Stereospecific Fluorination of Bioactive N-Heterocycles

A thesis submitted in partial fulfilment of the requirements for the degree of

Masters of Research

by

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Abstract

Prior investigations on deoxyfluorination reactions of N-heterocyclic azepanes have led to the observation of unusual C-F bond epimerisation. It was hypothesised that a complex aziridinium-based intermediate involving both nitrogen and fluorine neighbouring group participation maybe responsible for the observed stereochemical outcomes. Experimental evidence suggested the formation of this complex intermediate is sensitive to the electron density on the nitrogen atom and the type of N-protecting group used. In this work a new, N-Benzyl protected azepane was prepared and deoxyfluorinated in order to test the validity of the hypothesized complex aziridinium-fluoronium intermediate. In the case of this N-Benzyl azepane, the deoxyfluorination proceeded through an aziridinium that does not require fluorine participation and led to the complete suppression of the C-F epimerised product. This confirms the hypothesis that the formation of the complex aziridinium-fluoronium intermediate is dependent on the nitrogen electron density. The investigation also resulted in the synthesis of a new N-Boc fluorohydrin azepane which will serve as an interesting test case for future deoxyfluorination investigations.

Declaration

I certify that in this work entitled "Stereospecific Fluorination of Bioactive N-Heterocycles" has not been previously submitted as part of requirements for a degree to any other university or institution other than Macquarie University. I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged. Finally, I certify that all information sources and literature used are indicated in the thesis.

Harold Vernon Spedding

(SN: 42063833)

10/10/2014

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List of Abbreviations and Symbols

°	degrees
$[\alpha]^{20}_{D}$	specific rotation at 20 °C and wavelength of sodium D line
Å	angstrom
Ac	acetyl
AcO	acetate
aq	Aqueous
Bn	benzyl
Boc	N–*tert*-Butoxycarbonyl
br	broad
Bu	butyl
COSY	correlation spectroscopy
°C	degrees Celsius
δ	NMR chemical shift in parts per million
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DFT	density functional theory
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
DAST	diethylaminosulphur trifluoride
Deoxofluor®	bis(2-methoxyethyl)aminosulphur trifluoride
dq	doublet of quintets
dt	doublet of triplets
ee	enantiomeric excess
ESI-MS	electrospray ionisation-mass spectrometry
Et	ethyl
g	gram
h	hour
HSQC	heteronuclear single bond correlation spectroscopy
HMBC	heteronuclear multiple bond correlation spectroscopy
Hz	hertz
i-Pr	isopropyl
J	coupling constant

Me	methyl
mg	milligram
min	minute
mmol	millimole
µ	micro
MS3Å	molecular sieve 3 angstrom
MS4Å	molecular sieve 4 angstrom
Nu	nucleophile
NOESY	nuclear overhauser effect spectroscopy
n	nano
Ph	phenyl
ppm	parts per million
q	quartet
r	correlation coefficient
R	any functional group
rt	room temperature
s	singlet
t	triplet
t-Bu	tertiary butyl
TBS	tertiary butyl dimethyl silyl
THF	tetrahydrofuran
TPP	triphenylphosphine
Tosyl	toluene sulphonyl
TFA	trifluoroacetic acid

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List of Schemes

1. Introduction:

Organo-fluorine chemistry is widely applied in pharmaceuticals, agrochemicals, materials and medicine.[1-3] Approximately 20% of all current pharmaceuticals and 30% of all agrochemicals contain fluorine[4,5], while the perfluoropolymer polytetrafluoroethylene (Teflon®) is a ubiquitous coating material.[5] In medicine the non-natural isotope fluorine-18 present in 2-[^{18}F]-fluoro-2-deoxyglucose is used in millions of positron emission tomography (PET) scans every year.[3,5,6]

The prominence of fluorine chemistry stems from the unique properties of fluorine and the carbon-fluorine bond.[2,7] Fluorine is the most electronegative element, and carbon-fluorine bonds are highly polarized, with significant electrostatic character.[2,7] As a consequence, carbon-fluorine bonds interact weakly via intermolecular electrostatic/ dipole interactions and strongly via intramolecular stereoelectronic interactions with neighbouring bonds or lone pairs of electrons.[2,7] Such fluorine-based electrostatic/ dipole interactions are frequently exploited in medicinal chemistry to increase the bioavailability, lipophilicity and protein-ligand interactions of drug leads through attractive polar interactions of the C-F bond with hydrogen bond donors, other fluorinated molecules, polar functional groups such as the carbonyl group and hydrophobic moieties.[2,3,5,7-9] The strong intramolecular stereoelectronic directing effects of the C-F bond are also utilized to exert entropic control over lead compounds with the potential to make them highly specific to target proteins.[3,8,10] More generally, imparting conformational bias to molecules via fluorination is fundamental to the design of high performance molecules that may have applications in both industry and research.[2,3,8,10,11]

Despite the widespread utility of fluorine, the formation of carbon-fluorine bonds remains a challenging and active field of research.[1,3,5] The difficulty in forming carbon-fluorine bonds arises from the extremely high electronegativity of fluorine, the high hydration energy of the fluoride anion and the strength of metal-fluorine bonds which in turn has made the development of general predictable and cost-efficient fluorinating reagents and catalysts difficult.[1,3,5] Over the past few decades however, significant progress has been made with the development of new fluorinating reagents including Selectfluor® and DAST (diethylaminosulphur trifluoride) in the 1980s and most recently, organo- and organometallic catalytic systems to install carbon-fluorine bonds.[1,5] Importantly the continued development of these systems necessitates a deeper understanding of fluorination chemistry and requires the detailed study of it in the context of different substrates and reaction conditions.[12]

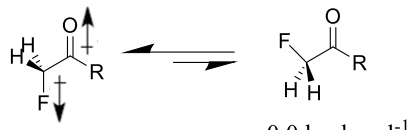
In this work, the stereoselective fluorination of N-heterocycles will be investigated using the seven-membered N-heterocycle azepane as a model system. Synthesis of azepanes will be conducted followed by stereoselective monofluorination and vicinal fluorination. The outcomes of these fluorination reactions will be studied and used to explore novel facets of fluorine chemistry. To provide context for this work, the following introduction section outlines the stereoelectronic properties of fluorine and the C-F bond, an overview of current fluorinating reagents and an overview of the immediate background leading to the current investigation.

1.1 Properties of Fluorine and the Carbon-Fluorine Bond:

Fluorine ($1s^2$, $2s^2$, $2p^5$) is the most electronegative element (Pauling electronegativity value of χ=4) and possesses the highest nuclear charge, second only to the noble gas neon.[7,13] As a result, electrons in the filled 2p orbital are held tightly by the nuclear charge and fluorine has the smallest atomic radius (1.47 Å)[14], highest endothermic ionization energy (401.2 kcal mol^{-1}) and most exothermic electron affinity (78.3 kcal mol^{-1}) of any Period 2 element.[7] Carbon-fluorine bonds are very strong sigma bonds (105.4 kcal mol^{-1}) with the highest degree of bond polarization. The strength of these bonds is derived from significant electrostatic interactions between $F^{\delta-}$ and $C^{\delta+}$ in addition to covalent bonding.[7] Carbon-fluorine bonds interact weakly through intermolecular electrostatic/ dipole interactions and strongly through intramolecular stereoelectronic directing effects, including dipole-dipole, charge-dipole and hyperconjugative effects.[2,3,7] These stereoelectronic directing effects are particularly relevant to entropic control in fluorinated molecules.[2,3,8,15]

1.1.1 Dipole-Dipole Interactions

The large dipole of the carbon fluorine bond leads to significant dipole-dipole interactions with its environment.[2,7] The conformation of a fluorinated molecule is influenced by the preferred *anti*-planar orientation of the C-F bond relative to adjacent polarized bonds to minimize electronic repulsion.[2,7] This stereoelectronic directing effect is intimately related to the strength of the participating dipoles. Shown in Figure 1.1, α-fluoroamides **1.1** and **1.2** have a strong conformational bias of 7.5 kcal mol^{-1} toward the *anti*- orientation of the C-F and amide dipoles versus the *syn* orientation. In addition, the energetic preference of this *anti*-conformation becomes progressively weaker moving from esters, to ketones and aldehydes which have progressively weaker C=O dipoles.[2,7]



0.0 kcal mol^{-1}

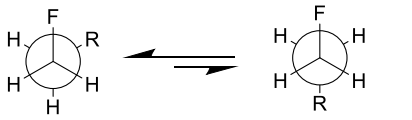
R = NH_2: -7.5 kcal mol^{-1}

R = OMe: -4.5 kcal mol^{-1}

Figure 1.1: Dipole-dipole interactions of the C-F bond.[7]

1.1.2 Charge-Dipole Interactions

The partially negatively charged fluorine atom of the polarized C-F bond interacts electrostatically with a proximal, formally charged heteroatom. As shown in Figure 1.2, the 3-fluoropiperidinium (**1.3**) and fluoroethylpyridinium (**1.4**) systems were used by Lankin, Snyder *et al*[16] to demonstrate favourable *gauche* conformations which bring the positively charged heteroatom and the partially negatively charged fluorine atom into close proximity.[2,7]



1.3 (R = NH_3^+): -5.8 kcal mol^{-1} 0.0 kcal mol^{-1}

1.4 (R = OH_2^+): -7.2 kcal mol^{-1}

Figure 1.2: Charge-dipole interactions of the C-F bond.[7]

1.1.3 Hyperconjugation Effects

The third and final stereoelectronic directing effect exerted by the C-F bond is the hyperconjugative effect. The C-F bond is highly polarized, and this extreme polarization results in the lowering the energy of the C-F sigma anti-bonding orbital, which acts as a good electron density acceptor from stereoelectronically aligned, electron rich sigma and pi bonds.[2,7] As shown in Figure 1.3, a stable *gauche* conformer is achieved to maximise orbital overlap between an electron donating sigma bond and the electron accepting C-F sigma anti-bonding orbital. The energetic preference of this conformation is related to the electron richness of the donating bond, whereas the C-H sigma bond (**1.5**), as opposed to the C-OH (**1.6**) sigma bond, has the greater electron donating capacity.[2,7]

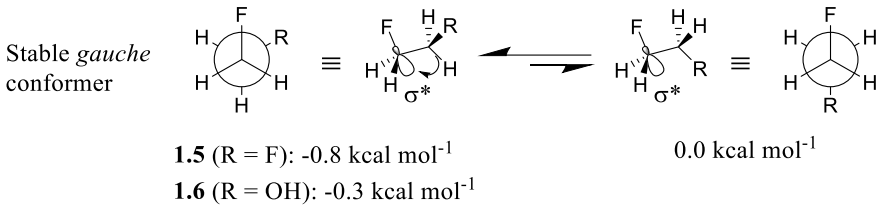


Figure 1.3: Hyperconjugation interactions of the C-F bond.[7]

1.2 Stereoselective Fluorination

Although fluorination chemistry has been investigated for the last 150 years, only in the past few decades have safe, efficient, regio- and stereoselective reagents and catalysts been developed.[1-3,7] The most recent advance in fluorine chemistry has been the development of several elegant organo- and organometallic catalytic systems for stereoselective fluorine and trifluoromethyl group installations.[2,3,5] However, many of the originally developed electrophilic and nucleophilic fluorination reagents are still in use today.[2,3,5] As will be explored in this section, these reagents allow fluorine installation onto a variety of aromatic and aliphatic substrates with varying degrees of regio- and stereocontrol. Their specific applications to the stereoselective fluorination of secondary/tertiary sp^3 carbon centres will be covered here.

1.2.1 Stereoselective Electrophilic Fluorination

Electrophilic fluorination involves the reaction of effectively a "fluoronium" (F^+) and a variety of nucleophilic substrates.[2,3,5,17] Historically, elemental fluorine under inert gas, organofluoroxy reagents (RO-F), such as acetyl hypofluorite and perchloryl fluoride have been used to install fluorine onto a variety of aromatic and aliphatic substrates. However, the extreme toxicity, difficulty in handling and lack of regio- and stereoselectivity of these reagents has limited their use.[2,3,5,17] Today, electrophilic fluorination is achieved using relatively less toxic, easy to handle "N-F" reagents including N-fluoropyridinium salts and derivatives, N-fluorobenzenesulphonimide (NFSI) and derivatives, and the Selectfluor® series of reagents, summarized in Figure 1.4.[2,3,5,17] These reagents are applicable to a variety of substrates including carbanions and enol ethers.[2,3,5,17] Other methods of stereoselective electrophilic fluorination can involve fluorination/ nucleophile addition cascades across double bonds and alkynes, which can be promoted with Lewis acids, organocatalysts or phase-transfer catalysts.[5]

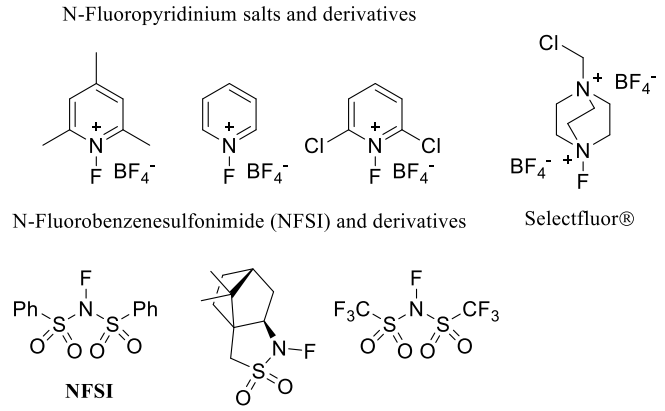
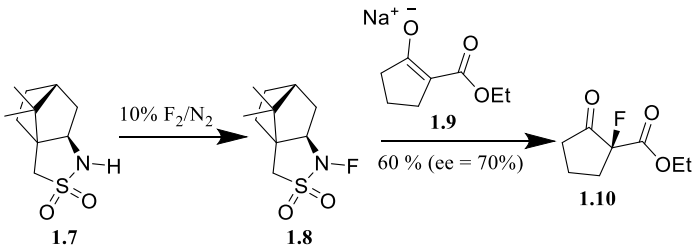


Figure 1.4: The "N-F" series of electrophilic fluorinating reagents including NFSI and selectfluor®.

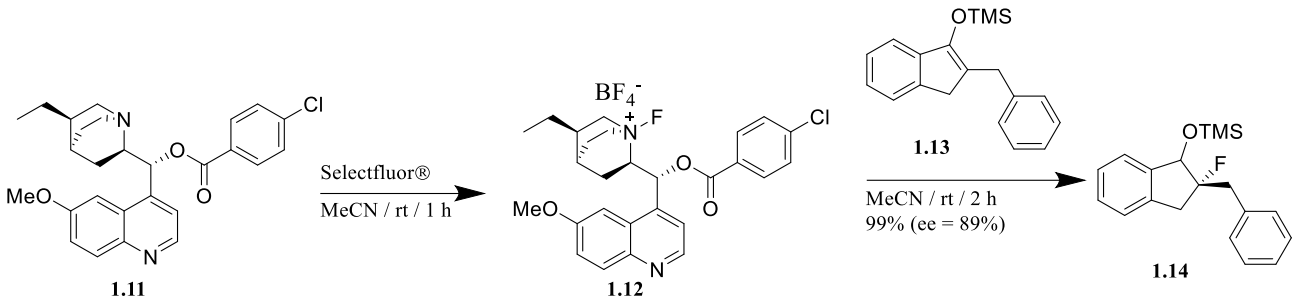
Differding and Lang reported the first enantioselective electrophilic fluorination reactions in 1988 using novel enantioselective fluorinating reagents, N-fluorocamphorsultams.[18] These reagents were applied to various metal enolates to achieve α-fluorination with up to 70% ee, thereby demonstrating the feasibility of stereoselective fluorination utilizing the N-F class of reagents.[1,3,5,18] As an extension of this work, Davis *et al* prepared (+)-N-fluoro-2,10-camphorsultam **1.8** (Scheme 1.1), by treatment of camphorsultam **1.7** with dilute elemental fluorine before using it for the fluorination of β-ketoester sodium enolate **1.9** to furnish fluorinated β-ketoester **1.10** in 60% yield and 70% ee.[19]



Scheme 1.1: Preparation and use of N-fluorocamphorsultam **1.8** for electrophilic fluorination.

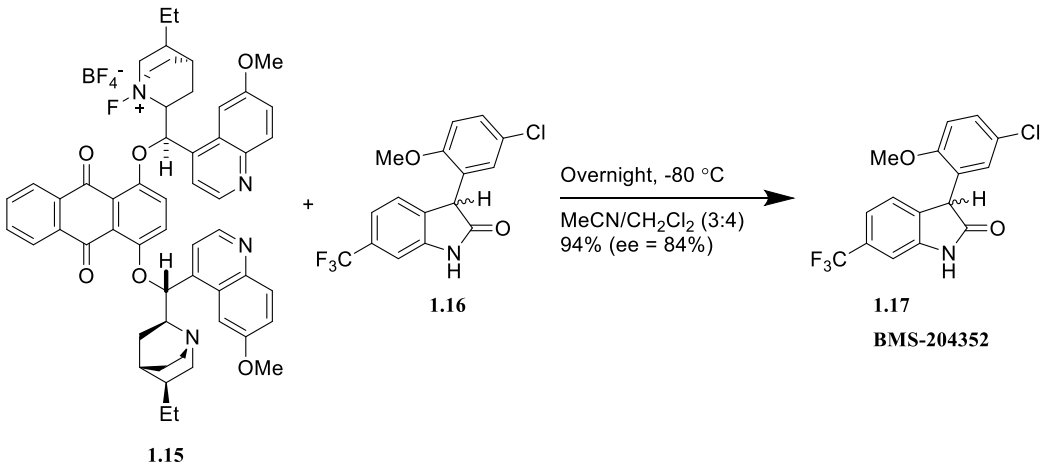
The next major advancement in stereoselective electrophilic fluorination was the development of the reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); Selectfluor® or F-TEDA-BF_4, by Banks *et al* in 1998 (Scheme 1.2).[20] Selectfluor® may be used directly, with the addition of a chiral additive, or indirectly to achieve enantioselective electrophilic fluorination.[20] Enders *et al*. reported the direct use of Selectfluor® in the regio- and enantioselective fluorination of α-silylketones using proline as a chiral additive, albeit with limited success.[21] The indirect use of Selectfluor® to achieve enantioselective electrophilic fluorination has been its most useful and widespread application to date.[3] The work of Shibata *et al* involved the use of Selectfluor® to trans-fluorinate chiral

cinchona alkaloid derivatives such as dihydroquinine 4-chlorobenzoate (**1.11**) seen in Scheme 1.2.[22] Applied in this manner, cinchona alkaloids function as organocatalysts and chiral fluorinating reagents which provide enantioinduction to the substrate.[22] Trans-fluorination using Selectfluor® *in situ* yielded the enantioselective N-fluoroammonium salt **1.12** which proceeded to fluorinate silane **1.13** in a one-pot reaction in acetonitrile.[22] The resultant fluoro-silane **1.14** was formed in 80% yield and 40% ee. The use of different cinchona alkaloid chiral auxiliaries increased this yield to 99% and the ee to 89%.[22]



Scheme 1.2: Preparation of and use N-fluorocinchona for enantioselective electrophilic fluorination.

Enantioselective electrophilic fluorination utilizing Selectfluor® and cinchona alkaloids as chiral auxiliaries has seen extensive application in the α-fluorination of silylenol ethers, α,α-cyanoester C-H acids, oxindoles and β-keto esters.[1,3,23] A specific example of their application is the enantioselective synthesis of BMS-204352 (MaxiPost®), an opener of potassium ion channels reported by Shibata *et al* in 2003[3,24] (Scheme 1.3). Fluorine was selectively installed at the asymmetric quaternary carbon centre C3 in the oxindole ring of trifluoroindolinone **1.16**, yielding BMS-204352 in 94% yield and 84% ee.[24]



Scheme 1.3: Enantioselective fluorine installation utilizing N-fluorocinchona alkaloid salts.

1.2.2 Stereoselective Nucleophilic Fluorination

Nucleophilic fluorination allows the formation of carbon-fluorine bonds with electrophilic substrates and poses unique challenges related to the extreme electronegativity of fluorine.[1,3,5,7] Such extreme electronegativity leads to high kinetic barriers to carbon-fluorine bond formation, despite the thermodynamic preference for the C-F bond, due to problems controlling the nucleophilicity and basicity of the fluoride anion.[1,3,5,7] Historically, nucleophilic fluorination has been achieved using cheap and abundant alkali-metal fluoride salts.[1,3,25,26] However, the substantial lattice energy of these salts makes them poor nucleophiles with poor solubility in organic solvent.[1,3,5,7,26] Conversely, the nucleophilicity of the fluoride anion is dramatically reduced upon solvation in protic solvents.[1,3,26]

The need for stereoselective nucleophilic fluorinations on complex organic molecules requires development of kinetically feasible, yet orthogonal chemistries with a large substrate scope and high degree of functional group tolerance.[1,3,5] Although nucleophilic fluorination at primary sp^3 carbon centres is well-established in terms of fluoride source as well as leaving group and choice of solvent, stereoselective nucleophilic fluorination at secondary and tertiary sp^3 carbon centres is more challenging and there are no general and facile methods currently available.[1,3,5] Regarding this latter point, several transition-metal catalyzed cross-coupling systems have been investigated involving the use of late-transition metals copper[27], ruthenium[28,29], palladium[30-34] and platinum[35], among others.[3,5] Complementary to this are deoxyfluorination and dethioflourination methods that utilize highly specialized reagents to replace alcohol, carbonyl and thiol functional groups at sp^2 carbons and secondary and tertiary sp^3 carbon centres with generally predictable stereochemical outcomes.[1,3,5] A related method involves the halofluorination of alkenes via the opening of epoxide or aziridine intermediates with nucleophilic fluoride.[1,3,5] The deoxyfluorination methodology will be the focus of this work here.

The seminal work of Middleton *et al*, realized the first deoxyfluorinating reagent, (diethylamino)sulphur trifluoride (DAST) in 1975, as seen in Figure 1.5.[36] Meanwhile, the first dethiofluorinating reagent, pyridinium poly(hydrogen fluoride) (Olah's reagent), was reported by Olah *et al* in 1979 (Figure 1.5).[37] Since then several bench-top stable, relatively non-toxic and stereoselective deoxyfluorinating and dethiofluorinating reagents have been developed as summarized in Figure 1.5.[1,3] These include several different reagents: 4-morpholinosulphur trifluoride (MOST)[38], bis(2-methoxyethyl)aminosulphur trifluoride (Deoxofluor®)[39], 4-*tert*-

butyl-2,6-dimethylphenylsulphur trifluoride (Fluolead®)[40], diethylaminodifluorosulphinium tetrafluoroborate (XtalFluor-E®)[41], N,N'-dimethyl-2,2-difluoroimidazolidine[42], TFEDMA[43], Ishikawa's reagent[44], Yarovenko's reagent[45], perfluoro-1-butanesulphonyl fluoride (PBSF)[46], triethylamine tris(hydrogen fluoride) (TREAT-HF)[47], sulphonyl fluoride/ TREAT-HF mixture[48] and nitrosonium tetrafluoroborate/ pyridinium poly(hydrogen fluoride).[49]

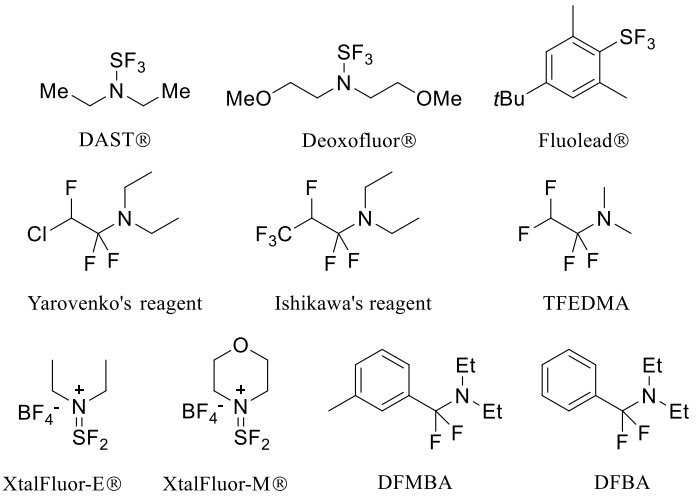


Figure 1.5: Common deoxy- and dethiofluorinating reagents.

The sulphur trifluoride compounds including DAST and Deoxofluor® are the most commonly used reagents for stereoselective nucleophilic fluorination and have been applied extensively to the fluorination of various alcohols, amino-alcohols, diols, carbohydrates, aldehydes, ketones, epoxides, ketoximes and peptides, among several other substrates.[1,3] The kinetic feasibility and generally predictable stereoselectivity of Deoxofluor® and related reagents may be accounted for by their mechanism of reaction.[1,3,50,51] As shown in Figure 1.6, the proposed reaction mechanism of Deoxofluor® involves the initial nucleophilic attack of the alcohol substrate to the sulphur atom, liberating hydrofluoric acid and forming the alkoxyaminodifluorosulphane intermediate **1.17**.[1,3,50,51] Subsequent thioiminium formation to yield **1.18** liberates nucleophilic fluoride for the next nucleophilic displacement of the activated alcohol.[1,3,50,51] This is via an S_N2 mechanism with exclusive inversion of stereochemistry at the participating carbon centre to yield the fluorinated product **1.19**.

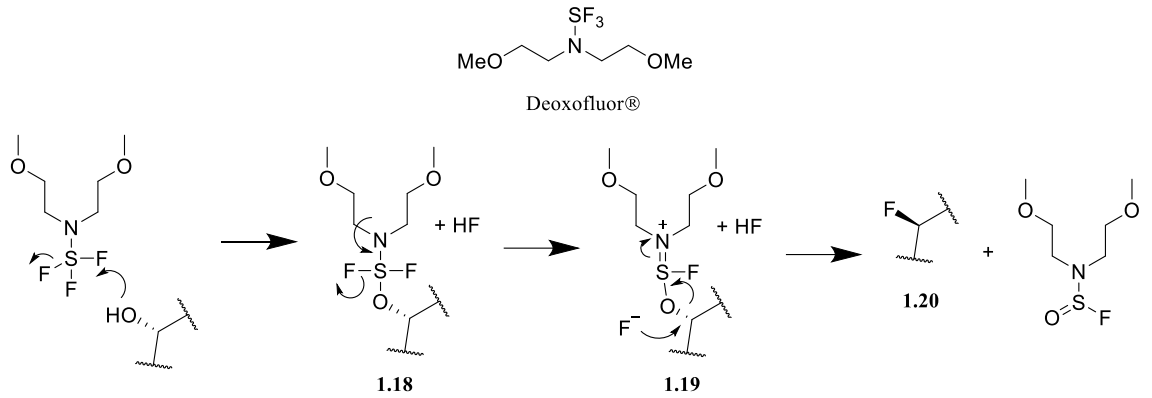
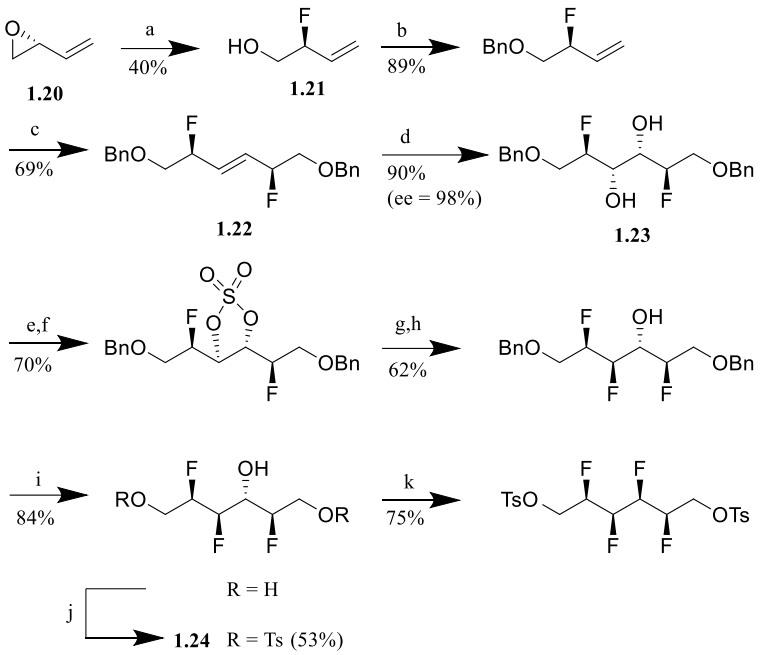


Figure 1.6: Proposed deoxyfluorination mechanism of Deoxofluor®.

Recently, Hunter *et al* has utilized Deoxofluor® to achieve the challenging enantioselective and diastereoselective preparation of multi-vicinal fluoroalkanes.[52-55] Multi-vicinal fluoroalkanes are particularly attractive molecules that exploit the strong stereoelectronic *gauche* preference of vicinal fluorine atoms to impart entropic control to molecules.[2,7,54] As such, these vicinal fluoroalkanes have the potential for widespread use as high performance molecules in industry and research.[2,7,54,55] They have already seen applications in novel organic liquid crystals, antiretroviral nucleotide analogues, difluorosuccinates and difluoropyrolidine-containing peptidase inhibitors.[2,7,54,55]

Seen in Scheme 1.4, Hunter *et al*, achieves the preparation of multivicinal fluoroalkanes via tandem Sharpless cyclic sulphate formation and a combination of nucleophilic fluorinating reagents including triethylamine tris(hydrogen fluoride) (TREAT-HF), tetrabutylammonium fluoride and Deoxofluor®.[52] In this synthetic pathway, enantiomerically pure 3,4-Epoxy-1-butene (**1.20**) precursor is subject to regioselective opening of the epoxide with hydrogen fluoride at the C2-position to yield hydroxyfluoroalkene **1.21**, with some loss of enantiopurity (80% ee).[52] This is followed by tosyl-protection of the alcohol and cross-metathesis using 2nd generation Grubb's catalyst to afford the symmetrical alkene intermediate **1.22** with exclusive E geometry. Subsequent, bis-hydroxylation with potassium permanganate, followed by cyclic sulphonation using thionyl chloride, ring-opening fluorination using TBAF, and tosyl group protection yielded tri-fluorohydrin **1.24**, with preservation of enantiopurity.[52] In the final key step, stereoselective fluorination with Deoxofluor® converted the free alcohol of **1.24** to the fluoro derivative with exclusive inversion of stereochemistry at the participating carbon centre, yielding the all-*syn* tetrafluoroalkane product as a crystalline solid.[52]



Scheme 1.4: Vicinal fluoroalkane synthesis reported by Hunter *et al*.[52] *Reagents and conditions:* (a) Et_3N-3HF, Na_2SO_4, 70 °C; (b) BnBr, NaH, DMF 40 °C; (c) Grubb's Δ (generation II), DCM; (d) $KMnO_4$, $MgSO_4$, EtOH, H_2O, -10 °C; (e) $SOCl_2$, pyridine, DCM, 0 °C; (f) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C; (g) TBAF, MeCN, rt; (h) H_2O, THF, rt; (i) H_2, Pd/C, MeOH, rt; (j) TsCl, 2,4,6-collidine, 50 °C; (k) Deoxofluor®, 70 °C.

As an aside, X-ray crystallographic analysis of this C_2 symmetric molecule determined dihedral angles of 66.7° (F9-C-C-F10) and 59.7° (F10-C-C-F10') between vicinal fluorines, consistent with the stable *gauche* conformer.[52] Subsequent work by Hunter *et al* utilizing variations of this synthetic methodology but which maintain the key deoxyfluorination step has resulted in the synthesis of diastereomic tetrafluoroalkanes[53,56], hexafluoroalkanes[53,56,57] and vicinal fluorinated β- and ϒ-amino acids[55], seen in Figure 1.7. These examples demonstrate clearly the wide utility of the deoxyfluorination approach for installing carbon-fluorine bonds.

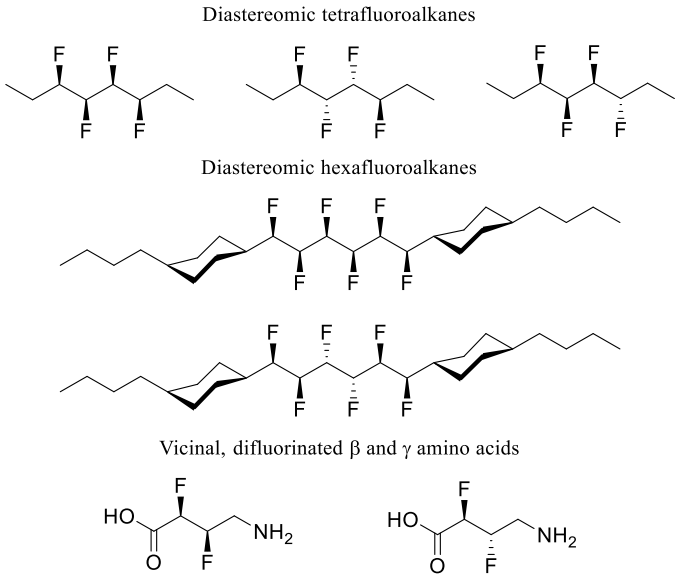
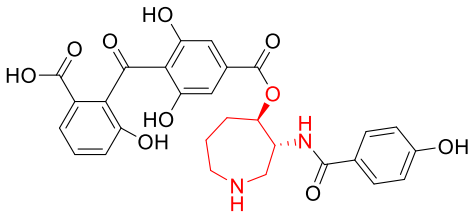


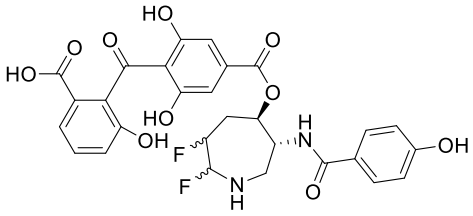
Figure 1.7: Vicinal fluoroalkanes and amino acids prepared by Hunter *et al*.[52,53,55-57]

1.3 Stereoselective, Vicinal Deoxyfluorination of the Bio-active N-heterocycle Azepane

As Deoxofluor® and related compounds are applied to substrates of increasing complexity, the outcomes of reactions become less predictable with potentially interesting and novel outcomes. The work of Liu *et al*, has investigated the first stereospecific deoxyfluorinations of seven-membered azepanes using Deoxofluor®.[10,11,15] Azepanes (Figure 1.8), are prevalent epitopes present in many bioactive natural products, in particular the AGC kinase inhibitor Balanol[58], and have demonstrated potential as a functional component of glycosidase inhibitors, antidiabetics, antivirals, and DNA minor groove binding agents.[10,11,15,59] Through stereoselective monofluorination and vicinal fluorination, the Liu group has sought to use fluorine to control this highly flexible, yet constrained heterocycle with the prospects of developing conformationally biased and highly isozyme specific inhibitor leads from fluorinated Balanol derivatives.[10,11,15,55]



(-) Balanol (IC_{50} = 4-9 nM)

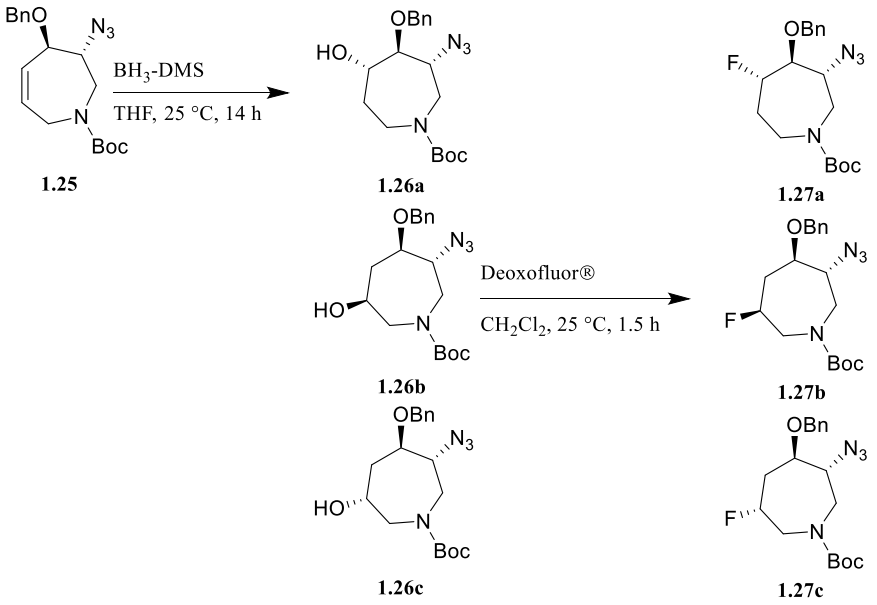


Fluorinated (-) Balanol derivative

Figure 1.8: (-)-Balanol with a 3,4-substituted azepane core (highlighted red) and fluorinated (-)-Balanol.

1.3.1 Azepane Monofluorination and Nitrogen Neighbouring Group Participation

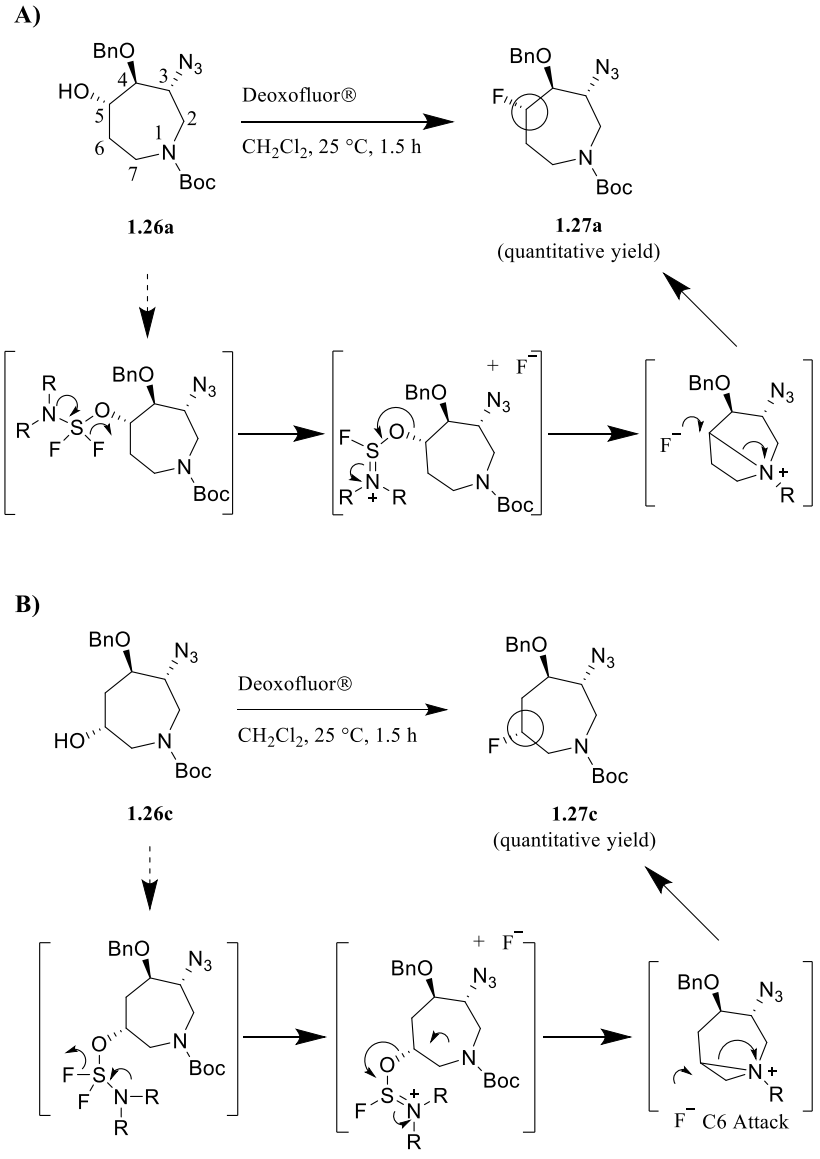
The initial case of monofluorination of azepane was investigated using tetrahydroazepine intermediate **1.25** as the starting model.[10,15] Stereoselective monofluorination of azepane was achieved as shown in Scheme 1.5, beginning with hydroboration to access azepanes **1.26a-c**. Following this, compounds **1.26a-c** were subject to deoxyfluorination with Deoxofluor® at room temperature yielding the fluoroazepanes **1.27a-c** in very good yields.[10,15]



Scheme 1.5: Stereoselective monofluorination of **1.26a-c** using Deoxofluor®.

Interestingly, the stereochemistry assigned to the C5 and C6 positions in each of the products **1.27a-c** upon 2D NMR analysis revealed the exclusive retention of stereochemistry at the

participating carbon centre, contradictory to the frequently observed inversion of stereochemistry.[10,15] It was rationalized that this apparent retention of stereochemistry was the result of nitrogen or carbamate neighbouring group participation via a double inversion reaction mechanism[10,15] involving formation of an azetidinium intermediate in the case of **1.27a** (Scheme 1.6A) or an aziridinium intermediate in the case of **1.27b** and **1.27c** (Scheme 1.6B). As a result, subsequent nucleophilic attack of fluoride is only sterically feasible from the opposite side of the C6-N bond, resulting in C-F bond formation with exclusive retention of stereochemistry at C6.[10,15]



Scheme 1.6: Proposed double-inversion mechanism in the case of monofluorination.

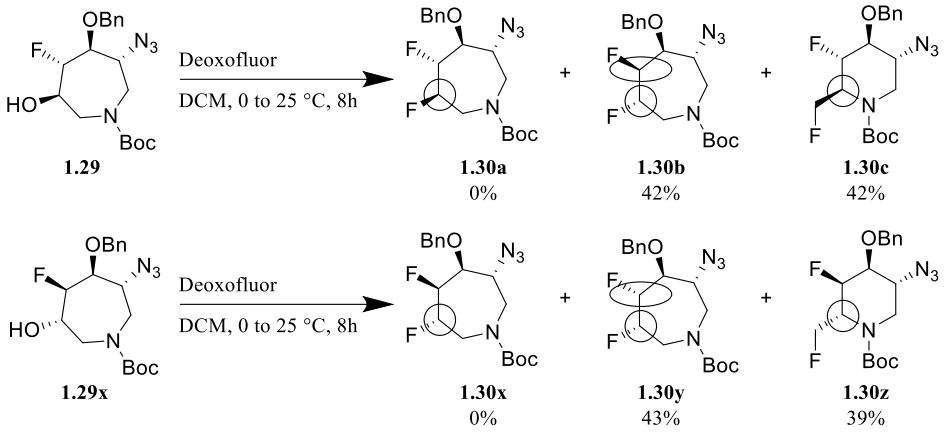
Overall, stereoselective monofluorination was shown to impart profound conformational bias to the azepane ring, as was confirmed by a combination of 2D NMR and DFT computational

analyses.[10,11,15] In the case of compound Boc de-protected **1.26c**, it was found that the installation of a single fluorine atom diastereoselectively biased the azepane ring toward one major conformation. This major conformer adopted an approximate twist-chair conformation, enforced by the fluorine-*gauche* effect involving the vicinal protonated amine in addition to the benzyloxy/ azido diequatorial preference and azido *gauche* effect. A minor conformer was also identified which differed from the major by a slight twist about the C3-C4 dihedral angle. This allowed it to better satisfy the azido-*gauche* effect while weakening the benzyloxy/ azido diequatorial preference and maintaining the fluorine-*gauche* effect. A population ratio of 82:18 and corresponding relative energy values of 0.00 kcal mol^{-1} and 0.77 kcal mol^{-1} were assigned to these low energy conformers.[10,11,15]

1.3.2 Initial Observations in the Stereoselective, Vicinal Fluorination of Azepanes

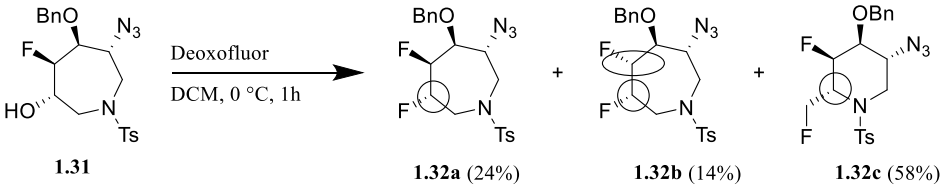
As an extension of the monofluorination of azepanes, stereoselective preparation of difluorinated azepanes at C5 and C6 positions were investigated using Deoxofluor®.[10,11,15] As shown in Scheme 1.7, deoxyfluorination was conducted at the C5 position of N-Boc protected fluorohydrin azepane **1.29** and its diastereomer, **1.29x**, yielding a mixture of products **1.30b-c** and **1.30x-z** with the expected difluorinated azepanes **1.30a** and **1.30x** not observed. Of these products, the expected difluoroazepanes (**1.30a/x**) with C6 retention of stereochemistry were not detected. Instead, difluoroazepanes **1.30b/y** were observed alongside six-membered di-fluoro piperidine product **1.30c/z**.[15] Most strikingly, the observed difluoroazepanes (**1.30b** and **1.30y**) exhibited C5-F epimerization in addition to C6 inversion of stereochemistry in the case of **1.30b** and C6 retention of stereochemistry in the case of **1.30y**.

The formation of the piperidine products **1.30c/y** could be rationalized by evoking formation of an aziridinium as discussed previously, whereas nucleophilic attack of fluoride to the charged aziridinium intermediate is possible at either the C6 or C7 position.[15] Fluoride attack at the C7 position of the aziridinium would explain the formation of **1.30c/z**. However, formation of the C5-F epimerized azepane **1.30b/y** cannot be accounted for by the simple aziridinium.[15] It was then hypothesized that the nitrogen neighbouring group participation in the case of the N-Boc protected substrate **1.29** and **1.29x** is complex and that reaction outcomes may be sensitive to the electron density on the nitrogen atom.



Scheme 1.7: Fluorination outcomes in the case of **1.29** and **1.29x**.

Subsequent deoxyfluorination of N-Tosyl protected azepane **1.31** confirmed this hypothesis, resulting in a new distribution of the azepane and piperidine products (Scheme 1.8). In this case, the formation of expected azepane **1.32a** was observed with suppression of the C5-F epimerized product **1.32b**. The piperidine product **1.32c** was also isolated as the major product. These results suggested that formation of the likely complex reaction intermediate is dependent upon nitrogen participation and in turn, the strength of the C6-N bond and the electron density on the nitrogen atom.[15]

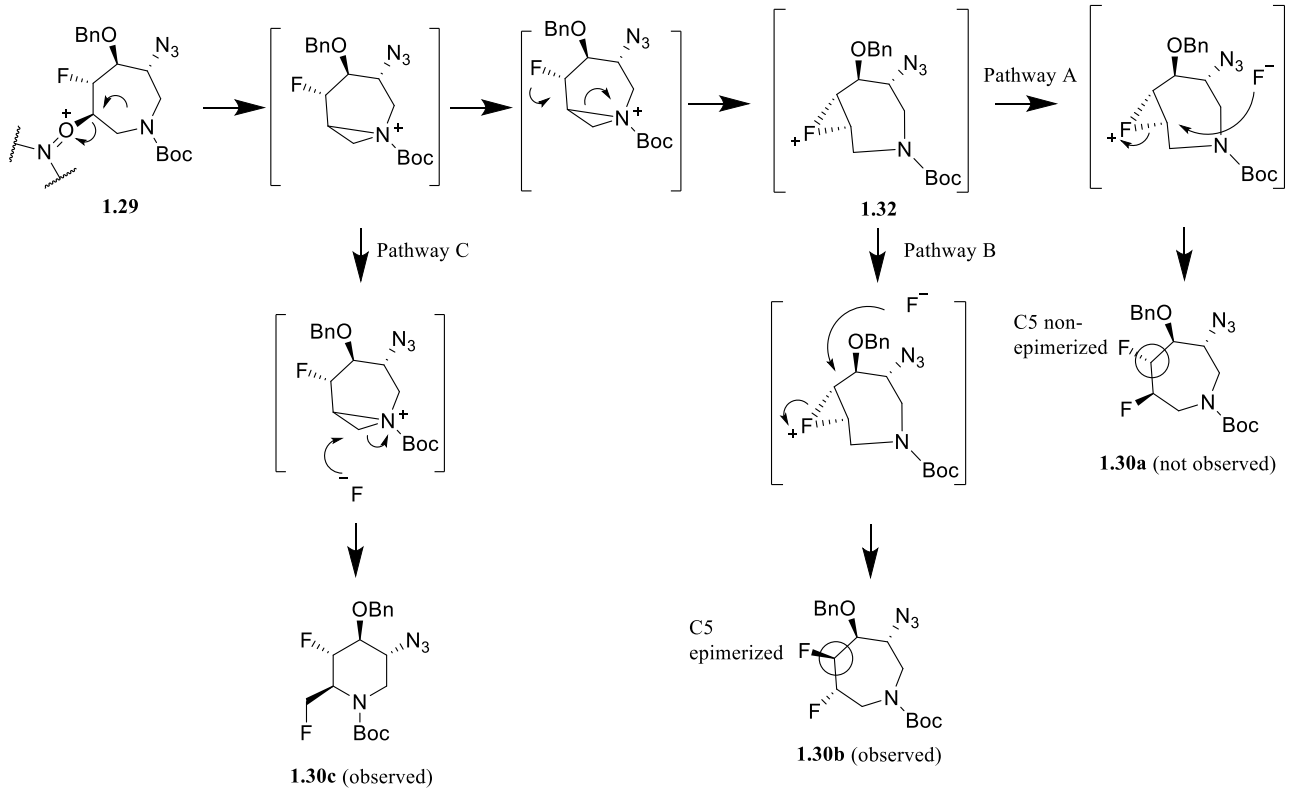


Scheme 1.8: Fluorination outcomes in the case of **1.31.**

A complex aziridinium intermediate was proposed to explain the experimental observations.[15] As part of this complex intermediate, C5 fluorine participation was suggested to rationalize the observed C5-F epimerization leading to two possible scenarios (Figure 1.9A and 1.9B). Specifically these structures are *cis* three-membered fluoronium ion **1.32** in the case of **1.29** (*trans* three-membered fluoronium ion for the case of **1.29x**) and hybrid-aziridinium intermediate **1.33**. As can be seen, scenario (i) may allow formation of fluoronium **1.32** via a cascade neighbouring group effect involving initial nitrogen participation, followed by fluorine participation at the electrophilic C6 carbon. Similarly, scenario (ii) entails a similar cascade effect to arrive at the hybrid intermediate **1.33**.

Both *cis* fluoronium ion **1.32** and hybrid intermediate **1.33** may account for the observed azepane and piperidine products (Figure 1.9A and 1.9B).[15] Pathway A represents a sterically feasible S_N2 trajectory *anti* with respect to the C6-F bond in both intermediates yielding the expected C5-F non-epimerized product **1.30a**, however this was not observed. The S_N2 trajectory in Pathway B which is *anti* with respect to the C5-F bond is also sterically feasible and yields the observed C5-F epimerized azepane. Finally, pathway C in both intermediates may lead to the observed piperidine product via fluoride attack at C7. Computationally, fluoronium intermediates, such as **1.32**, have been investigated and found to be very energetically costly. Therefore, a complex aziridinium-fluoronium intermediate such as **1.33** may be a more viable alternative for explaining the observed azepane stereochemistry.

A) Scenario (i) - *cis* fluoronium intermedatiate



B) Scenario (ii) - Hybrid aziridinium-fluoronium intermediate

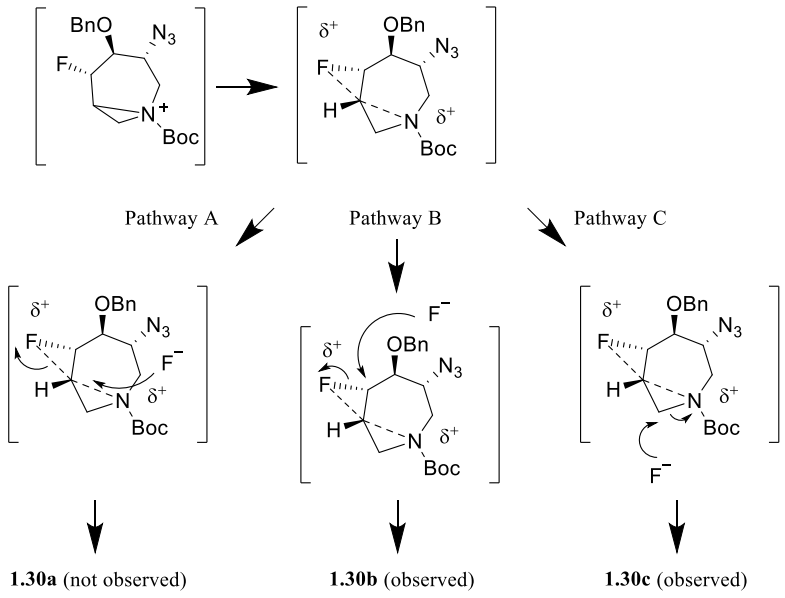
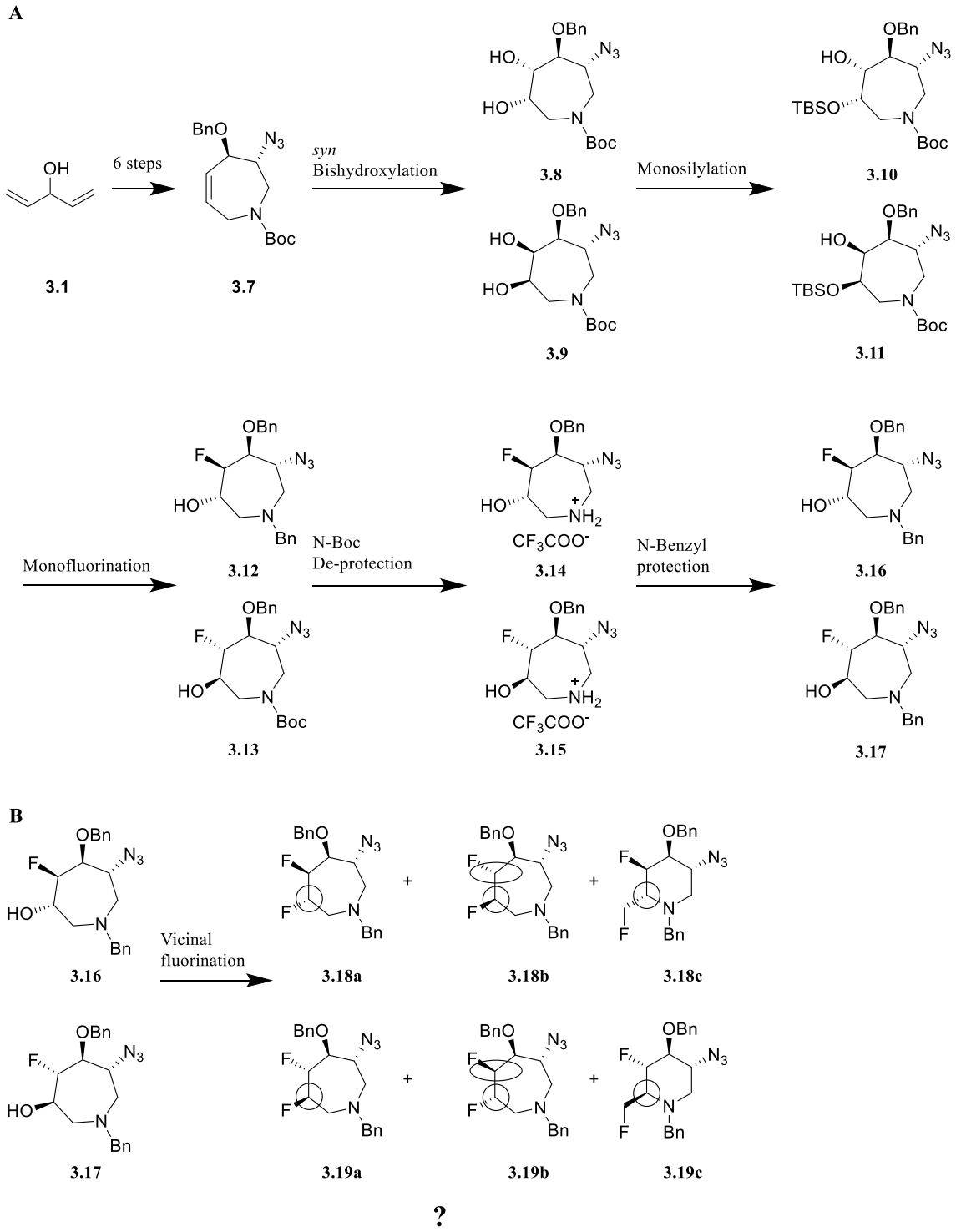


Figure 1.9: Proposed reaction intermediates in the case of vicinal fluorination.

1.4 Project Outline

In order to understand the reactive intermediates in the formation of C5-F epimerized azepanes in deoxyfluorination reactions of flurohydrin azepanes, the dependency of the reaction outcomes on the electron density of the nitrogen atom will be further tested by changing the protecting group to a benzyl group. The N-Bn protection will provide a highly electron rich nitrogen and potentially produce a much more stabilised aziridinium. A more stabilised azirindium may not then require C5-F fluorine participation and should suppress product formation due to C5-F participation. This will serve as an important point of comparison to the previous N-Boc and N-Tosyl cases with significant implications for the nature of the complex reaction intermediate involved. The primary aims of this project were thus twofold: first to conduct a targeted synthesis of an appropriate N-benzyl protected azepane system (Scheme 1.9A) and second, to fluorinate this substrate and investigate the reaction outcomes (Scheme 1.9B).



Scheme 1.9: Concise summary of the project aims.

2. Experimental

Synthetic procedures, characterization and spectral data of all compounds are discussed in the following sections. The compound numbering follows that in the results/discussion section. All relevant spectra for novel compounds are presented in Appendix A at the end of the thesis.

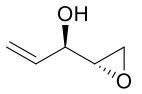
2.1 General Methods

Unless stated otherwise, all reactions were conducted in flame-dried glassware and under nitrogen atmosphere. Dichloromethane (DCM), tetrahydrofuran, *N,N*-dimethylformamide (DMF) and triethylamine were distilled from calcium hydride. Titanium tetraisopropoxide, benzyl bromide and *tert*-Butyldimethylsilyl chloride were purified by Kügelrhor distillation and all other commercially obtained reagents were used as received.

All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed using silica-gel (0.032-0.063 mm particle size) from Fisher Scientific. ^{1}H NMR spectra were obtained at 25 °C on either a Bruker DRX600K or DPX400 NMR spectrometer and are reported in ppm using the specified solvent as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR spectra were obtained using the same instruments and reported in ppm, using the specified solvent as the internal standard ($CDCl_3$ at 77.37 ppm). Polarimetry data was collected on a JASCO polarimeter (model no. P-1010). Low-resolution mass-spectrometry (LRMS) was conducted using a Shimadzu LCMS 2010EV instrument.

2.2 Synthetic Procedures and Characterization of Intermediates:

(2S,3R)-1,2-Epoxy-4-penten-3-ol (3.2)

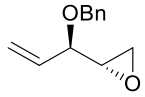


3.2

Crushed 4 Å molecular sieves (2.40g) were added to CH_2Cl_2 (72.0 mL) and cooled to -35 °C. Pre-cooled (-35 °C) titanium tetraisopropoxide (2.11 mL, 7.13 mmol) and (R,R)-(-)-diisopropyl tartrate (2.24 mL, 10.7 mmol) were then added dropwise via glass syringe. After 30 minutes pre-cooled (-35 °C) divinylcarbinol (6.00 g, 71.3 mmol) followed by cumene hydroperoxide (21.3 mL, 143 mmol) were added dropwise via glass syringe and the reaction mixture was left to stir at -35 °C for 36 hours. The reaction was then allowed to warm to ambient temperature and quenched by addition of aqueous saturated Na_2SO_4 (5 mL) solution. The reaction mixture was then diluted with Et_2O (5 mL) and the resultant slurry was passed through a Buchner funnel

(coarse grade) with filtrate collected into a flask cooled by liquid N_2. Filtrate was concentrated under vacuum at 0 °C to furnish crude residue, a viscous, light yellow solution. Crude was subjected to flash chromatography (petroleum ether/ EtOAc, 4/1, then 100% Et_2O) to give **3.2** (4.09 g, 67 %) as colourless oil with optical rotation and ^{1}H NMR spectral data matching those reported previously.[11] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87-5.76 (m, 1H), 5.35 (br d, J = 17.4 Hz, 1H), 5.22 (d, J = 10.7 Hz, 1H), 4.27 (br s, 1H), 3.04 (dd, J = 6.4, 3.5 Hz, 1H), 2.77-2.69 (m, 2H), 2.32 (br, s, 1H).

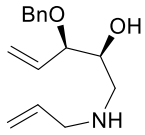
(S)-2-((R)-1-Benzyloxy-allyl)-oxirane (3.3)



3.3

To a solution of epoxyalcohol **3.2** (4.50 g, 44.9 mmol) and $(n\text{-}Bu)_4NI$ (1.66 g, 4.49 mmol) in THF (98.9 mL), NaH (1.19 g, 49.4 mmol) was added slowly followed by benzyl bromide (10.7 mL , 89.9 mmol) dropwise via glass syringe after 5 minutes. The resultant mixture was stirred at 25 °C for 14 hours under N_2 atmosphere. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$(20 mL) solution. The aqueous layer was then extracted with Et_2O (3 x 20 mL) and the organic phases were combined, dried and concentrated via rotary evaporation to obtain crude material, a viscous, colourless oil. Crude was subject to flash column chromatography (petroleum ether/ EtOAc, 9/1) to give **3.3** (5.48 g, 77.5%) as a colourless oil with ^{1}H NMR spectral data matching those reported previously.[11] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.22 (m, 5H), 5.88-5.75 (m, 1H), 5.38-5.30 (m, 2 H), 4.63 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 3.80 (dd, J = 7.5, 4.2 Hz, 1H), 3.09-3.05 (m, 1H), 2.76 (dd, J = 5.3, 4.0 Hz, 1H), 2.67 (dd, J = 5.3, 2.6 Hz, 1H).

(2S,3R)-1-Allylamino-3-benzyloxy-pent-4-en-2-ol (3.4)

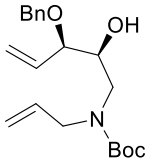


3.4

Epoxide **3.3** (5.48 g, 28.8 mmol) was refluxed in freshly distilled allylamine (43.2 mL, 576 mmol) for 40 hours. Excess allylamine was then removed under reduced pressure, yielding amine **3.4** (7.12 g, 28.8 mmol) as a pale yellow oil with ^{1}H NMR spectral data matching those reported previously.[11] No further purification was performed. ^{1}H NMR ($CDCl_3$, 400 MHz): δ

7.30-7.18 (m, 5H), 5.86-5.73 (m, 2H), 5.33-5.22 (m, 2H), 5.12-4.98 (m, 2H), 4.57 (d, J = 11.9 Hz, 1H), 4.32 (d, J = 11.9 Hz, 1H), 3.73-3.67 (m, 2H), 3.22-3.09 (m, 2H), 2.67 (dd, J = 12.3, 3.3 Hz, 1H), 2.63-2.55 (m, 1H).

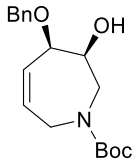
(2S,3R)-Allyl-(3-benzyloxy-2-hydroxy-pent-4-enyl)-carbamic acid-tert-butyl ester (3.5)



3.5

A solution of amine **3.4** (7.12 g, 28.8 mmol) and Et_3N (5.62 mL, 40.3 mmol) in CH_2Cl_2 (290 mL) was cooled to 0 °C and combined with a solution di-*tert*-butyl dicarbonate (6.91 g, 31.7 mmol) in CH_2Cl_2 (290 mL). The resulting mixture was left to stir for 2 hours at 25 °C and under N_2 atmosphere. The reaction was quenched by the addition of water (20 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL). Combined organic phases were washed with aqueous saturated NH_4Cl (2 x 20 mL) and brine (20 mL), then dried with Na_2SO_4 prior to rotary evaporation to obtain crude material, a viscous, colourless oil. Crude material was subject to flash column chromatography (petroleum ether/ EtOAc, 6/1) to obtain diene **3.5** (8.22 g, 82 %) as a viscous colourless oil with ^1H NMR spectral data matching those reported previously.[11] ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.25 (m, 5H), 5.89-5.68 (m, 2H), 5.41-5.31 (m, 2H), 5.13-5.03 (m, 2H), 4.63 (d, J = 11.8 Hz, 1H), 4.37 (d, J = 11.9 Hz, 1H), 3.88-3.67 (m, 4H), 3.41-3.34 (m, 2H), 1.44 (s, 9H).

(3S,4R)-4-Benzyloxy-3-hydroxy-2,3,4,7- tetrahydroazepine-1-carboxylic acid-*tert*-butyl ester (3.6)

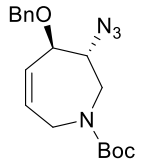


3.6

Grubb's catalyst (Generation I) (156 mg, 0.189mmol)) was added to a solution of diene **3.5** (1.11 g, 3.19 mmol) in CH_2Cl_2 (550 mL) and left to reflux for 48 hours with additional Grubb's catalyst (104 mg, 0.126 mmol) added at 22 hours. Solvent was then evaporated and the crude material, a viscous dark brown oil, was subject to flash column chromatography (petroleum ether/ EtOAc, 5/1 to 2/1) to provide tetrahydroazepine **3.6** (920 mg, 90%) as a viscous, pale yellow oil with NMR spectral data matching those reported previously.[11] ^1H NMR ($CDCl_3$, 400

MHz): δ 7.37-7.27 (m, 5H), 5.79-5.65(m, 2H), 4.74-4.61 (m, 1H), 4.58-4.46 (m, 1H), 4.45-4.10 (m, 3H),4.03-3.87 (m, 1H), 3.82-3.62 (m, 1H), 3.31-3.10 (m, 1H), 2.54-2.44 (br m,1H), 1.40 (s, 9H).

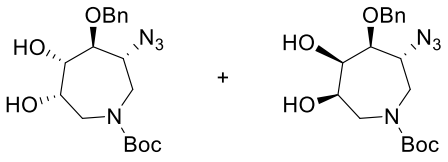
(3R,4R)-3-Azido-4-benzyloxy-2,3,4,7-tetrahydroazepine-1-carboxylic acid-*tert*-butyl ester (3.7)



3.7

Diethyl azodicarboxylate (DEAD, 1.20 mL, 7.66 mmol) was added dropwise to a well-stirred solution of tetrahydroazepine **3.6** (612 mg, 1.92 mmol), PPh_3 (2.01 g, 7.66 mmol) and diphenylphosphorylazide (DPPA, 1.72 mL, 7.66 mmol) in dry THF (48 mL) under N_2 atmosphere at 25 °C. The reaction mixture was stirred at ambient temperature and monitored by thin-layer chromatography (TLC) until completion (8 hours). The reaction mixture was then suspended in EtOAc (15 mL) and filtered through a pad of silica gel. Filtrate was washed with aqueous saturated NH_4Cl solution (10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated by rotary evaporation to yield crude material, a viscous, pale yellow oil. Crude was then subject to flash column chromatography (pentane/ *tert*-butyldimethylether, 20/1) to yield tetrahydroazepine **3.7** (292.1 mg, 44 %) as a viscous, pale yellow oil with NMR spectral data matching those reported previously.[11] ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.23 (m, 5H), 5.80-5.69 (brm, 2H), 4.72-4.52 (m, 2H), 4.29-4.19 (m, 2H), 3.90-3.49 (m, 4H), 1.47 (s, 9H).

(3R,4S,5S,6S)–3–azido–4–benzyloxy–5,6–dihydroxyazepane–1–carboxylic acid–tert–butyl ester (3.8) and (3R,4S,5R,6R)–3–azido–4–benzyloxy–5,6–dihydroxyazepane–1–carboxylic acid–tert–butyl ester (3.9)



3.8 **3.9**

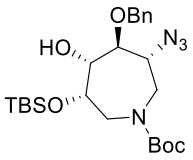
N-Methylmorpholine-*N*-oxide (298 mg, 2.54mmol) and OsO_4 (270μL, 42.0 μmol as a 4 % w/w solution in water) was added to a solution of tetrahydroazepine **3.7** (292 mg, 0.850mmol) in acetone/ water (2.10 mL) and stirred at ambient temperature for 5 hours. The reaction was

quenched by the addition of aqueous saturated $Na_2S_2O_3$ (4 mL) and diluted with EtOAc (4 mL). Combined organic phases were then dried with Na_2SO_4 and rotary evaporated to yield crude material, a viscous, colourless oil. Crude material was subject to flash column chromatography (petroleum ether/ EtOAc, 2/3) to obtain bishydroxyazepane **3.8** (118.9 mg, 37%) and **3.9** (44.6 mg, 14%) as viscous, colourless oils with NMR spectral data matching those reported previously.[11] A mixture of **3.8** and **3.9** (36.0 mg, 11%) was also isolated from the column.

3.8: $[\alpha]_D^{24}$ +57.2(c 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.44–7.31 (m, 5H), 4.98 (d, *J* = 11.1 Hz, 1H), 4.61 (dd, J = 13.5 Hz, 11.8 Hz, 1H), 4.36–4.26 (m, 1H), 4.10–4.00 (m, 1H), 3.83–3.68 (m, 1H), 3.65–3.52 (m, 1H), 3.22-3.11 (m, 2H), 2.42 (br s, 1H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$):δ155.0, 137.7, 128.9, 128.5, 81, 80.8, 75.6, 73.2, 72.9, 69.6, 68.7, 64.5, 63.1, 50.6, 49.7, 48.3, 47.6, 28.5.

3.9: $[\alpha]_D^{24}$ – 24.8(c 0.80, $CHCl_3$).^{1}H NMR (600 MHz, $CDCl_3$):δ7.40–7.29 (m, 5H), 4.72-4.56 (m, 2H), 4.20–4.06 (m, 1H), 4.00–3.93 (m, 1H), 3.93–3.85 (m, 1H), 3.80-3.64 (m, 2H), 3.63-3.41 (m, 2H), 3.32-3.17 (m, 1H), 2.89 (br s, 2H), 1.45 (s,9H); ^{13}C NMR (150 MHz, $CDCl_3$):δ156.4, 155.3, 150.4, 130.4, 129.1, 129.0, 128.8, 128.6, 128.5, 85.1, 83.2, 81.3, 80.8, 74.0, 73.5, 72.7, 71.8, 71.4, 70.4, 61.8, 60.8, 51.4, 51.2, 49.8, 49.0, 28.7.

(3R,4S,5S,6S)–3–azido–4–benzyloxy–6–(*tert*–butyldimethylsilyl)oxy–5–hydroxyazepane–1–carboxylic acid–tert–butyl ester (3.10)

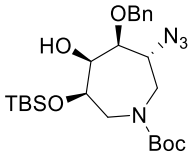


3.10

A solution of *tert*-butyldimethylsilyl chloride (57.8 mg, 0.383 mmol) in DMF (250 µL) was combined with a solution of bishydroxyazepane **3.8** (120.9 mg, 0.319 mmol) and imidazole in DMF (250 µL) at 25 °C under N_2 atmosphere. The reaction mixture was allowed to stir at ambient temperature for 10 hours before being quenched by the addition of water (1 mL). The aqueous phase was extracted with EtOAc (1 mL) and the combined organic phases were washed with water (3 x 1 mL) and brine (1 mL), dried with $MgSO_4$ and concentrated by rotary evaporation to yield crude material, a viscous, colourless oil. Crude material was subject to flash column chromatography (petroleum ether/ EtOAc, 9/1) to yield azepane **3.10** exclusively

(123.3 mg, 78%) as a viscous, colourless oil with NMR spectral data matching those reported previously.[11] ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 4.90 (dd, J = 32.7 Hz, 1H), 4.58 (dd, J = 28.0 Hz, 11.2 Hz, 1H), 4.30-4.20 (m, 1H), 4.04–3.95 (m, 1H), 3.89-3.70 (m, 3H), 3.63–3.52 (m, 1H), 3.30-2.98 (m, 2H), 2.57 (d, J = 15.0 Hz, 1H), 1.44 (s, 9H), 0.92 (s, 9H), 0.12-0.08 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.2, 138.0, 129.1, 129.0, 128.6, 82.0, 81.9, 80.9, 80.7, 75.6, 74.8, 74.1, 74.0, 73.7, 71.6, 71.0, 64.7, 62.5, 51.4, 50.7, 46.7, 46.3, 28.7, 26.2, -4.23, -4.65.

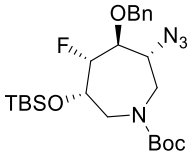
(3R,4S,5R,6R)–3–azido–4–benzyloxy–6–(*tert*–butyldimethylsilyl)oxy–5–hydroxyazepane–1–carboxylic acid–tert–butyl ester (3.11)



3.11

Same procedure followed as for the synthesis of compound **3.10** to give the (5S,6S) TBS protected azepane compound **3.11** from the corresponding bishydroxyazepane **3.9**.^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 4.76-4.57 (m, 2H), 4.05 (d, J = 15.0 Hz, 1H), 4.01-3.82 (m, 3H), 3.78-3.60 (m, 2H), 3.47-3.25 (m 2H), 2.97 (ddd, J = 54.2 Hz, 14.0 Hz, 11.5 Hz, 1H), 2.40 (d, J = 12.3 Hz, 1H), 1.47 (s, 9H), 0.88 (s, 9H), 0.10-0.03 (m, 6H).^{13}C NMR (150 MHz, $CDCl_3$): δ 137.8, 128.8, 128.6, 128.5, 128.3, 81.3, 80.8, 75.6, 75.4, 73.4, 73.2, 70.9, 70.4, 63.6, 62.8, 49.8, 49.6, 28.8, 28.6, 26.1, -4.28, -4.62.

(3R,4S,5R,6R)–3–azido–4–benzyloxy–6–(tert–butyldimethylsilyl)oxy–5–fluoroazepane–1–carboxylic acid–tert–butyl ester (3.12b)

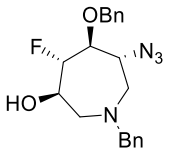


3.12b

Deoxofluor® (35.8 mg, 0.162 mmol) in DCM (0.34 mL) was added to dropwise via glass syringe to a solution of azepane **3.10** (53.2 mg, 0.108 mmol) in DCM (1.54 mL) at 0 °C. The reaction mixture was then allowed to equilibrate ambient temperature over 8 hours before the solvent was removed via rotary evaporation yielding crude material, a viscous, light orange oil. Crude material was subject to flash column chromatography (petroleum ether/ EtOAc 9/1) to

yield partially purified compound **3.12b** (6.3 mg, 12.0%) as a viscous, colourless oil which was characterized by 2D NMR spectroscopy. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 4.75 (dq, $^{1}J_{HF}$ = 44.1 Hz, 5.1 Hz, 1H), 4.63 (dd, J = 38.2 Hz, 11.7 Hz, 1H), 4.57 (dd, J = 95.7 Hz, 11.8 Hz, 1H), 4.33-4.17 (m, 1 H), 4.05-3.95 (m, 1H), 3.86-3.80 (m, 1H), 3.62-3.52 (m, 1H), 3.29-3.09 (m, 2H); ^{13}C NMR (150 MHz,$CDCl_3$): δ 154.92, 137.4, 128.9, 128.8, 128.5, 128.4, 128.3, 88.9 (dd, $^{1}J_{CF}$ = 176.2 Hz, 37.5 Hz), 81.5 (dd, $^{2}J_{CF}$ = 71.6 Hz, 12.5 Hz), 81.1, 80.9, 74.2, 73.2, 72.8, 65.0, 62.2, 47.7, 47.3, 46.4, 46.2, 45.1, 44.9; LRMS (ESI): $[M+H]^+$, *m/z* calculated for $C_{19}H_{31}FN_4O_2Si$ (Boc deprotected **3.12b**) 395.22, found 395.

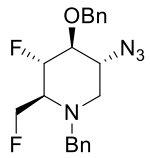
(3*S*,5*S*,6*R*)–6–azido–5–benzyloxy–1–benzylazepan–3–ol (3.17)



3.17

Anhydrous K_2CO_3 (0.013 mg, 0.09 mmol) and $(n\text{-}Bu)_4NI$ (9.23 mg, 0.025 mmol) were added to a solution of fluorohydroxyazepane **3.15** (13.3 mg, 0.05 mmol) in anhydrous acetonitrile (1.82 mL). Benzyl bromide (6.77 µL, 0.06 mmol) was then added dropwise via glass syringe at 25 °C and under N_2 atmosphere. Reaction was left to proceed at 50 °C with magnetic stirring and was monitored by TLC until completion. Crude reaction mixture consisted of a pale yellow solution with flocculent white precipitate. Crude material was subject to flash column purification to obtain N-benzylfluoroazepanol **3.17** (9.9 mg, 53%).^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43-7.26 (m, 10H), 4.77 (dd, J = 55.2 Hz, 10.9 Hz, 2H), 4.71 (dt, $^{1}J_{HF}$ = 47.4 Hz, 6.1 Hz, 1H), 3.93 (s, J = 5.4 Hz, 1H), 3.74-3.62 (m, 4H), 2.91 (dd, J = 13.6 Hz, 3.1 Hz, 1H), 2.80-2.77 (d, J = 5.4 Hz, 2H), 2.46 (dd, J = 13.5 Hz, 8.7 Hz, 1H); ^{13}C NMR (150 MHz,$CDCl_3$): δ 137.9, 129.3, 128.9, 128.8, 128.6, 128.3, 128.1, 128.0, 127.3, 97.9 (d, $^{1}J_{CF}$ = 175.1 Hz), 84.0 (d, $^{2}J_{CF}$ = 21.8 Hz), 74.9, 69.4 (d, $^{2}J_{CF}$ = 25.7 Hz), 63.7, 62.6, 57.7, 56.2; LRMS (ESI): $[M+H]^+$, *m/z* calculated for $C_{20}H_{23}FN_4O_2$ 371.18, found 371.

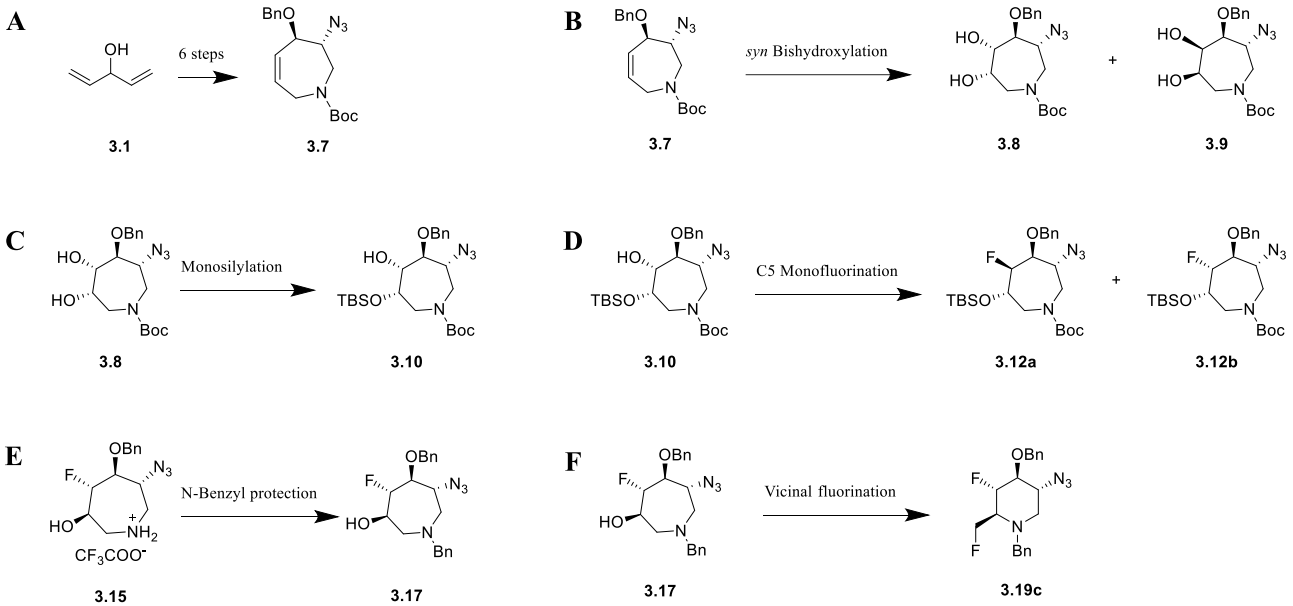
tert-Butyl-(2R,3S,4S,5R)-5-azido-4-(benzyloxy)-3-fluoro-2-(fluoromethyl)piperidine-1-carboxylate (3.19c)



3.19c

Solutions of Deoxofluor® (2.88 mg, 0.013 mmol) in DCM (260 uL) and N-benzylazepanol **3.17** (3.6 mg, 0.010 mmol) in DCM (240uL) were chilled to 0 °C and combined by dropwise addition via syringe. The reaction was then left to proceed and equilibrate to room temperature with reaction completion determined by TLC analysis (5% EtOAc in n-Hex). After 2 hours the complete reaction comprised a translucent yellow solution which was washed with aqueous $NaHCO_3$ solution (10% w/v) and dried with $MgSO_4$ to afford crude material. Subsequent flash column purification of crude material yielded fluoromethylpiperidine **3.19c** as a viscous colourless oil (3.5 mg, 97%) which was characterized by 2D NMR spectroscopy. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43-7.24 (m, 10H), 4.87 (dd, $^1J_{HF}$ = 48.1 Hz, 11.0 Hz, 1H), 4.83 (dd, J = 75.0 Hz, 11.0 Hz, 2H), 4.71 (dd, $^1J_{HF}$ = 46.1 Hz, 11.0 Hz, 1H), 4.50 (ddd, $^1J_{HF}$ = 50.0 Hz, 9.6 Hz, 8.2 Hz, 1H), 4.19 (d, J = 13.4 Hz, 1H), 3.75 (dd, J = 520.1 Hz, 13.8 Hz, 2H), 3.52-3.41 (m, 3H), 2.89 (dd, J = 12.3 Hz, 4.6 Hz, 1H), 2.62 (dq, J = 27.1 Hz, 1H), 1.92 (dd, J = 11.7 Hz, 11.0 Hz, 1H); ^{13}C NMR (150 MHz,$CDCl_3$): δ 137.8, 129.1, 128.9, 128.8, 128.6, 128.3, 127.9, 91.5 (dd, $^1J_{CF}$ = 180.0 Hz, 5.9 Hz), 83.5 (d, $^2J_{CF}$ = 17.8 Hz), 80.4 (dd, $^1J_{CF}$ = 173.8 Hz, 3.9 Hz), 75.0, 20.6 (dd, J = 22.9 Hz, 17.9 Hz), 60.2 (d, J = 11.5), 56.7, 54.0. LRMS (ESI): $[M+H]^+$, *m/z* calculated for $C_{20}H_{22}F_2N_4O$ 373.18, found 373.

3. Results and Discussion



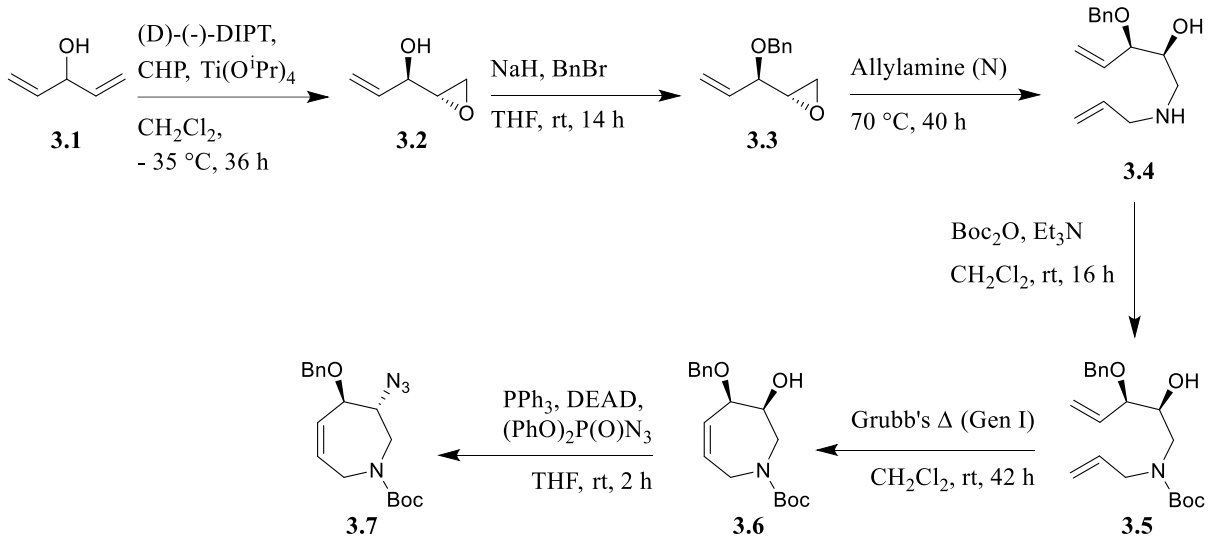
Scheme 3.1: Concise summary of project outcomes.

Our earlier work has found that stereoselective, C6-deoxyfluorination of N-Boc and N-Tosyl protected fluorohydrin azepanes led to the formation of an unexpected C5-F epimerized azepane (Introduction, page 15). This was rationalized by evoking a complex aziridinium intermediate involving both nitrogen and fluorine participation. As such it was hypothesized that the reactivity of this aziridinium-based intermediate is dependent upon the electron density of the nitrogen and the type of N-protecting group used. Therefore, the primary aim of this research project was to access N-benzylated fluorohydrin azepane **3.17** in order to investigate the deoxyfluorination reaction outcome of this molecule with Deoxofluor®. The N-benzyl protecting group does not contain an oxygen atom and also renders the nitrogen more electron-rich. This will answer the question if nitrogen is likely the participation centre over oxygen and if an electron-rich nitrogen would suppress the need for C5-fluorine participation.

In addition, it was necessary to optimize the reaction conditions of the capricious monofluorination reaction using monosilylated azepane **3.10.** Our previous work has shown that silylated fluorohydrin **3.12a**, which is needed for subsequent C6-deoxyfluorination investigations, was accessible from **3.8** via a monosilyation-monofluorination sequence. However, the yield was moderate with significant purification difficulties. Therefore, an attempt was made to investigate the monofluorination reaction further using monosilylated azepane **3.10**.

Here in this work, compound **3.17** was accessed via an 11 step synthesis from tetrahydroazepine intermediate **3.7** (Scheme 3.1A) using Fürstner*'s* approach. The subsequent *syn* dihydroxylation of **3.7** provided a diastereomeric mixture of bishydroxyazepanes **3.8** and **3.9** (Scheme 3.1B). Diastereomer **3.8** was used for investigating the monosilyation-monofluorination sequence (Scheme 3.1C-D) while the fluorohydrin **3.17** was used for investigating the vicinal fluorination reaction at C6 (Scheme 3.1E). Consistent with our hypothesis, C6-deoxyfluorination of **3.17** resulted in complete suppression of the C5-F epimerization pathway, yielding exclusively difluoropiperidine product **3.19c** without any azepane product detected (Scheme 3.1F). This suggests that electron-rich nitrogen prefers the formation of a stable aziridinium intermediate without the need for fluorine participation. The optimisation for **3.12a** synthesis was unsuccessful as the reaction conditions attempted resulted in poor conversion of the starting material. However, a new silylated fluorohydrin azepane **3.12b** was isolated which serendipitously provided a new substrate for further deoxyfluorination investigations.

3.1 Synthesis of N-Boc Tetrahydroazepine 3.7



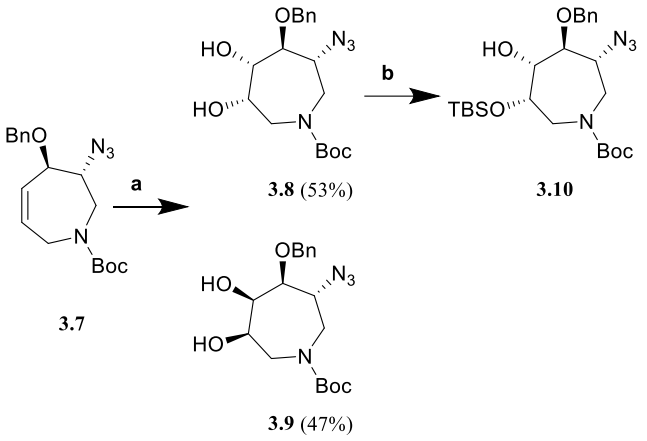
Scheme 3.2: Synthesis of **3.7**. *Reagents and conditions:* (a) (D)-(-)-DIPT, CHP, Ti(O^{i}Pr)$_4$, dry DCM, -35 °C, 48 h, 67%; (b) NaH, BnBr, dry THF, 25 °C, 78%; (c) Allylamine, 70 °C, 40 h, quant.; (d) Boc_2O, Et_3N, dry DCM, 25 °C, 16 h (82%); (e) Grubb's Δ (generation I), dry DCM, reflux, 42 h, 90%; (f) PPh_3, DEAD, $(PhO)_2P(O)N_3$, THF, 25 °C, 4 h, 44%.

Tetrahydroazepine **3.7** was synthesized via a concise six-step synthesis reported by Fürstner and Thiel (Scheme 3.2).[60] Asymmetric Sharpless epoxidation furnished epoxide **3.2** from the commercially available starting material, divinylcarbinol **3.1**, which was followed by benzyl protection, epoxide opening with allylamine and Boc protection to yield hydroxypentene-

carbamate **3.5**. Subsequent olefin ring closing metathesis provided the azepine **3.6** in good yields (80-90%) with Grubb's catalyst (generation I). Finally, single-step conversion of the C3 alcohol to the corresponding azide was achieved using the Mitsunobu reaction to produce compound **3.7**.

Overall, comparable yields were obtained for the synthesis of compounds **3.1**–**3.6** as reported previously[60]; however the azide Mitsunobu reaction exhibited some problems in conversion. In addition, purification of azide **3.7** from dihydro-DEAD and triphenylphosphine oxide was difficult. Initially reactions were set-up in the standard fashion by preparing a solution of the alcohol **3.6**, triphenylphosphine and diethylazodicarboxylate in tetrahydrofuran followed by dropwise addition of neat diethylazodicarboxylate to initiate the reaction at 0 °C; however this resulted in little to no reaction. The order of addition of the reagents was then changed to preform the betaine by initial combination of diethylazodicarboxylate and triphenylphosphine, followed by the addition of **3.6**. This resulted in formation of azide **3.7** at a comparatively low isolated yield of 44% and further optimization will be necessary in the future.

3.2 Synthesis of Monosilylated Bis-Diol 3.10



Scheme 3.3: Synthesis of **3.10**. *Reagents and conditions:* (a) OsO_4 (4% w/v solution in water), NMO, 8:1 acetone/water, 25 °C, 5 h, 62%; (b) TBS-Cl, Imidazole, DMF, 30 °C, 8 h, 78%.

Initial dihydroxylation of tetrahydroazepine **3.7** was achieved using a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine-N-Oxide to yield exclusively the *syn* (5R, 6R) and (5S, 6S) bishydroxyazepane diastereomers **3.8** and **3.9** in a reproducible 8:17 ratio (Scheme 3.3). Regioselective monoprotection of these diols at the C6 position was then conducted using the *tert*-Butyldimethylsilyl (TBS) protecting group. Protection in this manner using the sterically bulky TBS functional group is advantageous as it is more heat, acid and base stable compared to the simplest trimethylsilane (TMS) silyl ether protecting group and

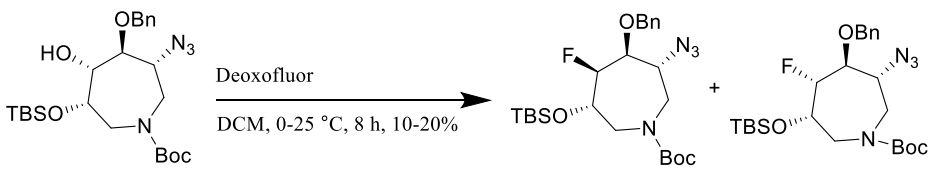
allows selective de-protection in the presence of the Boc, azide and O-Benzyl groups of the azepane substrates. The TBS group would also favour C6 monoprotection and disfavour C5-C6 silyl migration as this would minimize steric interactions between the C4 O-benzyl protecting group and bulky *tert*-butyldimethylsilyl group.

Conditions were optimised to maximize the yield of the monosilyated product **3.10** without overprotection. Previously reported conditions for TBS monoprotection employed 1.1 molar equivalents of imidazole and TBS-Cl at a concentration of 0.1 M and ambient temperature to favour monosilylation over disilylation. However, this resulted in limited conversion and required recycling of unconverted starting material. To increase conversion a higher equivalent of imidazole was trialled. Imidazole serves an important catalytic role to activate TBS-Cl for nucleophilic attack by the substrate alcohol via a highly electrophilic, charged iminium intermediate and also as a base in the reaction. By increasing the molar equivalents of this reagent it may be possible to increase conversion, albeit at the possibility of forming the C5-OTBS or di-OTBS protected azepanes.

Corey's conditions for TBS protection were used as a starting point for optimization.[61] These included 2.5 equivalents of imidazole and 2 equivalents of TBS-Cl at a reaction concentration of 1 M and reaction temperature of 35 °C. Under these conditions, conversion was complete, however the substantial formation of side products, possibly the C5-OTBS and di-OTBS azepanes, was also noted and may explain the low yields of less than 30% of the desired C6-OTBS compound. The use of 2 equivalents of imidazole with 1.5 equivalents of TBS-Cl at a concentration of 0.01 M and a reaction temperature of 30 °C were sufficient to exclusively produce the desired C6-OTBS compound **10** in 78% isolated yield.

3.3 Synthesis of N-Boc C6-OTBS Azepane 3.12.

From silylated azepane **3.10**, the deoxyfluorination at C5 was expected to proceed stereospecifically with inversion of stereochemistry as observed previously (Scheme 3.4).[11] This inversion occurs as the reaction proceeds through an S_N2 mechanism involving substitution of the activated alcohol by nucleophilic fluoride with no involvement from the heterocyclic nitrogen.



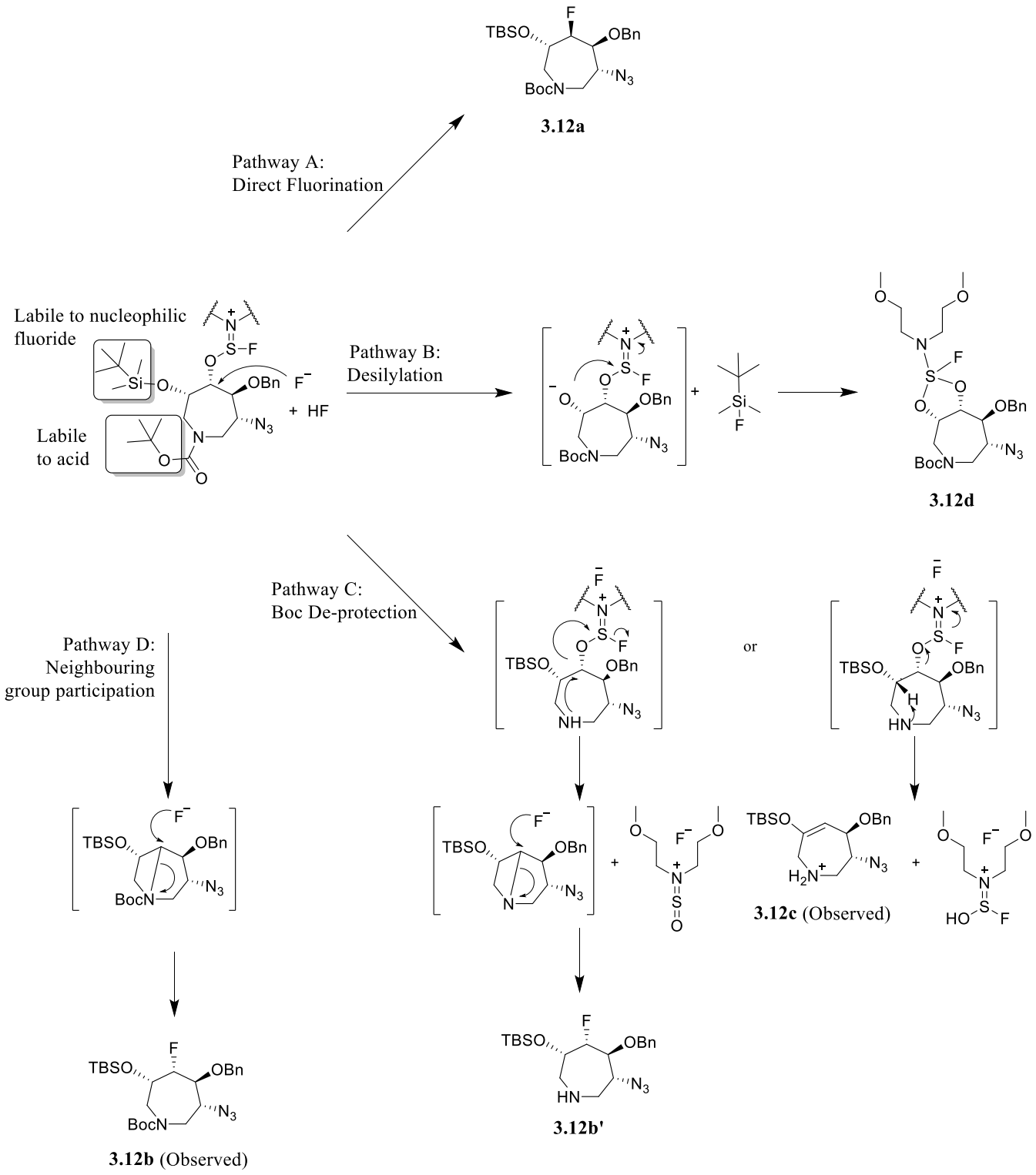
3.10 **3.12a** (<5%) **12b** (12%)

Scheme 3.4: Proposed mechanism of reaction of Deoxofluor® and synthesis of **3.12a**, **3.12b** and **3.14**.

Compound **3.12a** is the previously observed azepane synthesized from bishydroxyazepane **3.8** via a monosilyation-deoxyfluorination-desilylation approach (Scheme 3.4). It was intended to be an intermediate for preparing vicinal fluorinated azepanes via sequential deoxyfluorination reactions. While there are other more expedient difluorination routes which involve the activation of both alcohols via cyclic sulphite formation, ditriflation or epoxide opening with nucleophilic fluoride, the sequential deoxyfluorination approach appeared to have suitably milder conditions to preserve other functional groups on the azepane ring. As such this approach was attempted here yielding compound **3.12b** with unexpected retention of stereochemistry in 10-20% yield instead of the expected product **3.12a** under optimized conditions.

The moderate yield and formation of **3.12b** can be explained by the complex set of concurrent reaction pathways that may be initiated in the presence of nucleophilic fluoride (Scheme 3.5). As opposed to direct fluorination (pathway A), which yields the previously observed azepane **3.12a**, pathways B, C and D are also possible following formation of the charged fluorosulphaniminium intermediate. Pathway B involves immediate TBS de-protection in the presence of nucleophilic fluoride due to the proximity of the silicon centre and the strength of the incipient Si-F bond. The liberated C6 alcohol may then attack the electrophilic sulphur centre leading to the formation of cyclic sulphite **3.12d** which in turn may be attacked by various nucleophiles including fluoride at either C5 or C6.

Degradation pathway C outlined in Scheme 3.5 involves immediate acid-catalyzed Boc de-protection following alcohol activation. The unmasked secondary amine acting as a nucleophile may then participate in the fluorination mechanism leading to a C5-monofluorinated product **3.12b'** with retention of stereochemistry or an elimination product **3.12c** (pathway C). Similarly, pathway D outlines a plausible pathway leading to the formation of observed monofluoroazepane **3.12b** involving nitrogen group participation at C5 in the presence of the N-Boc group. Formation of a four-membered azetidinium ring promotes nucleophilic attack approximately *anti* with respect to the C5-N bond, yielding the observed double inversion product **3.12b**.

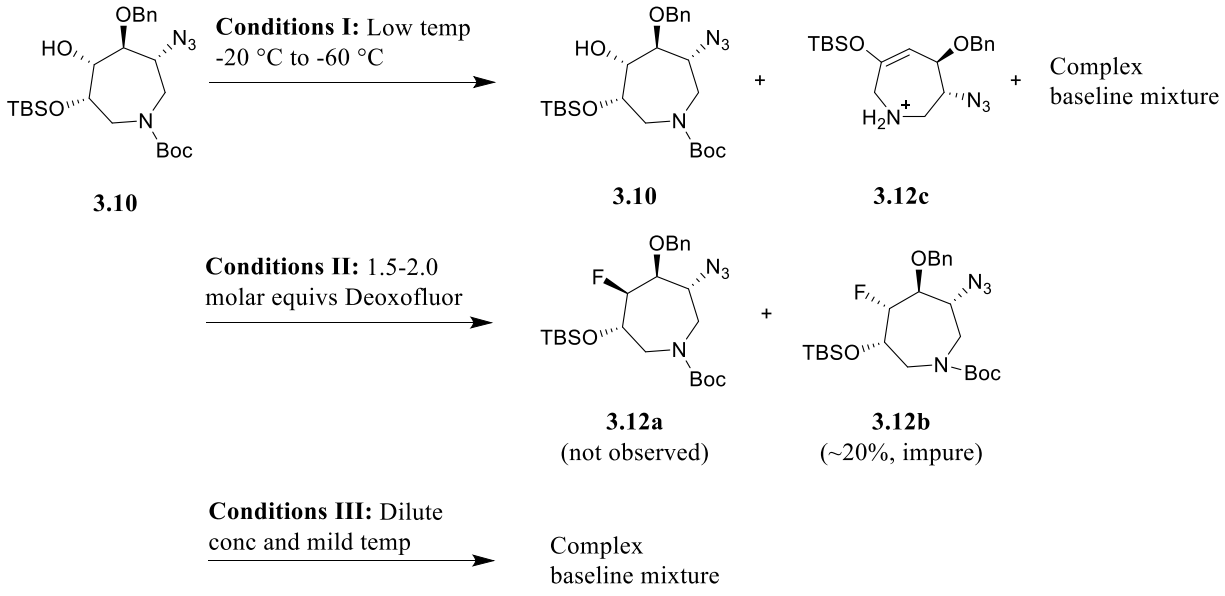


Scheme 3.5: Plausible pathways of reaction for silyloxyazepenols with Deoxofluor®.

It was reasoned that molar excess of Deoxofluor®, temperature and concentration would influence greatly reaction outcomes given the variety of pathways possible. Initial stereoselective monofluorination of **3.10** was attempted using previously reported conditions which involved the addition of one molar equivalent of Deoxofluor® to a dilute solution of

azepane **3.10** at 0 °C. However, this condition did not yield compound **3.12a** at all. Instead a complex mixture of at least three inseparable azepane compounds was isolated in poor yields (10-20%). Therefore different reaction conditions were trialled in order to promote pathway A (Scheme 3.5) for preparing the desired product **3.12a**.

Three sets of different reaction conditions were trialled in order to improve reaction yields of **3.12a** as summarized in Scheme 3.6. Conditions I involving low temperatures were trialled under the hypothesis that reducing the rate of reaction would perhaps disfavour rapid HF formation and subsequent Boc de-protection leading to pathway B and C (Scheme 3.5). At the other extreme, conditions II were trialled, including ambient temperature and the use of high (1.5-2.0) molar equivalents of Deoxofluor® to push for faster conversion with an increased concentration of nucleophilic fluoride in solution that may expedite pathway A (Scheme 3.5). Finally conditions III were also trialled which are the same as those previously reported with the exception of a higher dilution of reagents. It was reasoned here that the reaction may need to be sufficiently warm, yet sufficiently dilute to promote formation of the desired product via pathway A (Scheme 3.5) while reducing side-reactions via pathways B, C and D.



Scheme 3.6: Trialled reaction conditions for monofluorination and their outcomes. Unless stipulated otherwise reactions were set-up as follows: Deoxofluor® (1.0-1.1 equivalents), DCM, 0 to 25 °C, 8 h.

Unfortunately none of the reaction conditions trialled produced the desired monofluorinated azepane **3.12a**. Reactions conducted at low temperatures showed very slow conversion with starting material still present after 8 hours according to TLC (R_f = 0.07 in 5% EtOAc/ n-

Hexanes) and NMR analysis. The majority of starting material had converted to a complex and highly polar mixture of materials at or near the baseline by TLC including a single spot at R_f = 0.08 (in 40% EtOAc/ n-Hexanes). Partial isolation of this compound by flash column chromatography, followed by NMR spectroscopy and low-resolution MS analysis revealed this to be a Boc-deprotected azepane of molecular mass 375 Da, consistent with silyl enol ether **3.12c** (Scheme 3.6 and Scheme 3.5, pathway B).

Monofluorination using conditions II with higher molar equivalents of Deoxofluor® resulted in the formation of a novel monofluorinated compound **3.12b** as the sole fluorinated product in low yields (20%). Compound **3.12b** was isolated impure and further purification was not possible leading to the tentative assignment by 2D NMR analysis (Figure 3.1 and Figure 3.2).

Strong evidence supporting the structure illustrated for **3.12b** is provided by the NMR data, particularly the HSQC and COSY data (Figure 3.1 and Figure 3.2). Proton and carbon NMR spectra indicate the expected total of 10 protons and 7 carbons for the azepane core of **3.12b** plus the benzylic methylene group, comparable to those observed for these same regions of **3.12a** (not shown). Comparison of the HSQC spectra of **3.12a** and **3.12b** (Figure 3.1) indicates that these two compounds are analogous, yet different. The most apparent example is the chemical shift of the monofluorinated C5 atom and its associated H5 proton. In **3.12a** the carbon atom occurs at 95.9 ppm (J_{CF} = 175.4 Hz), while in compound **3.12b** it occurs at 88.9 ppm (J_{CF} = 175.0 Hz). In addition, the H5 proton of **3.12a** occurs as a complex multiplet between 4.5 and 5.0 ppm (result of Boc rotamers), while H5 in **3.12b** occurs as a doublet of quintets at 4.74 ppm ($^2J_{HF}$ = 44.Hz). Substantial changes are also noted for the other ring methines including C3/H3, C4/H4 and C6/H6 which exhibit wide variations in carbon and proton chemical shifts between the two compounds.

A COSY experiment was used to substantiate the tentative HSQC assignment of **3.12b** (Figure 3.2). Strong COSY couplings for H5 to H6 but not H4 are consistent with H5 being *trans* to H4 and *cis* to H6. This is indicative of **3.12b** having *S* stereochemistry at C5. Overall, strong evidence is provided by the HSQC and COSY that the **3.12b** is a fluorinated azepane very much analogous to **3.12a** and likely the diastereomer of **3.12a**. However, a conclusive structural assignment of the purified molecule will be required in future along with additional experiments such as HMBC, H2BC, and NOESY to fully secure this structural assignment.

Additional strong evidence for the formation of **3.12b** is by low-resolution MS by ESI. A sample of **3.12b** treated with TFA yielded a molecular mass of 394 Da, consistent with the Boc-

deprotected species. The fact that Boc de-protection via TFA was required to ionize this compound using ESI-MS confirms that this molecule is Boc protected. Analysis by TLC also confirmed the presence of the Boc group as the R_f of the product was reduced to baseline upon Boc removal by TFA.

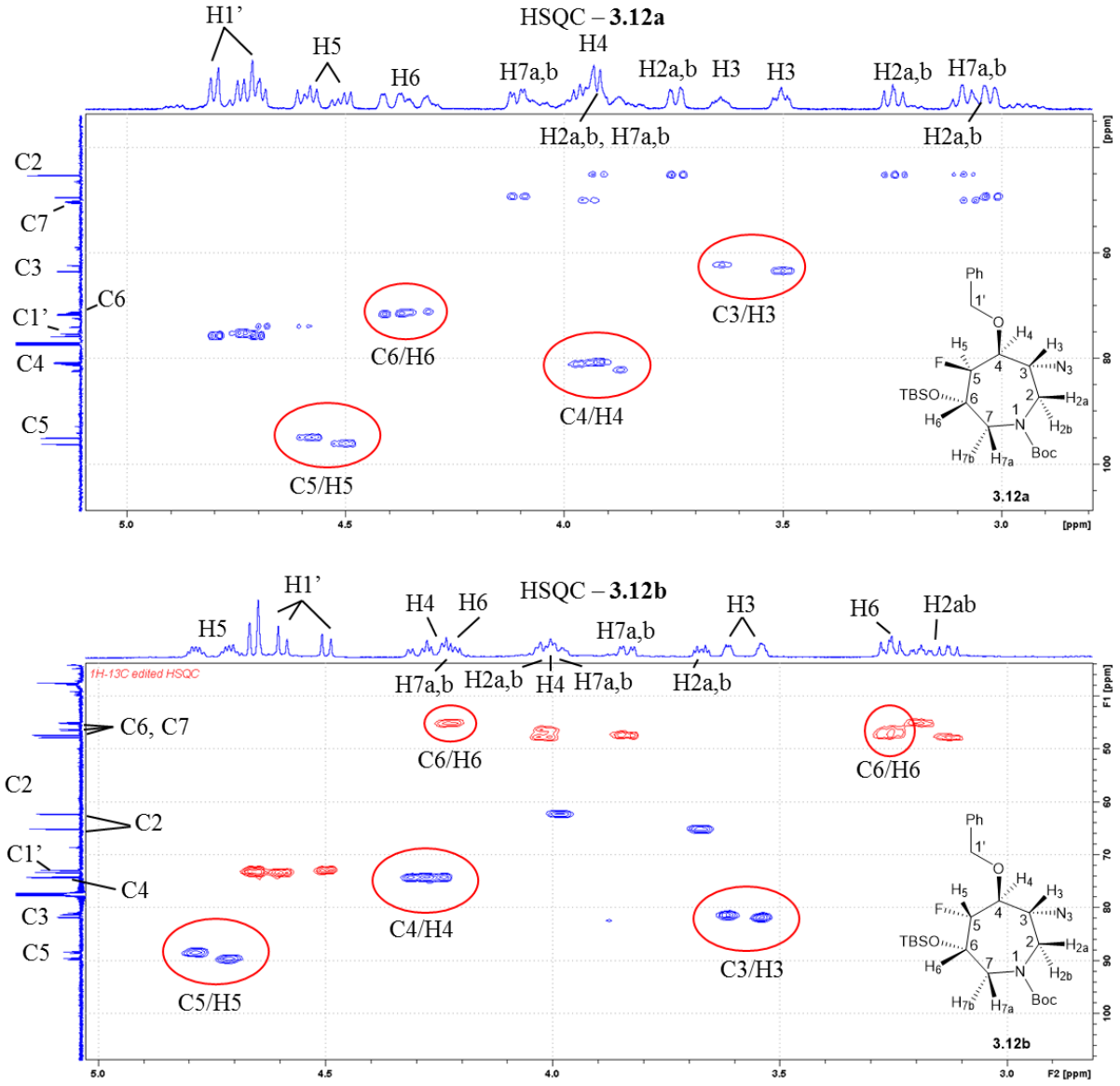


Figure 3.1: Comparison of HSQC NMR spectra of monofluorinated azepanes **3.12a** and **3.12b** with key assignments and differences highlighted.

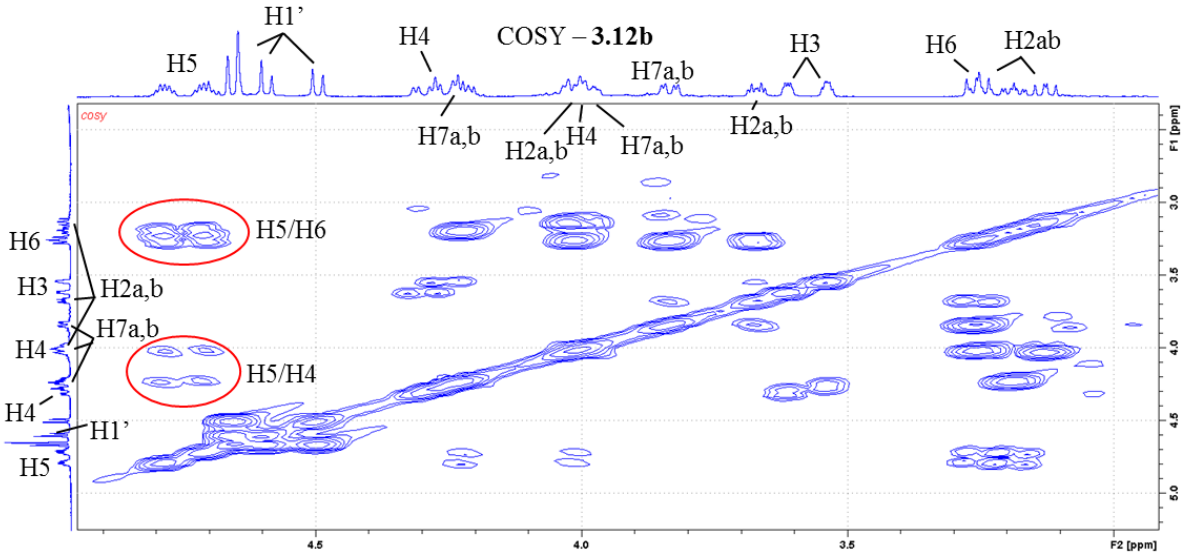


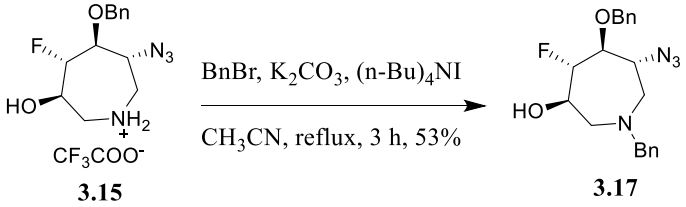
Figure 3.2: COSY spectrum of compound **3.12b**.

Mechanistically, the formation monofluoro azepane **12b** must involve N-Boc group participation at C5 to form likely a four-membered azetidinium intermediate as was discussed previously (Scheme 3.5). The exclusive formation of **12b** over **12a** under very similar conditions is peculiar and warrants further investigation in the future.

Finally, reactions conducted under conditions III involving mild and dilute conditions resulted in the complete conversion of material, albeit to a complex mixture of polar degradation products. Analysis of the non-polar mixture of compounds indicated at least one type of azepane compound was present, however it was not fluorinated due to the lack of characteristic C-F coupling by ^{13}C NMR spectroscopy. Unfortunately, these compounds were unable to be resolved by flash column chromatography for further analysis.

Overall, this investigation highlighted the complexity and highly condition dependent nature of stereoselective fluorination on constrained N-heterocycles such as azepanes. This investigation also highlighted the sensitivity of the N-Boc and TBS groups under deoxyfluorination conditions. Future work will involve the presence of a sterically hindered base such as Hünig's base to trap acidic protons and preserve the Boc group during deoxyfluorination. In addition alternative protecting groups will be explored which are more inert towards nucleophilic fluoride in order to improve reaction yields and prevent side-reactions. Although optimization was unsuccessful in this instance the formation of **3.12b** is a welcome surprise as it presents a new opportunity for investigating the case of azepane vicinal fluorination with potential C5-F bond epimerisation.

3.4 Synthesis of N-Benzyl Fluorohydrin 3.17



Scheme 3.7: Synthesis of **3.17**. *Reagents and conditions:* (a) BnBr, K_2CO_3, $(n\text{-}Bu)_4NI$, acetonitrile, reflux, 3 h, 53 %.

To test the effect of an electron rich nitrogen in deoxyfluorination of C5-F/C6-OH fluorohydrin azepane, N-benzyl fluorohydrin **3.17** was synthesized under un-optimized conditions in relatively moderate yield from **3.15** (not prepared in this work but from a prior batch).[11] The solution structure of **3.17** was characterized by 2D NMR spectroscopy with the HSQC and COSY spectra shown in Figure 3.3. Characteristic HSQC crosspeaks for compound **3.17** include the fluorinated C5-H5 crosspeak with C5 occurring as a doublet at 98.0 ppm (J_{CF} = 176.3 Hz) and H5 as a doublet of triplets at 4.71 ppm ($^2J_{HF}$ = 47.4 Hz, $^3J_{HH}$ = 6.1Hz). Methylene cross peaks are also clearly visible including the O-Benzyl benzylic carbon (C1') at 74.9 ppm and the benzylic protons (H1') as a doublet of doublets at 4.77 ppm (J = 55.2 Hz, 10.9 Hz). The crosspeak for the newly installed N-benzyl group was also clear with the benzylic carbon (C1") occurring at 63.7 ppm and the benzylic protons (H1") occurring as a singlet at 3.70 ppm. The HSQC assignment was confirmed by a COSY experiment (Figure 3.3). Strong COSY crosspeaks were observed between H5 and its vicinal H3 and H4 protons. Proton H6 displays strong coupling to H5 and H7a,b, while methylenes H7a,b and H2a,b show strong couplings to H6 and H3, respectively.

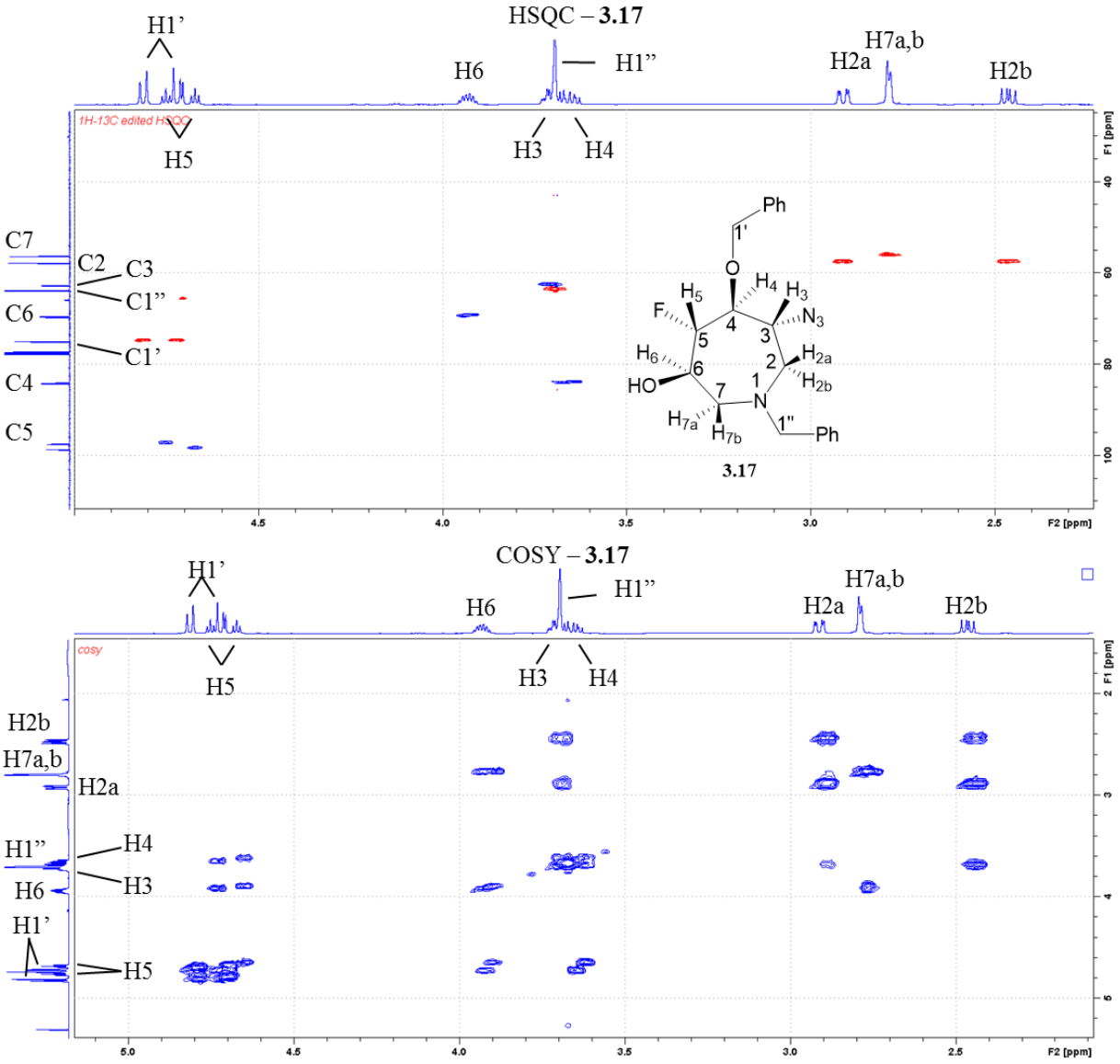
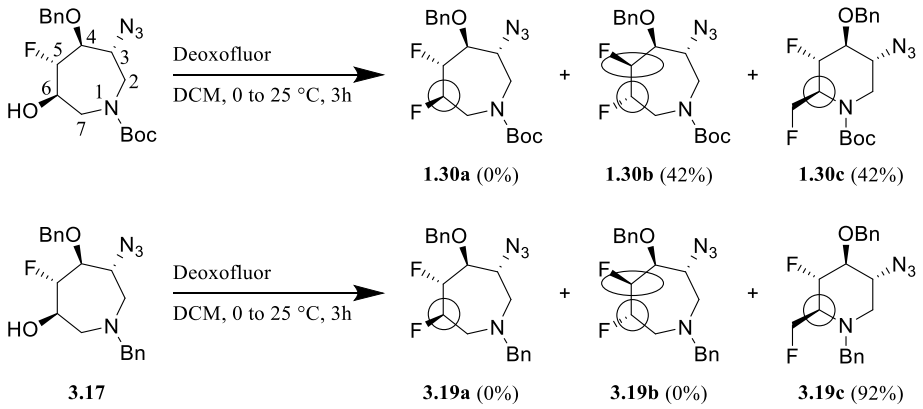


Figure 3.3: HSQC and NOESY spectra of N-benzyl fluorohydrin **3.17**.

3.5 Deoxyfluorination of 3.17

Vicinal fluorination of N-benzyl protected azepane **3.17** resulted in exclusive formation of the piperidine product **3.19c** (Scheme 3.8) with azepane **3.19a** (retention of C6 stereochemistry) and azepane **3.19b** (C5-F epimerisation) not observed at all by NMR and TLC analysis.



Scheme 3.8: Concise summary of vicinal fluorination experiments.

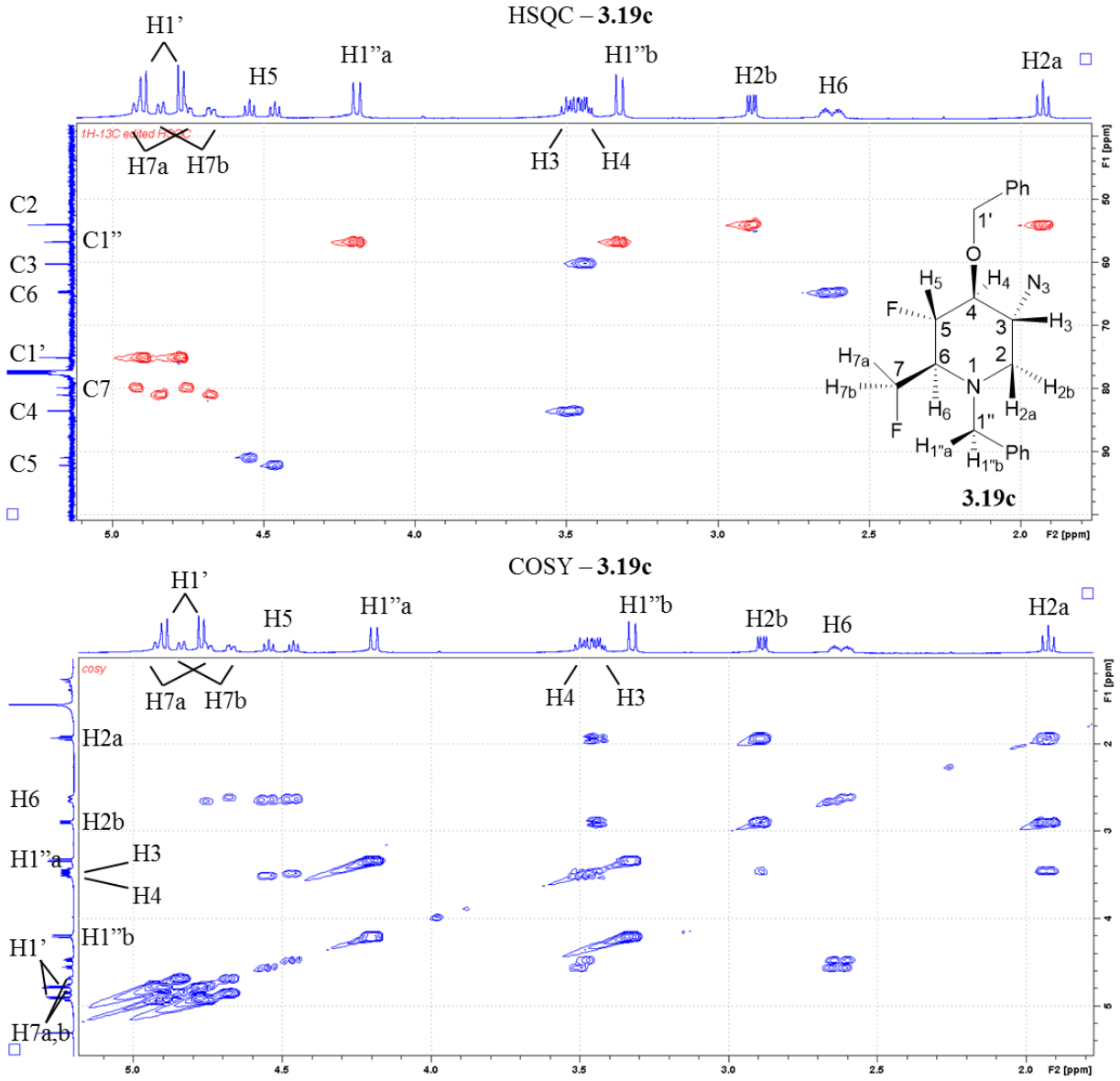


Figure 3.4: Annotated HSQC and COSY spectra of **3.19c**.

The solution structure of **3.19c** was confirmed by two-dimensional NMR spectroscopy with the HSQC and COSY spectra shown in Figure 3.4. Characteristic HSQC crosspeaks include the C7/H7a,b cross peak with a doublet carbon signal at 80.4 ppm ($^{1}J_{CF}$ = 173.8 Hz) and a complex set of multiplets for H7a at 4.87 ppm ($^{2}J_{HF}$ = 48.1 Hz, $^{2}J_{HH}$ = 11.0 Hz) and H7b at 4.83 ppm ($^{2}J_{HF}$ = 46.1 Hz, $^{2}J_{HH}$ = 11.0 Hz). The second fluorinated site is also clearly visible as the C5/H5 crosspeak with a doublet carbon signal of 91.5 ppm ($^{1}J_{CF}$ = 180.0 Hz) and proton signals as doublets of doublets of doublets at 4.50 ppm ($^{2}J_{HF}$ = 50.0 Hz, $^{3}J_{HH}$ = 9.6 Hz, 8.2 Hz). The $^{3}J_{HH}$ value found for H5 is indicative of this proton being *trans* to H4 and having the *S* configuration. A notable feature of the HSQC spectrum is the wide separation between the N-benzylic proton peaks. The N-benzylic carbon signal (C1") occurs at 60.2 ppm, however the corresponding protons H1"a and H1"b are separated by 3.32 ppm indicative of complex

through-bond deshielding effects at this prochiral centre by the ring fluorine atoms. Confirmation of the HSQC assignments was again performed using the COSY spectrum (Figure 3.4). Strong COSY couplings are visible between H4 and H5 and H6. Couplings are also visible between protons sharing prochiral methylene centres including crosspeaks between H2a and b, H7a and b, H1' a and b, and H1" a and b.

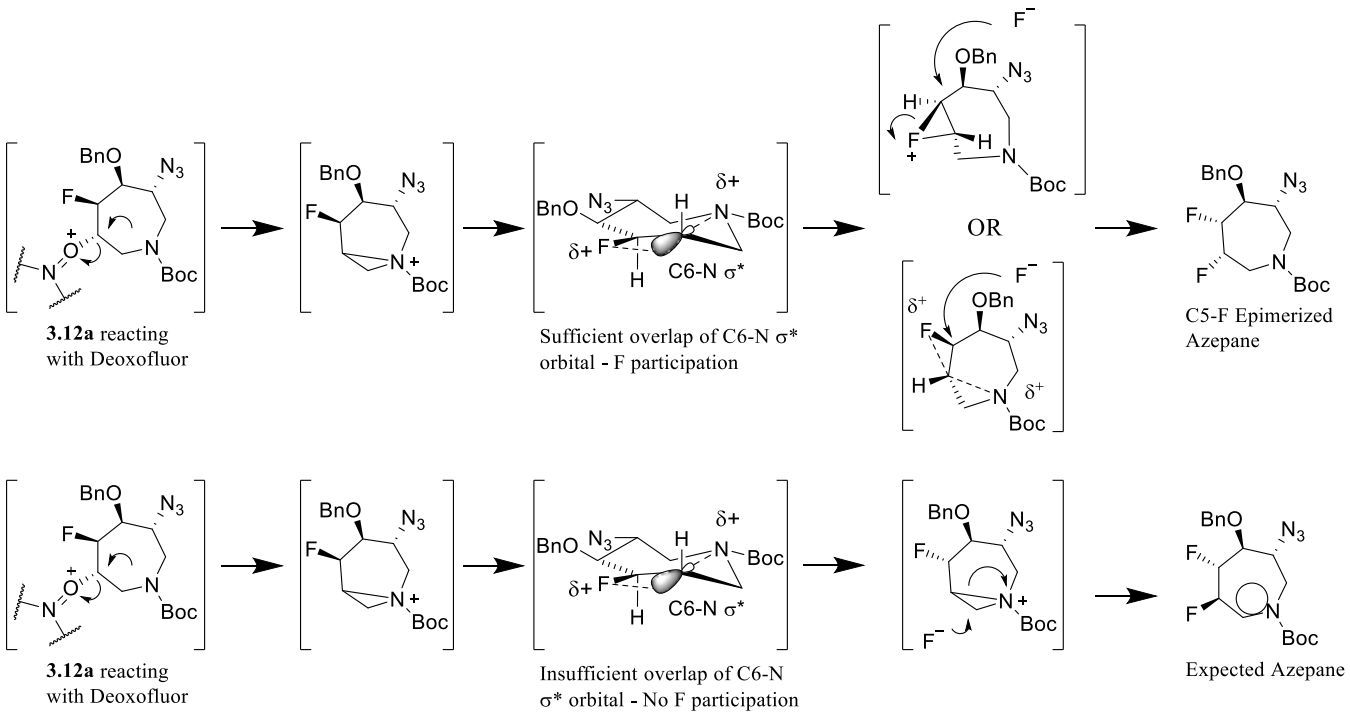
Vicinal fluorination of N-benzylated substrate **3.17** proceeded fast (3 hours) and in near quantitative yield of the piperidine product **3.19c** (Scheme 3.8). This provides a stark contrast to the vicinal fluorination outcomes in the cases of the N-Boc and N-tosyl protected azepanes (see the introduction section 1.3.2) in which the reaction proceeded over 8 hours and yielded mixtures of azepanes and piperidines. This suggests that neighbouring group participation by the heterocyclic nitrogen must occur and confirms that reaction outcomes are sensitive to the electron density of the nitrogen. It is also likely that the enhanced rate of reaction in the case of the N-benzylated substrate **3.17** is due to the increase in electron density on the nitrogen atom. The fact that this reaction proceeded very rapidly and in high yield in the presence of a basic heterocyclic nitrogen suggests that the use of base may be needed in deoxyfluorination to prevent acid catalyzed decomposition as was speculated previously.

3.6 Conclusion and Future Directions

Investigation of the deoxyfluorination of N-benzylated fluorohydrin **3.17** presents important evidence for the crucial role of nitrogen in initiating a cascade neighbouring group effect. In contrast to the cases with N-Boc and N-Tosyl protection, the N-Benzyl group increases the electron density of the nitrogen atom and is expected to favour formation of the simple aziridinium, leading to the exclusive formation of the piperidine product while bypassing the C5-F epimerisation. It also provides strong evidence that the formation of the complex aziridinium in the cases of N-Boc and N-tosyl protection is indeed dependent upon the stability of the aziridinium C6-N bond. Further computational work will be required to help characterize this unusual aziridinium with fluorine participation.

Serendipitously, monofluorinated azepane **3.12b** will potentially serve as a new and important substrate to explore our current hypothesis on azepane vicinal fluorination. As can be seen in Scheme 3.9 the C5-F stereochemistry (*S*) of **3.12b** may not allow fluorine to stabilize the adjacent electrophilic carbon centre during nitrogen participation. Studying the reaction outcomes of this reaction will provide a deeper understanding of the stereoelectronic subtleties

of the cascade neighbouring group effect leading to the C5-F epimerization product. This, in combination with additional computational work, will be the basis of future work to ascertain the precise nature of the complex aziridinium-fluoronium intermediate and their role in stereospecific deoxyfluorination.



Scheme 3.9: Proposed reaction outcomes for vicinal fluorination of **3.12b**.

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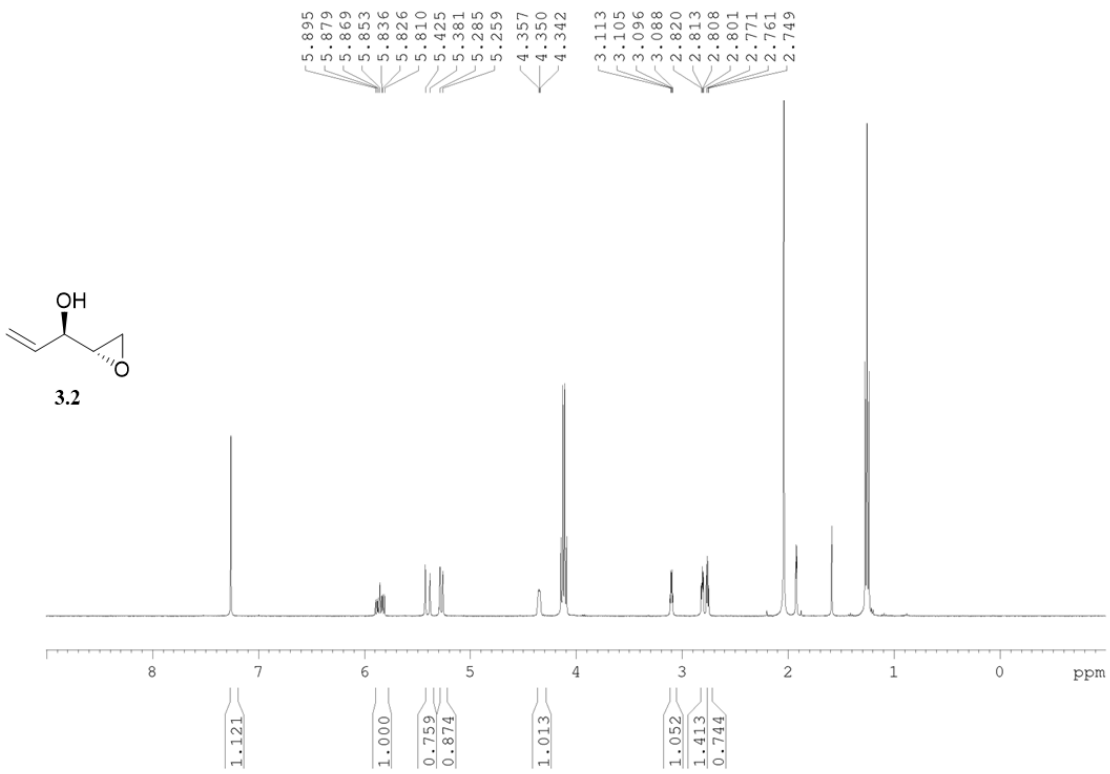
Appendices:

Table of Contents:

Appendix A:

Full NMR spectra of compounds discussed in Chapter 3

^{1}H-**3.2**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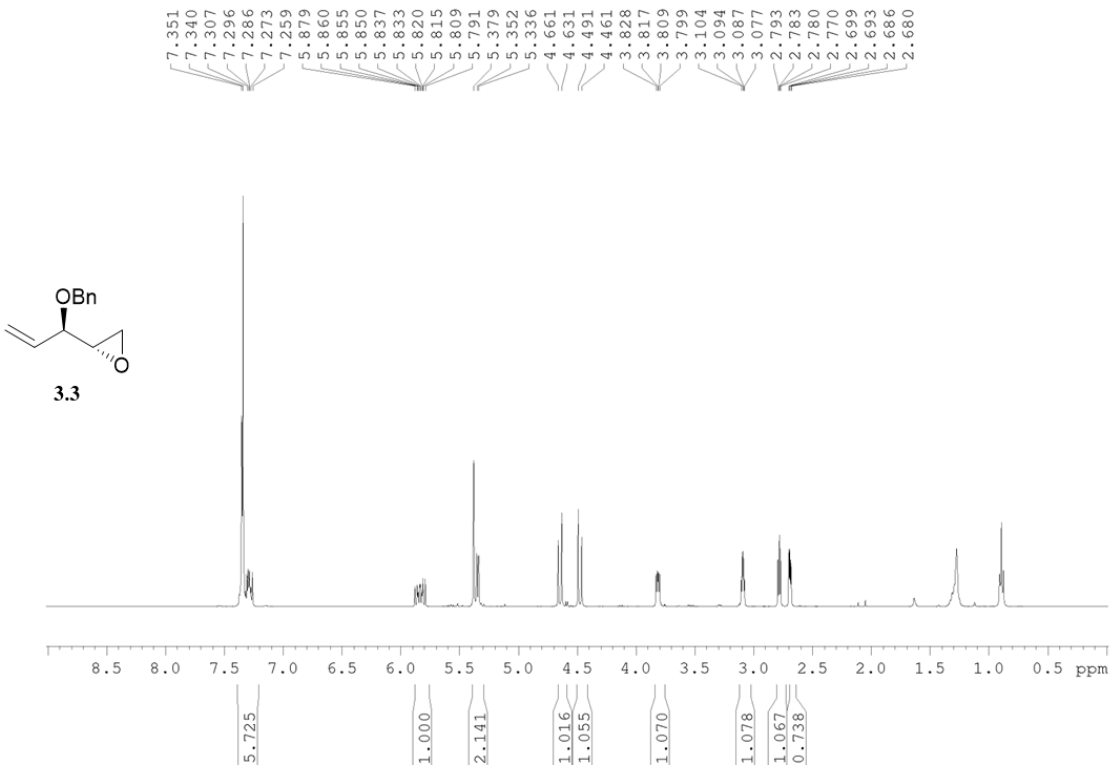
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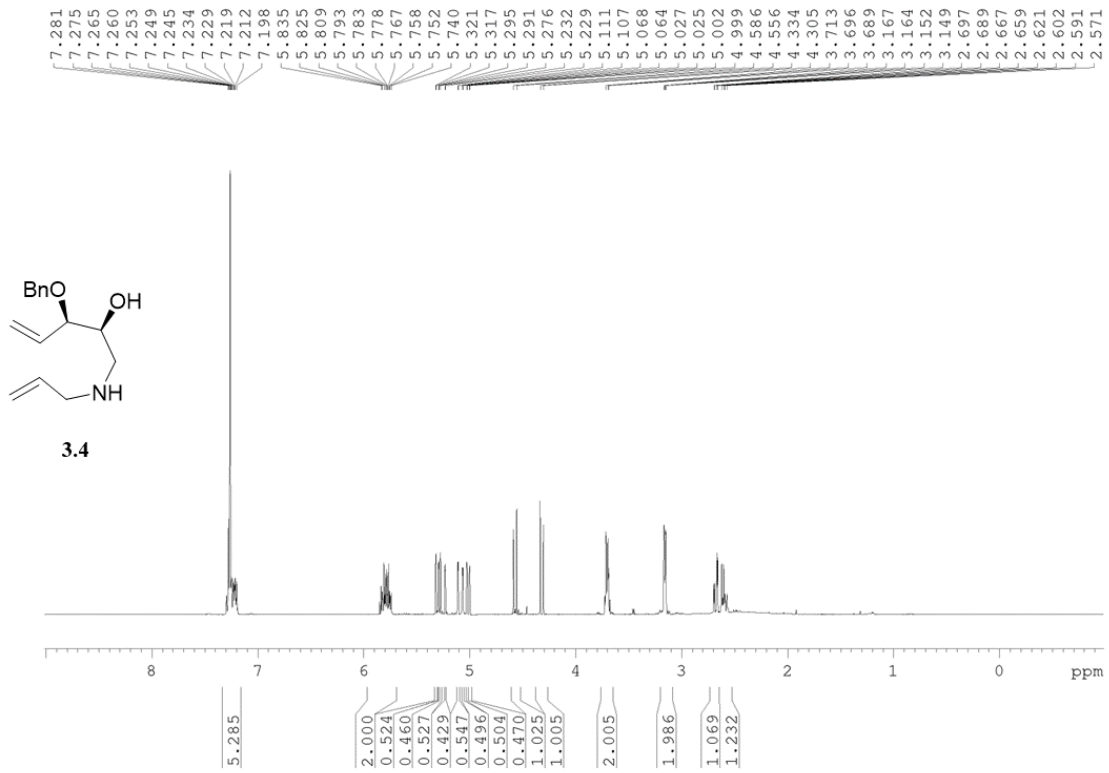
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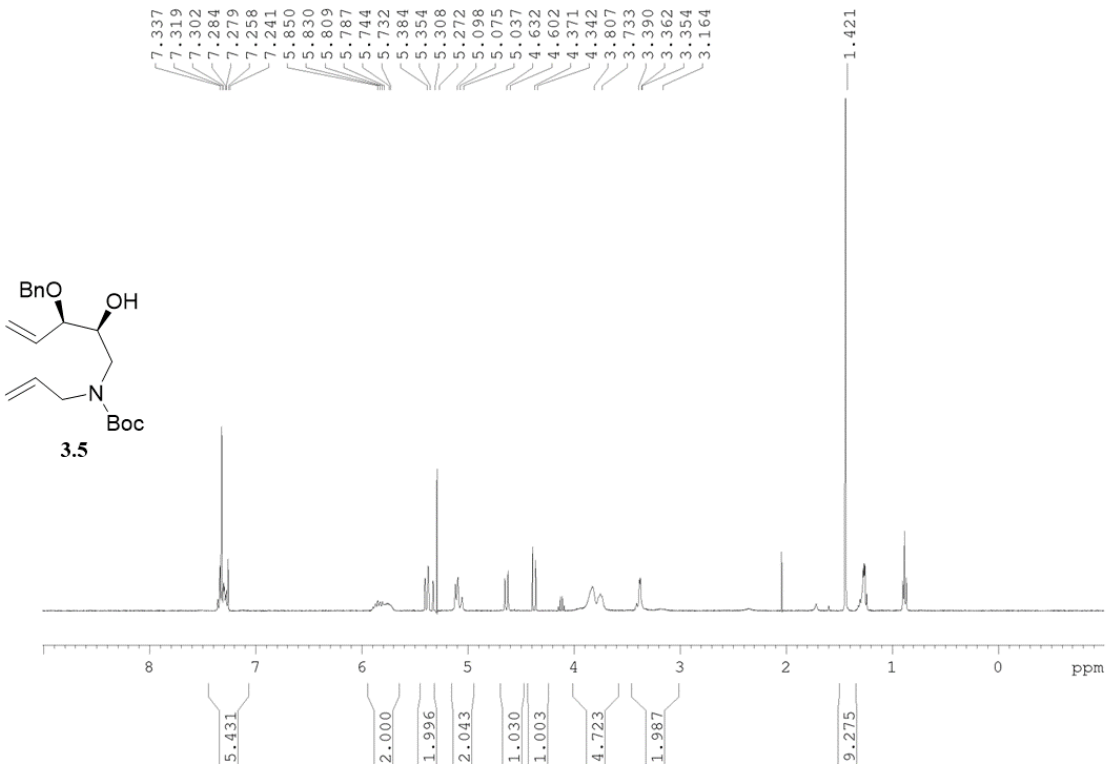
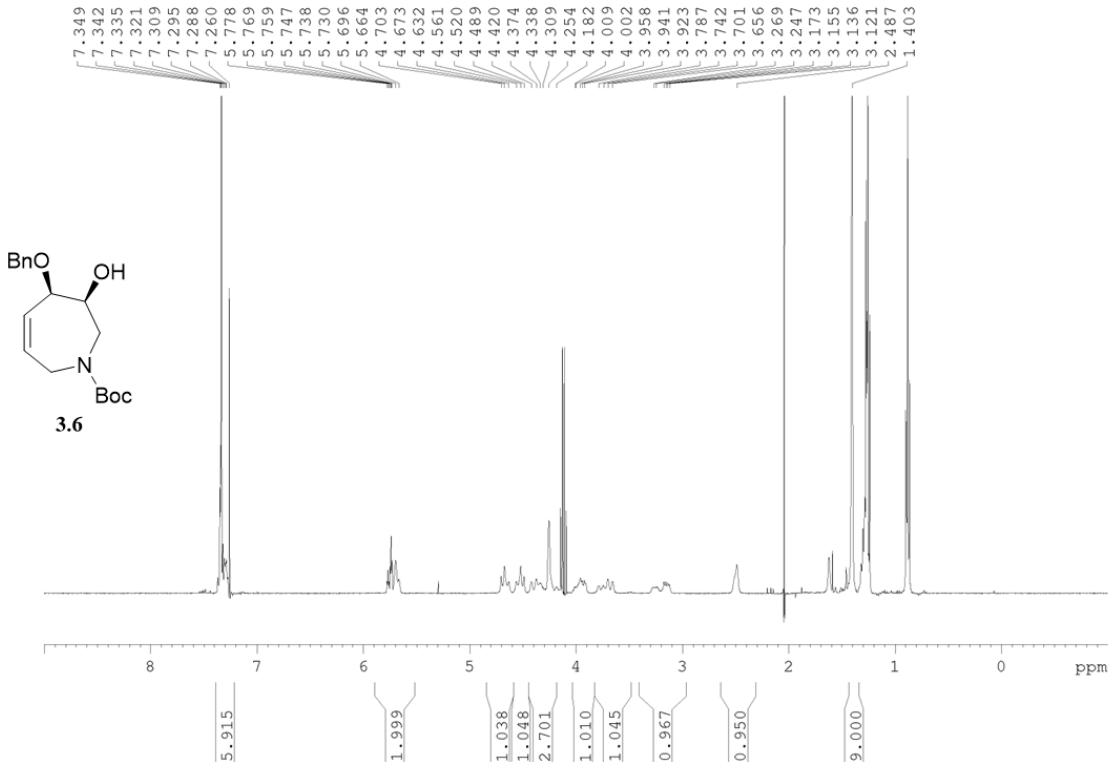
0.527
0.429
0.547
0.496
0.504
0.470
1.025
1.005
2.005
1.986
1.069
1.232

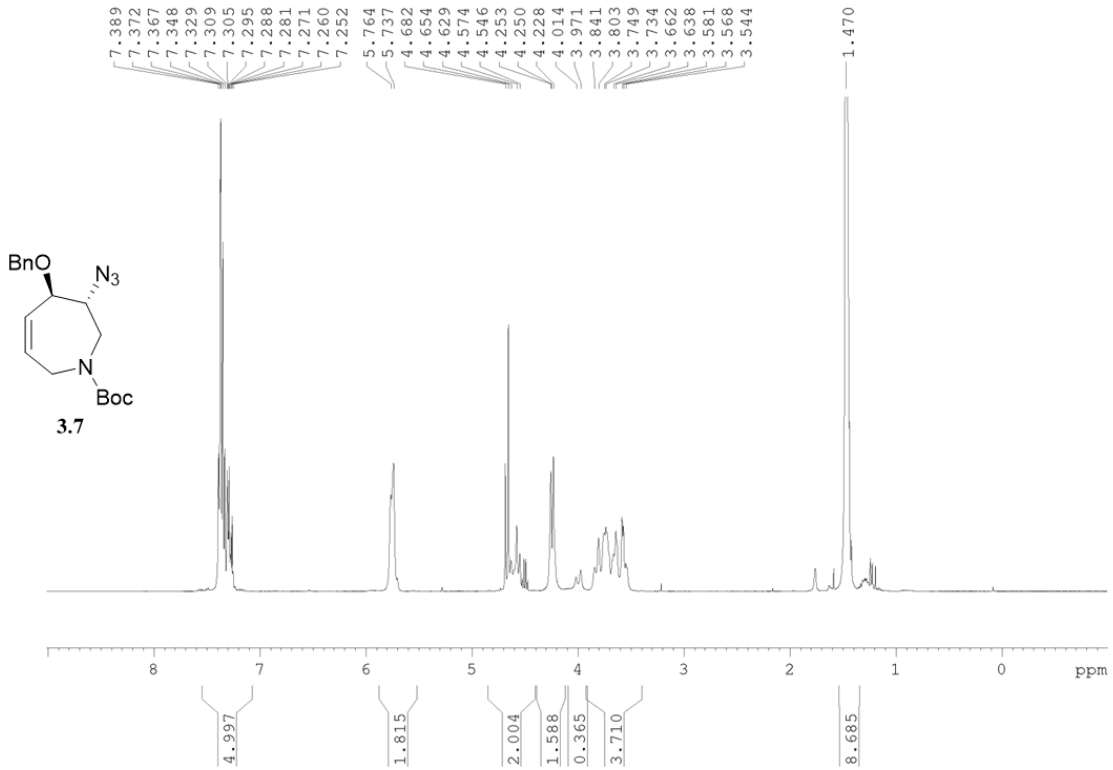
^{1}H-**3.5**


7.337
7.319
7.302
7.284
7.279
7.258
7.241
5.850
5.830
5.809
5.787
5.744
5.732
5.384
5.354
5.308
5.272
5.098
5.075
5.037
4.632
4.602
4.371
4.342
3.807
3.733
3.390
3.362
3.354
3.164
1.421
BnO
OH
N
Boc
3.5
ppm
5.431
2.000
1.996
2.043
1.030
1.003
4.723
1.987
9.275

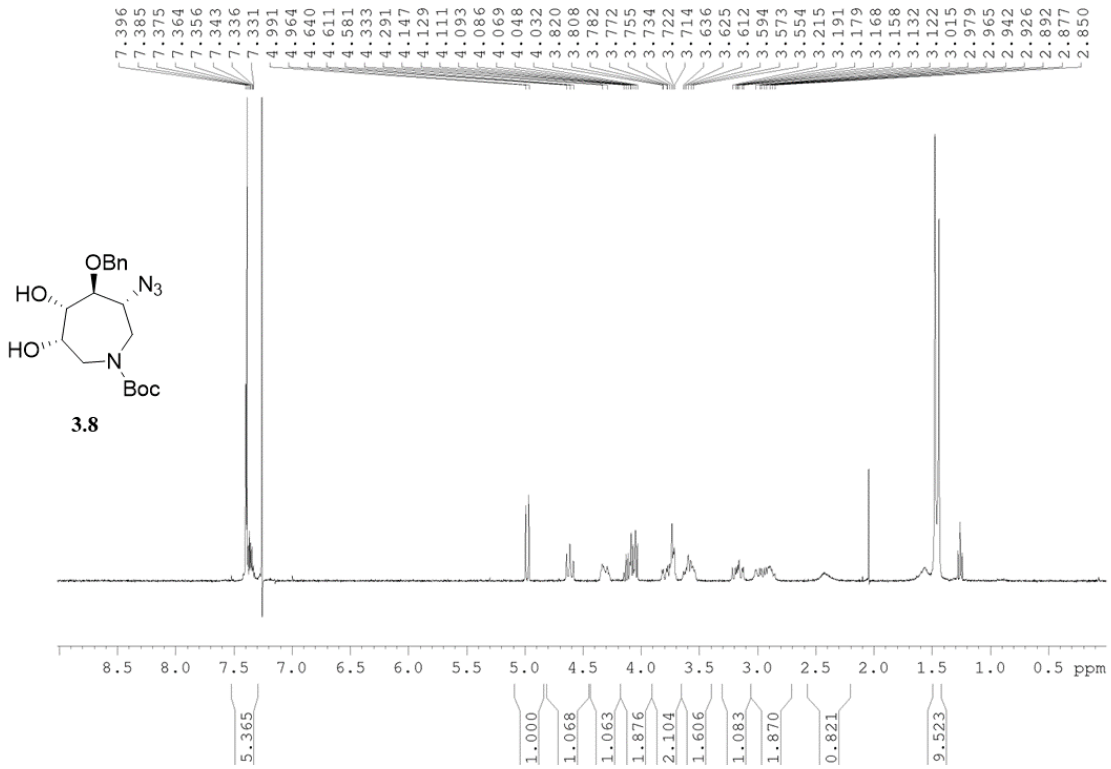
^{1}H-**3.6**


7.349
7.342
7.335
7.321
7.309
7.295
7.288
7.260
5.778
5.769
5.759
5.747
5.738
5.730
5.696
5.664
4.703
4.673
4.632
4.561
4.520
4.489
4.420
4.374
4.338
4.309
4.254
4.182
4.009
4.002
3.958
3.941
3.923
3.787
3.742
3.701
3.656
3.269
3.247
3.173
3.155
3.136
3.121
2.487
1.403
BnO
OH
N
Boc
3.6
8
7
6
5
4
3
2
1
0
ppm
5.915
1.999
1.038
1.048
2.701
1.010
1.045
0.967
0.950
9.000

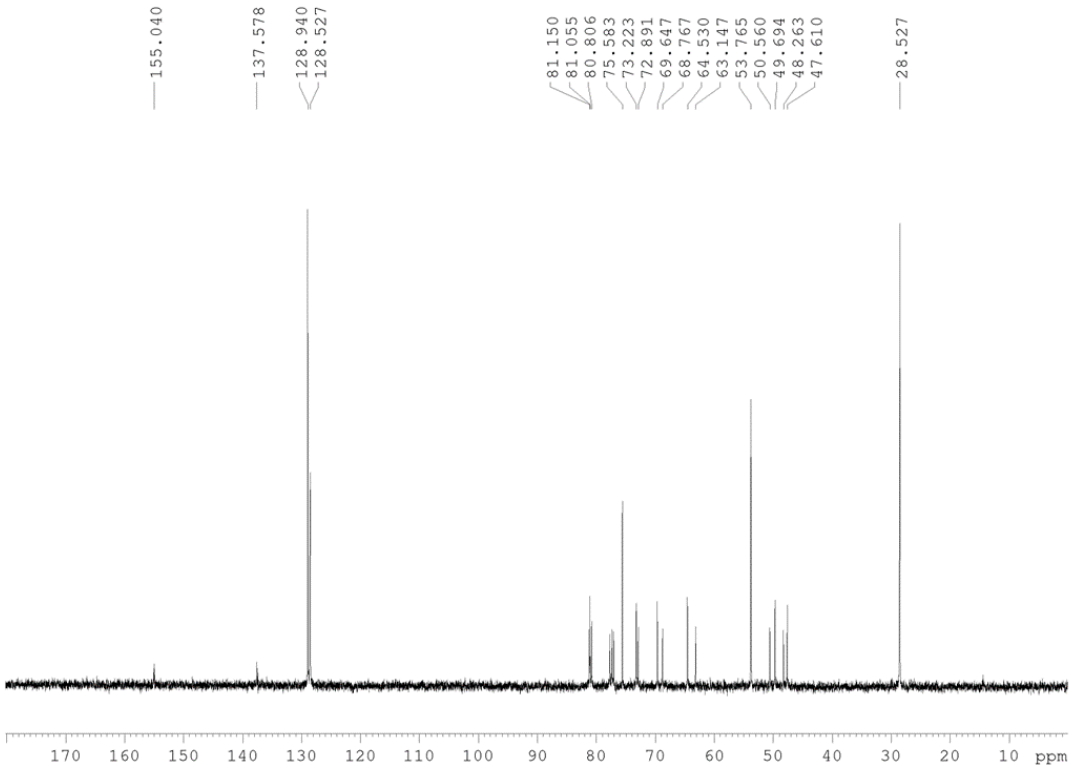
^{1}H-**3.7**


7.389
7.372
7.367
7.348
7.329
7.309
7.305
7.295
7.288
7.281
7.271
7.260
7.252
5.764
5.737
4.682
4.654
4.629
4.574
4.546
4.253
4.250
4.228
4.014
3.971
3.841
3.803
3.749
3.734
3.662
3.638
3.581
3.568
3.544
1.470
BnO
N3
N
Boc
3.7
8
7
6
5
4
3
2
1
0
ppm
4.997
1.815
2.004
1.588
0.365
3.710
8.685

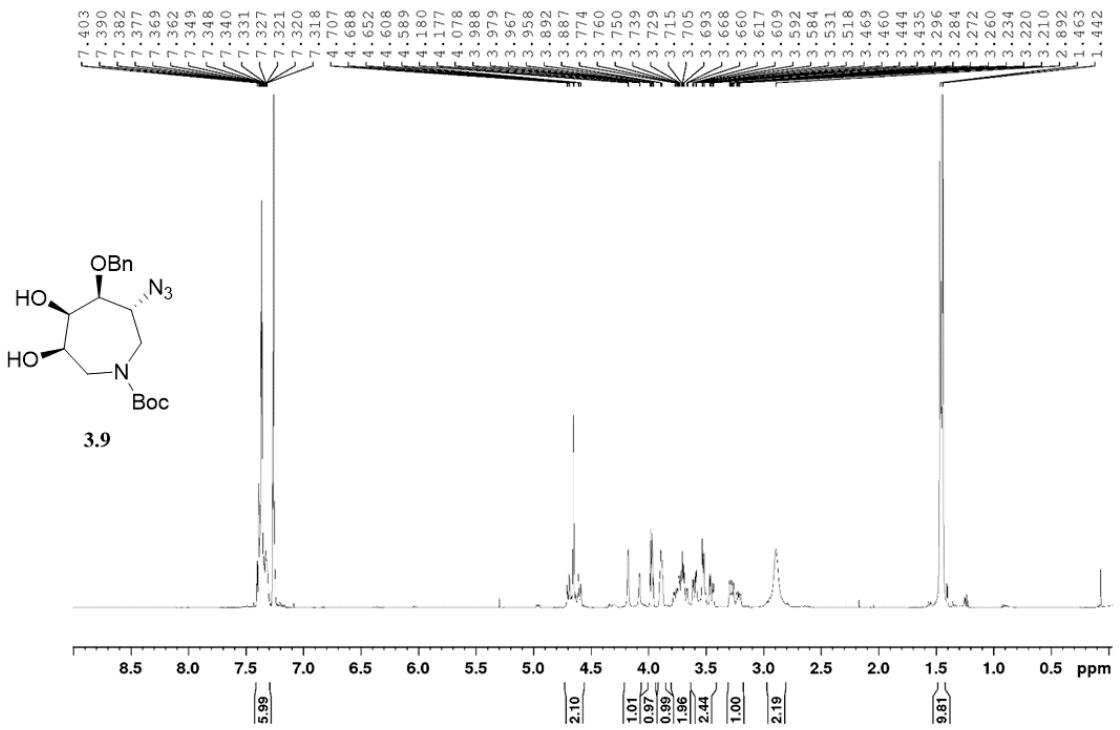
^{1}H-**3.8**


7.396
7.385
7.375
7.364
7.356
7.343
7.336
7.331
4.991
4.964
4.640
4.611
4.581
4.333
4.291
4.147
4.129
4.111
4.093
4.086
4.069
4.048
4.032
3.820
3.808
3.782
3.772
3.755
3.734
3.722
3.714
3.636
3.625
3.612
3.594
3.573
3.554
3.215
3.191
3.179
3.168
3.158
3.132
3.122
3.015
2.979
2.965
2.942
2.926
2.892
2.877
2.850
OBn
N3
HO
HO
N
Boc
3.8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.365
1.000
1.068
1.063
1.876
2.104
1.606
1.083
1.870
0.821
9.523

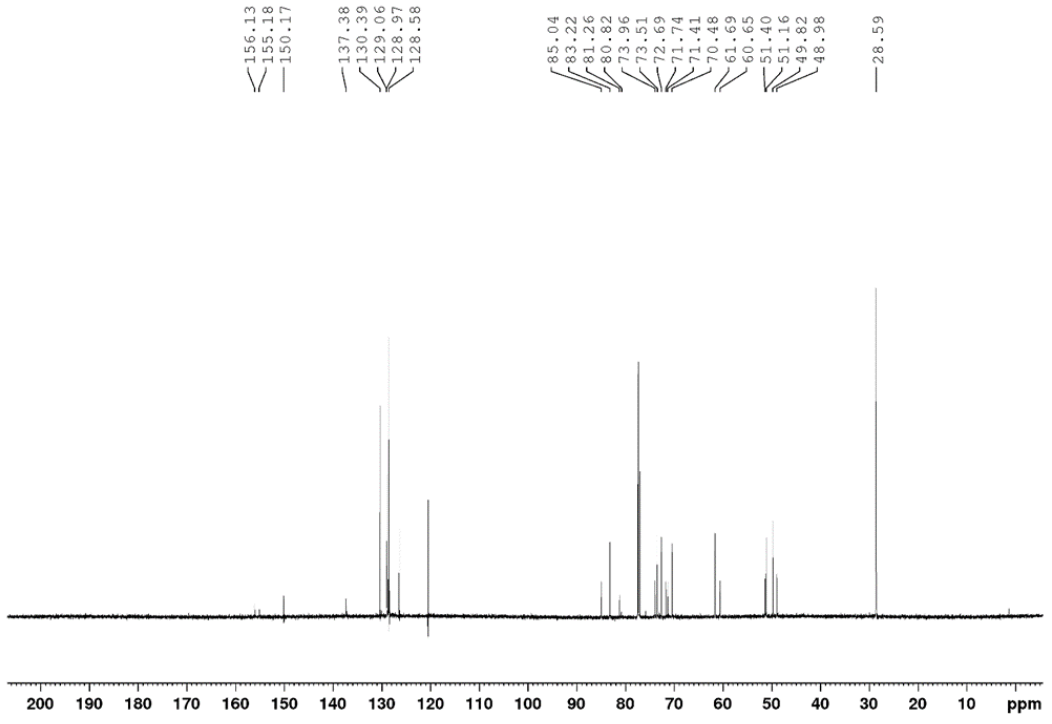
^{13}C-**3.8**


155.040
137.578
128.940
128.527
81.150
81.055
80.806
75.583
73.223
72.891
69.647
68.767
64.530
63.147
53.765
50.560
49.694
48.263
47.610
28.527
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

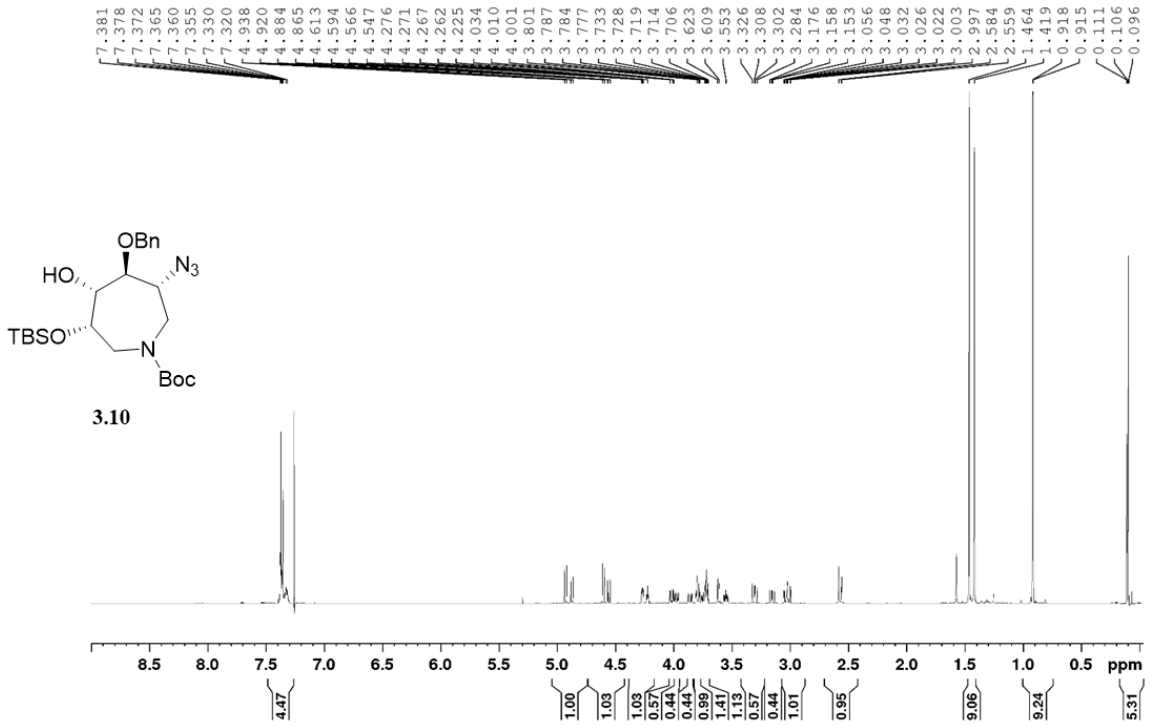
^{1}H-**3.9**


7.403
7.390
7.382
7.377
7.369
7.362
7.349
7.348
7.340
7.331
7.327
7.321
7.320
7.318
4.707
4.688
4.652
4.608
4.589
4.180
4.177
4.078
3.988
3.979
3.967
3.958
3.892
3.887
3.774
3.760
3.750
3.739
3.729
3.715
3.705
3.693
3.668
3.660
3.617
3.609
3.592
3.584
3.531
3.518
3.469
3.460
3.444
3.435
3.296
3.284
3.272
3.260
3.234
3.220
3.210
2.892
1.463
1.442
OBn
N3
HO
HO
N
Boc
3.9
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.99
2.10
1.01
0.97
0.99
1.96
2.44
1.00
2.19
9.81

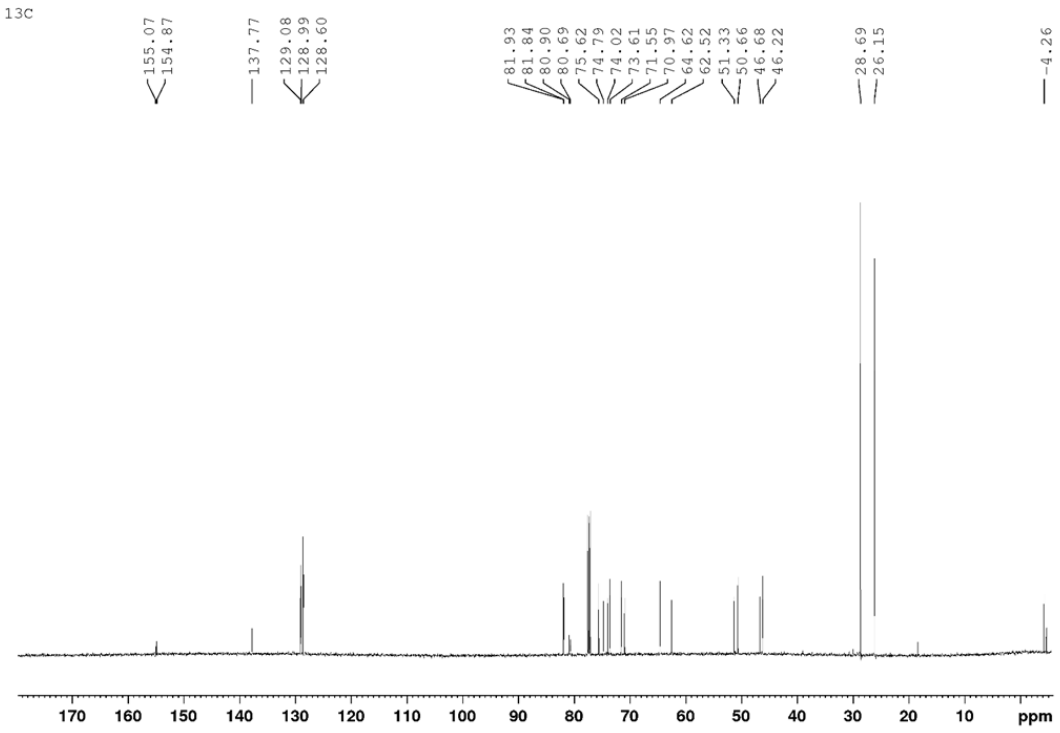
^{13}C-**3.9**


156.13
155.18
150.17
137.38
130.39
129.06
128.97
128.58
85.04
83.22
81.26
80.82
73.96
73.51
72.69
71.74
71.41
70.48
61.69
60.65
51.40
51.16
49.82
48.98
28.59
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

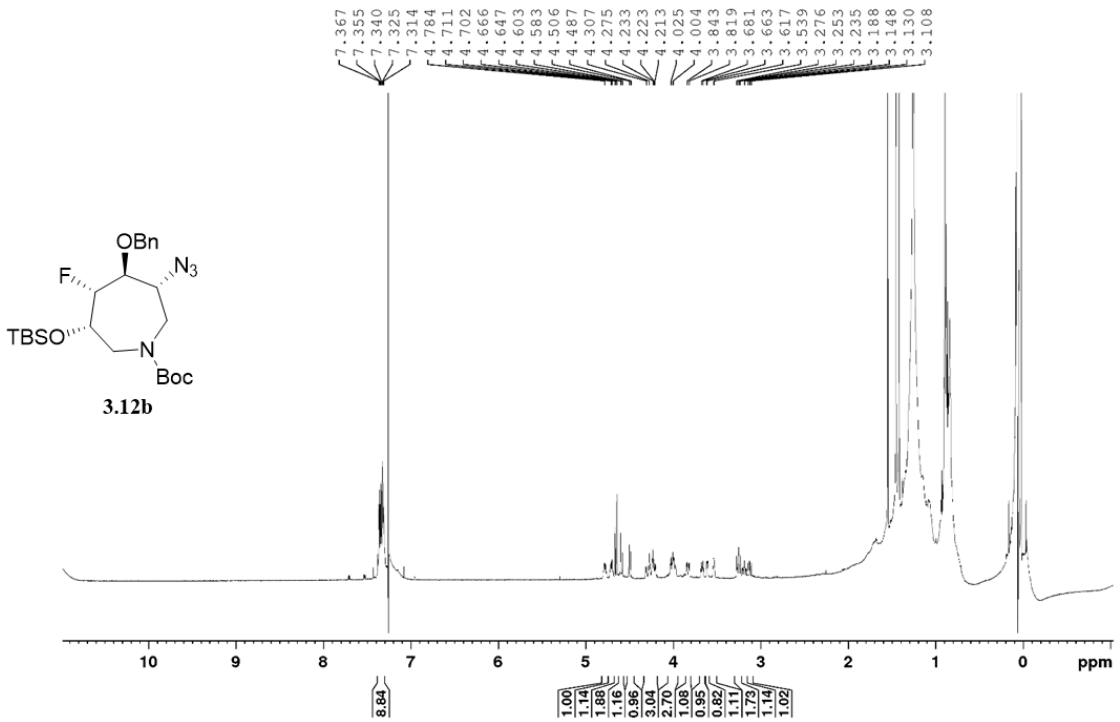
^{1}H-**3.10**



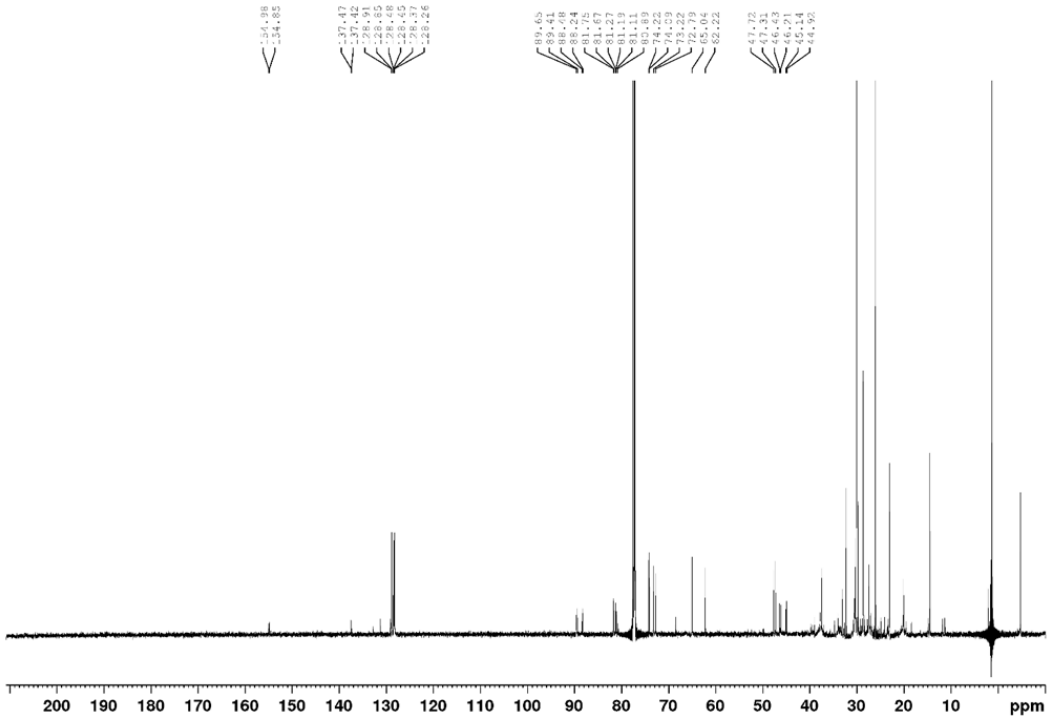
^{13}C-**3.10**

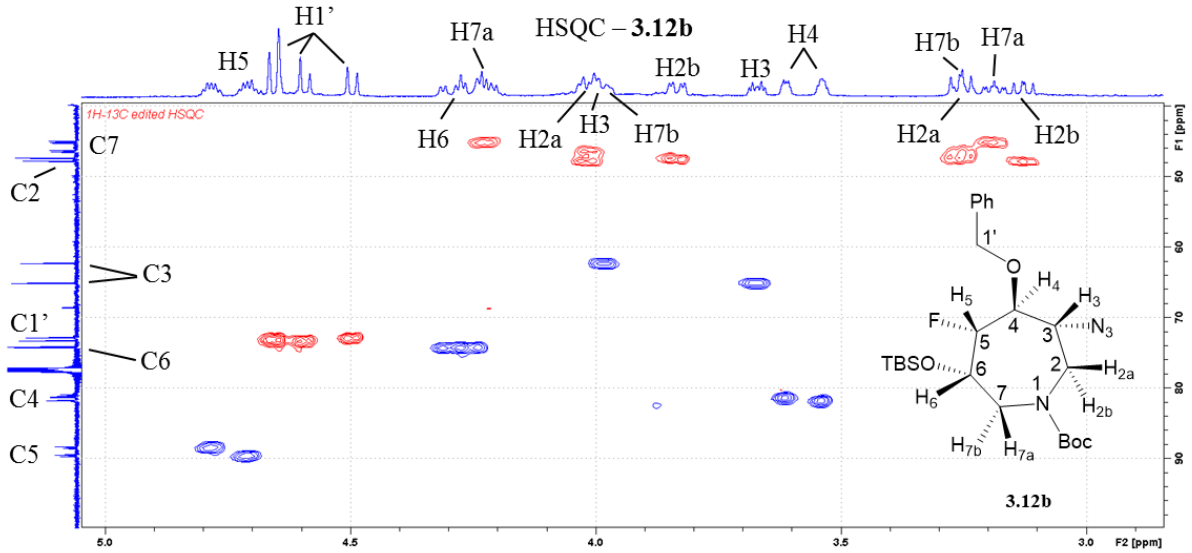


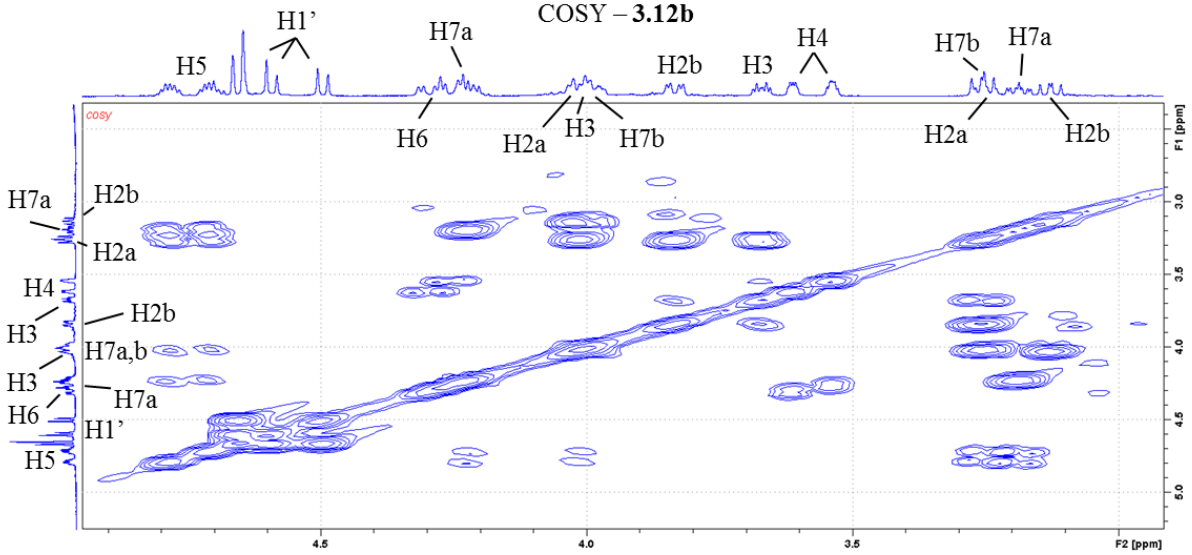
^{1}H-**3.12b**



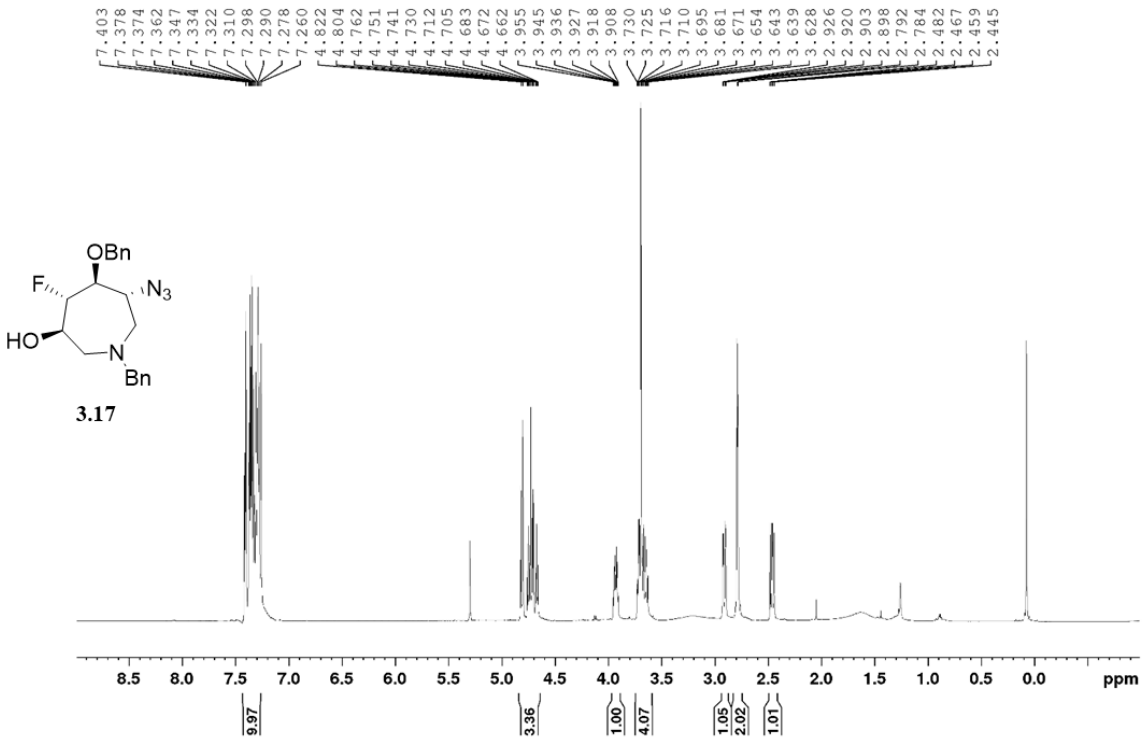
^{13}C-**3.12b**



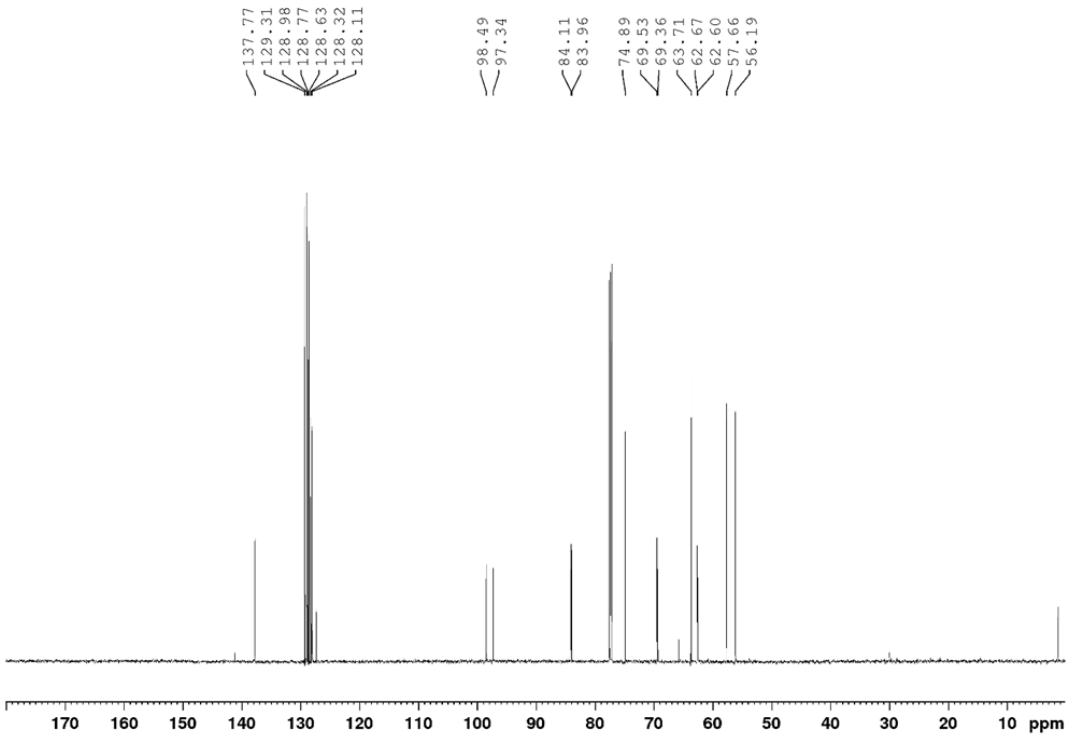

HSQC – 3.12b
H1'
H5
H7a
H6
H2a
H3
H7b
H2b
H4
H7b
H7a
H2a
H2b
1H-13C edited HSQC
C7
C2
C3
C1'
C6
C4
C5
Ph
1'
O
H4
H5
H3
F
4
3
N3
5
TBSO
6
2
H2a
H6
7
1
N
H2b
H7b
H7a
Boc
3.12b
F1 [ppm]
F2 [ppm]

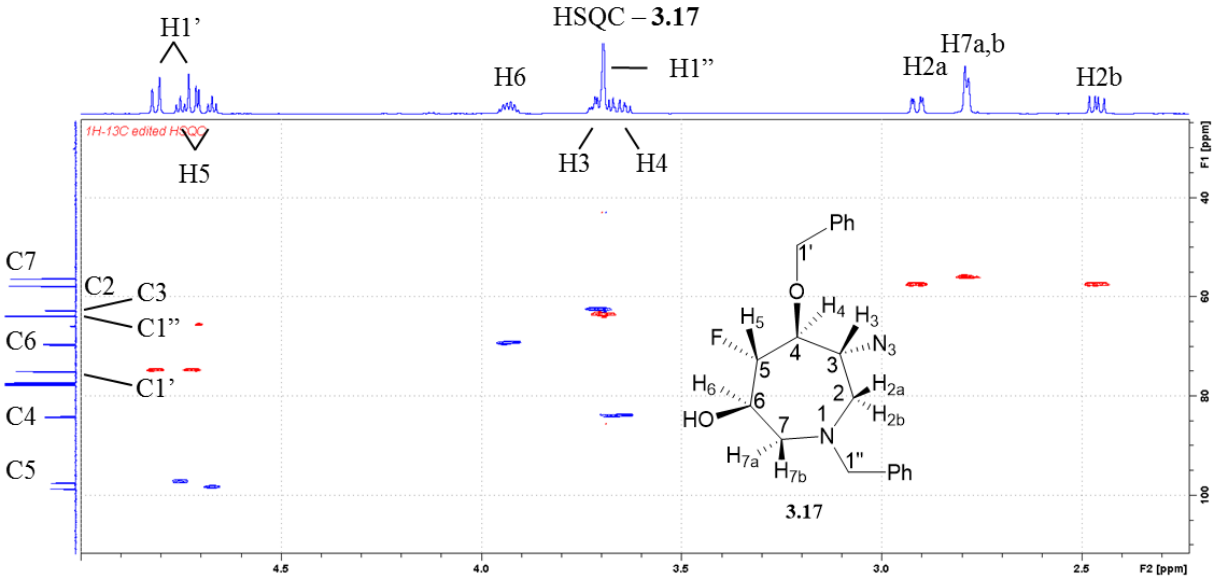

COSY – 3.12b
H1'
H5
H7a
H6
H2a
H3
H7b
H2b
H4
H7b
H7a
H2a
H2b
cosy
H7a
H2b
H2a
H4
H3
H2b
H7a,b
H3
H7a
H6
H1'
H5
F1 [ppm]
F2 [ppm]

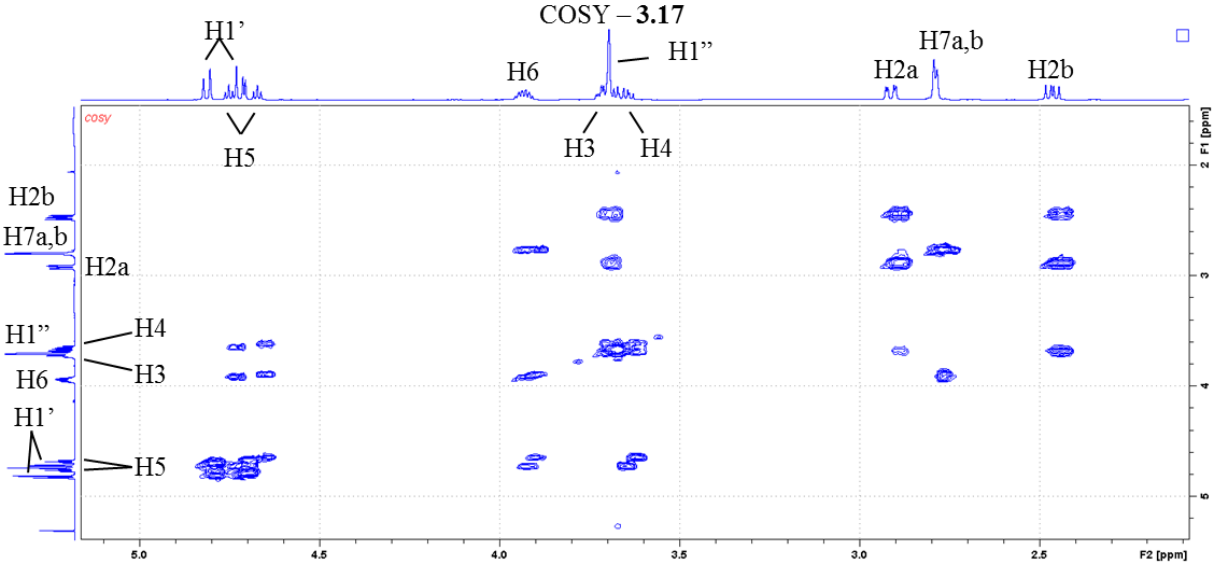
^{1}H-**3.17**



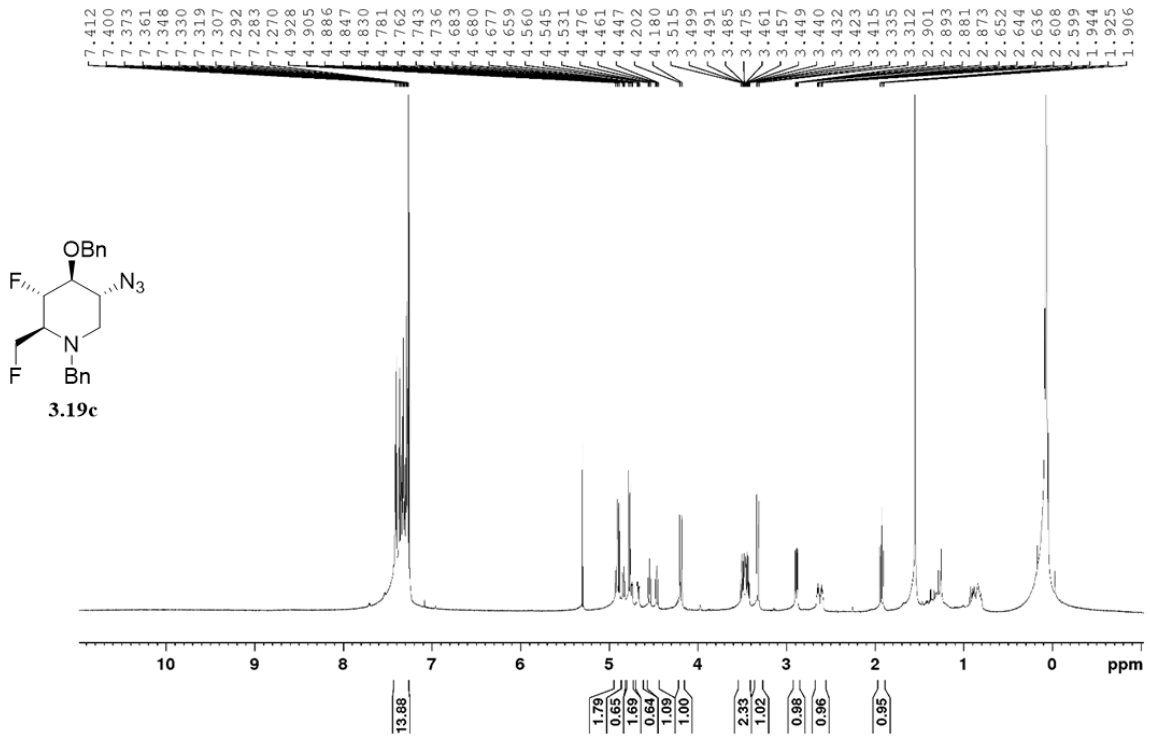
^{13}C-**3.17**



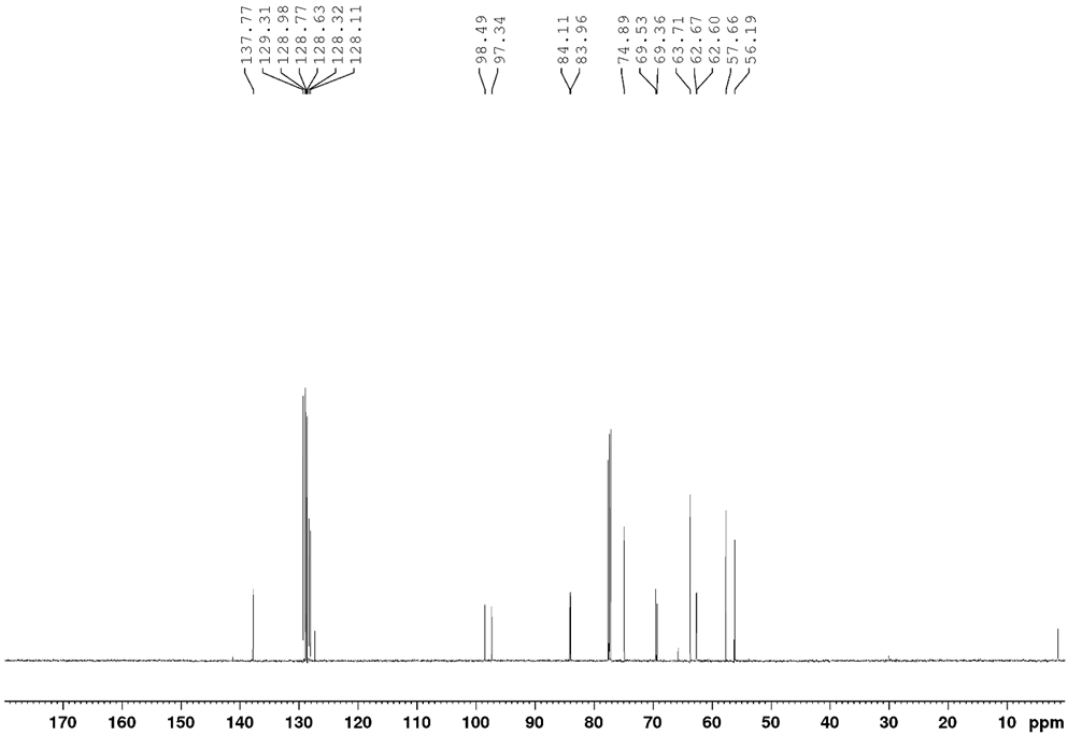

HSQC – 3.17
H1'
H6
H1"
H7a,b
H2a
H2b
H5
H3
H4
C7
C2
C3
C1"
C6
C1'
C4
C5
Ph
1'
O
H4
H3
H5
F
N3
4
5
3
2
H6
H2a
6
1
HO
7
N
H2b
H7a
H7b
1"
Ph
3.17
F2 [ppm]
F1 [ppm]

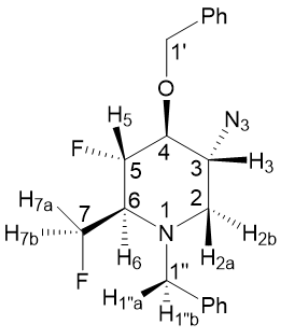

COSY – 3.17
H1'
H6
H1"
H7a,b
H2a
H2b
H5
H3
H4
H2b
H7a,b
H2a
H1"
H4
H3
H6
H1'
H5
F2 [ppm]
F1 [ppm]

^{1}H-**3.19c**



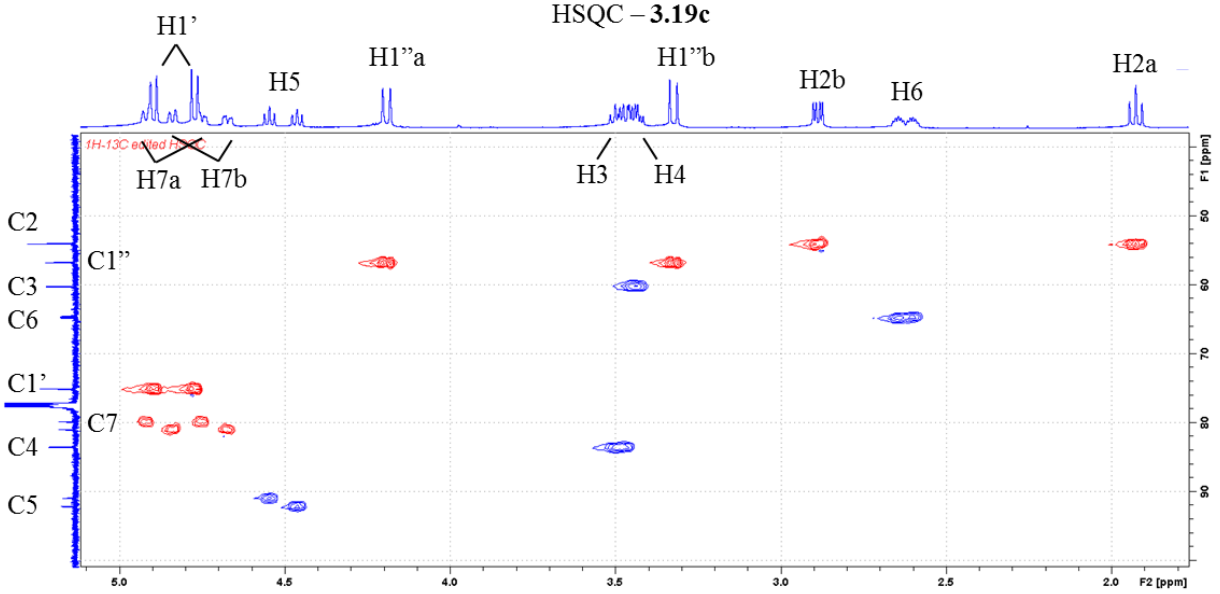
^{13}C-**3.19c**



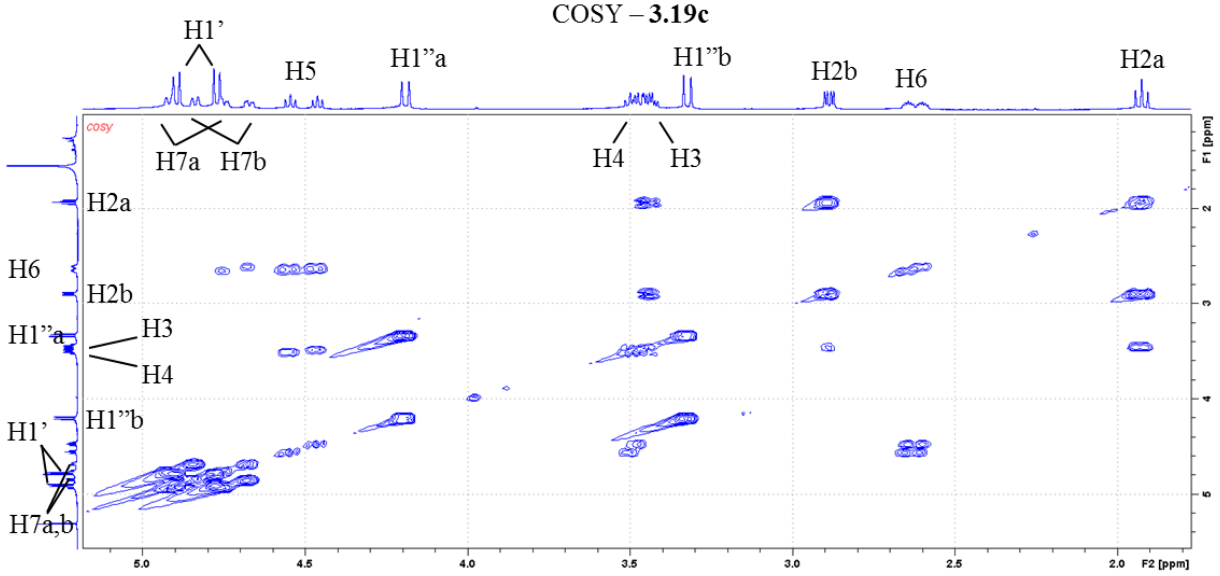


3.19c

HSQC – **3.19c**

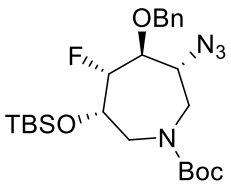


COSY – **3.19c**

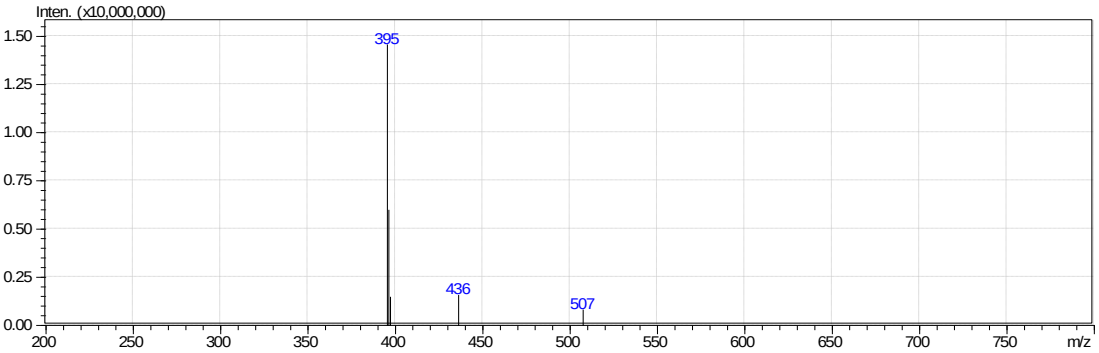


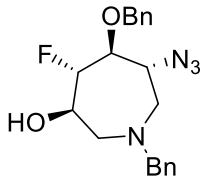
Appendix B:

Low-Resolution Mass Spectra of Compounds **3.12b**, **3.17** and **3.19c**.

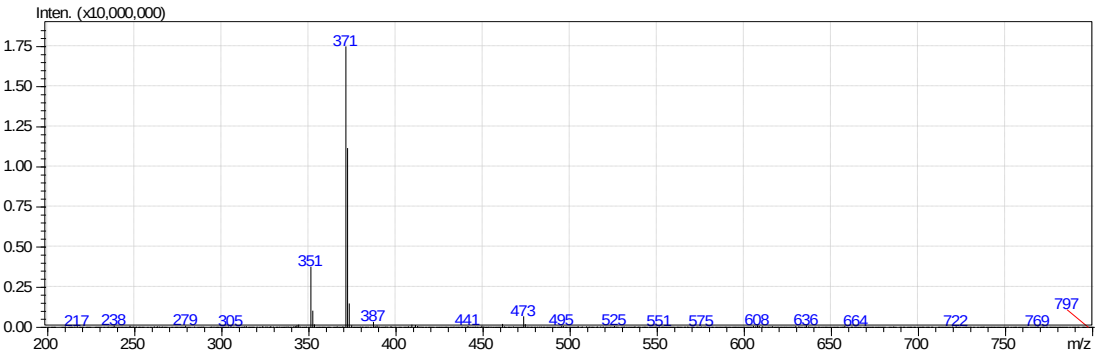


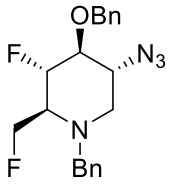
3.12b





3.16





3.17c