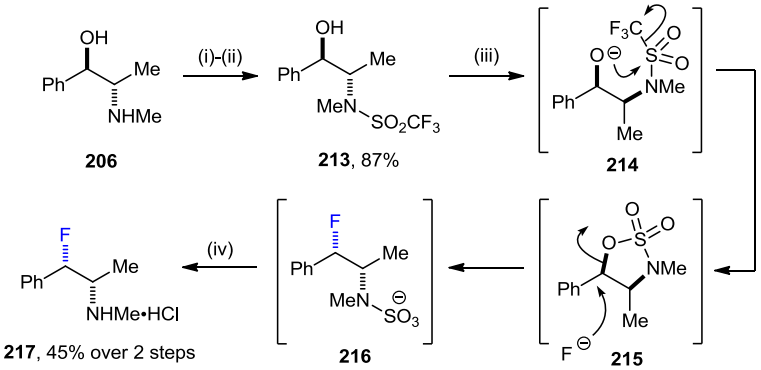


Figure 23. ^{18}F-Labelled *N*-methyl-β-fluoroamphetamines as *in vivo* radiotracers.

The β-fluoro β-aryl amine motif has also appeared as a core structural element in SAR studies directed towards the identification of agrochemical fungicides,[90] nitric oxide synthase inhibitors[91] and monoamine oxidase inhibitors,[92] the latter of which hold promise in the treatment of various CNS diseases.

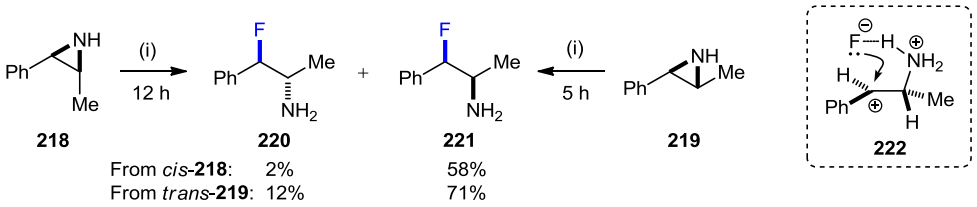
2.2.4.2. Existing Methods for the Synthesis of β-Fluoro β-Aryl Amines

β-Fluoro β-aryl amines have previously been synthesised from the corresponding β-hydroxy β-aryl amines (or derivatives thereof) by direct deoxyfluorination[93] or *via* the ring-opening fluorination of cyclic sulfamidates.[89,94] Although the former method often suffers from stereorandomisation at the benzylic centre due to the intermediacy of carbocations, the latter protocol has proven effective for the enantiospecific synthesis of *N*-methyl-β-fluoroamphetamines. For example, Lyle *et al.* showed that the treatment of *N*-trifyl ephedrine **213** (derived from ephedrine **206** in 2 steps) with TBAF caused cyclisation to sulfamidate **215**; subsequent *in-situ* ring-opening of **215** with fluoride ion generated *N*-sulfonate salt **216**, and hydrolysis with 3 M aq HCl gave *N*-methyl-β-fluoroamphetamine HCl salt **217** in 45% yield from **213** (Scheme 53).[94]



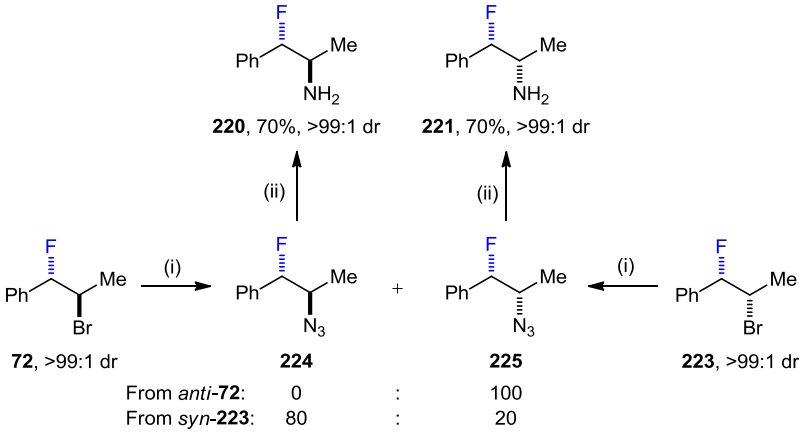
Scheme 53. *Reagents and conditions:* (i) TMS-imidazole, CH_2Cl_2; (ii) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C then aqueous acid; (iii) TBAF, MeCN, 70 °C, 1 h; (iv) 3 M aq HCl, 70 °C, 15 min.

Another method for the synthesis of β-fluoro β-aryl amines involves the ring-opening fluorination of aryl aziridines with HF, although this method suffers from poor yields and a lack of stereospecificity.[68,95] Thus, Wade and co-workers showed that the treatment of both *cis*- and *trans*-aziridines **218** and **219**, respectively, with PPHF gave a mixture of diastereoisomeric β-fluoro β-aryl amines, with **221** as the major product in both cases.[68] The authors suggested that an S_N1-type mechanism was operative in which hydrogen bond-directed delivery of fluoride occurred within the more stable *trans*-configured benzylic carbocation intermediate **222** (Scheme 54).



Scheme 54. *Reagents and conditions:* (i) PPHF, benzene, rt.

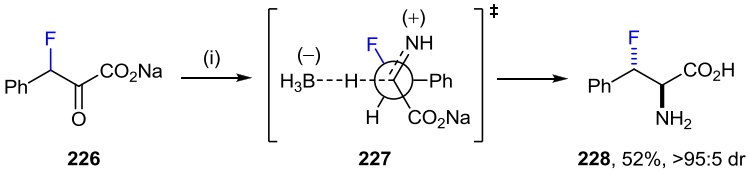
β-Fluoro β-aryl amines have also been synthesised in racemic form *via* an azide displacement-reduction sequence from the corresponding β-fluoro bromides,[19,20] the latter of which may be prepared by bromofluorination of aryl alkenes or by the deoxyfluorination of bromohydrins.[19] For example, Hamman, Béguin and Benaïssa have shown that the treatment of diastereoisomeric β-fluoro bromides **72** and **223** with NaN_3 provides access to β-fluoro azides **224** and **225**, respectively.[19] These azides were then subjected to Staudinger reduction with PPh_3 to give the requisite β-fluoroamphetamines **220** and **221**, respectively (Scheme 55).[20]



Scheme 55. *Reagents and conditions:* (i) NaN_3, TBAB (0.6 equiv), 50 °C, 168 h; (ii) PPh_3 (1 equiv), H_2O (1.5 equiv), THF, rt, 24 h.

Alternatively, introduction of the amino moiety *via* reductive amination has been utilised in the synthesis of the β-fluoro β-phenyl amine *erythro*-3-fluorophenylalanine **228**. Thus, α-fluoro keto acid sodium salt **226**, prepared *via* treatment of the corresponding methyl ester with elemental fluorine, followed by saponification, was reductively aminated with aq NH_3 and $NaBH_4$ to give *erythro*-3-fluorophenylalanine **228** in 52% yield

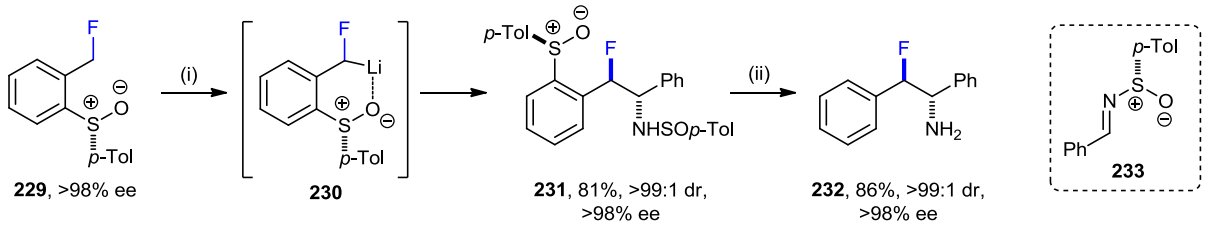
and >95:5 dr.[96] It was proposed that a through-space C−F--N^+ stabilising interaction[97] between the fluorine and the neighbouring iminium ion favoured a transition state **227** for the reduction (Scheme 56).[96]



226 **227** **228**, 52%, >95:5 dr

Scheme 56. *Reagents and conditions:* (i) 25% aq NH_3, 37 °C, 3 h then $NaBH_4$ (3 equiv), 10 °C to 30 °C, 2 h.

García Ruano, Fustero and co-workers have recently reported an asymmetric synthesis of β-fluoro β-aryl amines reliant on the doubly diastereoselective reaction of a lithiated benzyl fluoride equivalent (bearing a sulfinyl chiral auxiliary) with a range of enantiopure *N*-sulfinylimines.[98] Thus, enantiopure benzyl fluoride surrogate **229** was lithiated with LDA to give a benzylic α-fluoro carbanion **230**, which was then added to enantiopure *N*-sulfinylimine **233** to give the benzylic fluoride adduct **231** in 81% yield as a single stereoisomer. Subsequent desulfinylation using ^{t}BuLi gave enantiopure β-fluoro β-phenyl amine **232** in 86% yield (Scheme 57).

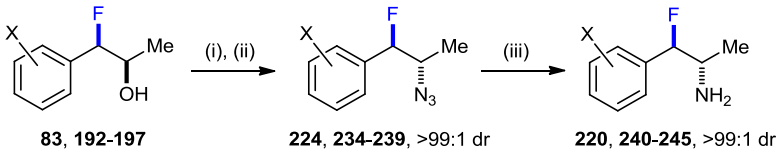


229, >98% ee **230** **231**, 81%, >99:1 dr, >98% ee **232**, 86%, >99:1 dr, >98% ee **233**

Scheme 57. *Reagents and conditions:* (i) LDA, THF, −78 °C then **233**; (ii) ^{t}BuLi (3.3 equiv), THF, −78 °C.

2.2.4.3. Synthesis of a Range of Aryl-Substituted β-Fluoroamphetamines

To showcase the utility of the ring-opening fluorination of aryl epoxides with BF_3•OEt_2 in the synthesis of a range of aryl-substituted β-fluoroamphetamines, it was reasoned that fluorohydrins **83** and **192**-**197** (*vide supra*) could be elaborated to β-fluoroamphetamines *via* the intermediacy of the corresponding β-fluoro azides. Thus, sequential treatment of fluorohydrins **83** and **192**-**197** with MsCl and NaN_3 gave the corresponding β-fluoro azides **224** and **234**-**239**, and subsequent Staudinger reduction provided β-fluoroamphetamines **220** and **240**-**245** in good yield and as single diastereoisomers (Scheme 58). The *anti*-configuration within **240**-**245** was assigned on the assumption that inversion of configuration occurred during azide displacement. In all cases, the ^{1}H-^{1}H ^3J NMR coupling constant between the C(1)*H* and C(2)*H* protons was within the range 5.3-5.6 Hz, which is supportive of the assigned *anti* stereochemistry (i.e. the ^3J value for *anti*-configured **220** has previously been reported as 5.5 Hz, compared to 6.6 Hz for its *syn*-diastereoisomer **221**).[99]



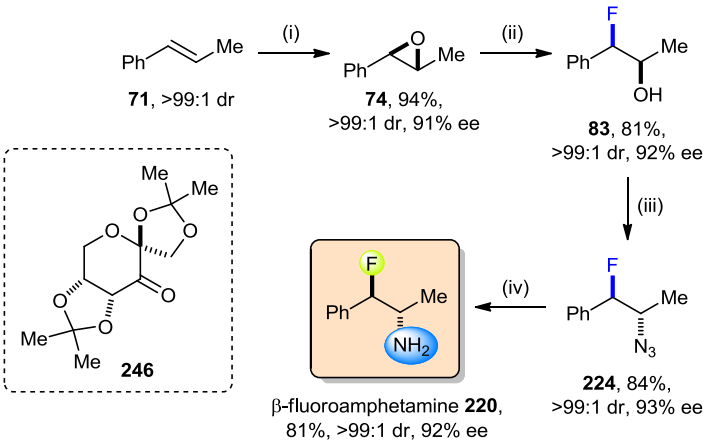
83, **192-197** **224**, **234-239**, >99:1 dr **220**, **240-245**, >99:1 dr

Fluorohydrin	X	β-Fluoro Azide Yield (2 steps)	β-Fluoroamphetamine Yield
83	H	**224**, 77%	**220**, 83%
192	*m*-OMe	**234**, 75%	**240**, 90%
193	*p*-Cl	**235**, 75%	**241**, 80%
194	*p*-Br	**236**, 74%	**242**, 78%
195	*m*-F	**237**, 65%	**243**, 80%
196	*m*-Cl	**238**, 63%	**244**, 87%
197	*m*-Br	**239**, 63%	**245**, 96%

Scheme 58. *Reagents and conditions:* (i) MsCl (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to rt, 1 h; (ii) NaN_3 (5 equiv), DMF, 100 °C, 24 h; (iii) PPh_3 (1.1 equiv), THF, rt, 30 min then H_2O (20 equiv), 50 °C, 2 h.

2.2.4.4. Asymmetric Synthesis of (α*S*,β*R*)-β-Fluoroamphetamine

To highlight the potential of the ring-opening fluorination of aryl epoxides with BF_3•OEt_2 in the enantioselective synthesis of β-fluoro β-aryl amines, a concise asymmetric synthesis of (α*S*,β*R*)-β-fluoroamphetamine **220** was next undertaken. Thus, following a literature procedure,[100] (*E*)-β-methylstyrene **71** was subjected to Shi asymmetric epoxidation[28] using commercially available D-fructose-derived ketone catalyst **246**, providing epoxide (*R*,*R*)-**74** in 94% yield, >99:1 dr and 91% ee.[101] Ring-opening fluorination of (*R*,*R*)-**74** with BF_3•OEt_2 under the optimised conditions gave fluorohydrin (*R*,*R*)-**83** in 81% yield, >99:1 dr and 92% ee.[102] Sequential treatment of fluorohydrin (*R*,*R*)-**83** with MsCl and NaN_3 then gave β-fluoro azide (1*R*,2*S*)-**224** in 84% yield, >99:1 dr and 93% ee.[103] Finally, Staudinger reduction of (1*R*,2*S*)-**224** provided (1*R*,2*S*)-β-fluoroamphetamine **220** in 81% yield, >99:1 dr and 92% ee,[104] in 52% overall yield from (*E*)-β-methylstyrene **71** (Scheme 59).



71, >99:1 dr **74**, 94%, >99:1 dr, 91% ee **83**, 81%, >99:1 dr, 92% ee

224, 84%, >99:1 dr, 93% ee β-fluoroamphetamine **220**, 81%, >99:1 dr, 92% ee

Scheme 59. *Reagents and conditions:* (i) Oxone®, **246** (35 mol%), KOH, Bu_4NHSO_4, MeCN/dimethoxymethane, −10 °C, 3.5 h; (ii) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, −20 °C, 5 min; (iii) MsCl, Et_3N, CH_2Cl_2 then NaN_3, DMF, 100 °C, 26 h; (iv) PPh_3, H_2O, THF, 50 °C, 2 h.

2.3. Conclusion

In conclusion, a highly regio- and stereoselective S_Ni-type ring-opening fluorination of *trans*-β-substituted aryl epoxides using BF_3•OEt_2 as a nucleophilic fluorinating agent has been developed. This robust and scalable protocol grants efficient access to a variety of functionalised benzylic fluoride building blocks, and provides a solution to the problem of stereocontrol in the synthesis of this class of compounds. To highlight the utility of the resultant *syn*-fluorohydrins in the synthesis of stereodefined β-fluoro β-aryl amines, their elaboration to a range of aryl-substituted β-fluoroamphetamines has been demonstrated.[77] One notable limitation of the fluorination reaction, however, is the inability of epoxides bearing electron-rich aryl groups to provide the corresponding fluorohydrin products upon treatment with BF_3•OEt_2, and studies seeking to address this problem are discussed in the next chapter.

2.4. References and Notes

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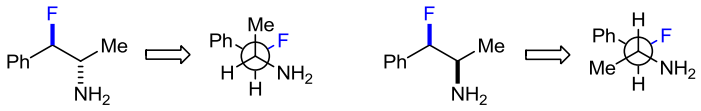

220 **221**

^3J = 5.5 (NH_2) ($CDCl_3$)
^3J = 2.6 (NH_3^+) (MeOD)

^3J = 6.6 (NH_2) ($CDCl_3$)
^3J = 9.2 (NH_3^+) (MeOD)

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[104] The enantiomeric excess of (1*R*,2*S*)-**220** was determined by chiral GC analysis (β-cyclodextrin column) by Dr Carole J. R. Bataille, Chemistry Research Laboratory, University of Oxford, U.K.

Chapter 3: Ring-Opening Fluorination of Aryl Epoxides with Alkoxy-Substituted Fluoroboranes

This chapter details investigations into the preparation and reactivity of alkoxy-substituted fluoroboranes as electronically-tuned analogues of BF_3 for the ring-opening fluorination of aryl epoxides. By virtue of the increased electron density on boron, these reagents should display lower Lewis acidity in the 8-B-3[1] form and an increased fluoride transfer ability on formation of an 8-B-4 adduct, relative to BF_3•OEt_2. Consequently, it is anticipated that alkoxy-substituted fluoroboranes may prove superior to BF_3•OEt_2 for the ring-opening fluorination of aryl epoxides bearing electron-rich aryl groups: substrates which exhibit a relatively higher rate of benzylic carbocation formation but a lower rate of fluoride trapping (Figure 24).

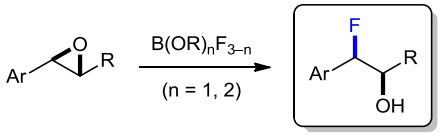
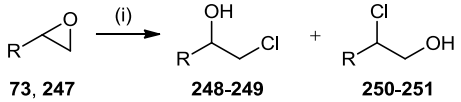


Figure 24. Ring-opening fluorination of aryl epoxides with alkoxy-substituted fluoroboranes.

3.1. Introduction

Decreasing the Lewis acidity of BCl_3 or BBr_3 by the introduction of less electronegative hydrido or alkyl *B*-ligands, or strong π-donor alkoxy or dialkylamido *B*-ligands,[2] is an established strategy for the ring-opening chlorination or bromination of epoxides[3,4] and other cyclic ethers[4b,5] by chloro or bromoborane reagents. The attenuated Lewis acidity of these modified haloborane reagents leads to enhanced chemoselectivity, and helps to minimise or prevent side reactions (e.g. carbocation formation, polymerisation) otherwise induced by the harshly Lewis acidic BCl_3 or BBr_3. For example, Brown and co-workers have described the utility of $(MeO)_2BCl$[4f] and $(MeO)_2BBr$[4g] [which may be prepared *in situ* by pre-mixing $B(OMe)_3$ with BCl_3 or BBr_3, respectively] as reagents for the ring-opening chlorination and bromination of epoxides. With $(MeO)_2BCl$, attack of chloride was found to occur preferentially at the less-substituted oxirane carbon for aliphatic terminal epoxides such as **247**, whereas styrene oxide **73** gave predominantly the benzylic chloride product **250** (Scheme 60).[4f] Despite this precedent, however, analogous ring-opening fluorination reactions using modified fluoroborane reagents are conspicuously absent in the literature.[6,7]

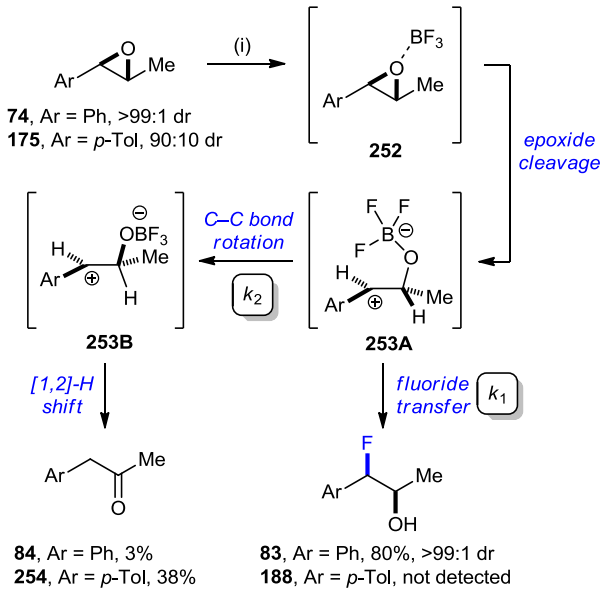


73, **247** **248-249** **250-251**

Substrate	1° : 2° Chloride Ratio	Combined NMR Yield
73, R = Ph	**248**:**250**, 5:95	50%
247, R = CH_2Ph	**249**:**251**, 96:4	90%

Scheme 60. *Reagents and conditions:* (i) $(MeO)_2BCl$ (1.2 equiv), *n*-pentane/CH_2Cl_2, −78 °C, 3.5 h.

During studies on the ring-opening fluorination of *trans*-β-substituted aryl epoxides with BF_3•OEt_2 (see chapter 2), it became apparent that the optimised protocol was unable to accommodate epoxides bearing electron-rich aryl groups, for which isomerisation to the corresponding ketone occurred in preference. For example, whereas treatment of epoxide **74** (>99:1 dr) with 0.33 equiv of BF_3•OEt_2 in CH_2Cl_2 at −20 °C for 5 min gave fluorohydrin **83** in 80% yield, reaction of epoxide **175** (90:10 dr) under analogous conditions gave ketone **254** as the major product in 38% yield, with no evidence of the corresponding fluorohydrin **188** in either the ^1H or ^{19}F NMR spectra of the crude product mixture. The inability of **175** to deliver the fluorohydrin product **188** may derive from a reduction in the rate (k_1) of intramolecular fluoride transfer from the alkoxytrifluoroborate moiety to the cationic centre within intermediate **253A**, relative to the rate (k_2) of C−C bond rotation to **253B** and subsequent [1,2]-H shift to give ketone **254**: the presence of the electron-rich aryl group presumably serves to stabilise the carbocation, so decreasing the rate of fluoride transfer (k_1) (Scheme 61).



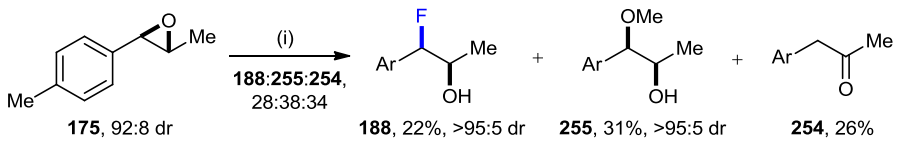
Scheme 61. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, −20 °C, 5 min.

The efficient ring-opening fluorination of aryl epoxides such as **74** with 0.33 equiv of BF_3•OEt_2 implies that the putative $ROBF_2$ and $(RO)_2BF$ intermediates formed during this process transfer fluoride in preference to their alkoxy group(s). Moreover, it has previously been established that the substitution of fluoro for alkoxy *B*-ligands on 6-B-3 fluoroboranes reduces their affinity for fluoride ion as a Lewis base, such that the order of fluoride-donating ability of the anionic 8-B-4 adducts is: $(MeO)_3BF^-$ > $(MeO)_2BF_2^-$ > BF_4^-.[8] With this in mind, it was envisaged that the replacement of BF_3•OEt_2 with alkoxy-substituted fluoroborane reagents may allow for the successful ring-opening fluorination of aryl epoxides bearing electron-rich aryl groups, by increasing the rate of fluoride transfer (k_1). Although in this scenario the rate of epoxide cleavage may also be retarded, this was not anticipated to be a problem for electron-rich substrates, for which the rate of benzylic carbocation formation was expected to be high.

3.2. Results and Discussion

3.2.1. Initial Studies on the Ring-Opening Fluorination of *trans*-2-(*p*-Tolyl)-3-methyloxirane

The preparation of alkoxydifluoroboranes ($ROBF_2$) and dialkoxyfluoroboranes [$(RO)_2BF$] has previously been achieved by a redistribution process involving the treatment of trialkylborates $B(OR)_3$ with BF_3 or BF_3•OEt_2, followed by distillation.[9,10] Encouraged by this precedent, and with the development of an operationally simple protocol in mind, the ability of a mixture of BF_3•OEt_2 and $B(OMe)_3$ to effect the ring-opening fluorination of epoxide **175** was investigated, employing conditions analogous to those previously used with BF_3•OEt_2 (see chapter 2). Thus, a 2:1 mixture of BF_3•OEt_2 and $B(OMe)_3$ (0.35 equiv and 0.18 equiv respectively) in CH_2Cl_2[11] was added to a solution of epoxide **175** (92:8 dr) in CH_2Cl_2 at −20 °C and the resultant mixture was stirred at this temperature for 5 min, then quenched by the addition of satd aq $NaHCO_3$ (this work up was used for all other ring-opening fluorinations performed in this chapter). Analysis of the crude product mixture by ^{1}H NMR spectroscopy revealed the presence of a mixture of compounds, of which the 3 main components were identified as fluorohydrin **188** (>95:5 dr), ether **255** (>95:5 dr) and ketone **254**, in a ratio of 28:38:34, respectively. It is crucial to note that there was *no* evidence of fluorohydrin **188** in either the ^{1}H or ^{19}F NMR spectra of the crude product mixture of the analogous reaction employing BF_3•OEt_2 alone. Chromatographic purification provided an analytical sample of each compound (fluorohydrin **188** in 22% yield and >95:5 dr, ether **255** in 31% yield and >95:5 dr and ketone **254** in 26% yield) (Scheme 62).



175, 92:8 dr — **188**, 22%, >95:5 dr — **255**, 31%, >95:5 dr — **254**, 26%

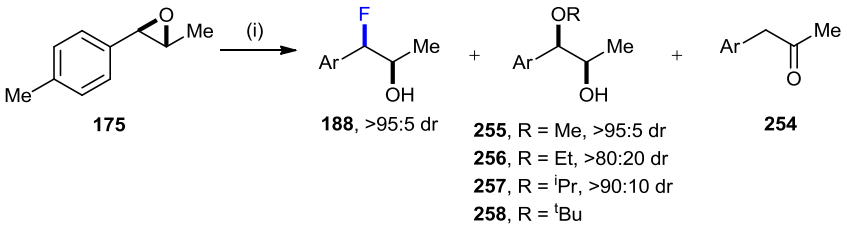
Scheme 62. *Reagents and conditions:* (i) [$B(OMe)_3$ (0.18 equiv) + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, –20 °C, 5 min. Ar = *p*-Tol.

The relative *syn*-configuration within fluorohydrin **188** was assigned by analogy to the ring-opening fluorination of aryl epoxides with BF_3•OEt_2 (see chapter 2). Furthermore, the ^{1}H-^{1}H NMR ^3J coupling constants between the C(1)*H* and C(2)*H* protons within 1-fluoro-1-arylpropan-2-ols is diagnostic of the relative configuration: for example, a value of J = 7.1 Hz was observed for *syn*-fluorohydrin **83**, versus 4.8 Hz for the corresponding *anti*-fluorohydrin **77** (see chapter 2). The observation of a C(1)*H*-C(2)*H* ^{1}H NMR ^3J coupling constant of 7.3 Hz within fluorohydrin **188** therefore allowed for confident configurational assignment. The relative *syn*-configuration within ether **255** was tentatively assigned by analogy to that within *syn*-fluorohydrin **188**, and from the fact that the ring-opening aryloxylation of aryl epoxides with $B(OAr)_3$ reagents has been previously reported to be highly *syn*-selective.[12] In an effort to promote the ring-opening fluorination reaction, the quantities of BF_3•OEt_2 and $B(OMe)_3$ were increased to

0.70 and 0.35 equiv, respectively, although this actually led to a decreased yield of fluorohydrin **188** (a 5:46:49 mixture of **188**:**255**:**254** was obtained), presumably due to fluoride abstraction from the product **188** by the excess reagent.[13]

3.2.1.1. Screening a Range of $B(OR)_3$ Additives

With proof of principle of this approach secured, a variety of $B(OR)_3$ additives bearing alkoxy groups with increasing steric demand were next screened, in order to assess their efficacy at promoting the ring-opening fluorination of epoxide **175** in conjunction with BF_3•OEt_2. In all cases, the fluorinating agents were prepared in a separate reaction vessel by pre-mixing $B(OR)_3$ with BF_3•OEt_2 (in the appropriate ratio) for 5 min at rt. Solutions of these mixtures in CH_2Cl_2 were then added to solutions of epoxide **175** in CH_2Cl_2 at −20 °C, and the resultant mixtures were stirred at this temperature for 5 min. After work up, the product distributions from these reactions were analysed by ^{1}H NMR spectroscopy. In all cases, a mixture of products was produced, of which the 3 main components were identified as fluorohydrin **188**, ketone **254**, and the corresponding ethers **255**-**258**. In these experiments, it was noted that integration of the resonance associated with the C(1)*H* proton (i.e. C*H*F) within fluorohydrin **188** at δ_H 5.12 ppm (1H, dd, *J* 48.1, 7.3) against the combined *p*-methyl CH_3 resonances associated with all compounds present in the mixture (a collection of singlet resonances at δ_H ~2.3-2.4 ppm) allowed for a more accurate quantification of the amount of fluorohydrin **188** in the mixture; the "NMR yield" calculated in this manner gave excellent correlation with the isolated yield of fluorohydrin **188** (Scheme 63).



Epoxide dr	$B(OR)_3$ (Equiv)	188 : Ether : 254 Ratio	Fluorohydrin 188 Isolated Yield (NMR Yield)	Ether Yield	Ketone 254 Isolated Yield
92:8	$B(OMe)_3$ (0.18 equiv)	28:38:34	22% (22%)	**255**, 31%	26%
90:10	$B(OMe)_3$ (0.70 equiv)	21:58:21	− (15%)	**255**, not isolated	not isolated
92:8	$B(OEt)_3$ (0.18 equiv)	28:37:35	23% (23%)	**256**, ~33%	28%
92:8	$B(OEt)_3$ (0.70 equiv)	30:54:16	− (26%)	**256**, not isolated	not isolated
90:10	$B(O^iPr)_3$ (0.18 equiv)	44:11:45	30% (30%)	**257**, ~7%	27%
90:10	**$B(O^iPr)_3$ (0.70 equiv)**	**53:19:28**	**41% (39%)**	**257**, not isolated	not isolated
90:10	$B(O^tBu)_3$ (0.18 equiv)[a]	22:0:78	− (11%)	**258**, 0%	not isolated
90:10	$B(O^tBu)_3$ (0.70 equiv)[a]	18:49:33	~14% (12%)	**258**, not isolated	not isolated

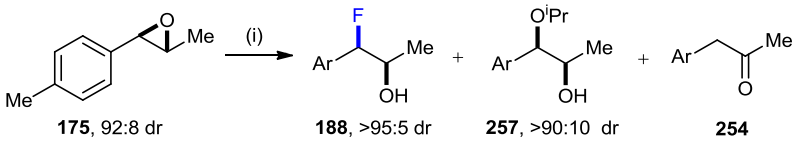
[a]On pre-mixing BF_3•OEt_2 and $B(O^tBu)_3$, some gelatinous material was formed that proved insoluble in CH_2Cl_2, and this material was not transferred into the reaction vessel containing epoxide **175**.

Scheme 63. *Reagents and conditions:* (i) [$B(OR)_3$ + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, –20 °C, 5 min. Ar = *p*-Tol.

Of the conditions examined, the use of $B(O^iPr)_3$ with BF_3•OEt_2 in the ratio 2:1 proved the most efficacious, and delivered a 53:19:28 mixture of fluorohydrin **188** to ether **257** to ketone **254**, from which **188** was isolated in 41% yield and >95:5 dr. In all cases, ethers **255-258** were tentatively assigned *syn* relative configurations, again by analogy to that within fluorohydrin **188**, and by analogy to the ring-opening aryloxylation of aryl epoxides with $B(OAr)_3$.[12]

3.2.1.2. Effect of the Reaction Temperature

The temperature of the ring-opening fluorination reaction of epoxide **175** using the 2:1 $B(O^iPr)_3/BF_3$•OEt_2 reagent combination was next optimised.[14] The reactions were performed sequentially, from 10 to −50 °C and,[15] as before, an NMR yield of fluorohydrin **188** was calculated from the ^1H NMR spectrum of the crude product mixture. The results of these studies indicated a temperature of −10 °C to be optimal (Scheme 64).

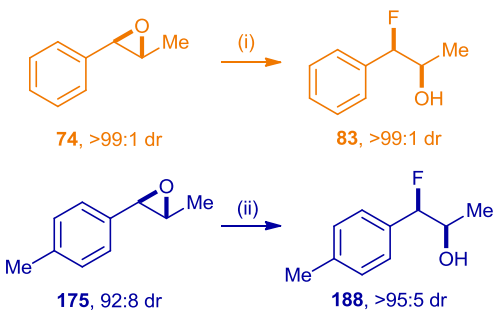


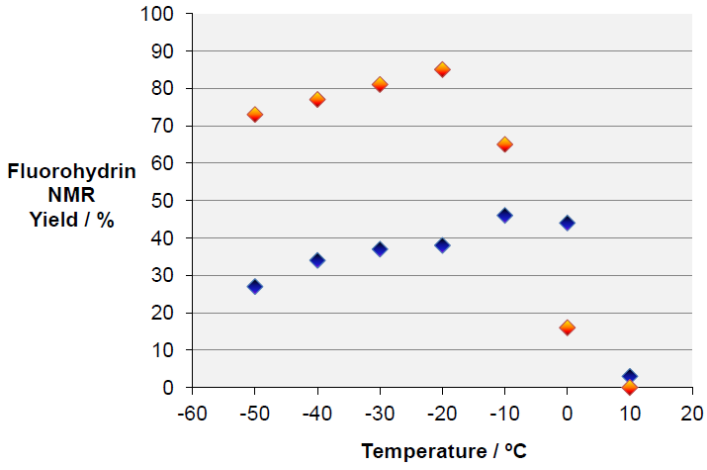
175, 92:8 dr — **188**, >95:5 dr — **257**, >90:10 dr — **254**

T °C	188:257:254 Ratio	Fluorohydrin 188 NMR Yield
10 °C	4 : 39 : 57	3%
0 °C	56 : 16 : 28	44%
−10 °C	**58 : 18 : 24**	**46%**
−20 °C	49 : 29 : 22	38%
−30 °C	47 : 32 : 21	37%
−40 °C	44 : 35 : 21	34%
−50 °C	35 : 44 : 21	27%

Scheme 64. *Reagents and conditions:* (i) [$B(O^iPr)_3$ (0.70 equiv) + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, T °C, 5 min. Ar = *p*-Tol.

Comparison of the temperature dependence of the ring-opening fluorination of epoxide **74** using BF_3•OEt_2 with that of epoxide **175** using the 2:1 $B(O^iPr)_3/BF_3$•OEt_2 reagent combination revealed a similar trend, albeit with the optimal temperature being lower in the former case (Scheme 65).





Scheme 65. *Reagents and conditions:* (i) BF_3•OEt_2 (0.33 equiv), CH_2Cl_2, T °C, 5 min; (ii) [$B(O^iPr)_3$ (0.70 equiv) + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, T °C, 5 min.

3.2.2. Tethering the Alkoxy Groups: *B*-Fluoro-1,3,2-dioxaboracycles as Fluorinating Agents

As an alternative to the use of fluoroboranes substituted with alkoxy groups derived from simple alcohols, the utility of diol-derived *B*-fluoro-1,3,2-dioxaboracycles **259** and **260** as fluorinating agents was next considered (Figure 25).

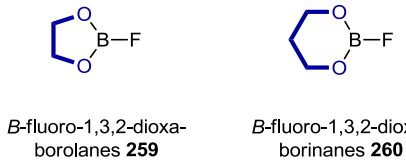


Figure 25. *B*-Fluoro-1,3,2-dioxaboracycles derived from 1,2- and 1,3-diols.

Although *B*-chloro-1,3,2-dioxaborolane (ethylene chloroboronate) **261**,[16] *B*-chloro-1,3,2-dioxaborinane **262**[17] and *B*-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolatoboron chloride [pinBCl]) **263**[18] have previously been prepared by treatment of the corresponding diols with BCl_3, the analogous preparation of the fluorine analogues has not been reported (Figure 26).

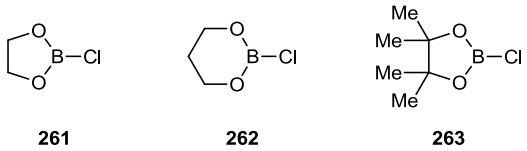
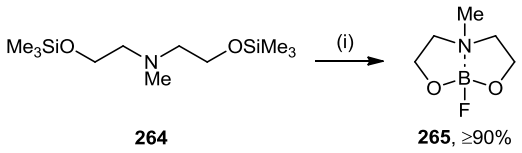


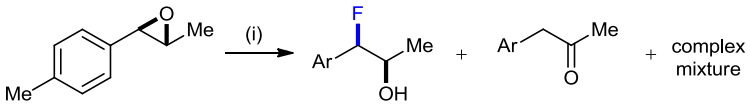
Figure 26. Known 2-chloro-1,3,2-dioxaborolanes and 2-chloro-1,3,2-dioxaborinanes.

Unfortunately, initial attempts at the use of this protocol with BF_3•OEt_2 were not productive, and therefore an alternative was sought. Notably, Aldridge and co-workers have pioneered a convenient metathesis approach to alkoxy-substituted fluoroboranes stabilised by amine or thioether donors, in which trimethylsilyl ethers serve as latent *B*-alkoxy ligands.[19] Thus, treatment of bis(*O*-trimethylsilyl) ether **264** with 1 equiv of BF_3•OEt_2 in benzene gave dialkoxyfluoroborane **265** in yields generally exceeding 90% (Scheme 66).

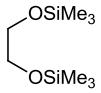
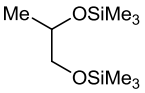
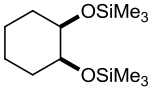
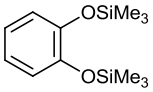
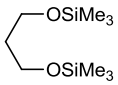
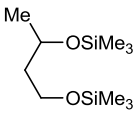
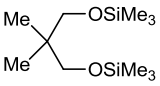
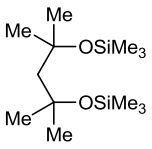
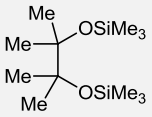


Scheme 66. *Reagents and conditions:* (i) BF_3•OEt_2 (1 equiv), benzene, rt to 55 °C, 96 h.

Encouraged by this and other precedent,[20] a range of bis(*O*-trimethylsilyl)ethers **266**-**274** were prepared by disilylation of the corresponding diols with Me_3SiCl; subsequently, 1.05 equiv of each of these bis(*O*-trimethylsilyl)ethers **266**-**274** was pre-mixed with 1.05 equiv of BF_3•OEt_2 for 5 min at rt. Solutions of these mixtures in CH_2Cl_2[21] were then added to solutions of epoxide **175** in CH_2Cl_2 at −10 °C. In each case the reactions produced fluorohydrin **188** and ketone **254**, in addition to other unidentified products (Scheme 67).



175, 92:8 dr **188**, >95:5 dr **254**

$R(OSiMe_3)_2$	188:254 Ratio	Fluorohydrin 188 Yield (NMR Yield)
 **266**	17:83	(6%)
 **267**	18:82	(8%)
 **268**	29:71	(15%)
 **269**	19:81	(5%)
 **270**	66:34	(36%)
 **271**	53:47	(32%)
 **272**	57:43	(36%)
 **273**	40:60[a]	(7%)
 **274**	**72:28**	**57% (56%)**

[a]The reaction gave incomplete conversion to a 9:13:78 ratio of fluorohydrin **188**, ketone **254** and starting material **175**.

Scheme 67. *Reagents and conditions:* (i) [$R(OSiMe_3)_2$ (1.05 equiv) + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, −10 °C, 5 min. Ar = *p*-Tol.

The results of these investigations allow the following trends to be discerned. The use of C_2-tether bis(*O*-trimethylsilyl)ethers **266**-**269** with BF_3•OEt_2 led to ketone **254** as the major product, with ≤15% NMR yield of fluorohydrin **188**, whereas C_3-tether bis(*O*-trimethylsilyl)ethers **270**-**272** gave fluorohydrin **188** as the major product in 32-36% NMR yield (Scheme 67). These results may be reconciled by the fact that 6-membered ring 1,3,2-dioxaborinanes are known to be less Lewis acidic than their 5-membered ring 1,3,2-dioxaborolane counterparts,[22,23] such that *B*-fluoro-1,3,2-dioxaborinanes would be expected to be stronger fluoride donors on formation of an 8-B-4 Lewis base adduct. Use of the tetramethyl-substituted C_3-tether bis(*O*-trimethylsilyl)ether **273** with BF_3•OEt_2 led to the incomplete consumption of starting material, which may be a consequence of the decreased Lewis acidity of **275** due to the development of severe 1,3-diaxial interactions within a chair conformation of the corresponding 8-B-4 Lewis base adduct **276** (Figure 27).[24]

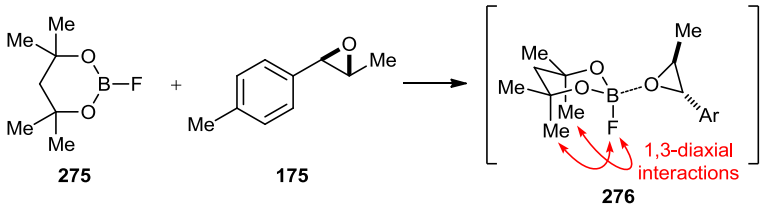
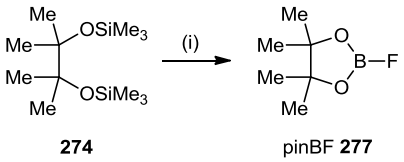


Figure 27. Mechanistic rationale for the low reactivity of *B*-fluoro-1,3,2-dioxaborinane **275** derived from **273**.

The use of bis(*O*-trimethylsilyl)pinacol **274** with BF_3•OEt_2 offered by far the best result (56% NMR yield of fluorohydrin **188**), with **188** isolated in 57% yield and >95:5 dr. In this case, and in contrast to the other bis(*O*-trimethylsilyl)ethers screened, products consistent with an alkoxy transfer process were formed in only trace quantities.[25] The active fluorinating agent in this case was presumed to be pinacolatoboron fluoride (pinBF) **277** (Scheme 68).

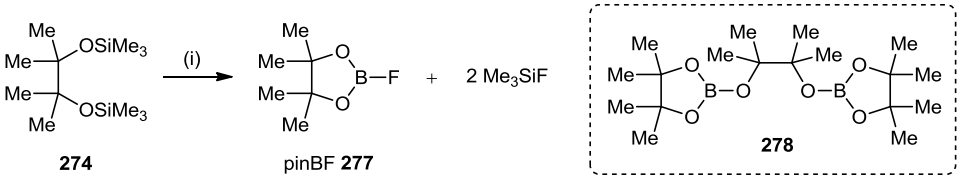


Scheme 68. *Reagents and conditions:* (i) BF_3•OEt_2 (1 equiv), CH_2Cl_2, rt.

Compared to the low fluorohydrin **188** to ketone **254** ratio (i.e. **188**:**254** ≤ 29:71) obtained with fluorinating agents derived from other C_2-tether bis(*O*-trimethylsilyl)ethers **266**-**269**, the significantly increased success of pinBF **277** as a fluoride donor (i.e. **188**:**254** = 72:28) may be due to a larger than normal bite angle to boron, as a consequence of bond length distortion effects arising from steric interaction between the *gem*-dimethyl groups. On the basis of "strain release Lewis acidity" arguments,[23] pinBF **277** would therefore be expected to exhibit comparatively stronger fluoride donating ability on formation of an 8-B-4 adduct, relative to a typical *B*-fluoro-1,3,2-dioxaborolane.

3.2.2.1. Characterisation of pinBF by NMR Spectroscopy and Mass Spectrometry

Upon mixing BF_3•OEt_2 and bis(*O*-trimethylsilyl)pinacol **274** in CD_2Cl_2 at rt, a colourless solution containing a small amount of an unidentified white precipitate was produced. Analysis of the solution by ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR spectroscopy showed that essentially complete consumption of BF_3•OEt_2 (<1% remaining) and bis(*O*-trimethylsilyl)pinacol **274** had occurred to give (in addition to Me_3SiF) a single fluorine-containing species, assigned as pinBF **277** (δ_B 20.6 ppm,[26] δ_F −152 ppm[27]), and a minor species tentatively assigned as bis(*O*-pinacolatoboryl)pinacol **278**[28] (Scheme 69).



Scheme 69. *Reagents and conditions:* (i) BF_3•OEt_2 (1 equiv), CD_2Cl_2, rt.

Analysis of the mixture by FI mass spectrometry provided further evidence for the presence of pinBF **277** (see peak at 146), in addition to hydrolysed products **279** and **280**, which may have been formed upon brief exposure to the atmosphere during introduction of the sample to the spectrometer (Figure 28).

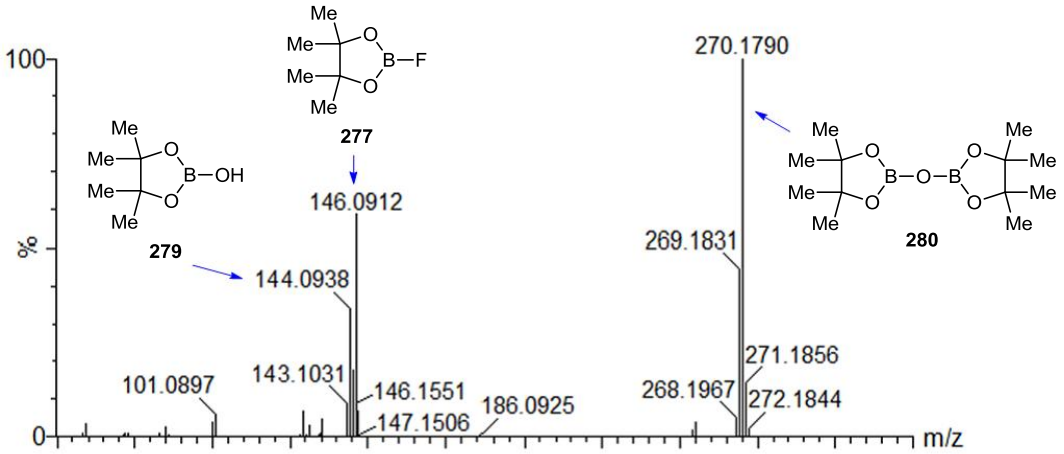


Figure 28. FI mass spectrum of the crude pinBF **277** reagent (some hydrolysis evident).

The yield of pinBF **277** was estimated at 60% based on integration of its tetramethyl resonance at 1.34 ppm in the ^{1}H NMR spectrum against the combined methyl resonances present for all compounds in the mixture (collection of singlet resonances at δ_H 1.25-1.40 ppm). If this is an accurate quantification of the amount of active fluorinating agent **277** in the mixture, it may account for the somewhat moderate yield (57%) of fluorohydrin **188** obtained from the treatment of epoxide **175** with *in situ* generated pinBF **277**. Unfortunately, several attempts to prepare pinBF **277** on larger scale (both with and without CH_2Cl_2 solvent) and isolate it *via* distillation proved unsuccessful, as even the most cautious evaporation of volatiles left nothing but an unidentified, white solid residue that contained no detectable **277**.

3.2.2.2. Mechanistic Considerations

The reaction of epoxide **175** with pinBF **277** may proceed *via* initial coordination of **277** to one of the (diastereoisotopic) non-bonded electron pairs of the oxirane ring, giving epoxide-fluoroborane complex **281** or **282** (or a mixture of the two) as the first intermediate(s).[29] Epoxide cleavage within **281** or **282** would then produce a benzylic carbocation intermediate in initial conformation **283A** or **283B**, respectively. Following rotation about the C–O bond within **283A** or **283B** to generate a conformation **283C**, an intramolecular fluoride transfer (*via* transition state model **284**) may proceed to give *O*-(pinacolatoboryl)fluorohydrin **285**, which is hydrolysed upon work up to fluorohydrin **188**. Alternatively, rotation about the B–O bond of intermediate **283C** may occur to give either **283D** or **283E**: conformations from which a competing alkoxy transfer process may, in principle, occur. However, in either case, developing steric interactions with the *gem*-dimethyl moiety on the pinacolato backbone may disfavour an alkoxy group transfer pathway. If alkoxy transfer *were* to occur from **283D** or **283E**, an 8-membered ring trioxaborocane system **286**, would result, and this compound would experience severe non-bonded 1,3-steric interactions (red arrows), in addition to the transannular, bond-widening and torsional strain already inherent in medium ring systems (Figure 29).

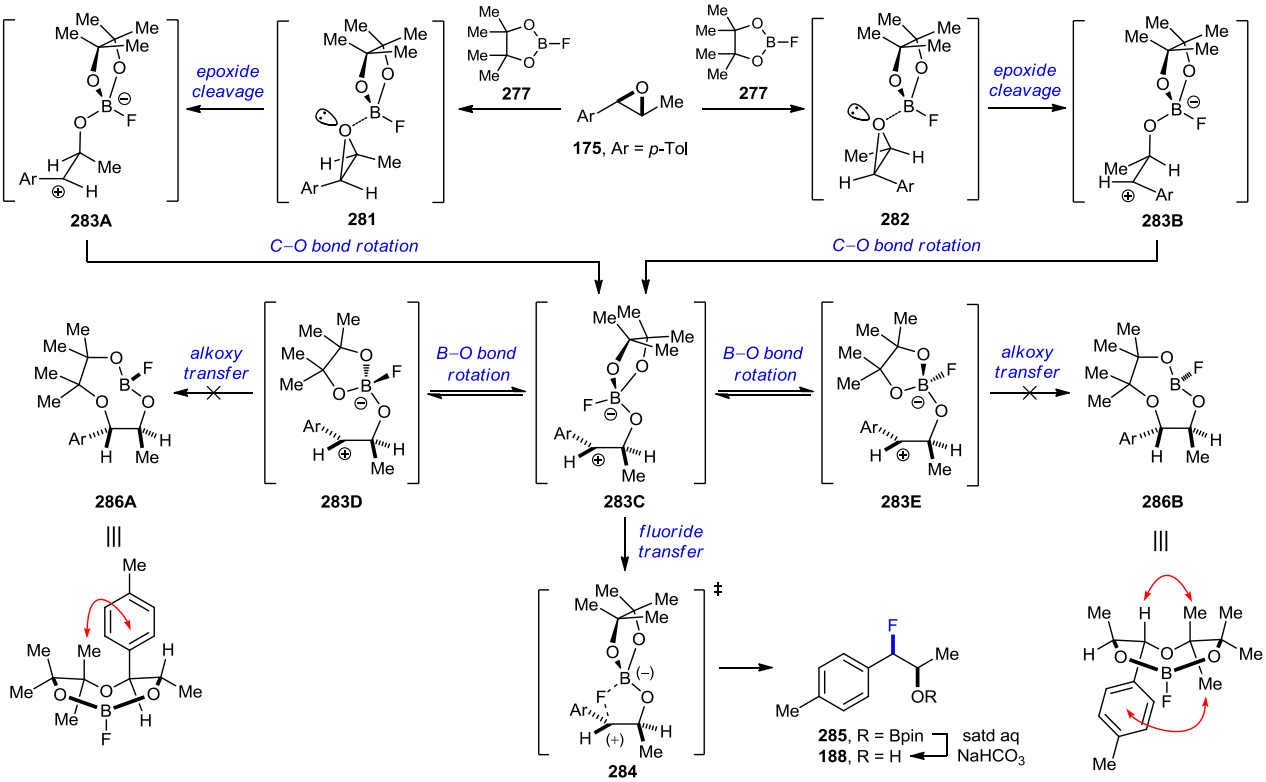
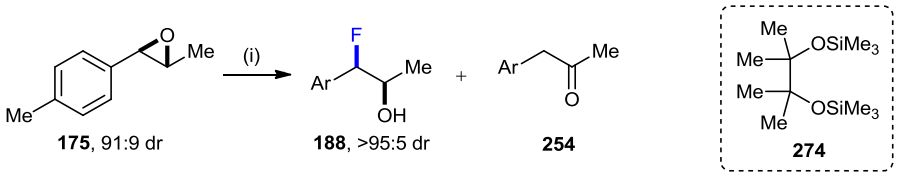


Figure 29. Mechanistic rationale for the suppression of alkoxy group transfer with the pinBF **277** fluorinating agent.

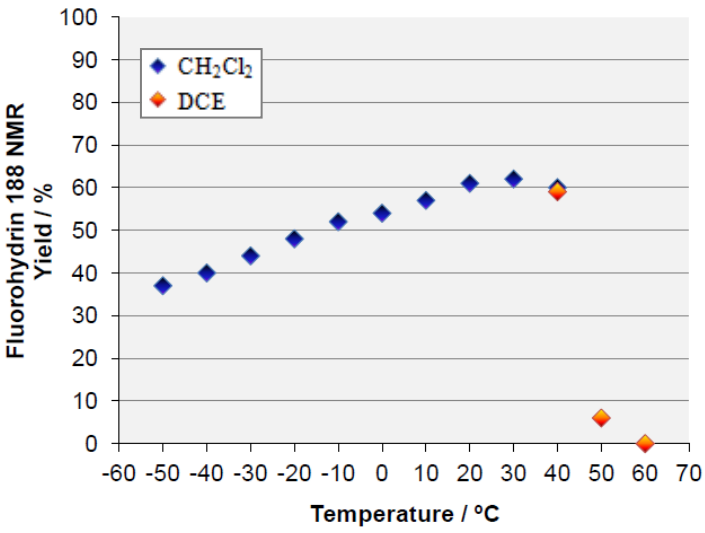
3.2.2.3. Temperature Optimisation of the Ring-Opening Fluorination with pinBF

Having established that pinBF **277** is an efficient fluorinating agent for epoxide **175**, the influence of the reaction temperature (ranging from −50 to 60 °C)[30] on the yield of fluorohydrin **188** was next assayed, with reaction at rt (20 °C) proving most efficacious. Under these conditions, a 77:23 mixture of fluorohydrin **188** to ketone **254** was produced, from which **188** was isolated in 59% yield and >95:5 dr.[31] A graphical representation of these results revealed an approximately linear increase in the yield of fluorohydrin **188** on increasing the temperature from −50 to 30 °C. However, on increasing the temperature still further (with a solvent switch to DCE for temperatures in excess of 40 °C), the yield of **188** fell rapidly to zero, with ketone **254** being the only identifiable compound in the crude product mixture (Scheme 70).



175, 91:9 dr — **188**, >95:5 dr — **254** — **274**

T °C	Solvent	188:254 Ratio	Fluorohydrin 188 Yield (NMR Yield)
−50 °C	CH_2Cl_2	61:39	(37%)
−40 °C	CH_2Cl_2	62:38	(40%)
−30 °C	CH_2Cl_2	65:35	(44%)
−20 °C	CH_2Cl_2	71:29	(48%)
−10 °C	CH_2Cl_2	74:26	(52%)
0 °C	CH_2Cl_2	77:23	(54%)
10 °C	CH_2Cl_2	77:23	(57%)
20 °C	**CH_2Cl_2**	**77:23**	**59% (61%)**
30 °C	CH_2Cl_2	73:27	(62%)
30 °C	DCE	76:24	(55%)
40 °C	CH_2Cl_2	73:27	(60%)
40 °C	DCE	81:19	(59%)
50 °C	DCE	12:88	(6%)
60 °C	DCE	0:100	(0%)

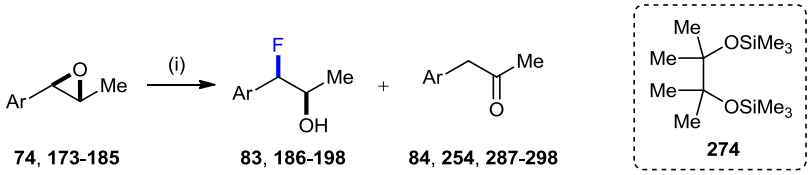


Scheme 70. *Reagents and conditions:* (i) [**274** (1.05 equiv) + BF_3•OEt_2 (0.35 equiv)], T °C, 5 min. Ar = *p*-Tol.

3.2.3. Ring-Opening Fluorination of a Range of *trans*-β-Methyl Aryl Epoxides with pinBF

With an optimised procedure in hand, the generality of this reaction across a number of *trans*-β-methyl aryl epoxides **74**, **173**, **174** and **176-185** was next assessed (Scheme 71). This range of epoxides, bearing aryl substituents with Brown-Okamoto σ^+ substituent constants ranging from –0.78 to +0.61,[32] was chosen so that the effect of the electronic nature of the aryl group on the efficacy of this procedure could be evaluated (the result for *p*-tolyl epoxide **175** has been included for comparison). As observed in analogous studies using BF_3•OEt_2 as the fluorinating agent (see chapter 2), extended reaction times were required for substrates bearing more electron-deficient aryl groups, in order to facilitate complete conversion. In spite of the

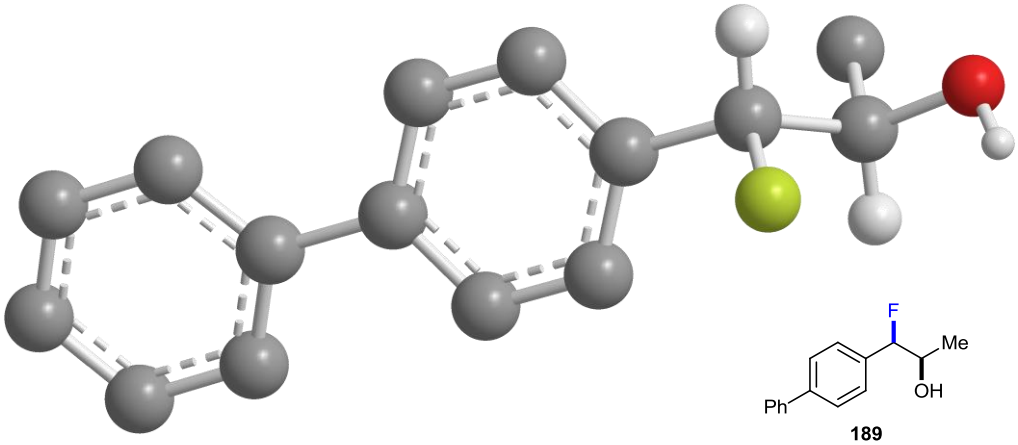
demonstrated competence of pinBF **277** in effecting the ring-opening fluorination of *p*-tolyl epoxide **175**, the subjection of highly electron-rich *p*-methoxy- and *p*-phenoxyphenyl substrates **173** and **174** to the optimised reaction conditions gave only the corresponding arylpropan-2-ones **287** and **288**, which were isolated in 69 and 78% yield, respectively. No traces of the corresponding fluorohydrins **186** and **187** were apparent by ^{1}H and ^{19}F NMR spectroscopic analyses of the crude product mixtures. In contrast to the results using BF_3•OEt_2 alone, however, ring-opening fluorination of the modestly electron-rich substrates **176** and **177** gave the corresponding fluorohydrins **189** and **190** as the major products, which were isolated in 53 and 56% yield, respectively, and in >95:5 dr in both cases. The relative *syn*-configuration within fluorohydrin **189** was established unambiguously by single crystal X-ray diffraction analysis (Figure 30).[33] As with the use of BF_3•OEt_2 as the fluorinating agent, epoxides **178**, **74** and **179** bearing relatively electron-neutral aryl groups gave complete conversion to the corresponding *syn*-fluorohydrins **191**, **83** and **192** within 5 min, which were isolated in 52, 63 and 54% yield, respectively, and >95:5 dr in each case. Meanwhile, the moderately electron-poor substrates **180** and **181** required a reaction time of 10 min to reach full conversion, giving *syn*-fluorohydrins **193** and **194** in 57 and 54% isolated yield, respectively, and in >95:5 dr in both cases. The relatively more electron-deficient epoxide substrates **182-184** required 15 min for complete consumption of starting material, and gave the corresponding fluorohydrins **195-197** in ≤90:10 dr in each case, consistent with an apparent erosion of the diastereoselectivity of the fluorination process. This may be due to a small amount of competing S_N2-type ring-opening, which has previously been observed during the formation of fluorohydrin products from very electron-poor aryl epoxides upon treatment with BF_3•OEt_2.[34] Finally, subjection of the extremely electron-deficient *p*-(trifluoromethyl)phenyl substrate **185** to the optimised conditions for 30 min resulted in no reaction, consistent with the reluctance of such electron-poor aryl epoxides to produce benzylic carbocation intermediates.[34]



74, 173-185 **83**, 186-198 **84**, 254, 287-298 **274**

Epoxide	Ar	σ^+	Time	Fluorohydrin Isolated Yield	Ketone Isolated Yield
173, 96:4 dr	4-$MeOC_6H_4$	−0.78	5 min	**186**, 0%	**287**, 69%
174, 96:4 dr	4-$PhOC_6H_4$	−0.50	5 min	**187**, 0%	**288**, 78%
175, 91:9 dr	4-MeC_6H_4	−0.31	5 min	**188**, 59%, >95:5 dr	**254**, not isolated
176, 98:2 dr	4-PhC_6H_4	−0.18	5 min	**189**, 53%, >95:5 dr	**289**, 25%
177, 96:4 dr	2-naphthyl	−0.13	5 min	**190**, 56%, >95:5 dr	**290**, 22%
178, 94:6 dr	4-FC_6H_4	−0.07	5 min	**191**, 52%, >95:5 dr	**291**, 10%
74, >99:1 dr	Ph	0.00	5 min	**83**, 63%, 98:2 dr	**84**, not isolated
179, 93:7 dr	3-$MeOC_6H_4$	+0.05	5 min	**192**, 54%, >95:5 dr	**292**, not isolated
180, 94:6 dr	4-ClC_6H_4	+0.11	10 min	**193**, 57%, >95:5 dr	**293**, 27%
181, 94:6 dr	4-BrC_6H_4	+0.15	10 min	**194**, 54%, >95:5 dr	**294**, 31%
182, 95:5 dr	3-FC_6H_4	+0.35	15 min	**195**, 55%, 90:10 dr	**295**, 22%
183, 92:8 dr	3-ClC_6H_4	+0.40	15 min	**196**, 56%, 89:11 dr	**296**, 23%
184, 91:9 dr	3-BrC_6H_4	+0.41	15 min	**197**, 51%, 88:12 dr	**297**, 20%
185, 94:6 dr	4-$CF_3C_6H_4$	+0.61	30 min	**198**, 0%	**298**, 0%

Scheme 71. *Reagents and conditions:* (i) [**274** (1.05 equiv) + BF_3•OEt_2 (0.35 equiv)], CH_2Cl_2, rt.



189

Figure 30. Chem3D representation of the single crystal X-ray diffraction structure of **189** (selected H atoms omitted for clarity).

3.3. Conclusion

In conclusion, the treatment of a range of *trans*-β-methyl aryl epoxides with pinacolatoboron fluoride (pinBF) **277** [generated *in situ* from BF_3•OEt_2 and bis(*O*-trimethylsilyl)pinacol **274**] results in highly stereoselective S_Ni-type epoxide ring-opening to give the corresponding *syn*-fluorohydrins. This operationally simple protocol, which benefits from short reaction time at ambient temperature, allows access to stereodefined benzylic fluoride building blocks bearing electron-rich aryl groups, which are inaccessible using the optimised protocol with BF_3•OEt_2 as the fluorinating agent.

3.4. References and Notes

[1] The N-X-L descriptors were introduced by Martin and co-workers to designate the bonding about any atom (X) in a resonance structure in terms of the number of valence shell electrons (N) formally associated directly with that atom and the number of ligands (L) directly bonded to it; see: Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753.
[2] Vianello, R.; Maksić, Z. *Inorg. Chem.* **2005**, *44*, 1095; Grant, D. J.; Dixon, D. A. *Inorg. Chem.* **2009**, *48*, 8811.
[3] For a review of the synthesis of halohydrins *via* the ring-opening of epoxides with metal halides see: Bonini, C.; Righi, G. *Synthesis* **1993**, 225.
[4] For selected examples see: (a) Bell, T. W.; Ciaccio, J. A. *Tetrahedron Lett.* **1986**, *27*, 827; (b) Guindon, Y.; Therien, M.; Girard, Y.; Yoskim, C. *J. Org. Chem.* **1987**, *52*, 1680; (c) Bovicelli, P.; Mincione, E.; Ortaggi, G. *Tetrahedron Lett.* **1991**, *32*, 3719; (d) Bovicelli, P.; Lupattelli, P.; Bersani, M. T. *Tetrahedron Lett.* **1992**, *33*, 6181; (e) Brown, H. C.; Roy, C. D. *Molecules Online* **1998**, *2*, 114; (f) Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2006**, *59*, 834; (g) Roy, C. D.; Brown, H. C. *J. Chem. Res.* **2006**, 639; (h) Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2007**, *60*, 139; (i) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 1608; (j) Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2006**, *59*, 834; (k) Roy, C. D.; Brown, H. C. *J. Chem. Res.* **2006**, 639.
[5] For selected examples see: Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969; Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure & Appl. Chem.* **1988**, *60*, 1705; Roy, C. D.; Brown, H. C. *Aust. J. Chem.* **2006**, *59*, 657.
[6] Bruns and Haufe have attempted the asymmetric ring-opening fluorination of cyclohexene oxide using *B*-fluorodiisopinocampheylborane (Ipc_2BF) as an "optically-active analogue of BF_3". However, apart from some remaining epoxide starting material, cyclohexanone was formed as the major product, with no fluorohydrin detected; see: Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247.
[7] On a related note, aryldifluoroboranes ($ArBF_2$) have been exploited as "tunable" and "non-volatile" alternatives to BF_3 as Lewis acids for the Diels-Alder reaction; see: de la Torre, M. F.; Caballero, M. C.; Whiting, A. *Tetrahedron* **1999**, *55*, 8547.
[8] Larson, J. W.; McMahon, T. B. *J. Am. Chem. Soc.* **1985**, *107*, 766.
[9] For the preparation of alkoxydifluoroboranes ($ROBF_2$) see: Gerrard, W.; Mooney, E. F.; Peterson, W. G. *J. Inorg. Nucl. Chem.* **1967**, *29*, 943. For the preparation of dialkoxyfluoroboranes [$(RO)_2BF$] see: Cook, H. C.; Ilett, J. O.; Saunders, B. C.; Starey, G. J. *J. Chem. Soc.* **1950**, 3126. Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta.* **1975**, *58*, 1094. It has been reported in several of these cases that $(RO)_2BF$ is unstable with respect to (slow) disproportionation into $ROBF_2$ and $B(OR)_3$; see also: Wiberg, E.; Sütterlin, W. *Z. Anorg. Chem.* **1931**, *202*, 22.
[10] On the basis of ^{11}B NMR, Raman and IR spectroscopy, alkoxydifluoroboranes ($ROBF_2$) are believed to exist entirely as trimers $(ROBF_2)_3$ in both the neat liquid and in benzene solution; see: de Moor, J. E.; van der Kelen, G. P. *J. Organomet. Chem.* **1966**, *6*, 235. Using *ab initio* computational methods supplemented by NMR studies, Rasul and Williams showed that $(MeOBF_2)_3$, which possesses a C_{3v}-symmetric "cyclohexane-like" structure, is the thermodynamic product when $B(OMe)_3$ and BF_3 are mixed in a 1:2 ratio; see: Rasul, G.; Williams, R. E. *Collect. Czech. Chem. Commun.* **1999**, *64*, 847. However, for the sake of simplicity, all alkoxydifluoroboranes in this chapter are denoted by their empirical formula $ROBF_2$.
[11] ^{11}B and ^{19}F NMR spectroscopic analysis of a 2:1 mixture of $BF_3{\bullet}OEt_2$ and $B(OMe)_3$ in CD_2Cl_2 revealed the presence of several species, including unconsumed $BF_3{\bullet}OEt_2$ and two other boron fluoride species.
[12] Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun.* **2005**, 1426; Bertolini, F.; Crotti, P.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 61. For the analogous reaction of $B(OAr_3)$ with oxetanes and azetidines see: Bertolini, F.; Crotti, S.; Di Bussolo, V.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **2008**, 73, 8998.
[13] Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769; Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555.
[14] ^{11}B and ^{19}F NMR spectroscopic analysis of a 2:1 mixture of $B(O^iPr)_3$ and $BF_3{\bullet}OEt_2$ in CD_2Cl_2 revealed the presence of several species, including unconsumed $BF_3{\bullet}OEt_2$ and two other boron fluoride species.
[15] The reaction at −20 °C was repeated after the last experiment (−50 °C) to ensure that the diminishing yield of **188** was not due to decomposition of the active fluorinating species over the time course of the experiments.
[16] (a) Gennari, C.; Colombo, L.; Poli, G. *Tetrahedron Lett.* **1984**, *25*, 2279; (b) Blau, J. A.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1957**, 4116.
[17] Finch, A.; Lockhart, J. C.; Pearn, J. *J. Org. Chem.* **1961**, *26*, 3250.
[18] Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4744.
[19] Aldridge, S.; Calder, R. J.; Coombs, D. L.; Jones, C.; Steed, J. W.; Coles, S.; Hursthouse, M. B. *New J. Chem.* **2002**, *26*, 677.
[20] Yamamoto, Y.; Hattori, K.; Ishii, J.-I.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294; Myers, E. L.; Butts, C. P.; Aggarwal, V. K. *Chem. Commun.* **2006**, 4434.
[21] In some cases, a small amount of a white precipitate formed, and this was also transferred to the reaction flask containing epoxide **175**.
[22] McAchran, G. E.; Shore, S. G. *Inorg. Chem.* **1966**, *5*, 2044, and references cited therein.
[23] The concept of "strain release Lewis acidity" has been used to rationalise the correlation between bond angles within Lewis acids and their acidity. For selected examples of the application of "strain release Lewis acidity" in reactions mediated by silicon Lewis acids see: Denmark, S. E.; Jacobs, R. T.; Dai-Ho, G.; Wilson, S. *Organometallics* **1990**, *9*, 3015; Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920.

[24] A similar explanation has been used to account for the exceptional stability of cyclic boronates of 2-methylpentane-2,4-diol with respect to hydrolysis; see: *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

[25] An unidentified minor product was observed in the ^{1}H NMR spectrum which was tentatively assigned as the alkoxy transfer product (*RS*,*RS*)-1-(2′,3′-dimethylbutan-2-hydroxy-3-yl)-1-(*p*-tolyl)propan-2-ol (<5% yield); δ_H (400 MHz, $CDCl_3$) [selected peak] 4.22 (d, *J* 7.9, C(1)*H*).

[26] A ^{11}B NMR chemical shift of δ_B 20.6 ppm for pinBF **277** is within the expected range for sp^2-hybridised boron (sp^2 ~ 30 ppm versus sp^3 ~ 0 ppm), and is indicative of a free Lewis acid rather than a complex with the Et_2O present in the mixture; see: Egawa, Y.; Gotoh, R.; Niina, S.; Anzai, J.-i. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3789.

[27] A ^{10}B satellite peak was also observed slightly upfield due to a $^{2}\Delta^{19}F(^{10/11}B)$ isotope-induced chemical shift effect; see: Tordeaux, M.; Magnier, E.; Guidotti, J.; Diter, P.; Wakselman, C. *Magn. Reson. Chem.* **2004**, *42*, 700.

[28] An analogous compound [diethylene ethylene di(borate)] has been reported to occur as a major by-product during the synthesis of ethylene chloroboronate **261** from the reaction of BCl_3 with ethylene glycol; see: ref. 16b.

[29] The B−F bond in these complexes may be oriented so as to allow a stabilising $n_O \rightarrow \sigma^*_{B-F}$ negative hyperconjugative interaction with the remaining oxirane lone pair (see: Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321): a geometrical arrangement which would further benefit from minimisation of non-bonded steric interactions between the bulky pinacolato moiety and the epoxide substituents.

[30] To minimise uncertainties in the internal temperature of the reaction, pinBF **277** was generated at the same temperature at which the solution of epoxide **175** was held, and was then quickly transferred across *via* syringe.

[31] Unfortunately, attempts to improve the yield of fluorohydrin **188** by increasing the quantity of pinBF **277** promoted the formation of ketone **254** at the expense of fluorohydrin **188**.

[32] Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

[33] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[34] Barili, P. L.; Bellucci, G.; Berti, G.; Macchia, B.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 477.

Chapter 4: Ring-Opening Fluorination of Epoxy Amines with HBF_4•OEt_2

This chapter describes investigations into the utility of HBF_4•OEt_2 as a nucleophilic fluorine source for the ring-opening fluorination of epoxy amines (Figure 31).

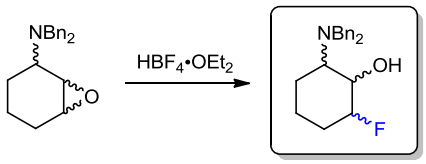


Figure 31. Ring-opening fluorination of epoxy amines with HBF_4•OEt_2.

4.1. Introduction

4.1.1. The Importance of Stereodefined Fluorinated Amines

In medicinal chemistry, the installation of fluorine atoms β- or γ- to amino groups is a powerful tool in lead optimisation for decreasing amine basicity, which facilitates membrane permeation and leads to increased bioavailability of orally-administered drugs (% dose reaching the circulatory system).[1] Additionally, fluorination can enhance the metabolic stability of amines by dissuading *N*-oxidation or *N*-dealkylation by cytochrome P450 enzymes,[1f] and may also modulate the target binding affinity, depending on whether the compound binds in its protonated or neutral form. In response to the demand for fluorinated amines in drug discovery programmes, there have been great strides in the development of stereoselective syntheses of the β-fluoro amine motif over recent years,[2] although the pursuit of more practical and economical preparations of β- and γ-fluoro amine building blocks remains an ongoing challenge. For example, during the development of cathepsin K inhibitors, such as MK-0764 **300** for the treatment of osteoporosis,[3] chemists at Merck invested significant time into the optimisation of a scalable synthetic route to (*S*)-γ-fluoroleucine **299** (Figure 32).[4]

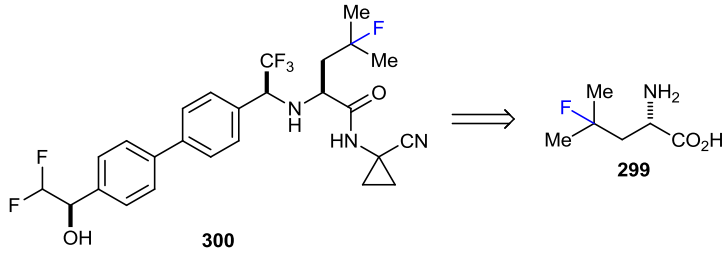


Figure 32. Merck's cathepsin K inhibitor MK-0764 **300** and the (*S*)-γ-fluoroleucine **299** building block required for its synthesis.

Other examples of γ-fluoro amine pharmaceutical candidates include the 4-fluoropiperidine antipyschotic drug **301**,[5] in which the 4-fluoro group served to increase the bioavailability of the compound by lowering the pK_{aH} of the piperidine by 1.9 units, as well as γ-fluorinated aminocyclohexanes **302**[6] and **303**[7], tested as NDMA receptor antagonists and influenza virus replication inhibitors respectively (Figure 33).

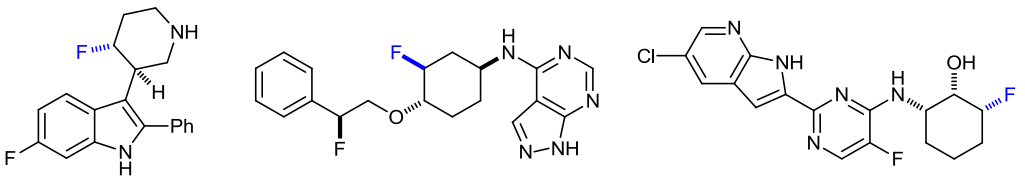


Figure 33. Examples of the γ-fluoro amine motif in pharmaceutical candidates from SAR studies.

There has also been considerable activity in the preparation and biological evaluation of fluorinated analogues of naturally-occurring amino compounds,[8] including α- and β-amino acids[9] (e.g. **304**[10]), aminosugars[11] (e.g. **305**[11j]), iminosugars[12] (e.g. **306**[12j]), amino- and diaminocyclitols[13] (e.g. **307**[13a]) and sphingoid bases and ceramides[14] (e.g. **308**[14a]) (Figure 34).

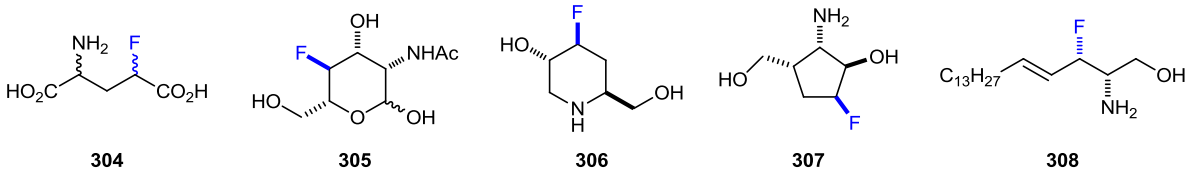


Figure 34. Fluorinated analogues of amine natural products.

4.1.2. Synthesis of β-Hydroxy γ-Fluoro Amines *via* Ring-Opening Fluorination of 2,3-Epoxy Amines

A recurrent feature in many of the fluorinated amines discussed above (particularly analogues of natural products) is the β-hydroxy γ-fluoro amine motif **310**, frequently with all three heteroatom substituents at stereogenic centres. One of the most expedient synthetic approaches to these compounds, particularly from the point of view of regio- and stereocontrol, would be the ring-opening fluorination of stereodefined 2,3-epoxy amines **309** with a nucleophilic source of fluorine (Figure 35).

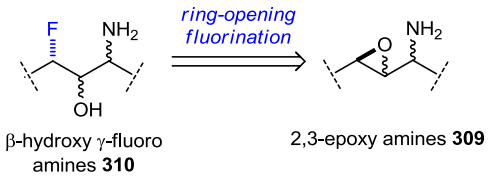
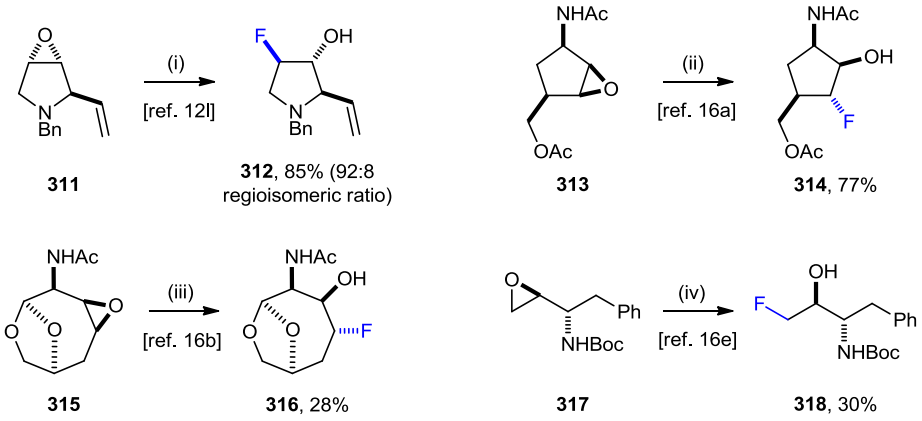
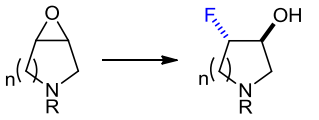


Figure 35. Synthesis of β-hydroxy γ-fluoro amines **310** *via* the ring-opening fluorination of 2,3-epoxy amines **309**.

However, despite the popularity of the ring-opening fluorination of epoxides as a stereoselective fluorination protocol,[15] this method has seldom been applied to the synthesis of β-hydroxy γ-fluoro amines.[12l,16] Of the few reported instances, all but one (i.e. **311**) has concerned 2,3-epoxy amines which are *N*-protected as amides or carbamates, and the majority of these examples are of *N*-protected 3,4-epoxy pyrrolidines **319**-**321** or piperidines **322**-**323** (Schemes 72 and 73). Amine-HF reagents such as PPHF and Et_3N•3HF have typically been the fluorinating agents of choice, although high reaction temperatures (80-155 °C) are required in the latter case for the reactions to proceed.



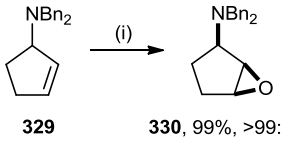
Scheme 72. *Reagents and conditions:* (i) PPHF, 60 °C, 24 h; (ii) PPHF, CH_2Cl_2; (iii) $Bu_4NH_2F_3$, KHF_2, DOWEX 50W; (iv) KHF_2, Bu_4NF, PhCl, 120 °C, 16 h.



Epoxy Amine	Fluoride Source	Amino Fluorohydrin Yield	Ref.
319, n = 1, R = Boc	Et_3N•3HF	**324**, 45%	16c
320, n = 1, R = Cbz	Et_3N•3HF	**325**, 40%	16d
320, n = 1, R = Cbz	PPHF	**325**, 17%	16g
321, n = 1, R = $COCCl_3$	PhCOF	**326**, 84% (80% ee)	16j
322, n = 2, R = Cbz	Et_3N•3HF	**327**, 53%	16f
323, n = 2, R = Boc	Et_3N•3HF	**328**, 58%	16i

Scheme 73.

As part of an ongoing research program into the olefinic oxidation of alkenyl amines,[17] Davies and co-workers have recently reported the highly diastereoselective synthesis of 2,3-epoxy amines *via* the ammonium-directed epoxidation of allylic amines.[17b,c-f] For example, the sequential treatment of 3-(*N*,*N*-dibenzylamino)cyclopent-1-ene **329** with Cl_3CCO_2H and *m*-CPBA in CH_2Cl_2 at rt for 3.5 h gave 2,3-*syn*-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cyclopentane **330** in 99% yield and >99:1 dr (Scheme 74).[17c]



Scheme 74. *Reagents and conditions:* (i) Cl_3CCO_2H (5 equiv), *m*-CPBA (1.05 equiv), CH_2Cl_2, rt, 3.5 h.

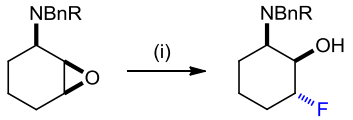
Considering the literature precedent for S_N2-type nucleophilic attack by fluoride transfer from the BF_4^- ion on chloriranium,[18] iodiranium[19] and thiiranium[20] ions, it was anticipated that commercially available HBF_4•OEt_2 may be a suitable nucleophilic fluorinating agent for these 2,3-epoxy amines. Although HBF_4•OEt_2 has been reported to *catalyse* the ring-opening of epoxides with anhydrous HF,[21] there have been no reported instances in the literature of the ring-opening fluorination of epoxides with HBF_4•OEt_2 *in the absence of other fluoride sources*.[22] To assess the potential of HBF_4•OEt_2 as a nucleophilic fluorinating agent

in its own right, the ring-opening fluorination of a variety of 2,3-epoxy amines with HBF_4•OEt_2 was investigated.

4.2. Results and Discussion

4.2.1. Ring-Opening Fluorination of 2,3-Epoxy Amines with HBF_4•OEt_2: Initial Studies

The ring-opening fluorination of 2,3-*syn*-3-(*N*-benzyl-*N*-methylamino)-1,2-epoxycyclohexane **331** as a model system was first examined. Remarkably, treatment of **331** with 1 equiv of HBF_4•OEt_2 in CH_2Cl_2 at rt for 5 min gave a mixture of products from which amino fluorohydrin **332** could be isolated in 78% yield as a single diastereoisomer (>99:1 dr). Alternatively, the use of 0.5 equiv of HBF_4•OEt_2 returned a mixture of products containing a 37:63 ratio of amino fluorohydrin **332** to unreacted starting material **331**, signifying that at least a stoichiometric quantity of HBF_4•OEt_2 is required. In an effort to increase the yield of **332**, the reaction was repeated with 2 equiv of HBF_4•OEt_2, giving clean conversion to **332**, which was isolated in 89% yield and >99:1 dr. With a satisfactory set of reaction conditions in hand, the ring-opening fluorination of 2,3-*syn*-3-(*N*,*N*-dibenzylamino)-1,2-epoxycyclohexane **333** was next attempted. The treatment of **333** with 2 equiv of HBF_4•OEt_2 in CH_2Cl_2 at rt for 5 min gave amino fluorohydrin **334** in quantitative yield and >99:1 dr (Scheme 75).



331, R = Me, >99:1 dr
333, R = Bn, >99:1 dr

332, R = Me, >99:1 dr
334, R = Bn, >99:1 dr

Epoxy Amine	HBF_4•OEt_2 Equiv	Amino Fluorohydrin Yield
331	0.5	not isolated[a]
331	1	**332**, 78%
331	2	**332**, 89%
333	2	**334**, quant

[a]A mixture of compounds containing a 37:63 ratio of **332**:**331** was produced.

Scheme 75. *Reagents and conditions:* (i) HBF_4•OEt_2, CH_2Cl_2, rt, 5 min.

The relative configurations within amino fluorohydrins **332** and **334** were assigned on the basis of ^{1}H-^{1}H and ^{1}H-^{19}F NMR coupling constant analyses (assuming a chair conformation with the NBnR group in an equatorial position). The multiplicities of the fluorine resonances in the ^{19}F NMR spectra of **332** and **334** were indicative of axial fluorine atoms – an apparent triplet was observed in each case with J ~ 45 Hz, consistent with $^2J_{HF}$ ~ 45 Hz and $^3J_{HF,anticoplanar}$ ~ 45 Hz (Figure 36).[23]

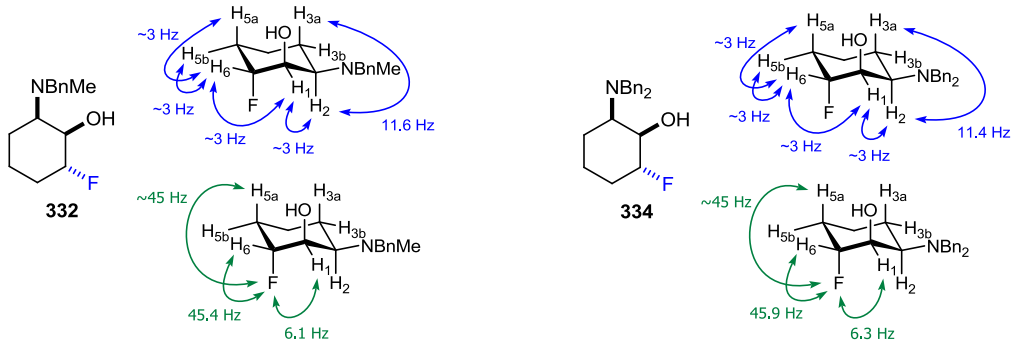


Figure 36. ^{1}H-^{1}H (**blue**) and ^{1}H-^{19}F (**green**) NMR coupling constants within **332** and **334**.

The relative configuration within **334** was subsequently confirmed unambiguously *via* single crystal X-ray diffraction analysis (Figure 37).[24]

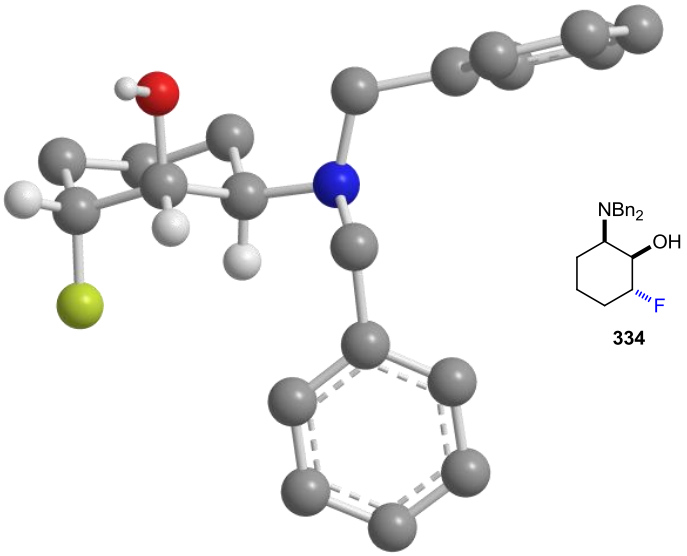
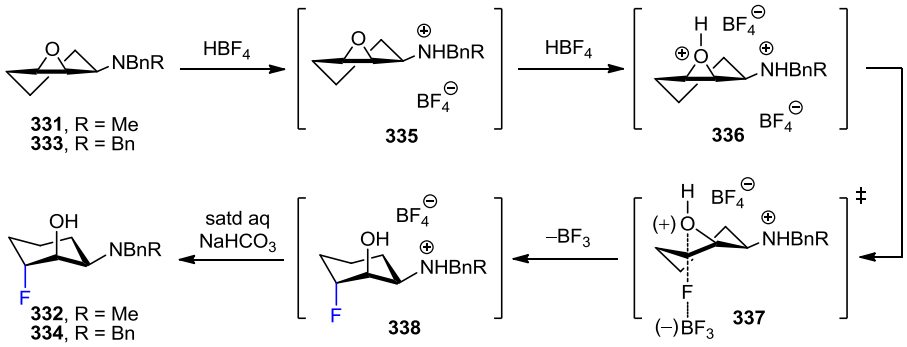


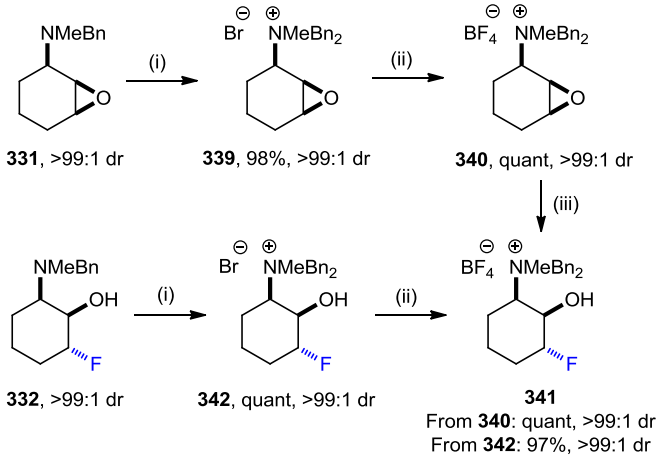
Figure 37. Chem3D representation of the single crystal X-ray diffraction structure of **334** (selected H atoms omitted for clarity).

A plausible mechanistic rationale for the ring-opening fluorination of 2,3-*syn* epoxy amines **331** and **333** with 2 equiv of HBF_4•OEt_2 is that initial *N*-protonation by HBF_4[25] may occur to give epoxy ammonium species **335**, followed by *O*-protonation[26] of the oxirane and S_N2-type ring-opening by transfer of fluoride from a BF_4^- ion.[27] The regioselectivity of the ring-opening process is consistent with previous observations concerning the ring-opening of 2,3-epoxy amines with a variety of Brønsted acids:[17] the destabilising electron-withdrawing influence of the ammonium moiety on the transition state **337** is less pronounced if ring-opening occurs at the carbon atom distal to it (Scheme 76).[28]



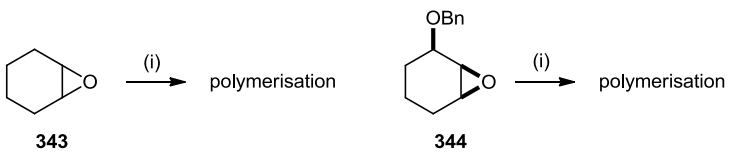
Scheme 76. Mechanistic rationale for the ring-opening fluorination of 2,3-epoxy amines **331** and **333** with 2 equiv of HBF_4•OEt_2.

In order to probe whether oxirane activation is necessary for ring-opening by fluoride transfer from a BF_4^- ion to occur, *N*,*N*-dibenzyl-*N*-methyl epoxy ammonium tetrafluoroborate salt **340** was synthesised as a model for the intermediate epoxy ammonium species **335**. Thus, *N*-benzyl-*N*-methyl 2,3-*syn* epoxy amine **331** was treated with BnBr in MeCN to give *N*,*N*-dibenzyl-*N*-methyl epoxy ammonium bromide salt **339**, and subsequent anion exchange by treatment with $Ag(MeCN)_4BF_4$[29] in CH_2Cl_2 gave the corresponding tetrafluoroborate salt **340** in 98% yield over the 2 steps. A solution of **340** in CD_2Cl_2 was allowed to stand at rt, and was monitored *via* ^1H and ^{19}F NMR spectroscopic analysis: no ring-opening of the epoxide by the BF_4^- ion was observed even after several days, signifying that oxirane activation is a prerequisite to fluorination. Addition of 1 equiv of HBF_4•OEt_2 to the solution of **340** followed by immediate ^1H and ^{19}F NMR spectroscopic analysis revealed that clean conversion of the epoxide to fluorohydrin **341** had occurred,[30] which was isolated in quantitative yield as a single diastereoisomer. An authentic sample of **341** was also prepared in 97% yield upon sequential *N*-benzylation of amino fluorohydrin **332** and anion exchange with $Ag(MeCN)_4BF_4$ (Scheme 77).



Scheme 77. *Reagents and conditions:* (i) BnBr, MeCN, reflux, 22 h; (ii) $Ag(MeCN)_4BF_4$, CH_2Cl_2, rt; (iii) HBF_4•OEt_2 (1 equiv), rt.

It was unclear at this point whether or not the amino group (or ammonium group *in-situ*) within 2,3-*syn* epoxy amines **331** and **333** was playing an active role in the ring-opening fluorination process with HBF_4•OEt_2.[31] To probe this matter, both cyclohexene oxide **343** and 2,3-*syn*-3-benzyloxy-1,2-epoxycyclohexane **344** were treated with 1 equiv of HBF_4•OEt_2 in CH_2Cl_2 at rt for 5 min. In both cases, the reactions returned polymeric[32] material presumably arising from cationic polymerisation of the oxiranes,[33] a process known to be initiated by HBF_4 (Scheme 78).[34] The polymerisation of cyclohexene oxide **343** has also been reported during its attempted ring-opening fluorination with anhydrous HF.[35]

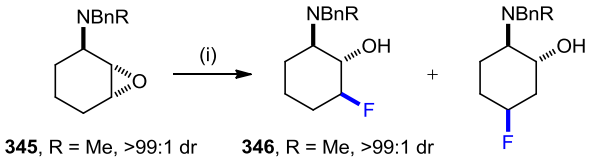


Scheme 78. *Reagents and conditions:* (i) HBF_4•OEt_2 (1 equiv), CH_2Cl_2, rt, 5 min.

These results indicate that the amino group present within 2,3-*syn* epoxy amines **331** and **333** (or rather the ammonium group formed *in situ*) is critical to the success of the ring-opening fluorination reaction with HBF_4•OEt_2. It is well precedented that electrostatic repulsion between like-charged monomers can retard polymerisation processes,[36] and it is plausible that polymerisation of the epoxy ammonium species **335** may be suppressed by the same effect.[37] Another mode of reactivity available to protonated epoxides is the formation of carbocationic intermediates arising from heterolysis of the oxirane C−O bond, followed by rearrangement processes which typically lead to carbonyl compounds (i.e. the Meinwald rearrangement).[38] However, the presence of electron-withdrawing substituents in close proximity to epoxides has been shown to suppress such rearrangement processes by detering the formation of carbocationic intermediates.[39] Hence, the ammonium moiety may also serve to disfavour ionisation of the protonated oxirane by imparting a strong inductive withdrawal effect, preventing carbocationic pathways from competing with nucleophilic attack by fluoride transfer from a BF_4^- ion.

4.2.2. Ring-Opening Fluorination of Carbocyclic 2,3-Epoxy Amines with HBF_4•OEt_2: Substrate Scope

The generality of the ring-opening fluorination reaction with HBF_4•OEt_2 was next assessed by application to a range of 5-, 6- and 7-membered carbocyclic 2,3-epoxy amines, allowing for assessment of the effects of both ring size and relative configuration on the reaction efficiency. In the 6-membered ring series, treatment of *N*-benzyl-*N*-methyl 2,3-*anti* epoxide **345** with 2 equiv of HBF_4•OEt_2 in CH_2Cl_2 at rt for 5 min gave a 92:8 mixture of amino fluorohydrin **346** to another fluorinated product tentatively assigned[40] as **347**, with chromatographic purification giving **346** in 71% yield and >99:1 dr. Similarly, *N*,*N*-dibenzyl 2,3-*anti* epoxide **348** gave a 98:2 mixture of amino fluorohydrin **349** to another fluorinated product tentatively assigned[40] as **350**, with chromatographic purification giving **349** in 73% yield and >99:1 dr (Scheme 79).[41] In addition to demonstrating that a *syn* relationship between the oxirane and the amino group is not a prerequisite for efficient fluorination, the regioselectivity of fluorine incorporation confirms that the inductive withdrawal effect of the ammonium group directing nucleophilic attack to C(1) overrides the preference for *trans*-diaxial ring-opening at C(2) according to the Fürst-Plattner rule.[42]



345, R = Me, >99:1 dr
348, R = Bn, >99:1 dr

346, R = Me, >99:1 dr
349, R = Bn, >99:1 dr

347, R = Me
350, R = Bn

Epoxy Amine	Amino Fluorohydrin Yield
345[a]	**346**, 71%
348[b]	**349**, 73%

[a]The reaction produced a 92:8 mixture of **346**:**347**.
[b]The reaction produced a 98:2 mixture of **349**:**350**.

Scheme 79. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

The relative configurations within amino fluorohydrins **346** and **349** were established by analysis of the ^1H-^1H and ^1H-^{19}F NMR coupling constants (assuming a chair conformation with the NBnR group in an equatorial position). The multiplicities of the fluorine resonances in the ^{19}F NMR spectra of **346** and **349** were characteristic of equatorial fluorine atoms: in both cases a broad doublet was observed with J ~ 50 Hz, consistent with $^2J_{HF}$ ~ 50 Hz and the lack of resolution of $^3J_{HF,gauche}$ couplings on account of their much smaller magnitude (Figure 38).[23]

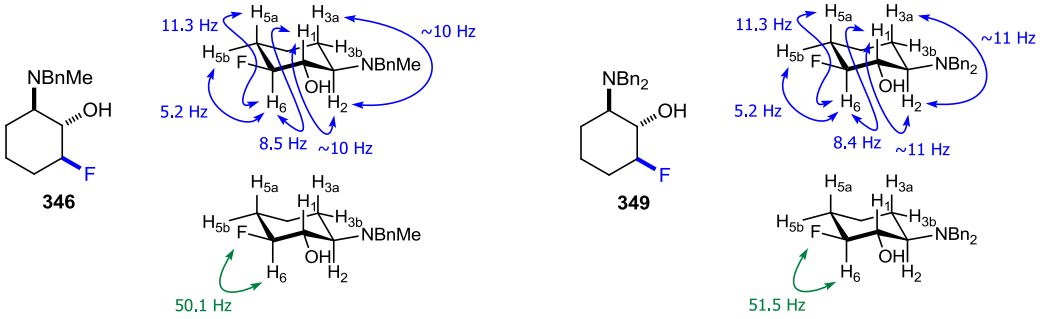


Figure 38. ^1H-^1H (**blue**) and ^1H-^{19}F (**green**) NMR coupling constants within **346** and **349**.

The relative configurations within both **346** and **349** were subsequently confirmed unambiguously *via* single crystal X-ray diffraction analyses (Figure 39).[24]

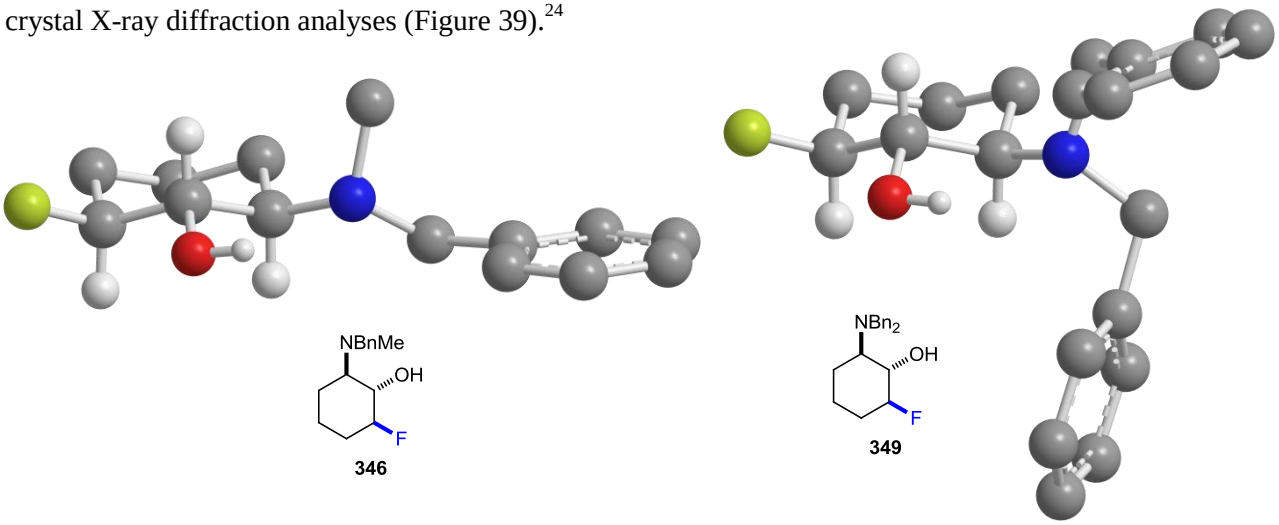
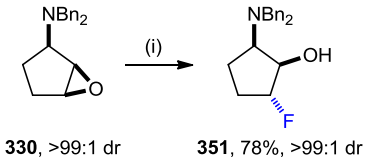


Figure 39. Chem3D representation of the single crystal X-ray diffraction structures of **346** and **349** (selected H atoms omitted for clarity).

In the 5-membered ring series, the reaction of *N*,*N*-dibenzyl 2,3-*syn* epoxide **330** with 2 equiv of HBF_4•OEt_2 gave amino fluorohydrin **351** in 78% yield and >99:1 dr (Scheme 80).



Scheme 80. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

The relative configuration within **351** was established unambiguously *via* single crystal X-ray diffraction analysis of the corresponding HBF_4 salt **351**•HBF_4 (Figure 40).[24]

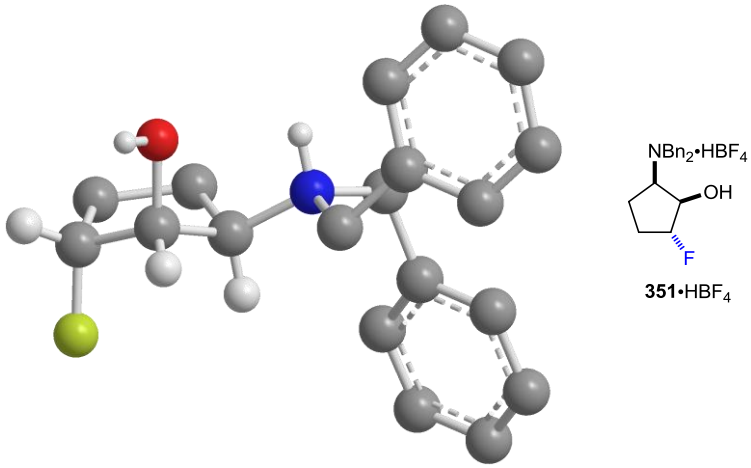
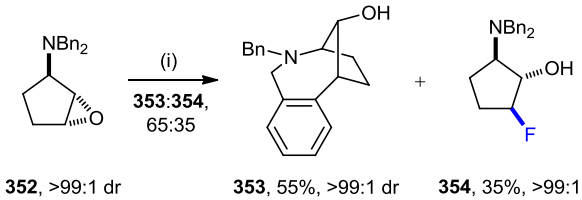


Figure 40. Chem3D representation of the single crystal X-ray diffraction structure of **351**•HBF_4 (selected H atoms and the BF_4^- counteranion omitted for clarity).

For *N*,*N*-dibenzyl 2,3-*anti* epoxide **352**, however, the reaction was accompanied by a competitive intramolecular electrophilic aromatic substitution reaction which resulted in the formation of bicycle **353** as the major product, somewhat compromising the yield of amino fluorohydrin **354**. Following chromatographic purification, bicycle **353** was isolated in 55% yield and >99:1 dr, whereas amino fluorohydrin **354** was isolated in 35% yield and >99:1 dr (Scheme 81).



Scheme 81. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

Examination of the single crystal X-ray diffraction structure of 2,3-epoxy amine **352**[43] reveals a solid state conformation in which the bicyclic system adopts a boat conformation[44] with a pseudoaxial *N*,*N*-dibenzylamino group. If maintained in solution, this conformation would provide ideal positioning of the *N*,*N*-dibenzylamino group for the intramolecular cyclisation reaction leading to bicycle **353** (Figure 41).

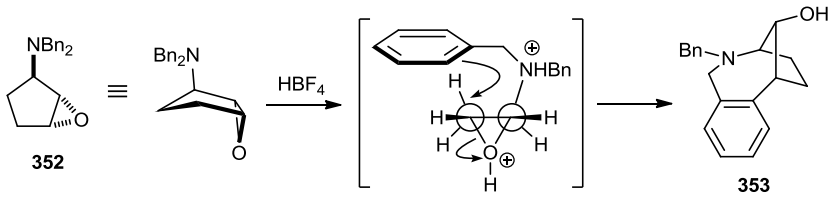


Figure 41. Mechanistic rationale for the formation of bicycle **353**.

The relative configuration within bicycle **353** was secured by single crystal X-ray diffraction analysis (Figure 42).[24] Meanwhile, the connectivity within fluorohydrin **354** was established *via* ^{1}H-^{1}H COSY analysis, and the relative configuration within **354** was assigned on the basis of the reaction proceeding *via* an S_N2-type mechanism.

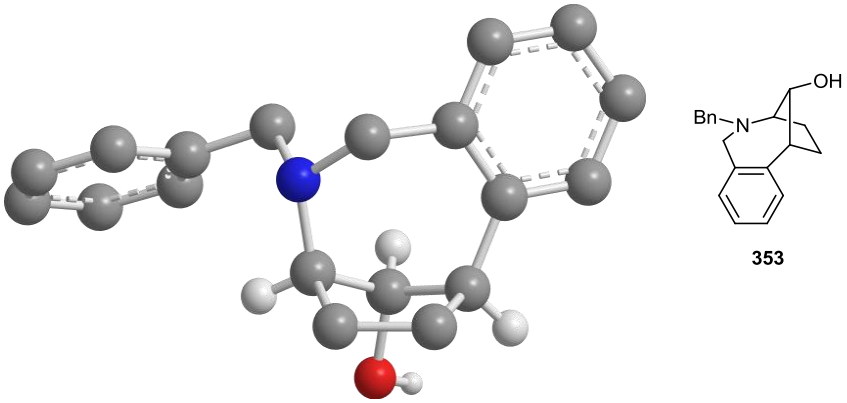
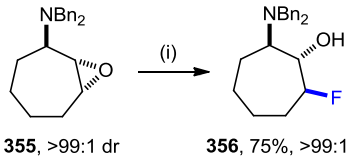


Figure 42. Chem3D representation of the single crystal X-ray diffraction structure of **353** (selected H atoms omitted for clarity).

In the 7-membered ring series, the reaction of *N*,*N*-dibenzyl 2,3-*anti* epoxide **355** with 2 equiv of HBF_4•OEt_2 gave an 80:8:8:4 mixture of amino fluorohydrin **356** to 3 unidentified fluorinated compounds (possibly arising from transannular reactions).[45] Chromatographic purification gave amino fluorohydrin **356** in 75% yield and >99:1 dr as the only product isolated (Scheme 82).



Scheme 82. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

The relative configuration within **356** was unambiguously assigned by single crystal X-ray diffraction analysis (Figure 43).[24]

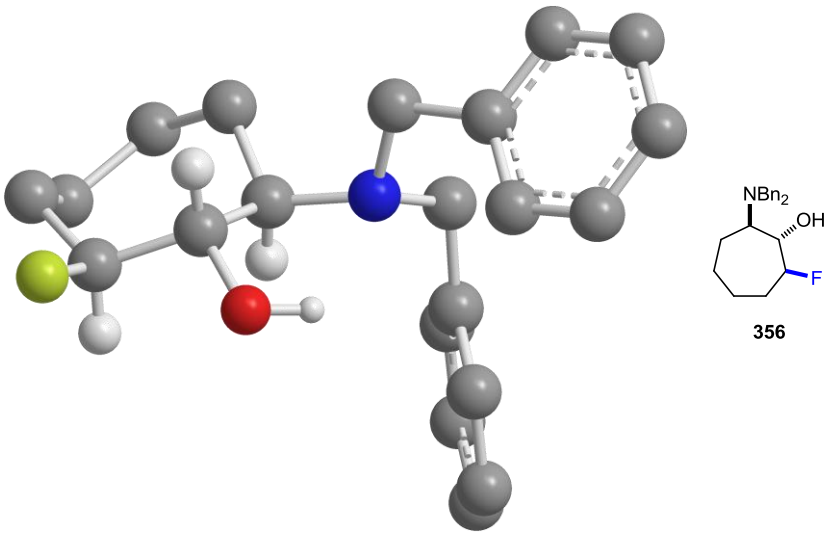
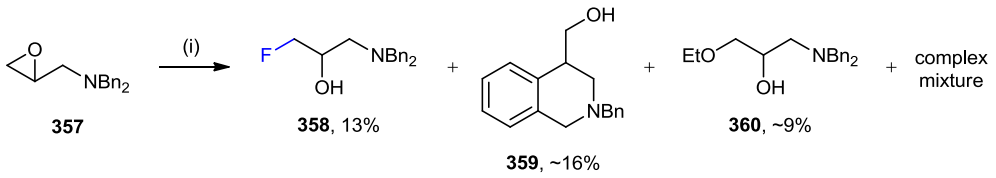


Figure 43. Chem3D representation of the single crystal X-ray diffraction structure of **356** (selected H atoms omitted for clarity).

4.2.3. Ring-Opening Fluorination of Acyclic 2,3- and 3,4-Epoxy Amines with HBF_4•OEt_2

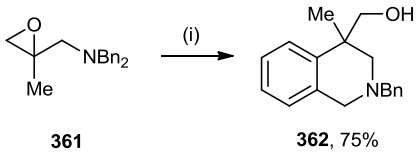
Having explored the generality of the reaction for carbocyclic substrates, the applicability of the ring-opening fluorination reaction with HBF_4•OEt_2 to a range of acyclic 2,3- and 3,4-epoxy amine substrates was next surmised. As for the carbocyclic 2,3-epoxy amine substrates, the standard fluorination conditions involved the reaction of each epoxide with 2 equiv of HBF_4•OEt_2 in CH_2Cl_2 at rt for 5 min. Under these conditions, terminal epoxide **357** returned a complex mixture of products, from which amino fluorohydrin **358** was isolated in 13% yield. Tetrahydroisoquinoline **359** arising from an intramolecular electrophilic aromatic substitution reaction was isolated as an impure sample in ~16% yield, and an impure sample of ether **360** was also isolated in ~9% yield, presumably arising from nucleophilic attack of Et_2O derived from HBF_4•OEt_2 on the activated epoxide (Scheme 83).[46] The behaviour of epoxide **357** under these conditions may be due to the exceptionally high reactivity of the protonated epoxide at the terminal position, leading to an indiscriminate reaction with any available nucleophiles in the medium, including Et_2O and the hydroxyl functionality of any ring-opened products. Attempts to improve the yield of amino fluorohydrin **358** by increasing the amount of HBF_4•OEt_2 to 10 equiv or by adding a solution of the epoxide **357** dropwise to the HBF_4•OEt_2 (2 equiv) gave no discernable difference in the product distribution.



Scheme 83. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

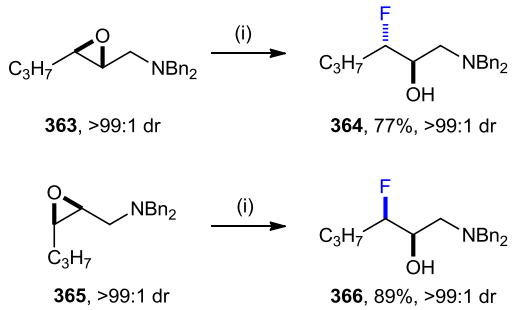
When *gem*-disubstituted terminal epoxide **361** was reacted under the same conditions with 2 equiv of HBF_4•OEt_2, tetrahydroisoquinoline **362** was obtained as the major product in 75% yield, and no amino fluorohydrin could be isolated (Scheme 84). Again, increasing the amount of HBF_4•OEt_2 to 10 equiv or

adding a solution of the epoxide **361** dropwise to the HBF_4•OEt_2 (2 equiv) did not alter the course of the reaction.



Scheme 84. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

In constrast to the behaviour of terminal epoxides **357** and **361**, the treatment of *vic*-disubstituted epoxides **363** and **365** with 2 equiv of HBF_4•OEt_2 gave clean conversion to amino fluorohydrins **364** and **366**, isolated as single diastereoisomers in yields of 77 and 89%, respectively (Scheme 85). Notably, no products arising from intramolecular electrophilic aromatic substitution were detected in either case.[47] The relative configurations within amino fluorohydrins **364** and **366** were proven unambiguously *via* single crystal X-ray diffraction analyses of the corresponding *p*-nitrobenzoate derivatives **367** and **368** (Figure 44).[24]



Scheme 85. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

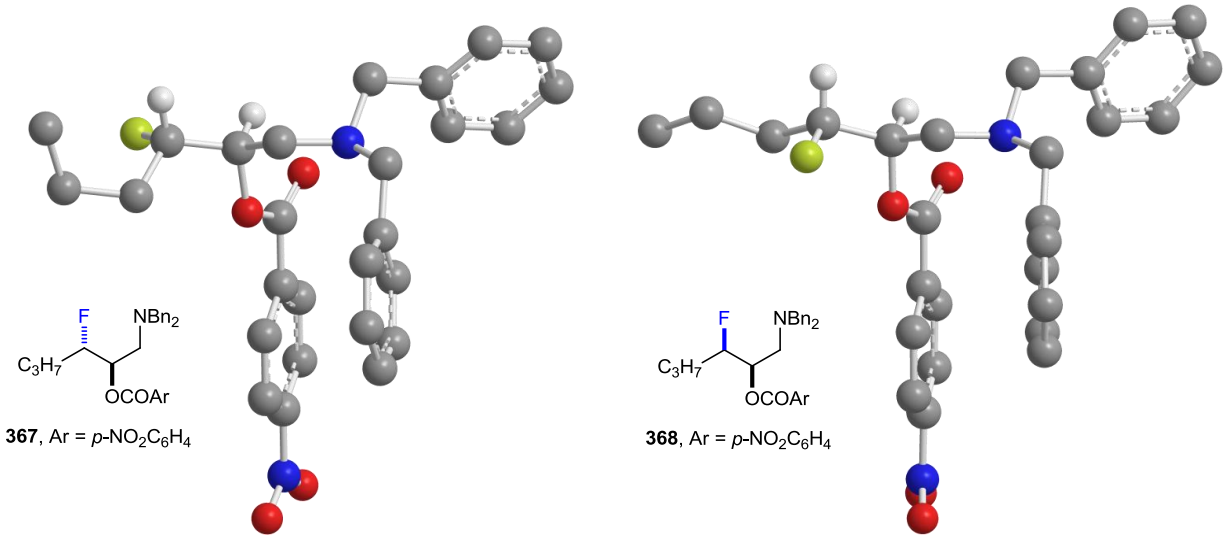
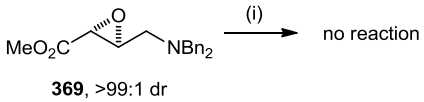


Figure 44. Chem3D representations of the single crystal X-ray diffraction structures of **367** and **368** (selected H atoms omitted for clarity).

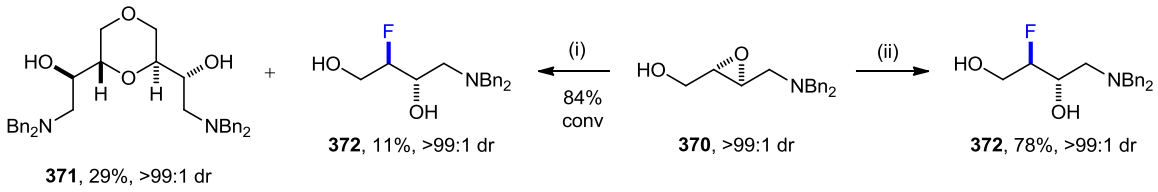
Considering the strikingly different behaviour of *vic*-disubstituted epoxides **363** and **365** *versus* terminal epoxides **357** and **361** in the ring-opening fluorination reaction, it became of interest to ascertain whether the inclusion of electron-withdrawing functionality on the oxirane carbon distal to the amino group would similarly affect the reaction efficiency. To this end, enantiopure epoxide **369** bearing a methyl ester group on

the oxirane ring (prepared as a single enantiomer in 3 steps from L-threonic acid hemicalcium salt) was subjected to 2 equiv of HBF_4•OEt_2 under the standard conditions. However, no reaction was observed, supporting the notion that the development of partial carbocationic character at the oxirane carbon is a prerequisite for efficient nucleophilic attack by fluoride transfer from a BF_4^- ion (Scheme 86).



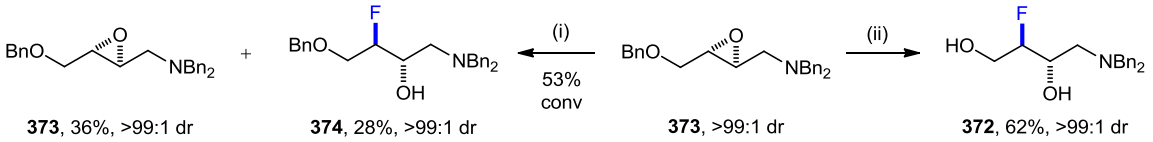
Scheme 86. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

Similarly, the treatment of enantiopure hydroxymethyl substituted epoxide **370** (derived from enantiopure epoxide **369**) with 2 equiv of HBF_4•OEt_2 gave incomplete (84%) conversion to a mixture of a C_2-symmetric 1,4-dioxane species **371**,[48] isolated in 29% yield, and the desired amino fluorohydrin **372**, isolated in 11% yield, both as single diastereoisomers. However, increasing the amount of HBF_4•OEt_2 to 10 equiv resulted in complete conversion, giving amino fluorohydrin **372** in 78% yield and >99:1 dr (Scheme 87).



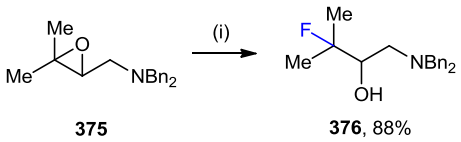
Scheme 87. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min; (ii) HBF_4•OEt_2 (10 equiv), CH_2Cl_2, rt, 5 min.

Protection of the hydroxyl function within epoxide **370** as a benzyl ether was also briefly investigated. Thus, treatment of (benzyloxy)methyl substituted epoxide **373** with 2 equiv of HBF_4•OEt_2 gave 53% conversion to amino fluorohydrin **374**, which was isolated in 28% yield as a single diastereoisomer, along with 36% of recovered starting material **373**. In an effort to increase the conversion, subjection of **373** to 10 equiv of HBF_4•OEt_2 gave complete consumption of starting material but also led to *O*-benzyl deprotection, furnishing amino fluorohydrin **372** in 62% yield and >99:1 dr (Scheme 88).



Scheme 88. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min; (ii) HBF_4•OEt_2 (10 equiv), CH_2Cl_2, rt, 5 min.

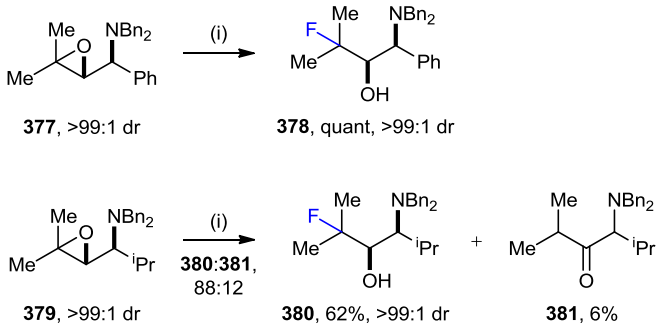
The effect of *gem*-disubstitution at the oxirane carbon distal to the amino group was next assessed. Thus, treatment of trisubstituted epoxide **375** with 2 equiv of HBF_4•OEt_2 under the optimised conditions gave clean conversion to amino fluorohydrin **376**, which was isolated in 88% yield (Scheme 89).



375 **376**, 88%

Scheme 89. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

Similarly, treatment of diastereoisomerically-pure epoxides **377** and **379** with 2 equiv of HBF_4•OEt_2 gave the corresponding amino fluorohydrins **378** and **380** in quantitative and 62% yield, respectively, both as single diastereoisomers. In the case of **379**, a small amount of competing isomerisation to ketone **381** was apparent, and this was isolated in 6% yield (Scheme 90).

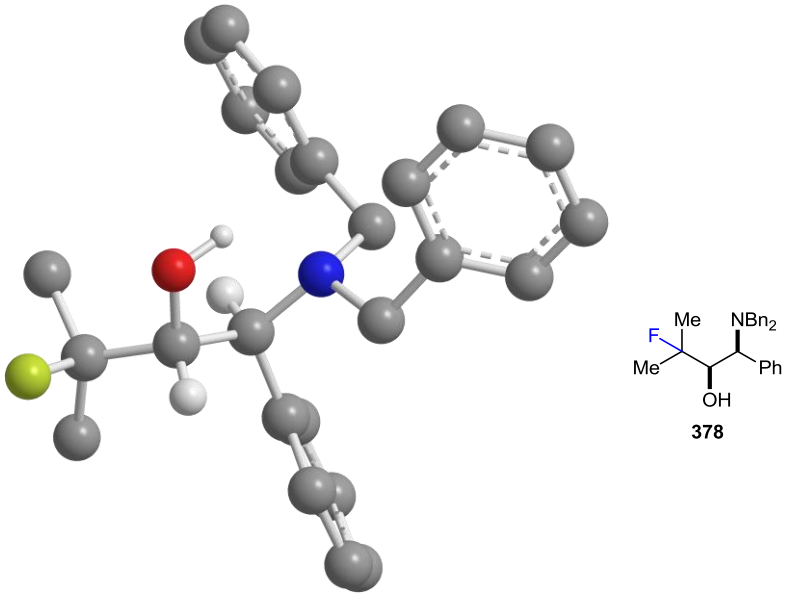


377, >99:1 dr **378**, quant, >99:1 dr

379, >99:1 dr **380**, 62%, >99:1 dr **381**, 6%

Scheme 90. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

The relative *syn*-configuration within amino fluorohydrin **378** was proven unambiguously *via* single crystal X-ray diffraction analysis (Figure 45).[24] By analogy, the relative configuration within amino fluorohydrin **380** was also assigned as *syn*, and this was supported by the fact that the configuration within epoxide **379** is known.[17e]

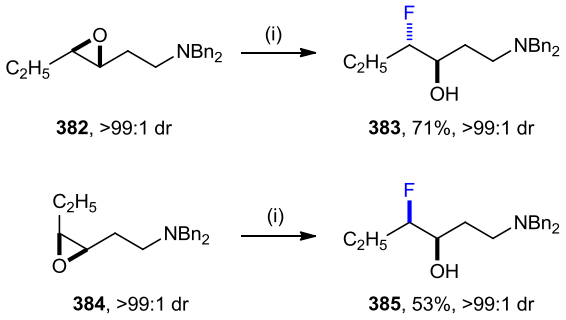


378

Figure 45. Chem3D representation of the single crystal X-ray diffraction structure of **378** (selected H atoms omitted for clarity).

The effect of increasing the through-bond distance between the oxirane and the amino group was next investigated. Thus, treatment of 3,4-epoxy amines **382** and **384** with 2 equiv of HBF_4•OEt_2 gave the corresponding amino fluorohydrins **383** and **385** as single diastereoisomers in 71 and 53% yield, respectively; the balance of the mass in each case comprised a complex mixture of unidentified products

(Scheme 91).[49,50] The relative configurations within **383** and **385** were assigned on the basis that both reactions proceed *via* S_N2-type ring-openings with inversion of configuration at the oxirane carbon undergoing attack.[51] The assignment of a *syn*-configuration within **385** was supported by the observation of a ^1H-^{19}F ^3J NMR coupling constant of 20.7 Hz between C(3)*H* and C(4)*F*, in close conformity with the value of 21.5 Hz for the C(2)*H* and C(3)*F* coupling constant within fluorohydrin **366** (for which the *syn*-configuration was unambiguously determined by single crystal X-ray diffraction analysis). The corresponding ^1H-^{19}F ^3J NMR coupling constant between C(3)*H* and C(4)*F* within fluorohydrin **383** could not be resolved, but it should be noted that a value of 11.5 Hz was observed for the C(2)*H* and C(3)*F* coupling within *anti*-configured fluorohydrin **364**.



Scheme 91. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

4.2.4. Application to the Synthesis of β-Fluoro Amines: *De Novo* Asymmetric Synthesis of (*S*,*S*)-3-Deoxy-3-fluorosafingol

Despite the growing importance of β-fluoro amines in medicinal chemistry, very few synthetic methods for accessing this motif in diastereo- and enantiomerically pure form have been developed to date.[2] With this in mind, it was envisaged that β-hydroxy γ-fluoro amines **387** or **391**, available from the ring-opening fluorination of 2,3-epoxy amines **386** or **390**, respectively, with HBF_4•OEt_2, could be used to access β-fluoro amines **389** or **393** *via* a rearrangement strategy involving aziridinium ion intermediates **388** or **392**.[52] If an enantioselective epoxidation protocol were used to prepare the starting epoxides **386** or **390**, this multistep sequence could comprise a valuable and stereospecific synthetic entry to enantiopure β-fluoro amines **389** and **393** (Figure 46).

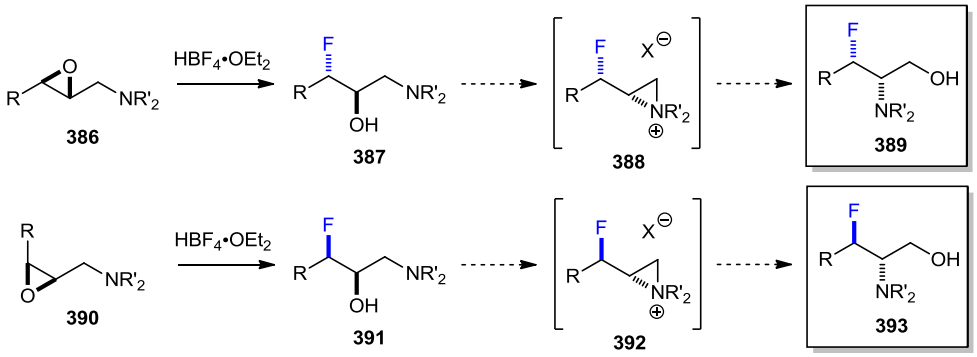


Figure 46. Stereospecific strategy for accessing β-fluoro amines **389** and **393**.

To exemplify this strategy in the context of preparing a fluorinated analogue of a biologically-active amine, (*S*,*S*)-3-deoxy-3-fluorosafingol **394** was selected as a target of interest. Safingol **395**, a non-naturally occurring diastereoisomer of the sphingoid base sphinganine **396**, has attracted considerable attention as a synthetic target[53] due to its promising anticancer properties: it has been shown to synergistically increase the potency of established chemotherapeutic agents such as doxorubicin[54] and cisplatin[55] in phase I clinical trials. The anticancer properties of safingol **395** have been attributed to its inhibitory effect on the activity of either protein kinase C (PKC) or sphingosine kinase (SK).[54,55] Crucially, there has also been interest in the synthesis and biological evaluation of 3-deoxy-3-fluoro analogues of sphingoid bases and ceramides,[14] including assessment of their apoptogenic activity[14b,d] and their ability to inhibit the activity of both PKC[14a] and SK[14c] enzymes (Figure 47).

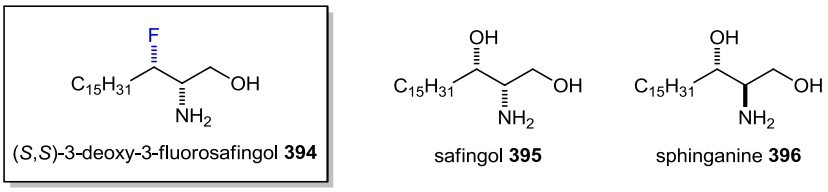
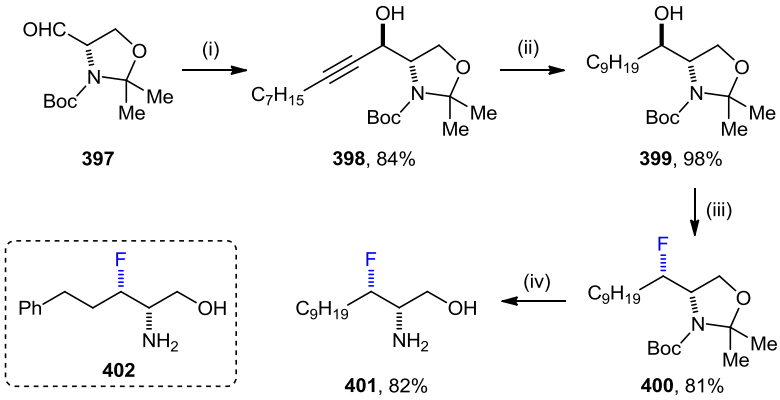


Figure 47. The structures of (*S*,*S*)-3-deoxy-3-fluorosafingol **394**, safingol **395** and sphinganine **396**.

4.2.4.1. Previous Enantiospecific Syntheses of 3-Deoxy-3-fluoro Sphingoid Bases and Analogues

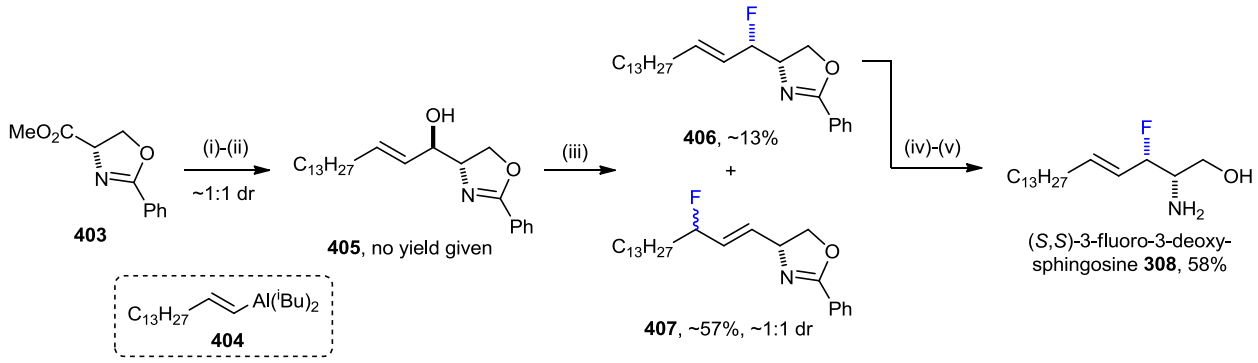
During studies on the synthesis of fluorinated ceramide and dihydroceramide analogues, Herdewijn and co-workers prepared short chain (*S*,*S*)-3-deoxy-3-fluoro sphingoid base analogues **401** and **402**, which are formally short chain analogues of (*S*,*S*)-3-deoxy-3-fluorosafingol **394**.[14b,e] Starting from Garner's aldehyde (*S*)-**397**, a route was devised relying on the dehydroxyfluorination of alcohol **399** with DAST as the key step, delivering fluoride **400** as a single diastereoisomer after removal of the protecting groups. A similar route was also used to synthesise **402** in 14% yield over 3 steps from **397** (Scheme 92).



Scheme 92. *Reagents and conditions:* (i) BuLi, non-1-yne, HMPA, THF, −78 °C; (ii) H_2, Pd/C, MeOH, rt; (iii) DAST, CH_2Cl_2, −78 °C; (iv) CF_3CO_2H/H_2O (3:1 v/v), rt.

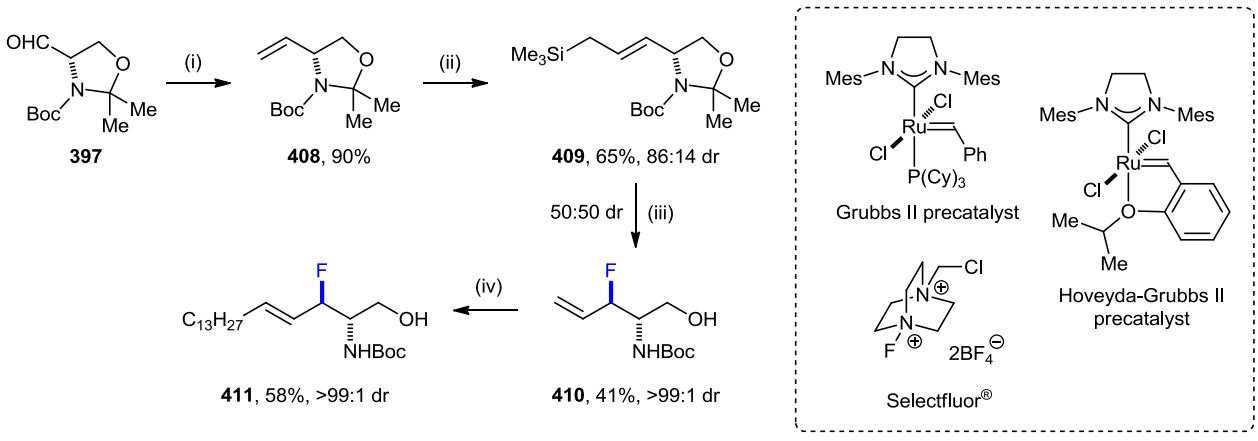
The synthesis of (*S*,*S*)-3-fluoro-3-deoxysphingosine **308** has also been reported by Kozikowski and Wu, using the dehydroxyfluorination of allylic alcohol **405** with 2-chloro-1,1,2-trifluoroethylamine (Yarovenko's reagent) as a key step.[14a] Under these conditions, a mixture of diastereoisomeric allylic fluorides **407** arising

from transposition of the double bond were formed as the major products in ~57% combined yield, in addition to **406** which was isolated in only ~13% yield. Deprotection of **406** under acidic conditions gave (*S*,*S*)-3-fluoro-3-deoxysphingosine **308** in 58% yield (Scheme 93). Herdewijn and co-workers have also prepared a short chain analogue of (*S*,*S*)-3-fluoro-3-deoxysphingosine **308** *via* the dehydroxyfluorination of an *N*-Boc protected allylic alcohol with DAST, and they too have reported similar problems with regio- and stereocontrol, as well as the formation of oxazolidinone by-products.[14c]



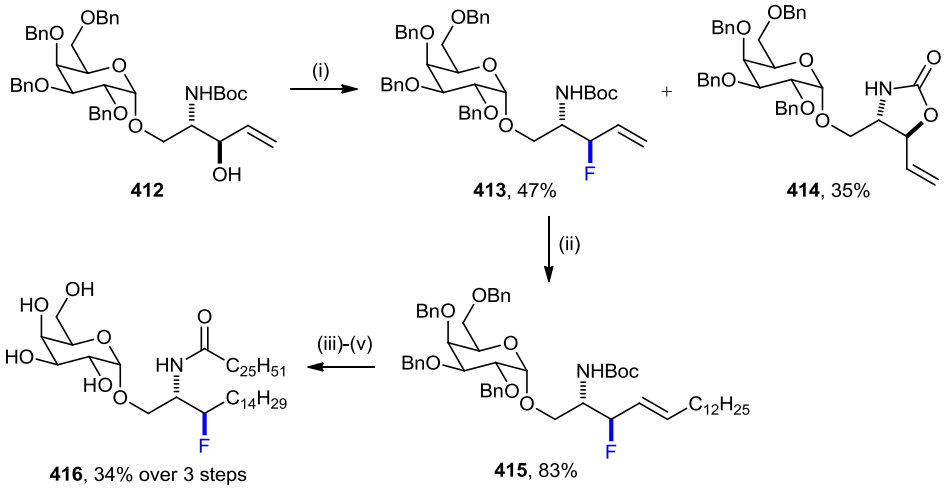
Scheme 93. *Reagents and conditions:* (i) DIBAL-H; (ii) **404**; (iii) 2-chloro-1,1,2-trifluoroethylamine, PhMe, 0 °C; (iv) 2 M aq HCl, THF; (v) 5% aq KOH, MeOH, H_2O.

To obviate the problems associated with double bond transposition and non-fluorinated by-product formation during the dehydroxyfluorination of allylic alcohols with DAST, Gouverneur *et al.* have devised an alternative and convergent approach to 3-deoxy-3-fluoro sphingoid bases reliant on the electrophilic fluorodesilylation of allyl silanes, culminating in a formal synthesis of (2*S*,3*R*)-3-fluoro-3-deoxysphingosine.[14g] The route relied on elaboration of Garner's aldehyde (*S*)-**397** to allyl silane **409** *via* Wittig methylenation and cross metathesis, followed by electrophilic fluorodesilylation using Selectfluor®. Although double bond transposition did not occur, the fluorination step did return a 50:50 mixture of diastereoisomeric allylic fluorides, from which **410** was isolated in 41% yield as a single diastereoisomer. To complete the formal synthesis, **410** was subjected to cross metathesis with pentadec-1-ene to give *N*-Boc protected (2*S*,3*R*)-3-fluoro-3-deoxysphingosine **411** in 58% yield and >99:1 dr (Scheme 94).



Scheme 94. *Reagents and conditions:* (i) $[MePPh_3]^+Br^-$ (2 equiv), KHMDS (2 equiv), THF, −78 °C to rt, 16 h; (ii) allyltrimethylsilane (3 equiv), Grubbs II precatalyst (10 mol%), $Ti(O^iPr)_4$ (30 mol%), CH_2Cl_2, reflux, 96 h; (iii) Selectfluor® (2.2 equiv), MeCN, rt, 48 h; (iv) pentadec-1-ene (5 equiv), Hoveyda-Grubbs II precatalyst (10 mol%), CH_2Cl_2, 70 °C (sealed tube), 16 h.

In a recent synthesis of 3-deoxy-3-fluoro sphingoid-derived α-galactoceramide analogues such as **416** for the treatment of cancer, a strategy combining a DAST-mediated dehydroxyfluorination reaction with Gouverneur's cross metathesis protocol was adopted.[14h] The relative *anti*-configuration within **413** was proven by single crystal X-ray diffraction analysis. Neighbouring group participation from the carbamate moiety would explain the retention of configuration during the fluorination step, and could also account for the observation that oxazolidinone **414** was formed as a by-product (Scheme 95).

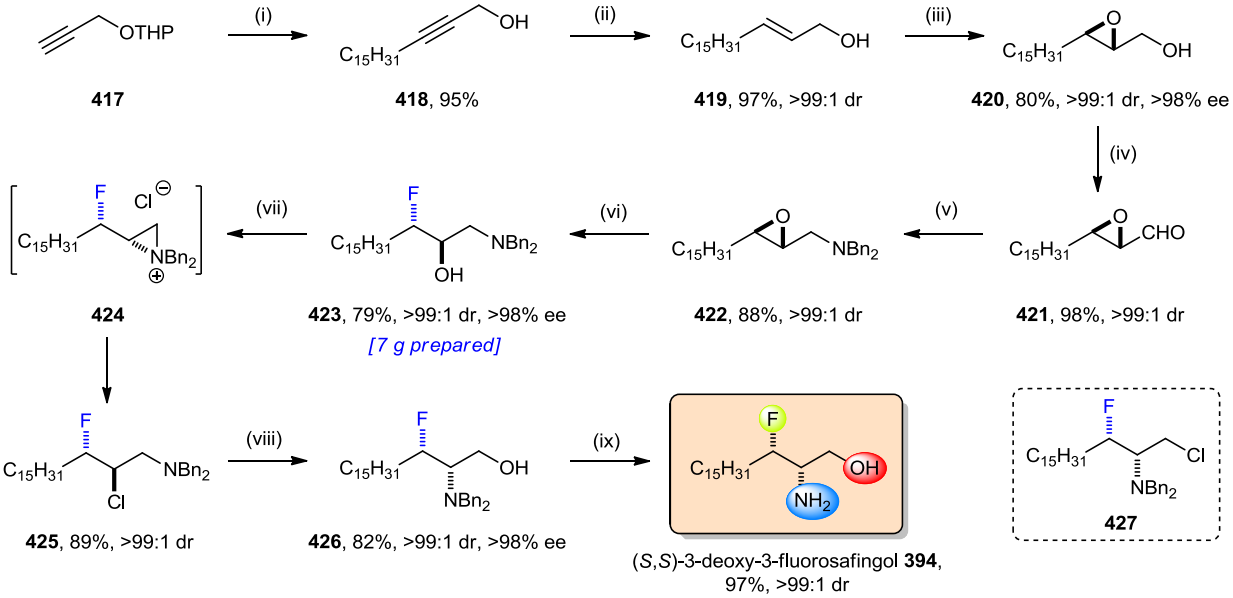


Scheme 95. *Reagents and conditions:* (i) DAST (1.2 equiv), CH_2Cl_2, rt, 10 min; (ii) tetradec-1-ene, Grubbs II precatalyst (5 mol%), CH_2Cl_2, reflux, 28 h; (iii) HCl, THF; (iv) hexacosanoyl chloride, DMAP, Et_3N, THF, reflux, 16 h; (v) H_2, Pd/C.

4.2.4.2. Asymmetric Synthesis of (*S*,*S*)-3-Deoxy-3-fluorosafingol

The synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol **394** began with alkylation of *O*-THP protected propargylic alcohol **417** (commercially available) by treatment with BuLi in the presence of DMPU and 1-bromopentadecane, which was followed by *O*-THP deprotection to give propargylic alcohol **418** in 95% yield. Reduction of **418** with $LiAlH_4$ gave allylic alcohol (*E*)-**419** in 97% yield and >99:1 dr. Sharpless asymmetric epoxidation[56] of **419** gave, after recrystallisation, 2,3-epoxy alcohol **420** in 80% isolated yield and >98% ee.[57] Oxidation of the hydroxyl functionality within **420** with IBX[58] followed by reductive amination of the resultant aldehyde **421** with $HNBn_2$ and $NaBH(OAc)_3$[59] gave 2,3-epoxy amine **422** in 86% yield (2 steps). Ring-opening fluorination of **422** using HBF_4•OEt_2 (performed on a 9.5 g scale) gave amino fluorohydrin **423** in 79% yield and as a single diastereoisomer in >98% ee.[57] The relative *anti*-configuration within **423** was assigned on the assumption that the ring-opening proceeds *via* an S_N2-type process, and this assignment was supported by inspection of a ^1H-^{19}F ^3J NMR coupling constant of 11.4 Hz between C(2)*H* and C(3)*F*, which is diagnostic of an *anti*-configuration [c.f. *anti*-**364** (J = 11.5 Hz) *versus syn*-**366** (J = 20.7 Hz)]. Chlorination of **423** under Appel conditions[60] for 40 min resulted in complete conversion to an 83:17 mixture of chlorides **427** and **425**, presumably *via* the intermediacy of aziridinium **424**. When the reaction time was extended to 18 h, clean conversion to chloride **425** was observed, consistent with reversible ring-opening of aziridinium **424** resulting initially in primary chloride **427** as the kinetic product

and secondary chloride **425** as the thermodynamic product.[61] Treatment of **425** with KOAc in DMF at 100 °C followed by methanolysis with K_2CO_3 in MeOH gave **426** as a single regio- and diastereoisomer, which was isolated in 82% yield and >98% ee[57] after chromatographic purification. Presumably, this reaction also proceeds *via* the intermediacy of aziridinium **424**, which undergoes irreversible ring-opening by acetate, with attack occurring at the least-substituted carbon atom. Finally, hydrogenolytic removal of the *N*-benzyl protecting groups within **426** completed the synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol **394**, which was isolated in 97% yield (36% overall yield in 11 steps from commercially available *O*-THP protected propargylic alcohol **417**) as a single diastereoisomer (Scheme 96). Given the known enantiomeric purities of **420**, **423** and **426** (i.e. >98% ee)[57] the enantiomeric purities of **421**, **422**, **425** and **394** can confidently be inferred as >98% ee.



Scheme 96. *Reagents and conditions:* (i) BuLi, $C_{15}H_{31}Br$, DMPU, THF, 50 °C, 20 h then Amberlyst H 15, MeOH, 40 °C, 3 h; (ii) $LiAlH_4$, THF, rt, 20 h; (iii) $Ti(O^iPr)_4$, (−)-DET, ^{t}BuOOH (3.43 M in PhMe), 4 Å MS, CH_2Cl_2, −20 °C, 21 h then recrystallisation (Et_2O); (iv) IBX, DMSO, rt, 3 h; (v) Bn_2NH, $NaBH(OAc)_3$, DCE, rt, 3 h; (vi) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, 0 °C, 5 min; (vii) PPh_3, CCl_4, Et_3N, MeCN, reflux, 18 h; (viii) KOAc, DMF, 100 °C, 24 h then K_2CO_3, MeOH, rt, 2.5 h; (ix) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 5.5 h.

The relative *syn*-configuration within **394** was unambiguously established by single crystal X-ray diffraction analysis (Figure 48).[24]

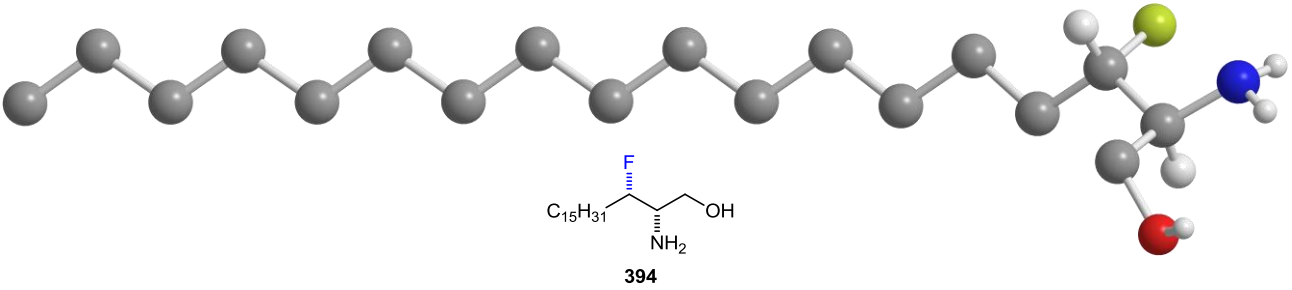


Figure 48. Chem3D representation of the single crystal X-ray diffraction structure of **394** (selected H atoms omitted for clarity).

4.3. Conclusion

In conclusion, a highly regioselective and stereospecific S_N2-type ring-opening fluorination of 2,3- and 3,4-epoxy amines using HBF_4•OEt_2 as a nucleophilic fluorine source has been developed. The reactions are both operationally simple to perform and readily scalable, and proceed to completion within 5 min at ambient temperature, providing a highly practical and economical route to stereodefined amino fluorohydrins. To highlight the synthetic utility of this reaction in the preparation of β-fluoro amines, a concise asymmetric synthesis of (*S*,*S*)-3-deoxy-3-fluorosafingol **394** has been performed.[62]

4.4. References and Notes

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[22] As discussed in chapter 5, an isolated example of amino fluorohydrin formation has previously been observed upon treatment of 3-(*N*-methyl-*N*-phenylamino)cyclohex-1-ene with HBF_4 (54% w/v in Et_2O, 3 equiv) and *m*-CPBA in CH_2Cl_2; see: Hewings, D. *Part II Thesis*, University of Oxford, **2009**.
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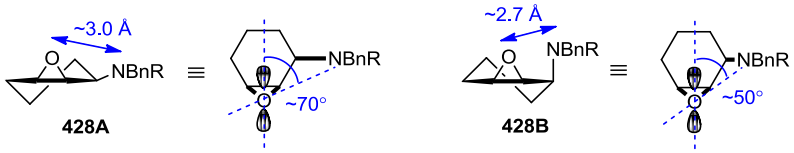
[24] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.
[25] On the basis that the pK_a of protonated Et_2O in acetonitrile is equal to 0.1 (see: Izutzu, K. *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*; Blackwell Scientific Publications: Oxford, 1990), the pK_a of HBF_4•OEt_2 in acetonitrile has been estimated as 0.1; see: Hu, X.; Brunschwig, B. S.; Peters, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 8988. Although there is no consensus on the pK_a of aqueous HBF_4, measurements indicate that 72.9% aqueous HBF_4 is slightly more acidic than 100% H_2SO_4, and is thus classified as a "superacid"; see: Fărcaşiu, D.; Hâncu, D. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2161.
[26] Intramolecular hydrogen bonding activation of the oxirane by the ammonium moiety was considered unlikely on geometrical grounds. Analysis of molecular models showed that, for a half-chair conformation **428A** with a psuedoequatorial NBnR group, the N−O distance is ~3.0 Å and the N−O−lp angle is ~70 ° (where "lp" denotes the endocyclic oxirane lone pair), although placement of the NBnR group in a psuedoaxial position in conformation **428B** may shorten the N−O distance to ~2.7 Å and reduce the N−O−lp angle to ~50 °. Although N−O distances for N--H--O hydrogen bonds in the range 2.4-3.2 Å are typical, it has been suggested that the optimum N−O−lp angle for hydrogen bonding to an oxirane is as close to 0 ° as possible; see: Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018.



[27] With only 1 equiv of HBF_4•OEt_2, a trace of BF_3 (produced from ring-opening by fluoride transfer from a slight excess of HBF_4•OEt_2) may serve to catalyse the ring-opening of the oxirane with the BF_4^- counteranion to give an *O*-trifluoroborate derivative of the amino fluorohydrin, which may be hydrolysed on work up. Alkoxytrifluoroborates are known to be labile with respect to alkaline hydrolysis; see: Plakhotnik, V. N.; Parkhomenko, N. G.; Karchenko, L. V.; Rossikhin, V. V.; Vaiman, G. E.; Panichkina, V. A. *Theor. Exp. Chem.* **1989**, *25*, 111.
[28] See: Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. For other related examples see: Wolinsky, J.; Thorstenson, J. H.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 875; Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.
[29] $AgBF_4$ proved to be completely insoluble in CH_2Cl_2.
[30] Addition of 1 equiv of *N*,*N*-dibenzyl-*N*-cyclohexylammonium tetrafluoroborate to the solution of **340** resulted in no reaction, implying that ring-opening is unlikely to be assisted by another ammonium species.
[31] It has been suggested that electrophiles adjacent to a cationic ammonium group exhibit greatly enhanced reactivities; see: Klumpp, D. A. In *Recent Developments in Carbocation and Onium Ion Chemistry*; Laali, K., Ed.; ACS Symposium Series 395; American Chemical Society: Washington, DC, 2007; pp 144; Raja, E. K.; Klumpp, D. A. *Tetrahedron* **2011**, *67*, 4494. However, the fact that fluoride transfer from the BF_4^- ion to simple iodiranium ions can occur efficiently (see: ref. 19) suggests that the presence of a neighbouring cationic group is not a prerequisite for efficient fluoride transfer from the BF_4^- ion.
[32] Extremely broad resonances in the crude ^{1}H NMR spectrum were indicative of polymeric material.
[33] For a representative example see: Malhotra, S. L.; Blanchard, L. P. *J. Macromol. Sci. Chem.* **1978**, *A12*, 1379.
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[35] Shahak, I.; Manor, S.; Bergmann, E. D. *J. Chem. Soc. C* **1968**, 2129.
[36] For selected examples of this phenomenon see: Drucker, A.; Morawetz, H. *J. Am. Chem. Soc.* **1956**, *78*, 346; Bovey, F. A. *J. Polym. Sci. Pol. Chem.* **1963**, *1*, 843; Ponratnam, S.; Kapur, S. L. *Macromol. Chem.* **1977**, *178*, 1029; Hamid, S. M.; Sherrington, D. C. *Polymer* **1987**, *28*, 332; Huang, P. C.; Reichert, K.-H. *Die Angew. Makromol. Chem.* **1988**, *162*, 19; van de Grampel, H. T.; Tan, Y. Y.; Challa, G. *Macromolecules* **1990**, *23*, 5209; Baldy, C. J.; Morrison, D. L.; Elliot, C. M. *Langmuir*, **1991**, *7*, 2376; Anseth, K. S.; Scott, R. A.; Peppas, N. A. *Macromolecules* **1996**, *29*, 8308.
[37] The strong inductive-withdrawal effect of the ammonium group may also serve to decrease the nucleophilicity of the oxirane lone pairs and further contribute to a rate decrease for polymerisation.
[38] For the first reported example of this rearrangement see: Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582.
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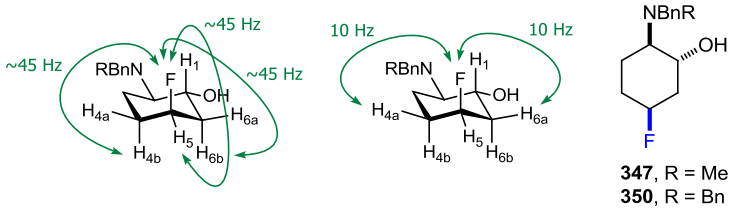
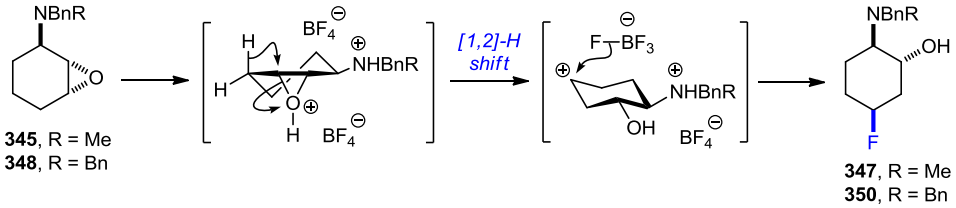
[40] The multiplicities of the fluorine resonances in the ^{19}F NMR spectra of minor fluorides **347** and **350** were indicative of a CHF moiety bearing an axial fluorine atom, flanked on either side by CH_2 groups. In both cases an apparent quartet of triplets was observed with $J_{quartet}$ ~ 45 Hz and $J_{triplet}$ = 10 Hz, consistent with $^2J_{HF}$ ~ 45 Hz, $^3J_{HF,anticoplanar}$ ~ 45 Hz and $^3J_{HF,gauche}$ ~ 10 Hz (see ref. 23).



[41] The formation of minor fluorides **347** and **350** is congruent with a reaction pathway involving a [1,2]-H shift followed by a stereoselective trapping of the resultant carbocation by fluoride transfer from a BF_4^- ion. The absence of this side reaction with 2,3-*syn*-configured epoxy amines **331** and **333** may be due to a more favourable orbital alignment for [1,2]-H migration with 2,3-*anti* epoxy amines **345** and **348**.



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[43] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 733896 (see ref. 17c).

[44] The preference for cyclopentene oxide to adopt a boat conformation to minimise torsional strain is well documneted; see: Kang, P.; Choo, J.; Jeong, M.; Kwon, Y. *J. Mol. Struct.* **2000**, *519*, 75; Mastryukov, V. S.; Osina, E. L.; Vilkov, L. V.; Hilderbrandt, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 6855; Cook, R. L.; Malloy, Jr., T. B. *J. Am. Chem. Soc.* **1974**, *96*, 1703; Grostic, M. F.; Duchamp, D. J.; Chidester, C. G. *J. Org. Chem.* **1971**, *36*, 2929.

[45] 2.4% of *cis*-cycloheptane-1,4-diol has been obtained as a by-product from the treatment of cycloheptene with peroxyformic acid; see: Cope, A. C.; Liss, T. A.; Wood, G. W. *J. Am. Chem. Soc.* **1957**, *79*, 6287.

[46] The attack of Et_2O derived from BF_3•OEt_2 on epoxides has previously been observed, and shown to occur with inversion of configuration at the oxirane carbon, consistent with an S_N2-type mechanism; see: Blunt, J. W.; Coxon, J. M.; Lim, C.-E.; Schuyt, H. A. *Aust. J. Chem.* **1983**, *36*, 97.

[47] The origin of the differential reactivity between *vic*-disubstituted epoxides **363** and **365** and terminal epoxides **357** and **361** is not clear, but it may be that the development of partial carbocationic character at the oxirane carbon distal to the amine moiety is necessary for efficient nucleophilic attack by fluoride transfer from the BF_4^- ion. The absence of tetrahydroisoquinoline products from epoxides **363** and **365** is possibly a consequence of destabilising steric interactions with the C(3)-alkyl groups in the transition states for intramolecular aromatic electrophilic substitution.

[48] For the formation of 1,4-dioxane during the attempted ring-opening fluorination of ethylene oxide see: Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Moroni, A. *J. Chem. Soc. Perkin Trans. 2* **1981**, 1336.

[49] The high regioselectivity apparent in the ring-opening fluorination of epoxides **382** and **384** (considering the presumably diminished inductive withdrawal effect of the ammonium moiety) may be a consequence of intramolecular hydrogen-bonding of the oxirane to the ammonium group, by direct analogy to the proposal by Crotti *et al.* of metal ion chelation in the nucleophilic ring-openings of 3,4-epoxy alcohols; see: Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601.

[50] Inverse addition experiments involving the dropwise addition of a solution of epoxide to a solution of HBF_4•OEt_2 in CH_2Cl_2 at ambient temperature gave no change in the ^1H NMR spectrum of the crude product mixture.

[51] The *p*-nitrobenzoates of **382** and **384** were both oils, preventing the obtainment of single-crystal X-ray structures of these derivatives.

[52] For a review on the rearrangement of β-amino alcohols *via* aziridinium ions see: Metro, T. X.; Duthion, B.; Pardo, D. G.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89.

[53] See: Kumar, P.; Dubey, A.; Puranik, V. G. *Org. Biomol. Chem.* **2010**, *8*, 5074 and references cited therein.

[54] Schwartz, G. K.; Ward, D.; Saltz, L.; Casper, E. S.; Spiess, T.; Mullen, E.; Woodworth, J.; Venuti, R.; Zervos, P.; Starniolo, A. M.; Kelsen, D. P. *Clin. Cancer Res.* **1997**, *3*, 537.

[55] Dickson, M. A.; Carvajal, R. D.; Merrill, Jr, A. H.; Gonen, M.; Cane, L. M.; Schwartz, G. K. *Clin. Cancer. Res.* **2011**, *17*, 2484

[56] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1985**, *63*, 66; Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

[57] The enantiomeric purity was determined by conversion to the corresponding Mosher's ester. For the original publication of this method by Mosher and co-workers see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[58] For a recent review on the utility of IBX as an oxidant in organic synthesis see: Duschek, A.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1524.

[59] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. For a review on the use of $NaBH(OAc)_3$ in the reductive amination of aldehydes and ketones see: Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971.

[60] Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801.

[61] Sivaprakasham, M.; Couty, F.; Evano, G.; Srinivas, B.; Sridhar, R.; Rao, K. R. *ARKIVOC* **2007**, 71.
[62] Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2011**, *76*, 4617.

Chapter 5: Hydroxyfluorination of Allylic Amines with HBF_4•OEt_2 and *m*-CPBA

This chapter describes investigations into the development of a protocol for the ammonium-directed hydroxyfluorination of allylic amines to give the corresponding amino fluorohydrins, using *m*-CPBA as the oxidant and HBF_4•OEt_2 in a dual role as both a Brønsted acid *N*-protecting agent and nucleophilic fluorine source (Figure 49).

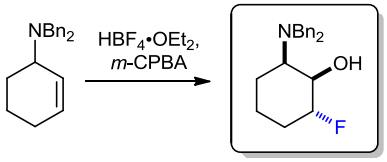
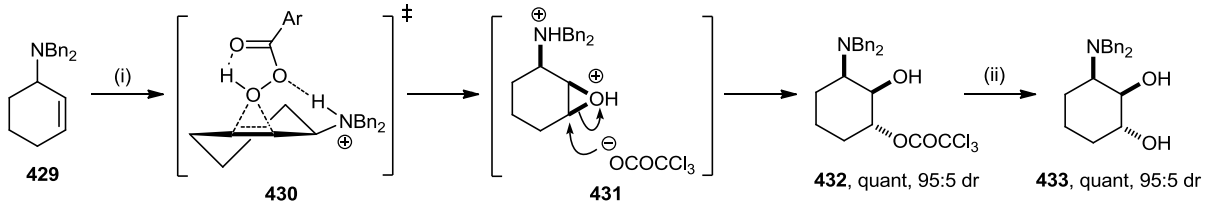


Figure 49. Hydroxyfluorination of allylic amines with HBF_4•OEt_2 and *m*-CPBA.

5.1. Introduction

5.1.1. Ammonium-Directed Hydroxyfluorination of Allylic Amines: Existing Precedent

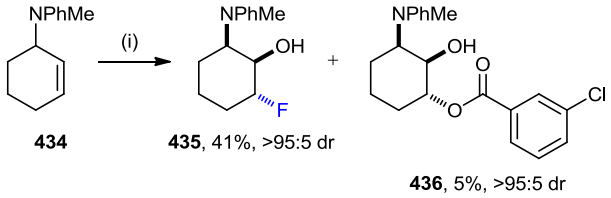
As part of an ongoing research programme concerning the olefinic oxidation of alkenyl amines,[1] Davies and co-workers have reported a highly diastereoselective, ammonium-directed dihydroxylation of allylic amines using *m*-CPBA as the oxidant in the presence of Cl_3CCO_2H as a strong Brønsted acid.[1a] For example, the sequential treatment of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **429** with 5 equiv of Cl_3CCO_2H followed by 1.6 equiv of *m*-CPBA in CH_2Cl_2 gave trichloroacetate ester **432** in quantitative yield and 95:5 dr. Subsequent transesterification on treatment with K_2CO_3 in MeOH gave amino diol **433** in quantitative yield and 95:5 dr.[1a] A mechanism was established in which initial *N*-protonation of the amine (which prevents competing *N*-oxidation) was followed by a hydrogen bond-directed epoxidation[2] of the olefin on the face *syn* to the ammonium group, giving intermediate *syn*-epoxide **431**. Subsequent regioselective S_N2-type ring-opening with the $Cl_3CCO_2^-$ counteranion (at the carbon atom distal from the electron-withdrawing ammonium group) then gave trichloroacetate ester **432** (Scheme 97).



Scheme 97. *Reagents and conditions:* (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2 then *m*-CPBA (1.6 equiv), rt, 21 h; (ii) K_2CO_3, MeOH, rt, 16 h. Ar = *m*-ClC_6H_4.

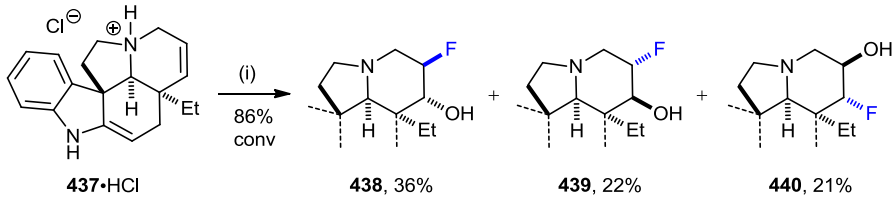
In subsequent studies by Davies *et al.*, the ammonium-directed oxidation of 3-(*N*-methyl-*N*-phenylamino)cyclohex-1-ene **434** with *m*-CPBA was attempted using HBF_4 (54% w/v in Et_2O, 3 equiv)[3] as the Brønsted acid *N*-protecting agent, in the hope that nucleophilic ring-opening of the epoxide intermediate could be averted. Surprisingly, however, amino fluorohydrin **435** was obtained as the major product in 41%

yield and >95:5 dr, in addition to *m*-CBA ester **436** in 5% yield and >95:5 dr (Scheme 98).[4] The relative configuration within **435** was tentatively assigned on the basis of ^{1}H NMR ^3J coupling constant analysis.



Scheme 98. *Reagents and conditions:* (i) HBF_4 (54% w/v in Et_2O, 3 equiv), *m*-CPBA (76% with H_2O, 1.6 equiv), CH_2Cl_2, rt, 15 min.

In a similar type of transformation, Berrier and co-workers have reported the serendipitous olefinic hydroxyfluorination of the *aspidosperma* alkaloid tabersonine **437** on treatment with 80% H_2O_2 in HF/SbF_5 to give amino fluorohydrins **438**-**440**, albeit with poor regio- and diastereoselectivity (Scheme 99).[5]



Scheme 99. *Reagents and conditions:* (i) 80% H_2O_2, HF/SbF_5, −35 °C, 1 h.

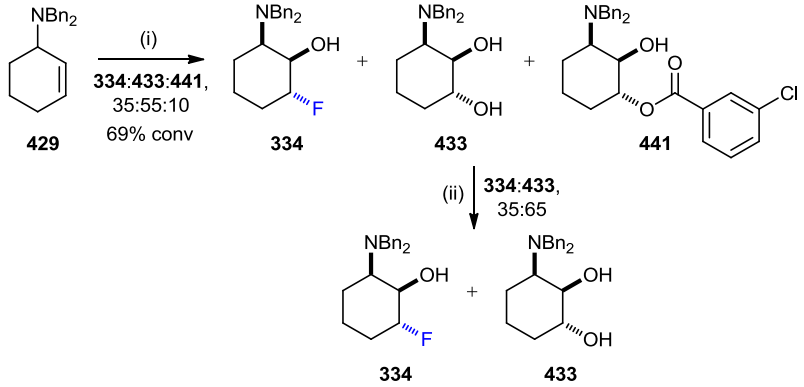
Other than these two examples, however, the only other reports of the hydroxyfluorination of olefins using *nucleophilic* fluorine sources have involved the reaction of simple polyhalogenated olefins with oxygen-transfer reagents in anhydrous HF.[6,7] Considering the substantial improvement in step-economy that would result from the direct conversion of allylic amines into amino fluorohydrins (without the need for independent preparation of 2,3-epoxy amines), the scope of ammonium-directed hydroxyfluorination of allylic amines using *m*-CPBA and HBF_4•OEt_2 was investigated further.

5.2. Results and Discussion

5.2.1. Initial Studies on the Hydroxyfluorination of 3-(*N*,*N*-Dibenzylamino)cyclohex-1-ene

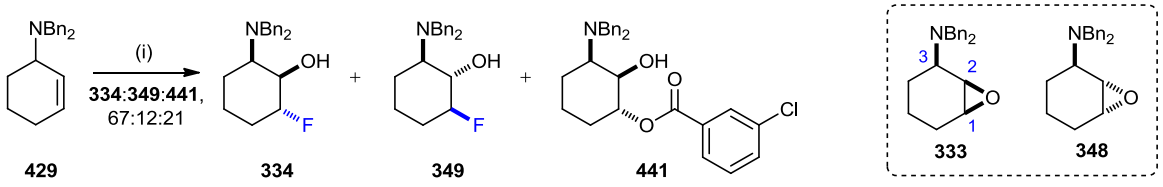
3-(*N*,*N*-Dibenzylamino)cyclohex-1-ene **429** was selected as a model substrate for initial investigations of the ammonium-directed hydroxyfluorination using *m*-CPBA and HBF_4•OEt_2. As the water present in commercially available *m*-CPBA (70-77% with H_2O) could promote the undesired formation of amino diol **433**, a solution of (titrated) *m*-CPBA in CH_2Cl_2 was pre-dried over $MgSO_4$ immediately prior to use – a convenient procedure (that was also used for all other hydroxyfluorination reactions performed in this chapter) which obviates the hazards associated with drying solid *m*-CPBA. Reaction conditions involving equimolar quantities of allylic amine **429**, HBF_4•OEt_2 and *m*-CPBA were initially elected, in order to provide a reference point for subsequent optimisation studies. Thus, a solution of allylic amine **429** in CH_2Cl_2 was treated sequentially with HBF_4•OEt_2 (1 equiv) and a pre-dried 0.5 M solution of *m*-CPBA (1 equiv) in CH_2Cl_2, such that the final concentration wrt **429** was 0.1 M. After stirring at rt for 18 h, the reaction mixture

was treated sequentially with satd aq Na_2SO_3 and satd aq $NaHCO_3$ (this work up was used for all other hydroxyfluorination reactions performed in this chapter). ^{1}H NMR spectroscopic analysis showed that the reaction had proceeded to 69% conversion to give a 35:55:10 mixture of amino fluorohydrin **334** (see chapter 4), amino diol **433** and *m*-CBA ester **441**, respectively. The relative configuration within *m*-CBA ester **441** was established unambiguously through transesterification with K_2CO_3 in MeOH, which resulted in conversion to amino diol **433** of known configuration[1a] (Scheme 100).



Scheme 100. *Reagents and conditions:* (i) HBF_4•OEt_2 (1 equiv), CH_2Cl_2 then *m*-CPBA (1 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

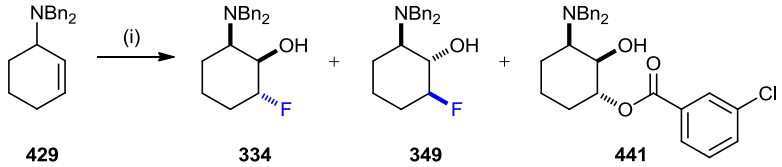
In an effort to improve the reaction conversion, the amount of *m*-CPBA was increased to 2 equiv, and the quantity of HBF_4•OEt_2 was similarly elevated to 2 equiv in a bid to increase the ratio of amino fluorohydrin **334** to amino diol **433**. Under these conditions, the reaction reached completion after 18 h (unoptimised) to give a 67:12:21 mixture of amino fluorohydrins **334** and **349**, and *m*-CBA ester **441**, respectively. Presumably, amino fluorohydrin **334** and *m*-CBA ester **441** arise from ring-opening of the (protonated) intermediate 2,3-*syn*-epoxide **333** at C(1) by fluoride transfer from a BF_4^- ion and by attack of *m*-CBA respectively, whilst amino fluorohydrin **349** (see chapter 4) arises from ring-opening of (protonated) intermediate 2,3-*anti*-epoxide **348** at C(1) by fluoride transfer from a BF_4^- ion (Scheme 101).



Scheme 101. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h.

This product distribution implies that the ratio of epoxide intermediates 2,3-*syn*-**333** to 2,3-*anti*-**348** produced was 88:12, as compared to 95:5 when the oxidation reaction is conducted under analogous conditions employing Cl_3CCO_2H (5 equiv) or TsOH (3 equiv) as the Brønsted acid *N*-protecting agent.[1a,b] To obtain further insight into this apparent erosion of diastereofacial selectivity, epoxidation of allylic amine **429** with *m*-CPBA in the presence of varying amounts of HBF_4•OEt_2 (between 1 and 40 equiv) was investigated. The quantity of CH_2Cl_2 solvent was adjusted accordingly to account for the volume of HBF_4•OEt_2 in each case,

ensuring a final concentration of 0.1 M (wrt **429**) across all experiments (Scheme 102). In these studies, the use of fewer than 2 equiv of HBF_4•OEt_2 (i.e. 1 or 1.5 equiv) led to complex mixtures of products, presumably as a consequence of insufficient protection of the amino group against competing *N*-oxidation. Between 2 and 20 equiv, the amount of amino fluorohydrin **349** produced in the reaction increased with increasing equivalents of HBF_4•OEt_2, until a plateau was reached beyond 30 equiv, when the ratio of amino fluorohydrins **334**:**349** was 10:90. Intriguingly, when the reaction conversion was monitored by ^{1}H NMR spectroscopic analysis, complete consumption of starting material occurred after 2 h when using 20 equiv of HBF_4•OEt_2, whilst even after 7 h using 2 equiv, starting material remained. This observation is congruent with the known rate acceleration of epoxidation of isolated alkenes by peracids in the presence of strong Brønsted acids, which has been attributed to protonation of the peracid to generate a more electrophilic, and hence more reactive, oxidising agent.[8]



429 **334** **349** **441**

HBF_4•OEt_2 Equiv	**334:349:441 Ratio**
1	complex mixture
1.5	complex mixture
2	67:12:21
5	43:48:9
10	26:70:4
20	16:84:0
30	10:90:0
40	10:90:0

Scheme 102. *Reagents and conditions:* (i) HBF_4•OEt_2, CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h.

The product distributions of these reactions presumably reflect the relative rate of epoxidation on the face of the olefin *syn* to the amino group (leading to **334**) over that on the face of the olefin *anti* to the amino group (leading to **349**). When using 2 equiv of HBF_4•OEt_2, epoxidation of **429** on the face of the olefin *syn* to the amino group is favoured, presumably as a result of hydrogen bonding of the peracid to the *in situ* formed ammonium ion.[2] However, increasing the amount of HBF_4•OEt_2 to 20 equiv promotes protonation of the *m*-CPBA by the HBF_4•OEt_2,[8] and this may serve to decrease the hydrogen bond acceptor ability of the peracid,[9] as well as introduce electrostatic repulsive interactions between the protonated peracid and the ammonium group. Consequently, a non hydrogen bond-directed epoxidation pathway on the face of the

olefin *anti* to the ammonium ion, in which unfavourable steric, electrostatic or dipole-dipole[10] repulsion effects are minimised, may predominate (Figure 50).

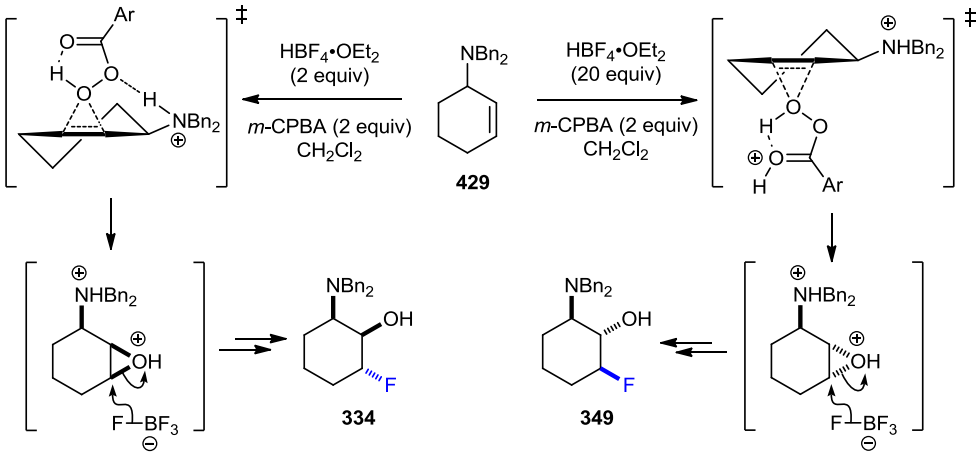
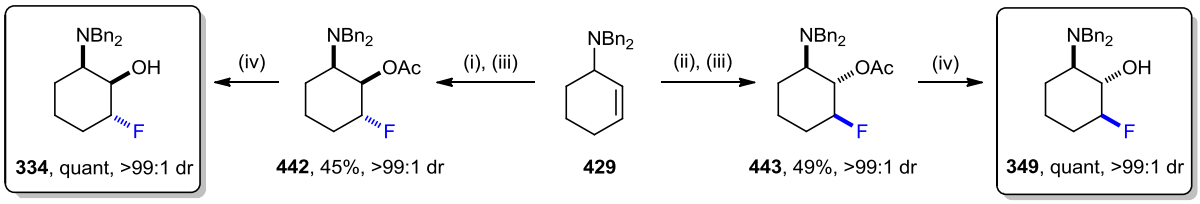


Figure 50. Mechanistic rationale for the effect of the concentration of HBF_4•OEt_2 on the diastereoselectivity of the hydroxyfluorination of **429**. Ar = *m*-ClC_6H_4. Some BF_4^- counteranions are omitted for clarity.

Unfortunately, attempted separation of the product mixtures from these hydroxyfluorination reactions *via* flash column chromatography proved unsuccessful. However, acetylation of the crude product mixtures with Ac_2O in pyridine facilitated the isolation of diastereoisomerically-pure samples of acetates **442** and **443**. Thus, hydroxyfluorination of **429** with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA, followed by acetylation of the crude product mixture, gave acetate **442** in 45% isolated yield and >99:1 dr, whilst hydroxyfluorination of **429** with 20 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA, followed by acetylation of the crude product mixture, gave acetate **443** in 49% isolated yield and >99:1 dr. The relative configurations within acetates **442** and **443** were unambiguously established *via* transesterification with K_2CO_3 in MeOH, which gave the corresponding amino fluorohydrins **334** and **349**, in quantitative yield in each case (Scheme 103).

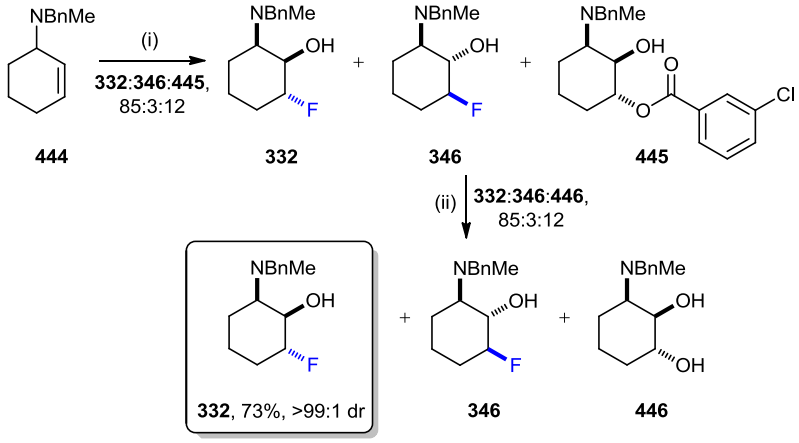


Scheme 103. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) HBF_4•OEt_2 (20 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (iii) Ac_2O, pyridine, rt, 20 h; (iv) K_2CO_3, MeOH, rt, 3 h.

5.2.2. Hydroxyfluorination of Other 6-Membered Ring Carbocyclic Allylic Amines

A variety of cyclohexene-derived allylic amines bearing different *N*-substituents were next investigated, in order to probe the generality of the hydroxyfluorination procedure and obtain further insight into the reversal of diastereofacial selectivity of epoxidation with increasing concentration of HBF_4•OEt_2. Under the optimised hydroxyfluorination conditions, treatment of 3-(*N*-benzyl-*N*-methylamino)cyclohex-1-ene **444** with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA gave an 85:3:12 mixture of amino fluorohydrins

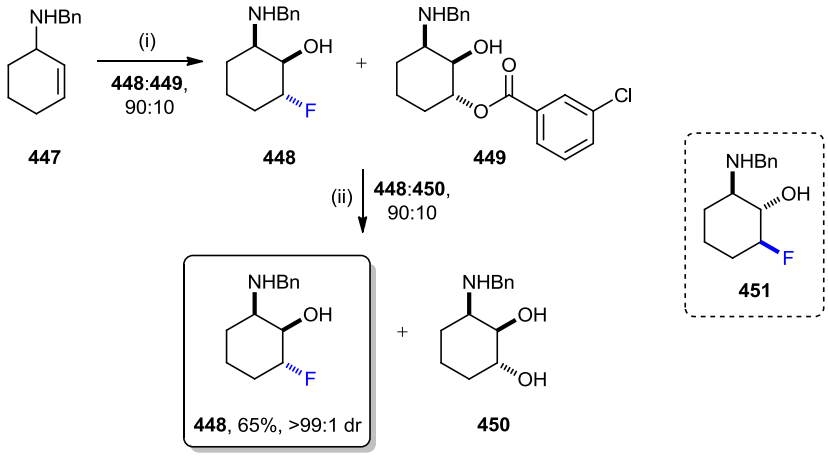
332 and **346**, and *m*-CBA ester **445**, respectively. Subjection of the mixture to K_2CO_3 in MeOH, to effect transesterification of *m*-CBA ester **445** to the corresponding known diol **446**[1i] (whilst leaving fluorohydrins **332** and **346** unaffected), enabled chromatographic separation to give amino fluorohydrin **332** in 73% yield as a single diastereoisomer (>99:1 dr). An increasing amount of the diastereoisomeric amino fluorohydrin **346** (arising from epoxidation on the face of the olefin *anti* to the ammonium group) was observed as the concentration of HBF_4•OEt_2 employed in the reaction was increased, although the extent of switchover of diastereoselectivity was less pronounced than for *N*,*N*-dibenzyl allylic amine **429** (Scheme 104).



HBF_4•OEt_2 Equiv	332:346:445 Ratio
2	85:3:12
5	68:25:7
10	46:50:4
20	35:63:2

Scheme 104. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

Under analogous conditions, hydroxyfluorination of 3-(*N*-benzylamino)cyclohex-1-ene **447** with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA gave an 89:11 mixture of amino fluorohydrin **448** and *m*-CBA ester **449**. Subsequent treatment with K_2CO_3 in MeOH to effect transesterification of *m*-CBA ester **449** to the corresponding known diol **450**,[1a] followed by chromatography, gave amino fluorohydrin **448** in 65% yield as a single diastereoisomer. Although erosion of the diastereoselectivity was noted on increasing the concentration of HBF_4•OEt_2, the effect was far less pronounced than for allylic amines **429** and **444**, and amino fluorohydrin **448** remained the major product even when 20 equiv of HBF_4•OEt_2 was employed (Scheme 105). The relative configuration within **448** was unambiguously established *via* single crystal X-ray diffraction analysis (Figure 51),[11] and the relative configuration within **451** was tentatively assigned by analogy to **349** and **346** (*vide supra*).[12]



HBF_4•OEt_2 Equiv	448:451:449 Ratio
2	89:0:11
5	86:5:9
10	82:11:7
20	77:17:6

Scheme 105. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

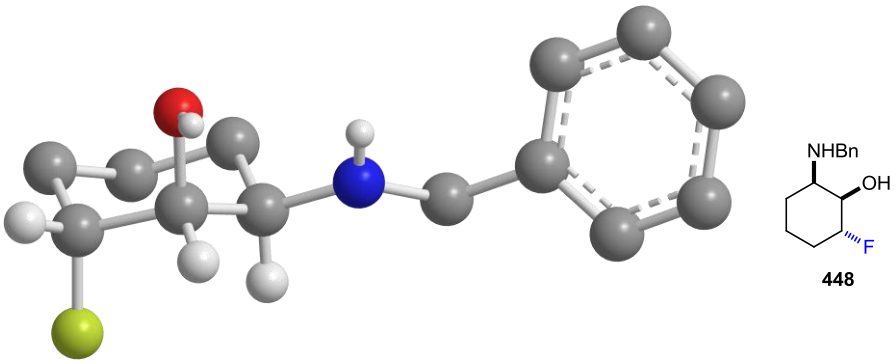
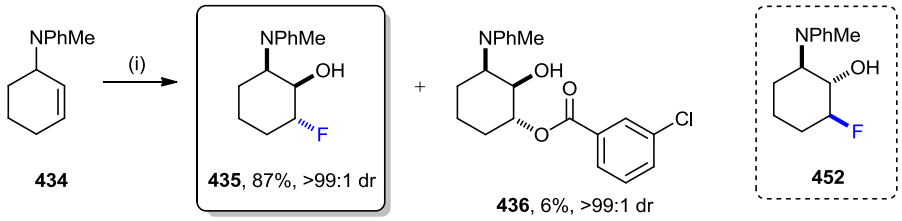


Figure 51. Chem3D representation of the single crystal X-ray diffraction structure of **448** (selected H atoms omitted for clarity).

For the hydroxyfluorination of 3-(*N*-methyl-*N*-phenylamino)cyclohex-1-ene **434**, a reaction time of 5 min proved sufficient for complete conversion, in accordance with the fact that the rate of epoxidation of the *N*-protio ammonium salt of **434** with *m*-CPBA is known to be extremely rapid.[4] Under these conditions, hydroxyfluorination of **434** upon treatment with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA gave a 93:7 mixture of amino fluorohydrin **435** to *m*-CBA ester **436**[4], with chromatographic purification providing **435** in 87% yield and **436** in 6% yield, both as single diastereoisomers. As with *N*-benzyl-substituted allylic amine **447**, an erosion in diastereoselectivity was observed upon increasing the concentration of HBF_4•OEt_2, although the effect was even less pronounced in this case (Scheme 106). The relative configuration within amino fluorohydrin **435** was unambiguously established *via* single crystal X-ray diffraction analysis (Figure 52).[11] The relative configuration within the diastereoisomeric amino fluorohydrin **452** was assigned on the basis of ^{1}H-^{1}H and ^{1}H-^{19}F NMR coupling constant analyses (assuming a chair conformation with the NPhMe group in an equatorial position). The multiplicity of the fluorine resonance in the ^{19}F NMR spectrum of **452** was indicative of an equatorial fluorine atom: a broad doublet was observed with J = 50.1 Hz, consistent with $^2J_{HF}$ ~ 50 Hz and the lack of resolution of $^3J_{HF,gauche}$ couplings on account of their much smaller magnitude (Figure 53).[13]



HBF_4•OEt_2 Equiv	435:452:436 Ratio
2	93:0:7
5	93:0:7
10	92:4:4
20	87:9:4

Scheme 106. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 5 min.

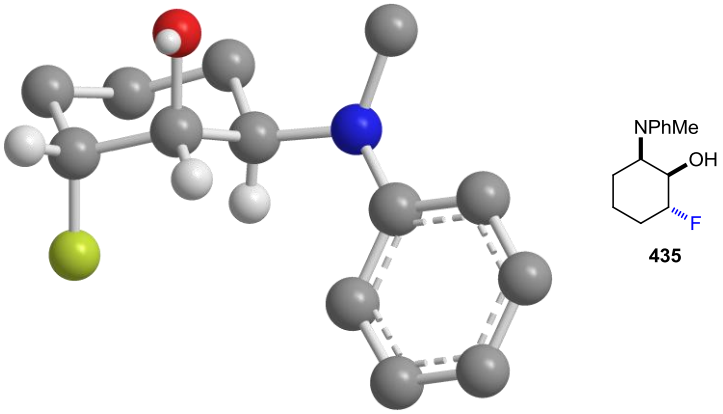


Figure 52. Chem3D representation of the single crystal X-ray diffraction structure of **435** (selected H atoms omitted for clarity).

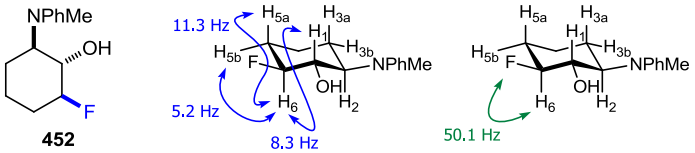
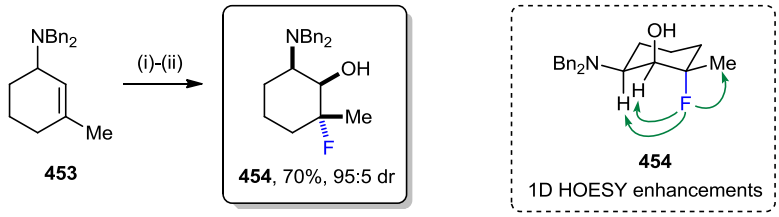


Figure 53. ^{1}H-^{1}H (**blue**) and ^{1}H-^{19}F (**green**) NMR coupling constants within **452**.

It is noteworthy that the rates of ammonium-directed olefinic oxidation of allylic amines **429**, **444**, **447** and **434** have previously been shown to increase in the order **429** (NBn_2) < **444** (NBnMe) < **447** (NHBn) < **434** (NPhMe).[1i,4] Presumably, the increased ability of the *in situ* formed ammonium ions derived from allylic amines **447** (NHBn) and **434** (NPhMe) to promote rapid hydrogen bond-directed epoxidation (leading to amino fluorohydrins **448** and **435**, respectively) means that, even at high concentrations of HBF_4•OEt_2, the non hydrogen bond-directed reaction (leading to amino fluorohydrins **451** and **452**, respectively) is not able to outpace it.[14]

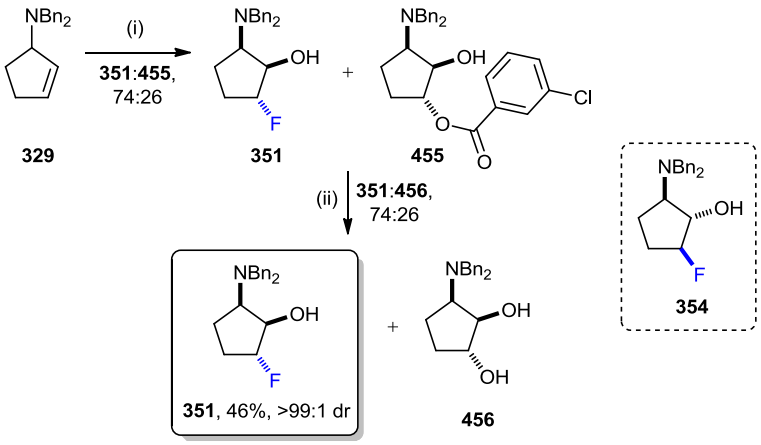
The effect of introducing a substituent at the C(1) position of the carbocyclic scaffold was also briefly investigated. Thus, hydroxyfluorination of 3-(*N*,*N*-dibenzylamino)-1-methylcyclohex-1-ene **453** with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA gave amino fluorohydrin **454** in 95:5 dr, and treatment with K_2CO_3 in MeOH (to transesterify any *m*-CBA ester by-product to the more easily separated diol) followed by chromatographic purification gave **454** in 70% yield and 95:5 dr. The relative configuration within **454** was assigned on the basis of ^{1}H-^{1}H and ^{1}H-^{19}F NMR ^3J coupling constant and ^{1}H-^{19}F NMR HOESY analyses (Scheme 107). When compared to allylic amine **429** [which lacks a C(1)-methyl group], the origin of the higher diastereoselectivity in the hydroxyfluorination of **453** (95:5 dr for **453** *versus* 88:12 dr for **429**) is unclear.



Scheme 107. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

5.2.3. Hydroxyfluorination of 5- and 7-Membered Ring Carbocyclic Allylic Amines

The effect of ring size on the hydroxyfluorination of carbocyclic allylic amines was next assessed. Thus, hydroxyfluorination of the 5-membered ring substrate 3-(*N*,*N*-dibenzylamino)cyclopent-1-ene **329** upon treatment with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA proceeded to give a 74:26 mixture of amino fluorohydrin **351** and *m*-CBA ester **455**. Subjection to K_2CO_3 in MeOH to effect transesterification of **455** to the corresponding known diol **456**[1c] (whilst leaving amino fluorohydrin **351** unaffected) enabled chromatographic separation of the mixture to give **351** in 46% yield as a single diastereoisomer. As previously observed during studies on the ammonium-directed oxidation of **329** using *m*-CPBA in the presence of Cl_3CCO_2H,[1c] the stereochemical outcome of this reaction is consistent with a hydrogen bond-directed epoxidation occurring on the face of the olefin *syn* to the *in situ* formed ammonium ion, although this mode of attack may also be inherently favoured due to minimisation of developing torsional strain in the transition state.[15] On increasing the amount of HBF_4•OEt_2 employed in the reaction, a reduction in the diastereoselectivity was observed, giving rise to increasing amounts of diastereoisomeric amino fluorohydrin **354**, although **351** remained the major product in each case (Scheme 108).

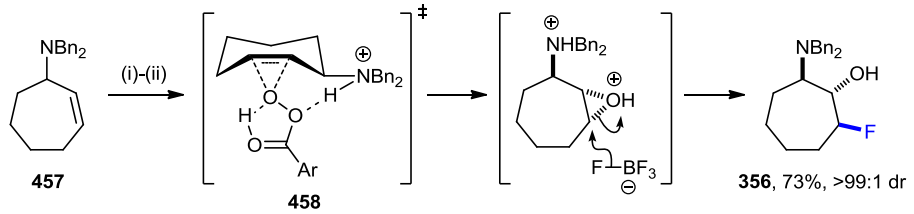


HBF_4•OEt_2 Equiv	351:354:455 Ratio
2	74:0:26
5	71:4:25
10	73:9:18
20	71:16:13

Scheme 108. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

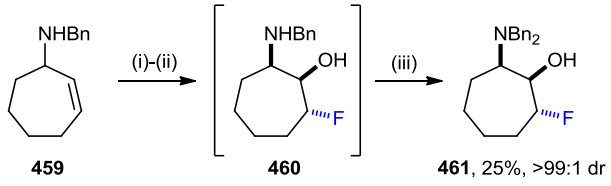
The behaviour of the 7-membered ring substrate 3-(*N*,*N*-dibenzylamino)cyclohept-1-ene **457** under the hydroxyfluorination conditions was next investigated: treatment of **457** with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA afforded a mixture of compounds containing an 80:8:8:4 ratio of amino fluorohydrin **356** and 3 unidentified fluorinated compounds (possibly arising due to transannular reactions).[16] Subjection

of the mixture to K_2CO_3 in MeOH (to transesterify any *m*-CBA ester by-product to the more easily separated diol) followed by chromatographic purification gave amino fluorohydrin **356** in 73% yield and >99:1 dr as the only product isolated (Scheme 109). A strong preference for allylic amine **457** to undergo epoxidation with *m*-CPBA on the face of the olefin *anti* to the *in situ* formed ammonium group has similarly been observed using Cl_3CCO_2H (5 equiv) as the *N*-protecting agent (96:4 dr).[1c] This diastereofacial selectivity may be ascribed to the cycloheptene ring adopting a chair conformation[17] **458** during the epoxidation step, in which the peracid, assisted by hydrogen bonding from the proximal ammonium group, attacks on the sterically most accessible face of the olefin (Scheme 109).[1c] Increasing the amount of HBF_4•OEt_2 employed in the hydroxyfluorination of **457** to 5, 10 and 20 equiv promoted the formation of unidentified by-products, although amino fluorohydrin **356** remained the major component in all cases.



Scheme 109. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h. Ar = *m*-ClC_6H_4.

An authentic sample of the diastereoisomeric amino fluorohydrin **461** was next prepared to establish whether any of this compound had been formed in the hydroxyfluorination of allylic amine **457**. Thus, the hydroxyfluorination of 3-(*N*-benzylamino)cyclohept-1-ene **459** (a substrate for which *syn*-epoxidation is preferred[1i]) proceeded efficiently with 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA to give amino fluorohydrin **460** as the major product. After treatment of the crude product mixture with K_2CO_3 in MeOH, an *N*-benzylation step was performed with BnBr and K_2CO_3 in refluxing MeCN. Unfortunately, these conditions led to partial decomposition of the fluorohydrin. Following chromatographic purification, **461** was isolated in 25% yield as a single diastereoisomer (Scheme 110). Notably, the ^1H and ^{19}F NMR spectra for **461** did not match any of the 3 minor fluorinated species obtained from the hydroxyfluorination of 3-(*N*,*N*-dibenzylamino)cyclohept-1-ene **457**, implying that the epoxidation of this compound under the hydroxyfluorination conditions proceeds with complete diastereoselectivity on the face of the olefin *anti* to the *in situ* formed ammonium group. Moreover, no trace of **461** was detected in the ^1H or ^{19}F NMR spectra of the crude product mixtures for the hydroxyfluorination of **457** using 5, 10 or 20 equiv of HBF_4•OEt_2.



Scheme 110. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h; (iii) BnBr, K_2CO_3, MeCN, reflux, 18 h.

The observation that the sense of diastereoselectivity of the hydroxyfluorination reactions of both 5-membered ring substrate **329** and 7-membered ring substrate **457** does not reverse when using 20 equiv of HBF_4•OEt_2 is consistent with the much faster rates of ammonium-directed epoxidation of both **329** and **457**, as compared to that of their 6-membered ring counterpart **429** (i.e. the hydrogen bond-directed epoxidation would be expected to be the dominant pathway for both **329** and **457**).[1i]

5.2.4. Hydroxyfluorination of Azacyclic Substrates

Fluorinated piperidine and pyrrolidine motifs are becoming increasingly widespread in medicinal chemistry.[18] Examples include Merck's h5-HT_{2A} receptor antagonist **301** for the potential treatment of schizophrenia,[18b] and Glenmark's diabetes treatment Melogliptin **462**, currently undergoing phase III clinical trials (Figure 54).[18e]

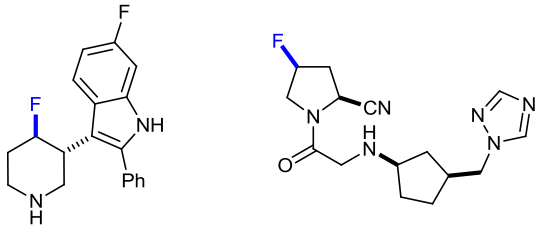
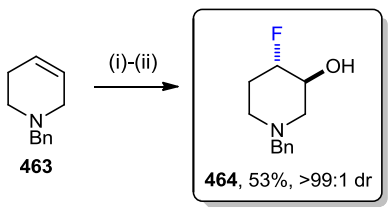


Figure 54. Bioactive compounds containing fluorinated piperidine and pyrrolidine motifs.

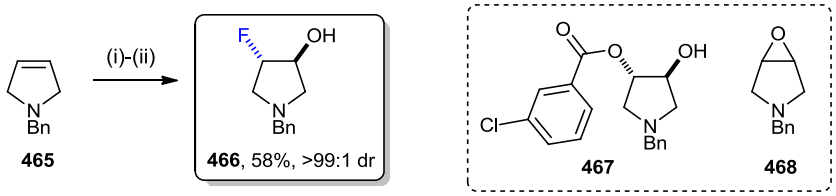
Considering the growing interest in such fluorinated azacycles, the extension of the hydroxyfluorination reaction to 1,2,3,6-tetrahydropyridine and 2,5-dihydropyrrole substrates was next investigated. Under the standard hydroxyfluorination conditions using 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA, *N*-benzyl-1,2,3,6-tetrahydropyridine **463** gave a mixture of compounds containing amino fluorohydrin **464** as the major component. Treatment of this mixture with K_2CO_3 in MeOH followed by chromatographic purification gave **464** in 53% yield as a single diastereoisomer (Scheme 111). The regiochemistry within **464** was assigned by ^{1}H-^{1}H NMR COSY analysis, and the relative *anti*-configuration was assigned on the basis of the reaction proceeding *via* an S_N2-type epoxide ring-opening step.[19]



Scheme 111. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

Subjection of *N*-benzyl-2,5-dihydropyrrole **465** to the standard hydroxyfluorination conditions using 2 equiv of HBF_4•OEt_2 and 2 equiv of *m*-CPBA gave clean conversion to epoxide **468** as the sole product. In an attempt to promote the subsequent ring-opening fluorination of epoxide **468**, the amount of HBF_4•OEt_2 employed in the oxidation reaction was increased to 5 equiv, leading to a 59:19:22 mixture of amino

fluorohydrin **466**, *m*-CBA ester **467** (tentatively assigned) and epoxide **468**, respectively. Increasing the amount of HBF_4•OEt_2 still further to 10 equiv proved beneficial, delivering an 80:17:3 mixture of **466**:**467**:**468**. Treatment of this mixture with K_2CO_3 in MeOH followed by chromatographic purification gave **466** in 58% yield as a single diastereoisomer (Scheme 112). The relative *anti*-configuration within **466** was assigned on the basis of the reaction proceeding *via* an S_N2-type epoxide ring-opening step.[20]

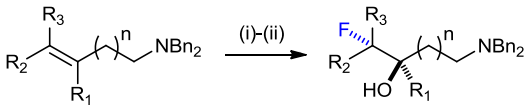


HBF_4•OEt_2 Equiv	466:467:468 Ratio
2	0:0:100
5	59:19:22
10	80:17:3

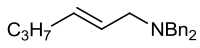
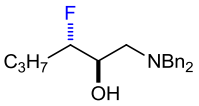
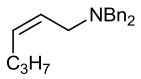
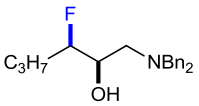
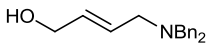
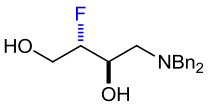
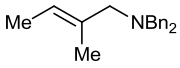
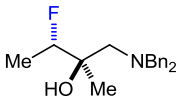
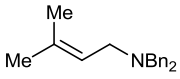
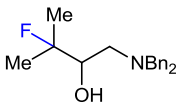
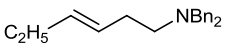
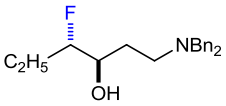
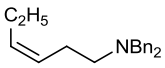
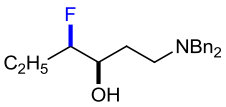
Scheme 112. *Reagents and conditions:* (i) HBF_4•OEt_2 (10 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

5.2.5. Hydroxyfluorination of Acyclic Allylic and Homoallylic Amines

The hydroxyfluorination of acyclic allylic and homoallylic amines was next investigated. Under the standard conditions using 2 equiv of HBF_4•OEt_2 (10 equiv for **471**) and 2 equiv of *m*-CPBA, alkenyl amines **469**-**475** gave the corresponding amino fluorohydrins as single diastereoisomers which, after treatment of the crude product mixture with K_2CO_3 in MeOH followed by chromatographic purification, were isolated in reasonable yield (24-57%) (Scheme 113). The relative configurations within **364** and **366** have been unambiguously established through single crystal X-ray diffraction analyses (see chapter 4), and therefore the relative configurations within the remaining amino fluorohydrin products were assigned on the basis of the reactions proceeding *via* an S_N2-type epoxide ring-opening step.



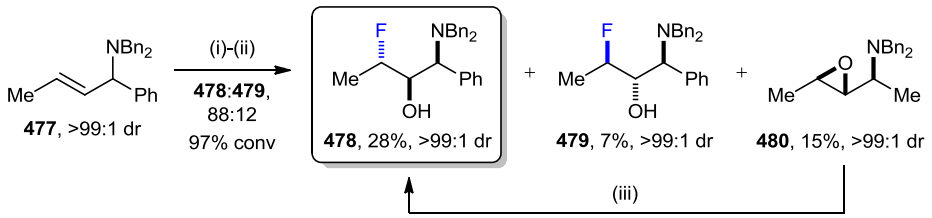
469-475, n = 0 or 1 n = 0 or 1

Alkenyl Amine	Amino Fluorohydrin Yield
 **469**, >99:1 dr	 **364**, 53%, >99:1 dr
 **470**, >99:1 dr	 **366**, 57%, >99:1 dr
 **471**, >99:1 dr	 **372**, 32%, >99:1 dr
 **472**, >99:1 dr	 **476**, 56%, >99:1 dr
 **473**	 **376**, 55%
 **474**, >99:1 dr	 **383**, 48%, >99:1 dr
 **475**, >99:1 dr	 **385**, 24%, >99:1 dr

Scheme 113. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv [10 equiv for **471**]), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

The feasibility of performing a diastereoselective, ammonium-directed hydroxyfluorination reaction with chiral acyclic allylic amines was next examined. Thus, hydroxyfluorination of (*E*)-configured allylic amine **477** upon treatment with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA proceeded to 97% conversion to give a mixture of products containing an 88:12 ratio of amino fluorohydrins **478**:**479**. After subjection of the crude product mixture to K_2CO_3 in MeOH and chromatographic purification, the major diastereoisomer **478** was isolated in 28% yield and the minor diastereoisomer **479** was isolated in 7% yield, in addition to a small amount of epoxide **480** in 15% yield (Scheme 114). The relative configuration within amino fluorohydrin **478** was unambiguously established *via* single crystal X-ray diffraction analysis (Figure 55),[11] which therefore allowed the relative configuration within **479** to be assigned (on the basis of a

stereospecific S_N2-type epoxide ring-opening step). The relative configuration within epoxide **480** was then established by chemical correlation: exposure of **480** to 2 equiv of HBF_4•OEt_2 gave **478** as the sole product (Scheme 114).



Scheme 114. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h; (iii) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 5 min.

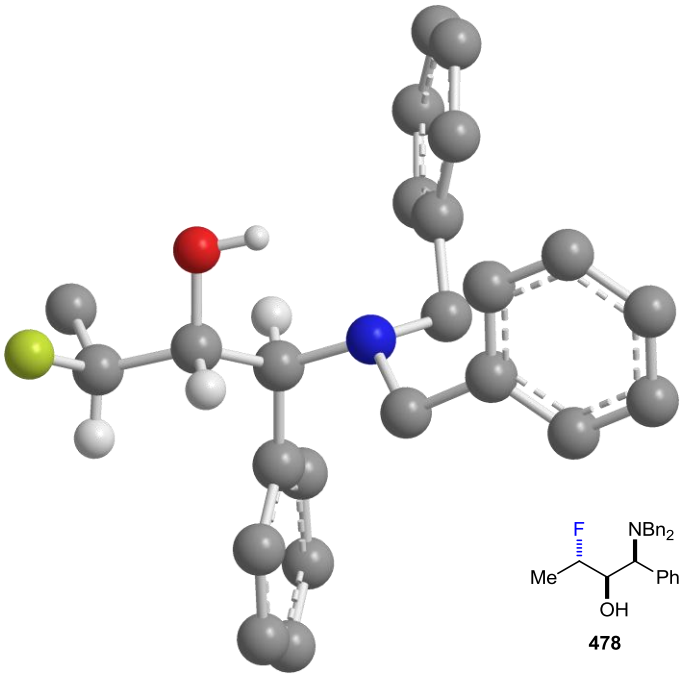
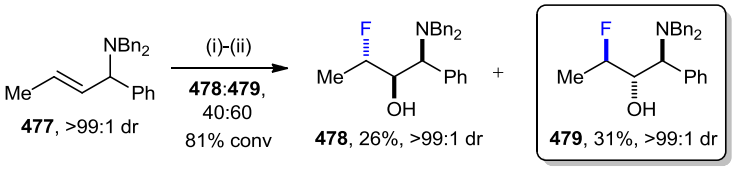


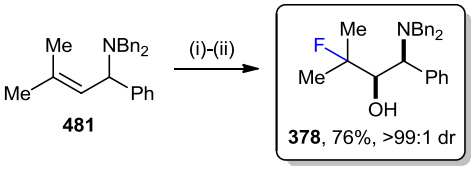
Figure 55. Chem3D representation of the single crystal X-ray diffraction structure of **478** (selected H atoms omitted for clarity).

In an effort to switchover the reaction diastereoselectivity of the hydroxyfluorination of **477**, in order to favour the formation of amino fluorohydrin **479**, the reaction was repeated under analogous conditions using 20 equiv of HBF_4•OEt_2. Under these conditions, the reaction proceeded to 81% conversion to give a mixture of products containing a 40:60 ratio of amino fluorohydrins **478**:**479**, consistent with a swap over in epoxidation diastereofacial selectivity. As before, treatment of the crude product mixture with K_2CO_3 in MeOH and subsequent chromatographic purification gave **478** in 26% yield and **479** in 31% yield, both as single diastereoisomers (Scheme 115).



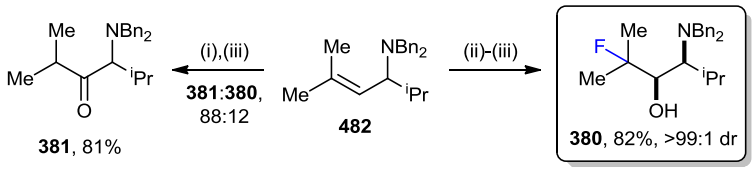
Scheme 115. *Reagents and conditions:* (i) HBF_4•OEt_2 (20 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

The effect of further olefinic substitution was next probed. In accordance with the expected higher level of 1,3-allylic strain,[21] hydroxyfluorination of allylic amine **481** upon treatment with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA gave amino fluorohydrin **378** (see chapter 4) as a single diastereoisomer. Following transesterification of any *m*-CBA ester by-product with K_2CO_3 in MeOH to the more easily separated diol, chromatographic purification of the mixture gave **378** in 76% isolated yield (Scheme 116).



Scheme 116. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h.

Under analogous conditions, hydroxyfluorination of allylic amine **482** gave an 88:12 mixture of ketone **381** and amino fluorohydrin **380** (see chapter 4), with **381** isolated in 81% yield. In an effort to suppress the formation of ketone **381**, the reaction time was reduced to 30 min, allowing for the isolation of amino fluorohydrin **380** in 82% yield as a single diastereoisomer (Scheme 117).



Scheme 117. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 30 min; (iii) K_2CO_3, MeOH, rt, 1 h.

Unfortunately, attempts to achieve a switchover in the sense of diastereoselectivity of the reaction by employing 20 equiv of HBF_4•OEt_2 in the hydroxyfluorinations of allylic amines **481** and **482** led to complex mixtures of products in both cases.

5.2.6. Application to the Diastereodivergent Synthesis of 4-Deoxy-4-fluoro Phytosphingosines

The synthetic utility of this methodology was next demonstrated by application to the synthesis of 4-deoxy-4-fluoro-L-*xylo*-phytosphingosine **484** and 4-deoxy-4-fluoro-L-*lyxo*-phytosphingosine **485**,[22] which are fluorinated analogues of the sphingoid bases L-*xylo*-phytosphingosine and L-*lyxo*-phytosphingosine, respectively.[23] Retrosynthetically, it was envisaged that **484** and **485** could be prepared *via* diastereodivergent hydroxyfluorination reactions of allylic amine **483**, readily accessible in enantiopure form from Garner's aldehyde (*R*)-**397** (Figure 56).

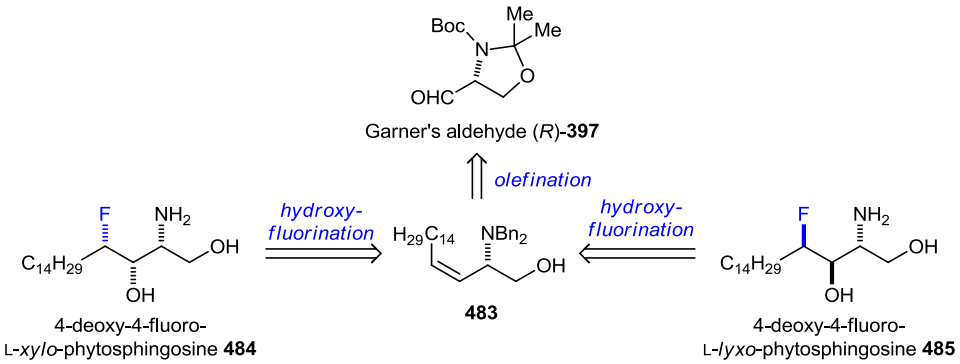
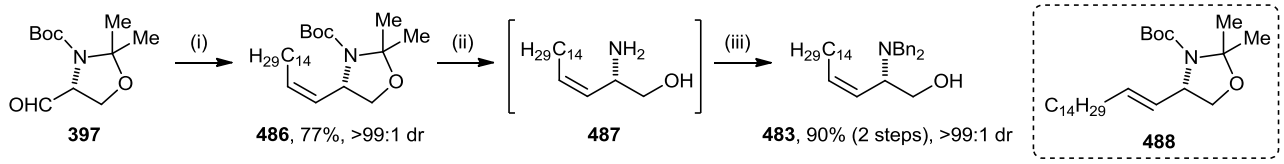


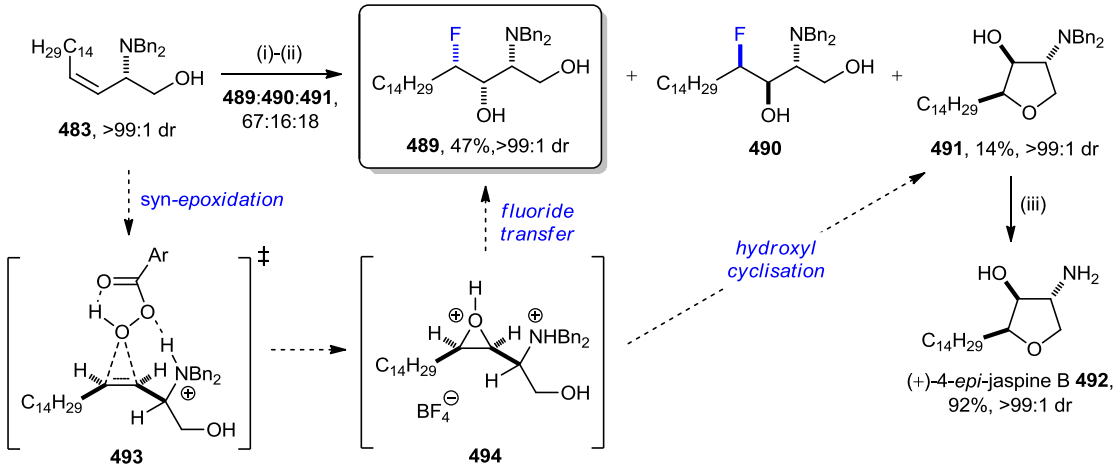
Figure 56. Retrosynthetic strategy for the syntheses of **484** and **485**.

Allylic amine **483** was prepared from commercially available Garner's aldehyde (*R*)-**397** *via* Wittig olefination of **397** upon treatment with $[C_{15}H_{31}PPh_3]^+Br^-$ and NaHMDS, which gave a mixture of olefin isomers (*Z*)-**486** and (*E*)-**488**,[24] which were separable *via* chromatography and isolated in 77 and 7% yield, respectively. Hydrolysis of the *N*,*O*-acetonide and *N*-Boc protecting groups within (*Z*)-**486** using methanolic HCl, followed by *N*,*N*-dibenzylation of **487** with BnBr and K_2CO_3, gave **483** in 90% yield (Scheme 118).



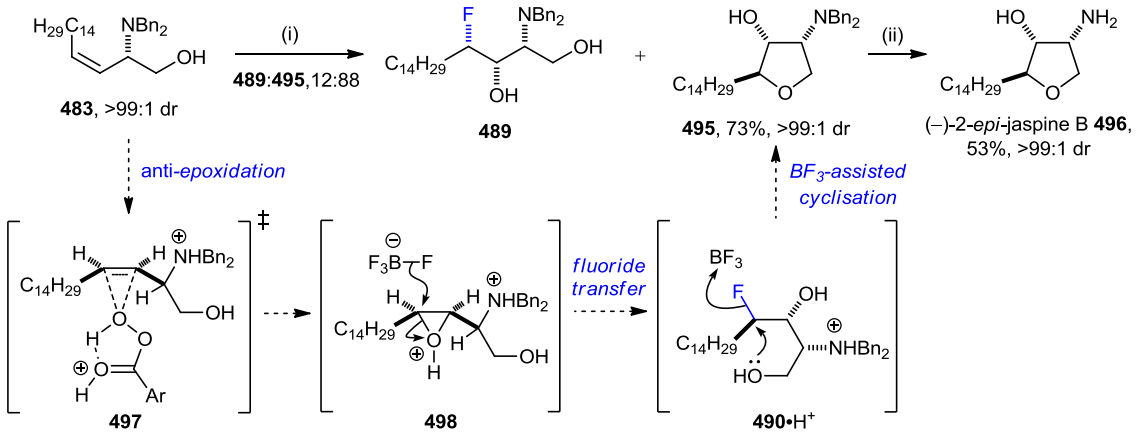
Scheme 118. *Reagents and conditions:* (i) $[C_{15}H_{31}PPh_3]^+Br^-$, NaHMDS, THF/*n*-hexane, –78 °C to rt, 42 h; (ii) conc aq HCl, MeOH, reflux, 17 h; (iii) BnBr, K_2CO_3, EtOH, reflux, 4 h.

To effect the hydroxyfluorination of **483**, this substrate was treated with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA and, after a reaction time of 18 h, gave a 67:16:18 mixture of amino fluorohydrins **489** and **490**, and functionalised tetrahydrofuran **491**, respectively. Following treatment of the crude product mixture with K_2CO_3 in MeOH and subsequent chromatographic purification, amino fluorohydrin **489** was isolated in 47% yield and tetrahydrofuran **491** was isolated in 14% yield, both as single diastereoisomers. The relative configuration within amino fluorohydrin **489** was initially assigned on the basis of an ammonium-directed epoxidation of **483** (*via* transition state model **493** in which 1,3-allylic strain[21] is minimised) to give the corresponding (protonated) epoxide **494**,[25] which undergoes *in situ* regioselective S_N2-type ring-opening by transfer of fluoride from a BF_4^- ion to the oxirane carbon atom distal to the ammonium group. The relative configuration within tetrahydrofuran **491** was unambiguously established through hydrogenolysis, which gave (+)-4-*epi*-jaspine B [(+)-4-*epi*-pachastrissamine] **492** in 92% yield.[26] A plausible mechanism for the production of **491** under the conditions of the hydroxyfluorination reaction would involve direct cyclisation of the terminal hydroxy group onto the epoxide functionality within **494**.[27] Furthermore, resubjection of amino fluorohydrin **489** to the reaction conditions led only to the recovery of starting material, indicating that tetrahydrofuran **491** does not arise from the *in situ* cyclisation of **489** (Scheme 119).



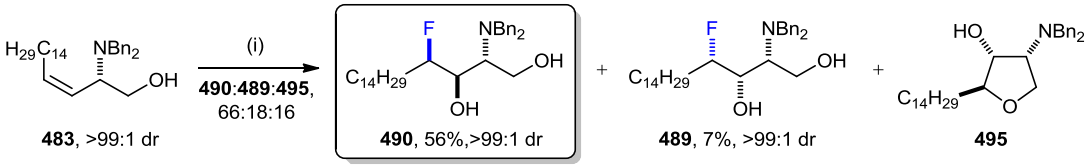
Scheme 119. *Reagents and conditions:* (i) HBF_4•OEt_2 (2 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) K_2CO_3, MeOH, rt, 1 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, EtOAc, rt, 4.5 h. Ar = *m*-ClC_6H_4. Some BF_4^- counteranions are omitted for clarity.

In an effort to switchover the reaction diastereoselectivity to favour the production of amino fluorohydrin **490**, allylic amine **483** was next subjected to 20 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA, which gave, after a reaction time of 18 h, a 12:88 mixture of amino fluorohydrin **489** (undesired in this case) to a different functionalised tetrahydrofuran **495**. Following chromatographic purification, **495** was isolated in 73% yield as a single diastereoisomer. The relative configuration within **495** was unambiguously established through hydrogenolysis, which gave (–)-2-*epi*-jaspine B [(–)-2-*epi*-pachasstrissamine][26] **496** in 53% yield. A mechanism accounting for the relative configuration within **495** would involve an epoxidation of **483** proceeding preferentially *via* transition state model **497**, in which 1,3-allylic strain[21] is minimised and protonated *m*-CPBA[28] attacks the face of the olefin *anti* to the ammonium group, giving intermediate epoxide **498** as the major product. Subsequent *in situ* regioselective and stereospecific S_N2-type ring-opening of **498** by transfer of fluoride from a BF_4^- ion to the oxirane carbon atom distal to the ammonium moiety would give amino fluorohydrin **490**•H^+, and a BF_3-assisted[29] S_N2-type (5-*exo*-*tet*)[30] cyclisation of **490**•H^+ would then generate tetrahydrofuran **495** (Scheme 120).



Scheme 120. *Reagents and conditions:* (i) HBF_4•OEt_2 (20 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h. Some BF_4^- counteranions are omitted for clarity.

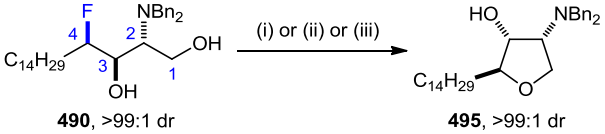
Optimisation of the reaction conditions revealed that the use of 4 equiv of *m*-CPBA and a reaction time of 30 min resulted in >95% consumption of starting material to give a 66:18:16 mixture of amino fluorohydrins **490** and **489**, and functionalised tetrahydrofuran **495**, respectively.[31] After chromatographic purification, amino fluorohydrin **490** was isolated in 56% yield, in addition to amino fluorohydrin **489** in 7% isolated yield, both as single diastereoisomers (Scheme 121).



483, >99:1 dr — **490**, 56%,>99:1 dr — **489**, 7%, >99:1 dr — **495**

Scheme 121. *Reagents and conditions:* (i) HBF_4•OEt_2 (20 equiv), CH_2Cl_2 then *m*-CPBA (4 equiv), rt, 30 min.

In support of the assertion that tetrahydrofuran **495** derives from *in situ* cyclisation of amino fluorohydrin **490**, resubjection of an authentic sample of **490** to the reaction conditions resulted in clean and quantitative conversion to **495**. Furthermore, whilst subjection of **490** to 2 equiv of HBF_4•OEt_2 gave no reaction after 18 h, sequential treatment with 1 equiv of HBF_4•OEt_2 followed by 1 equiv of BF_3•OEt_2 for 18 h gave complete conversion to tetrahydrofuran **495**, which was isolated in quantitative yield (Scheme 122). Presumably, the higher concentration of BF_3•OEt_2 present (as a contaminant in HBF_4•OEt_2) when using 20 equiv as opposed to 2 equiv of HBF_4•OEt_2 is sufficient to promote cyclisation of **490** to **495**. On the basis of these experiments, the relative configuration between C(2) and C(3) within amino fluorohydrin **490** could be confidently assigned as 2,3-*anti*. If both amino fluorohydrins **489** and **490** arise *via* a ring-opening fluorination occurring with inversion of configuration at the oxirane carbon atom distal to the ammonium moiety, the relative configuration between C(2) and C(3) within amino fluorohydrin **489** must necessarily be 2,3-*syn*.

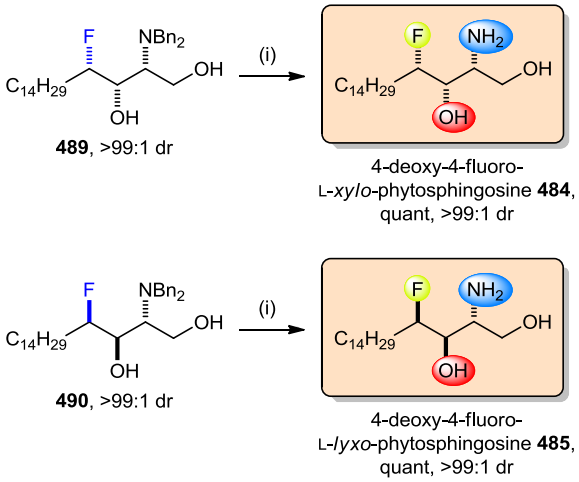


490, >99:1 dr — **495**, >99:1 dr

Conditions	Conv to 495	495 Yield
(i)	100%	–
(ii)	0%	–
(iii)	100%	quant

Scheme 122. *Reagents and conditions:* (i) HBF_4•OEt_2 (20 equiv), CH_2Cl_2 then *m*-CPBA (2 equiv), rt, 18 h; (ii) HBF_4•OEt_2 (2 equiv), CH_2Cl_2, rt, 18 h; (iii) HBF_4•OEt_2 (1 equiv) then BF_3•OEt_2 (1 equiv), CH_2Cl_2, rt, 18 h.

Hydrogenolytic *N*-debenzylation of **489** completed the synthesis of 4-deoxy-4-fluoro-L-*xylo*-phytosphingosine **484**, in 5 steps and 33% overall yield from Garner's aldehyde (*R*)-**397**, whilst an analogous procedure applied to amino fluorohydrin **490** gave 4-deoxy-4-fluoro-L-*lyxo*-phytosphingosine **485**, in 5 steps and 39% overall yield from Garner's aldehyde (*R*)-**397** (Scheme 123).



Scheme 123. *Reagents and conditions:* (i) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h.

5.3. Conclusion

In conclusion, a highly regioselective and stereospecific protocol for the hydroxyfluorination of allylic amines to give the corresponding amino fluorohydrins has been developed, using *m*-CPBA as the oxidant and HBF_4•OEt_2 in a dual role as both a Brønsted acid *N*-protecting agent and nucleophilic fluorine source. The reaction is relatively general across carbocyclic, azacyclic and acyclic allylic amine substrates, and may also be performed with acyclic homoallylic amines, albeit with somewhat lower efficiency. With chiral allylic amines which are conformationally biased or constrained, sequential treatment with 2 equiv of HBF_4•OEt_2 followed by 2 equiv of *m*-CPBA promotes epoxidation of the olefin on the face proximal (typically *syn*) to the amino group, under hydrogen bonded direction from the *in situ* formed ammonium ion. Regioselective and stereospecific epoxide ring-opening by transfer of fluoride from a BF_4^- ion (an S_N2-type process at the carbon atom distal to the ammonium moiety) then occurs *in situ* to give the corresponding amino fluorohydrin. For certain substrates, an analogous reaction using 20 equiv of HBF_4•OEt_2 results in preferential epoxidation of the face of the olefin *anti* to the amino group which, after a similar ring-opening fluorination of the epoxide intermediate *in situ*, leads to the corresponding diastereoisomeric amino fluorohydrin. The synthetic utility of this diastereodivergent hydroxyfluorination protocol has been demonstrated *via* its application to the synthesis of 4-deoxy-4-fluoro-L-*xylo*-phytosphingosine **484** and 4-deoxy-4-fluoro-L-*lyxo*-phytosphingosine **485**, each in 5 steps from Garner's aldehyde (*R*)-**397**.

5.4. References and Notes

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Jpn.) **2010**, *68*, 1295; (h) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216; (i) Brennan, M. B.; Davies, S. G.; Fletcher, A. M.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Schoonen, A. K.; Thomson, J. E. *Manuscript in preparation*.

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[6] German, L. S.; Knunyantz, I. L. *Angew. Chem. Int. Ed.* **1969**, *8*, 349.

[7] The use of *electrophilic* fluorine sources such as XeF_2 or Selectfluor® in the presence of H_2O has also been described; see: Shellhamer, D. F.; Carter, D. L.; Chiaco Chua, M.; Harris, T. E.; Henderson, R. D.; Low, W. S. C.; Metcalf, B. T.; Willis, M. C.; Heasley, V. L.; Chapman, R. D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 401; Xhou, C.; Li, J.; Lü, B.; Fu, C.; Ma, S. *Org. Lett.* **2008**, *10*, 581; Wang, W.; Xu, B.; Hammond, G. B. *Synthesis* **2011**, 2383.

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[9] Whether the protonated (cationic) *m*-CPBA retains the ability to accept a hydrogen bond from the ammonium group is unclear, but it cannot be assumed that the site of protonation on the peracid (possibly the carbonyl oxygen; see ref. 8) is *necessarily* the same site that is involved in hydrogen bond acceptance when the peracid is neutral.

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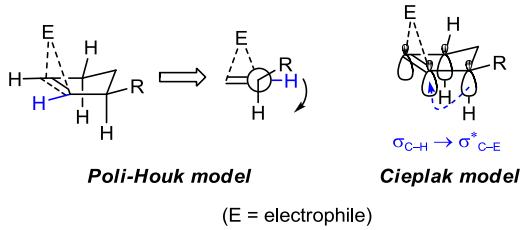
[11] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[12] In support of this assignment, the multiplicity of the fluorine resonance in the ^{19}F NMR spectrum of **451** was indicative of an equatorial fluorine atom: a broad doublet was observed with J = 53.9 Hz, consistent with $^2J_{HF}$ ~ 50 Hz and the lack of resolution of $^3J_{HF,gauche}$ couplings on account of their much smaller magnitude; see: Eliel, E. L.; Martin, R. J. L. *J. Am. Chem. Soc.* **1968**, *90*, 682.

[13] Eliel, E. L.; Martin, R. J. L. *J. Am. Chem. Soc.* **1968**, *90*, 682.

[14] It is unclear whether hydrogen bond-directed epoxidation on the face of the olefin *syn* to the ammonium group involves a protonated (cationic) or a non-protonated (neutral) peracid molecule at high concentrations of HBF_4•OEt_2, and it is possible that a low, equilibrium concentration of non-protonated peracid is participating in this pathway.

[15] Several instances of *syn*-selective osmylation and epoxidation reactions of 3-substituted cyclopentenes which proceed in the absence of any obvious associative interactions (e.g. hydrogen bonding) in the transition state have been reported; see: Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946; Ward, S. E.; Holmes, A. B.; McCague, R. *Chem. Commun.* **1997**, 2085; Aggarwal, V. K.; Monteiro, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2531. Poli has proposed a model to account for these observations, in which attack on the *syn*-face is favoured due to minimisation of developing torsional strain in the transition state; see: Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385. Houk has coined the term "torsional steering" for this effect; see: Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513. A Cieplak model is another possible explanation for this phenomenon:



[16] 2.4% of *cis*-cycloheptane-1,4-diol has been obtained as a by-product from the treatment of cycloheptene with peroxyformic acid; see: Cope, A. C.; Liss, T. A.; Wood, G. W. *J. Am. Chem. Soc.* **1957**, *79*, 6287.

[17] In the solid state structures of both allylic amine **457** and *anti*-epoxide **355**, the 7-membered ring adopts a well defined chair conformation; see ref. 1c. In solution, the chair conformation has been predicted to be the lowest in energy for both cycloheptene and cycloheptene oxide, although a range of slightly higher energy conformations are also readily accessible in these cases; see: Leong, M. K.; Mastryukov, V. S.; Boggs, J. E. *J. Mol. Struct.* **1998**, *445*, 149; Abraham, R. J.; Castellazzi, I.; Sancassan, F.; Smith, T. A. D. *J. Chem. Soc., Perkin Trans. 2* **1999**, 99.

[18] For selected examples see: (a) van Niel, M. B.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. S.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L. *J. Med. Chem.* **1999**, *42*, 2087;

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[19] Unfortunately, unresolved or overlapping resonances in the ^{1}H NMR spectrum of **464** in $CDCl_3$ or benzene-d_6 prevented assignment of the relative configuration *via* ^{1}H-^{1}H ^3J coupling constant analysis. ^{1}H-^{1}H NOE and ^{1}H-^{19}F HOESY analyses also proved inconclusive. The formation of salts of **464** failed to provide suitably crystalline material for single crystal X-ray diffraction analysis, as did the formation of the corresponding *p*-nitrobenzoate derivative (and salts thereof).

[20] ^{1}H-^{1}H NMR ^3J coupling constant analysis, as well as ^{1}H-^{1}H NOE and ^{1}H-^{19}F HOESY analyses, all proved inconclusive in assigning the relative configuration within **466**. The formation of salts of **466** failed to provide suitably crystalline material for single crystal X-ray diffraction analysis, as did the formation of the corresponding *p*-nitrobenzoate derivative (and salts thereof).

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[22] For related syntheses of 4-fluoro-4,5-dihydroceramides and their triazolo analogues, see: Olendorf, J.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4463; Koroniak, K.; Haufe, G. *Synthesis* **2010**, 498.

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[24] Peak overlap in the ^{1}H NMR spectrum of the crude reaction mixture precluded determination of the (*E*):(*Z*) ratio.

[25] From the data obtained from this reaction, it can be deduced that the intermediate epoxide **494** is formed in 84:16 dr under these reaction conditions.

[26] For syntheses of all diastereoisomers of jaspine B (pachastrissamine) see: Canals, D.; Mormeneo, D.; Fabriàs, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235; Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3843; Passiniemi, M.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2011**, *9*, 1774. For a review on the synthesis and structural assignment of jaspine B and 2-*epi*-jaspine B see: Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027.

[27] For other examples of cyclisations of 3,4-epoxy alcohols to generate tetrahydrofurans see: Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717 and references cited within.

[28] In support of protonated *m*-CPBA being the active oxidant (see ref. 8), the reaction of **483** employing 20 equiv of HBF_4•OEt_2 was noticeably faster (i.e. 2 h to consume all of **483**) relative to that employing 2 equiv of HBF_4•OEt_2 (i.e. 3 h to consume ~50% of **483**).

[29] Coxon, J. M.; Morokuma, K.; Thorpe, A. J.; Whalen, D. *J. Org. Chem.* **1998**, *63*, 3875; Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555.

[30] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[31] From the data obtained from this reaction, it can be deduced that the intermediate epoxide **498** is formed in 82:18 dr under these reaction conditions.

Chapter 6: Experimental

6.1. General Experimental

Reactions: All reactions involving organometallic or other moisture-sensitive reagents were carried out under a N_2 atmosphere using glassware that was flame-dried and cooled under a flow of N_2 prior to use.

Previously prepared substrates: Samples of epoxy amines **333**[1], **348**[1], **330**[2], **352**[2] and **355**[2] and allylic amines **329**[2] and **457**[2] were already available in our laboratory having been synthesised *via* published procedures. Samples of epoxy amines **331**[3] and **345**[3] were kindly provided by Mr David Hewings. Samples of epoxy amines **377**[4] and **379**[4] and allylic amines **459**[3], **477**[5], **481**[5] and **482**[5] were kindly provided by Dr Ai Fletcher.

Solvents and reagents: Solvents were dried according to the procedure outlined by Grubbs and co-workers[6] or by storage over molecular sieves.[7] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and was titrated against diphenylacetic acid prior to use. *m*-CPBA was supplied as a damp solid (70-77% with H_2O) and was titrated prior to use (*vide infra*). Dry 0.5 M solutions of *m*-CPBA were freshly prepared by treating a solution of titrated *m*-CPBA (70-77% with H_2O) in CH_2Cl_2 with $MgSO_4$, followed by filtration of the supernatant solution through a Pasteur pipette (packed to half depth with $MgSO_4$) into a volumetric flask, and addition of further CH_2Cl_2 as necessary. All other solvents and reagents were used as supplied.

Work up procedures: Organic layers were dried over $MgSO_4$ (unless otherwise specified) and the dessicant removed *via* filtration prior to concentration *in vacuo*.

Chromatography: Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were typically visualised using UV light (254 nm) or 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform.

Compound characterisation: Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded using an ATR module, with selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Coupling constants were determined using the first order approximation. ^1H-^1H COSY and ^1H-^{13}C HMQC, HSQC and HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

6.2. General Experimental Procedures

Procedure for Titration of *m*-CPBA

Following a literature titration procedure,[8] *m*-CPBA (70-77% with H_2O, 250 mg) and CH_2Cl_2 were added to a 25 mL volumetric flask to give a 1% w/v solution. A 0.40 M aq solution of AcOH was also prepared by addition of glacial AcOH (11.45 mL) and H_2O to a 500 mL volumetric flask. Aliquots of the 1% w/v *m*-CPBA solution (10.0 mL) and the 0.40 M aq AcOH solution (50.0 mL) (both measured in volumetric flasks) were transferred to a 250 mL stoppered conical flask, followed by KI (1.00 g). A solution of 0.07 M aq sodium thiosulfate [prepared by addition of sodium thiosulfate (8.69 g) and H_2O to a 500 mL volumetric flask] was then added dropwise *via* burette.[9] A few drops of 2% w/v aq starch indicator were added near the end point to provide a more obvious colour change (yellow-brown to opaque white), with a typical (mean) titre in the range 11.5-12.5 mL. The % purity of *m*-CPBA was then calculated using the formula: % *m*-CPBA = $T \times 6.04$ (where T is the mean titre in mL). The titrated *m*-CPBA was then labelled with its % purity and stored in the fridge at 0 °C (Note: the percentage decomposition of *m*-CPBA is <1% after 1 year at rt according to Sigma-Aldrich).

General Procedure 1 for Reduction of Ketones with $NaBH_4$

$NaBH_4$ (1.1 equiv) was added portionwise to a stirred solution of the requisite ketone (1 equiv, 0.4 M in MeOH, with THF added as necessary to homogenise the mixture) at 0 ºC and the resultant mixture was stirred at this temperature until effervescence had ceased. The reaction mixture was then allowed to warm to rt over the time stated and was concentrated *in vacuo*. The residue was partitioned between Et_2O and H_2O and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 2 for Conversion of α-Bromo Ketones to Epoxides

$NaBH_4$ (1.1 equiv) was added portionwise to a stirred solution of the requisite ketone (1 equiv, 0.4 M in MeOH, with THF added as necessary to homogenise the mixture) at 0 ºC and the resultant mixture was stirred at this temperature until effervescence had ceased. The reaction mixture was then allowed to warm to rt over 2.5 h and K_2CO_3 (1 equiv) was added. The resultant mixture was stirred at rt for 18 h and was then concentrated *in vacuo*. The residue was partitioned between Et_2O and H_2O and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 3 for Epoxidation of Alkenes with *m*-CPBA

m-CPBA (1.5 equiv) was added to a stirred solution of the requisite alkene (1 equiv, 0.2 M in CH_2Cl_2) at 0 ºC and the resultant mixture was allowed to warm to rt over the time stated. Satd aq Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant. The layers were separated and the organic layer was washed three times with satd aq $NaHCO_3$. The combined aqueous layers were extracted twice with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 4 for Ring-Opening Hydrofluorination of Aryl Epoxides with BF_3•OEt_2

BF_3•OEt_2 was added in one portion to a stirred solution of the requisite aryl epoxide (1 equiv, 0.25 M in CH_2Cl_2) at the temperature stated and the resultant mixture was stirred at this temperature for the time stated. Satd aq $NaHCO_3$ was then added and the mixture was stirred vigorously until both phases became clear. The layers were separated and the organic layer was washed once with satd aq $NaHCO_3$. The combined aqueous layers were extracted twice with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 5 for Grignard Reaction

The requisite Grignard reagent (solution in Et_2O, 1.1 equiv) was added dropwise to a stirred solution of the requisite carbonyl compound (1 equiv, 0.3 M in Et_2O) at –78 ºC and the resultant mixture was allowed to warm to rt over the time stated. Satd aq NH_4Cl was then added and the resultant mixture was partitioned between Et_2O and H_2O. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 6 for Dehydration of Alcohols with TsOH

Dry TsOH (3 mol%) was added to a stirred solution of the requisite alcohol (1 equiv, 0.7 M in PhMe) and the resultant mixture was heated at reflux for 2 h under Dean-Stark conditions. The resultant mixture was then allowed to cool to rt and was concentrated *in vacuo*.

General Procedure 7 for Dehydration of Alcohols with $KHSO_4$

$KHSO_4$ (0.5 equiv) was added to the requisite alcohol (neat, 1 equiv) and the resultant mixture was stirred at 160 ºC in an open flask for the time stated, then allowed to cool to rt.

General Procedure 8 for Conversion of Fluorohydrins to Fluoroazides

Step 1: Et_3N (2 equiv) and MsCl (1.5 equiv) were added sequentially to a stirred solution of the requisite fluorohydrin (1 equiv, 0.6 M in CH_2Cl_2) at 0 ºC and the resultant mixture was allowed to warm to rt over 1 h. 1 M aq HCl was then added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

Step 2: NaN_3 (5 equiv) and DMF were then added to the residue (from step 1) and the resultant mixture was heated at 100 ºC for 24 h. The reaction mixture was allowed to cool to rt and was partitioned between Et_2O and H_2O. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed five times with H_2O then dried and concentrated *in vacuo*.

General Procedure 9 for Staudinger Reduction of Azides

PPh_3 (1.1 equiv) was added portionwise to a stirred solution of the requisite azide (1 equiv, 0.5 M in THF) at rt and the resultant mixture was stirred at this temperature until effervescence had ceased. H_2O (20 equiv) was then added and the resultant mixture was heated at 50 ºC for 2 h. The reaction mixture was then allowed to cool to rt and partitioned between CH_2Cl_2 and 2 M aq HCl. The layers were separated and the organic layer was extracted twice with 2 M aq HCl. The combined aqueous extracts were washed three times with CH_2Cl_2 then cooled to 0 ºC and basified to pH 12 by portionwise addition of solid NaOH (*cautiously!*). The aqueous mixture was extracted three times with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 10 for Ring-Opening Fluorination of Aryl Epoxides with Alkoxy-Substituted Fluoroboranes

A flame-dried vial was charged sequentially with the requisite trialkyl borate or trimethylsilylated alcohol/diol and BF_3•OEt_2 under a N_2 atmosphere and the resultant mixture was stirred at rt for 5 min and then diluted with CH_2Cl_2[10]. The resultant solution was transferred *via* syringe to a stirred solution of the requisite epoxide in CH_2Cl_2[10] at the temperature stated under a N_2 atmosphere, and the resultant mixture was stirred at this temperature for 5 min. Satd aq $NaHCO_3$ was then added and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ and the combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 11 for Trimethylsilylation of Alcohols or Diols

Me_3SiCl (1.25 equiv for alcohols or 2.5 equiv for diols) was added dropwise to a stirred solution of the requisite alcohol or diol (1 equiv) and Et_3N (1.5 equiv for alcohols or 3 equiv for diols) in CH_2Cl_2 (0.6 M wrt Me_3SiCl) at 0 °C and the resultant mixture was allowed to warm to rt over the time stated. The mixture was then cooled to 0 ºC and satd aq NH_4Cl was added and the resultant mixture was filtered through a pad of Celite (eluent CH_2Cl_2). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*, and the resultant residue was triturated with Et_2O then filtered through a pad of Celite (eluent Et_2O) and concentrated *in vacuo*.

General Procedure 12 for Ring-Opening Fluorination of Aryl Epoxides with pinBF

BF_3•OEt_2 (1.05 equiv) was added in one portion to a stirred solution of **274** (1.05 equiv) in CH_2Cl_2[10] under a N_2 atmosphere at the temperature stated and the resultant mixture was stirred at this temperature for 5 min. The solution was then transferred *via* syringe to a stirred solution of the requisite epoxide (1 equiv) in CH_2Cl_2[10] at the temperature stated under a N_2 atmosphere, and the resultant mixture was stirred at this temperature for the time stated. Satd aq $NaHCO_3$ was then added and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ and the combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 13 for Ring-Opening Hydrofluorination of Epoxy Amines with HBF_4•OEt_2

HBF_4•OEt_2 was added in one portion to a stirred solution of the requisite epoxy amine (1 equiv, 0.25 M in CH_2Cl_2) at rt and the resultant mixture was stirred at this temperature for 5 min. Satd aq $NaHCO_3$ was then added and the layers were separated. The organic layer was washed twice with satd aq $NaHCO_3$ and the combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*.

General Procedure 14 for Epoxidation of Alkenyl Alcohols with *m*-CPBA

m-CPBA (1.5 equiv) was added to a stirred solution of the requisite alkenyl alcohol (1 equiv, 0.25 M in CH_2Cl_2) at 0 ºC and the resultant mixture was allowed to warm to rt over the time stated. Satd aq Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant. Satd aq $NaHCO_3$ was added and the layers were separated. The organic layer was washed twice with satd aq $NaHCO_3$ and the combined aqueous layers were saturated with NaCl and extracted twice with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 15 for Mesylation of Alcohols

Et_3N (2 equiv) and MsCl (1.5 equiv) were added sequentially to a stirred solution of the requisite alcohol (1 equiv, 0.6 M in CH_2Cl_2) at 0 ºC and the resultant mixture was allowed to warm to rt over 1 h. 1 M aq HCl was then added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 16 for Amination of Mesylates

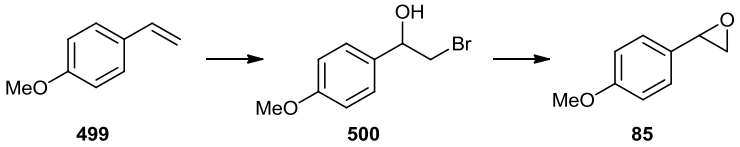
Dibenzylamine (2.5 equiv) was added to a stirred solution of the requisite mesylate (1 equiv, 0.4 M in EtOH) and the resultant mixture was heated at reflux for the time stated. The resultant mixture was then allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ and CH_2Cl_2 and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 17 for Hydroxyfluorination of Alkenyl Amines with *m*-CPBA and HBF_4•OEt_2

HBF_4•OEt_2 was added to a stirred solution of the requisite alkenyl amine (1 equiv in CH_2Cl_2[11]) at rt and the resultant mixture was stirred for 5 min. A solution of pre-dried *m*-CPBA (0.5 M in CH_2Cl_2, 2 equiv) was added and the resultant mixture was stirred at rt for the time stated. Satd aq Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant. Satd aq $NaHCO_3$ was added and the layers were separated. The organic layer was washed twice with satd aq $NaHCO_3$ and the combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*.

6.3. Chapter 2 Experimental

Preparation of (*RS*)-2-(4′-methoxyphenyl)oxirane [*p*-methoxystyrene oxide] 85

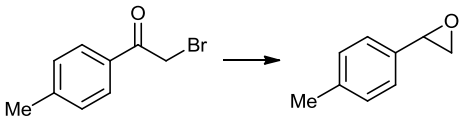


499 **500** **85**

Step 1: Following *General Procedure 1*, 2-bromo-4′-methoxyacetophenone **499** (1.95 g, 8.50 mmol) in MeOH (21 mL) and THF (9.3 mL) was treated with $NaBH_4$ (354 mg, 9.35 mmol) for 4.5 h. Purification *via* flash column chromatography (gradient elution, 6→70% Et_2O in 30-40 °C petrol) gave **500** as a colourless oil (1.09 g, 56%);[12] R_f 0.18 (30-40 °C petrol/Et_2O, 70:30); δ_H (400 MHz, $CDCl_3$) 2.61 (1H, br s, O*H*), 3.51-3.63 (2H, m, C(2)H_2), 3.82 (3H, s, O*Me*), 4.89 (1H, dd, *J* 9.2, 3.4, C(1)*H*), 6.89-6.94 (2H, m, *Ar*), 7.29-7.34 (2H, m, *Ar*).

Step 2: K_2CO_3 (408 mg, 2.95 mmol) was added to a stirred solution of **500** (682 mg, 2.95 mmol) in MeOH (7.4 mL) at rt and the resultant mixture was stirred at this temperature for 1 h and then concentrated *in vacuo*. The residue was partitioned between Et_2O (20 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **85** as a colourless oil (438 mg, 99%);[13] δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 5.3, 2.9, C(3)H_A), 3.13 (1H, dd, *J* 5.3, 3.9, C(3)H_B), 3.81 (3H, s, O*Me*), 3.83 (1H, dd, *J* 3.9, 2.9, C(2)*H*), 6.87-6.92 (2H, m, *Ar*), 7.19-7.23 (2H, m, *Ar*).

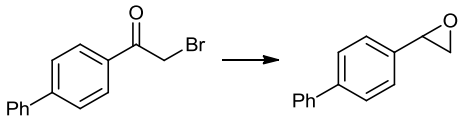
Preparation of (*RS*)-2-(*p*-tolyl)oxirane [*p*-methylstyrene oxide] 86



501 **86**

Following *General Procedure 2*, 2-bromo-4′-methylacetophenone **501** (4.04 g, 19.0 mmol) in MeOH (48 mL) and THF (9.5 mL) was treated with $NaBH_4$ (789 mg, 20.9 mmol) and K_2CO_3 (2.62 g, 19.0 mmol). Purification *via* distillation at reduced pressure (1.2 mmHg) gave **86** as a colourless oil (2.15 g, 84%);[14] bp 36 °C (1.2 mmHg) {lit.[15] bp 54 °C (1.2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, *Me*), 2.81 (1H, dd, *J* 5.5, 2.5, C(3)H_A), 3.14 (1H, dd, *J* 5.5, 3.9, C(3)H_B), 3.85 (1H, dd, *J* 3.9, 2.5, C(2)*H*), 7.15-7.21 (4H, m, *Ar*).

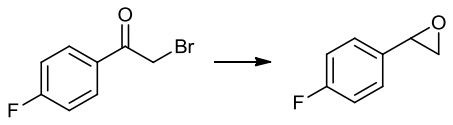
Preparation of (*RS*)-2-(biphenyl-4′-yl)oxirane [*p*-phenylstyrene oxide] 87



502 **87**

Following *General Procedure 2*, 2-bromo-4′-phenylacetophenone **502** (700 mg, 2.54 mmol) in MeOH (6.4 mL) and THF (8.2 mL) was treated with $NaBH_4$ (106 mg, 2.79 mmol) and K_2CO_3 (351 mg, 2.54 mmol). Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **87** as a white crystalline solid (429 mg, 86%);[16] R_f 0.30 (30-40 °C petrol/Et_2O, 90:10); mp 84-85 °C {lit.[16] mp 85-87 °C}; δ_H (400 MHz, $CDCl_3$) 2.86 (1H, dd, *J* 5.5, 2.7, C(3)H_A), 3.20 (1H, dd, *J* 5.5, 4.0, C(3)H_B), 3.92 (1H, dd, *J* 4.0, 2.7, C(2)*H*), 7.34-7.62 (9H, m, *Ar*).

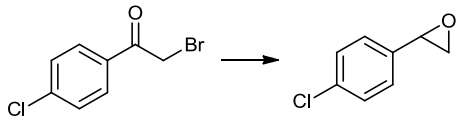
Preparation of (*RS*)-2-(4′-fluorophenyl)oxirane [*p*-fluorostyrene oxide] 88



503 **88**

Following *General Procedure 2*, 2-bromo-4′-fluoroacetophenone **503** (5.07 g, 23.3 mmol) in MeOH (58 mL) was treated with $NaBH_4$ (971 mg, 25.7 mmol) and K_2CO_3 (3.23 g, 23.3 mmol). Purification *via* distillation at reduced pressure (1.2 mmHg) gave **88** as a colourless oil (2.36 g, 73%);[14] bp 23-25 °C (1.2 mmHg) {lit.[17] bp 92 °C (14 mmHg)}; δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 5.4, 2.4, C(3)H_A), 3.15 (1H, dd, *J* 5.4, 4.0, C(3)H_B), 3.89 (1H, dd, *J* 4.0, 2.4, C(2)*H*), 7.01-7.09 (2H, m, *Ar*), 7.22-7.29 (2H, m, *Ar*).

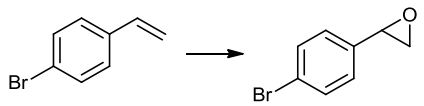
Preparation of (*RS*)-2-(4′-chlorophenyl)oxirane [*p*-chlorostyrene oxide] 89



504 **89**

Following *General Procedure 2*, 2-bromo-4′-chloroacetophenone **504** (7.54 g, 32.3 mmol) in MeOH (81 mL) and THF (47 mL) was treated with $NaBH_4$ (1.34 g, 35.5 mmol) and K_2CO_3 (4.46 mg, 32.3 mmol). Purification *via* distillation at reduced pressure (1.2 mmHg) gave **89** as a colourless oil (4.06 g, 81%);[14] bp 75-76 °C (1.2 mmHg) {lit.[15] bp 72 °C (0.5 mmHg)}; δ_H (400 MHz, $CDCl_3$) 2.76 (1H, dd, *J* 5.5, 2.5, C(3)H_A), 3.16 (1H, dd, *J* 5.5, 4.0, C(3)H_B), 3.85 (1H, dd, *J* 4.0, 2.5, C(2)*H*), 7.20-7.24 (2H, m, *Ar*), 7.30-7.36 (2H, m, *Ar*).

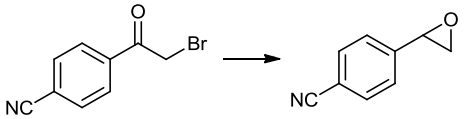
Preparation of (*RS*)-2-(4′-bromophenyl)oxirane [*p*-bromostyrene oxide] 90



505 **90**

Following *General Procedure 3*, 4-bromostyrene **505** (2.00 g, 10.9 mmol) in CH_2Cl_2 (55 mL) was treated with *m*-CPBA (74% with H_2O, 3.87 g, 16.4 mmol) for 40 h to give **90** as a colourless oil (2.07 g, 95%);[14] δ_H (400 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 5.5, 2.4, C(3)H_A), 3.15 (1H, dd, *J* 5.5, 4.1, C(3)H_B), 3.83 (1H, dd, *J* 4.1, 2.4, C(2)*H*), 7.13-7.18 (2H, m, *Ar*), 7.45-7.50 (2H, m, *Ar*).

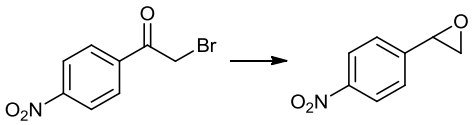
Preparation of (*RS*)-2-(4′-cyanophenyl)oxirane [*p*-cyanostyrene oxide] 91



506 **91**

Following *General Procedure 2*, 4-(bromoacetyl)benzonitrile **506** (4.18 g, 18.7 mmol) in MeOH (47 mL) and THF (25 mL) was treated with $NaBH_4$ (777 mg, 20.5 mmol) and K_2CO_3 (2.58 g, 18.7 mmol). Purification *via* distillation at reduced pressure (1.2 mmHg) gave **91** as a colourless oil (2.36 g, 87%);[14] bp 84-86 °C (1.2 mmHg) {lit.[18] bp 111 °C (2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 5.5, 2.5, C(3)H_A), 3.20 (1H, dd, *J* 5.5, 4.0, C(3)H_B), 3.91 (1H, dd, *J* 4.0, 2.5, C(2)*H*), 7.39 (2H, d, *J* 8.5, *Ar*), 7.64 (2H, d, *J* 8.5, *Ar*).

Preparation of (*RS*)-2-(4′-nitrophenyl)oxirane [*p*-nitrostyrene oxide] 92



507 **92**

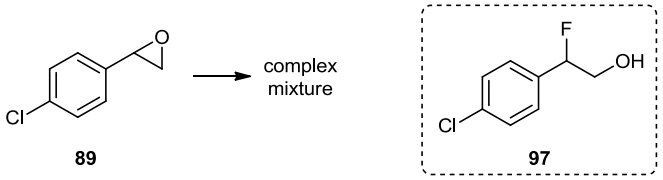
Following *General Procedure 2*, 4-nitrophenacyl bromide **507** (5.00 g, 20.5 mmol) in MeOH (51 mL) and THF (32 mL) was treated with $NaBH_4$ (853 mg, 22.5 mmol) and K_2CO_3 (2.83 g, 20.5 mmol). Purification *via* recrystallisation (Et_2O) gave **92** as a yellow crystalline solid (1.43 g, 42%);[14] mp 78-79 °C (Et_2O) {lit.[14] mp 84-85 °C}; δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 5.5, 2.4, C(3)H_A), 3.24 (1H, dd, *J* 5.5, 4.1, C(3)H_B), 3.97 (1H, dd, *J* 4.1, 2.4, C(2)*H*), 7.44-7.49 (2H, m, *Ar*), 8.20-8.25 (2H, m, *Ar*).

Ring-opening fluorination of (*RS*)-styrene oxide 73

73 **76**

Following *General Procedure 4*, (*RS*)-styrene oxide **73** (0.76 mL, 6.7 mmol) in CH_2Cl_2 (27 mL) was treated with BF_3•OEt_2 (0.27 mL, 2.2 mmol) at −20 °C for 5 min to give a complex mixture of products containing **76** (8%[19]). Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave an impure sample of (*RS*)-2-fluoro-2-phenylethanol **76** as a colourless oil (116 mg);[20] R_f 0.24 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.15 (1H, br s, O*H*), 3.67-4.01 (2H, m, C(1)H_2), 5.58 (1H, ddd, *J* 49.1, 7.9, 3.1, C(2)*H*), 7.28-7.45 (5H, m, *Ph*); δ_F (377 MHz, $CDCl_3$) –186.8 (ddd, 49.1, 29.7, 20.7, C(2)*F*).

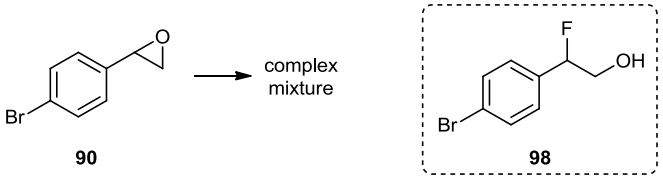
Ring-opening fluorination of (*RS*)-2-(4′-chlorophenyl)oxirane 89



89 **97**

Following *General Procedure 4*, **89** (187 mg, 1.20 mmol) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –40 °C for 1 h to give a complex mixture of products containing (*RS*)-1-(4′-chlorophenyl)-2-fluoroethanol **97** (10%[19]). Data for **97**: δ_F (377 MHz, $CDCl_3$) –187.0 (ddd, *J* 48.2, 29.0, 19.8, C(2)*F*).

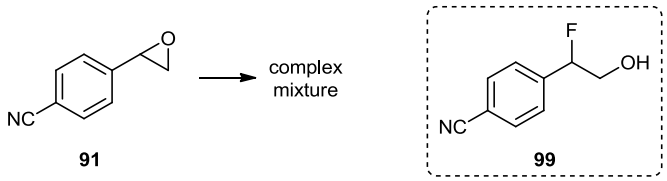
Ring-opening fluorination of (*RS*)-2-(4′-bromophenyl)oxirane 90



90 **98**

Following *General Procedure 4*, **90** (239 mg, 1.20 mmol) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –40 °C for 1 h to give a complex mixture of products containing (*RS*)-1-(4′-bromophenyl)-2-fluoroethanol **98** (11%[19]). Data for **98**: δ_F (377 MHz, $CDCl_3$) –187.5 (ddd, *J* 48.2, 28.7, 19.5, C(2)*F*).

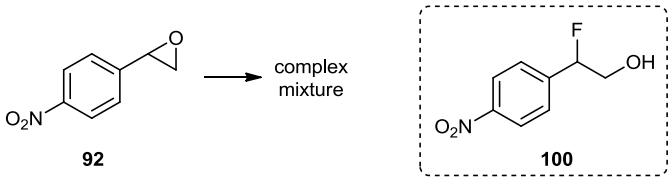
Ring-opening fluorination of (*RS*)-2-(4′-cyanophenyl)oxirane 91



91 **99**

Following *General Procedure 4*, **91** (174 mg, 1.20 mmol) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –40 °C for 1 h to give a complex mixture of products containing a compound tentatively assigned as (*RS*)-2-(4′-cyanophenyl)-2-fluoroethanol **99** (<1%[19]). Data for **99**: δ_F (377 MHz, $CDCl_3$) –190.5 (m, C(2)*F*).

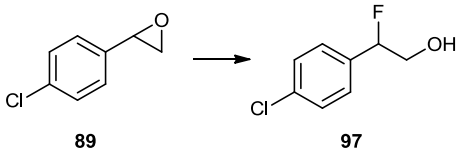
Ring-opening fluorination of (*RS*)-2-(4′-nitrophenyl)oxirane 92



92 **100**

Following *General Procedure 4*, **92** (198 mg, 1.20 mmol) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –40 °C for 1 h to give a complex mixture of products containing a compound tentatively assigned as (*RS*)-2-fluoro-2-(4′-nitrophenyl)ethanol **100** (<1%[19]). Data for **100**: δ_F (377 MHz, $CDCl_3$) –190.4 (m, C(2)*F*).

Preparation of (*RS*)-1-(4′-chlorophenyl)-2-fluoroethanol 97

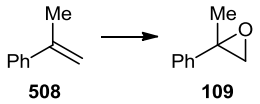


89 **97**

BF_3•OEt_2 (96 μL, 0.80 mmol) was added to a stirred solution of **89** (647 mg, 4.20 mmol) and Et_3N•3HF (2.0 mL, 12 mmol) in CH_2Cl_2 (50 mL) at rt and the resultant mixture was stirred at this temperature for 17 h. Ice-water (200 mL) was then added and the reaction mixture was neutralised by addition of 25% aq NH_3. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with 0.1 M aq HCl (2 × 40 mL) and 5% aq $NaHCO_3$ (3 × 40 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **97** as a colourless oil (297 mg, 41%); R_f 0.18 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3363 (O–H), 2933, 2871 (C–H), 1494, 1450, 1090, 1048; δ_H (400 MHz, $CDCl_3$) 2.11 (1H, br s, O*H*), 3.76-3.96 (2H, m, C(1)H_2), 5.55 (1H, ddd, *J* 48.5, 7.4, 3.2, C(2)*H*), 7.27-7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 66.4 (d, *J* 24.6, *C*(1)), 94.1 (d, *J* 173, *C*(2)), 127.1 (d, *J* 7.0, *o*-*Ph*), 128.8 (*m*-*Ph*),

134.7 (*p-Ph*), 134.9 (d, *J* 20.2, *i-Ph*); δ_F (377 MHz, $CDCl_3$) –187.1 (ddd, *J* 48.5, 29.2, 19.8, C(2)*F*); *m*/*z* (FI^+) 174 ($[M]^+$, 100%); HRMS (FI^+) $C_8H_8ClFO^+$ ($[M]^+$) requires 174.0242; found 174.0249.

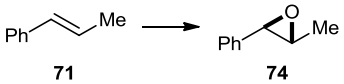
Preparation of (*RS*)-2-methyl-2-phenyloxirane 109



508 **109**

N-Bromosuccinimide (5.74 g, 25.4 mmol) was added to a stirred solution of α-methylstyrene **508** (3.3 mL, 25 mmol) in H_2O/acetone (40:60 v/v, 35 mL) and the resultant mixture was stirred vigorously at rt for 2 h. The acetone was then removed *in vacuo* and the aqueous mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with satd aq $Na_2S_2O_3$ (50 mL) then dried and concentrated *in vacuo*. K_2CO_3 (3.51 g, 25.4 mmol) and MeOH (65 mL) were added to the residue and the resultant mixture was stirred at rt for 27 h, then filtered and concentrated *in vacuo*. The residue was partitioned between H_2O (50 mL) and Et_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **109** as a pale yellow oil (3.15 g, 92%);[21] δ_H (400 MHz, $CDCl_3$) 1.74 (3H, s, C(2)*Me*), 2.82 (1H, d, *J* 5.3, C(3)H_A), 2.99 (1H, d, *J* 5.3, C(3)H_B), 7.26-7.40 (5H, m, *Ph*).

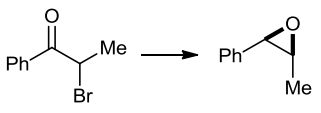
Preparation of (*RS*,*RS*)-2-methyl-3-phenyloxirane 74



71 **74**

Following *General Procedure 3*, (*E*)-β-methylstyrene **71** (6.6 mL, 51 mmol, >99:1 dr) in CH_2Cl_2 (250 mL) was treated with *m*-CPBA (74% with H_2O, 17.9 g, 76.8 mmol) for 28 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave **74** as a colourless oil (6.57 g, 96%, >99:1 dr);[21] bp 45-46 °C (1.2 mmHg) {lit.[22] bp 50 °C (0.2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 5.1, C(2)*Me*), 3.05 (1H, qd, *J* 5.1, 2.1, C(2)*H*), 3.59 (1H, d, *J* 2.1, C(3)*H*), 7.25-7.38 (5H, m, *Ph*).

Preparation of (*RS*,*SR*)-2-methyl-3-phenyloxirane 110

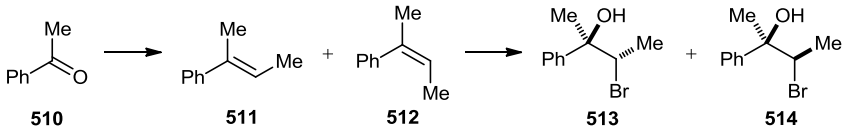


509 **110**

$NaBH_4$ (1.39 g, 36.8 mmol) was added portionwise to a stirred solution of 2-bromopropiophenone **509** (5.0 mL, 34 mmol) in MeOH (80 mL) at –78 °C and the resultant mixture was stirred at this temperature until effervescence had ceased. The reaction mixture was allowed to warm to rt over 24 h and then K_2CO_3

(4.63 g, 33.5 mmol) was added. The resultant mixture was stirred at rt for a further 16 h and then concentrated *in vacuo*. The residue was partitioned between Et_2O (50 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* distillation at reduced pressure (1.2 mmHg) gave **110** as a colourless oil (3.18 g, 71%, >99:1 dr);[21] bp 27-30 °C (1.2 mmHg) {lit.[23] bp 92-93 °C (25 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 5.5, C(2)*Me*), 3.36 (1H, qd, *J* 5.5, 4.2, C(2)*H*), 4.08 (1H, d, *J* 4.2, C(3)*H*), 7.26-7.39 (5H, m, *Ph*).

Preparation of (*RS*,*SR*)- and (*RS*,*RS*)-2-phenyl-3-bromobutan-2-ol (*RS*,*SR*)-513 and (*RS*,*RS*)-514

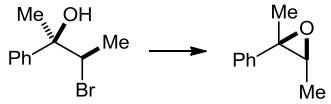


Step 1: BuLi (1.5 M in hexanes, 34 mL, 50 mmol) was added dropwise to a stirred suspension of $[EtPPh_3]^+Br^-$ (18.5 g, 49.9 mmol) in THF (170 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 30 min. The mixture was then cooled to 0 °C and a solution of acetophenone **510** (4.2 mL, 36 mmol) in THF (50 mL) was added dropwise *via* cannula. The resultant mixture was allowed to warm to rt over 110 h and then satd aq NH_4Cl (10 mL) was added and the mixture was dried and concentrated *in vacuo*. The residue was then triturated with 30-40 °C petrol and concentrated *in vacuo*. Purification *via* filtration through a pad of silica gel (eluent 30-40 °C petrol) gave a 51:49 mixture of **511**:**512** as a colourless oil (3.74 g, 79% combined). Data for **511**:**512** mixture: R_f 0.36-0.54 (30-40 °C petrol). Data for **511**:[24] δ_H (400 MHz, $CDCl_3$) 1.85 (3H, d, *J* 6.8, C(4)H_3), 2.08 (3H, s, C(1)H_3), 5.91 (1H, q, *J* 6.8, C(3)*H*), 7.22-7.44 (5H, m, *Ph*). Data for **512**:[24] δ_H (400 MHz, $CDCl_3$) 1.65 (3H, app dd, *J* 6.8, 1.4, C(4)H_3), 2.08 (3H, s, C(1)H_3), 5.62 (1H, qd, *J* 6.8, 1.4, C(3)*H*), 7.22-7.44 (5H, m, *Ph*).

Step 2: *N*-Bromosuccinimide (5.13 g, 22.7 mmol) was added to a stirred solution of a 51:49 mixture of **511**:**512** (3.00 g, 22.7 mmol) in H_2O/acetone (40:60 v/v, 30 mL) and the resultant mixture was stirred vigorously at rt for 2.5 h. The acetone was then removed *in vacuo* and the aqueous mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with satd aq $Na_2S_2O_3$ (50 mL) then dried and concentrated *in vacuo* to give a 54:46 mixture of **513**:**514**. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **513** as a colourless oil (2.59 g, 50%, >99:1 dr); R_f 0.46 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3556 (O–H), 3089, 3060, 3028, 2980, 2932, 2870, 2819 (C–H), 1494, 1447, 1172; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.8, C(4)H_3), 1.75 (3H, s, C(1)H_3), 2.34 (1H, s, O*H*), 4.54 (1H, q, *J* 6.8, C(3)*H*), 7.26-7.48 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)

21.2 (*C*(4)), 31.1 (*C*(1)), 63.1 (*C*(3)), 75.8 (*C*(2)), 125.1 (*p-Ph*), 127.2, 128.3 (*o-*, *m-Ph*), 143.0 (*i-Ph*); *m*/*z* (FI^+) 230 ([M(^{81}Br)]$^+$, 100%), 228 ([M(^{79}Br)]$^+$, 96%); HRMS (FI^+) $C_{10}H_{13}{}^{79}BrO^+$ ([M]$^+$) requires 228.0144; found 228.0151. Further elution gave **514** as a colourless oil (2.08 g, 40%, >99:1 dr); R_f 0.36 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3475 (O–H), 3088, 3060, 3028, 2983, 2935, 2871, 2824 (C–H), 1682, 1495, 1447, 1030; δ_H (400 MHz, $CDCl_3$) 1.67 (3H, d, *J* 7.0, C(4)H_3), 1.67 (3H, s, C(1)H_3), 2.64 (1H, s, O*H*), 4.58 (1H, q, *J* 7.0, C(3)*H*), 7.27-7.51 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*(4)), 24.3 (*C*(1)), 63.4 (*C*(3)), 76.3 (*C*(2)), 125.3 (*p-Ph*), 127.6, 128.3 (*o-*, *m-Ph*), 144.6 (*i-Ph*); *m*/*z* (FI^+) 230 ([M(^{81}Br)]$^+$, 100%), 228 ([M(^{79}Br)]$^+$, 100%); HRMS (FI^+) $C_{10}H_{13}{}^{79}BrO^+$ ([M(^{79}Br)]$^+$) requires 228.0144; found 228.0145.

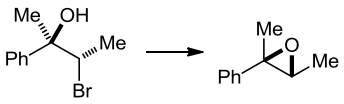
Preparation of (*RS*,*SR*)-2,3-dimethyl-2-phenyloxirane 111



514 **111**

K_2CO_3 (1.06 g, 7.68 mmol) was added to a stirred solution of **514** (1.76 g, 7.68 mmol, >99:1 dr) in MeOH (20 mL) and the resultant mixture was stirred at rt for 20 h, then filtered and concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **111** as a colourless oil (1.12 g, 99%, >99:1 dr);[25] δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 5.5, C(3)*Me*), 1.65 (3H, s, C(2)*Me*), 3.18 (1H, q, *J* 5.5, C(3)*H*), 7.25-7.39 (5H, m, *Ph*).

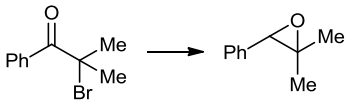
Preparation of (*RS*,*RS*)-2,3-dimethyl-2-phenyloxirane 112



513 **112**

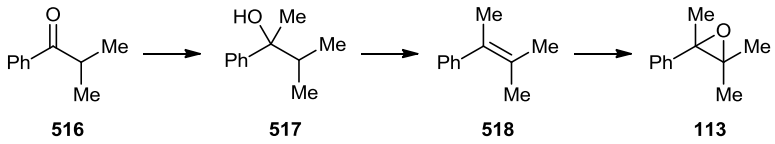
K_2CO_3 (1.38 g, 10.0 mmol) was added to a stirred solution of **513** (2.29 g, 10.0 mmol, >99:1 dr) in MeOH (25 mL) and the resultant mixture was stirred at rt for 20 h, then filtered and concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **112** as a colourless oil (1.44 g, 97%, >99:1 dr);[26] δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 5.5, C(3)*Me*), 1.67 (3H, s, C(2)*Me*), 2.96 (1H, q, *J* 5.5, C(3)*H*), 7.24-7.40 (5H, m, *Ph*).

Preparation of (*RS*)-2,2-dimethyl-3-phenyloxirane 75



$NaBH_4$ (281 mg, 7.43 mmol) was added portionwise to a stirred solution of 2-bromoisobutyrophenone **515** (1.14 mL, 6.75 mmol) in MeOH (20 mL) at 0 °C and the resultant mixture was stirred at this temperature until effervescence had ceased. The reaction mixture was allowed to warm to rt over 2.5 h and then K_2CO_3 (933 mg, 6.75 mmol) was added. The mixture was stirred at rt for 18 h then filtered and concentrated *in vacuo*. The residue was partitioned between Et_2O (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **75** as a colourless oil (803 mg, 80%);[21] δ_H (400 MHz, $CDCl_3$) 1.09 (3H, s, C(2)*Me*$_A$), 1.50 (3H, s, C(2)*Me*$_B$), 3.88 (1H, s, C(3)*H*), 7.27-7.39 (5H, m, *Ph*).

Preparation of (*RS*)-2,2,3-trimethyl-3-phenyloxirane 113

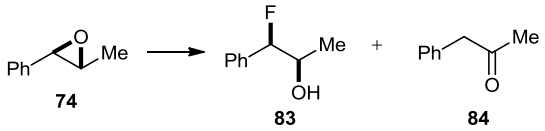


Step 1: Following *General Procedure 5*, isobutyrophenone **516** (3.2 mL, 21 mmol) in Et_2O (70 mL) was treated with MeMgBr (3.0 M in Et_2O, 7.8 mL, 23 mmol) for 2 h to give crude 3-methyl-2-phenylbutan-2-ol **517** as a colourless oil (3.50 g);[27] δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.8, C(3)*Me*$_A$), 0.90 (3H, d, *J* 6.8, C(3)*Me*$_B$), 1.54 (3H, s, C(1)*H*$_3$), 1.65 (1H, br s, O*H*), 2.03 (1H, septet, *J* 6.8, C(3)*H*), 7.21-7.46 (5H, m, *Ph*).

Step 2: Following *General Procedure 6*, crude 3-methyl-2-phenylbutan-2-ol **517** (3.50 g) in PhMe (30 mL) was treated with dry TsOH (110 mg, 0.64 mmol) to give crude 3-methyl-2-phenylbut-2-ene **518** as a yellow oil (2.92 g);[28] δ_H (400 MHz, $CDCl_3$) 1.60 (3H, s, *Me*), 1.82 (3H, s, *Me*), 1.98 (3H, s, *Me*), 7.12-7.38 (5H, m, *Ph*).

Step 3: Following *General Procedure 3*, crude 3-methyl-2-phenylbut-2-ene **518** (2.92 g) in CH_2Cl_2 (100 mL) was treated with *m*-CPBA (74% with H_2O, 7.45 g, 32.0 mmol) for 2 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave **113** as a colourless oil (2.45 g, 71% over 3 steps);[21] bp 50-53 °C (1.2 mmHg) {lit.[29] bp 128 °C (20 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.63 (3H, s, *Me*), 7.22-7.37 (5H, m, *Ph*).

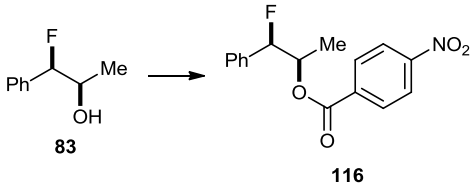
Ring-opening fluorination of (*RS*,*RS*)-2-methyl-3-phenyloxirane 74



Following *General Procedure 4*, **74** (330 mg, 2.46 mmol, >99:1 dr) in CH_2Cl_2 (9.8 mL) was treated with BF_3•OEt_2 (101 μL, 0.82 mmol) at –20 °C for 5 min to give a 96:4 mixture of **83**:**84** (85% of **83**[19]). Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-phenylpropan-2-one **84** as a colourless oil (10.6 mg, 3%);[30] R_f 0.26 (30-40 °C petrol/EtOAc, 90:10); δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, C(3)H_3), 3.71 (2H, s, C(1)H_2), 7.19-7.24 (2H, m, *Ph*), 7.26-7.31 (1H, m, *Ph*), 7.32-7.38 (2H, m, *Ph*). Further elution gave (*RS*,*RS*)-1-fluoro-1-phenylpropan-2-ol **83** as a colourless oil (305 mg, 80%, >99:1 dr);[31] R_f 0.14 (30-40 °C petrol/EtOAc, 90:10); ν_{max} 3417 (O–H), 3089, 3065, 3035, 2979, 2934 (C–H), 1371, 1261, 1147, 1083, 1005; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, dd, *J* 6.4, 0.9, C(3)H_3), 2.67 (1H, br s, O*H*), 4.09 (1H, ddq, *J* 14.0, 7.1, 6.4, C(2)*H*), 5.17 (1H, dd, *J* 48.0, 7.1, C(1)*H*), 7.32-7.44 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 70.6 (d, *J* 24.0, *C*(2)), 98.7 (d, *J* 171, *C*(1)), 126.6 (d, *J* 6.4, *o*-*Ph*), 128.6 (*m*-*Ph*), 129.0 (*p*-*Ph*), 136.7 (d, *J* 19.2, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –181.4 (dd, *J* 48.0, 14.0, C(1)*F*); *m*/*z* (FI^+) 154 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{11}FO^+$ ($[M]^+$) requires 154.0788; found 154.0788.

Following *General Procedure 4*, **74** (4.50 g, 33.5 mmol, >99:1 dr) in CH_2Cl_2 (135 mL) was treated with BF_3•OEt_2 (1.38 mL, 11.2 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **83** as a colourless oil (4.31 g, 83%, >99:1 dr).

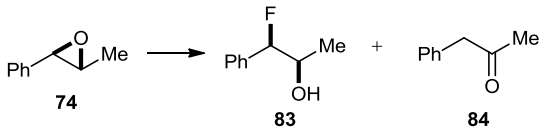
Preparation of (*RS*,*RS*)-1-fluoro-1-phenylpropan-2-yl *p*-nitrobenzoate 116



p-Nitrobenzoyl chloride (166 mg, 0.90 mmol) was added to a stirred solution of **83** (126 mg, 0.81 mmol, >99:1 dr) in pyridine (5.0 mL) and the resultant mixture was stirred at rt for 28 h. 1 M aq HCl (20 mL) was then added and the mixture was extracted with CH_2Cl_2 (30 mL). The organic extract was washed sequentially with 1 M aq HCl (2 × 20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **116** as a white crystalline solid (208 mg, 85%, >99:1 dr); R_f 0.26 (30-40 °C petrol/EtOAc, 90:10); $C_{16}H_{14}FNO_4$ requires C, 63.4; H, 4.65; N, 4.6%; found C, 63.4; H, 4.7; N, 4.6%; mp

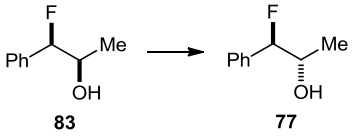
94-95 °C; ν_{max} 3113, 3082, 3036, 2989, 2939, 2877 (C–H), 1727 (C=O), 1528 (NO_2), 1274; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C(3)H_3), 5.44-5.63 (2H, m, C(1)*H*, C(2)*H*), 7.36-7.43 (5H, m, *Ph*), 8.18-8.23 (2H, m, *Ar*), 8.27-8.32 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.0 (*C*(3)), 73.5 (d, *J* 24.0, *C*(2)), 95.0 (d, *J* 179, *C*(1)), 123.6, 126.4 (d, *J* 6.4), 128.7, 129.3, 130.8, 135.5, 135.9 (d, *J* 19.2), 150.6 (*Ar*, *Ph*), 164.0 (O*C*(O)Ar); δ_F (377 MHz, $CDCl_3$) –184.0 (dd, *J* 44.8, 16.1, C(1)*F*); *m*/*z* (FI^+) 303 ($[M]^+$, 100%); HRMS (FI^+) $C_{16}H_{14}FNO_4^+$ ($[M]^+$) requires 303.0901; found 303.0905.

Ring-opening fluorination of (*RS*,*SR*)-2-methyl-3-phenyloxirane 110



Following *General Procedure 4*, **110** (500 mg, 3.73 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) was treated with BF_3•OEt_2 (153 μL, 1.24 mmol) at –20 °C for 5 min to give a complex mixture of products containing a ~7:1 ratio of **84**:**83** (<5% of **83**[19]). Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **84** as a colourless oil (191 mg, 38%). Further elution gave an impure sample of **83** as a colourless oil.

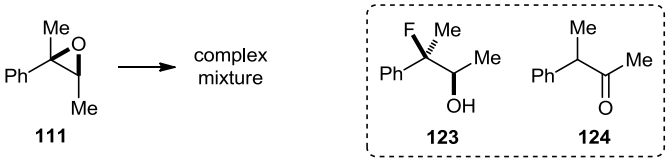
Preparation of (*RS*,*SR*)-1-fluoro-1-phenylpropan-2-ol 77



PPh_3 (993 mg, 3.79 mmol) and *p*-nitrobenzoic acid (475 mg, 2.84 mmol) were added to a stirred solution of **83** (292 mg, 1.89 mmol, >99:1 dr) in THF (30 mL) and the resultant solution was cooled to 0 °C. DEAD (0.51 mL, 3.2 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 6.5 h and was then concentrated *in vacuo*. K_2CO_3 (1.05 g, 7.58 mmol) and MeOH (30 mL) were added to the residue and the resultant mixture was stirred at rt for 15 h and was then concentrated *in vacuo*. The residue was partitioned between Et_2O (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **77** as a pale yellow oil (167 mg, 57%, >99:1 dr);[31] R_f 0.21 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3384 (O–H), 3091, 3066, 3035, 2982, 2933 (C–H), 1496, 1454, 1093, 983; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, dd, *J* 6.4, 1.4, C(3)H_3), 1.81 (1H, br s, O*H*), 4.02-4.14 (1H, dqd, *J* 15.1, 6.4, 4.8, C(2)*H*), 5.33 (1H, dd, *J* 46.7, 4.8, C(1)*H*), 7.34-7.44 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (d, *J* 4.6, *C*(3)), 70.2 (d, *J* 25.8, *C*(2)), 96.8 (d, *J* 175,

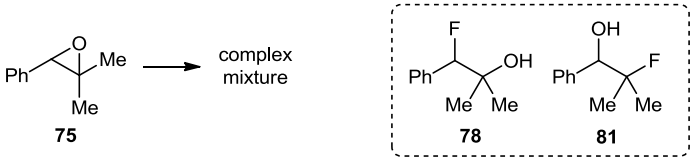
C(1)), 126.3 (d, *J* 7.3, *o-Ph*), 128.4 (*m-Ph*), 128.6 (d, *J* 1.1, *p-Ph*), 136.6 (d, *J* 20.3, *i-Ph*); δ_F (377 MHz, $CDCl_3$) –189.3 (dd, *J* 46.7, 15.1, C(1)*F*); *m*/*z* (FI^+) 154 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{11}FO^+$ ($[M]^+$) requires 154.0788; found 154.0789.

Ring-opening fluorination of (*RS*,*SR*)-2,3-dimethyl-2-phenyloxirane 111



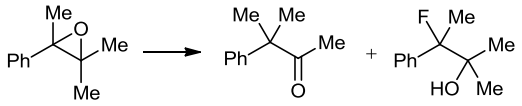
Following *General Procedure 4*, **111** (178 mg, 1.20 mmol, >99:1 dr) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –20 °C for 5 min to give a complex mixture of products containing a 63:37 ratio of **123**:**124** (13% of **123**[19]). Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave an impure sample of (*RS*)-3-phenylbutan-2-one **124** as a colourless oil;[32] R_f 0.31 (30-40 °C petrol/EtOAc, 90:10); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.40 (3H, d, *J* 6.9, C(4)H_3), 2.06 (3H, s, C(1)H_3), 3.75 (1H, q, *J* 6.9, C(3)*H*). Further elution gave an impure sample of (*RS*,*SR*)-3-fluoro-3-phenylbutan-2-ol **123** as a colourless oil (>99:1 dr); R_f 0.13 (30-40 °C petrol/EtOAc, 90:10); ν_{max} 3417 (O–H), 3091, 3061, 3030, 2985, 2939, 2877 (C–H), 1722, 1496, 1447, 1373, 1057; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, dd, *J* 6.4, 0.9, C(1)H_3), 1.74 (3H, d, *J* 23.5, C(4)H_3), 1.82 (1H, br s, O*H*), 3.95 (1H, ddt, *J* 17.7, 6.6, 6.4, C(2)*H*), 7.29-7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3 (d, *J* 4.8, *C*(1)), 23.1 (d, *J* 25.6, *C*(4)), 73.2 (d, *J* 25.6, *C*(2)), 99.2 (d, *J* 176, *C*(3)), 124.6 (d, *J* 11.2, *o-Ph*), 127.6 (*p-Ph*), 128.3 (*m-Ph*), 142.0 (d, *J* 22.3, *i-Ph*); δ_F (377 MHz, $CDCl_3$) –163.4 (m, C(3)*F*); *m*/*z* (FI^+) 168 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{13}FO^+$ ($[M]^+$) requires 168.0945; found 168.0954.

Ring-opening fluorination of (*RS*)-2,2-dimethyl-3-phenyloxirane 75



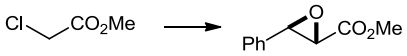
Following *General Procedure 4*, **75** (178 mg, 1.20 mmol) in CH_2Cl_2 (4.8 mL) was treated with BF_3•OEt_2 (49 μL, 0.40 mmol) at –20 °C for 5 min to give a complex mixture of products containing **78** (<1%[19]) and **81** (<2%[19]). Data for (*RS*)-1-fluoro-2-methyl-1-phenylpropan-2-ol **78**:[33] δ_F (377 MHz, $CDCl_3$) –187.3 (d, *J* 45.3, C(1)*F*). Data for (*RS*)-2-fluoro-2-methyl-1-phenylpropan-1-ol **81**:[33] δ_F (377 MHz, $CDCl_3$) –146.3 (dectet, *J* 11.8, C(2)*F*).

Ring-opening fluorination of (*RS*)-2,2,3-trimethyl-3-phenyloxirane 113



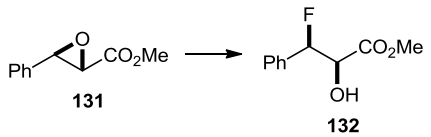
Following *General Procedure 4*, **113** (593 mg, 3.66 mmol) in CH_2Cl_2 (15 mL) was treated with BF_3•OEt_2 (150 μL, 1.22 mmol) at –20 °C for 5 min to give a mixture of products containing a 69:31 ratio of **129**:**130** (6% of **130**[19]). Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave 3-methyl-3-phenylbutan-2-one **129** as a colourless oil (339 mg, 57%);[32] R_f 0.40 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 1.49 (6H, s, C(3)*Me*$_2$), 1.92 (3H, s, C(1)*H*$_3$), 7.24-7.29 (3H, m, *Ph*), 7.33-7.38 (2H, m, *Ph*). Further elution gave (*RS*)-3-fluoro-2-methyl-3-phenylbutan-2-ol **130** as a colourless oil (50.3 mg, 8%); R_f 0.10 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3454 (O–H), 3092, 3061, 3029, 2986, 2944 (C–H), 1448, 1373, 1061, 760, 702; δ_H (400 MHz, $CDCl_3$) 1.22 (6H, d, *J* 4.3, C(1)*H*$_3$, C(2)*Me*), 1.78 (3H, d, *J* 24.0, C(4)*H*$_3$), 1.88 (1H, br s, O*H*), 7.28-7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (d, *J* 24.0, C(3)*Me*), 24.7 (*C*(1), C(2)*Me*), 74.4 (d, *J* 25.6, *C*(2)), 101.1 (d, *J* 176, *C*(1)), 125.8 (d, *J* 9.6, *o*-*Ph*), 127.5 (*p*-*Ph*), 127.8 (*m*-*Ph*), 141.8 (d, *J* 22.4, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –155.7 (q, *J* 24.0, C(3)*F*); *m*/*z* (FI^+) 182 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{15}FO^+$ ($[M]^+$) requires 182.1101; found 182.1101.

Preparation of (*RS*,*SR*)-2-(methylcarboxy)-3-phenyloxirane [methyl *trans*-3-phenylglycidate] 131



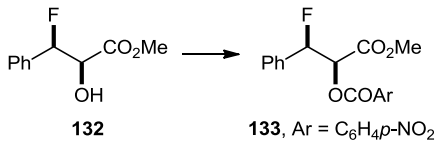
A mixture of benzaldehyde (5.1 mL, 50 mmol) and methyl chloroacetate **519** (6.6 mL, 75 mmol) was added dropwise to a freshly prepared solution of sodium (1.72 g, 75.0 mmol) in MeOH (30 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 21 h. The mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* distillation at reduced pressure (1.2 mmHg) gave **131** as a colourless oil (7.47 g, 84%, >99:1 dr);[34] bp 96-99 °C (1.2 mmHg) {lit.[34] bp 108-111 °C (0.6 mmHg)}; δ_H (400 MHz, $CDCl_3$) 3.52 (1H, d, *J* 1.8, C(2)*H*), 3.82 (3H, s, O*Me*), 4.11 (1H, d, *J* 1.8, C(3)*H*), 7.27-7.40 (5H, m, *Ph*).

Ring-opening fluorination of (*RS,SR*)-2-(methylcarboxy)-3-phenyloxirane 131



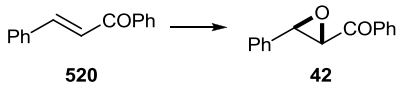
Following *General Procedure 4*, **131** (500 mg, 2.81 mmol, >99:1 dr) in CH_2Cl_2 (11 mL) was treated with BF_3•OEt_2 (115 μL, 0.94 mmol) at –20 °C for 30 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave methyl (*RS,RS*)-2-hydroxy-3-fluoro-3-phenylpropanoate **132** as a colourless oil which solidified on standing to a white crystalline solid (363 mg, 65%, >99:1 dr);[35] R_f 0.23 (30-40 °C petrol/EtOAc, 80:20); $C_{10}H_{11}FO_3$ requires C, 60.6; H, 5.6%; found C, 60.7; H, 5.6%; mp 35-37 °C; ν_{max} 3494 (O–H), 3093, 3066, 3035, 3011, 2956, 2853 (C–H), 1744 (C=O), 1497, 1454, 1440, 1273, 1213, 1128, 1027; δ_H (400 MHz, $CDCl_3$) 3.13 (1H, d, *J* 7.1, O*H*), 3.87 (3H, s, O*Me*), 4.46 (1H, ddd, *J* 27.3, 7.1, 2.3, C(2)*H*), 5.81 (1H, dd, *J* 45.0, 2.3, C(3)*H*), 7.35-7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 53.1 (O*Me*), 73.7 (d, *J* 24.0, *C*(2)), 93.2 (d, *J* 181, *C*(3)), 126.0 (d, *J* 6.4, *o*-*Ph*), 128.5 (*m*-*Ph*), 128.8 (*p*-*Ph*), 135.6 (d, *J* 20.8, *i*-*Ph*), 171.8 (*C*=O); δ_F (377 MHz, $CDCl_3$) –194.5 (dd, *J* 45.0, 27.3, C(3)*F*); *m*/*z* (FI^+) 198 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{11}FO_3^+$ ($[M]^+$) requires 198.0687; found 198.0695.

Preparation of methyl (*RS,RS*)-2-(*p*-nitrobenzoyloxy)-3-fluoro-3-phenylpropanoate 133



p-Nitrobenzoyl chloride (128 mg, 0.69 mmol) was added to a stirred solution of **132** (125 mg, 0.63 mmol, >99:1 dr) in pyridine (4.0 mL) and the resultant mixture was stirred at rt for 12 h. 1 M aq HCl (20 mL) was then added and the mixture was extracted with CH_2Cl_2 (30 mL). The organic extract was washed sequentially with 1 M aq HCl (2 × 20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **133** as a white crystalline solid (67.5 mg, 31%, >99:1 dr); R_f 0.30 (30-40 °C petrol/Et_2O, 80:20); mp 109-111 °C; ν_{max} 3113, 3081, 3056, 3036, 3011, 2957, 2850 (C–H), 1772, 1728 (C=O), 1525, 1347, 1259, 1131; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, O*Me*), 5.64 (1H, dd, *J* 27.5, 3.2, C(2)*H*), 6.14 (1H, dd, *J* 44.7, 3.2, C(3)*H*), 7.33-7.46 (5H, m, *Ph*), 8.17-8.22 (2H, m, *Ar*), 8.27-8.32 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 53.1 (O*Me*), 75.4 (d, *J* 22.4, *C*(2)), 91.8 (d, *J* 182, *C*(3)), 123.7, 125.6 (d, *J* 8.0), 128.7, 129.3, 131.1, 134.1, 134.5 (d, *J* 20.8), 150.9 (*Ar*, *Ph*), 163.7 (O*C*(O)Ar), 166.6 (d, *J* 4.8, O*C*(O)Me)); δ_F (377 MHz, $CDCl_3$) –191.9 (dd, *J* 44.7, 27.5); *m*/*z* (FI^+) 347 ($[M]^+$, 100%); HRMS (FI^+) $C_{17}H_{14}FNO_6^+$ ($[M]^+$) requires 347.0800; found 347.0810.

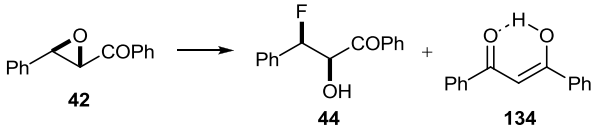
Preparation of (*RS*,*SR*)-2-benzoyl-3-phenyloxirane [(*E*)-chalcone oxide] 42



520 **42**

H_2O_2 (35% in H_2O, 6.6 mL, 75 mmol) was added dropwise to a mixture of (*E*)-chalcone **520** (3.12 g, 15.0 mmol, >99:1 dr) and 6 M aq NaOH (3.0 mL) in MeOH (100 mL) at 0 °C and the resultant mixture was stirred at this temperature for 2 h. Satd aq Na_2SO_3 was then added until starch-iodide paper indicated that no oxidant remained and the resultant precipitate was collected *via* filtration. The precipitate was dissolved in EtOAc (100 mL) and the resultant solution was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **42** as a white crystalline solid (2.46 g, 73%, >99:1 dr);[36] R_f 0.28 (30-40 °C petrol/EtOAc, 90:10); mp 85-87 °C {lit.[36] mp 78.5-80 °C}; δ_H (400 MHz, $CDCl_3$) 4.09 (1H, d, *J* 1.7), 4.32 (1H, d, *J* 1.7) (C(2)*H*, C(3)*H*), 7.35-7.55 (7H, m, *Ph*), 7.60-7.68 (1H, m, *Ph*), 7.99-8.07 (2H, m, *Ph*).

Ring-opening fluorination of (*RS*,*SR*)-2-benzoyl-3-phenyloxirane 42



42 **44** **134**

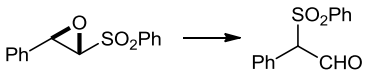
Following *General Procedure 4*, **42** (300 mg, 1.34 mmol, >99:1 dr) in CH_2Cl_2 (5.4 mL) was treated with BF_3•OEt_2 (55 μL, 0.45 mmol) at –20 °C for 5 min to give a 69:31 mixture of **44**:**134**. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave (*Z*)-3-hydroxy-1,3-diphenylprop-2-en-1-one **134** as a yellow solid (108 mg, 36%);[37] R_f 0.46 (30-40 °C petrol/EtOAc, 90:10); mp 74-76 °C {lit.[38] mp 77-78 °C}; δ_H (400 MHz, $CDCl_3$) 7.08-7.16 (2H, m, *Ph*), 7.20-7.43 (8H, m, *Ph*), 8.65 (1H, d, *J* 5.3, C(3)*H*), 15.9 (1H, d, *J* 5.3, O*H*). Further elution gave (*RS*,*RS*)-1-fluoro-2-hydroxy-1,3-diphenylpropan-3-one **44** as a white solid (138 mg, 42%, >99:1 dr);[39] R_f 0.15 (30-40 °C petrol/EtOAc, 90:10); mp 111-112 °C {lit.[39] mp 110-113 (hexane)}; ν_{max} 3463 (O–H), 3089, 3064, 3034, 3009, 2934 (C–H), 1685 (C=O), 1598, 1450, 1266; δ_H (400 MHz, $CDCl_3$) 3.93 (1H, br s, O*H*), 5.40 (1H, dd, *J* 22.0, 2.4, C(2)*H*), 5.80 (1H, dd, *J* 44.9, 2.4, C(3)*H*), 7.27-7.72 (8H, m, *Ph*), 7.94-8.00 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 75.4 (d, *J* 25.6, *C*(2)), 93.3 (d, *J* 182, *C*(3)), 126.0 (d, *J* 8.0), 128.4, 128.8, 128.8, 129.0, 134.0, 134.3, 135.7 (d, *J* 21.1) (*Ph*), 198.0 (*C*=O); δ_F (377 MHz, $CDCl_3$) –192.1 (dd, *J* 44.9, 22.0, C(1)*F*); *m*/*z* (ESI^+) 511 ($[2M+Na]^+$, 100%), 267 ($[M+Na]^+$, 81%); HRMS (ESI^+) $C_{15}H_{13}FNaO_2^+$ ($[M+Na]^+$) requires 267.0792; found 267.0790.

Preparation of (*RS*,*RS*)-2-(phenylsulfonyl)-3-phenyloxirane 135

521 **135**

Following a literature procedure,[40] BuLi (2.4 M in hexanes, 1.7 mL, 4.1 mmol) was added to a solution of ^{t}BuOOH (5.0-6.0 M solution in decane, 1.1 mL, 5.6-6.8 mmol) in THF (10 mL) at –78 °C. The resultant solution was stirred at –78 °C for 5 min, then a solution of phenyl (*E*)-styryl sulfone **521** (919 mg, 3.76 mmol, >99:1 dr) in THF (5.0 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 22 h and then solid Na_2SO_3 (400 mg) was added and the mixture was stirred until starch-iodide paper indicated no remaining oxidant. The mixture was then diluted with Et_2O (10 mL), filtered through a pad of Celite (eluent Et_2O) and concentrated *in vacuo*. Purification *via* recrystallisation (MeOH) gave **135** as a white crystalline solid (933 mg, 95%, >99:1 dr);[41] mp 100-102 °C (MeOH) {lit.[41] mp 104-105 °C (CCl_4, petrol)}; δ_H (400 MHz, $CDCl_3$) 4.19 (1H, d, *J* 1.9, OC*H*), 4.60 (1H, d, *J* 1.9, OC*H*) 7.25-7.31 (2H, m, C(3)*Ph*), 7.35-7.41 (3H, m, C(3)*Ph*), 7.62-7.69 (2H, m, SO_2*Ph*), 7.72-7.79 (1H, m, SO_2*Ph*), 7.99-8.03 (2H, m, SO_2*Ph*).

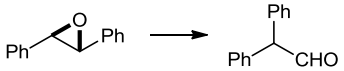
Attempted ring-opening fluorination of (*RS*,*RS*)-2-(phenylsulfonyl)-3-phenyloxirane 135



135 **137**

Following *General Procedure 4*, **135** (250 mg, 0.96 mmol, >99:1 dr) in CH_2Cl_2 (3.8 mL) was treated with BF_3•OEt_2 (40 μL, 0.32 mmol) at –20 °C for 5 min to give a compound tentatively assigned as (*RS*)-2-phenyl-2-(phenylsulfonyl)acetaldehyde **137** as a white solid (228 mg, 91%). Attempted purification of **137** *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) led to decomposition. Data for **137**:[42] δ_H (400 MHz, $CDCl_3$) 4.98 (1H, d, *J* 2.7, C(2)*H*), 7.21-7.51 (7H, m, *Ph*), 7.60-7.69 (3H, m, *Ph*), 10.04 (1H, d, *J* 2.7, C*H*O).

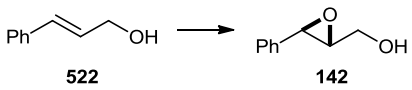
Attempted ring-opening fluorination of (*E*)-stilbene oxide 138



138 **141**

Following *General Procedure 4*, **138** (200 mg, 1.02 mmol, >99:1 dr) in CH_2Cl_2 (4.1 mL) was treated with BF_3•OEt_2 (42 μL, 0.34 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave 2,2-diphenylacetaldehyde **141** as a yellow oil (160 mg, 80%);[43] R_f 0.16 (30-40 °C petrol/Et_2O, 96:4); δ_H (400 MHz, $CDCl_3$) 4.91 (1H, d, *J* 2.4, C(2)*H*), 7.22-7.26 (4H, m, *Ph*), 7.30-7.36 (2H, m, *Ph*), 7.37-7.42 (4H, m, *Ph*), 9.97 (1H, d, *J* 2.4, C*H*O).

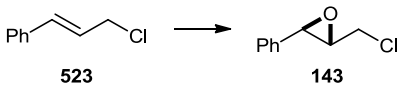
Preparation of (*RS*,*RS*)-2-(hydroxymethyl)-3-phenyloxirane [*trans*-3-phenylglycidol] 142



522 142

m-CPBA (71% with H_2O, 19.9 g, 82.0 mmol) was added to a stirred solution of cinnamyl alcohol **522** (10.0 g, 74.5 mmol, >99:1 dr) in a biphasic mixture of CH_2Cl_2 (300 mL) and satd aq $NaHCO_3$ (200 mL) and the resultant mixture was stirred vigorously at rt for 5 h. The layers were separated and the organic layer was washed sequentially with satd aq Na_2SO_3, until starch-iodide paper indicated no remaining oxidant, and satd aq $NaHCO_3$ (200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave **142** as a pale yellow oil (8.16 g, 73%, >99:1 dr);[44] R_f 0.25 (30-40 °C petrol/EtOAc, 60:40); δ_H (400 MHz, $CDCl_3$) 2.43 (1H, dd, *J* 7.2, 5.4, O*H*), 3.24 (1H, ddd, *J* 4.0, 2.3, 2.1, C(2)*H*), 3.80 (1H, ddd, *J* 12.7, 7.2, 4.0, C(2)CH_A), 3.94 (1H, d, *J* 2.1, C(3)*H*), 4.05 (1H, ddd, *J* 12.7, 5.4, 2.3, C(2)CH_B), 7.27-7.39 (5H, m, *Ph*).

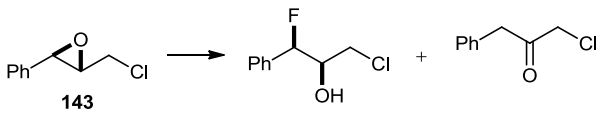
Preparation of (*RS*,*SR*)-2-(chloromethyl)-3-phenyloxirane 143



523 143

Following *General Procedure 3* cinnamyl chloride **523** (0.91 mL, 6.6 mmol, >99:1 dr) in CH_2Cl_2 (33 mL) was treated with *m*-CPBA (71% with H_2O, 2.39 g, 9.83 mmol) for 16 h. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **143** as a colourless oil (945 mg, 86%, >99:1 dr);[21] R_f 0.28 (30-40 °C petrol/Et_2O, 96:4); δ_H (400 MHz, $CDCl_3$) 3.29-3.34 (1H, m, C(2)*H*), 3.36-3.77 (2H, m, CH_2Cl), 3.85 (1H, d, *J* 2.1, C(3)*H*), 7.26-7.41 (5H, m, *Ph*).

Ring-opening fluorination of (*RS*,*SR*)-2-(chloromethyl)-3-phenyloxirane 143

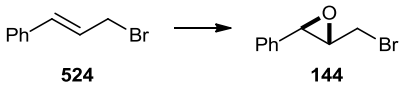


143 149 155

Following *General Procedure 4*, **143** (400 mg, 2.37 mmol, >99:1 dr) in CH_2Cl_2 (9.5 mL) was treated with BF_3•OEt_2 (98 μL, 0.79 mmol) at –20 °C for 5 min to give a 78:22 mixture of **149**:**155**. Purification *via* flash column chromatography (gradient elution, 7→60% Et_2O in 30-40 °C petrol) gave an impure sample of 1-chloro-3-phenylpropan-2-one **155**;[45] R_f 0.47 (30-40 °C petrol/Et_2O, 70:30); δ_H (400 MHz, $CDCl_3$) 3.90 (2H, s, C(3)H_2), 4.13 (2H, s, C(1)H_2), 7.21-7.39 (5H, m, *Ph*). Further elution gave (*RS*,*SR*)-3-chloro-1-fluoro-1-phenylpropan-2-ol **149** as a colourless oil which solidified on standing to a white crystalline solid

(312 mg, 70%, >99:1 dr); R_f 0.30 (30-40 °C petrol/Et_2O, 70:30); mp 31-33 °C; ν_{max} 3417 (O–H), 3111, 3090, 3066, 3036, 3010, 2963, 2935 (C–H), 1496, 1455, 1098, 1076; δ_H (400 MHz, $CDCl_3$) 2.64 (1H, d, *J* 4.3, O*H*), 3.40 (1H, dd, *J* 11.6, 5.6, C(3)H_A), 3.65 (1H, ddd, *J* 11.6, 4.6, 1.3, C(3)H_B), 4.08-4.19 (1H, m, C(2)*H*), 5.58 (1H, dd, *J* 46.9, 5.8, C(1)*H*), 7.35-7.46 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 44.9 (*C*(3)), 74.1 (d, *J* 24.0, *C*(2)), 94.1 (d, *J* 174, *C*(1)), 126.2 (d, *J* 6.4, *o-Ph*), 128.8 (*p-Ph*), 129.3 (*m-Ph*), 136.7 (d, *J* 18.1, *i-Ph*); δ_F (377 MHz, $CDCl_3$) –191.6 (dd, *J* 46.9, 16.2, C(1)*F*); *m*/*z* (FI^+) 188 ($^{35}Cl[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{35}ClFO^+$ ($[M]^+$) requires 188.0399; found 188.0402.

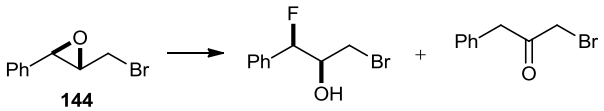
Preparation of (*RS*,*SR*)-2-(bromomethyl)-3-phenyloxirane 144



524 **144**

Following *General Procedure 3*, cinnamyl bromide **524** (1.00 g, 6.09 mmol, >99:1 dr) in CH_2Cl_2 (53 mL) was treated with *m*-CPBA (71% with H_2O, 1.85 g, 7.61 mmol) for 16 h. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **144** as a white crystalline solid (968 mg, 75%, >99:1 dr);[46] R_f 0.28 (30-40 °C petrol/Et_2O, 96:4); mp 45-46 °C {lit.[46] mp 46 °C}; δ_H (400 MHz, $CDCl_3$) 3.33 (1H, app td, *J* 5.8, 1.9, C(2)*H*), 3.52 (1H, app s, C$H_A$$H_B$Br), 3.53 (1H, app s, C$H_A$$H_B$Br), 3.83 (1H, d, *J* 1.9, C(3)*H*), 7.27-7.40 (5H, m, *Ph*).

Ring-opening fluorination of (*RS*,*SR*)-2-(bromomethyl)-3-phenyloxirane 144

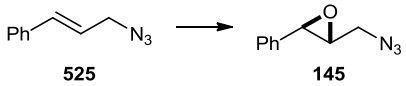


144 **150** **156**

Following *General Procedure 4*, **144** (400 mg, 1.88 mmol, >99:1 dr) in CH_2Cl_2 (7.5 mL) was treated with BF_3•OEt_2 (77 μL, 0.63 mmol) at –20 °C for 5 min to give a 78:22 mixture of **150**:**156**. Purification *via* flash column chromatography (gradient elution, 7→60% Et_2O in 30-40 °C petrol) gave 1-bromo-3-phenylpropan-2-one **156** as a colourless oil (82.9 mg, 21%);[47] R_f 0.48 (30-40 °C petrol/Et_2O, 70:30); δ_H (400 MHz, $CDCl_3$) 3.93 (2H, s, CH_2) 3.96 (2H, s, CH_2), 7.22-7.39 (5H, m, *Ph*). Further elution gave (*RS*,*SR*)-3-bromo-1-fluoro-1-phenylpropan-2-ol **150** as a colourless oil which solidified on standing to a white crystalline solid (314 mg, 72%, >99:1 dr); R_f 0.29 (30-40 °C petrol/Et_2O, 70:30); mp 44-45 °C; ν_{max} 3417 (O–H), 3108, 3089, 3065, 3035, 2969, 2934 (C–H), 1495, 1455, 1095, 1049, 1005; δ_H (400 MHz, $CDCl_3$) 2.68 (1H, d, *J* 4.8, O*H*), 3.23 (1H, dd, *J* 10.9, 5.6, C(3)H_A), 3.50 (1H, ddd, *J* 10.9, 4.4, 1.3, C(3)H_B), 4.06-4.17 (1H, m, C(2)*H*), 5.56 (1H, dd, *J* 46.8, 5.8, C(1)*H*), 7.33-7.47 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.7 (*C*(3)), 73.6 (d, *J* 24.0, *C*(2)), 94.8 (d, *J* 176, *C*(1)), 126.3 (d, *J* 6.4, *o-Ph*), 128.8 (*p-Ph*), 129.3 (*m-Ph*), 135.7 (d, *J* 20.8, *i-Ph*); δ_F (377 MHz,

$CDCl_3$) –190.2 (dd, *J* 47.0, 16.1, C(1)*F*); *m*/*z* (FI^+) 232 ($^{81}Br[M]^+$, 98%), 230 ($^{79}Br[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{79}BrFO^+$ ($[M]^+$) requires 231.9894; found 231.9899.

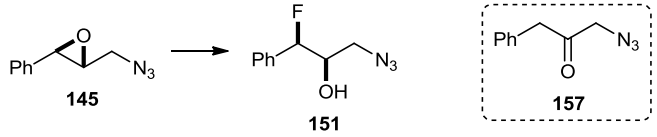
Preparation of (*RS*,*RS*)-2-(azidomethyl)-3-phenyloxirane 145



525 **145**

Following *General Procedure 3*, cinnamyl azide **525** (1.02 g, 6.43 mmol, >99:1 dr) in CH_2Cl_2 (32 mL) was treated with *m*-CPBA (71% with H_2O, 2.34 g, 9.61 mmol) for 24 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **145** as a yellow oil (699 mg, 62%, >99:1 dr);[48] R_f 0.29 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3090, 3066, 3030, 2994, 2923, 2858 (C–H), 2101 (N_3), 1278; δ_H (400 MHz, $CDCl_3$) 3.25 (1H, ddd, *J* 5.1, 3.3, 1.8, C(2)*H*), 3.47 (1H, dd, *J* 13.6, 5.1, C$H_A$$H_B$$N_3$), 3.67 (1H, dd, *J* 13.6, 3.3, C$H_A$$H_B$$N_3$), 3.88 (1H, d, *J* 1.8, C(3)*H*), 7.23-7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 51.7 (*C*H_2N_3), 56.4 (*C*(3)), 60.3 (*C*(2)), 125.7, 128.6, 128.6 (*o*-, *m*-, *p*-*Ph*), 136.1 (*i*-*Ph*); *m*/*z* (FI^+) 175 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_9N_3O^+$ ($[M]^+$) requires 175.0740; found 175.0740.

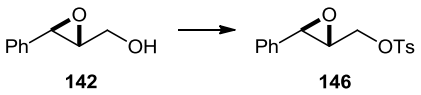
Ring-opening fluorination of (*RS*,*RS*)-2-(azidomethyl)-3-phenyloxirane 145



145 **151** **157**

Following *General Procedure 4*, **145** (400 mg, 2.28 mmol, >99:1 dr) in CH_2Cl_2 (9.1 mL) was treated with BF_3•OEt_2 (94 μL, 0.76 mmol) at –20 °C for 5 min to give a mixture of products containing a 92:8 ratio of **151**:**157**. Purification *via* flash column chromatography (gradient elution, 7→60% Et_2O in 30-40 °C petrol) gave (*RS*,*RS*)-3-azido-1-fluoro-1-phenylpropan-2-ol **151** as a colourless oil (289 mg, 65%, >99:1 dr); R_f 0.26 (30-40 °C petrol/Et_2O, 70:30); ν_{max} 3425 (O–H), 3109, 3090, 3066, 3036, 3012, 2933 (C–H), 2105 (N_3), 1290; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, d, *J* 2.0, O*H*), 3.17 (1H, dd, *J* 12.9, 5.8, C(3)H_A), 3.37 (1H, dd, *J* 12.9, 3.5, C(3)H_B), 4.02-4.13 (1H, m, C(2)*H*), 5.45 (1H, dd, *J* 47.1, 6.6, C(1)*H*), 7.33-7.47 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 52.0 (d, *J* 4.8, *C*(3)), 74.0 (d, *J* 24.0, *C*(2)), 94.8 (d, *J* 174, *C*(1)), 126.3 (d, *J* 6.4, *o*-*Ph*), 128.8 (*p*-*Ph*), 129.3 (*m*-*Ph*), 135.6 (d, *J* 20.8, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –189.0 (dd, *J* 47.0, 16.1, C(1)*F*); *m*/*z* (FI^+) 195 ($[M]^+$, 31%), 175 ($[M–HF]^+$, 100%), 167 ($[M–N_2]^+$, 23%); HRMS (FI^+) $C_9H_{10}FN_3O^+$ ($[M]^+$) requires 195.0802; found 195.0805. Data for 1-azido-3-phenylpropan-2-one **157**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.75 (2H, s, C(3)H_2), 3.98 (2H, s, C(1)H_2).

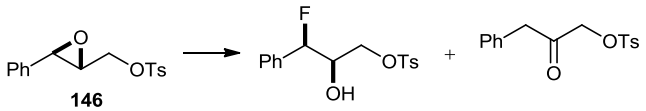
Preparation of ((*RS*,*RS*)-2-(*p*-toluenesulfonyloxymethyl)-3-phenyloxirane 146



142 **146**

TsCl (1.36 g, 7.13 mmol) was added to a stirred solution of **142** (1.02 g, 6.79 mmol, >99:1 dr), Et_3N (2.8 mL, 20 mmol) and DMAP (16.6 mg, 2 mol%) in CH_2Cl_2 (11 mL) at 0 °C and the resultant mixture was stirred at this temperature for 3 h, then allowed to warm to rt over 20 h. H_2O (20 mL) was added and the organic layer was separated then washed sequentially with 1 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **146** as a colourless oil which solidified on standing to a white solid (1.68 g, 81%, >99:1 dr);[49] R_f 0.26 (30-40 °C petrol/EtOAc, 80:20); mp 59-60 °C {lit.[49] mp 66-68 °C}; δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, *Me*), 3.23-3.26 (1H, m, C(2)*H*), 3.76 (1H, d, *J* 1.9, C(3)*H*), 4.14 (1H, dd, *J* 11.5, 5.5, C(2)CH_A), 4.34 (1H, dd, *J* 11.5, 3.6, C(2)CH_B), 7.19-7.39 (7H, m, *Ar*, *Ph*), 7.81-7.85 (2H, m, *Ar*).

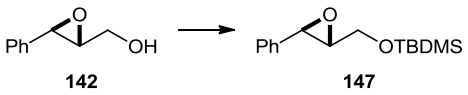
Ring-opening fluorination of ((*RS*,*RS*)-2-(*p*-toluenesulfonyloxymethyl)-3-phenyloxirane 146



146 **152** **158**

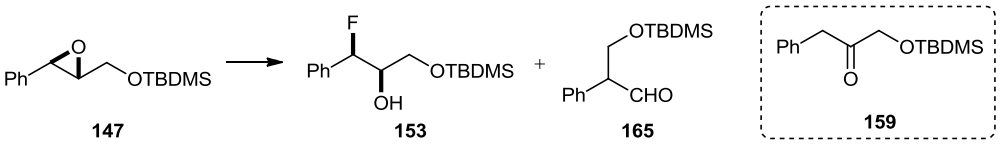
Following *General Procedure 4*, **146** (390 mg, 1.28 mmol, >99:1 dr) in CH_2Cl_2 (5.1 mL) was treated with BF_3•OEt_2 (53 μL, 0.43 mmol) at –20 °C for 5 min to give a 84:16 mixture of **152**:**158**. Purification *via* flash column chromatography (gradient elution, 6→70% EtOAc in 30-40 °C petrol) gave 1-(*p*-toluenesulfonyloxy)-3-phenylpropan-2-one **158** as a colourless oil (62.3 mg, 16%);[50] R_f 0.38 (30-40 °C petrol/EtOAc, 70:30); δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, *Me*), 3.81 (2H, s, CH_2), 4.56 (2H, s, CH_2), 7.13-7.42 (7H, m, *Ph*, *Ar*), 7.76-7.85 (2H, m, *Ar*). Further elution gave (*RS*,*RS*)-1-fluoro-1-phenyl-3-(*p*-toluenesulfonyloxy)propan-2-ol **152** as a colourless oil (349 mg, 84%, >99:1 dr); R_f 0.27 (30-40 °C petrol/EtOAc, 70:30); $C_{16}H_{17}FO_4S$ requires C, 59.2; H, 5.3%; found C, 59.3; H, 5.2%; ν_{max} 3521 (O–H), 3091, 3066, 3036, 2955, 2926 (C–H), 1598, 1455, 1360, 1190, 1176, 1097, 988; δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, *Me*), 3.90-3.97 (1H, m, C(3)H_A), 4.07-4.17 (2H, m, C(2)*H*, C(3)H_B), 5.48 (1H, dd, *J* 46.6, 5.1, C(1)*H*), 7.29-7.41 (7H, m, *Ph*, *Ar*), 7.77-7.80 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (*Me*), 69.3 (d, *J* 6.3, *C*(3)), 72.3 (d, *J* 23.7, *C*(2)), 93.1 (d, *J* 175, *C*(1)), 126.1 (d, *J* 7.1, *o-Ph*), 128.0 (*Ar*), 128.8 (*m-Ph*), 129.2 (d, *J* 1.4, *p-Ph*), 130.0 (*Ar*), 132.3 (*Ar*), 135.3 (d, *J* 19.2, *i-Ph*), 145.2 (*Ar*); δ_F (377 MHz, $CDCl_3$) –192.3 (dd, *J* 46.6, 19.2, C(1)*F*); *m*/*z* (FI^+) 324 ($[M]^+$, 19%), 306 ($[M–F]^+$, 100%), 304 ($[M–HF]^+$, 100%); HRMS (FI^+) $C_{16}H_{17}FO_4S^+$ ($[M]^+$) requires 324.0826; found 324.0837.

Preparation of (*RS*,*RS*)-2-(*tert*-butyldimethylsilyloxymethyl)-3-phenyloxirane 147



TBDMSCl (435 mg, 2.89 mmol) was added to a stirred solution of **142** (434 mg, 2.89 mmol, >99:1 dr), imidazole (295 mg, 4.33 mmol) and DMAP (7.1 mg, 2 mol%) in CH_2Cl_2 (7.2 mL) and the resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and washed with 1 M aq HCl (10 mL), then dried and concentrated *in vacuo* to give **147** as a colourless oil (725 mg, 95%, >99:1 dr);[21] δ_H (400 MHz, $CDCl_3$) 0.11 (3H, s, Si*Me*$_A$), 0.12 (3H, s, Si*Me*$_B$), 0.93 (9H, s, SiC*Me*$_3$), 3.16 (1H, ddd, *J* 4.4, 3.1, 2.1, C(2)*H*), 3.82 (1H, d, *J* 2.1, C(3)*H*), 3.83 (1H, dd, *J* 12.3, 4.4, C(2)C*H*$_A$), 3.98 (1H, dd, *J* 12.3, 3.1, C(2)C*H*$_B$), 7.27-7.39 (5H, m, *Ph*).

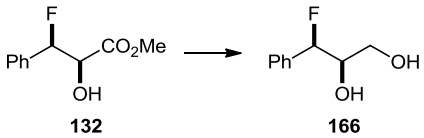
Ring-opening fluorination of (*RS*,*RS*)-2-(*tert*-butyldimethylsilyloxymethyl)-3-phenyloxirane 147



Following *General Procedure 4*, **147** (2.00 g, 7.56 mmol, >99:1 dr) in CH_2Cl_2 (30 mL) was treated with BF_3•OEt_2 (0.31 mL, 2.5 mmol) at –20 °C for 5 min to give a 35:10:55 mixture of **153**:**159**:**165**. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave 3-(*tert*-butyldimethylsilyloxy)-2-phenylpropanal **165** as a pale yellow oil (829 mg, 41%);[51] R_f 0.45 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, Si*Me*$_A$), 0.02 (3H, s, Si*Me*$_B$), 0.86 (9H, s, SiC*Me*$_3$), 3.76 (1H, ddd, *J* 7.5, 5.7, 2.0, C(2)*H*), 3.98 (1H, dd, *J* 10.2, 5.7, C(3)*H*$_A$), 4.26 (1H, dd, *J* 10.2, 7.5, C(3)*H*$_B$), 7.21-7.41 (5H, m, *Ph*), 9.84 (1H, d, *J* 2.0, C*H*O). Further elution gave an impure sample of 1-(*tert*-butyldimethylsilyloxy)-3-phenylpropan-2-one **159**; R_f 0.34 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, Si*Me*$_2$), 0.94 (9H, s, SiC*Me*$_3$), 3.83 (2H, s, C(3)*H*$_2$), 4.26 (2H, s, C(1)*H*$_2$), 7.20-7.50 (5H, m, *Ph*). Further elution gave (*RS*,*RS*)-3-(*tert*-butyldimethylsilyloxy)-1-fluoro-1-phenylpropan-2-ol **153** as a colourless oil (659 mg, 31%, >99:1 dr); R_f 0.16 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3443 (O–H), 3090, 3066, 3035, 2955, 2930, 2885, 2858 (C–H), 1256, 1119; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*), 0.91 (9H, s, SiC*Me*$_3$), 2.52 (1H, br s, O*H*), 3.50 (1H, dd, *J* 10.3, 5.3, C(3)*H*$_A$), 3.65 (1H, ddd, *J* 10.3, 4.7, 1.6, C(3)*H*$_B$), 3.88-3.98 (1H, m, C(2)*H*), 5.51 (1H, dd, *J* 47.7, 5.8, C(1)*H*), 7.30-7.46 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.5 (Si*Me*), –5.4 (Si*Me*), 18.3 (Si*C*Me$_3$), 25.9 (SiC*Me*$_3$), 62.9 (d, *J* 6.4, *C*(3)), 74.6 (d, *J* 22.4, *C*(2)), 94.1 (d, *J* 174, *C*(1)), 126.3 (d, *J* 8.0, *o*-*Ph*), 128.5 (*m*-*Ph*), 128.8 (*p*-*Ph*), 136.8 (d, *J* 20.8, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –191.6 (dd, *J* 47.7, 18.4, C(1)*F*);

m/*z* (FI^+) 227 ($[M–C_4H_9]^+$, 100%); HRMS (FI^+) $C_{11}H_{16}FO_2Si^+$ ($[M–C_4H_9]^+$) requires 227.0898; found 227.0828.

Preparation of (*RS*,*RS*)-1-fluoro-1-phenylpropane-2,3-diol 166



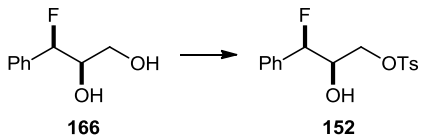
132 **166**

$NaBH_4$ (76.4 mg, 2.02 mmol) was added portionwise to a stirred solution of **132** (200 mg, 1.01 mmol, >99:1 dr) in MeOH (2.5 mL) at 0 °C and the resultant mixture was stirred at 0 °C until effervescence had ceased. The reaction mixture was allowed to warm to rt over 46 h and was then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→10% MeOH in CH_2Cl_2) gave **166** as a colourless oil (139 mg, 81%, >99:1 dr); R_f 0.16 (CH_2Cl_2/MeOH, 95:5); ν_{max} 3376 (O–H), 3091, 3065, 3035, 2936, 2887 (C–H), 1455, 1103, 1041; δ_H (400 MHz, $CDCl_3$) 2.91 (2H, br s, 2 × O*H*), 3.46 (1H, dd, *J* 11.9, 5.7, C(1)H_A), 3.60 (1H, ddd, *J* 11.9, 3.5, 1.6, C(1)H_B), 3.98 (1H, dddd, *J* 15.9, 6.8, 5.7, 3.5, C(2)*H*), 5.46 (1H, dd, *J* 47.9, 6.8, C(3)*H*), 7.28-7.44 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 62.3 (d, *J* 6.4 Hz, *C*(1)), 75.0 (d, *J* 22.4 Hz, *C*(2)), 94.9 (d, *J* 173 Hz, *C*(3)), 126.4 (d, *J* 6.4, *o*-*Ph*), 128.7 (*m*-*Ph*), 129.1 (*p*-*Ph*), 136.2 (d, *J* 19.2, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –188.2 (dd, *J* 47.9, 16.1, C(1)*F*); *m*/*z* (FI^+) 170 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{11}FO_2^+$ ($[M]^+$) requires 170.0738; found 170.0741.

153 **166**

TBAF (1.0 M in THF, 3.5 mL, 3.5 mmol) was added to **153** (659 mg, 2.32 mmol, >99:1 dr) and the resultant mixture was stirred at rt for 12 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→10% MeOH in CH_2Cl_2) gave **166** as a colourless oil (305 mg, 77%, >99:1 dr).

Preparation of (*RS*,*RS*)-1-fluoro-1-phenyl-3-(*p*-toluenesulfonyloxy)propan-2-ol 152

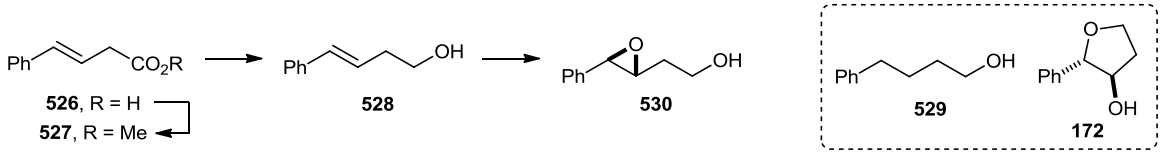


166 **152**

TsCl (40.1 mg, 0.21 mmol) was added to a stirred solution of **166** (35.8 mg, 0.21 mmol, >99:1 dr), Et_3N (88 μL, 0.63 mmol) and DMAP (1 crystal) in CH_2Cl_2 (0.4 mL) at 0 °C and the resultant mixture was stirred

at this temperature for 30 min, then allowed to warm to rt over 17 h. H_2O (5 mL) and CH_2Cl_2 (10 mL) were added and the organic phase was separated then washed sequentially with 1 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 6→70% EtOAc in 30-40 °C petrol) gave **152** as a colourless oil (35.4 mg, 52%, >99:1 dr).

Preparation of (*RS*,*RS*)-2-(hydroxyethyl)-3-phenyloxirane 530



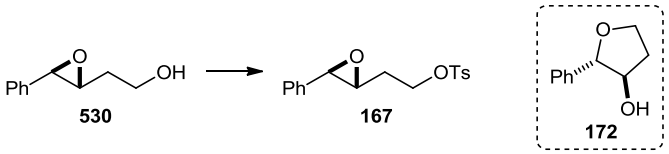
Step 1: H_2SO_4 (1 drop) was added to a solution of (*E*)-styrylacetic acid **526** (1.00 g, 6.17 mmol, >99:1 dr) and MeOH (1.3 mL, 31 mmol) in CH_2Cl_2 (30 mL) and the resultant mixture was heated at reflux for 24 h. The mixture was allowed to cool to rt and was washed sequentially with H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL), then dried, filtered through a pad of silica gel (eluent CH_2Cl_2) and concentrated *in vacuo* to give methyl (*E*)-4-phenylbut-3-enoate **527** as a yellow oil (1.04 g, 95%, >99:1 dr);[52] δ_H (400 MHz, $CDCl_3$) 3.27 (2H, dd, *J* 7.2, 1.4, C(2)H_2), 3.73 (3H, s, O*Me*), 6.27-6.36 (1H, m, C(3)*H*), 6.50 (1H, d, *J* 16.0, C(4)*H*), 7.22-7.42 (5H, m, *Ph*).

Step 2: $LiBH_4$ (2.0 M in THF, 27 mL, 54 mmol) was added dropwise to a stirred solution of **527** (4.34 g, 24.6 mmol, >99:1 dr) in THF (120 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 20 h. The mixture was then cooled to 0 °C and satd aq NH_4Cl (60 mL) was added dropwise (*cautiously!*). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave a 95:5 mixture of **528**:**529**. Data for (*E*)-4-phenylbut-3-en-1-ol **528**:[53] R_f 0.36 (30-40 °C petrol/EtOAc, 60:40); δ_H (400 MHz, $CDCl_3$) 2.50 (2H, dtd, *J* 7.1, 6.3, 1.3, C(2)H_2), 3.77 (2H, t, *J* 6.3, C(1)H_2), 6.22 (1H, dt, *J* 15.9, 7.1, C(3)*H*), 6.52 (1H, d, *J* 15.9, C(4)*H*), 7.18-7.40 (5H, m, *Ph*). Data for 4-phenylbutan-1-ol **529**:[54] δ_H (400 MHz, $CDCl_3$) 1.58-1.77 (4H, m, C(2)H_2, C(3)H_2), 2.66 (2H, t, *J* 7.5, C(4)H_2), 3.67 (2H, t, *J* 6.4, C(1)H_2), 7.18-7.35 (5H, m, *Ph*).

Step 3: Following *General Procedure 3*, a 95:5 mixture of **528**:**529** (2.76 g, 17.7 mmol of **528**) in CH_2Cl_2 (89 mL) was treated with *m*-CPBA (71% with H_2O, 6.45 g, 26.6 mmol) for 18 h. Purification *via* flash column chromatography (gradient elution, 12→100% EtOAc in 30-40 °C petrol) gave a 75:25 mixture of **530**:**172** as a colourless oil (2.55 g, 88% combined from **528**); R_f 0.39 (30-40 °C petrol/EtOAc, 50:50). Data

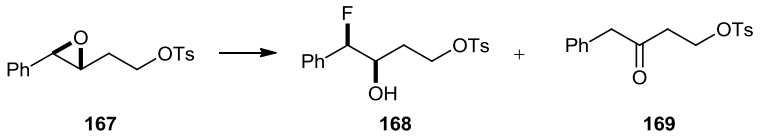
for **530**:[55] δ_H (400 MHz, $CDCl_3$) 1.81-2.25 (2H, obsc m, CH_2CH_2OH), 3.16 (1H, ddd, *J* 6.4, 4.4, 2.2, C(2)*H*), 3.74 (1H, d, *J* 2.2, C(3)*H*), 3.84-3.92 (2H, m, CH_2OH), 7.24-7.39 (5H, obsc m, *Ph*).

Preparation of ((*RS*,*RS*)-2-(*p*-toluenesulfonyloxyethyl)-3-phenyloxirane 167



TsCl (435 mg, 2.28 mmol) was added to a stirred solution of a 75:25 mixture of **530**:**172** (500 mg, 2.28 mmol of **530**), Et_3N (0.96 mL, 6.9 mmol) and DMAP (5.6 mg, 2 mol%) in CH_2Cl_2 (3.8 mL) at 0 °C and the resultant mixture was stirred at this temperature for 3 h, then was allowed to warm to rt over 21 h. H_2O (10 mL) was added and the organic layer was separated then washed sequentially with 1 M aq HCl (10 mL), H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **167** as a colourless oil which solidified on standing to a white solid (508 mg, 70% from **530**, >99:1 dr); mp 45-47 °C; ν_{max} 3089, 3065, 3032, 2985, 2925 (C–H), 1359, 1177 (S=O); δ_H (400 MHz, $CDCl_3$) 1.91-2.01 (1H, m, C(2)CH_AH$_B$), 2.08-2.19 (1H, m, C(2)CH$_A$$H_B$), 2.44 (3H, s, *Me*), 2.94-2.99 (1H, m, C(2)*H*), 3.63 (1H, d, *J* 1.8, C(3)*H*), 4.17-4.28 (2H, m, CH_2OTs), 7.18-7.24 (2H, m, *Ar*), 7.28-7.37 (5H, m, *Ph*), 7.76-7.81 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (*Me*), 32.0 (C(2)*C*H$_2$), 58.5, 59.1 (*C*(2), *C*(3)), 67.0 (*C*H$_2$OTs), 125.6, 127.9, 128.3, 128.5, 128.9, 132.8, 136.8, 145.0 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 659 ([2M+Na]$^+$, 100%), 341 ([M+Na]$^+$, 36%); HRMS (ESI$^+$) $C_{17}H_{18}NaO_4S^+$ ([M+Na]$^+$) requires 341.0818; found 341.0811.

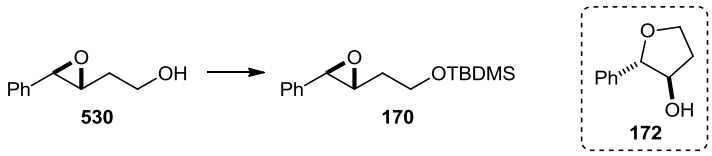
Ring-opening fluorination of ((*RS*,*RS*)-2-(*p*-toluenesulfonyloxyethyl)-3-phenyloxirane 167



Following *General Procedure 4*, **167** (440 mg, 1.38 mmol, >99:1 dr) in CH_2Cl_2 (5.5 mL) was treated with BF_3•OEt_2 (57 μL, 0.46 mmol) at –20 °C for 5 min to give a 94:6 mixture of **168**:**169**. Purification *via* flash column chromatography (gradient elution, 7→60% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*)-1-fluoro-1-phenyl-4-(*p*-toluenesulfonyloxy)butan-2-ol **168** as a colourless oil (399 mg, 85%, >99:1 dr); R_f 0.26 (30-40 °C petrol/EtOAc, 70:30); ν_{max} 3533 (O–H), 3090, 3066, 3035, 2962, 2926 (C–H), 1357, 1176 (S=O); δ_H (400 MHz, $CDCl_3$) 1.63-1.77 (2H, m, C(3)H_2), 2.44 (3H, s, *Me*), 3.97-4.07 (1H, m, C(2)*H*), 4.10-4.18 (1H, m, C(4)H_A), 4.19-4.26 (1H, m, C(4)H_B), 5.21 (1H, dd, *J* 47.1, 6.1, C(1)*H*), 7.25-7.43 (7H, m, *Ar*, *Ph*), 7.74-7.79 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (*Me*), 31.2 (d, *J* 6.4, *C*(3)), 67.0 (*C*(4)), 70.3 (d, *J* 24.0,

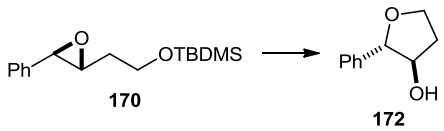
C(2)), 96.9 (d, *J* 174, *C*(1)), 126.5 (d, *J* 6.4), 127.9, 128.7, 129.2, 129.9, 132.8, 135.9 (d, *J* 20.8), 144.9 (*Ar*, *Ph*); δ_F (377 MHz, $CDCl_3$) –184.9 (dd, *J* 47.1, 17.2, C(1)*F*); *m*/*z* (ESI$^+$) 699 ([2M+Na]$^+$, 79%), 361 ([M+Na]$^+$, 78%), 328 (100%); HRMS (ESI$^+$) $C_{17}H_{19}FNaO_4S^+$ ([M+Na]$^+$) requires 361.0880; found 361.0875. Data for 1-(*p*-toluenesulfonyloxy)-4-phenylpropan-3-one **169**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.83 (2H, app td, *J* 6.3, 0.8, C(2)H_2), 3.68 (2H, s, C(4)H_2).

Preparation of (*RS*,*RS*)-2-(*tert*-butyldimethylsilyloxyethyl)-3-phenyloxirane 170



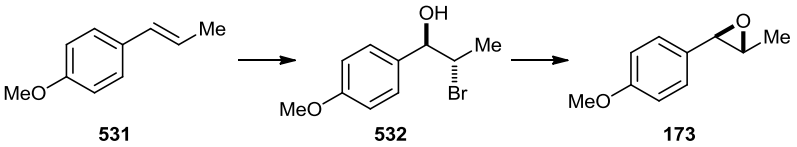
TBDMSCl (344 mg, 2.28 mmol) was added to a stirred solution of a 75:25 mixture of **530**:**172** (500 mg, 2.28 mmol of **530**), imidazole (233 mg, 3.43 mmol) and DMAP (5.6 mg, 2 mol%) in CH_2Cl_2 (23 mL) and the resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and washed with 1 M aq HCl (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **170** as a colourless oil (306 mg, 48% from **530**, >99:1 dr); ν_{max} 3089, 3066, 3030, 2955, 2929, 2885, 2857 (C–H), 1471, 1463, 1255, 1099; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, Si*Me*$_2$), 0.91 (9H, s, SiC*Me*$_3$), 1.81-1.91 (1H, m, C(2)CH_A), 1.92-2.02 (1H, m, C(2)CH_B), 3.11 (1H, ddd, *J* 6.4, 4.7, 2.0, C(2)*H*), 3.69 (1H, d, *J* 2.0, C(3)*H*), 3.81-3.86 (2H, m, CH_2OTBDMS), 7.24-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.4 (Si*Me*$_A$), –5.3 (Si*Me*$_B$), 18.3 (Si*C*Me$_3$), 25.9 (SiC*Me*$_3$), 35.7, 58.7 (*C*(3)), 59.8 (*C*(2)), 60.7 (*C*H$_2$OTBDMS), 125.6 (*p*-*Ph*), 128.0, 128.5 (*o*-, *m*-*Ph*), 137.8 (*i*-*Ph*); *m*/*z* (ESI$^+$) 579 ([2M+Na]$^+$, 100%), 301 ([M+Na]$^+$, 33%), 279 ([M+H]$^+$, 14%); HRMS (ESI$^+$) $C_{16}H_{27}O_2Si^+$ ([M+H]$^+$) requires 279.1775; found 279.1769.

Attempted ring-opening fluorination of (*RS*,*RS*)-2-(*tert*-butyldimethylsilyloxyethyl)-3-phenyloxirane 170



Following *General Procedure 4*, **170** (277 mg, 0.99 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL) was treated with BF_3•OEt_2 (41 μL, 0.33 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 12→100% EtOAc in 30-40 °C petrol) gave (*RS*,*SR*)-2-phenyltetrahydrofuran-3-ol **172** as a pale yellow oil (143 mg, 88%, >99:1 dr);[56] δ_H (400 MHz, $CDCl_3$) 1.90-2.00 (1H, m, C(4)H_A), 2.06-2.24 (2H, m, C(4)H_B, O*H*), 4.10-4.32 (3H, m, C(3)*H*, C(5)H_2), 4.79 (1H, d, *J* 3.2, C(2)*H*), 7.25-7.39 (5H, m, *Ph*).

Preparation of (*RS*,*RS*)-2-(4′-methoxyphenyl)-3-methyloxirane 173

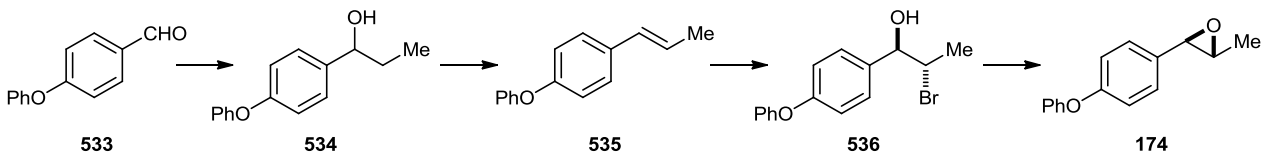


531 **532** **173**

Step 1: 40% aq HBF_4 (5.7 mL, 34 mmol) and H_2O (10 mL) were added to a stirred solution of (*E*)-anethole **531** (5.1 mL, 34 mmol, >99:1 dr) in acetone (150 mL) at 0 °C. *N*-Bromosuccinimide (9.01 g, 50.6 mmol) was then added portionwise and the resultant mixture was warmed to rt over 30 min. Satd aq $Na_2S_2O_3$ (100 mL) was then added and the acetone was removed *in vacuo*. The mixture was partitioned between Et_2O (150 mL) and H_2O (250 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 150 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 150 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (*RS*,*SR*)-2-bromo-1-(4′-methoxyphenyl)propan-1-ol **532** as a colourless oil (7.98 g, 97%, 96:4 dr);[57] R_f 0.30 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 1.56 (3H, d, *J* 6.8, C(3)*H*$_3$), 2.42 (1H, br s, O*H*), 3.82 (3H, s, O*Me*), 4.35-4.43 (1H, m, C(2)*H*), 4.94-4.98 (1H, m, C(1)*H*), 6.90 (2H, d, *J* 8.4, *Ar*), 7.30 (2H, d, *J* 8.4, *Ar*). Data for minor diastereoisomer:[57] δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.90 (3H, s, O*Me*), 4.58 (1H, dd, *J* 8.1, 2.3, C(1)*H*).

Step 2: K_2CO_3 (5.00 g, 32.6 mmol) was added to a stirred solution of **532** (7.98 g, 32.6 mmol, >99:1 dr) in MeOH (82 mL) and the resultant mixture was stirred at rt for 1 h then filtered and concentrated *in vacuo*. The residue was partitioned between Et_2O (150 mL) and H_2O (300 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **173** as a colourless oil (5.21 g, 97%, 96:4 dr);[57] δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 5.1, C(3)*Me*), 3.04 (1H, qd, *J* 5.1, 2.1, C(3)*H*), 3.54 (1H, d, *J* 2.1, C(2)*H*), 3.80 (3H, s, O*Me*), 6.86-6.90 (2H, m, C(3′)*H*, C(5′)*H*)), 7.16-7.21 (2H, m, C(2′)*H*, C(6′)*H*)). Data for *cis*-epoxide:[57] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.10 (3H, d, *J* 5.5, C(3)*Me*), 3.28-3.35 (1H, m, C(3)*H*), 3.90 (3H, s, O*Me*), 4.03 (1H, d, *J* 4.1, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(4′-phenoxyphenyl)-3-methyloxirane 174



533 **534** **535** **536** **174**

Step 1: Following *General Procedure 5*, 4-phenoxybenzaldehyde **533** (5.00 g, 25.2 mmol) in Et_2O (84 mL) was treated with EtMgBr (3.0 M in Et_2O, 9.3 mL, 28 mmol) for 72 h to give crude

(*RS*)-1-(4′-phenoxyphenyl)propan-1-ol **534** as a yellow oil (5.76 g); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, app t, *J* 7.4, C(3)H_3), 1.70-1.90 (3H, m, C(2)H_2, O*H*), 4.60 (1H, app t, *J* 6.6, C(1)*H*), 6.97-7.04 (4H, m, *Ar*), 7.08-7.14 (1H, m, *Ar*), 7.29-7.37 (4H, m, *Ar*).

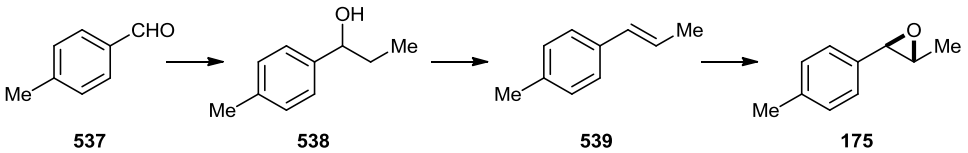
Step 2: Following *General Procedure 6*, crude **534** (5.76 g) in PhMe (36 mL) was treated with dry TsOH (130 mg, 0.76 mmol). Purification *via* flash column chromatography (30-40 °C petrol) gave (*E*)-4′-phenoxy-β-methylstyrene **535** as a colourless oil (2.65 g, 50% over 2 steps, 94:6 dr);[58] R_f 0.35 (30-40 °C petrol); ν_{max} 3026, 2962, 2932, 2913, 2880, 2731 (C−H), 1505, 1487, 1232; δ_H (400 MHz, $CDCl_3$) 1.92 (3H, dd, *J* 6.6, 1.5, C(β)*Me*), 6.20 (1H, dq, *J* 15.7, 6.6, C(β)*H*), 6.42 (1H, d, *J* 15.7, C(α)*H*), 6.94-7.17 (5H, m, *Ar*), 7.29-7.41 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(β)*Me*), 118.7, 119.1, 123.1, 124.9, 127.1, 129.7, 130.2, 133.4, 156.0, 157.4 (*C*(α), *C*(β), *Ar*); *m*/*z* (GC ToF CI^+) 211 ($[M+H]^+$, 100%); HRMS (GC ToF CI^+) $C_{15}H_{15}O^+$ ($[M+H]^+$) requires 211.1117; found 211.1144. Data for (*Z*)-alkene:[58] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.95 (3H, dd, *J* 7.3, 1.8, C(β)*Me*), 5.75-5.85 (1H, m, C(3)*H*).

Step 3: 40% aq HBF_4 (1.92 mL, 12.2 mmol) and H_2O (4.0 mL) were added dropwise to a stirred solution of **535** (2.57 g, 12.2 mmol, 94:6 dr) in acetone (57 mL) at 0 °C. *N*-Bromosuccinimide (3.26 g, 18.3 mmol) was then added portionwise and the resultant mixture was warmed to rt over 30 min. Satd aq $Na_2S_2O_3$ (40 mL) was then added and the acetone was removed *in vacuo*. The mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 80:20) gave (*RS*,*SR*)-2-bromo-1-(4′-phenoxyphenyl)propan-1-ol **536** as a pale yellow oil (3.58 g, 96%, 96:4 dr); R_f 0.26 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3435 (O−H), 3039, 2978, 2928, 2871 (C−H), 1488, 1233, 748; δ_H (400 MHz, $CDCl_3$) 1.58 (3H, d, *J* 6.8, C(3)H_3), 2.54 (1H, br s, O*H*), 4.42 (1H, qd, *J* 6.7, 3.5, C(2)*H*), 5.00 (1H, app t, *J* 3.2, C(3)*H*), 6.98-7.06 (4H, m, *Ar*), 7.10-7.17 (1H, m, *Ar*), 7.32-7.40 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.9 (*C*(3)), 56.2 (*C*(2)), 76.9 (*C*(1)), 118.5, 119.1, 123.5, 127.9, 129.8, 134.3, 156.9, 157.1 (*Ar*); *m*/*z* (FI^+) 306 ($[M(^{81}Br)]^+$, 99%), 308 ($[M(^{79}Br)]^+$, 100%); HRMS (FI^+) $C_{10}H_{13}{}^{79}BrO^+$ ($[M]^+$) requires 306.0250; found 306.0249. Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.33 (1H, app quin, *J* 7.0, C(2)*H*), 4.62 (1H, dd, *J* 7.8, 3.0, C(3)*H*).

Step 4: K_2CO_3 (276 mg, 2.00 mmol) was added to a stirred solution of **536** (614 mg, 2.00 mmol, 96:4 dr) in MeOH (10 mL) and the resultant mixture was stirred at rt for 2 h then filtered and concentrated *in vacuo*. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **174** as a pale yellow oil (422 mg, 93%, 96:4 dr); ν_{max} 3040, 2986, 2927 (C−H), 1508, 1489,

1230, 839, 749, 691; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 5.2, C(3)*Me*), 3.06 (1H, qd, *J* 5.2, 2.0, C(3)*H*), 3.58 (1H, d, *J* 2.0, C(2)*H*), 6.96-7.06 (4H, m, *Ar*), 7.08-7.16 (1H, m, *Ar*), 7.21-7.27 (2H, m, *Ar*), 7.31-7.38 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 58.9 (*C*(3)), 59.2 (*C*(2)), 118.9, 123.4, 127.1, 129.8, 132.5, 157.1, 157.2 (*Ar*); *m*/*z* (FI^+) 226 ($[M]^+$, 100%); HRMS (FI^+) $C_{15}H_{14}O_2^+$ ($[M]^+$) requires 226.0988; found 226.1005. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.13 (3H, d, *J* 5.6, C(3)*Me*), 3.31-3.38 (1H, m, C(3)*H*), 4.06 (1H, d, *J* 4.0, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(*p*-tolyl)-3-methyloxirane 175



537 **538** **539** **175**

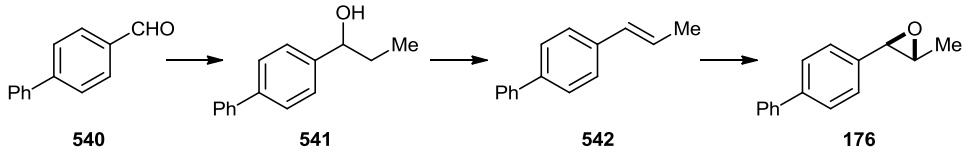
Step 1: Following *General Procedure 5*, *p*-tolualdehyde **537** (6.9 mL, 58 mmol) in Et_2O (194 mL) was treated with EtMgBr (3.0 M in Et_2O, 21 mL, 63 mmol) for 26 h to give crude (*RS*)-1-(4′-methylphenyl)propan-1-ol **538** as a pale yellow oil (8.76 g);[59] δ_H (400 MHz, $CDCl_3$) 0.92 (3H, app t, *J* 7.3, C(3)H_3), 1.67-1.90 (3H, m, C(2)H_2, O*H*), 2.36 (3H, s, C(4′)*Me*), 4.57 (1H, app t, *J* 6.7, C(1)*H*), 7.14-7.20 (2H, m, C(3′)*H*, C(5′)*H*), 7.22-7.27 (2H, m, C(2′)*H*, C(6′)*H*).

Step 2: Following *General Procedure 6*, crude **538** (8.76 g) in PhMe (80 mL) was treated with dry TsOH (305 mg, 1.78 mmol). Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-4′-methyl-β-methylstyrene **539** as a colourless oil (4.66 g, 61% over 2 steps, 95:5 dr);[60] bp 47-49 °C (2.2 mmHg) {lit.[60] bp 58 °C (4 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.88 (3H, dd, *J* 6.5, 1.5, C(β)*Me*), 2.33 (3H, s, C(4′)*Me*), 6.20 (1H, dq, *J* 15.8, 6.5, C(β)*H*), 6.38 (1H, app dd, *J* 15.8, 1.5, C(α)*H*), 7.09-7.14 (2H, m, C(3′)*H*, C(5′)*H*), 7.22-7.26 (2H, m, C(2′)*H*, C(6′)*H*). Data for (*Z*)-alkene:[60] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.91 (3H, dd, *J* 7.2, 2.1, C(β)*Me*), 2.36 (3H, s, C(4′)*Me*), 5.76 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **539** (4.66 g, 35.3 mmol, 95:5 dr) in CH_2Cl_2 (177 mL) was treated with *m*-CPBA (74% with H_2O, 12.4 g, 52.9 mmol) for 17 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **175** as a colourless oil (2.92 g, 56%, 90:10 dr); bp 66-72 °C (2.2 mmHg) {lit.[61] bp 76-80 °C (2.5 mmHg)}; ν_{max} 2986, 2926, 2865 (C–H), 1518, 1021, 865, 809; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 5.1, C(3)*Me*), 2.36 (3H, s, C(4′)*Me*), 3.05 (1H, qd, *J* 5.1, 2.0, C(3)*H*), 3.56 (1H, d, *J* 2.0, C(2)*H*), 7.13-7.24 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 21.2 (C(4′)*Me*), 58.9, 59.6 (*C*(2), *C*(3)), 125.6, 129.2 (*C*(2′), *C*(3′), *C*(5′), *C*(6′)), 134.7, 137.8 (*C*(1′), *C*(4′)); *m*/*z* (GC ToF CI^+) 166 ($[M+NH_4]^+$, 100%); HRMS (GC ToF CI^+) $C_{10}H_{16}NO^+$ ($[M+NH_4]^+$) requires 166.1226; found 166.1225. Data for *cis*-epoxide:[62]

δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.11 (3H, d, *J* 5.3, C(3)*Me*), 2.38 (3H, s, C(4′)*Me*), 3.31-3.37 (1H, m, C(3)*H*), 4.05 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(biphenyl-4′-yl)-3-methyloxirane 176



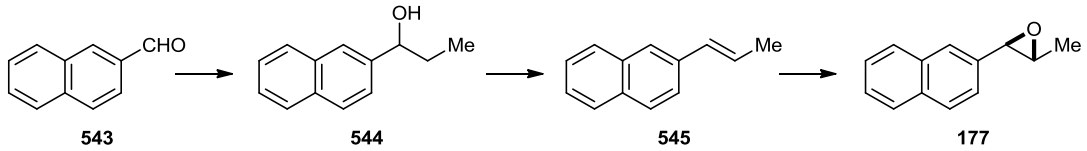
540 **541** **542** **176**

Step 1: Following *General Procedure 5*, biphenyl-4-carboxaldehyde **540** (5.00 g, 27.4 mmol) in Et_2O (92 mL) was treated with EtMgBr (3.0 M in Et_2O, 10 mL, 30 mmol) for 27 h to give crude (*RS*)-1-(biphenyl-4′-yl)propan-1-ol **541** as a white solid (5.83 g);[63] δ_H (400 MHz, $CDCl_3$) 0.97 (3H, app t, *J* 7.3, C(3)H_3), 1.75-1.93 (3H, m, C(2)H_2, O*H*), 4.63-4.70 (1H, m, C(1)*H*), 7.33-7.49 (5H, m, *Ar*), 7.56-7.63 (4H, m, *Ar*).

Step 2: Following *General Procedure 6*, crude **541** (5.83 g) in PhMe (39 mL) was treated with dry TsOH (142 mg, 0.82 mmol). Purification *via* recrystallisation (Et_2O) gave (*E*)-4′-phenyl-β-methylstyrene **542** as a pale yellow solid (2.20 g, 41% over 2 steps, 98:2 dr);[64] mp 104-107 °C (Et_2O) {lit.[65] mp 103-103.5 °C}; δ_H (400 MHz, $CDCl_3$) 1.92 (3H, dd, *J* 6.5, 1.4, C(β)*Me*), 6.30 (1H, dq, *J* 15.9, 6.5, C(β)*H*), 6.45 (1H, app dd, *J* 15.9, 1.4, C(α)*H*), 7.31-7.64 (9H, m, *Ar*). Data for (*Z*)-alkene:[64] δ_H (400 MHz, $CDCl_3$) [selected peak] 5.85 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, crude **542** (2.20 g, 11.3 mmol, 98:2 dr) in CH_2Cl_2 (57 mL) was treated with *m*-CPBA (74% with H_2O, 3.97 g, 17.0 mmol) for 25 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **176** as a white solid (1.89 g, 79%, 98:2 dr); R_f 0.18 (30-40 °C petrol/Et_2O, 96:4); mp 62-64 °C; ν_{max} 3056, 3028, 2989, 2928 (C–H), 1487, 1217, 1020, 841, 818; δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 5.2, C(3)*Me*), 3.10 (1H, qd, *J* 5.2, 1.9, C(3)*H*), 3.64 (1H, d, *J* 1.9, C(2)*H*), 7.32-7.39 (3H, m, *Ar*), 7.42-7.49 (2H, m, *Ar*), 7.56-7.64 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(3)*Me*), 59.1, 59.4 (*C*(2), *C*(3)), 126.0, 127.1, 127.2, 127.4, 128.8, 136.8, 140.7, 141.0 (*Ar*); *m*/*z* (GC ToF CI^+) 228 ($[M+NH_4]^+$, 100%); HRMS (GC ToF CI^+) $C_{15}H_{18}NO^+$ ($[M+NH_4]^+$) requires 228.1383; found 228.1382. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.16 (3H, d, *J* 5.3, C(3)*Me*), 3.37-3.43 (1H, m, C(3)*H*), 4.12 (1H, d, *J* 4.0, C(2)*H*).

Preparation of (*RS*,*RS*)-2-methyl-3-(naphthalen-2-yl)oxirane 177



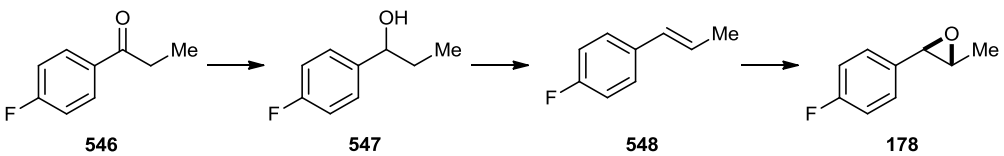
543 **544** **545** **177**

Step 1: Following *General Procedure 5*, 2-napthaldehyde **543** (4.69 g, 30.0 mmol) in Et_2O (100 mL) was treated with EtMgBr (3.0 M in Et_2O, 11 mL, 33 mmol) for 18 h to give crude (*RS*)-1-(naphthalen-2-yl)propan-1-ol **544** as a yellow oil (5.59 g);[66] δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 7.4, C(3)H_3), 1.79-2.07 (3H, m, C(2)H_2, O*H*), 4.73-4.82 (1H, m, C(1)*H*), 7.42-7.53 (3H, m, *Ar*), 7.75-7.87 (4H, m, *Ar*).

Step 2: Following *General Procedure 6*, crude **544** (5.59 g) in PhMe (43 mL) was treated with dry TsOH (155 mg, 0.90 mmol) to give crude (*E*)-2′-(prop-1-en-1-yl)naphthalene **545** as a yellow oil (5.05 g, 96:4 dr);[67] δ_H (400 MHz, $CDCl_3$) 1.99 (3H, dd, *J* 6.7, 1.5, C(3)H_3), 6.35-6.47 (1H, m, C(2)*H*), 6.61 (1H, d, *J* 15.7, C(1)*H*), 7.41-7.52 (2H, m, *Ar*), 7.61 (1H, dd, *J* 8.5, 1.7, *Ar*), 7.70 (1H, s, *Ar*), 7.77-7.85 (3H, m, *Ar*). Data for (*Z*)-alkene:[67] δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.03 (3H, dd, *J* 7.3, 1.8, C(3)H_3), 5.93 (1H, dq, *J* 11.6, 7.2, C(2)*H*).

Step 3: Following *General Procedure 3*, crude **545** (5.05 g, 96:4 dr) in CH_2Cl_2 (150 mL) was treated with *m*-CPBA (77% with H_2O, 8.02 g, 36.0 mmol) for 22 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **177** as a pale orange oil which solidified on standing to a white solid (3.39 g, 61% over 3 steps, 96:4 dr);[68] R_f 0.38 (30-40 °C petrol/Et_2O, 90:10); mp 49-50 °C {lit.[68] mp 56-57 °C}; ν_{max} 3054, 2998, 2967, 2928, 2863 (C−H), 816; δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* 5.1, C(2)*Me*), 3.17 (1H, qd, *J* 5.1, 2.0, C(2)*H*), 3.78 (1H, d, *J* 1.7, C(3)*H*), 7.36 (1H, dd, *J* 8.5, 1.2, *Ar*), 7.46-7.55 (2H, m, *Ar*), 7.78-7.89 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(2)*Me*), 59.1 (*C*(2)), 59.8 (*C*(3)), 123.0, 125.1, 126.0, 126.3, 127.8, 128.3, 133.2, 133.3, 135.3 (*Ar*); *m*/*z* (GC ToF CI$^+$) 202 ([M+NH_4]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{13}H_{16}NO^+$ ([M+NH_4]$^+$) requires 202.1226; found 202.1247. Data for *cis*-epoxide:[69] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.16 (3H, d, *J* 5.5, C(2)*Me*), 3.45 (1H, app quin, *J* 5.1, C(2)*H*), 4.26 (1H, d, *J* 4.3, C(3)*H*).

Preparation of (*RS*,*RS*)-2-(4′-fluorophenyl)-3-methyloxirane 178



546 **547** **548** **178**

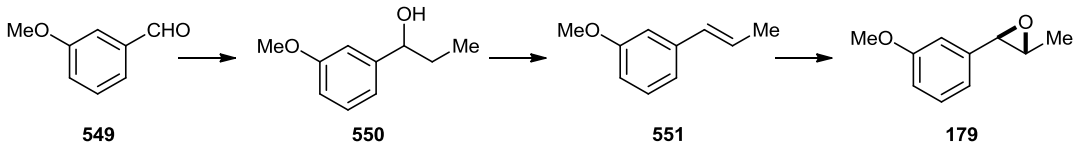
Step 1: Following *General Procedure 1*, 4′-fluoropropiophenone **546** (6.4 mL, 46 mmol) in MeOH (120 mL) was treated with $NaBH_4$ (1.91 g, 50.6 mmol) for 26 h to give crude (*RS*)-1-(4′-fluorophenyl)propan-1-ol **547**

as a colourless oil (6.26 g);[70] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* 7.5, C(3)H_3), 1.66-1.94 (3H, m, C(2)H_2, O*H*), 4.59 (1H, app t, *J* 6.7, C(1)*H*), 7.00-7.07 (2H, m, C(3′)*H*, C(5′)*H*), 7.28-7.34 (2H, m, C(2′)*H*, C(6′)*H*).

Step 2: Following *General Procedure 6*, crude **547** (6.26 g) in PhMe (54 mL) was treated with dry TsOH (210 mg, 1.22 mmol). Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-4′-fluoro-β-methylstyrene **548** as a colourless oil (2.32 g, 37% over 2 steps, 96:4 dr);[71] bp 31-32 °C (2.2 mmHg) {lit.[72] bp 99 °C (17 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.88 (3H, dd, *J* 6.6, 1.5, C(β)*Me*), 6.16 (1H, dq, *J* 15.6, 6.6, C(β)*H*), 6.37 (1H, app dd, *J* 15.6, 1.5, C(α)*H*), 6.95-7.02 (2H, m, C(3′)*H*, C(5′)*H*), 7.26-7.32 (2H, m, C(2′)*H*, C(6′)*H*). Data for (*Z*)-alkene:[71] δ_H (400 MHz, $CDCl_3$) [selected peak] 5.79 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **548** (2.32 g, 17.0 mmol, 96:4 dr) in CH_2Cl_2 (85 mL) was treated with *m*-CPBA (74% with H_2O, 5.99 g, 25.6 mmol) for 17 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **178** as a colourless oil (2.24 g, 87%, 94:6 dr); bp 52-53 °C (2.2 mmHg); ν_{max} 2989, 2930 (C–H), 1514, 1223, 822; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 5.2, C(3)*Me*), 3.00 (1H, qd, *J* 5.2, 1.8, C(3)*H*), 3.56 (1H, d, *J* 1.8, C(2)*H*), 6.98-7.07 (2H, m, C(3′)*H*, C(5′)*H*), 7.19-7.30 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 59.0, 59.0 (*C*(2), *C*(3)), 115.4 (d, *J* 22.4, *C*(3′), *C*(5′)), 127.2 (d, *J* 8.0, *C*(2′), *C*(6′)), 133.5 (d, *J* 3.2, *C*(1′)), 162.6 (d, *J* 246, *C*(4′)); *m*/*z* (GC ToF CI^+) 170 ($[M+NH_4]^+$, 91%), 70 (100%); HRMS (GC ToF CI^+) $C_9H_{13}FNO^+$ ($[M+NH_4]^+$) requires 170.0976; found 170.0975. Data for *cis*-epoxide:[62] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.08 (3H, d, *J* 5.3, C(3)*Me*), 3.29-3.37 (1H, m, C(3)*H*), 4.04 (1H, d, *J* 4.0, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(3′-methoxyphenyl)-3-methyloxirane 179



549 **550** **551** **179**

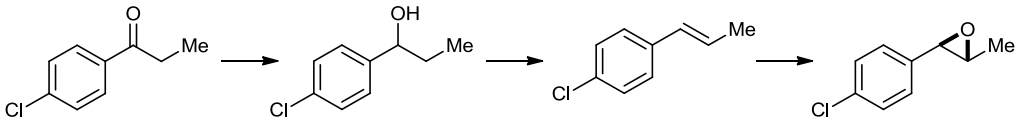
Step 1: Following *General Procedure 5*, *m*-anisaldehyde **549** (9.0 mL, 73 mmol) in Et_2O (245 mL) was treated with EtMgBr (3.0 M in Et_2O, 27 mL, 81 mmol) for 43 h to give crude (*RS*)-1-(3′-methoxyphenyl)propan-1-ol **550** as a yellow oil (12.2 g);[73] δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.5, C(3)H_3), 1.70-1.89 (3H, m, C(2)H_2, O*H*), 3.83 (3H, s, O*Me*), 4.59 (1H, app t, *J* 6.5, C(1)*H*), 6.80-6.85 (1H, m, *Ar*), 6.90-6.95 (2H, m, *Ar*), 7.24-7.30 (1H, m, *Ar*).

Step 2: Following *General Procedure 6*, crude **550** (12.2 g) in PhMe (105 mL) was treated with dry TsOH (379 mg, 2.20 mmol). Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-3′-methoxy-β-methylstyrene **551** as a colourless oil (7.11 g, 65% over 2 steps, 94:6 dr);[74] bp 73-76 °C (2.2 mmHg) {lit.[75]

bp 128-129 °C (20 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.89 (3H, dd, *J* 6.5, 1.5, C(β)*Me*), 3.82 (3H, s, O*Me*), 6.25 (1H, dq, *J* 15.7, 6.5, C(β)*H*), 6.39 (1H, app dd, *J* 15.7, 1.5, C(α)*H*), 6.76 (1H, dd, *J* 8.2, 2.7, C(4′)*H*), 6.87-6.90 (1H, m, C(2′)*H*), 6.94 (1H, d, *J* 7.9, C(6′)*H*), 7.22 (1H, app t, *J* 7.9, C(5′)*H*). Data for (*Z*)-alkene:[74] δ_H (400 MHz, $CDCl_3$) [selected peak] 5.81 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **551** (7.00 g, 47.3 mmol, 94:6 dr) in CH_2Cl_2 (237 mL) was treated with *m*-CPBA (74% with H_2O, 16.6 g, 70.9 mmol) for 19 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **179** as a colourless oil (5.38 g, 69%, 93:7 dr); bp 94-99 °C (2.2 mmHg); $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.4%; found C, 73.2; H, 7.3%; ν_{max} 2991, 2967, 2930, 2836 (C–H), 1604, 1586, 1491, 1468, 1275, 1260, 1243, 1156, 1046, 842, 786, 695; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 5.2, C(3)*Me*), 3.03 (1H, qd, *J* 5.2, 1.9, C(3)*H*), 3.57 (1H, d, *J* 1.9, C(2)*H*), 3.81 (3H, s, O*Me*), 6.78-6.92 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*), 7.22-7.30 (1H, m, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 55.3 (O*Me*), 59.0, 59.5 (*C*(2), *C*(3)), 110.5 (*C*(2′)), 113.8 (*C*(4′)), 118.1 (*C*(6′)), 129.5 (*C*(5′)), 139.5 (*C*(1′)), 159.9 (*C*(3′)); *m*/*z* (GC ToF CI^+) 182 ($[M+NH_4]^+$, 100%); HRMS (GC ToF CI^+) $C_{10}H_{16}NO_2^+$ ($[M+NH_4]^+$) requires 182.1176; found 182.1173. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.12 (3H, d, *J* 5.3, C(3)*Me*), 3.31-3.37 (1H, m, C(3)*H*), 4.05 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(4′-chlorophenyl)-3-methyloxirane 180



552 **553** **554** **180**

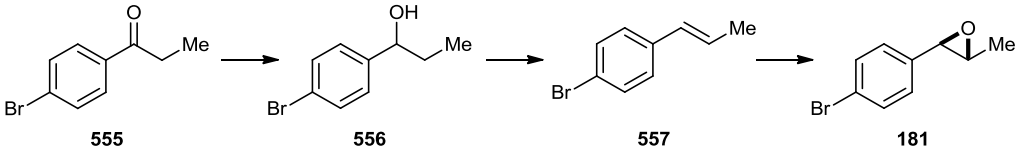
Step 1: Following *General Procedure 1*, 4′-chloropropiophenone **552** (10.0 g, 59.3 mmol) in MeOH (148 mL) was treated with $NaBH_4$ (2.47 g, 65.2 mmol) for 22 h to give crude (*RS*)-1-(4′-chlorophenyl)propan-1-ol **553** as a yellow oil (10.1 g);[76] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* 7.3, C(3)H_3), 1.66-1.87 (3H, m, C(2)H_2, O*H*), 4.59 (1H, app t, *J* 6.7, C(1)*H*), 7.25-7.35 (4H, m, *Ar*).

Step 2: Following *General Procedure 6*, crude **553** (10.1 g) in PhMe (80 mL) was treated with dry TsOH (306 mg, 1.78 mmol). Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-4′-chloro-β-methylstyrene **554** as a colourless oil (7.66 g, 85% over 2 steps, 95:5 dr);[77] bp 61-62 °C (2.2 mmHg) {lit.[58] bp 75-76 °C (6 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.89 (3H, dd, *J* 6.5, 1.5, C(β)*Me*), 6.23 (1H, dq, *J* 15.7, 6.5, C(β)*H*), 6.36 (1H, dq, *J* 15.7, 1.5, C(α)*H*), 7.22-7.28 (4H, m, *Ar*). Data for (*Z*)-alkene:[60] δ_H (400 MHz, $CDCl_3$) [selected peak] 5.83 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **554** (7.65 g, 50.1 mmol, 95:5 dr) in CH_2Cl_2 (251 mL) was treated with *m*-CPBA (74% with H_2O, 17.6 g, 75.2 mmol) for 48 h. Purification *via* distillation at reduced pressure

(2.2 mmHg) gave **180** as a colourless oil (7.34 g, 87%, 94:6 dr); bp 79-83 °C (2.2 mmHg) {lit.[61] bp 65-66 °C (0.5 mmHg)}; ν_{max} 2989, 2928 (C–H), 1496, 1091, 1016, 836, 806; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 5.1, C(3)*Me*), 2.99 (1H, qd, *J* 5.1, 1.5, C(3)*H*), 3.55 (1H, d, *J* 1.5, C(2)*H*), 7.16-7.22 (2H, m, C(2′)*H*, C(6′)*H*), 7.28-7.34 (2H, m, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 58.9, 59.2 (*C*(2), *C*(3)), 126.9 (*C*(2′), *C*(6′)), 128.6 (*C*(3′), *C*(5′)), 133.7, 136.4 (*C*(1′), *C*(4′)); *m*/*z* (GC ToF CI^+) 186 ($[M(^{35}Cl)+NH_4]^+$, 100%); HRMS (GC ToF CI^+) $C_9H_{13}{}^{35}ClNO^+$ ($[M(^{35}Cl)+NH_4]^+$) requires 186.0680; found 186.0674. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.07 (3H, d, *J* 5.6, C(3)*Me*), 3.31-3.37 (1H, m, C(3)*H*), 4.03 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(4′-bromophenyl)-3-methyloxirane 181



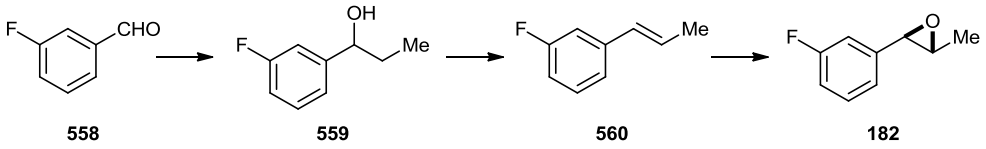
Step 1: Following *General Procedure 1*, 4′-bromopropiophenone **555** (10.0 g, 46.9 mmol) in MeOH (117 mL) was treated with $NaBH_4$ (1.95 g, 51.6 mmol) for 22 h to give crude (*RS*)-1-(4′-bromophenyl)propan-1-ol **556** as a colourless oil (10.1 g);[76] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* 7.5, C(3)H_3), 1.66-1.90 (3H, m, C(2)H_2, O*H*), 4.58 (1H, app t, *J* 6.5, C(1)*H*), 7.20-7.25 (2H, m, C(2′)*H*, C(6′)*H*), 7.45-7.50 (2H, m, C(3′)*H*, C(5′)*H*).

Step 2: Following *General Procedure 6*, crude **556** (10.1 g) in PhMe (65 mL) was treated with dry TsOH (242 mg, 1.41 mmol). Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-4′-bromo-β-methylstyrene **557** as a colourless oil which solidified on standing to a white crystalline solid (7.80 g, 84% over 2 steps, 92:8 dr);[78] bp 80-81 °C (2.2 mmHg) {lit.[79] bp 102 °C (0.2 mmHg)}; mp 34-36 °C {lit.[80] mp 35 °C}; δ_H (400 MHz, $CDCl_3$) 1.89 (3H, dd, *J* 6.1, 1.4, C(β)*Me*), 6.24 (1H, dq, *J* 15.7, 6.1, C(β)*H*), 6.35 (1H, app dd, *J* 15.7, 1.4, C(α)*H*), 7.17-7.23 (2H, m, C(2′)*H*, C(6′)*H*), 7.39-7.44 (2H, m, C(3′)*H*, C(5′)*H*). Data for (*Z*)-alkene:[78] δ_H (400 MHz, $CDCl_3$) [selected peak] 5.84 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **557** (7.60 g, 38.6 mmol, 92:8 dr) in CH_2Cl_2 (193 mL) was treated with *m*-CPBA (74% with H_2O, 13.5 g, 57.8 mmol) for 48 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **181** as a colourless oil (7.36 g, 89%, 94:6 dr); bp 93-97 °C (2.2 mmHg); C_9H_9BrO requires C, 50.7; H, 4.3%; found C, 50.8; H, 4.2%; ν_{max} 2988, 2927 (C–H), 1490, 1069, 1021, 1011, 832, 804; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 5.3, C(3)*Me*), 2.95-3.02 (1H, m, C(3)*H*), 3.54 (1H, app s, C(2)*H*), 7.10-7.16 (2H, m, C(2′)*H*, C(6′)*H*), 7.43-7.48 (2H, m, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 58.9, 59.1 (*C*(2), *C*(3)), 121.8 (*C*(4′)), 127.2 (*C*(2′), *C*(6′)), 131.6 (*C*(3′), *C*(5′)), 136.9 (*C*(1′));

m/*z* (GC ToF CI$^+$) 232 ([M(^{81}Br)+NH$_4$]$^+$, 87%), 230 ([M(^{79}Br)+NH$_4$]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_9H_{13}{}^{79}BrNO^+$ ([M(^{79}Br)+NH$_4$]$^+$) requires 230.0175; found 230.0174. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.07 (3H, d, *J* 5.6, C(3)*Me*), 3.31-3.37 (1H, m, C(3)*H*), 4.01 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(3′-fluorophenyl)-3-methyloxirane 182



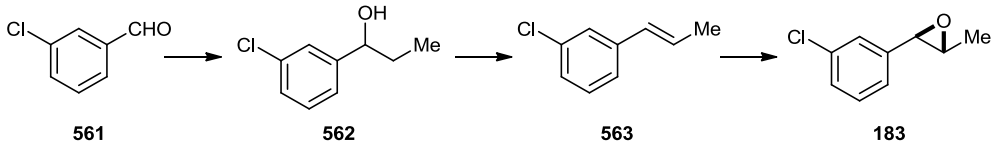
Step 1: Following *General Procedure 5*, 3-fluorobenzaldehyde **558** (8.6 mL, 81 mmol) in Et_2O (269 mL) was treated with EtMgBr (3.0 M in Et_2O, 30 mL, 90 mmol) for 43 h to give crude (*RS*)-1-(3′-fluorophenyl)propan-1-ol **559** as an orange oil (12.4 g);[81] δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.5, C(3)H_3), 1.69-1.88 (3H, m, C(2)H_2, O*H*), 4.62 (1H, app t, *J* 6.7, C(1)*H*), 6.93-7.01 (1H, m, C(2′)*H*), 7.05-7.14 (2H, m, C(4′)*H*, C(6′)*H*), 7.28-7.35 (1H, m, C(5′)*H*).

Step 2: Following *General Procedure 6*, crude **559** (12.4 g) in PhMe (115 mL) was treated with dry TsOH (416 mg, 2.42 mmol) to give partially degraded starting material as a yellow oil (12.8 g).

Step 3: Following *General Procedure 7*, the latter residue (from step 2) was treated with $KHSO_4$ (5.49 g, 40.3 mmol) for 3 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave (*E*)-3′-fluoro-β-methylstyrene **560** as a colourless oil (2.65 g, 24% over 3 steps, 96:4 dr);[82] bp 35-37 °C (2.2 mmHg) {lit.[82] bp 46-47 °C (2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.91 (3H, dd, *J* 6.4, 1.5, C(β)*Me*), 6.27 (1H, dq, *J* 15.9, 6.4, C(β)*H*), 6.39 (1H, app d, *J* 15.9, C(α)*H*), 6.87-6.93 (1H, m, *Ar*), 7.02-7.08 (1H, m, *Ar*), 7.08-7.12 (1H, m, *Ar*), 7.22-7.29 (1H, m, *Ar*). Data for (*Z*)-alkene: δ_H (400 MHz, $CDCl_3$) [selected peak] 5.86 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **560** (2.57 g, 18.9 mmol, 96:4 dr) in CH_2Cl_2 (95 mL) was treated with *m*-CPBA (74% with H_2O, 6.64 g, 28.4 mmol) for 19 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **182** as a colourless oil (2.53 g, 88%, 95:5 dr); bp 74-76 °C (2.2 mmHg); ν_{max} 3068, 2991, 2931 (C–H), 1591, 1492, 845, 788, 690; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 5.2, C(3)*Me*), 3.00 (1H, qd, *J* 5.2, 1.8, C(3)*H*), 3.58 (1H, d, *J* 1.8, C(2)*H*), 6.92-7.02 (2H, m, C(2′)*H*, C(4′)*H*), 7.07 (1H, d, *J* 7.8, C(6′)*H*), 7.30 (1H, app td, *J* 7.8, 5.8, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 58.8, 59.2 (*C*(2), *C*(3)), 112.3 (d, *J* 22.4, *C*(2′)), 114.9 (d, *J* 20.8, *C*(4′)), 121.3 (d, *J* 3.2, *C*(6′)), 130.0 (d, *J* 8.0, *C*(5′)), 140.6 (d, *J* 8.0, *C*(1′)), 163.1 (d, *J* 246, *C*(3′)); *m*/*z* (GC ToF CI$^+$) 170 ([M+NH$_4$]$^+$, 80%), 152 (100%); HRMS (GC ToF CI$^+$) $C_9H_{13}FNO^+$ ([M+NH$_4$]$^+$) requires 170.0976; found 170.0973. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.10 (3H, d, *J* 5.6, C(3)*Me*), 3.32-3.38 (1H, m, C(3)*H*), 4.05 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(3′-chlorophenyl)-3-methyloxirane 183

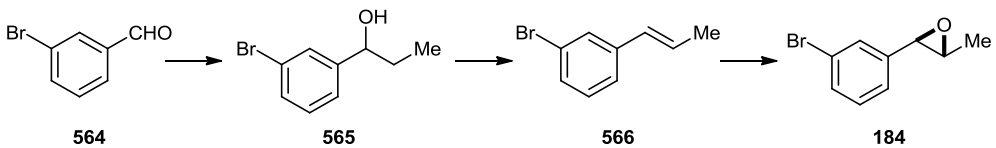


Step 1: Following *General Procedure 5*, 3-chlorobenzaldehyde **561** (8.1 mL, 72 mmol) in Et_2O (237 mL) was treated with EtMgBr (3.0 M in Et_2O, 26 mL, 78 mmol) for 24 h to give crude (*RS*)-1-(3′-chlorophenyl)propan-1-ol **562** as a pale yellow oil (10.3 g);[76] δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.7, C(3)H_3), 1.69-1.87 (3H, m, C(2)H_2, O*H*), 4.60 (1H, app t, *J* 6.5, C(1)*H*), 7.20-7.31 (3H, m, *Ar*), 7.34-7.38 (1H, m, *Ar*).

Step 2: Following *General Procedure 7*, crude **562** (10.3 g) was treated with $KHSO_4$ (4.12 g, 30.2 mmol) for 4 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave (*E*)-3′-chloro-β-methylstyrene **563** as a colourless oil (6.99 g, 64% over 2 steps, 94:6 dr);[60] bp 61-68 °C (1.2 mmHg) {lit.[60] bp 80.5 °C (7 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.91 (3H, dd, *J* 6.1, 1.0, C(β)*Me*), 6.27 (1H, dq, *J* 15.9, 6.1, C(β)*H*), 6.36 (1H, app dd, *J* 15.9, 1.0, C(α)*H*), 7.15-7.35 (4H, m, *Ar*). Data for (*Z*)-alkene: δ_H (400 MHz, $CDCl_3$) [selected peak] 5.86 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **563** (6.99 g, 45.8 mmol, 94:6 dr) in CH_2Cl_2 (229 mL) was treated with *m*-CPBA (74% with H_2O, 16.1 g, 68.7 mmol) for 14 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **183** as a colourless oil (7.01 g, 91%, 92:8 dr); bp 78-81 °C (2.2 mmHg); ν_{max} 3064, 2990, 2929 (C–H), 1601, 1482, 871, 786, 689; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 5.2, C(3)*Me*), 3.00 (1H, qd, *J* 5.2, 1.8, C(3)*H*), 3.55 (1H, d, *J* 1.8, C(2)*H*), 7.12-7.19 (1H, m, C(6′)*H*), 7.22-7.30 (3H, m, C(2′)*H*, C(4′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 58.8, 59.2 (*C*(2), *C*(3)), 123.8 (*C*(6′)), 125.6 (*C*(2′)), 128.1 (*C*(4′)), 129.7 (*C*(5′)), 134.5 (*C*(3′)), 140.0 (*C*(1′)); *m*/*z* (GC ToF CI^+) 186 ($[M(^{35}Cl)+NH_4]^+$, 100%); HRMS (GC ToF CI^+) $C_9H_{13}{}^{35}ClNO^+$ ($[M(^{35}Cl)+NH_4]^+$) requires 186.0680; found 186.0674. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.09 (3H, d, *J* 5.6, C(3)*Me*), 3.31-3.38 (1H, m, C(3)*H*), 4.03 (1H, d, *J* 4.3, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(3′-bromophenyl)-3-methyloxirane 184



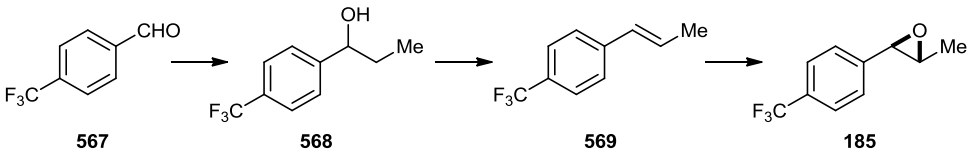
Step 1: Following *General Procedure 5*, 3-bromobenzaldehyde **564** (10.0 g, 54.0 mmol) in Et_2O (180 mL) was treated with EtMgBr (3.0 M in Et_2O, 20 mL, 60 mmol) for 21 h to give crude (*RS*)-1-(3′-bromophenyl)propan-1-ol **565** as a pale yellow oil (11.6 g);[76] δ_H (400 MHz, $CDCl_3$) 0.93 (3H,

app t, *J* 7.3, C(3)H_3), 1.68-1.87 (3H, m, C(2)H_2, O*H*), 4.59 (1H, app t, *J* 6.7, C(1)*H*), 7.19-7.29 (2H, m, C(5′)*H*, C(6′)*H*), 7.38-7.43 (1H, m, C(4′)*H*), 7.52 (1H, s, C(2′)*H*).

Step 2: Following *General Procedure 7*, crude **565** (11.6 g) was treated with $KHSO_4$ (3.68 g, 27.0 mmol) for 4 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave (*E*)-3′-bromo-β-methylstyrene **566** as a colourless oil (7.91 g, 75% over 2 steps, 93:7 dr);[61] bp 74-79 °C (1.2 mmHg) {lit.[61] bp 113-166 °C (15 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.90 (3H, dd, *J* 6.0, 1.0, C(β)*Me*), 6.26 (1H, dq, *J* 15.7, 6.0, C(β)*H*), 6.34 (1H, app d, *J* 15.7, C(α)*H*), 7.16 (1H, app t, *J* 7.9, C(5′)*H*), 7.21-7.26 (1H, m, C(6′)*H*), 7.30-7.34 (1H, m, C(4′)*H*), 7.49 (1H, app t, *J* 1.7, C(2′)*H*). Data for (*Z*)-alkene: δ_H (400 MHz, $CDCl_3$) [selected peak] 5.85 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **566** (7.91 g, 40.1 mmol, 93:7 dr) in CH_2Cl_2 (201 mL) was treated with *m*-CPBA (74% with H_2O, 14.1 g, 60.2 mmol) for 14 h. Purification *via* distillation at reduced pressure (2.2 mmHg) gave **184** as a colourless oil (7.82 g, 92%, 91:9 dr); bp 92-99 °C (2.2 mmHg) {lit.[61] bp 102-104 °C (2 mmHg)}; C_9H_9BrO requires C, 50.7; H, 4.3%; found C, 50.8; H, 4.25%; ν_{max} 3062, 2989, 2928 (C–H), 1571, 1479, 864, 783, 690; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 5.1, C(3)*Me*), 2.99 (1H, qd, *J* 5.1, 1.9, C(3)*H*), 3.54 (1H, d, *J* 1.9, C(2)*H*), 7.17-7.22 (2H, m, C(5′)*H*, C(6′)*H*), 7.38-7.45 (2H, m, C(2′)*H*, C(4′)*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 58.7, 59.2 (*C*(2), *C*(3)), 122.7 (*C*(3′)), 124.3 (*C*(6′)), 128.5 (*C*(2′)), 130.0 (*C*(5′)), 131.1 (*C*(4′)), 140.3 (*C*(1′)); *m*/*z* (GC ToF CI^+) 232 ([M(^{81}Br)+NH_4]$^+$, 95%), 230 ([M(^{79}Br)+NH_4]$^+$, 78%), 133 (100%); HRMS (GC ToF CI^+) $C_9H_{13}{}^{79}BrNO^+$ ([M(^{79}Br)+NH_4]$^+$) requires 230.0175; found 230.0178. Data for *cis*-epoxide: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.09 (3H, d, *J* 5.3, C(3)*Me*), 3.31-3.38 (1H, m, C(3)*H*), 4.02 (1H, d, *J* 4.0, C(2)*H*).

Preparation of (*RS*,*RS*)-2-(4′-trifluoromethylphenyl)-3-methyloxirane 185



567 **568** **569** **185**

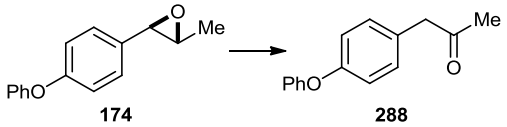
Step 1: Following *General Procedure 5*, 4-(trifluoromethyl)benzaldehyde **567** (2.69 g, 15.4 mmol) in Et_2O (51 mL) was treated with EtMgBr (3.0 M in Et_2O, 5.7 mL, 17 mmol) for 26 h to give crude (*RS*)-1-(4′-trifluoromethylphenyl)propan-1-ol **568** as a yellow oil (3.15 g);[83] δ_H (400 MHz, $CDCl_3$) 0.94 (3H, app t, *J* 7.3, C(3)H_3), 1.70-1.88 (2H, m, C(2)H_2), 1.95 (1H, br s, O*H*), 4.69 (1H, app t, *J* 6.3, C(1)*H*), 7.44-7.49 (2H, m, C(2′)*H*, C(6′)*H*), 7.58-7.64 (2H, m, C(3′)*H*, C(5′)*H*).

Step 2: Following *General Procedure 7*, crude **568** (3.15 g) was treated with $KHSO_4$ (1.05 g, 7.71 mmol) for 1 h. Purification *via* filtration through a pad of silica gel (eluent 30-40 °C petrol) gave (*E*)-4′-trifluoromethyl-

β-methylstyrene **569** as a colourless semi-solid (1.61 g, 56% over 2 steps, 94:6 dr);[84] δ_H (400 MHz, $CDCl_3$) 1.92 (3H, d, *J* 5.8, C(β)*Me*), 6.36 (1H, dq, *J* 15.9, 5.8, C(β)*H*), 6.44 (1H, app d, *J* 15.9, C(α)*H*), 7.39-7.44 (2H, m, C(2′)*H*, C(6′)*H*), 7.52-7.56 (2H, m, C(3′)*H*, C(5′)*H*). Data for (*Z*)-alkene: δ_H (400 MHz, $CDCl_3$) [selected peak] 5.92 (1H, dq, *J* 11.6, 7.2, C(β)*H*).

Step 3: Following *General Procedure 3*, **569** (1.61 g, 8.64 mmol, 94:6 dr) in CH_2Cl_2 (43 mL) was treated with *m*-CPBA (74% with H_2O, 3.03 g, 13.0 mmol) for 15 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave **185** as a colourless oil (1.48 g, 85%, 94:6 dr); bp 30-32 °C (1.2 mmHg); ν_{max} 2993, 2933 (C–H), 1326 (CF_3), 1166, 1125, 1106, 1067; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 5.1, C(2)*Me*), 3.01 (1H, qd, *J* 5.1, 1.8, C(2)*H*), 3.64 (1H, d, *J* 1.8, C(3)*H*), 7.38 (2H, d, *J* 8.2, C(2′)*H*, C(6′)*H*), 7.60 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(2)*Me*), 58.7, 59.4 (*C*(2), *C*(3)), 125.4 (q, *J* 4.0, *C*(3′), *C*(5′)), 125.8 (*C*(2′), *C*(6′)), 130.2 (q, *J* 32.8, *C*(4′)), 142.0 (*C*(1′));[85] *m*/*z* (GC ToF CI^+) 220 ($[M+NH_4]^+$, 35%), 133 (100%); HRMS (GC ToF CI^+) $C_{10}H_{13}F_3NO^+$ ($[M+NH_4]^+$) requires 220.0944; found 220.0940. Data for *cis*-epoxide:[62] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.08 (3H, d, *J* 5.3, C(2)*Me*), 3.36-3.43 (1H, m, C(2)*H*), 4.10 (1H, d, *J* 4.0, C(3)*H*), 7.43 (2H, d, *J* 8.2, C(2′)*H*, C(6′)*H*).

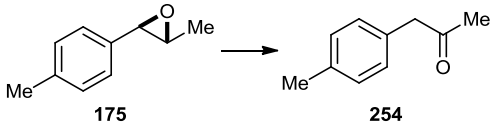
Attempted ring-opening fluorination of (*RS*,*RS*)-2-(4′-phenoxyphenyl)-3-methyloxirane 174



174 **288**

Following *General Procedure 4*, **174** (158 mg, 0.70 mmol, 96:4 dr) in CH_2Cl_2 (2.8 mL) was treated with BF_3•OEt_2 (29 μL, 0.23 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(4′-phenoxyphenyl)propan-2-one **288** as a pale yellow oil (84.8 mg, 54%); R_f 0.40 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3039 (C−H), 1711 (C=O), 1588, 1506, 1487, 1230, 1158, 871, 749, 692; δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, C(3)H_3), 3.69 (2H, s, C(1)H_2), 6.95-7.06 (4H, m, *Ar*), 7.08-7.20 (3H, m, *Ar*), 7.31-7.40 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 29.3 (*C*(3)), 50.1 (*C*(1)), 119.0, 123.4, 129.0, 129.8, 130.7, 156.4, 157.1 (*Ar*), 206.4 (*C*=O); *m*/*z* (FI^+) 226 ($[M]^+$, 100%); HRMS (FI^+) $C_{15}H_{14}O_2^+$ ($[M]^+$) requires 226.0988; found 226.1000.

Attempted ring-opening fluorination of (*RS*,*RS*)-2-(*p*-tolyl)-3-methyloxirane 175

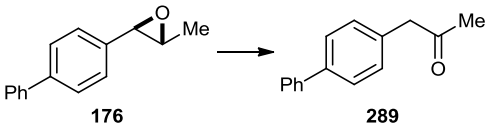


175 **254**

Following *General Procedure 4*, **175** (500 mg, 3.37 mmol, 90:10 dr) in CH_2Cl_2 (14 mL) was treated with BF_3•OEt_2 (140 μL, 1.13 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient

elution, 2→20% EtOAc in 30-40 °C petrol) gave 1-(*p*-tolyl)propan-2-one **254** as a colourless oil (191 mg, 38%);[86] R_f 0.26 (30-40 °C petrol/EtOAc, 90:10); δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, C(3)H_3), 2.35 (3H, s, C(4′)*Me*), 3.66 (2H, s, C(1)H_2), 7.07-7.18 (4H, m, *Ar*).

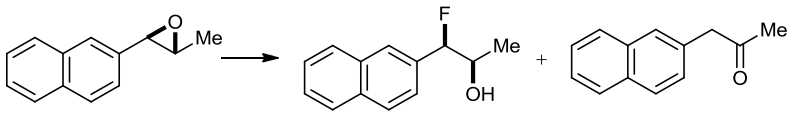
Attempted ring-opening fluorination of (*RS*,*RS*)-2-(biphenyl-4′-yl)-3-methyloxirane 176



176 **289**

Following *General Procedure 4*, **176** (500 mg, 2.38 mmol, 98:2 dr) in CH_2Cl_2 (9.5 mL) was treated with BF_3•OEt_2 (98 μL, 0.79 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave 1-(biphenyl-4′-yl)propan-2-one **289** as a white solid (207 mg, 41%);[87] R_f 0.19 (30-40 °C petrol/Et_2O, 80:20); mp 50-52 °C {lit.[88] mp 48-50 °C}; δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, C(3)H_3), 3.76 (2H, s, C(1)H_2), 7.26-7.32 (2H, m, *Ar*), 7.33-7.39 (1H, m, *Ar*), 7.42-7.48 (2H, m, *Ar*), 7.55-7.62 (4H, m, *Ar*).

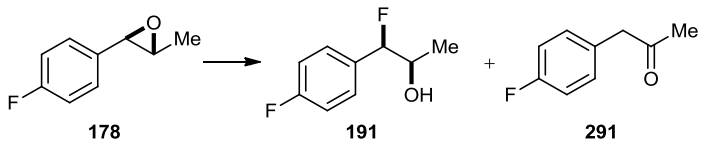
Ring-opening fluorination of (*RS*,*RS*)-2-methyl-3-(naphthalen-2-yl)oxirane 177



177 **190** **290**

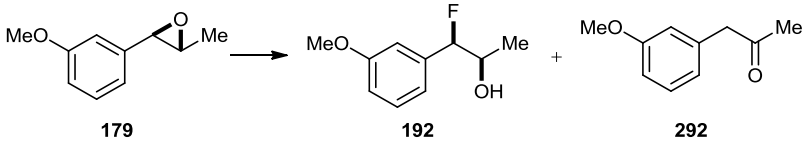
Following *General Procedure 4*, **177** (129 mg, 0.70 mmol, 94:6 dr) in CH_2Cl_2 (2.8 mL) was treated with BF_3•OEt_2 (29 μL, 0.23 mmol) at –20 °C for 5 min to give a 43:57 mixture of **190**:**290**. Purification *via* flash column chromatography (gradient elution, 10→20% EtOAc in 30-40 °C petrol) gave 1-(naphthalen-2′-yl)propan-2-one **290** as a white solid (40.6 mg, 31%);[89] R_f 0.41 (30-40 °C petrol/EtOAc, 80:20); mp 29-30 °C {lit.[90] mp 34-35 °C}; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, C(3)H_3), 3.87 (2H, s, C(1)H_2), 7.29-7.36 (1H, m, *Ar*), 7.42-7.53 (2H, m, *Ar*), 7.64-7.71 (1H, m, *Ar*), 7.79-7.89 (3H, m, *Ar*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(naphthalen-2′-yl)propan-2-ol **190** as a white crystalline solid (30.4 mg, 21%, >99:1 dr); R_f 0.26 (30-40 °C petrol/EtOAc, 80:20); mp 96-98 °C; ν_{max} 3377 (O−H), 2988 (C−H), 1076, 1006, 978, 906, 822, 745; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(3)H_3), 2.57 (1H, br s, O*H*), 4.21 (1H, app dquin, *J* 13.8, 6.7, C(2)*H*), 5.35 (1H, dd, *J* 48.0, 7.1, C(1)*H*), 7.43-7.49 (1H, m, *Ar*), 7.51-7.57 (2H, m, *Ar*), 7.81-7.92 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.8 (d, *J* 5.6, *C*(3)), 70.6 (d, *J* 24.0, *C*(2)), 98.8 (d, *J* 172, *C*(1)), 123.8 (d, *J* 5.6), 126.3 (d, *J* 7.2), 126.6 (d, *J* 7.2), 127.8, 128.1, 128.5, 133.0, 133.5 (d, *J* 1.6), 133.9, 134.1 (*Ar*); δ_F (377 MHz, $CDCl_3$) –181.2 (dd, *J* 48.0, 13.8, C(1)*F*); *m*/*z* (FI^+) 204 ($[M]^+$, 100%); HRMS (FI^+) $C_{13}H_{13}FO^+$ ($[M]^+$) requires 204.0945; found 204.0959.

Ring-opening fluorination of (*RS*,*RS*)-2-(4′-fluorophenyl)-3-methyloxirane 178



Following *General Procedure 4*, **178** (500 mg, 3.29 mmol, 94:6 dr) in CH_2Cl_2 (13 mL) was treated with BF_3•OEt_2 (135 μL, 1.10 mmol) at –20 °C for 5 min to give an 88:12 mixture of **191**:**291**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(4′-fluorophenyl)propan-2-one **291** as a pale yellow oil (49.1 mg, 10%);[91] R_f 0.37 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C(3)H_3), 3.68 (2H, s, C(1)H_2), 6.98-7.05 (2H, m, C(3')*H*, C(5')*H*), 7.13-7.19 (2H, m, C(2')*H*, C(6')*H*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(4′-fluorophenyl)propan-2-ol **191** as a colourless oil (431 mg, 76%, >99:1 dr); R_f 0.29 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 2981, 2936 (C–H), 1606, 1513, 1227, 1005, 834; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.6, C(3)H_3), 2.44 (1H, br s, O*H*), 4.06 (1H, ddq, *J* 13.8, 7.1, 6.6, C(2)*H*), 5.14 (1H, dd, *J* 47.3, 7.1, C(1)*H*), 7.05-7.12 (2H, m, C(3')*H*, C(5')*H*), 7.29-7.36 (2H, m, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 70.6 (d, *J* 24.0, *C*(2)), 98.0 (d, *J* 173, *C*(1)), 115.6 (d, *J* 20.8, *C*(3'), *C*(5')), 128.5 (dd, *J* 8.0, 6.4, *C*(2'), *C*(6')), 132.5 (dd, *J* 20.8, 3.2, *C*(1')), 163.1 (dd, *J* 248, 3.2, *C*(4')); δ_F (377 MHz, $CDCl_3$) –180.0 (dd, *J* 47.3, 13.8, C(1)*F*), –112.5 (m, C(4')*F*); *m*/*z* (FI^+) 172 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}F_2O^+$ ($[M]^+$) requires 172.0694; found 172.0698.

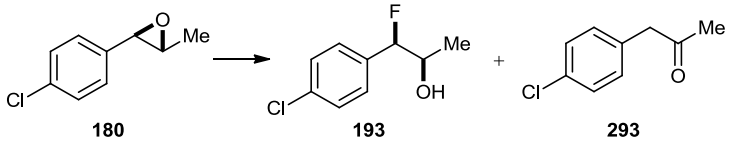
Ring-opening fluorination of (*RS*,*RS*)-2-(3′-methoxyphenyl)-3-methyloxirane 179



Following *General Procedure 4*, **179** (1.50 g, 9.14 mmol, 97:3 dr) in CH_2Cl_2 (37 mL) was treated with BF_3•OEt_2 (0.38 mL, 3.1 mmol) at –20 °C for 5 min to give a 90:10 mixture of **192**:**292**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(3′-methoxyphenyl)propan-2-one **292** as a yellow oil (108 mg, 7%);[91] R_f 0.31 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, C(3)H_3), 3.67 (2H, s, C(1)H_2), 3.80 (3H, s, O*Me*), 6.73-6.77 (1H, m, C(2')*H*), 6.78-6.85 (2H, m, C(4')*H*, C(6')*H*), 7.22-7.29 (1H, m, C(5')*H*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(3′-methoxyphenyl)propan-2-ol **192** as a colourless oil (1.36 g, 81%, >99:1 dr); R_f 0.18 (30-40 °C petrol/EtOAc, 80:20); $C_{10}H_{13}FO_2$ requires C, 65.2; H, 7.1%; found C, 65.25; H, 7.1%; ν_{max} 3419 (O–H), 2977, 2937, 2838 (C–H), 1605, 1588, 1490, 1457, 1437, 1289, 1270, 1161, 1045, 1007; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.3, C(3)H_3), 2.44 (1H, br s, O*H*), 3.83 (3H, s, O*Me*), 4.07 (1H, ddq, *J* 13.8, 6.8, 6.3, C(2)*H*), 5.13 (1H, dd, *J* 47.4, 6.8, C(1)*H*), 6.86-6.95 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.31

(1H, app t, *J* 7.8, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 55.3 (O*Me*), 70.6 (d, *J* 22.4, *C*(2)), 98.5 (d, *J* 174, *C*(1)), 112.1 (d, *J* 8.0, *C*(2')), 114.4 (*C*(4')), 118.9 (d, *J* 6.4, *C*(6')), 129.7 (*C*(5')), 138.2 (d, *J* 19.2, *C*(1')), 159.7 (*C*(3')); δ_F (377 MHz, $CDCl_3$) –182.1 (dd, *J* 47.4, 13.8, C(1)*F*); *m*/*z* (FI^+) 184 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{13}FO_2^+$ ($[M]^+$) requires 184.0894; found 184.0903.

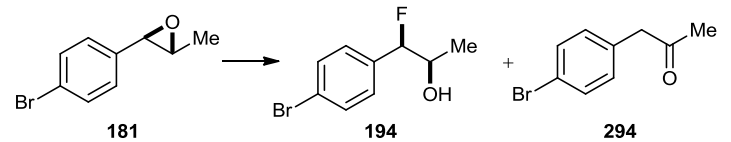
Ring-opening fluorination of (*RS*,*RS*)-2-(4′-chlorophenyl)-3-methyloxirane 180



180 **193** **293**

Following *General Procedure 4*, **180** (1.50 g, 8.90 mmol, 94:6 dr) in CH_2Cl_2 (36 mL) was treated with BF_3•OEt_2 (0.37 mL, 3.0 mmol) at –20 °C for 10 min to give an 87:13 mixture of **193**:**293**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(4′-chlorophenyl)propan-2-one **293** as a pale yellow oil (94.3 mg, 6%);[92] R_f 0.26 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C(3)H_3), 3.68 (2H, s, C(1)H_2), 7.10-7.16 (2H, m, C(2')*H*, C(6')*H*), 7.28-7.34 (2H, m, C(3')*H*, C(5')*H*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(4′-chlorophenyl)propan-2-ol **193** as a colourless oil (1.27 g, 76%, >99:1 dr); R_f 0.17 (30-40 °C petrol/EtOAc, 80:20); $C_9H_{10}ClFO$ requires C, 57.3; H, 5.3%; found C, 57.4; H, 5.3%; ν_{max} 3396 (O–H), 2890, 2935 (C–H), 1494, 1091, 1011; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.5, C(3)H_3), 2.45 (1H, br s, O*H*), 4.04 (1H, ddq, *J* 14.9, 6.8, 6.5, C(2)*H*), 5.14 (1H, dd, *J* 47.8, 6.8, C(1)*H*), 7.27 (2H, d, *J* 8.5, C(3')*H*, C(5')*H*), 7.37 (2H, d, *J* 8.5, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 70.5 (d, *J* 24.0, *C*(2)), 97.8 (d, *J* 173, *C*(1)), 128.0 (d, *J* 6.4, *C*(2'), *C*(6')) 128.8 (*C*(3'), *C*(5')), 135.0 (d, *J* 19.2, *C*(1')), 135.3 (*C*(4')); δ_F (377 MHz, $CDCl_3$) –182.3 (dd, *J* 47.8, 14.9, C(1)*F*); *m*/*z* (FI^+) 188 ($^{35}Cl[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{35}ClFO^+$ ($[M]^+$) requires 188.0399; found 188.0405.

Ring-opening fluorination of (*RS*,*RS*)-2-(4′-bromophenyl)-3-methyloxirane 181

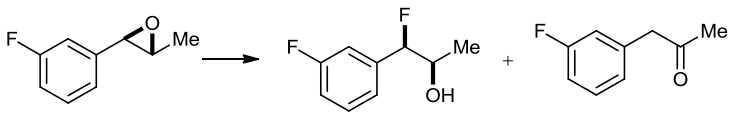


181 **194** **294**

Following *General Procedure 4*, **181** (1.50 g, 7.04 mmol, 94:6 dr) in CH_2Cl_2 (28 mL) was treated with BF_3•OEt_2 (0.29 mL, 2.4 mmol) at –20 °C for 10 min to give an 89:11 mixture of **194**:**294**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(4′-bromophenyl)propan-2-one **294** as a colourless oil (147 mg, 10%);[93] R_f 0.31 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C(3)H_3), 3.67 (2H, s, C(1)H_2), 7.03-7.11 (2H, m, C(2')*H*, C(6')*H*),

7.42-7.49 (2H, m, C(3')*H*, C(5')*H*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(4′-bromophenyl)propan-2-ol **194** as a colourless oil (1.28 g, 78%, >99:1 dr); R_f 0.21 (30-40 °C petrol/EtOAc, 80:20); $C_9H_{10}BrFO$ requires C, 46.4; H, 4.3%; found C, 46.4; H, 4.2%; ν_{max} 3396 (O–H), 2979, 2934 (C–H), 1490, 1071, 1010; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, dd, *J* 6.5, 0.7, C(3)H_3), 2.54 (1H, br s, O*H*), 4.03 (1H, ddq, *J* 14.9, 6.8, 6.5, C(2)*H*), 5.13 (1H, dd, *J* 47.2, 6.8, C(1)*H*), 7.21 (2H, d, *J* 8.4, C(3')*H*, C(5')*H*), 7.52 (2H, d, *J* 8.4, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 70.4 (d, *J* 24.0, *C*(2)), 97.8 (d, *J* 174, *C*(1)), 123.0 (*C*(4')), 128.2 (d, *J* 6.4, *C*(2'), *C*(6')) 131.7 (*C*(3'), *C*(5')), 135.7 (d, *J* 19.2, *C*(1')); δ_F (377 MHz, $CDCl_3$) –182.7 (dd, *J* 47.2, 14.9, C(1)*F*); *m*/*z* (FI^+) 234 ($^{81}Br[M]^+$, 93%), 232 ($^{79}Br[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{79}BrFO^+$ ($[M]^+$) requires 231.9894; found 231.9899.

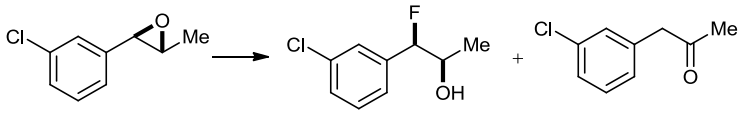
Ring-opening fluorination of (*RS*,*RS*)-2-(3′-fluorophenyl)-3-methyloxirane 182



182 **195** **295**

Following *General Procedure 4*, **182** (1.50 g, 9.86 mmol, 95:5 dr) in CH_2Cl_2 (39 mL) was treated with BF_3•OEt_2 (0.41 mL, 3.3 mmol) at –20 °C for 10 min to give an 89:11 mixture of **195**:**295**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(3′-fluorophenyl)propan-2-one **295** as a pale yellow oil (82.7 mg, 6%);[92] R_f 0.38 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, C(3)H_3), 3.70 (2H, s, C(1)H_2), 6.89-7.02 (3H, m, C(2')*H*, C(4')*H*), C(6')*H*), 7.26-7.35 (1H, m, C(5')*H*). Further elution gave (*RS*,*RS*)-1-fluoro-1-(3′-fluorophenyl)propan-2-ol **195** as a colourless oil (1.13 g, 67%, >99:1 dr); R_f 0.21 (30-40 °C petrol/EtOAc, 80:20); $C_9H_{10}F_2O$ requires C, 62.8; H, 5.85%; found C, 62.8; H, 5.8%; ν_{max} 3405 (O–H), 2981, 2936 (C–H), 1593, 1492, 1451, 1269, 1141, 1012; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.3, C(3)H_3), 2.34 (1H, br s, O*H*), 4.06 (1H, ddq, *J* 13.8, 6.8, 6.3, C(2)*H*), 5.17 (1H, dd, *J* 47.3, 6.8, C(1)*H*), 7.02-7.15 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.33-7.41 (1H, m, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 70.5 (d, *J* 22.4, *C*(2)), 97.6 (d, *J* 174, *C*(1)), 113.6 (dd, *J* 22.4, 6.4, *C*(2')), 115.9 (d, *J* 24.0, *C*(4')), 122.2 (dd, *J* 6.4, 3.2, *C*(6')), 130.2 (d, *J* 8.0, *C*(5')), 139.1 (dd, *J* 21.1, 7.0, *C*(1')), 162.8 (d, *J* 247, *C*(3')); δ_F (377 MHz, $CDCl_3$) –183.4 (dd, *J* 47.3, 13.8, C(1)*F*), –112.2 (m, C(3')*F*); *m*/*z* (FI^+) 172 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}F_2O^+$ ($[M]^+$) requires 172.0694; found 172.0702.

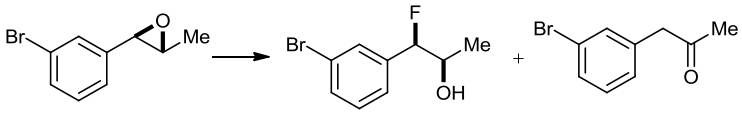
Ring-opening fluorination of (*RS*,*RS*)-2-(3′-chlorophenyl)-3-methyloxirane 183



183 **196** **296**

Following *General Procedure 4*, **183** (1.50 g, 8.90 mmol, 92:8 dr) in CH_2Cl_2 (36 mL) was treated with BF_3•OEt_2 (0.37 mL, 3.0 mmol) at –20 °C for 10 min to give a 95:5 mixture of **196**:**296**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave an impure sample of 1-(3′-chlorophenyl)propan-2-one **296** as a pale yellow oil;[92] R_f 0.33 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.19 (3H, s, C(3)H_3), 3.69 (2H, s, C(1)H_2). Further elution gave (*RS*,*RS*)-1-fluoro-1-(3′-chlorophenyl)propan-2-ol **196** as a colourless oil (1.08 g, 64%, >99:1 dr); R_f 0.18 (30-40 °C petrol/EtOAc, 80:20); $C_9H_{10}ClFO$ requires C, 57.3; H, 5.3%; found C, 57.4; H, 5.3%; ν_{max} 3396 (O–H), 2980, 2935 (C–H), 1432, 1146, 1082, 1010; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.5, C(3)H_3), 2.45 (1H, br s, O*H*), 4.05 (1H, ddq, *J* 14.9, 6.8, 6.5, C(2)*H*), 5.14 (1H, dd, *J* 47.8, 6.8, C(1)*H*), 7.20-7.25 (1H, m, C(6')*H*), 7.30-7.38 (3H, m, C(2')*H*, C(4')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (*C*(3)), 70.4 (d, *J* 22.4, *C*(2)), 97.6 (d, *J* 174, *C*(1)), 124.7 (d, *J* 6.4, *C*(6')), 126.7 (d, *J* 8.0, *C*(2')), 129.1 (*C*(4')), 129.9 (*C*(5')), 134.6 (*C*(3')), 138.7 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –183.7 (dd, *J* 47.8, 14.9, C(1)*F*); *m*/*z* (FI^+) 188 ($^{35}Cl[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{35}ClFO^+$ ($[M]^+$) requires 188.0399; found 188.0406.

Ring-opening fluorination of (*RS*,*RS*)-2-(3′-bromophenyl)-3-methyloxirane 184

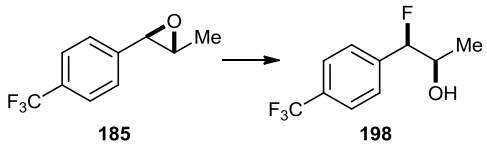


184 **197** **297**

Following *General Procedure 4*, **184** (1.50 g, 7.04 mmol, 91:9 dr) in CH_2Cl_2 (28 mL) was treated with BF_3•OEt_2 (0.29 mL, 2.4 mmol) at –20 °C for 10 min to give an 87:13 mixture of **197**:**297**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave an impure sample of 1-(3′-bromophenyl)propan-2-one **297** as a pale yellow oil;[93] R_f 0.34 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.18 (3H, s, C(3)H_3), 3.68 (2H, s, C(1)H_2). Further elution gave (*RS*,*RS*)-1-fluoro-1-(3′-bromophenyl)propan-2-ol **197** as a colourless oil (1.10 g, 67%, >99:1 dr); R_f 0.23 (30-40 °C petrol/EtOAc, 80:20); $C_9H_{10}BrFO$ requires C, 46.4; H, 4.3%; found C, 46.4; H, 4.2%; ν_{max} 3396 (O–H), 3066, 2979, 2934 (C–H), 1428, 1099, 1073, 1010; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5, C(3)H_3), 2.37 (1H, br s, O*H*), 4.05 (1H, ddq, *J* 14.9, 6.8, 6.5, C(2)*H*), 5.13 (1H, dd, *J* 47.4, 6.8, C(1)*H*), 7.24-7.30 (2H, m, C(5')*H*, C(6')*H*), 7.47-7.53 (2H, m, C(2')*H*, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (d, *J* 6.4, *C*(3)), 70.5 (d, *J* 22.4, *C*(2)), 97.5 (d, *J* 174, *C*(1)), 122.7 (*C*(3')), 125.2 (d, *J* 8.0, *C*(6')), 129.6 (d, *J* 8.0, *C*(2')), 130.1 (*C*(5')),

132.0 (*C*(4')), 138.9 (d, *J* 19.2, *C*(1')); δ_F (377 MHz, $CDCl_3$) –183.7 (dd, *J* 47.4, 14.9, C(1)*F*); *m*/*z* (FI^+) 234 ($^{81}Br[M]^+$, 96%), 232 ($^{79}Br[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}{}^{79}BrFO^+$ ($[M]^+$) requires 231.9894; found 231.9897.

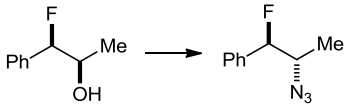
Ring-opening fluorination of (*RS*,*RS*)-2-(4′-trifluoromethylphenyl)-3-methyloxirane 185



185 **198**

Following *General Procedure 4*, **185** (400 mg, 1.98 mmol, 94:6 dr) in CH_2Cl_2 (7.9 mL) was treated with BF_3•OEt_2 (81 μL, 0.66 mmol) at –20 °C for 10 min to give a mixture of products containing a 74:26 ratio of starting material **185** and **198**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave an impure sample of (*RS*,*RS*)-1-fluoro-1-(4′-trifluoromethylphenyl)propan-2-ol **198** as a colourless oil; R_f 0.21 (30-40 °C petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.13 (3H, d, *J* 6.6, C(3)H_3), 2.39 (1H, br s, O*H*), 4.08 (1H, ddq, *J* 16.1, 6.6, 6.6, C(2)*H*), 5.25 (1H, dd, *J* 47.8, 6.6, C(1)*H*), 7.47 (2H, d, *J* 8.0, C(2′)*H*, C(6′)*H*), 7.67 (2H, d, *J* 8.0, C(3′)*H*, C(5′)*H*); δ_F (377 MHz, $CDCl_3$) –186.0 (dd, *J* 47.8, 16.1, C(1)*F*), –62.7 (m, CF_3).

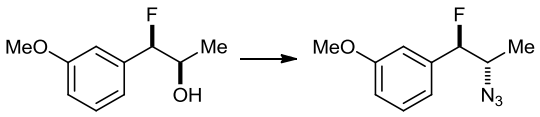
Preparation of (*RS*,*SR*)-2-azido-1-fluoro-1-phenylpropane 224



83 **224**

Following *General Procedure 8*, **83** (86.3 mg, 0.56 mmol, >99:1 dr), MsCl (65 μL, 0.84 mmol), Et_3N (160 μL, 1.15 mmol), CH_2Cl_2 (0.9 mL), NaN_3 (182 mg, 2.80 mmol) and DMF (0.9 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **224** as a colourless oil (77.1 mg, 77%, >99:1 dr);[94] R_f 0.18 (30-40 °C petrol/Et_2O, 99:1); ν_{max} 3092, 3067, 3036, 2986, 2937 (C–H), 2108 (N_3), 1454, 1264, 1245, 1006, 975; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, dd, *J* 6.8, 1.3, C(3)H_3), 3.77 (1H, dqd, *J* 17.2, 6.8, 4.6, C(2)*H*), 5.43 (1H, dd, *J* 46.6, 4.6, C(1)*H*), 7.30-7.47 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*(3)), 60.6 (d, *J* 25.6, *C*(2)), 95.5 (d, *J* 181, *C*(1)), 126.0 (d, *J* 8.0, *o*-*Ph*), 128.5 (*m*-*Ph*), 128.9 (*p*-*Ph*), 136.3 (d, *J* 19.2, *i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –187.2 (dd, *J* 46.6, 17.2, C(1)*F*); *m*/*z* (FI^+) 179 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{10}FN_3{}^+$ ($[M]^+$) requires 179.0853; found 179.0856.

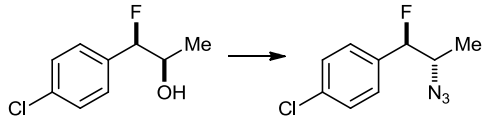
Preparation of (*RS*,*SR*)-2-azido-1-fluoro-1-(3′-methoxyphenyl)propane 234



192 **234**

Following *General Procedure 8*, **192** (500 mg, 2.71 mmol, >99:1 dr), MsCl (0.32 mL, 4.1 mmol), Et_3N (0.76 mL, 5.4 mmol), CH_2Cl_2 (4.5 mL), NaN_3 (882 mg, 13.6 mmol) and DMF (4.5 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **234** as a colourless oil (428 mg, 75%, >99:1 dr); R_f 0.26 (30-40 °C petrol/Et_2O, 96:4); $C_{10}H_{12}FN_3O$ requires C, 57.4; H, 5.8; N, 20.1%; found C, 57.5; H, 5.7; N, 20.0%; ν_{max} 2985, 2940, 2838 (C–H), 2120, 2095 (N_3), 1605, 1588, 1492, 1457, 1289, 1267, 1045; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.8, C(3)H_3), 3.74 (1H, dqd, *J* 17.2, 6.8, 4.6, C(2)*H*), 3.84 (3H, s, O*Me*), 5.41 (1H, dd, *J* 46.2, 4.6, C(1)*H*), 6.88-6.95 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.29-7.36 (1H, m, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 13.6 (d, *J* 6.4, *C*(3)), 55.3 (O*Me*), 60.6 (d, *J* 25.6, *C*(2)), 95.3 (d, *J* 179, *C*(1)), 111.6 (d, *J* 8.0, *C*(2')), 114.2 (*C*(4')), 118.2 (d, *J* 6.4, *C*(6')), 129.6 (*C*(5')), 137.9 (d, *J* 20.8, *C*(1')), 159.7 (*C*(3')); δ_F (377 MHz, $CDCl_3$) –187.9 (dd, *J* 46.2, 17.2, C(1)*F*); *m*/*z* (FI^+) 209 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{12}FN_3O^+$ ($[M]^+$) requires 209.0959; found 209.0961.

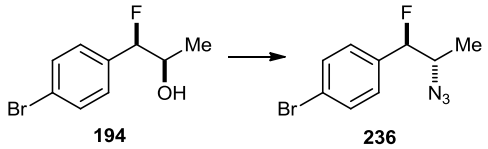
Preparation of (*RS*,*SR*)-2-azido-1-(4′-chlorophenyl)-1-fluoropropane 235



193 **235**

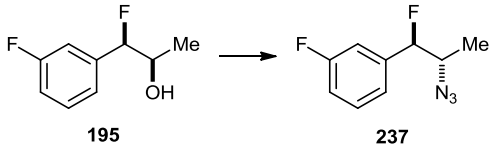
Following *General Procedure 8*, **193** (667 mg, 3.54 mmol, >99:1 dr), MsCl (0.41 mL, 5.3 mmol), Et_3N (0.99 mL, 7.1 mmol), CH_2Cl_2 (5.9 mL), NaN_3 (1.15 g, 17.7 mmol) and DMF (5.9 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **235** as a colourless oil (568 mg, 75%, >99:1 dr); R_f 0.22 (30-40 °C petrol/Et_2O, 99:1); $C_9H_9ClFN_3$ requires C, 50.6; H, 4.25; N, 19.7%; found C, 50.6; H, 4.2; N, 19.6%; ν_{max} 2986, 2938 (C–H), 2109 (N_3), 1495, 1263, 1092, 1015; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(3)H_3), 3.75 (1H, dqd, *J* 16.1, 6.8, 4.8, C(2)*H*), 5.37 (1H, dd, *J* 45.8, 4.8, C(1)*H*), 7.26-7.32 (2H, m, C(2')*H*, C(6')*H*), 7.36-7.43 (2H, m, C(3')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (d, *J* 4.8, *C*(3)), 60.5 (d, *J* 25.6, *C*(2)), 94.9 (d, *J* 181, *C*(1)), 127.5 (d, *J* 8.0, *C*(2'), *C*(6')), 128.8 (*C*(3'), *C*(5')), 134.6, 134.8 (*C*(1'), *C*(4')); δ_F (377 MHz, $CDCl_3$) –186.2 (dd, *J* 45.8, 16.1, C(1)*F*); *m*/*z* (FI^+) 213 ($^{35}Cl[M]^+$, 100%); HRMS (FI^+) $C_9H_9{}^{35}ClFN_3{}^+$ ($[M]^+$) requires 213.0464; found 213.0469.

Preparation of (*RS*,*SR*)-2-azido-1-(4′-bromophenyl)-1-fluoropropane 236



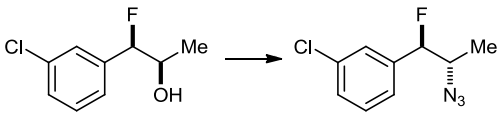
Following *General Procedure 8*, **194** (688 mg, 2.95 mmol, >99:1 dr), MsCl (0.34 mL, 4.4 mmol), Et_3N (0.82 mL, 5.9 mmol), CH_2Cl_2 (4.9 mL), NaN_3 (959 mg, 14.8 mmol) and DMF (4.9 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **236** as a colourless oil (563 mg, 74%, >99:1 dr); R_f 0.13 (30-40 °C petrol/Et_2O, 99:1); $C_9H_9BrFN_3$ requires C, 41.9; H, 3.5; N, 16.3%; found C, 41.9; H, 3.6; N, 16.3%; ν_{max} 2985, 2937 (C–H), 2108 (N_3), 1490, 1262, 1073, 1011; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(3)H_3), 3.75 (1H, dqd, *J* 16.1, 6.8, 4.8, C(2)*H*), 5.36 (1H, dd, *J* 45.9, 4.8, C(1)*H*), 7.19-7.26 (2H, m, C(2')*H*, C(6')*H*), 7.52-7.58 (2H, m, C(3')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 13.8 (d, *J* 4.8, *C*(3)), 60.4 (d, *J* 24.0, *C*(2)), 95.0 (d, *J* 179, *C*(1)), 123.0 (*C*(4')), 127.8 (d, *J* 6.4, *C*(2'), *C*(6')), 131.7 (*C*(3'), *C*(5')), 135.2 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –186.6 (dd, *J* 45.9, 16.1, C(1)*F*); *m*/*z* (FI^+) 259 ($^{81}Br[M]^+$, 100%), 257 ($^{79}Br[M]^+$, 99%); HRMS (FI^+) $C_9H_9{}^{79}BrFN_3{}^+$ ($[M]^+$) requires 256.9958; found 256.9967.

Preparation of (*RS*,*SR*)-2-azido-1-fluoro-1-(3′-fluorophenyl)propane 237



Following *General Procedure 8*, **195** (500 mg, 2.90 mmol, >99:1 dr), MsCl (0.34 mL, 4.4 mmol), Et_3N (0.81 mL, 5.8 mmol), CH_2Cl_2 (4.8 mL), NaN_3 (944 mg, 14.5 mmol) and DMF (4.8 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **237** as a colourless oil (373 mg, 65%, >99:1 dr); R_f 0.18 (30-40 °C petrol/Et_2O, 99:1); ν_{max} 3074, 2987, 2939 (C–H), 2124, 2098 (N_3), 1593, 1492, 1451, 1270, 1254; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.8, C(3)H_3), 3.75 (1H, dqd, *J* 17.2, 6.8, 4.8, C(2)*H*), 5.41 (1H, dd, *J* 46.6, 4.8, C(1)*H*), 7.04-7.14 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.35-7.43 (1H, m, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 13.7 (d, *J* 4.8, *C*(3)), 60.4 (d, *J* 25.6, *C*(2)), 94.7 (d, *J* 181, *C*(1)), 113.2 (dd, *J* 22.4, 8.0, *C*(2')), 115.8 (d, *J* 22.4, *C*(4')), 121.6 (dd, *J* 8.0, 3.2, *C*(6')), 130.2 (d, *J* 8.0, *C*(5')), 138.8 (dd, *J* 20.8, 6.4, *C*(1')), 162.8 (d, *J* 246, *C*(3')); δ_F (377 MHz, $CDCl_3$) –187.8 (dd, *J* 46.6, 17.2, C(1)*F*), –112.1 (m, C(3')*F*); *m*/*z* (FI^+) 197 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_9F_2N_3{}^+$ ($[M]^+$) requires 197.0759; found 197.0768.

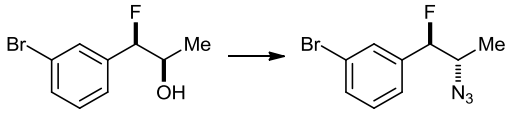
Preparation of (*RS*,*SR*)-2-azido-1-(3′-chlorophenyl)-1-fluoropropane 238



196 **238**

Following *General Procedure 8*, **196** (522 mg, 2.77 mmol, >99:1 dr), MsCl (0.32 μL, 4.1 mmol), Et_3N (0.77 mL, 5.5 mmol), CH_2Cl_2 (4.6 mL), NaN_3 (900 mg, 13.8 mmol) and DMF (4.6 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **238** as a colourless oil (375 mg, 63%, >99:1 dr); R_f 0.13 (30-40 °C petrol/Et_2O, 99:1); $C_9H_9ClFN_3$ requires C, 50.6; H, 4.25; N, 19.7%; found C, 50.6; H, 4.2; N, 19.7%; ν_{max} 2986, 2938 (C–H), 2117, 2095 (N_3), 1577, 1480, 1433, 1382, 1261, 1207, 1015; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.8, C(3)H_3), 3.75 (1H, dqd, *J* 17.2, 6.8, 4.8, C(2)*H*), 5.38 (1H, dd, *J* 46.1, 4.8, C(1)*H*), 7.19-7.26 (1H, m, C(6')*H*), 7.32-7.40 (3H, m, C(2')*H*, C(4')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 13.7 (d, *J* 4.8, *C*(3)), 60.4 (d, *J* 24.0, *C*(2)), 94.7 (d, *J* 181, *C*(1)), 124.2 (d, *J* 6.4, *C*(6')), 126.2 (d, *J* 8.0, *C*(2')), 129.1 (*C*(4')), 129.8 (*C*(5')), 134.6 (*C*(3')), 138.3 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –187.9 (dd, *J* 46.1, 17.2, C(1)*F*); *m*/*z* (FI^+) 213 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_9ClFN_3^+$ ($[M]^+$) requires 213.0464; found 213.0470.

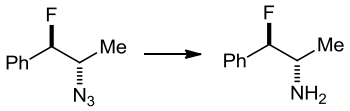
Preparation of (*RS*,*SR*)-2-azido-1-(3′-bromophenyl)-1-fluoropropane 239



197 **239**

Following *General Procedure 8*, **197** (513 mg, 2.20 mmol, >99:1 dr), MsCl (0.26 mL, 3.4 mmol), Et_3N (0.61 mL, 4.4 mmol), CH_2Cl_2 (3.7 mL), NaN_3 (715 mg, 11.0 mmol) and DMF (3.7 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave **239** as a colourless oil (357 mg, 63%, >99:1 dr); R_f 0.11 (30-40 °C petrol/Et_2O, 99:1); $C_9H_9BrFN_3$ requires C, 41.9; H, 3.5; N, 16.3%; found C, 42.0; H, 3.5; N, 16.2%; ν_{max} 3069, 2985, 2937 (C–H), 2114 (N_3), 1572, 1477, 1428, 1261, 1020; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.6, C(3)H_3), 3.75 (1H, dqd, *J* 16.1, 6.6, 4.6, C(2)*H*), 5.37 (1H, dd, *J* 45.9, 4.6, C(1)*H*), 7.25-7.32 (2H, m, C(5')*H*, C(6')*H*), 7.49-7.55 (2H, m, C(2')*H*, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 13.7 (d, *J* 4.8, *C*(3)), 60.4 (d, *J* 25.6, *C*(2)), 94.6 (d, *J* 182, *C*(1)), 122.7 (*C*(3')), 124.7 (d, *J* 8.0, *C*(6')), 129.1 (d, *J* 8.0, *C*(2')), 130.1 (*C*(5')), 132.0 (*C*(4')), 138.5 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –187.8 (dd, *J* 45.9, 16.1, C(1)*F*); *m*/*z* (FI^+) 259 ($^{81}Br[M]^+$, 94%), 257 ($^{79}Br[M]^+$, 100%); HRMS (FI^+) $C_9H_9{}^{79}BrFN_3^+$ ($[M]^+$) requires 256.9958; found 256.9967.

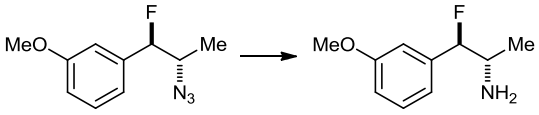
Preparation of (*RS*,*SR*)-1-fluoro-1-phenylpropan-2-amine [(α*RS*,β*SR*)-β-fluoroamphetamine] 220



224 **220**

Following *General Procedure 9*, **224** (100 mg, 0.56 mmol, >99:1 dr) in THF (1.1 mL) was treated with PPh_3 (161 mg, 0.61 mmol) and H_2O (0.20 mL, 11 mmol) to give **220** as a colourless oil (71.3 mg, 83%, >99:1 dr);[95] δ_H (400 MHz, $CDCl_3$) 1.14 (3H, dd, *J* 6.6, 1.3, C(3)*H*$_3$), 1.25 (2H, br s, N*H*$_2$), 3.29 (1H, dqd, *J* 13.8, 6.6, 5.6, C(2)*H*), 5.19 (1H, dd, *J* 46.9, 5.6, C(1)*H*), 7.25-7.32 (5H, m, *Ph*).

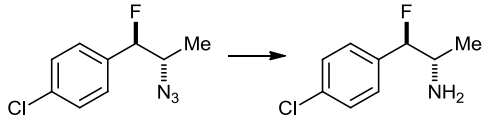
Preparation of (*RS*,*SR*)-1-fluoro-1-(3'-methoxyphenyl)propan-2-amine [(α*RS*,β*SR*)-β-fluoro-3-methoxyamphetamine] 240



234 **240**

Following *General Procedure 9*, **234** (250 mg, 1.19 mmol, >99:1 dr) in THF (2.4 mL) was treated with PPh_3 (345 mg, 1.31 mmol) and H_2O (0.43 mL, 24 mmol) to give **240** as a colourless oil (195 mg, 90%, >99:1 dr); $C_{10}H_{14}FNO$ requires C, 65.55; H, 7.7; N, 7.6%; found C, 65.5; H, 7.7; N, 7.6%; ν_{max} 3380, 3313 (N–H), 2967, 2933, 2838 (C–H), 1605, 1587, 1490, 1456, 1289, 1268; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.6, C(3)*H*$_3$), 3.27 (1H, dqd, *J* 14.9, 6.6, 5.6, C(2)*H*), 3.82 (3H, s, O*Me*), 5.15 (1H, dd, *J* 46.9, 5.6, C(1)*H*), 6.85-6.93 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.26-7.34 (1H, m, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 18.4 (d, *J* 4.8, *C*(3)), 51.2 (d, *J* 25.6, *C*(2)), 55.3 (O*Me*), 98.2 (d, *J* 176, *C*(1)), 111.9 (d, *J* 8.0, *C*(2')), 113.9 (*C*(4')), 118.6 (d, *J* 8.0, *C*(6')), 129.4 (*C*(5')), 139.1 (d, *J* 20.8, *C*(1')), 159.6 (*C*(3')); δ_F (377 MHz, $CDCl_3$) –184.2 (dd, *J* 46.9, 14.9, C(1)*F*); *m*/*z* (FI^+) 183 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{14}FNO^+$ ($[M]^+$) requires 183.1054; found 183.1055.

Preparation of (*RS*,*SR*)-1-(4'-chlorophenyl)-1-fluoropropan-2-amine [(α*RS*,β*SR*)-β-fluoro-4-chloroamphetamine] 241

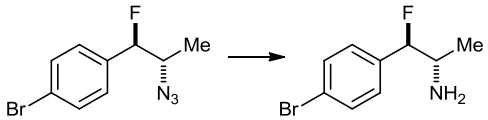


235 **241**

Following *General Procedure 9*, **235** (518 mg, 2.43 mmol, >99:1 dr) in THF (4.9 mL) was treated with PPh_3 (700 mg, 2.67 mmol) and H_2O (0.87 mL, 49 mmol) to give **241** as a colourless oil (365 mg, 80%, >99:1 dr);[96] $C_9H_{11}ClFN$ requires C, 57.6; H, 5.9; N, 7.5%; found C, 57.6; H, 5.8; N, 7.4%; ν_{max} 3384, 3300

(N–H), 2970, 2930, 2879 (C–H), 1494, 1090; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.3, C(3)*H*$_3$), 1.16 (2H, br s, N*H*$_2$), 3.26 (1H, dqd, *J* 13.8, 6.3, 5.6, C(2)*H*), 5.17 (1H, dd, *J* 46.2, 5.6, C(1)*H*), 7.24-7.30 (2H, m, C(2')*H*, C(6')*H*), 7.34-7.40 (2H, m, C(3')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (d, *J* 4.8, *C*(3)), 51.1 (d, *J* 24.0, *C*(2)), 97.6 (d, *J* 176, *C*(1)), 127.7 (d, *J* 8.0, *C*(2'), *C*(6')), 128.6 (*C*(3'), *C*(5')), 134.3 (*C*(4')), 135.9 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –184.6 (dd, *J* 46.2, 13.8, C(1)*F*); *m*/*z* (GC ToF CI$^+$) 188 ([M+H]$^+$, 48%), 168 (100%); HRMS (GC ToF CI$^+$) $C_9H_{12}ClFN^+$ ([M+H]$^+$) requires 188.0637; found 188.0637.

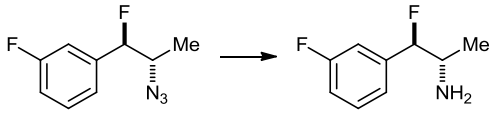
Preparation of (*RS*,*SR*)-1-(4'-bromophenyl)-1-fluoropropan-2-amine [(α*RS*,β*SR*)-β-fluoro-4-bromoamphetamine] 242



236 **242**

Following *General Procedure 9*, **236** (488 mg, 1.89 mmol, >99:1 dr) in THF (3.8 mL) was treated with PPh_3 (546 mg, 2.08 mmol) and H_2O (0.68 μL, 38 mmol) to give **242** as a colourless oil (340 mg, 78%, >99:1 dr); $C_9H_{11}BrFN$ requires C, 46.6; H, 4.8; N, 6.0%; found C, 46.5; H, 4.7; N, 6.0%; ν_{max} 3382, 3315 (N–H), 2969, 2929, 2878 (C–H), 1489, 1011, 987, 820, 791; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.6, C(3)*H*$_3$), 1.16 (2H, br s, N*H*$_2$), 3.25 (1H, dqd, *J* 14.9, 6.6, 5.3, C(2)*H*), 5.15 (1H, dd, *J* 46.2, 5.3, C(1)*H*), 7.17-7.24 (2H, m, C(2')*H*, C(6')*H*), 7.49-7.55 (2H, m, C(3')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (d, *J* 4.8, *C*(3)), 51.1 (d, *J* 25.6, *C*(2)), 97.6 (d, *J* 176, *C*(1)), 122.5 (d, *J* 3.2, *C*(4')), 128.0 (d, *J* 6.4, *C*(2'), *C*(6')), 131.5 (*C*(3'), *C*(5')), 136.4 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –185.1 (dd, *J* 46.2, 14.9, C(1)*F*); *m*/*z* (GC ToF CI$^+$) 234 (^{81}Br[M+H]$^+$, 42%), 232 (^{79}Br[M+H]$^+$, 44%), 212 (100%); HRMS (GC ToF CI$^+$) $C_9H_{12}{}^{79}BrFN^+$ ([M+H]$^+$) requires 232.0132; found 232.0132.

Preparation of (*RS*,*SR*)-1-fluoro-1-(3'-fluorophenyl)propan-2-amine [(α*RS*,β*SR*)-β,3-difluoroamphetamine] 243

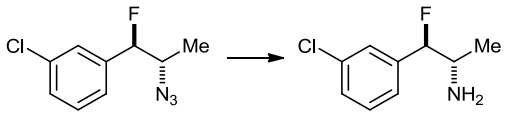


237 **243**

Following *General Procedure 9*, **237** (250 mg, 1.27 mmol, >99:1 dr) in THF (2.5 mL) was treated with PPh_3 (366 mg, 1.39 mmol) and H_2O (0.46 mL, 25 mmol) to give **243** as a colourless oil (175 mg, 80%, >99:1 dr); ν_{max} 3385, 3300 (N–H), 2971, 2932 (C–H), 1592, 1450, 789; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.3, C(3)*H*$_3$), 1.16 (2H, br s, N*H*$_2$), 3.26 (1H, dqd, *J* 16.1, 6.3, 5.3, C(2)*H*), 5.19 (1H, dd, *J* 46.9, 5.3, C(1)*H*),

7.00-7.12 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 7.31-7.39 (1H, m, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (d, *J* 4.8, *C*(3)), 51.2 (d, *J* 24.0, *C*(2)), 97.5 (d, *J* 176, *C*(1)), 113.3 (dd, *J* 22.4, 8.0, *C*(2')), 115.3 (d, *J* 20.8, *C*(4')), 121.8 (dd, *J* 8.0, 3.2, *C*(6')), 129.9 (d, *J* 8.0, *C*(5')), 140.1 (dd, *J* 20.8, 6.4, *C*(1')), 162.8 (d, *J* 248, *C*(3')); δ_F (377 MHz, $CDCl_3$) –185.8 (dd, *J* 46.9, 16.1, C(1)*F*), –112.5 (m, C(3')*F*); *m*/*z* (GC ToF CI^+) 172 ($[M+H]^+$, 100%); HRMS (GC ToF CI^+) $C_9H_{12}F_2N^+$ ($[M+H]^+$) requires 172.0932; found 172.0935.

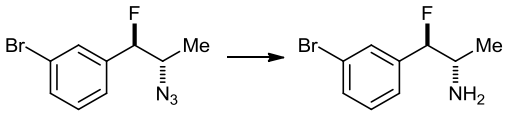
Preparation of (*RS*,*SR*)-1-(3′-chlorophenyl)-1-fluoropropan-2-amine [(α*RS*,β*SR*)-β-fluoro-3-chloroamphetamine] 244



238 **244**

Following *General Procedure 9*, **238** (334 mg, 1.56 mmol, >99:1 dr) in THF (3.1 mL) was treated with PPh_3 (451 mg, 1.72 mmol) and H_2O (0.56 mL, 31 mmol) to give **244** as a colourless oil (254 mg, 87%, >99:1 dr); $C_9H_{11}ClFN$ requires C, 57.6; H, 5.9; N, 7.5%; found C, 57.5; H, 5.9; N, 7.4%; ν_{max} 3383, 3300 (N–H), 2970, 2931, 2878 (C–H), 1576, 1431, 990, 782; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.6, C(3)H_3), 1.27 (2H, br s, NH_2), 3.27 (1H, dqd, *J* 14.9, 6.6, 5.3, C(2)*H*), 5.18 (1H, dd, *J* 46.8, 5.3, C(1)*H*), 7.17-7.23 (1H, m, C(6')*H*), 7.29-7.39 (3H, m, C(2')*H*, C(4')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 18.2 (d, *J* 4.8, *C*(3)), 51.2 (d, *J* 25.6, *C*(2)), 97.4 (d, *J* 176, *C*(1)), 124.4 (d, *J* 6.4, *C*(6')), 126.4 (d, *J* 8.0, *C*(2')), 128.6 (*C*(4')), 129.7 (*C*(5')), 134.4 (*C*(3')), 139.5 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –186.1 (dd, *J* 46.8, 14.9, C(1)*F*); *m*/*z* (GC ToF CI^+) 188 ($[M+H]^+$, 59%), 168 (100%); HRMS (GC ToF CI^+) $C_9H_{12}ClFN^+$ ($[M+H]^+$) requires 188.0637; found 188.0638.

Preparation of (*RS*,*SR*)-1-(3′-bromophenyl)-1-fluoropropan-2-amine [(α*RS*,β*SR*)-β-fluoro-3-bromoamphetamine] 245

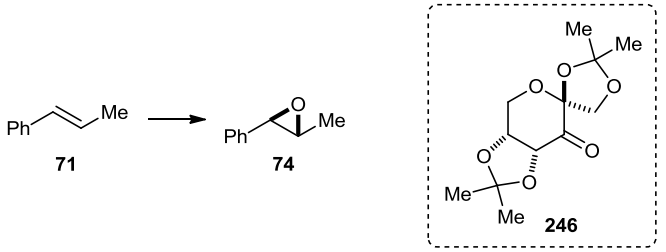


239 **245**

Following *General Procedure 9*, **239** (100 mg, 0.39 mmol, >99:1 dr) in THF (0.8 mL) was treated with PPh_3 (112 mg, 0.43 mmol) and H_2O (140 μL, 7.75 mmol) to give **245** as a colourless oil (87.0 mg, 96%, >99:1 dr); $C_9H_{11}BrFN$ requires C, 46.6; H, 4.8; N, 6.0%; found C, 46.6; H, 4.7; N, 6.0%; ν_{max} 3383 (N–H), 2969, 2929 (C–H), 1571, 998, 779; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.6, C(3)H_3), 1.24 (1H, br s, O*H*), 3.27 (1H, dqd, *J* 14.9, 6.6, 5.3, C(2)*H*), 5.17 (1H, dd, *J* 46.9, 5.3, C(1)*H*), 7.22-7.30 (2H, m, C(5')*H*, C(6')*H*), 7.43-7.56

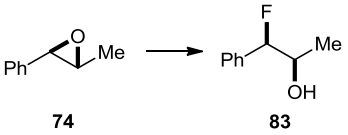
(2H, m, C(2')*H*, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (d, *J* 4.8, *C*(3)), 51.2 (d, *J* 24.0, *C*(2)), 97.4 (d, *J* 176, *C*(1)), 122.6 (*C*(3')), 124.9 (d, *J* 8.0, *C*(6')), 129.3 (d, *J* 8.0, *C*(2')), 129.9 (*C*(5')), 131.5 (*C*(4')), 139.8 (d, *J* 20.8, *C*(1')); δ_F (377 MHz, $CDCl_3$) –185.9 (dd, *J* 46.9, 14.9); *m*/*z* (GC ToF CI$^+$) 234 (^{81}Br[M+H]$^+$, 98%), 232 (^{79}Br[M+H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_9H_{12}{}^{79}BrFN^+$ ([M+H]$^+$) requires 232.0132; found 232.0133.

Preparation of (*R*,*R*)-2-methyl-3-phenyloxirane 74



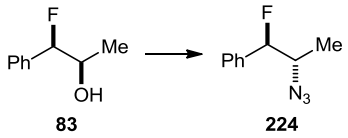
(*E*)-β-Methylstyrene **71** (6.2 mL, 48 mmol, >99:1 dr), Shi's D-fructose-derived diketal catalyst **246** (4.30 g, 16.6 mmol, 35 mol%), tetrabutylammonium hydrogensulfate (356 mg, 1.05 mmol), K_2CO_3-AcOH buffer[97] (285 mL), MeCN (317 mL) and dimethoxymethane (159 mL) were added to a 2 L, three-necked, round-bottomed flask equipped with a 5 cm, egg-shaped, Teflon-coated stirrer bar. The resultant mixture was cooled[98] to −10 °C (internal temperature) and stirred vigorously, then a solution of Oxone® (43.9 g, 71.4 mmol) in 4×10^{-4} M aq Na_2(EDTA) (162 mL) and a solution of aq KOH (1.47 M, 162 mL) were each added dropwise[99] over 2.5 h. Stirring was continued at −10 °C for 1 h and then 30-40 °C petrol (250 mL) was added and the layers were separated. The aqueous layer was extracted with 30-40 °C petrol (2 × 250 mL) and the combined organic extracts were dried and concentrated *in vacuo* (50 mbar, 40 °C). Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) on neutralised silica gel gave (*R*,*R*)-**74** as a colourless oil (6.03 g, 94%, >99:1 dr, 91% ee[100]); $[\alpha]_D^{20}$ +40.8 (*c* 1.0 in $CHCl_3$) {lit.[101] $[\alpha]_D^{25}$ +40.8 (*c* 0.92 in $CHCl_3$)}.

Preparation of (*R*,*R*)-1-fluoro-1-phenylpropan-2-ol 83



Following *General Procedure 4*, (*R*,*R*)-**74** (4.50 g, 33.5 mmol, >99:1 dr, 91% ee) in CH_2Cl_2 (134 mL) was treated with BF_3•OEt_2 (1.4 mL, 11 mmol) at –20 °C for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (*R*,*R*)-**83** as a colourless oil (4.18 g, 81%, >99:1 dr, 92% ee[102]); $[\alpha]_D^{20}$ –38.9 (*c* 1.0 in $CHCl_3$).

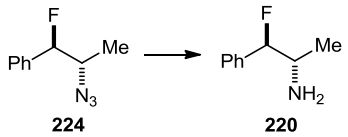
Preparation of (1*R*,2*S*)-2-azido-1-fluoro-1-phenylpropane 224



83 **224**

Following *General Procedure 8*, (*R*,*R*)-**83** (1.40 g, 9.08 mmol, >99:1 dr, 92% ee), MsCl (1.1 mL, 14 mmol), Et_3N (2.5 mL, 18 mmol), CH_2Cl_2 (15 mL), NaN_3 (2.95 g, 45.4 mmol) and DMF (15 mL) were reacted. Purification *via* flash column chromatography (gradient elution, 0→2% Et_2O in 30-40 °C petrol) gave (1*R*,2*S*)-**224** as a colourless oil (1.37 g, 84%, >99:1 dr, 93% ee[103]); $[\alpha]_D^{20}$ –56.9 (*c* 1.0 in $CHCl_3$).

Preparation of (1*R*,2*S*)-1-fluoro-1-phenylpropan-2-amine [(α*S*,β*R*)-β-fluoroamphetamine] 220

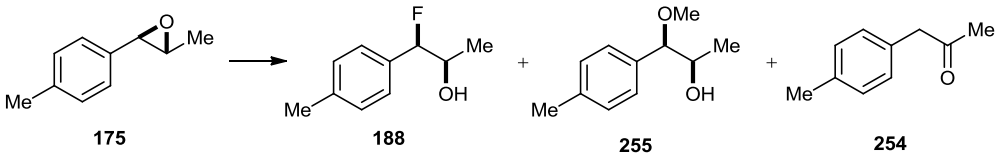


224 **220**

Following *General Procedure 9*, (1*R*,2*S*)-**224** (1.33 g, 7.42 mmol, >99:1 dr, 93% ee) in THF (15 mL) was treated with PPh_3 (2.14 g, 8.16 mmol) and H_2O (2.7 mL, 150 mmol) to give (1*R*,2*S*)-**220** as a colourless oil (924 mg, 81%, >99:1 dr, 92% ee[104]); $[\alpha]_D^{20}$ –16.3 (*c* 1.0 in $CHCl_3$).

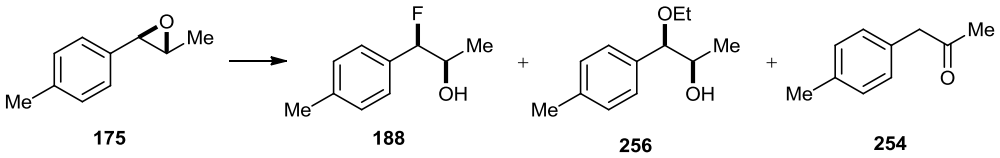
6.4. Chapter 3 Experimental

Ring-opening fluorination of (*RS*,*RS*)-2-(*p*-tolyl)-3-methyloxirane 175



Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 92:8 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(OMe)_3$ (14 μL, 0.12 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 28:38:34 mixture of **188**:**255**:**254** (22% of **188**[105]). Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 70:30) gave 1-(*p*-tolyl)propan-2-one **254** as a colourless oil (26.9 mg, 26%); R_f 0.38 (30-40 °C petrol/Et_2O, 70:30). Further elution gave (*RS*,*RS*)-1-fluoro-1-(*p*-tolyl)propan-2-ol **188** as a colourless oil (26.1 mg, 22%, >95:5 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 70:30); ν_{max} 3576, 3404 (O−H), 3029, 2978, 2927 (C−H), 1001, 812; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.3, C(3)H_3), 2.38 (3H, s, C(4′)*Me*), 2.47 (1H, s, O*H*), 4.02-4.14 (1H, m, C(2)*H*), 5.12 (1H, dd, *J* 48.1, 7.3, C(1)*H*), 7.18-7.26 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.6 (d, *J* 5.6, *C*(3)), 21.2 (C(4′)*Me*), 70.6 (d, *J* 23.2, *C*(2)), 98.7 (d, *J* 172, *C*(1)), 126.6 (d, *J* 5.6, *C*(2′), *C*(6′)), 129.2 (*C*(3′), *C*(5′)), 133.6 (d, *J* 20.0, *C*(1′)), 138.9 (d, *J* 2.4, *C*(4′)); δ_F (377 MHz, $CDCl_3$) –181.4 (dd, *J* 48.1, 14.9, C(1)*F*); *m*/*z* (FI^+) 168 ($[M]^+$, 100%); HRMS (FI^+) $C_{10}H_{13}FO^+$ ($[M]^+$) requires 168.0945; found 168.0956. Further elution gave (*RS*,*RS*)-1-methoxy-1-(*p*-tolyl)propan-2-ol **255** as a colourless oil (39.4 mg, 31%, >95:5 dr); R_f 0.18 (30-40 °C petrol/Et_2O, 70:30); ν_{max} 3461 (O−H), 3023, 2977, 2932, 2878, 2824 (C−H), 1098, 1082, 970, 812; δ_H (400 MHz, $CDCl_3$) 0.93-1.00 (3H, m, C(3)H_3), 2.36 (3H, s, C(4′)*Me*), 3.10 (1H, s, O*H*), 3.23 (3H, s, O*Me*), 3.78-3.83 (2H, m, C(1)*H*, C(2)*H*), 7.17 (4H, br s, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*(3)), 21.2 (C(4′)*Me*), 56.6 (O*Me*), 71.4 (*C*(2)), 89.4 (*C*(1)), 127.6, 129.1, 135.3, 138.0 (*Ar*); *m*/*z* (ESI^+) 203 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{16}NaO_2^+$ ($[M+Na]^+$) requires 203.1043; found 203.1044.

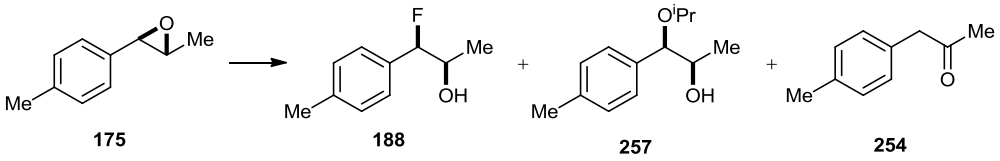
Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 92:8 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(OMe)_3$ (55 μL, 0.49 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 21:58:21 mixture of **188**:**255**:**254** (15% of **188**[105]).



175 **188** **256** **254**

Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 92:8 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(OEt)_3$ (21 μL, 0.12 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 28:37:35 mixture of **188**:**256**:**254** (23% of **188**[105]). Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 80:20) gave **254** as a colourless oil (29.4 mg, 28%); R_f 0.29 (30-40 °C petrol/Et_2O, 80:20). Further elution gave an impure sample of (*RS*,*RS*)-1-ethoxy-1-(*p*-tolyl)propan-2-ol **256** as a colourless oil (45.2 mg, ~33%, >80:20 dr); R_f 0.18 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3565, 3457 (O−H), 2974, 2929, 2874 (C−H), 1088, 810, 755; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.3, C(3)*H*$_3$), 1.18 (3H, app t, *J* 6.9, OCH_2*Me*), 2.36 (3H, s, C(4′)*Me*), 3.15 (1H, s, O*H*), 3.28-3.45 (2H, m, OCH_2Me), 3.74-3.83 (1H, m, C(2)*H*), 3.91 (1H, d, *J* 8.1, C(1)*H*), 7.11-7.23 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.3 (OCH_2*Me*), 17.9 (*C*(3)), 21.2 (C(4′)*Me*), 64.2 (OCH_2Me), 71.3 (*C*(2)), 87.5 (*C*(1)), 127.5, 129.1, 136.0, 137.8 (*Ar*); *m*/*z* (FI^+) 194 ($[M]^+$, 100%); HRMS (FI^+) $C_{12}H_{18}O_2^+$ ($[M]^+$) requires 194.1301; found 194.1308. Further elution gave **188** as a colourless oil (27.6 mg, 23%, >95:5 dr); R_f 0.15 (30-40 °C petrol/Et_2O, 80:20).

Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 92:8 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(OEt)_3$ (83 μL, 0.49 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 30:54:16 mixture of **188**:**256**:**254** (26% of **188**[105]).

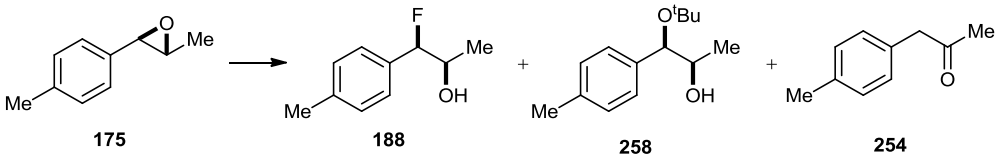


175 **188** **257** **254**

Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 90:10 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(O^iPr)_3$ (28 μL, 0.12 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 44:11:45 mixture of **188**:**257**:**254** (30% of **188**[105]). Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 80:20) gave **254** as a colourless oil (27.5 mg, 27%). Further elution gave an impure sample of (*RS*,*RS*)-1-(*iso*-propoxy)-1-(*p*-tolyl)propan-2-ol **257** as a colourless oil (10.7 mg, ~7%, >90:10 dr); R_f 0.25 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3569, 3464 (O−H), 2971, 2928, 2879 (C−H), 1052, 808; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.3, C(3)*H*$_3$), 1.06 (3H, d, *J* 6.3, CH*Me*$_A$Me$_B$), 1.17 (3H, d, *J* 6.0, CHMe$_A$*Me*$_B$), 2.36 (3H, s, C(4′)*Me*), 3.10 (1H, s, O*H*), 3.47-3.55 (1H, m, C*H*Me$_2$), 3.70-3.77 (1H, m, C(2)*H*), 4.01 (1H, d, *J* 8.2, C(1)*H*), 7.13-7.21 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.9 (*C*(3)), 21.1

($CHMe_AMe_B$, C(4′)*Me*), 23.5 ($CHMe_AMe_B$), 69.0 (*C*HMe_2), 71.3 (*C*(2)), 84.7 (*C*(1)), 127.5, 129.0, 136.6, 137.7 (*Ar*); *m*/*z* (FI^+) 208 ($[M]^+$, 100%); HRMS (FI^+) $C_{13}H_{20}O_2^+$ ($[M]^+$) requires 208.1458; found 208.1461. Further elution gave **188** as a colourless oil (35.6 mg, 30%, >95:5 dr); R_f 0.15 (30-40 °C petrol/Et_2O, 80:20).

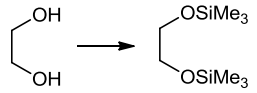
Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 90:10 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(O^iPr)_3$ (115 μL, 0.50 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 53:19:28 mixture of **188**:**257**:**254** (39% of **188**[105]). Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 80:20) gave **188** as a colourless oil (48.3 mg, 41%, >95:5 dr).



Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 90:10 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(O^tBu)_3$ (35 μL, 0.12 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a complex mixture of products containing a 22:0:78 ratio of **188**:**258**:**254** (11% of **188**[105]).

Following *General Procedure 10*, **175** (104 mg, 0.70 mmol, 90:10 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (30 μL, 0.25 mmol) and $B(O^tBu)_3$ (140 μL, 0.49 mmol) in CH_2Cl_2 (1.4 mL) at –20 °C to give a 18:49:33 mixture of **188**:**258**:**254** (12% of **188**[105]). Purification *via* flash column chromatography (30-40 °C petrol/Et_2O, 80:20) gave a 78:22 mixture of **254**:**258** as a colourless oil (24.1 mg); R_f 0.29 (30-40 °C petrol/Et_2O, 80:20). Further elution gave a 90:10 mixture of **258**:**254** as a colourless oil (47.3 mg). Data for **258**:**254** mixture: R_f 0.26 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3562, 3472 (O−H), 2973, 2932, 2903, 2873 (C−H), 1365, 1191, 1053, 1019, 810; *m*/*z* (FI^+) 222 ($[M]^+$, 100%); HRMS (FI^+) $C_{14}H_{22}O_2^+$ ($[M]^+$) requires 222.1614; found 222.1621. Data for (*RS*,*RS*)-1-(*tert*-butoxy)-1-(*p*-tolyl)propan-2-ol **258**: δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.3, C(3)*H*$_3$), 1.13 (9H, s, O^t*Bu*), 2.34 (3H, s, C(4′)*Me*), 3.04 (1H, s, O*H*), 3.57-3.66 (1H, m, C(2)*H*), 4.12 (1H, d, *J* 8.1, C(1)*H*), 7.10-7.14 (2H, m, *Ar*), 7.17-7.21 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 21.1 (C(4′)*Me*), 29.0 (OC*Me*$_3$), 71.5 (*C*(2)), 75.0 (O*C*Me$_3$), 80.2 (*C*(1)), 127.1, 128.8, 137.0, 139.5 (*Ar*). Further elution gave an impure sample of **188** as a colourless oil (16.4 mg, ~14%, >95:5 dr).

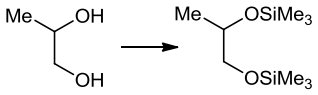
Preparation of 1,2-bis(trimethylsilyloxy)ethane 266



570 **266**

Following *General Procedure 11*, ethylene glycol **570** (1.1 mL, 20 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **266** as a colourless oil (3.42 g, 83%);[106] bp 49-50 ºC (14 mmHg) {lit.[107] bp 165-166 ºC (760 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.12 (18H, s, 2 × OSi*Me*$_3$), 3.65 (4H, s, C(1)*H*$_2$, C(2)*H*$_2$).

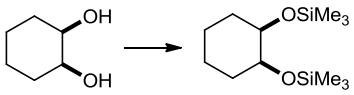
Preparation of 1,2-bis(trimethylsilyloxy)propane 267



571 **267**

Following *General Procedure 11*, propane-1,2-diol **571** (1.4 mL, 20 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **267** as a colourless oil (3.50 g, 79%); bp 51-52 ºC (14 mmHg) {lit.[107] bp 97 ºC (58 mmHg)}; ν_{max} 2958, 2904, 2867 (C−H), 1250, 1098, 833; δ_H (400 MHz, $CDCl_3$) 0.11 (9H, s, O_ASi*Me*$_3$), 0.12 (9H, s, O_BSi*Me*$_3$), 1.12 (3H, d, *J* 6.1, C(3)*H*$_3$), 3.35 (1H, dd, *J* 10.2, 5.8, C(1)*H*$_A$), 3.48 (1H, dd, *J* 10.2, 6.0, C(1)*H*$_B$), 3.76-3.85 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) −0.5, 0.2 (2 × OSi*Me*$_3$), 20.4 (*C*(3)), 68.2, 69.1 (*C*(1), *C*(2)); *m*/*z* (GC ToF CI$^+$) 221 ([M+H]$^+$, 92%), 90 (100%, $Me_3SiNH_3^+$); HRMS (GC ToF CI$^+$) $C_9H_{25}O_2Si_2^+$ ([M+H]$^+$) requires 221.1388; found 221.1419.

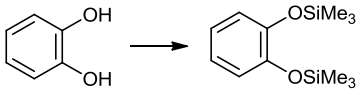
Preparation of *cis*-1,2-bis(trimethylsilyloxy)cyclohexane 268



572 **268**

Following *General Procedure 11*, *cis*-cyclohexane-1,2-diol **572** (1.00 g, 8.61 mmol, >99:1 dr) in CH_2Cl_2 (36 mL) was treated with Me_3SiCl (2.7 mL, 21 mmol) and Et_3N (3.6 mL, 26 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **268** as a colourless oil (2.08 g, 93%, >99:1 dr);[108] bp 90 ºC (14 mmHg) {lit.[109] bp 72 ºC (0.5 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.11 (18H, s, 2 × OSi*Me*$_3$), 1.17-1.30 (2H, m, C(4)*H*$_A$, C(5)*H*$_A$), 1.33-1.43 (2H, m, C(3)*H*$_A$, C(6)*H*$_A$), 1.55-1.77 (4H, m, C(3)*H*$_B$, C(4)*H*$_B$, C(5)*H*$_B$, C(6)*H*$_B$), 3.59-3.68 (2H, m, C(1)*H*, C(2)*H*).

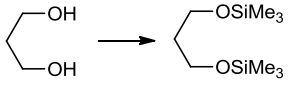
Preparation of 1,2-bis(trimethylsilyloxy)benzene 269



573 **269**

Following *General Procedure 11*, 1,2-catechol **573** (2.20 g, 20.0 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.35 mL, 50.0 mmol) and Et_3N (8.36 mL, 60.0 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **269** as a colourless oil (4.51 g, 89%);[110] bp 97-98 ºC (14 mmHg) {lit.[111] bp 118-125 ºC (30 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.27 (18H, s, 2 × OSi*Me*$_3$), 6.82-6.87 (4H, m, *Ar*).

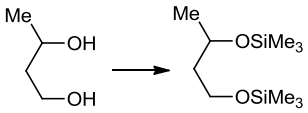
Preparation of 1,3-bis(trimethylsilyloxy)propane 270



574 **270**

Following *General Procedure 11*, propane-1,3-diol **574** (1.52 g, 20.0 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **270** as a colourless oil (3.55 g, 80%);[112] bp 61-62 ºC (14 mmHg) {lit.[107] bp 69 ºC (11 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.11 (18H, s, 2 × OSi*Me*$_3$), 1.74 (2H, quin, *J* 6.3, C(2)*H*$_2$), 3.66 (4H, t, *J* 6.3, C(1)*H*$_2$, C(3)*H*$_2$).

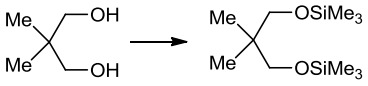
Preparation of 1,3-bis(trimethylsilyloxy)butane 271



575 **271**

Following *General Procedure 11*, butane-1,3-diol **575** (1.80 g, 20.0 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **271** as a colourless oil (3.97 g, 85%);[113] bp 66-67 ºC (14 mmHg) {lit.[114] bp 86 ºC (14.9 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.11 (9H, s, O_ASi*Me*$_3$), 0.12 (9H, s, O_BSi*Me*$_3$), 1.16 (3H, d, *J* 6.1, C(4)*H*$_3$), 1.56-1.71 (2H, m, C(2)*H*$_2$), 3.57-3.67 (2H, m, C(1)*H*$_2$), 3.90-4.00 (1H, m, C(3)*H*).

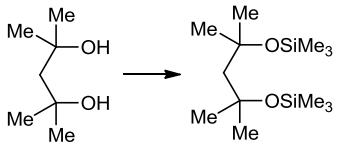
Preparation of 1,3-bis(trimethylsilyloxy)-2,2-dimethylpropane 272



576 **272**

Following *General Procedure 11*, neopentyl glycol **576** (2.08 g, 20.0 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 30 min. Purification *via* distillation at reduced pressure (14 mmHg) gave **272** as a colourless oil (4.24 g, 85%);[115] bp 66-67 ºC (14 mmHg) {lit.[107] bp 73 ºC (11 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.09 (18H, s, 2 × OSi*Me*$_3$), 0.80 (6H, s, C(2)*Me*$_2$), 3.29 (4H, s, C(1)*H*$_2$, C(3)*H*$_2$).

Preparation of 2,4-bis(trimethylsilyloxy)-2,4-dimethylpentane 273



577 **273**

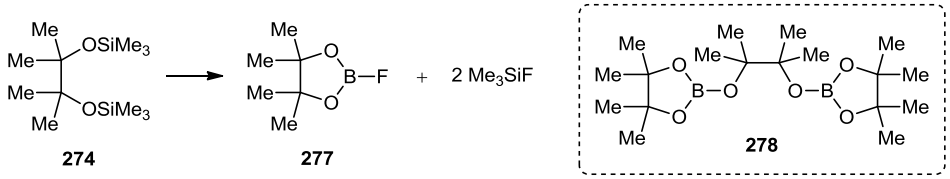
Following *General Procedure 11*, 2,4-dimethylpentane-2,4-diol **577** (2.9 mL, 20 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 24 h. Purification *via* distillation at reduced pressure (14 mmHg) gave **273** as a colourless oil (4.80 g, 87%); bp 76-77 ºC (14 mmHg); ν_{max} 2963, 2906 (C−H), 1035, 833; δ_H (400 MHz, $CDCl_3$) 0.11 (18H, s, 2 × OSi*Me*$_3$), 1.31 (12H, s, C(1)*H*$_3$, C(2)*Me*, C(4)*Me*, C(5)*H*$_3$), 1.65 (2H, s, C(3)*H*$_2$); δ_C (100 MHz, $CDCl_3$) 2.7 (2 × OSi*Me*$_3$), 31.6 (*C*(1), C(2)*Me*, C(4)*Me*, *C*(5)), 57.0 (*C*(3)), 74.6 (*C*(2), *C*(4)).[116]

Preparation of 2,3-bis(trimethylsilyloxy)-2,3-dimethylbutane 274

578 **274**

Following *General Procedure 11*, pinacol **578** (2.36 g, 20.0 mmol) in CH_2Cl_2 (83 mL) was treated with Me_3SiCl (6.4 mL, 50 mmol) and Et_3N (8.4 mL, 60 mmol) for 48 h. Purification *via* distillation at reduced pressure (14 mmHg) gave **274** as a colourless oil (4.35 g, 83%);[117] d 0.832 (20 °C); bp 54-55 ºC (14 mmHg) {lit.[117] bp 80 ºC (12 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.10 (18H, s, 2 × OSi*Me*$_3$), 1.20 (12H, s, C(1)*H*$_3$, C(2)*Me*, C(3)*Me*, C(4)*H*$_3$).

Preparation of pinacolatoboron fluoride [*B*-fluoro-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinBF)] 277



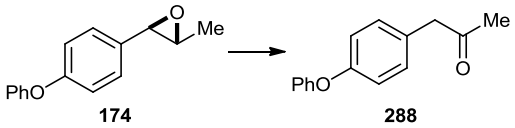
BF_3•OEt_2 (91 μL, 0.74 mmol) was added in one portion to a stirred solution of **274** (193 mg, 0.74 mmol) in CD_2Cl_2 (1.4 mL) under a N_2 atmosphere at rt and the resultant mixture was stirred at this temperature for 5 min. A colourless solution containing a small amount of an unidentified white precipitate was produced. Analysis of an aliquot of the mixture by ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectroscopy showed that complete consumption of **274** and BF_3•OEt_2 (~1% remaining) had occurred to give **277**, Me_3SiF and a compound tentatively assigned as bis-*O*-(pinacolatoboryl)pinacol **278**[118] as major components. The yield of **277** was estimated at 60% based on integration of its tetramethyl resonance at 1.34 ppm in the ^{1}H NMR spectrum against the combined methyl resonances present for all compounds in the mixture (collection of singlet resonances at δ_H 1.25-1.40 ppm). Data for **277**: δ_H (500 MHz, CD_2Cl_2) 1.34 (12H, s, 4 × *Me*); δ_C (125 MHz, CD_2Cl_2) 24.7 (4 × *Me*), 84.5 (*C*(4), *C*(5)); δ_F (470 MHz, CD_2Cl_2) −151.93 (app d, *J* 9.3, ^{11}B*F*), −151.88 (^{10}B*F* satellite); δ_B (160 MHz, CD_2Cl_2) 20.6 (br s); *m*/*z* (FI^+) 270 ($[2M+H_2O-2HF]^+$, 100%), 146 ($[M]^+$, 59%), 144 ($[M+H_2O-HF]^+$, 34%); HRMS (FI^+) $C_6H_{12}BFO_2^+$ ($[M]^+$) requires 146.0909; found 146.0912. Data for bis-*O*-(pinacolatoboryl)pinacol **278** (tentatively assigned): δ_H (500 MHz, CD_2Cl_2) [selected peaks] 1.30 (24H, s, 8 × *Me*), 1.38 (12H, s, 4 × *Me*); δ_C (125 MHz, CD_2Cl_2) 22.9 (4 × *Me*), 82.2, 83.4 (quaternary carbons); δ_B (160 MHz, CD_2Cl_2) 21.1 (br s). Data for Me_3SiF:[119] δ_H (500 MHz, CD_2Cl_2) 0.26 (9H, d, *J* 7.3, Si*Me*$_3$); δ_C (125 MHz, CD_2Cl_2) −0.02 (d, *J* 15.3, Si*Me*$_3$); δ_F (470 MHz, CD_2Cl_2) −158.0 (s). Data for BF_3•OEt_2:[119] δ_F (470 MHz, CD_2Cl_2) −153.2 (s); δ_B (160 MHz, CD_2Cl_2) 0.12 (br s). Data for Et_2O: 1.20 (6H, t, *J* 6.9, 2 × C*H*$_3$) and 3.49 (4H, q, *J* 6.9, 2 × C*H*$_2$).

Attempted ring-opening fluorination of (*RS*,*RS*)-2-(4′-methoxyphenyl)-3-methyloxirane 173

Following *General Procedure 12*, **173** (115 mg, 0.70 mmol, 96:4 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(4′-methoxyphenyl)propan-2-one **287** as a colourless oil (79.6 mg, 69%);[120] R_f 0.38 (30-40 °C

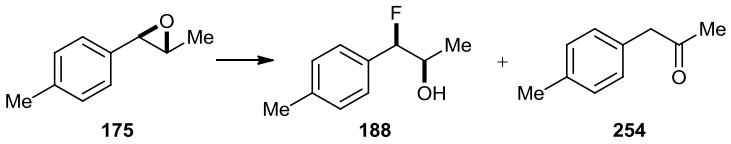
petrol/EtOAc, 80:20); δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, C(3)H_3), 3.64 (2H, s, C(1)H_2), 3.81 (3H, s, O*Me*), 6.85-6.90 (2H, m, *Ar*), 7.10-7.15 (2H, m, *Ar*).

Attempted ring-opening fluorination of (*RS*,*RS*)-2-(4′-phenoxyphenyl)-3-methyloxirane 174



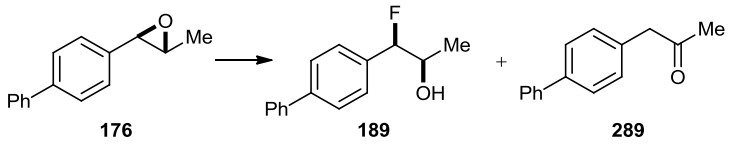
Following *General Procedure 12*, **174** (158 mg, 0.70 mmol, 96:4 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **288** as a colourless oil (124 mg, 78%).

Ring-opening fluorination of (*RS*,*RS*)-2-(*p*-tolyl)-3-methyloxirane 175



Following *General Procedure 12*, **175** (104 mg, 0.70 mmol, 91:9 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 77:23 mixture of **188**:**254** (61% of **188**[105]). Purification *via* flash column chromatography (gradient elution, 4→50% Et_2O in 30-40 °C petrol) gave **188** as a yellow oil (69.6 mg, 59%, >95:5 dr).

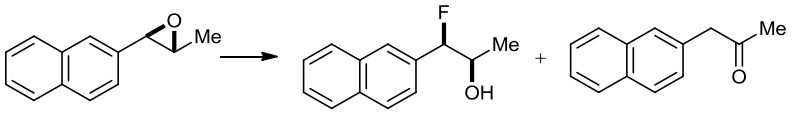
Ring-opening fluorination of (*RS*,*RS*)-2-(biphenyl-4′-yl)-3-methyloxirane 176



Following *General Procedure 12*, **176** (147 mg, 0.70 mmol, 99:1 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 70:30 mixture of **189**:**289**. Purification *via* flash column chromatography (gradient elution, 10→20% EtOAc in 30-40 °C petrol) gave 1-(biphenyl-4′-yl)propan-2-one **289** as a pale yellow solid (37.3 mg, 25%); R_f 0.38 (30-40 °C petrol/EtOAc, 80:20). Further elution gave (*RS*,*RS*)-1-(biphenyl-4′-yl)-1-fluoropropan-2-ol **189** as a white crystalline solid (85.9 mg, 53%, >95:5 dr); R_f 0.23 (30-40 °C petrol/EtOAc, 80:20); mp 82-84 °C; ν_{max} 3431 (O−H), 3061, 3032, 2996, 2915 (C−H), 1084, 991, 832, 761, 723, 690; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.4, 0.6, C(3)H_3), 2.48 (1H, br s, O*H*), 4.15 (1H, app dquin, *J* 13.5, 6.5, C(2)*H*), 5.23 (1H, dd, *J* 48.0, 7.1, C(1)*H*), 7.35-7.50 (5H, m, *Ar*), 7.58-7.67 (4H, m, *Ar*);

δ_C (100 MHz, $CDCl_3$) 17.7 (d, *J* 5.6, *C*(3)), 70.6 (d, *J* 23.2, *C*(2)), 98.5 (d, *J* 173, *C*(1)), 127.07 (d, *J* 6.4), 127.13, 127.3, 127.6, 128.9, 135.5 (d, *J* 20.0), 140.4, 141.9 (d, *J* 2.4) (*Ar*); δ_F (377 MHz, $CDCl_3$) –181.5 (dd, *J* 48.0, 13.5, C(1)*F*); *m*/*z* (FI^+) 230 ($[M]^+$, 100%); HRMS (FI^+) $C_{15}H_{15}FO^+$ ($[M]^+$) requires 230.1101; found 230.1111.

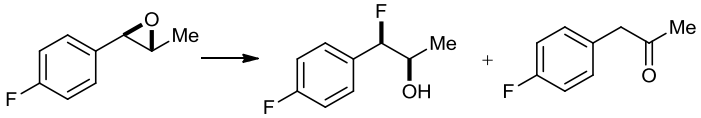
Ring-opening fluorination of (*RS*,*RS*)-2-methyl-3-(naphthalen-2-yl)oxirane 177



177 **190** **290**

Following *General Procedure 12*, **177** (129 mg, 0.70 mmol, 96:4 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 73:27 mixture of **190**:**290**. Purification *via* flash column chromatography (gradient elution, 10→20% EtOAc in 30-40 °C petrol) gave **290** as a white crystalline solid (28.3 mg, 22%). Further elution gave **190** as a white crystalline solid (79.9 mg, 56%, >95:5 dr).

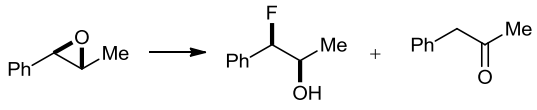
Ring-opening fluorination of (*RS*,*RS*)-2-(4′-fluorophenyl)-3-methyloxirane 178



178 **191** **291**

Following *General Procedure 12*, **178** (107 mg, 0.70 mmol, 94:6 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 77:23 mixture of **191**:**291**. Purification *via* flash column chromatography (gradient elution, 10→20% EtOAc in 30-40 °C petrol) gave **291** as a colourless oil (10.6 mg, 10%). Further elution gave **191** as a colourless oil (62.8 mg, 52%, >95:5 dr).

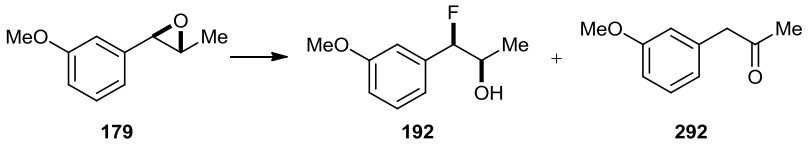
Ring-opening fluorination of (*RS*,*RS*)-2-methyl-3-phenyloxirane 74



74 **83** **84**

Following *General Procedure 12*, **74** (93.9 mg, 0.70 mmol, >99:1 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 81:19 mixture of **83**:**84**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **83** as a colourless oil (67.8 mg, 63%, 98:2 dr).

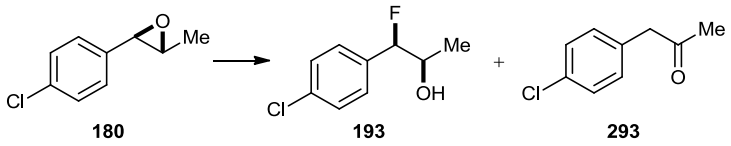
Ring-opening fluorination of (*RS*,*RS*)-2-(3′-methoxyphenyl)-3-methyloxirane 179



179 **192** **292**

Following *General Procedure 12*, **179** (115 mg, 0.70 mmol, 93:7 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 5 min to give a 66:34 mixture of **192**:**292**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **192** as a colourless oil (69.5 mg, 54%, >95:5 dr).

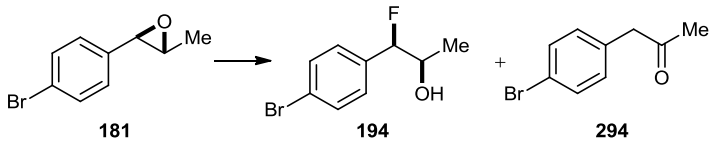
Ring-opening fluorination of (*RS*,*RS*)-2-(4′-chlorophenyl)-3-methyloxirane 180



180 **193** **293**

Following *General Procedure 12*, **180** (118 mg, 0.70 mmol, 94:6 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 10 min to give a 68:32 mixture of **193**:**293**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **293** as a yellow oil (31.6 mg, 27%). Further elution gave **193** as a yellow oil (75.0 mg, 57%, >95:5 dr).

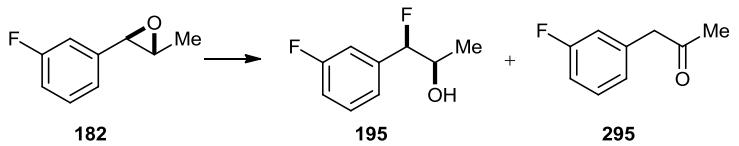
Ring-opening fluorination of (*RS*,*RS*)-2-(4′-bromophenyl)-3-methyloxirane 181



181 **194** **294**

Following *General Procedure 12*, **181** (149 mg, 0.70 mmol, 94:6 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 10 min to give a 62:38 mixture of **194**:**294**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **294** as a yellow oil (45.8 mg, 31%). Further elution gave **194** as a pale yellow oil (88.0 mg, 54%, >95:5 dr).

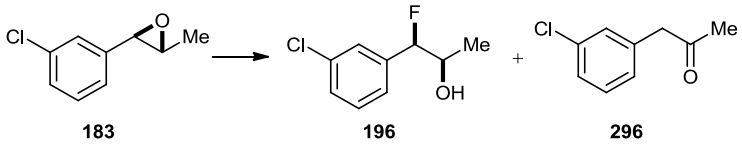
Ring-opening fluorination of (*RS,RS*)-2-(3′-fluorophenyl)-3-methyloxirane 182



182 **195** **295**

Following *General Procedure 12*, **182** (107 mg, 0.70 mmol, 95:5 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 15 min to give a 72:28 mixture of **195**:**295**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **295** as a colourless oil (23.9 mg, 22%). Further elution gave **195** as a colourless oil (66.6 mg, 55%, 89:11 dr). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.21 (3H, dd, *J* 6.5, 1.4, C(3)H_3), 5.34 (1H, dd, *J* 46.7, 4.6, C(1)*H*); δ_F (377 MHz, $CDCl_3$) [selected peak] −190.2 (dd, *J* 46.7, 16.1, C(1)*F*).

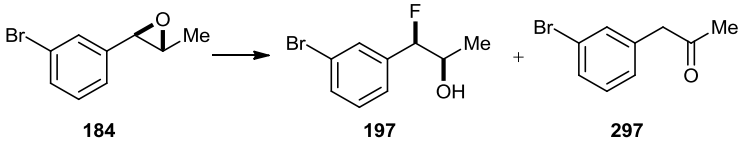
Ring-opening fluorination of (*RS,RS*)-2-(3′-chlorophenyl)-3-methyloxirane 183



183 **196** **296**

Following *General Procedure 12*, **183** (118 mg, 0.70 mmol, 92:8 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 15 min to give a 74:26 mixture of **196**:**296**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **296** as a colourless oil (27.2 mg, 23%). Further elution gave **196** as a colourless oil (73.6 mg, 56%, 87:13 dr). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.21 (3H, dd, *J* 6.5, 1.5, C(3)H_3), 5.31 (1H, dd, *J* 46.9, 4.6, C(1)*H*); δ_F (377 MHz, $CDCl_3$) −190.2 (dd, *J* 46.9, 16.1).

Ring-opening fluorination of (*RS,RS*)-2-(3′-bromophenyl)-3-methyloxirane 184



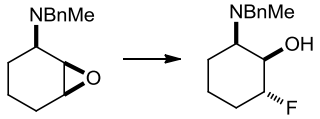
184 **197** **297**

Following *General Procedure 12*, **184** (149 mg, 0.70 mmol, 91:9 dr) in CH_2Cl_2 (1.4 mL) was treated with a solution of BF_3•OEt_2 (91 μL, 0.74 mmol) and **274** (193 mg, 0.74 mmol) in CH_2Cl_2 (1.4 mL) at rt for 15 min to give a 71:29 mixture of **197**:**297**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave **297** as a colourless oil (29.5 mg, 20%). Further elution gave **197** as a colourless oil (82.9 mg, 51%, 88:12 dr). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected

peaks] 1.21 (3H, dd, *J* 6.5, 1.4, C(3)H_3), 5.30 (1H, dd, *J* 46.2, 4.8, C(1)*H*); δ_F (377 MHz, $CDCl_3$) −190.0 (dd, *J* 46.2, 14.9).

6.5. Chapter 4 Experimental

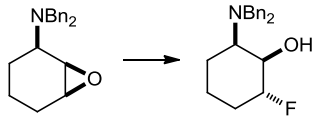
Ring-opening fluorination of (1*RS*,2*SR*,3*SR*)-1,2-epoxy-3-(*N*-benzyl-*N*-methylamino)cyclohexane 331



331 **332**

Following *General Procedure 13*, **331** (217 mg, 1.00 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL) was treated with HBF_4•OEt_2 (275 μL, 2.02 mmol). Purification *via* flash column chromatography (gradient elution, 7→60% EtOAc in 30-40 °C petrol) on neutralised silica gel gave (*RS*,*RS*,*RS*)-2-(*N*-benzyl-*N*-methylamino)-6-fluorocyclohexan-1-ol **332** as a yellow oil (211 mg, 89%, >99:1 dr); R_f 0.28 (30-40 ºC petrol/EtOAc, 70:30; neutralised silica gel); $C_{14}H_{20}FNO$ requires C, 70.9; H, 8.5; N, 5.9; found C, 71.0; H, 8.6; N, 5.85; ν_{max} 3424 (O–H), 3086, 3063, 3028, 2943, 2869, 2797 (C–H), 1454, 1070, 1002; δ_H (400 MHz, $CDCl_3$) 1.44-1.93 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.21 (3H, s, N*Me*), 2.63 (1H, dddd, *J* 11.6, 4.7, 2.9, 2.6, C(2)*H*), 3.43 (1H, br s, O*H*), 3.56 (1H, d, *J* 13.4, N(C$H_A$$H_B$Ph)), 3.74 (1H, d, *J* 13.4, N(C$H_A$$H_B$Ph)), 4.20 (1H, app dt, *J* 6.1, 3.1, C(1)*H*), 4.93 (1H, app dq, *J* 45.4, 3.1, C(6)*H*), 7.24-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (*C*(4)), 23.9 (*C*(3)), 25.3 (d, *J* 20.8, *C*(5)), 38.3 (N*Me*), 58.2 (N(*C*H_2Ph)), 60.8 (*C*(2)), 65.7 (d, *J* 30.4, *C*(1)), 90.5 (d, *J* 165, *C*(6)), 127.2 (*p*-*Ph*), 128.4, 128.9 (*o*-, *m*-*Ph*), 138.9 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –193.8 (app td, *J* 44.7, 9.2, C(6)*F*); *m*/*z* (ESI^+) 507 ($[2M+MeOH+H]^+$, 100%), 238 ($[M+H]^+$, 69%); HRMS (ESI^+) $C_{14}H_{21}FNO^+$ ($[M+H]^+$) requires 238.1602; found 238.1599.

Ring-opening fluorination of (1*RS*,2*SR*,3*SR*)-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cyclohexane 333

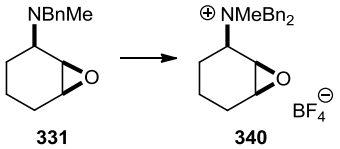


333 **334**

Following *General Procedure 13*, **333** (108 mg, 0.37 mmol, >99:1 dr) in CH_2Cl_2 (1.5 mL) was treated with HBF_4•OEt_2 (100 μL, 0.74 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-6-fluorocyclohexan-1-ol **334** as a colourless oil which solidified on standing to a white crystalline solid (117 mg, quant, >99:1 dr); R_f 0.46 (30-40 ºC petrol/EtOAc, 80:20); $C_{20}H_{24}FNO$ requires C, 76.65; H, 7.7; N, 4.5; found C, 76.7; H, 7.8; N, 4.4; mp 74-77 ºC; ν_{max} 3443 (O–H), 3085, 3062, 3028, 3004, 2941, 2869, 2805, 2730 (C–H), 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.43-1.87 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.95 (1H, br s, O*H*), 3.01-3.09 (1H, m, C(2)*H*), 3.82 (4H, A_2, N(CH_2Ph)$_2$), 4.17-4.22 (1H, app dt, *J* 6.3, 3.3, C(1)*H*), 4.84 (1H, app dq, *J* 45.5, 3.0, C(6)*H*), 7.21-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(4)), 23.8 (*C*(3)), 25.6 (d, *J* 20.8, *C*(5)), 54.7

(N(*C*H_2Ph)$_2$), 59.3 (*C*(2)), 67.2 (d, *J* 28.8, *C*(1)), 90.8 (d, *J* 166, *C*(6)), 127.0 (*p-Ph*), 128.4, 128.6 (*o-*, *m-Ph*), 139.8 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –191.8 (app t, *J* 45.9, C(6)*F*); *m*/*z* (ESI$^+$) 649 ([2M+Na]$^+$, 100%), 314 ([M+H]$^+$, 82%); HRMS (ESI$^+$) $C_{20}H_{25}FNO^+$ ([M+H]$^+$) requires 314.1915; found 314.1912.

Preparation of (1*RS*,2*RS*,3*SR*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-2,3-epoxycyclohexane tetrafluoroborate 340



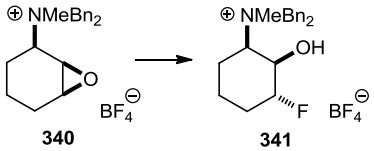
331 **340**

Step 1: BnBr (0.36 mL, 3.0 mmol) was added to a stirred solution of **331** (652 mg, 3.00 mmol, >99:1 dr) in MeCN (15 mL) and the resultant mixture was heated at reflux for 22 h then was allowed to cool to rt and was concentrated *in vacuo*. The residue was triturated with Et_2O and the precipitate was collected by filtration and washed with Et_2O to give (1*RS*,2*RS*,3*SR*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-2,3-epoxycyclohexane bromide **339** as a pale orange hygroscopic solid (1.14 g, 98%, >99:1 dr); ν_{max} 3004, 2924 (C−H), 1497, 752, 703; δ_H (400 MHz, $CDCl_3$) 1.27-1.42 (1H, m, C(5)H_A), 1.67-1.91 (3H, m, C(4)H_2, C(5)H_B), 1.98-2.11 (1H, m, C(6)H_A), 2.18-2.30 (1H, m, C(6)H_B), 3.02 (3H, s, N*Me*), 3.30-3.38 (1H, m, C(3)*H*), 3.84 (1H, app d, *J* 4.0, C(2)*H*), 4.04-4.13 (1H, m, C(1)*H*), 4.60 (1H, d, *J* 13.3, N(CH_AH$_B$Ph)$_A$), 4.90 (1H, d, *J* 12.9, N(CH_AH$_B$Ph)$_B$), 5.21 (1H, d, *J* 12.9, N(CH$_A$$H_B$Ph)$_B$), 5.40 (1H, d, *J* 13.3, N(CH$_A$$H_B$Ph)$_A$), 7.34-7.49 (6H, m, *Ph*), 7.55-7.63 (2H, m, *Ph*), 7.66-7.73 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (*C*(5)), 20.9 (*C*(6)), 21.7 (*C*(4)), 46.3 (N*Me*), 49.5 (*C*(2)), 54.4 (*C*(3)), 64.1 (N(*C*H_2Ph)$_A$), 64.5 (N(*C*H_2Ph)$_B$), 68.3 (*C*(1)), 127.29, 127.33, 129.36, 129.38, 130.7, 130.8, 133.2, 133.6 (*Ph*); *m*/*z* (ESI$^+$) 308 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M]$^+$) requires 308.2009; found 308.2001.

Step 2: MeCN (82 µL, 1.6 mmol) and CH_2Cl_2 (2.5 mL) were added sequentially to $AgBF_4$ (68.1 mg, 0.35 mmol) and the resultant solution was added to a stirred solution of **339** (136 mg, 0.35 mmol, >99:1 dr) in CH_2Cl_2 (1.0 mL) and the mixture was stirred at rt for 5 min then filtered and concentrated *in vacuo* to give **340** as a hygroscopic white solid (138 mg, quant, >99:1 dr); ν_{max} 3036, 2956 (C−H), 1050, 1030, 754, 727, 703; δ_H (400 MHz, $CDCl_3$ [neutralised over Al_2O_3]) 1.30-1.44 (1H, m, C(5)H_A), 1.71-1.94 (3H, m, C(4)H_2, C(5)H_B) 1.99-2.19 (2H, m, C(6)H_2), 2.93 (3H, s, N*Me*), 3.34-3.39 (1H, m, C(3)*H*), 3.65 (1H, app d, *J* 4.0, C(2)*H*), 3.81 (1H, app dd, *J* 9.1, 5.6, C(1)*H*), 4.36 (1H, d, *J* 13.4, N(CH_AH$_B$Ph)$_A$), 4.54 (1H, d, *J* 12.9, N(CH_AH$_B$Ph)$_B$), 4.82-4.93 (2H, m, N(CH$_A$$H_B$Ph)$_A$, N(CH$_A$$H_B$Ph)$_B$), 7.38-7.56 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$ [neutralised over Al_2O_3]) 19.7 (*C*(6)), 20.3 (*C*(5)), 21.6 (*C*(4)), 46.0 (N*Me*), 48.9 (*C*(2)), 54.4 (*C*(3)), 64.0 (N(*C*H_2Ph)$_A$), 64.5 (N(*C*H_2Ph)$_B$), 68.2 (*C*(1)), 126.70, 126.72, 129.5, 130.9, 131.0,

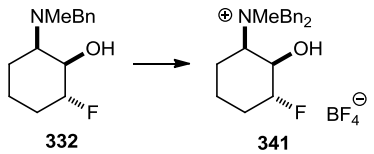
132.9, 133.4 (*Ph*); δ_F (377 MHz, $CDCl_3$ [neutralised over Al_2O_3]) −151.2 (s, BF_4^-); *m*/*z* (ESI$^+$) 308 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M]$^+$) requires 308.2009; found 308.2003.

Ring-opening fluorination of (1*RS*,2*RS*,3*SR*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-2,3-epoxycyclohexane tetrafluoroborate 340



HBF_4•OEt_2 (8.6 μL, 0.06 mmol) was added to a stirred solution of **340** (25.0 mg, 0.06 mmol) in CD_2Cl_2 (0.25 mL) at rt and the resultant mixture was stirred at rt for 5 min to give a 1:1 mixture of **341**:BF_3•OEt_2. Satd aq $NaBF_4$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried ($NaBF_4$) and concentrated *in vacuo* to give **341** as a colourless oil (26.3 mg, quant, >99:1 dr); ν_{max} 3500 (O−H), 3036, 2953, 2876 (C−H), 1057, 1033, 1009, 750, 726, 703; δ_H (400 MHz, $CDCl_3$) 1.50-1.95 (4H, m, C(4)H_2, C(5)H_2), 2.26-2.45 (2H, m, C(6)H_2), 2.83 (3H, s, N*Me*), 3.39 (1H, d, *J* 11.9, C(1)*H*), 4.28 (1H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_A$), 4.37-4.47 (2H, m, N(C$H_A$$H_B$Ph)$_B$, O*H*), 4.63-4.83 (3H, m, C(2)*H*, C(3)*H*, N(CH$_A$$H_B$Ph)$_A$), 5.32 (1H, d, *J* 12.9, N(CH$_A$$H_B$Ph)$_B$), 7.23-7.30 (2H, m, *Ph*), 7.37-7.52 (6H, m, *Ph*), 7.54-7.60 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (d, *J* 32.8, *C*(4)), 24.1 (d, *J* 20.0, *C*(5)), 29.7 (*C*(6)), 45.4 (N*Me*), 64.1, 64.7, 64.8, 65.1 (*C*(2), N(*C*H$_2$Ph)$_A$, N(*C*H$_2$Ph)$_B$), 67.3 (*C*(1)), 91.3 (d, *J* 175, *C*(3)), 126.6, 127.0, 129.3, 129.5, 130.8, 131.1, 132.6, 133.6 (*Ph*); δ_F (377 MHz, $CDCl_3$) −187.2 (C(3)*F*), −150.9 (BF_4^-); *m*/*z* (ESI$^+$) 328 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}FNO^+$ ([M]$^+$) requires 328.2071; found 328.2069.

Preparation of (*RS*,*RS*,*RS*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-3-fluorocyclohexan-2-ol tetrafluoroborate 341

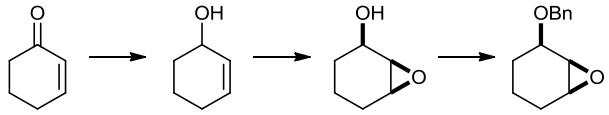


Step 1: BnBr (175 μL, 1.47 mmol) was added to a stirred solution of **332** (344 mg, 1.45 mmol, >99:1 dr) in MeCN (7.2 mL) and the resultant mixture was heated at reflux for 16 h then was allowed to cool to rt and was concentrated *in vacuo*. The residue was triturated with Et_2O and the precipitate was collected by filtration and washed with Et_2O to give (*RS*,*RS*,*RS*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-3-fluorocyclohexan-2-ol bromide **342** as a pale brown hygroscopic solid (592 mg, quant, >99:1 dr);

δ_H (400 MHz, $CDCl_3$) 1.50-1.95 (4H, m, C(4)H_2, C(5)H_2), 2.30-2.55 (2H, m, C(6)H_2), 3.02 (3H, s, N*Me*), 3.36 (1H, app d, *J* 12.1, C(1)*H*), 4.37 (1H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_A$), 4.53 (1H, d, *J* 13.0, N(C$H_A$$H_B$Ph)$_B$), 4.65-4.88 (2H, m, C(2)*H*, C(3)*H*), 4.97 (1H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_A$), 5.60 (1H, d, *J* 13.0, N(C$H_A$$H_B$Ph)$_B$), 6.08 (1H, d, *J* 6.8, O*H*), 7.27-7.51 (8H, m, *Ph*), 7.76-7.84 (2H, m, *Ph*).

Step 2: MeCN (71 μL, 1.4 mmol) and CH_2Cl_2 (2.0 mL) were added sequentially to $AgBF_4$ (58.4 mg, 0.30 mmol) and the resultant solution was added to a stirred solution of **342** (123 mg, 0.30 mmol, >99:1 dr) in CH_2Cl_2 (1.0 mL) and the mixture was stirred at rt for 5 min then filtered and concentrated *in vacuo* to give (*RS*,*RS*,*RS*)-1-(*N*,*N*-dibenzyl-*N*-methylammonio)-3-fluorocyclohexan-2-ol tetrafluoroborate **341** as a hygroscopic white solid (121 mg, 97%, >99:1 dr).

Preparation of (1*RS*,2*RS*,3*SR*)-1,2-epoxy-3-(*O*-benzyloxy)cyclohexane 344



579 **580** **581** **344**

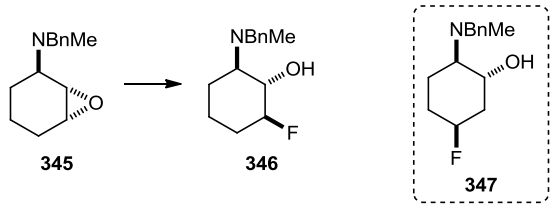
Step 1: DIBAL-H (1.0 M in hexanes, 100 mL, 100 mmol) was added dropwise to a stirred solution of **579** (8.8 mL, 91 mmol) in CH_2Cl_2 (75 mL) at 0 ºC and the resultant solution was allowed to warm to rt and was stirred at this temperature for 3 h. The mixture was then cooled to 0 ºC and satd aq Rochelle's salt (400 mL) was added dropwise (*cautiously!*) and the resultant mixture was stirred at rt for 12 h. The mixture was then filtered through a pad of Celite (eluent Et_2O) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 350 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give (*RS*)-cyclohex-2-enol **580** as a yellow oil (8.92 g, quant);[3] δ_H (400 MHz, $CDCl_3$) 1.51-2.10 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 4.16-4.25 (1H, m, C(1)*H*), 5.72-5.79 (1H, m, CH_A=CH_B), 5.81-5.88 (1H, m, CH_A=CH_B).

Step 2: Following *General Procedure 14*, **580** (8.92 g, 90.9 mmol) in CH_2Cl_2 (200 mL) was treated with *m*-CPBA (71% with H_2O, 33.1 g, 136 mmol) for 20 h. Purification *via* flash column chromatography (gradient elution, 40%→100% Et_2O in 30-40 ºC petrol) gave (1*RS*,2*SR*,3*SR*)-1,2-epoxy-3-hydroxycyclohexane **581** as a pale yellow oil (2.82 g, 27%, 98:2 dr);[4] R_f 0.26 (Et_2O); δ_H (200 MHz, $CDCl_3$) 1.08-2.19 (7H, C(4)H_2, C(5)H_2, C(6)H_2, O*H*), 3.28-3.39 (2H, m, C(1)*H*, C(2)*H*), 3.92-4.10 (1H, app s, C(3)*H*). Data for minor diastereoisomer:[4] δ_H (200 MHz, $CDCl_3$) [selected peaks] 3.09 (1H, d, *J* 4.1), 3.21-3.27 (1H, m) (C(1)*H*, C(2)*H*).

Step 3: NaH (60% dispersion with mineral oil, 701 mg, 17.5 mmol) and BnBr (1.1 mL, 9.2 mmol) were sequentially added to a stirred solution of **581** (1.00 g, 8.76 mmol, 98:2 dr) in THF (30 mL) and the resultant mixture was heated at 50 ºC for 15 h. The mixture was then allowed to cool to rt and H_2O (10 mL) was

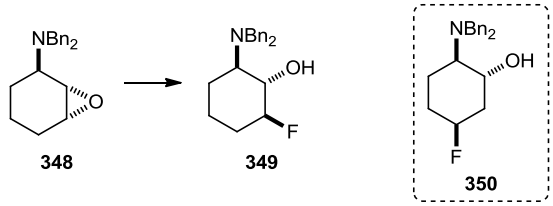
added. The mixture was diluted with Et_2O (70 mL) and washed with H_2O (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5%→40% Et_2O in 30-40 ºC petrol) gave **344** as a pale yellow oil (1.34 g, 75%, >99:1 dr);[5] R_f 0.27 (30-40 ºC petrol/Et_2O, 80:20); δ_H (400 MHz, $CDCl_3$) 1.15-1.30 (1H, m, CH_2), 1.49-1.71 (3H, m, CH_2), 1.76-1.90 (2H, m, CH_2), 3.25-3.30 (1H, m, C(1)*H*), 3.32 (1H, dd, *J* 4.1, 2.1, C(2)*H*), 3.37-3.85 (1H, m, C(3)*H*), 4.70 (2H, A_2, OCH_2Ph), 7.26-7.43 (5H, m, *Ph*).

Ring-opening fluorination of (1*RS*,2*SR*,3*RS*)-1,2-epoxy-3-(*N*-benzyl-*N*-methylamino)cyclohexane 345



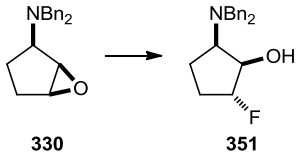
Following *General Procedure 13*, **345** (217 mg, 1.00 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL) was treated with HBF_4•OEt_2 (275 μL, 2.02 mmol) to give a 92:8 mixture of **346**:**347**. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) on neutralised silica gel gave (1*RS*,2*SR*,6*RS*)-2-(*N*-benzyl-*N*-methylamino)-6-fluorocyclohexan-1-ol **346** as a colourless oil which solidified on standing to a white crystalline solid (169 mg, 71%, >99:1 dr); R_f 0.13 (30-40 ºC petrol/EtOAc, 90:10; neutralised silica gel); $C_{14}H_{20}FNO$ requires C, 70.9; H, 8.5; N, 5.9; found C, 71.0; H, 8.35; N, 5.95; mp 77-79 ºC; ν_{max} 3441 (O–H), 3086, 3062, 3028, 2943, 2867, 2801 (C–H), 1453, 1079, 1010; δ_H (400 MHz, $CDCl_3$) 1.15-1.32 (2H, m, C(3)H_A, C(4)H_A), 1.40-1.56 (1H, m, C(5)H_A), 1.76-1.94 (2H, m, C(3)H_B, C(4)H_B), 2.07-2.17 (1H, m, C(5)H_B), 2.22 (3H, s, N*Me*), 2.35-2.45 (1H, m, C(2)*H*), 3.47 (1H, d, *J* 13.0, N(C$H_A$$H_B$Ph)), 3.55 (1H, ddd, *J* 12.8, 10.2, 8.3, C(1)*H*), 3.74 (1H, d, *J* 13.0, N(C$H_A$$H_B$Ph)), 4.37 (1H, dddd, *J* 51.5, 11.2, 8.3, 5.2, C(6)*H*), 7.24-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.64 (d, *J* 12.0, *C*(4)), 20.64 (d, *J* 2.4, *C*(3)), 30.3 (d, *J* 18.4, *C*(5)), 36.5 (N*Me*), 58.2 (N(*C*H_2Ph)), 65.8 (d, *J* 9.6, *C*(2)), 72.6 (d, *J* 16.0, *C*(1)), 95.2 (d, *J* 177, *C*(6)), 127.3 (*p*-*Ph*), 128.5, 128.8 (*o*-, *m*-*Ph*), 138.7 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –178.7 (app d, *J* 51.5, C(6)*F*); *m*/*z* (ESI^+) 497 ($[2M+Na]^+$, 100%), 238 ($[M+H]^+$, 74%); HRMS (ESI^+) $C_{14}H_{21}FNO^+$ ($[M+H]^+$) requires 238.1602; found 238.1599. Data for (1*RS*,2*RS*,5*SR*)-2-(*N*-benzyl-*N*-methylamino)-5-fluorocyclohexan-1-ol **347** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.84-5.01 (1H, m, C(5)*H*); δ_F (377 MHz, $CDCl_3$) −182.1 (app qt, *J* 45.9, 10.3, C(5)*F*).

Ring-opening fluorination of (1*RS*,2*SR*,3*RS*)-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cyclohexane 348



Following *General Procedure 13*, **348** (402 mg, 1.37 mmol, >99:1 dr) in CH_2Cl_2 (5.5 mL) was treated with HBF_4•OEt_2 (375 μL, 2.76 mmol) to give a 98:2 mixture of **349**:**350**. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave (1*RS*,2*SR*,6*RS*)-2-(*N*,*N*-dibenzylamino)-6-fluorocyclohexan-1-ol **349** as a colourless oil which solidified on standing to a white crystalline solid (314 mg, 73%, >99:1 dr); R_f 0.26 (30-40 ºC petrol/Et_2O, 80:20); $C_{20}H_{24}FNO$ requires C, 76.65; H, 7.7; N, 4.5; found C, 76.5; H, 7.6; N, 4.3; mp 77-79 ºC; ν_{max} 3453 (O–H), 3085, 3062, 3028, 2941, 2866 (C–H), 1454, 1068, 1027, 750, 700; δ_H (400 MHz, $CDCl_3$) 1.08-1.22 (1H, m, C(4)H_A), 1.29 (1H, app qd, *J* 12.6, 3.3, C(3)H_A), 1.40-1.54 (1H, m, C(5)H_A), 1.80-1.90 (1H, m, C(4)H_B), 1.90-1.98 (1H, m, C(3)H_B), 2.03-2.13 (1H, m, C(5)H_B), 2.37-2.47 (1H, app td, *J* 11.0, 2.8, C(2)*H*), 3.40 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.62 (1H, ddd, *J* 13.0, 10.0, 8.4, C(1)*H*), 3.76 (1H, br s, O*H*), 3.90 (2H, d, *J* 13.1, N(CH$_A$$H_B$Ph)$_2$), 4.23 (1H, dddd, *J* 51.5, 11.3, 8.4, 5.2, C(6)*H*), 7.24-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (d, *J* 12.8, *C*(4)), 21.3 (*C*(3)), 30.2 (d, *J* 17.6, *C*(5)), 53.7 (N(*C*H_2Ph)$_2$), 61.2 (d, *J* 9.6, *C*(2)), 72.4 (d, *J* 17.6, *C*(1)), 95.1 (d, *J* 176, *C*(6)), 127.4 (*p-Ph*), 128.6, 129.0 (*o*-, *m*-*Ph*), 138.9 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –179.0 (app d, *J* 51.5, C(6)*F*); *m*/*z* (FI^+) 313 ($[M]^+$, 100%); HRMS (FI^+) $C_{20}H_{24}FNO^+$ ($[M]^+$) requires 313.1836; found 313.1843. Data for (1*RS*,2*RS*,5*SR*)-2-(*N*,*N*-dibenzylamino)-5-fluorocyclohexan-1-ol **350** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.88 (1H, app d, *J* 47.5, C(5)*H*); δ_F (377 MHz, $CDCl_3$) −182.4 (app qt, *J* 46.5, 10.3, C(5)*F*).

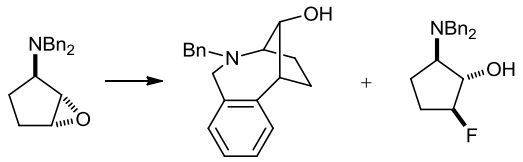
Ring-opening fluorination of (1*RS*,2*SR*,3*SR*)-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cyclopentane 330



Following *General Procedure 13*, **330** (140 mg, 0.50 mmol, >99:1 dr) in CH_2Cl_2 (2.0 mL) was treated with HBF_4•OEt_2 (140 μL, 1.03 mmol). Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-5-fluorocyclopentan-1-ol **351** as a white crystalline solid (118 mg, 78%, >99:1 dr); R_f 0.31 (30-40 °C petrol/EtOAc, 90:10); $C_{19}H_{22}FNO$ requires C, 76.2; H, 7.4; N, 4.7; found C, 76.4; H, 7.4; N, 4.6; mp 68-71 °C; ν_{max} 3457 (O–H), 3085, 3063, 3029, 2967, 2942, 2919, 2847 (C–H), 1494, 1453, 1046; δ_H (400 MHz, $CDCl_3$) 1.67-1.91 (2H, m, C(3)H_A,

C(4)H_A), 1.95-2.07 (1H, m, C(4)H_B), 2.21-2.41 (1H, m, C(3)H_B), 3.27-3.37 (1H, m, C(2)*H*), 3.50 (1H, br s, O*H*), 3.74 (4H, A_2 system, N(CH_2Ph)$_2$), 4.16 (1H, dd, *J* 10.2, 4.1, C(1)*H*), 4.95 (1H, app ddd, *J* 50.9, 6.5, 1.7, C(5)*H*), 7.24-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.9 (*C*(3)), 29.5 (d, *J* 22.4, *C*(4)), 55.7 (N(*C*H_2Ph)$_2$), 65.5 (*C*(2)), 74.1 (d, *J* 30.4, *C*(1)), 97.3 (d, *J* 174, *C*(5)), 127.3 (*p-Ph*), 128.5, 129.0 (*o-*, *m-Ph*), 138.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –176.8 (m, C(5)*F*); *m*/*z* (ESI$^+$) 300 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{23}FNO^+$ ([M+H]$^+$) requires 300.1758; found 300.1756.

Ring-opening fluorination of (1*RS*,2*SR*,3*RS*)-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cyclopentane 352

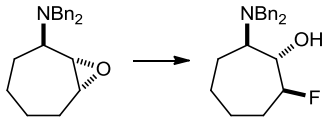


352 **353** **354**

Following *General Procedure 13*, **352** (140 mg, 0.50 mmol, >99:1 dr) in CH_2Cl_2 (2.0 mL) was treated with HBF_4•OEt_2 (140 μL, 1.03 mmol) to give a 35:65 mixture of **354**:**353**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (1*RS*,2*SR*,5*RS*)-2-(*N*,*N*-dibenzylamino)-5-fluorocyclopentan-1-ol **354** as a white crystalline solid (52.2 mg, 35%, >99:1 dr); R_f 0.28 (30-40 °C petrol/EtOAc, 80:20); mp 79-81 °C; ν_{max} 3419 (O–H), 3085, 3062, 3028, 3004, 2962, 2882, 2836, 2805 (C–H), 1494, 1454, 1365, 1075, 1056, 1028; δ_H (400 MHz, $CDCl_3$) 1.73-2.26 (5H, m, C(3)H_2, C(4)H_2, O*H*), 3.02 (1H, app dd, *J* 8.9, 8.0, C(2)*H*), 3.58 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.82 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 4.21 (1H, ddd, *J* 23.2, 8.0, 3.8, C(1)*H*), 4.66-4.86 (1H, m, C(5)*H*), 7.22-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*(3)), 27.7 (d, *J* 22.4, *C*(4)), 54.9 (N(*C*H_2Ph)$_2$), 65.9 (*C*(2)), 77.9 (d, *J* 24.0, *C*(1)), 98.1 (d, *J* 179, *C*(5)), 127.1 (*p-Ph*), 128.4, 128.6 (*o-*, *m-Ph*), 139.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –180.5 (m, C(5)*F*); *m*/*z* (ESI$^+$) 621 ([2M+Na]$^+$, 100%), 322 ([M+Na]$^+$, 92%), 300 ([M+H]$^+$, 86%); HRMS (ESI$^+$) $C_{19}H_{23}FNO^+$ ([M+H]$^+$) requires 300.1758; found 300.1756. Further elution gave (*RS*,*RS*,*RS*)-4,5-benzo-*N*-benzyl-2-azabicyclo[4.2.1]nonan-9-ol **353** as a white crystalline solid (77.4 mg, 55%, >99:1 dr); R_f 0.08 (30-40 °C petrol/EtOAc, 80:20); $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0; found C, 81.8; H, 7.4; N, 4.9; mp 139-143 °C; ν_{max} 3385 (O–H), 3062, 3027, 2923 (C–H), 1493, 1452, 1028; δ_H (400 MHz, $CDCl_3$) 1.65 (1H, br s, O*H*), 1.96-2.15 (2H, m, C(7)H_A, C(8)H_A), 2.31-2.43 (1H, m, C(7)H_B), 2.43-2.55 (1H, m, C(8)H_B), 3.24 (1H, app d, *J* 9.4, C(1)*H*), 3.35 (1H, d, *J* 15.9, C(3)H_A), 3.54 (1H, app d, *J* 6.6, C(6)*H*), 3.62 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.74 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.20 (1H, d, *J* 15.9, C(3)H_B), 4.26 (1H, s, C(9)*H*), 6.94 (1H, app d, *J* 7.3, *Ph*), 7.06-7.14 (1H, m, *Ph*), 7.19 (2H, app d, *J* 4.0, *Ph*), 7.24-7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.7 (*C*(7)), 29.5 (*C*(8)), 51.2 (*C*(3)), 54.5 (*C*(1)), 57.2

(NCH_2Ph), 71.5 (*C*(6)), 76.9 (*C*(9)), 126.0, 127.1, 127.4, 128.4, 129.0, 129.1, 130.8, 138.2, 139.3, 143.2 (*Ar*); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO^+$ ([M+H]$^+$) requires 280.1696; found 280.1694.

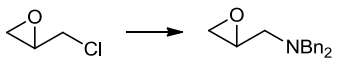
Ring-opening fluorination of (1*RS*,2*SR*,3*SR*)-1,2-epoxy-3-(*N*,*N*-dibenzylamino)cycloheptane 355



355 **356**

Following *General Procedure 13*, **355** (307 mg, 1.00 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL) was treated with HBF_4•OEt_2 (275 μL, 2.02 mmol) to give a 80:8:8:4 mixture of **356** and 3 unidentified fluorinated compounds. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (1*RS*,2*SR*,7*RS*)-2-(*N*,*N*-dibenzylamino)-7-fluorocycloheptan-1-ol **356** as a colourless oil which solidified on standing to a white crystalline solid (247 mg, 75%, >99:1 dr); R_f 0.36 (30-40 °C petrol/EtOAc, 90:10); $C_{21}H_{26}FNO$ requires C, 77.0; H, 8.0; N, 4.3; found C, 76.8; H, 7.9; N, 4.2; mp 81-82 °C ($CHCl_3$: *n*-heptane); ν_{max} 3375 (O–H), 3105, 3086, 3062, 3028, 3006, 2937, 2863, 2813 (C–H), 1495, 1454; δ_H (400 MHz, $CDCl_3$) 1.25-1.50 (3H, m, C(3)H_A, C(4)H_A, C(5)H_A), 1.56-1.93 (4H, m, C(4)H_B, C(5)H_B, C(6)H_2), 1.99-2.11 (1H, m, C(3)H_B), 2.46 (1H, app t, *J* 10.0, C(2)*H*), 3.34 (2H, d, *J* 13.3, N(CH_AH$_B$Ph)$_2$), 3.73 (1H, ddd, *J* 19.3, 9.9, 6.1, C(1)*H*), 3.86 (2H, d, *J* 13.3, N(CH$_A$$H_B$Ph)$_2$), 4.35 (1H, dddd, *J* 47.2, 8.8, 6.1, 3.4, C(7)*H*), 4.72 (1H, s, O*H*), 7.23-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (d, *J* 9.6, *C*(5)), 21.9 (*C*(3)), 25.4 (*C*(4)), 29.0 (d, *J* 21.6, *C*(6)), 53.1 (N(*C*H$_2$Ph)$_2$), 58.7 (d, *J* 10.4, *C*(2)), 74.5 (d, *J* 22.4, *C*(1)), 97.6 (d, *J* 169, *C*(7)), 127.5 (*p-Ph*), 128.6, 129.2 (*o*-, *m-Ph*), 138.4 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –171.2 (m, C(7)*F*); *m*/*z* (ESI$^+$) 677 ([2M+Na]$^+$, 100%), 328 ([M+H]$^+$, 96%); HRMS (ESI$^+$) $C_{21}H_{27}FNO^+$ ([M+H]$^+$) requires 328.2071; found 328.2067. Data for 3 unidentified fluorinated compounds: δ_F (377 MHz, $CDCl_3$) –177.5 (app tt, *J* 45.9, 12.6), –166.0 (m), –163.3 (m).

Preparation of (*RS*)-3-(*N*,*N*-dibenzylamino)-1,2-epoxypropane 357

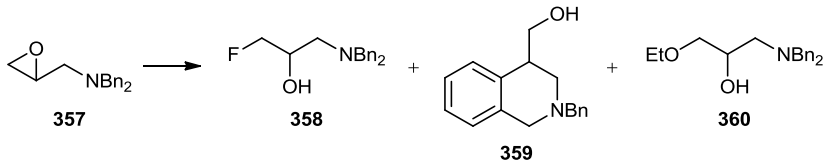


582 **357**

Dibenzylamine (2.2 mL, 11 mmol) was added dropwise to a stirred solution of epichlorohydrin **582** (0.85 mL, 11 mmol) in MeOH (36 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 1.5 h. K_2CO_3 (1.57 g, 11.3 mmol) was added and the resultant mixture was stirred at rt for 20 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (40 mL) and CH_2Cl_2 (40 mL) and the layers

were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **357** as a colourless oil (732 mg, 27%);[121] R_f 0.28 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 2.41-2.50 (2H, m, C(3)H_A, C(1)H_A), 2.71 (1H, app t, *J* 4.6, C(3)H_B), 2.81 (1H, dd, *J* 13.7, 3.4, C(1)H_B), 3.07-3.15 (1H, m, C(2)*H*), 3.68 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 3.84 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 7.23-7.46 (10H, m, *Ph*).

Ring-opening fluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)-1,2-epoxypropane 357

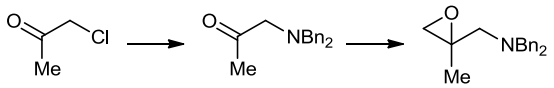


357 **358** **359** **360**

Following *General Procedure 13*, **357** (200 mg, 0.79 mmol) in CH_2Cl_2 (3.2 mL) was treated with HBF_4•OEt_2 (215 μL, 1.58 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave 1-(*N*,*N*-dibenzylamino)-3-fluoropropan-2-ol **359** as a colourless oil (27.5 mg, 13%); R_f 0.47 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3425 (O–H), 3086, 3062, 3028, 3004, 2946, 2890, 2833, 2805 (C–H), 1495, 1453, 1372, 1071, 1027, 1015, 748, 699; δ_H (400 MHz, $CDCl_3$) 2.57 (1H, dd, *J* 12.9, 4.3, C(1)H_A), 2.66 (1H, dd, *J* 12.9, 9.4, C(1)H_B), 3.53 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.81 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.86-4.00 (1H, m, C(2)*H*), 4.23 (0.5H, dd, *J* 9.6, 5.1, C(3)H_A), 4.30-4.38 (1H, m, C(3)H_A, C(3)H_B), 4.45 (0.5H, dd, *J* 9.6, 3.5, C(3)H_B), 7.24-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 55.0 (d, *J* 7.2, C(1)*H*), 58.7 (N(*C*H_2Ph)$_2$), 66.7 (d, *J* 20.0, C(2)*H*), 85.0 (d, *J* 170, C(3)*H*), 127.4 (*p-Ph*), 128.5, 129.0 (*o-*, *m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −231.5 (td, *J* 47.0, 19.5, C(3)*F*); *m*/*z* (FI$^+$) 273 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{17}H_{20}FNO^+$ ([M]$^+$) requires 273.1523; found 273.1532. Further elution gave an impure sample of 1-(*N*,*N*-dibenzylamino)-3-ethoxypropan-2-ol **359** as a colourless oil (21.2 mg, ~9%); R_f 0.29 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3444 (O–H), 3085, 3062, 3028, 2974, 2929, 2869, 2802 (C–H), 1494, 1453, 1372, 1116, 1077, 747, 699; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, *J* 6.9, OCH$_2$*Me*), 2.53-2.60 (2H, d, *J* 7.1, C(1)H_2), 3.33 (1H, dd, *J* 9.9, 6.3, C(3)H_A), 3.40 (1H, dd, *J* 9.9, 4.3, C(3)H_B), 3.47 (2H, q, *J* 7.1, OCH_2Me), 3.52 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.78 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.89-3.97 (1H, m, C(2)*H*), 7.22-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (OCH$_2$*Me*), 56.3 (*C*(1)), 58.6 (N(*C*H_2Ph)$_2$), 66.8 (O*C*H_2Me), 67.1 (*C*(2)), 73.0 (*C*(3)), 127.2 (*p-Ph*), 128.4, 129.0 (*o-*, *m-Ph*), 138.7 (*i-Ph*); *m*/*z* (ESI$^+$) 322 ([M+Na]$^+$, 100%), 300 ([M+H]$^+$, 66%); HRMS (ESI$^+$) $C_{19}H_{26}NO_2^+$ ([M+H]$^+$) requires 300.1958; found 300.1952. Further elution gave an impure sample of *N*-benzyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline **360** as a colourless oil (31.9 mg, ~16%); R_f 0.11 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3385 (O–H), 3084, 3062, 3027, 2921, 2887,

2805, 2763 (C–H), 1494, 1454, 1368, 1085, 1029, 746, 700; δ_H (400 MHz, $CDCl_3$) 2.72 (1H, ddd, *J* 11.4, 3.8, 2.0, C(3)H_A), 2.91 (1H, br s, C(4)*H*), 3.22 (1H, app dt, *J* 11.4, 1.5, C(3)H_B), 3.37 (1H, d, *J* 14.9, C(1)H_A), 3.71 (2H, AB system, J_{AB} 12.9, NCH_2Ph), 3.88-3.95 (2H, m, C(1)H_B, C(4)CH_AH$_B$OH), 4.06 (1H, dd, *J* 10.1, 2.8, C(4)CH$_A$$H_B$OH), 7.01 (1H, d, *J* 7.1, *Ar*), 7.14-7.41 (8H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 39.8 (*C*(4)), 55.6 (*C*(3)), 55.9 (*C*(1)), 63.1 (N*C*H$_2$Ph), 70.1 (C(4)*C*H$_2$OH), 126.2, 126.4, 126.7, 127.6, 128.3, 128.6, 129.1, 135.1, 135.2, 137.2 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 276 ([M+Na]$^+$, 69%), 254 ([M+H]$^+$, 73%), 252 (100%); HRMS (ESI$^+$) $C_{17}H_{20}NO^+$ ([M+H]$^+$) requires 254.1539; found 254.1535.

Preparation of (*RS*)-3-(*N*,*N*-dibenzylamino)-1,2-epoxy-2-methylpropane 361



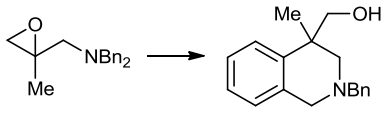
583 **584** **361**

Step 1: Dibenzylamine (3.2 mL, 17 mmol) was added to a stirred solution of chloroacetone **583** (1.2 mL, 15 mmol) and K_2CO_3 (6.22 g, 45.0 mmol) in MeCN (75 mL) and the resultant mixture was heated at reflux for 5.5 h then was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 1% Et_3N in 30-40 °C petrol) gave *N*,*N*-dibenzylaminoacetone **584** as a pale yellow oil (1.34 g, 35%); R_f 0.29 (30-40 °C petrol/EtOAc, 90:10); ν_{max} 3085, 3062, 3028, 3005, 2919, 2886, 2833, 2805, 2718 (C−H), 1714 (C=O), 1494, 1454, 1371, 1354, 1075, 1028, 746, 699; δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s, C(2)*Me*), 3.21 (2H, s, C(1)H_2), 3.69 (4H, s, N(CH_2Ph)$_2$), 7.26-7.32 (2H, m, *Ph*), 7.33-7.38 (4H, m, *Ph*), 7.39-7.44 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.6 (*C*(3)), 58.7 (N(*C*H$_2$Ph)$_2$), 63.5 (*C*(1)), 127.3 (*p*-*Ph*), 128.4, 128.9 (*o*-, *m*-*Ph*), 138.7 (*i*-*Ph*), 209.0 (*C*=O); *m*/*z* (ESI$^+$) 276 ([M+Na]$^+$, 77%), 254 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{20}NO^+$ ([M+H]$^+$) requires 254.1539; found 254.1531.

Step 2: NaH (60% dispersion with mineral oil, 112 mg, 2.81 mmol) was added to a stirred solution of trimethylsulfoxonium iodide (617 mg, 2.81 mmol) in DMSO (4.0 mL) and the resultant mixture was stirred for 30 min. A solution of **584** (500 mg, 1.87 mmol) in DMSO (2.7 mL) was added dropwise and the resultant mixture was stirred at rt for 10 h. EtOAc (20 mL) and H_2O (20 mL) were then added sequentially and the layers were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were washed with H_2O (4 × 20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **361** as a colourless oil (417 mg, 83%); R_f 0.38 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3085, 3062, 3029, 2984, 2969, 2929, 2801, 2717

(C−H), 1494, 1453, 1372, 1126, 1075, 1062, 1028, 905, 747, 698; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, C(2)*Me*), 2.40 (1H, d, *J* 13.3, C(1)H_A), 2.56 (1H, d, *J* 5.1, C(3)H_A), 2.60 (1H, d, *J* 5.1, C(3)H_B), 2.66 (1H, d, *J* 13.3, C(1)H_B), 3.51 (2H, d, *J* 13.6, N(CH_AH$_B$Ph)$_2$), 3.77 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 7.21-7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.5 (C(2)*Me*), 52.0 (*C*(3)), 56.3 (*C*(2)), 58.9 (N(*C*H$_2$Ph)$_2$), 126.9 (*p-Ph*), 128.3, 128.8 (*o-*, *m-Ph*), 139.5 (*i-Ph*); *m*/*z* (ESI$^+$) 290 ([M+Na]$^+$, 43%), 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{22}NO^+$ ([M+H]$^+$) requires 268.1696; found 268.1689.

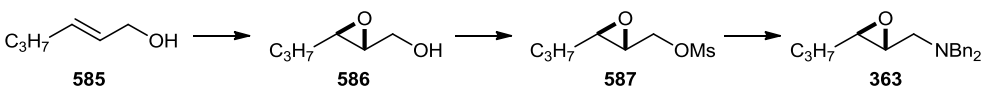
Attempted ring-opening fluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)-1,2-epoxy-2-methylpropane 361



361 **362**

Following *General Procedure 13*, **361** (267 mg, 1.00 mmol) in CH_2Cl_2 (4.0 mL) was treated with HBF_4•OEt_2 (275 μL, 2.02 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (*RS*)-*N*-benzyl-4-hydroxymethyl-4-methyl-1,2,3,4-tetrahydroisoquinoline **362** as a colourless oil (200 mg, 75%); R_f 0.23 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3387 (O–H), 3062, 3028, 2959, 2930, 2872, 2809 (C–H), 1494, 1467, 1453, 1368, 1093, 1073, 1032, 758, 731, 700; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, s, C(4)*Me*), 2.49 (1H, dd, *J* 11.4, 2.5, C(3)H_A), 3.07 (1H, dd, *J* 11.4, 1.5, C(3)H_B), 3.39 (1H, d, *J* 14.7, C(1)H_A), 3.63-3.74 (3H, m, NCH_2Ph, C(4)CH_AH$_B$OH), 3.78 (1H, d, *J* 9.9, C(4)CH$_A$$H_B$OH), 3.91 (1H, d, *J* 14.7, C(1)H_B), 5.57 (1H, br s, O*H*), 7.01 (1H, d, *J* 7.6, *Ar*), 7.17 (1H, app td, *J* 7.5, 1.0, *Ar*), 7.26 (1H, app t, *J* 7.3, *Ar*), 7.30-7.41 (6H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.4 (C(4)*Me*), 38.9 (*C*(4)), 56.8 (*C*(1)), 62.9 (N*C*H$_2$Ph), 63.6 (*C*(3)), 76.1 (C(4)*C*H$_2$OH), 125.6, 126.1, 126.2, 127.1, 127.6, 128.6, 129.1, 134.9, 136.9, 139.5 (*Ar*, *Ph*); *m*/*z* (ESI$^+$) 290 ([M+Na]$^+$, 53%), 266 (100%); HRMS (ESI$^+$) $C_{18}H_{22}NO^+$ ([M+H]$^+$) requires 268.1696; found 268.1697.

Preparation of (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxyhexane 363



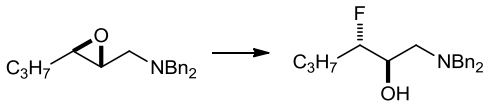
585 **586** **587** **363**

Step 1: Following *General Procedure 14*, (*E*)-hex-2-en-1-ol **585** (5.9 mL, 50 mmol, >99:1 dr) in CH_2Cl_2 (200 mL) was treated with *m*-CPBA (75% with H_2O, 17.2 g, 74.9 mmol) for 19 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave (*RS*,*RS*)-2,3-epoxyhexan-1-ol **586** as a colourless oil (4.55 g, 78%, >99:1 dr);[122] bp 54-56 °C (1.2 mmHg) {lit.[123] bp 57 °C (1.2 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 7.2, C(6)H_3), 1.40-1.61 (4H, m, C(4)H_2, C(5)H_2), 1.94 (1H, br s, O*H*), 2.90-3.00 (2H, m, C(2)*H*, C(3)*H*), 3.58-3.68 (1H, m, C(1)H_A), 3.92 (1H, ddd, *J* 12.6, 5.1, 2.4, C(1)H_B).

Step 2: Following *General Procedure 15*, **586** (2.00 g, 17.2 mmol, >99:1 dr) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.8 mL, 34 mmol) and MsCl (2.0 mL, 26 mmol). Purification *via* filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*RS*)-2,3-epoxyhexyl methanesulfonate **587** as a yellow oil (3.20 g, 96%, >99:1 dr);[124] δ_H (400 MHz, $CDCl_3$) 0.97 (3H, app t, *J* 7.2, C(6)H_3), 1.39-1.65 (4H, m, C(4)H_2, C(5)H_2), 2.92 (1H, app td, *J* 5.5, 2.1, C(3)*H*), 3.06 (1H, app dt, *J* 6.5, 2.6, C(2)*H*), 3.08 (3H, s, SO_2Me), 4.12 (1H, dd, *J* 12.0, 6.5, C(1)H_A), 4.48 (1H, dd, *J* 12.0, 3.1, C(1)H_B).

Step 3: Following *General Procedure 16*, **587** (500 mg, 2.57 mmol, >99:1 dr) in EtOH (6.4 mL) was treated with dibenzylamine (1.25 mL, 6.50 mmol) for 48 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **363** as a colourless oil (280 mg, 37%, >99:1 dr);[125] R_f 0.35 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 0.92-1.01 (3H, m, C(6)H_3), 1.38-1.55 (4H, m, C(4)H_2, C(5)H_2), 2.53 (1H, dd, *J* 13.6, 5.8, C(1)H_A), 2.62-2.69 (1H, br m, C(3)*H*), 2.73 (1H, dd, *J* 13.6, 4.0, C(1)H_B), 2.86-2.92 (1H, br m, C(2)*H*), 3.60 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.81 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 7.18-7.50 (10H, m, *Ph*).

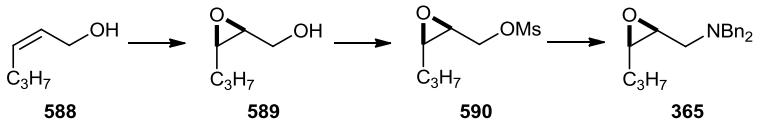
Ring-opening fluorination of (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxyhexane 363



363 **364**

Following *General Procedure 13*, **363** (156 mg, 0.53 mmol, >99:1 dr) in CH_2Cl_2 (2.1 mL) was treated with HBF_4•OEt_2 (145 μL, 1.07 mmol). Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3-fluorohexan-2-ol **364** as a colourless oil (129 mg, 77%, >99:1 dr); R_f 0.28 (30-40 °C petrol/Et_2O, 80:20); $C_{20}H_{26}FNO$ requires C, 76.2; H, 8.3; N, 4.4; found C, 76.3; H, 8.45; N, 4.3; ν_{max} 3444 (O–H), 3086, 3063, 3029, 2960, 2935, 2874, 2838, 2807 (C–H), 1454, 1076, 1027, 749, 700; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.2, C(6)H_3), 1.27-1.69 (4H, m, C(4)H_2, C(5)H_2), 2.58-2.76 (2H, m, C(1)H_2), 3.36 (1H, br s, O*H*), 3.49 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.72 (1H, dddd, *J* 11.5, 9.6, 5.8, 3.8, C(2)*H*), 3.83 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 4.29 (1H, dddd, *J* 48.5, 8.1, 5.8, 3.6, C(3)*H*), 7.23-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(6)), 18.3 (d, *J* 3.2, *C*(5)), 33.3 (d, *J* 20.8, *C*(4)), 55.3 (d, *J* 4.8, *C*(1)), 58.6 (N(*C*H_2Ph)$_2$), 68.3 (d, *J* 24.0, *C*(2)), 95.1 (d, *J* 169, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o*-, *m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –194.6 (m, C(3)*F*); *m*/*z* (FI$^+$) 315 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{20}H_{26}FNO^+$ ([M]$^+$) requires 315.1993; found 315.2003.

Preparation of (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxyhexane 365

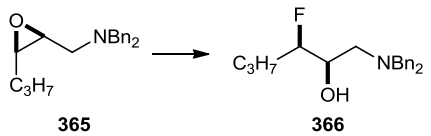


Step 1: Following *General Procedure 14*, (*Z*)-hex-2-en-1-ol **588** (5.9 mL, 50 mmol, >99:1 dr) in CH_2Cl_2 (200 mL) was treated with *m*-CPBA (75% with H_2O, 17.2 g, 74.9 mmol) for 19 h. Purification *via* distillation at reduced pressure (1.2 mmHg) gave (*RS*,*SR*)-2,3-epoxyhexan-1-ol **589** as a colourless oil (4.39 g, 76%, >99:1 dr);[122] bp 63-65 °C (1.2 mmHg) {lit.[126] bp 103-104 °C (20 mmHg)}; δ_H (400 MHz, $CDCl_3$) 0.91-1.03 (3H, m, C(6)H_3), 1.39-1.64 (4H, m, C(4)H_2, C(5)H_2), 1.92 (1H, br s, O*H*), 3.01-3.08 (1H, m, C(3)*H*), 3.16 (1H, app dt, *J* 7.1, 4.1, C(2)*H*), 3.68 (1H, ddd, *J* 10.6, 7.2, 3.4, C(1)H_A), 3.86 (1H, ddd, *J* 11.9, 7.2, 4.1, C(1)H_B).

Step 2: Following *General Procedure 15*, **589** (2.00 g, 17.2 mmol, >99:1 dr) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.8 mL, 34 mmol) and MsCl (2.0 mL, 26 mmol). Purification *via* filtration through a pad of silica gel (eluent CH_2Cl_2) gave (*RS*,*SR*)-2,3-epoxyhexyl methanesulfonate **590** as a yellow oil (3.20 g, 96%, >99:1 dr);[124] δ_H (400 MHz, $CDCl_3$) 0.96-1.02 (3H, m, C(6)H_3), 1.41-1.62 (4H, m, C(4)H_2, C(5)H_2), 3.06-3.12 (1H, m, C(3)*H*) overlapping 3.11 (3H, s, SO_2Me), 3.28 (1H, app dt, *J* 7.6, 4.0, C(2)*H*), 4.24 (1H, dd, *J* 11.7, 7.6, C(1)H_A), 4.47 (1H, dd, *J* 11.7, 3.9, C(1)H_B).

Step 3: Following *General Procedure 16*, **590** (500 mg, 2.57 mmol, >99:1 dr) in EtOH (6.4 mL) was treated with dibenzylamine (1.25 mL, 6.50 mmol) for 48 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **365** as a colourless oil (429 mg, 56%, >99:1 dr);[125] R_f 0.33 (30-40 °C petrol/Et_2O, 90:10); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 6.7, C(6)H_3), 1.30-1.60 (4H, m, C(4)H_2, C(5)H_2), 2.51 (1H, dd, *J* 13.6, 6.5, C(1)H_A), 2.82 (1H, dd, *J* 13.6, 3.8, C(1)H_B), 2.87-2.94 (1H, m, C(3)*H*), 3.17 (1H, app dt, *J* 6.5, 4.1, C(2)*H*), 3.56 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.87 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 7.20-7.50 (10H, m, *Ph*).

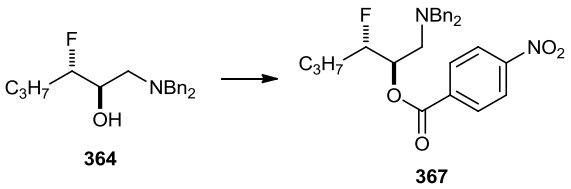
Ring-opening fluorination of (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxyhexane 365



Following *General Procedure 13*, **365** (286 mg, 0.97 mmol, >99:1 dr) in CH_2Cl_2 (3.9 mL) was treated with HBF_4•OEt_2 (265 μL, 1.95 mmol). Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-3-fluorohexan-2-ol **366** as a colourless oil (271 mg, 89%, >99:1 dr); R_f 0.28 (30-40 °C petrol/Et_2O, 80:20); $C_{20}H_{26}FNO$ requires C, 76.2; H, 8.3; N, 4.4;

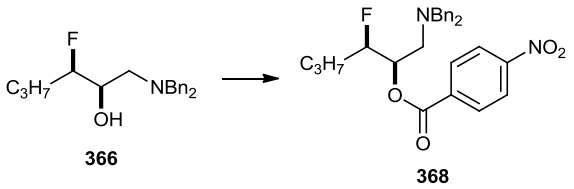
found C, 76.3; H, 8.4; N, 4.3; ν_{max} 3443 (O–H), 3086, 3063, 3028, 2960, 2934, 2873, 2833, 2806 (C–H), 1453, 748, 699; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, app t, *J* 7.1, C(6)H_3), 1.31-1.57 (3H, m, C(4)H_2, C(5)H_A), 1.64-1.80 (1H, m, C(5)H_B), 2.53 (1H, dd, *J* 12.6, 3.7, C(1)H_A), 2.75 (1H, dd, *J* 12.6, 9.8, C(1)H_B), 3.18 (1H, br s, O*H*), 3.50 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 3.69 (1H, dddd, *J* 21.5, 9.8, 3.7, 3.5, C(2)*H*), 3.84 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 4.33 (1H, dddd, *J* 48.5, 9.0, 3.5, 3.4, C(3)*H*), 7.22-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(6)), 18.4 (d, *J* 4.8, *C*(5)), 32.9 (d, *J* 22.4, *C*(4)), 55.4 (d, *J* 6.4, *C*(1)), 58.6 (N(*C*H_2Ph)$_2$), 68.7 (d, *J* 20.8, *C*(2)), 93.9 (d, *J* 174, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o-*, *m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –196.5 (m, C(3)*F*); *m*/*z* (FI^+) 315 ($[M]^+$, 100%); HRMS (FI^+) $C_{20}H_{26}FNO^+$ ($[M]^+$) requires 315.1993; found 315.2006.

Preparation of (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3-fluorohexan-2-yl 4′-nitrobenzoate 367



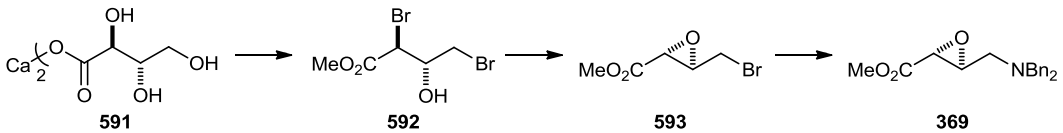
p-Nitrobenzoyl chloride (110 mg, 0.59 mmol) was added to a stirred solution of **364** (93.3 mg, 0.30 mmol, >99:1 dr) in pyridine (1.5 mL) and the resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **367** as a pale yellow oil which solidified on standing to a white crystalline solid (104 mg, 74%, >99:1 dr); R_f 0.36 (30-40 °C petrol/Et_2O, 90:10); mp 79-80 °C; ν_{max} 3111, 3086, 3062, 3029, 2962, 2935, 2875, 2834, 2802 (C–H), 1727 (C=O), 1528, 1273; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 7.3, C(6)H_3), 1.18-1.39 (2H, m, C(4)H_A, C(5)H_A), 1.43-1.73 (2H, m, C(4)H_B, C(5)H_B), 2.76 (1H, dd, *J* 13.9, 4.8, C(1)H_A), 2.86 (1H, ddd, *J* 13.9, 7.8, 1.5, C(1)H_B), 3.59 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.70 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 4.67 (1H, app ddt, *J* 48.0, 9.9, 2.9, C(3)*H*), 5.47-5.58 (1H, m, C(2)*H*), 7.21-7.32 (10H, m, *Ph*), 8.15 (2H, d, *J* 8.8, *Ar*), 8.31 (2H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (*C*(6)), 18.6 (d, *J* 3.2, *C*(5)), 32.1 (d, *J* 20.8, *C*(4)), 52.6 (d, *J* 6.4, *C*(1)), 59.0 (N(*C*H_2Ph)$_2$), 73.9 (d, *J* 20.8, *C*(2)), 93.2 (d, *J* 174, *C*(3)), 123.5 (*C*(3′), *C*(5′)), 127.2 (*p-Ph*), 128.3, 129.0 (*o-*, *m-Ph*), 131.0 (*C*(2′), *C*(6′)), 135.5 (*C*(1′)), 138.8 (*i-Ph*), 150.6 (*C*(4′)), 164.0 (*C*=O); δ_F (377 MHz, $CDCl_3$) −192.9 (m, C(3)*F*); *m*/*z* (ESI^+) 487 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{29}FN_2NaO_4^+$ ($[M+Na]^+$) requires 487.2004; found 487.2002.

Preparation of (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-3-fluorohexan-2-yl 4′-nitrobenzoate 368



p-Nitrobenzoyl chloride (263 mg, 1.42 mmol) was added to a stirred solution of **366** (224 mg, 0.71 mmol, >99:1 dr) in pyridine (3.5 mL) and the resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **368** as a pale yellow oil which solidified on standing to a white crystalline solid (252 mg, 77%, >99:1 dr); R_f 0.36 (30-40 °C petrol/Et_2O, 90:10); mp 105-107 °C; ν_{max} 3111, 3086, 3062, 3029, 2962, 2935, 2875, 2832, 2802 (C–H), 1727 (C=O), 1528, 1273; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* 7.1, C(6)H_3), 1.31-1.52 (3H, m, C(4)H_A, C(5)H_2), 1.55-1.72 (1H, m, C(4)H_B), 2.83 (1H, dd, *J* 13.6, 5.0, C(1)H_A), 2.92 (1H, dd, *J* 13.6, 7.6, C(1)H_B), 3.52 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.80 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 4.70 (1H, app ddt, *J* 47.2, 8.8, 3.3, C(3)*H*), 5.36 (1H, dddd, *J* 24.3, 7.6, 5.0, 2.9, C(2)*H*), 7.20-7.33 (10H, m, *Ph*), 8.19 (2H, d, *J* 8.8, *Ar*), 8.31 (2H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (*C*(6)), 18.3 (d, *J* 4.8, *C*(5)), 33.1 (d, *J* 20.8, *C*(4)), 53.9 (d, *J* 4.8, *C*(1)), 59.1 (N(*C*H_2Ph)$_2$), 73.2 (d, *J* 19.2, *C*(2)), 91.8 (d, *J* 176, *C*(3)), 123.5 (*C*(3′), *C*(5′)), 127.1 (*p-Ph*), 128.3, 128.9 (*o*-, *m-Ph*), 131.0 (*C*(2′), *C*(6′)), 135.4 (*C*(1′)), 138.8 (*i-Ph*), 150.7 (*C*(4′)), 164.1 (*C*=O); δ_F (377 MHz, $CDCl_3$) −196.2 (m, C(3)*F*); *m*/*z* (ESI$^+$) 487 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{29}FN_2NaO_4^+$ ([M+Na]$^+$) requires 487.2004; found 487.1999.

Preparation of methyl (2*R*,3*S*)-4-(*N*,*N*-dibenzylamino)-2,3-epoxybutanoate 369



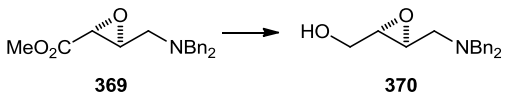
Step 1: HBr (33% in AcOH, 58 mL, 320 mmol) was added to L-threonic acid hemicalcium salt **591** (10.0 g, 32.2 mmol, >99:1 dr) and the resultant mixture was stirred at rt for 24 h. MeOH (120 mL) was then added and the solution was stirred at rt for 24 h then heated at reflux for 2 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with brine (50 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to give methyl (2*S*,3*S*)-2,4-dibromo-3-hydroxybutanoate **592** as a brown oil (15.8 g,

89%, >99:1 dr);[127] δ_H (400 MHz, $CDCl_3$) 3.09 (1H, br s, O*H*), 3.76-3.86 (5H, m, C(4)H_2, CO_2*Me*), 4.22-4.29 (1H, m, C(3)*H*), 4.34 (1H, dd, *J* 8.9, 1.7, C(2)*H*).

Step 2: K_2CO_3 (22.3 g, 161 mmol) and acetone (90 mL) were added to **592** (15.8 g, 57.3 mmol) and the resultant mixture was stirred at rt for 15 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* recrystallisation (30-40 °C petrol) gave methyl (*R*,*R*)-4-bromo-2,3-epoxybutanoate **593** as a white crystalline solid (5.43 g, 43%, >99:1 dr);[128] mp 45-47 °C (30-40 °C petrol) {lit.[128] mp 53-54 °C (EtOAc/pentane)}; $[\alpha]_D^{20}$ −7.6 (*c* 1.0 in $CHCl_3$) {lit.[128] (for enantiomer) $[\alpha]_D^{20}$ +7.5 (*c* 1.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.39 (1H, dd, *J* 10.9, 5.5, C(4)H_A), 3.43-3.48 (2H, m, C(2)*H*, C(4)H_B), 3.54 (1H, app td, *J* 5.6, 1.7, C(3)*H*), 3.81 (3H, s, CO_2*Me*).

Step 3: Dibenzylamine (3.4 mL, 17 mmol) was added to a stirred solution of **593** (1.66 g, 8.53 mmol, >99:1 dr) and KI (142 mg, 0.85 mmol) in DMF (21 mL) and the resultant mixture was stirred at rt for 25 h. Satd aq $NaHCO_3$ (150 mL) and Et_2O (100 mL) were then added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with H_2O (4 × 100 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **369** as a colourless oil (2.23 g, 84%, >99:1 dr); R_f 0.21 (30-40 °C petrol/EtOAc, 90:10); $[\alpha]_D^{20}$ −15.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3165, 3085, 3062, 3028, 3005, 2952, 2886, 2802, 2720 (C−H), 1754 (C=O), 1453, 1291, 1205, 1028, 744, 699; δ_H (400 MHz, $CDCl_3$) 2.52 (1H, dd, *J* 14.1, 6.1, C(4)H_A), 2.88 (1H, dd, *J* 14.1, 3.4, C(4)H_B), 3.22 (1H, d, *J* 1.9, C(2)*H*), 3.35 (1H, ddd, *J* 6.1, 3.4, 1.9, C(3)*H*), 3.61 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.77 (3H, s, CO_2*Me*), 3.83 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 7.22-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 51.0 (*C*(2)), 52.5 (CO_2*Me*), 54.2 (*C*(4)), 57.2 (*C*(3)), 58.8 (N(*C*H_2Ph)$_2$), 127.1 (*p-Ph*), 128.3, 128.8 (*o-*, *m-Ph*), 138.9 (*i-Ph*), 169.4 (*C*O_2Me); *m*/*z* (ESI^+) 334 ($[M+Na]^+$, 100%), 312 ($[M+H]^+$, 85%); HRMS (ESI^+) $C_{19}H_{22}NO_3^+$ ($[M+H]^+$) requires 312.1594; found 312.1595.

Preparation of (*S*,*S*)-4-(*N*,*N*-dibenzylamino)-2,3-epoxybutan-1-ol 370

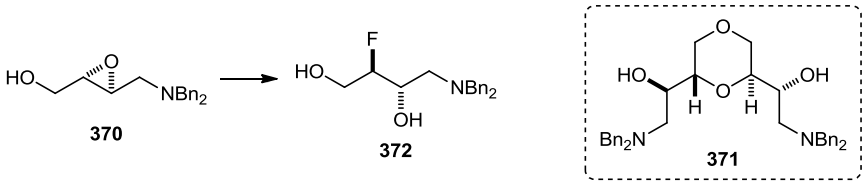


369 **370**

$NaBH_4$ (1.16 mg, 30.6 mmol) was added portionwise to a stirred solution of **369** (3.81 g, 12.2 mmol, >99:1 dr) in MeOH (31 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 4.5 h with stirring and was then concentrated *in vacuo*. The residue was partitioned between Et_2O (100 mL) and H_2O

(100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were dried, filtered through a pad of silica gel (eluent Et_2O) and concentrated *in vacuo* to give (*S*,*S*)-**370** as a colourless oil (2.82 g, 82%, >99:1 dr); $[\alpha]_D^{20}$ −9.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3418 (O−H), 3104, 3085, 3061, 3027, 3002, 2985, 2925, 2868, 2801, 2719 (C−H), 1494, 1453, 1076, 1028, 747, 699; δ_H (400 MHz, $CDCl_3$) 2.04 (1H, br s, O*H*), 2.58 (1H, dd, *J* 13.9, 6.1, C(4)H_A), 2.77 (1H, dd, *J* 13.9, 3.9, C(4)H_B), 2.82-2.88 (1H, m, C(2)*H*), 3.10-3.16 (1H, m, C(3)*H*), 3.45-3.53 (1H, m, C(1)H_A), 3.59 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.79 (1H, ddd, *J* 12.6, 5.6, 2.0, C(1)H_B) overlapping 3.83 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 7.24-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 54.7 (*C*(3)), 55.1 (*C*(4)), 56.7 (*C*(2)), 59.2 (N(*C*H$_2$Ph)$_2$), 61.4 (*C*(1)), 127.1 (*p-Ph*), 128.3, 128.8 (*o-*, *m-Ph*), 139.3 (*i-Ph*); *m*/*z* (ESI$^+$) 306 ([M+Na]$^+$, 100%), 284 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_{18}H_{22}NO_2^+$ ([M+H]$^+$) requires 284.1645; found 284.1644.

Ring-opening fluorination of (*S*,*S*)-4-(*N*,*N*-dibenzylamino)-2,3-epoxybutan-1-ol 370

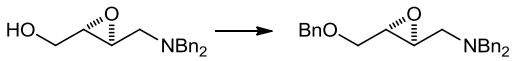


Following *General Procedure 13*, (*S*,*S*)-**370** (142 mg, 0.50 mmol, >99:1 dr) in CH_2Cl_2 (2.0 mL) was treated with HBF_4•OEt_2 (140 μL, 1.03 mmol). Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave (2*S*,6*S*,1′*R*)-2,6-bis(2'-(*N*,*N*-dibenzylamino)-1'-hydroxyethyl)-1,4-dioxane **371** as a white crystalline solid (41.0 mg, 29%, >99:1 dr); R_f 0.46 (30-40 °C petrol/EtOAc, 60:40); mp 135-137 °C; $[\alpha]_D^{20}$ −87.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3482 (O−H), 3086, 3061, 3029, 2989, 2933, 2874, 2834, 2808 (C−H), 1128, 1090, 1027, 884, 750, 745, 732, 697; δ_H (400 MHz, $CDCl_3$) 2.55 (2H, dd, *J* 13.0, 9.9, C(2′)H_A), 2.75 (2H, dd, *J* 13.0, 3.5, C(2′)H_B), 3.21 (2H, ddd, *J* 8.4, 5.4, 3.2, C(2)*H*, C(6)*H*), 3.45 (4H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 3.60 (2H, dd, *J* 11.8, 3.2, C(3)H_A, C(5)H_A), 3.74 (2H, dd, *J* 11.8, 5.6, C(3)H_B, C(5)H_B), 3.85 (4H, d, *J* 13.3, N(CH$_A$$H_B$Ph)$_2$), 3.88-3.96 (2H, m, C(1′)*H*), 7.23-7.39 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 56.5 (*C*(2′)), 58.7 (N(*C*H$_2$Ph)$_2$), 64.5, 64.6 (*C*(2), *C*(3), *C*(5), *C*(6)), 75.3 (*C*(1′)), 127.4 (*p-Ph*), 128.5, 129.1 (*o-*, *m-Ph*), 138.5 (*i-Ph*); *m*/*z* (ESI$^+$) 567 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{43}N_2O_4^+$ ([M+H]$^+$) requires 567.3217; found 567.3214. Further elution gave starting material (*S*,*S*)-**370** as a colourless oil (22.6 mg, 16%, >99:1 dr); R_f 0.31 (30-40 °C petrol/EtOAc, 60:40). Further elution gave (2*R*,3*S*)-4-(*N*,*N*-dibenzylamino)-2-fluorobutane-1,3-diol **372** as a colourless oil (17.0 mg, 11%, >99:1 dr); R_f 0.23 (30-40 °C petrol/EtOAc, 60:40); $[\alpha]_D^{20}$ −53.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3394 (O−H), 3086, 3062, 3028, 2933, 2837, 2808 (C−H), 1494, 1452, 1028, 739, 698; δ_H (400 MHz, $CDCl_3$) 2.64 (1H, dd, *J* 12.9, 9.6, C(4)H_A), 2.76 (1H, dd, *J* 12.9, 3.7, C(4)H_B), 2.81 (2H, br s, O*H*), 3.49 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.71-3.96 (5H, m, C(1)H_2,

C(3)*H*, N($CH_AH_BPh)_2$), 4.18-4.36 (1H, m, C(2)*H*), 7.23-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 55.7 (d, *J* 4.0, *C*(4)), 58.6 (N($CH_2Ph)_2$), 62.3 (d, *J* 21.6, *C*(1)), 66.3 (d, *J* 25.6, *C*(3)), 94.5 (d, *J* 172, *C*(2)), 127.5 (*p-Ph*), 128.6, 129.1 (*o-*, *m-Ph*), 138.1 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −200.0 (m, C(2)*F*); *m*/*z* (ESI^+) 304 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{23}FNO_2^+$ ($[M+H]^+$) requires 304.1707; found 304.1700.

Following *General Procedure 13*, (*S*,*S*)-**370** (142 mg, 0.50 mmol, >99:1 dr) in CH_2Cl_2 (1.3 mL) was treated with HBF_4•OEt_2 (0.68 mL, 5.0 mmol). Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave (2*R*,3*S*)-**372** as a colourless oil (119 mg, 78%, >99:1 dr).

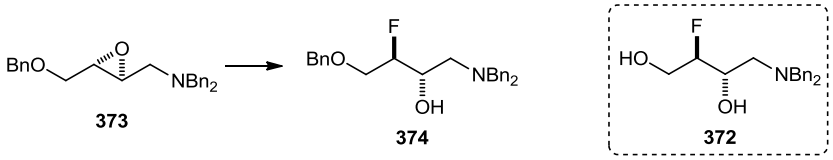
Preparation of (*S*,*S*)-4-(*N*,*N*-dibenzylamino)-1-benzyloxy-2,3-epoxybutane 373



370 **373**

NaH (60% dispersion with mineral oil, 66.0 mg, 1.65 mmol) was added to a stirred solution of (*S*,*S*)-**370** (425 mg, 1.50 mmol, >99:1 dr) in THF (7.5 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 30 min. BnBr (200 μL, 1.68 mmol) was then added and the resultant mixture was stirred at rt for 21 h then filtered through a pad of Celite (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **373** as a colourless oil (219 mg, 39%, >99:1 dr); R_f 0.21 (30-40 °C petrol/Et_2O, 90:10); $[\alpha]_D^{20}$ −0.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3085, 3062, 3028, 2985, 2924, 2853, 2799, 2719 (C−H), 1494, 1453, 1098, 1028, 734, 696; δ_H (400 MHz, $CDCl_3$) 2.54 (1H, dd, *J* 13.9, 6.1, C(4)H_A), 2.76 (1H, dd, *J* 13.9, 3.9, C(4)H_B), 2.87-2.95 (1H, m, C(2)*H*), 3.02 (1H, ddd, *J* 6.1, 3.9, 2.1, C(3)*H*), 3.39 (1H, dd, *J* 11.6, 5.7, C(1)H_A), 3.59 (2H, d, *J* 13.9, N($CH_AH_BPh)_2$) overlapping 3.63 (1H, dd, *J* 11.6, 3.3, C(1)H_B), 3.82 (2H, d, *J* 13.9, N($CH_AH_BPh)_2$), 4.56 (2H, AB system, J_{AB} 12.1, OCH_2Ph), 7.23-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 54.7 (*C*(3)), 55.1 (*C*(4)), 55.2 (*C*(2)), 59.0 (N($CH_2Ph)_2$), 70.1 (*C*(1)), 73.3 (OCH_2Ph), 127.0, 127.7, 128.3, 128.4, 128.8, 137.9, 139.3 (*Ph*); *m*/*z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}NO_2^+$ ($[M+H]^+$) requires 374.2115; found 374.2098.

Ring-opening fluorination of (*S*,*S*)-4-(*N*,*N*-dibenzylamino)-1-benzyloxy-2,3-epoxybutane 373



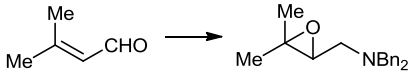
373 **374** **372**

Following *General Procedure 13*, **373** (112 mg, 0.30 mmol, >99:1 dr) in CH_2Cl_2 (1.2 mL) was treated with HBF_4•OEt_2 (82 μL, 0.60 mmol) to give a 53:47 mixture of **374**:**373**. Purification *via* flash column

chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave starting material (*S*,*S*)-**373** as a colourless oil which solidified on standing to a white solid (39.9 mg, 36%, >99:1 dr); R_f 0.31 (30-40 °C petrol/EtOAc, 90:10). Further elution gave (2*S*,3*R*)-4-(benzyloxy)-1-(*N*,*N*-dibenzylamino)-3-fluorobutan-2-ol **374** as a colourless oil (32.9 mg, 28%, >99:1 dr); R_f 0.15 (30-40 °C petrol/EtOAc, 90:10); mp 60-62 °C; $[\alpha]_D^{20}$ −34.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3447 (O−H), 3086, 3063, 3029, 2930, 2850, 2708 (C−H), 1495, 1453, 1098, 1076, 1055, 1027, 736, 697; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, dd, *J* 12.9, 9.6, C(1)H_A), 2.74 (1H, ddd, *J* 12.9, 4.0, 1.5, C(1)H_B), 3.49 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.58-3.76 (2H, m, C(4)H_2), 3.82 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.88-3.97 (1H, m, C(2)*H*), 4.43 (1H, dddd, *J* 48.3, 6.3, 5.6, 2.8, C(3)*H*), 4.54 (2H, A_2, OCH_2Ph), 7.23-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 55.5 (d, *J* 4.8, *C*(1)), 58.6 (N(*C*H_2Ph)$_2$), 65.8 (d, *J* 24.8, *C*(2)), 69.4 (d, *J* 20.8, *C*(4)), 73.5 (O*C*H_2Ph), 93.8 (d, *J* 174, *C*(3)), 127.4, 127.68, 127.71, 128.4, 128.5, 129.1, 137.8, 138.3 (*Ph*); δ_F (377 MHz, $CDCl_3$) −197.0 (app dtd, *J* 48.3, 27.5, 10.3, C(3)*F*); *m*/*z* (ESI$^+$) 394 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{29}FNO_2^+$ ([M+H]$^+$) requires 394.2177; found 394.2163.

Following *General Procedure 13*, **373** (112 mg, 0.30 mmol, >99:1 dr) in CH_2Cl_2 (0.8 mL) was treated with HBF_4•OEt_2 (0.41 mL, 3.0 mmol). Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave (2*R*,3*S*)-**372** as a colourless oil (52.8 mg, 62%, >99:1 dr).

Preparation of (*RS*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxy-3-methylbutane 375

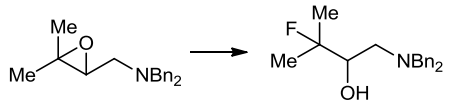


594 **375**

H_2O_2 (35% in H_2O, 1.5 mL, 17 mmol) was added dropwise to a stirred mixture of 3-methylbut-2-enal **594** (1.45 mL, 15.0 mmol) and $KHCO_3$ (1.35 g, 13.5 mmol) in H_2O (9.4 mL) at 0 °C and the resultant mixture was stirred at this temperature for 2.5 h. Satd aq Na_2SO_3 was then added until starch-iodide paper indicated no remaining oxidant. The mixture was saturated with NaCl and extracted with CH_2Cl_2 (5 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in DCE (50 mL) then dibenzylamine (3.2 mL, 17 mmol) and $NaBH(OAc)_3$ (4.46 g, 21.0 mmol) were added sequentially and the resultant mixture was stirred at rt for 17 h. Satd aq $NaHCO_3$ (50 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **375** as a colourless oil (1.66 g, 39%); R_f 0.41 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3085, 3062, 3028, 2961, 2925, 2884, 2797 (C–H), 1494, 1453, 1377, 738, 698; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, C(3)*Me*$_A$), 1.26 (3H, s, C(3)*Me*$_B$), 2.58 (1H, dd, *J* 13.6, 5.8, C(1)H_A), 2.76 (1H, dd,

J 13.6, 4.5, C(1)H_B), 2.97 (1H, app t, *J* 5.2, C(2)*H*), 3.57 (2H, d, *J* 13.6, N(CH_AH$_B$Ph)$_2$), 3.83 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 7.23-7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.9, 24.7 (C(3)*Me*$_2$), 52.9 (*C*(1)), 57.5 (*C*(3)), 58.9 (N(*C*H$_2$Ph)$_2$), 63.0 (*C*(2)), 127.0 (*p-Ph*), 128.3, 128.8 (*o-*, *m-Ph*), 139.4 (*i-Ph*); *m*/*z* (ESI$^+$) 304 ([M+Na]$^+$, 86%), 282 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}NO^+$ ([M+H]$^+$) requires 282.1852; found 282.1851.

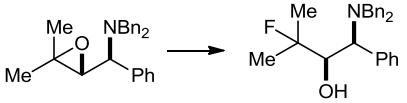
Ring-opening fluorination of (*RS*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxy-3-methylbutane 375



375 **376**

Following *General Procedure 13*, **375** (200 mg, 0.71 mmol) in CH_2Cl_2 (2.8 mL) was treated with HBF_4•OEt_2 (195 μL, 1.43 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave 1-(*N*,*N*-dibenzylamino)-3-fluoro-3-methylbutan-2-ol **376** as a colourless oil (189 mg, 88%); R_f 0.36 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3442 (O–H), 3086, 3063, 3029, 2982, 2936, 2889, 2838, 2807 (C–H), 1495, 1453, 1372, 1241, 1155, 1096, 1074, 1028, 749, 699; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 22.2, C(3)*Me*$_A$), 1.29 (3H, d, *J* 22.0, C(3)*Me*$_B$), 2.55-2.68 (2H, m, C(1)H_2), 3.48 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$), 3.61 (1H, br s, O*H*), 3.65-3.75 (1H, m, C(2)*H*), 3.88 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 7.25-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.5 (d, *J* 24.0, C(3)*Me*$_A$), 23.5 (d, *J* 24.0, C(3)*Me*$_B$), 53.8 (d, *J* 4.8, *C*(1)), 58.3 (N(*C*H$_2$Ph)$_2$), 71.5 (d, *J* 25.6, *C*(2)), 96.1 (d, *J* 168, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o-*, *m-Ph*), 138.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –149.7 (m, C(3)*F*); *m*/*z* (ESI$^+$) 324 ([M+Na]$^+$, 100%), 302 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_{19}H_{25}FNO^+$ ([M+H]$^+$) requires 302.1915; found 302.1916.

Ring-opening fluorination of (3*RS*,4*SR*)-2,3-epoxy-4-(*N*,*N*-dibenzylamino)-2-methyl-4-phenylbutane 377

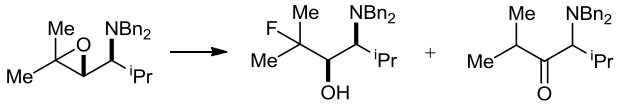


377 **378**

Following *General Procedure 13*, **377** (143 mg, 0.40 mmol, >99:1 dr) in CH_2Cl_2 (1.6 mL) was treated with HBF_4•OEt_2 (110 μL, 0.81 mmol). Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3-fluoro-3-methyl-1-phenylbutan-2-ol **378** as a colourless oil which solidified on standing to a white crystalline solid (151 mg, quant, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 90:10); $C_{25}H_{28}FNO$ requires C, 79.5; H, 7.5; N, 3.7; found C, 79.65; H, 7.3; N, 3.7; mp 114-120 °C; ν_{max} 3316 (O−H), 3105, 3087, 3063, 3029, 3004, 2980, 2934, 2896, 2847 (C−H), 1548,

1495, 1370, 1241, 1151, 1074, 1029, 761, 752, 701; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 22.0, C(3)*Me*$_A$), 1.11 (3H, d, *J* 22.2, C(3)*Me*$_B$), 3.04 (2H, d, *J* 13.1, N(C*H*$_A$H$_B$Ph)$_2$), 3.81 (1H, d, *J* 10.1, C(1)*H*), 3.96 (2H, d, *J* 13.1, N(CH$_A$*H*$_B$Ph)$_2$), 4.27 (1H, app t, *J* 10.1, C(2)*H*), 5.41 (1H, br s, O*H*), 7.24-7.50 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.0 (d, *J* 24.0, C(3)*Me*$_A$), 24.4 (d, *J* 25.6, C(3)*Me*$_B$), 53.6 (N(*C*H$_2$Ph)$_2$), 62.2 (*C*(1)), 71.9 (d, *J* 24.0, *C*(2)), 96.8 (d, *J* 171, *C*(3)), 127.5, 128.0, 128.3, 128.7, 129.2, 130.2 (*o*-, *m*-, *p*-*Ph*), 134.4, 138.2 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) –144.3 (app spt d, *J* 21.8, 9.2, C(3)*F*); *m*/*z* (FI$^+$) 377 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{25}H_{28}FNO^+$ ([M]$^+$) requires 377.2149; found 377.2168.

Ring-opening fluorination of (3*RS*,4*SR*)-2,3-epoxy-4-(*N*,*N*-dibenzylamino)-2-methyl-4-*iso*-propylbutane 379

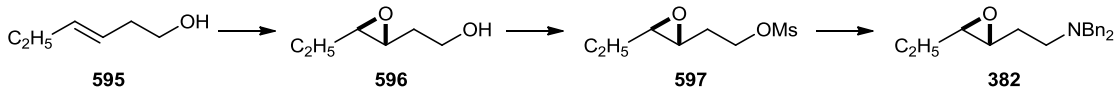


379 **380** **381**

Following *General Procedure 13*, **379** (241 mg, 0.75 mmol, >99:1 dr) in CH_2Cl_2 (3.0 mL) was treated with HBF_4•OEt_2 (205 μL, 1.51 mmol) to give an 83:17 mixture of **380**:**381**. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave 4-(*N*,*N*-dibenzylamino)-2,5-dimethyl-3-oxohexane **381** as a colourless oil (15.2 mg, 6%); R_f 0.24 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3086, 3063, 3028, 2966, 2932, 2871, 2838, 2807 (C−H), 1705 (C=O), 1494, 1465, 1454, 1382, 1366, 1071, 1028, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.6, C(5)*Me*$_A$), 0.90 (3H, d, *J* 7.1, C(2)*Me*$_A$), 1.10 (3H, d, *J* 6.6, C(2)*Me*$_B$), 1.16 (3H, d, *J* 6.6, C(5)*Me*$_B$), 2.24-2.38 (1H, m, C(5)*H*), 2.53 (1H, spt, *J* 6.9, C(2)*H*), 3.20 (1H, d, *J* 10.4, C(4)*H*), 3.58 (2H, d, *J* 14.2, N(C*H*$_A$H$_B$Ph)$_2$), 3.96 (2H, d, *J* 14.2, N(CH$_A$*H*$_B$Ph)$_2$), 7.20-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 18.1, 20.58, 20.64 (C(2)*Me*$_2$, C(5)*Me*$_2$), 27.0 (*C*(5)), 41.2 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 68.8 (*C*(4)), 127.0 (*p*-*Ph*), 128.3, 128.8 (*o*-, *m*-*Ph*), 139.8 (*i*-*Ph*), 214.3 (*C*=O); *m*/*z* (FI$^+$) 323 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{22}H_{29}NO^+$ ([M]$^+$) requires 323.2244; found 323.2246. Further elution gave (*RS*,*SR*)-4-(*N*,*N*-dibenzylamino)-2-fluoro-2,5-dimethylhexan-3-ol **380** as a colourless oil (159 mg, 62%, >99:1 dr); R_f 0.12 (30-40 °C petrol/Et_2O, 96:4); $C_{22}H_{30}FNO$ requires C, 76.9; H, 8.8; N, 4.1; found C, 77.0; H, 8.85; N, 4.0; ν_{max} 3241 (O−H), 3107, 3087, 3064, 3029, 2980, 2958, 2881, 2842, 2812 (C−H), 1455, 1368, 1153, 1062, 750, 700; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 21.5, C(2)*Me*$_A$), 1.12 (3H, dd, *J* 7.3, 0.5, C(5)*Me*$_A$), 1.17 (3H, dd, *J* 7.1, 0.8, C(5)*Me*$_B$), 1.45 (3H, d, *J* 23.0, C(2)*Me*$_B$), 2.34 (1H, app spt d, *J* 7.3, 2.3, C(5)*H*), 2.77 (1H, dd, *J* 8.3, 2.3, C(4)*H*), 3.54 (2H, d, *J* 12.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.74 (1H, dd, *J* 8.3, 3.0, C(3)*H*), 3.96 (2H, d, *J* 12.9, N(CH$_A$*H*$_B$Ph)$_2$), 5.40 (1H, br s, O*H*), 7.23-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (d, *J* 24.0, C(2)*Me*$_A$), 20.0 (d, *J* 4.8, C(5)*Me*$_B$), 22.4 (d, *J* 6.4, C(5)*Me*$_A$), 26.5 (*C*(5)), 27.4 (d, *J* 24.0, C(2)*Me*$_B$), 54.3 (N(*C*H$_2$Ph)$_2$), 61.1 (*C*(4)), 70.4 (d, *J* 30.4, *C*(3)), 96.8 (d, *J* 168, *C*(2)), 127.4 (*p*-*Ph*),

128.5, 129.4 (*o*-, *m*-*Ph*), 138.7 (*i*-*Ph*); δ_F (377 MHz, $CDCl_3$) −145.8 (app spt, *J* 21.8, C(2)*F*); *m*/*z* (FI^+) 343 ($[M]^+$, 100%); HRMS (FI^+) $C_{22}H_{30}FNO^+$ ($[M]^+$) requires 343.2306; found 343.2318.

Preparation of (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-3,4-epoxyhexane 382

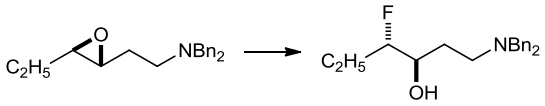


Step 1: Following *General Procedure 14*, (*E*)-hex-3-en-1-ol **595** (3.72 g, 37.1 mmol, >99:1 dr) in CH_2Cl_2 (148 mL) was treated with *m*-CPBA (75% with H_2O, 12.8 g, 55.7 mmol) for 28 h. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*)-3,4-epoxyhexan-1-ol **596** as a colourless oil (3.89 g, 90%, >99:1 dr);[122] R_f 0.18 (30-40 °C petrol/EtOAc, 60:40); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, app td, *J* 7.6, 1.5, C(6)H_3), 1.48-1.73 (3H, m, C(2)H_A, C(5)H_2), 1.89-2.00 (1H, m, C(2)H_B), 2.39 (1H, br s, O*H*), 2.73-2.79 (1H, m, C(4)*H*), 2.86 (1H, app ddt, *J* 6.4, 4.3, 2.0, C(3)*H*), 3.75 (2H, app td, *J* 6.0, 2.0, C(1)H_2).

Step 2: Following *General Procedure 15*, **596** (2.00 g, 17.2 mmol, >99:1 dr) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.8 mL, 34 mmol) and MsCl (2.0 mL, 26 mmol) to give (*RS*,*RS*)-3,4-epoxyhexyl methanesulfonate **597** as an orange oil (2.73 g, 82%, >99:1 dr);[129] δ_H (400 MHz, $CDCl_3$) 1.00 (3H, app t, *J* 7.5, C(6)H_3), 1.54-1.63 (2H, m, C(5)H_2), 1.85 (1H, app ddt, *J* 14.7, 6.8, 5.3, C(2)H_A), 2.11 (1H, dddd, *J* 14.7, 7.7, 6.6, 4.4, C(2)H_B), 2.74 (1H, app td, *J* 5.5, 2.2, C(4)*H*), 2.83 (1H, ddd, *J* 6.7, 4.4, 2.2, C(3)*H*), 3.04 (3H, s, OSO_2*Me*), 4.35 (1H, dd, *J* 5.1, 1.4, C(1)H_A), 4.37 (1H, d, *J* 5.5, C(1)H_B).

Step 3: Following *General Procedure 16*, **597** (500 mg, 2.57 mmol, >99:1 dr) in EtOH (6.4 mL) was treated with dibenzylamine (1.25 mL, 6.50 mmol) for 23 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **382** as a colourless oil (500 mg, 66%, >99:1 dr); R_f 0.41 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3085, 3062, 3027, 2968, 2934, 2876, 2798 (C–H), 1494, 1453, 1367, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, app t, *J* 7.5, C(6)H_3), 1.45-1.74 (3H, m, C(2)H_A, C(5)H_2), 1.82 (1H, app dq, *J* 13.6, 6.8, C(2)H_B), 2.57-2.65 (3H, m, C(1)H_2, C(4)*H*), 2.72 (1H, app td, *J* 5.7, 2.0, C(3)*H*), 3.60 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 7.22-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.8 (*C*(6)), 25.0 (*C*(5)), 30.1 (*C*(2)), 50.4 (*C*(1)), 57.2 (*C*(3)), 58.3 (N(*C*H_2Ph)$_2$), 60.0 (*C*(4)), 126.9 (*p*-*Ph*), 128.2, 128.7 (*o*-, *m*-*Ph*), 139.6 (*i*-*Ph*); *m*/*z* (ESI^+) 318 ($[M+Na]^+$, 48%), 312 (100%), 296 ($[M+H]^+$, 98%); HRMS (ESI^+) $C_{20}H_{26}NO^+$ ($[M+H]^+$) requires 296.2009; found 296.2009.

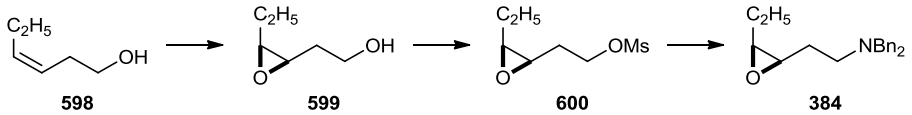
Ring-opening fluorination of (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-3,4-epoxyhexane 382



382 **383**

Following *General Procedure 13*, **382** (236 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (3.2 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-4-fluorohexan-3-ol **383** as a colourless oil (179 mg, 71%, >99:1 dr); R_f 0.33 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3260 (O–H), 3086, 3063, 3029, 3005, 2967, 2935, 2881, 2826 (C–H), 1495, 1454, 1375, 1105, 1075, 1028, 952, 749, 733, 699; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, app t, *J* 7.5, C(6)H_3), 1.49-1.87 (4H, m, C(2)H_2, C(5)H_2), 2.68-2.81 (2H, m, C(1)H_2), 3.46 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.54-3.64 (1H, m, C(3)*H*), 3.72 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.84-4.05 (1H, m, C(4)*H*), 6.17 (1H, br s, O*H*), 7.22-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (d, *J* 4.8, *C*(6)), 24.3 (d, *J* 20.8, *C*(5)), 27.0 (d, *J* 3.2, *C*(2)), 51.7 (*C*(1)), 58.5 (N(*C*H_2Ph)$_2$), 73.8 (d, *J* 25.6, *C*(3)), 96.3 (d, *J* 171, *C*(4)), 127.5 (*p-Ph*), 128.5, 129.4 (*o-*, *m-Ph*), 137.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –193.6 (m, C(4)*F*); *m*/*z* (ESI$^+$) 338 ([M+Na]$^+$, 93%), 316 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{27}FNO^+$ ([M+H]$^+$) requires 316.2071; found 316.2073.

Preparation of (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3,4-epoxyhexane 384



598 **599** **600** **384**

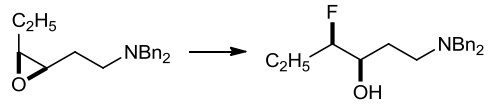
Step 1: Following *General Procedure 14*, (*Z*)-hex-3-en-1-ol **598** (4.54 g, 45.3 mmol, >99:1 dr) in CH_2Cl_2 (181 mL) was treated with *m*-CPBA (75% with H_2O, 15.6 g, 68.0 mmol) for 28 h. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave (*RS*,*SR*)-3,4-epoxyhexan-1-ol **599** as a colourless oil (4.38 g, 83%, >99:1 dr);[130] R_f 0.16 (30-40 °C petrol/EtOAc, 60:40); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, app td, *J* 7.5, 1.4, C(6)H_3), 1.44-1.74 (3H, m, C(2)H_A, C(5)H_2), 1.80-1.91 (1H, m, C(2)H_B), 2.34 (1H, br s, O*H*), 2.87-2.94 (1H, m, C(4)*H*), 3.05-3.13 (1H, m, C(3)*H*), 3.75-3.90 (2H, m, C(1)H_2).

Step 2: Following *General Procedure 15*, **599** (2.00 g, 17.2 mmol, >99:1 dr) in CH_2Cl_2 (29 mL) was treated with Et_3N (4.8 mL, 34 mmol) and MsCl (2.0 mL, 26 mmol) to give (*RS*,*SR*)-3,4-epoxyhexyl methanesulfonate **600** as an orange oil (2.96 g, 89%, >99:1 dr);[124] δ_H (400 MHz, $CDCl_3$) 1.05 (3H, app td, *J* 7.5, 1.4, C(6)H_3), 1.46-1.63 (2H, m, C(5)H_2), 1.79-1.90 (1H, m, C(2)H_A), 2.09 (1H, ddddd, *J* 14.7, 8.2, 6.3,

4.7, 1.6, C(2)H_B), 2.92-2.98 (1H, m, C(4)*H*), 3.04 (3H, s, OSO_2*Me*) overlapping 3.03-3.10 (1H, m, C(3)*H*), 4.33-4.46 (2H, m, C(1)H_2).

Step 3: Following *General Procedure 16*, **600** (500 mg, 2.57 mmol, >99:1 dr) (500 mg, 2.57 mmol) in EtOH (6.4 mL) was treated with dibenzylamine (1.25 mL, 6.50 mmol) for 23 h. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **384** as a colourless oil (558 mg, 74%, >99:1 dr); R_f 0.38 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3085, 3062, 3027, 2970, 2935, 2876, 2798 (C–H), 1494, 1453, 1368, 745, 699; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, app t, *J* 7.5, C(6)H_3), 1.34-1.59 (2H, m, C(5)H_2), 1.63-1.86 (2H, m, C(2)H_2), 2.56-2.70 (2H, m, C(1)H_2), 2.79-2.87 (1H, m, C(4)*H*), 2.95-3.03 (1H, m, C(3)*H*), 3.62 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.19-7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.6 (*C*(6)), 21.1 (*C*(5)), 25.7 (*C*(2)), 50.6 (*C*(1)), 55.8 (*C*(3)), 58.2 (*C*(4)), 58.4 (N(*C*H_2Ph)$_2$), 126.9 (*p-Ph*), 128.2, 128.8 (*o-*, *m-Ph*), 139.6 (*i-Ph*); *m*/*z* (ESI$^+$) 318 ([M+Na]$^+$, 61%), 312 (100%), 296 ([M+H]$^+$, 64%); HRMS (ESI$^+$) $C_{20}H_{26}NO^+$ ([M+H]$^+$) requires 296.2009; found 296.2010.

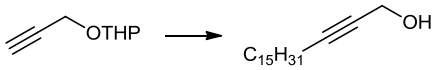
Ring-opening fluorination of (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3,4-epoxyhexane 384



384 **385**

Following *General Procedure 13*, **384** (200 mg, 0.68 mmol, >99:1 dr) in CH_2Cl_2 (2.7 mL) was treated with HBF_4•OEt_2 (185 μL, 1.36 mmol). Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave (*RS*,*RS*)-1-(*N*,*N*-dibenzylamino)-4-fluorohexan-3-ol **385** as a colourless oil (114 mg, 53%, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3386 (O–H), 3086, 3063, 3029, 2968, 2935, 2880, 2824 (C–H), 1495, 1453, 1377, 1137, 1109, 1075, 1028, 953, 749, 733, 699; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, app t, *J* 7.4, C(6)H_3), 1.47-1.78 (3H, m, C(2)H_A, C(5)H_2), 1.94 (1H, app dtd, *J* 14.4, 10.5, 3.9, C(2)H_B), 2.62 (1H, app dt, *J* 12.9, 4.3, C(1)H_A), 2.76-2.85 (1H, m, C(1)H_B), 3.29 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.64 (1H, dddd, *J* 20.7, 10.0, 3.8, 2.6, C(3)*H*), 3.89 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 4.16 (1H, app ddt, *J* 48.1, 8.4, 4.1, C(4)*H*), 5.59 (1H, br s, O*H*), 7.25-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.7 (d, *J* 6.4, *C*(6)), 23.6 (d, *J* 20.8, *C*(5)), 27.9 (d, *J* 4.8, *C*(2)), 52.2 (*C*(1)), 58.5 (N(*C*H_2Ph)$_2$), 73.4 (d, *J* 24.0, *C*(3)), 97.2 (d, *J* 173, *C*(4)), 127.4 (*p-Ph*), 128.5, 129.3 (*o-*, *m-Ph*), 137.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –195.9 (m, C(4)*F*); *m*/*z* (ESI$^+$) 653 ([2M+Na]$^+$, 100%), 338 ([M+Na]$^+$, 92%), 316 ([M+H]$^+$, 68%); HRMS (ESI$^+$) $C_{20}H_{27}FNO^+$ ([M+H]$^+$) requires 316.2071; found 316.2071.

Preparation of 1-octadec-2-yn-1-ol 418



417 **418**

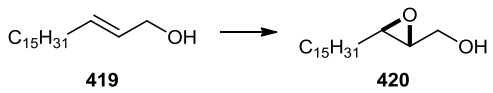
BuLi (2.5 M in hexanes, 14 mL, 36 mmol) was added dropwise to a stirred solution of 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran **417** (5.0 mL, 36 mmol) in THF (40 mL) at –78 °C and the resultant mixture was stirred at this temperature for 30 min. DMPU (4.7 mL, 39 mmol) was then added and stirring was continued for a further 10 min. 1-Bromopentadecane (9.3 mL, 33 mmol) was then added dropwise and the resultant mixture was allowed to warm to rt and then heated at 50 °C for 20 h. The mixture was allowed to cool to rt and satd aq NH_4Cl (50 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic extracts were then dried, filtered through a pad of silica gel (eluent Et_2O) and concentrated *in vacuo*. The residue was dissolved in MeOH (80 mL) and Amberlyst H 15 (1.08 g) was added. The resultant mixture was stirred at 40 °C for 3 h then filtered and concentrated *in vacuo*. The residue was dissolved in hot 30-40 °C petrol and the resultant solution was allowed to cool to rt. Cooling of the solution to −78 °C and collection of the resultant precipitate by filtration (eluent 30-40 °C petrol) gave **418** as a cream solid (8.25 g, 95%). Purification of an aliquot *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave an analytical sample of **418** as a white solid;[131] R_f 0.24 (30-40 °C petrol/Et_2O, 80:20); mp 59-60 °C {lit.[131] mp 62-64 °C (pentane)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(18)H_3), 1.21-1.42 (24H, m, C(6)H_2-C(17)H_2), 1.47-1.55 (2H, m, C(5)H_2), 2.21 (2H, tt, *J* 7.1, 2.1, C(4)H_2), 4.26 (1H, br s, C(1)H_2).

Preparation of (*E*)-octadec-2-en-1-ol 419

418 **419**

A solution of **418** (8.25 g, 31.0 mmol) in THF (80 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.0 M solution in THF, 34 mL, 34 mmol) in THF (25 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 20 h. Satd aq Rochelle's salt (100 mL) was then added dropwise (*cautiously!*) and the resultant mixture was stirred at rt for 18 h. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic extracts were dried, filtered through a pad of silica gel (eluent Et_2O) and concentrated *in vacuo* to give **419** as a white solid (8.05 g, 97%, >99:1 dr);[132] mp 45 °C {lit.[132] mp 46-48 °C}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(18)H_3), 1.20-1.43 (26H, m, C(5)H_2-C(17)H_2), 2.04 (2H, dt, *J* 7.5, 6.1, C(4)H_2), 4.09 (2H, br m, C(1)H_2), 5.59-5.75 (2H, m, C(2)*H*, C(3)*H*).

Preparation of (*R*,*R*)-2,3-epoxyoctadecan-1-ol 420

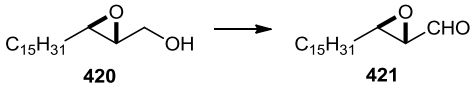


419 **420**

$Ti(O^iPr)_4$ (10.6 mL, 35.7 mmol) and diethyl D-(–)-tartrate (8.1 mL, 47.6 mmol) were added sequentially to CH_2Cl_2 (330 mL) over powdered 4 Å molecular sieves (21.5 g) at a temperature between –20 °C and –30 °C (dry ice/acetone bath) and the resultant mixture was stirred at this temperature for 15 min. A solution of **419** (7.99 g, 29.7 mmol, >99:1 dr) in CH_2Cl_2 (60 mL) was added *via* syringe and stirring was continued for a further 10 min. Pre-cooled (–20 °C) ^tBuOOH (3.43 M solution in PhMe,[133] 26 mL, 89 mmol) was then added dropwise and the resultant mixture was placed in a freezer at –20 °C for 21 h. The reaction was then transferred to an ice bath and a pre-cooled (0 °C) solution of $FeSO_4•7H_2O$ (49.6 g, 178 mmol) and D-(–)-tartaric acid (13.4 g, 89.2 mmol) in H_2O (135 mL) was added. The resultant mixture was stirred vigorously at 0 °C for 10 min, then allowed to warm to rt over 1 h. Celite was then added until the aqueous slurry became granular, and the mixture was filtered through a pad of Celite (eluent CH_2Cl_2) and the filtrate was collected. The filter cake was swirled in hot EtOAc then filtered through a pad of Celite (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and all filtrates were combined then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with a pre-cooled (0 °C) solution of 1 M aq NaOH in brine (300 mL) at 0 °C and was stirred at this temperature for 1 h. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 200 mL), then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* recrystallisation (Et_2O) gave **420** as a white crystalline solid (6.77 g, 80%, >99:1 dr, >98% ee);[132] mp 79-80 °C (Et_2O) {lit.[132] mp 77-78 °C (petrol)}; $[\alpha]_D^{20}$ +21.4 (*c* 1.0 in $CHCl_3$) {lit.[132] $[\alpha]_D^{23}$ +22.5 (*c* 0.79 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, app t, *J* 6.7, C(18)H_3), 1.19-1.71 (28H, m, C(4)H_2-C(17)H_2), 2.91-2.99 (2H, m, C(2)*H*, C(3)*H*), 3.64 (1H, ddd, *J* 12.4, 7.4, 4.3, C(1)H_A), 3.92 (1H, ddd, *J* 12.4, 5.4, 2.6, C(1)H_B). The enantiomeric purity of **420** was determined by Mosher′s ester analysis according to the following procedure: (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (26 µL, 0.14 mmol) was added to a stirred solution of **420** (15.5 mg, 0.05 mmol), Et_3N (30 µL, 0.21 mmol) and DMAP (1.3 mg, 20 mol%) in CH_2Cl_2 (0.5 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq NH_4Cl (10 mL) and CH_2Cl_2 (10 mL) were added sequentially and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (3 × 10 mL) then dried and concentrated *in vacuo* to give the crude Mosher′s ester as a yellow oil (32.5 mg, >99:1 dr, >98% ee); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, app t, *J* 6.8, C(18)H_3), 1.21-1.48 (26H, m, C(5)H_2-C(17)H_2), 1.51-1.59 (2H, m, C(4)H_2), 2.85 (1H, app td, *J* 5.6, 2.2, C(3)*H*), 3.02 (1H, ddd, *J* 5.6, 3.5, 2.2,

C(2)*H*), 3.58 (3H, d, *J* 1.3, O*Me*), 4.23 (1H, dd, *J* 12.1, 5.6, C(1)H_A), 4.59 (1H, dd, *J* 12.1, 3.5, C(1)H_B), 7.39-7.45 (3H, m, *Ph*), 7.51-7.61 (2H, m, *Ph*); δ_F (377 MHz, $CDCl_3$) −71.7 (s, CF_3).

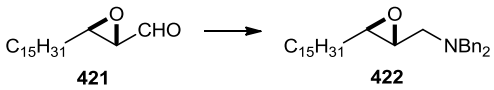
Preparation of (2*S*,3*R*)-2,3-epoxyoctadecanal 421



420 **421**

A solution of **420** (6.79 g, 23.9 mmol, >99:1 dr, >98% ee) in THF (70 mL) was added dropwise to a solution of IBX (16.7 g, 59.7 mmol) in DMSO (200 mL) and the resultant mixture was stirred at rt for 3 h. EtOAc (800 mL) and H_2O (800 mL) were then added sequentially and the resultant mixture was filtered through a pad of Celite (eluent EtOAc). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 350 mL) and the combined organic extracts were washed with H_2O (4 × 500 mL) then dried and concentrated *in vacuo*. The residue was dissolved in hot Et_2O and filtered through a pad of Celite (eluent Et_2O) then concentrated *in vacuo* to give **421** as a white solid (6.62 g, 98%, >99:1 dr); mp 58-59 °C; $[\alpha]_D^{20}$ −41.1 (*c* 1.0 in $CHCl_3$); ν_{max} 2953, 2914, 2849 (C−H), 1738, 1715, 1470, 854, 719; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.8, C(18)H_3), 1.21-1.72 (28H, m, C(4)H_2-C(17)H_2), 3.14 (1H, dd, *J* 6.2, 2.0, C(2)*H*), 3.24 (1H, ddd, *J* 5.9, 5.1, 2.0, C(3)*H*), 9.02 (1H, d, *J* 6.3, C*H*O); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 25.8, 29.2, 29.3, 29.4, 29.5, 29.58, 29.64, 29.7, 31.2, 31.9 (*C*(4)-*C*(17)), 56.8 (*C*(3)), 59.1 (*C*(2)), 198.5 (*C*HO); *m*/*z* (FI^+) 282 ($[M]^+$, 100%); HRMS (FI^+) $C_{18}H_{34}O_2^+$ ($[M]^+$) requires 282.2553; found 282.2558.

Preparation of (*R*,*R*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxyoctadecane 422

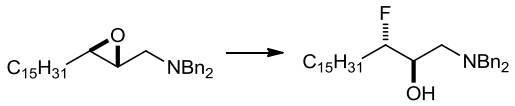


421 **422**

Dibenzylamine (4.5 mL, 23 mmol) and $NaBH(OAc)_3$ (6.95 g, 32.8 mmol) were added sequentially to a stirred solution of **421** (6.62 g, 23.4 mmol, >99:1 dr) in DCE (160 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 3 h. Satd aq $NaHCO_3$ (300 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **422** as a colourless oil which solidified on standing to give a white solid (9.60 g, 88%, >99:1 dr); R_f 0.44 (30-40 °C petrol/Et_2O, 90:10); $C_{32}H_{49}NO$ requires C, 82.9; H, 10.65; N, 3.0; found C, 82.9; H, 10.6; N, 3.0; mp 29-30 °C; $[\alpha]_D^{20}$ +6.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3086, 3063, 3028, 2924, 2853, 2798 (C−H), 1495, 1454, 1370, 745, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.21-1.51 (28H, m, C(4)H_2-C(17)H_2), 2.52 (1H, dd, *J* 13.7, 6.0, C(1)H_A), 2.63 (1H, app td, *J* 5.4, 2.3, C(3)*H*), 2.70 (1H, dd,

J 13.7, 4.0, C(1)H_B), 2.87 (1H, ddd, *J* 6.0, 4.0, 2.3, C(2)*H*), 3.58 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.79 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 7.21-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 26.0, 29.36, 29.44, 29.5, 29.6, 29.66, 29.70, 31.8, 31.9 (*C*(4)-*C*(17)), 55.5 (*C*(1)), 57.0 (*C*(2)), 57.3 (*C*(3)), 58.9 (N(*C*H_2Ph)$_2$), 126.9 (*p-Ph*), 128.2, 128.8 (*o*-, *m-Ph*), 139.4 (*i-Ph*); *m*/*z* (ESI^+) 464 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{50}NO^+$ ($[M+H]^+$) requires 464.3887; found 464.3881.

Preparation of (2*R*,3*S*)-1-(*N*,*N*-dibenzylamino)-3-fluorooctadecan-2-ol 423

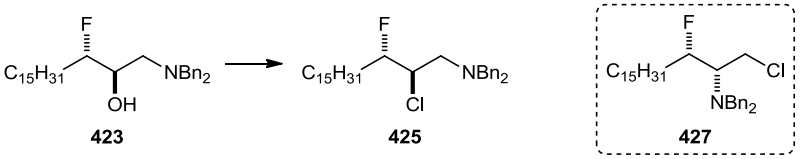


422 **423**

HBF_4•OEt_2 (5.6 mL, 41 mmol) was added in one portion to a stirred solution of **422** (9.46 g, 20.4 mmol, >99:1 dr) in CH_2Cl_2 (82 mL) at 0 °C and the resultant mixture was stirred at this temperature for 5 min. Satd aq $NaHCO_3$ (100 mL) was then added and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 100 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* recrystallisation (MeCN) gave **423** as a white crystalline solid (6.98 g, 71%, >99:1 dr, >98% ee). Purification from the mother liquor *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave additional **423** as a colourless oil which solidified on standing to a white crystalline solid (825 mg, 8%, >99:1 dr, >98% ee); R_f 0.21 (30-40 °C petrol/Et_2O, 90:10); mp 42-43 °C; $[\alpha]_D^{20}$ +35.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3452 (O−H), 3063, 3029, 2924, 2853 (C−H), 1454, 748, 699; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.15-1.68 (28H, m, C(4)H_2-C(17)H_2), 2.63 (1H, dd, *J* 12.6, 9.6, C(1)H_A), 2.70 (1H, ddd, *J* 12.6, 3.9, 1.4, C(1)H_B), 3.36 (1H, br s, O*H*), 3.48 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 3.71 (1H, dddd, *J* 11.4, 9.7, 5.7, 3.9, C(2)*H*), 3.83 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 4.17-4.37 (1H, m, C(3)*H*), 7.26-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 25.0 (d, *J* 3.2), 29.36, 29.44, 29.5, 29.57, 29.64, 29.66, 29.70, 31.2 (d, *J* 20.8), 31.9 (*C*(4)-*C*(17)), 55.3 (d, *J* 5.6, *C*(1)), 58.5 (N(*C*H_2Ph)$_2$), 68.2 (d, *J* 24.0, *C*(2)), 95.4 (d, *J* 169, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o*-, *m-Ph*), 138.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −194.3 (m, C(3)*F*); *m*/*z* (ESI^+) 464 ($[M-F]^+$, 100%), 484 ($[M+H]^+$, 96%); HRMS (ESI^+) $C_{32}H_{51}FNO^+$ ($[M+H]^+$) requires 484.3949; found 484.3946. The enantiomeric purity of **423** was determined by Mosher′s ester analysis according to the following procedure: (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (17 μL, 0.09 mmol) was added to a stirred solution of **423** (17.9 mg, 0.04 mmol, >99:1 dr, >98% ee), Et_3N (21 μL, 0.15 mmol) and DMAP (0.9 mg, 20 mol%) in CH_2Cl_2 (0.4 mL) and the resultant mixture was stirred at rt for 14 h. Satd aq NH_4Cl (10 mL) and CH_2Cl_2 (10 mL) were added sequentially and the layers were separated. The organic layer was

washed with satd aq $NaHCO_3$ (3 × 10 mL) then dried and concentrated *in vacuo* to give the crude Mosher's ester as a yellow oil (41.9 mg, >99:1 dr, >98% ee); δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.81-1.53 (31H, m, C(4)H_2-C(17)H_2, C(18)H_3), 2.59-2.66 (2H, m, C(1)H_2), 3.45 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.54 (3H, s, O*Me*), 3.69 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 4.57-4.76 (1H, m, C(3)*H*), 5.45 (1H, app dtd, *J* 18.2, 6.5, 2.1, C(2)*H*); δ_F (377 MHz, $CDCl_3$) −190.9 (m, C(3)*F*), −71.5 (s, CF_3).

Preparation of (2*R*,3*S*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-fluorooctadecane 425

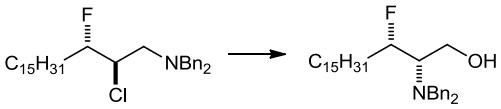


Method A: CCl_4 (0.29 mL, 3.0 mmol) was added dropwise to a stirred mixture of **423** (145 mg, 0.30 mmol, >99:1 dr), PPh_3 (197 mg, 0.75 mmol) and Et_3N (0.42 mL, 3.0 mmol) in MeCN (1.2 mL) at rt and the resultant mixture was heated at reflux for 40 min then allowed to cool to rt and concentrated *in vacuo*. Purification *via* filtration through a pad of silica gel (eluent CH_2Cl_2) gave an 83:17 mixture of **427**:**425** as a yellow oil (153 mg, quant combined). Data for **427**:**425** mixture: *m*/*z* (FI^+) 501 ([M(^{35}Cl)]$^+$, 100%); HRMS (FI^+) $C_{32}H_{49}ClFN^+$ [M(^{35}Cl)]$^+$) requires 501.3532; found 501.3549. Data for (2*R*,3*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-fluorooctadecane **427**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.88-2.01 (1H, m, C(4)H_A), 2.80-2.92 (1H, m, C(2)*H*), 3.59 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.86 (1H, dd, *J* 10.9, 8.8, C(1)H_A), 3.92 (1H, dd, *J* 10.9, 4.7, C(1)H_B), 4.03 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.79 (1H, dddd, *J* 48.2, 8.0, 4.7, 3.3, C(3)*H*). A solution of the 83:17 mixture of **427**:**425** (50.0 mg, 0.10 mmol) was heated at reflux in MeCN (0.4 mL) for 18 h and then concentrated *in vacuo* to give **425** as a yellow oil (50.0 mg, quant, >99:1 dr).

Method B: CCl_4 (14 mL, 145 mmol) was added dropwise to a stirred mixture of **423** (6.81 g, 14.1 mmol, >99:1 dr), PPh_3 (9.23 g, 35.2 mmol) and Et_3N (20 mL, 143 mmol) in MeCN (56 mL) at 0 °C and the resultant mixture was allowed to warm to rt and then heated at reflux for 18 h. The mixture was then allowed to cool to rt and was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and filtered through a pad of silica gel (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **425** as a yellow oil (6.28 g, 89%, >99:1 dr); R_f 0.53 (30-40 °C petrol/Et_2O, 96:4); $[\alpha]_D^{20}$ −13.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3087, 3063, 3028, 2924, 2853 (C−H), 1454, 747, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 0.99-1.70 (28H, m, C(4)H_2-C(17)H_2), 2.76 (1H, ddd, *J* 13.9, 6.6, 2.3, C(1)H_A), 2.88 (1H, dd, *J* 13.9, 7.6, C(1)H_B), 3.51 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 3.75 (2H, d, *J* 13.5, N(CH$_A$$H_B$Ph)$_2$), 4.12-4.22 (1H, m, C(2)*H*), 4.67 (1H, dddd, *J* 47.5, 9.7, 3.9, 2.3, C(3)*H*), 7.25-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 25.1 (d,

J 2.4), 29.4, 29.5, 29.6, 29.65, 29.67, 29.69, 29.71, 29.8, 31.9 (*C*(4)-*C*(17)), 56.6 (d, *J* 6.4, *C*(1)), 59.1 (N(*C*H_2Ph)$_2$), 60.9 (d, *J* 21.6, *C*(2)), 93.9 (d, *J* 174, *C*(3)), 127.3 (*p-Ph*), 128.3, 129.0 (*o-*, *m-Ph*), 138.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −184.8 (m, C(3)*F*); *m*/*z* (ESI$^+$) 502 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}{}^{37}ClFN^+$ ([M(^{37}Cl)+H]$^+$) requires 504.3584; found 504.3595; $C_{32}H_{50}{}^{35}ClFN^+$ ([M(^{35}Cl)+H]$^+$) requires 502.3610; found 502.3606.

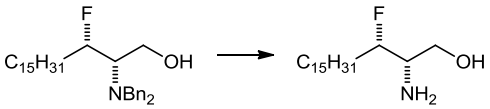
Preparation of (*S*,*S*)-2-(*N*,*N*-dibenzylamino)-3-fluorooctadecan-1-ol 426



KOAc (1.67 g, 17.1 mmol) was added to a stirred solution of **425** (857 mg, 1.71 mmol, >99:1 dr) in DMF (34 mL) and the resultant suspension was stirred at 100 °C for 23 h. The reaction mixture was then allowed to cool to rt and was partitioned between EtOAc (300 mL) and satd aq $NaHCO_3$ (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic extracts were then washed with H_2O (4 × 200 mL), dried and concentrated *in vacuo*. K_2CO_3 (236 mg, 1.71 mmol), MeOH (4.3 mL) and THF (4.3 mL) were added to the residue and the resultant mixture was stirred at rt for 2.5 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **426** as a yellow oil which solidified on standing to a cream solid (681 mg, 82%, >99:1 dr, >98% ee); R_f 0.28 (30-40 °C petrol/EtOAc, 90:10); $C_{32}H_{50}FNO$ requires C, 79.45; H, 10.4; N, 2.9; found C, 79.5; H, 10.4; N, 2.8; mp 40-41 °C; $[\alpha]_D^{20}$ −50.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3423 (O−H), 3086, 3063, 3029, 2924, 2853 (C−H), 1455, 750, 699; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.22-1.68 (28H, m, C(4)H_2-C(17)H_2), 3.00 (1H, app dq, *J* 12.8, 7.9, C(2)*H*), 3.13 (1H, br s, O*H*), 3.42 (2H, app d, *J* 7.6, C(1)H_2), 3.82 (2H, d, *J* 12.9, N(C$H_A$$H_B$Ph)$_2$), 3.92 (2H, d, *J* 12.9, N(CH$_A$$H_B$Ph)$_2$), 4.79 (1H, app dtd, *J* 50.0, 8.5, 2.3, C(3)*H*), 7.24-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 24.6 (d, *J* 4.0), 29.37, 29.44, 29.5, 29.56, 29.64, 29.66, 29.70, 31.9, 32.9 (d, *J* 20.8) (*C*(4)-*C*(17)), 54.5 (d, *J* 3.2, N(*C*H_2Ph)$_2$), 57.7 (d, *J* 10.4, *C*(1)), 61.0 (d, *J* 16.8, *C*(2)), 94.4 (d, *J* 173, *C*(3)), 127.3 (*p-Ph*), 128.5, 129.3 (*o-*, *m-Ph*), 139.2 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −186.9 (m, C(3)*F*); *m*/*z* (ESI$^+$) 484 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{51}FNO^+$ ([M+H]$^+$) requires 484.3949; found 484.3940. The enantiomeric purity of **426** was determined by Mosher′s ester analysis according to the following procedure: (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl

chloride (17 μL, 0.09 mmol) was added to a stirred solution of **426** (17.9 mg, 0.04 mmol, >99:1 dr, >98% ee), Et_3N (21 μL, 0.14 mmol) and DMAP (0.9 mg, 20 mol%) in CH_2Cl_2 (0.4 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq NH_4Cl (10 mL) and CH_2Cl_2 (10 mL) were added sequentially and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (3 × 10 mL) then dried and concentrated *in vacuo* to give the crude Mosher′s ester as an orange oil (44 mg, >99:1 dr, >98% ee); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.74-1.90 (1H, m, C(4)H_A), 2.85 (1H, dddd, *J* 28.3, 7.0, 5.7, 3.9, C(2)*H*), 3.54 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$) overlapping 3.55 (3H, s, O*Me*), 3.97 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.42 (1H, app ddt, *J* 48.5, 8.0, 4.2, C(3)*H*), 4.56 (1H, dd, *J* 11.3, 7.0, C(1)H_A), 4.76 (1H, dd, *J* 11.3, 5.7, C(1)H_B); δ_F (377 MHz, $CDCl_3$) −191.1 (m, C(3)*F*), −71.1 (s, CF_3).

Preparation of (*S*,*S*)-2-amino-3-fluorooctadecan-1-ol [(*S*,*S*)-3-deoxy-3-fluorosafingol] 394

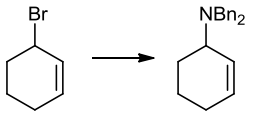


426 **394**

$Pd(OH)_2$/C (100 mg, 50% w/w wrt **426**) was added to a vigorously stirred solution of **426** (200 mg, 0.41 mmol, >99:1 dr, >98% ee) in degassed MeOH (2.1 mL) and the resultant suspension was stirred at rt under H_2 (5 atm) for 5.5 h. The reaction mixture was then filtered through a pad of Celite (eluent hot MeOH) and concentrated *in vacuo* to give **394** as a white crystalline solid (121 mg, 97%, >99:1 dr); $C_{18}H_{38}FNO$ requires C, 71.2; H, 12.6; N, 4.6; found C, 71.3; H, 12.8; N, 4.5; mp 80-81 °C; $[\alpha]_D^{20}$ −6.2 (*c* 1.0 in MeOH); ν_{max} 3354, 3270, 3196, 3095, 2953, 2918, 2847 (C−H), 1626, 1468, 1071, 1052, 938, 907, 872, 722; δ_H (400 MHz, MeOH-d_4) 0.91 (3H, app t, *J* 6.8, C(18)H_3), 1.23-1.84 (28H, m, C(4)H_2-C(17)H_2), 2.76-2.88 (1H, m, C(2)*H*), 3.51 (1H, dd, *J* 10.9, 6.3, C(1)H_A), 3.60 (1H, dd, *J* 10.9, 5.8, C(1)H_B), 4.50 (1H, app ddt, *J* 48.8, 8.8, 4.2, C(3)*H*); δ_C (100 MHz, MeOH-d_4) 13.5 (*C*(18)), 22.7, 25.4 (d, *J* 4.0), 29.5, 29.6, 29.68, 29.71, 29.77, 29.79, 31.7 (d, *J* 20.8), 32.1 (*C*(4)-*C*(17)), 55.8 (d, *J* 19.2, *C*(2)), 62.9 (d, *J* 5.6, *C*(1)), 94.0 (d, *J* 169, *C*(3)); δ_F (377 MHz, MeOH-d_4) −198.7 (m, C(3)*F*); *m*/*z* (ESI^+) 304 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{39}FNO^+$ ($[M+H]^+$) requires 304.3010; found 304.3006.

6.6. Chapter 5 Experimental

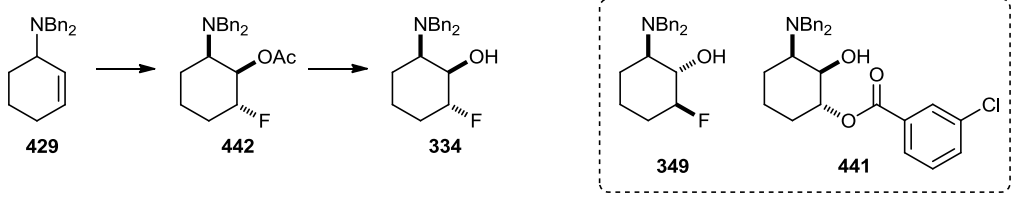
Preparation of (*RS*)-3-(*N*,*N*-dibenzylamino)cyclohex-1-ene 429



601 **429**

Following a modified literature procedure,[1] dibenzylamine (18 mL, 94 mmol) was added to 3-bromocyclohex-1-ene **601** (6.00 g, 37.3 mmol) at 0 °C and the resultant mixture was allowed to warm rt with stirring and was then heated at 60 °C for 30 min. The residue was allowed to cool to rt and was partitioned between CH_2Cl_2 (400 mL) and H_2O (400 mL). The organic layer was separated and washed sequentially with 10% aq citric acid (3 × 200 mL) and satd aq $NaHCO_3$ (3 × 200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **429** as a colourless syrup which crystallised on standing to a white crystalline solid (7.08 g, 68%);[1,134] R_f 0.40 (30-40 °C petrol/Et_2O, 96:4); mp 35-36 °C; δ_H (400 MHz, $CDCl_3$) 1.39-1.60 (2H, m, C(5)H_2), 1.73-2.10 (4H, m, C(4)H_2, C(6)H_2), 3.35 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.74 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 5.70-5.86 (2H, m, C(1)*H*, C(2)*H*), 7.16-7.44 (10H, m, *Ph*).

Hydroxyfluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)cyclohex-1-ene 429



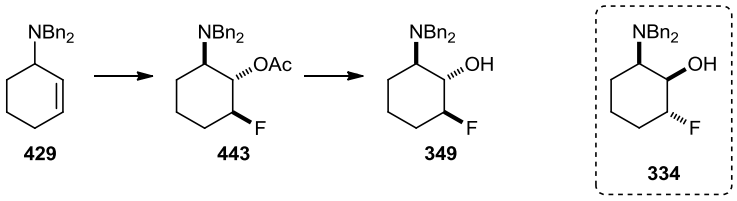
429 **442** **334** **349** **441**

Step 1: Following *General Procedure 17*, **429** (166 mg, 0.60 mmol) in CH_2Cl_2 (3.4 mL) was treated with HBF_4•OEt_2 (165 μL, 1.21 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.4 mL, 1.2 mmol) for 18 h to give a 67:12:21 mixture of **334**:**349**:**441**. Data for (*RS*,*RS*,*RS*)-1-(3'-chlorobenzoyloxy)-3-(*N*,*N*-dibenzylamino)cyclohexan-2-ol **441** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peak] 5.23-5.28 (1H, m, C(1)*H*).

Step 2: Pyridine (1.0 mL) and Ac_2O (0.57 mL, 6.0 mmol) were added to the residue (from step 1) and the resultant mixture was stirred at rt for 20 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5%→40% Et_2O in 30-40 °C petrol) gave (*RS*,*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-6-fluoro-1-acetoxycyclohexane **442** as a colourless oil which solidified on standing to a white crystalline solid (95.2 mg, 45%, >99:1 dr); R_f 0.42 (30-40 °C petrol/Et_2O, 80:20); mp 87-89 °C; ν_{max} 3085, 3063, 3027, 2943, 2871, 2835, 2804 (C−H), 1743 (C=O), 1229, 747, 736; δ_H (400 MHz, $CDCl_3$) 1.49-1.72 (3H, m, C(4)H_2, C(5)H_A), 1.75-1.92 (3H, m, C(3)H_2, C(5)H_B), 2.04 (3H, s, CO*Me*), 3.04 (1H,

app dq, *J* 12.1, 3.4, C(2)*H*), 3.75 (4H, A_2 system, N(CH_2Ph)$_2$), 4.58-4.75 (1H, m, C(6)*H*), 5.42-5.47 (1H, m, C(1)*H*), 7.19-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (*C*(4)), 21.3 (CO*Me*), 23.0 (*C*(3)), 26.1 (d, *J* 20.8, *C*(5)), 53.9 (*C*(2)), 55.1 (N(*C*H_2Ph)$_2$), 71.2 (d, *J* 29.6, *C*(1)), 88.1 (d, *J* 173, *C*(6)), 126.8 (*p-Ph*), 128.2, 128.3 (*o-*, *m-Ph*), 140.3 (*i-Ph*), 170.0 (*C*=O); δ_F (377 MHz, $CDCl_3$) −188.8 (m, C(6)*F*); *m*/*z* (ESI$^+$) 378 ([M+Na]$^+$, 89%), 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{27}FNO_2^+$ ([M+H]$^+$) requires 356.2020; found 356.2012.

Step 3: K_2CO_3 (36.0 mg, 0.27 mmol) was added to a solution of **442** (95.2 mg, 0.27 mmol, >99:1 dr) in MeOH (0.7 mL) and the resultant mixture was stirred at rt for 3 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **334** as a white crystalline solid (83.9 mg, quant, >99:1 dr).



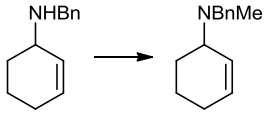
Step 1: Following *General Procedure 17*, **429** (166 mg, 0.60 mmol) in CH_2Cl_2 (2.0 mL) was treated with HBF_4•OEt_2 (1.6 mL, 12 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.4 mL, 1.2 mmol) for 18 h to give a 16:84 mixture of **334**:**349**.

Step 2: Pyridine (1.0 mL) and Ac_2O (0.57 mL, 6.0 mmol) were added to the residue (from step 1) and the resultant mixture was stirred at rt for 20 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5%→40% Et_2O in 30-40 °C petrol) gave (1*RS*,2*SR*,6*RS*)-2-(*N*,*N*-dibenzylamino)-6-fluoro-1-acetoxycyclohexane **443** as a colourless oil which solidified on standing to a white crystalline solid (105 mg, 49%, >99:1 dr); R_f 0.37 (30-40 °C petrol/Et_2O, 80:20); mp 109-111 °C; ν_{max} 3086, 3064, 3030, 2951, 2854, 2810 (C−H), 1733 (C=O), 1367, 1234, 1039, 1028, 747, 733, 696; δ_H (400 MHz, $CDCl_3$) 1.04-1.18 (1H, m, C(4)H_A), 1.40 (1H, app qd, *J* 12.8, 3.7, C(3)H_A) overlapping 1.44-1.58 (1H, m, C(5)H_A), 1.77-1.88 (1H, m, C(4)H_B), 1.95-2.05 (1H, m, C(5)H_B), 2.08-2.17 (1H, m, C(3)H_B), 2.25 (3H, s, CO*Me*), 2.62-2.71 (1H, m, C(2)*H*), 3.47 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.85 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 4.27 (1H, dddd, *J* 50.6, 11.6, 8.8, 5.2, C(6)*H*), 5.26 (1H, ddd, *J* 12.3, 10.7, 8.8, C(1)*H*), 7.19-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (d, *J* 12.8, *C*(4)), 21.4 (CO*Me*), 23.6 (d, *J* 1.6, *C*(3)), 30.6 (d, *J* 17.6, *C*(5)), 53.7 (N(*C*H_2Ph)$_2$), 58.8 (d, *J* 8.0, *C*(2)), 73.9 (d, *J* 16.0, *C*(1)), 93.1 (d, *J* 181, *C*(6)), 126.9 (*p-Ph*), 128.2, 128.7 (*o-*, *m-Ph*), 139.7 (*i-Ph*), 170.4 (*C*=O); δ_F (377 MHz, $CDCl_3$) −180.5 (app d, *J* 50.6,

C(6)*F*); *m*/*z* (ESI$^+$) 733 ([2M+Na]$^+$, 100%), 378 ([M+Na]$^+$, 85%), 356 ([M+H]$^+$, 87%), 336 ([M−F]$^+$, 71%); HRMS (ESI$^+$) $C_{22}H_{27}FNO_2^+$ ([M+H]$^+$) requires 356.2020; found 356.2013.

Step 3: K_2CO_3 (40.8 mg, 0.30 mmol) was added to a solution of **443** (105 mg, 0.30 mmol, >99:1 dr) in MeOH (0.7 mL) and the resultant mixture was stirred at rt for 3 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **349** as a white crystalline solid (92.6 mg, quant, >99:1 dr).

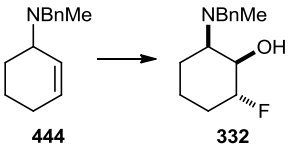
Preparation of (*RS*)-3-(*N*-benzyl-*N*-methylamino)cyclohex-1-ene 444



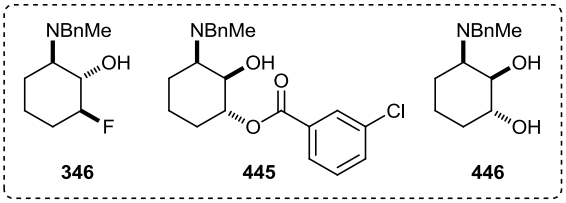
447 **444**

A mixture of **447** (1.00 g, 5.34 mmol), HCHO (37% in H_2O, 10 mL) and HCO_2H (10 mL) was stirred at reflux for 19 h. The mixture was then allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between Et_2O (40 mL) and 1 M aq NaOH (40 mL) and the layers were separated. The organic layer was washed with 1 M aq NaOH (2 × 40 mL) and the combined aqueous layers were extracted with Et_2O (2 × 40 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* filtration through a pad of silica gel (neat) gave **444** as a pale yellow oil (858 mg, 80%);[3,134] δ_H (400 MHz, $CDCl_3$) 1.49-1.63 (2H, m, C(4)H_A, C(5)H_A), 1.79-1.90 (2H, m, C(4)H_B, C(5)H_B), 1.97-2.04 (2H, m, C(6)H_2), 2.23 (3H, s, N*Me*), 3.33-3.41 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 13.3, NCH_AH$_B$Ph), 3.67 (1H, d, *J* 13.3, NCH$_A$$H_B$Ph), 5.71-5.71-5.77 (1H, m, C(2)*H*), 5.82-5.89 (1H, m, C(1)*H*), 7.21-7.37 (5H, m, *Ph*).

Hydroxyfluorination of (*RS*)-3-(*N*-benzyl-*N*-methylamino)cyclohex-1-ene 444



444 **332**

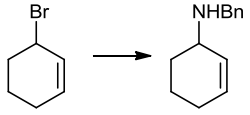


346 **445** **446**

Following *General Procedure 17*, **444** (161 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h to give a 85:3:12 mixture of **332**:**346**:**445**. Data for (*RS*,*RS*,*RS*)-1-(3'-chlorobenzoyloxy)-3-(*N*-benzyl-*N*-methylamino)cyclohexan-2-ol **445** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peak] 5.42-5.47 (1H, m, C(1)*H*). K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned

between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 85:3:12 mixture of **332**:**346**:**446**. Purification *via* flash column chromatography (gradient elution, 7→60% EtOAc in 30-40 °C petrol) on neutralised silica gel gave **332** as a yellow oil (139 mg, 73%, >99:1 dr). Data for (*RS*,*RS*,*RS*)-3-(*N*-benzyl-*N*-methylamino)cyclohexane-1,2-diol **446**:[3] δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.20 (3H, s, N*Me*), 2.69-2.75 (1H, m, C(3)*H*), 3.95 (1H, app t, *J* 3.8, C(2)*H*), 4.14 (1H, app q, *J* 3.5, C(1)*H*).

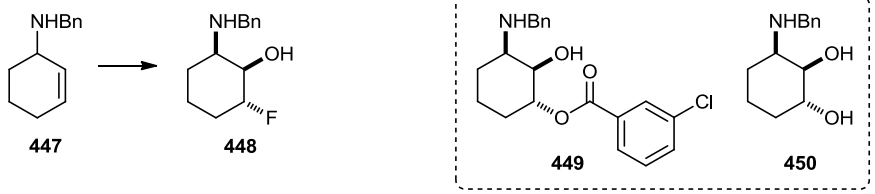
Preparation of (*RS*)-3-(*N*-benzylamino)cyclohex-1-ene 447



601 **447**

Following a modified literature procedure,[1] benzylamine (6.6 mL, 60 mmol) was added to 3-bromocyclohex-1-ene **601** (3.90 g, 24.2 mmol) at 0 °C and the resultant mixture was allowed to warm to rt with stirring and was then heated at 60 °C for 30 min. The residue was allowed to cool to rt and was partitioned between CH_2Cl_2 (100 mL) and satd aq $NaHCO_3$ (100 mL). The organic layer was separated and washed with satd aq $NaHCO_3$ (2 × 100 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 80:20) on neutralised silica gel gave **447** as a yellow oil (3.46 g, 76%);[1,134] R_f 0.18 (30-40 °C petrol/EtOAc, 80:20; neutralised silica gel); δ_H (400 MHz, $CDCl_3$) 1.42 (1H, br s, N*H*) overlapping 1.45-1.63 (2H, m, C(4)H_A, C(5)H_A), 1.72-1.82 (1H, m, C(5)H_B), 1.87-2.10 (3H, m, C(4)H_B, C(6)H_2), 3.20-3.27 (1H, m, C(3)*H*), 3.86 (2H, AB system, J_{AB} 13.0, NCH_2Ph), 5.71-5.83 (2H, m, C(1)*H*, C(2)*H*), 7.22-7.39 (5H, m, *Ph*).

Hydroxyfluorination of (*RS*)-3-(*N*-benzylamino)cyclohex-1-ene 447

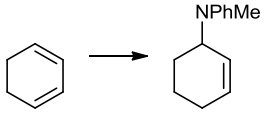


447 **448** **449** **450**

Following *General Procedure 17*, **447** (150 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h to give an 89:11 mixture of **448**:**449**. Data for (*RS*,*RS*,*RS*)-1-(3'-chlorobenzoyloxy)-3-(*N*-benzylamino)cyclohexan-2-ol **449** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peak] 5.24-5.29 (1H, m, C(1)*H*). K_2CO_3 (11.1 mg,

0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give an 89:11 mixture of **448**:**450**. Purification *via* flash column chromatography (gradient elution, 7→60% EtOAc in 30-40 °C petrol) on neutralised silica gel gave **448** as a white crystalline solid (116 mg, 65%, >99:1 dr); R_f 0.16 (30-40 °C petrol/EtOAc, 70:30; neutralised silica gel); $C_{13}H_{18}FNO$ requires C, 69.9; H, 8.1; N, 6.3; found C, 70.1; H, 8.1; N, 6.2; mp 82-83 °C; ν_{max} 3329 (O–H), 3087, 3063, 3029, 2941, 2867 (C–H), 1455, 1073, 699; δ_H (400 MHz, $CDCl_3$) 1.39-1.51 (1H, m, C(3)H_A), 1.54-1.77 (4H, m, C(3)H_B, C(4)H_2, C(5)H_A), 1.79-1.98 (1H, m, C(5)H_B), 2.43 (1H, br s, O*H*), 2.98-3.07 (1H, m, C(2)*H*), 3.73-3.83 (2H, AB system, NCH_2Ph) overlapping 3.82-3.88 (1H, m, C(1)*H*), 4.77 (1H, dtd, *J* 48.0, 5.7, 3.3, C(6)*H*), 7.24-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (d, *J* 4.8, *C*(4)), 26.4 (*C*(3)), 27.2 (d, *J* 19.2, *C*(5)), 51.1 (N*C*H_2Ph), 55.8 (*C*(2)), 68.9 (d, *J* 27.2, *C*(1)), 91.5 (d, *J* 168, *C*(6)), 127.2 (*p-Ph*), 128.1, 128.6 (*o-*, *m-Ph*), 140.1 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –191.8 (m, C(6)*F*); *m*/*z* (FI^+) 223 ($[M]^+$, 100%); HRMS (FI^+) $C_{13}H_{18}FNO^+$ ($[M]^+$) requires 223.1367; found 223.1367. Data for (*RS*,*RS*,*RS*)-3-(*N*-benzylamino)cyclohexane-1,2-diol **450** (tentatively assigned):[1] δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.37 (1H, dd, *J* 8.3, 4.4, C(3)*H*), 3.54-3.62 (1H, m, C(2)*H*). Data for (1*RS*,2*SR*,6*RS*)-2-(*N*-benzylamino)-6-fluorocyclohexan-1-ol **451** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.42-2.50 (1H, m, C(2)*H*), 3.37-3.47 (1H, m, C(1)*H*), 4.24-4.45 (1H, m, C(6)*H*); δ_F (377 MHz, $CDCl_3$) –181.7 (app d, *J* 53.9, C(6)*F*).

Preparation of (*RS*)-3-(*N*-methyl-*N*-phenylamino)cyclohex-1-ene 434

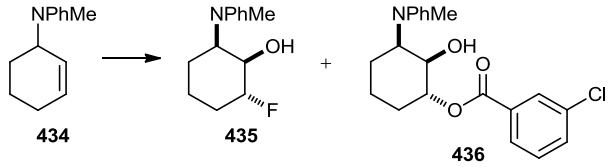


602 **434**

Following a modified literature procedure,[135] to a Schlenk tube containing PhMe (1.0 mL) was added sequentially $Pd(PPh_3)_4$ (220 mg, 0.19 mmol), 1,3-cyclohexadiene **602** (2.6 mL, 27 mmol), *N*-methylaniline (1.00 mL, 9.23 mmol) and F_3CCO_2H (69 μL, 0.92 mmol). The resultant mixture was then stirred at rt under a N_2 atmosphere. Additional $Pd(PPh_3)_4$ was added after 24 h (100 mg, 0.09 mmol), 48 h (100 mg, 0.09 mmol) and 72 h (200 mg, 0.17 mmol). After a further 7 days, the residues were absorbed onto Celite and all volatile components were removed *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0→8% Et_2O in 30-40 °C petrol) gave **434** as a yellow oil (1.59 g, 92%);[135] R_f 0.33 (30-40 °C petrol/Et_2O, 96:4); δ_H (400 MHz, $CDCl_3$) 1.53-1.73 (2H, m, C(5)H_A, C(4)H_A), 1.78-1.93 (2H, m, C(5)H_B, C(4)H_B), 1.98-2.15

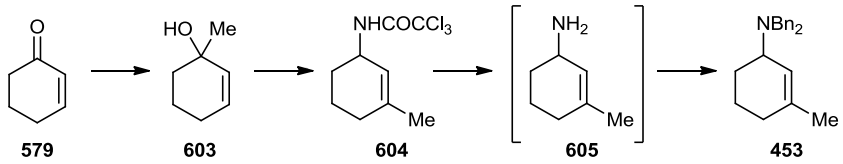
(2H, m, C(6)H_2), 2.80 (3H, s, N*Me*), 4.41-4.51 (1H, m, C(3)*H*), 5.60-5.68 (1H, m, C(1)*H*), 5.89-5.96 (1H, m, C(2)*H*), 6.71 (1H, t, *J* 7.3, *p-Ph*), 6.81 (2H, d, *J* 8.5, *o-Ph*), 7.25 (2H, dd, *J* 8.5, 7.3, *m-Ph*).

Hydroxyfluorination of (*RS*)-3-(*N*-methyl-*N*-phenylamino)cyclohex-1-ene 434



Following *General Procedure 17*, **434** (100 mg, 0.53 mmol) in CH_2Cl_2 (3.1 mL) was treated with HBF_4•OEt_2 (145 μL, 1.07 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.1 mL, 1.1 mmol) for 5 min to give a 93:7 mixture of **435**:**436**. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*,*RS*)-2-fluoro-6-(*N*-methyl-*N*-phenylamino)cyclohexan-1-ol **436** as a white crystalline solid (102 mg, 87%, >99:1 dr); R_f 0.21 (30-40 °C petrol/EtOAc, 90:10); $C_{13}H_{18}FNO$ requires C, 69.9; H, 8.1; N, 6.3; found C, 70.1; H, 8.0; N, 6.3; mp 62-63 °C; ν_{max} 3444 (O–H), 3094, 3061, 3025, 2941, 2873, 2820 (C–H), 1598, 1505, 996, 749; δ_H (400 MHz, $CDCl_3$) 1.56-2.04 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.28 (1H, br s, O*H*), 2.95 (3H, s, N*Me*), 3.80-3.89 (1H, m, C(6)*H*), 4.23 (1H, app s, C(1)*H*), 4.79 (1H, app d, *J* 46.2, C(2)*H*), 6.83 (1H, t, *J* 7.3, *p-Ph*), 6.89 (2H, d, *J* 8.0, *o-Ph*), 7.28 (2H, app t, *J* 8.0, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*(4)), 24.2 (*C*(5)), 25.4 (d, *J* 20.8, *C*(3)), 35.2 (N*Me*), 56.9 (*C*(6)), 68.6 (d, *J* 28.8, *C*(1)), 91.5 (d, *J* 169, *C*(2)), 114.9 (*o-Ph*), 118.4 (*p-Ph*), 129.3 (*m-Ph*), 149.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –190.1 (m, *J* 45.9, C(6)*F*); *m*/*z* (FI^+) 223 ($[M]^+$, 100%); HRMS (FI^+) $C_{13}H_{18}FNO^+$ ($[M]^+$) requires 223.1367; found 223.1372. Further elution gave (*RS*,*RS*,*RS*)-1-(3'-chlorobenzoyloxy)-3-(*N*-methyl-*N*-phenylamino)cyclohexan-2-ol **435** as a colourless oil (11.0 mg, 6%, >99:1 dr);[136] R_f 0.15 (30-40 °C petrol/EtOAc, 90:10); δ_H (400 MHz, $CDCl_3$) 1.63-2.17 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 2.98 (3H, s, N*Me*), 3.98 (1H, app d, *J* 11.9, C(3)*H*), 4.21 (1H, app s, C(2)*H*), 5.29 (1H, app d, *J* 3.0, C(1)*H*), 6.76 (1H, t, *J* 7.2, *p-Ph*), 6.82 (2H, d, *J* 8.0, *o-Ph*), 7.20 (2H, app t, *J* 8.0, *m-Ph*), 7.45 (1H, app t, *J* 7.8, C(5')*H*), 7.60 (1H, dd, *J* 8.0, 0.9, C(4')*H*), 8.00 (1H, d, *J* 7.9, C(6')*H*), 8.08 (1H, s, C(2')*H*). Data for (1*RS*,2*SR*,6*RS*)-2-fluoro-6-(*N*-methyl-*N*-phenylamino)cyclohexan-1-ol **452** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.42-3.51 (1H, m, C(1)*H*), 4.50 (1H, dddd, *J* 51.0, 11.3, 8.3, 5.2, C(6)*H*); δ_F (377 MHz, $CDCl_3$) –179.6 (app d, *J* 51.0, C(6)*F*).

Preparation of (*RS*)-3-(*N*,*N*-dibenzylamino)-1-methylcyclohex-1-ene 453



Step 1: Following a literature procedure,[137] MeMgCl (3.0 M in THF, 50 mL, 150 mmol) was added dropwise to a stirred solution of cyclohex-2-enone **579** (9.7 mL, 100 mmol) in THF (350 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (150 mL) was then added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 150 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification *via* distillation at reduced pressure (1.2 mmHg) gave (*RS*)-1-methylcyclohex-2-enol **603** as a colourless oil (7.54 g, 67%);[137] bp 24-26 °C (1.2 mmHg) {lit.[137] bp 63 °C (13 mmHg)}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*), 1.51 (1H, br s, O*H*), 1.59-1.80 (4H, m, C(5)H_2, C(6)H_2), 1.88-2.09 (2H, m, C(4)H_2), 5.61-5.67 (1H, m, C(2)*H*), 5.76 (1H, app dt, *J* 9.9, 3.8, C(3)*H*).

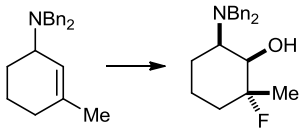
Step 2: Following a literature procedure,[137] a solution of **603** (5.00 g, 44.6 mmol) in Et_2O (25 mL) was added dropwise to a stirred suspension of KH (268 mg, 6.69 mmol) in Et_2O (30 mL) at 0 °C and the resultant mixture was stirred at this temperature for 30 min. The mixture was then added dropwise *via* cannula to a stirred solution of Cl_3CCN (4.5 mL, 45 mmol) in Et_2O (50 mL) and the resultant mixture was stirred at rt for 44 h. Satd aq NH_4Cl (10 mL) was then added and the resultant mixture was dried, filtered through a pad of silica gel (eluent Et_2O) and concentrated *in vacuo*. Purification *via* recrystallisation (30-40 °C petrol) gave (*RS*)-3-trichloroacetamido-1-methylcyclohex-1-ene **604** as a white crystalline solid (6.07 g, 53%);[137] mp 71-73 °C (30-40 °C petrol) {lit.[137] mp 77-78 °C (*n*-hexane)}; δ_H (400 MHz, $CDCl_3$) 1.55-1.74 (4H, m, C(4)H_2, C(5)H_2) overlapping 1.72 (3H, s, *Me*), 1.84-2.01 (2H, m, C(6)H_2), 4.42 (1H, app s, C(3)*H*), 5.34-5.40 (1H, m, C(2)*H*), 6.56 (1H, br s, N*H*).

Step 3: 10 M aq NaOH (12 mL, 120 mmol) was added dropwise to a stirred solution of **604** (6.07 g, 23.7 mmol) in EtOH (34 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 17 h. The mixture was then extracted with Et_2O/30-40 °C petrol (80:20 v/v, 3 × 50 mL) and the combined organic extracts were washed with H_2O (2 × 50 mL), then dried and (carefully) concentrated *in vacuo*.

Step 4: BnBr (1.2 mL, 10 mmol), K_2CO_3 (2.13 g, 15.4 mmol) and MeCN (26 mL) were added to the residue (from step 3) and the resultant mixture was heated at reflux for 18 h and then concentrated *in vacuo*. The residue was partitioned between EtOAc (30 mL) and H_2O (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **453** as a colourless oil (1.13 g, 16% over 2 steps[138]); R_f 0.37 (30-40 °C petrol/Et_2O, 96:4);

ν_{max} 3104, 3084, 3062, 3026, 3003, 2962, 2928, 2859, 2830, 2799, 2723 (C–H), 1494, 1453, 743, 697; δ_H (400 MHz, $CDCl_3$) 1.38-1.53 (2H, m, C(4)H_A, C(5)H_A), 1.70 (3H, s, C(1)*Me*), 1.76-2.05 (4H, m, C(4)H_B, C(5)H_B, C(6)H_2), 3.34 (1H, br s, C(3)*H*), 3.55 (2H, d, *J* 14.1, N(C$H_A$$H_B$Ph)$_2$), 3.77 (2H, d, *J* 14.1, N(C$H_A$$H_B$Ph)$_2$), 5.49 (1H, br s, C(2)*H*), 7.19-7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0, 22.8 (*C*(4), *C*(5)), 23.8 (C(1)*Me*), 30.3 (*C*(6)), 53.8 (N(*C*H_2Ph)$_2$), 54.9 (*C*(3)), 125.0 (*C*(2)), 126.5 (*p-Ph*), 128.1, 128.5 (*o-*, *m-Ph*), 137.4, 141.1 (*i-Ph*, *C*(1)); *m*/*z* (ESI^+) 292 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}N^+$ ($[M+H]^+$) requires 292.2060; found 292.2059.

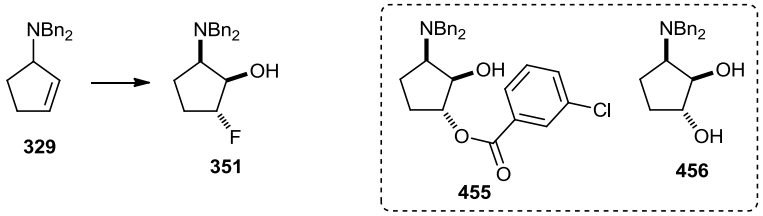
Hydroxyfluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)-1-methylcyclohex-1-ene 453



453 **454**

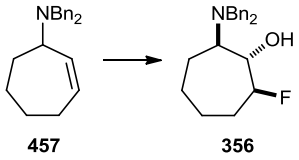
Following *General Procedure 17*, **453** (233 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **454** (95:5 dr). Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave (*RS*,*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-6-fluoro-6-methylcyclohexan-1-ol **454** as a colourless oil which solidified on standing to a white crystalline solid (184 mg, 70%, 95:5 dr); R_f 0.32 (30-40 °C petrol/Et_2O, 80:20); mp 55-59 °C; ν_{max} 3457 (O–H), 3085, 3062, 3028, 2937, 2870 (C–H), 1494, 1453, 1374, 1152, 1072, 1058, 1029, 747, 737, 699; δ_H (400 MHz, $CDCl_3$) 1.25-1.39 (1H, m, C(3)H_A), 1.45 (3H, d, *J* 23.0, C(6)*Me*), 1.50-1.78 (5H, m, C(3)H_B, C(4)H_2, C(5)H_2), 3.12 (1H, ddd, *J* 12.5, 6.7, 3.2, C(2)*H*), 3.78 (2H, d, *J* 14.6, N(C$H_A$$H_B$Ph)$_2$), 3.87 (2H, d, *J* 14.6, N(C$H_A$$H_B$Ph)$_2$) overlapping 3.89-3.93 (1H, m, C(1)*H*), 7.21-7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (d, *J* 1.6, *C*(4)), 23.5 (*C*(3)), 25.2 (d, *J* 22.4, C(6)*Me*), 31.0 (d, *J* 21.6, *C*(5)), 54.5 (N(*C*H_2Ph)$_2$), 60.4 (*C*(2)), 70.9 (d, *J* 32.8, *C*(1)), 95.9 (d, *J* 165, *C*(6)), 126.9 (*p-Ph*), 128.4, 128.5 (*o-*, *m-Ph*), 140.0 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −156.7 (m, C(6)*F*); *m*/*z* (ESI^+) 677 ($[2M+Na]^+$, 100%), 350 ($[M+Na]^+$, 59%), 328 ($[M+H]^+$, 89%); HRMS (ESI^+) $C_{21}H_{27}FNO^+$ ($[M+H]^+$) requires 328.2071; found 328.2070. Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.14 (3H, d, *J* 23.4, C(6)*Me*), 2.36-2.45 (1H, m, C(2)*H*), 3.38 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$); δ_F (377 MHz, $CDCl_3$) −133.0 (m, C(6)*F*).

Hydroxyfluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)cyclopent-1-ene 329



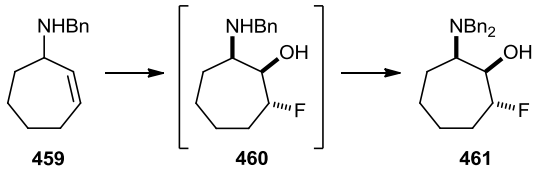
Following *General Procedure 17*, **329** (211 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h to give a 74:26 mixture of **351**:**455**. Data for (*RS*,*RS*,*RS*)-1-(3'-chlorobenzoyloxy)-3-(*N*,*N*-dibenzylamino) cyclopentan-2-ol **455** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.23 (1H, app d, *J* 4.0, C(2)*H*), 5.29 (1H, app dd, *J* 7.1, 3.8, C(1)*H*). K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 74:26 mixture of **351**:**456**. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **351** as a white crystalline solid (110 mg, 46%, >99:1 dr). Data for (*RS*,*RS*,*RS*)-3-(*N*,*N*-dibenzylamino)cyclopentane-1,2-diol **354**:[2] δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.92 (1H, app d, *J* 4.4, C(2)*H*), 4.20-4.25 (1H, m, C(1)*H*).

Hydroxyfluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)cyclohept-1-ene 457



Following *General Procedure 17*, **457** (175 mg, 0.60 mmol) in CH_2Cl_2 (3.4 mL) was treated with HBF_4•OEt_2 (165 μL, 1.21 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.4 mL, 1.2 mmol) for 18 h to give a 80:8:8:4 mixture of **356** to 3 unidentified fluorinated compounds. K_2CO_3 (8.3 mg, 0.06 mmol) and MeOH (1.5 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave **356** as a white crystalline solid (144 mg, 73%, >99:1 dr). Data for 3 unidentified fluorinated compounds: δ_F (377 MHz, $CDCl_3$) –177.5 (app tt, *J* 44.7, 11.5), –166.0 (m), –163.3 (m).

Preparation of (*RS*,*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-7-fluorocycloheptan-1-ol 461

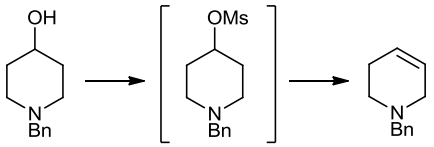


459 **460** **461**

Step 1: Following *General Procedure 17*, **459** (161 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h to give a mixture of compounds containing **460** as the major component. Data for (*RS*,*RS*,*RS*)-2-(*N*-benzylamino)-7-fluorocycloheptan-1-ol **460**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.95 (1H, app dd, *J* 8.8, 3.9, C(2)*H*), 3.78-3.81 (2H, m, NCH_2Ph), 3.98 (1H, ddd, *J* 20.1, 6.4, 2.6, C(1)*H*), 4.64 (1H, dddd, *J* 47.8, 9.5, 6.4, 2.6, C(7)*H*); δ_F (377 MHz, $CDCl_3$) −190.2 (m, C(7)*F*). K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*.

Step 2: BnBr (105 μL, 0.88 mmol), K_2CO_3 (332 mg, 2.40 mmol) and MeCN (4.0 mL) were added to the residue (from step 1) and the resultant mixture was heated at reflux for 18 h, then was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **461** as a colourless oil (65.8 mg, 25% over 2 steps, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 80:20); ν_{max} 3437 (O−H), 3085, 3062, 3028, 2933, 2861, 2801 (C−H), 1070, 967, 746, 735, 697; δ_H (400 MHz, $CDCl_3$) 1.27-1.49 (2H, m, C(4)H_A, C(5)H_A), 1.57-2.00 (6H, m, C(3)H_2, C(4)H_B, C(5)H_B, C(6)H_2), 2.80 (1H, m, O*H*), 2.96-3.05 (1H, m, C(2)*H*), 3.70 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.84 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 4.15 (1H, ddd, *J* 16.2, 6.2, 4.0, C(1)*H*), 4.57 (1H, dddd, *J* 47.2, 8.8, 6.2, 2.8, C(7)*H*), 7.21-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.4 (d, *J* 9.6, *C*(5)), 23.6, 27.3 (*C*(3), *C*(4)), 31.3 (d, *J* 21.6, *C*(6)), 55.4 (N(*C*H_2Ph)$_2$), 58.0 (d, *J* 7.2, *C*(2)), 74.9 (d, *J* 24.0, *C*(1)), 96.4 (d, *J* 170, *C*(7)), 127.0 (*p-Ph*), 128.4, 128.5 (*o-*, *m-Ph*), 139.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −174.0 (m); *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}FNO^+$ ([M+H]$^+$) requires 328.2071; found 328.2070.

Preparation of *N*-benzyl-1,2,3,6-tetrahydropyridine 463

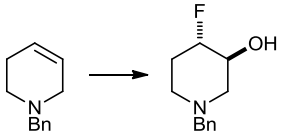


606 **607** **463**

Step 1: Following a literature procedure,[139] MsCl (11 mL, 140 mmol) was added dropwise to a stirred solution of *N*(1)-benzyl-4-hydroxypiperidine **606** (24.0 g, 125 mmol) and Et_3N (19 mL, 140 mmol) in PhMe (300 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 1.5 h. H_2O (75 mL) was then added and the layers were separated. The organic layer was washed with H_2O (75 mL) then dried and filtered.

Step 2: PhMe (150 mL), *N*,*N*-dimethylacetamide (100 mL) and ^tBuOK (18.3 g, 163 mmol) were added sequentially to the filtrate (from step 1) and the resultant mixture was stirred at rt for 1 week.[140] H_2O (150 mL) was then added and the layers were separated. The organic layer was washed with H_2O (2 × 150 mL) then dried and concentrated *in vacuo*. Purification *via* distillation at reduced pressure (1.1 mmHg) gave **463** as a colourless oil (17.6 g, 81% over 2 steps);[141] bp 75-78 °C (1.1 mmHg) {lit.[139] bp 75 °C (0.11 mmHg)}; δ_H (400 MHz, $CDCl_3$) 2.15-2.22 (2H, m, C(3)H_2), 2.58 (2H, t, *J* 5.6, C(2)H_2), 2.97-3.01 (2H, m, C(6)H_2), 3.60 (2H, s, NCH_2Ph), 5.65-5.71 (1H, m, C(4)*H*), 5.74-5.81 (1H, m, C(5)*H*), 7.24-7.40 (5H, m, *Ph*).

Hydroxyfluorination of *N*-benzyl-1,2,3,6-tetrahydropyridine 463

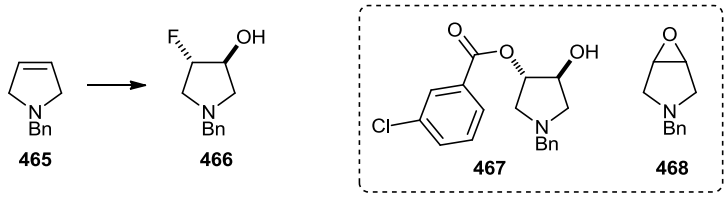


463 **464**

Following *General Procedure 17*, **463** (200 mg, 1.15 mmol) in CH_2Cl_2 (6.6 mL) was treated with HBF_4•OEt_2 (0.32 mL, 2.4 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 4.6 mL, 2.3 mmol) for 18 h. K_2CO_3 (16.0 mg, 0.12 mmol) and MeOH (2.9 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 12→100% EtOAc in 30-40 °C petrol) gave (*RS*,*RS*)-*N*(1)-benzyl-4-fluoropiperidin-3-ol **464** as a pale yellow oil (130 mg, 53%, >99:1 dr); R_f 0.43 (30-40 °C petrol/EtOAc, 50:50); $C_{12}H_{16}FNO$ requires C, 68.9; H, 7.7; N, 6.7; found C, 69.0; H, 7.6; N, 6.6; ν_{max} 3385 (O–H), 3087, 3062, 3029, 2951, 2935, 2807 (C–H), 1454, 1060, 1026, 748, 700; δ_H (400 MHz, $CDCl_3$) 1.77-1.91 (1H, m, C(5)H_A), 1.98-2.14

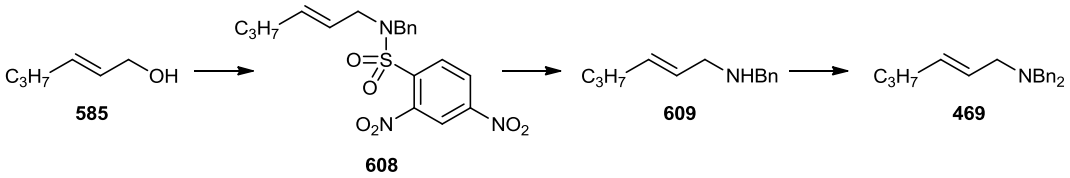
(1H, m, C(5)H_B), 2.30-2.46 (2H, m, C(2)H_A, C(6)H_A), 2.53-2.64 (1H, m, C(6)H_B), 2.80 (1H, app dt, *J* 11.8, 4.3, C(2)H_B), 3.02 (1H, br s, O*H*), 3.54 (2H, app s, NCH_2Ph), 3.78-3.86 (1H, m, C(3)*H*), 4.38-4.58 (1H, m, C(4)*H*), 7.24-7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (d, *J* 19.1, *C*(5)), 49.4 (d, *J* 5.7, *C*(6)), 55.8 (*C*(2)), 62.3 (N*C*H_2Ph), 68.4 (d, *J* 20.0, *C*(3)), 91.8 (d, *J* 177, *C*(4)), 127.3 (*p-Ph*), 128.4, 129.1 (*o-*, *m-Ph*), 137.7 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –188.1 (m, C(4)*F*); *m*/*z* (FI^+) 209 ($[M]^+$, 100%); HRMS (FI^+) $C_{12}H_{16}FNO^+$ ($[M]^+$) requires 209.1210; found 209.1213.

Hydroxyfluorination of *N*-benzyl-2,5-dihydropyrrole 465



Following *General Procedure 17*, **465** (421 mg, 2.64 mmol) in CH_2Cl_2 (12 mL) was treated with HBF_4•OEt_2 (3.6 mL, 26 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 10.6 mL, 5.29 mmol) for 18 h to give an 80:17:3 mixture of **466**:**467**:**468**. Data for (*RS*,*RS*)-*N*-benzyl-3-(3'-chlorobenzoyloxy)pyrrolidin-4-ol **467** (tentatively assigned): δ_H (400 MHz, $CDCl_3$) [selected peaks]: 3.91-3.97 (1H, m, C(4)*H*), 5.02-5.08 (1H, m, C(3)*H*). Data for (3*RS*,4*SR*)-*N*-benzyl-3,4-epoxypyrrolidine **468**:[142] δ_H (400 MHz, $CDCl_3$) 2.57 (2H, d, *J* 11.8, C(2)H_A, C(5)H_A), 3.21 (2H, d, *J* 11.8, C(2)H_B, C(5)H_B), 3.63 (2H, app s, C(3)*H*, C(4)*H*), 3.74 (2H, s, NCH_2Ph), 7.22-7.37 (5H, m, *Ph*). K_2CO_3 (36.5 mg, 0.26 mmol) and MeOH (6.6 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) on neutralised silica gel gave (*RS*,*RS*)-*N*(1)-benzyl-4-fluoropyrrolidin-3-ol **466** as a pale yellow oil (297 mg, 58%, >99:1 dr); R_f 0.26 (30-40 °C petrol/EtOAc, 60:40; neutralised silica gel); $C_{11}H_{14}FNO$ requires C, 67.7; H, 7.2; N, 7.2; found C, 67.8; H, 7.3; N, 7.1; ν_{max} 3375 (O–H), 3088, 3063, 3030, 2961, 2932, 2804 (C–H), 1454, 1096, 1029, 757, 701; δ_H (400 MHz, $CDCl_3$) 2.56 (1H, dd, *J* 10.2, 3.2, C(2)H_A), 2.69 (1H, dd, *J* 29.0, 11.6, C(5)H_A), 2.92 (1H, dd, *J* 10.2, 5.3, C(2)H_B), 3.08 (1H, dddd, *J* 26.8, 11.6, 5.6, 3.2, C(5)H_B), 3.68 (2H, AB system, J_{AB} 12.9, NCH_2Ph), 4.31 (1H, app dt, *J* 18.4, 4.1, C(3)*H*), 4.90 (1H, app dd, *J* 52.8, 5.3, C(4)*H*), 7.25-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 58.2 (d, *J* 24.0, *C*(5)), 55.5-59.6 (*C*(2)), 59.8 (N*C*H_2Ph), 75.7 (d, *J* 27.2, *C*(3)), 98.3 (d, *J* 181, *C*(4)), 127.3 (*p-Ph*), 128.4, 128.8 (*o-*, *m-Ph*), 137.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) –177.0 (m, C(4)*F*); *m*/*z* (FI^+) 195 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{14}FNO^+$ ($[M]^+$) requires 195.1054; found 195.1056.

Preparation of (*E*)-1-(*N*,*N*-dibenzylamino)hex-2-ene 469

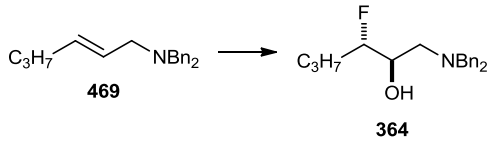


Step 1: DEAD (1.4 mL, 8.9 mmol) was added dropwise to a stirred solution of (*E*)-hex-2-en-1-ol **585** (888 mg, 8.86 mmol, >99:1 dr), *N*-benzyl-2,4-dinitrobenzenesulfonamide (2.30 g, 6.82 mmol) and PPh_3 (2.32 g, 8.86 mmol) in THF (8.0 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 19 h and was then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave (*E*)-*N*-benzyl-*N*-(hex-2-enyl)-2',4'-dinitrobenzenesulfonamide **608** as a yellow solid (2.86 g, quant, >99:1 dr);[143] R_f 0.25 (30-40 °C petrol/EtOAc, 80:20); mp 68-69 °C {lit.[143] mp 63.4-63.9 °C (EtOAc/*n*-hexane)}; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3, C(6)H_3), 1.31 (2H, app sxt, *J* 7.3, C(5)H_2), 1.90-1.98 (2H, m, C(4)H_2), 3.87 (2H, d, *J* 6.6, C(1)H_2), 4.53 (2H, s, NCH_2Ph), 5.23 (1H, dtd, *J* 15.2, 6.6, 1.5, C(2)*H*), 5.52 (1H, dt, *J* 15.2, 6.9, C(3)*H*), 7.21-7.33 (5H, m, *Ph*), 8.13 (1H, d, *J* 8.5, *Ar*), 8.39 (1H, dd, *J* 8.5, 2.2, *Ar*), 8.48 (1H, d, *J* 2.2, *Ar*).

Step 2: 2-Mercaptoacetic acid (0.71 mL, 10 mmol) was added to a stirred solution of **608** (2.86 g, 6.82 mmol, >99:1 dr) and Et_3N (1.9 mL, 14 mmol) in CH_2Cl_2 (34 mL) and the resultant solution was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc (40 mL) then washed with 5% aq NaOH (3 × 40 mL) then dried and concentrated *in vacuo* to give *(E)*-*N*(1)-benzylaminohex-2-ene **609** as an orange oil (1.17 g, 91%, >99:1 dr);[143] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.5, C(6)H_3), 1.40 (2H, app sxt, *J* 7.4, C(5)H_2), 1.51 (1H, br s, N*H*), 1.97-2.06 (2H, m, C(4)H_2), 3.23 (2H, d, *J* 5.1, C(1)H_2), 3.79 (2H, s, NCH_2Ph), 5.51-5.66 (2H, m, C(2)*H*, C(3)*H*), 7.23-7.39 (5H, m, *Ph*).

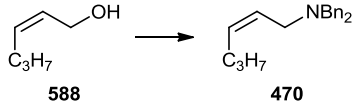
Step 3: BnBr (0.59 mL, 5.0 mmol) was added to a stirred solution of **609** (945 mg, 4.99 mmol, >99:1 dr) and K_2CO_3 (2.07 g, 15.0 mmol) in MeCN (25 mL) and the resultant mixture was heated at reflux for 20 h. The mixture was then allowed to cool to rt and was filtered through Celite (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **469** as a colourless oil (1.21 g, 87%, >99:1 dr); R_f 0.34 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3062, 3027, 2957, 2926, 2872, 2792, 2711 (C−H), 1494, 1454, 970, 732, 696; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, C(6)H_3), 1.41 (2H, app sxt, *J* 7.3, C(5)H_2), 2.03 (2H, app q, *J* 6.7, C(4)H_2), 3.03 (2H, d, *J* 5.8, C(1)H_2), 3.58 (4H, s, N(CH_2Ph)$_2$), 5.49-5.65 (2H, m, C(2)*H*, C(3)*H*), 7.21-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (*C*(6)), 22.5 (*C*(5)), 34.6 (*C*(4)), 55.5 (*C*(1)), 57.6 (N(*C*H_2Ph)$_2$), 126.7 (*p-Ph*), 127.3 (*C*(3)), 128.1, 128.8 (*o-*, *m-Ph*), 134.0 (*C*(2)), 139.9 (*i-Ph*); *m*/*z* (ESI^+) 280 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}N^+$ ($[M+H]^+$) requires 280.2060; found 280.2055.

Hydroxyfluorination of (*E*)-1-(*N*,*N*-dibenzylamino)hex-2-ene 469



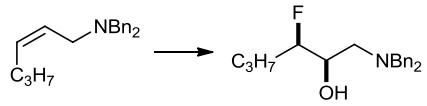
Following *General Procedure 17*, **469** (224 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **364** as a colourless oil (134 mg, 53%, >99:1 dr).

Preparation of (*Z*)-1-(*N*,*N*-dibenzylamino)hex-2-ene 470



N-Bromosuccinimide (1.78 g, 10.0 mmol) was added portionwise to a stirred solution of (*Z*)-hex-2-en-1-ol **588** (1.00 g, 10.0 mmol) and PPh_3 (2.62 g, 10.0 mmol) in THF (20 mL) at 0 °C and the resultant mixture was stirred at this temperature for 1 h. Dibenzylamine (3.9 mL, 20 mmol) was then added and the resultant mixture was allowed to warm to rt over 24 h. Et_2O (50 mL) was added and the mixture was stirred for 10 min, then filtered through a pad of Celite (eluent Et_2O) and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and satd aq $NaHCO_3$ (50 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **470** as a colourless oil (2.23 g, 80%, >99:1 dr); R_f 0.33 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3063, 3026, 2958, 2871, 2822, 2792, 2710 (C−H), 1494, 1454, 740, 696; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5, C(6)H_3), 1.38 (2H, app sxt, *J* 7.4, C(5)H_2), 1.99 (2H, app q, *J* 6.8, C(4)H_2), 3.09 (2H, d, *J* 5.1, C(1)H_2), 3.60 (4H, s, N(CH_2Ph)$_2$), 5.53-5.65 (2H, m, C(2)*H*, C(3)*H*), 7.22-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*(6)), 22.8 (*C*(5)), 29.6 (*C*(4)), 50.1 (*C*(1)), 58.0 (N(*C*H_2Ph)$_2$), 126.8 (*p-Ph*), 127.1 (*C*(3)), 128.1, 128.8 (*o-*, *m-Ph*), 132.9 (*C*(2)), 139.9 (*i-Ph*); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}N^+$ ([M+H]$^+$) requires 280.2060; found 280.2058.

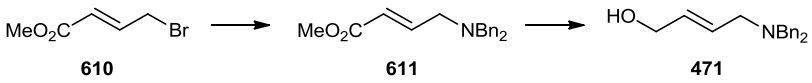
Hydroxyfluorination of (*Z*)-1-(*N*,*N*-dibenzylamino)hex-2-ene 470



470 **366**

Following *General Procedure 17*, **470** (224 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **366** as a pale yellow oil (145 mg, 57%, >99:1 dr).

Preparation of (*E*)-4-(*N*,*N*-dibenzylamino)but-2-en-1-ol 471



610 **611** **471**

Step 1: Dibenzylamine (6.4 mL, 33 mmol) was added to a stirred solution of methyl 4-bromocrotonate **610** (85%, 4.2 mL, 30 mmol) and K_2CO_3 (12.4 g, 90.0 mmol) in MeCN (150 mL) and the resultant mixture was heated at reflux for 21 h and then concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and H_2O (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave (*E*)-methyl 4-(*N*,*N*-dibenzylamino)but-2-enoate **611** as a pale yellow oil (7.00 g, 79%, >99:1 dr); R_f 0.24 (30-40 °C petrol/Et_2O, 90:10); ν_{max} 3085, 3062, 3028, 2949, 2924, 2796, 2713 (C−H), 1721 (C=O), 1269, 1169, 737, 697; δ_H (400 MHz, $CDCl_3$) 3.23 (2H, app dd, *J* 5.8, 1.0, C(4)H_2), 3.62 (4H, s, N(CH_2Ph)$_2$), 3.76 (3H, s, O*Me*), 6.10 (1H, d, *J* 15.8, C(2)*H*), 7.05 (1H, dt, *J* 15.8, 5.8, C(3)*H*), 7.23-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 51.5 (O*Me*), 54.1 (*C*(4)), 61.8 (N(*C*H_2Ph)$_2$), 122.4 (*C*(2)), 127.1 (*p-Ph*), 128.3, 128.7 (*o-*, *m-Ph*), 139.0 (*i-Ph*), 146.8 (*C*(3)), 166.8 (*C*=O); *m*/*z* (ESI$^+$) 296 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_2^+$ ([M+H]$^+$) requires 296.1645; found 296.1642.

Step 2: DIBAL-H (1.0 M in hexanes, 48 mL, 48 mmol) was added dropwise to a stirred solution of **611** (6.35 g, 21.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the resultant solution was allowed to warm to rt and was stirred at this temperature for 18 h. The mixture was then cooled to 0 °C and satd aq Rochelle's salt (100 mL) was added dropwise (*cautiously!*) and the resultant mixture was stirred vigorously at rt for 23 h. The

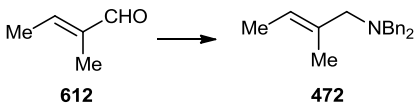
mixture was then filtered through a pad of Celite (eluent Et_2O) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→80% EtOAc in 30-40 °C petrol) gave **471** as a colourless oil (5.72 g, 99%, >99:1 dr); R_f 0.13 (30-40 °C petrol/EtOAc, 80:20); ν_{max} 3328 (O−H), 3085, 3062, 3027, 2921, 2794, 2712 (C−H), 971, 733, 696; δ_H (400 MHz, $CDCl_3$) 1.64 (1H, br s, O*H*), 3.11 (2H, d, *J* 4.3, C(4)H_2), 3.62 (4H, s, N(CH_2Ph)$_2$), 4.12 (2H, d, *J* 3.8, C(1)H_2), 5.73-5.86 (2H, m, C(2)*H*, C(3)*H*), 7.23-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 55.2 (*C*(4)), 58.1 (N(*C*H_2Ph)$_2$), 63.3 (*C*(1)), 126.9 (*p-Ph*), 128.2, 128.8 (*o-*, *m-Ph*), 129.7, 131.9 (*C*(2), *C*(3)), 139.6 (*i-Ph*); *m*/*z* (ESI$^+$) 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{22}NO^+$ ([M+H]$^+$) requires 268.1696; found 268.1694.

Hydroxyfluorination of (*E*)-4-(*N*,*N*-dibenzylamino)but-2-en-1-ol 471

471 **372**

Following *General Procedure 17*, **471** (160 mg, 0.60 mmol, >99:1 dr) in CH_2Cl_2 (2.8 mL) was treated with HBF_4•OEt_2 (0.82 mL, 6.0 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.4 mL, 1.2 mmol) for 18 h. K_2CO_3 (8.3 mg, 0.06 mmol) and MeOH (1.5 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10→80% EtOAc in 30-40 °C petrol) gave **372** as a colourless oil (58.3 mg, 32%, >99:1 dr).

Preparation of (*E*)-1-(*N*,*N*-dibenzylamino)-2-methylbut-2-ene 472

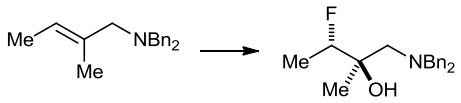


612 **472**

Dibenzylamine (2.9 mL, 15 mmol) and $NaBH(OAc)_3$ (4.45 g, 21.0 mmol) were added sequentially to a stirred solution of tiglic aldehyde **612** (1.5 mL, 15 mmol, >99:1 dr) in THF (100 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 4 h. Satd aq $NaHCO_3$ (200 mL) was then added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **472** as a colourless oil (2.14 g, 54%, >99:1 dr); R_f 0.51 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3062, 3027, 2977, 2919, 2878, 2792, 2709 (C−H), 1495, 1453, 744,

697; δ_H (400 MHz, $CDCl_3$) 1.63-1.68 (3H, m, C(4)H_3), 1.71-1.75 (3H, m, C(2)*Me*), 2.94 (2H, s, C(1)H_2), 3.54 (4H, s, N(CH_2Ph)$_2$), 5.46-5.44 (1H, m, C(3)*H*), 7.23-7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4, 14.6 (C(2)*Me*, *C*(4)), 57.9 (*C*(1)), 62.8 (N(*C*H_2Ph)$_2$), 121.9 (*C*(3)), 126.7 (*p-Ph*), 128.2, 128.8 (*o-*, *m-Ph*), 134.2 (*C*(2)), 140.2 (*i-Ph*); *m*/*z* (ESI$^+$) 266 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}N^+$ ([M+H]$^+$) requires 266.1903; found 266.1904.

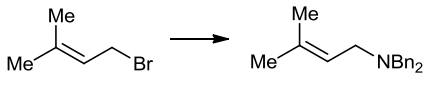
Hydroxyfluorination of (*E*)-1-(*N*,*N*-dibenzylamino)-2-methylbut-2-ene 472



472 **476**

Following *General Procedure 17*, **472** (212 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.0 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% EtOAc in 30-40 °C petrol) gave (*RS*,*SR*)-1-(*N*,*N*-dibenzylamino)-3-fluoro-2-methylbutan-2-ol **476** as a colourless oil (135 mg, 56%, >99:1 dr); R_f 0.33 (30-40 °C petrol/EtOAc, 90:10); ν_{max} 3453 (O−H), 3086, 3063, 3028, 2983, 2937, 2804 (C−H), 1064, 744; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 1.5, C(2)*Me*), 1.26 (3H, dd, *J* 24.8, 6.3, C(4)H_3), 2.57 (1H, dd, *J* 14.1, 1.3, C(1)H_A), 2.91 (1H, dd, *J* 14.1, 1.8, C(1)H_B), 2.99 (1H, br s, O*H*), 3.62 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.85 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 4.42 (1H, app dq, *J* 47.7, 6.3, C(3)*H*), 7.26-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7 (d, *J* 22.4, *C*(4)), 20.1 (C(2)*Me*), 59.5 (d, *J* 1.6, *C*(1)), 60.4 (N(*C*H_2Ph)$_2$), 71.8 (d, *J* 21.6, *C*(2)), 92.7 (d, *J* 172.6, *C*(3)), 127.4 (*p-Ph*), 128.5, 129.1 (*o-*, *m-Ph*), 138.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −180.6 (dq, *J* 47.7, 24.1, C(3)*F*); *m*/*z* (ESI$^+$) 324 ([M+Na]$^+$, 62%), 302 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{25}FNO^+$ ([M+H]$^+$) requires 302.1915; found 302.1903.

Preparation of 1-(*N*,*N*-dibenzylamino)-3-methylbut-2-ene 473

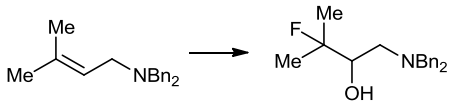


613 **473**

Dibenzylamine (16 mL, 84 mmol) was added to 3,3-dimethylallyl bromide **613** (3.9 mL, 34 mmol) at 0 °C and the resultant mixture was stirred at this temperature for 30 min. The residue was then partitioned

between H_2O (400 mL) and CH_2Cl_2 (400 mL). The organic layer was separated and washed sequentially with 10% aq citric acid (3 × 200 mL) and satd aq $NaHCO_3$ (3 × 200 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **473** as a colourless syrup (5.98 g, 67%); R_f 0.26 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3062, 3027, 2969, 2924, 2879, 2854, 2792 (C–H), 1494, 1452, 744, 736, 698; δ_H (400 MHz, $CDCl_3$) 1.59 (3H, s, C(3)Me_A), 1.75 (3H, s, C(3)Me_B), 3.03 (2H, d, *J* 6.8, C(1)H_2), 3.58 (4H, s, N(CH_2Ph)$_2$), 5.35 (1H, t, *J* 6.7, C(2)*H*), 7.20-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1, 25.9 (C(3)Me_2), 51.1 (*C*(1)), 58.0 (N(*C*H_2Ph)$_2$), 121.9 (*C*(2)), 126.7 (*p-Ph*), 128.1, 128.8 (*o-*, *m-Ph*), 134.9 (*C*(3)), 140.0 (*i-Ph*); *m*/*z* (ESI$^+$) 266 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}N^+$ ([M+H]$^+$) requires 266.1903; found 266.1903.

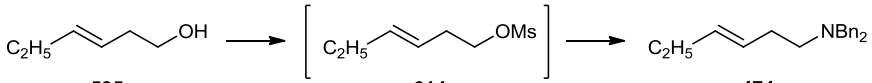
Hydroxyfluorination of 1-(*N*,*N*-dibenzylamino)-3-methylbut-2-ene 473



473 **376**

Following *General Procedure 17*, **473** (212 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **376** as a colourless oil (132 mg, 55%).

Preparation of (*E*)-1-(*N*,*N*-dibenzylamino)hex-3-ene 474



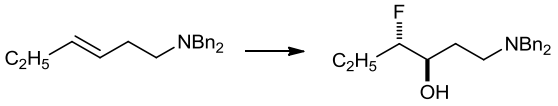
595 **614** **474**

Step 1: Following *General Procedure 14*, (*E*)-hex-3-en-1-ol **595** (2.3 mL, 20 mmol, >99:1 dr) in CH_2Cl_2 (33 mL) was treated with Et_3N (5.6 mL, 40 mmol) and MsCl (2.3 mL, 30 mmol).

Step 2: Dibenzylamine (9.6 mL, 50 mmol) and EtOH (50 mL) were added to the residue (from step 1) and the resultant mixture was heated at 70 °C for 16 h then was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and satd aq $NaHCO_3$ (100 mL) and the layers were separated. The organic layer was washed sequentially with 10% aq citric acid (3 × 100 mL) and satd aq $NaHCO_3$ (100 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography

(gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **474** as a colourless oil (3.11 g, 56% over 2 steps, >99:1 dr); R_f 0.38 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3063, 3027, 2961, 2932, 2873, 2845, 2795 (C–H), 1494, 1453, 1367, 1127, 1073, 1028, 966, 743, 698; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.5, C(6)H_3), 1.98-2.07 (2H, m, C(5)H_2), 2.21-2.30 (2H, app q, *J* 7.1, C(2)H_2), 2.52 (2H, t, *J* 7.6, C(1)*H*), 3.61 (4H, s, N(CH_2Ph)$_2$), 5.32-5.42 (1H, m, C(3)*H*), 5.45-5.54 (1H, m, C(4)*H*), 7.22-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*(6)), 25.6 (*C*(5)), 30.4 (*C*(2)), 53.5 (*C*(1)), 58.2 (N(*C*H_2Ph)$_2$), 126.7 (*p-Ph*), 127.2 (*C*(3)), 128.1, 128.8 (*o-*, *m-Ph*), 133.0 (*C*(4)), 140.0 (*i-Ph*); *m*/*z* (ESI^+) 280 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}N^+$ ($[M+H]^+$) requires 280.2060; found 280.2059.

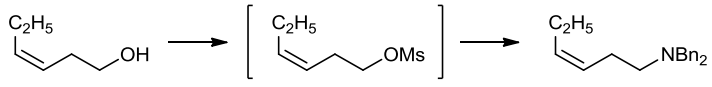
Hydroxyfluorination of (*E*)-1-(*N*,*N*-dibenzylamino)hex-3-ene 474



474 **383**

Following *General Procedure 17*, **474** (200 mg, 0.72 mmol, >99:1 dr) in CH_2Cl_2 (4.1 mL) was treated with HBF_4•OEt_2 (195 μL, 1.43 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.9 mL, 1.5 mmol) for 18 h. K_2CO_3 (9.7 mg, 0.07 mmol) and MeOH (1.8 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **383** as a colourless oil (109 mg, 48%, >99:1 dr).

Preparation of (*Z*)-1-(*N*,*N*-dibenzylamino)hex-3-ene 475



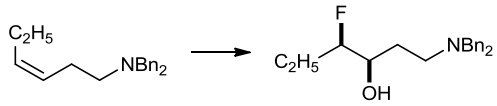
598 **615** **475**

Step 1: Following *General Procedure 14*, (*Z*)-hex-3-en-1-ol **598** (2.4 mL, 20 mmol, >99:1 dr) in CH_2Cl_2 (33 mL) was treated with Et_3N (5.6 mL, 40 mmol) and MsCl (2.3 mL, 30 mmol).

Step 2: Dibenzylamine (9.6 mL, 50 mmol) and EtOH (50 mL) were added to the residue (from step 1) and the resultant mixture was heated at 70 °C for 16 h then was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) and the layers were separated. The organic layer was washed sequentially with 10% aq citric acid (3 × 100 mL) and satd aq $NaHCO_3$ (100 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography

(gradient elution, 1→8% Et_2O in 30-40 °C petrol) gave **475** as a colourless oil (3.28 g, 59% over 2 steps, >99:1 dr); R_f 0.38 (30-40 °C petrol/Et_2O, 96:4); ν_{max} 3085, 3063, 3027, 3007, 2962, 2932, 2873, 2795 (C–H), 1494, 1453, 1366, 1126, 1072, 1028, 743, 698; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.6, C(6)H_3), 2.02 (2H, app quin, *J* 7.33 C(5)H_2), 2.25-2.33 (2H, app q, *J* 7.2, C(2)H_2), 2.50 (2H, t, *J* 7.8, C(1)H_2), 3.62 (4H, s, N(CH_2Ph)$_2$), 5.27-5.36 (1H, m, C(3)*H*), 5.37-5.45 (1H, m, C(4)*H*), 7.22-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(6)), 20.6 (*C*(5)), 24.9 (*C*(2)), 53.3 (*C*(1)), 58.2 (N(*C*H_2Ph)$_2$), 126.75 (*p-Ph*), 126.81 (*C*(3)), 128.1, 128.8 (*o-*, *m-Ph*), 132.5 (*C*(4)), 139.9 (*i-Ph*); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}N^+$ ([M+H]$^+$) requires 280.2060; found 280.2058.

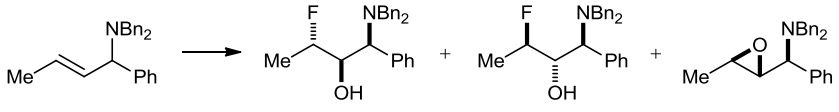
Hydroxyfluorination of (*Z*)-1-(*N*,*N*-dibenzylamino)hex-3-ene 475



475 **385**

Following *General Procedure 17*, **475** (200 mg, 0.72 mmol, >99:1 dr) in CH_2Cl_2 (4.1 mL) was treated with HBF_4•OEt_2 (195 μL, 1.43 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 2.9 mL, 1.5 mmol) for 18 h. K_2CO_3 (9.7 mg, 0.07 mmol) and MeOH (1.8 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **385** as a colourless oil (55 mg, 24%, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 80:20); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, app t, *J* 7.4, C(6)H_3), 1.47-1.78 (3H, m, C(2)H_A, C(5)H_2), 1.94 (1H, app dtd, *J* 14.4, 10.5, 3.9, C(2)H_B), 2.62 (1H, app dt, *J* 12.9, 4.3, C(1)H_A), 2.76-2.85 (1H, m, C(1)H_B), 3.29 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.64 (1H, dddd, *J* 20.7, 10.0, 3.8, 2.6, C(3)*H*), 3.89 (2H, d, *J* 13.1, N(CH$_A$$H_B$Ph)$_2$), 4.16 (1H, app ddt, *J* 48.1, 8.4, 4.1, C(4)*H*), 5.59 (1H, br s, O*H*), 7.25-7.39 (10H, m, *Ph*).

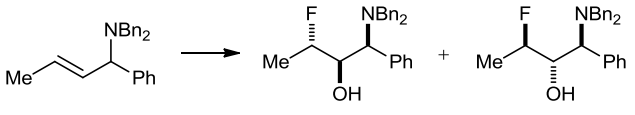
Hydroxyfluorination of (*RS*,*E*)-1-(*N*,*N*-dibenzylamino)-1-phenylbut-2-ene 477



477 **478** **479** **480**

Following *General Procedure 17*, **477** (100 mg, 0.31 mmol, >99:1 dr) in CH_2Cl_2 (1.8 mL) was treated with HBF_4•OEt_2 (83 μL, 0.61 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 1.2 mL, 0.60 mmol) for 18 h. K_2CO_3 (4.2 mg, 0.03 mmol) and MeOH (0.8 mL) were added to the residue and the resultant mixture was

stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a mixture of products containing an 88:12 ratio of **478**:**479**. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave starting material as a colourless oil (8.5 mg, 3%, >99:1 dr); R_f 0.69 (30-40 °C petrol/Et_2O, 80:20). Further elution gave (1*RS*,2*SR*,3*SR*)-1-(*N*,*N*-dibenzylamino)-2,3-epoxy-1-phenylbutane **480** as a colourless oil (15.6 mg, 15%, >99:1 dr); R_f 0.51 (30-40 °C petrol/Et_2O, 80:20); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 5.1, C(4)H_3), 2.78 (1H, app qd, *J* 5.2, 2.2, C(3)*H*), 3.16 (1H, dd, *J* 7.9, 2.2, C(2)*H*), 3.47 (1H, d, *J* 7.7, C(1)*H*), 3.71 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.89 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 7.19-7.49 (15H, m, *Ph*). Further elution gave (1*RS*,2*SR*,3*RS*)-1-(*N*,*N*-dibenzylamino)-3-fluoro-1-phenylbutan-2-ol **478** as a colourless oil which solidified on standing to a white crystalline solid (30.9 mg, 28%, >99:1 dr); R_f 0.38 (30-40 °C petrol/Et_2O, 80:20); mp 111-113 °C; ν_{max} 3496 (O−H), 3086, 3059, 3028, 2984, 2956, 2919, 2848 (C−H), 749, 699; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, dd, *J* 24.8, 6.3, C(4)H_3), 3.06 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 3.54 (1H, dd, *J* 10.8, 0.5, C(1)*H*), 3.98 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 4.29 (1H, app dqd, *J* 46.2, 6.3, 2.9, C(3)*H*), 4.53 (1H, ddd, *J* 15.4, 10.8, 2.9, C(2)*H*), 4.58 (1H, s, O*H*), 7.22-7.50 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (d, *J* 23.2, *C*(4)), 53.4 (N(*C*H_2Ph)$_2$), 63.4 (d, *J* 9.6, *C*(1)), 69.6 (d, *J* 20.8, *C*(2)), 91.4 (d, *J* 169, *C*(3)), 127.5, 128.4, 128.6, 128.7, 129.1, 129.8, 133.1, 138.2 (*Ph*); δ_F (377 MHz, $CDCl_3$) −178.2 (m, C(3)*F*); *m*/*z* (ESI$^+$) 749 ([2M+Na]$^+$, 30%), 386 ([M+Na]$^+$, 80%), 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{27}FNO^+$ ([M+H]$^+$) requires 364.2071; found 364.2060. Further elution gave (1*RS*,2*RS*,3*SR*)-1-(*N*,*N*-dibenzylamino)-3-fluoro-1-phenylbutan-2-ol **479** as a colourless oil which solidified on standing to a white crystalline solid (7.8 mg, 7%, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 80:20); mp 108-110 °C; ν_{max} 3458 (O−H), 3086, 3063, 3029, 3004, 2935, 2838 (C−H), 748, 698; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, dd, *J* 25.3, 6.1, C(4)H_3), 1.66 (1H, br s, O*H*), 3.10 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 3.66 (1H, d, *J* 9.7, C(1)*H*), 3.88 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 4.66 (1H, ddd, *J* 14.0, 9.7, 2.9, C(2)*H*), 5.25 (1H, app dqd, *J* 46.7, 6.3, 2.9, C(3)*H*), 7.24-7.53 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.2 (d, *J* 22.4, *C*(4)), 54.6 (N(*C*H_2Ph)$_2$), 64.2 (d, *J* 8.0, *C*(1)), 71.7 (d, *J* 21.6, *C*(2)), 91.7 (d, *J* 164, *C*(3)), 127.3, 128.0, 128.4, 128.5, 129.1, 130.0, 134.2 (*Ph*); δ_F (377 MHz, $CDCl_3$) −180.7 (m, C(3)*F*); *m*/*z* (ESI$^+$) 749 ([2M+Na]$^+$, 99%), 386 ([M+Na]$^+$, 95%), 364 ([M+H]$^+$, 100%), 344 ([M−F]$^+$, 47%); HRMS (ESI$^+$) $C_{24}H_{27}FNO^+$ ([M+H]$^+$) requires 364.2071; found 364.2058.



477 **478** **479**

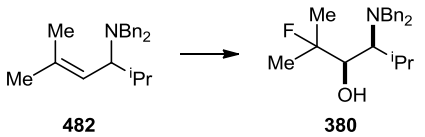
Following *General Procedure 17*, **477** (100 mg, 0.31 mmol, >99:1 dr) in CH_2Cl_2 (1.1 mL) was treated with HBF_4•OEt_2 (0.83 mL, 6.1 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 1.2 mL, 0.60 mmol) for 18 h. K_2CO_3 (4.2 mg, 0.03 mmol) and MeOH (0.8 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a mixture of products containing a 40:60 ratio of **478**:**479**. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave starting material as a colourless oil (19.0 mg, 19%, >99:1 dr). Further elution gave **478** as a colourless oil (28.6 mg, 26%, >99:1 dr). Further elution gave **479** as a white solid (34.5 mg, 31%, >99:1 dr).

Hydroxyfluorination of (*RS*)-1-(*N*,*N*-dibenzylamino)-3-methyl-1-phenylbut-2-ene 481

481 **378**

Following *General Procedure 17*, **481** (273 mg, 0.80 mmol) in CH_2Cl_2 (4.6 mL) was treated with HBF_4•OEt_2 (220 μL, 1.62 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 3.2 mL, 1.6 mmol) for 18 h. K_2CO_3 (11.1 mg, 0.08 mmol) and MeOH (2.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **378** as a white solid (229 mg, 76%, >99:1 dr); R_f 0.23 (30-40 °C petrol/Et_2O, 90:10); mp 114-120 °C; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 22.0, C(3)Me_A), 1.11 (3H, d, *J* 22.2, C(3)Me_B), 3.04 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 3.81 (1H, d, *J* 10.1, C(1)*H*), 3.96 (2H, d, *J* 13.1, N(C$H_A$$H_B$Ph)$_2$), 4.27 (1H, app t, *J* 10.1, C(2)*H*), 5.41 (1H, br s, O*H*), 7.24-7.50 (15H, m, *Ph*).

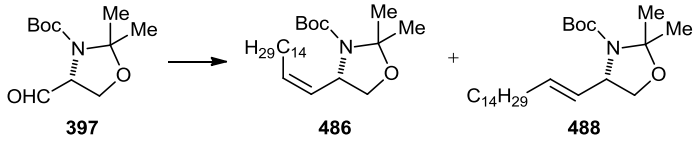
Hydroxyfluorination of (*RS*)-3-(*N*,*N*-dibenzylamino)-2,5-dimethylhex-4-ene 482



482 **380**

Following *General Procedure 17*, **482** (123 mg, 0.40 mmol) in CH_2Cl_2 (2.3 mL) was treated with HBF_4•OEt_2 (110 μL, 0.81 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 1.6 mL, 0.80 mmol) for 30 min. K_2CO_3 (5.5 mg, 0.04 mmol) and MeOH (1.0 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **380** as a colourless oil (112 mg, 82%, >99:1 dr); R_f 0.38 (30-40 °C petrol/Et_2O, 90:10).

Preparation of *tert*-butyl (*S*,*Z*)-4-(hexadec-1′-en-1′-yl)-2,2-dimethyloxazolidine-3-carboxylate 486

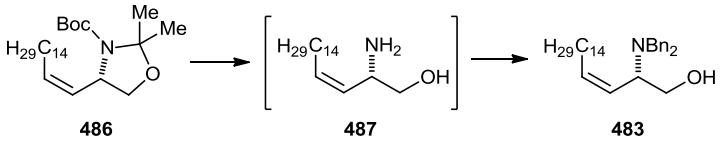


397 **486** **488**

NaHMDS (1.0 M in THF, 28 mL, 28 mmol) was added dropwise to a stirred suspension of $[C_{15}H_{31}PPh_3]^+Br^-$ (16.7 g, 30.2 mmol) in THF (300 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 30 min. The mixture was cooled to −78 °C and *n*-hexane (450 mL) was added, followed by the dropwise addition of a solution of Garner's aldehyde (*R*)-**397** (3.01 g, 13.1 mmol) in THF (150 mL). The resultant mixture was then allowed to warm to rt with stirring over 42 h. The reaction was quenched by addition of satd aq NH_4Cl (20 mL) and concentrated *in vacuo*. The residue was partitioned between Et_2O (200 mL) and H_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **486** as a colourless oil (4.26 g, 77%, >99:1 dr);[144] R_f 0.38 (30-40 °C petrol/Et_2O, 90:10); $[\alpha]_D^{20}$ −41.9 (*c* 1.0 in $CHCl_3$) {lit.[145] (for enantiomer) $[\alpha]_D^{26}$ +53.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.8, C(16′)H_3), 1.20-1.64 (24H, m, C(4′)H_2-C(15′)H_2), 1.93-2.25 (2H, br m, C(3′)H_2), 3.64 (1H, dd, *J* 8.7, 3.2, C(5)H_A), 4.06 (1H, dd, *J* 8.7, 6.2, C(5)H_B), 4.49-4.78 (1H, br m, C(4)*H*), 5.33-5.57 (2H, br m, C(1′)*H*, C(2′)*H*). Further elution gave the (*E*)-alkene isomer **488** as an white semi-solid (378 mg, 7%, >99:1 dr);[144] R_f 0.28 (30-40 °C petrol/Et_2O, 90:10); $[\alpha]_D^{20}$ +3.5 (*c* 1.0 in $CHCl_3$) {lit.[144] (for enantiomer) $[\alpha]_D^{21}$ −5.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.8, C(16′)H_3), 1.22-1.66 (24H, m, C(4′)H_2- C(15′)H_2), 1.98-2.06

(2H, m, C(3′)H_2), 3.71 (1H, dd, *J* 8.7, 2.0, C(5)H_A), 4.01 (1H, dd, *J* 8.7, 6.0, C(5)H_B), 4.14-4.50 (1H, br m, C(4)*H*), 5.34-5.72 (2H, m, C(1′)*H*, C(2′)*H*).

Preparation of (*S*,*Z*)-2-(*N*,*N*-dibenzylamino)octadec-3-en-1-ol 483

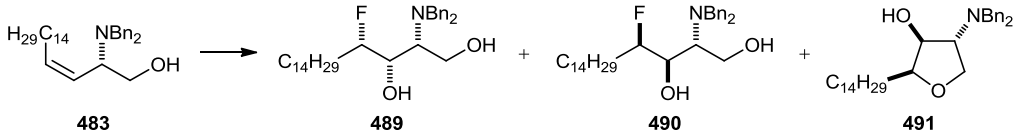


486 **487** **483**

Step 1: Conc aq HCl (1.7 mL) was added to a stirred solution of **486** (4.26 g, 10.1 mmol, >99:1 dr) in MeOH (32 mL) and the resultant mixture was heated at reflux for 17 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 1 M aq NaOH (100 mL) and the layers were separated. The organic layer was washed with 1 M aq NaOH (2 × 50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo*.

Step 2: BnBr (2.6 mL, 22 mmol), K_2CO_3 (4.17 g, 30.2 mmol) and EtOH (50 mL) were added to the residue (from step 1) and the resultant mixture was heated at reflux for 4 h and then concentrated *in vacuo*. The residue was partitioned between Et_2O (100 mL) and H_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave **483** as a colourless oil (4.21 g, 90% over 2 steps, >99:1 dr); R_f 0.28 (30-40 °C petrol/Et_2O, 90:10); $[\alpha]_D^{20}$ +7.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3461 (O−H), 3086, 3063, 3028, 3005, 2922, 2852 (C−H), 1029, 744, 729; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, J 6.8, C(18)H_3), 1.19-1.45 (24H, m, C(6)H_2-C(17)H_2), 1.87-2.04 (2H, m, C(5)H_2), 3.33 (1H, dd, *J* 10.4, 5.2, C(1)H_A), 3.36 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 3.60 (1H, app t, *J* 10.4, C(1)H_B), 3.65-3.73 (1H, app td, *J* 10.1, 5.2, C(2)*H*), 3.91 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 5.38-5.46 (1H, m, C(3)*H*), 5.80 (1H, app dt, *J* 11.0, 7.5, C(4)*H*), 7.23-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 28.1, 29.37, 29.39, 29.5, 29.6, 29.66, 29.70, 30.0, 31.9 (*C*(5)-*C*(17)), 53.5 (N(*C*H_2Ph)$_2$), 56.8 (*C*(2)), 61.2 (*C*(1)), 122.1 (*C*(4)), 127.2 (*p-Ph*), 128.5, 128.8 (*o*-, *m-Ph*), 137.3 (*C*(3)), 139.3 (*i-Ph*); *m*/*z* (ESI$^+$) 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}NO^+$ ([M+H]$^+$) requires 464.3887; found 464.3871.

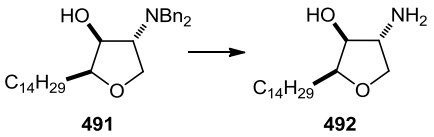
Hydroxyfluorination of (*S*,*Z*)-2-(*N*,*N*-dibenzylamino)octadec-3-en-1-ol 483



483 **489** **490** **491**

Following *General Procedure 17*, **483** (2.78 g, 6.00 mmol, >99:1 dr) in CH_2Cl_2 (34 mL) was treated with HBF_4•OEt_2 (1.6 mL, 12 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 24 mL, 12 mmol) for 18 h. K_2CO_3 (82.9 mg, 0.60 mmol) and MeOH (15 mL) were added to the residue and the resultant mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 67:16:18 mixture of **489**:**490**:**491**. Purification *via* flash column chromatography (gradient elution, 5→40% EtOAc in 30-40 °C petrol) gave (2*S*,3*S*,4*R*)-4-(*N*,*N*-dibenzylamino)-2-tetradecyltetrahydrofuran-3-ol **491** as a colourless oil which solidified on standing to a white solid (397 mg, 14%, >99:1 dr); R_f 0.54 (30-40 °C petrol/EtOAc, 80:20); mp 44-45 °C; $[\alpha]_D^{20}$ +1.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3455, 3381 (O−H), 3086, 3062, 3028, 2917, 2850 (C−H), 1067, 1028, 747, 732, 697; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.7, C(14′)H_3), 1.13-1.65 (26H, m, C(1′)H_2-C(13′)H_2), 3.37 (1H, app td, *J* 7.5, 1.6, C(4)*H*), 3.57-3.67 (3H, m, C(5)H_A, N(C$H_A$$H_B$Ph)$_2$), 3.68-3.74 (1H, m, C(2)*H*), 3.79 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 4.07 (1H, app t, *J* 8.6, C(5)H_B), 4.27-4.33 (1H, br m, C(3)*H*), 7.21-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(14′)), 22.7, 26.3, 28.6, 29.4, 29.56, 29.58, 29.7, 29.8, 31.9 (*C*(1′)-*C*(13′)), 55.7 (N(*C*H$_2$Ph)$_2$), 68.4 (*C*(5)), 71.1 (*C*(4)), 74.0 (*C*(3)), 82.9 (*C*(2)), 127.1 (*p-Ph*), 128.3, 128.7 (*o*-, *m-Ph*), 139.2 (*i-Ph*); *m*/*z* (ESI$^+$) 480 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}NO_2^+$ ([M+H]$^+$) requires 480.3836; found 480.3814. Further elution gave (2*R*,3*S*,4*S*)-2-(*N*,*N*-dibenzylamino)-4-fluorooctadecane-1,3-diol **489** as a colourless oil which solidified on standing to an oily, white solid (1.42 g, 47%, >99:1 dr); R_f 0.27 (30-40 °C petrol/EtOAc, 80:20); mp 34-36 °C; $[\alpha]_D^{20}$ −17.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3383 (O−H), 3085, 3062, 3027, 2953, 2916, 2849 (C−H), 746, 723, 697; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.19-1.58 (25H, m, C(5)H_A, C(6)H_2-C(17)H_2), 1.66-1.81 (1H, m, C(5)H_B), 1.89 (1H, br s, O*H*), 3.05 (1H, app dt, *J* 9.0, 5.4, C(2)*H*), 3.65-3.78 (3H, m, C(3)*H*, N(C$H_A$$H_B$Ph)$_2$), 3.88-3.97 (2H, m, C(1)H_2), 4.01 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.43-4.61 (1H, m, C(4)*H*), 7.23-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 25.5 (d, *J* 4.0), 29.35, 29.43, 29.5, 29.6, 29.65, 29.69, 30.8 (d, *J* 20.8), 31.9 (*C*(5)-*C*(17)), 54.7 (N(*C*H$_2$Ph)$_2$), 59.1 (*C*(1)), 59.4 (d, *J* 4.0, *C*(2)), 69.8 (d, *J* 20.8, *C*(3)), 93.4 (d, *J* 173, *C*(4)), 127.4 (*p-Ph*), 128.6, 129.1 (*o*-, *m-Ph*), 138.9 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −197.9 (m, C(4)*F*); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{51}FNO_2^+$ ([M+H]$^+$) requires 500.3898; found 500.3892.

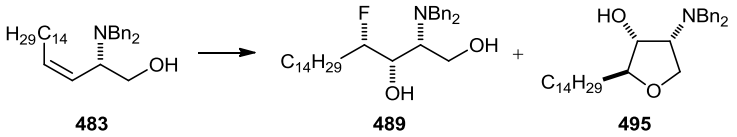
Preparation of (2*S*,3*S*,4*R*)-4-amino-2-tetradecyltetrahydrofuran-3-ol [(+)-4-*epi*-jaspine B] 492



491 **492**

$Pd(OH)_2/C$ (47.3 mg, 50% w/w wrt **491**) was added to a vigorously stirred solution of **491** (94.6 mg, 0.20 mmol, >99:1 dr) in degassed MeOH (1.0 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The reaction mixture was then filtered through a pad of Celite (eluent MeOH) and concentrated *in vacuo* to give **492** as a white solid (799 mg, 92%, >99:1 dr);[146,147] mp 83-85 °C {lit.[146] (for enantiomer) mp 87-88 °C}; $[\alpha]_D^{20}$ +1.4 (*c* 1.0 in MeOH) {lit.[147] (for enantiomer) $[\alpha]_D^{25}$ −1.17 (*c* 0.99 in MeOH)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.7, C(14′)H_3), 1.17-1.70 (26H, m, C(1′)H_2-C(13′)H_2), 1.92 (3H, br s, O*H*, NH_2), 3.41 (1H, dd, *J* 9.2, 3.4, C(5)H_A), 3.45-3.52 (1H, m, C(2)*H*), 3.80-3.85 (1H, m, C(3)*H*), 3.87-3.94 (1H, m, C(4)*H*), 4.22 (1H, dd, *J* 9.2, 6.0, C(5)H_B).

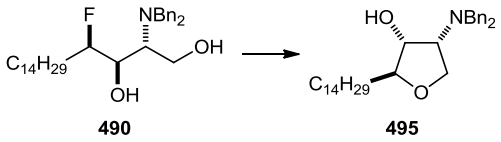
Attempted hydroxyfluorination of (*S*,*Z*)-2-(*N*,*N*-dibenzylamino)octadec-3-en-1-ol 483



483 **489** **495**

Following *General Procedure 17*, **483** (139 mg, 0.30 mmol, >99:1 dr) in CH_2Cl_2 (1.0 mL) was treated with HBF_4•OEt_2 (0.82 mL, 6.0 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 1.2 mL, 0.6 mmol) for 18 h to give an 88:12 mixture of **495**:**489**. Purification *via* flash column chromatography (gradient elution, 2→20% Et_2O in 30-40 °C petrol) gave (2*S*,3*R*,4*R*)-4-(*N*,*N*-dibenzylamino)-2-tetradecyltetrahydrofuran-3-ol **495** as a colourless oil (105 mg, 73%, >99:1 dr); R_f 0.17 (30-40 °C petrol/Et_2O, 90:10); $[\alpha]_D^{20}$ −19.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3423 (O−H), 3086, 3063, 3028, 2923, 2853 (C−H), 749, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(14′)H_3), 1.20-1.54 (26H, m, C(1′)H_2-C(13′)H_2), 3.25-3.33 (1H, m, C(4)*H*), 3.64 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.68-3.74 (1H, m, C(5)H_A) overlapping 3.74 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.82 (1H, dd, *J* 5.3, 1.8, C(3)*H*), 3.90-3.96 (2H, m, C(2)*H*, C(5)H_B), 3.99 (1H, br s, O*H*), 7.25-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(14′)), 22.7, 25.8, 29.4, 29.6, 29.66, 29.69, 31.9, 34.3 (*C*(1′)-*C*(13′)), 56.0 (N(*C*H_2Ph)$_2$), 65.4 (*C*(4)), 68.2 (*C*(5)), 73.7 (*C*(3)), 86.6 (*C*(2)), 127.5 (*p-Ph*), 128.5, 129.0 (*o-*, *m-Ph*), 137.6 (*i-Ph*); *m*/*z* (FI^+) 479 ($[M]^+$, 100%); HRMS (FI^+) $C_{32}H_{49}NO_2^+$ ($[M]^+$) requires 479.3758; found 479.3771.

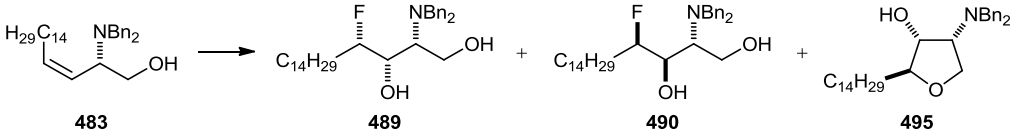
Preparation of (2*S*,3*R*,4*R*)-4-(*N*,*N*-dibenzylamino)-2-tetradecyltetrahydrofuran-3-ol 495



490 **495**

HBF_4•OEt_2 (14 μL, 0.10 mmol) and BF_3•OEt_2 (12 μL, 0.10 mmol) were sequentially added to a stirred solution of **490** (50.0 mg, 0.10 mmol, >99:1 dr) in CH_2Cl_2 (0.4 mL) and the resultant mixture was stirred at rt for 18 h. Satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (10 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5→40% Et_2O in 30-40 °C petrol) gave **495** as a colourless oil (51.2 mg, quant, >99:1 dr).

Hydroxyfluorination of (*S*,*Z*)-2-(*N*,*N*-dibenzylamino)octadec-3-en-1-ol 483

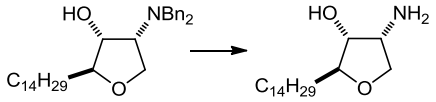


483 **489** **490** **495**

HBF_4•OEt_2 (2.6 mL, 19 mmol) and *m*-CPBA (0.5 M solution in CH_2Cl_2, 7.7 mL, 3.9 mmol) were sequentially added to **483** (446 mg, 0.96 mmol, >99:1 dr) and the resultant mixture was stirred at rt for 30 min. The reaction mixture was then added dropwise to a stirred mixture of satd aq Na_2SO_3 (20 mL) and satd aq $NaHCO_3$ (80 mL). EtOAc (100 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The layers were separated and the organic layer was washed with satd aq $NaHCO_3$ (2 × 50 mL) and the combined aqueous layers were extracted with EtOAc (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 66:18:16 mixture of **490**:**489**:**495**. Purification *via* flash column chromatography (gradient elution, 7→60% EtOAc in 30-40 °C petrol) gave **489** as a yellow oil (33.1 mg, 7%, >99:1 dr); R_f 0.49 (30-40 °C petrol/EtOAc, 70:30). Further elution gave (*R*,*R*,*R*)-2-(*N*,*N*-dibenzylamino)-4-fluorooctadecane-1,3-diol **490** as a yellow oil which solidified on standing to an oily, pale yellow solid (267 mg, 56%, >99:1 dr); R_f 0.26 (30-40 °C petrol/EtOAc, 70:30); $[\alpha]_D^{20}$ +13.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3376 (O−H), 3085, 3029, 2952, 2919, 2850 (C−H), 1113, 1022, 744, 698; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, app t, *J* 6.8, C(18)H_3), 1.19-1.78 (26H, m, C(5)H_2- C(17)H_2), 2.67 (1H, br s, O*H*), 2.89 (1H, app q, *J* 6.2, C(2)*H*), 3.73 (2H, d, *J* 13.9, N(CH_AH$_B$Ph)$_2$), 3.80-3.91 (4H, m, C(1)H_A, C(3)*H*, N(CH$_A$$H_B$Ph)$_2$), 3.95 (1H, dd, *J* 11.4, 6.6, C(1)H_B), 4.64 (1H, app ddt, *J* 48.3, 8.6, 4.2, C(4)*H*), 7.22-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 22.7, 25.1 (d, *J* 4.8), 29.4, 29.5, 29.6, 29.66, 29.70, 31.2 (d, *J* 20.8), 31.9 (*C*(5)-*C*(17)), 54.6 (N(*C*H$_2$Ph)$_2$), 59.0 (*C*(1)), 59.3 (d, *J* 3.2, *C*(2)), 71.8 (d, *J* 19.2, *C*(3)),

93.9 (d, *J* 170, *C*(4)), 127.2 (*p-Ph*), 128.4, 128.9 (*o-*, *m-Ph*), 139.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −196.3 (m, C(4)*F*); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{51}FNO_2^+$ ([M+H]$^+$) requires 500.3898; found 500.3883.

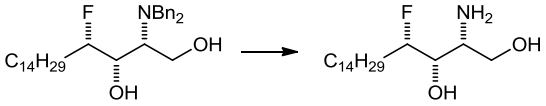
Preparation of (2*S*,3*R*,4*R*)-4-amino-2-tetradecyltetrahydrofuran-3-ol [(−)-2-*epi*-jaspine B] 496



495 **496**

$Pd(OH)_2$/C (47.3 mg, 50% w/w wrt **495**) was added to a vigorously stirred solution of **495** (94.6 mg, 0.20 mmol, >99:1 dr) in degassed EtOAc (1.0 mL) and the resultant suspension was stirred at rt under H_2 (5 atm) for 4.5 h. The reaction mixture was then filtered through a pad of Celite (eluent EtOAc) and concentrated *in vacuo* to give **496** as a white solid (31.9 mg, 53%, >99:1 dr);[146,147] mp 94-96 °C {lit.[146] (for enantiomer) mp 101-102 °C}; $[\alpha]_D^{20}$ −13.3 (*c* 1.0 in MeOH) {lit.[146] (for enantiomer) $[\alpha]_D^{25}$ +14.8 (*c* 0.97 in MeOH)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, app t, *J* 6.8, C(14′)H_3), 1.18-1.65 (26H, m, C(1′)H_2-C(13′)H_2), 2.21 (3H, br s, O*H*, NH_2), 3.40 (1H, dd, *J* 8.6, 6.8, C(5)H_A), 3.43-3.50 (1H, m, C(2)*H*), 3.58-3.66 (2H, m, C(3)*H*, C(4)*H*), 4.12 (1H, dd, *J* 8.6, 6.3, C(5)H_B).

Preparation of (2*R*,3*S*,4*S*)-2-Amino-4-fluorooctadecane-1,3-diol [4-deoxy-4-fluoro-L-*xylo*-phytosphingosine] 484

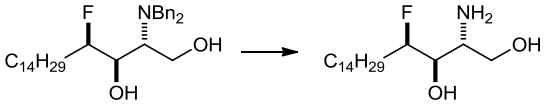


489 **484**

$Pd(OH)_2$/C (624 mg, 50% w/w wrt **489**) was added to a vigorously stirred solution of **489** (1.25 g, 2.50 mmol, >99:1 dr) in degassed MeOH (25 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The reaction mixture was then filtered through a pad of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with satd aq $NaHCO_3$ (3 × 50 mL) and the combined aqueous layers were then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **484** as a white solid (799 mg, quant, >99:1 dr); mp 97-98 °C; $[\alpha]_D^{20}$ −6.7 (*c* 1.0 in MeOH); ν_{max} 3376, 3324 (O−H, N−H), 2916, 2850 (C−H), 1470, 1115, 1035, 748; δ_H (400 MHz, MeOH-d_4) 0.91 (3H, app t, *J* 6.9, C(18)H_3), 1.22-1.86 (26H, m, C(5)H_2-C(17)H_2), 2.90 (1H, app q, *J* 5.3, C(2)*H*), 3.46-3.58 (2H, m, C(1)H_A, C(3)*H*), 3.64 (1H, dd, *J* 10.9, 5.3, C(1)H_B), 4.58 (1H, app ddt, *J* 48.5, 8.8, 3.7, C(4)*H*); δ_C (100 MHz, MeOH-d_4) 13.5 (*C*(18)), 22.7, 25.2 (d, *J* 4.8), 29.5, 29.68, 29.70, 29.72, 29.72, 29.78, 29.80, 31.4 (d, *J* 20.8), 32.1 (*C*(5)-*C*(17)), 54.4 (d, *J* 4.0,

C(2)), 63.4 (*C*(1)), 72.3 (d, *J* 18.4, *C*(3)), 94.9 (d, *J* 171, *C*(4)); δ_F (377 MHz, MeOH-d_4) –198.5 (m, C(4)*F*); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 45%), 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{39}FNO_2^+$ ([M+H]$^+$) requires 320.2959; found 320.2949.

Preparation of (*R*,*R*,*R*)-2-Amino-4-fluorooctadecane-1,3-diol [4-deoxy-4-fluoro-L-*lyxo*-phytosphingosine] 485



490 **485**

$Pd(OH)_2$/C (65.3 mg, 50% w/w wrt **490**) was added to a vigorously stirred solution of **490** (131 mg, 0.26 mmol, >99:1 dr) in degassed MeOH (2.6 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The reaction mixture was then filtered through a pad of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with satd aq $NaHCO_3$ (3 × 20 mL) and the combined aqueous layers were then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **485** as a white solid (83.1 mg, quant, >99:1 dr); mp 96-98 °C; $[\alpha]_D^{20}$ +5.2 (*c* 1.0 in MeOH); ν_{max} 3353, 3287 (O−H, N−H), 2914, 2848 (C−H), 1469, 1077, 1055, 1042, 880; δ_H (400 MHz, MeOH-d_4) 0.92 (3H, app t, *J* 6.9, C(18)H_3), 1.13-1.71 (25H, m, C(5)H_A, C(6)H_2-C(17)H_2), 1.78-1.91 (1H, m, C(5)H_B), 2.96 (1H, br s, C(2)*H*), 3.41 (1H, app dd, *J* 28.1, 6.3, C(3)*H*), 3.53-3.61 (1H, m, C(1)H_A), 3.81 (1H, app d, *J* 8.2, C(1)H_B), 4.64-4.80 (1H, m, C(4)H); δ_C (100 MHz, MeOH-d_4) 14.5 (*C*(18)), 23.8, 26.4 (d, *J* 4.8), 30.5, 30.68, 30.73, 30.76, 30.81, 30.82, 30.84, 32.3 (d, *J* 21.0), 33.1 (*C*(5)-*C*(17)), 55.0 (*C*(2)), 64.6 (*C*(1)), 74.3 (d, *J* 18.1, *C*(3)), 94.4 (d, *J* 172, *C*(4)); δ_F (377 MHz, MeOH-d_4) –200.4 (m, C(4)*F*); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 59%), 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{39}FNO_2^+$ ([M+H]$^+$) requires 320.2959; found 320.2951.

6.7. References and Notes

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[99] Each solution was added *via* syringe pump at a rate of 64.4 mL h^{-1} using 20 mL disposable syringes which were continually replaced over the course of the addition.
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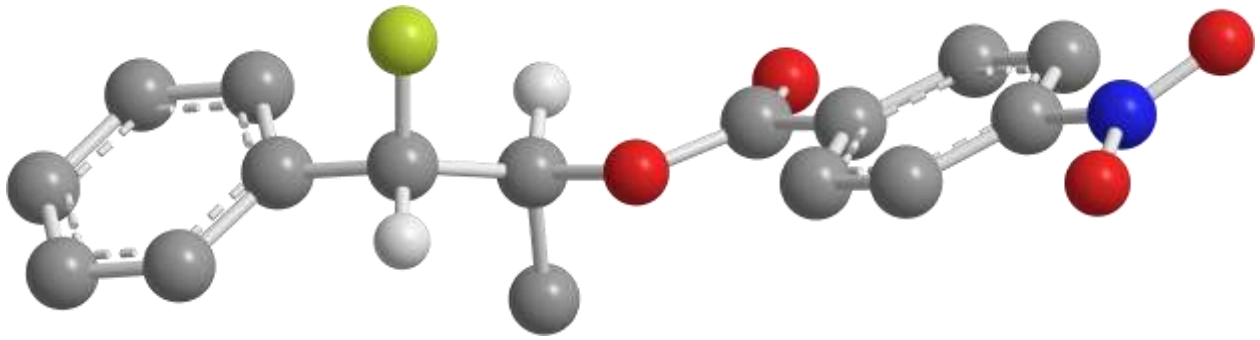
Appendix I: X-Ray Crystal Structure Data

X-Ray crystal structure data for 116

(Some H atoms omitted for clarity)



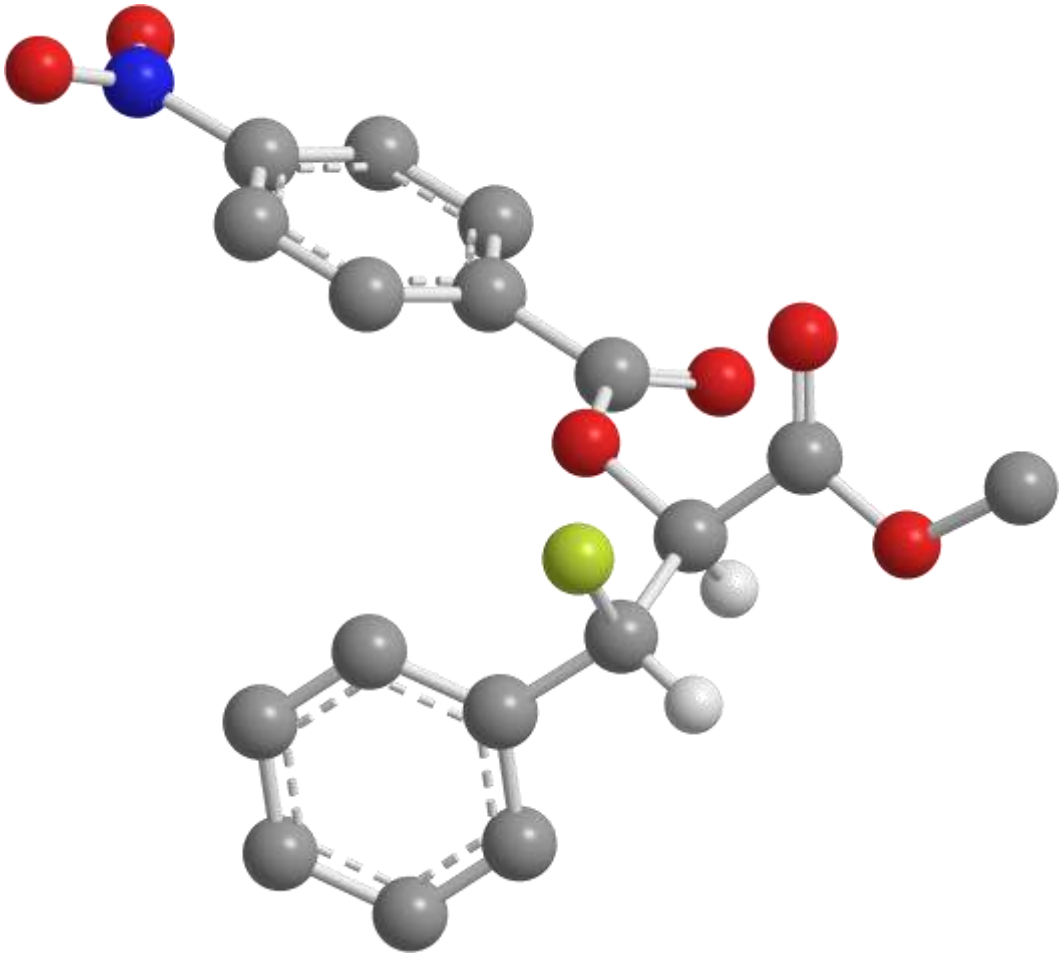
X-ray crystal structure determination for 116

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **116** [$C_{16}H_{14}NO_4$]: M = 303.29, triclinic, space group $P\,{-1}$, a = 8.6915(2) Å, b = 9.3006(3) Å, c = 9.3702(4) Å, α = 102.9809(12)º, β = 105.8251(12)º, γ = 90.4610(19)º, V = 708.18(4) Å^3, Z = 2, μ = 0.111 mm^{-1}, colourless plate, crystal dimensions = 0.20 × 0.30 × 0.30 mm^3. A total of 3199 unique reflections were measured for 5 < θ < 27 and 2006 reflections were used in the refinement. The final parameters were wR_2 = 0.044 and R_1 = 0.044 [I>2.0σ (I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 133

(Some H atoms omitted for clarity)



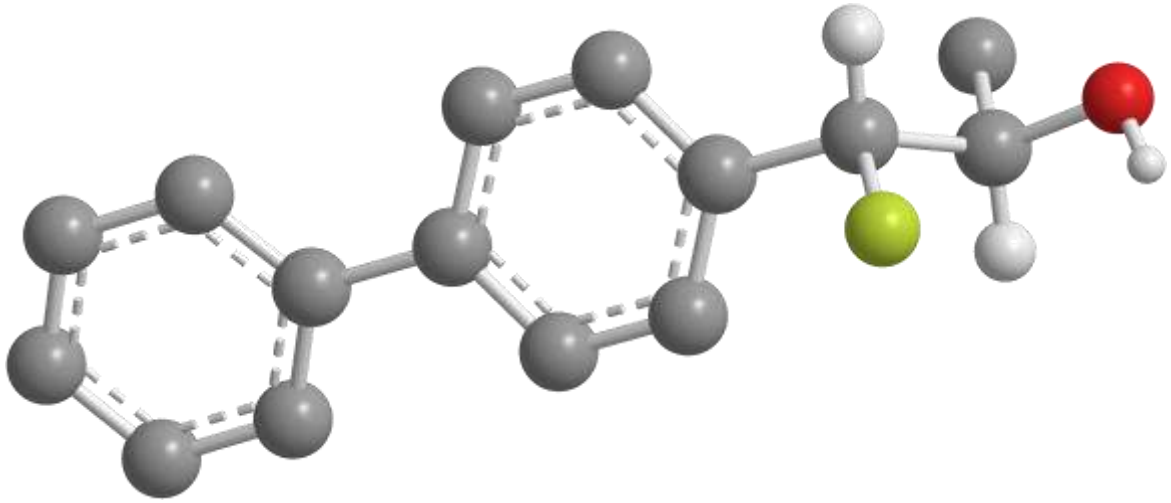
X-ray crystal structure determination for 133

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **133** [$C_{17}H_{14}FNO_6$]: M = 347.30, monoclinic, space group $P\ 2_1/c$, a = 7.22350(10) Å, b = 7.31770(10) Å, c = 29.8512(6) Å, β = 93.2847(8)º, V = 1575.32(4) Å^3, Z = 4, μ = 0.119 mm^{-1}, colourless plate, crystal dimensions = 0.22 × 0.24 × 0.35 mm^3. A total of 3587 unique reflections were measured for 5 < θ < 27 and 2295 reflections were used in the refinement. The final parameters were wR_2 = 0.040 and R_1 = 0.038 [I>2.5σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 189

(Some H atoms omitted for clarity)



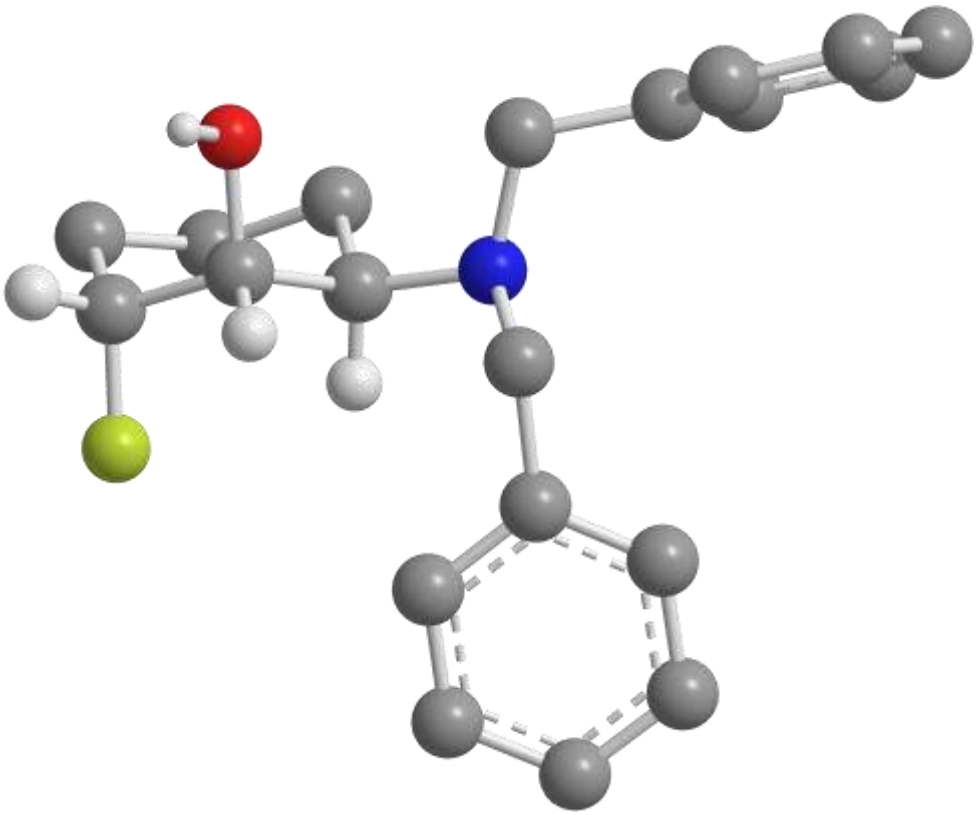
X-ray crystal structure determination for 189

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **189** [$C_{15}H_{15}FO$]: M = 230.28, monoclinic, space group $P\ 2_1/a$, a = 9.4670(2) Å, b = 5.2810(1) Å, c = 24.0898(8) Å, β = 92.3592(10)°, V = 1203.35(5) Å^3, Z = 4, μ = 0.088 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.27 × 0.33 mm^3. A total of 2702 unique reflections were measured for $5 < \theta < 27$ and 1570 reflections were used in the refinement. The final parameters were wR_2 = 0.073 and R_1 = 0.061 [I>2.5σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 334

(Some H atoms omitted for clarity)



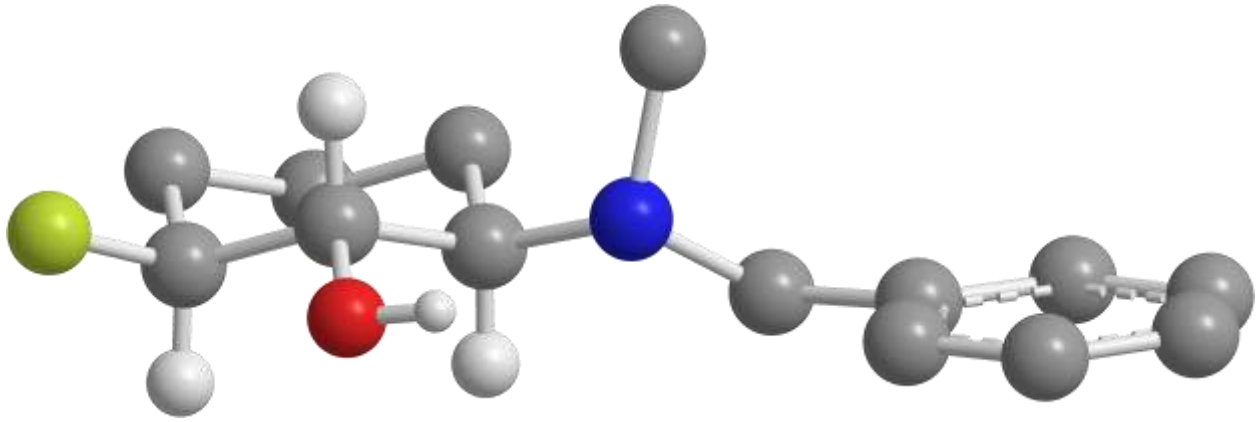
X-ray crystal structure determination for 334

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **334** [$C_{20}H_{24}FNO$]: M = 313.41, triclinic, space group $P\,{-1}$, a = 5.6912(1) Å, b = 11.1440(3) Å, c = 12.9653(4) Å, α = 85.9331(12)º, β = 84.5582(12)º, γ = 87.1641(16)º, V = 815.77(4) Å^3, Z = 2, μ = 0.0.085 mm^{-1}, colourless plate, crystal dimensions = 0.07 × 0.11 × 0.23 mm^3. A total of 3696 unique reflections were measured for $5 < \theta < 27$ and 2331 reflections were used in the refinement. The final parameters were wR_2 = 0.046 and R_1 = 0.043 [$I>3.0\sigma\ (I)$].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 346

(Some H atoms omitted for clarity)



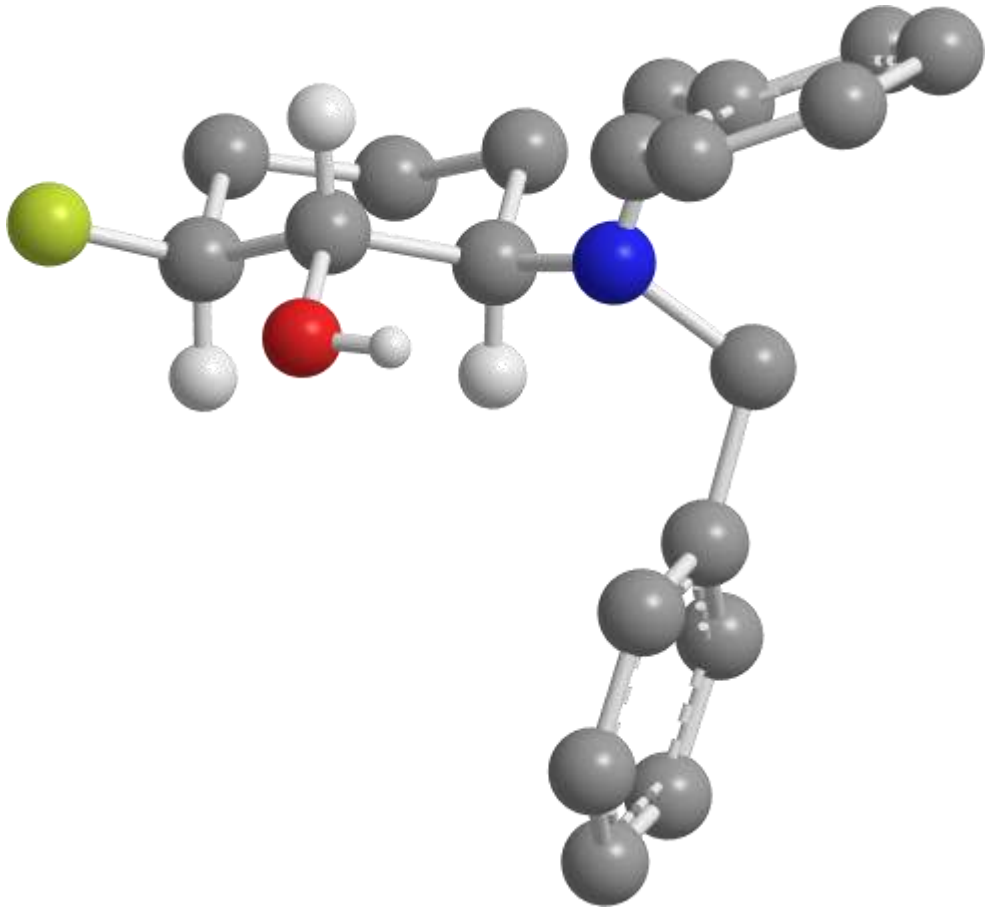
X-ray crystal structure determination for 346

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **346** [$C_{14}H_{20}FNO$]: M = 237.32, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 7.2525(2) Å, b = 10.3974(3) Å, c = 16.8918(6) Å, V = 1273.76(7) Å^3, Z = 4, μ = 0.087 mm^{-1}, colourless plate, crystal dimensions = 0.14 × 0.19 × 0.24 mm^3. A total of 1676 unique reflections were measured for $5 < \theta < 27$ and 1676 reflections were used in the refinement. The final parameters were wR_2 = 0.136 and R_1 = 0.070 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 349

(Some H atoms omitted for clarity)



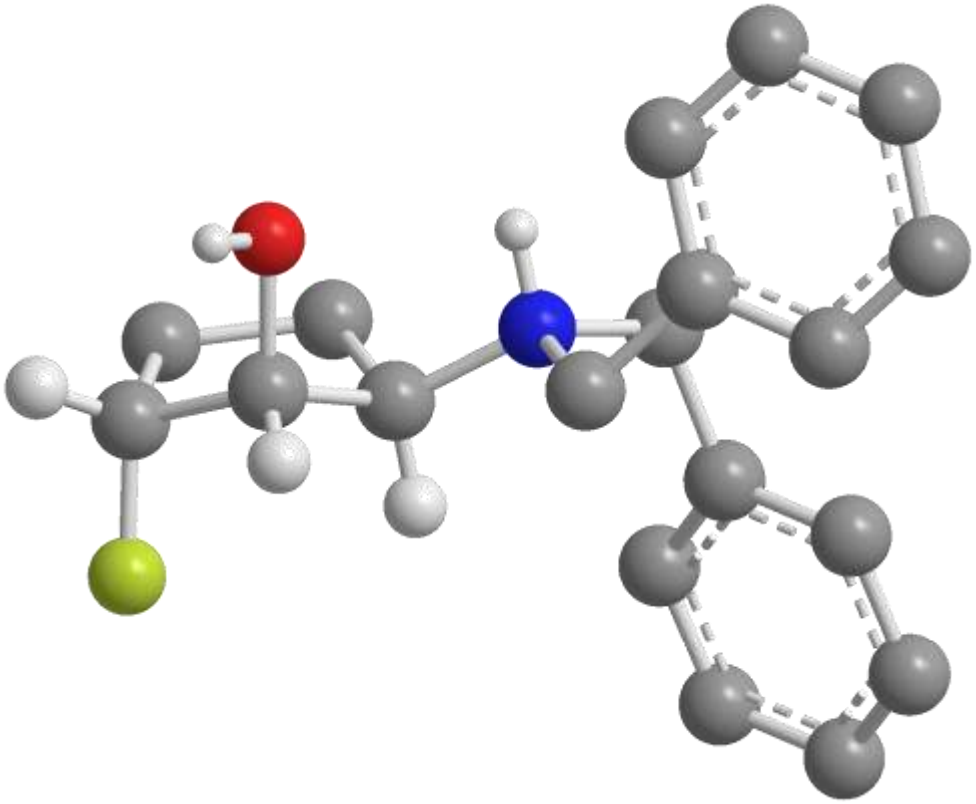
X-ray crystal structure determination for 349

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **349** [$C_{20}H_{24}FNO$]: M = 313.41, monoclinic, space group $P\ 2_1/n$, a = 6.5113(1) Å, b = 14.8776(2) Å, c = 35.9265(6) Å, β = 95.0616(6)°, V = 3466.72(9) Å^3, Z = 8, μ = 0.080 mm^{-1}, colourless plate, crystal dimensions = 0.16 × 0.19 × 0.27 mm^3. A total of 7783 unique reflections were measured for 5 < θ < 27 and 5599 reflections were used in the refinement. The final parameters were wR_2 = 0.106 and R_1 = 0.084 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 351•HBF_4

(Some H atoms omitted for clarity)



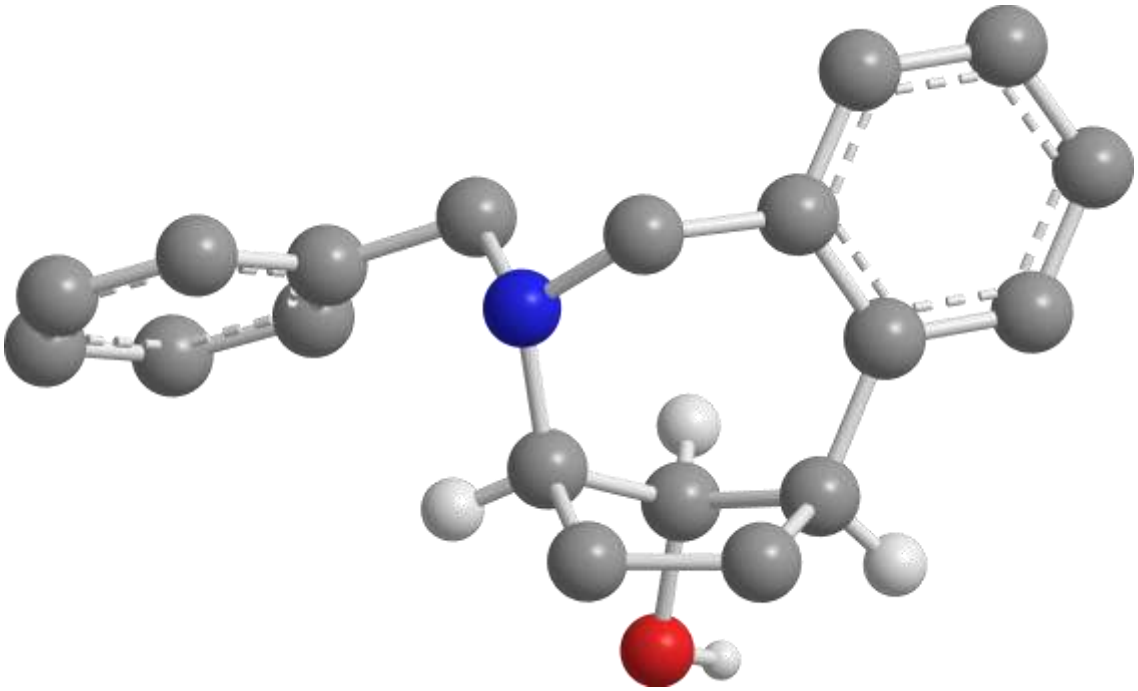
X-ray crystal structure determination for 351•HBF_4

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **351•HBF_4** [$C_{20}H_{24}BCl_3F_5NO$]: M = 506.58, monoclinic, space group $P\ 2_1/c$, a = 15.0623(3) Å, b = 9.4128(2) Å, c = 17.4909(4) Å, β = 110.5782(9)°, V = 2321.60(9) Å^3, Z = 4, μ = 0.447 mm^{-1}, colourless prism, crystal dimensions = 0.08 × 0.08 × 0.23 mm^3. A total of 5283 unique reflections were measured for 5 < θ < 27 and 5383 reflections were used in the refinement. The final parameters were wR_2 = 0.186 and R_1 = 0.089 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 353

(Some H atoms omitted for clarity)



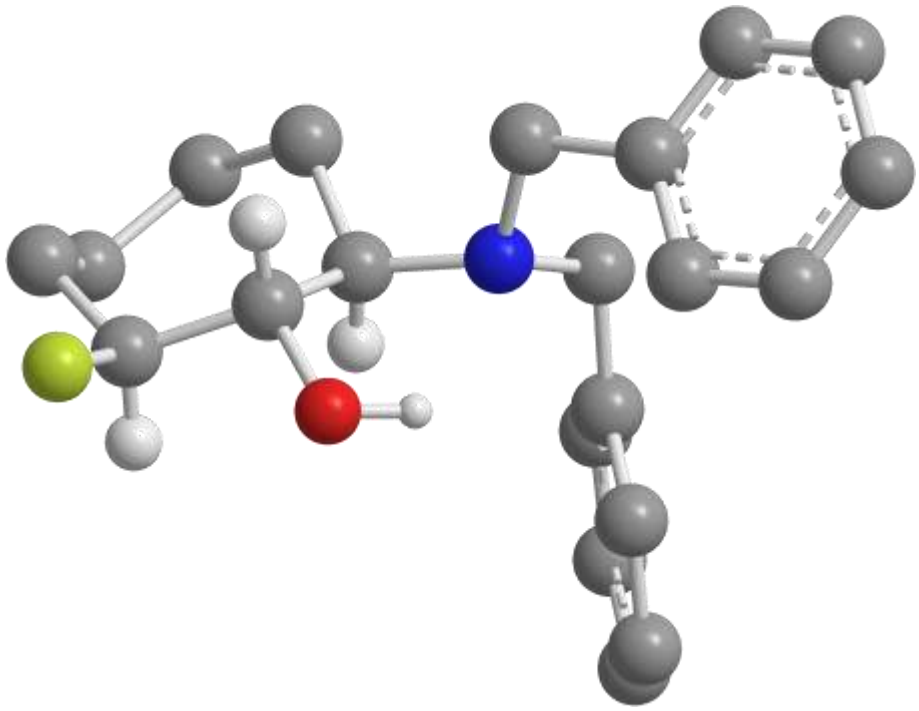
X-ray crystal structure determination for 353

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **353** [$C_{19}H_{21}NO$]: M = 279.38, monoclinic, space group $P\ 2_1/n$, a = 6.0856(1) Å, b = 17.5630(4) Å, c = 14.1524(3) Å, β = 101.7525(10)º, V = 1480.92(5) Å^3, Z = 4, μ = 0.077 mm^{-1}, colourless block, crystal dimensions = 0.16 × 0.19 × 0.23 mm^3. A total of 3351 unique reflections were measured for 5 < θ < 27 and 2637 reflections were used in the refinement. The final parameters were wR_2 = 0.083 and R_1 = 0.041 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 356

(Some H atoms omitted for clarity)



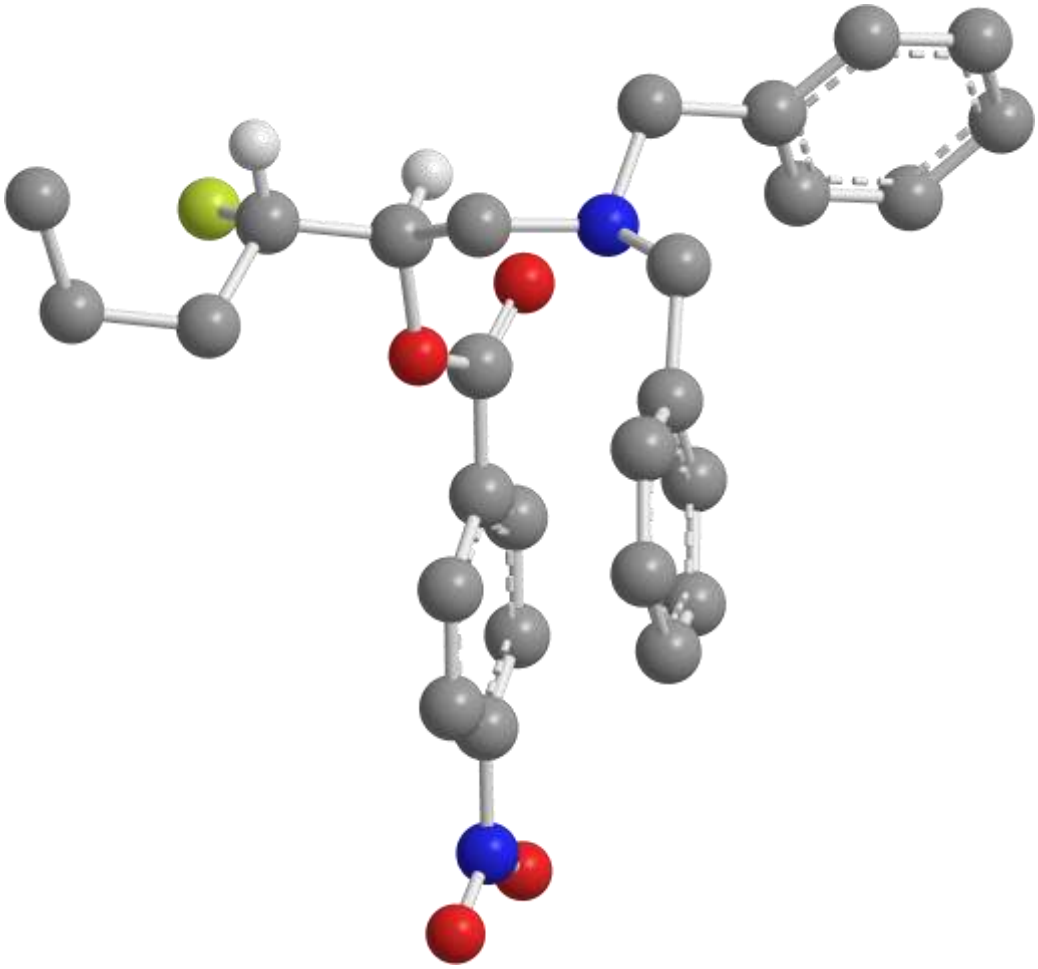
X-ray crystal structure determination for 356

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **356** [$C_{21}H_{26}FNO$]: M = 327.44, monoclinic, space group $P\ 2_1/c$, a = 9.8827(2) Å, b = 15.4422(3) Å, c = 12.2289(3) Å, β = 108.2352(9)°, V = 1772.54(7) Å^3, Z = 4, μ = 0.082 mm^{-1}, colourless block, crystal dimensions = 0.20 × 0.23 × 0.27 mm^3. A total of 4024 unique reflections were measured for 5 < θ < 27 and 3095 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.049 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 367

(Some H atoms omitted for clarity)



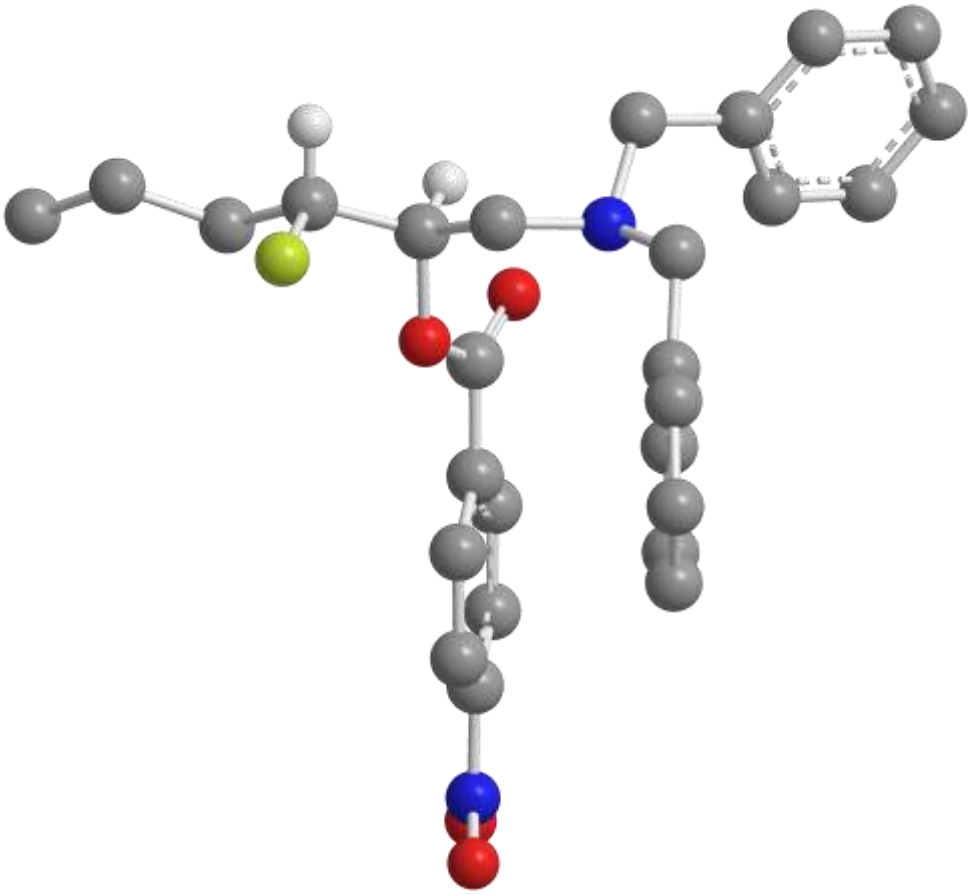
X-ray crystal structure determination for 367

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **367** [$C_{27}H_{29}FN_2O_4$]: M = 464.54, triclinic, space group $P\,{-1}$, a = 8.0438(2) Å, b = 10.6147(2) Å, c = 14.3517(3) Å, α = 79.2464(10)°, β = 84.2125(10)°, γ = 87.7064(8)°, V = 1197.45(5) Å^3, Z = 2, μ = 0.092 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.12 × 0.17 mm^3. A total of 5404 unique reflections were measured for $5 < \theta < 27$ and 4445 reflections were used in the refinement. The final parameters were wR_2 = 0.095 and R_1 = 0.045 [$I > -3.0\sigma(I)$].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 368

(Some H atoms omitted for clarity)



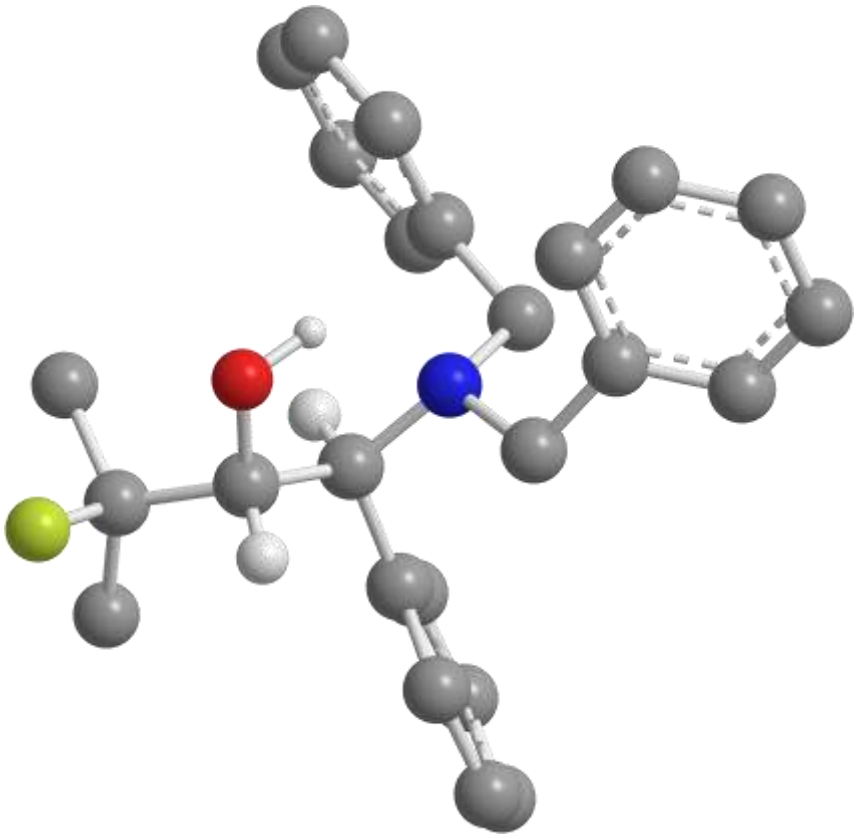
X-ray crystal structure determination for 368

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **368** [$C_{27}H_{29}FN_2O_4$]: M = 464.54, monoclinic, space group $P\ 2_1/n$, a = 8.5321(1) Å, b = 15.4179(2) Å, c = 18.4954(3) Å, β = 97.3110(7)°, V = 2413.24(6) Å^3, Z = 4, μ = 0.091 mm^{-1}, colourless plate, crystal dimensions = 0.10 × 0.19 × 0.22 mm^3. A total of 5438 unique reflections were measured for 5 < θ < 27 and 5438 reflections were used in the refinement. The final parameters were wR_2 = 0.010 and R_1 = 0.055 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 378

(Some H atoms omitted for clarity)



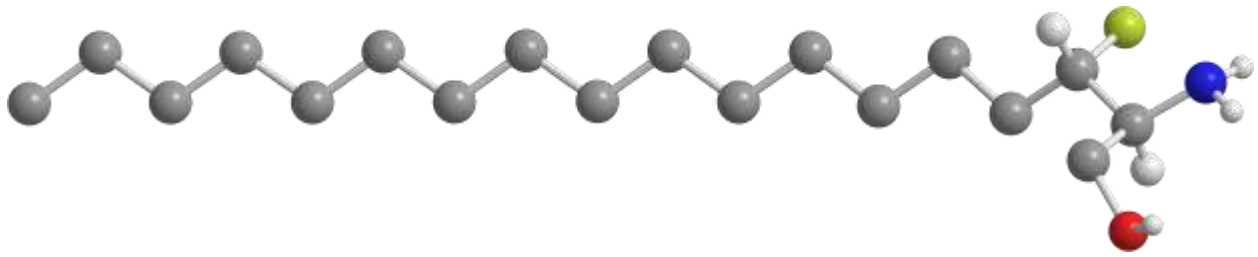
X-ray crystal structure determination for 378

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **378** [$C_{25}H_{28}FNO$]: M = 377.50, monoclinic, space group $P\ 2_1/c$, a = 10.1973(2) Å, b = 8.2488(1) Å, c = 24.7522(5) Å, β = 96.2440(6)°, V = 2069.69(6) Å^3, Z = 4, μ = 0.079 mm^{-1}, colourless block, crystal dimensions = 0.19 × 0.21 × 0.33 mm^3. A total of 4699 unique reflections were measured for 5 < θ < 27 and 3111 reflections were used in the refinement. The final parameters were wR_2 = 0.114 and R_1 = 0.064 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 394

(Some H atoms omitted for clarity)



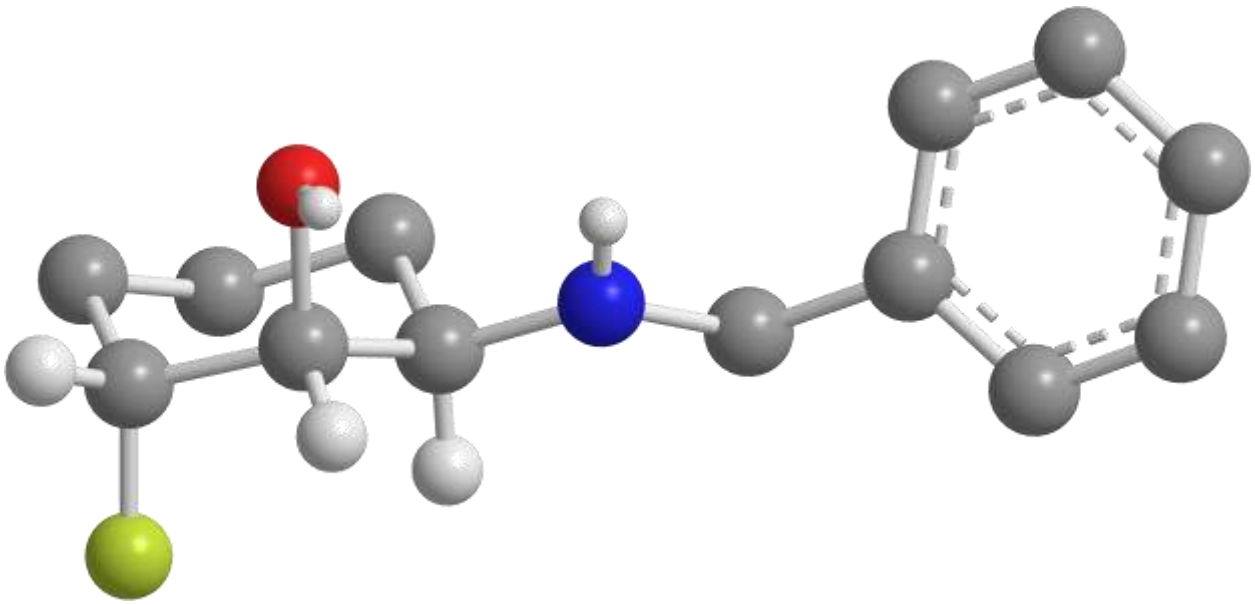
X-ray crystal structure determination for 394

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **394** [$C_{18}H_{38}FNO$]: M = 303.50, monoclinic, space group $C\,2$, a = 5.73792(11) Å, b = 7.6761(2) Å, c = 42.7479(9) Å, β = 90.9711(18)º, V = 1882.56(7) Å^3, Z = 4, μ = 0.556 mm^{-1}, colourless plate, crystal dimensions = 0.04 × 0.16 × 0.29 mm^3. A total of 3777 unique reflections were measured for 5 < θ < 27 and 3581 reflections were used in the refinement. The final parameters were wR_2 = 0.079 and R_1 = 0.072 [I>3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 448

(Some H atoms omitted for clarity)



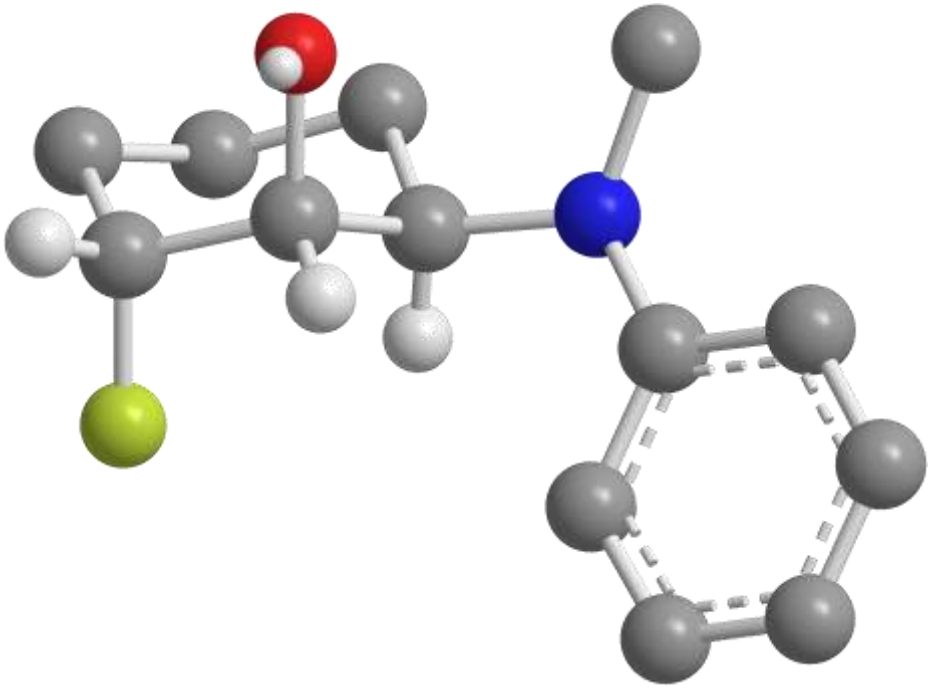
X-ray crystal structure determination for 448

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **448** [$C_{13}H_{18}FNO$]: M = 223.29, monoclinic, space group $P\ 2_1/n$, a = 12.5153(4) Å, b = 5.4840(2) Å, c = 17.6551(5) Å, β = 103.7195(13)°, V = 1177.17(7) Å^3, Z = 4, μ = 0.090 mm^{-1}, colourless plate, crystal dimensions = 0.21 × 0.24 × 0.33 mm^3. A total of 2659 unique reflections were measured for 5 < θ < 27 and 2103 reflections were used in the refinement. The final parameters were wR_2 = 0.103 and R_1 = 0.050 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 435

(Some H atoms omitted for clarity)



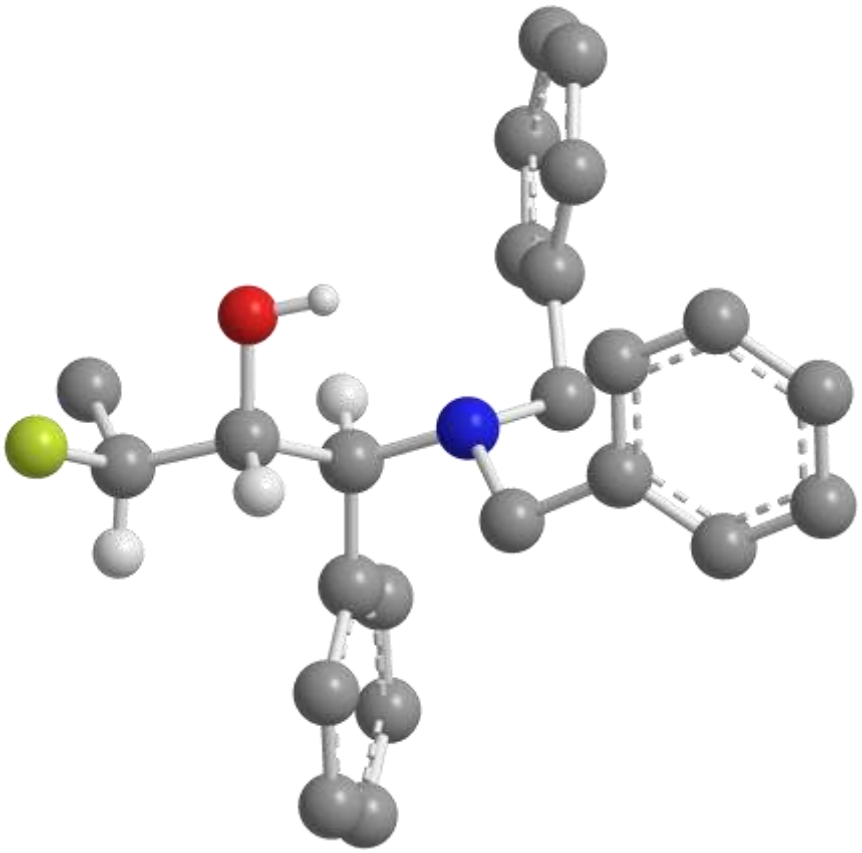
X-ray crystal structure determination for 435

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **435** [$C_{13}H_{18}FNO$]: M = 223.29, monoclinic, space group $P\ 2_1/n$, a = 9.9511(2) Å, b = 11.5777(2) Å, c = 20.5968(4) Å, β = 95.5037(9)°, V = 2362.04(8) Å^3, Z = 8, μ = 0.090 mm^{-1}, colourless block, crystal dimensions = 0.16 × 0.18 × 0.24 mm^3. A total of 5337 unique reflections were measured for $5 < \theta < 27$ and 3195 reflections were used in the refinement. The final parameters were wR_2 = 0.069 and R_1 = 0.100 [$I>3.0\sigma(I)$].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 478

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 478

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **478** [$C_{24}H_{26}FNO$]: M = 363.47, orthorhombic, space group $P\ b\ c\ a$, a = 11.27558(11) Å, b = 17.01873(18) Å, c = 20.3064(2) Å, V = 3896.73(7) Å^3, Z = 8, μ = 0.647 mm^{-1}, colourless block, crystal dimensions = 0.14 × 0.30 × 0.32 mm^3. A total of 4041 unique reflections were measured for $5 < \theta < 27$ and 4041 reflections were used in the refinement. The final parameters were wR_2 = 0.097 and R_1 = 0.044 [I>–3.0σ(I)].[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

References and Notes

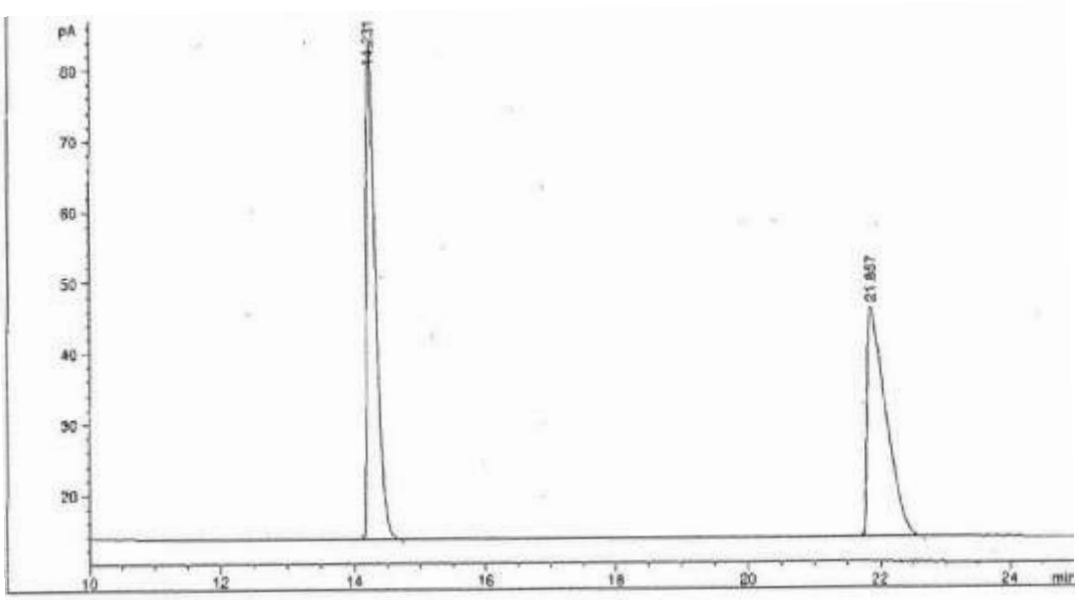
[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] The ^{1}H NMR spectrum (in $CDCl_3$) of the single crystal used in the X-ray diffraction analysis was found to be identical to that of the bulk material.
[3] The ^{1}H NMR spectrum (in MeOH-d_4) of the single crystal used in the X-ray diffraction analysis was found to be identical to that of the bulk material.

Appendix II: Chiral GC Traces

Chiral GC trace for 74

Column: ChiralDex G–TA (0.22 mm × 25 m, thickness 0.25 μm); carrier gas: He; flow rate: 2.5 mL min^{-1}, T injector 220 °C; T detector (FID) 250 °C; T 80 °C, isothermal. t_R = 14.23 min (*R*), 21.86 min (*S*). determined by chiral GC analysis (Chiraldex γ-TA column) Chiral GC analysis was performed by Dr Johannes Kloesges, Organic Chemistry Institute, University of Münster, Germany.

Racemic:



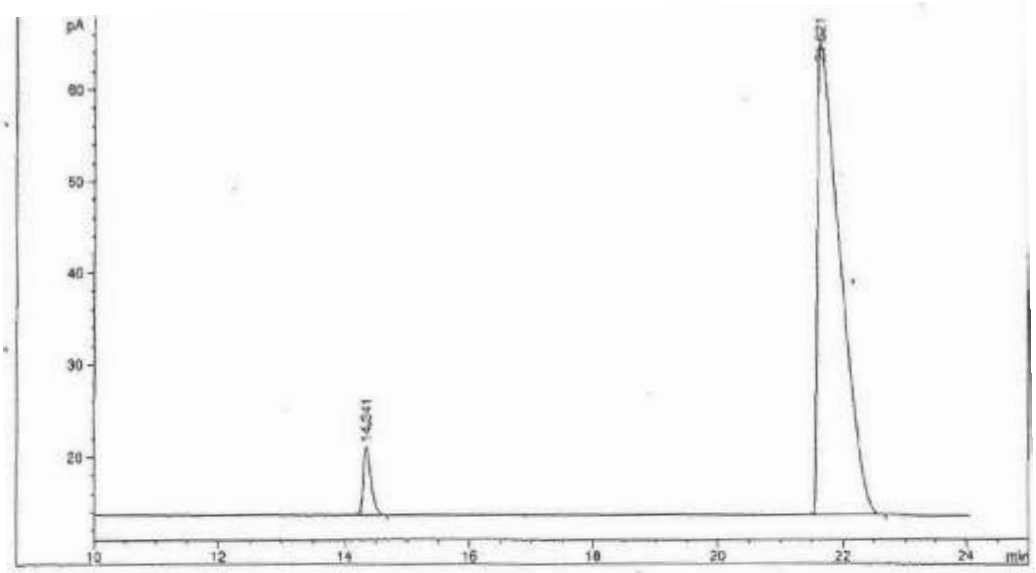
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.231	BB	0.1244	647.07410	69.99446	50.04672
2	21.857	BB	0.2360	645.86584	32.47749	49.95328
Totals :				1292.93994	102.47195	

Enantioenriched (er = 95.3:4.7):



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

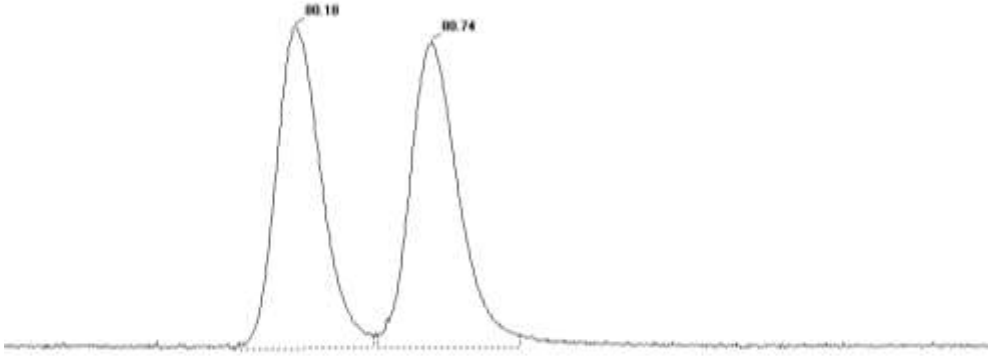
Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.341	BB	0.1197	63.68766	7.48871	4.65508
2	21.621	BB	0.2969	1304.44348	51.77442	95.34492
Totals :				1368.13114	59.26313	

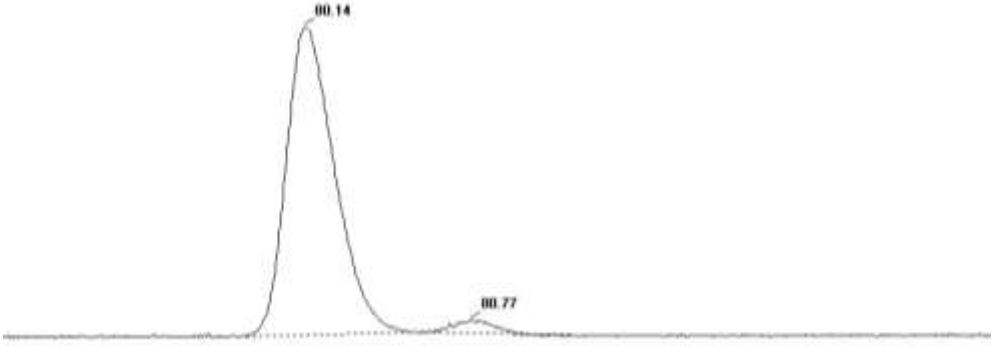
Chiral GC trace for 224

Column: β-cyclodextrin (0.22 mm × 30 m, thickness 0.25 μm); carrier gas: He; flow rate: 1.0 mL min^{-1}, T injector 220 °C; T detector (FID) 250 °C; T initial 40 °C, 1 °C min^{-1} to 120 °C. t_R = 80.2 min (*R*), 80.7 min (*S*). Chiral GC analysis was performed by Dr Carole J. R. Bataille, Chemistry Research Laboratory, University of Oxford, U.K.

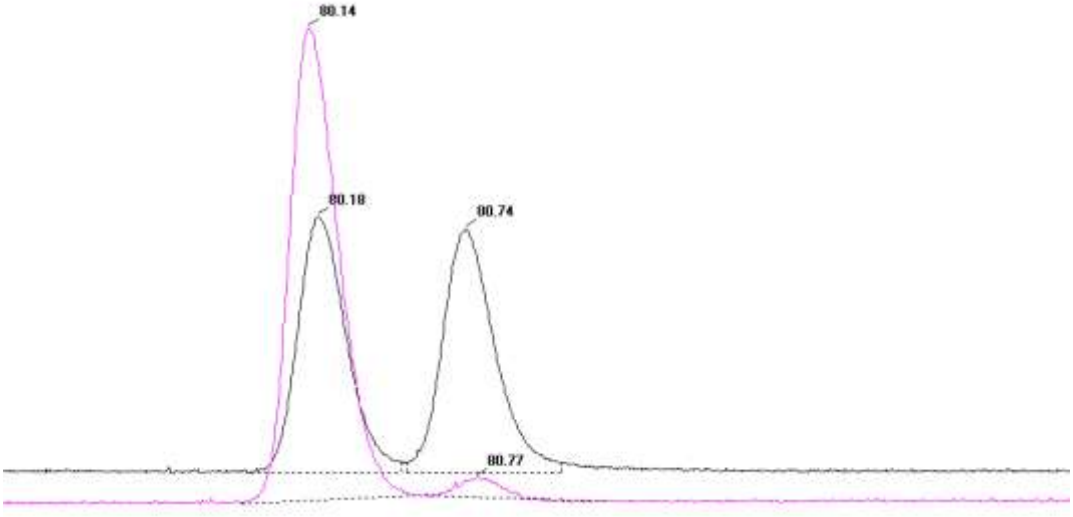
Racemic:



Enantioenriched (er = 96.5:3.5):



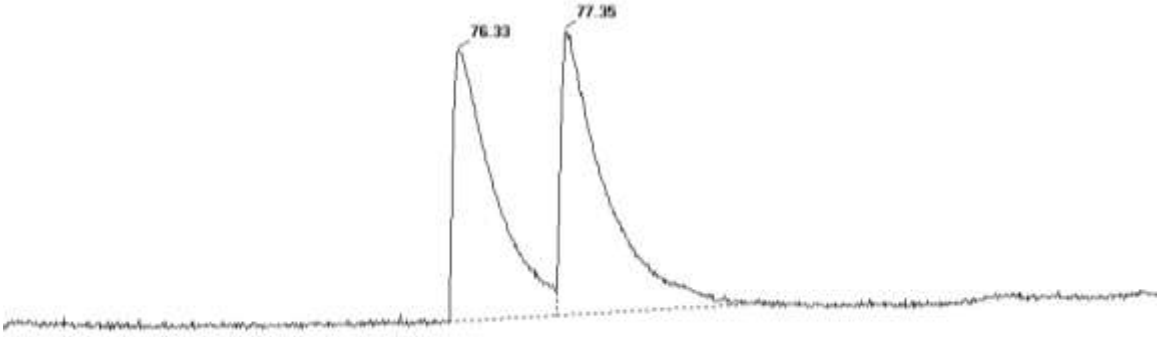
Overlay racemic/enantioenriched:



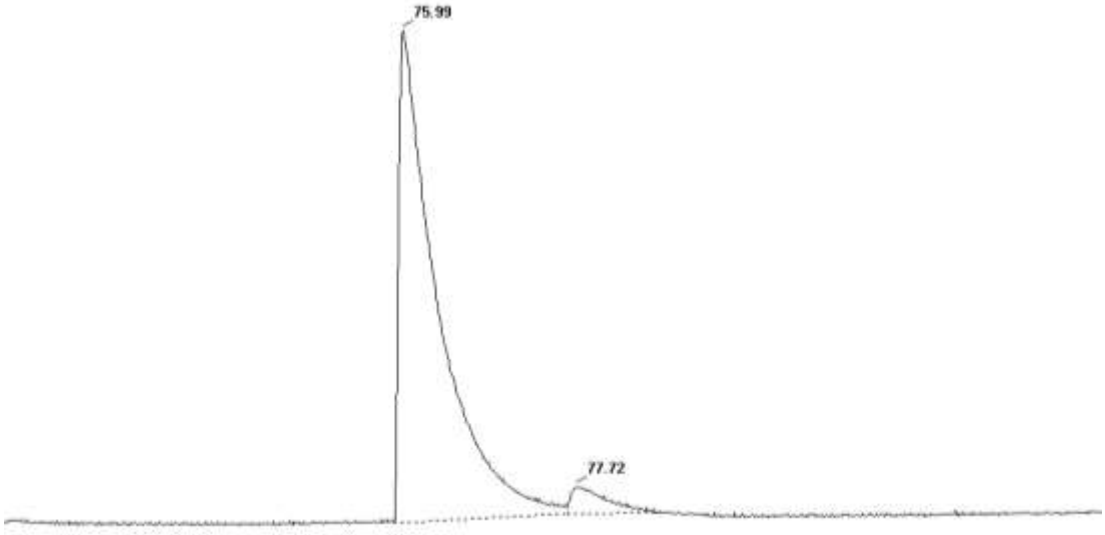
Chiral GC trace for 220

Column: β-cyclodextrin (0.22 mm × 30 m, thickness 0.25 μm); carrier gas: He; flow rate: 1.0 mL min^{-1}, T injector 220 °C; T detector (FID) 250 °C; T initial 40 °C, 1 °C min^{-1} to 140 °C. t_R = 76.0 min (*R*), 77.7 min (*S*). Chiral GC analysis was performed by Dr Carole J. R. Bataille, Chemistry Research Laboratory, University of Oxford, U.K.

Racemic:



Enantioenriched (er = 96:4):



Overlay racemic/enantioenriched: