UNIVERSITY OF SOUTHAMPTON

Approaches to Spiro-Heterocycles: Novel Scaffolds for Drug Discovery

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ABSTRACT

FACULTY OF SCIENCE

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Doctor of Philosophy

APPROACHES TO SPIRO-HETEROCYCLES: NOVEL SCAFFOLDS FOR DRUG DISCOVERY

By James Dudley Hart

The tachykinins are a family of neuropeptides found in the body that have been implicated in a variety of deleterious conditions, ranging from asthma and pain transmission in migraine to ulcerative colitis and Crohn's disease.

The work contained in this thesis is primarily concerned with the synthesis of potential tachykinin receptor antagonists based on a 1-oxa-8-azaspiro[4.5]decan-4-one skeleton. This has been achieved *via* the addition of ethoxyethyl-protected cyanohydrin **222** to a range of substituted piperidones with ensuing hydrolysis to the unsaturated hydroxyketone.

Ring-closure to form the spirocyclic furanone core was facilitated *via* an acid-mediated 5-*endo*-trig cyclisation. Reductive amination and deprotection of furanone **328** led to the isolation of amines **428** and **434** which served as ideal scaffolds for the synthesis of compound libraries.

Contents

For my parents, for everything.

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Everyone at the Southampton X-ray Crystallography service.

'I have of late
-But wherefore I know not-
Lost all my mirth'

William Shakespeare
Hamlet; Act II, scene II

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Australia for generously relinquishing the rugby world cup to England!

Lastly and most importantly for my family, in particular my parents ... without your unceasing love and support over all these years, none of this or anything else would have been possible.

Abbreviations

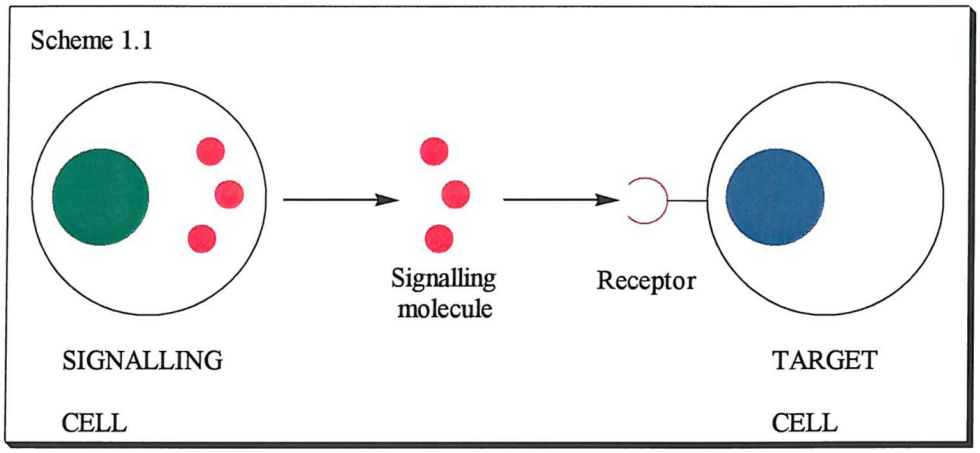
5-HT	5-Hydroxytryptamine (Serotonin)
Ac	Acetyl
Alloc	Allyloxycarbonyl
Aq.	Aqueous
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
br	Broad (NMR and IR)
BSA	Bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
CAS	Chemical Abstracts
cat.	Catalytic
CDI	Carbonyldiimidazole
CNS	Central nervous system
CSA	Camphor Sulfonic Acid
Cy	Cyclohexyl
d	Doublet (NMR)
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	1,3-Diisopropylcarbodiimide
DIPEA	Di*iso*propylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Ethylene glycol dimethyl ether (1,2-dimethoxyethane)
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl Azide
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
EDC	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Et	Ethyl
GC	Gas chromatography
Gly	Glycine
GPCR	G-Protein coupled receptor
h	Hour
HMDS	Hexamethyldisilazane
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
i	*iso*
IPA	Isopropyl alcohol
IR	Infra red
J	Coupling constant (NMR)

kDa	Kilodaltons
LDA	Lithium diisopropylamide
Leu	Leucine
m	Multiplet (NMR) or medium (IR)
M	Molar
Me	Methyl
Met	Methionine
MIBK	Methyl isobutyl ketone
min	Minute
m.p.	Melting point
Ms	Methanesulfonyl (mesyl)
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
m/z	Mass/charge ratio
N	Normal
Naphth	Naphthalene
NBS	*N*-Bromosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
Ns	2-Nitrobenzenesulfonyl (nosyl)
Nu	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
Phe	Phenylalanine
Pr	Propyl
*p*TSA	*p*Toluenesulfonic acid
q	Quartet (NMR)
rt	Room temperature
s	Singlet (NMR) or Strong (IR)
sat.	Saturated
t	Triplet (NMR)
t	*tert*
TBS/TBDMS	ᵗButyldimethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Trityl	Triphenylmethyl
Ts	*p*Toluenesulfonyl (tosyl)
UV	Ultraviolet
w	Weak (IR)

1. Introduction

1.1 Cell Signalling

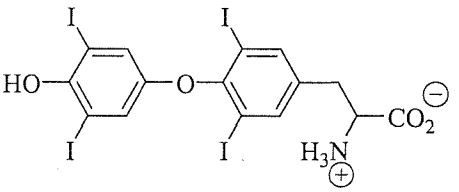
The mechanisms that enable one cell to influence the behaviour of another are almost certain to have existed long before multicellular organisms ever appeared on earth. The evidence of this comes from observing modern day single cell eukaryotes such as yeast cells; cells that normally exist independently but are also able to influence and communicate with one another. This communication arises by the release of signalling molecules from the cell, and the subsequent binding of that molecule by specific proteins on the target cell known as receptors (scheme 1.1).[1]



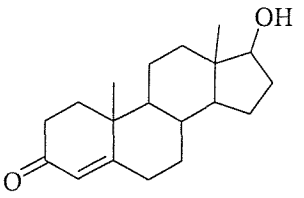
It is the function of the receptor to bind the signalling molecule, and then initiate a response in the target cell. Normally this occurs at very low concentrations, typically $\leq 10^{-8}$ M, with the receptors having a very high affinity for the signalling molecules, the affinity constant generally being $K_a \geq 10^8$ L/M.

It is usual for these receptors to be transmembrane proteins on the surface of the target cell; when an extracellular signalling molecule (a ligand) is bound, the receptors become activated, generating a cascade of intracellular signals that in turn alter the chemical behaviour of the cell. Huge numbers of organic compounds can act in this way; including hormones, neurotransmitters, proteins and small peptides; some of the most widely known examples of which are shown below (scheme 1.2).

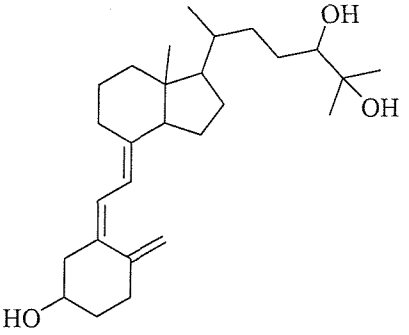
Scheme 1.2



Thyroxine **1**



Testosterone **2**



Vitamin D_3 **3**

Currently there are 3 known classes of cell-surface receptor proteins:

- Ion-Channel-Linked
- Enzyme-Linked
- G-Protein-Coupled

Of these three different types of proteins, it is the G-protein coupled receptors (GPCR) that are of specific interest in this thesis.

1.2 G-Proteins

1.2.1 Background

G-Proteins (guanine nucleotide binding regulatory proteins) are heterotrimers that play a pivotal role in signal transduction,[2] their function is to couple receptors to effectors within eukaryotic cell membranes.[3] It was the initial discovery that guanine

nucleotides mediate hormonal stimulation of adenylyl cyclase[4] that led to the eventual isolation of a large family of heterotrimeric, signal-transducing G-proteins.[5]

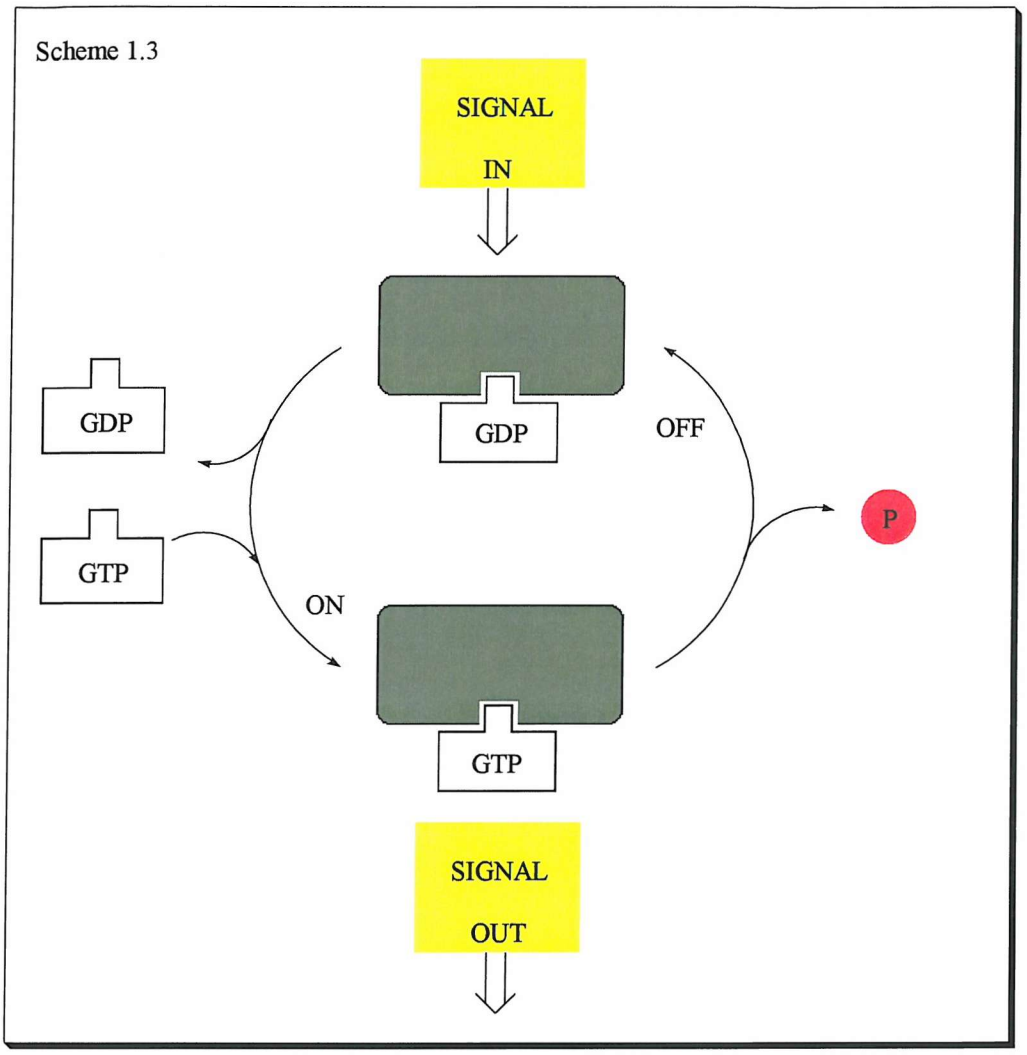
Intensive studies on the G-protein family have shown that most members contain seven hydrophobic domains of 20-25 amino acids, which are believed to represent the transmembrane regions. These regions are all understood to be α-helices and are oriented in such a way as to form a ligand binding pocket. The ligand binding sites are thought to be contained in the transmembrane region of the receptor in situations where the ligand is small, but where the stimulus is much larger in size the extracellular region of the receptor also plays a role.

1.2.2 G-Protein Activation

The cycle of G-protein activation can be broken down into four basic states (scheme 1.3):[6]

1. The Basal State; in which the G-protein is a heterotrimer with GDP bound to the α-subunit.
2. Receptor Mediated GDP Release; the activated receptor interacts with the G-protein and dramatically accelerates the rate of GDP release.
3. Subunit Dissociation and Effector Regulation; binding of GTP initiates a conformational change in the G-protein, causing dissociation and interaction with effector proteins.
4. Deactivation; GTPase activity causes cleavage of the terminal phosphate group of GTP, initiating the re-association of the GDP-bound G-protein, resulting in deactivation and return to the basal state.

The activation of the target protein will either alter the concentration of these mediator proteins (if the target is an enzyme), or will alter the permeability of the plasma membrane (if the target is an ion channel).



The sheer number of G-proteins in this family has meant that specific G-proteins regulating olfaction, visual transduction, cell growth and ionic events at the cell membrane have been isolated. This combined with increased knowledge of the 3-D structure of G-proteins has provided us with the basis of relating protein structure to function.

1.3 Chemistry of G-Proteins

1.3.1 Background

The work in this report is concerned with a family of neuropeptides called the tachykinins. This family includes undecapeptide substance P, the decapeptides neurokinin A and B, and the recently discovered neuropeptides K and γ.[7] The most

widely recognised of these; substance P was initially discovered as an hypotensive and spasmodic in 1931.[8] It was first hypothesised that substance P could be a neurotransmitter in 1953,[9] but not until 1975 was it first demonstrated to be a neuropeptide widely distributed in the nervous system.[10,11] All the tachykinin peptides have the same C-terminal sequence of Phe-X-Gly-Leu-Met-NH_2,[α] and the term "tachykinin" was coined as a means of describing the rapid development of smooth muscle contraction caused by these peptides.[12] The reason for our interest in these neuropeptides arises from the receptors for these tachykinins being identified as G-protein coupled receptors NK_1, NK_2 and NK_3. The whole neurokinin family have been shown to successfully bind to all three receptors, but substance P displays a greater selectivity for NK_1, neurokinin A for NK_2 and neurokinin B for NK_3. For further information on mammalian tachykinin receptors, consult the excellent review by Maggi.[13]

1.3.2 Therapeutic Utility

The scope for potential tachykinin receptor antagonists is huge. Members of the tachykinin family have been shown to pay a pivotal role in many deleterious disorders, including the pain and inflammation associated with sickle cell disease, anxiety, arthritis, cough, pain, pre-eclampsia, migraine, emesis, schizophrenia and many others.[14-18] It has been further indicated that neurokinin receptors can be associated with the pathogenesis of neurogenic inflammation, including allergic diseases such as asthma.[19] The tachykinins have also been implicated in diseases of the gastrointestinal tract (inflammatory bowel disease, ulcerative colitis and Crohn's disease etc.).[7] In particular substance P has been implicated in the activation and proliferation of cytokine release; one of the key responses for tumour progression.[20]

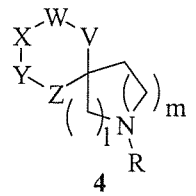
[α] Substance P, X = Phe; Neurokinin A and B, X = Val

1.4 Tachykinin Receptor Antagonists

There are obvious benefits to being able to synthesise tachykinin receptor antagonists, as these systems would have the potential to be invaluable in the pharmaceutical arena. It is this and other facts that make the area of such interest to so many research groups, and ours is no exception. There are a vast number of such syntheses in the literature, but a common facet to many of these is the presence of a spiro-piperidine system. Indeed spiro-piperidines are now considered as pharmacologically relevant molecules for various targets within the G-protein coupled receptor group.[21,22] This class of structure is often referred to as a privileged structure and is defined as a class of molecules that are capable of binding to multiple receptors with high affinity.[23] The sheer quantity of research carried out in the area is staggering, and to attempt to encompass the entire genre into a section of a thesis would be impossible and not do justice to the subject; however, to not take the opportunity to include a brief synopsis of some of the work in this area would be a travesty. Therefore, the following section will detail a small fraction of research conducted in the area of neurokinin receptor antagonists based around a central spiro-piperidine moiety.

To begin, a large number of potential antagonists have been synthesised by Merck, based on the general structure **4** (scheme 1.4).[24]

Scheme 1.4

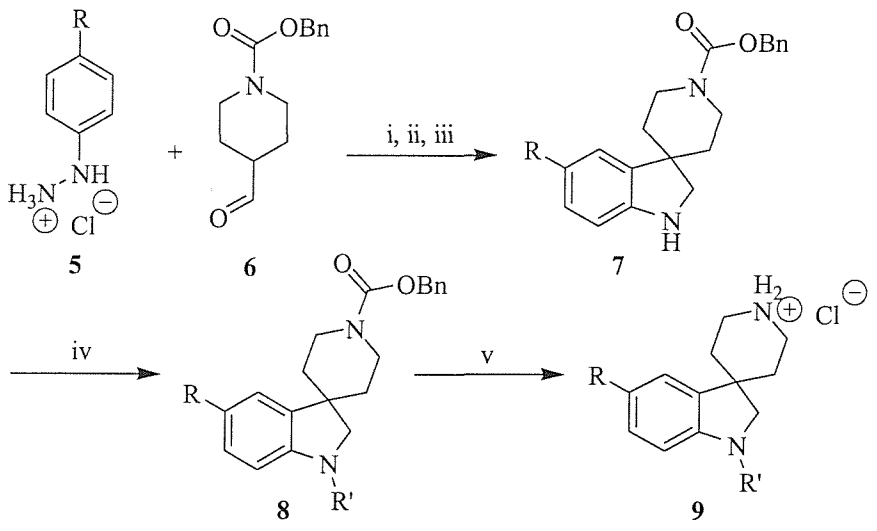


4

Where l and m = 0, 1, 2, 3, 4, or 5

A large amount of diversity has been introduced at the various positions V-Z resulting in a library containing a vast number of compounds, two typical syntheses of which are shown below (scheme 1.5, 1.6).

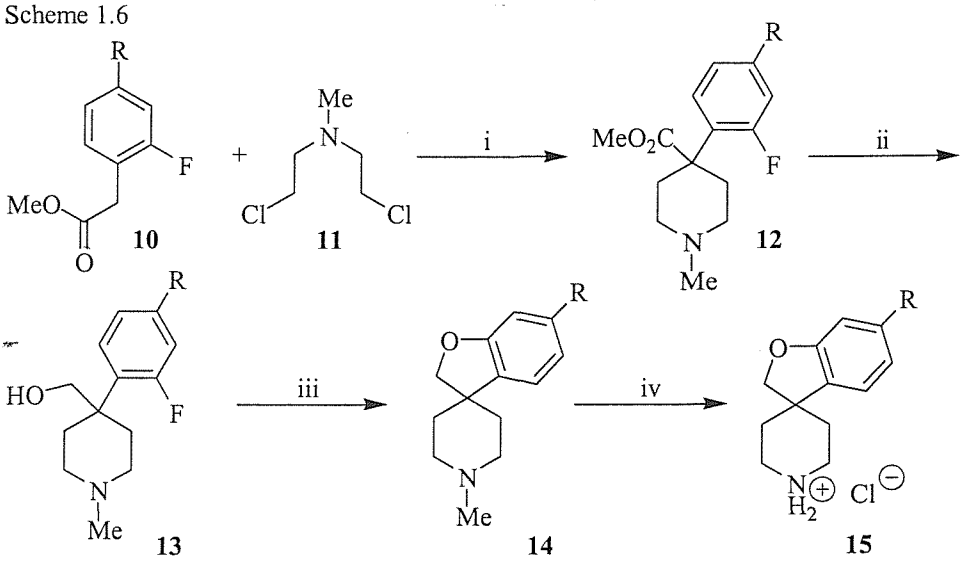
Scheme 1.5



Reagents/conditions: i) Pyridine, toluene, CH_3CN; ii) TFA, 60 °C; iii) $NaBH_4$, MeOH; iv) R'-X; v) H_2, Pd/C, HCl

In the first example, substituted phenylhydrazine **5** can be reacted as per the Fischer indole reaction, with subsequent reduction of the intermediate imine using sodium borohydride. It is then a simple matter for the indoline nitrogen to undergo electrophilic attack from an acyl or sulfonyl chloride, and the piperidine nitrogen to be deprotected using H_2, Pd/C and HCl, to give the substituted spiro(indoline-3,4'-piperidine) **9**.

Scheme 1.6

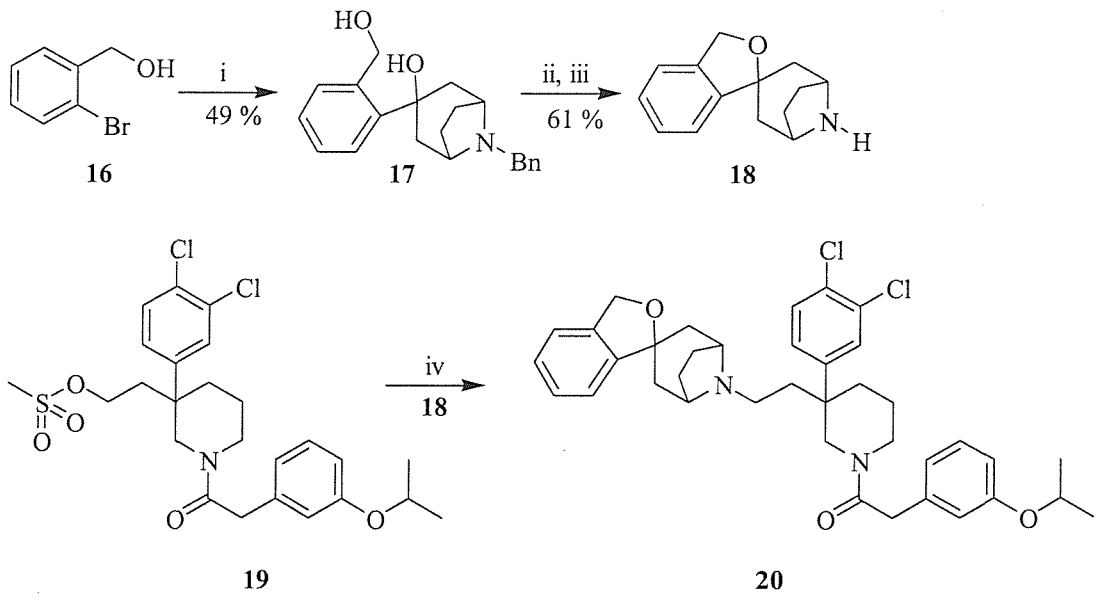


Reagents/conditions: i) NaH; ii) $LiAlH_4$, THF; iii) NaH, DMF; iv) DCE, 1-chloroethyl chloroformate, reflux

In scheme 1.6, we can see the synthesis of a spiro(2,3-dihydrobenzofuran-3,4'-piperidine) derivative **15**. Methyl ester **10** was treated with mechlorethamine hydrochloride (**11**) to give piperidine **12**, which was in turn reduced with lithium aluminium hydride to give the corresponding 4-hydroxymethyl compound **13**. Treatment of alcohol **13** with sodium hydride, provided cyclisation to the benzofuran derivative **14**, which underwent cleavage of the *N*-methyl group to give the desired spiroether **15** as the hydrochloride salt.

In a similar vein, a short synthesis of an NK_1 receptor antagonist by Kubota *et al* is described below (scheme 1.7).[25]

Scheme 1.7



16 **17** **18** **19** **20**

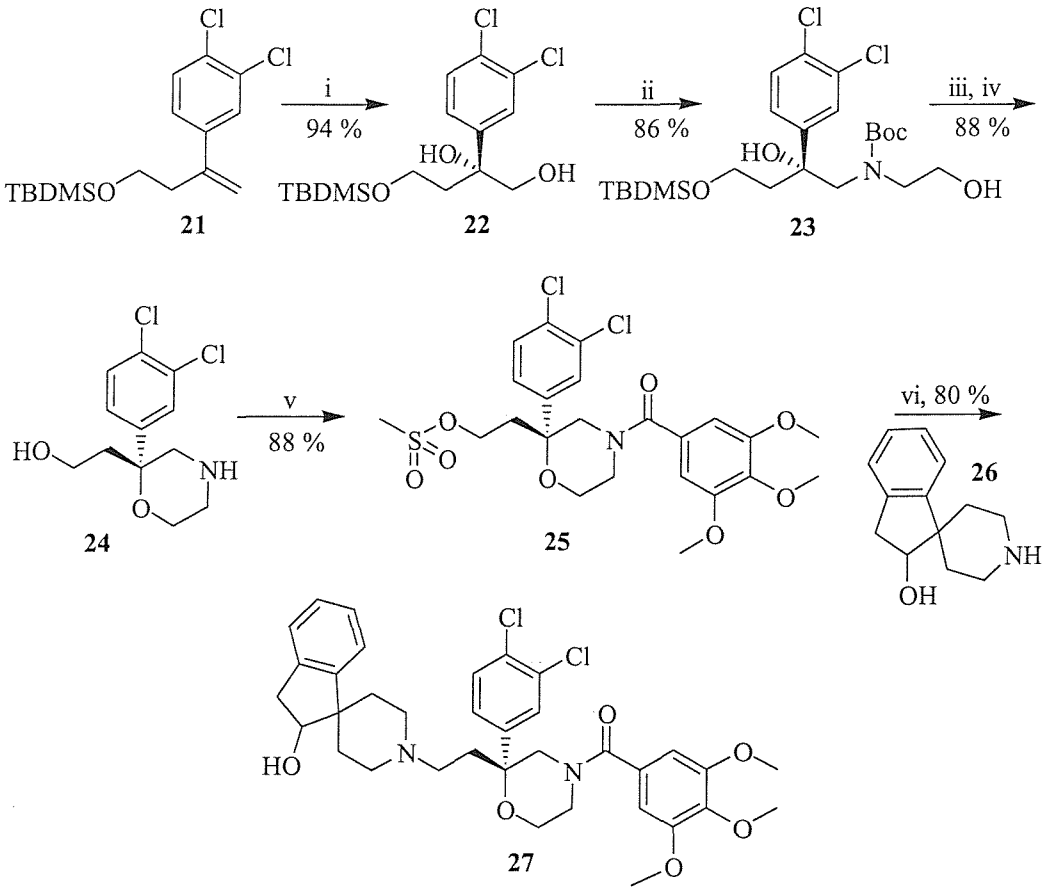
Reagents/conditions: i) 2 eq. *n*BuLi, THF/Et_2O/*n*-hexane, -78 °C then 8-benzyl-3-tropinone, -78 °C; ii) TsCl, pyridine/CH_2Cl_2, rt; iii) HCl then 20 % $Pd(OH)_2$ - C, H_2/MeOH, rt; iv) Et_3N/DMF, 70 °C

2-Bromobenzyl alcohol (**16**) was converted to its dianion with *n*-BuLi and treated with 8-benzyl-3-tropinone to give diol **17**, the primary hydroxy group was then tosylated and displaced by the tertiary alcohol in the presence of pyridine to give the cyclic ether. Hydrogenolysis using catalytic $Pd(OH)_2$ cleaved the benzyl group to give free amine **18**, which then displaced mesylate **19** to give the target compound **20**, isolated as the

hydrochloride salt. When tested for antagonistic activity, piperidine **20** displayed an IC_{50} of 105 nM for the NK_1 receptor.

Nishi *et al* devised the synthesis of morpholine analogues (scheme 1.8) that display excellent affinities for all 3 neurokinin receptors.[26,27] The structures all show a high degree of similarity to those of Kubota *et al*, in particular the spirocyclic piperidine ring and the dichloro-aryl moiety.

Scheme 1.8



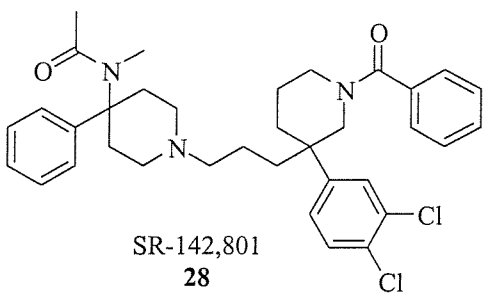
Reagents/conditions: i) AD-mix-β, *t*-BuOH-H_2O; ii) TsCl, pyridine then $H_2N(CH_2)_2OH$, $LiClO_4$, CH_3CN then Boc_2O, Et_3N, CH_2Cl_2; iii) DEAD, Ph_3P, toluene; iv) 4N HCl/dioxane then 5 % NaOH; v) Et_3N, CH_2Cl_2, 3,4,5-trimethoxybenzoyl chloride then MsCl, pyridine; vi) $NaHCO_3$, KI, DMF, 80 °C

In the synthesis, olefin **21** was dihydroxylated with AD-mix-β to obtain (*R*)-diol **22** with high enantiomeric purity (>97 % ee). Selective tosylation of the primary alcohol, followed by substitution with ethanolamine and Boc protection of the resulting

secondary amine provided diol **23** in excellent yield. Treatment of the diol with diethylazodicarboxylate and triphenylphosphine initiated cyclisation to morpholine **24** and coupling with 3,4,5-trimethoxybenzoyl chloride followed by mesylation provided amide **25** also in very good yield. Straightforward displacement of this mesylate with amine **26** gave the target compound in excellent yield. Interestingly the binding affinity varied enormously with the stereochemistry, ranging from IC_{50} values of 2.7 (*S,R*) to >1000 (*R,S*).

A communication by Harrison *et al* showed the synthesis of a series of scaffolds with the potential to treat anxiety and psychosis.[28] The structures were all derived from a common structural template SR-142,801 (**28**) from Sanofi known to be active in this area (scheme 1.9).[29]

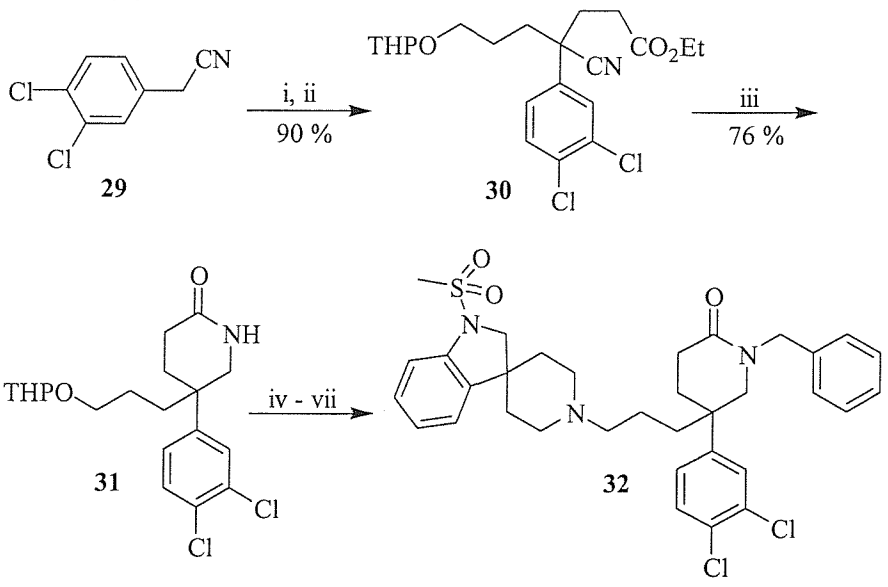
Scheme 1.9



SR-142,801
28

Harrison *et al* decided to generate their series with transposition of the benzylamide carbonyl into the piperidine ring, and a range of cyclic amines replacing the phenylacetamidopiperidine moiety. It was their hope that these simple transformations would lead to the scaffolds being high affinity ligands for human cloned NK_2 and NK_3 receptors, and that this in turn would be of great value in the search for definition of the pharmacophore for these receptors and to further clarify the significance of neurokinin receptor subtypes in the CNS. Interestingly their findings indicated that with the carbonyl exocyclic, the systems displayed the highest affinity for NK_3 receptors, but after transposition of the carbonyl group into the piperidine ring the substrates displayed highest affinity for the NK_2 receptor subtypes. One of the most interesting examples is shown below (scheme 1.10).

Scheme 1.10

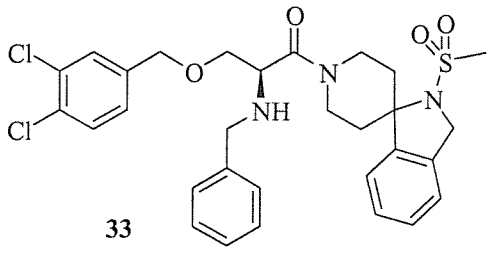


Reagents/conditions: i) $THPO(CH_2)_3Br$, THF, NaH; ii) ethyl acrylate, triton B, dioxane; iii) H_2, Raney Ni, EtOH; iv) NaH, BnBr, THF; v) HCl, MeOH; vi) MsCl, Et_3N, CH_2Cl_2; vii) K_2CO_3, DMF, R_1R_2NH.

The synthesis was relatively facile, deprotonation of cyanide **29** with sodium hydride and coupling with a THP-protected hydroxybromide, followed by addition of ethyl acrylate provided entry to ester **30**. Hydrogenation of the cyano group with Raney nickel initiated intramolecular cyclisation onto the ester moiety, furnishing lactam **31** in good yield. Simple *N*-benzylation followed by *O*-deprotection and mesylation gave the intermediate mesylate, which was then displaced with the requisite amine to give target **32** with an IC_{50} of 2.2 nM for human NK_2 (hNK_2).

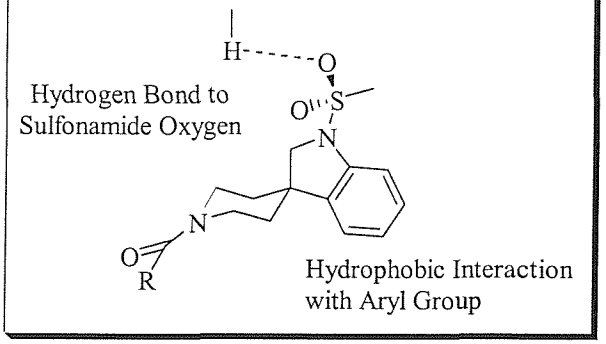
Elliott *et al*, worked on the synthesis of novel serine based NK_1 receptor antagonists, developing a rigid spirocyclic arylsulfonamide **33** (hNK_1 - IC_{50} 1.0 nm) (scheme 1.11).

Scheme 1.11



Further communications from the same group highlighted the effects of variation to the spirocyclic portion of the molecule.[30] Their studies allowed them to propose a minimum pharmacophore for the aryl sulfonamide (scheme 1.12).

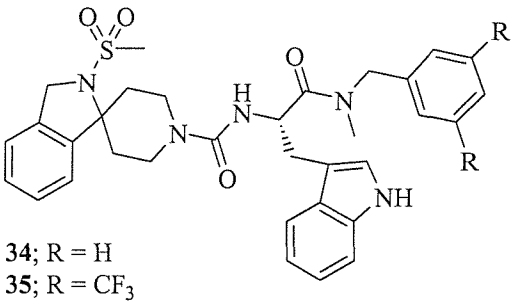
Scheme 1.12



It was established that for the system to achieve an acceptable binding affinity it was necessary for the piperidine moiety to be present in a spirocyclic environment, or at the very least be an acyclic equivalent able to mimic the desired conformation.

There are a range of neurokinin antagonists containing this pharmacophore developed by Qi *et al* that also contain an L-tryptophan residue (scheme 1.13).[31]

Scheme 1.13



34; R = H
35; R = CF_3

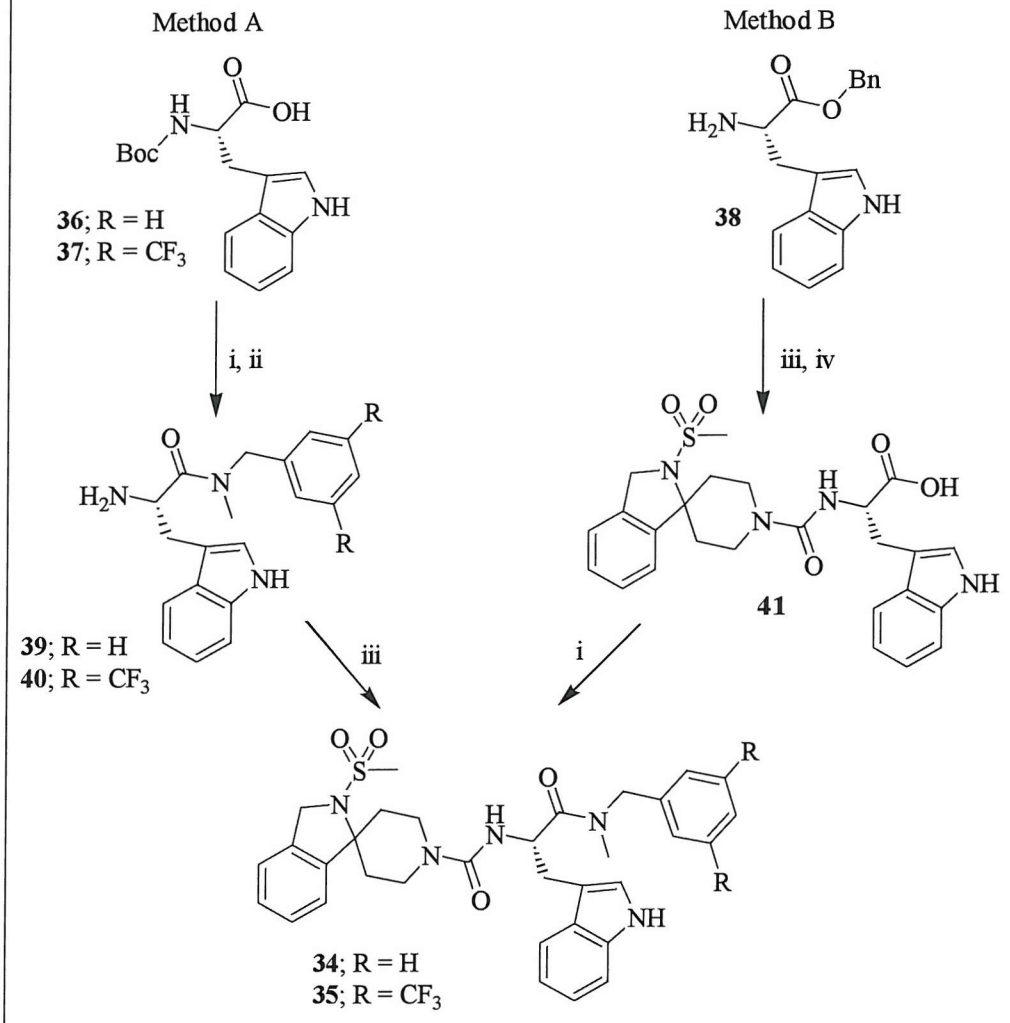
Qi *et al* observed that a simple alteration of the aryl substituents could have a profound effect on the selectivity and binding affinity of the scaffolds (table 1.1) and can produce antagonists selective purely for NK_1 receptors or for both NK_1 and NK_2 receptors.[31]

Table 1.1 **Affinity of L-Trp Ureas for the Cloned Human NK_1 and NK_2 Receptors**

	IC_{50} (nM)	
Scaffold	**hNK_1**	**hNK_2**
34	14	24
35	1.0	4200

In order to simplify the synthesis of the tryptophan ureas, two methods were developed for more convenient derivatisation of the termini (scheme 1.14).

Scheme 1.14

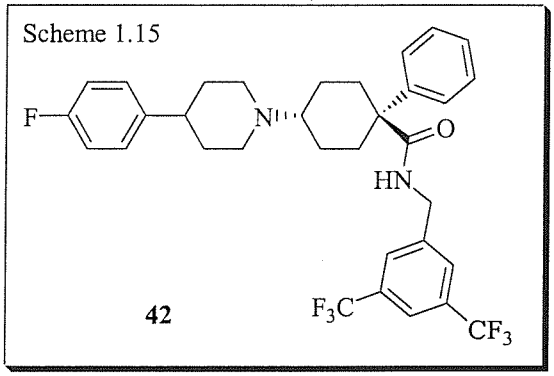


Reagents/conditions: i) EDC, HOBt, NMM, Ar-$CH_2NH(Me)$, CH_2Cl_2; ii) TFA, anisole; iii) CDI, spiroamine, THF; iv) H_2, Pd/C, EtOH

Method A was used for easy modification of the *N*-terminal urea; *N*-Boc-L-Trp was coupled with the benzyl amine under standard peptide coupling conditions (EDC/HOBt), followed by Boc group removal effected by TFA to give the required amides **39/40**. The primary amines were treated with CDI and then the spirocyclic amine to give the target ureas. As an alternative, the order could be reversed to facilitate more convenient *C*-terminal modification; thus in method B free amine **38** was coupled with the spirocyclic amine fragment using CDI followed by hydrogenation to remove the benzyl group. Reaction of the now free acid **41** with the requisite benzyl amines under standard peptide coupling conditions furnished neurokinin antagonists **34/35**.

Cooper *et al* identified a suitable lead compound **42** for a cyclohexyl based series of NK_1 receptor antagonists during a targeted screening program (scheme 1.15).[32]

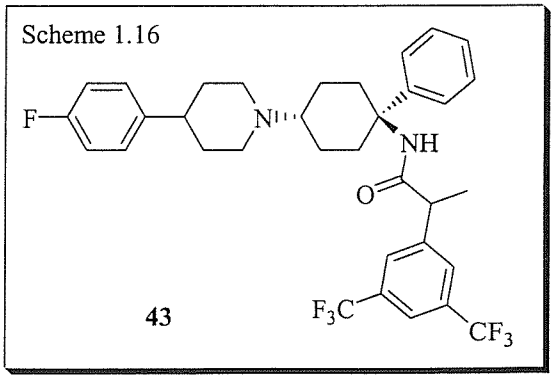
Scheme 1.15



42

It was found that the best combination of NK_1 binding affinity and *in vivo* properties were obtained by the reversal of the amide moiety and by the introduction of an α-methyl substituent, leading to compound **43** (scheme 1.16).

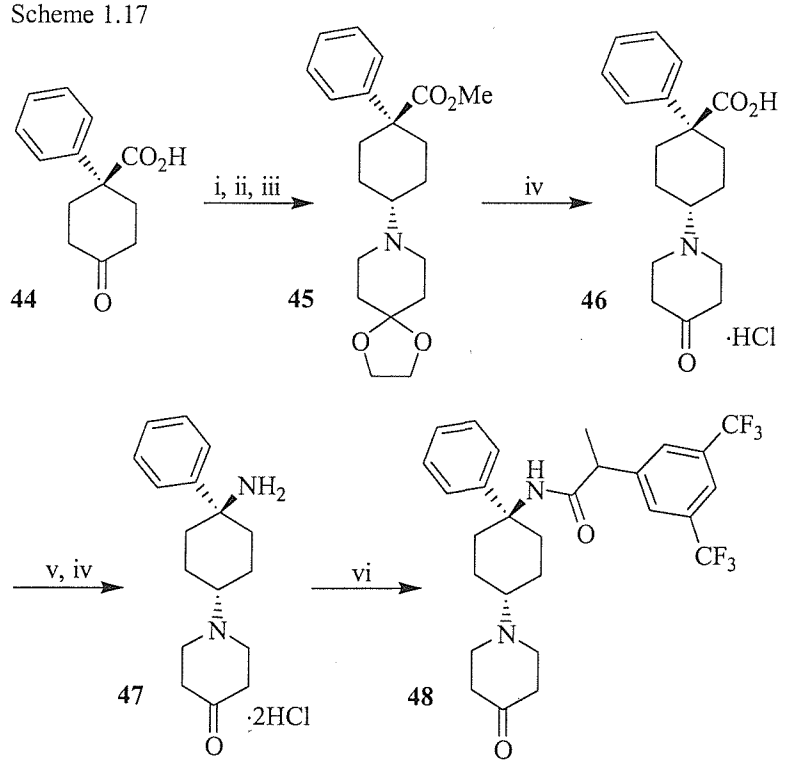
Scheme 1.16



43

The major modifications to the lead structures however came in the modification of the piperidine segment of the molecule. A brief synopsis of the synthesis of the skeleton can be observed below (scheme 1.17).

Scheme 1.17

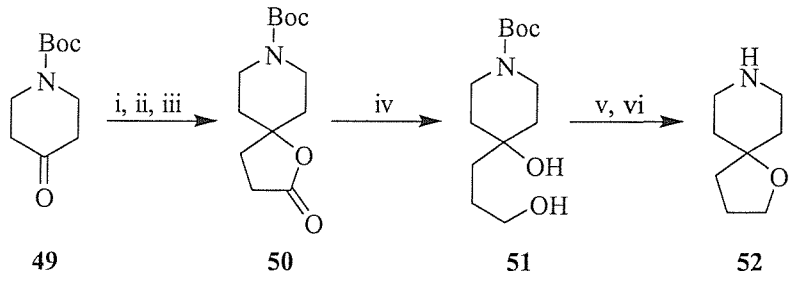


Reagents/conditions: i) 1,4-Dioxa-8-azaspiro[4.5]decane, $NaBH(OAc)_3$, DCE, rt, 16 h; ii) AcCl, MeOH, reflux, 24 h; iii) separation of *trans*-ester and *cis*-acid; iv) HCl, H_2O, reflux, 16 h; v) DPPA, Et_3N, toluene, 90 °C, 1.5 h; vi) (±)-3,5-$(CF_3)_2C_6H_3CH(Me)COCl$, Et_3N, CH_2Cl_2, rt, 16 h

Reductive amination of keto-acid **44** with 1,4-dioxa-8-azaspiro[4.5]decane and sodium triacetoxyborohydride gave a mixture of *cis* and *trans* carboxylic acids. However it was found the *trans* isomer could be selectively esterified with methanol, allowing the insoluble *cis*-acid to be removed by filtration, isolating *trans*-ester **45**. Treatment with aqueous HCl effected hydrolysis of both the ester and ketal functionalities granting *trans*-acid **46**. The carboxylic acid **46** was then treated with DPPA and triethylamine to initiate a Curtius rearrangement[33-35] with hydrolysis to give primary amine **47**. Coupling of the amine with α-methyl-3,5-bis(trifluoromethyl)phenylacetyl chloride gave amide **48**, further derivatised by reductive amination of the piperidone carbonyl

with a range of amines, including a number of spirocyclic amines. The synthesis of the amine that bestowed the best binding affinity can be seen below (scheme 1.18).

Scheme 1.18

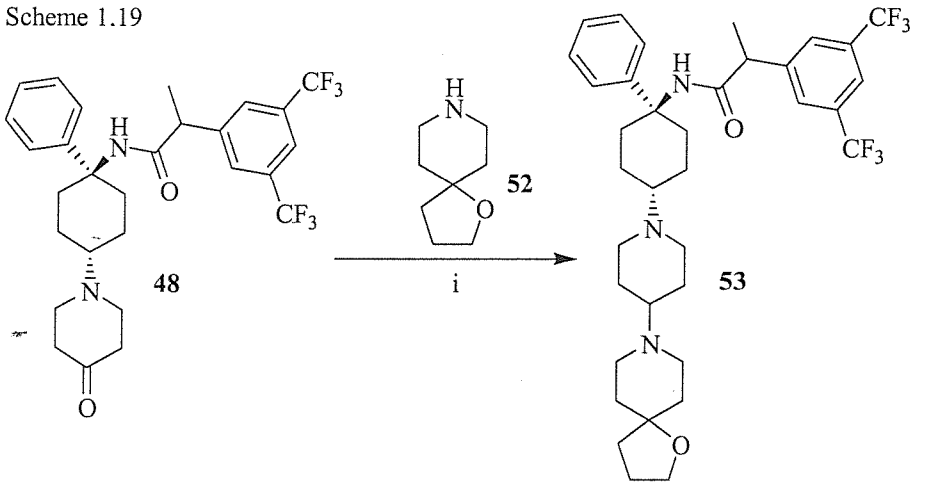


49 **50** **51** **52**

Reagents/conditions: i) *n*-BuLi, ethyl propiolate, THF, -78 °C, 1 h; ii) H_2, Pd/C, EtOH, rt, 45 psi, 1.5 h; iii) *p*TSA, toluene, reflux, 3 h; iv) DIBAL, CH_2Cl_2, -78 to 0 °C, 5 h; v) PPh_3, DEAD, THF, 0 °C to rt, 16 h; vi) AcCl, MeOH, 0 °C to rt, 16 h.

Reaction of the anion of ethyl propiolate with *N*-Boc-4-piperidone (**49**), followed by hydrogenation and cyclisation provided entry to lactone **50**. Ring opening of the lactone with DIBAL granted diol **51**, a Mitsunobu reaction provided an excellent method for cyclisation and Boc deprotection of the amine gave a simple route to cyclic ether **52**. Coupling of amine **52** with piperidone **50** was carried out using a simple reductive amination reaction (scheme 1.19).

Scheme 1.19

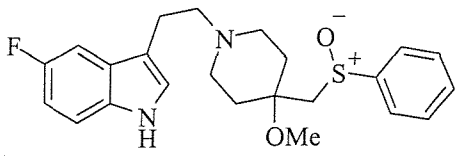


Reagents/conditions: i) $NaCNBH_3$, $ZnCl_2$, MeOH, rt, 16 h

In vivo testing of spiroether antagonist **53** realised an excellent affinity for the NK_1 receptor of 0.22 nM.

Smith *et al*, formed a hypothesis that an indole and a phenyl ring were essential elements for effective NK_2 binding.[36] This idea led to the isolation of sulfoxide **54** as a lead compound in their drug discovery program (scheme 1.20).

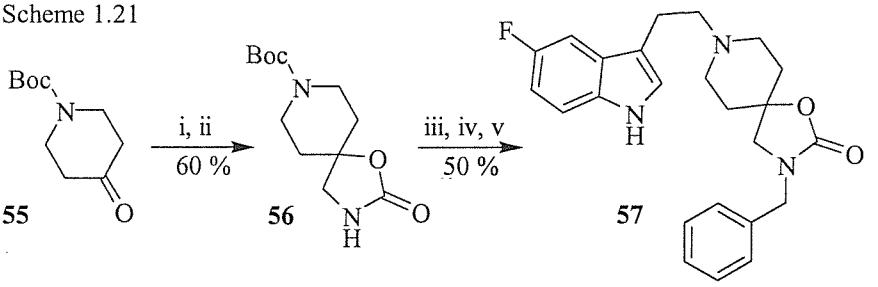
Scheme 1.20



54

With sulfoxide **54** as a lead compound, they discovered a novel series of spiropiperidine-containing NK_2 receptor antagonists, the synthesis of one member of which can be seen below (scheme 1.21).

Scheme 1.21



Reagents/conditions: i) CH_3CO_2Et, LiHMDS then NaOH, MeOH;
ii) DPPA, Et_3N; iii) NaH, DMF, BnBr; iv) HCl/dioxane;
v) 2-(5-fluoro-1*H*-3-yl)ethyl bromide

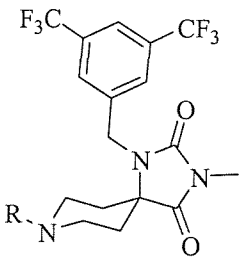
N-Boc-4-Piperidone was reacted with the lithium enolate of ethyl acetate and the nascent ethyl ester hydrolysed with sodium hydroxide. Treatment of the hydroxy acid with DPPA effected cyclisation *via* a Curtius rearrangement, providing oxazolidinone **56** in 60 % over the two steps. Deprotonation of the oxazolidinone nitrogen with sodium hydride and the addition of benzyl bromide was followed by Boc deprotection with HCl in dioxane. The indole was introduced *via* a straightforward S_N2 reaction of

the piperidine nitrogen with the requisite halide. A range of alkyl halides were coupled to the oxazolidinone however the compound that displayed the greatest binding affinity was spirocycle **57**, where a simple benzyl group is introduced, with a pK_i of 8.9.

Bleicher *et al* were searching for novel small molecule ligands that targeted the NK_1 receptor. Their focused library synthesis strategy combined the concepts of both privileged structure motifs and the needle component.[37] The terminus 'needle' is described in the literature as a fragment of an active molecule showing very specific interactions with one particular biological target.[38] Following this idea of combining the two concepts, a library design was generated to couple a 3,5-bis(trifluoromethyl)phenyl needle to all available positions in a spiropiperidino-hydantoin core structure (scheme 1.22).

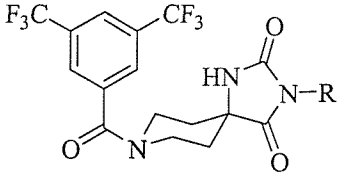
Scheme 1.22

Library A



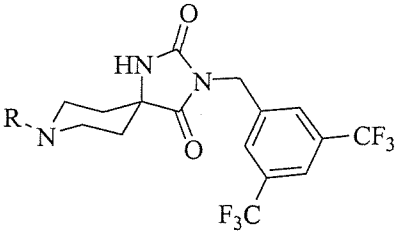
58

Library B



59

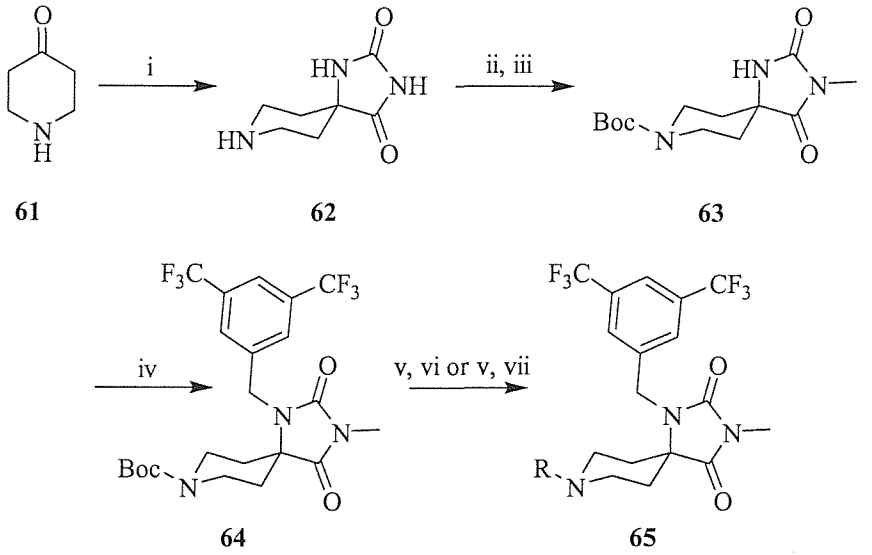
Library C



60

The scientific basis for this library design were both the identification of spiropiperidino-hydantoin as a privileged structure for GPCR's and the identification of 3,5-bis(trifluoromethyl)phenyl as an NK_1 specific 'needle'.[39] Libraries B and C were synthesised using a solid-supported synthesis protocol, which will be outlined later; library A on the other hand was synthesised in solution phase with initial spirocyclisation of readily available starting materials and subsequent modification of the piperidine nitrogen (scheme 1.23).

Scheme 1.23

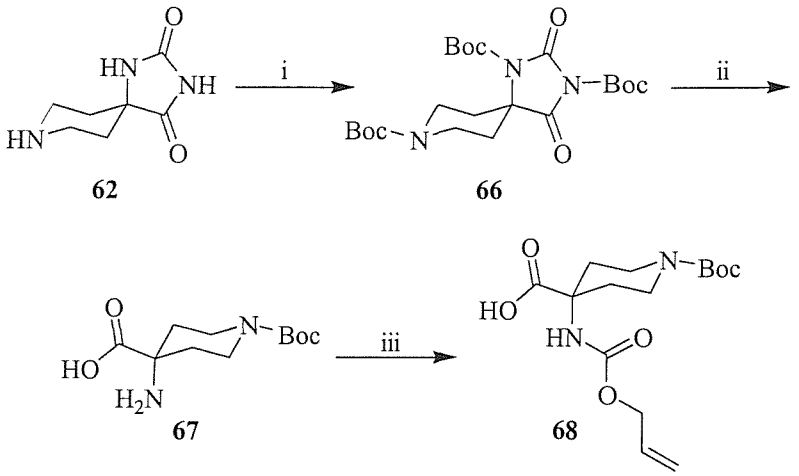


Reagents/conditions: i) NaCN, $(NH_4)_2CO_3$, $EtOH/H_2O$ (4:1), 80 °C, 3.5 atm, 18 h; ii) Boc_2O, Et_3N, dioxane/H_2O (1:1), 2 h; iii) NaH, MeI, DMA, rt, 72 h; iv) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, DMA, rt, 48 h; v) TFA/CH_2Cl_2, rt, 2h; vi) R-CO_2H, DIC, rt, 16 h; vii) bromoacetic acid, DIC, rt, 16 h then R-NH_2, rt, 16 h

Commercially available 4-piperidone monohydrate (**61**) was transformed into the corresponding hydantoin **62** using sodium cyanide and ammonium carbonate, Boc protection and monomethylation with iodomethane and sodium hydride provided intermediate **63**. Deprotonation with a further equivalent of sodium hydride and displacement of 3,5-bis(trifluoromethyl)benzyl bromide enabled access to compound **64**, the skeleton of the scaffold. The Boc group was removed with TFA in dichloromethane allowing the free piperidine nitrogen to be derivatised for the generation of library A. Library generation was achieved either by a simple DIC coupling with a carboxylic acid, or coupling to bromoacetic acid with subsequent halide displacement by a range of amines to give final target **65**.

The synthesis of hydantoins from the corresponding α-amino acids is well documented,[40] so due to the literature precedent the syntheses of libraries B and C were undertaken on the solid-phase. It was necessary however to generate the orthogonally protected amino acid in solution prior to immobilisation onto a solid-support (scheme 1.24).

Scheme 1.24

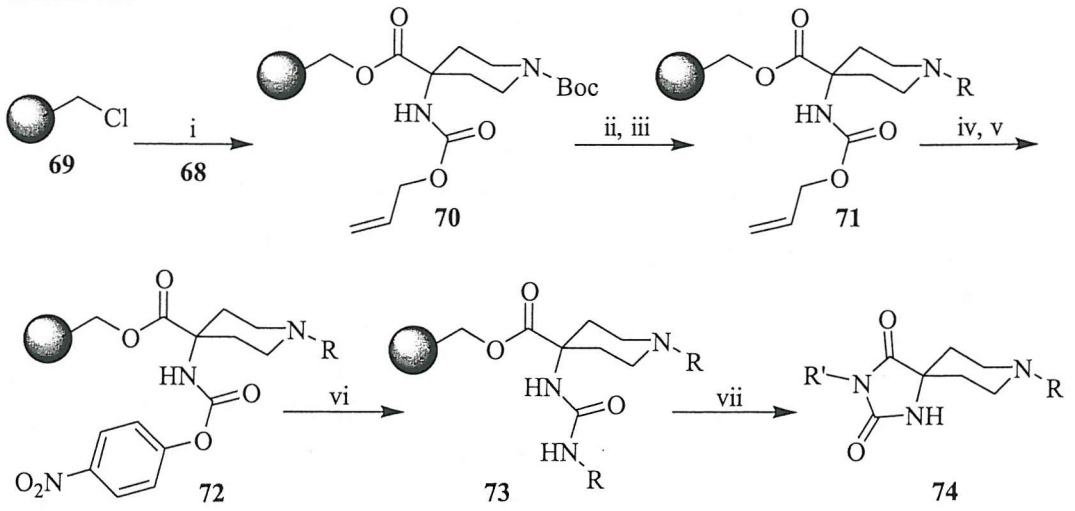


Reagents/conditions: i) Boc_2O, DMAP, Et_3N, DME, rt, 18 h; ii) 1N NaOH/DME (2:1), rt, 20 h; iii) allyl chloroformate, 5 % aq Na_2CO_3 dioxane/H_2O (1:2), rt, 16 h

The previously generated hydantoin **62** was treated with an excess of Boc anhydride to facilitate the complete Boc protection of all the nitrogen functionality in the system. Basic ring-opening with sodium hydroxide provided access to the corresponding amino acid **67** that was then protected with the orthogonal Alloc group. This afforded amino acid **68**, which formed the common precursor for both libraries B and C.

For library B, acid **68** was immobilised onto the solid-support by treatment with Cs_2CO_3 and KI, inducing displacement of commercially available Merrifield's resin[41] **69**, granting resin **70** in one step (scheme 1.25).

Scheme 1.25



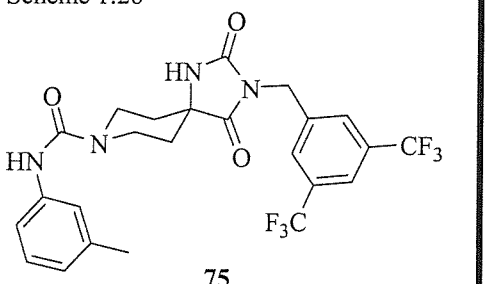
Reagents/conditions: i) Cs_2CO_3, KI, 60 °C, 16 h; ii) TFA/CH_2Cl_2, rt, 2 h; iii) 3,5-bis(trifluoromethyl)benzoyl chloride, Et_3N, CH_2Cl_2, rt; iv) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, rt, 2 h; v) 4-nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt, 1 h; vi) R-NH_2, CH_2Cl_2, rt, 16 h; vii) isopropylamine 80 °C, 2 h

Deprotection of the Boc group was achieved using TFA in CH_2Cl_2, allowing the free piperidine nitrogen to be coupled to 3,5-bis(trifluoromethyl)benzoyl chloride, installing the NK_1 needle as before. The Alloc group was cleaved under mild conditions using a palladium catalyst to form a π-allyl species, and cleavage with morpholine as the nucleophile. The free amine was coupled with 4-nitrophenyl chloroformate providing carbamate **72**. Activated carbamate **72** was then treated with a range of amines as per library A, converting the urethane to urea **73** by liberation of bright yellow 4-nitrophenolate. This step had the obvious advantage of the distinct colour change allowing straightforward monitoring of the reaction progress. Synthesis of this library was concluded with the cyclisation and cleavage from the solid-support; this could be achieved using acidic or basic conditions but the authors opted for the latter, due to increased yields and ease of transfer to parallel synthesis procedures. The cyclisation/cleavage strategy with isopropylamine provided the members of the library with both excellent yields and purity.

The compounds generated for library C differed mainly in the point of attachment of the needle and the pendant R groups, the rest of the synthesis being the same as for library B. Similar binding affinities were obtained for members of all three libraries,

although those members of library C were slightly greater, with compound **75** displaying the greatest pK_i value of 7.34 (scheme 1.26).

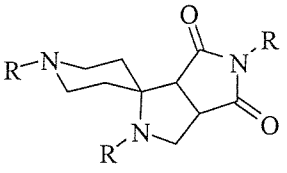
Scheme 1.26



75

Further work by Bleicher *et al* in the same area of neurokinin receptor ligands combined this use of the 3,5-bis(trifluoromethyl)phenyl needle with a slight modification to the spiropiperidine moiety, replacing it with a spiropyrrolo-pyrrole centre **76** (scheme 1.27).[42]

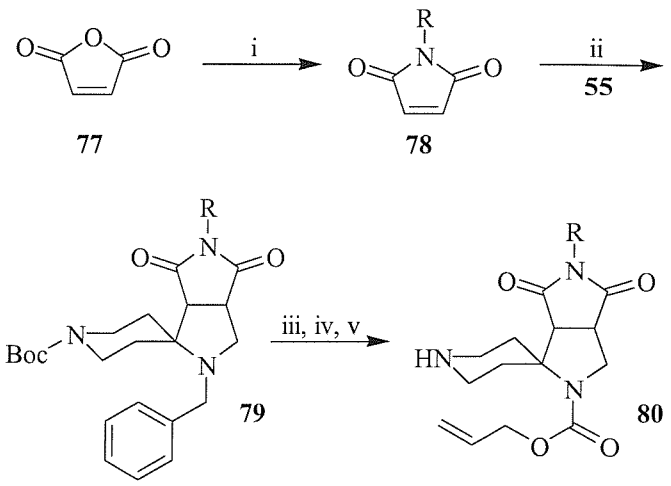
Scheme 1.27



76

As in the previous example, three libraries were generated utilising both solution and solid-phase chemistries, differing only in the position of attachment of the needle and pendant chains. The greatest binding affinities were obtained with the needle attached to the nitrogen of the piperidine moiety, a library that was generated on the solid-phase. The solution-phase synthesis of the scaffold began with the reaction of commercially available maleic anhydride **77** with a range of primary amines to introduce the first point of diversity into the system (scheme 1.28).

Scheme 1.28

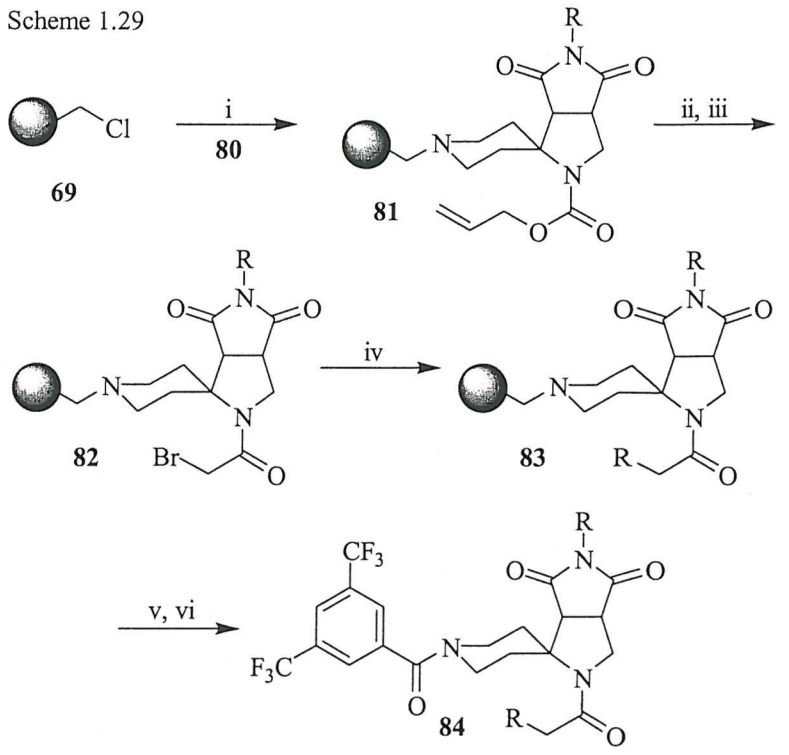


Reagents/conditions: i) R-NH_2, CH_2Cl_2, rt, 1 h, evaporation, NaOAc, Ac_2O, 90 °C, 16 h; ii) *N*-benzylglycine, DIPEA, PhMe, reflux, 16 h; iii) Pd/C, H_2, 2 atm, MeOH/CH_2Cl_2, rt, 2 h; iv) Alloc-Cl, BSA, CH_2Cl_2, 0 °C, 72 h; v) TFA/CH_2Cl_2, rt, 2 h

The range of maleimides **78** prepared in this way was then reacted with Boc-piperidone **55**, DIPEA and *N*-benzylglycine in a [3+2] cycloaddition reaction with spontaneous decarboxylation, generating intermediate **79**. Hydrogenolysis of the benzyl group, followed by re-protection with an Alloc group and Boc deprotection led directly to spiropyrrolo-pyrrole **80**.

For the solid-phase synthesis, Merrifield's resin **69** was swelled in CH_2Cl_2, and treated with piperidine **80** and DIPEA in order to achieve immobilisation of the scaffold (scheme 1.29). Removal of the Alloc protecting group with $Pd(PPh_3)_4$ and morpholine, and coupling of the nascent free pyrrolidine with bromoacetic acid under standard conditions enabled the isolation of bromide **82**. Nucleophilic displacement of the bromide was then undertaken with a set of secondary amines to create amide **83** and confer the second centre of diversity into the library. Cleavage from the trityl resin with TFA in CH_2Cl_2, and isolation and coupling of the crude material with 3,5-bis(trifluoromethyl)benzoyl chloride generated the final targets for the library.

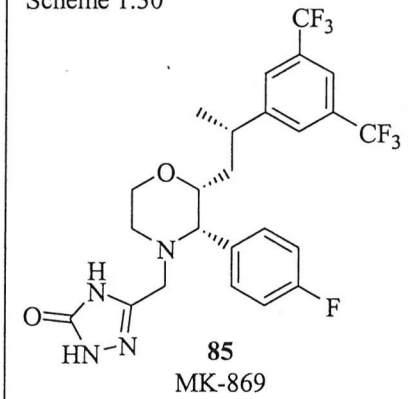
Scheme 1.29



Reagents/conditions: i) DIPEA, CH_2Cl_2, rt, 16 h; ii) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, rt, 16 h; iii) bromoacetic acid, DIC, DMF, rt, 16 h; iv) R-NH_2, DMF, rt, 4 h; v) TFA/CH_2Cl_2, rt, 2 h; vi) 3,5-bis(trifluoromethyl)benzoyl chloride, BSA, CH_2Cl_2

Seward *et al* described a series of novel NK1 antagonists based on a series of [4.5] and [5.5] spiroketal templates.[43] Their work was initially based on MK-869 (**85**) a new class of anti-emetic (scheme 1.30).[44]

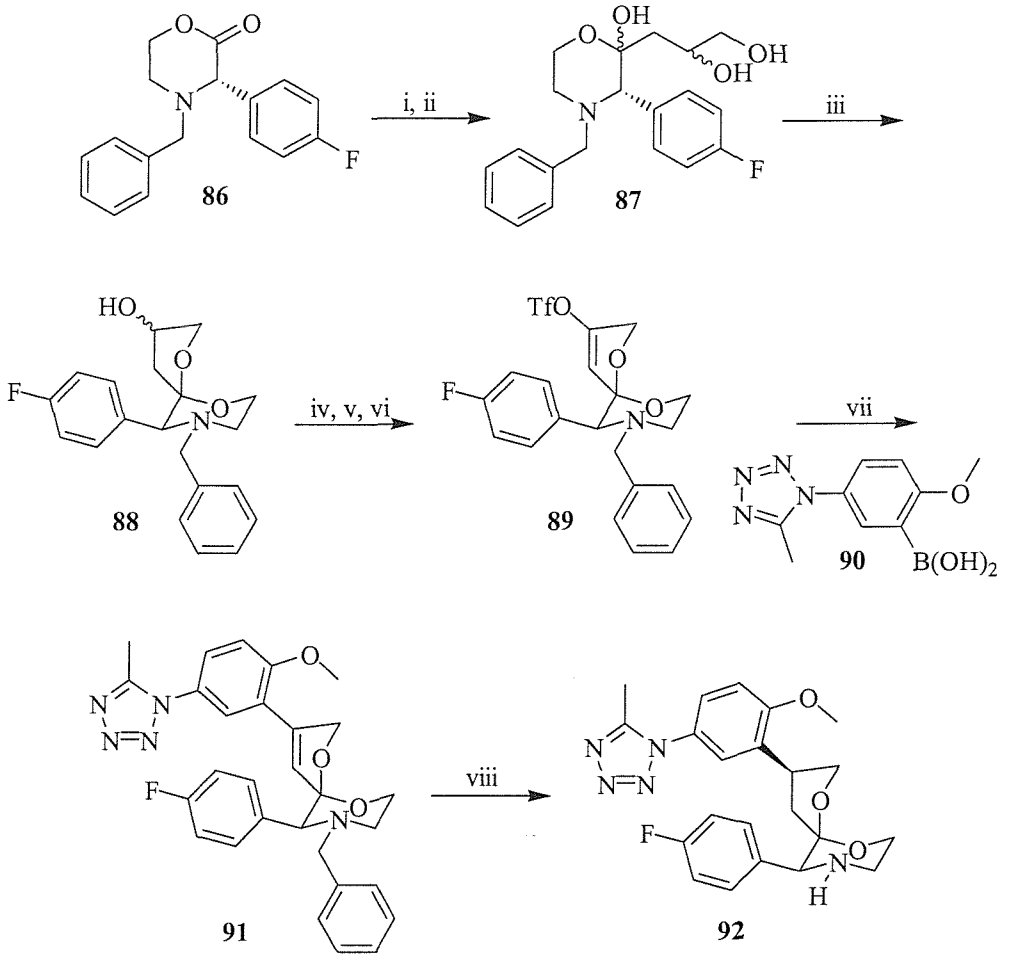
Scheme 1.30



85
MK-869

They were interested in developing conformationally restricted ligands in which the structural framework would fix the position of the two aromatic rings. The most interesting fruits of their labours were those structures based upon the [4.5] spiroketal subunit (scheme 1.31).

Scheme 1.31



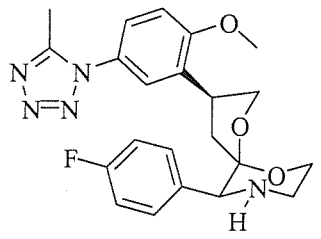
Reagents/conditions: i) allylmagnesium chloride, THF, -78 °C; ii) OsO_4, NMO, THF, *t*-BuOH, H_2O; iii) 6 N HCl, MeOH, 65 °C; iv) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C then Et_3N; v) NaHMDS, THF, -78 °C; vi) 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine; vii) $Pd(PPh_3)_4$, LiCl, Na_2CO_3, DME, H_2O, 80 °C; viii) Pd/C, HCO_2NH_4, MeOH, reflux

In this procedure, (*S*)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one **86** was reacted with allyl Grignard to afford the allylated lactol, and the olefin dihydroxylated using catalytic osmium tetraoxide and *N*-methylmorpholine-*N*-oxide granting triol **87** as a mixture of isomers. Refluxing the triol in mineral acid effected cyclisation to spiroketal **88** as a mixture of diastereoisomers, which were subjected to a Swern

oxidation. The two ketones formed were separated by chromatography and the desired isomer converted to enol triflate **89** with sodium hexamethyldisilazane and 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine.[45] Suzuki coupling of the enol triflate with boronic acid **90** provided the dihydropyran intermediates. These were in turn reduced to the tetrahydrofurans by hydrogenation with concomitant debenzylation to give the desired 3*S* isomers **91**, the selectivity in this instance arising from the 10-aryl substituent blocking one face of the olefin from the catalyst. The 2-methoxy-5-(trifluoromethyl)tetrazolyl derivative generated from this pathway, showed excellent CNS penetration and high affinity (IC_{50} = 0.1 nm).

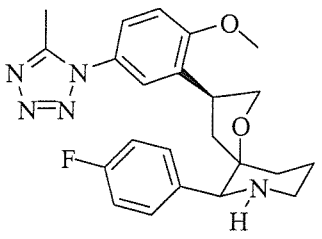
As a follow up to this research, Williams *et al* were investigating the efficacy of [4.5] spiroethers as neurokinin antagonists.[46] The compounds synthesised in this study contained spiropiperidine functionality rather than the spiromorpholine centre detailed in the previous examples but were generated by the same route. The binding affinities displayed by these targets were comparable with the analogous spiromorpholine series (scheme 1.32).

Scheme 1.32



92

IC_{50} = 0.1 nM

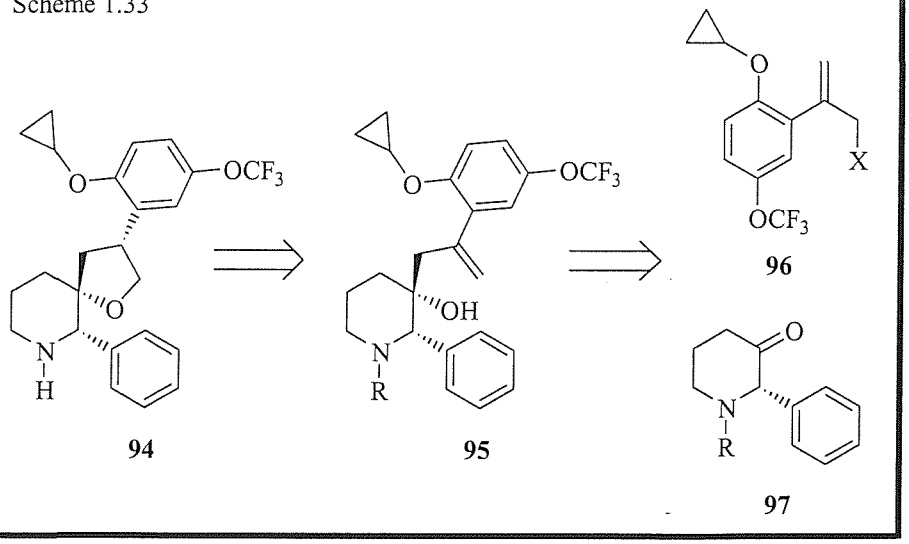


93

IC_{50} = 0.11 nM

Antidepressant activity has recently been observed in a neurokinin antagonist developed by Merck and has stimulated further research in the area of substance P antagonists.[47] As a result of this, Maligres *et al* undertook the synthesis of a spirocyclic NK_1 receptor antagonist with a 6-phenyl-1-oxa-7-azaspiro[4.5]decane skeleton, the structure of the candidate and its retrosynthetic analysis can be seen below (scheme 1.33).[48]

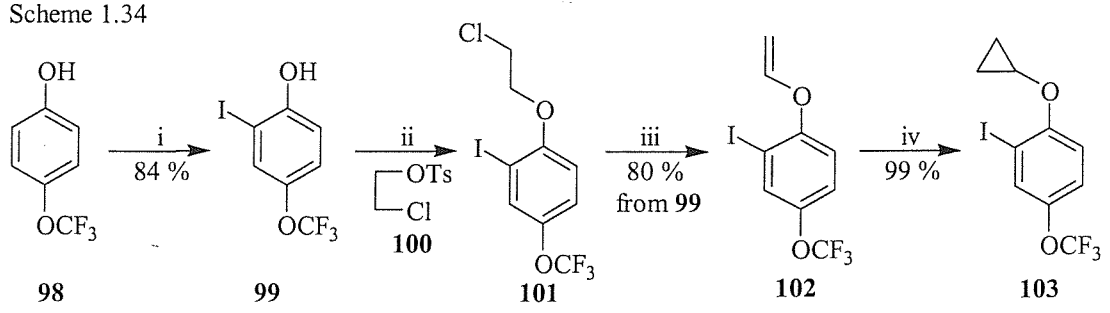
Scheme 1.33



In the retrosynthesis, spiroether **94** is taken back to homoallylic alcohol **95**, which in turn comes from key fragments piperidone **97** and an aryl fragment **96** already bearing the cyclopropoxy function.

In the forward synthesis, piperidone **97** was prepared as the Boc protected derivative according to the method of Harrison *et al.*[49] The synthesis of homoallylic fragment **96** was much less straightforward, commencing with the conversion of commercially available 4-trifluoromethoxyphenol (**98**) to aryl iodide **103** (scheme 1.34).

Scheme 1.34

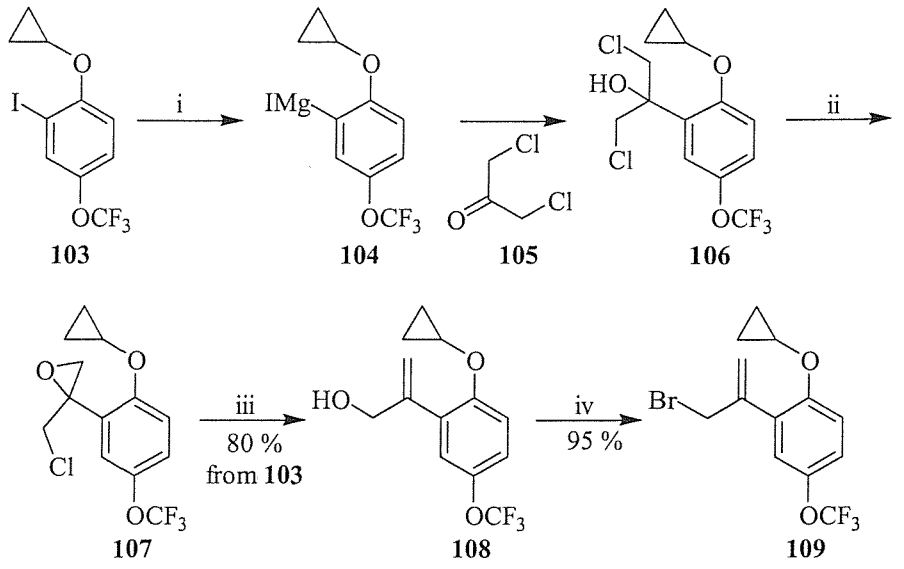


Reagents/conditions: i) I_2, NaI, Me_2NH; ii) K_2CO_3; iii) KO*t*-Bu, THF; iv) Et_2Zn, $ClCH_2I$

Phenol **98** was iodinated with iodine and sodium iodide in good yield to give iodophenol **99**. Deprotonation with potassium carbonate and displacement of aliphatic tosylate **100** gave access to chloroalkane **101**. Treatment with potassium *tert*-butoxide initiated elimination of chloride generating enol ether **102** in 80 % yield over the two

steps. Finally, conversion of the olefin to the cyclopropane was performed in excellent yield using diethylzinc and iodochloromethane, isolating intermediate **103**. With the cyclopropoxy functionality in place, the next step was to install the allylic fragment (scheme 1.35).

Scheme 1.35

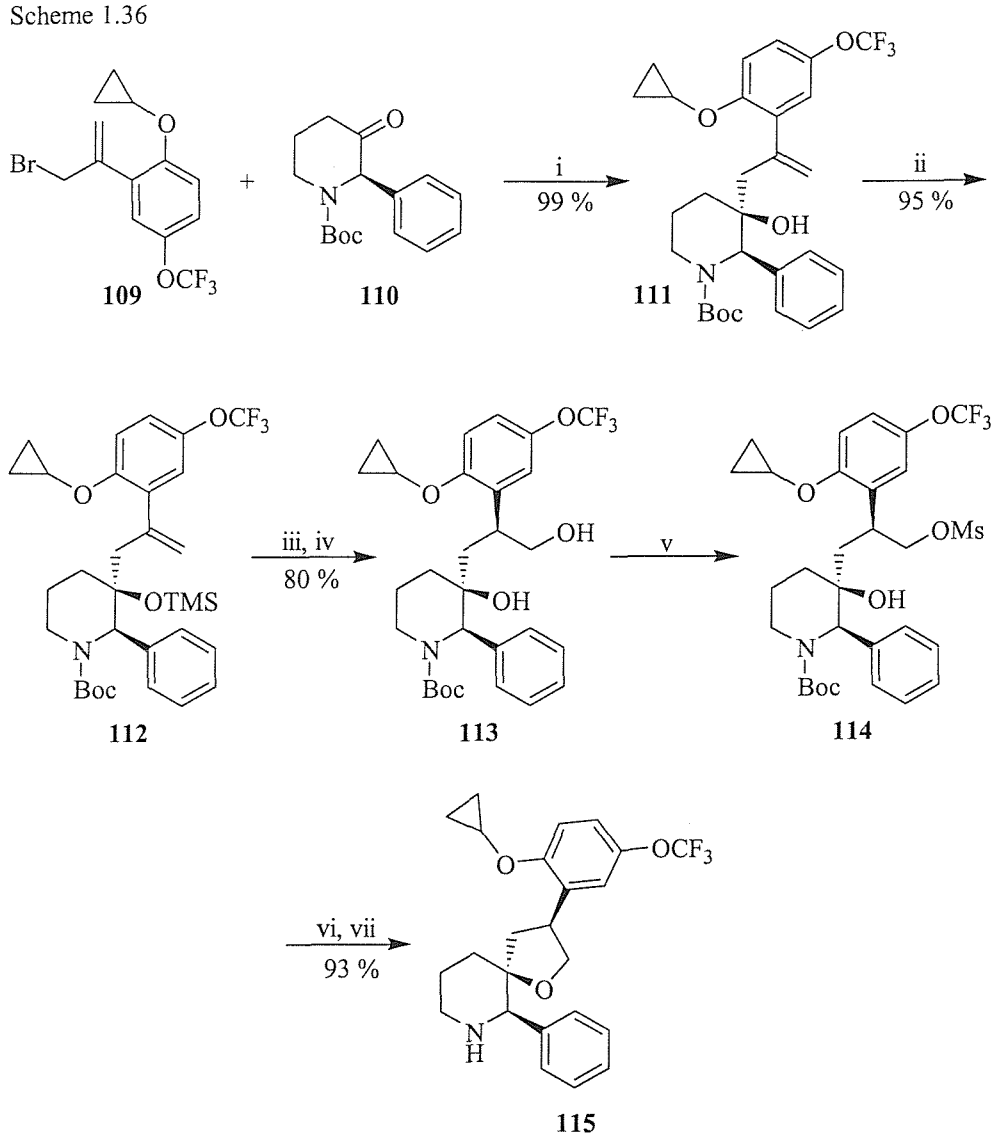


Reagents/conditions: i) Mg, MTBE; ii) KO^t-Bu; iii) LiI, MIBK; iv) PPh_3, Br_2

Aryliodide **103** was converted to the corresponding Grignard reagent with magnesium metal in MTBE and reacted with 1,3-dichloroacetone to generate dichlorohydrin **106**. Deprotonation with potassium *tert*-butoxide caused displacement of chloride to the epichlorohydrin **107**, addition of lithium iodide in MIBK provided alcohol **108** in excellent yield for the four steps. Mixing allylic alcohol **108** with triphenylphosphine and bromine provided entry to allyl bromide **109**.

To complete the synthesis of the drug candidate, a zinc mediated coupling was used to fix the two halves of the scaffold, concluding with a few, simple functional group manipulations. Initial attempts at effecting the coupling with Rieke zinc met with extensive racemisation, so to overcome this, gradual addition to ordinary zinc dust provided intermediate **111** in excellent yield and ee (99 % yield, 98 % ee) (scheme 1.36).

Scheme 1.36



Reagents/conditions: i) Zn, DMF; ii) TMSCl, LiHMDS; iii) BH_3-THF then H_2O_2, aq. NaOH; iv) aq. HF, MeCN; v) MsCl, DIPEA; vi) NaHMDS, THF; vii) HBr, EtOAC

Tertiary alcohol **111** was protected as the TMS ether, and hydroboration of olefin **112** led to a 9:1 mixture of diastereomeric alcohols, the complete purification of which proved difficult. However, careful cleavage of the TMS ether with HF in acetonitrile and simple purification by column chromatography granted diol **113** in excellent yield (80 %) containing <1 % of the minor diastereoisomer. The primary alcohol was then protected as the mesylate and displaced with the tertiary alcohol, using NaHMDS as the base and finally removal of the Boc group with HBr in ethyl acetate provided target **115**. It was discerned that the reaction favoured cyclisation of the correct diastereoisomer, granting a further opportunity for rejection of the remaining undesired

isomeric diol. The major diastereoisomer **115** was isolated in 40 % overall yield from 4-trifluoromethoxyphenol (**98**).

With all this wealth of research as an inspiration, it was our intention to formulate a concise and efficient route to a selection of novel scaffolds with the potential to function as neurokinin receptor antagonists. The decision was made to establish this route around the central notion of incorporating the spiro-piperidine template into the skeleton.

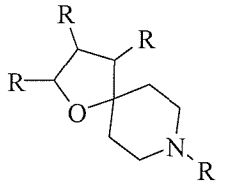
2. Spirocycle Skeleton Generation

2.1 Genesis

In the previous section, it was stated that spiro-piperidine containing systems are considered to be privileged structures for receptor antagonists within the G-protein coupled receptor group.[21,22] Inspired by this and complementary research from various other sources it was our intention to devise a route to analogous spiro-heterocycles, with the potential to act as scaffolds for drug discovery in this area.

The targets devised were based around the central spiro-piperidine unit with attached pendant groups providing diversity into the library. Initially this idea was focussed on a central spiro[4.5]decane skeleton **201** (scheme 2.1).

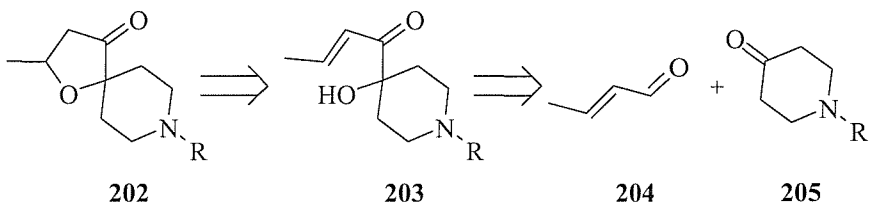
Scheme 2.1



201

A viable retrosynthesis for this system would have to be derived from cheap, commercially available starting materials (scheme 2.2).

Scheme 2.2



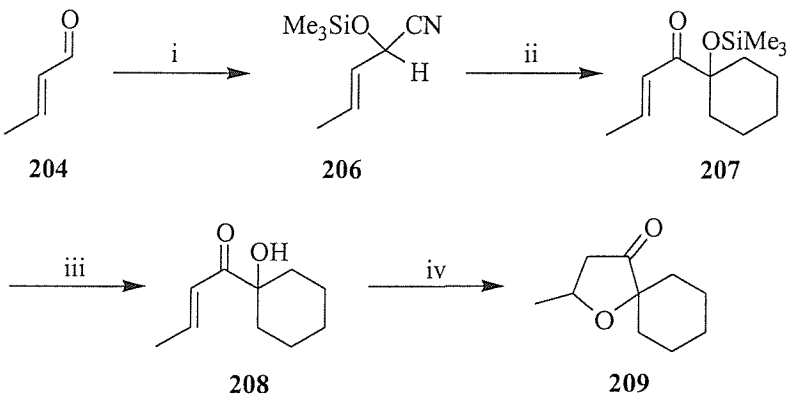
202 **203** **204** **205**

It was envisaged that the ring closure to form spiro-ether **202** could be initiated *via* a cyclisation from the corresponding α,β-unsaturated hydroxyketone **203**. This in turn

could be generated by the addition of some form of acyl anion equivalent **204** to the easily accessible piperidone **205**.

The use of acyl anion equivalents is well documented in the literature.[50-54] Jacobson *et al* have carried out particularly relevant work in the area of acyl anion and homoenolate equivalents, in an attempt to build up a similar basic skeleton to those of the spiro-piperidine targets (scheme 2.3).[55]

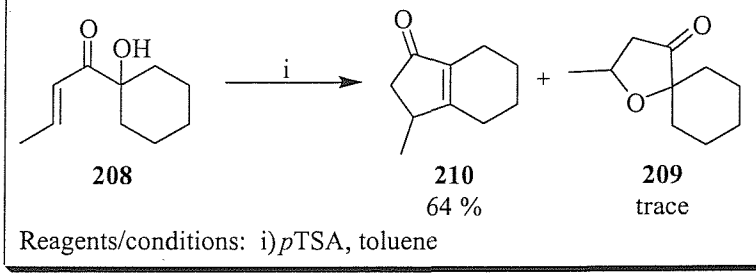
Scheme 2.3



Reagents/conditions: i) TMS-CN, ZnI_2; ii) LDA, cyclohexanone, THF; iii) HCl / THF; iv) *p*TSA, MeOH, PhMe

The spiro-cyclisation to ether **209** was in this case discovered by accident as a side-product of an alternative reaction from previous research within the same group;[56] this concentrated on the formation of cyclopentenones *via* the Nazarov cyclisation.[57] It was ascertained that in cases where there was little or no π-conjugate stabilisation for the intermediate carbocation, a small amount of the furanone was isolated as a by-product in addition to the major Nazarov product **210** (scheme 2.4).

Scheme 2.4



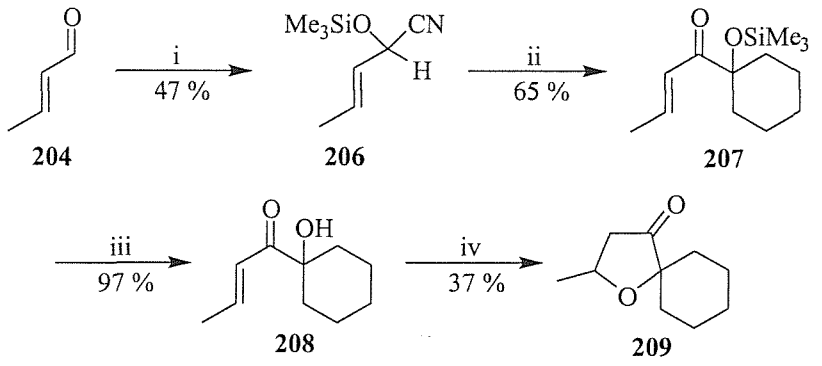
Reagents/conditions: i) *p*TSA, toluene

Baldwin's rules are a set of guidelines for ring closure reactions, and as such dictate which procedures are favoured or disfavoured.[58] The acid-mediated cyclisation shown above is designated as a 5-*endo*-trig process, one of the few disfavoured processes, accounting for the low yield. However, it was decided that the yields for this reaction could potentially be optimised to an acceptable level, so the route was chosen to provide entry to the desired spirocyclic scaffolds.

2.2 Acyl Anion Chemistry

Preliminary forays into this area involved the repetition of the work by Jacobson *et al*, to ensure the reproducibility of the synthesis (scheme 2.5).

Scheme 2.5

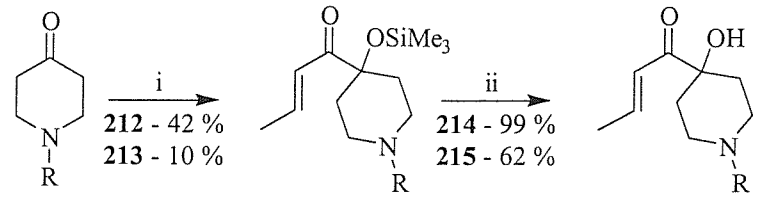


Reagents/conditions: i) TMS-CN, ZnI_2; ii) LDA, cyclohexanone, THF; iii) HCl / THF; iv)*p*TSA, MeOH, PhMe

Commercially available crotonaldehyde (**204**) was converted to its TMS-cyanohydrin with trimethylsilyl cyanide and catalytic zinc iodide in moderate yield (47 %). Deprotonation with lithium diisopropylamide created the acyl anion equivalent and treatment with cyclohexanone resulted in the isolation of TMS-ether **207**. Cleavage of the TMS-ether then gave α-hydroxyketone **208** in excellent yield, the initial acid-mediated cyclisation to the furanone then took place in moderate yield. The optimisation of this critical step was the subject of a great deal of time and effort and will be discussed in depth at a later stage (section 3).

It had now been established that the synthesis was practically viable, the next step was to introduce more functionality into the system, bringing it more in line with the desired spiro-piperidine system. To this end, cyanohydrin **206** was reacted with a selection of simple piperidones, to introduce nitrogen into the skeleton (scheme 2.6).

Scheme 2.6



210 R = CO_2Et
211 R = Ts

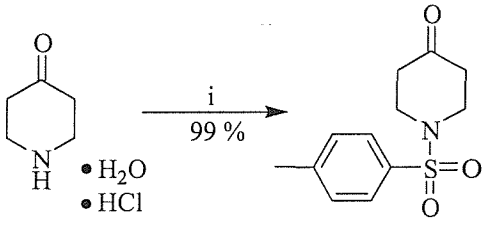
212 R = CO_2Et
213 R = Ts

214 R = CO_2Et
215 R = Ts

Reagents/conditions: i) LDA, THF, **206**, - 78 °C; ii) HCl, THF

Protected cyanohydrin **206** was again deprotonated with lithium diisopropylamide and treated with either commercially available 1-carbethoxy-4-piperidone (**210**) or 1-(toluene-4-sulfonyl)-4-piperidone (**211**), synthesised in excellent yield according to the method of Speckamp *et al* (scheme 2.7).[59]

Scheme 2.7



216 **211**

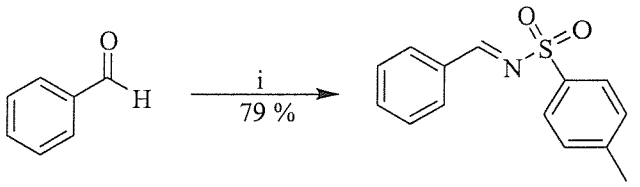
Reagents/conditions: i) TsCl, NEt_3, CH_2Cl_2

Intermediate ethers **212** and **213** were generated in this way in 42 and 10 % yield respectively. Cleavage of the TMS-ether was effected with HCl in THF, delivering the α-hydroxyketone scaffolds in good yield (99 and 62 %). These results showed that protected cyanohydrins could indeed be used to isolate the cyclisation precursors, but the yields for the addition reactions were very poor. Possible explanations for this are

the anion simply not forming or reacting, the ketone being deprotonated by the acyl anion or simple thermal instability. Attempts to overcome these problems involved the idea of transmetallation with anhydrous cerium chloride, the use of which is well documented in the literature as having the effect of dramatically reducing the basicity of an anion without hampering the nucleophilicity.[60-62] Cerium chloride heptahydrate was dried *in vacuo* to generate the anhydrous cerium chloride, a suspension of this in THF was treated with *n*-BuLi and the cyanohydrin Addition of a range of piperidinones to this solution failed to bestow any beneficial effect upon the reaction, and in most cases actually had an adverse effect on the yield.

Many of the designated targets to be synthesised contained more functionality; this could potentially be achieved using the reaction of acyl anions with imines. To investigate this, benzaldehyde (**217**) was condensed with toluene-4-sulfonamide to form *N*-benzylidene-4-toluenesulfonamide **218** in good yield (scheme 2.8).[63,64]

Scheme 2.8

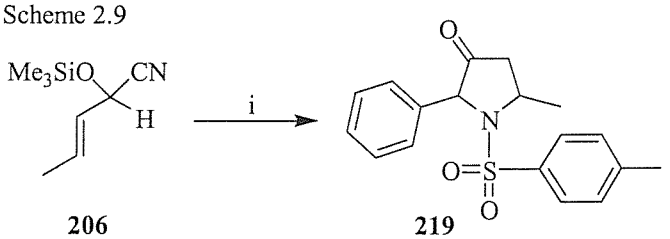


217 **218**

Reagents/conditions: i) toluene-4-sulfonamide, $BF_3 \cdot Et_2O$, PhMe

Protected cyanohydrin **206** was deprotonated with *n*-BuLi and treated with *N*-benzylidene-4-toluenesulfonamide (**218**). It was hoped that not only addition to the imine would be observed, but also a cyclisation leading to amine **219** (scheme 2.9).

Scheme 2.9

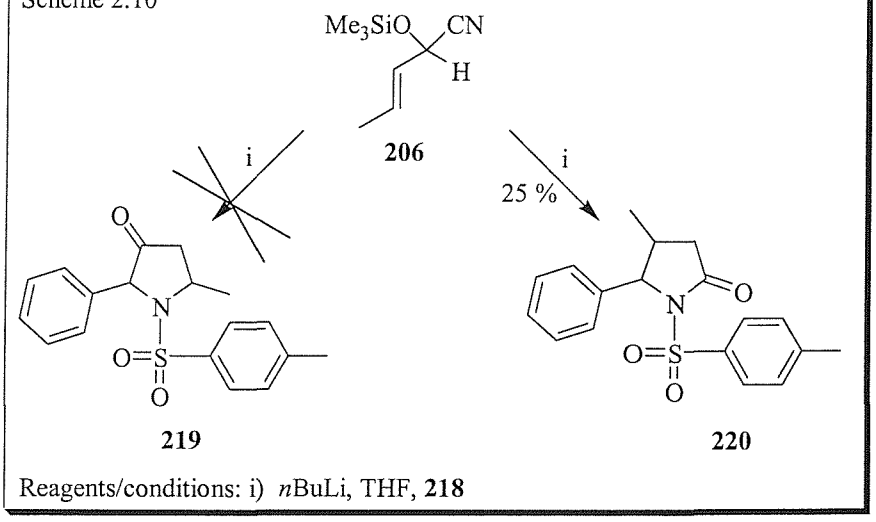


206 **219**

Reagents/conditions: i) *n*-BuLi, THF, **218**

When the reaction was carried out, a white precipitate was recovered the structure of which was tentatively assigned by NMR analysis as being amine **219**. However, further structural elucidation obtained by more in depth spectroscopic techniques, indicated that a cyclised product had indeed been recovered, but the structure was that of lactam **220** not amine **219**. This unexpected result can be explained by the cyanohydrin reacting not as an acyl anion but as a homoenolate equivalent, inducing gamma-addition of the anion to the imine rather than the expected alpha-addition (scheme 2.10).

Scheme 2.10



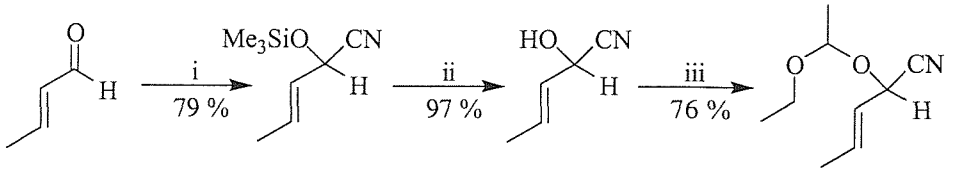
219 **220**

Reagents/conditions: i) *n*BuLi, THF, **218**

It was known that reagent **206** could act as both acyl anion and homoenolate equivalents,[55] but it was hoped that careful modification of the reaction conditions could favour the desired alpha-addition. Attempts at altering the temperature and concentration of the reaction failed however to improve either the selectivity or yield of these reactions. Taking into account both the capricious nature of the reactivity of the anion and the poor yields of the additions, it was decided to instead tailor the reagent to the objectives rather than adapt the conditions to suit the reagent.

Work by Jacobson *et al* stated that replacement of the trimethylsilyl cyanohydrin with an ethoxyethyl equivalent would confer much greater thermal stability to the anion as well as inducing almost exclusive alpha-addition to electrophiles (scheme 2.11).[55]

Scheme 2.11



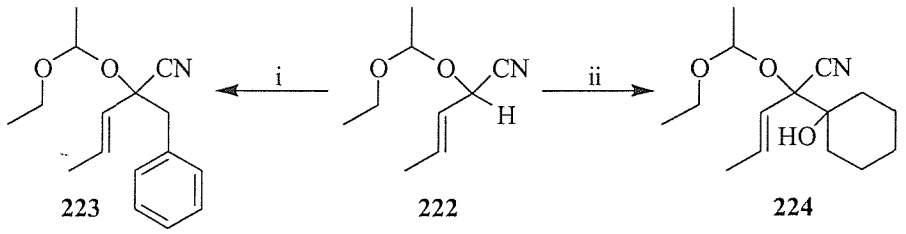
204 **206** **221** **222**

Reagents/conditions: i) TMS-CN, ZnI_2; ii) HCl/THF; iii) ethyl vinyl ether, TFA

Crotonaldehyde (**204**) was treated with trimethylsilyl cyanide as before, generating protected cyanohydrin **206**, this time in good yield. Cleavage of the TMS ether with HCl in THF regenerated the free hydroxyl, which was then re-protected with ethyl vinyl ether and catalytic TFA in excellent yield. An alternative procedure for the synthesis of TMS-protected cyanohydrins was demonstrated by Yoneda *et al*;[65] crotonaldehyde was treated with lithium cyanide (prepared by the method of Livinghouse)[66] and trimethylsilyl chloride, however when this procedure was repeated in the laboratory the reaction proved to be impractical due to both the extreme toxicity of the reagents and the poor yield of the method (32 %).

It was important at this stage to test the reactivity of the new reagent. Ethoxyethyl protected cyanohydrin **222** was reacted with benzyl bromide and cyclohexanone to determine the optimum conditions (scheme 2.12).

Scheme 2.12



223 **222** **224**

Reagents/conditions: i) Base, benzyl bromide, THF; ii) base, cyclohexanone, THF

The reactions were carried out varying the base and temperature, the results can be seen below (table 2.1).

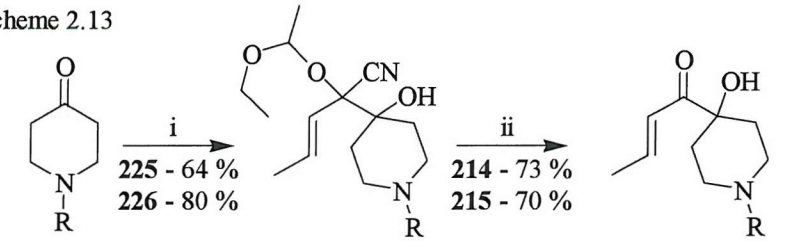
Table 2.1 **Conditions for the Reaction of Cyanohydrin 222**

Conditions		Yield	
Base	**Temperature (°C)**	**Benzyl adduct 223**	**Cyclohexyl adduct 224**
n-BuLi	0	71 %	50 %
n-BuLi	-78	60 %	64 %
LDA	-78	68 %	79 %

It can be seen from table 2.1 that in the case of a simple alkyl halide there was little change in the yield with the varying conditions. However, in the example with cyclohexanone it can be clearly seen that the reaction is favoured when LDA is used to generate the anion, and the method is carried out at -78 °C.

With the specific conditions now in hand, the application of this to more complicated systems became the priority of the research. As with the trimethylsilyl cyanohydrin, reagent **222** was reacted with piperidones **210-211** to generate the α-hydroxyenone intermediates (scheme 2.13).

Scheme 2.13



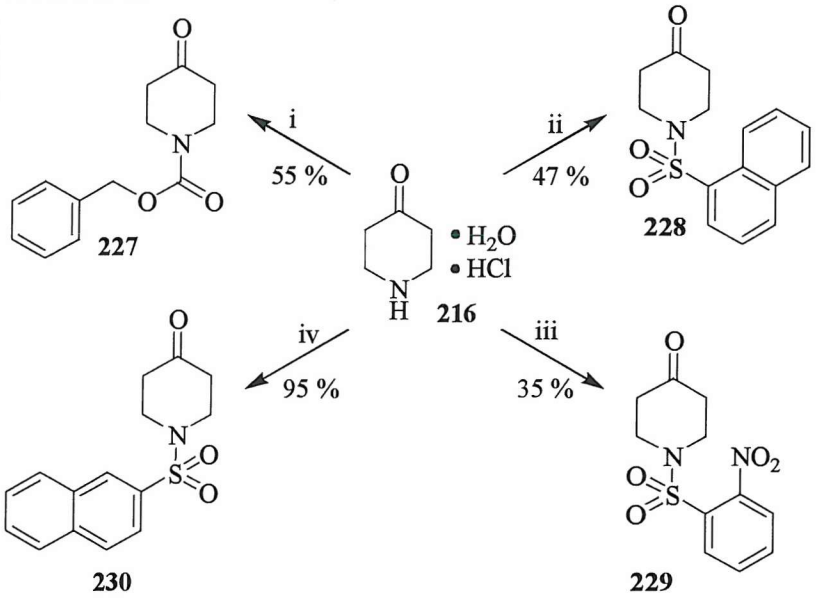
210 R = CO_2Et **225** R = CO_2Et **214** R = CO_2Et
211 R = Ts **226** R = Ts **215** R = Ts

Reagents/conditions: i) LDA, THF, **222**, - 78 °C; ii) H_2SO_4, THF

The acyl anion equivalent was generated using LDA at -78 °C in THF and treated with either carbethoxypiperidone **210** or tosylpiperidone **211**. In each case the respective adduct was isolated in a far superior yield to that obtained with the TMS version, and pleasingly there was no sign of any gamma-addition products in the reaction mixture. Hydrolysis of the ethoxyethyl protecting groups was achieved with sulfuric acid in THF, liberating the free cyanohydrins, which upon basic work-up generated the unsaturated ketones in good yield.

An important point to note at this stage is the protecting groups used for the piperidone nitrogen. It is easy to envisage potential difficulties associated with the removal of both the tosyl and carbethoxy groups. In an effort to prevent this occurring, a further series of piperidones were synthesised with a selection of different protecting groups (scheme 2.14). For more information on protecting groups there are many excellent sources available.[67-70]

Scheme 2.14



Reagents/conditions: i) Benzyl chloroformate, Et_3N, CH_2Cl_2, Na_2SO_4; ii) 1-naphthalenesulfonyl chloride, Et_3N, CH_2Cl_2; iii) NsCl, Et_3N, CH_2Cl_2; iv) 2-naphthalenesulfonyl choride, K_2CO_3, NaOH, H_2O, CH_2Cl_2

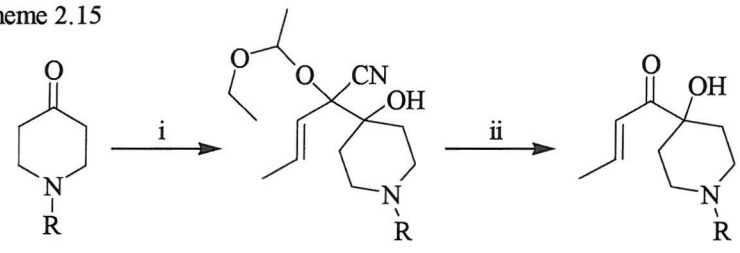
Piperidone **216** was treated with benzyl chloroformate and triethylamine in a highly exothermic procedure, initially failing to provide any product. Optimisation of the reaction led to the generation of CBZ-protected piperidone **227** in average yield.[71] Selected results can be seen below (table 2.2).

Table 2.2 Conditions Tested for the Synthesis of CBZ-Piperidone 227

Electrophile	Base	Additive	Yield
Benzyl chloroformate (2 eq)	Et_3N (2 eq)	-	0 %
Benzyl chloroformate (4 eq)	Et_3N (4 eq)	-	16 %
Benzyl chloroformate (3 eq)	Et_3N (4 eq)	Na_2SO_4 (2 eq)	41 %

Replacement of the benzyl chloroformate with 1-naphthalenesulfonyl chloride (generated in 49 % yield by the method of Zollinger *et al*)[72] or 2-nitrobenzenesulfonyl chloride, in turn provided 1-(naphthalene-1-sulfonyl)-4-piperidone (**228**) and *N*-(2-nitrobenzenesulfonyl)-4-piperidone (**229**) respectively in average yield.[59] In a slight modification to this procedure, piperidone **216** was treated with commercially available 2-naphthalenesulfonyl chloride in a biphasic reaction system, furnishing piperidone **230** in a greatly improved 95 % yield.[73] This new high yielding procedure was paramount in increasing the efficiency of the overall synthesis. The newly synthesised piperidones were reacted with cyanohydrin **222** in the same manner as before (scheme 2.15).

Scheme 2.15



Reagents/conditions: i) LDA, THF, **222**, - 78 °C; ii) H_2SO_4, THF

Cyanohydrin **222** was taken up into THF and treated with a series of piperidones, affording the intermediate alcohols. Hydrolysis of the cyanohydrin to liberate the unsaturated ketone was facilitated with sulfuric acid at reflux and a basic work-up. The yields for the reactions can be seen below (table 2.3).

Table 2.3 Reaction of Cyanohydrin 222 with Piperidones 210-211 + 227-229

Piperidone (protecting group)	Yield of Alcohol	Yield of Enone
210 (ethyl carbamate)	89 % (**225**)	62 % (**214**)
211 (tosyl)	80 % (**226**)	84 % (**215**)
227 (benzyl carbamate)	55 % crude (**231**)	46 % (**234**)
228 (naphthalene-1-sulfonyl)	89 % crude (**232**)	91 % (**235**)
229 (nitrobenzenesulfonyl)	0 % (**233**)	-

N-Carbethoxy-4-piperidone (**210**) was coupled with cyanohydrin **222** in high yield (89 %) and hydrolysed to enone **214** in 91 % yield. Similarly when using *N*-(toluene-4-sulfonyl)-4-piperidone (**211**) as the substrate, the desired adduct was isolated in excellent yield (80 %) and the subsequent deprotection to give enone **215** was also facile. Unfortunately the attempted coupling reaction of cyanohydrin **222** with 1-(2-nitrobenzenesulfonyl)-piperidin-4-one (**229**) failed to furnish any of the desired adduct, possibly due to interaction of the anion with the nitro moiety. Reaction of cyanohydrin **222** with the naphthalene-1-sulfonyl **228** and benzyl carbamate **227** protected piperidones gave products that were extremely difficult to separate from the starting materials. As a result of this it became necessary to undertake hydrolysis of the crude reaction mixtures to simplify purification. For a synthesis to be practical these shortcomings in purification are not acceptable; to overcome this, the work-up procedure for the cyanohydrin addition was modified. Quenching was now achieved at –78 °C with saturated ammonium chloride solution, these more careful controls resulted in much cleaner transformations in each case and far simpler purification, significantly boosting the yields for both the addition reactions and the subsequent hydrolysis (table 2.4).

Table 2.4 **Yields Obtained in the Modified Reaction of Cyanohydrin 222**

Piperidone (protecting group)	Yield of Alcohol	Yield of Enone
210 (ethyl carbamate)	89 % (**225**)	80 % (**214**)
211 (tosyl)	80 % (**226**)	84 % (**215**)
227 (benzyl carbamate)	92 % (**231**)	85 % (**234**)
228 (naphthalene-1-sulfonyl)	92 % (**232**)	91 % (**235**)
229 (nitrobenzenesulfonyl)	0 % (**233**)	-
230 (naphthalene-2-sulfonyl)	80 % (**236**)	86 % (**237**)

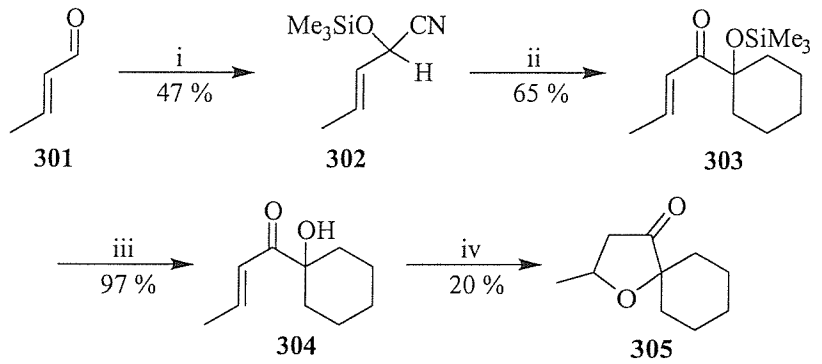
Table 2.4 shows clearly that the yields for the cyclisation precursors had now reached appropriate levels to make the synthesis viable. It was now critically important to devote sufficient time to the cyclisation reaction, in order to enhance the yield to a similar echelon.

3. Spirocycle Generation

3.1 Acid Mediated Ring Closures – Thermal Initiation

The crucial stage in the quest to achieve a library of spiro-piperidines was to be the ring closure reaction. Initial ventures into the area involved an acid-mediated cyclisation in a vastly simplified system (scheme 3.1).

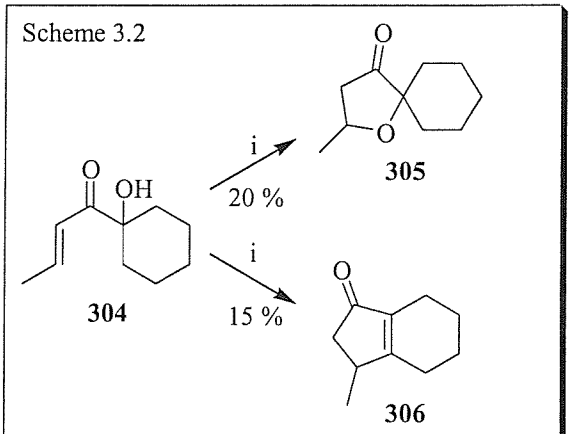
Scheme 3.1



Reagents/conditions: i) TMS-CN, ZnI_2; ii) LDA, cyclohexanone, THF; iii) HCl / THF; iv) *p*TSA, MeOH, PhMe, 8 h

The low yield of the cyclisation to form furanone **305** was further complicated by the presence of a substantial amount of by-product, that of the equivalent Nazarov cyclisation product **306** (scheme 3.2).[57]

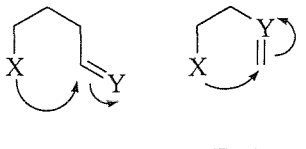
Scheme 3.2



Reagents/conditions: i) *p*TSA, MeOH, toluene

Under the conditions tested the Nazarov cyclisation was in competition with the desired 5-*endo*-trig cyclisation disfavoured by Baldwin's rules. As stated in the previous section, Baldwin's rules are a set of guidelines for the closings of 3- to 7-membered rings.[58,74] This set of rules distinguish two particular types of ring closure, *exo* and *endo*; where *exo* refers to cases where the bond being broken is outside of the ring being formed, and *endo* refers to cases where the bond being broken forms part of the new ring (scheme 3.3).

Scheme 3.3



Exo *Endo*

There are also three further epithets, referring to the hybridisation of the atom that is attacked; tet = sp^3, trig = sp^2 and dig = sp. A summation of the rules is detailed below:

Rule 1:

- 3 to 7-*exo*-tet are all favoured processes
- 5 and 6-*endo*-tet are disfavoured

Rule 2:

- 3 to 7-*exo*-trig are favoured
- 3 to 5-*endo*-trig are disfavoured
- 6 and 7-*endo*-trig are favoured

Rule 3:

- 3 and 4-*exo*-dig are disfavoured
- 5 to 7-*exo*-dig are favoured
- 3 to 7-*endo*-dig are favoured

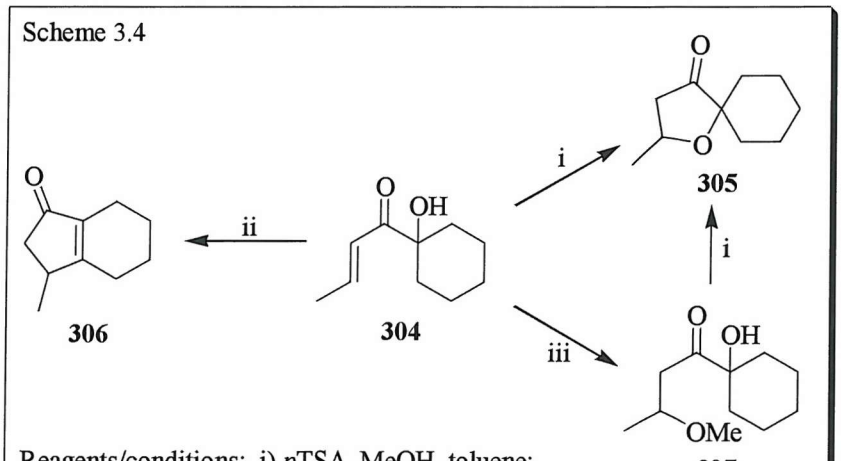
It is important to realise that 'disfavoured' does not mean 'impossible', only that to get the reaction to proceed successfully is much more difficult than in the favoured cases. Logically therefore, with careful manipulation of the reaction conditions, the yield of the 5-*endo*-trig cyclisation illustrated in scheme 3.2 could be significantly increased. With this in mind, the cyclisation to form furanone **305** was heavily optimised; the results from the study can be seen below (table 3.1).

Table 3.1 **Optimisation of Acid-Mediated Cyclisation to Furanone 305**

Reagents/Conditions	Solvent	Major Product
0.2 eq *p*TSA/reflux	Toluene	Pentenone **306**
0.2 eq *p*TSA, 1 eq MeOH/reflux	Toluene	Pentenone **306**
0.2 eq *p*TSA, 2 eq MeOH/reflux	Toluene	Furanone **305**
0.5 eq *p*TSA, 2 eq MeOH/reflux	Toluene	Furanone **305** (37 % yield)
0.2 eq *p*TSA, 4 eq MeOH/reflux	Toluene	Furanone **305**
0.2 eq *p*TSA/reflux	MeOH	Addition product **307**

Pentenone **306** was isolated as the sole product when no methanol was added to the reaction mixture; with one equivalent added the pentenone was still the major product, furanone **305** could now be detected, albeit in low yield (~5-10 %). Increasing the amount of methanol further gave rise to furanone **305** as the major product, however; too much methanol induced the formation of addition product **307** (scheme 3.4).

Scheme 3.4

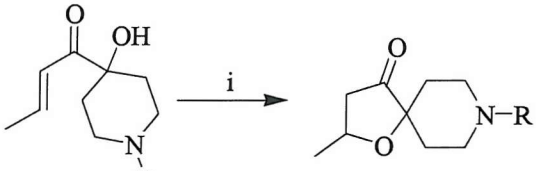


Reagents/conditions: i) *p*TSA, MeOH, toluene;
ii) *p*TSA, toluene; iii) *p*TSA, MeOH

Exposing methanol adduct **307** to the cyclisation conditions initiated conversion to furanone **305**. The logical conclusion to infer from this is that the ring closure proceeds initially by a 1,4-addition of methanol to the unsaturated ketone, with subsequent displacement of methoxide; rather than by the aforementioned 5-*endo*-trig method. However when monitoring the cyclisation of alcohol **307** to furanone **305** by GC, complete elimination of methanol leading to the regeneration of enone **304** is seen to occur before any cyclisation takes place. It was clear that determining the ideal conditions would require careful modification.

The optimum reaction conditions of 0.5 equivalents of tosic acid and 2 equivalents of methanol in toluene at reflux were then used to cyclise the piperidones synthesised in the previous section (scheme 3.5).

Scheme 3.5



308-311 **312-315**

Reagents/conditions: i) *p*TSA, MeOH, PhMe, 16 h

The ring closures to form these furanones proved to be quite capricious; the results can be seen in the following table (table 3.2).

Table 3.2 **Acid-Catalysed Cyclisation of Enone 308-311 to Furanone 312-315**

Furanone (protecting group)	Reagents	Yield
312 (CO_2Et)	0.5 ≡ *p*TSA, 2 ≡ MeOH	63 %
313 (CBZ)	0.5 ≡ *p*TSA, 2 ≡ MeOH	27 %
314 (Ts)	0.5 ≡ *p*TSA, 2 ≡ MeOH	63 %
315 (naphthalene-1-sulfonyl)	0.5 ≡ *p*TSA, 2 ≡ MeOH	40 %

The conversion of the tosyl and ethylcarbamate-protected unsaturated hydroxyketones to their respective furanones occurred in good yield (63 %), but furanone **315** was only

achieved in average yield (40 %) and CBZ protected piperidine **313** in poor yield (27 %).

Previous optimisation had shown that two equivalents of methanol was the optimum quantity to be added; the poor yields exhibited in some of these reactions (particularly that of the CBZ-series) however, meant that it was necessary to invest more time in the cyclisation. This time the amount of acid present in the reactions and the nature of the alcohol added were varied (table 3.3).

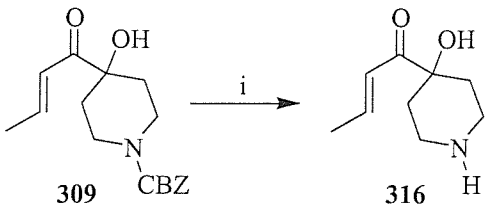
Table 3.3 Optimisation of the Acid-Mediated Cyclisation of CBZ-Hydroxyketone 309

Acid	Alcohol	Yield
0.2 ≡ *p*TSA	2 ≡ MeOH	< 10 %
0.4 ≡ *p*TSA	2 ≡ MeOH	27 %
0.4 ≡ *p*TSA	2 ≡ IPA	26 %
0.4 ≡ CSA	2 ≡ MeOH	< 10 %
1 ≡ *p*TSA	2 ≡ IPA	17 %
1 ≡ *p*TSA	2 ≡ MeOH	18 %

It can be seen from the table above that *p*TSA is a more suitable reagent for the cyclisation than camphor sulfonic acid, also that when the amount of acid added is decreased to only 0.2 equivalents, there is a significant drop-off in the yield. There does not appear to be a drastic difference in the yields of the other examples though, the seemingly universal poor yield for the reaction of the CBZ-enone was puzzling.

A detailed spectral analysis of the reaction mixture from this example provided the answer. As well as the furanone and unreacted starting material, the presence of a significant quantity of deprotected starting material was also detected (scheme 3.6).

Scheme 3.6

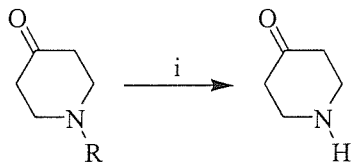


309 316

Reagents/conditions: i) *p*TSA, MeOH, PhMe, reflux

It is known that a CBZ group can be cleaved under strongly acidic conditions, but it was a serious concern that the nitrogen deprotection could also be adversely affecting the cyclisation of the other substrates. To determine whether this protecting group cleavage was taking place in all cases, piperidones **317-321** were all exposed to the ring closure conditions (*p*TSA, MeOH, toluene, reflux) (scheme 3.7).

Scheme 3.7



317-321 **322-326**

Reagents/conditions: i) *p*TSA, MeOH, PhMe, reflux

As expected, the harsh acidic conditions effected cleavage of the CBZ group, but none of the other piperidones were deprotected, confirming the use of the acid-mediated cyclisations could continue. This important result was the last experiment undertaken with the CBZ protected series; instead, focus was shifted to the sulfonyl-protected systems.

Cyclisation of 1-[4-hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (**311**) was further investigated in the same manner illustrated earlier (table 3.3). With camphor sulfonic acid confirmed as unsuitable for this transformation, the amount of acid added to the reaction was varied along with the quantity and nature of the alcohol. Selected results from the study can be seen below (table 3.4).

Table 3.4 **Acid-Mediated Cyclisation of (Naphthalene-1-sulfonyl)-Hydroxyketone 311**

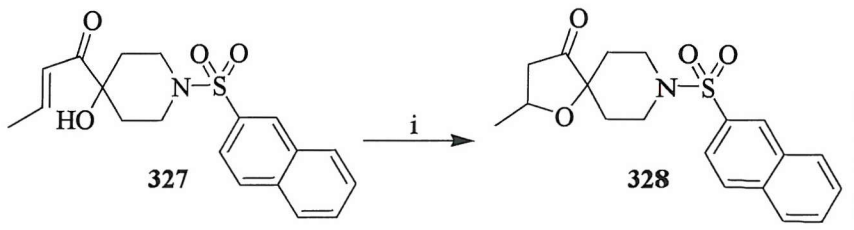
Acid	Alcohol	Yield
0.2 ≡ *p*TSA	2 ≡ MeOH	33 %
0.2 ≡ *p*TSA	2 ≡ IPA	25 %
1 ≡ *p*TSA	2 ≡ MeOH	52 %

It can be discerned from this table that methanol is more suitable for the reaction than isopropyl alcohol, also that the ring closure is more effective with stoichiometric quantities of acid. The yields achieved for the reactions were again not to an acceptable standard for the synthesis though, so a faster way of optimising the cyclisation had to be found.

3.2 Acid Mediated Ring Closures – Microwave Initiation

Microwave reactors are fast becoming one of the most powerful tools available to the organic chemist. They have a tremendous ability to vastly increase the rate of reactions, making them exceptionally expedient when it comes to reaction optimisation and the rapid synthesis of compound collections. In the view of this fact, the acid-mediated furanone formation was investigated utilising a microwave reactor (scheme 3.8).

Scheme 3.8



327 **328**

Reagents/conditions: i) *p*TSA, MeOH, PhMe, microwave

Selected results from the microwave study are detailed below (table 3.5).

Table 3.5 **Microwave Initiated Cyclisation of Enone 327**

Enone (mg)	*p*TSA (eq)	MeOH (eq)	Toluene (mL)	Conditions	Yield (%)	
					Enone	Furanone
20	5	5	2.5	10 min @ 150 °C	14	46
20	5	5	2.5	15 min @ 150 °C	15	45
20	3.5	5	2.5	20 min @ 150 °C	8	53
20	5	5	2.5	20 min @ 130 °C	8	54
20	5	5	4.5	20 min @ 150 °C	24	60
20	5	0	2.5	20 min @ 150 °C	9	24

It can be seen from the table above that the reaction times have been reduced from over 16 hours under thermal conditions, to only 20 minutes with microwave initiation. The most important point to note is that the yields seem to be consistent, and even in the case where no methanol is added there was still a 24 % yield of furanone **328**. Due to the extreme temperatures involved in the reaction, there was a substantial amount of starting material degradation, although where the system is more dilute, the effect is greatly reduced. Keeping all of these factors in mind, converting these microwave-induced conditions to the equivalent thermally initiated reaction should be relatively facile. Indeed that proved to be the case and the ideal conditions are indicated below (table 3.6).

Table 3.6 **Conversion of Microwave-Induced Cyclisation to Thermal Initiation**

Enone (mg)	*p*TSA (eq)	MeOH (eq)	Toluene (mL)	Conditions	Yield (%)	
					Enone	Furanone
500	5	5	50	3 h, reflux	Trace	79
500	5	5	50	5 h, reflux	Trace	91

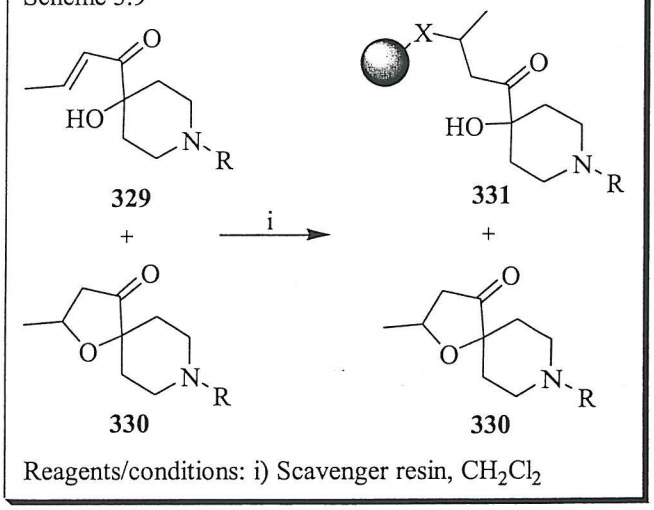
Five equivalents of *p*TSA and methanol and a reaction time of only three hours, granted furanone **328** in an excellent 79 % yield, at the first attempt. Increasing the reaction time to five hours provided the furanone in a superb 91 % yield. Most importantly of all this result was reproducible, meaning that all the steps in the

synthetic pathway could now be achieved in excellent yields. To confirm the nature of the product, an X-ray crystal structure was obtained for furanone **328** (appendix 1).

3.3 Acid Mediated Ring Closures – Reaction Purification

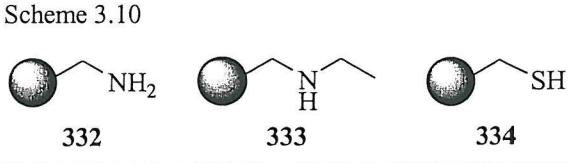
The only problem now remaining with the 5-*endo*-trig cyclisations was the element of purification. Separation of the furanone from the starting unsaturated ketone was extremely problematic by standard chromatographic methods. Many alternative purification procedures were investigated to overcome this, including HPLC methods, recrystallisation, radial chromatography and compound derivatisation. The most facile and convenient to implement though, was the use of a scavenger resin to remove the unreacted starting material (scheme 3.9).

Scheme 3.9



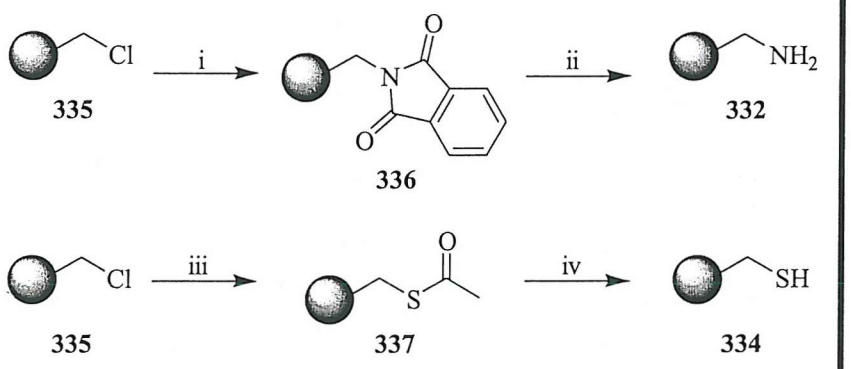
The scavenger resins that were tested for this purpose all shared the structural similarity of a nucleophilic centre to attack the unsaturated ketone, but crucially were all very simple and quick to prepare (scheme 3.10).

Scheme 3.10



Ethylamine resin **333** was available in house without the need for synthesis; aminomethyl polystyrene (**332**) and mercaptomethyl polystyrene (**334**) are both commercially available but expensive, and so were prepared before use. The syntheses can be seen below (scheme 3.11)

Scheme 3.11



Reagents/conditions: i) Potassium phthalimide, DMF; ii) $H_2NNH_2 \cdot H_2O$, EtOH; iii) Potassium thioacetate, DMF; iv) $LiBH_4$, THF, MeOH

Commercially available Merrifield resin (**335**) was coupled with potassium phthalimide in DMF, furnishing phthalimido-resin **336**. Cleavage of the phthalimide protecting group was effected with hydrazine hydrate in ethanol, granting aminomethyl polystyrene (**332**). For the mercapto-resin; Merrifield resin (**335**) was coupled with potassium thioacetate, then reduced with lithium borohydride, providing thiol resin **334**.

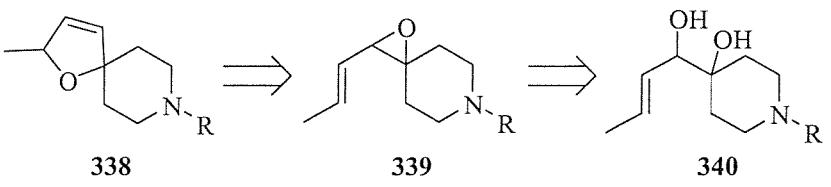
Upon adding the scavenger resins to a solution of furanone and unsaturated ketone, in the majority of cases there was no enone remaining in solution after only 2 hours at room temperature. Cleavage and regeneration of the starting material from the aminomethyl scavenger resin was attempted *via* exhaustive methylation of the amine with subsequent elimination of the unsaturated ketone, and in the case of the thiol scavenger resin, oxidation with mCPBA and subsequent elimination. However, in both cases there was never any successful cleavage of starting material from the resin. Despite this, aminomethyl polystyrene (**332**) proved to be an invaluable reagent for the purification of this step.

With a high yielding entry into spirocyclic systems now available, investigation was undertaken into other possible cyclisation methods.

3.4 Palladium Catalysed Cyclisations

It had been established that spirocycle generation could now be achieved in excellent yield by using the combined approach of acyl anion chemistry and a Baldwin disfavoured acid-mediated cyclisation. However, in the previous section it was reported that the presence of any acid-sensitive functionality in the system prevents the cyclisation reaction from occurring to any satisfactory degree. As an alternative to the acid-mediated step, a route to these spirocyclic systems was devised using a palladium-catalysed cyclisation (scheme 3.12).

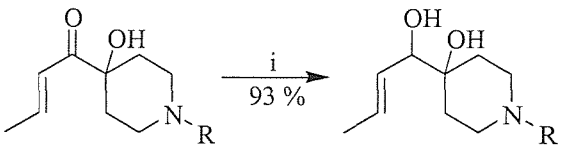
Scheme 3.12



338 **339** **340**

In the retrosynthesis, spirocycle **338** is taken back to allylic epoxide **339**, it was hoped that ring opening of the epoxide and cyclisation onto the pendant olefin could be instigated using palladium chemistry, for which there was literature precedent.[75-77] Epoxide **339** could in turn be generated from diol **340**, *via* an internal displacement reaction. In the forward synthesis, α-hydroxyenones **309** and **311** were first converted to the corresponding diols in excellent yield *via* a Luche reduction (scheme 3.13).[78,79]

Scheme 3.13



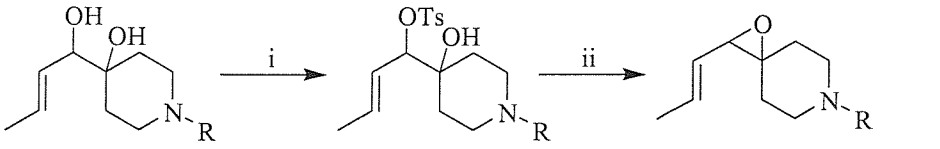
309 R = CBZ
311 R = SO_2Naphth(1)

341 R = CBZ
342 R = SO_2Naphth(1)

Reagents/conditions: i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$

To create the epoxides, the diols were treated with tosyl chloride in an attempt to tosylate the secondary alcohol. This could then be treated with base to cause a displacement of the tosylate with the vicinal tertiary alcohol (scheme 3.14).

Scheme 3.14



341 R = CBZ
342 R = SO_2Naphth(1)

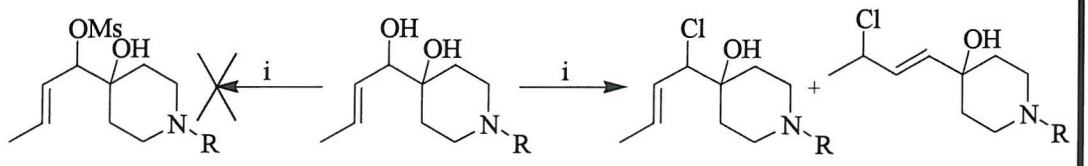
343 R = CBZ
344 R = SO_2Naphth(1)

345 R = CBZ
346 R = SO_2Naphth(1)

Reagents/conditions: i) TsCl, Et_3N, CH_2Cl_2; ii) Base

Upon treatment of diols **341-342** with tosyl chloride however, there was no observable reaction, presumably due to steric congestion. In an attempt to increase the reactivity, tosyl chloride was exchanged for trifluoromethanesulfonic anhydride, however the use of this highly reactive reagent led only to degradation of the starting material. Replacement of the tosyl chloride in the reaction with methanesulfonyl chloride proved to be more successful, however the products isolated from the reaction were not the desired mesylates (scheme 3.15).

Scheme 3.15



347-348 **341-342** **349-350** **351-352**

Reagents/conditions: i) MsCl, Et_3N, CH_2Cl_2; ii) Base

Rather than isolating the necessary mesylates, the only products from the reaction were the unstable allylic chlorides **349-352**, the formation of which can be explained by initial mesylation with subsequent displacement by chloride in either an S_N2 or S_N2^* fashion. The yields of the reactions are shown below (table 3.7).

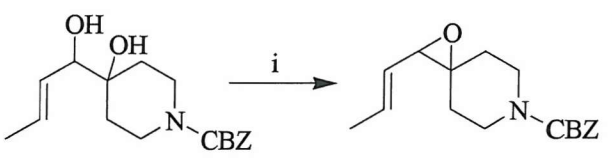
Table 3.7 Yields for Formation of Allylic Chlorides 349-352

Diol (protecting group)	Yield (%)		
	Recovered Diol	349-350	351-352
341 (CBZ)	46	15	32
342 (naphthalene-1-sulfonyl)	75	Trace	13

The low yields of the reaction go some way towards bestowing an idea of the poor reactivity of the neopentyl alcohol.

It had become clear from the attempted displacement reactions that the synthesis of epoxide **345-346** would not be achieved in this fashion. As an alternative, epoxide formation was attempted using an internal Mitsunobu reaction (scheme 3.16).

Scheme 3.16

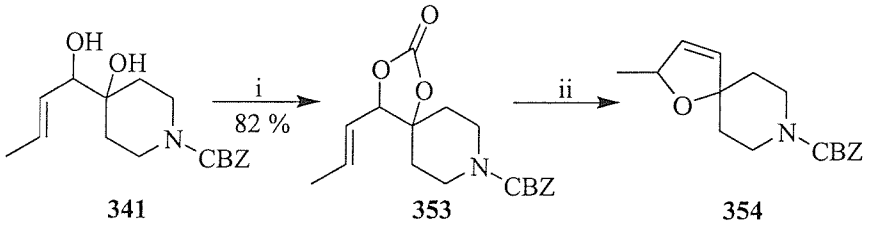


341 **345**

Reagents/conditions: i) PPh_3, DEAD, Et_3N, THF

Unfortunately, this procedure also failed to provide any of the epoxide for use in the attempted palladium-catalysed cyclisations. In the literature there was precedent for allylic carbonates acting as internal nucleophiles in palladium chemistry.[80,81] Based on this, diol **341** was converted to the allylic carbonate (scheme 3.17).

Scheme 3.17

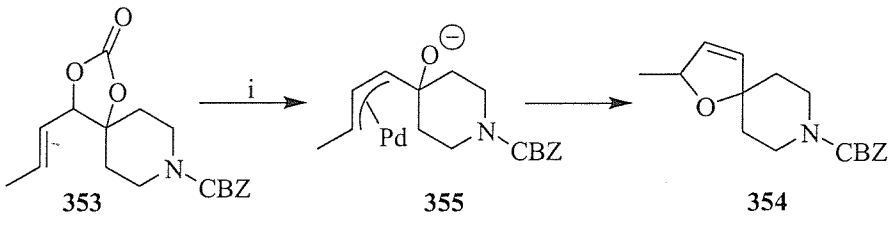


341 **353** **354**

Reagents/conditions: i) CDI, CH_2Cl_2; ii) "Pd"

CBZ-Protected diol **341** was reacted with dimethylcarbonate and sodium methoxide in methanol, furnishing carbonate **353** in moderate yield (56 %). In an improved procedure, treatment with carbonyldiimidazole in CH_2Cl_2 provided allylic carbonate **353** in 82 % yield. A substrate was now in hand with the potential to yield epoxide **354** in a palladium cyclisation, the idea being that formation of a π-allyl palladium complex would ring-open the carbonate, liberating carbon dioxide and allowing the nascent alkoxide to close back onto the palladium complex (scheme 3.18).

Scheme 3.18



353 **355** **354**

Reagents/conditions: i) $Pd_2(dba)_3{\cdot}CHCl_3$, DPPE, THF

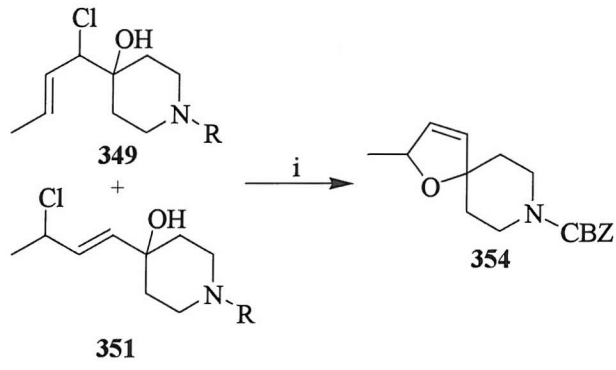
The palladium cyclisation was attempted on carbonate **353**, using a range of catalysts and ligands. Selected results from this study are summarised below (table 3.8).

Table 3.8 **Study into the Palladium-catalysed Cyclisation of Allylic Carbonate 353**

Catalyst	Ligand	Solvent	Yield (%)
$Pd(PPh_3)_4$	DPPE	THF	0
$Pd(PPh_3)_4$	DPPF	THF	0
$Pd_2(dba)_3{\cdot}CHCl_3$	DPPE	THF	0
$Pd_2(dba)_3{\cdot}CHCl_3$	DPPE	PhMe	0
$Pd_2(dba)_3{\cdot}CHCl_3$	DPPF	THF	0

Despite the best efforts of varying catalyst, ligand, solvent and temperature of the reaction, it was not possible to effect any cyclisation to form spirocycle **354**. In all cases, only unreacted starting material was recovered from the reactions. It was however hoped that the unstable allylic chlorides synthesised previously could also potentially cyclise under the same conditions to form spiro-ether **354** (scheme 3.19).

Scheme 3.19



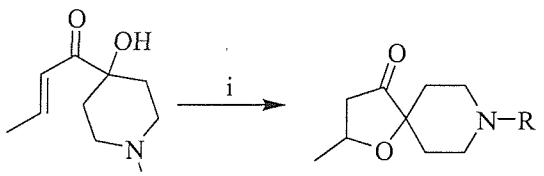
Reagents/conditions: i) $Pd_2(dba)_3{\cdot}CHCl_3$, DPPE, THF

Allylic chlorides **349** + **351** were exposed to the same reaction conditions as detailed for the previous attempted cyclisation. Unfortunately, none of the desired spiro-ether **354** was isolated from the reaction mixture, the only compounds isolated being degradation products from the unstable allylic chlorides.

3.5 Alternative Cyclisation Pathways

In a final attempt to discover a substitute for the acid-mediated 5-*endo*-trig cyclisation, efforts were focussed on alternative ways to initiate the same transformation (scheme 3.20).

Scheme 3.20



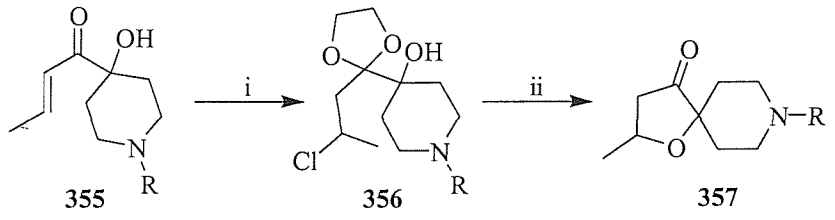
308-311 **312-315**

Reagents/conditions: i) Lewis Acid

The first option was to replace the Brönsted acid with a Lewis acid. To this end, the synthesis was attempted with a large selection of Lewis acids present in the reaction mixture to initiate cyclisation. However, regardless of the nature of the Lewis acid used, no cyclisation to the furanone occurred.

Another method was to derivatise the olefin to an alkyl halide, then close the ring by a simple S_N2 displacement (scheme 3.21).[82]

Scheme 3.21



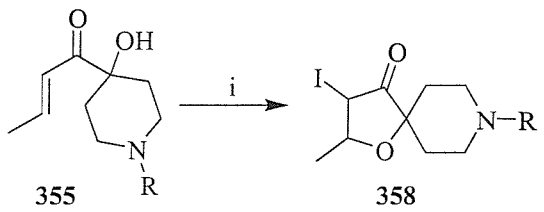
355 **356** **357**

Reagents/conditions: i) $HOCH_2CH_2OH$, TMS-Cl; ii) Base then hydrolysis

The first attempt was unsuccessful, and despite subtle alterations to the synthesis, it remained impossible to isolate any of ketal **356** from the reaction. The starting material was recovered unreacted with a small amount of degradation products. For a

final option, there was substantial literature precedent for 5-*endo*-trig iodocyclisations of homoallylic alcohols (scheme 3.22).[83,84]

Scheme 3.22



355 358

Reagents/conditions: i) I_2, $NaHCO_3$

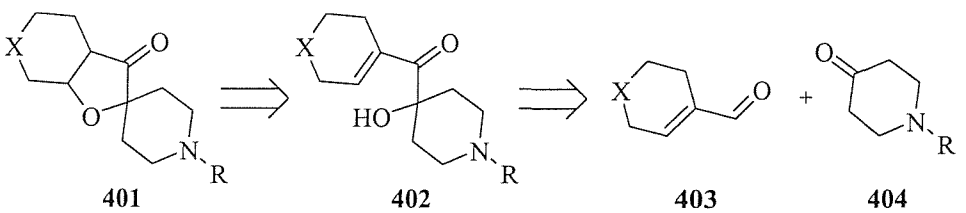
Regardless of the wealth of literature precedent for this transformation, using the conditions given it was not possible to achieve the iodocyclisations; once again, the starting material was recovered unreacted. The possibility of devising an alternative cyclisation method was still a reality, but the priority was to derivatise the spirocyclic systems.

4. Spirocycle Derivatisation

4.1 Tricyclic Systems

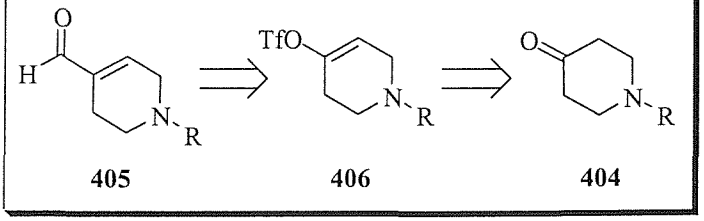
It has been shown that a spirocyclic skeleton can be easily built-up using the chemistry of cyanohydrins. This approach would appear to be ideal for bicyclic systems, but with subtle modifications to the procedure, it may be possible to expand the scope of the synthesis to include tricyclic systems. With this target in mind, a retrosynthesis was devised based on the original bicyclic target (scheme 4.1).

Scheme 4.1



Furanone **401** can be disconnected in the same manner as per the bicycle to give unsaturated ketone **402**; this ring would be closed using the 5-*endo*-trig cyclisation developed previously. Using the acyl anion chemistry, aldehyde **403** would be converted to its cyanohydrin and coupled with piperidone **404**, generating intermediate alcohol **402**. It was envisaged that α,β-unsaturated aldehyde **403** could be synthesised from piperidone **404** creating an elegant, convergent synthesis (scheme 4.2).

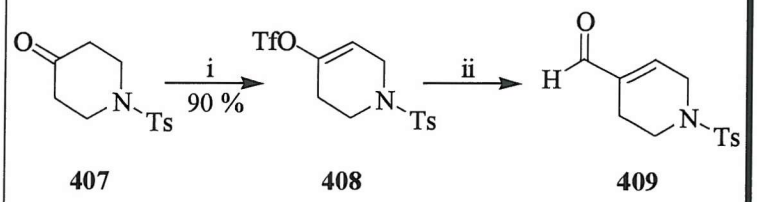
Scheme 4.2



Formation of aldehyde **405** can be initiated using a carbonylation reaction from the corresponding enol triflate **406** or vinyl halide.[85,86] The obvious disconnection is to

take the enol triflate back to ketone **404**, enabling both halves of the compound to be created from a common starting material (scheme 4.3).

Scheme 4.3



407 **408** **409**

Reagents/conditions: i) Tf_2O, di-*t*-butylpyridine, CH_2Cl_2; ii) "Pd"

(Toluene-4-sulfonyl)-4-piperidone (**407**) was transformed to enol triflate **408** using trifluoromethanesulfonic anhydride and 2,6-di-*t*-butylpyridine in CH_2Cl_2 in excellent yield. However, the attempted carbonylation of enol triflate **408** with carbon monoxide and a range of palladium catalysts and ligands proved to be much more problematic. Initial attempts to generate the aldehyde using $Pd(OAc)_2$ with DPPP as the ligand and triethylsilane as the hydride source proved to be unsuccessful; introducing variation in the amount of base and triethylsilane, as well as changing the rate of addition had no effect. Kotsuki *et al* have demonstrated vastly increased yields of carbonylated products when utilising DPPF and trioctylsilane in place of DPPP and triethylsilane. Therefore, carbonylation of enol triflate **408** was attempted using these reagents (table 4.1).[87]

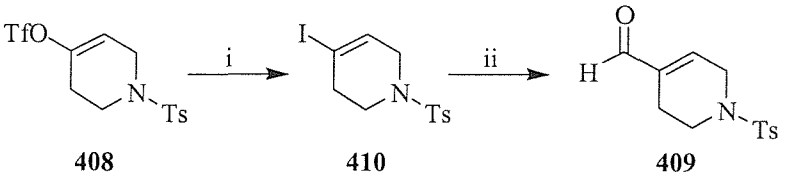
Table 4.1 **Palladium Catalysed Carbonylation of Enol Triflate 408**

Catalyst	Ligand	Base	Hydride source	Yield
$Pd(OAc)_2$ (5 mol %)	DPPP	Et_3N	Et_3SiH (2 eq)	0 %
$Pd(OAc)_2$ (5 mol %)	DPPF	Et_3N	Oct_3SiH (2 eq)	0 %
$Pd(PPh_3)_4$ (5 mol %)	DPPP	Et_3N	Et_3SiH (2 eq)	0 %
$Pd(PPh_3)_4$ (5 mol %)	DPPF	Et_3N	Oct_3SiH (2 eq)	0 %
$Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %)	DPPP	Et_3N	Et_3SiH (2 eq)	0 %

Even with the range of catalysts used for the carbonylation there was no product obtained from the reaction, only recovered starting material and trace quantities of reduced starting material (with a hydride replacing the triflate). It was hoped however,

that aldehyde **409** could still be accessed from enol triflate **408**; attempts were made to lithiate the corresponding vinyl iodide and react the resulting vinyl lithium with DMF (scheme 4.4).[88]

Scheme 4.4



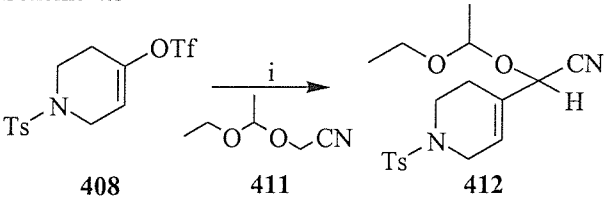
408 **410** **409**

Reagents/conditions: i) I_2, C_6H_{12}, Et_3N or NaI, TMS-Cl, CH_2Cl_2; ii) *n*-BuLi, DMF, THF

It was attempted to generate vinyl iodide **410** *via* the reaction of enol triflate **408** with sodium iodide or trimethylsilyl iodide. Unfortunately however, it did not prove possible to isolate any vinyl halide; the only compounds obtained from the reaction were recovered starting material and numerous degradation products.

The use of aryl or vinyl triflates in palladium-catalysed coupling reactions is well documented.[86,89-92] In one area of particular interest, Uno *et al* have shown cyanoacetates to be excellent reagents for these coupling reactions.[93] In a similar manner, the idea was conceived that perhaps cyanohydrin **412** could be accessed directly *via* a palladium-catalysed organozinc coupling of enol triflate **408** with cyanohydrin **411** (scheme 4.5).[94]

Scheme 4.5

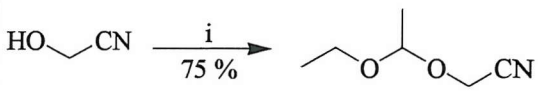


408 **411** **412**

Reagents/conditions: i) "Pd", base, THF

Commercially available glycolonitrile (**413**) was protected with ethyl vinyl ether in the presence of catalytic trifluoroacetic acid granting cyanohydrin **411** in 75 % yield (scheme 4.6).

Scheme 4.6



413 **411**

Reagents/conditions: i) TFA, ethyl vinyl ether

Ethoxyethyl protected glycolonitrile **411** was then subjected to a range of coupling conditions with enol triflate **412**, the results of which are summarised in the following table (table 4.2).

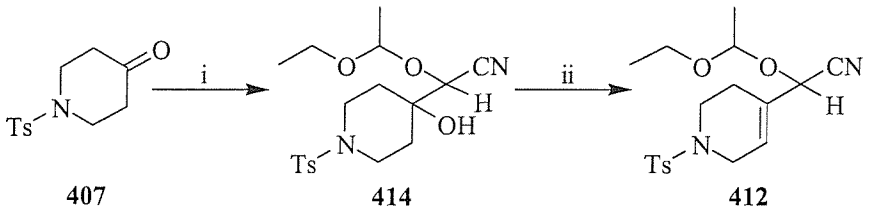
Table 4.2 Palladium-Catalysed Coupling of Enol Triflate 412 with Cyanohydrin 411

Catalyst	Base	Temperature (°C)	Yield
$Pd(PPh_3)_4$ (5 mol %)	*n*-BuLi/$ZnCl_2$ (1.5 eq)	-78 → 0	0 %
$Pd(PPh_3)_4$ (5 mol %)	*n*-BuLi/$ZnCl_2$ (1.5 eq)	-78 → 0	0 %
$Pd(OAc)_2$ (5 mol %)	*t*-BuOK (1.5 eq)	0 → Reflux	0 %
$Pd(OAc)_2$ (5 mol %)	*t*-BuOK (1.5 eq)	0 → Reflux	0 %
$Pd(OAc)_2$ (5 mol %)	*t*-BuOK (1.5 eq)	0 → Reflux	0 %

Each experimental procedure was carried out with a number of repetitions, but on every occasion, the starting triflate **408** was recovered unreacted. Interestingly none of cyanohydrin **411** could ever be detected, NMR analysis indicated that dimerisation of this reagent had occurred.

It was still hoped that cyanohydrin **411** could be used to generate the desired product. The possibility existed that addition of cyanohydrin **411** to tosylpiperidone **407** providing alcohol **414**, followed by elimination would grant the desired product **412** (scheme 4.7).

Scheme 4.7



407 414 412

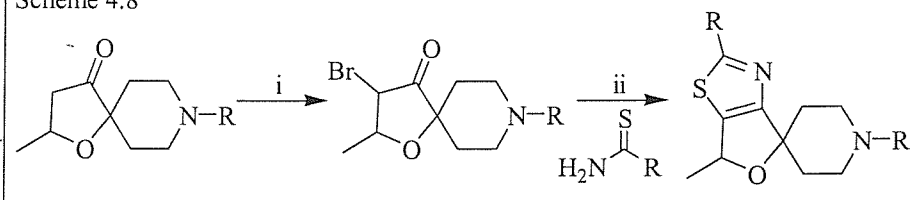
Reagents/conditions: i) **411**, LDA, THF, -78 °C; ii) elimination

The reaction was conducted using the conditions described above, however again none of the desired product was isolated. As perhaps may be expected from previous results, under the basic reaction conditions cyanohydrin **411** had once again reacted with itself. It was decided at this point to change the approach slightly and investigate the derivatisation of the spirocyclic skeleton, in an attempt to introduce more diversity into the system.

4.2 Heterocycle Formation

The presence of a thiazole moiety has been known in the structures of many natural products with important antibiotic properties for several years. The synthesis of thiazoles is known as the Hantzsch synthesis and is an excellent way of introducing such a heterocyclic structure into a compound.[95-101] Bromination of the spirocycle alpha to the ketone and reaction with a substituted thioamide or thiourea should allow the inclusion of a thiazole or aminothiazole into the scaffold (scheme 4.8).

Scheme 4.8



415 416 417 418

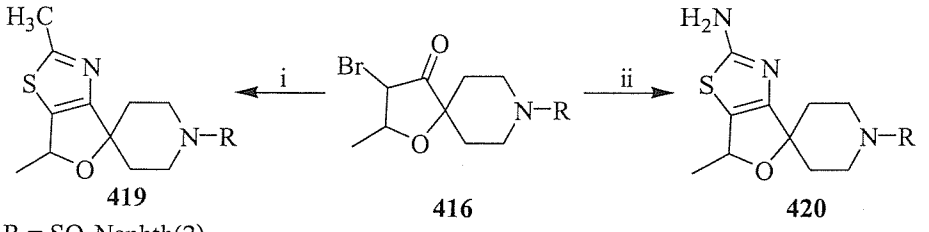
R = SO_2Naphth(2)

Reagents/conditions: i) $CuBr_2$, EtOAc; ii) $NaHCO_3$, DME

Deprotonation of furanone **415** with LDA and Bromination with *N*-bromosuccinimide granted bromide **416** but only in poor yield (23 %). Replacing NBS with phenyltrimethylammonium tribromide increased the yield to a more respectable 64 %, but the reaction proved capricious and the results were not reproducible. In an effort to find a more reliable method, furanone **415** was brominated with cupric bromide in ethyl acetate in a moderate but consistent yield (32 %), a small amount of the geminal dibromide **416a** (10 %) was also isolated.

Bromide **416** was then reacted with thioacetamide and thiourea with a view to granting the thiazole and aminothiazole (scheme 4.9).

Scheme 4.9



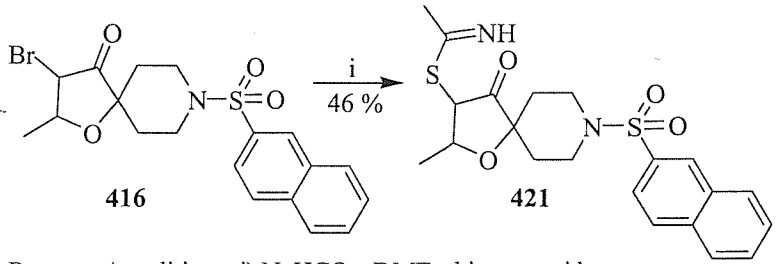
419 **416** **420**

R = SO_2Naphth(2)

Reagents/conditions: i) $NaHCO_3$, DME, thioacetamide; ii) $NaHCO_3$, DME, thiourea

Unfortunately, the products from the reactions were not what were expected; the condensation with thioacetamide gave an acyclic product rather than the expected heterocycle (scheme 4.10).

Scheme 4.10



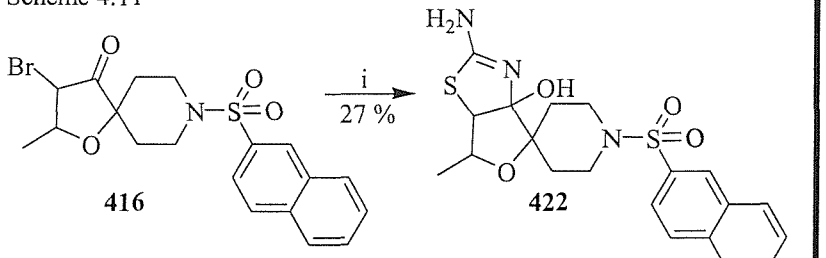
416 **421**

Reagents/conditions: i) $NaHCO_3$, DME, thioacetamide

Displacement of the bromide occurred successfully, however, closure onto the ketone did not transpire. Instead imine **421** was isolated in average yield as the only product from the reaction; efforts at inducing cyclisation of the imine onto the ketone proved

fruitless, despite a range of stringent conditions. It was hoped the reaction using the more nucleophilic thiourea would display improved results (scheme 4.11).

Scheme 4.11



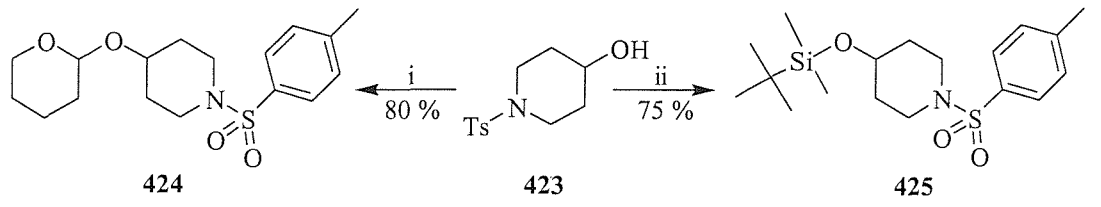
Reagents/conditions: i) $NaHCO_3$, DME, thiourea

Bromide displacement again occurred as expected and this time cyclisation onto the ketone moiety was successful. However, elimination of alcohol **422** to grant aminothiazole **420** was not achievable. Varieties of reaction conditions were investigated in an effort to effect formation of the desired heterocycle, but all met with no success. The decision was made at this juncture, to instead concentrate on the deprotection and derivatisation of the piperidine nitrogen and the carbonyl group of furanone **415**, with a view to further structural elaboration.

4.3 Piperidine Deprotection

To derivatise furanone **415** at the piperidine nitrogen centre, it was first necessary to establish a high-yielding means of effecting the sulfonyl deprotection. Rather than waste valuable furanone material on an initial deprotection study, piperidinol **423** (previously synthesised within the group) was coupled with orthogonal protecting groups to serve as the substrate for this study (scheme 4.12).

Scheme 4.12

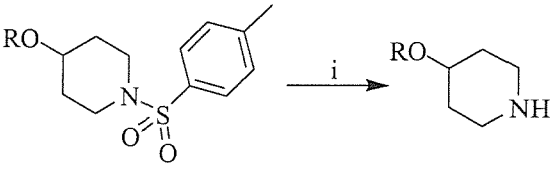


424 **423** **425**

Reagents/conditions: i) DHP, *p*TSA, CH_2Cl_2; ii) TBS-Cl, imidazole, CH_2Cl_2

Alcohol **423** was transformed into THP ether **424** with dihydropyran and toluene-4-sulfonic acid in excellent yield (80 %), protection as the TBS-ether was facilitated using TBS-Cl and imidazole in good yield (75 %). There are many ways of effecting the removal of a tosyl group, but one way that attracted particular interest due to the relatively mild conditions was the use of magnesium metal in methanol (scheme 4.13).[102-105]

Scheme 4.13



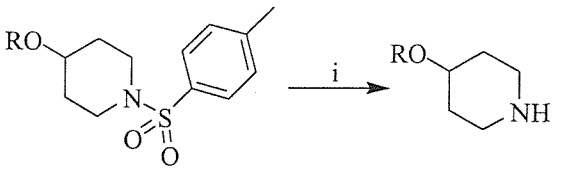
424/425 **426/427**

Reagents/conditions: i) Mg^0, MeOH, NH_4Cl

The sulfonamides were taken up into methanol and treated with magnesium metal and ammonium chloride at room temperature, reflux, and with sonication at various concentrations, but no reaction of any kind was observed. This was disappointing, especially with the vast literature precedent favouring the reaction; as an interesting alternative the use of TBAF to effect the same deprotection on THP-ether **424** was appealing due again to the mild nature of the reagent.[106] Reaction of THP-protected alcohol **424** with TBAF resulted in no reaction however, and the starting material was recovered unchanged.

In a more forcing approach, there was literature precedent for desulfonation being initiated with trimethylsilyl iodide (scheme 4.14).

Scheme 4.14

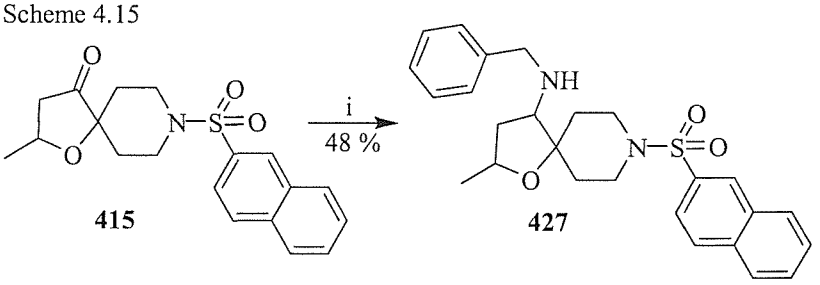


424 **426**

Reagents/conditions: i) TMS-Cl, NaI, CH_3CN, 4 h

There was some concern that this more stringent reagent could cause deprotection of the hydroxy centre rather than the desired piperidine nitrogen. To overcome this, and to ensure that deprotection could be facilitated on a more useful structure, furanone **415** was converted to the corresponding benzylamine in a reductive amination procedure (scheme 4.15).[107]

Scheme 4.15

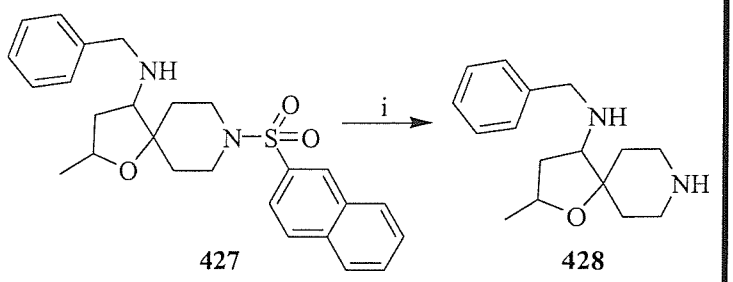


415 **427**

Reagents/conditions: i) Benzylamine, $NaB(OAc)_3H$, DCE, AcOH

Furanone **415** was taken up into 1,2-dichloroethane and reacted with benzylamine and sodium triacetoxyborohydride in the presence of acetic acid, providing amine **427** as a mixture of diastereoisomers (~50:50) in moderate yield (48 %). The desulfonation of amine **427** was then attempted with trimethylsilyl iodide in acetonitrile (scheme 4.16).

Scheme 4.16



427 428

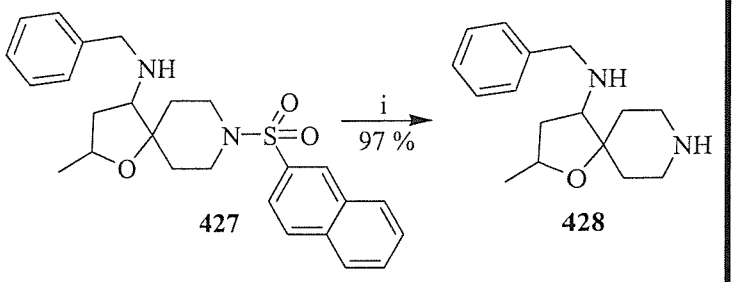
Reagents/conditions: i) TMS-Cl, NaI, CH_3CN, reflux, 4 h

Reaction of amine **427** with trimethylsilyl iodide unfortunately failed to yield any diamine. Instead, unreacted starting material was recovered along with a number of degradation products.

Perhaps a more widely recognised method of effecting desulfonation of sulfonamides is the use of aluminium or sodium amalgam. Aluminium foil was mixed with an aqueous solution of mercuric chloride, generating the aluminium amalgam; this was added to amine **427** however no reaction arose. In a similar vein, mercury was treated with sodium to create sodium amalgam; when reacted with amine **427** however, there was again no reaction.

In a final attempt at nitrogen deprotection, amine **427** was treated with sodium naphthalenide (scheme 4.17).

Scheme 4.17



427 428

Reagents/conditions: i) Na^0, naphthalene, DME

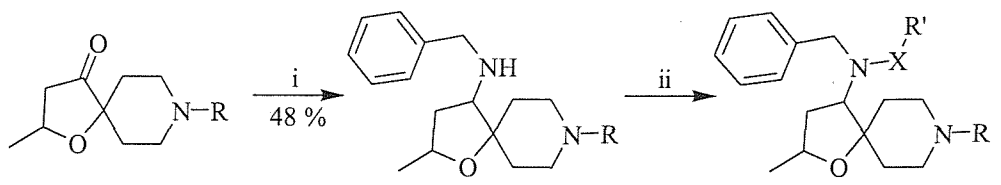
Initial attempts at this method provided diamine **428** in only poor yield (17 %); increasing the equivalents of the sodium naphthalenide and the length of the reaction,

dramatically enhanced the yield to an excellent 97 %. This was a very pleasing result and meant that it was now possible to derivatise the scaffolds at this position, bestowing the potential for library generation.

4.4 Ketone Derivatisation

The synthesis of furanone **415** and the subsequent nitrogen deprotection had now been sufficiently optimised as to provide a concise and high-yielding entry to spirocyclic systems. The major goal of this research though, was to be able to derivatise the furanone substructure in order to create libraries. It was decided that this would initially be attempted by improving the reductive amination of the ketone moiety, and then performing coupling reactions at that centre (scheme 4.18).

Scheme 4.18



415 **427** **429**

R = SO_2Naphth(2); X = -CO-, -SO_2- or -CO-N-

Reagents/conditions: i) Benzylamine, $NaB(OAc)_3H$, DCE, AcOH; ii) R'-COCl or R'-SO_2Cl or R'-N=C=O

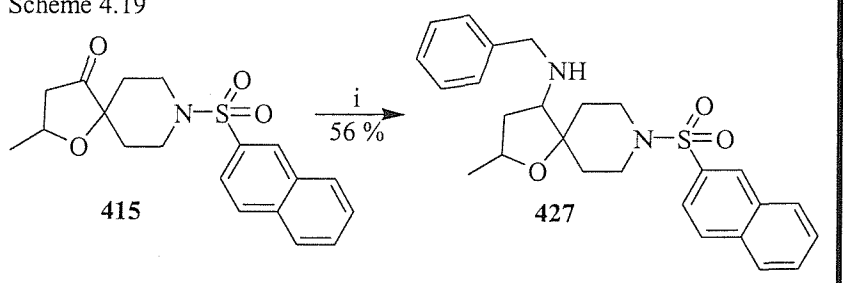
The reductive amination procedure with benzylamine attempted earlier was transferred to a microwave reactor. Despite numerous repetitions with a range of reagent concentrations, it did not prove possible to improve on the original 48 % yield. Increasing the internal temperature of the system appeared to vastly increase the rate of the reaction but the situation was complicated by severe degradation of the starting material. Microwave initiation of the reductive amination seemed from these results to not be a suitable means of instigating the amine synthesis.

The reaction was thus taken back to a standard thermal synthetic procedure, this time mediated with titanium (IV) isopropoxide and sodium borohydride.[108] Preliminary one-step processes with these reagents resulted in reduction of the ketone moiety to the

alcohol. Replacement of the sodium borohydride with sodium cyanoborohydride alleviated this problem, granting amine **427** in 40 % yield, however, this was still no improvement upon the original procedure. Substitution of the titanium (IV) isopropoxide with a number of other Lewis acids also failed to increase the yield.

It was clear that using Lewis acids to mediate the amination was a much less effective procedure than using Brönsted acids. Therefore, the procedure was again modified; this time to include the more commonly used acetic acid to mediate the amination, and sodium cyanoborohydride as the reducing agent (scheme 4.19).

Scheme 4.19



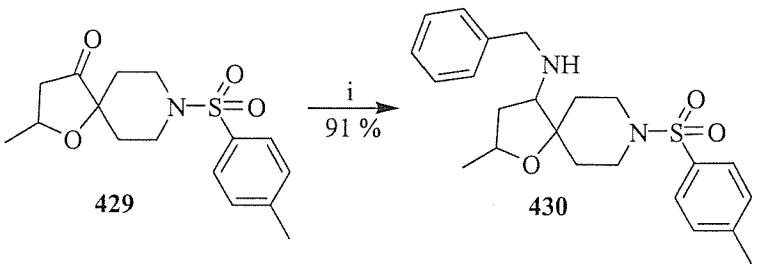
415 **427**

Reagents/conditions: i) Benzylamine, $NaBH_3CN$, EtOH, AcOH

This version of the reductive amination increased the yield to a level of 56 %. It was hoped that this could be further boosted by the inclusion of a drying agent to drive the formation of the intermediate imine. To this end, the reaction was repeated in refluxing methanol with the addition of molecular sieves (4 Å) to remove the water; it was pleasing to note that this resulted in a dramatic increase of the yield to 82 % (45:55 dr). Sequential purification of amine **427** by column and radial chromatography, allowed the isolation of both diasteroisomers of the amine (**438** + **440**).

The reaction was repeated with a tosyl protecting group in place of the naphthalene-2-sulfonyl group, this gave an even better yield of 91 % (scheme 4.20).

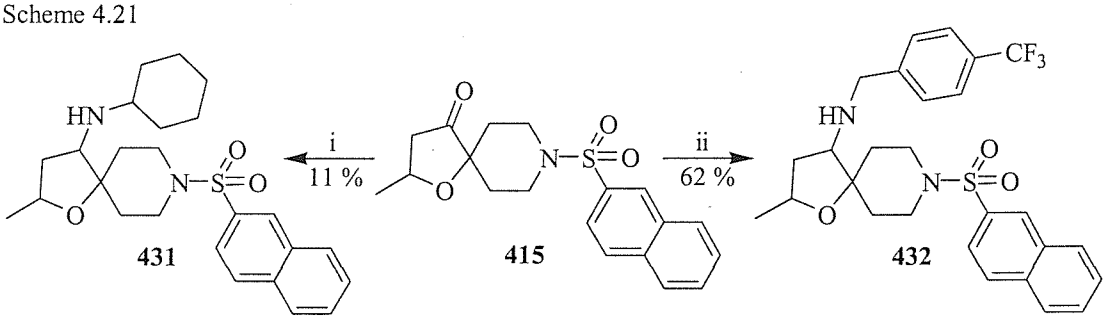
Scheme 4.20



Reagents/conditions: i) Benzylamine, AcOH, $NaBH_3CN$, MeOH

To test how easily this procedure could be used to create a library of compounds, furanone **415** was reacted with cyclohexyl and trifluoromethylbenzylamine under the same reductive amination conditions (scheme 4.21).

Scheme 4.21



Reagents/conditions: i) Cyclohexylamine, AcOH, $NaBH_3CN$, MeOH; ii) trifluoromethylbenzylamine, AcOH, $NaBH_3CN$, MeOH

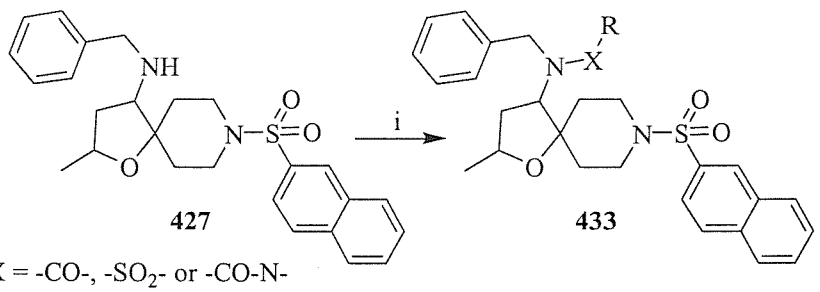
Reductive amination of furanone **415** with trifluoromethylbenzylamine provided amine **432** in satisfactory yield (62 %), however, the cyclohexyl derivative **431** was only synthesised in 11 % yield. It had been shown that the reaction conditions developed for the creation of amine **427** could be applied to other related systems, but at a reduced yield. Due to this fact it was decided to focus the final section of work on the synthesis of compound libraries by far simpler methods.

4.5 *Library Generation*

4.5.1 Benzylamine Derivatisation

This increase in the yield of the reductive amination procedure for benzylamine **427** meant that it was now possible to manufacture enough starting material to attempt the synthesis of a library. With the resources available at Ferring Pharmaceuticals (Southampton), amine **427** was reacted with a range of acid chlorides, sulfonyl chlorides and isocyanates, in an effort to obtain the corresponding amides, sulfonamides and ureas (scheme 4.22).

Scheme 4.22



427 **433**

X = -CO-, -SO_2- or -CO-N-

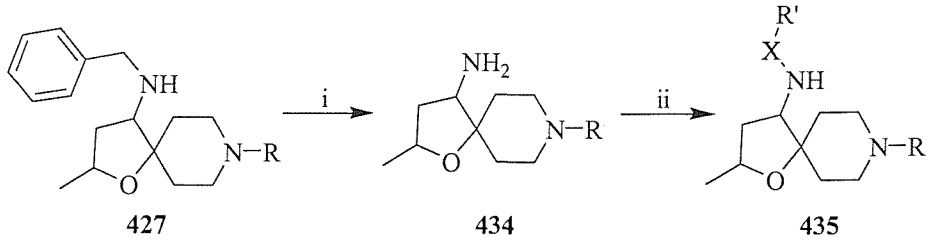
Reagents/conditions: i) R-COCl or R-SO_2Cl or R-N=C=O

However, the reactivity of amine **427** proved less than satisfactory, possibly due to the steric hindrance at that centre and it was not possible to synthesise enough of the products for analysis.

4.5.2 Primary Amine Derivatisation

It was hoped that the failure of the library synthesis would only be a temporary setback. Cleaving the benzyl group should render the resulting primary amine much more reactive (scheme 4.23).

Scheme 4.23



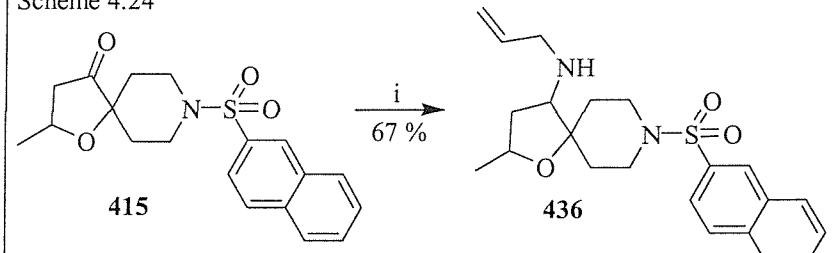
427 434 435

R = SO_2Naphth(2); X = -CO-, -SO_2- or -CO-N-

Reagents/conditions: i) Debenzylation; ii) R'-COCl or R'-SO_2Cl or R'-N=C=O

There were a number of ideas of how to accomplish the synthesis of the primary amine. It was thought that perhaps the steric hindrance around the benzylamine might cause debenzylation to be a difficult process. Therefore, the first option chosen was to convert furanone **415** into the corresponding allylamine **436** and then effect deallylation to amine **434** (scheme 4.24).

Scheme 4.24



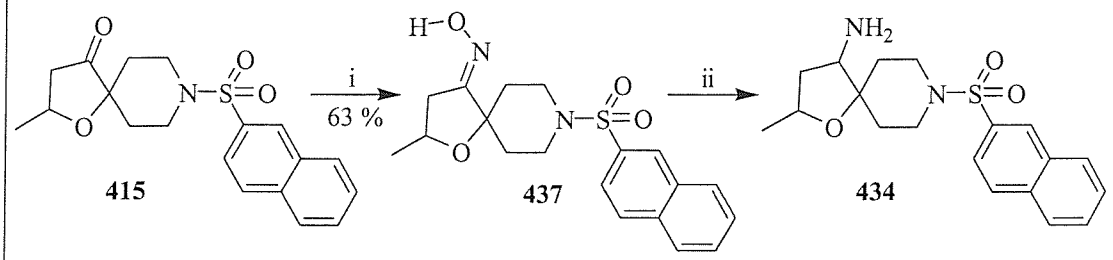
415 436

Reagents/conditions: i) Allylamine, $NaBH_3CN$, MeOH, AcOH

Reaction of furanone **415** with allylamine under the same reductive amination conditions developed earlier, furnished amine **436** in good yield (67 %). However, all attempts at cleavage of the allyl group to the primary amine using palladium catalysis were unsuccessful.

It was also feasible to generate amine **434** by the conversion of furanone **415** to oxime **437** followed by reduction to the free amine (scheme 4.25).

Scheme 4.25

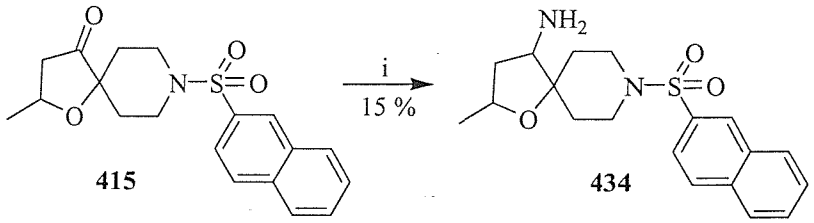


Reagents/conditions: i) Hydroxylamine hydrochloride, NaOAc, MeOH; ii) Reduction

Reaction of furanone **415** with hydroxylamine hydrochloride and sodium acetate in methanol provided oxime **437** in moderate yield (63 %). Subsequent reduction of the oxime with lithium aluminium hydride did generate the desired primary amine, but the reaction was very messy and purification proved extremely challenging; granting amine **434** in an abysmal 4 % yield.

Attempts were made to access primary amine **434** in one step from furanone **415** *via* direct amination with ammonium acetate (scheme 4.26).[109]

Scheme 4.26

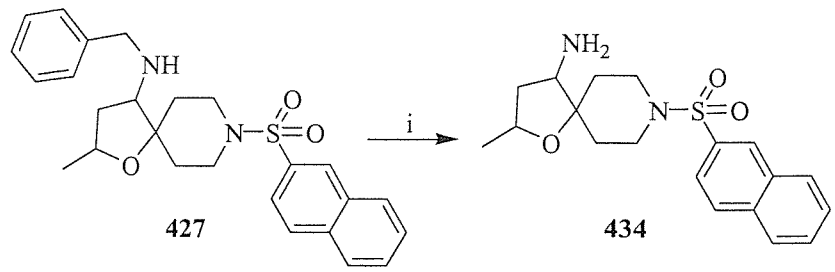


Reagents/conditions: i) NH_4OAc, $NaBH_3CN$, MeOH

Condensation of furanone **415** with ammonium acetate and reduction with sodium cyanoborohydride indeed granted amine **434**. Analysis of the crude reaction mixture by ^1H NMR indicated that substantial conversion (>50 %) to the amine had occurred, however, again purification was exceptionally gruelling providing the pure amine in only 15 % yield.

It was decided at this point to generate amine **434** *via* the debenzylation of benzylamine **427** (scheme 4.27).

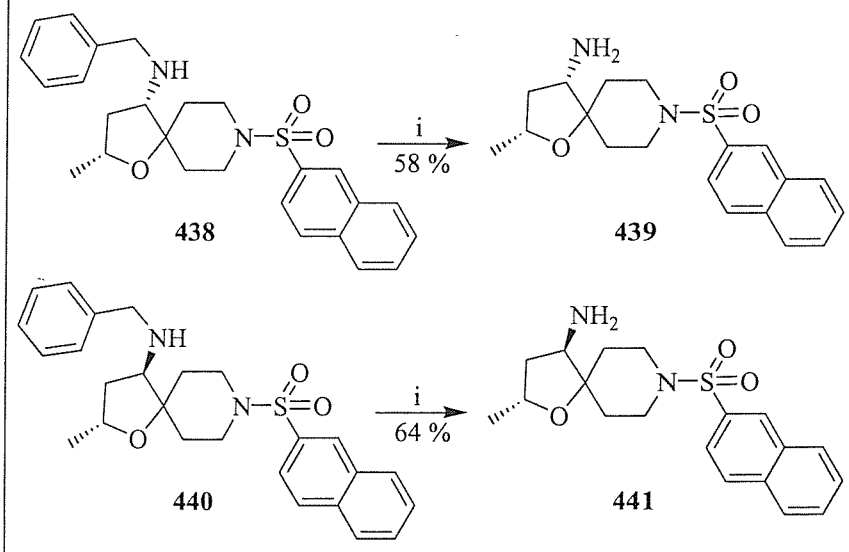
Scheme 4.27



Reagents/conditions: i) H_2, Pd/C, CH_2Cl_2

The primary attempt at cleaving the benzyl group was conducted using hydrogen gas and palladium on carbon, as feared the substrate proved to be completely unreactive under these conditions. In a slight modification, benzylamine **427** was mixed with palladium on carbon in methanol and ammonium formate was added as the hydride source. The reaction was carried out in a microwave reactor for 15 min at 150 °C and fortunately this time met with greater success, isolating amine **434** as a white solid in 48 % yield. Conversion of the microwave conditions to the thermal equivalent generated the amine in a disappointing 39 % yield; greatly increasing the quantity of ammonium formate to twenty equivalents had the effect of boosting the yield to a more acceptable level (scheme 4.28).

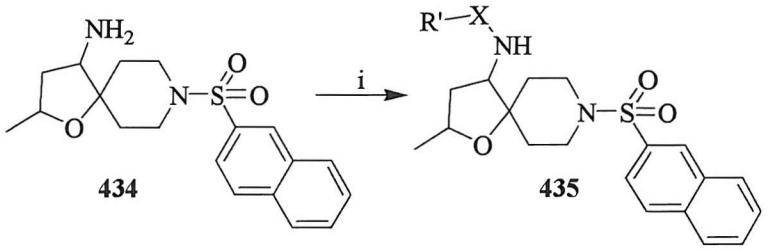
Scheme 4.28



Reagents/conditions: i) NH_4CO_2, Pd/C, MeOH

The fact that it was now possible to achieve the debenzylation meant that it was possible to attempt a second library synthesis. Amine **434** was reacted with an 80-well rack, containing 40 different acid chlorides, 20 sulfonyl chlorides and 20 isocyanates and isothiocyanates, generating the corresponding amides, sulfonamides, ureas and thioureas (scheme 4.29).

Scheme 4.29



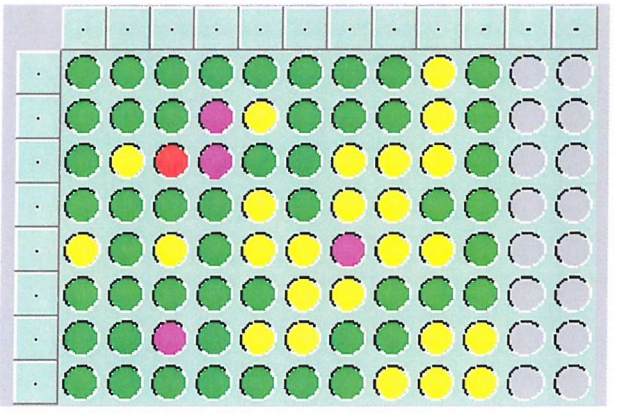
434 **435**

X = -CO-, -SO_2-, -CO-N- or -CS-N-

Reagents/conditions: i) Et_3N, R'-COCl or R'-SO_2Cl or R'-N=C=O (S)

Thankfully in this synthesis, amine **434** proved to be sufficiently reactive. Analysis of the plate took place using HPLC and MS on each well, with computer analysis of the raw data providing a means of discerning at a glance whether each reaction had worked (figure 4.1).[β]

Figure 4.1 **Library 1: Produced using Amine 434**

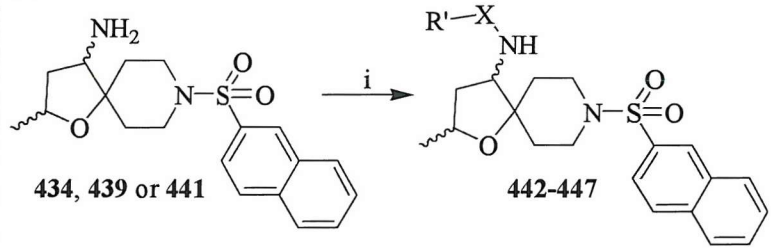


[β] Green = Purity >60 % by UV at 254 nm
Yellow = Purity less than 60 %
Red = Fail, target mass not found
Purple = Target mass not found, another target mass found

It can be seen from figure 4.1, that >90 % of the reactions were successful, with only one outright failure and four other vessels not containing the correct product; the plates were then sent off for biological testing. It was anticipated that the same procedure for plate generation and subsequent analysis by HPLC and MS techniques could be implemented using diamine **428**, hopefully with equally excellent results.

In order to test the effectiveness of the coupling reactions in a standard laboratory environment, amines **434**, **439** and **441** were coupled with three acid chlorides, two sulfonyl chlorides and one isocyanate taken from the 80-well rack (scheme 4.30).

Scheme 4.30



434, 439 or 441 **442-447**

X = -CO- or -SO_2- or -CO-N-

Reagents/conditions: i) Et_3N, R'-COCl or R'-SO_2Cl or R'-N=C=O

Each of the attempted couplings was successful and the results can be seen in the following table (table 4.3).

Table 4.3 Coupling of Amines 434, 439 and 441 with Electrophiles

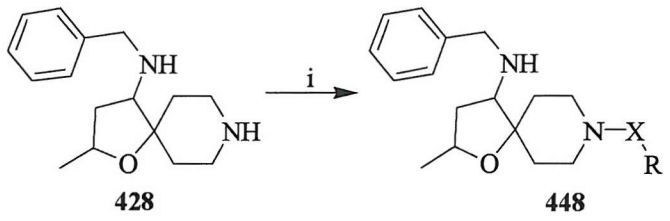
Starting Material	Electrophile	Yield (product)
439	1-Naphthoyl chloride	76 % (**442**)
441	Hydrocinnamoyl chloride	56 % (**443**)
434	Naphthalene-2-sulfonyl chloride	47 % (**444**)
439	Ethanesulfonyl chloride	39 % (**445**)
434	Benzoyl chloride	71 % (**446**)
441	Allyl isocyanate	83 % (**447**)

Chemical elaboration of primary amine **434** had now generated a library of potential neurokinin receptor antagonists. The final remaining goal for the project would be to manufacture another library, this time with manipulation of the piperidine moiety.

4.5.3 Piperidine Derivatisation

The minimal reactivity of benzylamine **427** had already been demonstrated. Because of this fact, it was hoped that amine **428** could be used to generate a library with alkylation occurring at only the piperidine nitrogen centre (scheme 4.31).

Scheme 4.31



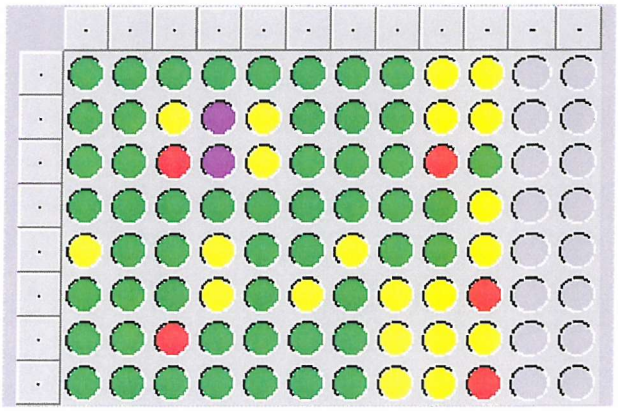
428 **448**

X = -CO-, -SO_2-, -CO-N- or -CS-N-

Reagents/conditions: i) Et_3N, R-COCl or R-SO_2Cl or R-N=C=O (S)

To this end, amine **428** was subjected to coupling reactions with the same 80-reagent rack used in the generation of the previous library. In the same manner as in the first library, HPLC and MS analysis was used to analyse the reactions. The computer software used generated the following results (figure 4.2).

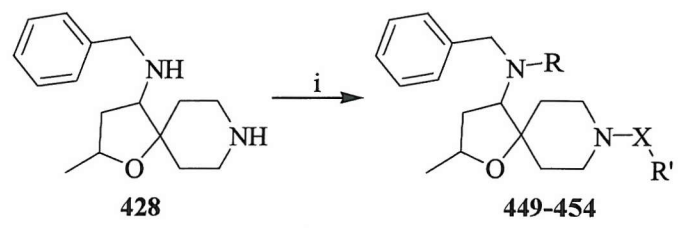
Figure 4.2 **Library 2: Produced using Amine 428**



The figure again illustrates >90 % success in the plate, with five direct failures and two vessels containing the wrong compound. These two purple cells were present in both

libraries and closer inspection of the data indicated that this was caused by the two reagents being put in the incorrect place in the rack. To demonstrate the effectiveness of this coupling procedure, amine **428** was coupled with two acid chlorides and one isocyanate from the 80-well rack (scheme 4.32).

Scheme 4.32



428 **449-454**

X = -CO- or -CO-N-

Reagents/conditions: i) Et_3N, R'-COCl or R'-N=C=O

It was pleasing to note that the coupling reactions carried out were all successful. However, the standard laboratory couplings were all undertaken on a slightly larger scale than those of the robot-controlled library generation. Under these moderately different circumstances, amine **428** proved to have a higher reactivity than that observed in the library synthesis. This resulted in not only the monoalkylated product but also the dialkylated products (table 4.4).

Table 4.4 Coupling of Amine 428 with Electrophiles

Starting Material	Electrophile	Yield (product)	
		Monoalkylated	Dialkylated
428	Benzoyl chloride	0 % (**449**)	52 % (**450**)
428	Hydrocinnamoyl chloride	16 % (**451**)	47 % (**452**)
428	Allyl isocyanate	0 % (**453**)	28 % (**454**)

Although very little monoalkylated material was obtained from the reactions, substantial amounts of the dialkylated products were isolated. It is important to remember that the reactions from this and the previous table were only attempted once; with optimisation it seems highly likely to be able to induce high yields of both mono- and dialkylated products.

4.6 Conclusions

The use of cyanohydrins as acyl anion equivalents has been optimised from poor yielding reactions with both alpha- and gamma-addition possible, to high yielding processes with exclusively one product.

A Baldwin disfavoured, acid-mediated 5-*endo*-trig cyclisation of an α,β-unsaturated hydroxyketone to the corresponding furanone has been heavily optimised from a poor yielding process with substantial degradation of starting material, to a highly clean reaction with excellent yields (> 80 %).

The combination of these two processes has enabled the short (4-step), high yielding (> 87 %) synthesis of a spiro-heterocyclic skeleton with the capacity to be derivatised at a number of distinct centres.

Reductive amination of the furanone system and the deprotection of the piperidine nitrogen have both been adapted to give extremely high-yielding (91 % and 97 % respectively) processes; generating scaffold that provide a tremendous entry into library synthesis.

The capability to generate compound libraries was confirmed by the coupling of two discrete scaffolds with a rack of 80 diverse electrophiles. Computer-aided analysis of the data from these undertakings displayed fantastic results, synthesising a significant number of scaffolds with the potential to act as neurokinin receptor antagonists.

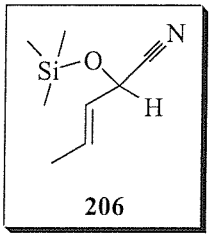
5. Experimental

5.1 General Procedures

IR spectra were recorded on a Nicolet Impact 400 spectrometer, fitted with a Spectra-Tech Thunderdome accessory. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the data. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC300 (300 and 75 MHz respectively), a Bruker AM300 (as for the AC300) or a Bruker DPX400 (400 and 100 MHz respectively). Chemical shifts are reported in δ units with $CHCl_3$ being used as an internal standard. The abbreviations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) are used when reporting the data. Coupling constants (*J*) are reported in Hz. Mass spectra were recorded in electron spray ionisation mode (ES), atmospheric pressure chemical ionisation (APCI), chemical ionisation (CI) or electron impact (EI), relative abundances are reported in brackets after the mass. Merck Kieselgel 60 was used for column chromatography. Thin layer chromatography was performed using Merck silica gel 60 F_{254}, and visualised under UV, with iodine, or by staining with solutions of potassium permanganate or phosphomolybdic acid. UV absorbance spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer. All solvents were purified and dried using standard techniques. All melting points were taken uncorrected. Unless otherwise stated, diastereomeric ratios are 1:1.

5.2 Synthesis

2-Trimethylsilanyloxy-pent-3-enenitrile (206)



206

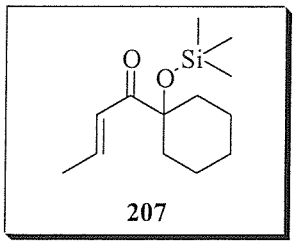
Following the method of Jacobsen *et al*,[55] zinc iodide (13 mg, 10 mol %) was added to crotonaldehyde (**204**) (35.0 mL, 0.422 mol) at 0 °C. Trimethylsilyl cyanide (34.0 mL, 0.255 mol) was then added in 2 mL aliquots and the reaction stirred at rt for 14 h. The crude mixture was purified by vacuum distillation through a Vigreux column (62-64 °C, ~ 5 mmHg) affording the (trimethylsilyl)cyanohydrin as a colourless oil (34.2 g, 0.202 mol, 79 %). The spectroscopic data was in accordance with that present in the literature.[55]

IR (neat) ν/cm^{-1}: 2959 (w), 2920 (w), 1671 (m), 1449 (m), 1380 (w), 1255 (s), 1099 (s), 1057 (s), 964 (m), 844 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 5.94 (1H, ddq, -C**H**=CH-CH(CN), *J*= 15.4, 1.0, 6.5 Hz), 5.52 (1H, ddq, CH=C**H**-CH(CN), *J*= 15.4, 6.0, 1.5 Hz), 4.86 (1H, dt, -C**H**(CN), *J*= 6.5, 1.0 Hz), 1.73 (3H, dd, -C**H**$_3$, *J*= 6.5, 1.5 Hz), 0.18 (9H, s, -Si(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 131.2 (CH=**C**H(CN)), 126.3 (**C**H=CH(CN)), 118.7 (-**C**N), 62.1 (-**C**H(CN)), 17.4 (-**C**H$_3$), -0.2 (-Si(**C**H$_3$)$_3$).

1-[1′-[(Trimethylsilyl)oxy]cyclohexyl]-2-buten-1-one (207)



207

Following the method of Jacobsen *et al*,[55] to a solution of diisopropylamine (1.22 mL, 8.71 mmol) in dry THF (20 mL) at 0 °C was added *n*-BuLi (2.5 M solution in hexane, 3.48 mL, 8.71 mmol) and the reaction stirred for 15 min at 0 °C. The system was cooled to –78 °C and 2-[(trimethylsilyl)oxy]-3-pentenenitrile (**206**) (1.50 g, 8.89 mmol) slowly added, an instant colour change to bright yellow was observed. After 10 min at –78 °C, cyclohexanone (0.83 mL, 8.00 mmol) was added at –78 °C and the reaction monitored by TLC. When the reaction was complete (40 min) the system was quenched with water, the mixture partitioned between Et_2O and water, and extracted with Et_2O (3 x 15 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*, affording the crude product as a yellow oil. Purification by distillation, provided the crude product as a colourless oil (1.39 g, 5.78 mmol, 65 %). The spectroscopic data was in accordance with that present in the literature.[55]

IR (neat) ν/cm^{-1}: 2936 (m), 2858 (w), 1698 (m), 1631 (m), 1446 (m), 1251 (s), 1083 (m), 1051 (m), 1023 (m), 886 (m), 839 (s).

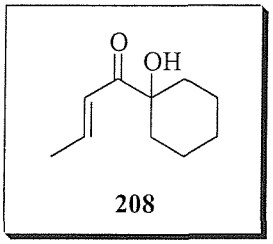
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.90 (1H, dq, =C**H**-CH_3, *J*= 15.4, 7.0 Hz), 6.55 (1H, dq, =C**H**-C=O, *J*= 15.2, 2.0 Hz), 1.90 (3H, dd, -C**H**$_3$, *J*= 7.0, 2.0 Hz), 1.75-1.50 (10H, m, -C**H**$_2$), 0.10 (9H, s, -Si(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 202.2 (**C**=O), 143.3 (=**C**H-CH_3), 126.5 (=**C**H-C=O), 80.5 (-**C**(OSi$(CH_3)_3$), 34.7 (-**C**H_2), 25.6 (-**C**H_2), 21.9 (-**C**H_2), 18.5 (-**C**H_3), 2.3 (-Si(**C**H_3)$_3$).

MS (EI; CH_2Cl_2) *m/z*: 224 (39), 170 (100), 72 (94).

CAS No.: 69849-16-7

1-[1′-(Hydroxy)cyclohexyl]-2-buten-1-one (208)



208

Following the method of Jacobsen *et al*,[55] to a solution of the trimethylsilyl enone **207** (800 mg, 3.40 mmol) in THF (5 mL) was added HCl (1N aq. solution, 5 mL) in THF (7 mL), the reaction was stirred at rt until hydrolysis was complete (5 min). The reaction was extracted into Et_2O (2 x 20 mL), washed with $NaHCO_3$ (2 x 10 mL, sat. aq. solution) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, giving the crude product as a pale yellow oil. Purification by distillation granted the pure hydroxy enone **208** (548 mg, 3.26 mmol, 97 %). The spectroscopic data was in accordance with that present in the literature.[55]

IR (neat) ν/cm^{-1}: 3467 (br m), 2933 (m), 2857 (w), 1683 (m), 1626 (m), 1446 (m), 1387 (w), 1292 (m), 1266 (w), 1130 (m), 1038 (m), 988 (m).

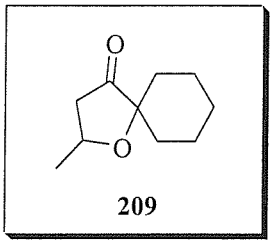
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.15 (1H, dq, =C**H**-CH_3, *J*= 15.4, 7.0 Hz), 6.54 (1H, dq, =C**H**-C=O, *J*= 15.3, 2.0 Hz), 3.81 (1H, br s, -O**H**), 1.94 (3H, dd, -C**H**$_3$, *J*= 7.0, 2.0 Hz), 1.79-1.50 (10H, m, -C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 202.6 (**C**=O), 146.2 (=**C**H-CH_3), 124.5 (=**C**H-C=O), 77.9 (-**C**(OH), 33.9 (-**C**H_2), 25.7 (-**C**H_2), 21.4 (-**C**H_2), 18.9 (-**C**H_3).

MS (EI; CH_2Cl_2) *m/z*: 168 $[M]^{+\bullet}$ (8), 150 (11), 98 (100).

CAS No.: 69849-15-6

2-Methyl-1-oxaspiro[4.5]decan-4-one (209)



209

Following the method of Jacobsen *et al*,[55] to a solution of the α-hydroxy enone **208** (300 mg, 1.78 mmol) in toluene (20 mL) was added methanol (144 μL, 3.57 mmol) and *p*TSA (68 mg, 0.36 mmol), the mixture was heated to reflux until cyclisation was complete (14 h, monitored by GC). The reaction was extracted into Et_2O (2 x 10 mL) and washed with water (2 x 10 mL), $NaHCO_3$ (2 x 10 mL, sat. aq. solution) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, to give the crude product as a yellow oil. Purification by column chromatography gave the furanone **209** as a colourless oil (111 mg, 0.66 mmol, 37 %). The spectroscopic data was in accordance with that present in the literature.[55]

IR (neat) ν/cm^{-1}: 2931 (m), 2858 (w), 1751 (s), 1448 (w), 1385 (w), 1190 (w), 1150 (w), 1067 (m), 1043 (w), 983 (m).

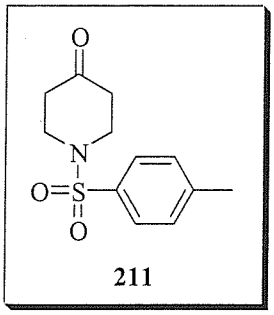
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.25 (1H, ddq, -C**H**(C-O-), *J*= 10.0, 6.0, 6.0 Hz), 2.51 (1H, dd, -C**H**CH(C=O), *J*= 17.9, 6.0 Hz), 2.12 (1H, dd, -CHC**H**(C=O), *J*= 17.9, 9.9 Hz), 1.75-1.40 (10H, m, -C**H**$_2$-), 1.37 (3H, d, -C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 218.4 (**C**=O), 82.7 (**C**-O-), 68.9 (**C**H-O-), 44.2 (**C**H$_2$C=O), 33.4 (**C**H$_2$), 29.5 (**C**H$_2$), 25.3 (**C**H$_2$), 21.8 (**C**H$_3$).

MS (EI; CH_2Cl_2) *m/z*: 168 $[M]^{+\bullet}$ (9), 139 (31).

CAS No.: 56503-80-1

1-(Toluene-4-sulfonyl)-piperidin-4-one (211)



211

To a solution of tosyl chloride (3.81 g, 20 mmol) in CH_2Cl_2 (10 mL) was added 4-piperidone monohydrate monohydrochloride (**216**) (3.07 g, 20 mmol) followed by triethylamine (5.58 mL, 40 mmol) and the reaction stirred at rt for 24 h. The reaction was partitioned between CH_2Cl_2 and water, and washed with HCl (2 x 10 mL, 2N aq. solution), water (2 x 10 mL), NaOH (2 x 10 mL, 2N aq. solution) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as an off-white solid. Purification by recrystallisation (EtOAc) gave the pure sulfonamide as a white solid (4.99 g, 19.7 mmol, 99 %). The spectroscopic data were in accordance with that published in the literature.[59]

MPt.: 126-129 °C.

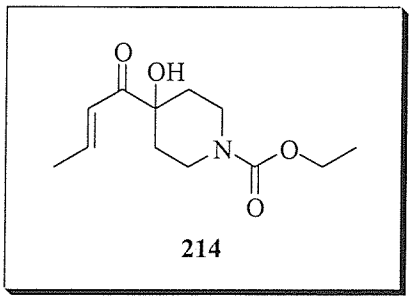
IR (neat) ν/cm^{-1}: 1717 (s), 1597 (w), 1470 (w), 1339 (s), 1216 (m), 1162 (s), 1090 (m), 919 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.68 (2H, d, aromatic C**H**, *J*= 8.8 Hz), 7.34 (2H, d, aromatic C**H**, *J*= 8.4 Hz), 3.38 (4H, t, C**H**$_2$, *J*= 6.6 Hz), 2.53 (4H, t, C**H**$_2$, *J*= 6.6 Hz), 2.44 (3H, s, -C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 205.8 (**C**=O), 144.3 (aromatic **C**), 133.4 (aromatic **C**), 130.1 (aromatic **C**H), 127.7 (aromatic **C**H), 46.0 (**C**H$_2$), 40.8 (**C**H$_2$), 21.7 (**C**H$_3$).

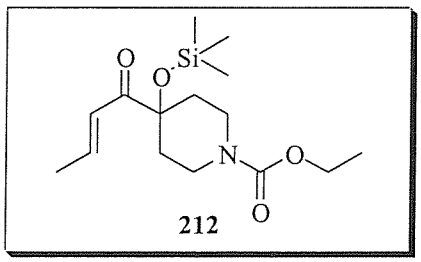
CAS No.: 33439-27-9

4-But-2-enoyl-4-hydroxy-piperidine-1-carboxylic acid ethyl ester (214)



214

Method 1: *via* 4-but-2-enoyl-4-trimethylsilanyloxypiperidine-1-carboxylic acid ethyl ester (**212**)



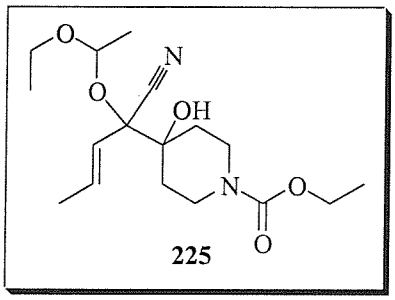
212

Based on the procedure of Jacobsen *et al*,[55] to a solution of diisopropylamine 1.47 mL, 10.50 mmol) in THF (50 mL) at 0 °C was added *n*-BuLi (7.05 mL, 10.50 mmol, 1.49 M solution in hexane) and the reaction stirred for 20 min at 0 °C. The system was cooled to –78 °C and the TMS-cyanohydrin **206** (1.86 g, 11.00 mmol) added, after 20 min piperidone **210** (1.52 mL, 10.00 mmol) was added and the reaction stirred at –78 °C for 3 h. The reaction was quenched with water (20 mL) at –78 °C, the mixture partitioned between Et_2O and water and extracted with Et_2O (3 x 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a thick yellow oil (2.50 g). Purification by column chromatography (20 % Et_2O/hexane), gave the TMS protected ether as a colourless oil (1.44 g, 4.62 mmol, 42 %).

The newly formed 4-but-2-enoyl-4-trimethylsilanyloxy-piperidine-1-carboxylic acid ethyl ester (**212**) (1.30 g, 4.15 mmol) was taken up into THF (10 mL); HCl (5 mL, 1N aq. solution) in THF (5 mL) was added and the reaction stirred until hydrolysis was

complete (5 min). The reaction was extracted into CH_2Cl_2 (2 x 10 mL) and washed with water (10 mL), $NaHCO_3$ (2 x 10 mL) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* leaving the crude product as a pale yellow oil (1.00 g). Purification by column chromatography (40 % Et_2O/hexane) provided the α-hydroxyenone **214** as a white solid (0.99 g, 99 %).

Method 2: *via* 4-[1-cyano-1-(1-ethoxyethoxy)but-2-enyl]-4-hydroxypiperidine-1-carboxylic acid ethyl ester (**225**)



225

Following the method of Jacobson *et al*,[55] to a solution of diisopropylamine (561 μL, 4.00 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (2.5 mL, 4.00 mmol, 1.6 M solution in hexane) and the solution stirred at -78 °C for 10 min then allowed to warm to 0 °C. Protected cyanohydrin **222** (677 mg, 4.00 mmol) was added and the reaction stirred at 0 °C for 10 min. *N*-Carbethoxy-4-piperidone (302 μL, 2.00 mmol) was added and the mixture stirred for 1.5 h at 0 °C. The reaction was quenched with water (10 mL), partitioned between Et_2O and water, washed with water and extracted with Et_2O (3 x 10 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as light brown oil (1.02 g). Purification by column chromatography (20 % Et_2O/hexane) gave the pure product **225** as a colourless oil (603 mg, 1.77 mmol, 89 %); the spectroscopic data for the intermediate is reported below for a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3402 (br w), 2968 (w), 2926 (w), 1672 (s), 1484 (m), 1440 (s), 1383 (m), 1245 (s), 1096 (m), 1041 (m), 967 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.32-6.14 (2 x 1H, m, H_3C-C**H**=CH), 5.59 (1H, br dd, H_3C-CH=C**H**, *J*= 15.5, 1.8 Hz), 5.44 (1H, br dd, H_3C-CH=C**H**, *J*= 15.5, 1.8 Hz), 4.92 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.5 Hz), 4.86 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.5 Hz), 4.20-4.03 (2 x 2H, m, -$NCO_2C\mathbf{H}_2CH_3$ + 2 x 2H, m, -$OC\mathbf{H}_2CH_3$), 3.75-3.37 (2 x 4H, m, -$C\mathbf{H}_2$-N-$C\mathbf{H}_2$-), 1.84-1.75 (2 x 2H, m, -$C\mathbf{H}_aH_b$-C-$C\mathbf{H}_aH_b$-), 1.83 (2 x 3H, dd, $\mathbf{H}_3C$-CH=CH, *J*= 6.4, 2.0 Hz), 1.61-1.59 (2 x 2H, br s, -$CH_a\mathbf{H}_b$-C-$CH_a\mathbf{H}_b$-), 1.38 (3H, d, -O-CH($C\mathbf{H}_3$)-O-, *J*= 5.5 Hz), 1.32-1.22 (2 x 3H, m, -$NCO_2CH_2C\mathbf{H}_3$ + 3H, d, -O-CH($C\mathbf{H}_3$)-O-, *J*= 5.5 Hz), 1.19 (3H, t, -$OCH_2C\mathbf{H}_3$, *J*= 7.3 Hz), 1.14 (3H, t, -$OCH_2C\mathbf{H}_3$, *J*= 7.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 155.5 (**C**=O), 132.1 (H_3C-CH=**C**H), 125.8 (H_3C-**C**H=CH), 119.1 (-**C**N), 99.4 (-O-**C**H(CH_3)-O-), 78.9 (-**C**-CN), 74.2 (-**C**-OH), 62.2 (-$NCO_2\mathbf{C}H_2CH_3$), 61.7 (-$O\mathbf{C}H_2CH_3$), 43.1 ($\mathbf{C}H_2$), 41.2 ($\mathbf{C}H_2$), 39.3 ($\mathbf{C}H_2$), 39.2 ($\mathbf{C}H_2$), 31.8 (-$\mathbf{C}H_3$), 30.3 (-$\mathbf{C}H_3$), 17.9 (-$\mathbf{C}H_3$), 14.8 (-$\mathbf{C}H_3$).

MS (CI; CH_2Cl_2) *m/z*: 341 $[M+H]^+$ (7), 295 (10), 251 (20), 172 (100).

4-[1-Cyano-1-(1-ethoxyethoxy)but-2-enyl]-4-hydroxypiperidine-1-carboxylic acid ethyl ester (**225**) (578 mg, 1.44 mmol) was taken up into THF (5 mL); H_2SO_4 (5 mL, 1N aq. solution) was added and the reaction heated to reflux. After 4 h, the reaction was diluted with water (5 mL), the phases separated and washed with NaOH (2N aq. solution, 3 x 5 mL) and water (3 x 5 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude material as a yellow oil (452 mg). Purification by column chromatography (40 % Et_2O/hexane) gave the pure enone as a colourless oil (279 mg, 1.15 mmol, 80 %).

MPt.: 85-88 °C (EtOH)

IR (neat) ν/cm^{-1}: 3412 (br s), 2973 (m), 2878 (w), 1695 (s), 1672 (s), 1627 (m), 1438 (s), 1278 (m), 1244 (s), 1148 (m), 1097 (m), 1032 (m).

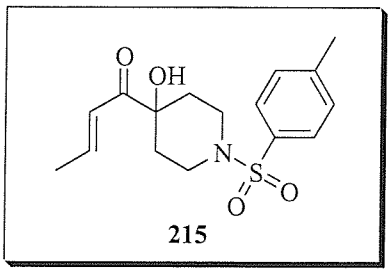
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.15 (1H, dq, =C**H**-CH_3, *J*= 15.3, 7.0 Hz), 6.47 (1H, dd, =C**H**-C=O, *J*= 15.1, 1.5 Hz), 4.21-4.03 (2H, m, -C**H**$_2$$CH_3$ + 2H, m, -C**H**$_a$$H_b$-N-C**H**$_a$$H_b$-), 3.18 (2H, br t, -$CH_a$**H**$_b$-N-$CH_a$**H**$_b$-, *J*= 11.9 Hz), 1.98 (3H, dd, =CH-C**H**$_3$, *J*= 1.5, 6.9 Hz), 1.95-1.88 (4H, m, -C**H**$_2$-C-C**H**$_2$-), 1.25 (3H, t, CH_2C**H**$_3$, *J*= 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 200.5 (**C**=O), 155.6 (-N-**C**=O), 147.4 (=**C**H-CH_3), 123.7 (=**C**H-C=O), 75.2 (**C**-OH), 61.5 (-O**C**H_2-), 39.6 (-**C**H_2-), 33.3 (-**C**H_2-), 18.8 (-**C**H_3), 14.8 (-**C**H_3).

MS (CI; CH_2Cl_2) *m/z*: 242 $[M+H]^+$ (70), 226 (100), 210 (52).

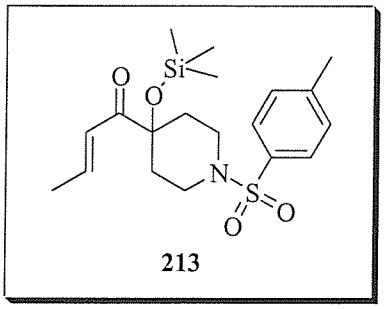
HRMS (EI) *m/z*: Found 241.13152; required for $C_{12}H_{19}NO_4$, $[M]^{+\bullet}$ = 241.13141.

1-[4-Hydroxy-1-(toluene-4-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (215)



215

Method 1: *via* 1-[1-(toluene-4-sulfonyl)-4-trimethylsilanyloxy-piperidine-4-yl]-but-2-en-1-one (**213**)



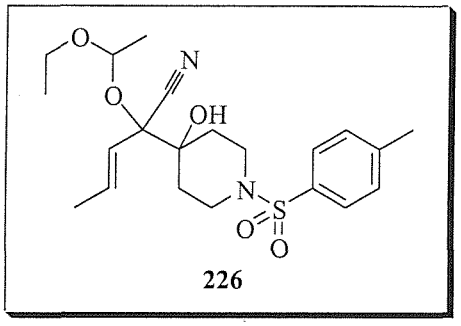
213

Based on the procedure of Jacobsen *et al*,[55] to a solution of *n*-BuLi (2.80 mL, 4 mmol, 1.43 M solution in hexane) in THF (10 mL) at –78 °C was added 2-trimethylsilanyloxy-pent-3-enenitrile (**206**) (677 mg, 4.0 mmol) and the reaction stirred at –78 °C for 15 min. Sulfonamide **211** (963 mg, 3.8 mmol) was added to the yellow solution at –78 °C and the reaction stirred for 4 h. The reaction was quenched with water, partitioned between Et_2O and water and washed with water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a thick yellow oil (1.30 g). Purification by column chromatography (10 % Et_2O/hexane) furnished the pure product as a colourless oil (120 mg, 0.38 mmol, 10 %).

1-[1-(Toluene-4-sulfonyl)-4-trimethylsilanyloxy-piperidine-4-yl]-but-2-en-1-one (**213**) (100 mg, 0.25 mmol) was taken up into THF (2 mL); HCl (1N aq. solution, 2 mL) in THF (2 mL) was added and the mixture stirred at rt for 30 min. The reaction was

partitioned between CH_2Cl_2 and water, washed with water (2 x 5 mL), $NaHCO_3$ (sat. aq. solution, 3 x 5 mL) and water (2 x 5 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, giving the crude α-hydroxyenone **215** as an off-white solid. Purification by recrystallisation (EtOAc) gave the enone as a white solid (50 mg, 0.16 mmol, 62 %).

Method 2: *via* 2-(1-ethoxyethoxy)-2-[4-hydroxy-1-(toluene-4-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (**226**)



226

Following the method of Jacobson *et al*[55], to a solution of diisopropylamine (336 μL, 2.4 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (1.86 mL, 2.4 mmol, 1.29 M solution in hexane) and the solution stirred at -78 °C for 10 min, then allowed to warm to 0 °C. Protected cyanohydrin **222** (400 mg, 2.4 mmol) was added and the reaction stirred at 0 °C for 15 min. *N*-Carbethoxy-4-piperidone (291 mg, 1.2 mmol) was added and the mixture stirred for 1.5 h at 0 °C. The reaction was quenched with water (10 mL), partitioned between Et_2O and brine, and extracted with Et_2O (3 x 20 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a brown oil (629 mg). Purification by column chromatography (20 % Et_2O/hexane) granted the pure product **226** as a colourless oil (406 mg, 0.96 mmol, 80 %). Data for the intermediate cyano compound is reported below as a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3497 (br w), 2974 (w), 2933 (w), 2878 (w), 2032 (w), 1666 (w), 1598 (m), 1446 (m), 1327 (s), 1160 (s), 1028 (s), 924 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.50 (2 x 2H, d, aromatic C**H**, *J*= 8.4 Hz), 7.19 (2 x 2H, d, aromatic C**H**, *J*= 8.4 Hz), 6.07 (2 x 1H, dq, =C**H**-CH_3, *J*= 15.4, 6.5 Hz), 5.35 (1H, dq, =C**H**-C-CN, *J*= 15.9, 2.0 Hz), 5.27 (1H, dq, =C**H**-C-CN, *J*= 15.9, 2.0 Hz), 4.75 (2 x 1H, q, -O-C**H**(CH_3)-O-, *J*= 5.5 Hz), 3.95 (2 x 2H, q, $CH_3C\underline{H}_2O$-, *J*= 6.9 Hz), 3.56-3.49 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.40 (2 x 2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.50-2.45 (2 x 2H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 2.28 (2 x 3H, s, Ar-C**H**$_3$), 1.79 (2 x 3H, br d, =CH-C**H**$_3$, *J*= 6.5 Hz), 1.70-1.58 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.33 (3H, d, -OCH(C**H**$_3$)O-, *J*= 5.5 Hz), 1.24 (3H, d, -OCH(C**H**$_3$)O-, *J*= 5.0 Hz), 1.16 (3H, t, -$OCH_2C\underline{H}_3$, *J*= 6.5 Hz), 1.09 (3H, t, -$OCH_2C\underline{H}_3$, *J*= 6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 144.0 (2 x aromatic **C**), 133.2 (2 x aromatic **C**), 132.5 (2 x H_3C-CH=**C**H), 129.8 (2 x aromatic **C**H), 129.6 (2 x aromatic **C**H), 127.5 (2 x aromatic **C**H), 127.4 (2 x aromatic **C**H), 125.3 (2 x H_3C-**C**H=CH), 116.0 (2 x **C**N), 99.4 (2 x -O-**C**H(CH_3)-O-), 78.4 (2 x -**C**-CN), 73.1 (2 x -**C**-OH), 58.2 (2 x -O**C**H_2CH_3), 45.7 (2 x **C**H_2), 40.5 (2 x **C**H_2), 31.2 (2 x **C**H_2), 29.7 (2 x **C**H_2), 21.4 (2 x H_3**C**-CH=), 21.4 (2 x -OCH(**C**H_3)O-) 18.2 (2 x -OCH_2**C**H_3), 17.6 (2 x Ar-**C**H_3).

MS (ES^+; CH_3CN) *m/z*: 423 (100) $[M+H]^+$, 440 (54) $[M+NH_4]^+$, 445 (12) $[M+Na]^+$.

HRMS (ES) *m/z*: Found 867.3647; required for $C_{21}H_{30}N_2O_5S$, $[2M+Na]^+$ = 867.3642.

2-(1-Ethoxyethoxy)-2-[4-hydroxy-1-(toluene-4-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (**226**) (180 mg, 0.56 mmol) was taken up into THF (5 mL); H_2SO_4 (5mL, 2N aq. solution) was added and the reaction heated to reflux. After 3 h, the reaction was extracted with Et_2O (3 x 5 mL) and washed with NaOH (3 x 5 mL, 2N aq. solution) and water (2 x 5 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude product as a white solid (150 mg). Purification by column chromatography (40 % Et_2O/hexane) gave the pure product **215** as a white solid (116 mg, 0.36 mmol, 64 %).

MPt.: 200-203 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3467 (w), 1685 (m), 1628 (m), 1443 (w), 1352 (s), 1327 (s), 1301 (m), 1268 (m), 1165 (s), 1088 (m), 1061 (m), 1039 (m), 920 (s).

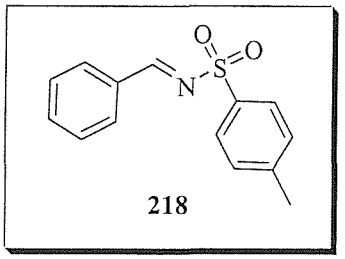
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.67 (2H, d, aromatic C**H**, *J*= 8.1 Hz), 7.34 (2H, d, aromatic C**H**, *J*= 8.1 Hz), 7.22 (1H, dq, =C**H**-CH_3, *J*= 13.9, 6.9 Hz), 6.45 (1H, dq, =C**H**-C=O, *J*= 13.9, 1.5 Hz), 3.79 (2H, ddd, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.0, 2.2, 2.2 Hz), 2.67 (2H, td, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-, *J*= 12.5, 3.0 Hz), 2.44 (3H, s, Ar-C**H**$_3$), 2.13 (2H, td, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 12.9, 5.0 Hz), 1.98 (3H, dd, =CH-C**H**$_3$, *J*= 1.5, 6.9 Hz), 1.45 (2H, br d, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-, *J*= 11.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 200.3 (**C**=O), 148.1 (=**C**H-CH_3), 143.8 (aromatic **C**), 133.3 (aromatic **C**), 129.9 (aromatic **C**H), 127.8 (aromatic **C**H), 123.4 (=**C**H-C=O), 74.2 (**C**-OH), 42.1 (-**C**H_2-), 33.2 (-**C**H_2-), 21.7 (-**C**H_3), 19.0 (-**C**H_3).

MS (ES^+; CH_3CN) *m/z*: 324 (100) $[M+H]^+$, 346 (69) $[M+Na]^+$, 669 (42) $[2M+Na]^+$, 992 (14) $[3M+Na]^+$.

HRMS (ES) *m/z*: Found 669.2277; required for $C_{16}H_{21}NSO_4$, $[2M+Na]^+$ = 669.2279.

N-Benzylidene-4-methyl-benzenesulfonamide (218)



218

Following the method of McKay *et al*,[110] to a solution of benzaldehyde (**217**) (5.08 mL, 50.0 mmol) in toluene (100 mL) was added *p*-toluenesulfonamide (8.56 g, 50.0 mmol), $BF_3{\cdot}Et_2O$ (101 μL, 0.8 mmol) and the mixture heated to reflux for 20 h. The reaction was basified (NaOH, 2N aq. solution), the phases separated and the reaction washed with NaOH (2N aq. solution, 2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, leaving the crude product as an off-white solid. Purification by recrystallisation (CH_2Cl_2/hexane) gave the pure product as an off-white/pink solid (10.24 g, 39.4 mmol, 79 %). The spectroscopic data was in accordance with that published in the literature.[110]

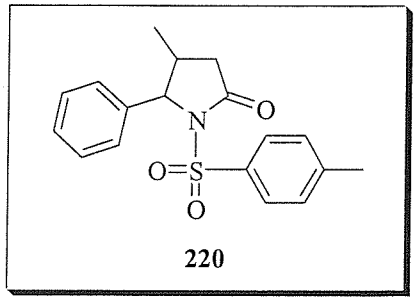
IR (neat) ν/cm^{-1}: 3726 (w), 1640 (w), 1597 (s), 1574 (m), 1496 (w), 1450 (m), 1317 (s), 1223 (w), 1157 (s), 1088 (s), 782 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 9.03 (1H, s, C**H**=N), 7.60 (2H, d, aromatic C**H**, *J*= 8.5 Hz), 7.36-7.19 (5H, m, aromatic C**H**), 7.00 (2H, d, aromatic C**H**, *J*= 7.0 Hz), 2.44 (3H, s, Ar-C$\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 170.3 (**C**=N), 144.8 (aromatic **C**), 135.2 (aromatic **C**), 135.1 (aromatic **C**H), 132.5 (aromatic **C**), 131.5 (aromatic **C**H), 130.0 (aromatic **C**H), 129.3 (aromatic **C**H), 128.3 (aromatic **C**H), 21.8 (Ar-**C**$\underline{H}_3$).

CAS No.: 51608-60-7.

4-Methyl-5-phenyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (220)



220

Based on the procedure of Jacobsen *et al*,[55] to a solution of *n*-BuLi (2.80 mL, 1.43 M solution in hexane, 4.0 mmol) in THF (10 mL) at –78 °C was added protected cyanohydrin **206** (677 mg, 4.0 mmol) and the reaction stirred at –78 °C for 10 min. *N*-Benzylidene-4-methyl-benzenesulfonamide (**218**) (985 mg, 3.8 mmol) was then added dropwise as a solution in THF (5 mL) and the reaction stirred at –78 °C for 4.5 h. The reaction was quenched by the addition of water (30 mL), the phases separated and the mixture extracted with Et_2O (3 x 10 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the product as a thick yellow oil, some of which crystallised on standing. Purification by recrystallisation (EtOAc/hexane) granted the pure pyrrolidinone as a white crystalline solid (313 mg, 0.95 mmol, 25 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 128-135 °C.

IR (neat) ν/cm^{-1}: 2906 (w), 1739 (s), 1599 (w), 1495 (w), 1457 (w), 1359 (s), 1272 (w), 1171 (s), 968 (m).

^{1}H NMR (400 MHz, $CDCl_3$) Isomer A; δ/ppm: 7.60 (2H, d, aromatic C**H**, *J*= 8.5 Hz), 7.36-7.19 (5H, m, aromatic C**H**), 7.00 (2H, d, aromatic C**H**, *J*= 7.0 Hz), 5.41 (1H, d, Ar-C**H**, *J*= 8.0 Hz), 2.98-2.85 (1H, m, -C**H**-CH_3), 2.60 (1H, dd, -C**H**$_a$H$_b$-C=O, *J*= 8.0, 17.1 Hz), 2.44 (3H, s, Ar-C**H**$_3$), 2.40 (1H, dd, -CH$_a$**H**$_b$-C=O, *J*= 5.0, 17.6 Hz), 0.71 (3H, d, -CHC**H**$_3$, *J*= 7.0 Hz).

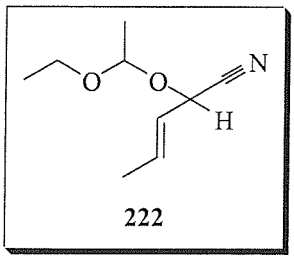
Isomer B; δ/ppm: 7.70 (2H, d, aromatic C**H**, *J*= 8.0 Hz), 7.36-7.29 (3H, m, aromatic C**H**), 7.26 (2H, d, aromatic C**H**, *J*= 8.0 Hz), 7.21-7.19 (2H, m, aromatic C**H**), 4.99 (1H, d, Ar-C**H**, *J*= 3.0 Hz), 2.85 (1H, dd, -C**H**$_a$H$_b$-C=O, *J*= 8.0, 17.6 Hz), 2.45 (3H, s, Ar-C**H**$_3$), 2.38-2.31 (1H, m, -C**H**-CH$_3$), 2.16 (1H, dd, -CH$_a$**H**$_b$C=O, *J*= 3.5, 17.6 Hz), 1.24 (3H, d, -CHC**H**$_3$, *J*= 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 173.4 (**C**=O), 173.4 (**C**=O), 145.1 (aromatic **C**), 145.0 (aromatic **C**), 140.2 (aromatic **C**), 136.0 (aromatic **C**), 135.5 (aromatic **C**), 135.5 (aromatic **C**), 129.4 (aromatic **C**H), 129.2 (aromatic **C**H), 128.9 (aromatic **C**H), 128.8 (aromatic **C**H), 128.7 (aromatic **C**H), 128.6 (aromatic **C**H), 128.4 (aromatic **C**H), 128.2 (aromatic **C**H), 127.5 (aromatic **C**H), 126.1 (aromatic **C**H), 70.7 (Ar-**C**H), 67.2 (Ar-**C**H), 38.7 (**C**H$_2$), 38.4 (**C**H$_2$), 36.6 (**C**H), 32.9 (**C**H), 21.8 (**C**H$_3$), 20.5 (**C**H$_3$), 20.5 (**C**H$_3$), 15.6 (**C**H$_3$).

MS (CI; CH_2Cl_2) *m/z*: 330 (28) $[M+H]^+$, 265 (100).

Microanalysis: Found C 65.33, H 5.77, N 4.15; required for $C_{18}H_{19}NSO_3$, C 65.63, H 5.81, N 4.25.

2-(1-Ethoxyethoxy)pent-3-enenitrile (222)



222

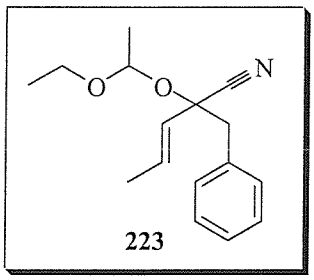
Following the method of Jacobson *et al*,[55] to a solution of protected cyanohydrin **206** (5.08 g, 30.0 mmol) in THF (15 mL) was added HCl (15 mL, 1N aq. solution) and the reaction heated to reflux. After 5 h, GC indicated hydrolysis was complete, the mixture was saturated with NaCl and extracted with Et_2O (3 x 15 mL). The organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave cyanohydrin **221** as a light yellow oil (2.84 g, 29.2 mmol, 97 %). The crude cyanohydrin (2.70 g, 29.0 mmol) was taken up in ethyl vinyl ether (3.47 mL, 36.0 mmol) and 2-3 drops of TFA were added **-CARE**, the reaction self-refluxed for 5 min at which time the mixture was basified with NaOH (2N aq. solution). Purification by distillation *in vacuo* (120-124 °C, ~ 1 mmHg), gave the pure ethoxyethyl protected cyanohydrin **222** as a colourless oil (3.73 g, 22.0 mmol, 76 %). The spectroscopic data were in accordance with that published in the literature[55], and are reported as a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 2980 (m), 2936 (w), 1448 (m), 1386 (m), 1131 (s), 1084 (s), 1053 (s), 1025 (s), 964 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.02 (2 x 1H, m, =C**H**-CH_3), 5.52 (2 x 1H, m, =C**H**-C=O), 4.93 (2 x 1H, d, -C**H**-CN, *J*= 5.5 Hz), 4.83 (2 x 1H, q, -O-C**H**(CH_3)-O-, *J*= 5.5 Hz), 3.57 (2 x 2H, m, -O**CH$_2$**CH_3), 1.76 (2 x 3H, dd, =CH-**CH$_3$**, *J*= 5.5, 1.2 Hz), 1.39 (3H, d, -O-CH(**CH$_3$**)-O-, *J*= 5.5 Hz), 1.35 (3H, d, -O-CH(**CH$_3$**)-O-, *J*= 5.5 Hz) 1.19 (2 x 3H, t, -OCH_2**CH$_3$**, *J*= 6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 133.0 (H_3C-CH=<u>C</u>H), 132.9 (H_3C-CH=<u>C</u>H), 123.9 (H_3C-<u>C</u>H=CH), 123.7 (H_3C-<u>C</u>H=CH), 118.2 (<u>C</u>N), 117.5 (<u>C</u>N), 99.4 (-O-<u>C</u>H(CH_3)-O-), 98.8 (-O-<u>C</u>H(CH_3)-O-), 63.4 (-<u>C</u>H-CN), 63.0 (-<u>C</u>H-CN), 61.0 (-O-<u>C</u>H_2CH_3), 60.9 (-O-<u>C</u>H_2CH_3), 19.6 (-<u>C</u>H_3), 19.6 (-<u>C</u>H_3), 17.6 (-<u>C</u>H_3), 17.5 (-<u>C</u>H_3), 15.2 (-<u>C</u>H_3), 15.0 (-<u>C</u>H_3).

2-Benzyl-2-(1-ethoxyethoxy)pent-3-enenitrile (223)



223

Following the method of Jacobson *et al*,[55], to a solution of diisopropylamine (168 μL, 1.2 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (826 μL, 1.20 mmol, 1.43 M solution in hexane) and the reaction stirred at -78 °C for 10 min, then allowed to warm to 0 °C. The ethoxyethyl protected cyanohydrin **222** (200 mg, 1.20 mmol) was added and the reaction stirred at 0 °C for 15 min. Benzyl bromide (137 μL, 1.15 mmol) was added and the mixture stirred at 0 °C for 4 h. The reaction was quenched with water (10 mL), partitioned between Et_2O and brine, and extracted with Et_2O (3 x 10 mL). The organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product **223** as a yellow oil (345 mg). Purification by column chromatography (10 % Et_2O/hexane) gave the pure product as a colourless oil (220 mg, 0.85 mmol, 71 %), the spectroscopic data is reported as a mixture of diastereoisomers.

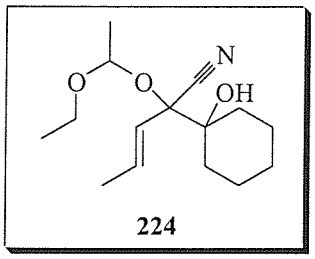
IR (neat) ν/cm^{-1}: 2977 (w), 2936 (m), 1664 (w), 1447 (m), 1383 (m), 1140 (s), 1082 (s), 1022 (s), 971 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.41-7.26 (2 x 5H, m, aromatic C<u>H</u>), 6.05 (2 x 1H, dq, H_3C-C<u>H</u>=CH, *J*= 15.7, 7.0 Hz), 5.40 (2 x 1H, dq, H_3C-CH=C<u>H</u>, *J*= 15.9, 2.0

Hz), 4.88 (2 x 1H, q, -O-C<u>H</u>(CH_3)-O-, *J*= 5.5 Hz), 3.46 (2 x 2H, m, -OC<u>H_2</u>CH_3), 3.13 (2 x 2H, m, benzylic C<u>H_2</u>), 1.78 (2 x 3H, m, <u>H_3</u>C-CH=CH), 1.33 (2 x 3H, d, -O-CH(C<u>H_3</u>)-O-, *J*= 5.0 Hz), 1.15 (2 x 3H, t, -OCH_2C<u>H_3</u>, *J*= 7.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 133.9 (2 x aromatic-<u>C</u>), 131.6 (2 x aromatic-<u>C</u>H), 129.6 (2 x aromatic-<u>C</u>H), 128.9 (2 x aromatic-<u>C</u>H), 127.5 (2 x H_3C-<u>C</u>H=CH), 123.7 (2 x H_3C-<u>C</u>H=CH), 118.8 (2 x -<u>C</u>N), 97.3 (2 x -O-<u>C</u>H(CH_3)-O-), 78.1 (2 x <u>C</u>-CN), 60.6 (2 x -OC<u>H_2</u>CH_3), 47.4 (2 x benzylic <u>C</u>H_2), 21.3 (2 x <u>C</u>H_3), 17.6 (2 x C<u>H_3</u>), 15.1 (2 x C<u>H_3</u>).

2-(1-Ethoxyethoxy)-2-(1-hydroxycyclohexyl)pent-3-enenitrile (224)



224

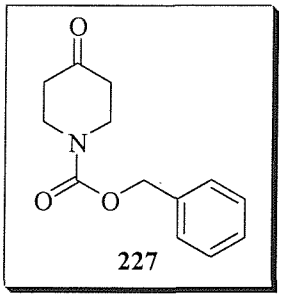
Following the method of Jacobson *et al*,[55] to a solution of diisopropylamine (168 μL, 1.20 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (826 μL, 1.20 mmol, 1.43 M solution in hexane) and the solution stirred at -78 °C for 10 min then allowed to warm to 0 °C. Protected cyanohydrin **222** (200 mg, 1.20 mmol) was added and the reaction stirred at 0 °C for 15 min, cyclohexanone (119 μL, 1.15 mmol) was added and the mixture stirred for 2 h at 0 °C. The reaction was quenched with water (10 mL), partitioned between Et_2O and brine, and extracted with Et_2O (3 x 15 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a yellow oil (270 mg). Purification by column chromatography (10 % Et_2O/hexane) provided the pure product **224** as a colourless oil (243 mg, 0.91 mmol, 79 %). The spectroscopic data is reported as a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3495 (br w), 2936 (m), 1695 (w), 1448 (m), 1383 (m), 1139 (s), 1082 (m), 1022 (s), 975 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.23-6.15 (2 x 1H, m, H_3C-C**H**=CH), 5.68-5.53 (2 x 1H, dd, H_3C-CH=C**H**, *J*= 17.4, 2.0 Hz), 4.90 (2 x 1H, q, -O-C**H**(CH_3)-O-, *J*= 5.5 Hz), 3.71-3.36 (2 x 2H, m, -OC**H**$_2$$CH_3$), 1.90-1.43 (2 x 10H, m, -C**H**$_2$-), 1.80 (2 x 3H, d, -C**H**$_3$, *J*= 5.5 Hz), 1.36 (2 x 3H, d, -C**H**$_3$, *J*= 5.5 Hz), 1.19 (2 x 3H, t, -C**H**$_3$, *J*= 6.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 133.7 (H_3C-CH=**C**H), 132.8 (H_3C-CH=**C**H), 125.5 (H_3C-**C**H=CH), 124.8 (H_3C-**C**H=CH), 118.1 (-**C**N), 117.7 (-**C**N), 97.7 (-O-**C**H(CH_3)-O-), 97.3 (-O-**C**H(CH_3)-O-), 84.2 (-**C**-CN), 83.5 (-**C**-CN), 75.8 (-**C**(OH)), 75.7 (-**C**(OH)), 61.1 (-O**C**$H_2$$CH_3$), 60.9 (-O**C**$H_2$$CH_3$), 33.1 (-**C**$H_2$-), 32.1 (-**C**$H_2$-), 31.3 (-**C**$H_2$-), 31.2 (-**C**$H_2$-), 25.8 (-**C**$H_2$-), 25.4 (-**C**$H_2$-), 21.3 (-**C**$H_3$), 21.1 (-**C**$H_3$), 17.7 (-**C**$H_3$), 17.4 (-**C**$H_3$), 14.9 (-**C**$H_3$), 14.8 (-**C**$H_3$).

4-Oxo-piperidine-1-carboxylic acid benzyl ester (227)



227

To 4-piperidone monohydrate monohydrochloride (**216**) (2.00 g, 13.0 mmol) in CH_2Cl_2 (20 mL) was added anhydrous sodium sulfate (3.69 g, 26.0 mmol) and the resulting suspension stirred at rt for 30 min. At which time benzyl chloroformate (5.57 mL, 39.0 mmol) was added, then triethylamine (7.25 mL, 52.0 mmol) dropwise -**CARE** at 0 °C; the reaction was allowed to warm to rt and stirred for 16 h. The reaction was partitioned between CH_2Cl_2 and water (20 mL) and washed with HCl (2N aq. solution, 2 x 20 mL), water (20 mL), NaOH (2N aq. solution, 2 x 20 mL) and water (2 x 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the

crude product as a yellow liquid (2.30 g). Purification by column chromatography (60 % CH_2Cl_2/hexane) gave the pure carbamate **227** as a colourless oil (1.67 g, 7.2 mmol, 55 %). The spectroscopic data were consistent with that published in the literature.[71]

IR (neat) ν/cm^{-1}: 3025 (w), 2969 (w), 2879 (w), 1698 (s), 1429 (s), 1311 (m), 1273 (m), 1228 (s), 1119 (m), 991 (m).

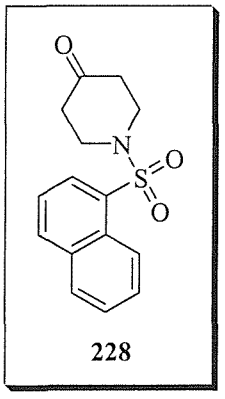
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.38-7.34 (5H, m, aromatic C**H**), 5.17 (2H, s, benzylic C$\underline{H}_2$), 3.79 (4H, t, -C$\underline{H}_2$-N-C$\underline{H}_2$-, *J*= 6.5 Hz), 2.45 (4H, br t, -C$\underline{H}_2$-CO-C$\underline{H}_2$-, *J*= 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 207.4 (**C**=O), 155.2 (-N-**C**=O), 136.5 (aromatic **C**), 128.7 (aromatic **C**H), 128.4 (aromatic **C**H), 128.2 (aromatic **C**H), 67.7 (benzylic **C**H_2), 43.2 (-**C**H_2-N-**C**H_2-), 41.2 (-**C**H_2-CO-**C**H_2-).

LRMS (CI; CH_2Cl_2) *m/z*: 234 $(M+H)^+$ (74), 91 $(Benzyl+H)^+$ (100).

CAS No.: 19099-93-5.

1-(Naphthalene-1-sulfonyl)-piperidin-4-one (228)



228

Based on the method of Speckamp *et al*,[59] to 4-piperidone monohydrate monohydrochloride (**216**) (2.00 g, 13.0 mmol) in CH_2Cl_2 (20 mL) was added

naphthalene-1-sulfonyl chloride (prepared by the method of Zollinger *et al*,[72] 2.95 g, 13.0 mmol). After 2 min, triethylamine (3.63 mL, 26.0 mmol) was added dropwise at 0 °C, and the reaction stirred at rt for 16 h. The reaction was quenched by the addition of water (20 mL), the phases separated and washed with HCl (2N aq. solution, 2 x 20 mL), water (2 x 20 mL), NaOH (2N aq. solution, 2 x 20 mL) and water (2 x 20 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as an oily yellow solid. Purification by recrystallisation (EtOAc) granted the pure sulfonamide as a white, crystalline solid (1.80 g, 6.2 mmol, 47 %).

MPt.: 87-90 °C (EtOAc)

IR (neat) ν/cm^{-1}: 2956 (w), 1715 (s), 1335 (s), 1297 (w), 1220 (m), 1159 (s), 1036 (m), 925 (s), 781 (m).

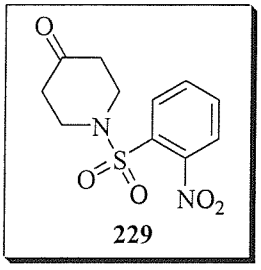
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.70 (1H, d, aromatic C**H**, *J*= 8.9 Hz), 8.28 (1H, dd, aromatic C**H**, *J*= 7.4, 1.5 Hz), 8.11 (1H, d, aromatic C**H**, 7.9 Hz), 7.96 (1H, dd, aromatic C**H**, *J*= 7.9, 1.5 Hz), 7.70-7.55 (3H, m, aromatic C**H**), 3.59 (4H, t, -C**H**$_2$-N-C**H**$_2$-, *J*= 6.5 Hz), 2.55 (4H, t, -C**H**$_2$-C-C**H**$_2$-, *J*= 6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 206.2 (**C**=O), 135.4 (aromatic **C**-SO_2), 134.0 (aromatic **C**), 131.0 (aromatic **C**H), 130.0 (aromatic **C**), 129.6 (aromatic **C**H), 128.4 (aromatic **C**H), 128.0 (aromatic **C**H), 127.5 (aromatic **C**H), 125.1 (aromatic **C**H), 124.6 (aromatic **C**H), 45.7 (**C**H$_2$-N-**C**H$_2$), 41.5 (**C**H$_2$-CO-**C**H$_2$).

MS (EI; CH_2Cl_2) *m/z*: 289 $[M]^{+\bullet}$ (100)

HRMS (ES) *m/z*: Found 290.0848; required for $C_{15}H_{15}NSO_3$, $[M+H]^+$ = 290.0846.

N-(2-Nitrobenzenesulfonyl)-piperidin-4-one (229)



229

To 4-piperidone monohydrate monohydrochloride (**216**) (5.00 g, 32.5 mmol) in CH_2Cl_2 (40 mL) was added 2-nitrobenzenesulfonyl chloride (7.21 g, 32.5 mmol) and triethylamine (9.07 mL, 65.0 mmol); the resulting mixture was stirred at rt for 24 h. The reaction was partitioned between CH_2Cl_2 and water (20 mL), washed with HCl (2N aq. solution, 2 x 20 mL) and water (2 x 20 mL). The organic phase dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as an olive coloured solid. Purification by recrystallisation (EtOAc) furnished the pure sulfonamide **229** as a mustard coloured solid (3.25 g, 11.4 mmol, 35 %).

MPt.: 118-121 °C (EtOAc).

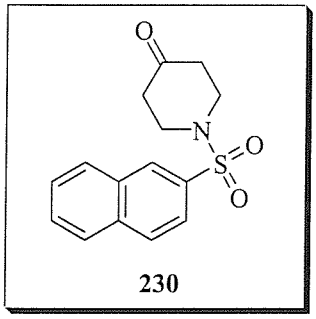
IR (neat) ν/cm^{-1}: 3087 (w), 2988 (w), 2874 (w), 1712 (s), 1551 (s), 1535 (s), 1365 (s), 1332 (s), 1224 (m), 1157 (s), 1128 (m), 1032 (m), 938 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.07-8.04 (1H, m, aromatic C**H**), 7.76-7.65 (3H, m, aromatic C**H**), 3.67 (4H, t, -C**H**$_2$-N-C**H**$_2$-, *J*= 6.5 Hz), 2.57 (4H, t, -C**H**$_2$-CO-C**H**$_2$-, *J*= 6.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 205.9 (**C**=O), 148.5 (aromatic **C**-NO_2), 134.6 (aromatic **C**H), 132.4 (aromatic **C**H), 132.3 (aromatic **C**), 131.3 (aromatic **C**H), 124.8 (aromatic **C**H), 45.9 (-**C**H$_2$-N-**C**H$_2$-), 41.6 (-**C**H$_2$-CO-**C**H$_2$-).

Microanalysis: Found C 46.34, H 4.42, N 9.76; required for $C_{11}H_{12}N_2SO_5$, C 46.47, H 4.25, N 9.85.

1-(Naphthalene-2-sulfonyl)-piperidin-4-one (230)



230

Based on the method of Speckamp *et al*,[59] 2-naphthalenesulfonyl chloride (13.0 g, 57.0 mmol) was added to a solution of 4-piperidone monohydrate monohydrochloride (**216**) (7.5 g, 49.0 mmol) and K_2CO_3 (13.5 g, 98.0 mmol) in CH_2Cl_2 (50 mL) and H_2O (50 mL). The reaction was stirred at rt for 15 h, diluted with $NaHCO_3$ (sat. aq. solution, 30 mL), the phases separated and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude material as an off-white powder (16.6 g). Purification by recrystallisation (EtOAc) gave the title compound as an amorphous white solid (13.5 g, 46.5 mmol, 95 %).

MPt.: 126-128 °C (EtOAc).

IR (neat) ν/cm^{-1}: 2922 (w), 1725 (s), 1600 (m), 1507 (w), 1328 (s), 1162 (s), 1077 (m), 911 (m).

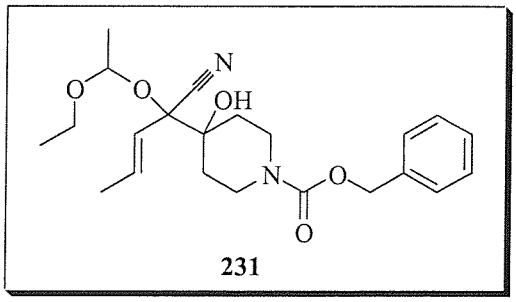
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.40 (1H, s, aromatic C**H**), 8.02-7.93 (3H, m, aromatic C**H**), 7.79 (1H, dd, aromatic C**H**, *J*= 1.7, 8.6 Hz), 7.69-7.65 (2H, m, aromatic C**H**), 3.49 (4H, t, -C**H**$_2$-N-C**H**$_2$-, *J*= 6.2 Hz), 2.57 (4H, t, -C**H**$_2$-C-C**H**$_2$-, *J*= 6.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 205.6 (**C**=O), 135.1 (aromatic **C**), 133.7 (aromatic **C**), 132.3 (aromatic **C**), 129.7 (aromatic **C**H), 129.4 (aromatic **C**H), 129.3 (aromatic **C**H), 129.1 (aromatic **C**H), 128.1 (aromatic **C**H), 127.9 (aromatic **C**H), 122.6 (aromatic **C**H), 46.0 (-**C**H$_2$-N-**C**H$_2$-), 40.8 (-**C**H$_2$-C-**C**H$_2$-).

MS (EI, CH_2Cl_2): 289 (12) $[M]^{+\bullet}$, 127 (100) $[naphthalene]^{+\bullet}$.

Microanalysis: Found C 62.11, H 5.43, N 4.70; required for $C_{15}H_{15}NSO_3$, C 62.27, H 5.23, N 4.84.

4-[1-Cyano-1-(1-ethoxyethoxy)but-2-enyl]-4-hydroxypiperidine-1-carboxylic acid benzyl ester (231)



231

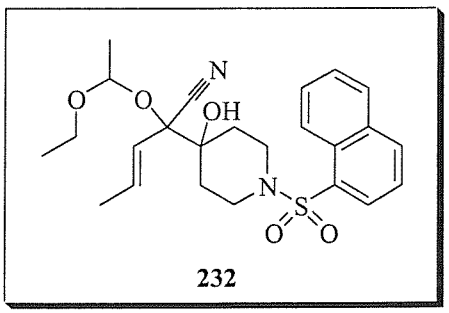
Following the method of Jacobson *et al*,[55] to a solution of diisopropylamine (420 μL, 3.0 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (2.42 mL, 3.0 mmol, 1.24 M solution in hexane) and the solution stirred at -78 °C for 10 min then allowed to warm to 0 °C. Protected cyanohydrin **222** (508 mg, 3.0 mmol) was then added and the reaction stirred at 0 °C for 15 min, 4-oxo-piperidine-1-carboxylic acid benzyl ester (**227**) (332 mg, 1.5 mmol) was added and the mixture stirred for 1.5 h at 0 °C. The reaction was quenched with water (10 mL), partitioned between Et_2O and brine, and extracted with Et_2O (3 x 20 mL). The organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a thick brown oil (790 mg). Purification by column chromatography (20 % Et_2O/hexane) gave the pure product **231** as a light yellow oil (1.10 g, 2.7 mmol, 91 %). The spectroscopic data is reported as a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3420 (br w), 2975 (w), 2931 (w), 2250 (w), 1690 (s), 1437 (m), 1382 (w), 1277 (w), 1244 (s), 1142 (m), 1076 (m), 910 (s), 731 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.28-7.22 (2 x 5H, m, aromatic C**H**), 6.20 (1H, dq, H_3C-C**H**=CH, *J*= 15.6, 6.5 Hz), 6.13 (1H, dq, H_3C-C**H**=CH, *J*= 15.9, 6.5 Hz), 5.52 (1H, br d, H_3C-CH=C**H**, *J*= 15.9 Hz), 5.37 (1H, br d, H_3C-CH=C**H**, *J*= 15.6 Hz), 5.05 (2 x 2H, s, benzylic C**H**$_2$), 4.86 (1H, q, -OC**H**(CH_3)O-, *J*= 5.3 Hz), 4.80 (1H, q, -OC**H**(CH_3)O-, *J*= 5.3 Hz), 4.07 (2 x 2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.78-3.64 (2 x 2H, m, -OC**H**$_2CH_3$), 3.10 (2 x 2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 1.76 (2 x 3H, d, **H**$_3$C-CH=CH, *J*= 6.2 Hz + 2 x 2H, br s, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.55 (2 x 2H, br s, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.33 (3H, d, -OCH(C**H**$_3$)O-, *J*= 5.2 Hz), 1.24 (3H, d, -OCH(C**H**$_3$)O-, *J*= 5.2 Hz), 1.15 (3H, t, -OCH$_2$C**H**$_3$, *J*= 7.2 Hz), 1.08 (3H, t, -OCH$_2$C**H**$_3$, *J*= 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 155.5 (2 x -N-**C**=O), 137.2 (2 x aromatic **C**), 135.2 (H_3C-CH=**C**H), 134.4 (H_3C-CH=**C**H), 129.0 (aromatic **C**H), 128.9 (aromatic **C**H), 128.7 (aromatic **C**H), 128.4 (aromatic **C**H), 128.4 (aromatic **C**H), 128.3 (aromatic **C**H), 125.3 (H_3C-**C**H=CH), 124.5 (H_3C-**C**H=CH), 117.9 (**C**N), 117.5 (**C**N), 98.8 (-O**C**H(CH_3)O-), 98.0 (-O**C**H(CH_3)O-), 84.2 (-O-**C**-CN), 83.5 (-O-**C**-CN), 74.9 (**C**-OH), 74.7 (**C**-OH), 67.5 (2 x benzylic **C**H$_2$), 62.6 (-O-**C**H$_2CH_3$), 61.7 (-O-**C**H$_2CH_3$), 39.8 (-**C**H$_2$-N-**C**H$_2$-), 39.8 (-**C**H$_2$-N-**C**H$_2$-), 32.0 (-**C**H$_2$-C-**C**H$_2$-), 31.6 (-**C**H$_2$-C-**C**H$_2$-), 21.7 (-OCH(**C**H$_3$)O-), 21.5 (-OCH(**C**H$_3$)O-), 18.3 (2 x H$_3$**C**-CH=CH), 15.5 (-O-CH$_2$**C**H$_3$), 15.3 (-O-CH$_2$**C**H$_3$).

2-(1-Ethoxyethoxy)-2-[4-hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (232)



232

Following the method of Jacobson *et al*,[55] to a solution of diisopropylamine (145 μL, 1.04 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (1.08 mL, 1.04 mmol, 1.12 M

solution in hexane) and the solution stirred at -78 °C for 5 min, then 0 °C for 10 min. The LDA was cooled to -78 °C and cyanohydrin **222** (176 mg, 1.04 mmol) added; the resulting yellow solution was stirred at -78 °C for 15 min. *N*-(1-Naphthalenesulfonyl)-4-piperidone (**228**) (200 mg, 0.69 mmol) was added and the reaction kept at -78 °C for 1.5 h. The reaction was poured into NH_4Cl (sat. aq. solution, 10 mL), partitioned between Et_2O (15 mL) and water (10 mL), and washed with water (3 x 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL), the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a yellow oil. Purification by column chromatography (30 % Et_2O/hexane) gave the title compound **232** as a colourless oil (290 mg, 0.63 mmol, 92 %). The spectroscopic data is reported for a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3481 (w), 2927 (w), 1508 (w), 1437 (w), 1384 (w), 1336 (m), 1247 (w), 1159 (s), 1080 (m), 1028 (s), 924 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.77 (2 x 1H, d, aromatic C**H**, *J*= 8.5 Hz), 8.21 (2 x 1H, d, aromatic C**H**, *J*= 7.3 Hz), 8.08 (2 x 1H, d, aromatic C**H**, *J*= 8.0 Hz), 7.93 (2 x 1H, d, aromatic C**H**, *J*= 8.3 Hz), 7.70-7.52 (2 x 3H, m, aromatic C**H**), 6.28-6.14 (2 x 1H, m, H_3C-C**H**=CH), 5.52 (1H, dd, H_3C-CH=C**H**, *J*= 1.5, 15.6 Hz), 5.35 (1H, dd, H_3C-CH=C**H**, *J*= 1.5, 15.6 Hz), 4.90 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.0 Hz), 4.84 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.3 Hz), 3.81 (2 x 2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.70-3.49 (2 x 2H, m, -O-C**H**$_2$$CH_3$), 2.97-2.83 (2 x 2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.72-2.18 (2 x 2H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.95-1.60 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.82 (2 x 3H, d, -C**H**$_3$, *J*= 6.5 Hz), 1.37 (3H, d, -C**H**$_3$, *J*= 5.0 Hz), 1.29 (3H, d, -C**H**$_3$, *J*= 5.3 Hz), 1.20 (3H, t, -O-CH_2C**H**$_3$, *J*= 7.0 Hz), 1.14 (3H, t, -OCH_2C**H**$_3$, *J*= 7.0 Hz).

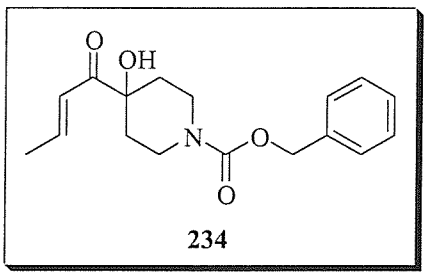
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 135.4 (2 x aromatic **C**H), 135.3 (2 x aromatic **C**), 134.8 (2 x H_3C-CH=**C**H), 134.6 (aromatic **C**), 133.6 (aromatic **C**), 130.7 (aromatic **C**H), 129.6 (aromatic **C**H), 129.3 (aromatic **C**H), 128.5 (aromatic **C**H), 128.3 (aromatic **C**H), 128.0 (2 x aromatic **C**), 127.3 (aromatic **C**H), 125.5 (2 x aromatic **C**H), 125.0 (2 x aromatic **C**H), 124.5 (H_3C-**C**H=CH), 124.2 (H_3C-**C**H=CH), 117.5 (-**C**N), 117.1 (-**C**N), 98.8 (-O-**C**H(CH_3)-O-), 98.1 (-O-**C**H(CH_3)-O-), 84.1 (**C**-CN), 83.4 (**C**-CN), 74.2 (**C**-OH), 74.1 (**C**-OH), 62.6 (-O-**C**$H_2$$CH_3$), 61.9 (-O-**C**$H_2$$CH_3$), 41.7 (-**C**$H_2$-

N-$\underline{C}H_2$-), 41.7 (-$\underline{C}H_2$-N-$\underline{C}H_2$-), 32.3 (-$\underline{C}H_2$-C-$\underline{C}H_2$-), 31.5 (-$\underline{C}H_2$-C-$\underline{C}H_2$-), 21.6 (-O-CH($\underline{C}H_3$)-O-), 21.4 (-O-CH($\underline{C}H_3$)-O-), 18.2 (2 x $H_3\underline{C}$-CH=CH), 15.5 (-O-$CH_2C\underline{H}_3$), 15.3 (-O-$CH_2C\underline{H}_3$).

HRMS (ES) *m/z*: Found 939.3653; required for $C_{24}H_{30}N_2SO_5$, $[2M+Na]^+ = 939.3642$.

Microanalysis: Found C 62.96, H 6.55, N 6.05; required for $C_{24}H_{30}N_2SO_5$, C 62.86, H 6.59, N 6.11.

4-But-2-enoyl-4-hydroxy-piperidine-1-carboxylic acid benzyl ester (234)



234

Following the method of Jacobson *et al*,[55] 4-[1-cyano-1-(1-ethoxyethoxy)-but-2-enyl]-4-hydroxy-piperidine-1-carboxylic acid benzyl ester (**231**) (290 mg, 0.721 mmol) was taken up into THF (5 mL); H_2SO_4 (2N aq. solution, 5 mL) was added and the mixture heated to reflux for 5 h. The reaction was partitioned between Et_2O (10 mL) and water (10 mL), washed with NaOH (3 x 10 mL, 2N aq. solution) and water (2 x 10 mL). The aqueous phases were extracted with Et_2O (3 x 10 mL), the combined organic phases dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a yellow oil (156 mg). Purification by column chromatography (50 % Et_2O/hexane) furnished the pure enone as an off-white solid 186 mg, 0.612 mmol, 85 %).

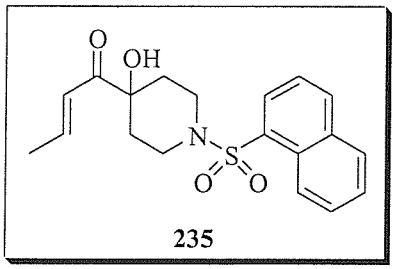
IR (neat) ν/cm^{-1}: 3426 (br w), 2922 (w), 2874 (w), 1695 (s), 1626 (m), 1433 (s), 1277 (m), 1242 (s), 1077 (m), 1031 (m), 972 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.33-7.25 (5H, m, aromatic C**H**), 7.09 (1H, dq, H_3C-**H**C=CH, *J*= 15.1, 6.7 Hz), 6.47 (1H, dd, H_3C-HC=C**H**, *J*= 15.1, 1.5 Hz), 5.09 (2H, s, benzylic C$\mathbf{H}_2$), 4.22 (1H, s, -O**H**), 4.07 (2H, br s, -C$\mathbf{H}_a$$H_b$-N-C$\mathbf{H}_a$$H_b$-), 3.18 (2H, br s, -$CH_a$$\mathbf{H}_b$-N-$CH_a$$\mathbf{H}_b$-), 1.87 (3H, dd, $\mathbf{H}_3$C-HC=CH, *J*= 6.9, 1.5 Hz), 1.82-1.75 (2H, m, -C$\mathbf{H}_a$$H_b$-C-C$\mathbf{H}_a$$H_b$-), 1.38 (2H, br d, -$CH_a$$\mathbf{H}_b$-C-$CH_a$$\mathbf{H}_b$-, *J*= 12.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 200.8 (**C**=O), 155.6 (N-**C**=O), 147.4 (=**C**H-CH_3), 137.2 (aromatic **C**), 128.9 (aromatic **C**H), 128.4 (aromatic **C**H), 128.3 (aromatic **C**H), 124.1 (=**C**H-C=O), 75.4 (**C**-OH), 67.6 (benzylic **C**H_2), 40.2 (-**C**H_2-), 33.5 (-**C**H_2-), 19.0 (-**C**H_3).

LRMS (CI; CH_2Cl_2) *m/z*: 304 $(M+H)^+$ (62), 91 $(Benzyl+H)^+$ (100).

1-[4-Hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (235)



235

Following the method of Jacobson *et al*,[55] 2-(1-ethoxyethoxy)-2-[4-hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (**232**) (490 mg, 1.07 mmol) was taken up into THF (10 mL); H_2SO_4 (2N aq. solution, 10 mL) was added and the mixture heated to reflux for 5 h. The reaction was partitioned between Et_2O (10 mL) and water (10 mL), washed with NaOH (3 x 10 mL, 2N aq. solution) and water (2 x 10 mL). The aqueous phases were extracted with Et_2O (3 x 10 mL), the combined organic phases dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the crude product as a yellow oil (370 mg). Purification by column chromatography (50 % Et_2O/hexane) furnished the pure enone as a white solid (351 mg, 0.98 mmol, 91 %).

MPt.: 155-158 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3458 (br w), 2965 (w), 2863 (w), 1690 (m), 1627 (s), 1348 (s), 1160 (s), 1133 (s), 1064 (m), 919 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.77 (1H, d, aromatic C**H**, *J*= 8.5 Hz), 8.21 (1H, d, aromatic C**H**, *J*= 6.6 Hz), 8.06 (1H, d, aromatic C**H**, *J*= 8.1 Hz), 7.91 (1H, d, aromatic C**H**, *J*= 7.7 Hz), 7.66-7.50 (3H, m, aromatic C**H**), 7.11 (1H, dq, =C**H**-CH_3, *J*= 15.1, 7.0 Hz), 6.34 (1H, dd, =C**H**-C=O, *J*= 15.4, 1.5 Hz), 3.87 (2H, br d, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.8 Hz), 2.99 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 2.2, 12.5 Hz), 2.94 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 2.2, 12.5 Hz), 2.07 (2H, td, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-, *J*= 12.9, 4.8 Hz), 1.95 (3H, dd, -CH=CH-C**H**$_3$, *J*= 7.0, 1.5 Hz), 1.41 (2H, br d, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 12.9 Hz).

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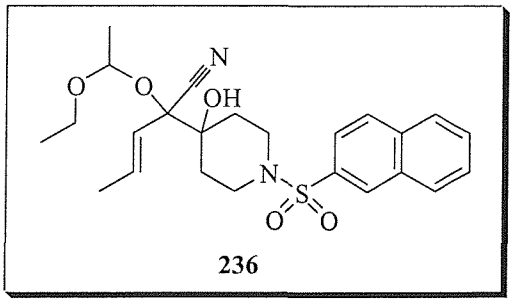
^{13}C **NMR** (75 MHz, $CDCl_3$) δ/ppm: 200.0 (C=O), 147.7 (=CH-CH_3), 134.9 (aromatic C), 134.4 (aromatic CH), 130.2 (=CH-C=O), 129.5 (aromatic C), 129.0 (aromatic CH), 128.1 (aromatic CH), 128.0 (aromatic C), 126.9 (aromatic CH), 125.1 (aromatic CH), 124.2 (aromatic CH), 123.4 (aromatic CH), 74.2 (C-OH), 41.5 (-CH_2-N-CH_2-), 33.0 (-CH_2-C-CH_2-), 18.7 (-CH_3).

HRMS (ES) *m/z*: Found 382.1092; required for $C_{19}H_{21}NSO_4$, $[M+Na]^+$ = 382.1083.

2-(1-Ethoxyethoxy)-2-[4-hydroxy-1-(naphthalene-2-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (236)



236

Following the method of Jacobson *et al*,[55] to diisopropylamine (3.73 mL, 26.6 mmol) in THF (150 mL) at –78 °C was added *n*-BuLi (1.85 M solution/hexane, 14.38 mL, 26.6 mmol) and the solution stirred at –78 °C for 10 min, 0 °C for 10 min, then cooled to –78 °C. Cyanohydrin **222** (4.50 g, 26.6 mmol) was added to the LDA and the resulting yellow solution stirred at –78 °C for 20 min. Piperidone **230** (7.00 g, 24.2 mmol) was added and the reaction stirred at –78 °C for 1.5 h then poured into cold NH_4Cl (sat. aq. solution). The phases were separated and washed with H_2O (3 x 50 mL), the aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a yellow foam (12.00 g). Purification by column chromatography (40 % Et_2O/hexane) gave the title compound as a white solid (8.92 g, 19.5 mmol, 80 %). The spectroscopic data is reported as for a mixture of diastereoisomers.

MPt.: 98-100 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3427 (w), 2930 (w), 1510 (w), 1444 (w), 1389 (w), 1336 (m), 1252 (w), 1156 (s), 1080 (m), 1028 (s), 915 (s).

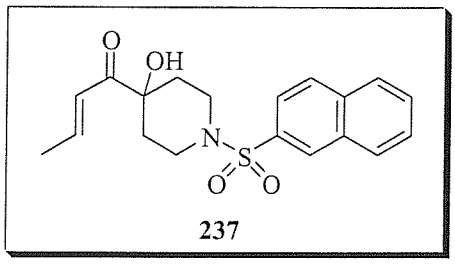
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.35 (2 x 1H, s, aromatic C**H**), 7.98 (2 x 1H, d, aromatic C**H**, *J*= 8.7 Hz), 7.95-7.92 (2 x 2H, m, aromatic C**H**), 7.78 (2 x 1H, dd, aromatic C**H**, *J*= 1.7, 8.7 Hz), 7.67-7.65 (2 x 2H, m, aromatic C**H**), 6.25 (2 x 1H, dq, =C**H**-CH_3, *J*= 15.6, 6.7 Hz), 5.53 (1H, dd, =C**H**-C-CN, *J*= 15.6, 1.5 Hz), 5.37 (1H, dd, =C**H**-C-CN, *J*= 15.6, 1.5 Hz), 4.92 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.2 Hz), 4.85 (1H, q, -O-C**H**(CH_3)-O-, *J*= 5.2 Hz), 3.84-3.80 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.68-3.50 (2 x 2H, m, -OC**H**$_2$$CH_3$), 2.69 (2 x 1H, dt, -$CH_a$**H**$_b$-N-$CH_aH_b$-, *J*= 3.0, 12.2 Hz), 2.66 (2 x 1H, dt, -CH_aH$_b$-N-CH_a**H**$_b$-, *J*= 3.0, 12.2 Hz), 2.03-1.68 (2 x 4H, m, -C**H**$_a$**H**$_b$-C-C**H**$_a$**H**$_b$-), 1.82 (2 x 3H, dd, =CH-C**H**$_3$, *J*= 1.5, 5.2 Hz), 1.38 (3H, d, -O-CH(C**H**$_3$)-O-, *J*= 5.2 Hz), 1.29 (3H, d, -O-CH(C**H**$_3$)-O-, *J*= 5.2 Hz), 1.21 (3H, t, -O-CH_2C**H**$_3$, *J*= 7.0 Hz), 1.15 (3H, t, -O-CH_2C**H**$_3$, *J*= 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 133.3 (2 x H_3C-CH=**C**H), 133.1 (2 x aromatic **C**), 132.5 (2 x aromatic **C**H), 131.8 (2 x aromatic **C**), 130.5 (2 x aromatic **C**), 127.5 (2 x aromatic **C**H), 127.4 (2 x aromatic **C**H), 127.1 (2 x aromatic **C**H), 127.0 (2 x aromatic **C**H), 126.1 (aromatic **C**H), 125.8 (aromatic **C**H), 122.8 (aromatic **C**H), 122.0 (aromatic **C**H), 121.1 (2 x H_3C-**C**H=CH), 115.3 (**C**N), 114.9 (**C**N), 96.7 (-O-**C**H(CH_3)-O-), 96.0 (-O-**C**H(CH_3)-O-), 81.9 (-O-**C**-CN), 81.2 (-O-**C**-CN), 71.8 (**C**-OH), 71.7 (**C**-OH), 60.4 (-O-**C**$H_2$$CH_3$), 59.7 (-O-**C**$H_2$$CH_3$), 40.0 (2 x -**C**$H_2$-N-$CH_2$-), 40.0 (2 x -$CH_2$-N-**C**$H_2$-), 29.9 (2 x -**C**$H_2$-C-$CH_2$-), 29.1 (2 x -$CH_2$-C-**C**$H_2$-), 19.4 (**C**$H_3$), 19.2 (**C**$H_3$), 16.0 (**C**$H_3$), 16.0 (**C**$H_3$), 13.3 (**C**$H_3$), 13.1 (**C**$H_3$).

LRMS (ES, CH_3CN): 459 (8) $[M+H]^+$, 481 (35) $[M+Na]^+$, 497 (100) $[M+K]^+$.

HRMS (ES) *m/z*: Found 939.3647; required for $C_{24}H_{30}N_2SO_5$, $[2M+Na]^+$ = 939.3642.

1-[4-Hydroxy-1-(naphthalene-2-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (237)



237

Following the method of Jacobson *et al*,[55] 2-(1-ethoxyethoxy)-2-[4-hydroxy-1-(naphthalene-2-sulfonyl)-piperidin-4-yl]-pent-3-enenitrile (**236**) (244 mg, 0.53 mmol) was taken up into THF (10 mL); H_2SO_4 (2N aq. solution, 10 mL) was added and the mixture heated to reflux for 6 h. The reaction was partitioned between Et_2O (10 mL) and water (10 mL), and washed with NaOH (3 x 10 mL, 2N aq. solution) and water (2 x 10 mL). The aqueous phases were extracted with Et_2O (3 x 10 mL), the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude product as a cloudy oil (172 mg). Purification by column chromatography (20 % Et_2O/hexane) furnished the pure enone as a white powder (163 mg, 0.45 mmol, 86 %).

MPt: 190-192 °C (EtOAc).

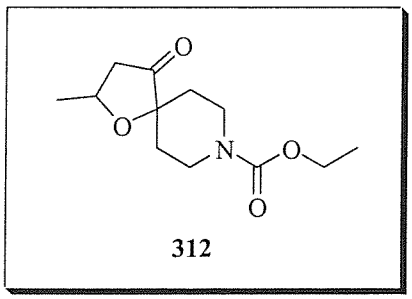
IR (neat) ν/cm^{-1}: 3499 (br w), 2978 (w), 2855 (w), 1682 (m), 1621 (s), 1503 (w), 1436 (w), 1318 (s), 1162 (s), 907 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.36 (1H, s, aromatic C**H**), 8.05-7.92 (3H, m, aromatic C**H**), 7.79 (1H, dd, aromatic C**H**, *J*= 8.4, 2.0 Hz), 7.70-7.60 (2H, m, aromatic C**H**), 7.22 (1H, dq, =C**H**-CH_3, *J*= 15.2, 7.0 Hz), 6.42 (1H, dd, =C**H**-C=O, *J*= 15.1, 1.5 Hz), 3.96 (1H, s, -O**H**), 3.90 (2H, ddd -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.4, 2.5, 2.5 Hz), 2.76 (2 x 1H, td, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-, *J*= 12.4, 2.5 Hz), 2.14 (2H, td, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-, *J*= 12.9, 5.0 Hz), 1.96 (3H, dd, -CH=CH-C**H**$_3$, *J*= 6.9, 1.7 Hz), 1.45 (2H, br d, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 11.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 200.3 (<u>C</u>=O), 148.1 (=<u>C</u>H-CH_3), 135.1 (aromatic <u>C</u>), 133.9 (aromatic <u>C</u>), 132.5 (aromatic <u>C</u>), 129.8 (aromatic <u>C</u>H), 129.7 (aromatic <u>C</u>H), 129.3 (aromatic <u>C</u>H), 129.3 (aromatic <u>C</u>H), 128.4 (aromatic <u>C</u>H), 128.0 (aromatic <u>C</u>H), 123.7 (aromatic <u>C</u>H), 123.3 (=<u>C</u>H-C=O), 74.2 (<u>C</u>-OH), 42.2 (-<u>C</u>H_2-N-<u>C</u>H_2), 33.3 (-<u>C</u>H_2-C-<u>C</u>H_2), 18.9 (-<u>C</u>H_3).

Microanalysis: Found C 63.25, H 5.93, N 3.77; required for $C_{19}H_{21}NSO_4$, C 63.49, H 5.89, N 3.89.

2-Methyl-4-oxo-1-oxa-8-spiro[4.5]decane-8-carboxylic acid ethyl ester (312)



312

Based on the procedure of Jacobsen *et al*,[55] to α-hydroxyenone **214** (250 mg, 1.04 mmol) in toluene (5 mL), were added MeOH (84 μL, 2.07 mmol) and *p*TSA (39 mg, 0.21 mmol) and the resulting mixture heated to reflux. After 24 h the reaction was partitioned between Et_2O and water and washed with water (5 mL), $NaHCO_3$ (3 x 5 mL) and water (2 x 5 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, leaving the crude product as a yellow oil (200 mg). Purification by column chromatography (10 % Et_2O/hexane) gave the pure furanone **312** as a colourless oil (158 mg, 0.66 mmol, 63 %).

IR (neat) ν/cm^{-1}: 2970 (br w), 1751 (s), 1695 (s), 1432 (s), 1378 (m), 1281 (m), 1245 (s), 1176 (m), 1077 (m), 919 (m), 731 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.32 (1H, ddq, -O-C<u>H</u>-CH_3, *J*= 10.1, 6.0, 6.0 Hz), 4.14 (2H, q, -OC<u>H</u>$_2$$CH_3$, *J*= 7.0 Hz), 3.89 (2H, br s, -C<u>H</u>$_a$$H_b$-N-C<u>H</u>$_a$$H_b$-), 3.14 (2H, br t,

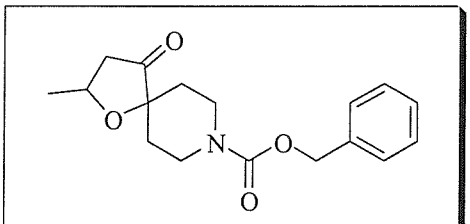
-$CH_a\underline{H}_b$-N-$CH_a\underline{H}_b$-, *J*= 13.6 Hz), 2.62 (1H, dd, -$CH_a\underline{H}_b$-C=O, *J*= 17.9, 5.4 Hz), 2.23 (1H, -$C\underline{H}_aH_b$-C=O, *J*= 18.4, 10.4 Hz), 1.71 (1H, ddd, -$C\underline{H}_aH_b$-C-CH_aH_b-, *J*= 5.0, 11.6, 13.4 Hz), 1.51 (3H, m, -$CH_a\underline{H}_b$-C-$CH_a\underline{H}_b$- + -CH_aH_b-C-$C\underline{H}_aH_b$-), 1.35 (3H, d, -$CHC\underline{H}_3$, 6.0 Hz), 1.19 (3H, t, -$OCH_2C\underline{H}_3$, *J*= 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 212.9 (<u>C</u>=O), 155.7 (-N-<u>C</u>=O), 76.6 (<u>C</u>-O), 74.6 (-O-<u>C</u>HCH_3), 61.5 (-O<u>C</u>H_2CH_3), 43.8 (<u>C</u>H_2), 39.5 (<u>C</u>H_2), 33.3 (<u>C</u>H_2), 19.1 (<u>C</u>H_3), 14.9 (<u>C</u>H_3).

MS (EI; CH_2Cl_2) *m/z*: 241 $[M]^{+\bullet}$ (3), 223 (10), 172 (100).

HRMS (EI) *m/z*: Found 241.13152; required for $C_{12}H_{19}NO_4$, $[M]^{+\bullet}$ = 241.13141.

2-Methyl-4-oxo-1-oxa-8-spiro[4.5]decane-8-carboxylic acid benzyl ester (313)



313

Based on the procedure of Jacobsen *et al*,[55] 4-but-2-enoyl-4-hydroxy-piperidine-1-carboxylic acid benzyl ester (**234**) (50 mg, 0.16 mmol) was taken up into toluene (3 mL). Methanol (13 μL, 0.33 mmol) and *p*TSA (6.3 mg, 0.05 mmol) were added and the reaction heated to reflux for 12 h then quenched with NaOH (2N aq. solution, 5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 10 mL) and water (2 x 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a yellow oil. Purification by column chromatography (20 % Et_2O/hexane) gave the title compound **313** as a colourless oil (14 mg, 0.04 mmol, 27 %).

IR (neat) ν/cm^{-1}: 2925 (br w), 1755 (m), 1698 (s), 1431 (m), 1362 (m), 1281 (m), 1244 (s), 1178 (s), 1075 (s).

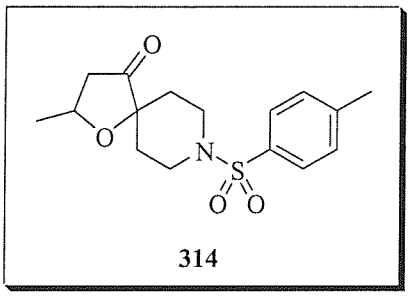
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.37-7.30 (5H, m, aromatic C**H**), 5.14 (2H, s, benzylic C**H**$_2$), 4.33 (1H, ddq, H_3C-C**H**-O-, *J*= 10.0, 10.0, 6.0 Hz), 4.00 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.25 (2H, br s, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.62 (1H, dd, -CH$_a$**H**$_b$-C=O, *J*= 10.0, 18.1 Hz), 2.24 (1H, dd, C**H**$_a$H$_b$-C=O, *J*= 10.0, 18.1 Hz), 1.80 (1H, br t, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 6.8 Hz), 1.63-1.50 (3H, br m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.43 (3H, d, -CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 216.9 (**C**=O), 155.7 (>N-**C**=O), 137.3 (aromatic **C**), 129.0 (aromatic **C**H), 128.5 (aromatic **C**H), 128.3 (aromatic **C**H), 80.9 (-O-**C**-C=O), 69.9 (benzylic **C**H$_2$), 67.6 (-O-**C**H-CH$_3$), 44.3 (**C**H$_2$), 40.3 (**C**H$_2$), 40.0 (**C**H$_2$), 22.0 (**C**H$_3$).

LRMS (CI, ammonia): 304 (24) $[M+H]^+$, 91 (100) $[benzyl]^{+\bullet}$.

HRMS (ES) *m/z*: Found 326.1362; required for $C_{17}H_{21}NO_4$, $[M+Na]^+$ = 326.1363.

2-Methyl-8-(toluene-4-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one (314)



314

Based on the procedure of Jacobsen *et al*,[55] to a solution of 1-[4-hydroxy-1-(toluene-4-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (**215**) (20 mg, 0.062 mmol) in toluene (2 mL) was added MeOH (5 μL, 0.124 mmol) and *p*TSA (6 mg, 0.031 mmol). The resulting mixture was heated to reflux for 24 h, then washed with water (2 x 5 mL), $NaHCO_3$ (sat. aq. solution, 3 x 10 mL) and water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*, leaving the crude product as a tan oil. Purification by column chromatography (10 % Et_2O/hexane) provided the pure furanone **314** as a colourless oil (13 mg, 0.039 mmol, 63 %).

MPt.: 198-200 °C (EtOAc).

IR (neat) ν/cm^{-1}: 2971 (w), 2927 (w), 2853 (w), 1753 (s), 1597 (w), 1465 (m), 1352 (s), 1226 (m), 1205 (m), 1163 (s), 1077 (s), 921 (s), 721 (s).

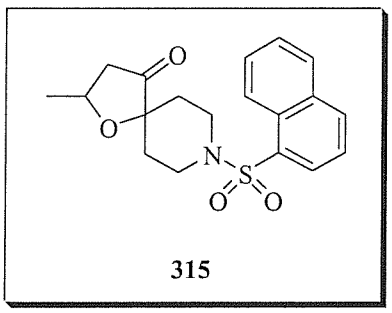
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.56 (2H, d, aromatic C**H**, *J*= 8.1 Hz), 7.26 (2H, d, aromatic C**H**, *J*= 8.3 Hz), 4.16 (1H, ddq, -C**H**CH_3, *J*= 10.0, 6.0, 6.0 Hz), 3.54 (2H, br td, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.2, 3.8 Hz), 2.71 (2H, br td, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-, *J*= 8.6, 2.9 Hz), 2.52 (1H, dd, -C**H**$_a$H$_b$-C=O, *J*= 5.5, 18.1 Hz), 2.36 (3H, s, Ar-C**H**$_3$), 2.09 (1H, dd, -CH$_a$**H**$_b$-C=O, *J*= 10.0, 18.1 Hz), 1.85 (1H, td, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*=13.4, 5.0 Hz), 1.61 (2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.51 (1H, br d, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 13.6 Hz), 1.25 (3H, d, -CHC**H**$_3$, *J*= 6.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 216.1 (C=O), 143.5 (aromatic C), 133.5 (aromatic C), 129.7 (aromatic CH), 127.6 (aromatic CH), 79.4 (C-C=O), 69.4 (O-CHCH$_3$), 43.7 (CH_2), 42.1 (CH_2), 41.7 (CH_2), 32.6 (CH_2), 29.0 (CH_2), 21.6 (-CH_3), 21.5 (-CH_3).

MS (CI; CH_2Cl_2) *m/z*: 324 (40) $[M+H]^+$, 168 (100).

HRMS (ES) *m/z*: Found 669.2276; required for $C_{16}H_{21}NSO_4$, $[2M+Na]^+$ = 669.2274.

2-Methyl-8-(naphthalene-1-sulfonyl)-1-oxa-8-azaspiro[4.5]decan-4-one (315)



315

1-[4-Hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (**235**) (33 mg, 0.09 mmol), was taken up into toluene (5 mL). Methanol (11 μL, 0.28 mmol) and *p*TSA (27 mg, 0.14 mmol) were added and the reaction heated to reflux for 72 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL). The phases were separated and washed with NaOH (2N aq. solution, 3 x 10 mL) and water (3 x 5 mL). The aqueous phases were extracted with Et_2O (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a dark brown oil. Purification by column chromatography (20 % Et_2O/hexane) gave the title compound **315** as a white solid (17 mg, 0.05 mmol, 52 %).

MPt: 186-188 °C (EtOH).

IR (neat) ν/cm^{-1}: 2974 (w), 2879 (w), 1749 (s), 1503 (w), 1351 (s), 1162 (s), 1044 (s), 916 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.66 (1H, d, aromatic C**H**, *J*= 8.5 Hz), 8.14 (1H, d, aromatic C**H**, *J*= 6.5 Hz), 8.00 (1H, d, aromatic C**H**, *J*= 8.3 Hz), 7.86 (1H, d, aromatic C**H**, *J*= 7.8 Hz), 7.60-7.45 (3H, m, aromatic C**H**), 4.15 (1H, ddq, H_3C-C**H**-O-, *J*= 10.8, 6.0, 6.0 Hz), 3.68 (1H, dt, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-, *J*= 3.0, 11.7 Hz), 3.64 (1H, dt, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 3.0, 11.7 Hz), 2.92 (2H, m, CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.49 (1H, dd, -CH$_a$**H**$_b$-C=O, *J*= 5.8, 18.0 Hz), 2.09 (1H, dd, C**H**$_a$H$_b$-C=O, *J*= 10.3, 18.3 Hz), 1.80 (1H, dt, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 4.8, 16.8 Hz), 1.63-1.47 (3H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.26 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

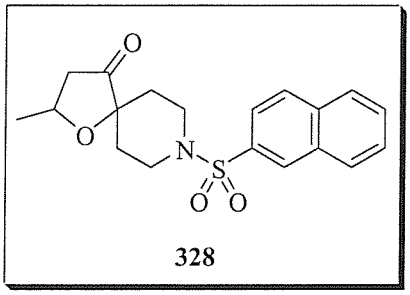
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 216.5 (**C**=O), 134.9 (aromatic **C**H), 133.8 (aromatic **C**), 130.8 (aromatic **C**H), 129.4 (aromatic **C**), 129.4 (aromatic **C**H), 128.6 (aromatic **C**H), 128.0 (aromatic **C**), 127.3 (aromatic **C**H), 125.6 (aromatic **C**H), 124.6 (aromatic **C**H), 80.1 (-O-**C**-C=O), 69.9 (-O-**C**H-CH$_3$), 44.2 (-**C**H$_a$H$_b$-C=O), 42.0 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 41.7 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 33.3 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 29.8 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 22.0 (**C**H$_3$).

LRMS (CI, ammonia) 360 (21) $[M+H]^+$, 128 (100) $[naphthyl+H]^+$.

HRMS (ES) *m/z*: Found 382.1091; required for $C_{19}H_{21}NSO_4$, $[M+Na]^+$ = 382.1083.

Microanalysis: Found C 63.07, H 5.94, N 3.82; required for $C_{19}H_{21}NSO_4$, C 63.49, H 5.89, N 3.89.

2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-azaspiro[4.5]decan-4-one (328)



328

Based on the method of Jacobson *et al*,[55] to unsaturated ketone **237** (500 mg, 2.2 mmol) in toluene (50 mL) was added *p*TSA (2.10 g, 11.0 mmol) and methanol (446 μL, 11.0 mmol) and the reaction heated to reflux for 5 h. The reaction was quenched by the addition of $NaHCO_3$ (sat. aq. solution), the phases separated and washed with $NaHCO_3$ (sat. aq. solution, 4 x 50 mL) and H_2O (3 x 50 mL). The aqueous phases were extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as an olive oil. The crude was subjected to purification by column chromatography (40 % Et_2O/hexane), then taken up into CH_2Cl_2 (10 mL) and aminomethyl polystyrene resin (~200 mg) was added, and the suspension agitated for 3 h. The resin was collected by filtration and the filtrate concentrated *in vacuo* to give the pure furanone as a white solid (455 mg, 2.0 mmol, 91 %).

MPt.: 185-188 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3057 (w), 2971 (w), 2930 (w), 2864 (w), 1752 (s), 1571 (m), 1466 (m), 1340 (s), 1226 (m), 1159 (s), 1073 (s), 918 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.36 (1H, s, aromatic C**H**), 7.99-7.94 (3H, m, aromatic C**H**), 7.78 (1H, dd, aromatic C**H**, *J*= 1.7, 8.6 Hz), 7.70-7.64 (2H, m, aromatic C**H**), 4.21 (1H, ddq, -O-C**H**-CH_3, *J*= 11.9, 6.6, 6.0 Hz), 3.75 (2H, td, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.7, 3.6 Hz), 2.77 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.3, 11.7 Hz), 2.75 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.3, 11.7 Hz), 2.58 (1H, dd, -C**H**$_a$H$_b$-C=O, *J*= 18.1, 5.7 Hz),

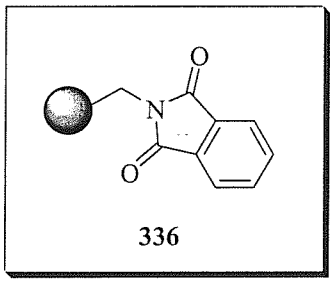
2.17 (1H, dd, -$CH_a\underline{H}_b$-C=O, *J*= 18.1, 10.0 Hz), 1.99 (1H, ddd, -$C\underline{H}_aH_b$-C-CH_aH_b-, *J*= 4.5, 12.2, 12.2 Hz), 1.77-1.62 (3H, m, -$CH_a\underline{H}_b$-C-$CH_a\underline{H}_b$- + -CH_aH_b-C-$C\underline{H}_aH_b$-), 1.31 (3H, d, -O-CH-$C\underline{H}_3$, *J*= 5.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 216.0 (<u>C</u>=O), 135.0 (aromatic <u>C</u>), 133.7 (aromatic <u>C</u>), 132.4 (aromatic <u>C</u>), 129.5 (aromatic <u>C</u>H), 129.4 (aromatic <u>C</u>H), 129.1 (aromatic <u>C</u>H), 129.0 (aromatic <u>C</u>H), 128.1 (aromatic <u>C</u>H), 127.7 (aromatic <u>C</u>H), 123.0 (aromatic <u>C</u>H), 79.5 (<u>C</u>-O-), 69.6 (-O-<u>C</u>H-CH_3), 43.9 (-$\underline{C}H_aH_b$-C=O), 42.4 (-$\underline{C}H_aH_b$-N-CH_aH_b-), 42.0 (-CH_aH_b-N-$\underline{C}H_aH_b$-), 32.8 (-$\underline{C}H_aH_b$-C-CH_aH_b-), 29.1 (-CH_aH_b-C-$\underline{C}H_aH_b$-), 21.6 (-O-CH-$\underline{C}H_3$).

MS (ES, CH_3CN): 360 (100) $[M+H]^+$, 377 (53) $[M+NH_4]^+$.

Microanalysis: Found C 63.20, H 5.91, N 3.77; required for $C_{19}H_{21}NSO_4$, C 63.49, H 5.89, N 3.89.

Phthalimido Polystyrene 336

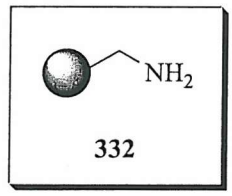


336

Commercially available Merrifield resin (**335**) (3.50 g, 5.5 mmol) was swollen in DMF (25 mL) for 30 min and potassium phthalimide (5.13 g, 5 eq) added portionwise. The resulting suspension was agitated at 120 °C for 16 h. The resin was collected by filtration and washed with DMF, DMF:H_2O (1:1), H_2O, dioxane, MeOH and Et_2O (3 x 15 mL each). The resin was dried *in vacuo* at 50 °C for 48 h, granting the phthalimido resin **336** as a buff resin (4.15 g).

IR (neat) ν/cm^{-1}: 3022 (w), 2918 (w), 2847 (w), 1769 (s), 1710 (s), 1491 (m), 1450 (m), 1427 (m), 1389 (s).

Aminomethyl Polystyrene (332)

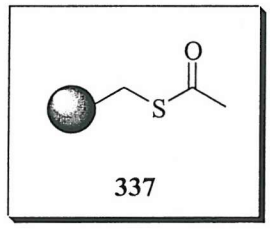


332

Phthalimido resin **336** (4.15 g) was swollen in EtOH (50 mL) for 30 min; hydrazine hydrate (1.73 mL, 10 eq) added and the suspension heated to reflux for 20 h. The resin was collected by filtration and washed with hot DMF, hot DMF:H_2O (1:1), hot H_2O, dioxane, methanol and Et_2O (3 x 20 mL each). The resin was then dried *in vacuo* at 50 °C for 48 h, granting aminomethyl polystyrene (**332**) as a buff resin (3.20 g).

IR (neat) ν/cm^{-1}: 3022 (w), 2916 (w), 2845 (w), 1599 (w), 1491 (m), 1449 (m).

Thioacetate Resin 337

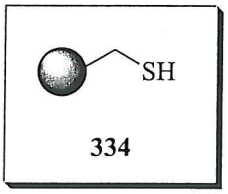


337

Commercially available Merrifield resin (**335**) (3.50 g, 5.5 mmol) was swollen in DMF (25 mL) and potassium thioacetate (3.14 g, 5 eq) added portionwise. The resulting suspension was agitated at 80 °C for 16 h. The resin was collected by filtration and washed with DMF, DMF:H_2O (1:1), H_2O, dioxane, methanol and Et_2O (3 x 15 mL each). The resin was then dried *in vacuo* at 50 °C for 48 h, granting resin **337** as a buff resin (3.95 g).

IR (neat) ν/cm^{-1}: 3022 (w), 2918 (w), 2847 (w), 1691 (s), 1489 (m), 1450 (m), 1427 (m), 1389 (w), 1140 (s).

Mercaptomethyl Polystyrene 334

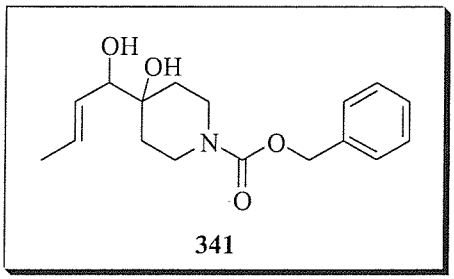


334

The thioacetate resin **337** (3.95 g) was swollen in MeOH (25 mL) and lithium borohydride (2N solution/THF, 7.50 mL, 15 mmol) added. The resulting suspension was agitated at rt for 16 h. The resin was collected by filtration and washed with DMF, DMF:H_2O (1:1), H_2O, dioxane, methanol and Et_2O (3 x 15 mL each). The resin was then dried *in vacuo* at 50 °C for 48 h, granting resin **337** as a buff resin (3.42 g).

IR (neat) ν/cm^{-1}: 3022 (w), 2916 (w), 2845 (w), 1599 (w), 1540 (w), 1491 (m), 1449 (m), 1073 (m).

4-Hydroxy-4-(1-hydroxy-but-2-enyl)-piperidine-1-carboxylic acid benzyl ester (341)



341

Following the method of Barco *et al*,[111] 4-but-2-enoyl-4-hydroxy-piperidine-1-carboxylic acid benzyl ester (**234**) (230 mg, 0.76 mmol) was taken up into dry MeOH (5 mL) and $CeCl_3 \cdot 7H_2O$ (287 mg, 0.77 mmol) and $NaBH_4$ (29 mg, 0.77 mmol) were added at 0 °C. After 5 min at 0 °C, the reaction was quenched by the dropwise addition of AcOH, partitioned between Et_2O (10 mL) and water (10 mL) and washed with NaOH (2N aq. solution, 3 x 10 mL) and water (2 x 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a colourless oil. Purification by column chromatography (50 % Et_2O/hexane) gave the title compound **341** as a colourless oil (215 mg, 0.71 mmol, 93 %).

IR (neat) ν/cm^{-1}: 3417 (br w), 2923 (w), 1677 (s), 1435 (s), 1276 (m), 1245 (s), 1080 (m), 1025 (s), 969 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.29-7.21 (5H, m, aromatic C**H**), 5.62 (1H, dq, H_3C-C**H**=CH, *J*= 15.3, 6.5 Hz), 5.43 (1H, br dd, H_3C-CH=**C**H, *J*= 6.5, 15.3 Hz), 5.03 (2H, s, benzylic C$\underline{H}_2$), 3.91 (2H, br s, -C$\underline{H}_a$H$_b$-N-C$\underline{H}_a$H$_b$-), 3.68 (1H, d, -C**H**-OH, *J*= 6.5 Hz), 3.08 (2H, br s, -CH$_a$$\underline{H}_b$-N-CH$_a$$\underline{H}_b$-), 2.48 (2H, br s, -C$\underline{H}_aH_b$-C-C$\underline{H}_aH_b$-), 1.63 (3H, d, C$\underline{H}_3$, *J*= 6.5 Hz), 1.60-1.35 (2H, m, -CH$_a$$\underline{H}_b$-C-CH$_a$$\underline{H}_b$-).

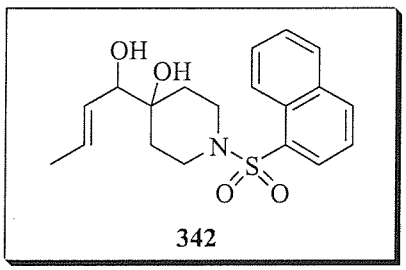
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 155.4 (-N-**C**=O), 136.9 (aromatic **C**), 130.6 (=**C**H-CH_3), 129.1 (aromatic **C**H), 128.6 (aromatic **C**H), 128.1 (aromatic **C**H), 127.9

(=CH-C=O), 79.5 (CH-OH), 71.6 (C-OH), 67.2 (benzylic CH_2), 39.9 (CH_2), 39.7 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 18.0 (CH_3).

LRMS (ES, CH_3CN): 306 (100) $[M+H]^+$, 628 (63) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 633.3155; required for $C_{17}H_{23}NO_4$, $[2M+Na]^+$ = 633.3146.

4-(1-Hydroxy-but-2-enyl)-1-(naphthalene-1-sulfonyl)-piperidin-4-ol (342)



342

Following the method of Barco *et al*,[111] 1-[4-hydroxy-1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-but-2-en-1-one (**235**) (230 mg, 0.76 mmol) was taken up into dry MeOH (5 mL), $CeCl_3 \cdot 7H_2O$ (287 mg, 0.77 mmol) and $NaBH_4$ (29 mg, 0.77 mmol) were added at 0 °C. After 5 min at 0 °C, the reaction was quenched by the dropwise addition of AcOH, partitioned between Et_2O (10 mL) and water (10 mL) and washed with NaOH (2N aq. solution, 3 x 10 mL) and water (2 x 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a colourless oil. Purification by column chromatography (50 % Et_2O/hexane) gave the title compound **342** as a colourless oil (215 mg, 0.71 mmol, 93 %).

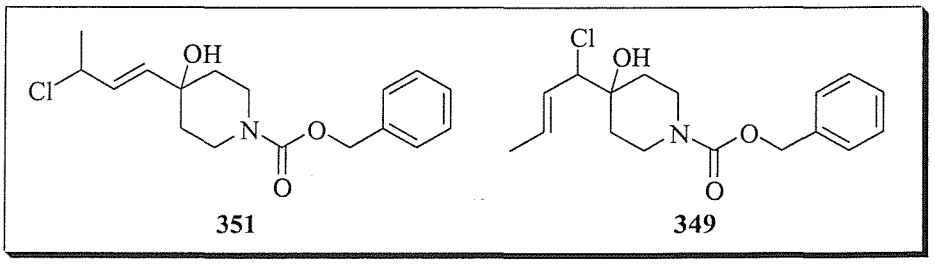
IR (neat) ν/cm^{-1}: 3417 (br w), 2923 (w), 1677 (s), 1435 (s), 1276 (m), 1245 (s), 1080 (m), 1025 (s), 969 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.66 (1H, d, aromatic CH, *J*= 8.5 Hz), 8.14 (1H, d, aromatic CH, *J*= 6.5 Hz), 8.00 (1H, d, aromatic CH, *J*= 8.3 Hz), 7.86 (1H, d,

aromatic C**H**, *J*= 7.8 Hz), 7.60-7.45 (3H, m, aromatic C**H**), 5.62 (1H, dq, H_3C-C**H**=CH, *J*= 15.2, 6.5 Hz), 5.43 (1H, br dd, H_3C-CH=C**H**, *J*= 8.0, 15.3 Hz), 3.91 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.68 (1H, d, -C**H**-OH, *J*= 7.3 Hz), 3.08 (2H, br s, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.55-2.45 (2H, br m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.63 (3H, d, C**H**$_3$, *J*= 6.5 Hz), 1.60-1.35 (2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 200.0 (**C**=O), 134.9 (aromatic **C**), 134.4 (aromatic **C**H), 129.7 (=**C**H-CH_3), 129.5 (aromatic **C**), 129.0 (aromatic **C**H), 128.1 (aromatic **C**H), 128.0 (aromatic **C**), 127.2 (=**C**H-C=O), 126.9 (aromatic **C**H), 125.1 (aromatic **C**H), 124.2 (aromatic **C**H), 123.4 (aromatic **C**H), 78.7 (**C**H-OH), 70.2 (**C**-OH), 41.5 (-**C**H_2-N-**C**H_2-), 33.0 (-**C**H_2-C-**C**H_2-), 18.7 (-**C**H_3).

4-(3-Chloro-but-1-enyl)-4-hydroxypiperidine-1-carboxylic acid benzyl ester (351) and 4-(1-chloro-but-2-enyl)-4-hydroxypiperidine-1-carboxylic acid benzyl ester (349)



351 **349**

4-Hydroxy-4-(1-hydroxy-but-2-enyl)-piperidine-1-carboxylic acid benzyl ester (**341**) (70 mg, 0.230 mmol) was taken up into CH_2Cl_2 (5 mL); MsCl (18 µL, 0.230 mmol) and triethylamine (33 µL, 0.230 mmol) were added, and the reaction stirred at rt for 20 h. The reaction was quenched with brine (5 mL), the phases were separated and washed with brine (2 x 10 mL) and water (2 x 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a thick yellow oil. Purification by column chromatography (20 % Et_2O/hexane) gave the unstable allylic chlorides **351** (24 mg, 0.074 mmol, 32 %) and **349** (11 mg, 0.035 mmol, 15 %) as air sensitive colourless oils.

4-(3-Chloro-but-1-enyl)-4-hydroxypiperidine-1-carboxylic acid benzyl ester (**351**):

IR (neat) ν/cm^{-1}: 2940 (w), 1678 (s), 1436 (s), 1361 (m), 1276 (m), 1242 (s), 1091 (m), 1015 (m), 968 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.43-7.30 (5H, m, aromatic C**H**), 5.86 (1H, dd, Cl-CH-C**H**=CH-, *J*= 15.4, 7.0 Hz), 5.77 (1H, d, Cl-CH-CH=C**H**-, *J*= 15.6 Hz), 5.14 (2H, s, benzylic C**H**$_2$), 4.56 (1H, dq, H_3C-C**H**-Cl, *J*= 6.7, 6.7 Hz), 3.95 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.29 (2H, br t, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-, *J*= 11.4 Hz), 1.68-1.21 (4H, m, -C**H**$_2$-C-C**H**$_2$-), 1.60 (3H, d, C**H**$_3$, *J*= 6.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 152.8 (**C**=O), 137.9 (aromatic **C**), 130.6 (CH=**C**H), 128.6 (aromatic **C**H), 128.1 (aromatic **C**H), 127.9 (aromatic **C**H), 125.6 (**C**H=CH), 69.4 (-**C**-OH), 67.2 (benzylic **C**H$_2$), 57.2 (-**C**H-Cl), 39.8 (**C**H$_2$), 39.8 (**C**H$_2$), 36.8 (**C**H$_2$), 30.4 (**C**H$_2$), 25.3 (**C**H$_3$).

Too unstable to characterise further.

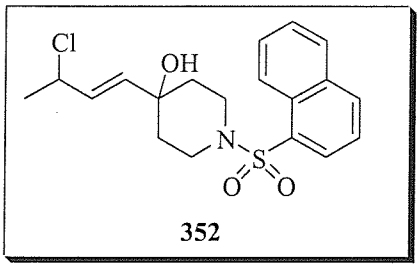
4-(1-Chloro-but-2-enyl)-4-hydroxypiperidine-1-carboxylic acid benzyl ester (**349**):

IR (neat) ν/cm^{-1}: 2940 (w), 1678 (s), 1436 (s), 1361 (m), 1276 (m), 1242 (s), 1091 (m), 1015 (m), 968 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.43-7.30 (5H, m, aromatic C**H**), 5.79 (1H, dq, =C**H**-CH$_3$, *J*= 15.1, 6.5 Hz), 5.61 (1H, dd, Cl-CH-**C**H=, *J*= 15.1, 9.7 Hz), 5.14 (2H, s, benzylic C**H**$_2$), 4.27 (1H, d, -C**H**-Cl, *J*= 9.4 Hz), 4.06 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.16 (2H, br s, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 1.82-1.49 (4H, m, -C**H**$_2$-C-C**H**$_2$-), 1.75 (3H, d, C**H**$_3$, *J*= 6.2 Hz).

Too unstable to characterise further.

4-(3-Chloro-but-1-enyl)-1-(naphthalene-1-sulfonyl)-piperidin-4-ol (352)



352

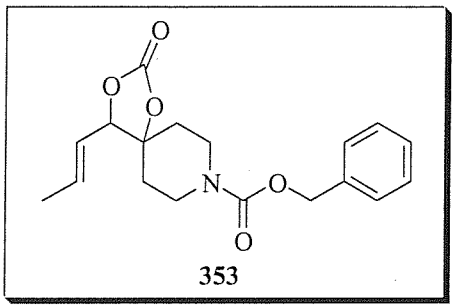
To diol **342** (50 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) was added MsCl (11 μL, 0.14 mmol) and triethylamine (19 μL, 0.14 mmol). The reaction was stirred at rt for 40 min, then quenched by the addition of brine (5 mL). The phases were separated and washed with brine (2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a yellow oil. Purification by column chromatography (20 % Et_2O/hexane) isolated allylic chloride **352** as an air sensitive colourless oil (7 mg, 0.018 mmol, 13 %).

IR (neat) ν/cm^{-1}: 2940 (w), 1678 (s), 1436 (s), 1361 (m), 1276 (m), 1242 (s), 1167 (s), 1091 (m), 1015 (m), 968 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.75 (1H, d, aromatic C**H**, *J*= 8.2 Hz), 8.21 (1H, d, aromatic C**H**, *J*= 7.2 Hz), 8.08 (1H, d, aromatic C**H**, *J*= 8.2 Hz), 7.97-7.93 (1H, m, aromatic C**H**), 7.68-7.53 (3H, m, aromatic C**H**), 5.84-5.69 (2H, m, CH=C**H** + **C**H=CH), 4.51 (1H, dq, H_3C-C**H**-Cl, *J*= 6.7, 6.7 Hz), 3.70 (2H, br d, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 12.4 Hz), 3.03 (2H, dt, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-, *J*= 2.5, 12.2 Hz), 1.80 (2H, dt, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 5.0, 13.9 Hz), 1.65-1.44 (5H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 134.9 (aromatic **C**H), 133.8 (aromatic **C**), 130.8 (aromatic **C**H), 130.6 (Cl-CH-**C**H=CH), 129.4 (aromatic **C**), 129.4 (aromatic **C**H), 128.6 (aromatic **C**H), 128.0 (aromatic **C**), 127.3 (aromatic **C**H), 125.6 (Cl-CH-CH=**C**H), 125.4 (aromatic **C**H), 124.6 (aromatic **C**H), 69.4 (-**C**-OH), 57.2 (H_3C-**C**H-Cl), 39.8 (**C**H$_2$), 39.8 (**C**H$_2$), 36.8 (**C**H$_2$), 30.4 (**C**H$_2$), 25.3 (**C**H$_3$).

2-Oxo-4-propenyl-1,3-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid benzyl ester (353)



353

To a solution of diol **341** (412 mg, 1.35 mmol) in CH_2Cl_2 (25 mL) was added CDI (438 mg, 2.70 mmol) batchwise and the reaction stirred at rt. After 20 h the reaction was concentrated *in vacuo* and the resulting crude material purified by column chromatography (60 % Et_2O/hexane) to grant the pure carbonate **353** as a colourless oil (365 mg, 1.10 mmol, 82 %).

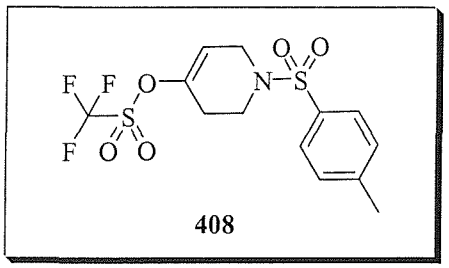
IR (neat) ν/cm^{-1}: 2931 (w), 1796 (s), 1697 (s), 1427 (m), 1370 (m), 1247 (m), 1195 (s), 1030 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.39-7.33 (5H, m, aromatic C**H**), 5.93 (1H, dq, =C**H**-CH_3, *J*= 15.6, 6.5 Hz), 5.46 (1H, br dd, -C**H**=CH-CH_3, *J*= 8.5, 15.1 Hz), 5.13 (2H, s, benzylic C**H**$_2$), 4.60 (1H, d, -C**H**-O-, *J*= 8.5 Hz), 4.14 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.18 (2H, br s, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 1.88-1.62 (4H, m, -C**H**$_a$**H**$_b$-C-C**H**$_a$**H**$_b$-), 1.80 (3H, dd, =CH-C**H**$_3$, *J*= 1.0, 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 155.1 (**C**=O), 153.5 (**C**=O), 136.6 (aromatic **C**), 135.5 (=**C**H-CH_3), 128.7 (aromatic **C**H), 128.3 (aromatic **C**H), 128.2 (aromatic **C**H), 122.1 (=**C**H-CH-O-), 86.2 (-**C**H-O-), 83.4 (**C**-O-), 67.6 (benzylic **C**H$_2$), 40.3 (**C**H$_2$), 39.9 (**C**H$_2$), 34.6 (**C**H$_2$), 31.3 (**C**H$_2$), 18.1 (**C**H$_3$).

HRMS (ES) *m/z*: Found 354.1312; required for $C_{18}H_{21}NO_5$, $[M+Na]^+$ = 354.1312.

Trifluoromethanesulfonic acid 1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-4-yl ester (408)



408

To a solution of *N*-(toluene-4-sulfonyl)-4-piperidone (**211**) (200 mg, 0.79 mmol) in CH_2Cl_2 (5 mL) was added di-*t*-butylpyridine (199 μL, 0.88 mmol). The solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (146 μL, 0.87 mmol) added dropwise; the reaction was allowed to warm slowly to rt and stirred for 72 h. The solvent was removed *in vacuo* to leave the crude product as a dark brown oily solid (700 mg). Purification by column chromatography (50 % Et_2O/hexane) isolated enol triflate **408** as a white solid (275 mg, 0.71 mmol, 90 %).

MPt.: 71-73 °C (Et_2O)

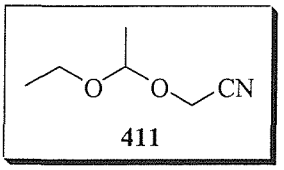
IR (neat) ν/cm^{-1}: 2955 (m), 2868 (w), 1460 (w), 1349 (m), 1241 (w), 1165 (s), 1098 (m), 1016 (m), 960 (w), 829 (s).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.68 (2H, d, aromatic C**H**, *J*= 7.9 Hz), 7.35 (2H, d, aromatic C**H**, *J*= 7.9 Hz), 5.74 (1H, dd, C**H**=COTf, *J*= 3.5, 2.0 Hz), 3.79 (2H, dd, C**H**$_2$-CH=COTf, *J*= 6.0, 3.0 Hz), 3.36 (2H, t, -C**H**$_2$-, *J*= 5.9 Hz), 2.51-2.46 (2H, m, -C**H**$_2$-), 2.45 (3H, s, Ar-C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 146.6 (CH_2-CH=**C**-OTf), 144.4 (-**C**F_3), 133.3 (aromatic **C**), 130.1 (aromatic-**C**H), 127.6 (aromatic-**C**H), 120.6 (aromatic **C**), 114.6 (-CH_2-**C**H=C-OTf), 43.5 (-**C**H_2-), 42.8 (-**C**H_2-), 28.0 (-**C**H_2-), 21.7 (Ar-**C**H_3).

MS (EI; CH_2Cl_2) *m/z*: 385 $[M]^{+\bullet}$ (12), 252 (100).

(1-Ethoxyethoxy)-acetonitrile (411)



411

Following the method of Sims *et al*,[112] glycolonitrile (**413**) (5.00 g, 55 wt % solution/water, 48.2 mmol) was distilled *in vacuo* to remove most of the water. The liquid was allowed to cool to rt and ethyl vinyl ether (5.76 mL, 60.3 mmol) was added, followed by TFA (2 drops) through a reflux condenser –**CARE**, the reaction vigourously self-refluxed for 5 min to leave a brown oil. Distillation *in vacuo* (80 °C, 1 mmHg) provided the pure cyanohydrin **411** as a colourless oil (4.68 g, 36.0 mmol, 75 %).

IR (neat) ν/cm^{-1}: 2983 (w), 2899 (w), 1445 (m), 1388 (m), 1342 (m), 1276 (w), 1133 (s), 1083 (s), 1054 (s).

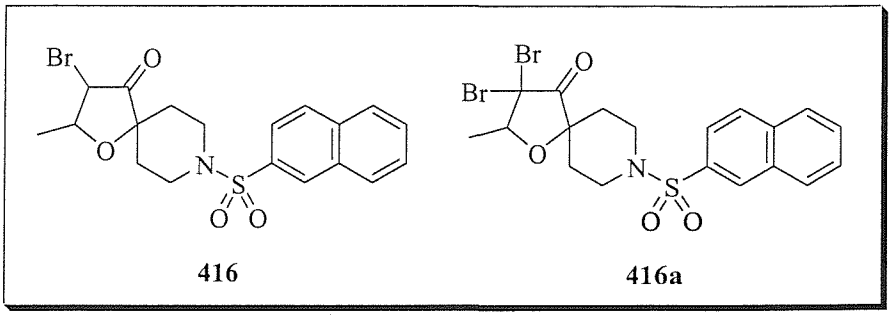
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.78 (1H, q, -OC**H**(CH_3)O-, *J*= 5.2 Hz), 4.20 (2 x 1H, d, C**H**$_a$H$_b$-CN + CH$_a$**H**$_b$-CN, *J*= 5.5 Hz), 3.59 (1H, dq, -OC**H**$_a$H$_b$CH$_3$, *J*= 9.5, 7.4 Hz), 3.45 (1H, dq, -OCH$_a$**H**$_b$CH$_3$, *J*= 9.5, 7.4 Hz), 1.27 (3H, d, -OCH(C**H**$_3$)O-, *J*= 5.5 Hz), 1.14 (3H, t, -OCH$_2$C**H**$_3$, *J*= 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 117.7 (**C**N), 100.7 (-O**C**H(CH_3)O-), 62.4 (O**C**H$_2$CN), 50.4 (O**C**H$_2$CH$_3$), 20.1 (**C**H$_3$), 16.0 (**C**H$_3$).

MS (CI; CH_2Cl_2) *m/z*: 130 $(M+H)^+$ (3), 73 $(M-OCH_2CN)^+$ (100).

CAS No.: 86240-35-9.

3-Bromo-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one (416) and 3,3-dibromo-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one (416a)



416 **416a**

Furanone **328** (726 mg, 2.02 mmol) was taken up into EtOAc (20 mL), cupric bromide (1.35 g, 6.06 mmol) added and the reaction heated to reflux for 5 h. At this time a further quantity of cupric bromide (1.35 g, 6.06 mmol) was added and heated to reflux for a further 5 h, then concentrated *in vacuo*. Purification by column chromatography gave bromide **416** as an olive solid (283 mg, 0.65 mmol, 32 %), and dibromide **416a** (104 mg, 0.20 mmol, 10 %) as a dark brown solid. The spectroscopic data is reported for a mixture of diastereoisomers.

3-Bromo-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one (**416**):

IR (neat) ν/cm^{-1}: 3187 (w), 3056 (w), 2974 (w), 2932 (w), 2868 (w), 1743 (s), 1593 (m), 1454 (w), 1325 (s), 1158 (s), 1076 (s), 915 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.33 (2 x 1H, s, aromatic C**H**), 8.03-7.95 (2 x 3H, m, aromatic C**H**), 7.77 (2 x 1H, dd, aromatic C**H**, *J*= 8.6, 1.7 Hz), 7.70 (2 x 1H, dt, aromatic C**H**, *J*= 1.0, 6.9 Hz), 7.65 (2 x 1H, dt, aromatic C**H**, *J*= 1.0, 6.9 Hz), 4.09-3.95 (2 x 1H, m, -O-C**H**-CH_3), 3.77-3.72 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 2.83 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 4.5, 16.2 Hz), 2.79 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 4.1, 16.2 Hz), 2.22 (2 x 1H, ddd, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 6.7, 15.6, 15.6 Hz), 2.02-1.76 (2 x1H,

m, -CH_aH_b-C-C$\underline{H}_aH_b$- + 2 x 2H, m, -$CH_a\underline{H}_b$-C-$CH_a\underline{H}_b$- + 2 x 1H, m, -C$\underline{H}$-Br), 1.45 (3H, d, -O-CH-C$\underline{H}_3$, J= 7.6 Hz), 1.41 (3H, d, -O-CH-C$\underline{H}_3$, J= 7.6 Hz).

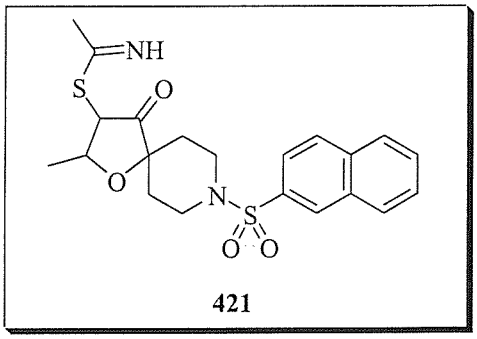
Too unstable to characterise further.

3,3-dibromo-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one (**416a**):

MS (ES, CH_3CN): 538 (52) $[M(Br^{79}Br^{79})+Na]^+$, 540 (100) $[M(Br^{79}Br^{81})+Na]^+$, 542 (50) $[M(Br^{81}Br^{81})+Na]^+$.

Too unstable to characterise further.

Thioacetlmidic acid 2-methyl-8-(naphthalene-2-sulfonyl)-4-oxo-1-oxa-8-aza-spiro[4.5]dec-3-yl ester 421



421

To bromoketone **416** (68 mg, 0.16 mmol) in methanol (5 mL) was added thioacetamide (13 mg, 0.17 mmol) and $NaHCO_3$ (26 mg, 0.31 mmol). The reaction was heated to reflux for 5 h, then concentrated *in vacuo*. Purification by column chromatography (40 % $Et_2\ddot{O}$/hexane) gave the pure imine as an oily white solid (31 mg, 0.07 mmol, 46 %).

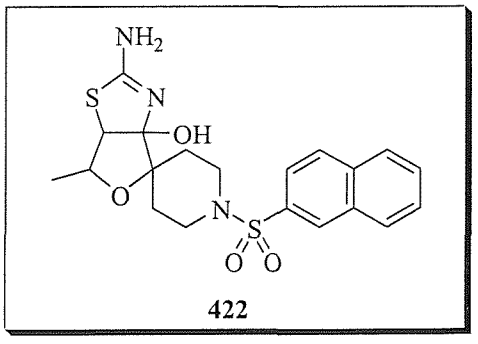
IR (neat) ν/cm^{-1}: 3348 (br m), 3175 (w), 2974 (w), 2928 (w), 2854 (w), 1737 (s), 1591 (m), 1468 (w), 1324 (s), 1168 (s), 1081 (s), 924 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.36 (1H, s, aromatic C**H**), 7.99 (2H, dd, aromatic C**H**, *J*= 7.5, 4.9 Hz), 7.94 (1H, d, aromatic C**H**, *J*= 7.9 Hz), 7.78 (1H, dd, aromatic C**H**, *J*= 7.6, 1.7 Hz), 7.67 (1H, dt, aromatic C**H**, *J*= 1.9, 7.6 Hz), 7.63 (1H, dt, aromatic C**H**, *J*= 1.9, 7.6 Hz), 4.22 (1H, d, -C**H**-S-, *J*= 3.9 Hz), 4.01 (1H, dq, -O-C**H**-CH_3, *J*= 4.9, 7.8), 3.77 (1H, br t, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-, *J*= 4.9 Hz), 3.74 (1H, br t, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 3.9 Hz), 2.77 (1H, ddd, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 15.7, 15.7, 3.9 Hz), 2.73 (1H, ddd, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.9, 15.6, 15.6 Hz), 2.12 (1H, ddd, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 6.8, 16.6, 16.6 Hz), 1.98-1.70 (3H, m, -CH$_a$H$_b$-C-C**H**$_a$H$_b$- + -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.32 (3H, d, -O-CH-C**H**$_3$, *J*= 7.8 Hz), 1.29 (3H, s, -C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 209.6 (**C**=O), 134.9 (aromatic **C**), 133.4 (aromatic **C**), 132.2 (aromatic **C**), 129.4 (aromatic **C**H), 129.3 (aromatic **C**H), 129.0 (aromatic **C**H), 128.9 (aromatic **C**H), 128.2 (**C**=NH) , 128.0 (aromatic **C**H), 127.6 (aromatic **C**H), 122.9 (aromatic **C**H), 79.4 (-**C**-O-), 71.8 (-O-**C**H-CH_3), 50.2 (-**C**H-S-), 42.2 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 41.9 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 35.2 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 29.0 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 21.4 (-**C**H$_3$), 18.1 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 433 (100) $[M+H]^+$, 455 (31) $[M+Na]^+$.

2-Amino-4-[spiro-4-(naphthalene-2-sulfonyl)piperidine]-6-methyl-6,6a-dihydro-furo[3,4-d]thiazol-3a-ol 422



422

To bromoketone **416** (15 mg, 34 μmol) in DME (1 mL) was added thiourea (5 mg, 71 μmol) and $NaHCO_3$ (6 mg, 71 μmol). The reaction was heated to reflux for 16 h, then

concentrated *in vacuo*. Purification by column chromatography (50 % Et_2O/hexane) gave the pure aminoalcohol **422** as a brown solid (4 mg, 9 μmol, 27 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 150 °C dec (EtOAc).

IR (neat) ν/cm^{-1}: 3352 (br m), 3187 (w), 3056 (w), 2974 (w), 2932 (w), 2868 (w), 1638 (s), 1591 (m), 1466 (w), 1323 (s), 1160 (s), 1074 (s), 913 (m).

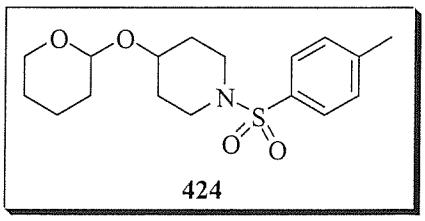
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.35 (2 x 1H, s, aromatic C**H**), 7.98 (2 x 2H, dd, aromatic C**H**, *J*= 2.0, 9.1 Hz), 7.92 (2 x 1H, d, aromatic C**H**, *J*= 7.6 Hz), 7.76 (2 x 1H, dd, aromatic C**H**, *J*= 2.0, 8.6 Hz), 7.66 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 7.1 Hz), 7.61 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 6.6 Hz), 4.22 (1H, dq, -O-C**H**-CH_3, *J*= 9.1, 6.1 Hz), 3.81-3.69 (2 x 1H, m, -C**H**$_a$H$_b$-N-CH$_a$H$_b$- + 1H, m, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.61 (1H, dq, -O-C**H**-CH_3, *J*= 9.4, 6.0 Hz + 1H, m, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.53 (2 x 1H, d, -C**H**-S-, *J*= 9.1 Hz), 2.71 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.6, 12.1 Hz), 2.63 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 2.5, 12.1 Hz), 2.00 (2 x 1H, dt, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 3.6, 12.6 Hz), 1.95 (2 x 1H, dt, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 5.1, 12.6 Hz), 1.86 (2 x 1H, ddd, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 2.5, 5.0, 13.6 Hz), 1.79 (1H, br dd, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 4.5, 12.1 Hz), 1.65 (1H, ddd, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 2.5, 5.6, 14.2 Hz), 1.19 (3H, d, -O-CH-C**H**$_3$, *J*= 6.1 Hz), 1.10 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 134.8 (2 x aromatic **C**), 133.8 (2 x aromatic **C**), 132.3 (2 x aromatic **C**), 129.3 (2 x aromatic **C**H), 129.2 (2 x aromatic **C**H), 128.9 (2 x aromatic **C**H), 128.7 (2 x aromatic **C**H), 127.9 (2 x aromatic **C**H), 127.5 (2 x aromatic **C**H), 123.0 (2 x aromatic **C**H), 115.6 (2 x H_2N-**C**=N-), 82.8 (-**C**-O-), 82.1 (-**C**-O-), 79.0 (-O-**C**H-CH_3), 77.3 (-O-**C**H-CH_3), 71.0 (-**C**H-S-), 66.0 (-**C**H-S-), 43.3 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.1 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.7 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 42.3 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 33.2 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.5 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 30.3 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 28.2 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 19.6 (-O-CH-**C**H_3), 18.2 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 434 (100) $[M+H]^+$, 456 (5) $[M+Na]^+$.

HRMS (ES) *m/z*: Found 434.1201; required for $C_{20}H_{23}N_3S_2O_4$, $[M+H]^+ = 434.1203$.

4-(Tetrahydropyran-2-yloxy)-1-(toluene-4-sulfonyl)-piperidine (424)



424

To 1-(toluene-4-sulfonyl)piperidin-4-ol (**423**) (100 mg, 0.39 mmol) in CH_2Cl_2 (2.5 mL) was added dihydropyran (39 μL, 0.43 mmol) and *p*TSA (15 mg, 20 mol %) and the reaction stirred at rt for 24 h. The reaction was quenched by the addition of NaOH (2N aq. solution, 10 mL), the phases separated and washed with NaOH (2N aq. solution, 3 x 10 mL) and water (2 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as an oily brown solid. Purification by column chromatography (30 % Et_2O/hexane) gave the protected alcohol **424** as a white solid (107 mg, 0.31 mmol, 80 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 120-122 °C (EtOH).

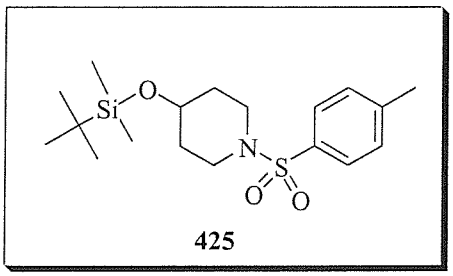
IR (neat) ν/cm^{-1}: 2941 (m), 2861 (w), 1597 (w), 1346 (s), 1164 (s), 1120 (m), 1076 (m), 1032 (s), 932 (m).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 (2 x 2H, d, aromatic C**H**, *J*= 8.2 Hz), 7.32 (2 x 2H, d, aromatic C**H**, *J*= 8.2 Hz), 4.62 (2 x 1H, t, -O-C**H**-O-, *J*= 4.7 Hz), 3.84-3.79 (2 x 1H, m, -O-C**H**$_a$H$_b$-), 3.67 (2 x 1H, tt, -O-C**H**-(CH$_2$)$_2$, *J*= 4.0, 4.0 Hz), 3.48-3.30 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$- + 2 x 1H, m, -O-CH$_a$**H**$_b$-), 2.81 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.5, 8.4 Hz), 2.77 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.5, 8.5 Hz), 2.44 (2 x 3H, s, Ar-C**H**$_3$), 1.98-1.60 (2 x 4H, m, -C**H**$_2$-C-C**H**$_2$-), 1.57-1.50 (2 x 6H, br s, -C**H**$_2$-).

MS (ES, CH_3CN): 340 (100) $[M+H]^+$, 362 (92) $[M+Na]^+$.

HRMS (ES) *m/z*: Found 362.1396; required for $C_{17}H_{25}NSO_4$, $[M+Na]^+ = 362.1396$.

4-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidine (425)



425

To 1-(toluene-4-sulfonyl)piperidin-4-ol (**423**) (40 mg, 0.16 mmol), in CH_2Cl_2 (2 mL) was added TBS-Cl (26 mg, 0.17 mmol) and imidazole (21 mg, 0.31 mmol). The reaction was stirred at rt for 3 h, then concentrated *in vacuo*. Purification by column chromatography (40 % Et_2O/hexane) gave the TBS ether **425** as a white solid (42 mg, 0.12 mmol, 75 %).

MPt.: 118-120 °C (Et_2O).

IR (neat) ν/cm^{-1}: 2953 (m), 2930 (m), 2894 (w), 2860 (m), 1600 (w), 1470 (m), 1334 (s), 1305 (m), 1254 (m), 1159 (s), 1080 (s), 1042 (s), 1013 (s), 940 (s), 828 (s).

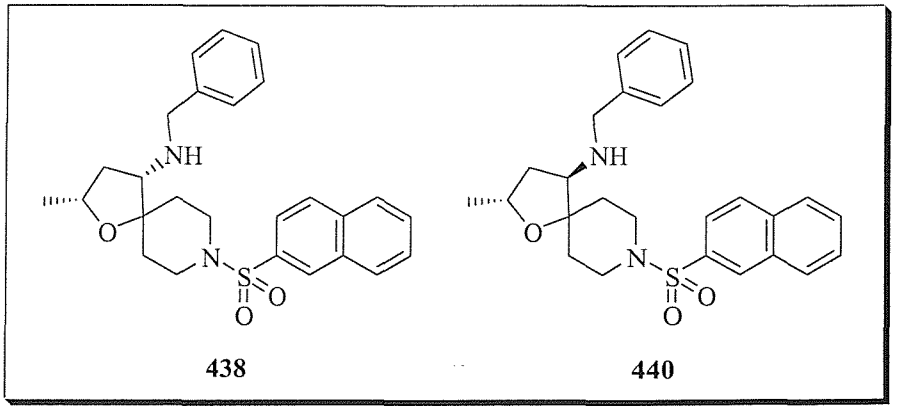
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 (2H, d, aromatic C**H**, *J*= 8.3 Hz), 7.33 (2H, d, aromatic C**H**, *J*= 7.9 Hz), 3.75 (2 x 1H, tt, -O-C**H**-, *J*= 3.0, 3.0 Hz), 3.14 (2 x 1H, td, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-, *J*= 8.9, 4.0 Hz), 3.12 (2 x 1H, td, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 8.4, 3.5 Hz), 2.99 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 4.0, 7.0 Hz), 2.96 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 4.0, 6.5 Hz), 2.44 (2 x 3H, s, Ar-C**H**$_3$), 1.80 (2 x 1H, dt, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 4.0, 7.4 Hz), 1.77 (2 x 1H, dt, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 3.5, 7.4 Hz), 1.63 (2 x 1H, dt, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 4.0, 7.0 Hz), 1.61 (2 x 1H, dt, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 3.0, 6.5 Hz), 0.78 (2 x 9H, s, -Si-C-(C**H**$_3$)$_3$), -0.02 (2 x 6H, s, -Si-(C**H**$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 143.5 (aromatic C), 133.2 (aromatic C), 129.7 (aromatic CH), 127.8 (aromatic CH), 65.7 (-O-CH-), 42.9 (-CH_2-N-CH_2-), 33.6 (-CH_2-C-CH_2-), 25.8 (-Si-C-(CH_3)$_3$), 21.6 (Ar-CH_3), 18.1 (-Si-C-(CH_3)$_3$), -4.7 (-Si-(CH_3)$_2$).

MS (ES, CH_3CN): 370 (100) $[M+H]^+$, 761 (56) $[2M+Na]^+$.

HRMS (ES) *m/z*: Found 761.3459; required for $C_{18}H_{31}NSO_3Si$, $[2M+Na]^+$ = 761.3480.

Benzyl-[(2R,4S)-2-methyl-8-(naphthalene-2-sulfonyl-1-oxa-8-aza-spiro[4.5]dec-4-yl-amine (438) and Benzyl-[(2R,4R)-2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amine (440)



438 **440**

To furanone **328** (861 mg, 2.40 mmol) in methanol (24 mL) was added benzylamine (262 μL, 2.40 mmol), sodium cyanoborohydride (226 mg, 3.59 mmol) and glacial acetic acid (137 μL, 2.40 mmol) and the reaction heated to reflux over molecular sieves (4 Å) for 16 h. The reaction was concentrated *in vacuo*, diluted with Et_2O (50 mL), basified (NaOH, 2N aq. solution) and the phases separated and washed with NaOH (2N aq. solution, 3 x 20 mL) and water (3 x 30 mL). The aqueous phase was extracted with Et_2O (4 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a white foam. Purification by column chromatography (50 % Et_2O/hexane) gave benzylamine **438** (400 mg, 0.89 mmol, 37 %) and benzylamine **440** (487 mg, 1.08 mmol, 45 %) as white solids (82 % combined yield).

Benzyl-[(2R,4S)-2-methyl-8-(naphthalene-2-sulfonyl)1-oxa-8-aza-spiro[4.5]dec-4-yl-amine (**438**):

MPt.: 120-122 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3305 (w), 3065 (w), 2928 (m), 2866 (m), 1592 (w), 1466 (m), 1335 (s), 1238 (m), 1158 (s), 1052 (s), 932 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.33 (1H, s, aromatic C**H**), 7.94 (2H, dd, aromatic C**H**, *J*= 3.5, 8.5 Hz), 7.88 (1H, d, aromatic C**H**, *J*= 7.8 Hz), 7.76 (1H, dd, aromatic C**H**, *J*= 1.8, 8.5 Hz), 7.61 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.57 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.30-7.20 (5H, m, aromatic C**H**), 3.85 (1H, ddq, -O-C**H**-CH_3, *J*= 11.8, 6.0, 6.0 Hz), 3.80-3.65 (4H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$- + benzylic C**H**$_2$), 2.88 (1H, dd, -C**H**-NH-Bn, *J*= 6.5, 9.5 Hz), 2.75 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 2.4, 12.1 Hz), 2.70 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 2.4, 12.1 Hz), 2.26 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 6.3, 6.3, 6.3 Hz), 1.88 (1H, ddd, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 13.1, 13.1, 4.8 Hz), 1.83 (1H, ddd, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 13.1, 13.1, 4.8 Hz), 1.54 (1H, br dd, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 2.5, 13.3 Hz), 1.48 (1H, br dd, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 2.5, 13.6 Hz), 1.29 (1H, dt, -CH$_a$**H**$_b$-CH-NH-, *J*= 12.1, 9.8 Hz), 1.08 (3H, d, -O-CH-C**H**$_3$, *J*= 6.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 140.2 (aromatic **C**), 134.9 (aromatic **C**), 134.0 (aromatic **C**), 132.3 (aromatic **C**), 129.3 (aromatic **C**H), 129.3 (aromatic **C**H), 128.9 (aromatic **C**H), 128.7 (aromatic **C**H), 128.5 (aromatic **C**H), 128.0 (aromatic **C**H), 128.0 (aromatic **C**H), 127.5 (aromatic **C**H), 127.1 (aromatic **C**H), 123.1 (aromatic **C**H), 79.2 (-**C**-O-), 71.8 (-O-**C**H-CH_3), 65.9 (-**C**H-NH-), 52.7 (benzylic **C**H$_2$), 43.5, (-**C**H$_a$H$_b$-NH-), 42.8 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 40.5 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 35.4 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.1 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 22.4 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 451 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 451.2049; required for $C_{26}H_{30}N_2SO_3$, $[M+H]^+$ = 451.2050.

Benzyl-[(2R,4R)-2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amine (**440**):

MPt.: 119-122 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3305 (w), 3065 (w), 2928 (m), 2866 (m), 1592 (w), 1466 (m), 1335 (s), 1238 (m), 1158 (s), 1052 (s), 932 (s).

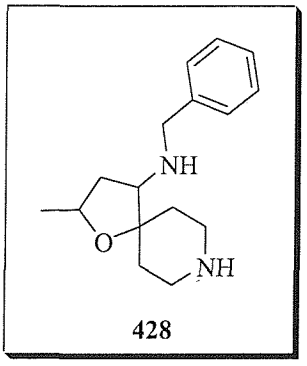
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.33 (1H, s, aromatic C**H**), 7.93 (2H, dd, aromatic C**H**, *J*= 3.5, 7.5 Hz), 7.88 (1H, d, aromatic C**H**, *J*= 8.0 Hz), 7.76 (1H, dd, aromatic C**H**, *J*= 1.5, 8.5 Hz), 7.61 (1H, dt, aromatic C**H**, *J*= 2.0, 7.5 Hz), 7.57 (1H, dt, aromatic C**H**, *J*= 2.0, 7.5 Hz), 7.30-7.20 (5H, m, aromatic C**H**), 4.01 (1H, ddq, -O-C**H**-CH_3, *J*= 6.0, 6.0, 6.0 Hz), 3.80-3.65 (4H, m, benzylic C**H**$_2$ + -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 2.88 (1H, t, -C**H**-NH-, *J*= 7.5 Hz), 2.73 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.0, 12.1 Hz), 2.68 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.0, 12.1 Hz), 1.93 (1H, dt, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 5.0, 13.3 Hz), 1.84-1.75 (3H, m, -CH$_a$**H**$_b$-C-CH$_a$H$_b$- + -C**H**$_2$-CH-NH-), 1.63 (1H, br dd, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 2.3, 13.3 Hz), 1.46 (1H, br dd, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 2.3, 13.3 Hz), 1.05 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 140.3 (aromatic **C**), 134.9 (aromatic **C**), 133.9 (aromatic **C**), 132.4 (aromatic **C**), 129.3 (aromatic **C**H), 129.3 (aromatic **C**H), 128.9 (aromatic **C**H), 128.7 (aromatic **C**H), 128.5 (aromatic **C**H), 128.0 (aromatic **C**H), 128.0 (aromatic **C**H), 127.5 (aromatic **C**H), 127.0 (aromatic **C**H), 123.1 (aromatic **C**H), 80.0 (-**C**-O-), 71.5 (-O-**C**H-CH_3), 64.7 (-**C**H-NH-), 52.9 (benzylic **C**H$_2$), 43.5 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.8 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 39.1 (-**C**H$_a$H$_b$-CH-NH-), 36.6 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 29.0 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.0 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 451 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 451.2049; required for $C_{26}H_{30}N_2SO_3$, $[M+H]^+$ = 451.2050.

Benzyl-(2-methyl-1-oxa-8-aza-spiro[4.5]dec-4-yl)amine (428)



428

To a solution of naphthalene (597 mg, 4.66 mmol) in DME (3 mL) was added sodium metal (107 mg, 4.66 mmol) with violent stirring at rt, until a deep green colour was observed. The sodium naphthalenide solution was added dropwise to a solution of the benzylamine **427** (210 mg, 0.466 mmol) in DME (2 mL) until a permanent deep red/purple colour was observed. After a further 1 h stirring at rt, the reaction was quenched by the addition of HCl (2N aq. solution, 5 mL), diluted with Et_2O (10 mL) and the phases separated. The mixture was extracted with HCl (2N aq. solution, 3 x 10 mL) and water (2 x 10 mL), the aqueous phases basified (NaOH, 2N aq. solution) and extracted with CH_2Cl_2 (5 x 10 mL). The CH_2Cl_2 phases were dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as an oily yellow solid. Purification by column chromatography (Et_2O → EtOAc → MeOH:CH_2Cl_2:NH_3; 4:95:1) granted the pure diamine as a yellow oil (117 mg, 0.451 mmol, 97 %). The spectroscopic data is reported as a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3361 (br w), 3025 (w), 2959 (m), 2926 (m), 2837 (m), 1600 (w), 1494 (m), 1452 (m), 1070 (m), 977 (m).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ/ppm: 7.30-7.19 (2 x 5H, m, aromatic C**H**), 4.09 (1H, ddq, -O-C**H**-CH_3, *J*= 6.5, 6.5, 6.0 Hz), 3.93 (1H, ddq, -O-C**H**-CH_3, *J*= 9.6, 6.0, 6.0 Hz), 3.79 (1H, s, Ph-C**H**$_a$H$_b$-NH-), 3.76 (1H, s, Ph-C**H**$_a$H$_b$-NH-), 3.67 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*= 4.5 Hz), 3.64 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*= 4.5 Hz), 2.92-2.72 (2 x 4H, m, -C**H**$_a$**H**$_b$-N-C**H**$_a$**H**$_b$- + 2 x 1H, m, -C**H**-NH-), 2.23 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, 12.0, 6.0, 6.0 Hz), 1.81 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 7.5, 7.5, 14.1 Hz), 1.74 (1H, ddd, -

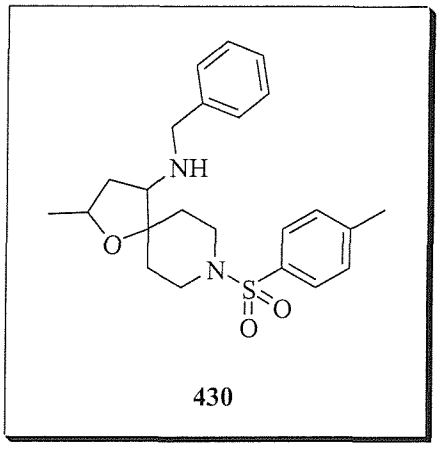
$CH_a\underline{H}_b$-CH-NH-, J= 7.0, 7.0, 13.5 Hz), 1.67-1.50 (2 x 2H, m, -C$\underline{H}_a$H$_b$-C-C$\underline{H}_a$H$_b$- + 1H, m, -$CH_a\underline{H}_b$-CH-NH-), 1.43-1.26 (2 x 2H, m, -$CH_a\underline{H}_b$-C-$CH_a\underline{H}_b$-), 1.17 (3H, d, -O-CH-C$\underline{H}_3$, J= 6.0 Hz), 1.12 (3H, d, -O-CH-C$\underline{H}_3$, J= 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 140.9 (2 x aromatic $\underline{C}$), 128.7 (2 x aromatic $\underline{C}$H), 128.3 (2 x aromatic $\underline{C}$H), 127.3 (2 x aromatic $\underline{C}$H), 82.0 (-$\underline{C}$-O-), 81.1 (-$\underline{C}$-O-), 71.7 (-O-$\underline{C}$H-CH_3), 71.6 (-O-$\underline{C}$H-CH_3), 66.6 (-$\underline{C}$H-NH-), 65.4 (-$\underline{C}$H-NH-), 53.2 (benzylic $\underline{C}H_2$), 53.0 (benzylic $\underline{C}H_2$), 43.9 (-$\underline{C}H_aH_b$-N-CH_aH_b-), 43.8 (-$\underline{C}H_aH_b$-N-CH_aH_b-), 43.1 (-CH_aH_b-N-$\underline{C}H_aH_b$-), 42.9 (-CH_aH_b-N-$\underline{C}H_aH_b$-), 40.7 (-$\underline{C}H_aH_b$-CH-NH-), 39.4 (-$\underline{C}H_aH_b$-CH-NH-), 38.7 (-$\underline{C}H_aH_b$-C-CH_aH_b-), 37.3 (-$\underline{C}H_aH_b$-C-CH_aH_b-), 33.8 (-CH_aH_b-C-$\underline{C}H_aH_b$-), 30.9 (-CH_aH_b-C-$\underline{C}H_aH_b$-), 23.5 (-O-CH-$\underline{C}H_3$), 23.0 (-O-CH-$\underline{C}H_3$).

MS (ES, CH_3CN): 261 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 261.1960; required for $C_{16}H_{24}N_2O$, $[M+H]^+$ = 261.1962.

Benzyl-2-methyl-8-(toluene-4-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl-amine (430)



430

To furanone **314** (600 mg, 1.85 mmol) in methanol (18 mL) was added benzylamine (203 μL, 1.85 mmol), sodium cyanoborohydride (175 mg, 2.78 mmol) and glacial acetic acid (102 μL, 1.85 mmol) and the reaction heated to reflux over molecular sieves (4 Å). After 16 h, the reaction was concentrated *in vacuo*, diluted with Et_2O (50 mL), basified (NaOH, 2N aq. solution), the phases separated and washed with NaOH (2N aq. solution, 3 x 20 mL) and water (3 x 30 mL). The aqueous phase was extracted with Et_2O (4 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a white foam. Purification by column chromatography (50 % Et_2O/hexane) gave benzylamine **430** (758 mg, 1.68 mmol, 91 %) as a white solid. The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 148-150 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3305 (w), 3065 (w), 2928 (m), 2866 (m), 1592 (w), 1466 (m), 1335 (s), 1238 (m), 1158 (s), 1052 (s), 932 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.70 (2H, d, aromatic C**H**, *J*= 8.0 Hz), 7.69 (2H, d, aromatic C**H**, *J*= 8.0 Hz), 7.38-7.31 (2 x 7H, m, aromatic C**H**), 4.12 (1H, ddq, -O-C**H**-CH_3, *J*= 6.0, 6.0, 6.0 Hz), 3.96 (1H, ddq, -O-C**H**-CH_3, *J*= 9.5, 3.5, 6.0 Hz), 3.89 (1H, s, Ph-C**H**$_a$H$_b$-NH-), 3.86 (1H, s, Ph-C**H**$_a$H$_b$-NH-), 3.77 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*=

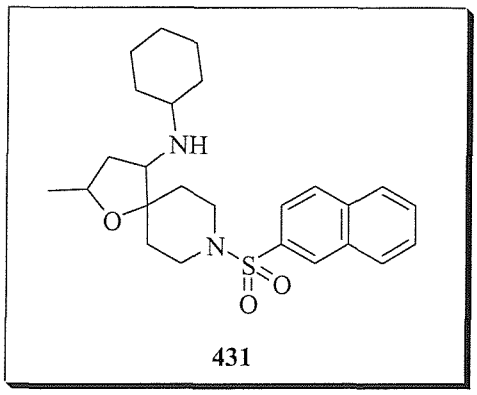
2.5 Hz), 3.76 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.74 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*= 2.0 Hz), 2.98 (1H, dd, -C**H**-NH-, *J*= 2.5, 7.0 Hz), 2.96 (1H, d, -C**H**-NH-, *J*= 6.5 Hz), 2.73 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.5, 12.6 Hz), 2.69 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.5, 12.6 Hz), 2.47 (2 x 3H, s, Ar-C**H**$_3$), 2.36 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 6.0, 6.0, 12.0 Hz), 2.01-1.80 (2 x 3H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$- + -CH$_a$**H**$_b$-CH-NH-), 1.68 (1H, td, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 13.5, 3.0 Hz), 1.60 (1H, td, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 13.0, 2.5 Hz), 1.52 (1H, dt, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 3.0, 11.0 Hz), 1.38 (1H, td, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-, *J*= 12.6, 9.5 Hz), 1.19 (2 x 3H, dd, -O-CH-C**H**$_3$, *J*= 16.5, 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 143.6 (2 x aromatic **C**), 140.6 (2 x aromatic **C**), 134.3 (aromatic **C**), 134.3 (aromatic **C**), 130.0 (2 x aromatic **C**H), 128.8 (2 x aromatic **C**H), 128.3 (2 x aromatic **C**H), 128.1 (2 x aromatic **C**H), 127.5 (2 x aromatic **C**H), 80.5 (-**C**-O-), 79.6 (-**C**-O-), 72.1 (-O-**C**H-CH$_3$), 71.8 (-O-**C**H-CH$_3$), 66.3 (-**C**H-NH-), 65.1 (-**C**H-NH-), 53.3 (benzylic **C**H$_2$), 53.1 (benzylic **C**H$_2$), 43.7 (2 x -**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.0 (2 x -CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 40.9 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 39.5 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 37.0 (-**C**H$_a$H$_b$-CH-NH-), 35.8 (-**C**H$_a$H$_b$-CH-NH-), 32.5 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 29.3 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.4 (-O-CH-**C**H$_3$), 22.8 (-O-CH-**C**H$_3$), 21.9 (2 x Ar-**C**H$_3$).

MS (ES, CH_3CN): 415 (100) $[M+H]^+$, 829 (15) $[2M+H]^+$.

HRMS (ES) *m/z*: Found 415.2050; required for $C_{23}H_{30}N_2SO_3$, $[M+H]^+$ = 415.2050.

Cyclohexyl-[2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amine (431)



431

To a solution of furanone **328** (150 mg, 0.417 mmol) in methanol (4 mL) was added cyclohexylamine (48 μL, 0.417 mmol), sodium cyanoborohydride (26 mg, 0.417 mmol) and glacial acetic acid (24 μL, 0.417 mmol) and the reaction heated to reflux over molecular sieves (4 Å). After 12 h, the reaction was concentrated *in vacuo* to leave the crude material as a brown solid. Purification by column chromatography (40 % Et_2O/hexane) isolated the pure amine **431** as a white solid (20 mg, 0.045 mmol, 11 %). The spectroscopic data is reported for the major diastereoisomer (2:1).

MPt.: 155-157 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3348 (w), 2925 (m), 2854 (m), 1653 (w), 1590 (w), 1464 (m), 1323 (s), 1229 (m), 1160 (s), 1076 (m), 1048 (m), 932 (s).

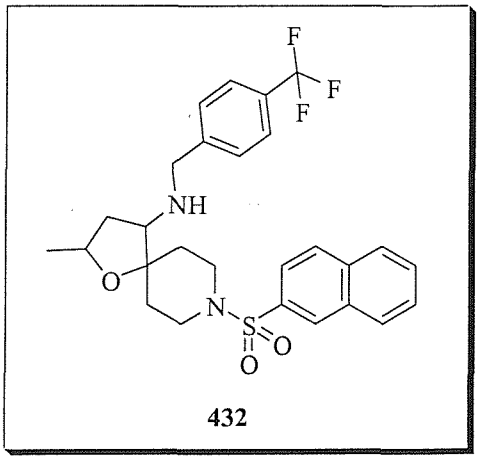
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.36 (1H, s, aromatic C**H**), 8.01-7.95 (3H, m, aromatic C**H**), 7.79 (1H, dd, aromatic C**H**, *J*= 8.6, 1.9 Hz), 7.65 (1H, dt, aromatic C**H**, *J*= 1.9, 7.1 Hz), 7.62 (1H, dt, aromatic C**H**, *J*= 1.9, 7.1 Hz), 4.00 (1H, ddq, -O-C**H**-CH_3, *J*= 6.2, 6.2, 6.2 Hz), 3.71 (2H, br t, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.0 Hz), 2.97 (1H, t, -CH_aH$_b$-C**H**-NH-, *J*= 8.1 Hz), 2.75 (1H, dt, -CH_a**H**$_b$-N-CH_aH$_b$-, *J*= 2.9, 11.4 Hz), 2.70 (1H, dt, -CH_aH$_b$-N-CH_a**H**$_b$-, *J*= 2.9, 11.4 Hz), 2.40 (1H, tt, -$(CH_2)_2$-C**H**-NH-, *J*= 10.5, 4.3 Hz), 1.95 (1H, td, -C**H**$_a$H$_b$-CH-NH-, *J*= 12.9, 4.8 Hz), 1.84-1.15 (14H, m, -C**H**$_a$**H**$_b$-C-C**H**$_a$**H**$_b$- + C_5**H**$_{10}$), 1.08 (3H, d, -O-CH-C**H**$_3$, *J*= 6.2 Hz).

^{13}**C NMR** (100 MHz, $CDCl_3$) δ/ppm: 134.8 (aromatic C), 133.9 (aromatic C), 132.3 (aromatic C), 129.3 (aromatic CH), 129.2 (aromatic CH), 128.8 (aromatic CH), 128.6 (aromatic CH), 127.9 (aromatic CH), 127.4 (aromatic CH), 123.1 (aromatic CH), 78.9 (-C-O-), 71.6 (-O-CH-CH_3), 63.1 (-CH-NH-), 55.2 (-$(CH_2)_2$-CH-NH-), 43.5 (-CH_aH_b-N-CH_aH_b-), 42.6 (-CH_aH_b-N-CH_aH_b-), 35.4 (-CH_aH_b-CH-NH-), 33.4 (-CH_aH_b-C-CH_aH_b-), 32.0 (-CH_aH_b-C-CH_aH_b-), 26.0 (-CH_2-), 24.9 (-CH_2-), 24.8 (-CH_2-), 22.4 (-O-CH-CH_3).

MS (ES, CH_3CN): 443 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 443.2363; required for $C_{25}H_{34}N_2SO_3$, $[M+H]^+ = 443.2363$.

[2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-(4-trifluoromethyl-benzyl)-amine (432)



432

To furanone **328** (150 mg, 0.417 mmol) in methanol (4 mL) was added 4-trifluoromethylbenzylamine (46 μL, 0.417 mmol), sodium cyanoborohydride (26 mg, 0.417 mmol) and glacial acetic acid (24 μL, 0.417 mmol) and the reaction heated to reflux over molecular sieves (4 Å). After 12 h, the reaction was concentrated *in vacuo* to leave the crude material as a brown solid. Purification by column chromatography

(40 % Et_2O/hexane) isolated the pure amine **432** as a white solid (134 mg, 0.258 mmol, 62 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 124-126 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3302 (w), 3064 (w), 2963 (w), 2934 (w), 2859 (w), 1619 (w), 1590 (w), 1466 (w), 1420 (w), 1323 (s), 1158 (s), 1121 (s), 1066 (s), 1047 (m), 932 (m).

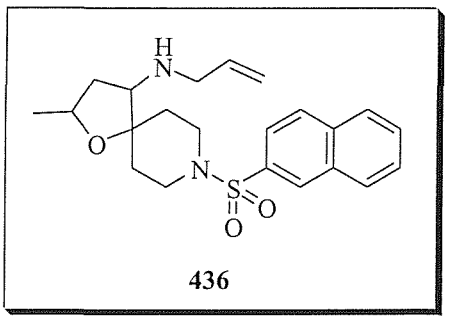
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.28 (2 x 1H, s, aromatic C**H**), 7.92-7.89 (2 x 2H, m, aromatic C**H**), 7.84 (2 x 1H, d, aromatic C**H**, *J*= 8.0 Hz), 7.70 (2 x 1H, d, aromatic C**H**, *J*= 7.5 Hz), 7.58 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 6.5 Hz), 7.52 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 6.5 Hz), 7.48 (2 x 2H, d, aromatic C**H**, *J*= 8.0 Hz), 7.33 (2 x 2H, br d, aromatic C**H**, *J*= 8.0 Hz), 3.97 (1H, q, -O-C**H**-CH_3, *J*= 6.5 Hz), 3.83-3.78 (2 x 1H, m, Ar-C**H**$_a$H$_b$-NH- + 1H, m, -O-C**H**-CH_3), 3.74-3.62 (2 x 3H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$- + Ar-CH$_a$**H**$_b$-NH-), 2.82 (2 x 1H, dd, -C**H**-NH-, *J*= 7.0, 10.0 Hz), 2.72-2.61 (2 x 2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.23 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 5.5, 5.5, 12.6 Hz), 1.83-1.74 (2 x 2H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.52-1.37 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + 2 x 1H, m, -CH$_a$**H**$_b$-CH-NH- + 1H, m, -C**H**$_a$H$_b$-CH-NH-), 1.04 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz), 1.00 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 142.7 (2 x aromatic **C**), 133.2 (2 x aromatic **C**), 132.5 (2 x aromatic **C**), 132.4 (2 x aromatic **C**), 130.7 (2 x aromatic **C**), 127.6 (2 x aromatic **C**H), 127.6 (2 x aromatic **C**H), 127.2 (2 x aromatic **C**H), 127.1 (2 x aromatic **C**H), 126.5 (2 x aromatic **C**H), 126.3 (2 x aromatic **C**H), 125.8 (2 x aromatic **C**H), 123.7 (2 x aromatic **C**H), 123.7 (2 x aromatic **C**H), 121.4 (2 x -**C**F_3), 78.3 (-**C**-O-), 77.5 (-**C**-O-), 70.1 (-O-**C**H-CH_3), 69.7 (-O-**C**H-CH_3), 64.4 (-**C**H-NH-), 63.2 (-**C**H-NH-), 50.6 (benzylic **C**H_2), 50.5 (benzylic **C**H_2), 41.7 (2 x -**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 41.0 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 41.0 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 38.8 (-**C**H$_a$H$_b$-CH-NH-), 37.4 (-**C**H$_a$H$_b$-CH-NH-), 35.0 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 33.7 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 30.5 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 27.3 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 21.3 (-O-CH-C**H**$_3$), 20.6 (-O-CH-C**H**$_3$).

MS (ES, CH_3CN): 519 (85) $[M+H]^+$.

HRMS (ES) *m/z*: Found 519.1924; required for $C_{27}H_{29}N_2SO_3F_3$, $[M+H]^+ = 519.1924$.

Allyl-[2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amine (436)



436

To furanone **328** (300 mg, 0.835 mmol) in methanol (5 mL) was added allylamine (63 μL, 0.835 mmol), sodium cyanoborohydride (53 mg, 0.835 mmol) and glacial acetic acid (48 μL, 0.835 mmol) and the reaction heated to reflux over molecular sieves (4 Å). After 12 h the reaction was diluted with Et_2O (10 mL), the phases separated and washed with NaOH (2N aq. solution, 2 x 10 mL) and water (2 x 10 mL). The aqueous phases were extracted with Et_2O (3 x 10 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude material as a brown oil. Purification by column chromatography (80 % Et_2O/hexane) isolated the pure amine as a colourless oil (224 mg, 0.559 mmol, 67 %). The spectroscopic data is reported for a mixture of diastereoisomers.

IR (neat) ν/cm^{-1}: 3055 (w), 2967 (w), 2926 (w), 2863 (w), 1644 (w), 1590 (w), 1505 (w), 1465 (m), 1329 (s), 1157 (s), 1073 (m), 1048 (s), 929 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.26 (2 x 1H, s, aromatic C**H**), 7.87 (2 x 2H, dd, aromatic C**H**, *J*= 2.5, 9.0 Hz), 7.82 (2 x 1H, d, aromatic C**H**, *J*= 8.0 Hz), 7.68 (2 x 1H, dd, aromatic C**H**, *J*= 2.0, 9.0 Hz), 7.58 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 8.0 Hz), 7.51 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 8.0 Hz), 5.78-5.68 (2 x 1H, m, -C**H**=CH_aH_b), 5.05 (2 x 1H, ddt, -CH=C**H**$_a$$H_b$, *J*= 17.0, 2.0, 2.0 Hz), 4.96 (2 x 1H, ddt, -CH=CH_a**H**$_b$, *J*= 10.6, 5.0, 1.0 Hz), 3.93 (1H, ddq, -O-C**H**-CH_3, *J*= 6.5, 6.5, 6.5 Hz), 3.80 (1H, ddq, -O-C**H**-

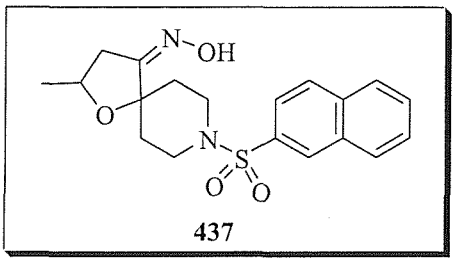
CH_3, *J*= 7.5, 6.0, 6.0 Hz), 3.72-3.60 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.18 (1H, tdd, -C**H**$_a$H$_b$-CH=CH_2, *J*= 1.5, 3.0, 5.5 Hz), 3.15 (1H, tdd, -C**H**$_a$H$_b$-CH=CH_2, *J*= 1.5, 3.0, 5.5 Hz), 3.08 (1H, tdd, -CH$_a$**H**$_b$-CH=CH_2, *J*= 1.5, 3.0, 6.0 Hz), 3.04 (1H, tdd, -CH$_a$**H**$_b$-CH=CH_2, *J*= 1.5, 3.0, 6.0 Hz), 2.82 (2 x 1H, dt, -C**H**-NH-, *J*= 8.5, 7.0 Hz), 2.75 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.0, 12.1 Hz), 2.70 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.0, 12.1 Hz), 2.19 (2 x 1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 12.0, 6.5, 5.5 Hz), 1.85 (1H, td, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 5.0, 13.5 Hz), 1.79-1.67 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.66 (1H, td, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 12.0, 4.5 Hz), 1.53 (1H, dq, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 13.6, 3.0 Hz), 1.47-1.38 (2 x 1H, m, -CH$_a$**H**$_b$-CH-NH- + 1H, m, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.02 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz), 0.99 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C **NMR** (100 MHz, $CDCl_3$) δ/ppm: 137.2 (2 x –**C**H=CH_2), 135.2 (2 x aromatic **C**), 134.3 (2 x aromatic **C**), 132.7 (2 x aromatic **C**), 129.6 (2 x aromatic **C**H), 129.2 (2 x aromatic **C**H), 129.0 (2 x aromatic **C**H), 128.7 (2 x aromatic **C**H), 128.3 (2 x aromatic **C**H), 127.8 (2 x aromatic **C**H), 123.5 (2 x aromatic **C**H), 116.4 (2 x –CH=**C**H_2), 80.3 (-**C**-O-), 79.5 (-**C**-O-), 72.1 (-O-**C**H-CH_3), 71.7 (-O-**C**H-CH_3), 66.3 (-**C**H-NH-), 65.0 (-**C**H-NH-), 51.8 (-NH-**C**H_2-), 51.7 (-NH-**C**H_2-), 43.8 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.8 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.1 (2 x -CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 41.0 (-**C**H$_a$H$_b$-CH-NH-), 39.5 (-**C**H$_a$H$_b$-CH-NH-), 37.0 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 35.8, (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.5 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 32.0 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.4 (-O-CH-**C**H_3), 22.7 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 401 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 401.1890; required for $C_{22}H_{28}N_2SO_3$, $[M+H]^+$ = 401.1894.

2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]decan-4-one oxime (437)



437

To furanone **328** (100 mg, 0.28 mmol) in methanol (5 mL) was added hydroxylamine hydrochloride (39 mg, 0.56 mmol) and sodium acetate (91 mg, 1.11 mmol). The reaction was heated to reflux for 12 h, then concentrated *in vacuo*. Purification of the residue by column chromatography (40 % Et_2O/hexane) gave the pure oxime **437** as a white solid (66 mg, 0.18 mmol, 63 %).

MPt.: 206-208 °C (EtOH).

IR (neat) ν/cm^{-1}: 3298 (br m), 2979 (w), 2927 (w), 2852 (w), 1735 (w), 1589 (w), 1504 (w), 1442 (w), 1347 (s), 1252 (m), 1167 (s), 1076 (s), 1050 (s), 919 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.37 (1H, s, aromatic C**H**), 8.00 (2H, d, aromatic C**H**, *J*= 8.6 Hz), 7.96 (1H, d, aromatic C**H**, *J*= 7.9 Hz), 7.79 (1H, dd, aromatic C**H**, *J*= 8.6, 1.9 Hz), 7.70 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.63 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 4.08 (1H, ddq, -O-C**H**-CH_3, *J*= 6.0, 6.0, 6.0 Hz), 3.74 (2H, br td, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.9, 4.3 Hz), 2.94 (1H, dd, -C**H**$_a$H$_b$-C=N-OH, *J*= 17.9, 5.9 Hz), 2.80 (2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.22 (1H, dd, -CH$_a$**H**$_b$-C=N-OH, *J*= 18.1, 9.3 Hz), 2.09 (1H, td, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 8.8, 5.0 Hz), 1.87-1.74 (3H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.23 (3H, d, -O-CH-C**H**$_3$, *J*= 6.2 Hz).

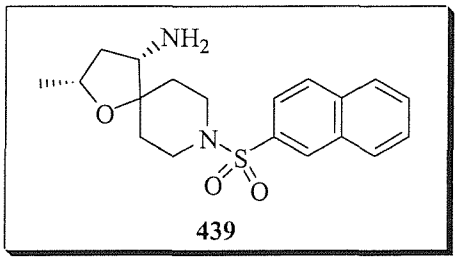
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 166.3 (**C**=N-OH), 135.1 (aromatic **C**), 134.1 (aromatic **C**), 132.5 (aromatic **C**), 129.5 (aromatic **C**H), 129.5 (aromatic **C**H), 129.1 (aromatic **C**H), 128.9 (aromatic **C**H), 128.2 (aromatic **C**H), 127.7 (aromatic **C**H),

123.2 (aromatic CH), 78.5 (-C-O-), 71.6 (-O-CH-CH_3), 43.0 (-CH_aH_b-N-CH_aH_b-), 42.6 (-CH_aH_b-N-CH_aH_b-), 35.6 (-CH_aH_b-C=N-OH), 34.9 (-CH_aH_b-C-CH_aH_b-), 33.1 (-CH_aH_b-C-CH_aH_b-), 21.3 (-O-CH-CH_3).

MS (ES, CH_3CN): 413 (100) $[M+K]^+$, 787 (51) $[2M+K]^+$.

HRMS (ES) *m/z*: Found 771.2475; required for $C_{19}H_{22}N_2SO_4$, $[2M+Na]^+$ = 771.2492.

(2R,4S)-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-ylamine (439)



439

To benzylamine **438** (150 mg, 0.33 mmol) in methanol (4 mL) was added Pd/C (71 mg, 10 mol %) and ammonium formate (210 mg, 3.30 mmol) and the reaction heated to reflux over molecular sieves (4 Å) for 12 h, then concentrated *in vacuo*. Purification by column chromatography (100 % CH_2Cl_2 → CH_2Cl_2:MeOH:NH_3; 90:9:1) gave the pure amine **439** as a white solid (69 mg, 0.19 mmol, 58 %).

MPt.: 155-157 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3386 (w), 2958 (w), 2930 (w), 2859 (m), 1625 (w), 1591 (w), 1504 (w), 1466 (m), 1329 (s), 1163 (s), 1075 (s), 1049 (s), 925 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.34 (1H, s, aromatic CH), 7.96 (2H, d, aromatic CH, *J*= 8.3 Hz), 7.91 (1H, d, aromatic CH, *J*= 7.8 Hz), 7.76 (1H, dd, aromatic CH, *J*= 8.5, 1.8 Hz), 7.70 (1H, dt, aromatic CH, *J*= 1.2, 7.0 Hz), 7.66 (1H, dt, aromatic CH, *J*= 1.2, 7.0 Hz), 3.88 (1H, ddq, -O-CH-CH_3, *J*= 9.0, 6.3, 6.3 Hz), 3.77 (1H, br d, -CH_aH_b-

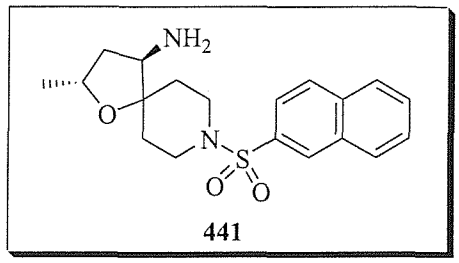
N-CH_aH_b-, *J*= 11.3 Hz), 3.71 (1H, td, -CH_aH_b-N-C**H**$_aH_b$-, *J*= 11.5, 2.8 Hz), 3.08 (1H, br t, -C**H**-NH_2, *J*= 7.0 Hz), 2.73 (1H, ddd, -CH_a**H**$_b$-N-CH_aH_b-, *J*= 2.5, 12.0, 14.8 Hz), 2.67 (1H, ddd, -CH_aH_b-N-CH_a**H**$_b$-, *J*= 2.5, 12.0, 14.8 Hz), 2.30 (1H, dt, -C**H**$_aH_b$-CH-NH_2, *J*= 6.8, 6.8 Hz), 1.76 (2H, ddd, -C**H**$_aH_b$-C-C**H**$_aH_b$-, *J*= 4.8, 12.8, 12.8 Hz), 1.56-1.50 (2H, m, -CH_a**H**$_b$-C-CH_a**H**$_b$-), 1.29 (1H, dt, -CH_a**H**$_b$-CH-NH_2, *J*= 12.5, 8.5 Hz), 1.10 (3H, d, -O-CH-C**H**$_3$, *J*= 6.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 134.9 (aromatic **C**), 133.9 (aromatic **C**), 132.4 (aromatic **C**), 129.3 (aromatic **C**H), 129.3 (aromatic **C**H), 129.0 (aromatic **C**H), 128.8 (aromatic **C**H), 128.0 (aromatic **C**H), 127.6 (aromatic **C**H), 123.1 (aromatic **C**H), 79.7 (-**C**-O-), 71.4 (-O-**C**H-CH_3), 60.1 (-**C**H-NH_2), 43.3 (-**C**H_aH_b-N-CH_aH_b-), 42.9 (-CH_aH_b-N-**C**H_aH_b-), 42.7 (-**C**H_aH_b-CH-NH_2), 34.2 (-**C**H_aH_b-C-CH_aH_b-), 31.7 (-CH_aH_b-C-**C**H_aH_b-), 22.6 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 361 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 361.1580; required for $C_{19}H_{24}N_2SO_3$, $[M+H]^+$ = 361.1581.

(2R,4R)-2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-ylamine (441)



441

To benzylamine **440** (180 mg, 0.40 mmol) in methanol (5 mL) was added Pd/C (85 mg, 10 mol %) and ammonium formate (252 mg, 4.00 mmol) and the reaction heated to reflux over molecular sieves (4 Å) for 12 h, then concentrated *in vacuo*. Purification by column chromatography (100 % CH_2Cl_2 → CH_2Cl_2:MeOH:NH_3; 90:9:1) gave the pure amine **441** as a white solid (92 mg, 0.26 mmol, 64 %).

MPt.: 155-157 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3386 (w), 2958 (w), 2930 (w), 2859 (m), 1625 (w), 1591 (w), 1504 (w), 1466 (m), 1329 (s), 1163 (s), 1075 (s), 1049 (s), 925 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.33 (1H, s, aromatic C**H**), 7.96 (2H, d, aromatic C**H**, *J*= 8.3 Hz), 7.90 (1H, d, aromatic C**H**, *J*= 7.8 Hz), 7.76 (1H, d, aromatic C**H**, *J*= 8.8 Hz), 7.64 (1H, dt, aromatic C**H**, *J*= 1.0, 7.0 Hz), 7.60 (1H, dt, aromatic C**H**, *J*= 1.0, 7.0 Hz), 3.98 (1H, ddq, -O-C**H**-CH_3, *J*= 6.3, 6.3, 6.3 Hz), 3.71 (2H, br t, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 15.6 Hz), 3.10 (1H, br s, -C**H**-NH_2), 2.65 (1H, dt, -CH_a**H**$_b$-N-CH_aH$_b$-, *J*= 2.8, 12.0 Hz), 2.61 (1H, dt, -CH_aH$_b$-N-CH_a**H**$_b$-, *J*= 2.8, 12.0 Hz), 1.87-1.68 (3H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$- + -C**H**$_a$H$_b$-CH-NH_2), 1.61 (1H, br d, -CH_a**H**$_b$-C-CH_aH$_b$-, *J*= 13.3 Hz), 1.47 (1H, br dd, -CH_aH$_b$-C-CH_a**H**$_b$-, *J*= 2.3, 13.5 Hz), 1.25-1.18 (1H, br m, -CH_a**H**$_b$-CH-NH_2), 1.07 (3H, d, -O-CH-C**H**$_3$, *J*= 6.3 Hz).

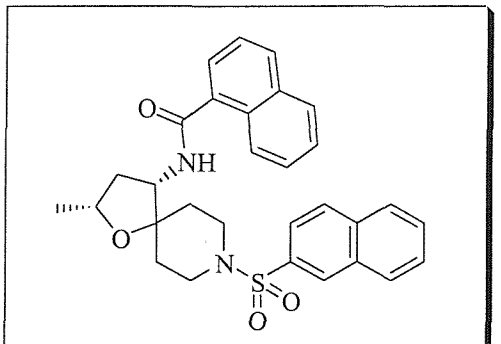
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 134.9 (aromatic **C**), 133.8 (aromatic **C**), 132.4 (aromatic **C**), 129.8 (aromatic **C**H), 129.3 (aromatic **C**H), 128.9 (aromatic **C**H), 128.8

(aromatic CH), 128.0 (aromatic CH), 127.5 (aromatic CH), 123.1 (aromatic CH), 80.4 (-C-O-), 71.6 (-O-CH-CH_3), 59.1 (-CH-NH_2), 43.3 (-CH_aH_b-N-CH_aH_b-), 42.9 (-CH_aH_b-N-CH_aH_b-), 41.6 (-CH_aH_b-CH-NH_2), 36.2 (-CH_aH_b-C-CH_aH_b-), 28.9 (-CH_aH_b-C-CH_aH_b-), 23.0 (-O-CH-CH_3).

MS (ES, CH_3CN): 361 (100) $[M+H]^+$.

HRMS (ES) *m/z*: Found 361.1580; required for $C_{19}H_{24}N_2SO_3$, $[M+H]^+$ = 361.1581.

Naphthalene-1-carboxylic acid [(2R,4S)-2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amide (442)



442

To amine **439** (35 mg, 0.097 mmol) in CH_2Cl_2 (1 mL) was added 1-naphthoyl chloride (16 mg, 0.097 mmol) and triethylamine (27 µL, 0.194 mmol). The reaction was stirred at rt for 4 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown solid by column chromatography (40 % Et_2O/hexane) gave the pure amide as a white solid (38 mg, 0.074 mmol, 76 %).

MPt.: 210-212 °C (CH_2Cl_2/Et_2O).

IR (neat) ν/cm^{-1}: 3318 (w), 3050 (w), 2966 (w), 2926 (w), 2860 (w), 1638 (s), 1594 (w), 1536 (m), 1329 (s), 1160 (s), 1089 (m), 929 (m).

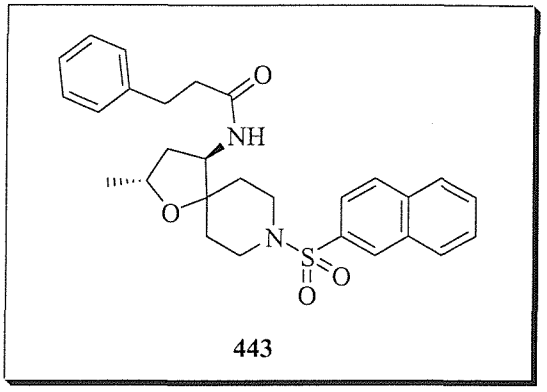
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.60 (1H, d, aromatic C**H**, *J*= 8.0 Hz), 8.46 (1H, s, aromatic C**H**), 8.22 (1H, d, aromatic C**H**, *J*= 8.0 Hz), 8.16 (2H, br t, aromatic C**H**, *J*= 8.5 Hz), 8.07 (1H, d, aromatic C**H**, *J*= 7.6 Hz), 8.03 (1H, dd, aromatic C**H**, *J*= 6.5, 2.5 Hz), 7.99 (1H, dd, aromatic C**H**, *J*= 9.0, 2.5 Hz), 7.78 (1H, d, aromatic C**H**, *J*= 8.6 Hz), 7.73 (1H, dt, aromatic C**H**, *J*= 1.5, 6.5 Hz), 7.69 (1H, dt, aromatic C**H**, *J*= 1.5, 6.5 Hz), 7.60-7.51 (3H, m, aromatic C**H**), 4.44 (1H, q, -C**H**-NH-, *J*= 8.5 Hz), 3.90 (1H, ddq, -O-C**H**-CH_3, *J*= 5.5, 10.5, 5.5 Hz), 3.65 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 2.57-2.50 (2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 2.27 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 5.0, 7.5, 12.6 Hz), 1.95 (1H, td, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 13.6, 4.5 Hz), 1.79 (1H, br d, -CH$_a$**H**$_b$-CH-NH-, *J*= 13.5 Hz), 1.68 (1H, td, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 13.6, 4.5 Hz), 1.65-1.56 (2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.04 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 168.9 (-NH-**C**=O), 134.7 (aromatic **C**), 134.7 (aromatic **C**), 133.4 (aromatic **C**), 133.3 (aromatic **C**), 132.2 (aromatic **C**), 130.2 (aromatic **C**H), 130.0 (aromatic **C**), 129.7 (aromatic **C**H), 129.7 (aromatic **C**H), 129.3 (aromatic **C**H), 128.9 (aromatic **C**H), 128.6 (aromatic **C**H), 128.3 (aromatic **C**H), 128.0 (aromatic **C**H), 127.1 (aromatic **C**H), 126.6 (aromatic **C**H), 125.7 (aromatic **C**H), 125.5 (aromatic **C**H), 125.3 (aromatic **C**H), 123.2 (aromatic **C**H), 79.4 (-**C**-O-), 71.2 (-O-**C**H-CH_3), 57.6 (-**C**H-NH-), 43.6 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.0 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 38.9 (-**C**H$_a$H$_b$-CH-NH-), 34.6 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.4 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 21.3 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 532 (50) $[M+NH_4]^+$, 1046 (7) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 515.2006; required for $C_{30}H_{30}N_2SO_4$, $[M+H]^+$ = 515.1999.

N-[2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-3-phenyl-propionamide (443)



443

To amine **441** (35 mg, 0.097 mmol) in CH_2Cl_2 (1 mL) was added hydrocinnamoyl chloride (14 mg, 0.097 mmol) and triethylamine (27 μL, 0.194 mmol). The reaction was stirred at rt for 5 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown solid by column chromatography (40 % Et_2O/hexane) gave the pure amide as a white solid (27 mg, 0.054 mmol, 56 %).

MPt.: 142-144 °C (EtOH).

IR (neat) ν/cm^{-1}: 3536 (w), 3299 (br w), 3063 (w), 2967 (w), 2926 (w), 2853 (w), 1642 (s), 1543 (s), 1460 (m), 1330 (s), 1161 (s), 1051 (s), 934 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.24 (1H, s, aromatic C**H**), 7.88 (2H, dd, aromatic C**H**, *J*= 8.6, 4.0 Hz), 7.84 (1H, d, aromatic C**H**, *J*= 8.0 Hz), 7.65 (1H, dd, aromatic C**H**, *J*= 8.5, 1.5 Hz), 7.57 (1H, dt, aromatic C**H**, *J*= 1.0, 7.0 Hz), 7.53 (1H, dt, aromatic C**H**, *J*= 1.0, 7.0 Hz), 7.24 (2H, dd, aromatic C**H**, *J*= 7.0, 7.5 Hz), 7.19 (1H, dd, aromatic C**H**, *J*= 4.0, 3.0 Hz), 7.12 (2H, d, aromatic C**H**, *J*= 7.0 Hz), 5.21 (1H, d, -N**H**-, *J*= 9.0 Hz), 4.17 (1H, dt, -C**H**-NH-, *J*= 7.5, 7.5 Hz), 3.83 (1H, ddq, -O-C**H**-CH_3, *J*= 6.5, 6.5,

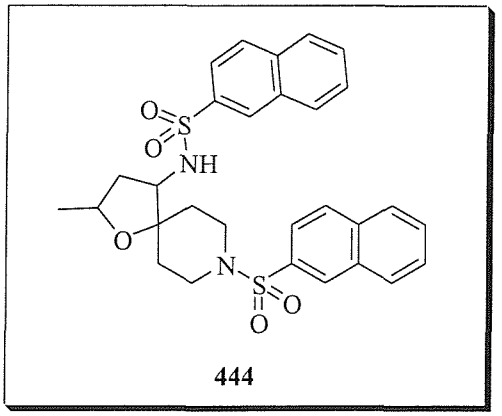
6.5 Hz), 3.58 (1H, m, Ph-C**H**$_a$H$_b$-), 3.51 (1H, m, Ph-CH$_a$**H**$_b$-), 2.86 (2H, br s, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-), 2.56 (1H, m, -C**H**$_a$H$_b$-C=O), 2.49 (1H, m, -CH$_a$**H**$_b$-C=O), 2.44-2.39 (2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$-), 1.76 (2H, ddd, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 8.1, 8.1, 16.6 Hz), 1.60 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 7.0, 13.0, 13.0 Hz), 1.45 (1H, br d, -CH$_a$**H**$_b$-CH-NH-, *J*= 13.6 Hz), 1.18 (2H, br s, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 0.98 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C **NMR** (100 MHz, $CDCl_3$) δ/ppm: 172.2 (-NH-**C**=O), 140.8 (aromatic **C**), 135.2 (aromatic **C**), 134.2 (aromatic **C**), 132.7 (aromatic **C**), 129.6 (aromatic **C**H), 129.2 (aromatic **C**H), 129.2 (aromatic **C**H), 129.1 (aromatic **C**H), 129.1 (aromatic **C**H), 128.8 (aromatic **C**H), 128.3 (aromatic **C**H), 127.9 (aromatic **C**H), 127.0 (aromatic **C**H), 123.4 (aromatic **C**H), 80.2 (-**C**-O-), 72.1 (-O-**C**H-CH$_3$), 56.1 (-**C**H-NH-), 43.4 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.9 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 39.0 (-**C**H$_a$H$_b$-C=O), 38.9 (-**C**H$_a$H$_b$-CH-NH-), 36.3 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.1 (Ph-**C**H$_a$H$_b$-), 29.5 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.0 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 493 (35) $[M+H]^+$, 510 (100) $[M+NH_4]^+$, 515 (30) $[M+Na]^+$, 1002 (15) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 515.1984; required for $C_{28}H_{32}N_2SO_4$, $[M+Na]^+$ = 515.1975.

Naphthalene-2-sulfonic acid [2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amide (444)



444

To amine **434** (35 mg, 97 μmol) in CH_2Cl_2 (1 mL) was added 2-naphthalenesulfonyl chloride (22 mg, 97 μmol) and triethylamine (27 μL, 0.194 mmol). The reaction was stirred at rt for 5 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown solid by column chromatography (40 % Et_2O/hexane) gave the pure sulfonamide as a white solid (25 mg, 46 μmol, 47 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 208-210 °C (EtOH).

IR (neat) ν/cm^{-1}: 3521 (m), 2969 (w), 2915 (w), 2872 (w), 1737 (m), 1592 (w), 1505 (w), 1451 (m), 1331 (s), 1155 (s), 1075 (s), 935 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.45 (2 x 1H, s, aromatic C**H**), 8.44 (2 x 1H, s, aromatic C**H**), 8.21-8.12 (2 x 4H, m, aromatic C**H**), 8.06 (2 x 2H, m, aromatic C**H**), 7.83 (2 x 1H, dd, aromatic C**H**, *J*= 8.5, 1.5 Hz), 7.77-7.65 (2 x 5H, m, aromatic C**H**), 3.87 (1H, dq, -O-C**H**-CH_3, *J*= 6.5, 6.5 Hz), 3.69-3.56 (2 x 2H, m, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$- + 1H, m, -O-C**H**-CH_3), 3.45-3.40 (2 x 1H, m, -C**H**-NH-), 2.46-2.40 (2 x 2H, m, -CH$_a$**H**$_b$-

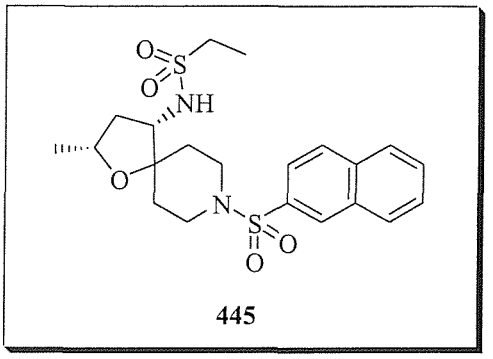
N-$CH_a\underline{H}_b$-), 1.82-1.49 (2 x 4H, m, -$C\underline{H}_aH_b$-C-$C\underline{H}_aH_b$- + -$C\underline{H}_a\underline{H}_b$-CH-NH-), 1.43-1.18 (2 x 2H, m, -$CH_a\underline{H}_b$-C-$CH_a\underline{H}_b$-), 0.87 (3H, d, -O-CH-$C\underline{H}_3$, *J*= 6.0 Hz), 0.81 (3H, d, -O-CH-$C\underline{H}_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 138.5 (2 x aromatic <u>C</u>), 134.8 (aromatic <u>C</u>), 134.6 (aromatic <u>C</u>), 132.3 (aromatic <u>C</u>), 132.1 (aromatic <u>C</u>), 129.9 (aromatic <u>C</u>H), 129.8 (aromatic <u>C</u>H), 129.7 (aromatic <u>C</u>H), 129.5 (aromatic <u>C</u>H), 129.2 (aromatic <u>C</u>H), 129.0 (aromatic <u>C</u>H), 128.4 (aromatic <u>C</u>H), 128.3 (aromatic <u>C</u>H), 128.2 (aromatic <u>C</u>H), 128.1 (aromatic <u>C</u>H), 127.8 (2 x aromatic <u>C</u>H), 123.3 (aromatic <u>C</u>H), 122.6 (aromatic <u>C</u>H), 79.6 (-<u>C</u>-O-), 78.5 (-<u>C</u>-O-), 71.2 (-O-<u>C</u>H-CH_3), 71.0 (-O-<u>C</u>H-CH_3), 61.1 (-<u>C</u>H-NH-), 60.2 (-<u>C</u>H-NH-), 43.6 (2 x -$\underline{C}H_aH_b$-N-CH_aH_b-), 42.9 (2 x -CH_aH_b-N-$\underline{C}H_aH_b$-), 38.7 (-$\underline{C}H_aH_b$-CH-NH-), 37.6 (-$\underline{C}H_aH_b$-CH-NH-), 35.6, (2 x -$\underline{C}H_aH_b$-C-CH_aH_b-), 33.9 (-CH_aH_b-C-$\underline{C}H_aH_b$-), 32.7 (-CH_aH_b-C-$\underline{C}H_aH_b$-), 22.4 (-O-CH-$\underline{C}H_3$), 21.5 (-O-CH-$\underline{C}H_3$).

MS (ES, CH_3CN): 551 (15) $[M+H]^+$, 568 (100) $[M+NH_4]^+$, 573 (20) $[M+Na]^+$, 1118 (10) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 573.1499; required for $C_{29}H_{30}N_2S_2O_5$, $[M+Na]^+$ = 573.1488.

Ethanesulfonic acid [(2R,4S)-2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-amide (445)



445

To amine **439** (35 mg, 97 μmol) in CH_2Cl_2 (1 mL) was added ethanesulfonyl chloride (9 μL, 97 μmol) and triethylamine (27 μL, 0.194 mmol). The reaction was stirred at rt for 3 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown solid by column chromatography (40 % Et_2O/hexane) gave the pure sulfonamide as a white solid (17 mg, 38 μmol, 39 %).

MPt.: 174-176 °C (EtOH).

IR (neat) ν/cm^{-1}: 3299 (br w), 2971 (w), 2931 (w), 2867 (w), 1540 (w), 1447 (m), 1317 (s), 1227 (m), 1154 (s), 1132 (s), 1050 (s), 932 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.28 (1H, s, aromatic C**H**), 7.91 (2H, dd, aromatic C**H**, *J*= 7.5, 4.0 Hz), 7.86 (1H, d, aromatic C**H**, *J*= 7.5 Hz), 7.69 (1H, dd, aromatic C**H**, *J*= 8.6, 1.5 Hz), 7.59 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.55 (1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 4.42 (1H, d, -N**H**-, *J*= 8.0 Hz), 3.82 (1H, ddq, -O-C**H**-CH_3, *J*= 12.0, 6.0, 6.0 Hz), 3.74 (1H, br d, -C**H**$_a$H$_b$-N-CH_aH_b-, *J*= 11.5 Hz), 3.66 (1H, br ddd, -CH_aH_b-N-C**H**$_a$H$_b$-, *J*= 11.5, 2.0, 2.0 Hz), 3.55 (1H, dt, -C**H**-NH-, *J*= 8.5, 8.5 Hz), 2.94 (2H, q, -SO_2-C**H**$_2$-CH_3, *J*= 7.6 Hz), 2.63 (1H, dt, -CH_a**H**$_b$-N-CH_aH_b-, *J*= 2.5, 12.5 Hz), 2.59 (1H, dt, -CH_aH_b-N-CH_a**H**$_b$-, *J*= 2.5, 12.5 Hz), 2.38 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*=

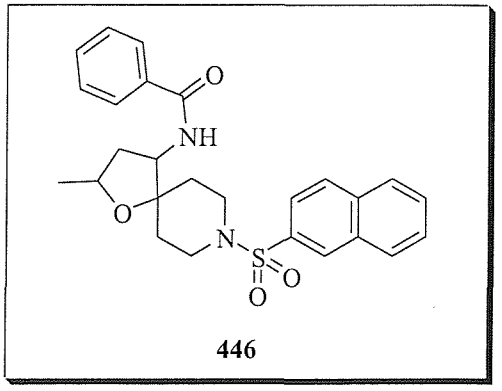
6.0, 6.0, 13.0 Hz), 1.78 (2H, ddt, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-, *J*= 2.0, 4.5, 13.6 Hz), 1.49 (2H, dtt, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-, *J*= 2.5, 2.5, 14.0 Hz), 1.41 (1H, dt, -CH$_a$**H**$_b$-CH-NH-, *J*= 12.5, 9.0 Hz), 1.28 (3H, t, -SO$_2$-CH$_2$-C**H**$_3$, *J*= 7.5 Hz), 1.06 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 135.3 (aromatic **C**), 134.2 (aromatic **C**), 132.7 (aromatic **C**), 129.7 (aromatic **C**H), 129.7 (aromatic **C**H), 129.3 (aromatic **C**H), 129.1 (aromatic **C**H), 128.3 (aromatic **C**H), 127.9 (aromatic **C**H), 123.4 (aromatic **C**H), 79.1 (-**C**-O-), 71.6 (-O-**C**H-CH$_3$), 61.7 (-**C**H-NH-), 48.9 (-SO$_2$-**C**H$_2$-CH$_3$), 43.4 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.9 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 41.4 (-**C**H$_a$H$_b$-CH-NH-), 34.2 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.8 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 22.3 (-O-CH-**C**H$_3$), 8.8 (-SO$_2$-CH$_2$-**C**H$_3$).

MS (ES, CH_3CN): 453 (50) $[M+H]^+$, 470 (100) $[M+NH_4]^+$, 922 (23) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 475.1337; required for $C_{21}H_{28}N_2S_2O_5$, $[M+Na]^+$ = 475.1332.

N-[2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-benzamide (446)



446

To amine **434** (35 mg, 97 μmol) in CH_2Cl_2 (1 mL) was added benzoyl chloride (11 μL, 97 μmol) and triethylamine (27 μL, 0.194 mmol). The reaction was stirred at rt for 4 h, quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown solid by column chromatography (40 % Et_2O/hexane) gave the pure amide as a white solid (32 mg, 69 μmol, 71 %). The spectroscopic data is reported for a mixture of diastereoisomers.

MPt.: 130-132 °C (EtOAc).

IR (neat) ν/cm^{-1}: 3394 (m), 3064 (w), 2958 (w), 2871 (w), 1641 (s), 1538 (s), 1324 (s), 1153 (s), 1048 (m), 932 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.25 (2 x 1H, s, aromatic C**H**), 7.87 (2 x 2H, dd, aromatic C**H**, *J*= 4.5, 8.6 Hz), 7.83 (2 x 1H, d, aromatic C**H**, *J*= 7.5 Hz), 7.67 (2 x 1H, dd, aromatic C**H**, *J*= 8.6, 2.0 Hz), 7.64-7.61 (2 x 2H, m, aromatic C**H**), 7.58 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.54 (2 x 1H, dt, aromatic C**H**, *J*= 1.5, 7.0 Hz), 7.42 (2 x 1H, d, aromatic C**H**, *J*= 7.5 Hz), 7.35 (2 x 2H, dd, aromatic C**H**, *J*= 7.5, 7.5 Hz), 6.02 (1H, d, -N**H**-, *J*= 7.0 Hz), 5.99 (1H, d, -N**H**-, *J*= 7.0 Hz), 4.44 (2 x 1H, ddd, -C**H**-

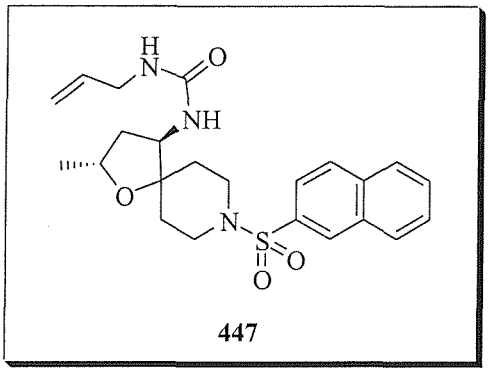
NH-, *J*= 5.0, 7.0, 7.0 Hz), 4.03 (1H, ddq, -O-C**H**-CH_3, *J*= 13.0, 4.0, 4.0 Hz), 3.91 (1H, ddq, -O-C**H**-CH_3, *J*= 9.0, 6.0, 6.0 Hz), 3.64 (2 x 2H, br d, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 8.6 Hz), 2.68 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.0, 11.6 Hz), 2.63 (1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.0, 11.6 Hz), 2.39 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 5.5, 7.0, 13.0 Hz), 2.00-1.85 (2H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.75-1.58 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + 2 x 1H, m, -CH$_a$**H**$_b$-CH-NH- + 1H, m, -C**H**$_a$H$_b$-CH-NH-), 1.09 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz), 1.07 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 167.6 (-NH-**C**=O), 167.5 (-NH-**C**=O), 135.2 (2 x aromatic **C**), 134.5 (aromatic **C**), 134.5 (aromatic **C**), 134.4 (aromatic **C**), 134.3 (aromatic **C**), 132.7 (2 x aromatic **C**), 132.2 (2 x aromatic **C**H), 129.6 (2 x aromatic **C**H), 129.3 (2 x aromatic **C**H), 129.1 (2 x aromatic **C**H), 128.6 (2 x aromatic **C**H), 128.3 (2 x aromatic **C**H), 127.9 (2 x aromatic **C**H), 127.3 (aromatic **C**H), 127.2 (aromatic **C**H), 124.9 (2 x aromatic **C**H), 123.4 (2 x aromatic **C**H), 80.7 (-**C**-O-), 80.1 (-**C**-O-), 72.4 (-O-**C**H-CH_3), 71.8 (-O-**C**H-CH_3), 57.6 (-**C**H-NH-), 56.8 (-**C**H-NH-), 43.5 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.4 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 43.1 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 43.0 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 40.6 (-**C**H$_a$H$_b$-CH-NH-), 39.2 (-**C**H$_a$H$_b$-CH-NH-), 36.7 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 34.4 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.7 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 30.1 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.0 (-O-CH-**C**H_3), 22.3 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 465 (70) $[M+H]^+$, 482 (100) $[M+NH_4]^+$, 487 (30) $[M+Na]^+$, 946 (17) $[2M+NH_4]^+$.

HRMS (ES) *m/z*: Found 487.1664; required for $C_{26}H_{28}N_2SO_4$, $[M+Na]^+$ = 487.1662.

1-Allyl-3-[(2R,4R)-2-methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-urea (447)



447

To amine **441** (35 mg, 97 μmol) in CH_2Cl_2 (1 mL) was added allyl isocyanate (9 μL, 97 μmol) and triethylamine (27 μL, 0.194 mmol). The reaction was stirred at rt for 3 h, then quenched by the addition of NaOH (2N aq. solution, 5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and washed with NaOH (2N aq. solution, 2 x 5 mL) and water (2 x 5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude brown oil by column chromatography (40 % Et_2O/hexane) gave the pure urea as a colourless oil (36 mg, 81 μmol, 83 %).

IR (neat) ν/cm^{-1}: 3358 (br w), 2964 (w), 2927 (w), 2864 (w), 1632 (s), 1561 (s), 1326 (s), 1267 (m), 1155 (s), 1073 (m), 1048 (m), 928 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.24 (1H, s, aromatic C**H**), 7.90 (2H, d, aromatic C**H**, *J*= 8.5 Hz), 7.85 (1H, dd, aromatic C**H**, *J*= 8.0, 1.0 Hz), 7.66 (1H, dd, aromatic C**H**, *J*= 8.6, 1.5 Hz), 7.58 (1H, dt, aromatic C**H**, *J*= 1.5, 7.5 Hz), 7.54 (1H, dt, aromatic C**H**, *J*= 1.5, 7.5 Hz), 5.76 (1H, ddt, -C**H**=CH_2, *J*= 17.0, 10.5, 5.5 Hz), 5.11 (1H, ddt, -CH=C**H**$_a$H$_b$, *J*= 17.1, 4.2, 1.5 Hz), 5.09 (1H, t, -N**H**-, *J*= 6.0 Hz), 5.02 (1H, ddt, -CH=CH$_a$**H**$_b$, *J*= 10.6, 3.0, 1.5 Hz), 5.00 (1H, d, -N**H**-, *J*= 7.5 Hz), 4.09 (1H, dt, -C**H**-NH-, *J*= 7.5, 7.5 Hz), 3.92 (1H, ddq, -O-C**H**-CH_3, *J*= 6.0, 6.0, 6.0 Hz), 3.70 (2H, dddd, -C**H**$_2$-NH-C=O, *J*= 2.0, 4.0, 6.0, 7.5 Hz), 3.63 (2H, br td, -C**H**$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 11.5, 4.5 Hz), 2.62 (1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 2.5, 12.0 Hz), 2.57 (1H, dt, -CH$_a$H$_b$-N-

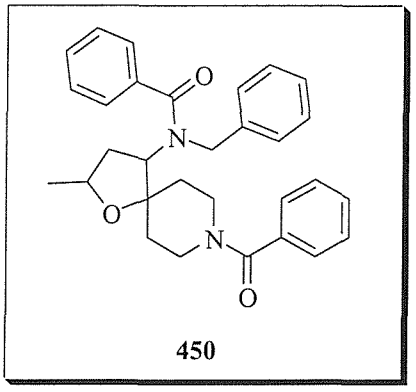
$CH_a\underline{H}_b$-, *J*= 2.0, 12.5 Hz), 1.91 (1H, td, -C$\underline{H}_a$H$_b$-C-CH$_a$H$_b$-, *J*= 13.5, 5.0 Hz), 1.84-1.75 (2H, m, -C$\underline{H}_a$H$_b$-CH-NH-), 1.62 (1H, td, -CH$_a$H$_b$-C-C$\underline{H}_a$H$_b$-, *J*= 13.1, 4.5 Hz), 1.52 (2H, br td, -CH$_a\underline{H}_b$-C-CH$_a\underline{H}_b$-, *J*= 11.0, 2.5 Hz), 1.01 (3H, d, -O-CH-C$\underline{H}_3$, *J*= 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.9 (-NH-$\underline{C}$=O-), 135.7 (-$\underline{C}$H=CH$_2$), 135.1 (aromatic $\underline{C}$), 133.5 (aromatic $\underline{C}$), 132.5 (aromatic $\underline{C}$), 129.5 (aromatic $\underline{C}$H), 129.4 (aromatic $\underline{C}$H), 129.0 (aromatic $\underline{C}$H), 129.0 (aromatic $\underline{C}$H), 128.1 (aromatic $\underline{C}$H), 127.7 (aromatic $\underline{C}$H), 123.0 (aromatic $\underline{C}$H), 115.8 (-CH=$\underline{C}$H$_2$), 79.8 (-$\underline{C}$-O-), 71.5 (-O-$\underline{C}$H-CH$_3$), 56.7 (-$\underline{C}$H-NH-), 43.5 (-NH-$\underline{C}$H$_2$-), 43.1 (-$\underline{C}$H$_a$H$_b$-N-CH$_a$H$_b$-), 42.8 (-CH$_a$H$_b$-N-$\underline{C}$H$_a$H$_b$-), 38.8 (-$\underline{C}$H$_a$H$_b$-CH-NH-), 36.0 (-$\underline{C}$H$_a$H$_b$-C-CH$_a$H$_b$-), 29.4 (-CH$_a$H$_b$-C-$\underline{C}$H$_a$H$_b$-), 22.9 (-O-CH-$\underline{C}$H$_3$).

MS (ES, CH_3CN): 444 (100) $[M+H]^+$, 887 (18) $[2M+H]^+$.

HRMS (ES) *m/z*: Found 466.1772; required for $C_{23}H_{29}N_3SO_4$, $[M+Na]^+$ = 433.1771.

N-(8-Benzoyl-2-methyl-1-oxa-8-aza-spiro[4.5]dec-4-yl)-*N*-benzyl-benzamide (450)



450

To benzylamine **428** (30 mg, 0.113 mmol) in CH_2Cl_2 (1.2 mL) was added triethylamine (31 μL, 0.226 mmol) and benzoyl chloride (26 μL, 0.226 mmol), the reaction was stirred at rt for 12 h then concentrated *in vacuo*. Purification by column chromatography (30 % Et_2O/hexane) provided the pure amide as a colourless oil (27 mg, 0.059 mmol, 52 %). The spectroscopic data is reported for a mixture of diastereoisomers.

The spectroscopic data was severely complicated by the presence of rotational isomers and diastereoisomers.

IR (neat) ν/cm^{-1}: 3062 (w), 3028 (w), 2969 (w), 2926 (w), 2876 (w), 1626 (s), 1577 (w), 1495 (w), 1435 (s), 1286 (m), 1074 (m), 971 (m), 920 (m).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.46-7.36 (2 x 10H, m, aromatic C**H**), 7.32 (2 x 2H, t, aromatic C**H**, *J*= 7.5 Hz), 7.21 (2 x 3H, m, aromatic C**H**), 4.95 (1H, d, Ph-C**H**$_a$H$_b$-, *J*= 11.2 Hz), 4.91 (1H, d, Ph-C**H**$_a$H$_b$-, *J*= 10.9 Hz), 4.72-4.65 (2 x 1H, br m, -C**H**-NH-), 4.46 (1H, d, Ph-CH$_a$**H**$_b$-, *J*= 16.5 Hz), 4.42 (1H, d, Ph-CH$_a$**H**$_b$-, *J*= 15.8 Hz), 4.30 (1H, ddq, -O-C**H**-CH$_3$, *J*= 13.3, 6.4, 6.4 Hz), 4.02-3.95 (2 x 1H, m, -C**H**$_a$H$_b$-N-CH$_a$H$_b$- + 1H, m, -O-C**H**-CH$_3$), 3.83-3.71 (2 x 1H, br m, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-), 3.25 (2 x 1H, dt, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-, *J*= 3.6, 12.3 Hz), 3.16 (2 x 1H, dt, -CH$_a$H$_b$-N-CH$_a$**H**$_b$-, *J*= 3.8, 12.8 Hz), 2.29 (2 x 1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 13.8, 12.4, 6.0 Hz), 1.90-1.74 (2

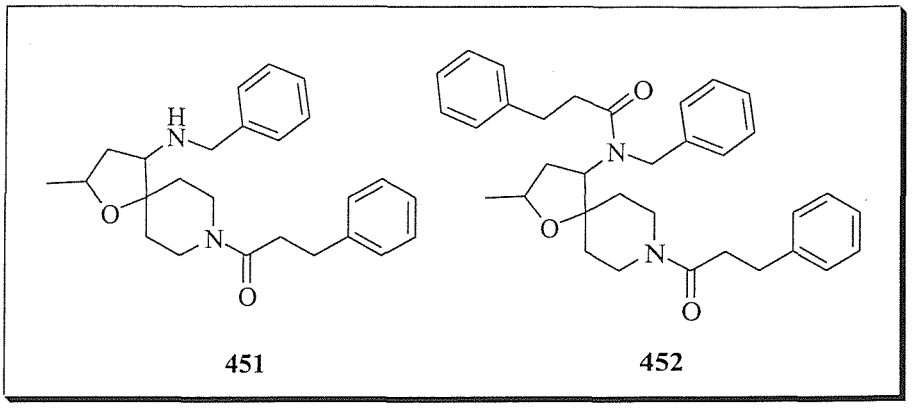
x 2H, m, -C**H**$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.69 (2 x 1H, td, -CH$_a$**H**$_b$-C-CH$_a$H$_b$-, *J*= 12.1, 4.7 Hz), 1.63-1.60 (2 x 1H, br m, -CH$_a$**H**$_b$-CH-NH-), 1.45-1.39 (2 x 1H, br s, -CH$_a$H$_b$-C-CH$_a$**H**$_b$-), 1.18 (3H, d, -O-CH-C**H**$_3$, *J*= 6.0 Hz), 1.16 (3H, d, -O-CH-C**H**$_3$, *J*= 6.1 Hz).

^{13}C **NMR** (100 MHz, $CDCl_3$) δ/ppm: 170.3 (4 x -NH-**C**=O), 138.6 (2 x aromatic **C**), 136.8 (2 x aromatic **C**), 136.2 (2 x aromatic **C**), 129.5 (2 x aromatic **C**H), 128.7 (2 x aromatic **C**H), 128.7 (2 x aromatic **C**H), 128.5 (2 x aromatic **C**H), 127.2 (2 x aromatic **C**H), 127.1 (2 x aromatic **C**H), 126.9 (2 x aromatic **C**H), 126.1 (2 x aromatic **C**H), 125.8 (2 x aromatic **C**H), 83.6 (2 x -**C**-O-), 71.1 (2 x -O-**C**H-CH$_3$), 62.1 (2 x benzylic **C**H$_2$), 44.5 (2 x -**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 38.8 (2 x -CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 36.8 (-**C**H$_a$H$_b$-CH-NH-), 36.2 (-**C**H$_a$H$_b$-CH-NH-), 35.8 (2 x -**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.4 (2 x -CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 20.6 (2 x -O-CH-**C**H$_3$).

MS (ES, CH_3CN): 469 (6) $[M+H]^+$, 491 (100) $[M+Na]^+$, 959 (20) $[2M+Na]^+$.

HRMS (ES) *m/z*: Found 491.2304; required for $C_{30}H_{32}N_2O_3$, $[M+Na]^+$ = 491.2305.

1-(4-Benzylamino-2-methyl-1-oxa-8-aza-spiro[4.5]dec-8-yl)-3-phenyl-propan-1-one (451) and *N*-benzyl-*N*-[2-methyl-8-(3-phenyl-propionyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-3-phenyl-propionamide (452)



451 452

To benzylamine **428** (30 mg, 0.113 mmol) in CH_2Cl_2 (1.2 mL) was added triethylamine (31 μL, 0.226 mmol) and hydrocinnamoyl chloride (34 μL, 0.226 mmol), the reaction was stirred at rt for 12 h then concentrated *in vacuo*. Purification by column chromatography (30 % Et_2O/hexane) gave the pure amide **451** as a colourless oil (7 mg, 0.018 mmol, 16 %) and diamide **452** also as a colourless oil (27 mg, 0.053 mmol, 47 %). The spectroscopic data is reported for a mixture of diastereoisomers.

The spectroscopic data was severely complicated by the presence of rotational isomers and diastereoisomers.

1-(4-Benzylamino-2-methyl-1-oxa-8-aza-spiro[4.5]dec-8-yl)-3-phenyl-propan-1-one (**451**):

IR (neat) ν/cm^{-1}: 3026 (w), 2969 (w), 2930 (w), 2871 (w), 1639 (s), 1453 (s), 1366 (m), 1219 (s), 1076 (m), 965 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.28-7.21 (2 x 4H, m, aromatic C**H**), 7.19 (2 x 3H, dd, aromatic C**H**, *J*= 3.0, 4.3 Hz), 7.14 (2 x 3H, d, aromatic C**H**, *J*= 7.0 Hz), 5.06-5.04 (2 x 1H, m, -C**H**-NH-), 4.49-4.29 (2 x 1H, m, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-), 4.11 (1H, ddq,

-O-C**H**-CH_3, *J*= 12.6, 6.3, 6.3 Hz), 3.97-3.88 (1H, br m, -O-C**H**-CH_3), 3.79 (1H, d, Ph-C**H**$_a$H$_b$-NH-, *J*= 3.8 Hz), 3.76 (1H, d, Ph-C**H**$_a$H$_b$-NH-, *J*= 3.8 Hz), 3.65 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*= 4.5 Hz), 3.62 (1H, d, Ph-CH$_a$**H**$_b$-NH-, *J*= 4.5 Hz), 3.52 (2 x 1H, br dd, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 12.8, 10.3 Hz), 3.31-3.20 (2 x 1H, m, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-), 2.93-2.81 (2 x 1H, m, -CH$_a$H$_b$-N-CH$_a$**H**$_b$- + 2 x 2H, m, Ph-C**H**$_2$-CH$_2$-C=O), 2.61-2.53 (2 x 2H, m, Ph-CH$_2$-C**H**$_2$-C=O), 2.27 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 12.0, 5.8, 2.8 Hz), 2.02 (2 x 1H, br s, -CH$_a$**H**$_b$-CH-NH-), 1.85-1.78 (2 x 1H, m, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-), 1.64-1.27 (2 x 1H, m, -CH$_a$H$_b$-C-C**H**$_a$H$_b$- + 2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$- + 1H, m, -C**H**$_a$H$_b$-CH-NH-), 1.18 (3H, dd, -O-CH-C**H**$_3$, *J*= 1.8, 5.8 Hz), 1.12 (3H, dd, -O-CH-C**H**$_3$, *J*= 5.0, 1.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 170.8 (2 x -NH-**C**=O), 141.9 (2 x aromatic **C**), 137.2 (2 x aromatic **C**), 128.9 (2 x aromatic **C**H), 128.7 (2 x aromatic **C**H), 128.4 (2 x aromatic **C**H), 127.6 (2 x aromatic **C**H), 126.5 (2 x aromatic **C**H), 125.7 (2 x aromatic **C**H), 81.7 (2 x -**C**-O-), 72.1 (-O-**C**H-CH_3), 72.0 (-O-**C**H-CH_3), 66.4 (-**C**H-NH-), 65.2 (-**C**H-NH-), 53.2 (2 x Ph-**C**H_2-NH-), 43.2 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.5 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 39.4 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 39.3 (-**C**H$_a$H$_b$-CH-NH-), 38.4 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 35.9 (-**C**H$_a$H$_b$-CH-NH-), 35.5 (2 x Ph-CH_2-**C**H_2-C=O), 33.5 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.5 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.1 (2 x Ph-**C**H_2-CH_2-), 30.8 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 29.3 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.4 (-O-CH-**C**H_3), 22.8 (-O-CH-**C**H_3).

MS (ES, CH_3CN): 393 (100) $[M+H]^+$, 785 (7) $[2M+H]^+$.

HRMS (ES) *m/z*: Found 393.2535; required for $C_{25}H_{32}N_2O_2$, $[M+H]^+$ = 393.2537.

N-Benzyl-*N*-[2-methyl-8-(3-phenyl-propionyl)-1-oxa-8-aza-spiro[4.5]dec-4-yl]-3-phenyl-propionamide (**452**):

IR (neat) ν/cm^{-1}: 3026 (w), 2964 (w), 2929 (w), 2872 (w), 1641 (s), 1542 (m), 1217 (m), 1076 (m), 965 (m).

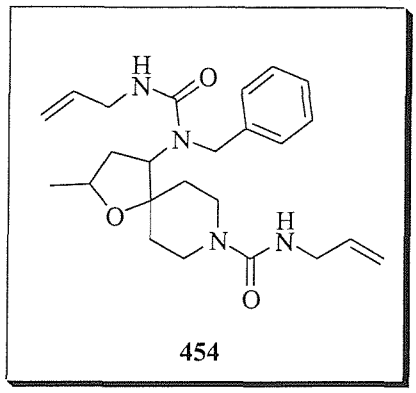
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.26-7.10 (2 x 12H, m, aromatic C**H**), 7.02-6.95 (2 x 3H, m, aromatic C**H**), 5.06-5.04 (2 x 1H, m, -C**H**-NH-), 4.54 (1H, d, Ph-C**H**$_a$H$_b$-NH-, *J*= 9.0 Hz), 4.49 (1H, d, Ph-C**H**$_a$H$_b$-NH-, *J*= 9.0 Hz), 4.43-4.24 (2 x 1H, m, Ph-CH$_a$**H**$_b$-NH- + 2 x 1H, m, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-), 4.13-4.04 (1H, m, -O-C**H**-CH$_3$), 3.95-3.87 (1H, m, -O-C**H**-CH$_3$), 3.54 (1H, br t, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 14.8 Hz), 3.50 (1H, br t, -CH$_a$H$_b$-N-C**H**$_a$H$_b$-, *J*= 14.8 Hz), 3.30-3.15 (2 x 1H, m, -CH$_a$**H**$_b$-N-CH$_a$H$_b$-), 2.92-2.81 (2 x 1H, m, -CH$_a$H$_b$-N-CH$_a$**H**$_b$- + 2 x 2H, m, Ph-C**H**$_2$-CH$_2$-C=O + 2 x 2H, m, Ph-C**H**$_2$-CH$_2$-C=O), 2.57-2.50 (2 x 2H, m, Ph-CH$_2$-C**H**$_2$-C=O + 2 x 2H, m, Ph-CH$_2$-C**H**$_2$-C=O), 2.43-2.30 (2 x 1H, m, -C**H**$_a$H$_b$-CH-NH-, 2.15 (1H, ddd, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 2.5, 5.0, 7.0 Hz), 2.05 (1H, dt, -C**H**$_a$H$_b$-C-CH$_a$H$_b$-, *J*= 2.5, 7.3, 8.8 Hz), 1.95-1.90 (1H, m, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.80-1.46 (2 x 1H, m, -CH$_a$**H**$_b$-CH-NH- + 1H, m, -CH$_a$H$_b$-C-C**H**$_a$H$_b$-), 1.41-1.18 (2 x 2H, m, -CH$_a$**H**$_b$-C-CH$_a$**H**$_b$-), 1.10 (3H, br d, -O-CH-C**H**$_3$, *J*= 7.5 Hz), 1.07 (3H, d, -O-CH-C**H**$_3$, *J*= 5.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 174.6 (-NH-**C**=O), 174.4 (-NH-**C**=O), 170.8 (-NH-**C**=O), 170.7 (-NH-**C**=O), 142.0 (aromatic **C**), 141.9 (aromatic **C**), 141.4 (aromatic **C**), 141.2 (aromatic **C**), 138.3 (aromatic **C**), 138.2 (aromatic **C**), 129.4 (aromatic **C**H), 129.4 (aromatic **C**H), 128.9 (aromatic **C**H), 128.9 (aromatic **C**H), 128.8 (aromatic **C**H), 128.8 (aromatic **C**H), 127.8 (aromatic **C**H), 127.7 (aromatic **C**H), 126.6 (aromatic **C**H), 126.5 (aromatic **C**H), 125.7 (aromatic **C**H), 125.6 (aromatic **C**H), 83.7 (-**C**-O-), 83.7 (-**C**-O-), 73.6 (-O-**C**H-CH$_3$), 71.3 (-O-**C**H-CH$_3$), 61.8 (-**C**H-NH-), 61.6 (-**C**H-NH-), 49.3 (2 x Ph-**C**H$_2$-NH-), 42.8 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 42.6 (-**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 38.7 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 38.5 (-CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 38.3 (-**C**H$_a$H$_b$-CH-NH-), 37.7 (-**C**H$_a$H$_b$-CH-NH-), 36.5 (2 x Ph-CH$_2$-**C**H$_2$-C=O), 36.1 (Ph-CH$_2$-**C**H$_2$-C=O), 36.0 (Ph-CH$_2$-**C**H$_2$-C=O), 33.5 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.9 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 32.6 (2 x Ph-**C**H$_2$-CH$_2$-), 32.1 (2 x Ph-**C**H$_2$-CH$_2$-), 31.9 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 31.8 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 21.1 (-O-CH-**C**H$_3$), 21.0 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 525 (100) $[M+H]^+$, 547 (60) $[M+Na]^+$.

HRMS (ES) *m/z*: Found 525.3112; required for $C_{34}H_{40}N_2O_3$, $[M+H]^+$ = 525.3112.

4-(3-Allyl-1-benzylureido)-2-methyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylic acid allylamide (454)



454

To benzylamine **428** (30 mg, 0.113 mmol) in CH_2Cl_2 (1.2 mL) was added triethylamine (31 μL, 0.226 mmol) and allyl isocyanate (20 μL, 0.226 mmol), the reaction was stirred at rt for 12 h then concentrated *in vacuo*. Purification by column chromatography (30 % Et_2O/hexane) gave the pure urea **454** as a colourless oil (13 mg, 0.032 mmol, 28 %). The spectroscopic data is reported for a mixture of diastereoisomers.

The NMR data was severely complicated by the presence of rotational isomers and diastereoisomers.

IR (neat) ν/cm^{-1}: 3355 (br w), 3064 (w), 2963 (w), 2921 (w), 2859 (w), 1625 (s), 1535 (s), 1455 (w), 1418 (w), 1253 (m), 1063 (w).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.37-7.20 (2 x 5H, m, aromatic C**H**), 5.94-5.82 (2 x 1H, m, CH_2=C**H**-), 5.77-5.65 (2 x 1H, m, CH_2=C**H**-), 5.17 (1H, ddt, C**H**$_a$H$_b$=CH-, *J*= 16.7, 1.5, 3.0 Hz), 5.10 (1H, ddt, CH$_a$**H**$_b$=CH-, *J*= 10.1, 1.5, 2.5 Hz), 4.98-4.93 (1H, m, C**H**$_a$H$_b$=CH-), 4.88 (1H, ddt, CH$_a$**H**$_b$=CH-, *J*= 17.2, 1.5, 3.0 Hz), 4.43 (2 x 2H, s, Ph-C**H**$_2$-), 4.20 (1H, ddd, -C**H**$_a$H$_b$-N-CH$_a$H$_b$-, *J*= 6.0, 13.6, 13.6 Hz), 3.96-3.75 (1H, m, -CH$_a$H$_b$-N-C**H**$_a$H$_b$- + 2 x 2H, m, -CH$_a$**H**$_b$-N-CH$_a$**H**$_b$- + 2 x 1H, m, -O-C**H**-CH$_3$ + 2 x 1H, m, -C**H**-NH-), 3.74-3.60 (2 x 2H, m, -NH-C**H**$_2$-CH=CH$_2$), 3.30-3.09 (2 x 2H, m, -NH-C**H**$_2$-CH=CH$_2$), 2.11 (1H, ddd, -C**H**$_a$H$_b$-CH-NH-, *J*= 4.6, 7.6, 7.6 Hz), 2.10 (1H, ddd, -

C**H**$_a$H$_b$-CH-NH-, *J*= 4.6, 7.6, 7.6), 1.99-1.90 (2 x 1H, m, -CH$_a$**H**$_b$-CH-NH-), 1.55 (8H, br s, -C**H**$_a$**H**$_b$-C-C**H**$_a$**H**$_b$-), 1.23 (3H, d, -O-CH-C**H**$_3$, *J*= 2.6 Hz), 1.21 (3H, d, -O-CH-C**H**$_3$, *J*= 2.5 Hz).

^{13}C **NMR** (100 MHz, $CDCl_3$) δ/ppm: 158.2 (2 x -NH-**C**=O-), 157.2 (2 x -NH-**C**=O-), 137.4 (2 x aromatic **C**), 135.8 (2 x -**C**H=CH$_2$), 135.1 (2 x -**C**H=CH$_2$), 129.2 (aromatic **C**H), 127.8 (2 x aromatic **C**H), 125.7 (2 x aromatic **C**H), 115.7 (2 x -CH=**C**H$_2$), 115.2 (2 x -CH=**C**H$_2$), 83.5 (2 x -**C**-O-), 77.2 (-O-**C**H-CH$_3$), 73.5 (-O-**C**H-CH$_3$), 62.5 (2 x -**C**H-NH-), 48.4 (2 x Ph-**C**H$_2$-), 43.5 (-NH-**C**H$_2$-), 43.2 (-NH-**C**H$_2$-), 41.1 (2 x -**C**H$_a$H$_b$-N-CH$_a$H$_b$-), 40.6 (-NH-**C**H$_2$-), 40.3 (-NH-**C**H$_2$-), 37.3 (2 x -CH$_a$H$_b$-N-**C**H$_a$H$_b$-), 36.0 (-**C**H$_a$H$_b$-CH-NH-), 33.4 (-**C**H$_a$H$_b$-C-CH$_a$H$_b$-), 30.7 (-CH$_a$H$_b$-C-**C**H$_a$H$_b$-), 23.5 (-O-CH-**C**H$_3$).

MS (ES, CH_3CN): 427 (100) $[M+H]^+$, 449 (38) $[M+Na]^+$.

HRMS (ES) *m/z*: Found 449.2526; required for $C_{24}H_{34}N_4O_3$, $[M+Na]^+$ = 449.2523.

Appendix 1 – X-ray Crystal Structure for 2-Methyl-8-(naphthalene-2-sulfonyl)-1-oxa-8-azaspiro[4.5]decan-4-one

Table 1. Crystal data and structure refinement.

Identification code	**02sot072**	
Empirical formula	$C_{19}H_{21}NO_4S$	
Formula weight	359.43	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C2/c*	
Unit cell dimensions	a = 28.2085(5) Å	α = 90°
	b = 6.3440(2) Å	β = 114.2060(10)°
	c = 20.8503(6) Å	γ = 90°
Volume	3403.20(16) Å^3	
Z	8	
Density (calculated)	1.403 Mg / m^3	
Absorption coefficient	0.215 mm^{-1}	
F(000)	1520	
Crystal	Block; Colourless	
Crystal size	0.14 × 0.12 × 0.10 mm^3	
θ range for data collection	3.01 – 25.03°	
Index ranges	$-33 \le h \le 33$, $-6 \le k \le 7$, $-24 \le l \le 24$	
Reflections collected	9799	
Independent reflections	2993 [R_{int} = 0.0446]	
Completeness to θ = 25.03°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9789 and 0.9706	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2993 / 0 / 311	
Goodness-of-fit on F^2	1.015	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0432, *wR2* = 0.0982	
R indices (all data)	*R1* = 0.0619, *wR2* = 0.1066	
Extinction coefficient	0.0007(2)	
Largest diff. peak and hole	0.930 and –0.382 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1803(1)	9732(1)	4126(1)	22(1)	1
O2	2240(1)	10360(3)	4744(1)	29(1)	1
O3	138(1)	13852(3)	3472(1)	27(1)	1
O1	1701(1)	7548(3)	3956(1)	28(1)	1
N1	1282(1)	10694(3)	4189(1)	21(1)	1
C10	1852(1)	11009(4)	3403(1)	19(1)	1
C11	1672(1)	10022(4)	2763(1)	20(1)	1
C19	2074(1)	13057(4)	3497(1)	21(1)	1
C16	1994(1)	14027(4)	1688(1)	23(1)	1
C17	1938(1)	13056(4)	2269(1)	20(1)	1
O4	−9(1)	12495(3)	5002(1)	36(1)	1
C9	872(1)	13507(4)	4591(1)	23(1)	1
C6	371(1)	10332(4)	3961(2)	27(1)	1
C18	2109(1)	14044(4)	2935(1)	21(1)	1
C12	1715(1)	11006(4)	2179(1)	20(1)	1
C13	1553(1)	10009(4)	1516(1)	25(1)	1
C8	1284(1)	12992(4)	4320(1)	22(1)	1
C14	1623(1)	10970(4)	975(1)	28(1)	1
C15	1846(1)	12996(4)	1061(1)	26(1)	1
C4	−67(1)	13002(4)	4417(1)	28(1)	1
C7	776(1)	9939(4)	3671(1)	24(1)	1
C5	339(1)	12668(4)	4114(1)	24(1)	1
C3	−532(1)	14023(5)	3856(2)	36(1)	1
C2	−420(1)	13927(6)	3205(2)	47(1)	1
C1	−638(1)	15548(6)	2667(2)	41(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–O2	1.4279(18)	C8–N1–S1	116.34(16)
S1–O1	1.4298(18)	C11–C10–C19	121.2(2)
S1–N1	1.645(2)	C11–C10–S1	119.61(18)
S1–C10	1.766(2)	C19–C10–S1	119.15(18)
O3–C5	1.433(3)	C10–C11–C12	120.5(2)
O3–C2	1.437(3)	C10–C11–H11	118.0(13)
N1–C7	1.472(3)	C12–C11–H11	121.4(13)
N1–C8	1.483(3)	C18–C19–C10	118.9(2)
C10–C11	1.369(3)	C18–C19–H19	122.2(15)
C10–C19	1.420(3)	C10–C19–H19	118.8(15)
C11–C12	1.418(3)	C15–C16–C17	120.7(2)
C11–H11	0.96(2)	C15–C16–H16	119.1(14)
C19–C18	1.366(3)	C17–C16–H16	120.1(14)
C19–H19	0.94(3)	C18–C17–C12	119.3(2)
C16–C15	1.366(4)	C18–C17–C16	122.0(2)
C16–C17	1.426(3)	C12–C17–C16	118.6(2)
C16–H16	0.96(3)	C5–C9–C8	112.5(2)
C17–C18	1.415(3)	C5–C9–H9B	107.5(15)
C17–C12	1.423(3)	C8–C9–H9B	110.9(14)
O4–C4	1.206(3)	C5–C9–H9A	110.0(14)
C9–C5	1.519(3)	C8–C9–H9A	109.9(14)
C9–C8	1.523(3)	H9B–C9–H9A	106(2)
C9–H9B	0.93(3)	C7–C6–C5	111.2(2)
C9–H9A	1.01(3)	C7–C6–H6A	107.2(18)
C6–C7	1.518(3)	C5–C6–H6A	111.1(18)
C6–C5	1.526(4)	C7–C6–H6B	111.3(15)
C6–H6A	0.91(3)	C5–C6–H6B	109.4(15)
C6–H6B	0.99(3)	H6A–C6–H6B	107(2)
C18–H18	0.97(3)	C19–C18–C17	121.4(2)
C12–C13	1.415(3)	C19–C18–H18	118.6(14)
C13–C14	1.366(4)	C17–C18–H18	119.9(14)
C13–H13	1.02(3)	C13–C12–C11	122.4(2)
C8–H8A	1.01(2)	C13–C12–C17	119.1(2)
C8–H8B	0.95(2)	C11–C12–C17	118.5(2)
C14–C15	1.410(4)	C14–C13–C12	120.6(2)
C14–H14	0.95(3)	C14–C13–H13	123.5(15)
C15–H15	0.90(3)	C12–C13–H13	115.8(15)
C4–C3	1.500(4)	N1–C8–C9	109.48(19)
C4–C5	1.532(3)	N1–C8–H8A	110.1(13)
C7–H7A	1.00(3)	C9–C8–H8A	109.5(13)
C7–H7B	0.94(3)	N1–C8–H8B	108.2(14)
C3–C2	1.517(4)	C9–C8–H8B	111.9(13)
C3–H3A	0.93(4)	H8A–C8–H8B	107.7(19)
C3–H3B	0.97(4)	C13–C14–C15	120.7(2)
C2–C1	1.459(5)	C13–C14–H14	120.2(17)
C2–H2	1.21(4)	C15–C14–H14	119.1(17)
C1–H1C	0.97(3)	C16–C15–C14	120.2(2)
C1–H1B	0.99(4)	C16–C15–H15	118.6(16)
C1–H1A	1.00(4)	C14–C15–H15	121.1(16)
		O4–C4–C3	128.0(2)
O2–S1–O1	120.39(11)	O4–C4–C5	124.6(2)
O2–S1–N1	107.04(10)	C3–C4–C5	107.4(2)
O1–S1–N1	106.44(10)	N1–C7–C6	108.5(2)
O2–S1–C10	107.55(11)	N1–C7–H7A	110.9(14)
O1–S1–C10	108.20(10)	C6–C7–H7A	108.6(14)
N1–S1–C10	106.46(10)	N1–C7–H7B	110.2(15)
C5–O3–C2	109.34(19)	C6–C7–H7B	111.0(15)
C7–N1–C8	112.6(2)	H7A–C7–H7B	108(2)
C7–N1–S1	116.73(16)	O3–C5–C9	109.54(19)

O3–C5–C6	110.5(2)
C9–C5–C6	110.4(2)
O3–C5–C4	103.69(19)
C9–C5–C4	112.8(2)
C6–C5–C4	109.75(19)
C4–C3–C2	104.2(2)
C4–C3–H3A	109(2)
C2–C3–H3A	110(2)
C4–C3–H3B	111(2)
C2–C3–H3B	115(2)
H3A–C3–H3B	108(3)
O3–C2–C1	111.8(3)
O3–C2–C3	104.4(2)
C1–C2–C3	118.9(3)
O3–C2–H2	106.7(18)
C1–C2–H2	106.4(19)
C3–C2–H2	108.0(19)
C2–C1–H1C	110.8(18)
C2–C1–H1B	113(2)
H1C–C1–H1B	108(3)
C2–C1–H1A	108(2)
H1C–C1–H1A	108(3)
H1B–C1–H1A	109(3)

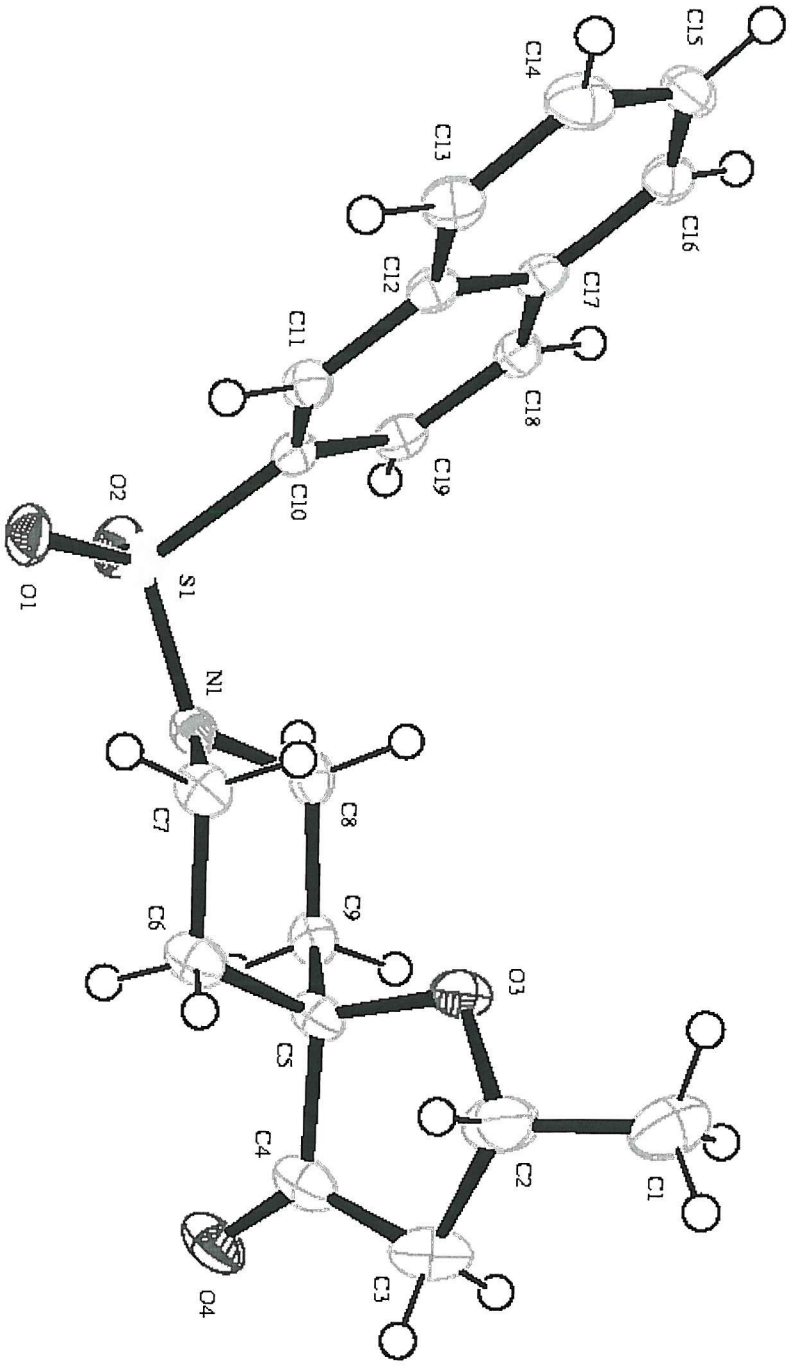
Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	29(1)	18(1)	19(1)	1(1)	10(1)	2(1)
O2	31(1)	29(1)	20(1)	2(1)	4(1)	4(1)
O3	20(1)	40(1)	22(1)	1(1)	10(1)	2(1)
O1	41(1)	16(1)	31(1)	2(1)	17(1)	2(1)
N1	26(1)	18(1)	20(1)	−2(1)	12(1)	−3(1)
C10	18(1)	19(1)	21(1)	1(1)	9(1)	3(1)
C11	20(1)	17(1)	24(1)	−2(1)	10(1)	−1(1)
C19	19(1)	23(1)	22(1)	−4(1)	8(1)	1(1)
C16	17(1)	24(1)	28(1)	2(1)	10(1)	1(1)
C17	15(1)	22(1)	23(1)	0(1)	7(1)	3(1)
O4	55(1)	31(1)	36(1)	−4(1)	33(1)	−9(1)
C9	29(1)	19(1)	20(1)	−2(1)	10(1)	−2(1)
C6	32(2)	26(1)	28(2)	−8(1)	18(1)	−10(1)
C18	19(1)	17(1)	27(1)	−2(1)	10(1)	−1(1)
C12	15(1)	23(1)	22(1)	−1(1)	7(1)	2(1)
C13	21(1)	28(2)	26(1)	−3(1)	10(1)	−1(1)
C8	25(1)	16(1)	23(1)	−2(1)	9(1)	−3(1)
C14	26(1)	36(2)	21(1)	-4(1)	9(1)	1(1)
C15	23(1)	35(2)	22(1)	7(1)	12(1)	4(1)
C4	37(2)	23(1)	32(2)	−12(1)	22(1)	−14(1)
C7	29(1)	23(2)	22(1)	−6(1)	12(1)	−6(1)
C5	28(1)	25(1)	23(1)	−2(1)	15(1)	−4(1)
C3	27(2)	49(2)	34(2)	−14(1)	16(1)	−8(1)
C2	32(2)	68(2)	47(2)	12(2)	23(1)	13(2)
C1	30(2)	56(2)	33(2)	−7(2)	9(1)	9(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H11	1533(8)	8630(40)	2730(11)	12(6)	1
H18	2268(9)	15430(40)	3004(12)	19(6)	1
H8A	1208(8)	13800(40)	3869(12)	15(6)	1
H15	1905(9)	13620(40)	710(13)	22(6)	1
H16	2144(9)	15410(40)	1737(12)	19(6)	1
H9B	959(9)	12930(40)	5037(14)	19(6)	1
H8B	1624(9)	13380(40)	4649(12)	15(6)	1
H9A	855(9)	15080(40)	4650(12)	22(6)	1
H13	1399(10)	8530(50)	1481(14)	35(7)	1
H1C	−502(11)	15420(50)	2310(16)	42(8)	1
H7A	671(9)	10710(40)	3217(14)	25(7)	1
H19	2202(9)	13670(40)	3947(13)	21(6)	1
H6A	462(11)	9550(50)	4360(16)	37(8)	1
H7B	796(9)	8500(40)	3580(13)	22(6)	1
H3A	−548(13)	15420(60)	3982(18)	63(11)	1
H6B	24(11)	9830(40)	3632(14)	26(7)	1
H14	1530(11)	10260(40)	538(16)	39(8)	1
H2	−579(15)	12250(70)	2920(20)	90(13)	1
H1B	−1022(14)	15510(50)	2432(18)	62(10)	1
H3B	−852(14)	13340(60)	3812(18)	68(11)	1
H1A	−529(15)	16940(70)	2900(20)	87(13)	1


C15
C14
C13
C16
C12
C17
C11
C18
C19
C10
O2
O1
S1
N1
C7
C8
C6
C9
O3
C5
C4
C2
C1
O4
C3

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