Development of methods for the synthesis of natural product-like macrocycles

Mark John Laurence Dow

Submitted in accordance with the requirements for the degree of a PhD

The University of Leeds

School of Chemistry

September, 2012

The candidate confirms that the work submitted is his ownand that appropriate credit has been given where reference has been made to the work of others

Acknowledgements

There are numerous people that I am hugely grateful to for their support and help throughout my PhD degree. First and foremost, I would like to my supervisors Prof. Adam Nelson and Dr. Stuart Warriner. They have been a constant source of ideas, un-thinkable amount of knowledge and expertise (not just chemistry!); but also enthusiasm and support. I would also like to thank Luis-Manuel Vaz my CASE supervisor, who was extremely helpful, and continued to provide support when I returned from placement. This PhD would not have been possible if it weren't for the generous funding from EPSRC and AstraZeneca.

I would like to express my thanks to the technical staff at the University of Leeds including Tanya Marinko-Covell, Simon Barrett and Martin Huscroft. In particular I would like to thank Simon Barrett for assisting with numerous NMR experiments.

During my PhD at I have met and worked alongside some brilliant chemists, they have provided not only a stimulating lab to work in but an enjoyable place to work. I owe particular thanks to Dr. Francesco Marchetti ('Franny') who worked alongside me on this project. Outside the project I would like to thank Tom James ('TOJ'), Ieuan Davies, Charles-Hugues Lardeau ('Chaz'), Tom Harman, Adrian Fowkes, Martin Fisher ('Fishy'), Sarah Murrison, Catherine O'Leary-Steele, Giorgia Magnatti, Paul MacLellan ('PM') and George Karageorgis ('GWhizz').

I would also like to thank my family for their constant love and support, in particular both my Grandads who kept supporting me throughout my studies. Last, but by no means least, thanks to my now wife Gemma Dow. I cannot thank you enough for the constant support you have provided during my studies, for which you uprooted from your home town and family to join me in Leeds so I could carry out my studies. Thank−you.

I dedicate this thesis to my grandad Dr Ronald Dow, who passed away whilst I was completing my corrections. I'm glad he was still here to learn that I successfully passed my *viva voce.*

Abstract

This thesis describes a modular diversity-oriented synthesis approach, which exploited a ‘build→couple→couple→pair’ reaction sequence, to generate a library of natural product-like macrocycles. The use of a fluorous−tagged building block allowed the expedient purification of the substrates between the ‘couple→couple’ stages of the sequence. Building blocks were iteratively linked onto the fluorous tagged building block to give linear substrates bearing two terminal alkenes. These substrates were subjected to ring-closing metathesis to yield diverse macrocyclic scaffolds. Subsequent, deprotection and diversification steps yielded natural product-like macrocycles. Using this approach, over 13 macrocyclic scaffolds were prepared which, in turn, after diversification, yielded over 55 diverse macrocycles, each with unique scaffolds. In addition this project also saw the synthesis of the corresponding linear compounds.

Chapter 1 discusses the importance of macrocycles in nature, how this class of molecules have been poorly explored and methods that have been used to explore chemical space. Chapter 2 describes the synthesis of the building blocks and the proposed method to prepare the library of diverse macrocycles. Chapter 3 explores the reactivity of the building blocks and developments required to improve the efficiency of the library synthesis. Chapter 4 describes the final library synthesis from building blocks to final compounds. This work aims to prepare compounds with potential bioactivity; however, the biological evaluation of the compounds is beyond the remit of the study.

Contents

Abbreviations

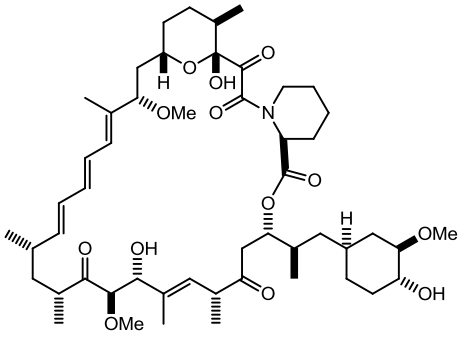
Ac	acetyl
app	apparent
Ar	aryl
Boc	*tert*-butyloxycarbonyl
br	broad
°C	degrees Celsius
ca.	*circa*; about
^{C}Pr	cyclopropyl
δ	chemical shift
d	doublet
DCC	*N*-dicylcohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DOS	diversity oriented synthesis
DPPA	Diphenylphosphoryl azide
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
e.g.	*exempli gratia*; for example
EI	electronic ionisation
eq.	equivalents
ESI	electrospray ionisation
etc.	*et cetera*; and so forth
Et	ethyl
ether	diethyl ether
^{F}DIPES	*fluorous* diisopropyl silyl
F-SPE	Fluorous Solid Phase Extraction
HG-II	Hoveyda—Grubbs' second generation catalyst
HPLC	High performance liquid chromatography
^{i}Pr	isopropyl
IR	infrared
J	spin-spin coupling constant
LCMS	Liquid chromatography mass−spectrometry
m.p.	melting point
MS	molecular sieves
m/*z*	mass to charge ratio
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl; nosyl
Ph	phenyl
ppm	parts per million
pyr	pyridine
qn	quintet
RCM	ring-closing metathesis
R_f	Retention factor
r.t.	room temperature
s	singlet
t	triplet
TBAF	tetra-*N*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert	tertiary

Tf	trifluoromethanesulfonate; triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TPSA	total polar surface area
ν	wavelength
wrt	with respect to

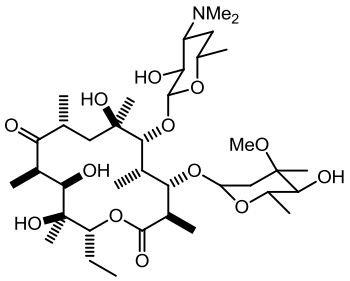
1 Introduction

1.1 The importance of macrocyclic small molecules

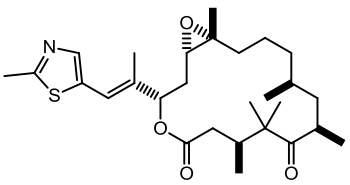
Macrocyclic small molecules are of tremendous interest both as targets for synthetic chemistry and as biologically functional compounds.[1] This interest has largely stemmed from macrocyclic natural products that exhibit interesting and diverse biological activity;[2] macrocycles may be used as chemical tools for probing biological mechanisms and as starting points for drug discovery. The medicinally-relevant properties of macrocyclic natural products include immunosupression,[3] anti-cancer and antibiotic activity; these activities are displayed by rapamycin **1**[4,5] epithilone B **3**[6,7,8] and erythromycin **2**[9] respectively (Figure 1).



1



2



3

Figure 1 The chemical structures of rapamycin **1**, erythromycin **2** and epithilone B **3**

1.1.1 Broad structural features of macrocycles

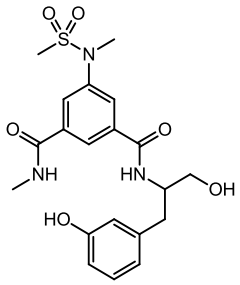
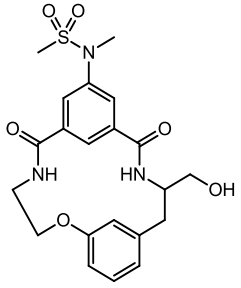
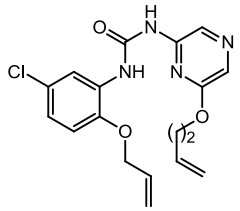
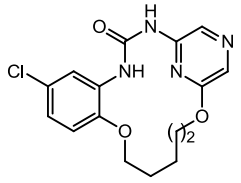
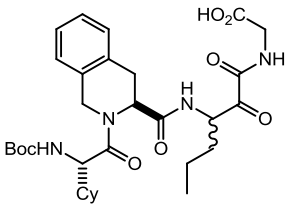
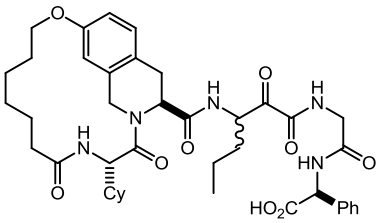
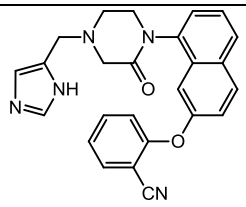
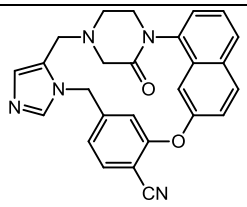
Macrocycles are an interesting class of molecules which bridge the gap between conventional small molecules and biological macromolecules;[1] the molecular masses of macrocycles typically do not generally comply with the Lipinski 'Rule of 5'[10–12] guidelines that have dominated medicinal chemistry. Macrocycles are considered to possess rings with 12 or more covalently bonded atoms.[2] The cyclic structure reduces

the number of rotatable bonds compared to comparable acyclic molecules,[13] restricting conformation and reducing the entropic penalty associated with binding to a protein. Macrocyclization also imparts topology into the molecule, often yielding two distinct 'faces', allowing a large surface area of protein binding site to be targeted.[11,12,13,6,14]

1.1.2 Effect of macrocyclization on biological activity

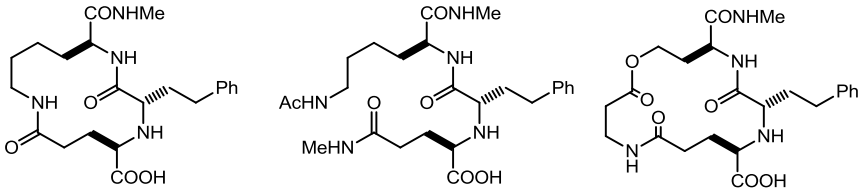
Macrocyclization has become a significant tactic in drug discovery programmes. Table 1 summarises selected cases where macrocyclization has had a beneficial effect on biological function. The structure of the complex between the bound linear compound **4** and BACE-1 highlighted the proximity of the two ends of the bound molecule; macrocyclization, to give **5**, resulted in a 34-fold improvement in affinity (entry 1). The researchers subsequently exploited the macrocycle **5** as a starting point for the discovery of compounds with low nanomolar affinity (not shown).[18] The checkpoint kinase-1 inhibitor **7** was developed following modelling studies of a linear compound (not shown);[19] a 440-fold increase in binding was observed relative to **6** (entry 2). The tetrahydroisoquinoline-3-carboxylamide **8** was identified as a micromolar inhibitor (K_i: 15 μM) of the hepatitis C virus non-structural protein 3 (HCV-NS3).[20] Crystallographic studies showed that, upon binding, the capping Boc group was in close proximity to the aromatic ring. The macrocyclic analogue **9** of the tetrahydroisoquinoline-3-carboxylamide **8** was then prepared and displayed a *ca.* 70-fold improvement in binding (entry 3). NMR experiments revealed that the piperazinone **10** undergoes a considerable conformational change on binding to farnesyl transferase (FTase). The cyclised variant **11**, which adopts a similar conformation to the bound ligand, was therefore prepared; its affinity for FTase was 55,000-fold higher than the comparable acyclic variant **10** (entry 4).[21]

Table 1 Biological activity of selected macrocycles and their acyclic counterparts

entry	linear analogue	activity	macrocycle	activity	Fold improvement
1[18]	 **4**	β-secretase IC_{50} >100 µM	 **5**	IC_{50} 2.9 µM	>34
2[19]	 **6**	ChK1 inhibition IC_{50} 4.4 µM	 **7**	IC_{50} 10 nM	440
3[20]	 **8**	HCV NS3 Protease K_i 15 µM	 **9**	K_i 0.015 µM	1000
4[21]	 **10**	FTase IC_{50} 5490 nM	 **11**	IC_{50} 0.1 nM	55,000

Macrocyclization may also be used as a tactic to control the selectivity of bioactive small molecules. Macrocyclization of the broad-spectrum matrix metalloproteinase (MMP) inhibitor **13**, to give **12**, resulted in significantly more selective ligands. Cyclisation increased inhibitory activity towards MMP8 (K_i: 293 nM for **13** compared to 17 nM for **12**), whilst activity against other MMPs remained either similar or was reduced (in the case of MMP2 and MMP9). The macrolactone **14** was also synthesised and displayed increased activity towards MMP8; however the inhibition of MMP2 and 3

was also improved.[22,23] It is likely that increased target specificity stems from the restricted conformation of the macrocycles compared to the acyclic variant **13**.



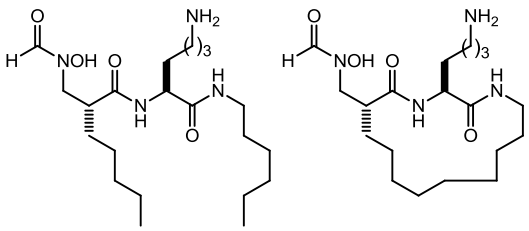
12 **13** **14**

	12	**13**	**14**
MMP1	2,500	2,860	8,400
MMP2	8,100	1,533	238
MMP3	13,500	14,088	2,900
MMP8	17	293	10
MMP9	6,600	404	5,800

Figure 2 Comparison of selectivity of the MMP inhibitors **12**, **13** and **14**; K_i (nM)

1.1.3 Effect of macrocyclization of pharmacokinetic properties

Macrocyclization can also improve the pharmokinetic properties of small molecules. Although peptides can be effective inhibitors they are generally susceptible to enzymatic hydrolysis.[24] However, in many cases, cyclisation can provide resistance to hydrolysis, in general by stabilising a conformation that is not targeted by proteases.[25,26] For example, the *in vitro* stability of linear compound **15** and macrocycle **16** were examined in rat plasma; after 5 h only *ca.* 70% of **15** remained, whereas the macrocycle **16** showed no detectable degradation.



15 **16**

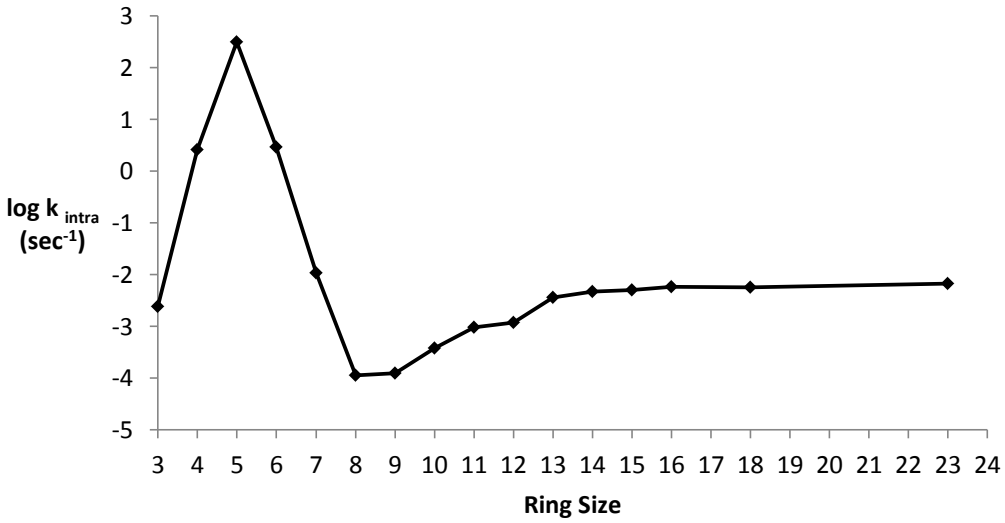
Figure 3 Chemical structures of peptide deformylase inhibitors **15** and **16**. **16** K_i 0.67 nM

Efficacious drugs must be able to reach their protein target *in vivo*. Macrocyclization can improve membrane permeability by satisfying hydrogen bonding requirements intramolecularly and through reducing the number of effective rotatable bonds.

Veber *et al.* examined the contribution of molecular rigidity to oral bioavailability. It was found that *ca.* 65% of molecules that have ≤7 rotatable bonds achieve ≥20% oral bioavailability in rats; in contrast only *ca.* 25% of molecules that have >10 rotatable bonds only achieve <20% oral bioavalability.[13]

1.2 Macrocyclization Methods

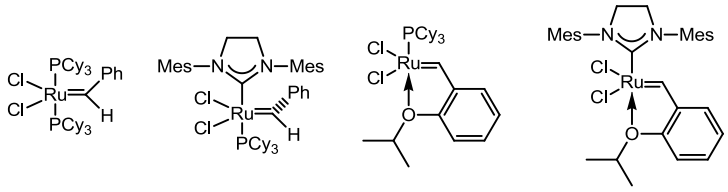
The key step in the synthesis of most macrocycles is the ring-forming step. Polyketide synthases carry out this step using the terminal thioesterase to effect the concomitant cyclisation and release of macrocycles.[27] The macrocyclization step can be problematic in the laboratory due to competing intermolecular reactions which can lead to low-yields for the required product and the formation of oligomers.[15,28] The rate of cyclization, however is extremely dependent on ring size (see Graph 1). Numerous methods have been developed or adapted to overcome these problems and facilitate macrocyclization; the main methods include macrolactonization (see Section 1.2.3), macrolactamization[29,30,31] and ring-closing metathesis,[32] often under high dilution conditions (see section 1.2.1). However other methods have been developed to facilitate ring-closure; S_NAr,[33] Wittig,[34] Stille,[35] Buchwald—Hartwig,[36] Sonogashira,[37–40]Heck[41,42] and Suzuki[43–46] reactions. Ultimately, the choice of ring closure depends on the functionality accepted within the target molecule. The kinetics of ring closing is well understood; Illuminati measured the rates of ring closure of ω-Bromo Acids to give the corresponding (macro)lactones (see Graph 1).[47] The study showed that whilst ring closing of large rings (>12) is considerably slower than small rings (4-6), it was considerably faster than that of medium rings (8-12).



Graph 1 Relative rate of cyclization of ω-Bromo Acids, $Br(CH_2)_{n-2}CO_2H$, in 99% aqueous DMSO[47]

1.2.1 Ring-closing metathesis

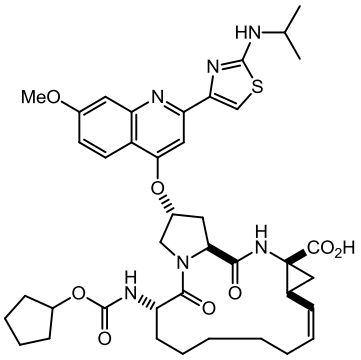
Ring-closing metathesis (RCM) has received huge interest, and has become a cornerstone of synthetic organic chemistry;[48,49,50] The approach is now one of the most utilised methods for macrocyclisation,[51,49] notably in the synthesis of natural products.[52] Metathesis catalysts have been developed to improve their stability, reactivity and selectivity.[50] The value of RCM stems from the lack of reactivity of carbon-double bonds under many reaction conditions (enables the synthesis of substrates), together with the high selectivity of the catalysts (in the cyclisation step). Ruthenium-based catalysts such as the Grubbs first- (**17**) and second- (**18**) generation catalysts and the Hoveyda—Grubbs first- (**19**) and second- (**20**) generation catalysts are most widely used in metathesis reactions; in particular, **19** and **20** have excellent reactivity and are tolerant to non-inert conditions.[53]



17 **18** **19** **20**

Figure 4 Structures of metathesis catalysis

The functional group created in ring-closing metathesis reactions is an alkene which can facilitate subsequent functionalization (e.g. *via* epoxidation, dihydroxylation or hydrogenation). The effectiveness of ring-closing metathesis is highlighted by the large scale synthesis of a HCV protease inhibitor BILN 2061 **21**.[54,55] The ring-closing step was facilitated by the treatment of the acyclic substrate (not shown) with 0.1 mol% of a customised ruthenium catalyst (not shown) in toluene at reflux; this method resulted in >90% yield, with quantitative conversion and was scaled up to 400 kg.

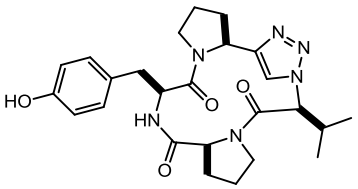


21

Figure 5 Chemical structure of BILN 2061 **21**

1.2.2 'Click' Macrocyclization

The 'click' cycloaddition[56] reaction between alkynes and azides is another viable method to prepare macrocycles; however this reaction can also suffer from significant dimer and oligomer formation. The approach has been used to synthesis bioactive macrocycles; however the resultant triazole moiety is inevitably part of the final molecule. Peptidomimetics, including the tyrosinase inhibitor **22** have been prepared using 'click' chemistry. Treatment of the acyclic variant of **22** (not shown) with copper(I) bromide yielded the cyclic triazole **22** in 36% yield.[57,58]

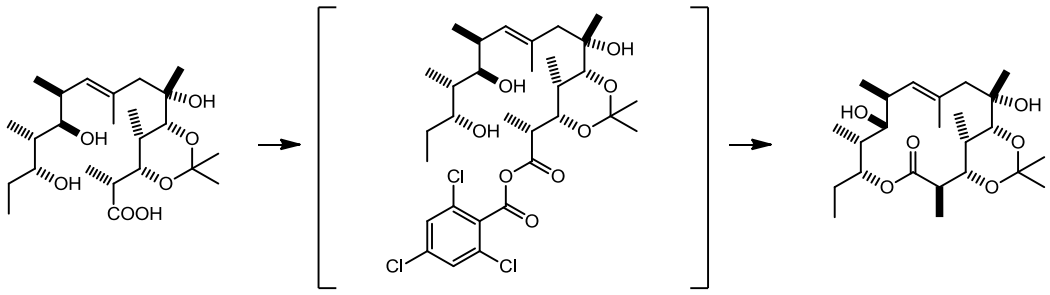


22

Figure 6 Chemical structure of tyrosinase inhibitor **22**[57,58] (IC_{50} = 0.6 mM)

1.2.3 Macrolactonization

Macrolactonization is an efficient method for the preparation of a variety of natural products;[59] many macrocyclic natural products are macrolactones[2], many of which are biosynthesised *via* polyketide synthase-catalysed cyclisation. Macrolactonization is a viable method for preparing macrocycles with ring size at least 12 (Graph 1). There are numerous methods that can facilitate macrolactonization; for example, the Mitsunobu reaction[60] and the Yamaguchi[61] method which proceeds *via* a mixed anhydride intermediate. The Yamaguchi mixed anhydride method can prove an efficient macrolactonization method. Erythronolide precursor **23**, a parent compound of several antibiotics, undergoes the Yamaguchi lactonization, to yield selectively the corresponding 14-membered macrocycle **25**, in 85% yield (Scheme 1).[62]



85%

23 **24** **25**

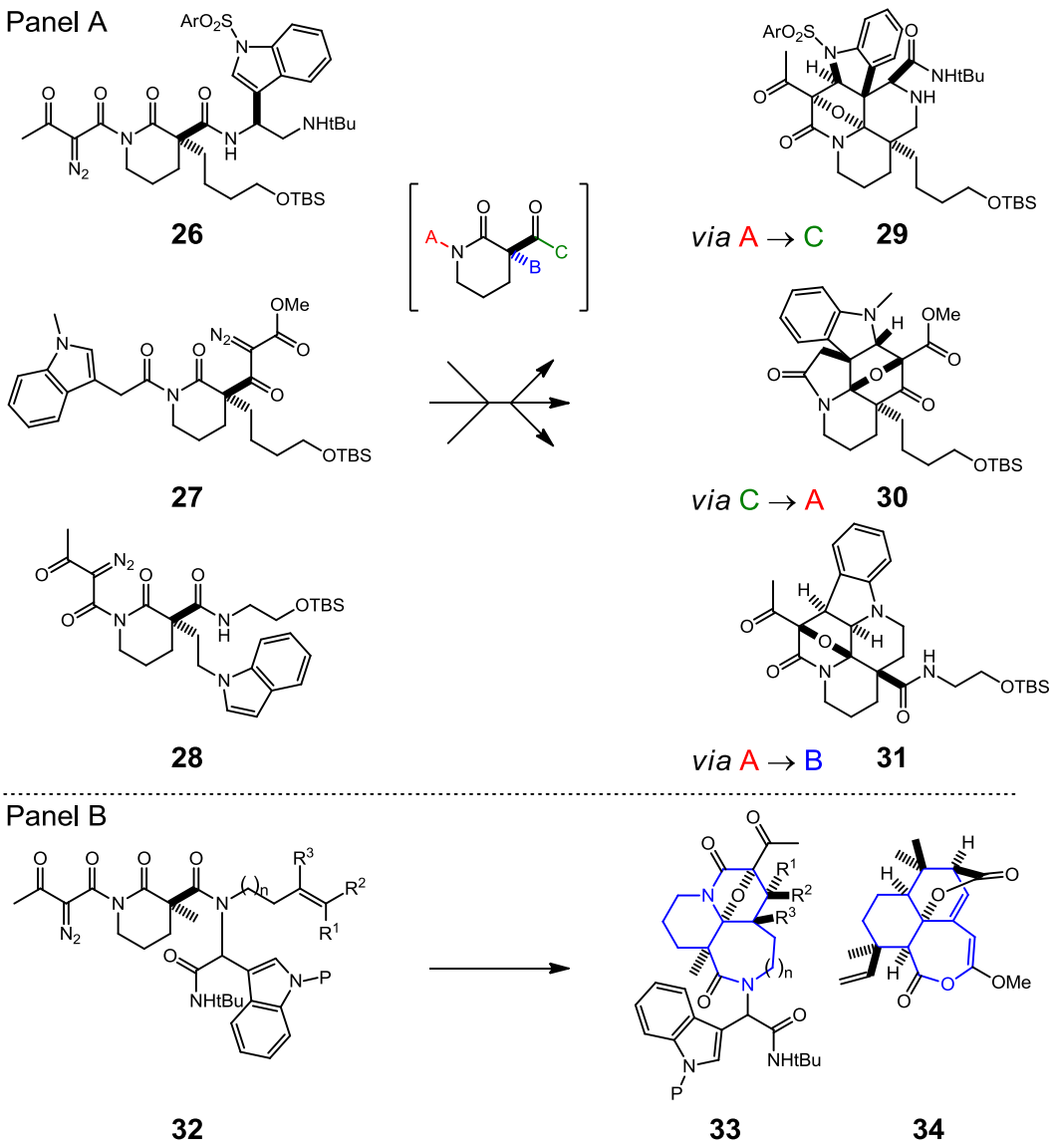
Scheme 1 Macrolactonization of **23** to give erythronolide precursor **25** *via* the Yamaguchi esterification

1.3 Diversity-oriented synthesis

Small molecules have aided enormous advances in the understanding of biological systems and our ability to treat disease.[63,64] Synthetic approaches that allow expedient access to libraries of diverse small molecules are hugely valuable. Diversity-orientated synthesis (DOS) aims to prepare a broad distribution of compounds in chemical space. As DOS does not aim for a specific target molecule compared to a target-orientated synthesis, retrosynthetic analysis cannot be applied. DOS has gathered interest in recent years as a method to access libraries of skeletally diverse compounds which ultimately can yield chemical probes of biological systems.[65–68]

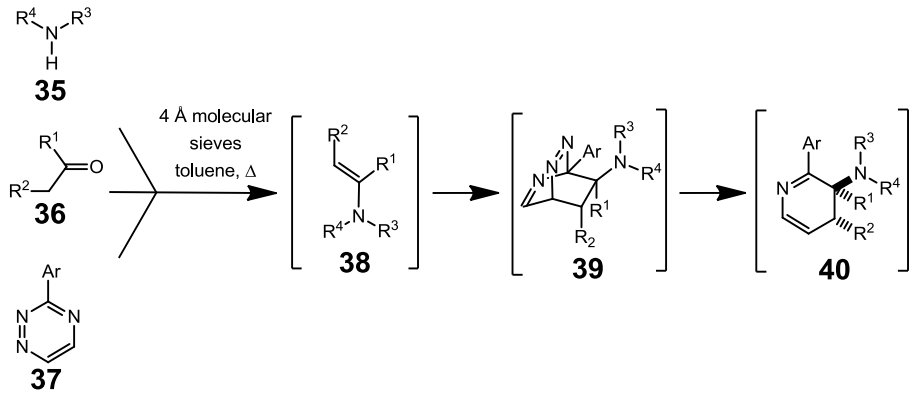
1.3.1 Folding pathways in Diversity-Oriented Synthesis

The folding path approach exploits common reaction conditions to convert multiple substrates into multiple products. Schreiber used rhodium(II)-catalyzed consecutive cyclisation-cycloaddition chemistry[69–71] to prepare alternative densely-functionalised polycyclic skeletons (Scheme 2, Panel A).[72] Appended to the substrates **26**, **27** and **28** were strategically-positioned α-diazo ketocarbonyl and indole moieties; upon treatment with a catalytic amount of rhodium(II) octanoate dimer in benzene, these substrates were converted into alternative products. Presumably, formation of a carbonyl ylid was followed by 1,3-dipolar cycloaddition with the indole to give polycyclic skeletons such as **29**, **30** and **31**. Oguri[73] used the same approach to generate alkaloid-like products (Scheme 2, Panel B). By varying the position of the reactive groups, the scaffolds of the natural products aspidophytine (not shown) and the transtaganolides **34** could be prepared.



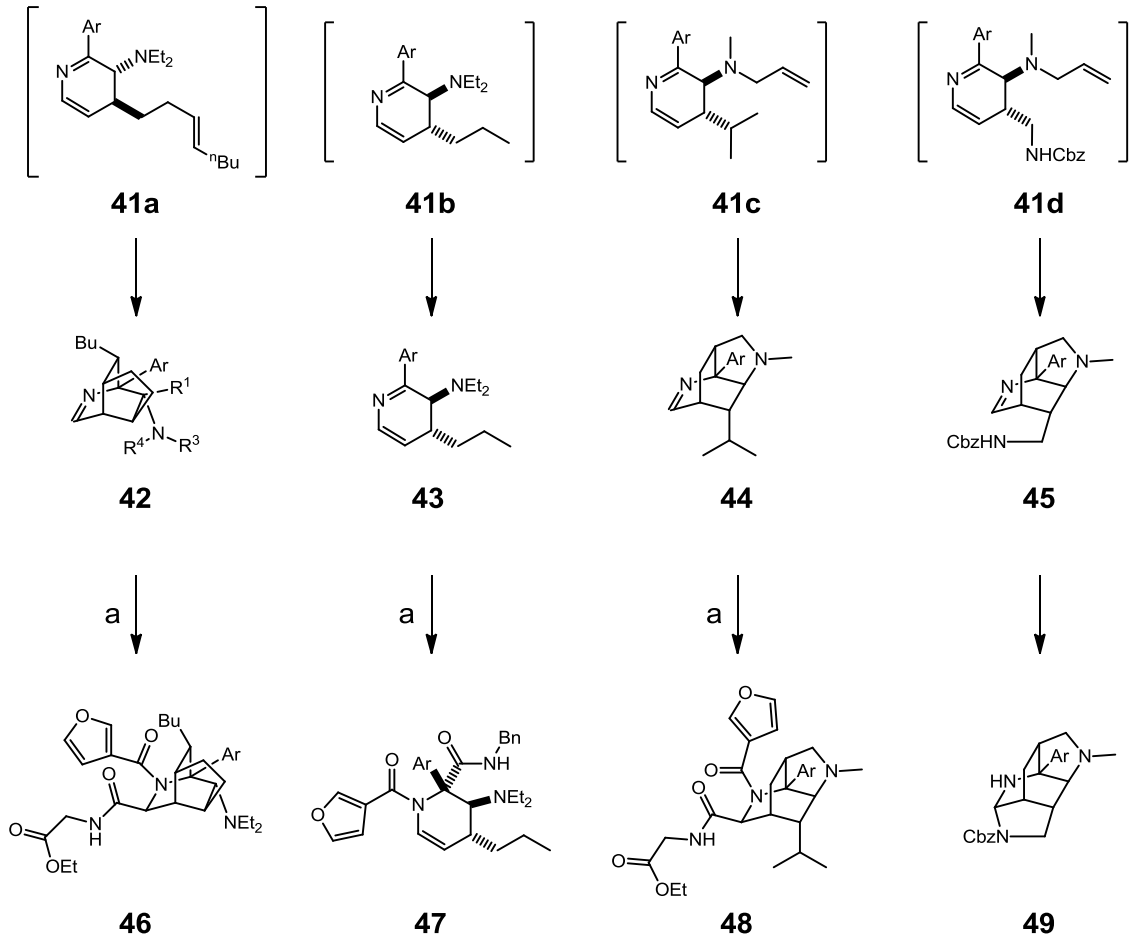
Scheme 2 Rhodium-catalysed ylid formation-cycloaddition approaches to natural product-like compounds. Panel A: Schreiber's approach to indole alkaloid-like compounds. Panel B: Oguri's approach to transtaganolides.

A multicomponent reaction, involving secondary amines **35**, carbonyl compounds **36** and triazines **37**, was used to generate the substrates for a folding pathway leading to alkaloid-like compounds (Scheme B).[74] The approach utilised a single reaction, using largely commercially available compounds, to synthesise the folding substrates and hence products. Condensation of secondary amines **35** with the carbonyl compounds **36** generated enamines **38** *in situ* which underwent an inverse-electron demand Diels—Alder reaction with the triazine **37** to yield compounds of general structure **39**. Expulsion of molecular nitrogen yielded 2-azadienes (**40**), some of which could undergo further reaction (e.g. Diels-Alder reaction) with functionality (sometimes known as σ-elements)[75] elsewhere in the molecule.



Scheme 3 Generation of folding substrates using a multicomponent reaction

The functional groups within **40** thus ultimately determined the final molecular scaffold obtained. Thus, with a tethered dienophile in place, an intramolecular Diels—Alder occurred (**41a**, **c** and **d** → **42**, **44** and **45**); in contrast, with an appropriate nucleophile, attack into the imine occurred (**41d** →**49** *via* **45**) (Scheme 4). The unreacted imine **43,** and the resultant imines from the Diels—Alder of **41a** and **41c**, were substrates for a second three-component coupling: a Joullié—Ugi reaction. The cyclic imines **42** and **44**, and the 2-aza diene **43**, were reacted with an isocyanide and carboxylic acid to give final compounds such as **46**, **47** and **48**.

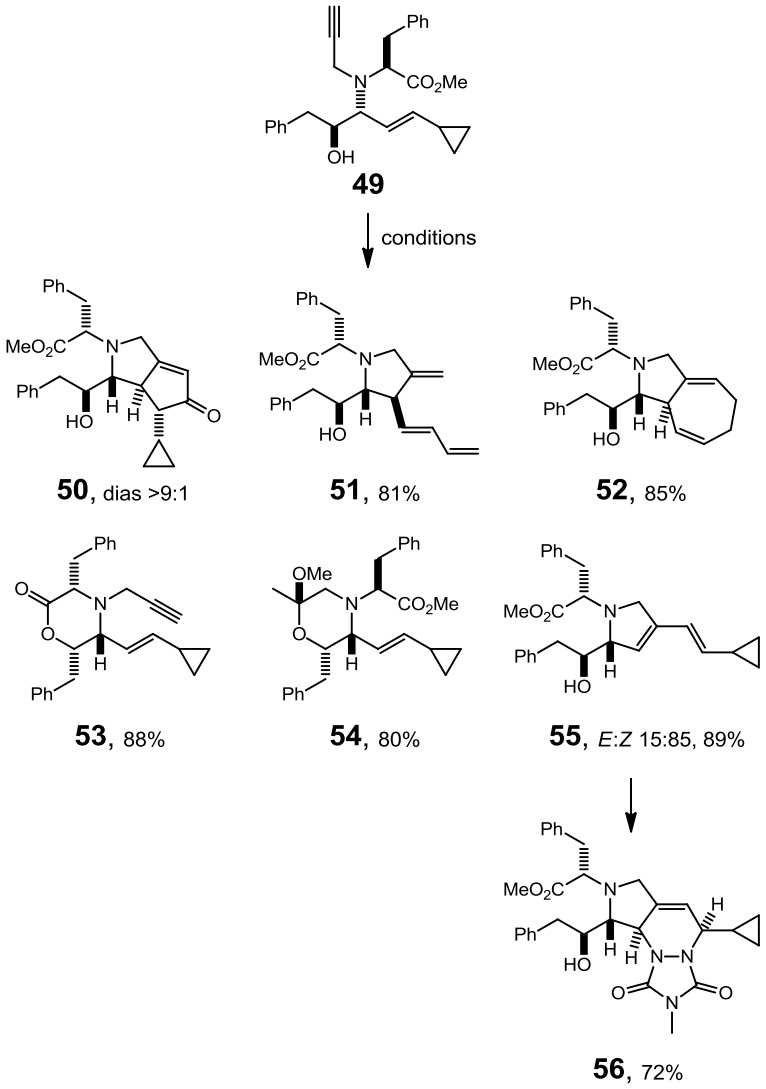


Scheme 4 Sarah Murrison's approach to a library of alkaloid-like compounds; a) 4 Å molecular sieves, toluene, imine, carboxylic acid, isocyanide, EtOH.

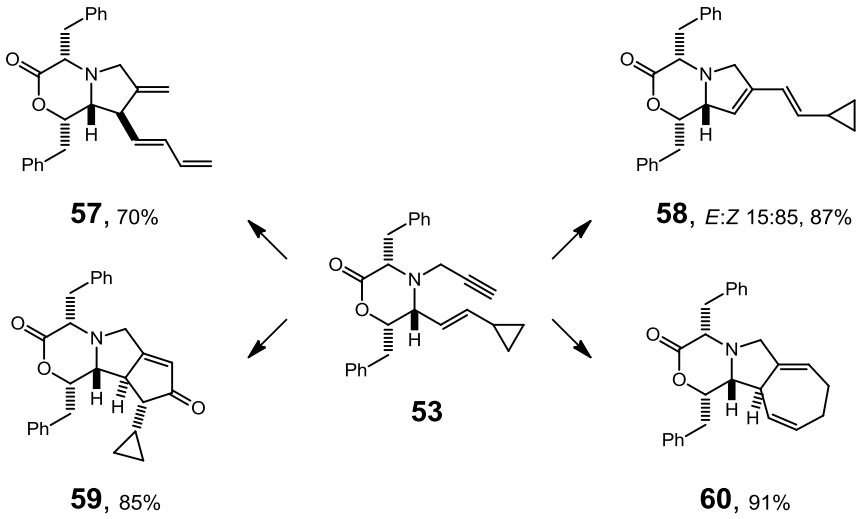
1.3.2 Branching pathways in Diversity-Oriented Synthesis

In contrast to folding pathways, branching pathways utilise complementary reactions to convert a common intermediate into a range of scaffolds.

A branching pathway exploited a range of cyclization reactions to generate six scaffolds, two of which can be further diversified to yield four more scaffolds (Scheme 5).[76] Using a four-component Petasis reaction, Schreiber *et al.* were able to synthesise versatile cyclization precursors (such as **49**). The cyclizations exploited the dense functionality of **49**: a Pauson—Khand reaction liberated **50**; a gold-catalysed cyclisation of an alcohol onto an alkyne liberated the acetal **54**; a ruthenium-catalysed reaction gave the cyclohepadiene **52**; and enyne metathesis, catalysed by the Hoveyda—Grubbs 2nd generation catalyst, liberated the diene **55**. Base-induced cyclization of **49** gave the lactone **53**, which was also subjected to the same metal catalysed cyclizations: this approach yielded the triene **57**, the cycloheptadiene **60**, the cyclopentenone **59** and the diene **58** (Scheme 6). The reactivity of the diene **55** was also investigated and it was shown that hetero-Diels—Alder with 4-methyl-1,2,4-triazoline-3,5-dione gave the adduct **56** (Scheme 5).

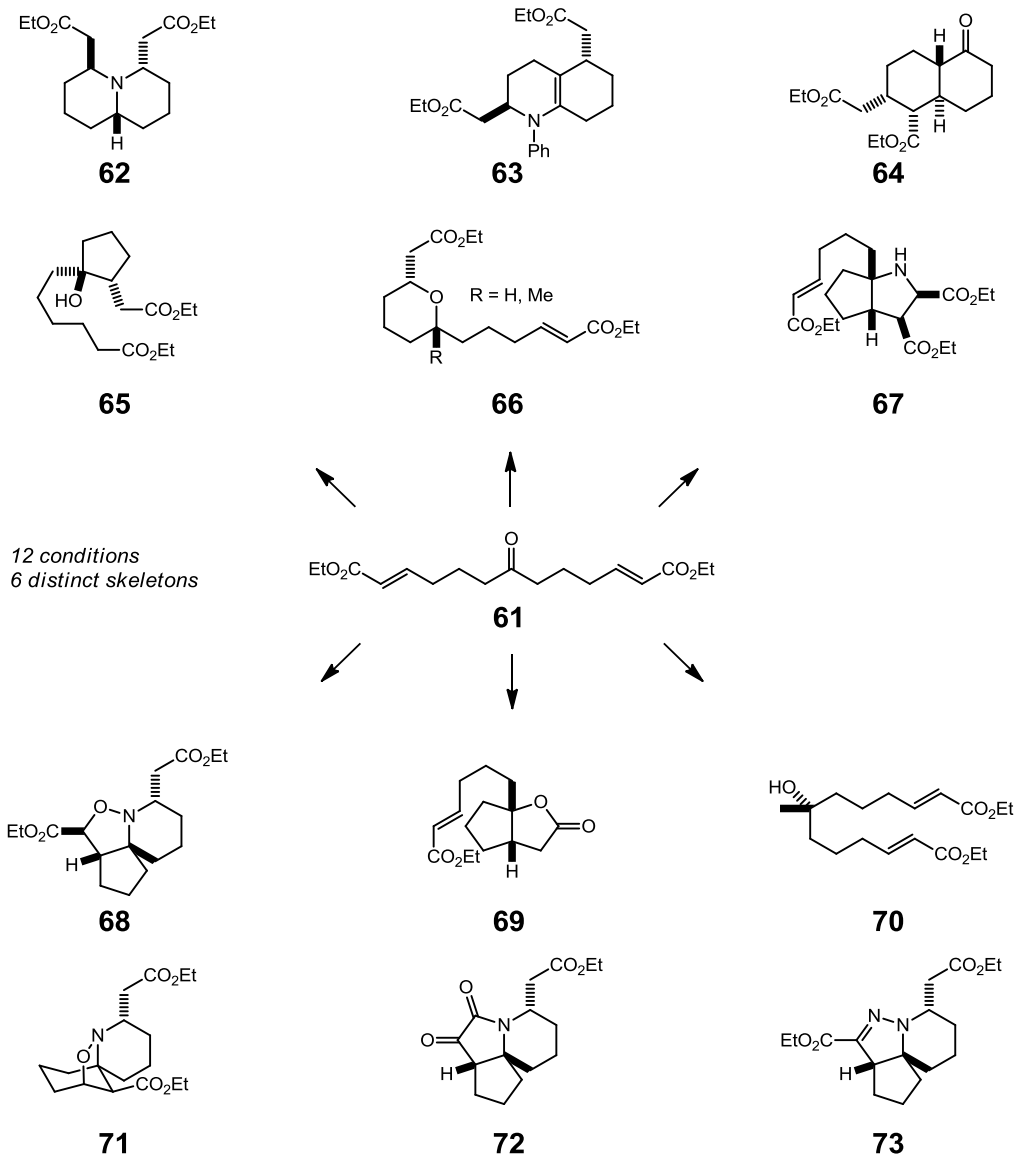


Scheme 5 Complementary metal-catalysed reactions leading to diverse scaffolds. **50**: $Co_2(CO)_8$, Et_3NO NH_4Cl, benzene, rt; **51**: $Pd(PPh_3)_2(OAc)_2$ (10 mol%) benzene, 80 °C; **52**: $CpRu(MeCN)_3PF_6$ (10 mol%), acetone, rt; **53**: NaH, toluene, rt; **54**: $NaAuCl_4$ (10 mol%), MeOH, rt; **55**: Hoveyda—Grubbs 2nd gen. cat (10 mol%), CH_2Cl_2; **56**: 4-methyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2,



Scheme 6 Exploitation of metal-catalysed reactions to convert **53** into diverse scaffolds. **57**: $Pd(PPh_3)_2(OAc)_2$ (10 mol%), benzene, 80 °C; **59**: $Co_2(CO)_8$, Et_3NO NH_4Cl, benzene, rt; **60**: 10 mol% $CpRu(MeCN)_3PF_6$ (10 mol%), acetone, rt; **58**: Hoveyda—Grubbs 2nd gen. cat. (10 mol%), CH_2Cl_2,

Stockman *et al.* have exemplified a powerful branching approach to twelve small and densely substituted natural product-like scaffolds (Scheme 7).[77] The approach exploits the diverse reactivity of ketones coupled with the promiscuity of *α,β*-unsaturated esters. Treatment of **61** with hydroxylamine hydrochloride to form an oxime was followed by a tandem aza-Michael/1,4-prototopic shift/intramolecular [3+2] cycloaddition which gave the azaspirocycle **68**. Amongst amine-based transformations of the central ketone of **61**, it was also shown that the ketone itself can be used as a pro-nucleophile: treatment of **61** with sodium hydride gave the *trans*-decalin **64**. Furthermore, treatment of the ketone **61** with two equivalents of SmI_2 gave the bicyclic lactone **69**; however, with five equivalents of SmI_2, the carbocycle **65** was obtained. The ketone of **61** was able to undergo some more conventional transformations: reduction and treatment with methyl lithium resulted in the secondary and tertiary alkoxides respectively and, through oxy-Michael additions, the corresponding tetrahydropyrans **66**. Treatment of **61** with methyl magnesium bromide liberated the expected tertiary alcohol **70**. Thus the approach yielded a small library of diverse scaffolds; using related chemistry it was also possible to synthesise a key intermediate (not shown) in a synthesis of the macrocycle halichlorine (not shown).[78]

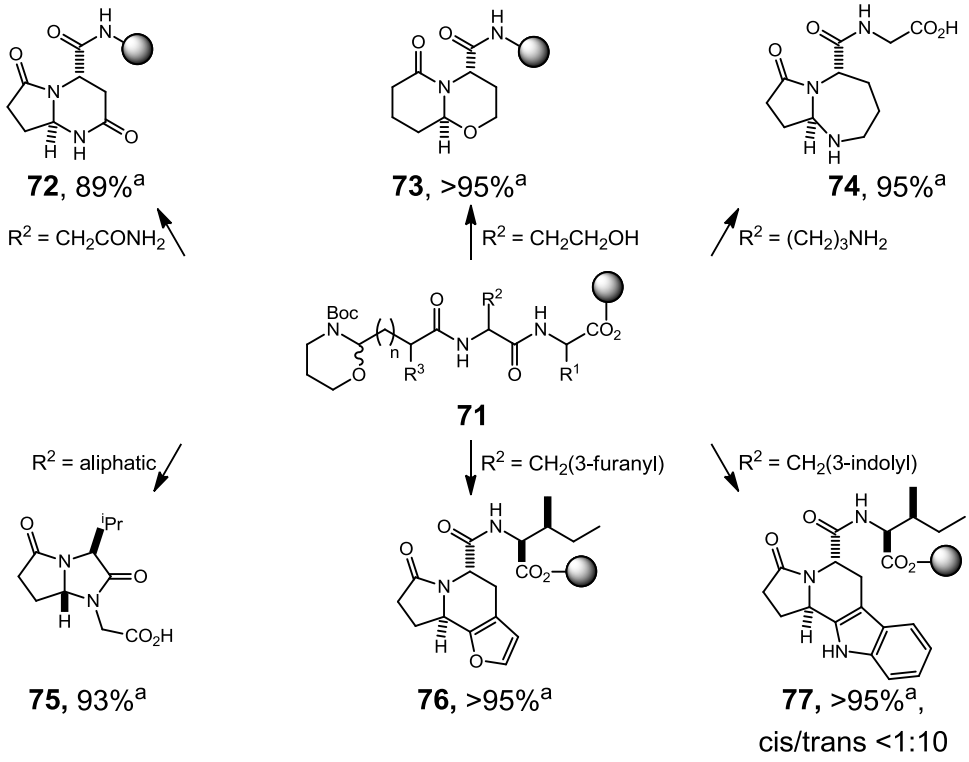


Scheme 7 Stockman's approach to scaffold diversity using the reactivity of *α,β*-unsaturated esters and ketones. Conditions to initiate scaffold construction; **62**, $NaBH_4$, NH_3, EtOH, $Ti(OEt)_4$ then AcOH, 74%; **63** $PhNH_2$, $TiCl_4$, CH_2Cl_2, 65%; **64**, 70%, NaH, THF; **65**, SmI_2 (5 eq.), THF/MeOH, −78 °C, 70%; **66**, super-hydride, THF, 50% or MeLi, 19%; **67**, glycine ethyl ester, DIPEA, 71%; **68**, NH_2OH•HCl, NaOAc, MeOH/MeCN, 60 °C, 68%; **69**, SmI_2 (2 eq.), THF/MeOH, −78 °C, 70%; **70**, MeMgBr, 85%; **71**, NH_2OH•HCl, NaOAc, MeCN then PhMe, mw 140 °C, 12%, or PhCl, reflux after **68**, 39%; **72**, NH_2OH•HCl, NaOEt, EtOH, 12%, or NaOEt after **68**, 89%; **73**, NH_2NHTs PhMe, reflux, 41%

1.3.3 Oligomer-based approaches in Diversity-Oriented synthesis

One powerful approach to synthesising a library of compounds combines elements of both folding and branching pathways in a so called 'build-couple-pair' approach.[79] This powerful strategy involves a 'build' phase where monomers with specific reactivity are prepared and joined in a 'couple' phase. Finally, the oligomeric substrates are then 'paired' in subsequent cyclisation reactions.[80]

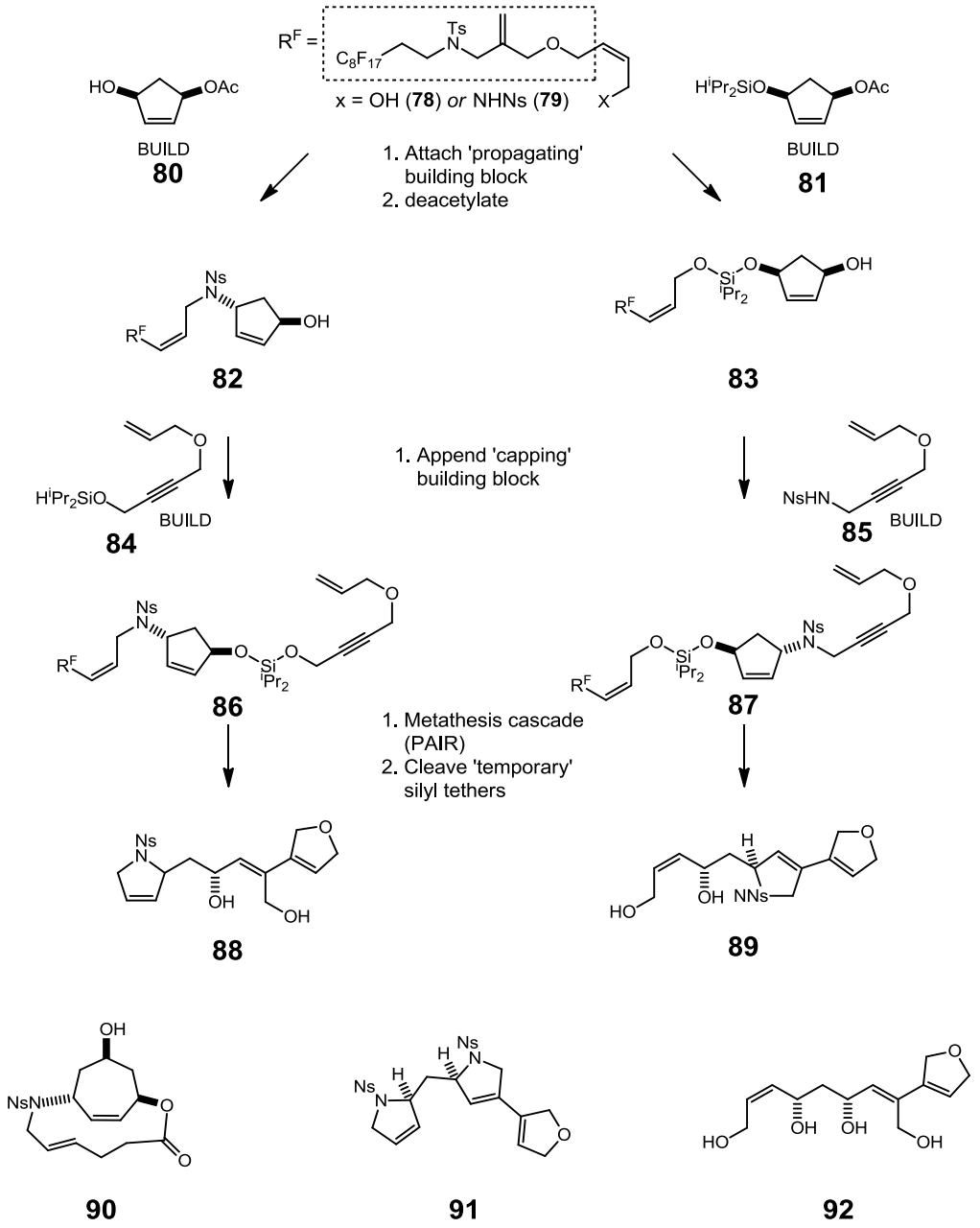
This approach was harnessed in the synthesis of small, densely substituted heterocycles (**72**→**77**) (Scheme 8).[81–84] Firstly, peptide synthesis was used to prepare peptides **71** which contained a masked aldehyde, an amine and a pendant nucleophile. Treatment of the solid supported peptides **71** with acid initiated unmasking of the latent aldehyde, *N*-acyliminium formation and interception by alternative nucleophiles (for example, a furan → **76**: an alcohol → **73**; an indole → **77**; and a carboxamide → **72**).



Scheme 8 Meldal's folding approach to a range of molecular scaffolds utilising *N*-acyliminium cyclizations; [a] HPLC purity

Metathesis cascades have provided rapid routes to skeletally-diverse small molecule libraries.[85,86] One compelling approach resulted in the preparation of over eighty distinct molecular scaffolds (Scheme 9). Oligomeric metathesis substrates were prepared by iterative attachment of unsaturated building blocks onto a fluorous-tagged linker; the iterative coupling reactions included the Fukuyama-Mitsunobu reaction, silaketal formation and esterification. Finally, treatment of the oligomers (e.g. **86** and **87**) with ruthenium-based catalysts 'reprogrammed' the scaffolds of the molecules. For example, the 'propagating' cylcopentene building blocks **80** or **81** could be attached to a fluorous-tagged 'initiating' building block **78** or **79** using either a Fukuyama—Mitsunobu reaction or silaketal (→ **82** or **83**, respectively). Deprotection, and attachment of a 'terminating' building block gave metathesis substrates (for example, **86** and **87**). Finally, metathesis 'reprogramming' of the substrates and concomitant release from the fluorous tag, and if applicable removal of the silaketals, yielded the

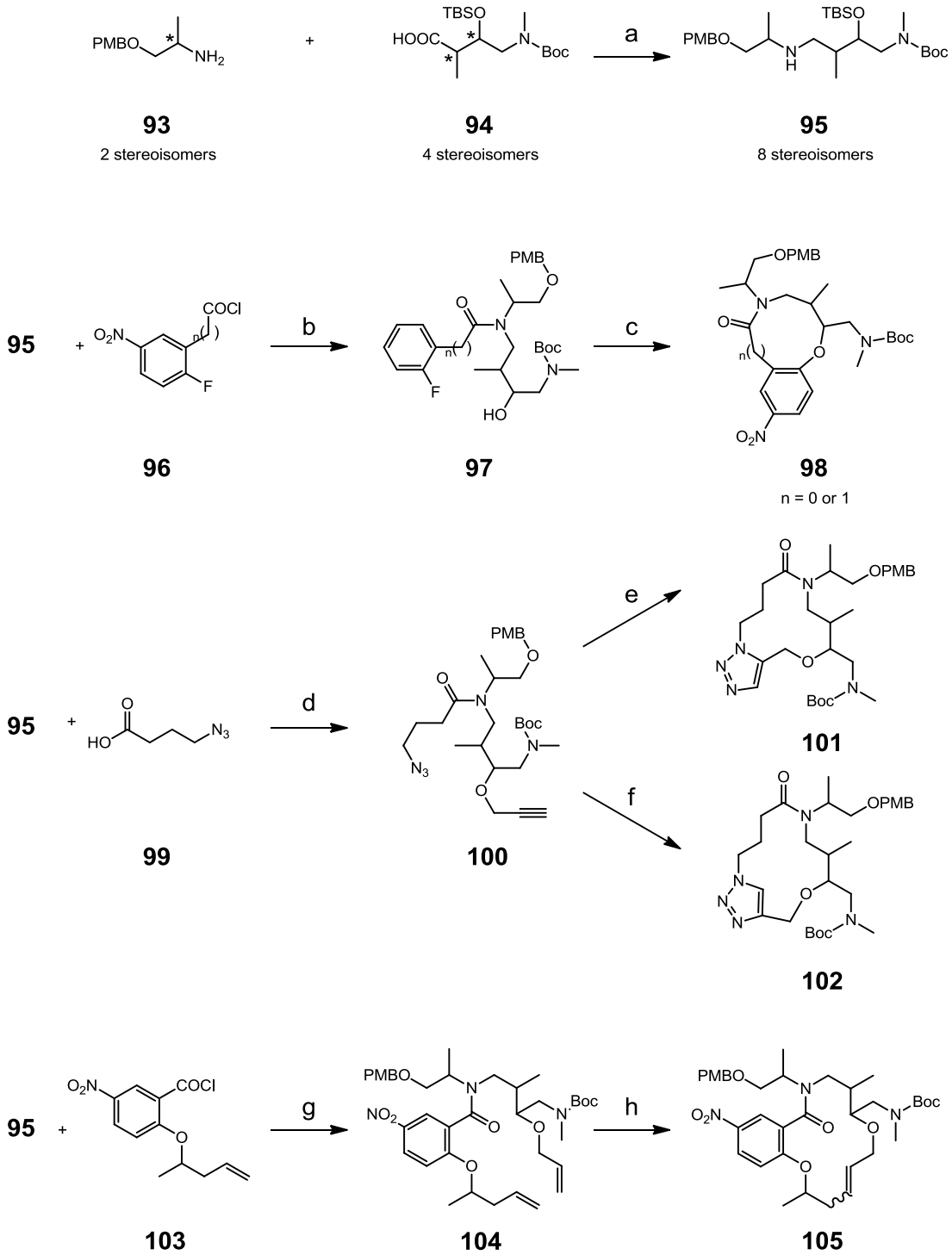
final products; this approach yielded over eighty distinct scaffolds (two-thirds of which were novel).



Scheme 9 Nelson's approach to scaffold diversity exploiting metathesis cascade chemistry. Examples of other products prepared include **90**-**92**

1.4 Diversity-oriented synthesis of macrocycles

The 'build-couple-pair' approach has been applied to the synthesis of a library of macrocycles (Scheme 10).[87] Initially, building blocks **93** and **94** were prepared stereoselectively. Combination of **93** and **94** led to numerous stereoisomeric intermediates **95**. Three reactions were exploited to cyclise substrates; the S_NAr reaction, the Huisgen [3+2] cycloaddition and ring-closing metathesis. For the S_NAr cyclisation, intermediates **95** were treated with 2-fluoro-5-nitrophenyl carbonyl chloride **96**; deprotected to give **97;** and treated with base to affect cyclisation to 8- or 9-membered rings **98**. Similarly, acylation of the amine **95** with the azido acid **99**, deprotection and propagarylation yielded the cycloaddition substrate **100**; treatment of the substrate **100** with either a ruthenium- or copper-based catalyst afforded respectively the regioisomeric macrocycles **101** and **102**; conversion of the intermediate **95** into a metathesis substrate **104**, and treatment with Hoveyda—Grubb 2nd generation catalyst, yielded the corresponding macrocycles **105**.



Scheme 10 Marcaurelles's oligomer-based approach to a library of macrocycles, of which many stereoisomers were prepared; a) 1) PyBOP, DIPEA, CH_2Cl_2, 0 °C, 15 h; 2) BH_3-DMS, THF, 65 °C; **b) 96**, Et_3N, CH_2Cl_2, 0 ˚C; **c)** CsF, DMF, 85 ˚C; or TBAF, NH_4F; NaH, THF; **d)** 1) **99,** PyBOP, DIPEA, CH_2Cl_2, rt then TBAF, THF, 72-93%; 2) $HC{\equiv}CCH_2Br$, NaHMDS, THF, DMF, −78 ˚C, 91-96%; **e)** $[Cp^*RuI]_4$, PhMe, 70 ˚C; **f)** PS-$CsPF_6$, PhMe, 55 ˚C; **g)** 1) DIPEA, CH_2Cl_2; 2) TBAF, THF, 0 ˚C; 3) NaH, allyl bromide, DMF, 0 ˚C, 50-77%; **h)** Hoveyda-Grubbs 2nd gen cat. (10 mol%)

1.4.1 Bioactive Macrocyclic Compounds discovered *via* DOS methodologies

Ultimately, the aim of DOS libraries is to explore biologically relevant chemical space.[88] The macrocycles **106**-**110** have all been identified to be useful tools for probing biological mechanisms and/or are potential starting points for drug discovery (Figure 7). The macrocycles **106** and **108** were identified from the same DOS library and target different proteins: **106** was identified a micromolar histone deacetylase (HDAC) inhibitor (IC_{50} class 1: 1.5 μM; class 2: 2.8 μM; and class 3: 4.4 μM).[87] Alternatively, macrocycle **108** was identified as a novel lead molecule for the treatment of malaria: it inhibits a multidrug-resistant strain of *P. falciparum* parasites (Dd2) with GI_{50}† 0.54 nM.[89] In a similar vein, screening identified **107** as a compound active against *β*-cell apoptosis which exhibited EC_{50} 0.78 μM.[90] Compounds **109** and **110** were identified, using small-molecule microarray technology, as inhibitors of the Shh signalling pathways which function by binding directly to the Sonic hedgehog protein.[91]

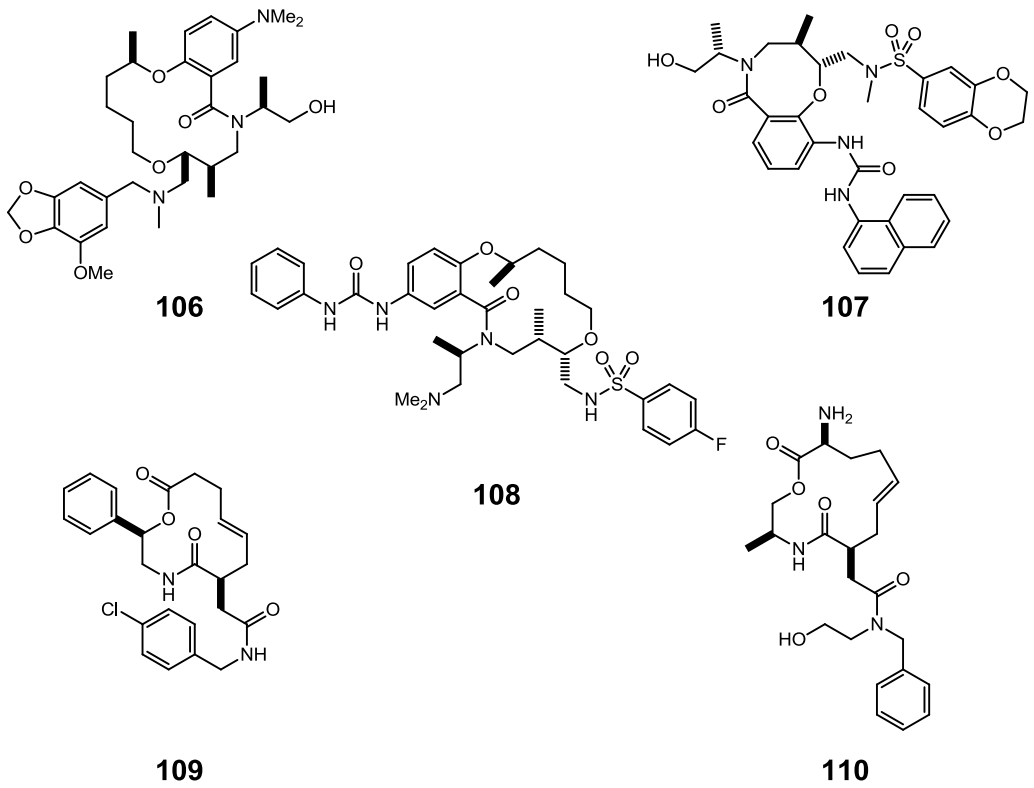


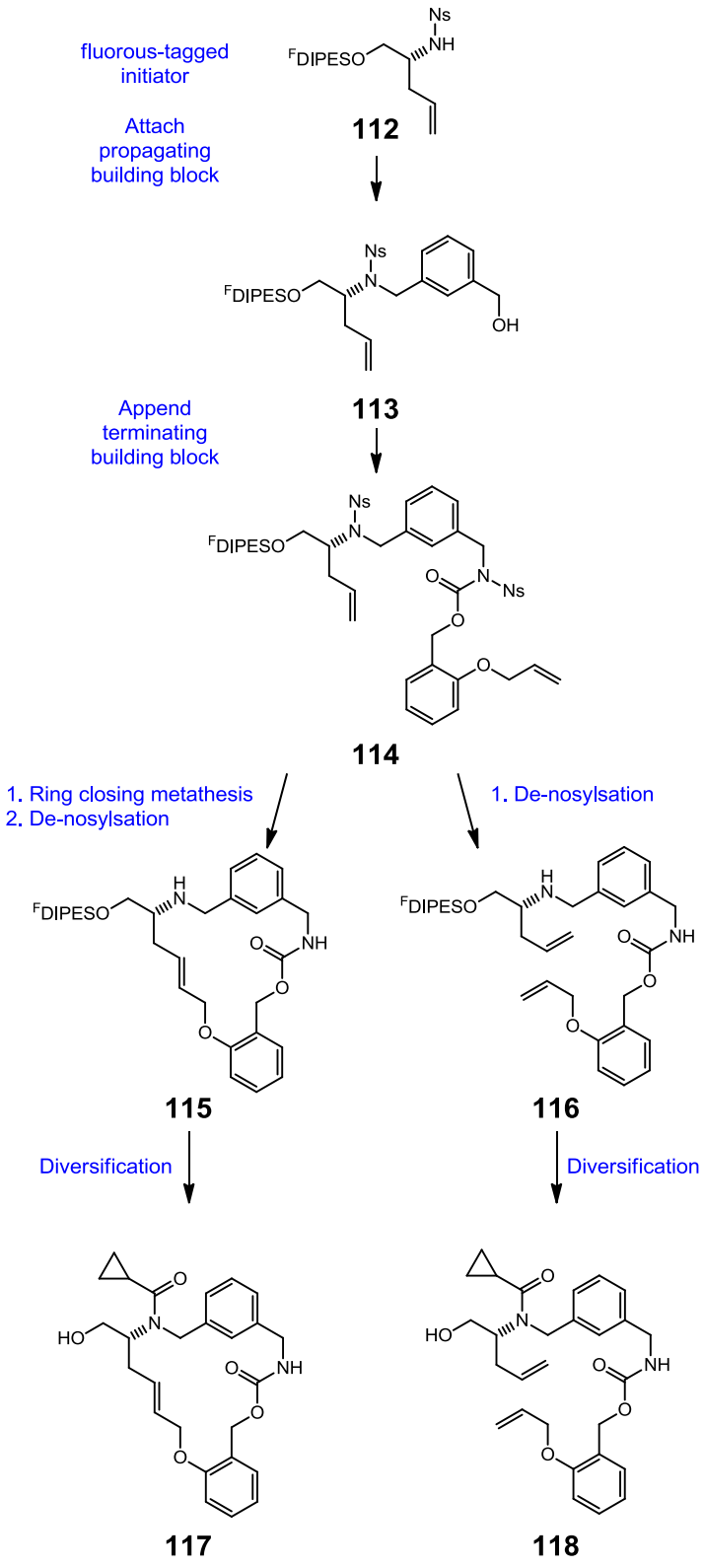
Figure 7 Bioactive macrocycles identified from DOS libraries

† GI_{50} – concentration required for 50% inhibition of cell proliferation

1.5 Project outline and design

In this project, it was proposed to develop a DOS strategy that would enable the expedient synthesis of a library of natural product-like macrocycles. Using only a few reactions, it was planned to combine building blocks to yield substrates for cyclisation; pairing the termini of the substrate together would generate the macrocyclic scaffolds. The cyclic and acyclic products would then be further diversified with a range of capping groups.

The envisaged 'build-couple-couple-pair' approach is outlined in Scheme 11; hydroxy acetate building blocks would be linked to a fluorous tagged building block such as **112**. After deacetylation, terminating building blocks would be appended to yield cyclisation substrates such as **114**. Ring-closing metathesis would then be used to cyclise the linear substrates to yield macrocycles **115**. After revealing a free amine, the macrocycles would subsequently be functionalised in a branching fashion by attachment of diversifying groups. The development and exemplification of this 'build-couple-couple-pair' approach will be described in the following Chapters. Furthermore, the synthesis of the acyclic analogues will be described; the synthesis of these analogues would allow direct comparison of the biological relevance of macrocyclic compounds with their acyclic counterparts.



Scheme 11 The proposed synthetic approach exploits 'build-couple-couple-pair' approach. The approach is illustrated through the proposed synthesis of the macrocycle **117** and its acyclic counterpart **118**

1.5.1 Fluorous-tagging technologies

It was essential that the library be synthesised efficiently as possible; it was decided that fluorous-tagging be used to allow expedient purification of intermediates. These technologies have numerous benefits over other purification methods such as solid-phase synthesis. The fluorous tag consists of a perfluorinated octane chain; generally the molecules are oils at room temperature, this allows the molecules to undergo homogeneous reactions and be analysed and purified by traditional methodologies (LC-MS, NMR, TLC, column chromatography).

Picture 1 Demonstration of the fluorous tag using a fluorous tagged dye and a dye containing no fluorous tag. The first picture shows the columns in their unloaded states, the second photo is showing the compounds being loaded and eluted with 15% water in methanol; this results in the third picture where the un-tagged blue dye has been washed out of the mixture. The fluorous tagged compound orange dye can now be eluted with methanol (structures not shown).

1.5.2 Synthetic methods to be exploited

It was proposed to use the Fukuyama—Mitsunobu reaction, which has been shown to be a reliable reaction within the Nelson group, to link building blocks; in addition, removal of the 2-nitrobenzenesulfonyl (Ns) group, would reveal an amine for derivatization. It was hoped *N*-Ns amides and carbamates would serve as competent nucleophiles, allowing easy differentiation between nitrogen atoms in the deprotected scaffolds (Figure 8). For example, if macrocycle **119** (X = H_2) was deprotected, then two secondary amines would be liberated which would subsequently be difficult to distinguish. However, with **119** (X = O), deprotection would liberate an amine and an amide which should be easily differentiated (to give **120**). An alternative approach was to use trifluoromethanesulfonylamides as nucleophiles leading to macrocycles such as **122** (X = Tf); subsequent deprotection would remove only the Ns group, thus liberating only one amine for conversion into final compounds (e.g. 123).

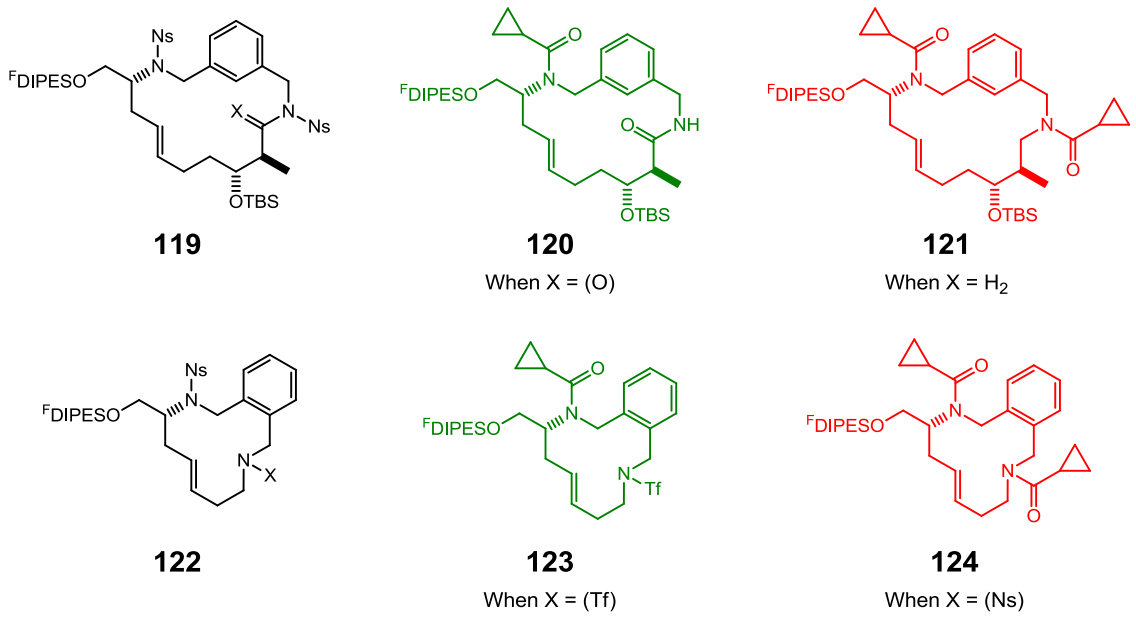


Figure 8 Careful selection of nucleophiles for the Fukuyama-Mitsunobu reaction would allow differentiation of the groups revealed upon Ns deprotection

It was also important to select the best methods for the ring-closing steps. It was imperative to select an approach in which the functionality needed for cyclisation was stable throughout the synthesis, and the use of protecting groups was minimised. 'Click' chemistry has been highlighted as being reliable for macrocyclisation;[92,93] however, a pitfall would be that all final compounds would inherit a triazole unit which may dominate their molecular properties. Lactonization and lactamization are proven methods for synthesising large rings; however the resulting functional groups (especially the lactones) are prone to hydrolysis in biological systems and, in any case, intricate protecting group chemistry would be required. Methods that rely on S_NAr reactions would also require extensive functional group interconversion and/or the use of protecting groups.

It was therefore decided that ruthenium-catalysed ring-closing metathesis would be used to initiate the cyclisation of the substrates: the required terminal alkenes are resistant to most reaction conditions and protecting group chemistry would not be required. The alkene product of ring-closing metathesis is both natural product-like, and serves to provide conformational restriction of the macrocycle.

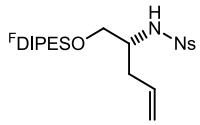
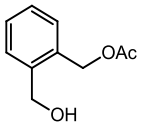
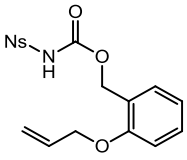
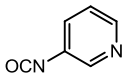
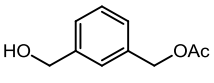
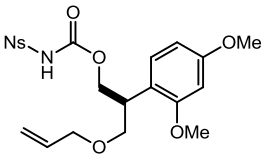
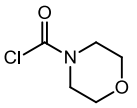
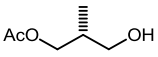
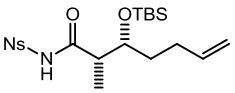
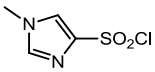
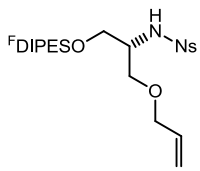
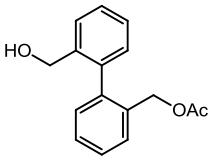
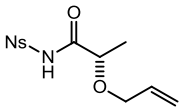
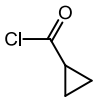
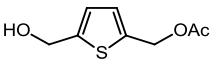
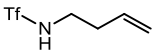
1.5.3 Design of building blocks and cyclisation substrates

The design of DOS libraries requires careful consideration.[94,66] It was decided to design final compounds that had some natural product-like features. In addition, although the final molecules were unlikely to be Lipinski-'Rule of 5' compliant, their molecular properties were carefully considered.

1.5.4 Molecular Properties

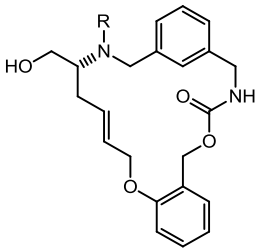
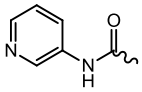
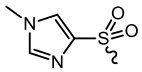
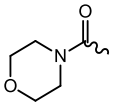
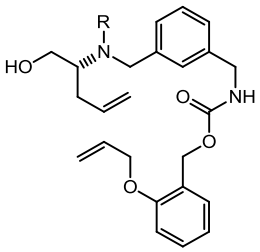
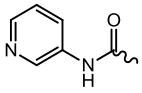
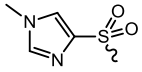
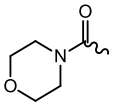
It is well documented that molecular properties that compounds posess can have a dramatic effect on their biological availability and activity.[11] Lipinski set out the four 'rules of five'; in general a orally active compound must have no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, the molecular weight must not exceed 500 Daltons and the octanol-water partition coefficient (clogP) must not exceed 5. Properties such as clogP are important to predict the distribution of a compound in a biological system, compounds that are hydrophobic will favour areas such as lipid bilayers whereas hydrophilic compounds will distribute in areas such as blood serum. The partition coefficient can be predicted using 2 common methods clogP and AlogP; clogP is a fragment based approach whereas AlogP is an atom based approach.

Table 2 Potential building blocks for the synthesis of a library of diverse macrocycles

'Initiating'	'Propagating'	'Terminating'	Diversifying Groups
 **112**	 **126**	 **131**	 **136**
	 **127**	 **132**	 **137**
	 **128**	 **133**	 **138**
 **125**	 **129**	 **134**	 **139**
	 **130**	 **135**	

The proposed 'initiating' building blocks were fluorous tagged 2-nitrobenzenesulfonamides which were expected to be competent substrates in Fukuyama—Mitsunobu reactions. It was proposed to append five different 'propagating' building blocks (e.g. the hydroxy acetates **126**-**130**). Deacetylation would then reveal an alcohol needed for a second Fukuyama—Mitsunobu reaction. It was proposed to append different terminating building blocks (e.g. the *N*-Ns carbamates **131** and **132**, the *N*-Ns amides **133** and **134**, and the trifluoromethanesulfonylamide **135**). Subsequent ring-closing metathesis and Ns deprotection would yield secondary amines such as **115** (Scheme 11). Diversification with a range of commercially available reagents would increase the molecular complexity and skeletal diversity. Some of the molecular properties of proposed final compounds are summarised in Table 3 (for selected compounds) and in Section 1.5.5

Table 3 Example molecular properties of a selection of potential final compounds

entry	scaffold	R	cLogP[a]	mW
1	 **140**	H	2.78	382.4
			2.66	502.6
			2.48	526.6
			3.15	450.5
			2.17	495.6
2	 **141**	H	3.9	410.5
			3.78	530.6
			3.59	554.7
			4.27	478.6
			3.29	523.6

[a] Calculated using ChemDraw Pro 12.0.2.1076

1.5.5 Design of a comparative study of acycles and macrocycles

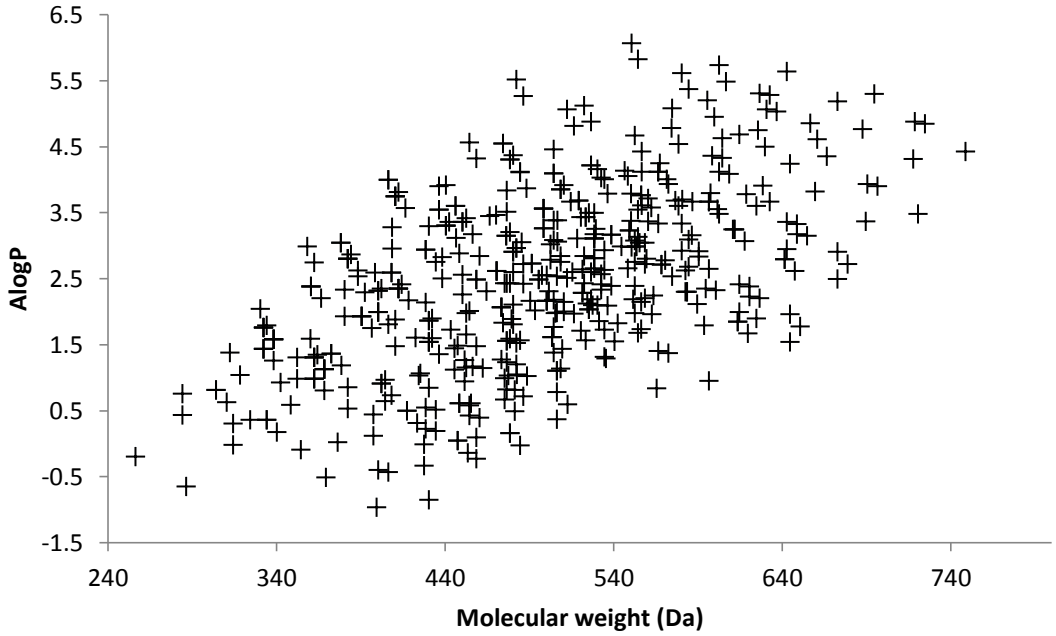
The macrocyclization of molecules can have a profound effect on their properties including their biological activity (see Section 1.1.3). To undertake a comparative study of the properties of macrocycles and their acyclic counterparts, we planned in addition, to synthesise the acyclic variants of all the proposed macrocycles. However, the biological evaluation of the compounds was beyond the scope of the project.

1.5.6 Molecular properties of the proposed library

The combination of building blocks shown in Table 3 would result in a library with ALogP values from 6.06 to −0.96 with an average of 2.49;[95] molecular weights from

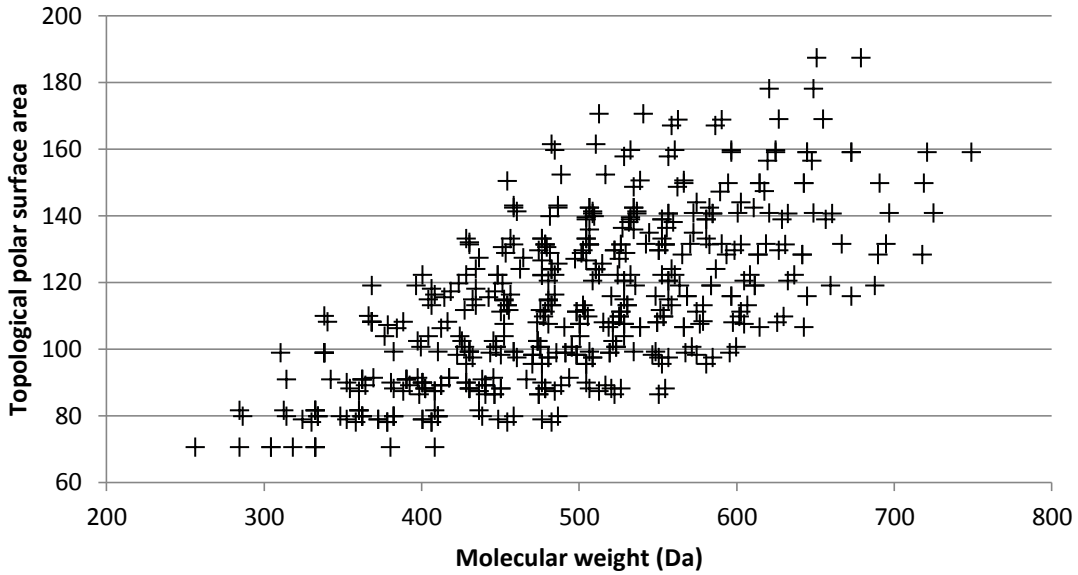
256.3 to 748.9 with an average of 493.5; ring sizes from 11 to 21 with the most common being 18; and TPSA from 70.6 to 187.3 with an average of 113.2 (see Graphs 2, 3 and 4). However, the predicted and actual polar surface may deviate dramatically, due to the many conformers that macrocycles can adopt there is possibility of 'burying' the polar surface area; although it has been shown there is a strong correlation between the predicted versus reality.[96] The molecular properties of many compounds did not comply with the Lipinski 'Rule of 5'; this was expected for a library of macrocycles.[97]

Graph 2 The distribution of molecular weights versus the atom based prediction[†] of the logP

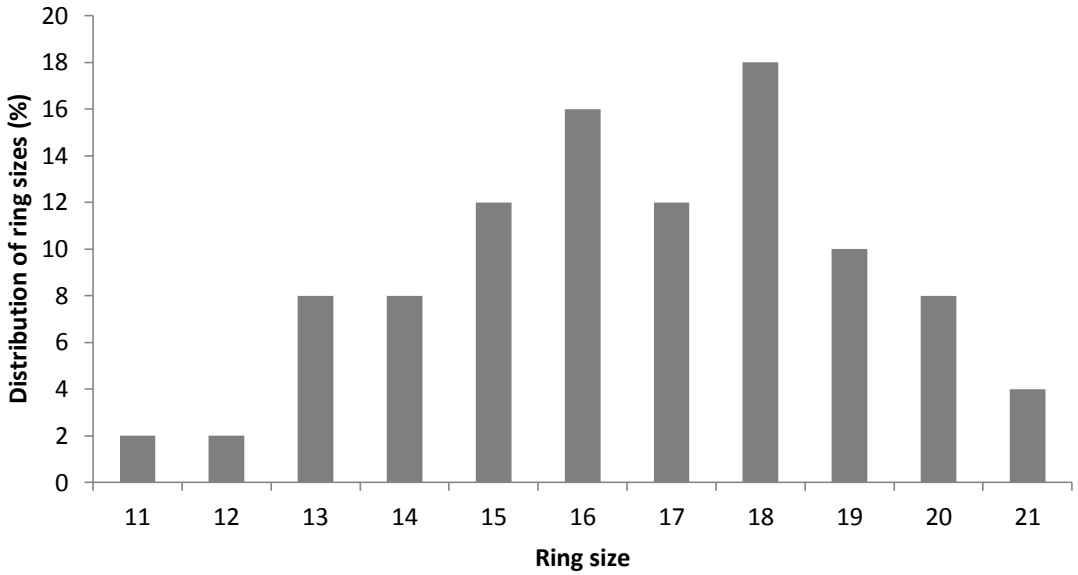


[†] Predicted using Accelrys Pipeline Pilot version 8.5

Graph 4 Distribution of the TPSA vs the molecular weights across the proposed library



Graph 5 Distribution of ring sizes across the proposed library



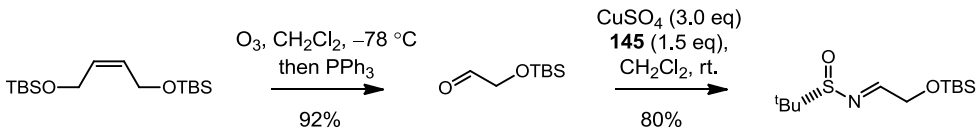
2 Building block synthesis

This Chapter outlines the synthesis of building blocks, for example those proposed in section 1.5.2. It was envisaged that there would be three types of building block: fluorous-tagged 'initiating' building blocks; 'propagating' building blocks; and 'terminating' building blocks.

2.1 Synthesis of initiating building blocks

(S_s)-2-methylpropane-2-sulfinamide **145** and initiating building block **112**

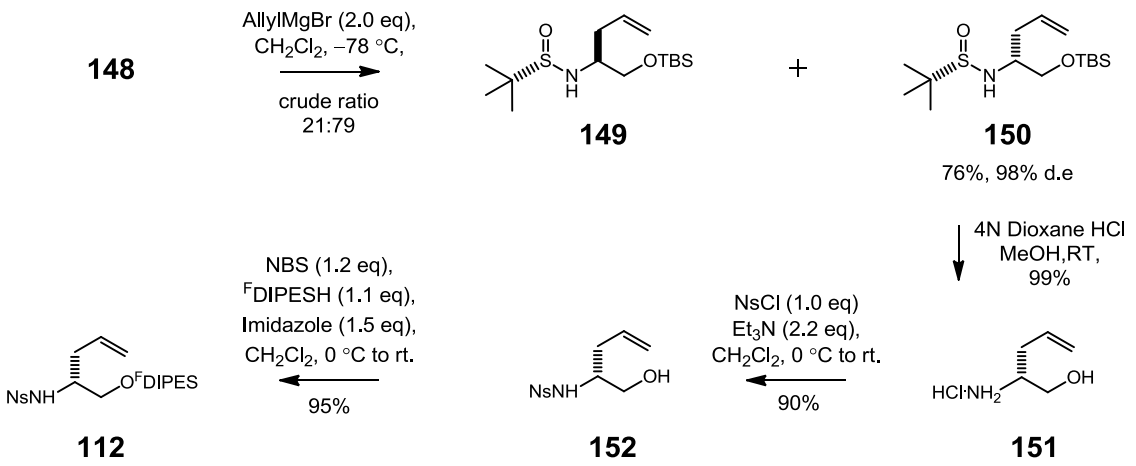
The synthesis of the initiating building block **112** exploited the chiral auxiliary **145**, developed by Ellman.[98–101] Ozonolytic cleavage of the alkene **146** afforded the aldehyde **147** in 92% yield; it was found that triphenylphosphine was a much better reductant than Me_2S because the by-product is highly crystalline, allowing facile purification, and the reaction proceeded rapidly at temperatures below 0 °C. The aldehyde **147** was condensed with (S_s)-2-methylpropane-2-sulfinamide **145**, mediated by $CuSO_4$, to give the sulfinimine **148** in 80% yield.



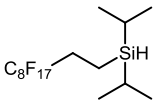
146 **147** **148**

Scheme 12. Preparation of sulfinimine **148**

The stereoselectivity of the addition of allyl magnesium bromide to the imine **148** depended strongly on the reaction conditions used. Initially, poor stereoselectivity was observed (*ca.* 40:60). However, the stereoselectivity was markedly improved by slow addition of the Grignard reagent, presumably allowing better control of the temperature of the reaction: under these conditions, a 21:79 mixture of the separable diastereoisomeric products was obtained (Scheme 13). The major sulfonamide **150** was deprotected by methanolysis under acidic conditions to give the hydrochloride salt **151** in 99% yield (Scheme 13). The amino alcohol **151** was converted into the 2-nitrobenzenesulfonamide **152** in 90% yield. The fluorous-tagged silane **153** was treated with NBS to form the corresponding bromosilane which was reacted *in situ*[102,103] with the alcohol **152** to give the silyl ether **112** in 95% yield. The synthesis was performed on a large scale to give 30 g of the sulfonamide **112**.



Scheme 13. *Synthesis of the initiating building block* **112**



153

Figure 9 Structure of ^{F}DIPESH

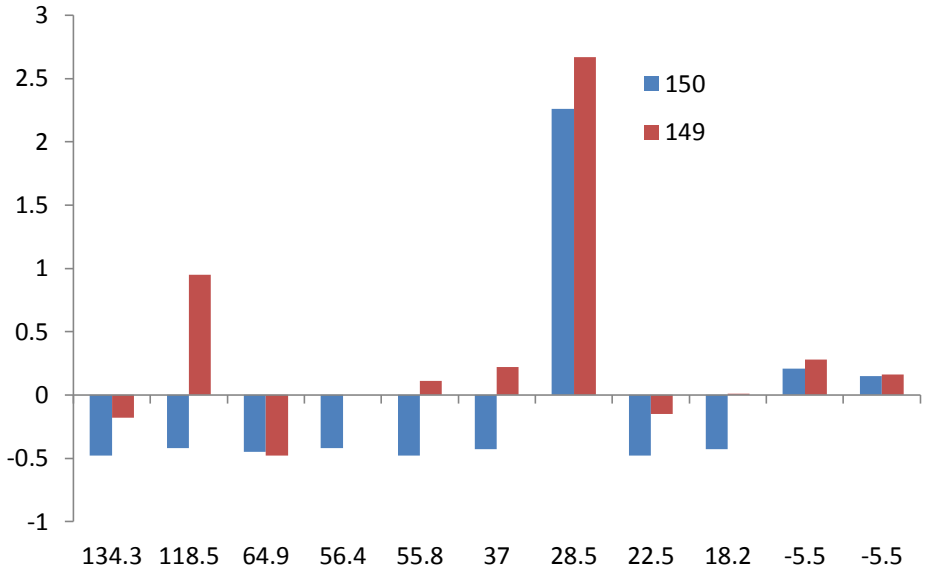
The sense of induction from the chiral auxiliary in **148** was independently determined using chiral HPLC (see figure 10). Surprisingly, it was found that the major diastereomer **150** did not have the relative configuration reported by Ellman. Deprotection of the major diastereomer **150** using acidic methanolysis gave the (*R*)-2-aminopent-4-enol, determined by optical rotation (-10.6 vs +14.1[98]). Further investigation concluded that the major diastereomer that we and Ellman *et al.*, had synthesised appeared to be the same compound by comparison of optical rotation (+57.6 vs +57.8) and 75 MHz ^{13}C NMR spectral data (Table 4)‡

‡ The signals in **150** were similarly shifted relative to those in Ellman's major product.

Table 4 ^{13}C spectra data for the products of the addition to the sulfinimine

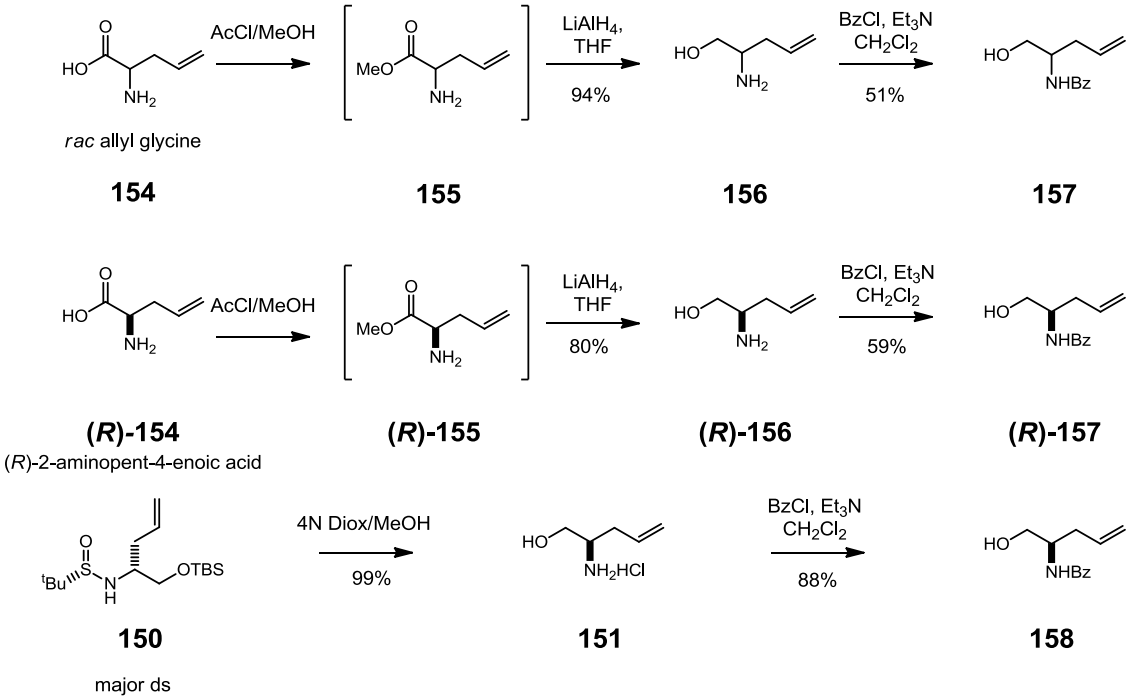
150[a]	deviation	Ellman major[b]	deviation	**149**[a]
134.78	-0.48 ↓	134.3	-0.18 ↓	134.48
118.92	-0.42 ↓	118.5	0.95 ↑	117.55
65.35	-0.45 ↓	64.9	-0.48↓	65.38
56.82	-0.42 ↓	56.4	0	56.4
56.23	-0.48 ↓	55.8	0.11 ↑	55.69
37.48	-0.43 ↓	37	0.22 ↑	36.78
26.24	2.26 ↑	28.5	2.67 ↑	25.83
22.98	-0.48 ↓	22.5	-0.15 ↓	22.65
18.63	-0.43 ↓	18.2	0.01 ↑	18.19
-5.29	0.21 ↑	-5.5	0.28 ↑	-5.22
-5.35	0.15 ↑	-5.5	0.16 ↑	-5.34

[a] Recorded in $CDCl_3$ at 75 MHz [b] Recorded at 100 MHz in $CDCl_3$



Graph 6 Deviations in the ^{13}C NMR of **149** and **150** from the major isomer that Ellman reports.

The racemic and enantiomerically pure amino alcohols were synthesised so that a quantitative method such as chiral HPLC could be used to determine the sense of induction. The *rac*-allyl glycinol was prepared from the parent allyl glycine **154**; methyl ester formation to give **155** followed by $LiAlH_4$ reduction to give amino alcohol **156** in 94% yield. In a similar vein, the enantiomerically pure (*R*)-2-aminopent-4-enoic acid **(*R*)-154** was converted into the amino-alcohol **(*R*)-156**. The amino alcohols **156**, **(*R*)-156** and **151** were converted into the corresponding benzamides **157**, **(*R*)-157** and **158** in 51%, 59%, and 88% yield respectively. Chiral HPLC showed good separation of the enantiomeric benzamides (Panel A, Figure 10) and conclusively showed that the amino-alcohol liberated from the major diastereomer prepared by Ellman was in fact the (*R*) isomer, and not the (*S*) isomer as stated. This was confirmed further through the determination of a crystal structure of one of the final compounds **159** (Figure 11).



Scheme 14 Synthesis of the molecules for chiral HPLC analysis

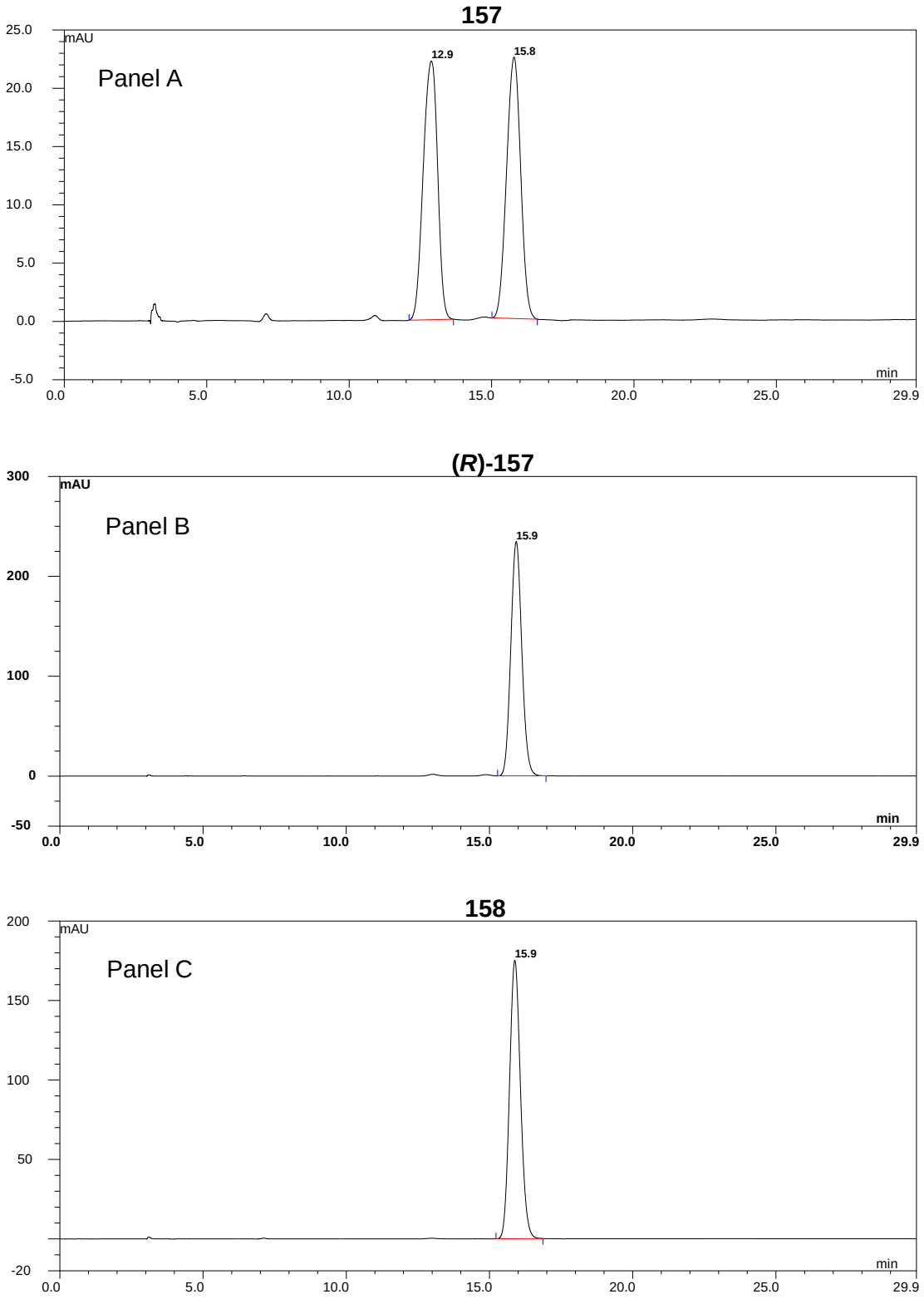
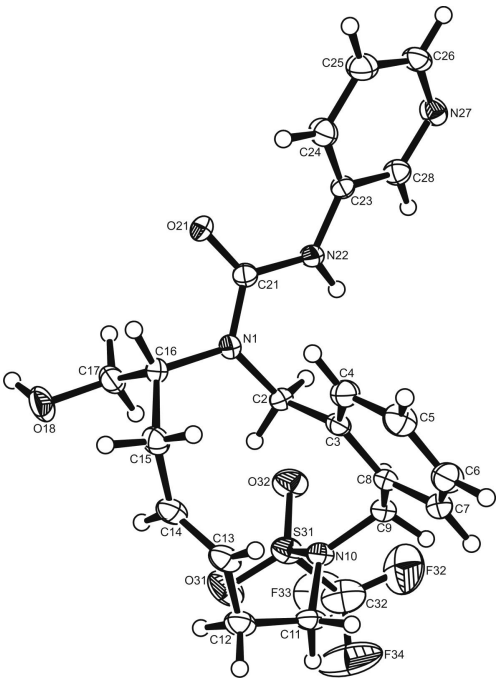
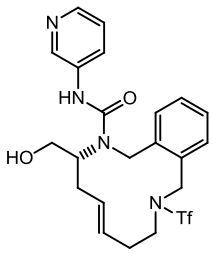


Figure 10 Chiral HPLC[§] chromatograms of the alcohols **157**, **(*R*) 157** and **158**.

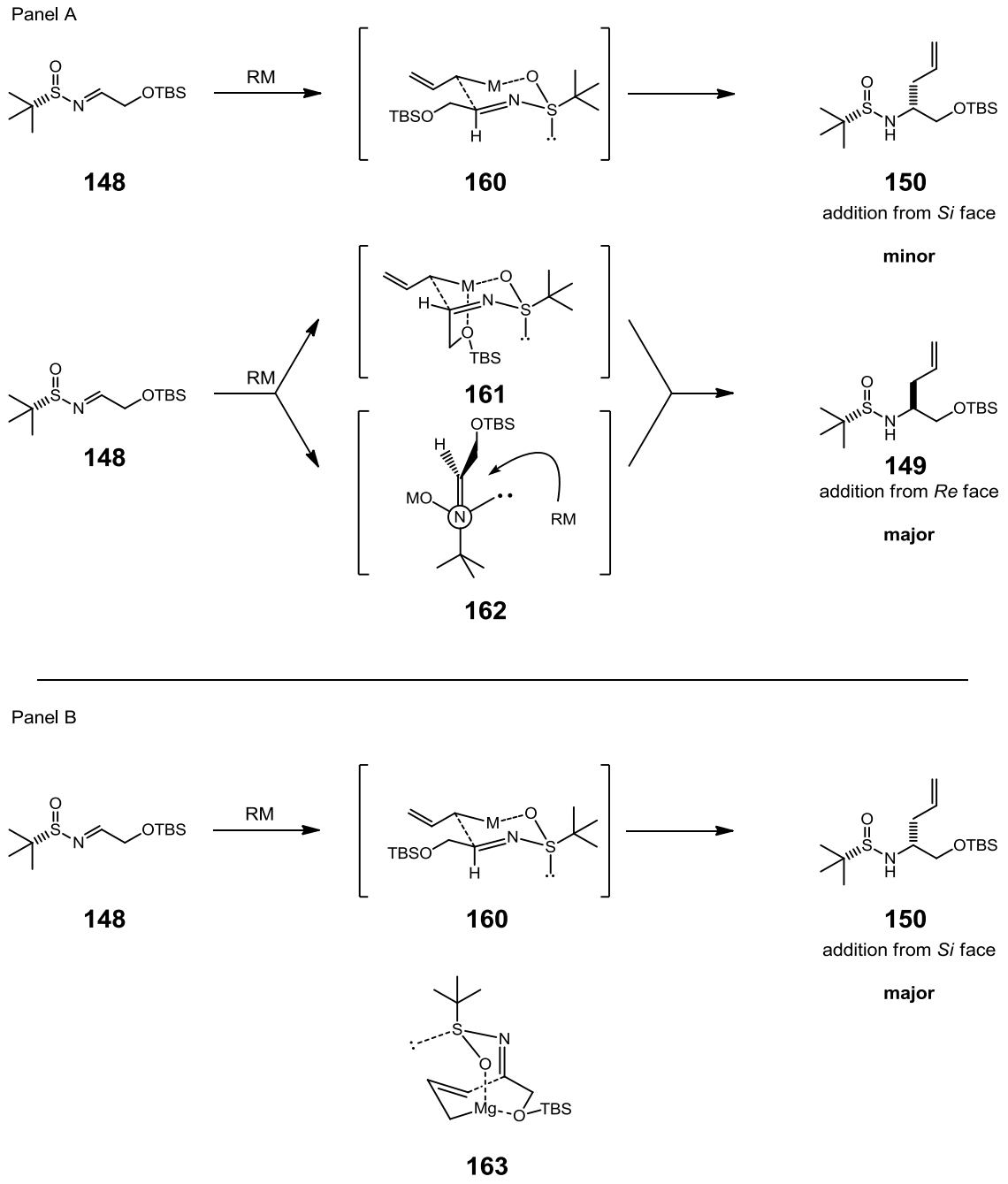
[§] 5% IPA/nHexane AD-H column





159

Figure 11 Left: Crystal structure of (5*E*,3*R*)-3-(hydroxymethyl)-*N*-(pyridin-3-yl)-9-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecine-2-carboxamide **159**. Right: Molecular structure of **159**

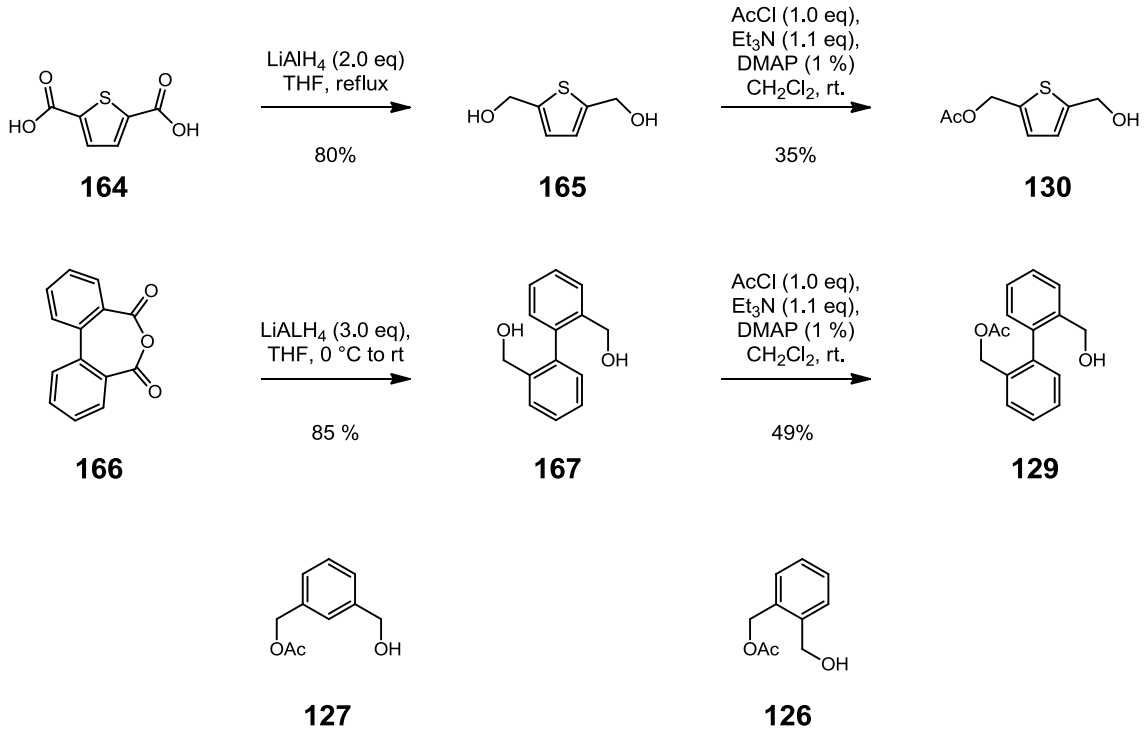


Scheme 15 Panel A Mechanism of induction of nucleophiles proposed by Ellman and Barrow. **Panel B** Revised sense of induction that is consistent with that experimentally determined.

Transition states previously proposed by Barrow[100] and Davis[104] propose that the induction arises from the chelated chair-like transition state **161** and the open transition state **162** respectively; however as these transitions predict the incorrect sense of induction for the addition of allyl magnesium bromide. We propose that the allyl group is delivered as in **160** or **163**. The sense of induction may be different for allylic nucleophiles because an S_E2' mechanism is possible.

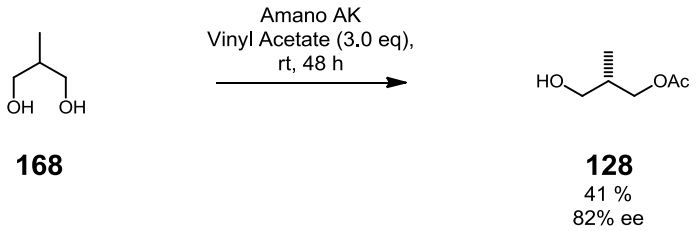
2.2 Synthesis of propagating building blocks

A series of hydroxy acetates was synthesised by reduction and acetylation of commercially-available bis-carboxylic acid derivatives. The bis-carboxylic acid **164** and diphenic anhydride **166** were reduced with $LiAlH_4$ in 80% and 85% yield, respectively; and acetylation with acetyl chloride gave the hydroxy acetates **130** and **129** in 35% and 49% yield (Scheme 16). The hydroxy acetates **127** and **126** were prepared by Francesco Marchetti.

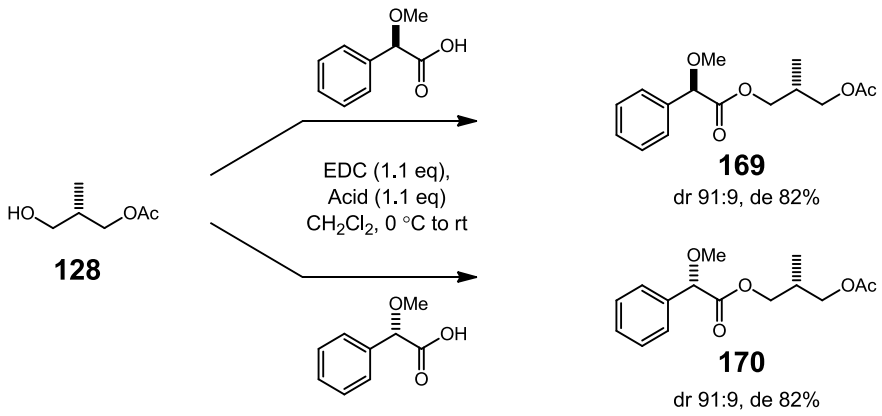


Scheme 16 Preparation of hydroxyl acetates

Enzymatic desymmetrization was used to prepare the hydroxy acetate **128** from the diol **168** in 41% yield (Scheme 17). Conversion of the hydroxyacetate **128** into the diastereoisomeric esters **169** and **170** (Scheme 18) allowed the determination of its enantiomeric excess (82% ee) by 500 MHz ^{1}H NMR spectroscopy



Scheme 17 Desymmetrization of 2-methyl-1,3-propanediol



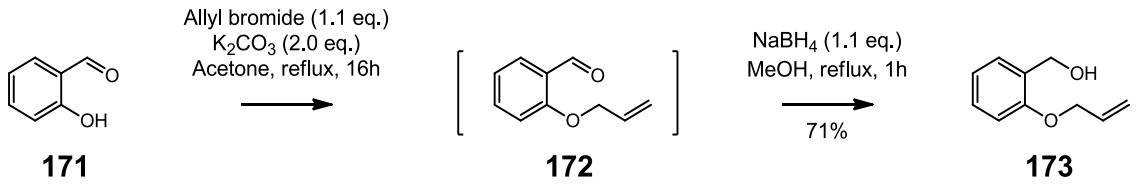
Scheme 18 Derivatization into the diastereomeric adducts

2.3 Synthesis of terminating building blocks

A variety of terminating building blocks were proposed in Section 1.5.2 for exploitation in Fukuyama—Mitsunobu reactions. Alcohols have been synthesised (Section 2.3.1) which were then carbamylated with a 2-nitrobenzenesulfonyl isocyanate (Section 2.3.3). A small series of 2-nitrobenzenesulfonyl amides and trifluoromethane sulfonamides was also synthesised, (Sections 2.3.2 and 2.3.4 respectively).

2.3.1 Terminating alcohol synthesis

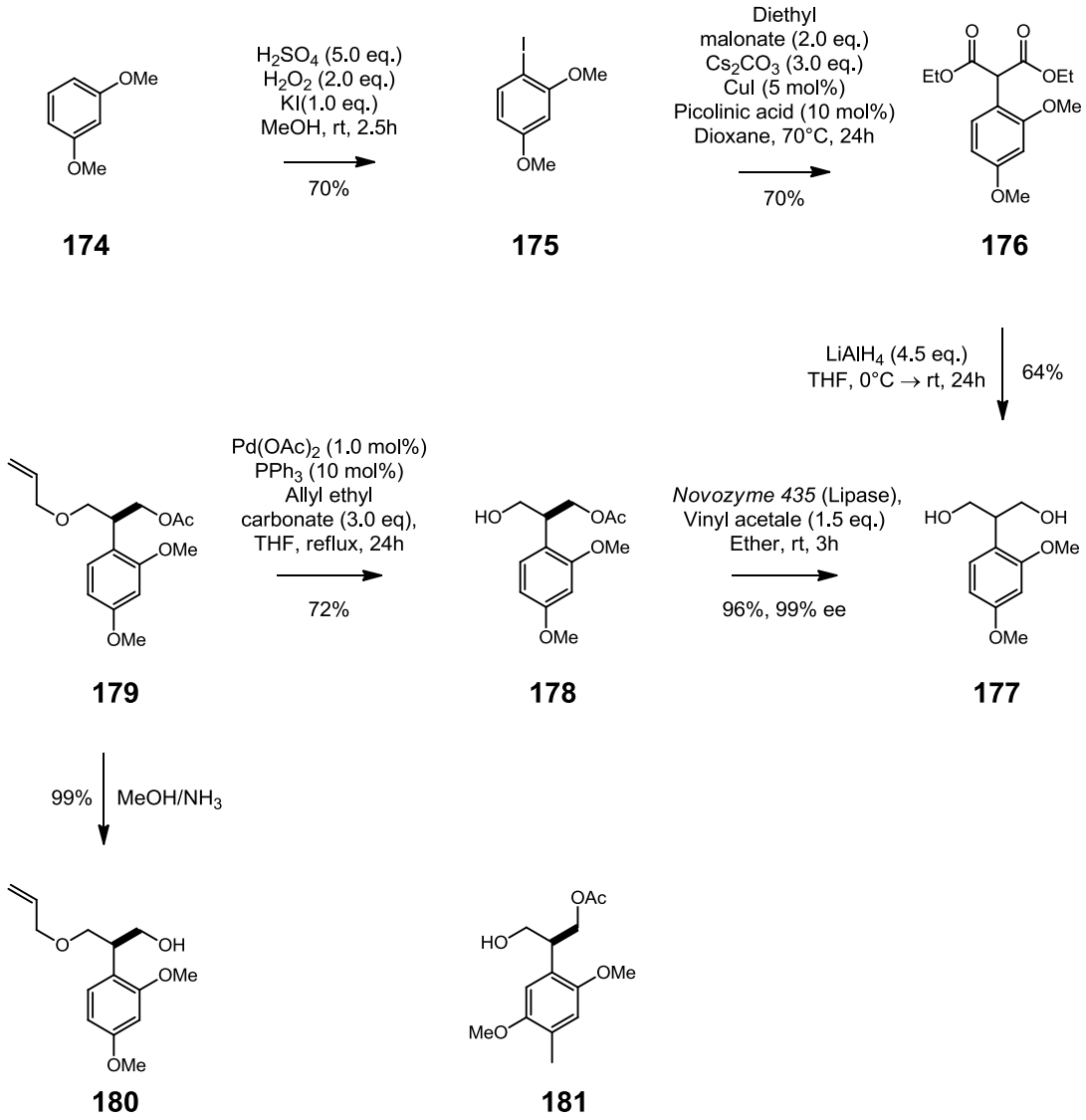
A range of alcohols was prepared so that through various functional group interconversions a range of terminating building blocks could be obtained. The alcohol **173** was synthesised in 71% overall yield (Scheme 19). Allylation of **171**, by treatment with allyl bromide and potassium carbonate, gave the aldehyde **172** which was not isolated; reduction with sodium borohydride gave the alcohol **173**.



Scheme 19 Synthesis of the salicaldehye-derived terminating building block **173**

Scheme 20 shows the preparation of building block **180**. Oxidative iodination of 1,3-dimethoxybenzene **174**, by treatment with sulfuric acid, hydrogen peroxide and potassium iodide, gave 2,4-dimethoxyiodobenzene **175** in 70% yield.[105] A copper-catalysed Ullman-type coupling of the aryl iodide **175** with diethyl malonate using picolinic acid as a ligand gave the aryl malonate **176** in 70% yield.[106] Subsequent reduction of the malonate **176** with $LiAlH_4$ gave the diol **177** in 64% yield. Biocatalytic desymmetrization of the diol **177** was carried out using *Candida Antarctica* lipase B and vinyl acetate; this procedure gave the hydroxy acetate **178** in 95% yield with >99% ee. The enantiomeric excess was determined using chiral HPLC by comparison with the racemic compound synthesised from the diol **177** using acetyl chloride. The absolute configuration of the hydroxyacetate **181** was assigned by analogy with related examples[107,108] such as **181**. Allylation of the hydroxyacetate **178** was undertaken in the absence of base as it was envisioned that the acetate group could migrate across the 1,3-diol leading to racemisation. Firstly, allylation was attempted with silver(I) oxide and allyl bromide; however this method gave a complex mixture and the allyl ether **179** could not be identified by LC-MS. A palladium(II) catalysed method was explored and gave the allyl ether **179** in 72% yield;[109,110] potentially racemization could have been an issue. However submitting the hydroxyacetate **178** to the same conditions without allyl

ethyl carbonate showed no erosion of the enantiomeric excess, again determined by chiral HPLC analysis of the crude reaction. Deprotection of the acetate **179** to give the alcohol **180** was achieved in 99% yield using methanolic ammonia.



Scheme 20 Asymmetric preparation of the chiral alcohol **180**

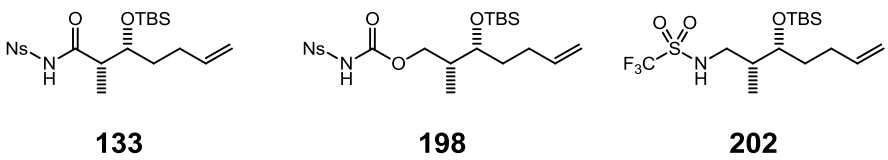
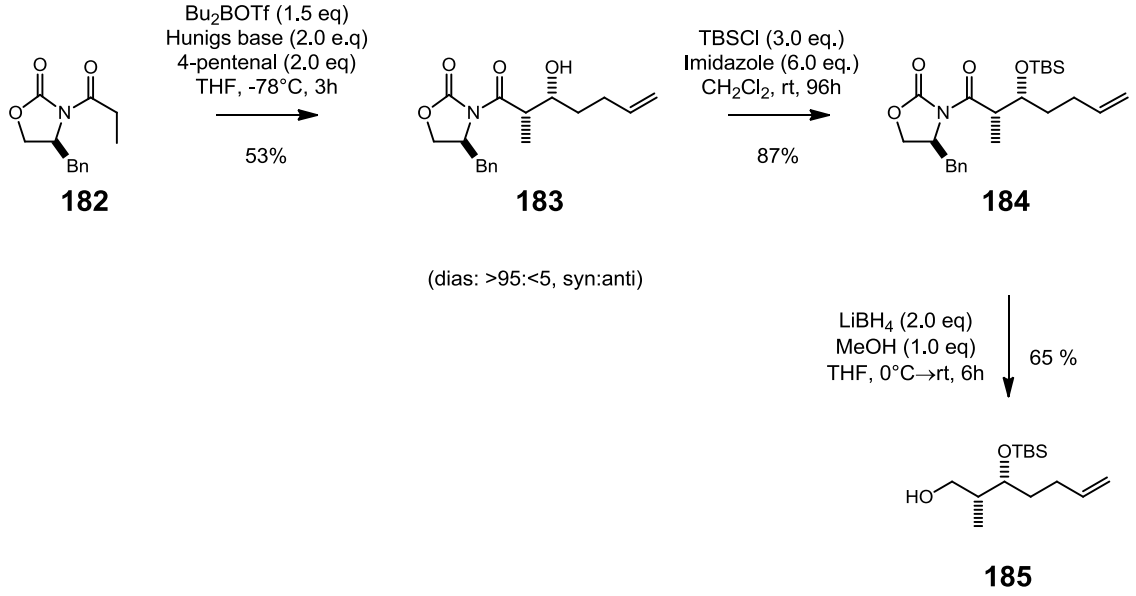


Figure 12

A chiral auxiliary was exploited to prepare a handful of terminating building blocks with varying nucleophilic groups (**133**, **198** and **202**). The aldol product **183** was prepared in the reaction between the boron enolate of **182** and 4-pentenal. The boron enolate was

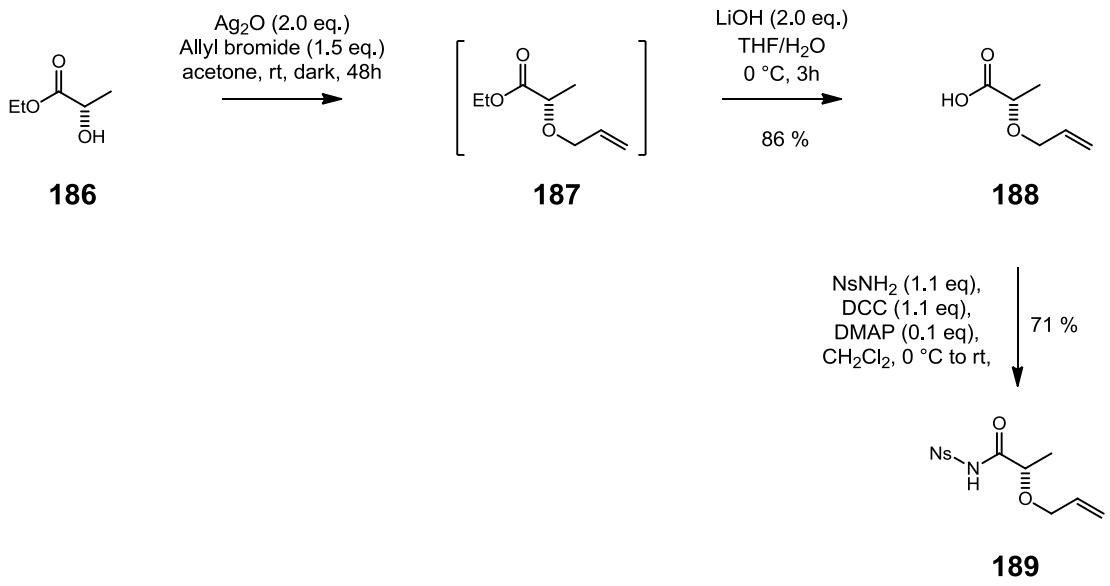
prepared by treatment of the *N*-acyl oxazolidinone **182** with dibutylboron trifluoromethanesulfonate in the presence of Hunig's base; a 53% yield of **183** was obtained with a >95:<5 diastereoselectivity. The sense of diasteroselectivity was assigned by comparison to literature[111] and ratio of diastereoisomers determined by 500 ^{1}H MHz NMR spectroscopy. Protection of the secondary alcohol of as a *tert*-butyldimethylsilyl ether was possible using the silyl chloride in 87% yield. Subsequently the chiral auxiliary was removed in two ways. Treatment of the *N*-acyl oxazolidinone **184** with $LiBH_4$ gave the alcohol **185** in 65% yield (Scheme 21) and hydrolysis of **184** yielded the acid **190** (Scheme 23)



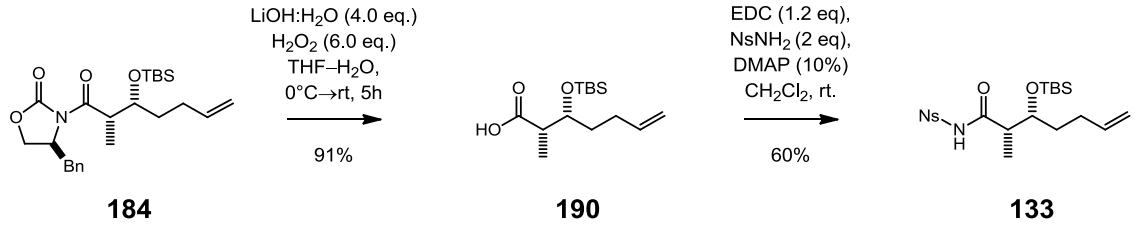
Scheme 21 Chiral auxiliary controlled aldol reaction and subsequent removal of the auxiliary

2.3.2 Synthesis of 2-nitrobenzenesulfonyl amides

Ethyl lactate **186** was allylated by treatment with silver(I) oxide and allyl bromide; subsequent hydrolysis with lithium hydroxide gave the carboxylic acid **188** in 86% yield.[112] The acyl sulfonamide **189** was obtained in 71% yield by DCC-mediated coupling of **188** with 2-nitrobenzenesulfonamide (Scheme 22). Treatment of the imide **184** with lithium hydroxide in the presence of hydrogen peroxide yielded the acid **190** (Scheme 23). The acyl sulfonamide **133** was formed in 60% yield by an EDC-mediated coupling of acid **190** with 2-nitrobenzenesulfonamide.



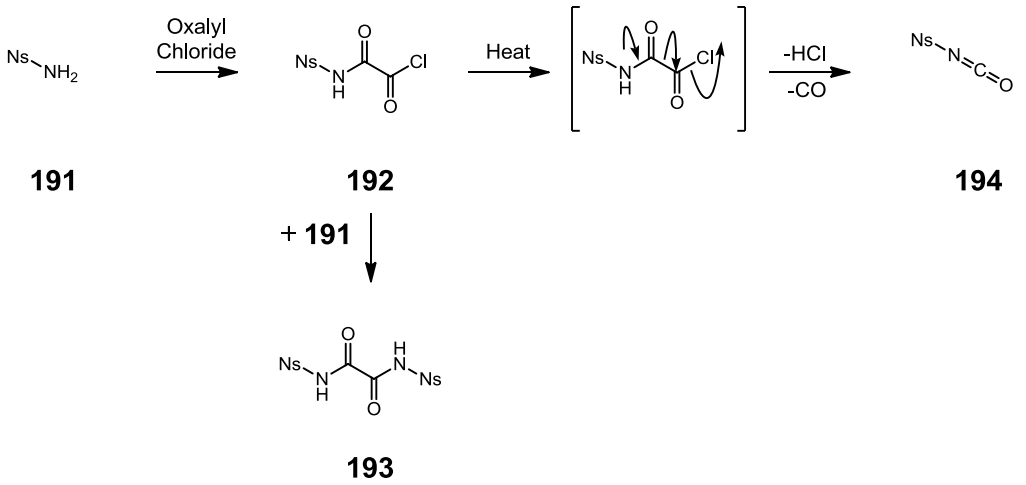
Scheme 22 Preparation of the acyl sulfonamide **189** from ethyl lactate



Scheme 23 Hydrolysis of the imide **184** and subsequent acyl sulfonamide formation

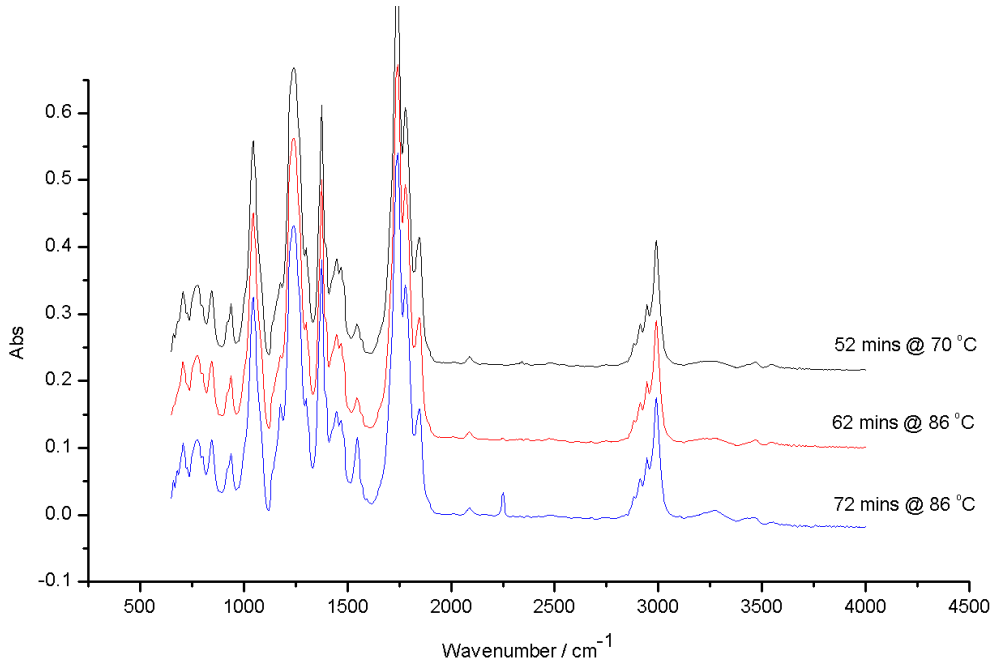
2.3.3 *N*-(2-nitrobenzenesulfonamide) isocyanate synthesis and subsequent synthesis of *N*-(2-nitrobenzenesulfonamide) carbamates

The synthesis of *N*-(2-nitrobenzenesulfonyl) carbamates required an efficient synthesis of 2-nitrobenzenesulfonyl isocyanate, which has been prepared previously;[113] however experimental detail and procedures are poor. Franz exploited thermal decomposition of the oxamic chloride[114]. Initial experiments were based on a procedure by Oh,[115] who showed that forming the oxamic chloride of anilines in ethyl acetate suppressed the formation of the bisoxamide; a solvent swap into dichlorobenzenes and heating under reflux achieved the thermal decomposition to the isocyanate.

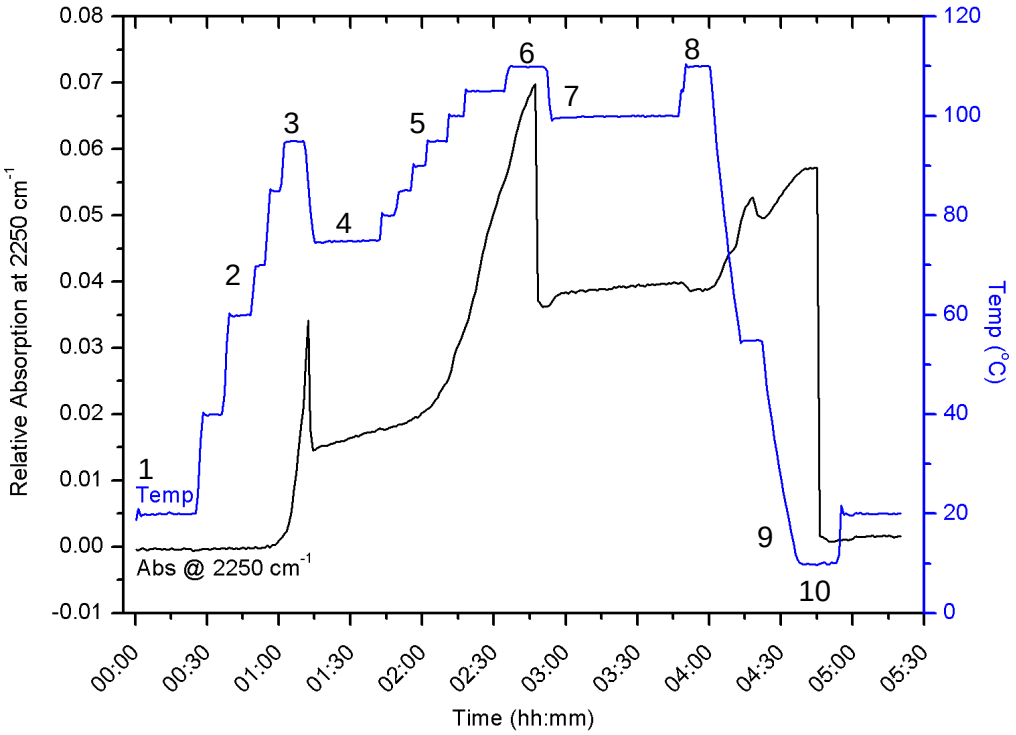


Scheme 24 Formation of isocyanate functionality by thermal decomposition of an oxamic chloride

ReactIR® was used to determine if toluene would serve as a suitable alternative solvent to dichlorobenzenes for thermal decomposition of **192**. This *in situ* monitoring technique is useful for accurately quantifying the generation reactive intermediates such as isocyanates. The practicability of using IR to monitor the reaction is facilitated by the diagnostic infrared stretch of isocyanates (ca. 2250 cm^{-1}), a region of the IR spectrum that it is diagnostic to few other functional groups. The formation and reaction of the isocyanate was followed by ReactIR® (See Graphs 6 and 7); elevated temperature (>86 ˚C) was required for efficient conversion of the oxamic chloride **192** to the isocyanate **194.** Graph 8 shows the stages throughout the synthesis of the nosyl isocyanate. The blue line depicts the temperature of the vessel in which the reaction was being carried out and the black line is the absorption at 2250 cm^{-1} (specifically the isocyanate region).

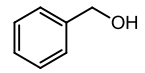
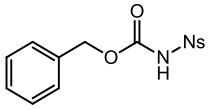
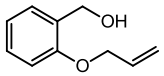
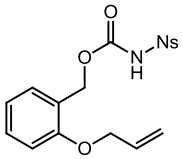
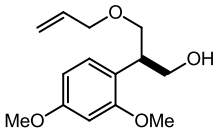
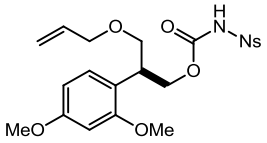
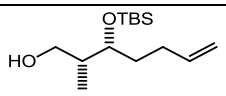
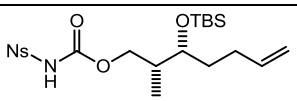
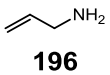
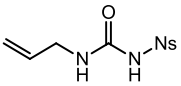


Graph 7. Formation of the isocyanate began at *c.a.* 86 °C. The relatively low intensity of the isocyanate band at 2250 cm^{-1} is due to the high concentration of ethyl acetate present.



Graph 8. IR and temperature profile of isocyanate formation followed by ReactIR®, monitoring absorption at 2250 cm^{-1}; 1) start point, PhMe added; 2) temperature ramped to 95 °C with holds; 3) temperature held at 95 °C and PhMe added (system dilution); 4) temperature hold at 78 °C; 5) ramp 5 °C/5 min; 6) temperature hold at 110 °C; 7) PhMe added; 8) temperature ramp to 110 °C; 9) system cooled to –10 °C; 10) benzyl alcohol addition. The reported temperature is the jacketed vessel temperature as the internal size of the vessel would not accommodate a temperature probe.

Table 5 Summary of the nucleophiles reacted with 2-nitrobenzenesulfonyl isocyanate

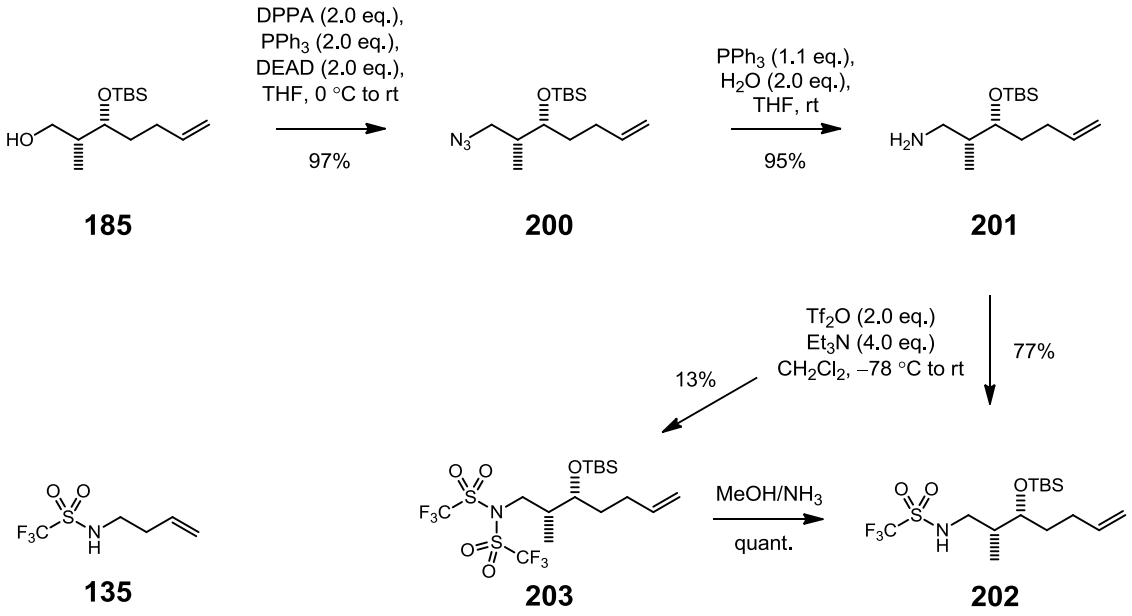
nucleophile	method	additive[a]	product	Yield (%)
 **195**	A	-	 **197**	77
 **173**	A	-	 **131**	77
 **180**	A	-	 **132**	95
 **185**	A	Et_3N	 **198**	25
 **196**	A	$Et(^iPr)_2N$	 **199**	51

Methods; A) $NsNH_2$ (2.0 eq.), $(COCl)_2$ (10 eq.), EtOAc, reflux; then PhMe distil EtOAc, reflux (110 °C); Nucleophile addition, rt. a) The base was added simultaneously with the nucleophile

The reactions of the isocyanate **194** with a range of nucleophiles are summarised in Table 5. Excess oxalyl chloride was reacted with 2-nitrobenzenesulfonamide, after heating under reflux in ethyl acetate a solvent swap into toluene allowed for the temperature required for the thermal decomposition (Scheme 24). After heating under reflux in toluene, the crude isocyanate **194** was used. The reaction of the isocyanate **194** with alcohols (**197**, **131**, and **132**) resulted in yields between 77 and 95%; however the reaction of alcohol **185** with isocyanate **194** resulted in a relatively low yield (25%), compared to reactions with **195**, **173** and **180**. Base was added simultaneously with alcohol **185** due to the nucleophile having an acid labile silyl protecting group. The addition of the organic base with allylamine **196** was to ensure the amine was not protonated in the crude acidic conditions. Purification of all the 2-nitrobenzenesulfonyl carbamates and ureas involved column chromatography, which was assisted by the low pKa (~4-5) of the carbamate proton. Eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH allowed for long retention of the products compared to the impurities; subsequent elution with 50:8 CH_2Cl_2—EtOH eluted the desired carbamates and ureas.

2.3.4 Synthesis of *N*-(trifluoromethanesulfonamide) terminating building blocks

In addition to *N*-(2-nitrobenzenesulfonyl) amides and carbamates, triflamides were also synthesised. The alcohol **185** was converted into the triflamide **202** in 3 steps (Scheme 25). The alcohol **185** was converted into the azide **200** in 97% yield by treatment with diphenylphosphoryl azide (DPPA). The azide **200** was reduced with triphenylphosphine in aqueous THF to give the amine **201** in 95% yield, which was reacted with trifluoromethanesulfonic anhydride to give the triflamide **202** in 77% yield. The ditriflamide **203** was observed as a minor by-product in 13% yield; gratifyingly it was shown that the ditriflamide **203** could be converted quantitatively back into the triflamide **202** using methanolic ammonia (Scheme 25).

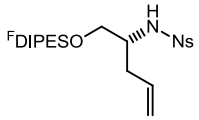
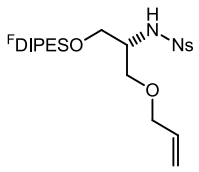
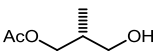
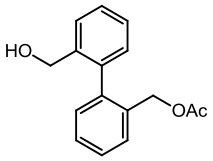
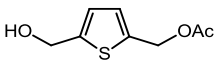
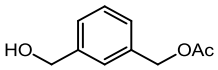
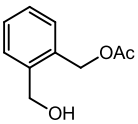
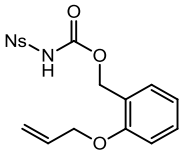
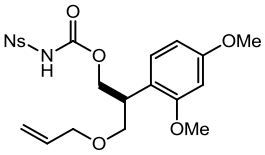
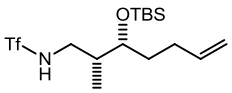
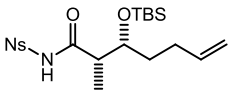
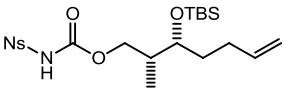
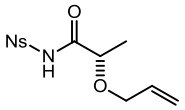
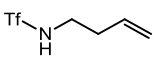


Scheme 25 Synthesis of the terminating building block **202**. The terminating building block **135** was synthesised by Francesco Marchetti

2.4 Summary of building blocks synthesised

The range of building blocks prepared is summarised in Table 6. Building blocks **125**, **127**, **126** and **135** were synthesised by Francesco Marchetti.

Table 6 Building Blocks synthesised

Initiator	Propagator	Terminator
 **112**  **125**	 **128**  **129**  **130**  **127**  **126**	 **131**  **132**  **202**  **133**  **198**  **134**  **135**

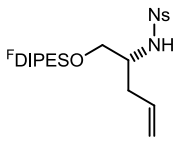
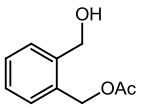
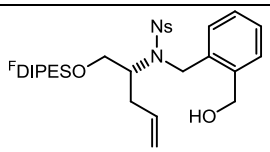
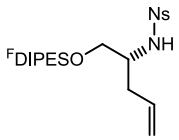
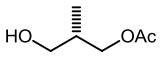
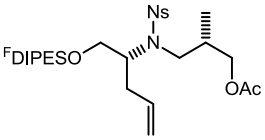
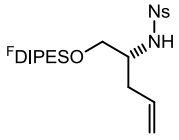
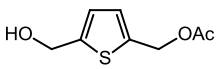
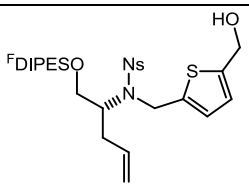
3 Development of methods for the synthesis of a diverse library of macrocycles

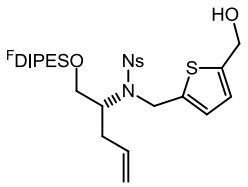
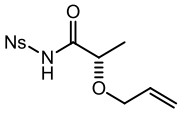
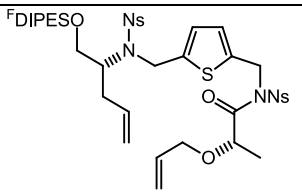
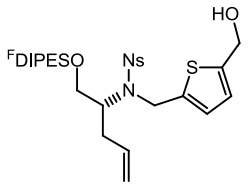
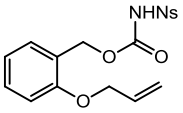
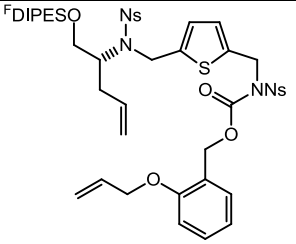
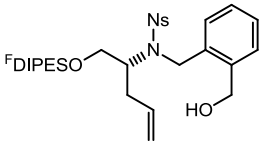
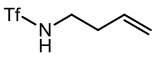
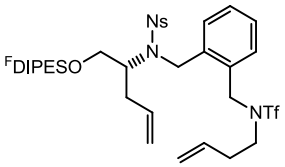
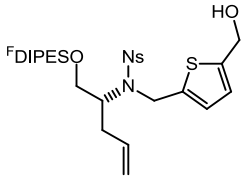
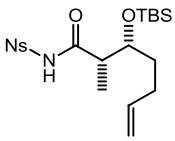
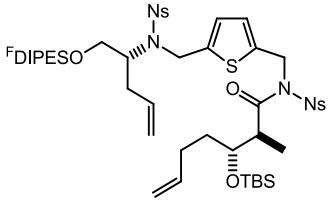
This Chapter describes the development of robust methods for the preparation of a diverse library of macrocycles. The specific methods involved Fukuyama—Mitsunobu reactions to iteratively combine the building blocks (Section 3.1); ring closing metathesis (Section 3.2); and reactions for diversification and the release of the final compounds from the fluorous tag (Section 3.4). The Fukuyama—Mitsunobu or Fukuyama amine synthesis relies on a nitrobenzene sulfonamide to increase the acidity of the NH whilst also preventing over alkylation of the nitrogen.[116]

3.1 Examination of the Fukuyama—Mitsunobu reaction as a method to link building blocks

This Section describes the investigation of the Fukuyama—Mitsunobu reaction to append building blocks onto a fluorous-tagged building block. The results of the study are summarised in Table 7.

Table 7 Examination of Fukuyama—Mitsunobu methods

Entry	Fluorous-tagged building block	building block	Method	Product	Mass recovery %,[a] [Purity][c]
1	 **112**	 **126**	M1, D	 **205**	99, [>95]
2	 **112**	 **128**	M1	 **206**	18[d]
3	 **112**	 **130**	M1, D	 **204**	70[b]

4	 **204**	 **134**	M2	 **207**	69 [81]
5	 **204**	 **131**	M2	 **208**	62[b]
6	 **205**	 **135**	M3	 **209**	93 [>95]
7	 **204**	 **133**	M3	 **210**	56 [85]

Methods; **M1**) PPh_3 (2 eq.), DEAD (2 eq.), ROH (2 eq.), THF (0.1 M), 0 °C → RT; **M2**) PPh_3 (4 eq.), DEAD (4 eq.), NucH (4 eq.), CH_2Cl_2 (0.1 M) 0 °C → RT; **M3**) PPh_3 (1.05 eq.), DEAD (1.05 eq.), CH_2Cl_2 (0.1 M), 0 °C → RT; **D**) sat. $MeOH/NH_3$; [a] Purified by F-SPE unless otherwise stated; [b] Purified by column chromatography; [c] Purity estimated by ^1H 500 MHz NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [d] Notably, loading of the hydroxy-acetate **130** to the sulfonamide **112** proceeded smoothly, with complete consumption of the sulfonamide (hydroxy-acetate **130** in 4-fold excess); however analysis by chromatography and ^1H NMR indicated that the thiophene **130** had polymerized; purification by conventional flash chromatography was required to isolate **204**

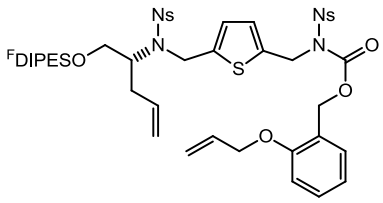
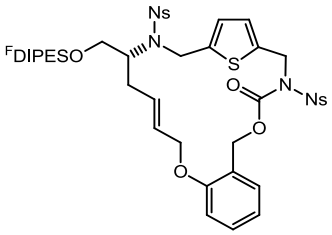
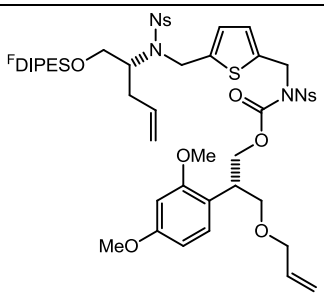
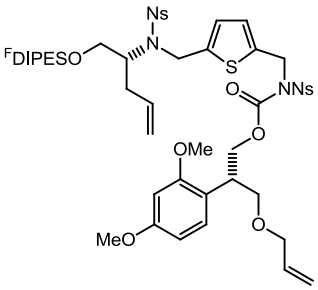
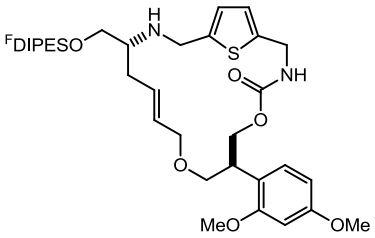
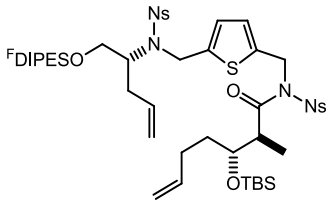
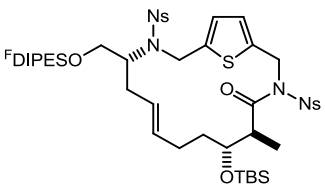
The 2-nitrobenzenesulfonamides have been shown in the literature[116] and previous work in our group[85] to be excellent nucleophiles; however it was crucial to determine whether the proposed building blocks reacted to give good yields of the required products (see Table 7). The sulfonamide **112** was treated with diethyl azodicarboxylate in the presence of triphenylphosphine and the corresponding alcohols **126**, **128** and **130** (entries 1, 2 and 3 respectively). This method worked well with the benzylic and heterobenzylic alcohols **126** and **130**; however use of the more hindered alkyl alcohol **128** led to poor conversion. The products from the Fukuyama—Mitsunobu reactions

were purified by fluorous-solid phase extraction. Subsequently, the acetate protecting groups were removed with saturated ammonia in methanol (entries 1 and 3), and the products from this step did not require purification. The second round of Fukuyama—Mitsunobu reactions appended the terminating building blocks onto the fluorous-tagged substrates (entries 4, 5, 6 and 7). The 2-nitrobenzenesulfonyl amides **133** and **134**, entries 4 and 7, proved to be effective nucleophiles; and the triflamide **135** was an excellent nucleophile, entry 6.

3.2 Optimisation of the metathesis reaction

As discussed in Section 1.5, ruthenium-catalysed metathesis was chosen to form the macrocyclic ring system. This section describes the development of a generic procedure for ring closing metathesis of substrates such as those products shown in the Table 7. Our studies are summarised in Table 8

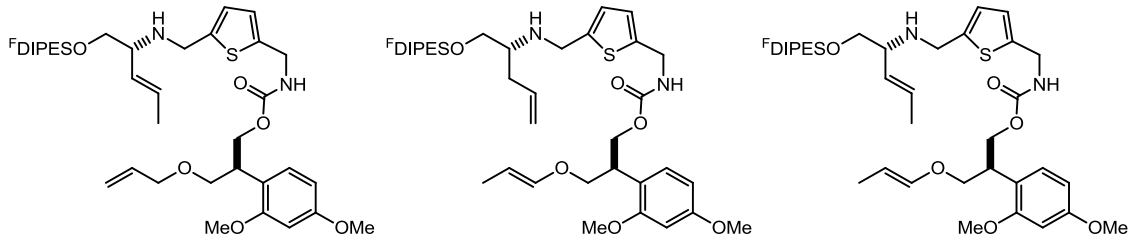
Table 8 Investigation of the cyclisation of potential metathesis substrates

entry	substrate	method	Metathesis time	product	Yield %,[a] (*E*/*Z*)[b]
1	 **208**	RCM1	16	 **211**	60 (>98:<2 *E*)
2	 **212**	RCM1	5 days	Complex mixture	-
3	 **212**	RCM3 then N1	24	 **213**	34[c]
4	 **210**	RCM2	24	 **214**	40

Methods: **RCM1**) Hoveyda-Grubbs 2nd gen cat. (1 mol%), MTBE (5 mM), 55 °C then $(HOCH_2)_3P$ (0.8 eq.), Et_3N (1 eq.), silica, rt; **RCM2**) Hoveyda—Grubbs 2nd gen cat. (2 mol%), 1,4-benzoquinone (4 mol%), MTBE (5 mM), 55 °C then $(HOCH_2)_3P$ (0.8 eq.), Et_3N (1 eq.), silica, rt; **RCM3**) Hoveyda—Grubbs 2nd generation (5 mol%), 1,4-benzoquinone (10 mol%), MTBE (5 mM), 55 °C then $(HOCH_2)_3P$ (0.8 eq.), Et_3N (1 eq.), silica, rt; **N1**) PhSH (10 eq.), K_2CO_3 (2.5 eq.), DMF, rt; [a] Purified by column chromatography [b] Determined using ^1H 500 MHz NMR [c] Mixture of starting material and product isolated, removal of the 2-nitrobenzene sulfonamides allowed for better separation.

Initially, ring-closing metathesis using Hoveyda—Grubbs 2nd generation catalyst in *t*-butyl methyl ether as the solvent[117] was found to be rather substrate-specific. The metathesis of substrate **208** resulted in complete consumption of starting material to give the desired macrocycle in <16 h (entry 1); however, the substrate **212** gave a complex mixture of isomers of the starting material. The complex mixture of products was analysed by ^1H NMR and appeared to be a mixture of internal alkenes of the linear substrates, that is, the products of double-bond migration (e.g. **215**-**217**). The reaction was carried out in the presence of 1,4-benzoquinone, a known suppressor of this alkene migration,[118] and, gratifyingly, under these conditions, **212** cyclised effectively (entry 3); after removal of the 2-nitrobenzenesulfonamide groups, the amine was obtained in 33% overall yield. Under these conditions the metathesis substrate **210** was ring-closed in 40% yield (entry 4).

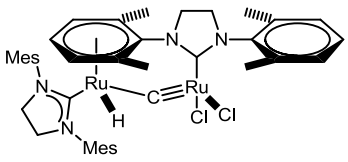
.



215 **216** **217**

Figure 13 Proposed isomerised products of **212**

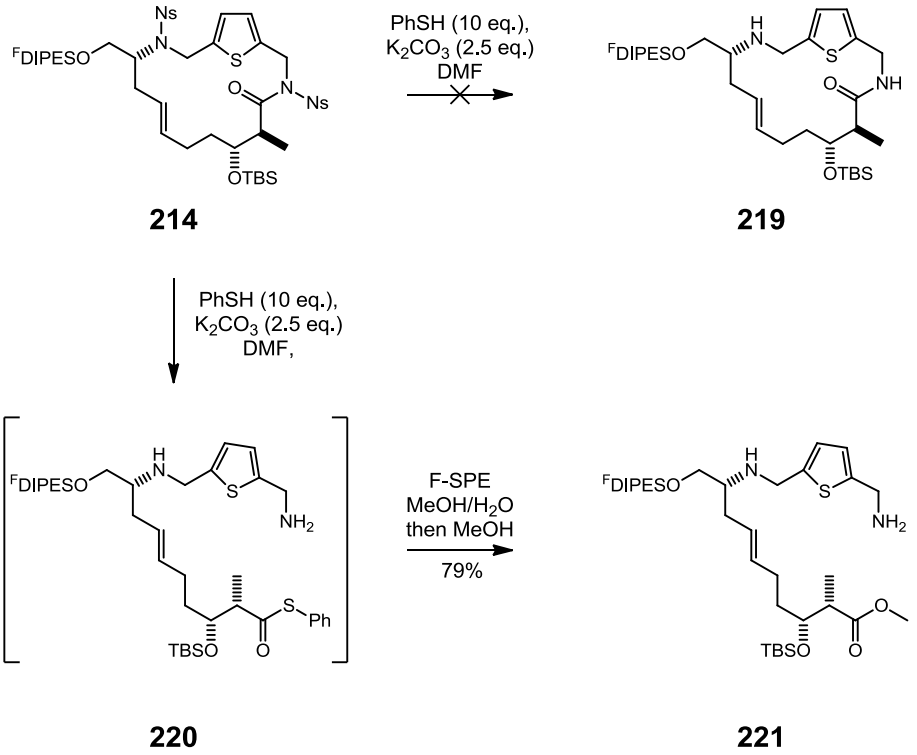
Double bond migration appears to be a common side reaction of ring closing metathesis; Grubbs *et al.,* have tried to suppress this isomerisation by using additives.[118] The isomerisation is proposed to stem from the formation of the ruthenium hydride species **218**. The mechanism for the formation of the Ru-H species is unknown; however it is hypothesised that it could be formed from a π-allyl species. Presumably the 1,4-benzoquinone is reduced rapidly in the presence of the proposed ruthenium hydride species.



218

Figure 14 Grubbs proposed Ruthenium hydride species

The application of *N*-(2-nitrobenzenesulfonyl) amides for the synthesis of macrocycles was reconsidered in the light of the result described in Scheme 26. Ring-closing metathesis of **210** to give **214** proceeded smoothly; however removal of the 2-nitrobenzenesulfonyl) group using thiophenol highlighted a problem. After removal of the 2-nitrobenzenesulfonyl group and F-SPE purification, the methyl ester **221** was isolated; presumably, thiophenolate attacked the amide to give the thioester intermediate **220**, (relief of ring-strain being the driving force) which was subsequently quenched with methanol during isolation. With this knowledge, 2-nitrobenzenesulfonyl amides were not used subsequently as terminating building blocks.



214 **219**

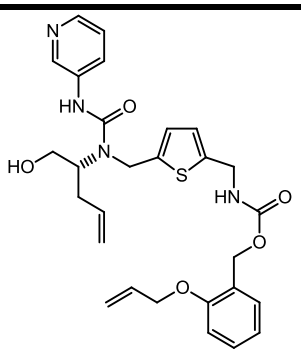
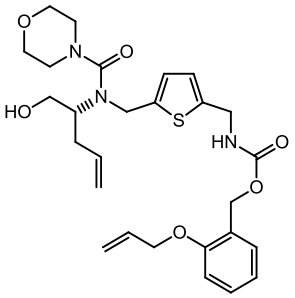
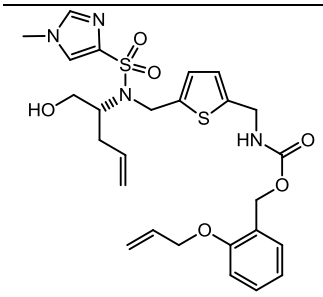
220 **221**

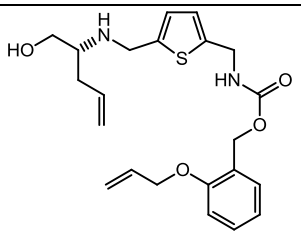
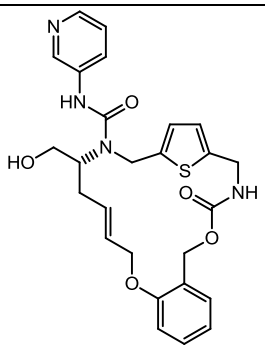
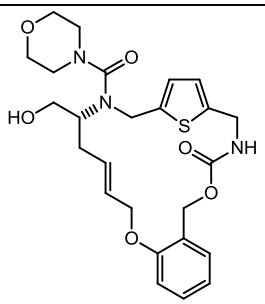
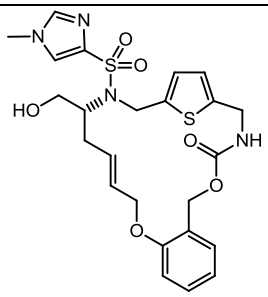
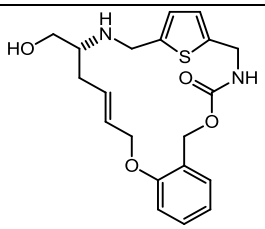
Scheme 26 Proposed thiophenol activation of 2-nitrobenzenesulfonyl amides and subsequent methanol ring opening

3.3 Diversification of the free amine cyclic and acyclic scaffolds

As discussed in Table 2 in Section 1.5, the acyclic and cyclic scaffolds were to be diversified with various electrophiles. As the diversifying groups **136**, **137**, **138** and **139** have already been examined for their molecular properties, the reactivity had to be confirmed; the results are outlined in Table 9.

Table 9 Diversification and removal of the fluorous tag

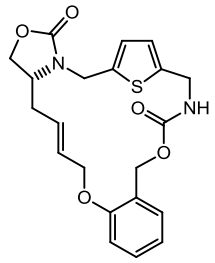
entry	Amine [purity][a]	Method, mass recovery [purity][a], amine	methods	final compound	yield over 2 steps
1a			A1, S2	 **224**	80
1b	**208**	N1, 86 [>95] **222**	A4, S2	 **225**	71
1c			A3, S2	 **226**	47

1d			S2	 **227**	27
2a			A1, S2	 **228**	71
2b	**211**	N1, 84 [>95], **223**	A4, S2	 **229**	59[e]
2c			A3, S2	 **230**	69
2d			S2	 **231**	96

Methods: **N1** PhSH (10 eq.), K_2CO_3 (2.5 eq.), DMF, rt; **N2** PhSH (5 eq.), K_2CO_3 (1.2 eq.), DMF, rt; **A1**) **136** (2 eq.), CH_2Cl_2 (0.1 M), rt; **A2**) **139** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt; **A3**) **138** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt; **A4**) **137** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt; **S1**) HF (10 eq., aq 50%), CH_2Cl_2/MeCN (50/50, 0.05 M), rt, TMSOMe (50 eq.); **S2**) TBAF

(5 eq., 1 M), CH_2Cl_2 (1 M), rt; [a] Purified by F-SPE unless otherwise indicated; [b] Purity estimated by ^1H 500 MHz NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [c] Purified by column chromatography; [d] Ratio of double bond isomers was determined using ^1H 500 MHz NMR spectroscopy; [e] The 2-oxazolidinone **232** was also isolated in a 34%

The diversifications described in Table 9 proceeded as planned with one exception: the conversion of the amine **223** into final compound **229** (entry 2b). In this case, the morpholine moiety of **229** was displaced by the alcohol to give **232** in 34% yield (along with the expected product **229** in 59% yield). This result is not surprising due to the proximity of the alcohol. In the light of this finding we did not subsequently use the derivatization agent **139**.



232

Figure 15 Unexpected 2-oxazolidinone from the displacement of the morpholine moiety in **229**

The fluorous tagging group was removed from the final compounds in two ways. We found that whilst tetra-n-butylammonium fluoride (TBAF) removed the fluorous-tag efficiently, it made the purification of the final compounds difficult. We therefore tried aqueous 48-51% hydrofluoric acid, which removed the fluorous tagging group just as efficiently as TBAF; however the purification was straighter forward. The reactions were quenched with methoxytrimethylsilane to remove the excess reagent.

3.4 Summary

This Chapter has outlined how the building blocks designed in section 1.5 and synthesised in Section 2.0 have been examined for their reactivity and stability towards the synthesis of a library of macrocycles. Section 3.1 described how the 2-nitrobenzenesulfonamides performed in Fukuyama—Mitsunobu reactions with the hydroxyl acetate building blocks. This study allowed the judicious selection of building blocks for the final library synthesis. Section 3.2 described the investigation of ring-closing metathesis using a small range of substrates. However this study allowed the most suitable conditions to be identified: specifically, the use of 1,4-benzoquinone as an additive with *tert*-butyl methyl ether as solvent. Section 3.3 described the investigation of the deprotection and derivatization of the final scaffolds. The study allowed the identification of a suitable set of derivatization reagents, and appropriate conditions for the preparation of the final compounds.

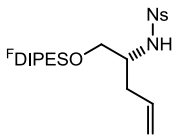
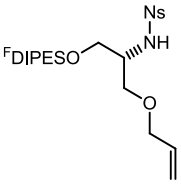
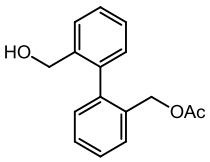
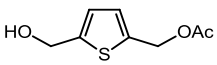
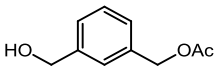
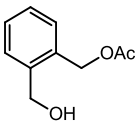
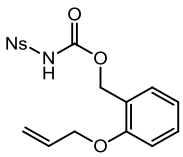
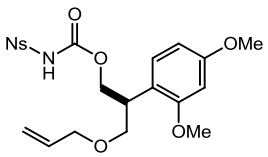
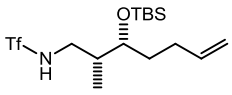
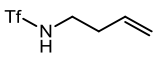
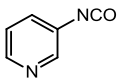
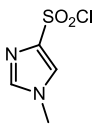
4 Synthesis of library intermediates and natural product-like macrocycles

This Section describes the synthesis of a library of natural product-like macrocycles. The building blocks described in Section 2.0 were combined in a 'branching' fashion using the robust methods that were described in Section 3.0.

4.0.1 Revised library design

This library of macrocycles was refined in view of the studies described in Chapter 3. Specifically, it was decided to focus on four benzylic and heterobenzylic alcohols as propagating building blocks; and two *N*-(2-nitrobenzenesulfonyl) carbamates and two triflamides as terminating building blocks. This revised library design was preferred as; the benzylic alcohols **129**, **130**, **127** and **126** completely consumed the fluorous tagged starting material c.f. the non-benzylic alcohol **128**, a key objective otherwise making the F-SPE obsolete; this complete consumption of fluorous tagged intermediate was not as much a problem with the terminating building blocks, however the stability of the final bonds formed was (Scheme 26)

Table 10 Revised building blocks

Initiating building block	Propagating building block	Terminating building block	Diversifier
 **112**  **125**	 **129**  **130**  **127[a]**  **126[a]**	 **131**  **132**  **202**  **135[a]**	 **136**  **139**  **138**

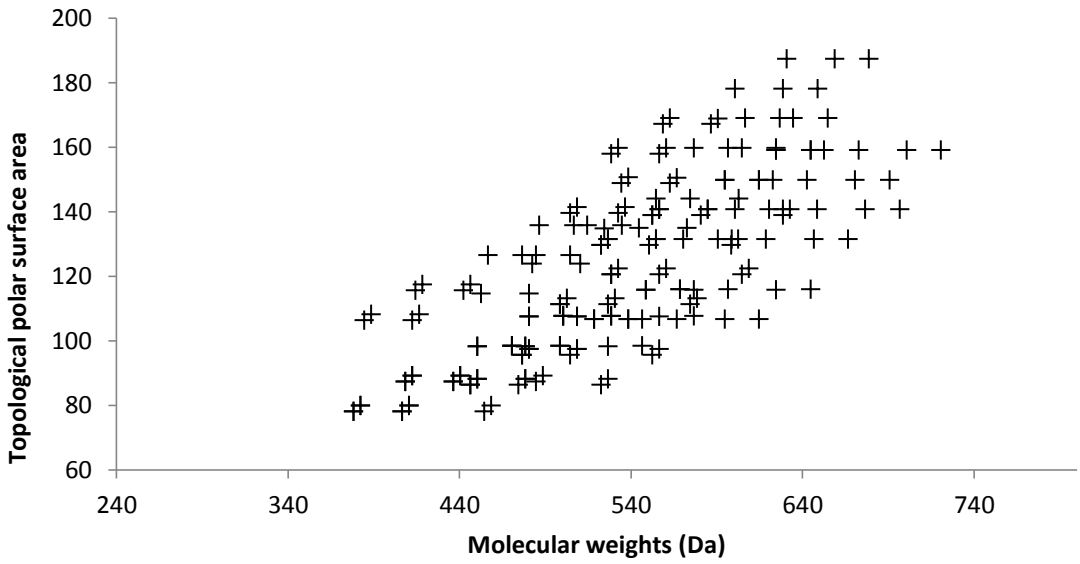
[a] Building block prepared by Francesco Marchetti

4.0.2 Molecular property distributions of the proposed library

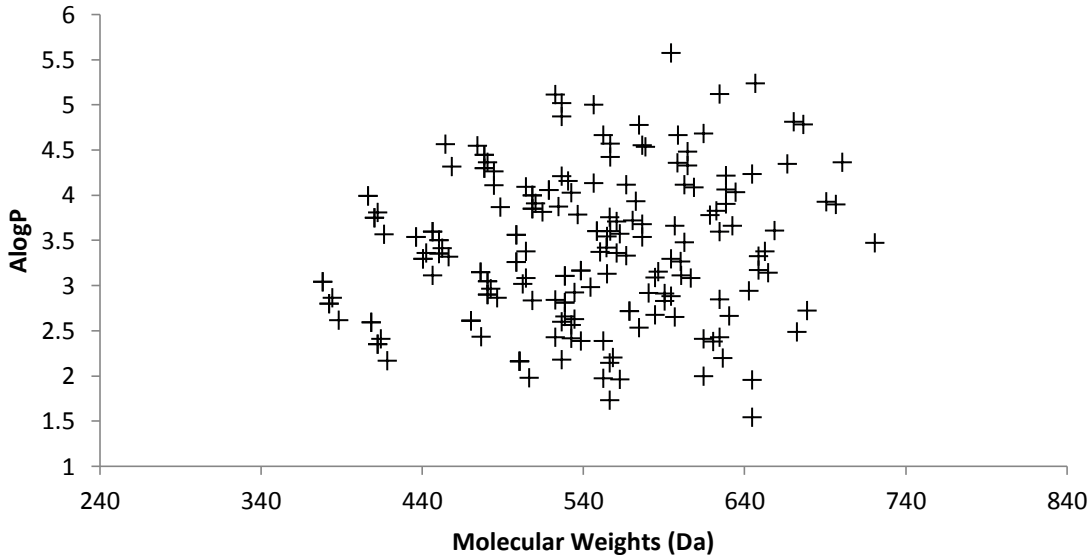
The revised building block selection led to reconsideration of the molecular properties of the proposed library. Changing of the building blocks that will compose the final

library will ultimately change the molecular properties of the final library. The molecular weights now ranged from 378.4 to 720.8 with an average molecular weight of 537.6 (an increase of 44.1 Da); the *A*logP now ranged from 1.54 to 5.57 with a mean of 3.4 (an increase of 0.91); and the TPSA now ranges from 78.0 to 187.3 with an average of 123.3. The most common ring size remained the same at 18. In section 1.5.4 it was discussed that a library of macrocycles may not fall within the 'Lipinski Rule of 5' and this was expected due to the general size of macrocyclic molecules. However it was gratifying to see that the averages were within the Rule of 5 for oral bioavailability; more importantly the compounds have a reasonable spread across the molecular property scales, important for a study where chemical space is being probed.

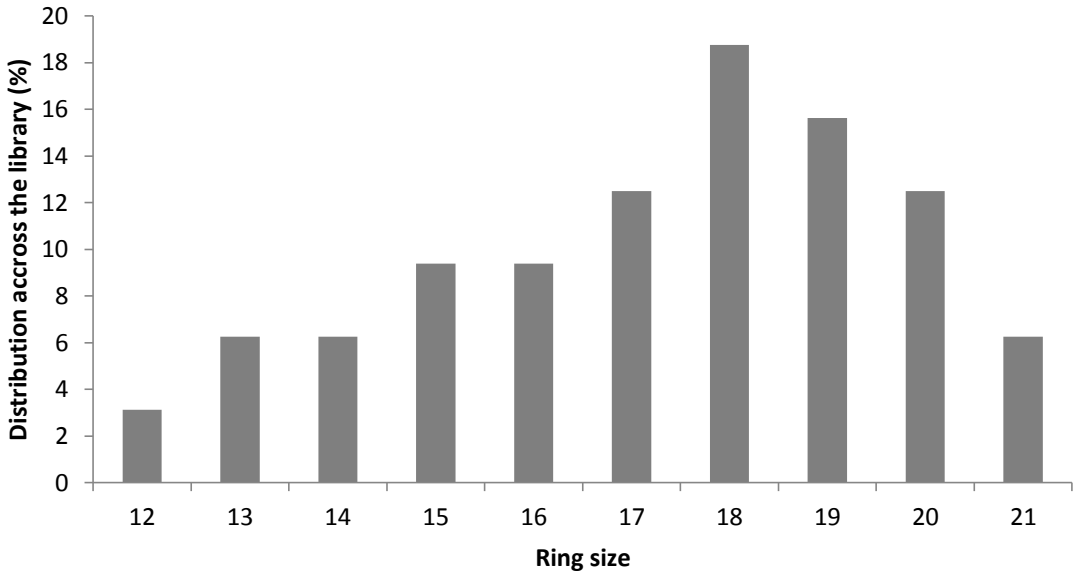
Graph 9 Distribution of the TPSA vs. the molecular weights across the revised final compound library (See Table 10)



Graph 10 The distribution of the predicted atom contribution partition coefficient of the molecules versus the molecular weights of the revised final compound library (See Table 10)



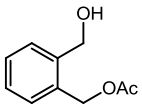
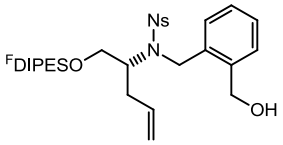
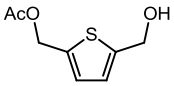
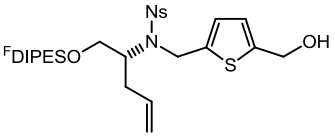
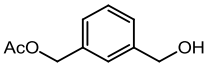
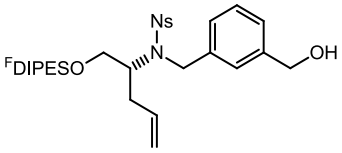
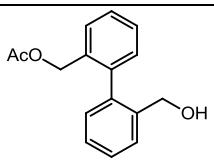
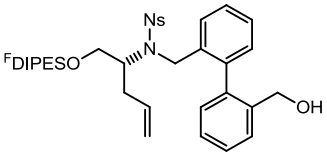
Graph 11 Distribution of ring sizes across the revised library (See Table 10)



4.1 Attachment of propagating building blocks to the fluorous-tagged initiating building block

The fluorous-tagged sulfonamide **112** was combined with four hydroxy acetates building blocks using Fukuyama—Mitsunobu reactions (Table 11). The sulfonamide **112**, triphenylphosphine and alcohols (**126**, **130**, **127** and **129**) were treated with diethylazodicarboxylate to yield 2-nitrobenzenesulfonyl secondary amines (→ **205**, **204**, **113** and **233**). The products were purified where possible by fluorous-solid phase extraction with generally high mass recoveries (>90%); however, in some cases, subsequent purification by flash chromatography was also required (entries 2 and 4). Following, the compounds were treated with saturated methanolic ammonia to give the corresponding benzylic alcohols.

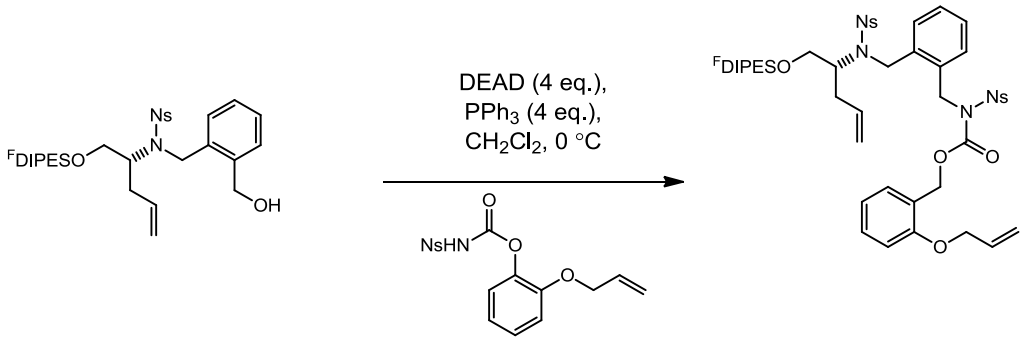
Table 11 Linking the fluorous-tagged initiating building block to the hydroxyl acetates

entry	propagator	method	product	mass recovery[a], [purity][b,c]
1	 **126**	M1, D	 **205**	99 [>95]
2	 **130**	M2, D	 **204**	70[c]
3	 **127**	M1, D	 **113**	90 [>95]
4	 **129**	M2, D	 **233**	82[c]

Methods; **M1**: PPh_3 (2 eq.), DEAD (2 eq.), ROH (2 eq.), THF (0.1 M), 0 °C → rt, F-SPE eluting with MeOH—H_2O (80:20) → MeOH; **M2**: PPh_3 (4 eq.), DEAD (4 eq.), ROH (4 eq.), THF (0.1 M), 0 °C → rt, F-SPE eluting with MeOH—H_2O (80:20) → MeOH; **D**: saturated methanolic ammonia (100 rel vols); [a] Purified by F-SPE unless otherwise indicated; [b] Purity estimated by 500 MHz ^{1}H NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [c] Purified by column chromatography

4.2 Attachment of terminating building blocks to yield metathesis substrates

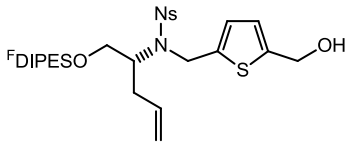
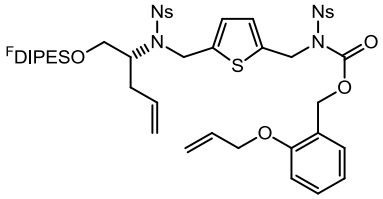
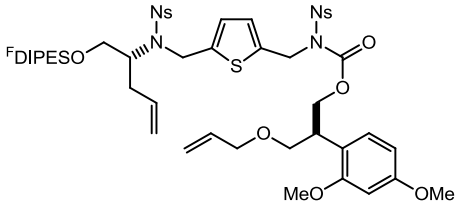
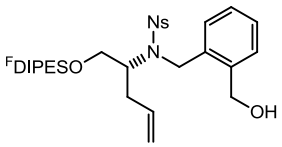
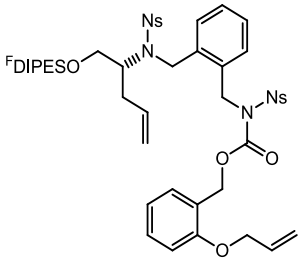
This Section outlines the preparation of substrates for ring closing metathesis. Terminating building blocks - two *N*-(2-nitrobenzenesulfonyl) carbamates and two triflamides - were appended using Fukuyama—Mitsunobu reactions (Table 12). The alcohol (**204**, **205**, **113** and **233**), triphenylphosphine and terminating building blocks (**131**, **132**, **135** and **205**) were treated with diethylazodicarboxylate to yield metathesis substrates. The products were initially purified by F-SPE; however if F-SPE purification was not sufficient, then conventional flash chromatography was used. Mass recoveries ranged from 56-115% with purities consistently >80%.

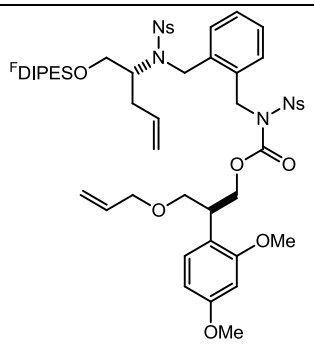
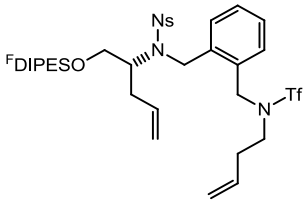
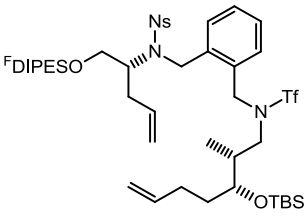
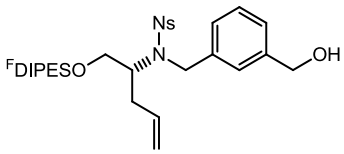
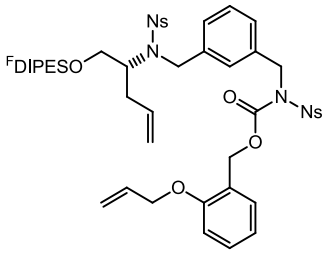
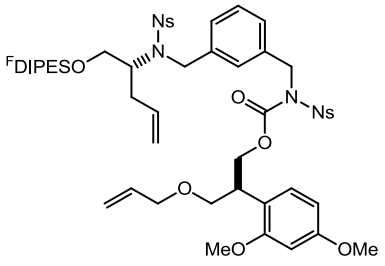


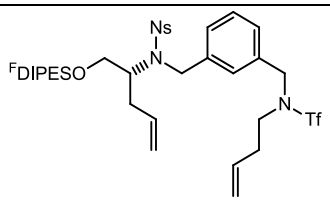
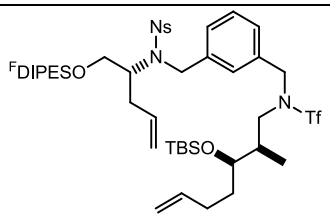
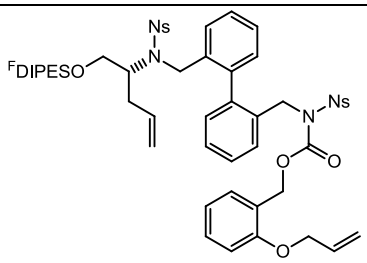
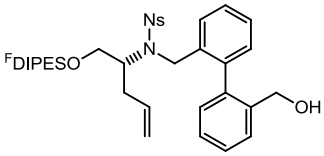
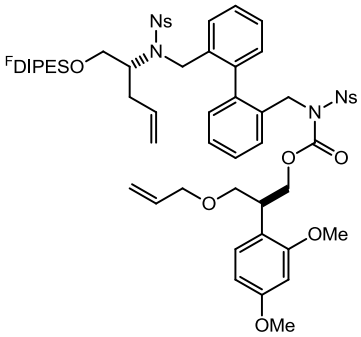
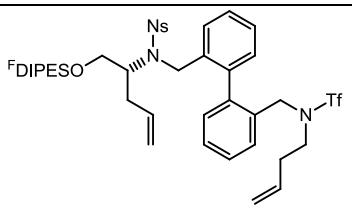
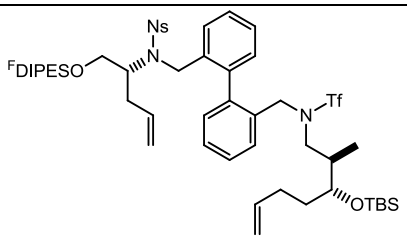
205 **131** **234**

Scheme 27 Fukuyama—Mitsunobu reaction linking the fluorous tagged intermediate **205** to the terminator **131**

Table 12 Linking of the terminating building blocks to the fluorous tagged alcohols prepared in Table 11

entry	substrate [purity][b]	nucleophile	method	product	mass recovery[a] %, [purity][b,c]
1a	 **204**	**131**	L2	 **211**	62[c]
1b		**132**	L2	 **212**	90 [93]
2a	 **205** [>95%]	**131**	L2	 **234**	77 [93]

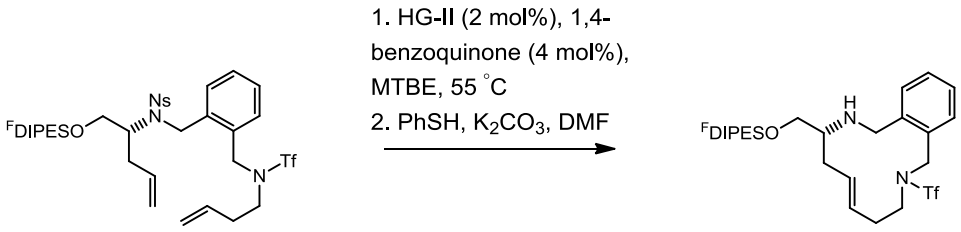
2b		**132**	L1	 **235**	66 [95]
2c		**135**	L1	 **209**	93 [>95]
2d		**205**	L1	 **236**	57[c]
3a	 **113** [>95%]	**131**	L3	 **114**	76 [94]
3b		**132**	L3	 **237**	112 [59]

3c		**135**	L3	 **238**	115 [83]
3d		**202**	L1	 **239**	93 [95]
4a		**131**	L2	 **240**	93 [85]
4b	 **233**	**132**	L2	 **241**	81 [83]
4c		**135**	L2	 **242**	96 [82]
4d		**205**	L1	 **243**	97 [93]

Methods: **L1**) NucH (1.1 eq.), DEAD (1.1 eq.), PPh_3 (1.1 eq.), CH_2Cl_2 (0. 25 M), 0 °C → rt; **L2**) NucH (4 eq.), DEAD (4 eq.), PPh_3 (4 eq.), CH_2Cl_2 (0.25 M), 0 °C → rt; **L3**) NucH (2.0 eq.), DEAD (2.0 eq.), PPh_3 (2.0 eq.), CH_2Cl_2 (0.25 M), 0 °C → rt; [a] Purified by F-SPE unless otherwise indicated; [b] Purity estimated by 500 MHz ^{1}H NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [c] Purified by column chromatography

4.3 Ring-closing metathesis reactions

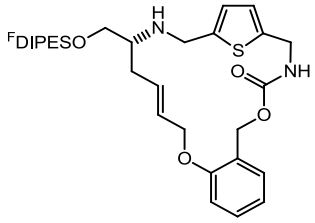
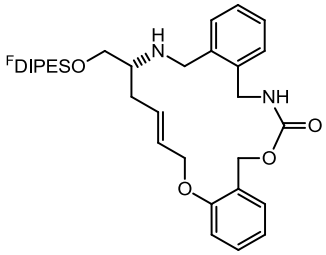
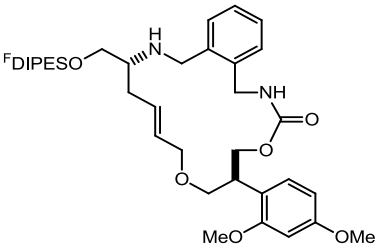
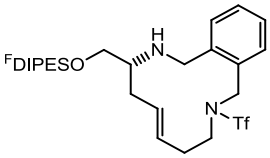
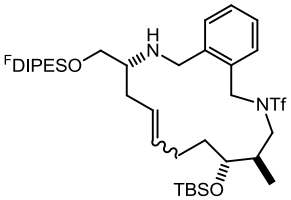
Ruthenium-catalysed ring-closing metathesis was used to cyclise the linear oligomeric substrates (Table 13). Accordingly, the linear substrates were treated with 1-5 mol% Hoveyda—Grubbs 2nd generation catalyst with 2-10 mol% 1,4-benzoquinone in MTBE at 55 °C. Subsequently, the catalyst was inactivated by the addition of tris(hydroxymethyl)phosphine and triethylamine; purification by flash chromatography gave the macrocycles as mixtures of geometrical isomers or in some cases as single geometrical isomers; mixtures of geometrical isomers were not separated at this point. Deprotection of the secondary amines and carbamates was facilitated by treatment of the macrocycle with thiophenol and potassium carbonate and the products were purified by fluorous-solid phase extraction. Subsequently, if possible, chromatography was used to separate mixtures of geometrical isomers; however if separation was not easily possible then the macrocycle was carried through as a mixture of geometrical isomers.

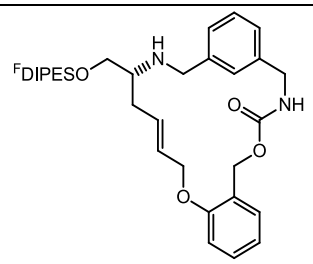
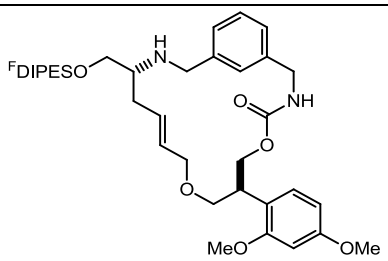
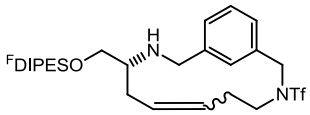
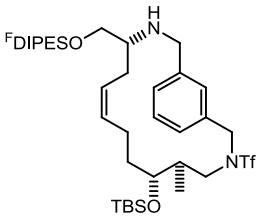
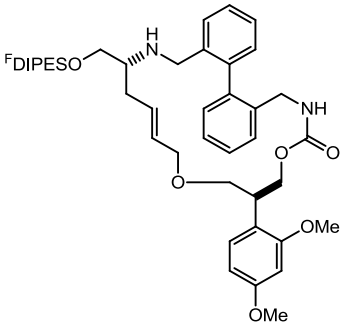
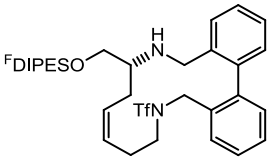


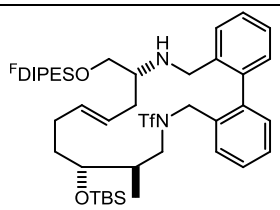
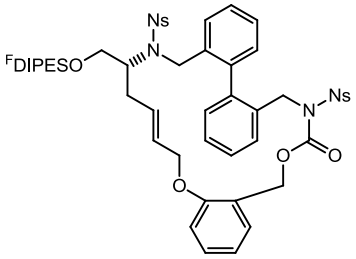
209 **246^D**

Scheme 28 Ring closing metathesis and subsequent denosylation of **209** to give the cyclic free-amine **246^D**

Table 13 Metathesis and thiophenol mediated removal of the 2-nitrobenzenesulfonyl group to obtain the cyclic free amines.

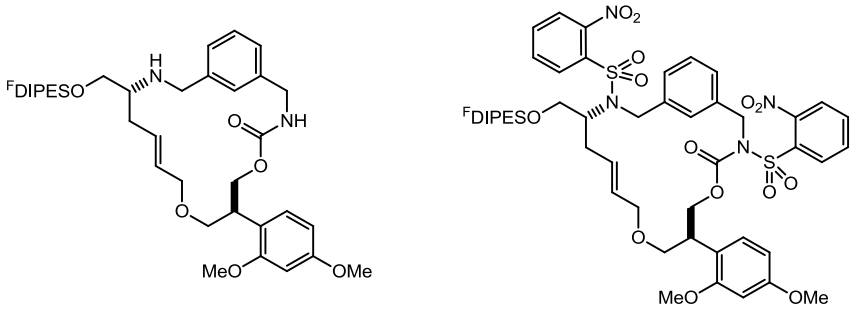
entry	substrate [purity]	methods	time (h)	product	metathesis yield % [a,b] (*E*/*Z*)	deprotection mass recovery % (*E*/*Z*)
1	**211**	RCM1, N1	16	 **223^{D}**	60[c,] (>98:<2) **223**	84 [95] (>98:<2) **223^{D}**
2	**234** [93]	RCM2, N1	24	 **244^{D}**	59[c] (>70:<30) **244**	8% *Z*, 44% *E* **244^{D}**
3	**235** [95]	RCM2, N1	24	 **245^{D}**	56[c, e] Undetermined **245**	64 [79] (70:30) **245^{D}**
4	**209** [>95]	RCM2, N2	6	 **246^{D}**	75[c] (>98:<2) **246**	82 [89] (>98:<2) **246^{D}**
5	**236**	RCM2, N2	24	 **247^{D}**	83[c, e] undetermined **247**	88 [81] (90:10) **247^{D}**

6	**114** [94]	RCM2, N1	48	 **115^{D}**	88$^{c, e}$ Undetermined **115**	15% *Z* 26% *E*^{c} **115^{D}**
7	**237** [59]	RCM2, N1	24	 **248**	56^{c,} (55:45) **255**	91 [95] (60:40) **248**
8	**238** [83]	RCM2, N2	16	 **249^{D}**	47$^{c, e}$ Undetermined **249**	28% *Z* 47% *E* **249^{D}**
9	**239** [78]	RCM2, N2	4	 **250^{D}**	78^{c} (<12:>88) **250**	87 [93] (<5:>95) **250^{D}**
10	**240** [83]	RCM2, N1	5	 **251^{D}**	- undetermined **250**	16^{e} (85:15) **251^{D}**
11	**241** [82]	RCM2, N2	3 Days	 **252**	38 (<2:>98) **252**	76 [93] (<2:> 98) **252^{D}**

12	**242** [93]	RCM2, N2	16	 **253**	na[f]	-
13	**243** [85]	RCM2	16	 **254**	na[f]	-

Methods: **RCM1**) Hoveyda—Grubbs 2nd gen cat. (2 mol%), MTBE (2.5 mM), 55 °C; **RCM2**) Hoveyda—Grubbs 2nd gen cat. (2 mol%), 1,4-benzoquinone (4 mol%), MTBE (2.5 mM), 55 °C; **N1** PhSH (10 eq.), K_2CO_3 (2.5 eq.), DMF, rt; **N2** PhSH (5 eq.), K_2CO_3 (1.2 eq.), DMF, rt; [a] Purified by F-SPE unless otherwise indicated; [b] Purity estimated by ^{1}H 500 MHz NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [c] Purified by column chromatography; [d] Ratio of double bond isomers was determined using 500 MHz ^{1}H NMR spectroscopy; [e] compound carried though to removal of the 2-nitrobenzenesulfonamides due to isolation of a complex mixture containing starting material and geometric isomers [f] Complex mixture isolated

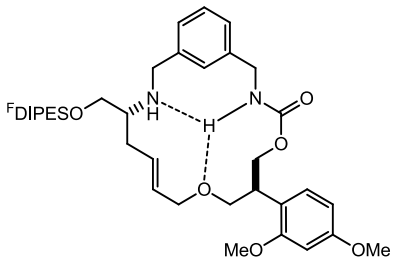
The reason that geometrical isomers became separable in some cases after removal of the 2-nitrobenzenesulfonyl group may have stemmed from significant intramolecular hydrogen bonding. It was observed that removal of the 2-nitrobenzenesulfonyl group often resulted in molecules with unexpected polarities; in some cases, the free amines were sometimes less polar than the 2-nitrobenzenesulfonyl-protected amines (Figure 17)



248 R_f : 0.37 (80:20 petrol–EtOAc)

255 R_f : 0.17 (70:30 petrol–EtOAc)

Figure 16 Comparisons of the relative polarity of macrocycles **248** and **255**.



248

Figure 17 Proposed intramolecular bonding, resulting in less-polar molecules

4.3.1 Dynamic behaviour of selected macrocyclic products

Macrocycles are known to have pre-organised architectures;[16] many of the macrocycles synthesised in this project were observed to slowly interconvert between alternative conformations on the NMR timescale, giving rise to broad peaks. This slow interconversion, could often be studied using variable temperature NMR. In this project, many spectra were recorded at elevated temperatures (to increase the rate of interconversion) or at low temperature (to decrease the rate of interconversion) to allow sharp spectra to be acquired.

4.3.2 Characterisation of the geometrical isomers of the 13-membered macrocycle 249

The macrocycles ***Z*-249^{D}** and ***E*-249^{D}** were separated by column chromatography after removal of the 2-nitrobenzenesulfonyl protecting group; however initially it was impossible to determine the geometry of the double bonds because the signals corresponding to the alkene protons were extremely broad (Figure 19 and 20). However, recording the 500 MHz ^{1}H NMR spectra of ***E*-249^{D}** and ***Z*-249^{D}** at 70 °C greatly improved the spectra and allowed assignment of the alkene geometries.

***Z*-249^{D}** ***E*-249^{D}**

Figure 18 Two stereoisomers isolated after removal of 2-nitrobenzenesulfonyl protecting groups

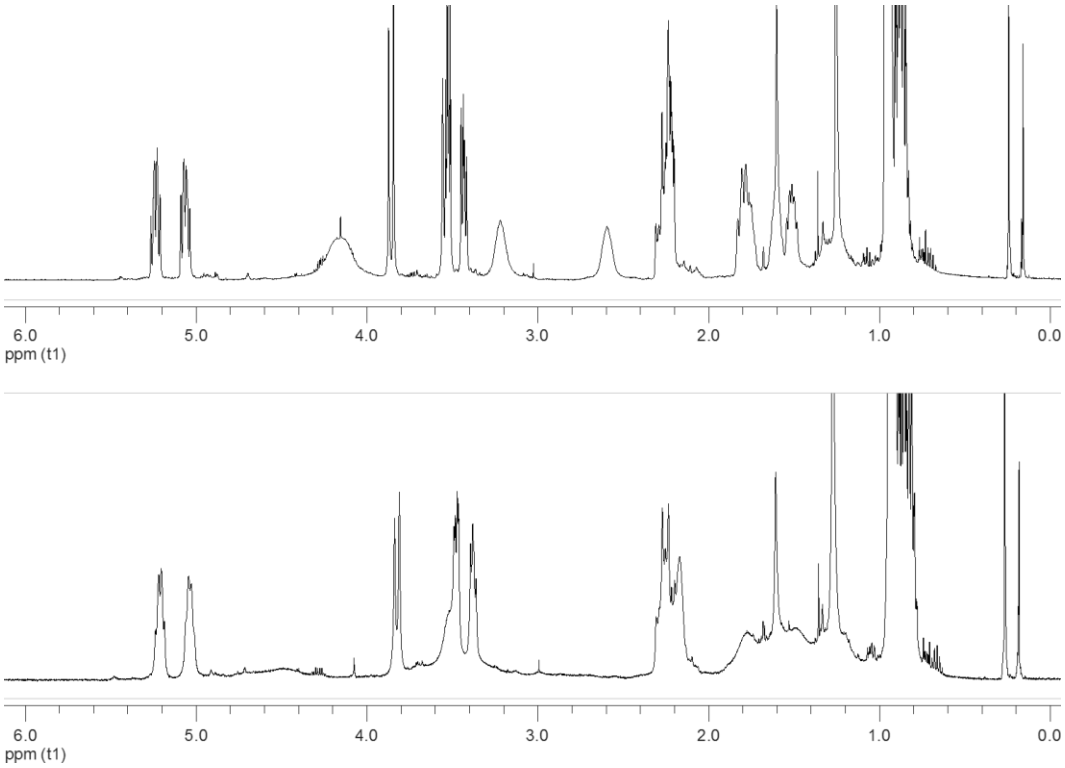


Figure 19 500 MHz ^{1}H NMR spectra of macrocycle ***Z*-249^{D}**: top spectrum 343K in C_6D_6; bottom spectrum 300K in C_6D_6

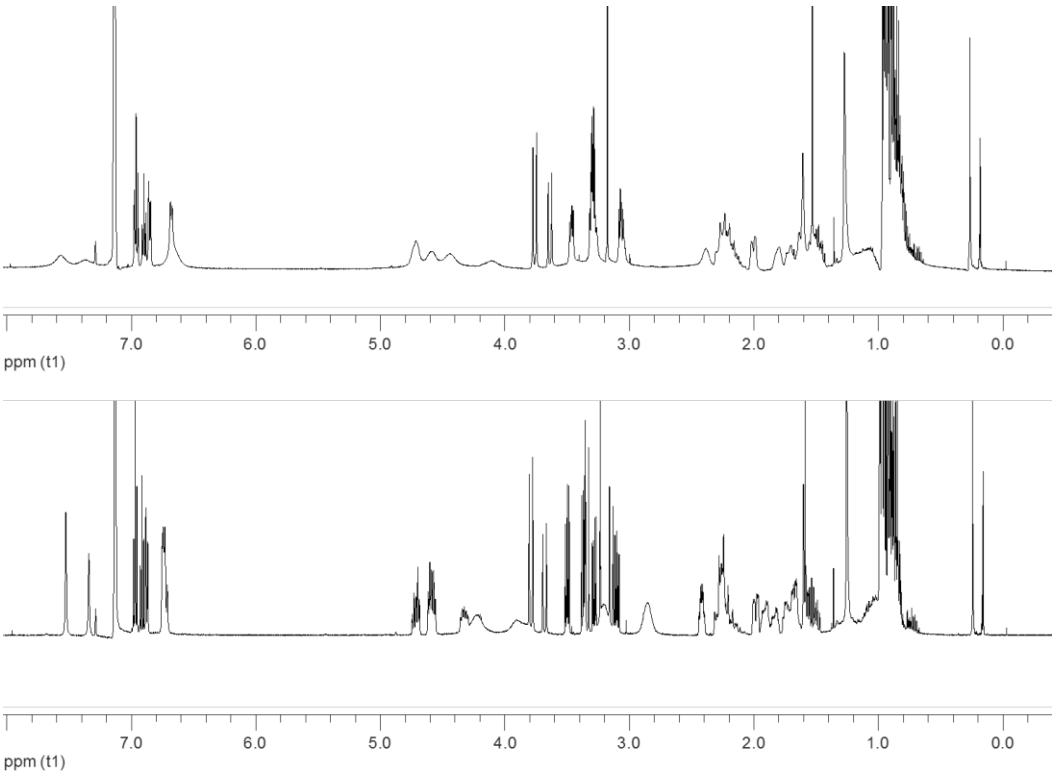
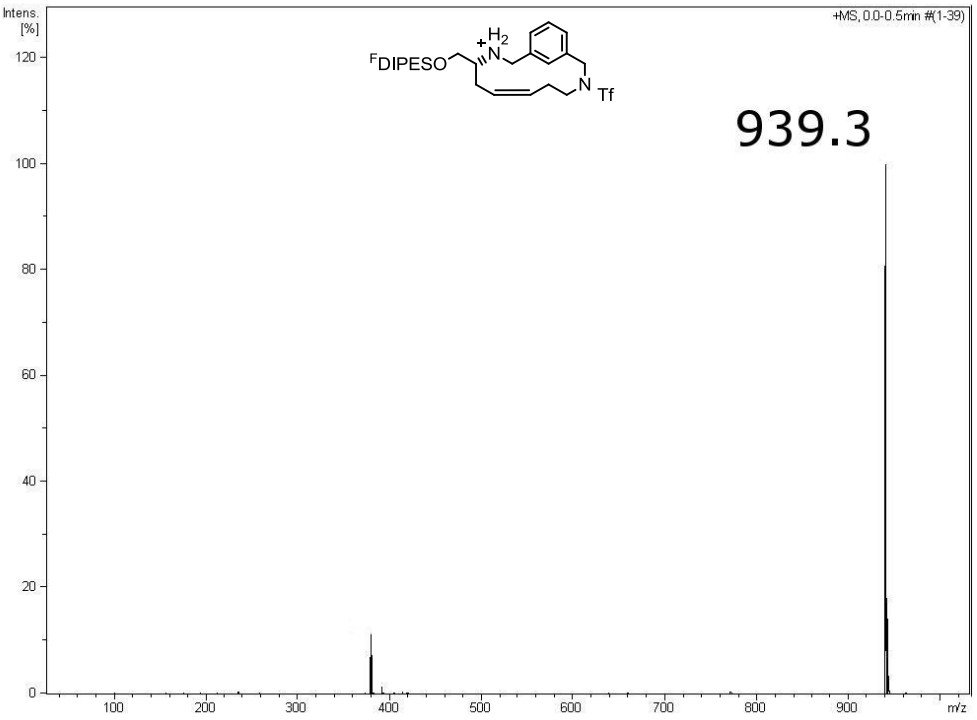
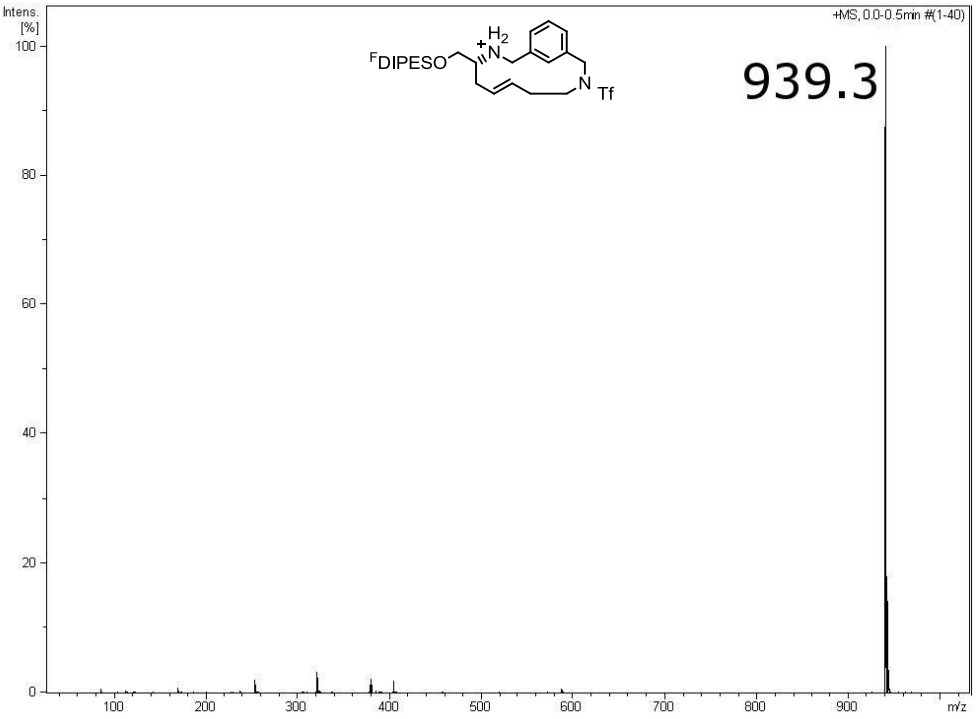


Figure 20 500 MHz ^{1}H NMR spectrum of macrocycle ***E*-249^{D}**; top spectrum 300K in C_6D_6; bottom spectrum 343K in C_6D_6

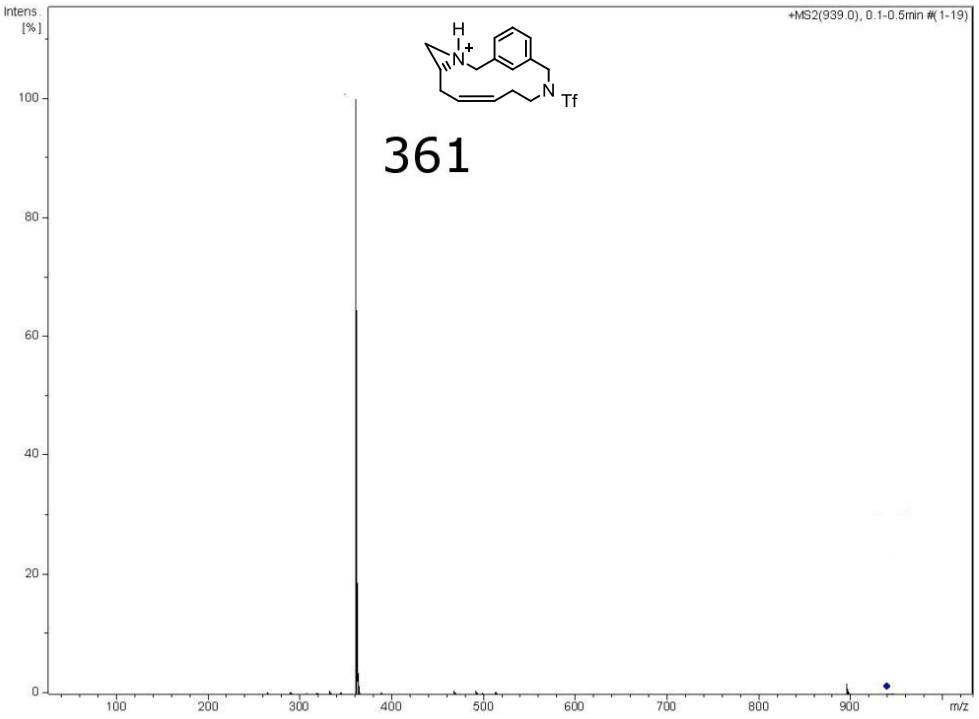
Analysis of the fragmentation patterns of macrocycles ***Z*-249^{D}** and ***E*-249^{D}** was used to complement the variable temperature NMR studies. The initial NMR spectrum of the macrocycle ***E*-249^{D}** at 300K in $CDCl_3$ had extremely broad signals for the alkene protons at anomalously low chemical shift. However, careful analysis of the fragmentation patterns of ***E*-249^{D}** and ***Z*-249^{D}** suggested that they were indeed geometric isomers. Specifically, the molecular ions (*m*/*z* = 939, Panel A1 and A2) for both compounds fragmented to give ions with *m*/*z* = 361, tentatively assigned to the arizidinium ions of ***E*-249^{D}** and ***Z*-249^{D}** (Panel B1 and B2). Accordingly, further fragmentation of the assigned arizidinium ions ***E*-249^{D}** and ***Z*-249^{D}** resulted in very similar fingerprint spectra (Panels C1 and C2).


Intens.
[%]
+MS, 0.0-0.5min #(1-39)
939.3
FDIPESO
Tf
m/z

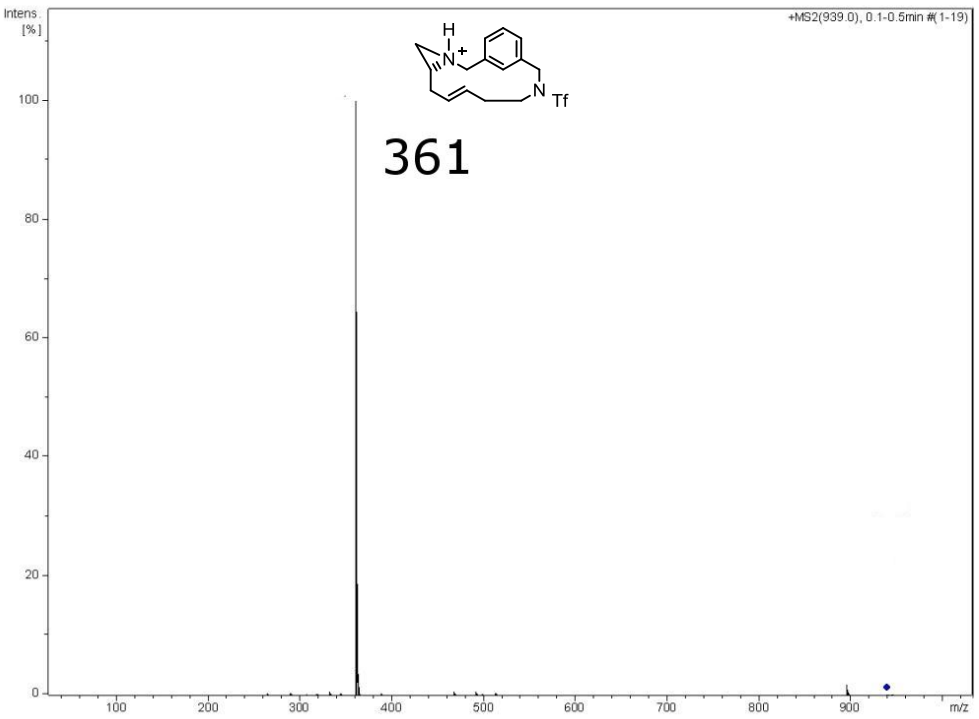
A1


Intens.
[%]
+MS, 0.0-0.5min #(1-40)
939.3
FDIPESO
Tf
m/z

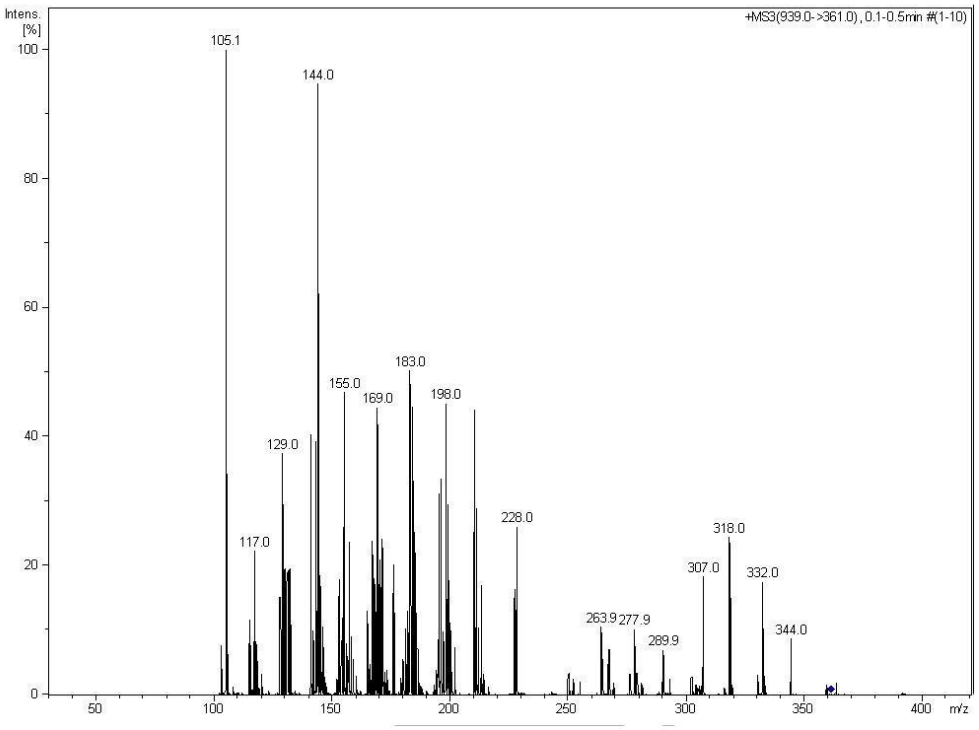
A2


Intens.
[%]
+MS2(939.0), 0.1-0.5min #(1-19)
361
Tf
100
80
60
40
20
0
100
200
300
400
500
600
700
800
900
m/z

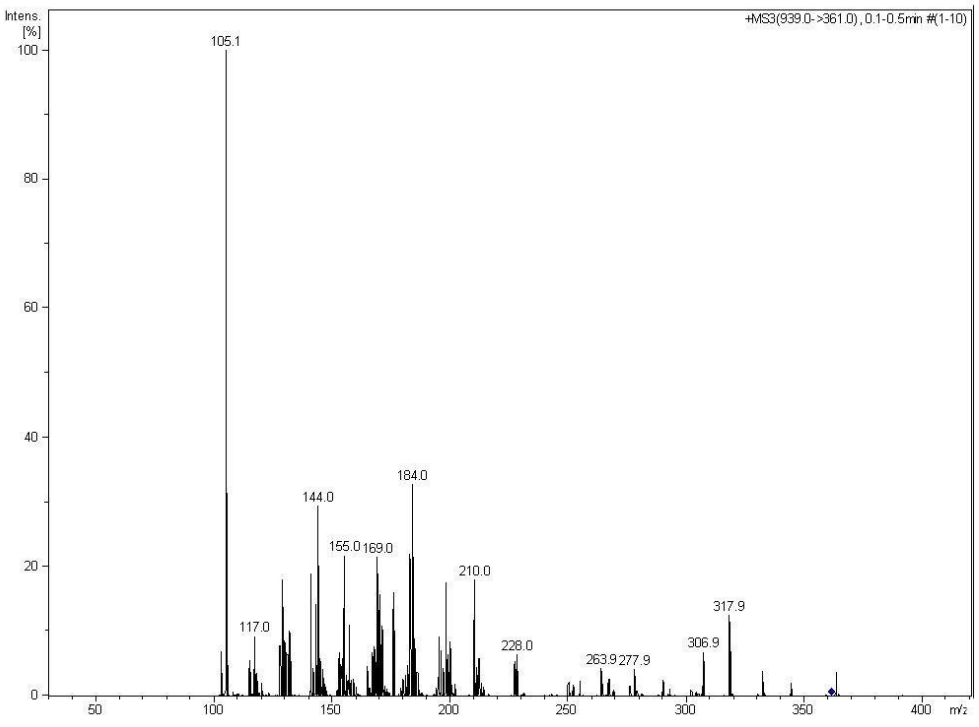
B1


Intens.
[%]
+MS2(939.0), 0.1-0.5min #(1-19)
361
Tf
100
80
60
40
20
0
100
200
300
400
500
600
700
800
900
m/z

B2



C1

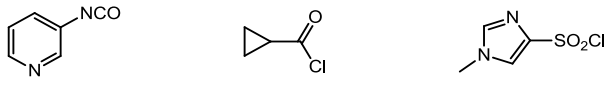


C2

Figure 21 Mass fragmentation patterns of ***E*-249^{D}** and ***Z*-249^{D}**; Panel A1 and A2, molecular ions (MS^1)**;** Panel B1 and B2, arizidinium ions MS^2 (*m*/*z* = 939 → ***E*-249^{D}** and ***E*-249^{D}**); Panel C1 and C2, fingerprint (MS^2) (*m*/*z* = 361→ fragments)

4.4 Derivatization of the scaffolds

To increase the diversity of the library, each scaffold was appended with a diversifying group. Thus, the free amines were reacted with the carbonyl chloride **139** and sulfonyl chloride **138** (used in excess in the presence of triethylamine); and the isocyanate **136** (in the absence of any other reagents). The products were purified using F-SPE, concentrated and the fluorous-tag was removed using either tetra-n-butylammonium fluoride or hydrofluoric acid. Column chromatography or mass-directed HPLC yielded the final compounds on a *ca.* 10 mg scale.

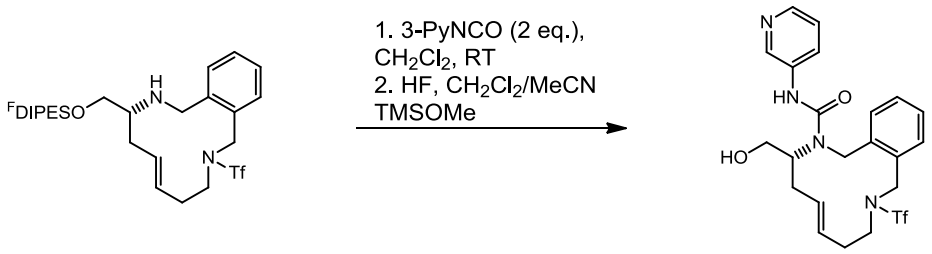


136 **139** **138**

Figure 22 The suffices of the compound numbers denote the derivatization group; compounds diversified with **136** will be denoted as '**XXa**'. Furthermore, diversification with **139, 137** and **138** → '**XXb**', '**XXe** and '**XXc**', respectively. Compounds that do not undergo any diversification will be denoted as '**XXd**'

4.4.1 Derivatization of the macrocyclic scaffolds

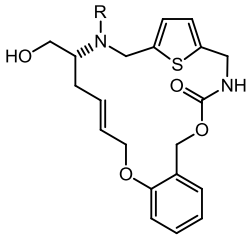
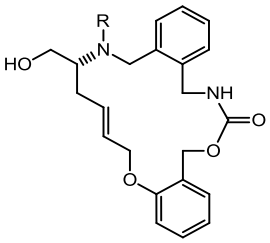
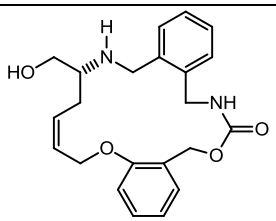
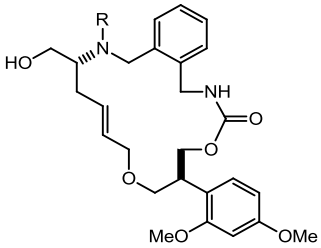
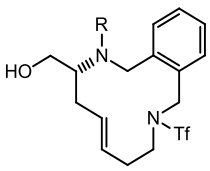
The derivatization reactions of the metathesis substrates are summarised in Table 14. Where the geometric isomers of macrocycles had been separated, both stereoisomers were derivatized if sufficient material was available; however, if it was not feasible to derivatize the minor isomer, then only the free amine of the minor isomer was prepared (see entry 2e).

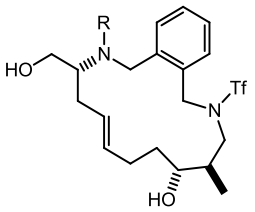
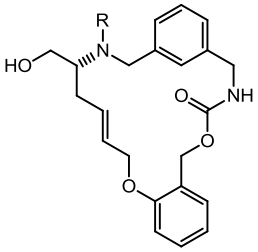
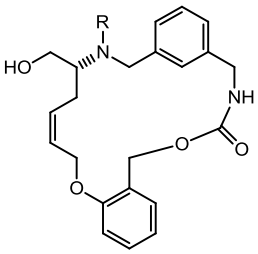
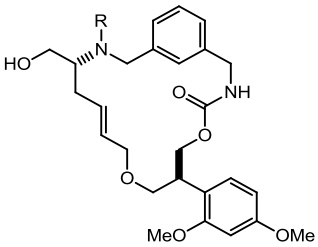
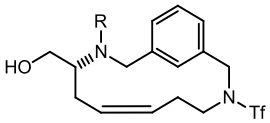


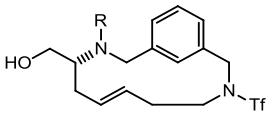
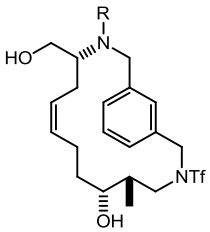
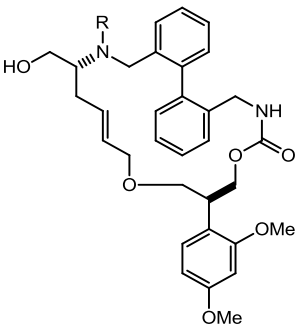
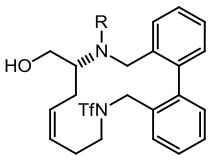
246^{D} **159**

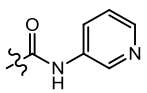
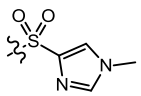
Scheme 29 Derivatisation and subsequest deprotection of the macrocyclic scaffold **246^{D}**

Table 14 Derivatization of the cyclic variants

entry	substrate	methods	scaffold	Yield % (2 steps)[a]	ratio (*E*/*Z*)
1a	**223** [95]	A1, S2	 **228-231**	73 **228**	>95/<5
22		A4, S2		59 **229**	>95/<5
1c		A3, S2		42 **230**	>95/<5
1d		S2		96 **231**	>95/<5
2a	***E*-244^{D}**	A1, S2	 **256**	99 **256a**	>95/<5
2b		A2, S2		78 **256b**	>95/<5
2c		A3, S2		88 **256c**	>95/<5
2d		S2		83 **256d**	>95/<5
2e	***Z*-244^{D}**	S1	 **257**	54 **257**	<5/>95
3a	**245^{D}** [79]	A1, S1	 **258**	62 **258a**	>75/<25
3b		A2, S1		63 **258b**	>90/<10
3c		A3, S1		43 **258c**	>80/<20
3d		S1		99 **258d**	>80/<20
4a	**246^{D}** [89]	A1, S1	 **159**	77 **159a**	>95/<5
4b		A2, S1		66 **159b**	>95/<5
4c		A3, S1		72 **159c**	>95/<5
4d		S1		46 **159d**	>95/<5

5a	**247**^{D} [81]	A1, S1	 **259**	12^{d} **259a**	n.d.
5b		A2, S1		42^{d} **259b**	>70/<30
5c		A3, S1		12^{d} **259c**	n.d.
5d		S1		22^{d} **259d**	n.d.
6a	***E*-115**^{D}	A1, S1	 ***E*-117**	79 ***E*-117a**	>95/<5
6b		A2, S1		60 ***E*-117b**	>95/<5
6c		A3, S1		87 ***E*-117c**	>95/<5
6d		S1		96 ***E*-117d**	>95/<5
7a	***Z*-115**^{D}	A1, S1	 ***Z*-117**	70 ***Z*-117a**	<5/>95
7b		A2, S1		69 ***Z*-117b**	<5/>95
7c		A3, S1		62 ***Z*-117c**	<5/>95
7d		S1		72 ***Z*-117d**	<5/>95
8a	**248**^{D} [95]	A1, S1	 **260**	24 **260a**	n.d
8b		A2, S1		20 **260b**	50/50
8c		A3, S1		57 **260c**	50/50
8d		S1		45 **260d**	n.d
9a	***Z*-249**^{D}	A1, S1	 ***Z*-261**	89 ***Z*-261a**	<5/>95
9b		A2, S1		67 ***Z*-261b**	<5/>95
9c		A3, S1		86 ***Z*-261c**	<5/>95
9d		S1		69 ***Z*-261d**	<5/>95

10a	***E*-249^{D}**	A1, S1	 ***E*-261**	69 ***E*-261a**	>95/<5
10b		A2, S1		70 ***E*-261b**	>95/<5
10c		A3, S1		79 ***E*-261c**	>95/<5
10d		S1		72 ***E*-261d**	>95/<5
11a	**250^{D}** [93]	A1, S1	 **262**	21 **262a**	<10/>90
11b		A2, S1		34 **262b**	<5/>95
11c		A3, S1		61 **262c**	<5/>95
11d		S1		21 **262d**	<10/>90
12a	**251^{D}**	A1, S1	 **263**	85 **263a**	n.d
12b		A2, S1		83 **263b**	>85/<15
12c		A3, S1		76 **263c**	n.d
12d		S1		69[d] **263d**	>80/<20
13a	**252^{D}** [93]	A1, S1	 **264**	95[d] **264a**	<5/>95
13b		A2, S1		78 **264b**	<5/>95
13c		A3, S1		50 **264c**	<5/>95
13d		S1		85[d] **264d**	<5/>95

			R = H
XXa	**XXb**	**XXc**	**XXd**

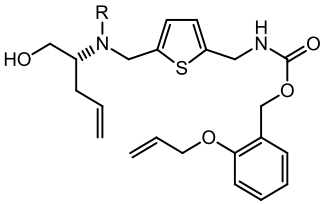
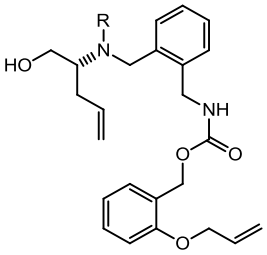
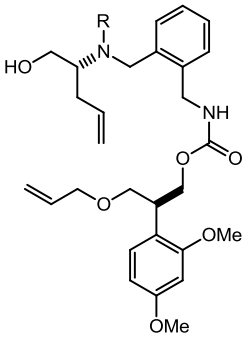
Methods: **A1**) **136** (2 eq.), CH_2Cl_2 (0.1 M), rt then F-SPE (80:20 MeOH/H_2O → MeOH); **A2**) **139** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A3**) **138** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A4**) **137** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **S1**) HF (10 eq., aq 50%), CH_2Cl_2/MeCN (50/50, 0.05 M), rt, TMSOMe (50 eq.); **S2**) TBAF (5 eq., 1 M), CH_2Cl_2 (1 M), rt; [a] Purified by F-SPE after the derivatization step, then by column chromatography after desilylation unless otherwise stated; [b] Purity estimated by 500 MHz ^{1}H NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an

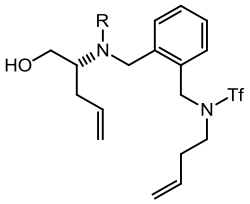
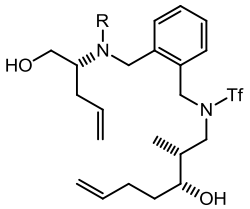
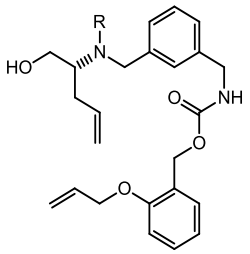
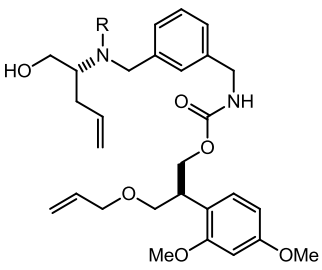
internal standard; [c] Purified by column chromatography; [d] Purified by mass-directed high performance liquid chromatography; [e] Ratio of double bond isomers was determined using 500 MHz ^{1}H NMR spectroscopy;

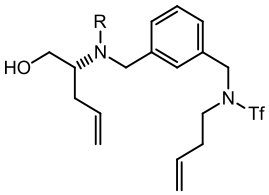
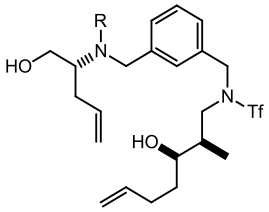
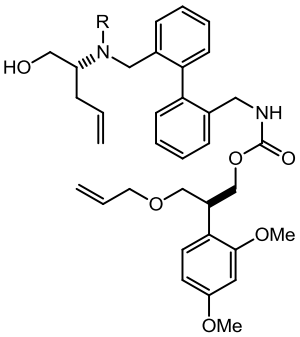
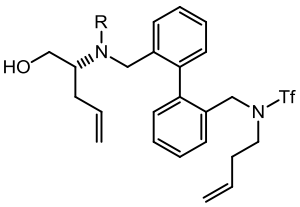
4.4.2 Derivatization of the linear scaffolds

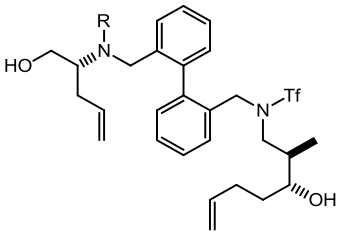
The acyclic variants were only derivatized upon successful completion of both the ring closing metathesis and removal of the 2-nitrobenzenesulfonamide of the corresponding macrocycle. Table 15 outlines removal of the 2-nitrobenzenesulfonamide from the linear substrates, followed by diversification and, ultimately, removal of the fluorous tag.

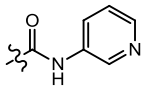
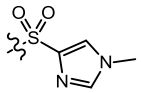
Table 15 Derivatization of the acyclic variants

entry	substrate [purity]	denosylation	mass recovery [purity]	methods	scaffold	Yield % [a,b]
1a	**211**	N1	86 [>95], **211^{D}**	A1, S2	 **224-227**	80 **224**
1b				A4, S2		71 **225**
1c				A3, S2		47 **226**
1d				S2		27 **227**
2a	**234** [93]	N1	81 [84], **234^{D}**	A1, S2	 **265**	58 **265a**
2b				A2, S2		72 **265b**
2c				A3, S2		64 **265c**
2d				S2		99 **265d**
3a	**235** [95]	N1	53 [82], **235^{D}**	A1, S1	 **266**	99 **266a**
3b				A2, S1		56 **266b**
3c				A3, S1		72 **266c**
3d				S1		63 **266d**

4a	**209** [>95]	N1	100 [89], **209^{D}**	A1, S1	 **267**	76 **267a**
4b				A2, S1		70 **267b**
4c				A3, S1		53 **267c**
4d				S1		92 **267d**
5a	**236**	N1	48 [88], **236^{D}**	A1, S1	 **268**	88 **268a**
5b				A2, S1		76 **268b**
5c				A3, S1		49 **268c**
5d				S1		77 **268d**
6a	**114** [94]	N1	87 [85], **114^{D}**	A1, S1	 **118**	41 **118a**
6b				A2, S1		27 **118b**
6c				A3, S1		73 **118c**
6d				S1		42 **118d**
7a	**237** [70]	N1	72 [89], **237^{D}**	A1, S1	 **269**	46 **269a**
7b				A2, S1		56 **269b**
7c				A3, S1		73 **269c**
7d				S1		34 **269d**

8a	**238** [>83]	N1	96 [99], **238^{D}**	A1, S1	 **270**	40 **270a**
8b				A2, S1		33 **270b**
8c				A3, S1		52 **270c**
8d				S1		47 **270d**
9a	**239** [>85]	N1	96 [>95], **239^{D}**	A1, S1	 **271**	87 **271a**
9b				A2, S1		22 **271b**
9c				A3, S1		41 **271c**
9d				S1		67 **271d**
10a	**240** [>83]	N1	98 [>92], **240^{D}**	A1, S1	 **272**	39 **272a**
10b				A2, S1		45 **272b**
10c				A3, S1		22 **272c**
10d				S1		50 **272d**
11a	**241** [>82]	N1	93 [>83], **241^{D}**	A1, S1	 **273**	72 **273a**
11b				A2, S1		88 **273b**
11c				A3, S1		73 **273c**
11d				S1		75 **273d**

12a				A1, S1		63 **274a**
12b	**242** [93]	N1	111 [89] **242^{D}**	A2, S1		66 **274b**
12c				A3, S1		69 **274c**
12d				S1	**274**	40[d] **274d**

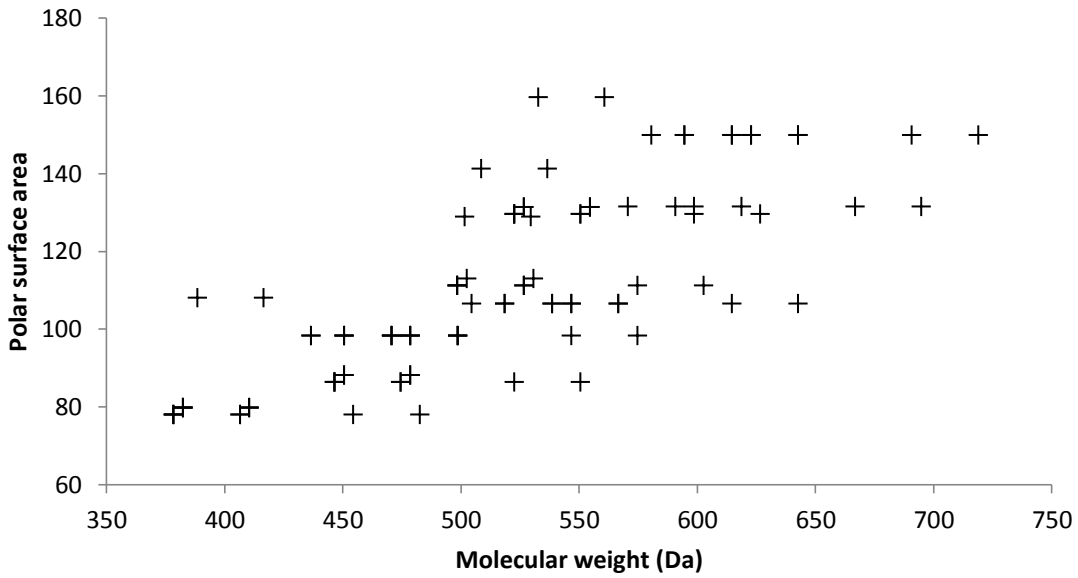
			R = H
XXa	**XXb**	**XXc**	**XXd**

Methods: **N1** PhSH (10 eq.), K_2CO_3 (2.5 eq.), DMF, rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **N2** PhSH (5 eq.), K_2CO_3 (1.2 eq.), DMF, rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A1**) **136** (2 eq.), CH_2Cl_2 (0.1 M), rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A2**) **139** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A3**) **138** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **A4**) **137** (5 eq.), Et_3N (10 eq.), CH_2Cl_2 (0.1 M), 0 °C → rt, then F-SPE (80:20 MeOH/H_2O → MeOH); **S1**) HF (10 eq., aq 50%), $CH2Cl_2$/MeCN (50/50, 0.05 M), rt, TMSOMe (50 eq.); **S2**) TBAF (5 eq., 1 M), CH_2Cl_2 (1 M), rt; [a] Purified by F-SPE unless otherwise indicated; [b] Purity estimated by 500 MHz ^{1}H NMR spectroscopy using the 1'-CH_2 of the fluorous tag as an internal standard; [c] Purified by column chromatography; [d] Purified by mass-directed high performance liquid chromatography;

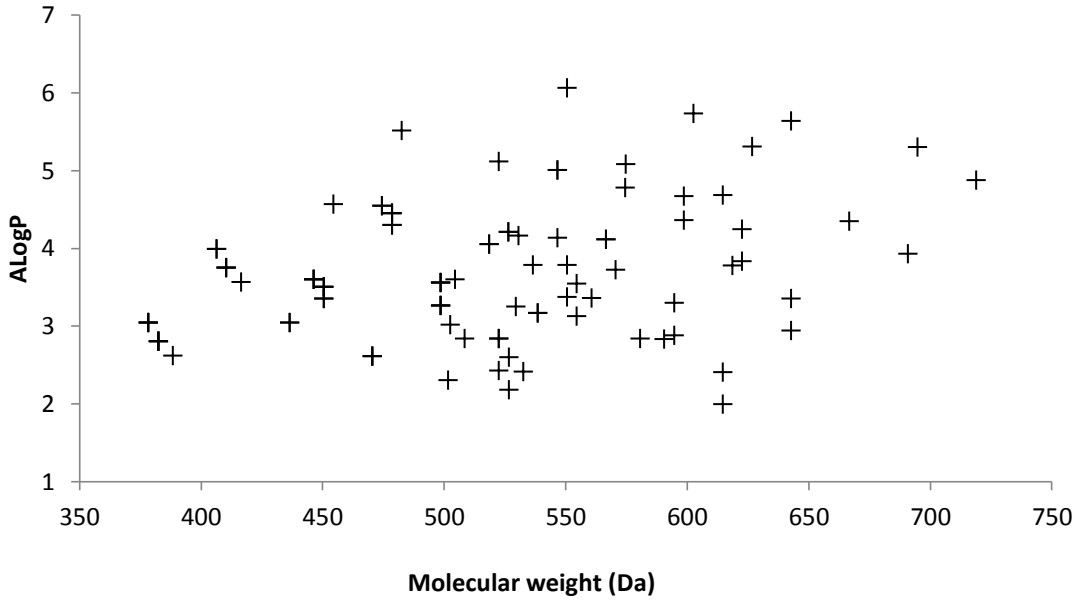
4.5 Review of molecular properties of the final library

The molecular properties of the compounds that were ultimately prepared were determined. The distribution of properties had been affected by the derivatization of the individual geometric isomers and by reactions that had not been successful. The TPSA and AlogP distributions of the final compounds that were prepared from the sulfonamide **112** are shown in Graphs 11 and 12 respectively. The molecular weights of the final library ranged from 378.4 to 718.8 with an average of 516.8; the topological surface area ranged from 78.0 to 159.6 with an average of 110.9; and the AlogP ranges from 1.99 to 6.06 with an average of 3.69. The most common ring size across the library was 18, shown in Graph 14 (the proportion of 18-membered macrocycles in the library had been increased by derivatization of the separated geometric isomers of **117** and **257**). The molecules synthesised in this diversity-oriented synthesis has produced compounds with physical properties that will lend themselves well to testing *in vitro*; the molecular weights of the compounds synthesised are higher than would be desired in a library of compounds to be tested *in vitro*,[10-12] but this was expected. The compounds synthesised are at the top end of lipophilic range, but possess an average (3.69) well within the accepted boundaries (<5.00).

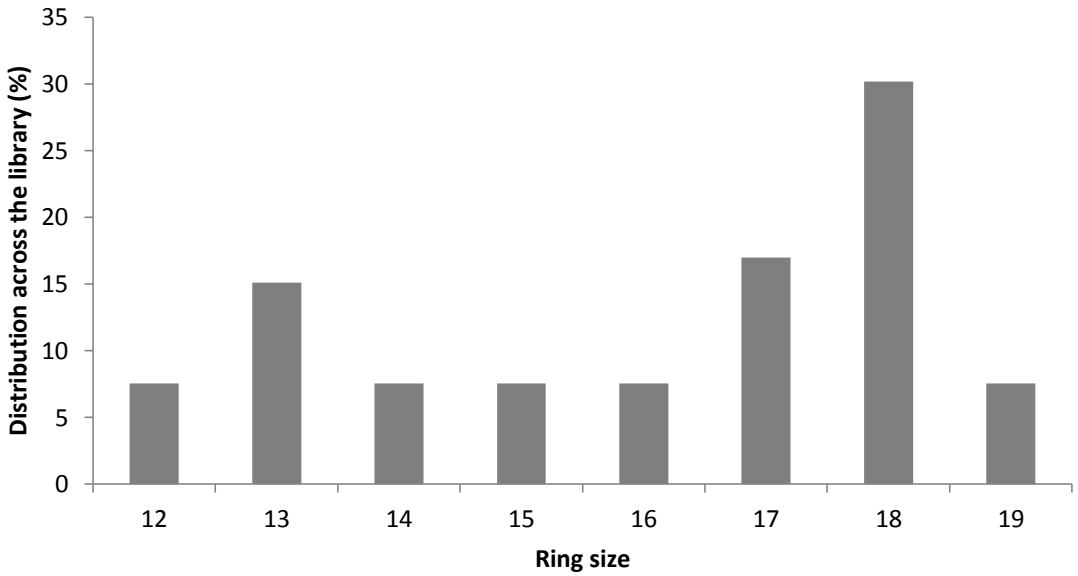
Graph 12 Distribution of the topological polar surface area versus the molecular weights for the final compounds prepared



Graph 13 Distribution of the atom based partition coefficient versus the molecular weights for the final compounds prepared



Graph 14 Distribution of ring sizes of the macrocycles prepared



Summary

A building block-based approach to a library of diverse natural product-like molecules has been developed. The strategy relied upon a minimal number of robust chemistries (*ca*. 6) and followed a 'build-couple-couple-pair' approach. Through an iterative combination of bespoke building blocks, ring closing metathesis and subsequent deprotection and amine diversification this approach has gleaned over 100 diverse natural product-like molecules, all with varying scaffolds and molecular properties. This efficient synthetic approach was aided considerably by the expedient purification facilitated by the fluorous tag. The development of robust syntheses of diverse macrocycles may enable the discovery of valuable chemical probes of biological mechanisms.

In this library synthesis many lessons were learnt that would improve future library design and synthesis. The fluorous tagged was critical to provide rapid and efficient purification of the intermediates; more standard purifications such as flash chromatography would have been more time consuming and costly in materials. The connective reactions used such as the Fukuyama—Mitsunobu were clean and provided bonds that would not be susceptible to cleavage in biological systems. Ring closing metathesis using the Hoveyda—Grubb's 2nd generation catalyst was an extremely reliable method and provided a natural product-like feature within the molecule, the major downside to the ring-closing metathesis was that the selectivity between geometric isomers could not be predicted nor controlled. However there is constant development in the field of metathesis design and more controllable ligands are being discovered.

The final products have all been prepared on milligram scales and the biological activity will be determined in a range of assays. This will allow for the direct comparison of the biological relevance of macrocycles and acycles.

5 Experimental

All reactions were carried out in oven-dried glassware under an atmosphere of N_2 from a Schlenk line fitted with a nitrogen bubbler, using dry techniques. Tetrahydrofuran, dichloromethane, toluene, acetonitrile were dried and purified by means of a Pure Solv MD solvent Purification System (Innovative Technology Inc.) or obtained from Oxford sure/seal™ bottles from Sigma-Aldrich. All other solvents used were chromatography or analytical grade. Chemicals used were supplied by Sigma-Aldrich, Alfa-Aesar, and Fluka.

Thin layer chromatography was carried out on aluminium backed silica (Merck silica gel 60 F_{254}) plates supplied by Merck. Visualisation of the plates was achieved using an ultraviolet lamp (λ_{max} = 254 nm), phosphomolybdic acid, $KMnO_4$ and anisaldehyde. Flash chromatography was carried out using silica gel 60 (35-70 μm particles).

Optical rotation measurements were carried out on a Perkin-Elmer AA-1000 and Polartronic H532 with a path length of 0.5 dm; concentrations are g/100mL and the optical rotations are given in 10^{-1} deg cm^2g^{-1}. Infrared spectra were recorded on a Perkin-Elmer one FT-IR spectrometer.

Proton and carbon NMR data were collected on an Avance 500, DPX500 and Bruker DPX 300. All shifts were recorded against an internal standard of tetramethylsilane (TMS). Solvents ($CDCl_3$, C_6D_6, DMSO-*d*6 and MeOD) used for NMR experiments were obtained from Sigma-Aldrich. Splitting patterns in this report have been recorded in an abbreviated manner, s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). NMR data was recorded in the following format, PPM (*number of protons*, *splitting pattern, coupling constant* (Hz)*, proton ID).* Signal assignments were made by the aid of COSY, DEPT 90 and 135, HMQC and HMBC.

Low resolution mass spectra data were recorded on a Agilent 1200 series LC system compromising a Bruker HCT Ultra ion trap mass spectrometer, a high vacuum degasser, a binary pump, a high performance autosampler, an autosampler thermostat, a thermostated column compartment a diode array detector. The system used two solvent systems: MeCN/H_2O + 0.1% formic acid with a Phenomenex Luna C18 50 × 2mm 5 micron column or MeCN/H_2O with a Phenomenex Luna C18 50 × 2mm 5 micron column

Nominal and high resolution mass spectrometry using electrospray ionization were recorded by Mrs Tanya Marinko-Covell on a Micromass LCT-KA11 or a Bruker Daltronics micrOTOF spectrometer. Field Desorption Ionisation mass spectra were

acquired on a Water-Micromass GCT premier spectrometer equipped with a Linden LIFDI probe.

Crystal structure measurements were carried out at 150 K on a Bruker-Nonius Apex X8 diffractometer equipped with an Apex II CCD detector and using graphite monochromated Mo-Kα radiation from a FR591 rotating anode generator by Colin Kilner. The structure was solved by direct methods and refined using SHELXL-97. Compound **159a** crystallises in the tetragonal space group $P4_1$ with one molecule in the asymmetric unit.

All non-hydrogen atoms were refined anisotropically.

All hydrogen atoms could be located in a difference Fourier map but, in the final stages of the refinement, they were placed in calculated positions and refined using a riding model.

4.1 General procedures

F-SPE purification. When F-SPE (Fluorous solid phase extraction) was utilised the compounds were loaded onto the column with the minimal amount of CH_2Cl_2, MeOH or DMF allowed for the size of column. The non-fluorous compounds were eluted with a MeOH—Water (80:20) mix until deemed complete by TLC; then the fluorous compounds were eluted using 100% MeOH.

A. Fukuyama—Mitsunobu of a Fluorous protected sulfonamide;

M1: The fluorous sulfonamide (2 eq.), triphenylphosphine (2 eq.) and the alcohol (2 eq.) were dissolved in anhydrous THF (*ca.* 0.01M) and cooled to 0 °C with an ice bath. Diethyl azodicarboxylate (4 eq.) was added dropwise and the reaction was stirred at room temperature until the endpoint was determined by TLC.

M2: procedure as **M1**; However, equivalents are fluorous sulfonamide (1 eq.), triphenylphosphine (4.0 eq.), alcohol (4.0 eq.) and diethyl azodicarboxylate (4 eq.)

B. Fukuyama—Mitsunobu of a Fluorous protected alcohol;

L1: The fluorous alcohol (1 eq.), triphenylphosphine (2.0 eq.) and the nucleophile (2.0 eq.) were dissolved in anhydrous CH_2Cl_2 (*ca.* 0.01M) and cooled to 0 °C with an ice bath. Diethyl azodicarboxylate (2 eq.) was added dropwise and the reaction was stirred at room temperature until the endpoint was determined by TLC. Upon completion the product was isolated using F-SPE

L2: procedure as **L1**; However, equivalents are fluorous alcohol (1 eq.), triphenylphosphine (4.0 eq.), nucleophile (4.0 eq.) and diethyl azodicarboxylate (4 eq.)

L3 procedure as **L1**; However, equivalents are fluorous alcohol (1 eq.), triphenylphosphine (1.1 eq.), nucleophile (1.1 eq.) and diethyl azodicarboxylate (1.1 eq.)

De-acetylation using saturated ammonia in methanol,

D: The acetate ester (1 eq.) was dissolved in NH_3 sat. MeOH (100 rel vols), stirred at room temperature until the endpoint is determined by TLC and the solvent, excess NH_3 and acetamide were removed *in vacuo.*

Ring-closing metathesis

RCM1: HG-II was added in one portion to the substrate dissolved in MTBE (*ca.* 2 mM) at room temperature and then heated to 55 °C. The reaction was then followed by TLC or LCMS. When the end point was determined the reaction was cooled to room

temperature, tris(hydroymethyl) phosphine (80 eq. WRT to HG-II), triethylamine (100 eq. WRT to HG-II) and silica (5 × amount of phosphine) were added and stirred for a minimum of 10 min. The reaction mixture was then passed through a pad of celite, washing with EtOAc, concentrated *in vacuo* to give the crude product.

RCM2 procedure as **RCM1**; However, 1,4-benzoquinone (4 mol%) was added

Denosylation

N1: The sulfonamide (1 eq.) and potassium carbonate (2.4 eq.) were dissolved in DMF (*ca.* >0.1 M), cooled to 0 °C and thiophenol (10 eq.) was added dropwise. The reaction was allowed to warm to room temperature and stirred until completion was determined by TLC. The crude product was loaded directly onto a F-SPE cartridge (in portions if necessary not to exceed the maximum loading capacity of the cartridge)

N2 procedure was as **N1**; however, the equivalents of thiophenol and K_2CO_3 were reduced to (5 eq.) and (1.2 eq.), respectively.

Diversification

A1: 3-pyridine isocyanate **136** (2 eq.) was added in one portion to the fluorous-tagged amine in anhydrous CH_2Cl_2 (0.1M) at room temperature. Completion of the reaction was determined by TLC (<1 h), the reaction was then concentrated *in vacuo* and purified using the generic F-SPE method.

A2: cyclopropane carbonyl chloride **139** (5 eq.) was added to a stirred solution of the fluorous-tagged amine and triethylamine (10 eq.) in anhydrous CH_2Cl_2. Completion of the reaction was determined by TLC. The reaction was then concentrated *in vacuo* and purified using the generic F-SPE method.

A3: 1-methyl-1H-imidazole-4-sulfonyl chloride **138** (5 eq.) was added to a stirred solution of the fluorous tagged amine and triethylamine (10 eq.) in anhydrous CH_2Cl_2. Completion of the reaction was determined by TLC. The reaction was then concentrated *in vacuo* and purified using the generic F-SPE method.

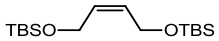
A4: morpholine-4-carbonyl chloride (5 eq.) **137** was added to a stirred solution of the fluorous tagged amine and triethylamine (10 eq.) in anhydrous CH_2Cl_2. Completion of the reaction was determined by TLC. The reaction was then concentrated *in vacuo* and purified using the generic F-SPE method.

Desilylation

S1: Aqueous hydrofluoric acid (0.2 mL, *ca.* 45%) was added in one portion to the silyl ether dissolved in CH_2Cl_2/MeCN (50:50, *ca.* 100 rel vols). Upon completion of the reaction determined by TLC, methoxytrimethylsilane (0.5 mL) was added and stirred for 16 h. The solution was concentrated onto silica-gel *in vacuo* and purified by column chromatography

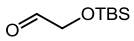
S2: Tetra-n-butylammonium fluoride (0.5 mL, 1.0 M, *ca.* 100 rel vols) was added to the silyl ether, upon completion determined by TLC the reaction was concentrated *in vacuo* onto silica-gel and purified by column chromatography.

1,4-Di[*tert*-butyldimethylsilyl)oxy]but-2-ene 146[119]



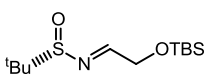
Imidazole (8.84 g, 130 mmol) and *tert*-butyldimethylsilyl chloride (20.0 g, 130 mmol) were dissolved in CH_2Cl_2 (50 mL); after 10 min, (*Z*)-but-2-ene-1,4-diol (5.6 g, 63 mmol) in CH_2Cl_2 (50 mL) was added at room temperature. After 16 h the reaction was filtered through a plug of silica and concentrated *in vacuo* to give the silyl ether **146** (19.5 g, 61.7 mmol, 98%) as a colourless oil, which was not purified; R_f 0.95 (90:10, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 5.19 (2H, t, *J* 4.5, 2-H), 3.59 (4H, d, *J* 5.5, 1-H), 0.81 (18H, s, SiC(CH_3)$_3$), 0.00 (12H, s, Si(CH_3)$_2$); ν_{max}/cm^{-1} (film) 3024, 1220, 1069 and 769

2-[(*Tert*-butyldimethylsilyl)oxy]acetaldehyde 147[120]



To a solution of **146** (10.0 g, 31.6 mmol) in CH_2Cl_2 (200 mL) at −78 °C, ozone was bubbled thorough the reaction until a pale blue colour persisted. Oxygen was then bubbled through the reaction until it became clear and colourless. Triphenylphosphine (8.44 g, 32.2 mmol) was added in one portion at −78 °C. The reaction was allowed to reach room 0 °C over a 16 h period; then concentrated *in vacuo*. Petrol (200 mL) was added and the slurry was filtered through a silica/Celite® plug, the filtrate was concentrate *in vacuo* to give the aldehyde **147** (10.1 g, 58.3 mmol, 92%) as a colourless volatile oil; R_f 0.87 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 9.60 (1H, s, C(O)*H*), 4.11 (2H, s, CH_2), 0.82 (9H, s, SiC(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 202.4 (*C*(O)H), 69.6 (*C*H_2), 25.9 (SiC(*C*H_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), -5.3 (Si(*C*H_3)$_2$); ν_{max}/cm^{-1} (film): 2929, 1739, 1253, 1123, 832 and 775; *m/z* (ES+) 175.2 (100%, MH$^+$)

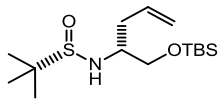
(*S*)-*N*-[(1*E*)-2-[(*Tert*-butyldimethylsilyl)oxy]ethylidene]-2-methylpropane-2-sulfinamide 148[98]



To a slurry of anhydrous copper(II) sulfate (23.9 g, 150 mmol) in CH_2Cl_2 (100 mL), aldehyde **147** (10.0g, 57 mmol) and (S_S)-2-methylpropane-2-sulfinamide (10.0 g, 86 mmol) were added. After 16 h at room temperature the reaction was filtered through a silica/Celite® plug and concentrated *in vacuo* to give the sulfinimine **148** (14.1 g, 51.2 mmol, 89%) as a pale yellow oil, which was not purified. For analytical purposes, a 500

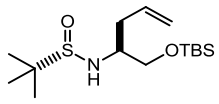
mg batch of the sulfinimine **148** was purified by column chromatography; hexanes—EtOAc (80:20); R_f 0.74 (80:20, hexanes—EtOAc); $[\alpha_D^{23}]$ 185 (*c* 1.00, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.96 (1H, t, *J* 3, 1-H), 4.44 (2H, d, *J* 3, 2-H), 1.07 (9H, s, ^{t}Bu), 0.81 (9H, s, SiC(CH_3)$_3$), 0.00 (6H, s, Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 168.9 (1-C), 65.5 (2-C), 56.8 (S^{t}Bu), 25.8 (SiC(CH_3)$_3$), 22.4 (SiC(CH_3)$_3$) and −5.4 (Si(CH_3)$_2$); ν_{max}/cm^{-1} (film) 3236, 2962, 1666, 1472, 1465, 1402, 1364, 1298; *m/z* (ES+) 300.1 (20%, $[M+Na]^+$)

_N_-[(2_S_)-1-[(_Tert_-butyldimethylsilyl)oxy]pent-4-en-2-yl}-2-methylpropane-2-sulfinamide 150[98]



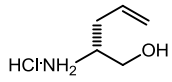
To a solution of sulfinimine **148** (0.9 g, 3.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C, allyl magnesium bromide 1M solution in ether (7.5 mL, 7.5 mmol) was added dropwise. After 1 h the reaction was stirred at 0 °C for 4 h and then allowed to reach room temperature. After 16 h the reaction was cooled with an ice-bath and sat. aqueous NH_4Cl was added dropwise; after 2 h the reaction was concentrated *in vacuo* to half volume and extracted into ethyl acetate (3 × 50 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography, eluting with petrol—EtOAc (80:20) gave the amine (S_sR_c) **150** (810 mg, 2.54 mmol, 70%) as a colourless oil and a single diastereomer; R_f 0.31 (petrol—EtOAc, 80:20); $[\alpha_D^{23.4}]$ +57.6 (*c* 1.01, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 5.75 (1H, ddt, *J* 7.2, 10.3 and 17.5, 4-H), 5.11 (1H, d, *J* 7.2, 5-H), 5.07 (1H, s, 5-H), 3.61 (1H, dd, *J* 4.3 and 10.3, 3-H$_a$), 3.47 (1H, dd, *J* 5.3 and 10.3), 3.46-3.43 (1H, m, N-H), 3.33-3.24 (1H, m, 2-H), 2.51-2.29 (2H, m, 1-H), 1.14 (9H, s, ^{t}Bu), 0.84 (9H, s, SiC(CH_3)$_3$), 0.00 (6H, s, Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 134.8 (4-C), 118.9 (5-C), 65.6 (1-C), 56.8 (2-C), 56.3 (SC(CH_3)$_3$), 37.5 (3-C), 26.3 (^{t}Bu), 22.9 (SiC(CH_3)$_3$), 18.6 (SiC(CH_3)$_3$), 0.41 (Si(CH_3)$_2$); ν_{max}/cm^{-1} (film): 2954, 2928, 2857, 1252, 1099, 1051, 855 and 775; *m/z* (ES+) 320.2 (100%, $[M+H]^+$)

_N_-[(2_S_)-1-[(_Tert_-butyldimethylsilyl)oxy]pent-4-en-2-yl]-2-methylpropane-2-sulfinamide 149[98]



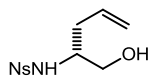
Also obtained was the diasteromer **149** (196 mg, 0.61 mmol, 17%); $[\alpha_D^{23.4}]$ +26.9 (*c* 1.0, $CHCl_3$); R_f 0.48 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 5.77 (1H, dddd, *J* 17.0, 10.4, 7.5 and 6.7, 4-H), 5.07 (1H, d , *J* 17, 5-H), 5.06 (1H, d, *J* 10.4, 5-H), 3.78 (1H, d, *J* 6.7, NH), 3.74 (1H, dd , *J* 9.9 and 4.6, 1-H), 3.60 (1H, dd , *J* 9.9 and 5.1, 1-H), 3.38 (1H, qt, *J* 6.4 and 4.8, 2-H), 2.40-2.21 (2H, m, 3-H); 1.21 (9H, s, tBu), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); δ_C (75 MHz; $CDCl_3$) 134.5 (4-C), 117.6 (5-C), 65.4 (1-C), 56.4 (2-C), 55.7 (SO^tBu), 36.8 (3-C), 25.8 (SO^tBu), 22.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.2 ($SiCH_3$), -5.3 ($SiCH_3$); ν_{max}/cm^{-1} (film) 3312, 2956, 2930, 2858, 1642, 1472, 1390, 1364 and 1324; *m/z* (ES+) 320.1 (20%, $[M+H]^+$)

(2*R*)-2-Aminopent-4-enol hydrochloride 151[98]



Sulfinamine **150** (4.0 g, 10 mmol) was dissolved in MeOH (40 mL) and 4N HCl in 1,4-dioxane (20 mL) was added dropwise at 0 °C for 1 h and then the reaction was stirred at room temperature for 4 h. The reaction was concentrated *in vacuo* to give a pale yellow solid. The solid was slurried in Et_2O (20 mL) and filtered to give the amine hydrochloride **151** (1.30 g, 9.5 mmol, 95%) as a white crystalline solid; $[\alpha_D^{23.7}]$ −10.3 (c. 0.7, MeOH); δ_H (500 MHz; MeOD) 5.84 (1H, ddt, *J* 7.1, 10.2 and 17.2), 5.31-5.20 (2H, m, 5-H_{trans} and 5-H_{cis}), 3.78 (1H, dd, *J* 3.8 and 11.6, 3-H_a), 3.58 (1H, dd, *J* 7.1 and 11.6, 3-H_b), 3.31-3.24 (1H, m, 2-H), 2.5-2.34 (2H, m, 1-H_{ab}); δ_C (75 MHz; MeOD) 131.9 (4-C), 118.8 (5-C), 60.5 (1-C), 52.5 (2-C) , 33.5 (3-C); ν_{max}/cm^{-1} (solid): 2472, 2071, 1121 and 972

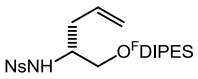
(2*R*)-1-Hydroxy-*S*-(2-nitrophenyl)pent-4-ene-2-sulfonamide 152



The amine hydrochloride **151** (1.6 g, 11.6 mmol) was dissolved in CH_2Cl_2 (50 mL), triethylamine (2.93 g, 29 mmol) was added and the reaction cooled to 0 °C. 2-Nitrobenzene sulfonyl chloride (2.58 g, 11.6 mmol) was added in one portion; after 1 h the ice bath was removed and the reaction was stirred at room temperature. After 16 h the reaction was poured into water (50 mL), separated and washed with HCl (0.5M, 50 mL), 10% $NaHCO_3$ (50 mL) and brine (100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the sulfonamide **152** (3.15 g, 11.1

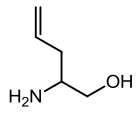
mmol, 95%) as a pale yellow viscous oil, which was not purified; R_f 0.71 (80:20, EtOAc—petrol); $[\alpha_D^{23.7}]$ −5.1 (c. 0.3, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.17-8.13 (1H, m, nosyl 3-H), 7.90-7.85 (1H, m, nosyl 6-H), 7.79-7.72 (2H, m, nosyl 4 and 5-H), 5.54 (1H, ddt, *J* 7.2, 10.0 and 17.2, 4-H), 5.01 (1H, *J* 17.0, 5-H_{trans}), 4.92 (1H, *J* 10.0, 5-H_{cis}), 3.66-3.53 (3H, m, 1-H_{ab} and 2-H), 2.35-2.22 (2H, m, 3-H_{ab}); δ_C (75 MHz; $CDCl_3$) 147.7 (nosyl 2-C), 134.5 (4-C), 133.6 (nosyl 1-C), 132.9 (nosyl 4 and 5-C), 130.7 (nosyl 6-C)), 125.4 (nosyl 3-C), 118.9 (5-C), 64.4 (1-C), 56.2 (2-C), 36.2 (3-C); ν_{max}/cm^{-1} (film) 3334, 1537, 1163 and 593; *m/z* (ES+) 309.1 (100%, $[M+Na]^+$); found 309.0515, $C_{11}H_{14}N_2O_5S$ requires *MNa,* 309.0516

_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]-2-nitrobenzene-1-sulfonamide 112



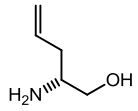
A solution of (1H, 1H, 2H, 2H-heptadecafluorodecyl)diisopropylsilane (6.6 g, 11.7 mmol) in CH_2Cl_2 (40.0 mL) was added slowly to a solution of *N*-bromosuccinimide (2.2 g, 12.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After 5 min at 0 °C the reaction was then stirred for 20 min at room temperature. A solution of sulfonamide **152** (3.15 g, 11.1 mmol) and imidazole (1.0 g, 14.6 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise at 0 °C. After 16 h at room temperature the reaction was concentrated *in vacuo*, dissolved in the petrol—EtOAc (50:50) and filtered through a silica/Celite® plug. The resulting filtrate was concentrated *in vacuo,* to give the sulfonamide **112** (9.3 g, 11.1 mmol, 99 %) as a pale yellow viscous oil which was not purified further. R_f 0.95 (80:20 EtOAc—petrol); $[\alpha_D^{23.7}]$ −2.4 (c. 1.5, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.14-8.12 (1H, m, Ns), 7.87-7.84 (1H, m, Ns), 7.73-7.69 (1H, m, Ns), 5.65 (1H, d, *J* 10, N-H), 5.61 (1H, ddt, *J* 9.5, 13 and 18, 4-H), 5.03 (1H, d, *J* 18, 5-H), 4.97 (1H, d, *J* 13, 5-H), 3.72-3.69 (1H, m, 3-H_a), 3.61-3.52 (2H, m, 3-H_b and 2-H), 2.35-2.26 (2H, m, 1-H), 2.15-1.94 (2H, m, 2'-H), 0.98 (14H, s, ^{i}Pr), 0.86-0.75 (2H, m, 1'-H); δ_C (75 MHz; $CDCl_3$) 135.1 (4-C), 133.4 (nosyl 1-C), 133.0 (nosyl 6-C), 132.9 (nosyl 4 or 5-C), 130.6 (nosyl 6-C), 125.4 (nosyl 3-C), 118.8 (5-C), 64.6 (1-C), 55.8 (2-C), 36.2 (3-C), 24.5 (^{i}Pr), 17.4 (^{i}Pr), 12.2 (^{i}Pr), -0.3 (1'-C), *nosyl 2-C missing*; ν_{max}/cm^{-1} (film): 2949, 2870, 1643, 1543, 1275 and 1259; *m/z* (ES+) 864.2 (100%, $[M+NH_4]^+$); found 864.1787, $C_{27}H_{35}F_{17}N_3O_5SSi$ requires *MNH_4,* 864.1790

2-Aminopent-4-enol 156



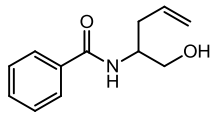
To a solution of MeOH (40 mL) was added acetyl chloride (4.0 g, 52 mmol); to this, 2-amino-4-petenoic acid (2.00 g, 17.4 mmol) in MeOH (60 mL) was added. The reaction was heated at reflux for 4 h, concentrated *in vacuo* to give the crude methyl ester hydrochloride. THF (100 mL) was added and the solution cooled to 0 °C, $LiAlH_4$ (1.97 g, 52 mmol) was added portionwise (*ca*. 0.5 g). After 16 h, aqueous sat. NH_4Cl was added until effervescence ceased, the resulting solution was concentrated *in vacuo* onto silica gel. Column chromatography eluting with CH_2Cl_2—MeOH (85:15) gave the amino alcohol **156** (1.62 g, 16 mmol, 92%) as a pale yellow oil. R_F 0.1 (90:10 CH_2Cl_2—MeOH); δ_H (300 MHz; $CDCl_3$) 5.58 (1H, ddt, *J* 17.1, 10.2 and 7.2, 4-H), 4.96-4.82 (2H, m, 5-H_{AB}), 3.39 (1H, dd, *J* 10.9, 3.9, 1-H_A), 3.16 (dd, *J* 10.9, 7.4, 1-H_B), 2.74 (1H, dq, *J* 9.7, 7.5 Hz, 2-H), 2.04 (1H, dt, *J* 12.5, 6.1, 3-H_A), 1.96-1.80 (1H, m, 2-H_B); δ_C (75 MHz; $CDCl_3$) 134.4 (4-C), 177.8 (5-C), 65.1 (1-C), 52.1 (2-C), 37.7 (3-C); ν_{max}/cm^{-1} (film) 3543, 3352, 2939, 2308, 1960, 1846, 1660, 1643, 1594, 1539, 1428, 1361

(*R*) 2-Aminopent-4-enol (*R*)-156



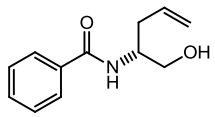
To a solution of MeOH (5 mL) was added acetyl chloride (3.4 g, 43 mmol); to this, (*R*)-2-amino-4-petenoic acid (1.00 g, 8.7 mmol) in MeOH (10 mL) was added. The reaction was refluxed for 4 h, concentrated *in vacuo* to give the crude methyl ester hydrochloride. THF (100 mL) was added and the solution cooled to 0 °C, $LiAlH_4$ (0.66 g, 17.4 mmol) was added portionwise (*ca*. 0.2 g). After 16 h, aqueous sat. NH_4Cl was added until effervescence ceased, the resulting solution was concentrated *in vacuo* onto silica gel. Column chromatography elution with CH_2Cl_2—EtOH—NH_4OH (86:13.5:1.5) gave the amino alcohol **(*R*)-156** (700 mg, 6.93 mmol, 80%) as a pale yellow oil; $[\alpha_D^{23.7}]$ −25.4 (c. 0.8, MeOH)

***N*-(1-Hydroxypent-4-en-2-yl)benzamide 157**



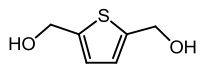
Benzoyl chloride (124 mg, 0.9 mmol) was added to a solution of **156** (100 mg, 0.99 mmol) and Et_3N (156 mg, 1.5 mmol) in CH_2Cl_2 (10 mL). After 24 h the reaction was concentrated *in vacuo* onto silica, column chromatography eluting with petrol—EtOAc (10:90 → 20:80) gave the amide **157** (104 mg, 0.51 mmol, 51% as an off white solid; R_F 0.29 (90:10 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.76 (2H, dd, *J* 8.3 and 1.4, Ar 2 and 6-H), 7.51 (1H, tt, *J* 7.5 and 1.4, Ar 4-H), 7.43 (2H, dd, *J* 8.3 and 7.5, Ar 3 and 5-H), 6.38 (1H, br s, NH), 5.86 (1H, ddt, *J* 17.2, 10.1 and 7.1, 4-H), 5.20 (1H, ddd, *J* 17.2, 1.7 and 1.6, 5-H_A), 5.17 (1H, ddd, *J* 10.1, 1.3 and 1.7, 5-H_B), 4.25-4.19 (1H, m, 2-H), 3.81 (1H, dd, *J* 11.1 and 3.7, 1-H_A), 3.75 (1H, dd, *J* 11.1 and 5.4, 1-H_B), 2.88 (1H, br s, OH), 2.51-2.38 (2H, m, 3-H_{AB}); δ_C (75 MHz; $CDCl_3$) 168.2 (C=O), 134.3 (5-C), 134.2 (Ar 1-C), 131.7 (Ar 4-C), 128.6 (Ar 2 and 6-C), 126.9 (Ar 3 and 5-C), 118.5 (4-C), 65.4 (1-C), 51.6 (2-C), 35.8 (3-C); ν_{max}/cm^{-1} (film) 3302, 2952, 1955, 1894, 1637, 1603, 1578, 1536, 1490, 1442; *m/z* (ES+) 228.1 (100%, $[M+Na]^+$); found 228.1002, $C_{12}H_{15}NO_2$ requires *MNa,* 228.0995

(*R*) *N*-(1-Hydroxypent-4-en-2-yl)benzamide



Benzoyl chloride (124 mg, 0.9 mmol) was added to a solution of **(*R*)-156** (101 mg, 0.1 mmol) and Et_3N (150 mg, 1.5 mmol) in CH_2Cl_2 (10 mL). After 24 h the reaction was concentrated *in* vacuo onto silica, column chromatography eluting with petrol—EtOAc (10:90 → 20:80) gave the amide **(*R*)-157** (120 mg, 0.58 mmol, 58%) as an off white solid. Data as **157**, $[\alpha_D^{23.7}]$ 11.3 (c. 0.5, MeOH)

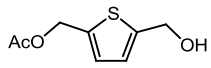
2,5-Di(hydroxylmethyl)thiophene 165[121,122]



To a slurry of $LiAlH_4$ (4.4 g, 116 mmol) in THF (800 mL) was added 2,5-thiophenedicarboxylic acid **164** (10.0 g, 58 mmol) portionwise at 0 °C. After addition the slurry was stirred at room temperature for 30 min and then refluxed for 24 h. The reaction was cooled to 0 °C and water was added until there was no more gas evolution. The reaction was then extracted with EtOAc (5 × 200 mL), dried ($MgSO_4$),

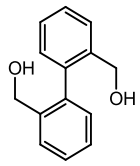
filtered and concentrated *in vacuo* to give **165** (6.8 g, 82 %) as a pale yellow oil, that was used without further purification; R_f 0.1 (60:40 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 6.93 (2H, s, 3-H), 4.84 (s, 4H, 1-H), 1.91 (s, 2H, OH); δ_C (75 MHz; $CDCl_3$) 144.7 (2-C), 125.7 (3-C), 60.6 (1-C); ν_{max}/cm^{-1} (film) 3350, 2870, 1731, 1653, 1359, 1205, 1159, 1008 and 808; *m/z* (ES+) 167.2 (100%, MNa^+)

[5-(Hydroxymethyl)thiophen-2-yl]methyl acetate 130



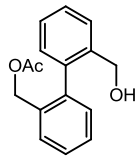
To a solution of **165** (10.0 g, 69 mmol), triethylamine (9.2 mL, 82 mmol) and DMAP (80 mg, 0.6 mmol) in CH_2Cl_2 (500 mL) at 0 °C, was added a solution of acetyl chloride (5.4 g, 69 mmol) in CH_2Cl_2 (20 mL). The reaction was then stirred for 16 h at room temperature and then concentrated *in vacuo*. Column chromatography, eluting with 60:40 petrol—EtOAc gave **130** (6.42 g, 49 %) as a pale yellow oil; R_f 0.47 (60:40 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.00 (1H, d, *J* 3.5, 6-H), 6.93 (1H, d, *J* 3.5 , 5-H), 5.26 (2H, s, 1-H), 4.84 (2H, d, *J* 5.38, 1'-H), 2.13 (s, 3H, Ac), 1.93 (1H, t, *J* 5.8, OH); δ_C (75 MHz; $CDCl_3$) 173.6 (Ac), 146.1 (4-C), 137.5 (6-C), 128.5 (2-C), 125.5 (3-C), 61.1 (1-C), 60.6 (1'-C), 21.4 (Ac); ν_{max}/cm^{-1} (film) 3448, 2864, 2250, 1740, 1379, 1235, 1023; *m/z* (ES^+) 169.0 (50%, $[M\text{-}H_2O]^+$) and 498.1 (100%, $[M_3+NH_4]^+$)

{2-[2-(Hydroxymethyl)phenyl]phenyl}methanol 167[123]



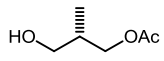
$LiAlH_4$ (2M in THF, 45 mL, 90 mmol) was added dropwise to diphenic anhydride **166** (10.0 g, 44.6 mmol) in THF (350 mL) at 0 °C. After 24 h the reaction was quenched with aqueous sat. NH_4Cl until no gas was evolved and then the pH was corrected to *ca.* 7 with 4N HCl. The slurry was filtered through a Celite® plug and concentrated *in vacuo*; the solution was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give the crude product which was recrystallized from toluene to give the diol **167** (8.01 g, 37.4 mmol, 85 %) as off-white needles; m.p 127-129 °C; R_f 0.63 (20:80 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.54 (2H, dd, *J* 1.1 and 7.6), 7.45 (2H, td, *J* 1.4 and 7.6), 7.40 (2H, td, *J* 1.4 and 7.4), 7.21 (2H, dd, *J* 1.1 and 7.4), 4.40 (4H, d, *J* 11.7, *benzylic*), 2.72 (2H, br s, O*H*); δ_C (75 MHz; $CDCl_3$) 140.4, 138.9, 130.1, 130.0, 128.5, 128.1, 63.3; ν_{max}/cm^{-1} (film) 3055, 2987, 2305, 1477, 1422, 1340, 1266; *m/z* (ES^+) 237.1 (100%, $[M+Na]^+$); found 237.0884, $C_{14}H_{14}O_2$ requires *MNa* 237.0886

{2-[2-(Hydroxymethyl)phenyl]phenyl}methyl acetate 129



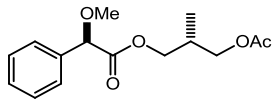
Acetyl chloride (182 mg, 2.3 mmol) was added dropwise to a stirring solution of diol **167** (500 mg, 2.3 mmol), triethylamine (255 mg, 2.5 mmol) and DMAP (28 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 2 h at room temperature the reaction was washed with water (5 mL), 1M HCl (5 mL) and brine (5 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Column chromatography, eluting with petrol--EtOAc (40:60) gave the mono acetate **129** (256 mg, 1.05 mmol, 46%) as a colourless oil; δ_H (300 MHz; $CDCl_3$) 7.50 (1H, d, *J* 8.0, Ar), 7.40 (1H, d, *J* 7.3, Ar), 7.36-7.23 (4H, m, Ar), 7.13 (1H, dd, *J* 1.6 and 7.2, Ar), 7.07 (1H, dd, *J* 1.2 and 7.6), 4.85-4.76 (2H, m, C*H*$_2$OAc), 4.39-4.28 (2H, m, C*H*$_2$OH), 1.94 (3H, s, Ac), 1.75 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 171.1 (CO), 140.5, 139.2, 139.1, 134.5, 130.4, 130.1, 129.3, 128.9, 128.7, 128.5, 128.4, 127.8, 65.7 63.4, 21.3; ν_{max}/cm^{-1} (film): 3406, 1732, 1379, 1223, 1024, 1006 and 775; *m/z* (ES^+) 279.1 (100%, $[M+Na]^+$); found 279.0996, $C_{16}H_{16}O_3$ requires *MNa* 279.0992

(2*S*)-3-Hydroxy-2-methylpropyl acetate 128[124]



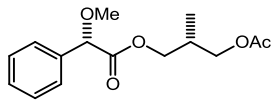
Vinyl acetate (5.7 g, 66 mmol) was added to 2-methyl propane 1,3-diol **168** (2.0g, 22 mmol) and chloroform (10 mL) at room temperature. *Pseudomonas Fluorescens* (100 mg) was added and the reaction stirred for 24 h. Once all the diol had been consumed, the reaction was filtered through Celite® and concentrated *in vacuo* to give the crude product. Column chromatography, eluting with petrol—EtOAc (50:50) gave the monoacetate **128** (1.2 g, 9.0 mmol, 41%) as a colourless oil; R_f 0.36 (50:50 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 4.13 (1H, dd, *J* 5.1 and 11.1, C*H*$_a$OAc), 4.05 (1H, dd, *J* 6.6 and 11.1, C*H*$_b$OAc) 3.56 (1H, dd, *J* 5.1 and 11.1, C*H*$_a$OH), 3.50 (1H, dd, *J* 6.6 and 11.1, C*H*$_b$OH) 2.08 (3H, s, Ac), 2.02-1.96 (1H, m, C*H*), 1.91 (1H, br s, O*H*), 0.96 (3H, d, *J* 6.9, CH_3); δ_C (75 MHz; $CDCl_3$) 171.7 (CO), 66.2 (*C*H_2OAc), 64.5 (*C*H_2OH), 35.4 (*C*H), 20.9 (Ac), 13.5 (CH_3); ν_{max}/cm^{-1} (film): 2963, 1736, 1715, 1367, 1221, 1031 and 988; *m/z* (ES^+) 155.1 (100%, $[M+H]^+$); found 155.0702, $C_6H_{12}O_3$ requires *MNa* 155.0679

(2*R*)-3-(Acetyloxy)-2-methylpropyl (2*R*)-2-methoxy-2-phenylacetate 169



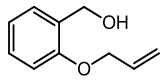
To a solution of (*S*)-(α)-Methoxyphenylacetic acid (100 mg, 0.6 mmol), hydroxyl acetate **128** (87.6 mg, 0.6 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) was added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (102.3 mg, 0.66 mmol). After 16 h the crude mixture was concentrated *in vacuo*, column chromatography eluting with 80:20 petrol—EtOAc gave the ester **169** (93 mg, 0.30 mmol, 45%) as a colourless oil; R_f 0.84 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.53-7.33 (5H, m, Ar), 4.81 (1H, s, (MeO)C*H*), 4.12 (1H, dd, *J* 11.1 and 6.2, 1-H_A), 4.08 (1H, dd, *J* 11.1 and 6.1, 1-H_B), 3.94 (1H, dd, *J* 11 and 5.6, 3-H_A), 3.86 (1H, dd, *J* 11 and 6.4, 3-H_B), 3.44 (3H, s, OMe), 2.20-2.08 (1H, m, 2-H), 2.05 (3H, s, Ac), 0.92 (3H, d, *J* 6.9, Me), 0.88 (d, *J* 6.9, Me^{min}); δ_C (75 MHz; $CDCl_3$) 171.4, 171.1, 136.6, 129.2, 129.1, 127.5, 82.9, 66.7, 65.9, 57.8, 32.7, 21.3, 14.1; ν_{max}/cm^{-1} (film) 3004, 2989, 1738, 1455, 1275, 1261; *m/z* (ES^+) 303.1 (100%, $[M+H]^+$); found 303.1199, $C_{15}H_{20}O_5$ requires *MH* 303.1209

(2*R*)-3-(Acetyloxy)-2-methylpropyl (2*S*)-2-methoxy-2-phenylacetate 170



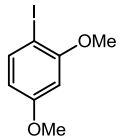
Using the same procedure as **169** gave the ester **170** (96 mg, 0.31 mmol, 52%) as a colourless oil; R_f 0.84 (70:30, Petrol−EtOAc); δ_H (500 MHz; $CDCl_3$) 7.48 (2H, 8.0 and 1.7, Ar), 7.44-7.36 (3H, Ar), 4.82 (1H, s, (MeO)C*H*), 4.14 (1H, dd, *J* 11 and 6.1, 1-H_A), 4.10 (1H, dd, *J* 11 and 5.9, 1-H_B), 3.94 (1H, dd, *J* 11.1 and 6.3, 3-H_A), 3.93 (1H, dd, *J* 11.1 and 5.8, 3-H_B); 3.87 (dd, *J* 11.1 and 6.4, 3-H_B^{min}), 3.46 (3H, s, OMe), 2.19-2.13 (1H, m, 2-H), 2.06 (3H, s Ac), 0.93 (d, Me), 0.89 (3H, d, *J* 6.8, Me); δ_C (75 MHz; $CDCl_3$) 170.9, 170.6, 136.3, 128.8, 128.7, 127.1, 126.6, 82.5, 66.3, 65.5, 57.3, 32.3, 20.8, 13.6, 13.5 (min); ν_{max}/cm^{-1} (film) 3001, 2988, 1738, 1274, 1260; *m/z* (ES^+) 303.1 (100%, $[M+H]^+$); found 303.1209, $C_{15}H_{20}O_5$ requires *MH* 303.1209

[2-(Prop-2-en-1-yloxy)phenyl]methanol 173[125]



To a solution of salicyladehyde (1.00 g, 8.19 mmol) and potassium carbonate (2.80 g, 20.2 mmol) in acetone (100 mL); was added allyl bromide (1.18 g, 9.83 mmol). The reaction was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 mL); washed with NaOH (1M, 20.0 mL), water (2 × 20.0 mL) and brine (2 × 20.0 mL). The CH_2Cl_2 solution was dried, $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. The oil obtained was dissolved into MeOH (200 mL) and $NaBH_4$ (1.00 g, 26.4 mmol) was added portionwise to the solution which self-heating and was not controlled. Once all the $NaBH_4$ was added the solution was refluxed for 1 h; the solution was poured into ice/water (50.0 mL and extracted with $CHCl_3$ (50.0 mL); the organic layer was dried, $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Flash chromatography, eluting with 30:70 EtOAc—hexanes gave the product **173** (0.94 g, 5.80 mmol, 71%) as a colourless oil. R_f 0.34 (70:30, EtOAc—hexanes); δ_H (500 MHz; $CDCl_3$) 7.32-7.21 (2H, m, Ph 3-H and 6-H), 6.95 (1H, t, *J* 7.2, Ph 5-H), 6.88 (1H, d, *J* 8.2, Ph 4-H), 6.07 (1H, m, propenyl 2-H), 5.42 (1H, dd, *J* 1.5, 17, propenyl 3-H_A), 5.30 (1H, dd, *J* 1.5, 10, propenyl 3-H_B), 4.72 (2H, d, *J* 6.1, C*H*$_2$OH), 4.60 (2H, dt, *J* 5.2 and 1.5, propenyl 1-H) 2.34 (1H, br s, O*H*); δ_C (75 MHz; $CDCl_3$) 156.5 (Ph 2-C), 133.0 (propenyl 2-C), 129.4 (Ph 1-C), 128.9 (Ph 4-C or 2), 128.8 (Ph 4-C or 2), 120.9 (Ph 5-C), 117.7 (propenyl 3-C), 111.5 (propenyl 3-C), 68.8 (propenyl 1-C), 62.2 (Ph*C*H_2OH); ν_{max}/cm^{-1} (film) 3368, 2921, 2871, 1602, 1491, 1423, 1236, 998 and 753; *m/z* (EI^+) 164.1 (75%, $[M]^+$); found 164.0834, $C_{10}H_{12}O_2$ requires *M* 164.0837

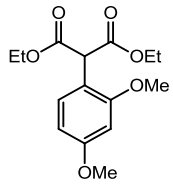
1-Iodo-2,4-dimethoxybenzene 175[126]



Sulfuric acid (18M, 2.00 mL, 36.0 mmol) was added to a stirred solution of methanol (40.0 mL). 1,3-Dimethoxybenzene (1.00 g, 7.20 mmol) and Potassium iodide (1.33 g, 8 mmol) were added, which resulted in a colour change from colourless to pale yellow. Hydrogen peroxide (30.0%, 2 mL, 16 mmol) was added, which caused a solution colour change to dark brown. After 2.5 h the reaction mixture was poured into CH_2Cl_2 (100 mL) and washed with $NaHSO_4$ (0.1 M, 60.0 mL) and water (60.0 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product

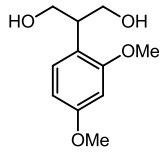
as brown oil which was purified by flash chromatography, eluting with CH_2Cl_2 to give purple fractions which were washed with sodium metabisulphite (10% w/v, 50.0 mL) to remove elemental I_2, dried, $MgSO_4$, filtered and concentrated *in vacuo* to give the product **175** as a colourless oil (1.62 g, 6.10 mmol, 84%); R_f 0.83 (CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.62 (1H, d, *J* 8.6, 6-H), 6.43 (1H, d, *J* 2.7, 2-H), 6.32 (1H, dd, *J* 8.6, 2.7 , 6-H), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe); δ_C (125 MHz; $CDCl_3$) 160.2 (2-C), 157.6 (4-C), 137.6 (6-C), 105.9 (5-C), 98.0 (3-C), 73.6 (1-C), 55.0 (OMe), 54.3 (OMe); ν_{max}/cm^{-1} (solid) 1575 and 822; *m/z* (EI^+) 264.0 (75%, $[M]^+$); found 263.9647, $C_8H_9IO_2$ requires *M* 263.9647

1,3-Diethyl 2-(2,4-dimethoxyphenyl)propanedioate 176[127]



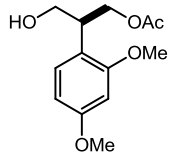
Caesium carbonate (3.68 g, 11.4 mmol) was added to a solution of **175** (1.00 g, 3.78 mmol) in dioxane (8.00 mL). Copper iodide (35.0 mg, 5 mol%) and picolinic acid (46.0 mg, 10 mol%) were added in one portion. The solution was stirred at room temperature for 5 min and diethyl malonate (1.20 g, 7.56 mmol) was added in one portion and the solution was heated at reflux for 48 h. On completion the reaction was filtered through a short silica pad, the silica was washed with CH_2Cl_2 (3 × 25.0 mL). The solution was dried, $MgSO_4$, filtered and concentrated *in vacuo* to give a viscous oil. Column chromatography, eluting with 20:80 Et_2O—hexanes gave **176** (0.79 g, 2.67 mmol, 71%) as a colourless needles; m.p. 53.5-54.1 °C (hexanes—Et_2O); R_f 0.65 (CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.25 (1H, br s, Ph 6-H), 6.50 (1H, dd, *J* 8.3 and 2.0, Ph 5-H), 6.46 (1H, dd, *J* 2.0, Ph 3-H), 5.02 (1H, s, propyl 2-H), 4.27-4.17 (4H, m, 2 x C*H*$_2$), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 1.26 (6H, t, *J* 7, C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 169.2 (2 x C=O), 161.1 (Ph 2-C), 158.4 (Ph 4-C), 130.5 (Aryl 6-C), 114.8 (Aryl 1-C), 105.0 (Aryl 5-C), 99.0 (Aryl 3-C), 62.2 (*C*H_2CH$_3$), 56.0 (OCH$_3$), 55.7 (OCH$_3$), 51.0 (C(O)*C*HC(O)), 14.4 (*C*H_3CH$_2$); ν_{max}/cm^{-1} (solid) 2970, 2442, 2159, 2029, 1738, 1366, 1217; *m/z* (EI^+) 297.5 (90%, $[M+H]^+$) and 223.4 (100%, $[M-C(O)OEt]^+$)

2-(2,4-Dimethoxyphenyl)propane-1,3-diol 177



Lithium aluminium hydride (0.40 g, 10.6 mmol) was slurried in THF (10.0 mL) and cooled to 0 °C. A solution of the α-aryl diethyl malonate **176** (0.7 g, 2.36 mmol) in THF (3.60 mL) was added dropwise. Once addition was complete the reaction was stirred for 5 min at 0 °C and then 24 h at room temperature. The reaction mixture was cooled to 0 °C and water (15.0 mL) was added. The reaction mixture was then filtered through a short silica pad; washing the silica with Et_2O (5 × 10.0 mL). The filtrate was separated and the aqueous layer was extracted with Et_2O (3 × 10.0 mL). The combined organic layers were dried, $MgSO_4$, and concentrated *in vacuo* to give the crude diol as a viscous oil. Column chromatography, eluting with 50:50 EtOAc—hexanes gave the diol **177** (0.27 g, 1.27 mmol, 53%) as colourless needles; m.p. 84.7-85.9 °C (from EtOAc—hexanes); R_f 0.11 (50:50, EtOAc—hexanes); δ_H (500 MHz; $CDCl_3$) 7.07 (1H, d, *J* 9, Aryl 6-H), 6.5-6.43 (2H, m, Aryl 5-H and 3-H), 4.05-3.85 (4H, m, propyl 1-H), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.50-3.39 (1H, m, propyl 2-H), 2.01 (2H, t, *J* 7.5, O*H*); δ_C (75 MHz; $CDCl_3$) 160.3 (Aryl 4-C) 158.8 (Aryl 2-*C*), 129.2 (Aryl 6-*C*), 120.2 (Aryl 1-C), 99.4 (Aryl 3-C), 104.8 (Aryl 5-C), 65.8 (propyl 1-C), 55.8 (OMe), 55.7 (OMe), 43.3 (propyl 2-C); ν_{max}/cm^{-1} (solid) 3234, 2509, 2159, 2030, 1615, 1469, 1040; *m/z* (ES^+) 235.1 (100%, $[M+H]^+$); found 235.0944, $C_{11}H_{16}O_4$ requires *MH* 235.0941

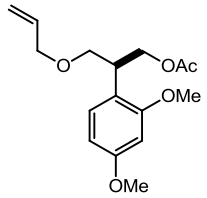
(2S)-2-(2,4-Dimethoxyphenyl)-3-hydroxypropyl acetate 178



Candida Antarctica (10.0 mg) immobilised on acrylic resin beads (Novozyme 435®) was added to the 1,3-diol **177** (50.0 mg, 0.23 mmol) dissolved in ether (2.00 mL). Vinyl acetate (30.0 mg, 0.35 mmol) was added. The reaction mixture was stirred gently as not to break up the enzyme resin beads for 20 min; after which the reaction was filtered and concentrated *in vacuo* to give the crude product as a viscous oil. Column chromatography, eluting with 50:50 EtOAc—hexanes gave the hydroxy acetate **178** (41.0 mg, 0.16 mmol, 70%) as a colourless film. R_f 0.27 (50:50, hexanes—EtOAc); $[\alpha]_D^{25}$ −16.4 (*c* 1.2, $CHCl_3$); δ_H (500 MHz; $CDCl_3$): 7.10 (1H, dd, *J* 6.9 and 2.4, Ar 6-H), 6.49-6.43 (2H, m, Ar 2 and 5-H), 4.38 (1H, dd, *J* 11.1 and 7.2, propyl 1-H_A), 4.34 (1H,

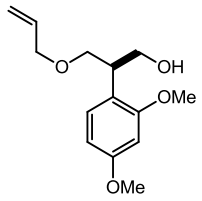
dd, *J* 11.1 and 5.9, propyl 1-H_B), 3.83 (2H, d, *J* 5.9, propyl 3-H_{AB}), 3.80 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.50 (1H, p, *J* 5.9, propyl 2-H), 2.05 (3H, s, C(O)CH_3), 1.90 (1H, brs, CH_2O*H*); δ_C (75 MHz; $CDCl_3$) 171.7 (*C*(O)CH_3), 160.4 (Ar 2-C or 4-C), 158.8 (Ar 2-C or 4-C), 129.4 (Ar 6-C), 119.7 (Ar 1-C), 104.7 (Ar 5-C), 99.3 (Ar 3-C), 64.9 (propyl 1-C), 63.4 (propyl 3-C), 55.8 (OMe), 55.7 (OMe), 40.7 (propyl 2-C), 21.3 (C(O)CH_3; ν_{max}/cm^{-1} (film) 3006, 1727, 1616, 1584, 1506, 1458; *m/z* (ES^+) 277.1 (100%, $[M+Na]^+$); found 277.1042, $C_{13}H_{18}O_5$ requires *MNa* 277.1046

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl acetate 179



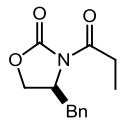
Alcohol **178** (15.0 g, 60.0 mmol) and allyl ethyl carbonate (23.0 g, 177 mmol) were dissolved in THF (500 mL) at room temperature. Palladium (II) acetate (132 mg, 0.59 mmol) and triphenylphosphine (1.54 g, 5.9 mmol) were added and the reaction was refluxed for 24 h. The reaction was concentrated *in vacuo* dissolved in EtOAc (200 mL) and passed through a short silica pad and concentrated *in vacuo* to give the crude product. Column chromatography, eluting with petrol—EtOAc (80:20) gave the allyl ether **179** (13 g, 58.1 mmol, 72%); R_f 0.91 (80:20 petrol—EtOAc,); $[\alpha_D^{18.9}]$ 4 (*c* 0.5, $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 7.11 (1H, d, *J* 9.0, Ph 6-H), 6.47-6.43 (2H, m, Ph 3-H and 5-H), 5.87 (1H, ddt, *J* 17.2, 10.7 and 5.5, propenyl 2-H), 5.24 (1H, d, *J* 17.2, propenyl 3-H_A), 5.15 (1H, d, *J* 10.7, propenyl 3-H_A), 4.38 (1H, dd, *J* 5.9 and 10.8, 1-H_a), 4.32 (1H, dd, *J* 6.2 and 10.8, propyl 1-H_B), 4.01 (2H, m, propenyl 1-H), 3.79 (6H, s, OMe), 3.67-3.56 (3H, m, propyl 2-H and 3-H_{ab}), 1.99 (3H, s, Ac); δ_C (75 MHz; $CDCl_3$) 171.2 (C=O), 159.6 (Ph 2 or 4-C), 158.3 (Ph 2 or 4-C), 134.9 (propenyl 2-C), 128.9 (Ph 6-C), 119.9 (Ph 1-C), 116.7 (propenyl 3-C), 104.0 (Ph 5-C), 98.6 (Ph 3-C), 64.9 (propenyl 1-C), 60.4 (propyl 1 and 3-C), 55.4 (OMe), 55.3 (OMe), 37.7 (propyl 2-C), 21.1 (Me); ν_{max}/cm^{-1} (film): 1735, 1612, 1506, 1233, 1207, 1032 and 541; *m/z* (ES^+) 317.1 (100%, $[M+Na]^+$); found 317.1360, $C_{16}H_{22}O_5$ requires *MNa* 317.1359

(2*R*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propan-1-ol 180



By general procedure **D**, acetate **179** (10.6 g, 36 mmol) was dissolved in sat. MeOH/NH_3 (500 mL), after 48 h the reaction was concentrated *in vacuo* to give **180** (7.5 g, 75%) as a colourless oil; R_f 0.18 (80:20, petrol—EtOAc); $[\alpha]_D^{23}$ 8.3 (*c*. 2.9 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.11 (1H, d, *J* 8.1, Ar), 5.51-6.47 (2H, m, Ar), 5.96 (1H, ddt, *J* 17.1, 10.5 and 5.6 , propenyl 2-H), 5.32 (1H, d, *J* 17.1, propenyl 3-H_A), 5.23 (1H, d, *J* 10.5, propenyl 3-H_B), 4.11-3.97 (4H, m, propenyl 1-H and 3-H_{AB}), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.83-3.79 (1H, m, 1-H_A), 3.76 (1H, dd, *J* 9.1 and 4.7, 1-H_B), 3.64-3.58 (1H, m, 2-H), 2.61 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 160.1 (Ar 2- or 4-C), 158.6 (Ar 2- or 4-C), 134.9 (propenyl 2-C) , 128.8 (Ar 6-C), 120.4 (Ar 1-C), 117.5 (propenyl 3-C), 104.5 (Ar 5-C), 99.2 (Ar 3-C), 73.8 (propyl 1-C), 72.6 (propenyl 1-C), 66.6 (propyl 3-C), 55.8 (OMe), 55.7 (OMe), 40.5 (propyl 2-C); ν_{max}/cm^{-1} (film) 3407, 2937, 1609, 1212 and 833; *m/z* (ES^+) 151 (100%, $[M\text{-Propyl}]^+$) and 275.0 (85%, $[M+Na]^+$); found 275.1261, $C_{14}H_{20}O_4$ requires *MH* 275.1254

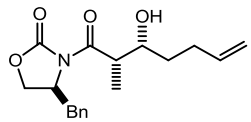
(4*S*)-4-Benzyl-3-propanoyl-1,3-oxazolidin-2-one 182[128]



n-Butyl lithium (18.75 mL, 1.6M in hexanes, 30 mmol) was added dropwise to a stirred solution of (*S*)-4-Benzyl-2-oxazolidinone (5.00 g, 28 mmol) in THF (100 mL) at −78 C. Propionyl chloride (2.94 mL, 30.0 mmol) was added dropwise after 1 h at −78 °C, the reaction was allowed to warm to room temperature over 16 h. Water (10.0 mL) was added and the reaction mixture was concentrated *in vacuo*; EtOAc (100 mL) was added; the organic layer was washed with water (3 × 50 mL) and dried $MgSO_4$, filtered and concentrated *in vacuo* to give the oxazolidinone **182** (6.29 g, 27.0 mmol, 96%) as a pale yellow solid; R_f 0.92, (50:50 EtOAc—petrol); m.p 44 °C (from EtOAc—hexanes) [Lit. 44-45]; $[\alpha]_D^{27.5}$ 59.2 (c. 1 in $CHCl_3$); [Lit. $[\alpha]_D$ 55 (*c*. 1.27 in $CHCl_3$)[128]]; δ_H (500 MHz; $CDCl_3$) 7.36-7.16 (5H, m, Ar), 4.65 (1H, dddd, *J* 10.4, 7.5, 3.3 and 3.0, 5-H), 4.22-4.11 (2H, m, 4-H), 3.28 (1H, dd, *J* 13.4 and 3.3, Bn-H_a), 2.94 (2H, q, *J* 7, Pr), 2.77 (1H, dd, *J* 13.4 and 10.4, Bn-H_b), 1.19 (3H, t, *J* 7, Pr); δ_C (75 MHz; $CDCl_3$) 6.8 (3'-C), 28.1 (2'-C), 36.5 (Bn-C), 53.9 (5-C), 65.2 (4-C), 126.3 (Ar), 127.9 (Ar), 128.3 (Ar), 134.4 (Ar),

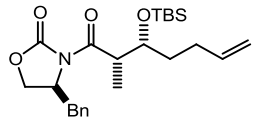
152.5 (2-C), 173.0 (1'-C); ν_{max}/cm^{-1} (solid): 3029, 2981, 2940, 1782, 1698, 1454, 1372; *m/z* (ES+) 234.1 (100%, $[M+H]^+$); found 234.1119, $C_{13}H_{16}NO_3$ requires *MH* 234.1125

(4*S*)-4-Benzyl-3-[(2'*S*,3'*R*)-3'-hydroxy-2'-methylhept-6'-enoyl]-1,3-oxazolidin-2-one 183 [111]



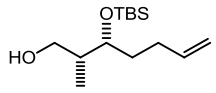
n-Dibutylboryl triflate (2.60 mL, 1M in CH_2Cl_2, 2.58 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL, 3.00 mmol) were added to a stirred solution of oxazolidinone **182** (0.50 g, 2.15 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction, after 30 min the reaction was cooled to −78 °C, following this 4-pentenal (0.90 g, 10.8 mmol) was added dropwise. The reaction was stirred at −78 °C for 3 h and then 0 °C for a further 30 min. Phosphate buffer (pH 7.2)/MeOH (10 mL, ½ v/v) and H_2O_2/MeOH (10 mL, ½ v/v) were added to the reaction at 0 °C. After 1 h the reaction was concentrated *in vacuo* and the aqueous solution was extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with sat. $NaHCO_3$ (50 mL), brine (50 mL) and concentrated *in vacuo* to give the crude product. Column chromatography, eluting with 70:30 petrol—EtOAc, gave the oxazolidinone **183** (365 mg, 1.15 mmol, 53%) as colourless needles; m.p. 81.7-83.9 °C (from EtOAc—hexanes); R_f 0.41 (90:10 hexanes—EtOAc); $[\alpha]_D^{27.5}$ 51.1 (c. 0.9, $CHCl_3$); [Lit. 82 (*c.* 0.83 in CH_2Cl_2)[111]]; δ_H (500 MHz; $CDCl_3$) 7.42-7.31 (3H, m, Ph), 7.27-7.21 (2H, m, Ph), 5.87 (1H, ddt, *J* 16.9, 10.3 and 6.7, 7'-H), 5.09 (1H, ddd, *J* 16.9, 3.4 and 1.6, 6'-H_A), 5.02 (1H, dd, *J* 10.3 and 1.6, 6'-H_B), 4.75 (1H, ddt, *J* 9.4, 7.2 and 3.3, 5-H), 4.31-4.20 (2H, m, 4-H_{AB}), 4.02 (1H, ddd, *J* 8.9, 4.1 and 2.8, 3'-H), 3.82 (1H, qd, *J* 7.0 and 2.8, 2'-H), 3.29 (1H, dd, *J* 13.4 and 3.3, Bn-H_A), 2.85 (1H, dd, *J* 13.4 and 9.4, Bn-H_B) 2.38-2.10 (m, 2H, 3'-H_{AB}), 1.78-1.64 (1H, m, 4'-H_A or 4'-H_B), 1.60-1.46 (1H, m, 4'-H_A or 4'-H_B), 1.31 (3H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 177.87 (1'-C), 153.4 (2-C), (Ar), 138.5 (6'-C), (Ar), 135.4 (Ar), 129.8 (Ar), 129.4 (Ar), 127.9 (Ar), 115.4 (7'-C), 71.3 (3'-C), 66.6 (4-C), 55.5 (5-C), 42.6 (2'-C), 38.2 (Bn), 33.4 (4'-C), 30.6 (5'-C), 10.9 (Me); ν_{max}/cm^{-1} (solid) 3497, 2940, 1771, 1675 and 897; *m/z* (ES^+) 318.2 (100%, $[M+H]^+$)

(4*S*)-4-Benzyl-3-[(2'*S*,3'*R*)-3'-[(*tert*-butyldimethylsilyl)oxy]-2'-methylhept-6'-enoyl]-1,3-oxazolidin-2-one 184



Imidazole (383 mg, 5.64 mmol), DMAP (10.0 mg, 0.08 mmol) and *tert*-butyldimethylsilyl chloride (423 mg, 2.82 mmol) were added to a stirred solution of alcohol **183** (300 mg, 0.94 mmol) in CH_2Cl_2 (30 mL) and stirred at room temperature for 4 days. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (50 mL). The combined organic layers were washed with water (2 × 20 mL), 0.1M HCl (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL); dried ($MgSO_4$) and concentrated *in vacuo* to give silyl ether **184** (352 mg, 0.81 mmol, 87 %) as a colourless waxy solid; m.p. 41.2-43.9 °C (from EtOAc—hexanes); R_f 0.73 (90:10, petrol—EtOAc); $[\alpha]_D^{26.5}$: 52 (c. 0.7, $CHCl_3$); δ_H NMR (500 MHz; $CDCl_3$) 7.36-7.18 (5H, m, Ar), 5.80 (1H, ddt, *J* 17.1, 10.3 and 6.4, 6'-H), 5.00 (1H, ddd, *J* 17.1, 3.5 and 1.7, 7'-H_A), 4.93 (1H, dd, *J* 10.3 and 1.7, 7'-H_B), 4.59 (1H, ddt, *J* 15.8, 9.5 and 3.3, 5-H), 4.19-4.10 (m, 2H, 4-H), 4.01 (1H, q, *J* 5.3, 3'-H), 3.86 (1H, ddd, *J* 13.7, 6.8 and 5.1, 2'-H), 3.28 (1H, dd, *J* 13.3 and 3.1, Bn-H_A), 2.75 (1H, dd, *J* 13.3 and 9.7, Bn-H_B), 2.17-1.99 (2H, m, 5'-H), 1.69-1.57 (2H, m, 4'-H), 1.20 (3H, d, *J* 6.8, Me), 0.87 (9H, s, (SiC(CH_3)$_3$)), 0.01 (6H, s, 2 × SiCH_3); δ_C (75 MHz; $CDCl_3$) 175.6 (1'-C), 153.5 (2-C), 138.9 (6'-C), 135.8 (Ar), 129.9 (Ar), 129.4 (Ar), 127.8 (Ar), 114.8 (7'-C), 72.9 (3'-C) , 66.4 (4-C), 56.2 (5-C), 43.2 (2'-C), 38.0 (Bn), 35.0 (4'-C), 29.6 (5'-C), 26.1 (SiC(CH_3)$_3$), 18.5 (SiC(CH_3)$_3$), 12.2 (Me), -2.5 (SiCH_3); ν_{max}/cm^{-1} (solid): 2929, 1783, 1704, 1382, 1208, 1108 and 837; *m/z* (ES^+) 432.3 (100%, $[M+H]^+$); found 454.2403, $C_{14}H_{30}O_2Si$ requires *MNa* 454.2384

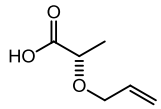
(2*R*,3*R*)-2-Methylhept-6-ene-1,3-diol 185



$LiBH_4$ (2.2 g, 100 mmol) was added portion-wise to a stirred solution of **184** (18 g, 42.5 mmol) in THF (100 mL) and ether (400 mL) at 0 °C over the period of 1 h. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was poured over crushed ice (*ca.* 50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were concentrated *in vacuo* to give the crude product. Column chromatography, eluting with CH_2Cl_2 gave the alcohol **185** (7.1g, 27.5 mmol, 65 %); R_f 0.46 (CH_2Cl_2); $[\alpha]_D^{26.5}$ 2.8 (c. 1.4, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 5.72 (1H, ddt, *J* 6.6, 10.2 and 16.9, 6-H), 4.93

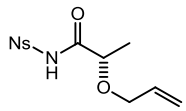
(1H, dd, *J* 3.5 and 16.9, 7-H_A), 4.87 (1H, dd, *J* 3.5 and 10.2, 7-H_B), 3.70-3.65 (1H, m, 1-H_a), 3.64-3.57 (1H, m, 1-H_b), 3.46-3.39 (1H, m, 3-H), 2.50 (1H, br s, OH), 2.13-2.03 (1H, m, 2-H), 1.95-1.83 (2H, m, 5-H), 1.55-1.41 (2H, m, 4-H), 0.80 (9H, s, (SiC(CH_3)$_3$), 0.72 (3H, d, *J* 7.1, 2-CH_3), -0.01 (6H, s, 2 × SiCH_3); δ_C (75 MHz; $CDCl_3$) 138.5 (6-C), 114.7 (7-C), 75.4 (3-C), 65.9 (1-C), 39.5 (2-C), 31.5 (4 or 5-C), 30.4 (4 or 5-C), 25.8 (TBS), 18.0 (TBS), 12.1 (CH_3), -4.4 (TBS); ν_{max}/cm^{-1} (film): 2929, 1251, 1031, 833 and 772; *m/z* (ES+) 259.2 (100%, MH+); found 281.1914, $C_{14}H_{30}O_2Si$ requires *MNa* 281.1900

(2*S*)-2-(Prop-2-enyloxy)propanoic acid 188



Allyl bromide (7.60 g, 63.0 mmol) and (*S*)-ethyl lactate **186** (5.00 g, 42.0 mmol) were added to a suspension of silver oxide(I) (19.6 g, 85.0 mmol) in acetone (100 mL) at room temperature. The reaction was stirred at room temperature in the dark for 2 days. The reaction was filtered through Celite and concentrated *in vacuo* to give the crude ethyl lactate. The crude product was dissolved in THF (50 mL) and 1M LiOH (100 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 3 h and then acidified with 1M HCl. The solution was then concentrated *in vacuo* to half volume and extracted with EtOAc (5 × 50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give **188** (5.10 g, 36.1 mmol, 84%) as a pale yellow oil; R_f: 0.53 (50:50 hexanes—EtOAc); $[\alpha]_D^{27.5}$ −65 (*c*. 1.10, $CHCl_3$); [Lit. −69 (*c.* 1.05, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 5.92 (1H, ddd, *J* 17.2, 10.2 and 5.8, propenyl 2-H), 5.32 (1H, dd, *J* 17.2 and 1.5, propenyl 3-H_A), 5.24 (1H, dd, *J* 1.5 and 10.2, propenyl 3-H_B), 4.16 (1H, dd, *J* 12.5 and 5.6, propenyl 1-H_A), 4.08 (1H, q, *J* 6.9, H-2), 4.03 (1H, dd, *J* 12.5 and 5.6, propenyl 1-H_B), 1.48 (3H, d, *J* 6.9, 3-H); δ_C (75 MHz; $CDCl_3$) 176.2 (1-C), 132.6 (propenyl 2-C), 117.3 (propenyl 3-C), 72.5 (2-C), 70.2 (propenyl 1-C), 17.2 (3-C); ν_{max}/cm^{-1} (film): 3083, 298, 2940, 1725, 1213, 1117; *m/z* (ES^+) 153.1 (100%, $[M+Na]^+$); found 153.0526, $C_6H_{10}O_3$ requires *MNa* 153.0522

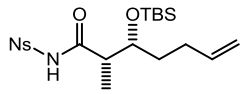
(2*S*)-*N*-[(2-Nitrobenzene)sulfonyl]-2-(prop-2-enyloxy)propanamide 189



Acid **188** (2.0 g, 15.4 mmol) and 2-nitrobenzene sulfonamide (3.42 g, 16.9 mmol) in CH_2Cl_2 (50 mL) were added dropwise to a stirred solution of *N,N'*-dicyclohexylcarbodiimide (3.48 g, 16.9 mmol) and DMAP (187 mg, 1.54 mmol) at 0 °C.

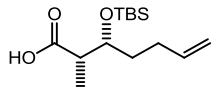
After 5 min the reaction was allowed to warm to room temperature. After 24 h the reaction was poured into water (50 mL), separated and the organic layer was washed with 1M HCl (20 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a viscous oil. Column chromatography, eluting with 50:50 petrol—EtOAc and 1% AcOH gave the sulfonamide **189** (3.43 g, 10.9 mmol, 71%) as a yellow viscous oil that solidified on standing; R_f 0.35 (petrol—EtOAc, 50:50); $[\alpha]_D^{18.9}$ 11.1 (c. 8.3, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 9.32 (1H, s, NH), 8.38-8.34 (1H, m, nosyl 3-H), 7.80-7.72 (3H, m, nosyl 4, 5 and 6-H), 5.85 (1H, ddt, *J* 5.6, 10.3 and 17.1, propenyl 2-H), 5.26 (1H, dd, *J* 1.5 and 17.1, propenyl 3-H_A), 5.20 (1H, dd, *J* 1.5 and 10.3, propenyl 3-H_B), 4.01 (2H, dt, *J* 1.3 and 5.9, propenyl 1-H_2), 3.88 (1H, q, *J* 6.8, 2-H), 1.30 (3H, d, *J* 6.8, CH_3); δ_C (75 MHz; $CDCl_3$) 171.4 (C=O), 148.2 (nosyl 2-C), 135.1 (nosyl 1-C), 133.6 (propenyl 2-C), 132.9, 132.6, 131.5, 124.9, 118.8 (propenyl 3-C), 75.5 (propenyl 1-C), 71.2 (2-C), 17.6 (Me); ν_{max}/cm^{-1} (film): 2932, 1729, 1540, 1404, 1358, 1100, 852 and 739; *m/z* (ES) 337.1 (70%, $[M+Na]^+$) and 315.1 (30%, $[M+H]^+$); found 315.0639, $C_{12}H_{15}N_2O_6S_1$ requires *MH* 315.0645

(2*S*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methyl-*N*-[(2-nitrobenzene)sulfonyl]hept-6-enamide 133



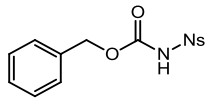
Acid **190** (800 mg, 2.94 mmol) and 2-nitrobenzene sulfonamide (1.18 g, 5.88 mmol) in CH_2Cl_2 (15 mL) were added to a stirred solution of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) (0.55 g, 3.52 mmol) and DMAP (24 mg, 0.2 mmol) at 0 °C. After 16 h, the reaction was concentrated *in vacuo*, column chromatography eluting with petrol—EtOAc (50:50) gave acyl sulfonamide **133** (800 mg, 60%) as a viscous yellow oil that solidified on standing; R_f 0.23 (50:50, petrol—EtOAc); $[\alpha]_D^{26.5}$ −16.1 (c. 0.9, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 10.24 (1H, br s, NH), 8.50-8.45 (1H, m, nosyl 6-H), 7.83-7.78 (3H, m, nosyl 3,4 and 5-H), 5.66 (1H, ddt, *J* 16.9, 10.6 and 6.5, 6-H), 4.90 (1H, dd , *J* 10.6 and 1.7, 7-H_A), 4.89 (1H, dd , *J* 16.9 and 1.7, 7-H_B), 3.80 (1H, dt, *J* 9.6 and 3.4, 3-H), 2.75 (1H, qd, *J* 7.1 and 3.6, 2-H), 2.33-2.19 (1H, m, 5-H_A), 2.03-1.87 (1H, m, 5-H_B), 1.50-1.20 (2H, m, 4-H_2), 1.08-1.03 (12H, m, (SiC(CH_3)$_3$) and Me), -0.1 (6H, s, (Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 170.9 (C=O), 147.2 (nosyl 2-C), 146.8 (nosyl 1-C)), 136.6, 133.6 (6-C), 132.9, 131.3, 123.5, 113.9 (7-C); 73.2 (3-C), 45.9 (2-C), 29.6 (3 or 4-C), 28.9 (3 or 4-C), 24.9 ((SiC(*C*H_3)$_3$)), 16.9 (Si*C*(CH_3)$_3$), 10.9 (Me), 0.02 (Si(*C*H_3)$_2$); ν_{max}/cm^{-1} (film) 2987, 1724, 1546, 1422, 1275, 1261; *m/z* (ES^+) 457.2 (20%, $[M+H]^+$) and 474.2 (100%, $[M+NH_4]^+$); found 235.0944, $C_{20}H_{32}N_2O_6SSi$ requires *MH* 457.1823

(2*S*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-enoic acid 190



Hydrogen peroxide 35% v/v (0.20 mL, 1.84 mmol) and LiOH (23.0 mg, 0.92 mmol) were added to a stirred solution of **184** (100 mg, 0.23 mmol) in THF/H_2O (10 mL, 4:1) at room temperature. Saturated sodium sulphite (5 mL) was added to the reaction mixture at 0 °C after 5 h and stirred for a further 30 min. The pH was adjusted to 14 using 1M NaOH, and the reaction was washed with ether (2 × 10 mL). The aqueous layer was then acidified to pH 3 with 1M H_2SO_4 and extracted with EtOAc (4 × 20 mL); the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Column chromatography, eluting with 90:10 petrol—EtOAc, gave the acid **190** (57 mg, 0.21 mmol, 91%) as a colourless oil; R_f 0.38, (50:50 EtOAc—petrol); $[\alpha]_D^{26.5}$ −18.0 (c. 0.6, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 5.69 (1H, ddt, *J* 16.9, 10.3 and 6.5, 6-H), 4.93 (1H, ddd, *J* 16.9, 1.6 and 1.3, 7-H_A), 4.88 (1H, dd, *J* 10.3 and 1.3, 7-H_B), 3.90 (1H, dd, *J* 6.0 and 5.3, 3-H), 2.51 (1H, ddd, *J* 14.1, 7.0 and 4.4, 2-H), 2.10-1.8 (2H, m, 5-H_{AB}), 1.55-1.45 (2H, m, 4-H_{AB}), 1.04 (3H, d, *J* 7.0, Me), 0.79 (9H, s, (SiC(CH_3)$_3$)), -0.02 (6H, s, (Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 178.2 (1-C), 138.3 (6-C), 115.4 (7-C), 73.6 (3-C), 44.8 (2-C), 33.5 (4-C), 29.9 (5-C), 26.2 (SiC(*C*H_3)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 11.7 (Me), -4.3 (Si(*C*H_3)$_2$); ν_{max}/cm^{-1} (film) 2983, 1737, 1439, 1201 and 1048; *m/z* (ES$^+$) 273.2 (100%, [M+H]$^+$) 295.2 (50%, [M+Na]$^+$); found 273.1876, $C_{14}H_{29}O_3Si$ requires *MH* 273.1886

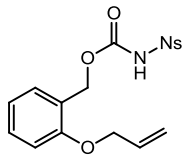
Benzyl *N*-[(2-nitrobenzene)sulfonyl]carbamate 197[129]



To a solution of oxalyl chloride (3.18 g, 25 mmol) in EtOAc (20 mL), 2-nitrobenzene sulfonamide (1.0 g, 4.9 mmol) dissolved in EtOAc (20 mL) was added dropwise and stirred at room temperature. After 1 h the reaction was concentrated to ½ volume using a standard distillation setup at atmospheric pressure. Toluene (20 mL) was added and the remaining EtOAc and oxalyl chloride were distilled out. The reaction was then heated to reflux, after 2 h the reaction was cooled to 0 °C and triethylamine (3.03 g, 30 mmol) was added, followed by benzyl alcohol (534 mg, 5 mmol). The reaction was allowed to warm to room temperature, after 2 h the reaction was concentrated *in vacuo* to give the crude product. Column chromatography, eluting with EtOAc—AcOH (97:3) gave the carbamate **197** (1.23 g, 3.6 mmol, 77%) as colourless prisms; m.p 112-115 (from EtOAc—hexanes); R_f 0.39 (99:1 EtOAc—AcOH); δ_H (500 MHz; $CDCl_3$) 8.24 (1H,

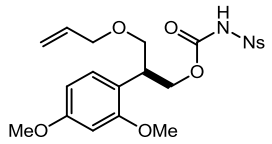
dd, *J* 1.4 and 7.9, nosyl 3-H), 7.84 (1H, br s, NsN*H*), 7.79 (1H, dd, *J* 1.3 and 7.9, nosyl 4-H), 7.72 (1H, td, *J* 1.4 and 7.7, nosyl 6-H), 7.64 (1H, td, *J* 1.3 and 7.7, nosyl 5-H) 7.31-7.26 (3H, m, Ar), 7.25-7.20 (2H, m, Ar), 5.07 (2H, s, $PhCH_2$); δ_C (75 MHz; $CDCl_3$) 149.9 (nosyl 2-C), 134.9 (nosyl 1-C), 134.0, 133.4, 132.6, 131.5, 128.9, 128.7, 128.6, 125.2, 69.1 (Ph*C*H_2), *C*=*O missing*; ν_{max}/cm^{-1} (solid) 3263, 1743, 1541, 1360, 1228, 1156, 1126, 854, 582 and 564; *m/z* (ES–) 335.1 (100%, MH–)

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-[(2-nitrobenzene)sulfonyl]carbamate 131



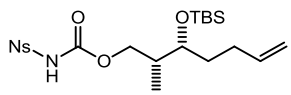
To a solution of 2-nitrobenzene sulfonamide (15.0 g, 72 mmol) in EtOAc (400 mL) at 0 °C was added a solution of oxalyl chloride (45.0 g, 360 mmol) in EtOAc (100 mL). The reaction was stirred at room temperature for 1 h and a further 24 h at reflux. The reaction was then distilled to ½ volume using a standard distillation setup, toluene (500 mL) was added and the reaction was distilled further until the vapour temperature was 105 °C at atmospheric pressure. The reaction was heated under reflux for a further 16 h and then cooled to 0 °C. A solution of alcohol **173** (6.1 g, 36 mmol) in THF (100 mL) was added and the reaction was stirred at room temperature for 16 h and then concentrated *in vacuo.* Column chromatography, eluting with 85:14:1 CH_2Cl_2—EtOH—NH_4OH gave **131** (10.9 g, 77%) as a pale yellow foam; R_f 0.19 (85:14:1, CH_2Cl_2—EtOH—NH_4OH); δ_H (500 MHz; MeOD) 8.05-7.95 (1H, m, nosyl 3-H), 7.54-7.44 (3H, m, nosyl 4,5 and 6-H), 7.20-7.05 (2H, m, Ar), 6.81-6.73 (2H, m, Ar), 5.94 (1H, ddt, *J* 17.3, 10.6 and 5.0, propenyl 2-H), 5.27 (1H, d, *J* 17.3, propenyl 3-H_A), 5.09 (1H, d, *J* 10.6, propenyl 3-H_B), 4.92 (2H, s, $PhCH_2$), 4.42 (2H, d, *J* 5, propenyl 1-H); δ_C (75 MHz; MeOD) 158.0 (C=O), 153.7 (Ph 1-C), 149.6 (nosyl 2-C), 135.7 (nosyl 1-C), 134.6 (propenyl 2-C), 133.8 (nosyl 5-C), 133.4 (Ar), 132.8 (nosyl 4-C), 131.1 (Ar), 130.9 (nosyl 3-C), 125.6 (Ph 2-C), 125.0 (nosyl 6-C), 121.6 (Ar), 117.4 (propenyl 3-C) , 113.0 (Ph 3-C), 69.8 (Ph*C*H_2), 64.8 (propenyl 1-C); ν_{max}/cm^{-1} (solid) 3238, 3024, 2898, 1746, 1496, 1365, 999, 851 and 739; *m/z* (ES+) 415.1 (100%, $[M+Na]^+$); found 415.0559, $C_{17}H_{16}N_2NaO_7S_1$ requires *MNa* 415.057

2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl-[(2-nitrobenzene)sulfonyl]carbamate 132



To a solution of 2-nitrobenzene sulfonamide (12.1 g, 60 mmol) in EtOAc (500 mL) at 0 °C was added oxalyl chloride (45.0 g, 360 mmol). The reaction was stirred for 1 h at room temperature and a further 24 h at reflux. The reaction was then distilled to ½ volume using a standard distillation setup, toluene (500 mL) was added and the reaction was distilled further until the vapour temperature was 105 °C at atmospheric pressure. The reaction was further reflux for 16 h and then cooled room temperature. A solution of alcohol **180** (4.3 g, 17 mmol) in THF (50 mL) was added and the reaction was stirred at room temperature for 1 h and then concentrated *in vacuo.* Column chromatography, eluting with 85:14:1 CH_2Cl_2—EtOH—NH_4OH gave **132** (7.8 g, 16.2 mmol, 95%) as a yellow foam; R_f 0.2 (85:14:1 CH_2Cl_2—EtOH—NH_4OH); $[\alpha]_D^{23}$ 12.0 (*c*. 1.5 in EtOH); δ_H (500 MHz; $CDCl_3$) 8.15 (1H, d, *J* 7.8, nosyl 3-H), 7.74 (1H, d, *J* 7.8, nosyl 4-H), 7.68 (1H, t, *J* 6.6, nosyl 5-H), 7.62 (1H, t, *J* 6.6, nosyl 6-H), 6.93 (1H, d, *J* 8.2, DMB 6-H), 6.31-6.26 (2H, m, DMB 3 and 5-H), 5.74 (1H, ddt, *J* 17.1, 10.4 and 5.5, propenyl 2-H), 5.11 (1H, d, *J* 17.1, propenyl 3-H_A), 5.03 (1H, d, *J* 10.4, propenyl 3-H_B), 4.39 (1H, dd, *J* 5.1 and 10.4, propyl 1-H_A), 4.28 (1H, dd, *J* 6.6 and 10.6, propyl 1-H_B), 3.86-3.78 (m, 2H, propenyl 1-H), 3.69 (3H, s, OMe), 3.66 (3H, s, OMe), 3.52-3.46 (m, 3H, 2-H and 3-H_{AB}); δ_C (75 MHz; $CDCl_3$) 160.2 (Ar 2- or 4-C), 158.6 (Ar 2- or 4-C), 150.4 (C=O), 148.5 (nosyl 2-C), 135.2 (nosyl 1-C), 135.1 (propenyl 2-C), 133.8 (), 132.9 (nosyl 4-C), 131.9 (nosyl 5-C), 129.3 (Ar 6-C), 125.5 (nosyl 6-C), 119.3 (DMB 1-C) , 117.4 (propenyl 3-C), 104.5 (DMB 5-C), 98.9 (DMB 3-C), 72.4 (1-C), 70.4 (3-C), 68.1 (propenyl 1-C), 55.7 (OMe), 55.7 (OMe), 38.7 (2-C); ν_{max}/cm^{-1} (solid) 3369, 3096, 1748, 1525, 1366, 1345, 1164 and 743; *m/z* (ES+) 503.1 (100%, $[M+Na]^+$); found 503.1088, $C_{21}H_{24}N_2O_9S$ requires *MNa* 503.1095

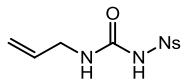
(2*R*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl *N*-[(2-nitrobenzene)sulfonyl]carbamate 198



To a solution of 2-nitrobenzene sulfonamide (1.59 g, 7.9 mmol) in EtOAc (100 mL) at 0 °C was added oxalyl chloride (4.95 g, 39 mmol). The reaction was stirred for 1 h at room temperature and a further 24 h at reflux. The reaction was then distilled to ½

volume using a standard distillation setup, toluene (100 mL) was added and the reaction was distilled further until the vapour temperature was 105 °C at atmospheric pressure. The reaction was further reflux for 16 h and then cooled room temperature. A solution of alcohol **185** (1.0 g, 3.9 mmol) and triethylamine (8.0 g, 80 mmol) in CH_2Cl_2 (50 mL) was added at 0 °C and the reaction was then stirred at room temperature for 1 h and then concentrated *in vacuo.* Column chromatography, eluting with 85:14:1 CH_2Cl_2—EtOH—NH_4OH gave **198** as a pale yellow foam (1.86 g, 25%); R_f 0.11 (85:14:1, CH_2Cl_2—EtOH—NH_4OH); $[\alpha]_D^{23}$ 15.7 (c. 2.3 in EtOH); δ_H (500 MHz; $CDCl_3$) 8.37-8.32 (1H, m, nosyl 3-H), 7.85-7.72 (3H, m, nosyl 4, 5 and 6-H), 5.74 (1H, ddt, *J* 16.9, 10.2 and 6.6, 6-H), 4.97 (1H, d, *J* 16.9, 7-H_A), 4.93 (1H, d, *J* 10.2, 7-H_A), 4.07 (1H, dd, *J* 10.4 and 6.9, 1-H_A), 3.95 (dd, *J* 10.4 and 7.1, 1H, 1-H_B), 3.67-3.62 (1H, m, 3-H), 2.02-1.90 (2H, m, 5-H_{AB}), 1.93-1.82 (1H, m, 2-H), 1.55-1.40 (m, 2H, 4-H_{AB}), 0.81 (12H, s, CH_3 and (SiC(CH_3)$_3$), 0.00 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3); δ_C (75 MHz, $CDCl_3$) 138.5 (6-C), 135.2 (nosyl 2-C), 133.8 (nosyl 1-C), 133.7 (nosyl 3-C), 132.9 (nosyl 4-C), 131.6 (nosyl 6-C), 125.5 (nosyl5-C), 115.2 (7-C), 71.7 (3-C), 70.2 (1-C), 37.0 (2-C), 33.5 (4-C), 30.3 (5-C), 26.2 (SiC(*C*H_3)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 10.7 (Me), -3.8 (Si*C*H$_3$), -4.4 (Si*C*H$_3$), *C=O is missing* ; ν_{max}/cm^{-1} (solid) 3260, 2929, 2857, 1747, 1546, 1462, 1229, 1168 and 836; *m/z* (ES+) 509.2 (80%, $[M+H]^+$); found 509.1752, $C_{21}H_{34}N_2O_7SSi$ requires *MH* 509.1748

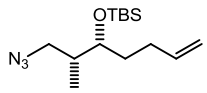
1-[(2-Nitrobenzene)sulfonyl]-3-(prop-2-en-1-yl)urea 199



To a solution of 2-nitrobenzene sulfonamide (200 mg, 0.99 mmol) in EtOAc (7.5 mL) at 0 °C was added oxalyl chloride (625 mg, 4.95 mmol). The reaction was stirred for 1 h at room temperature and a further 24 h at reflux. The reaction was then distilled to ½ volume using a standard distillation setup, toluene (20 mL) was added and the reaction was distilled further until the vapour temperature was 105 °C at atmospheric pressure. The reaction was further reflux for 16 h and then cooled room temperature. A solution of allyl amine **196** (56 mg, 0.99 mmol) and diisopropylethylamine (645 mg, 5 mmol) was added at 0 °C and the reaction was then stirred at room temperature for 1 h and then concentrated *in vacuo.* Column chromatography, eluting with 85:14:1 CH_2Cl_2—EtOH—NH_4OH gave **199** as a pale yellow foam (143 mg, 51%); R_f 0.11 (50:8:1, CH_2Cl_2—EtOH—NH_4OH); δ_H (300 MHz; $CDCl_3$/MeOD) 8.14-8.04 (1H, m, nosyl 3-H), 7.58-7.39 (3H, m, nosyl 4, 5 and 6-H), 5.62 (1H, ddt, *J* 17.2, 10.5 and 5.4, propenyl 2-H), 5.07-4.96 (1H, m, propenyl 3-H_A), 4.95-4.87 (1H, m, propenyl 3-H_B), 3.67 (0.6H, *J*

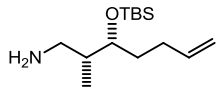
14.4 and 5.4, propenyl 1-H^{rotB}), 3.56 (1.4H, *J* 14.4 and 5.4, propenyl 1-H ^{rotA}); δ_C (75 MHz; $CDCl_3$) 164.9 (C=O^{rotA}), 163.5 (C=O^{rotB}), 148.3 (nosyl 2-C), 135.7 (nosyl 1-C), 134.3 (propenyl 2-C^{rotA}), 134.0 (propenyl 2-C^{rotB}), 133.2 (nosyl 1-C), 132.7 (nosyl 5-C), 132.5 (nosyl 4-C), 132.4 (nosyl 4-C), 131.6 (nosyl 6-C), 131.2 (nosyl 6-C), 124.5 (nosyl 3-C), 123.6 (nosyl 3-C), 116.7 (propenyl 3-C^{rotA}), 115.9 (propenyl 3-C^{rotB}), 42.8 (propenyl 1-C^{rotA}), 42.2 (propenyl 1-C^{rotB}); ν_{max}/cm^{-1} (solid) 3360, 2342, 1671, 1537, 1364, 1166; *m/z* (ES+) 308.0 (100%, $[M+Na]^+$); found 308.0322, $C_{10}H_{11}N_3O_5S$ requires *MNa* 308.0312

{[(2*R*,3*R*)-1-Azido-2-methylhept-6-en-3-yl]oxy}(*tert*-butyl)dimethylsilane 200



DPPA (2.09 g, 7.6 mmol) was added dropwise to a stirred solution of alcohol **185** (1.00 g, 3.8 mmol), Triphenylphosphine (1.99 g, 7.6 mmol) and diethylazodicarboxylate (1.32 g, 7.6 mmol) in THF (50 mL) at −18 ˚C. After 30 min the reaction was concentrated *in vacuo.* Column chromatography, eluting with petrol gave the azide **200** (1.05 g, 97%) as a colourless oil. R_f 0.66 (Petrol); $[\alpha]_D^{23}$ 38.5 (c. 0.9, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 5.84 (1H, ddt, *J* 16.9, 10.2 and 6.6, 6-H), 5.06 (1H, dd , *J* 16.9 and 1.4, 7-H_A), 5.02 (1H, dd, *J* 10.2 and 1.4, 7-H_B), 3.74 (1H, td, *J* 6.6 and 2.9, 3-H), 3.41 (1H, dd, *J* 11.9 and 6.6, 1-H_A), 3.15 (1H, dd, *J* 11.9 and 7.6, 1-H_B), 2.18-1.96 (2H, m, 5-H_{AB}), 1.86 (1H, qd, *J* 6.9 and 2.9, 2-H), 1.67-1.46 (2H, m, 4-H_{AB}), 0.97-0.87 (12H, m, (SiC(C*H*$_3$)$_3$) and Me), 0.1 (3H, s, $SiCH_3$), 0.09 (3H, s, Si*C*H_3); δ_C (75 MHz; $CDCl_3$) 138.7 (6-C), 115.2 (7-C), 72.6 (3-C), 54.9 (1-C); 38.1 (2-C), 33.4 (4-C), 30.5 (5-C), 26.3 ((SiC(*C*H_3)$_3$)), 18.5 ((Si*C*(CH$_3$)$_3$)), 12.3 (Me), -3.8 (Si*C*H_3), -4.2 (Si*C*H_3); ν_{max}/cm^{-1} (film) 2956, 2931, 2100, 1472, 1463, 1275; *m/z* (ES+) 306.2 (100%, $[M+Na]^+$) and 256.2 (100%, $[MH-N_2]^+$; found 306.1964, $C_{14}H_{29}N_3OSi$ requires *MNa* 306.1972

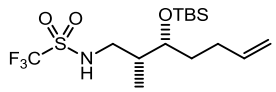
{[(2*R*,3*R*)-1-Amino-2-methylhept-6-en-3-yl]oxy}(*tert*-butyl)dimethylsilane 201



Triphenylphosphine (3.66 g, 13.9 mmol) was added in one portion to a solution of azide **200** (3.6 g, 12.7 mmol) in THF (130 mL) at room temperature. Water (0.5 mL) was added, after 24 h the reaction was concentrated *in vacuo* and column chromatography eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the amine **201** (3.1 g, 95%) as a colourless oil; R_f 0.2 (EtOAc); $[\alpha]_D^{23}$ 5.1 (*c*. 0.3 $CHCl_3$); δ_H (500 MHz; MeOD) 5.74 (1H, ddt, *J* 16.9, 10.2 and 6.6, 6-H), 4.93 (1H, ddd , *J* 16.9, 3.7 and 1.7 , 7-H_A), 4.86 (1H, ddd , *J* 10.2, 3.0 and 1.7, 7-H_B), 3.63 (1H, ddd , *J* 6.7, 5.8 and 3.2, 3-H), 2.68 (1H, dd, *J*

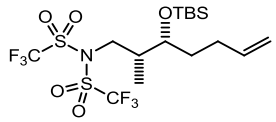
12.6 and 5.7, 1-H_A), 2.37 (1H, dd, *J* 12.6 and 8, 1-H_B), 2.10-1.87 (2H, m, 5-H_{AB}), 1.66-1.54 (1H, m, 2-H), 1.54-1.35 (2H, m, 4-H_{AB}), 0.83 (9H, s, (SiC(CH_3)$_3$), 0.81 (3H, d, *J* 7, Me), 0.01 (6H, s, 2 × SiCH_3); δ_C (75 MHz; $CDCl_3$) 140.0 (6-C), 115.3 (7-C), 75.5 (3-C), 45.8 (1-C), 41.8 (4-C), 34.5 (5-C), 31.6 (2-C), 26.7 (SiC(CH_3)$_3$), 19.3 ((SiC(CH_3)$_3$)), 12.9 (Me), -3.7 (SiCH_3), -3.9 (SiCH_3); ν_{max}/cm^{-1} (film) 2956, 2931, 1672, 1463, 1261, 837; *m/z* (ES+) 258.2 (100%, $[M+H]^+$); found 258.2253, $C_{14}H_{32}NOSi$ requires *MH* 258.2248

_N_-[(2_R_,3_R_)-3-[(_Tert_-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl]-1,1,1-trifluoromethanesulfonamide 202



Trifluoromethanesulfonic anhydride (7.3 g, 26 mmol) was made up to 10 mL with CH_2Cl_2, this solution was added using a syringe pump at 0.5 mL/min to amine **201** (3.33 g, 13 mmol) and Et_3N (5.2 g, 52 mmol) in CH_2Cl_2 (52 mL). The reaction was concentrated *in vacuo* and column chromatography, eluting with 90:10 petrol—EtOAc gave the triflamide **202** (3.9 g, 77%) as a colourless oil; R_f 0.4 (70:30, petrol—EtOAc); $[\alpha]_D^{23}$ 16.1 (*c*. 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 6.39 (1H, br s, NH), 5.76 (1H, ddt, *J* 16.9, 10.2 and 6.5, 6-H), 5.01 (1H, dd , *J* 16.9 and 1.6, 7-H_A), 4.96 (1H, dd , *J* 10.2 and 1.6, 7-H_B), 3.68 (1H, ddd, *J* 7.8, 4.3 and 2.9, 3-H), 3.29 (1H, d, *J* 12, 1-H_A), 3.24 (1H, d, *J* 12, 1-H_B), 2.26-1.88 (3H, m, 5-H_{AB} and 2-H), 1.57-1.42 (2H, m, 4-H_{AB}), 0.89-0.84 (12H, m, (SiC(CH_3)$_3$) and Me), 0.08 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); δ_C (75 MHz; $CDCl_3$) 138.2 (6-C), 115.6 (7-C), 76.8 (3-C), 47.4 (1-C), 38.0 (5-C), 30.8 (2-C or 4-C), 30.7 (2-C or 4-C), 26.2 (SiC(CH_3)$_3$), 18.3 (SiC(CH_3)$_3$), 14.5 (Me), -3.8 (SiCH_3), -4.2 (SiCH_3); ν_{max}/cm^{-1} (film) 3311, 3005, 2957, 2708, 2306, 1835, 1641, 1473, 1425, 1370; *m/z* (ES^+) 412.2 (100%, $[M+Na]^+$); found 412.1580, $C_{15}H_{30}F_3NO_3SSi$ *MNa* requires 412.1560;

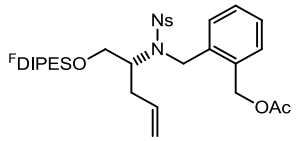
_N_-[(2_R_,3_R_)-3-[(_Tert_-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl]-1,1,1-trifluoro-N-(trifluoromethane)sulfonylmethanesulfonamide 203



Also obtained was the ditriflamide **203** (680 mg, 10%) R_f 0.70 (90:10, petrol—EtOAc); $[\alpha]_D^{23}$ 15.7 (*c*. 2.3 in EtOH); δ_H (500 MHz; $CDCl_3$) 5.71 (1H, ddt, *J* 16.9, 10.2 and 6.6, 6-H), 4.96 (1H, dd , *J* 16.9 and 1.7, 7-H_A), 4.92 (1H, dd, *J* 10.2 and 1.3, 7-H_B), 4.00 (1H,

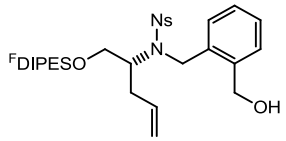
dd, *J* 14.5 and 3.5, 1-H), 3.79 (1H, dd, *J* 14.5 and 10.9, 1-H), 3.59 (1H, td, *J* 6.7 and 2.7, 3-H), 2.09-1.84 (3H, m, 5-H_{AB} and 2-H), 1.59-1.36 (2H, m, 4-H_{AB}), 0.91 (3H, d, *J* 6.9, Me), 0.82 (9H, s, (SiC(CH_3)$_3$), 0.00 (3H, s, SiCH_3), -0.02 (3H, s, SiCH_3); δ_C (75 MHz; $CDCl_3$) 137.6 (6-C), 118.9 (q *J* 325, CF_3) , 115.2 (7-C), 72.9 (3-C), 57.9 (1-C), 36.6 (5-C), 32.8 (2-C), 29.9 (4-C), 25.7 (SiC(*C*H_3)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 10.4 (Me), -4.1 (Si*C*H_3), -4.8 (Si*C*H_3); ν_{max}/cm^{-1} (film) 3082, 2955, 2859, 2329, 1832, 1643, 1453, 1431; *m/z* (ES$^+$) 522.1 (100%, [M+H]$^+$); found 522.1233, $C_{16}H_{29}F_6NO_5S_2Si$ *MH* requires 522.1233;

[2-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]methyl acetate 205'



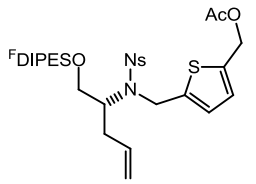
Following general procedure **M2**, diethyl azodicarboxylate (288 mg, 1.65 mmol), sulfonamide **112** (350 mg, 0.41 mmol), hydroxyacetate **126** (297 mg, 1.65 mmol) and triphenylphosphine (435 mg, 1.65 mmol) were stirred for 3 h at room temperature. The reaction was concentrated *in vacuo* and purified by F-SPE. The acetate **205'** (410 mg, 0.4 mmol, 99 %, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) was obtained as a colourless viscous oil; R_f 0.61 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.72 (1H, d, *J* 7.8, nosyl 3-H), 7.63-7.77 (2H, m, Ar), 7.48-7.41 (2H, m, Ar), 7.29-7.25 (1H, m, Ar), 7.20-7.11 (2H, m, Ar), 5.57 (1H, ddt, *J* 7.1, 10.1 and 17.1, 4-H), 5.19 (2H, d, *J* 2.4, PhCH_2OAc), 5.00 (1H, dd, *J* 1.4 and 17.1, 5-H_A), 4.90 (1H, d, *J* 10.1, 5-H_B), 4.81 (1H, d, *J* 16.8, N(Ns)CH_APh), 4.64 (1H, d, 16.8, N(Ns)CH_APh), 4.10-4.04 (1H, m, 2-H), 3.74 (1H, dd, *J* 5.6 and 10.5, 3-H_A), 3.50 (1H, dd, *J* 5.6 and 10.5, 3-H_B), 2.43-2.38 (2H, m, 1-H_2), 2.10 (3H, s, Ac), 2.08-1.97 (2H, m, $C_8F_{17}CH_2CH_2$), 0.96 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.78-0.73 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 171.8 (C=O), 148.5 (nosyl 2-C), 136.8 (nosyl 1-C), 134.6 (4-C), 134.3, 133.6, 133.5, 131.9, 131.7, 130.4, 129.3, 128.9, 127.9, 124.4, 118.4 (5-C), 65.0 (1-C), 64.4 (Ph*C*H_2OAc), 60.4 (2-C), 45.5 N(Ns)*C*H_2Ph), 34.6 (3-C), 21.3 (Ac), 17.8 (SiCH(*C*H_3)$_2$), 12.5 (Si*C*H(CH_3)$_2$), 0.04 ($C_8F_{17}CH_2CH_2$), *$C_8F_{17}CH_2CH_2$ missing*; ν_{max}/cm^{-1} (film) 2948, 2869, 1741, 1546, 1372; *m/z* (ES$^+$) 1031.2 (100%, [M+Na]$^+$); found 1026.2435, $C_{37}H_{45}F_{17}N_3O_7SSi$ *MNa* requires 1026.2471

***N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]-*N*-{[2-(hydroxymethyl)phenyl]methyl}-2-nitrobenzene-1-sulfonamide 205**



Following the general procedure **D**, acetate ester **205'** (100 mg, 0.1 mmol) was dissolved in NH_3 sat. MeOH (4 mL) and stirred for 16 h, concentrated *in vacuo* to give the alcohol **205** (96 mg, 0.099 mmol, 99%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless viscous oil. R_f 0.4 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.52 (2H, m, nosyl 3 and 6-H), 7.49 (2H, m, nosyl 4 and 5-H), 7.36 (1H, d, *J* 7.5, Ph 3-H), 7.30 (1H, d, *J* 7.5, Ph 4-H), 7.18 (1H, t, *J* 7.3, Ph 6-H), 7.08 (1H, t, *J* 7.3, Ph 5-H), 5.61 (1H, ddt, *J* 7.0, 10.0 and 17.0, 4-H), 5.02 (1H, d, *J* 17.0, 5-H_A), 4.91 (1H, d, *J* 10.0, 5-H_B), 4.85 (1H, d, *J* 16.3, N(Ns)CH_APh), 4.78 (1H, d, *J* 12.6, PhCH_AOH), 4.74 (1H, d, *J* 12.6, PhCH_BOH), 4.70 (1H, d, *J* 16.3, N(Ns)CH_BPh), 4.14-4.05 (1H, m, 2-H), 3.72 (1H, dd, *J* 5.9 and 10.5, 1-H_A), 3.52 (1H, dd, *J* 5.9 and 10.5, 1-H_B), 2.50-2.33 (2H, m, 3-H), 2.13-1.96 (2H, m, $C_8F_{17}CH_2CH_2$), 0.96 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.80-0.72 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 148.1 (nosyl 2-C), 136.4 (nosyl 1-C), 134.1 (4-C), 134.0, 133.8, 133.6, 132.1, 131.7, 130.2, 129.5, 128.9, 127.8, 124.6, 118.7 (5-C), 65.2 (1-C), 63.1 (PhCH_2OH), 60.4 (2-C), 44.3 (N(Ns)CH_2Ph), 35.1 (3-C), 17.8 (2 × SiCH(CH_3)$_2$) , 12.4 (2 × SiCH(CH_3)$_2$), 0.04 ($C_8F_{17}CH_2CH_2$), *$C_8F_{17}CH_2CH_2$ missing*; ν_{max}/cm^{-1} (film) 3079, 2949, 2869, 2733, 1643, 1591, 1547; *m/z* (ES$^+$) 989.2 (100%, [M+Na]$^+$); found 989.1951, $C_{35}H_{39}F_{17}N_2O_6SSi$ *MNa* requires 989.1916;

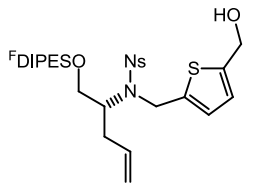
[5-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)thiophen-2-yl]methyl acetate 204'



Following general procedure **M2**, diethyl azodicarboxylate (4.22 g, 24 mmol), sulfonamide **112** (5.08 g, 6.5 mmol), hydroxyacetate **130** (4.45 g, 24 mmol) and triphenylphosphine (6.2 g, 24 mmol) were stirred for 2 h at room temperature. F-SPE, followed by column chromatography, eluting with 70:30 $CHCl_3$—CH_2Cl_2 gave **204'** (4.8 g, 73%) as a colourless oil. R_f 0.71 (50:50, petrol—EtOAc); $[\alpha]_D^{23}$ −1.8 (c. 3.4, $CHCl_3$);

δ_H (500 MHz; $CDCl_3$) 7.91-7.88 (1H, m, nosyl 3-C), 7.69-7.64 (2H, m, nosyl 6 and 4-C), 7.58-7.54 (1H, m, nosyl 5-C), 6.91 (1H, d, *J* 3.4, Thio 3 or 4-H), 6.87 (1H, d, *J* 3.4 , Thio 3 or 4-H), 5.64 (1H, ddt, *J* 17.1, 10.1 and 6.9, 4-H), 5.15 (2H, s, ThioCH_2OAc), 5.07 (1H, d, *J* 17.1, 5-H_A), 4.97 (1H, d, *J* 10.1, 5-H_B), 4.88 (1H, d, *J* 16.5, N(Ns)CH_A), 4.71 (1H, d, *J* 16.5, N(Ns)CH_A), 4.03 (1H, quin, *J* 6.6, 2-H), 3.85 (1H, dd, *J* 10.4 and 5.5, 1-H_A), 3.63 (1H, dd, *J* 10.4 and 6.0 1-H_B), 2.48 (2H, t, *J* 7.2, 3-H_{AB}), 2.19-2.05 (2H, m, $C_8F_{17}CH_2CH_2$), 2.11 (3H, s, Ac), 1.04 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.86-0.83 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 170.8 (C=O), 148.0 (nosyl 2-C), 142.8 (Thio 2- or 4-C), 139.2 (Thio 2- or 4-C), 134.6 (nosyl 1-C), 134.3 (4-C), 133.5, 131.7, 131.5, 127.8, 127.4 (5' or 6'-C), 124.5 (5' or 6'-C), 118.3 (5-C), 65.1 (1-C), 60.8 (ThioCH_2OAc), 60.3 (2-C), 43.9 (N(Ns)CH_2Thio), 34.7 (3-C), 25.9 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 21.2 (Ac), 17.8 (SiCH(CH_3)$_2$), 17.7 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2948, 2870, 2159, 1976, 1744, 1546, 1440, 1371, 1024 and 736; *m/z* (ES$^+$) 1032.2 (100%, [M+NH_4]$^+$); found 1037.1620, $C_{35}H_{39}F_{17}N_2O_7S_2Si$ requires *MNa* 1037.1589

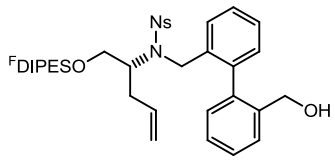
_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]-_N_-{[5-(hydroxymethyl)thiophen-2-yl]methyl}-2-nitrobenzene-1-sulfonamide 204



Following the general procedure **D**, acetate ester **204'** (4.8 g, 4.73 mmol) was dissolved in NH_3 sat. MeOH (500 mL) and gave the crude product after 16 h. The crude product was concentrated *in vacuo* to give the alcohol **204** (4.45 g, 4.58 mmol, 97%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil which was used without further purification; R_f 0.54 (50:50, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.91 (1H, d, *J* 7.6, nosyl 3-H), 7.69-7.65 (2H, m, nosyl 6 and 4-H), 7.58-7.55 (1H, m, nosyl 5-H), 6.92 (1H, d, *J* 3.5, Thio 3 or 4-H), 6.81 (1H, d, *J* 3.5, Thio 3 or 4-H), 5.65 (1H, ddt, *J* 17.2, 10.2 and 6.8, 4-H), 5.07 (1H, d, *J* 17.2, 5-H_A), 4.98 (1H, d, *J* 10.2, 5-H_B), 4.88 (1H, d, *J* 16.5, N(Ns)CH_AThio), 4.72 (2H, s, ThioCH_2OH), 4.72 (1H, d, *J* 16.5, N(Ns)CH_BThio), 4.08-4.02 (1H, m, 2-H), 3.86 (1H, dd, *J* 10.5 and 5.6, 1-H_A), 3.64 (1H, dd, *J* 10.5 and 4.2, 1-H_B), 2.49 (2H, t, *J* 7.1, 3-H_2), 2.17-2.05 (2H, m, $C_8F_{17}CH_2CH_2$), 1.05 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.88-0.82 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 148.0 (nosyl 2-C), 145.2 (Thio 2 or 5-C), 141.6(Thio 2 or 5-C), 134.7 (nosyl 1-C), 134.4 (4-C), 133.5 (Ns), 131.7 (Ns), 131.5 (Ns), 127.5 (Thio 3 or 4-C),

125.3 (nosyl 3-C), 124.5 (Thio 3 or 4-C), 118.3 (5-C), 65.0 (1-C), 60.4 (2-C), 60.3 (Thio*C*H_2OH), 43.9 (N(Ns)*C*H_2Thio), 34.8 (3-C), 25.6 (C_8F_{17}*C*H_2*C*H_2), 17.8 (Si*C*H(*C*H_3)$_2$), 17.7 (Si*C*H(*C*H_3)$_2$), 12.5 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2$*C*H_2); ν_{max}/cm^{-1} (film) 3393, 2947, 2869, 2159, 1976, 1546, 1371, 1207 and 1063; *m/z* (ES$^+$) 990.2 (100%, [M+NH$_4$]$^+$); found 990.1965, $C_{33}H_{37}F_{17}N_2O_{12}S_2Si$ requires *MNH$_4$* 990.1929

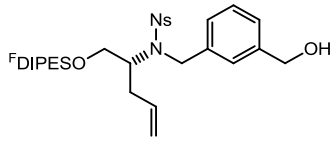
_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]-_N_-({2-[2-(hydroxymethyl)phenyl]phenyl}methyl)-2-nitrobenzene-1-sulfonamide 233



Following general procedure **M2**, diethyl azodicarboxylate (165 mg, 0.95 mmol), sulfonamide **112** (200 mg, 0.24 mmol), hydroxyacetate **129** (240 mg, 0.95 mmol) and triphenylphosphine (248 mg, 0.95 mmol) gave the crude product after 16 h at room temperature. The crude product was concentrated *in vacuo* and purified by F-SPE, to give the acetate ester (213 mg). Following the general procedure **D**, the acetate ester (100 mg, 0.1 mmol) was dissolved in NH_3 sat. MeOH (4 mL) was stirred for 16 h and concentrated *in vacuo* to give the alcohol **233** (175 mg, 0.17 mmol, 99%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless viscous oil. R_f 0.41 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$, *minor atropisomer denoted where possible*) 7.87 (1H, d, *J* 7.8, nosyl 3-H), 7.78 (1H, *J* 7.9, nosyl 3-H^{min}), 7.65-7.09 (11H, m, Ar), 5.43 (1H, ddt, *J* 7.1, 10.1 and 17.1, 4-H^{min}), 5.10 (1H, ddt, *J* 7.3, 10.1 and 17.0, 4-H), 4.81 (1H, d, *J* 10.1, 5-H$_A^{min}$), 4.70 (1H, *J* 17.1, 5-H$_B^{min}$), 4.62 (1H, d, *J* 16.8, N(Ns)CH$_A$), 4.57 (1H, d, *J* 10.1, *5-H$_A$*), 4.52-4.36 (5H, m, Ph*C*H$_2$OH, *5-H$_B$,* N(Ns)C*H*$_2$Ph), 4.10 (1H, d, *J* 16.8, N(Ns)CH$_B$Ph^{min}), 3.98-3.90 (1H, m, 2-H^{min}), 3.89-3.81 (1H, m, 2-H), 3.59-3.50 (2H, m, 1-H$_A$ and 1-H$_B^{min}$), 3.34 (1H, dd, *J* 5.9 and 10.5, 1-H$_A^{min}$), 3.14 (1H, dd, *J* 7.7 and 9.7, 1-H$_B$), 2.20-1.81 (4H, m, 3-H$_{AB}$ and C_8F_{17}C*H*$_2$CH$_2$), 0.91 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.86 (14H, s, 2 × SiCH(CH$_3$)$_2^{min}$), 0.73-0.63 (2H, m, $C_8F_{17}CH_2$C*H*$_2$); δ_C (500 MHz; $CDCl_3$) 148.2 (nosyl 2-C), 139.8 (nosyl 1-C), 139.2 (Ns^{min}), 139.1 (5-C), 139.0 (5-C^{min}), 136.1, 135.8^{min}, 134.6, 134.0^{min}, 133.7, 133.6^{min}, 131.77, 131.74^{min}, 131.73, 131.68^{min}, 130.3^{min}, 130.2^{min}, 130.1, 129.9, 129.1, 128.8, 128.8, 128.7, 128.6, 128.6, 128.2, 128.1, 127.9, 127.8, 127.3, 124.4 124.3^{min}, 118.2 (4-C^{min}), 118.1 (4-C), 65.5 (1-C), 64.6 (1-C^{min}), 63.17 (PhCH$_2$OH^{min}), 63.12 (PhCH$_2$OH), 60.13 (2-C), 60.11 (2-C^{min}), 46.5 (N(Ns)CH$_2$Ph^{min}), 45.9 (N(Ns)CH$_2$Ph), 34.9 (3-C^{min}), 34.1 (3-

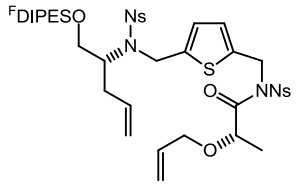
C), 25.6 ($C_8F_{17}CH_2CH_2$), 23.0 (Ac), 17.78 ($SiCH(CH_3)_2$ ^{min}), 17.71 ($SiCH(CH_3)_2$), 12.45 ($SiCH(CH_3)_2^{min}$), 12.35 ($SiCH(CH_3)_2$), -0.05 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3325, 2914, 2743, 1927, 1661, 1599, 1455, 1275 and 1260; *m/z* (ES^+) 1060.3 (100%, $[M+NH_4]^+$); found 1060.2702, $C_{50}H_{55}F_{17}N_5O_{12}S_3Si$ requires *MNH*$_4$ 1060.2678

_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]-_N_-{[3-(hydroxymethyl)phenyl]methyl}-2-nitrobenzene-1-sulfonamide 113



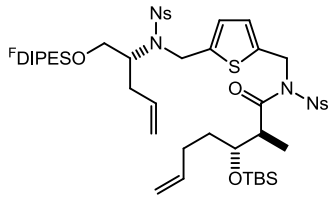
Following general procedure **M1**, diethyl azodicarboxylate (2.1 g, 12 mmol), sulfonamide **112** (5.00 g, 6 mmol), hydroxyacetate **127** (2.15 mg, 12 mmol) and triphenylphosphine (3.14 mg, 12 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE, to give the acetate ester (6.3 g). Following the general procedure **D**, the acetate ester (6.3 g) was dissolved in NH_3 sat. MeOH (200 mL) was stirred for 16 h and concentrated *in vacuo* to give the alcohol **113** (5.2 g, 5.3 mmol, 90%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy); R_f 0.33 (70:30, petrol—EtOAc); δ_H (300 MHz; $CDCl_3$) 7.83 (1H, d, *J* 7.3, nosyl 3-H), 7.63-7.59 (2H, m, nosyl 6-H and Ph), 7.50 (1H, ddd, *J* 8.0, 5.6 and 3.2, Ph), 7.30-7.21 (4H, m, Ph), 5.55 (1H, ddt, *J* 17.1, 10.1 and 7.1, 4-H), 4.99 (1H, dd, *J* 17.1 and 1.5, 5-H_B), 4.88 (1H, dd, *J* 10.1 and 1.5, 5-H_B), 4.75 (1H, d, *J* 16, N(Ns)CH_A), 4.88 (2H, ap d, *J* 5.9, PhCH_2OH), 4.75 (1H, d, *J* 16, N(Ns)CH_B), 3.99 (1H, p, *J* 6.9, 2-H), 3.68 (1H, dd, *J* 10.4 and 5.7, 1-H_A), 3.38 (1H, dd, *J* 10.4 and 6.5, 1-H_B), 2.35 (2H, ap t, *J* 7.3, 3-H_{AB}), 2.14-1.93 (2H, m, $C_8F_{17}CH_2CH_2$), 1.06-0.93 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.78-0.70 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 148.1 (nosyl 2-C), 141.6 (nosyl 1-C), 138.2, 134.7 (4-C), 134.4, 133.5, 131.8, 131.7, 129.1, 128.0, 127.1, 126.7, 124.4, 118.2 (5-C), 65.4 (1-C), 65.1 (PhCH_2OH), 60.5 (2-C), 48.9 (N(Ns)CH_2Ph), 34.8 (3-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 0.4 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2989, 1545, 1462, 1275, 1260 and 748; *m/z* (ES^+) 989.2 (100%, $[M+Na]^+$); found 989.1939, $C_{35}H_{39}F_{17}N_2O_6SSi$ requires *MNa* 989.1919

(2*S*)-*N*-{[5-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)thiophen-2-yl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]-2-(prop-2-en-1-yloxy)propanamide 207



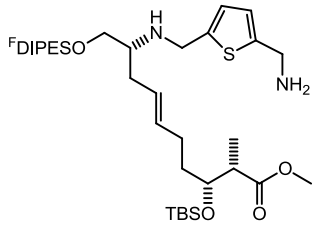
Following general procedure **L1**, alcohol **204** (103 mg, 0.1 mmol), acyl sulfonamide **134** (99 mg, 0.32 mmol), triphenylphosphine (82 mg, 0.32 mmol) and diethyl azodicarboxylate (55 mg, 0.32 mmol) gave the crude product in 24 h. The crude product was concentrated *in vacuo* and purified by F-SPE, to give **207** (88 mg, 69%, >81% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.69 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) *rotamers denoted where possible* 8.45 (1H, dd, *J* 8.5 and 1.9, nosyl 3-H), 8.11 (dd, *J* 8.5 and 1.9, nosyl 3-H^{rot}), 7.94-7.63 (6H, m, Ns), 7.62-7.53 (1H, m, Ns), 6.90 (1H, d, *J* 2.9, Thio 3-H), 6.88 (1H, d, *J* 2.9, Thio 4-H), 6.82-6.71 (1H, m, Thio 3-H^{rot} and 4-H^{rot}), 5.92 (ddt, *J* 16.7, 10.1 and 5.2, propenyl 3-H^{rot}), 5.84 (1H, ddt, *J* 17.1, 10.5 and 5.2, propenyl 3-H), 5.67 (1H, ddt, *J* 16.7, 11.4 and 7.2, 4-H), 5.61 (ddt, *J* 16.7, 10.7 and 7.2, 4-H^{rot}), 5.33 (d, *J* 16.7, propenyl 2-H$_A$), 5.26 (d, *J* 10.1, propenyl 2-H$_B^{rot}$), 5.23 (1H, d, *J* 17.1, propenyl 2-H$_A^{rot}$), 5.19 (1H, d, *J* 16.7, 5-H$_A$), 5.16 (1H, d, *J* 10.5, 5-H$_B$), 5.12-4.95 (4H, m, propenyl 1-H and ThioC*H*$_2$N(CO)), 4.89-4.59 (2H, m, N(Ns)C*H*$_2$Thio), 4.55-4.40 (1H, m, COC*H*(CH$_3$)), 4.12-3.95 (1H, m, 2-H), 3.90-3.55 (2H, m, 1-H$_2$), 2.48-2.46 (2H, m, 3-H$_2$), 2.43-2.39 (2H, m, 3-H$_2^{rot}$), 2.20-2.03 (2H, m, $C_8F_{17}CH_2CH_2$), 1.44 (3H, d, *J* 6.8, CH$_3^{rot}$), 1.35 (3H, d, *J* 7.3, CH$_3$), 1.06 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.88-0.79 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 173.4 (C=O^{rot}), 173.0 (C=O), 148.3 (nosyl 2-C), 148.0 (nosyl 2-C^{rot}), 142.1 (Thio 1-C), 139.7 (Thio 5-C), 135.4, 135.0, 134.5, 134.4, 134.3, 134.2, 133.8, 133.8, 133.3, 132.8, 132.8, 131.9, 131.7, 131.5, 131.4, 131.2, 127.7, 127.2, 127.0, 126.8, 125.9, 125.3, 124.4, 118.4 (propenyl 2-C or 4-C^{rot}), 118.3 (propenyl 2-C or 4-C), 118.3 (propenyl 2-C or 4-C^{rot}), 76.1 (1'''-C *rot*), 74.5 (1'''-C), 71.2 (propenyl 1-C^{rot}), 70.7 (propenyl 1-C), 64.9 (1-C), 60.3 (2-C), 45.36 (Thio*C*H$_2$N(CO)), 43.9 (Thio*C*H$_2$N(CO)^{rot}), 43.8 (N(Ns)*C*H$_2$Thio), 43.0 (N(Ns)*C*H$_2$Thio^{rot}); 35.0 (3-C), 34.8 (3-C *rot*), 25.6 ($C_8F_{17}CH_2CH_2$), 17.9 (SiCH(*C*H$_3$)$_2$), 12.4 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2963, 2533, 1643, 1545, 1370, 1241, 1165 and 1063; *m/z* (ES$^+$) 1291.2 (60%, [M+NH$_4$]$^+$); found 1291.2009, $C_{45}H_{49}F_{17}N_4O_{11}S_3Si$ requires *MNH*$_4$ 1291.1950

(2*S*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-*N*-{[5-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)thiophen-2-yl]methyl}-2'-methyl-*N*-[(2-nitrobenzene)sulfonyl]hept-6'-enamide 210



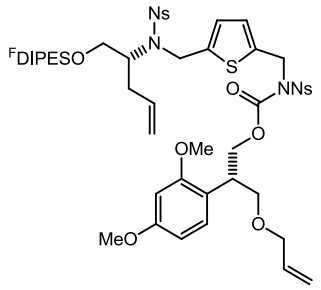
Following general procedure **L1**, alcohol **204** (1.0 mg, 1.02 mmol), acyl sulfonamide **133** (0.49 g, 1.08 mmol), triphenylphosphine (293 mg, 1.12 mmol) and diethyl azodicarboxylate (195 mg, 1.12 mmol) gave the crude product in 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE, to give **210** (800 mg, 0.57 mmol, 56%, >82% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.78 (80:20 petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 8.45-8.35 (2H, m, nosyl 3-H), 8.25-8.20 (3H, m, Ns), 7.85-7.44 (3H, m, Ns), 6.83-6.69 (2H, m, Thio), 5.77 (1H, ddt, *J* 16.8, 10.3 and 6.4, 4-H), 5.67-5.43 (1H, m, 6'-H), 5.17 (1H, d , *J* 12.9, (CO)N(Ns)CH_AThio), 5.06-4.43 (5H, m, (CO)N(Ns)CH_BThio, 5-H_{AB} and 7'-H_{AB}), 4.05 (1H, ap p, *J* 5.5, 3'-H), 3.98-3.72 (2H, m, N(Ns)CH_2Thio), 3.68 (1H, dd , *J* 10.5 and 5.7, 1-H_A), 3.60 (1H, ap p, *J* 6.3, 2-H), 3.47 (1H, dd, *J* 10.5 and 6.3, 1-H_B), 2.45-2.27 (2H, m, 3-H_{AB}), 2.19-1.90 (4H, m, $C_8F_{17}CH_2CH_2$ and 5'-H_{AB}), 1.59-1.52 (1H, m, 2'-H), 1.23-1.15 (3H, m, Me), 0.99-0.91 (14H, m, Si(CH(CH_3)$_2$)$_2$), 0.83 (9H, SiC(CH_3)$_3$), 0.79 (9H, SiC(CH_3)$_3^{min}$), 0.8-0.67 (2H, $C_8F_{17}CH_2CH_2$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3), -0.07 (s, SiCH_3^{min}), -0.14 (s, SiCH_3^{min}); δ_C (75 MHz; $CDCl_3$) 176.3 (*C*=O), 173.6 (*C*=O), 145.4, 144.5, 144.4, 140.1, 139.9, 138.5, 138.4, 135.4, 130.4, 129.1, 126.8, 126.4, 126.0, 125.8, 124.5, 124.4, 118.1^{min}, 117.6, 115.0, 114.9^{min}, 74.7^{min}, 74.5, 69.4, 65.4, 65.3^{min}, 57.8^{min}, 57.8, 46.5, 45.9, 45.7, 38.6, 36.1, 36.0, 34.2, 32.1^{min}, 31.9, 30.4, 30.2^{min}, 26.1, 25.9 (SiC(*C*H_3)$_3$), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 18.1 (Si*C*(CH$_3$)$_3$), 13.1 (Me), 0.00 ($C_8F_{17}CH_2CH_2$), -4.26 (Si*C*H$_3$), -4.30 (Si*C*H$_3$); ν_{max}/cm^{-1} (film) 3323, 3077, 2937, 1832, 1668, 1546; *m/z* (ES$^+$) 1041.1 (100%, [M+H]$^+$)

Methyl (2*S*,3*R*,6*E*,9*R*)-9-({[5-(aminomethyl)thiophen-2-yl]methyl}amino)-3-[(*tert*-butyldimethylsilyl)oxy]-10-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}-2-methyldec-6-enoate 221



Following general procedure **N1**, potassium carbonate (41 mg, 0.30 mmol), sulfonamide **214** (210 mg, 0.151 mmol) and thiophenol (167 mg, 1.5 mmol) gave the crude product after 16 h. The reaction was purified by F-SPE and column chromatography, eluting with 70:30 petrol—EtOAc gave the methyl ester **221** (125 mg, 0.120 mmol, 80%) as a colourless oil; R_f 0.44 (70:30, petrol—EtOAC); δ_H (500 MHz; $CDCl_3$) 6.72 (1H, d, *J* 3.4, Thio 3 or 4-H), 6.65 (1H, d, *J* 3.4, Thio 3 or 4-H), 6.31 (1H, br s, NH), 5.36 (1H, dt, *J* 15.3 and 6.2, 6-H), 5.29 (1H, dt, *J* 15.3 and 6.9, 7-H), 5.17 (1H, br s, NH), 4.45 (1H, d, *J* 12.9, NHCH_APh), 4.44 (1H, d, *J* 12.9, NHCH_BPh), 3.88 (1H, d, *J* 14.3, NH_2CH_APh), 3.85 (1H, d, *J* 14.3, NH_2CH_BPh), 3.70-3.64 (1H, m, 3-H), 3.52-3.46 (2H, m, 10-H_{AB}), 3.25 (3H, s, OMe), 2.62 (1H, p, *J* 6.1, 9-H), 2.42 (1H, qd, *J* 7.1 and 3.9, 2-H), 2.13-1.94 (5H, $C_8F_{17}CH_2CH_2$, 5-H and 8-H), 1.90-1.80 (1H, 5-H), 1.48-1.37 (2H, 4-H), 0.99 (3H, d, *J* 7.1, Me), 0.94 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.82 (9H, s, SiC(CH_3)$_3$), 0.77-0.73 (2H, m, $C_8F_{17}CH_2CH_2$), 0.01 (6H, s, 2 × SiCH_3); δ_C (125 MHz; $CDCl_3$) 184.4 (C=O), 149.3 (Thio 2 or 5-C), 145.8 (Thio 2 or 5-C), 138.7 (4-C), 131.9 (Thio 3 or 4-C), 137.7 (Thio 3 or 4-C); 130.4 (5-C), 79.2 (8-C), 74.3 (1-C), 70.7 (2-C); 61.9 (9-C), 51.1 (CH_2NH_2), 40.2 (NHCH_2Ph), 39.4 (6-C); 31.1 (3-C), 30.7 (7-C); 22.2 (Me), 22.1 ($C_8F_{17}CH_2CH_2$), 18.0 (SiC(CH_3)$_3$), 17.9 (SiCH(CH_3)$_2$), 5.28 ($C_8F_{17}CH_2CH_2$), 0.2 (SiCH_3), 0.00 (SiCH_3), SiCH(CH_3)$_2$ missing; ν_{max}/cm^{-1} (film) 3110, 2996, 1739 and 1562; *m/z* (ES$^+$) 1045.4 (100%, [M+H]$^+$); found 1045.3713, $C_{40}H_{62}F_{17}N_2O_4SSi_2$ requires *MH* 1045.3692

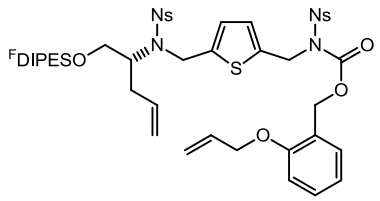
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[5-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)thiophen-2-yl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 212



Following general procedure **L2**, alcohol **204** (164 mg, 0.17 mmol), acyl sulfonamide **208** (323 mg, 0.67 mmol), triphenylphosphine (88 mg, 0.34 mmol) and diethylazodicarboxylate (59 mg, 0.34 mmol) gave the crude product after 24 h. The crude product was concentrated *in vacuo* and purified using F-SPE; to give **212** (218 mg, 89 %, >93% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.27 (80:20 CH_2Cl_2—petrol); δ_H (500 MHz; $CDCl_3$) 8.14 (1H, d, *J* 7.8, nosyl 3-H), 7.70-7.63 (3H, m, Ns), 7.61-7.56 (1H, m, Ns), 7.51-7.47 (2H, m, Ns), 7.41-7.36 (1H, m, Ns), 6.90 (1H, d, *J* 8.3, DMB 6-H), 6.68 (1H, d, *J* 3.5, Thio 3-H), 6.61 (1H, d, *J* 3.5, Thio 4-H), 6.31 (1H, d, *J* 2.3, Ar, DMB 3-H), 6.28 (1H, dd, *J* 8.3 and 2.3, DMB 5-H), 5.75 (1H, ddt, *J* 17.2, 10.4 and 5.6, propenyl 2-H), 5.62 (1H, ddt, *J* 17.1, 10.1 and 7.2, 4-H), 5.12 (1H, d, *J* 17.2, propenyl 3-H_A), 5.05 (1H, d, *J* 10.4, propenyl 3-H_B), 5.00 (1H, d, *J* 17.1, 5-H_A), 4.92 (1H, d, *J* 10.1, 5-H_B), 4.81-4.78 (2H, m, ThioCH_2N(Ns)CO)), 4.65 (2H, d, *J* 9.5, N(Ns)CH_2Thio), 4.56-4.41 (1H, m, propyl 1-H_A), 4.36-4.30 (1H, m, propyl 1-H_B), 4.05-3.97 (1H, m, 2-H, 2-H), 3.86-3.80 (2H, m, propenyl 1-H), 3.76 (1H, dd, *J* 10.5 and 5.5, 1-H_B), 3.70 (3H, s, OMe), 3.66 (3H, s, OMe), 3.63 (1H, dd, *J* 10.5 and 5.5, 1-H_A), 3.50-3.42 (3H, m, propyl 2- and 3-H_2), 2.47-2.33 (2H, m, 3-H_2), 2.10-1.95 (2H, m, $C_8F_{17}CH_2CH_2$), 0.95 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.79-0.72 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 160.2 (DMB 2- or 4-C), 158.6 (DMB 2- or 4-C), 151.8 (C=O), 148.1 (nosyl 2-C), 147.7 (nosyl 2-C), 141.4 (Thio 2-C), 139.8 (Thio 5-C), 134.9 , 134.8, 134.8 (propenyl 3-C), 134.7, 134.5 (5-C), 133.6, 133.0, 132.2, 131.8, 131.3, 129.2, 127.8 (Thio 3-C), 127.6 (Thio 4-C), 124.8, 124.3, 119.1, 118.4 (4-C), 117.3 (propenyl 2-C), 104.5 (DMB 5-C), 98.9 (DMB 3-C), 72.3 (propenyl 1-C), 70.5 (propyl 3-C), 68.6 (1-C), 65.0 (propyl 1-C) , 60.1 (2-C), 55.6 (2 × OMe), 45.8 (ThioCH_2N(CO)), 43.8 (N(Ns)CH_2Thio), 38.4 (propyl 2-C), 35.0 (3-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 17.7 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 12.4 (SiCH(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2947, 2869, 1737, 1545, 1440,

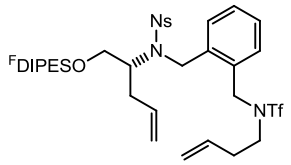
1370, 1163 and 779; *m/z* (ES^+) 1457.3 (100%, $[M+NH_4]^+$); found 1457.2730, $C_{50}H_{55}F_{17}N_5O_{12}S_3Si$ requires *MNa* 1457.2580

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)thiophen-2-yl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 211



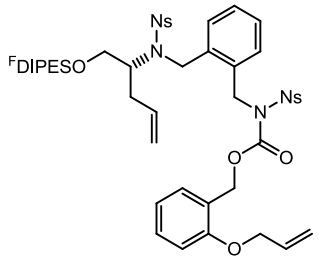
Following general procedure **L2**, alcohol **204** (195 mg, 0.2 mmol), acyl sulfonamide **131** (314 mg, 0.8 mmol), triphenylphosphine (104 mg, 0.4 mmol) and diethyl azodicarboxylate (70 mg, 0.4 mmol gave the crude product after 36 h. The crude product was concentrated *in vacuo*, purified by F-SPE and column chromatography, eluting with CH_2Cl_2 to give **211** (190 mg, 70%) as a colourless oil. R_f 0.89 (CH_2Cl_2); $[\alpha]_D^{22}$ −2.0 (c. 2.0, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.17 (1H, d, *J* 7.9, nosyl 3-H), 7.80-7.68 (3H, m, Ns), 7.63-7.56 (2H, m, Ns), 7.49 (2H, t, *J* 8.1, nosyl 5-H), 7.36 (1H, t, *J* 8.1, Ph 6-H), 7.24 (1H, d, *J* 7.5, Ph 4-H), 6.96 (1H, t, *J* 7.5, Ph 3-H), 6.89 (1H, d, *J* 3.5, Thio 4-H), 6.87 (1H, d, *J* 8.1, Ph 5-H), 6.83 (1H, d, *J* 3.5, Thio 3-H), 5.99 (1H, ddt, *J* 17.2, 10.6 and 5.1, 4-H), 5.75 (1H, ddt, *J* 17.0, 9.9 and 7.0, propenyl 2-H), 5.37 (1H, d, *J* 17.2, 5-H_A), 5.29 (1H, d, *J* 16.2, PhC*H*$_A$O), 5.28 (1H, d, *J* 16.2, PhC*H*$_A$O), 5.27 (1H, d, *J* 10.6, 5-H_B), 5.13 (1H, d, *J* 17.0, propenyl 3-H_A), 5.05 (d, *J* 9.9, propenyl 3-H_B), 5.03 (2H, s, ThioC*H*$_2$N(CO)), 4.79 (1H, d, *J* 16.3, 1''-H_a), 4.73 (1H, d, *J* 16.3, 1''-H_b), 4.52-4.49 (2H, m, propenyl 1-H_2), 4.18-4.11 (1H, m, 2-H), 3.90 (1H, dd, *J* 10.5 and 5.5, 1-H_A), 3.77 (1H, dd, *J* 10.5 and 5.1, 1-H_B), 2.57-2.47 (2H, m, 3-H_2), 2.22-2.09 (2H, m, $C_8F_{17}CH_2CH_2$), 1.07 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.90-0.86 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 157.2 (C=O), 151.7 (nosyl 2-C), 148.1 (Ph 2-C), 147.7 (nosyl 2-C), 141.5, 139.8, 134.8 (4-C), 134.7 (Thio 3-C), 134.7 (Thio 4-C), 134.5, 133.6, 133.1, 133.0, 131.8, 131.3, 131.1, 130.8, 128.2 (Thio 2-C), 127.6 (Thio 5-C), 124.7 (nosyl 3-C), 124.2 (nosyl 3-C), 122.8, 120.9 (Ph 5-C), 117.8 (5-C), 117.4 (propenyl 3-C), 112.0 (Ph 3-C), 69.1 (propenyl 1-C), 65.7 (PhCH_2O), 65.1 (1-C), 60.1 (2-C), 45.8 (ThioCH_2N(CO)), 43.9 (N(Ns)CH_2Thio), 35.0 (3-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 17.7 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH$_3$)$_2$), 12.4 (SiCH(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3629, 2490, 2029, 1738, 1544, 1370, 1207, 736 and 586; *m/z* (ES^+) 1364.3 (100%, $[M+NH_4]^+$); found 1364.2536, $C_{50}H_{51}F_{17}N_4O_{12}S_3Si$ requires *MNH*$_4$ 1364.2502

***N*-[(2-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 209**



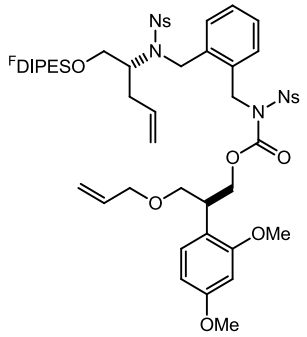
Following general procedure **L1**, trifluoromethanesulfonamide **135** (1.17 g, 5.8 mmol), alcohol **205** (1.4 g, 1.45 mmol), triphenylphosphine (0.76 g, 2.9 mmol) and diethyl azodicarboxylate (0.5 g, 2.9 mmol) gave the crude product after 1 h. The crude product was concentrated *in vacuo* and purified with F-SPE; to give **209** (1.55 g, 1.35 mmol, 93%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.88 (80:20, petrol—EtOAc); δ_H (300 MHz; $CDCl_3$) 7.75 (1H, d, *J* 7.8, Ar), 7.7-7.63 (2H, m, Ar), 7.57-7.49 (2H, m, Ar), 7.37-7.21 (3H, m, Ar), 5.6 (2H, ddt, *J* 17, 10.1 and 6.8, 4'-H and 3-H), 5.08-5.02 (2H, m, 4-H_A and 5'-H_A), 4.99 (1H, dd, *J* 8.7 and 1.7, 5'-H_B), 4.92 (1H, d, *J* 10.3, 4-H_B), 4.97.4.57 (2H, br s, PhCH_2NTf), 4.85 (1H, d, *J* 16.6, N(Ns)CH_BPh), 4.67 (1H, d, *J* 16.6, N(Ns)CH_APh), 4.10 (1H, ap p, *J* 6.7, 2'-H), 3.77-3.69 (1H, dd, *J* 10.9 and 6.4, 1'-H_A), 3.55-3.33 (1H, m, 1'-H_B), 3.41 (2H, t, *J* 7.7, 1-H_2), 2.39 (2H, ap t, *J* 7.7, 3'-H), 2.31-1.96 (4H, m, 2'-H and $C_8F_{17}CH_2CH_2$), 0.99 (14H, s, Si(C*H*(CH_3)$_2$)$_2$); δ_C (75 MHz; $CDCl_3$) 148.2 (nosyl 2-C), 136.3 (nosyl 1-C), 134.3, 134.1 (3-C), 133.8 (4'-C), 133.5, 132.6 (nosyl 5-C), 132.4, 131.9, 131.7 (nosyl 4-C), 130.1, 129.3, 129.1, 128.9 (nosyl 6-C), 128.5, 124.5 (nosyl 3-C), 118.6 (4-C and 5'-C), 64.8 (1'-C), 60.5 (2'-C), 50.6 (N(Ns)CH_2Ph), 48.8 (1-C), 46.0 (PhCH_2Tf); 34.5 (3'-C), 33.2 (2-C), 25.6 (t, *J* 24, $C_8F_{17}CH_2CH_2$), 17.7 ((SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$), *CF_3 missing*; ν_{max}/cm^{-1} (film) 2948, 2870, 2357, 1643, 1574, 1390; *m/z* (ES$^+$) 1169.2 (100%, [M+NH_4]$^+$); found 1169.2490, $C_{40}H_{45}F_{20}N_3O_7S_2Si$ requires *MNH_4* 1169.2487

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[2-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 235



Following general procedure **L2**, sulfonamide **131** (2.2 g, 5.8 mmol), alcohol **205** (1.4 g, 1.45 mmol), triphenylphosphine (1.5 g, 5.8 mmol) and diethyl azodicarboxylate (1.0 g, 5.8 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **235** (1.5 g, 1.12 mmol, 77%, >93% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.71 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 8.16 (1H, d, *J* 7.9, nosyl 3-C), 7.73 (1H, dd, *J* 8.1 and 1, nosyl 3-C), 7.66 (1H, td, *J* 7.5 and 1, nosyl 6-C), 7.58 (1H, dd, *J* 8.4 and 1, nosyl 6-C), 7.54-7.50 (2H, m, Ar), 7.47-7.43 (1H, m, Ar), 7.36 (1H, d, *J* 7.9, Ar), 7.34 (1H, d, *J* 7.9, Ar), 7.30-7.25 (2H, m, Ar), 7.20-7.17 (1H, m, Ar), 7.07-7.03 (2H, m, Ar), 6.88-6.84 (1H, m, Ph 3-H), 6.76 (1H, d, *J* 8.3, Ph 4-H), 5.89 (1H, ddt, *J* 17.2, 10.3 and 5, propenyl 2-H), 5.67 (1H, ddt, *J* 17.1, 10.1 and 7.0, 4-H), 5.29 (1H, dd, *J* 17.2 and 1.7, propenyl 3-H_A), 5.21 (1H, dd, *J* 10.3 and 1.4, propenyl 3-H_B); 5.18 (2H, s, PhC*H*$_2$O), 5.13 (1H, d, *J* 17, PhCH_2N(CO)), 5.09 (1H, d, *J* 17.1, 5-H_A), 5.0 (1H, d, *J* 17, PhCH_2N(CO)), 4.96 (1H, d, *J* 10.1, 5-H_B), 4.68 (1H, d, *J* 16.1, N(Ns)C*H*$_A$Ph), 4.60 (1H, d, *J* 16.1, N(Ns)C*H*$_B$Ph), 4.40-4.32 (2H, m, propenyl 1-H_2), 4.21-4.15 (1H, m, 2-H), 3.74 (1H, dd, *J* 10.5 and 6.2, 1-H_A), 3.57 (1H, dd, *J* 10.5 and 5.9, 1-H_B), 2.53 (1H, dt, *J* 13.5 and 6.6, 3-H_A), 2.41 (1H, dt, *J* 13.5 and 7.7, 3-H_B), 2.16-2.02 (2H, m, $C_8F_{17}CH_2CH_2$), 0.99 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.83-0.78 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 157.1 (Ph 2-C), 152.1 (C=O), 148.3 (nosyl 2-C), 147.9 (nosyl 2-C), 135.4 (nosyl 1-C), 135.0 (nosyl 1-C), 134.8 (Ph 1-C), 134.7 (4-C), 134.7, 134.1, 133.2 (propenyl 2-C), 133.1, 133.0, 131.9, 131.7, 130.7, 130.1, 128.4, 127.5, 126.9, 124.7, 124.4, 122.9, 120.9 (Ph 5-C), 118.2 (5-C), 117.7 (propenyl 3-C), 111.9 (Ph 3-C); 69.0 (propenyl 1-C), 65.7 (PhCH_2O), 64.5 (1-C), 60.3 (2-C), 48.5 (PhCH_2N(CO)), 45.8 (N(Ns)CH_2Ph), 34.7 (3-C), 25.6 (t, *J* 23.4, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3075, 2946, 2869, 1734, 1544, 1369, 1243; *m/z* (ES$^+$) 1358.3 (100%, [M+NH$_4$]$^+$); found 1358.2931, $C_{52}H_{53}F_{17}N_4O_{12}S_2Si$ requires *MNH*$_4$ 1358.2937

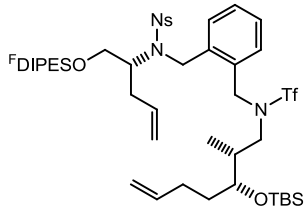
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 235



Following general procedure **L2**, sulfonamide **132** (2.7 g, 5.8 mmol), alcohol **205** (1.4 g, 1.45 mmol), triphenylphosphine (1.5 g, 5.8 mmol) and diethyl azodicarboxylate (1.0 g, 5.8 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **235** (1.3 g, 0.91 mmol, 63%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.67 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 8.31 (1H, d, *J* 7.8, nosyl 3-H), 7.81-7.76 (2H, m, Ar), 7.74-7.70 (2H, m, Ar), 7.66 (1H, d, *J* 7.8, nosyl 4-H), 7.64-7.59 (1H, m, Ar), 7.47-7.42 (2H, m, Ar), 7.34-7.30 (1H, m, Ar), 7.26-7.22 (1H, m, Ar), 7.16-7.11 (1H, m, Ar), 6.92 (1H, d, *J* 8.2, DMB 6-H), 6.39-6.34 (2H, m, DMB 3 and 5-H), 5.84 (1H, ddt, *J* 16.9, 10.6 and 5.5, 4-H), 5.68 (1H, ddt, *J* 16.9, 10.0 and 6.9, propenyl 2-H), 5.22 (1H, ddt, *J* 16.9 and 1.7, propenyl 3-H_A), 5.17-5.11 (3H, m, $PhCH_AN(CO)$, 5-H_A and 3-H_B), 5.09-5.03 (1H, m, $PhCH_BN(CO)$), 4.99 (1H, d, *J* 10.1, 5-H_B), 4.79 (1H, d, *J* 16, $N(Ns)CH_APh$), 4.67 (1H, d, *J* 16, $N(Ns)CH_APh$), 4.52 (1H, dd, *J* 10.7 and 5.6, propyl 1-H_A), 4.42 (1H, dd, *J* 10.7 and 6.6, propyl 1-H_B), 4.23-4.16 (1H, m, 2-H), 3.89 (2H, dd, *J* 5.6 and 1.7, propenyl 1-H_2), 3.84-3.79 (4H, m, 1-H_A and OMe), 3.75 (3H, s, OMe), 3.58-3.47 (4H, m, 1-H_B, propyl 2-H and propyl 3-H_{AB}), 2.56 (1H, dt, *J* 13.9 and 6.9, 3-H_A), 2.48 (1H, dt, *J* 13.9 and 7.6, 3-H_B), 2.20.2.08 (2H, m, $C_8F_{17}CH_2CH_2$), 1.04-1.02 (14H, m, $Si(CH(CH_3)_2)_2$), 0.87-0.82 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 160.1 (DMB 4-C), 158.5 (DMB 2-C), 152.2 (C=O), 148.3 (nosyl 2-C), 147.9 (nosyl 2-C), 135.2 (propenyl 2-C), 135.1 (4-C), 134.9, 134.8, 134.7, 134.6, 134.1, 133.4, 133.0, 132.2, 131.9, 131.8, 129.9, 129.1, 128.5, 127.4, 126.5, 124.9, 124.5, 119.1, 118.3 (propenyl 3-C), 117.1 (5-C), 104.4 (DMB 5-C), 98.9 (DMB 3-C), 72.2 (propyl 3-), 70.1 (propenyl 1-C), 68.4 (1-C), 64.6 (propyl 1-C), 60.5 (2-C), 55.6 (2 × OMe), 48.7 ($N(Ns)CH_2Ph$), 45.8 ($PhCH_2N(CO)$), 38.1 (propyl 2-C) , 34.7 (3-C), 25.6 (t, *J* 23.4, $C_8F_{17}CH_2CH_2$) 17.8 ($SiCH(CH_3)_2$), 12.5 ($SiCH(CH_3)_2$), 0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3300, 2946,

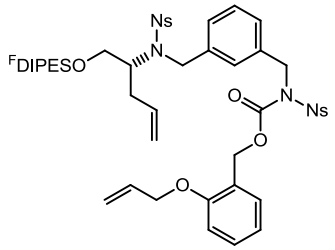
1869, 1740, 1548, 1371; *m/z* (ES^+) 1451.3 (100%, $[M+Na]^+$); found 1451.3013, $C_{56}H_{61}F_{17}N_4O_{14}S_2Si$ requires *MNa* 1451.3016

_N_-{[2-({_N_-[(2_R_,3_R_)-3-[(_Tert_-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 236



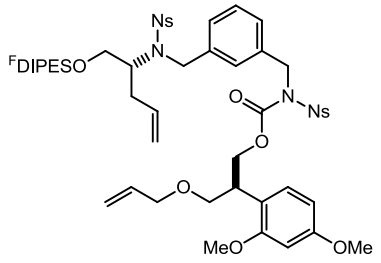
Following general procedure **L3**, sulfonamide **202** (220 mg, 0.57 mmol), alcohol **205** (519 mg, 0.54 mmol), triphenylphosphine (148 mg, 0.57 mmol) and diethyl azodicarboxylate (98 mg, 0.57 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo,* column chromatography eluting with 80:20 petrol−EtOAc gave the sulfonamide **236** (430 mg, 0.32 mmol, 57%) as a colourless oil; R_f 0.89 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.76 (1H, d, *J* 7.9, nosyl 3-H), 7.71-7.62 (2H, m, Ar), 7.57-7.43 (2H, m, Ar), 7.34 (1H, d, *J* 7.1, Ar), 7.28 (1H, d, *J* 7.8, Ar), 7.23-7.19 (1H, m, Ar), 5.78 (0.5H, br s, 4'-H^{rot}), 5.68 (1H, ddt, *J* 18.2, 9.5 and 16.5, 6-H), 5.57-5.46 (0.5H, m, 4'-H), 4.99-4.96 (2H, m, 5'-H_{AB}), 4.94-4.79 (5H, m, 7-H_{AB}, N(Ns)CH_APh and PhCH_ANTf), 4.6 (1H, d, *J* 16.8, N(Ns)CH_BPh), 4.63-4.78 (1H, br s, PhCH_BNTf), 4.03-3.98 (1H, m, 2'-H), 3.68-3.60 (1H, m, 1'-H_A), 3.50-3.21 (4H, m, 1'-H_B and 1-H_{AB} and 3-H), 2.39-2.30 (2H, m, 3'-H_2), 2.10-1.97 (2H, m, $C_8F_{17}CH_2CH_2$), 1.84-1.69 (2H, m, 5-H_2), 1.60-1.56 (1H, m, 2-H), 1.43-1.21 (2H, m, 4-H), 0.97-0.93 (14H, m, Si(CH(CH_3)$_2$)$_2$), 0.82 (12H, s, Me and SiC(CH_3)$_3$), 0.77-0.72 (2H, m, $C_8F_{17}CH_2CH_2$), 0.00 (3H, s, SiCH_3), -0.07 (3H, s, SiCH_3); δ_C (75 MHz; $CDCl_3$) 148.2 (nosyl 2-C), 138.5 (nosyl 1-C), 135.9 (6-C), 134.2 (4'-C), 134.1, 133.8, 133.5, 131.9, 131.9, 130.4, 128.9, 128.8, 128.6; 122.8, 118.4 (5'-C), 115.1 (7-C), 73.7 (3-C), 64.7 (1'-C), 60.6 (2'-C), 52.3 (PhCH_2NTf), 46.5 (N(Ns)CH_2Ph), 36.6 (1-C), 34.3 (3'-C), 33.5 (5-C), 30.2 (2-C), 26.1 (SiC(CH_3)$_3$), 25.6 (t, *J* 23, $C_8F_{17}CH_2CH_2$), 18.4 (SiC(CH_3)$_3$), 17.8 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 11.3 (CH_3), 0.00 ($C_8F_{17}CH_2CH_2$), -3.77 (SiCH_3), -4.4 (SiCH_3); ν_{max}/cm^{-1} (film) 2951, 2867, 1642, 1547, 1372, 1227; *m/z* (ES^+) 1355.4 (100%, $[M+NH_4]^+$); found 1355.3869, $C_{50}H_{67}F_{20}N_3O_8S_2Si_2$ requires *MNH*$_4$ 1355.3927

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 114



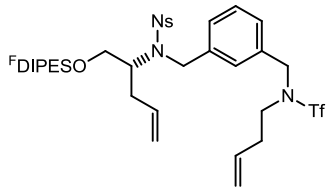
Following general procedure **L1**, sulfonamide **131** (973 mg, 2.4 mmol), alcohol **113** (1.2 g, 1.2 mmol), triphenylphosphine (628 mg, 2.4 mmol) and diethyl azodicarboxylate (417 mg, 2.4 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **114** (1.22 g, 0.91 mmol, 76%, >94% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.23 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 8.14 (1H, dd, *J* 8.1 and 1.3, nosyl 3-H), 7.71 (1H, dd, *J* 7.8 and 1.3, nosyl 6-H), 7.70 (1H, dd, *J* 8.1 and 1.8, nosyl 3-H), 7.67 (1H, dd, *J* 3.8 and 1.3, Ar), 7.65 (1H, dd, *J* 3.8 and 1.3, Ar); 7.58-7.51 (2H, m, Ar), 7.47-7.39 (3H, m, Ar), 7.27-7.23 (2H, m, Ar), 7.13 (1H, apt, *J* 7.3, Ar), 7.08 (1H, dd, *J* 7.5 and 1.7, Ar), 6.86 (1H, td, *J* 7.5 and 1, Ar), 6.78 (1H, dd, *J* 8.3 and 1.0, Ar), 5.91 (1H, ddt, *J* 17.2, 10.4 and 5.1, propenyl 2-C), 5.64 (1H, ddt, *J* 17.1, 10.1 and 7.0, 4-H), 5.29 (1H, ddd, *J* 17.2, 3.3 and 1.6, propenyl 3-H_A), 5.19 (1H, ddd, *J* 10.4, 2.9 and 1.6, propenyl 3-H_B), 5.19 (2H, s, PhCH_2O), 5.02 (1H, dd, *J* 17.1 and 1.6, 5-H_A), 4.92 (1H, dd, *J* 10.1 and 1.6, 5-H_B), 4.91 (2H, s, PhCH_2N(CO)), 4.63 (1H, d, *J* 15.8, N(Ns)CH_APh), 4.48 (1H, d, *J* 15.8, N(Ns)CH_BPh), 4.40 (2H, dt, *J* 5.1 and 1.7, propenyl 1-C_2), 4.08-4.03 (1H, m, 2-H), 3.76 (1H, dd, *J* 10.5 and 5.8, 1-H_A), 3.53 (1H, dd, *J* 10.5 and 5.9, 1-H_B), 2.41 (1H, dt, *J* 13.9 and 6.9, 3-H_A), 2.34 (1H, dt, *J* 13.9 and 7.5, 3-H_B), 2.16-2.02 (2H, m, $C_8F_{17}CH_2CH_2$), 1.06-0.96 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.82-0.78 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 156.7 (C=O), 151.7 (Ph 2-C), 147.8 (nosyl 2-C), 147.6 (nosyl 2-C), 137.5 nosyl 1-C), 137.2 (nosyl 1-C), 134.6 (4-C), 134.5 (propenyl 2-C), 134.3, 132.9, 132.8, 132.7, 132.2, 132.0, 131.94, 131.9, 131.6, 131.3, 131.3, 130.3, 128.7, 128.6, 128.4, 127.9, 127.8, 127.1, 124.3, 124.0, 122.7, 120.5 (Ph 5-C)), 117.8 (5-C), 117.4 (propenyl 3-C), 111.6 (Ph 3-C), 68.7 (propenyl 1-C), 65.2 (PhCH_2O), 64.6 (1-C), 60.0 (2-C), 50.8 (PhCH_2N(CO)), 48.5 (N(Ns)CH_2Ph), 34.7 (3-C), 25.3 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.4 (SiCH(CH_3)$_2$), 17.4 (SiCH(CH_3)$_2$), 12.3 (SiCH(CH$_3$)$_2$), -0.03 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3521, 2957, 1737, 1651, 1538, 1372 and 1254; *m/z* (ES$^+$) 1363.3 (100%, [M+Na]$^+$); found 1363.2414, $C_{52}H_{53}F_{17}N_4O_{12}S_2Si$ requires *MNa* 1363.2491

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]methyl}-*N*-[(2-nitrobenzene)sulfonyl]carbamate 237



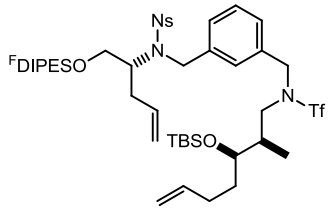
Following general procedure **L1**, sulfonamide **132** (993 mg, 2.07 mmol), alcohol **113** (1.00 g, 1.04 mmol), triphenylphosphine (542 mg, 2.07 mmol) and diethyl azodicarboxylate (360 mg, 2.07 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **237** (1.65 g, 1.16 mmol, 112%, >59% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.39 (70:30, petrol—EtOAc); δ_H (500 MHz; MeOD; 323K) 8.15 (1H, dd, *J* 7.6 and 1.1, nosyl 3-H), 7.90-7.82 (2H, m, Ar), 7.77-7.69 (3H, m, Ar), 7.65-7.58 (2H, m, Ar), 7.34-7.15 (4H, Ar), 6.91 (1H, dd, *J* 8.5, DMB 6-H), 6.43 (1H, d, *J* 2.4, DMB 3-H), 6.35 (1H, dd, *J* 8.4 and 2.5, DMB 5-H), 5.80 (1H, ddt, *J* 17.2, 10.4 and 5.5, propenyl 2-H), 5.59 (1H, ddt, *J* 17.3, 10.2 and 7.1, 4-H), 5.16 (1H, ddd, *J* 17.2, 1.7 and 1.7, propenyl 3-H_A), 5.08 (1H, dd, *J* 10.4 and 1.7, propenyl 3-H_B), 5.01 (1H, dd, *J* 17.3 and 1.6, 5-H_A), 4.88 (1H, dd, *J* 10.2 and 1.8, 5-H_B), 4.80 (2H, s, PhCH_2N(CO)), 4.56 (1H, d, *J* 16, N(Ns)CH_APh), 4.50 (1H, d, *J* 16, N(Ns)CH_APh), 4.44 (1H, dd, *J* 10.6 and 5.3, propyl 1-H_A), 4.36 (1H, dd, *J* 10.6 and 7.0, propyl 1-H_B), 4.08-3.99 (2H, m, 1-H_{AB}), 3.87-3.84 (2H, m, propenyl 1-C), 3.76 (3H, s, OMe), 3.72 (3H, s, OMe); 3.50-3.40 (4H, m, 2-H, propyl 2-H and 3-H_{AB} propyl), 2.40-2.31 (2H, m, 3-H_{AB}), 2.21-2.09 (2H, m, $C_8F_{17}CH_2CH_2$), 0.99 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.85-0.77 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; MeOD) 165.7 (C=O), 161.5 (DMB 4-C), 159.8 (DMB 2-C), 153.2 (nosyl 2-C), 149.2 (nosyl 2-C), 143.4 (nosyl 1-C) , 139.5, 139.3, 138.9, 136.1, 136.7, 134.8, 133.1, 132.8, 132.2, 130.1, 129.8, 129.5, 129.0, 128.8, 128.8 (DMB 6-C), 127.9, 125.8, 125.4, 125.3, 120.0 (DMB 1-C), 118.1 (propenyl 3-C), 117.0 (5-C), 105.9 (DMB 5-C), 99.7 (DMB 3-C), 72.9 (3-C propyl), 72.3 (propenyl 1-C), 69.2 (Ph*C*H_2N(CO)), 65.8 (N(Ns)*C*H_2Ph), 64.9 (2-C), 61.6 (1-C), 55.9 (OMe), 55.8 (OMe), 51.8 (1-H propyl), 39.5 (2-C propyl), 35.7 (3-C); 26.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.9 (SiCH(*C*H_3)$_2$), 13.4 (Si*C*H(CH$_3$)$_2$), 0.8 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3573, 3080, 2946, 2868, 1843, 1735, 1643, 1658, 1543; *m/z* (ES$^+$) 1446.3 (100%, [M+NH_4]$^+$); found 1446.3394, $C_{65}H_{51}F_{17}N_4O_{14}S_2Si$ requires *MNH*$_4$ 1446.3462

***N*-[(3-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 238**



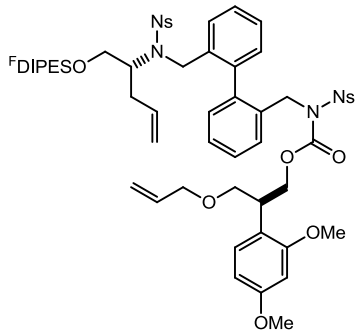
Following general procedure **L1**, sulfonamide **135** (478 mg, 2.4 mmol), alcohol **113** (1.21 g, 1.2 mmol), triphenylphosphine (628 mg, 2.4 mmol) and diethyl azodicarboxylate (417 mg, 2.4 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **238** (1.6 g, 1.25 mmol,115%, >83% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.75 (50:50, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.89 (1H, d, *J* 8.0 and 1.3, nosyl 3-H), 7.66-7.60 (2H, m, Ar), 7.54 (1H, ddd, *J* 8.7, 7 and 1.8, Ar), 7.36 (1H, d, *J* 7.3, Ar), 7.32-7.28 (2H, m, Ar), 7.26-7.22 (1H, m, Ar), 5.62 (1H, ddt, *J* 17.1, 10.3 and 6.9, 3-H), 5.52 (1H, ddt, *J* 17.5, 9.8 and 6.7, 4'-H), 5.08-5.01 (2H, m, 5'-H_{AB}), 4.96 (1H, dd, *J* 17.1 and 1.6, 4-H_A), 4.87 (1H, d, *J* 10.3, 4-H_B), 4.74 (1H, d, *J* 16.2, N(Ns)C*H*$_A$Ph), 4.53 (1H, d, *J* 16.2, N(Ns)C*H*$_A$Ph), 4.45 (2H, br s, PhCH_2NTf), 3.96 (1H, ap p, *J* 6.8, 2'-H), 3.67 (1H, dd, *J* 10.4 and 5.8, 1'-H_A), 3.39 (1H, dd, *J* 10.4 and 6.3, 1'-H_B), 3.32 (2H, t, *J* 7.8, 1-H_2), 2.32-2.19 (4H, m, 3'-H and 2-H), 2.09-1.96 (2H, m, $C_8F_{17}CH_2CH_2$), 0.95 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.76-0.72 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 147.8 (nosyl 2-C), 138.8 (nosyl 1-C), 134.8 (4'-C), 134.8 (3-C), 134.0, 133.8, 133.3, 133.2, 131.4, 131.3, 129.2, 128.5, 127.9, 127.6, 124.2, 118.1 (4-C), 117.9 (5'-C), 64.5 (1'-C), 60.1 (2'-C), 51.8 (N(Ns)*C*H_2Ph), 48.4 (1-C), 47.4 (Ph*C*H_2NTf), 34.5 (3'-C), 32.5 (2-C), 17.4 (SiCH(*C*H_3)$_2$), 17.3 (SiCH(*C*H_3)$_2$), 12.1 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2948, 2870, 1574, 1390, 1372, 1203; *m/z* (ES$^+$) 1174.4 (100%, [M+Na]$^+$); found 1174.2080, $C_{40}H_{45}F_{20}N_3O_7S_2Si$ requires *MNa* 1174.2041

***N*-{[3-({*N*-[(2*R*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 239**



Following general procedure **L3**, sulfonamide **202** (465 mg, 1.19 mmol), alcohol **113** (1.0 g, 1.14 mmol), triphenylphosphine (311 mg, 1.19 mmol) and diethyl azodicarboxylate (207 mg, 1.19 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **239** (1.41 g, 1.06 mmol, 93%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.89 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.88 (1H, dd, *J* 7.9 and 1.3, nosyl 3-H), 7.66-7.59 (2H, m, nosyl 6 and 4-H), 7.56-7.48 (1H, m,), 7.37 (1H, d , *J* 7.5, Ar), 7.31-7.22 (3H, m, nosyl 5-H), 5.72 (1H, ddt, *J* 16.9, 10.3 and 6.6, 6-H), 5.59-5.50 (1H, 4'-H), 4.99-4.87 (4H, m, 5'-H_{AB} and 7-H_{AB}), 4.75 (1H, d, *J* 16.5, N(Ns)CH_APh), 4.74 (1H, d, *J* 16.3, N(Ns)CH_BPh), 4.68-4.20 (2H, br , PhCH_2NTf), 4.51 (1H, d, *J* 16.5, N(Ns)C*H*$_A$Ph^{rot}), 4.49 (1H, d, *J* 16.3, N(Ns)C*H*$_B$Ph^{rot}), 4.02-3.94 (1H, m, 1'-H_A^{rot}), 3.72-3.64 (1H, m, 1'-H_B^{rot}), 3.49 (1H, br s, 3-H), 3.41-3.24 (2.5H, m, 1'-H_{AB}^{rot} and 1-H_{AB}), 2.35 (1H, ap t, *J* 7.6, 2'-H), 2.32-2.27 (2H, m, 3'-H), 2.10-1.97 (2H, m, $C_8F_{17}CH_2CH_2$), 1.93-1.79 (2H, m, 5-H), 1.72 (1H, br s, 2-H), 1.5-1.37 (2H, m, 4-H), 0.96 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.83 (9H, SiC(CH_3)$_3$), 0.80 (3H, d, *J* 7, Me), 0.77-0.72 (2H, m, $C_8F_{17}CH_2CH_2$), 0.00 (3H, SiCH_3), -0.08 (3H, SiCH_3); δ_C (75 MHz; $CDCl_3$) 148.2, 139.2, 139.4, 134.5, 134.3, 133.7, 133.5, 131.8, 131.7, 129.5, 129.1, 128.9, 128.2, 128.1, 127.9, 124.5, 118.3 (4'-C), 115.2 (7-C), 73.5 (3-C), 64.9 (1'-C), 60.5 (2'-C), 48.8 (N(Ns)*C*H$_2$Ph), 36.1 (1-C), 34.9 (2-C), 34.8 (3'-C), 33.3 (5-C), 30.3 (4-C), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 18.4 (Si*C*(CH$_3$)$_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 12.5 (Si*C*H(CH$_3$)$_2$), 12.4 (Me), 11.4 (TBS), 0.4 ($C_8F_{17}CH_2CH_2$), −3.8 (Si*C*H$_3$), −4.3 (Si*C*H$_3$); ν_{max}/cm^{-1} (film) 3080, 2851, 2868, 2736, 2391, 1836, 1720, 1642, 1592, 1547 ; *m/z* (ES$^+$) 1355.4 (100%, [M+NH$_4$]$^+$); found 1355.3877, $C_{50}H_{67}F_{20}N_3O_8S_2Si_2$ requires *MNH*$_4$ 1355.3927

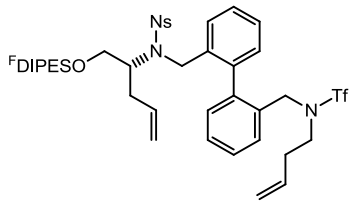
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-({2-[2-({*N*-[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl](2-nitrobenzene)sulfonamido}methyl)phenyl]phenyl}methyl)-*N*-[(2-nitrobenzene)sulfonyl]carbamate 241



Following general procedure **L2**, sulfonamide **132** (2.7 g, 5.8 mmol), alcohol **233** (1.4 g, 1.45 mmol), triphenylphosphine (1.5 g, 5.8 mmol) and diethyl azodicarboxylate (1.0 g, 5.8 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **241** (1.3 g, 0.91 mmol, 63%, >90% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.6 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) *atropisomers denoted where possible* 8.24-8.20 (1H, m, Ar), 7.97-7.55 (m, Ar), 7.51-7.31 (m, Ar), 7.28-7.24 (m, Ar), 7.23-7.10 (m, Ar), 6.89 (0.5H, d, *J* 8.4), 6.83 (0.5H, d, *J* 8.4), 6.46 (0.5H, d, *J* 2.4), 6.39 (0.5H, d, *J* 2.4), 6.36 (0.5H, d, *J* 8.4 and 2.5), 6.33 (0.5H, d, *J* 8.4 and 2.4), 5.88-5.79 (m, propenyl 2-H), 5.58-5.36 (0.5H, m, 4-H^{atrop}), 5.23-5.17 (0.5H, m, 4-H^{atrop}), 5.14-5.10 (2H, m, propenyl 3-H_{AB}), 4.83-4.33 (7H, m, 5-H_A and propyl 1-H_{AB} and N(Ns)CH_2Ph and PhCH_2N(Ns)(CO)), 4.21 (1H, d, *J* 17, 5-H_B), 4.15-4.06 (m, 2-H), 3.90-3.87 (2H, s, propenyl 1-H_2), 3.80 (s, OMe), 3.79 (s, OMe), 3.75 (s, OMe), 3.71 (s, OMe), 3.69-3.39 (m, 1-H_A, propyl 2-H and 3-H_{AB}), 3.31 (1H, dd, *J* 10.3 and 7.1, 1-H_B), 3.26 (1H, dd, *J* 10.3 and 7.3, 1-H_B^{atrop}), 2.27-2.09 (3H, m, $C_8F_{17}CH_2CH_2$ and 3-H_A), 2.06-1.97 (1H, m, 3-H_B), 1.03-0.90 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.87-0.82 ($C_8F_{17}CH_2CH_2^{atrop}$), 0.80-0.76 (2H, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 163.8, 159.7, 158.1, 151.7, 148.0, 147.9, 138.3, 138.2, 135.7. 135.6, 135.5, 134.7, 134.6, 134.4, 134.2, 134.0, 132.9, 132.5, 132.4, 132.2, 131.6, 131.5, 131.4, 131.3, 131.1, 129.9, 129.7, 129.2, 129.1, 128.6, 128.0, 127.8, 127.6, 127.2, 127.1, 125.6, 124.4, 124.3, 123.6, 123.4, 122.5, 119.1, 118.7, 118.6, 117.7, 117.6, 117.5, 116.7, 104.1, 103.9, 98.6, 98.4, , 71.9, 71.8, 69.8, 67.9, 67.9, 64.6, 63.4, 60.4, 59.8, 59.5, 55.2, 55.1, 49.6, 49.5, 45.9, 45.8, 45.5, 38.3, 37.6, 34.4, 33.9, 29.7, 25.3 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.5, 17.4, 17.3, 12.1, 12.0, 0.01; ν_{max}/cm^{-1} (film) 3055, 2987, 2306, 1737, 1546, 1422, 1273; *m/z* (ES$^+$) 1527.3 (100%, [M+Na]$^+$); found 1527.3407, $C_{62}H_{65}F_{17}N_4O_{14}S_2Si$ requires *MNa* 1527.3329

full carbon assignment was not possible to mixture atropisomers

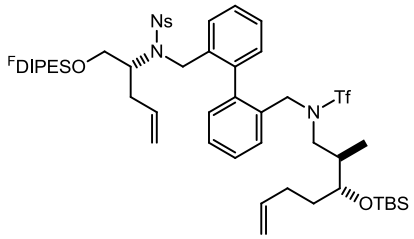
_N_-{[2-(2-{[_N_-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)phenyl]methyl}-_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 242



Following general procedure **L2**, sulfonamide **135** (689 mg, 3.4 mmol), alcohol **233** (920 mg, 0.84 mmol), triphenylphosphine (890 mg, 3.4 mmol) and diethyl azodicarboxylate (591 mg, 3.4 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **242** (1.02 g, 0.81 mmol, 96%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.83 (60:40, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) *minor atropisomer denoted where possible (ca. 43:57)* 7.88 (1H, d, *J* 7.4, nosyl 3-H), 7.80 (d, *J* 7.9, nosyl 3-H^{min}), 7.74-7.29 (7H, m, Ar), 7.26-7.23 (1H, m, Ar), 7.18 (1H, dd, *J* 7.8 and 1.2, nosyl 5-H), 7.16 (1H, d, *J* 7.3, Ar), 7.12-7.09 (1H, m, Ar); 5.57-5.41 (2H, m, 4'-H and 3-H), 5.02-4.76 (4H, m, 4-H$_{AB}$ and 5'-H$_{AB}$), 4.63 (1H, d, *J* 16, PhC*H*$_A$NTf), 4.49 (d, *J* 9.8, 5-H$_B^{min}$), 4.46 (1H, d, *J* 16.6, N(Ns)C*H*$_A$Ph), 4.27 (d, *J* 17, N(Ns)C*H*$_A$Ph^{min}), 4.19 (1H, d, *J* 16.6, N(Ns)C*H*$_B$Ph), 3.96 (1H, dq, *J* 8.2 and 6.0, 2'-H^{min}), 3.88 (1H, d, *J* 16.9, PhC*H*$_B$NTf), 3.82 (1H, br s, 2-H); 3.52 (1H, dd, *J* 9.9 and 5.1, 1'-H$_A$), 3.59-3.40 (m, 1'-H$_A$ ^{min}), 3.38-3.24 (1H, m, 1'-H$_B$), 3.13 (2H, dt, *J* 15 and 7.8, 1-H^{min}), 3.05 (2H, dt, *J* 15 and 7.8, 1-H$_2$), 2.97 (1H, br s, 1-H$_B^{min}$); 2.23-2.08 (2H, m, 3'-H$_{AB}$), 2.08-1.96 (4H, m, 2-H and $C_8F_{17}CH_2CH_2$), 0.94-0.69 (16H, m, Si(C*H*(C*H*$_3$)$_2$)$_2$ and $C_8F_{17}CH_2CH_2$), 0.64-0.58 (2H, m, $C_8F_{17}CH_2CH_2^{min}$); δ_C (75 MHz; $CDCl_3$) *minor atropisomer denoted where possible* 148.4 (nosyl 3-C^{min}), 148.3 (nosyl 3-C), 140.00 (nosyl 1-C), 139.9 (nosyl 1-C^{min}), 138.3, 138.2 (^{min}), 136.5, 136.2 (^{min}), 134.5 (3-C), 134.2, 134.0 (4'-C), 133.9, 133.8, 133.7, 133.6, 133.5, 133.3, 131.7, 131.6, 130.3 (^{min}), 130.2, 129.9, 129.8 (^{min}), 129.2 (^{min}), 129.1, 129.0, 128.8, 128.7 (^{min}), 128.6 (^{min}), 128.2, 127.8 (^{min}), 124.3, 124.31 (^{min}), 120.1 (q, *J* 320, CF_3), 118.2 (5'-C), 118.1 (4-C), 118.0 (4-C^{min}), 66.7 (1'-C), 63.8 (1'-C^{min}), 60.3 (2-C), 60.1 (2-C^{min}), 48.5 (N(Ns)CH_2Ph^{min}), 48.4 (N(Ns)CH_2Ph), 46.3 (PhCH_2NTf^{min}), 45.2 (PhCH_2NTf), 35.4 (1-C), 33.7 (3-C), 32.7 (3'-C^{min}), 32.6 (2-C), 30.1 (2-C^{min}), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.7 (SiCH(C*H*$_3$)$_2$), 17.6 (SiCH(C*H*$_3$)$_2$), 12.5-12.2 (m, (SiCH(CH$_3$)$_2$), 0.12 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3005,

2947, 2868, 1723, 1642, 1462, 1388; *m/z* (ES^+) 1245.3 (100%, $[M+NH_4]^+$); found 1245.2756, $C_{26}H_{49}F_{20}N_3O_7S_2Si$ requires MNH_4 1245.2800

_N_-({2-[2-({_N_-[(2_R_,3_R_)-3-[(_Tert_-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]phenyl}methyl)-_N_-[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]-2-nitrobenzene-1-sulfonamide 243

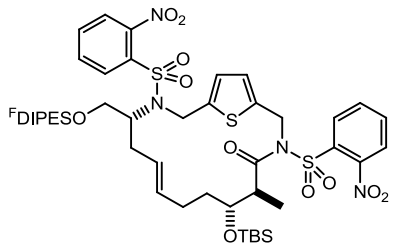


Following general procedure **L2**, sulfonamide **202** (540 mg, 1.39 mmol), alcohol **233** (1.37 g, 1.26 mmol), triphenylphosphine (364 mg, 1.39 mmol) and diethyl azodicarboxylate (241 mg, 1.39 mmol) gave the crude product after 16 h. The crude product was concentrated *in vacuo* and purified by F-SPE to give the sulfonamide **243** (1.78 g, 1.22 mmol, 97%, >80% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a colourless oil; R_f 0.81 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) *50:50 atropisomers denoted where possible* 7.91 (0.5H, dd, *J* 7.9 and 1.3, nosyl 3-H^{atrop}), 7.86 (0.5H, dd, *J* 8.0 and 1.3, nosyl 3-H^{atrop}), 7.82-7.75 (1H, m, Ar), 7.72-7.56 (3H, m, Ar), 7.58-7.43 (2H, m, Ar), 7.40-7.34 (2H, m, Ar), 7.28 (0.5H, dd, *J* 7.5 and 1.3, Ar^{atrop}), 7.23 (0.5H, dd, *J* 7.5 and 1.3, Ar^{atrop}), 7.21-7.17 (1H, m, Ar), 7.17-7.13 (1H, Ar), 5.74 (1H, ddt, *J* 17.1, 10.4 and 6.6, 4'-H), 5.54 (0.5H, ddt, *J* 17.1, 10.3 and 7.0, 6-H^{atrop}), 5.15 (0.5H, ddt, *J* 16.9, 10.3 and 6.4, 6-H^{atrop}), 4.99-4.99 (2H, m, 5-H_{AB}), 4.86 (0.5H, dd , *J* 10.3 and 1.6, 7-H_A^{atrop}), 4.80 (0.5H, dd, *J* 17.1 and 1.4, 7-H_B^{atrop}), 4.76 (0.5H, d, *J* 15.2, PhCH_ANTf), 4.67 (0.5H, d, *J* 15.2, PhCH_BNTf), 4.65 (0.5H, d, *J* 16.7, N(Ns)C$H_A$$Ph^{atrop}$), 4.57 (0.5H, dd, *J* 10.4 and 1.5, 7-H_A^{atrop}), 4.43 (0.5H, dd, *J* 16.9 and 1.4, 7-H_B^{atrop}), 4.41 (0.5H, d, *J* 17.3, N(Ns)C$H_A$$Ph^{atrop}$), 4.25 (0.5H, d, *J* 17.3, N(Ns)C$H_B$$Ph^{atrop}$), 4.12-4.06 (1H, m, Ph(C$H_2$$NTf^{atrop}$), 4.01 (1H, p, *J* 7, 2'-H), 3.96 (0.5H, d, *J* 16.7, N(Ns)C$H_B$$Ph^{atrop}$), 3.97-3.92 (1H, m, 3-H), 3.55 (1H, dd, *J* 10.2 and 5.9, 1'-H_A), 3.5 (1H, 1-H_2^{atrop}), 3.30-3.21 (1H, m, 1-H_2), 3.19 (1H, dd, *J* 10.2 and 7.4, 1'-H_B), 2.21-2.02 (4H, m, 3'-H_{AB} and $C_8F_{17}CH_2CH_2$), 1.93-1.73 (3H, m, 2-H and 5-H_{AB}), 1.68-1.53 (1H, m, 4-H_A), 1.49-1.38 (1H, m, 4-H_B), 0.99-0.96 (14H, m, Si(CH(CH_3)$_2$)$_2$), 0.94-0.90 (12H, m, SiC(CH_3)$_3$ and Me), 0.08-0.71 (2H, m, $C_8F_{17}CH_2CH_2$), 0.05 (3H, s, SiCH_3), 0.00 (s, SiCH_3^{atrop}), -0.02 (3H, s, SiCH_3); δ_C (75 MHz; $CDCl_3$) 149.6 (nosyl 2-C), 141.0, 139.7, 139.4, 139.2, 137.6, 135.4, 135.3, 134.9, 134.6, 133.1, 132.8, 132.3, 131.6, 130.9, 130.8, 130.0, 129.9, 129.8, 129.7, 129.6, 124.5, 129.3, 128.9, 128.6,

125.4, 118.2, 118.1, 115.3, 115.1, 74.6, 74.4, 66.4, 64.9, 61.6, 61.4, 55.1, 53.1, 51.3, 47.3, 46.4, 37.7, 36.9, 36.0, 35.3, 35.1, 34.8, 30.9, 30.8, 26.4, 18.9, 17.9, 17.8, 13.5, 13.4, 11.2, 11.1, 0.99 ($C_8F_{17}CH_2\mathit{C}H_2$), -3.8 (Si*C*$H_3$), -3.82 (Si*C*$H_3$), -4.3 (Si*C*$H_3$), -4.4 (TBS); ν_{max}/cm^{-1} (film) 3311, 3010, 2956, 2707, 2305, 1834, 1641, 1473, 1429 and 1350; *m/z* (ES^+) 1436.4 (100%, $[M+Na]^+$); found 1436.3791, $C_{56}H_{71}F_{20}N_3O_8S_2Si_2$ requires *MNa* 1436.3794

full carbon assignment was not possible to mixture atropisomers

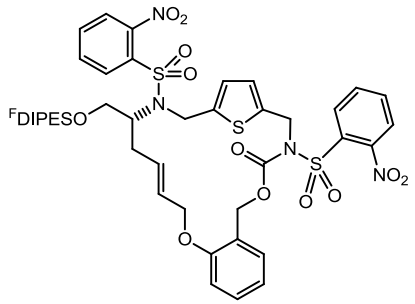
(5*S*,6*R*,9*E*)-6-[(*Tert*-butyldimethylsilyl)oxy]-12-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5-methyl-3,13-bis[(2-nitrobenzene)sulfonyl]-18-thia-3,13-diazabicyclo[13.2.1]octadeca-1(17),9,15-trien-4-one 214



Following general procedure **L2**, **HG-II** (5 mg, 2 mol%), 1,4-benzoquinone (1.7 mg, 4 mol%) and acyl sulfonamide **210** (550 mg, 0.39 mmol) were stirred in MTBE (195 mL) at 55 ˚C for 16 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 80:20 petrol—EtOAc gave the macrocycle **214** (220 mg, 0.16 mmol, 40%, *E*/*Z* >61:<29); R_f 0.55 (CH_2Cl_2); $[\alpha]_D^{23.7}$ −17.1 (c. 0.7, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.28 (1H, dt, *J* 7.7 and 1, nosyl 3-H), 8.12-8.07 (1H, m, nosyl 3-H), 7.82-7.56 (6H, m, nosyl 4-, 5-, and 6-H), 6.90-6.83 (1, m, Ar^Z), 6.81 (1H, d , *J* 3.5, Thio 3-H), 6.66 (1H, d , *J* 3.5, Thio 4-H), 5.71 (1H, d, *J* 12.5, ThioCH_2N(CO)), 5.60 (d, *J* 12.4, ThioCH_2N$(CO)^Z$), 5.41-5.31 (1H, m, 10-H^Z), 5.25 (1H, dt, *J* 15.3 and 6.1, 10-H), 5.19-5.10 (1H, m, 9-H^Z), 5.04 (1H, dt, *J* 15.3 and 6.8, 9-H), 4.91 (d, *J* 12.4, ThioCH_2N$(CO)^Z$), 4.88 (1H, d, *J* 12.5, ThioCH_2N(CO)), 4.81 (1H, d, *J* 15.9, 14-H_A), 4.45 (1H, d, *J* 15.9, 14-H_B), 3.86 (1H, dd, *J* 10.2 and 6.6, SiOCH_A), 3.77-3.66 (2H, m, 8-H_A and 6-H), 3.60 (1H, dd, *J* 10.2 and 5.8, SiOCH_B), 3.54-3.37 (2H, m, 5-H and 8-H_B), 2.67-2.53 (1H, m, 12-H), 2.20-1.77 (4H, m, $C_8F_{17}CH_2CH_2$ and 11-H_{AB}), 1.34 (3H, d, *J* 6.8, Me), 1.27-1.09 (2H, m, 7-H_{AB}), 0.97 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.84 (9H, s, SiC(CH_3)$_3$), 0.81-0.72 (2H, m, $C_8F_{17}CH_2CH_2$), 0.04 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); δ_C (75 MHz; CDCl3) 177.1 (C=O), 148.7 (nosyl 2-C), 148.2 (nosyl 2-C), 144.3 (nosyl 1-C), 143.7 (nosyl 1-C), 137.7 (nosyl 4-C), 134.9 (nosyl 4-C), 134.8 (Thio 2 or 5-C), 134.1 (Thio 2 or 5-C), 134.0, 133.9 (Thio 3 or 4-C), 133.7 (9-C), 132.9, 132.3, 131.9 (Thio 3 or 4-C); 130.6 (Ns), 129.9, 127.7, 125.4 (10-C), 124.6, 74.2 (6-C); 65.7 (2-C), 64.4 (2-

C^Z), 64.1 (SiO*C*H_2), 63.5 (12-C), 46.2 (14-C), 35.7 (5-C), 34.8 (11-C), 33.4 (8-C), 32.5 (7-C), 26.2 SiC(*C*H_3)$_3$, 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 18.4 (Si*C*$(CH_3)_3$), 17.9 (SiCH(*C*H_3)$_2$), 17.8 (SiCH(*C*H_3)$_2$), 16.8 (Me), 12.5 (Si*C*H$(CH_3)_2$), 0.01 ($C_8F_{17}CH_2CH_2$), -3.7 (Si*C*H_3), -4.0 (Si*C*H_3); ν_{max}/cm^{-1} (film) 2953, 2867, 1601, 1545, 1367, 1207; *m/z* (ES$^+$) 1400.4 (100%, [M+NH_4]$^+$); found 1405.3144, $C_{51}H_{63}F_{17}N_4O_{11}S_3Si_2$ requires *MNa* 1405.2815

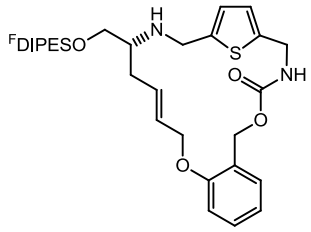
(15*E*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3,19-bis[(2-nitrobenzene)sulfonyl]-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaen-4-one 211



Following general procedure **RCM1**, **HG-II** (0.8 mg, 1 mol%) and sulfonamide **211** (180 mg, 0.13 mmol) were stirred in MTBE (60 mL) at 55 ˚C for 16 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 70:30 CH_2Cl_2−petrol gave the macrocycle **223** (103 mg, 0.78 mmol, 60%, *E*/*Z* >99<1) as a colourless oil; R_f 0.15 (70:30, CH_2Cl_2—petrol); $[\alpha]_D^{23.7}$ −0.9 (*c*. 2.2 in $CDCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98 (1H, s, nosyl 3-H), 7.73-7.61 (3H, m, Ar), 7.59-7.48 (2H, m, Ar) 7.44, (2H, t, *J* 7.2, Ar), 7.31 (1H, td, *J* 7.9 and 1.7, 8-H), 7.11 (1H, dd, *J* 7.6 and 1.7, 11-H), 6.88-6.80 (4H, m, Ar), 5.74 (1H, dt, *J*, 15.9 and 5.8, 16-H), 5.38 (1H, dt, *J*, 15.9 and 6.9, 15-H), 5.33 (1H, d, *J* 10.8, 2-H_A), 4.91 (2H, s, 6-H_2), 4.83 (1H, d, 10.8, 2-H_B), 4.77 (1H, d, *J* 15.8, 20-H_A), 4.46 (1H, d, *J* 15.8, 20-H_B), 4.42 (1H, dd, *J* 12.4 and 4.3, 14-H_A), 4.35 (1H, dd, *J* 12.4 and 6.4, 14-H_B), 4.13 (1H, dq, *J* 9.9 and 5.0, 18-H), 3.80 (1H, dd, *J* 10.6 and 5.5, SiOC*H*$_A$), 3.76 (1H, dd, *J* 10.5 and 5.5, SiOC*H*$_B$), 2.49-2.30 (2H, m, 17-H_{AB}), 2.09-1.96 (2H, m, $C_8F_{17}CH_2CH_2$), 0.97 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.78-0.73 (2H, M $C_8F_{17}CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 158.3 (4-C), 151.8 (12-C), 148.3 (nosyl 2-C), 148.1 (nosyl 2-C), 140.4 (7-C), 135.1 (1-C), 134.9 (21-C), 134.5 (nosyl 1-C), 133.1, 132.2, 132.1, 132.0, 131.8, 131.2, 129.6 (16-C), 128.8, 128.6 (15-C), 128.4, 124.8, 124.1, 122.8, 120.5 (9-C), 112.7 (11-C), 68.9 (14-C), 66.0 (1'-C), 65.8 (6-C), 60.5 (18-C), 45.7 (2-C), 44.1 (20-C), 33.5 (17-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(*C*H_3)$_2$), 12.5 ((Si*C*H$(CH_3)_2$), 1.4 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2948, 2869,

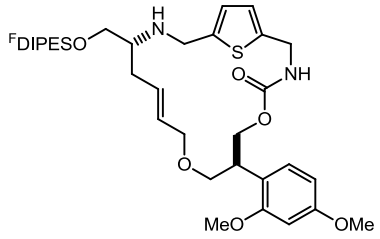
2159, 2029, 1736, 1545, 1371, 1208 and 1166; *m/z* (ES^+) 1336.2 (100%, $[M+NH_4]^+$); found 1336.2221, $C_{48}H_{47}F_{17}N_4O_{12}S_3Si$ requires *MNH*$_4$ 1336.2189

(15*E*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaen-4-one 223^{D}



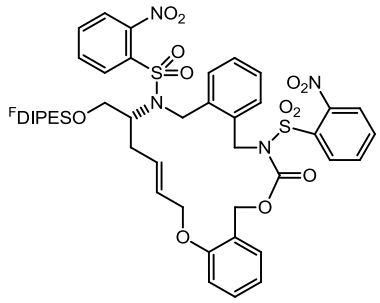
Following general procedure **N1**; thiophenol (264 mg, 2.4 mmol), sulfonamide **223** (320 mg, 0.24 mmol) and potassium carbonate (80 mg, 0.58 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **223^{D}** (190 mg, 0.20 mmol, 84%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow foam; δ_H (500 MHz; $CDCl_3$) 7.4-7.28 (2H, m, Ar), 6.94 (1H, ap t, *J* 7.4, Ar), 6.88 (1H, d, *J* 8.2, Ar), 6.70 (1H, d, *J* 3.9, Thio 3 or 4-H), 6.64 (1H, d, *J* 3.9, Thio 3 or 4-H), 5.74 (2H, s, 15-H and 16-H), 5.32 (1H, d, *J* 10.7, 6-H_A), 5.09 (1H, NH); 4.98 (1H, d, *J* 10.7, 6-H_B), 4.62-4.46 (3H, m, 2-H_{AB} and 14-H_A), 4.38 (1H, dd, *J* 15.8 and 5.4, 14-H_B), 4.04 (1H, d, *J* 14.7, 20-H_B), 3.96 (1H, d, *J* 14.7, 20-H_B), 3.60 (2H, d, *J* 5.1, SiOC*H*$_2$), 2.83-2.63 (1H, m, 18-H), 2.28-2.00 (4H, m, $C_8F_{17}CH_2CH_2$ and 17-H_{AB}), 1.05 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.9-0.83 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 158.2 (12-C), 156.9 (C=O), 144.6 (Thio 2 or 5-C), 143.1 (Thio 2 or 5-C), 132.3 (14-C), 130.8, 130.1 (15-C), 129.9, 127.9, 124.6 ,120.8 (9-C), 112.6 (11-C), 69.1 (SiO*C*H$_2$), 65.4 (14-C), 64.1 (2-C), 55.9 (18-C), 45.6 (2-C), 40.7 (20-C), 34.9 (17-C), 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(*C*H$_3$)$_2$), 12.6 (Si*C*H(CH$_3$)$_2$), 0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2945, 2159, 2029, 1716, 1206; *m/z* (ES^+) 949.2 (100%, $[M+H]^+$); found 949.2372, $C_{36}H_{41}F_{17}N_2O_4SSi$ requires *MH* 949.2358

(7*S*,11*E*,14*R*)-7-(2,4-Dimethoxyphenyl)-14-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3,15-bis[(2-nitrobenzene)sulfonyl]-5,9-dioxa-20-thia-3,15-diazabicyclo[15.2.1]icosa-1(19),11,17-trien-4-one 213



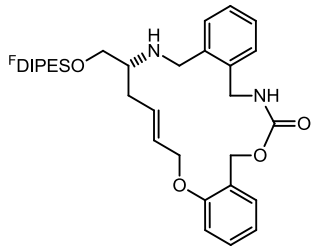
Following general procedure **RCM2**, **HG-II** (7 mg, 5 mol%), 1,4-benzoquinone (2 mg, 10 mol%) and sulfonamide **212** (300 mg, 0.2 mmol) were stirred in MTBE (100 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo*. Following general procedure **N1**, thiophenol (116 mg, 1.06 mmol), crude product (150 mg) and potassium carbonate (10 mg, 0.25 mmol) gave the amine crude product after 16 h. The crude product was purified by F-SPE and column chromatography, eluting with 80:20 petrol—EtOAc to give the amine **213** (71 mg, 0.068 mmol, 34%; 63/37 *E*/*Z*) as a pale yellow oil; R_f 0.31 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.13 (1H, m, DMB 6-H), 6.74 (d, *J* 3.4, Thio 3 or 4-H), 6.70 (1H, d, *J* 3.5, Thio 3 or 4-H), 6.66 (1H, d, *J* 3.5, Thio 3 or 4-H), 6.45-6.40 (2H, m, DMB 3 and 5-H), 5.66 (1H, dt, *J* 15.4 and 8.1, 12-H), 5.56 (1H, dt, *J* 15.4 and 5.6, 11-H), 5.52-5.45 (m, *E isomer* 11-H and 12-H), 5.04 (1H, br s, NH), 4.54-4.19 (4H, m, 2-H and 6-H), 4.11 (1H, d, *J* 14.1, 16-H), 3.91 (1H, d, *J* 14.1, 16-H), 4.02-3.87 (2H, m, 10-H), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 3.74-3.50 (5H, 7-H, 8-H and SiOCH_2), 2.76 (1H, br s, 14-H), 2.28-2.07 (3H, m, $C_8F_{17}CH_2CH_2$ and 13-H), 2.00 (1H, dt, *J* 15.3 and 8.1, 13-H), 1.06 (14H, Si(CH(CH_3)$_2$)$_2$), 0.90-0.86 (2H, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 168.4 (C=O), 159.8 (DMB 4-C), 158.2 (DMB 2-C), 129.6 (11-C), 129.1 (DMB 6-C), 2 x124.2 (Thia), 104.4 (DMB 5-C), 98.8 (DMB 3-C), 71.9 (10-C), 65.6 (6-C), 65.5 (7-C), 57.2 (14-C), 55.4 (OMe), 55.2 (OMe), 46.1 (16-C), 38.1 (7-C), 34.7 (13-C), 25.6 ($C_8F_{17}CH_2CH_2$), 17.5 (SiCH(CH_3)$_2$), 17.4 (SiCH(CH_3)$_2$), 12.4 (SiCH(CH_3)$_2$), -0.02 ($C_8F_{17}CH_2CH_2$); *Thio 1 and 4 missing*; ν_{max}/cm^{-1} (film) 2952, 2857, 1715 and 1165; *m/z* (ES$^+$) 1037.3 (100%, [M+H]$^+$); found 1037.2894, $C_{40}H_{49}F_{17}N_2O_6SSi$ requires *MH* 1037.2882

(15*E*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3,19-bis[(2-nitrobenzene)sulfonyl]-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one 244



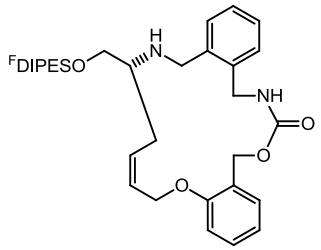
Following general procedure **L2**, **HG-II** (9.4 mg, 2 mol%), 1,4-benzoquinone (3.2 mg, 4 mol%) and sulfonamide **234** (1.0 g, 0.75 mmol) were stirred in MTBE (360 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 90:10 CH_2−petrol gave the macrocycle **244** (550 mg, 0.42 mmol, 56%; >65/<35 *E*/*Z*); R_f 0.85 (90:10, CH_2Cl_2—petrol); $[\alpha]_D^{23.7}$ 32 (c. 1, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) *minor isomer denoted where possible* 8.41-8.38 (1H, m, nosyl 3-H^Z), 8.17 (1H, d, *J* 8, nosyl 3-H), 7.72-6.91 (13H, m, nosyl 3-H. 2 × nosyl 4, 5 and 6 H, 8-H, 9-H and Ar); 6.79 (t, *J* 7.4, 11-H^Z), 6.67-6.63 (1H, m, 10-H and 11-H); 6.54 (1H, d, *J* 8.2, 10-H^Z), 5.87 (1H, dt, *J* 14.9 and 7.2, 15-H), 5.60 (1H, dt, *J* 14.9 and 5.2, 16-H), 5.58-5.51 (2H, m, 15 and 16-H^Z), 5.19-5.12 (1H, m, 6-H), 4.96-4.88 (3H, 2-H and 6-H_{AB}), 4.83 (d, *J* 11, 2-H^Z), 4.55 (1H, d, *J* 15.5, 20-H_A), 4.47 (1H, d, *J* 15.5, 20-H_B), 4.36-4.14 (3H, m, 18-H and 14-H), 3.85-3.76 (2H, m, SiOCH_2), 3.57 (dd, *J* 11.1 and 5.4, SiOC$H_A{}^Z$), 3.37 (1H, ap t, *J* 9.9, SiOC$H_B{}^Z$), 2.64 (2H, ap t, *J* 6.7, 17-H), 2.39 (2H, ap dt, *J* 16.9 and 8.9, 17-H^Z), 2.10-1.95 (2H, m, $C_8F_{17}CH_2CH_2$), 0.94 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.89 (14H, s, Si(C*H*(CH_3)$_2$)$_2{}^Z$), 0.80-0.75 (2H, m, $C_8F_{17}CH_2CH_2$), 0.75-0.68 (2H, m, $C_8F_{17}CH_2CH_2{}^Z$); δ_C (75 MHz; $CDCl_3$) 157.5 (12-C), 152.3 (nosyl 2-C^Z), 151.9 (nosyl 2-C), 148.0 (nosyl 2-C^Z), 147.9 (nosyl 2-C), 134.9 (nosyl 1-C), 134.7 (nosyl 1-C^{min}), 134.6 (nosyl 1-C), 133.7, 133.5, 133.3, 132.7, 132.0, 131.9, 131.8, 131.4, 131.2, 130.9, 129.6 (17-C), 128.5 (16-C), 128.3, 127.3, 127.2, 124.9 (17-C^Z), 124.8 (17-C^Z), 124.6, 124.4, 123.3 (nosyl 3-C), 122.8 (nosyl 3-C), 120.4 (9-C), 112.1 (11-C^Z), 111.5 (11-C), 67.6 (6-C), 66.4 (14-C), 65.2 (SiO*C*H$_2$), 64.3 (SiO*C*H$_2{}^Z$), 62.7 (18-C^Z), 60.3 (18-C), 48.8, 48.2, 46.1, 34.0 (17-C), 29.6 (17-C^Z), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(*C*H$_3$)$_2$), 12.5 (SiCH(*C*H$_3$)$_2$), 12.4 (SiCH(*C*H$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3597, 3006, 1712, 1423, 1367, 1223; *m/z* (ES$^+$) 1330.3 (100%, [M+NH$_4$]$^+$); found 1330.2669, $C_{50}H_{49}F_{17}N_4O_{12}S_2Si$ requires *MNH$_4$* 1330.2624

(15*E*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one *E*-244^{D}



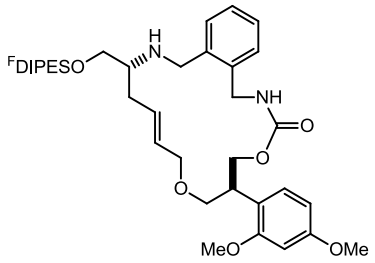
Following general procedure **N1**; thiophenol (443 mg, 4.03 mmol), sulfonamide **244** (530 mg, 0.40 mmol) and potassium carbonate (140 mg, 1.00 mmol) gave the crude product after 4 h. The crude product was purified by F-SPE and column chromatography to give the amine ***E*-244^{D}** (152 mg, 0.16 mmol, 40%) as a colourless oil; R_f 0.58 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ −1.6 (c. 1.2, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.44 (1H, br s, NH), 7.27-7.10 (6H, m, 11-H, 8-H and Ar), 6.80 (1H, ap t, *J* 7.4, 9-H), 6.75 (1H, d, *J* 8.3, 10-H), 6.10 (1H, dt, *J* 15.2 and 7.0, 16-H), 5.54 (1H, d, *J* 15.2, 15-H), 5.21 (1H, d, *J* 11.2, 6-H_A), 4.88 (1H, d, *J* 11.2, 6-H_B), 4.57 (1H, d, *J* 14.1, 2-H_A), 4.52 (1H, d, *J* 14.1, 2-H_B), 4.34 (1H, dd, *J* 13.5 and 6.3, 14-H_A), 4.29 (1H, d, *J* 13.5, 14-H_B), 3.74-3.63 (3H, m, 20-H_{AB} and SiOCH_A), 3.48 (1H, dd, *J* 10.1 and 5.2, SiOCH_B), 2.77 (1H, br s, 18-H), 2.27-2.21 (1H, m, 17-H_A), 2.18-1.96 (3H, m, $C_8F_{17}CH_2CH_2$ and 17-H_B), 0.96 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.82-0.76 (2H, m, 1'-H); δ_C (75 MHz; $CDCl_3$) 138.6, 131.7, 130.8, 130.7, 130.6, 130.2, 128.6, 128.5, 128.1, 126.7, 120.4 (9-C), 111.4 (11-C), 65.8 (6 or 14-C), 64.3 (6 or 14-C), 60.1 (18-C), 50.6 (20-C), 44.9 (2-C), 35.5 (17-C), 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 17.7 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 0.01 ($C_8F_{17}CH_2CH_2$); *12-C and C=O missing*; ν_{max}/cm^{-1} (film) 2964, 2867, 1714, 1275 and 1260; *m/z* (ES$^+$) 943.3 (100%, [M+H]$^+$); found 943.2815, $C_{38}H_{43}F_{17}N_2O_4Si$ requires *MH* 943.2793

(15*Z*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(21),7,9,11,15,22,24-heptaen-4-one *Z*-244^{D}



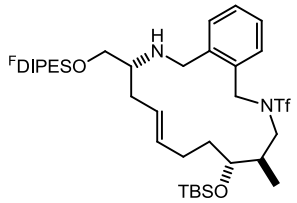
Also obtained was the geometric isomer ***Z*-244^{D}** (51 mg, 0.054 mmol; 13%) as a colourless oil; R_f 0.75 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ −16.5 (c. 2.2, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 8.23 (1H, s, NH), 7.28-7.23 (2H, m, Ar), 7.22-7.14 (3H, m, Ar), 7.11-7.07 (1H, m, Ar), 6.85-6.82 (1H, m, Ar), 6.74 (1H, d, *J* 8.2, Ar), 5.72 (1H, dt, *J* 11 and 5.9, 15-H), 5.51 (1H, dt, *J* 11 and 7.5, 16-H), 5.21 (1H, d, *J* 10.8, 6-H_A), 4.78 (1H, d, *J* 10.8, 6-H_B), 4.57 (1H, dd, *J* 13.3 and 5.1, 14-H_A), 4.47 (1H, dd, *J* 13.3 and 5.3, 14-H_B), 4.35 (1H, d, *J* 13.4, 2-H_A), 4.23 (1H, dd, *J* 13.4 and 6.2, 2-H_B), 3.73 (1H, d, *J* 11.2, 19-H_A), 3.64-3.58 (2H, m, 19-H and SiOCH_A), 3.25 (1H, ap t, *J* 6.9, SiOCH_B), 2.73-2.67 (1H, m, 18-H), 2.49-2.38 (2H, m, 17-H_{AB}), 2.05-1.91 (2H, m, $C_8F_{17}CH_2CH_2$), 0.91 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.76-0.72 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 157.6 (4-C), 157.0 (12-C), 138.9 (Ar), 137.6 (Ar), 132.9 , 132.5, 131.1, 130.7, 130.3, 128.6 (16-C), 125.8 (15-C), 125.6, 120.9, 112.8 (11-C), 65.2 (14-C), 64.3 (6-C), 63.7 (SiO*C*H_2), 59.9 (18-C), 50.4 (2-C), 46.1 (20-C), 30.2 (17-C), 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.9 (SiCH(*C*H_3)$_2$), 17.8 (SiCH(*C*H_3)$_2$), 12.6 (Si*C*H(CH$_3$)$_2$), 0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film): 2947, 2868, 1713, 1495, 1457, 1275 and 1260; *m/z* (ES$^+$) 943.3 (100%, [M+H]$^+$); found 943.3005, $C_{38}H_{43}F_{17}N_2O_4Si$ requires *MH* 943.2793

(10*E*,6*S*,13*R*)-6-(2,4-Dimethoxyphenyl)-13-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-2,3,5,6,7,9,12,13,14,15-decahydro-1H-4,8,2,14-benzodioxadiazacycloheptadecin-3-one 245^{D}



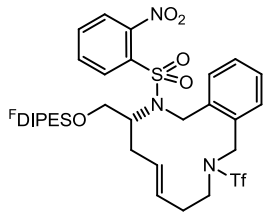
Following general procedure **RCM2**, **HG-II** (6.5 mg, 2 mol%), 1,4-benzoquinone (2.5 mg, 4 mol%) and sulfonamide **235** (750 mg, 0.52 mmol) were stirred in MTBE (260 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo*. Following general procedure **N1**, thiophenol (297 mg, 2.7 mmol), crude product (400 mg) and potassium carbonate (94 mg, 0.68 mmol) gave the amine crude product after 16 h. The crude product was purified by F-SPE and column chromatography, eluting with 80:20 petrol—EtOAc to give the amine **245^{D}** (180 mg, 0.17 mmol, 33%; >60<40 *E*/*Z*) as a pale yellow oil; R_f 0.50 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ 9.5 (c. 1.2, CH_2Cl_2); δ_H (500 MHz; C_6D_6) 7.21 (1H, dd, *J* 7.5 and 1.5, Ar), 7.16-6.96 (4H, m, Ar), 6.35 (1H, ap t, *J* 2.6, DMB 3-H), 6.32 (1H, dt, *J* 8.4 and 2.6, DMB 5-H), 6.06 (1H, dt, *J* 15.9 and 5.9, 10-H^{E}), 5.63 (1H, ddd, *J* 11, 7,2 and 5.5, 10-H^{Z}), 5.49-5.42 (2H, m, 11-H^{ZE}), 4.74-4.64 (2H, m,), 4.55-4.36 (6H, m, 15-H_{AB}, 5-H_{AB} and 1-H_{AB}), 4.09 (1H, dd, *J* 12.4 and 7.4, 5 or 7H^{E}), 3.94-3.52 (7H, m, 7-H_{AB}, 6-H, SiOC*H*$_{AB}$ and 9-H_{AB}), 3.39 (3H, s, OMe$^{E\ or\ Z}$), 3.38 (3H, s, OMe$^{E\ or\ Z}$), 3.27 (3H, s, OMe$^{E\ or\ Z}$), 3.26 (3H, s, OMe$^{E\ or\ Z}$), 2.76 (1H, qd, *J* 5.9 and 3.5, 13-H^{E}), 2.70 (1H, m, 13-H^{Z}), 2.60-2.53 (1H, m, 12-H^{Z}), 2.38-2.31 (1H, m, 12-H^{Z}), 2.26-2.16 (3H, m, $C_8F_{17}CH_2CH_2$ and 12-H_A^{E}), 2.14-2.06 (1H, m, 12-H_B^{E}), 0.98-0.93 (16H, m, Si(C*H*(C*H*$_3$)$_2$)$_2$ and $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 160.3 (DMB 2 or 4-C), 158.4 (DMB 2 or 4-C), 156.4 (C=O), 130.2, 129.4, 129.2, 121.4 (DMB 1-C), 105.0 (DMB 5-C), 99.4 (DMB 3-C), 99.3 (DMB 3-C), 72.2 (7-C), 66.6 (9-C), 66.4 (SiO*C*H$_2$), 65.3 , 60.0 (13-C), 54.9 (OMe), 54.8 (OMe), 54.7 (OMe), 50.8 (1-C), 44.3 (5-C), 38.4 (15-C^{Z}), 38.1 (15-C) , 34.6 (12-C), 29.9 (6-C), 26.2 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.4 (SiCH(*C*H$_3$)$_2$), 17.3 (SiCH(*C*H$_3$)$_2$), 12.6 (SiCH(*C*H$_3$)$_2$), -0.4 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2946, 2869, 1718, 1508, 1465, 1243, 1208; *m/z* (ES$^+$) 1031.3 (100%, [M+H]$^+$); found 1031.3294, $C_{42}H_{51}F_{17}N_2O_6Si$ requires *MH* 1031.3318

(8*E*,4*R*,5*R*,11*R*)-5-[(*Tert*-butyldimethylsilyl)oxy]-11-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-4-methyl-2-(trifluoromethane)sulfonyl-2,3,4,5,6,7,10,11,12,13-decahydro-1H-2,12-benzodiazacyclopentadecine 247^{D}



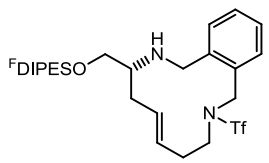
Following general procedure **RCM1**, **HG-II** (4 mg, 2 mol%), 1,4-benzoquinone (1.38 mg, 4 mol%) and sulfonamide **236** (430 mg, 0.32 mmol) were stirred in MTBE (160 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo*, column chromatography eluting with 90:10 petrol−EtOAc gave the sulfonamide as a complex mixture which was used directly in the next step. Following general procedure **N1**, thiophenol (330 mg, 3.0 mmol), sulfonamide **247** (399 mg, 0.3 mmol) and potassium carbonate (126 mg, 0.9 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE, to give the amine **247^{D}** (300 mg, 0.27 mmol, 84%; >99% purity as estimated using 500 MHz ^{1}H NMR spectroscopy, <32/>68 *E*/*Z*) as a pale yellow oil; R_f 0.53 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ −4.3 (c. 1.1, CH_2Cl_2);δ_H (500 MHz; $CDCl_3$) 7.41-7.21 (4H, m, Ar), 5.44 (1H, dt, *J* 14.9 and 7.4, 8-H^{E}), 5.38-5.27 (3H, m, 8-H^{Z}, 9-H$^{E\ and\ Z}$), 5.15-4.57 (2H, m, 1-H_{AB}), 3.93 (0.5H, d , *J* 12.8, 13-H_A^{Z}), 3.87 (0.5H, d , *J* 12.5, 13-H_A^{E}), 3.79 (0.5H, d, *J* 12.8, 13-H_B^{Z}), 3.78-3.68 (2H, m, SiOCH_2), 3.66 (0.5H, d, *J* 12.5, 13-H_B^{E}), 3.64-3.20 (2H, 3-H_{AB}), 3.06 (1H, dd, *J* 14.3 and 3.8, 5-H), 2.78-2.68 (1H, m, 11-H), 2.32-1.98 (5H, m, $C_8F_{17}CH_2CH_2$ and 10-H_A and 7-H_{AB}), 1.95-1.85 (1H, m, 10-H_B), 1.80-1.35 (3H, m, 6-H_{AB} and 4-H), 1.09 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.95-0.89 (2H, $C_8F_{17}CH_2CH_2$), 0.88-0.8 (12H, SiC(CH_3)$_3$ and Me), 0.00 (3H, SiCH_3), -0.06 (3H, SiCH_3); δ_C (75 MHz; $CDCl_3$) 138.4, 138.1, 134.0, 133.9, 133.7, 133.4, 132.0, 131.8, 131.6, 130.2, 130.0, 128.1, 128.0, 127.9, 127.7, 126.7, 124.7, 120.2 q *J* 325, 73.7, 71.8, 65.7, 65.1, 60.8, 59.6, 59.1, 52.8, 50.6, 49.9, 48.7, 47.5, 39.0, 35.9, 34.8, 34.3, 33.9, 33.8, 33.5, 32.8, 30.9, 29.9, 29.3, 29.2, 25.9, 25.7, 25.4, ν_{max}/cm^{-1} (film) 2950, 2867, 1734, 1547, 1463, 1389; *m/z* (ES^{+}) 1125.4 (100%, [M+H]$^{+}$); found 1125.3605, $C_{42}H_{60}F_{20}N_2O_4SSi_2$ requires *MH* 1125.3566

(3*R*,5*E*)-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-2-[(2-nitrobenzene)sulfonyl]-9-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecine 246



Following general procedure **RCM2**, **HG-II** (30 mg, 5 mol%), 1,4-benzoquinone (11 mg, 10 mol%) and sulfonamide **209** (1.1 g, 0.95 mmol) were stirred in MTBE (477 mL) at 55 ˚C for 6 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 70:30 petrol−EtOAc gave the macrocycle **246** (805 mg, 0.72 mmol, 76%) as a colourless oil; R_f 0.61 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ 6.5 (c. 0.9, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 8.06 (1H, d, *J* 7.7, nosyl 3-H), 7.67-7.55 (3H, m, nosyl 4,5 and 6-H and Ar), 7.32 (1H, t, *J* 7.5, Ar), 7.21 (1H, br s, Ar), 7.09 (1H, br s, Ar), 7.46 (1H, br s, Ar), 5.47 (2H, br s, 5 and 6-H), 4.83 (1H, d, *J* 14, 1-H or 10-H), 4.73 (3H, br s, 1-H or 10-H), 4.17 (1H, br s, SiOCH_A), 3.84 (1H, br s, 3-H), 3.52 (1H, br s, SiOCH_A), 3.33-3.02 (2H, m, 8-H_{AB}) 2.52 (1H, br s, 7-H_A), 2.39-2.27 (1H, br s, 4-H_A), 2.17 (1H, br s, 7-H_B), 2.02-1.88 (2H, m, $C_8F_{17}CH_2CH_2$), 1.81 (1H, br s, 4-H_B), 0.86 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.66-0.61 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) *broad peaks* 148.5 (nosyl 2-C), 134.8 (nosyl 1-C), 134.4 (6-C), 134.2 (nosyl 4-C), 132.3 (nosyl 3-C), 131.9, 130.0 (5-C), 128.8, 127.6, 124.8, 123.2, 121.0 (q, *J* 325, CF_3), 118.9, 115.7; 60.4 (3-C), 53.5 (2-C), 49.9 (10-C), 47.5 (8-C), 33.8 (4-C), 32.2 (7-C); 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.9 (SiCH(CH_3)$_2$), 12.6 (SiCH(CH$_3$)$_2$), 0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2949, 1546, 1388, 1145; *m/z* (ES$^+$) 1141.2 (100%, [M+NH$_4$]$^+$); found 1141.2204, $C_{38}H_{41}F_{20}N_3O_7S_2Si$ requires *MNH*$_4$ 1141.2174

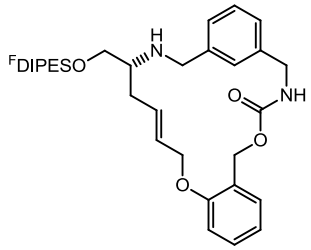
(5*E*,8*R*)-8-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-2-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecine 246^D



Following general procedure **N1**; thiophenol (616 mg, 5.6 mmol), sulfonamide **246** (630 mg, 0.56 mmol) and potassium carbonate (232 mg, 1.68 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **246^D** (430 mg,

0.20 mmol, 82%, >89% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.84 (80:20, petrol—EtOAc); δ_H (500 MHz; MeOD) 7.34-7.25 (4H, m, Ar), 5.31 (1H, ddd, *J* 15.7, 8.8 and 4.4, 6-H), 5.24 (1H, dd, *J* 15.7 and 6.4, 5-H), 5.10 (1H, d, *J* 16, 1-H_A), 4.85 (1H, d, *J* 16, 1-H_B), 4.10 (1H, d, *J* 13.7, 10-H_A), 3.75 (1H, dd, *J* 9.7 and 6.0, SiOC*H*$_A$); 3.73 (1H, d, *J* 13.7, 10-H_B), 3.67 (1H, dd, *J* 9.7 and 5.8, SiOCH_B), 3.66-3.62 (1H, m, 3-H_A), 3.49-3.42 (1H, m, 3-H_B), 2.68 (1H, dtd, *J* 10.4, 5.9 and 2.6, 8-H), 2.33-2.20 (5H, m, 7-H_A, 4-H_{AB} and $C_8F_{17}CH_2CH_2$), 1.76 (1H, ddd, *J* 13.7, 10.5 and 8.8, 7-H_B), 1.13-1.10 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.97-0.92 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 139.1 (5-C), 133.2 (6-C), 130.9, 130.5, 128.4, 127.8, 127.7, 119.5, 67.1 (SiOCH_2), 58.4 (8-C), 50.2 (1-C), 49.7 (10-C), 35.3 (7-C), 32.7 (4-C), 25.9 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 16.9 (SiCH(CH_3)$_2$), 16.99 (SiCH(CH_3)$_2$), 12.7 (SiCH(CH$_3$)$_2$), 0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3005, 2948, 2868, 1547, 1463, 1387; *m/z* (ES$^+$) 939.2 (100%, [M+H]$^+$); found 939.2137, $C_{32}H_{38}F_{20}N_2O_3SSi$ requires *MNH*$_4$ 939.2126

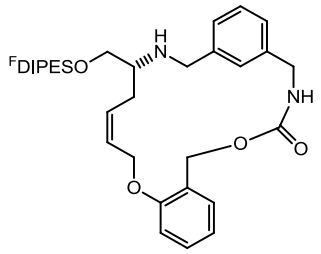
(15*E*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one *E*-115^D



Following general procedure **RCM1**, **HG-II** (5.5 mg, 2 mol%) and sulfonamide **114** (600 mg, 0.45 mmol) were stirred in MTBE (250 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo* as a complex mixture of geometric isomers and starting material **114**. Following general procedure **N1**, thiophenol (407 mg, 3.7 mmol), sulfonamide **115** (490 mg, 0.37 mmol) and potassium carbonate (128 mg, 0.93 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and column chromatography, eluting with 70:30 petrol—EtOAc to give the amine ***E*-115^D** (107 mg, 0.114 mmol, 25%) as a pale yellow oil; R_f 0.31 (70:30, petrol—EtOAc); $[\alpha]_D^{18.9}$ 6 (c. 0.9, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.35-7.10 (4H, m, Ar), 7.10-6.99 (2H, m, Ar), 6.97-6.88 (2H, m, Ar), 5.95-5.86 (1H, m, 17-H), 5.61-5.54 (1H, m, 16-H), 5.43 (1H, d, 6-H_A), 4.99-4.91 (2H, m, 6-H_B and 2-H_A); 4.76-4.63 (1H, m, 14-H_A), 4.58-4.48 (2H, m, 14-H_B and 2-H_B), 4.28 (1H, dd, *J* 15.6 and 5.6, 20-H_A), 3.83 (1H, d, *J* 12.9, 20-H_B), 3.78-3.71 (2H, m, SiOC*H*$_A$), 3.61-3.57 (1H, m, SiOC*H*$_B$), 2.80-2.69 (1H, m, 18-H), 2.40-2.23 (2H, m, 17-H_{AB}), 2.20-2.07 (2H, m, $C_8F_{17}CH_2CH_2$), 1.06

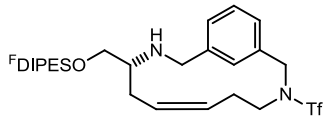
(14H, s, Si(C*H*($C*H_3$)$_2$)$_2$), 0.91-0.84 (2H, $C_8F_{17}CH_2C*H_2$); δ_C (75 MHz; $CDCl_3$) 157.9 (12-C), 157.1 (C=O) 139.7, 131.9, 131.1, 130.6, 130.2, 129.0, 128.5, 127.9, 127.2, 126.2, 125.6, 120.9, 112.5, 68.4 (14-C), 66.0 (6-C), 64.9 (SiO*C*H_2), 58.8 (18-C), 51.9 (1-C), 44.7 (20-C), 30.6 (17-C), 25.6 (t, *J* 25, $C_8F_{17}*C*H_2CH_2$), 17.8 (SiCH($*C*H_3$)$_2$), 17.7 (SiCH($*C*H_3$)$_2$), 12.6 (Si*C*H(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2*C*H_2$); ν_{max}/cm^{-1} (film) 3109, 2868, 2756, 1617, 1471 and 1345; *m/z* (ES$^+$) 943.3 (100%, [M+H]$^+$); found 943.2803, $C_{38}H_{43}F_{17}N_2O_4Si$ requires *MH* 943.2793

(15*Z*,18*R*)-18-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one *Z*-115^D



Also obtained was the geometric isomer ***Z*-115^D** (66 mg, 0.07 mmol; 16%) as a colourless oil; R_f 0.85 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ 1.8 (*c.* 2, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.35-7.30 (3H, m, Ar), 7.21 (1H, ap t, *J* 7.5, Ar), 7.10 (1H, d, *J* 7.7, Ar), 7.05 (1H, d, *J* 7.6, Ar), 6.94 (1H, ap t, *J* 7.4, Ar), 6.88 (1H, d, *J* 8, Ar), 5.88 (1H, dt, *J* 14.5 and 7, 16-H), 5.79 (1H, dt, *J* 14.5 and 4.7, 15-H), 5.18 (1H, d, *J* 10.4, 6-H_A), 5.10 (2H, d, *J* 10.4, 6-H_B and NH), 4.51 (2H, d, *J* 4.6, 14-H_{AB}), 4.47 (1H, dd, *J* 15.6 and 6.7, 2-H_A), 4.36 (1H, dd, *J* 15.6 and 6 , 2-H_B), 3.81 (2H, s, 20-H_{AB}), 3.64 (1H, dd, *J* 9.8 and 6.0, SiOC*H*$_A$), 3.58 (1H, dd, *J* 9.8 and 5.7, SiOC*H*$_B$), 2.77-2.71 (1H, m, 18-H), 2.35-2.21 (2H, m, 17-H_{AB}), 2.17-2.04 (2H, m, $C_8F_{17}C*H_2*CH_2$), 1.02 (14H, s, Si(C*H*($C*H_3$)$_2$)$_2$), 0.87-0.82 (2H, m, $C_8F_{17}CH_2C*H_2$); δ_C (75 MHz; $CDCl_3$) 157.9 (12-C), 157.2 (C=O), 139.6, 132.3, 130.8, 128.8, 127.9, 127.6, 126.3, 124.3, 120.9 (9-C), 112.1 (11-C), 68.4 (14-C), 65.4 (SiO*C*H_2), 64.5 (6-C), 57.3 (18-C), 51.3 (1-C), 44.6 (20-C), 34.5 (17-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2C*H_2$), 17.8 (SiCH($*C*H_3$)$_2$), 17.7 (SiCH($*C*H_3$)$_2$), 12.6 SiCH($*C*H_3$)$_2$, 0.3 ($C_8F_{17}CH_2*C*H_2$); ν_{max}/cm^{-1} (film) ; *m/z* (ES$^+$) 943.3 (100%, [M+H]$^+$); found 943.2820, $C_{38}H_{43}F_{17}N_2O_4Si$ requires *MH* 943.2793

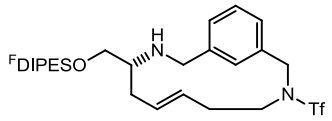
(6*Z*,9*R*)-9-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(16),6,12,14-tetraene *Z*-249^{D}



Following general procedure **RCM2**, **HG-II** (10 mg, 2 mol%), 1,4-benzoquinone (3.6 mg, 4 mol%) and sulfonamide **238** (998 mg, 0.86 mmol) were stirred in MTBE (400 mL) at 55 ˚C for 16 h. After the workup procedure the crude product was concentrated *in vacuo* and column chromatography gave the sulfonamide (460 mg) as a mixture of geometric isomers. Following general procedure **N1**, thiophenol (429 mg, 3.9 mmol), sulfonamide **249** (440 mg, 0.39 mmol) and potassium carbonate (162 mg, 1.17 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and column chromatography, eluting with 95:5 petrol—EtOAc to give the amine ***Z*-249^{D}** (100 mg, 0.106 mmol, 12%) as a pale yellow oil; R_f 0.1 (90:10, petrol—EtOAc); $[\alpha]_D^{23.7}$ 14.1 (c. 1.2, CH_2Cl_2); δ_H (500 MHz; C_6D_6) *Exists as atropisomers* 7.53 (1H, s, Ar^{major}), 7.34 (1H, s, Ar^{minor}), 6.99-6.86 (2H, m, Ar), 6.76-6.71 (1H, m, Ar), 4.71 (1H, dt, *J* 13.9 and 6.5, 7-H^{major}), 4.59 (1H, dt, *J* 13.9 and 6.4, 6-H^{major} and 7-H^{minor}), 4.33 (1H, dt, *J* 14.8 and 6.9, ^{minor}), 4.22 (1H, br s, 2-H_A), 3.90 (1H, br s, 2-H_B), 3.79 (1H, d, *J* 14.5, 11-H^{major}), 3.68 (1H, d, *J* 14.5, 11-H^{minor}), 3.50 (1H, dd, *J* 9.7 and 5.7, SiOCH_A^{major}), 3.37 (1H, dd, *J* 9.7 and 6.2, SiOCH_B^{major}), 3.34 (1H, d, *J* 14.5, 11-H^{major}), 3.28 (1H, dd, *J* 10.4 and 4.8, SiOCH_A^{minor}), 3.21 (1H, br s, 4-H_A), 3.15 (1H, d, *J* 14.5, 11-H^{minor}), 3.10 (1H, dd, *J* 10.4 and 6.1, SiOCH_B^{minor}), 2.85 (1H, br s, 4-H_B), 2.45-2.38 (1H, m, 9-H^{minor}); 2.33-2.14 (2H, m, 9-H^{major} and $C_8F_{17}CH_2CH_2$), 2.02-1.95 (1H, m, 8-H_A), 1.95-1.87 (1H, m, 5-H_A), 1.87-1.79 (1H, m, 5-H_A), 1.78-1.63 (1H, m, 5-H_B), 1.61-1.46 (1H, m, 8-H_B and 5-H_B), 1.02-0.81 (14H, m, Si(C*H*(CH_3)$_2$)$_2$); δ_C (126 MHz; C_6D_6) 142.8, 135.8, 135.6, 131.6, 131.1, 130.9, 130.7, 128.3; 127.7, 127.6, 126.3, 122.5, 119.9, 105.2, 92.2, 92.1, 67.5, 65.4, 59.9, 59.5, 54.5, 52.6, 52.5, 50.7, 50.6, 38.5, 35.8, 35.7, 32.6, 32.5, 31.4, 25.9; 17.4, 12.6, 12.4, 0.3; ν_{max}/cm^{-1} (film) 2945, 2869, 1463, 1391, 1226, 1147; *m/z* (ES$^+$) 939.2 (100%, [M+H]$^+$); found 939.2103, $C_{32}H_{38}F_{20}N_2O_3SSi$ requires *MH* 939.2126

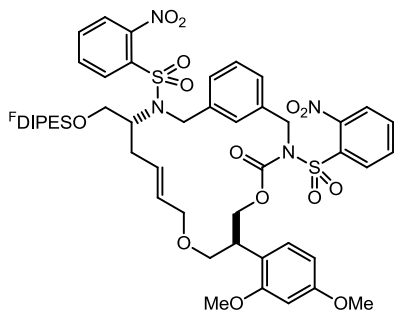
Full ^{13}C assignment was not possible due to atropisomers

(6*E*,9*R*)-9-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(16),6,12,14-tetraene *E*-249^{D}



Also obtained was the geometric isomer ***E*-249^{D}** (173 mg, 0.184 mmol; 21%) as a colourless oil; R_f 0.25 (90:10, petrol—EtOAc); $[\alpha]_D^{23.7}$ 3.2 (c. 1.1, CH_2Cl_2); δ_H (500 MHz; C_6D_6; 343 K) 7.14-7.09 (1H, m, Ar), 7.06-6.99 (3H, m, Ar), 5.24 (1H, ddd, *J* 17.3, 9.3 and 6.7, 7-H), 5.06 (1H, ddd, *J* 17.3, 10.8 and 8.6, 6-H), 4.16 (2H, br s, 2-H), 3.86 (1H, d , *J* 14.1, 11-H_A), 3.54 (1H, d, *J* 14.1, 11-H_B), 3.53 (1H, dd , *J* 9.7 and 4.4, SiOCH_A), 3.43 (1H, dd, *J* 9.7 and 6.3, SiOCH_B), 3.22 (1H, br s, 4-H_A), 2.59 (1H, br s, 4-H_B), 2.32-2.19 (3H, m, $C_8F_{17}CH_2CH_2$ and 9-H), 1.84-1.72 (2H, m, 8-H_A and 5-H_A), 1.66-1.56 (1H, m, 5-H_B), 1.56-1.44 (1H, m, 8-H_B), 0.97-0.84 (16H, m, $C_8F_{17}CH_2CH_2$ and Si(C*H*(CH_3)$_2$)$_2$); δ_C (126 MHz; C_6D_6; 343 K) 134.8 (7-C), 130.2, 129.7 (6-C), 128.9, 128.4, 126.8, 65.7 (SiO*C*H_2), 59.7 (9-C), 53.8 (2-C), 52.7 (4-C), 48.9 (11-C), 38.5 (5-C), 31.4 (8-C), 29.8 (7-C), 27.4, 26.0 (t, *J* 24.4, $C_8F_{17}CH_2CH_2$), 17.4 (SiCH(*C*H_3)$_2$), 17.3 (SiCH(*C*H_3)$_2$), 12.6 (Si*C*H(CH_3)$_2$), 0.4 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2949, 2868, 1462, 1388, 1275, 1260, 760; *m/z* (ES$^+$) 939.2 (100%, [M+H]$^+$); found 939.2121, $C_{32}H_{38}F_{20}N_2O_3SSi$ requires *MH* 939.2126

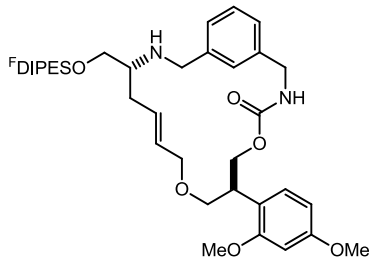
(11*E*)-7-(2,4-Dimethoxyphenyl)-14-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-3,15-bis[(2-nitrobenzene)sulfonyl]-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(20),11,17(21),18-tetraen-4-one 248



Following general procedure **RCM2**, **HG-II** (0.8 mg, 2 mol%), 1,4-benzoquinone (1.6 mg, 4 mol%) and sulfonamide **237** (540 mg, 0.37 mmol) were stirred in MTBE (185 mL) at 55 ˚C for 24 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 70:30 petrol—EtOAc gave the macrocycle **248** (295 mg, 0.21 mmol, 56%; 60/40 *E*/*Z*) as a colourless oil; R_f 0.17 (70:30, petrol—

EtOAc); $[\alpha]_D^{23.7}$ 22.8 (c. 0.9, CH_2Cl_2); δ_H (500 MHz; C_6D_6; 343 K) 8.19 (0.5H, dd, *J* 8.0 and 1.4, nosyl 3-H^Z), 8.11 (0.5H, dd, *J* 8.0 and 1.4, nosyl 3-H^E), 7.7-6.60 (11H, m, 2 × nosyl 4-H, 5-H and 6-H, and Ar), 6.39-6.21 (3H, m, DMB 3-, 5- and 6-H), 5.68 (1H, dt, *J* 14.6 and 7.0, 12-H^E), 5.55-5.46 (1H, m, 11-H^E, 12-H^Z and 11-H^Z), 5.10-4.96 (2H, m, 16-H_{AB}), 4.75-4.57 (2H, m, 2-H_{AB}), 4.55-4.45 (1H, 6-H_A), 4.37-4.24 (2H, 14-H and 6-H_B), 3.90-3.75 (3H, 10-H_2 and 7-H), 3.60-3.39 (4H, SiOCH_2 and 8-H_{AB}), 3.36 (3H, OMe), 3.19 (3H, OMe), 2.71-2.38 (2H, 13-H_{AB}), 2.35-2.22 (2H, $C_8F_{17}CH_2CH_2$), 1.07-0.78 (16H, Si(CH(CH_3)$_2$)$_2$ and $C_8F_{17}CH_2CH_2$); δ_C (125 MHz; C_6D_6; 343 K) 160.1, 160.0, 157.9, 157.8, 151.5, 151.5, 148.0, 147.8, 137.9, 137.5, 137.2, 134.4, 134.1, 134.0, 133.3, 133.2, 132.8, 132.7, 132.3, 132.3, 130.5, 130.4, 128.8, 128.7, 128.4, 128.1, 123.5, 123.4, 119.8 (DMB 1-C), 119.4 (DMB 1-C), 104.5 (DMB 5-C), 104.4 (DMB 5-C), 98.8 (DMB 3-C), 70.9 (10-C), 69.4 (10-C), 69.1 (8-C), 67.8 (8-C), 67.0 (6-C), 66.4 (6-C), 64.6 (SiOCH_2), 64.3 (SiOCH_2), 60.1 (13-C), 59.9 (13-C), 54.4 (2 × OMe), 50.8 (2-C), 50.7 (2-C), 49.8 (16-C), 48.7 (16-C), 37.9 (7-C), 37.6 (7-C), 33.7 (13-C), 29.6 (13-C), 25.6 ($C_8F_{17}CH_2CH_2$), 17.1 (SiCH(CH_3)$_2$), 12.1 (SiCH(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3006, 2990, 2318, 1737, 1588, 1545, 1463, 1370; *m/z* (ES$^+$) 1418.3 (100%, $[M+NH_4]^+$); found 1418.3110, $C_{54}H_{53}F_{17}N_4O_{14}S_2Si$ requires *MNH*$_4$ 1418.3149

(7*S*,11*E*,14*R*)-7-(2,4-Dimethoxyphenyl)-14-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(21),11,17,19-tetraen-4-one 248

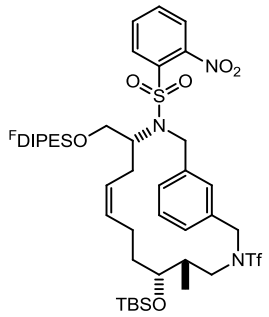


Following general procedure **N1**; thiophenol (231 mg, 2.1 mmol), sulfonamide **255** (298 mg, 0.212 mmol) and potassium carbonate (58 mg, 0.42 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **248** (198 mg, 0.19 mmol, 91%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy; 60/40 *E*/*Z*) as a pale yellow foam; R_f 0.37 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.60-5.56 (1H, s, Ar), 7.35-7.14 (3H, m, Ar), 6.90-6.83 (1H, m, Ar), 6.48-6.43 (2H, m, Ar), 5.86-5.77 (1H, m, 12-H^Z and 11-H^E), 5.69 (0.5H, dt, *J* 15.6 and 4.7, 11-H^Z), 5.53 (0.5H, dd, *J* 17.5 and 8.3, 12-H^E); 4.80-3.73 (11H, m, 2-H_{AB}, 6-H_{AB}, 8-H_{AB}, 10-H_{AB} and 16-H_{AB}), 3.7-3.64 (1H, m, SiOCH_A), 3.64-3.57 (1H, m, SiOCH_B), 3.48 (3H, s, OMe), 3.47 (3H, s, OMe), 2.83-2.73 (1H, m, 14-H), 2.4-2.15 (4H, 13-H_{AB}, $C_8F_{17}CH_2CH_2$), 1.06-0.93 (16H, m, $C_8F_{17}CH_2CH_2$ and Si(CH(CH_3)$_2$)$_2$); δ_C (75 MHz; $CDCl_3$) 160.6, 158.8,

140.7, 140.5, 130.5 (11 or 12-C), 130.4 (11 or 12-C), 129.8 (11 or 12-C), 129.7 (11 or 12-C), 127.5, 127.1, 127.0, 126.7, 121.8, 121.6, 105.3, 105.2, 99.6 (DMB 3-C), 71.9 (10-C), 67.5 (8-C), 66.5 (6-C), 65.6 (SiO*C*H_2), 59.1 (14-C^E), 58.5 (14-C), 55.2 (OMe), 55.1 (OMe), 52.1 , 52.0 , 45.1 (16-C), 38.9 (7-C), 34.9 (13-C), 26.3 (t, *J* 24.8, C_8F_{17}*C*H_2CH$_2$), 17.6 (SiCH(*C*H_3)$_2$), 17.6 (SiCH(*C*H_3)$_2$), 12.8 (Si*C*H(CH$_3$)$_2$), 0.7 ($C_8F_{17}CH_2$*C*H_2); ν_{max}/cm^{-1} (film) 3331, 2943, 2868, 1712, 1614, 1546, 1464; *m/z* (ES$^+$) 1031.3 (100%, [M+H]$^+$); found 1031.3302, $C_{42}H_{51}F_{17}N_2O_6Si$ requires *MH* 1031.3318

Full ^{13}C assignment was not possible due to a mixture of stereoisomers

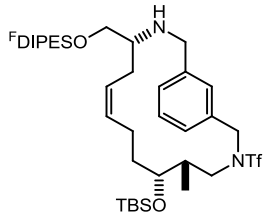
(4*R*,6*E*,10*R*,11*R*)-10-[(*Tert*-butyldimethylsilyl)oxy]-4-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-11-methyl-3-[(2-nitrobenzene)sulfonyl]-13-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(19),6,15,17-tetraene 250



Following general procedure **RCM2**, **HG-II** (7.5 mg, 2 mol%), 1,4-benzoquinone (2.7 mg, 4 mol%) and sulfonamide **239** (860 mg, 0.64 mmol) were stirred in MTBE (320 mL) at 55 ˚C for 4 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 90:10 petrol—EtOAc gave the macrocycle **250** (650 mg, 0.50 mmol, 78%, <12/>88 *E*/*Z*) as a colourless oil; R_f 0.24 (90:10, petrol—EtOAc); $[\alpha]_D^{23.7}$ 16 (c. 0.5, CH_2Cl_2); δ_H (500 MHz; C_6D_6; 343 K) 7.77 (1H, dd, *J* 7.9 and 1.4, nosyl 3-H), 7.68 (dd, *J* 8.1 and 1.4, nosyl 3-H^E), 7.37 (1H, d , *J* 7.9, Ar), 7.20-7.09 (1H, m, Ar), 6.99 (1H, d , *J* 7.7, Ar), 6.93 (1H, dd, *J* 7.9 and 1.3, Ar), 6.87 (dd, *J* 7.8 and 1.4, Ar^E), 6.81 (1H, td, *J* 7.7 and 1.4, Ns), 6.78 (1H, m, Ar^E), 6.74 (1H, td, *J* 7.4 and 1.4, Ns), 5.33 (1H, td, *J* 10.1 and 5.2, 6-H), 5.20 (1H, td, *J* 10.1 and 5.7, 7-H), 5.17-5.15 (m, 7-H^E), 5.00 (1H, d, *J* 16.3, 1-H), 4.45 (1H, br s, 14-H), 4.35 (1H, d, *J* 16.4, 1-H), 4.20 (1H, ddt, *J* 11.4, 8.2 and 4.2, 4-H), 3.82 (1H, br s, 14-H), 3.77-3.60 (3H, SiOCH_{AB} and 11-H), 3.27-3.22 (1H, m, 10-H), 2.84 (1H, d, *J* 14.1, 12-H), 2.28-2.08 (3H, m, 5-H and $C_8F_{17}C$*H*$_2$CH$_2$), 1.97 (1H, m, *J* 14.5 and 10.0, 5-H), 1.61-1.50 (1H, m, 11-H), 1.44-1.22 (4H, m, 8-H and 9-H), 0.98-0.80 (28H, SiC(CH_3)$_3$, Si(C*H*(CH_3)$_2$)$_2$, $C_8F_{17}CH_2C$*H*$_2$ and Me); δ_C (125 MHz; C_6D_6; 343 K) 148.3 (nosyl 2-C), 138.1 (nosyl 1-

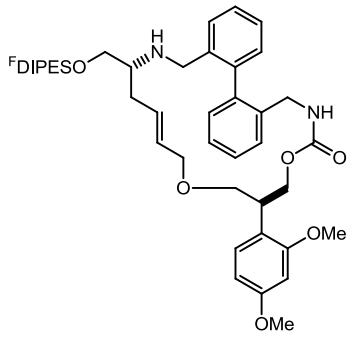
C), 134.2 (nosyl 4-C), 132.5 (nosyl 5-C), 131.5 (Ar), 131.0 (7-C), 130.7 (nosyl 6-C), 130.5 (Ar), 126.4 (6-C), 123.7 (nosyl 3-C); 71.4 (10-C), 62.7 (CH_2OSi), 60.1 (4-C), 53.8 (12-C), 48.6 (2-C), 34.1 (8-C), 33.5 (5-C), 31.2 (9-C), 25.4 ($SiC(CH_3)_3$), 22.5 (11-H), 17.7 ($SiCH(CH_3)_2$), 16.9 ($SiCH(CH_3)_2$), 12.0 ($SiCH(CH_3)_2$), 9.3 (Me), 0.00 ($C_8F_{17}CH_2CH_2$), -4.5 ($SiCH_3$), -5.3 ($SiCH_3$); *CF_3 missing*; ν_{max}/cm^{-1} (film) 2952, 2867, 1547, 1463, 1440, 1388 and 1373; *m/z* (ES^+) 1327.4 (100%, $[M+NH_4]^+$); found 1327.3558, $C_{48}H_{63}F_{20}N_3O_8S_2Si_2$ requires *MNH_4* 1327.3614

(5*R*,6*R*,9*E*,12*R*)-6-[(*Tert*-butyldimethylsilyl)oxy]-12-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-5-methyl-3-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(19),9,15,17-tetraene 250^D



Following general procedure **N1**; thiophenol (251 mg, 2.29 mmol), sulfonamide **250** (600 mg, 0.46 mmol) and potassium carbonate (126 mg, 0.91 mmol) gave the crude product after 2 h. The crude product was purified by F-SPE to give the amine **250^D** (450 mg, 0.40 mmol, 87%, >93% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow foam; R_f: 0.81 (60:40, petrol—EtOAc); δ_H (500 MHZ; C_6D_6) 7.23-7.09 (4H, m, Ar), 5.52 (dt, *J* 15.6 and 6.8, 10-H^{trans} >7%), 5.38 (1H, dt, *J* 11.1 and 8.4, 10-H^{cis}), 5.31 (1H, dt, *J* 11.1 and 6.1, 9-H^{cis}), 5.25 (dt, *J* 15.6 and 6.1, 9-H^{trans}, >7%), 4.47 (1H, br s, 2-H_A), 4.11 (1H, br s, 2-H_B), 3.85 (1H, d , *J* 14, 14-H_A), 3.63-3.58 (3H, m, $CH_{AB}OSi$ and 4-H_A), 3.58 (1H, d , *J* 14, 14-H_B), 3.36 (1H, br s, 6-H), 3.02 (1H, br d, *J* 11.2, 4-H_B), 2.62 (1H, ap p, *J* 5.9, 12-H), 2.35-2.15 (3H, m, $C_8F_{17}CH_2CH_2$ and 11-H_A), 2.01 (1H, dt, *J* 13.9 and 6.8, 11-H_B), 1.76-1.70 (2H, m, 8-H_{AB}), 1.59 (1H, br s, 5-H), 1.35-1.48 (2H, m, 7-H_{AB}), 1.06 (14H, s, $Si(CH(CH_3)_2)_2$), 0.9-0.83 (9H, m, $SiC(CH_3)_3$), 0.79 (3H, d, *J* 6.8, Me), 0.08-0.11 (6H, m, 2 × $SiCH_3$); δ_C (126 MHz; C_6D_6) 135.3 (10-C), 132.1, 129.2, 128.5 (9-C), 127.2, 126.5, 72.9 (6-C), 65.9 ($SiOCH_2$), 59.3 (12-C), 53.7 (2-C), 53.2 (4-C), 51.6 (14-C), 34.9 (8-C), 34.7 (11-C), 30.2 (5-C), 29.9 (7-C), 25.8 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 23.1 ($SiC(CH_3)_3$), 19.9 ($SiC(CH_3)_3$), 18.1 ($SiCH(CH_3)_2$), 12.6 (Me), -4.2 ($SiCH_3$), -4.8 ($SiCH_3$); ν_{max}/cm^{-1} (film) 3055, 2988, 2306, 1603, 1550, 1422, 1388, 1264 and 1152; *m/z* (ES^+) 1225.4 (100%, $[M+H]^+$); found 1125.3563, $C_{42}H_{60}F_{20}N_2O_4SSi_2$ requires *MH* 1125.3566

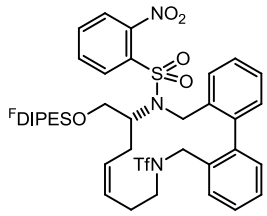
(13*S*,17*E*,20*R*)-13-(2,4-Dimethoxyphenyl)-20-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-11,15-dioxa-9,21-diazatricyclo[21.4.0.0^{2,7}]heptacosa-1(27),2,4,6,17,23,25-heptaen-10-one 251^{D}



Following general procedure **RCM1**, **HG-II** (6.56 mg, 2 mol%), 1,4-benzoquinone (2.2 mg, 4 mol%) and sulfonamide **240** (810 mg, 0.52 mmol) were stirred in MTBE (208 mL) at 55 ˚C for 5 h. After the workup procedure the crude product was concentrated *in vacuo* and column chromatography eluting with 80:20 → 70:30 petrol—EtOAc gave the sulfonamide (475 mg) as a complex mixture. Following general procedure **N1**, thiophenol (286 mg, 7.6 mmol), sulfonamide **251** (400 mg, 0.26 mmol) and potassium carbonate (91 mg, 0.66 mmol) gave the crude product after 16 h. The crude product was purified by column chromatography, eluting with 80:20 petrol—EtOAc to give the amine **251^{D}** (93 mg, 0.084 mmol, 16%) as a pale yellow oil; R_f 0.11 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ 3.2 (c. 1.1, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.42-7.38 (1H, m, BiPh), 7.37-7.28 (4H, m, BiPh), 7.20-7.10 (3H, m, BiPh), 6.95 (1H, d , *J* 8.3, DMB 6-H), 6.52-6.41 (1H, m, DMB 3-H), 6.40 (1H, dd, *J* 8.3 and 2.5, DMB 5-H), 5.67 (1H, dt, *J* 15.4 and 6.6, 17-H), 5.58 (1H, dt, *J* 15.4 and 6.8, 18-H), 5.55-5.44 (m, 17 and 18-H^{cis}), 4.36 (1H, dd, *J* 13.7 and 3.7, 12-H_A), 4.06 (1H, dd, *J* 13.7 and 4.4, 12-H_B), 4.03-3.98 (1H, m, 16-H_A), 3.92 (1H, dd, *J* 13.8 and 5.3, 16-H_B), 3.88-3.84 (2H, m, 14-H_{AB}), 3.79 (3H, s, OMe), 3.77 (3H, s, OMe), 3.68-3.52 (4H, m, 22-H_{AB} and 8-H_{AB}), 3.48-3.39 (1H, m, 13-H), 3.14 (2H, br s, $CH_{AB}OSi$), 2.57 (1H, br s, 20-H), 2.38 (1H, br s, 19-H_A), 2.20 (1H, brs, 19-H_B), 2.14-2.03 (2H, m, $C_8F_{17}CH_2CH_2$), 1.00 (14H, s, $Si(CH(CH_3)_2)_2$), 0.88-0.83 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 160.0 (DMB 4-C^{trans}), 159.9 (DMB 4-C^{cis}), 158.6 (DMB 2-C^{trans}), 158.5 (DMB 2-C^{cis}), 156.6 (CO), 141.2, 140.8, 136.8, 136.2, 131.4, 130.6, 130.1, 130.0, 129.8, 129.7, 129.3, 129.2, 128.9, 128.2, 128.2, 128.1, 127.9, 127.7, 127.4, 120.5, 120.2, 104.6, 104.5, 98.9, 98.8, 69.5 , 67.2 , 64.4, 64.3 , 59.3 (20-C), 55.6 (OMe), 55.5 (OMe), 50.7, 45.0, 37.1, 33.1, 32.3, 30.0, 29.9, 29.7, 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$) 24.2, 23.0, 17.8 ($SiCH(CH_3)_2$), 17.7 ($SiCH(CH_3)_2$), 12.6 ($SiCH(CH_3)_2$), 12.5 ($SiCH(CH_3)_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3005, 2946, 2868, 1712, 1614, 1587, 1543, 1508, 1465, 1274 and 1260; *m/z* (ES$^+$) 1107.4 (100%, [M+H]$^+$); found 1107.3655, $C_{48}H_{56}F_{17}N_2O_6Si$ requires *MH* 1107.3631

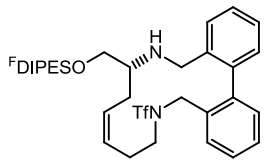
Full ^{13}C assignment was not possible due to a mix of rotamers and geometric isomers

(12*Z*)-10-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-9-[(2-nitrobenzene)sulfonyl]-16-(trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(18),2,4,6,12,19,21-heptaene 252^{D}



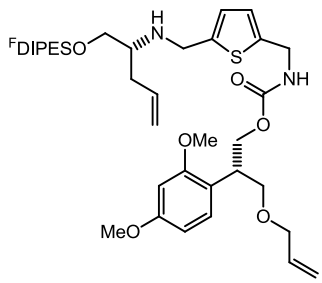
Following general procedure **RCM2**, **HG-II** (6.0 mg, 2 mol%), 1,4-benzoquinone (2.1 mg, 4 mol%) and sulfonamide **241** (611 mg, 0.48 mmol) were stirred in MTBE (192 mL) at 55 ˚C for 4 h. After the workup procedure the crude product was concentrated *in vacuo*; column chromatography, eluting with 90:10→80:20 petrol−EtOAc gave the macrocycle **252^{D}** (220 mg, 0.18 mmol, 38%) as a colourless oil; R_f 0.11 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ 6.9 (c. 1, CH_2Cl_2); δ_H (500 MHz; DMSO-*d6*; 343 K) 8.03 (1H, dd, *J* 7.9 and 1.3, nosyl 3-H), 7.94 (1H, d , *J* 8.4, nosyl 6-H), 7.92-7.85 (2H, m, nosyl 5-H), 7.82-7.79 (1H, m, Ar), 7.58-7.52 (2H, m, nosyl 4-H and Ar), 7.46-7.40 (2H, m, Ar), 7.36 (1H, td, *J* 7.5 and 1.4, Ar), 7.29 (1H, dd, *J* 7.7 and 1.4, Ar), 7.27-7.25 (1H, m, Ar), 5.34 (1H, dd, *J* 10.3 and 5.1, 12-H), 5.32-5.25 (1H, m, 13-H), 5.11 (1H, d, *J* 16.7, 8-H_A), 4.91 (1H, d, *J* 16.5, 17-H_A), 4.21 (1H, d, *J* 16.7, 8-H_B), 4.10 (1H, d, *J* 16.5, 17-H_B), 4.02-3.95 (1H, m, 10-H), 3.25 (1H, dd, *J* 10.4 and 6.0, CH_AOSi), 3.18 (1H, dd, *J* 10.4 and 7.6, CH_BOSi), 3.18-3.13 (1H, m, 15-H_A), 3.05-2.98 (1H, m, 15-H_B), 2.22-2.06 (2H, m, $C_8F_{17}CH_2CH_2$), 2.06-1.89 (2H, m, 14-H_{AB}), 1.79-1.64 (2H, m, 11-H_{AB}), 0.96 (14H, s, $Si(CH(CH_3)_2)_2$), 0.77-0.72 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (125 MHz; DMSO-*d6*; 343 K) 147.2 (nosyl 2-C), 137.2 (nosyl 1-C), 136.2 (nosyl 5-C), 134.3 (nosyl 4-C), 134.1, 131.8, 131.7, 131.4, 131.3, 131.1, 130.6, 129.8 (nosyl 6-C), 129.2 (12-C), 128.5, 128.0, 127.7, 127.2, 126.9, 126.5, 126.4 (13-C), 124.8 (nosyl 3-C), 123.9, 64.2 (CH_2OSi), 58.1 (10-C), 49.5 (8-C), 47.8 (15-C), 43.6 (17-C), 27.3 (14-C), 24.7 ($C_8F_{17}CH_2CH_2$), 16.5 ($SiCH(CH_3)_2$), 11.3 ($SiCH(CH_3)_2$), -1.01 ($C_8F_{17}CH_2CH_2$); *CF_3 missing*; ν_{max}/cm^{-1} (film) 2926, 2870, 1547, 1390, 1202; *m/z* (ES^+) 1222.2 (100%, $[M+Na]^+$); found 1222.2096, $C_{44}H_{45}F_{20}N_3O_7S_2Si$ requires *MNa* 1222.2041

(12*Z*,15*R*)-15-({[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}methyl)-9-(trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(22),2,4,6,12,18,20-heptaene 252



Following general procedure **N2**; thiophenol (93 mg, 0.85 mmol), sulfonamide **252**^{D} (210 mg, 0.169 mmol) and potassium carbonate (46 mg, 0.34 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **252** (123 mg, 0.12 mmol, 76%, >93% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.41 (90:10, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$; 323 K) 7.71 (1H, d, *J* 7.8, Ar), 7.57 (1H, dd, *J* 7.7 and 1.2, Ar), 7.44 (1H, td, *J* 7.6 and 1.4, Ar), 7.37 (1H, td, *J* 7.6 and 1.5, Ar), 7.33 (1H, td, *J* 7.5 and 1.3, Ar), 7.28 (1H, td, *J* 7.5 and 1.3, Ar), 7.15 (1H, dd, *J* 7.7 and 1.3, Ar), 7.02 (1H, dd, *J* 7.5 and 1.3, Ar), 5.28 (1H, dd, *J* 10.9 and 7.7, 13-H), 5.23 (1H, dd, *J* 10.9 and 6.3, 12-H), 4.75 (1H, d, *J* 16.1, 8-H_A), 4.05 (1H, d, *J* 16.1, 8-H_B), 3.70 (1H, d, *J* 13.2, 17-H_A), 3.62 (1H, d, *J* 13.2, 17-H_B), 3.59 (1H, dd, *J* 10.0 and 5.9, CH_AOSi), 3.56 (1H, dd, *J* 10.0 and 7.4, CH_BOSi), 3.37 (1H, ddd, *J* 15.3, 11.6 and 4.9, 10-H_A), 2.93 (1H, ddd, *J* 15.3, 10.9, and 6.2, 10-H_B), 2.65-2.61 (1H, m, 15-H), 2.20-1.99 (4H, m, $C_8F_{17}CH_2CH_2$ and 11-H), 1.98-1.86 (2H, m, 14-H), 1.06 (14H, s, Si(C*H*(CH_3)$_2$)$_2$); δ_C (125 MHz; $CDCl_3$; 323 K) *Exists as atropisomers* 139.7, 138.4, 138.2, 133.4, 130.5, 130.1, 129.5, 129.2, 128.6, 128.2, 128.0, 127.7 (12 or 13-C), 127.4 (12 or 13-C), 127.2, 126.6, 120.4 (q, *J* 325, CF_3), 65.3 (CH_2OSi), 61.2 (15-C), 51.2 (8-C), 51.0 (10-C), 50.9 (17-C); 28.2 (11-C), 28.1 (14-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.4 (SiCH(CH_3)$_2$), 12.5 (SiCH(CH_3)$_2$), 12.4 (SiCH(CH_3)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3058, 3009, 2946, 2868, 1461, 1441, 1387, 1274, 1265 and 1227; *m/z* (ES$^+$) 1015.2 (100%, [M+H]$^+$); found 1015.2460, $C_{38}H_{42}F_{20}N_2O_3SSi$ requires *MH* 1015.2439

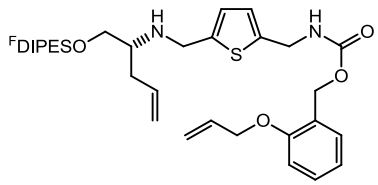
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[5-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)thiophen-2-yl]methyl}carbamate 275



Following general procedure **N1**; thiophenol (68 mg, 0.62 mmol), sulfonamide **212** (90 mg, 0.062 mmol) and potassium carbonate (20 mg, 0.15 mmol) gave the crude product

after 2 h. The crude product was purified by F-SPE to give the amine **275** (58 mg, 0.054 mmol, 87%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow foam; R_f 0.46 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.10 (1H, d, *J* 8.4, DMB), 6.77-6.68 (2H, m, Thio 3 and 4-H), 6.44 (1H, s, DMB), 6.43 (1H, s, DMB), 5.86 (1H, ddt, *J* 16.4, 10.9 and 5.4, propenyl 2-H), 5.76 (1H, ddt, *J* 17.5, 10.6, and 7.8, 4-H), 5.22 (1H, dd , *J* 17.5 and 1.8, propenyl 3-H_A), 5.13 (1H, dd , *J* 10.6 and 1.7, propenyl 3-H_B), 5.07 (1H, d, *J* 16.4, 5-H_A), 5.06 (1H, d, *J* 10.9, 5-H_B), 4.46-4.31 (4H, m, PhC*H*$_2$N(CO) and propyl 1-H_{AB}), 3.98-3.92 (4H, m, propenyl 1-H_2 and NHC*H*$_2$Ph), 3.78 (6H, s, 2 x OMe), 3.66-3.58 (5H, 1-H, propyl 3-H_{AB} and 2-H), 2.75 (1H, p, *J* 5.9, 2-H), 2.28-2.18 (2H, 3-H_{AB}), 2.17-2.05 (2H, $C_8F_{17}CH_2CH_2$), 1.04 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.88-0.83 (2H, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 159.8 (DMB 4-C), 158.5 (DMB 2-C), 144.5 (Thio 2-C), 140.3 (Thio 5-C), 135.3 (propenyl 2-C), 135.1 (DMB 6-C), 129.1 (4-C); 125.3 (DMB 1-C), 124.4 (Thio 4-C), 120.3 (Thio 3-C), 117.4 (propenyl 3-C), 116.6 (5-C), 104.3 (DMB 5-C), 98.8 (DMB 3-C), 77.3 (propenyl 1-C), 72.0 (1-C), 70.6 (propyl 3-C), 2 × 65.3 (NHCH$_2$Ph and PhCH$_2$N(CO)), 57.9 (2-C), 55.5 (OMe), 55.4 (OMe), 46.4 (propyl 1-C), 38.4 (propyl 2-C), 35.9 (3-C), 25.6 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.6 (SiCH(*C*H$_3$)$_2$), 12.5 (Si*C*H(CH$_3$)$_2$), 0.06 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3325, 2914, 2746, 1927, 1720, 1661, 1455, 1275; *m/z* (ES$^+$) 1065.3 (100%, [M+H]$^+$); found 1065.3109, $C_{42}H_{53}F_{17}N_2O_6SSi$ requires *MH* 1065.3122

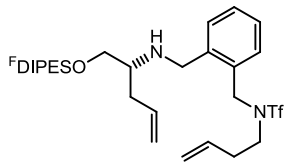
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)thiophen-2-yl]methyl}carbamate 211^D



Following general procedure **N1**; thiophenol (286 mg, 2.6 mmol), sulfonamide **211** (350 mg, 0.26 mmol) and potassium carbonate (90 mg, 0.52 mmol) gave the crude product after 4 h. The crude product was purified by F-SPE to give the amine **211^D** (220 mg, 0.22 mmol, 86%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.37 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.34 (1H, dd, *J* 7.5 and 1.8, Ar), 7.29-7.24 (1H, m, Ar), 6.94 (1H, td, *J* 7.5 and 1.8, Ar), 6.87 (1H, dd, *J* 8.4, Ar), 6.79-6.77 (1H, br s, Ar), 6.72 (1H, dd, *J* 3.3, Ar), 6.04 (1H, ddt, *J* 17.4, 10.4 and 5, propenyl 2-H), 5.77 (1H, ddt, *J* 17.3, 10.3 and 7.1, 4-H), 5.41 (1H, dd, *J* 17.3 and 1.7, propenyl 3-H_A), 5.26 (1H, dd, *J* 10.4 and 1.7, propenyl 3-H_B), 5.23 (2H, s, PhCH$_2$O), 5.08 (1H, d, *J* 10.3, 5-H_A), 5.05-5.01 (2H, m, NH and 5-H_B), 4.56 (2H, dt, *J* 5.1 and 1.7,

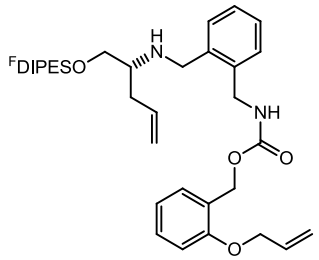
propenyl 1-H_2), 4.49 (2H, d, *J* 5.8, PhCH_2N(CO)), 3.95 (2H, d, *J* 4.4, NHCH_2Thio), 3.63 (1H, dd, *J* 9.9 and 5.1, 1-H_A), 3.59 (1H, dd, *J* 9.9 and 5.9, 1-H_B), 2.76 (1H, p, *J* 5.9, 2-H), 2.27-2.18 (2H, m, 3-H_{AB}), 2.17-2.05 (2H, m, $C_8F_{17}CH_2CH_2$); 1.04-1.00 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.86-0.79 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 156.7 (phenyl 1-C), 144.7, 144.6, 140.4, 135.4 (4-C), 133.4 (propenyl 2-C), 129.8, 129.6, 129.3, 125.6, 125.3, 124.6, 120.9, 117.7 (5-C), 117.5 (propenyl 3-C), 111.9, 69.1 (propenyl 1-C), 65.3 (1-C), 62.7 (PhCH_2O), 57.9 (2-C), 46.5 (ThioCH_2NCO), 40.5 (NHCH_2Thio), 36.1 (3-C), 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.8 (SiCH(*C*H_3)$_2$), 17.7 (SiCH(*C*H_3)$_2$), 12.6 (Si*C*H(CH_3)$_2$), 12.4 (Si*C*H(CH_3)$_2$); ν_{max}/cm^{-1} (film) 3326, 2945, 2159, 2029, 1719, 1494, 1458; *m/z* (ES$^+$) 977.3 (100%, [M+H]$^+$); found 977.2703, $C_{38}H_{46}F_{17}N_2O_4SSi$ requires *MH* 977.2671

_N_-(But-3-en-1-yl)-1,1,1-trifluoro-_N_-{[2-({[(2_R_)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}methanesulfonamide 209^D



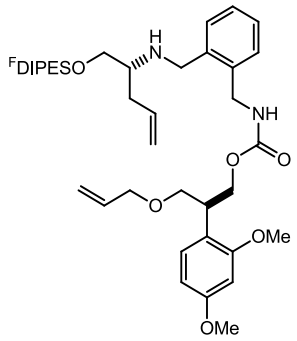
Following general procedure **N1**; thiophenol (429 mg, 3.9 mmol), sulfonamide **209** (450 mg, 0.39 mmol) and potassium carbonate (161 mg, 1.17 mmol) gave the crude product after 4 h. The crude product was purified by F-SPE to give the amine **209^D** (385 mg, 0.39 mmol, 100%, >89% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f: 0.79 (80:20, petrol—EtOAc); δ_H (300 MHz; $CDCl_3$) 7.46-7.29 (4H, m, Ar), 5.84 (1H, ddt, *J* 17.4, 10.4 and 7.1, 4-H), 5.59 (1H, ddt, *J* 17.1, 10.3 and 6.8, 3-H), 5.12 (1H, d, *J* 17.4, 5'-H_A), 5.11 (1H, d, *J* 10.4, 5'-H_B), 5.02 (1H, d, *J* 10.3, 4-H_A), 4.97 (1H, dd, *J* 17.1 and 1.7, 4-H_B), 4.81 (2H, br s, PhCH_2NTf), 3.90 (1H, d, *J* 12.5, NHCH_APh), 3.83 (1H, d, *J* 12.5, NHCH_BPh), 3.71 (1H, dd, *J* 9.9 and 5.1, 1'-H_A), 3.64 (1H, dd, *J* 9.9 and 5.7, 1'-H_B), 3.42 (2H, t, *J* 7.9, 1-H_2), 2.79 (1H, ap p, *J* 5.8, 2'-H), 2.39-2.23 (2H, m, 3-H_{AB}), 2.23-2.03 (4H, m, 2-H_2 and $C_8F_{17}CH_2CH_2$), 1.08 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.94-0.86 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 138.9, 135.6, 133.8, 133.6, 130.1, 129.0, 128.7, 128.2, 120.5 (q, *J* 324.1, CF_3), 117.9 (5'-C), 115.5 (4-C), 65.2 (1'-C), 59.2 (2-C), 49.9 (NHCH_2Ph), 49.7 (PhCH_2NTf), 48.4 (1-C), 36.2 (3'-C), 33.2 (2-C), 25.7 (t, *J* 23.7, $C_8F_{17}CH_2CH_2$), 17.7 (SiCH(*C*H_3)$_2$), 12.6 (Si*C*H(CH_3)$_2$); ν_{max}/cm^{-1} (film) 2870, 1642, 1461, 1389, 1275 and 1261;*m/z* (ES$^+$) 967.2 (100%, [M+H]$^+$); found 967.2465, $C_{34}H_{42}F_{20}N_2O_3SSi$ requires *MH* 967.2439

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 234^{D}



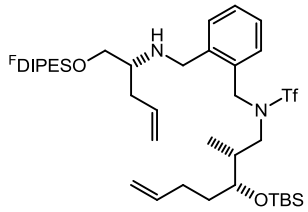
Following general procedure **N1**; thiophenol (572 mg, 5.2 mmol), sulfonamide **234** (700 mg, 0.52 mmol) and potassium carbonate (180 mg, 1.3 mmol) gave the crude product after 4 h. The crude product was purified by F-SPE to give the amine **234^{D}** (410 mg, 0.42 mmol, 81%, >84% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.24 (60:40, petrol—EtOAc); δ_H (300 MHz; $CDCl_3$) 7.71-7.20 (6H, m, Ar), 7.01-6.84 (2H, m, Ar), 6.05 (1H, ddt, *J* 17.1, 10.3 and 4.8, 4-H), 5.79 (1H, ddt, *J* 17.7, 10.3 and 7.3, propenyl 2-H), 5.43 (1H, ddt, *J* 17.1 and 1.8, 4-H_A), 5.31-5.21 (3H, m, PhCH_2O and 4-H_B), 5.07 (1H, d , *J* 17.7, propenyl 3-H_A), 5.06 (1H, d , *J* 10.3, propenyl 3-H_B), 4.57 (2H, d, *J* 4.7), 4.54-4.39 (2H, m,), 3.89 (1H, d, *J* 11.7, NHCH_APh), 3.80 (1H, d, *J* 11.7, NHCH_BPh), 3.75 (1H, dd , *J* 10 and 4.7, 1-H_A), 3.61 (1H, dd, *J* 10 and 5.5, 1-H_B), 2.81 (1H, ap p, *J* 5.6, 2-H), 2.35-2.25 (2H, m, 3-H_{AB}), 2.23-2.02 (2H, m, $C_8F_{17}CH_2CH_2$), 1.04 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.91-0.84 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 138.5, 133.6, 130.5, 129.4, 129.2, 128.3, 120.9, 118.0 (propenyl 3-C), 117.4 (5-C), 111.9 (Ar 3-C), 69.1 (propenyl 1-C), 64.6 (1-C), 62.1 (PhOCH_2), 59.2 (2-C), 50.6 (PhCH_2N(CO)), 44.4 (NHCH_2Ph), 36.2 (3-C), 17.9 (SiCH(CH_3)$_2$), 17.8 (SiCH(CH_3)$_2$), 12.6 (SiCH(CH$_3$)$_2$), 0.14 ($C_8F_{17}CH_2CH_2$), *CO missing*; ν_{max}/cm^{-1} (film) 3054, 2987, 2305, 1713, 1455, 1275 and 1262; *m/z* (ES$^+$) 971.3 (100%, [M+H]$^+$); found 971.3153, $C_{40}H_{48}F_{17}N_2O_4Si$ requires *MH* 971.3106

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 235^{D}



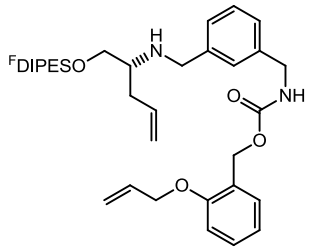
Following general procedure **N1**; thiophenol (246 mg, 2.2 mmol), sulfonamide **235** (320 mg, 0.22 mmol) and potassium carbonate (76 mg, 0.55 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **235^{D}** (123 mg, 0.116 mmol, 57%, >82% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.49 (70:30, petrol—EtOAc); δ_H (300 MHZ; $CDCl_3$) *very broad* 7.42-7.00 (5H, m, Ar), 6.46-6.34 (2H, m, Ar), 5.91-5.68 (2H, m, 4-H and propenyl 2-H), 5.24-5.01 (4H, m, 5-$H_{AB}$and propenyl 3-H_{AB}), 4.42-4.23 (4H, m, PhCH_2N(CO) and propyl 1-H_{AB}, 3.92 (2H, d, *J* 5.9, propenyl 1-H_2), 3.83-3.67 (11H, 2 × OMe, 1-H_A, propyl 2-H, propyl 3-H_{AB}, NHCH_APh), 3.66-3.51 (2H, m, 1-H_B and NHCH_BPh), 2.74 (1H, p, *J* 5.8, 2-H), 2.25-2.00 (4H, m, $C_8F_{17}CH_2CH_2$ and 3-H_{AB}), 1.04 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.9-0.83 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 159.7, 158.6, 138.4, 135.3, 130.2, 129.2, 128.3, 128.0, 120.5, 117.8, 116.7, 104.2, 98.8, 72.1 (propyl 3-C), 70.7 (propyl 1-C), 64.5 (1-C), 59.2 (2-C), 55.5 (OMe), 55.4 (OMe), 50.5 (NH*C*H_2Ph), 38.5 (propyl 2-C), 36.2 (3-C), 17.7 (SiCH(*C*H_3)$_2$), 17.6 (SiCH(*C*H_3)$_2$), 12.5 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$), *PhCH$_2$N(CO) missing*; ν_{max}/cm^{-1} (film) 2947, 2868, 1719, 1546, 1275, 1260, 1153; *m/z* (ES$^+$) 1059.4 (100%, [M+H]$^+$); found 1059.3661, $C_{44}H_{56}F_{17}N_2O_6Si$ requires *MH* 1059.3631

***N*-[(2R,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl]-1,1,1-trifluoro-*N*-{[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}methanesulfonamide 236^{D}**



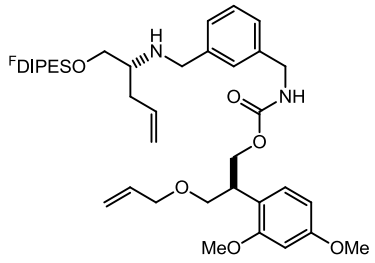
Following general procedure **N1**; thiophenol (246 mg, 2.2 mmol), sulfonamide **236** (600 mg, 0.45 mmol) and potassium carbonate (123 mg, 0.89 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **236^{D}** (250 mg, 0.22 mmol, 48%, >88% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.33 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.41 (1H, d, *J* 7.6, Ar), 7.33 (1H, dt, *J* 7.5 and 4.3, Ar), 7.30-7.26 (2H, m, Ar), 5.82 (1H, ddt, *J* 17.3, 10.2 and 7, 4'-H), 5.68 (1H, ddt, *J* 16.9, 10.4 and 6.5, 6-H), 5.12 (2H, br s, PhCH_2NTf), 5.10 (1H, d, *J* 17.3, 5'-H_A), 5.09 (1H, d, *J* 10.2, 5'-H_B), 4.91 (1H, d, *J* 10.4, 7--H_A), 4.90 (1H, d, *J* 16.9, 7-H_B), 3.86 (1H, d, *J* 12.6, NHCH_APh), 3.81 (1H, d, *J* 12.6, NHCH_BPh), 3.70-3.63 (2H, m, 1'-H_{AB}), 3.44 (1H, br s, 1-H_A), 3.37 (2H, br s, 1-H_B and 3-H), 2.76 (1H, p, *J* 5.9, 2-H), 2.31 (1H, dt, *J* 13.5 and 6.3, 3-H_A), 2.22 (1H, dt, *J* 13.5 and 6.5, 3'-H_B), 2.20-2.08 (2H, m, $C_8F_{17}CH_2CH_2$), 1.80-1.68 (2H, m, 5-H_{AB}), 1.50-1.34 (3H, m, 4-H_{AB} and 2-H), 1.09-1.04 (14H, m, Si(C*H*(CH_3)$_2$)$_2$), 0.93-0.86 (2H, $C_8F_{17}CH_2CH_2$); 0.81 (12H, SiC(CH_3)$_3$ and Me), 0.00 (3H, SiCH_3), -0.08 (3H, SiCH_3); δ_C (75 MHz; $CDCl_3$) 138.35, 138.24, 135.6, 133.9, 130.3, 130.0, 129.1, 128.7, 128.4, 128.1; 120.5 (q, *J* 325, CF_3), 117.6 (5'-C), 114.9 (7-C), 73.3 (3-C), 65.2 (1'-C), 59.1 (2'-C), 53.9 (1-C), 50.0 (NHCH_2Ph), 36.2 (3'-C), 35.9 (2-C), 33.5 (4-C), 30.0 (5-C), 26.0 ($C_8F_{17}CH_2CH_2$), 18.2 (SiCH_3), 17.7 ($C_8F_{17}CH_2CH_2$), 12.6 (SiCH(CH_3)$_2$), 11.0 (Me), 0.25 ($C_8F_{17}CH_2CH_2$), -3.9 (SiCH_3), -4.6 (SiCH_3); ν_{max}/cm^{-1} (film) 2950, 2867, 1642, 1464, 1391, 1227; *m/z* (ES$^+$) 1153.4 (100%, [M+H]$^+$); found 1153.3828, $C_{44}H_{64}F_{20}N_2O_4SSi_2$ requires *MH* 1153.3879

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 116



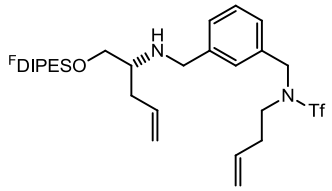
Following general procedure **N1**; thiophenol (517 mg, 4.7 mmol), sulfonamide **114** (630 mg, 0.47 mmol) and potassium carbonate (194 mg, 1.4 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **116** (397 mg, 0.41 mmol, 87%, >85% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.41 (50:50, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.40-7.15 (6H, m, Ar), 6.94 (1H, ap t, *J* 7.5, Ar), 6.87 (1H, d, *J* 8.5, Ar), 6.04 (1H, ddt, *J* 17, 10.2 and 5, propenyl 2-H), 5.78 (1H, ddt, *J* 16.3, 10.6 and 7.1, 4-H), 5.41 (1H, dd , *J* 17 and 1.7, propenyl 3-H_A), 5.28-5.23 (3H, m, propenyl 3-H_B and $PhCH_2O$), 5.11-5.04 (2H, m, 5-H_{AB}), 4.57 (2H, d, *J* 4.8, propenyl 1-H_2), 4.38 (2H, d, *J* 5.9, PhCH_2N(CO)), 3.83 (1H, d, *J* 13.3, NHCH_APh), 3.77 (1H, d, *J* 13.3, NHCH_APh), 3.65-3.59 (2H, m, 1-H_{AB}), 2.72 (1H, p, *J* 6, 2-H), 2.28-2.16 (2H, m, 3-H_{AB}), 2.17-2.00 (2H, m, $C_8F_{17}CH_2CH_2$), 1.03 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.89-0.82 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 156.6 (CO), 141.3 (Ar), 138.9 (Ar), 135.5 (4-C), 133.4 (propenyl 2-C), 129.9, 129.6, 129.1, 127.5, 127.4, 126.4, 125.4, 120.9, 117.6 (5-C), 117.4 (propenyl 3-C), 111.9, 69.1 (propenyl 1-C), 65.4 (1-C), 62.6 ($PhOCH_2$), 58.5 (2-C), 45.4 (PhCH_2N(CO)), 36.1 (3-C), 25.7 ($C_8F_{17}CH_2CH_2$), 17.8 (SiCH(CH_3)$_2$), 12.6 (SiCH(CH_3)$_2$), 0.27 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2945, 2869, 1710, 1456, 1242, 1207; *m/z* (ES$^+$) 971.3 (100%, [M+H]$^+$); found 971.3098, $C_{40}H_{48}F_{17}N_2O_4Si$ requires *MH* 970.3028

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 237^{D}



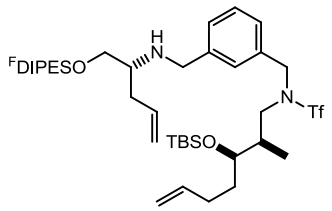
Following general procedure **N1**; thiophenol (378 mg, 3.43 mmol), sulfonamide **237** (491 mg, 0.34 mmol) and potassium carbonate (94 mg, 0.69 mmol) gave the crude product after 3 h. The crude product was purified by F-SPE to give the amine **237^{D}** (260 mg, 0.25 mmol, 72%, >89% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.52 (50:50, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.34-7.16 (4H, m, Ar), 7.15-7.10 (1H, m, Ar), 6.45-6.42 (2H, m, DMB 3 or 5), 5.86 (1H, ddt, *J* 16.2, 10.7 and 5.5, propenyl 2-H), 5.78 (1H, ddt, *J* 17.5, 10.4 and 3.6, 4-H), 5.22 (1H, dd , *J* 17.5 and 1.8, 5-H_A), 5.13 (1H, dd, *J* 10.4 and 1.8, 5-H_B), 5.08 (1H, d, *J* 16.2, propenyl 3-H_A), 5.07 (1H, d, *J* 10.7, propenyl 3-H_B), 4.88 (1H, br s, NH), 4.42 (1H, dd, *J* 10.5 and 5.3, propyl 1-H_A), 4.36 (1H, dd, *J* 10.5 and 5.7, propyl 1-H_B), 4.32 (2H, d, *J* 5.8, PhC*H*$_2$N(CO)), 3.98-3.91 (2H, br s, propenyl 1-H_2), 3.84-3.74 (8H, m, 2 × OMe, 1-H_{AB} and NHC*H*$_{AB}$Ph), 3.65-3.59 (3H, m, propyl 3-H_{AB} and propyl 2-H), 2.76-2.69 (1H, m, 2-H), 2.30-2.19 (2H, m, 3-H_{AB}), 2.17-2.05 (2H, m, $C_8F_{17}CH_2CH_2$), 1.04 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.88-0.84 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 159.9, 158.6, 156.9, 141.4, 141.3, 141.2, 138.9, 135.5, 135.2, 129.2, 129.0, 128.9, 127.6, 127.4, 126.9, 126.4, 125.9, 120.3 (Ar), 117.6 (5-C), 116.9 (propenyl 3-C), 104.3 (DMB 3 or 5), 98.9 (DMB 3 or 5), 80.2, 72.2 (propenyl 1-C), 70.7 (1-C), 65.6 (propyl 3-C), 65.4 (propyl 1-C), 58.5 (2-C), 55.6 (OMe), 51.7 (NH*C*H$_2$Ph), 45.3 (Ph*C*H$_2$C(O)N), 38.4 (propyl 2-C), 36.1 (3-C), 25.6 (C_8F_{17}*C*H$_2$CH$_2$), 17.7 (SiC*H*(C*H*$_3$)$_2$), 12.6 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2$*C*H$_2$); ν_{max}/cm^{-1} (film) 2946, 2868, 1718, 1508, 1243, 1208; *m/z* (ES$^+$) 1059.3 (100%, [M+H]$^+$); found 1059.3588, $C_{44}H_{55}F_{17}N_2O_6Si$ requires *MH* 1059.3631

***N*-(But-3-en-1-yl)-1,1,1-trifluoro-*N*-{[3-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 238^{D}**



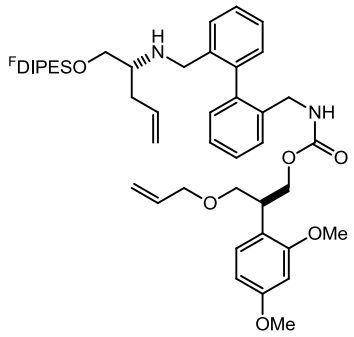
Following general procedure **N1**; thiophenol (248 mg, 2.25 mmol), sulfonamide **238** (520 mg, 0.45 mmol) and potassium carbonate (124 mg, 0.9 mmol) gave the crude product after 3 h. The crude product was purified by F-SPE to give the amine **238^{D}** (420 mg, 0.43 mmol, 96%, >99% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.55 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.35-7.21 (4H, m, Ar), 5.78 (1H, ddt, *J* 17.4, 10.4 and 7.1, 4'-H), 5.60 (1H, ddt, *J* 17.1, 10.3 and 6.8, 3-H), 5.11-4.97 (4H, m, 4-H_{AB} and 5'-H_{AB}), 4.52 (2H, br s, PhCH_2NTf), 3.85 (1H, d , *J* 13.4, NHCH_APh), 3.81 (1H, d, *J* 13.4, NHCH_BPh), 3.63 (2H, qd, *J* 9.9 and 5.5, 1'-H_A), 3.32 (2H, t, *J* 7.8, 1-H_B), 2.75-2.69 (1H, m, 2'-H), 2.31-2.17 (4H, m, 2-H_2 and 3'-H_2), 2.17-2.06 (2H, m, $C_8F_{17}CH_2CH_2$); 1.04 (14H, s, Si(CH(CH_3)$_2$)$_2$), 0.88-0.84 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 135.2 (Ar), 134.4 (Ar), 133.4 (Ar), 129.1 (Ar), 128.3 (Ar), 128.0 (4-C), 127.0 (3-C), 117.9 (4-C or 5'-C), 117.4 (4-C or 5'-C), 65.1 (1'-C), 58.1 (2'-C), 52.1 (PhCH_2NTf), 51.3 (NHCH_2Ph), 47.4 (1-C), 35.8 (2-C), 32.5 (3'-C), 17.5 (SiCH(CH_3)$_2$), 17.4 (SiCH(CH_3)$_2$), 12.3 (SiCH(CH_3)$_2$), 0.29 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2946, 2869, 1642, 1463, 1391, 1226; *m/z* (ES$^+$) 967.2 (100%, [M+H]$^+$); found 967.2485, $C_{34}H_{43}F_{20}N_2O_3SSi$ requires *MH* 967.2439

***N*-[(2*R*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl]-1,1,1-trifluoro-*N*-{[3-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 239^{D}**



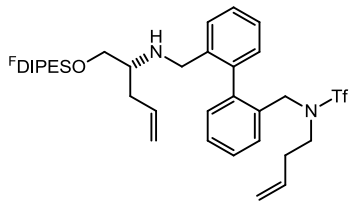
Following general procedure **N1**; thiophenol (163 mg, 1.49 mmol), sulfonamide **239** (400 mg, 0.30 mmol) and potassium carbonate (82 mg, 0.59 mmol) gave the crude product after 2 h. The crude product was purified by F-SPE to give the amine **239^{D}** (330 mg, 0.29 mmol, 96%, >95% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.45 (60:40, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) 7.33-7.28 (3H, m, Ar), 7.25-7.19 (1H, m, Ar), 5.80 (1H, ddt, *J* 17.2, 10.1 and 7.1, 4'-H), 5.71 (1H, ddt, *J* 16.9, 10.3 and 6.6, 6-H), 5.08 (1H, d, *J* 17.2, 5'-H_A), 5.07 (1H, d, *J* 10.1, 5'-H_B), 4.94 (1H, d, *J* 16.9, 7-H_A), 4.93 (1H, d, *J* 10.3, 7-H_B), 4.65-4.41 (2H, br m, PhCH_2NTf), 3.84-3.81 (2H, m, NHCH_2Ph), 3.65 (2H, dd, *J* 7.8 and 5.5, 1'-H_2), 3.46 (1H, td, *J* 6.5 and 2.7, 3-H), 3.38-3.31 (1H, m, 1-H_A), 3.27 (1H, dd, *J* 14.1 and 4.2, 1-H_B), 2.77-2.71 (1H, m, 2'-H), 2.32-2.18 (2H, m, 3'-H_{AB}), 2.19-2.07 (2H, m, $C_8F_{17}CH_2CH_2$), 1.88-1.83 (2H, m, 5-H_{AB}), 1.77 (1H, br s, 2-H), 1.50-1.37 (2H, m, 4-H_{AB}), 1.05 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.9-0.86 (2H, m, $C_8F_{17}CH_2CH_2$), 0.84 (9H, s, TBS), 0.81 (3H, d, *J* 6.7, CH_3), -0.01 (3H, s, TBS), -0.08 (3H, s, TBS); δ_C (75 MHz; $CDCl_3$) 141.8 , 137.9, 135.3 (6-C), 134.9 (4'-C), 128.9, 128.0, 127.9, 126.8, 117.1 (5'-C), 114.7 (7-C), 75.3 (3-C), 65.4 (1'-C), 58.4 (2'-C), 51.4 (NH*C*H_2Ph), 35.9 (3'-C), 35.7 (5-C), 33.3 (4-C), 29.8 (2-C), 25.8 ($C_8F_{17}CH_2CH_2$), 17.9 (SiCH(*C*H_3)$_2$), 17.5 (SiCH(*C*H_3)$_2$), 12.4 (Si*C*H(CH_3)$_2$), 10.9 (CH_3), -4.22 (TBS), -4.76 (TBS), *PhCH$_2$Tf and 1-C missing*; ν_{max}/cm^{-1} (film) 2948, 2868, 1642, 1548, 1464, 1204; *m/z* (ES$^+$) 1153.4 (100%, [M+H]$^+$); found 1153.3903, $C_{44}H_{64}F_{20}N_2O_3SSi$ requires *MH* 1153.3879

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-({2-[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4-en-2-yl]amino}methyl)phenyl]phenyl}methyl)carbamate 240^{D}



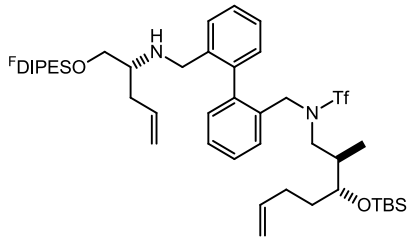
Following general procedure **N1**; thiophenol (319 mg, 2.9 mmol), sulfonamide **240** (450 mg, 0.29 mmol) and potassium carbonate (120 mg, 0.87 mmol) gave the crude product after 4 h. The crude product was purified by F-SPE to give the amine **240^{D}** (335 mg, 0.28 mmol, 98%, >92% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.33 (60:40, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$) *Atropisomers denoted in italics where possible* 7.57-7.23 (7H, m, Ar), 7.21-7.03 (4H, m, Ar), 6.44-6.39 (2H, m, Ar), 6.21 (1H, br s, NH), 5.83 (1H, ddt, *J* 17.3, 10.2 and 5.5, propenyl 2-H), *5.64 (0.5H, ddt, J 17.1, 10.1 and 7, 4-H^{min})*, 5.52 (0.5H, ddt, *J* 17.3, 10.1 and 7.2, 4-H), 5.18 (1H, dd, *J* 17.3 and 1.9, propenyl 3-H_A), 5.08 (1H, dd , *J* 10.5 and 1.5, propenyl 3-H_B), 5.02-4.84 (2H, m, 5-H_{AB}), 4.42-4.26 (1H, m, propyl 3-H_A), 4.26-4.08 (1H, m, propyl 3-H_B), 3.90 (2H, d, *J* 5.9, propenyl 1-H_2), 3.77 (3H, s, OMe), 3.75 (3H, s, OMe), *3.73 (3H, s, OMe^{min})*, 3.65-3.38 (8H, 1-H_A, propyl 1-H_{AB} and 2-H, $NHCH_2Ph$, $N(CO)CH_2Ph$), 3.30-3.18 (1H, m, 1-H_B), *2.67-2.62 (2-H^{min})*, 2.57-2.47 (1H, m, 2-H), 2.22-1.98 (4H, m, $C_8F_{17}CH_2CH_2$ and 3-H_{AB}), 1.01 (14H, s, $Si(CH(CH_3)_2)_2$), *0.98 (s, $SiCH(CH_3)_2^{min}$)*, 0.97-0.67 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 159.8 (DMB 4-C), *158.7*, 158.6 (DMB 2-C), 156.9 (CO), 141.4, 140.7, 140.4, 140.3, 140.2, 137.7, 137.2 (4-C or propenyl 2-C), *135.4*, 135.2, *134.0* (4-C or propenyl 2-C), *130.9*, *130.8*, 130.2, 129.9, 129.8, 129.7, 129.6, 129.5, 129.2, 129.1, 128.9, *128.4*, *128.4*, 128.2, *127.8*, 127.7, *127.5*, 127.4, 127.3, 127.2, 120.5, 117.8 (propenyl 3-C or 5-C), 117.3 (propenyl 3-C or 5-C), 116.7 (propenyl 3-C or 5-C), 104.3 (DMB 5-C), 98.8 (DMB 3-C), *98.79 (DMB 3-C)*, 72.1 (propenyl 1-C), 70.8 (1-C), 64.8 (propyl 3-C); *60.1*, 60.0 (Propyl 1-C), 59.4, *59.24 (2-C)*, 55.5 (2 x OMe), 49.5 (CN(CO)Ph), 49.4 (CN(CO)Ph), 43.2, *42.7 (NHCPh)*, 38.5 (propyl 2-C), 35.9 (3-C), *35.3 (3-C)*; 25.7 ($C_8F_{17}CH_2CH_2$), 17.7 ($SiCH(CH_3)_2$), 12.4 ($SiCH(CH_3)_2$), -0.01 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 2944, 2867, 1697, 1508, 1464, 1275, 1260; *m/z* (ES$^+$) 1135.4 (100%, $[M+H]^+$); found 1135.3972, $C_{50}H_{59}F_{17}N_2O_6Si$ requires *MH* 1135.3944

***N*-(But-3-en-1-yl)-1,1,1-trifluoro-*N*-({2-[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]amino}methyl)phenyl]phenyl}methyl)methanesulfonamide 241^{D}**



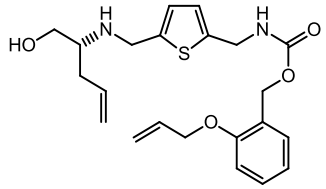
Following general procedure **N1**; thiophenol (177 mg, 1.61 mmol), sulfonamide **241** (409 mg, 0.32 mmol) and potassium carbonate (89 mg, 0.64 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE to give the amine **241^{D}** (324 mg, 0.30 mmol, 93%, >83% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.37 (70:30, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$; 323 K) 7.57 (1H, d, *J* 7.8, Ar), 7.49 (1H, d, *J* 8.5, Ar), 7.47 (1H, d, *J* 7.6, Ar), 7.42 (1H, td, *J* 7.6 and 1.3, Ar), 7.39-7.34 (1H, m, Ar); 7.30 (1H, t, *J* 7.5, Ar), 7.19 (1H, td, *J* 7.4 and 1.2, Ar), 7.10 (1H, d, *J* 7.5, Ar), 5.63 (1H, ddt, *J* 17.3, 11.6 and 7.1, 4'-H), 5.50 (1H, ddt, *J* 17.1, 10.3 and 6.8, 3-H), 5.0-4.92 (3H, m, 4'-H_A and 5-H_{AB}), 4.88 (1H, d, *J* 17.1, 4'-H_B), 4.53 (1H, d, *J* 15.8, PhCH_ANTf), 4.13 (1H, d, *J* 15.8, PhCH_BNTf), 3.53-3.47 (1H, m, 1'-H_A), 3.45-3.38 (3H, m, 1'-H_B and NHCH_2Ph), 3.26 (1H, dt, *J* 14.8 and 7.9, 1-H_A), 3.15 (1H, dtd, *J* 14.8, 7.8 and 3.6, 1-H_B), 2.52 (1H, dp, *J* 8.7 and 5.9, 2'-H), 2.20-1.93 (6H, m, $C_8F_{17}CH_2CH_2$, 3'-H_2 and 2-H_2), 1.01 (14H, s, Si(C*H*(CH_3)$_2$)$_2$), 0.86-0.79 (2H, m, $C_8F_{17}CH_2CH_2$); δ_C (125 MHz; $CDCl_3$; 323 K) *50:50 atropisomers* 140.67, 140.65, 139.4, 139.3, 139.0, 138.9, 135.3 (4'-C), 135.2 (4'-C), 133.4 (3-C), 132.96, 132.93, 130.12, 130.08, 129.50, 129.47, 129.2, 129.1, 128.3, 128.2, 128.12, 128.06, 127.8, 127.1, 127.0, 120.2 (q, *J* 325, *C*F_3), 117.6 (4-C), 117.1 (4-C), 116.9 (5'-C), 65.4 (1'-C), 65.2 (1'-C), 58.89 (2'-C), 58.87 (2'-C), 49.5 (Ph*C*NTf), 49.3 (Ph*C*NH), 49.1 (Ph*C*NH), 47.9 (1-C), 36.0 (2-C), 35.7 (2-C), 32.4 (3'-C), 25.7 (t, *J* 25, $C_8F_{17}CH_2CH_2$), 17.5 (SiCH(CH_3)$_2$), 17.4 (SiCH(*C*H_3)$_2$), 12.45 (Si*C*H(CH$_3$)$_2$), 12.43 (Si*C*H(CH$_3$)$_2$), 0.00 ($C_8F_{17}CH_2CH_2$); ν_{max}/cm^{-1} (film) 3065, 3005, 2947, 2868, 1642, 1462, 1388; *m/z* (ES$^+$) 1043.3 (100%, [M+H]$^+$); found 1043.2794, $C_{40}H_{47}F_{20}N_2O_2SSi$ requires *MH* 1043.2752

***N*-[(2*R*,3*R*)-3-[(*Tert*-butyldimethylsilyl)oxy]-2-methylhept-6-en-1-yl]-1,1,1-trifluoro-*N*-({2-[2-({[(2*R*)-1-{[(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)bis(propan-2-yl)silyl]oxy}pent-4'-en-2'-yl]amino}methyl)phenyl]phenyl}methyl)methanesulfonamide 243^{D}**



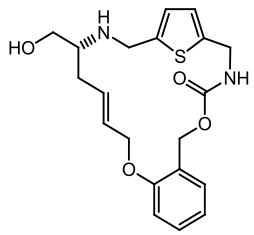
Following general procedure **N1**; thiophenol (169 mg, 1.54 mmol), sulfonamide **243** (450 mg, 0.31 mmol) and potassium carbonate (85 mg, 0.62 mmol) gave the crude product after 3 h. The crude product was purified by F-SPE to give the amine **243^{D}** (437 mg, 0.34 mmol, 111%, >89% purity as estimated using 500 MHz ^{1}H NMR spectroscopy) as a pale yellow oil; R_f 0.36 (80:20, petrol—EtOAc); δ_H (500 MHz; $CDCl_3$; 323 K) *Atropisomers denoted where possible* 7.59 (1H, d, *J* 7.9, Ar), 7.50-7.47 (1H, m, Ar), 7.45 (1H, dd, *J* 7.7 and 1.3, Ar), 7.41 (1H, tt, *J* 7.7 and 1.8, Ar), 7.36 (1H, tdd, *J* 7.6, 2.4 and 1.4, Ar), 7.33-7.26 (1H, m, Ar), 7.19-7.13 (1H, m, Ar), 7.08 (1H, dd, *J* 7.5 and 1.4, Ar), 5.75-5.57 (2H, m, 4'-H and 6-H), 4.99-4.89 (4H, m, 7-H_{AB} and 5'-H_{AB}), 4.69 (0.5H, d, *J* 16.1, NTfC*H*$_2$Ph), 4.62 (0.5H, d, *J* 16.7, NTfC*H*$_2$Ph), 4.09-3.93 (1H, m, NTfC*H*$_2$Ph), 3.53-3.29 (5H, m, 1-H_2, 3-H and NHC*H*$_2$Ph), 3.23-3.07 (2H, m, 1'-H), 2.50 (1H, ddd, *J* 7.7, 6.5 and 4.9, 2'-H), 1.47-1.35 (6H, m, $C_8F_{17}C$*H*$_2$CH$_2$, 5'-H and 3'-H), 1.65-1.55 (1H, m, 2-H), 1.46-1.35 (2H, m, 4-H_2), 1.00 (14H, s, Si(C*H*(C*H*$_3$)$_2$)$_2$), 0.86-0.79 (11H, TBS and $C_8F_{17}CH_2C$*H*$_2$), 0.70 (3H, d, *J* 6.8, Me), -0.04 (3H, TBS), -0.08 (3H, TBS); δ_C (125 MHz; $CDCl_3$; 323 K) *50:50 atropisomers* 140.4 (Ar), 140.3 (Ar), 139.7 (Ar), 139.6 (Ar), 139.5 (Ar), 139.2 (Ar), 138.2 (4' or 6-C), 138.1 (4' or 6-C), 135.5 (4' or 6-C), 135.4 (4' or 6-C), 133.7 (Ar), 133.2 (Ar), 130.4 (Ar), 130.1 (Ar), 129.5 (Ar), 129.4 (Ar), 129.3 (Ar), 129.2 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 127.2 (Ar), 127.1 (Ar), (120.5, q, *J* 325), 117.2 (5- or 7'-C), 117.0 (5'- or 7-C), 114.9 (5'- or 7-C), 114.8 (5'- or 7-C), 73.6 (3-C), 73.3 (3-C), 65.5 (1'-C), 65.3 (1'-C), 59.0 (2'-C), 58.9 (2'-C), 54.9 (NTf*C*H$_2$Ph), 53.0 (NTf*C*H$_2$Ph), 52.2 (1-H), 50.4 (1-H), 49.5 (NH*C*H$_2$Ph) , 49.1 (NH*C*H$_2$Ph), 36.6 (2-C) , 36.2 (2-C) , 35.9 (3'-C), 35.8 (3'-C), 29.9 (5-C), 29.8 (5-C), 26.0 (4-C), 25.8 (SiC(*C*H$_3$)$_3$), 25.6 (t, *J* 25, C_8F_{17}*C*H$_2$CH$_2$), 18.2 (Si*C*(CH$_3$)$_3$), 17.6 (SiCH(*C*H$_3$)$_2$), 12.6 (Si*C*H(CH$_3$)$_2$), 11.3 (Me), 10.7 (Me), 0.15 ($C_8F_{17}CH_2$*C*H$_2$), -3.99 (Si*C*H$_3$), -4.01 (Si*C*H$_3$); ν_{max}/cm^{-1} (film) 2950, 2867, 1738, 1641, 1548, 1464, 1390; *m/z* (ES$^+$) 1229.4 (100%, [M+H]$^+$); found 1229.4240, $C_{50}H_{68}F_{20}N_2O_4SSi_2$ requires *MH* 1229.4192

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({[(2*R*)-1-hydroxypent-4-en-2-yl]amino}methyl)thiophen-2-yl]methyl}carbamate 227



Following general procedure **S2**, tetra-n-butylammonium fluoride (1M, 0.1 mL) was added to the amine **211^{D}** (52 mg, 0.053 mmol); on completion of the reaction the crude product was purified by column chromatography, eluting with EtOAc gave the amine **227** (6 mg, 0.014 mmol, 27%) as a yellow oil; R_f 0.1 (EtOAc); α_D^{25} 4.8 (c. 0.5, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.41-7.37 (1H, m, Ph 3-H), 7.34-7.29 (1H, m, Ph 5-H), 7.00 (1H, ap t, *J* 7.41, Ph 6-H), 6.92 (1H, d, *J* 8.22, Ph 4-H), 6.84 (1H, s, Thio 3 or 4-H), 6.79 (1H, s, Thio 3 or 4-H), 6.09 (1H, ddt, *J* 17.6, 10.2 and 5.5, propenyl 2-H), 5.80 (1H, ddt, *J* 16.6, 11.0 and 7.2, 3-H), 5.46 (1H, dd, *J* 17.6 and 1.7, propenyl 3-H_A), 5.32 (1H, dd, *J* 10.2 and 1.1, propenyl 3-H_B), 5.29 (2H, s, PhCH_2O), 5.17 (1H, d, *J* 16.6, 5-H_A), 5.15 (1H, d, *J* 11, 5-H_B), 4.62 (2H, ap d, *J* 5.5, propenyl 1-H_2), 4.54 (2H, ap d, *J* 7.2, ThioCH_2NCO), 4.03 (1H, d, *J* 14, NHCH_2Ph), 3.96 (1H, d, *J* 14, NHCH_2Ph), 3.69 (1H, dd, *J* 10.7 and 4.2, 1-H_A), 3.39 (1H, dd, *J* 10.7 and 5.9, 1-H_B), 2.87-2.81 (1H, m, 2-H), 2.35-2.24 (2H, m, 3-H_{AB}), 1.88 (1H, br s, OH); δ_C (75 MHz; CDCl3) 156.8 (Ph 1-C), 156.6 (C=O), 144.3 (Thio 3 or 4-C), 140.9 (Thio 3 or 4-C), 135.0 (propenyl 2-C), 133.6 (4-C), 130.0, 129.8, 125.7, 125.4, 124.9, 121.0 (Ph 4-C), 118.5 (5-C), 117.6 (propenyl 3-C), 112.1 (Ph 6-C), 69.2 propenyl (1-C), 63.4 (1-C), 62.8 (PhCH_2NCO), 57.5 (2-C), 46.3 (NHCH_2Ph), 40.6 , 36.5 (3-C); ν_{max}/cm^{-1} (film) 3316, 3073, 2925, 1704, 1494, 1245;*m/z* (ES$^+$) 417.2 (100%, $[M+H]^+$); found 417.1853, $C_{22}H_{28}N_2O_4S_3$ requires *MH* 417.1843

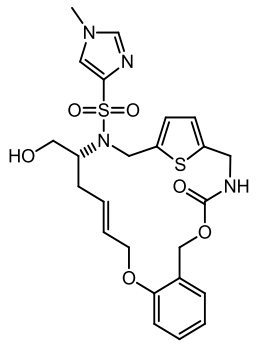
(15*E*,18*R*)-18-(Hydroxymethyl)-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaen-4-one 231



Following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the amine **223^{D}** (38 mg, 0.04 mmol); on completion of the reaction, the crude product was purified by column chromatography, eluting with EtOAc gave the amine **231** (15 mg, 0.038 mmol, 96%) as a pale yellow glass; R_f 0.1 (EtOAc); α_{23}^{D} 4 (c. 0.9,

$CDCl_3$); δ_H (300 MHz; MeOD) 7.29-7.15 (2H, m, Ar), 6.88-6.76 (2H, m, Ar), 6.69 (2H, s, Ar), 5.68 (1H, dd, *J* 16.1 and 3.8, 15-H), 5.62 (1H, dd, *J* 16.1 and 4.1, 16-H), 5.03 (1H, d, *J* 10.4, 6-H_A), 4.85 (1H, d, *J* 10.4, 6-H_B), 4.41 (1H, d, *J* 12.1, 2-H_A), 4.36 (1H, d, *J* 12.1, 2-H_B), 4.32 (1H, d, *J* 15.5, 14-H_A), 4.23 (1H, d, *J* 15.5, 14-H_B), 3.92 (2H, s, 20-H), 3.43 (1H, dd, *J* 11 and 5, , C*H*$_A$OH), 3.39 (1H, dd, *J* 11 and 5.7, , C*H*$_B$OH), 2.58-2.48 (1H, m, 18-H), 2.05 (2H, br s, 17-H); δ_C (75 MHz; $CDCl_3$) 159.5 (12-C), 145.4 (Thio 2 or 5-C), 143.2 (Thio 2 or 5-C), 133.3 (8 or 9-C), 131.8 (8 or 9-C), 130.3 (7-C), 129.8 (15 or 16-C), 127.1 (15 or 16-C), 126.1 (Thio 3 or 4-C), 125.7 (Thio 3 or 4-C), 121.7 (10-C), 113.4 (11-C), 69.9 (14-C), 64.9 (*C*H_2OH), 64.6 (Ph*C*H_2O), 56.9 (18-C), 45.8 (2-C), 41.1 (20-C), 34.9 (17-C), *C=O missing*; ν_{max}/cm^{-1} (film) 3336, 2935, 2480, 1677, 1438; *m/z* (ES$^+$) 389.2 (100%, [M+H]$^+$); found 389.1541, $C_{20}H_{24}N_2O_4S$ requires *MH* 389.1530

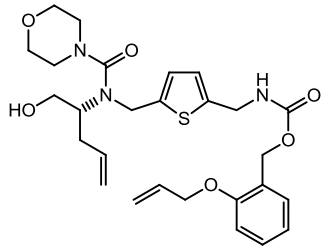
(15*E*,18*R*)-18-(Hydroxymethyl)-19-(1-methyl-1H-imidazole-4-sulfonyl)-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaen-4-one; ethane 230



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (28 mg, 0.16 mmol), triethylamine (32 mg, 0.32 mmol) and amine **223^D** (38 mg, 0.04 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **230** (9 mg, 0.017 mmol, 42%) as a colourless oil; R_f 0.09 (60:40 petrol—EtOAc); $[\alpha]_D^{23.7}$ 1.3 (c. 0.9, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.52 (2H, s, Ar), 7.32 (1H, d, *J* 8, Ar), 7.28 (1H, d, *J* 8, Ar), 6.98-6.79 (4H, m, Ar), 5.92 (1H, br s, NH), 5.65 (1H, dt, *J* 15.0 and 7.5, 15-H), 5.36 (1H, dt, *J* 15 and 5.3, 16-H), 5.23 (1H, d, *J* 12.3, 6-H_A), 5.22 (1H, br s,), 5.02 (1H, d, *J* 12.3, 6-H_B), 4.52 (1H, d, *J* 15, 2-H_A), 4.43 (4H, ap s, 14-H_2 and 20-H_2), 4.17 (1H, m, 18-H), 4.16 (1H, d, *J* 15, 2-H_A), 3.92-3.80 (1H, m, C*H*$_2$OH), 3.77 (3H, s, NCH_3), 3.75-3.66 (1H, m, C*H*$_2$OH), 2.41-2.20 (1H, m, 17-H_A), 2.18-2.02 (1H, m, 17-H_B); δ_C (75 MHz; $CDCl_3$) 156.4 (12-C), 143.4 (Thio 2 or 5-C), 141.4 (Thio 2 or 5-C), 138.5 (Imid 4-C), 131.6 (Thio 3 or 4-C), 130.5 (Thio 3 or 4-C), 129.3 , 127.9 ,

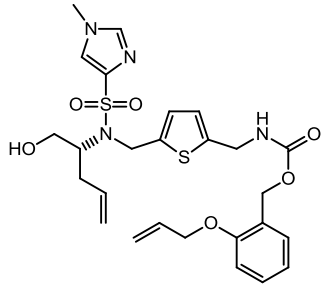
127.3 , 125.9 , 124.2 , 120.5 , 112.5 (11-C), 68.5 (6-C), 64.3 (*C*H_2OH), 61.9 (18-C), 34.2 (17-C), 29.7 (NMe); ν_{max}/cm^{-1} (film) 2919, 1701, 1531, 1330, 1255, 1157, 1120; *m/z* (ES$^+$) 533.2 (100%, [M+H]$^+$) and 555.1 (10%, [M+Na]$^+$); found 533.1530, $C_{24}H_{28}N_4O_6S_2$ requires *MH* 533.1523

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({[(2*R*)-1-hydroxypent-4-en-2-yl][(morpholin-4-yl)carbonyl]amino}methyl)thiophen-2-yl]methyl}carbamate 225



Following general procedure **A2**, 4-morpholinecarbonyl chloride (15.6 mg, 0.1 mmol), triethylamine (20 mg, 0.2 mmol) and amine **211^D** (51 mg, 0.052 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with EtOAc gave the urea **225** (20 mg, 0.037 mmol, 71%) as a pale yellow oil; R_f 0.5 (EtOAc); $[\alpha]_D^{23.7}$ 2.8 (c. 2, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.34 (1H, dd, *J* 7.6 and 1.6, Ph 3-H), 7.31 (1H, dt, *J* 8.3 and 1.6, Ph 6-H), 6.99 (1H, ap t, *J* 7.6, Ph 4-H), 6.95 (1H, d, *J* 8.3, Ph 5-H), 6.83 (2H, ap s, Thio 3 and 4-H), 6.08 (1H, ddt, *J* 17.3, 10.5 and 4.9, propenyl 2-H), 5.79 (1H, ddt, *J* 17.6, 10.5 and 7.5, 4-H); 5.45 (1H, ddd, *J* 17.6, 3.6 and 1.5, 5-H_A), 5.30 (1H, ddd, *J* 10.5 3.6 and 1.5, 5-H_B); 5.22 (2H, s, PhCH_2O); 5.15 (1H, ddd, *J* 17.3, 2.9 and 1.4, propenyl 3-H_A), 5.12-5.07 (1H, m, propenyl 3-H_B), 4.59-4.57 (2H, m, propenyl 1-H_2), 4.54-4.49 (2H, m, , Ph*C*H_2N(CO)), 4.51 (1H, d, *J* 16, N(CO)NCH_2Ph), 4.45 (1H, d, *J* 16, N(CO)NCH_2Ph), 3.98 (1H, br s, 2-H), 3.77-3.63 (5H, m, O(CH_2)$_2$ and 1-H_A); 3.63-3.52 (1H, m, 1-H_B), 3.37 (4H, dd, *J* 4.4 and 5.7, N(CH_2)$_2$), 2.58-2.34 (2H, m, 3-H_{AB}), 1.29 (1H, OH); δ_C (75 MHz; $CDCl_3$) 164.9 (C=O), 141.7 (Thio 2 or 5-C) ,141.4 (Thio 2 or 5-C), 135.3 (propenyl 2-C), 133.5 (4-C), 130.1, 129.8 , 126.1, 125.9 (Thio 3 or 4-C), 125.3 (Thio 3 or 4-C), 121.0, 118.1 (5-C), 117.6 (propenyl 3-C), 112.1 (Ph 6-C), 69.2 (propenyl 1-C), 67.0 (O(*C*H_2)$_2$), 63.6 (Ph*C*H_2O), 62.8 (1-C), 61.1 (2-C), 47.7 (N(*C*H_2)$_2$), 46.5 Ph*C*H_2(CO), 40.5 N(CO)*C*H_2Ph, 34.0 (3-C); ν_{max}/cm^{-1} (film) 3323, 3077, 2925, 1669, 1581, 1549, 1453 ; *m/z* (ES$^+$) 530.2 (100%, [M+H]$^+$); found 530.2332, $C_{27}H_{35}N_3O_6S_1$ requires *MH* 530.2319

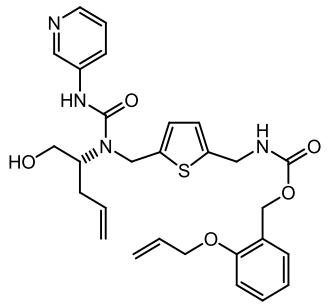
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]1-methyl-1H-imidazole-4-sulfonamido}methyl)thiophen-2-yl]methyl}carbamate 226



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (38 mg, 0.21 mmol), triethylamine (42 mg, 0.42 mmol) and amine **211^{D}** (52 mg, 0.053 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with EtOAc gave the sulfonamide **226** (14 mg, 0.025 mmol, 60%) as a colourless glass; R_f 0.1 (EtOAc); $[\alpha]_D^{23.7}$ 2.9 (c. 1.4, CH_2Cl_2); δ_H (500 MHZ; $CDCl_3$) 7.44 (1H, ap d, *J* 4.3, Imid), 7.34 (1H, d, *J* 7.8, Ph 3-H), 7.31-7.23 (1H, m, Ph 6-H), 6.95 (1H, td, *J* 7.4 and 2.5, Ph 4-H), 6.90-6.71 (4H, m, Thio 3 and 4-H, Imid, Ph 5-H), 6.04 (1H, ddt, *J* 16.3, 10.8 and 5.1, propenyl 2-H), 5.74 (1H, br ddt, *J* 17.3, 9.9 and 7.1, 4-H), 5.41 (1H, d, *J* 17.3, propenyl 3-H_A), 5.26 (1H, d, *J* 9.9, propenyl 3-H_B), 5.23 (2H, s, PhCH_2O), 5.11 (1H, d, *J* 16.3, 5-H_A^{rotA}), 5.10 (1H, d, *J* 10.8, 5-H_B^{rotA}), 4.97 (1H, d, *J* 16.3, 5-H_A^{rotB}), 4.96 (1H, d, *J* 10.8, 5-H_B^{rotB}), 4.57 (2H, ap dt, *J* 4.8 and 1.8, propenyl 1-H_2), 4.41 (1H, d, *J* 14.3, PhCH_2N(CO)^{rotA}), 4.33 (1H, d, *J* 15.8, PhCH_2N(CO)^{rotB}), 4.05-3.86 (2H, m, PhCH_2N(CO)^{rotA,B}), 3.72 (2H, s, N(SO_2Imid)CH_2), 3.64 (1H, dd, *J* 10.8 and 4.1, 1-H_A), 3.49 (3H, s, NMe), 3.34 (1H, dd, *J* 10.8 and 6.0, 1-H_B), 2.79 (1H, m, 2-H), 2.42-2.18 (2H, m, 3-H); δ_C (75 MHz; $CDCl_3$) 156.8 (Ph 1-C), 144.3 (Imid 1-C), 142.6 (Thio 2 or 5-C), 141.8 (Thio 2 or 5-C), 140.9, 139.9, 138.9, 135.0, 133.5, 130.0 (Ph 5-C), 129.8 (Ph 3-C), 127.8, 125.7, 125.5, 124.9, 124.6, 121.1, 121.0, 118.5 (5-C or propenyl 3-C^{rotB}), 117.9 (5-C or propenyl 3-C^{rotB}), 117.7 (5-C or propenyl 3-C^{rotB}), 117.6 (5-C or propenyl 3-C^{rotB}), 112.1 (Ph 6-C), 69.2 (propenyl 1-C), 64.6 (1-C), 63.4 (Ph*C*H_2O^{rotA}), 62.8 (Ph*C*H_2O^{rotB}), 57.5 (2-C), 46.5 (NSO_2ImidCH_2Ph^{rotA}), 46.3 (NSO_2ImidCH_2Ph^{rotB}), 40.6 (PhCH_2N(CO)), 37.3 (3-C^{rotA}), 36.5 (3-C), 34.6 (NMe); ν_{max}/cm^{-1} (film) 3317, 2926, 1713, 1604, 1531, 1494, 1455, 1334, 1275, 1260, 1158 and 1119; *m/z* (ES$^+$) 561.0 (100%, $[M+H]^+$); found 561.1829, $C_{26}H_{32}N_4O_6S_2$ requires *MH* 561.1836

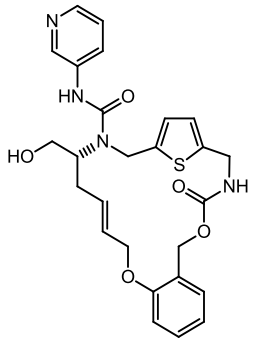
Full carbon assignment was not possible due to rotamers

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[5-({[(2*R*)-1-hydroxypent-4-en-2-yl][(pyridin-3-yl)carbamoyl]amino}methyl)thiophen-2-yl]methyl}carbamate 224



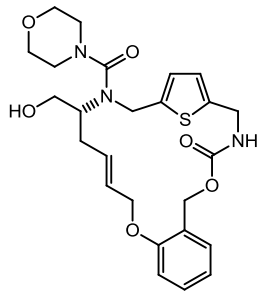
Following general procedure **A1**, 3-pyridyl isocyanate (15.5 mg, 0.129 mmol) and amine **211^{D}** (63 mg, 0.065 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with EtOAc gave the urea **224** (27 mg, 0.05 mmol, 77%) as a pale yellow oil; R_f 0.1 (EtOAc); $\alpha_D^{23.3}$: 3 º (c. 0.4, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 9.24 (1H, br s, NH), 8.22 (1H, d, *J* 2.8, Py 2-H), 8.11 (1H, d, *J* 4.4, Py 4-H), 8.04 (1H, d, *J* 8.1, Py 6-H), 7.3 (1H, d, *J* 7.1, Ph 5-H), 7.25 (1H, ddd, *J* 8,8 and 1.5, Ph 3-H), 7.18 (1H, ddd, *J* 8.1 and 4.4, Py 5-H), 6.95-6.79 (3H, m, Ph 6-H and 4-H , Thio 3 or 4-H), 6.75 (1H, d, *J* 3.2, Thio 3 or 4-H), 6.02 (1H, ddt, *J* 17.2, 10.4 and 4.8, propenyl 2-H), 5.67 (1H, ddt, *J* 17.2, 9.9 and 6.8, 4-H), 5.45 (1H, br s, NH), 5.39 (1H, dd, *J* 17.2 and 1.9, propenyl 3-H_A), 5.25 (1H, dd, *J* 10.4 and 1.9, propenyl 3-H_B), 5.19 (2H, s, PhCH_2O), 5.05 (1H, d, *J* 17.2, 5-H_A), 5.04 (1H, d, *J* 9.9, 5-H_B), 4.64-4.60 (2H, m,), 4.54 (2H, d, *J* 4.8, propenyl 1-H), 4.46-4.43 (2H, m, PhCH_2N(CO)), 3.85 (3H, m, 1-H_2 and 2-H); 2.47 (2H, br s, 3-H_{AB}), 1.19 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 157.1 (Ph 1-C), 156.8 (C=O), 143.1 (Py 2-C), 142.3 (Py 6-C), 141.7 (Thio 2 or 5-C), 140.5 (Thio 2 or 5-C), 137.4 (Py 3-C), 134.6 (propenyl 2-C), 133.5 (4-C), 129.9 (Ar), 129.8 (Py 5-C), 127.4 (Ar), 126.4 (Ar), 125.6 (Thio 3 or 4-C), 125.4 (Thio 3 or 4-C), 124.3 (Py 4-C), 121.0 (Ph 4-C), 118.6 (5-C), 117.6 (propenyl 3-C), 112.1 (Ph 5-C), 69.2 (propenyl 1-C), 64.4 (1-C), 62.8 (PhCH$_2$O), 60.4 (2-C), 46.2, 40.5 (PhCH$_2$N(CO)), 34.1 (3-C); ν_{max}/cm^{-1} (film) 3301, 2929, 1700, 1660, 1532, 1242; *m/z* (ES$^+$) 537.2 (100%, [M+H]$^+$); found 537.2178, $C_{28}H_{32}N_4O_5S$ requires *MH* 537.2166

(15*E*,18*R*)-18-(Hydroxymethyl)-4-oxo-*N*-(pyridin-3-yl)-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaene-19-carboxamide 228



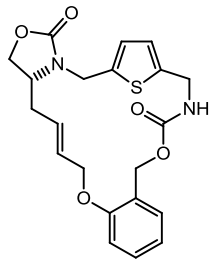
Following general procedure **A1**, 3-pyridyl isocyanate (10 mg, 0.082 mmol) and amine **223^{D}** (39 mg, 0.041 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **228** (15 mg, 0.03 mmol, 73%) as a brown oil; R_f 0.05 (EtOAc); $\alpha_D^{23.3}$ −16 (c. 0.5, MeOH); δ_H (500 MHz; $CDCl_3$) 8.77 (1H, br s, Py 2-H), 8.26 (1H, s, Py 6-H), 8.21 (1H, d, *J* 4.6, Py 5-H), 8.14 (1H, d, *J* 7.9, Py 4-H), 7.31 (2H, d, *J* 5.7, 8 or 9-H), 7.25 (1H, dd, *J* 8.5 and 4.4, 8 or 9-H), 7.03 (1H, br s, Thio 3 or 4-H), 6.95 (1H, ap t, *J* 7.5, 11-H), 6.88-6.84 (2H, m, Thio 3 or 4-H and 10-H), 5.72 (1H, d, *J* 15.2, 16-H), 5.62 (1H, d, *J* 15.2, 15-H), 5.29-5.02 (4H, m, 6-H_2 and 2-H_2), 4.61-3.81 (7H, m, 18-H, C*H*$_2$OH, N(CO)PyC*H*$_2$ and 14-H_2), 2.60 (1H, br s, 17-H_A), 2.07 (1H, br s, 17-H_B); δ_C (75 MHz; $CDCl_3$) 157.8, 156.6, 143.9, 143.0, 140.3, 140.0, 131.8, 130.5, 128.8, 128.4, 126.8, 126.6, 125.3, 124.4, 123.9, 120.8, 112.6, 68.5, 64.3, 63.0, 59.1, 45.7, 40.1, 32.3, 29.7; ν_{max}/cm^{-1} (film) 3303, 2925, 1695, 1661, 1532, 1254; *m/z* (ES$^+$) 509.2 (100%, [M+H]$^+$); found 509.1848, $C_{26}H_{28}N_4O_5S$ requires *MH* 509.1853

(15*E*,18*R*)-18-(Hydroxymethyl)-19-[(morpholin-4-yl)carbonyl]-5,13-dioxa-24-thia-3,19-diazatricyclo[19.2.1.0^{7,12}]tetracosa-1(23),7,9,11,15,21-hexaen-4-one 229



Following general procedure **A2**, cyclopropane carbonyl chloride (13 mg, 0.086 mmol), triethylamine (13 mg, 0.129 mmol) and amine **223^{D}** (41 mg, 0.043 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **229** (11 mg, 0.022 mmol, 51%) as a colourless glass; R_f 0.27 (90:10, $CHCl_3$—MeOH); $\alpha_D^{23.3}$ 18.7 (c. 0.2, MeOH); δ_H (500 MHz; $CDCl_3$) 7.37-7.28 (2H, m, 8 and 11-H), 6.95 (1H, t, *J* 7.3, 9-H), 6.88 (1H, d, *J* 8.3, 10-H), 6.75 (1H, s, Thio 3 or 4-H), 6.72 (1H, s, Thio 3 or 4-H), 5.81 (1H, dt, *J* 15.8 and 7.7, 16-H), 5.70 (1H, d , *J* 15.8, 15-H), 5.35 (1H, d, *J* 10.6, 6-H_A), 5.29-4.98 (1H, m, NH), 4.95 (1H, d, J 10.6, 6-H_B), 4.66-4.32 (6H, m, O(CH_2)$_2$ and 2-H_{AB}), 3.93 (1H, d, *J* 12.2, 20-H_A), 3.75-3.57 (5H, m, CH_2OH, 14-H_{AB} and 20-H_B), 3.49 (2H, ddd, *J* 13.3, 6.5 and 3.1, N(CH_A)$_2$), 3.39-3.26 (2H, m, N(CH_B)$_2$), 3.23 (1H, br s, 18-H), 2.61 (1H, dt, *J* 14.7 and 6.7, 17-H_A), 2.55 (1H, dt, J 14.7 and 7.5, 17-H_B); δ_C (75 MHz; $CDCl_3$) 164.5 (C=O), 157.7 (12-C), 156.4 (C=O), 143.6 (Thio 2-C), 139.9 (Thio 5-C), 131.9 (15-C), 130.6, 129.2, 127.1 (16-C), 126.0 (Thio 3-C), 124.9 (Thio 4-C), 124.1, 120.7 (9-C), 112.4 (11-C), 68.3 (*C*H_2OH), 66.7 (O(*C*H_2)$_2$), 61.2 (14-C), 59.0 (18-C), 49.5 (20-C), 47.4 (N(*C*H_2)$_2$), 40.1 (2-C), 31.9 (17-C); ν_{max}/cm^{-1} (film) 3321, 2856, 1703, 1606, 1455, 1252, 1115; *m/z* (ES$^+$) 502.2 (100%, [M+H]$^+$) and 524.2 (60%, [M+Na]$^+$); found 502.2006, $C_{25}H_{31}N_3O_5S$ requires *MH* 502.2006.

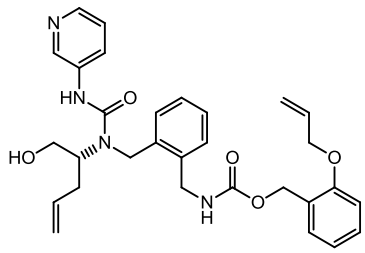
(7*R*,9*E*)-5,12,20-Trioxa-27-thia-3,22-diazatetracyclo[22.2.1.0^{3},7.0^{13,18}]heptacosa-1(26),9,13,15,17,24-hexaene-4,21-dione 232



Also obtained was the 2-oxazolidinone **232** (4 mg, 9.6 µM, 23%) as a colourless glass; R_f 0.24 (90:10, $CHCl_3$—MeOH) δ_H (500 MHz; C_6D_6; 343 K) 7.13-7.04 (2H, m, 16-H and 17-H), 6.72-6.78 (1H, 14-H), 6.67 (1H, d, J 3.5, Thio 3 or 4-H), 6.53 (1H, d, *J* 8.3, 15-H), 6.36 (1H, s, Thio 3 or 4-H), 5.33-5.26 (2H, m, 9 and 10-H), 5.23 (1H, d, *J* 10.8, 18-H_A), 5.11 (1H, s, NH), 4.58 (1H, d, *J* 15.4, 2 or 22-H), 4.30 (1H, s, 15-H), 4.08-3.98 (4H, m, 11-H_{AB} and 2 or 22-H), 3.83 (1H, br s, 2 or 22-H), 3.55 (1H, ap t, *J* 8.4, 6-H_A), 3.27 (1H, ap t, *J* 7.6, 6-H_B), 3.13-3.04 (1H, m, 7-H), 2.11-1.87 (2H, 8-H_{AB}); v_{max}/cm^{-1} (film) 3307, 3008, 2920, 1713, 1619, 1533, 1490, 1275, 1260; *m/z* (ES$^+$) 437.1 (100%, $[M+Na]^+$); found 437.1157, $C_{24}H_{30}N_2O_4$ requires *MH* 437.1142

Unable to obtain a ^{13}C NMR due to insufficient material

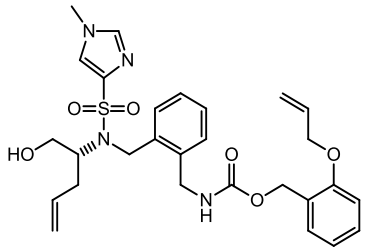
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[2-({[(2*R*)-1-hydroxypent-4-en-2-yl][(pyridin-3-yl)carbamoyl]amino}methyl)phenyl']methyl}carbamate 265a



Following general procedure **A1**, 3-pyridyl isocyanate (15 mg, 0.13 mmol) and amine **234^{D}** (70 mg, 0.068 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **265a** (21 mg, 0.04 mmol, 58%) as a pale yellow oil; R_f 0.19 (70:30 petrol−EtOAc); $[\alpha]_D^{23.7}$ 12.1 (c. 1, CH_2Cl_2); δ_H (500 MHz; MeOD) 8.38 (1H, br s, Py 2-H), 8.03 (1H, d, *J* 4.3, Py 6-H), 7.72 (1H, d, *J* 8.5, Py 4-H), 7.29-7.01 (7H, m, Py 5-H and Ph and Ph'), 6.83 (1H, d, *J* 8.4, Ph 6-H), 6.80 (1H, ap t, *J* 7.4, Ph 5-H), 5.93 (1H, ddt, *J* 17.4, 10.2 and 4.9, propenyl 2-H), 5.76-5.66 (1H, m, 4-H), 5.28 (1H, dd, *J* 17.4 and 1.8,

propenyl 3-H_A), 5.11 (1H, dd, *J* 10.2 and 1.8, propenyl 3-H_B), 5.05 (2H, s, PhCH_2O), 4.99 (1H, d, *J* 17.3, 5-H_A), 4.94 (1H, d, *J* 10.3, 5-H_B), 4.70 (1H, d, *J* 17.7, N(CO)PyCH_2Ph), 4.59 (1H, d, *J* 17.7, N(CO)PyCH_2Ph), 4.45 (2H, d, *J* 4.6, propenyl 1-H_2), 4.26 (2H, s, PhCH_2N(CO)O), 4.14 (1H, br s, 2-H), 3.59-3.48 (2H, m, CH_2OH), 2.41-2.25 (2H, m, 3-H_2); δ_C (75 MHz; $CDCl_3$) 159.3 (C=O), 158.9 (Ph 1-C), 157.9 (C=O), 144.2 (Py 6-C), 142.8 (Py 2-C), 138.8 (Py 3-C), 137.8 , 137.4, 136.5, 135.1, 130.7, 130.4, 130.0, 128.8, 128.7, 128.2, 126.8, 125.3, 121.9 (Ph 4-C), 118.4 (5-C), 117.6 (propenyl 3-C), 113.2 (Ph 6-C), 70.1 (propenyl 1-C), 64.2 , 63.5, 60.3 (2-C), 46.6, 42.9, 35.3 (3-C); ν_{max}/cm^{-1} (film) 3439, 3292, 3054, 2987, 2305, 1714, 1665, 1605, 1589, 1520, 1485, 1455, 1422, 1336 and 1273; *m/z* (ES^+) 531.3 (100%, $[M+H]^+$); found 531.2615, $C_{30}H_{34}N_4O_5$ requires *MH* 531.2602

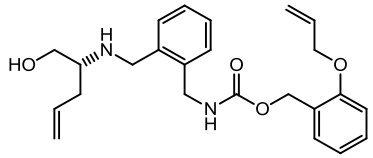
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[2-({*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]1-methyl-1H-imidazole-4-sulfonamido}methyl)phenyl']methyl}carbamate 265c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (62 mg, 0.34 mmol), pyridine (1 mL) and amine **234^D** (72 mg, 0.069 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **265c** (20.9 mg, 0.038 mmol, 55%) as a colourless glass; R_f 0.1 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 2 (c. 1, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.43-7.38 (2H, m,), 7.32-7.22 (2H, m,), 7.22-7.13 (4H, m,), 6.86 (1H, ap t, *J* 6.5), 6.78 (1H, d, *J* 7.9), 5.95 (1H, ddt, *J* 15.9, 10.2 and 4.9, propenyl 2-H), 5.58 (1H, br s, NH), 5.49-5.36 (1H, m, 4-H), 5.32 (1H, dd, *J* 17.3 and 1.7, propenyl 3-H_A), 5.18 (1H, dd, *J* 10.2 and 1.7, propenyl 3-H_B), 5.12 (2H, s, benzyl o(o)), 4.89-4.84 (2H, m, 5-H_A and 5-H_B), 4.48 (2H, d, *J* 5, propenyl 1-H), 4.42 (1H, d, *J* 15, N(SO_2Imid)CH_A), 4.34 (2H, d, *J* 6.1, PhCH_2N(CO)), 4.24 (1H, d, *J* 15, N(SO_2Imid)CH_B), 4.04-3.97 (1H, m, 2-H), 3.74-3.66 (1H, m, CH_2OH), 3.62 (3H, s, NMe), 3.55 (1H, dd, *J* 12.5 and 3.7, CH_2OH), 2.29 (1H, dt, *J* 14.1 and 6.7, 3-H), 2.10 (1H, dt, *J* 14.1 and 7.6, 3-H); δ_C (75 MHz; $CDCl_3$) 156.3 (Ph 1-C), 155.7 (C=O), 139.7 (Imid 1-C), 138.9, 136.3, 136.1, 135.5, 133.6, 129.2 (Imid 5-C), 128.9, 128.2, 127.1, 126.6, 126.5, 125.1, 125.0, 120.3 (Ph 4-C), 116.9 (5-C), 116.5 (propenyl 3-C), 111.9

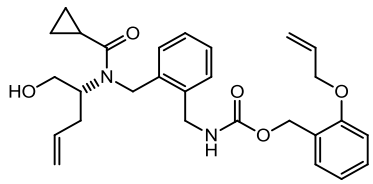
(Ph 6-C), 68.1 (propenyl 1-C), 61.8 (Ph*C*H_2O), 60.9 (1-C), 60.4 (2-C), 45.0 N(SO_2Imid)*C*H_2Ph, 41.0 (Ph*C*H_2N(CO)), 33.9 (3-C), 33.5 (NMe); ν_{max}/cm^{-1} (film) 3285, 1713, 1531, 1455, 1336, 1275; *m/z* (ES^+) 577.2 (100%, $[M+Na]^+$); found 555.2280, $C_{28}H_{34}N_4O_6S$ requires *MNa* 555.2272

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[2-({[(2*R*)-1-hydroxypent-4-en-2-yl]amino}methyl)phenyl']methyl}carbamate 265d



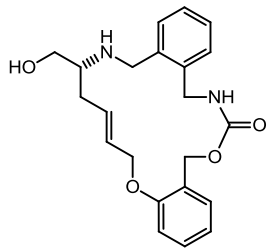
Following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the amine **234^D** (70 mg, 0.07 mmol); on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$−MeOH gave the amine **265d** (29 mg, 0.070 mmol, 99%) as a pale yellow oil; R_f 0.45 (90:10 $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 5.6 (c. 1.5, CH_2Cl_2); δ_H (500 MHZ; $CDCl_3$) 7.24-7.09 (6H, m, Ar), 6.83 (1H, d, *J* 8.2, Ph 5-H), 6.80 (1H, t, *J* 7.5, Ph 6-H), 5.94 (1H, ddt, *J* 16, 10.3 and 5, propenyl 2-H), 5.71 (1H, ddt, *J* 17.3, 10.1 and 7, 4-H), 5.29 (1H, dd, *J* 16 and 1.9, propenyl 3-H_A), 5.11 (1H, dd, *J* 1.3 and 10.3, propenyl 3-H_B), 5.05 (2H, s, PhC*H*$_2$O), 4.97 (1H, dd, *J* 17.3 and 1.9, 5-H_A), 4.93 (1H, dd, *J* 10.1 and 2.0, 5-H_B), 4.45 (2H, d, *J* 5, propenyl 1-H_2), 4.29 (2H, s, PhC*H*$_2$N(CO)), 3.78 (1H, d, *J* 12.5, NHC*H*$_A$Ph), 3.73 (1H, d, *J* 12.5, NHC*H*$_B$Ph), 3.50 (1H, d, *J* 11.2 and 4.8, 1-H_A), 3.37 (1H, d, *J* 11.2 and 6.4, 1-H_B), 2.67-2.61 (1H, m, 2-H), 2.20-2.09 (2H, m, 3-H_2); δ_C (75 MHz; $CDCl_3$) 159.2 (Ph 1-C), 157.9 (C=O), 139.2 (Ph'), 139.1 (Ph'), 136.8 (propenyl 2-C), 135.1 (4-C); 131.3 (Ph'), 130.3 (Ph'), 130.6 (Ph'), 130.4 (Ph), 129.1 (Ph'), 129.9 (Ph); 121.8 (Ph 4-C), 118.2 (5-C), 117.6 (propenyl 3-C), 113.1 (Ph 6-C), 70.1 (propenyl 1-C), 64.4 (1-C), 63.4 (Ph*C*H_2O), 60.2 (2-C), 50.0, 43.8 , 36.9 (3-C); ν_{max}/cm^{-1} (film) 3260, 2925, 2858, 1698, 1540, 1494, 1454, 1361; *m/z* (ES^+) 411.2 (100%, $[M+H]^+$); found 411.2286, $C_{24}H_{30}N_2O_4$ requires *MH* 411.2278

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-[(2-{[1-cyclopropyl-*N*-(1-hydroxypent-4-en-2-yl)formamido]methyl}phenyl)methyl]carbamate 265b



Following general procedure **A2**, cyclopropane carbonyl chloride (37 mg, 0.36 mmol), triethylamine (73 mg, 0.72 mmol) and amine **234^{D}** (75 mg, 0.072 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **265b** (15 mg, 0.031 mmol, 44%) as a colourless glass; R_f 0.41 ($CHCl_3$); $[\alpha]_D^{23.7}$ 8 (c. 1.5, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.47-7.22 (6H, m, Ar), 6.94 (1H, t, *J* 7.4, Ar 3-C), 6.88 (1H, d, *J* 8.3, Ar 4-C), 6.04 (1H, ddt, *J* 17.3, 10.4 and 5, propenyl 2-H), 5.75 (1H, ddt, *J* 17.1, and 6.9, 4-H), 5.41 (1H, dd , *J* 17.3 and 1.5, propenyl 3-H_A), 5.30-5.22 (3H, m, $PhCH_2O$ and propenyl 3-H_B), 5.13-5.03 (3H, m, NH and 5-H_{AB}), 4.87 (1H, d, *J* 17.5, N(CO)CH_APh), 4.67 (1H, d, *J* 17.5, N(CO)CH_BPh), 4.57 (2H, d, *J* 4.9, $PhCH_2NH(CO)$), 4.42 (2H, d, *J* 5.8, propenyl 1-H2), 4.12-4.00 (1H, m, 2-H), 3.76 (1H, d, *J* 10.3, 1-H_A), 3.64 (1H, br s, 1-H_B), 3.47 (1H, br s, OH), 2.42 (2H, ap t, *J* 6.9, 3-H_{AB}), 1.49 (1H, br s, ^{C}Pr), 1.08-0.95 (2H, ^{C}Pr), 0.77-0.69 (2H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 134.8, 133.1, 129.6, 128.9, 128.3, 127.6, 126.5, 124.9, 120.6 (Ar 3-C), 117.7 (propenyl 3-C), 117.2 (5-C), 111.8 (Ar 4-C); 77.2 (propenyl 1-C), 68.8 ($PhCH_2O$), 64.1 (1-C), 60.0 (2-C), 47.8 (N(CO)CH_2Ph), 43.4 ($PhCH_2NH(CO)$); 33.1 (3-C), 12.4 (^{C}Pr), 8.4 (^{C}Pr); *missing Ar 2-C and C=O*; ν_{max}/cm^{-1} (film) 3307, 2920, 2352, 2319, 1713, 1619, 1532, 1493, 1455; *m/z* (ES$^+$) 479.3 (20%, $[M+H]^+$) and 552.3 (100%, $[M+MeCN+MeOH]^+$); found 479.2562, $C_{28}H_{34}N_2O_5$ requires *MH* 479.2540

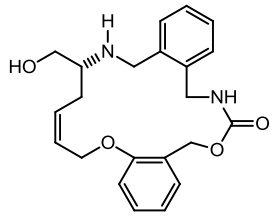
(15*E*,18*R*)-18-(Hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one 256d



Following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the amine ***E*-244^{D}** (33 mg, 0.035 mmol); on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **256d** (11.1 mg, 0.029 mmol, 83%) as a pale yellow film; $[\alpha]_D^{23.7}$ 14.4 (c. 0.6, MeOH); δ_H (500 MHz; MeOD/DMSO-*d6*) 7.33-7.21 (5H, m, 8-H, 22-H, 23-H, 24-H and 25-H), 7.18 (1H, d, *J* 7.2, 9-H), 6.83 (1H, d, *J* 8.4, 11-H), 6.78 (1H, d, *J* 7.2, 10-H), 6.09 (1H, br s, 16-H), 5.68 (1H, d, *J* 15.8, 15-H), 5.08 (1H, d, *J* 11.6, 6-H), 5.02 (1H, d, *J* 11.6, 6-H), 4.42 (2H, s, 14-H), 4.24 (1H, d, *J* 14.4, 2-H), 4.15 (1H, d, *J*

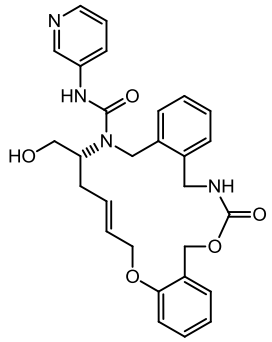
14.4, 2-H), 4.02 (1H, s, 18-H), 3.71-3.52 (2H, m, 20-H), 3.25-2.92 (2H, m, CH_{AB}OH), 2.37 (2H, br s, 17-H); δ_C (125 MHz; MeOD/DMSO-*d6*) 159.7 (12-C), 159.4 (CO), 133.2 , 132.1, 130.3, 129.8, 122.4 , 113.9 (9-C), 106.4 (11-C), 68.6 (14-C), 64.9 (6-C), 62.3 (*C*H_2OH), 44.7 (20-C), 31.4 (17-C), *2-C and aromatic carbons missing*; ν_{max}/cm^{-1} (film) 3006, 2989, 2409, 1715, 1459; *m/z* (ES$^+$) 383.2 (100%, [M+H]$^+$); found 383.1955, $C_{24}H_{30}N_2O_4$ requires *MH* 383.1965

(15*E*,18*R*)-18-(Hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one 257



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine ***Z*-244^D** (50 mg, 0.05 mmol); on completion of the reaction it was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2-MeOH gave the amine **159d** (10.4 mg, 0.027 mmol, 54%) as a pale yellow film; R_f 0.51 (CH_2Cl_2—EtOH—NH_4OH 50:8:1); $[\alpha]_D^{23.7}$ 0.3 (c. 1, MeOH); δ_H (500 MHz; MeOD/DMSO-*d6*) 7.38-7.20 (6H, m, Ar), 7.05-6.94 (1H, m, 11-H), 6.90 (1H, t, *J* 7.4, 9-H), 5.83 (1H, dt, *J* 11.6 and 6.0, 15-H), 5.7 (1H, dt, *J* 11.6 and 7.1, 16-H), 5.19 (1H, d , *J* 10.9, 6-H_A), 4.91 (1H, d, *J* 10.9, 6-H_B), 4.62 (1H, dd, *J* 12.1 and 6.3, 14-H_A), 4.57 (1H, dd, *J* 12.1 and 5.8, 14-H_B), 4.37 (1H, d, *J* 13.8, 2-H_A), 4.29 (1H, d, *J* 13.8, 2-H_B), 3.88 (1H, d, *J* 12.1, 20-H_A), 3.78 (1H, d, *J* 12.1, 20-H_B), 3.66 (1H, dd, *J* 11.2 and 4.1, CH_AOH), 3.41 (1H, dd, *J* 11.2 and 6.6, CH_BOH), 2.84-2.78 (1H, m, 18-H), 2.47 (1H, dt, *J* 15.3 and 6.7, 17-H_A), 2.37 (1H, dt, *J* 15.3 and 7.6, 17-H_B); δ_C (125 MHz; MeOD/DMSO-*d6*) 158.7 (12-C), 138.1, 133.6, 132.9 (16-C), 131.5, 131.3, 128.9, 126.9 (15-C), 121.8 (9-C), 114.4 (11-C), 66.1 (2-C), 64.6 (6-C), 64.1 (*C*H_2OH), 60.8 (18-C), 50.1 (20-C), 31.0 (17-C), *C=O missing*; ν_{max}/cm^{-1} (film) 3055, 2988, 2305, 1669, 1605, 1522, 1421, 1262; *m/z* (ES$^+$) 383.2 (100%, [M+H]$^+$); found 383.1965, $C_{24}H_{30}N_2O_4$ requires *MH* 383.1965

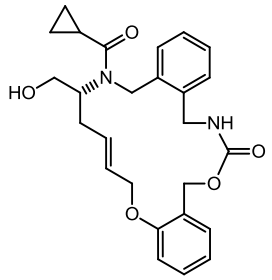
(15*E*,18*R*)-18-(Hydroxymethyl)-4-oxo-*N*-(pyridin-3-yl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaene-19-carboxamide 256a



Following general procedure **A1**, 3-pyridyl isocyanate (10 mg, 0.06 mmol) and amine ***E*-244^{D}** (31 mg, 0.033 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **256a** (18 mg, 0.033 mmol, 99%) as a pale yellow film; R_f 0.41 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 12 (c. 0.8, CH_2Cl_2); δ_H (500 MH_Z; MeOD; 333 K) 8.38 (1H, s, Ar), 8.09 (1H, s, Ar), 7.69 (1H, s, Ar), 7.50 (1H, s, *J* 7.7, Ar), 7.32-7.11 (6H, m, Ar), 6.91-6.86 (2H, m, 10 and 11-H), 5.87 (1H, dd, *J* 15.1 and 6.6, 15 or 16-H), 5.85-5.81 (1H, m, 15 or 16-H), 4.96-4.05 (9H, m, 2-H, 6-H, 14-H, 18-H and 20-H); 3.81-3.74 (2H, m, CH_{AB}OH), 2.63 (1H, br s, 17-H), 2.49 (1H, d, *J* 12.6, 17-H); δ_C (75 MHz; MeOD; 333 K) 159.0 (12-C), 158.8 (C=O), 158.6 (C=O), 144.2 (Py), 142.7 (Py), 132.6, 131.4, 130.5, 129.8 (15 or 16-C), 129.4 (15 or 16-C), 128.3 (Py), 124.9, 121.5, 113.2 (11-C), 69.1 (14-C), 64.8 (6-C), 54.7 (20-C), 39.6 (2-C), 30.7 (17-C) ; ν_{max}/cm^{-1} (film) 3281, 3053, 2926, 2127, 1707, 1661, 1531, 1456, 1421, 1262; *m/z* (ES$^+$) 503.2 (100%, $[M+H]^+$); found 503.2311, $C_{28}H_{30}N_4O_5$ requires *MH* 503.2289

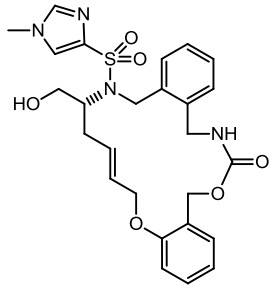
full carbon assignment was not possible due to rotamers

(15*E*,18*R*)-19-Cyclopropanecarbonyl-18-(hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one 256b



Following general procedure **A2**, cyclopropane carbonyl chloride (19.3 mg, 0.2 mmol), triethylamine (100 mg, 1 mmol) and amine ***E*-244^{D}** (35 mg, 0.037 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **256b** (8.1 mg, 0.018 mmol, 47%); as a pale yellow oil; R_f 0.23 ($CHCl_3$); $[\alpha]_D^{23.7}$ 5.5 (c. 0.4, MeOH); δ_H (500 MHz; MeOD; 233 K) 7.71 (1H, d, *J* 7.7, Ar), 7.45-7.16 (5H, m, Ar), 7.01 (1H, d, *J* 8.4, Ar); 6.89 (1H, t, *J* 7.3, 9-H), 6.13 (1H, d, *J* 10.9, 6-H_A), 5.93 (1H, dd, *J* 15.5 and 9.1, 15-H), 5.64 (1H, d, *J* 15.5, 16-H), 5.24-5.19 (1H, m, 18-H), 4.94 (1H, d, *J* 18.3, 2-H_A), 4.84 (1H, d, *J* 13.6, 20-H_A), 4.58 (1H, ap t, *J* 9.1, 14-H_A), 4.49 (1H, d, *J* 18.3, 2-H_B), 4.38-4.32 (2H, m, 14-H_B and 6-H_B), 4.01 (1H, d, *J* 13.6, 20-H_B), 3.62-3.56 (2H, m, C*H*$_{AB}$OH), 2.5-2.29 (2H, m, 17-H_{AB}), 1.29 (1H, s, ^{C}Pr), 0.85-0.80 (1H, m, ^{C}Pr), 0.36 (1H, d, *J* 7, ^{C}Pr), 0.25 (1H, d, J 7, ^{C}Pr), 0.15 (1H, br s, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 180.2 (C=O), 159.2 (12-C), 158.5 (7-C), 140.2, 134.6 (15-C), 132.7, 132.1, 131.9, 131.8, 130.1, 129.9 (16-C), 128.2, 127.6, 125.8, 121.2 (9-C), 112.0 (11-C), 69.7 (14-C), 64.2 (*C*H_2OH), 62.7 (6-C), 57.0 (18-C), 45.4 (20-C), 43.6 (2-C), 34.5 (17-C), 14.2 (^{C}Pr), 10.5 (^{C}Pr); v_{max}/cm^{-1} (film) 3307, 1688, 1623, 1530, 1495, 1456; *m/z* (ES$^+$) 451.2 (100%, [M+H]$^+$); found 451.2241, $C_{26}H_{30}N_4O_6S_1$ requires *MH* 451.2227

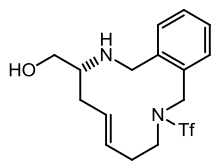
(15*E*,18*R*)-18-(Hydroxymethyl)-19-(1-methyl-1H-imidazole-4-sulfonyl)-5,13-dioxa-3,19-diazatricyclo[19.4.0.0^{7,12}]pentacosa-1(25),7,9,11,15,21,23-heptaen-4-one 256c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (23 mg, 0.13 mmol), pyridine (1 mL) and amine ***E*-244^{D}** (30 mg, 0.03 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **256c** (14.4 mg, 0.29 mmol, 88%) as a colourless film; R_f 0.24 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 10 (c. 0.7, CH_2Cl_2); δ_H (500 MHz; MeOD; 333 K) 7.65 (1H, br s, Ar), 7.50 (2H, br s, Ar), 7.35-7.09 (5H, m, Ar), 6.94-6.87 (3H, m, 9, 10 and 11-H); 5.60 (2H, br s, 15 and 16-H), 5.21 (1H, br s, 6-H), 5.04 (1H, br s, 6-H), 4.53-4.28 (4H, 14-H and 20-H), 3.92 (1H, dd, *J* 11.2 and 6.7, C*H*$_A$OH), 3.86-3.65 (3H, m, 18-H and 2-H), 3.59 (1H, dd, *J* 11.2 and 6.5, C*H*$_B$OH), 3.35 (3H, s, Me), 2.52-2.36 (2H, m, 17-H); δ_C (75 MHz; $CDCl_3$) 159.1 (12-C), 158.5 (C=O), 141.7 (Imid 4-C), 140.7 (Imid 2-C), 132.5, 131.4, 130.5, 128.9, 128.4, 126.3, 121.3 (9-C), 112.9 (11-C), 68.7 (14-C), 65.0 (*C*H_2OH), 64.8 (6-C), 44.7 (20-C), 40.7 (2-C), 34.9 (17-C), 34.2 (NMe); ν_{max}/cm^{-1} (film) 3308, 2822, 1942, 1708, 1604, 1530, 1495, 1455, 1331; *m/z* (ES$^+$) 527.2 (100%, [M+Na]$^+$); found 527.1948, $C_{26}H_{30}N_4O_6S_1$ requires *MNa* 527.1959

Full carbon assignment was not possible due to rotamers

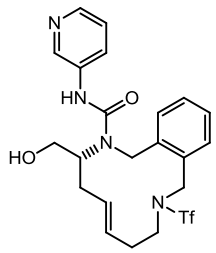
[(5*E*,3*R*)-9-(Trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecin-3-yl]methanol 159d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **246^{D}** (66 mg, 0.07 mmol); on completion of the reaction it was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product

was purified by column chromatography, eluting with CH_2Cl_2:EtOH:NH_4OH 50−8−1 gave the amine **159d** (12.2 mg, 0.032 mmol, 46%) as a pale yellow film; R_f 0.71 (CH_2Cl_2—EtOH—NH_4OH, 50:8:1); $[\alpha]_D^{23.7}$ 3.8 (c. 0.6, MeOH); δ_H (500 MHz; MeOD; 333 K) 7.40-7.27 (4H, m, Ar), 5.34 (1H, ddd, *J* 15.8, 8.4 and 3.9, 5 or 6-H), 5.25 (1H, ddd, *J* 15.8, 10. and 5.6, 5 or 6-H), 5.09 (1H, d, *J* 15.9, 10-H_A), 4.85 (1H, d, *J* 15.9, 10-H_B), 4.02 (1H, d, *J* 13.6, 1-H_A), 3.73 (1H, d, *J* 13.6, 1-H_B), 3.66 (1H, ddd, *J* 15, 6.8 and 4.3, C*H*$_A$OH), 3.55 (1H, dd, *J* 10.7 and 5.9, 8-H_A), 3.54 (1H, dd, *J* 10.7 and 3.6, 8-H_B), 3.45 (1H, ddd, *J* 15 and 7.7, 3.6, C*H*$_B$OH), 2.68 (1H, dtd, *J* 11.4, 5.8 and 2.6, 3-H), 2.35-2.28 (2H, m, 4-H_A and 7-H_A), 2.27-2.18 (1H, m, 7-H_B), 1.84-1.72 (1H, m, 4-H_B); δ_C (125 MHz; MeOD) 140.1 (Ar), 134.3 (Ar); 132.3 (5 or 6 C), 132.1 (5 or 6 C), 130.7 (Ar), 129.9 (Ar), 129.3 (Ar), 129.1 (Ar); 121.6 (q, *J* 318, (CF_3), 79.8 (10-C), 66.4 (*C*H_2OH), 59.4 (3-C), 51.7 (1-C), 49.2 (8-C), 36.5 (4-C), 34.1 (7-C); ν_{max}/cm^{-1} (film) 3348, 2928, 2353, 2256, 2128, 1723, 1644, 1455, 1384; *m/z* (ES^+) 379.1 (100%, $[M+H]^+$); found 379.1309, $C_{16}H_{21}F_3N_2O_3S_1$ requires *MH* 379.1298

(5*E*,3*R*)-3-(Hydroxymethyl)-*N*-(pyridin-3-yl)-9-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecine-2-carboxamide 159a

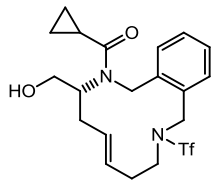


Following general procedure **A1**, 3-pyridyl isocyanate (18 mg, 0.15 mmol) and amine **246^D** (70 mg, 0.075 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product; on completion of the reaction it was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the urea **159a** (28.8 mg, 0.058 mmol, 77%) as a colourless solid; m.p. 78.9-81.2 ˚C (DMSO); R_f 0.89 (50:8:1, CH_2Cl_2—EtOH—NH_4OH); $[\alpha]_D^{23.7}$ 1.6 (c. 1.4, MeOH); δ_H (300 MHz; DMSO-*d6*; 343 K) 8.60 (1H, d, *J* 2.6, Py 2-H), 8.56 (1H, s, NH), 8.16 (1H, dd, *J* 4.6 and 1.6, Py 6-H), 7.84 (1H, ddd, *J* 8.3, 2.6 and 1.6, Py 4-H), 7.48-7.23 (5H, m, Ar and Py 5-H), 5.22 (1H, br s, 5- or 6-H), 4.97 (1H, br s, 5- or 6-H), 4.85 (1H, d, *J* 14.4, 1-H_A or 10-H_A), 4.80 (1H, d, *J* 16.6, 1-H_A or 10-H_A), 4.63 (1H, d, *J* 16.6, 1-H_B or 10-H_B), 4.39 (1H, d, *J* 14.4, 1-H_B or 10-H_B), 4.31 (1H, s, 3-H), 3.72 (2H, s, C*H*$_{AB}$OH), 3.54 (1H, d, 8-H_A), 3.45-3.31 (1H, m, 8-H_B), 2.60-2.46 (1H, m, 4-H_A), 2.38-2.21 (1H, m, 4-H_B), 2.07-1.93 (2H, m, 7-H_{AB}); δ_C (75 MHz; DMSO-*d6*/MeOD; 333 K)

158.5 (C=O), 144.3 (Py 2-C), 142.9 (Py 4-C), 129.9, 129.6, 128.4, 125.0, 120.8, 62.9 (CH_2OH), 53.6 (8-C), 33.9 (7-C), 33.7 (4-C), *10-C, 3-C and CF_3 missing*; ν_{max}/cm^{-1} (film) 3006, 2989, 1638, 1588, 1532, 1478, 1424, 1388; *m/z* (ES^+) 499.2 (100%, $[M+H]^+$); found 499.1610, $C_{22}H_{25}F_3N_4O_4S$ requires *MH* 499.1621

Full carbon assignment was not possible due to rotamers

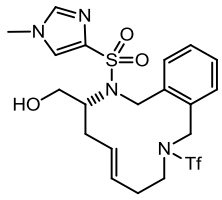
[(5*E*,3*R*)-2-Cyclopropanecarbonyl-9-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecin-3-yl]methanol 159b



Following general procedure **A2**, cyclopropane carbonyl chloride (35 mg, 0.34 mmol), triethylamine (69 mg, 0.68 mmol) and amine **246^D** (64 mg, 0.068 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product; on completion of the reaction it was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 70:30 petrol—EtOAc gave the amide **159b** (20 mg, 0.045 mmol, 66%) as a pale yellow oil; R_f 0.41 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ 3 (c. 1.3, CH_2Cl_2); δ_C (500 MHz; DMSO-*d6*; 343 K) 7.30-6.75 (4H, m, Ar), 5.37-2.80 (10H, m, 5-H, 6-H, 1-H_2, 8-H_2, 10-H_2 and CH_2OH), 2.35-2.23 (1H, m, 3-H), 2.18-1.81 (2H, m, 4-H_A and 7-H_A), 1.80-1.53 (2H, m, 4-H_B and 7-H_B), 0.74-0.32 (5H, m, ^{C}Pr); δ_C (125 MHz; DMSO-*d6*; 343 K) 173.5, 128.9, 128.5, 127.0, 124.1, 121.5, 118.9, 59.6, 54.7, 51.5, 47.3, 32.3, 30.8, 30.5, 28.9, 11.0, 7.9, 7.8, 7.3, *CF_3 missing*; ν_{max}/cm^{-1} (film) 3388, 3007, 2989, 2949, 1726, 1625, 1455, 1428, 1387, ; *m/z* (ES^+) 447.2 (100%, $[M+H]^+$); found 447.1567, $C_{20}H_{25}F_3N_2O_4S$ requires *MH* 447.1560

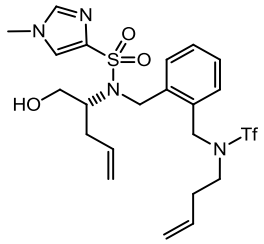
Full proton and carbon assignment was not possible due to severely broad peaks

[(5*E*,3*R*)-2-(1-Methyl-1H-imidazole-4-sulfonyl)-9-(trifluoromethane)sulfonyl-1,2,3,4,7,8,9,10-octahydro-2,9-benzodiazacyclododecin-3-yl]methanol 159c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (68 mg, 0.33 mmol), triethylamine (73 mg, 0.72 mmol) and amine **246^{D}** (68 mg, 0.072 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product; on completion of the reaction it was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc → 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the sulfonamide **159c** (27 mg, 0.051 mmol, 72%) as a colourless glass; R_f 0.31 (EtOAc); $[\alpha]_D^{23.7}$ 28.1 (c. 1.4, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.87 (1H, s, Imid), 7.85 (1H, s, Imid), 7.50-7.38 (4H, m, Ar), 4.99 (1H, d, *J* 17, 10-H_A), 4.96-4.85 (2H, m, 5- and 6-H), 4.51 (1H, d, *J* 16, 1-H_A), 4.45 (1H, d, *J* 17, 10-H_B), 4.20 (1H, d, *J* 16, 1-H_B), 3.76 (4H, s, NMe and 3-H), 3.69-3.50 (4H, CH_2OH and 8-H_{AB}), 2.46-2.38 (1H, m, 4-H_A), 2.33-2.26 (1H, m, 7-H_A), 2.10-2.03 (1H, m, 4-H_B), 2.02-1.95 (1H, m, 7-H_B); δ_C (125 MHz; DMSO-*d6*; 343 K) 139.7 (Imid 4-C), 139.3 (Imid 2-C), 128.2, 127.6, 125.5, 122.2 (q, *J* 325, CF_3), 59.6 (*C*H_2OH), 50.3 (1-C), 47.7 (8-C), 33.6 (NMe), 32.8 (4-C), 31.6 (7-C), *10-C missing*; ν_{max}/cm^{-1} (film) 3286, 3056, 2947, 2306, 1712, 1532, 1455, 1438, 1423, 1382, 1327; *m/z* (ES$^+$) 523.1 (100%, $[M+H]^+$); found 523.1295, $C_{20}H_{25}F_3N_4O_5S_2$ requires *MH* 523.1291

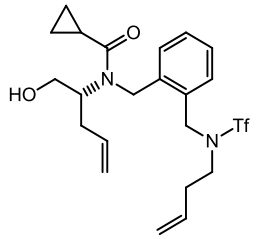
(2*R*)-*N*-[(2-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-1-hydroxy-*S*-(1-methyl-1H-imidazol-4-yl)pent-4'-ene-2'-sulfonamido 267c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (89.5 mg, 0.49 mmol), triethylamine (100 mg, 0.99 mmol) and amine **209^{D}** (96 mg, 0.1 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and

following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc gave the sulfonamide **267c** (29 mg, 0.052 mmol, 53%); R_f 0.23 (EtOAc); $[\alpha]_D^{23.7}$ 3.1 (c. 1.4, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.62 (1H, d, *J* 5.8, Ar), 7.52 (1H, d, *J* 1.4, Imid), 7.37 (1H, d, *J* 1.4, Imid), 7.36-7.31 (3H, m, Ar), 5.61-5.48 (1H, m, 4'-H or 3-H), 5.52 (1H, ddt, *J* 16.9, 10.3 and 6.1, 3-H or 4'-H), 5.01-4.95 (3H, m, 4-H_A or 5'-H_A , 5'-H_B and 4-H_B), 4.92 (1H, dd, *J* 17.1 and 1.6, 4-H_B or 5'-H_B), 4.68 (2H, br s, PhC*H*$_2$NTf), 4.45 (1H, d, *J* 15.9, N(SO_2Imid)C*H*$_2$Ph), 4.35 (1H, d, *J* 15.9, N(SO_2Imid)C*H*$_2$Ph), 4.08 (1H, m, 2'-H), 3.76 (4H, m, NMe and C*H*$_A$OH), 3.67 (1H, dd, *J* 12.6 and 3.6, C*H*$_B$OH), 3.30 (2H, t, *J* 8, 1-H), 2.47-2.18 (2H, m, 3'-H), 2.10 (2H, br s, 2-H), 1.66 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 138.6 (Imid 4-C), 136.9 (Imid 2-C), 133.3, 132.8, 131.3, 130.5, 128.5, 126.9, 126.7, 126.2, 122.8, 120.3, 115.9 (5'-C or 4-C), 115.7 (5'-C or 4-C), 62.1 (1'-C), 60.6 (2'-C), 48.2 (Ph*C*H_2NTf), 46.3 (N(SO_2Imid)*C*H_2Ph), 34.9 (3'-C), 32.2 (NMe), 30.8 (2-C), *CF_3 missing*; ν_{max}/cm^{-1} (film) 3006, 2988, 2318, 1642, 1532, 1456, 1386, 1337; *m/z* (ES^+) 551.2 (100%, $[M+H]^+$); found 551.1613, $C_{22}H_{29}F_3N_4O_5S_2$ requires *MH* 551.1604

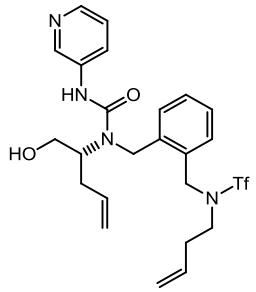
_N_-[(2-{[_N_-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-_N_-[(2_R_)-1-hydroxypent-4'-en-2'-yl]cyclopropanecarboxamide 267b



Following general procedure **A2**, cyclopropane carbonyl chloride (55.4 mg, 0.53 mmol), triethylamine (107 mg, 1.06 mmol) and amine **209^D** (103 mg, 0.106 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the amide **267b** (35 mg, 0.073 mmol, 70%) as a colourless oil; R_f 0.93 (EtOAc); $[\alpha]_D^{23.7}$ 4.8 (c. 1.7, CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 7.55-7.26 (4H, m, Ar), 5.79 (1H, ddt, *J* 17.1, 9.7 and 7.4, 4'-H), 5.52 (1H, ddt, *J* 17, 10.2 and 6.8, 3-H), 5.15-5.06 (2H, m, 5'-H_2), 4.99 (1H, d, *J* 10.2, 4-

H_A), 4.90 (1H, d, *J* 17, 4-H_B), 4.91 (1H, d, *J* 18.4, N(C=O)C*H*$_2$Ph), 4.71 (1H, d, *J* 18.4, N(C=O)C*H*$_2$Ph), 4.51 (2H, br s, PhC*H*$_2$NTf), 4.16-4.06 (1H, m, 2'-H), 3.80 (1H, dt, *J* 11.8 and 3.8, 1'-H_A), 3.67 (1H, dt, *J* 11.8 and 6.9, 1'-H_B), 3.40-3.26 (2H, 1-H_2), 2.45 (2H, ap t, *J* 7.4, 2-H_2), 2.17-2.09 (2H, br s, 3'-H_{AB}), 1.46-1.36 (1H, m, ^{C}Pr), 1.21-1.01 (2H, m, ^{C}Pr), 0.81-0.69 (2H, m, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 176.6 (C=O), 134.5 (4'-C), 133.0 (3-C), 130.1, 129.5, 127.8, 127.0, 118.1 (5'-C), 117.9 (4-C), 64.1 (1'-C), 60.1 (2'-C), 50.7 (N(C=O)*C*H$_2$Ph), 48.2 (Ph*C*H$_2$NTf), 47.8 (1-C), 33.2 (3'-C), 33.0 (2-C), 12.5 (^{C}Pr), 8.6 (^{C}Pr), 8.5 (^{C}Pr); *CF_3 missing*; ν_{max}/cm^{-1} (film) 3284, 3079, 3006, 2984, 1727, 1664, 1587, 1536, 1484; *m/z* (ES$^+$) 475.2 (20%, [M+H]$^+$) and 548.3 (100%, [M+MeOH,MeCN,H]$^+$); found 475.1884 , $C_{22}H_{29}F_3N_2O_4S_1$ requires *MH* 475.1873

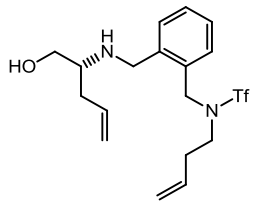
3-[(2-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-3-[(2*R*)-1-hydroxypent-4'-en-2'-yl]-1-(pyridin-3-yl)urea 267a



Following general procedure **A1**, 3-pyridyl isocyanate and amine **209^D** (99 mg, 0.1 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the urea **267a** (40 mg, 0.076 mmol, 76%) as a colourless glass; R_f 0.77 (50:8:1 CH_2Cl_2—EtOH—NH_4OH); $[\alpha]_D^{23.7}$ 1.96 (c. 2, MeOH); δ_H (500 MHz; $CDCl_3$) 9.27 (1H, br s, NH), 8.29 (1H, s, Py), 8.22-8.05 (2H, m, Py), 7.46-7.30 (4H, m, Ar), 7.30-7.18 (1H, m, Ar), 5.73 (1H, ddt, *J* 15.9, 11.2 and 7, 4'-H), 5.55 (1H, ddt, *J* 17.1, 10.4 and 6.8, 3-H), 5.09 (1H, d , *J* 11.2, 5'-H_A), 5.08 (1H, d, *J* 15.9, 5-H_B), 4.99 (1H, d, *J* 10.4, 4-H_A), 4.95 (1H, d, *J* 17.1, 4-H_B), 4.67 (4H, br s, PhC*H*$_2$NTf and N(C=O)C*H*$_2$Ph), 3.80-3.58 (3H, m, 1'-H_2 and 2'-H), 3.39 (2H, t, *J* 8, 1-H_2), 2.58 (1H, dt, *J* 14.8 and 7.6, 3'-H_A), 2.42 (1H, dt, *J* 14.8 and 7.1, 3'-H_B), 2.22-2.10 (2H, m, 2-H); δ_C (75 MHz; $CDCl_3$) 156.7 (C=O), 142.6 (Py), 139.7 (Py), 137.2 (Py), 136.4, 134.0 (4'-C), 133.1 (3-C), 132.8, 129.2, 128.7, 128.6, 128.1, 126.9 (Py), 124.0; 118.5 (4-C), 118.1 (5'-C), 64.1 (1'-C), 59.9 (2'-C), 49.8 (1-C), 48.6 (N(C=O)*C*H$_2$Ph), 47.8 (Ph*C*H$_2$NTf), 33.3 (3'-C), 32.8 (2-C),

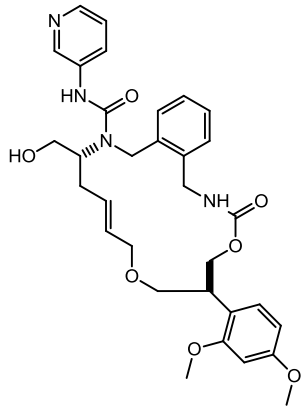
CF_3 missing; ν_{max}/cm^{-1} (film) 3006, 2989, 1715, 1614, 1587, 1508, 1464; *m/z* (ES^+) 527.2 (100%, $[M+H]^+$); found 527.1937, $C_{24}H_{29}F_3N_4O_4Si$ requires *MH* 527.1934

_N_-(But-3-en-1-yl)-1,1,1-trifluoro-_N_-{[2-({[(2_R_)-1-hydroxypent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 267d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **209^D** (104 mg, 0.107 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2−EtOH−NH_4OH gave the amine **267d** (40 mg, 0.098 mmol, 92%) as a pale yellow oil; R_f 0.89 (50:8:1 CH_2Cl_2—EtOH—NH_4OH); $[\alpha]_D^{23.7}$ −2 (c. 2, CH_2Cl_2); δ_H (500 MHz; MeOD) 7.37-7.22 (4H, m, Ar), 5.74 (1H, ddt, *J* 17.2, 10.1 and 7.1, 4'-H), 5.47 (1H, ddt, *J* 17.1, 10.3 and 6.9, 3-H), 5.00 (1H, ddd, *J* 17.2, 3.2 and 1.4, 5'-H_A), 4.96 (1H, dd, *J* 10.1 and 1.4, 5'-H_B), 4.86 (1H, d, *J* 10.3, 4-H_A), 4.83-4.76 (1H, m, 4-H_B), 4.85-4.54 (2H, br s, PhC*H_2*NTf), 3.85 (1H, d, *J* 13, NHC*H_A*Ph), 3.78 (1H, d, *J* 13, NHC*H_B*Ph), 3.51 (1H, dd, *J* 11 and 4.9, 1'-H_A), 3.38 (1H, dd, *J* 11 and 6.4, 1'-H_B), 3.31 (2H, t, *J* 7.8, 1-H_2), 3.21 (1H, ap p, *J* 1.6, OH), 2.65 (1H, qd, *J* 6.3 and 4.7, 2'-H), 2.20-2.13 (2H, m, 3'-H_2), 1.95 (2H, br s, 2-H_2); δ_C (75 MHz; $CDCl_3$) 140.2 (Ar), 136.9 (4'-C), 135.4 (3-C), 134.9 (Ar), 131.5 (Ar), 130.8 (Ar), 130.0 (Ar), 129.2 (Ar), 121.9 (d, *J* 323.9, *C*F_3), 118.3 (4-H and 5'-H), 118.1 (4-H and 5'-H), 64.5 (1'-C), 60.2 (2'-C), 51.5 (1-C), 50.0 (Ph*C*H_2NTf), 49.7 (NH*C*H_2Ph), 37.0 (3'-C), 34.7 (2-C); ν_{max}/cm^{-1} (film) 3402, 3079, 2984, 2881, 1642, 1456, 1387; *m/z* (ES^+) 407.2 (100%, $[M+H]^+$); found 407.1623, $C_{18}H_{25}F_3N_2O_3S$ requires *MH* 407.1611

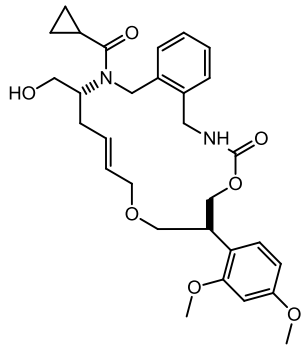
(6*S*,10*E*,13*R*)-6-(2,4-Dimethoxyphenyl)-13-(hydroxymethyl)-3-oxo-*N*-(pyridin-3-yl)-2,3,5,6,7,9,12,13,14,15-decahydro-1H-4,8,2,14-benzodioxadiazacycloheptadecine-14-carboxamide 258a



Following general procedure **A1**, 3-pyridyl isocyanate (10 mg, 0.068 mmol) and amine **245^{D}** (35 mg, 0.034 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction the crude product was purified by column chromatography, eluting with EtOAc gave the amine **258a** (12.5 mg, 0.021 mmol, 62%) as a yellow glass; $[\alpha]_D^{23.7}$ 0.6 (c. 0.6, CH_2Cl_2); R_f 0.29 (EtOAc); δ_H (500 MHz; $CDCl_3$; 323 K) *E*/*Z* >75/<25 8.24-8.17 (2H, m, Py 2 and 6-H), 7.96 (1H, d, Py 4-H^{min}), 7.91 (1H, d, *J* 7.4, Py 4-H), 7.57 (1H, d, *J* 7.7, Py 5-H), 7.49 (1H, d, *J* 7.7, Py 5-H^{min}), 7.36-7.05 (5H, m, Ar), 6.92 (1H, d, *J* 8.4, DMB 6-H), 6.42 (1H, dd, *J* 10.7 and 2.5, DMB 5-H), 6.38 (1H, dd, *J* 8.4 and 2.5, DMB 5-H^{min}), 6.13 (1H, s, DMB 3-H^{min}), 5.72 (1H, ddd, *J* 15.9, 6.9 and 3.7, 10-H), 5.71-5.65 (2H, m,11-H and 10-H^{min}), 5.62 (1H, dt, *J* 11.1 and 7.2, 11-H^{min}), 5.21 (1H, br s, NH), 5.12 (1H, br s, NH), 4.83-4.01 (6H, m, 1-H_2, 20-H_2 and 5-H_2) 3.96-3.72 (7H, m, OMe, 9-H_{AB} and CH_{AB}OH), 3.71 (3H, s, OMe), 3.64 (1H, dd, *J* 9.7 and 4.8, 7-H_A), 3.58 (1H, dd, *J* 9.7 and 6.7, 7-H_B), 3.56-3.46 (1H, m, 6-H), 3.40 (1H, br s, 13-H), 2.63-2.53 (1H, m, 12-H_A), 2.49-2.37 (1H, m, 12-H_B); δ_C (75 MHz; MeOD; 333 K) 159.9, 159.6, 158.0, 157.9, 156.9, 156.8, 156.3, 143.6, 141.2, 140.9, 136.9, 136.4, 134.6, 131.3, 130.6, 129.0, 128.9, 128.8, 128.5, 127.7, 127.4, 127.3, 127.0, 123.6, 123.5, 120.4, 104.4, 104.1, 98.8, 71.2, 71.1, 69.1, 66.7, 65.7, 64.6, 60.3, 55.4 (OMe), 55.3 (OMe), 55.3, 44.4, 38.1, 32.3, 27.8 ; ν_{max}/cm^{-1} (film) 3281, 3053, 2926, 2127, 1707, 1661, 1605, 1531, 1495, 1484, 1456; *m/z* (ES$^+$) 591.3 (100%, [M+H]$^+$); found 591.2827, $C_{32}H_{38}N_4O_7$ requires *MH* 591.2813

Full carbon assignment was not possible due to geometric isomers and rotamers

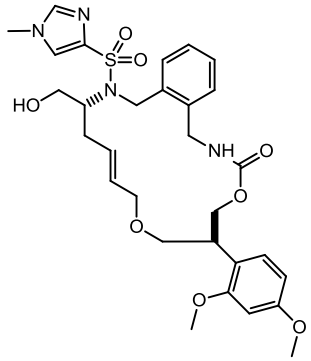
(6*S*,10*E*,13*R*)-14-Cyclopropanecarbonyl-6-(2,4-dimethoxyphenyl)-13-(hydroxymethyl)-2,3,5,6,7,9,12,13,14,15-decahydro-1H-4,8,2,14-benzodioxadiazacycloheptadecin-3-one 258b



Following general procedure **A2**, cyclopropane carbonyl chloride (14 mg, 0.14 mmol), triethylamine (28 mg, 0.28 mmol) and amine **245^{D}** (29 mg, 0.028 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction; the crude product was purified by column chromatography, eluting with 50:50 EtOAc—petrol gave the amide **258b** (11.9 mg, 0.022 mmol, 79%); R_f 0.66 (50:50, petrol—EtOAc); $[\alpha]_D^{23.7}$ 0.7 (c. 0.6, MeOH); δ_H (500 MHz; $CDCl_3$; 333 K) >90/<10 *E*/*Z* 7.51-7.01 (5H, m, Ar), 6.47-6.35 (2H, m, DMB), 5.73-5.63 (2H, m, 10 and 11-H), 5.11-3.10 (20H, m, 1-H_{AB}, 5-H_{AB}, 6-H, 7-H_{AB}, 9-H_{AB}, 15-H_{AB}, CH_{AB}OH and 2 x OMe), 2.71-2.25 (2H, 12-H_{AB}), 1.55 (1H, ^{C}Pr), 1.06 (2H, ^{C}Pr), 0.73 (2H, ^{C}Pr); δ_C (125 MHz; $CDCl_3$) 176.3 (C=O), 176.1 (C=O), 174.9 (C=O), 159.8, 159.6, 159.3, 157.9, 157.8, 156.6, 156.0, 137.3, 136.9, 134.3, 131.8, 131.2, 130.9, 130.8, 130.7, 129.8, 129.1, 128.9, 128.8, 128.5, 128.2, 127.7, 127.4, 127.2, 126.9, 126.7, 126.4, 126.3, 120.3, 120.1, 103.8, 103.7, 103.6, 98.5, 98.5, 98.4, 98.3, 71.5 (9-C), 71.1 (9-C), 67.8, 66.7, 65.9, 64.4, 63.7, 55.4 (OMe), 55.4 (OMe), 44.2, 37.9, 37.3, 31.9, 12.6 (^{C}Pr), 12.4 (^{C}Pr), 12.1 (^{C}Pr), 8.8 (^{C}Pr), 8.7 (^{C}Pr), 8.5 (^{C}Pr); ν_{max}/cm^{-1} (film) 3301, 3101, 2996, 2131, 1706, 1591, 1611, 1526 and 1444; *m/z* (ES$^+$) 539.3 (100%, $[M+H]^+$); found 539.2776, $C_{30}H_{38}N_2O_7$ requires *MH* 539.2752

Full carbon assignment was not possible to mixture of geometric isomers and rotamers

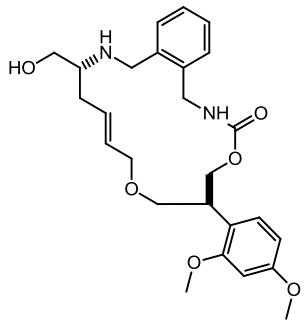
(6*S*,10*E*,13*R*)-6-(2,4-Dimethoxyphenyl)-13-(hydroxymethyl)-14-(1-methyl-1H-imidazole-4-sulfonyl)-2,3,5,6,7,9,12,13,14,15-decahydro-1H-4,8,2,14-benzodioxadiazacycloheptadecin-3-one 258c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (10.8 mg, 0.06 mmol), triethylamine (9.1 mg, 0.09 mmol) and amine **245**^{D} (31 mg, 0.03 mmol) gave the crude product after 9 h. The crude product was purified by F-SPE and following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the crude product; on completion of the reaction the crude. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **258c** (8 mg, 0.013 mmol, 43%) as a colourless glass; R_f 0.31 (90:10, $CHCl_3$−MeOH); $[\alpha]_D^{23.7}$ 2.9 (c. 0.4, MeOH); δ_H (500 MHZ; DMSO-*d6*) >80/<20 *E*/*Z*; 7.69 (1H, d, *J* 1.4, Imid), 7.51 (1H, d, *J* 1.4, Imid), 7.50-7.43 (1H, m, Ar), 7.20-7.08 (3H, Ar), 7.03 (1H, d, *J* 8.4, DMB 6-H), 6.45 (1H, d, *J* 2.5, DMB 3-H), 6.37 (1H, dd, *J* 8.4 and 2.5, DMB 5-H), 5.37 (1H, br s, 10 or 11-H), 5.21 (1H, br s, 10 or 11-H), 4.59-4.39 (2H, m, 1-H_A and 5-H_A), 4.32-4.18 (2H, m, 1-H_B and 5-H_B), 4.18-4.02 (1H, m, 15-H_A), 3.91 (1H, d, 15-H_B), 3.86-3.73 (2H, m, 9-H_{AB}), 3.71 (3H, s, OMe), 3.64 (3H, s, OMe), 3.58-3.35 (5H, CH_{AB}OH, 7-H_2 and 6-H or 13-H), 3.50 (3H, s, NMe), 3.33-3.20 (1H, 6-H or 13-H), 2.34-2.31 (1H, m, 12-H_A), 2.11 (1H, dt, *J* 15.4 and 9.4, 12-H_B); δ_C (75 MHz; DMSO-*d6*) 159.4, 157.6, 155.5, 139.7, 139.5, 129.8, 129.6, 128.3, 127.1, 126.5, 124.6, 120.3, 105.0, 99.9, 98.7, 69.9, 67.5, 63.9, 55.7, 55.2, 37.3, 33.3, 32.3, 28.9; ν_{max}/cm^{-1} (film) 3056, 2988, 2305, 2257, 2129, 1651; *m/z* (ES$^+$) 615.2 (95%, $[M+NH_4]^+$) and 637.2 (100%, $[M+Na]^+$); found 637.2320, $C_{30}H_{38}N_4O_8S$ requires *MNa* 637.2303

Full carbon assignment was not possible to mixture of geometric isomers and rotamers

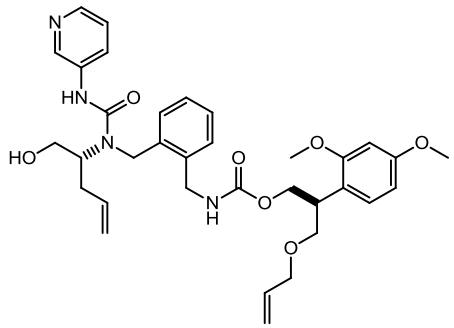
(6*S*,13*R*)-6-(2,4-Dimethoxyphenyl)-13-(hydroxymethyl)-2,3,5,6,7,9,12,13,14,15-decahydro-1H-4,8,2,14-benzodioxadiazacycloheptadecin-3-one 258d



Following general procedure **S2**, tetra-*n*-butylammonium fluoride (1M, 0.1 mL) was added to the amine **245^{D}** (50 mg, 0.048 mmol); on completion of the reaction, the crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **258d** (23 mg, 0.048 mmol, 99%) as a pale yellow glass; R_f 0.16 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 1.7 (c. 1.2, MeOH); δ_H (500 MHz; $CDCl_3$) >80/<20 *E*/*Z* 7.40-7.22 (5H, m, DMB 6-H and Ar), 7.12-7.03 (1H, m,), 6.51 (1H, d, *J* 2.4, DMB 3-H), 6.45-6.38 (1H, m, DMB 5-H), 5.89 (1H, dt, *J* 14.1 and 6.7, 11-H), 5.69-5.61 (m, 11-H^{min} and 10-H^{min}), 5.57 (1H, dt, *J* 14.1 and 4.7, 10-H), 4.43-4.29 (2H, m, 1-H_2 and 15-H_2) 4.06-3.84 (4H, 9-H_{AB} and 5-H_{AB}), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 3.74-3.51 (4H, C*H*$_{AB}$OH and 7-H_{AB}), 2.91 (1H, 13-H), 2.82 (p, 13-H^{min}), 2.57-2.50 (12-H^{min}), 2.45-2.36 (1H, 12-H), 2.28-2.21 (1H, 12-H); δ_C (75 MHz; $CDCl_3$) 160.2 (DMB 2 or 4-C^{min}), 160.1(DMB 2 or 4-C), 158.4 (DMB 2 or 4-C), 158.4 (DMB 2 or 4-C^{min}), 156.9 (C=O), 138.9, 138.1, 131.1, 131.0, 130.9 (10-C), 130.7 (11-C), 129.7, 129.4, 129.3, 128.6, 128.4, 127.1, 120.8, 104.5 (DMB 5-C), 99.1 (DMB 3-C^{min}), 98.9 (DMB 3-C), 74.0 (min), 71.7 (9-C), 70.1 (9-C^{min}), 67.6 (8-C^{min}), 67.1 (8-C), 66.5, 64.4 (*C*H_2OH), 63.3 (*C*H_2OHmin), 59.9 (13-C), 59.5 (13-C^{min}), 55.7 (2 × OMe), 50.9 (1-C), 50.3 (1-C^{min}), 45.4 (5-C^{min}), 44.6 (5-C), 38.4 (15-C), 37.3 (12-C^{min}), 35.0 (12-C), 30.1 (6-C); ν_{max}/cm^{-1} (film) 3278, 2913, 2449, 2414, 1683, 1614, 1507, 1464, 1438; *m/z* (ES$^+$) 471.3 (100%, $[M+H]^+$); found 471.2496, $C_{26}H_{34}N_2O_6$ requires *MH* 471.2490

Full carbon assignment was not possible to mixture of geometric isomers and rotamers

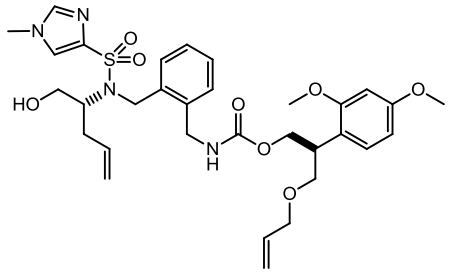
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({[(2*R*)-1-hydroxypent-4-en-2-yl][(pyridin-3-yl)carbamoyl]amino}methyl)phenyl]methyl}carbamate 266a



Following general procedure **A1**, 3-pyridyl isocyanate (8 mg, 0.066 mmol) and amine **235^{D}** (35 mg, 0.033 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **266a** (20.3 mg, 0.033 mmol, 99%) as a colourless glass; R_f 0.13 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ −1.5 (c. 1, MeOH); δ_H (500 MHz; $CDCl_3$) 8.94 (s, Py)^{min}, 8.84 (1H, s, Py), 8.52 (s, Py) ^{min}, 8.32 (1H, s, Py), 8.12 (1H, s, Py), 7.54 (1H, s, Py), 7.45-6.54 (5H, Ar), 6.45-6.30 (2H, m, DMB 3 and 5-H), 5.81 (1H, ddt, *J* 17.4, 10.6 and 7.1, propenyl 2-H), 5.69-5.62 (1H, m, 4-H), 5.17 (1H, dd , *J* 17.4 and 1.8, propenyl 3-H_A), 5.08 (1H, d, *J* 10.6, propenyl 3-H_B), 5.01-4.91 (2H, m, 5-H_{AB}), 4.64 (1H, s, N(COPy)CH_2Ph or PhCH_2N(CO)), 4.46 (1H, s, N(COPy)CH_2Ph or PhCH_2N(CO)), 4.39-4.09 (5H, propyl 1-H_2, 2-H, N(COPy)CH_2Ph or PhCH_2N(CO)), 3.90 (2H, d, *J* 5.6, propenyl 2-H_2), 3.81-3.46 (11H, 2 x OMe, propyl 3-H_2 and propyl 2-H, CH_2OH), 2.35-2.12 (2H, m, 3-H); δ_C (125 MHz; C_6D_6/MeOH; 343 K) 160.3 (DMB 2 or 4-C), 158.8 (DMB 2 or 4-C), 138.9, 135.2, 129.8, 129.33, 129.3, 128.9, 120.5, 119.9 (5-C), 117.5 (propenyl 3-C) ^{min}, 116.0 (propenyl 3-C), 105.1(DMB 5-C), 99.2 (DMB 3-C), 71.9 (propenyl 1-C), 71.0 (propenyl 1-C)^{min}, 70.9 (propyl 3-C), 66.1 (1-C), 63.1^{min}, 62.5 (2-C) , 56.9, 55.2 (OMe), 54.9 (OMe), 54.1^{min}, 49.4 (propyl 1-C), 46.4, 43.4^{min}, 41.7, 38.7 (propyl 2-C), 35.8^{min}, 33.9 (3-C), 32.1^{min}; ν_{max}/cm^{-1} (film) 3333, 2930, 2852, 1681, 1613, 1566, 1508, 1466; *m/z* (ES$^+$) 619.3 (100%, [M+H]$^+$); found 619.3149 , $C_{34}H_{42}N_4O_7$ requires *MH* 619.3126

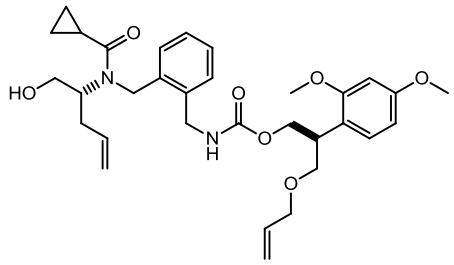
Full carbon assignment was not possible to mixture of rotamers

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]1-methyl-1H-imidazole-4-sulfonamido}methyl)phenyl]methyl}carbamate 266c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (30 mg, 0.16 mmol), triethylamine (32 mg, 0.32 mmol) and amine **235**^{D} (34 mg, 0.032 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **266c** (14.8 mg, 0.023 mmol, 73%) as a colourless oil; R_f 0.06 (70:30 petrol—EtOAc); $[\alpha]_D^{23.7}$ 0.8 (c. 0.7, MeOH); δ_H (500 MHz; $CDCl_3$) 7.46 (2H, s, Ar), 7.35 (1H, s, Ar), 7.32-7.28 (1H, m, Ar), 7.27-7.19 (2H, m, Ar), 7.10 (1H, d, Ar), 6.44-6.41 (2H, m, DMB 3 and 5-H), 5.85 (1H, ddt, *J* 17.3, 10.7 and 5.5, propenyl 2-H), 5.55-5.41 (2H, 4-H and NH), 5.22 (1H, dd, *J* 17.3 and 1.8, propenyl 3-H_A), 5.12 (1H, dd, *J* 10.5 and 1.8, propenyl 3-H_B), 4.96-4.90 (2H, m, 5-H_{AB}), 4.46 (1H, d, N(SO_2Imid)CH_APh), 4.39-4.27 (5H, propyl 1-H_{AB} PhCH_2N(CO) and N(SO_2Imid)CH_BPh), 4.04 (1H, t, *J* 9.5, 2-H), 3.94 (2H, s, propenyl 1-H_2), 3.77 (6H, 2 x OMe), 3.71 (3H, NMe), 3.64-3.57 (5H, 1-H_{AB} and propyl 3-H_{AB} and propyl 2-H), 2.39-2.31 (1H, 3-H_A), 2.15 (1H, dt, *J* 15 and 7.7, 3-H_B); δ_C (75 MHz; $CDCl_3$) 159.6 (DMB 2 or 4-C), 158.3 (DMB 2 or 4-C), 156.7 (C=O), 140.9 (Imid), 138.7 (propenyl 2-C) , 137.2 (Imid), 134.9, 134.8, 133.9, 130.7, 129.6, 128.9, 128.1, 127.5, 124.5, 120.1, 117.5 (propenyl 3-C), 116.7 (5-C), 104.0 (DMB 5-C), 98.6 (DMB 3-C); 71.9 (propenyl 1-C), 70.4 (1-C), 65.3 (propyl 1-C), 63.5 (2-C), 62.6 (propyl 3-C), 55.4 (OMe), 55.3 (OMe), 48.8 (N(SO_2Imid)CH_2Ph), 42.1 PhCH_2N(CO), 37.9 (propyl 2-C), 36.7 (3-C), 34.2 (NMe); ν_{max}/cm^{-1} (film) 3055, 2987, 2305, 1713, 1612, 1508, 1421 and 1264; *m/z* (ES$^+$) 665.3 (100%, [M+Na]$^+$); found 665.2584, $C_{32}H_{42}N_4O_8S$ requires *MNa* 665.2616

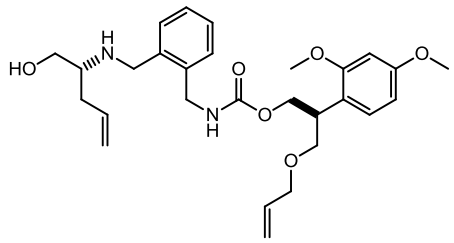
(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({1-cyclopropyl-*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]formamido}methyl)phenyl]methyl}carbamate 266b



Following general procedure **A2**, cyclopropane carbonyl chloride (15 mg, 15 mmol), triethylamine (30 mg, 30 mmol) and amine **235^{D}** (32 mg, 0.03 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amide **266b** (7.6 mg, 0.017 mmol, 56%) as a colourless glass; R_f 0.66 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ 1.3 (c. 0.5, MeOH); δ_H (500 MHz; C_6D_6) 7.41 (1H, d, *J* 7.6, Ar), 7.31-7.20 (1H, m, Ar), 7.12 (1H, t, *J* 7.8, Ar), 7.06 (1H, t, *J* 7.6, Ar), 6.99 (1H, d, *J* 7.4, Ar), 6.48-6.45 (2H, m, DMB 3 and 5-H), 5.85 (1H, ddt, *J* 17.4, 10.6 and 5.4, propenyl 2-H), 5.76 (1H, ddt, *J* 17.2, 10.1 and 7.4, 4-H), 5.22 (1H, dd , *J* 17.4 and 1.9, propenyl 3-H_A), 5.09 (1H, dd, *J* 17.2 and 1.8, 5-H_A), 5.04 (1H, d, *J* 10.6, propenyl 3-H_B), 5.01 (1H, d, *J* 10.1, 5-H_B), 4.79 (1H, dd, *J* 10.7 and 7.2, propyl 1-H_A), 4.69 (1H, dd, *J* 10.7 and 6.3, propyl 1-H_B), 4.63 (1H, br s, PhC*H*$_A$N(CO)), 4.51 (1H, br s, PhC*H*$_B$N(CO)), 4.16 (2H, d, *J* 6, propyl 1-H), 4.11 (1H, br s, propyl 2-H), 3.94 (1H, p, 2-H), 3.89 (2H, s, propenyl 1-H_2), 3.76-3.74 (2H, m, N(CO^{C}Pr)C*H*$_2$Ph), 3.61 (2H, br s, propyl 3-H), 3.47 (3H, s, OMe), 3.39 (3H, s, OMe), 2.43 (1H, br s, OH), 1.49-1.11 (3H, m, ^{C}Pr and 3-H), 0.66-0.44 (2H, m, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 160.4 (DMB 2 and 4-C), 135.5, 129.5, 128.9, 124.8, 121.0, 117.1 (propenyl 2-C), 115.8 (5-C), 105.0 (DMB 3-C), 72.0 (propenyl 1-C), 71.3 (1-C), 65.9 (propyl 1-C), 63.9 (propyl 3-C), 60.3 (2-C), 55.1 (OMe), 54.9 (OMe), 42.6 (PhC*H*$_A$N(CO), 39.2 (3-C), 12.5 (^{C}Pr), 8.1 (^{C}Pr), 7.9 (^{C}Pr), N(CO^{C}Pr)*C*H$_2$Ph *missing*; ν_{max}/cm^{-1} (film) 3326, 3006, 2959, 2929, 1713, 1614, 1508, 1463 and 1439; *m/z* (ES$^+$) 567.3 (100%, [M+H]$^+$); found 567.3057, $C_{32}H_{42}N_2O_7$ requires *MH* 567.3065

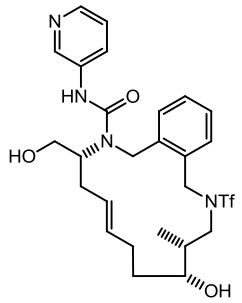
Full carbon assignment was not possible to mixture of rotamers

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-({[(2*R*)-1-hydroxypent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 266d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **235^{D}** (30 mg, 0.03 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **266d** (9.4 mg, 0.019 mmol, 63%) as a pale yellow oil; R_f 0.34 (90:10, petrol—EtOAc); $[\alpha]_D^{23.7}$ 80.4 (c. 0.5, MeOH); δ_H (500 MHz; $CDCl_3$) 7.36-7.26 (4H, m, Ar), 7.12 (1H, d, Ar), 6.48-6.42 (2H, m, DMB 3 and 5-H), 5.88 (1H, ddt, *J* 16.8, 10.2 and 5.5, propenyl 2-C), 5.81 (1H, ddt, *J* 17.1, 9.9 and 7.3, 4-H), 5.24 (1H, d , *J* 16.8, propenyl 3-H_A), 5.18-5.12 (3H, m, propenyl 3-H_B and 5-H_{AB}), 4.46-4.33 (4H, m, propyl 1-H_2 and PhC*H*$_2$N(CO)), 3.97 (2H, s, propenyl 1-H_2), 3.90-3.80 (8H, m, OMe and NHC*H*$_2$Ph), 3.65 (4H, br s, 1-H_A, propyl 2-H and propyl 3-H_{AB}), 11.1 and 5.9 (1H, dd , *J* 11.1 and 5.9, 1-H_A), 2.28 (1H, ap t , *J* 5.6, 2-H), 2.31 (2H, ap t, *J* 6.9, 3-H); δ_C (75 MHz; $CDCl_3$) 159.5 (DMB 2 and 4-C), 158.4 (C=O), 134.9, 134.5, 132.5, 130.4, 128.9, 127.9, 121.9, 120.1, 118.1 (propenyl 3-C), 116.7 (5-C), 103.9 (DMB 5-C), 98.6 (DMB 3-C), 71.9 (propenyl 1-C), 70.6 (1-C), 63.5 (2-C), 55.4 (OMe), 55.3 (OMe), 38.1 (propyl 2-C), 35.5 (3-C), N(CO^{C}Pr)*C*H$_2$Ph and NH*C*H$_2$Ph *missing*; ν_{max}/cm^{-1} (film) 3326, 3004, 2922, 1705, 1614, 1587, 1508, 1464; *m/z* (ES$^+$) 499.3 (100%, [M+H]$^+$); found 499.2797, $C_{28}H_{38}N_2O_6$ requires *MH* 499.2803

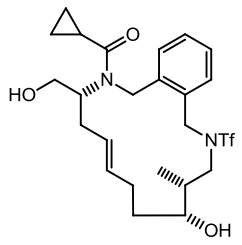
(3*R*,9*R*,10*R*)-9-Hydroxy-3-(hydroxymethyl)-10-methyl-*N*-(pyridin-3-yl)-12-(trifluoromethane)sulfonyl-2,3,4,7,8,9,10,11,12,13-decahydro-1H-2,12-benzodiazacyclopentadecine-2-carboxamide 259a



Following general procedure **A1**, 3-pyridyl isocyanate (14 mg, 0.112 mmol) and amine **247^{D}** (63 mg, 0.056 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by mass−directed liquid chromatography and gave the urea **259a** (3.8 mg, 0.0067 mmol, 12%) as a colourless film; R_f 0.4 (EtOAc); ν_{max}/cm^{-1} (film) 2921, 2851, 1667, 1580, 1385, 1260, 1225, 1188, 1107 and 1025; *m/z* (ES$^+$) 553.2 (100%, [M−H_2O]$^+$); found 533.2094, $C_{26}H_{31}F_3N_4O_4S$ requires *M*−H_2O 553.2091

Unable to obtain ^{1}H and ^{13}C spectra due to insufficient material

(4*R*,5*R*,11*R*)-12-Cyclopropanecarbonyl-11-(hydroxymethyl)-4-methyl-2-(trifluoromethane)sulfonyl-2,3,4,5,6,7,10,11,12,13-decahydro-1H-2,12-benzodiazacyclopentadecin-5-ol 259b

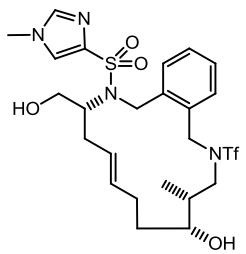


Following general procedure **A2**, cyclopropane carbonyl chloride (31 mg, 0.29 mmol), triethylamine (60 mg, 0.59 mmol) and amine **247^{D}** (67 mg, 0.059 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by mass−directed liquid column chromatography and gave the amide **259b** (12.8 mg, 0.025 mmol, 42%) as a

colourless glass; R_f 0.39 (EtOAc); $[\alpha]_D^{23.7}$ 11.4 (c. 0.6, MeOH); δ_H (500 MHz; $CDCl_3$) 7.64 (d, *J* 7.8, Ar^{min}), 7.40-7.17 (4H, m, Ar), 5.52 (1H, dd, *J* 10.8 and 5.8, 8 or 9-H^Z), 5.49-5.43 (1H, m, 8 or 9-$H^{Z\ and\ E}$), 5.12 (1H, d, *J* 14, 1-H_A^Z), 5.08-4.99 (m, mix 1-$H_A^E{}_B^Z$), 4.92 (1H, d, *J* 16.7, 1-H_B^E), 4.25 (1H, m, *J* 11.2 and 5.7, CH_A^ZOH), 4.18 (1H, dd, *J* 11.2 and 5.4, CH_B^ZOH), 3.98 (d, *J* 13.5, 13-H_A^E), 3.93 (d, *J* 13.5, 13-H_B^E), 3.83 (1H, d, *J* 11.7, 13-H_{AB}^Z), 3.79 (1H, s, 5-H^Z), 3.66 (1H, d, *J* 11.7, 13-H^Z), 3.55 (d, *J* 9.5, CH_B^EOH), 3.45 (1H, dd, *J* 14.6 and 10.7, 3-H_A), 3.13 (1H, dd, *J* 14.6 and 4.8, 3-H_B), 3.01-2.90 (1H, 11-H), 2.42 (d, *J* 13.5, 10-H_A^E), 2.28 (1H, dt, *J* 14.7 and 9.5, 10-H_{AB}^Z), 2.14 (2H, s, 10-H_B^E, 7-H_{AB}^Z), 2.08-1.48 (9H, m, ^{C}Pr, 4-H, 7-H_{AB}, 10-H_{AB}, 6-H_{AB}), 1.06-1.01 (2H, m, ^{C}Pr), 0.94-0.85 (2H, m, ^{C}Pr), 0.70 (3H, d, *J* 6.9, Me^Z), 0.54 (d, *J* 6.5, Me^E); δ_C (75 MHz; $CDCl_3$) 174.7, 164.9, 138.2, 132.7, 130.7, 129.4, 128.2, 128.0, 127.8, 127.2, 76.7, 66.7, 65.7, 63.5, 56.9, 56.6, 53.3, 50.1, 49.8, 47.9, 32.5, 30.9, 22.8, 12.8, 9.6, 9.4, 8.4, 8.3; ν_{max}/cm^{-1} (film) 3759, 3586, 2940, 1725, 1456, 1383, 1274, 1266, 1225; *m/z* (ES^+) 519.2 (100%, $[M+H]^+$); found 519.2155, $C_{24}H_{33}F_3N_2O_5S$ requires *MH* 519.2135

full carbon assignment was not possible to mixture of geometric isomers and rotamers

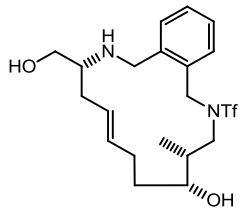
(4*R*,5*R*,11*R*)-11-(Hydroxymethyl)-4-methyl-12-(1-methyl-1H-imidazole-4-sulfonyl)-2-(trifluoromethane)sulfonyl-2,3,4,5,6,7,10,11,12,13-decahydro-1H-2,12-benzodiazacyclopentadecin-5-ol 259c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (52 mg, 0.29 mmol), triethylamine (58 mg, 0.58 mmol) and amine **247^D** (65 mg, 0.057 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by mass−directed preparative liquid chromatography, and gave the sulfonamide **266c** (4.1 mg, 0.007 mmol, 12%) as a colourless glass; R_f 0.12 ($CHCl_3$); $[\alpha]_D^{23.7}$ 0.3 (c. 0.4, MeOH); ν_{max}/cm^{-1} (film) 3006, 2990, 1462, 1384, 1335; *m/z* (ES^+) 617.1 (100%, $[M+Na]^+$); found 595.1898, $C_{24}H_{33}F_3N_4O_6S_2$ requires *MH* 595.1872

Unable to obtain ^1H and ^{13}C spectra due to insufficient material

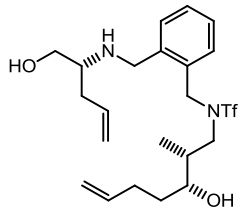
(4*R*,5*R*,11*R*)-11-(Hydroxymethyl)-4-methyl-2-(trifluoromethane)sulfonyl-2,3,4,5,6,7,10,11,12,13-decahydro-1H-2,12-benzodiazacyclopentadecin-5-ol 259d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **247^{D}** (61 mg, 0.054 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by mass−directed liquid column chromatography, and gave the amine **259d** (5.2 mg, 0.012 mmol, 22%) as a pale yellow oil; R_f 0.15 (95:5 $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −1.2 (c. 0.5, MeOH); ν_{max}/cm^{-1} (film) 3580, 3387, 2933, 1658, 1457, 1384, 1257; *m/z* (ES$^+$) 451.2 (100%, $[M+H]^+$); found 451.1878, $C_{20}H_{29}F_3N_2O_4S$ requires *MH* 451.1873

Unable to obtain ^1H and ^{13}C spectra due to insufficent material

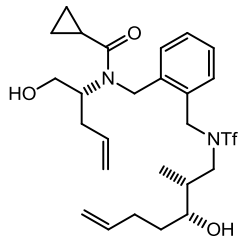
1,1,1-Trifluoro-*N*-[(2*R*,3*R*)-3-hydroxy-2-methylhept-6-en-1-yl]-*N*-{[2'-({[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 268d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **114^{D}** (48 mg, 0.042 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by mass−directed liquid column chromatography, and gave the amine **268d** (15.5 mg, 0.032 mmol, 77.2%) as a colourless oil; R_f 0.21 ($CHCl_3$); $[\alpha]_D^{23.7}$ 3.2 (c. 1.5, MeOH); δ_H (500 MHz; $CDCl_3$) 7.53-7.42 (4H, m, Ar), 5.95-5.77 (2H, m, 4'-H and 6-H), 5.34 (1H, dd, *J* 17.3 and 1.6, 7-H_A), 5.29 (1H, d , *J* 10.6, 7-H_B), 5.03 (1H, dd, *J* 17.1 and 1.7, 5'-H_A), 4.98 (1H, dd, *J* 10.1 and 1.7, 5'-H_A), 4.56 (1H, d, *J* 13.5, PhCH_ANTf), 4.50 (1H, d, *J* 13.5, PhCH_BNTf), 4.02 (1H, dd, *J* 12.3 and 3.6, 1'-H_A), 3.84 (1H, dd, *J* 12.3 and 5, 1'-H_B), 3.54-3.42 (2H, m, NHCH_{AB}Ph), 3.28 (1H, d, *J* 7.3, 1-H_A), 3.25 (1H, d, *J* 7.3, 1-H_B), 3.28-3.23 (1H, m, 3-H), 2.66-2.59 (1H, m, 2'-H), 2.12-2.02 (1H, m, 3'-H_A), 1.99-1.91 (1H, m, 3'-H_B), 1.47-1.22 (8H, m, CH_3, 2-H, 4-H_{AB} and 5-H_{AB}); δ_C (125 MHz;

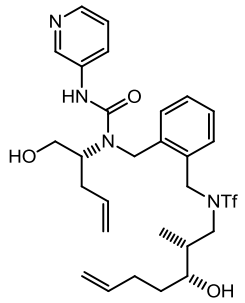
$CDCl_3$) 139.4, 136.6, 133.8, 132.8, 131.7, 131.4, 130.6, 125.7, 120.3, 115.3, 63.8, 60.7, 59.0, 48.0, 38.5, 38.0, 33.6, 32.8, 31.5, 28.7, 14.5, 9.3; ν_{max}/cm^{-1} (film) 3250, 3034, 1538 and 1372; *m/z* (ES^+) 479.2 (100%, $[M+H]^+$); found 479.2204, $C_{22}H_{33}F_3N_2O_4S$ requires *MH* 479.2186

_N_-{[2-({_N_-[(2_R_,3_R_)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-_N_-[(2'_R_)-1'-hydroxypent-4'-en-2'-yl]cyclopropanecarboxamide 268b



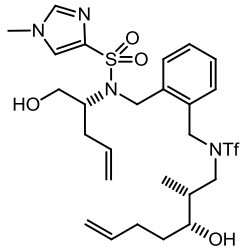
Following general procedure **A2**, cyclopropane carbonyl chloride (22 mg, 0.21 mmol), triethylamine (43 mg, 0.43 mmol) and amine **236^D** (49 mg, 0.043 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amide **268b** (17.9 mg, 0.033 mmol, 76%) as a colourless oil; R_f 0.76 ($CHCl_3$); $[\alpha]_D^{23.7}$ 5 (c. 0.9, MeOH); δ_H (500 MHz; $CDCl_3$) 7.46 (1H, dd, *J* 7.3 and 1.3, Ar), 7.41-7.22 (3H, m, Ar), 5.84-5.69 (2H, m, 6-H and 4'-H), 5.19-5.05 (2H, m, 7-H or 5'-H), 4.99-4.93 (2H, m, 7-H or 5'-H), 4.89 (1H, br s, PhCH_ANTf), 4.63 (1H, br s, PhCH_BNTf), 4.16 (1H, dd, *J* 11.2 and 4.7, 1'-H_A), 4.07 (1H, dd, *J* 11.2 and 6.0, 1'-H_B), 3.88 (1H, d, *J* 12.1, NCH_APh), 3.76 (1H, d, *J* 12.1, NCH_BPh), 3.70-3.18 (3H, m, 3-H and 1-H), 2.95 (1H, p, *J* 5.9, 2'-H), 2.33 (1H, dt, *J* 13.1 and 6.3, 3'-H_A), 2.24 (1H, dt, *J* 13.1 and 7.2, 3'-H_B), 2.09-2.00 (1H, m, 5-H_A), 1.93-1.85 (1H, m, 5-H_B), 1.75 (1H, br s, 2-H), 1.62 (1H, tt, *J* 8.1 and 4.7, ^{C}Pr), 1.48-1.40 (2H, m, 4-H_{AB}), 1.02-0.98 (2H, m, ^{C}Pr), 0.91-0.86 (2H, m, ^{C}Pr), 0.66 (3H, br s, Me); δ_C (75 MHz; $CDCl_3$) 174.8, 138.3, 137.7, 134.4, 134.2, 130.2, 129.0, 128.5, 128.2, 118.2, 114.8, 77.2, 65.8, 56.2, 53.5, 51.2, 49.5, 36.9, 36.1, 33.3, 30.5, 12.8 (^{C}Pr), 10.2 (^{C}Pr), 8.6 (^{C}Pr); ν_{max}/cm^{-1} (film) 3424, 3077, 2979, 2939, 1726, 1641, 1455, 1385, 1275 and 1261; *m/z* (ES^+) 529.6 (100%, $[M-OH]^+$); found 547.2457, $C_{26}H_{37}F_3N_2O_3S$ requires *MH* 547.2448

3-{[2-({*N*-[(2*R*,3*R*)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-3'-[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]-1'-(pyridin-3-yl)urea 268a



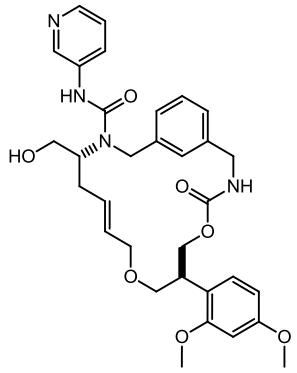
Following general procedure **A1**, 3-pyridyl isocyanate (25.2 mg, 0.21 mmol) and amine **236^{D}** (49 mg, 0.043 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the urea **268a** (22.6 mg, 0.037 mmol, 88%) as a colourless oil; R_f 0.27 (90:10, $CHCl_3$−MeOH); $[\alpha]_D^{23.7}$ 2.3 (c. 1.1, MeOH); δ_H (500 MHz; $CDCl_3$) 9.78 (1H, br s, NH), 8.29-8.10 (3H, m, Py), 7.51 (1H, d, Py), 7.43-7.19 (4H, m, Ar), 5.87-5.65 (2H, m, 6-H and 4'-H), 5.17 (1H, s, NPyCH_APh), 5.16 (1H, d, *J* 9.8, 7-H_A or 5'-H_A), 5.10 (1H, d, *J* 17.5, 7-H_B or 5'-H_B), 4.98 (1H, d, *J* 16.5, 7-H_B or 5'-H_B), 4.93 (1H, d, *J* 10.2, 7-H_A or 5'-H_A), 4.65 (2H, s, NTfC*H*$_{AB}$Ph), 4.18 (2H, s, NPyC*H*$_2$), 3.70 (1H, dd, *J* 10.8 and 4.8, 1'-H), 3.66-3.50 (3H, m, 1'-H, 2'-H and 3-H), 3.40-3.25 (2H, 1-H_{AB}), 2.67 (1H, td, *J* 14.5 and 7.2, 3'-H_A), 2.47 (1H, td, *J* 14.5 and 7, 3'-H_B), 2.18-2.08 (1H, m, 5-H_A), 1.98-1.84 (1H, m, 5-H_B), 1.60-1.42 (2H, m, 4-H_A and 2-H), 1.29-1.13 (1H, m, 4-H_B), 0.72 (3H, *J* 6.9, Me); δ_C (75 MHz; $CDCl_3$) 156.4, 142.6, 139.5, 138.2, 137.2, 136.1, 133.9, 128.7, 128.5, 128.4, 126.9, 124.1, 118.6, 114.8, 77.2, 64.2, 60.0, 52.9, 50.9, 37.4, 33.5, 30.7; ν_{max}/cm^{-1} (film) 3287, 3056, 2984, 2939, 2305, 1658, 1539, 1484, 1422 and 1385; *m/z* (ES$^+$) 599.8 (100%, [M+H]$^+$); found 599.2509, $C_{28}H_{37}F_3N_4O_3$ requires *MH* 599.2510

(2*R*)-1-Hydroxy-*N*-{[2-({*N*-[(2*R*,3*R*)-3-hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-*S*-(1-methyl-1H-imidazol-4-yl)pent-4-ene-2-sulfonamido 268c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (36 mg, 0.2 mmol), triethylamine (40 mg, 0.4 mmol) and amine **236^{D}** (47 mg, 0.04 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **268c** (12.4 mg, 0.019 mmol, 49.8%) as a colourless glass; R_f 0.31 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 5.2 (c. 0.6, MeOH); δ_H (500 MHz; $CDCl_3$) 7.57-7.54 (1H, m, Ar), 7.48 (1H, d, *J* 1.4, Ar), 7.40-7.37 (1H, m, Ar), 7.35 (1H, d, *J* 1.5, Ar), 7.33-7.28 (2H, m, Ar), 5.77 (1H, ddt, *J* 16.9, 10.1 and 6.6, 6-H), 5.58 (1H, ddt, *J* 17.1, 10.3 and 7.0, 4'-H), 5.00 (1H, dd , *J* 17.1 and 1.8, 5'-H_A), 4.98-4.92 (3H, m, 5'-H_B and 7-H_{AB}), 4.72 (2H, s, PhCH_2NTf), 4.50 (1H, d, *J* 15.8, N(Imid)CH_APh), 4.42 (1H, d, *J* 15.8, N(Imid)CH_BPh), 3.98 (1H, dd, *J* 12.5 and 9.6, 1'-H_A), 3.81 (1H, s, 2'-H), 3.71 (3H, s, NMe), 3.65 (1H, dd, *J* 12.5 and 3.7, 1'-H_B), 3.54 (1H, s, 3-H), 3.42 (1H, dd, *J* 14.5 and 8.8, 1-H_A), 3.23 (1H, dd, *J* 14.5 and 6.3, 1-H_B), 2.35 (1H, dt, *J* 15 and 6.4, 3'-H_A), 2.19 (1H, dt, *J* 15 and 7.9, 3'-H_B), 2.12-2.04 (1H, m, 5-H_A), 1.98-1.90 (1H, m, 5-H_B), 1.54-1.42 (1H, 4-H_A), 1.38 (1H, q, *J* 6.9, 2-H), 1.24-1.15 (1H, m, 4-H_B), 0.70 (3H, d, *J* 6.9, Me); δ_C (75 MHz; $CDCl_3$) 141.2, 138.7, 138.2, 135.0, 134.7, 133.6, 130.6, 128.9, 128.3, 128.1, 124.4, 117.5, 114.8, 76.7, 63.6, 62.6, 53.6, 51.6, 37.1, 36.5, 33.9, 33.4, 30.4, 10.4; ν_{max}/cm^{-1} (film) 3388, 2981, 2940, 1641, 1533, 1456, 1385, 1337, 1275; *m/z* (ES$^+$) 645.3 (100%, [M+Na]$^+$); found 645.1983, $C_{26}H_{37}F_3N_4O_6S_2$ requires *MNa* 645.1999

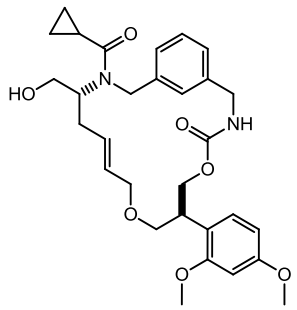
(7*S*,11*E*,14*R*)-7-(2,4-Dimethoxyphenyl)-14-(hydroxymethyl)-4-oxo-*N*-(pyridin-3-yl)-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(20),11,17(21),18-tetraene-15-carboxamide 260a



Following general procedure **A1**, 3-pyridyl isocyanate (30.3 mg, 0.252 mmol) and amine **248^{D}** (52 mg, 0.05 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **260a** (7.2 mg, 24 mmol, 24%) as a brown oil; R_f 0.12 (95:5 $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 5.7 (c. 0.7, MeOH); ν_{max}/cm^{-1} (film) 3300, 3006, 2924, 2851, 1711, 1660, 1612, 1539, 1508, 1483, 1464, and 1422; *m/z* (ES$^+$) 591.3 (100%, [M+H]$^+$); found 591.2812, $C_{32}H_{38}N_4O_7$ requires *MH* 591.2813

Unable to obtain ^{1}H and ^{13}C spectra due to a mix of geometric isomers and conformers

(7*S*,11*E*,14*R*)-15-Cyclopropanecarbonyl-7-(2,4-dimethoxyphenyl)-14-(hydroxymethyl)-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(20),11,17(21),18-tetraen-4-one 260b

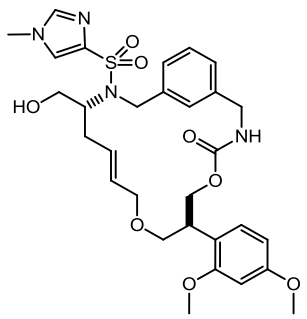


Following general procedure **A2**, cyclopropane carbonyl chloride (18.6 mg, 0.179 mmol), triethylamine (36 mg, 0.36 mmol) and amine **248^{D}** (37 mg, 0.036 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following

general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with CH_2Cl_2 gave the amide **260b** (3.96 mg, 0.0072 mmol, 20.4%) as a pale yellow glass; R_f 0.89 (CH_2Cl_2); $[\alpha]_D^{23.7}$ 4.4 (c. 0.2, MeOH); δ_H (500 MHz; $CDCl_3$; 323 K) *very broad* 7.69-7.58 (1H, m, Ar), 7.51-7.04 (4H, m, Ar and DMB 6-H), 6.46-6.37 (2H, m, DMB 3 and 5-H), 5.73-4.93 (4H, m, 11-H and 12-H), 4.51-3.36 (17H, m, 2 × OMe, 7-H, 10-H_{AB}, CH_{AB}OH, 8-H_{AB}, 2-H_{AB} and 16-H_{AB}), 2.95-2.83 (1H, m, 14-H), 2.35-1.95 (2H, m, 13-H_{AB}), 1.66-1.57 (1H, m, ^{C}Pr), 1.02-0.97 (2H, m, ^{C}Pr), 0.89-0.83 (2H, m, ^{C}Pr); δ_C (125 MHz; $CDCl_3$; 323 K) 174.6, 158.1, 131.5, 131.4, 130.9; 128.9, 128.5, 127.1, 124.2, 104.9, 104.4, 98.8; 66.4, 66.2, 62.4, 55.4, 55.3, 54.8, 32.9; 12.8; 8.4; ν_{max}/cm^{-1} (film) 3322, 2925, 1720, 1612, 1587, 1543, 1507, 1463, 1402 and 1344; *m/z* (ES$^+$) 540.5 (100%, $[M+H]^+$) and 539.3 (17%, $[M+Na]^+$); found 539.2753, $C_{30}H_{38}N_2O_7$ requires *MH* 539.2752

full carbon assignment was not possible to mixture of geometric isomers and rotamers

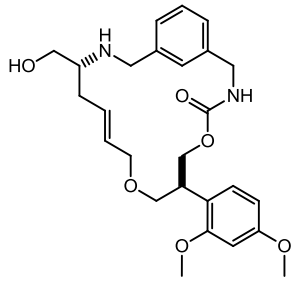
(7*S*,11*E*,14*R*)-7-(2,4-Dimethoxyphenyl)-14-(hydroxymethyl)-15-(1-methyl-1H-imidazole-4-sulfonyl)-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(20),11,17(21),18-tetraen-4-one 260c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (32 mg, 0.179 mmol), triethylamine (36 mg, 0.359 mmol) and amine **248^D** (37 mg, 0.0359 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the sulfonamide **260c** (12.5 mg, 0.020 mmol, 57%) as a colourless oil; R_f 0.37 ($CHCl_3$); $[\alpha]_D^{23.7}$ 3.7 (c. 0.6, MeOH); δ_H (500 MHz; $CDCl_3$) 7.83 (1H, dd, *J* 5.9 and 1.3, Ar), 7.78-7.74 (1H, m, Ar), 7.43 (1H, s, Ar), 7.37-7.28 (2H, d , Ar), 7.23-7.18 (1H, m, Ar), 7.12 (1H, d, *J* 8.6, Ar), 6.55 (1H, dd, *J* 4.2 and 2.5, DMB), 6.49 (1H, ddd, *J* 8.5, 3.4 and 2.5, DMB), 5.47-5.22

(2H, m, 11- and 12-H), 4.77 (1H, br s, 2-H_A^{min}), 4.64 (1H, br s, 2-H_B^{min}), 4.46 (1H, d, *J* 15.8, 16-H_A), 4.44 (1H, br s, 2-H_{AB}), 4.33 (1H, d, *J* 15.8, 16-H_B), 4.24-4.10 (3H, m, 6-H_A and 10-H_{AB}), 4.09-4.02 (1H, m, 6-H_B), 3.79 (3H, s, NMe), 3.77 (3H, s, OMe^{min}), 3.76 (3H, s, OMe), 3.75 (3H, s, OMe), 3.74 (3H, s, OMe ^{min}); 3.79-3.29 (6H, m, CH_{AB}OH, 14-H, 7-H and 8-H_{AB}), 2.27-2.14 (2H, 13-H_{AB}); δ_C (75 MHz; $CDCl_3$) 159.8, 158.1, 158.1, 156.5, 141.8, 141.6, 138.5, 138.1, 129.5, 129.1, 128.8, 128.7, 128.7, 127.7, 124.2, 120.5, 104.4, 104.35, 98.8, 98.7, 77.1, 66.2, 62.2, 55.4, 55.3, 45.1, 44.8, 37.9, 34.1, 29.6; ν_{max}/cm^{-1} (film) 3304, 2921, 2850, 1712, 1612, 1587, 1531, 1508, 1454, 1332; *m/z* (ES^+) 638.1 (100%, $[M+Na]^+$); found , $C_{30}H_{38}N_4O_8S$ requires *MH*

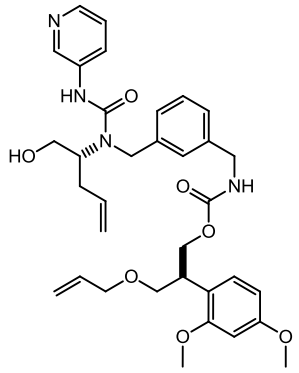
(7*S*,11*E*,14*R*)-7-(2,4-Dimethoxyphenyl)-14-(hydroxymethyl)-5,9-dioxa-3,15-diazabicyclo[15.3.1]henicosa-1(20),11,17(21),18-tetraen-4-one 260d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **248^D** (38 mg, 0.037 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **260d** (7.82 mg, 0.017 mmol, 45%) as a colourless oil; R_f 0.1 (95:5 $CHCl_3$−MeOH); ν_{max}/cm^{-1} (film) 3319, 2924, 2853, 1701, 1612, 1587, 1507 and 1463, *m/z* (ES^+) 471.3 (100%, $[M+H]^+$); found 471.2501, $C_{26}H_{34}N_2O_6$ requires *MH* 471.2490

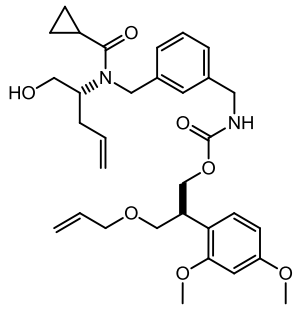
Unable to obtain ^1H and ^{13}C spectra due to geometric isomers

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({[(2*R*)-1-hydroxypent-4-en-2-yl][(pyridin-3-yl)carbamoyl]amino}methyl)phenyl]methyl}carbamate 269a



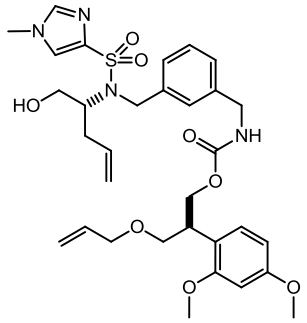
Following general procedure **A1**, 3-pyridyl isocyanate (31 mg, 0.26 mmol) and amine **237^{D}** (55 mg, 0.052 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the urea **269a** (14.8 mg, 0.024 mmol, 46%) as a colourless oil; R_f 0.08 ($CHCl_3$); $[\alpha]_D^{23.7}$ 6.1 (c. 0.7, MeOH); δ_H (500 MHz; $CDCl_3$) 8.60 (1H, NH), 8.29 (1H, s, Ar), 8.15 (1H, d, *J* 4.2, Ar), 7.94 (1H, d, *J* 8.1, Ar), 7.35-7.02 (6H, m, Ar), 6.43 (2H, s, Ar), 5.85 (1H, ddt, *J* 16.2, 10.7 and 5.5, propenyl 2-H), 5.74 (1H, ddt, *J* 17.4, 107 and 6.9, 4-H), 5.27 (1H, br s, NH), 5.21 (1H, dd , *J* 17.4 and 1.7, 5-H_A), 5.14-5.07 (3H, m, 5-H_B and propenyl 3-H_{AB}), 4.70 (1H, d, *J* 16.4, N(Py)C*H*$_A$Ph), 4.48 (1H, d, *J* 16.4, N(Py)C*H*$_B$Ph), 4.37 (1H, dd, *J* 10.7 and 5.8, propyl 1-H_A), 4.31 (1H, dd, *J* 10.7 and 6.3, propyl 1-H_B), 4.25 (2H, s, PhC*H*$_2$O(CO)), 3.94 (3H, br s, 2-H and propenyl 1-H_2), 3.78 (3H, s, OMe), 3.76 (3H, s, OMe), 3.69 (1H, d, *J* 10.9, propyl 3-H_A), 3.65-3.48 (4H, m, propyl 3-H_B and 1-H_{AB} and propyl 2-H), 2.48 (1H, dt, 3-H_A), 2.42-2.29 (1H, m, 3-H_B); δ_C (75 MHz; $CDCl_3$) 159.6, 158.3, 157.3, 156.9, 143.1, 140.5, 139.4, 138.9, 136.8, 134.8, 134.3, 129.0, 128.9, 126.7, 126.6, 126.5, 126.3, 123.6, 119.9, 117.9, 116.7, 104.1, 98.6, 71.9, 70.4, 65.5, 64.1, 59.6, 55.4, 55.3, 48.7, 44.9, 38.1, 33.7; ν_{max}/cm^{-1} (film) 3318, 3060, 3005, 2936, 1703, 1660, 1613, 1587, 1537, 1508, 1483, 1465 and 1422; *m/z* (ES$^+$) 641.4 (100%, [M+Na]$^+$); found 619.3138, $C_{34}H_{42}N_4O_7$ requires *MH* 619.3126

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({1-cyclopropyl-*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]formamido}methyl)phenyl]methyl}carbamate 269b



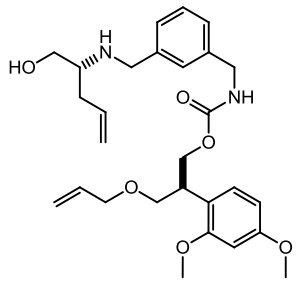
Following general procedure **A2**, cyclopropane carbonyl chloride (27.9 mg, 0.269 mmol), triethylamine (54 mg, 0.54 mmol) and amine **237b** (57 mg, 0.054 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **269b** (17 mg, 0.030 mmol, 55.6%) as a colourless oil; R_f 0.4 (EtOAc); $[\alpha]_D^{23.7}$ 3.7 (c. 0.9, MeOH); δ_H (500 MHz; $CDCl_3$) 7.41-7.06 (5H, m, Ph and DMB 6-H), 6.44 (1H, d, *J* 1.8, DMB 5-H), 6.42 (1H, s, DMB 3-H), 5.86 (1H, ddt, *J* 17.2, 10.7 and 5.8, propenyl 2-H), 5.75 (1H, ddt, *J* 17.3, 10.3 and 7.3, 4-H), 5.21 (1H, dd , *J* 17.3 and 1.7, propenyl 3-H_A), 5.13-5.01 (3H, m, 5-H_{AB} and propenyl 3-H_B), 4.99-4.53 (3H, m, NH and N(^{C}Pr)CH_{AB}Ph), 4.42 (1H, dd, *J* 10.8 and 5.8, propyl 1-H_A), 4.36 (1H, dd, *J* 10.8 and 6.2, propyl 1-H_B), 4.30 (2H, s, $PhCH_2N(CO)O$), 4.16-4.00 (2H, m, 1-H_{AH}), 3.96 (1H, dd, *J* 12.5 and 5, propenyl 1-H_A), 3.91 (1H, dd, *J* 12.5 and 6.4, propenyl 1-H_B); 3.87 (6H, s, 2 × OMe), 3.74-3.56 (3H, m, propyl 3-H_{AB} and propyl 2-H), 2.91 (1H, p, 2-H), 2.43 (1H, br s, 3-H_A), 2.34-2.24 (1H, m, 3-H_B), 1.06-0.97 (2H, m, ^{C}Pr), 0.89-0.83 (2H, m, ^{C}Pr), 0.72 (1H, br s, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.6, 159.7, 158.5, 138.9, 135.0, 135.0, 129.0, 128.7, 120.3, 120.3, 116.4 (propenyl 3-C or 5-H), 116.3 (propenyl 3-C or 5-H), 104.4 (DMB), 104.4 (DMB), 98.8 (DMB); 71.9 (propenyl 1-C), 70.7, 66.1, 63.9, 55.4 (2-H), 55.3 (OMe), 51.1, 38.4, 33.2, 12.9, 12.8, 8.4, 8.3; ν_{max}/cm^{-1} (film) 3359, 3075, 3007, 2936, 1721, 1613, 1508, 1463; *m/z* (ES^+) 589.4 (100%, $[M+Na]^+$); found 567.3088, $C_{32}H_{42}N_2O_7$ requires *MH* 567.3065

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]1-methyl-1H-imidazole-4-sulfonamido}methyl)phenyl]methyl}carbamate 269c



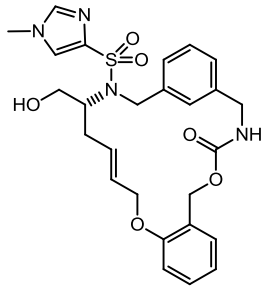
Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (45 mg, 0.25 mmol), triethylamine (50 mg, 0.5 mmol) and amine **237^{D}** (53 mg, 0.05 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the sulfonamide **269c** (23.3 mg, 0.036 mmol, 73%) as a pale yellow oil; R_f 0.2 ($CHCl_3$); $[\alpha]_D^{23.7}$ 10.2 (c. 1.0, MeOH); δ_H (500 MHz; $CDCl_3$) 7.49-7.08 (7H, m, Ar), 6.44 (2H, d, *J* 2.3, DMB), 5.86 (1H, ddt, *J* 17.3, 10.6 and 5.5, propenyl 2-H), 5.61-5.52 (1H, m, 4-H), 5.47 (1H, br s, NH), 5.22 (1H, dd , *J* 17.3 and 1.7, propenyl 3-H_A), 5.13 (1H, dd, *J* 10.6 and 1.7, propenyl 3-H_B); 4.97-4.86 (2H, m, 5-H_{AB}), 4.45-4.16 (6H, N(Imid)CH_{AB}Ph, propyl 3-H_{AB} and PhCH_2N(CO)O), 4.02-3.86 (3H, propenyl 1-H_2 and 2-H), 3.78 (6H, s, 2 × OMe), 3.68 (3H, Me), 3.66-3.58 (5H, propyl 2-H, propyl 3-H_{AB} and 1-H_{AB}), 2.26 (1H, dt, *J* 13.8 and 6.8, 3-H_A), 2.14 (1H, dt, *J* 13.8 and 6.9, 3-H_B); δ_C (75 MHz; $CDCl_3$) 159.6, 158.4, 156.6, 141.4, 138.7, 138.5, 137.3, 134.9, 134.7, 128.9, 128.6, 127.9, 126.7, 124.2, 120.1, 117.3 (5-C), 116.6 (propenyl 3-C), 104.1 (DMB), 98.6 (DMB); 71.9 (propenyl 1-C), 70.5 (1-C), 65.4 (propyl 3-C), 63.9 (2-C), 62.4 (propyl 1-C), 55.4 (OMe), 55.3 (OMe), 50.8 (N(Imid)CH_2Ph, or PhCH_2N(CO)O), 44.8 (N(Imid)CH_2Ph, or PhCH_2N(CO)O), 38.1 (Propyl 2-C), 36.7 (3-C), 34.1 (NCH_3); ν_{max}/cm^{-1} (film) 3317, 2938, 1713, 1612, 1531, 1508, 1465, 1334, 1275 and 1262; *m/z* (ES^+) 665.3 (100%, $[M+Na]^+$); found 665.2629, $C_{32}H_{42}N_4O_8S$ requires *MNa* 665.2616

(2*S*)-2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[3-({[(2*R*)-1-hydroxypent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 269d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **237^{D}** (53 mg, 0.05 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **269d** (8.4 mg, 0.017 mmol, 33.7%) as a pale yellow oil; R_f 0.15 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 7.5 (c. 0.4, MeOH); δ_H (500 MHz; $CDCl_3$) 7.30-7.25 (2H, Ar), 7.22 (1H, d, *J* 7.4, Ar), 7.14 (1H, d, *J* 6.3, Ar), 7.11 (1H, d, *J* 8.6, Ar), 6.44 (2H, s, DMB 3 and 5-H), 5.86 (1H, ddt, *J* 16.2, 10.8 and 5.5, propenyl 2-H), 5.75 (1H, ddt, *J* 17.6, 9.6 and 7.4, 4-H), 5.23 (1H, dd , *J* 16.2 and 1.7, propenyl 3-H_A), 5.14-5.09 (3H, m, propenyl 3-H_A and 5-H_{AB}), 4.95 (1H, br s, NH), 4.42 (1H, dd, *J* 10.6 and 5.4, propyl 1-H_A), 4.37 (1H, dd, *J* 10.6 and 5.6, propyl 1-H_B), 4.32 (2H, ap d, *J* 5.5, PhCH_2N(CO)O), 3.95 (2H, s, propenyl 1-H_2), 3.82 (1H, d, *J* 13.1, NHCH_APh), 3.78 (6H, s, OMe), 3.76 (1H, d, *J* 13.1, NHCH_BPh), 3.68-3.59 (5H, m, 1-H_A, propyl 2-H, propyl 3-H_{AB} and 2-H), 3.36 (1H, dd, 1-H_B), 2.77 (1H, p, *J* 5.6, 2-H), 2.31-2.21 (2H, m, 3-H_{AB}); δ_C (75 MHz; $CDCl_3$) 159.6, 158.4, 156.6, 138.9, 134.9, 134.6, 128.9, 128.8, 127.3, 120.1, 118.1, 116.6, 104.1, 98.6, 71.9, 70.5, 62.8, 57.6, 55.4, 55.3, 50.9, 44.9, 38.1, 36.0; ν_{max}/cm^{-1} (film) 3331, 3054, 3005, 2936, 2839, 1712, 1613, 1508 and 1464, ; *m/z* (ES$^+$) 499.3 (100%, $[M+H]^+$); found 499.2814, $C_{28}H_{38}N_2O_6$ requires *MH* 499.2803

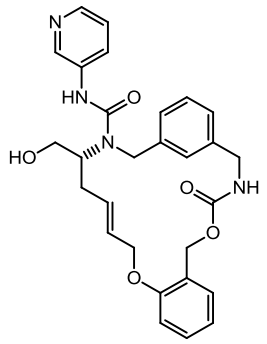
(15*E*,18*R*)-18-(Hydroxymethyl)-19-(1-methyl-1H-imidazole-4-sulfonyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *E*-117c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (15.3 mg, 0.085 mmol), triethylamine (17.1 mg, 0.169 mmol) and amine ***E*-115^{D}** (17 mg, 0.017 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 CH_2Cl_2—MeOH gave the amine ***E*-117c** (8.1 mg, 0.014 mmol, 87%) as a colourless glass; R_f 0.4 (EtOAc); ν_{max}/cm^{-1} (film) 3280, 3006, 2919, 2850, 1708, 1605, 1533, 1496, 1456 and 1332; *m/z* (ES$^+$) 549.2 (100%, [M+H]$^+$); found 549.1779, $C_{26}H_{30}N_4O_6S$ requires *MH* 527.1959

Unable to obtain ^{1}H and ^{13}C spectra due to excessive H_2O contamination

(15*E*,18*R*)-18-(Hydroxymethyl)-4-oxo-*N*-(pyridin-3-yl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaene-19-carboxamide *E*-117a

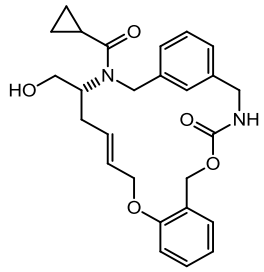


Following general procedure **A1**, 3-pyridyl isocyanate (4 mg, 0.034 mmol) and amine ***E*-115^{D}** (17 mg, 0.017 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product

was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea ***E*-117a** (6.7 mg, 0.013 mmol, 79%); R_f 0.1 ($CHCl_3$); ν_{max}/cm^{-1} (film) 2922, 2851, 1710, 1554, 1463, 1380, 1275 and 1083; *m/z* (ES^+) 503.2 (100%, $[M+H]^+$); found 503.2291, $C_{28}H_{30}N_4O_5$ requires *MH* 503.2289

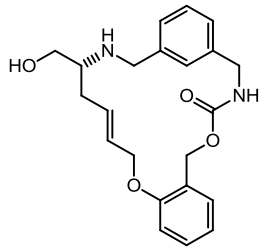
Unable to obtain ^1H and ^{13}C spectra due to excessive H_2O contamination

(15*E*,18*R*)-19-Cyclopropanecarbonyl-18-(hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *E*-117b



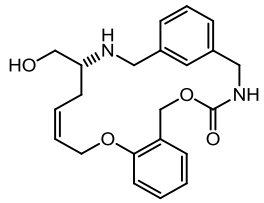
Following general procedure **A2**, cyclopropane carbonyl chloride (12.5 mg, 0.12 mmol), triethylamine (24.2 mg, 0.24 mmol) and amine ***E*-115^D** (24 mg, 0.024 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amide ***E*-117b** (6.5 mg, 0.014 mmol, 60.2%) as a colourless glass; R_f 0.44 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −8.9 (c. 0.3, MeOH); δ_H (300 MHz; $CDCl_3$) 8.18 (1H, br s, NH), 7.40-7.25 (5H, m, Ar), 7.15 (1H, d, *J* 7.3, Ar), 6.96 (1H, t, *J* 7.5, 10-H), 6.88 (1H, d, *J* 8.3, 11-H), 5.88 (1H, dd, *J* 16 and 4.4, 15- or 16-H), 5.82 (1H, dd, *J* 16 and 6.2, 15- or 16-H), 5.30-5.26 (1H, m, OH), 5.17 (1H, d, *J* 10.7, 6-H_A), 5.11 (1H, d, *J* 10.7, 6-H_B), 5.57-5.48 (2H, m, 14-H_{AB}), 4.46 (1H, dd, *J* 15.9 and 7.1, 20-H_A), 4.39 (1H, dd, *J* 15.9 and 6.1, 20-H_B), 4.16 (1H, dd, *J* 11.6 and 4.6, C*H*$_A$OH), 4.11 (1H, dd, *J* 11.6 and 5.6, C*H*$_B$OH), 4.02 (2H, s, 2-H_{AB}), 3.01-2.97 (1H, m, 18-H), 2.46-2.38 (2H, m, 17-H_{AB}), 1.66-1.60 (1H, m, ^{C}Pr), 1.03-0.98 (2H, ^{C}Pr), 0.92-0.87 (2H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.6, 157.7, 156.8, 139.7, 131.9, 130.4, 128.7, 127.7, 126.5, 120.7, 112.1, 77.1, 76.8, 67.9, 54.3, 50.3, 31.4, 12.7, 8.5; ν_{max}/cm^{-1} (film) 3320, 3007, 2920, 2850, 1714, 1606, 1539, 1496, 1455 and 1403; *m/z* (ES^+) 451.2 (100%, $[M+H]^+$); found 451.2241, $C_{26}H_{30}N_2O_5$ requires *MH* 451.2227

(15*E*,18*R*)-18-(Hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *E*-117d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine ***E*-115^{D}** (15 mg, 0.015 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the amine ***E*-117d** (5.5 mg, 0.0144 mmol, 96.2%) as a colourless film; R_f 0.12 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 10.7 (c. 0.3, MeOH); δ_H (500 MHz; $CDCl_3$/MeOD; 333 K) 7.38-7.04 (5H, m, Ph), 6.96 (1H, d, *J* 7.4, Ph), 6.81 (1H, td, *J* 7.5 and 1.0, 10-H), 6.73 (1H, d, *J* 8.3, 11-H), 5.75 (1H, br s, 15 or 16-H), 5.66 (1H, br d, *J* 15.3, 15 or 16-H), 5.12 (1H, d, *J* 10.6, 6-H_A), 5.07 (1H, d, *J* 10.6, 6-H_B), 4.30 (1H, dd, *J* 13.1 and 3.8, 14-H_A), 4.27 (1H, dd, *J* 13.1 and 4.7, 14-H_B), 4.26-4.14 (2H, m, 2-H_{AB}), 3.74 (2H, s, 20-H_{AB}), 3.53 (1H, dd, *J* 11 and 5.1, C*H*$_A$OH), 3.45 (1H, dd, *J* 11 and 5.9, C*H*$_B$OH), 2.70 (1H, p, 18-H), 2.22 (2H, s, 17-H_{AB}); δ_C (125 MHz; C_6D_6 ; 343 K) 157.8, 131.7, 130.1, 128.3, 126.2, 124.6, 112.2, 91.9, 68.1, 56.7; ν_{max}/cm^{-1} (film) 3304, 2921, 2471, 1682, 1607, 1591, 1548, 1455; *m/z* (ES$^+$) 383.2 (100%, $[M+H]^+$); found 383.1974, $C_{22}H_{26}N_2O_4$ requires *MH* 393.1965

(15*Z*,18*R*)-18-(Hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.07,12]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *Z*-117d

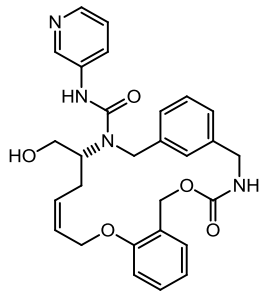


Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine ***Z*-115^{D}** (15 mg, 0.015 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was

purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the amine ***Z*-117d** (4.4 mg, 0.012 mmol, 72%) as a colourless film; R_f 0.41 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 15.7 (c. 0.3, MeOH); δ_H (500 MHz; $CDCl_3$) 7.36-7.25 (3H, m, Ar), 7.20 (1H, t, *J* 7, Ar), 7.11 (1H, d, *J* 7.6, Ar), 7.03 (1H, br s, Ar), 6.95 (1H, td, *J* 7.4, Ar), 6.92 (1H, d, *J* 8.1, Ar), 5.95-5.90 (1H, m, 15-H), 5.56 (1H, br s, 16-H), 5.42 (1H, br s, NH), 4.91 (2H, br s, 6-H_{AB}), 4.70 (1H, dd, *J* 11.1 and 8.6, 2 or 20-H_{AB}), 4.55 (1H, br s, 2 or 20-H_{AB}), 4.49 (1H, dd, *J* 11.1 and 3.7, 2 or 20-H_{AB}), 4.27 (1H, dd, *J* 15.4 and 5.9, 2 or 20-H_{AB}), 3.76 (1H, br s, 18-H), 3.73 (2H, s, 6-H_{AB}), 3.69 (1H, dd, CH_AOH), 3.43 (1H, dd, CH_AOH), 2.81-2.77 (1H, m, OH), 2.43 (1H, dt, *J* 14.9 and 9.4, 17-H_A), 2.23 (1H, d, *J* 14.9, 17-H_B); ν_{max}/cm^{-1} (film) 3318, 3006, 2990, 1686, 1606, 1550, 1497; *m/z* (ES^+) 383.2 (100%, $[M+H]^+$); found 383.1963, $C_{26}H_{34}N_2O_6$ requires *MH* 383.1965

Unable to obtain ^{13}C NMR due to insufficient material

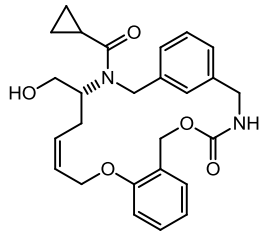
(15*Z*,18*R*)-18-(Hydroxymethyl)-4-oxo-*N*-(pyridin-3-yl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaene-19-carboxamide *Z*-117a



Following general procedure **A1**, 3-pyridyl isocyanate (3.83 mg, 0.032 mmol) and amine ***Z*-115^D** (16 mg, 0.016 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$−MeOH gave the urea ***Z*-117a** (5.6 mg, 0.011 mmol, 70%); R_f 0.4 (EtOAc); ν_{max}/cm^{-1} (film) 3321, 2925, 2853, 1709, 1605, 1537, 1462 and 1388; *m/z* (ES^+) 503.2 (100%, $[M+H]^+$); found 503.2285, $C_{28}H_{30}N_4O_5$ requires *MH* 503.2289

Unable to obtain ^1H or ^{13}C spectra due to excessive H_2O contamination

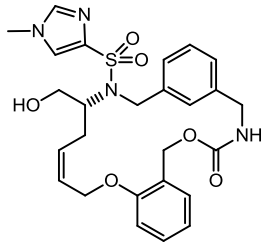
(15*Z*,18*R*)-19-Cyclopropanecarbonyl-18-(hydroxymethyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *Z*-117b



Following general procedure **A2**, cyclopropane carbonyl chloride (8.3 mg, 0.08 mmol), triethylamine (16.2 mg, 0.16 mmol) and amine ***Z*-115^{D}** (16 mg, 0.016 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the amide ***Z*-117b** (4.9 mg, 0.011 mmol, 69%); R_f 0.44 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 7.9 (c. 0.3, MeOH); δ_H (500 MHz; $CDCl_3$) 7.46-7.06 (6H, m, Ar), 6.93 (1H, t, *J* 7.4, Ar), 6.89 (1H, br s, Ar), 5.74 (1H, br s, 15 or 14-H), 5.39 (1H, br s, 6-H_A), 5.29 (1H, br s, 15 or 14-H), 5.01 (1H, d, *J* 8.6, 6-H_B), 4.95 (1H, s, NH), 4.82 (1H, br s, 2 or 20-H_{AB}), 4.54 (1H, br s, 2 or 20-H_{AB}), 4.40 (2H, br s, 2 or 20-H_{AB}), 3.74 (2H, s, 14-H_{AB}), 3.54 (1H, br s, 18-H), 2.77 (1H, br s, C*H*$_A$OH), 2.48-2.41 (1H, m, C*H*$_B$OH), 1.75 (2H, s, 17-H_{AB}), 1.57 (1H, br s, ^{C}Pr), 1.03 (2H, s, ^{C}Pr), 0.79-0.71 (2H, m, ^{C}Pr); ν_{max}/cm^{-1} (film) 3309, 3009, 2930, 1710, 1606, 1535, 1494, 1456; *m/z* (ES$^+$) 473.2 (100%, [M+Na]$^+$); found 473.2053, $C_{26}H_{29}N_2O_5$ requires *MNa* 473.2047

Unable to obtain ^{13}C NMR due to insufficient material

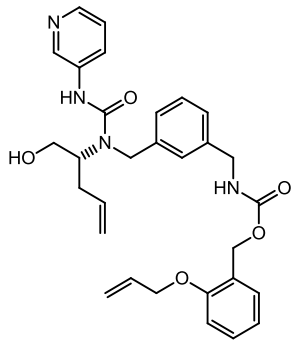
(15*E*,18*R*)-18-(Hydroxymethyl)-19-(1-methyl-1H-imidazole-4-sulfonyl)-5,13-dioxa-3,19-diazatricyclo[19.3.1.0^{7,12}]pentacosa-1(24),7,9,11,15,21(25),22-heptaen-4-one *Z*-117c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (11.7 mg, 0.065 mmol), triethylamine (13.1 mg, 0.129 mmol) and amine ***Z*-115^{D}** (13 mg, 0.0129 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the amine ***Z*-117c** (4.19 mg, 0.0079 mmol, 62%); R_f 0.12 ($CHCl_3$); ν_{max}/cm^{-1} (film) 2922, 2851, 1701, 1554, 1463 and 1378; *m/z* (ES$^+$) 549.2 (100%, [M+Na]$^+$); found 549.2674, $C_{26}H_{30}N_4O_6$ requires *MNa* 549.1778

Unable to obtain ^1H or ^{13}C spectra due to excessive H_2O contamination

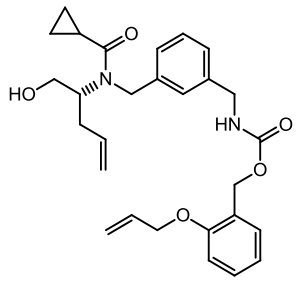
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({[(2*R*)-1-hydroxypent-4-en-2-yl][(pyridin-3-yl)carbamoyl]amino}methyl)phenyl]methyl}carbamate 118a



Following general procedure **A1**, 3-pyridyl isocyanate (23 mg, 0.19 mmol) and amine **116** (80 mg, 0.077 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the

urea **118a** (16.9 mg, 0.032 mmol, 41%); R_f 0.11 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ 9.3 (c. 1.5, MeOH); δ_H (500 MHz; $CDCl_3$) 8.60 (1H, br s, Py), 8.32 (1H, s, Py), 8.18 (1H, d, *J* 4.8, Py), 7.98 (1H, dd, *J* 8.4 and 1.8, Py), 7.39-7.17 (6H, Ar), 6.94 (1H, ap t, *J* 7.4, Ar 3-H), 6.89 (1H, d, *J* 6.9, Ar 5-H), 6.05 (1H, ddt, *J* 15.9, 10.2 and 5, propenyl 2-H), 5.78 (1H, ddt, *J* 16.7, 9.5 and 6.8, 4-H), 5.43 (1H, d, *J* 16.7, propenyl 3-H_A), 5.42 (1H, br s, NH), 5.28 (1H, dd, *J* 10.2 and 1.6, propenyl 3-H_B), 5.24 (1H, d, *J* 12.7, PhC*H*$_2$O), 5.20 (1H, d, *J* 12.7, PhC*H*$_2$O), 5.12 (1H, d, *J* 16.7, 5-H_A), 5.11 (1H, d, *J* 9.5, 5-H_B), 4.76 (1H, d, *J* 16.3, N(Py)CH_APh), 4.58 (2H, d, *J* 5, propenyl 1-H_2), 4.49 (1H, d, *J* 16.3, N(Py)CH_BPh), 4.39-4.29 (2H, m, PhCH_2N(CO)O), 4.05-3.99 (1H, m, 2-H), 3.71 (1H, dd, *J* 11.1 and 2.7, 1-H_A), 3.54 (1H, dd, *J* 11.1 and 8.5, 1-H_B), 2.51 (1H, dt, *J* 14.3 and 7.5, 3-H_A), 2.39 (1H, dt, *J* 14.3 and 7, 3-H_B); δ_C (75 MHz; $CDCl_3$) 157.3, 156.9, 156.4, 142.9, 140.4, 139.0, 136.9, 134.3, 133.1, 129.6, 129.4, 129.1, 126.8, 126.6, 126.5, 126.4, 124.9, 123.7, 120.6, 118.0, 117.2, 111.7, 68.8 (propenyl 1-C), 64.1 (1-C), 62.5 (PhCH_2O), 59.6 (2-C), 48.5 (N(Py)CH_2Ph), 44.9 (Ph*C*H_2N(CO), 33.7 (3-C); ν_{max}/cm^{-1} (film) 3055, 2988, 2305, 1714, 1655, 1604, 1551 and 1422; *m/z* (ES$^+$) 531.3 (100%, $[M+H]^+$); found 531.2593, $C_{30}H_{34}N_4O_5$ requires *MH* 531.2602

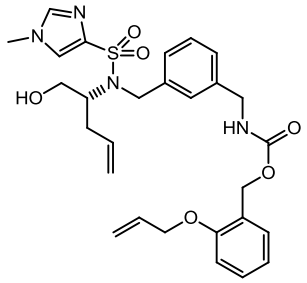
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({1-cyclopropyl-*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]formamido}methyl)phenyl]methyl}carbamate 118b



Following general procedure **A3**, cyclopropane carbonyl chloride (45 mg, 0.43 mmol), triethylamine (87 mg, 0.87 mmol) and amine **116** (86 mg, 0.083 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc gave the amide **118b** (10.6 mg, 0.022 mmol, 26.7%); R_f 0.81 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ 6.2 (c. 0.5, MeOH); δ_H (500 MHz; $CDCl_3$) 7.28 (1H, d, *J* 7.4), 7.25-7.13 (4H, m, Ar), 7.11 (1H, d, *J* 7.4), 6.87 (1H, ap t, *J* 7.4), 6.80 (1H, d, *J* 8.2), 5.97 (1H, ddt, *J* 15.8, 10.2 and 5, propenyl 2-H), 5.70 (1H, ddt, *J* 17.3, 10.4 and 7.1, 4-H), 5.34 (1H, dd , *J* 17.3 and 1.7, propenyl 3-H_A), 5.21-5.16 (3H, m, propenyl 3-H_B, NH

and $PhCH_AO$), 5.06-5.00 (3H, m, 5-H_{AB} and $PhCH_BO$), 4.5 (2H, d, *J* 5, propenyl 1-H_2), 4.32 (2H, d, *J* 6, $PhCH_2N(CO)O$), 4.03 (1H, dd, *J* 11.2 and 5.1, 1-H_A), 3.98 (1H, dd, *J* 11.2 and 5.6, 1-H_B), 3.76 (1H, d, *J* 13.5, $N(CO)CH_APh$), 3.73 (1H, d, *J* 13.5, $N(CO)CH_BPh$), 2.81 (1H, p, *J* 5.9, 2-H); 2.23 (1H, dt, *J* 13.0 and 6.5, 3-H_A), 2.16 (1H, *J* 13.0 and 7.1, 3-H_B) 1.59-1.49 (1H, ^{C}Pr), 0.94-0.89 (2H, ^{C}Pr), 0.82-0.76 (2H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.9 (C=O), 159.6 (C=O), 153.4, 140.8, 138.7, 134.6, 133.2, 129.6, 129.3, 128.8, 127.3, 126.3, 125.1, 120.6, 118.1 (5-C), 117.1 (propenyl 3-C), 111.7 (Ph 3-C), 68.8 (propenyl 1-C), 65.9 (1-C), 62.3 (2-C), 55.2 ($PhCH_2O$), 51.3 $N(CO)CH_2Ph$, 45.1 ($PhCH_2N(CO)$, 36.3 (3-C), 12.9 (^{C}Pr), 8.6 (^{C}Pr); ν_{max}/cm^{-1} (film) 3329, 3054, 2987, 2686, 2305, 1714, 1606, 15165, 1493, 14221361 and 1265; *m/z* (ES^+) 479.3 (80%, $[M+H]^+$) and 411.2 (100%, $[M-\ ^C Pr]^+$); found 479.2537, $C_{28}H_{34}N_2O_5$ requires *MH* 479.2540

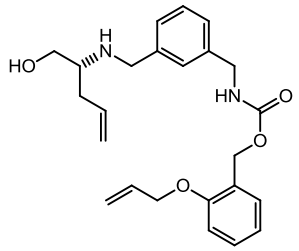
[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({*N*-[(2*R*)-1-hydroxypent-4-en-2-yl]1-methyl-1H-imidazole-4-sulfonamido}methyl)phenyl]methyl}carbamate 118c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (81 mg, 0.45 mmol), triethylamine (90 mg, 0.9 mmol) and amine **116** (86 mg, 0.083 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **118c** (33.5 mg, 0.06 mmol, 73%); R_f 0.41 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 3.7 (c. 1.7, MeOH); δ_H (500 MHz; $CDCl_3$) 7.43 (1H, s, Ar), 7.39-7.17 (7H, m, Ar), 6.95 (1H, ap t, *J* 7.4, Ar 3-H), 6.87 (1H, d, *J* 8.2, Ar 5-H), 6.04 (1H, ddt, *J* 17.2, 10.3 and 5.0, propenyl 2-H), 5.56 (1H, ddt, *J* 17.1, 9.8 and 7.4, 4-H), 5.45 (1H, br s, NH), 5.41 (1H, dd , *J* 17.2 and 1.8, propenyl 3-), 5.26 (1H, dd, *J* 10.6 and 1.8, propenyl 3-H_B), 5.24 (2H, s, $PhCH_2O$), 5.22-5.17 (1H, br s, OH), 4.94 (1H, d, *J* 9.8, 5-H_A), 4.91 (1H, d, *J* 17.1, 5-H_B), 4.57 (2H, d, *J* 5, propenyl 1-H_2), 4.36 (1H, d, *J* 15.8, N(Imid)CH_APh), 4.34 (2H, s, $PhCH_2N(CO)$), 4.23 (1H, d, *J* 15.8, N(Imid)CH_APh), 4.00-3.94 (1H, m, 1-H_A), 3.91 (1H, br s, 2-H), 3.66 (3H,

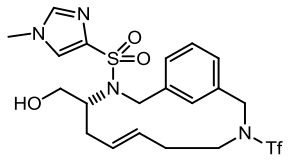
s, Me), 3.62 (1H, d, *J* 10.1, 1-H_B), 2.27 (1H, dt, *J* 13.8 and 6.8, 3-H_A), 2.14 (1H, dt, *J* 13.8 and 7.5, 3-H_B); δ_C (75 MHz; $CDCl_3$) 156.6 (C=O), 156.4 (C=O), 141.3, 138.6, 138.5, 137.3, 134.7, 133.2 (4-C), 129.6, 129.4, 128.6 (propenyl 2-C), 127.9, 127.8, 126.7, 125.1, 124.3, 120.7, 117.4 (5-C), 117.3 (propenyl 3-C), 111.7 (Ph 3-C), 68.8 (propenyl 1-C), 63.9 (2-C), 62.4 (PhCH_2O(CO)) 63.3 (1-C), 50.8 (N(Imid)*C*H_2Ph), 44.9 (Ph*C*H_2N(CO)), 36.8 (3-C), 34.1 (CH_3); ν_{max}/cm^{-1} (film) 3310, 3006, 2987, 2318, 2127, 1713, 1642, 1605, 1590, 1532, 1493, 1454 and 1333; *m/z* (ES^+) 577.2 (100%, $[M+H]^+$); found 577.2104, $C_{28}H_{34}N_4O_6S$ requires *MH* 577.2091

[2-(Prop-2-en-1-yloxy)phenyl]methyl *N*-{[3-({[(2*R*)-1-hydroxypent-4-en-2-yl]amino}methyl)phenyl]methyl}carbamate 118d



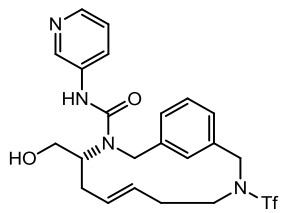
Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **116** (81 mg, 0.078 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **118d** (13.5 mg, 0.033 mmol, 42%); R_f 0.3 (EtOAc); $[\alpha]_D^{23.7}$ 4.5 (c. 1.2, MeOH); δ_H (500 MHz; $CDCl_3$) 7.38 (1H, d, *J* 7.4, Ar), 7.35-7.19 (5H, m, Ar), 6.98 (1H, apt, *J* 7.5, Ar), 6.90 (1H, d, *J* 8.3, Ar), 6.07 (1H, ddt, *J* 15.7, 10.2 and 5.0, propenyl 2-H), 5.77 (1H, ddt, *J* 17.2, 10.3 and 7.2, 4-H), 5.45 (1H, d, *J* 17.2, propenyl 3-H_A), 5.31-5.26 (3H, m, PhCH_2O and propenyl 3-H_B), 5.14 (1H, d, *J* 15.7, 5-H_A), 5.13 (1H, d, *J* 10.2, 5-H_B), 5.08 (1H, br s, NH), 4.60 (2H, d, *J* 5.1, propenyl 1-H_2), 4.42 (2H, d, *J* 6, PhCH_2N(CO)), 3.87 (1H, d, *J* 13.1, NHCH_APh), 3.81 (1H, d, *J* 13.1, NHCH_BPh), 3.69 (1H, dd , *J* 10.8 and 4, 1-H_A), 3.40 (1H, dd, *J* 10.8 and 5.8, 1-H_B), 2.84-2.79 (1H, m, 2-H), 2.34-2.21 (3H, m, 3-H_{AB} and OH); δ_C (75 MHz; $CDCl_3$) 156.6, 156.4, 139.9, 138.9, 134.5, 133.2, 129.6, 129.4, 128.9, 127.3, 126.5, 125.1, 120.6 (Ar 5-C), 118.2 (5-C), 117.2 (propenyl 3-C), 111.7 (Ar 3-C); 68.8 (propenyl 1-C), 62.7 (1-C or Ph*C*H_2O), 62.4 (1-C or Ph*C*H_2O), 57.6 (2-C), 50.8 (NH*C*H_2Ph), 45.0 (Ph*C*H_2N(CO)), 35.9 (3-C); ν_{max}/cm^{-1} (film) 3323, 2925, 1702, 1523, 1493, 1455; *m/z* (ES^+) 411.2 (100%, $[M+H]^+$); found 411.2295, $C_{24}H_{30}N_2O_4$ requires *MH* 411.2278

[(4*R*,6*E*)-3-(1-Methyl-1H-imidazole-4-sulfonyl)-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(15),6,12(16),13-tetraen-4-yl]methanol *E*-261c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (33 mg, 0.181 mmol), triethylamine (36 mg, 0.362 mmol) and amine ***E*-249^{D}** (34 mg, 0.036 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the amine ***E*-261c** (16.1 mg, 0.03 mmol, 83%); R_f 0.44 (EtOAc); δ_H (500 MHz; $CDCl_3$) 7.83 (1H, s, Imid 3-H), 7.80 (1H, s, Imid 5-H), 7.72 (1H, s, Ar), 7.34-7.23 (3H, m, Ar), 4.83 (1H, br s, 7-H), 4.58 (1H, d, *J* 14.7, 2-H_A), 4.50-4.42 (2H, m, 2-H_B and 11-H_A), 4.30 (1H, d, *J* 15.9, 11-H_B), 4.26 (1H, br s, 6-H), 3.76 (3H, s, Me), 3.75-3.71 (1H, s, 4-H), 3.68 (1H, dd, *J* 11 and 5.9, C*H*$_A$OH), 3.64-3.55 (2H, m, 9-H_{AB}), 3.52 (1H, dd, *J* 11 and 6.3, C*H*$_B$OH), 2.13-2.03 (3H, m, 5-H_{AB} and 8-H_A), 1.99-1.87 (1H, m, 8-H_B); δ_C (75 MHz; $CDCl_3$) 139.7, 139.6, 131.3, 128.3 (7-C), 128.1, 127.8 (6-C), 127.7, 127.6, 124.9, 79.1 (CH_2OH), 61.7 (4-C), 54.5 (2-C), 51.6 (11-C), 33.8 (5-C), 33.5 (NMe), 32.3 (8-C), *9-C missing*; ν_{max}/cm^{-1} (film) 3295, 2943, 1638, 1612, 1532, 1454, 1386, 1335, 1224; *m/z* (ES$^+$) 545.1 (100%, [M+H]$^+$); found 545.1103, $C_{26}H_{34}N_2O_6$ requires *MH* 545.1111

(4*R*,6*E*)-4-(Hydroxymethyl)-N-(pyridin-3-yl)-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(15),6,12(16),13-tetraene-3-carboxamide *E*-261a

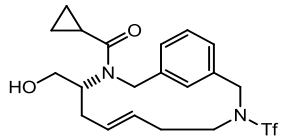


Following general procedure **A1**, 3-pyridyl isocyanate and amine ***E*-249^{D}** (34 mg, 0.067 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was

purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea ***E*-261a** (15 mg, 0.03 mmol, 89%); R_f 0.12 (60:40, EtOAc—petrol); ν_{max}/cm^{-1} (film) 3319, 2938, 1662, 1550, 1510, 1382; *m/z* (ES^+) 499.2 (20%, $[M+H]^+$) and 543.2 (100%, $[M+PEG]^+$); found 499.1618, $C_{22}H_{25}F3N_4O_4S$ requires *MH* 499.1635

NMR extremely broad compound confirmed by high-resolution mass spectroscopy, see ***E*-261d** *for the free-amine scaffold NMR assignment*

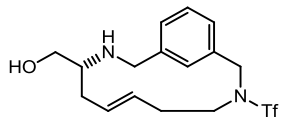
[(4*R*,6*E*)-3-Cyclopropanecarbonyl-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(15),6,12(16),13-tetraen-4-yl]methanol *E*-261b



Following general procedure **A2**, cyclopropane carbonyl chloride (19 mg, 0.181 mmol), triethylamine (36 mg, 0.36 mmol) and amine ***E*-249^D** (34 mg, 0.036 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc gave the amide ***E*-261d** (11 mg, 0.025 mmol, 69%); R_f: 0.77 (EtOAc); $[\alpha]_D^{23.7}$ 2.1 (c. 1.1, MeOH); ν_{max}/cm^{-1} (film) 3402, 2050, 1630, 1459, 1387; *m/z* (ES^+) 447.2 (100%, $[M+H]^+$); found 447.1571, $C_{20}H_{25}F_3N_2O_4S$ requires *MH* 447.1560

NMR extremely broad; compound confirmed by high-resolution mass spectroscopy, see ***E*-261d** *for the free-amine scaffold NMR*

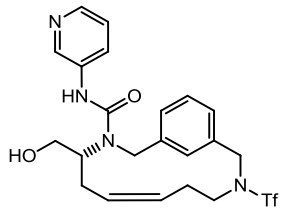
[(4*R*,6*E*)-10-(Trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(15),6,12(16),13-tetraen-4-yl]methanol *E*-261d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine ***E*-249^D** (31 mg, 0.033 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc gave the amine ***E*-261d** (8.6 mg, 0.023 mmol, 69%); R_f 0.18 (EtOAc); $[\alpha]_D^{23.7}$ 5.3 (c. 0.9, MeOH); δ_H (500 MHz; $CDCl_3$) 7.62 (1H, s, Ar), 7.31 (1H, ap t, *J* 7.4, Ar), 7.24 (1H, d, *J* 6.8, Ar), 7.23 (1H, d, *J*

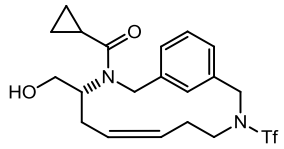
7.4, Ar), 4.74 (1H, dd, *J* 16 and 5.8, 7-H), 4.69 (1H, dd, *J* 16 and 5.3, 6- H), 4.61 (1H, d, *J* 15.3, 11-H_A), 4.53 (1H, d, *J* 15.3, 11-H_B), 4.04 (1H, d, *J* 14.2, 2-H_A), 3.64 (1H, d, *J* 14.2, 2-H_B), 3.67-3.64 (1H, m, 9-H_A), 3.45 (1H, dd, *J* 10.7 and 6.1, CH_AOH), 3.45-3.40 (1H, m, 9-H_B), 3.39 (1H, dd, *J* 10.7 and 5.8, CH_BOH), 2.52 (1H, 4-H), 2.22-2.14 (1H, m, 5-H_A), 2.07-2.00 (1H, m, 5-H_B), 1.97 (1H, d, *J* 14.2, 8-H_A), 1.76-1.69 (1H, m, 8-H_B); δ_C (75 MHz; $CDCl_3$) 135.3, 130.5 (6-C), 128.5, 127.7, 127.4 (7-C), 126.9, 63.9 (*C*H_2OH), 59.7 (4-C), 53.9 (11-C), 51.3 (2-C), 50.7 (9-C), 34.5 (5-C), 31.9 (8-C); ν_{max}/cm^{-1} (film) 3369, 2930, 1610, 1454, 1384; *m/z* (ES$^+$) 379.1 (100%, [M+H]$^+$); found 379.1316, $C_{16}H_{21}F_3N_2O_3S$ requires *MH* 379.1298

(4*R*,6*Z*)-4-(Hydroxymethyl)-N-(pyridin-3-yl)-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(15),6,12(16),13-tetraene-3-carboxamide *Z*-261a



Following general procedure **A1**, 3-pyridyl isocyanate and amine ***Z*-249^D** (30 mg, 0.032 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH then EtOAc gave the amine ***Z*-261a** (11 mg, 0.022 mmol, 69%); R_f 0.5 (EtOAc); $[\alpha]_D^{23.7}$ 3.7 (c. 1.1, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 9.02 (1H, br s, NH), 8.62 (1H, d, *J* 2.5, Ar), 8.18 (1H, dd, *J* 4.7 and 1.4, Ar), 7.89 (1H, ddd, *J* 8.3, 2.6 and 1.5, Ar), 7.58 (1H, s, Ar), 7.54-7.41 (2H, m, Ar), 7.32 (1H, d, *J* 7.4, Ar), 7.27 (1H, dd, *J* 7.4 and 4.7, Ar), 5.49 (1H, td, *J* 11.4 and 4.0, 7-H), 5.24 (1H, td, *J* 11.4 and 3.5, 6-H); 4.82-4.71 (1H, m, 2-H_A or 11-H_A), 4.71-4.50 (3H, m, 2-H_A or 11-H_A and 2-H_B or 11-H_B), 3.88-3.82 (1H, m, CH_AOH), 3.80-3.70 (1H, m, CH_BOH), 3.56 (1H, dt , *J* 13.8 and 6.6, 8-H_A), 3.30 (1H, br s, 8-H_B), 2.11 (1H, br s, 4-H), 1.80-1.61 (4H, m, 5-H and 7-H_{AB}); δ_C (75 MHz; DMSO-*d6*; 343 K) 155.7, 142.7, 141.6, 140.1, 137.2, 135.2, 134.9, 129.3, 129.1, 128.6, 128.3, 127.6, 126.7, 126.3, 123.0, 120.7 q *J* 325, 61.7, 53.8, 49.7, 28.6, 28.2, 26.9; ν_{max}/cm^{-1} (film) 3054, 2987, 2305, 1669, 1614, 1559, 1485, 1422, 1387; *m/z* (ES$^+$) 499.2 (100%, [M+H]$^+$); found 499.1623, $C_{22}H_{25}F_3N_4O_4S$ requires *MH* 499.1621

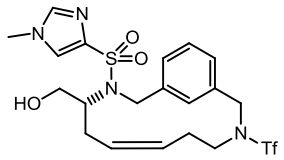
[(4*R*,6*Z*)-3-Cyclopropanecarbonyl-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(16),6,12,14-tetraen-4-yl]methanol *Z*-261b



Following general procedure **A2**, cyclopropane carbonyl chloride (16 mg, 0.149 mmol), triethylamine (30 mg, 0.298 mmol) and amine ***Z*-249^{D}** (28 mg, 0.029 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with EtOAc gave the amine ***Z*-261b** (9 mg, 0.02 mmol, 70%); R_f 0.8 (EtOAc); $[\alpha]_D^{23.7}$ 7.9 (c. 1.8, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) *very broad* 7.64-7.24 (4H, m, Ar), 5.51-5.38 (1H, m, 6-H), 5.32-5.18 (1H, m, 7-H), 4.87-3.96 (5H, m, 2-H_{AB} and 11-H_{AB} and 4-H), 3.75 (1H, s, CH_AOH), 3.68-3.37 (2H, m, 9-H_A and CH_BOH), 3.13 (1H, br s, 9-H_B), 2.12-1.86 (2H, m, 5-H_{AB}), 1.83-1.56 (2H, m, 8-H_{AB}), 1.44-1.34 (1H, m, ^{C}Pr), 0.96-0.70 (4H, m, ^{C}Pr); ν_{max}/cm^{-1} (film) 3369, 3013, 2932, 2883, 1725, 1611, 1454, 1428, 1386; *m/z* (ES$^+$) 447.2 (100%, [M+H]$^+$); found 447.1565, $C_{26}H_{34}N_2O_6$ requires *MH* 447.1560

Unable to obtain a ^{13}C spectrum due to interconversion of conformers

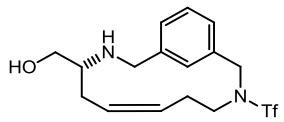
[(4*R*,6*Z*)-3-(1-Methyl-1H-imidazole-4-sulfonyl)-10-(trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(16),6,12,14-tetraen-4-yl]methanol *Z*-261c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (26 mg, 0.144 mmol), triethylamine (30 mg, 0.29 mmol) and amine ***Z*-249^{D}** (27 mg, 0.029 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:8:1 CH_2Cl_2—EtOH—NH_4OH gave the amine ***Z*-261c** (12 mg, 0.023 mmol, 79%); R_f 0.4 (EtOAc); $[\alpha]_D^{23.7}$ 4.1 (c. 1.2, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.82 (1H, Ar), 7.79 (1H, Ar), 7.66 (1H, Ar),

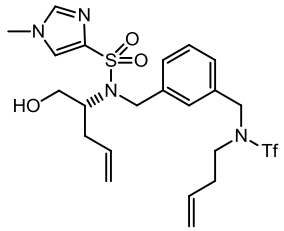
7.41-7.29 (3H, Ar), 5.45 (1H, ap t, *J* 11, 6-H), 5.29 (1H, ap t, *J* 11, 7-H), 4.74 (1H, d, *J* 14.5, 11-H_A), 4.60 (1H, d, *J* 15.6, 2-H_A), 4.48 (1H, d, *J* 14.5, 11-H_B), 4.14 (1H, d, *J* 15.6, 2-H_B), 3.89 (1H, br s, 4-H), 3.75 (3H, Me), 3.67 (1H, dd, *J* 11.3 and 7.1, CH_AOH), 3.55 (2H, br s, 9-H_{AB}), 3.51 (1H, dd, *J* 11.3 and 6.1, CH_BOH), 1.80 (1H, d, *J* 16.4, 5-H_A), 1.68 (1H, d, *J* 16.4, 5-H_B), 1.58-1.40 (2H, m, 8-H_{AB}); δ_C (125 MHz; DMSO-*d6* 343 K) 139.7, 139.5, 138.8, 135.6, 129.6, 128.8, 128.4, 127.8, 126.2, 124.5, 61.4 (CH_2OH), 61.1 (4-C), 54.1 (11-C), 50.3 (9-C), 48.5 (2-C), 33.5 (Me), 29.1 (5-C), 26.6 (8-C); ν_{max}/cm^{-1} (film) 3303, 2936, 1532, 1454, 1384, 1332; *m/z* (ES^+) 545.1 (100%, $[M+Na]^+$); found 545.1106, $C_{20}H_{22}F_3N_4O_5S_2$ requires *MNa* 545.1111

[(4*R*,6*Z*)-10-(Trifluoromethane)sulfonyl-3,10-diazabicyclo[10.3.1]hexadeca-1(16),6,12,14-tetraen-4-yl]methanol *Z*-261d



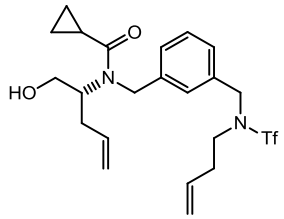
Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine ***Z*-249^D** (32 mg, 0.034 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine ***Z*-261d** (9.3 mg, 0.024 mmol, 72%); R_f 0.32 (EtOAc); $[\alpha]_D^{23.7}$ 10.7 (c. 0.9, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.84 (1H, s, Ph), 7.68 (1H, d, *J* 7.5, Ph), 7.58 (1H, ap t, *J* 7.5, Ph), 7.49-7.44 (1H, m, Ph), 5.38 (1H, td, *J* 10.5 and 5.5, 7-H), 5.34 (1H, td, *J* 10.5 and 5.6, 6-H), 4.68-4.48 (2H, m, 11-H_{AB}), 4.29 (1H, d, *J* 13.5, 2-H_A), 4.13 (1H, d, *J* 13.5, 2-H_B), 3.71 (1H, dd, *J* 11.8 and 3.3, CH_AOH), 3.57-3.50 (3H, m, CH_BOH 9-H_{AB}); 2.68 (1H, s, 4-H), 1.96-1.65 (4H, 5-H_{AB} and 8-H_{AB}); δ_C (125 MHz; DMSO-*d6*; 343 K) 135.3, 132.1, 130.7, 130.1, 129.6, 127.8 (6-C), 126.5 (7-C), 59.9 (CH_2OH), 58.9 (4-C), 53.5 (11-C), 53.3 (9-C), 49.3 (2-C), 48.6 , 27.4 (5-C), 25.6 (8-C); ν_{max}/cm^{-1} (film) 3292, 2730, 2640, 2049, 1597, 1456, 1381, 1359; *m/z* (ES^+) 379.1 (100%, $[M+H]^+$); found 379.1312, $C_{16}H_{21}F_3N_2O_3S$ requires *MH* 379.1298

(2*R*)-*N*-[(3-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-1'-hydroxy-*S*-(1-methyl-1H-imidazol-4-yl)pent-4'-ene-2'-sulfonamido 270c



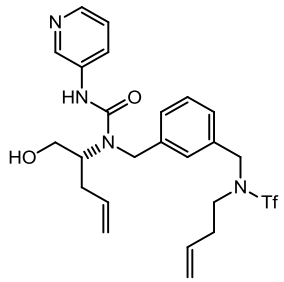
Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (80 mg, 0.49 mmol), triethylamine (89 mg, 0.89 mmol) and amine **238^{D}** (86 mg, 0.089 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **270c** (25.5 mg, 0.046 mmol, 52%); R_f 0.56 (EtOAc); $[\alpha]_D^{23.7}$ 8.7 (c. 2.5, MeOH); δ_H (500 MHz; $CDCl_3$) 7.51 (1H, s, Imid), 7.45-7.43 (2H, m, Imid), 7.38 (1H, s, Imid), 7.35 (1H, ap t, *J* 7.6, Ph), 7.28 (1H, d, *J* 7.6, Ph), 5.61 (1H, ddt, *J* 17.4, 10.2 and 6.9, 3-H), 5.55 (1H, ddt, *J* 17.2, 9.8 and 7, 4'-H), 5.45 (1H, dd, *J* 8.0 and 4.5, OH), 5.05 (1H, dd, *J* 10.2 and 1.6, 4-H_A), 5.02 (1H, dd, *J* 17.4 and 1.6, 4-H_B), 4.92 (1H, d, *J* 9.8, 5'-H_A), 4.90 (1H, d, *J* 17.2, 5'-H_B), 4.51 (2H, br s, PhCH_2NTf), 4.39 (1H, d, *J* 15.7, N(Imid)C*H*$_A$Ph), 4.27 (1H, d, *J* 15.7, N(Imid)C*H*$_B$Ph), 3.99 (1H, ddd, *J* 12.1, 10.0 and 4, 1'-H_A), 3.88 (1H, td, *J* 10.0 and 6.7, 2-H), 3.75 (3H, s, Me), 3.64 (1H, ddd, *J* 12.1, 8 and 3.6, 1'-H_B), 3.33 (2H, t , *J* 7.7, 1-H_2), 2.29 (3H, m, 3'-H_A and 2-H_2), 2.14 (1H, dt, *J* 14.3 and 7.8, 3'-H_B); δ_C (75 MHz; $CDCl_3$) 141.3, 138.6, 138.1, 134.6 (3-C), 134.5, 133.4 (4'-C), 129.1, 128.8, 127.7, 124.3, 120.1 (q, *J* 325, CF_3), 118.0 (5'-C), 117.4 (4-C), 63.9 (2'-C), 62.2 (1'-C), 52.0 (Ph*C*H_2NTf), 50.9 (N(Imid)*C*H_2Ph), 47.5 (1-C), 37.0 (3-C), 34.2 (CH_3), 32.5 (2-C); ν_{max}/cm^{-1} (film) 3278, 3055, 2987, 2686, 2522, 2411, 2305, 2126, 1720, 1642, 1609, 1532; *m/z* (ES$^+$) 573.1 (100%, [M+Na]$^+$); found 551.1592, $C_{22}H_{29}F_3N_4O_5S_2$ requires *MH* 551.1604

***N*-[(3-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-*N*-[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]cyclopropanecarboxamide 270b**



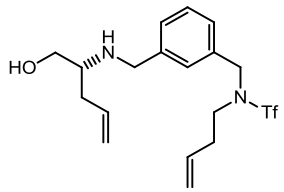
Following general procedure **A2**, cyclopropane carbonyl chloride (45 mg, 0.43 mmol), triethylamine (86 mg, 0.86 mmol) and amine **238^{D}** (83 mg, 0.086 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amide **270b** (13.3 mg, 0.028 mmol, 33%); R_f 0.56 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 15.2 (c. 1.3, MeOH); δ_H (500 MHz; $CDCl_3$) 7.37-7.21 (4H, m, Ar), 5.77 (1H, ddt, *J* 17.7, 10.8 and 7.7, 4'-H), 5.61 (1H, ddt, *J* 17.1, 10.2 and 6.8, 3-H), 5.12 (1H, d , *J* 17.7, 5-H_A), 5.11 (1H, d , *J* 10.8, 5-H_B), 5.04 (1H, d, *J* 10.2, 4-H_A), 5.01 (1H, d, *J* 17.1, 4-H_B), 4.55 (2H, br s, PhC*H*$_2$NTf), 4.11 (1H, dd , *J* 11.2 and 5.1, 1'-H_A), 4.06 (1H, dd, *J* 11.2 and 5.6, 1'-H_B), 3.87 (1H, d, *J* 13.4, N(^{C}Pr)C*H*$_A$Ph), 3.84 (1H, d, *J* 13.4, N(^{C}Pr)C*H*$_B$Ph), 3.34 (2H, t, *J* 7.7, 1-H_2), 2.89 (1H, p, *J* 5.7, 2'-H), 2.34-2.17 (4H, m, 3'-H_{AB} and 2-H_2), 1.66-1.59 (1H, m, ^{C}Pr), 1.02-0.98 (2H, m, ^{C}Pr), 0.90-0.86 (2H, m, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.8 (C=O), 141.5, 134.5, 134.4, 133.4, 129.1, 128.4, 128.1, 127.1, 120.0 (q, *J* 324, CF_3), 118.0 (5'-C or 4-C), 117.9 (5'-C or 4-C), 65.9 (1'-C), 55.3 (2'-C), 52.2 (Ph*C*H_2NTf), 51.1 (N(^{C}Pr)*C*H_2Ph), 47.4 (1-C), 36.4 (3'-C), 32.5 (2-C), 12.8 (^{C}Pr), 8.5 (^{C}Pr); ν_{max}/cm^{-1} (film) 3060, 3006, 2984, 1725, 1641, 1457, 1387, 1275, 1266, and 1225; *m/z* (ES$^+$) 475.2 (100%, $[M+H]^+$); found 475.1874, $C_{26}H_{34}F_3N_2O_6$ requires *MH* 475.1873

3-[(3-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)methyl]-3-[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]-1-(pyridin-3-yl)urea 270a



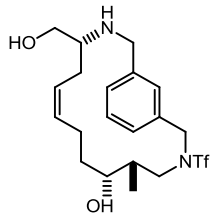
Following general procedure **A1**, 3-pyridyl isocyanate (23.8 mg, 0.199 mmol) and amine **238**^{D} (96 mg, 0.099 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$−MeOH gave the urea **270a** (21 mg, 0.039 mmol, 40%); R_f 0.1 (EtOAc); $[\alpha]_D^{23.7}$ 1.7 (c. 2.1, MeOH); δ_H (500 MHz; $CDCl_3$) 8.90 (1H, br s, NH), 8.26 (1H, d, *J* 2.6, Py-2), 8.14 (1H, dd, *J* 4.8 and 1.5, Py-6), 8.08 (1H, d, *J* 8.7, Py-4), 7.39-7.24 (3H, m, Py-5 and Ar), 7.27-7.21 (2H, m, Ar), 5.70 (1H, ddt, *J* 17.1, 8.6 and 7.6, 4'-H), 5.57 (1H, ddt, *J* 17.1, 10.3 and 6.8, 3-H), 5.07 (1H, d, *J* 10.3, 4-H_A), 5.08 (1H, d, *J* 17.1, 4-H_B), 5.01 (1H, d, *J* 8.6, 5'-H_A), 4.97 (1H, d, *J* 17.1, 5'-H_B), 4.59 (2H, s, N(Py)C*H*$_2$Ph), 4.51 (2H, br s, PhC*H*$_2$NTf), 3.88 (1H, m, 2'-H), 3.83 (1H, dd, *J* 11.1 and 2.4, 1'-H_A), 3.74 (1H, dd, *J* 11.1 and 6.9, 1'-H_B), 3.32 (2H, t, *J* 7.7, 1-H_2), 2.45 (2H, dq, *J* 18.3 and 7.2, 3'-H_2), 2.20 (2H, br s, 2-H_2); δ_C (75 MHz; $CDCl_3$) 156.9 (C=O), 142.6 (Py), 139.9 (Py), 139.7 (Py), 137.1 (Py-3), 135.0 (4'-C), 134.1 (3-C), 133.3, 129.4, 127.8, 127.4, 127.2, 126.9, 123.9, 119.8 (q, *J* 327, CF_3), 118.2 (4-C or 5'-C), 118.0 (4-C or 5'-C), 63.9 (1'-C), 59.9 (2'-C), 52.1 (Ph*C*H$_2$NTf), 49.7 (N(Py)CPh), 47.6 (1-C), 33.8 (3'-C), 32.5 (2-C); ν_{max}/cm^{-1} (film) 3006, 2988, 1734, 1660, 1539, 1485, 1423, 1386; *m/z* (ES$^+$) 527.2 (100%, $[M+H]^+$); found 527.1946, $C_{24}H_{29}F_3N_4O_4S$ requires *MH* 527.1934

***N*-(But-3-en-1-yl)-1,1,1-trifluoro-*N*-{[3'-({[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 270d**



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **238^{D}** (81 mg, 0.084 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **270d** (16 mg, 0.039 mmol, 46%); R_f 0.19 (90;10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 3.7 (c. 1.6, MeOH); δ_H (500 MHz; $CDCl_3$) 7.39-7.28 (3H, m, Ar), 7.24 (1H, d, *J* 7.7, Ar), 5.76 (1H, ddt, *J* 16.5, 10.8 and 7.2, 4'-H), 5.62 (1H, ddt, *J* 17.1, 10.3 and 6.9, 3-H), 5.12 (1H, d, *J* 16.5, 5'-H_A), 5.11 (1H, d, *J* 10.8, 5'-H_B), 5.05 (1H, dd , *J* 10.5 and 1.5, 4-H_A), 5.01 (1H, dd , *J* 17.1 and 1.5, 4-H_B), 4.53 (2H, br s, PhCH_2Ntf), 3.86 (1H, d, *J* 13.3, NHCH_APh), 3.80 (1H, d, *J* 13.3, NHCH_BPh), 3.66 (1H, dd, *J* 10.8 and 4.1, 1'-H_A), 3.37 (1H, dd, *J* 10.8 and 6.4, 1'-H_B), 3.34 (2H, t, *J* 8.1, 1-H_2), 2.80-2.74 (1H, m, 2'-H), 2.32-2.19 (3H, m, 3'-H_{AB} and 2-H_A), 2.01 (2H, br s, 2-H_B and OH); δ_C (75 MHz; $CDCl_3$) 141.2, 134.7 (4'-C), 134.6 (3-C), 133.4, 129.2, 128.4, 128.1, 127.2, 119.9 (q, *J* 325, CF_3), 118.1 (5'-C or 4-C), 117.9 (5'-C or 4-C), 62.9 (1'-C), 57.5 (2'-C), 52.1 (PhCH_2NTf), 50.8 (NHCH_2Ph), 47.5 (1-C), 36.2 (3'-C), 32.5 (2-C); ν_{max}/cm^{-1} (film) 3300, 3079, 3005, 2982, 2933, 1642, 1457, 1387; *m/z* (ES$^+$) 407.2 (100%, $[M+H]^+$); found 407.1621, $C_{18}H_{25}F_3N_2O_2$ requires *MH* 407.1611

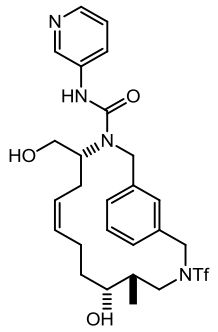
(5*R*,6*R*,9*Z*,12*R*)-12-(Hydroxymethyl)-5-methyl-3-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(18),9,15(19),16-tetraen-6-ol 262d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **250^{D}** (119 mg, 0.106 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **262d** (10 mg, 0.022 mmol, 21%); R_f 0.18 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −14.9 (c. 1, MeOH); δ_H (500 MHz; $CDCl_3$) 7.38-7.17 (4H, m, Ar), 5.39 (1H, dd, *J* 11 and 6.3, 9-H),

5.35 (1H, dd, *J* 11 and 7.3, 10-H), 4.68 (1H, d, *J* 15, 2-H_A), 4.48 (1H, d, *J* 15, 2-H_B); 4.30 (1H, br s, 6-H), 4.05 (1H, d, *J* 5.5, CH_2OH), 3.92 (1H, d, *J* 13.7, 14-H_A), 3.67 (1H, d, *J* 13.7, 14-H_B), 4.45-4.30 (3H, m, CHAOH, 4-H_{AB}), 3.28-3.19 (1H, m, CH_BOH), 2.56 (1H, p, *J* 5.9, 12-H), 2.09 (1H, dt, *J* 13.3 and 6.7, 11-H_A), 2.02 (1H, dt, *J* 13.3 and 6.1, 11-H_B), 1.85-1.79 (2H, m, 8-H_{AB}), 1.44-1.29 (2H, m, 7-H_{AB}), 1.11-0.97 (1H, m, 5-H), 0.66 (3H, d, *J* 6.6); δ_C (75 MHz; $CDCl_3$) 135.1, 131.6 (10-C), 128.7, 128.3, 127.9 (9-C), 126.4, 68.9 (CH_2OH), 62.9 (4-C), 58.9 (12-C), 53.9 (2-C), 52.8 (14-C), 34.5, 33.4 (11-C), 25.6 (7-C), 22.8 (8-C), 21.9, (5-C), 10.2 (Me), *6-C missing*; ν_{max}/cm^{-1} (film) 2925, 2854, 2318, 1462, 1377; *m/z* (ES^+) 451.2 (100%, $[M+H]^+$); found 451.1894, $C_{20}H_{29}F_3N_2O_3S$ requires *MH* 451.1873

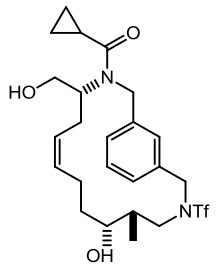
(4*R*,6*E*,10*R*,11*R*)-10-Hydroxy-4-(hydroxymethyl)-11-methyl-*N*-(pyridin-3-yl)-13-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(19),6,15,17-tetraene-3-carboxamide 262a



Following general procedure **A1**, 3-pyridyl isocyanate (27.5 mg, 0.229 mmol) and amine **250^D** (129 mg, 0.115 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the urea **262a** (14 mg, 0.024 mmol, 21.4%); R_f 0.31 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −17.9 (c. 1.4, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 8.66 (1H, d, *J* 2.4, Py), 8.18 (1H, dd, *J* 4.7 and 1.5, Py), 7.95-7.88 (1H, m, Py), 7.44-7.37 (3H, m, Ar and Py), 7.34 (1H, d, *J* 7.8, Ar), 7.28 (1H, dd, *J* 8.2 and 4.5, Ar), 5.36 (1H, dt, *J* 11.1 and 6.7, 6-H), 5.29 (1H, dt, *J* 11.1 and 7.2, 7-H), 5.00 (1H, br s, OH), 4.85 (1H, d, *J* 16.7, 2-H_A), 4.65 (1H, d, *J* 15.4, 14-H_A), 4.62 (1H, d, *J* 15.4, 14-H_B), 4.49 (1H, d, *J* 16.7, 2-H_B), 4.06 (1H, br s, 4-H), 3.67-3.58 (2H, m, CH_2OH), 3.52 (1H, dd, *J* 13.9 and 10.9, 12-H_A), 3.21 (1H, dd, *J* 13.9 and 4.8, 12-H_B), 3.15-3.10 (1H, m, 10-H), 2.17 (1H, dt, *J* 14.1 and 8.4, 5-H_A), 1.96 (1H, dt, *J* 14.1 and 5.5, 5-H_B), 1.65-1.47 (3H, m, 11-H and 8-H_2), 1.36-1.31 (2H, m, 9-H_2), 0.71 (3H, d, *J* 6.8, Me); δ_C (75 MHz; DMSO-*d6*; 343 K) 156.2 (C=O), 142.7 (6-Py), 141.7 (2-Py), 141.0 (3-Py), 135.2, 130.9 (9-C), 128.8, 127.5 (10-C),

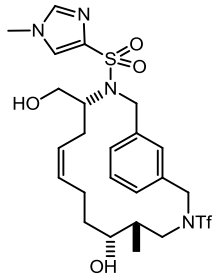
126.7, 126.6, 125.9, 123.0; 61.1 (*C*H_2OH), 59.2 (12-C), 53.8 (2-C), 46.7 (14-C), 45.9 (4-C), 33.6 (11-C), 32.9 (7-C), 28.8 (5-C), 22.4 (8-C), 9.3 (Me); ν_{max}/cm^{-1} (film) 3289, 2931, 1662, 1609, 1384, 1275; *m/z* (ES$^+$) 571.1 (100%, [M+H]$^+$); found 571.2185, $C_{26}H_{33F}N_2O_6$ requires *MH* 571.2197

(5*R*,6*R*,9*E*,12*R*)-13-Cyclopropanecarbonyl-12-(hydroxymethyl)-5-methyl-3-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(18),9,15(19),16-tetraen-6-ol 262b



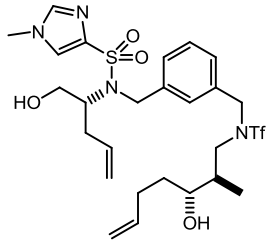
Following general procedure **A2**, cyclopropane carbonyl chloride (31 mg, 0.3 mmol), triethylamine (62 mg, 0.61 mmol) and amine **250^D** (69 mg, 0.061 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$−MeOH gave the amide **262b** (11.1 mg, 0.021 mmol, 34%); R_f 0.26 (80:20, petrol—EtOAc); $[\alpha]_D^{23.7}$ −22 (c. 1.1, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.41-7.20 (4H, m, Ar), 5.44 (1H, dt, *J* 11 and 7.0, 9-H), 5.36 (1H, dt, *J* 11 and 7.9, 10-H), 4.69 (1H, d , *J* 15.2, 2-H_A), 4.48 (1H, d , *J* 15.2, 2-H_B), 4.07-4.03 (2H, m, C*H*$_2$OH), 3.91 (1H, d, *J* 13.5, 14-H_A); 3.68 (1H, d, *J* 13.5, 14-H_B), 3.34 (1H, dd, *J* 14 and 8.3, 4-H_A), 3.25 (1H, dd, *J* 14 and 6.3, 4-H_B), 3.20 (1H, dd, *J* 10.3 and 5.4, 6-H), 2.78 (1H, p, *J* 5.9, 12-H), 2.17-2.05 (2H, m, 11-H_2), 1.88-1.82 (2H, m, 8-H_2), 1.74 (1H, br s, OH), 1.68-1.63 (2H, m, ^{C}Pr), 1.42-1.31 (2H, m, 7-H_2), 1.09-1.05 (1H, m, OH), 0.91-0.85 (4H, m, ^{C}Pr); 0.67 (3H, d, *J* 6.8, Me); δ_C (125 MHz; DMSO-*d*6, 343K) 173.7 (Ar), 141.5 (Ar), 135.1 (Ar), 132.3 (9-C), 128.8 (Ar), 128.2 (Ar), 127.9 (Ar), 126.4 (10-C), 125.7 (Ar), 119.1 (q, *J* 325, CF_3), 68.9 (6-C), 65.9 (CH_2OH), 55.6 (12-C), 53.9 (4-C), 52.9 (2-C), 50.9 (14-C), 34.7 (7-C), 29.6 (11-C), 22.9 (8-C), 12.5 (CH_3), 9.8 (^{C}Pr), 7.8 (^{C}Pr); ν_{max}/cm^{-1} (film) 3585, 3388, 3011, 2938, 1724, 1610, 1454, 1384; *m/z* (ES$^+$) 519.2 (100%, [M+H]$^+$); found 519.2154, $C_{24}H_{33}F_3N_2O_5S_1$ requires *MH* 519.2135

(5*R*,6*R*,9*E*,12*R*)-12-(Hydroxymethyl)-5-methyl-13-(1-methyl-1H-imidazole-4-sulfonyl)-3-(trifluoromethane)sulfonyl-3,13-diazabicyclo[13.3.1]nonadeca-1(18),9,15(19),16-tetraen-6-ol 262c



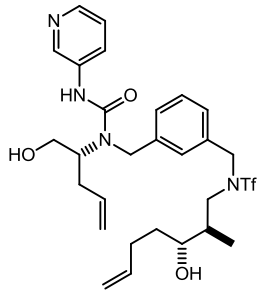
Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (59 mg, 0.33 mmol), triethylamine (68 mg, 0.67 mmol) and amine **250^{D}** (76 mg, 0.067 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$—MeOH gave the sulfonamide **262c** (24.1 mg, 0.041 mmol, 60.6%); R_f 0.28 (95:5, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −0.3 (c. 1.2, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.81 (1H, d, *J* 1.4, Imid), 7.78 (1H, d, *J* 1.4, Imid), 7.47-7.40 (2H, m, Ar), 7.40 (1H, t, *J* 7.8, Ar), 7.36-7.32 (1H, m, Ar), 5.27 (1H, dd, *J* 10.8 and 5.1, 9-H or 10-H), 5.24 (1H, dd, *J* 10.8 and 6.3, 9-H or 10-H), 4.66 (1H, d, *J* 15.8, 2-H_A), 4.57 (1H, d, *J* 15.8, 2-H_B), 4.54 (1H, d, *J* 16.2, 14-H_A), 4.31 (1H, d, *J* 16.2, 14-H_B), 4.14 (1H, br s, OH), 3.79 (1H, ddt, *J* 9.7, 7.1 and 5.0, 12-H), 3.72 (3H, s, NMe), 3.52 (2H, m, 4-H_A an CH_AOH), 3.44 (1H, dd, *J* 11.6 and 4.4, CH_BOH), 3.24 (1H, dd, 13.9 and 4.7, 4-H_B), 3.09 (2H, s, OH and 6-H), 2.07-1.99 (1H, m, 11-H_A), 1.88 (1H, dt, 10.5 and 5, 11-H_B), 1.59-1.51 (1H, m, 8-H_A), 1.49-1.40 (2H, m, 8-H_B and 5-H), 1.34-1.23 (2H, m, 7-H_2), 0.73 (d, *J* 6.7, Me <10% trans), 0.69 (3H, d, *J* 6.7, Me); δ_C (125 MHz; DMSO-*d6*; 343 K) 139.7 (Imid), 139.6 (Imid), 139.5 (Ar), 135.4 (Ar), 130.7 (9- or 10-C); 128.7 (Ar), 128.1 (Ar), 127.9 (Ar), 126.5 (9- or 10-C), 126.4 (Ar), 124.7 (Imid); 120.1 (q *J* 325, CF_3), 68.8 (6-C), 60.8 (12-C), 60.7 (CH_2OH), 54.6 (4-C), 52.9 (2-C), 48.2 (14-C); 33.5 (Me), 33.0 (7-C), 33.0 (11-C), 30.4 (5-C), 22.4 (8-C), 9.3 (Me); ν_{max}/cm^{-1} (film) 3401, 2941, 1639, 1533, 1491, 1448, 1384; *m/z* (ES$^+$) 617.2 (100%, [M+H]$^+$); found 617.1684, $C_{24}H_{33}F_3N_4O_6S_2$ requires *MH* 617.1686

(2*R*)-1-Hydroxy-*N*-{[3-({*N*-[(2*R*,3*R*)-3-hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-*S*-(1-methyl-1H-imidazol-4-yl)pent-4'-ene-2'-sulfonamido 271c



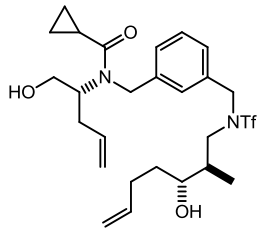
Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (64 mg, 0.36 mmol), triethylamine (72 mg, 0.71 mmol) and amine **239^{D}** (82 mg, 0.071 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$—MeOH gave the sulfonamide **271c** (18 mg, 0.028 mmol, 40.8%); R_f 0.35 (95:5, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ −3.1 (c. 0.9, MeOH); δ_H (500 MHz; $CDCl_3$) 7.51 (1H, d, *J* 1.4, Ar), 7.44 (1H, d, *J* 1.4, Ar), 7.41 (1H, s, Ar), 7.40-7.30 (4H, m, Ar), 5.77 (1H, ddt, *J* 16.9, 10.2 and 6.7, 6-H), 5.57 (1H, ddt, *J* 17.1, 10.2 and 7.1, 4'-H), 5.45 (1H, br s, OH), 5.01 (1H, dd , *J* 17.1 and 1.6, 7-H_A), 4.98 (3H, m, 7-H_B and 5'-H_{AB}), 4.64 (2H, br s, PhC*H*$_2$NTf), 4.38 (1H, d, *J* 15.8, N(SO_2)C*H*$_A$Ph), 4.28 (1H, d, *J* 15.8, N(SO_2)C*H*$_B$Ph), 3.99-3.88 (2H, m, 1'-H_A and 2'-H), 3.75 (3H, s, CH_3), 3.64 (1H, d, *J* 11.2, 1'-H_B), 3.56 (1H, br s, 3-H), 3.44 (1H, br s, 1-H_A), 3.15 (1H, br s, 1-H_B), 2.28-2.08 (3H, m, 3'-H_{AB} and 5-H_A), 2.01-1.93 (1H, 5-H_A); 1.64-1.45 (2H, 2-H and 4-H_A), 1.21 (1H, 4-H_B), ch3 (3H, CH_3); δ_C (75 MHz; $CDCl_3$) 141.2, 138.6, 138.3, 137.9, 134.9, 134.6, 129.1, 128.9, 128.0, 124.3; 117.6 (7-C or 5'-C), 114.9 (7-C or 5'-C), 79.9 (3-C), 63.7 (2'-C), 62.2 (1'-C), 53.4 (Ph*C*H_2NTf), 52.1 (1-C), 50.6 (N(SO_2)*C*H_2Ph), 36.9 (5-C or 3'-C), 36.3 (4-C), 34.25 (me), 32.9 (5-C or 3'-C), 30.6 (2-C), 10.6 (CH_3 *extracted from HMQC*); ν_{max}/cm^{-1} (film) 3370, 2977, 2939, 1641, 1533, 1450, 1384, 1335; *m/z* (ES$^+$) 645.3 (100%, [M+Na]$^+$); found 623.2163, $C_{26}H_{37}F_3N_4O_6S_2$ requires *MH* 623.2179

3-{[3-({*N*-[(2*R*,3*R*)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-3'-[(2'*R*)-1'-hydroxypent-4'-en-2'-yl]-1'-(pyridin-3-yl)urea 271a



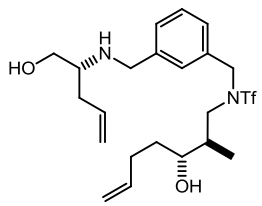
Following general procedure **A1**, 3-pyridyl isocyanate (16.3 mg, 0.14 mmol) and amine **239^{D}** (78 mg, 0.067 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 CH_2Cl_2—MeOH gave the urea **271a** (35 mg, 0.058 mmol, 87.4%); R_f 0.15 (90:10, CH_2Cl_2—MeOH); $[\alpha]_D^{23.7}$ −2.2 (c. 3.5, MeOH); δ_H (300 MHz; $CDCl_3$) 8.96 (1H, br s, NH), 8.20 (1H, d, *J* 2.7, 2-Py), 8.12 (1H, dd, *J* 4.8 and 1.4, 4-Py), 8.00 (1H, ddd, *J* 8.4, 2.7 and 1.4, 5-Py), 7.41-7.17 (5H, m, Ar and 6-Py), 5.81-5.65 (2H, m, 4'-H and 6-H), 5.09 (1H, d, *J* 10.4, 7-H_A or 5'-H_A), 5.08 (1H, d, *J* 16, 7-H_B or 5'-H_B), 4.99 (1H, d, *J* 17, 7-H_B or 5'-H_B), 4.97 (1H, d, *J* 9.4, 7-H_A or 5'-H_A), 4.62 (1H, d, *J* 15.8, N(CO)C*H*$_A$Ph), 4.54 (1H, d, *J* 15.8, N(CO)C*H*$_B$Ph), 4.53 (2H, br s, PhCH_2NTf), 3.96-3.86 (1H, m, 2'-H), 3.80-3.63 (2H, m, 1'-H_2), 3.52 (1H, br s, 3-H), 3.34 (1H, dd, *J* 13.7 and 8, 1-H_A), 3.17 (1H, br s, 1-H_B), 2.55-2.34 (2H, m, 3'-H_{AB}), 2.14-1.88 (2H, m, 5-H_{AB}), 1.67 (1H, d, *J* 6.8, 2-H), 1.44 (1H, d, *J* 7.1, 4-H_A), 1.32-1.17 (1H, m, 4-H_B), 0.71 (3H, d, *J* 6.8, Me); δ_C (75 MHz; $CDCl_3$) 157.1 (CO), 142.7, 139.9, 139.4, 138.1, 136.9, 135.4, 134.1, 129.5, 127.9, 127.8, 127.0, 123.9, 122.3, 118.3 (5'-C), 115.1 (7-C), 77.2 (3-C), 63.9 (1'-C), 60.0 (2'-C), 53.6 (N(CO)CH_2Ph), 52.0 (PhCH_2NTf), 49.2 (1-C), 36.4 (5-C), 33.8 (3'-C), 33.0 (2-C), 30.5 (4-C), *CF_3 missing*; ν_{max}/cm^{-1} (film) 3316, 3054, 2980, 2937, 1730, 1662, 1587, 1540, 1484, 1384; *m/z* (ES$^+$) 599.3 (100%, [M+H]$^+$); found 599.2506, $C_{28}H_{37}F_3N_4O_5S$ requires *MH* 599.2510

***N*-{[3-({*N*-[(2*R*,3*R*)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]methyl}-*N*-[(2*R*)-1'-hydroxypent-4'-en-2'-yl]cyclopropanecarboxamide 271b**



Following general procedure **A2**, cyclopropane carbonyl chloride (41 mg, 0.4 mmol), triethylamine (80 mg, 0.8 mmol) and amine **239^{D}** (90 mg, 0.08 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$−MeOH gave the amide **271b** (9.7 mg, 0.018 mmol, 22.2%); R_f 0.64 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 1.2 (c. 0.9, MeOH); δ_H (500 MHz; $CDCl_3$; 323 K) *Mixture of rotamers* 7.41-7.26 (4H, m, Ar), 5.82-5.70 (2H, m, 4'-H and 6-H), 5.14-4.94 (4H, m, 5'-H_{AB} and 7-H_{AB}), 4.67-4.38 (4H, m, N(CO)CH_2Ph and PhCH_2NTf), 4.13-4.04 (1H, m, 3-H), 3.72-3.41 (4H, m, 1-H_{AB} and 1'-H_{AB}), 3.20-3.10 (1H, m, 2'-H), 2.41 (1H, s, 3'-H_A), 2.35-2.20 (1H, m, 3-H_B), 2.21-2.02 (1H, m, 5-H_A), 2.01-1.92 (1H, m, 5-H_B), 1.69-1.52 (2H, m, 4-H_{AB}), 1.39-0.69 (6H, m, ^{C}Pr and 2-H); 0.75 (3H, d, *J* 6.8, Me); δ_C (125 MHz; DMSO-*d6*; 343 K) 138.5, 131.9, 128.4, 127.8, 126.6, 116.2 (5-C), 114.4 (7-C), 69.5 (3-C), 65.7 (1'-C), 58.1 (2'-C), 54.9 (N(CO)CH_2Ph), 52.6 (PhCH_2NTf), 50.2 (1-C), 35.8 (2-C), 33.6 (3'-C), 29.7 (4-C), 12.5 (^{C}Pr), 10.2 (Me), 7.7 (^{C}Pr), *CF_3 missing*; ν_{max}/cm^{-1} (film) 3386, 3055, 2981, 2938, 2306, 1725, 1640, 1546, 1450 and 1384; *m/z* (ES$^+$) 547.3 (100%, [M+H]$^+$); found 547.2461, $C_{26}H_{37}F_3N_2O_5S$ requires *MH* 547.2448

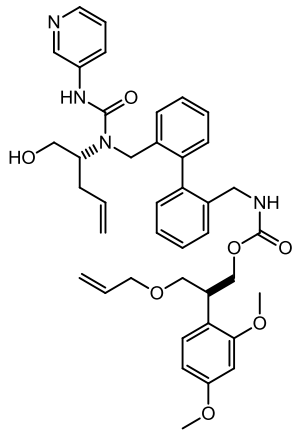
1,1,1-Trifluoro-*N*-[(2*R*,3*R*)-3-hydroxy-2-methylhept-6-en-1-yl]-*N*-{[3-({[(2*R*)-1'-hydroxypent-4'-en-2'-yl]amino}methyl)phenyl]methyl}methanesulfonamide 271d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **239^{D}** (79 mg, 0.069 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was

purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **271d** (22 mg, 0.046 mmol, 67%); R_f 0.2 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 6.8 (c. 1.1, MeOH); δ_H (500 MHz; $CDCl_3$) 7.49-7.34 (4H, m, Ar), 5.87 (1H, ddt, *J* 17.4, 10.3 and 7.1, 4'-H), 5.81 (1H, ddt, *J* 16.9, 10.6 and 5.4, 6-H), 5.15 (1H, dd , *J* 17.4 and 1.9, 5'-H_A), 5.12 (1H, dd, *J* 10.3 and 1.7, 5'-H_B), 5.02 (1H, ddd, *J* 16.9, 1.4 and 1.4, 7-H_A), 4.97 (1H, ddd, *J* 10.6, 1.4 and 1.4, 7-H_B), 4.67 (1H, d, *J* 14.5, $PhCH_ANTf$), 4.61 (1H, d, *J* 14.5, $PhCH_BNTf$), 3.93 (1H, d, *J* 13.3, $NHCH_APh$), 3.89 (1H, d, *J* 13.3, $NHCH_BPh$), 3.66 (1H, dd, *J* 11.1 and 4.7, 1'-H_A), 3.53 (1H, dd, *J* 11.1 and 6.3, 1'-H_B), 3.49-3.47 (3H, m, 3-H and 1-H_{AB}), 2.79 (1H, qd, *J* 6.3 and 4.7, 2'-H), 2.33-2.29 (2H, m, 3'-H_{AB}), 2.14-2.06 (1H, m, 5'-H_A), 2.02-1.92 (1H, m, 5'-H_B), 1.76-1.68 (1H, m, 2-H), 1.53-1.44 (1H, m, 4-H_A), 1.36-1.26 (1H, m, 4-H_B), 0.82 (3H, d, *J* 6.9, Me); δ_C (75 MHz; CDCl3) 141.8 (Ar 1- or 3-C), 139.5 (Ar 1- or 3-C), 136.9 (6'-C), 136.4 (4-C), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 128.6 (Ar), 121.8 (q, *J* 324, CF_3); 117.8 (7-C), 115.1 (5'-C), 71.7 (3-C), 64.1 (1'-C), 59.4 (2'-C), 54.6 (1-C), 54.5 (Ph*C*H_2NTf), 51.8 (NH*C*), 37.7 (2-C), 36.6 (3'-C), 34.9 (5-C), 31.3 (4-C), 10.8 (Me); ν_{max}/cm^{-1} (film) 3390, 3054, 3005, 2986, 2937, 1640, 1451 and 1384; *m/z* (ES^+) 479.2 (100%, $[M+H]^+$); found 479.2199, $C_{22}H_{33}F_3N_2O_4S$ requires *MH* 479.2186

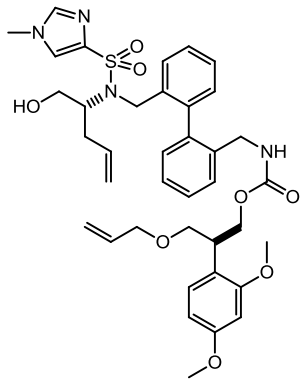
2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-(2-{[(1-hydroxypent-4-en-2-yl)[(pyridin-3-yl)carbamoyl]amino]methyl}phenyl)phenyl]methyl}carbamate



Following general procedure **A1**, 3-pyridyl isocyanate (11.2 mg, 0.093 mmol) and amine **240^D** (53 mg, 0.046 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$—MeOH gave the urea **272a** (12.5 mg, 0.018 mmol, 39%); R_f 0.2 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ 16.2 (c. 0.6, MeOH); δ_H (300 MHz; $CDCl_3$) *very broad and atropisomers denoted in italics*

where possible 8.41-8.32 (1H, m, Py), 8.24-8.13 (1H, m, Py), 7.98-7.86 (1H, m, Py), 7.81-7.69 (1H, m, Ar), 7.50 (1H, ap t, *J* 6.6, Ar), 7.45-7.23 (4H, m, Ar), 7.22-7.07 (3H, m, Ar), 7.00 (1H, dd, *J* 8.2 and 6.6, DMB 6-H), 6.46-6.36 (2H, m, DMB 3-H and 5-H); 5.81 (1H, ddt, *J* 16.1, 10.5 and 5.5, propenyl 2-H), 5.69 (1H, ddt, *J* 17, 9.9 and 6.9, 4-H), 5.32 (1H, br s, NH), 5.19 (1H, dd, *J* 17 and 1.5, propenyl 3-H_A), 5.11 (1H, d, *J* 9.9, propenyl 3-H_B), 5.07-4.93 (2H, m, 5-C_{AB}), 4.40-3.86 (9H, propenyl 1-H_2, 2 x Benzylic CH2, propyl 1-H and 2-H), 3.78 (3H, s, OMe), 3.74 (3H, s, OMe), 3.69-3.45 (5H, 1-H, propyl 3-H and 2-H), 2.44-2.30 (2H, 3-H); δ_C (75 MHz; $CDCl_3$) 159.6 (DMB 4-C), 158.3 (DMB 2-C), 157.0 (C=O), 156.8 (C=O), 143.5, 136.6, 134.9, 134.6, 128.9, 128.3, 127.6, 127.5, 127.4, 123.3, 117.7 (5-C or propenyl 3-C), 116.7 (5-C or propenyl 3-C), 104.1 (DMB 5-C), 98.6 (DMB 3-C), 71.9 (propenyl 1-C), 70.5 (1-C), 65.6 (propyl 3-C), 62.4 (propyl 1-C), 59.5 (2-C); 55.3 (OMe), 50.5 (N(CO)CPh), 45.7 (NPyCPh), 38.2 (propyl 2-C), 33.6 (3-C); ν_{max}/cm^{-1} (film) 3332, 2937, 1711, 1623, 1598, 1534, 1357, 1208, 1159, and 1099 ;*m/z* (ES^+) 695.3 (100%, $[M+H]^+$); found 695.3441, $C_{40}H_{46}N_4O_7$ requires *MH* 695.3439

2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-(2-{[*N*-(1-hydroxypent-4-en-2-yl)1-methyl-1H-imidazole-4-sulfonamido]methyl}phenyl)phenyl]methyl}carbamate 272c

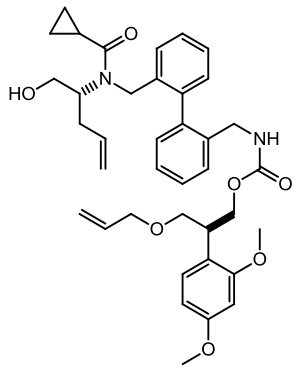


Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (52 mg, 0.29 mmol), triethylamine (58.6 mg, 0.59 mmol) and amine **240^D** (65 mg, 0.057 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amine sulfonamide **272c** (9.1 mg, 0.013 mmol, 22.2%); R_f 0.4 (EtOAc); $[\alpha]_D^{23.7}$ 4.8 (c. 0.5, MeOH); δ_H (500 MHz; $CDCl_3$; 323 K) *atropisomers denoted where possible* 7.82 (1H, d, *J* 7.9), 7.66-

7.22 (7H, m,), 7.20-7.02 (3H, m,), 6.44-6.38 (2H, m,), 5.84 (1H, ddt, *J* 16.8, 11 and 5.4, propenyl 2-H), 5.84 (ddt, *J* 16.1, 10.2 and 5.2, propenyl 2-H^{atrop}), 5.55 (1H, ddt, *J* 17.3, 10 and 6.9, 4-H), 5.55 (ddt, *J* 17.1, 10.2 and 6.6, 4-H^{atrop}), 5.20 (1H, dd , *J* 17.3 and 1.8, 5-H_A), 5.10 (1H, dd, *J* 10.2 and 1.6, 5-H_B), 4.94-4.81 (2H, m, propenyl 3-H_{AB}), 4.44-4.27 (2H, m, propyl 1-H_{AB}), 4.10 (1H, dd, *J* 16.8 and 5.6, N(SO_2)CH_APh or PhCH_AN(CO)O), 4.08-3.97 (1H, m, N(SO_2)CH_BPh or PhCH_BN(CO)O), 3.95-3.87 (2H, m, propenyl 1-H), 3.78-3.74 (6H, m, 2 × OMe), 3.66 (3H, s, NMe), 3.64 (s, NMe^{atrop}), 3.63-3.43 (8H, propyl 2-H and 3-H_{AB}, 2-H, 1-H_{AB} and N(SO_2)CH_2Ph or PhCH_2N(CO)O), 2.31-2.20 (1H, 3-H_A), 2.18-2.05 (1H, 3-H_B); δ_C (125 MHz; $CDCl_3$; 323 K) 159.7, 158.4 (^{atrop}), 157.1 (^{atrop}), 138.5, 135.0, 134.8, 129.8, 129.8, 129.6, 129.0, 128.9, 128.3, 128.1, 128.0, 127.8, 127.8, 127.02, 127.0, 124.2, 120.4, 117.2, 117.1, 116.4, 104.4, 98.8, 71.9, 70.6, 63.8, 62.6, 62.2, 55.4, 55.3, 38.3, 33.9 (Me); ν_{max}/cm^{-1} (film) 3691, 3056, 2987, 2685, 2411, 2306, 1714, 1607, 1550, 1508, 1422, 1277; *m/z* (ES$^+$) 741.3 (100%, [M+Na]$^+$); found 741.2919, $C_{38}H_{46}N_4O_8S$ requires *MNa* 741.2929

full carbon assignment was not possible to mixture of atropisomers

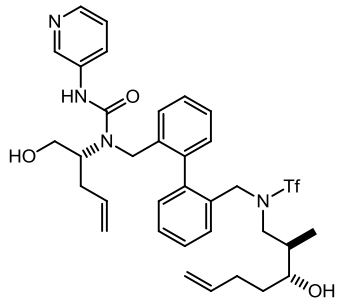
2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-(2-{[1-cyclopropyl-*N*-(1-hydroxypent-4-en-2-yl)formamido]methyl}phenyl)phenyl]methyl}carbamate 272b



Following general procedure **A2**, cyclopropane carbonyl chloride (36.4 mg, 0.35 mmol), triethylamine (70.4 mg, 0.69 mmol) and amine **240^D** (79 mg, 0.069 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:50 petrol—EtOAc gave the amide **272b** (19.9 mg, 0.031 mmol, 45%); R_f 0.5 (70:30, petrol—EtOAc); $[\alpha]_D^{23.7}$ −5.9 (c. 1, MeOH); δ_H (300 MHz; $CDCl_3$; 323 K) *very broad* 7.95-7.25 (5H, m, Ar), 7.21-7.03 (4H, m, Ar), 6.44 (2H, s, DMB), 5.84 (1H, 16.1, 10.7 and 5.4, propenyl 2-H), 5.70-5.59 (1H, 4-H), 5.21 (1H,

16.1, propenyl 3-H_A), 5.12 (1H, 10.7, propenyl 3-H_B), 5.06-4.83 (2H, 5-H_{AB}), 4.67-3.28 (20H, N(CO)CH_2Ph, PhCH_2N(CO)O, 2 × OMe, 2-H, 1-H, propenyl 1-H, Propyl 1H_{AB}, 2-H and 3-H_{AB}), 2.46-1.85 (2H, 3-H), 1.54-1.45 (1H, ^{C}Pr), 1.05-0.63 (4H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 159.7 (DMB 4-C), 158.3 (DMB 2-C), 146.1 (C=O), 138.9, 134.9 (propenyl 2-C), 131.6, 129.8, 129.8, 128.9, 128.4, 128.3, 128.2, 127.6, 127.5, 127.2, 117.5 (propenyl 3-C or 5-C), 116.7 (propenyl 3-C of 5-C), 104.1 (DMB 5-C), 98.6 (DMB 3-C), 71.9 (propenyl 1-C), 70.6 (1-C), 65.4 (propyl 1-C), 64.0 (propyl 3-C), 63.9 (N(CO)*C*H_2Ph), 59.9 (2-C), 55.4 (OMe), 55.3 (OMe), 49.2 (Ph*C*H_2N(CO)O), 38.2 (propyl 2-C), 33.1 (3-C), 12.3 (^{C}Pr), 8.4 (^{C}Pr); ν_{max}/cm^{-1} (film) 3332, 3061, 3006, 2937, 1713, 1614, 1588, 1544, 1508, 1463, 1358, 1261, 1208, 1159, and 1099; *m/z* (ES^+) 665.3 (100%, $[M+Na]^+$); found 643.3395, $C_{38}H_{46}N_2O_7$ requires *MH* 643.3378

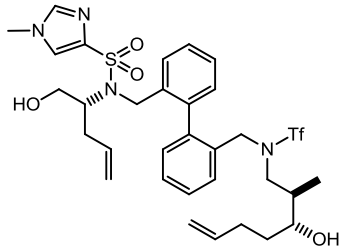
3-({2-[2-({*N*-[(3*R*)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]phenyl}methyl)-3-(1-hydroxypent-4-en-2-yl)-1-(pyridin-3-yl)urea 274a



Following general procedure **A1**, 3-pyridyl isocyanate (21.5 mg, 0.179 mmol) and amine **242** (110 mg, 0.089 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:50 petrol—EtOAc gave the urea **274a** (37.7 mg, 0.056 mmol, 63%); R_f 0.25 (50:50 EtOAc—petrol); $[\alpha]_D^{23.7}$ 10.9 (c. 1.1, MeOH);δ_H (500 MHz; $CDCl_3$) 9.52 (0.5H, br s, NH), 9.23 (0.5H, br s, NH), 8.22 (1H, d, *J* 11.7), 8.10 (2H, m, Ar), 7.68-7.06 (9H, Ar), 5.74 (1H, ddt, J 17.1, 10.4 and 6.7, 6-H), 5.63-5.54 (1H, m, 4'-H), 5.02-4.84 (4H, m, 5'-H_{AB} and 7-H_{AB}), 4.68 (0.5H, d, J 16.8, PhCH_ANTf), 4.40 (0.5H, d, J 16.5, PhCH_ANTf^{atrop}), 4.35 (1H, br s, PhCH_BNTf), 4.18-3.99 (1H, m, 3-H), 3.89-3.38 (5H, m, 1'-H_{AB}, 2'-H, N(COPy)CH_2Ph), 3.34 (1H, dd , *J* 14.4 and 9.2, 1-H_A), 3.20 (1H, dd, *J* 14.4 and 6.6, 1-H_B), 2.45 (0.5H, dt, *J* 13.8 and 6.9, 3'-H_A), 2.38-2.23 (1.5H, m, 3'-H_B and 3'H_{AB}^{atrop}), 2.15-1.83 (2H, m, 5-H_{AB}), 1.64-1.53 (0.5H, 4-H_A^{atrop}), 1.51-1.41 (1.5H, 2-H and 4-H_B^{atrop}), 1.32-1.19 (1H, 4-H_{AB}), 0.69 (3H, d, *J* 6.9, Me); δ_C (75 MHz; $CDCl_3$) 157.2, 156.9, 142.4, 142.3, 139.7, 139.6, 139.3, 139.2,

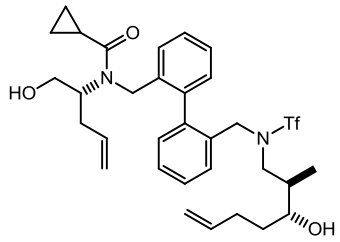
138.5, 138.3, 138.2, 135.8, 134.0, 133.8, 133.2, 129.7, 129.6, 129.7, 128.6, 128.4, 128.0, 127.5, 127.4, 127.3, 127.1, 124.1, 118.3, 118.2, 114.9, 114.8, 63.7, 63.6, 60.9, 60.1, 54.5, 52.6, 51.2, 48.9, 36.8, 33.8, 33.6, 33.4, 33.2, 30.6, 30.4, 10.5; ν_{max}/cm^{-1} (film) 3285, 3063, 2979, 2939, 1663, 1588, 1546, 1484, 1424, 1385 and 1341; *m/z* (ES$^+$) 675.3 (100%, [M+H]$^+$); found 675.2833, $C_{34}H_{41}F_3N_4O_5S$ requires *MH* 675.2823

1-Hydroxy-*N*-({2-[2-({*N*-[(3*R*)-3-hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]phenyl}methyl)-*S*-(1-methyl-1H-imidazol-4-yl)pent-4-ene-2-sulfonamido 274c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (93 mg, 0.517 mmol), triethylamine (104 mg, 1.03 mmol) and amine **242** (127 mg, 0.103 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:50 EtOAc—petrol gave the sulfonamide **274c** (50.7 mg, 0.071 mmol, 69.2%); R_f 0.35 (50:50, EtOAc—petrol); δ_H (500 MHz; $CDCl_3$) 7.95 (1H, d, *J* 7.8, Imid 2-H), 7.89 (1H, d, *J* 7.8, Imid 2-H^{atrop}), 7.57 (1H, d, *J* 7.7, Ar^{atrop}), 7.50-7.30 (6.5H, m, Ar), 7.17-7.12 (1H, m, Ar), 7.07-7.01 (1H, m, Ar), 5.74 (1H, ddt, *J* 16.8, 9.8 and 6.7, 4'-H), 5.61 (0.5H, ddt, *J* 16.8, 10.2 and 7.6, 6-H), 5.43 (0.5H, br s, 6H^{atrop}), 5.03-4.72 (4H, m, 5'-H_{AB} and 7-H_{AB}), 4.67-4.04 (4H, m, N(Imid)CH_2Ph and PhCH_2NTf), 3.97 (d, *J* 17, N(Imid)CH_2Ph or PhCH_2NTf), 3.92-3.84 (1H, 3-H); 3.73 (3H, s, NMe), 3.71 (s, NMe^{atrop}), 3.60-3.36 (5H, 1'-H_2, 2'-H and 1-H_2), 3.33 (1H, dd , 1-H_A^{atrop}), 3.29 (1H, br s, 1-H_B^{atrop}), 2.32-1.84 (4H, 3'-H_2 and 5-H_2), 1.79-1.60 (0.5H, 4-H_A), 1.53-1.37 (2H, 2-H and 4-H_B and 4-H_A^{atrop}), 1.30-1.17 (0.5H, 4-H_B^{atrop}), 0.65 (3H, d , *J* 6.7, CH_3); δ_C (75 MHz; $CDCl_3$) 140.6, 140.5, 139.3, 139.0, 138.8, 138.7, 138.3, 138.1, 137.8, 135.9, 135.4, 134.7, 134.6, 133.8, 132.4, 130.1, 129.9, 129.5, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.6, 127.4, 124.6, 117.7, 117.3, 115.1, 114.9, 63.1, 62.5, 61.7, 54.4, 51.5, 60.1, 47.0, 36.9, 36.2, 34.2, 34.1, 32.9, 30.5, 30.4, 16.6, 12.3, 12.1, 10.6; ν_{max}/cm^{-1} (film) 3368, 3146, 3061, 2942, 2307, 1941, 1830, 1713, 1640, 1600, 1532 and 1447; *m/z* (ES$^+$) 721.2 (100%, [M+Na]$^+$); found 721.2324, $C_{32}H_{41}F_3N_4O_6S$ requires *MNa* 721.2312

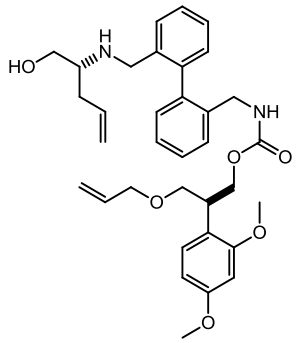
***N*-({2-[2-({*N*-[(3*R*)-3-Hydroxy-2-methylhept-6-en-1-yl](trifluoromethane)sulfonamido}methyl)phenyl]phenyl}methyl)-*N*-(1'-hydroxypent-4'-en-2'-yl)cyclopropanecarboxamide 274b**



Following general procedure **A2**, cyclopropane carbonyl chloride (52 mg, 0.49 mmol), triethylamine (98.9 mg, 0.98 mmol) and amine **242** (122 mg, 0.099 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **274b** (40.7 mg, 0.065 mmol, 66%); R_f 0.4 ($CHCl_3$); δ_H (500 MHz; DMSO-*d6*) 7.59-7.30 (6H, m, Ar), 7.22-7.17 (1H, m, Ar), 7.09 (1H, ap t, *J* 7.6, Ar), 5.8-5.59 (2H, m, 6-H and 4'-H), 4.99-4.87 (4H, m, 5'-H_{AB} and 7-H_{AB}), 4.49 (0.5H, d, *J* 16.4, PhCH_ANTf), 4.44 (0.5H, d, J 16.3, PhCH_ANTf^{atrop}), 4.27-4.10 (1H, m, PhCH_BNTf), 3.88-3.74 (2H, m, N(CO)CH_{AB}Ph), 3.48-3.06 (5H, m, 3-H, 1-H_{AB} and 1'-H_{AB}), 2.64 (1H, ap t, *J* 5.4, 2'-H), 2.11-1.97 (3H, m, 3'-H_A and 5-H_{AB}), 1.93-1.84 (1H, m, 3'-H_B), 1.54-1.02 (4H, m, ^{C}Pr , 2-H and 4-H_{AB}), 0.87-0.77 (4H, m, ^{C}Pr), 0.64 (3H, d, Me); δ_C (75 MHz; $CDCl_3$) 173.57, 173.54, 139.8, 139.7, 138.8, 138.7, 138.5, 138.4, 135.1, 132.9, 132.8, 129.9, 129.2, 129.1, 128.9, 127.9, 127.8, 127.5, 127.3, 126.6, 116.8, 116.7, 114.4, 114.3, 69.5, 69.4, 65.7, 55.5, 54.1, 53.5, 50.9, 50.4, 48.2, 48.1, 36.4, 36.1, 33.6, 33.5, 29.7, 12.4, 10.3, 10.2, 7.7; ν_{max}/cm^{-1} (film) 3402, 3075, 2979, 2254, 2127, 1998, 1827, 1708, 1640, 1545, 1448 and 1383; *m/z* (ES^+) 623.3 (100%, $[M+H]^+$); found 623.2786, $C_{32}H_{41}F_3N_2O_5S$ requires *MH* 623.2761

Full ^{13}C assignment was not possible due to atropisomers

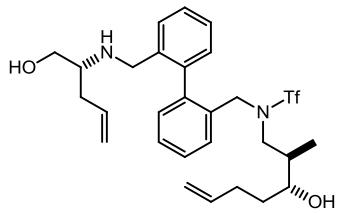
2-(2,4-Dimethoxyphenyl)-3-(prop-2-en-1-yloxy)propyl *N*-{[2-(2-{[(1-hydroxypent-4-en-2-yl)amino]methyl}phenyl)phenyl]methyl}carbamate 272d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **240^{D}** (63 mg, 0.055 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by preparative mass−directed column chromatography and gave the amine **272d** (15.9 mg, 0.028 mmol, 50.4%); R_f 0.21 (EtOAc); ν_{max}/cm^{-1} (film) 3441, 3056, 3005, 2936, 2305, 1711, 1614, 1587, 1544, 1508 and 1465; *m/z* (ES$^+$) 575.3 (100%, [M+H]$^+$); found 575.3142, $C_{34}H_{42}N_2O_6$ requires *MH* 575.3116

Unable to obtain ^{1}H or ^{13}C spectra, see **272c** *and* **272b** *for spectra of the same scaffolds*

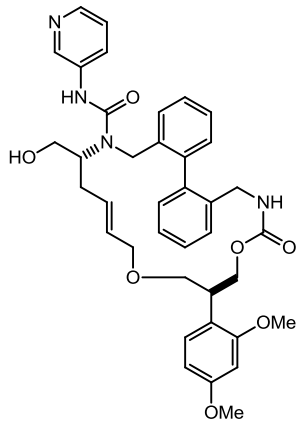
1,1,1-trifluoro-*N*-[(3*R*)-3-hydroxy-2-methylhept-6-en-1-yl]-*N*-{[2-(2-{[(1-hydroxypent-4-en-2-yl)amino]methyl}phenyl)phenyl]methyl}methanesulfonamide 274d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **242** (90 mg, 0.073 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by preparative mass−directed column chromatography and gave the amine **274d** (40 mg, 0.072 mmol, 99%); R_F 0.33 (EtOAc); ν_{max}/cm^{-1} (film) 3591, 3424, 3063, 2979, 2937, 2320, 1936, 1829, 1713, 1640, 1546, 1447 and 1384; *m/z* (ES$^+$) 555.3 (100%, [M+H]$^+$); found 555.2514, $C_{28}H_{37}F_3N_2O_4S$ requires *MH* 555.2499

Unable obtain ^{1}H and ^{13}C due to severe atropisomers

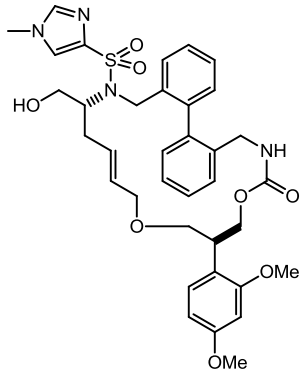
(17*E*)-13-(2,4-Dimethoxyphenyl)-20-(hydroxymethyl)-10-oxo-*N*-(pyridin-3-yl)-11,15-dioxa-9,21-diazatricyclo[21.4.0.0^{2,7}]heptacosa-1(27),2,4,6,17,23,25-heptaene-21-carboxamide 263a



Following general procedure **A1**, 3-pyridyl isocyanate (5.28 mg, 0.44 mmol) and amine **251^{D}** (24.3 mg, 0.022 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 50:50 petrol−EtOAc gave the urea **263a** (11.9 mg, 0.018 mmol, 82%); R_f 0.12 (CH_2Cl_2); $[\alpha]_D^{23.7}$ 4.1 (c. 1.2, MeOH); ν_{max}/cm^{-1} (film); *m/z* (ES$^+$) 667.3 (100%, [M+H]$^+$); found 667.3126, $C_{38}H_{42}N_4O_7$ requires *MH* 667.312610

Unable obtain ^{1}H and ^{13}C due to severe atropisomers

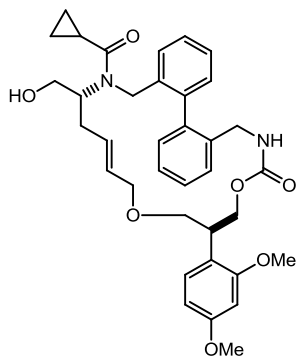
(17*E*)-13-(2,4-Dimethoxyphenyl)-20-(hydroxymethyl)-21-(1-methyl-1H-imidazole-4-sulfonyl)-11,15-dioxa-9,21-diazatricyclo[21.4.0.0^{2,7}]heptacosa-1(27),2,4,6,17,23,25-heptaen-10-one 263c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (18.9 mg, 0.105 mmol), triethylamine (21.2 mg, 0.21 mmol) and amine **251^{D}** (23.5 mg, 0.21 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with CH_2Cl_2 gave the amine **263c** (11.4 mg, 0.016 mmol, 76%); R_f 0.1 (CH_2Cl_2); $[\alpha]_D^{23.7}$ 3.1 (c. 1.1, MeOH); ν_{max}/cm^{-1} (film) 3321, 3005, 2924, 2852, 1711, 1612, 1586, 1531, 1507, 1463 and 1335; *m/z* (ES$^+$) 713.3 (20%, [M+H]$^+$); found 713.2614, $C_{36}H_{42}N_4O_8S$ requires *MH* 713.2616

Unable to obtain a ^{1}H or ^{13}C spectra due to geometric isomers and atropisomers

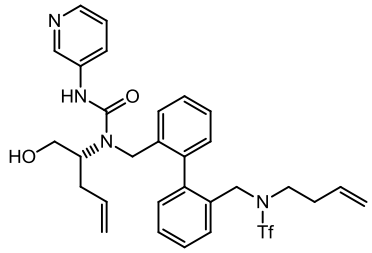
(17*E*)-21-Cyclopropanecarbonyl-13-(2,4-dimethoxyphenyl)-20-(hydroxymethyl)-11,15-dioxa-9,21-diazatricyclo[21.4.0.0^{2,7}]heptacosa-1(27),2,4,6,17,23,25-heptaen-10-one 263b



Following general procedure **A2**, cyclopropane carbonyl chloride (10.9 mg, 0.105 mmol), triethylamine (21.2 mg, 0.21 mmol) and amine **251^{D}** (22.7 mg, 0.021 mmol)

gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **263b** (11.1 mg, 0.018 mmol, 86%); R_f 0.32 ($CHCl_3$); $[\alpha]_D^{23.7}$ 3.2 (c. 0.7, MeOH); δ_H (500 MHz; $CDCl_3$) 8.01 (1H, s, Ar), 7.82 (0.1H, br s, Ar^{atrop}), 7.56-7.04 (8H, m, Ar), 6.46-6.37 (2H, m, DMB), 5.60-5.20 (2H, m, 17 and 18 H), 4.65-2.99 (21H, m, 2 × OMe, 20-H, CH_{AB}OH, 16-H_{AB}, 14-H_{AB}, 13-H, 12-H_{AB}, 8-H_{AB} and 22-H_{AB}), 2.44 (1H, br s, 19-H_A), 2.25-1.88 (1H, 19-H_B), 1.26 (2H, ^{C}Pr), 1.10-0.67 (3H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 162.4, 130.7, 129.5, 129.1, 128.7, 128.2, 127.5, 127.3, 127.3, 126.3, 104.4, 68.9, 65.6, 63.9, 63.9, 60.8, 55.4, 55.3, 36.3, 31.7, 31.4, 29.6, 16.5, 12.3, 12.2, 8.6; ν_{max}/cm^{-1} (film) 3388, 3060, 3006, 2926, 2854, 2255, 2127, 1712, 1614, 1587, 1536, 1508 and 1436; *m/z* (ES^+) 615.3 (100%, $[M+H]^+$); found 637.2875, $C_{36}H_{42}N_2O_7$ requires *MNa* 637.2884

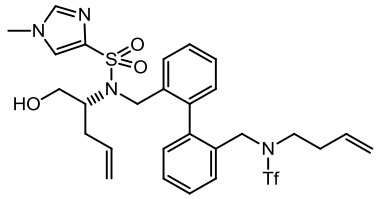
3-{[2-(2-{[*N*-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)phenyl]methyl}-3-(1-hydroxypent-4-en-2-yl)-1-(pyridin-3-yl)urea 273a



Following general procedure **A1**, 3-pyridyl isocyanate (13.8 mg, 0.114 mmol) and amine **241^D** (60.3 mg, 0.057 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$—MeOH gave the urea **273a** (25.2 mg, 0.041 mmol, 72%); R_f 0.23 (95:5, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 4.9 (c. 1, MeOH); δ_H (500 MHz; $CDCl_3$) 8.27 (1H, s, Pyridyl 2-H), 8.17 (1H, d, *J* 4.7, Pyridyl 6-H), 8.10 (1H, Pyridyl 4-H^{atrop}), 8.03-7.94 (2H, m, Pyridyl 4-H and NH), 7.61-7.56 (2H, m, Ar), 7.48-7.33 (3H, m, Ar), 7.19 (2H, dd, *J* 7.4 and 1.6, pyridyl 5-H), 7.15 (1H, dd, *J* 7.4 and 1.4, Ar), 5.61 (1H, ddt, *J* 17.1, 10.6 and 6.7, 4'-H), 5.57-5.47 (1H, m, 3-H), 5.00-4.88 (4H, m, 4-H_{AB} and 5'-H_{AB}), 4.56-4.47 (1H, br d, *J* 16.2, NTfCH_2Bn), 4.45 (0.5H, d, *J* 16.8, NPyCH_A^{atrop}), 4.35 (0.5H, d, *J* 16.9, NPyCH_A), 4.15 (1H, br s, NTfCH_2Bn^{atrop}), 4.10 (0.5H, d, *J* 16.9, NPyCH_B), 3.99 (0.5H, d, *J* 16.8, NPyCH_B^{atrop}),

3.84-3.78 (1H, m, 2'-H), 3.77-3.72 (m, 1-H_{AB}^{atrop}), 3.69-3.64 (1H, m, 1-H_A), 3.57 (1H, dd, *J* 11.2 and 7, 1-H_B), 3.36-3.28 (1H, m, 1'-H_A), 3.19 (1H, dt, *J* 14.5 and 7.3, 1'-H_B), 2.38-2.24 (2H, m, 3'-H_{AB}), 2.09-2.02 (2H, m, 2-H_{AB}); δ_C (75 MHz; $CDCl_3$) 156.9, 156.8, 142.7, 139.9, 139.8, 139.7, 138.4, 137.1, 134.1, 133.2, 133.2, 132.8, 129.9, 129.8, 129.6, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.5, 127.5, 127.1, 127.0, 123.9, 118.1, 118.0, 117.9, 117.8, 63.7, 60.2, 59.9, 49.4, 48.1, 48.0, 46.9, 33.7, 33.6, 32.4; ν_{max}/cm^{-1} (film) 3291, 3053, 3006, 2872, 1665, 1588, 1541, 1422, 1275, 1261, 1225 and 1198; *m/z* (ES^+) 603.2(100%, $[M+H]^+$); found 603.2259, $C_{30}H_{33}F_3N_4O_4S$ requires *MH* 603.2247

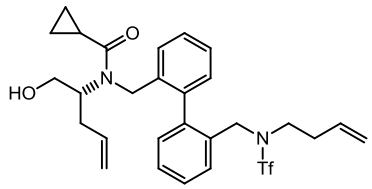
_N_-{[2-(2-{[_N_-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)phenyl]methyl}-1-hydroxy-_S_-(1-methyl-1H-imidazol-4'-yl)pent-4'-ene-2'-sulfonamido 273c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (45.9 mg, 0.25 mmol), triethylamine (51.5 mg, 0.510 mmol) and amine **241^D** (53.3 mg, 0.051 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the sulfonamide **273c** (23.2 mg, 0.037 mmol, 73%); R_f 0.15 ($CHCl_3$); $[\alpha]_D^{23.7}$ 3.9 (c. 1.2, MeOH); δ_H (500 MHz; DMSO-*d6*; 343 K) 7.79 (1H, d, *J* 7.8, Ar), 7.71-7.69 (1H, m, Ar), 7.59-7.56 (1H, m, Imid), 7.55-7.49 (2H, m, Imid and Ar), 7.48-7.38 (2H, m, Ar), 7.38-7.31 (1H, m, Ar), 7.21 (1H, d, *J* 7.1, Ar), 7.09 (1H, dt, *J* 7.3 and 1.7, Ar), 5.62-5.52 (2H, m, 3-H and 4'-H), 5.44 (ddt, *J* 17.1, 10.2 and 7, 3-H^{atrop}), 4.97-4.93 (1H, m, 4-H_A), 4.89 (0.5H, dd, *J* 17.3 and 1.7, 4-H_B), 4.88 (0.5H, *J* 17.3 and 1.7, 4'-H_B^{atrop}), 4.84 (0.5H, d, *J* 10.2 and 1.9, 5'-H_A), 4.78 (0.5H, d , *J* 16.9, 5'-H_B), 4.75 (0.5H, d , *J* 10, 5'-H_A^{atrop}), 4.66 (0.5H, dd, *J* 17.1 and 1.8, 5'-H_B^{atrop}), 4.57-4.40 (2H, m, N(SO_2)CH_2Ph or PhCH_2NTf), 4.33-4.16 (2H, m, N(SO_2)CH_2Ph or PhCH_2NTf); 3.91 (d, *J* 17.3, N(SO_2)CH_2Ph^{atrop}), 3.76-3.67 (1H, m, 2'-H), 3.66 (3H, s, Me), 3.37-3.11 (4H, m, 1-H_2 and 1'-H_{AB}), 2.20-1.94 (3H, m, 2-H and 3'-H_A), 1.92-1.83 (1H, m, 3'-H_B); δ_C (125 MHz; DMSO-*d6*; 343 K) 139.5 (Imid), 139.3 (min Imid), 139.2 (Imid), 137.2, 137.1, 137.1, 136.9, 135.3 (3'-C or 4-C ^{atrop}), 135.2 (3'-C or 4-C), 133.8, 133.7, 132.7, 132.6 (Imid ^{atrop}), 130.1 (Bip ^{atrop}), 130.0, 129.0, 129.9, 128.2

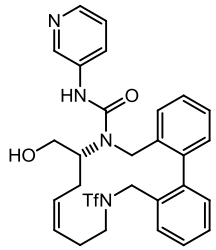
(3'-C or 4-C), 128.1, 128.0, 127.7, 127.5, 126.7, 126.6 , 124.7 , 124.6, 119.6 q *J* 325, CF_3), 117.4 (5'-C^{atrop}), 117.3 (5'-C), 116.4 (min 4-C), 116.3 (4-C), 62.4 (1'-C), 61.7 (1'-C^{atrop}), 60.4 (2'-C^{atrop}), 60.1 (2'-C), 49.5 (Ph*C*H_2NTf^{atrop}), 49.4 (Ph*C*H_2NTf), 48.4 (1-C^{atrop}), 48.2 (1-C), 45.7 (N(SO_2)*C*H_2Ph^{atrop}), 45.5 (N(SO_2)*C*H_2Ph), 33.9 (3-C^{atrop}), 33.5 (3'-C), 33.4 (Me), 31.9 (2-C); ν_{max}/cm^{-1} (film) 3301, 3146, 3061, 3005, 2984, 2941, 2306, 1716, 1642, 1531, 1446, 1422, 1386 and 1338; *m/z* (ES$^+$) 649.2 (100%, [M+Na]$^+$); found 649.1755, $C_{28}H_{33}F_3N_4O_5S$ requires *MNa* 649.1737

_N_-{[2-(2-{[_N_-(But-3-en-1-yl)(trifluoromethane)sulfonamido]methyl}phenyl)phenyl]methyl}-_N_-(1'-hydroxypent-4'-en-2'-yl)cyclopropanecarboxamide 273b



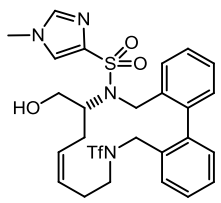
Following general procedure **A2**, cyclopropane carbonyl chloride (24.9 mg, 0.24 mmol), triethylamine (48.5 mg, 0.48 mmol) and amine **241^D** (49.8 mg, 0.048 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ gave the amide **273b** (23.1 mg, 0.042 mmol, 88%); R_f 0.56 ($CHCl_3$); $[\alpha]_D^{23.7}$ 1.6 (c. 0.8, MeOH); δ_H (500 MHz; $CDCl_3$) 7.79-7.06 (8H, m, Ar), 5.62 (1H, ddt, 3-H), 5.50 (1H, ddt, 4'-H), 5.07-4.94 (3H, m, 5'-H_A and 4-H_{AB}), 4.87 (1H, d , *J* 17.3, 5'-H_B), 4.50 (1H, PhC*H*$_A$NTf), 4.12 (1H, PhC*H*$_B$NTf), 3.95 (1H, dd , *J* 11.3 and 4.7, 1'-H_B), 3.89-3.82 (1H, m, 1'-H_B), 3.56-3.36 (2H, m, C(CO)C*H*$_{AB}$Ph), 3.33-3.08 (2H, m, 1-H_2), 2.71-2.63 (1H, m, 2'-H), 2.14-1.93 (4H, m, 3'-H_{AB} and 2-H_2), 1.61-1.52 (1H, m, ^{C}Pr), 1.00-0.93 (2H, m, ^{C}Pr), 0.91-0.82 (2H, m, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.8 (C=O), 140.3, 134.5, 133.3, 128.4, 127.9, 127.3, 117.8, 104.9, 68.2 (1'-C), 65.9 (2'-C), 55.7, 49.2, 49.2, 47.6, 36.2, 35.9, 32.2, 30.9, 12.7 (^{C}Pr), 8.6 (^{C}Pr); ν_{max}/cm^{-1} (film) 3327, 3061, 3006, 2985, 2850, 1841, 1726, 1641, 1531, 1445, 1387, 1275, 1262, 1225 and 1191; *m/z* (ES$^+$) 551.2 (100%, [M+H]$^+$); found 551.5188, $C_{28}H_{34}F_3N_2O_4S$ requires *MH* 551.2186

(12*Z*)-10-(Hydroxymethyl)-*N*-(pyridin-3-yl)-16-(trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(18),2,4,6,12,19,21-heptaene-9-carboxamide 264a



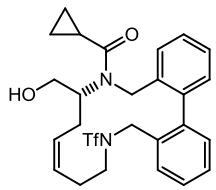
Following general procedure **A1**, 3-pyridyl isocyanate (6.8 mg, 0.062 mmol) and amine **252^{D}** (32.1 mg, 0.031 mmol) gave the crude product after 1 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by preparative mass−directed column chromatography, to give the amine **264a** (16.6 mg, 0.029 mmol, 93%); R_f 0.14 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 2.7 (c. 1.7, MeOH); δ_H (500 MHz; $CDCl_3$) 8.67 (1H, s, Ar), 8.43 (1H, s, Ar), 8.23 (1H, s, Ar), 8.09 (1H, d, *J* 7.9, Ar), 7.66 (1H, d, *J* 7.9, Ar), 7.64 (1H, d , *J* 7.6, Ar), 7.49 (1H, td, *J* 7.6 and 1.4, Ar), 7.38 (2H, t, *J* 8, Ar), 7.32 (1H, t, *J* 7.4, Ar), 7.30 (1H, br s, Ar), 7.19 (1H, dd, *J* 7.7 and 1.4, Ar), 7.09 (1H, dd, *J* 7.7 and 1.4, Ar), 5.52 (1H, d , *J* 16.8, 8-H_A), 5.48 (1H, dd, *J* 10.2 and 6.8, 13-H), 5.45 (1H, dd, *J* 10.2 and 4.7, 12-H), 4.97 (1H, d, *J* 16.7, 17-H_A), 4.32 (1H, d, *J* 16.7, 17-H_B), 4.01 (1H, d, *J* 16.8, 8-H_B), 3.89-3.82 (1H, m, 10-H), 3.62 (1H, dd, *J* 10.5 and 2.5, C*H*$_A$OH), 3.53-3.50 (1H, m, 15-H_A), 3.24 (1H, ap t, *J* 10.5, C*H*$_B$OH), 2.84-2.77 (1H, m, 15-H_B), 2.08-1.97 (3H, m, 11-H_A and 14-H_{AB}), 1.97-1.91 (1H, m, 11-H_B); δ_C (75 MHz; $CDCl_3$) 157.6, 138.4, 136.9, 136.7, 132.0, 131.5, 131.1, 129.4, 128.8, 128.4, 127.4, 126.8, 126.7, 64.1 (CH_2OH), 59.1 (10-C), 48.7 (17-C), 46.9 (15-C), 43.6 (8-C), 28.1 (11-C), 25.1 (14-C); ν_{max}/cm^{-1} (film) 3279, 3058, 3024, 2951, 2250, 1667, 1588, 1539, 1483, 1422 and 1386; *m/z* (ES$^+$) 575.2 (100%, [M+H]$^+$); found 575.1935, $C_{28}H_{29}F_3N_4O_4S$ requires *MH* 575.1934

[(12*Z*)-9-(1-Methyl-1H-imidazole-4-sulfonyl)-16-(trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(18),2,4,6,12,19,21-heptaen-10-yl]methanol 264c



Following general procedure **A3**, 1-methyl-1H-imidazole-4-sulfonyl chloride (29.7 mg, 0.165 mmol), triethylamine (33 mg, 0.33 mmol) and amine **252^{D}** (33.7 mg, 0.033 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the sulfonamide **264c** (10.2 mg, 0.017 mmol, 51%); R_f 0.47 (90:10, $CHCl_3$—MeOH); δ_H (500 MHz; $CDCl_3$/MeOD; 323 K) 8.11 (1H, dt, *J* 8.0 and 1.1, Ar), 7.65 (1H, d , Ar), 7.50 (1H, td, *J* 7.7 and 1.4, Ar), 7.47 (1H, d, *J* 1.5, Ar), 7.45 (1H, d, *J* 1.5, Ar), 7.44 (1H, td, *J* 7.5 and 1.5, Ar), 7.36-7.30 (2H, m, Ar), 7.06 (1H, dd, *J* 4.1 and 1.4, Ar), 7.05 (1H, dd, *J* 4.1 and 1.4, Ar), 5.38 (1H, dtd, *J* 10.3, 7.6 and 1.7, 13-H), 5.32 (1H, td, *J* 10.3 and 4.9, 12-H), 4.93 (1H, d, *J* 16.7, 8-H_A), 4.85 (1H, d, *J* 16.5, 17-H_A), 4.33 (1H, d, *J* 16.7, 8-H_B), 4.12 (1H, d, *J* 16.5, 17-H_B), 3.74 (3H, s, NMe), 3.73-3.67 (1H, m, 10-H), 3.43 (1H, dd, *J* 12 and 3.1, C*H*$_A$OH), 3.41-3.35 (1H, m, 15-H_A), 3.27 (1H, dd, *J* 12 and 7.5, C*H*$_B$OH), 2.97-2.89 (1H, m, 15-H_B), 2.16 (1H, tdd, *J* 12.8, 7.8 and 4.9, 14-H_A), 2.03-1.91 (2H, m, 14-H_B and 11-H_A), 1.80-1.73 (1H, m, 11-H_B); δ_C (75 MHz; $CDCl_3$) 140.8, 138.9, 138.1, 137.4, 136.0, 132.3, 131.9, 130.9, 129.9, 129.4, 128.8, 128.5, 127.7, 127.2, 127.0, 126.7, 124.2, 120.1 (q, *J* 325, *C*F_3), 62.9 (*C*H_2OH), 61.6 (10-C), 50.7 (Me), 49.4 (17-C), 47.9 (15-C), 46.0 (8-C), 27.7 (11-C), 25.5 (14-C); ν_{max}/cm^{-1} (film) 2988, 1836, 1649, 1529, 1469, 1384, 1336, 1275, 1261, 1225 and 1188; *m/z* (ES$^+$) 599.2 (100%, $[M+H]^+$); found 599.1612, $C_{26}H_{29}F_3N_4O_5S_2$ requires *MH* 599.1604

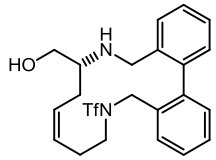
[(12*Z*)-9-Cyclopropanecarbonyl-16-(trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(18),2,4,6,12,19,21-heptaen-10-yl]methanol 264b



Following general procedure **A2**, cyclopropane carbonyl chloride (17.2 mg, 0.165 mmol), triethylamine (33 mg, 0.33 mmol) and amine **252^{D}** (33.3 mg, 0.033 mmol) gave the crude product after 16 h. The crude product was purified by F-SPE and following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the crude product and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with $CHCl_3$ → 95:5 $CHCl_3$—MeOH gave the amide **264b** (13.1 mg, 0.025 mmol, 76%); R_f 0.46 ($CHCl_3$); $[\alpha]_D^{23.7}$ 1.7 (c. 1.3, MeOH); δ_H (500 MHz;

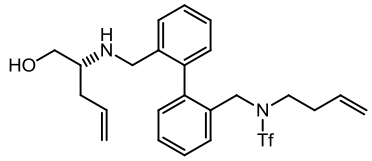
$CDCl_3$) 7.71 (1H, d, *J* 7.9, Ar), 7.59 (1H, d, *J* 7.8, Ar), 7.45 (1H, t, *J* 7.6, Ar), 7.39 (1H, t, *J* 7.5, Ar), 7.34 (1H, t, *J* 7.5, Ar), 7.30 (1H, t, *J* 7.4, Ar), 7.17 (1H, d, *J* 7.5, Ar), 7.02 (1H, d, *J* 7.5, Ar), 5.33-5.22 (2H, m, 12- and 13-H), 4.75 (1H, d, *J* 15.8, 8-H_A), 4.08-3.99 (3H, m, CH_{AB}OH and 8-H_B), 3.75 (1H, d, *J* 13.1, 17-H_A), 3.67 (1H, d, *J* 13.1, 17-H_B), 3.40 (1H, t, *J* 12.1, 15-H_A), 2.89 (1H, s, 15-H_B), 2.77 (1H, s, 10-H), 2.15-1.86 (4H, 11-H_{AB} and 14-H_{AB}), 1.65-1.59 (1H, ^{C}Pr); 1.01-0.99 (2H, ^{C}Pr), 0.90-0.85 (2H, ^{C}Pr); δ_C (75 MHz; $CDCl_3$) 174.5 (C=O), 139.6, 138.2, 133.2, 130.6, 129.9, 128.8, 128.4, 128.3, 128.1, 127.3, 126.8, 126.7, 119.4 (q, *J* 325, *C*F_3), 65.7 (CH_2OH), 57.9 (10-C), 51.3 (8-C), 51.1 (17-C), 50.5 (15-C), 28.5 (11-C), 28.2 (14-C), 12.8 (^{C}Pr), 8.4 (^{C}Pr), 8.3 (^{C}Pr); ν_{max}/cm^{-1} (film) 3014, 2951, 1728, 1456, 1387, 1275, 1261, 1226 and 1183; *m/z* (ES$^+$) 523.1 (100%, [M+H]$^+$); found 523.1874, $C_{26}H_{29}F_3N_2O_4S$ requires *MH* 523.1873

[(12*Z*)-16-(Trifluoromethane)sulfonyl-9,16-diazatricyclo[16.4.0.0^{2,7}]docosa-1(18),2,4,6,12,19,21-heptaen-10-yl]methanol 264d



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **252^D** (35 mg, 0.034 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 90:10 $CHCl_3$—MeOH gave the amine **264d** (13.2 mg, 0.029 mmol, 85%); R_f 0.11 (90:10, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 3.5 (c. 1.3, MeOH); δ_H (500 MHz; $CDCl_3$/MeOD; 323 K) 7.79 (1H, br s, Ar), 7.74 (1H, d, *J* 7.9, Ar), 7.49 (1H, ap t, *J* 7.6, Ar), 7.43 (1H, br s, Ar), 7.39 (1H, d, *J* 8, Ar), 7.36 (1H, d, *J* 7.7, Ar), 7.15 (1H, d, *J* 7.8, Ar), 7.07 (1H, d, *J* 7.6, Ar), 5.29 (1H, td, *J* 11.2 and 7.4, 12-H), 5.23 (1H, br s, 13-H), 4.80 (1H, d, *J* 16, 17-H_A), 4.12 (1H, d, *J* 16, 17-H_B), 3.99 (2H, br s, 8-H_{AB}), 3.70 (1H, br s, CH_AOH), 3.56 (1H, br s, CH_BOH), 3.38 (1H, br s, 10-H), 2.98 (1H, br s, 15-H_A), 2.81 (1H, br s, 15-H_B), 2.18-1.96 (4H, m, 11-H_{AB} and 14-H_{AB}); δ_C (125 MHz; $CDCl_3$/MeOD; 323 K) 138.1, 133.1, 130.9, 130.6, 129.4, 129.3, 128.7, 128.6, 127.8, 127.8, 125.7, 120.1 (q, *J* 325, *C*F_3), 77.1 (*C*H_2OH), 51.1 (17-C or 8-C), 50.7 (17-C or 8-C), 27.5 (11-C), *14-C, 15-C, 10-C missing*; ν_{max}/cm^{-1} (film) 3371, 3052, 3025, 2925, 2255, 2127, 1662, 1440, 1386, 1226 and 1190; *m/z* (ES$^+$) 455.2 (100%, [M+H]$^+$); found 455.1619, $C_{22}H_{25}F_3N_2O_3S$ requires *MH* 455.1611

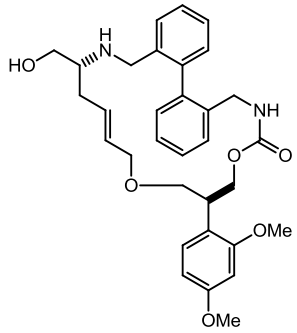
***N*-(But-3-en-1-yl)-1,1,1-trifluoro-*N*-{[2-(2-{[(1'-hydroxypent-4'-en-2'-yl)amino]methyl}phenyl)phenyl]methyl}methanesulfonamide 273d**



Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **241^{D}** (51 mg, 0.049 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified by column chromatography, eluting with 95:5 $CHCl_3$—MeOH gave the amine **273d** (17.8 mg, 0.037 mmol, 77%); R_f 0.31 (95:5, $CHCl_3$—MeOH); $[\alpha]_D^{23.7}$ 10.7 (c. 1.7, MeOH); δ_H (300 MHz; $CDCl_3$) 7.58 (1H, d, Ar), 7.48 (1H, d, Ar), 7.46-7.32 (4H, m, Ar), 7.25-7.19 (1H, m, Ar), 7.12 (1H, d, *J* 7.5, Ar), 5.59 (1H, ddt, *J* 17.4, 10.5 and 7.1, 4'-H), 5.53 (1H, *J* 17.1, 10.1 and 6.9, 3-H), 5.05-4.94 (3H, m, 4-H_A and 5'-$_{AB}$), 4.88 (1H, ddd, *J* 17.1, 3.4 and 1.7, 4-H_B), 4.48 (1H, br s, PhC*H*$_A$NTf), 4.11 (1H, br s, PhC*H*$_B$NTf), 3.54 (1H, d, *J* 12.5, NHC*H*$_A$Ph), 3.48 (1H, d, *J* 13.5, 1-H), 3.41 (1H, d, *J* 13.5, 1-H), 3.35 (1H, d, *J* 12.5, NHC*H*$_B$Ph), 3.34-3.12 (2H, m, 1'-H_{AB}), 2.58-2.48 (1H, m, 2'-H), 2.11-1.94 (3H, m, 3'-H_{AB} and 2-H_A), 1.68 (1H, br s, 2-H_B); δ_C (75 MHz; $CDCl_3$) 140.3, 139.3, 134.6, 134.5, 133.2, 132.5, 132.1, 130.2, 129.9, 129.6, 129.3, 128.5, 128.4, 128.1, 128.0, 127.6, 127.4, 127.4, 122.1, 117.9, 117.9, 117.8, 62.8 (1'-C), 57.9 (2'-C), 57.7 (2'-C), 49.2 (PhCH_2NTf), 49.0 (PhCH_2NTf), 48.9 (1-C), 48.6 (1-C), 47.6 (NHCH_2Ph), 47.5 (NHCH_2Ph), 36.1 (3'-C), 35.9 (3'-C), 32.2 (2-C), 30.9 (2-C); ν_{max}/cm^{-1} (film) 3055, 3006, 2988, 2305, 1641, 1457, 1387, 1275 and 1262; *m/z* (ES$^+$) 483.2 (100%, $[M+H]^+$); found 483.1934, $C_{24}H_{29}F_3N_2O_3S$ requires *MH* 483.1924

full carbon assignment was not possible to mixture of atropisomers

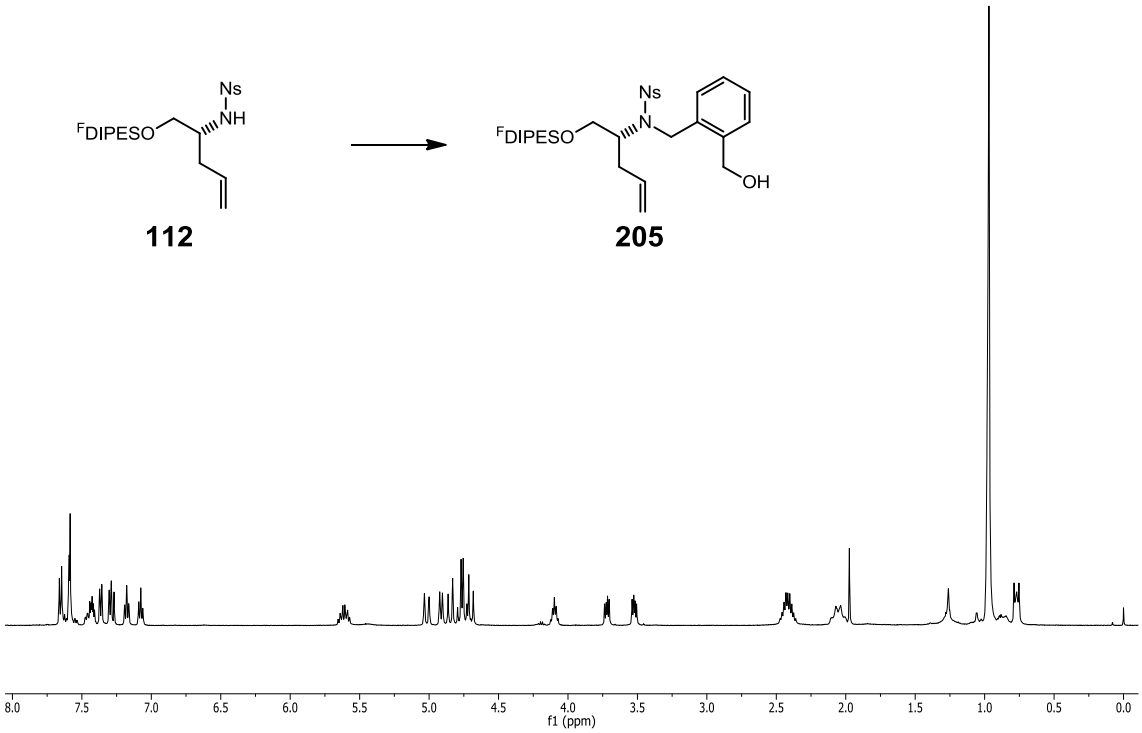
(17*E*)-13-(2,4-Dimethoxyphenyl)-20-(hydroxymethyl)-11,15-dioxa-9,21-diazatricyclo[21.4.0.0^{2,7}]heptacosa-1(27),2,4,6,17,23,25-heptaen-10-one 263d



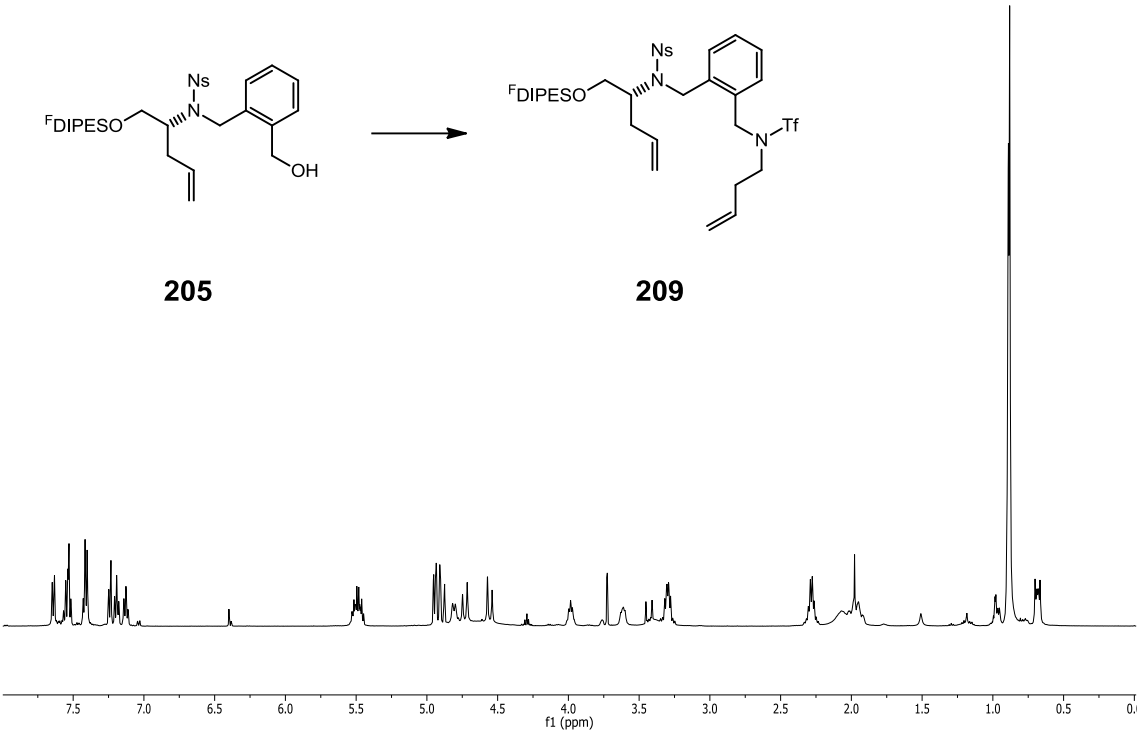
Following general procedure **S1**, hydrofluoric acid (0.2 mL, *ca.* 45-51%) was added to the amine **251^{D}** (24.4 mg, 0.022 mmol) and on reaction completion was quenched with methoxytrimethylsilane (0.5 mL) and stirred for a further 16 h. The crude product was purified mass−directed preparative liquid chromatography and gave the amine **263d** (8.2 mg, 0.015 mmol, 68%); R_f 0.42 (95:5, $CHCl_3$—MeOD); $[\alpha]_D^{23.7}$ 15.7 (c. 0.8, MeOH); δ_H (500 MHz; C_6D_6; 343 K) *Z/E <20>80*; 7.48 (d, *J* 7.5, *Z*), 7.38 (d, *J* 7.5, Ar), 7.29-7.25 (2H, m, Ar), 7.22-7.16 (1H, m, Ar), 7.16-6.95 (6H, m, Ar), 6.40-6.34 (2H, m, DMB), 5.54 (1H, dt, *J* 15.5 and 7.0, 18-H), 5.49-5.43 (2H, m, 18-H and 17-H *Z*), 5.40 (1H, dt, *J* 15.5 and 5.6, 17-H *E*), 4.51-4.34 (3H, m, 8- and 12-H *E*), 4.28 (1H, dd, *J* 10.7 and 8.6, 8-H), 4.17-4.10 (m, 12-H *Z*), 4.04 (1H, dd, *J* 14 and 4.2, 12-H), 3.83-3.64 (4H, m, 16-H and 14-H), 3.62 (1H, d, *J* 11.5, 22-H), 3.45 (1H, d, *J* 11.5, 22-H), 3.40 (3H, s, OMe *E*), 3.39 (s, OMe *Z*), 3.36-3.30 (1H, m, 13-H), 3.29 (s, OMe *Z*), 3.28 (3H, s, OMe *E*), 3.20 (1H, dd, *J* 11 and 4.8, CH_BOH), 3.11 (1H, dd, *J* 11. and 6.4, CH_BOH), 2.42-2.35 (1H, m, 20-H), 2.06-1.94 (2H, m, 19-H); δ_C (125 MHz; C_6D_6; 343 K) 160.2, 158.6, 155.9, 151.7, 140.7, 130.1, 129.8, 129.5, 129.2, 127.2, 121.0, 112.9, 104.9, 99.2, 64.2, 63.8, 59.5, 54.9, 49.9, 44.6, 38.6, 37.7; ν_{max}/cm^{-1} (film) 2929, 2852, 1709, 1613, 1587, 1542, 1508, 1465, 1275, 1261 and 1037; *m/z* (ES$^+$) 547.3 (100%, [M+H]$^+$); found 547.2816, $C_{32}H_{38}N_2O_6$ requires *MH* 547.2803

Appendix 1 Example NMR spectra from final compound

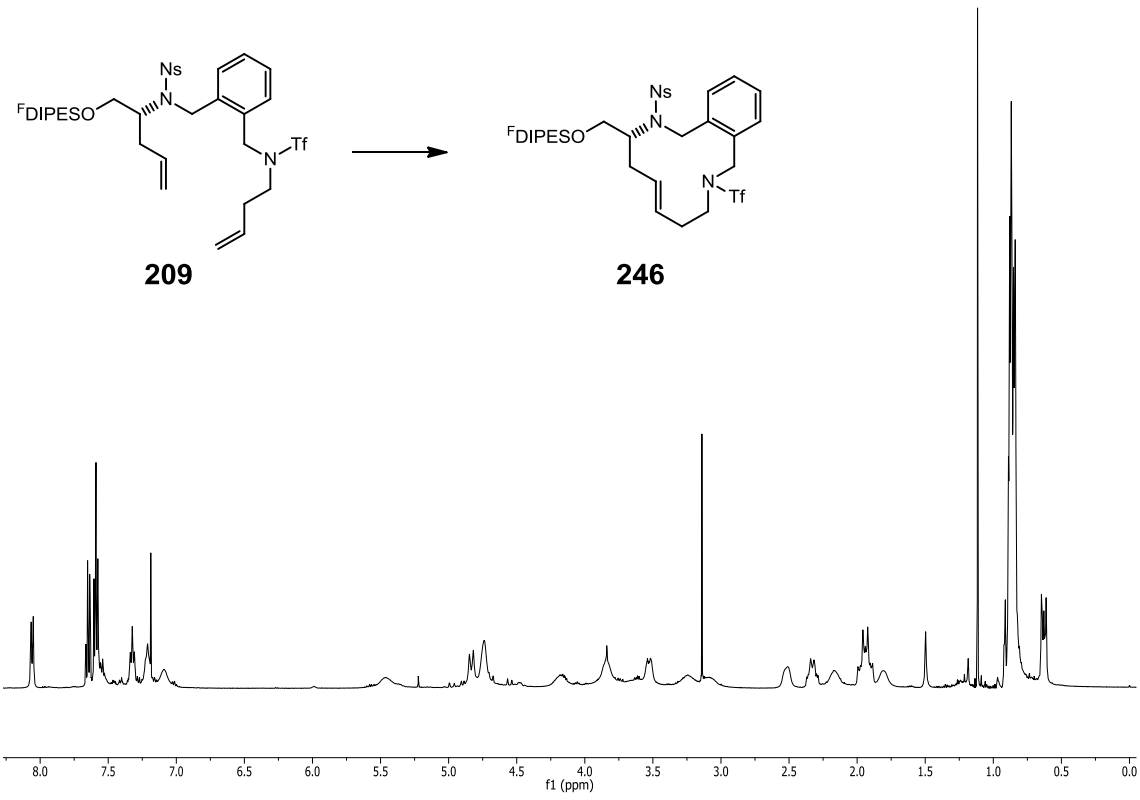
The fluorous tag allowed the expedient and efficient purification of the intermediates at multiple steps throughout the series; this is exemplified in Spectra 1-5. Spectrum 1 shows the product of the first coupling reaction, mediated by the Fukuyama—Mitsunobu reaction followed by deacetylation. Spectrum 2 shows the product of the final coupling reaction to append the capping building block. Spectrum 3 shows the purified product (**246**) from a ring closing metathesis reaction; notably, the spectrum is broad, suggesting slow interconversionbetween conformers. Spectrum 4 shows the product **246^{D}** after removal of the 2-nitrobenzenesulfonamide group; the spectrum is sharp suggesting faster interconversion between conformers. Finally, Spectrum 5 is that of a final compound after diversification and release from the fluorous tag.



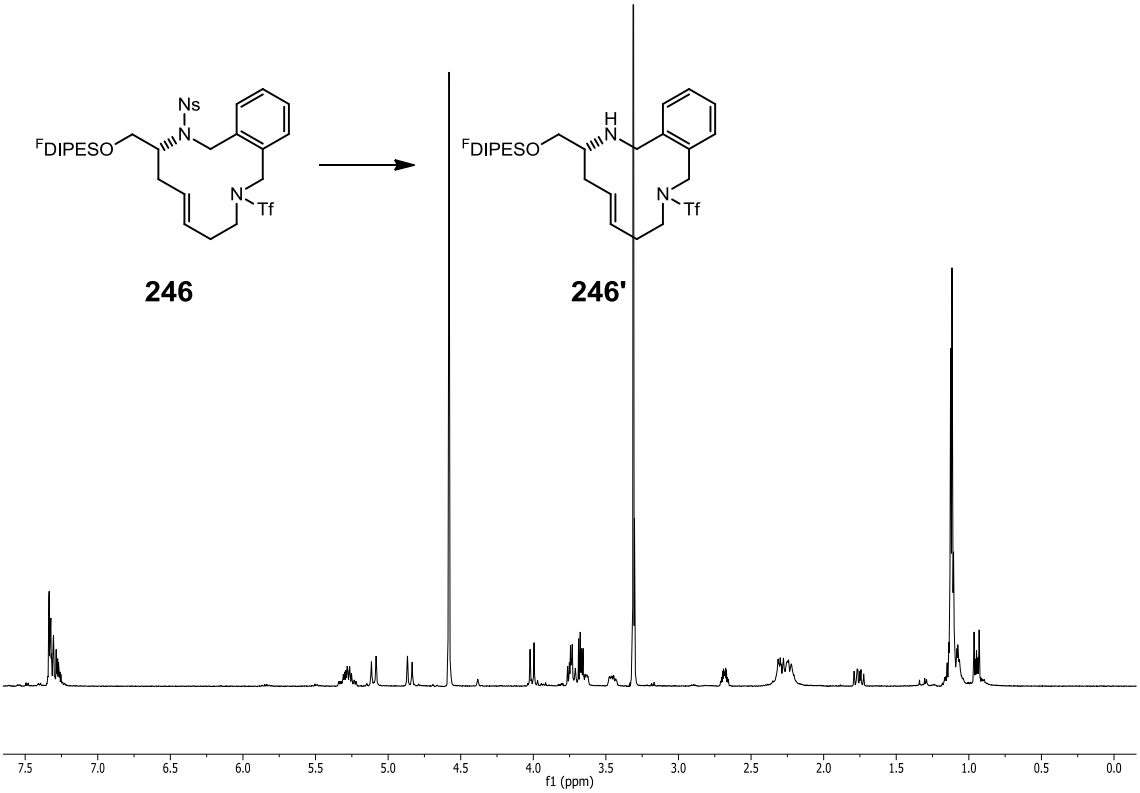
Spectrum 1 500 MHz ^{1}H NMR spectrum following a Fukuyama—Mitsunubo reaction, F-SPE and deacetylation



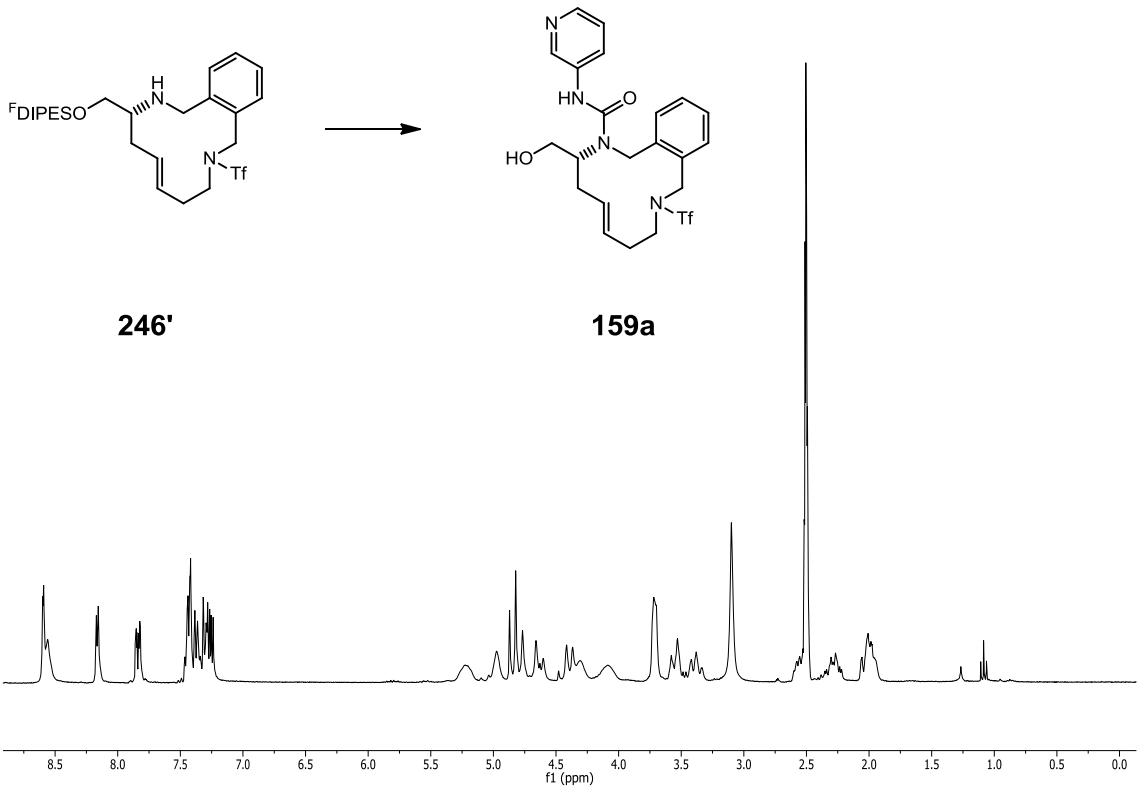
Spectrum 2 500 MHz ^{1}H NMR spectrum following a Fukuyama—Mitsunubo reaction and F-SPE



Spectrum 3 500 MHz ^{1}H NMR spectrum following ring-closing metathesis followed by column chromatography

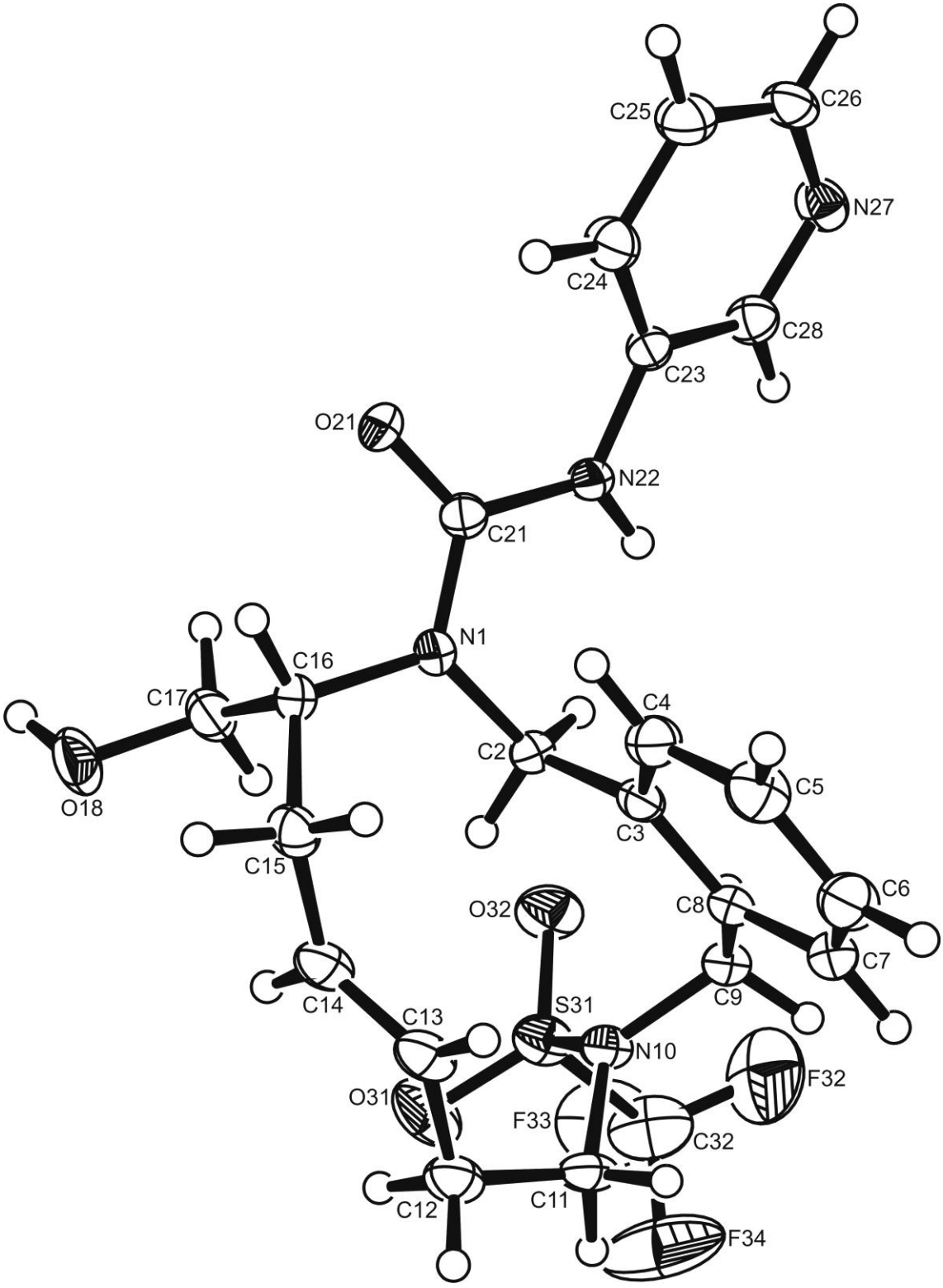


Spectrum 4 500 MHz ^{1}H NMR spectrum following removal of the 2-nitrobenzenesulfonamide and F-SPE



Spectrum 5 500 MHz ^{1}H NMR spectrum following the reaction between the amine **246^{D}** and 3-pyridyl isocyanate followed by F-SPE; removal of the silyl protecting group with HF, followed by column chromatography to give the macrocycle **159a**

Appendix 2 Crystal structure of 159a



View of **159a**. Ellipsoid probability: 50%.

Table 1. Crystal data and structure refinement for 159a.

Archive code	11_04_13	
Identification code	159a	
Formula	$C_{22}H_{25}F_3N_4O_4S$	
Formula weight	498.52	
Size	0.53 x 0.06 x 0.06 mm	
Crystal morphology	Colourless needle	
Temperature	150(2) K	
Wavelength	0.71073 Å [Mo-K_α]	
Crystal system	Tetragonal	
Space group	$P4_1$	
Unit cell dimensions	a = 11.6528(4) Å	α = 90°
	b = 11.6528(4) Å	β = 90°
	c = 17.6255(6) Å	γ = 90°
Volume	2393.33(14) Å^3	
Z	4	
Density (calculated)	1.384 Mg/m^3	
Absorption coefficient	0.194 mm^{-1}	
F(000)	1040	
Data collection range	$1.75 \leq \theta \leq 28.31°$	
Index ranges	$-15 \leq h \leq 15$, $-10 \leq k \leq 15$, $-19 \leq l \leq 23$	
Reflections collected	18591	
Independent reflections	5631 [R(int) = 0.0503]	
Observed reflections	4660 [$I > 2\sigma(I)$]	
Absorption correction	multi-scan	
Max. and min. transmission	0.9884 and 0.7039	
Refinement method	Full	
Data / restraints / parameters	5631 / 1 / 308	
Goodness of fit	1.011	
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0397, wR_2 = 0.0780	
R indices (all data)	R_1 = 0.0554, wR_2 = 0.0846	
Largest diff. peak and hole	0.172 and -0.214e.Å^{-3}	
Absolute structure parameter	0.03(6)	

Table 2. Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^4) with standard uncertainties (s.u.s) in parentheses. U_{eq} is defined as $^1/_3$ of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
N(1)	-2775.3(13)	5806.2(13)	2054.8(9)	206(3)
C(2)	-2085.6(16)	5305.1(16)	1448.6(11)	206(4)
C(3)	-1535.2(15)	6181.9(16)	922.9(11)	218(4)
C(4)	-1770.2(17)	7346.8(17)	987.1(13)	274(4)
C(5)	-1230.7(19)	8149.8(19)	518.1(14)	332(5)
C(6)	-461.2(18)	7784.6(19)	-22.6(14)	353(5)
C(7)	-235.8(17)	6618.2(18)	-101.3(12)	285(5)
C(8)	-761.3(15)	5806.9(17)	364.4(12)	225(4)
C(9)	-500.1(17)	4553.6(17)	231.7(12)	258(4)
N(10)	197.0(13)	4035.1(14)	856.3(10)	250(4)
C(11)	1359.8(15)	4543.3(17)	990.9(13)	277(5)
C(12)	1539.6(18)	5025.6(18)	1785.5(13)	309(5)
C(13)	648.0(17)	5865.3(18)	2034.9(13)	295(5)
C(14)	-94.6(17)	5658.5(18)	2589.8(13)	288(5)
C(15)	-1048.7(17)	6441.2(17)	2830.9(12)	266(4)
C(16)	-2280.1(16)	5937.6(17)	2822.6(11)	234(4)
C(17)	-2357.6(18)	4790(2)	3226.4(13)	317(5)
O(18)	-1860.2(14)	4887.9(17)	3960.3(10)	473(5)
O(21)	-4470.8(11)	6577.2(11)	2454.4(8)	230(3)
C(21)	-3880.4(15)	6141.6(16)	1947.8(11)	203(4)
N(22)	-4321.9(13)	5970.2(14)	1229.7(9)	225(4)
C(23)	-5375.4(15)	6403.4(16)	965.4(11)	210(4)
C(24)	-5951.6(18)	7331.4(18)	1283.7(12)	298(5)
C(25)	-6944.2(18)	7712.5(19)	935.4(13)	330(5)
C(26)	-7338.6(17)	7180.3(18)	293.8(12)	280(5)
N(27)	-6810.3(14)	6274.4(15)	-11.9(10)	281(4)
C(28)	-5854.7(17)	5902.5(17)	326.5(12)	258(4)
S(31)	-51.7(4)	2737.1(5)	1099.8(3)	320.7(13)
O(31)	608.6(15)	2459.1(14)	1749.8(11)	478(5)
F(32)	57.8(19)	2054.1(16)	-317.5(11)	809(6)
O(32)	-1251.3(12)	2517.5(13)	1064.0(11)	414(4)
C(32)	555(3)	1829(2)	347(2)	553(8)
F(33)	372.9(18)	728.1(13)	500.9(14)	847(6)
F(34)	1658.6(16)	1992.3(17)	276.3(15)	981(8)

Table 3. Anisotropic displacement parameters ($Å^2$ x 10^3). The anisotropic displacement factor exponent takes the form:

$$-2\pi^2[h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	20.9(8)	23.7(8)	17.1(8)	-0.3(6)	-1.3(7)	1.2(6)
C(2)	18.6(9)	23.3(10)	20.0(10)	-1.0(8)	1.0(7)	1.5(7)
C(3)	16.9(9)	25.4(10)	23.1(10)	3.0(8)	-3.0(7)	0.6(7)
C(4)	24.9(10)	28.2(10)	29.1(11)	1.9(9)	1.3(8)	1.7(8)
C(5)	33.4(12)	27.0(11)	39.1(13)	4.8(9)	-2.2(10)	-0.6(9)
C(6)	27.3(11)	38.0(13)	40.6(14)	16.3(11)	0.5(10)	-4.1(9)
C(7)	21.4(10)	38.8(12)	25.4(12)	5.9(9)	0.6(8)	0.5(9)
C(8)	15.6(9)	30.1(10)	21.7(10)	2.2(8)	-2.1(8)	1.6(8)
C(9)	20.1(10)	32.8(11)	24.4(11)	0.0(9)	-0.4(8)	2.4(8)
N(10)	19.7(8)	24.7(8)	30.4(10)	2.4(7)	-0.4(7)	0.7(6)
C(11)	14.3(9)	29.2(10)	39.7(13)	4.9(9)	1.2(9)	-1.1(7)
C(12)	21.0(10)	33.8(12)	37.8(13)	4.5(10)	-3.0(9)	-4.4(8)
C(13)	23.3(11)	27.5(11)	37.8(13)	4.2(9)	-7.2(9)	-3.2(8)
C(14)	21.3(10)	29.8(11)	35.2(13)	3.0(9)	-6.4(9)	-3.3(8)
C(15)	25.0(10)	29.3(11)	25.5(11)	-2.2(9)	-5.1(8)	-3.8(8)
C(16)	22.2(10)	31.6(11)	16.5(10)	-3.0(8)	-0.9(8)	2.9(8)
C(17)	24.6(11)	43.9(13)	26.8(12)	10.6(10)	-4.6(9)	-5.0(10)
O(18)	34.5(9)	80.4(14)	27.0(9)	25.0(9)	-8.1(7)	-17.4(8)
O(21)	23.1(7)	28.5(7)	17.4(7)	-2.9(6)	3.1(6)	2.1(6)
C(21)	18.4(9)	20.8(9)	21.7(11)	0.2(8)	-0.4(8)	-3.0(7)
N(22)	18.4(8)	29.4(9)	19.7(9)	-4.5(7)	-1.0(6)	4.2(7)
C(23)	16.7(9)	25.1(10)	21.2(10)	3.0(8)	1.0(7)	-2.3(7)
C(24)	30.6(11)	31.9(11)	26.7(12)	-7.5(9)	-4.8(9)	5.8(9)
C(25)	29.8(11)	34.4(12)	34.9(13)	-4.7(10)	-0.6(9)	8.4(9)
C(26)	17.3(9)	33.3(11)	33.5(13)	4.9(9)	-3.2(9)	-0.9(8)
N(27)	24.5(9)	30.4(9)	29.3(10)	1.5(8)	-5.8(7)	-5.0(7)
C(28)	23.6(10)	25.9(10)	27.9(12)	-2.0(8)	0.5(9)	-0.9(8)
S(31)	27.4(3)	27.1(3)	41.7(3)	4.0(2)	-2.4(2)	-2.9(2)
O(31)	46.7(10)	37.8(10)	58.9(13)	17.7(8)	-19.0(9)	-8.3(8)
F(32)	113.2(16)	69.8(12)	59.6(13)	-26.6(10)	5.2(11)	11.0(11)
O(32)	28.4(8)	40.8(9)	55.0(11)	6.8(8)	-1.5(8)	-11.7(7)
C(32)	49.4(17)	36.7(15)	80(2)	-15.2(15)	6.9(15)	0.9(12)
F(33)	98.4(15)	30.7(9)	125.0(17)	-16.1(10)	-2.1(13)	0.7(9)
F(34)	52.2(11)	82.1(14)	160(2)	-58.3(14)	34.7(12)	1.3(9)

Table 4. Hydrogen atom co-ordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^2) with s.u.s in parentheses.

	x	y	z	U_{eq}
H(2a)	-2579.	4790.	1143.	25.
H(2b)	-1473.	4830.	1679.	25.
H(4)	-2307.	7602.	1356.	33.
H(5)	-1395.	8944.	572.	40.
H(6)	-86.	8326.	-340.	42.
H(7)	287.	6369.	-480.	34.
H(9a)	-1231.	4126.	184.	31.
H(9b)	-78.	4472.	-253.	31.
H(11a)	1486.	5166.	618.	33.
H(11b)	1946.	3945.	897.	33.
H(12a)	1555.	4380.	2150.	37.
H(12b)	2299.	5405.	1805.	37.
H(13)	610.	6585.	1783.	35.
H(14)	-15.	4955.	2857.	35.
H(15a)	-1038.	7123.	2496.	32.
H(15b)	-882.	6710.	3352.	32.
H(16)	-2782.	6486.	3106.	28.
H(17a)	-3171.	4555.	3272.	38.
H(17b)	-1946.	4197.	2930.	38.
H(18)	-2291.	4573.	4281.	57.
H(22)	-3911.	5557.	912.	27.
H(24)	-5670.	7694.	1729.	36.
H(25)	-7353.	8345.	1142.	40.
H(26)	-8013.	7466.	57.	34.
H(28)	-5479.	5253.	116.	31.

Table 5. Interatomic distances (Å) with s.u.s in parentheses.

N(1)-C(21)	1.359(2)	N(1)-C(2)	1.459(2)
N(1)-C(16)	1.479(2)	C(2)-C(3)	1.521(3)
C(3)-C(4)	1.389(3)	C(3)-C(8)	1.405(3)
C(4)-C(5)	1.398(3)	C(5)-C(6)	1.376(3)
C(6)-C(7)	1.391(3)	C(7)-C(8)	1.394(3)
C(8)-C(9)	1.510(3)	C(9)-N(10)	1.496(3)
N(10)-C(11)	1.498(2)	N(10)-S(31)	1.5986(17)
C(11)-C(12)	1.523(3)	C(12)-C(13)	1.493(3)
C(13)-C(14)	1.328(3)	C(14)-C(15)	1.500(3)
C(15)-C(16)	1.550(3)	C(16)-C(17)	1.518(3)
C(17)-O(18)	1.422(3)	O(21)-C(21)	1.236(2)
C(21)-N(22)	1.381(2)	N(22)-C(23)	1.407(2)
C(23)-C(28)	1.386(3)	C(23)-C(24)	1.391(3)
C(24)-C(25)	1.383(3)	C(25)-C(26)	1.369(3)
C(26)-N(27)	1.335(3)	N(27)-C(28)	1.336(3)
S(31)-O(31)	1.4175(17)	S(31)-O(32)	1.4226(15)
S(31)-C(32)	1.838(3)	F(32)-C(32)	1.333(4)
C(32)-F(34)	1.306(3)	C(32)-F(33)	1.328(3)

Table 6. Angles between interatomic vectors (°) with s.u.s in parentheses.

C(21)-N(1)-C(2)	122.38(16)	C(21)-N(1)-C(16)	117.83(15)
C(2)-N(1)-C(16)	119.77(15)	N(1)-C(2)-C(3)	114.17(15)
C(4)-C(3)-C(8)	119.17(18)	C(4)-C(3)-C(2)	121.58(17)
C(8)-C(3)-C(2)	119.25(17)	C(3)-C(4)-C(5)	121.1(2)
C(6)-C(5)-C(4)	119.7(2)	C(5)-C(6)-C(7)	119.6(2)
C(6)-C(7)-C(8)	121.4(2)	C(7)-C(8)-C(3)	118.93(18)
C(7)-C(8)-C(9)	118.45(18)	C(3)-C(8)-C(9)	122.60(17)
N(10)-C(9)-C(8)	112.71(16)	C(9)-N(10)-C(11)	116.63(16)
C(9)-N(10)-S(31)	118.77(13)	C(11)-N(10)-S(31)	119.71(13)
N(10)-C(11)-C(12)	114.58(17)	C(13)-C(12)-C(11)	114.62(18)
C(14)-C(13)-C(12)	123.5(2)	C(13)-C(14)-C(15)	125.6(2)
C(14)-C(15)-C(16)	116.95(16)	N(1)-C(16)-C(17)	108.34(16)
N(1)-C(16)-C(15)	114.13(16)	C(17)-C(16)-C(15)	112.60(16)
O(18)-C(17)-C(16)	109.36(18)	O(21)-C(21)-N(1)	123.05(17)
O(21)-C(21)-N(22)	120.93(17)	N(1)-C(21)-N(22)	116.02(16)
C(21)-N(22)-C(23)	125.23(16)	C(28)-C(23)-C(24)	117.42(18)
C(28)-C(23)-N(22)	118.01(17)	C(24)-C(23)-N(22)	124.52(18)
C(25)-C(24)-C(23)	118.32(19)	C(26)-C(25)-C(24)	120.1(2)
N(27)-C(26)-C(25)	122.45(19)	C(28)-N(27)-C(26)	117.43(18)
N(27)-C(28)-C(23)	124.21(19)	O(31)-S(31)-O(32)	121.88(11)
O(31)-S(31)-N(10)	109.56(9)	O(32)-S(31)-N(10)	109.66(9)
O(31)-S(31)-C(32)	104.06(13)	O(32)-S(31)-C(32)	104.01(12)
N(10)-S(31)-C(32)	106.33(12)	F(34)-C(32)-F(33)	108.5(2)
F(34)-C(32)-F(32)	108.4(3)	F(33)-C(32)-F(32)	107.5(2)
F(34)-C(32)-S(31)	111.3(2)	F(33)-C(32)-S(31)	110.3(2)
F(32)-C(32)-S(31)	110.74(19)		

Table 7. Torsion angles (°) with s.u.s in parentheses.

C(21)-N(1)-C(2)-C(3)	82.7(2)	C(16)-N(1)-C(2)-C(3)	-98.72(19)
N(1)-C(2)-C(3)-C(4)	-5.5(3)	N(1)-C(2)-C(3)-C(8)	173.77(17)
C(8)-C(3)-C(4)-C(5)	-1.5(3)	C(2)-C(3)-C(4)-C(5)	177.81(19)
C(3)-C(4)-C(5)-C(6)	0.7(3)	C(4)-C(5)-C(6)-C(7)	0.6(3)
C(5)-C(6)-C(7)-C(8)	-0.9(3)	C(6)-C(7)-C(8)-C(3)	0.1(3)
C(6)-C(7)-C(8)-C(9)	178.33(18)	C(4)-C(3)-C(8)-C(7)	1.1(3)
C(2)-C(3)-C(8)-C(7)	-178.22(17)	C(4)-C(3)-C(8)-C(9)	-177.05(18)
C(2)-C(3)-C(8)-C(9)	3.6(3)	C(7)-C(8)-C(9)-N(10)	110.6(2)
C(3)-C(8)-C(9)-N(10)	-71.3(2)	C(8)-C(9)-N(10)-C(11)	-61.2(2)
C(8)-C(9)-N(10)-S(31)	143.63(14)	C(9)-N(10)-C(11)-C(12)	120.77(19)
S(31)-N(10)-C(11)-C(12)	-84.3(2)	N(10)-C(11)-C(12)-C(13)	-53.0(2)
C(11)-C(12)-C(13)-C(14)	112.5(2)	C(12)-C(13)-C(14)-C(15)	-176.15(19)
C(13)-C(14)-C(15)-C(16)	123.6(2)	C(21)-N(1)-C(16)-C(17)	97.9(2)
C(2)-N(1)-C(16)-C(17)	-80.7(2)	C(21)-N(1)-C(16)-C(15)	-135.81(17)
C(2)-N(1)-C(16)-C(15)	45.6(2)	C(14)-C(15)-C(16)-N(1)	-74.4(2)
C(14)-C(15)-C(16)-C(17)	49.6(3)	N(1)-C(16)-C(17)-O(18)	178.58(16)
C(15)-C(16)-C(17)-O(18)	51.4(2)	C(2)-N(1)-C(21)-O(21)	-179.30(17)
C(16)-N(1)-C(21)-O(21)	2.1(3)	C(2)-N(1)-C(21)-N(22)	0.6(3)
C(16)-N(1)-C(21)-N(22)	-177.97(16)	O(21)-C(21)-N(22)-C(23)	9.8(3)
N(1)-C(21)-N(22)-C(23)	-170.08(17)	C(21)-N(22)-C(23)-C(28)	-161.77(18)
C(21)-N(22)-C(23)-C(24)	20.8(3)	C(28)-C(23)-C(24)-C(25)	-1.6(3)
N(22)-C(23)-C(24)-C(25)	175.87(19)	C(23)-C(24)-C(25)-C(26)	0.0(3)
C(24)-C(25)-C(26)-N(27)	1.3(3)	C(25)-C(26)-N(27)-C(28)	-1.0(3)
C(26)-N(27)-C(28)-C(23)	-0.7(3)	C(24)-C(23)-C(28)-N(27)	2.0(3)
N(22)-C(23)-C(28)-N(27)	-175.59(18)	C(9)-N(10)-S(31)-O(31)	-173.64(15)
C(11)-N(10)-S(31)-O(31)	31.92(19)	C(9)-N(10)-S(31)-O(32)	-37.41(18)
C(11)-N(10)-S(31)-O(32)	168.15(16)	C(9)-N(10)-S(31)-C(32)	74.47(18)
C(11)-N(10)-S(31)-C(32)	-79.97(19)	O(31)-S(31)-C(32)-F(34)	-55.5(3)
O(32)-S(31)-C(32)-F(34)	176.0(2)	N(10)-S(31)-C(32)-F(34)	60.2(3)
O(31)-S(31)-C(32)-F(33)	65.1(2)	O(32)-S(31)-C(32)-F(33)	-63.5(2)
N(10)-S(31)-C(32)-F(33)	-179.3(2)	O(31)-S(31)-C(32)-F(32)	-176.09(19)
O(32)-S(31)-C(32)-F(32)	55.3(2)	N(10)-S(31)-C(32)-F(32)	-60.4(2)

Table 9. Hydrogen bonded distances (Å) and angles (°). Standard uncertainties are included in parentheses for values which do not involve constrained hydrogen atoms.

Atoms (D-H…A)	D-H	H…A	D…A	∠DHA
O(18)-H(18)...N(27)[(b)]	0.84	1.9	2.742(2)	174.4
N(22)-H(22)...O(21)[(a)]	0.88	2.19	3.034(2)	161.8

Key giving operations for symmetry related atoms:

(a) -1-y, +x, -1/4+z
(b) -1-x, 1-y, 1/2+z

1. T. Nicholas K, *Drug Discov. Today*, 2010, **7**, 97–104.

2. L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera, and W. Brandt, *Mol. Divers.*, 2005, **9**, 171–186.

3. J. F. Gummert, T. Ikonen, and R. E. Morris, *J. Am. Soc. Nephrol.*, 1999, **10**, 1366–1380.

4. A. Kudelski and S. N. Sehgal, *J. Antibiot.*, 1975, **XXVIII**, 721–726.

5. P. Nghiem, G. Pearson, and R. G. Langley, *J. Am. Acad. Dermatol.*, 2002, **46**, 228–241.

6. E. Nogales, S. Grayer Wolf, I. A. Khan, R. F. Luduena, and K. H. Downing, *Nature*, 1995, **375**, 424–427.

7. S. Goodin, M. P. Kane, and E. H. Rubin, *J. Clin. Oncol.*, 2004, **22**, 2015–2025.

8. F. Feyen, J. Gertsch, M. Wartmann, and K.-H. Altmann, *Angew. Chem. Int. Ed.*, 2006, **45**, 5880–5885.

9. P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, U. C. Quarck, R. R. Chauvette, and R. Monahan, *J. Am. Chem. Soc.*, 1957, **79**, 6062–6070.

10. C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, *Adv. Drug Deliver. Rev.*, 1997, **23**, 3–25.

11. C. A. Lipinski, *J. Pharmacol. Toxicol.*, 2001, **44**, 235–249.

12. C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, *Adv. Drug Deliver. Rev.*, 2001, **46**, 3–26.

13. D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward, and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615–2623.

14. E. Marsault and M. L. Peterson, *J. Med. Chem.* 2011, **54**, 1961–2004.

15. L. A. Wessjohann and E. Ruijter, *Natural Products Synthesis I: Targets Methods Concepts*, 2005, **243**, 137–184.

16. E. M. Driggers, S. P. Hale, J. Lee, and N. K. Terrett, *Nat. Rev. Drug Discov.*, 2008, **7**, 608–624.

17. C. M. Madsen and M. H. Clausen, *Eur. J. Org. Chem.*, 2011, **2011**, 3107–3115.

18. S. J. Stachel, C. A. Coburn, S. Sankaranarayanan, E. A. Price, B. L. Pietrak, Q. Huang, J. Lineberger, A. S. Espeseth, L. Jin, J. Ellis, M. K. Holloway, S. Munshi, T. Allison, D. Hazuda, A. J. Simon, S. L. Graham, and J. P. Vacca, *J. Med. Chem.*, 2006, **49**, 6147–6150.

19. Z.-F. Tao, L. Wang, K. D. Stewart, Z. Chen, W. Gu, M.-H. Bui, P. Merta, H. Zhang, P. Kovar, E. Johnson, C. Park, R. Judge, S. Rosenberg, T. Sowin, and N.-H. Lin, *J. Med. Chem.*, 2007, **50**, 1514–1527.

20. K. X. Chen, F. G. Njoroge, J. Pichardo, A. Prongay, N. Butkiewicz, N. Yao, V. Madison, and V. Girijavallabhan, *J. Med. Chem.*, 2005, **49**, 567–574.

21. C. J. Dinsmore, M. J. Bogusky, J. C. Culberson, J. M. Bergman, C. F. Homnick, C. B. Zartman, S. D. Mosser, M. D. Schaber, R. G. Robinson, K. S. Koblan, H. E. Huber, S. L. Graham, G. D. Hartman, J. R. Huff, and T. M. Williams, *J. Am. Chem. Soc.*, 2001, **123**, 2107–2108.

22. R. J. Cherney, L. Wang, D. T. Meyer, C.-B. Xue, Z. R. Wasserman, K. D. Hardman, P. K. Welch, M. B. Covington, R. A. Copeland, E. C. Arner, W. F. DeGrado, and C. P. Decicco, *J. Med. Chem.*, 1998, **41**, 1749–1751.

23. R. J. Cherney, L. Wang, D. T. Meyer, C.-B. Xue, E. C. Arner, R. A. Copeland, M. B. Covington, K. D. Hardman, Z. R. Wasserman, B. D. Jaffee, and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1279–1284.

24. *Amino Acids, Peptides and Proteins in Organic Chemistry, Protection Reactions, Medicinal Chemistry, Combinatorial Synthesis.* Vol 4, John Wiley & Sons, 2011.

25. X. Hu, K. T. Nguyen, V. C. Jiang, D. Lofland, H. E. Moser, and D. Pei, *J. Med. Chem.*, 2004, **47**, 4941–4949.

26. X. Hu, K. T. Nguyen, C. L. M. J. Verlinde, W. G. J. Hol, and D. Pei, *J. Med. Chem.*, 2003, **46**, 3771–3774.

27. F. Kopp and M. A. Marahiel, *Nat. Prod. Rep.*, 2007, **24**, 735–749.

28. G. M. Bennett, *Transactions of the Faraday Society*, 1941, **37**, 794–803

29. S. Wen, G. Packham, and A. Ganesan, *J. Org. Chem.*, 2008, **73**, 9353–9361.

30. D. Bai, Y. Bo, and Q. Zhou, *Tetrahedron Lett.*, 1990, **31**, 2161–2164.

31. K. L. Bailey and T. F. Molinski, *J. Org. Chem.*, 1999, **64**, 2500–2504.

32. R. H. Grubbs, *Tetrahedron*, 2004, **60**, 7117–7140.

33. C. Fotsch, G. Kumaravel, S. K. Sharma, A. D. Wu, J. S. Gounarides, N. R. Nirmala, and R. C. Petter, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2125–2130.

34. J. Tilley, G. Kaplan, N. Fotouhi, B. Wolitzky, and K. Rowan, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1163–1165.

35. M. A. J. Duncton and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1* 1999, 1235–1246.

36. V. Balraju and J. Iqbal, *J. Org. Chem.*, 2006, **71**, 8954–8956.

37. V. Balraju, D. S. Reddy, M. Periasamy, and J. Iqbal, *Med. Chem. Lett.*, 2005, **2005**, 9626–9628.

38. A. C. Spivey, J. McKendrick, R. Srikaran, and B. A. Helm, *J. Org. Chem.*, 2003, **68**, 1843–1851.

39. C. Park and K. Burgess, *J. Comb. Chem.*, 2001, **3**, 257–266.

40. A. G. M. Barrett, A. J. Hennessy, R. L. Ve, P. W. Seale, S. Stefaniak, R. J. Upton, A. J. P. White, and D. J. Williams, *J. Org. Chem.,* 2004, **69** 1028–1037.

41. K. Akaji, K. Teruya, M. Akaji, and S. Aimoto, *Tetrahedron*, 2001, **57**, 2293–2303.

42. P. R. Reddy, V. Balraju, G. R. Madhavan, B. Banerji, and J. Iqbal, *ChemInform*, 2003, **34**, 353–356.

43. B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck and A. Domling, *Org. Lett.*, 2003, **5**, 1047–1050.

44. K. Burgess, D. Lim, M. Bois-Choussy, and J. Zhu, *Tetrahedron Lett.*, 1997, **38**, 3345–3348.

45. H. Shimamura, S. P. Breazzano, J. Garfunkle, F. S. Kimball, J. D. Trzupek, and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 7776–7783.

46. A. Berthelot and S. Piguel, *J. Org. Chem.,* 2003, **68**, 9835–9838.

47. C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*, 1977, **99**, 2591–2597.

48. M. Schuster and S. Blechert, *Angew. Chem. Int. Ed.*, 1997, **36**, 2036–2056.

49. R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446–452.

50. R. Grubbs, *Tetrahedron*, 1998, **54**, 4413–4450.

51. M. Schuster and S. Blechert, *Angew. Chem. Int. Ed.*, 1997, **36**, 2036–2056.

52. A. Gradillas and J. Pérez-Castells, *Angew. Chem. Int. Ed.* 2006, **45**, 6086–6101.

53. G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787.

54. N. K. Yee, V. Farina, I. N. Houpis, N. Haddad, R. P. Frutos, F. Gallou, X. Wang, X. Wei, R. D. Simpson, X. Feng, V. Fuchs, Y. Xu, J. Tan, L. Zhang, J. Xu, L. L. Smith-keenan, J. Vitous, M. D. Ridges, E. M. Spinelli, M. Johnson, K. Donsbach, T. Nicola, M. Brenner, E. Winter, P. Kreye, W. Samstag, R. Metathesis, and P. O. Box, *J. Org. Chem.*, 2006, **71**, 7133–7145.

55. C. Shu, X. Zeng, M.-H. Hao, X. Wei, N. K. Yee, C. A. Busacca, Z. Han, V. Farina, and C. H. Senanayake, *Org. Lett.*, 2008, **10**, 1303–1306.

56. V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2596–2599.

57. V. D. Bock, D. Speijer, H. Hiemstra, and J. H. van Maarseveen, *Org. Biomol. Chem.*, 2007, **5**, 971–975

58. V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra, and J. H. van Maarseveen, *Org. Lett.*, 2006, **8**, 919–922.

59. A. Parenty, X. Moreau, and J. M. Campagne, *Chem. Rev.*, 2006, **106**, 911–939.

60. O. Mitsunobu, *Synthesis*, 1981, 28.

61. A. K. Ghosh and Y. Wang, *Tetrahedron Lett.*, 2001, **42**, 3399–3401.

62. J. Mulzer, H. M. Kirstein, J. Buschmann, C. Lehmann, and P. Luger, *J. Am. Chem. Soc.*, 1991, **113**, 910–923.

63. D. P. Walsh and Y.-T. Chang, *Chem. Rev.*, 2006, **106**, 2476–2530.

64. D. R. Spring, *Chem. Soc. Rev.*, 2005, **34**, 472–482.

65. S. L. Schreiber and A. Chemie, *Nature*, 2009, **457**, 153–154.

66. M. D. Burke and S. L. Schreiber, *Angew. Chemie. Int. Ed.*, 2004, **43**, 46–58.

67. S. L. Schreiber, *Nat. Chem. Biol.*, 2005, **1**, 64–66.

68. W. R. J. D. Galloway, A. Isidro-Llobet, and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80.

69. D. L. Hertzog, D. J. Austin, W. R. Nadler, and A. Padwa, *Tetrahedron Lett.*, 1992, **33**, 4731–4734.

70. J. M. MejÃa-Oneto and A. Padwa, *Org. Lett.*, 2004, **6**, 3241–3244.

71. A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223–270.

72. H. Oguri and S. L. Schreiber, *Org. Lett.*, 2005, **7**, 47–50.

73. H. Mizoguchi, H. Oguri, K. Tsuge, and H. Oikawa, *Org. Lett.*, 2009, **11**, 3016–3019.

74. S. Murrison, S. K. Maurya, C. Einzinger, B. McKeever-Abbas, S. Warriner, and A. Nelson, *Euro. J. Org. Chem.*, 2011, 2354–2359.

75. M. D. Burke, E. M. Berger, and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 14095–14104.

76. N. Kumagai, G. Muncipinto, and S. L. Schreiber, *Angew. Chemie. Int. Ed.*, 2006, **45**, 3635–3638.

77. D. Robbins, A. F. Newton, C. Gignoux, J.-C. Legeay, A. Sinclair, M. Rejzek, C. A. Laxon, S. K. Yalamanchili, W. Lewis, M. A. O'Connell, and R. A. Stockman, *Chem. Sci.*, 2011, **2**, 2232–2235.

78. C. Gignoux, A. F. Newton, A. Barthelme, W. Lewis, M.-L. Alcaraz, and R. A Stockman, *Org. Biomol. Chem.*, 2012, **10**, 67–69.

79. T. E. Nielsen and M. Meldal, *Org. Lett.*, 2005, **7**, 2695–2698.

80. T. E. Nielsen and S. L. Schreiber, *Angew. Chemie Int. Ed.*, 2008, **47**, 48–56.

81. T. E. Nielsen, S. Le Quement, and M. Meldal, *Org. Lett.*, 2005, **7**, 3601–3604.

82. S. T. Le Quement, T. E. Nielsen, and M. Meldal, *J. Combi. Chem.*, 2007, **9**, 1060–1072.

83. T. E. Nielsen and M. Meldal, *J. Comb. Chem.*, 2005, **7**, 599–610.

84. T. E. Nielsen and M. Meldal, *J. Org. Chem.*, 2004, **69**, 3765–3773.

85. D. Morton, S. Leach, C. Cordier, S. Warriner, and A. Nelson, *Angew. Chemie Int. Ed.*, 2009, **48**, 104–109.

86. D. A. Spiegel, F. C. Schroeder, J. R. Duvall, and S. L. Schreiber, *J. Am. Chem. Soc.*, 2006, **128**, 14766–14767.

87. L. a Marcaurelle, E. Comer, S. Dandapani, J. R. Duvall, B. Gerard, S. Kesavan, M. D. Lee, H. Liu, J. T. Lowe, J.-C. Marie, C. a Mulrooney, B. a Pandya, A. Rowley, T. D. Ryba, B.-C. Suh, J. Wei, D. W. Young, L. B. Akella, N. T. Ross, Y.-L. Zhang, D. M. Fass, S. a Reis, W.-N. Zhao, S. J. Haggarty, M. Palmer, and M. a Foley, *J. Am. Chem. Soc.*, 2010, **132**, 16962–16976.

88. C. M. Dobson, *Nature*, 2004, **432**, 824–828.

89. R. W. Heidebrecht, C. Mulrooney, C. P. Austin, R. H. Barker, J. A. Beaudoin, K. C.-C. Cheng, E. Comer, S. Dandapani, J. Dick, J. R. Duvall, E. H. Ekland, D. A. Fidock, M. E. Fitzgerald, M. Foley, R. Guha, P. Hinkson, M. Kramer, A. K. Lukens, D. Masi, L. A. Marcaurelle, X.-Z. Su, C. J. Thomas, M. Weïwer, R. C. Wiegand, D. Wirth, M. Xia, J. Yuan, J. Zhao, M. Palmer, B. Munoz, and S. Schreiber, *Med. Chem. Lett.*, 2012, **3**, 112–117.

90. D. H.-C. Chou, J. R. Duvall, B. Gerard, H. Liu, B. a Pandya, B.-C. Suh, E. M. Forbeck, P. Faloon, B. K. Wagner, and L. a Marcaurelle, *Med. Chem. Lett.*, 2011, **2**, 698–702.

91. B. Z. Stanton, L. F. Peng, N. Maloof, K. Nakai, X. Wang, J. L. Duffner, K. M. Taveras, J. M. Hyman, S. W. Lee, A. N. Koehler, J. K. Chen, J. L. Fox, A. Mandinova, and S. L. Schreiber, *Nat. Chem. Biol.*, 2009, **5**, 154–156.

92. J. M. Holub and K. Kirshenbaum, *Chem. Soc. Rev.*, 2010, **39**, 1325–1337.

93. G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278–308.

94. D. W. Young, *Nat. Chem. Biol.*, 2010, **6**, 174–175.

95. A. K. Ghose, V. N. Viswanadhan, and J. J. Wendoloski, *J. Phys.Chem. A*, 1998, **102**, 3762–3772.

96. P. Ertl, B. Rohde, and P. Selzer, *J. Med. Chem.*, 2000, **43**, 3714–3717.

97. R. A. Bauer, J. M. Wurst, and D. S. Tan, *Curr. Opin. Chem. Biol.*, 2010, **14**, 308–314.

98. J. C. Rech, M. Yato, D. Duckett, B. Ember, P. V. LoGrasso, R. G. Bergman, and J. A. Ellman, *J. Am. Chem. Soc.*, 2007, **129**, 490–491.

99. T. P. Tang, S. K. Volkman, and J. A. Ellman, *J. Org. Chem.*, 2001, **66**, 8772–8778.

100. J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, and P. G. Nantermet, *Tetrahedron Lett.*, 2001, **42**, 2051–2054.

101. J. A. Ellman, T. D. Owens, and T. P. Tang, *Accounts Chem. Res.*, 2002, **35**, 984–995.

102. M. Petit, G. Chaqui, C. Aubert, and M. Malacria, *Org. Lett.*, 2003, **5**, 2037–2040.

103. C. Cordier, D. Morton, S. Leach, T. Woodhall, C. O'Leary-Steele, S. Warriner, and A. Nelson, *Org. Biomol. Chem.*, 2008, **6**, 1734–1737.

104. F. A. Davis and W. McCoull, *J. Org. Chem.*, 1999, **64**, 3396–3397.

105. J. Iskra, S. Stavber, and M. Zupan, *Synthesis*, 2004, **2004**, 1869–1873.

106. E. J. Hennessy and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 269–272.

107. I. Yamamura, Y. Fujiwara, T. Yamato, O. Irie, and K. Shishido, *Tetrahedron Lett.*, 1997, **38**, 4121–4124.

108. K. Takabatake, I. Nishi, M. Shindo, and K. Shishido, *J. Chem. Soc., Perk. Trans. 1*, 2000, 1807–1808.

109. J. Calveras, Y. Nagai, I. Sultana, Y. Ueda, T. Higashi, M. Shoji, and T. Sugai, *Tetrahedron*, **66**, 4284–4291.

110. R. Lakhmiri, P. Lhoste, and D. Sinou, *Tetrahedron Lett.*, 1989, **30**, 4669–4672.

111. D. A. Evans and W. C. Black, *J. Am.Chem.Soc.*, 1993, **115**, 4497–4513.

112. K. Krohn, A. Vidal, J. Vitz, B. Westermann, M. Abbas, and I. Green, *Tetrahedron: Asymmetr.*, 2006, **17**, 3051–3057.

113. H. Ulrich, *Chem. Rev.*, 1965, **65**, 369–376.

114. J. E. Franz and C. Osuch, *J. Org.Chem.*, 1964, **29**, 2592–2595.

115. L. M. Oh, P. G. Spoors, and R. M. Goodman, *Tetrahedron Lett.*, 2004, **45**, 4769–4771.

116. T. Fukuyama, C. K. Jow, and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373–6374.

117. K. M. Kuhn, T. M. Champagne, S. H. Hong, W.-H. Wei, A. Nickel, C. W. Lee, S. C. Virgil, R. H. Grubbs, and R. L. Pederson, *Org. Lett.*, **12**, 984–987.

118. S. H. Hong, D. P. Sanders, C. W. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 17160–17161.

119. J. A. Lafontaine, D. P. Provencal, C. Gardelli, and J. W. Leahy, *J. Org. Chem.*, 2003, **68**, 4215–34.

120. S. F. Vanier, G. Larouche, R. P. Wurz, and A. B. Charette, *Org. Lett.*, 2010, **12**, 672–675.

121. T. Ikeda, M. Higuchi, A. Sato, and D. G. Kurth, *Org. Lett.*, 2008, **10**, 2215–2218.

122. J. M. Griffing and L. F. Salisbury, *J. Am. Chem. Soc.*, 1948, **70**, 3416–3419.

123. U. Azzena, S. Demartis, L. Pilo, and E. Piras, *Tetrahedron*, 2000, **56**, 8375–8382.

124. E. Santaniello, P. Ferraboschi, and P. Grisenti, *Tetrahedron Lett.*, 1990, **31**, 5657–5660.

125. L.-W. Ye, X.-L. Sun, C.-Y. Li, and Y. Tang, *J. Org. Chem.,* 2007, **72**, 1335–1340.

126. J. Iskra, S. Stavber, and M. Zupan, *Synthesis*, 2004, 1869–1873.

127. S. F. Yip, H. Y. Cheung, Z. Y. Zhou, and F. Y. Kwong, *Org. Lett.*, 2007, **9**, 3469–3472.

128. A. E. May, P. H. Willoughby, and T. R. Hoye, *J. Org. Chem.*, 2008, **73**, 3292–3294.

129. T. Fukuyama, M. Cheung, and T. Kan, *Synlett*, 1999, 1301–1303.