Synthesis of 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones: selective antagonists of muscarinic (M_3) receptors†

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Two approaches to tetrahydro-[1*H*]-2-benzazepin-4-ones of interest as potentially selective, muscarinic (M_3) receptor antagonists have been developed. Base promoted addition of 2-(*tert*-butoxycarbonylamino)methyl-1,3-dithiane **5** with 2-(*tert*-butyldimethylsiloxymethyl)benzyl chloride **14** gave the corresponding 2,2-dialkylated 1,3-dithiane **15** which was taken through to the dithiane derivative **19** of the parent 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one by desilylation, oxidation and cyclisation *via* a reductive amination. After conversion into the *N*-*tert*-butyloxycarbonyl, *N*-toluene *p*-sulfonyl and *N*-benzyl derivatives **20–22**, hydrolysis of the dithiane gave the *N*-protected tetrahydro-[1*H*]-2-benzazepin-4-ones **23–25**. However, preliminary attempts to convert these into 5-cycloalkyl-5-hydroxy derivatives were not successful. In the second approach, ring-closing metathesis was used to prepare 2,3-dihydro-[1*H*]-2-benzazepines which were hydroxylated and oxidized to give the required 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones. Following preliminary studies, ring-closing metathesis of the dienyl *N*-(2-nitrophenyl)sulfonamide **48** gave the dihydrobenzazepine **50** which was converted into the 2-butyl-5-cyclobutyl-5-hydroxytetrahydrobenzazepin-4-one **55** by hydroxylation and *N*-deprotection followed by *N*-alkylation *via* reductive amination, and oxidation. This chemistry was then used to prepare the 2-[(*N*-arylmethyl)aminoalkyl analogues **69**, **72**, **76** and **78**. *N*-Acylation followed by amide reduction using the borane–tetrahydrofuran complex was also used to achieve *N*-alkylation of dihydrobenzazepines and this approach was used to prepare the 5-cyclopentyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **103** and the 5-cyclobutyl-8-fluoro-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **126**. The structures of 2-*tert*-butyloxycarbonyl-4,4-propylenedithio-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **20** and (4*RS*,5*SR*)-2-butyl-5-cyclobutyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **53** were confirmed by X-ray diffraction. The racemic 5-cycloalkyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones were screened for muscarinic receptor antagonism. For M_3 receptors from guinea pig ileum, these compounds had $\log_{10}K_B$ values of up to 7.2 with selectivities over M_2 receptors from guinea pig left atria of approximately 40.

Introduction

Muscarinic receptors are intimately involved in many metabolic processes.[1] The M_3 receptor is prevalent in smooth muscle and its regulation has therapeutic applications in muscle relaxation ranging from the alleviation of chronic obstructive pulmonary disease to treatments for urinary tract incontinence involving bladder relaxation.[2] Preferential selectivity against other sub-types of muscarinic receptors is important, the M_2 receptor on stimulation regulating the parasympathetic control of heart rate. Amongst other sites, M_2 receptors are also found in the ileum, antagonism producing constipation. Darifenacin (**1**), which shows some 40-fold selectivity against M_2-receptors, was the first pharmaceutical commercially available to treat urinary incontinence by the control of M_3 receptor antagonism.[3] More selective therapies are currently under investigation.

From an *ab initio* approach using a model of muscarinic receptors based on bacteriorhodopsin, 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones with the general structure **2**, were identified as potential muscarinic antagonists with possibly improved selectivity for the M_3 receptor.[4] The use of tetrahydro-[1*H*]-2-benzazepines was seen to have two potential advantages. Firstly, the alignment of α-helices on the bacteriorhodopsin receptor structure[5] indicated that M_3 selectivity over M_2-receptors might be achieved by contact of the fused aromatic ring with residue 151 (Ala M_1, M_3, M_5; Val M_2, M_4). Secondly, early data on analogues of NPC-14695 **3**[6] indicated that an α-hydroxy keto group linked through a CH_2 group to a piperazine ring, has

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an advantage in overall binding even in the presence of the second nitrogen atom (pK_A ~6.6) due to the close contact distance of this atom with a backbone hydrogen atom. The possibility existed, therefore, that improved potency might be achieved with tetrahydrobenzazepinones even if the presence of a non-interacting nitrogen atom (−2.5 $\log_{10}$ units on the given model) would require increased lipophilic character for optimum pharmacodynamics and potency. The remainder of the target structure was completed by a benzylamino C_2 or C_3 linkage to give compounds **2**.

We report syntheses of these compounds and of *N*-acyl and *N*-alkyl derivatives of 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **4** together with aspects of their biological activities. Prior to this work, 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones were unknown.

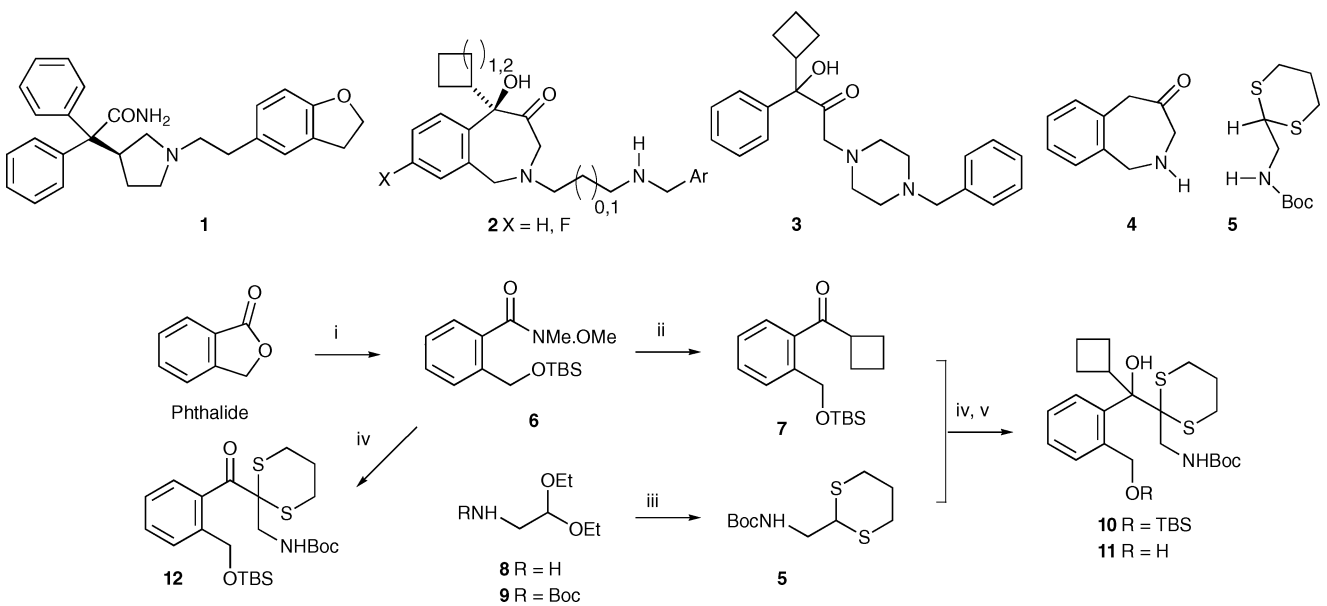
Two strategies for the assembly of the 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones have been investigated. In the first approach, the 2-(*tert*-butoxycarbonylaminomethyl)-1,3-dithiane **5**[7] was used as an *umpolung* reagent to prepare intermediates for a ring-closing reductive amination. In the second, more intensively investigated approach, ring-closing metathesis,[8] which has been used to prepare seven-membered ring heterocycles[9] including 2,3-dihydro-[1*H*]-2-benzazepines,[10] was used to prepare 5-cycloalkyl-2,3-dihydro-[1*H*]-2-benzazepines which were hydroxylated and oxidised to give the required 5-hydroxytetrahydrobenzazepin-4-ones **2**.

Results and discussion

Synthesis of 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones by dithiane alkylation

The Weinreb amide **6** was prepared from phthalide by treatment with *N*,*O*-dimethylhydroxylamine followed by immediate protection of the alcohol as its *tert*-butyldimethylsilyl ether to prevent reversion to the lactone, see Scheme 1. The amide **6** then gave the aryl cyclobutyl ketone **7** on reaction with an excess of cyclobutyllithium. 2-(*tert*-Butoxycarbonylamino)methyl-1,3-dithiane **5** has been prepared from the *tert*-butoxycarbonyl (Boc) protected aminoacetal **9** using propane-1,3-dithiol and boron trifluoride diethyletherate[7] but, in our hands, this procedure was complicated by competing loss of the Boc-group.[11] However, conversion of the unprotected aminoacetal **8** into 2-aminomethyl-1,3-dithiane followed by Boc-protection gave a reliable procedure for the synthesis of the required dithiane **5**. Lithiation of dithiane **5** using two equivalents of *n*-butyllithium followed by addition of the ketone **7** gave the tertiary alcohol **10**. In this reaction, it would appear that deprotonation of the carbamate prevented elimination of the Boc fragment. Indeed, the lithiated dithiane also reacted with the Weinreb amide **6** to give ketone **12**. Desilylation of the adduct **10** to the diol **11** was carried out at 0 °C[12] using tetra-*n*-butylammonium fluoride since prolonged reaction at room temperature appeared to result in cleavage of the dithiane–benzylic carbon bond.

The diol **11** contains most of the elements required for a synthesis of 5-hydroxytetrahydro-[1*H*]-2-benzazepin-4-ones but attempts to effect an oxidation of the primary alcohol in anticipation of ring formation using reductive amination were complicated by the presence of the tertiary alcohol. Alternative procedures could be imagined for this cyclisation, *e.g. via* a Mitsunobu reaction,[13] although this would require protection of the tertiary alcohol to avoid competing formation of a tetrahydrofuran ring. To avoid these complications, it was decided to prepare the core 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one ring system first with incorporation of the 5-hydroxy and 5-cycloalkyl substituents later in the synthesis. This strategy would have the advantage of allowing the cycloalkyl group to be varied more easily.



Scheme 1 *Reagents and conditions*: i, (a) NHMe·OMe·HCl, $AlMe_3$, CH_2Cl_2, 0 °C to r.t. (b) TBSCl, imid., DMF (60% over the two steps); ii, bromocyclobutane, *t*-BuLi, −78 °C, 1 h, add **6** (59%); iii, (a) propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t. (b) Boc_2O, Et_3N, CH_2Cl_2 (63% over the two steps); iv, **5**, *n*-BuLi, DMPU, THF, −40 to −20 °C, add to **7** or **6**, −78 °C (**10**, 42%; **12**, 69%); v, TBAF, THF, 0 °C (71%).

1,2-Bis(hydroxymethyl)benzene was protected as its mono-*tert*-butyldimethylsilyl ether **13**[14] which was converted into the chloride **14** using thionyl chloride with simultaneous addition of pyridine to avoid desilylation, see Scheme 2. Alkylation of the dithiane **5** using the chloride **14** gave the 2,2-bis-alkyldithiane **15** which was desilylated and the alcohol **16** oxidised to the aldehyde **17** at room temperature using manganese dioxide. Attempts to carry out this oxidation at reflux in dichloromethane led to the formation of side-products which were not fully identified.

Removal of the Boc-group was achieved using concentrated aqueous hydrogen chloride in ethyl acetate for 5 h at room temperature[15] and generated the imine **18**. This was reduced using sodium cyanoborohydride[16] to give the tetrahydrobenzazepine **19** in an overall yield of 73%. If the deprotection step was quenched after 1 h, side-products were isolated after the reduction. Protection of the tetrahydrobenzazepine **19** using Boc-anhydride or toluene *p*-sulfonyl chloride gave the corresponding derivatives **20** and **21** and reductive amination with benzaldehyde gave the *N*-benzyl derivative **22**. The ^{1}H NMR spectrum of the Boc-protected azepine **20** was broadened due to the interconversion of rotamers in solution, but its structure was confirmed by X-ray diffraction. Fig. 1 shows a projection of the compound as established by a single crystal X-ray study which confirmed the structure as shown. In all cases hydrolysis of the dithiane using mercuric oxide and boron trifluoride[17] gave the parent ketones **23–25**. Perhaps of interest was the position of the carbonyl stretching peak in the IR spectrum of the *N*-benzyltetrahydro[1*H*]-2-benzazepin-4-one **25** which was observed at 1749 cm^{-1} indicative of little bonding interaction between the tertiary amine and the ketone.

Ketones **23–25** have the required tetrahydro-[1*H*]-2-benzazepin-4-one structure albeit protected on nitrogen, but it remained to introduce the hydroxyl and alkyl substituents at C-5 and the aminoalkyl groups on nitrogen, to complete syntheses of the derivatives **2** required for evaluation as muscarinic receptor antagonists. To effect a regioselective oxidation, the conversion of ketones **23** and **24** into silyl enol ethers was investigated. Initial attempts to prepare the triethylsilyl enol ethers **26** and **27** using

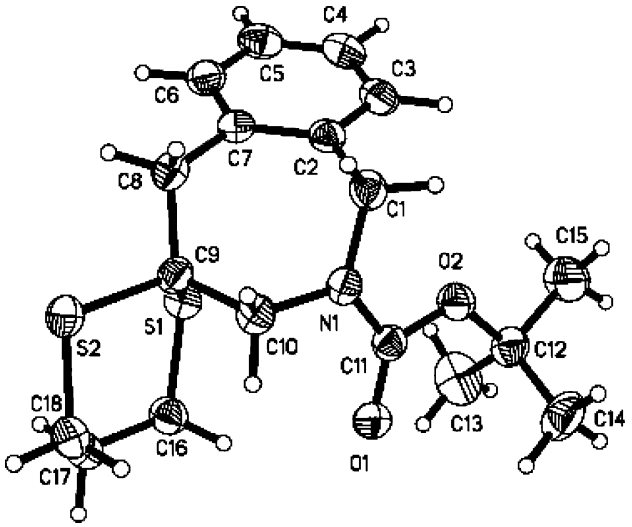
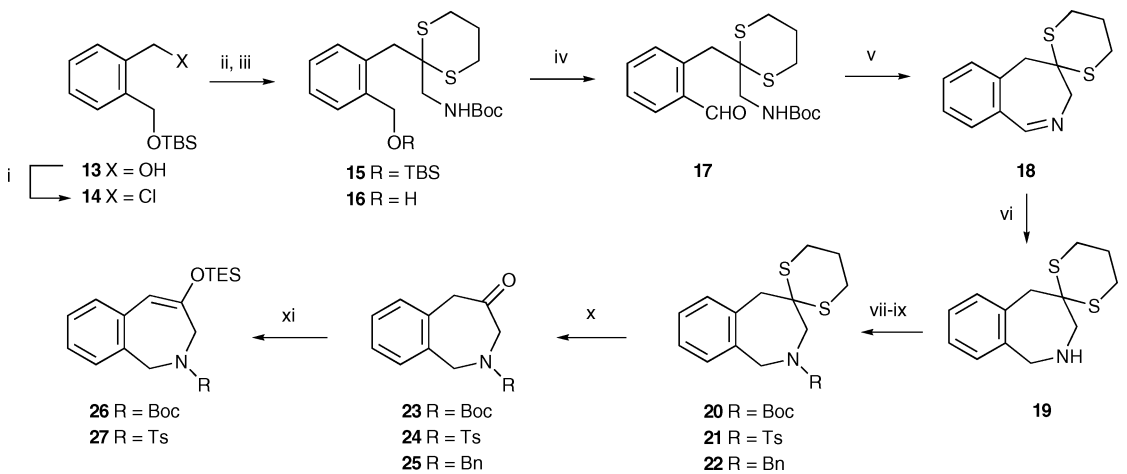


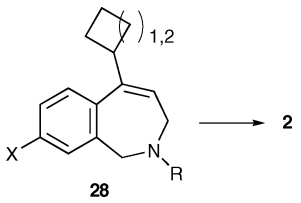
Fig. 1 ORTEP projection of the 2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **20** as determined by X-ray crystallography, ellipsoids shown at the 30% probability.

lithium di-isopropylamide and lithium hexamethyldisilazide with an *in situ* quench using triethylsilyl trifluoromethanesulfonate[18] gave rise to the formation of mixtures of regioisomers, but the use of triethylamine as base at room temperature[19] was more successful. The structures of the enol ethers were confirmed by NOE data, but attempts to use them to introduce an oxygen substituent *via* epoxidation using dimethyl dioxirane[20] and rearrangement of the epoxides so formed using fluoride, acid or base, led to mixtures of products which could not be identified.

At this point, it was decided to embark on an alternative route based on ring-closing metathesis[9,10] to prepare 2,3-dihydro-[1*H*]-2-benzazepines **28** which would be hydroxylated and oxidised to give 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones **2**. Using an asymmetric Sharpless hydroxylation, this route could provide an asymmetric synthesis of these compounds.



Scheme 2 *Reagents and conditions*: i, $SOCl_2$, py., CH_2Cl_2, 0 °C (53%); ii, **5**, *n*-BuLi, THF, −40 to −20 °C, DMPU, −78 °C, add **14** (67%); iii, TBAF, THF, 0 °C (89%); iv, MnO_2, CH_2Cl_2 (70%); v, aq. HCl, EtOAc, 5 h, r.t.; vi, $NaBH_3CN$, MeOH, cat. HCl, r.t. (73% over the two steps); vii, Boc_2O, Et_3N, CH_2Cl_2, r.t. (*ca.* 100%); viii, TsCl, py., r.t. (68%); ix, PhCHO, $NaBH_3CN$, THF, r.t. (66%); x, HgO, $BF_3{\cdot}Et_2O$, THF, H_2O, r.t. (**23**, 86%; **24**, 72%; **25**, 84%); xi, Et_3N, TESOTf, CH_2Cl_2, r.t. (**26**, 65%; **27**, 67%).



Preliminary studies of the synthesis of 2,3-dihydro-[1*H*]-2-benzazepines using ring-closing metathesis

Ring-closing metathesis has been used to prepare 2,3-dihydro-[1*H*]-2-benzazepines albeit lacking alkyl or aryl substituents at the 4- or 5-positions.[10] Initial studies were undertaken to confirm this approach in our hands. *o*-Ethenylbenzaldehyde **29**[21] was converted into the amine **30** by reductive amination and the amine protected as its toluene *p*-sulfonyl (tosyl) and 2-nitrobenzene sulfonyl (nosyl)[22] derivatives **31** and **32**. Ring-closing metathesis using Grubbs' I catalyst, see Fig. 2,[23,24] gave the 2,3-dihydro-[1*H*]-2-benzazepines **33** and **34** in excellent (≥90%) yields and deprotection of the nosyl derivative **34** using thiophenol under basic conditions[22] gave the parent 2,3-dihydro-[1*H*]-2-benzazepine **35**. Hydroxylation of the protected dihydrobenzazepines **33** and **34** using the Upjohn conditions in aqueous acetone[25] gave the *cis*-diols **36** and **37**, and deprotection of the *N*-nosyl protected diol **37** gave the water soluble dihydroxytetrahydrobenzazepine **38** which was converted into 2-butyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **39** by reductive amination using butanal, see Scheme 3.

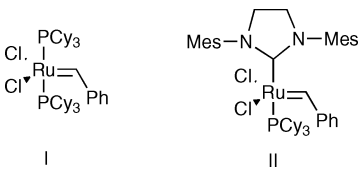
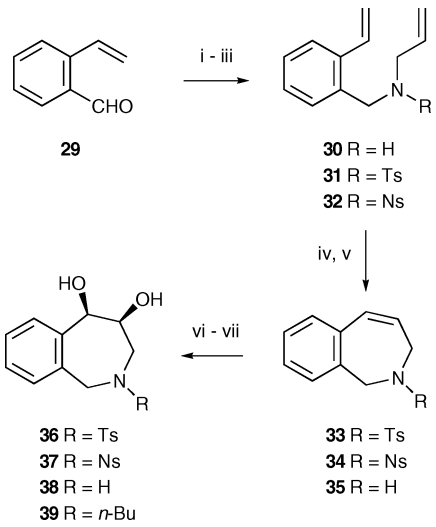


Fig. 2 Structures of Grubbs' I and II catalysts.

This work confirmed the viability of ring-closing metathesis for the synthesis of 2,3-dihydro-[1*H*]-2-benzazepines and further functionalisation by hydroxylation and reductive amination. It now remained to use this chemistry to prepare tetrahydrobenzazepines with cycloalkyl groups at C-5.

Synthesis of *N*-alkyl-5-cyclobutyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones by ring closing metathesis followed by *N*-alkylation using reductive amination

In the earlier work, the aryl cyclobutyl ketone **7** had been prepared from the reaction of the Weinreb amide **6** with cyclobutyllithium generated from cyclobutyl bromide. Cyclobutyl bromide is commercially available and can be prepared from cyclobutyl carboxylic acid *via* a Hunsdiecker reaction.[26] However, subsequently it was found to be more convenient to prepare ketone **7** from cyclobutyl phenyl carbinol **40**[27] by ortho lithiation[28] and addition of formaldehyde to give diol **41**, see Scheme 4. After regioselective protection of the primary alcohol, oxidation of the secondary alcohol using the Dess–Martin periodinane[29] gave the ketone **7** in an excellent yield. This was converted into the alkene **43** using the Petasis reagent[30] since the standard Wittig reaction was difficult to drive to completion. After desilylation and oxidation of

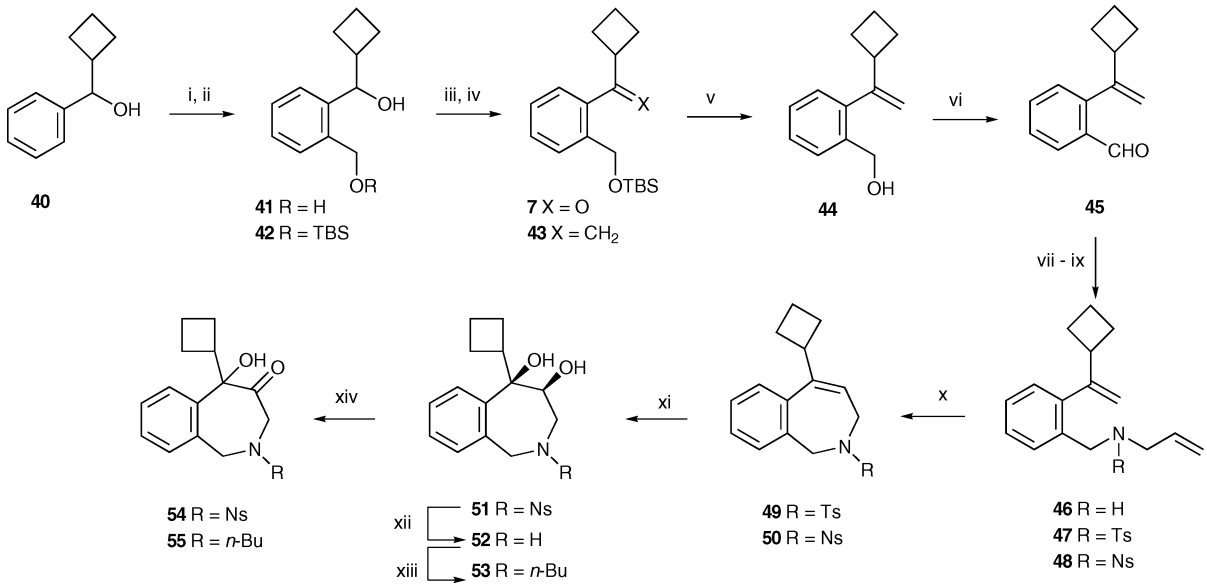


Scheme 3 *Reagents and conditions*: i, prop-2-enylamine, $MgSO_4$, r.t., 18 h, then $NaBH_4$, MeOH, r.t., 1 h (61%); ii, TsCl, py., DMAP (cat.), r.t., 48 h (50%); iii, NsCl, Et_3N, DMAP (cat.), r.t., 1.5 h (85%); iv, Grubbs' I (10 mol%), CH_2Cl_2, r.t. (**33**, 97%; **34**, 90%); v, PhSH, K_2CO_3, 18-*c*-6 (cat.), DMF, r.t., 4 h (84%); vi, NMO, OsO_4 (2–2.5 mol%), acetone, water, r.t., 24 h (**36**, 58%; **37**, 82%); vii, PhSH, K_2CO_3, acetonitrile, r.t., 15 h, then *n*-PrCHO, $NaBH(OAc)_3$, THF, $MeCO_2H$, r.t., 24 h (**39**, 46%).

the alcohol **44** to the aldehyde **45**, reductive amination using prop-2-enylamine gave amine **46** which was protected as its toluene *p*-sulfonyl and 2-nitrobenzene sulfonyl derivatives **47** and **48**. Initial studies of ring-closing metathesis of the tosyl derivative **47** using Grubbs' I catalyst[23] were rather inefficient with only a low yield of the dihydrobenzazepine **49** (18%) together with unchanged starting material (60%) and what appeared to be a dimeric material being isolated after heating for 24 h under reflux in benzene. However, the use of Grubbs' II catalyst,[31] see Fig. 2, was much more effective and, in the case of the nosyl protected amine **48**, gave the required dihydrobenzazepine **50** in an excellent yield (96%).

Hydroxylation of the dihydrobenzazepine **50** gave the racemic *cis*-diol **51**. This was deprotected to give the 4,5-dihydroxy-2,3,4,5-tetrahydro[1*H*]-2-benzazepine **52** which was immediately converted into the *N*-butyl derivative **53** by reductive amination. It remained to oxidise the vicinal diol to generate the required 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one system. The Swern oxidation procedure was initially selected for this to avoid over oxidation and C–C-bond cleavage which can be a problem in the oxidation of vicinal diols.[32] In the event, oxidation under Swern conditions of the *N*-nosyl tetrahydrobenzazepine **51** gave hydroxyketone **54** and a similar oxidation of the *N*-butyl analogue **53** gave the 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **55** in an acceptable yield of 73%.

The structures assigned to the products in Scheme 4 were consistent with their spectroscopic data and the structure of the 2-butyl-5-cyclobutyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **53** was confirmed by X-ray crystallography, see Fig. 3. The ^1H and ^{13}C NMR spectra of the hydroxyketones obtained on oxidation of the diols **51** and **53** indicated that single products had been obtained in each case, consistent with the formation of **54** and **55**, respectively. However, α-hydroxyketones can undergo 1,2-rearrangements[33] and so it was necessary to confirm that the hydroxytetrahydrobenzazepine **55**



Scheme 4 *Reagents and conditions*: i, *n*-BuLi, THF, Et_2O, 0 °C–reflux, 2 h, HCHO, r.t., 12 h (74%); ii, TBSCl, imid., DMF, −10 °C, 2 h (80%); iii, Dess–Martin periodinane, CH_2Cl_2, r.t., 2 h (96%); iv, Cp_2TiMe_2, THF, reflux, 15 h (92%); v, TBAF, THF, r.t., 2 h (83%); vi, MnO_2, CH_2Cl_2, r.t., 48 h (93%); vii, prop-2-enylamine, $MgSO_4$, CH_2Cl_2, r.t., 24 h, then $NaBH_4$, MeOH, r.t., 2 h (91%); viii, TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, r.t., 4 h (96%); ix, NsCl, Et_3N, DMAP (cat.), r.t., 3 h (79%); x, Grubbs' I cat., benzene, reflux, 24 h (**49**, 18%) or Grubbs' II (cat.), CH_2Cl_2, reflux, 18 h (**50**, 96%); xi, NMO, OsO_4 (10 mol%), acetone, water, r.t., 18 h (80%); xii, PhSH, K_2CO_3, DMF (86%); xiii, *n*-PrCHO, $NaBH(OAc)_3$, $MeCO_2H$, r.t., 15 h (53%); xiv, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 °C (**54**, 58%; **55**, 73%).

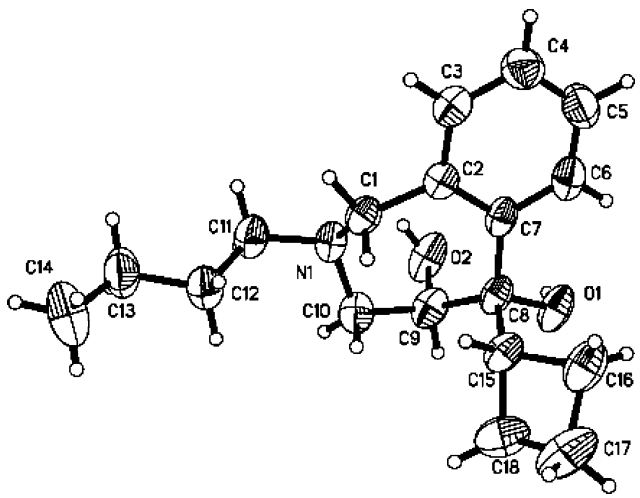


Fig. 3 ORTEP projection of the 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **53** as determined by X-ray crystallography, ellipsoids shown at 30% probability.

and not one of the isomeric hydroxyketones **55a** or **55b** was the product isolated on oxidation of the diol **53**, see Fig. 4. NOe spectroscopy confirmed hydrogen proximity and HMBC and HMQC spectra established the long-range ^1H-^{13}C coupling and carbon–hydrogen correlations consistent with structure **55**. However 2D ^{13}C-^{13}C INADEQUATE spectra unambiguously confirmed the presence of the bonds shown in bold in structure **55**, see Fig. 4, and ruled out the alternative structures **55a** and **55b**. Again the carbonyl stretching peak at 1728 cm^{-1} indicated little interaction between the tertiary amine and the ketone carbonyl group.

It now remained to attach the arylmethylaminoalkyl side-chains to the nitrogen of the tetrahydrobenzazepinones to complete syntheses of the derivatives **2** required for biological evaluation. Syntheses of the side-chains are outlined in Scheme 5. 3-(*N*-Benzyl-*N*-trifluoroacetyl)aminopropanal **56** is a known compound.[34] 2-(*N*-Benzyl-*N*-2-nitrophenylsulfonyl)aminoethanal **59** was prepared by ozonolysis of the *N*-(2-nitrophenylsulfonyl) derivative **58**[35] of *N*-benzylprop-2-enylamine **57**. 3-(*N*-Naphth-2-ylmethyl-*N*-2-nitrophenylsulfonyl)aminopropanal **62** was prepared by *N*-nosylation of 3-(*N*-naphth-2-ylmethyl)aminopropan-1-ol[36] followed by oxidation, and the 6-methylnaphth-2-yl analogue **66** was similarly prepared from the alcohol **64** which had been obtained by reductive amination of 6-methyl-2-naphthaldehyde **63**.[37]

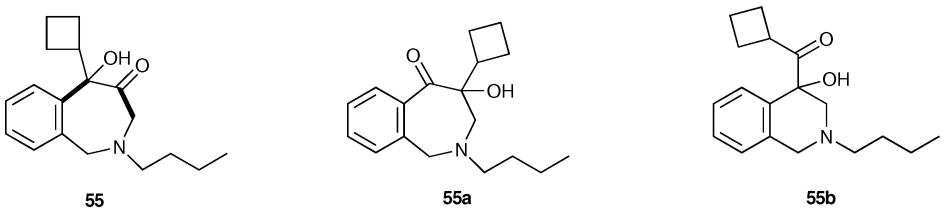
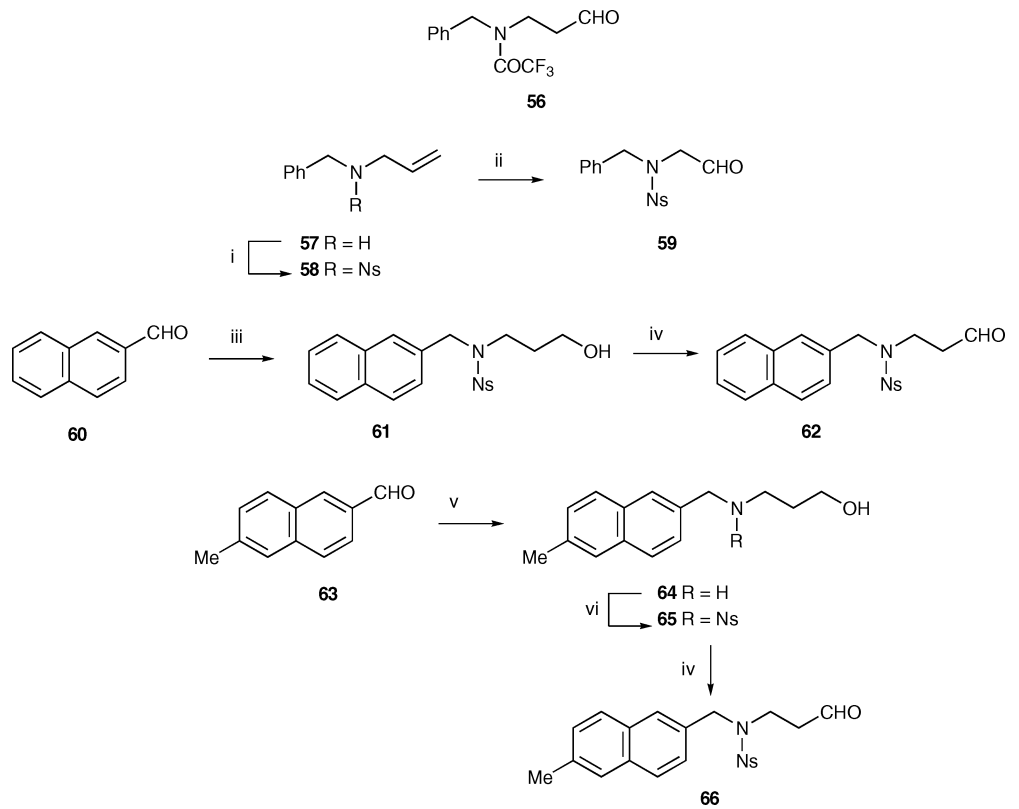


Fig. 4 Isomeric hydroxyketones which could originate from oxidation of 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **53**.



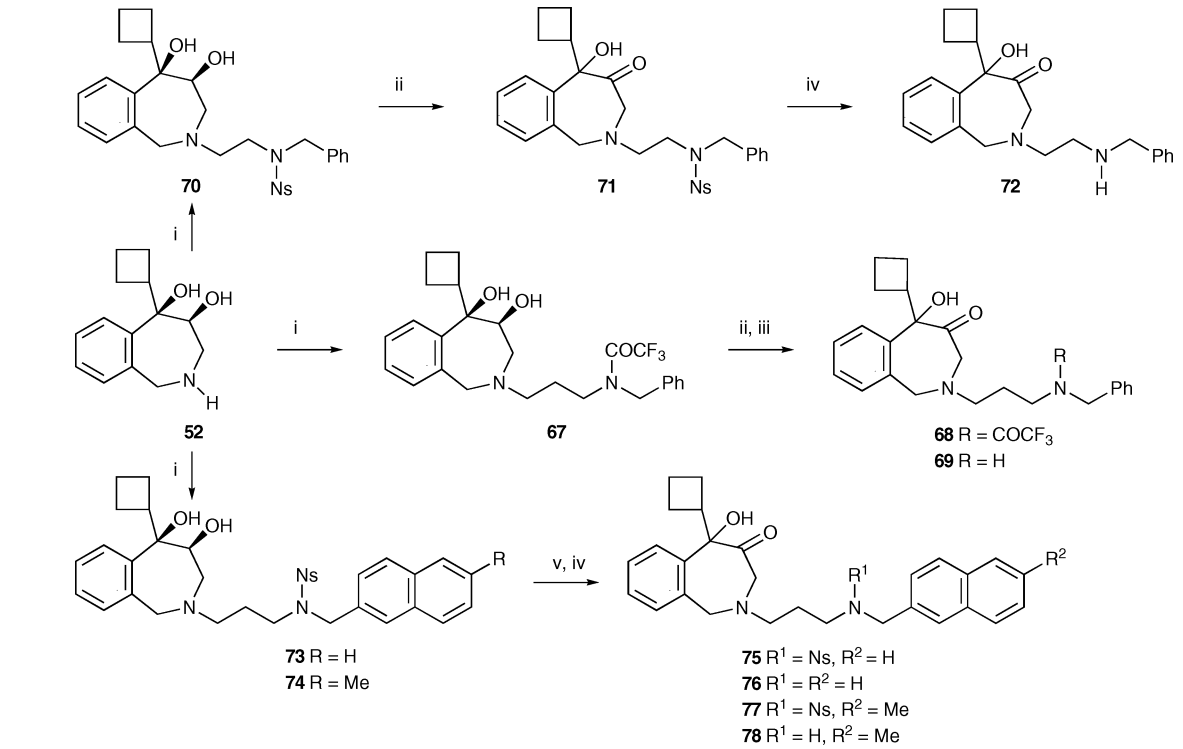
Scheme 5 *Reagents and conditions*: i, NsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 3 h (76%); ii, ozone, CH_2Cl_2, −78 °C, 30 min, then Me_2S, r.t., 15 h (92%); iii, (a) **60**, 3-aminopropanol, $MgSO_4$, CH_2Cl_2, then $NaBH_3CN$, MeOH (75%) (b) NsCl, Na_2CO_3, *n*-Bu_4NI, acetone, water, r.t., 4 h (68%); iv, Dess–Martin periodinane, CH_2Cl_2, r.t. (**62**, 41%; **66**, 97%); v, 3-aminopropanol, $MgSO_4$, CH_2Cl_2, r.t., 24 h, then $NaBH_3CN$, r.t., 1 h (58%); vi, NsCl, Na_2CO_3, *n*-Bu_4NI, acetone, water (77%).

Reductive amination of the *N*-benzyl-*N*-trifluoroacetyl-aminopropanal **56** by the tetrahydro-[1*H*]-2-benzazepine **52** was carried out using sodium cyanoborohydride and gave the *N*-alkylated tetrahydrobenzazepine **67** in an acceptable yield of 76%. Following this procedure the *N*-nosyl protected aldehydes **59**, **62** and **66** gave the corresponding *N*-alkylated dihydroxytetrahydrobenzazepines **70**, **73** and **74**, in modest to acceptable yields (31–66%). Oxidation of the dihydroxytetrahydro-[1*H*]-2-benzazepines under Swern conditions, or using the Dess–Martin periodinane, gave the corresponding *N*-alkyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones **68**, **71**, **75** and **77**, and these were deprotected to give the target compounds **69**, **72**, **76** and **78**, see Scheme 6.

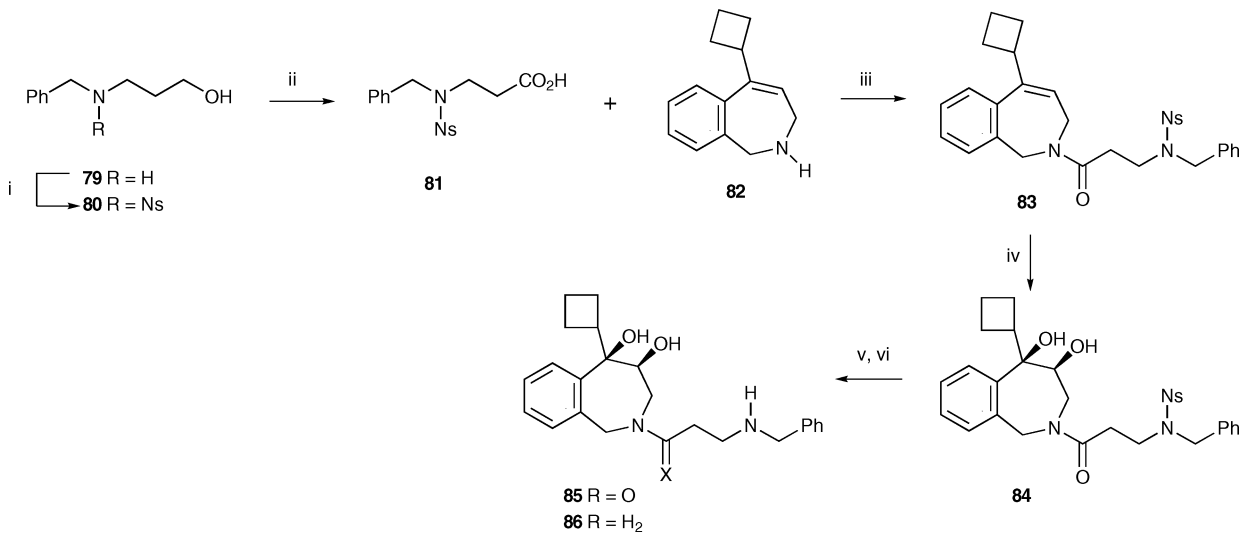
Structures were assigned to these products on the basis of spectroscopic data. In particular, the protons attached to C-3 were observed as two doublets with very similar chemical shifts and coupling constants to those observed for hydroxyketone **55** (**55**, δ 3.95, 4.18, *J* 16; **69**, δ 3.85, 4.14, *J* 16; **72**, δ 3.76, 4.15, *J* 16.5; **76** δ 3.90, 4.18, *J* 16; **78**, δ 3.84, 4.12, *J* 16). These chemical shifts contrast with those of the protons attached to C-3 for the 4,5-dihydroxytetrahydrobenzazepines, *e.g.* **53**, **70**, **73** and **74**, which were all within the range δ 2.7–3.1. These data confirmed that no α-hydroxyketone rearrangement to give isomeric hydroxyketones analogous to **55a** and **55b** had occurred. However, the carbonyl stretching peak in the IR spectrum of **72** was observed at 1693 cm^{-1}, *i.e.* at a lower frequency than had been observed earlier for the simpler compounds **25** and **55**. This may be due to additional hydrogen bonding. These compounds together with the *N*-butyl analogue **55** were subjected to biological evaluation, see below.

Introduction of *N*-alkyl side-chains into 2,3,4,5-tetrahydro-[1*H*]-2-benzazepines *via* *N*-acylation and reduction

Although *N*-alkylation of the tetrahydrobenzazepine **52** by reductive amination had delivered sufficient quantities of the adducts for further investigation, it was decided to see whether *N*-acylation and reduction was more generally useful, see Scheme 7. 3-[*N*-Benzyl-*N*-(2-nitrophenyl)sulfonylamino]propanoic acid **81** was prepared from 3-(*N*-benzylamino)propan-1-ol **79** by *N*-nosylation to give the amide **80**[38] followed by oxidation. It was coupled with the 2,3-dihydro-[1*H*]-2-benzazepine **82** prepared by deprotection of the *N*-nosyl derivative **50** to give the *N*-acyl-2,3-dihydro-2-benzazepine **83** in a reasonable yield (79%). Since it was thought that a tertiary amine might cause problems at the dihydroxylation stage, it was decided to carry out the dihydroxylation and removal of the side-chain *N*-nosyl protecting group before reduction of the amide. In the event, dihydroxylation of the dihydrobenzazepine **83** under the Upjohn conditions gave the diol **84** which was denosylated to give the *N*-acyldihydroxytetrahydrobenzazepine **85**. Reduction using the borane·THF complex then proceeded smoothly to give the *N*-alkyl-4,5-dihydroxy-2,3,4,5-tetrahydrobenz-[1*H*]-2-azepine **86**. Although slightly longer than the reductive amination route, this preparation of the



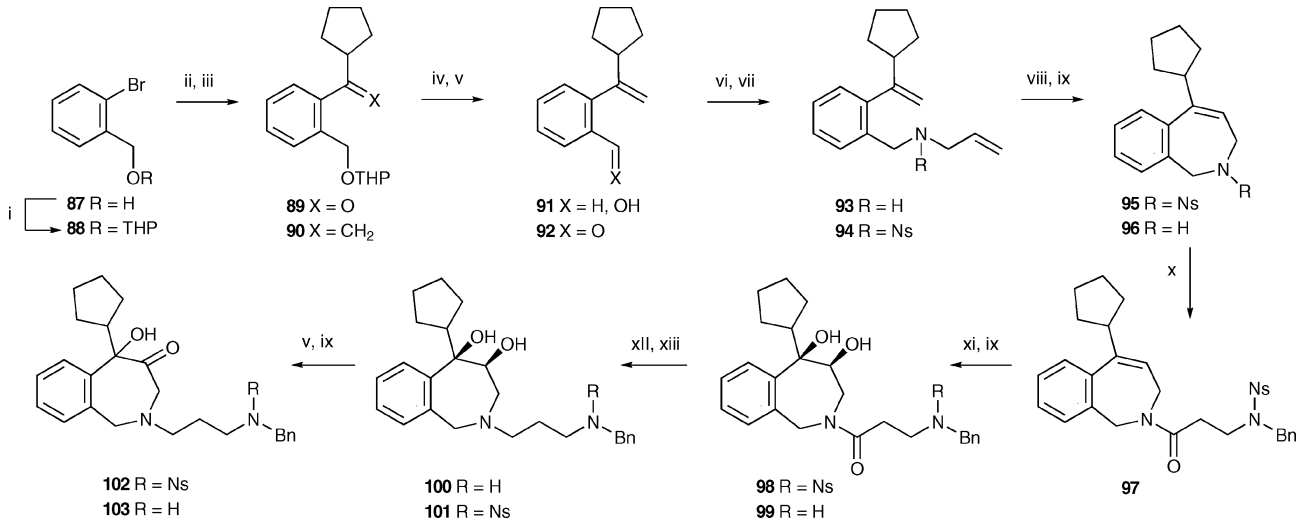
Scheme 6 *Reagents and conditions*: i, **56**, **59**, **62** or **66**, $NaBH_3CN$, MeOH, *c.*HCl (cat.), r.t. (**67**, 76%; **70**, 66%; **73**, 32%; **74**, 31%); ii, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C (**68**, 67%; **71**, 77%); iii, K_2CO_3, MeOH, water, r.t., 24 h (80%); iv, PhSH, K_2CO_3, DMF, r.t., 18 h (**72**, 52%; **76**, 41%; **78**, 97%); v, Dess–Martin periodinane, CH_2Cl_2, r.t., 2 h (**75**, 85%; **77**, 80%).



Scheme 7 *Reagents and conditions*: i, NsCl, Na_2CO_3, *n*-Bu_4NI, acetone, r.t., 2 h (78%); ii, (a) Dess–Martin periodinane, CH_2Cl_2, r.t., 2 h (b) $NaOCl_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–water, r.t., 12 h (81% from **80**); iii, **81**, TBTU, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, add **82**, r.t., 12 h (79%); iv, NMO, OsO_4 (10 mol%), *t*-BuOH–water, r.t., 12 h (*ca.* 99%); v, PhSH, K_2CO_3, DMF, r.t., 12 h (94%); vi, BH_3·THF, THF, 0 °C–r.t. 3 h, then aq. HCl, reflux, 1 h (57%).

N-alkylbenzazepines by acylation and reduction was found to be more reliable for less reactive tetrahydrobenzazepines, *vide infra.*

The benzazepine acylation and reduction procedure was used to prepare the 5-cyclopentyl-5-hydroxytetrahydro-[1*H*]-2-benzazepin-4-one **103**, see Scheme 8. In this case, the tetrahydropyranyl ether **88**, prepared from (2-bromophenyl)methanol **87**, was converted into the corresponding aryllithium reagent which was reacted with cyclopentanecarboxaldehyde followed by oxidation to give ketone **89**. Following a Wittig reaction, deprotection and oxidation, reductive amination and nosyl protection gave the metathesis precursor **94**. Metathesis using the Grubbs' II

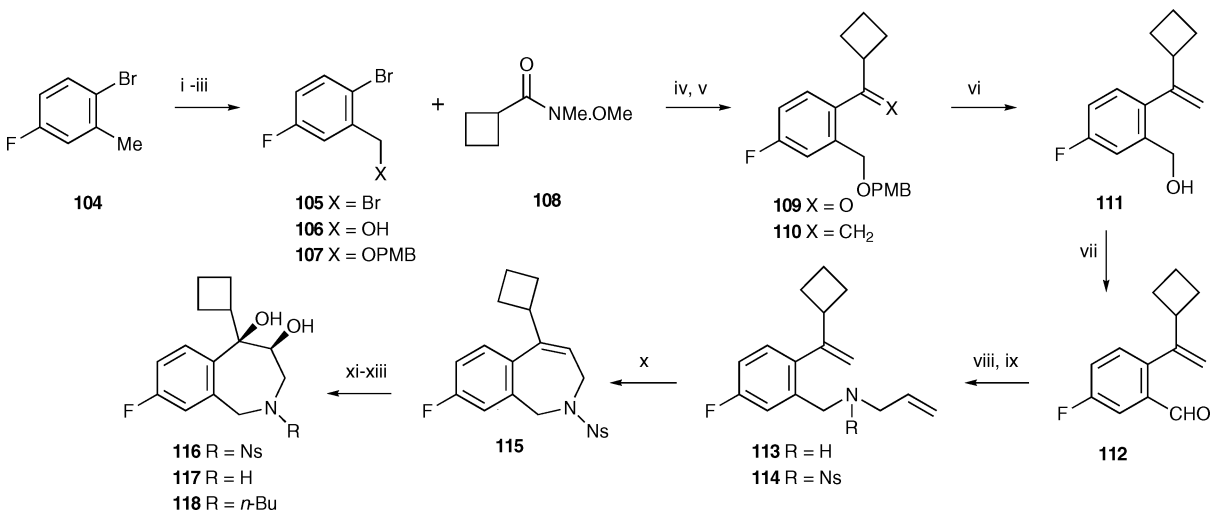


Scheme 8 *Reagents and conditions*: i, DHP, TsOH (cat.), CH_2Cl_2, r.t., 3 h (98%); ii, (a) *t*-BuLi, THF, −78 °C, 15 min, then cyclopentanecarboxaldehyde, THF, −78 °C, 30 min (89%) (b) Dess–Martin periodinane, CH_2Cl_2, py., r.t., 4 h (98%); iii, $Ph_3PMe^+Br^-$, *n*-BuLi, r.t., 30 min, then add **89**, r.t., 18 h (80%); iv, TsOH (cat.), MeOH, r.t., 4 h (86%); v, Dess–Martin, CH_2Cl_2, r.t., 2 h (**92**, 86%; **102**, 60%); vi, prop-2-enylamine, CH_2Cl_2, $MgSO_4$, r.t., 24 h, then $NaBH_4$, MeOH, r.t., 3 h (91%); vii, NsCl, DMAP (cat.), Et_3N, CH_2Cl_2, r.t., 20 min (92%); viii, Grubbs' II (cat.), CH_2Cl_2, 45 °C, 24 h (40%); ix, PhSH, K_2CO_3, DMF, r.t., 24 h (**99**, 75%; **103**, 75%); x, **81**, TBTU, CH_2Cl_2, *i*-Pr_2NEt, r.t., 15 min, then add **96**, r.t. 16 h (91% from **95**); xi, NMO, OsO_4 (cat.), acetone, *t*-BuOH, water, r.t., 12 h (91%); xii, BH_3·THF, THF, r.t., 12 h, then aq. HCl, 80 °C, 1 h (60%); xiii, NsCl, Na_2CO_3, *n*-Bu_4NI, acetone, water, r.t., 4 h.

catalyst then gave the 2,3-dihydro-[1*H*]-2-benzazepine **95** which was converted to the *N*-acyl-2,3-dihydro-[1*H*]-2-benzazepine **97** by denosylation and *N*-acylation. After hydroxylation and removal of the side-chain *N*-nosyl group, reduction of the amide **99** using the borane·THF complex gave the tertiary amine **100**. The secondary amine then had to be reprotected before selective oxidation of the secondary alcohol gave the cyclopentyl substituted 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **103** after a final deprotection. The activity of this compound towards muscarinic receptors was also evaluated, *vide infra.*

Preparation of 8-fluorinated 2,3,4,5-tetrahydro-[1*H*]-2-benzazepines

8-Fluorinated 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones were of interest to check the effect of the additional aromatic substituent on the selectivity of binding to the muscarinic M_3 and M_2 receptors. 1-Bromo-2-bromomethyl-4-fluorobenzene **105**[39] is commercially available and can also be prepared by free-radical bromination of 2-bromo-5-fluorotoluene **104**, see Scheme 9. Hydrolysis gave the benzyl alcohol **106**[40]



Scheme 9 *Reagents and conditions*: i, NBS, $(BzO)_2$ (cat.), CCl_4, reflux (99%); ii, $CaCO_3$, dioxane, water, 100 °C, 24 h (99%); iii, NaH, THF, DMF, 0 °C–r.t., 2 h, PMBCl, r.t. (94%); iv, Mg, THF, reflux, 3 h, then **108**, r.t., 12 h (60%); v, Cp_2TiMe_2, THF, 0 °C–65 °C, 15 h (93%); vi, DDQ, CH_2Cl_2, water, r.t., 2 h (94%); vii, Dess–Martin periodinane, CH_2Cl_2, r.t., 12 h (85%); viii, prop-2-enylamine, $MgSO_4$, CH_2Cl_2, r.t., 24 h, then $NaBH_4$, MeOH, r.t., 2 h (99%); ix, NsCl, Et_3N, DMAP (cat.), CH_2Cl_2, r.t., 12 h (86%); x, Grubbs' II (cat.), CH_2Cl_2, reflux, 20 h (97%); xi, NMO, OsO_4 (cat.), acetone, water, r.t., 36–48 h (97%); xii, PhSH, K_2CO_3 (*ca.* 100%); xiii, *n*-PrCHO, MeOH, $NaBH_3CN$, r.t., 12 h (90%).

which was protected as its *p*-methoxybenzyl ether **107**. The Grignard reagent generated from this bromide was reacted with the Weinreb amide **108** derived from cyclobutyl carboxylic acid to give the ketone **109** which was converted into the alkene **110** using the Petasis reagent. After deprotection and oxidation, reductive amination of the aldehyde **112** with prop-2-enylamine gave the sulfonamide **114** after nosylation. Ring-closing metathesis using Grubbs' II catalyst then gave the 2,3-dihydro-[1*H*]-2-benzazepine **115** which was hydroxylated and deprotected to give the 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **117**. Reductive amination of this secondary amine with butanal gave the *N*-butyltetrahydrobenzazepine **118**, but the use of other more complex aldehydes, *e.g.*, **66**, were unsuccessful, perhaps due to the reduced nucleophilicity of the nitrogen because of the fluorine substituent. However, the *N*-alkyl side-chain could be attached by acylation.

Denosylation of the dihydrobenzazepine **115** followed by *N*-acylation and dihydroxylation, gave the 4,5-dihydroxytetrahydro-[1*H*]-2-benzazepine **121** which was also available by *N*-acylation of the parent 4,5-dihydroxytetrahydro-[1*H*]-2-benzazepine **117**, see Scheme 10. Following removal of the side-chain nosyl group, reduction gave the tertiary amine **123** which was renosylated before Swern oxidation to give the hydroxyketone **125**. A final deprotection gave the required 8-fluoro-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **126** which was subjected to binding assays.

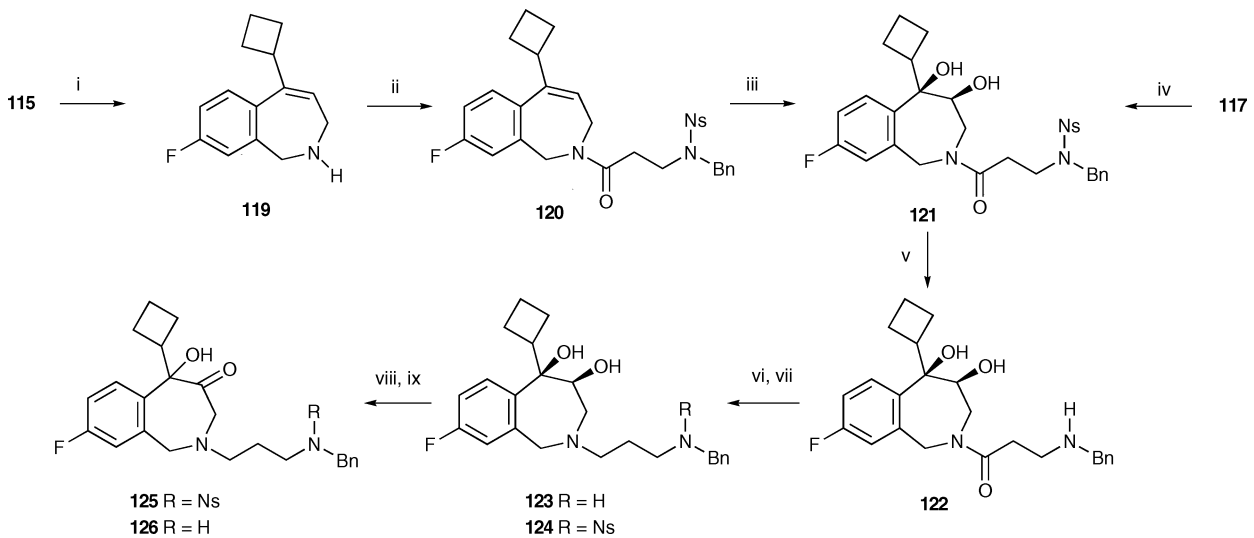
Biological evaluation of 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones and related compounds

Binding data '*in vitro*' using contraction of the guinea pig ileum (M_3) and guinea pig left atria (M_2) were evaluated. Both M_3 and M_2 muscarinic tests utilised methacholine as agonist, the measurements being determined as a percentage inhibition of contractility (M_3) and of twitch height (M_2), respectively. Binding constants were determined from the dose-response curves. A number of the compounds showed membrane sensitization at higher doses. For these compounds, data at 30% response only were utilised to determine the binding constant or measurements were confined to lower doses of the antagonist. The results for selected compounds including representative 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepines, are given in Tables 1 and 2.

The value of $\log_{10}K_B$ for the racemic 5-cyclobutyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one **69** with the 3-(*N*-phenylmethyl)aminopropyl group on nitrogen, for the M_3 receptors in the guinea pig ileum was 6.7 with a selectivity over the M_2 receptors from the guinea pig left atria of about 40, see Table 1. This selectivity is comparable to that of darifenacin (**1**) but the overall potency was less (by one to two orders of magnitude). The potency of the cyclopentyl analogue **103** was slightly, but not significantly, higher, whereas analogue **72**, with the 2-aminoethyl side-chain, was a little less potent. The 8-fluorinated benzazepinone **126** did not show any increase in selectivity for the M_3 over the M_2 receptors. However, the simpler 2-butyltetrahydrobenzazepinone **55** was significantly less potent towards the M_3 receptors, as were the analogues **76** and **78** with (*N*-naphthylmethyl)aminopropyl substituents. The 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepines **53**, **86**, **100** and **118** showed only moderate binding to both the M_3 and M_2 receptors, see Table 2.

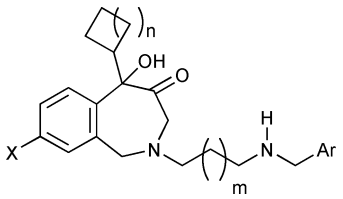
Summary and conclusions

A series of 2,3-dihydro-[1*H*]-2-benzazepines has been prepared using ring-closing metathesis as the key step and converted into 5-cycloalkyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones **2**, a hitherto unknown class of benzazepine derivative, by hydroxylation and selective oxidation. Reductive amination or *N*-acylation followed by reduction were used for



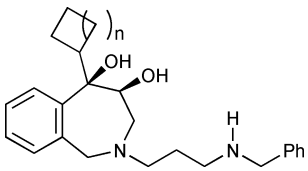
Scheme 10 *Reagents and conditions*: i, PhSH, K_2CO_3, DMF, rt, 16 h (*ca.* 100%); ii, **81**, EDC, DMAP, DMF, rt, 16 h (73%); iii, NMO, OsO_4, acetone, *t*-butanol, water, rt, 16 h (94%); iv, **81**, *i*-Pr_2EtN, TBTU, CH_2Cl_2, rt, 16 h (95%); v, PhSH, K_2CO_3, DMF, r.t., 16 h (87%); vi, $LiAlH_4$, THF, reflux, 4 h; vii, nosyl chloride, *i*-Pr_2EtN, CH_2Cl_2, rt, 16 h (91% from **122**); viii, DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, Et_3N, 0 °C, 30 min (81%); ix, PhSH, K_2CO_3, MeCN, rt, 16 h (95%).

Table 1 Activities of tetrahydrobenzazepin-4-ones as muscarinic (M_3) and (M_2) antagonists

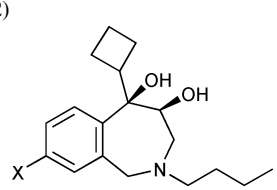


Compound no.	*n*	X	m	Ar	$Log_{10}K_B$ guinea pig ileum	$Log_{10}K_B$ guinea pig left atria	Log_{10}selectivity
69	1	H	1	Ph	6.7 ± 0.4(4)	5.2 ± 0.3(4)	1.5 ± 0.3(4)
72	1	H	0	Ph	6.5 ± 0.4(4)	4.9 ± 0.6(4)	1.6 ± 0.7(4)
76	1	H	1	2-Naph	<5.0	—	—
78	1	H	1	2-(6-Me-naph)	<5.0	—	—
103	2	H	1	Ph	7.2	—	—
126	1	F	1	Ph	6.4 ± 0.3(2)	5.4 ± 0.1	1.0 ± 0.3(2)
55	1	H	2-Butyl		<5.0	—	—

Table 2 Activities of racemic dihydroxytetrahydrobenzazepines as muscarinic (M_3) and (M_2) antagonists



Compound no.	*n*	$Log_{10}K_B$ guinea pig ileum	$Log_{10}K_B$ guinea pig left atria
86	1	5.5	—
100	2	5.6 ± 0.5(2)	5.4 ± 0.1



Compound No.	X	$Log_{10}K_B$ guinea pig ileum	$Log_{10}K_B$ guinea pig left atria	Log_{10}selectivity
53	H	6.2 ± 0.2(2)	< 5.0	>1.2
118	F	5.4	—	—

the synthesis of *N*-alkylated derivatives and 8-fluorinated analogues were also prepared. The 5-cycloalkyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones **2**, albeit racemic, were antagonists towards the M_3 receptors in the guinea pig ileum with useful selectivities over the M_2 receptors in the guinea pig left atria, but the overall potencies were 10–100 times less than optimal. Preliminary work also showed the usefulness of the dithiane **5** for the preparation of 2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones. In the accompanying paper, a Mitsunobu reaction is used to form a more complex 2,3-dihydro-[1*H*]-2-benzazepine when ring-closing metathesis was unsuccessful.

Experimental

General

Flash column chromatography was performed using Merck silica gel (60H; 40–60 μ, 230–240 mesh). Light petroleum was redistilled before use and refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran was dried over sodium-benzophenone and was distilled prior to use. Dichloromethane was dried over CaH_2 and was distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Electron impact (EI) or chemical ionisation using ammonia (CI) mass spectra were recorded using a Fisons VG Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films unless otherwise stated. Nuclear magnetic resonance spectra were recorded in deuteriated chloroform unless otherwise indicated on either a Varian Unity 500 (500 MHz), Varian INOVA 300 (300 MHz), or a Varian Gemini 200 (200 MHz) spectrometer. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts relative to tetramethylsilane.

2-(*tert*-Butyldimethylsilyloxymethyl)phenyl cyclobutyl ketone 7

tert-Butyllithium (1.7 M in pentane, 16 cm^3, 27.31 mmol) was added dropwise at −78 °C under argon to cyclobutyl bromide (1.3 cm^3, 13.66 mmol) in tetrahydrofuran (THF) (15 cm^3). The solution was stirred for 1 h before adding *via* a cannula to the amide **6** (2.11 g, 6.83 mmol) in THF (30 cm^3) at −78 °C. After 1 h, saturated aqueous ammonium chloride (50 cm^3) was added and the mixture was warmed to room temperature. Following extraction with ether (3 × 50 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (8 : 1 → 5 : 1) afforded the *title compound* **7** (1.10 g, 59%) as a clear oil (found: M^+, 304.1847. $C_{18}H_{28}O_2Si$ requires *M*, 304.1859); ν_{max} 3067, 1676, 1601, 1573, 1471, 1253, 1217, 1194, 1129, 1081 and 967 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.02 (6 H, s, 2 × $SiCH_3$), 0.83 [9 H, s, $C(CH_3)_3$], 1.74 and 1.91 (each 1 H, m, CH), 2.08–2.18 and 2.19–2.31 (each 2 H, m, CH_2), 3.82 (1 H, pent, *J* 8.5, CH), 4.95 (2 H, s, OCH_2), 7.19 and 7.39 (each 1 H, t, *J* 7.5, ArH) and 7.52 and 7.73 (each 1 H, d, *J* 7.5, ArH); δ_C (75 MHz, $CDCl_3$) −5.40, 17.87, 18.35, 25.15, 25.95, 43.61, 63.47, 126.04, 126.64, 128.98, 131.97, 133.05, 143.77 and 203.78; *m/z* (EI) 304 (2%), 247 (50), 155 (40) and 75 (100).

The alcohol **42** (10.32 g, 33.73 mmol) was added to the Dess–Martin periodinane (21.45 g, 50.59 mmol) in dichloromethane (170 cm^3, 0.2 M) at room temperature and the mixture was stirred for 2 h then cooled to 0 °C and aqueous sodium hydroxide (1.3 M, 200 cm^3) was added. After 10 min, the aqueous phase was extracted with ether (3 × 150 cm^3) and the organic extracts were washed with aqueous sodium hydroxide (1.3 M, 200 cm^3), deionised water (150 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to give the ketone **7** (9.87 g, 32.47 mmol, 96%).

2-(4-Methylphenyl)sulfonyl-2,3-dihydro-[1*H*]-2-benzazepine 33

Toluene *p*-sulfonyl chloride (419 mg, 2.20 mmol) and 4-dimethylaminopyridine (*ca.* 2 mg) were added to the amine **30** (362 mg, 2.09 mmol) in pyridine (20 cm^3) at room temperature. After stirring for 2 days, ether (50 cm^3) and aqueous hydrogen chloride (3.5 M, 50 cm^3) were added. The aqueous phase was extracted with ether (3 × 50 cm^3) and the organic extracts were washed with saturated aqueous copper sulfate (50 cm^3) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (5 : 1) gave the *N*-(2-ethenylphenyl)methyl-*N*-prop-2-enyl toluene *p*-sulfonamide **31** (339 mg, 50%) as a colourless solid, used without further purification (found: M^+ + H, 328.1372. $C_{19}H_{22}NO_2S$ requires *M*, 328.1371); δ_H (300 MHz, $CDCl_3$) 2.50 (3 H, s, CH_3), 3.78 (2 H, d, *J* 7, NCH_2), 4.21 (2 H, s, $ArCH_2$), 4.92–5.08 (2 H, m, 3-H_2), 5.29 (1 H, dd, *J* 1, 11, 2″-H), 5.49 (1 H, m, 2-H), 5.62 (1 H, dd, *J* 1, 17.5, 2″-H′), 7.03 (1 H, dd, *J* 11, 17.5, 1″-H), 7.21–7.38 (3 H, m, ArH), 7.39 (2 H, d, *J* 8, ArH), 7.52 (1 H, dd, *J* 1, 7.5, ArH) and 7.79 (2 H, d, *J* 8, ArH); *m/z* (CI) 345 (M^+ + 18, 25%) and 328 (M^+ + 1, 100).

Grubbs' I catalyst (83 mg, 0.10 mmol, 10 mol%) was added to a degassed solution of the dienylsulfonamide **31** (330 mg, 1.01 mmol) in dichloromethane (25 cm^3) and the mixture was stirred at room temperature for 15 h before silica (*ca.* 1 g) was added and the solvent removed under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (5 : 1) as eluent gave the *title compound* **33** (292 mg, 97%) as a colourless solid recrystallised from ether, m.p. 116–118 °C (found: C, 68.0; H, 5.75; N, 4.65; S, 10.35%. $C_{17}H_{17}NO_2S$ requires C, 68.2; H, 5.7; N, 4.7; S, 10.7%. Found: M^+ + H, 300.1056. $C_{17}H_{18}NO_2S$ requires *M*, 300.1058); δ_H (300 MHz, $CDCl_3$) 2.36 (3 H, s, CH_3), 4.28 (2 H, m, 3-H_2), 4.49 (2 H, s, 1-H_2), 5.69 (1 H, dt, *J* 12.5, 3, 4-H), 6.33 (1 H, dt, *J* 12.5, 1.5, 5-H), 6.97 (1 H, m, ArH), 7.06 (2 H, d, *J* 8, ArH), 7.18–7.28 (3 H, m, ArH) and 7.39 (2 H, d, *J* 8, ArH); δ_C (75 MHz, $CDCl_3$) 21.33, 51.20, 52.70, 127.05, 127.28, 127.63, 127.76, 128.56, 128.97, 129.98, 130.66, 135.19, 135.81, 136.31 and 142.62; *m/z* (CI) 317 (M^+ + 18, 60%) and 300 (M^+ + 1, 100).

2-(2-Nitrophenyl)sulfonyl-2,3-dihydro-[1*H*]-2-benzazepine 34

Following the procedure outlined for the synthesis of the dihydrobenzazepine **33**, the dienyl sulfonamide **32** (444 mg, 1.24 mmol) and Grubbs' I catalyst (102 mg, 0.12 mmol, 10 mol%) in dichloromethane (25 cm^3) gave, after stirring for 4 h and chromatography using light petroleum–ethyl acetate (3 : 1) as eluent, the *title compound* **34** (368 mg, 90%) as a pale grey solid, which was recrystallised from dichloromethane, m.p. 114–116 °C (found: C, 57.8; H, 4.3; N, 8.5; S, 10.05%; M^+, 330.0670. $C_{16}H_{14}N_2O_4S$ requires C, 58.2; H, 4.2; N, 8.5; S, 9.7%; *M*, 330.0674); ν_{max} (CH_2Cl_2) 3097, 3073, 3025, 1533, 1437, 1373, 1340, 1164, 1076 and 907 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.41 (2 H, m, 3-H_2), 4.62 (2 H, s, 1-H_2), 5.85 (1 H, dt, *J* 12.5, 3.5, 4-H), 6.46 (1 H, dt, *J* 12.5, 1, 5-H), 7.09 (1 H, d, *J* 7.5, ArH), 7.18–7.29 (3 H, m, ArH), 7.37 (1 H, dt, *J* 1.5, 7.5, ArH) and 7.49–7.62 (3 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 51.02, 52.75, 123.44, 127.19, 127.88, 128.17, 128.34, 129.69, 130.36, 130.78, 130.83, 132.66, 132.86, 134.97, 135.50 and 147.85; *m/z* (CI) 348 (M^+ + 18, 100%) and 331 (M^+ + 1, 30).

(2-Hydroxymethylphenyl)cyclobutylcarbinol 41

n-Butyllithium (2.5 M, 2.47 cm^3, 6.17 mmol) was added to cyclobutylphenylcarbinol **40**[27] (0.5 g, 3.09 mmol) in diethyl ether (21 cm^3) at 0 °C. The mixture was heated under reflux for 2 h and then allowed to cool to room temperature. An excess of paraformaldehyde was heated and the formaldehyde produced was bubbled through the orange/red solution until it became colourless. The reaction mixture was stirred overnight at room temperature, then deionised water (30 cm^3) was added and the aqueous layer was extracted with ethyl acetate (5 × 30 cm^3). The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1 : 1) as eluent gave the *title compound* **41** (0.44 g, 74%) as an oil (found: M^+ + NH_4, 210.1499. $C_{12}H_{20}NO_2$ requires *M*, 210.1494); ν_{max} 3334, 3065, 3028, 1452, 1000 and 755; δ_H (300 MHz, $CDCl_3$) 1.75 (1 H, m), 1.82–2.01 (3 H, m), 2.11 and 2.27 (each 1 H, m), 2.93 (1 H, sex, *J* 8.5), 3.12 (2 H, br. s, 2 × OH), 4.66 and 4.83 (each 1 H, d, *J* 12, HC*H*O), 4.87 (1 H, d, *J* 8.5, 1-H) and 7.29–7.41 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.79, 24.78, 25.35, 39.90, 63.82, 75.75, 126.78, 127.85, 128.21, 130.03, 138.86 and 140.54; *m/z* (CI) 192 (M^+, 23%), 173 (32) and 157 (100).

1-(2-*tert*-Butyldimethylsilyloxymethyl)phenyl-1-cyclobutylethene 43

The ketone **7** (476 mg, 1.57 mmol) and Cp_2TiMe_2 (700 mg, 3.37 mmol) in THF (20 cm^3) were heated to reflux for 15 h under nitrogen in a foil covered apparatus. Light petroleum (100 cm^3) was added and the reaction mixture filtered through Celite®. The residue was washed with light petroleum (2 × 50 cm^3) before silica (*ca.* 5 g) was added and the solvent removed under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (19 : 1) gave the *title compound* **43** (434 mg, 92%) as a clear oil (found: M^+, 302.2062. $C_{19}H_{30}OSi$ requires *M*, 302.2066); δ_H (300 MHz, $CDCl_3$) −0.08 (6 H, s, 2 $SiCH_3$), 0.84 [9 H, s, $C(CH_3)_3$], 1.61 (1 H, m), 1.69–2.01 (5 H, m), 3.10 (1 H, pent, *J* 8, CH), 4.58 (2 H, s, OCH_2), 4.79 and 5.06 (each 1 H, d, *J* 1.5, 2-H), 6.94 (1 H, d, *J* 7.5, ArH), 7.09 and 7.17 (each 1 H, t, *J* 7.5, ArH) and 7.44 (1 H, d, *J* 7.5, ArH); δ_C (75 MHz, $CDCl_3$) −5.33, 17.63, 18.35, 25.92, 28.04, 41.97, 62.64, 112.06, 126.17, 126.69, 126.73, 127.92, 138.00, 140.18 and 151.89; *m*/*z* (CI) 320 (M^+ + 18, 5%), 303 (M^+ + 1, 10) and 171 (100).

***N*-[2-(1-Cyclobutylethenyl)phenyl]methyl-*N*-prop-2-enyl 2-nitrobenzene sulfonamide 48**

The amine **46** (200 mg, 0.881 mmol), triethylamine (0.18 cm^3, 1.29 mmol), 2-nitrophenylsulfonyl chloride (215 mg, 0.970 mmol) and 4-dimethylaminopyridine (*ca.* 2 mg) in dichloromethane (10 cm^3) were stirred at room temperature for 3 h. Ether (25 cm^3) and water (25 cm^3) were added and the aqueous layer was extracted with ether (2 × 15 cm^3). The organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (3 : 1) as eluent gave the *title compound* **48** (285 mg, 79%) as a clear viscous oil (found: M^+ + H, 413.1528. $C_{22}H_{25}N_2O_4S$ requires *M*, 413.1535); ν_{max} 3075, 1543, 1372, 1352, 1163, 1126, 915 and 778; δ_H (300 MHz, $CDCl_3$) 1.70 (1 H, m), 1.82–2.11 (5 H, m), 3.16 (1 H, pent, *J* 8, CH), 3.94 (2 H, d, *J* 6, 1-H_2), 4.61 (2 H, s, $ArCH_2$), 4.88 (1 H, s, 2″-H), 5.01–5.12 (2 H, m, 3-H_2), 5.22 (1 H, t, *J* 1.5, 2″-H′), 5.61 (1 H, m, 2-H), 7.08 (1 H, m, ArH), 7.18–7.26 (2 H, m, ArH), 7.38 (1 H, m, ArH), 7.63–7.76 (3 H, m, ArH) and 8.04 (1 H, d, *J* 7.5, ArH); δ_C (75 MHz, $CDCl_3$) 17.59, 28.00, 42.00, 48.09, 49.58, 112.78, 119.00, 124.06, 126.84, 127.09, 127.20, 128.64, 130.99, 131.59, 131.99, 132.17, 133.36, 134.03, 141.85, 143.80 and 151.63; *m*/*z* (CI) 430 (M^+ + 18, 15%), 413 (M^+ + 1, 5), 383 (30), 228 (50) and 171 (100).

5-Cyclobutyl-2-(4-methylphenyl)sulfonyl-2,3-dihydro-[1*H*]-2-benzazepine 49

The dienyl sulfonamide **47** (35 mg, 0.0919 mmol) and Grubbs' I catalyst (12 mg, 0.0146 mmol, 16 mol%) in benzene (10 cm^3) were heated under reflux for 24 h. Silica (*ca.* 1 g) was added and the mixture was concentrated under reduced pressure. Chromatography of the residue using (light petroleum–ethyl acetate (9 : 1 → 3 : 1) gave recovered starting material **47** (21 mg, 60%) and then the *title compound* **49** (6 mg, 18%) as a solid (found: M^+, 353.1452. $C_{21}H_{23}NO_2S$ requires *M*, 353.1449); δ_H (300 MHz, $CDCl_3$) 1.50–1.62 (3 H, m), 1.79 (1 H, m), 1.93–2.04 (2 H, m), 2.36 (3 H, s, CH_3), 3.28 (1 H, br. pent, *J* 8, CH), 3.49 (2 H, d, *J* 7.25, 3-H_2), 4.01 (2 H, s, 1-H_2), 5.45 (1 H, dt, *J* 2, 7, 4-H), 7.05–7.31 (6 H, m, ArH) and 7.67 (2 H, d, *J* 8, ArH); *m*/*z* (CI) 354 (M^+ + 1, 80%), 198 (100) and 184 (70). The third fraction off the column was provisionally identified as a dimer (7 mg, 20%); *m*/*z* (CI) 752 (M^+ + 18, 1%).

5-Cyclobutyl-2-(2-nitrophenylsulfonyl)-2,3-dihydro-[1*H*]-2-benzazepine 50

The dialkenyl sulfonamide **48** (885 mg, 2.12 mmol) and the Grubbs' II catalyst (90 mg, 0.106 mmol) were heated under reflux for 18 h in degassed dichloromethane (100 cm^3). The reaction mixture was cooled to room temperature and silica (*ca.* 3 g) was added. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (3 : 1) as eluent gave the *title compound* **50** (780 mg, 96%) as a clear viscous oil (found: M^+ + H, 385.1224. $C_{20}H_{21}N_2O_4S$ requires *M*, 385.1222); ν_{max} 1543, 1373, 1164, 1125, 911, 851, 766 and 745; δ_H (300 MHz, $CDCl_3$) 1.77 (1 H, m), 1.83–2.04 (3 H, m), 2.13–2.24 (2 H, m), 3.49 (1 H, pent, *J* 8, CH), 3.67 (2 H, d, *J* 7.5, 3-H_2), 4.19 (2 H, s, 1-H_2), 5.90 (1 H, dt, *J* 2, 7.5, 4-H), 7.25–7.32 (2 H, m, ArH), 7.35–7.42 (2 H, m, ArH), 7.64–7.77 (3 H, m, ArH) and 8.05 (1 H, dd, *J* 2, 5.5, ArH); δ_C (75 MHz, $CDCl_3$) 17.80, 28.39, 39.55, 43.00, 49.22, 116.95, 124.05, 126.04, 127.95, 128.35, 129.80, 130.53, 131.42, 132.95, 133.16, 133.29, 139.94 and 151.00; *m*/*z* (CI) 385 (M^+ + 1, 5%), 355 (20), 198 (90) and 94 (100%).

(4*RS*,5*SR*)-5-Cyclobutyl-2-(2-nitrophenylsulfonyl)-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 51

N-Methylmorpholine-*N*-oxide (40 mg, 0.341 mmol) and osmium tetroxide (8 mg, 0.0315 mmol, 10 mol%) were added at room temperature to the dihydrobenzazepine **50** (120 mg, 0.313 mmol) in acetone (5 cm^3) and water (2.5 cm^3) and the mixture was vigorously stirred for 18 h. Dichloromethane (15 cm^3) and water (15 cm^3) were added and the mixture was acidified with aqueous hydrogen chloride (3 M) until the pH was 2. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3) and the organic extracts were dried ($MgSO_4$). Concentration under reduced pressure followed by chromatography of the residue using light petroleum–ethyl acetate (2 : 1) gave the *title compound* **51** (104 mg, 80%) as a solid further purified by reprecipitation from ether and petroleum ether, m.p. 140–142 °C (found: M^+ + H, 419.1274. $C_{20}H_{23}N_2O_6S$ requires *M*, 419.1277); ν_{max} ($CDCl_3$) 3540, 3093, 1590, 1545, 1445, 1371, 1352, 1266, 1164 and 1065 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (1 H, m), 1.78–1.90 (3 H, m), 2.13–2.38 (2 H, m), 2.49 (1 H, d, *J* 9, OH), 2.91 (1 H, pent, *J* 8, CH), 3.22 (1 H, s, OH), 3.53 (1 H, dd, *J* 1, 15, 3-H), 3.86 (1 H, m, 4-H), 4.03 (1 H, ddd, *J* 2, 4, 15, 3-H′), 4.46 (1 H, d, *J* 16, 1-H), 4.83 (1 H, dd, *J* 2, 16, 1-H′), 7.23–7.26 (2 H, m, ArH), 7.38 (1 H, m, ArH), 7.67–7.81 (3 H, m, ArH), 7.86 (1 H, d, *J* 7.5, ArH) and 8.11 (1 H, dd, *J* 2, 7, ArH); δ_C (75 MHz, $CDCl_3$) 17.55, 21.60, 21.75, 39.34, 50.92, 54.16, 72.51, 79.21, 124.24, 127.65, 128.23, 129.24, 130.17, 131.41, 131.74, 132.17, 132.80, 133.90, 140.84 and 147.90; *m*/*z* (CI) 436 (M^+ + 18, 10%), 419 (M^+ + 1, 5), 389 (20), 232 (40) and 94 (100).

(4*RS*,5*SR*)-5-Cyclobutyl-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 52

Thiophenol (80 μL, 0.78 mmol) was added at room temperature to a mixture of the 2-nitrophenylsulfonamide **51** (256 mg, 0.61 mmol) and potassium carbonate (296 mg, 2.14 mmol) in

N,*N*-dimethylformamide (15 cm^3) and the mixture was stirred for 24 h. Ethyl acetate (25 cm^3) and water (25 cm^3) were added and the aqueous layer was extracted with ethyl acetate (5 × 25 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–methanol (3 : 1) containing 1% triethylamine gave the *title compound* **52** (122 mg, 86%) as an amorphous colourless solid (found: M^+ + H, 234.1498. $C_{14}H_{20}NO_2$ requires *M*, 234.1494); ν_{max} 3363, 3059, 1667, 1652, 1446, 1264, 1148, 1083, 1000, 967, 755 and 734; δ_H (300 MHz) 1.32 (1 H, m), 1.69–1.88 (3 H, m), 2.07–2.28 (2 H, m), 2.88 (1 H, m, CH), 3.05 (1 H, d, *J* 13.5, 3-H), 3.18 (1 H, dd, *J* 3.5, 13.5, 3-H′), 3.26 (3 H, br. s, 2 × OH, NH), 3.66 (1 H, d, *J* 3.5, 4-H), 3.84 and 4.00 (each 1 H, d, *J* 15, 1-H), 7.01 (1 H, d, *J* 7.5, ArH), 7.16 and 7.28 (each 1 H, t, *J* 7.5, ArH) and 7.80 (1 H, d, *J* 7.5, ArH); δ_C (75 MHz) 17.59, 21.57, 21.81, 39.66, 51.92, 55.84, 73.16, 79.79, 126.90, 127.10, 128.85, 129.53, 136.34 and 141.73; *m*/*z* (CI) 234 (M^+ + 1, 100%).

(4*RS*,5*SR*)-2-Butyl-5-cyclobutyl-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 53

Butanal (150 μL, 1.70 mmol), sodium triacetoxyborohydride (359 mg, 1.70 mmol) and glacial acetic acid (32 μL, 0.56 mmol) were added to the crude tetrahydrobenzazepine **52** in THF (10 cm^3) prepared from the 2-nitrophenylsulfonamide **51** (472 mg, 1.13 mmol), thiophenol (130 μL, 1.27 mmol) and potassium carbonate (500 mg, 3.62 mmol) in *N*,*N*-dimethylformamide (20 cm^3). After stirring at room temperature for 15 h, ether (25 cm^3) and water (25 cm^3) were added and the mixture was basified to *ca.* pH 10 with aqueous sodium hydroxide (1 M). The aqueous layer was extracted with ether (5 × 25 cm^3) and the ethereal extracts were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (3 : 1 → 1 : 1) containing triethylamine (1%) as eluent gave the *title compound* **53** (172 mg, 53%) as a colourless solid recrystallised from ethyl acetate as colourless needles, m.p. 96–98 °C (found: M^+ + H, 290.2108. $C_{18}H_{28}NO_2$ requires *M*, 290.2120); ν_{max} ($CDCl_3$) 3437, 3054, 1265 and 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7, 4′-H_3), 1.33 (3 H, m, 3′-H_2 and 3″-H), 1.49–1.59 (2 H, m, 2 × CH), 1.71–1.87 (3 H, m), 2.14–2.29 (2 H, m), 2.55–2.68 (2 H, m, 1′-H_2), 2.82 (1 H, pent, *J* 8.5, CH), 2.90 (1 H, dd, *J* 1, 13, 3-H), 3.04 (2 H, br. s, 2 × OH), 3.11 (1 H, ddd, *J* 2.5, 5, 13, 3-H′), 3.64 (1 H, dd, *J* 2.5, 14.5, 1-H), 3.71 (1 H, d, *J* 5, 4-H), 3.76 (1 H, d, *J* 14.5, 1-H′), 7.05 (1 H, dd, *J* 1, 7.5, ArH), 7.17 (1 H, dt, *J* 1.5, 7.5, ArH), 7.26 (1 H, dt, *J* 1, 7.5, ArH) and 7.81 (1 H, dd, *J* 1.5, 7.5, ArH); δ_C (75 MHz, $CDCl_3$) 13.99, 17.75, 20.39, 21.70, 21.80, 29.59, 39.68, 59.45, 59.59, 63.28, 73.03, 79.56, 126.98, 127.12, 129.05, 129.95, 135.49 and 141.81; *m*/*z* (CI) 290 (M^+ + 1, 100%).

5-Cyclobutyl-5-hydroxy-2-(2-nitrophenylsulfonyl)-1,2,3,5-tetrahydro-[1*H*]-2-benzazepin-4-one 54

Dimethyl sulfoxide (120 μL, 0.1.69 mmol) was added dropwise at −78 °C to oxalyl chloride (84 μL, 0.963 mmol) in dichloromethane (2 cm^3) and the solution was stirred at −78 °C for 10 min before the diol **51** (100 mg, 0.239 mmol) in dichloromethane (2 cm^3) was added. The mixture was stirred for 15 min at −78 °C before triethylamine (200 μL, 1.435 mmol) was added and then for a further 15 min before saturated aqueous ammonium chloride (10 cm^3) was added. The mixture was warmed to room temperature, dichloromethane (10 cm^3) was added, and the aqueous phase was extracted with dichloromethane (2 × 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1 : 1) as eluent gave the *title compound* **54** (57 mg, 58%) as a viscous yellow oil (found: M^+ + NH_4, 434.1377. $C_{20}H_{24}N_3O_6S$ requires *M*, 434.1386); ν_{max} ($CDCl_3$) 3481, 3092, 1713, 1545, 1440, 1361, 1168, 1126 and 1095 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.51–1.84 (5 H, m), 2.31 (1 H, m), 3.27 (1 H, m, CH), 3.99 and 4.12 (each 1 H, d, *J* 17, 1-H and 3-H), 4.59 and 4.90 (each 1 H, dd, *J* 2.5, 17, 1-H′ and 3-H′), 7.06 (1 H, d, *J* 7, ArH), 7.15–7.29 (2 H, m, ArH), 7.60–7.74 (4 H, m, ArH) and 7.96 (1 H, dd, *J* 2, 7, ArH); δ_C (75 MHz, $CDCl_3$) 16.79, 21.52, 21.71, 42.36, 53.14, 57.07, 83.70, 124.42, 127.83, 127.94, 128.11, 128.24, 129.37, 131.03, 131.60, 131.93, 133.71, 134.25, 139.05 and 206.40; *m*/*z* (CI) 434 (M^+ + 18, 20%) and 230 (100).

2-Butyl-5-cyclobutyl-5-hydroxy-1,2,3,5-tetrahydro-[1*H*]-2-benzazepin-4-one 55

Dimethyl sulfoxide (162 μL, 2.28 mmol) was added dropwise at −78 °C to oxalyl chloride (120 μL, 1.38 mmol) in dichloromethane (5 cm^3) under nitrogen. After 10 min, the diol **53** (132 mg, 0.46 mmol) in dichloromethane (4 cm^3) was added dropwise by syringe and the stirring was continued for 2 h during which time the temperature was allowed to rise from −78 °C to 0 °C. Triethylamine (0.38 cm^3, 2.72 mmol) was added and, after a further 15 min, ether (15 cm^3) and water (15 cm^3) were added. The aqueous layer was extracted with ether (3 × 25 cm^3) and the organic extracts were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (5 : 1) containing triethylamine (1%) gave the *title compound* **55** (96 mg, 73%) as a yellow oil (found: M^+ + H, 288.1972. $C_{18}H_{26}NO_2$ requires *M*, 288.1963); ν_{max} 3469, 3156, 3054, 1728, 1705, 1466, 1455, 1375, 1264, 1249 and 1168 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7.25, 4′-H_3), 1.32 (2 H, sex, *J* 7.25, 3′-H_2), 1.45–1.53 (2 H, m, CH_2), 1.68 (1 H, m), 1.79 (3 H, m), 1.90 and 2.29 (each 1 H, m), 2.38–2.45 (2 H, m), 3.54 (1 H, dd, *J* 1, 16, 1-H), 3.59 (1 H, pent, *J* 8, CH), 3.74 (1 H, d, *J* 16, 1-H′), 3.95 and 4.18 (each 1 H, d, *J* 16, 3-H), 7.06 (1 H, dd, *J* 1, 7.5, ArH), 7.21 and 7.25 (each 1 H, dt, *J* 1, 7.5, ArH) and 7.86 (1 H, dd, *J* 1.5, 7.5, ArH); δ_C (100 MHz, $CDCl_3$) 13.85, 17.20, 20.20, 21.66, 21.78, 29.23, 41.51, 54.47, 60.35, 64.11, 83.91, 127.16, 127.24, 127.37, 129.42, 134.86, 138.34 and 208.01; *m*/*z* (CI) 288 (M^+ + 1, 100%).

(4*SR*,5*RS*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-phenylmethyl-*N*-trifluoroacetyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 67

The crude diol **52** [prepared from the 2-nitrophenylsulfonamide **51** (120 mg, 0.287 mmol), potassium carbonate (129 mg, 0.933 mmol) and thiophenol (44 μL, 0.428 mmol) in *N*,*N*-dimethylformamide (5 cm^3)], the aldehyde **56**[34] (223 mg, 0.861 mmol) and sodium cyanoborohydride (18 mg, 0.286 mmol) were dissolved in

methanol (5 cm^3) containing a drop of conc. aqueous hydrogen chloride and the solution was stirred at room temperature for 15 h. The mixture was extracted with ether (5 × 25 cm^3) which was washed with aqueous sodium hydroxide (1 M, 25 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (3 : 1 → 1 : 1) containing triethylamine (1%) as eluent gave the *title compound* **67** (104 mg, 76%), as an oil, a 60 : 40 mixture of rotamers (found: M^+, 476.2287. $C_{26}H_{31}F_3N_2O_3$ requires *M*, 476.2290); δ_H (300 MHz, $CDCl_3$) 1.37 (1 H, m), 1.63–1.91 (4 H, m), 2.14–3.10 (9 H, m), 3.20–3.90 (5 H, m), 4.52 (0.4 H, d, *J* 14.5, NHC*H*Ph), 4.56 and 4.69 (each 0.6 H, d, *J* 15.5, NHC*H*Ph), 4.82 (0.4 H, d, *J* 14.5, NHC*H*Ph), 7.05–7.18 (2 H, m, ArH), 7.22 (1 H, m, ArH), 7.25–7.45 (5 H, m, ArH) and 7.84 (1 H, m, ArH); *m*/*z* (CI) 477 (M^+ + 1, 100%).

5-Cyclobutyl-5-hydroxy-2-[3-(*N*-phenylmethyl-*N*-trifluoroacetyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 68

Dimethyl sulfoxide (133 μL, 1.87 mmol) was added to oxalyl chloride (98 μL, 1.12 mmol) in dichloromethane (3 cm^3) at −78 °C. After 10 min, the hydroxytetrahydrobenzazepine **67** (179 mg, 0.376 mmol) in dichloromethane (5 cm^3) was added and the reaction mixture was allowed to warm to 0 °C over 1 h. Triethylamine (0.31 cm^3, 2.22 mmol) was added and, after 30 min, water (25 cm^3) and ether (25 cm^3). The aqueous layer was extracted with ether (4 × 25 cm^3) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (5 : 1) containing triethylamine (1%) as eluent gave the *title compound* **68** (120 mg, 67%), a mixture of rotamers, as a yellow oil (found: M^+ + H, 475.2205. $C_{26}H_{30}F_3N_2O_3$ requires *M*, 475.2208); ν_{max} 3466, 3065, 1690, 1452, 1202 and 1144 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.49–1.98 (8 H, m), 2.18–2.40 (2 H, m, CH_2), 3.28–3.60 (4 H, m), 3.74–3.90 (2 H, m), 4.23 (1 H, m), 4.55–4.73 (3 H, m, CH_2 and OH), 6.98 (1 H, m, ArH), 7.10–7.45 (7 H, m, ArH) and 7.77 (1 H, m, ArH); *m*/*z* (CI) 475 (M^+ + 1, 5%), 261 (40), 221 (80), 108 (100) and 91 (90).

5-Cyclobutyl-5-hydroxy-2-[3-(phenylmethylamino)propyl]-1,2,3,5-tetrahydro-[1*H*]-2-benzazepin-4-one 69

Potassium carbonate (117 mg, 0.847 mmol) in water (0.6 cm^3) was added to the trifluoroacetamide **68** (80 mg, 0.169 mmol) in methanol (10 cm^3) and the solution was stirred for 24 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (1 : 2) containing triethylamine (1%) as eluent gave the *title compound* **69** (50 mg, 80%) as a yellow oil (found: M^+ + H, 379.2381. $C_{24}H_{31}N_2O_2$ requires *M*, 379.2385); δ_H (300 MHz, $CDCl_3$) 1.41–1.88 (7 H, m), 2.20 (1 H, m), 2.38 (2 H, dt, *J* 3.5, 7, CH_2), 2.59 (2 H, t, *J* 7, CH_2), 3.45 (1 H, m, CH), 3.45 and 3.68 (each 1 H, d, *J* 16, 1-H), 3.69 (2 H, s, $ArCH_2N$), 3.85 and 4.14 (each 1 H, d, *J* 16, 3-H), 6.97 (1 H, d, *J* 7.5, ArH), 7.11 (1 H, dt, *J* 1.5, 7.5, ArH), 7.14–7.26 (6 H, m, ArH) and 7.67 (1 H, d, *J* 7.5, ArH); δ_C (75 MHz, $CDCl_3$) 17.16, 21.55, 21.71, 27.35, 30.25, 41.71, 47.08, 52.50, 60.14, 64.07, 83.99, 126.96, 127.29, 127.41, 128.04, 128.35, 129.59, 134.49, 138.38 and 207.74; *m*/*z* (CI) 379 (M^+ + 1, 50%), 284 (50), 267 (55) and 108 (100).

(4*SR*,5*RS*)-5-Cyclobutyl-4,5-dihydroxy-2-[2-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethylamino)-ethyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 70

Sodium cyanoborohydride (33 mg, 0.525 mmol) and concentrated aqueous hydrogen chloride (1 drop) were added to the tetrahydrobenzazepine **52** (122 mg, 0.524 mmol) and the aldehyde **59** (350 mg, 1.048 mmol) in methanol (5 cm^3) at room temperature. After 15 h, ethyl acetate (25 cm^3) and water (25 cm^3) were added and the pH was adjusted to *ca.* 12 with aqueous sodium hydroxide (1 M). The aqueous phase was extracted with ethyl acetate (2 × 25 cm^3) and dichloromethane (3 × 25 cm^3). The organic extracts were dried ($MgSO_4$), silica (*ca.* 2.5 g) was added and the mixture was concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1 : 1) → neat ethyl acetate containing triethylamine (1%) as the eluent gave the *title compound* **70** (189 mg, 66%) as a viscous yellow oil (found: M^+ + H, 552.2172. $C_{29}H_{34}N_3O_6S$ requires *M*, 552.2168); ν_{max} ($CDCl_3$) 3468, 3065, 1544, 1455, 1370, 1162, 1068, 1000 and 911 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (1 H, m), 1.57–1.77 (3 H, m), 2.05–2.22 (2 H, m), 2.50–2.62 (2 H, m, 1′-H_2), 2.71 (1 H, pent, *J* 8.5, CH), 2.82–2.93 (2 H, m, 3-H_2), 3.25–3.50 (3 H, m, 1-H, 2′-H_2), 3.58 (1 H, d, *J* 3.5, 4-H), 3.69 (1 H, d, *J* 15, 1-H′), 4.40 and 4.48 (each 1 H, d, *J* 14 NHC*H*Ph), 6.91 (1 H, d, *J* 7.5, ArH), 7.10 (1 H, dt, *J* 1.5, 7.5, ArH), 7.18–7.31 (6 H, m, ArH), 7.53–7.67 (3 H, m, ArH), 7.73 (1 H, dd, *J* 1.5, 8, ArH) and 7.95 (1 H, d, *J* 8, ArH); δ_C (100 MHz, $CDCl_3$) 17.72, 21.67, 21.79, 39.60, 45.52, 52.18, 57.54, 60.17, 62.96, 73.06, 79.30, 124.22, 126.86, 127.17, 128.09, 128.16, 128.70, 128.82, 130.17, 130.79, 131.61, 133.11, 133.46, 134.49, 135.16, 141.43 and 147.83;. *m*/*z* (CI) 552 (M^+ + 1, 2%), 363 (10) and 108 (100).

5-Cyclobutyl-4-hydroxy-2-[2-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethylamino)ethyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 71

Dimethyl sulfoxide (60 μL, 0.846 mmol) was added to oxalyl chloride (42 μL, 0.481 mmol) in dichloromethane (1 cm^3) at −78 °C followed, after 15 min, by the addition of the diol **70** (60 mg, 0.109 mmol) in dichloromethane (2 cm^3). The mixture was allowed to warm to −10 °C, then triethylamine (100 μL, 0.718 mmol) was added. After 30 min, water (20 cm^3) and ether (20 cm^3) were added and the aqueous phase was extracted with ether (4 × 20 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (3 : 1 → 1 : 1) containing triethylamine (1%) as eluent gave the *title compound* **71** (46 mg, 77%) as a yellow oil (found: M^+ + H, 550.2021. $C_{29}H_{32}N_3O_6S$ requires *M*, 550.2012); ν_{max} 3466, 3065, 1698, 1544, 1454, 1369 and 1163 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.55 (1 H, m), 1.65–1.88 (4 H, m), 2.22 (1 H, pent, *J* 9, CH), 2.33 (2 H, t, *J* 7, 1′-H_2), 3.34–3.39 (3 H, m), 3.38 and 3.64 (each 1 H, d, *J* 15, 1-H), 3.76 and 4.04 (each 1 H, d, *J* 16, 3-H), 4.50 (2 H, s, NCH_2Ph), 4.54 (1 H, br. s, OH), 6.91 (1 H, d, *J* 7.5, ArH), 7.10 (1 H, dt, *J* 1.5, 7.5, ArH), 7.18–7.31 (6 H, m, ArH), 7.53–7.67 (3 H, m, ArH), 7.73 (1 H, dd, *J* 1.5, 8, ArH) and 7.95 (1 H, dd, *J* 1, 8, ArH); *m*/*z* (CI) 550 (M^+ + 1, 20%), 363 (40), 106 (90) and 94 (100).

5-Cyclobutyl-5-hydroxy-2-[2-(phenylmethylamino)ethyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 72

Potassium carbonate (212 mg, 1.534 mmol) and thiophenol (60 μL, 0.584 mmol) were added to the 2-nitrophenylsulfonamide **71** (260 mg, 0.474 mmol) in *N*,*N*-dimethylformamide (5 cm^3). After 18 h, water (25 cm^3) and ethyl acetate (25 cm^3) were added, and the aqueous layer was extracted with ethyl acetate (5 × 15 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1 : 1 → 1 : 2) containing triethylamine (1%) as eluent gave the *title compound* **72** (90 mg, 52%) as a yellow oil (found: M^+ + H, 365.2220. $C_{23}H_{29}N_2O_2$ requires *M*, 365.2229); ν_{max} 3454, 3054, 1693, 1673, 1453, 1265, 1133 and 1106 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.44 (1 H, m), 1.58–1.76 (4 H, m), 2.08–2.16 (1 H, m), 2.48 and 2.71 (each 2 H, t, *J* 6, 1′-H_2 and 2′-H_2), 3.26 (1 H, pent, *J* 8.5, CH), 3.44 and 3.75 (each 1 H, d, *J* 15.5, 1-H), 3.76 (1 H, d, *J* 16.5, 3-H), 3.90 and 3.96 (each 1 H, d, *J* 13.5, NHC*H*Ph), 4.15 (1 H, d, *J* 16.5, 3-H′), 6.84 (1 H, d, *J* 7.5, ArH), 7.05 (1 H, dt, *J* 1, 7.5, ArH), 7.11–7.36 (6 H, m, ArH) and 7.64 (1 H, d, *J* 7.5, ArH); *m*/*z* (CI) 365 (M^+ + 1, 80%), 347 (30%), 108 (100) and 74 (80).

5-Cyclobutyl-2,3-dihydro-[1*H*]-2-benzazepine 82

Potassium carbonate (0.63 g, 4.56 mmol) and thiophenol (0.19 g, 1.69 mmol) were added to the 2-nitrobenzene sulfonamide **50** (0.50 g, 1.302 mmol) in *N*,*N*-dimethylformamide (33 cm^3) at room temperature and the mixture was stirred for 16 h. Deionised water (50 cm^3) was added and the aqueous phase was extracted with ethyl acetate (5 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **82** (0.259 g, 1.302 mmol, *ca.* 100%) as an oil used without further purification (found: M^+ + H, 200.1434. $C_{14}H_{17}N$ requires *M*, 200.1439); ν_{max} 3059, 1713, 1633, 1589, 1563, 1517, 1334, 1304, 851, 752 and 734; δ_H (300 MHz, $CDCl_3$) 1.6–2.2 (6 H, m), 3.16 (2 H, d *J* 7, 3-H_2), 3.22 (1 H, pent, *J* 7.5, 1′-H), 3.84 (2 H, s, 1-H_2), 5.85 (2 H, br. m, 2-H and 4-H) and 7.1–7.6 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.94, 28.47, 39.85, 40.76, 47.07, 117.57, 126.24, 128.07, 128.67, 130.40, 133.72, 140.16 and 151.68; *m*/*z* (CI) 200 (M^+ + 1, 100%).

5-Cyclobutyl-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)-aminopropanoyl]-2,3-dihydro-[1*H*]-2-benzazepine 83

O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) (177.5 mg, 0.553 mmol) and diisopropylethylamine (130 mg, 1.01 mmol) were added to the sulfonylaminopropanoic acid **81** (183 mg, 0.50 mmol) in dichloromethane (3.2 cm^3) at 0 °C and the reaction mixture was stirred for 15 min before the dihydrobenzazepine **82** (100 mg, 0.50 mmol) in dichloromethane (1 cm^3) was added. The reaction mixture was stirred at room temperature overnight, dichloromethane (10 cm^3) was added and the mixture was washed with aqueous hydrogen chloride (3 × 15 cm^3), deionised water (1 × 15 cm^3), saturated aqueous ammonium chloride (3 × 15 cm^3) and deionised water (1 × 15 cm^3) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1 : 1) containing triethylamine (1%) as eluent gave the *title compound* **83** (215 mg, 79%) as an oil (found: M^+ + H, 546.2069. $C_{30}H_{32}N_3O_5S$ requires *M*, 546.2063); ν_{max} 3059, 1669, 1634, 1543, 1455, 1434, 1372, 1346, 1162, 768 and 736; δ_H (300 MHz, dimethyl sulfoxide-*d*6, 150 °C) 1.80 (1 H, m), 1.87–2.02 (3 H, m), 2.17–2.28 (2 H, m), 2.52 (2 H, t, *J* 7.5, 2′-H_2), 3.51–3.73 (5 H, m), 4.22 (2 H, s, 1-H_2), 4.57 (2 H, s, ArCH_2N), 5.87 (1 H, dt, *J* 2, 7, 4-H), 7.38–7.23 (9 H, m, Ar-H), 7.88–7.76 (3 H, m, Ar-H) and 8.01 (1 H, d, *J* 12, ArH); δ_C (75.5 MHz, dimethyl sulfoxide-*d*6, 150 °C) 17.94, 28.92, 28.96, 33.30, 43.37, 43.41, 45.02, 48.81, 52.51, 120.33, 124.99, 126.93, 128.00, 128.33, 128.39, 128.83, 129.11, 129.84, 130.72, 132.87, 134.94, 136.43, 137.09, 139.92, 147.01 and 168.63; *m*/*z* (CI) 546 (M^+ + 1, 3%), 481 (3), 359 (35), 198 (90) and 94 (100).

(4*SR*,5*RS*)-5-Cyclobutyl-4,5-dihydroxy-2-[3-(*N*-phenylmethyl)-aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 86

The *N*-acyltetrahydrobenzazepine **85** (48 mg, 0.12 mmol) in tetrahydrofuran (1 cm^3) was added to the borane in tetrahydrofuran (1 M, 0.61 cm^3, 0.61 mmol) cooled to 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and deionised water (1 cm^3) was added followed by aqueous hydrogen chloride (1 M, 1 cm^3). The reaction mixture was then heated under reflux for 1 h, cooled and concentrated under reduced pressure. The solid residue was dissolved in deionised water (~3 cm^3) and the pH was adjusted to 12 by the addition of solid sodium hydroxide. The aqueous phase was then extracted with dichloromethane (3 × 10 cm^3) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **86** (27 mg, 57%) as an oil (found: M^+ + H, 381.2547. $C_{24}H_{33}N_2O_2$ requires *M*, 381.2543); ν_{max} 3406, 3059, 3023, 1455, 1310, 1277, 1243, 1217, 1158, 1142, 1081, 998, 747 and 699; δ_H (300 MHz, $CDCl_3$) 1.35 (1 H, m) 1.73–1.96 (5 H, m), 2.14–2.33 (2 H, m, CH_2), 2.64–2.83 (5 H, m), 2.87 (1 H, d, *J* 13, 3-H), 3.16 (1 H, br. s, OH), 3.24 (1 H, ddd, *J* 13, 5, 2, 3-H′), 3.88–3.61 (5 H, m), 7.05 (1 H, d, *J* 8, ArH), 7.16–7.37 (7 H, m, ArH) and 7.85 (1 H, d, *J* 8, ArH); δ_C (75.5 MHz, $CDCl_3$) 17.97, 21.90, 22.12, 26.79, 39.91, 47.59, 53.32, 58.86, 59.21, 64.46, 73.21, 79.47, 127.20, 127.57, 127.75, 128.69, 128.89, 129.33, 130.29, 135.31 and 142.41; *m*/*z* (CI) 381 (M^+ + 1, 100%).

5-Cyclopentyl-2-(2-nitrophenylsulfonyl)-2,3-dihydro-[1*H*]-2-benzazepine 95

A solution of the dienylamine **94** (1.00 g, 2.40 mmol) in dichloromethane (100 cm^3) was degassed by repeated freezing under a nitrogen atmosphere and thawing under reduced pressure. Grubbs' II catalyst (99 mg, 0.174 mmol) was added and the resulting mixture was heated in a sealed tube at 45 °C for 24 h. It was then filtered and concentrated under reduced pressure. Chromatography of the residue using dichloromethane as eluent gave the *title compound* **95** (380 mg, 40%) as a colourless oil (found: M^+ + Na, 421.1189. $C_{21}H_{22}N_2O_4SNa$ requires *M*, 421.1192); ν_{max} 1540, 1354, 1163, 1126, 1065, 914 and 777 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.36 (2 H, m), 1.54–1.68 (4 H, m), 1.84 (2 H, m), 2.98 (1 H, m), 3.61 (2 H, d *J* 7.5, 3-H_2), 4.24 (2 H, s, 1-H_2), 5.89 (1 H, dt, *J* 1.5, 7.5, 4-H), 7.29 (1 H, m, ArH), 7.35–7.41 (3 H, m, ArH), 7.64–7.72 (3 H, m, ArH) and 8.03 (1 H, dd, *J* 1.5, 7.5, ArH); δ_C (125 MHz, $CDCl_3$) 152.15, 141.89, 133.31, 131.87, 130.17, 128.90, 128.36, 127.53, 127.51, 126.76, 126.61, 124.58, 116.76, 49.61, 45.22, 43.40, 32.03 and 24.82; *m*/*z* (ES) 437 (100%) and 421 (M^+ + 23, 25).

(4*RS*,5*SR*)-5-Cyclopentyl-2-(3-phenylmethylamino)propyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 100

N-Methylmorpholine-*N*-oxide (4.2 mg, 0.0413 mmol) and osmium tetraoxide (1 mg, 0.00376 mmol) were added to the dihydrobenzazepine **97** (21 mg, 0.0376 mmol) in acetone (1 cm^3), *tert*-butanol (1 cm^3) and water (270 μL) and the mixture was stirred for 16 h at room temperature then was poured into rapidly stirred aqueous sodium sulfite (5 cm^3). The mixture was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (3 : 7) as eluent gave 5-cyclopentyl-4,5-dihydroxy-2-[3-*N*-(2-nitrophenylsulfonyl)-*N*-(phenylmethyl)amino]propanoyl-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **98** (117 mg, 91%), a mixture of rotamers, as a colourless oil (found: M^+ + H, 594.2272. $C_{31}H_{36}N_3O_7S$ requires *M*, 594.2268); ν_{max} 3436, 1631, 1543, 1452, 1371 and 1162 cm^{-1}; *m*/*z* (ES) 616 (100%) and 594 (M^+ + 1, 50).

Potassium carbonate (49 mg, 0.36 mmol) and thiophenol (14.5 μL, 0.134 mmol) were added to 2-nitrobenzene sulfonamide **98** (59 mg, 0.103 mmol) in *N*,*N*-dimethylformamide (1.5 cm^3) and the solution was stirred for 24 h. Water (3 cm^3) was added and the mixture extracted with ethyl acetate (3 × 5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using methanol–ethyl acetate (1 : 4) containing triethylamine (1%) as eluent gave 5-cyclopentyl-4,5-dihydroxy-2-[3-(*N*-phenylmethyl)aminopropanoyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **99** (22 mg, 75%), a mixture of rotamers, as a colourless oil (found: M^+ + H, 409.2487. $C_{25}H_{33}N_2O_3$ requires *M*, 409.2486); ν_{max} 3412, 1633 and 1453 cm^{-1}; *m*/*z* (ES) 409 (M^+ + 1, 100%).

Borane–tetrahydrofuran complex (1 M in THF; 7.72 mmol, 7.72 cm^3) was added to the 2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **99** (590 mg, 1.54 mmol) in THF (15 cm^3) and the mixture was stirred for 16 h at room temperature. Aqueous hydrogen chloride (1 M; 1 cm^3) and water (1 cm^3) were added and the reaction mixture was heated at 80 °C for 1 h then cooled and extracted with ethyl acetate (3 × 5 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using methanol–ethyl acetate (1 : 4) containing triethylamine (1%) gave the *title compound* **100** (360 mg, 60%) as a colourless oil (found: M^+ + H, 395.2688. $C_{25}H_{35}N_2O_2$ requires *M*, 395.2693); ν_{max} 3391, 1453, 1320 and 1062 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.75–0.86 (2 H, m), 1.18–1.26 (2 H, m), 1.41–1.67 (6 H, m), 1.82 (1 H, m), 2.26 (1 H, m), 2.51–2.68 (4 H, m, 2 × CH_2), 2.87 (1 H, d, *J* 13.5, 3-H), 3.10 (1 H, br. s, OH), 3.15 (1 H, dd, *J* 13.5, 3, 3-H′), 3.47 (1 H, dd, *J* 14.5, 2, 1-H), 3.57 and 3.62 (each 1 H, d, *J* 13, NHC*H*Ph), 3.79 (1 H, d, *J* 14.5, 1-H′), 3.88 (1 H, m, 4-H), 6.59 (1 H, d, *J* 7, ArH), 7.01 (1 H, m, ArH), 7.10 (1 H, dt, *J* 7.5, 1, ArH), 7.16–7.20 (5 H, m, ArH) and 7.75 (1 H, d, *J* 8, ArH); δ_C (125 MHz, $CDCl_3$) 25.00, 25.61, 26.18, 26.90, 27.30, 44.53, 47.71, 53.40, 59.01, 59.30, 64.55, 74.69, 80.41, 127.17, 127.29, 128.75, 128.97, 129.34, 129.51, 130.42, 130.56, 135.43 and 144.48; *m*/*z* (ES) 396 (25%) and 395 (M^+ + 1, 100).

5-Cyclopentyl-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)-aminopropyl]-4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 101

Sodium carbonate (79 mg, 0.739 mmol), tetra-*n*-butylammonium iodide (25 mg, 0.067 mmol) and 2-nitrophenylsulfonyl chloride (149 mg, 0.673 mmol) were added to the 2-aminopropyltetrahydrobenzazepine **100** (43 mg, 0.11 mmol) in acetone (5 cm^3) and water (3.25 cm^3) and the solution was stirred for 4 h at room temperature then extracted with ethyl acetate (2 × 15 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* **101** as an oil used without further purification (found: M^+ + H, 580.2481. $C_{31}H_{38}N_3O_6S$ requires *M*, 580.2476); ν_{max} 3435, 1543, 1371 and 1162 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.8 (1 H, m), 1.2 (2 H, m), 1.35–1.63 (7 H, m), 2.18, 2.28 and 2.44 (each 1 H, m), 2.68–2.85 (2 H, m), 3.14 (2 H, m, 3-H_2), 3.32 and 3.57 (each 1 H, d, *J* 10, 1-H), 3.64 (1 H, m, 4-H), 4.30 and 4.42 (each 1 H, d, *J* 12, NHC*H*Ph), 6.86 (1 H, d, *J* 7, ArH), 7.02–7.2 (7 H, m, ArH), 7.47 (1 H, dt, *J* 1.5, 7, ArH), 7.5–7.6 (2 H, m, ArH) and 7.70 and 7.80 (each 1 H, d, *J* 7.5, ArH); *m*/*z* (ES) 580 (M^+ + 1, 100%).

5-Cyclopentyl-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)-aminopropyl]-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 102

Pyridine (19 mg, 0.248 mmol) was added to the Dess–Martin periodinane (21 mg, 0.049 mmol) in dichloromethane (1 cm^3) and the mixture was stirred for 20 min then added to the 4,5-dihydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine **101** (24 mg, 0.0414 mmol) in dichloromethane (1 cm^3). After 2 h, aqueous sodium sulfite (1 cm^3) was added and the mixture was stirred for 1 h then extracted with dichloromethane (3 × 5 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using methanol–ethyl acetate (1 : 4) containing triethylamine (1%) as eluent gave the *title compound* **102** (17 mg, 60%) as a colourless oil (found: M^+ + H, 578.2318. $C_{31}H_{36}N_3O_6S$ requires *M*, 578.2319); ν_{max} 3430, 1649, 1452, 1364 and 1076 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.80–1.65 (10 H, m), 2.05–2.18 (2 H, m, 1′-H_2), 2.90 (1 H, quin, *J* 8.5, 1″-H), 3.18 and 3.28 (each 1 H, m, 3′-H), 3.40 (1 H, d, *J* 15), 3.74 (1 H, d, *J* 16) 3.92 (1 H, d, *J* 15), 4.23 (1 H, d, *J* 16), 4.34 (1 H, br. s, OH), 4.41 and 4.44 (each 1 H, d, *J* 14, NHC*H*Ph), 6.93 (1 H, d, *J* 7.5, ArH), 7.18 (1 H, t, *J* 7, ArH), 7.27–7.33 (5 H, m, ArH), 7.58–7.71 (4 H, m, ArH) and 7.83 and 7.96 (each 1 H, d, *J* 8, ArH); *m*/*z* (ES) 601 (25%), 600 (70) and 578 (M^+ + 1, 100).

5-Cyclopentyl-2-[3-(phenylmethylamino)propyl]-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 103

Potassium carbonate (49 mg, 0.36 mmol) and thiophenol (19 mg, 0.173 mmol) were added to the 2-nitrophenylsulfonamide **102** (100 mg, 0.173 mmol) in *N*,*N*-dimethylformamide (3.5 cm^3) and the solution was stirred for 24 h. Water (3 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 5 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using methanol–ethyl acetate (1 : 4) containing triethylamine (1%) as eluent gave the *title compound* **103** (50 mg, 75%) as a colourless oil (found: M^+ + H, 393.2542. $C_{25}H_{33}N_2O_2$ requires *M*, 393.2537); ν_{max} 3437, 1668, 1520, 1454, 1361, 1208, 1176 and 1026 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.80 (1 H, m), 1.08–1.70 (9 H, m), 2.27 and 2.55 (each 2 H, m, 1′-H_2 and 3′-H_2), 3.03 (1 H, quin, *J* 8, 1″-H), 3.48 (1 H, d, *J* 15.5, 1-H), 3.69 (2 H, s, CH_2Ph), 3.83 (1 H, d, *J* 16, 3-H), 3.98 (1 H, d, *J* 15.5, 1-H′), 4.32 (1 H, d, *J* 16, 3-H′), 4.38 (1 H, br. s, NH), 6.98

(1 H, d, *J* 7, ArH), 7.10–7.16 (6 H, m, ArH), 7.42 (1 H, m, ArH) and 7.78 (1 H, dd, *J* 8, 1, ArH); *m/z* (ES) 393 (M^+ + 1, 100%).

5-Cyclobutyl-8-fluoro-2-(2-nitrophenyl)sulfonyl-2,3-dihydro-[1*H*]-2-benzazepine 115

Grubbs' II catalyst (313 mg, 5 mol%) was added to the diene **114** (3.20 g, 7.44 mmol) in degassed dichloromethane (500 cm^3) at room temperature under nitrogen and the reaction was heated under reflux for 20 h then filtered through celite and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum (1 : 1) as eluent gave the *title compound* **115** (2.90 g, 97%) (found: M^+, 402.1041. $C_{20}H_{19}FN_2O_4S$ requires *M*, 402.1050); ν_{max} 1549, 1492, 1461, 1377, 1355, 1244 and 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.58–2.12 (6 H, m, 3 × CH_2), 3.33 (1 H, m, 1′-H), 3.55 (2 H, d, *J* 7, 3-H_2), 4.16 (2 H, s, 1-H_2), 5.77 (1 H, td, *J* 7, 2, 4-H), 6.91–7.02 (2 H, m, ArH), 7.16 (1 H, dd, *J* 8, 5.5, ArH), 7.70–7.52 (3 H, m, ArH) and 7.94 (1 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.75, 28.30, 39.63, 43.09, 48.80, 115.22 and 115.50 (d, $^2J_{C\text{-}F}$ 21), 116.41 and 116.70 (d, $^2J_{C\text{-}F}$ 22), 116.93, 124.10, 127.77 and 127.88 (d, $^3J_{C\text{-}F}$ 8), 130.54, 131.56, 132.70, 133.54, 135.33 and 135.42 (d, $^3J_{C\text{-}F}$ 7), 135.83 and 135.87 (d, $^4J_{C\text{-}F}$ 3), 148.07, 150.19, and 160.06 and 163.36 (d, $^1J_{C\text{-}F}$ 247.5); *m/z* (CI) 420 (M^+ + 18, 40%), 297 (20) and 232 (100).

(4*RS*,5*SR*)-5-Cyclobutyl-8-fluoro-2-(2-nitrophenyl)sulfonyl-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 116

N-Methylmorpholine-*N*-oxide (592 mg, 4.98 mmol) was added to the dihydrobenzazepine **115** (500 mg, 1.244 mmol) and osmium tetraoxide (48 mg, 15 mol%) in acetone and water (5 : 1, 60 cm^3) and the mixture was stirred at room temperature for 48 h. Aqueous sodium sulfite was added and the mixture was concentrated under reduced pressure. Chromatography of the residue using ether as eluent followed by repeated chromatography using methanol–ether (1 : 19) as eluent gave the *title compound* **116** (526 mg, 97%) as an oil (found: $M^+ + NH_4$, 454.1445. $C_{20}H_{25}FN_3O_6S$ requires *M*, 454.1448); ν_{max} 3542–3435, 1609, 1590, 1541, 1461, 1376, 1241, 1165, 1002 and 905 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.37 (1 H, m), 1.70–1.90 (3 H, m), 2.08–2.38 (2 H, m), 2.53 (1 H, d, *J* 9, 4-OH), 2.85 (1 H, m), 3.22 (1 H, d, *J* 2, 5-OH), 3.53 (1 H, d, *J* 15, 3-H), 3.86 (1 H, ddd, *J* 9, 4, 2, 4-H), 4.02 (1 H, ddd, *J* 15, 4, 2, 3-H′), 4.42 (1 H, d, *J* 16, 1-H), 4.75 (1 H, dd, *J* 16, 2, 1-H′), 6.95–7.10 (2 H, m, ArH), 7.69–7.89 (4 H, m, ArH) and 8.14 (1 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.97, 22.01, 22.20, 39.87, 51.28, 54.12, 66.27, 72.74, 79.47, 114.98 and 115.14 (d, $^2J_{C\text{-}F}$ 20), 117.41 and 117.58 (d, $^2J_{C\text{-}F}$ 21.5), 124.84, 131.82 and 131.88 (d, $^3J_{C\text{-}F}$ 7.5), 132.01, 132.48, 134.55, 135.37 and 135.43 (d, $^3J_{C\text{-}F}$ 7.5), 137.04 and 137.07 (d, $^4J_{C\text{-}F}$ 2.5), 148.32, and 161.02 and 162.98 (d, $^1J_{C\text{-}F}$ 245); *m/z* (CI) 454 (M^+ + 18, 20%), 419 (15), 407 (47), 250 (90) and 94 (100).

(4*RS*,5*SR*)-5-Cyclobutyl-8-fluoro-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 117

Thiophenol (56 μL, 0.55 mmol) was added to benzazepine **116** (80 mg, 0.183 mmol) and potassium carbonate (101 mg, 0.733 mmol) in acetonitrile (3.1 cm^3) and the reaction mixture was stirred at room temperature for 16 h. Water (30 cm^3) was then added and the aqueous phase was extracted with ethyl acetate (4 × 30 cm^3). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using methanol–ether (up to 10% methanol) containing triethylamine (1%) as eluent gave the *title compound* **117** (46 mg, 100%) as a dark coloured oil (found: M^+ + H, 252.1389. $C_{14}H_{19}FNO_2$ requires *M*, 252.1394); ν_{max} 3318, 1610, 1590, 1490, 1445, 1412, 1238, 1144, 1098, 1074, 1056, 1002, 981, 909, 865, 815 and 732 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 (1 H, m), 1.69–1.92 (3 H, m), 2.05–2.31 (2 H, m), 2.85 (1 H, m, 5-CH), 3.14 (1 H, dd, *J* 13.5, 1.0, 3-H), 3.24 (1 H, dd, *J* 13.5, 4.5, 3-H′), 3.69 (1 H, dd, *J* 4.5, 1, 4-H), 3.84 and 4.02 (each 1 H, d, *J* 15, 1-H), 6.75 (1 H, dd, *J* 9.5, 3, 9-H), 6.95 (1 H, td, *J* 8.5, 3, 7-H) and 7.79 (1 H, dd, *J* 9, 6, 6-H); δ_C (75 MHz, $CDCl_3$) 17.90, 21.89, 22.09, 40.13, 52.36, 56.17, 73.40, 80.10, 113.39 and 113.66 (d, $^2J_{C\text{-}F}$ 19.5), 116.37 and 116.65 (d, $^2J_{C\text{-}F}$ 21.5), 131.52 and 131.62 (d, $^3J_{C\text{-}F}$ 7.5), 137.54 and 137.51 (d, $^4J_{C\text{-}F}$ 3), 139.19 and 139.27 (d, $^3J_{C\text{-}F}$ 6.5) and 159.94 and 163.20 (d, $^1J_{C\text{-}F}$ 244.5); *m/z* (ES) 252 (M^+ + 1, 100%).

2-Butyl-5-cyclobutyl-8-fluoro-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine-4,5-diol 118

Sodium cyanoborohydride (54 mg, 1.0 eq) and few drops of concentrated aqueous hydrogen chloride were added to a mixture of the diol **117** (200 mg, 0.86 mmol) and butanal (185 mg, 2.38 mmol) in methanol (15 cm^3) and the mixture was stirred at room temperature for 12 h. Water and potassium carbonate were added and the mixture was extracted with dichloromethane, then filtered, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **118** (238 mg, 90%) as an oil (found: M^+, 307.1949. $C_{18}H_{26}FNO_2$ requires *M*, 307.1947); ν_{max} 3449–3409, 1609, 1587, 1491, 1459, 1405, 1372, 1304, 1240, 1143, 1098, 1070, 1011 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 7, 4′-H_3), 1.16 (3 H, m), 1.32–1.52 (2 H, m), 1.57–1.78 (3 H, m), 2.0–2.2 (2 H, m), 2.4–2.6 (2 H, m, 1′-H_2), 2.68 (1 H, m, CH), 2.8 (1 H, d, *J* 13, 3-H), 3.94 (1 H, d, *J* 9, 4-OH), 3.00 (1 H, m, 3-H′), 3.06 (1 H, s, 5-OH), 3.48 (1 H, dd, *J* 16, 1.5, 1-H), 3.58 (1 H, dd, *J* 9, 6, 4-H), 3.63 (1 H, d, *J* 16, 1-H′), 6.67 (1 H, dd, *J* 9.5, 2.5, ArH), 6.84 (1 H, td, *J* 8.5, 2.5, ArH) and 7.68 (1 H, dd, *J* 9, 6, ArH); δ_C (75 MHz, $CDCl_3$) 13.89, 17.63, 20.30, 21.58, 21.70, 29.51, 39.73, 59.30, 59.53, 62.76, 72.74, 79.24, 113.13 and 113.37 (d, $^2J_{C\text{-}F}$ 18), 116.36 and 116.64 (d, $^2J_{C\text{-}F}$ 21), 130.97 and 131.07 (d, $^3J_{C\text{-}F}$ 7.5), 137.37 and 137.41 (d, $^4J_{C\text{-}F}$ 3), 137.52 and 137.60 (d, $^3J_{C\text{-}F}$ 6), and 159.61 and 162.87 (d, $^1J_{C\text{-}F}$ 244.5); *m/z* (CI) 309 (M^+ + 2, 30%) and 308 (100%).

(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-8-fluoro-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)-aminopropanoyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 121

Thiophenol (305 μL, 2.98 mmol) was added to benzazepine **115** (920 mg, 2.29 mmol) and potassium carbonate (1.105 g, 8.01 mmol) in *N*,*N*-dimethylformamide (19 cm^3) and the reaction mixture was stirred at room temperature for 16 h. Water (90 cm^3) was then added and the aqueous phase was extracted with ethyl acetate (5 × 90 cm^3). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude dihydrobenzazepine **119** (479 mg, *ca.* 100%) which was used without purification.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (746 mg, 3.89 mmo) and 4-dimethylaminopyridine (28 mg,

0.23 mmol) were added to the crude acid **81** (1.09 g, 2.98 mmol) in *N*,*N*-dimethylformamide (6.5 cm^3) and the reaction mixture was stirred for 15 min. The amine **119** (497 mg, 2.29 mmol) in *N*,*N*-dimethylformamide (4.5 cm^3) was then added and the mixture was stirred for 16 h at room temperature before aqueous hydrogen chloride (1 M, 90 cm^3) and dichloromethane (200 cm^3) were added. The organic layer was washed with aqueous hydrogen chloride (1 M, 90 cm^3) and saturated aqueous sodium hydrogen carbonate (90 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude amide **120** (936 mg, 73%) (found: M^+ + H, 564.1969. $C_{30}H_{31}FN_3O_5S$ requires *M*, 564.1963) as an oil used without further purification; *m*/*z* (ES) 602 (M^+ + 39, 16%), 593 (100), 586 (15) and 564 (5).

N-Methylmorpholine-*N*-oxide (214 mg, 1.83 mmol) and osmium tetraoxide (42 mg, 0.17 mmol) were added to the crude amide **120** (936 mg, 1.66 mmol) in acetone (26 cm^3), *tert*-butanol (26 cm^3) and water (13 cm^3). The reaction mixture was stirred for 16 h at room temperature then saturated aqueous sodium sulfite (140 cm^3) was added. The mixture was then stirred for a further 30 min before extracting with ethyl acetate (4 × 180 cm^3). The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (50 : 50) containing triethylamine (1%) as eluent gave the *title compound* **121** (936 mg, 94%), a 50 : 50 mixture of rotamers, as a white foam (found: M^+ + Na, 620.1837. $C_{30}H_{32}FN_3NaO_7S$ requires *M*, 620.1837); ν_{max} 3430, 1633, 1590, 1543, 1493, 1455, 1371, 1346, 1267, 1239, 1163, 1126, 1095, 999, 982, 939, 852, 816, 776, 735 and 703 cm^{-1}; δ_H (500 MHz, $CDCl_3$–D_2O) 1.22 (1 H, m), 1.58–1.80 (2.5 H, m), 1.94–2.06 (2 H, m), 2.06–2.20 (1.5 H, m), 2.33 (0.5 H, m), 2.47–2.62 (1.5 H, m), 2.77 (0.5 H, m), 3.04 (0.5 H, d, *J* 15), 3.31–3.48 (2 H, m), 3.53 (0.5 H, m), 3.62 (0.5 H, d, *J* 3.5), 3.72 (0.5 H, dd, *J* 15.5, 3.5), 3.75 (0.5 H, d, *J* 3), 3.87 (0.5 H, d, *J* 15), 4.23 (1 H, s), 4.33 (0.5 H, d, *J* 15.5), 4.38 (0.5 H, d, *J* 15.5), 4.43 (0.5 H, d, *J* 15.5), 4.50 (0.5 H, d, *J* 15.5), 4.95 (0.5 H, d, 15), 6.43 (0.5 H, dd, *J* 8.5, 2.5, 9-H), 6.82 (0.5 H, td, *J* 8.5, 2.5, 7-H), 6.85–6.91 (1 H, m, 7-H and 9-H), 7.15–7.28 (5 H, m, ArH), 7.47 (0.5 H, t, *J* 7.5, ArH), 7.53–7.64 (3 H, m, 6-H and ArH), 7.69 (0.5 H, dd, *J* 8.5, 6, 6-H), 7.78 and 7.87 (each 0.5 H, d, *J* 8, ArH); δ_C (125 MHz, $CDCl_3$) 16.50, 20.60, 20.66, 20.86, 20.99, 31.22, 31.77, 38.52, 39.09, 43.56, 43.58, 46.92, 49.77, 49.84, 51.85, 52.38, 52.45, 72.16, 72.63, 77.89, 78.08, 112.85 and 113.01 (d, $^2J_{C\text{-}F}$ 20), 113.17 and 113.32 (d, $^2J_{C\text{-}F}$ 19), 115.04 and 115.21 (d, $^2J_{C\text{-}F}$ 22), 116.61 and 116.78 (d, $^2J_{C\text{-}F}$ 22), 123.22, 123.24, 127.00, 127.23, 127.43, 127.70, 127.85, 129.75, 129.91, 129.98, 130.04, 130.58, 130.64, 130.82, 130.84, 131.78, 131.95, 132.50, 132.68, 133.50, 133.56, 134.64, 134.70, 134.90, 135.03, 135.13, 136.47, 136.49, 146.93, 146.98, 159.24 and 161.26 (d, $^1J_{C\text{-}F}$ 246.5), 159.50 and 161.46 (d, $^1J_{C\text{-}F}$ 245), 169.43 and 170.77; *m*/*z* (ES) 620 (M^+ + 23, 100%) and 598 (M^+ + 1, 4).

TBTU (65 mg, 0.20 mmol) was added to the acid **81** (67 mg, 0.18 mmol) and Hünig's base (64 μL, 0.37 mmol) in dichloromethane (1.0 cm^3) and the mixture was stirred for 15 min. The amine **117** (46 mg, 0.18 mmol) in dichloromethane (0.7 cm^3) was then added and the mixture was stirred for 16 h at room temperature. Saturated aqueous sodium hydrogen carbonate (20 cm^3) and dichloromethane (20 cm^3) were added. The aqueous layer was washed with dichloromethane (3 × 20 cm^3) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (50 : 50) containing triethylamine (1%) gave the hydroxy-amide **121** (104 mg, 95%) as a white foam.

(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-8-fluoro-2-[3-(*N*-phenylmethyl)aminopropanoyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 122

Thiophenol (125 μL, 1.22 mmol) was added to the amide **121** (560 mg, 0.94 mmol) and potassium carbonate (453 mg, 3.28 mmol) in *N*,*N*-dimethylformamide (19 cm^3) and the mixture was stirred at room temperature for 16 h. Water (90 cm^3) was then added and the aqueous phase was extracted with ethyl acetate (4 × 140 cm^3). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using methanol–dichloromethane (up to 5% methanol) containing triethylamine (1%) as eluent gave the *title compound* **122** (336 mg, 87%) as a pale yellow foam (found: M^+ + H, 413.2229. $C_{24}H_{30}FN_2O_3$ requires *M*, 413.2235); ν_{max} 3402, 1631, 1590, 1490, 1455, 1372, 1302, 1267, 1240, 1142, 1092, 1003, 980, 816, 736 and 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.13–2.92 (11 H, m, cyclobutyl-H, 5-CH, 2′-H_2 and 3-H_2), 3.10 (0.33 H, d, *J* 14.5, 3-H), 3.31 (3 H, br s, 2 × OH and NH), 3.36–3.52 (2.67 H, m, 3-H and NCH_2Ph), 3.60 (0.67 H, d, *J* 3, 4-H), 3.70 (0.33 H, d, *J* 4, 4-H), 3.94 (0.67 H, d, *J* 15, 1-H), 3.99 (0.67 H, dd, *J* 15.5, 2, 3-H′), 4.39 and 4.48 (each 0.33 H, d, *J* 16.5, 1-H), 4.70 (0.33 H, d, *J* 14, 3-H′), 5.10 (0.67 H, d, *J* 15, 1-H′), 6.74 (1 H, m, 9-H and 7-H), 6.80 (0.33 H, td, *J* 8.5, 2.5, 7-*H*), 6.95 (0.67 H, dd, *J* 9, 2.5, 9-H), 7.03 (1.33 H, d, *J* 7, ArH), 7.06 (0.67 H, d, *J* 7, ArH), 7.15–7.28 (3 H, m, ArH) and 7.56 (1 H, m, 6-H); δ_C (125 MHz, $CDCl_3$) 17.51, 17.53, 21.69, 21.72, 21.98, 22.01, 31.40, 33.00, 39.63, 40.22, 44.75, 45.70, 48.29, 51.44, 51.81, 53.46, 54.00, 54.18, 73.16, 73.85, 78.87, 79.19, 113.65 and 113.81 (d, $^2J_{C\text{-}F}$ 20), 114.19 and 114.35 (d, $^2J_{C\text{-}F}$ 19), 115.72 and 115.89 (d, $^2J_{C\text{-}F}$ 22), 117.56 and 117.73 (d, $^2J_{C\text{-}F}$ 21), 127.29, 127.55, 128.4,0 128.57, 128.62, 131.02, 131.08, 132.08, 132.15, 135.65, 135.71, 137.04, 137.07, 137.63, 160.16, 160.20, 162.16, 171.80 and 173.63; *m*/*z* (ES) 435 (M^+ + Na, 35%) and 413 (M^+ + 1, 100).

(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-8-fluoro-2-[3-(*N*-phenylmethyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 123

A solution of the amide **122** (319 mg, 0.77 mmol) and lithium aluminium hydride (235 mg, 6.19 mmol) in terahydrofuran (7 cm^3) was heated under reflux for 4 h. The mixture was then cooled to 0 °C and aqueous sodium hydroxide (2 M, 30 cm^3) was added cautiously followed by ethyl acetate (25 cm^3). The aqueous phase was extracted with ethyl acetate (2 × 25 cm^3) and the organic extracts were washed with water, brine and dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **123** (327 mg) as a pale yellow oil used without further purification (found: M^+ + H, 399.2445. $C_{24}H_{32}FN_2O_2$ requires *M*, 399.2442); ν_{max} 3435, 1610, 1590, 1492, 1454, 1242, 1144, 1077, 1005, 845, 814, 735 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.20–1.29 (2 H, m), 1.60–1.77 (5 H, m, 2′-H_2, cyclobutyl-H and NH), 2.01–2.18 (2 H, m), 2.54–2.73 (5 H, m, 5-CH, 1′-H_2 and 3′-H_2), 2.80 (1 H, d, *J* 13, 3-H), 2.99–3.08 (2 H, m, 3-H′ and OH), 3.47 (1 H, dd, *J* 14.5, 2, 1-H), 3.59–3.72 (4 H, m, 1-H′, 4-H and NCH_2Ph), 6.66 (1 H, dd, *J* 9, 3, 9-H), 6.86 (1 H, td, *J* 8.5, 2.5, 7-H), 7.10–7.24 (5 H, m, ArH) and 7.70 (1 H, dd, *J* 8.5, 6, 6-H); δ_C (75 MHz, $CDCl_3$) 17.91, 21.87, 22.04, 27.92, 39.99, 47.63, 54.06, 58.43, 59.48, 63.38, 73.06, 79.43, 113.52 and 113.78 (d, $^2J_{C\text{-}F}$ 19.5), 116.66 and 116.95 (d, $^2J_{C\text{-}F}$ 21.5),

127.34, 128.37, 128.69, 131.33 and 131.43 (d, $^{3}J_{C\text{-}F}$ 8), 137.77 and 137.85 (d, $^{4}J_{C\text{-}F}$ 3), 159.90 and 163.16 (d, $^{1}J_{C\text{-}F}$ 245.5); *m*/*z* (ES) 421 (M^+ + 23, 19%) and 399 (M^+ + 1, 100).

(4*RS*,5*SR*)-5-Cyclobutyl-4,5-dihydroxy-8-fluoro-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)-aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepine 124

2-Nitrobenzene sulfonyl chloride (167 mg, 0.75 mmol) in dichloromethane (7 cm^3) was added to the amine **123** (300 mg, 0.75 mmol) and Hünig's base (130 μL, 0.75 mmol) in dichloromethane (5 cm^3) and the mixture was stirred at room temperature for 16 h. Water (20 cm^3) was then added and the aqueous phase was extracted with dichloromethane (4 × 20 cm^3). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (50 : 50 → 100 : 0) containing triethylamine as eluent gave the *title compound* **124** (399 mg, 91%) as a pale foam (found: M^+ + Na, 606.2047. $C_{30}H_{34}FN_3NaO_6S$ requires *M*, 606.2045); ν_{max} 3468, 1609, 1590, 1543, 1494, 1455, 1372, 1348, 1265, 1242, 1162, 1126, 1076, 1003, 932, 852, 815, 780, 735, 700 and 652 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.09–1.31 (2 H, m), 1.40–1.75 (4 H, m, 2′-H_2 and cyclobutyl-H), 1.99–2.15 (2 H, m), 2.32 and 2.44 (each 1 H, m, 1′-H), 2.54–2.69 (2 H, m, 5-CH and OH), 2.69 (1 H, d, *J* 13, 3-H), 2.81 (1 H, dd, *J* 13, 4.5, 3-H′), 2.97 (1 H, br s, OH), 3.16–3.24 (2 H, m, 3′-H_2), 3.26 (1 H, d, *J* 15, 1-H), 3.49–3.55 (2 H, m, 1-H′ and 4-H), 4.39 and 4.45 (each 1 H, d, *J* 15.5, NHC*H*Ph), 6.58 (1 H, dd, *J* 9, 2.5, 9-H), 6.86 (1 H, td, 8.5, 2.5, 7-H), 7.15–7.25 (5 H, m, ArH), 7.51–7.64 (3 H, m, ArH), 7.68 (1 H, dd, *J* 8.5, 6, 6-H) and 7.87 (1 H, d, *J* 8, ArH); δ_C (125 MHz, $CDCl_3$) 16.63, 20.55, 20.69, 25.24, 38.60, 44.99, 51.04, 55.50, 58.42, 61.39, 71.77, 78.14, 112.40 and 112.56 (d, $^{2}J_{C\text{-}F}$ 20), 115.69 and 115.86 (d, $^{2}J_{C\text{-}F}$ 22), 123.17, 127.07, 127.19, 127.75, 129.94, 129.99 and 130.05 (d, $^{3}J_{C\text{-}F}$ 8), 130.65, 132.30, 132.55, 134.75, 136.03 and 136.08 (d, $^{3}J_{C\text{-}F}$ 7.5), 136.35 and 136.37 (d, $^{4}J_{C\text{-}F}$ 2.5), 146.91 and 159.29 and 161.24 (d, $^{1}J_{C\text{-}F}$ 244); *m*/*z* (ES) 606 (M^+ + 23, 100%) and 584 (M^+ + 1, 4).

5-Cyclobutyl-8-fluoro-5-hydroxy-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenylmethyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 125

Dimethyl sulfoxide (26 μL, 0.36 mmol) in dichloromethane (475 μL) was added dropwise to oxalyl chloride (19 μL, 0.22 mmol) in dichloromethane (0.52 cm^3) at −78 °C and the mixture was stirred for 30 min before the diol **124** (42 mg, 0.07 mmol) in dichloromethane (1 cm^3) was added. The mixture was stirred for 30 min then triethylamine (60 μL, 043 mmol) was added. The mixture was allowed to warm to 0 °C and was stirred for 30 min before water (20 cm^3) was added. Following extraction with ether (4 × 20 cm^3), the organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (25 : 75 → 50 : 50) as eluent gave the *title compound* **125** (34 mg, 81%) as a pale yellow gum (found: M^+ + Na, 604.1872. $C_{30}H_{32}FN_3NaO_6S$ requires *M*, 604.1888); ν_{max} 3461, 3068, 3031, 1698, 1610, 1588, 1543, 1489, 1456, 1440, 1371, 1349, 1163, 1127, 1013, 910, 852, 780 and 734 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.48–1.53 (3 H, m, 2′-H_2 and cyclobutyl-H), 1.53–1.80 (4 H, m), 2.05–2.17 (3 H, m, 1′-H_2 and cyclobutyl-H), 3.11–3.31 (4 H, m, 3-H, 5-CH and 3′-H_2), 3.55–3.62 (2 H, m, 1-H and 3-H′), 3.96 (1 H, d, *J* 16.5, 1-H′), 4.40 and 4.44 (each 1 H, d, *J* 15.5, NHC*H*Ph), 4.61 (1 H, br s, 5-OH), 6.54 (1 H, dd, *J* 9, 2.5, 9-H), 6.85 (1 H, td, 8.5, 2.5, 7-H), 7.18–7.26 (5 H, m, ArH), 7.51–7.67 (4 H, m, ArH and 6-H) and 7.89 (1 H, d, *J* 8, ArH); δ_C (125 MHz, $CDCl_3$) 16.05, 20.33, 20.52, 24.39, 40.79, 44.47, 49.68, 50.75, 58.20, 62.52, 82.70, 112.90 and 113.06 (d, $^{2}J_{C\text{-}F}$ 20), 115.15 and 115.32 (d, $^{2}J_{C\text{-}F}$ 21), 123.27, 127.09, 127.22, 127.78, 128.46 and 128.52 (d, $^{3}J_{C\text{-}F}$ 7.5), 129.90, 130.66, 132.40, 132.54, 133.10 and 133.12 (d, $^{4}J_{C\text{-}F}$ 2.5), 134.61, 135.53 and 135.58 (d, $^{3}J_{C\text{-}F}$ 6.5), 146.88, 159.62 and 161.60 (d, $^{1}J_{C\text{-}F}$ 246.5) and 206.01; *m*/*z* (ES) 604 (M^+ + 23, 100%), 582 (M^+ + 1, 15) and 564 (9).

2-(3-Benzylaminopropyl)-5-cyclobutyl-8-fluoro-5-hydroxy-1,2,3,5-tetrahydro-[1*H*]-2-benzazepin-4-one 126

Thiophenol (18 μL, 0.175 mmol) was added to the sulfonamide **125** (34 mg, 0.058 mmol) and potassium carbonate (32 mg, 0.234 mmol) in acetonitrile (0.98 cm^3) and the mixture was stirred for 16 h at room temperature. Water (20 cm^3) and ether (20 cm^3) were added and the aqueous phase was extracted with ether (3 × 20 cm^3). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum (50 : 50 → 100 : 0) containing triethylamine (1%) followed by methanol–ether (10 : 90) containing triethylamine (1%) as eluent gave the *title compound* **126** (22 mg, 95%) as a pale oil (found: M^+ + H, 397.2295. $C_{24}H_{30}FN_2O_2$ requires *M*, 397.2286); ν_{max} 3456, 3313, 3059, 3028, 1701, 1610, 1588, 1490, 1454, 1365, 1261, 1241, 1220, 1122, 1099, 1013, 977, 863, 810, 736, 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.48–1.75 (7 H, m, 2′-H_2, cyclobutyl-H and NH), 1.81 and 2.16 (each 1 H, m), 2.35–2.46 (2 H, m, 1′-H_2), 2.55–2.64 (2 H, m, 3′-H_2), 3.42 (1 H, m, 5-CH), 3.45 and 3.68 (each 1 H, d, *J* 16, 3-H), 3.70 (2 H, s, NCH_2Ph), 3.79 and 4.10 (each 1 H, d, *J* 16.5, 1-H), 4.77 (1 H, br s, 5-OH), 6.68 (1 H, dd, *J* 9.5, 2.5, 9-H), 6.86 (1 H, td, *J* 8.5, 2.5, 7-H), 7.15–7.27 (5 H, m, ArH) and 7.65 (1 H, dd, *J* 9, 6, 6-H); δ_C (125 MHz, $CDCl_3$) 16.14, 20.50, 20.62, 26.24, 40.87, 45.98, 51.43, 52.80, 58.85, 62.85, 82.65, 112.87 and 113.03 (d, $^{2}J_{C\text{-}F}$ 20), 114.98 and 115.15 (d, $^{2}J_{C\text{-}F}$ 22), 126.15, 127.18, 127.46, 128.51 and 128.57 (d, $^{3}J_{C\text{-}F}$ 8), 133.20 and 133.23 (d, $^{4}J_{C\text{-}F}$ 2.5), 135.97 and 136.00 (d, $^{3}J_{C\text{-}F}$ 5.5), 139.01, 159.71 and 161.67 (d, $^{1}J_{C\text{-}F}$ 245) and 206.58; *m*/*z* (ES) 419 (M^+ + 23, 2%) and 397 (M^+ + 1, 100).

Crystal data for the 4,4-trimethylenedithiotetrahydrobenzazepine 20

$C_{18}H_{25}NO_2S_2$, M = 351.51, monoclinic, a = 10.712(6), b = 11.368(4), c = 15.945(4) Å, β = 103.78(3)°, U = 1885.6(13) Å^3, T = 296(1)°, space group $P\,2_1/n$ (no. 142), Z = 2, μ(CuKα) = 2.621 mm^{-1}, 7554 reflections measured, 3619 unique (R_{int} = 0.041), 2942 reflections with $I > 2.00\,\sigma(I)$ were used in the final refinement. The final R = 0.055 for reflections with $I > 2.00\,\sigma(I)$, $wR2$ = 0.169 (all data). Data deposited with the Cambridge Crystallographic Data Centre, number CCDC 655337.‡

‡ CCDC reference numbers 655337 and 655338. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b801206g

Crystal data for the 4,5-dihydroxy-2,3,4,5-tetrahydrobenzazepine 53

$C_{18}H_{27}NO_2$, $M = 289.41$, triclinic, $a = 7.783(2)$, $b = 9.850(4)$, $c = 12.119(2)$ Å, $\alpha = 110.81(2)$, $\beta = 103.93(4)$, $\gamma = 97.43(2)°$, $U = 819.0(4)$ Å^3, $T = 293(1)°$, space group $P\bar{1}$ (no. 2) $Z = 4$, $\mu(\text{MoK}\alpha) = 0.075$ mm^{-1}, 3092 measured reflections, 2860 unique reflection ($R_{\text{int}} = 0.015$), 1644 reflections with $I > 2.00\ \sigma(I)$ were used in the final refinement. The final $R = 0.056$ for reflections with $I > 2.00\ \sigma(I)$, $wR2 = 0.1409$ (all data). Data deposited with the Cambridge Crystallographic Data Centre, number CCDC 655338.‡

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